Synthesis of Rebeccamycin and 11-Dechlororebeccamycin

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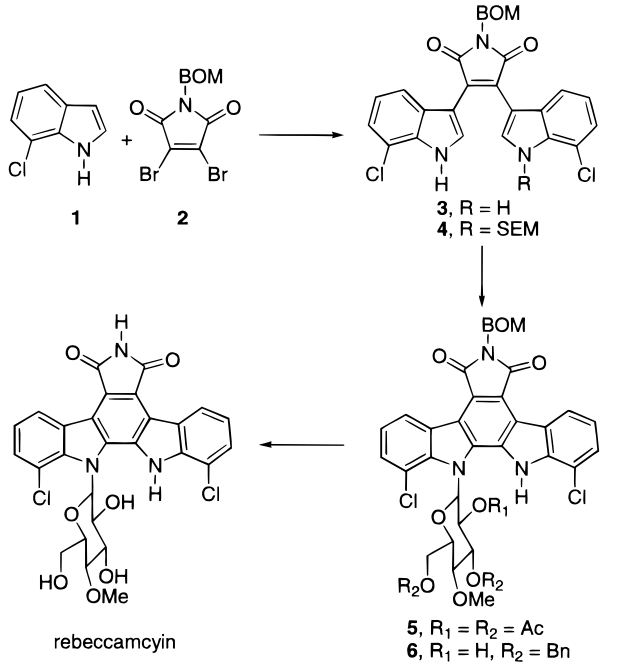
Glycosylated 7-chloroindole-3-acetamide **9**, prepared in four steps and 26% yield from 7-chloroindole **(1)**, was condensed with methyl 7-chloroindole-3-glyoxylate **11** and methyl indole-3-glyoxylate **12** to provide bisindolylmaleimides **7** and **8** in 86% and 84% yield, respectively. Oxidation of **7** and **8** followed by debenzylation provided a new approach to the synthesis of rebeccamycin and completed for the first time a synthesis of 11-dechlororebeccamycin.

Introduction

The indolocarbazoles are a well-known class of natural products that have been reported to inhibit protein kinase C and topoisomerase activity.[1] Of this family of compounds several members possess a single *N*-glycosidic bond. The most well-known of this subgroup of compounds is rebeccamycin, isolated in 1985 from an actinomycete.[2] The structure and absolute configuration of rebeccamycin have been determined by X-ray crystallography. Rebeccamcyin contains a symmetrical indolocarbazole chromophore and a 4-*O*-methylglucose residue linked by a β-glycosidic bond. 11-Dechlororebeccamycin has a similar structure but lacks the chlorine at C_{11}.[3] Both compounds are potent antitumor agents and, recently, water soluble derivatives with increased potency have been prepared and are being evaluated in clinical trials.[4]

Two total syntheses of rebeccamycin have been reported (Scheme 1). In 1985 Kaneko and Clardy reported the first synthesis of rebeccamycin via the symmetrical bisindolylmaleimide **3**, prepared in two steps and 27% yield, using the indole-Grignard chemistry developed by Steglich.[5] Treatment of **3** with Ag_2O and 1-bromo-2,3,6-tri-*O*-acetyl-4-*O*-methyl-D-glucose in refluxing benzene accomplished the oxidation and glycosylation in one step to afford **5** in 32% yield. Removal of the BOM and acetyl protecting groups completed a six-step synthesis of rebeccamycin.[6] Using a similar strategy, Danishefsky prepared the unsymmetrical bisindolylmaleimide **4** in four steps and 60% yield.[7] Selective preparation of the β-glycoside in 48% yield by reaction of the sodium salt of **4** with the α-1,2-anhydrosugar **19**, followed by SEM

Scheme 1



deprotection and oxidation gave indolocarbazole **6** in 22% yield. Although removal of the benzyl and BOM protecting groups was complicated by competing hydrogenolysis of the carbon−chlorine bonds, treatment of **6** with Pearlman's catalyst followed by ammonolysis afforded rebeccamycin in 13 steps.

We recently reported a new method for the synthesis of symmetrical and unsymmetrical bisindolylmaleimides by condensation of methyl indole-3-glyoxylates with indole-3-acetamides using a 1.0 M solution of potassium *tert*-butoxide in THF.[8,9] To further illustrate the generality of this reaction, we would like to report its application

(1) Gribble, G. W.; Berthel, S. J. *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science Publishers: Amsterdam, 1993, Vol. 12.

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(3) Matson, J. *Chem. Abstr.* **1985**, *103*, 159104.

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(5) Brenner, M.; Rexhausen, H.; Steffan, B.; Steglich, W. *Tetrahedron* **1988**, *44*, 2887.

(6) Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4015.

(7) Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343.

(8) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053.

(9) After the work reported herein had been completed and accepted for publication, a paper describing the application of a similar condensation to the synthesis of the maleimide Didemnimide A was published: 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.

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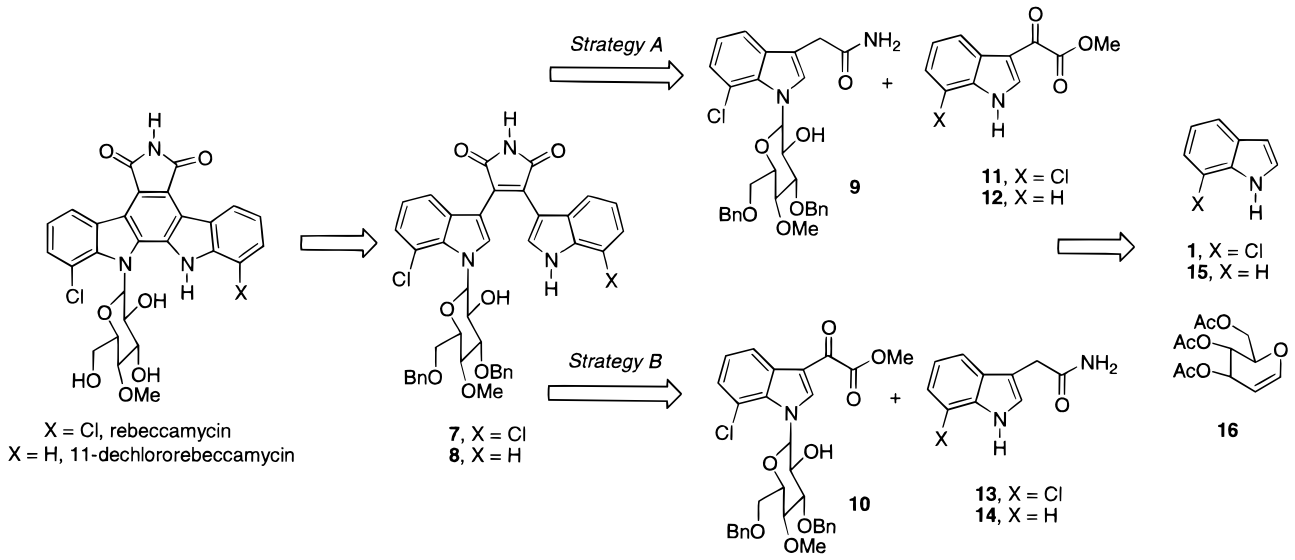
Scheme 2



in a new synthesis of rebeccamcyin and to describe for the first time a synthesis of 11-dechlororebeccamycin.

