A Stereoselective Synthesis of Indole-β-N-glycosides: An Application to the Synthesis of Rebeccamycin

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Sodium salts of indoles have been found to open α-1,2-anhydrosugars with inversion yielding indole-β-N-glycosides. This methodology constitutes a concise route from glycals to the biologically active indole-N-glycosides. An application to the total synthesis of rebeccamycin is described.

Introduction

A variety of natural products in which indolocarbazoles are glycosidically joined to various sugars have been described. Several members of this family have a single indole-N-glycosidic bond while others contain two such linkages. Several of the compounds posessing such single N-glycosidic bonds exhibit antitumor activity. The most potent antitumor agent of this group is rebeccamycin[1] (1) which was isolated in 1985 from an actinomycete.[2] Its structure and absolute configuration were determined by X-ray crystallography after early insights were provided by NMR spectroscopy. The total synthesis of rebeccamycin has been accomplished.[2,3]

Rebeccamycin consists of a symmetrical indolocarbazole chromophore and a 4-*O*-methylglucose residue linked by a β-N-glycosidic bond. It has shown activity against P388 leukemia, L1210 leukemia, and B16 melanoma implanted in mice. Furthermore, rebeccamycin causes single stranded breaks in the DNA of human lung adenocarcinoma cells. This capacity may be the source of its growth inhibitory effects upon such cells. Recently, water-soluble derivatives of rebeccamycin have shown increased potency and are presently advancing in clinical trials.[4] Other weaker antitumor agents, containing single N-glycosidic bonds, include tjizpanazole-E (2) (β-glucopyranoside),[5] the tjizpanazoles B, F1, F2 (β-isorhamnopyranoside), RK-286D[6] (α-2-deoxyrhamnopyranoside), and the more complex β-linked disaccharides AT2433 (A1,A2,B1 and B2).[7] Indolocarbazole glycosides displaying bis-N-glycosidic linkages include staurosporine[8] (3), RK-1409[9] (7-oxo-staurosporine), UCN-01, UCN-02,[10] TAN-999, TAN-1030A,[11] and K-252a.[12] These compounds are potent inhibitors of protein kinase C.[13] The most active member of this group is staurosporine.[14]

Synthetic efforts to date have concentrated mainly on construction of the aglycon moiety of these compounds.[15] Rebeccamycin and the tjizpanazoles E and G2 are the only indolocarbazole glycosides which have been synthesized. However, an effective general methodology for the crucial glycosidation step, which would facilitate the synthesis of these indolocarbazole glycosides or potentially interesting analogues, has not yet been described. It was our hope that 1,2-anhydrosugars could serve as glycosyl donors to indoles to meet this challenge.

Results and Discussion

Previous studies in our laboratory have revealed that 1,2-anhydrosugars, obtained from the direct epoxidation of glycals with dimethyldioxirane, serve as glycosyl donors toward a variety of nucleophiles.[16] We hoped that indoles would react with 1α,2α-anhydrosugars with inversion of configuration at the anomeric carbon to produce the desired indole-N-glycosides. In practice, various attempts

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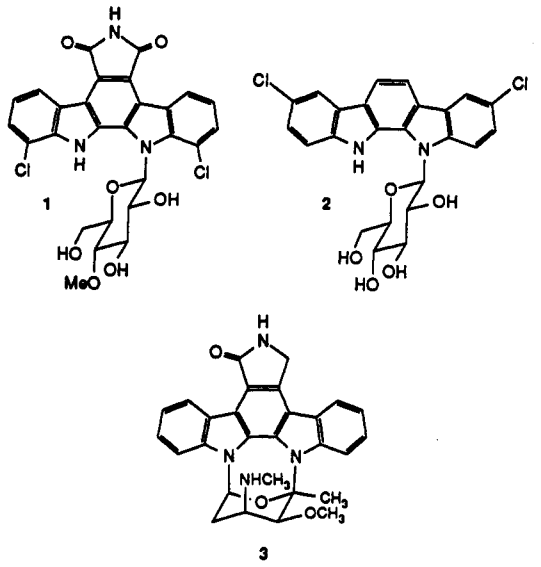
Chart I



Scheme I

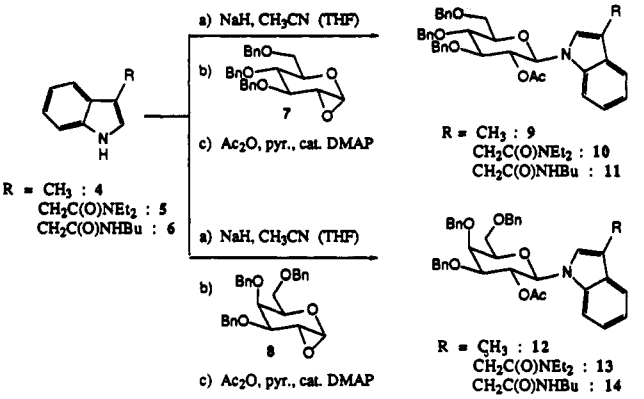
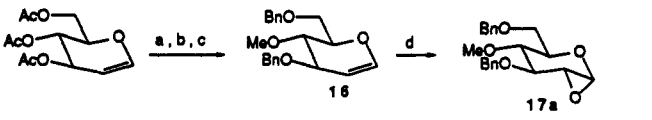


Table I.[a] Glycosidation of C3-Protected Indoles

indoles	1,2-anhydro-sugar	stoichiometry[c]	indole-glycosides	yields[d] (%)
4	7[b]	1:1	9	14
		2:1		41
5	7[b]	1:1	10	23
		1:2		24
		2:1		48
6	7[b]	1:2	11	27
		3:1		51
4	8	2:1	12	44
5	8	1:1	13	32
		2:1		50
6	8	1:2	14	57
		2:1		74

[a] All indoleglycosides were characterized as their C2-acetate derivatives. [b] In the case of the 1,2-anhydrosugar 7, a small amount (5–8%) of indolyl α-D-mannopyranoside, arising from the minor β-epoxide, was observed but was not characterized or included in the above yields. [c] Indole/1,2-anhydrosugars. [d] Overall yield (glycosidation and acetylation).

Scheme II[a]



α (17a) / β (17b); 15:1[21]

[a] Reagents and conditions: (a) cat. MeONa, MeOH, 98%; (b) (i) Bu_2SnO (1.0 equiv), MeOH, (ii) BnBr (2.0 equiv), Bu_4NBr (2.0 equiv), PhH, reflux, 10 h, 15, 47%; (c) NaH, MeI, DMF, 16, 85%; (d) dimethyldioxirane (1.1 equiv), 0 °C, CH_2Cl_2, quantitative.

at Lewis acid catalyzed ($ZnCl_2$, BF_3·OEt_2) condensations of indoles with 1,2-anhydrosugars were unsuccessful. However, it was discovered that deprotonated indoles react with 1,2-anhydrosugars to form β-N-glycosides without any additional promoters. Previously, indole glycosidation has been performed via displacement of anomeric halides by indole (or indoline) anions and by standard Koenigs–Knorr techniques.[17] One benefit of our approach lies in its utilization of glycals as starting materials. Differentiation of the three hydroxyl groups in such compounds is much simpler than in the case of fully oxygenated pyranoses. Furthermore, a unique unprotected hydroxyl group is unveiled at C-2 during the glycosidation. This feature could, in principle, allow for deoxygenation in an envisioned synthesis of staurosporine.[18]

