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Studies on Lignan Lactone Antitumor Agents. I. Synthesis of Aminoglycosidic Lignan Variants Related to Podophyllotoxin

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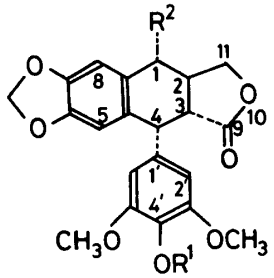
D-(and L-)Aminoglycosidic variants of 4′-*O*-demethyl-1-epipodophyllotoxin were synthesized by glycosidation of 4′-*O*-benzyloxycarbonyl- or 4′-*O*-chloroacetyl-4′-*O*-demethyl-1-epipodophyllotoxin (**8** or **22**) with the corresponding aminosugar derivatives. Cyclic acetals of 1-*O*-(2-amino-2-deoxy- and 3-amino-3-deoxy-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxins (**13** and **21**) gave a significant survival time increase in mice with leukemia L-1210, and showed superior activity to VP-16-213 (etoposide, **5**).

Keywords——podophyllotoxin aminoglycosidic variant; 1-*O*-(2-amino-2-deoxy-4 : 6-*O*-ethylidene-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin; 1-*O*-(3-amino-3-deoxy-4 : 6-*O*-ethylidene-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin; 1-*O*-(2-deoxy-4 : 6-*O*-ethylidene-2-methylamino-L-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin

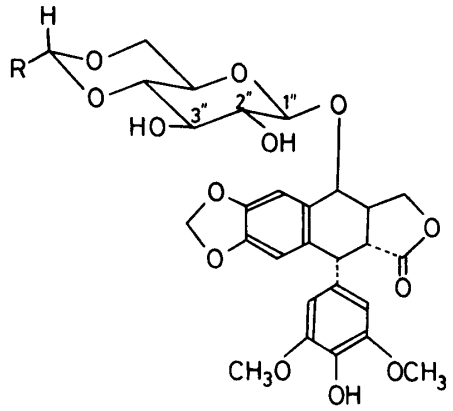
The naturally occurring lignan lactones, podophyllotoxins (**1**, **2**)[1-3] and podophyllotoxin glycosides (**3**, **4**)[1,4-6] exert a marked specific inhibition of mitosis.[1,7-11] Although these natural products were tested for activity against cancer, their effects were not satisfactory in clinical trials because of nonspecific side effects.[1,12-14] Extensive attempts to chemically modify podophyllotoxin to obtain a more useful agent have led to podophyllotoxin glycoside derivatives, VP-16-213 (etoposide, **5**) and VM-26 (teniposide, **6**), which are useful in the treatment of lung cancer, *etc.*[1,15-22] Their clinical efficacy and their intriguing mechanism of action[1,23-31] have stimulated interest in the synthesis of new active analogues of podophyllotoxin. glycoside.

In order to investigate the relationships between the structure and antitumor activity,



1: podophyllotoxin; $R^1=CH_3$, $R^2=OH$
2: 4′-demethylpodophyllotoxin; $R^1=H$, $R^2=OH$
3: podophyllotoxin β-D-glucopyranoside; $R^1=CH_3$, $R^2=$ β-D-glucopyranoside
4: 4′-demethylpodophyllotoxin β-D-glucopyranoside; $R^1=H$, $R^2=$ β-D-glucopyranoside

Fig. 1



5: VP-16-213 (etoposide); R = CH_3

6: VM-26 (teniposide); R = 

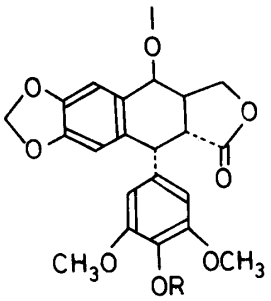
Fig. 2

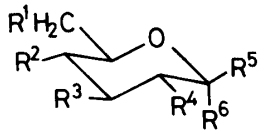
structural modifications have been made either on the sugar or on the lignan moiety.[1,32-37] It appears so far that such alterations have a profound effect on the antitumor activity and that the 4″:6″-*O*-cyclic acetal or ketal group of the sugar moiety plays an important role in increasing the antitumor activity.[1,32] Under these circumstances we focussed our effort on the replacement of the sugar moeity of **5** with an aminosugar.

The syntheses of analogues of podophyllotoxin aminoglycosides were carried out as follows. Condensation of 4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (**8**) with 3,4,6-tri-*O*-acetyl-2-benzyloxycarbonylamino-β-D-glucopyranose (**7**) in dichloromethane in the presence of boron trifluoride etherate[32] afforded the corresponding α- and β-D-glucopyranosides (**9** and **10**) in yields of 14 and 78%, respectively. Acetyl groups of **9** and **10** were removed with zinc acetate in methanol under reflux to give (2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranosyl)-4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (**14**) and its β-isomer (**11**), respectively. The indispensable 4″:6″-*O*-ethylidene group was introduced into **11** and **14** by treatment with acetaldehyde diethyl acetal in acetonitrile in the presence of *p*-toluenesulfonic acid to give the corresponding 4:6-*O*-ethylidene-β-D-glucopyranoside (**12**) and its α-isomer (**15**), respectively. The subsequent hydrogenolysis of each isomer (**12** and **15**) with a palladium black catalyst gave the final products, 1-*O*-(2-amino-2-deoxy-4:6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (**13**) and its α-isomer (**16**), respectively. On the other hand, 1-*O*-(2-amino-2-deoxy-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (**17**) was prepared by hydrogenolysis of **11**.

