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Synthesis of Dissymmetric Indolocarbazole Glycosides Using the Mitsunobu Reaction at the Glycosylation Step

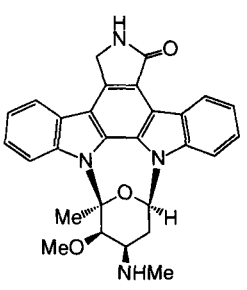
Mitsuru Ohkubo*, Teruyuki Nishimura, Hideki Jona, Teruki Honma, Satoru Ito and Hajime Morishima

Banyu Tsukuba Research Institute in collaboration with Merck Research Laboratories,
Okubo 3, Tsukuba 300-33, Japan

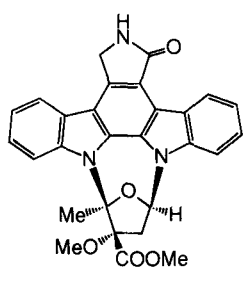
Abstract: A novel method for the synthesis of *N*-glycosylated dissymmetric indolo[2,3-*a*]pyrrolo-[3,4-*c*]carbazole derivatives was developed by applying the Mitsunobu reaction to the *N*-glycosylation reaction of substituted indole substrates. © 1997 Elsevier Science Ltd.

INTRODUCTION

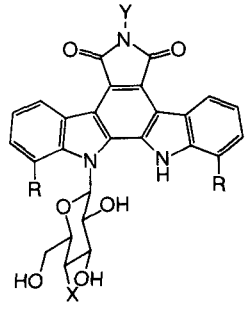
Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole compounds such as staurosporine (**1**)[1], K-252a (**2**)[2] and rebeccamycin (**3**)[3] are known to have various biological effects. We recently reported that NB-506 (**4**)[4] is a potent antitumor agent that has a wider therapeutic index in mice than currently available anticancer drugs against murine and human solid tumors.



staurosporine (**1**)



K-252a (**2**)



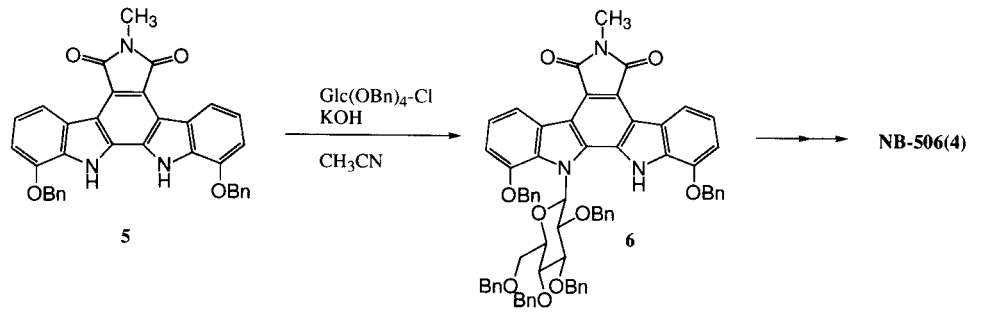
rebeccamycin (**3**) R = Cl, X = OMe, Y = H
NB-506 (**4**) R = OH, X = OH, Y = NHCHO

Fig. 1

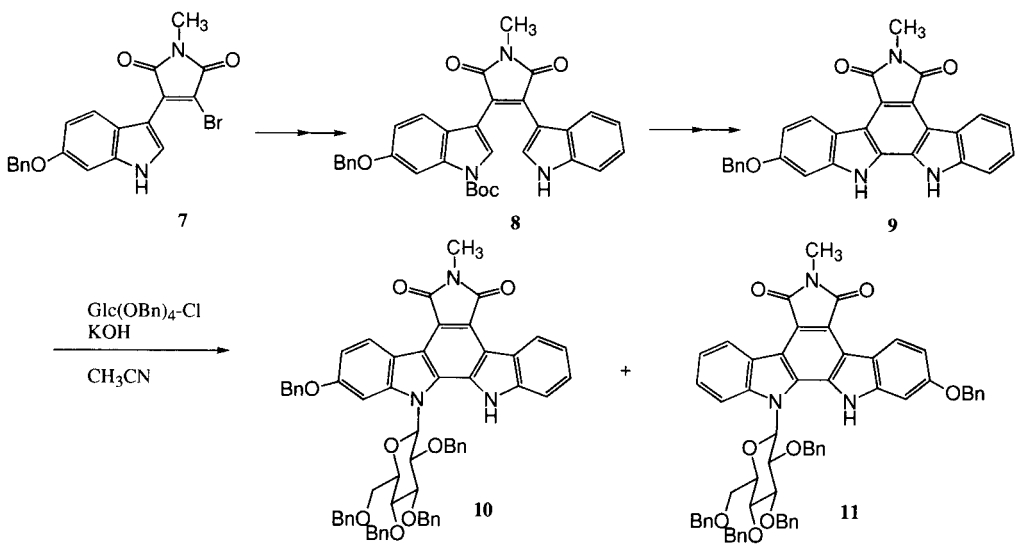
To discover anticancer agents more potent than NB-506, the synthesis of dissymmetric indolocarbazole glycosides was planned. However, the method of synthesizing NB-506[4b] shown in Scheme 1 could not be applied to the synthesis of an dissymmetric indolocarbazole glycoside because of lack of regioselectivity (**1 0:1 1**

= 1:1) (Scheme 2). The glycosylation of compound **7** or **8**[5] was also unsuccessful because these compounds were unstable to KOH. Glycosylation reactions proceeding under neutral conditions were subsequently investigated, and the Mitsunobu reaction was found to be applicable to the glycosylation of compounds **7** or **8**.

This communication reports the details of glycosylation by the Mitsunobu reaction.



Scheme 1

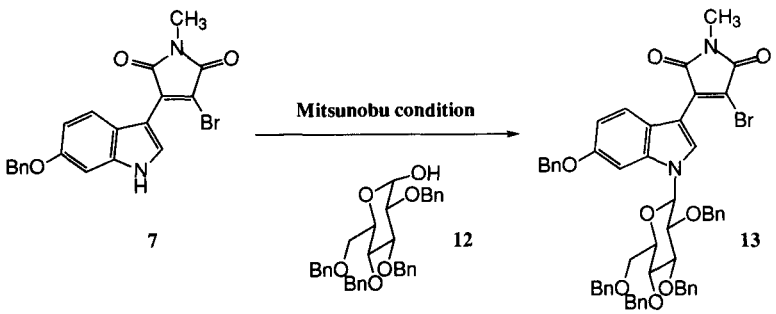


Scheme 2

RESULTS AND DISCCUSSION

The Mitsunobu reaction[6] is widely used for the alkylation of various acids (or nucleophiles; HA) utilizing diethyl azodicarboxylate (DEAD) - triphenylphosphine (PPh_3) with the Walden inversion. However, few applications to a glycosylation reaction have been reported[7] probably because the pKa of HA is required to be

lower than 13[8]. Since the pKa value of compound **7** was supposed[9] to be less than 13, we tried to apply the Mitsunobu reaction to the glycosylation of compound **7**. We tested several reagents[8] which were developed to improve the Mitsunobu reaction. As shown in Table 1, the glycosylation of compound **7** with 2,3,4,6-tetra-*O*-benzyl-α-D-glucose **12** in the presence of both DIAD and PPh_3 yielded the desired β-glucoside **13** in 79-82% yields without formation of an α-anomer.