The indole glycosylation reaction was studied using skatole (4) and two 3-acetamidoindoles 5 and 6 as glycosyl acceptors. The 1,2-anhydrosugars 7 and 8[19] derived, respectively, from the epoxidation of tri-*O*-benzyl-D-glucal and tri-*O*-benzyl-D-galactal with dimethyldioxirane were used as glycosyl donors (Scheme I). In practice, these 1,2-anhydrosugars were cannulated into a solution of the sodium indolides in acetonitrile (generated with NaH) and stirred overnight at 50 °C to give the desired indole-β-N-glucosides and galactosides. Acetylation at C2 (Ac_2O, cat. DMAP, pyridine) provided compounds **9–14** in moderate to good overall yields (Table I). In these model experiments we found that operating with a 2:1 stoichiometry of indoles/epoxides was a sound optimization since it allowed for an efficient usage of material and resulted in improved yields. No isomeric α-indolylglycosides arising from these α-1,2-anhydrosugars were detected reflecting the stereoselectivity of the process. *Thus, the methodology herein constitutes a very general stereospecific synthesis of indole-N-glucosides and galactosides.*

Total Synthesis of Rebeccamycin

We now describe the application of this methodology to the total synthesis of rebeccamycin. Retrosynthetic analysis of rebeccamycin calls for the preparation of the glucal 16 (Scheme II) and the bis(indolyl)maleimide 21 (Scheme III). The secoaglycon 21 was found to be more nucleophilic than the corresponding indolocarbazole; therefore, it was used as the glycosyl acceptor. One of the two indolic nitrogens was protected in order to avoid the possibility of double glycosidation.

The required 3,6-di-*O*-benzyl-4-*O*-methyl-D-glucal (16) was prepared from commercially available tri-*O*-acetyl-D-glucal. Removal of the acetate protecting groups with catalytic sodium methoxide in methanol produced the 3,4,6-trihydroxy-D-glucal in 98% yield. The triol was

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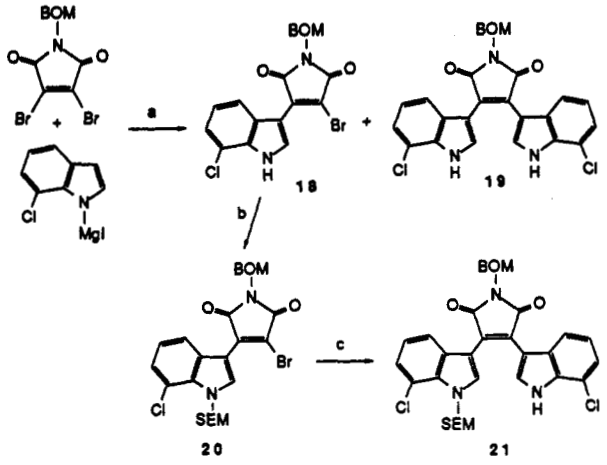
(18) Gervay, J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5448 and references cited therein.

(19) Epoxidation of 3,4,6-tri-*O*-benzyl-D-glucal gave a 20:1 mixture of the α:β 1,2-anhydrosugars in 99% yield, with the epoxide 7 being the major isomer. Epoxidation of 3,4,6-tri-*O*-benzyl-D-galactal gave only the α-1,2-anhydrosugar 8 in quantitative yield.[16a]

Scheme III[a]



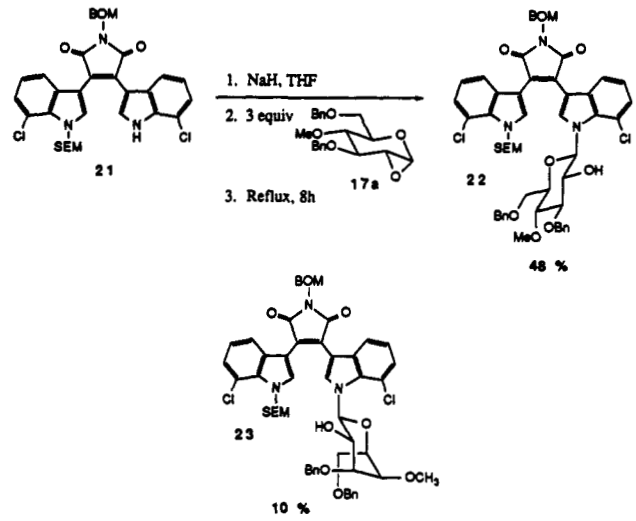
[a] Reagents and conditions: (a) (i) to 7-chloroindole was added MeMgI (1.05 equiv), PhH, 25 °C, 15 min, (ii) added to *N*-BOM dibromomaleimide (0.5 equiv), PhH, 25 °C, 12 h, **18** (91%), **19** (3%); (b) (i) NaH, THF, 25 °C, 15 min, (ii) SEM-Cl, 25 °C, 30 min, **20**, 94%; (c) (i) see a (i), (ii) added to **20** (0.5 equiv), PhH, 25 °C, 12 h, **21**, 69% (77% corrected).

selectively dibenzylated at the 3 and 6 positions utilizing stannylene technology[20] to give glucal **15** in 47% yield. Methylation at the 4 position (NaH, MeI, DMF) yielded the desired precursor **16** in 85% yield. When treated with 2,2-dimethyldioxirane at 0 °C in CH_2Cl_2, glucal **16** yielded the α-1,2-anhydrosugar **17a** as the major product [15:1 ratio of α(**17a**)/β(**17b**)] in high overall yield.[21]

The synthesis of the secoaglycon **21** capable of leading to rebeccamycin was accomplished utilizing sequential indole Grignard additions to a protected dibromomaleimide. Following a route patterned after the one described by Kaneko, Doyle, and Clardy,[3] this chemistry allowed the preparation of the desired aglycon in 60% overall yield (Scheme III). Thus, 7-chloroindole[22] was deprotonated using MeMgI (1.05 equiv). The resultant solution was cannulated into a solution of *N*-(benzyloxymethyl)-protected dibromomaleimide[3] (0.5 equiv) to produce the monoindole adduct **18** in 91% yield[23] along with only 3% of the bisindole **19**. Protection of the indolic nitrogen with a [2-(trimethylsilyl)ethoxy]methyl[24] (SEM) protecting group (NaH, SEM-Cl, THF) was achieved in 94% yield. In a similar fashion, the subsequent addition of 7-chloroindole Grignard gave the desired secoaglycon **21** in 69% yield. *The stage for the all important glycosidation was at hand.*

It was found that the glycosidation of the secoaglycon **21** required an excess of the glycosyl donor. Two equiv of the 1,2-anhydrosugar **17** (15:1 **17a**/**17b**) obtained from the epoxidation of glucal **16** with dimethyldioxirane was added to the sodium salt of the monoprotected bisindole **21** generated by treatment with 1.1 equiv of sodium

Scheme IV



hydride. Refluxing the reaction mixture produced the desired β-glucopyranoside **22** in 42% yield along with 8% of the α-mannopyranoside **23** which arose from the α- and β-1,2-anhydrosugars, respectively[25] (Scheme IV). Yields could be increased to 48% and 9% if 3 equiv of the glycosyl donor **17** were used. The structures of these stereoisomers were assigned by analysis of the ^1H NMR coupling constants in the C1–C4 region as well as a 2-D-COSY experiment on **22**. Compound **22** revealed a $J_{1,2}$ = 9.0 Hz and $J_{2,3}$ = 8.8 Hz, consistent with a β-glucopyranoside in a chair conformation having equatorial substituents, while the minor isomer **23** revealed a $J_{1,2}$ = 8.2 Hz, $J_{2,3}$ = 3.4 Hz, and $J_{3,4}$ = 4.0 Hz, consistent with an α-mannopyranoside in a chair conformation having axial substituents at position 3, 4, and 5.

