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Abstract—The syntheses of rebeccamycin analogues possessing a 7-azaindole moiety instead of an indole unit, and with both indole and azaindole moieties linked to the carbohydrate are described. In these bridged aza compounds, the oxygen of the pyranose heterocycle is oriented towards either the indole, or the azaindole unit. In these series, compounds bearing a free imide nitrogen were synthesized by coupling the corresponding aglycones with a sugar pre-tosylated in 2-position via a Mitsunobu reaction. To obtain a precursor for bridged aza-rebeccamycin analogues substituted in 6-position on the sugar moiety, a 2,6-ditosylated sugar was used.

1. Introduction

Rebeccamycin, isolated from cultures of *Saccharothrix aerocolonigenes*, contains an indolocarbazole framework, an imide upper heterocycle and a sugar part linked to one of the indole nitrogens like other natural products such as some tjipanazoles E, F1 and F2 and AT2433-A1 and B1 but unlike staurosporine and UCN-01 in which the carbohydrate moiety is linked to both indole nitrogens (Fig. 1).[1–4] Rebeccamycin is a topoisomerase I inhibitor without inhibitory properties toward kinases such as CDK1/cyclinB, CDK5/p25 and PKC whereas staurosporine and UCN-01 are not topoisomerase I poisons but exhibit inhibitory properties against a variety of kinases.[5–7] In the course of structure–activity relationship studies on rebeccamycin analogues, we have synthesized 7-aza-rebeccamycin analogues in which one or both indole moieties have been replaced by a 7-azaindole unit.[8,9] When only one azaindole was introduced, the sugar part was linked either to the indole or to the azaindole (Fig. 2). Important differences in DNA binding properties and in topoisomerase I poisoning were observed between the two series. Compounds with the sugar moiety attached to the indole moiety exhibited strong DNA binding and topoisomerase I inhibitory properties whereas with compounds in which the sugar was attached to the azaindole, DNA binding and topoisomerase I poisoning were highly weakened or completely abolished. However, compounds in both series could exhibit strong in vitro cytotoxicities toward some tumor cell lines with IC_{50} values in the nanomolar range, suggesting other biological targets

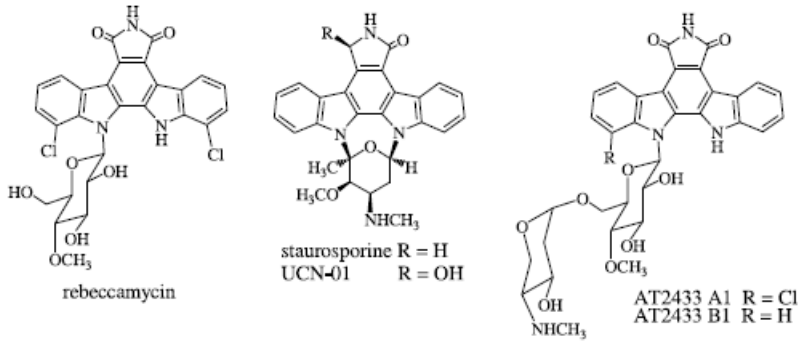

Figure 1. Chemical structures of the bacterial metabolites rebeccamycin, staurosporine, UCN-01, AT2433 A1 and B1.

Keywords: Staurosporine; Rebeccamycin; 7-Azaindole; Antitumor compounds; Enzyme inhibitors.
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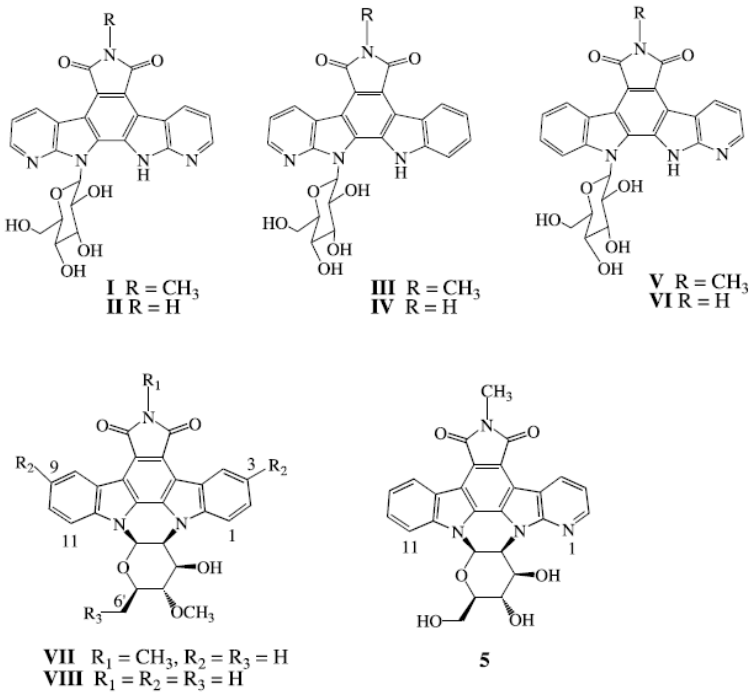
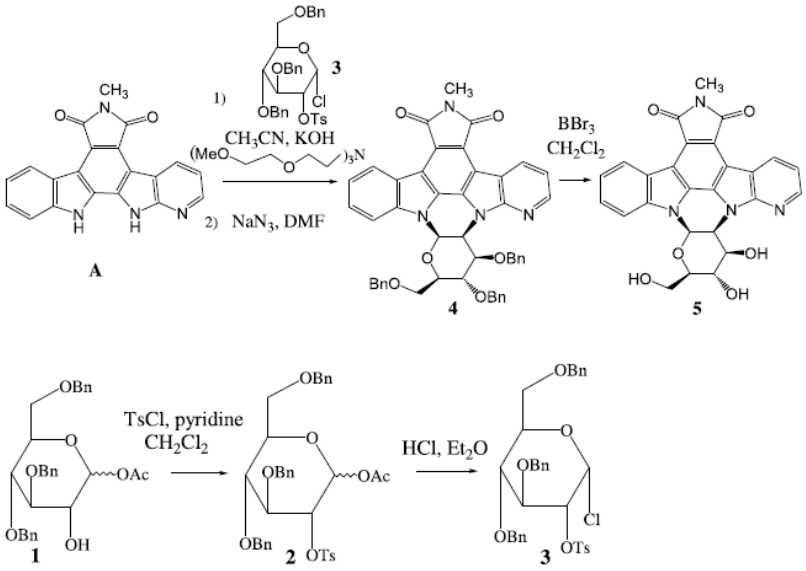


Figure 2. Aza-rebeccamycin analogues previously described.

than DNA and topoisomerase I for compounds in which the sugar is linked to the azaindole. To get an insight into the structural parameters inducing enzyme selectivity, we have synthesized staurosporine analogues from rebeccamycin by coupling the sugar moiety to the second indole nitrogen in non aza series at first and recently, one *N*-methylated compound has been prepared in 7-azaindole series.[10–12] In a previous brief communication, we described the synthesis of the 7-aza staurosporine analogue **5** with the sugar attached to both indole and azaindole nitrogens, with a methyl group on the imide nitrogen and with the oxygen heteroatom of the sugar ring oriented toward the indole unit (Fig. 2).[12] This compound was synthesized by coupling an α-1-chloro-glucose on the *N*-methylated indolocarbazole aglycone in the presence of a phase transfer catalyst. As deduced from the crystal structures of staurosporine in complex with various kinases, a free nitrogen in the upper heterocycle seems to be necessary to establish a hydrogen bond with the carbonyle of glutamate 81 in the ATP binding pocket of the kinases.[13,14] In this paper, the syntheses of new 7-aza bridged compounds, without the methyl group on the imide nitrogen and with the oxygen of the sugar ring oriented either toward the indole or toward the azaindole moiety, are reported. The replacement of an indole moiety



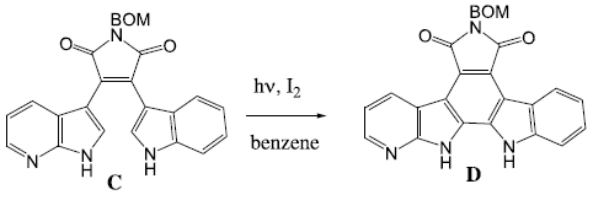
Scheme 1. Synthetic scheme for compound **5**.

by an azaindole in the bridged series could increase the affinity for the binding site of the target enzyme(s) and modify the electronic distribution on the aromatic framework and the lipophilicity. Because, it has been shown that substitutions in 6-position of the sugar unit can modify the biological target[15,16], we use a sugar unit ditosylated in 2- and 6-positions allowing access to bridged aza compounds substituted in 6-position of the sugar moiety with an azido group, a precursor for amino and amido substituents.

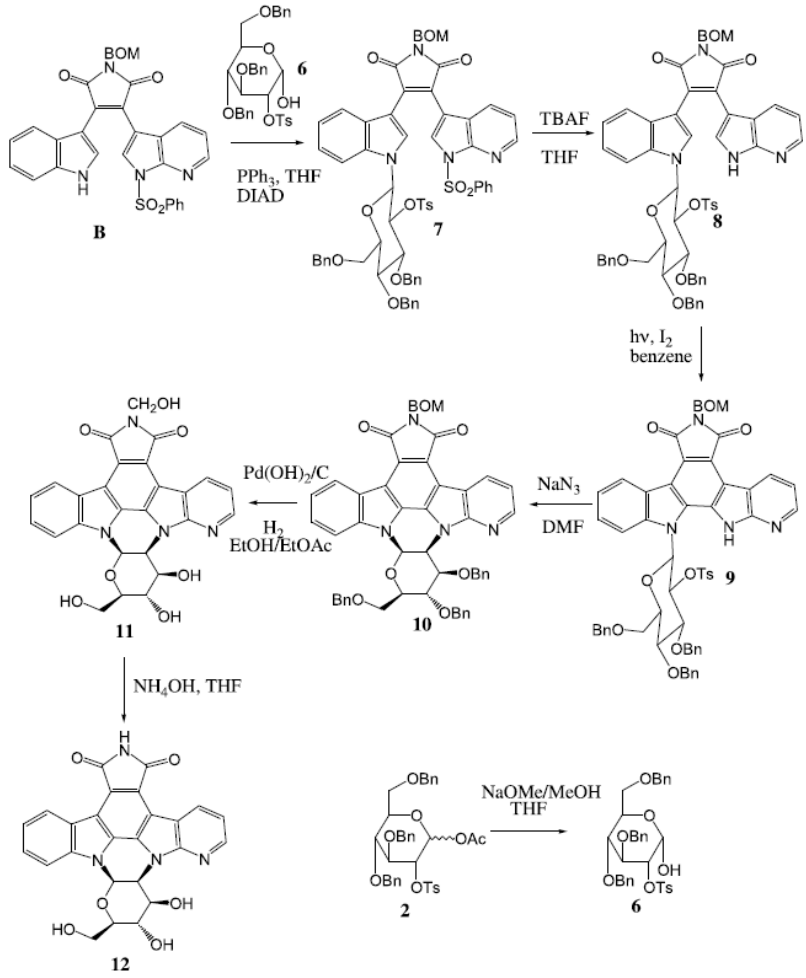
2. Results and discussion

2.1. Chemistry

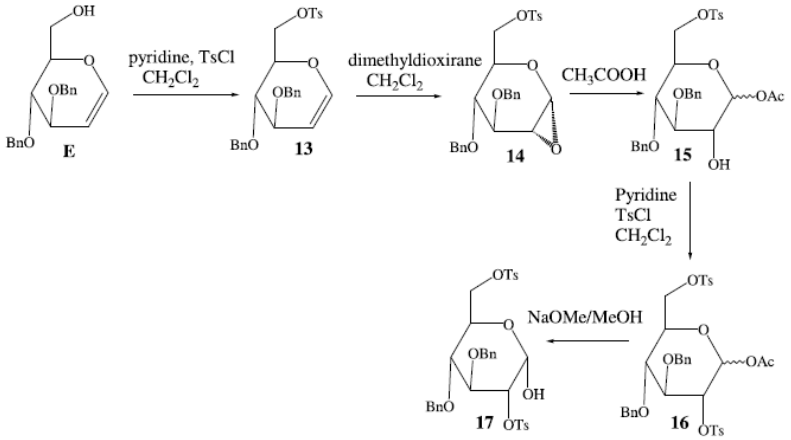
The synthesis of compound **5** is outlined in Scheme 1. The chloro sugar **3** was prepared from acetylated compound **1** which could be obtained from the commercial triacetylated glycal as described in literature.[17–19] Tosylation of **1** yielded tosylate **2** as a mixture of both α and β anomers, which was further treated with HCl gas to give the α-chloro anomer **3**.[12] This chloro sugar was coupled to the aglycone **A**[20] using potassium hydroxide and a phase transfer catalyst to yield the required coupling product, which was further treated with sodium azide to give the bridged compound **4** formed via a nucleophilic attack of the deprotonated azaindolic nitrogen on the carbon bearing the tosyl group. Elimination of the benzyl protecting groups of the sugar moiety was carried out using boron tribromide. For the synthesis of compound **12** (Scheme 3), the same procedure as described for the synthesis of **5** was tried from aglycone **D**, which was obtained from **C**[9] by oxidative photocyclization (Scheme 2). However, the coupling reaction with the chloro sugar **3** did not work. A Mitsunobu reaction was then performed from aglycone **B**[9] and sugar **6** prepared from **2** by reaction with MeONa/MeOH in THF (Scheme 3). Compound **7** was obtained in 88% yield. After deprotection of the azaindole nitrogen, oxidative photocyclization in the presence of iodine gave **9** in 62% yield. Reaction of **9** with sodium azide led to the bridged compound **10** in 72% yield. Unlike for compound **4**, debenzylation of **10** using boron



Scheme 2. Photocyclization of aglycone **C**.



