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Evaluation of alternative approaches for the synthesis of macrocyclic bisindolylmaleimides†

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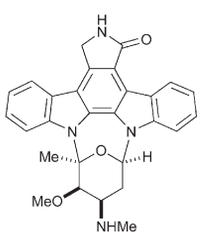
Received 5th April 2004, Accepted 10th August 2004
First published as an Advance Article on the web 10th September 2004

Approaches for the synthesis of macrocyclic bisindolylmaleimides, in which the indole nitrogens are linked with a tether, are described. Two alternative approaches were investigated: macrocyclisation in either the 'southern' (by adding the tether to the bisindolylmaleimide ring system) or the 'northern' district. With two-, three- and four-atom tethers, both of these approaches were unsuccessful for a wide range of attempted macrocyclisation reactions (palladium-catalysed π-allyl substitution, ring-closing metathesis, McMurry reaction, iodocyclisation, formation of a silylene derivative, substitution of an α,ω-disubstituted electrophile). The failure of all of these reactions was ascribed to the strained nature of the target ring system. However, with longer tethers (six to ten atoms), the macrocycles could prepared using either a ring-closing metathesis reaction or by substitution of an α,ω-dibromide). Fourteen successful macrocyclisation reactions are described; deprotection gave eleven macrocyclic bisindolylmaleimides in which an imide substituent had been removed.

Introduction

The indolocarbazole alkaloids, such as staurosporine (**1**) and K252a (**2**) are potent, broad spectrum inhibitors of many protein kinases.[1] The lack of specificity of staurosporine renders it a rather blunt tool for studying protein kinases. Nonetheless, the indolocarbazoles have proved to be useful leads in the discovery of selective inhibitors of specific protein kinases. A fruitful strategy has been to disrupt the planarity of the indolocarbazole ring system to give bisindolylmaleimides.[2] The selectivity and potency of inhibition has been refined through the formation of macrocyclic bisindolylmaleimide analogues; for example, the bisindolylmaleimide LY333531 (**3**) selectively inhibits the β isoforms of protein kinase C (PKCβ) (IC_{50} = 4.7 nM for PKCβI and 5.9 nM for PKCβII).[2c,d] PKCβ is selectively activated by elevated glucose in many vascular tissues, and the bisindolylmaleimide **3** can produce significant improvements in diabetic retinopathy, nephropathy, neuropathy and cardiac dysfunction.[3]



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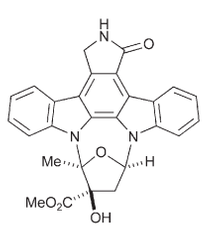

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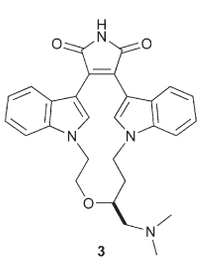

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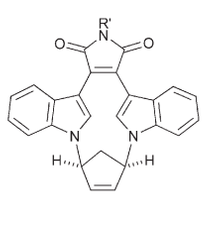


4a

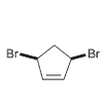
We are interested in how the conformation of macrocyclic bisindolylmaleimides **4**, including cyclopentene analogues (*e.g.* **4a**) of K252a (**2**), may be exploited in biology and chemistry. Some bis(benzothiophenyl)maleimides, which are structurally related to bisindolylmaleimides, are photochromic compounds which may be exploited in optical switching devices.[4] Two alternative approaches for the synthesis of macrocyclic bisindolylmaleimides of general structure **4** may be envisaged (Strategies A and B, Scheme 1).[5] Strategy A would involve the substitution of a bifunctional electrophile **7** with two indole molecules (→**5**); the macrocycle would then be formed through the formation of the 'northern' district to give a bisindolylmaleimide **4**. Alternatively, an intact bisindolylmaleimide could be reacted directly with an electrophile **7** to give an acyclic intermediate **6** (Strategy B); closure of the ring in the 'southern' district would then yield the required macrocycle **4**. In this paper, we describe the potential of a range of different reactions in the synthesis of macrocyclic bisindolylmaleimides. The relative merits of the two alternative strategies, and the scope and limitations of each cyclisation reaction, are discussed.

Strategy A: preparation of intermediates for macrocyclisation in the 'northern' district

One approach to the synthesis of bisindoles **5** would involve the palladium-catalysed substitution of allylically substituted cyclopentenes with indole nucleophiles[6] (see Scheme 2 and Table 1).‡ The $Pd_2(dba)_3$-catalysed reactions between the racemic allylic acetate§ **14** and the anions of the indoles **15** and **17** were efficient, and gave the corresponding products **16** and

† Electronic supplementary information (ESI) available: synthesis and characterisation for all compounds not mentioned in the Experimental; results of molecular modelling of macrocycles **60** (*n* = 5, 6, 7); crystal structure data for **20**. See http://www.rsc.org/suppdata/ob/b4/b405010j/

‡ An alternative approach, which was briefly investigated, would have involved elaboration of a bisaniline (ref. 7). The dibromocyclopentene **8** (ref. 8) was substituted with aniline; however, the reaction was not stereospecific, and the bisaniline **9** was obtained as a 65:35 *cis*:*trans* mixture of diastereoisomers (77% yield). The more hindered nucleophile, 2-iodoaniline, was unreactive, and only the monosubstituted cyclopentene **10** was obtained in 15% yield.



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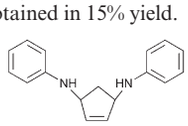

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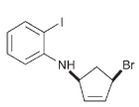

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§ The allylic acetate **14** was prepared in four steps from furyl alcohol using a known reaction sequence (ref. 9).

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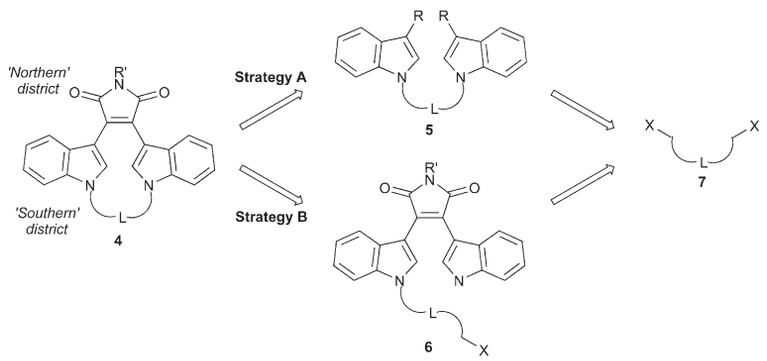


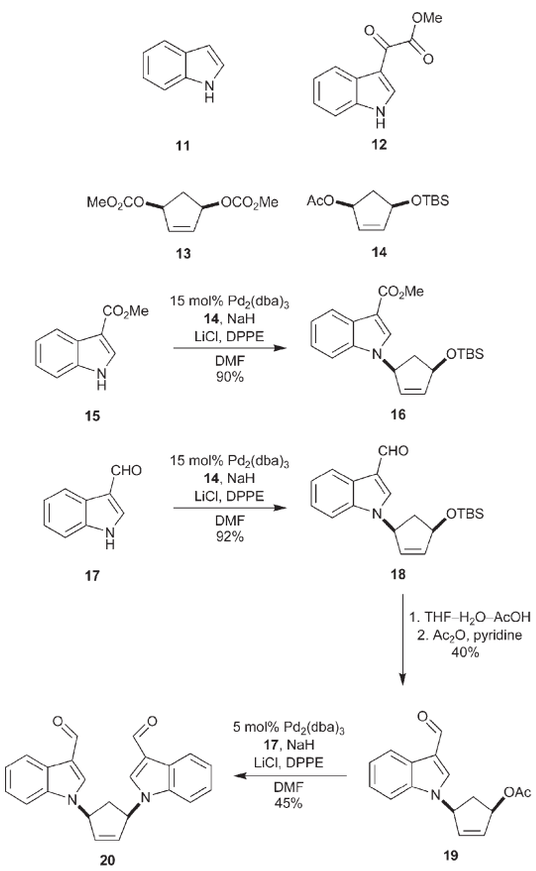
Scheme 1 Closure of macrocycle in the 'northern' (Strategy A) and 'southern' districts (Strategy B).

Table 1 Palladium-catalysed substitution reactions with indole nucleophiles

Entry	Indole	Electrophile	Conditions	Product	Yield[a] (%)
1	**11**	**13**	NaH, DMF, cat. $Pd(PPh_3)_4$	[b]	—
2	**12**	**13**	NaH, DMF, cat. $Pd(PPh_3)_4$	[b]	—
3	**15**	**13**	NaH, DMF, cat. $Pd(PPh_3)_4$	[b]	—
4	**12**	**14**	15 mol% $Pd_2(dba)_3$, NaH, LiCl, DPPE, DMF	[b]	—
5	**15**	**14**	15 mol% $Pd_2(dba)_3$, NaH, LiCl, DPPE, DMF	**16**	90
6	**17**	**14**	15 mol% $Pd_2(dba)_3$, NaH, LiCl, DPPE, DMF	**18**	92
7	**17**	**19**	5 mol% $Pd_2(dba)_3$, NaH, LiCl, DPPE, DMF	**20**	45

[a] Yield of purified product. [b] No reaction.