The 2,2′-bisindole bond was constructed by photocyclization[15g,26] after the removal of the SEM protecting group with tetrabutylammonium fluoride in 63% yield (Scheme V).[24] Photolysis of **24** using a Hanovia medium-pressure Hg lamp equipped with a Vycor filter (3000 Å) gave rise to the indolocarbazole glucopyranoside **25** in 74% yield.

The final deprotection step proved to be nontrivial. Prolonged hydrogenation over metal catalysts often resulted in hydrogenolysis of the carbon–chlorine bonds. However, hydrogenation of **25** over Pearlman's catalyst (50% wt) followed by ammonolysis to complete the benzyloxymethyl deprotection yielded rebeccamycin (**1**) in 72% yield. Under these conditions only 14% of the material had suffered reductive cleavage of chloride. *The synthetic material thus obtained gave ^1H and ^{13}C NMR, HRMS, melting point, and optical rotation which were identical to those reported for the natural product rebeccamycin.*[8]

Summary

In summary, we have utilized α-1,2-anhydrosugars obtained from the epoxidation of glycals with dimethyl-

(20) Cruzado, C.; Bernabe, M.; Martin-Lomas, M. *J. Org. Chem.* **1989**, *54*, 465.

(21) Epoxidation of glucal **16**, followed by methanolysis, acetylation at C2, and separation of the resulting α- and β-methyl glucopyranosides (12.5:1 of β/α) confirmed that the epoxide **17a**, generated during the epoxidation, was the major isomer.

(22) Sugasawa, T.; Adachi, M.; Sasakura, K.; Kitigawa, A. *J. Org. Chem.* **1979**, *44*, 578.

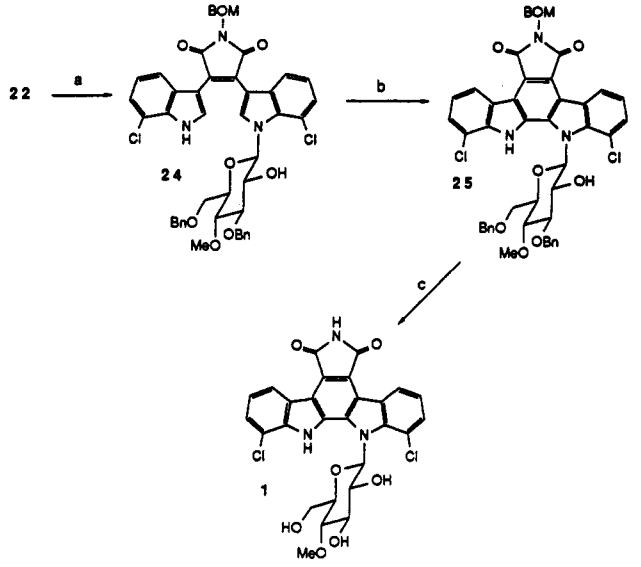
(23) The highest yield was obtained when 2 equiv of the indole Grignard was added to the protected maleimide at room temperature (at higher temperatures loss of the benzyloxymethyl was observed). The excess of 7-chloroindole could be recovered and reused.

(24) Edwards, M. P.; Doherty, A. M.; Ley, S. T.; Organ, H. M. *Tetrahedron* **1986**, *42*, 3723.

(25) The 5:1 ratio of **22**/**23** versus the 15:1 of α (**17a**)/β (**17b**) 1,2-anhydrosugars obtained from the epoxidation of glucal **16** must be attributed to the greater reactivity of the minor β epoxide **17b** (1,2-anhydro-3,6-di-*O*-benzyl-4-*O*-methyl-D-mannopyranoside) relative to the major α epoxide **17a**.

(26) Tominaga, Y.; Lee, M. L.; Castle, R. N. *J. Heterocycl. Chem.* **1981**, *18*, 967.

Scheme V[a]



[a] Reagents and conditions: (a) TBAF (2.0 equiv), 4 Å powdered molecular sieves THF, reflux, 2 h, **24** (63%); (b) *hν* (Hanovia medium-pressure Hg lamp, 450 W, Vycor filter), cat. I_2, air, PhH, 8 h, **25** (74%); (c) (i) $Pd(OH)_2$ (50% w), H_2, EtOH/EA (4:1), 5 h, (ii) saturated NH_3 in THF, 25 °C, 2 h, **26** (72%, (14% mixture of –Cl and $-Cl_2$)).

dioxirane to N-glycosylate indoles in a stereospecific fashion. The successful implementation of this chemistry has lead to an improved total synthesis of the antitumor indolocarbazole glycoside rebeccamycin. We are currently pursuing applications of these findings in a proposed synthesis of staurosporine. Results of those efforts will be described in due course.

Experimental Section

General Methods. All reagents were obtained from commercial sources and used without further purification. All reactions were carried out under inert atmosphere. CH_2Cl_2 was distilled from calcium hydride. THF and benzene were distilled from sodium–benzophenone. Flash chromatography was performed on silica gel (Merck, 230–400 mesh).

^1H and ^{13}C NMR were recorded on a Bruker WM-250, Yale-490, or AM-500 instrument. The 2-D COSY experiment was conducted on a General Electric Omega-500 instrument. Infrared spectra were recorded on a Perkin-Elmer Model 1420 spectrometer. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter, and high-resolution mass spectra (HRMS) were recorded on a Kratos Model MS-80RFA instrument. Melting points were determined using a Hoover capillary melting apparatus and are uncorrected.

General Procedure for Indole Glycosylation. A solution of 1 equiv of glycal (0.05–0.1 M) in dry CH_2Cl_2 was chilled to 0 °C and treated with 1.1 equiv of a 0.09 M solution of dimethyldioxirane in acetone until the glycal was completely consumed by TLC (30–45 min). The solvents were removed in vacuo, and the resulting anhydrosugar was dissolved in a minimal amount of CH_3CN. In a separate flask 2 equiv of indole were dissolved in a minimal amount of CH_3CN and were treated with 2.1 equiv of NaH (60% dispersion in mineral oil). The resulting solution was stirred at room temperature for 30 min. The anhydrosugar was cannulated dropwise into the indole solution and was allowed to stir at room temperature for 15 min. After being heated overnight at 50 °C (80 °C for skatole), the reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The crude material was dissolved in pyridine, chilled to 0 °C, and treated with acetic anhydride and a catalytic amount of DMAP. The mixture was slowly warmed to room temperature and stirred for 5 h. The crude mixture was poured into saturated $NaHCO_3$ and extracted with ethyl acetate (3×). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was flash chromatographed on silica gel to yield the indole glycoside. In the case of skatole (**4**), the solvents were removed in vacuo after the acetylation and the residue was flash chromatographed directly.

