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Synthesis of NB-506, A New Anticancer Agent

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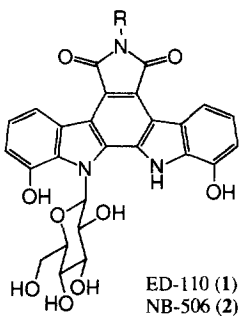
Abstract: 6-*N*-formylamino-12,13-dihydro-1,11-dihydroxy-13-(β-D-glucopyranosyl)-5*H*-indolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (NB-506, **2**), a derivative of the naturally occurring antitumor compound, BE-13793C (**3**), is a new indolopyrrolocarbazole anticancer agent which potently inhibits topoisomerase I. The synthesis of NB-506 was accomplished starting from dibromomaleimide **4** and indole compound **5.** The key step, a glycosylation of indolocarbazole, was precisely studied to develop a practical synthesis method using KOH as a base. Copyright © 1996 Elsevier Science Ltd

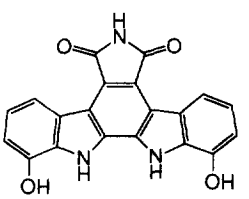
Introduction

Recently, we found a new indolocarbazole compound, BE-13793C (**3**)[1], in the course of the screening for new anticancer agents. BE-13793C, originally isolated from the culture broth of a *Streptoveriticillium* species, has two hydroxyl groups at the C1 and C11 positions. It showed potent cytotoxicities against various cell lines by the inhibition of topoisomerase I. Its antitumor effect, however, was not so remarkable possibly due to low aqueous solubility. In order to increase its aqueous solubility, BE-13793C was glycosylated to give ED-110 (**1**)[2], a 13-*N*-β-D-glucopyranosyl derivative, which as expected, showed better antitumor effects than BE-13793C.

Further modification of ED-110 lead to NB-506 (**2**)[3] which has remarkably improved antitumor activities in mice, and is now under clinical trial. Here we report the synthesis of NB-506.



ED-110 (**1**) R = H
NB-506 (**2**) R = NHCHO

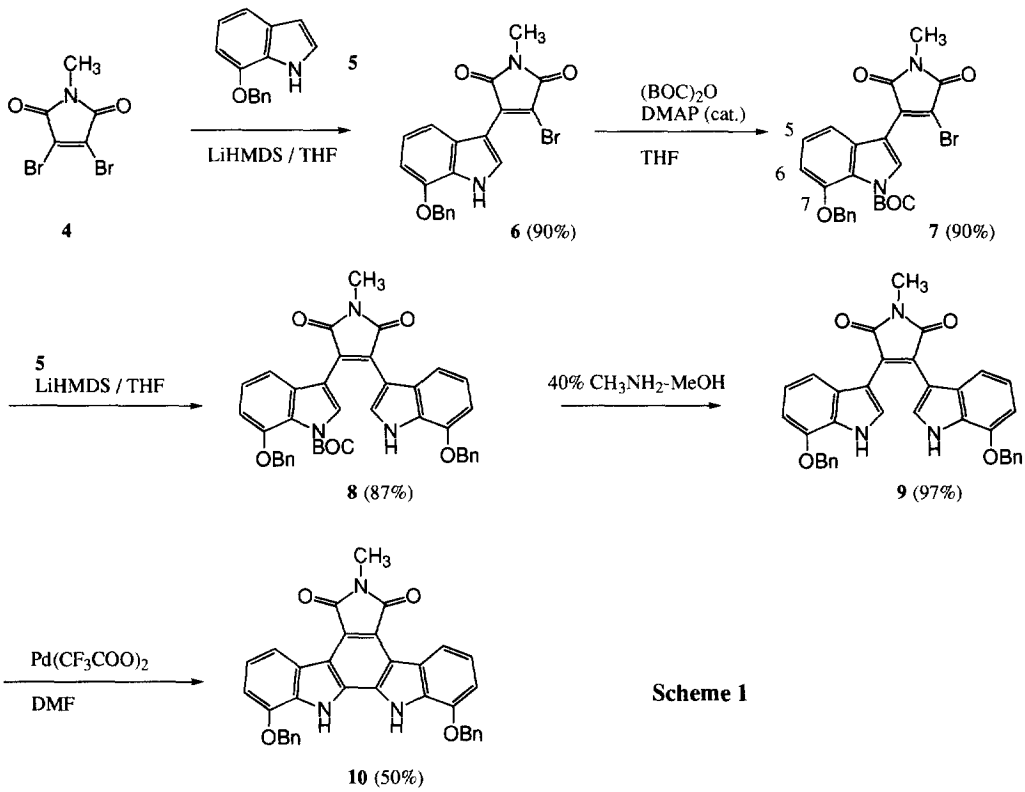


BE-13793C (**3**)

