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Synthesis, Structure and AM1 Conformational Study of [3]Paracyclo[3](1,3)indolophane, a Novel Chiral Cyclophane.

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Abstract: The title compound 5 was synthesized in seven steps with an overall yield of 22%. The two bridges were formed by a conjugate addition of indole to a Michael acceptor and by an intramolecular N-alkylation, respectively. A dynamic NMR study revealed the presence of a conformational process with an activation barrier of 10.9±0.2 kcal/mol, which was assigned to a ring flipping process that interconverts two enantiomeric sets of equilibrating bridge conformers. In the crystal structure of 5, both bridges adopt the *pseudo-chair* conformation, in accord with the lowest energy conformation identified by an AM1 conformational search. © 1999 Elsevier Science Ltd. All rights reserved.

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Introduction

A cyclophane is a molecule consisting of one or more "aromatic" core units linked by a number of bridges in such a fashion that the core unit(s) form part of a cycle. An impressive array of core units have been incorporated into cyclophanes, including benzenoid, non-benzenoid, polynuclear, non-aromatic, antiaromatic, homoaromatic and heteroaromatic systems.[1] Under the latter category, many different types of heteroaromatic moieties have been embodied in cyclophanes in a variety of ways.[2] With this in mind, it is perhaps surprising that indole, a very widely distributed heteroaromatic entity in nature, has, to the best of our knowledge, only four times[3-5] found itself as an aromatic component of a cyclophane when bridged at the reactive 1 and 3 positions.[6] In the case of 1,[3] the cyclophane was the only product (12%) obtained from the attempted Favorskii rearrangement of 3-(2-bromopropionyl)indole. Indolophanes 2 and 3[4] were prepared by the reaction of indolylmagnesium bromide with oxalyl chloride and phosgene in 53% and 21% yields, respectively. Compound 4 was the result of a tetramerization (45%) of the ketene derived from indole-3-carboxylic acid


1   2   3   4   5   6
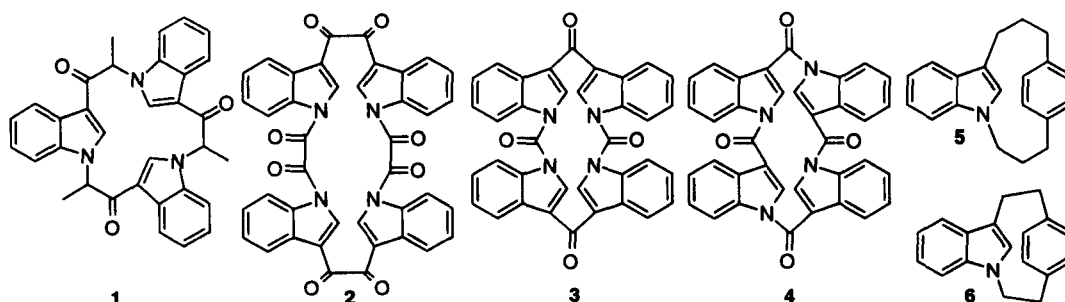
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chloride. The isomeric compounds 3 and 4 clearly fit the cyclophane definition, but closely resemble calix[4]arenes, a class of compounds that are generally considered separately from cyclophanes.

Our ongoing general interest in the synthesis, structure and conformational behaviour of cyclophanes[7] led us to pursue targeted syntheses of (1,3)indolophanes. Systems such as [3]paracyclo[3](1,3)indolophane 5 and [2]paracyclo[2](1,3)indolophane 6 were identified as natural first targets and we now present our initial work on the former cyclophane 5.
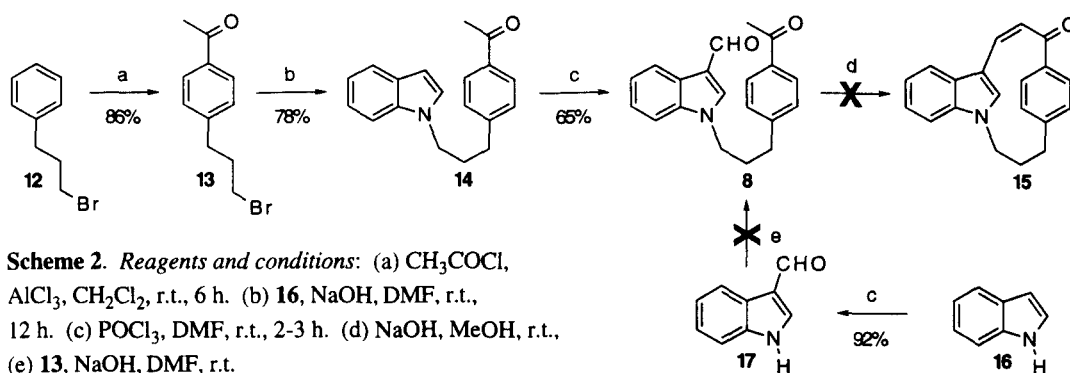
Results and Discussion

The retrosynthetic analysis of 5 is outlined in Scheme 1. The use of standard methodology for the formation of cyclophanes[1] was duly considered and deemed to be more applicable to the synthesis of 6, which is currently in progress. For the preparation of 5, four types of bridge-forming / ring-closing reactions were considered at the outset, namely A) conjugate addition of an indole to an α,β-unsaturated aryl ketone, B) aldol condensation, C) N-alkylation/acylation and D) enolate alkylation. Only the final ring closures are shown in Scheme 1, but compounds 7 and 8 can be taken back further according to cuts C and D, and compounds 9-11 can be taken back further according to cuts A and B.
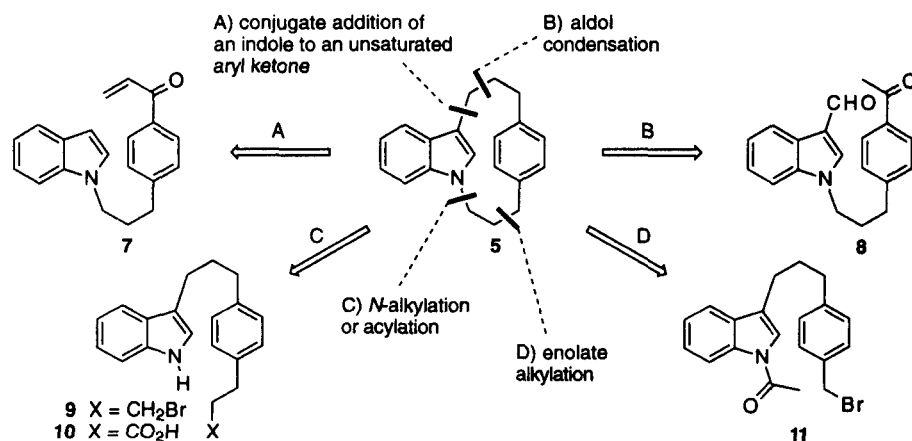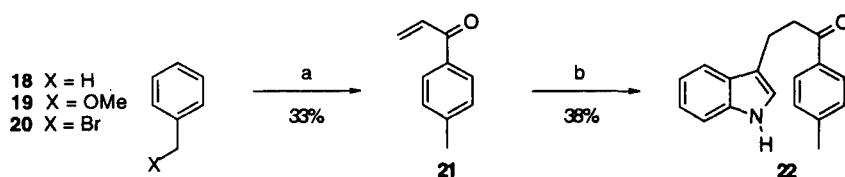

Scheme 1. Retrosynthetic analysis of indolophane 5.

The first approach to receive attention was the preparation and intramolecular aldol condensation of ketoaldehyde 8 (Scheme 2). 1-Bromo-3-phenylpropane 12 was acylated to give 13 in 86% yield. The lower bridge was then installed by the N-alkylation of indole[8] 16 with 13 in 78% yield. Formylation of the resulting compound 14 with POCl3/DMF[9] then afforded ketoaldehyde 8 (65%). An attempt to prepare 8 by the N-alkylation of 3-formylindole 17, which was prepared in 92% yield from indole 16,[8] yielded none of the desired product. The same was true for attempts to perform the intramolecular aldol reaction of 8 under high dilution. Monitoring the reaction by tlc indicated that the starting material was slowly converted into baseline material, which suggests that intermolecular oligomerization was favoured under the conditions employed.

Attention was then turned to the use of a conjugate addition to form the upper bridge and an N-acylation or N-alkylation to form the lower bridge. The conjugate addition of indoles to α,β-unsaturated ketones is well
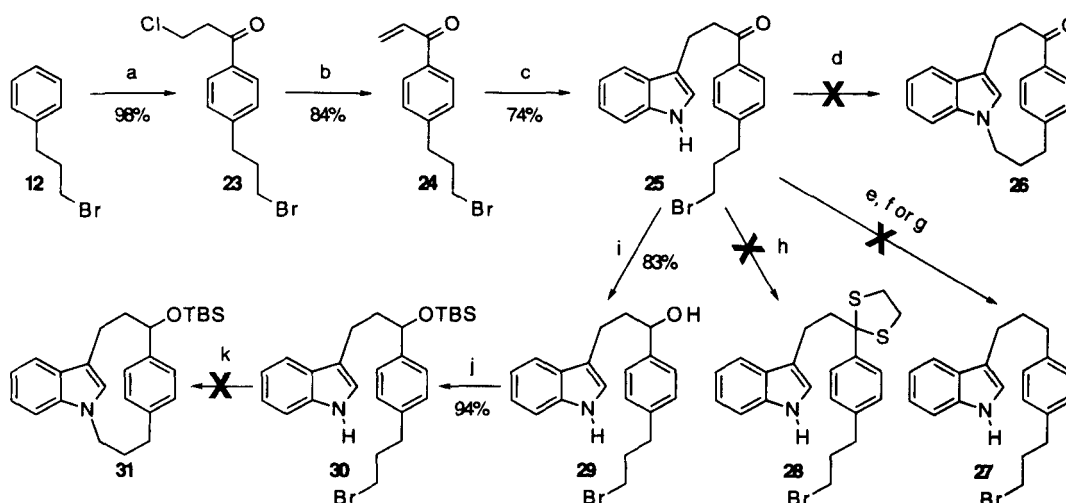
Scheme 2. *Reagents and conditions*: (a) CH₃COCl, AlCl₃, CH₂Cl₂, r.t., 6 h. (b) **16**, NaOH, DMF, r.t., 12 h. (c) POCl₃, DMF, r.t., 2-3 h. (d) NaOH, MeOH, r.t., (e) **13**, NaOH, DMF, r.t.

known[10] and it has recently been shown by Kerr[11] that this transformation can be achieved under catalysis by Yb(OTf)₃ at both ambient and high pressure. A brief model study was undertaken to ascertain whether this method would be applicable to our studies (Scheme 3). Friedel-Crafts acylation of toluene **18** with acryloyl chloride afforded ketone **21** in 33% yield and ambient pressure reaction of this compound with indole in the presence of 2.5 mol% Yb(OTf)₃ provided adduct **22** in an equally disappointing yield of 38%. The use of high pressure was not investigated, but has not been ruled out for future studies. It was also found that attempted acylations of methoxymethylbenzene **19** and benzyl bromide **20** failed completely under the conditions used for the preparation of **21**. The incompatibility of substrates with a benzylic substituent in the acylation reaction led us to discard routes involving cut D in the retrosynthetic analysis.