3-Methyl-1-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indole (9). From 88.1 mg (0.67 mmol) of skatole (**4**), 28.2 mg (0.71 mmol) of NaH, and 139.9 mg (0.34 mmol) of tri-*O*-benzyl-D-glucal was obtained 81.9 mg of **9** (40%) after flash chromatography (toluene/ethyl acetate (25:1)) and recrystallized from ether: mp 122–124 °C (Et_2O); $[\alpha]^{25}_D$ +8.7 (*c* 0.87, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 2875, 1750, 1465, 1370, 1240, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.98–7.48 (m, 20 H), 5.45 (app t, *J* = 9.2 Hz, 1 H), 5.38 (d, *J* = 9.2 Hz, 1 H), 4.82 (d, *J* = 11.6 Hz, 1 H), 4.81 (d, *J* = 10.5 Hz, 1 H), 4.65 (d, *J* = 11.6 Hz, 1 H), 4.60 (d, *J* = 10.5 Hz, 1 H), 4.53 (d, *J* = 12.1 Hz, 1 H), 4.03 (d, *J* = 12.1 Hz, 1 H), 3.75–3.93 (m, 2 H), 3.65–3.75 (m, 3 H), 2.23 (s, 3 H), 1.53 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.8, 138.1, 138.0, 136.8, 129.7, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6, 122.2, 121.9, 119.7, 119.1, 112.8, 109.6, 83.9, 83.3, 78.0, 77.9, 75.2, 73.6, 72.4, 68.7, 20.3, 9.6; HRMS (FAB) calcd for $C_{38}H_{39}NO_6$ 605.2767, found 605.2774.

3-Acetamido-*N*,*N*-diethyl-1-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indole (10). From 148.0 mg (0.64 mmol) of **5**, 31.2 mg (0.78 mmol) of NaH, and 128.7 mg (0.31 mmol) of tri-*O*-benzyl-D-glucal was obtained 104.8 mg of **10** (48%) after flash chromatography (hexanes/EtOAc (1:2)): mp 104–105 °C (Et_2O); $[\alpha]^{25}_D$ +13.5 (*c* 0.71, $CHCl_3$); IR (melted) ν_{max} 2900, 1745, 1630, 1460, 1365 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.9, 0.7 Hz, 1 H), 7.39 (d, *J* = 8.3 Hz, 1 H), 7.34–7.11 (m, 18 H), 5.46 (dd, *J* = 9.2, 8.6 Hz, 1 H), 5.43 (d, *J* = 9.2 Hz, 1 H), 4.85 (d, *J* = 10.5 Hz, 1 H), 4.85 (d, *J* = 11.9 Hz, 1 H), 4.70 (d, *J* = 11.4 Hz, 1 H), 4.64 (d, *J* = 10.7 Hz, 1 H), 4.57 (d, *J* = 12.0 Hz, 1 H), 4.48 (d, *J* = 12.0 Hz, 1 H), 3.93 (dd, *J* = 9.4, 9.2 Hz), 3.87 (dd, *J* = 9.0, 8.7 Hz, 1 H), 3.78 (dd, *J* = 11.1, 4.2 Hz, 1 H), 3.75 (d, *J* = 1.6 Hz, 2 H), 3.74–3.71 (m, 2 H), 3.40–3.25 (m, 4 H), 1.55 (s, 3 H), 1.12–1.06 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 168.6, 138.0, 137.8, 136.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.5, 122.9, 122.2, 120.2, 119.4, 110.9, 109.8, 83.6, 83.4, 77.9, 77.7, 75.1, 73.5, 72.2, 68.4, 42.3, 40.1, 31.5; HRMS (FAB) calcd for $C_{43}H_{48}N_2O_7$ 704.3461, found 704.3460. Anal. Calcd for $C_{43}H_{48}N_2O_7$: C, 73.27; H, 6.86; H, 3.97. Found: C, 73.36; H, 6.95; N, 4.02.

3-Acetamido-N-butyl-1-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indole (11). From 80.3 mg (0.35 mmol) of **6**, 32.4 mg (0.81 mmol) of NaH, and 49.6 mg (0.12 mmol) or tri-*O*-benzyl-D-glucal was obtained 43.1 mg of **11** (51%) after flash chromatography (benzene/ethyl acetate (1:2)): mp 150–152 °C (EtOAc); $[\alpha]^{25}_D$ +64.7 (*c* 0.68, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3380, 2900, 1740, 1650, 1530, 1460, 1365 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.7 Hz, 1 H), 7.37–7.16 (m, 18 H), 7.10 (dt, *J* = 7.4, 0.9 Hz, 1 H), 6.07 (br, t, *J* = 5.9, 1 H), 5.41 (d, *J* = 8.9 Hz, 1 H), 5.17 (t, *J* = 9.2 Hz, 1 H), 4.86 (d, *J* = 10.8 Hz, 1 H), 4.83 (d, *J* = 11.6 Hz, 1 H), 4.68 (d, *J* = 11.7 Hz, 1 H), 4.64 (d, *J* = 10.9 Hz 1 H), 4.60 (d, *J* = 12.2 Hz, 1 H), 4.54 (d, *J* = 12.1 Hz, 1 H), 3.91–3.84 (m, 2 H), 3.81–3.75 (m, 3 H), 3.69 (s, 2 H), 3.14 (m, *J* = 6.5 Hz, 2 H), 1.39–1.27 (m, 2 H), 1.29 (s, 3 H), 1.23–1.08 (m, 2 H), 0.80 (t, *J* = 7.17 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.1, 168.8, 138.1, 137.9, 137.8, 136.4, 128.5, 128.4, 128.0, 127.9, 127.7, 127.6, 124.3, 122.6, 120.4, 119.2, 110.9, 109.6, 83.1, 83.0, 78.3, 77.6, 75.2, 74.6, 73.6, 68.6, 39.3, 33.3, 31.4, 19.9, 13.6; HRMS (FAB) calcd for $C_{43}H_{48}N_2O_7$ 704.3461, found 704.3403.

3-Methyl-1-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-1*H*-indole (12). From 89.1 mg (0.68 mmol) of skatole (**4**), 28.5 mg (0.71 mmol) of NaH, and 141.5 mg (0.34 mmol) of tri-*O*-benzyl-D-galactal was obtained 91.1 mg of **12** (44%) after flash chromatography (toluene/ethyl acetate (25:1)) and recrystallization from ether: mp 144–146 °C (Et_2O); $[\alpha]^{25}_D$ +13.8 (*c*, 1.66, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 2850, 1743, 1454, 1361, 1220, 1060 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.95–7.5 (m, 20 H), 5.86 (app t, *J* = 9.3 Hz, 1 H), 5.34 (d, *J* = 9.3 Hz, 1 H), 4.98 (d, *J* = 11.5 Hz, 1 H), 4.68 (d, *J* = 12.3 Hz, 1 H), 4.60 (d, *J* = 11.5 Hz, 1 H), 4.52 (d, *J* = 12.3 Hz, 1 H), 4.35 (d, *J* = 11.8 Hz, 1 H), 4.38 (d, *J* = 11.8 Hz, 1 H), 4.07 (app d, *J* = 2.4 Hz, 1 H), 3.45–3.8 (m, 4 H), 2.21 (s, 3 H), 1.63 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.8, 138.6, 138.0, 137.8, 136.7, 129.7, 128.4, 128.3, 128.0, 127.8, 127.6, 127.4, 122.7, 121.8, 119.6, 119.0, 112.5, 109.8, 83.9, 81.2, 76.0, 74.7,

73.6, 73.1, 72.1, 70.5, 68.4, 20.5, 9.6; HRMS (FAB) calcd for $C_{38}H_{39}NO_6$ 605.2767, found 605.2796.

