Indole-fused tetraazacyclooctadecanes: double-helical macrocycles

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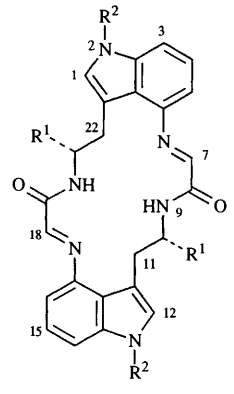
Transannular hydrogen bonding stabilizes a left-handed double helical conformation in the tryptophan-derived tetraazacyclooctadecane 1 both in solution and the solid state, whereas the analogous tryptamine-derived macrocycle 2 shows less tendency towards intramolecular hydrogen bonding and does not exist as a helix in the crystal. Azamacrocycles 1 and 2 are synthesized by a novel method and their secondary structure analysed by NMR spectroscopy, circular dichroism and X-ray diffraction. Molecular modelling does not account for the conformational differences between 1 and 2.

Molecular helicity can take on many forms,[1] but in no case is this type of chirality more visually arresting than in the idealized double helix. Despite the fact that nature makes extensive use of this motif, and that man employs it in both aesthetic and structural roles, relatively few non-natural examples of double-helical molecules or systems of molecules are known.[2,3]

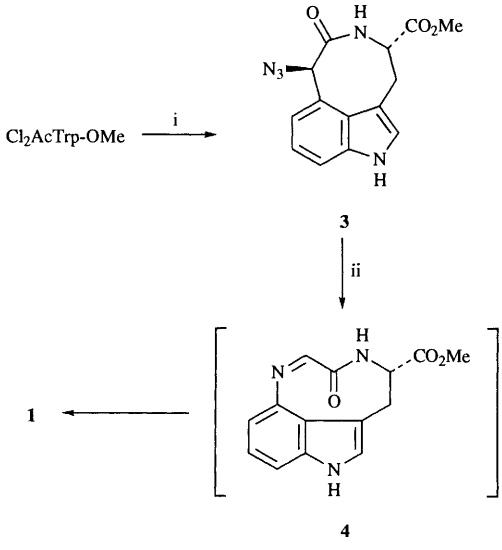
We recently reported the first example of a macrocycle which existed in the form of a double helix.[4] This molecule, **1**, derived from the amino acid L-tryptophan, folds itself into a left-handed, double-helical conformation stabilized by transannular hydrogen-bonding (Fig. 1). It was noted that a reversal of helical screw sense was rendered impossible by steric considerations involving the tryptophan asymmetric centres, thus we undertook to prepare the analogous, *tryptamine*-derived macrocycle **2** in an attempt to examine the kinetics of interconversion between the open-chain form and the *M* and *P* helical isomers. We now describe in full the preparation of **1** along with studies of both its solution and solid state structure, and report the synthesis, crystal structure, and hydrogen bonding behaviour of the decarboxy analogue **2**.



1 $R^1 = CO_2Me$, $R^2 = H$

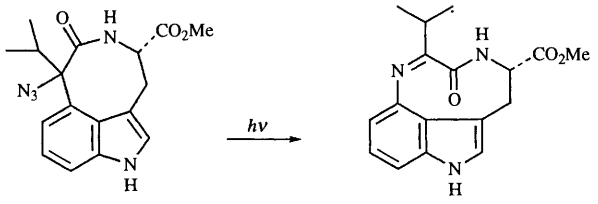
2 $R^1 = H$, $R^2 = Si[CH(CH_3)_2]_3$

Macrocycle **1** was prepared according to Scheme 1. Thus dichloroacetyltryptophan methyl ester was irradiated with UV



Scheme 1 *Reagents and conditions:* i, *hv*, MeCN, then NaN_3; ii, heat or *hv*

light to effect Witkop cyclization as has been previously described.[5] Subsequent work up in the presence of azide gave tricycle **3** in 41% yield.[6] Thermal or photochemical decomposition of the azide function and concomitant aryl migration leads to the ring expanded lactam **4**, which spontaneously dimerizes to give **1**. Compound **4** has never been isolated, but its intermediacy is strongly suggested by an analogous reaction[7] which gives a product (**5**) sterically prevented from dimerization by the presence of an isopropyl group at the imine carbon (Scheme 2). Interestingly, the method of decomposition of the azide makes little difference to the outcome of the reaction. The yield is not high in either case (maximum of *ca.* 35% thermally, 25% photochemically) and the balance of the mass is accounted for by the observation of an insoluble, dark yellow solid, which is presumed to be polymeric in nature. The mechanism of dimerization appears to be head to



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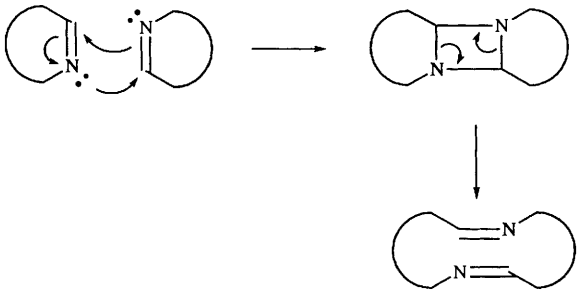
Scheme 2

tail addition of one imine function to another followed by double bond metathesis (Scheme 3).



Scheme 3

The helical nature of **1** was first revealed by X-ray crystallography (Fig. 1)[4] and later substantiated by an in-depth circular dichroism study. The UV spectrum is principally composed of two maxima, one at 216 nm (ε = 66 700 dm^3 mol^{-1} cm^{-1}) and another at 364 (ε = 8500 dm^3 mol^{-1} cm^{-1}) (Fig. 2). The latter absorption is not exciton coupled as a single prominent CD band is observed positive in sign (Fig. 3). This transition is specifically associated with the azomethine function as it is irretrievably lost under hydrolytic conditions (Fig. 2). The stronger, far-UV band has associated with it a relatively complex CD structure derived from exciton coupling between the two indole rings. Centred at 216 nm, a positive bisignate couplet is observed which is expected for two (near) long axis, electric dipole allowed transitions of the indole