Fig. 1

Results and Discussion

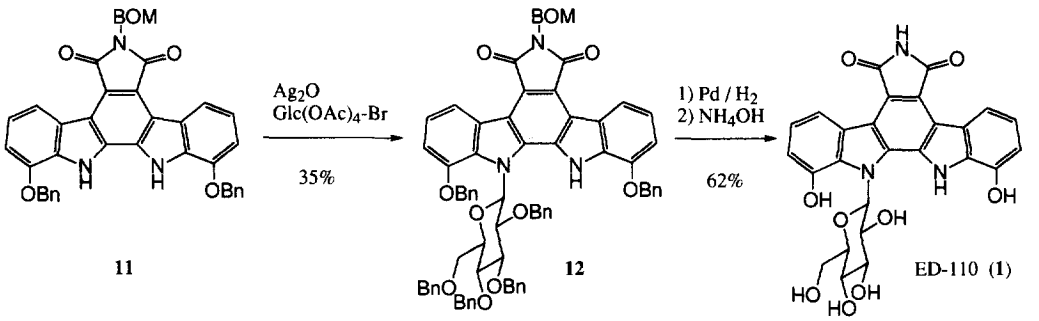
In our previous paper[4], we reported the practical synthesis of indolocarbazoles. An aglycon **10** was synthesized according to our method with partial modifications (Scheme 1).



Scheme 1

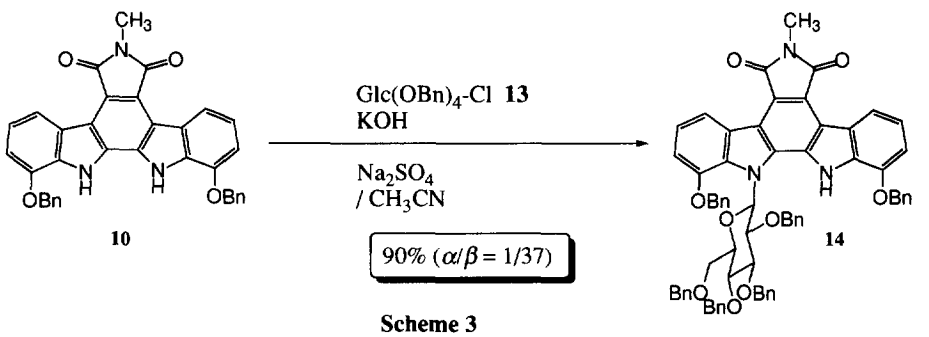
The indolylation of **4**[5] with 1.0 equiv of indole **5** using 2.0 equiv of lithium hexamethyldisilazide(LiHMDS) gave **6** in 90% yield, which was protected with *t*-butyloxycarbonyl (BOC) group to obtain **7** in 90% yield.

In our previous paper[4], the secondary indole coupling reaction was carried out under the same condition as the first indolylation in the compound substituted with a benzyloxyl group at the C6 position, however compound **7**, which has a benzyloxyl group at the C7 position, was not reacted with the indole **5** under the same condition. The corresponding bisindolyl compound **8** was, however, obtained by the use of 2.4 equiv of indole **5** and 2.4 equiv of LiHMDS in 87% yield. The diminished reactivity of the lithiated 7-benzyloxyindole compared with that of lithiated 5 or 6-benzyoxylindole might be due to the formation of a five-membered ring chelation between an oxygen at the C7 position and an indolyl nitrogen atom. Removal of the BOC group with methylamine gave compound **9** in 97% yield. Oxidative cyclization of compound **9** with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), $PdCl_2$ and $Pd(OAc)_2$ was unsuccessful, however, the use of palladium(II) trifluoroacetate gave the desired product **10** in 50% yield. Thus the key intermediate **10** in the synthesis of NB-506 was prepared from dibromomaleimide **4** with a satisfactory yield.



