Cyclization Strategies for the Synthesis of Macrocyclic Bisindolylmaleimides

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Three new approaches to the synthesis of macrocyclic bisindolylmaleimides **1**−**4** have been identified. Two strategies afford **8**, the penultimate intermediate for the synthesis of **1**−**4**, in 73% and 32% yield by intramolecular cyclization of **31** and **40**, respectively. The optimum synthesis of **1** was achieved in nine steps and 15% yield by intramolecular formation of the macrocycle and maleimide in one step by reaction of the sodium indolate of **12** with methyl indole-3-glyoxylate **47**. The mechanism of this reaction has been elucidated, using the trityl-protected derivative, to involve initial formation of the tricarbonyl imide **48**, followed by irreversible alkylation of the indole nitrogen to generate the 17-membered macrocycle **49**. Cyclization of **49** to hydroxymaleimide **50** and subsequent dehydration afforded **8a**. This approach eliminated the problem of dimerization observed in the intramolecular cyclization reactions.

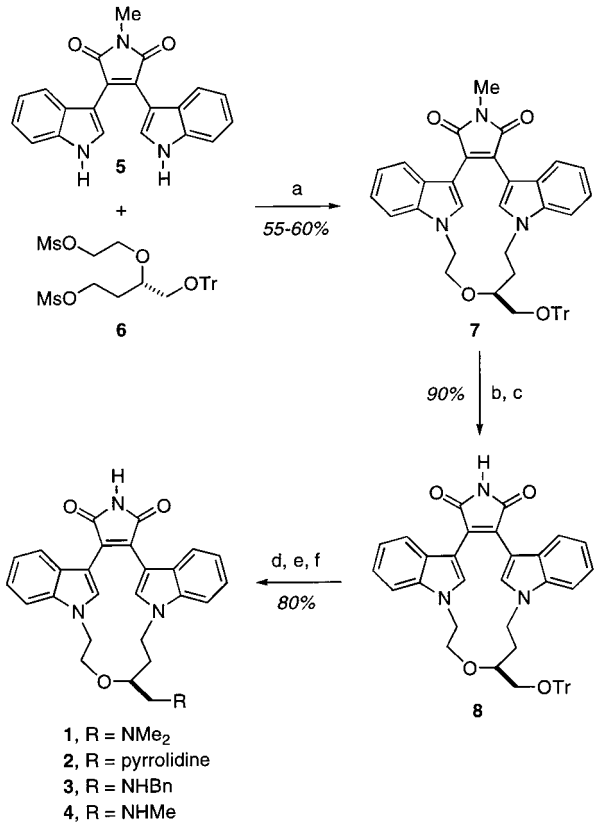
Introduction

Macrocyclic bisindolylmaleimides **1**−**4** have been identified as competitive reversible inhibitors of PKCβ and **1** is currently under development as a treatment of retinopathy associated with diabetic complications.[1] We have previously reported a synthesis of **1** in 13 steps, 14% overall yield, by intermolecular cyclization of bisindolylmaleimide **5** with alkylating agent **6** (Scheme 1).[2] However, this route presents a number of challenges: (i) synthesis of **5** required two steps and proceeded in only 53% yield from dichloromaleic anhydride, an expensive starting material; (ii) the key intermolecular cyclization, performed by slow addition of **6** to a dilute (0.029 M) solution of **5** in DMF afforded **7** in only 55−60% yield; and (iii) use of the N-Me-protected maleimide **7** required a two-step hydrolysis/ammonolysis sequence to prepare **8**, the penultimate intermediate in the synthesis of **1**−**4**. To overcome these issues and determine a more efficient route to prepare **1**−**4**, alternative syntheses were evaluated. This paper describes the first full disclosure of our work that has resulted in identification of three new cyclization strategies to prepare this class of compounds.

Results and Discussion

We recently reported a new method for the synthesis of symmetrical and unsymmetrical bisindolylmaleimides by reaction of an indole-3-acetamide and a methyl indole-3-glyoxylate in the presence of *tert*-BuOK.[3] This reaction has proven to be extremely efficient and versatile.[4,5] Application of this methodology to the synthesis of macrocyclic bisindolylmaleimides **1**−**4** allowed us to propose three new retrosynthetic approaches to this class

Scheme 1[a]



[a] (a) Cs_2CO_3, DMF, syringe pump addition, 100 °C; (b) 10 N KOH/EtOH; (c) NH_4OH, THF; (d) 6 N HCl, EtOH; (e) Ms_2O, pyridine, CH_2Cl_2; (f) amine (Me_2NH for **1**, pyrrolidine for **2**, $BnNH_2$ for **3**, $MeNH_2$ for **4**), DMF or DMA.

(1) Jirousek, M. R.; Gillig, J. R.; Heath, W. F.; Johnston, C. M.; McDonald, J. H., III; Neel, D. A.; Rito, C. J.; Singh, U.; Stramm, L. E.; Melikian-Badalian, A.; Baevsky, M.; Ballas, L. M.; Hall, S. E.; Faul, M. M.; Winneroski, L. L. *J. Med. Chem.* **1996**, *39*, 2664.

(2) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A.; Sullivan, K. A.; Gillig, J. R.; Neel, D. A.; Rito, C. J.; Jirousek, M. R. *J. Org. Chem.* **1998**, *63*, 1961.

(3) (a) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053. (b) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *Tetrahedron Lett.* **1999**, *40*, 1109.

(4) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1999**, *64*, 2465.

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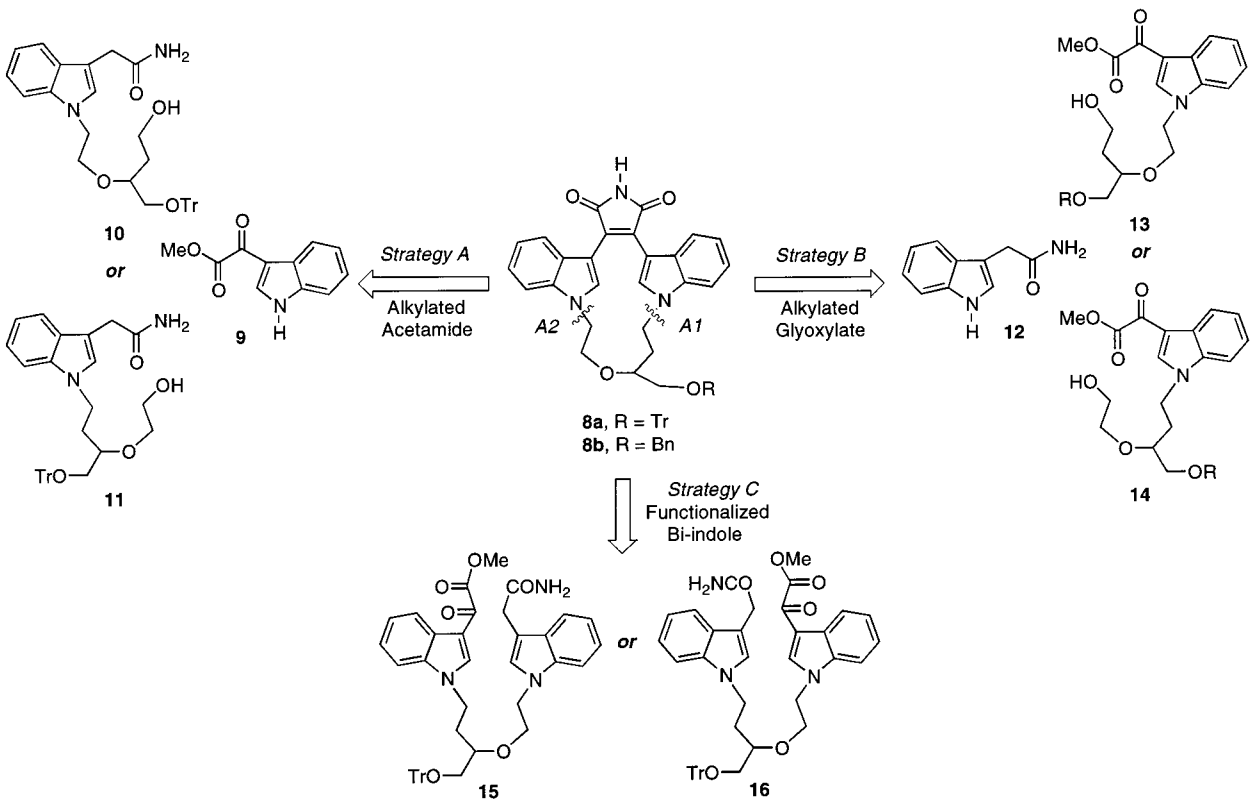
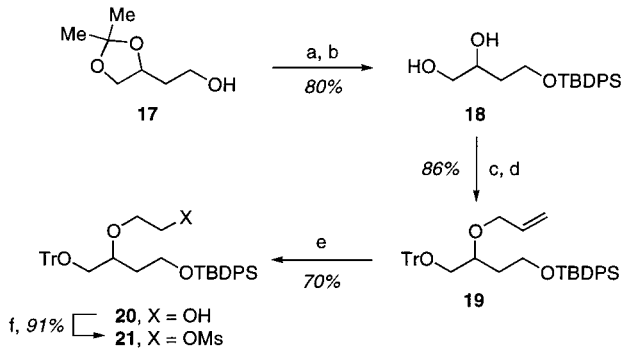
Scheme 2



of compounds (Scheme 2). Since the six-atom linker present in **8** is unsymmetrical two approaches can be represented for each strategy, depending upon on whether disconnection of the indole−carbon bond occurs at the three-carbon (A1) or carbon−ether (A2) side of **8**. Therefore, it was envisioned that **8** could be obtained (i) by reaction of alkylated indole-3-acetamides **10** or **11** with methyl indole-3-glyoxylate **9** (*Strategy A*); (ii) by the reverse sequence, involving reaction of alkylated methyl indole-3-glyoxylates **13** or **14** with indole-3-acetamide **12** (*Strategy B*); or (iii) by intramolecular formation of the maleimide ring via the functionalized bi-indoles **15** or **16** (*Strategy C*). Each of these synthetic strategies has been evaluated in racemic form, and the results are outlined below.

