Conformational Control in the Rebeccamycin Class of Indolocarbazole Glycosides

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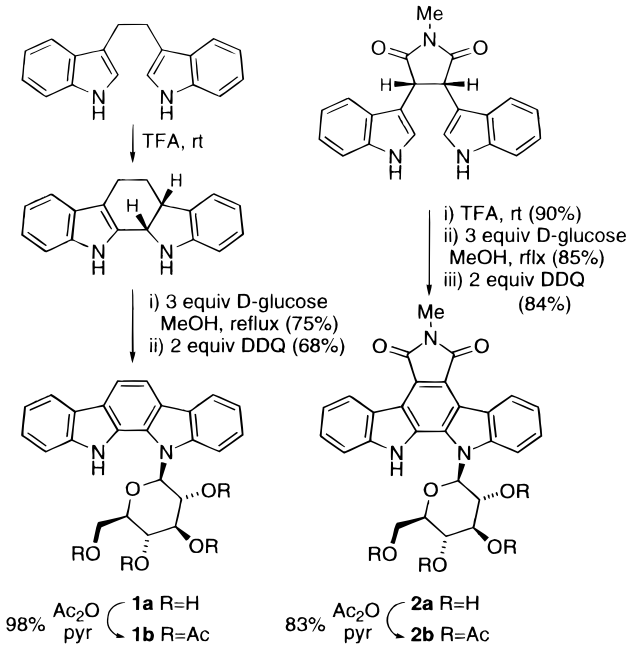
Indolocarbazole glycosides are balanced between two conformations: a "closed" conformation containing a cyclic hydrogen bond between the indolocarbazole NH and the pyranose oxygen and an "open" conformation in which the indolocarbazole NH is hydrogen bonded to solvent. The open conformation never has a commanding advantage, even in DMSO, but in nonpolar environments the cyclic conformation predominates.

Introduction

The indolocarbazole glycosides have two basic conformational designs. The staurosporine class is rigid because the pseudocarbohydrate moiety is connected to the indolocarbazole in two places. In contrast, the rebeccamycin class seems to offer greater flexibility because it is connected only at the anomeric position as a β-glycoside. For solubility, ^{1}H NMR data for most of the indolocarbazole glycosides has been obtained in highly polar solvents where two conformations are observed. This conformational dichotomy is widely recognized yet unexplained. In this paper we show that the indolocarbazole NH forms a cyclic hydrogen bond with the pyranose oxygen−an effect that is only apparent in nonpolar environments. This conformational control element may preorganize the molecule for biological activity.

Members of the rebeccamycin class of indolocarbazole glycosides have shown activity in a variety of mouse xenograft models and have since advanced to human clinical trials.[1−3] These antitumor natural products are generally regarded as "inhibitors" of human topoisomerase I.[4] Topoisomerases resolve topological problems of double-stranded DNA by changing supercoiling topology. Topoisomerase I relaxes supercoiling by cleaving one strand of DNA, allowing it to unwind, and then rejoining the temporary strand break.[5] Rebeccamycins do not inhibit the cleavage step; they inhibit the rejoining step.[6] This mechanism is selective for rapidly dividing cells which undergo programmed cell death if DNA damage is detected.[7]

Scheme 1



Results and Discussion

1. Synthesis. Mannich dimerization and glycosylation have made it possible to easily prepare a wide range of indolocarbazole glycosides. To understand the conformational bias of the indolocarbazole glycosides, we first looked at a simple indolocarbazole glycoside **1a** prepared by Mannich cyclization of 1,2-bis(3-indolyl)ethane, carbohydrate capture of D-glucose, and oxidative aromatization with DDQ. This route is general and provides access to the tjipanazoles, which have only modest antifungal activity, and potent antitumor antibiotics such as AT2433-B2, a member of the rebeccamycin class of natural products (Scheme 1).[8−10]

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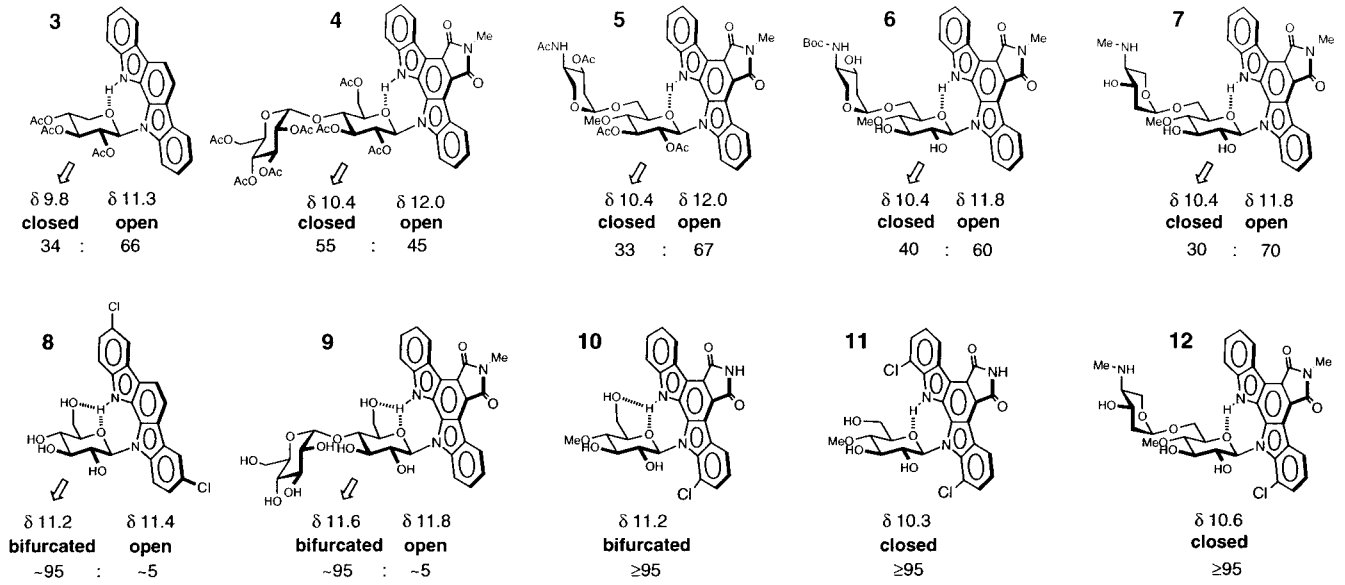
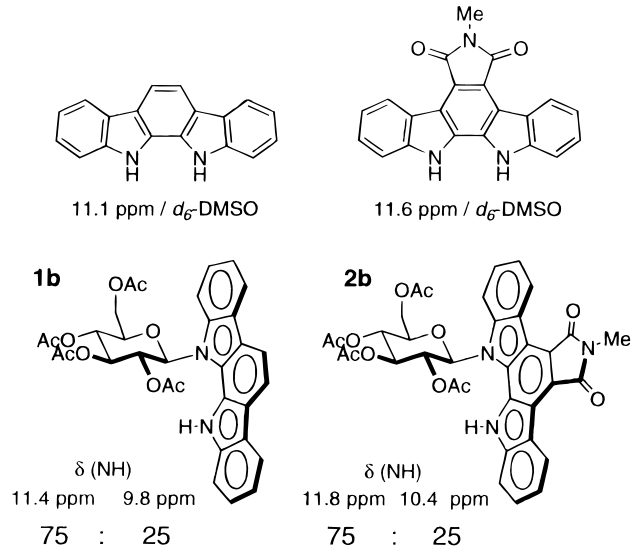


Figure 1. ^{1}H NMR chemical shifts of the indolocarbazole NH in d_6-DMSO correspond to one of three different conformations: closed, open, or bifurcated. For compounds **3**−**9**, the arrow indicates which NH chemical shift corresponds to the structure shown.