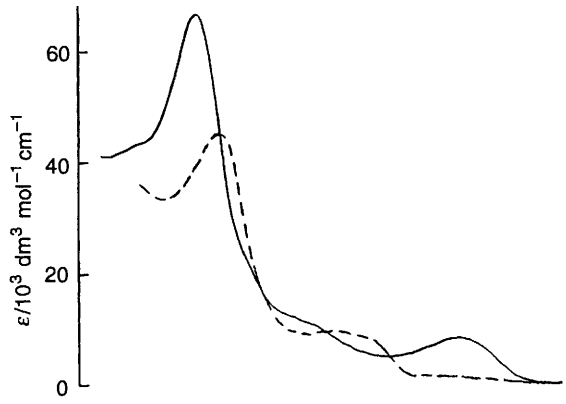


Fig. 2 —— Electronic absorption spectrum of **1** in MeCN; - - - - electronic absorption spectrum of **1** after heating to 81 °C in MeOH–H_2O (8:92)

chromophores, compatible with the geometry indicated by the X-ray crystal structure. The chiroptic behaviour of **1** was found to be insensitive to solvent (MeCN *vs.* MeOH) (Fig. 3) and temperature (no change up to 72 °C in MeCN), indicating that the helix does not anneal in the traditional sense. This was also supported by NMR spectroscopy. Here, no significant differences in spectra measured between −55 and 65 °C in $CDCl_3$ and between 25 and 125 °C in [$^2H_6$]dimethyl sulfoxide ([$^2H_6$]DMSO) could be seen. It is particularly noteworthy that the H-bonding amide protons vary no more than ±0.3 ppm across the temperature range in either solvent, and that there is little difference in their chemical shift from one solvent to the other (δ 10.2 in $CDCl_3$ *vs.* 9.8 in [$^2H_6$]DMSO at 25 °C). The $[\alpha]_D$ value did however show a trend toward decrease in solvents of increasing hydrogen-bonding character (1619 in $CDCl_3$, 1303 in MeOH and 1133 in DMSO), and this might be interpreted in terms of a partial unwinding of the helix in solvents which can compete for H-bonds. However, even the least of these values compares favourably with that of the reduced macrocycle **6** ($[\alpha]_D$ 39), which according to models cannot participate in intramolecular hydrogen bonding and therefore possesses only the chirality of the tryptophan

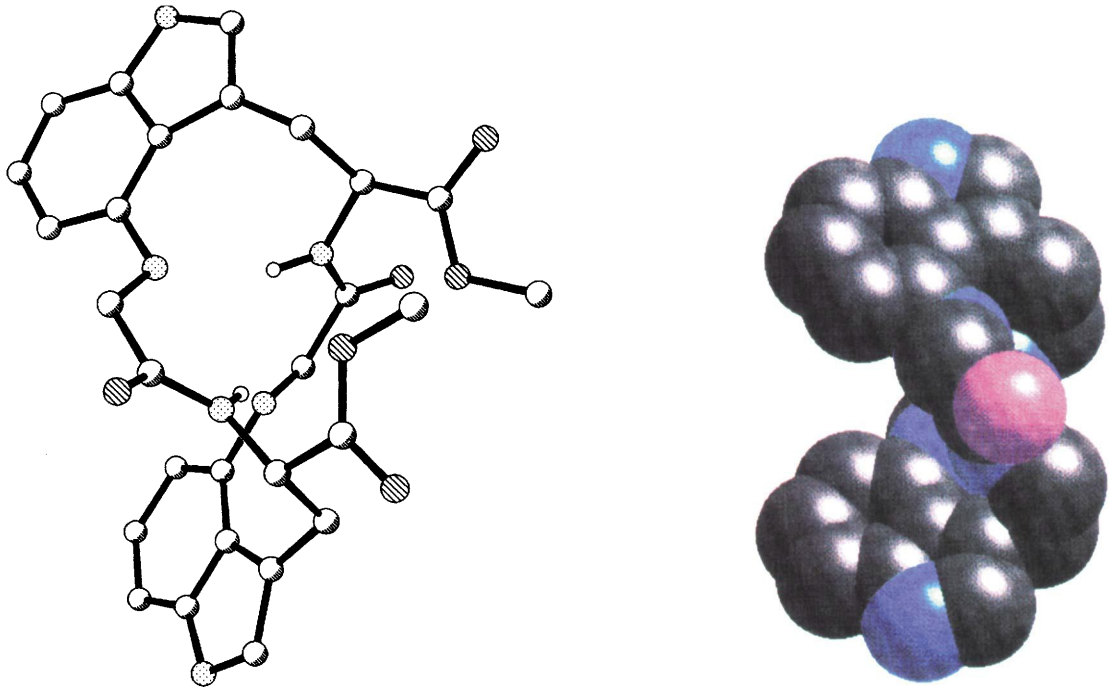


Fig. 1 Left, plot of the X-ray crystal structure of **1** (H-bonding protons shown, others omitted for clarity); right, space-filling representation concentrating on the helical macrocyclic region

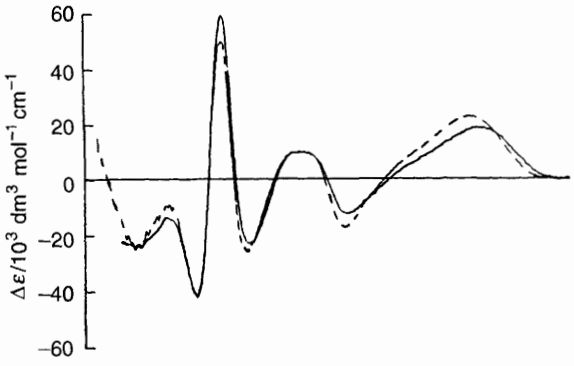
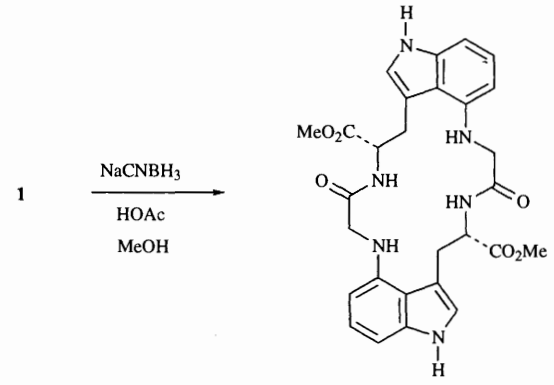


Fig. 3 —— CD spectrum of **1** in MeOH at 21 °C; - - - - CD spectrum of **1** in MeCN at 21 °C

asymmetric centres. Compound **6** could be prepared by cyanoborohydride reduction of the imine functions in **1** (Scheme 4).