Scheme 3. *Reagents and conditions*: (a) acryloyl chloride, AlCl₃, CH₂Cl₂, 0 °C - r.t., 6 h. (b) **16**, 2.5 mol% Yb(OTf)₃, CH₃CN, r.t., 24 h.

A two step procedure for the generation of the Michael acceptor proved to be more successful, as did the use of classical conditions for the conjugate addition (Scheme 4).[12] Friedel-Crafts acylation of bromide **12** with 3-chloropropionyl chloride gave **23** (98%) and subsequent elimination with DBU afforded **24** in 84% yield. Treatment of **24** with indole **16** in HOAc/Ac₂O led to the formation of adduct **25** in 74% yield. The earlier conversion of **13** to **14** in good yield had demonstrated that a free ketone could indeed be present during the *N*-alkylation of indole, so direct cyclization of **25** to ketocyclophane **26** was attempted. However, none of the desired product was obtained using a variety of bases, such as K₂CO₃, NaH, NaOH and KOH, in DMF and/or DMSO. Traces of what appeared (by ¹H NMR) to be an arylcyclopropane were isolated, but not in a sufficiently pure form or large enough amount to be confidently assigned. The ketone functionality of **25** was likely the problem, not only due to its acidic α hydrogens, but also possibly due to the sp² hybridization of the carbon atom. Examination of molecular models indicated that the presence of the carbonyl group makes it

slightly more difficult for the molecule to adopt a geometry in which intramolecular *N*-alkylation can occur than in a system with an sp³ hybridized carbon atom in the place of the carbonyl group.

Scheme 4. *Reagents and conditions*: (a) 3-chloropropionyl chloride, AlCl₃, CH₂Cl₂, 0 °C - r.t., 6 h. (b) DBU, CH₂Cl₂, r.t., 1 h. (c) 16, CH₂Cl₂/HOAc/Ac₂O, reflux, 6 h. (d) base, DMF or DMSO. (e) NaBH₄, TFA, r.t.. (f) Raney Ni, EtOH, reflux. (g) Et₃SiH, TFA, r.t.. (h) 1,2-ethanedithiol, BF₃·Et₂O, or TiCl₄, or AlCl₃ or ZnCl₂. (i) NaBH₄, EtOH, 0 °C, 5 h. (j) TBSCl, imidazole, DMF, 12 h. (k) KOH, DMSO, r.t..

The direct reduction of the carbonyl group of **25** to give bromide **27** was investigated first. The presence of the bromine atom augured poorly for Wolff-Kishner and Clemmensen reductions, so alternative methods were investigated. However, the reactions of **25** with NaBH₄/TFA,[13] Raney Ni[14] and Et₃SiH/TFA[15] all failed. A Mozingo reaction was then considered, but the reaction of 1,2-ethanedithiol with **25** in the presence of each of BF₃·Et₂O, TiCl₄,[16] AlCl₃[17] and ZnCl₂[18] failed to give any of the desired dithiolane **28**. Stepwise reduction was then looked at. Treatment of **25** with NaBH₄ afforded alcohol **29** in 83% yield and this was protected as its TBS ether (94%). However, reaction of **30** with KOH/DMSO[8] did not produce any of the cyclophane **31**. The hybridization of the oxygen-bearing carbon alone does not seem to be a deciding factor.

The strategy was then modified to allow for Wolff-Kishner reduction of the ketone before introduction of the leaving group necessary for cyclization (Scheme 5). 3-Phenyl-1-propanol **32** was protected as its methyl ether **33** (88%) and this compound was acylated as before to give chloroketone **34** (78%). Interestingly, the same product was obtained in 66% yield when **33** was acylated with eight equivalents of acryloyl chloride and ten equivalents of AlCl₃. Treatment of **34** with DBU afforded α,β-unsaturated ketone **35** in 78% yield and the addition of indole **16** led to the formation of **36** in 74% yield. In line with the model study, the direct conversion of **33** into **35** (2 equivalents of acryloyl chloride and 4.4 equivalents of AlCl₃ - 39%) and the Yb(OTf)₃ catalyzed addition of indole **16** (30%) were found to be lower yielding options. Wolff-Kishner reduction of **37** proceeded in 87% yield and the methyl ether was then cleaved with BBr₃ to afford bromide **27**, but the yield was only 33%. An attempt to effect the same conversion using concentrated HBr solution under phase transfer catalysis (Aliquot® 336) resulted in no reaction.
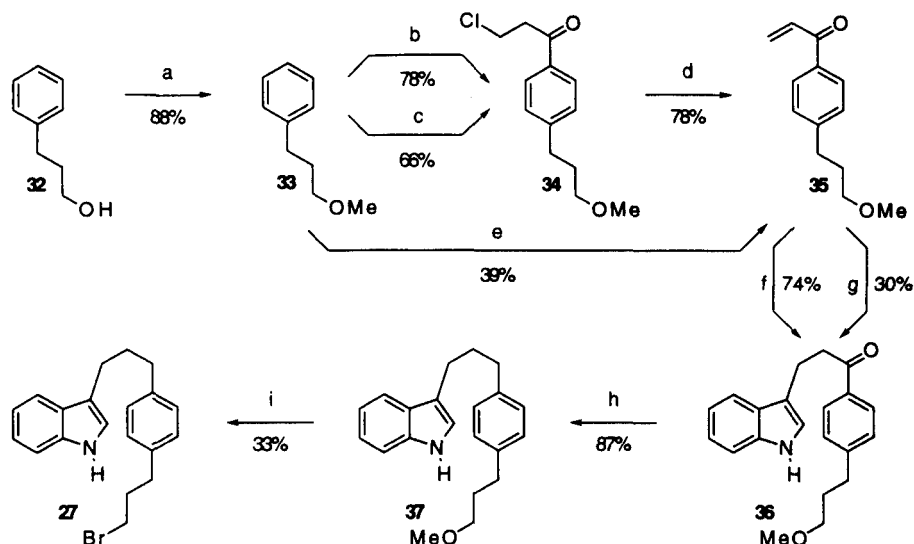
Scheme 5. *Reagents and conditions*: (a) NaH, MeI, THF, r.t., 10 h. (b) 3-chloropropionyl chloride, AlCl₃, CH₂Cl₂, 0 °C - r.t., 6 h. (c) 8 eq. acryloyl chloride, 10 eq. AlCl₃, CH₂Cl₂, 0 °C - r.t., 6 h. (d) DBU, CH₂Cl₂, r.t., 1 h. (e) 2 eq. acryloyl chloride, 4.4 eq. AlCl₃, CH₂Cl₂, 0 °C - r.t., 6 h. (f) **16**, CH₂Cl₂/HOAc/Ac₂O, reflux, 6 h. (g) **15**, 2.5 mol% Yb(OTf)₃, CH₃CN, r.t., 6 d. (h) H₂NNH₂·H₂O, KOH, diethylene glycol, 200 °C, 6 h. (i) BBr₃, CH₂Cl₂, 0 °C, 4 h.

Although the desired bromide **27** had been successfully prepared, the poor yield of the deprotection step was unsatisfactory. A more successful route involved the use of a different protecting group (Scheme 6). The pivaloyl ester was chosen because it could conceivably be removed during the Wolff-Kishner reduction, thereby saving a step. Accordingly, **32** was esterified with pivaloyl chloride (96%) and the resulting ester **38** was subjected to the sequence of acylation (**39** - 86%), elimination (**40** - 87%) and conjugate addition of indole **16** (**42** - 91%). The elimination reaction to give **40** proceeds in excellent yield when allowed to react for one hour, but if the reaction time is increased to 12 h, the only product isolated is **41** (11%), which appears to be the result of a self-Baylis-Hillman type reaction. Wolff-Kishner reduction of **42** cleanly reduced the ketone and removed the protecting group to afford alcohol **43** in 77% yield. Bromination of **43** with PPh₃/NBS[19] then provided the desired bromide **27** in 91% yield. Cyclization could then be effected upon slow addition of a THF solution of **27** to a refluxing slurry of NaH (10 equivalents) in THF under moderately high dilution. Under these conditions, 49% of the targeted cyclophane **5** was obtained, along with 19% of the cyclic dimer **44**. The overall yield of **5** is 22% over seven steps.