Scheme 3. Synthesis of compound **12**.

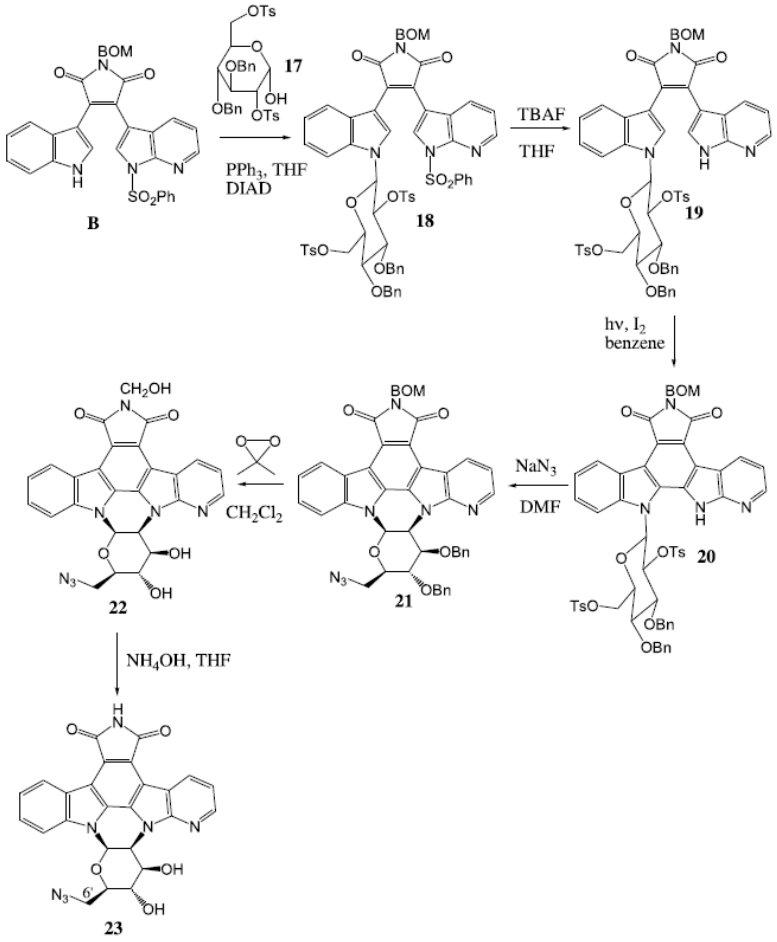


Scheme 4. Synthesis of di-tosylated sugar **17**.

tribromide gave an inexploitable mixture. Removal of the protective groups was achieved in two steps: hydrogenolysis with $Pd(OH)_2/C$ as the catalyst leading to **11** in 52% yield, followed by aminolysis giving the required compound **12** in 71% yield.

To introduce substituents selectively in 6′ position on the sugar moiety of **12**, the Mitsunobu reaction was carried out using 2,6-ditosyl-sugar **17**, which was prepared from glycal **E** as shown in Scheme 4.

Glycal **E** was prepared according to known procedures.[21] Tosylation of **E** at 6-position led to compound **13**. Epoxidation performed using dimethyldioxirane provided



Scheme 5. Synthesis of 6′-azido compound **23**.

the anhydro sugar **14** as the major isomer. Reaction of **14** with glacial acetic acid gave compound **15** in 77% yield as a mixture of both α and β anomers in 0.3:2 ratio, respectively. Tosylation of **15** led to a mixture of both α and β anomers in 1:3.9 ratio, respectively, in only 24% yield. 31% of the unreacted β anomer was recovered. The final step was deacetylation with sodium methoxide/methanol affording **17** in 66% yield. The Mitsunobu reaction between **17** and aglycone **B** led to compound **18** in 52% yield. Deprotection of the azaindole nitrogen using tetrabutylammonium fluoride gave **19** in 83% yield. Compound **19** was further photocyclized to give **20**. Reaction of **20** with sodium azide in DMF induced the coupling of the sugar part with the azaindole nitrogen and concomitant substitution at 6′-position to give **21** (Scheme 5). Contrary to compound **10**, debenzylation by hydrogenolysis could not be achieved with compound **21**. A mixture of compounds reduced on the aromatic rings was obtained. Debenzylation carried out using dimethyldioxirane[22,23] afforded the required compound **22** in 45% yield. Removal of the hydroxymethyl substituent by aminolysis gave **23** in 77% yield.

Because in non-bridged aza rebeccamycins, important differences in the biological activities were observed between compounds in which the carbohydrate was linked either to the indole nitrogen or to the azaindole unit, bridged compounds with a nitrogen atom in 11-position instead of 1-position in the azaindolocarbazole were also synthesized (Scheme 6). A similar sequence of reactions as for the synthesis of **12** was performed from aglycone **F**[9] until elimination of the benzenesulfonyl protective group leading to **25**. Photocyclization of **25** in the presence of iodine did not afford the required compound **26**, only degradation was observed. Cyclization was successfully achieved in 56% yield using palladium triflate in DMF at 90 °C according to a method described by Faul et al.[24] for the synthesis of rebeccamycin. Reaction of **26** with sodium azide led to **27** in 93% yield. Debenzylation carried out using trifluoroacetic acid or dimethyldioxirane or by hydrogenolysis proved to be unsuccessful. The required compound **28** was finally obtained in 27% yield by debenzylation with boron tribromide followed by aminolysis.

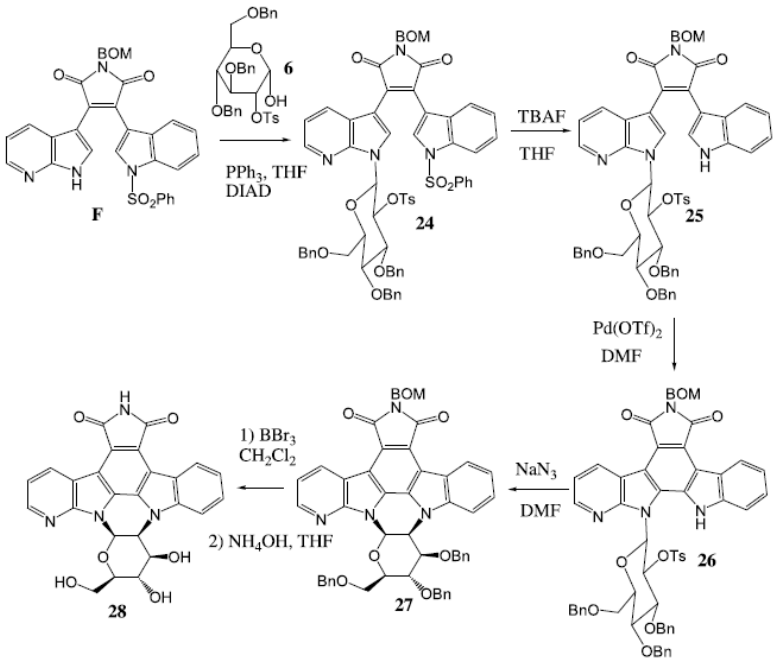
3. Conclusion

In conclusion, we have developed methods to synthesize bridged aza-rebeccamycin analogues from 2-*O*-tosyl-glucopyranose. Both analogues in which the anomeric carbon of the sugar part is linked to either the azaindole or the indole moiety have been synthesized. The use of 2,6-*O*-ditosyl-glucopyranose, in the Mitsunobu reaction, allowed the introduction of an azido group in 6′-position. This method can also be applied for introducing a wide range of substituents in 6-position of the sugar moiety. The cytotoxicities and the inhibitory activities of these new compounds toward various kinases are now under investigation.

4. Experimental

4.1. Chemistry

IR spectra were recorded on a Perkin Elmer 881 spectrometer. NMR spectra were performed on a Bruker AVANCE 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) (chemical shifts δ in ppm, the following abbreviations are used: singlet (s), doublet (d), triplet (t), pseudo-triplet (pt), doubled triplet (dt), multiplet (m), br s (broad signal), tertiary carbons (C tert), quaternary carbons (C quat). The signals were assigned from ^{1}H–^{1}H COSY and ^{13}C–^{1}H correlations.



Scheme 6. Synthesis of the bridged compound **28**.

Low-resolution mass spectra (ESI+ and APCI+) were determined on a MS Hewlett Packard engine. HRMS spectra (FAB+) were determined on a high resolution Fisons Autospec-Q spectrometer at CESAMO (Talence, France). Chromatographic purifications were performed by flash silicagel Geduran SI 60 (Merck) 0.040–0.063 mm or Kieselgel 60 (Merck) 0.063–0.200 mm column chromatography. For purity tests, TLC were performed on fluorescent silica gel plates (60 F_{254} from Merck).

4.1.1. 1-*O*-Acetyl-2-*O*-tosyl-3,4,6-tri-*O*-benzyl-α and β-D-glucopyranose 2. To a solution of **1** (548 mg, 1.11 mmol, α/β ratio 3:10) in pyridine (6 mL) and CH_2Cl_2 (15 mL) was added tosyl chloride (766 mg, 5.55 mmol). After refluxing for 72 h, 2 N HCl (15 mL) was added. After extraction with EtOAc, the organic phase was washed with saturated aqueous $NaHCO_3$ and then with brine. The organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 9:1 to 7:3) to give **2** as a colorless oil (603 mg, 0.93 mmol, 84% yield) as a mixture of β and α anomers in 8:5 ratio, respectively. Unreacted **1** (β anomer, 150 mg) was recovered.

Compound **2**. IR (NaCl film), $\nu_{C=O}$ 1739, 1760 cm^{-1}. HRMS (FAB+) $[M+Na]^+$, calcd for $C_{36}H_{38}NaO_9S_1$ 669.2134, found 669.2147. ^1H NMR (400 MHz, $CDCl_3$): $^{\beta}$ major anomer, $^{\alpha}$ minor anomer 1.92 ($3H^{\beta}$, s, CH_3), 2.11 ($3H^{\alpha}$, s, CH_3), 2.35 ($3H^{\beta}$, s, CH_3), 2.39 ($3H^{\alpha}$, s, CH_3), 3.54–3.86 ($5H^{\beta}+5H^{\alpha}$, m), 4.43–4.82 ($7H^{\beta}+7H^{\alpha}$, m), 5.65 ($1H^{\beta}$, d, $J=8.0$ Hz, H_1), 6.18 ($1H^{\alpha}$, d, $J=3.5$ Hz, H_1), 7.04–7.10 ($2H^{\beta}+2H^{\alpha}$, m), 7.14–7.36 ($15H^{\beta}_{arom}+15H^{\alpha}_{arom}$), 7.73–7.79 ($2H^{\beta}+2H^{\alpha}$, m). ^{13}C NMR (100 MHz, $CDCl_3$): 20.7, 20.9, 21.6, 21.8 (CH_3), 67.7, 67.8 (C_6), 73.6, 73.7, 75.2, 75.4, 75.5, 75.7 (CH_2), 72.6, 75.8, 77.0, 77.4, 78.1, 79.5, 79.7, 82.4, 89.6, 91.5 (C_1, C_2, C_3, C_4, C_5), 127.6–128.6, 129.7, 130.0 (C tert arom), 133.2, 134.7, 137.6, 137.7, 137.8, 137.9, 144.7, 145.3 (C quat arom), 168.6, 169.3 (C=O).