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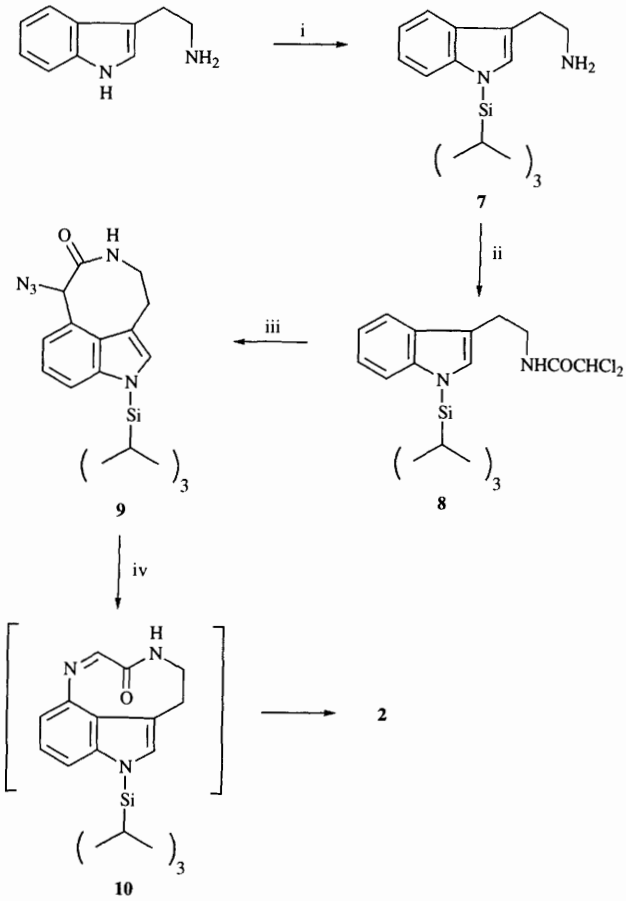
Scheme 4

Since these experiments indicated that the secondary helical structure of **1** was extraordinarily stable, it was undertaken to isolate this chirality by synthesising an analogous macrocycle from a precursor without an asymmetric carbon and, if possible, separate the helical enantiomers. The preparation of the unsubstituted macrocycle **2** was approached by the same method as for **1**, simply substituting tryptamine for tryptophan. For purposes of solubility, the tryptamine was first silylated at the indole nitrogen to give **7** (Scheme 5). Compound **7** was acylated with dichloroacetyl chloride (89%) and irradiated according to the described procedure.[5] It was found that for *N*-silyl substituted indoles the presence of a base (triethylamine) was necessary during irradiation to suppress desilylation. Work up of the reaction with azide then gave **9** in 50% yield. As above, thermolysis or photolysis was equally effective for producing the macrocycle **2** (32%), again presumably *via* a monomer (**10**).

The consistently modest yield of macrocycle in these reactions may be interpreted in terms of conformational preferences to migration to the electrophilic nitrogen atom during ring expansion. The crystal structure of the azide **9** (Fig. 4) shows that it is the proton which is best situated to move into the p-orbital of the azide nitrogen, with an N–N–C–H dihedral angle of 77°, compared to 43° for the CONHR group and only 16° for the phenyl ring. Since migration of the proton would result in the formation of a C=NH type imine, the observation of substantial polymer/decomposition product is not unexpected.

Preliminary analysis suggested that **2** was not necessarily structurally equivalent to **1**. In particular, the amide NH



Scheme 5 *Reagents and conditions:* i, NaH, THF, then TIPSCl; ii, $Cl_2CHCOCl$, CH_2Cl_2–H_2O–$NaHCO_3$, 0 °C; iii, *hv*, TEA, MeCN, then NaN_3; iv, *hv*, MeCN

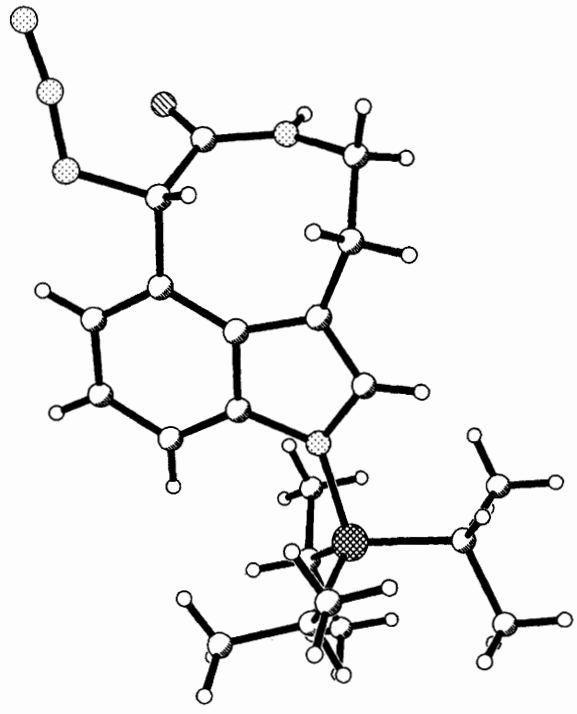


Fig. 4 X-Ray crystal structure of azide **9**

protons in the NMR spectrum of **2** showed less evidence of hydrogen bonding, resonating at 8.3 ppm, which is *ca.* 1.5 ppm downfield of their normal range in $CDCl_3$ but 2 ppm *upfield* of those in **1**. These protons also showed a marked δ/T relationship, shifting downfield with decreasing temperature to