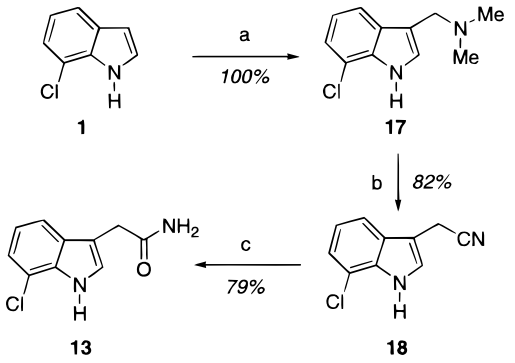
Results and Discussion

Retrosynthetic Analysis. Our retrosynthetic analysis of rebeccamycin and 11-dechlororebeccamycin is shown in Scheme 2. Bisindolylmaleimides **7** and **8**, containing an unprotected maleimide, were selected as pivotal intermediates to be converted into the natural products by oxidation followed by debenzylation. Using our new methodology we envisioned that bisindolylmaleimides **7** and **8** could be prepared either (i) by condensation of glycosylated 7-chloroindole-3-acetamide **9** with methyl indole-3-glyoxylates **11** and **12** (strategy A); or (ii) by condensation of glycosylated methyl 7-chloroindole-3-glyoxylate **10** with indole-3-acetamides **13** or **14** (strategy B). Both of these approaches have been evaluated, and their success in the synthesis of rebeccamycin and 11-dechlororebeccamycin will be described.

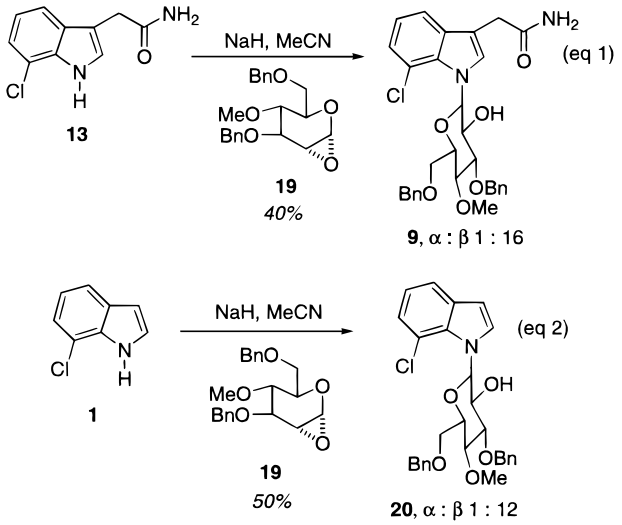
Synthesis of 7-Chloroindole-3-acetamide (13). Treatment of 7-chloroindole **(1)**[10] with *N*,*N*-dimethylmethyleneammonium chloride in CH_2Cl_2 afforded gramine **17** in quantitative yield (Scheme 3).[11] Treatment of **17** with NaCN in DMSO/EtOAc gave 7-chloroindole-3-acetonitrile **18** in 82% yield. Hydrolysis of **18** using KOH in *tert*-butyl alcohol completed the synthesis of 7-chloroindole-3-acetamide **13** in three steps and 65% yield.

Glycosylation. Selective formation of the β-*N*-glycosides of 7-chloroindole-3-acetamide **(13)** and 7-chloroindole **(1)** was accomplished using the method of Danishefsky.[7] The α-1,2-anhydrosugar **19** was prepared in four steps, 80% yield, and 15:1 α:β-selectivity from commercially available tri-*O*-acetyl-D-glucal **16**. Deprotonation of **13** and **1** (2.0 equiv) with NaH (2.1 equiv) in MeCN, followed by treatment with **19** (1.0 equiv) at 50 °C overnight, afforded β-*N*-glucosides **9** and **20** in 40% and 50% yield, respectively (eqs 1 and 2). Although the selectivity of the reaction was >1:12 α:β, the minor α-isomer was removed by chromatography to afford the β-isomer in >98% diastereomeric purity prior to the condensation reaction. Glycosylation of **13** was also accomplished in 1 h using Cs_2CO_3 in DMF at 100 °C affording **9** in 40% isolated yield, although the selectivity of the reaction was lower [α:β = 1:8].

Scheme 3[a]



[a] (a) $CH_2{=}NMe_2Cl$, CH_2Cl_2; (b) NaCN, DMSO, EtOAc, 80 °C; (c) KOH, *t*-BuOH.

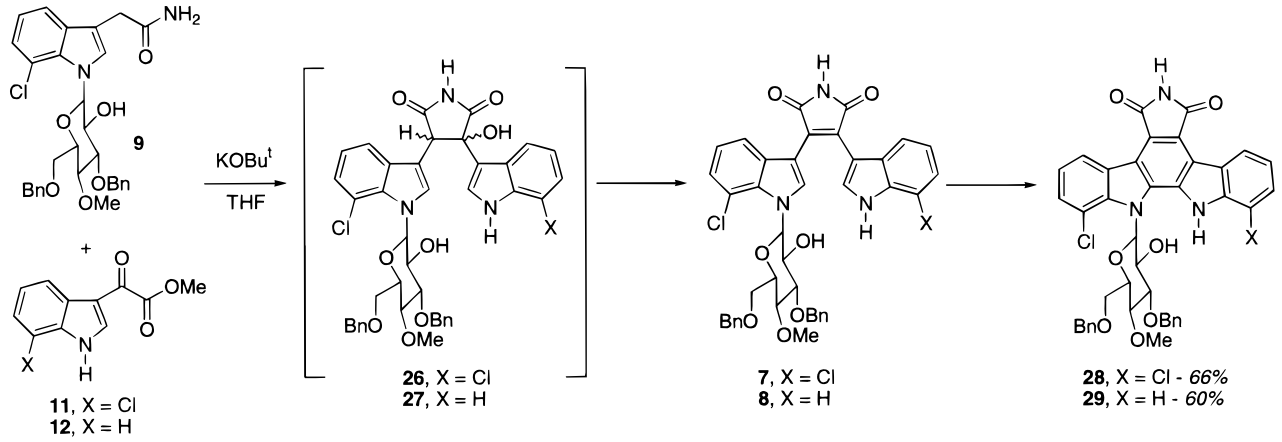


Glyoxylate Ester Formation. Treatment of 7-chloroindole **(1)** with oxalyl chloride at room temperature