Strategy A. In developing the most efficient synthesis of **8**, selection of indole-3-acetamide **10** or **11** was dependent upon their ease of synthesis. The alkylating agent required for the synthesis of **10** was prepared, as previously described, using racemic malic acid (Scheme 3).[2] *O*-Silylation of 1,2,4-triol acetonide **17**,[6] derived from malic acid, with TBDPSCl and DMAP (10 mol %), followed by cleavage of the acetonide with *p*-TsOH in methanol, afforded diol **18** in 80% yield.[7] Selective protection of the primary alcohol using TrCl/Et_3N in CH_2Cl_2, followed by allylation with allyl-Br and NaH, afforded **19** in 86% yield. Ozonolysis/$NaBH_4$ reduction of olefin **19** and mesylation of alcohol **20** afforded alkylating agent **21**, required for the synthesis of **10**, in six steps and 44% overall yield.

Scheme 3[a]



[a] (a) TBDPSCl, 10 mol % DMAP, Et_3N, CH_2Cl_2; (b) *p*-TsOH, MeOH; (c) TrCl, Et_3N, CH_2Cl_2; (d) NaH, allyl-Br, THF, 45 °C; (e) O_3/$NaBH_4$, CH_2Cl_2:MeOH 1:1, −50 °C; (f) MsCl, Et_3N, CH_2Cl_2.

Alkylating agent **25**, required for preparation of **11**, was derived from glycidol **22** (Scheme 4). Tritylation of **22**, under standard conditions, followed by regioselective opening of the epoxide with vinyl-MgBr and 5 mol % CuI afforded **23** in 84% yield. Alkylation of **23** with *tert*-butyl bromoacetate and $LiAlH_4$ reduction of the ester gave a 33% yield of **24**. Protection of the primary alcohol with TBDPSCl/imidazole, ozonolysis/$NaBH_4$ reduction of the olefin, and mesylation provided **25** in seven steps and 13% overall yield. The lower yield for the synthesis of alkylating agent **25** relative to **21** led us to continue our evaluation of strategy A using **21**.

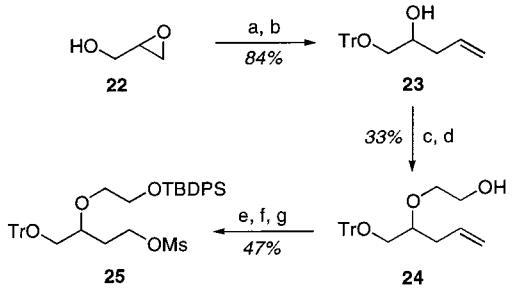
Alkylation of indole-3-acetamide **12** with **21** using NaH in DMF, followed by in-situ desilylation of **26** with TBAF/THF afforded acetamide **10** in 57% yield (Scheme 5).

(5) This reaction was identified independently and applied successfully to the synthesis of the Didemnimides: (a) Piers, E.; Britton, R.; Andersen, R. J. *J. Org. Chem.* **2000**, *65*, 530. (b) Berlinck, R. G. S.; Britton, R.; Piers, E.; Lim, L.; Roberge, M.; Moreira da Rocha, R.; Andersen, R. J. *J. Org. Chem.* **1998**, *63*, 9850.

(6) Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933.

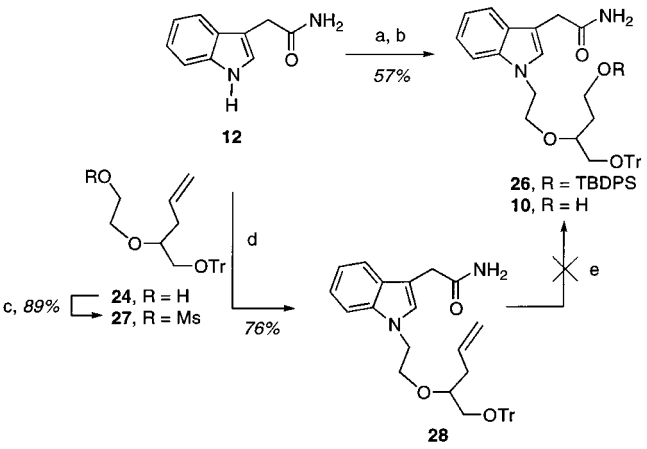
(7) (a) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 793. (b) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1383. (c) Achmatowicz, B.; Kabat, M. M.; Krajewski, J.; Wicha, J. *Tetrahedron* **1992**, *48*, 10201.

Scheme 4[a]



[a] (a) TrCl, Et_3N, CH_2Cl_2; (b) vinyl-MgBr, 5 mol % CuI, −30 °C, THF; (c) $BrCH_2CO_2$-*t*-Bu, NaH, THF; (d) $LiAlH_4$, Et_2O; (e) TBDPSCl, imidazole, CH_2Cl_2; (f) $O_3/NaBH_4$, CH_2Cl_2:MeOH 1:1, −50 °C; (g) MsCl, Et_3N, CH_2Cl_2.

Scheme 5[a]



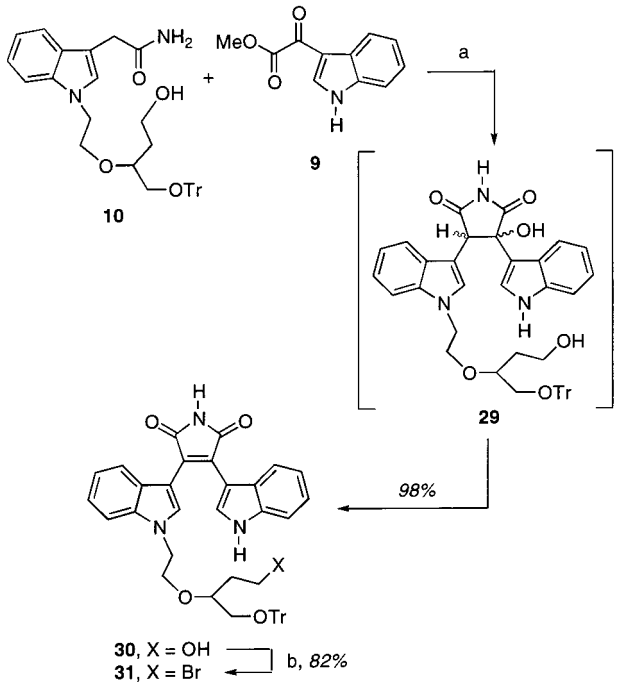
[a] (a) NaH, DMF, **21**; (b) TBAF, THF; (c) Ms_2O, pyridine, CH_2Cl_2; (d) NaH, DMF; (d) $O_3/NaBH_4$, CH_2Cl_2:MeOH 1:1, −50 °C.

Attempts to improve the yield of **10** were unsuccessful. Alternatively, alkylation of **12** with mesylate **27** followed by ozonolysis/$NaBH_4$ reduction of the olefin were unsuccessful due to the competitive reactivity of the indole ring.

Reaction of acetamide **10** with methyl indole-3-glyoxylate **9** using *tert*-BuOK in THF afforded bisindolylmaleimide **30** in 98% yield (Scheme 6). Bromination of alcohol **30** with $Br_2/P(OPh)_3$ and pyridine afforded **31** in 82% yield. The corresponding mesylate was also prepared but was unstable at room temperature.

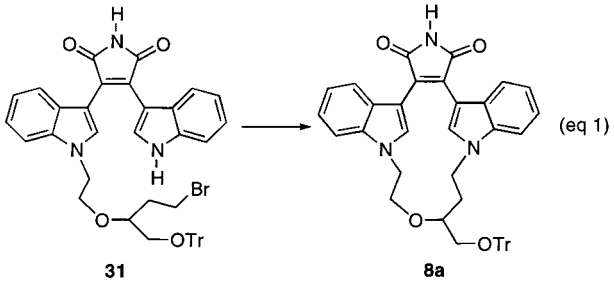
A variety of solvents and bases were examined for intramolecular cyclization of bromide **31** to **8a** (eq 1, Table 1). Due to the potential for dimer formation from competing intermolecular alkylation at the maleimide and indole nitrogens, all reactions were performed at high dilution (0.003M). Cs_2CO_3 and K_2CO_3, proved to be the optimal bases affording **8a** in 73% and 71% yield, respectively, with <7% formation of dimer **32** generated by alkylation of the maleimide nitrogen of **8** (entries 1 and 2, Figure 1). Other bases (Na_2CO_3, NaH, *tert*-BuOK, and NaOH) afforded lower yields of **8** (40−65%) (entries 3−6). DMF proved to be the optimal solvent. THF, acetone, and acetonitrile were examined but gave no reaction. However, when combined with DMF, cyclization to **8a** was achieved albiet in lower yield (44−50%) and with increased formation of **32** (10−19%) (entries 7−9). Interestingly no dimer due to intermolecular alkylation of the indole nitrogen was observed. Conversion of **8a** to **1** was achieved using the conditions previously reported (Scheme 1).[2]

Scheme 6[a]



[a] (a) *tert*-BuOK, THF; (b) $Br_2/P(OPh)_3$, pyridine, CH_2Cl_2, −20 °C.

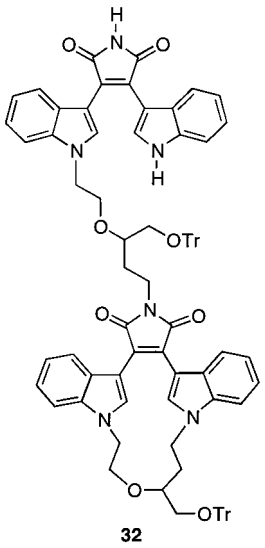
Table 1. Solvents and Bases Examined for Formation of 8a by Intramolecular Cyclization of 31 (eq 1)



entry	solvent[a]	base	% yield, **8a**[b]	% yield, **32**[c]
1	DMF	Cs_2CO_3	73	4
2	DMF	K_2CO_3	71	7
3	DMF	Na_2CO_3	40	8
4	DMF	NaH	65	10
5	DMF	*tert*-BuOK	51	7
6	DMF	NaOH	53	8
7	DMF/THF	Cs_2CO_3	50	10
8	DMF/ACN	Cs_2CO_3	45	17
9	DMF/acetone	Cs_2CO_3	44	19

[a] All reactions were performed by syringe pump addition of **31** into a slurry of base (1.0 equiv) in the indicated solvent at 100 °C unless otherwise indicated. [b] Yield of **8a** after chromatographic purification. [c] Determined by HPLC.