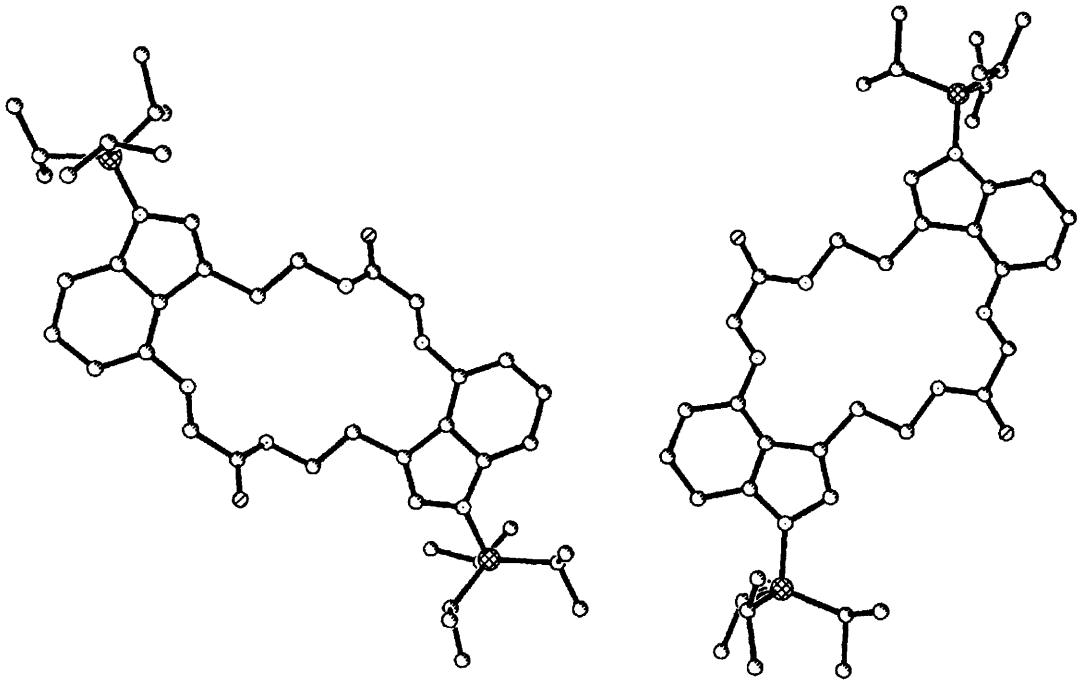


Fig. 5 The two conformational states of macrocycle **2** as they occur in the crystal

a maximum of 10.3 ppm at about −50 °C. Because the δ value at any single temperature was found to be independent of concentration, this effect could be attributed to increasing intramolecular hydrogen bonding. Yet it can be said that **2** exhibits only at −50 °C the same degree of intramolecular hydrogen bonding as found in **1** over a range of temperatures.

X-Ray crystallography confirmed that **2** was not helical in the solid state. Bright yellow needles of **2** could be grown from carbon tetrachloride, and the crystal structure showed that two unique conformers of the macrocycle coexist in the crystal. Both conformers possess an open cavity, which is entirely flat in one case and symmetrically distorted about the N=C–CONH system in the other (Fig. 5). Remarkably, no hydrogen bonding, intra- or inter-molecular, is observed.

A modelling study provided no arguments for the presence of helical secondary structure in **1**, or its absence in **2**. A Monte Carlo-type simulation[8] of the unsubstituted macrocycle **2** suggested a minimized structure (127 kJ mol^{-1}) (Fig. 6) which was not closely related to either crystallographically observed conformer. Indeed none of the 205 conformers proposed in the simulation closely matched the structures in Fig. 5, but minimization starting from the crystal coordinates to nearby saddle points gave energy values of 159 and 169 kJ mol^{-1} for the puckered and flat forms of **2**, respectively. No helical structure exactly matching the ring in **1** was found either, but a number of approximate fits were observed between 138 and 145 kJ mol^{-1}. That this sort of structure appears at all is encouraging, considering MM2's rather basic treatment of hydrogen bonding. However, the hydrogen bonds found in these simulated conformers were of a poor quality, with N • • • H distances of 2.4 Å and N–H • • • N angles of 125° (*cf.* 2.0 Å and 160° in **1**) indicating that H-bonding was no major stabilising influence in the selection of these conformers. This suggests that the twisted structure of the helix *per se* is not particularly disfavoured on conformational grounds, although all evidence suggests that it is not favoured by **2**.

A Monte Carlo run for compound **1** gave a similar result to that of **2**, with a number of open-cavity conformers at the low energy end of the scale (minimum 209 kJ mol^{-1}). Of the 458 structures found, eight left-handed helixes occurred in the range 228 to 245 kJ mol^{-1}. These again showed some overlap with the structure of **1**, but with much inferior hydrogen bonding.

Although molecular mechanics sheds little light on the

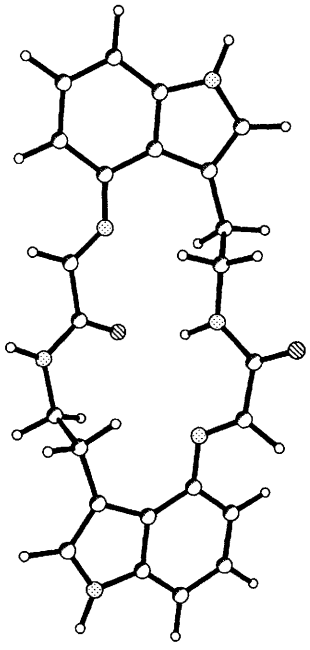
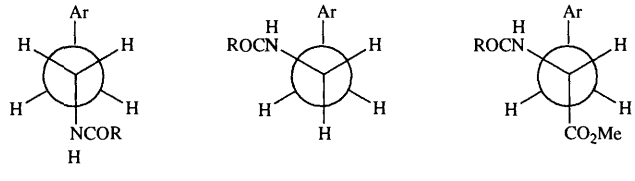


Fig. 6 Modelled representation of the minimum-energy structure of **2**



2 (flat ring) **2** (helical) **1** (helical)

Fig. 7

structure of these macrocycles, a case for the helical preference of **1** can be argued by conformational analysis of the two C_{sp^3}–C_{sp^3} bonds. Fig. 7 shows how the gauche interaction in the helical conformation is compensated in **1** by the presence of the ester group, which is of course absent in **2**.

Finally, the pseudotetrahedral arrangement of N sites about the centre of the cavity of **1** (and potentially **2**) invites attempts

to prepare cyclic metallohelicates analogous to those described under ref. 2. This will be the subject of a separate report.