18 in >90% yield (entries 5–6, Table 1). In contrast, attempted two-directional[10] reactions involving the biscarbonate **13** were unsuccessful (entries 1–3).



Scheme 2

Desilylation of **18**, and acetylation, gave the allylic acetate[10] **19** (Scheme 2) whose relative configuration was confirmed by the observation of diagnostic NOE measurements (Fig. 1); the allylic acetate **19** underwent smooth palladium-catalysed substitution with the indole-3-carboxyaldehyde (**17**) to give the required *meso* bisindole **20** (entry 7, Table 1). The relative configuration of **20** was confirmed by X-ray crystallography (Fig. 2) and by the diastereotopicity of its methylene protons (2-CH_AH_B) which was revealed by ^{1}H NMR spectroscopy. The dialdehyde **20** was converted into the diene **21** using a Wittig homologation (Scheme 3).

The bisindole **22** with its unsubstituted butane-1,4-diyl linker was prepared in excellent yield by reaction of the sodium anion

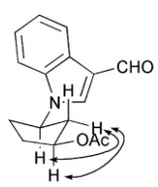


Fig. 1 Diagnostic NOE measurements for **19**.

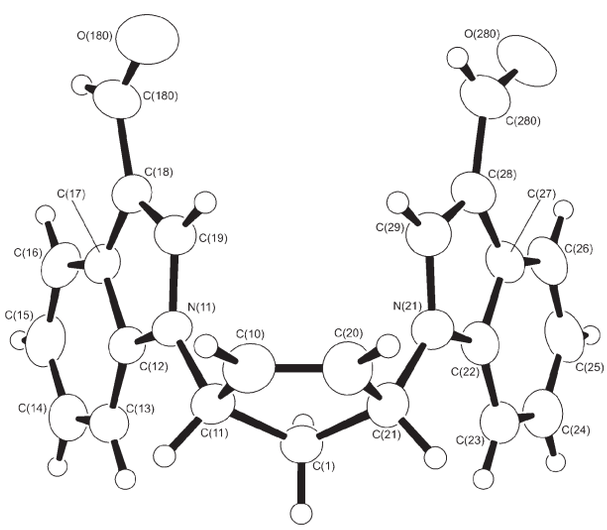
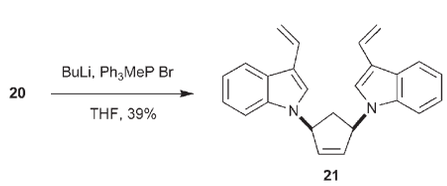
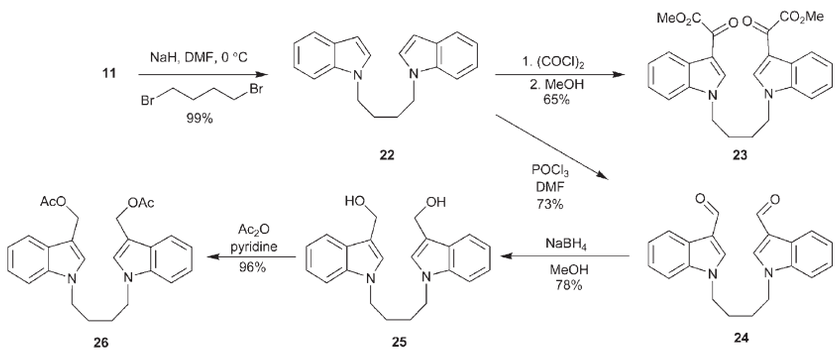


Fig. 2



Scheme 3

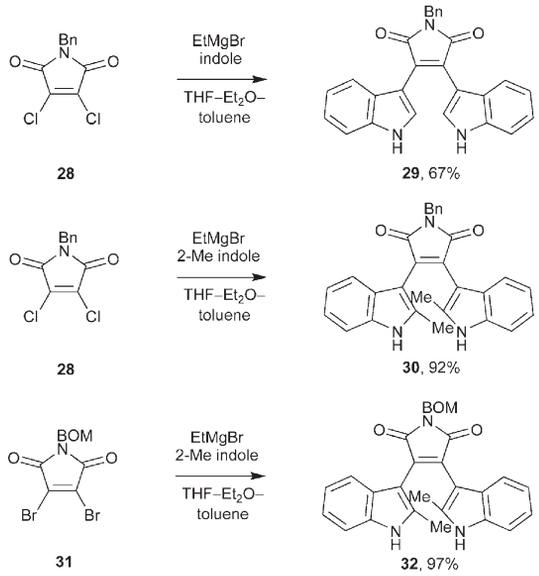


Scheme 4

of indole with 1,4-dibromobutane (Scheme 4).¶ The indole rings of **22** were functionalised in a two-directional sense. Hence, reaction with oxalyl chloride, and methanolysis of the resulting glyoxylyl chloride,[12] gave the bisglyoxylate ester **23**. Similarly, Vilsmeier carbonylation[13] of **22** gave the required dialdehyde **24**; the dialdehyde **24** was reduced to give the corresponding diol **25** which, after acetylation, gave the diacetate **26**.

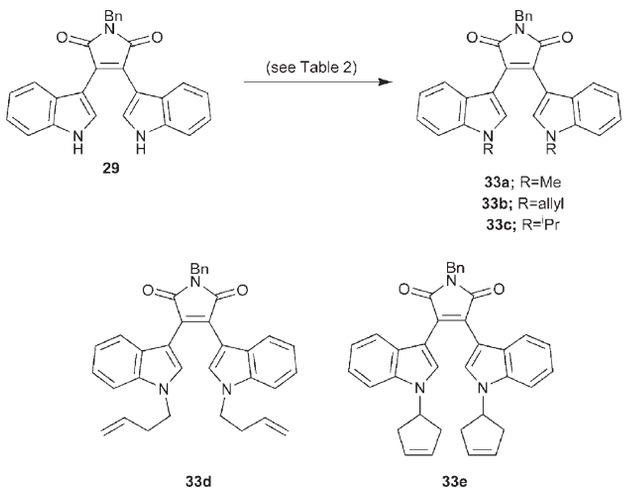
Strategy B: preparation of intermediates for macrocyclisation in the 'southern' district

The bisindolylmaleimides **29**, **30** and **32** were prepared from the 3,4-dihalomaleimides[14] **28** and **31** (Scheme 5). Hence, treatment of indole and 2-methylindole with EtMgBr in THF–Et_2O–toluene gave the corresponding indolyl anions which were reacted with either **28** or **31**; the required bisindolylmaleimides could be obtained in high purity by direct precipitation from the reaction mixture.[15]



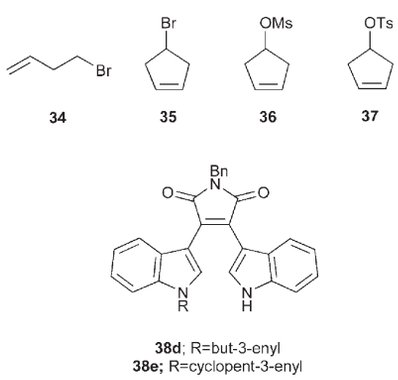
Scheme 5

The alkylation of the bisindolylmaleimide **29** was studied with a range of simple electrophiles (Scheme 6 and Table 2). Although most alkylations of **29** were routine (entries 1–4, Table 2), cyclopent-3-enylation[16,17] required considerable optimisation: reaction of **29** with either the mesylate **36** or the tosylate **37** under optimised conditions (Cs_2CO_3, DMF, 50 mol% Bu_4NI) gave similar yields of the disubstituted bisindolylmaleimide **33e**,



Scheme 6

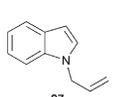
the monosubstituted bisindolylmaleimide **38e** and recovered starting material (**29**) (entries 5b–c).



Palladium-catalysed substitution of the bisindolylmaleimide ring system was also investigated. Initially, we studied the $Pd_2(dba)_3$-catalysed reaction of the sodium dianion derived from **29** with the racemic allyl acetate **14** (entry 1, Table 3). An essentially statistical mixture of products was obtained: the required monosubstituted bisindolylmaleimide **42** (48%) and the disubstituted product **43** (20%), presumably as a mixture of diastereoisomers, were obtained.

However, when one of the indolyl nitrogens was blocked, good yields of substitution products could be obtained: the reaction of the cyclopent-3-enyl-substituted bisindolylmaleimide **38e** gave the substitution product **44** in 65% yield (entry 2, Table 3). Similarly, the SEM-protected bisindolylmaleimide[18]‖ **39** reacted smoothly, to give the bisindolylmaleimide **45** in 57% yield (Scheme 7 and entry 3, Table 3).

¶ The corresponding bisindole with a hexane-1,6-diyl linker has been prepared in an analogous manner (ref. 11). The corresponding reaction with 1,3-dibromopropane, however, resulted in E2 elimination to give *N*-allyl indole **27** (92%).



‖ The required SEM-protected bisindolylmaleimide **39** was prepared in two alternative ways: (a) by protection of the bisindolylmaleimide **29** (reaction with 1.0 equivalent of SEMCl gave a roughly statistical mixture of **39**, 52%, and **40**, 23%), or (b) by the following reaction sequence: monosubstitution of the 3,4-dichloromaleimide **28** and SEM protection (→**41**), followed by a second substitution by indole (→**39**) (ref. 14).