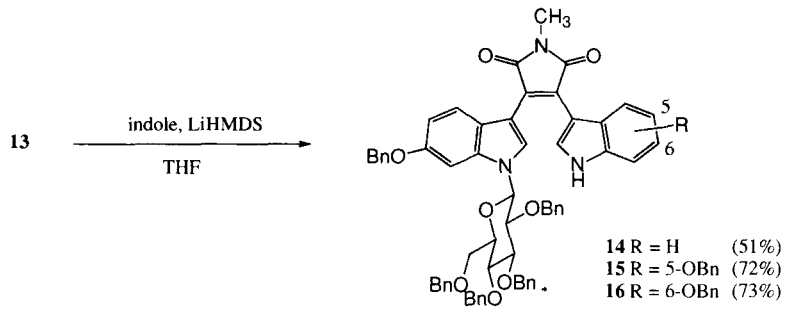
Scheme 3

Table 1 Glycosylations of 7 with 12 under several Mitsunobu conditions[a]

Mitunobu reagent (eq.)[b]		Phosphine (eq.)		**12** (eq.)	yield (%)[c]
DEAD	(1.5)	PPh_3	(1.5)	1.5	73
DEAD	(1.5)	PBu_3	(1.5)	1.5	48
DIAD	(1.5)	PPh_3	(1.5)	1.5	79
DBAD	(1.5)	PPh_3	(1.5)	1.5	41[d]
TMAD	(1.5)	PBu_3	(1.5)	1.5	56[d]
ADDP	(1.5)	PBu_3	(1.5)	1.5	34
DIAD	(3.0)	PPh_3	(3.0)	3.0	82

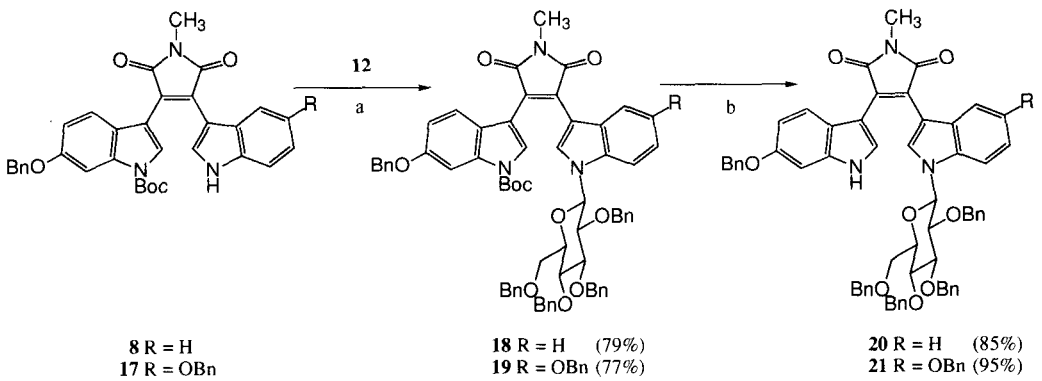
a) The reaction was carried out at -40-0 °C for 1-2 h.
b) DEAD (diethylazodicarboxylate), DIAD (diisopropylazodicarboxylate), DBAD (di-*tert*-butylazodicarboxylate), TMAD (*N,N,N',N'*-tetramethylazocarboxamide), ADDP [1,1'-(azodicarbonyl)dipiperazine]
c) The yield of β-glucoside **10**; α-anomer was not observed.
d) The reaction mixture was left overnight, but the reaction was almost over after 2 h.

A second indolylation reaction of bromide **13** with three kinds of indole using a two-fold excess of Litium hexamethyldisilazide (LiHMDS) afforded dissymmetric compounds **14** and **15** as well as a symmetric compound **16** in good yields. (Scheme 4).



Scheme 4

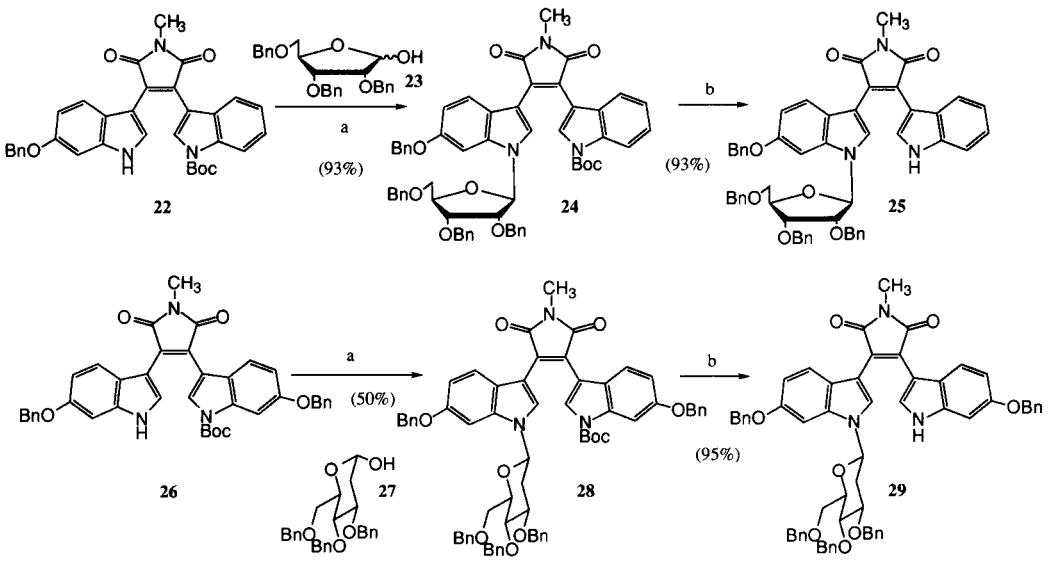
As shown in Scheme 5, the Mitsunobu reaction was also applicable to the glycosylation of dissymmetric bisindolyl compounds **8** and **17**[5] to respectively give β-glucosides **18** and **19** in good yields; in these cases, α-anomers were not detected. The removal of the Boc group of compounds **18** and **19** using methylamine afforded glycosylated bisindolylmaleimides **20** and **21**, respectively, in good yields.