The completion of the synthesis of **8a** afforded a new approach for preparation of macrocyclic bisindolylmaleimide **1** in 13 steps and 15% overall yield from 1,2,4-butanetriol acetonide **17**. This strategy successfully demonstrates the application of our bisindolylmaleimide technology to the synthesis of highly functionalized unsymmetrical bisindolylmaleimides, as exemplified by **30**, and ultimately to the synthesis of **1**. However, the overall yield of **1** obtained by this approach is comparable to that previously reported via the intermolecular cyclization reaction. Therefore, as we evaluated strategy B, we sought



32

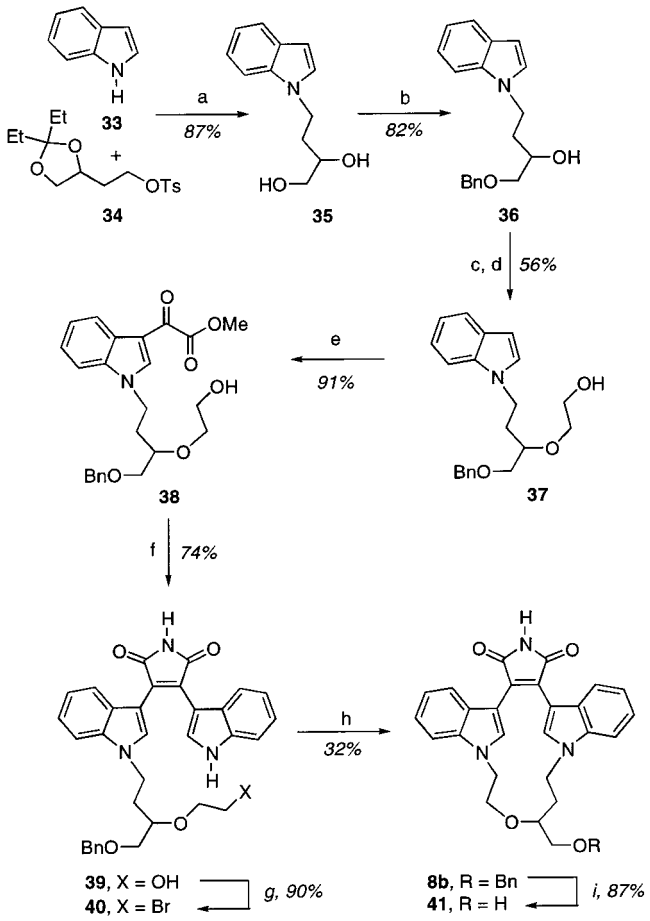
Figure 1.

to improve this synthesis by determining a more efficient method for preparation of alkylating agent **21** that would minimize the need for multiple protecting groups.

Strategy B. During our previous mechanistic work on the reaction of an unsubstituted indole-3-acetamide with an alkylated methyl indole-3-glyoxylate in the presence of *tert*-BuOK, we determined that acidic conditions were required to generate the maleimide from an intermediate hydroxymaleimide. Therefore, to evaluate strategy B, involving reaction of an alkylated methyl indole-3-glyoxylate **13** or **14** with indole-3-acetamide **12**, we decided to exchange the trityl protecting group for the acid-stable benzyl protecting group. In addition, to overcome the problems identified in strategy A (vide supra) we believed that it would be more efficient to build the linker directly on indole prior to glyoxylation.

Alkylation of indole **33** with tosylate **34** derived from 1,2,4-butanetriol acetonide using NaH in DMF, followed by in-situ deketalization, afforded diol **35** in 87% yield. Selective benzylation of the primary alcohol using Bu_2SnO/BnBr with CsF proceeded smoothly to provide **36** in 82% yield.[8] Deprotonation of **36** with NaH in THF using HMPA (1.1 equiv) followed by alkylation with *tert*-butylbromoacetate provided the corresponding ester, that was reduced with $LiBH_4$ to furnish alcohol **37** in 56% overall yield. In the absence of HMPA the yield of ester was only 33%. All attempts to improve the yield of the alkylation reaction using alternative bases and solvents were unsuccessful. Reaction of **37** with $(COCl)_2$/NaOMe in THF afforded glyoxylate **38** in 91% yield. Despite the low yield in the alkylation step this approach provided an efficient five-step synthesis of the carbon-linked glyoxylate in 36% overall yield. Reaction of glyoxylate **38** with indole-3-acetamide **12** in the presence of *tert*-BuOK, followed by dehydration of the intermediate hydroxymaleimide with concentrated HCl, afforded the benzyl protected bisindolylmaleimide **39** in 74% yield. Bromination of **39** with $Br_2/P(OPh)_3$ gave **40** in 90% yield. Finally, intramolecular cyclization of **40**, using the conditions identified in strategy A (Cs_2CO_3 (1 equiv), DMF (0.003 M), 100 °C, 6 h syringe pump addition) afforded macrocycle **8b** in only 32% yield. In addition to **8b**, a 17% yield of **42** from alkylation of the maleimide nitrogen of **8b**, and a 24% yield of **43** arising from alkylation of the indole nitrogen of **40** were obtained (Figure 2).[9] Debenzylation of **8b** using TMSI in CH_2Cl_2 at 0 °C afforded alcohol **41** in 87% yield. Mesylation of **42**, followed by displacement with Me_2NH, completed a new 10-step synthesis of **1** in 6% overall yield from indole.

Scheme 7[a]



[a] (a) (i) NaH, DMF; (ii) H_3O^+; (b) Bu_2SnO, BnBr, CsF, THF; (c) $BrCH_2CO_2$-*t*-Bu, NaH, HMPA, THF; (d) $LiBH_4$, THF/EtOH; (e) (i) $(COCl)_2$, Et_2O, rt; (ii) NaOMe, MeOH; (f) (i) *tert*-BuOK, THF, **12**; (ii) concentrated HCl; (g) Br_2, $P(OPh)_3$, CH_2Cl_2; (h) Cs_2CO_3 (1 equiv), DMF (200 vol equiv), 100 °C, 6 h syringe pump addition; (I) (i) TMSI, CH_2Cl_2, 0 °C. (ii) TBAF, THF.

Although the overall yield for strategy B was low, the results obtained for intramolecular cyclization of **40** were unexpected and appeared to indicate that the yield of this reaction was dependent on both the size of the ether protecting group and mode of cyclization (A1 vs A2, Scheme 2). Support for this hypothesis was obtained by comparison of the yield obtained upon intramolecular cyclization of three substrates **31**, **44**, and **40** under the standard conditions (Cs_2CO_3 (1 equiv), DMF (0.003 M), 100 °C, 6 h syringe pump addition) (Figure 3). Cyclization of bisindolylmaleimide **31**, trityl protecting group/A1 mode of cyclization, afforded **8a** in 73% yield with 4% dimer **32**. In contrast, using **44**, trityl protecting group/A2 mode of cyclization, the yield of **8a** decreased to 58%,

(8) Ohno, M. *Chem. Pharm. Bull.* **1991**, *39*, 1972.

(9) Complete characterization of **42** and **43** proved difficult. The structures were assigned based upon ^{1}H NMR data. Dimer **42** was identified by the presence of the maleimide-NH and the macrocylcic ring. The presence of two maleimide protons and two bisindolylmaleimide supported structure **43** for the second dimer.

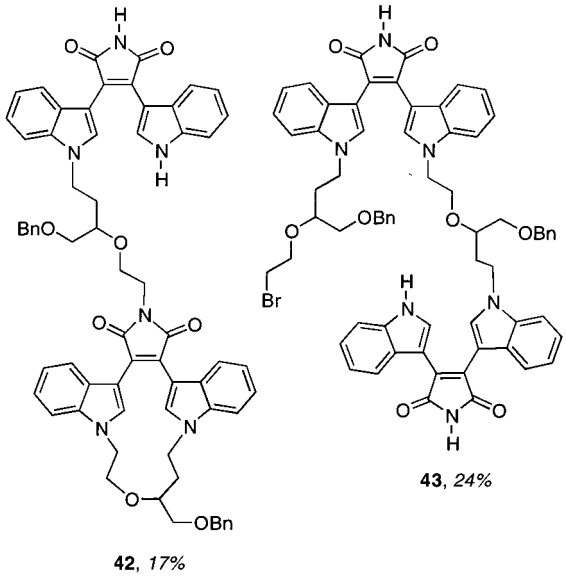


Figure 2.

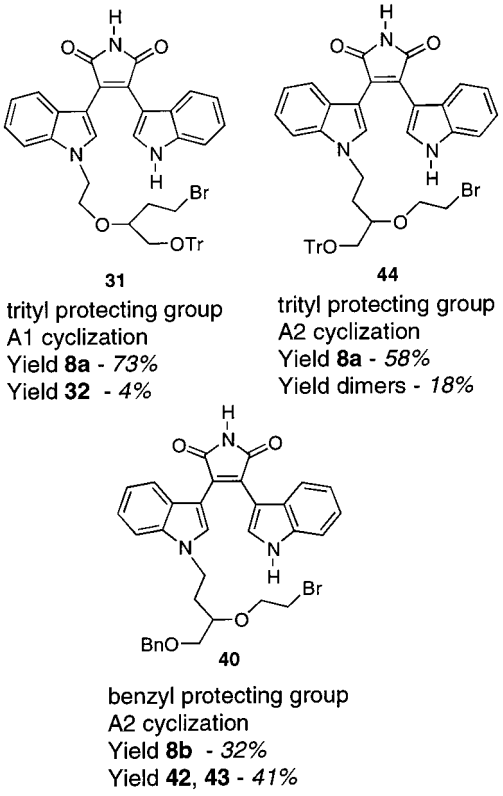
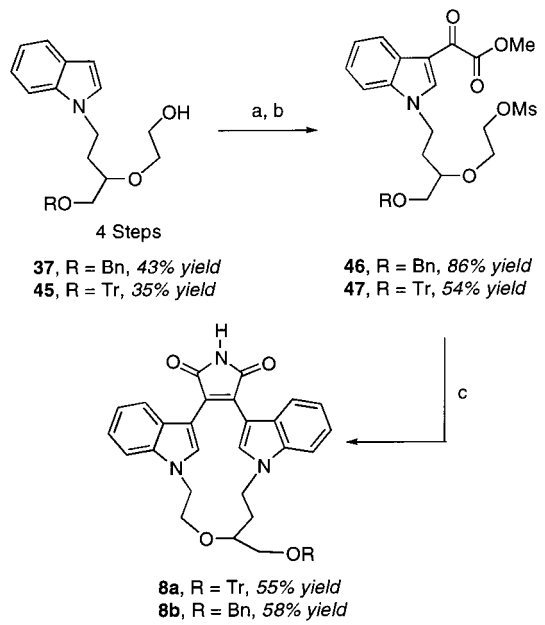


Figure 3.

while dimer formation increased to 18%, supporting the hypothesis that final formation of the indole−carbon bond A1 is favored over A2. Finally, using bisindolylmaleimide **40**, benzyl protecting group/A2 mode of cyclization, macrocycle **8b** was isolated in only 32% yield with 41% formation of dimers **42** and **43**, confirming that the choice of protecting group was also critical for a successful reaction.