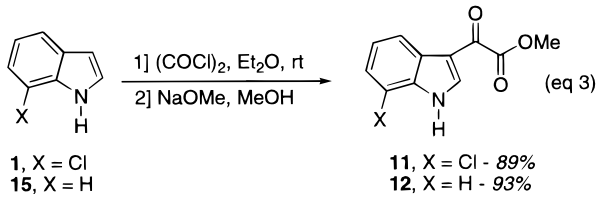
(10) (a) Sugasawa, T.; Adachi, M.; Sasakura, K.; Kitigawa, A. *J. Org. Chem.* **1979**, *44*, 578. (b) Bartoli, G.; Palmieri, G. *Tetrahedron Lett.* **1989**, *30*, 2129.

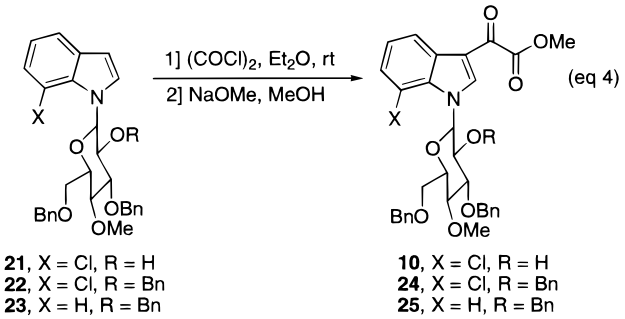
(11) (a) Brewster, J. H.; Eliel, E. L. *Org. React.* **1953**, *7*, 99. (b) Kozikowski, A. P.; Ishida, H. *Heterocycles* **1980**, *14*, 55.

Scheme 4



for 3 h followed by quench with NaOMe at −50 °C afforded methyl 7-chloroindoleglyoxylate (**11**) in 89% yield (eq 3). However, using analogous conditions, we were unable to prepare the glyoxylate ester of 7-chloro-





indole derivatives **21** or **22** (eq 4). In fact, treatment of glycosylated indole **23** with excess oxalyl chloride (8 equiv) at room temperature overnight afforded only a 40% yield of methyl glyoxylate **25**, much lower than the 93% yield of methyl indole-3-glyoxylate **(12)** obtained when indole **15** was employed (eq 3). On the basis of these data, we believe that the reduced reactivity of the indole-C_3 position is due to the presence of both the 7-chloro substituent and the *N*-glucose moiety. Alternative approaches to **10** using either the C_3-organometallic derivative of **21** or **22** or direct glycosylation of the sodium indolate of **11** were also unsuccessful. Since the synthesis of **10** and **24** was problematic, we directed our efforts to the synthesis of rebeccamycin and 11-dechlororebeccamycin by condensation of glycosylated 7-chloroindole-3-acetamide **(9)** and methyl indole-3-glyoxylates **11** and **12** (strategy A).

Bisindolylmaleimide Formation. Glycosylated 7-chloroindole-3-acetamide **9** (1.0 equiv) and methyl 7-chloroindole-3-glyoxylate **11** (2.0 equiv) were treated with a 1.0 M solution of potassium *tert*-butoxide in THF (4.5 equiv) at room temperature for 1 h to generate hydroxyimide **26** (Scheme 4). In-situ treatment of **26** with concentrated HCl at reflux generated bisindolylmaleimide **7** in 86% yield. If the condensation reaction was performed at lower temperatures, the unsubstituted bisindolylmaleimide **30** was generated as a byproduct (Figure 1). The reaction was also successful using 1.2 equiv of **11** to afford **7** in 80% yield. The lower yield was due to the competing hydrolysis of **11** to glyoxylic acid **31**. Glyoxylic acid **31** was easily removed from the reaction by base extraction during workup.

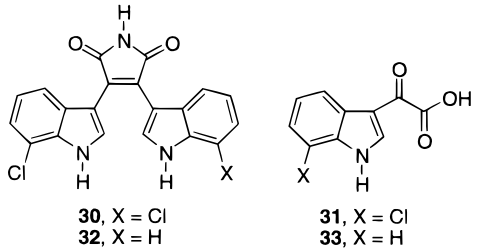


Figure 1.

Treatment of glycosylated 7-chloroindole-3-acetamide (**9**) (1.0 equiv) and methyl indole-3-glyoxylate **(12)** (2.0 equiv) with a 1.0 M solution of potassium *tert*-butoxide in THF (4.0 equiv) at room temperature for 20 h afforded bisindolylmaleimide **8** in 84% yield. In this case dehydration of hydroxyimide **27** occurred under the basic reaction conditions, and formation of the unsubstituted bisindolylmaleimide **32** was not observed.

In our previous mechanistic work on this reaction we indicated that if the indole-3-acetamide was *N*-substituted, dehydration of the intermediate hydroxyimides occurred under the basic reaction conditions.[8] Although this result was true for formation of **8**, in the synthesis of bisindolylmaleimide **7**, the first case we have examined involving condensation of an *N*-alkylated indole-3-acetamide and glyoxylate containing substitution on the indole-aromatic ring, represents an example where this is not the case. This result suggests that dehydration of the hydroxyimides is dependent on the functionality present in both reacting partners.

Oxidation, Deprotection, and Synthesis of Rebeccamycin and 11-Dechlororebeccamycin. Although a number of methods have been reported to successfully oxidize bisindolylmaleimides to indolocarbazoles [Pd(OAc)$_2$, $PdCl_2$, *hv*/O_2 or I_2, DDQ, $CuCl_2$],[12] they proved

(12) (a) Harris, W.; Hill, C. H.; Keech, E.; Malsher, P. *Tetrahedron Lett*. **1993**, *34*, 8361. (b) Ohkubo, M.; Nishimura, T.; Jona, H.; Honma, T.; Morishima, H. *Tetrahedron* **1996**, *52*, 8099.

unsuccessful in oxidizing bisindolylmaleimides **7** and **8**, affording only trace amounts of the desired products. However, using $Pd(OTf)_2$ in DMF at 90 °C for 2.5 h, indolocarbazoles **28** and **29** were prepared in 66% and 60% yield, respectively, from **7** and **8** (Scheme 4).[13]