3-Acetamido-*N*,*N*-diethyl-1-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-1*H*-indole (13). From 114.1 mg (0.50 mmol) of **5**, 22.8 mg (0.58 mmol) of NaH, and 92.0 mg (0.22 mmol) of tri-*O*-benzyl-D-galactal was obtained 78.1 mg of **13** (50%) after flash chromatography (hexanes/EtOAc (1:2)): mp 97–99 °C (Et_2O); $[\alpha]^{25}_D$ +9.82 (*c* = 0.83, $CHCl_3$); IR (melted) ν_{max} 2900, 1745, 1630, 1460, 1365, 1220 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (dt, *J* = 7.9, 0.6 Hz, 1 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 7.44–7.40 (m, 15 H), 7.17–7.09 (m, 3 H), 5.88 (t, *J* = 9.5 Hz, 1 H), 5.37 (d, *J* = 9.1 Hz, 1 H), 5.04 (d, *J* = 11.5 Hz, 1 H), 4.73 (d, *J* = 12.3 Hz, 1 H), 4.65 (d, *J* = 11.5 Hz, 1 H), 4.57 (d, *J* = 12.2 Hz, 1 H), 4.46 (d, *J* = 11.7 Hz, 1 H), 4.41 (d, *J* = 11.7 Hz, 1 H), 4.13 (d, *J* = 2.4 Hz, 1 H), 3.83 (dd, *J* = 7.2, 6.1 Hz, 1 H), 3.75 (dd, *J* = 9.9, 2.7 Hz, 1 H), 3.75 (d, *J* = 2.4 Hz, 2 H), 3.69 (dd, *J* = 9.1, 7.6 Hz, 1 H), 3.59 (dd, *J* = 9.2, 5.5 Hz, 1 H), 3.43–3.25 (m, 4 H), 1.66 (s, 3 H), 1.11–1.06 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 168.6, 138.5, 137.8, 137.6, 136.3, 128.4, 128.2, 127.9, 127.8, 127.5, 127.4, 123.5, 122.2, 120.1, 119.3, 110.3, 84.2, 80.8, 75.9, 14.6, 73.6, 72.8, 71.9, 70.3, 68.2, 42.3, 40.0, 31.6; HRMS (FAB) calcd for $C_{43}H_{48}N_2O_7$ 704.3461, found 704.3478. Anal. Calcd for $C_{43}H_{48}N_2O_7$: C, 73.27; H, 6.86; N, 3.97. Found: C, 73.16; H, 6.79; N, 4.01.

3-Acetamido-*N*-butyl-1-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-1*H*-indole (14). From 135.7 mg (0.59 mmol) of **6**, 48.0 mg (1.20 mmol) of NaH, and 120.6 mg (0.29 mmol) of tri-*O*-benzyl-D-galactal was obtained 150.4 mg of **14** (74%) after flash chromatography (benzene/ethyl acetate (1:2)): mp 147–148 °C (EtOAc); $[\alpha]^{25}_D$ +55.7 (*c* 0.61, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3380, 2900, 1745, 1645, 1525, 1460, 1370 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.7, 0.7 Hz, 1 H), 7.40–7.23 (m, 17 H), 7.18 (t, *J* = 7.29 Hz, 1 H), 7.09 (t, *J* = 7.28 Hz, 1 H), 6.05 (br t, 1 H), 5.59 (dd, *J* = 9.8, 8.9 Hz, 1 H), 5.34 (d, *J* = 8.8 Hz, 1 H), 5.01 (d, *J* = 11.5 Hz, 1 H), 4.71 (d, *J* = 12.3 Hz, 1 H), 4.64 (d, *J* = 11.5 Hz, 1 H), 4.58 (d, *J* = 12.3 Hz, 1 H), 4.45 (d, *J* = 11.8 Hz, 1 H), 4.44 (d, *J* = 11.8 Hz, 1 H), 4.11 (d, *J* = 2.7 Hz, 1 H), 3.86 (dd, *J* = 6.6, 6.2 Hz, 1 H), 3.76 (dd, *J* = 10.1, 2.9 Hz, 1 H), 3.73–3.61 (m, 2 H), 3.67 (s, 2 H), 3.20–3.07 (m, 2 H), 1.43 (s, 3 H), 1.35–1.26 (m, 2 H), 1.14 (dt, *J* = 7.9, 7.1 Hz, 2 H), 0.78 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.5, 138.3, 137.7, 137.5, 136.3, 128.4, 128.4, 128.3, 127.9, 127.7, 127.4, 124.9, 122.4, 120.3, 119.0, 110.2, 109.8, 83.6, 80.0, 76.3, 74.8, 73.6, 73.6, 73.0, 72.4, 72.4, 72.2, 68.3, 39.4, 33.0, 31.2, 19.8, 13.6; HRMS (FAB) calcd for $C_{43}H_{48}N_2O_7$ 704.3461, found 704.3490.

1,5-Anhydro-3,6-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranose (15). To a solution of 3.310 g (22.7 mmol) of 3,4,6-trihydroxy-D-glucal in 75 mL of dry MeOH was added 5.639 g (22.7 mmol) of dibutyltin oxide. The reaction mixture was refluxed for approximately 5 h until it became homogeneous. The MeOH was evaporated in vacuo, and the residue was submitted to three azeotropic distillations using dry benzene to remove the MeOH. To the resulting white solid was added 200 mL of dry benzene, 16.30 g (50.6 mmol) of tetrabutylammonium bromide, and 5.9 mL (49.6 mmol) of benzyl bromide. The reaction mixture was refluxed utilizing a Dean-Stark trap for 10 h. The benzene was evaporated in vacuo, and the residue was dissolved in ethyl acetate and washed with water (3×) and then brine. The organic extract was dried over $MgSO_4$, filtered, and concentrated. The residual oil was flash chromatographed on silica gel (hexanes/ethyl acetate (4:1, 3:1)) to yield 3.488 g of glucal **15**, a colorless oil (47%): $[\alpha]^{25}_D$ −22.2 (*c* 2.50, $CHCl_3$); IR (neat) ν_{max} 3400, 2830, 1640, 1450, 1230, 1090 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.36–7.28 (m, 10 H), 6.37 (dd, *J* = 6.1, 1.5 Hz, 1 H), 4.83 (dd, *J* = 6.2, 2.3 Hz, 1 H), 4.68 (d, *J* = 11.8 Hz, 1 H), 4.62 (d, *J* = 12.1 Hz, 1 H), 4.59 (d, *J* = 11.8 Hz, 1 H), 4.55 (d, *J* = 12.0 Hz, 1 H), 4.08 (ddd, *J* = 5.7, 2.3, 1.6 Hz, 1 H), 3.98–3.94 (m, 2 H), 3.80–3.78 (m, 2 H), 2.55 (br d, 1 H, OH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 144.6, 138.4, 137.9, 128.3, 127.6, 100.1, 77.0, 76.3, 70.7, 69.2, 68.9; MS (FAB (M + Na^+)) *m/e* 349, 325 (M − H), 269, 235, 219, 181, 163.