Strategy C. The final approach to synthesis of **8** involved intramolecular formation of the maleimide ring and the 14-membered macrocycle in one step via functionalized bi-indoles **15** or **16**. In comparison to strategies A and B, it was expected that formation of the macrocycle

Scheme 8[a]



[a] (a)Ms_2O, pyridine, THF; (b) (i) $(COCl)_2$, Et_2O, rt; (ii) NaOMe, MeOH; (c) NaH (3.3 equiv), **12**, DMF (20 vol equiv), 0 °C.

via strategy C would be independent of protecting group and mode of cyclization.

Mesylation of the benzyl-protected alcohol **37** using Ms_2O/pyridine in THF, followed by glyoxylation under standard conditions, afforded **46** in 86% yield. A similar procedure was employed to prepare the trityl-protected derivative **47** in six steps and 20% overall yield from indole.

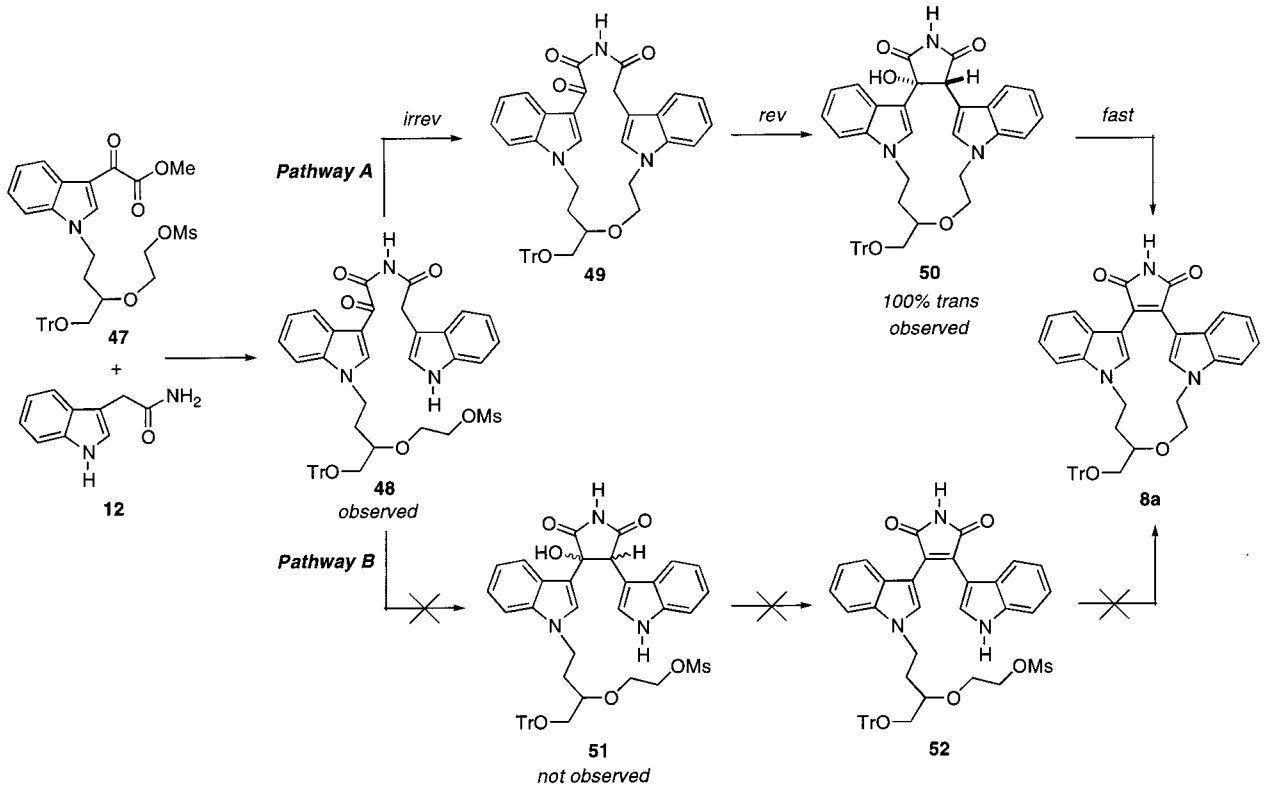
It was expected that **15** would be prepared upon alkylation of the sodium salt of indole-3-acetamide **12** with **46** or **47** in DMF. However, to our delight, upon treatment of the sodium indolate derived from **12** with glyoxylates **46** and **47** in DMF, macrocycles **8a** and **8b** were obtained in 55% and 58% yield, respectively (Scheme 8).

In contrast to the conditions employed in the intramolecular cyclization reactions described in strategies A and B (Cs_2CO_3 (1 equiv), DMF (0.0025 M), 100 °C, 6 h syringe pump addition), reaction of the sodium salt of **12** with **46** and **47** was performed at high concentrations (0.13 M) and was complete after 2 h at 0 °C with both substrates present in the reaction vessel. Successful formation of **8** in good yield under these conditions encouraged us to explore the mechanism of this reaction.

Two intermediates were observed by HPLC upon reaction of **12** with either **46** or **47**. In an attempt to isolate these intermediates **12** was treated with NaH (1.1 equiv) in DMF prior to reaction with **47** to minimize conversion to **8a**. As outlined in our retrosynthetic analysis, we believed the first step of the reaction would be alkylation of the indole nitrogen of **12**. However, the first reaction intermediate was identified as tricarbonyl **48**.[10] The second reaction intermediate isolated was determined to be the trans-substituted hydroxymaleimide **50**.[11] With the structure of the intermediates identified, we propose that reaction of tricarbonyl **48** to **8a** proceeds via pathway A (Scheme 9). Formation of **48**, followed by

(10) Tricarbonyl **48** was difficult to fully characterize due to instability. Its structure was determined by the presence of the imide-NH, indole-NH, and mesylate (CH_3) peaks in the ^1H NMR spectrum.

Scheme 9



irreversible alkylation of the indole nitrogen generates the 17-membered macrocycle **49**. Cyclization of **49** to hydroxymaleimide **50** and subsequent dehydration affords **8a**. Although tricarbonyl **48** can also be converted to **8a** via pathway B, this is disfavored for two reasons: (1) based upon our previous work,[3a] dehydration of hydroxymaleimide **51** to maleimide **52** would require acidic conditions, while in the current reaction, dehydration occurs under basic conditions, and (ii) in analogy to the results obtained for **44**, intramolecular cyclization of **52** to **8b** would require high dilution to reduce dimer formation, although the current reaction occurs in DMF at 0.13 M concentration and no dimers have been isolated.

The results outlined in strategy C represent an efficient nine-step synthesis of macrocyclic bisindolylmaleimide **1** in 15% overall yield from indole and 1,2,4-butanetriol **34** using the benzyl protecting group. Using the same sequence but with a trityl protecting group, macrocycle **1** was obtained in 9% overall yield.

Conclusion

Three new approaches to the synthesis of macrocyclic bisindolylmaleimide **8**, a penultimate intermediate for the syntheses of **1**−**4**, have been identified. In strategies A and B, unsymmetrical bisindolylmaleimide **30** and **39** were generated in 98% and 74% yield, respectively, by reaction of an indole-3-glyoxylate with an indole-3-acetamide. Intramolecular cyclization of **31**, via strategy A, afforded a 73% yield of macrocycle **8a**, while in strategy B, formation of the macrocycle using the benzyl-protected intermediate **41** afforded **8b** in only 32% yield. The optimal approach to **1** was identified as a novel one-step synthesis of the maleimide and macrocycle by reaction of indole-3-acetamide **12** with methyl indole-3-glyoxylate **47**. The mechanism of this reaction, which has been determined, enables the reaction to be performed at 0 °C and high concentration (0.13 M), overcoming the issues associated with the intramolecular cyclization outlined in strategies A and B. This work completes a new highly efficient nine-step synthesis of **1** from indole.

Experimental Section

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. TLC was performed on Kiesegel 60 F254 plates (Merck) using reagent grade solvents. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). ^{1}H NMR was performed at 300 MHz and ^{13}C NMR at 75 MHz in $CDCl_3$ unless otherwise specified. Chemical shifts are in ppm downfield from internal tetramethylsilane. Mass spectral, combustion, and infrared analyses were performed by the Eli Lilly and Co. Physical Chemistry Department.

2-{1-[(Triphenylmethoxy)methyl]but-3-enyloxy}ethan-1-ol (24). To a solution of **23** (1.30 g, 3.77 mmol) in THF (20 mL) was added NaH (0.22 g, 5.66 mmol, 60% mineral oil dispersion), followed by HMPA (1.0 mL, 5.66 mmol), and the reaction mixture heated at 45 °C for 1 h. *tert*-Butyl bromoacetate (1.11 mL, 7.54 mmol) was added and the reaction mixture heated at 45 °C for an additional 3 h, cooled to room temperature, quenched with saturated aqueous NH_4Cl, and diluted with EtOAc. The organic layer was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to yield an oil that was purified by column chromatography (9:1 hexanes:EtOAc) to afford 0.65 g (38%) of *tert*-butyl 2-{1-[(triphenylmethoxy)methyl]but-3-enyloxy}-acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.41 (m, 6H), 7.39−7.09 (m, 9H), 5.82−5.68 (m, 1H), 5.28−4.94 (m, 2H), 4.09 (s,

(11) The presence of **50** was determined by HRMS: HRMS (FAB+) calcd for $C_{45}H_{39}N_3O_5$ 701.2890. Found *m*/*z* (M^+) 701.2897 (100%). The formation of the trans-isomer was determined by absence of a cross-peak between the methine and hydroxyl protons in the NOESY spectrum as described in our initial publication (see ref 3a).

2H), 3.57−3.50 (m, 1H), 3.22−3.13 (m, 2H), 2.39−2.26 (t, 2H, J = 6.5 Hz), 1.45 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.4, 143.8, 134.4, 128.3, 127.9, 127.0, 117.1, 86.1, 80.6, 78.1, 67.2, 64.7, 35.9, 27.8. IR ($CHCl_3$) ν 2982, 1743, 1490, 1449, 1369, 1127 cm^{-1}; MS (FD) calcd for $C_{30}H_{34}O_4$ 458.2457, found m/z (M^+) 242.9525 (100%), 457.9037 (52%).