Final deprotection of indolocarbazoles **28** and **29** was achieved using Pearlman's catalyst to afford rebeccamycin and 11-dechlororebeccamycin in 83% and 86% yield, respectively. In the absence of maleimide protection, the hydrogenation conditions were sufficiently mild that competition from hydrogenolysis of the aromatic carbon−chlorine bonds was not observed. The synthetic material thus obtained gave ^{1}H NMR, ^{13}C NMR, HRMS, and optical rotation data identical to those reported for the natural products rebeccamycin[14] and 11-dechlororebeccamycin.[3]

Summary

In summary, we have reported a new method to prepare functionalized bisindolylmaleimides in high yield by condensation of indole-3-acetamides with methyl indole-3-glyoxylates. The success of this methodology is demonstrated by an improved synthesis of the antitumor indolocarbazole glycoside rebeccamycin in 12 steps and 12% overall yield. The versatility of this method lies in the fact that a number of different analogues can be prepared from a single functionalized indole-3-acetamide, as demonstrated by the first total synthesis of 11-dechlororebeccamycin in 12 steps and 11% overall yield from the same glycosylated indole-3-acetamide **9**. Further evaluation of the generality of this method to the synthesis of other members of the bisindolymaleimide, indolocarbazole, and staurosporine family of compounds is being performed and will be reported in due course.

Experimental Section

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. TLC was performed on Kieselgel 60 F254 plates (Merck) using reagent grade solvents. Flash chromatography was performed using E. M. Merck silica gel 60 (230−400 mesh). Mass spectral and combustion analysis were performed by the Eli Lilly and Co. Physical Chemistry Department.

7-Chloro-*N*,*N*-dimethyl-1*H*-indole-3-methanamine (17). To a solution of 7-chloroindole **(1)** (4.00 g, 26.4 mmol) in CH_2Cl_2 (70 mL) was added *N*,*N*-dimethylmethyleneammonium chloride (3.21 g, 34.3 mmol) in one portion, and the resultant mixture was stirred at room temperature for 2 h under N_2. Water, followed by 1 M NaOH (34 mL, 34.0 mmol) were added, and the reaction mixture was extracted with EtOAc. The combined organic layers were then washed with saturated NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to give 5.51 g (100%) of **17**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.22 (bs, 1H), 7.52 (d, 1H, J = 7.8 Hz), 7.23 (d, 1H, J = 2.2 Hz), 7.09 (d, 1H, J = 7.6 Hz), 6.93 (t, 1H, J = 7.7 Hz), 3.47 (s, 2H), 2.08 (bs, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 133.1, 129.5, 125.6, 124.9, 120.4, 119.3, 118.2, 115.7, 113.1, 54.2; IR (KBr) 2967, 2943 cm^{-1}. LRMS (EI) *m*/*z* 209 (100%). Anal. Calcd for $C_{11}H_{13}N_2Cl$: C, 63.31, H, 6.28, N, 13.42. Found: C, 63.02, H, 6.17, N, 13.23.

7-Chloro-1*H*-indole-3-acetonitrile (18). A solution of **17** (450 mg, 2.18 mmol), NaCN (320 mg, 6.53 mmol), and EtOAc (960 mg, 1.06 mL, 10.9 mmol) in dry DMSO (10 mL) was heated at 80 °C under N_2 for 6 h. The reaction mixture was then cooled, diluted with EtOAc, and washed with water. The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to give 410 mg of **18**. Purification by column chromatography (2:1 hexanes:EtOAc) afforded 340 mg (82%) of **18**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.48 (bs, 1H), 7.53 (d, 1H, J = 7.9 Hz), 7.37 (bs, 1H), 7.18 (d, 1H, J = 7.5 Hz), 7.03 (t, 1H, J = 7.7 Hz), 4.02 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.0, 127.8, 123.9, 122.7, 121.5, 118.3, 117.5, 117.2, 106.2, 14.8; IR (KBr) 3324, 2257 cm^{-1}. HRMS (EI) exact mass calcd for $C_{10}H_7N_2Cl$ M^+ 190.0298, found 190.0297. Anal. Calcd for $C_{10}H_7N_2Cl$: C, 63.01, H, 3.70, N, 14.69, Cl, 18.60. Found: C, 62.85, H, 3.49, N, 14.59, Cl, 18.59.

7-Chloro-1*H*-indole-3-acetamide (13). A solution of **18** (2.77 g, 14.5 mmol) and powdered 85% KOH (7.66 g, 116 mmol) in *tert*-butyl alcohol (30 mL) was heated at reflux for 1.5 h. The reaction mixture was then cooled to room temperature, diluted with water (30 mL), and acidified with 1 N HCl (116 mL, 116 mmol) to give a slurry that was filtered and rinsed with water and then Et_2O (40 mL). The solid was dried in a vacuum oven at 40 °C to give 2.39 g (79%) of **13**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.18 (bs, 1H), 7.47 (d, 1H, J = 7.8 Hz), 7.30 (bs, 1H), 7.21 (bs, 1H), 7.10 (d, 1H, J = 7.5 Hz), 6.94 (t, 1H, J = 7.7 Hz), 6.81 (bs, 1H), 3.42 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.5, 133.8, 130.2, 126.0, 121.3, 120.2, 118.7, 116.6, 111.4, 33.3; IR (KBr) 3443, 3339, 3188, 1626 cm^{-1}. HRMS (EI) exact mass calcd for $C_{10}H_9N_2OCl$ M^+ 208.0403, found 208.0411. Anal. Calcd for $C_{10}H_9N_2OCl$: C, 57.57, H, 4.35, N, 13.43. Found: C, 57.84, H, 4.19, N, 13.26.

Methyl 7-Chloro-α-oxo-1*H*-indole-3-acetate (11). To a solution of 7-chloroindole **(1)** (2.00 g, 13.2 mmol) in Et_2O (24 mL) was added oxalyl chloride (2.33 g, 1.60 mL, 18.3 mmol), and the resultant mixture was stirred at room temperature for 3 h. The reaction mixture was cooled to −50 °C, treated dropwise with a 25 wt % solution of NaOMe (7.94 g, 8.40 mL, 36.7 mmol), and then allowed to warm to room temperature and stirred for 15 min. The reaction was diluted with EtOAc and washed with 5% aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo. The resulting solid was triturated with Et_2O (35 mL) and filtered to give 2.80 g (89%) of **11**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.79 (bs, 1H), 8.43 (s, 1H), 8.08 (d, 1H, J = 7.9 Hz), 7.35 (d, 1H, J = 7.7 Hz), 7.24 (t, 1H, J = 7.8 Hz), 3.85 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.6, 164.3, 139.7, 134.5, 128.3, 124.9, 124.3, 121.0, 117.9, 114.1, 53.5; IR (KBr) 3139, 1732, 1634, 1625, 1614 cm^{-1}. HRMS (EI) exact mass calcd for $C_{11}H_8NO_3Cl$ M^+ 237.0193, found 237.0188. Anal. Calcd for $C_{11}H_8NO_3Cl$: C, 55.60, H, 3.39, N, 5.89, Cl, 14.92. Found: C, 55.86, H, 3.33, N, 5.92, Cl, 15.19.