Scheme 5 reagents; (a) DIAD,PPh_3; (b) 40% $MeNH_2$-MeOH

This glycosylation was utilized for synthesizing other sugar derivatives. As shown in Scheme 6, the glycosylation of compound **22** with ribofuranose **23** ($\alpha:\beta$ = 1:1) proceeded at -40 °C to provide only β-ribofuranoside **24**. The yield of **24** depended on the number of equivalents of **23** that were used: 1.0, 2.0 and 3.0 equiv of **23** gave **24** in 20 , 84 and 93% yields, respectively. The anomeric configuration of **24** was determined by ROE studies in the C1-C4 region as well as 2D-COSY experiments. Furthermore, the glycosylation of **26**[5] with 2-deoxyglucose **27**(α-anomer) afforded β-2-deoxyglucoside **28** in 50% yield; the configuration was determined by analysis of the ^1H NMR coupling constants and a 2D-COSY experiment.

Removal of the Boc group of **24** and **28** with methylamine afforded deprotected compounds **25** and **29**, respectively, in good yields.

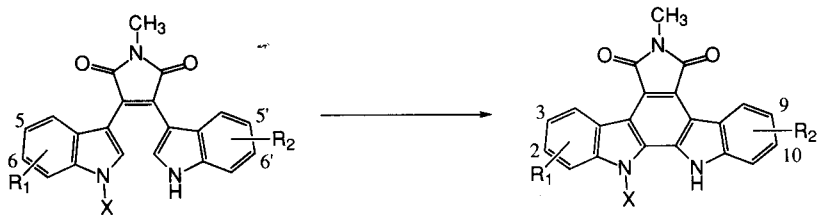


Scheme 6 reagents; (a) DIAD, PPh_3; (b) 40% $MeNH_2$-MeOH

We also tried to glycosylate bisindolylmaleimide **30** and indolocarbazole **31**[5] in a similar manner, but the reactions did not proceed. The absence of an electron-withdrawing group such as Br or Boc in these compounds may have caused the decrease in reactivity.

Fig. 2

The oxidative cyclization of glycosylated bisindolyl compounds with $CuCl_2$ and $PdCl_2$ gave the corresponding indolopyrrolocarbazole glycosides in good yields (Table 2). In contrast, the use of DDQ[5] was unsuccessful.



14 R_1 = 6-OBn, R_2 = H, X = Glc(OBn)$_4$
15 R_1 = 6-OBn, R_2 = 5'-OBn, X = Glc(OBn)$_4$
16 R_1 = 6-OBn, R_2 = 6'-OBn, X = Glc(OBn)$_4$
20 R_1 = H, R_2 = 6'-OBn, X = Glc(OBn)$_4$
21 R_1 = 5-OBn, R_2 = 6'-OBn, X = Glc(OBn)$_4$
25 R_1 = H, R_2 = 6'-OBn, X = Rib(OBn)$_3$
29 R_1 = 6-OBn, R_2 = 6'-OBn, X = 2-deoxy-Glc(OBn)$_3$

32 R_1 = 2-OBn, R_2 = H, X = Glc(OBn)$_4$
33 R_1 = 2-OBn, R_2 = 9-OBn, X = Glc(OBn)$_4$
34 R_1 = 2-OBn, R_2 = 10-OBn, X = Glc(OBn)$_4$
35 R_1 = H, R_2 = 10-OBn, X = Glc(OBn)$_4$
36 R_1 = 3-OBn, R_2 = 10-OBn, X = Glc(OBn)$_4$
37 R_1 = H, R_2 = 10-OBn, X = Rib(OBn)$_3$
38 R_1 = 2-OBn, R_2 = 10-OBn, X = 2-deoxy-Glc(OBn)$_3$

Scheme 7

Table 2 Oxidative cyclization of glycosylated bisindolylmaleimide

bisindole	reagent	solvent[a)]	temp (°C)	product	yield (%)
14	$CuCl_2$	MEK	70	**32**	80
15	$CuCl_2$	MEK	60	**33**	80
16	$CuCl_2$	MEK	30	**34**	84
20	$PdCl_2$	DMF	100	**35**	78
21	$PdCl_2$	DMF	110	**36**	77
25	$CuCl_2$	MEK	80	**37**	98
29	$CuCl_2$	MEK	60	**38**	71

a) MEK (methylethylketone), DMF (*N,N*-dimethylformamide)

SUMMARY

The synthesis of dissymmetric indolocarbazole glycosides was achieved by applying the Mitsunobu reaction at the glycosylation step, which made it possible to evaluate the influence of differences in the position of a hydroxyl group on antitumor activities

EXPERIMENTAL

^1H and ^{13}C NMR were recorded on a Varian VXR-300, Jeol JNM-EX 400 or JNM-A 500 instrument. Infrared spectra were recorded on a Horiba FT-200 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Jeol JMS-SX 102A instrument, and optical rotations were measured on a Fisons Model EA 1108 polarimeter. Melting points were determined on a Mettler FP 62 or Yanako Model MP-S3 melting point apparatus and are uncorrected.

General Procedure for the Mitsunobu Glycosylation: DIAD was added to a solution of indole (0.01-0.1 M), PPh_3 and sugar in dry THF at -78 to 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at -40 to 0°C until TLC indicated complete consumption of the indole (15-60 min). The reaction mixture

was poured into 0.2 M aqueous hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic phase was successively washed with aqueous $NaHCO_3$, H_2O and saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel to yield the indolyl β-glycoside.

4-Bromo-2,5-dihydro-3-[6-benzyloxy-1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indol-3-yl]-1-methyl-1*H*-pyrrolo-2,5-dione (13): From **7** (200 mg, 0.49 mmol), PPh_3 (382 mg, 1.47 mmol), 2,3,4,6-tetra-*O*-benzyl-D-glucose **12** (α- dominant, Sigma, 787 mg, 1.47 mmol) and DIAD (0.28 mL, 1.47 mmol), **13** (373 mg, 0.40 mmol) was obtained as a yellow amorphous substrate (82%) after chromatography (toluene-ethyl acetate (50:1-15:1)). $[\alpha]^{20}_D$ -46.4° (c 0.16, DMSO); IR (KBr) ν_{max} 1767, 1707, 1603, 1454, 1379, 1090 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (1H, d, J = 8.9 Hz), 7.93 (1H, s), 7.17-7.41 (20H, m), 6.97-7.17 (5H, m), 6.71 (2H, dd, J = 1.3, 8.9 Hz), 5.29 (1H, d, J = 8.4 Hz), 5.00 (1H, d, J = 7.8 Hz), 4.97 (1H, d, J = 7.8 Hz), 4.93 (1H, d, J = 11.9 Hz), 4.92 (1H, d, J = 10.8 Hz), 4.90 (1H, d, J = 11.9 Hz), 4.68 (1H, d, J = 10.8 Hz), 4.61 (1H, d, J = 11.9 Hz), 4.52 (1H, d, J = 11.9 Hz), 4.17 (1H, d, J = 10.0 Hz), 3.75-3.96 (5H, m), 3.71 (1H, br d, J = 9.6 Hz), 3.56 (1H, br d, J = 9.6 Hz), 3.56 (1H, d, J = 10.0 Hz), 3.16 (3H, s); HRMS (FAB) calcd for $C_{54}H_{49}N_2O_5Br$ 932.2627, found 932.2694.