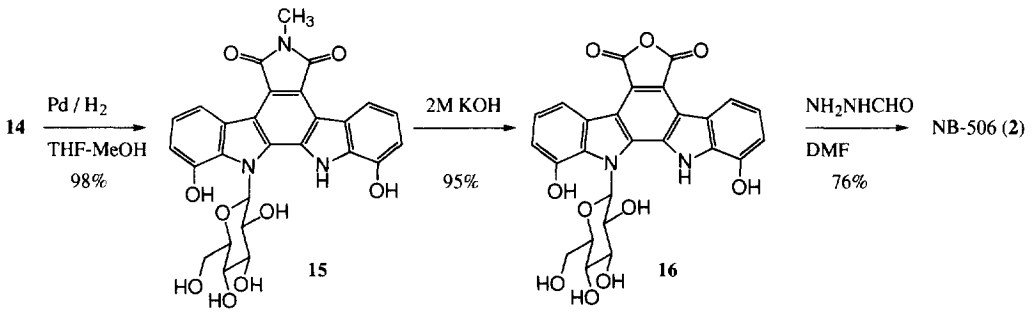
Scheme 2

Next, the glycosylation of compound **10** was investigated precisely. In our previous paper on the synthesis of ED-110 (**1**)[2a], the glycosylation of the indolocarbazole **11** by the Keonigs-Knorr method was reported, however the yield was not satisfactory (scheme 2). In order to improve the chemical yield, we studied the Keonigs-Knorr conditions (Ag_2CO_3, AgOTf, $HgBr_2$ and $HgCN_2$) and the reactions with some Lewis acids (BF_3-Et_2O, $SnCl_4$ and TMSOTf), however satisfactory results could not be obtained. In 1983, F. Seela et al.[6] reported the synthesis of several nucleosides using phase transfer catalysts in the key glycosylation of nucleobase anions with protected sugars. We applied this reaction condition to the glycosylation of the indolocarbazole compound **10** with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride **13**[7] to give glycosylated compound **14** in good yield with a high stereoselectivity. We investigated the reaction and found that none of the phase transfer catalyst was necessary for this reaction (Scheme 3).



Scheme 3

The indolyl dianion of **10**, generated by powdered KOH in acetonitrile in the presence of sodium sulfate (for dryness), was reacted with α-halogenose **13** under an nitrogen atomosphere to form the desired β-glucoside **14** in 90% yield with a high stereoselectivity (α/β = 1/37) (Scheme 3).



Scheme 4

The benzyl group of the glucoside **14** was removed by hydrogenolysis with a catalytic amount of palladium black in chloroform-methanol (1:1) followed by hydrolysis with aqueous potassium hydroxide to yield the anhydride compound **16**. The treatment of compound **16** with formic hydrazide in DMF (dimethylformamide) at 80 °C gave NB-506(**2**) in 76% yield (Scheme 4).

Summary

We achieved the synthesis of NB-506 from 7-benzyloxyindole and dibromomaleimide with improved glycosylation using KOH as a base.

Experimental

^{1}H and ^{13}C NMR were recorded on a Varian VXR-300 or Jeol JNM-EX 400 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.

Preparation of 7-benzyloxyindole (5)

3-Benzyloxy-2-nitrotoluene: A stirred mixture of 3-methyl-2-nitrophenol (250 g, 1.63 mol), potassium carbonate (225.8 g, 1.63 mol) and benzyl chloride (227.2 g, 1.79 mol) in 3.26 L of DMF was heated at 100 ℃ for 4 h. The reaction mixture was poured into water and then extracted with ethyl acetate. The organic phase was washed with 1 M NaOH (x 2), 2 % aqeous NaCl (x 2) and saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel (4 Kg) using hexane-ethyl acetate (10:1) to elute 3-benzyloxy-2-nitrotoluene (396.0 g, 1.63 mol) as colorless prisms (100%).

IR (KBr) ν_{max} 1616, 1581, 1537, 1477, 1465, 1456, 1371, 1276, 1064 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 8.08 (1H, d, J = 9.7Hz), 7.30-7.43 (5H, m),6.85-6.89 (2H, m), 5.13 (2H, s), 2.63 (3H, s); HRMS (FAB) calcd for $C_{14}H_{15}NO_3$ 243.0895, found 243.0887.