1-[4-*O*-Methyl-2,3,6-tris-*O*-(phenylmethyl)-*β*-D-glucopyranosyl]-1*H*-indole (23). To a solution of indole (329 mg, 2.81 mmol) in MeCN (10 mL) was added NaH (118 mg, 2.95 mmol), and the mixture was stirred at room temperature for 45 min. The α-anhydro sugar **19** (500 mg, 1.40 mmol) in MeCN (2 mL) was added, and the reaction was heated at 50 °C for 2 h. The heat was removed, and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was diluted with EtOAc and quenched with saturated NH_4Cl. The organic layer was washed with saturated NaCl and dried ($MgSO_4$), and the solvent was removed in vacuo to give a brown oil that was purified by column chromatography (4:1 hexanes:EtOAc) to afford 310 mg (47%) 1-[4-*O*-methyl-3,6-bis-*O*-(phenylmethyl)-*β*-D-glucopyranosyl]-1*H*-indole as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.61−7.05 (m, 15H), 6.48 (d, 1H, J = 3.3 Hz), 5.57 (d, 1H, J = 8.8 Hz), 4.92 (d, 1H, J = 11.7 Hz), 4.78 (d, 1H, J = 11.7 Hz), 4.45 (d, 2H, J = 9.1 Hz), 4.01 (t, 1H, J = 7.7 Hz), 3.67−3.48 (m, 6H), 3.46 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.3, 138.0, 135.8, 129.2, 128.4, 128.2, 127.8, 127.5, 125.1, 122.0, 121.0, 120.0, 116.4, 110.7, 103.2, 96.6, 86.0, 85.2, 79.3, 77.8, 75.3, 73.5, 72.9, 68.6, 60.8; HRMS (FAB) calcd for $C_{29}H_{31}NO_5$ 473.2202, found 473.2208.

To a solution of the above glycosylated indole (300 mg, 633 μmol) in THF (3 mL) was added NaH (30.4 mg, 760 μmol),

(13) Ohkubo, M.; Kawamoto, H.; Ohno, T.; Nakano, M.; Morishima, H. *Tetrahedron* **1997**, *53*, 585

(14) (a) Furusaki, A.; Hashiba, N.; Matsumoto, T.; Hirano, A.; Iwai, Y.; Omura, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3681. (b) Omura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Masuma, R. *J. Antibiot.* **1977**, *30*, 275.

and the mixture was heated at reflux for 1 h. Benzyl bromide (226 uL, 1.90 mmol) was added, and the reaction was heated at reflux overnight, cooled to room temperature, diluted with EtOAc, and quenched with saturated NH_4Cl. The organic layer was washed with saturated aqueous NaCl and dried ($MgSO_4$), and the solvent was removed in vacuo to give a brown oil which was purified by column chromatography (4:1 hexanes:EtOAc) to afford 140 mg of **23** (39%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.67−7.04 (m, 18H), 6.68 (d, 2H, J = 6.6 Hz), 6.57 (d, 1H, J = 3.3 Hz), 5.73 (d, 1H, J = 9.1 Hz), 4.80 (s, 2H), 4.55 (d, 1H, J = 12.1 Hz), 4.47 (d, 1H, J = 12.1 Hz), 4.20 (d, 1H, J = 10.6 Hz), 4.02 (d, 1H, J = 9.2 Hz), 3.83−3.52 (m, 6H), 3.49 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.3, 138.1, 136.9, 135.5, 129.2, 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 127.4, 125.8, 122.0, 121.0, 120.2, 111.4, 103.1, 86.4, 85.2, 80.9, 79.4, 77.9, 75.7, 74.5, 73.5, 68.7, 60.9; HRMS (FAB) calcd for $C_{36}H_{37}NO_5$ 563.2672, found 563.2677 (100%).

Methyl α-Oxo-[4-*O*-methyl-2,3,6-tris-*O*-(phenylmethyl)-*β*-D-glucopyranosyl]-1*H*-indole-3-acetate (25). To a solution of **23** (50.0 mg, 88.7 μmol) in Et_2O (10 mL) was added oxalyl chloride (46.5 μL, 531 μmol), and the resultant mixture was stirred at room temperature for 6 h. The reaction was cooled to −60 °C and treated dropwise with a 25 wt % solution of NaOMe in MeOH (304 uL, 1.33 mmol). The reaction was then allowed to warm to room temperature and stirred for 15 min. The reaction was diluted with EtOAc and washed with saturated NH_4Cl. The organic layer was washed with saturated NaCl and dried ($MgSO_4$), and the solvent was removed in vacuo to give a crude oil which was purified by column chromatography (4:1 hexanes:EtOAc) to afford 23.0 mg of **25** (40%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43−8.40 (m, 2H), 7.65 (d, 1H, J = 7.3 Hz), 7.40−6.94 (m, 17H), 6.63 (d, 2H, J = 6.6 Hz), 5.73 (d, 1H, J = 8.9 Hz), 4.80 (s, 2H), 4.61 (d, 1H, J = 11.0 Hz), 4.53 (d, 1H, J = 11.0 Hz), 4.25 (d, 1H, J = 11.9 Hz), 3.94 (s, 3H), 3.95−3.50 (m, 5H), 3.48 (s, 3H); HRMS (FAB) calcd for $C_{39}H_{40}NO_8$ 650.2754, found 650.2741 (100%).