To a solution of the ester prepared above (0.50 g, 1.16 mmol) in Et_2O (5 mL) at 0 °C was added dropwise $LiAlH_4$ (52.8 mg, 1.39 mmol) in Et_2O (5 mL), and the mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched at 0 °C by adding, in succession, water (53 μL), 15% NaOH (53 μL), and water (159 μL). The resulting white slurry was stirred at room temperature for 1 h. The solids were filtered and rinsed with Et_2O, and the resulting organic layer was dried ($MgSO_4$). The solvent removed in vacuo to give a colorless oil that was purified by column chromatography (3:1 hexanes:EtOAc) to afford 0.39 g of **24** (87%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.43−7.23 (m, 15H), 5.77−5.61 (m, 1H), 5.02−4.90 (m, 2H), 4.58 (t, 1H, J = 5.0 Hz), 3.58−3.40 (m, 5H), 3.04−2.94 (m, 2H), 2.50 (bs, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 143.9, 134.8, 128.0, 127.6, 127.3, 127.2, 127.1, 127.0, 116.9, 85.9, 78.0, 71.3, 64.8, 60.6, 59.8, 36.0. IR ($CHCl_3$) ν 3063, 3010, 2930, 2875, 1490, 1449, 1155, 1119, 1071, 993, 921, 899, 707, 632 cm^{-1}. Anal. Calcd for $C_{26}H_{28}O_3$ C, 80.38, H, 7.26, found C, 80.30, H, 7.18.

2-[1-(2-{3-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-1-[(triphenylmethoxy)methyl]propoxy}ethyl)indol-3-yl]-ethanamide (26). To a solution of NaH (1.93 g, 48.3 mmol, 60% dispersion in mineral oil) in DMF (260 mL) at 0 °C was added indole-3-acetamide **12** (14.0 g, 80.6 mmol) in DMF (200 mL), and the mixture was allowed to warm to room temperature and stir for 1 h. The reaction mixture was cooled to 0 °C, and **21** (38.1 g, 53.7 mmol) in DMF (300 mL) was added dropwise over 15 min. The reaction mixture was warmed to room temperature, stirred overnight, and then diluted with EtOAc and quenched with saturated aqueous NH_4Cl. The organic layer was washed (3×) with 5% aqueous LiCl and saturated aqueous NaCl and dried ($MgSO_4$) and the solvent removed in vacuo to give **26** as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 6H, J = 8.0 Hz), 7.52−7.41 (m, 14H), 7.36−7.27 (m, 10H), 5.42 (bs, 10H), 5.10 (bs, 1H), 4.32 (t, 2H, J = 5.8 Hz), 4.16−4.08 (m, 1H), 3.90−3.74 (m, 4H), 3.74 (s, 2H), 3.20 (d, 2H, J = 4.7 Hz), 1.84−1.65 (m, 2H), 1.12 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 139.4, 132.2, 131.0, 129.3, 129.2, 125.2, 124.1, 123.5, 123.3, 123.2, 123.0, 122.6, 117.7, 115.2, 114.5, 105.2, 103.4, 82.2, 64.9, 61.7, 55.7, 42.2, 30.8, 28.6, 22.6, 14.9. IR ($CHCl_3$) ν 3009, 2931, 1673, 1468, 1449, 1105, 1112 cm^{-1}. HRMS (FAB) calcd for $C_{51}H_{54}N_2O_4Si$ 786.3853, found m/z (M^+) 786.3858. Anal. Calcd for $C_{51}H_{54}N_2O_4Si$: C, 77.83, H, 6.92, N, 3.56, found C, 77.58, H, 6.77, N, 3.75.

2-{1-[(Triphenylmethoxy)methyl]but-3-enyloxy}ethyl 4-Methylsulfonate (27). To a solution of **24** (0.51 g, 1.31 mmol) in CH_2Cl_2 (10 mL) at −10 °C were added pyridine (0.32 mL, 3.93 mmol) and methanesulfonic anhydride (0.47 g, 2.62 mmol), and the reaction mixture was stirred at −10 °C for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl and dried ($MgSO_4$) and the solvent removed in vacuo to give 0.55 mg **27** (89%) as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.45−7.19 (m, 15H), 5.87−5.62 (m, 1H), 5.10−4.92 (m, 2H), 4.38−4.24 (m, 2H), 3.81−3.67 (m, 2H), 3.54 (t, 1H, J = 4.8 Hz), 3.14 (s, 3H), 3.01 (t, 2H, J = 4.0 Hz), 2.25 (t, 2H, J = 6.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 135.1, 134.4, 128.1, 127.7, 127.5, 127.4, 127.0, 126.9, 117.2, 80.0, 78.2, 70.2, 69.9, 67.3, 64.9, 62.6, 35.6. IR ($CHCl_3$) ν 3062, 1490, 1449, 1356, 1175, 1115, 1070, 1017, 970, 922, 706, 632, 527 cm^{-1}. MS (FD) calcd for $C_{27}H_{30}O_5S$ 466.59, found m/z (M + 1) 243.43 (due to loss of mesylate).

2-[1-(2-{3-Hydroxy-1-[(triphenylmethoxy)methyl]-propoxy}ethyl)indol-3-yl]ethanamide (10). To a solution of **26** in THF (55 mL) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (53.7 mL, 53.7 mmol)**,** and the mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with EtOAc and quenched with water. The organic layer was washed with saturated aqueous NaCl and dried ($MgSO_4$) and the solvent removed in vacuo to give a brown oil that was purified by column chromatography (gradient: 1:1 hexanes:acetone to 100% acetone) to afford 16.8 g **10** (57%) as a brown oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.56 (d, 1H, J = 7.8 Hz), 7.43−7.19 (m, 18H), 7.09 (t, 1H, J = 7.0 Hz), 7.03 (t, 1H, J = 7.2 Hz), 6.86 (s, 1H), 4.33 (t, 1H, J = 5.0 Hz), 4.27 (t, 2H, J = 5.5 Hz), 3.90−3.84 (m, 1H), 3.76−3.69 (m, 1H), 3.60−3.56 (m, 1H), 3.44 (s, 2H), 3.34−3.28 (m, 2H), 3.04−2.91 (m, 2H), 1.57 (q, 2H, J = 6.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 143.8, 136.2, 130.6, 128.3, 127.9, 127.7, 127.5, 127.0, 121.0, 118.9, 118.4, 109.6, 108.5, 85.9, 76.0, 68.8, 65.6, 57.2, 45.8, 35.1, 32.3. IR ($CHCl_3$) ν 3009, 1671, 1480, 1467, 1449, 1090, 1069 cm^{-1}. MS (FD) calcd for $C_{35}H_{36}N_2O_4$ 548, found m/z (M^+) 548 (100%). Anal. Calcd for $C_{35}H_{36}N_2O_4$: C, 76.62, H, 6.61, N, 5.11, found C, 76.33, H, 6.58, N, 5.41.

2-[1-(2-{1-[(Triphenylmethoxy)methyl]but-3-enyloxy}-ethyl)indol-3-yl]ethanamide (28). To a solution of NaH (2.57 g, 64.3 mmol, 60% dispersion in mineral oil) in DMF (400 mL) at 0 °C was added indole-3-acetamide **12** (11.2 g, 64.3 mmol) and the mixture stirred at room temperature for 30 min. The reaction mixture was cooled to 0 °C, and **27** (20.0 g, 42.9 mmol) in DMF (60 mL) was added. The reaction mixture was stirred at room-temperature overnight, diluted with EtOAc, and quenched with saturated aqueous NH_4Cl. The organic layer was washed (3×) with 5% aqueous LiCl and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to give a brown oil that was purified by column chromatography (1:1 hexanes:acetone) to afford 17.7 g of **28** (76%) as a pale orange oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.54 (d, 1H, J = 7.9 Hz), 7.42−7.22 (m, 16H), 7.08 (t, 1H, J = 7.1 Hz), 7.00 (t, 1H, J = 7.3 Hz), 6.82 (bs, 2H), 5.59−5.50 (m, 1H), 4.93−4.84 (m, 2H), 4.26 (t, 2H, J = 5.3 Hz), 4.28−3.71 (m, 2H), 3.42 (s, 2H), 3.01−2.92 (m, 3H), 2.20−2.14 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3, 134.5, 127.7, 127.4, 127.0, 127.1, 127.0, 126.9, 120.9, 118.3, 117.0, 109.6, 78.1, 68.6, 64.6, 45.7, 35.8, 32.3. IR ($CHCl_3$) ν 3515, 3400, 3061, 3009, 2932, 2872, 1671, 1093, 707, 632 cm^{-1}. HRMS (FAB) calcd for $C_{36}H_{36}N_2O_3$: 544.2726, found m/z (M^+) 544.2734 (100%). Anal. Calcd for $C_{36}H_{36}N_2O_3$: C, 79.38, H, 6.66, N, 5.14, found C, 79.38, H, 6.50, N, 5.23.

4-[1-(2-{3-Hydroxy-1-[(triphenylmethoxy)methyl]-propoxy}ethyl)indol-3-yl]-3-indol-3-yl-3-pyrroline-2,5-dione (30). To a solution of **10** (24.9 g, 45.3 mmol) and methyl indole-3-glyoxylate **9** (18.4 g, 90.7 mmol) in THF (250 mL) at 0 °C was added dropwise a 1.0 M solution of *tert*-BuOK in THF (181 mL, 181 mmol) and the reaction mixture allowed to stir at room-temperature overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$) and filtered through a pad of silica. The solvent was removed in vacuo to afford 31.6 g of **30** (98%) as a red solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.63 (d, 1H, J = 2.5 Hz), 10.91 (s, 1H), 7.82 (s, 1H), 7.70 (d, 1H, J = 2.8 Hz), 7.46 (d, 1H, J = 8.3 Hz), 7.38−7.19 (m, 16H), 7.02−6.90 (m, 2H), 6.79 (t, 2H, J = 7.8 Hz), 6.66−6.53 (m, 2H), 4.39−4.30 (m, 3H), 3.86−3.70 (m, 2H), 3.57−3.51 (m, 1H), 3.31 (q, 2H, J = 5.7 Hz), 2.97 (dd, 1H, J = 10.0, 5.3 Hz), 2.91 (dd, 1H, J = 10.0, 5.3 Hz), 1.57 (q, 2H, J = 6.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.0, 172.9, 143.8, 136.1, 136.0, 132.5, 130.3, 129.1, 128.2, 127.8, 127.6, 127.2, 126.9, 125.8, 125.4, 121.5, 121.2, 121.0, 119.5, 119.3, 111.7, 110.2, 105.7, 105.0, 85.9, 76.0, 68.3, 65.4, 65.4, 57.2. IR ($CHCl_3$) ν 1714, 1533, 1339 cm^{-1}. MS (FD) calcd for $C_{45}H_{39}N_3O_5$: 701, found m/z (M^+) 701 (100%). Anal. Calcd for $C_{45}H_{39}N_3O_5$: C, 77.01, H, 5.60, N, 5.99. Found C, 76.91, H, 5.72, N, 5.69.