Table 2 Substitution reactions of bisindolylmaleimides

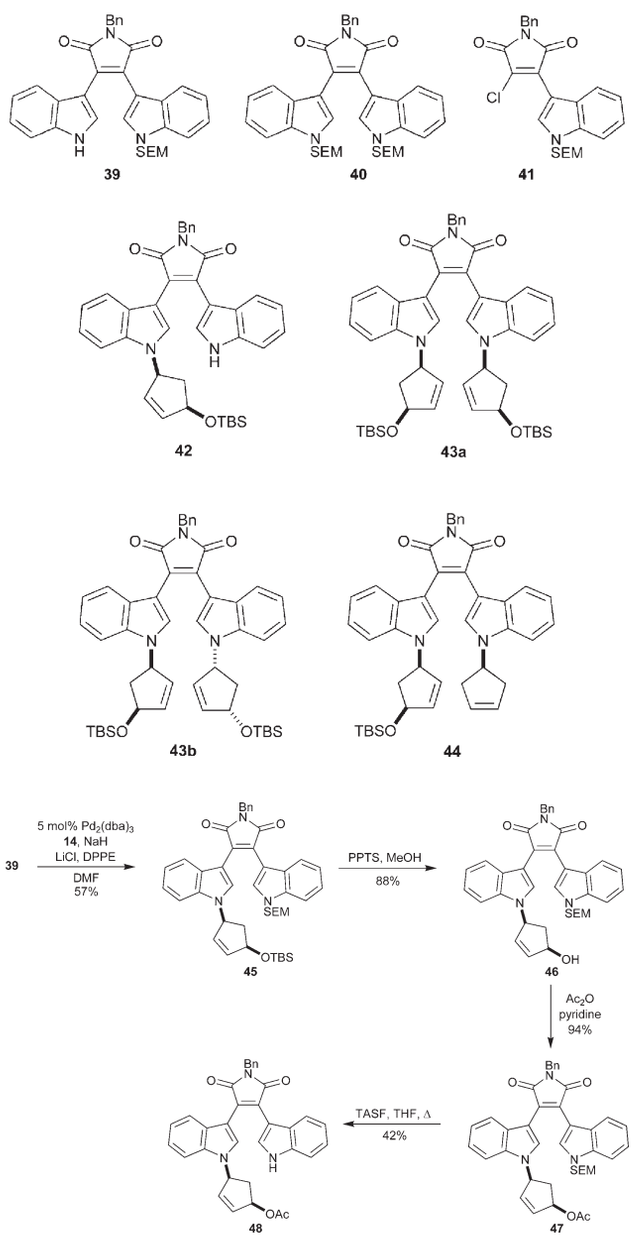
Entry	Reagent	Conditions	Product	Yield[a] (%)	Product	Yield[a] (%)
1	MeI[b]	NaH, DMF, 23 °C, 18 h	**33a**	90	—	—
2	allyl bromide[b]	NaH, DMF, 23 °C, 72 h	**33b**	84	—	—
3a	^{i}PrI[b]	NaH, THF, 23 °C, 84 h	[c]	—	—	—
3b	^{i}PrI[b]	NaH, DMF, 23 °C, 84 h	**33c**	86	—	—
3c	^{i}PrI[b]	K_2CO_3, DMF, 23 °C, 84 h	**33c**	47	—	—
3d	^{i}PrI[b]	K_2CO_3, DMF, 52 °C, 84 h	**33c**	73	—	—
3e	^{i}PrI[b]	Cs_2CO_3, DMF, 23 °C, 84 h	**33c**	64	—	—
3f	^{i}PrI[b]	Cs_2CO_3, DMF, 52 °C, 84 h	**33c**	95	—	—
4	**34**	NaH, DMF, 23 °C, 24 h	**33d**	79	—	—
5a	**35**[d]	Cs_2CO_3, 50 mol% Bu_4NI, DMF, 52 °C, 96 h	[c,e]	—	—	—
5b	**36**[d]	Cs_2CO_3, 50 mol% Bu_4NI, DMF, 52 °C, 96 h	**33e**	30[f]	**38**	37
5c	**37**[d]	Cs_2CO_3, 50 mol% Bu_4NI, DMF, 52 °C, 96 h	**33e**	31[f]	**38**	36

[a] Yield of purified product. [b] 2.6 equivalents. [c] No reaction. [d] 1.1 equivalents. [e] **29** was recovered (>98%). [f] **29** was recovered (33%).

Table 3 Palladium-catalysed substitution of bisindolylmaleimides

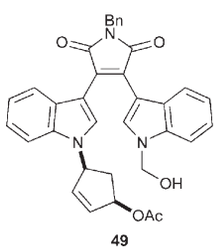
Entry	Starting material	Conditions	Product	Yield[a] (%)
1	**29**	15 mol% $Pd_2(dba)_3$, **14**, NaH, LiCl, DPPE, DMF	**42**[b]	48
2	**38**	5 mol% $Pd_2(dba)_3$, **14**, NaH, LiCl, DPPE, DMF	**44**	65
3	**39**	5 mol% $Pd_2(dba)_3$, **14**, NaH, LiCl, DPPE, DMF	**45**	57

[a] Yield of purified product. [b] The bisindolylmaleimides **43a** and **43b** were also isolated in a combined yield of 20%.



Scheme 7

Treatment of the TBS ether **45** with PPTS in methanol gave the required SEM-protected bisindolylmaleimide **46** in 88% yield, which was acetylated to give **47**. Clean removal of the SEM group from **47** was problematic: treatment of **47** with THF–water–acetic acid resulted in fragmentation of the SEM group to give the hydroxymethyl-substituted bisindolyl-maleimide **49** (62%) as well as the required product **48** (12%). However, removal of the SEM group was much more efficient using TASF[19] in THF, and gave the bisindolylmaleimide **48** without competing deacetylation or acyl transfer.



Strategy A: studies towards the closure of the macrocycle in the 'northern' district

Our synthetic studies had provided a range of bisindoles (**20**, **21** and **23**–**25**) which were suitably functionalised for macrocyclisation in the 'northern' district (see Strategy A, Scheme 1). Possible reactions which might be exploited in the macrocyclisation step are summarised in Fig. 3.

Unfortunately, none of these approaches proved fruitful. Ring-closing metathesis (RCM), a method of choice for the formation of macrocyclic rings,[20] afforded none of the required product. Similarly, the McMurry reaction, which has been used to prepare a wide range of strained cyclic molecules,[21] was also unsuccessful: the cyclisation of **20**, **23** and **24** was studied under a range of alternative reaction conditions[22] but macrocyclic products were never isolated.* Finally, the attempted formation of a cyclic bis(di-*tert*-butylsilylene) derivative from the diol **25** did not yield a macrocyclic product.

* Less strained macrocyclic bisindolylmaleimides (with a six-atom tether linking the indole rings) have previously been prepared using a McMurry reaction (ref. 11).

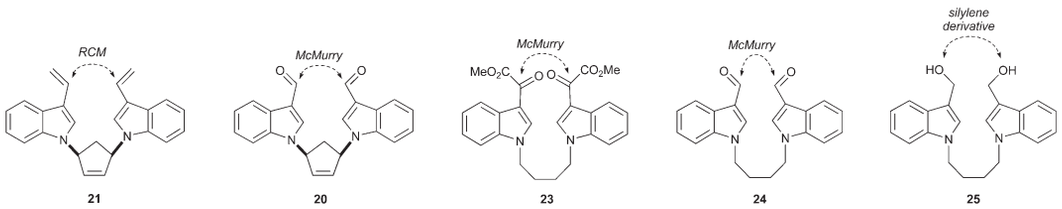


Fig. 3 Attempted cyclisations in the 'northern' district.

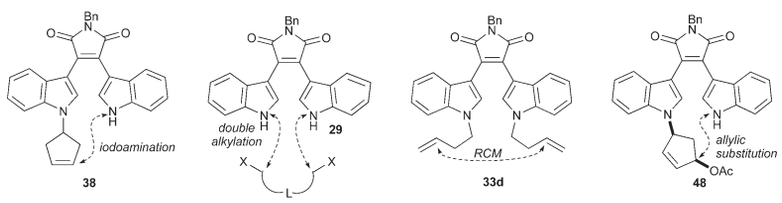


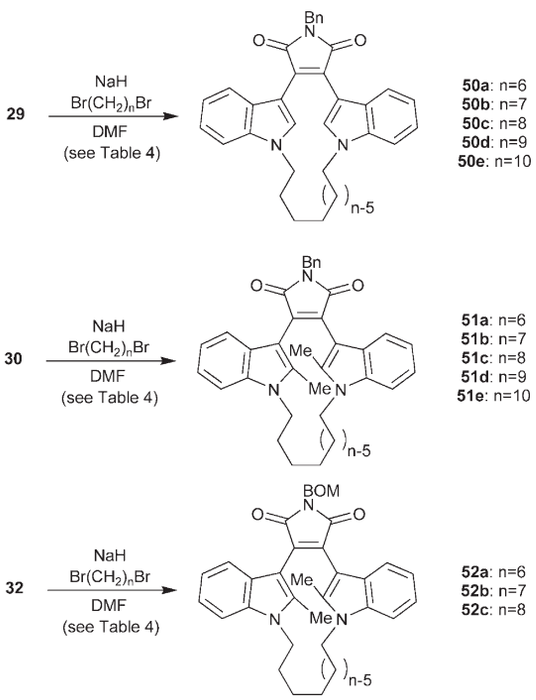
Fig. 4 Possible methods for cyclisation in the 'southern' district.