7-Chloro-1-[4-*O*-methyl-3,6-bis-*O*-(phenylmethyl)-*β*-D-glucopyranosyl]-1*H*-indole (21). To a solution of 7-chloroindole **(1)** (88 mg, 5.78 mmol) in dry MeCN (10 mL) was added NaH (240 mg, 6.07 mmol, 60% dispersion in mineral oil), and the reaction mixture was stirred at room temperature under N_2 for 30 min. The α-anhydro sugar **19** (1.03 g, 2.89 mmol) in dry MeCN (10 mL) was then added and the reaction mixture heated at 50 °C for 20 h. The reaction was cooled to room temperature, diluted with EtOAc, and washed with saturated NH_4Cl and saturated NaCl. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give **21** as a dark oil. HPLC analysis indicated an α:β ratio of 1:12.[15] The oil was purified by column chromatography (4:1 hexanes:EtOAc) to afford 710 mg (50%) of **21** (HPLC analysis indicated 98:2 β:α). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, 1H, J = 3.4 Hz), 7.55 (d, 1H, J = 7.9 Hz), 7.46−7.19 (m, 11H), 7.07 (t, 1H, J = 7.7 Hz), 6.60 (d, 1H, J = 3.4 Hz), 6.22 (d, 1H, J = 9.0 Hz), 5.66 (d, 1H, J = 7.1 Hz), 4.96 (d, 1H, J = 11.3 Hz), 4.80 (d, 1H, J = 11.3 Hz), 4.47 (d, 1H, J = 11.8 Hz), 4.40 (d, 1H, J = 12.0 Hz), 4.17−4.08 (m, 1H), 3.71−3.63 (m, 2H), 3.46 (s, 3H), 3.35−3.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.1, 128.0, 127.7, 127.5, 127.4, 127.3, 127.2, 127.1, 124.9, 123.7, 120.8, 119.7, 103.0, 85.9, 83.9, 78.9, 75.7, 74.0, 72.1, 71.3, 66.8, 59.8; IR (KBr) 1731 cm^{-1}. LRMS (EI) m/z 508. Anal. Calcd for $C_{29}H_{30}N_1O_5Cl$: C, 68.57, H, 5.95, N, 2.76. Found: C, 68.78, H, 5.88, N, 2.60.

7-Chloro-1-[4-*O*-methyl-2,3,6-tris-*O*-(phenylmethyl)-*β*-D-glucopyranosyl]-1*H*-indole (22). To a solution of **21** (700 mg) in THF (10 mL) was added NaH (70.0 mg, 1.65 mmol, 60% dispersion in mineral oil), and the reaction was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and benzyl bromide (305 mg, 246 μL, 2.07 mmol) added. The reaction mixture was heated at reflux overnight, cooled to room temperature, diluted with EtOAc, washed with saturated NH_4Cl and saturated NaCl, and dried ($MgSO_4$). The solvent was removed in vacuo to afford an oil that was purified by column chromatography (4:1 hexanes:EtOAc) to yield 600 mg (73%) of **22**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, 1H, J = 3.4 Hz), 7.59 (d, 1H, J = 7.2 Hz), 7.37−7.21 (m, 14H), 7.13−7.05 (m, 2H), 6.78 (d, 1H, J = 7.2 Hz), 6.68 (d, 1H, J = 3.4 Hz), 6.50 (d, 1H, J = 9.0 Hz), 4.84 (d, 2H, J = 3.8 Hz), 4.55 (d, 1H, J = 12.1 Hz), 4.45 (d, 1H, J = 12.1 Hz), 4.18 (t, 1H, J = 8.8 Hz), 4.07 (d, 1H, J = 10.9 Hz), 3.88−3.65 (m, 6H), 3.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.2, 128.1, 127.9, 127.6, 127.5, 127.4, 127.3, 127.2, 124.0, 120.9, 119.9, 103.9, 85.0, 82.9, 80.2, 80.2, 79.4, 76.1, 75.0, 73.2, 72.1, 68.4, 59.9; IR (KBr) 2926, 20908, 2870, 1564 cm^{-1}. LRMS (EI) m/z 598. Anal. Calcd for $C_{36}H_{36}NO_5Cl$: C, 72.29, H, 6.07, N, 2.34. Found: C, 72.54, H, 5.82, N, 2.48.

7-Chloro-1-[4-*O*-methyl-3,6-bis-*O*-(phenylmethyl)-*β*-D-glucopyranosyl]-1*H*-indole-3-acetamide (9). To a solution of **13** (1.20 g, 5.75 mmol) in dry MeCN (10 mL) was added NaH (240 mg, 6.04 mmol, 60% dispersion in mineral oil), and the resultant mixture was stirred at room temperature under N_2 for 30 min. The α-anhydro sugar **19** (1.02 g, 2.88 mmol) in dry MeCN (10 mL) was added and the reaction heated at 50 °C for 20 h. The reaction was cooled to room temperature, diluted with EtOAc, and washed with saturated NH_4Cl and saturated NaCl. The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to give a dark oil. HPLC analysis indicated an α:β ratio of 1:16.[16] The oil was purified by column chromatography (1:1:1 hexanes:EtOAc:acetone) to afford 660 mg (40%) **9** (HPLC analysis indicated 100% β). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.36 (m, 5H), 7.33−7.26 (m, 7H), 7.23 (d, 1H, J = 7.6 Hz), 7.06 (t, 1H, J = 7.8 Hz), 6.34 (d, 1H, J = 8.6 Hz), 5.62 (bs, 1H), 5.43 (bs, 1H), 5.00 (d, 1H, J = 11.4 Hz), 4.87 (d, 1H, J = 11.4 Hz), 4.59 (d, 1H, J = 11.9 Hz), 4.49 (d, 1H, J = 11.9 Hz), 4.03 (t, 1H, J = 8.7 Hz), 3.77 (d, 2H, J = 2.3 Hz), 3.67 (t, 2H, J = 9.0 Hz), 3.58 (s, 4H), 3.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 138.8, 138.4, 133.0, 131.4, 129.0, 128.7, 128.4, 128.4, 128.2, 128.0, 125.5, 125.4, 121.6, 118.1, 117.4, 110.8, 86.1, 84.4, 80.0, 75.7, 73.9, 72.7, 69.1, 60.9, 33.1; IR (KBr) 3466, 3336, 1630 cm^{-1}. HRMS (EI) exact mass calcd for $C_{31}H_{33}N_2O_6Cl$ M^+ 564.2027, found 564.2021. Anal. Calcd for $C_{31}H_{33}N_2O_6Cl$: C, 65.89, H, 5.89, N, 4.96, Cl, 6.27. Found: C, 66.03, H, 5.70, N, 4.95, Cl, 6.39.