A conformer search of **5** was carried out at the AM1 level of theory using the Spartan software package (Version 4.0). Five conformers were identified within 5 kcal/mol of the global minimum (Figure 1). The lowest energy conformer (C$_{chair}$,N$_{chair}$) has both bridges in the *pseudo-chair* conformation.[20,21] Flipping the bridge attached to the C-terminus of the indole unit affords a conformer (C$_{boat}$,N$_{chair}$) that is 0.92 kcal/mol higher in energy, whereas flipping the bridge attached to the N-terminus of the indole moiety to give the C$_{chair}$,N$_{boat}$ conformer is almost twice as costly in energy (1.68 kcal/mol). Although the energy differences in
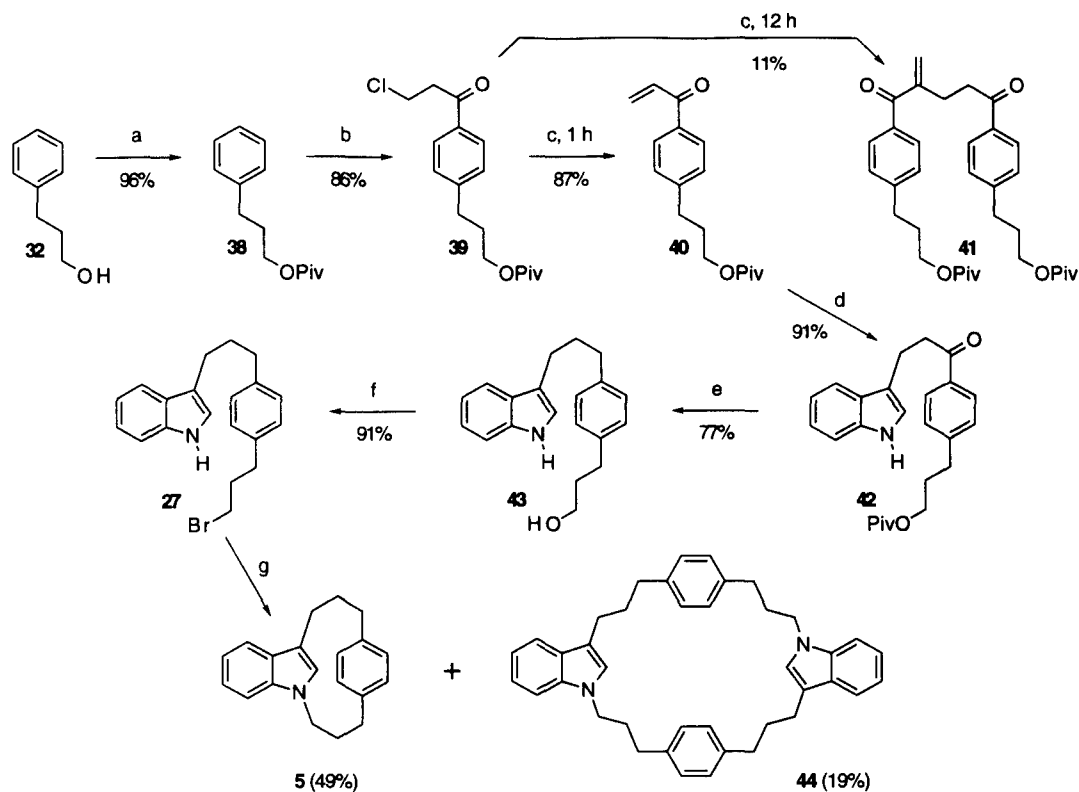
Scheme 6. *Reagents and Conditions*: (a) pivaloyl chloride, Et₃N, CH₂Cl₂, 25 °C, 12 h. (b) 3-chloropropionyl chloride, AlCl₃, CH₂Cl₂, 0 °C - r.t., 7 h. (c) DBU, CH₂Cl₂, r.t.. (d) 16, CH₂Cl₂/HOAc/Ac₂O, reflux, 2 d. (e) H₂NNH₂·H₂O, KO*t*-Bu, diethylene glycol, 200 °C, 2 d. (f) PPh₃, NBS, DMF, 50 °C, 40 min, then r.t., 24 h. (g) NaH, THF, reflux, 21 h.

these processes are rather small, the significant difference in energy between the two bridge flips is somewhat surprising. The origin of this difference is not immediately obvious. The C_boat,N_boat conformer is calculated to lie 3.65 kcal/mol above the global minimum. The fifth conformer (tilt-C_boat,N_boat - 4.40 kcal/mol) was unexpected. It resembles the C_boat,N_boat conformer, but the angle between the indole nucleus and the benzene ring is considerably greater.
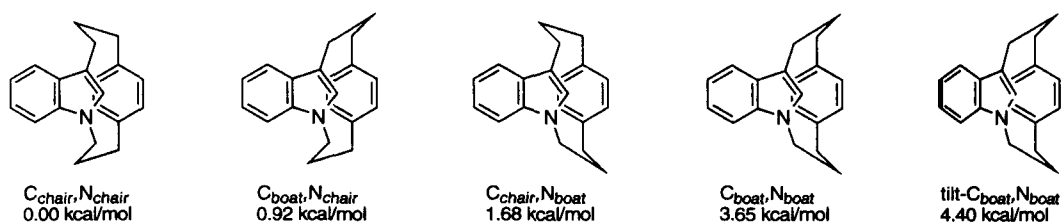

Figure 1. AM1-calculated low energy conformers of **5** and their relative energies.

The ^{1}H NMR spectrum of indolophane **5** exhibits a sharp singlet at δ 5.59, which is assigned to the internal proton of the indole deck. By comparison, the internal proton of [3.3]metaparacyclophane is observed at δ 5.55.[21] The high field shift of this proton indicates that, as expected, it occupies an average position well inside the shielding cone of the benzenoid ring in solution. The analogous proton of **27**, the direct precursor of **5**, is observed at δ 6.95. The protons of the benzenoid deck are observed as a slightly broadened AB system at δ 6.65 and 6.57. That only one AB system is observed suggests that a degenerate ring flipping process (Figure 2) analogous to that described for [2.2]metaparacyclophanes[22] occurs rapidly on the NMR time scale at room temperature. The slight broadening observed in the AB spectrum suggests that room temperature is not too distant from the coalescence temperature for the conformational process. The signals of the diastereotopic NCH_2 group are observed as a narrow multiplet centered at δ 4.00 and the remaining bridge protons are observed as a series of multiplets in the range of δ 2.05-2.85. Cyclic dimer **44** exhibits a simpler ^{1}H NMR spectrum than **5**. The internal protons of the indole unit appear as a singlet at δ 6.70 and the bridge protons all give clean triplets or quintets. The NCH_2 signals are observed as a well resolved triplet ($J = 6.6$ Hz) at δ 4.03.

A dynamic NMR study of **5** was undertaken to determine the energy barrier of the ring flip. Upon cooling, the AB spectrum for the benzenoid deck and the signals for the bridge protons all broaden further. At -90 °C, the protons of the benzenoid deck are resolved into two AB systems. The higher field system is observed at δ 6.21 and 6.00, whereas the lower field system can be seen at δ 7.04 and 6.94, overlapped somewhat with two of the external aromatic signals of the indole moiety. Since the NCH_2 signals were well separated from other resonances, these were used for the determination of the energy barrier. The low temperature spectrum consists of two doublets of doublets centered at δ 4.25 and 3.63. The coalescence temperature (T_c) of these signals is 236±3 K and $\Delta\nu = 185.5$ Hz, giving $k_c = 412.1$ and $\Delta G^{\ddagger} = 10.9 \pm 0.2$ kcal/mol, according to the Gutowsky-Holm equation.[23] We are unaware of any determination of the energy barrier for the ring flip in any [3.3]metaparacyclophane with no internal substituent, although the reported ^{1}H NMR spectra indicate rapid interconversion at room temperature.[21,24]

Since none of the bridge flips that interconvert the various bridge conformers shown in Figure 1 result in an exchange in the environments of the diastereotopic NCH_2 protons (or any of the other diastereotopic CH_2 groups in the bridges), it must be a ring flip that was observed in the dynamic NMR study. A ring flip of the C_{chair},N_{chair} conformation gives rise to a C_{boat},N_{boat} conformer, which can then undergo two bridge flips to arrive at another C_{chair},N_{chair} conformation (Figure 2). This new C_{chair},N_{chair} conformer is the enantiomer of the starting conformer and the ring flip is thus a mechanism for racemization of the chiral cyclophane **5**.

In fact, the full set of conformational processes is more complicated than that depicted in Figure 2. Each of the bridge conformers shown in Figure 1 (and others that lie higher in energy than 5 kcal/mol above the calculated minimum) can undergo a ring flip that is necessarily accompanied by a flip of both bridge conformations and inverts the enantiomeric sense of the molecular skeleton. With an energy barrier between these two enantiomeric sets of bridge conformers of 10.9±0.2 kcal/mol, the prospects of resolving them, even at low temperature, are bleak. Intuitively, one would conclude that the introduction of a bulky substituent at the internal position of the indole nucleus and/or the shortening of the bridges should significantly enhance the chances of doing so. In consulting the literature, the energy barrier to ring inversion of [2.2]metaparacyclophane has been observed to be 20.6 kcal/mol.[22] It would therefore seem that both a shortening of the bridges and the presence of an internal substituent will be required for resolution to be viable.
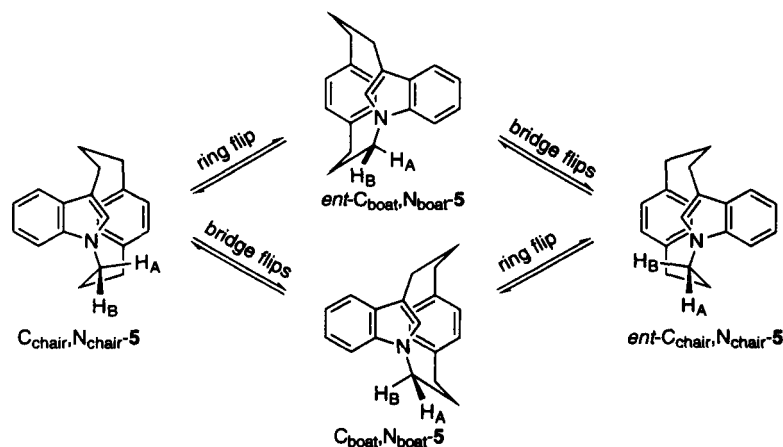
Figure 2. Selected conformational processes in **5**.

An X-ray crystal structure determination of **5** (Figure 3) revealed that the two aromatic core units are very close to being aligned along the same pseudo mirror plane. The indole moiety is virtually planar, while the benzene ring slightly boat shaped, with $\alpha = 6.0$ ° at the end where the bridge leads to the to N terminus of the indole unit and 5.6 ° at the end where the bridge leads to the to C terminus of the indole unit. The angle formed by the best planes of the indole ring system and the benzene ring is 9.0 °. The internal H atom of the indole unit lies, as expected, directly over the benzene ring. The bond lengths and angles of **5** are within normal ranges, except for the C-C-C and C-C-N bond angles of the bridges, which are somewhat greater than normal, ranging from 113.1 ° at C(11) to 118.1 ° C(19).