4.1.2. 1-Chloro-1-deoxy-2-*O*-tosyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranose 3. HCl gas was bubbled for 20 min in a solution of **2** (444 mg, 0.69 mmol) in diethylether. After stirring for 48 h at room temperature, the solvent was removed, the residue was dissolved in CH_2Cl_2 then the solvent was removed. The residue was purified by flash chromatography (eluent cyclohexane/EtOAc 7:3) to give **3** (α anomer) as a colorless oil (272 mg, 0.438 mmol, 66% yield). Unreacted α anomer **2** (56 mg) was recovered. The reaction performed with pure β anomer **2** afforded **3** in 86% yield.

Compound **3**. IR (NaCl film) $\nu_{S=O}$ 1739 cm^{-1}. HRMS (FAB+) $[M+Na]^+$, calcd for $C_{34}H_{35}ClNaO_7S$ 645.1690, found 645.1699. ^1H NMR (400 MHz, $CDCl_3$): 2.39 (3H, s, CH_3), 3.66 (1H, dd, $J_1=11.0$ Hz, $J_2=2.0$ Hz), 3.76–3.83 (2H, m), 4.05 (1H, t, $J=9.5$ Hz), 4.10 (1H, m), 4.48 (1H, d, $J=10.5$ Hz), 4.49 (1H, d, $J=12.0$ Hz), 4.60 (1H, d, $J=12.0$ Hz), 4.61 (1H, dd, $J_1=9.5$ Hz, $J_2=4.0$ Hz), 4.69 (1H, d, $J=11.0$ Hz), 4.74 (1H, d, $J=11.0$ Hz), 4.75 (1H, d, $J=10.5$ Hz), 6.21 (1H, d, $J=4.0$ Hz, H_1), 7.08–7.11 (2H, m), 7.16–7.23 (4H, m), 7.25–7.37 ($11H_{arom}$), 7.80 (2H, d, $J=8.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 21.7 (CH_3), 67.4 (C_6), 73.6, 75.4, 75.6 (CH_2), 73.4, 76.6, 78.6, 79.1, 91.8 (C_1, C_2, C_3, C_4, C_5), 127.7, 127.8–128.1, 128.3, 128.4, 128.5 (C tert arom), 133.0, 137.5, 137.6, 137.7, 145.3 (C quat arom).

4.1.3. 6-Methyl-5,7-dihydro-12,13-(3,4,6-tri-*O*-benzyl-β-D-mannopyranose-1,2-diyl)-pyrrolo[3,4-*c*]pyrido[2′,3′:4,5] pyrrolo[2,3-*a*]carbazole-5,7-dione 4. To a solution of aglycone **A** (73 mg, 0.214 mmol) in acetonitrile (8.5 mL) were added powdered KOH (92 mg) and tris[2-(2-methoxyethoxy) ethyl]amine (34 μL). After stirring at room temperature for 15 min, a solution of **3** (290 mg, 0.466 mmol) in acetonitrile (4.5 mL) was added dropwise. The mixture was stirred at room temperature for 48 h. After acidification with 1 N HCl (10 mL), the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent was removed. The residue was partly purified by flash chromatography (eluent cyclohexane/EtOAc from 9:1 to 5:5 then EtOAc 100%) to give a mixture of glycosylated compounds (24 mg). To the mixture of the glycosylated compounds in DMF (1 mL) was added NaN_3 (32 mg, 0.50 mmol). After stirring at 70 °C for 48 h, water was added and the mixture was extracted with EtOAc. The organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 9:1 to 5:5 then EtOAc 100%) affording **4** (20 mg, 0.026 mmol, 12% yield from **A**) as a yellow solid.

Compound **4**. Mp 67–69 °C. IR (KBr) $\nu_{C=O}$ 1700 cm^{-1}. HRMS (FAB+) $[M+H]^+$, calcd for $C_{47}H_{39}N_4O_6$ 755.2870, found 755.2871. The ^1H NMR signals were assigned from ^1H–^1H COSY correlations. ^1H NMR (400 MHz, $CDCl_3$): 3.30 (3H, s, CH_3), 3.79 (1H, d, $J=11.0$ Hz), 3.91 (1H, dd, $J_1=10.5$ Hz, $J_2=5.5$ Hz, $H_{6'}$), 3.96–4.03 (2H, m, $H_{3'}$, $H_{6'}$), 4.09 (1H, t, $J=9.5$ Hz, $H_{4'}$), 4.42 (1H, m, $H_{5'}$), 4.43 (1H, d, $J=11.0$ Hz), 4.64 (1H, d, $J=11.0$ Hz), 4.66 (1H, d, $J=12.0$ Hz), 4.75 (1H, d, $J=11.5$ Hz), 4.91 (1H, d, $J=11.0$ Hz), 5.52 (1H, m, $H_{2'}$), 6.15 (1H, d, $J=3.5$ Hz, $H_{1'}$), 6.45 (2H, d, $J=7.0$ Hz), 6.89 (2H, t, $J=7.5$ Hz), 7.03 (1H, t, $J=7.5$ Hz), 7.14–7.18 (2H, m), 7.24–7.30 (3H, m), 7.32–7.39 (2H, m), 7.40–7.47 (6H, m), 7.99 (1H, m), 8.52 (1H, dd, $J_1=4.0$ Hz, $J_2=1.0$ Hz), 8.82 (1H, m), 8.95 (1H, dd, $J_1=8.0$ Hz, $J_2=1.0$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 23.9 (NCH_3), 58.3, 74.5, 78.3, 80.4, 85.0 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 68.9 ($C_{6'}$), 73.8, 75.1, 75.9 (CH_2), 110.4, 113.3, 116.5, 117.7, 121.9, 125.3, 127.4, 130.2, 136.1, 137.6, 137.9, 143.3, 152.3 (C quat arom), 113.6, 117.3, 122.9, 125.6, 127.7–128.7, 134.1, 146.5 (C tert arom), 170.0, 170.1 (C=O).

4.1.4. 6-Methyl-5,7-dihydro-12,13-(β-D-mannopyranose-1,2-diyl)-pyrrolo[3,4-*c*]pyrido[2′,3′:4,5]pyrrolo[2,3-*a*]-carbazole-5,7-dione 5. To a solution of **4** (10 mg, 0.013 mmol) in CH_2Cl_2 (5 mL) cooled to −78 °C was added 1 M BBr_3 in CH_2Cl_2 (87 μL, 0.08 mmol). After stirring for 10 min at −78 °C, water was added, the mixture was allowed to reach room temperature then it was extracted with EtOAc. The organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent from EtOAc 100% to EtOAc/MeOH 9:1) to give **5** (5.6 mg, 0.012 mmol, 90% yield) as a yellow solid.

Compound **5**. Mp 245–250 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1700 cm^{-1}, ν_{OH} 3040–3680 cm^{-1}. HRMS (FAB+) $[M+H]^+$, calcd for $C_{26}H_{21}N_4O_6$ 485.1461, found 485.1465. ^1H NMR (400 MHz, DMSO-d_6): 3.19 (3H, s, NCH_3), 3.59–3.66 (2H, m), 3.79 (1H, m), 3.97 (1H, m), 4.06 (1H, m), 5.18–5.28 (3H, m, 2OH, $H_{2'}$), 5.40 (1H, d, J= 5.5 Hz, OH), 6.42 (1H, d, J=4.0 Hz, $H_{1'}$), 7.49 (1H, dd, J_1=8.0 Hz, J_2=5.0 Hz), 7.51 (1H, t, J=7.5 Hz), 7.64 (1H, dt, J_1=7.5 Hz, J_2=1.0 Hz), 8.24 (1H, d, J=8.0 Hz), 8.63 (1H, dd, J_1=5.0 Hz, J_2=1.5 Hz), 8.72 (1H, d, J=7.5 Hz), 8.89 (1H, dd, J_1=8.0 Hz, J_2=1.5 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 23.6 (CH_3), 61.1 ($C_{6'}$), 59.2 ($C_{2'}$), 70.1, 73.6, 76.8 ($C_{3'}$, $C_{4'}$, $C_{5'}$), 84.6 ($C_{1'}$), 109.2, 114.6, 116.1, 120.1, 120.9, 124.4, 127.6, 130.2, 143.0, 152.8 (C quat arom), 114.1, 116.9, 122.1, 124.2, 127.7, 132.1, 146.9 (C tert arom), 169.5, 169.6 (C=O).

4.1.5. 2-Benzyloxymethyl-5,7-dihydro-12*H*,13*H*-pyrrolo[3,4-*c*]pyrido[2′,3′:4,5]pyrrolo[2,3-*a*]carbazole-5,7-dione D. To a solution of aglycone **C** (218 mg, 0.486 mmol) in benzene (300 mL) was added iodine (1.32 g, 5.32 mmol). The mixture was irradiated for 7 h with a medium pressure mercury lamp (400 W). The solvent was removed, and the residue dissolved in EtOAc (250 mL) and washed with saturated aqueous sodium thiosulfate (100 mL) and then with brine. The organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent EtOAc/cyclohexane 5:5) to give **D** (120 mg, 0.267 mmol, 55% yield) as a yellow solid.

Compound **D**. Mp >290 °C (degradation). IR (KBr) $\nu_{C=O}$ 1700, 1750 cm^{-1}, ν_{NH} 3000–3600 cm^{-1}. Mass (ESI+) $[M+H]^+$ 447. ^1H NMR (400 MHz, DMSO-d_6): 4.67 (2H, s, CH_2), 5.08 (2H, s, CH_2), 7.24–7.43 (7H, m), 7.57 (1H, t, J=7.5 Hz), 7.78 (1H, d, J=8.0 Hz), 8.55 (1H, d, J= 3.5 Hz), 8.90 (1H, d, J=8.0 Hz), 9.05 (1H, d, J=7.5 Hz), 11.45 (1H, s, NH), 12.08 (1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 66.4, 70.3 (CH_2), 112.1, 116.6, 120.4, 124.1, 127.1, 127.4, 127.5 (2C), 128.2 (2C), 132.1, 147.3 (C tert arom), 113.0, 114.1, 116.1, 118.5, 118.8, 121.1, 127.8, 128.8, 137.8, 140.2, 151.8 (C quat arom), 168.9, 169.0 (C=O).

4.1.6. 2-*O*-Tosyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranose 6. To a solution of **2** (300 mg, 0.462 mmol, anomeric ratio α/β 5:8) in THF/MeOH (5 mL, 1:1 v/v) at 0 °C was added dropwise 1 M NaOMe/MeOH (60 µL). The mixture was stirred at 0 °C for 1 h, the solvent was removed and the residue purified by flash chromatography (eluent cyclohexane/EtOAc 7:3) affording **6** (204 mg, 0.038 mmol, 73% yield) as a white solid.