3-[(7-Chloro-1*H*-indol-3-yl)-4-[7-chloro-1-[4-*O*-methyl-3,6-bis-*O*-(phenylmethyl)-*β*-D-glucopyranosyl]-1*H*-indol-3-yl]-1*H*-pyrrole-2,5-dione (7). To a solution of **9** (100 mg, 0.18 mmol) and **11** (80.0 mg, 0.35 mmol) in dry THF (3 mL) was rapidly added 1.0 M potassium *tert*-butoxide in THF (710 μL, 710 mmol) at room temperature. The reaction was stirred under N_2 for 1 h and then quenched with concentrated HCl (0.50 mL) and heated at reflux for 1 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with water. The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to give a red foam that was purified by column chromatography (2:1 hexanes:EtOAc) to give 130 mg (86%) of **7**. $[\alpha]^{20}_D$ +69.3 ° (*c*, 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.07 (s, 1H), 11.01 (s, 1H), 8.02 (s, 1H), 7.78 (d, 1H, J = 2.9 HZ), 7.42 (d, 2H, J = 7.1 Hz), 7.35 (t, 2H, J = 7.3 Hz, J = 7.8 Hz), 7.29−7.22 (m, 7H), 7.06 (d, 1H, J = 7.5 Hz), 6.98 (d, 1H, J = 7.5 Hz), 6.76 (d, 1H, J = 8.2 Hz), 6.72 (d, 1H, J = 6.8 Hz), 6.66 (t, 1H, J = 7.8 Hz, J = 7.8 Hz), 6.60 (t, 1H, J = 8.0 Hz, J = 7.8 Hz), 6.24 (d, 1H, J = 9.6 Hz), 5.82 (d, 1H, J = 6.6 Hz), 4.93 (d, 1H, J = 11.7 Hz), 4.79 (d, 1H, J = 11.2 Hz), 4.56 (d, 1H, J = 11.9 Hz), 4.42 (d, 1H, J = 11.7 Hz), 4.0 (m, 1H), 3.74−3.61 (m, 4H), 3.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 172.3, 138.9, 138.3, 133.8, 133.1, 130.8, 130.0, 129.3, 129.1, 129.0, 128.7, 128.4, 127.4, 126.0, 122.8, 122.1, 122.0, 121.7, 121.4, 117.7, 117.2, 108.1, 107.8, 86.1, 84.6, 80.4, 76.5, 76.2, 73.8, 72.3, 69.2, 62.7, 61.3, 45.6, 30.6, 29.7; IR (KBr) 3402, 3273, 1757, 1706 cm^{-1}. HRMS (EI) exact mass calcd for $C_{41}H_{35}N_3O_7Cl_2$ M^+ 751.1852, found 751.1860.

(15) HPLC conditions: Column Zorbax SB−CN, flow rate 1 mL/min, 233 nm, 50:50 MeCN: 0.1% TFA. t_R **21** α-isomer = 7.9 min, t_R **21** β-isomer = 8.9 min, t_R **1** = 5.0 min.

(16) HPLC conditions: Column Zorbax SB−CN, flow rate 1 mL/min, 233 nm, 50: 50 MeCN: 0.1% TFA. t_R **9**α-isomer = 9.0 min, t_R **9**β-isomer = 10.5 min, t_R **13** = 4.0 min.

3-[(1*H*-Indol-3-yl)-4-[7-chloro-1-[4-*O*-methyl-3,6-bis-*O*-(phenylmethyl)-*β*-D-glucopyranosyl]-1*H*-indol-3-yl]-1-*H*-pyrrole-2,5-dione (8). To a solution of **9** (350 mg, 0.61 mmol) and methyl indole-3-glyoxylate **(12)** (250 mg, 1.22 mmol) in dry THF (10 mL) was rapidly added 1.0 M potassium *tert*-butoxide in THF (3.66 mL, 3.66 mmol) at room temperature. The reaction was stirred under N_2 for 20 h and then quenched with saturated NH_4Cl. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to give a red foam that was purified by column chromatography (2:1 hexanes: EtOAc) to afford 370 mg (84%) of **8**. $[\alpha]^{20}_D$ −110.9° (*c* 1.01, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.72 (s, 1H), 11.02 (s, 1H), 7.99 (s, 1H), 7.79 (d, 1H, J = 3.0 Hz), 7.43 (d, 2H, J = 7.1 Hz), 7.36−7.21 (m, 10 H), 7.05 (d, 1H, J = 7.5 Hz), 6.90 (t, 1H, J = 7.3 Hz, J = J.8 Hz), 6.79 (d, 1H, J = 8.2 Hz), 6.75 (d, 1H, J = 7.1 Hz), 6.63 (d, 1H, J = 8.0 Hz, J = 7.8 Hz), 6.59 (t, 1H, J = 7.5 Hz, J = 7.3 Hz), 6.23 (d, 1H, J = 8.9 Hz), 5.83 (d, 1H, J = 7.55 Hz), 4.94 (d, 1H, J = 11.4 Hz), 4.79 (d, 1H, J = 11.2 Hz), 4.50 (d, 1H, J = 11.9 Hz), 4.43 (d, 1H, J = 11.9 Hz), 3.99 (m, 1H), 3.73−3.66 (m, 4H), 3.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 172.7, 138.9, 138.4, 136.7, 133.1, 131.3, 130.9, 130.5, 129.2, 129.1, 129.0, 128.7, 128.6, 128.4, 126.4, 125.8, 125.7, 123.2, 122.8, 122.0, 121.2, 117.6, 112.1, 108.1, 107.0, 86.0, 84.6, 80.4, 76.6, 76.1, 73.8, 72.3, 69.5, 61.3; IR ($CHCl_3$) 3465, 1758, 1714 cm^{-1}. Anal. Calcd for $C_{41}H_{36}N_3O_7$-Cl: C, 69.02, H, 5.66, N, 5.62. Found. C, 68.71, H, 5.53, N, 5.95.

1, 11-Dichloro-12,13-dihydro-12-[4-*O*-methyl-3,6-bis-*O*-(phenylmethyl)-*β*-D-glucopyranosyl]-5-*H*-indolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (28). A mixture of **7** (400 mg, 0.53 mmol) and $Pd(OTf)_2$ (530 mg, 1.59 mmol) in DMF (20 mL) were heated at 90 °C for 2 h under N_2. The reaction was then cooled, diluted with EtOAc (50 mL), and washed with 0.5 N HCl (100 mL). The organic layer was dried ($MgSO_4$) and filtered through Hyflo, and the solvent was removed in vacuo to give the crude carbazole that was purified by column chromatography (2:1 hexanes:EtOAc) to give 262 mg (66%) of **28**. $[\alpha]^{20}_D$ +141.7° (*c*, 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.5 (s, 1H), 8.73 (d, 1H, J = 7.72 Hz), 7.84 (d, 1H, J = 7.74 Hz), 7.80 (s, 1H), 7.44−7.38 (m, 3H), 7.32−7.19 (m, 9H), 7.10 (t, 1H, J = 7.69 Hz), 7.06 (d, 1H, J = 7.54 Hz), 6.70 (t, 1H, J = 7.69 Hz), 5.03 (d, 1H, J = 11.55 Hz), 4.97 (d, 1H J = 11.55 Hz), 4.66 (d, 1H, J = 12.60 Hz), 4.57 (d, 1H, J = 12.60 Hz), 4.43 (t, 1H, J = 8.94 Hz), 4.16−3.96 (m, 4H), 3.89 (t, 1H, J = 8.40 Hz), 3.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 169.1, 138.6, 137.7, 137.4, 130.7, 129.9, 129.8, 128.7, 128.6, 128.4, 128.2, 128.1, 127.1, 124.7, 123.3, 123.2, 122.1, 121.7, 120.1, 118.8, 116.9, 116.5, 86.3, 85.0, 80.1, 79.3, 76.2, 73.7, 73.3, 68.4, 61.47; IR ($CHCl_3$) 3439, 3339, 1755, 1707 cm^{-1}. HRMS (EI) exact mass calcd for $C_{41}H_{33}N_3O_7Cl_2$ M$^+$ 750.1774, found 750.1765.