Figure 3. ORTEP representation of **5** in the crystal. The crystallographic numbering shown differs from systematic. Selected bond angles (°): C(2)-C(9)-C(10) 115.7(3), C(9)-C(10)-C(11) 116.9(3), C(10-C(11)-C(12) 113.1(3), C(15)-C(18)-C(19) 113.2(3), C(18)-C(19)-C(20) 118.1(3), C(19)-C(20)-N(1) 115.9(2).

The crystal structure of the macrocyclic dimer **44** was also determined by X-ray methods (Figure 4). The two monomeric units of **44** are related by crystallographic symmetry. The molecule has adopted a two tiered structure with each tier containing an indole ring, a benzene ring and five of the six bridge carbons. The

distance across the central cavity, as measured by the distance between hydrogen atoms attached to the two crystallographically equivalent C8 atoms, is 6.91 Å. The aromatic nuclei do not deviate significantly from planarity. As in the case of 5, the bond lengths and angles are within normal ranges, except for the C-C-C and C-C-N bond angles of the bridge atoms. These range from 113.2 ° at C20 to 114.9 ° at C18. Whereas the unexpectedly high values might be explained by a small amount of molecular strain in 5, the same argument cannot be made for 44. Crystal packing forces may well be responsible for this phenomenon.
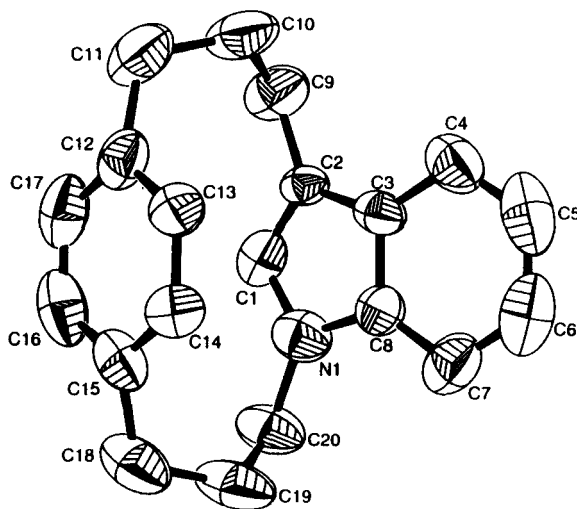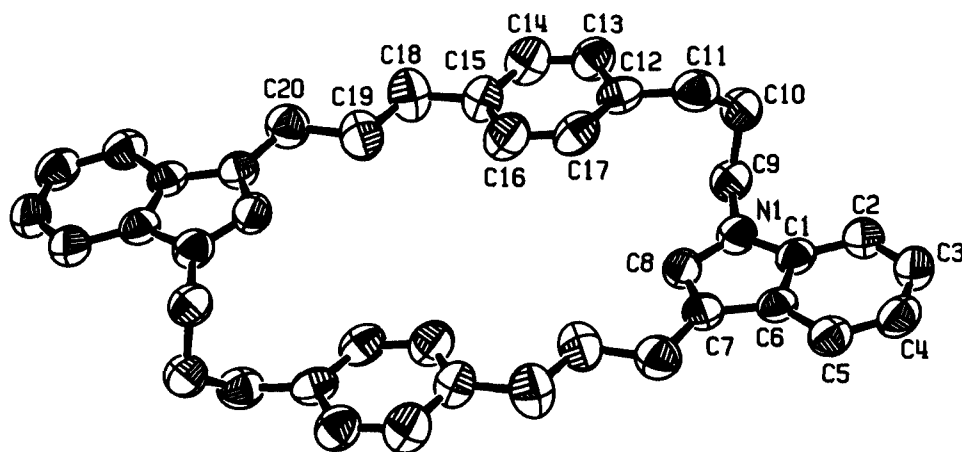

Figure 4. ORTEP representation of 44 in the crystal. The crystallographic numbering shown differs from systematic. Selected bond angles (°): N(1)-C(9)-C(10) 113.0(3), C(9)-C(10)-C(11) 114.8(4), C(10)-C(11)-C(12) 114.8(4), C(15)-C(18)-C(19) 114.9(4), C(18)-C(19)-C(20) 113.6(4), C(7)-C(20)-C(19) 113.2(4).

Conclusions

The first targeted synthesis of a (1,3)indolophane was achieved by a relatively short synthetic pathway in a respectable (22%) overall yield and the solid state structures of 5 and its cyclic dimer 44 were determined. A ring flip that interconverts two enantiomeric sets of equilibrating bridge conformers of 5 with an energy barrier of 10.9±0.2 kcal/mol was observed by way of a dynamic NMR study.

Experimental Section

General. Reactions were performed under air unless otherwise indicated. Those experiments with moisture or air sensitive compounds were performed in anhydrous solvents under nitrogen in flame-dried glassware. Solvents for reactions were dried and distilled according to standard procedures. All other solvents were used as received. Chromatographic purification was accomplished with 230-400 mesh silica gel. TLC plates were visualized using a short wave (254 nm) UV lamp. Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. IR spectra (cm⁻¹) were recorded on neat samples or nujol suspensions in KBr discs using a Mattson Polaris FT instrument. ¹H NMR spectra were obtained from $CDCl_3$ solutions using a General

Electric GE-300 NB instrument operating at 300.1 MHz. Chemical shifts (δ) are relative to internal TMS standard. Coupling constants are reported in Hz. Reported multiplicities are apparent. ^{13}C NMR spectra were recorded at 75.47 MHz. Chemical shifts are relative to solvent (δ 77.0 for CDCl$_3$). Low resolution mass spectroscopic data were obtained on a V.G. Micromass 7070HS instrument operating at 70 eV. Combustion analyses were performed by the Microanalytical Services Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta.

1-Bromo-3-(4-acetylphenyl)propane **13**. To a suspension of AlCl$_3$ (5.87 g, 44.0 mmol) in CH$_2$Cl$_2$ (60 mL) at 0 °C was injected acetyl chloride (3.14 g, 40.0 mmol). A solution of 1-bromo-3-phenylpropane **12** (3.98 g, 20.0 mmol) in CH$_2$Cl$_2$ (20 mL) was then added dropwise with stirring to the resulting mixture. After stirring at room temperature for 6 h, the reaction mixture was poured into a mixture of ice water (100 mL) and HCl solution (12 N, 10 mL) and extracted with CH$_2$Cl$_2$ (2x50 mL). The combined organic layers were washed with brine (3x100 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (20% EtOAc/hexane) afforded **13** (4.15 g, 86%) as a clear, colorless liquid. IR (KBr) v = 1682 (s), 1607 (m) cm^{-1}. MS *m/z* (%) = 242 (11), 240 (11, M+ [79]Br), 227 (99), 225 (100), 183 (11), 181 (34), 133 (13), 118 (20). ^{1}H NMR (CDCl$_3$) δ = 2.14-2.24 (m, 2H), 2.59 (s, 3H), 2.83-2.87 (m, 2H), 3.39 (t, *J* = 6.7 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.90 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (CDCl$_3$): δ = 26.6, 32.7, 33.6, 33.9, 128.6, 128.8, 135.4, 146.3, 197.7. Anal. Calcd. for C$_{11}$H$_{13}$BrO: C, 54.79; H, 5.43. Found: C, 55.09; H, 5.67.

1-(3-(4-Acetylphenyl)propyl)indole **14**. To a suspension of freshly ground NaOH (664 mg, 16.6 mmol) in DMF (20 mL) at room temperature was added a solution of indole **16** (970 mg, 8.28 mmol) in DMF (5 mL). After the mixture was further stirred for 1 h, a solution of **13** (1.00 g, 4.15 mmol) in DMF (10 mL) was added. After stirring for 12 h, the reaction mixture was diluted with a mixture of H$_2$O (50 mL) and HCl solution (12 N, 1.5 mL), and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine (3x100 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (18% EtOAc/hexane) gave **14** (896 mg, 78%) as a clear, colorless oil. IR (KBr) v = 1735 (m), 1680 (s), 1607 (m) cm^{-1}. MS *m/z* (%) = 278 (7), 277 (34, M+), 131 (77), 130 (100). ^{1}H NMR (CDCl$_3$): δ = 2.14-2.23 (m, 2H), 2.57 (s, 3H), 2.63-2.68 (m, 2H), 4.12 (t, *J* = 7.0 Hz, 2H), 6.50 (d, *J* = 2.9 Hz, 1H), 7.06-7.29 (m, 6H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (CDCl$_3$): δ = 26.5, 31.1, 32.9, 45.5, 101.2, 109.2, 119.3, 121.0, 121.4, 127.6, 128.5, 128.6, 135.3, 135.9, 146.7, 197.7. Anal. Calcd. for C$_{19}$H$_{19}$NO: C, 82.28; H, 6.90; N, 5.05. Found: C, 81.85; H, 6.67; N, 5.03.

3-Formyl-1-(3-(4-acetylphenyl)propyl)indole **8**. POCl$_3$ (153 mg, 1.00 mmol) was mixed with DMF (3 mL) at room temperature. A solution of **14** (116 mg, 0.418 mmol) in DMF (3 mL) was added dropwise to the resulting solution. After stirring at room temperature for 2 h, the reaction mixture was poured into some ice, treated with aqueous NaOH solution (0.5 N, 10 mL), quickly boiled for 3 min, and extracted with EtOAc (2x25 mL). The combined organic layers were washed with brine (3x50 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (60% EtOAc/hexane) gave **8** (83 mg, 65%) as a light yellow powder. M.p. = 74-76 °C. IR (nujol) v = 1680 (m), 1657 (s), 1606 (m) cm^{-1}. MS *m/z* (%) = 306 (20), 305 (83, M+), 159 (73), 158 (66), 130 (100). ^{1}H NMR (CDCl$_3$): δ = 2.23-2.33 (m, 2H), 2.59 (s, 3H), 2.71-2.76 (m, 2H), 4.21 (t, *J* = 7.1 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.30-7.36 (m, 3H), 7.69 (s, 1H), 7.90 (d, *J* = 8.3 Hz, 2H), 8.30-8.33 (m, 1H),

10.01 (s, 1H). ^{13}C NMR (CDCl$_3$): δ = 26.6, 30.6, 328, 46.4, 109.9, 118.3, 122.2, 123.0, 124.03, 125.5, 128.5, 128.8, 135.6, 137.0, 137.9, 145.7, 184.4, 197.6. Anal. Calcd. for C$_{20}$H$_{19}$NO$_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.35; H, 6.35; N, 4.48.