Scheme 2



The proton NMR spectra of **1b** and **2b** exhibit two sets of signals in d_6-DMSO, corresponding to two conformations. In one conformation, the indolocarbazole NH appears to be bound to d_6-DMSO (Scheme 2), but the NH chemical shift of the other conformation is upfield by about 1.5 ppm. This divisive effect of strong hydrogen-bonding solvents on indolocarbazole glycosides is common and also affects glycosides **3**−**7** in Figure 1.[11−14]

2. ^{1}H NMR and Molecular Mechanics−Two Conformations. Molecular mechanics with the MM2* force field provides insight into the identity of the two conformations. As shown in Figure 2, the closed conformation possesses a hydrogen bond between the pyranose oxygen and the indole NH, whereas the open conformation places the indole NH underneath the plane of the pyranose in a solvent-accessible location. In both the open and closed conformations, the anomeric C−H bond is about 30° out of the plane of the aromatic ring. The forces which disfavor other conformations can be loosely described as $A_{1,3}$ strain and $A_{1,2}$ strain.

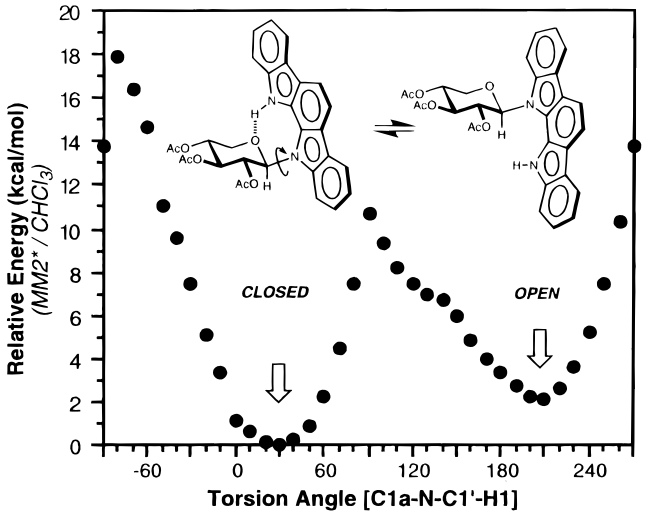


Figure 2. Molecular mechanics (MM2*/$CHCl_3$) predicts two low-energy conformations: closed and open. The closed conformation is slightly lower in energy than the open conformation.

Molecular mechanics (MM2*/$CHCl_3$) predicts that rotation about the glycosidic bond will have an activation energy of around 11 kcal/mol in glycoside **3** (Figure 2). Qualitatively, this result calculated with chloroform solvation is in good agreement with experiments in DMSO. The coalescence temperature for H5′$_{eq}$ of **3** in d_6-DMSO ($\Delta\nu = 140$ Hz) is about 50 °C, suggesting a barrier around 15 kcal/mol at room temperature. For glucoside **6** (Figure 1) with a disaccharide moiety, the coalescence temperature of the anomeric proton is about 75 °C ($\Delta\nu = 124$ Hz), corresponding to a rotational barrier of about 16 kcal/mol.

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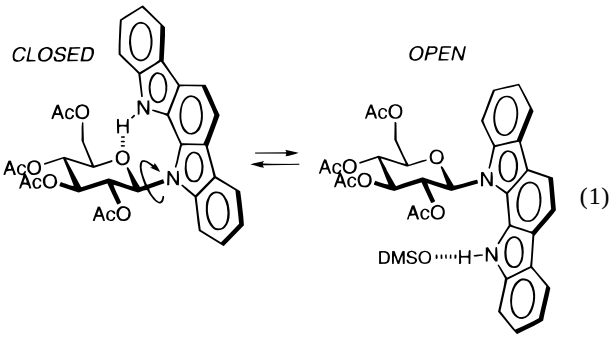
Unfortunately, molecular mechanics neglects the critical role of solvents such as DMSO, which can hydrogen bond to the indolocarbazole NH in competition with the pyranose oxygen. The ratio of closed to open conformations in different solvents decreases in the order $CDCl_3$, CD_3NO_2, d_6-acetone, d_6-DMSO (eq 1). As expected, this trend follows hydrogen-bond acceptor ability better than solvent polarity (Table 1).



(1)

Table 1. Effect of Solvent on the Conformation of 1b

solvent	closed/open	ϵ
$CDCl_3$	>99:<1	5
CD_3NO_2	90:10	36
d_6-acetone	70:30	21
d_6-DMSO	25:75	47

3. Evidence for the Closed Conformation. To date, all of the indolocarbazole β-pyranosides we have prepared adopt a single conformation in nonpolar environments such as chloroform. The NH stretch of glycosides **2b** and **3** are around 3400 cm^{-1} in chloroform, consistent with a hydrogen-bonded indole NH.[15] In deuteriochloroform, evidence for the closed conformation comes from steady-state NOEs observed in glycosides such as **3** (Figure 3a). Irradiation of the indole NH leads to enhancement of the crossring axial protons H3′ and H5′ of the pyranose. Irradiation of the H1′ proton of the pyranose ring leads to enhancement of the peri proton H2 (and also H3 through excitation transfer). A similar NOE enhancement was reported for the indolocarbazole glycoside RK-286D,[16] although the implication of this conformation was not commented upon.

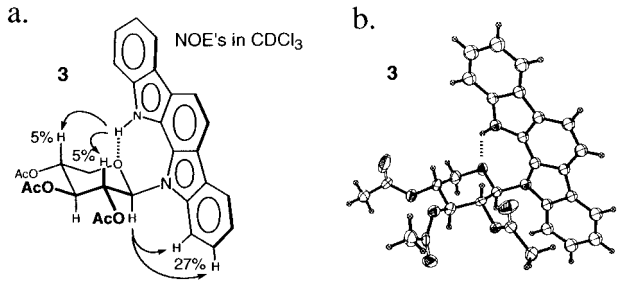


Figure 3. (a) Steady-state NOEs confirm a closed conformation for **3** in deuteriochloroform. (b) Glycoside **3** crystallizes from ethyl acetate in the closed conformation.