7-Benzyloxyindole (5): A stirred mixture of 3-benzyloxy-2-nitrotoluene (6.0 g, 24.7 mmol), *N*,*N*-dimethylformamide dimethylacetal (8.8 g, 47.1 mol) and pyrrolidine (5.2 g, 47.1 mol) was heated at 110 ℃ for 5 h and allowed to cool to room temperature. This crude mixture was diluted with ethanol (100 mL) which was heat to 80 °C. To the dark red solution was added hydrazine monohydrate (12.4 mL, 148.2 mmol) and a suspension of nickel boride (prepared from 54.3 mmol of nickel acetate) in 100 mL of ethanol. After an additional 1 h, hydrazine monohydrate (12.4 mL, 148.2 mmol) was added, and the mixture was stirred for 10 h. After cooling, the mixture was filtered through a pad of Celite and the filtrate was evaporated in vacuo. The resulting colorless residue was diluted with ethyl acetate, and then the organic phase was successively washed with 2M HCl (x 3), aqueous $NaHCO_3$ and saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was passed through a short column of Florisil® (60 g), eluting with chloroform-hexane (1:1). The resulting solution was concentrated in vacuo and the residue was recrystallized from hexane to get **5** (3.20 g, 14.3 mol) as a colorless powder (58%): IR (KBr) ν_{max} 3401, 1575, 1488, 1419, 1342, 1253, 1066 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 8.40 (1H, NH, br s), 7.28-7.52 (6H, m) 7.17 (1H, dd, J = 2.7, 2.9Hz), 7.02 (1H, t, J = 7.7Hz), 6.72 (1H, d, J = 7.7Hz), 6.53 (1H, dd, J = 2.2, 3.1Hz), 5.21 (2H, s); HRMS (FAB) calcd for $C_{15}H_{13}NO$ 223.0997, found 223.0996.

Synthesis of NB-506 (3)

4-Bromo-2,5-dihydro-3-[7-benzyloxy-1*H*-indol-3-yl]-1-methyl-1*H*-pyrrole-2,5-dione (6): In an N_2 atmosphere, 161.3 mL of LiHMDS (1 M in THF) at -20 ℃ was added to a solution of 7-benzyloxyindole **5** (15 g, 67.3 mmol) in THF (150 mL), and the mixture was stirred for 45 min. A solution of 2,3-dibromo-*N*-methylmaleimide **4** (18.1 g, 67.3 mol) in THF (180 mL) was then added by drip over 10 min, followed by stirring for 30 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 recrystallized from hexane-ethyl acetate to get **6** (26.9 g, 65.2 mmol) as an orange powder (97%), mp 152 ℃ (decompose): IR (KBr) ν_{max} 1705, 1628, 1576, 1433, 1383, 1259, 1076 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 9.03 (1H, br s), 7.94 (1H, d, J = 3.0Hz), 7.69 (1H, d, J = 8.0Hz), 7.64 (1H, d, J = 8.0Hz), 7.30-7.53 (5H, m), 7.15 (1H, t, J = 8.0Hz), 6.82 (1H, d, J = 8.0Hz), 5.22 (2H, s), 3.16 (3H, s); HRMS (FAB) calcd for $C_{20}H_{15}N_2O_3Br$ 410.0248, found 410.0273.

4-Bromo-2,5-dihydro-3-[7-benzyloxy-1-(*tert*-butyloxycarbonyl)-1*H*-indol-3-yl]-1-methyl-1*H*-pyrrole-2,5-dione (7): Di-*tert*-butyl dicarbonate (16.9 g, 77.4 mmol) and a catalytic amount of DMAP (4-dimethylaminopyridine) (136 mg, 1.11 mmol) were added to a solution of **6** (29.0 g, 70.3 mmol) in THF (200 mL), and the mixture was stirred for 1 h at 20 °C. After removal of the solvent in vacuo, the yellow residue was chromatographed (chloroform) and recrystallized from chloroform-ethyl acetate-hexane to obtain **7** (32.9 g, 64.3 mmol) as a yellow powder (92%), mp 97-98 ℃: IR (KBr) ν_{max} 1765, 1712, 1438, 1369, 1261, 1149 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 8.04 (1H, s), 7.20-7.62 (7H, m), 6.95 (1H, d, J = 7.9Hz), 5.23 (2H, s), 3.18 (3H, s), 1.53 (9H, s); HRMS (FAB) calcd for $C_{25}H_{23}N_2O_5Br$ 510.0790, found 510.0815.