General Procedure for the indolylation: LiHMDS (1 M in THF, 2.1-2.4 equiv) was added to a solution of 1.0-1.2 equiv of the appropriate indole (0.05 M) in THF at -20 °C under a nitrogen atmosphere and stirred for 30-45 min. A solution of the bromide (0.1 M) in THF was then added by drip over 30-60 min, followed by stirring for 15 min at 0 °C. The reaction mixture was poured into 0.2 M aqueous hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic phase was successively washed with aqueous $NaHCO_3$, H_2O and saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed to obtain the glycosylated bisindolylmaleimide.

2,5-Dihydro-3-[6-benzyloxy-1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indol-3-yl]-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrolo-2,5-dione (14): From indole (27 mg, 0.21 mmol), LiHMDS (1 M in THF, 0.51 mL, 0.51 mmol) and **13** (200 mg, 0.21 mmol), the bisindolyl maleimide **14** (104 g, 0.11 mmol) was obtained as an orange amorphous substrate (51%) after chromatography on silica gel (toluene-ethyl acetate (50:1-15:1)). $[\alpha]^{20}_D$ -61.6° (c 0.50, DMSO); IR (KBr) ν_{max} 3411, 1697, 1540, 1456, 1093, 1027 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 8.40 (1H, s), 7.95 (1H, s), 7.61 (1H, d, J = 1.5 Hz), 7.03-7.40 (26H, m), 6.79 (2H, dd, J = 1.5, 7.8 Hz), 6.65 (1H, d, J = 8.7 Hz), 6.63 (1H, dd, J = 1.8, 9.0 Hz), 6.42 (1H, dd, J = 2.1, 9.0 Hz), 5.32 (1H, d, J = 8.4 Hz), 4.83-4.93 (5H, m), 4.66 (1H, d, J = 10.2 Hz), 4.57 (2H, q, J = 11.7 Hz), 4.12 (1H, d, J = 9.6 Hz), 3.93 (2H, t, J = 9.3 Hz), 3.80-3.83 (4H, m), 3.68 (2H, d, J = 10.2 Hz), 3.19 (3H, s); HRMS (FAB) calcd for $C_{69}H_{61}N_3O_9$ 969.3989, found 969.3990.

2,5-Dihydro-3-[6-benzyloxy-1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indol-3-yl]-4-(5-benzyloxy-1*H*-indol-3-yl)-1-methyl-1*H*-pyrrolo-2,5-dione (15): From 5-benzyloxyindole (49 mg, 0.21 mmol), LiHMDS (1 M in THF, 0.51 mL, 0.51 mmol) and **13** (200 mg, 0.21 mmol), the bisindolyl maleimide **15** (163 mg, 0.15 mmol) was obtained as an orange amorphous substrate (72%) after chromatography on silica gel (toluene-ethyl acetate (50:1-25:1)) . $[\alpha]^{20}_D$ -13.6° (c 0.50, DMSO); IR (KBr) ν_{max} 3412, 1697, 1456, 1218, 1093 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (1H, s), 7.78 (1H, d, J = 1.8 Hz),

7.75 (1H, s), 7.03-7.35 (31H, m), 6.92 (1H, d, J = 9.0 Hz), 6.75 (1H, dd, J = 2.1, 8.4 Hz), 6.70 (2H, d, J = 8.4 Hz), 6.56 (1H, dd, J = 2.4, 9.0 Hz), 6.54 (1H, d, J = 2.4 Hz), 5.25 (1H, d, J = 9.0 Hz), 4.87 (2H, d, J = 8.1 Hz), 4.84 (2H, s), 4.62 (1H, d, J = 11.1 Hz), 4.42 (1H, d, J = 12.3 Hz), 4.33 (1H, d, J = 11.4 Hz), 4.32 (1H, d, J = 11.4 Hz), 4.24 (1H, d, J = 12.3 Hz), 4.13 (1H, d, J = 10.2 Hz), 3.89 (2H, dt, J = 3.0, 9.3 Hz), 3.77 (1H, d, J = 9.3 Hz), 3.70 (1H, dd, J = 3.1, 11.1 Hz), 3.62 (1H, d, J = 10.2 Hz), 3.52 (1H, m), 3.40 (1H, d, J = 9.9 Hz), 3.19 (3H, s); HRMS (FAB) calcd for $C_{69}H_{61}N_3O_9$ 1075.4408, found 1075.4392.

2,5-Dihydro-3-[6-benzyloxy-1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indol-3-yl]-4-(6-benzyloxy-1*H*-indol-3-yl)-1-methyl-1*H*-pyrrolo-2,5-dione (16): From 6-benzyloxyindole (360 mg, 1.61 mmol), LiHMDS (1 M in THF, 3.45 mL, 3.45 mmol) and **13** (1480 mg, 1.59 mmol), the bisindolyl maleimide **16** (1234 mg, 1.15 mmol) was obtained as an orange amorphous substrate (73%) after chromatography on silica gel (hexane-ethyl acetate (4:1)). $[\alpha]^{20}_D$ -67.2° (c 0.25, DMSO); IR (KBr) ν_{max} 3311, 1697, 1621, 1533, 1454, 1385, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (1H, d, J = 2.7 Hz), 7.96 (1H, s), 7.52 (1H, d, J = 2.7 Hz), 7.19-7.40 (25H, m), 7.03-7.16 (5H, m), 6.78-6.84 (3H, m), 6.67 (1H, d, J = 8.8 Hz), 6.45 (1H, dd, J = 2.2, 8.8 Hz), 6.34 (1H, dd, J = 2.2, 8.8 Hz), 5.34 (1H, d, J = 8.7 Hz), 4.82-4.94 (7H, m), 4.67 (1H, d, J = 10.7 Hz), 4.62 (1H, d, J = 12.2 Hz), 4.53 (1H, d, J = 12.2 Hz), 4.12 (1H, d, J = 10.2 Hz), 3.67-3.98 (7H, m), 3.18 (3H, s); HRMS (FAB) calcd for $C_{69}H_{61}N_3O_9$ 1075.4408, found 1075.4392.