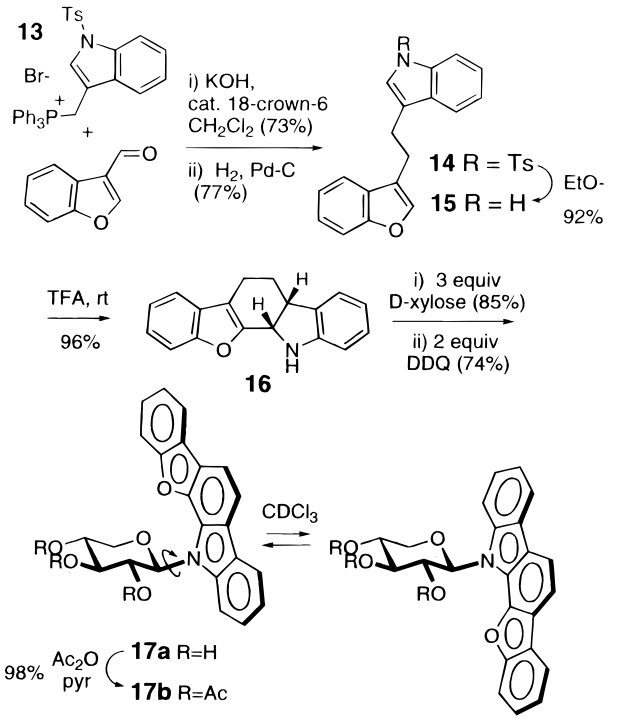
Additional evidence for a cyclic hydrogen bond comes from solid-state studies. The X-ray structure of **3** (Figure 3b) and the published crystal structure of rebeccamycin[14] clearly demonstrate the dominance of the closed conformation.

4. Controlled Mannich Cyclization—A Test of Conformational Control. The Mannich cyclization/glycosylation approach is powerful and allows one to construct variants of the indolocarbazole glycosides with surgical precision. To unambiguously assess the importance of the closed conformation, we engineered an oxa-analogue incapable of enjoying a pyranose—indolocarbazole hydrogen bond.[17]

Regiocontrol is an essential advantage of indole-Mannich cyclizations. We modified the route in Scheme 1 to include an indole-benzofuran system. Our prediction was that protonation of the indole would lead to electrophilic aromatic substitution of the benzofuran — not the other way around.

The bifunctional substrate was prepared by Wittig coupling[18] of 3-formylbenzofuran[19] and a skatolyl phosphonium ylide.[20] The double bond (1:1 mixture of *E* and *Z* isomers) was hydrogenated, and the *N*-tosyl group was removed under nucleophilic conditions to afford the Mannich cyclization substrate. The cyclization is a satisfying example of regiocontrol, giving only the desired indoline in over 90% yield. Glycosylation and rearomatization gives the single atom mutant **17a**.

Scheme 3



Two conformations are present in d_6-DMSO because there is no hydrogen bonding to stabilize either the closed conformation or the open conformation. Analysis of coupling constants in acetone at low temperature confirms that the pyranose retains the all-equatorial chair

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form in both conformations. This situation is different from indolocarbazole glycoside **3**, in which solvent and pyranose oxygen *compete* for the indolocarbazole NH. Once **17a** is acetylated, the importance of the missing NH is revealed. Without a cyclic hydrogen bond to fix the conformation in deuteriochloroform, the dramatic distinction between glycosidic rotamers is lost, and the two conformations compete ineffectually for dominance (Scheme 3).

5. Bifurcated Hydrogen Bond. Indolocarbazole β-pyranosides with hydroxymethyl groups at the 5′-position of the pyranose ring exist primarily in one conformation, even in d_6-DMSO. The 6′-OH group of glycosides **1a**, **2a**, and **8**−**10** offers the opportunity for a bifurcated hydrogen bond that exerts a pincerlike grip on the indole NH. For such derivatives, the major bifurcated conformation (>95%) is generally accompanied by a much smaller amount (<5%) of the open conformation. Both conformations exhibit downfield NH shifts above 11 ppm, consistent with strong hydrogen bonding.

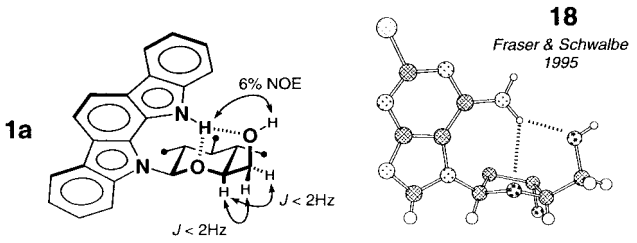

Figure 4. Bifurcated conformation in glycoside **1a** in d_6-DMSO and an isonucleoside **18**.

Evidence for the bifurcated conformation comes from NOE studies of glucoside **1a** in d_6-DMSO. The small $J_{5',6'}$ coupling constants suggest that the hydroxy group is pointed up (antiperiplanar to the 5′-H), and this is confirmed by a 6% steady-state NOE between the 6′-OH and the indolocarbazole NH. A similar bifurcated hydrogen bond has been observed in the crystal structure of a ribofuranoside derivative **18**[21] (Figure 4). As expected, the open conformation of the indolocarbazole glycosides reasserts itself when the 6-hydroxy group is acetylated.

The bifurcated arrangement is probably unnecessary for biological activity. Glycosylation of the 6′-OH in AT2433-B1 (**7**) and AT2433-A1 (**12**) prevents participation in a bifurcated hydrogen bond, an effect attributable to sterics. Yet the AT2433 antibiotics are potent antitumor agents. Rebeccamycin (**11**) also shows no evidence for a bifurcated hydrogen bond in d_6-DMSO. Rather, the chemical shift of the indole NH supports a closed conformation that involves only the pyranose oxygen. In this case, the chloro group peri to the free NH discourages participation by the 6′-OH.

6. Aglycone Substituent Effects. In the indolocarbazole glycoside natural products, substituents are found where they can best improve the hydrogen bond donor ability of the indolocarbazole NH. In d_6-DMSO such substitutents lead to downfield shifts of the indolocarbazole NH. The electronic pathway is traced in Figure 5 for several aglycones of natural products.[22−25] This acidifying effect improves hydrogen bonding to acceptor solvents and to the pyranose oxygen, but in the absence of a hydrogen bond acceptor solvent, only the pyranose oxygen can benefit from this effect.

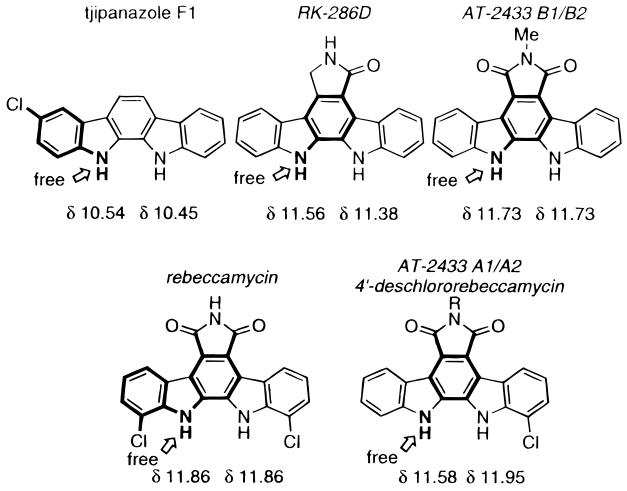

Figure 5. Downfield ^{1}H NMR shifts in d_6-DMSO suggest that electron-withdrawing groups enhance the acidity of indole protons. In indolocarbazole glycoside natural products, aryl substituents are found in positions that acidify the free NH.