Compound **6**. Mp 118–120 °C. IR (KBr) ν_{OH} 3240–3600 cm^{-1}. Mass (ESI+) $[M+H]^+$ 604, $[M+Na]^+$ 627. ^1H NMR (400 MHz, $CDCl_3$): 2.17 (3H, s, CH_3), 3.35–3.50 (4H, m), 3.80–3.90 (2H, m), 4.23 (1H, d, J=10.0 Hz), 4.24 (1H, d, J=11.5 Hz), 4.30 (1H, d, J=12.0 Hz), 4.39 (1H, d, J=11.5 Hz), 4.48 (2H, s), 4.53 (1H, d, J=11.0 Hz), 5.24 (1H, br s, H_1), 6.85–6.89 (2H, m), 6.94–6.98 (4H, m), 7.04–7.16 ($11H_{arom}$), 7.58 (2H, d, J=8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 21.7 (CH_3), 68.3 (C_6), 73.5, 75.1, 75.2 (CH_2), 70.0, 77.9, 79.0, 80.0, 90.9 (C_1, C_2, C_3, C_4, C_5), 127.5–128.5, 129.6, 129.8 (C tert arom), 133.3, 137.6, 137.8, 138.0, 144.9 (C quat arom).

4.1.7. 1-Benzyloxymethyl-2,5-dihydro-3-[1-(2-*O*-tosyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranos-1-yl)-indol-3-yl]-4-[1-phenylsulfonyl-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione 7. To a solution of **B** (89 mg, 0.152 mmol) in THF (8 mL) were added **6** (205 mg, 0.338 mmol) and triphenylphosphine (89 mg, 0.338 mmol). The mixture was cooled to −78 °C then diisopropyl azodicarboxylate (DIAD) (65.5 µM, 0.338 mmol) was added dropwise. The mixture was allowed to reach room temperature then was stirred for 18 h. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 8:2) to give **7** (156 mg, 0.133 mmol, 88% yield) as a red solid.

Compound **7**. Mp 47–50 °C. IR (KBr) $\nu_{C=O}$ 1710, 1770 cm^{-1}. Mass (ESI+) $[M+H]^+$ 1175. ^1H NMR (400 MHz, $CDCl_3$): 1.93 (3H, s, CH_3), 3.53–3.59 (2H, m), 3.63 (1H, dd, J_1=9.0 Hz, J_2=3.5 Hz), 3.70 (1H, t, J= 9.0 Hz), 3.84 (1H, t, J=9.5 Hz), 4.34 (1H, d, J=12.0 Hz), 4.42 (1H, d, J=12.0 Hz), 4.43–4.47 (2H, m), 4.57 (2H, s), 4.58 (1H, d, J=8.5 Hz), 4.62 (1H, d, J=10.5 Hz), 5.03 (1H, d, J=9.0 Hz), 5.07 (2H, s), 5.34 (1H, d, J=9.0 Hz, $H_{1'}$), 6.19–6.28 (2H, m), 6.56 (2H, d, J=8.0 Hz), 6.62 (1H, dd, J_1=8.0 Hz, J_2=3.5 Hz), 6.82 (1H, t, J=8.0 Hz), 6.91–6.97 (2H, m), 7.02–7.19 ($20H_{arom}$), 7.23 (2H, d, J=8.0 Hz), 7.31 (2H, t, J=7.5 Hz), 7.43 (1H, dt, J_1=8.0 Hz, J_2=1.0 Hz), 7.90 (1H, s), 7.96 (2H, d, J=8.0 Hz), 7.98 (1H, s), 8.07 (1H, d, J=5.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 22.0 (CH_3), 67.4, 68.0 (CH_2), 71.8, 73.5, 75.2, 75.4 ($C_{6'}$+CH_2), 70.1, 77.5, 78.2, 79.9, 83.0 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 119.3, 121.4, 121.5, 123.0, 127.2, 127.5–128.5, 129.1, 129.3, 131.4, 134.1, 145.4 (C tert arom), 106.5, 109.5, 123.6, 126.0, 131.1, 133.3, 135.6, 137.5, 137.6, 137.7, 137.8, 138.0, 144.3, 146.6 (C quat arom), 170.7 (2 C=O).

4.1.8. 1-Benzyloxymethyl-2,5-dihydro-3-[1-(2-*O*-tosyl-3,4,6-*O*-benzyl-β-D-glucopyranos-1-yl)-indol-3-yl]-4-[1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione 8. To a solution of **7** (160 mg, 0.136 mmol) in THF (5 mL) was added a 1.1 M solution of tetrabutylammonium fluoride in THF (409 µL, 0.448 mmol). The mixture was stirred for 2.5 h at room temperature. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 3:2) to give **8** (114 mg, 0.110 mmol, 81% yield) as a red solid.

Compound **8**. Mp 75–80 °C. IR (KBr) $\nu_{C=O}$ 1765, 1710 cm^{-1}, ν_{NH} 3240–3600 cm^{-1}. Mass (ESI+) $[M+H]^+$ 1035. ^1H NMR (400 MHz, $CDCl_3$): 2.12 (3H, s, CH_3), 3.72–3.86 (3H, m), 3.94 (1H, t, J=9.0 Hz), 4.04 (1H, t, J= 9.0 Hz), 4.53 (1H, d, J=12.0 Hz), 4.60 (1H, d, J=12.0 Hz), 4.67 (1H, d, J=11.0 Hz), 4.80 (4H, s+m), 4.85 (1H, d, J= 10.5 Hz), 5.30 (3H, s+m), 5.56 (1H, d, J=9.0 Hz, $H_{1'}$), 6.69–6.78 (5H, m), 7.02 (1H, m), 7.15–7.21 (2H, m), 7.26–7.40 (19H), 7.47 (2H, d, J=7.5 Hz), 7.55 (1H, t, J= 8.0 Hz), 8.00 (2H, d, J=9.5 Hz), 8.14 (1H, d, J=4.5 Hz), 12.4 (1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 21.5 (CH_3), 67.2, 68.2 (CH_2), 71.7, 73.5, 75.3, 75.4 ($C_{6'}$ +CH_2), 77.6, 78.2, 80.1, 83.1 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 116.7, 120.9, 122.1, 122.8, 127.0, 127.5–128.5, 129.1, 129.8, 131.4, 142.8 (C tert

arom), 105.3, 107.4, 119.0, 126.4, 126.9, 133.2, 135.6, 137.5–137.9, 144.2, 148.6 (C quat arom), 171.3, 171.7 (C=O).

4.1.9. 6-Benzyloxymethyl-12-(3,4,6-tri-*O*-benzyl-2-*O*-tosyl-β-D-glucopyranos-1-yl)-5,7-dihydro-13*H*-pyrido-[3′,2′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione 9. To a solution of **8** (50 mg, 0.048 mmol) in benzene (150 mL) was added iodine (18 mg, 0.071 mmol). The mixture was irradiated for 1.5 h with a medium pressure mercury lamp (400 W). The solvent was removed, and the residue was dissolved in EtOAc (250 mL) and washed with saturated aqueous sodium thiosulfate (50 mL) and then with brine. The organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent EtOAc/cyclohexane 3:7) to give **9** (31 mg, 0.030 mmol, 62% yield) as a yellow solid.

Compound **9**. Mp 37–40 °C. IR (KBr) $\nu_{C=O}$ 1710, 1755 cm^{-1}, ν_{NH} 3200–3600 cm^{-1}. Mass (ESI+) $[M+H]^+$ 1033. ^1H NMR (400 MHz, $CDCl_3$): 2.10 (3H, s, CH_3), 3.65 (1H, dd, $J_1=10.0$ Hz, $J_2=2.5$ Hz), 3.81 (1H, d, $J=10.0$ Hz), 3.93 (1H, d, $J=10.0$ Hz), 3.99 (1H, t, $J=9.0$ Hz), 4.17 (1H, d, $J=10.5$ Hz), 4.44 (1H, d, $J=10.0$ Hz), 4.47 (1H, d, $J=9.0$ Hz), 4.70 (1H, d, $J=10.5$ Hz), 4.74 (2H, s), 4.76 (1H, d, $J=11.5$ Hz), 5.00 (1H, d, $J=10.5$ Hz), 5.03 (1H, d, $J=13.5$ Hz), 5.15 (1H, t, $J=9.0$ Hz), 5.30 (2H, s), 5.99 (1H, d, $J=9.0$ Hz, $H_{1'}$), 6.37 (2H, d, $J=8.0$ Hz), 6.46 (2H, d, $J=8.0$ Hz), 6.74 (2H, d, $J=7.5$ Hz), 6.76–6.83 (2H, m), 6.90 (1H, m), 6.95–7.00 (3H, m), 7.10–7.45 (14H), 7.50 (2H, dd, $J_1=7.5$ Hz, $J_2=0.5$ Hz), 8.56 (1H, dd, $J_1=5.0$ Hz, $J_2=1.5$ Hz), 9.02 (1H, d, $J=8.0$ Hz), 9.43 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 11.10 (1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 21.5 (CH_3), 65.2, 66.9 (CH_2), 71.6, 73.2, 75.3, 76.2 ($C_{6'}$ + CH_2), 76.3, 78.4, 79.7, 82.3, 83.4 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 109.4, 115.3, 115.7, 115.8, 117.5, 120.5, 120.8, 121.5, 125.9, 126.0, 126.6, 126.7, 127.2, 127.3, 127.6, 127.8–129.3, 129.7, 130.3, 133.8, 148.3 (C tert arom), 119.3, 120.5, 120.8, 121.9, 132.2, 137.2, 137.3, 137.6 (2C), 140.7, 144.3, 153.5 (C quat arom), 169.4 (2C, C=O).

4.1.10. 6-Benzyloxymethyl-5,7-dihydro-12,13-(3,4,6-tri-*O*-benzyl-β-D-mannopyranose-1,2-diyl)-pyrrolo[3,4-*c*]-pyrido[2′,3′:4,5]pyrrolo[2,3-*a*]carbazole-5,7-dione 10. To a solution of **9** (60 mg, 0.06 mmol) in DMF (2 mL) was added NaN_3 (37 mg, 0.60 mmol). The mixture was stirred for 48 h at 70 °C, then water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 4:1) to give **10** (37 mg, 0.043 mmol, 72% yield) as a yellow solid.

Compound **10**. Mp 38–40 °C. IR (KBr) $\nu_{C=O}$ 1700, 1750 cm^{-1}. Mass (ESI+) $[M+H]^+$ 861. ^1H NMR (400 MHz, $CDCl_3$): 3.60 (1H, dd, $J_1=10.0$ Hz, $J_2=4.5$ Hz), 3.63 (1H, d, $J=11.5$ Hz), 3.70 (1H, d, $J=12.0$ Hz), 3.71 (1H, m), 3.76 (1H, m), 4.23 (1H, d, $J=12.0$ Hz), 4.31 (1H, d, $J=11.5$ Hz), 4.32 (1H, m), 4.49 (1H, d, $J=12.0$ Hz), 4.57 (1H, m), 4.58 (1H, d, $J=12.0$ Hz), 4.68 (2H, s), 5.16 (2H, AB system, $J=11.0$ Hz, $\Delta\nu=13.0$ Hz), 5.56 (1H, dd, $J_1=5.5$ Hz, $J_2=3.5$ Hz, $H_{2'}$), 6.18 (2H, t, $J=8.0$ Hz), 6.20 (1H, d, $J=6.0$ Hz, $H_{1'}$), 6.71 (2H, t, $J=7.5$ Hz), 6.86 (1H, t, $J=7.5$ Hz), 7.10–7.38 (17H, m), 7.42 (1H, dt, $J_1=7.5$ Hz, $J_2=1.0$ Hz), 7.85 (1H, d, $J=8.0$ Hz), 8.36 (1H, dd, $J_1=5.0$ Hz, $J_2=1.5$ Hz), 8.71 (1H, d, $J=7.5$ Hz), 8.84 (1H, dd, $J_1=7.5$ Hz, $J_2=1.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 52.6, 72.8, 72.9, 75.4, 80.7 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 66.7 ($C_{6'}$), 70.2, 71.5, 71.8, 72.3, 73.2 (CH_2), 109.3, 114.2, 117.5, 120.2, 120.4, 124.6, 128.8, 129.0, 136.1, 137.4, 137.8, 138.0, 142.5, 151.7 (C quat arom), 113.4, 117.3, 122.3, 125.3, 127.4, 127.6–128.7, 133.4, 146.6 (C tert arom), 169.6 (2 C=O).