1-Chloro-12,13-dihydro-12-[4-*O*-methyl-3,6-bis-*O*-(phenylmethyl)-*β*-D-glucopyranosyl]-5-*H*-indolo-[2,3-*a*]-pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (29). A mixture of **8** (200 mg, 0.28 mmol) and $Pd(OTf)_2$ (280 mg, 0.83 mmol) in DMF (10 mL) was heated at 90 °C for 2 h under N_2. The reaction was then cooled, diluted with EtOAc (25 mL), and washed with 0.5 N HCl (50 mL). The organic layer was dried ($MgSO_4$) and filtered through Hyflo, and the solvent was removed in vacuo to give the crude carbazole that was purified by column chromatography (2:1 hexanes:EtOAc) to give 120 mg (60%) of **29**. $[\alpha]^{20}_D$ +123.1° (*c*, 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.82 (s, 1H), 8.95 (d, 1H, J = 7.8 Hz), 8.31 (d, 1H, J = 8.0 Hz), 7.66 (s, 1H), 7.59 (d, 1H, J = 7.5 Hz), 7.41−7.13 (m, 13H), 6.91 (t, 1H, J = 7.8 Hz, 7.1 Hz), 4.92 (s, 2H), 4.88 (d, 1H, J = 12.6 Hz), 4.75 (d, 1H, J = 12.1 Hz), 4.28 (bs, 2H), 4.12−3.97 (m, 4H), 3,85 (t, 1H, J = 8.9 Hz, J = 8.9 Hz), 3.77 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 169.7, 141.4, 138.9, 138.4, 137.6, 131.5, 130.6, 129.5, 129.4, 129.1, 128.8, 128.6, 128.4, 126.6, 125.9, 125.2, 123.6, 122.9, 121.6, 120.8, 119.7, 119.3, 117.4, 111.8, 86.5, 85.0, 78.9, 78.1, 76.8, 74.9, 73.0, 68.2, 61.9; IR (KBr) 3331, 1753, 1706 cm^{-1}. HRMS (FAB) exact mass calcd for $C_{41}H_{34}N_3O_7Cl$ M$^+$ 716.1870, found 716.1678.

Rebeccamycin. To a solution of indolocarbazole **28** (0.18 g, 240 μmol) in THF (10 mL) was added $Pd(OH)_2$ (90.0 mg). The reaction was stirred for 2 h under a H_2 atmosphere and then filtered through Hyflo using THF to rinse. The solvent was partially removed in vacuo to give a concentrated THF solution of product that was absorbed onto silica and purified by column chromatography (15 g silica gel, 100% EtOAc) to give 110 mg (83%) of rebeccamycin. $[\alpha]^{20}_D$ +143.0° (*c*, 1.02, THF); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.32 (s, 1H), 10.70 (s, 1H), 9.27 (d, 1H, J = 7.7 Hz), 9.08 (d, 1H, J = 7.8 Hz), 7.72 (d, 1H, J = 7.6 Hz), 7.68 (d, 1H, J = 7.6 Hz), 7.44 (t, 2H, J = 7.6 Hz), 6.97 (d, 1H, J = 9.1 Hz), 5.40 (d, 1H, J = 5.5 Hz), 5.31 (br t, 1H), 5.01 (d, 1H, J = 5.4 Hz), 4.01 (bs, 2H), 3.87 (d, 1H, J = 9.3 Hz), 3.73−3.58 (m, 3H), 3.62 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.3, 171.2, 138.6, 138.1, 130.8, 130.6, 127.9, 126.0, 124.9, 124.4, 124.2, 123.4, 123.0, 121.5, 120.3, 118.6, 117.1, 117.1, 85.3, 81.1, 80.1, 78.3, 73.1, 61.0, 60.8; IR ($CHCl_3$) 3350, 1753, 1703 cm^{-1}. HRMS (EI) exact mass calcd for $C_{27}H_{21}N_3O_7Cl_2$ M$^+$ 570.0834, found 570.0839.

11-Dechlororebeccamycin. To a solution of indolocarbazole **29** (200 mg, 280 μmol) in THF (20 mL) was added $Pd(OH)_2$ (100 mg). The reaction was stirred for 4 h under a H_2 atmosphere and then filtered through Hyflo using THF to rinse. The solvent was partially removed in vacuo and a concentrated THF solution of product absorbed onto silica and purified by column chromatography to afford 128 mg (86%) of 11-dechlororebeccamycin as a yellow solid. $[\alpha]^{20}_D$ +128.1° (*c*, 1.01, THF); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.81 (s, 1H), 11.24 (s, 1H), 9.26 (d, 1H, J = 8.0 Hz), 9.11 (d, 1H, J = 8.0 Hz), 7.76 (d, 1H, J = 8.0 Hz), 7.63 (m, 2H), 7.41 (t, 2H, J = 6.9 Hz, J = 8.0 Hz), 6.91 (d, 1H, J = 8.8 Hz), 6.29 (bs, 1H), 5.24 (d, 1H, J = 6.2 Hz), 4.90 (d, 1H, J = 5.4 Hz), 4.01 (bs, 2H), 3.91 (d, 1H, J = 9.9 Hz), 3.68 (t, 1H, J = 9.1 Hz, J = 9.5 Hz), 3.62 (s, 3H), 3.53 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.7, 170.6, 140.6, 138.1, 130.4, 129.9, 129.4, 127.3, 125.5, 124.6, 123.8, 122.7, 122.3, 121.1, 120.6, 119.4, 119.1, 117.3, 116.4, 112.1, 83.8, 77.5, 77.0, 76.5, 72.0, 60.0, 58.6; IR ($CHCl_3$) 3317, 1747, 1703 cm^{-1}. HRMS (EI) exact mass calcd for $C_{27}H_{22}N_3O_7Cl$ M$^+$ 536.1225, found 536.1230.

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