The chloro substituent of AT-2433 A1/A2 appears to be too far from the free NH to affect the acidity. Molecular mechanics (MM2*/$CDCl_3$) suggests that this pattern of chloro substitution destabilizes the open conformation by about 1 kcal/mol. Thus, the chloro groups of rebeccamycin favor the closed conformation in two different ways. The chloro group peri to the free NH enhances its ability to act as a hydrogen bond donor, whereas the chloro group peri to the *N*-glycoside destabilizes the open conformation.

Conclusion

Indolocarbazole glycosides are balanced between two conformations: a closed conformation containing a cyclic hydrogen bond and an open conformation that is favored by intermolecular hydrogen bonding. The open conformation never has a commanding advantage, even in DMSO. In addition, one finds that indolocarbazole glycoside natural products are substituted in such a way as to strengthen preorganization in the closed conformation. In fact, there is no evidence that either rebeccamycin (**11**) or AT-2433-A1 (**12**) ever adopt an open conformation, even in DMSO.

The forces that favor the closed conformation are intrinsic to indolocarbazole glycoside structure. Consequently, any complex involving an indolocarbazole glycoside must act either with or against these forces. Currently, there are two basic models for the ternary interaction of topoisomerase I and DNA with inhibitors: the intercalation model depicted by Prudhomme and coworkers for indolocarbazole glycosides[26] and the base-flipped shelf model developed by Hol and co-workers for camptothecin.[27] There is still no detailed mechanistic model for the interaction of indolocarbazole glycosides

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with DNA and topoisomerase I. Because the structure of the covalent complex between DNA and human topoisomerase has recently been solved, such a model for indolocarbazole glycoside inhibition is certainly within reach.

Experimental Section

11-(β-D-Glucopyranosyl)-indolo[2,3-*a*]carbazole (1a). To (±)-5,6,6a(s),11a(s)-tetrahydroindolo[2,3-*a*]carbazole (0.40 g, 1.54 mmol) suspended in MeOH (10 mL) was added D-glucose (0.83 g, 4.6 mmol). The mixture was stirred at reflux for 24 h and then concentrated in vacuo. The residue was preadsorbed on silica gel, and the glycosylation products were separated from the excess D-glucose by silica gel chromatography (5% MeOH/EtOAc) to afford a 1:1 mixture of diastereomers (0.51 g, 78%). The mixture of diastereomers was carried on directly by taking up into 1,4-dioxane (4.8 mL). DDQ (0.56 g, 2.05 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. Saturated $NaHCO_3$ and EtOAc were added, and the solution was stirred vigorously for 15 min. The mixture was then extracted with EtOAc. The organic layers were combined, washed with H_2O and brine, and dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo afforded a residue that was preadsorbed on silica gel. Purification by silica gel chromatography (5% MeOH/EtOAc) provided **1a** (0.37 g, 73%): $[\alpha]^{23}_D = -30.0°$ (*c* 0.5, 10% MeOH/$CHCl_3$); mp 196−200 (dec) °C (CH_2Cl_2); $R_f = 0.40$ in 5% MeOH/EtOAc; IR (KBr) 3571, 3058, 2923 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 8.17 (d, $J = 7.9$, 1H), 8.15 (d, $J = 8.0$, 1H), 8.02 (d, $J = 8.2$, 1H), 7.97 (d, $J = 8.2$, 1H), 7.81 (d, $J = 8.4$, 1H), 7.55 (d, $J = 8.0$, 1H), 7.39 (m, 2H), 7.21 (m, 2H), 6.10 (d, $J = 8.4$, 1H), 5.90 (s (br), 1H), 5.32 (s (br), 1H), 5.10 (s (br), 1H), 4.84 (s (br), 1H), 4.06 (m, 1H), 4.01 (m, 1H), 3.87 (d, $J = 9.8$, 1H), 3.79 (d, $J = 11.0$, 1H), 3.56 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 140.5, 139.5, 126.4, 124.8, 124.58, 124.55, 123.8, 123.4, 122.2, 121.4, 119.7, 119.4, 119.3, 119.0, 112.9, 111.7, 111.5, 111.3, 84.3, 78.4, 76.9, 73.3, 67.6, 58.5; LRMS (FAB) 418 (100); HRMS (CI) calcd for $C_{24}H_{22}N_2O_5$ 418.1528, found 343.1527.

11-(β-D-Tetra-*O*-acetylglucopyranosyl)-indolo[2,3-*a*]-carbazole (1b). To **1a** (0.30 g, 0.07 mmol) in pyridine (0.3 mL) was added acetic anhydride (0.059 g, 0.57 mmol). The reaction mixture was stirred at room temperature for 24 h and then concentrated in vacuo. The residue was preadsorbed on silica gel and purified by silica gel chromatography (30% EtOAc/Hex) to afford **1b** (0.040 g, 98%): $[\alpha]^{23}_D = +23.4°$ (*c* 0.5, 10% MeOH/$CHCl_3$); mp 296−298 °C (CH_2Cl_2); $R_f = 0.29$ in 30% EtOAc/Hex; IR (KBr) 3418, 3048, 2948, 1750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.17 (d, $J = 7.8$, 1H), 8.09 (d, $J = 7.7$, 1H), 8.06 (d, $J = 8.2$, 1H), 7.92 (d, $J = 8.2$, 1H), 7.66 (d, $J = 8.0$, 1H), 7.47 (m, 3H), 7.31 (d, $J = 7.9$, 1H), 7.27 (d, $J = 8.0$, 1H), 6.09 (d, $J = 8.8$, 1H), 5.72 (t, $J = 9.9$, 1H), 5.56 (m, 2H), 4.74 (d, $J = 10.3$, 1H), 4.33 (m, 2H), 2.27 (s, 3H), 2.14 (s, 3H), 1.94 (s, 3H), 1.13 (s, 3H); a carbon resonance in the 109−130 ppm range could not be resolved; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 170.2, 169.3, 167.7, 139.9, 139.7, 126.6, 125.12, 125.1, 124.9, 123.39, 123.35, 120.8, 120.2, 120.1, 120.0, 114.3, 112.1, 111.6, 109.7, 84.4, 75.7, 73.1, 71.2, 67.3, 61.2, 21.2, 20.6, 20.5, 19.2, 18.6; LRMS (FAB) 586 (100); HRMS (CI) calcd for $C_{32}H_{30}N_2O_9$ 586.1951, found 586.1951.