Strategy B: studies towards the closure of the macrocycle in the 'southern' district

Strategy B involved cyclisation reactions in which the bisindolylmaleimide ring system was intact (Strategy B, Scheme 1), and a number of potential cyclisation precursors (*e.g.* **29**, **38** and **48**) had been prepared. Possible methods for cyclisation in the 'southern' district are summarised in Fig. 4.

A particularly direct approach would involve the reaction of a bisindolylmaleimide with a bifunctional electrophile (see structure **29**, Fig. 4). Indeed, this general approach has previously been applied in the synthesis of macrocyclic bisindolylmaleimides with a six atom tether linking the indole rings (as in **3**).[2c,4] Macrocyclisation reactions were, therefore, investgated using the 1,3- to 1,10- α,ω-dibromoalkanes (see Scheme 8 and Table 4). The reactions of the bisindolylmaleimide **29** were perfomed in parallel under dilute conditions (0.025 M). Good yields of the macrocyclic bisindolylmaleimides **50a**–**e**, which have six- to ten-atom tethers, were obtained (entries 1–5, Table 4). The procedure was amenable to automation on a ChemSpeed automated synthetic workstation. However, with the shorter α,ω-dibromoalkanes, the results were less promising. With 1,3-dibromopropane, alkylation was followed by elimination, and the diallylated bisindolylmaleimide **33b** was obtained.†† Attempts to prepare macrocyclic bisindolylmaleimides **50** with four- and five-atom tethers (n = 4 and 5) were also unsuccessful, which presumably reflects the strained nature of these ring systems.

Under the same conditions, the bis(2-methylindolyl)-maleimides **51a**–**e** and **52a**–**c** were also prepared (Scheme 8). The yields of the macrocyclic products **51** and **52** were generally rather lower than those of the macrocycles **50**, presumably because the indolyl 2-methyl substituents increase the strain of the macrocyclic ring system.

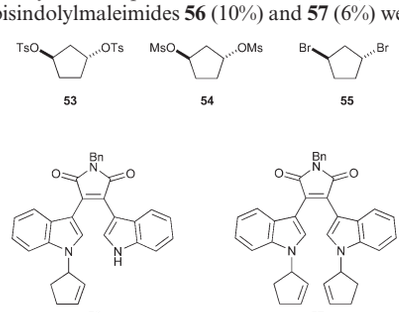


Scheme 8

Ring-closing metathesis could also be exploited in the cyclisation step (Scheme 9). In marked contrast to the attempted cyclisation of the diene **21**, the cyclisation of **33d** with 5 mol% Grubbs' second generation catalyst (**58**) proceeded smoothly: the macrocycle **59** was obtained in 74% yield as a single geometric isomer of unknown configuration. The length of the tether had a critical impact on the outcome of the cyclisation step: the diallylated bisindolylmaleimide **33c** did not undergo RCM, and was, instead, recovered from the reaction mixture.

All other attempts to promote macrocyclisation in the 'southern' district were unsuccessful.‡‡ Our success with *inter*molecular palladium-catalysed substitution reactions (see Scheme 8 and Table 3) led us to investigate an intramolecular version too.[25] Unfortunately, attempted macrocyclisation of **48** was unsuccessful with a range of palladium catalysts [$Pd_2(dba)_3$; $Pd(PPh_3)_4$] and phosphine ligands (DPPE; DPPF) of varying bite angle.

†† The bifunctional electrophiles **53**, **54** and **55** were prepared from commercially available cyclopentane-1,3-diol, which was available (Aldrich) as a >95:5 mixture of *trans* and *cis* diastereomers. Alkylations of **29** were investigated in the presence of Bu_4NI in the hope of promoting a Walden inversion (ref. 23) which would allow macrocyclisation to occur. Analysis of the crude reaction mixtures by analytical HPLC revealed, with **53** and **54**, only starting material was present, suggesting that elimination may, in fact, be competitive with even the *first* alkylation step. With the dibromide **55**, low yields of the substituted bisindolylmaleimides **56** (10%) and **57** (6%) were obtained.

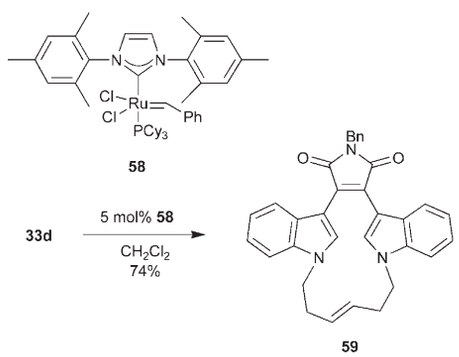


‡‡ In addition, iodocyclisation (see refs. 18a and 24) of the cyclopent-3-enyl substituted bisindolylmaleimide **38** was attempted under two alternative reaction conditions (DBU, KI, I_2, THF; KO^{t}Bu, I_2, THF). In both cases, trace quantities of a less polar dimeric compound (MH^+, m/z = 965) was observed by LC-MS.

Table 4 Preparation of macrocyclic bisindolylmaleimides

Entry	Starting material	*n*	Product	Yield[a] (%)
1	**29**	6	**50a**	69
2	**29**	7	**50b**	73
3	**29**	8	**50c**	62
4	**29**	9	**50d**	74
5	**29**	10	**50e**	71
6	**30**	6	**51a**	44
7	**30**	7	**51b**	76
8	**30**	8	**51c**	62
9	**30**	9	**51d**	53
10	**30**	10	**51e**	63
11	**32**	6	**52a**	35
12	**32**	7	**52b**	44
13	**32**	8	**52c**	54

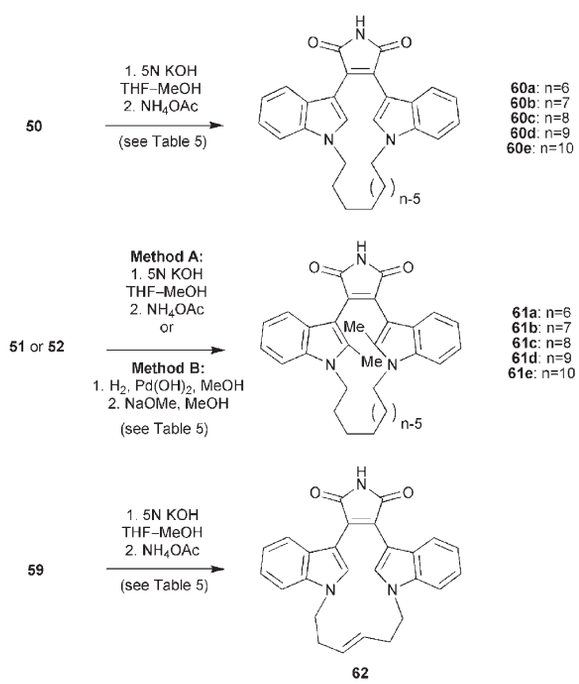
[a] Yield of purified product.



Scheme 9

Deprotection of the macrocyclic bisindolylmaleimides

The macrocyclic bisindolylmaleimides **50** and **59** were deprotected using a three-step protocol[26] (Scheme 10): alkaline hydrolysis gave, after acidification, the corresponding anhydrides which, on heating with ammonium acetate, yielded the required bisindolylmaleimides **60a**–**e** and **62** (entries 1–5 and 11, Table 5). Deprotection of the bisindolylmaleimides **51a**–**e** was attempted in the same way (entries 6a, 7a, 8a, and 9–10). With the larger macrocycles **51d** and **51e** (with $n = 9$ and 10), good yields of the products **61d**–**e** were observed. In contrast, at best trace quantities of the smaller homologues **61a**–**c** were obtained. We suggest that the 2-methyl substituents increase the ring strain of the smaller homologues which may, for example, preclude efficient anhydride formation at an intermediate stage. The bisindolylmaleimides **61a**–**c** could be prepared by hydrogenolysis[27] of the BOM-protected bisindolylmaleimides **52a**–**c** (entries 6b, 7b and 8b). The yields were also low, perhaps because the imides were susceptible to ring-opening.



Scheme 10

Table 5 Deprotection of macrocyclic bisindolylmaleimides

Entry	Starting material	*n*	Method[a]	Product	Yield[b] (%)
1	**50a**	6	A	**60a**	74
2	**50b**	7	A	**60b**	69
3	**50c**	8	A	**60c**	78
4	**50d**	9	A	**60d**	59
5	**50e**	10	A	**60e**	62
6a	**51a**	6	A	**61a**	[c]
6b	**52a**	6	B	**61a**	16
7a	**51b**	7	A	**61b**	[c]
7b	**52b**	7	B	**61b**	14
8a	**51c**	8	A	**61c**	[c]
8b	**52c**	8	B	**61c**	22
9	**51d**	9	A	**61d**	68
10	**51e**	10	A	**61e**	51
11	**59**	—	A	**62**	63

[a] Method A: (i) 5 N KOH, THF–MeOH; (ii) NH_4OAc; Method B: (i) H_2, $Pd(OH)_2$, MeOH; (ii) NaOMe, MeOH. [b] Yield of purified product. [c] The required product **61** was not isolated.