4-[1-(2-{3-Bromo-1-[(triphenylmethoxy)methyl]propoxy}ethyl)indol-3-yl]-3-indol-3-yl-3-pyrroline-2,5-dione (31). To a solution of Br_2 (55.0 uL, 1.07 mmol) in CH_2Cl_2 (5 mL) at −30 °C was added triphenylphosphite (280 μL, 1.07 mmol), turning the solution from dark red to pale yellow. Pyridine (144 μL, 1.78 mmol) was added to the solution followed by syringe pump addition of **30** (0.50 g, 712 umol) in CH_2Cl_2 (5 mL) over 30 min. After the addition was complete, the reaction mixture was allowed to stir at room temperature for 1 h. The reaction mixture was quenched with saturated

aqueous NH_4Cl and diluted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl and dried ($MgSO_2$), and the solvent was removed in vacuo to give a red residue that was purified by column chromatography (1:1 hexanes: acetone) to afford 0.45 g **31** (82%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.63 (d, 1H, J = 2.5 Hz), 10.91 (s, 1H), 7.82 (s, 1H), 7.68 (d, 1H, J = 2.8 Hz), 7.45 (d, 1H, J = 8.3 Hz), 7.38−7.20 (m, 16H), 7.02−6.91 (m, 2H), 6.82 (d, 1H, J = 7.8 Hz), 6.75 (d, 1H, J = 7.5 Hz), 6.65−6.54 (m, 2H), 4.37 (t, 2H, J = 4.5 Hz), 3.84−3.79 (m, 1H), 3.69−3.65 (m, 1H), 3.50−3.42 (m, 1H), 3.32−3.26 (m, 2H), 3.05 (dd, 1H, J = 10.0, 5.8 Hz), 2.93 (dd, 1H, J = 10.2, 5.5 Hz), 2.00−1.85 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.0, 172.9, 143.6, 135.9, 132.5, 130.3, 129.0, 128.2, 127.9, 127.5, 127.3, 127.0, 125.8, 125.5, 121.5, 121.3, 120.9, 119.5, 119.3, 111.7, 110.2, 105.7, 105.0, 86.1, 76.6, 68.5, 64.5, 46.1, 35.1, 30.9, 30.7. IR ($CHCl_3$) ν 1713, 1533, 1338 cm^{-1}. HRMS (ES+) calcd for $C_{45}H_{38}BrN_3O_4$: 763.2046, found m/z (M^+) 763.2054 (100%).

6,7,10,11-Tetrahydro-9-[(triphenylmethoxy)methyl]-9*H*,18*H*,-5,21:12,17-dimethenodibenzo[*e*,*k*]-pyrrolo[3,4-*h*]-[1,4,13]oxadiazacyclohexadecine-18,20(19*H*)-dione (8a) from Strategy A. To a slurry of Cs_2CO_3 (0.21 g, 660 μmol) in DMF (77 mL) at 100 °C was added **31** (0.50 g, 654 μmol) in DMF (23 mL) by syringe pump over 6 h. The reaction mixture was stirred at 100 °C for 1 h and then cooled to room-temperature overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was washed with water (5×) and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to give a purple solid that was purified by column chromatography (1:1 hexanes:EtOAc) to afford 0.33 g **8a** (73%) as a purple solid and **32** as a purple solid. Dimer (**32**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65 (s, 1H), 10.93 (s, 1H), 8.00 (s, 2H), 7.87−7.72 (m, 4H), 7.54−7.18 (m, 32H), 7.10 (q, 2H, J = 7.3 Hz), 6.92 (t, 2H, J = 7.7 Hz), 6.82 (d, 2H, J = 8.2 Hz), 6.77 (d, 2H, J = 7.9 Hz), 6.63−6.55 (m, 4H), 4.42−4.07 (m, 6H), 3.73−3.56 (m, 6H), 3.33−3.12 (m, 2H), 3.10−2.93 (m, 4H), 2.10−1.75 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 172.8, 170.8, 143.7, 143.5, 135.8, 135.6, 132.4, 131.3, 128.9, 128.1, 127.8, 127.7, 127.2, 126.9, 126.8, 126.4, 125.7, 125.3, 121.5, 121.4, 121.1, 120.8, 120.0, 119.3, 119.1, 111.5, 110.0, 105.6, 105.0, 103.2, 86.2, 76.4, 76.0, 68.3, 64.7, 63.7, 46.1, 45.8, 42.3, 35.7, 34.1, 31.4, 30.5, 29.5. IR ($CHCl_3$) ν 3010, 1714, 1697, 1534, 1469, 1449, 1391, 1338 cm^{-1}. HRMS (ES+) calcd for C $C_{90}H_{74}N_6O_8$: 1367.5646, found m/z (M^+) 1367.5623 (100%).

4-Indolylbutane-1,2-diol (35). Indole (5.00 g, 42.7 mmol) in DMF (50 mL) was added to a suspension of NaH (2.13 g, 100 mmol, 60% mineral oil dispersion) in DMF (50 mL) over 30 min. The reaction mixture was stirred at room temperature for 1 h, and then tosylate **34** (17.5 g, 55.5 mmol)[12] in DMF (100 mL) was added over 20 min. The reaction mixture was stirred at room temperature for 16 h, quenched with saturated aqueous NH_4Cl, and diluted with EtOAc. The organic layer was washed with 5% aqueous LiCl and saturated sodium chloride and dried ($MgSO_4$). The solvent was removed in vacuo to afford an oil that was purified by column chromatography (2:1 CH_2Cl_2:hexanes) to afford 11.1 g (96%) of the indole acetonide as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 1H, J = 7.92 Hz), 7.38 (d, 1H, J = 8.22 Hz), 7.22 (t, 1H, J = 6.95, 3.87 Hz), 7.18−7.07 (m, 2H,), 6.49 (d, 1H, J = 2.48 Hz), 4.33−4.30 (m, 2H), 3.99−3.91 (m, 2H), 3.45−3.39(m, 1H), 2.10−21.92 (m, 2H), 1.72−1.25 (dq, 4H), 0.96−0.87 (dt, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 135.5, 128.4, 128.1, 124.9, 121.0, 120.4, 118.8, 111.7, 109.6, 100.6, 73.2, 68.9, 42.4, 33.8, 29.3, 29.0, 8.1, 7.8. IR ($CHCl_3$) ν 3008, 2976, 2942, 2882, 1512, 1464, 1316 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_2$ C, 74.69, H,. 8.48, N, 5.12, found C, 74.41, H, 8.25, N, 5.34.

To a solution of the acetonide (19.0 g, 69.5 mmol), prepared above, in THF (190 mL) was added 1 N HCl (190 mL), and the mixture was allowed to stir at room-temperature overnight. The reaction mixture was diluted with EtOAc, and the aqueous layer was removed. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to give an oil that was purified by column chromatography (1:2 CH_2Cl_2/EtOAc) to afford 12.9 g of **35** (91%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.54 (d, 1H, J = 7.8 Hz), 7.45 (d, 1H, J = 8.3 Hz), 7.34 (d, 1H, J = 3.2 Hz), 7.13 (t, 1H, J = 7.3 Hz), 7.01 (t, 1H, J = 7.4 Hz), 6.41 (d, 1H, J = 2.8 Hz), 4.74 (d, 1H, J = 4.8 Hz), 4.55 (t, 1H, J = 5.5 Hz), 4.29−4.23 (m, 2H), 3.47−3.17 (m, 3H), 2.03−1.90 (m, 1H), 1.72−1.58 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 135.6, 128.6, 128.1, 120.9, 120.4, 118.8, 109.7, 100.4, 68.6, 65.9, 42.4, 34.1. IR ($CHCl_3$) ν 3009, 2943, 1512, 1464, 1317, 1049 cm^{-1}; HRMS (ES+) calcd for $C_{12}H_{15}NO_2$ 206.1181, found m/z (M^+) 206.1183 (100%).

4-Indolyl-1-(phenylmethoxy)butan-2-ol (36). To a solution of **35** (9.00 g, 43.9 mmol) in toluene (100 mL) was added dibutyltin oxide (10.9 g, 43.9 mmol) and the mixture heated at reflux overnight under a Dean−Stark apparatus to remove water. The solvent was removed in vacuo to afford a white solid that was heated at 50 °C under vacuum for 1 h. Cesium fluoride (12.9 g, 85.2 mmol) was added and the mixture heated under vacuum at 50 °C for an additional 1 h. The solids were taken up in DMF (100 mL), and following addition of benzyl bromide (9.10 mL, 76.8 mmol), the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was washed with water and saturated aqueous NaCl and dried ($MgSO_4$) and the solvent removed in vacuo to give a brown oil that was purified by column chromatography (4:1 hexanes:EtOAc) to afford 10.6 g of **36** (82%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.55 (d, 1H, J = 7.8 Hz), 7.46 (d, 1H, J = 8.0 Hz), 7.35−7.23 (m, 6H), 7.13 (t, 1H, J = 7.0 Hz), 7.02 (t, 1H, J = 7.3 Hz), 6.43 (d, 1H, J = 2.7 Hz), 4.98 (d, 1H, J = 5.5 Hz), 4.44 (s, 2H), 4.28 (t, 2H, J = 7.3 Hz), 3.63−3.56 (m, 1H), 3.42−3.27 (m, 2H), 2.05−1.92 (m, 1H), 1.82−1.67 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.5, 135.7, 128.6, 128.2, 128.1, 127.6, 127.4, 126.6, 126.5, 121.0, 120.4, 118.8, 109.8, 100.4, 74.6, 72.3, 66.5, 63.0, 42.3, 34.4. IR ($CHCl_3$) ν 3010, 1512, 1485, 1464, 1454, 1317, 1090 cm^{-1}. HRMS (FAB+) calcd for $C_{19}H_{21}NO_2$ 296.1651, found m/z (M + 1) 296.1648 (100%).