6-Methyl-12-[β-D-glucopyranosyl]-6,7,12,13-tetrahydroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione (2a). *cis*-*N*-Methyl-2,3-bis(3-indolyl) succinimide (0.836 g, 2.43 mmol) was dissolved in 20 mL of trifluoroacetic acid. After 30 min, the TFA was removed in vacuo, and the reaction mixture was taken up in 50 mL of ethyl acetate. The reaction mixture was then poured into saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were then dried (Na_2SO_4) and concentrated in vacuo. Purification by silica gel chromatography (40% EtOAc/Hex) afforded (±)-6-methyl-4b,4c,6,7,7a,12,12b,13-octahydroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione (0.760 g, 91% yield) as an orange foam: mp 178−182 °C; $R_f = 0.36$ (40% EtOAc/Hex); IR (film) 3368, 1607 cm^{-1}; ^1H NMR (500 MHz, CD_3CN, 500 MHz) δ 9.19 (s, 1H), 7.82 (d, $J = 7.6$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 1H), 7.16 (d, $J = 7.6$, 1H), 7.10 (t, $J = 7.6$, 1H), 7.02 (t, $J = 7.6$, 1H), 6.94 (t, $J = 7.6$, 1H), 6.67 (t, $J = 7.6$, 1H), 6.56 (d, $J = 7.6$, 1H), 4.97 (s, 1H), 4.80 (d, $J = 7.6$, 1H), 4.30 (d, $J = 7.2$, 1H), 4.20 (d, $J = 7.6$, 1H), 4.01 (dd, $J = 7.6$, 2.0, 1H), 2.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 177.9, 150.6, 137.4, 135.2, 130.1, 129.0, 126.8, 123.6, 123.3, 121.4, 120.4, 119.6, 111.9, 110.8, 106.4, 54.5, 41.1, 40.7, 38.8, 25.1; MS (CI) 345, 344, 343, 285, 232; HRMS (CI) calcd for $C_{21}H_{17}N_3O_2$ 343.1321, found 343.1320. Anal. Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.51; H, 5.04; N, 12.27.

(±)-6-Methyl-4b,4c,6,7,7a,12,12b,13-octahydroindolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole-5,7-dione (101 mg, 0.292 mmol) was dissolved in 3 mL of methanol. α-D-Glucose (158 mg, 0.876 mmol) was then added, and the reaction mixture was heated to reflux. After 60 h the reaction mixture was allowed to cool to room temperature and purified by silica gel chromatography (9% MeOH/$CHCl_3$) to give a 1:1 mixture of diastereomers by ^1H NMR (0.128 g, 87%). This was dissolved in 2 mL of 1,4-dioxane, and DDQ (127 mg, 0.56 mmol) was added. After 24 h the reaction mixture was taken up in 40 mL of ethyl acetate and washed with saturated $NaHCO_3$ solution. The organic layer was then dried (Na_2SO_4) and concentrated. Purification using silica gel chromatography (3% MeOH/EtOAc) gave **2a** (107 mg, 84%) as an orange solid: mp 331 °C (dec); $[\alpha]^{23}_D = +198.5$ (*c* 0.9, THF); $R_f = 0.38$ (5% MeOH/EtOAc); IR (film) 3341, 2990, 1688 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 11.30 (s, 1H), 9.08 (d, $J = 7.6$, 1H), 8.84 (d, $J = 8.0$, 1H), 7.79 (d, $J = 8.3$, 1H), 7.51 (d, $J = 8.3$, 1H), 7.48 (t, $J = 7.7$, 1H), 7.36 (t, $J = 8.2$ Hz, 1H), 7.27 (t, $J = 7.6$, 1H), 7.22 (t, $J = 7.6$, 1H), 6.30 (d, $J = 9.2$, 1H), 5.11 (t, $J = 3.7$, 1H), 4.77 (s, 1H), 4.66 (s, 1H), 4.48 (d, $J = 5.2$, 1H), 4.38 (dd, $J = 9.6$, 3.6, 1H), 4.08−4.11 (m, 3H), 3.90−3.94 (m, 2H), 2.79 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 170.4, 170.3, 143.2, 142.1, 130.8, 129.2, 127.6, 125.8, 125.4, 122.7, 122.6, 121.4, 121.1,121.0, 119.7, 119.1, 118.7, 112.6, 112.5, 111.8, 86.1, 80.1, 78.2, 74.6, 69.0, 60.1, 23.5; MS (FAB) 517, 502, 501, 368, 339, 273, 255; HRMS (FAB) calcd for $C_{27}H_{23}N_3O_7$ 501.1536, found 501.1522. Anal. Calcd for $C_{27}H_{23}N_3O_7 \cdot H_2O$: C, 62.45; H, 4.85; N, 8.09. Found: C, 62.46; H, 4.84; N, 8.03.

6-Methyl-12-[2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl]-6,7,12,13-tetrahydroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione (2b). Compound **2a** (0.06 mmol, 29 mg) was dissolved in 1 mL of pyridine. Acetic anhydride (1.35 mmol, 100 μL) was then added. After 25 h the reaction was taken up in ethyl acetate and washed with 1 N HCl. The organic layer was then dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (60% EtOAc/Hex) afforded **2b** (33 mg, 83%): mp 268−270 °C (ethyl acetate); $[\alpha]^{23}_D = +67.4$ (*c* 1.65, $CHCl_3$); *Rf* = 0.49 (50% EtOAc/Hex); IR ($CHCl_3$) 3393, 3024, 2942, 1753, 1698, 1582 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.90 (s, 1H), 9.26 (d, $J = 8.0$, 1H), 9.22 (d, $J = 8.0$, 1H), 7.66 (d, $J = 8.0$, 1H), 7.56−7.59 (m, 2H), 7.51 (d, $J = 8.4$, 1H), 7.41 (dt, $J = 7.1$, 7.5, 2H), 6.10 (d, $J = 9.2$, 1H), 5.68 (dd, $J = 9.9$, 9.6, 1H), 5.58 (dd, $J = 9.5$, 9.2, 1H), 5.47 (dd, $J = 9.5$, 9.2, 1H), 4.81 (dd, $J = 12.7$, 3.2, 1H), 4.47−4.42 (m, 2H), 3.24 (s, 3H), 2.29 (s, 3H), 2.14 (s, 3H), 1.92 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 169.9, 169.8, 169.7, 169.2, 167.8, 141.1, 140.7, 129.9, 128.3, 127.4, 127.2, 126.0, 125.8, 122.7, 122.6, 122.0, 121.8, 121.4, 119.8, 119.4, 119.2, 111.4, 109.5, 84.3, 76.2, 70.7, 67.1, 61.0, 23.7, 21.2, 20.5, 20.4, 19.0; MS (FAB+) 669, 368, 339, 282; HRMS (FAB+) calcd for $C_{35}H_{31}N_3O_{11}$ 669.1958, found 669.1957. Anal. Calcd for $C_{35}H_{31}N_3O_{11}$: C, 62.78; H, 4.67; N, 6.27. Found: C, 62.63; H, 4.69; N, 6.24.