Summary

Our attempts to prepare macrocyclic bisindolylmaleimides **4** were plagued by the strained nature of these compounds. A wide range of reactions were investigated for preparation of macrocycles **4** with three- and four-atom tethers, L (including cyclopentene-bridged structures, **4a**). In all cases, an alternative, more favourable process (such as elimination) intervened, or no reaction was observed at all. Even one of the most reliable of all for the synthesis of strained rings—the McMurry reaction—was spectacularly unsuccessful. We ascribe the problems encountered to extremely unfavourable transannular steric effects.

As soon as the tether was lengthened, however, the problems disappeared. Ring-closing metathesis, which had proved fruitless with lower homologues, enabled the smooth preparation of the macrocycle **59**. Furthermore, macrocyclic bisindolylmaleimides with six- to ten-atom tethers (*e.g.* **60a**–**e**) were easily prepared by a double alkylation protocol. The macrocycle ring strain in the bisindolylmaleimides **60** was estimated using molecular modeling: we estimate that the ring strain may increase from about 15 kJ mol^{-1} with six- and seven-carbon linkers (**60** with $n = 6$ or 7) to over 20 kJ mol^{-1} with a five-carbon linker (**60**, $n = 5$). In view of the increased strain energy of the smaller macrocycles ($n \leq 5$), these results are, perhaps, not surprising.

The addition of a 2-methyl substituent to each of indole rings appears to increase the strain in the bisindolylmaleimide ring system significantly. Although the macrocycles **51a**–**e** could still be prepared, the yields were lower and deprotection was less routine. Applications which exploit the conformational properties of macrocyclic bisindolylmaleimides will be reported in due course.

Experimental

All non-aqueous reactions were performed under an atmosphere of nitrogen. High pressure reactions were carried out in a Parr hydrogenation reaction vessel. Solvents were removed under reduced pressure using either a Büchi rotary evaporator and a Vacuubrand diaphragm pump, or a Genevac HT-4 evaporation system. Automated synthesis was carried out on a Chemspeed ASW2000 synthetic workstation. Flash column chromatography[28] was carried out using silica (35–70 μm particles). Thin layer chromatography was carried out on commercially available pre-coated plates (Merck silica

Kieselgel $60F_{254}$). Analytical HPLC was performed using either a Thermo Hypersil-Keystone achiral column (250 × 4.6 mm 8 μ Hyperprep HSC18) or, an Ultron chiral column (150 × 4.6 mm ES-OVM) with a Dionex P580 pump and a PDA-100 UV detector at 254 nm. Preparative HPLC was conducted with a Waters 2525 binary gradient pump with detection by a Micromass ZQ mass spectrometer; an XTerra® preparative HPLC column (19 × 50 mm) was used.

Proton and carbon NMR spectra were recorded on a Bruker Avance 500 or Avance DPX300 spectrophotometer. Carbon NMR spectra were recorded with composite pulse decoupling using the waltz 16 pulse sequence. NMR spectra were recorded at 300 K, unless otherwise stated. Variable temperature NMR experiments were carried out on a Bruker Avance DRX500 spectrophotometer. Infra-red spectra were recorded using a Perkin-Elmer Spectrum One FT-IR spectrophotometer. Melting points were recorded on a Reichert hot stage microscope and are uncorrected. Mass spectra were recorded either on a VG autospec mass spectrometer, operating at 70 eV, using both the electron impact and fast atom bombardment methods of ionisation, or using a Micromass LCT-KA111 electrospray mass spectrometer. Accurate molecular weights were generally obtained using electrospray mass spectrometry using reserpine as the lock mass and sodium iodide as the standard. X-Ray crystal structures were recorded and solved by departmental staff using a Nonius Kappa CCD area detector diffractometer. Microanalyses were carried out by staff of the School of Chemistry using a Carlo Erba 1106 automatic analyser.

(1*R**)-[3(*S**)-3-(*tert*-Butyldimethylsilyloxy)cyclopent-4-enyl]-indole-3-carboxylic acid methyl ester 16

Indole-3-carboxylic acid methyl ester (43.8 mg, 0.25 mmol) in dry DMF (2 ml) was added slowly to NaH (20 mg of a 60% dispersion in oil, 0.5 mmol) in dry DMF (1.5 ml), and the mixture was stirred at room temperature under nitrogen for 1 h. To this mixture was added a solution of the allylic acetate[10] **14** (64 mg, 0.25 mmol), tris(dibenzylideneacetone)dipalladium(0) (12 mg, 5 mol%, 12.5 μmol), bis(diphenylphosphino)ethane (15 mg, 15 mol%, 37.5 μmol) and lithium chloride (cat.) in dry DMF (2 ml). The resulting mixture was stirred for 24 h under nitrogen, then diluted in EtOAc (10 ml) and washed with water (2 × 10 ml) and brine (10 ml). The organics were separated and dried ($MgSO_4$) and evaporated under reduced pressure to leave a crude product which was purified by column chromatography, eluting with 0–20% EtOAc in petrol to yield the *indole* **16** (84 mg, 90%) as a viscous oil, R_F 0.58 (20% EtOAc in petrol); ν_{max}/cm^{-1} (film) 2952, 2856, 1705, 1533 and 1460; δ_H (300 MHz; $CDCl_3$), 8.12–8.08 (1H, m, indole 4-H), 7.94 (1H, s, indole 2-H), 7.42 (1H, d, *J* 7.1 Hz, indole 7-H), 7.21 (1H, dd, *J* 7.1, indole 6-H), 7.17 (1H, dd, *J* 7.1 Hz, indole 5-H), 6.08 (1H, dt, *J* 5.5 and 1.9 Hz, cp 4-H or 5-H), 5.89 (1H, ddd, *J* 5.5, 2.1 and 1.0 Hz, cp 4-H or 5-H), 5.27–5.21 (1H, m, cyclopentene, 1-H or 3-H), 4.84–4.79 (1H, m, cyclopentene, 1-H or 3-H), 3.80 (3H, s, OMe), 2.85 (1H, ddd, *J* 14.1, 8.1 and 7.2 Hz, cp 2-H_a/H_b), 1.75 (1H, dt, *J* 14.1 and 4.2 Hz, cp 2-H_a/H_b), 0.81 (9H, s, *t*-Bu), 0.04 (3H, s, SiMe) and 0.00 (3H, s, SiMe) ppm; δ_C (75 MHz; $CDCl_3$) 165.8, 136.6, 133.1, 131.3, 129.2, 127.5, 122.9, 122.1, 110.6, 107.6, 75.8, 60.2, 51.3, 42.4, 31.4, 26.3, 18.5, −4.2 and −4.3 ppm; *m*/*z* (EI) 314 (100%, M − ^{t}Bu); found M^+ 371.1905; $C_{21}H_{29}NO_3Si$ requires M^+ 371.1917.

(1*R**)-[3(*S**)-3-(*tert*-Butyldimethylsilyloxy)cyclopent-4-enyl]-indole-3-carboxyaldehyde 18

By the same general method, indole-3-carboxyaldehyde (36.3 mg, 0.25 mmol), NaH (17 mg of a 60% dispersion in oil), the allylic acetate[10] **14** (64 mg, 0.25 mmol), tris(dibenzylideneacetone)dipalladium (0) (12 mg, 5 mol%, 12.5 μmol), bis(diphenylphosphino)ethane (15 mg, 15 mol%, 37.5 μmol) and lithium chloride (cat.) gave a crude product after 24 h, which was purified by column chromatography, eluting with 0–20% EtOAc in petrol to yield the *indole* **18** (84 mg, 92%) as a viscous oil, R_F 0.28 (20% EtOAc in petrol); ν_{max}/cm^{-1} (film) 3058, 2929, 2857, 1662 and 1531; δ_H (500 MHz; $CDCl_3$) 9.97 (1H, s, aldehyde–H), 8.34–8.31 (1H, m, indole 4-H), 7.95 (1H, s, indole 2-H), 7.52–7.49 (1H, m, indole 7-H), 7.33–7.29 (2H, m, indole 5-H and 6-H), 6.21 (1H, dt, *J* 3.6 and 2.1 Hz, cp 4-H or 5-H), 6.00 (1H, ddd, *J* 5.6, 2.1 and 0.8 Hz, cp 4-H or 5-H), 5.37–5.34 (1H, m, cp 1-H or 3-H), 4.91 (1H, ddt, *J* 7.1, 2.1 and 0.8 Hz, cp 1-H or 3-H), 2.93 (1H, ddd, *J* 14.3, 8.2 and 7.1 Hz, cp 2-H_a/H_b), 1.86 (1H, dt, *J* 14.3 and 3.7 Hz, cp 2-H_a/H_b), 0.91 (9H, s, ^{t}Bu), 0.13 (3H, s, $SiMe_2$) and 0.09 (3H, s, $SiMe_2$) ppm; δ_C (125 MHz; $CDCl_3$) 184.7 (CHO), 139.3, 137.2, 131.0, 125.7, 122.3, 118.6, 110.1 (indole 7-C), 106.2 (indole 3-C), 75.4, 59.9 (cp 1-C or 3-C), 41.9 (cp 2-C), 30.9, 25.9, (*t*Bu), 25.8, 18.1, −4.6 (SiMe) and −4.7 (SiMe) ppm; *m*/*z* (ES) 364 (100%, MNa^+); found MNa^+ 364.1703; $C_{20}H_{27}NO_2NaSi$ requires M^+ 364.1709.