4.1.11. 6-Hydroxymethyl-5,7-dihydro-12,13-(β-D-mannopyranose-1,2-diyl)-pyrrolo[3,4-*c*]pyrido[2′,3′:4,5]-pyrrolo[2,3-*a*]carbazole-5,7-dione 11. To a suspension of **10** (50 mg, 0.058 mmol) in EtOH/EtOAc (5 mL, 4:1 v/v) was added $Pd(OH)_2$/C (20%) (50 mg). The mixture was hydrogenated under pressure (40 psi) at room temperature for 3 days. After filtration over Celite, the filtrate was evaporated. The residue was purified by flash chromatography (eluent CH_2Cl_2/MeOH 95:5) to give **11** (15 mg, 0.030 mmol, 52% yield) as a yellow solid. 16 mg of a mixture of partially debenzylated compounds could be recovered and recycled.

Compound **11**. Mp >200 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1700, 1750 $cm^{-1;}$ ν_{OH} 3100–3600 cm^{-1}. HRMS (FAB+) $[M+H]^+$, calcd for $C_{26}H_{20}N_4O_7$ 501.1410, found 501.1416. ^1H NMR (400 MHz, DMSO-d_6): 3.33 (1H, m, $H_{6'}$), 3.47–3.61 (2H, m, $H_{4'}+H_{6'}$), 3.70 (1H, m, $H_{5'}$), 4.30 (1H, m, $H_{3'}$), 4.35 (1H, t, $J=5.5$ Hz, $OH_{6'}$), 5.10 (2H, d, $J=6.5$ Hz, CH_2OH), 5.35 (1H, d, $J=2.5$ Hz, $H_{2'}$), 5.48 (1H, d, $J=5.0$ Hz, $OH_{4'}$), 6.46 (1H, t, $J=7.0$ Hz, CH_2OH), 6.97 (1H, s, $H_{1'}$), 7.55 (1H, t, $J=8.0$ Hz), 7.66 (1H, dd, $J_1=8.0$ Hz, $J_2=5.0$ Hz), 7.74 (1H, dt, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 8.04 (1H, d, $J=8.0$ Hz), 8.20 (1H, d, $J=12.5$ Hz, $OH_{3'}$), 8.68 (1H, dd, $J_1=5.0$ Hz, $J_2=1.5$ Hz), 8.71 (1H, d, $J=7.5$ Hz), 9.06 (1H, dd, $J_1=7.5$ Hz, $J_2=1.5$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 59.8, 59.9 ($C_{6'}$, CH_2), 64.5 ($C_{2'}$), 66.6 ($C_{4'}$), 73.0 ($C_{3'}$), 79.8 ($C_{1'}$), 80.6 ($C_{5'}$), 109.6, 113.4, 117.2, 120.2, 120.3, 123.3, 129.7, 130.2, 140.8, 151.7 (C quat arom), 111.8, 117.5, 122.1, 124.4, 127.7, 133.7, 144.9 (C tert arom), 168.5, 168.6 (C=O).

4.1.12. 5,7-Dihydro-12,13-(β-D-mannopyranose-1,2-diyl)-6*H*-pyrrolo[3,4-*c*]pyrido[2′,3′:4,5]pyrrolo[2,3-*a*]-carbazole-5,7-dione 12. To a solution of **11** (30 mg, 0.060 mmol) in THF (6 mL) was added 28% aqueous NH_4OH (12 mL). The mixture was stirred overnight at room temperature. The solvent was removed and the residue was purified by flash chromatography (eluent CH_2Cl_2/MeOH 95:5) to give **12** (20 mg, 0.0425 mmol, 71% yield) as a yellow solid.

Compound **12**. Mp >300 °C. IR (KBr) $\nu_{C=O}$ 1620, 1670 cm^{-1}, $\nu_{NH,OH}$ 3200–3500 cm^{-1}. Mass (APCI+) $[M+H]^+=471$. HRMS (FAB+) $[M+H]^+$, calcd for $C_{25}H_{18}N_4O_6$ 471.1304, found 471.1300. ^1H NMR (400 MHz, DMSO-d_6): 3.30 (1H, m, $H_{6'}$), 3.46–3.59 (2H, m, $H_{4'}$ + $H_{6'}$), 3.70 (1H, m, $H_{5'}$), 4.29 (1H, dt, $J_1=12.5$ Hz, $J_2=3.0$ Hz, $H_{3'}$), 4.35 (1H, t, $J=5.5$ Hz, $OH_{6'}$), 5.28 (1H, d, $J=2.0$ Hz, $H_{2'}$), 5.47 (1H, d, $J=5.0$ Hz, $OH_{4'}$), 6.93 (1H, s, $H_{1'}$), 7.48 (1H, t, $J=7.5$ Hz), 7.60 (1H, dd, $J_1=7.5$ Hz,

J_2=5.0 Hz), 7.68 (1H, t, J_1=8.0 Hz), 8.00 (1H, d, J=8.0 Hz), 8.22 (1H, d, J=12.0 Hz, $OH_{3'}$), 8.60–8.67 (2H, m), 9.00 (1H, d, J=7.5 Hz), 11.17 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 59.9 ($C_{6'}$), 64.4, 66.6, 73.0, 79.8, 80.6 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 109.5, 113.4, 117.4, 121.5, 121.6, 123.5, 129.6, 130.1, 140.8, 151.7 (C quat arom), 111.8, 117.3, 122.0, 124.5, 127.5, 133.9, 144.7 (C tert arom), 170.6 (2 C=O).

4.1.13. 3,4-Di-*O*-benzyl-6-*O*-tosyl-D-glucal 13. To a solution of glucal **E** (700 mg, 2.14 mmol) in pyridine (3 mL) and CH_2Cl_2 (7.5 mL) was added tosyl chloride (1.45 g, 7.6 mmol). The mixture was refluxed overnight, then 2 N HCl (15 mL) was added. After extraction with EtOAc, the organic phase was washed with saturated aqueous $NaHCO_3$ then with brine, dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 9:1) to give **13** (503 mg, 1.048 mmol, 49% yield) as a colorless oil.

Compound **13**. IR (NaCl film) $\nu_{C=O}$ 1647, 1733 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 503. ^{1}H NMR (400 MHz, $CDCl_3$): 2.45 (3H, s, CH_3), 3.84 (1H, dd, J_1=8.0 Hz, J_2=6.0 Hz, H_4), 4.16 (1H, m, H_5), 4.22 (1H, m, H_3), 4.34 (1H, dd, J_1=11.0 Hz, J_2=2.5 Hz, H_6), 4.45 (1H, dd, J_1=11.0 Hz, J_2=5.5 Hz, H_6), 4.57 (1H, d, J=12.0 Hz), 4.68 (1H, d, J=11.0 Hz), 4.69 (1H, d, J=11.0 Hz), 4.89 (1H, d, J=11.0 Hz), 4.96 (1H, dd, J_1=6.5 Hz, J_2=3.0 Hz, H_2), 6.35 (1H, d, J=6.0 Hz, H_1), 7.30–7.45 (12H, m), 7.85 (2H, d, J=8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 21.7 (CH_3), 68.2, 70.4, 73.5 (C_6+2CH_2), 73.4, 74.5, 74.7 (C_3, C_4, C_5), 100.1 (C_2), 127.6–128.9, 129.9 (C tert arom), 144 (C_1), 132.8, 137.9, 138.2, 145.0 (C quat arom).

4.1.14. 1-*O*-Acetyl-3,4-di-*O*-benzyl-6-*O*-tosyl-α- and β-D-glucopyranose 15. To a solution of **13** (291 mg, 0.606 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added a solution of dimethyldioxirane in acetone (0.07–0.09 M, 20 mL). The mixture was stirred at 0 °C for 1 h, the solvent was removed at room temperature and compound **14** was dried under vacuum for 2 h. Glacial acetic acid (6 mL) was added to **14** under nitrogen atmosphere. The mixture was stirred at room temperature overnight. After evaporation of acetic acid, the residue was dissolved in CH_2Cl_2 then saturated aqueous $NaHCO_3$ was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 8:2 to 7:3) to give **15** (258 mg, 0.465 mmol, 77% yield from **E**) as a colorless oil. The anomeric ratio calculated from ^{1}H NMR spectrum on $H_{1'}$ at 5.98 ppm (α anomer) and 5.34 ppm (β anomer) was 0.3:2, respectively.

Compound **15**. IR (NaCl film) $\nu_{C=O}$ 1710, 1757 cm^{-1}, ν_{OH} 3517 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 579. ^{1}H NMR (400 MHz, $CDCl_3$) of the major anomer: 2.00 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.54 (1H, br s, OH), 3.49 (4H, br s), 4.11 (1H, d, J=10.5 Hz), 4.17 (1H, d, J=10.0 Hz), 4.43 (1H, d, J=10.5 Hz), 4.73 (1H, d, J=10.5 Hz), 4.77 (1H, s), 4.78 (1H, d, J=8.5 Hz), 5.34 (1H, d, J=7.0 Hz, H_1), 7.08–7.29 (12H, m), 7.67 (2H, d, J=8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) of the major anomer: 20.9, 21.6 (CH_3), 67.8 ($C_{6'}$), 74.9, 75.3 (CH_2), 72.8, 73.5, 76.1, 84.3, 93.7 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 127.6–128.6, 129.9 (C tert arom), 132.6, 137.5, 138.2, 145.0 (C quat arom), 169.4; 169.5 (C=O).

4.1.15. 1-*O*-Acetyl-3,4-di-*O*-benzyl-2,6-di-*O*-tosyl-α- and β-D-glucopyranose 16. To a solution of **15** (558 mg, 1.00 mmol) in pyridine (2 mL) and CH_2Cl_2 (4 mL) was added tosyl chloride (315 mg, 1.65 mmol). The mixture was refluxed for 72 h, then 2 N HCl (15 mL) was added. After extraction with EtOAc, the organic phase was washed with saturated aqueous $NaHCO_3$ then with brine, dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 8:2 to 7:3) to give **16** (171 mg, 0.241 mmol, 24% yield) as a colorless oil. The anomeric ratio calculated from ^{1}H NMR spectrum on $H_{1'}$ at 6.15 ppm, (α anomer) and 5.62 ppm (β anomer) was 1:3.9, respectively. 171 mg of unreacted **15** (β anomer) was recovered.

Compound **16**. $^{\beta}$Major anomer, $^{\alpha}$minor anomer. IR (NaCl film) $\nu_{C=O}$ 1737, 1767 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 733. ^{1}H NMR (400 MHz, $CDCl_3$): 2.06 ($3H^{\beta}$, s, CH_3), 2.09 ($3H^{\alpha}$, s, CH_3), 2.35 ($3H^{\beta}$, s, CH_3), 2.39 ($3H^{\alpha}$, s, CH_3), 2.42 ($3H^{\beta}$, s, CH_3), 2.43 ($3H^{\alpha}$, s, CH_3), 3.58–4.01 (m, $3H^{\beta}$+$3H^{\alpha}$), 4.19–4.32 ($2H^{\beta}$+$2H^{\alpha}$, m), 4.43–4.52 ($1H^{\alpha}$+$1H^{\beta}$, m), 4.64–4.73 ($3H^{\beta}$+$3H^{\alpha}$, m), 4.74–4.80 ($1H^{\beta}$+$1H^{\alpha}$, m), 5.62 ($1H^{\beta}$, d, J=8.0 Hz, H_1), 6.15 ($1H^{\alpha}$, d, J=3.5 Hz, H_1), 7.10–7.40 ($10H^{\beta}$+$10H^{\alpha}$), 7.77 ($2H^{\beta}$+$2H^{\alpha}$, pt, J=8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 20.5, 20.7 (CH_3), 21.5, 21.6 (CH_3), 67.3, 67.5 ($C_{6'}$), 75.2, 75.5 (CH_2), 70.7, 73.5, 76.2, 76.3, 77.6, 79.2, 82.1, 89.1, 91.1 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 127.4–128.5, 129.7, 129.9 (C tert arom), 132.4, 132.5, 132.8, 134.0, 137.1, 137.4, 137.6, 144.8, 145.1, 145.4 (C quat arom), 168.3 (C=O).