2,5-Dihydro-3-[7-benzyloxy-1-(*tert*-butyloxycarbonyl)-1*H*-indol-3-yl]-4-(7-benzyloxy-1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione (8): In an N_2 atmosphere, 0.48 mL of LiHMDS (1 M in THF, 0.48 mmol) was added to a solution of 7-benzyloxyindole **5** (107.2 mg, 0.48 mmol) in THF (3 mL) at -20 ℃ and stirred for 15 min. A solution of **7** (102.2 mg, 0.20 mmol) in THF (2 mL) was then added by drip over 20 min, and the mixture was stirred for 30 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 on silica gel [hexane-ethyl acetate (4:1)] to obtain the bisindolyl maleimide **8** (112.7 mg, 0.17 mmol) as a yellow powder (86%), mp 139-141 ℃: IR (KBr) ν_{max} 1759, 1734, 1579, 1498, 1430, 1261, 1155 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 8.78 (1H, br s), 7.90 (1H, s), 7.75(1H, s), 7.29-7.52 (10H, m), 6.58-6.82 (6H, m), 5.17 (2H, s), 5.15 (2H, s), 3.19 (3H, s), 1.53 (9H, s); HRMS (FAB) calcd for $C_{40}H_{35}N_3O_6$ 653.2526, found 653.2529.

2,5-Dihydro-3,4-bis-(7-benzyloxy-1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione (9): 40% methylamine in methanol (1 mL) was added to compound **8** (69 mg, 0.10 mmol) and the reaction mixture was stirred for 10 min at room temperature. The solvent was removed in vacuo and the residue was recrystallized from ethyl acetate-hexane to obtain the deprotected compound **9** (55.2 mg, 0.09 mmol) as a red powder (95%), mp 229-231 ℃: IR (KBr) ν_{max} 1691, 1577, 1531, 1423, 1384, 1259, 1083 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 8.73 (2H, s), 7.69 (2H, s), 7.30-7.49 (10H, m), 6.60-6.75 (6H, m), 5.16 (4H, s), 3.17 (3H, s); HRMS (FAB) calcd for $C_{35}H_{27}N_3O_4$ 553.2002, found 553.1982.

12,13-Dihydro-1,11-dibenzyloxy-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-methyl-5,7-(6*H*)dione (10): Palladium trifluoroacetate (49.9 mg, 0.15 mmol) was added to a solution of **9** (30.0 mg, 0.054 mmol) in DMF (2.5 mL), and the mixture was stirred at 90 ℃ for 30min. After cooling, the reaction mixture was poured into 0.2 M aqueous hydrochloric acid, and extracted with ethyl acetate. The organic layer 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 Sephadex LH-20 with methanol to yield **10** (14.6 mg, 0.026 mmol) as a yellow powder (49%), mp 255-257 ℃: IR (KBr) ν_{max} 1742, 1695, 1684, 1577, 1406, 1377, 1251, 1103 cm^{-1}; ^1H NMR (300MHz, DMSO) δ 11.67 (2H, s), 8.52-8.55 (2H, m), 7.62 (4H, d, J = 7.1Hz), 7.46 (4H, d, J = 7.1Hz), 7.40 (2H, d, J = 7.1Hz), 7.23-7.28 (4H, m), 5.37 (4H, s), 3.30 (3H, s); HRMS (FAB) calcd for $C_{35}H_{25}N_3O_4$ 551.1845, found 551.1839.

12,13-Dihydro-1,11-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 (14): **10** (483 mg, 0.87 mmol) was added to a suspension of powdered potassium hydroxide (360 mg) and sodium sulfate (2.2 g) in dry acetonitrile (40 mL) in a nitrogen atmosphere. The resulting dark purple solution was allowed to stir for 30 min at room temperature and 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride **13** (1.06 g, 1.89 mmol) in dry acetonitrile (12 mL) was then added to the purple solution. The final reaction mixture was stirred at room temperature for 15 h and was then poured into 2 M HCl and extracted with ethyl acetate. The organic extract was sequentially washed with water, aqueous $NaHCO_3$, water and saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residual red oil (α / β = 1 / 37, determined by ^1H NMR) was chromatographed on silica gel [hexane-ethyl