(1*R**)-[3(*S**)-3-*O*-Acetyl]indole-3-carboxyaldehyde 19

Acetic acid (40 ml) was added to a solution of the aldehyde **18** (1.53 g, 4.48 mmol) in THF (15 ml) and water (15 ml), and the mixture was heated at 70 °C for 4 h. EtOAc (30 ml) and water (30 ml) were added and the organics separated, washed with $NaHCO_3$ solution (30 ml), brine (30 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the crude reaction mixture dissolved in pyridine (25 ml) and acetic anhydride (3 ml). The reaction mixture was stirred for 3 h, and pyridine and acetic anhydride were removed under reduced pressure to yield the *acetate* **19** (472 mg, 1.75 mmol, 40% over 2 steps) as colourless plates, m.p. 92–94 °C; δ_H (300 MHz; $CDCl_3$) 10.00 (1H, s, aldehyde–H), 8.32–8.28 (1H, m, indole 4-H), 7.79 (1H, s, indole 2-H), 7.50–7.43 (1H, m, indole 7-H), 7.36–7.30 (2H, m, indole 5-H and 6-H), 6.38–6.33 (1H, m, cp 4-H or 5-H), 6.23–6.20 (1H, m, cp 4-H or 5-H), 5.78–5.72 (1H, m, cp 1-H or 3-H), 5.50–5.41 (1H, m, cp 1-H or 3-H), 3.15 (1H, dt, *J* 14.9 and 7.9 Hz, cp 2-H_a/H_b), 2.07 (3H, s, $COCH_3$) and 1.93 (1H, dt, *J* 14.9 and 4.0 Hz, cp 2-H_a/H_b) ppm; δ_C (75 MHz; $CDCl_3$) 185.0, 170.9, 137.4, 136.2, 136.1, 134.3, 134.2, 126.1, 124.5, 123.6, 122.7, 119.1, 110.5, 60.2, 38.9 and 21.5 ppm; *m*/*z* (FAB) 270 (100%, MH^+); found MNa^+ 292.0945; $C_{16}H_{15}NO_3Na$ requires M^+ 292.0950.

(1*R**,3*S**)-Bis(3-formylindolyl)cyclopent-4-ene 20

Indole-3-carboxyaldehyde (29 mg, 0.2 mmol) in dry DMF (0.7 ml) was added slowly to NaH (12 mg of a 60% dispersion in oil, 0.3 mmol) in dry DMF (0.8 ml), and the mixture was stirred at room temperature under nitrogen for 1 h. To this mixture was added a solution of the allylic acetate **19** (54 mg, 0.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (9 mg, 5 mol%, 0.01 mmol), bis(diphenylphosphino)ethane (12 mg, 15 mol%, 0.03 mmol) and lithium chloride (cat.) in dry DMF (1 ml). The resulting mixture was stirred for 24 h under nitrogen, then diluted in EtOAc (10 ml) and washed with water (2 × 10 ml) and brine (10 ml). The organics were separated and dried ($MgSO_4$) and evaporated under reduced pressure to leave a crude product which was purified by column chromatography, eluting with 0–60% EtOAc in petrol to yield the *bisindole* **20** (32 mg, 45%) as colourless plates, R_F 0.2 (60% EtOAc in petrol); δ_H (300 MHz; $CDCl_3$) 9.98 (2H, s, aldehyde–H), 8.51 (2H, s, indole 2-H), 8.15 (2H, d, *J* 8.1, indole 4-H), 7.79 (2H, d, *J* 7.6 Hz, indole 7-H), 7.37 (2H, dt, *J* 7.6 and 7.1 Hz, indole 6-H), 7.30 (2H, dt, *J* 8.1 and 7.1 Hz, indole 5-H), 6.63 (2H, s, cp, 4-H and 5-H), 5.92 (2H, t, *J* 7.1 Hz, cp, 1-H and 3-H), 3.59 (2H, dt, *J* 13.4 and 7.1 Hz, cp 2-H_a/H_b), 1.86 (2H, dt, *J* 13.4 and 7.1 Hz, cp 2-H_a/H_b) ppm; δ_C (75 MHz; $CDCl_3$) 185.2 (C=O), 138.5 (indole 2-C), 137.2 (cp 4-C and 5-C), 134.8, 125.1 (indole 4-C), 124.1, 123.1, 121.5, 118.1, 111.5 (indole 7-C), 105.4 (indole 3-C) and 60.42 ppm; *m*/*z* (ES) 377 (100%, MNa^+); found MNa^+ 377.1273; $C_{23}H_{18}N_2O_2Na$ requires M^+ 377.1266.

Crystal data for 20

$C_{23}H_{18}N_2O_2$, M = 354.39, tetragonal, a = 12.05800(10) Å, α = 90°, b = 12.05800(10) Å, β = 90°, c = 23.7500(2) Å, γ = 90°, U = 3453.14(5) Å^3, T = 150(2) K, space group $P4_12_12$, Z = 8, μ(Mo–Kα) = 0.088 mm^{-1}, 58154 reflections measured, 2008 unique (R_{int} = 0.0657), which were used in all calculations. The final wR (F^2) was 0.1827 (all data). CCDC reference number 235422. See http://www.rsc.org/suppdata/ob/b4/b405010j/ for crystallographic data in .cif format.

1-Benzyl-3-{1-[(1*R,4*S**)-4-(*tert*-butyldimethylsilyloxy)-cyclopent-2-enyl]-1*H*-indol-3-yl}-4-(1*H*-indol-3-yl)pyrrole-2,5-dione 42 and 1-benzyl-3,4-bis{1-[(1*R**,4*S**)-4-*tert*-butyldimethylsilyloxy)cyclopent-2-enyl]-1*H*-indol-3-yl}pyrrole-2,5-dione 43**

The bisindolylmaleimide **29** (84 mg, 0.2 mmol) in dry DMF (1 ml) was added slowly to NaH (12 mg of 60% dispersion in oil, 0.3 mmol) in dry DMF (1.5 ml), and the mixture was stirred at ambient temperature under nitrogen for 1 h; a colour change from red to blue was observed. To this mixture was added a solution containing the allylic acetate[10] **14** (51 mg, 0.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (10 mg, 5 mol%, 0.01 mmol), bis(diphenylphosphino)ethane (12 mg, 15 mol%, 0.03 mmol) and lithium chloride (cat.) in dry DMF (4 ml). The resulting mixture was stirred for 20 h under nitrogen, then diluted with ethyl acetate (20 ml) and washed with water (3 × 10 ml) and brine (10 ml). The organics were separated, dried ($MgSO_4$) and evaporated under reduced pressure to leave a crude product which was purified by column chromatography, eluting with 20–30% EtOAc in petrol to yield the *monosubstituted indole* **42** (59 mg, 48%) as a red film, R_F 0.15 (20% EtOAc in petrol); ν_{max}/cm^{-1} (film) 3385, 2929, 2851, 1753, 1694, 1531 and 1461; δ_H (500 MHz; $CDCl_3$) 8.47 (1H, s, br NH), 7.72 (1H, d, J 2.8 Hz, indole 2-H), 7.71 (1H, s, indole 2′-H), 7.49–7.41 (3H, m), 7.34–7.30 (4H, m), 7.08–7.01 (3H, m), 6.93 (1H, d, J 8.0), 6.76–6.71 (2H, m), 6.05 (1H, dt, J 5.5 and 2.0 Hz, cp 2-H or 3-H), 5.86 (1H, dt, J 5.5 and 1.6 Hz, cp 2-H or 3-H), 5.29–5.25(1H, m, cp 1-H or 4-H), 4.86–4.80 (1H, m, cp 1-H or 4-H), 4.84 (2H, s, CH_2Ph), 2.91 (1H, dt, J 13.8 and 6.2 Hz, cp 5-H$_{a/b}$), 1.80 (1H, dt, J 13.8 and 5.2 Hz, cp 5-H$_{a/b}$), 0.87 (9H, s, ^{t}*Bu*SiMe$_2$), 0.09 (3H, s, SiMe) and 0.06 (3H, s, SiMe) ppm; δ_C (125 MHz; $CDCl_3$) 172.1, 171.9, 138.6, 137.1, 135.9, 135.8, 131.4, 130.3, 128.6, 128.2, 127.9, 127.6, 126.7, 126.6, 125.3, 122.6, 122.4, 122.2, 121.9, 120.3, 111.1 (indole 7-C or 7′-C), 110.0 (indole 7-C or 7′-C), 107.5 (indole 4-C or 4′-C), 106.1 (indole 4-C or 4′-C), 75.5, 60.0, 42.1, 41.8, 25.9, 25.8, 18.1, −4.6 and −4.7 ppm; *m*/*z* (EI) 613 (100%, M$^+$), 556 (20%, M$^+$ − ^{t}Bu), 417 (35%, M$^+$ − cp).