4-Methyl-1-(1-oxo-2-propenyl)benzene **21.** To a suspension of AlCl$_3$ (1.33 g, 10.0 mmol) in CH$_2$Cl$_2$ (8 mL) at 0 °C was injected acryloyl chloride (540 mg, 5.97 mmol). A solution of toluene **18** (460 mg, 4.99 mmol) in CH$_2$Cl$_2$ (2 mL) was added dropwise to the resulting stirred mixture. After stirring in the dark at room temperature for 6 h, the reaction mixture was poured into a mixture of ice water (50 mL) and HCl solution (12 N, 20 mL), and extracted with CH$_2$Cl$_2$ (3x50 mL). The combined organic layers were washed with saturated aqueous NaHCO$_3$ solution (3x100 mL) and brine (100 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (67% CH$_2$Cl$_2$/hexane) gave **21** (242 mg, 33%) as a slightly yellow liquid. IR (KBr) ν = 1668 (s), 1605 (m) cm^{-1}. MS *m/z* (%) = 147 (3), 146 (27, M$^+$), 119 (100), 91 (58). ^{1}H NMR (CDCl$_3$): δ = 2.42 (σ, 3H), 5.90 (dd, *J* = 10.4, 1.6 Hz, 1H), 6.43 (dd, *J* = 16.8, 1.5 Hz, 1H), 7.16 (dd, *J* = 17.1, 10.5 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (CDCl$_3$): δ = 21.6, 128.8, 129.3, 129.7, 132.3, 134.7, 143.9, 190.5. Anal. Calcd. for C$_{10}$H$_{10}$O: C, 82.16; H, 6.89. Found: C, 81.91; H, 6.84.

3-(3-(4-Methylphenyl)-3-oxopropyl)indole **22.** To a solution of **21** (146 mg, 1.00 mmol) in CH$_3$CN (3 mL) at room temperature was added indole **16** (234 mg, 2.00 mmol). Yb(OTf)$_3$ (16 mg, 0.026 mmol) was added to the resulting solution. After stirring for 24 h, the reaction mixture was columned directly (15% EtOAc/hexane) to afford **22** (100 mg, 38%) as a white solid. M.p. = 134-136 °C. IR (nujol) ν = 1668 (s), 1608 (m) cm^{-1}. MS *m/z* (%) = 264 (6), 263 (33, M$^+$), 144 (65), 130 (100), 119 (21). ^{1}H NMR (CDCl$_3$): δ = 2.39 (s, 3H), 3.18-3.23 (m, 2H), 3.33-3.38 (m, 2H), 7.02 (d, *J* = 2.6 Hz, 1H), 7.10-7.20 (m, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.98 (bs, 1H). ^{13}C NMR (CDCl$_3$): δ = 19.8, 21.6, 39.2, 111.2, 115.5, 118.7, 119.3, 121.6, 122.0, 127.2, 128.1, 129.2, 134.45, 136.3, 143.7, 199.6. Anal. Calcd. for C$_{18}$H$_{17}$NO: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.95; H, 6.69; N, 5.35.

1-(3-Chloro-1-oxopropyl)-4-(3-bromopropyl)benzene **23.** To a suspension of AlCl$_3$ (1.60 g, 12.0 mmol) in CH$_2$Cl$_2$ (15 mL) at 0 °C was injected 3-chloropropionyl chloride (1.27 g, 10.0 mmol). A solution of 1-bromo-3-phenylpropane **12** (1.00 g, 5.02 mmol) in CH$_2$Cl$_2$ (5 mL) was added dropwise to the resulting stirred mixture. After stirring at room temperature for 6 h, the reaction mixture was poured into a mixture of ice water (50 mL) and HCl solution (12 N, 10 mL), and extracted with CH$_2$Cl$_2$ (3x40 mL). The combined organic layers were washed with H$_2$O (3x50 mL) and brine (3x50 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (20% EtOAc/hexane) gave **23** (1.42 g, 98%) as a white powder. M.p. = 75-77 °C. IR (nujol) ν = 1677 (s), 1606 (m) cm^{-1}. MS *m/z* (%) = 290 (1), 288 (1, M$^+$ ^{79}Br), 227 (99), 225 (100), 181 (22), 118 (16). ^{1}H NMR (CDCl$_3$): δ = 2.14-2.24 (m, 2H), 2.83-2.88 (m, 2H), 3.39 (t, *J* = 6.4 Hz, 2H), 3.44 (t, *J* = 7.1 Hz, 2H), 3.93 (t, *J* = 7.1 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (CDCl$_3$): δ = 32.7, 33.6, 34.0, 38.7, 41.2, 128.4, 128.9, 134.6, 146.9, 196.3. Anal. Calcd. for C$_{12}$H$_{14}$BrClO: C, 49.77; H, 4.87. Found: C, 49.79; H, 4.78.

1-(1-Oxo-2-propenyl)-4-(3-bromopropyl)benzene **24.** A solution of **23** (290 mg, 1.00 mmol) in CH$_2$Cl$_2$ (15 mL) was treated with DBU (152 mg, 1.00 mmol) at room temperature for 1 h. The reaction was quenched with HCl solution (0.12 N, 30 mL) and extracted with CH$_2$Cl$_2$ (3x25 mL). The combined organic layers were

washed with brine (4x50 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (CH$_2$Cl$_2$) gave **24** (213 mg, 84%) as a slightly yellow liquid. IR (KBr) v = 1668 (s), 1605 (s) cm^{-1}. MS *m/z* (%) = 254 (23), 252 (25, M$^+$ ^{79}Br), 227 (99), 225 (100), 145 (29), 117 (43). ^{1}H NMR (CDCl$_3$): δ = 2.15-2.24 (m, 2H), 2.83-2.88 (m, 2H), 3.40 (t, *J* = 6.3 Hz, 2H), 5.92 (dd, *J* = 10.7, 1.9 Hz, 1H), 6.44 (dd, *J* = 16.9, 1.4 Hz, 1H), 7.16 (dd, *J* = 16.9, 10.3 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (CDCl$_3$): δ = 32.7, 33.6, 34.0, 128.8, 129.1, 129.9, 132.3, 135.4, 146.2, 190.5. Anal. Calcd. for C$_{12}$H$_{13}$BrO: C, 56.94; H, 5.18. Found: C, 57.08; H, 5.20.

3-(3-(4-(3-Bromopropyl)phenyl)-3-oxopropyl)indole **25**. A solution of **24** (3.80 g, 15.0 mmol) and indole **16** (6.79 g, 58.0 mmol) in CH$_2$Cl$_2$ (40 mL), HOAc (30 mL), and Ac$_2$O (10 mL) was refluxed for 6 h. The reaction mixture was concentrated, diluted with saturated aqueous NaHCO$_3$ solution (100 mL), and extracted with CH$_2$Cl$_2$ (3x100 mL). The combined organic layers were washed with brine (2x50 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (25% EtOAc/hexane) gave **25** (4.11 g, 74%) as a yellow solid. M.p. = 98-100 °C. IR (nujol) v = 3401 (s), 1675 (s), 1603 (m) cm^{-1}. MS *m/z* (%) = 371 (8), 369 (8, M$^+$ ^{79}Br), 227 (12), 225 (12), 144 (72), 130 (100), 117 (16). ^{1}H NMR (CDCl$_3$): δ = 2.12-2.22 (m, 2H), 2.81-2.85 (m, 2H), 3.19-3.24 (m, 2H), 3.34-3.40 (m, 4H), 7.05 (d, *J* = 2.0 Hz, 1H), 7.10-7.23 (m, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.97 (bs, 1H). ^{13}C NMR (CDCl$_3$): δ = 19.7, 32.7, 33.6, 33.9, 39.2, 111.1, 115.5, 118.7, 119.3, 121.5, 122.0, 127.2, 128.4, 128.8, 135.2, 136.3, 146.1, 199.5. Anal. Calcd. for C$_{20}$H$_{20}$BrNO: C, 64.87; H, 5.44; N, 3.78. Found: C, 65.56; H, 5.55; N, 3.74. A triplet at δ = 3.51 and a multiplet at δ = 2.06-2.10 due to a minor unidentified impurity were observed in the ^{1}H NMR spectrum. Neither crystallization, chromatography, nor sublimation succeeded in removing this impurity. Acceptable analytical data were not obtained for this compound.

(±)-3-(3-(4-(3-Bromopropyl)phenyl)-3-hydroxypropyl)indole **29**. To a suspension of **25** (100 mg, 0.270 mmol) in EtOH (15 mL) at 0 °C was added NaBH$_4$ (102 mg, 2.70 mmol) portionwise. After stirring at room temperature for 5 h, the reaction mixture was concentrated, treated with HCl solution (1.2 N, 20 mL), and extracted with CH$_2$Cl$_2$ (3x20 mL). The combined organic layers were washed with brine (3x50 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (40% EtOAc/hexane) gave **29** (83 mg, 83%) as a sticky, yellow liquid. IR (KBr) v = 3545 (w), 3418 (s), 1618 (w) cm^{-1}. MS *m/z* (%) = 373 (3), 371 (3, M$^+$ ^{79}Br), 144 (12), 131 (100), 130 (73), 118 (12), 117 (13). ^{1}H NMR (CDCl$_3$): δ = 2.01-2.18 (m, 4H), 2.41 (bs, 1H), 2.65-2.84 (m, 4H), 3.43 (t, *J* = 6.6 Hz, 2H), 4.58-4.62 (m, 1H), 6.76 (d, *J* = 2.1 Hz, 1H), 7.03-7.21 (m, 7H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.92 (bs, 1H). ^{13}C NMR (CDCl$_3$): δ = 21.4, 33.1, 33.5, 34.0, 39.0, 73.8, 111.1, 115.6, 118.8, 119.0, 121.2, 121.7, 126.1, 127.3, 128.5, 136.2, 139.7, 142.4. Anal. Calcd. for C$_{20}$H$_{22}$BrNO: C, 64.52; H, 5.96; N, 3.76. Found: C, 64.88; H, 5.98; N, 3.52. The same impurity signals as described for **25** were found once again here and similar attempts to fully purify the product failed. Nevertheless, acceptable analytical data were indeed obtained for this compound.