2,5-Dihydro-3-[6-benzyloxy-1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indol-3-yl]-4-[1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]-1-methyl-1*H*-pyrrolo-2,5-dione (18): From **8** (4.0 g, 7.3 mmol), PPh_3 (5.74 g, 21.9 mmol), 2,3,4,6-tetra-*O*-benzyl-D-glucose **12** (11.8 g, 21.9 mmol) and DIAD (4.3 mL, 21.9 mmol), **18** (6.2g, 5.8 mmol) was obtained as a yellow amorphous substrate (79%) after chromatography (toluene-ethyl acetate (50:1)). $[\alpha]^{20}_D$ -27.2° (c 1.00, DMSO); IR (KBr) ν_{max} 1734, 1701, 1585, 1541, 1456, 1363, 1217, 1153, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (1H, s), 7.95 (1H, s), 7.78 (1H, br s), 7.52 (1H, d, J = 8.7 Hz), 6.96-7.45 (24H, m), 6.92 (1H, d, J = 8.3 Hz), 6.65-6.85 (4H, m), 6.23 (1H, dd, J = 2.6, 8.7 Hz), 5.43 (1H, d, J = 8.9 Hz), 4.78-4.92 (5H, m), 4.48-4.70 (3H, m), 4.14 (1H, d, J = 9.9 Hz), 3.60-4.03 (7H, m), 3.20 (3H, s), 1.64 (9H, s); HRMS (FAB) calcd for $C_{67}H_{63}N_3O_{10}$ 1069.4514, found 1069.4513.

2,5-Dihydro-3-[6-benzyloxy-1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indol-3-yl]-4-[5-benzyloxy-1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]-1-methyl-1*H*-pyrrolo-2,5-dione (19): From **17** (8.50 g, 13.0 mmol), PPh_3 (8.52 g, 32.5 mmol), 2,3,4,6-tetra-*O*-benzyl-D-glucose **12** (17.57 g, 32.5 mmol) and DIAD (6.4 mL, 32.5 mmol), **10** (11.71 g, 9.96 mmol) was obtained as a yellow amorphous substrate (77%) after chromatography (hexane-ethylacetate(3:1), toluene-ethyl acetate (50:1)). $[\alpha]^{20}_D$ -35.2° (c 1.00, DMSO); IR (KBr) ν_{max} 1734, 1701, 1616, 1454, 1369, 1213, 1153, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (1H, s), 7.84 (1H, s), 7.81 (1H, br s), 7.42 (1H, d, J = 9.1 Hz), 7.04-7.37 (28H, m), 7.00 (1H, d, J = 8.8 Hz), 6.72-6.81 (3H, m), 6.34-6.40 (2H, m), 5.38 (1H, d, J = 8.8 Hz), 4.80-4.93 (5H, m), 4.65 (1H, d, J = 10.7 Hz), 4.62 (1H, d, J = 12.1 Hz), 4.54 (1H, d, J = 12.1 Hz), 3.62-4.18 (10H, m), 3.21 (3H, s), 1.51 (9H, s); HRMS (FAB) calcd for $C_{74}H_{69}N_3O_{11}$ 1175.4932, found 1175.4969.

General Procedure for Boc deprotection: 40% methylamine in methanol was added to the Boc-protected compound and the reaction mixture was stirred for 0.5-2 h at room temp. The solvent was removed in vacuo and the residue was purified to afford the deprotected compound.

2,5-Dihydro-3-[6-benzyloxy-1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indol-3-yl]-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrolo-2,5-dione (20): From **18** (6.2 g, 5.79 mmol) and 40% methylamine in methanol (100 mL), compound **20** (4.78 g, 4.93 mmol) was obtained as an orange amorphous substrate (85%) after chromatography (hexane-ethyl acetate (2:1)). $[\alpha]^{20}_{D}$ -28.0° (c 0.25, DMSO); IR (KBr) ν_{max} 3241, 1697, 1539, 1456, 1385, 1159, 1093, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (1H, br s), 8.06 (1H, s), 7.48-7.58 (3H, m), 6.99-7.39 (24H, m), 6.67-6.85 (5H, m), 6.30 (1H, dd, J = 2.3, 8.3 Hz), 5.45 (1H, d, J = 8.9 Hz), 4.80-4.92 (5H, m), 4.66 (1H, d, J = 10.9 Hz), 4.61 (1H, d, J = 12.5 Hz), 4.53 (1H, d, J = 12.5 Hz), 4.16 (1H, d, J = 8.1 Hz), 3.60-4.08 (7H, m), 3.19 (3H, s); HRMS (FAB) calcd for $C_{62}H_{53}N_3O_8$ 969.3989, found 969.3956.

2,5-Dihydro-3-[6-benzyloxy-1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indol-3-yl]-4-(5-benzyloxy-1*H*-indol-3-yl)-1-methyl-1*H*-pyrrolo-2,5-dione (21): From **19** (122 mg, 0.10 mmol) and 40% methylamine in methanol (1 mL), compound **21** (105 mg, 0.097 mmol) was obtained as an orange amorphous substrate (95%) after chromatography (hexane-ethyl acetate (2:1)). $[\alpha]^{20}_{D}$ -41.6° (c 0.25, DMSO); IR (KBr) ν_{max} 3402, 1697, 1541, 1456, 1387, 1157, 1093, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (1H, d, J = 2.3 Hz), 8.15 (1H, s), 7.05-7.45 (31H, m), 6.46 (1H, dd, J = 2.3, 9.8 Hz), 6.23 (1H, d, J = 2.3 Hz), 5.39 (1H, d, J= 8.8 Hz), 4.83-4.92 (3H, m), 4.80 (2H, s), 4.64 (1H, d, J = 10.8 Hz), 4.59 (1H, d, J = 12.2 Hz), 4.52 (1H, d, J = 12.2 Hz), 4.00-4.15 (4H, m), 3.46-3.90 (5H, m), 3.18 (3H, s); HRMS (FAB) calcd for $C_{69}H_{61}N_3O_9$ 1075.4408, found 1075.4349.

2,5-Dihydro-3-(6-benzyloxy-1*H*-indol-3-yl)-4-[1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]-1-methyl-1*H*-pyrrolo-2,5-dione (22): From 6-benzyloxyindole (1.78 g, 8.00 mmol), LiHMDS (1M in THF, 17.6 mL, 17.6 mmol) and 4-bromo-2,5-dihydro-3-[(1-*tert*-butoxycarbonyl)-1*H*-indol-3-yl]-1-methyl-1*H*- pyrrol - 2,5-dione (2.95 g, 7.28 mmol), the bisindolyl maleimide **22** (3.42 g, 6.25 mmol) was obtained as an orange solid (86%) after chromatography on silica gel (hexane-ethyl acetate (3:1)). mp 129-132 °C: IR (KBr) ν_{max} 3363, 1734, 1697, 1541, 1456, 1387, 1373, 1252, 1236, 1153, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (1H, br s), 8.14 (1H, d, J = 8.7 Hz), 8.05 (1H, s), 7.70 (1H, d, J = 2.1 Hz), 7.10-7.42 (6H, m), 6.72-6.99 (4H, m), 6.55 (1H, dd, J = 2.4, 8.9 Hz), 5.01 (2H, s), 3.19 (3H, s), 1.68 (9H, s); HRMS (FAB) calcd for $C_{33}H_{29}N_3O_5$ 547.2107, found 547.2098.