Also isolated was the *disubstituted indole* **43** (32 mg, 20%) as a red film, R_F 0.60 (20% EtOAc in petrol); δ_H (500 MHz; $CDCl_3$) 7.71 (1H, s, indole 2-H), 7.69 (1H, s, indole 2′-H), 7.62–7.58 (2H, m), 7.42–7.30 (10H, m), 7.26–7.24 (4H, m), 6.99–6.85 (8H, m), 6.75–6.65 (4H, m), 5.96–5.93 (2H, m, cp 2-H or 3-H), 5.88–5.86 (2H, m, cp 2-H or 3-H), 5.26–5.21 (2H, m, cp 1-H or 4-H), 4.88–4.84 (2H, m, cp 1-H or 4-H), 4.83 (2H, s, CH_2Ph), 2.91–2.83 (2H, m, cp 5-H$_{a/b}$), 1.79–1.68 (2H, m, cp 5-H$_{a/b}$), 0.88 (9H, s, ^{t}*Bu*SiMe$_2$), 0.87 (9H, s, ^{t}*Bu*SiMe$_2$), 0.06 (3H, s, SiMe) and 0.06 (3H, s, SiMe) ppm; δ_C (125 MHz; $CDCl_3$) 172.1 (C=O), 143.3, 138.9, 138.6, 138.5, 137.2, 135.9, 131.5, 131.5, 131.2, 130.5, 130.2, 128.9, 128.6, 128.7, 127.5, 127.0, 126.9, 126.5, 126.5, 125.5, 122.5, 121.9, 120.1, 120.1, 110.1, 106.3, 75.5 (cp 1-H or 4-H), 60.1 (cp 1-H or 4-H), 42.0, 41.8, 25.9 (^{t}*Bu*SiMe$_2$) and −4.6 (SiMe$_2$) ppm; *m*/*z* (EI) 810 (100%, M$^+$), 613 (20%, M$^+$ − cp), 417 (20%, M$^+$ − 2cp); found MNa$^+$ 832.3897; $C_{49}H_{58}N_3O_4NaSi_2$ requires M$^+$ 832.3859.

1-Benzyl-3-{1-[(1*R,4*S**)-4-*tert*-butyldimethylsilyloxy)-cyclopent-2-enyl]-1*H*-indol-3-yl}-4-(1-cyclopent-3-enyl-1*H*-indol-3-yl)pyrrole-2,5-dione 44**

Bisindolylmaleimide **38e** (96 mg, 0.2 mmol) in dry DMF (1 ml) was added slowly to NaH (12 mg of 60% dispersion in oil, 0.3 mmol) in dry DMF (1.5 ml), and the mixture was stirred at ambient temperature under nitrogen for 1 h; a colour change from red to blue was observed. To this mixture was added a solution containing the allylic acetate[10] **14** (51 mg, 0.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (10 mg, 5 mol%, 0.01 mmol), bis(diphenylphosphino)ethane (12 mg, 15 mol%, 0.03 mmol) and lithium chloride (cat.) in dry DMF (4 ml). The resulting mixture was stirred for 23 h under nitrogen, then diluted with ethyl acetate (20 ml) and washed with water (3 × 10 ml) and brine (10 ml). The organics were separated, dried ($MgSO_4$) and evaporated under reduced pressure to leave a crude product, which was purified by column chromatography, eluting with 20% EtOAc in petrol to yield the *substituted indole* **44** (89 mg, 65%) as a red film, R_F 0.90 (40% EtOAc in petrol); (Found: C, 75.1; H, 6.65; N, 5.7; $C_{43}H_{45}N_3O_3Si$ requires C, 75.9; H, 6.65; N, 6.1%); ν_{max}/cm^{-1} (film) 3063, 2929, 2856, 1698, 1609, 1531 and 1462; δ_H (500 MHz; $CDCl_3$) 7.69 (1H, s, indole 2-H or 2′-H), 7.61 (1H, s, indole 2-H or 2′-H), 7.48–7.42 (2H, m), 7.42–7.41 (1H, m), 7.38–7.32 (1H, m), 7.10–6.98 (4H, m), 6.80–6.73 (2H, m), 6.06 (1H, dt, J 5.6 and 2.0 Hz, cp 2-H), 5.88 (1H, ddd, J 5.6, 2.0 and 3.0 Hz, cp 3-H), 5.76 (2H, s, cp 3′-H and 4′-H), 5.29–5.25 (1H, m, cp 1-H), 5.11 (1H, septet, J 4.2 Hz, cp 1′-H), 4.87–4.84 (1H, m, cp 4-H), 4.83 (2H, s, CH_2Ph), 2.99–2.90 (3H, m, cp 2′-H$_a$, 5′-H$_a$ and 5-H$_a$), 2.66–2.58 (2H, m, cp 2′-H$_b$ and 5′-H$_b$), 1.81 (1H, dt, J 13.7 and 5.1 Hz, cp 5-H$_b$), 0.87 (9H, s, ^{t}*Bu*SiMe$_2$), 0.10 (3H, s, SiMe) and 0.06 (3H, s, SiMe) ppm; δ_C (500 MHz; $CDCl_3$) 172.1 (C=O), 172.0 (C=O), 138.6, 137.2, 135.9, 135.7, 131.5, 130.1, 129.7, 129.0, 128.9, 128.6, 128.6, 128.4, 127.5, 126.3, 122.7, 122.5, 121.9, 120.1, 120.1, 110.0, 109.7, 106.2, 106.1, 75.5, 60.0 (cp 1-C), 54.7 (cp 1′-C), 42.1 (CH_2Ph), 41.8 (cp 2-C), 39.9 (cp 2′-C and 5′-C), 25.8 (^{t}*Bu*SiMe$_2$), 18.1, −4.6 (Si*Me*) and −4.7 (Si*Me*) ppm; *m*/*z* (EI) 679 (65%, M$^+$); found MNa$^+$ 702.3117; $C_{43}H_{45}N_3O_3NaSi$ requires M$^+$ 702.3128.

1-Benzyl-3-{1-[(1*R,4*S**)-4-(*tert*-butyldimethylsilyloxy)-cyclopent-2-enyl]-1*H*-indol-3-yl}-4-{1-[2-(trimethylsilyl)-ethoxymethyl]-1*H*-indol-3-yl}pyrrole-2,5-dione 45**

The bisindolylmaleimide **39** (6.47 g, 11.8 mmol) in dry DMF (24 ml) was added slowly to NaH (710 mg, of 60% dispersion in oil, 17.8 mmol) in dry DMF (34 ml), and the mixture was stirred at ambient temperature under nitrogen for 1 h; a colour change from red to blue was observed. To this mixture was added a solution of the allylic acetate[10] **14** (3.03 g, 11.8 mmol), tris(dibenzylideneacetone)dipalladium(0) (542 mg, 5 mol%, 0.6 mmol), bis(diphenylphosphino)ethane (707 mg, 15 mol%, 1.8 mmol) and lithium chloride (cat.) in dry DMF (60 ml). The resulting mixture was stirred for 20 h under nitrogen, then diluted with ethyl acetate (400 ml) and washed with water (2 × 300 ml) and brine (300 ml). The organics were separated, dried ($MgSO_4$) and evaporated under reduced pressure to leave a crude product which was purified by column chromatography eluting with 10–20% EtOAc in petrol to yield the *bisindolylmaleimide* **45** (5.0 g, 57%) as a red foam, R_F 0.64 (20% EtOAc in petrol); δ_H (500 MHz; $CDCl_3$) 7.80 (1H, s, indole 2-H), 7.78 (1H, s, indole 2′-H), 7.54–7.45 (4H, m), 7.40–7.30 (3H, m), 7.16–7.03 (3H, m), 6.89 (1H, d, J 8.0 Hz), 6.78 (2H, t, J 7.7 Hz), 6.12–6.08 (1H, m, cp 2-H or 3-H), 5.94–5.91 (1H, m, cp 2-H or 3-H), 5.52 (2H, s, NCH_2O), 5.38–5.30 (1H, m, cp 1-H or 4-H), 4.91–4.87 (1H, m, cp 1-H or 4-H), 4.87 (2H, s, CH_2Ph), 3.54 (2H, t, J 8.0 Hz, OCH_2CH$_2$SiMe$_3$), 3.02–2.91 (1H, m, cp 5-H$_{a/b}$), 1.78 (1H, m, cp 5-H$_{a/b}$), 0.96–0.90 (11H, m, CH_2SiMe$_3$ and ^{t}*Bu*Si), 0.14 (3H, s, SiMe), 0.11 (3H, s, SiMe) and 0.00 (9H, s, SiMe$_3$) ppm; *m*/*z* (ES) 766 (100%, MNa$^+$).