Experimental

General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Ultraviolet spectra were recorded on a Philips model 8720 spectrometer, and infrared spectra on a Perkin-Elmer 1600 series FT-IR instrument. ^{1}H NMR spectra were measured on Bruker WM 250 or AM 400 spectrometers, while ^{13}C spectra were measured on a JEOL EX-270 or Bruker AM 400 (67.8 and 100.6 MHz, respectively). NMR spectra were referenced to the residual solvent peaks and coupling constants (J) are given in Hz. Mass spectra were obtained on a VG Micromass 70E or VG Autospec spectrometer. Photolyses were carried out using a Rayonet type RS photochemical reactor equipped with 8 RUL 2534 Å lamps. Silica gel (230–400 mesh) was used for column chromatography. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

Methyl 7-azido-1,3,4,5,6,7-hexahydro-6-oxopyrrolo[4,3,2-*fg*]-[3]benzazocine-4-carboxylate 3

A solution of *N*-dichloroacetyltryptophan methyl ester[5] (1.50 g, 4.56 mmol) in acetonitrile (600 cm^3) was prepared in a quartz vessel and a stream of nitrogen was passed through for 1 h. The sample was then irradiated at 254 nm for 1.5 h. The resulting rust coloured solution was concentrated to a volume of *ca.* 10 cm^3 and a solution of sodium azide (0.60 g, 9.2 mmol) in the minimum amount of water was added. The mixture was agitated intermittently for 15 min, after which the solution was dried with sodium sulfate. The reaction mixture was decanted and the remaining solids washed thoroughly with acetonitrile. The solvent was evaporated and the residue pre-absorbed onto silica gel. After chromatography (30% ethyl acetate in diethyl ether) the fractions containing the product were combined and concentrated to a volume of *ca.* 5 cm^3. The title compound **3** (560 mg, 41%) crystallized out on standing overnight at 0 °C in the form of beige needles. Three different crystalline modifications of this azide have been observed: one which melts 180–182 °C, another 195–196 °C with gas evolution, and a third which suddenly turns opaque around 100 °C, then melts 216–217 °C (Found: C, 56.2; H, 4.3; N, 23.2. $C_{14}H_{13}N_5O_3$ requires C, 56.2; H, 4.4; N, 23.4%); $[\alpha]_D$ −118.7 (*c* 0.90 in MeOH); ν_{max}(CHCl$_3$)/cm^{-1} 3474 (indole N–H), 3384 (amide N–H), 3006, 2113 (azide), 1742 (ester C=O), 1679 (amide C=O), 1437, 1283 and 773; λ_{max}(MeOH)/nm 209 (log ε 4.41) and 293 (3.80); δ_H([$^2H_6$]DMSO) 3.50 (1 H, dd, *J* 9.4 and 15.2, 3-H), 3.67 (1 H, t, *J* 12.9, 3-H), 3.81 (3 H, s, OMe), 4.17 (1 H, m, 4-H), 6.33 (1 H, s, 7-H), 7.01 (1 H, d, *J* 7.2, 8-H), 7.09, (1 H, t, *J* 7.7, 9-H), 7.26 (1 H, s, 2-H), 7.31 (1 H, d, *J* 8.0, 10-H), 7.61 (1 H, d, *J* 6.1, 5-H) and 9.46 (1 H, s, 1-H); δ_C([$^2H_6$]DMSO) 27.9 (3-C), 52.6 (OMe), 55.8 (4-C), 61.8 (7-C), 109.3 (2a-C), 111.3 (10-C), 114.1 (8-C), 121.4 (9-C), 124.3 (2-C), 124.4 (10b-C), 127.9 (7a-C), 136.2 (10a-C), 172.0 and 173.1; *m/z* (EI) 299 (M$^+$, 42%), 271 (32, M − N_2), 229 (28), 212 (29), 197 (12), 195 (8), 184 (13), 169 (59), 168 (30), 157 (82), 156 (67), 155 (100), 142 (19), 130 (21), 129 (22), 128 (16), 115 (20, Ar$^{\bullet+}$) and 28 (33).

Dimethyl 2,8,9,10,11,13,19,20,21,22-decahydro-8,19-dioxodiindolo[4,4a,3-*e*,*f*: 4′,4a′,3′-*n*,*o*][1,4,10,13]-tetraazacyclooctadecine-10,21-dicarboxylate 1

Method A; by photolysis of azide 3. A solution of azide **3** (128 mg, 0.43 mmol) in acetonitrile (50 cm^3) was prepared in a quartz vessel and a stream of nitrogen was passed through for 1 h. The sample was then irradiated at 254 nm for 50 min. The resulting bright yellow solution was evaporated and the residue was pre-absorbed onto silica gel and chromatographed (6% methanol in dichloromethane) giving the *title compound* **1** (26 mg, 23%) as a dark yellow solid. A sample crystallized from acetonitrile solution gave bright yellow plates of **1**·MeCN, mp 330–340 °C (decomp.) (Found: M$^+$, 542.1911. $C_{28}H_{26}N_6O_6$ requires 542.1914); $[\alpha]_D$ +1303 (*c* 0.132 in MeOH); ν_{max}(CHCl$_3$)/cm^{-1} 3475 (indole N–H), 3266 (amide N–H), 3026, 3011, 2956, 2929, 2857, 1748, 1733, 1673 (amide C=O), 1621, 1548, 1437, 1359, 1273, 1232, 1180, 1135, 1090, 984, 957, 841 and 809; λ_{max}(MeCN)/nm 216 (log ε 4.82) and 364 (3.93); δ_H(CDCl$_3$) 3.33 (2 H, dd, *J* 12.2 and 14.5, 11- and 22-H), 3.52 (2 H, dd, *J* 2.8 and 14.6, 11- and 22-H), 3.81 (6 H, s, OMe), 4.61 (2 H, ddd, *J* 3.1, 6.7 and 12.8, 10- and 21-H), 6.41 (2 H, dd, *J* 0.4 and 7.5, 5- and 16-H), 7.09 (2 H, t, *J* 7.8, 4- and 15-H), 7.24 (2 H, d, *J* 2.0, 1- and 12-H), 7.35 (2 H, dd, *J* 0.4 and 8.2, 3- and 14-H), 7.71 (2 H, s, 7- and 18-H), 8.61 (2 H, s, 2- and 13-H) and 10.22 (2 H, d, *J* 6.9, 9- and 20-H); δ_C(CDCl$_3$) 27.3 (11- and 22-C), 52.4 (OMe), 57.5 (10- and 21-C), 109.2 (3- and 14-C), 111.5 (5- and 16-C), 112.3 (11a- and 22a-C), 121.6 (11b- and 22b-C), 122.6 (4- and 15-C), 124.6 (1- and 12-C), 137.1 (2a- and 13a-C), 142.4 (5a- and 16a-C), 155.3 (7- and 18-C), 164.1 (8- and 19-C) and 171.4 (*C*O$_2$Me); *m/z* (EI) 542 (M$^+$, 44%), 510 (2, M − MeOH), 483 (3, M − CO$_2$Me), 455 (3), 427 (2), 283 (5), 282 (5), 271 (8), 244 (6), 242 (6), 227 (18), 200 (7), 184 (13), 169 (17), 157 (55), 156 (43), 155 (29), 145 (13), 130 (17), 41 (100, MeCN molecule of solvation) and 40 (50).