2,5-Dihydro-3-[6-benzyloxy-1-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-1*H*-indol-3-yl]-4-[1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]-1-methyl-1*H*-pyrrolo-2,5-dione (24): From **22** (2.19 g, 4.00 mmol), PPh_3 (3.12 g, 11.9 mmol), 2,3,5-tri-*O*-benzyl-D-ribofuranose **23** (α/β = 1/1, 5.0 g, 11.9 mmol) and DIAD (2.34 mL, 11.9 mmol), **24** (3.49 g, 3.68 mmol) was obtained as a yellow amorphous powder (93%) after chromatography (toluene-ethyl acetate (30:1)). $[\alpha]^{20}_{D}$ -70.0° (c 1.00, DMSO); IR (KBr) ν_{max} 1734, 1701, 1568, 1541, 1456, 1371, 1209, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (1H, d, J = 8.2 Hz), 8.03 (1H, s), 7.89 (1H, s), 7.10-7.40 (22H, m), 7.00 (1H, d, J = 8.9 Hz), 6.86 (1H, d, J = 7.9 Hz), 6.75 (1H, d, J = 7.3 Hz), 6.58 (1H, dd, J = 2.2, 9.1 Hz), 6.08 (1H, d, J = 5.6 Hz), 4.93 (2H, s), 4.33-4.62 (6H, m), 4.26-4.32

(1H, m), 4.17 (1H, t, J = 5.1 Hz), 3.99 (1H, t, J = 4.4 Hz), 3.58 (1H, dd, J = 3.2, 10.6 Hz), 3.45 (1H, dd, J = 3.2, 10.6 Hz), 3.18 (3H, s), 1.65 (9H, s); HRMS (FAB) calcd for $C_{59}H_{55}N_3O_9$ 949.3938, found 949.3934

2,5-Dihydro-3-[6-benzyloxy-1-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-1*H*-indol-3-yl]-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrolo-2,5-dione (25): From **24** (3.49 g, 3.68 mmol) and 40% methylamine in methanol (40 mL), compound **25** (2.90 g, 3.41 mmol) was obtained as an orange amorphous powder (93%) after chromatography (hexane-ethyl acetate (2:1)). $[\alpha]^{20}_D$ -34.4° (c 0.50, DMSO); IR (KBr) ν_{max} 3362, 1697, 1541, 1456, 1387, 1209, 1124 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.39-8.45 (1H, m), 7.83 (1H, s), 7.68 (1H, d, J = 2.8 Hz), 7.00-7.40 (24H, m), 6.91 (1H, d, J = 8.8 Hz), 6.74 (1H, t, J = 7.1 Hz), 6.54 (1H, dd, J = 2.2, 8.8 Hz), 6.10 (1H, d, J = 5.6 Hz), 4.95 (2H, s), 4.28-4.62 (7H, m), 4.21 (1H, t, J = 5.4 Hz), 3.99 (1H, dd, J = 4.1, 5.0 Hz), 3.60 (1H, dd, J = 3.3, 10.7 Hz), 3.48 (1H, dd, J = 3.3, 10.8 Hz), 3.17 (3H, s); HRMS (FAB) calcd for $C_{54}H_{47}N_3O_7$ 849.3414, found 849.3424.

2,5-Dihydro-3-[6-benzyloxy-1-(2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indol-3-yl]-4-[6-benzyloxy1-1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]-1-methyl-1*H*-pyrrolo-2,5-dione (28): From **26** (1.0 g, 1.53 mmol), PPh_3 (790 mg, 3.0 mmol), 2-deoxy-3,4,6-tri-*O*-benzyl-α-D-glucopyranose **27** (1.3 g, 3.0 mmol) and DIAD (0.58 mL, 3.0 mmol), **28** (818 mg, 0.76 mmol) was obtained as a yellow amorphous powder (50%) after chromatography (toluene-ethyl acetate (30:1)). $[\alpha]^{20}_D$ -22.2° (c 0.25, DMSO); IR (KBr) ν_{max} 1733, 1701, 1540, 1456, 1369, 1218, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (1H, s), 7.84 (1H, s), 7.71 (1H, s), 7.18-7.39 (25H, m), 6.98 (1H, d, J = 9.0 Hz), 6.93 (1H, d, J = 2.4 Hz), 6.75 (1H, d, J = 8.4 Hz), 6.57 (2H, dt, J = 2.4, 9.0 Hz), 5.40 (1H, dd, J = 1.5, 10.8 Hz), 5.00 (2H, s), 4.95 (2H, s), 4.69 (1H, d, J = 11.7 Hz), 4.62 (2H, d, J = 11.1 Hz), 4.59 (1H, d, J = 11.1 Hz), 4.52 (2H, d, J = 11.7 Hz), 3.77-3.88 (1H, m), 3.75 (2H, s), 3.65-3.69 (2H, m), 3.18 (3H, s), 2.44 (1H, dd, J = 1.5, 10.8 Hz), 2.17 (1H, q, J = 11.7 Hz), 1.65 (9H ,s); HRMS (FAB) calcd for $C_{67}H_{63}N_3O_{10}$ 1069.4513, found 1069.4496.

2,5-Dihydro-3-[6-benzyloxy-1-(2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indol-3-yl]-4-[1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]-1-methyl-1*H*-pyrrolo-2,5-dione (29): From **28** (818 mg, 0.77 mmol) and 40% methylamine in methanol (50 mL), compound **29** (705 mg, 0.73 mmol) was obtained as an orange amorphous powder (95%) after chromatography (hexane-ethyl acetate (2:1)). $[\alpha]^{20}_D$ -16.0° (c 0.12, DMSO); IR (KBr) ν_{max} 3368, 1693, 1616, 1538, 1454, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (1H, s), 7.69 (1H, s), 7.56 (1H, d, J = 1.5 Hz), 7.17-7.40 (25H, m), 6.96 (1H, d, J = 9.0 Hz), 6.87 (1H, d, J = 9.0 Hz), 6.85 (1H, d, J = 2.4 Hz), 6.58 (1H, dd, J = 2.4, 9.0 Hz), 6.53 (1H, dd, J = 2.1, 9.0 Hz), 5.41 (1H, d, J = 9.6 Hz), 4.99 (2H, s), 4.95 (2H, s), 4.95 (1H, d, J = 10.8 Hz), 4.70 (1H, d, J = 10.8 Hz), 4.62 (1H, d, J = 10.8 Hz), 4.60 (1H, 11.7 Hz), 4.52 (1H, d, J = 10.2 Hz), 4.48 (1H, d, J = 10.5 Hz), 3.75-3.90 (2H, m), 3.76 (1H, s), 3.67 (2H, d, J = 9.0 Hz), 3.17 (3H, s), 2.50 (1H, dd, J = 1.8, 9.6 Hz), 2.19 (1H, q, J = 10.8 Hz); HRMS (FAB) calcd for $C_{62}H_{55}N_3O_8$ 969.3989, found 969.3983.