4.1.16. 3,4-*O*-Benzyl-2,6-di-*O*-tosyl-α-D-glucopyranose 17. To a solution of **16** (170 mg, 0.24 mmol) in THF/MeOH (2 mL, 1:1) at 0 °C was added dropwise 1 M MeONa/MeOH (31 μL). The mixture was stirred at 0 °C for 2 h, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 7:3) affording **17** (106 mg, 0.158 mmol, 66% yield) as a colorless oil.

Compound **17**. IR (NaCl film), $\nu_{C=O}$ 1589, 1735 cm^{-1}, ν_{OH} 3500 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 691. ^{1}H NMR (400 MHz, $CDCl_3$): 2.26 (3H, s, CH_3), 2.31 (3H, s, CH_3), 3.40 (1H, t, J=9.5 Hz), 3.55 (1H, m), 3.89 (1H, t, J=9.5 Hz), 3.94 (1H, d, J=10.0 Hz), 4.06 (1H, dd, J_1=10.5 Hz, J_2=1.5 Hz), 4.13 (1H, dd, J_1=11.0 Hz, J_2=3.5 Hz), 4.21 (1H, dd, J_1=10.0 Hz, J_2=3.5 Hz), 4.32 (1H, d, J=10.5 Hz), 4.54 (2H, s), 4.61 (1H, d, J=10.5 Hz), 5.24 (1H, d, J=3.0 Hz, H_1), 6.97–7.23 (14H), 7.66 (4H, pt, J=10.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 21.6 (CH_3), 68.3 ($C_{6'}$), 75.1, 75.3 (CH_2), 68.4, 77.0, 78.8, 79.6, 90.8 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 127.4–128.5, 129.9 (C tert arom), 132.6, 133.0, 137.4, 137.8, 145.1 (2C) (C quat arom).

4.1.17. 1-Benzyloxymethyl-2,5-dihydro-3-[1-(3,4-di-*O*-benzyl-2,6-di-*O*-tosyl-β-D-glucopyranos-1-yl)-indol-3-yl]-4-[1-phenylsulfonyl-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione 18. To a solution of **B** (41 mg, 0.070 mmol) in THF (4 mL) were added **17** (104 mg, 0.155 mmol) and triphenylphosphine (41 mg, 0.155 mmol). The mixture was

cooled to −78 °C then diisopropyl azodicarboxylate (DIAD) (30 μM, 0.155 mmol) was added dropwise. The mixture was allowed to reach room temperature then was stirred for 18 h. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 8:2 then CH_2Cl_2/EtOAc 9:1) to give **18** (45 mg, 0.036 mmol, 52% yield) as a red solid.

Compound **18**. Mp 65–68 °C. IR (KBr) $\nu_{C=O}$ 1708, 1760 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 1261. ^1H NMR (400 MHz, $CDCl_3$): 2.02 (3H, s, CH_3), 2.19 (3H, s, CH_3), 3.68 (1H, m), 3.75–3.84 (2H, m), 4.05 (1H, dd, $J_1=11.0$ Hz, $J_2=2.0$ Hz), 4.17 (1H, dd, $J_1=11.0$ Hz, $J_2=4.0$ Hz), 4.53 (2H, t, $J=10.5$ Hz), 4.64 (1H, d, $J=11.0$ Hz), 4.67 (2H, s), 4.73 (1H, d, $J=10.5$ Hz), 5.10 (1H, m), 5.17 (2H, AB system, $J=11.0$ Hz, $\Delta\nu=5$ Hz), 5.37 (1H, d, $J=9.0$ Hz, $H_{1'}$), 6.34–6.42 (2H, m), 6.66 (2H, d, $J=8.0$ Hz), 6.71 (1H, dd, $J_1=8.0$ Hz, $J_2=5.0$ Hz), 6.94 (1H, dt, $J_1=7.0$ Hz, $J_2=1.5$ Hz), 7.03 (2H, d, $J=8.0$ Hz), 7.05–7.10 (2H, m), 7.11–7.29 (14H), 7.30–7.35 (3H, m), 7.42 (2H, t, $J=8.5$ Hz), 7.53 (1H, t, $J=7.5$ Hz), 7.63 (2H, d, $J=8.0$ Hz), 7.90 (1H, s), 8.07 (2H, dd, $J_1=8.5$ Hz, $J_2=1.5$ Hz), 8.10 (1H, s), 8.16 (1H, dd, $J_1=5.0$ Hz, $J_2=1.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 21.5 (CH_3), 21.6 (CH_3), 67.4, 67.5 (CH_2), 71.8 ($C_{6'}$), 75.3, 75.5 (CH_2), 75.9, 76.6, 79.4, 82.9 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 119.4, 121.5, 123.2, 127.0–130.0, 131.4, 134.2, 145.5 (C tert arom), 106.9, 109.4, 121.2, 124.1, 126.0, 130.8, 132.1, 133.1, 135.6, 136.8, 137.4, 137.6, 138.0, 144.5, 145.1, 146.6 (C quat arom), 170.6 (C=O).

4.1.18. 1-Benzyloxymethyl-2,5-dihydro-3-[1-(3,4-di-*O*-benzyl-2,6-di-*O*-tosyl-β-D-glucopyranos-1-yl)-indol-3-yl]-4-[pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione 19. To a solution of **18** (45 mg, 0.036 mmol) in THF (2 mL) was added a 1.1 M solution of tetrabutylammonium fluoride in THF (109 μL, 0.120 mmol). The mixture was stirred for 2.5 h at room temperature. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent CH_2Cl_2/EtOAc 4:1) to give **19** (33 mg, 0.030 mmol, 83% yield) as a red solid.

Compound **19**. Mp 105–107 °C. IR (KBr) $\nu_{C=O}$ 1708, 1764 cm^{-1}, ν_{NH} 3402 cm^{-1}. Mass (ESI+) $[M+H]^+$ 1099, $[M+Na]^+$ 1121. ^1H NMR (400 MHz, $CDCl_3$): 2.01 (3H, s, CH_3), 2.18 (3H, s, CH_3), 3.68 (1H, m), 3.72–3.85 (2H, m), 4.11 (2H, br s), 4.50 (1H, d, $J=10.5$ Hz), 4.64 (2H, s), 4.68 (2H, s), 4.74 (1H, d, $J=10.5$ Hz), 5.13 (1H, t, $J=8.5$ Hz), 5.18 (2H, s), 5.37 (1H, d, $J=9.0$ Hz, $H_{1'}$), 6.60–6.70 (5H, m), 6.93 (1H, m), 7.02 (2H, d, $J=8.0$ Hz), 7.06–7.11 (2H, m), 7.13–7.28 (14H), 7.34 (2H, d, $J=7.5$ Hz), 7.43 (1H, d, $J=8.0$ Hz), 7.62 (2H, d, $J=8.0$ Hz), 7.78 (1H, s), 7.89 (1H, s), 8.03 (1H, br s), 11.57 (1H, br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 21.5 (CH_3), 21.6 (CH_3), 67.3, 67.5 (CH_2), 71.7 ($C_{6'}$), 75.4 (2C) (CH_2), 75.8, 75.9, 76.7, 79.6, 83.0 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 116.9, 121.1, 122.1, 123.0, 127.0–130.0, 131.5, 143.0 (C tert arom), 105.5, 107.6, 119.0, 126.4, 127.0, 132.2, 133.1, 135.6, 136.9, 137.5, 137.7, 144.4, 144.5, 145.1, 148.3 (C quat arom), 171.3, 171.6 (C=O).

4.1.19. 12-(3,4-Di-*O*-benzyl-2,6-di-*O*-tosyl-β-D-glucopyranos-1-yl)-13*H*-2,5-dihydro-pyrido[3′,2′:4,5]pyrrolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole-5,7-dione 20. To a solution of **19** (381 mg, 0.346 mmol) in benzene (300 mL) was added iodine (137 mg, 0.52 mmol). The mixture was irradiated for 1 h with a medium pressure mercury lamp (400 W). The solvent was removed, and the residue dissolved in EtOAc (250 mL) and washed with saturated aqueous sodium thiosulfate (50 mL) and then with brine. The organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent CH_2Cl_2/EtOAc 9:1) to give **20** (228 mg, 0.208 mmol, 60% yield) as a yellow solid.

Compound **20**. Mp 82–85 °C. IR (KBr) $\nu_{C=O}$ 1710, 1760 cm^{-1}, ν_{NH} 3300–3500 cm^{-1}. Mass (APCI+) $[M]^+$ 1097. ^1H NMR (400 MHz, $CDCl_3$): 1.99 (6H, s, CH_3), 3.84 (1H, t, $J=6.0$ Hz, $H_{4'}$), 4.19 (1H, t, $J=5.5$ Hz, $H_{3'}$), 4.28 (1H, m, $H_{5'}$), 4.34 (2H, d, $J=11.0$ Hz), 4.42 (1H, dd, $J_1=11.0$ Hz, $J_2=5.5$ Hz), 4.61 (1H, d, $J=11.5$ Hz), 4.70 (1H, d, $J=9.0$ Hz), 4.72 (2H, s), 5.06 (1H, dd, $J_1=9.0$ Hz, $J_2=4.5$ Hz), 5.15 (1H, d, $J=11.0$ Hz), 5.27 (2H, s), 6.04 (1H, d, $J=9.0$ Hz, $H_{1'}$), 6.19 (2H, d, $J=8.0$ Hz), 6.47 (2H, d, $J=7.5$ Hz), 6.69 (2H, d, $J=8.0$ Hz), 7.10–7.30 (19H, m), 7.50 (2H, d, $J=7.5$ Hz), 8.50 (1H, d, $J=4.5$ Hz), 8.99 (1H, d, $J=8.0$ Hz), 9.33 (1H, d, $J=8.0$ Hz), 10.07 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 21.1 (CH_3), 21.4 (CH_3), 66.9, 68.4, 71.7, 73.7, 74.0 (CH_2), 74.6, 78.6, 79.0, 79.6, 81.3 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 109.3, 117.6, 121.9, 125.7, 126.1, 127.0–129.0, 129.4, 133.7, 148.3 (C tert arom), 114.7, 116.4, 119.1, 119.9, 120.8, 121.7, 126.9, 131.1, 132.4, 136.4, 136.7, 137.6, 140.6, 144.5, 144.8, 152.7 (C quat arom), 169.2 (2 C=O).

4.1.20. 6-Benzyloxymethyl-5,7-dihydro-12,13-(6-azido-3,4-di*O*-benzyl-6-deoxy-β-D-mannopyranose-1,2-diyl)-pyrido[3′,2′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione 21. To a solution of **20** (12.5 mg, 0.011 mmol) in DMF (1 mL) was added NaN_3 (7.3 mg, 0.112 mmol). The mixture was stirred overnight at 70 °C. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent CH_2Cl_2 100% to CH_2Cl_2/EtOAc 9:1) to give **21** (7.5 mg, 0.0094 mmol, 82% yield) as a yellow solid.

Compound **21**. Mp 45–47 °C. IR (KBr) $\nu_{C=O}$ 1704, 1754 cm^{-1}, ν_{N3} 2100 cm^{-1}. Mass (ESI+) $[M+H]^+$ 796. ^1H NMR (400 MHz, $CDCl_3$): 3.62 (1H, dd, $J_1=13.0$ Hz, $J_2=6.0$ Hz, $H_{6'}$), 3.66 (1H, dd, $J_1=13.0$ Hz, $J_2=7.0$ Hz, $H_{6'}$), 3.79 (1H, m, $H_{4'}$), 3.76 (1H, m), 3.81 (1H, d, $J=13.0$ Hz), 3.87 (1H, d, $J=12.0$ Hz), 4.22 (1H, dd, $J_1=11.0$ Hz, $J_2=6.5$ Hz, $H_{5'}$), 4.53 (1H, d, $J=12.0$ Hz), 4.69 (1H, m, $H_{3'}$), 4.70 (1H, d, $J=11.5$ Hz), 4.78 (2H, s), 5.32 (2H, s), 5.69 (1H, dd, $J_1=5.5$ Hz, $J_2=3.5$ Hz, $H_{2'}$), 6.34 (1H, d, $J=6.0$ Hz, $H_{1'}$), 6.37 (2H, d, $J=7.5$ Hz), 6.87 (2H, t, $J=7.5$ Hz), 6.99 (1H, t, $J=7.5$ Hz), 7.20–7.50 (11H, m), 7.60 (1H, t, $J=7.5$ Hz), 7.94 (1H, d, $J=8.0$ Hz), 8.48 (1H, dd, $J_1=5.0$ Hz, $J_2=1.0$ Hz), 8.85 (1H, d, $J=8.0$ Hz), 8.99 (1H, dd, $J_1=7.5$ Hz, $J_2=0.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 52.5 ($C_{6'}$), 52.6, 73.0, 73.4, 75.0, 80.8 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 66.8, 71.5, 72.1, 72.5 (CH_2), 109.5, 114.4, 117.6, 120.3, 120.7, 124.7, 128.6, 135.9, 137.0, 137.8, 142.3, 151.7

(C quat arom), 113.0, 117.4, 122.5, 125.5, 127.7–128.9, 133.6, 146.7 (C tert arom), 169.6 (2 C=O).