(±)-3-(3-(4-(3-Bromopropyl)phenyl)-3-tert-butyldimethylsilyloxypropyl)indole **30**. To a solution of **29** (400 mg, 1.07 mmol) and imidazole (374 mg, 5.49 mmol) in DMF (25 mL) at room temperature was added TBS-Cl (829 mg, 5.50 mmol). After stirring for 12 h, the reaction mixture was quenched with H$_2$O (50 mL), and extracted with diethyl ether (3x50 mL). The combined organic layers were washed with H$_2$O (2x50 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (15% EtOAc/hexane) gave **30** (497 mg, 94%) as a

clear, colorless oil. IR (KBr) $v = 3423$ (s), 1619 (w) cm^{-1}. MS m/z (%) = 487 (0.2), 485 (0.2, M$^+$ ^{79}Br), 355 (3), 353 (3), 309 (20), 204 (13), 131 (45), 130 (100), 117 (17). ^{1}H NMR (CDCl$_3$): δ -0.14 (s, 3H), 0.05 (s, 3H), 0.92 (s, 9H), 2.02-2.14 (m, 4H), 2.73-2.83 (m, 4H), 3.51 (t, J = 6.7 Hz, 2H), 4.73-4.77 (m, 1H), 6.92 (d, J = 2.1 Hz, 1H), 7.06-7.36 (m, 7H), 7.54 (d, J = 7.8 Hz, 1H), 7.84 (bs, 1H). ^{13}C NMR (CDCl$_3$): δ -4.9, -4.6, 18.3, 21.2, 25.9, 32.4, 34.0, 41.0, 44.3, 74.6, 111.0, 116.6, 118.9, 119.0, 120.8, 121.9, 126.1, 127.5, 128.1, 136.3, 139.1, 143.5. Anal. Calcd. for C$_{26}$H$_{36}$BrNOSi: C, 64.18; H, 7.46; N, 2.88. Found: C, 69.01; H, 7.98; N, 2.96. No trace of the impurity observed in the NMR spectra of **25** and **28** was observed here. Nevertheless the results of combustion analysis were repeatedly ≥5% too high for C.

1-Methoxy-3-phenylpropane **33**. To a suspension of NaH (8.00 g, 200 mmol) in anhydrous THF (40 mL) at room temperature was added dropwise a solution of 3-phenyl-1-propanol **32** (13.6 g, 100 mmol) in THF (50 mL). The mixture was stirred for 0.5 h, and MeI (56.8 g, 400 mmol) was injected slowly. After stirring for 10 h, the reaction mixture was quenched with H$_2$O (50 mL), and extracted with diethyl ether (4x100 mL). The combined organic layers were washed with H$_2$O (4x100 mL) and brine (150 mL), dried over MgSO$_4$, filtered and concentrated carefully. Vacuum distillation (79-80 °C, 3 mm Hg) gave **33** (13.2 g, 88%) as a clear, colorless liquid. IR (KBr) $v = 1603$ (w) cm^{-1}. MS m/z (%) = 150 (1, M$^+$), 118 (100), 117 (68), 91 (60). ^{1}H NMR (CDCl$_3$): δ = 1.84-1.94 (m, 2H), 2.66-2.71 (m, 2H), 3.34 (s, 3H), 3.38 (t, J = 6.5 Hz, 2H), 7.18-7.31 (m, 4H). ^{13}C NMR (CDCl$_3$): δ = 31.3, 32.3, 58.5, 71.9, 125.8, 128.3, 128.4, 142.0. Anal. Calcd. for C$_{10}$H$_{14}$O: C, 79.96; H, 9.39. Found: C, 79.89; H, 9.50.

1-(3-Chloro-1-oxopropyl)-4-(3-methoxypropyl)benzene **34**. Method A. To a suspension of AlCl$_3$ (1.60 g,12.0 mmol) in CH$_2$Cl$_2$ (18 mL) at 0 °C was injected 3-chloropropionyl chloride (1.27 g, 10.0 mmol). A solution of **33** (751 mg, 5.00 mmol) in CH$_2$Cl$_2$ (5 mL) was added dropwise to the resulting stirred mixture. After stirring at room temperature for 6 h, the reaction mixture was poured into a mixture of ice water (50 mL) and HCl solution (12 N, 10 mL) and extracted with CH$_2$Cl$_2$ (3x40 mL). The combined organic layers were washed with H$_2$O (3x50 mL) and brine (3x50 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (20% EtOAc/hexane) gave **34** (939 mg, 78%) as white crystals. M.p. = 47-49 °C. IR (nujol) $v = 1675$ (s), 1607 (m) cm^{-1}. MS m/z (%) = 241 (1, M$^+$), 208 (19), 177 (54), 145 (100). ^{1}H NMR (CDCl$_3$): δ = 1.86-1.95 (m, 2H), 2.74-2.79 (m, 2H), 3.35 (s, 3H), 3.38 (t, J = 6.4 Hz, 2H), 3.44 (t, J = 6.9 Hz, 2H), 3.93 (t, J = 7.1 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 7.9 Hz, 2H). ^{13}C NMR (CDCl$_3$): δ = 30.8, 32.4, 38.8, 41.1, 58.6, 71.5, 128.2, 128.8, 134.2, 148.4, 196.3. Anal. Calcd. for C$_{13}$H$_{17}$ClO$_2$: C, 64.86; H, 7.12. Found: C, 64.89; H, 7.17.

Method B. To a suspension of AlCl$_3$ (66.7 g, 500 mmol) in CH$_2$Cl$_2$ (100 mL) at 0 °C was injected acryloyl chloride (36.2 g, 400 mmol). A solution of **33** (7.51 g, 50.0 mmol) in CH$_2$Cl$_2$ (50 mL) was added dropwise to the resulting stirred mixture. After stirring at room temperature for 6 h with protection of aluminum foil from light, the reaction mixture was poured into ice water (500 mL) containing HCl solution (12 N, 50 mL), and extracted with CH$_2$Cl$_2$ (3x200 mL). The combined organic layers were washed with H$_2$O (3x200 mL) and brine (3x200 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (20% EtOAc/hexane) gave **34** (7.94 g, 66%) as white crystals.

4-(3-Methoxypropyl)-1-(1-oxo-2-propenyl)benzene **35**. A solution of **34** (6.02 g, 25.0 mmol) in CH_2Cl_2 (150 mL) was treated with DBU (4.57 g, 30.0 mmol) at room temperature for 1 h. The reaction was quenched with HCl solution (0.12 N, 200 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with brine (3x200 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% EtOAc/hexane) gave **35** (3.98 g, 78%) as a clear, colorless oil. IR (KBr) v = 1659 (s), 1605 (s) cm^{-1}. MS *m/z* (%) = 204 (1, M^+), 172 (62), 145 (100), 117 (24). ^1H NMR ($CDCl_3$): δ = 1.86-1.95 (m, 2H), 2.74-2.79 (m, 2H), 3.34 (s, 3H), 3.38 (t, J = 6.2 Hz, 2H), 5.90 (dd, J = 10.6, 1.9 Hz, 1H), 6.43 (dd, J = 17.2, 1.6 Hz, 1H), 7.17 (dd, J = 16.9, 10.4 Hz, 1H), 7.30 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ = 30.8, 32.3, 58.5, 71.5, 128.7, 128.9, 129.7, 132.2, 135.0, 147.8, 190.4. Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.08; H, 8.01.

3-(3-(4-(3-Methoxypropyl)phenyl)-3-oxopropyl)indole **36**. A solution of **35** (3.06 g, 15.0 mmol) and indole **16** (7.03 g, 60.0 mmol) in CH_2Cl_2 (40 mL), HOAc (30 mL), and Ac_2O (10 mL) was refluxed for 6 h. The reaction mixture was concentrated, diluted with saturated aqueous $NaHCO_3$ solution (100 mL) and extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were washed with brine (2x50 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (30% EtOAc/hexane) gave **36** (3.48 g, 74%) as a white powder. M.p. = 82-84 °C. IR (nujol) v = 3262 (s), 1673 (s), 1607 (w) cm^{-1}. MS *m/z* (%) = 322 (7), 321 (30, M^+), 144 (79), 130 (100), 117 (18). ^1H NMR ($CDCl_3$): δ = 1.84-1.94 (m, 2H), 2.71-2.76 (m, 2H), 3.19-3.24 (m, 2H), 3.34 (s, 3H), 3.35-3.39 (m, 4H), 7.04 (d, J = 2.0 Hz, 1H), 7.10-7.27 (m, 4H), 7.35 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 8.00 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ = 19.7, 30.9, 32.3, 39.2, 58.6, 72.6, 111.1, 115.5, 118.7, 119.3, 121.6, 122.0, 127.2, 128.2, 128.7, 134.9, 136.3, 147.7, 199.6. Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.43; H, 7.13; N, 4.24.

3-(3-(4-(3-Methoxypropyl)phenyl)propyl)indole **37**. To a suspension of **36** (1.00 g, 3.11 mmol) in diethylene glycol (30 mL) were added freshly ground KOH (505 mg, 9.00 mmol) and hydrazine hydrate (85%, 1.5 mL). The reaction mixture was heated at 200 °C in a silicone oil bath for 6 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine (3x50 mL), dried with $MgSO_4$, filtered and concentrated. Column chromatography (25% EtOAc/hexane) gave **37** (831 mg, 87%) as a light yellow oil. IR (KBr) v = 3420 (s), 3314 (m), 1619 (w) cm^{-1}. MS *m/z* (%) = 308 (5), 307 (19, M^+), 131 (74), 130 (100), 117 (11). ^1H NMR ($CDCl_3$): δ = 1.83-1.92 (m, 2H), 1.97-2.08 (m, 2H), 2.62-2.70 (m, 4H), 2.76-2.81 (m, 2H), 3.33 (s, 3H), 3.38 (t, J = 6.4 Hz, 2H), 6.91 (d, J = 1.7 Hz, 1H), 7.06-7.19 (m, 6H), 7.30 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.90 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ = 24.7, 31.3, 31.7, 31.9, 35.3, 58.5, 72.0, 111.0, 116.5, 118.9, 119.0, 121.1, 121.8, 127.5, 128.3, 128.4, 136.3, 139.1, 139.9. Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.77; H, 8.23; N, 4.50.