1-Benzyl-3-[1-((1*R,4*S**)-4-hydroxycyclopent-2-enyl)-1*H*-indol-3-yl]-4-{1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-indol-3-yl}pyrrole-2,5-dione 46**

PPTS (904 mg, 3.6 mmol) was added in one portion to a stirred solution of the silyl ether **45** (2.2 g, 3.0 mmol) in methanol

(45 ml). The reaction mixture was stirred for 50 h at ambient temperature under nitrogen. The solution was evaporated under reduced pressure, the residue partitioned between ethyl acetate (100 ml) and water (150 ml). The organics were separated, washed with 5% aqueous $NaHCO_3$ solution (100 ml), dried ($MgSO_4$) and evaporated under reduced pressure to leave a crude product which was purified by column chromatography, eluting with 40% EtOAc in petrol to yield the *alcohol* **46** (1.65 g, 88%) as a red foam, R_F 0.17 (30% EtOAc in petrol); (Found: C, 72.5; H, 6.35; N, 6.3; $C_{38}H_{39}N_3O_4Si$ requires C, 72.5; H, 6.2; N, 6.7%); ν_{max}/cm^{-1} (film) 3417 (br), 2954, 2873, 1697, 1610 and 1532; δ_H (500 MHz; $CDCl_3$) 7.82 (1H, s, indole 2-H or 2′-H), 7.62 (1H, s, indole 2-H or 2′-H), 7.53–7.12 (10H, m), 6.85–6.80 (3H, m), 6.14 (1H, d, *J* 5.4 Hz, cp 2-H or 3-H), 5.97 (1H, d, *J* 5.4 Hz, cp 2-H or 3-H), 5.52 (2H, s, NCH_2O), 5.36–5.32 (1H, m, cp 1-H or 4-H), 4.87 (2H, s, CH_2Ph), 4.84–4.80 (1H, m, cp 1-H or 4-H), 3.54 (2H, t, *J* 8.0 Hz, OCH_2CH_2Si), 3.05 (1H, m, cp 5-$H_{a/b}$), 1.69 (2H, m, cp 5-$H_{a/b}$ and OH (br)), 0.94 (2H, t, *J* 8.0 Hz, CH_2SiMe_3) and 0.00 (9H, s, $SiMe_3$) ppm; δ_C (75 MHz; $CDCl_3$) 173.3, 173.2, 139.6, 138.4, 137.3, 133.7, 133.4, 130.8, 130.2, 130.0, 128.9, 127.5, 123.9, 123.9, 123.8, 123.6, 121.9, 121.9, 111.7, 111.0, 78.6, 77.5, 76.6, 67.5, 60.9, 43.2, 43.1, 40.1, 31.7, 30.2, 24.3, 19.1, 15.4 and −0.7 ppm; *m*/*z* (ES) 653 (100%, MNa^+).

Acetic acid (1*R**,4*S**)-4-(3-{1-benzyl-2,5-dioxo-4-{1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-indol-3-yl}-2,5-dihydro-1*H*-pyrrol-3-yl}indol-1-yl)cyclopent-2-enyl ester 47

Acetic anhydride (1.2 ml) was added to a solution of the alcohol **46** (1.62 g, 2.58 mmol), in pyridine (12 ml). The reaction mixture was stirred at ambient temperature under nitrogen for 4 h. The mixture was diluted with ether (50 ml), washed with HCl (3 M, 3 × 50 ml), saturated aqueous $NaHCO_3$ solution (3 × 50 ml) and brine (50 ml). The organics were dried ($MgSO_4$) and evaporated under reduced pressure to leave the *acetate* **47** (1.63 g, 94%) as a red foam R_F 0.8 (50% EtOAc in petrol); (Found: C, 70.8; H, 6.15; N, 6.2; $C_{40}H_{41}N_3O_5Si$ requires C, 71.5; H, 6.15; N, 6.3%); ν_{max}/cm^{-1} (film) 3060, 2956, 1720, 1698, 1530 and 1398; δ_H (500 MHz; $CDCl_3$) 7.82 (1H, s, indole 2-H or 2′-H), 7.74 (1H, s, indole 2-H or 2′-H), 7.52–7.28 (7H, m), 7.13–7.04 (3H, m), 6.86–6.76 (3H, m), 6.23 (1H, d, *J* 5.4 Hz, cp 2-H or 3-H), 6.12 (1H, d, *J* 5.4 Hz, cp 2-H or 3-H), 5.71–5.67 (1H, m, cp 1-H or 4-H), 5.53 (2H, s, NCH_2O), 5.45 (1H, m, cp 1-H or 4-H), 4.88 (2H, s, CH_2Ph), 3.54 (2H, t, *J* 8.0 Hz, O$CH_2CH_2SiMe_3$), 3.13 (1H, m, cp 5-$H_{a/b}$), 2.10 (3H, s, OCOCH_3), 1.92 (1H, m, cp 5-$H_{a/b}$), 0.94 (2H, t, *J* 8.0 Hz, CH_2SiMe_3) and 0.00 (9H, s, $SiMe_3$) ppm; *m*/*z* (ES) 694 (100%, MNa^+); found MH^+ 672.2910; $C_{40}H_{42}N_3O_5Si$ requires M^+ 672.2894.

Acetic acid (1*R**,4*S**)-4-{3-[1-benzyl-4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]indol-1-yl}cyclopent-2-enyl ester 48

Tris(dimethylamino)sulfur (trimethylsilyl) difluoride (TASF) (220 mg, 0.8 mmol), was added to a solution of SEM protected bisindolylmaleimide **47** (400 mg, 0.6 mmol) in THF (10 ml), and heated at reflux for 70 h. The reaction mixture was diluted with ethyl acetate (80 ml) and washed with water (50 ml), 5% aqueous $NaHCO_3$ solution (50 ml) and brine (50 ml). The combined aqueous layers were extracted with ethyl acetate (50 ml). The organics were dried ($MgSO_4$) and evaporated under reduced pressure to leave a crude product which was purified by column chromatography, eluting with 30–40% EtOAc in petrol to yield the *bisindolylmaleimide* **48** (136 mg, 42%) as a red foam R_F 0.45 (50% EtOAc in petrol); ν_{max}/cm^{-1} (film) 3060, 2922, 2851, 2241, 1755, 1693 and 1610; δ_H (500 MHz; $CDCl_3$) 8.67 (1H, br s, NH), 7.68 (1H, d, *J* 2.7 Hz, indole 2-H), 7.66 (1H, s, indole 2′-H), 7.47–7.03 (10H, m), 6.89 (1H, d, *J* 8.1 Hz), 6.78 (1H, t, *J* 7.5 Hz), 6.73 (1H, t, *J* 7.9 Hz), 6.16 (1H, dt, *J* 5.6 and 2.0 Hz, cp 2-H or 3-H), 6.07 (1H, dt, *J* 5.6 and 0.9 Hz, cp 2-H or 3-H), 5.67–5.62 (1H, m, cp 1-H or 4-H), 5.39–5.32 (1H, m, cp 1-H or 4-H), 4.84 (2H, s, NCH_2Ph), 3.14–3.04 (1H, m, cp 5-$H_{a/b}$), 2.03 (3H, s, OCOCH_3) and 1.95–1.87 (1H, m, cp 5-$H_{a/b}$) ppm; *m*/*z* (ES) 564 (50%, MNa^+), 483 (100%, M − OAc); found MNa^+ 564.1889; $C_{34}H_{27}N_3O_4Na$ requires M^+ 564.1899.

19-Benzyl-6,7,10,11-tetrahydro-5,21:12,17-dimethenodibenzo[*i*,*o*]-pyrrolo[3,4-*l*]-[1,8]diazacyclohexadecene-18,20(19*H*)-dione 59

Grubbs' second generation catalyst **58** (7 mg, 5 mol%) was added to a stirred solution of the diene **33d** (86 mg, 0.16 mmol) in $CDCl_3$ (2 ml). The reaction mixture was stirred for 6 h and followed by NMR spectroscopy. On completion the reaction mixture was preabsorbed onto silica and the product isolated by column chromatography, eluting with 0–30% EtOAc in petrol to yield the *macrocyclic compound* **59** (60 mg, 74%) as a purple film R_F 0.25 (30% EtOAc in petrol); δ_H (500 MHz; $CDCl_3$) 7.98 (2H, d, *J* 7.3 Hz, indole 4-H), 7.53 (2H, d, *J* 7.0 Hz, *o*-Ph), 7.21–7.38 (9H, m, *m*-Ph, *p*-Ph, indole 7-H, indole 5-H and indole 6-H), 6.79 (2H, s, indole 2-H), 5.12 (2H, t, *J* 4.0 Hz, *CH*=*CH*), 4.87 (2H, s, NCH_2Ph), 4.06–4.02 (4H, m, NCH_2CH_2) and 2.48–2.45 (4H, m, NCH_2CH_2) ppm; δ_C (125 MHz; $CDCl_3$) 171.2 (C=O), 137.2, 135.7, 131.1, 130.2 (*C*H=*C*H), 129.7 (indole 2-C), 128.8 (Ph-C), 128.6 (Ph-C), 127.6 (Ph-C), 127.1, 122.3 (indole 4-C), 122.2, 120.9, 109.1 (indole 7-C), 104.3 (indole 3-C), 45.8 (NCH_2CH_2), 41.7 (NCH_2Ph) and 33.7 (NCH_2CH_2) ppm; *m*/*z* (ES) 498 (100%, MH^+); found MH^+ 498.2162; $C_{33}H_{28}N_3O_2$ requires M^+ 498.2182.

Acknowledgements

We thank EPSRC for a project studentship, Stuart Warriner and Andrew Leach for helpful discussions, and Colin Kilner for determining the structure of the bisindole **20**.

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