Method B; by thermolysis of azide 3. A solution of azide **3** (250 mg, 0.84 mmol) in benzonitrile (5 cm^3) was added all at once (*via* syringe down the condenser) to refluxing benzonitrile (75 cm^3). The mixture was heated for 2 h at reflux (191 °C) under nitrogen. After cooling to room temperature the solvent was stripped and the crude product was purified as described above to give the title compound **1** (83 mg, 37%).

Dimethyl 2,6,7,8,9,10,11,13,17,18,19,20,21,22-tetradecahydro-8-19-dioxodiindolo[4,4a,3-*e*,*f*: 4′,4a′,3′-*n*,*o*][1,4,10,13]-tetraazacyclooctadecine-10,21-dicarboxylate 6

To a solution of **1** (33 mg, 0.061 mmol) in methanol (5 cm^3) was added sodium cyanoborohydride (8 mg, 0.13 mmol) followed by acetic acid (5 drops). The characteristic bright yellow colour of the dimer gradually faded to pale gold and after 1 h the mixture was evaporated and chromatographed on silica gel (5% methanol–dichloromethane), giving reduced macrocycle **6** (28 mg, 86%) as an amorphous tan powder; $[\alpha]_D$ +39 (*c* 0.125 in MeOH); ν_{max}(CHCl$_3$)/cm^{-1} 3479 (indole N–H), 3420 (amide N–H), 3028, 3006, 2954, 1741 (ester C=O), 1690 (amide C=O), 1610, 1585, 1514, 1478, 1439, 1428, 1413, 1371, 1352, 1277, 1180, 1117, 1086 and 984; δ_H(CDCl$_3$) 3.44 (4 H, m, 11- and 22-H), 3.62 (4 H, m, 7- and 18-H), 3.71 (6 H, s, OMe), 4.95 (2 H, d, *J* 5.9, 6- and 17-H), 5.23 (2 H, m, 10- and 21-H), 5.93 (2 H, d, *J* 7.6, 5- and 16-H), 6.08 (2 H, d, *J* 8.9, 9- and 20-H), 6.70 (2 H, d, *J* 2.0, 1- and 12-H), 6.75 (2 H, d, *J* 8.3, 3- and 14-H), 6.96 (2 H, t, *J* 7.9, 4- and 15-H) and 8.05 (2 H, s, 2- and 13-H); δ_C(CDCl$_3$) 29.5 (11- and 22-C), 47.0 (7- and 18-C), 52.2 (OMe), 54.5 (10- and 21-C), 100.2, 102.2, 109.0 (11a- and 22a-C), 115.6 (11b- and 22b-C), 121.8, 123.5, 137.3 (2a- and 13a-C), 141.6 (5a- and 16a-C), 168.7 (8- and 19-C) and 171.5 (*C*O$_2$Me); *m/z* (FAB) 547 (MH$^+$, 11%), 259 (13), 229 (11), 169 (17), 157 (20), 145 (11), 130 (13) and 115 (Ar$^{\bullet+}$).

1-(Triisopropylsilyl)indole-3-ethanamine 7

To a stirred suspension of sodium hydride (160 mg, 6.8 mmol) in dry THF (10 cm^3) at −78 °C under nitrogen was added dropwise a solution of tryptamine (1.0 g, 6.2 mmol) in dry THF (10 cm^3). The reaction was allowed to come to room temperature and stirred until the evolution of hydrogen ceased. The mixture was then cooled to −78 °C and triisopropylsilyl chloride (TIPSCl) (1.3 cm^3, 1.2 g, 6.2 mmol) added dropwise over a 5 min period. The reaction was stirred for 2 h and then allowed to come to room temperature. Water (70 cm^3) was added and the mixture was extracted with dichloromethane (3 × 40 cm^3). The combined organic extracts were dried over $MgSO_4$ and evaporated. The crude product was chromato-

graphed on silica gel (8% methanol + 1% ammonia in dichloromethane) to give the title compound **7** as a pale yellow solid (1.7 g, 88%) mp 56.5–57 °C (Found: C, 71.90; H, 10.42; N, 8.82. $C_{19}H_{32}N_2Si$ requires C, 72.09; H, 10.19; N, 8.85%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3667, 3474, 3230 (br), 2946, 2863, 1682, 1639, 1608, 1462, 1346, 1304, 1140, 995, 962, 887 and 645; λ_{max}(EtOH)/nm 224 (log ε 5.03), 275 (4.44), 281 (4.45) and 291 (4.37); $\delta_H(CDCl_3)$ 1.14 [18 H, d, *J* 7.5, SiCH(CH_3)$_2$], 1.37 (2 H, br s, NH_2), 1.69 (3 H, septet, *J* 7.5, SiC*H*Me$_2$), 2.90 (2 H, t, *J* 6.0, $ArCH_2$ or CH_2NH_2), 3.02 (2 H, t, *J* 6.0, $ArCH_2$ or CH_2NH_2), 7.07 (1 H, s, 2-H), 7.13 (2 H, m, 5-H and 6-H), 7.47 (1 H, m, 7-H) and 7.59 (1 H, m, 4-H); $\delta_C(CDCl_3)$ 12.7 (SiCHMe$_2$), 18.0 [SiCH(CH_3)$_2$], 29.3 ($ArCH_2$), 42.0 (CH_2NH_2); 113.8 (7-C), 115.2 (3-C), 118.5 (4-C), 119.1 (5-C), 121.3 (6-C), 128.8 (2-C), 130.8 (3a-C) and 141.3 (7a-C); *m*/*z* (EI) 316 (M^+, 12%), 286 (100), 162 (45), 131 (56), 115 (59) and 103 (55).