1,5-Anhydro-3,6-di-*O*-benzyl-4-*O*-methyl-2-deoxy-D-*arabino*-hex-1-enopyranose (16). To a solution of 3.468 g (10.6 mmol) of glucal **15** in 40 mL of dry DMF at 0 °C was added 514 mg (60% dispersion in oil, 12.9 mmol) of NaH. The mixture was stirred at 0 °C for 30 min before the addition of 3.30 mL (53.0 mmol) of MeI. The reaction mixture was allowed to slowly reach room temperature and stir overnight. The crude mixture was diluted with ether and washed with water (3×) and then brine. The organic extract was dried over $MgSO_4$, filtered, and concentrated. The residual oil was flash chromatographed on silica gel (hexanes/ethyl acetate (5:1)) to yield the glucal **16** as a colorless oil (3.059 g, 85%): $[\alpha]^{23}_D$ −9.8 (*c*, 1.40, $CHCl_3$); IR (neat) ν_{max} 2850, 1640, 1450, 1240, 1010 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.28 (m, 10 H), 6.43 (dd, *J* = 6.2, 1.4 Hz, 1 H, H1), 4.88 (dd, *J* = 6.2, 2.2 Hz, 1 H, H2), 4.68 (d, *J* = 11.7 Hz, 1 H), 4.64 (d, *J* = 12.1 Hz, 1 H), 4.60 (d, *J* = 11.7 Hz, 1 H), 4.58 (d, *J* = 12.1 Hz, 1 H), 4.12 (ddd, *J* = 5.8, 2.9, 1.3 Hz, 1 H), 4.07 (ddd, *J* = 8.1, 5.1, 3.2 Hz, 1 H), 3.84 (dd, *J* = 10.7, 5.1 Hz, 1 H), 3.77 (dd, *J* = 10.7, 3,3 Hz, 1 H), 3.63 (dd, *J* = 8.1, 5.8 Hz, 1 H), 3.12 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 144.5, 138.5, 138.1, 128.3, 127.6, 127.5, 127.5, 99.8, 76.5, 76.4, 74.9, 73.4, 70.4, 68.5, 59.2; HRMS (FAB) calcd for $C_{21}H_{24}O_4$ 339.1596, found 339.1628.

1,2-Anhydro-3,6-di-*O*-benzyl-4-*O*-methyl-D-glucopyranose (17a). To a solution of 94.2 mg (0.277 mmol) of **16** in 2 mL of dry CH_2Cl_2 at 0 °C was added dropwise over 10 min 3.40 mL (0.306 mmol) of a 0.09 M solution of dimethyldioxirane in dry acetone. The reaction mixture was stirred at 0 °C until the glucal was completely consumed by TLC (30 min). The solvents were evaporated in vacuo, and the residual colorless oil was dried on a mechanical pump for 1 h to give 99.1 mg of **17** (15:1 **17a**/**17b**) in quantitative yield: $[\alpha]^{25}_D$ 36.4 (*c* 0.77, $CHCl_3$); IR (neat) ν_{max} 3020, 2920, 1700, 1455, 1430, 1365, 1255, 1205 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.25 (m, 10 H), 4.95 (d, *J* = 2.3 Hz, 1 H), 4.78 (d, *J* = 11.6 Hz, 1 H), 4.70 (d, *J* = 11.6 Hz, 1 H), 4.63 (d, *J* = 12.1 Hz, 1 H), 4.54 (d, *J* = 12.1 Hz, 1 H), 3.85 (dd, *J* = 7.9, 1.0 Hz, 1 H), 3.72 (dd, *J* = 11.1, 4.1 Hz, 1 H), 3.66–3.60 (m, 2 H), 3.48 (s, 3 H), 3.36 (dd, *J* = 9.7, 8.0 Hz, 1 H), 3.02 (d, *J* = 2.3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 137.6, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 78.5, 77.4, 75.8, 73.4, 72.2, 69.4, 68.1, 60.1, 52.5.

4-Bromo-3,4-dihydro-3-[7-chloro-1-[[2-(trimethylsilyl)-ethoxy]methyl]-1*H*-indol-3-yl]-1-(benzyloxymethyl)-1*H*-pyrrole-2,5-dione (20). To a solution of 2.300 g (5.16 mmmol) of **18** in 40 mL of dry THF at 0 °C was added 256 mg (60% dispersion in oil, 6.40 mmol) of NaH. The resulting dark purple solution was stirred at 0 °C for 15 min, and 1.40 mL (7.90 mmol) of [2-(trimethylsilyl)ethoxy]methyl chloride was added. The reaction mixture was stirred at room temperature for 15 min until an orange solution was obtained. The crude mixture was diluted with ether and washed with water and then brine. The organic extract was dried over Na_2SO_4, filtered, and concentrated. The residual orange oil was flash chromatographed on silica gel (hexanes/ethyl acetate (6:1)) to yield the protected indole **20** as an orange foam (2.979 g, 94%): IR ($CHCl_3$) ν_{max} 2950, 1770, 1715, 1615, 1150, 1090 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.87 (s, 1 H), 7.77 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.34–7.24 (m, 6 H), 7.16 (t, *J* = 7.9 Hz, 1 H), 5.89 (s, 2 H), 5.16 (s, 2 H), 4.66 (s, 2 H), 3.59 (m, *J* = 8.2, 8.0 Hz, 2 H), 0.93 (m, *J* = 8.2, 8.0 Hz, 2 H), −0.05 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.9, 167.1, 144.2, 137.4, 134.7, 132.1, 128.4, 127.8, 127.6, 125.3, 122.1, 121.9, 117.8, 105.9, 95.6, 77.8, 71.8, 67.9, 66.3, 17.8; MS (FAB (M^+)) *m/e* 576 (M^+), 505, 457, 398, 274, 226.

3,4-Dihydro-3-[7-chloro-1-[[2-(trimethylsilyl)ethoxy]-methyl]-1*H*-indol-3-yl]-4-(7-chloro-1*H*-indol-3-yl)-1-(benzyloxymethyl)-1*H*-pyrrole-2,5-dione (21). To a solution of 1.449 g (9.56 mmol) of 7-chloroindole in 25 mL of dry benzene was added 3.30 mL (9.9 mmol) of a 3.0 M solution of MeMgI in ether. The solution was stirred at room temperature for 15 min after which it was cannulated dropwise (15 min) into a solution of 2.733 g (4.73 mmol) of **20** in 25 mL of dry benzene at 0 °C. The resulting dark purple solution was stirred at 0 °C for 30 min and then at room temperature for 12 h. The benzene was removed in vacuo, and the residue was dissolved in ether and washed with water. The aqueous phase was washed with two portions of ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residual red oil was flash chromatographed on silica gel (hexanes/ethyl acetate (6:1, 5:1)) to yield the monoprotected bisindole **21** (2.111 g, 69% (77% corrected)) as an orange foam along with unreacted starting material (**20**, 285 mg): IR ($CHCl_3$) ν_{max} 3440, 2940, 1760, 1705, 1540, 1415 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.75 (s, 1 H), 7.82 (d, *J* = 2.8 Hz, 1 H), 7.79 (s, 1 H), 7.38–7.20 (m, 5 H), 7.06 (dd,

J = 7.5, 0.9 Hz, 1 H), 7.06 (d, J = 7.8 Hz, 1 H), 6.79 (d, J = 8.1 Hz, 1 H), 6.73 (dd, J = 8.1, 1.2 Hz, 1 H), 6.66 (dd, J = 8.0, 7.8 Hz, 1 H), 6.63 (dd, J = 8.0, 7.5 Hz, 1 H), 5.86 (s, 2 H), 5.20 (s, 2 H), 4.69 (s, 2 H), 3.57 (t, J = 8.0 Hz, 2 H), 0.92 (t, J = 8.0 Hz, 2 H), −0.37 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.2, 137.7, 134.3, 133.1, 131.5, 129.7, 129.1, 128.3, 128.2, 127.7, 127.6, 127.0, 126.9, 124.7, 122.0, 121.4, 121.2, 120.4, 120.2, 117.1, 116.6, 107.8, 106.6, 77.4, 71.7, 67.3, 65.9, 17.8; HRMS (FAB) calcd for $C_{34}H_{33}Cl_2N_2O_4Si$ 645.1617, found 645.1665.