4.1.21. 6-Hydroxymethyl-5,7-dihydro-12,13-(6-azido-6-deoxy-β-D-mannopyranos-1,2-diyl)-pyrido[3′,2′:4,5]-pyrrolo[2,3-*a*] pyrrolo[3,4-*c*]carbazole-5,7-dione 22. To a solution of **21** (96 mg, 0.120 mmol) in CH_2Cl_2 (6 mL) was added a solution of dimethyldioxirane in acetone (0.07–0.09 M, 60 mL) during 7 days. After removal of the solvent, the residue was purified by flash chromatography (eluent from cyclohexane/EtOAc 2:8 to EtOAc 100%) to give **22** (28.3 mg, 0.054 mmol, 45% yield).

Compound **22**. Mp 145–148 °C. IR (KBr) $\nu_{C=O}$ 1702, 1753 cm^{-1}, ν_{N3} 2100 cm^{-1}, ν_{OH} 3038–3653 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 3.15 (1H, dd, $J_1=13.5$ Hz, $J_2=6.0$ Hz, $H_{6'}$), 3.37 (1H, m, $H_{6'}$), 3.50 (1H, m, $H_{4'}$), 3.97 (1H, m, $H_{5'}$), 4.34 (1H, dt, $J_1=12.5$ Hz, $J_2=3.0$ Hz, $H_{3'}$), 4.90 (2H, m, CH_2OH), 5.32 (1H, d, $J=2.5$ Hz, $H_{2'}$), 5.76 (1H, d, $J=5.0$ Hz, $OH_{4'}$), 6.37 (1H, t, $J=7.0$ Hz, CH_2OH), 7.03 (1H, s, $H_{1'}$), 7.47 (1H, t, $J=8.0$ Hz), 7.57 (1H, dd, $J_1=8.0$ Hz, $J_2=5.0$ Hz), 7.70 (1H, dt, $J_1=8.5$ Hz, $J_2=1.0$ Hz), 7.98 (1H, d, $J=8.5$ Hz), 8.26 (1H, d, $J=12.0$ Hz, $OH_{3'}$), 8.57 (1H, d, $J=8.0$ Hz), 8.60 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 8.90 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 50.1 ($C_{6'}$), 59.6 (CH_2OH), 64.2, 67.4, 72.6, 78.8, 79.6 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 109.6, 113.6, 117.1, 120.2, 123.4, 129.5, 130.0, 139.1, 140.8, 151.5 (C quat arom), 111.7, 117.5, 122.2, 124.4, 127.7, 133.7, 144.9 (C tert arom), 168.3, 168.4 (2 C=O).

4.1.22. 12,13-(6-Azido-6-deoxy-β-D-mannopyranos-1,2-diyl)-6*H*-pyrido[3′,2′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7-dione 23. To a solution of **22** (28 mg, 0.053 mmol) in THF (6 mL) was added 28% aqueous NH_4OH (11 mL). The mixture was stirred for 5 h at room temperature. The solvent was removed and the residue was purified by flash chromatography (eluent EtOAc 100%) to give **23** (20 mg, 0.041 mmol, 77% yield) as a yellow solid.

Compound **23**. Mp >200 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1719, 1746 cm^{-1}, ν_{N3} 2100 cm^{-1}, $\nu_{NH,OH}$ 3138–3618 cm^{-1}. HRMS (ESI+) $[M+H]^+$, calcd for $C_{25}H_{18}N_7O_5$ 496.1369, found 496.1372. ^1H NMR (400 MHz, DMSO-d_6): 3.20 (1H, dd, $J_1=13.5$ Hz, $J_2=6.0$ Hz, $H_{6'}$), 3.40 (1H, dd, $J_1=13.5$ Hz, $J_2=2.0$ Hz, $H_{6'}$), 3.54 (1H, m, $H_{4'}$), 3.99 (1H, dt, $J_1=9.0$ Hz, $J_2=2.0$ Hz, $H_{5'}$), 4.31 (1H, dt, $J_1=13.0$ Hz, $J_2=3.0$ Hz, $H_{3'}$), 5.40 (1H, d, $J=2.5$ Hz, $H_{2'}$), 5.76 (1H, d, $J=5.0$ Hz, $OH_{4'}$), 7.05 (1H, s, $H_{1'}$), 7.53 (1H, dt, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 7.67 (1H, dd, $J_1=8.0$ Hz, $J_2=5.0$ Hz), 7.73 (1H, dt, $J_1=7.5$ Hz, $J_2=1.0$ Hz), 8.03 (1H, d, $J=8.0$ Hz), 8.33 (1H, d, $J=12.0$ Hz, $OH_{3'}$), 8.66–8.72 (2H, m), 9.08 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 11.25 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 50.2 ($C_{6'}$), 64.2, 67.5, 72.7, 78.8, 79.6 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 109.6, 113.6, 117.3, 121.1, 121.6, 123.5, 129.5, 130.0, 140.7, 151.6 (C quat arom), 111.7, 117.4, 122.1, 124.5, 127.5, 133.9, 144.7 (C tert arom), 170.5 (2 C=O).

4.1.23. 1-Benzyloxymethyl-3-(1-phenylsulfonyl-1*H*-indol-3-yl)-4-[1-(2-*O*-tosyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranos-1-yl)-pyrrolo[2,3-*b*]pyridin-3-yl]-2,5-dihydropyrrole-2,5-dione 24. To a solution of **F** (200 mg, 0.341 mmol) in THF (18 mL) were added **6** (459 mg, 0.76 mmol) and triphenylphosphine (199 mg, 0.76 mmol). The mixture was cooled to −78 °C then diisopropyl azodicarboxylate (DIAD) (147 μM, 0.76 mmol) was added dropwise. The mixture was allowed to reach room temperature then was stirred for 18 h. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent CH_2Cl_2/EtOAc 9:1) to give **24** as the major product of the reaction (190 mg, 0.161 mmol, 47% yield) as a red solid.

Compound **24**. Mp 80–82 °C. IR (KBr), $\nu_{C=O}$ 1711 cm^{-1}. Mass (ESI+) $[M+H]^+$ 1175. ^1H NMR (400 MHz, $CDCl_3$): 2.13 (3H, s, CH_3), 3.69–3.80 (2H, m), 3.77 (1H, d, $J=9.5$ Hz), 3.91–3.99 (2H, m), 4.55 (1H, d, $J=12.0$ Hz), 4.62 (1H, d, $J=10.5$ Hz), 4.63 (1H, d, $J=12.5$ Hz), 4.65 (1H, d, $J=12.5$ Hz), 4.75 (1H, d, $J=13.5$ Hz), 4.76 (2H, s), 4.80 (1H, d, $J=10.5$ Hz), 5.20 (1H, m, $H_{2'}$), 5.27 (2H, s), 6.19 (1H, d, $J=9.0$ Hz, $H_{1'}$), 6.34 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 6.65 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 6.75 (2H, d, $J=8.0$ Hz), 6.84 (1H, t, $J=7.5$ Hz), 7.02 (1H, d, $J=8.0$ Hz), 7.07–7.13 (2H, m), 7.16 (1H, t, $J=8.0$ Hz), 7.21–7.40 (18H), 7.42 (2H, d, $J=7.5$ Hz), 7.51 (2H, t, $J=8.0$ Hz), 7.63 (1H, t, $J=7.5$ Hz), 7.95–8.01 (3H, m), 8.06 (1H, d, $J=1.5$ Hz), 8.08 (1H, s), 8.34 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 21.5 (CH_3), 67.5, 68.2, 71.9, 73.5, 75.3, 75.4 ($C_{6'}+5CH_2$), 77.7, 78.2, 80.5, 83.0 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 113.5, 117.2, 122.5, 124.0, 125.3, 127.0–128.6, 128.7, 129.5, 129.7, 130.5, 134.2, 143.7 (C tert arom), 105.8, 112.4, 118.6, 124.7, 130.8, 133.5, 134.4, 137.5, 137.7, 137.9, 144.2, 147.8 (C quat arom), 170.5 (2C, C=O).

4.1.24. 1-Benzyloxymethyl-3-(1*H*-indol-3-yl)-4-[1-(2-*O*-tosyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranos-1-yl)-pyrrolo[2,3-*b*]pyridin-3-yl]-2,5-dihydro-pyrrole-2,5-dione 25. To a solution of **24** (160 mg, 0.136 mmol) in THF (5 mL) was added a 1.1 M solution of tetrabutylammonium fluoride in THF (409 μL, 0.448 mmol). The mixture was stirred for 2.5 h at room temperature. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent from CH_2Cl_2 100% to CH_2Cl_2/EtOAc 9:1) to give **25** (90 mg, 0.087 mmol, 64% yield) as a red solid.

Compound **25**. Mp 38–40 °C. IR (KBr) $\nu_{C=O}$ 1706, 1743 cm^{-1}, ν_{NH} 3163–3608 cm^{-1}. Mass (ESI+) $[M+H]^+$ 1035. ^1H NMR (400 MHz, $CDCl_3$): 2.13 (3H, s, CH_3), 3.67 (1H, d, $J=10.0$ Hz), 3.72–3.80 (2H, m), 3.92 (1H, t, $J=9.0$ Hz), 3.97 (1H, t, $J=9.0$ Hz), 4.47 (1H, d, $J=12.0$ Hz), 4.55 (1H, d, $J=12.0$ Hz), 4.62 (1H, d, $J=11.0$ Hz), 4.80 (3H, s+m), 4.82 (1H, d, $J=10.5$ Hz), 5.00 (1H, m), 5.27 (3H, s+m), 6.17 (1H, d, $J=9.0$ Hz, $H_{1'}$), 6.45 (1H, br s), 6.67 (1H, dd, $J_1=7.5$ Hz, $J_2=4.5$ Hz), 6.72 (2H, d, $J=8.0$ Hz), 6.82 (1H, t, $J=8.0$ Hz), 7.00–7.40 (23H), 7.44 (2H, d, $J=7.5$ Hz), 7.71 (1H, d, $J=2.0$ Hz), 8.08 (2H, s), 8.88 (1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 22.0 (CH_3), 67.3, 68.3, 71.7, 73.5, 75.3, 75.5 ($C_{6'}+5CH_2$), 70.1, 77.7, 78.1, 80.7, 83.1 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 111.4, 116.9, 121.1, 122.1, 122.8, 126.8–129.1, 129.7, 130.5, 143.4 (C tert arom), 106.5, 106.6, 118.9, 125.3, 126.2, 133.5, 135.9,

137.6, 137.7, 137.8, 138.0, 143.9, 147.7 (C quat arom), 171.2, 171.5 (C=O).

4.1.25. 6-Benzyloxymethyl-13-(2-*O*-tosyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranos-1-yl)-5,7-dihydro-12*H*-pyrido[3′,2′:4,5]pyrrolo[3,2-*a*]-pyrrolo[3,4-*c*]carbazole-5,7-dione 26. To a solution of **25** (54 mg, 0.052 mmol) in DMF (2 mL) was added $Pd(OTf)_2$ (52 mg, 0.158 mmol). The mixture was stirred at 90 °C for 5 h. EtOAc was added, then 0.5 N HCl (10 mL). After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent from cyclohexane/CH_2Cl_2 3:7 to CH_2Cl_2 100%) to give **26** (30 mg, 0.029 mmol, 56% yield) as a yellow solid.