2-{3-Indolyl-1-[(phenylmethoxy)methyl]propoxy}ethan-1-ol (37). To a solution of **36** (0.50 g, 1.69 mmol) in THF (10 mL) was added NaH (81 mg, 2.03 mmol, 60% dispersion in mineral oil) and the mixture heated to 45 °C for 1 h. HMPA (323 μL, 1.86 mmol) was added follwed by *tert*-butyl bromoacetate (500 μL, 3.38 mmol) and the reaction mixture heated at 45 °C for 18 h. The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl, and diluted with EtOAc. The organic layer was washed with saturated aqueous NaCl and dried ($MgSO_4$) and the solvent removed in vacuo to give a brown oil that was purified by column chromatography (4:1 hexanes:EtOAc) to afford 0.40 g *tert*-butyl 2-{3-indolyl-1-[(phenylmethoxy)methyl]propoxy}-acetate (58%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 1H, J = 7.9 Hz), 7.41−7.25 (m, 6H), 7.25−7.06 (m, 3H), 6.48 (d, 1H, J = 2.7 Hz), 4.47 (s, 2H), 4.38 (q, 2H, J = 7.0 Hz), 4.18−4.50 (dd, 2H, J = 16.2 Hz), 3.56−3.49 (m, 3H), 2.12−2.01 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 137.8, 135.8, 128.5, 128.3, 127.9, 127.6, 127.5, 121.2, 120.8, 119.0, 109.4, 100.9, 81.4, 76.5, 73.2, 72.7, 68.0, 42.4, 32.5, 28.0. IR ($CHCl_3$) ν 3009, 1743, 1464, 1455, 1369, 1138 cm^{-1}. HRMS (FD) calcd for $C_{25}H_{31}NO_4$ 409.2253, found m/z (M^+) 409.2145 (100%).

To a solution of the ester (5.50 g, 13.4 mmol), prepared above, in THF (60 mL) at 0 °C was added $LiBH_4$ (0.59 g, 26.9 mmol) and the mixture stirred at 0 °C for 30 min and then allowed to warm to room temperature. EtOH (6 mL) was added, and after 1 h the reaction mixture was quenched with water and diluted with EtOAc. The organic layer was washed with saturated aqueous NaCl and dried ($MgSO_4$) and the solvent removed in vacuo to give a yellow oil that was purified through a pad of silica gel (1:1 hexanes:EtOAc) to afford 4.40 g of **37** (97%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 1H, J = 7.5 Hz), 7.41−7.11 (m, 9H), 6.50 (d, 1H, J = 2.6 Hz), 4.50 (s, 2H), 4.26 (t, 2H, J = 7.6 Hz), 3.80−3.57 (m,

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4H), 3.48 (s, 3H), 2.42 (s, 1H), 2.12−2.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 135.8, 128.6, 128.4, 127.8, 127.7, 121.4, 120.9, 119.2, 109.2, 101.1, 76.1, 73.4, 71.9, 71.3, 62.2, 42.4, 32.5. IR ($CHCl_3$) ν 3009, 2931, 2868, 1464, 1455, 1317, 1089, 1049 cm$^{-1.}$ Anal. Calcd for $C_{21}H_{25}NO_3$ C, 74.31, H, 7.42, N, 4.13. Found C, 74.50, H, 7.59, N, 4.14.

Methyl 2-{1-[3-(2-Hydroxyethoxy)-4-(phenylmethoxy)-butyl]indol-3-yl}-2-oxoacetate (38). To a solution of **37** (2.00 g, 5.89 mmol) in Et_2O (40 mL) at 0 °C was added oxalyl chloride (1.03 mL, 11.8 mmol), and the mixture was allowed to stir at 0 °C for 30 min and then cooled to −60 °C, and a 25 wt % solution of NaOMe in MeOH (5.22 mL, 24.2 mmol) was added. The reaction mixture was stirred at −60 °C for 30 min, allowed to warm to room temperature, quenched with water, and diluted with EtOAc. The organic layer was washed with saturated aqueous NaCl and dried ($MgSO_4$) and the solvent removed in vacuo to give a yellow oil that was purified by column chromatography (1:1 hexanes:EtOAc) to afford 2.27 g of **38** (91%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46−8.39 (m, 2H), 7.42−7.24 (m, 8H), 4.50 (s, 2H), 4.39−4.30 (m, 2H), 3.94 (s, 3H), 3.84−3.70 (m, 3H), 3.63−3.54 (m, 1H), 3.50−3.38 (m, 3H), 2.30 (s, 1H), 2.17−2.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 163.4, 139.8, 137.4, 136.4, 128.4, 127.8, 127.7, 127.2, 124.0, 123.5, 122.9, 112.8, 110.0, 75.5, 73.4, 71.4, 71.3, 62.2, 52.6, 43.5, 31.9; IR ($CHCl_3$) ν 3012, 1727, 1644, 1521, 1401, 1282, 1176, 1141, 1089, 1060 cm^{-1}. Anal. Calcd for $C_{24}H_{27}NO_6$ C, 67.75, H, 6.40, N, 3.29. Found C, 68.07, H, 6.33, N, 3.69.

3-{1-[3-(2-Hydroxyethoxy)-4-(phenylmethoxy)butyl]indol-3-yl}-4-indol-3-yl-3-pyrroline-2,5-dione (39). To a solution of **38** (2.00 g, 4.70 mmol) and indole-3-acetamide **12** (0.98 g, 5.64 mmol) in THF (60 mL) at 0 °C was added dropwise a 1.0 M solution of *tert*-BuOK in THF (23.5 mL, 23.5 mmol) and the mixture allowed to warm to room temperature and stir for 6 h. After the reaction mixture was cooled to 0 °C, concentrated HCl (3.90 mL, 47.0 mmol) was added and the slurry stirred overnight at room temperature. The reaction mixture was quenched with water and diluted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to give a red residue that was purified by column chromatography (EtOAc) to afford 1.91 g **39** (74%) as a red solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (d, 1H, J = 2.5 Hz), 10.92 (s, 1H), 7.80 (d, 1H, J = 2.8 Hz), 7.75 (s, 1H), 7.46 (d, 1H, J = 8.3 Hz), 7.40−7.21 (m, 6H), 7.05 (t, 1H, J = 7.3 Hz), 7.00−6.86 (m, 2H), 6.78−6.63 (m, 2H), 6.57 (t, 1H, J = 7.2 Hz), 4.77−4.57 (bs, 1H), 4.48 (s, 2H), 4.35 (t, 2H, J = 6.2 Hz), 3.64−3.25 (m, 7H), 2.05−1.79 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.0, 172.9, 138.4, 136.0, 135.7, 132.2, 131.9, 129.3, 128.3, 128.1, 127.5, 127.4, 127.1, 126.2, 125.2, 121.7, 121.6, 121.2, 120.9, 119.6, 119.3, 111.8, 110.2, 105.6, 105.1, 75.2, 72.4, 71.8, 71.2, 60.6, 42.3, 32.1. IR ($CHCl_3$) ν 3468, 1715, 1533, 1457, 1338, 1101 cm^{-1}. Anal. Calcd for $C_{33}H_{31}N_3O_5$ C, 72.12, H, 5.69, N, 7.65, found C, 71.89, H, 5.72, N, 7.57.

3-{1-[3-(2-Bromoethoxy)-4-(phenylmethoxy)butyl]indol-3-yl}-4-indol-3-yl-3-pyrroline-2,5-dione (40). To a solution of bromine (253 μL, 4.91 mmol) in CH_2Cl_2 (20 mL) at −30 °C was added triphenyl phosphite (1.29 mL, 4.91 mmol) by syringe, and the dark red solution becomes colorless. Pyridine (792 μL, 9.81 mmol) was added to the reaction followed by a solution of **39** (1.80 g, 3.27 mmol) in CH_2Cl_2 (20 mL) and the mixture allowed to warm to room temperature. The reaction mixture was quenched with 1 N HCl and diluted with EtOAc. The organic layer was washed with saturated aqueous NaCl and dried ($MgSO_4$) and the solvent removed in vacuo to give a red residue that was purified by column chromatography (1:1 hexanes:EtOAc) to afford 1.80 g **40** (90%) as a red solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (d, 1H, J = 2.5 Hz), 10.92 (s, 1H), 7.80 (d, 1H, J = 2.8 Hz), 7.72 (s, 1H), 7.47 (d, 1H, J = 8.3 Hz), 7.42−7.21 (m, 6H), 7.05 (t, 1H, J = 7.5 Hz), 7.00−6.89 (m, 2H), 6.72 (m, 2H, J = 7.6 Hz), 6.57 (t, 1H, J = 7.6 Hz), 4.48 (s, 2H), 4.33 (t, 2H, J = 6.7 Hz), 3.92−3.80 (m, 1H), 3.66−3.52 (m, 3H), 3.46 (d, 2H), 3.41−3.30 (m, 1H), 2.06−1.81 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 138.3, 136.1, 135.6, 131.8, 129.3, 128.3, 128.1, 127.5, 127.1, 126.2, 125.2, 121.8, 121.6, 121.4, 120.9, 119.6, 119.4, 111.8, 110.1, 105.5, 105.2, 75.3, 72.4, 72.0, 69.2, 42.4, 33.0, 32.0. IR ($CHCl_3$) ν 3469, 1758, 1716, 1533, 1457, 1178, 1134, 1117, 1101 cm^{-1}. Anal. Calcd for $C_{33}H_{30}N_3O_4Br$ C, 64.10, H, 4.94, N, 6.86, Br, 13.05. Found C, 63.92, H, 5.17, N, 6.48, Br, 13.24.