N-Dichloroacetyl-1-(triisopropylsilyl)indole-3-ethanamine 8

A two phase system of **7** (1.0 g, 3.2 mmol) in dichloromethane (15 cm^3) and sodium hydrogen carbonate (0.53 g, 6.3 mmol) in water (15 cm^3) was stirred at 0 °C. Dichloroacetyl chloride (0.51 g, 0.33 cm^3, 3.5 mmol) was added dropwise over a 10 min period and the mixture stirred at 0 °C for 1 h. The reaction mixture was poured into water (100 cm^3) and extracted with dichloromethane (3 × 30 cm^3). The combined organic extracts were dried over $MgSO_4$ and evaporated. The resulting off-white solid was chromatographed on silica gel (30% light petroleum in dichloromethane) to give the title compound **8** as a white solid (1.2 g, 89%) mp 143.5–145 °C (Found: C, 58.97; H, 7.82; N, 6.62; Cl, 16.61. $C_{21}H_{32}Cl_2N_2OSi$ requires C, 59.00; H, 7.54; N, 6.55; Cl, 16.59%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3415 (N–H), 2949, 2868, 1693 (C=O), 1452, 1304, 1142, 962 and 851; λ_{max}(EtOH)/nm 206 (log ε 4.77), 227 (4.82), 275 (4.27), 282 (4.27) and 292 (4.20); $\delta_H(CDCl_3)$ 1.15 [18 H, d, *J* 7.5, SiCH(CH_3)$_2$], 1.71 (3 H, septet, *J* 7.5, SiC*H*Me$_2$), 3.05 (2 H, t, *J* 6.5, $ArCH_2$), 3.69 (2 H, q, *J* 6.5, CH_2NH), 5.88 (1 H, s, $COCHCl_2$), 6.61 (1 H, br s, NH), 7.11 (1 H, s, 2-H), 7.17 (2 H, m, 5-H and 6-H), 7.52 (1 H, dd, *J* 2.0 and 6.7, 7-H) and 7.60 (1 H, m, 4-H); $\delta_C(CDCl_3)$ 12.8 (SiCHMe$_2$), 18.1 [SiCH(CH_3)$_2$], 24.9 ($ArCH_2$), 40.0 (CH_2NH), 66.4 ($COCHCl_2$), 113.7 (3-C), 114.2 (7-C), 118.4 (4-C), 119.6 (5-C), 121.8 (6-C), 129.2 (2-C), 130.3 (3a-C), 141.5 (7a-C) and 163.9 (C=O); *m*/*z* (EI) 426 (M^+, 17%), 286 (100, M − $CH_2NHCOCHCl_2$), 115 (20, $Ar^{\bullet+}$) and 59 (25).

7-Azido-1,3,4,5,6,7-hexahydro-6-oxo-1-(triisopropylsilyl)pyrrolo[4,3,2-*fg*][3]benzazocine 9

A solution of **8** (1.5 g, 3.5 mmol) in dry acetonitrile (11) was prepared in a quartz vessel and a stream of nitrogen was passed through for 1 h. Triethylamine (0.98 cm^3, 0.71 g, 7.0 mmol) was added and the sample was irradiated at 254 nm for 1.5 h. The resulting pale yellow solution was concentrated to a volume of *ca.* 10 cm^3 and a solution of sodium azide (0.68 g, 11 mmol) in the minimum volume of water was added. The mixture was stirred for 15 min and evaporated to leave a brown residue. To this was added dichloromethane (40 cm^3) and water (100 cm^3). The layers were separated and the aqueous phase was back-extracted with dichloromethane (2 × 40 cm^3). The combined organic fractions were dried over $MgSO_4$ and evaporated to leave a brown solid which was chromatographed on silica gel (diethyl ether) to give the title compound **9** as a white solid (700 mg, 50%) mp 73.5–76 °C (Found: M^+, 397.2281. $C_{21}H_{31}N_5OSi$ requires 397.2298); $\nu_{max}(CHCl_3)/cm^{-1}$ 3397 (NH), 2949, 2869, 2111 (azide), 1674 (C=O), 1463, 1355, 1309, 1149, 987, and 885; λ_{max}(EtOH)/nm 214 (log ε 4.38), 229 (4.39), 285 (3.94) and 293 (3.91); $\delta_H(CDCl_3)$ 1.12 [18 H, d, *J* 7.5, SiCH(CH_3)$_2$], 1.66 (3 H, septet, *J* 7.5, SiC*H*Me$_2$), 3.19 (1 H, m, 3-H), 3.50 (2 H, m, 3-H and 4-H), 3.84 (1 H, m, 4-H), 6.10 (1 H, s, 7-H), 6.82 (1 H, br s, 5-H), 7.03 (1 H, s, 2-H), 7.14 (1 H, t, *J* 7.9, 9-H), 7.32 (1 H, d, *J* 7.3, 8-H) and 7.41 (1 H, d, *J* 8.3, 10-H); $\delta_C(CDCl_3)$ 12.7 (SiCHMe$_2$), 18.1 [SiCH(CH_3)$_2$], 26.8 (3-C), 42.8 (4-C), 62.1 (7-C), 113.3 (2a-C), 114.2 (10-C), 116.4 (8-C), 121.9 (9-C), 127.3 (7a-C or 10b-C), 127.5 (7a-C or 10b-C), 130.2 (2-C), 141.6 (10a-C) and 172.0 (6-C); *m*/*z* (EI) 397 (M^+, 23%), 369 (M − N_2, 77), 354 (12), 340 (11), 326 (53), 312 (30), 157 (16), 115 ($Ar^{\bullet+}$, 36), 103 (11), 87 (33), 73 (47) and 59 (100).