11-(Tri-*O*-acetyl-β-D-xylopyranosyl)indolo[2,3-*a*]carbazole (3). To a stirred suspension of (±)-5,6,6a(s),11a(s)-tetrahydroindolo[2,3-*a*]carbazole (2.04 g, 7.84 mmol) in MeOH (45 mL) was added D-xylose (3.54 g, 23.5 mmol). The reaction mixture was stirred at reflux for 12 h and then concentrated

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in vacuo. The residue was preadsorbed on silical gel and purified by silica gel chromatography (1% MeOH/EtOAc) to afford a 1:1 mixture of diastereomers (2.60 g, 85%). A portion of the mixture of diastereomers (0.21 g, 0.52 mmol) was taken on directly by taking up into 1,4-dioxane (2.1 mL). DDQ (0.242 g, 1.06 mmol) was then added, and the reaction mixture was stirred at room temperature for 12 h. Saturated $NaHCO_3$ and EtOAc were added, and the solution was stirred vigorously for 15 min. The mixture was then extracted with EtOAc. The organic layers were combined, washed with H_2O and brine, and dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo afforded a residue that was preadsorbed on silica gel. Purification by silica gel chromatography (2% MeOH/EtOAc) provided 11-(*β*-D-xylopyranosyl)indolo[2,3-*a*]carbazole (0.14 g, 70%): $[\alpha]^{23}_D = +10.4°$ (*c* 0.5, 10% MeOH/$CHCl_3$); mp 288 °C (dec, CH_2Cl_2); $R_f = 0.55$ in 1% MeOH/EtOAc; IR (KBr) 3398, 3058, 2923, cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 90 °C) δ 10.27 (s (br), 1H), 8.12 (m, 2H), 7.95 (m, 2H), 7.77 (m, 1H), 7.69 (m, 1H), 7.38 (m, 2H), 7.21 (m, 2H), 6.02 (d, $J = 8.8$, 1H), 4.84 (m, 1H), 4.65 (m (br), 2H), 4.22 (m, 1H), 3.88 (m, 2H), 3.75 (m, 1H), 3.64 (m, 1H); the ^{13}C NMR showed two sets of signals at room temperature which were not fully resolved in the 110−126 ppm region and the 67−70 ppm region; ^{13}C NMR (125 MHz, DMSO-d_6, 23 °C) δ 140.8, 139.5, 139.2, 137.6, 127.1, 126.0, 125.2, 124.9, 124.7, 124.3, 123.9, 123.4, 123.2, 122.4, 122.1, 121.6, 120.4, 119.7, 119.6, 119.4, 119.0, 114.0, 112.9, 112.6, 112.3, 111.9, 111.6, 111.4, 111.2, 87.5, 85.7, 78.0, 77.2, 73.2, 70.7, 69.6, 69.5, 69.2, 68.3; MS (FAB) 388 (100), 273 (15), 256 (39); HRMS (FAB) calcd for $C_{23}H_{20}N_2O_4$ 388.1422, found 388.1421.

To 11-(*β*-D-xylopyranosyl)indolo[2,3-*a*]carbazole (0.14 g, 0.36 mmol) in pyridine (1.2 mL) was added acetic anhydride (0.19 g, 1.82 mmol). The reaction mixture was stirred at room temperature for 17 h and then concentrated in vacuo. The residue was preadsorbed on silica gel and purified by silica gel chromatography (30−45% EtOAc/Hex) to provide **3** (0.14 g, 76%): $[\alpha]^{23}_D = -41.2°$ (*c* 1.0, $CHCl_3$); mp 316 °C (dec, EtOAc); $R_f = 0.30$ in 30% EtOAc/Hex; IR (KBr) 3402, 3040, 2952, 1753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.16 (d, $J = 7.8$, 1H), 8.08 (d, $J = 7.8$, 1H), 8.05 (d, $J = 8.1$, 1H), 7.91 (d, $J = 8.1$, 1H), 7.65 (d, $J = 8.0$, 1H), 7.47 (m, 3H), 7.29 (m, 2H), 6.00 (d, $J = 9.0$, 1H), 5.57 (t, $J = 9.5$, 1H), 5.40 (m, 2H), 4.78 (m, 1H), 3.91 (t, $J = 11.2$, 1H), 2.16 (s, 3H), 1.94 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 169.9, 167.8, 140.0, 139.4, 127.5, 125.2, 125.1, 125.0, 124.9, 123.4, 123.1, 120.7, 120.1, 119.9, 114.3, 112.0, 111.5, 110.1, 110.0, 107.5, 84.9, 72.3, 71.2, 68.7, 66.2, 20.7, 20.5, 19.1; MS (FAB) 514 (100); HRMS (FAB) calcd for $C_{29}H_{26}N_2O_7$ 514.1739, found 514.1731. Anal. Calcd for $C_{29}H_{26}N_2O_7$: C, 67.70; H, 5.09; N, 5.44. Found: C, 67.53; H, 5.14; N, 5.38.

6-Methyl-12-[*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-*β*-D-glucopyranosyl]-6,7,12,13-tetrahydroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione (4). 6-Methyl-4b,4c,6,7,7a,12,12b,13-octahydroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione (93 mg, 0.268 mmol) and maltose (290 mg, 0.804 mmol) were suspended in 3 mL of methanol. $(NH_4)_2SO_4$ (4 mg, 0.04 mmol) was added, and the reaction was heated to reflux for 62 h. The reaction mixture was then cooled to room temperature and purified by silica gel chromatography (20% methanol/chloroform). This gave 132 mg (74% yield) of the glycosylated indolindolines, which was dissolved in 6 mL of dioxane, and DDQ (99 mg, 0.433 mmol) was added. The reaction was then heated to 70 °C for 16 h. The solvent was then removed in vacuo. The crude reaction mixture was dissolved in 5 mL of pyridine, and acetic anhydride (27.3 mmol, 2 mL) was added. After 38 h the reaction mixture was poured into 100 mL of 1 N HCl and extracted with $CHCl_3$. The extracts were then dried (Na_2SO_4) and concentrated in vacuo. Purification via silica gel chromatography (1:1 Hex/EtOAc) gave **4** (157 mg, 58%): mp 156−158 °C (ethyl acetate); $[\alpha]^{23}_D = +183.7$ (*c* 0.6, $CHCl_3$); $R_f = 0.14$ (50% EtOAc/Hex); IR ($CHCl_3$) 3390, 3030, 2958, 1753, 1699, 1582 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 9.21 (d, $J = 7.8$, 1H), 9.18 (d, $J = 7.9$, 1H), 7.64 (d, $J = 8.0$, 1H), 7.59 (dd, $J = 7.2$, 7.8, 1H), 7.52 (dd, $J = 7.6$, 7.5, 1H), 7.44 (d, $J = 10.1$, 1H), 7.41 (d, $J = 7.5$, 1H), 7.36 (dd, $J = 7.6$, 7.5, 1H), 6.09 (d, $J = 9.2$, 1H), 5.60 (dd, $J = 9.0$, 8.9, 1H), 5.56 (d, $J = 4.0$, 1H), 5.46 (t, $J = 10.1$, 1H), 5.33 (t, $J = 9.2$, 1H), 5.17 (t, $J = 9.9$, 1H), 4.92 (dd, $J = 10.5$, 3.8, 1H), 4.81 (d, $J = 4.9$, 1H), 4.72 (dd, $J = 12.5$, 2.4, 1H), 4.54 (t, $J = 9.3$, 1H), 4.38 (td, $J = 9.9$, 2.4, 1H), 4.31 (dd, $J = 12.4$, 3.2, 1H), 4.22 (dd, $J = 12.6$, 1.6, 1H), 4.04 (td, $J = 10.2$, 2.5, 1H), 3.12 (s, 3H), 2.28 (s, 3H), 2.18 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 1.90 (s, 3H), 1.06 (s, 3H); one carbon resonance in the 110−150 ppm range could not be resolved; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 170.4, 169.9, 169.7, 169.5, 169.4, 169.0, 141.1, 140.6, 129.8, 128.0, 127.4, 127.1, 126.0, 125.9, 122.7, 122.3, 121.9, 121.6, 121.5, 119.7, 119.4, 119.1, 111.2, 109.5, 95.9, 83.7, 76.2, 75.3, 72.1, 71.4, 70.1, 69.1, 68.9, 67.9, 62.3, 61.3, 29.2, 23.5, 21.2, 20.7, 20.6, 20.5, 19.0. MS (FAB+) 957, 619, 307; HRMS (FAB+) calcd for $C_{47}H_{47}N_3O_{19}$ 957.2803, found 957.2824. Anal. Calcd for $C_{47}H_{47}N_3O_{19}$: C, 58.92; H, 4.95; N, 4.39. Found: C, 59.04; H, 5.02; N, 4.30.