6,7,10,11-Tetrahydro-9-[(phenylmethoxy)methyl]-9*H*,-18*H*,-5,21:12,17-dimethenodibenzo[*e*,*k*]-pyrrolo[3,4-*h*][1,4,-13]oxadiazacyclohexadecine-18, 20(19*H*)-dione (8b) from Strategy B. To a slurry of Cs_2CO_3 (0.13 g, 408 μmol) in DMF (30 mL) at 100 °C was added a solution of **40** (0.25 g, 408 μmol) in DMF (20 mL) by syringe pump over 6 h. The heat was removed and the reaction mixture allowed to cool to room temperature, diluted with EtOAc, and quenched with saturated aqueous NH_4Cl. The organic layer was washed with water and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to give a red residue that was purified by column chromatography (1:1 hexanes:EtOAc) to afford 68 mg **8b** (32%), 52 mg **43** (24%), and 37 mg **42** (17%) as dark red solids. **8b**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.9 (s, 1H), 7.82 (t, 2H, J = 8.7 Hz), 7.53−7.42 (m, 4H), 7.35−7.09 (m, 9H), 4.39 (s, 2H), 4.34−4.21 (m, 2H), 4.16 (bs, 2H), 3.88−3.83 (m, 1H), 3.64−3.56 (m, 1H), 3.49−3.37 (m, 3H), 2.18−1.95 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.3, 138.1, 135.6, 132.1, 131.6, 131.4, 131.3, 128.2, 127.5, 127.4, 126.6, 121.6, 121.5, 121.4, 120.1, 110.1, 110.0, 103.2, 103.1, 75.5, 72.3, 70.4, 66.4, 45.8, 42.5, 31.7. IR ($CHCl_3$) ν 1767, 1721, 1535, 1470, 1390, 1337 cm^{-1}. HRMS (FAB+) calcd for $C_{33}H_{29}N_3O_4$ 532.2236, found m/z (M + 1) 532.2245 (100%). **42**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.70 (s, 1H), 10.85 (s, 1H), 7.91 (m, 4H), 7.78−7.75 (m, 2H), 7.68 (s, 2H), 7.55−7.17 (m, 12H), 7.08 (t, 2H, J = 7.4 Hz), 6.91 (t, 4H, J = 7.8 Hz), 6.68 (t, 2H, J = 7.3 Hz), 6.50−6.40 (m, 2H), 4.50 (s, 2H), 4.40 (s, 2H), 4.35 (bm, 2H), 4.25−4.03 (bm, 4H), 3.94−3.78 (bm, 4H), 3.60−3.33 (m, 6H), 2.16−1.92 (bm, 2H). IR ($CHCl_3$) ν 3468, 3439, 3010, 2942, 2867, 1759, 1714, 1698, 1533, 1470, 1393, 1338, 1104 cm^{-1}. HRMS (FAB+) calcd for $C_{66}H_{59}BrN_6O_8$ 1063.4394. Found m/z (M + 1) 1063.4378 (100%).

Methyl 2-(1-{3-[2-(Methylsulfonyloxy)ethoxy]-4-(phenylmethoxy)butyl}indol-3-yl)-2-oxoacetate (46). To a solution of **37** (1.00 g, 2.95 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added pyridine (953 μL, 11.8 mmol) and methanesulfonic anhydride (1.05 g, 5.89 mmol), and the mixture was allowed to warm to room temperature for 15 min. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous NH_4-Cl. The organic layer was washed with 1 N HCl and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to give a yellow oil that was purified by column chromatography (2:1 hexanes:EtOAc) to afford 1.17 g (95%) of mesylate as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.62 (d, 1H, J = 7.9 Hz), 7.40−7.25 (m, 7H), 7.20 (t, 1H, J = 7.6 Hz), 7.10 (t, 1H, J = 7.3 Hz), 6.50 (d, 1H, J = 3.0 Hz), 4.47 (s, 2H), 4.36−4.31 (m, 2H), 4.31−4.23 (m, 2H), 3.96−3.86 (dt, 1H), 3.70−3.60 (dt, 1H), 3.48−3.36 (m, 3H), 3.00 (s, 3H), 2.10−1.97 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 137.7, 135.8, 128.5, 128.4, 127.7, 127.6, 121.4, 120.9, 119.2, 109.2, 101.2, 76.2, 73.3, 72.1, 69.2, 69.0, 67.6, 42.3, 37.5, 32.2; IR ($CHCl_3$) ν 3009, 1464, 1454, 1358, 1318, 1175, 1020, 971, 923 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_5S$ C, 63.28, H, 6.52, N, 3.35, found C, 62.89, H, 6.53, N, 3.26.

To a solution of the mesylate (1.75 g, 4.19 mmol), prepared above, in Et_2O (40 mL) at 0 °C was added oxalyl chloride (731 μL, 8.38 mmol) and the mixture allowed to stir at 0 °C for 30 min and then cooled to −60 °C. A 25 wt % solution of NaOMe in MeOH (3.80 mL, 17.6 mmol) was added and the reaction mixture stirred at −60 °C for 30 min and then allowed to come to room temperature. The reaction mixture was quenched with water and diluted with EtOAc. The organic layer was washed with saturated aqueous NaCl and dried ($MgSO_4$) and the solvent removed in vacuo to afford 1.90 g **46** (90%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47−8.40 (m, 1H), 8.38 (s, 1H), 7.43−7.24 (m, 8H), 4.47 (s, 2H), 4.41−4.30 (m, 4H), 4.02−3.87 (m, 1H), 3.87 (s, 3H), 3.72−3.63 (m, 1H), 3.50−3.39 (m, 3H), 3.03 (s, 3H), 2.16−2.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 163.3, 139.6, 137.5, 136.4, 128.4, 127.8, 127.6, 127.1, 124.1, 123.5, 122.8, 112.8, 110.1, 75.8, 73.4, 71.8, 69.1,

67.7, 53.5, 52.6, 43.4, 37.5, 31.8. IR ($CHCl_3$) ν 3009, 1728, 1644, 1521, 1359, 1282, 1176, 1141, 971, 923 cm^{-1}. Anal. Calcd for $C_{25}H_{29}NO_8S$ C, 59.63, H, 5.81, N, 2.78, found C, 59.58, H, 5.86, N, 2.87.

Methyl 2-(1-{3-[2-(Methylsulfonyloxy)ethoxy]-4-(triphenylmethoxy)butyl}indol-3-yl)-2-oxoacetate (47). To a solution of **45** (3.00 g, 6.10 mmol) in CH_2Cl_2 (60 mL) at 0 °C were added pyridine (1.97 mL, 24.4 mmol) and methanesulfonic anhydride (2.20 g, 12.2 mmol) and the mixture allowed to warm to room temperature and stir for 15 min. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl. The organic layer was washed with 1 N HCl and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to give a yellow oil that was purified by column chromatography (2:1 hexanes:EtOAc) to afford 3.30 g (95%) of mesylate as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 1H, J = 7.9 Hz), 7.42−7.35 (m, 6H), 7.32−7.02 (m, 13H), 6.47 (d, 1H, J = 3.1 Hz), 4.37−4.30 (m, 2H), 4.26−4.17 (m, 2H), 3.91−3.82 (m, 1H), 3.60−3.51 (m, 1H), 3.32−3.24 (m, 1H), 3.17−3.14 (m, 2H), 2.97 (s, 3H), 2.11−2.02 (m, 2H). This material was used directly in the glyoxylation.

To a solution of mesylate, prepared above (2.00 g, 3.51 mmol), in Et_2O (40 mL) at 0 °C was added oxalyl chloride (612 μL, 7.02 mmol) and the mixture allowed to stir at 0 °C for 1 h, becoming a bright yellow slurry. The reaction mixture was cooled to −60 °C and a 25 wt % solution of NaOMe in MeOH (3.79 mL, 17.6 mmol) added. The mixture was stirred at −60 °C for 15 min and then allowed to come to room temperature, again becoming a yellow slurry. The reaction mixture was quenched with water and diluted with EtOAc. The organic layer was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to afford a yellow solid that was purified by column chromatography (2:1 hexanes:EtOAc) to afford 1.30 g of **47** (57%) as a yellow solid. ^1H NMR (300 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.24−8.20 (m, 1H), 7.67−7.57 (m, 1H), 7.38−7.05 (m, 17H), 4.43−4.30 (m, 4H), 3.89 (s, 3H), 3.89−3.82 (m, 1H), 3.62−3.54 (m, 1H), 3.37 (s, 2H), 3.37−3.32 (m, 1H), 3.14−3.01 (bs, 3H), 2.10−1.85 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.1, 163.8, 143.6, 140.6, 136.4, 128.1, 127.8, 127.0, 126.1, 123.9, 123.2, 121.5, 111.6, 111.2, 86.1, 76.0, 69.8, 67.5, 65.0, 52.5, 43.2, 36.7, 31.5; IR ($CHCl_3$) ν 1728, 1644, 1521, 1359, 1176 cm^{-1}. MS (FD) calcd for $C_{37}H_{37}NO_8S$ 655.7, found m/z (M + 1) 656.2 (100%).

6,7,10,11-Tetrahydro-9-[(phenylmethoxy)methyl]-9*H*,-18*H*,-5,21:12,17-dimethenodibenzo[*e*,*k*]-pyrrolo[3,4-*h*][1,4,-13]oxadiazacyclohexadecine-18,20(19*H*)-dione (8b) from Strategy C. To a solution of NaH (0.52 g, 13.1 mmol, 60% dispersion in mineral oil) in DMF (10 mL) at 0 °C was added indole-3-acetamide **12** (0.76 g, 4.37 mmol) and the reaction mixture stirred at room temperature for 45 min. The reaction mixture was then cooled to 0 °C and **46** (1.0 g, 1.99 mmol) in DMF (10 mL) added. After stirring at 0 °C for 30 min, the reaction mixture was allowed to warm to room temperature for 1 h and quenched with saturated NH_4Cl and diluted with EtOAc. The organic layer was washed with 5% aqueous LiCl and saturated NaCl and dried ($MgSO_4$). The resulting dark red solid was purified by column chromatography (1:1 hexanes:EtOAc) to afford 0.62 g (58%) yield of **8b**.

6,7,10,11-Tetrahydro-9-[(triphenylmethoxy)methyl]-9*H*,18*H*,-5,21:12,17-dimethenodibenzo[*e*,*k*]-pyrrolo[3,4-*h*]-[1,4,13]oxadiazacyclohexadecine-18,20(19*H*)-dione (8a) from Strategy C. To a solution of indole-3-acetamide **12** (0.21 g, 1.23 mmol) in DMF (5 mL) at 0 °C was added NaH (0.05 g, 1.23 mmol, 60% dispersion in mineral oil) and the reaction mixture warmed to room temperature and stirred for 1 h. Upon cooling to 0 °C, **47** (0.47 g, 0.82 mmol) was added, and the mixture was allowed to stir at room-temperature overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was washed with saturated aqueous NaCl and water and dried ($MgSO_4$). The solvent was removed in vacuo to give an oil that was purified by column chromatography (gradient: 1:1 hexane:EtOAc to 100% EtOAc) to afford 0.29 g (55%) **8a** as a red solid.

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Supporting Information Available: Complete analytical and spectroscopic characterization for **25** and **37** and intermediates required for their synthesis. This material is available free of charge via the Internet at http://pubs.acs.org.

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