Dimethyl 2,13-bis(triisopropylsilyl)-2,8,9,10,11,13,19,20,21,22-decahydro-8,19-dioxodiindolo[4,4a,3-*e*,*f*:4′,4a′,3′-*n*,*o*]-[1,4,10,13]tetraazoxycyclooctadiene-10,21-dicarboxylate 2

A solution of azide **9** (0.10 g, 0.25 mmol) in acetonitrile (100 cm^3) was prepared in a quartz vessel and a stream of nitrogen was passed through for 1 h. The sample was then irradiated at 254 nm for 15 min. The resulting yellow solution was evaporated and the residue was chromatographed on silica gel (diethyl ether) to give the title compound **2** as a bright yellow solid (30 mg, 32%) mp 268–271 °C (Found: C, 68.17; H, 8.68; N, 11.03. $C_{42}H_{62}N_6O_2Si_2$ requires C, 68.25; H, 8.45; N, 11.37%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3399 (NH), 3251, 2949, 2866, 1727, 1674 (C=O), 1616 (C=N), 1557, 1464, 1350, 1317, 1150, 996, 955, 908, 887 and 645; λ_{max}(EtOH)/nm 223 (log ε 5.23), 274 (4.48), 282 (4.46), 291 (4.39) and 323 (3.81); $\delta_H(CDCl_3)$ 1.15 [36 H, d, *J* 7.5, SiCH(CH_3)$_2$], 1.70 (6 H, septet, *J* 7.5, SiC*H*Me$_2$), 3.24 (4 H, t, *J* 7.7, 11- and 22-H), 3.71 (4 H, m, 10- and 21-H), 6.78 (2 H, d, *J* 7.5, 5- and 16-H), 7.11 (2 H, t, *J* 7.9, 4- and 15-H), 7.17 (2 H, s, 1- and 12-H), 7.45 (2 H, d, *J* 8.3, 3- and 14-H), 7.95 (2 H, s, 7- and 18-H) and 8.32 (2 H, br s, NH); $\delta_C(CDCl_3)$ 12.7 (SiCHMe$_2$), 18.0 [SiCH(CH_3)$_2$], 27.0 (11- and 22-C), 42.1 (10- and 21-C), 108.2 (3- and 14-C), 114.3 (5- and 16-C), 115.1 (11a- and 22a-C), 121.8 (4- and 15-C), 125.7 (11b- and 22b-C), 130.8 (1- and 12-C), 141.4 (5a- and 16a-C or 2a- and 13a-C), 142.5 (5a- and 16a-C or 2a- and 13a-C), 153.0 (7- and 18-C) and 163.8 (8- and 19-C); *m*/*z* (FAB) 739 (M^+, 14%), 352 (6), 325 (18), 313 (16), 169 (12), 154 (8), 115 ($Ar^{\bullet+}$, 72), 101 (24) 87 (95), 73 (100) and 59 (100).

X-Ray crystal structure determinations

Crystal data for compound 2. Yellow needles, $C_{42}H_{62}N_6O_2Si_2{\cdot}CCl_4$, M = 892.98, crystal dimensions 0.12 × 0.14 × 0.78 mm, triclinic, a = 13.400(6), b = 18.066(5), c = 12.436(4) Å, α = 104.02(2), β = 107.32(3), γ = 70.89(3)°, V = 2680(1) Å^3, space group $P\bar{1}$ (#2), Z = 2 (two molecules, each about a centre of symmetry), D_C = 1.106 g cm^{-3}, μ(Cu-Kα) = 27.20 cm^{-1}, F(000) = 948.0. 7952 Independent reflections were collected on a Rigaku AFC7S diffractometer, ω–2θ scan method, $5 \leqslant 2\theta \leqslant 120°$, T = 298 K, graphite monochromated Cu-Kα radiation (λ = 1.541 84 Å) with 2898 observed [$I > 3\sigma(I)$]. An empirical absorption correction was applied (transmission factors 0.5700–1.000). Over the course of data collection, the standards decreased by 14.4%, and a linear correction factor was applied to the data to account for this phenomenon. The structure was solved by direct methods, and the non-hydrogen atoms refined anisotropically. The hydrogen atoms were idealized. Two half-weighted molecules of disordered CCl_4 were located. High thermal anisotropy was noted in these fragments, as well as in the TIPS methyl groups, and this may account for the high agreement indices. Refinement was by full-matrix least squares on F to give R = 0.1276, R_w = 0.255[$w^{-1} = \sigma^2(F_o)$] for 549 parameters. The maximum residual electron density in the final ΔF map was 1.68 e Å^{-3} and the maximum shift/error in the final refinement cycle was 0.25. All calculations were carried out using the TEXSAN[9] crystallographic software package.

Crystal data for compound 9. Colourless needles, $C_{21}H_{31}N_5OSi{\cdot}0.25\ C_4H_{10}O$, M = 416.13, crystal dimensions 0.60 × 0.20 × 0.10 mm, monoclinic, a = 12.964(7), b = 15.731(4), c = 23.372(4) Å, β = 94.76(2)°, V = 4750(3) Å^3, space group $P2_1/n$ (#14), Z = 8, D_C = 1.164 g cm^{-3}, μ = 10.5 cm^{-1}, F(000) = 1796. 4338 Independent reflections were collected on an Enraf-Nonius CAD4 diffractometer, θ–2θ scan

method, $T = 298$ K, Ni-filtered Cu-Kα radiation ($\lambda = 1.541\,84$ Å) with 2170 observed [$I > 2\sigma(I)$]. The structure was solved by direct methods using MULTAN.[10] The asymmetric unit contains two crystallographically independent molecules of **9** and a half-occupied diethyl ether solvent molecule, which is located near an inversion centre and severely disordered. The two molecules of **9** exhibit similar conformations but differ in the orientations of the isopropyl groups. In one of the molecules of **9**, one isopropyl group is disordered with one of its methyl groups occupying two positions, C(22A) and C(22D), with occupancies of 0.6 and 0.4, respectively. Other isopropyl carbon atoms show high atomic displacement parameters, which may also be indicative of minor disorder. Refinement of 435 variables (Si, O and outlying N and C atoms anisotropic, inner N and C isotropic, H atoms 'riding') by full-matrix least squares against F^2 using a Chebyshev weighting scheme in SHELXL-93[11] gave $R_1 = 0.094$ [$I > 2\sigma(I)$], $wR_2 = 0.28$ for all data, goodness-of-fit 0.94 and $\Delta\rho_{max} = 0.38$, $\Delta\rho_{min} = -0.40$ e Å^{-3}.

Atomic coordinates, thermal parameters, bond lengths and bond angles for compounds **2** and **9** have been deposited at the Cambridge Crystallographic Data Centre (CCDC), see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/45. For details of the crystal structure determination of compound **1**, see reference 4.

Molecular modelling

Modelling of **1** and **2** was carried out using MACROMODEL,[12] version 4.0, with the MM2 force field. Monte Carlo simulations were performed using the automatic set-up routine in the program and the default variables.

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