12,13-Dihydro-2-benzyloxy-13-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-5*H*-indolo-[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-methyl-5,7(6*H*)-dione (32): Cupric chloride (1.4 g, 10 mmol) was added to a solution of **14** (1.0 g, 1.03 mmol) in the presence of molecular sieves 4A (1.0 g) in MEK (200mL), followed by stirring at 70 °C for 2 h. The precipitate was filtered off and the filtrate was concentrated. The

residue was dissolved in ethyl acetate and the organic mixture was successively washed with 1M HCl, aqueous $NaHCO_3$, H_2O and saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane-acetone (3:1)) to yield **32** (800 mg, 0.83 mmol) as a yellow powder (80%). $[\alpha]^{20}_D$ +98.4° (c 1.00, $CHCl_3$); IR (KBr) ν_{max} 3334, 1749, 1697, 1618, 1577, 1496, 1454, 1375, 1153, 1079 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.68 (1H, s), 9.25 (2H, d, J = 8.4 Hz), 7.13-7.50 (27H, m), 7.00 (1H, t, J = 8.7 Hz), 6.87 (1H, t, J = 8.7 Hz), 6.20 (2H, d, J = 8.4 Hz), 5.87 (2H, d, J = 8.9 Hz), 5.20 (2H, d, J = 2.5 Hz), 5.00 (1H, d, J = 10.6 Hz), 4.88 (2H, s), 4.75 (2H, t, J = 12.3 Hz), 4.63 (1H, d, J = 10.6 Hz), 4.38 (1H, d, J = 9.8 Hz), 3.93-4.06 (4H, m), 3.86 (2H, d, J = 9.8 Hz), 3.33 (3H, s); HRMS (FAB) calcd for $C_{62}H_{53}N_3O_8$ 967.3833, found 967.3808.

12,13-Dihydro-10-benzyloxy-13-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-5*H*-indolo-[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-methyl-5,7(6*H*)-dione (35): Palladium chloride (53 mg, 0.30 mmol) was added to a solution of **20** (50 mg, 0.052 mmol) in DMF (2.5 mL), followed by stirring at 100 °C for 16 h. After cooling, the reaction mixture was poured into aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane-ethyl acetate (4:1)) to yield **35** (39 mg, 0.040 mmol) as a yellow amorphous powder (78%). $[\alpha]^{20}_D$ +63.2° (c 1.00, $CHCl_3$); IR (KBr) ν_{max} 3343, 1749, 1697, 1456, 1375, 1124, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.76 (1H, s), 9.38 (1H, d, J = 8.2 Hz), 9.15 (1H, d, J = 9.6 Hz), 7.10-7.67 (25H, m), 6.98 (1H, t, J = 7.7 Hz), 6.86 (2H, t, J = 7.6 Hz), 6.07 (2H, d, J = 6.9 Hz), 5.99 (1H, d, J = 8.9 Hz), 5.18 (1H, d, J = 11.7 Hz), 5.08 (1H, d, J = 11.7 Hz), 4.97 (1H, d, J = 10.7 Hz), 4.80-4.92 (2H, m), 4.75 (1H, d, J = 13.3 Hz), 4.67 (1H, d, J = 10.7 Hz), 4.57 (1H, d, J = 13.3 Hz), 4.32 (1H, t, J = 9.1 Hz), 3.89-4.09 (4H, m), 3.83 (1H, d, J = 9.6 Hz), 3.80 (1H, d, J = 9.1 Hz), 3.34 (3H, s), 2.90 (1H, d, J = 9.6 Hz); HRMS (FAB) calcd for $C_{62}H_{53}N_3O_8$ 967.3833, found 967.3831.

12,13-Dihydro-3,10-dibenzyloxy-13-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-methyl-5,7(6*H*)-dione (36): Palladium chloride (42.5 mg, 0.24 mmol) was added to a solution of **21** (52 mg, 0.048 mmol) in DMF (2.0 mL), followed by stirring at 110 °C for 1 h. After cooling, the precipitate was filtered off and the filtrate was poured into 2 M HCl and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane-ethyl acetate (3:1)) to yield **36** (40 mg, 0.037 mmol) as a yellow powder (77%). $[\alpha]^{20}_D$ +65.2° (c 1.00, $CHCl_3$); IR (KBr) ν_{max} 3334, 1749, 1697, 1616, 1456, 1375, 1252, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.71 (1H, s), 9.14 (1H, d, J = 9.5 Hz), 9.08 (1H, d, J = 2.6 Hz), 6.80-7.65 (34H, m), 6.14 (2H, dd, J = 1.4, 6.9 Hz), 5.81 (1H, d, J = 8.8 Hz), 5.35 (2H, s), 5.17 (1H, d, J = 11.5 Hz), 5.07 (1H, d, J = 11.8 Hz), 4.96 (1H, d, J = 10.7 Hz), 4.85 (2H, d, J = 2.3 Hz), 4.74 (1H, d, J = 13.0 Hz), 4.66 (1H, d, J = 10.6 Hz), 4.56 (1H, d, J = 13.0 Hz), 4.31 (1H, t, J = 9.5 Hz), 3.75-4.05 (5H, m), 3.34 (3H, s); HRMS (FAB) calcd for $C_{69}H_{59}N_3O_9$ 1073.4251, found 1073.4279.