3-Phenylpropyl 2,2-dimethylpropanoate **38**. To a solution of 3-phenyl-1-propanol **32** (13.6 g, 100 mmol) in CH_2Cl_2 (50 mL) and triethylamine (100 mL) at 0 °C was added dropwise a solution of pivaloyl chloride (13.3 g, 110 mmol) in CH_2Cl_2 (50 mL) over 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The solution was quenched with H_2O (40 mL) and extracted with EtOAc (3x100 mL). The combined organic layers were washed with HCl solution (1.2 N, 2x100 mL) and brine (2x100 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (5% EtOAc/petroleum ether) afforded **38** (21.2 g, 96%) as a clear, colorless liquid. IR (KBr) v = 1729 (s), 1604 (w) cm^{-1}. MS *m/z* (%) = 220 (1, M^+),

118 (100), 117 (42). ^{1}H NMR (CDCl$_3$): δ = 1.21 (s, 9H), 1.91-2.01 (m, 2H), 2.67-2.72 (m, 2H), 4.08 (t, J = 6.5 Hz, 2H), 7.17-7.32 (m, 5H). ^{13}C NMR (CDCl$_3$): δ = 27.2, 30.3, 32.1, 38.7, 63.5, 126.0, 128.4, 141.2, 178.5. Anal. Calcd. for C$_{14}$H$_{20}$O$_2$: C, 76.33; H, 9.15. Found: C, 76.40; H, 9.40.

3-(4-(3-Chloro-1-oxopropyl)phenyl)propyl 2,2-dimethylpropanoate **39**. To a suspension of AlCl$_3$ (20.5 g,154 mmol) in CH$_2$Cl$_2$ (250 mL) at 0 °C was injected 3-chloropropionyl chloride (16.3 g, 128 mmol). A solution of **38** (18.8 g, 85.3 mmol) in CH$_2$Cl$_2$ (100 mL) was added dropwise to the resulting stirred mixture. After stirring at room temperature for 7 h, the reaction mixture was poured into ice water (400 mL) containing HCl solution (12 N, 30 mL) and extracted with CH$_2$Cl$_2$ (2x100 mL). The combined organic layers were washed with brine (4x300 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (20% EtOAc/petroleum ether) gave **39** (22.8 g, 86%) as a clear, colorless oil. IR (KBr) ν = 1725 (s), 1685 (s), 1604 (m) cm^{-1}. MS *m/z* (%) = 313 (1), 311 (3, M$^+$), 208 (15), 145 (100). ^{1}H NMR (CDCl$_3$): δ = 1.22 (s, 9H), 1.94-2.03 (m, 2H), 2.74-2.79 (m, 2H), 3.44 (t, J = 6.7 Hz, 2H), 3.92 (t, J = 6.8 Hz, 2H), 4.08 (t, J = 6.3 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CDCl$_3$): δ = 27.2, 29.9, 32.2, 38.7, 41.2, 63.2, 128.3, 128.8, 134.5, 147.6, 178.5, 196.3. Anal. Calcd. for C$_{17}$H$_{23}$ClO$_3$: C, 65.69; H, 7.46. Found: C, 65.44; H, 7.59.

3-(4-(1-Oxo-2-propenyl)phenyl)propyl 2,2-dimethylpropanoate **40**. A solution of **39** (335 mg, 1.08 mmol) in CH$_2$Cl$_2$ (15 mL) was treated with DBU (182 mg, 1.20 mmol) at room temperature for 1 h. The reaction was quenched with HCl solution (0.12 N, 10 mL), diluted with H$_2$O (20 mL) and extracted with EtOAc (3x25 mL). The combined organic layers were washed with brine (2x30 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (20% EtOAc/petroleum ether) gave **40** (256 mg, 87%) as a slightly yellow oil. IR (KBr) ν = 1727 (s), 1670 (s), 1606 (s) cm^{-1}. MS *m/z* (%) = 274 (1, M$^+$), 172 (72), 145 (100), 117 (23). ^{1}H NMR (CDCl$_3$): δ = 1.22 (s, 9H), 1.95-2.04 (m, 2H), 2.74-2.79 (m, 2H), 4.09 (t, J = 6.6 Hz, 2H), 5.92 (dd, J = 10.2, 1.8 Hz, 1H), 6.44 (dd, J = 17.2, 1.9 Hz, 1H), 7.17 (dd, J = 17.3, 10.7 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.90 (8.6 Hz, 2H). ^{13}C NMR (CDCl$_3$): δ = 27.2, 29.9, 32.2, 38.8, 63.3, 128.7, 129.0, 129.9, 132.3, 135.3, 147.0, 178.5, 190.5. Anal. Calcd. for C$_{17}$H$_{22}$O$_3$: C, 74.42; H, 8.08. Found: C, 74.15; H, 8.08.

2-Methylene-1,5-bis(4-(3-(2,2-dimethylpropanoxy)propyl)phenyl)-1,5-dioxopentane **41**. A solution of **39** (9.50 g, 30.6 mmol) in CH$_2$Cl$_2$ (170 mL) was treated with DBU (5.63 g, 37.0 mmol) at room temperature for 12 h. The reaction was quenched with a mixture of H$_2$O (100 mL) and HCl solution (12 N, 6 mL), and extracted with CH$_2$Cl$_2$ (2x50 mL). The combined organic layers were washed with brine (2x100 mL), dried over MgSO$_4$, filtered and concentrated. Column chromatography (20% EtOAc/hexane) gave **41** (891 mg, 11%) as a light yellow oil. IR (KBr) ν = 1727 (s), 1684 (s), 1654 (s), 1608 (m) cm^{-1}. MS *m/z*(%) = 549 (6), 548 (15, M$^+$), 446 (16), 301 (38), 247 (47), 199 (14), 145 (65). ^{1}H NMR (CDCl$_3$): δ = 1.21 (s, 18H), 1.95-2.04 (m, 4H), 2.73-2.78 (m, 4H), 2.90 (t, J = 7.5 Hz, 2H), 3.21 (t, J = 7.3 Hz, 2H), 4.05-4.11 (m, 4H), 5.65 (s, 1H), 5.93 (s, 1H), 7.24-7.28 (m, 4H), 7.70 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CDCl$_3$): δ = 27.2, 27.5, 29.9, 32.1, 37.1, 38.7, 63.2, 126.4, 128.3, 128.3, 128.6, 129.9, 134.8, 135.6, 146.2, 146.8, 146.9, 178.4, 197.7, 198.8. Anal. Calcd. for C$_{34}$H$_{44}$O$_6$: C, 74.42; H, 8.08. Found: C, 74.25; H, 8.36.

3-(4-(3-(3-Indolyl)-1-oxopropyl)phenyl)propyl 2,2-dimethylpropanoate **42**. A solution of **40** (8.51 g, 31.0 mmol) and indole **16** (4.45 g, 38.0 mmol) in CH$_2$Cl$_2$ (100 mL), HOAc (120 mL), and Ac$_2$O (40 mL) was reflux for 2 d. The reaction mixture was concentrated, diluted with saturated aqueous NaHCO$_3$ solution (200 mL),

and extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (2x50 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% EtOAc/petroleum ether) gave **42** (11.1 g, 91%) as a light yellow solid. M.p. = 53-55 °C. IR (nujol) ν = 3436 (s), 1721 (s), 1673 (s), 1602 (m) cm^{-1}. MS m/z (%) = 392 (7), 391 (27, M$^+$), 145 (34), 144 (59), 130 (100), 117 (13). ^{1}H NMR (CDCl$_3$): δ = 1.21 (s, 9H), 1.92-2.03 (m, 2H), 2.71-2.76 (m, 2H), 3.19-3.24 (m, 2H), 3.34-3.39 (m, 2H), 4.06 (t, J = 6.6 Hz, 2H), 7.03 (d, J = 1.8 Hz, 1H), 7.10-7.22 (m, 2H), 7.24 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 7.7 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 8.6 Hz, 2H), 8.04 (bs, 1H). ^{13}C NMR (CDCl$_3$): δ = 19.8, 27.2, 29.9, 32.2, 38.8, 39.3, 63.3, 111.2, 115.4, 118.7, 119.3, 121.6, 122.0, 127.2, 128.4, 128.6, 135.1, 136.3, 146.8, 178.6, 199.6. Anal. Calcd. for $C_{25}H_{29}NO_3$: C, 76.70; H, 7.47; N, 3.58. Found: C, 76.76; H, 7.67; N, 3.58.

3-(4-(3-(3-Indolyl)-1-oxopropyl)phenyl)propan-1-ol **43**. To a suspension of **42** (10.3 g, 26.3 mmol) in diethylene glycol (200 mL) were added potassium *tert*-butoxide (8.87 g, 79.0 mmol) and hydrazine hydrate (85%, 15 mL). The reaction mixture was heated at 200 °C in a silicone oil bath for 2 d. The reaction mixture was diluted with H_2O (100 mL), and extracted with EtOAc (4x100 mL). The combined organic layers were washed with brine (2x100 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (50% EtOAc/petroleum ether) gave **43** (5.94 g, 77%) as a light yellow solid. M.p. = 42-44 °C. IR (nujol) ν = 3385 (s), 3242 (m), 1616 (w) cm^{-1}. MS m/z (%) = 294 (3), 293 (12, M$^+$), 131 (49), 130 (72), 87 (55). ^{1}H NMR (CDCl$_3$): δ = 1.35 (bs, 1H), 1.82-1.92 (m, 2H), 1.98-2.08 (m, 2H), 2.64-2.70 (m, 4H), 2.76-2.81 (m, 2H), 3.66 (t, J = 6.6 Hz, 2H), 6.95 (d, J = 1.9 Hz, 1H), 7.07-7.22 (m, 6H), 7.33 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.91 (bs, 1H). ^{13}C NMR (CDCl$_3$): δ = 24.7, 31.6, 31.7, 34.2, 35.3, 62.3, 111.0, 116.5, 118.9, 119.0, 121.1, 121.8, 127.5, 128.3, 128.5, 136.3, 139.0, 140.0. Anal. Calcd. for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.74; H, 8.15; N, 4.76.