acetate (10:1) and toluene-ethyl acetate (90:1)] to obtain β-glucoside **14** (840 mg, 0.78 mmol) as a yellow amorphous powder (90%). $[\alpha]^{20}_{D}$ +101.0° (c 1.00, $CHCl_3$); IR (KBr) ν_{max} 2617, 1699, 1581, 1377, 1257, 1097 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 10.55 (1H, s), 9.08 (1H, d, J = 7.3Hz), 8.87 (1H, d, J = 8.3Hz), 6.90-7.53 (31H, m), 6.86 (2H, t, J = 7.6Hz), 6.17 (2H, d, J = 6.9Hz), 5.30 (1H, d, J = 11.5Hz), 5.20 (2H, d, J = 11.5Hz), 5.14 (1H, d, J = 11.5Hz), 4.73 (1H, d, J = 10.9Hz), 4.64 (1H, d, J = 10.9Hz), 4.59 (1H, d, J= 11.0Hz), 4.57 (1H, d, J = 13.1Hz), 4.52 (1H, d, J = 13.2Hz), 4.10 (1H, d, J = 11.0Hz), 4.00(1H, t, J = 9.1Hz), 3.83 (1H, d, J = 9.6Hz), 3.52-3.76 (5H, m), 3.49 (3H, s), 2.95 (1H, d, J = 9.6Hz); HRMS (FAB) calcd for $C_{69}H_{59}N_3O_9$ 1073.4269, found 1073.4251.

α-Glucoside; IR (KBr) ν_{max} 2925, 1749, 1697, 1579, 1473, 11454, 1255, 1097 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 10.90 (1H, s), 9.15 (1H, d, J = 8.3Hz), 8.78 (1H, d, J = 8.3Hz), 7.61 (H-1', 1H, d, J = 2.4Hz), 6.99-7.43 (31H, m), 6.98 (1H, d, J = 7.3Hz), 6.87 (1H, dd, J = 7.3, 7.8Hz), 6.68 (2H, t, J = 8.3Hz), 6.35 (2H, d, J = 8.3Hz), 5.16 (1H, d, J = 11.2Hz), 5.04 (1H, d, J = 11.2Hz), 5.02 (2H, q, J = 6.8Hz), 4.50 (1H, d, J = 11.2Hz), 4.30-4.40 (6H, m), 3.82-3.92 (3H, m), 3.50-3.63 (4H, m); HRMS (FAB) calcd for $C_{69}H_{59}N_3O_9$ 1073.4269, found 1073.4277.

12,13-Dihydro-1,11-dihydroxy-13-(β-D-glucopyranosyl)-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole-6-methyl-5,7(6*H*)-dione (15): A catalytic amount of palladium black was added to a solution of **14** (270 mg, 0.25 mmol) in chloroform-methanol [(1:1) 15 mL]. The mixture was stirred for 4 h in a hydrogen atmosphere. The catalyst was filtered off and washed with methanol. The solvent was removed in vacuo and the residue was recrystallized from methanol-chloroform-hexane to yield **15** (130 mg, 0.24 mmol) as a red powder (98%), mp >300 ℃: $[\alpha]^{20}_{D}$ +101.6° (c 0.50, DMF); IR (KBr) ν_{max} 3371, 1741, 1638, 1587, 1577, 1387 cm^{-1}; ^1H NMR (300MHz, DMSO) δ 10.89 (1H, s), 10.34 (1H, s), 9.95 (1H, s), 8.71 (1H, d, J = 7.7Hz), 8.53 (1H, d, J = 7.7Hz), 7.18 (2H, t, J = 7.7Hz), 7.05 (1H, d, J = 9.1Hz, 1'-H), 7.01 (1H, d, J = 7.7Hz), 6.99 (1H, d, J = 7.7Hz), 4.50-5.80 (4H, br, OH x 4), 3.95-4.08 (2H, m), 3.58-3.80 (3H, m), 3.39 (1H, dd, J = 8.6, 9.1Hz), 3.18 (3H, s); HRMS (FAB) calcd for $C_{27}H_{23}N_3O_9$ 533.1434, found 533.1419.