12,13-Dihydro-2,9-dibenzyloxy-13-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-methyl-5,7(6*H*)-dione (33): Cupric chloride (29 mg, 0.14 mmol) was added to a solution of **15** (100 mg, 0.093 mmol) in MEK (2 mL), followed by stirring at 60 °C for 1 h. The precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was purified by

chromatography on silica gel (toluene:ethyl acetate (50:1)) to yield **33** (79 mg, 0.074 mmol) as a yellow powder (80%). $[\alpha]^{20}_{D}$ +141.6° (c 1.00, $CHCl_3$); IR (KBr) ν_{max} 3336, 1749, 1697, 1456, 1203, 1079 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.50 (1H, s), 9.23 (1H, d, J = 8.7 Hz), 8.94 (1H, d, J = 1.8 Hz), 7.60 (2H, d, J = 7.8 Hz), 7.00-7.45 (28H, m), 6.87 (2H, t, J = 8.4 Hz), 6.19 (2H, d, J = 8.7 Hz), 5.84 (1H, d, J = 9.3 Hz), 5.31(2H, s), 5.18 (2H, d, J = 2.4 Hz), 5.00 (1H, d, J = 10.2 Hz), 4.86 (2H, s), 4.74 (1H, d, J = 10.2 Hz), 4.71 (1H, d, J = 12.0 Hz), 4.60 (1H, d, J = 12.0 Hz), 4.35 (1H, t, J = 9.6 Hz), 4.03 (2H, t, J = 9.0 Hz), 3.95 (1H, d, J = 9.6 Hz), 3.93 (1H, d, J = 9.3 Hz), 3.86 (2H, m), 3.34 (3H, s), 2.99 (1H, d, J = 9.3 Hz); HRMS (FAB) calcd for $C_{69}H_{59}N_3O_9$ 1073.4251, found 1073.4277.

12,13-Dihydro-2,10-dibenzyloxy-13-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-methyl-5,7(6*H*)-dione (34): Cupric chloride (29 mg, 0.14 mmol) was added to a solution of **16** (52 mg, 0.048 mmol) in the presence of molecular sieves 4A (50 mg) in MEK (1 mL), followed by stirring at 25 °C for 2 h. The precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel (dichloromethane) to yield **34** (42 mg, 0.024 mmol) as a yellow powder (84%). $[\alpha]^{20}_{D}$ +109.6° (c 1.00, $CHCl_3$); IR (KBr) ν_{max} 3332, 1749, 1621, 1496, 1284 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.06 (1H, s), 9.24 (1H, d, J = 9.5 Hz), 9.13 (1H, d, J = 9.5 Hz), 7.07-7.50 (29H, m), 6.98-7.03 (1H, m), 6.83-6.91 (2H, m), 6.18 (2H, m), 5.84 (1H, d, J = 8.9 Hz), 5.12-5.22 (2H, m), 5.18 (1H, d, J = 11.5 Hz), 5.08 (1H, d, J = 11.5 Hz), 4.97 (1H, d, J = 10.7 Hz), 4.89 (1H, d, J = 10.7 Hz), 4.84 (1H, d, J = 10.7 Hz), 4.74 (1H, d, J = 13.0 Hz), 4.67 (1H, d, J = 10.7 Hz), 4.56 (1H, d, J = 13.0 Hz), 4.32 (1H, t, J = 9.6 Hz), 3.98-4.07 (2H, m), 3.82-3.97 (3H, m), 3.79 (1H, dd, J = 2.7, 10.2 Hz), 3.33 (3H, s), 3.00 (1H, d, J = 9.7 Hz); HRMS (FAB) calcd for $C_{69}H_{59}N_3O_9$ 1073.4251, found 1073.4237.

12,13-Dihydro-10-benzyloxy-13-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-5*H*-indolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole-6-methyl-5,7(6*H*)-dione (37): Cupric chloride (47.4 mg, 0.35 mmol) was added to a solution of **25** (100 mg, 0.12 mmol) in the presence of calcium carbonate (400 mg) in MEK (20 mL), followed by stirring at 80 °C for 1 h. The reaction mixture was poured into 0.2 M HCl and extracted with ethyl acetate. The organic phase was successively washed with aqueous $NaHCO_3$, H_2O and saturated brine, dried over Na_2SO_4 and concentrated in vacuo to yield **37** (98 mg, 0.12 mmol) as a yellow amorphous powder (98%).

$[\alpha]^{20}_{D}$ +116.8° (c 1.00, $CHCl_3$); IR (KBr) ν_{max} 3358, 1749, 1697, 1578, 1456, 1377, 1329, 1190, 1120, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.06 (1H, s), 9.23 (1H, d, J = 7.8 Hz), 9.21 (1H, d, J = 9.0 Hz), 7.50 (1H, d, J = 6.9 Hz), 7.26-7.45 (20H, m), 7.14 (1H, dd, J = 1.8, 9.0 Hz), 6.96 (1H, t, J = 7.3 Hz), 6.85 (2H, t, J = 7.3 Hz), 6.57 (2H, d, J = 7.3 Hz), 6.30 (1H, d, J = 7.3 Hz), 5.19 (2H, s), 4.70-4.90 (3H, m), 4.56 (1H, t, J = 7.1 Hz), 4.46 (1H, d, J = 11.5 Hz), 4.22-4.30 (2H, m), 3.98-4.09 (3H, m), 3.80 (1H, dd, J = 2.0, 11.6 Hz), 3.35 (3H, s); HRMS (FAB) calcd for $C_{54}H_{45}N_3O_7$ 847.3258, found 847.3240.

12,13-Dihydro-2,10-dibenzyloxy-13-(2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-methyl-5,7(6*H*)-dione (37): Cupric chloride (82 mg, 0.30 mmol) was added to a solution of **29** (150 mg, 0.15 mmol) in the presence of molecular seives 4A (200 mg) in MEK (10 mL), followed by stirring at 60 °C for 0.5 h. The precipitate was filtered off and the filtrate was concentrated. The residue was dissolved in ethyl acetate and the organic mixture was successively washed with 1

M HCl, aqueous $NaHCO_3$, H_2O and saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (toluene-acetone (50:1)) to yield **37** (107 mg, 0.11 mmol) as a yellow amorphous powder (71%). $[\alpha]^{20}_D$ +97.4° (c 1.00, $CHCl_3$); IR (KBr) ν_{max} 3334, 1749, 1697, 1454, 1375, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.76 (1H, s), 9.22 (1H, d, J = 8.7 Hz), 9.10 (1H, d, J = 8.7 Hz), 7.02-7.53 (30H, m), 5.94 (1H, dd, J = 4.0, 9.8 Hz), 5.23 (2H, s), 5.13 (1H, d, J = 11.4 Hz), 5.03 (1H, d, J = 10.8 Hz), 5.02 (1H, d, J = 11.7 Hz), 4.78 (1H, d, J = 13.2 Hz), 4.67 (1H, d, J = 10.5 Hz), 4.60 (1H , d, J = 13.2 Hz), 4.53 (2H, q, J = 11.7 Hz), 4.23 (1H, t, J = 9.2 Hz), 4.03 (1H, d, J = 10.0 Hz), 3.91 (1H, ddd, J = 5.8, 9.2, 9.8 Hz), 3.85 (1H, d, J = 9.2 Hz), 3.78 (1H, dd, J = 2.5, 10.0 Hz), 3.31 (3H, s), 2.21 (1H, dd, J = 4.0, 9.8 Hz); HRMS (FAB) calcd for $C_{67}H_{53}N_3O_{10}$ 967.3833, found 967.3803.

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