3,4-Dihydro-3-[7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-indol-3-yl]-4-[7-chloro-1-(3,6-di-*O*-benzyl-4-*O*-methyl-β-D-glucopyranosyl)-1*H*-indole-3-yl]-1-(benzyloxymethyl)-1*H*-pyrrole-2,5-dione (22). To a solution of 324.2 mg (0.952 mmol) of glucal **16** in 4 mL of dry CH_2Cl_2 at 0 °C was added dropwise 13 mL (1.2 mmol) of a 0.09 M solution of dimethyldioxirane in acetone. The reaction mixture was stirred at 0 °C until TLC indicated complete consumption of **16** (30 min). The solution was evaporated in vacuo and dried on a mechanical pump for 1 h to afford the 1,2-anhydro sugars **17a** and **17b** (15:1) in quantitative yield. To a solution of 210.2 mg (0.325 mmol) of the secoaglycon **21** in 5 mL of dry THF was added 16.4 mg (0.41 mmol, 60% dispersion in oil) of NaH. The resulting dark purple solution was allowed to stir for 30 min. A solution of **17a,b** in 5 mL of dry THF was then added dropwise (15 min) to the purple solution. The final reaction mixture was stirred at room temperature for 1 h and then was refluxed for 8 h. The mixture was poured into saturated $NaHCO_3$ and extracted with ethyl acetate (3×). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residual red oil was flash chromatographed on silica gel (benzene/ethyl acetate (2, 5, 10%)), to yield 157.3 mg (48%) of the β-glucopyranoside **22**, an orange glass, and 33.4 mg (10%) of the α-mannopyranoside **23** along with 29.6 mg of the starting secoaglcon **21**. **22**: $[\alpha]^{25}_D$ +7.14 (*c* 1.42, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3540, 2930, 1765, 1705, 1560, 1540 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1 H), 7.77 (s, 1 H), 7.39–7.21 (m, 15 H), 7.06 (dd, J = 7.6, 0.9 Hz, 1 H), 7.02 (dd, J = 7.6, .9 Hz, 1 H), 6.83 (dd, J = 8.4, 1.0 Hz, 1 H), 6.74 (dd, J = 8.3, 1.00 Hz, 1 H), 6.66 (dd, J = 8.1, 7.7 Hz, 1 H), 6.63 (dd, J = 8.1, 7.7 Hz, 1 H), 6.31 (d, J = 9.0 Hz, 1 H), 5.82 (d, J = 10.8 Hz, 1 H), 5.81 (d, J = 10.8 Hz, 1 H), 5.18 (d, J = 10.9 Hz, 1 H), 5.17 (d, J = 10.9 Hz, 1 H), 4.98 (d, J = 11.4 Hz, 1 H), 4.80 (d, J = 11.4 Hz, 1 H), 4.68 (s, 2 H), 4.58 (d, J = 12.0 Hz, 1 H), 4.48 (d, J = 12.0 Hz, 1 H), 3.95 (br t, J = 8.9 Hz, 1 H), 3.77–3.76 (m, 2 H), 3.68–3.66 (m, 1 H), 3.64 (t, J = 8.8 Hz, 1 H), 3.55 (s, 3 H), 3.54 (t, J = 8.0 Hz, 2 H), 3.52 (t, J = 9.3 Hz, 1 H), 2.27 (br d, 1 H), 0.91 (t, J = 8.0 Hz, 2 H), −0.04 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.1, 138.4, 138, 137.7, 134.6, 132.3, 131.6, 129.8, 129.5, 129.4, 128.6, 128.3, 127.9, 127.7, 127.5, 127.2, 126.9, 125.3, 124.7, 121.6, 121.4, 120.6, 120.4, 117.2, 116.9, 107.6, 106.5, 85.6, 84.2, 79.6, 77.5, 75.2, 73.5, 72.4, 71.6, 68.7, 67.3, 65.9, 65.1, 60.5, 17.7, −1.4; HRMS (FAB) calcd for $C_{55}H_{57}Cl_2N_3O_9Si$ 1001.3241, found 1001.3317. Anal. Calcd for $C_{55}H_{57}Cl_2N_3O_9Si$: C, 65.86; H, 5.73; N, 4.19. Found: C, 66.00; H, 5.88; N, 3.93.

3,4-Dihydro-3-[7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-indol-3-yl]-4-[7-chloro-1-(3,6-di-*O*-benzyl-4-*O*-methyl-α-D-mannopyranosyl)-1*H*-indol-3-yl]-1-(benzyloxymethyl)-1*H*-pyrrole-2,5-dione (23): $[\alpha]^{25}_D$ −17.8 (*c* 1.94, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3540, 2940, 1760, 1705, 1560, 1540, 1350 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.98 (s, 1 H), 7.78 (s, 1 H), 7.37–7.21 (m, 15 H), 7.02 (dd, J = 7.9, 2.3 Hz, 2 H), 6.99 (d, J = 8.2 Hz, 1 H), 6.77 (dd, J = 8.3, 7.3 Hz, 2 H), 6.63 (t, J = 7.8 Hz, 2 H), 6.60 (t, J = 7.8 Hz, 2 H), 5.84 (d, J = 10.9 Hz, 1 H), 5.82 (d, J = 10.8 Hz, 1 H), 5.19 (s, 2 H), 4.75 (d, J = 11.6 Hz, 1 H), 4.69 (s, 2 H), 4.66 (d, J = 10.3 Hz, 1 H), 4.53 (d, J = 12.1 Hz, 1 H), 4.52 (d, J = 12.1 Hz, 1 H), 4.20–4.12 (m, 2 H), 4.07 (t, J = 3.6 Hz, 1 H), 3.91 (dd, J = 10.1, 6.6 Hz, 1 H), 3.80 (dd, J = 10.1, 6.3 Hz, 1 H), 3.64 (dd, J = 4.0, 2.7 Hz, 1 H), 3.55 (dd, J = 8.3, 7.7 Hz, 2 H), 3.42 (s, 3 H), 2.46 (br d, 1 H), 0.92 (d, J = 8.3, 7.7 Hz, 2 H), −0.03 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.2, 171.0, 138.0, 137.8, 137.3, 134.5, 132.3, 131.6, 130.2, 129.7, 129.3, 128.7, 128.3, 128.2, 128.0, 127.8, 127.7, 127.4, 125.2, 124.8, 121.6, 121.1, 120.6, 120.5, 117.1, 116.7, 107.8, 106.7, 79.4, 78.3, 75.8, 75.5, 73.5, 73.3, 71.7, 69.1, 68.2, 67.4, 65.9, 58.0, 17.8, −1.4; HRMS (FAB) calcd for $C_{55}H_{57}Cl_2N_3O_9Si$ 1001.3241, found 1001.3276.