11,12-Dihydro-1,10-dihydroxy-12-(β-D-glucopyranosyl)-indolo[2,3-*a*]carbazole-5,6-dicarboxylic anhydride (16): The compound **15** (70 mg, 0.13 mmol) was dissolved in 2 M aqueous potassium hydroxide (2 mL) at room temperature and the solution was acidified after 0.5 h with 2 M HCl. The mixture was extracted with ethyl acetate-MEK (1:1) and the extract was washed with saturated brine, dried over Na_2SO_4 and concentrated. The residual solid was washed with chloroform to obtain the anhydride compound **16** (65 mg, 0.13 mmol) as a red crystal (95%), mp >300 ℃: $[\alpha]^{20}_{D}$ +80.0° (c 1.00, DMSO); IR (KBr) ν_{max} 3353, 1816, 1743, 1587, 1388, 1249 cm^{-1}; ^1H NMR (400MHz, DMSO) δ 11.11 (1H, s), 10.52 (1H, s), 10.13 (1H, s), 8.52 (1H, d, J = 7.8Hz), 8.37 (1H, d, J = 7.8Hz), 7.26 (2H, t, J = 7.8Hz), 7.11 (1H, d, J = 9.8Hz, 1'-H), 7.08 (1H, d, J = 7.8Hz), 7.06 (1H, d, J = 7.8Hz), 5.43 (1H, d J = 5.9Hz, OH), 5.34 (1H, d, J = 5.4Hz), 5.25 (1H, d, J = 5.4Hz), 4.97 (1H, d, J = 5.4Hz), 4.01 (2H, m), 3.77 (1H, m), 3.67 (1H, td, J = 8.8, 5.9Hz), 3.61 (1H, td, J = 8.8, 5.4Hz), 3.42 (1H, td, J = 8.8, 5.4Hz); ^{13}C NMR (100MHz, DMSO) δ 164.5,144.1, 143.6, 130.8, 130.2, 130.1, 123.1, 122.5, 122.2, 122.1, 119.5, 119.3, 117.4, 114.8, 114.5, 114.3, 112.1, 85.3, 81.1, 77.4, 72.4, 69.8, 60.9; HRMS (FAB) calcd for $C_{26}H_{20}N_2O_{10}$ 520.1118, found 520.1117.

NB-506 (3): A solution of formic hydrazide (4.35 g, 72.4 mmol) in DMF (54 mL) was added to a solution of the anhydride **16** (30.2 g, 58.1 mmol) in DMF (43 mL) by drip over 25 h at 80 °C, and the mixture was stirred for 4 h. After the purple mixture was cooled to room temperature, methanol (178 mL) and water (533 mL) were successively added to the purple solution and then stirred overnight at 0 °C. The dark, red crystal was filtered, washed with methanol and suspended in hot methanol followed by filtration to obtain NB-506 (**3**) (25.0 g, 44.4 mmol) as a clear, red, crystalline powder (76%), mp >300 °C; $[\alpha]^{20}_{D}$ +106° (c 5.00, DMF); IR (KBr) ν_{max} 3353, 1816, 1743, 1587, 1388, 1249 cm^{-1}; ^{1}H NMR (400MHz, DMSO) δ 11.1 (1H, s), 10.8 (1H, s), 10.4 (1H, s), 10.0 (1H, s), 8.64 (1H, dd, J = 1.0, 7.8Hz), 8.48 (1H, d, J = 7.8Hz), 8.45 (1H, s, CHO), 7.21 (2H, t, J = 7.8Hz), 7.06 (1H, d, J = 9.3Hz, 1'-H), 7.05 (1H, dd, J = 1.0, 7.8Hz), 7.03 (1H, d, J = 7.8Hz), 5.43 (1H, d J = 5.9Hz, OH), 5.37 (1H, d, J = 5.4Hz), 5.23 (1H, d, J = 5.4Hz), 4.92 (1H, d, J = 5.4Hz), 4.03 (2H, m), 3.76 (1H, m), 3.65 (1H, td, J = 8.8, 5.9Hz), 3.62 (1H, td, J = 8.8, 5.4Hz), 3.40(1H, td, J = 8.8, 5.4Hz); ^{13}C NMR (100MHz, DMSO) δ 166.5, 166.3, 160.6, 143.9, 143.4, 131.0, 130.2, 129.8, 129.7, 123.4, 122.7, 121.8, 121.6, 119.7, 117.9, 117.4, 116.0, 115.4, 115.1, 114.1, 111.9, 85.2, 81.1, 77.4, 72.3, 69.9, 61.0; HRMS (FAB) calcd for $C_{27}H_{22}N_4O_{10}$ 562.1336, found 562.1321.

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