6-Methyl-12-[*O*-(α-D-glucopyranosyl)−(1→4)-*β*-D-glucopyranosyl]-6,7,12,13-tetrahydroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione (9). 6-Methyl-4b,4c,6,7,7a,12,12b,13-octahydroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione (0.653 mmol, 224 mg), maltose (1.95 mmol, 670 mg), and $(NH_4)_2SO_4$ (0.04 mmol, 1 mg) were suspended in 7 mL of methanol and warmed to reflux. After 72 h the reaction was preabsorbed on silica gel and purified by silica gel chromatography (20% methanol/chloroform) to give a mixture of diastereomers (308 mg, 71%). This mixture was dissolved in 10 mL of dioxane, and DDQ (1.02 mmol, 230 mg) was added. After 48 h the reaction was concentrated in vacuo and purified by reverse phase HPLC (70% methanol/30% 0.1% aqueous TFA) to give 26 mg (8%) of 6-methyl-12-[*O*-(α-D-glucopyranosyl)−(1→4)-*β*-D-glucopyranosyl]-6,7,12,13-tetrahydroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione (extensive decomposition was observed with this buffer system; further experiments are in progress to find alernative conditions for purification): mp 345 °C (dec); $[\alpha]^{23}_D = +151.0$ (*c* 0.05, 1:1 MeOH/DMF); $R_f = 0.22$ (25% MeOH/$CHCl_3$); IR (KBr) 3329, 2922, 1745, 1690, 1572 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 11.62 (s, 1H), 9.17 (d, $J = 8.0$, 1H), 9.10 (d, $J = 8.0$, 1H), 7.96 (d, $J = 8.5$, 1H), 7.75 (d, $J = 8.1$, 1H), 7.55−7.61 (m, 2H), 7.36−7.40 (m, 2H), 6.36 (d, $J = 9.0$, 1H), 6.04 (bs, 1H), 5.72 (bs, 1H), 5.54 (bs, 1H), 5.30 (d, $J = 3.5$, 1H), 5.10−5.21 (m, 3H), 4.69 (bs, 1H), 4.26 (bd, $J = 9.6$, 1H), 4.16−4.21 (m, 2H), 3.92 (t, $J = 8.4$, 1H), 3.84 (bd, $J = 10.7$, 1H), 3.78 (d, $J = 11.0$, 1H), 3.66−3.69 (m, 1H), 3.55−3.63 (m, 3H), 3.50 (t, $J = 9.1$, 1H), 3.34−3.36 (m, 1H), 3.15 (t, $J = 9.4$, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 169.7, 169.6, 142.2, 140.9, 129.5, 128.0, 127.1, 126.9, 124.3, 124.2, 121.4, 121.0, 120.7, 120.5, 120.1, 118.5, 118.4, 117.2, 112.4, 111.8, 100.9, 84.0, 77.8, 77.0, 76.0, 73.8, 73.4, 72.5, 70.0, 61.1, 58.4, 23.7. LRMS (FAB+) 686 (M + Na), 413, 365, 301; HRMS (FAB+) calcd for $C_{33}H_{33}N_3O_{12}$ 663.2064, found 663.2081.

1-(*N*-Tosyl-3-indolyl)-2-(3-benzofuryl)ethane (14). To the aldehyde **13** (0.47 g, 3.2 mmol) in methylene chloride (7 mL) at 0 °C was added 1-*p*-toluenesulfonyl-indole-3-methyltriphenylphosphonium bromide (2.24 g, 3.2 mmol), 18-crown-6 (0.05 g, 0.18 mmol), and crushed potassium hydroxide (0.39 g, 7.1 mmol). The reaction was allowed to warm to room temperature, and stirring was contiued for 5 h. The reaction was then added to H_2O, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine and dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo afforded a solid that was preadsorbed on silica gel. Purification by silica gel chromatography (10% EtOAc/Hex) provided a 1:1 mixture of E:Z olefin isomers (0.97 g, 73%) that were carried on directly to the next step.

To the 1:1 mixture of E:Z olefin isomers (1.51 g, 3.65 mmol) in a 250 mL Paar hydrogenation bottle was added ethyl acetate (50 mL) followed by 10% Pd/C (226 mg, 15% w/w). The reaction was put under a 50 psi hydrogen atmosphere on a Parr shaker for 96 h at room temperature. The reaction mixture was then passed through a plug of Celite, washing with chloroform. The filtrate was concentrated in vacuo to afford a solid that was preadsorbed on silica gel. Purification by silica gel chromatography (5−10% EtOAc/Hex) provided **14** (1.16 g, 77%): mp

128−130 °C (CH_3CN); R_f = 0.5 in 10% EtOAc/Hex; IR (KBr) 3104, 3021, 2906, 1379, 1173 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.3, 1H), 7.66 (d, J = 8.4, 2H), 7.55 (d, J = 7.6, 1H), 7.48 (d, J = 8.1, 2H), 7.27 (m, 6H), 7.19 (d, J = 8.1, 2H), 3.06 (m, 4H), 2.34 (s, 3H); two carbon resonances in the 110−150 ppm range could not be resolved; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 144.7, 141.3, 135.3, 135.2, 130.8, 129.8, 127.9, 126.7, 124.7, 124.3, 123.1, 122.4, 122.3, 119.4, 119.3, 113.9, 111.5, 24.6, 23.2, 21.6; MS (CI) 415 (46), 284 (100), 130 (91); HRMS (CI) calcd for $C_{25}H_{21}NO_2$ 415.1242, found 415.1243. Anal. Calcd for $C_{25}H_{21}NO_2$: C, 72.27; H, 5.09; N, 3.37. Found: C, 72.24; H, 5.11; N, 3.42.