3-(3-(4-(3-Bromopropyl)phenyl)propyl)indole **27**. Method A. To a solution of **37** (587 mg, 1.91 mmol) in CH_2Cl_2 (30 mL) at 0 °C was injected dropwise BBr$_3$ (1.0 M in CH_2Cl_2, 5.7 mL). The reaction mixture was then stirred at room temperature for 4 h. The reaction mixture was quenched with H_2O (5 mL) and extracted with diethyl ether (4x100 mL). The combined organic layers were washed with brine (2x50 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (15% EtOAc/petroleum ether) gave **27** (224 mg, 33%) as a white solid. M.p. = 44-45 °C. IR (nujol) ν = 3421 (s), 1618 (w) cm^{-1}. MS m/z (%) = 357 (8), 355 (8, M$^+$ ^{79}Br), 131 (77), 130 (100), 117 (10). ^{1}H NMR (CDCl$_3$): δ = 1.98-2.18 (m, 4H), 2.65-2.81 (m, 6H), 3.38 (t, J = 6.7 Hz, 2H), 6.95 (d, J = 1.9 Hz, 1H), 7.07-7.22 (m, 6H), 7.33 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.84 (bs, 1H). ^{13}C NMR (CDCl$_3$): δ = 24.7, 31.7, 33.3, 33.5, 34.2, 35.3, 111.0, 116.5, 119.0, 119.0, 121.1, 121.8, 127.5, 128.4, 128.5, 136.3, 137.8, 140.3. Anal. Calcd. for $C_{20}H_{22}BrN$: C, 67.42; H, 6.22; N, 3.93. Found: C, 67.65; H, 6.39; N, 3.94.

Method B. To a solution of **43** (1.76 g, 6.00 mmol) and triphenylphosphine (1.89 g, 7.21 mmol) in DMF (60 mL) at 20 °C was added dropwise a solution of *N*-bromosuccinimide (1.28 g, 7.19 mmol) in DMF (30 mL). The resulting solution was warmed to 50 °C for 40 min and then stirred at room temperature for 24 h. The reaction mixture was quenched with methanol (10 mL), diluted with H_2O (100 mL) and extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (15% EtOAc/petroleum ether) gave **27** (1.98 g, 91%) as a white solid.

[3]Paracyclo[3](1,3)indolophane **5** *and [3]paracyclo[3](1,3)indolo[3]paracyclo[3](1,3)indolophane* **44**. To a refluxing suspension of NaH (60% dispersion in mineral oil, 292 mg, 7.30 mmol) in anhydrous THF (200 mL) was injected by a syringe pump a solution of **27** (260 mg, 0.730 mmol) in THF (50 mL) over 20 h. The resulting mixture was further refluxed for 1 h. The reaction mixture was quenched with H_2O (4 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with brine (2x50 mL), dried over $MgSO_4$, filtered and concentrated carefully. Column chromatography (5% EtOAc/petroleum ether) gave **5** (99 mg, 49%) and **44** (38 mg, 19%), both as white crystals. **5**: M.p. = 64-66 °C. IR (nujol) v = 1612 (w) cm^{-1}. MS m/z (%) = 276 (23), 275 (100, M$^+$), 157 (24), 145 (43), 144 (74). ^1H NMR (CDCl$_3$): δ = 2.07-2.21 (m, 4H), 2.55-2.58 (m, 2H), 2.71-2.75 (m, 2H), 2.79-2.83 (m, 2H), 3.98-4.01 (m, 2H), 5.59 (s, 1H), 6.57 (d, 2H, J = 6.8 Hz), 6.65 (d, 2H, J = 7.4 Hz), 6.99-7.18 (m, 3H), 7.48 (d, J = 7.5 Hz, 1H). ^{13}C NMR (CDCl$_3$): δ = 24.4, 27.5, 28.1, 35.0, 36.1, 46.7, 109.4, 113.4, 117.7, 119.1, 120.1, 126.4, 127.2, 127.6, 128.8, 133.9, 137.5, 139.5. Anal. Calcd. for $C_{20}H_{21}N$: C, 87.23; H, 7.69; N, 5.09. Found: C, 87.13; H, 7.83; N, 5.07. **44**: M.p. = 173-175 °C. MS m/z (%) = 551 (14), 550 (32, M$^+$), 275 (39), 145 (22), 144 (57). ^1H NMR (CDCl$_3$): δ = 2.01-2.11 (m, 4H), 2.14-2.24 (m, 4H), 2.54 (t, J = 6.6 Hz, 4H), 2.65-2.70 (m, 4H), 2.77 (t, J = 7.1 Hz, 4H), 4.03 (t, J = 6.6 Hz, 4H), 6.70 (s, 2H), 7.07-7.24 (m, 12H), 7.36 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 7.7 Hz, 2H). ^{13}C NMR (CDCl$_3$): δ = 23.8, 29.7, 30.6, 31.5, 34.5, 44.5, 109.4, 114.4, 118.5, 119.1, 121.2, 125.9, 128.3, 128.6, 128.7, 136.3, 137.9, 140.4. Anal. Calcd. for $C_{40}H_{42}N_2$: C, 87.23; H, 7.69; N, 5.09. Found: C, 87.01; H, 7.71; N, 5.02.

Crystal Structure Determination of **5**: colorless irregular crystal (0.30 x 0.25 x 0.40 mm) from methanol, $C_{20}H_{21}N$, M = 275.39, monoclinic, C2/c (#15), Z = 8, a = 16.729(2), b = 10.208(2), c = 19.902(2) Å, β = 113.601(7), V = 3115.3(7) Å^3, D$_c$ = 1.174 g cm^{-3}, F(000) = 1184, μ(Cu-Kα) = 5.10 cm^{-1}. Data collection with a Rigaku AFC6S diffractometer 26 °C with graphite monochromated Cu-Kα radiation (λ = 1.54178 Å), ω-2θ scan type with ω scan width = 1.42 + 0.14 tan θ, ω scan speed 8.0° min^{-1} (up to 5 rescans for weak reflections), 2569 reflections measured, 2470 unique (R$_{int}$ = 0.013), Lorentz-polarization, empirical absorbtion (max., min. corrections = 1.00, 0.95) and secondary extinction (coefficient: 1.46717 x 10^{-6}) corrections, giving 1877 with I > 2σ(I). Solution and refinement by direct methods (SIR92) using the teXsan package of the Molecular Structure Corporation; all non-hydrogen atoms were refined anisotropically; full matrix least squares refinement with 191 variable parameters led to R = 0.058 and R_w = 0.059, GOF = 3.46.

Crystal Structure Determination of **44**: colorless irregular crystal (0.15 x 0.15 x 0.45 mm) from heptane, $C_{40}H_{42}N_2$, M = 550.79, monoclinic, P2$_1$/c (#14), Z = 2, a = 15.426(2), b = 5.384(2), c = 20.049(1) Å, β = 111.592(7), V = 1548.4(5) Å^3, D$_c$ = 1.181 g cm^{-3}, F(000) = 592, μ (Cu-Kα) = 5.13 cm^{-1}. Data collection with a Rigaku AFC6S diffractometer at 26 °C with graphite monochromated Cu-Kα radiation (λ = 1.54178 Å), ω-2θ scan type with ω scan width = 1.31 + 0.14 tan θ, ω scan speed 8.0° min^{-1} (up to 10 rescans for weak reflections), 2683 reflections measured, 2579 unique (R$_{int}$ = 0.034), Lorentz-polarization and secondary extinction (coefficient: 1.13855 x 10^{-6}) corrections, giving 1413 with I > 2σ(I). Solution and refinement by direct methods (SIR92) using the teXsan package of the Molecular Structure Corporation; all non-hydrogen atoms were refined anisotropically; full matrix least squares refinement with 254 variable parameters led to R = 0.053 and R_w = 0.052, GOF = 2.32.

References and Notes

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6. There are many naturally occurring indole alkaloids as well as non-natural indole-based compounds that feature aliphatic rings fused to the indole nucleus. Although such compounds technically fit the definition of a cyclophane, we consider these to be outside the scope of the current investigation. This blanket omission is directly analogous to that of many orthocyclophanes from the benzenoid family. For example [2]-, [3]-, [4]- and [5]orthocyclophane are not normally viewed as cyclophanes, but rather as benzocyclobutene, indan, 1,2,3,4-tetrahydronaphthalene and benzocycloheptene, respectively. This is not to say, however, that the ortho mode of bridge attachment necessarily disqualifies a compound from being a cyclophane. See for example: (a) Bodwell, G. J. *Dissertation* **1989**, TU Braunschweig. (b) Bodwell, G. J.; Ernst, L.; Haenel, M.; Hopf, H. *Angew. Chem.* **1989**, *101*, 509-510; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 455. (c) Bodwell, G. J.; Ernst., L.; Hopf., H. *Chem. Ber.* **1989**, *122*, 1013-1016. (d) Bodwell, G. J.; Ernst, L.; Hopf, H.; Jones, P. G. *Tetrahedron Lett.* **1989**, *30*, 6005-6008. (e) Jones, P. G.; Bodwell, G. J.; Hopf, H. *Z. Naturforsch.* **1990**, *45B*, 1213-1215. (f) Bodwell, G. J.; Ernst, L.; Hopf, H.; Jones, P. G.; McNally, J. P.; Schomburg, D. *Chem. Ber.* **1990**, *123*, 2381-2386. (g) Tobe, Y.; Kawaguchi, M.; Kakiuchi, K. *J. Am. Chem. Soc.* **1993**, *115*, 1173-1174.

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