Compound **26**. Mp 147–149 °C. IR (KBr) $\nu_{C=O}$ 1710, 1760 cm^{-1}, ν_{NH} 3200–3600 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 1055. ^1H NMR (400 MHz, $CDCl_3$): 2.02 (3H, s, CH_3), 3.55 (1H, d, $J=10.0$ Hz), 3.75 (1H, d, $J=10.5$ Hz), 3.84 (1H, d, $J=10.0$ Hz), 3.96 (1H, t, $J=8.5$ Hz), 4.26 (1H, d, $J=9.5$ Hz), 4.31 (1H, d, $J=11.0$ Hz), 4.46 (2H, t, $J=12.0$ Hz), 4.58 (1H, d, $J=10.0$ Hz), 4.62 (2H, s), 4.81 (1H, d, $J=10.0$ Hz), 4.83 (1H, d, $J=10.5$ Hz), 5.05 (1H, dt, $J_1=9.0$ Hz, $J_2=1.0$ Hz), 5.18 (2H, s), 6.35 (2H, d, $J=8.0$ Hz), 6.41 (2H, d, $J=7.5$ Hz), 6.67 (1H, dd, $J_1=9.5$ Hz, $J_2=1.0$ Hz), 6.95–7.30 (25H), 8.28 (1H, d, $J=5.0$ Hz), 9.03 (1H, d, $J=8.0$ Hz), 9.06 (1H, d, $J=8.0$ Hz), 10.31 (1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 21.5 (CH_3), 66.6, 67.0, 71.7, 74.2, 75.6, 76.5 (CH_2), 76.4, 77.9, 79.7, 80.4, 83.7 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 112.0, 117.7, 121.6, 125.7, 126.1 (2C), 127.5–129.0, 134.0, 146.8 (C tert arom), 115.2, 116.3, 119.3, 120.3, 121.0, 122.6, 127.0, 130.1, 133.0, 136.6, 137.3, 137.6, 137.8, 141.8, 144.3, 151.4 (C quat arom), 169.3, 169.4 (C=O).

4.1.26. 6-Benzyloxymethyl-5,7-dihydro-13,12-(3,4,6-tri-*O*-benzyl-β-D-mannopyranose-1,2-diyl)-pyrido[3′,2′:4,5]pyrrolo[2,3-*a*] pyrrolo[3,4-*c*]carbazole-5,7-dione 27. To a solution of **26** (15 mg, 0.0145 mmol) in DMF (1 mL) was added NaN_3 (10 mg, 0.154 mmol). The mixture was stirred overnight at 70 °C. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 4:1 then CH_2Cl_2/EtOAc 9:1) to give **27** (11.6 mg, 0.0137 mmol, 93% yield) as a yellow solid.

Compound **27**. Mp 59–61 °C. IR (KBr) $\nu_{C=O}$ 1700, 1750 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 883. ^1H NMR (400 MHz, $CDCl_3$): 3.34 (1H, dd, $J_1=10.0$ Hz, $J_2=4.0$ Hz), 3.47 (1H, dd, $J_1=11.0$ Hz, $J_2=2.5$ Hz, $H_{6'}$), 3.58 (1H, dd, $J_1=11.5$ Hz, $J_2=4.0$ Hz, $H_{6'}$), 3.95 (1H, m, $H_{5'}$), 3.97 (2H, s), 4.11 (1H, t, $J=8.5$ Hz, $H_{4'}$), 4.30 (1H, dd, $J_1=9.0$ Hz, $J_2=3.0$ Hz, $H_{3'}$), 4.56 (1H, d, $J=11.0$ Hz), 4.65 (2H, s), 4.74 (2H, s), 4.84 (1H, d, $J=11.0$ Hz), 5.08 (1H, s, $H_{2'}$), 5.11 (1H, d, $J=3.5$ Hz), 6.41 (1H, s, $H_{1'}$), 6.64 (2H, d, $J=8.0$ Hz), 6.91 (2H, t, $J=7.5$ Hz), 7.02 (1H, t, $J=7.5$ Hz), 7.12 (1H, t, $J=7.5$ Hz), 7.15–7.35 (15H, m), 7.40 (1H, t, $J=8.0$ Hz), 7.47 (1H, t, $J=8.0$ Hz), 8.43–8.48 (2H, m), 8.88 (1H, d, $J=7.5$ Hz), 8.91 (1H, d, $J=6.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 60.5, 73.1, 78.6, 80.0, 80.5 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 66.7, 68.2, 71.5, 73.1, 73.3, 75.0 (CH_2), 114.5, 118.2, 122.0, 125.8, 127.4–129.4, 133.7, 146.8 (C tert arom), 111.0, 115.2, 120.3, 120.9, 124.5, 129.2, 131.3, 136.6, 137.7, 142.9, 151.8 (C quat arom), 169.3, 169.4 (C=O).

4.1.27. 5,7-Dihydro-13,12-(β-D-mannopyranose-1,2-diyl)-6*H*-pyrido[3′,2′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7-dione 28. To a suspension of **27** (135 mg, 0.157 mmol) in CH_2Cl_2 (18 mL) at −78 °C was added a 1 M solution of BBr_3 in CH_2Cl_2 (3.16 mL). The mixture was stirred at −78 °C for 30 min, then it was allowed to reach room temperature. After extraction with EtOAc, the organic phase was dried over $MgSO_4$ and the solvent was removed. The residue was dried under vacuum for 1 h. To a solution of the residue (56 mg) in THF (6 mL) was added 28% aqueous NH_4OH (12 mL). The mixture was stirred overnight at room temperature. The solvent was removed and the residue was purified by flash chromatography (eluent from EtOAc 100% to EtOAc/MeOH 95:5) to give **28** (20 mg, 0.0425 mmol, 27% yield) as a yellow solid.

Compound **28**. Mp >300 °C. IR (KBr) $\nu_{C=O}$ 1703, 1747 cm^{-1}, $\nu_{NH,OH}$ 3038–3619 cm^{-1}. Mass (ESI+) $[M+H]^+$ 471. HRMS (FAB+) $[M+H]^+$, calcd for $C_{25}H_{18}N_4O_6$ 471.1304, found 471.1291. ^1H NMR (400 MHz, DMSO-d_6): 3.30 (1H, dd, $J_1=12.5$ Hz, $J_2=5.5$ Hz, $H_{6'}$), 3.55 (1H, dd, $J_1=12.5$ Hz, $J_2=1.5$ Hz, $H_{6'}$), 3.70 (1H, d, $J=9.5$ Hz, $H_{5'}$), 3.76 (1H, m, $H_{4'}$), 4.43 (1H, t, $J=5.5$ Hz, $OH_{6'}$), 4.58 (1H, m, $H_{3'}$), 5.16 (1H, d, $J=2.0$ Hz, $H_{2'}$), 5.60 (1H, br s, $OH_{4'}$), 6.74 (1H, d, $J=4.0$ Hz, $OH_{3'}$), 6.90 (1H, s, $H_{1'}$), 7.47 (1H, t, $J=7.5$ Hz), 7.60 (1H, dd, $J_1=8.0$ Hz, $J_2=5.0$ Hz), 7.64 (1H, dt, $J_1=7.0$ Hz, $J_2=1.5$ Hz), 8.68 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 8.84 (1H, d, $J=8.0$ Hz), 8.94 (1H, dd, $J_1=7.5$ Hz, $J_2=1.5$ Hz), 9.08 (1H, d, $J=8.5$ Hz), 11.17 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 60.2 ($C_{6'}$), 64.3, 65.8, 72.3, 79.5, 80.9 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 109.3, 113.6, 117.0, 120.9, 121.4, 123.4, 129.1, 131.1, 143.0, 151.0 (C quat arom), 116.4, 118.0, 121.0, 124.2, 127.0, 132.6, 146.7 (C tert arom), 170.7, 171.0 (2 C=O).

References and notes

1. Bush, J. A.; Long, B. H.; Catino, J. J.; Bradner, W. T.; Tomita, K. *J. Antibiot.* **1987**, *40*, 668–678.
2. Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 397–402.
3. Matson, J. A.; Claridge, C.; Bush, J. A.; Titus, J.; Bradner, W. T.; Doyle, T. W.; Horan, A. C.; Patel, M. *J. Antibiot.* **1989**, *42*, 1547–1555.
4. Takahashi, I.; Kobayashi, E.; Asano, K.; Yoshida, M.; Nakano, H. *J. Antibiot.* **1987**, *40*, 1782–1784.
5. Rodrigues Pereira, E.; Belin, L.; Sancelme, M.; Prudhomme, M.; Ollier, M.; Rapp, M.; Sevère, D.; Riou, J-F. ; Fabbro, D.; Meyer, T. *J. Med. Chem.* **1996**, *39*, 4471.
6. Moreau, P.; Gaillard, N.; Marminon, C.; Anizon, F.; Dias, N.; Baldeyrou, B.; Bailly, C.; Pierré, A.; Hickman, J.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Bioorg. Med. Chem.* **2003**, *11*, 4871.

7. Prudhomme, M. *Curr. Pharm. Des.* **1997**, *3*, 265–290.
8. Marminon, C.; Pierré, A.; Pfeiffer, B.; Pérez, V.; Léonce, S.; Renard, P.; Prudhomme, M. *Bioorg. Med. Chem.* **2003**, *11*, 679–687.
9. Marminon, C.; Pierré, A.; Pfeiffer, B.; Pérez, V.; Léonce, S.; Joubert, A.; Bailly, C.; Renard, P.; Hickman, J.; Prudhomme, M. *J. Med. Chem.* **2003**, *46*, 609–622.
10. Anizon, F.; Moreau, P.; Sancelme, M.; Voldoire, A.; Prudhomme, M.; Ollier, M.; Sevère, D.; Riou, J-F. ; Bailly, C.; Fabbro, D.; Meyer, T.; Aubertin, A-M. *Bioorg. Med. Chem.* **1998**, *6*, 1597–1604.
11. Marminon, C.; Anizon, F.; Moreau, P.; Léonce, S.; Pierré, A.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *J. Med. Chem.* **2002**, *45*, 1330–1339.
12. Messaoudi, S.; Anizon, F.; Pfeiffer, B.; Golsteyn, R.; Prudhomme, M. *Tetrahedron Lett.* **2004**, *45*, 4643–4647.
13. Gray, N.; Détivaud, L.; Doerig, C.; Meijer, L. *Curr. Med. Chem.* **1999**, *6*, 859–875.
14. Zhao, B.; Bower, M. J.; McDewitt, P. J.; Zhao, H.; Davis, S. T.; Johanson, K. O.; Green, S. M.; Concha, N. O.; Zhou, B. B. *J. Biol. Chem.* **2002**, *277*, 46609–46615.
15. Anizon, F.; Moreau, P.; Sancelme, M.; Laine, W.; Bailly, C.; Prudhomme, M. *Bioorg. Med. Chem.* **2003**, *11*, 3709–3722.
16. Prudhomme, M. *Curr. Med. Chem. Anti-Cancer Agents* **2004**, *4*, 509–521.
17. Bovin, N. V.; Zurabyan, S. E.; Khorlin, A. Y. *Carbohydr. Res.* **1981**, *98*, 25–35.
18. Timer, C. M.; van Straten, N. C. R.; van der Marel, G. A.; van Boom, J. H. *J. Carbohydr. Chem.* **1998**, *17*, 471–487.
19. Takahashi, T.; Ebata, S.; Yamada, H. *Synlett* **1998**, 381–382.
20. Routier, S.; Ayerbe, N.; Mérour, J.-Y.; Coudert, G.; Bailly, C.; Pierré, A.; Pfeiffer, B.; Caignard, D.-H.; Renard, P. *Tetrahedron* **2002**, *58*, 6621–6630.
21. Alonso, R. A.; Vite, G. D.; McDevitt, R. E.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 573–584.
22. Marples, B. A.; Muxworthy, J. P.; Baggaley, K. H. *Synlett* **1992**, 646.
23. Csuk, R.; Dörr, P. *Tetrahedron* **1994**, *50*, 9983–9988.
24. Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1999**, *64*, 2465–2470.