1-(3-Indolyl)-2-(3-benzofuryl)ethane (15). To **14** (1.16 g, 2.80 mmol) in ethanol (22 mL) was added aqueous 3 N NaOH (12 mL). The reaction mixture was stirred at reflux for 24 h. Water was added (150 mL) to the cooled reaction mixture, and the resulting white solid was filtered to provide **15** (0.67 g, 92%): mp 122−124 °C (Et_2O); R_f = 0.5 in 15% EtOAc/Hex; IR (KBr) 3409, 3042, 2907, 2848 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (s (br), 1H), 7.64 (d, J = 7.8, 1H), 7.55 (d, J = 7.6, 1H), 7.47 (d, J = 8.2, 1H), 7.38 (s, 1H), 7.35 (d, J = 8.1, 1H), 7.28 (m, 1H), 7.22 (m, 2H), 7.13 (m, 1H), 6.93 (d, J = 2.0, 1H), 3.17 (m, 2H), 3.08 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 141.3, 136.3, 128.3, 127.3, 124.1, 122.2, 122.0, 121.4, 120.3, 119.6, 119.3, 118.8, 115.9, 111.4, 111.1, 24.9, 24.4; MS (CI) 261 (61). 130 (100); HRMS (CI) calcd for $C_{18}H_{15}NO$ 261.1153, found 261.1153. Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.73; H, 5.83; N, 5.32.

Benzofurylindoline (16). To **15** (0.30 g, 1.15 mmol) was added TFA (3.8 mL), and the reaction mixture was stirred for 15 min. After concentration in vacuo, the residue was taken up into methylene chloride, and saturated $NaHCO_3$ was added. The solution was stirred vigorously for 10 min and then extracted with CH_2Cl_2. The organic layers were combined, washed with H_2O and brine, and dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo provided **16** (0.28 g, 96%). An analytically pure sample was obtained by preadsorbing on silica gel and purifying by silica gel chromatography (5% EtOAc/Hex): R_f = 0.3 in 3% EtOAc/Hex; IR (KBr) 3431, 3048, 2922 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.21 (m, 3H), 7.02 (t, J = 7.5, 1H), 6.76 (t, J = 7.4, 1H), 6.63 (d, J = 7.7, 1H), 4.89 (d, J = 8.0, 1H), 4.40 (s (br), 1H), 3.83 (m, 1H), 2.65 (m, 2H), 2.32 (m, 1H), 2.14 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 152.6, 150.1, 130.1, 127.8, 127.7, 123.9, 123.2, 122.3, 119.3, 119.2, 115.2, 111.0, 110.6, 55.6, 41.9, 24.0, 17.9; MS (CI) 261 (100); HRMS (CI) calcd for $C_{18}H_{15}NO$ 261.1153, found 261.1143. Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.56; H, 5.83; N, 5.26.

12-Oxo-11-(β-D-xylopyranosyl)indolo[2,3-*a*]carbazole (17a). To **16** (0.18 g, 0.69 mmol) in MeOH (5.0 mL) was added D-xylose (0.31 g, 2.06 mmol). The reaction mixture was stirred at reflux for 6.5 h and then concentrated in vacuo. The residue was preadsorbed on silica gel, and the glycosylation products were separated from the unused D-xylose by silica gel chromatography (2% MeOH/EtOAc) to provide a 1:1 mixture of diastereomers (0.23 g, 85%). The mixture of diastereomers was carried on directly by taking up into 1,4-dioxane (2.5 mL). DDQ (0.27 g, 1.17 mmol) was added, and the reaction was stirred at room temperature for 24 h. Saturated $NaHCO_3$ and EtOAc were added, and the mixture was stirred vigorously for 15 min, followed by extraction with EtOAc. The combined organic layers were washed with H_2O and brine and dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo afforded a solid that was preadsorbed on silica gel. Purification by silica gel chromatography (2% MeOH/EtOAc) provided **17a** (0.16 g, 74%): $[\alpha]^{23}_D$ = +112° (*c* 1.0, $CHCl_3$); mp 146 °C (sintered) ($CHCl_3$); R_f = 0.56 in EtOAc; IR (KBr) 3386, 3052, 2921, 2849 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 120 °C) δ 8.14 (m, 3H), 7.89 (m, 1H), 7.77 (d, J = 8.3, 1H), 7.73 (d, J = 8.2, 1H), 7.43 (m, 3H), 7.27 (m, 1H), 6.13 (d (br), J = 6.7, 1H), 4.64 (s (br), 2H), 4.59 (s (br), 1H), 4.31 (m (br), 1H), 4.06 (dd, J = 5.4, 11.1, 1H), 3.90 (s (br), 1H), 3.56 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6, 112 °C) δ 154.7, 140.7, 139.0, 125.9, 124.9, 124.0, 123.7 (br). 123.1 (br). 122.6, 121.5, 119.9, 119.5, 119.4, 114.7, 111.9 (br), 111.5, 110.9, 86.8 (br), 78.5, 77.7, 71.0 (br), 69.1, 68.3; MS (FAB): 389 (70), 257 (100); HRMS (FAB) calcd for $C_{23}H_{19}NO_5$ 389.1263, found 389.1258.

12-Oxo-11-(β-D-tetra-*O*-acetylglucopyranosyl)indolo-[2,3-*a*]carbazole (17b). To **17a** (0.15 g, 0.39 mmol) in pyridine (2.0 mL) was added acetic anhydride (0.20 g, 2.0 mmol). The reaction mixture was stirred at room temperature for 25 h and then concentrated in vacuo. The residue was preadsorbed on silica gel and purified by silica gel chromatography (30% EtOAc/Hex) to provide **17b** (0.19 g, 98%): $[\alpha]^{23}_D$ = +144° (*c* 1.0, $CHCl_3$); mp 228−230 °C ($CHCl_3$); R_f = 0.45 in 30% EtOAc/Hex; IR (KBr) 3051, 2935, 2862, 1758 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 112 °C) δ 8.17 (d, J = 7.7, 2H), 8.13 (d, J = 7.1, 1H), 7.96 (d, J = 8.1, 1H), 7.86 (d, J = 8.3, 1H), 7.81 (d, J = 8.2, 1H), 7.51 (m, 3H), 7.30 (m, 1H), 6.53 (d, J = 8.7, 1H), 6.02 (m (br), 1H), 5.62 (m, 2H), 4.29 (m, 1H), 4.01 (m, 1H), 2.10 (s, 3H), 1.97 (s, 3H), 1.33 (s, 3H); two carbon resonances in the 110−155 ppm region and one carbon resonance in the 80−85 ppm range could not be resolved; ^{13}C NMR (125 MHz, DMSO-d_6, 112 °C) δ 168.8, 168.7, 167.4, 154.8, 140.6, 139.1 (br), 126.2, 125.4, 123.9, 123.6 (br), 123.3 (br), 122.7, 121.7, 120.2, 120.1, 119.6, 114.9, 112.4, 110.8, 72.5, 70.1 (br), 67.9, 64.1, 19.7, 19.5, 18.6; MS (FAB) 515 (100), 257 (50); HRMS (FAB) calcd for $C_{29}H_{25}NO_8$ 515.1580, found 515.1575.

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Supporting Information Available: General experimental procedures and ^1H NMR spectra for **1a**, **1b**, **9**, **17a**, and **17b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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