3,4-Dihydro-3-(7-chloro-1*H*-indol-3-yl)-4-[7-chloro-1-(3,6-di-*O*-benzyl-4-*O*-methyl-β-D-glucopyranosyl)-1*H*-indol-3-yl]-1-(benzyloxymethyl)-1*H*-pyrrole-2,5-dione (24). To a solution of 223.9 mg (0.223 mmol) of **22** in 20 mL of dry THF was added ~0.5 g of flame-dried powdered molecular sieves 4 Å, followed by 0.45 mL (0.45 mmol) of TBAF (1.0 M in THF). The reaction mixture was stirred at room temperature for 30 min and then was refluxed for 2 h. The dark purple mixture was cooled to room temperature and filtered, and the molecular sieves were washed with ethyl acetate. The organic phase was washed with water (3×) and then brine. The organic extract was dried over Na_2SO_4, filtered, and concentrated. The residual orange oil was flash chromatographed on silica gel (benzene/ethyl acetate (10:1)) to yield 122.9 mg of **24** (63% (73% corrected)), an orange glass, along with 29.1 mg of the starting material **22**: $[\alpha]^{25}_D$ +27.2 (*c* 7.20, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3540, 3440, 2920, 1760, 1705, 1535, 1415, 1350 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.99 (s, 1 H), 7.88 (s, 1 H), 7.49 (d, J = 2.8 Hz, 1 H), 7.46–7.21 (m, 15 H), 7.07 (dd, J = 7.2, 1.6 Hz, 1 H), 7.02 (dd, J = 7.7, 0.8 Hz, 1 H), 6.98 (d, J = 8.0 Hz, 1 H), 6.73 (dd, J = 8.0, 1.6 Hz, 1 H), 6.69 (d, J = 7.9 Hz, 1 H), 6.68 (t, J = 7.9 Hz, 1 H), 6.67 (dd, J = 8.1, 7.2 Hz, 1 H), 6.30 (d, J = 9.1 Hz, 1 H), 5.13 (d, J = 10.9 Hz, 1 H), 5.09 (d, J = 10.9 Hz, 1 H), 4.96 (d, J = 11.2 Hz, 1 H), 4.83 (d, J = 11.2 Hz, 1 H), 4.66 (s, 2 H), 4.62 (d, J = 11.9 Hz, 1 H), 4.48 (d, J = 11.9 Hz, 1 H), 3.92 (dt, J = 8.9, 3.10 Hz, 1 H), 3.76–3.59 (m, 4 H), 3.56 (s, 3 H), 3.29 (t, J = 9.2 Hz, 1 H), 3.24 (br s, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.4, 170.9, 138.3, 137.8, 137.6, 133.2, 132.3, 129.8, 128.7, 128.6, 128.3, 128.1, 127.9, 129.6, 126.5, 125.3, 122.2, 121.4, 120.9, 120.7, 117.0, 116.7, 107.5, 107.2, 85.4, 83.9, 79.5, 75.4, 73.2, 71.9, 71.7, 68.5, 67.3, 60.5; HRMS (FAB) calcd for $C_{49}H_{43}Cl_2N_3O_8$ 871.2427, found 871.2464.

6-(Benzyloxymethyl)-1,11-dichloro-12-(3,6-di-*O*-benzyl-4-*O*-methyl-β-D-glucopyranosyl)indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7-dione (25). A solution containing 95.8 mg (0.11 mmol) of **24**, catalytic I_2 (10 mg, 0.04 mmol) in 80 mL of benzene was placed in a quartz tube and was irradiated (Hanovia medium-pressure Hg lamp, 450-W, Vycor filter, 3000 Å), while air was bubbling slowly through the solution for 3 h. The benzene was evaporated in vacuo, and the residual red oil was flash chromatographed (benzene/ethyl acetate (5, 10, 20%)) to yield 70.7 mg of **25** (74%): $[\alpha]^{25}_D$ +80.4 (*c*, 1.15, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3500, 3330, 2930, 1755, 1700, 1570, 1345 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (br s, 1 H), 9.30 (d, J = 7.6 Hz, 1 H), 8.21 (d, J = 7.5 Hz, 1 H), 7.59 (d, J = 7.7 Hz, 1 H), 7.38–7.33 (m, 2 H), 7.28 (d, J = 9.3 Hz, 1 H), 7.23–7.07 (m, 16 H), 5.08 (d, J = 11.4 Hz, 1 H), 4.95 (d, J = 11.4 Hz, 1 H), 4.95 (d, J = 11.1 Hz, 1 H), 4.72 (ddd, J = 14.4, 8.9, 5.5 Hz, 1 H), 4.69 (d, J = 12.7 Hz, 1 H), 4.58 (d, J = 12.5 Hz, 1 H), 4.44 (d, J = 12.1 Hz, 1 H), 4.42 (d, J = 12.1 Hz, 1 H), 4.18 (br d, J = 11.0 Hz, 1 H), 4.10–3.91 (m, 6 H), 3.72 (s, 3 H), ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.4, 168.3, 138.6, 137.9, 137.5, 137.3, 130.8, 130.1, 128.2, 128.1, 128.0, 127.7, 127.5, 127.3, 125.0, 124.6, 122.9, 122.7, 122.0, 120.8, 119.9, 118.8, 118.3, 116.9, 116.4, 86.0, 84.8, 79.6, 79.1, 75.8, 73.6, 73.5, 71.7, 68.1, 66.9, 61.1; HRMS (FAB) calcd for $C_{49}H_{41}C_2N_3O_8$ 869.2272, found 869.2328. Anal. Calcd for $C_{49}H_{41}Cl_2N_3O_8$: C, 67.59; H, 4.75; N, 4.83. Found: C, 67.34; H, 4.90; N, 4.60.

Rebeccamycin (1). To a solution of 29.5 mg (0.0339 mmol) of **25** in 2.5 mL of EtOH/ethyl acetate (4:1) was added 15 mg of $Pd(OH)_2$. The mixture was stirred for 5 h under a hydrogen atmosphere. The catalyst was filtered off and washed with ethyl acetate. The solvents were evaporated in vacuo, and the residue was dissolved in 2 mL of dry THF and was chilled to 0 °C. NH_3 was bubbled in the solution for 10 min. The reaction mixture was then allowed to stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the residue (preadsorbed on silica gel with THF) was flash chromatographed on silica gel (benzene/ethyl acetate (2:1)) to yield 13.9 mg of **1** (72%) as a light yellow solid, along with 2.7 mg (~14%) of a mixture of compounds suffering lost of chlorine. A analytical sample of **1** was obtained by trituration in hot MeOH follow by a filtration. The residual light yellow solid and then dried in vacuo at 80 °C: mp 327–332 °C; $[\alpha]^{25}_D$ +137.7 (*c* 0.86, THF); IR ($CHCl_3$) ν_{max} 3400, 3340, 3040, 2900, 1745, 1700, 1570, 1460, 1405, 1375, 1320, 1270 cm^{-1}; ^{1}H NMR (490 MHz, DMSO) δ 11.36 (s, 1 H), 10.69 (s, 1 H), 9.27 (d, J = 7.8 Hz, 1 H), 9.08 (d, J = 8.0 Hz, 1 H), 7.73 (d, J = 7.7 Hz, 1 H), 7.69 (d, J = 7.8 Hz, 1 H), 7.45 (t, J = 7.8

Hz, 2 H), 6.96 (d, J = 9.2 Hz, 1 H), 5.43 (d, J = 6.0 Hz, 1 H), 5.32 (br t, 1 H), 5.03 (d, J = 5.7 Hz, 1 H), 3.96 (app d, J = 3.0 Hz, 2 H), 3.84 (dt, J = 9.8, 3.2 Hz, 1 H), 3.69 (t, J = 8.8 Hz, 1 H), 3.64 (t, J = 9.5 Hz, 1 H), 3.60 (s, 3 H), 3.58 (t, J = 8.8 Hz, 1 H); ^{13}C NMR (62.5 MHz, DMSO) δ 170.3, 170.1, 137.6, 137.1, 129.8, 129.6, 126.9, 125.0, 124.0, 123.4, 123.2, 122.4, 122.0, 120.5, 119.3, 117.6, 116.1, 84.3, 80.1, 79.1, 77.3, 72.1, 59.9, 59.8; HRMS (FAB, M + H) calcd for $C_{27}H_{22}Cl_2N_3O_7$ 570.0835, found 570.0858.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of most compounds (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.