A similar scheme was also applied for the preparation of 1-*O*-(3-amino-3-deoxy-4:6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (**21**) starting from **8** and **18**. Glycosidation occurred stereospecifically to give the β-D-anomer as a sole product.

A slightly modified process was employed for the preparation of the 1-*O*-(2-methylamino-2-deoxy-L-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin derivatives. In this case, the 4″:6″-*O*-ethylidene group was introduced before glycosidation as a protecting group, and the other hydroxyl group was protected with a more base-labile chloroacetyl group in place of the acetyl group mentioned above. Treatment of 2-*N*-(benzyloxycarbonyl)-2-deoxy-2-methylamino-L-glucopyranose (**23**) with paracetaldehyde in the presence of a small amount of sulfuric acid gave a 2-*N*-(benzyloxycarbonyl)-2-deoxy-4:6-*O*-ethylidene-2-methylamino-L-glucopyranose (**24**). Treatment of **24** with benzyloxycarbonyl chloride in dioxane in the presence of aqueous sodium hydroxide solution gave benzyloxycarbonyl 2-*N*-

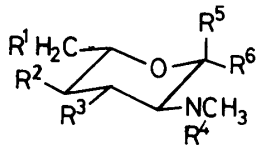




X_1: R = Z
X_2: R = $COCH_2Cl$
X_3: R = H
8: X_1H
22: X_2H

7: $R^1=R^2=R^3=OAc$, $R^4=NHZ$, $R^5=OH$, $R^6=H$
9: $R^1=R^2=R^3=OAc$, $R^4=NHZ$, $R^5=H$, $R^6=X_1$
10: $R^1=R^2=R^3=OAc$, $R^4=NHZ$, $R^5=X_1$, $R^6=H$
11: $R^1=R^2=R^3=OH$, $R^4=NHZ$, $R^5=X_1$, $R^6=H$
12: $R^1,R^2=$  $-CH_3$, $R^3=OH$, $R^4=NHZ$, $R^5=X_1$, $R^6=H$
13: $R^1,R^2=$ $-CH_3$, $R^3=OH$, $R^4=NH_2$, $R^5=X_3$, $R^6=H$
14: $R^1=R^2=R^3=OH$, $R^4=NHZ$, $R^5=H$, $R^6=X_1$
15: $R^1,R^2=$ $-CH_3$, $R^3=OH$, $R^4=NHZ$, $R^5=H$, $R^6=X_1$
16: $R^1,R^2=$ $-CH_3$, $R^3=OH$, $R^4=NH_2$, $R^5=H$, $R^6=X_3$
17: $R^1=R^2=R^3=OH$, $R^4=NH_2$, $R^5=X_3$, $R^6=H$
18: $R^1=R^2=R^4=OAc$, $R^3=NHZ$, $R^5=OH$, $R^6=H$
19: $R^1=R^2=R^4=OAc$, $R^3=NHZ$, $R^5=X_1$, $R^6=H$
20: $R^1,R^2=$ $-CH_3$, $R^3=NHZ$, $R^4=OAc$, $R^5=X_1$, $R^6=H$
21: $R^1,R^2=$ $-CH_3$, $R^3=NH_2$, $R^4=OH$, $R^5=X_3$, $R^6=H$

Chart 1



23: $R^1=R^2=R^3=OH$, $R^4=Z$, $R^5,R^6=H,OH$
24: $R^1,R^2=$ $-CH_3$, $R^3=OH$, $R^4=Z$, $R^5,R^6=H,OH$
25: $R^1,R^2=$ $-CH_3$, $R^3=OH$, $R^4=Z$, $R^5,R^6=H,OZ$
26: $R^1,R^2=$ $-CH_3$, $R^3=OCOCH_2Cl$, $R^4=Z$, $R^5,R^6=H,OZ$
27: $R^1,R^2=$ $-CH_3$, $R^3=OCOCH_2Cl$, $R^4=Z$, $R^5,R^6=H,OH$
28: $R^1,R^2=$ $-CH_3$, $R^3=OH$, $R^4=Z$, $R^5=H$, $R^6=X_3$
29: $R^1,R^2=$ $-CH_3$, $R^3=OH$, $R^4=Z$, $R^5=X_3$, $R^6=H$
30: $R^1,R^2=$ $-CH_3$, $R^3=OH$, $R^4=R^5=H$, $R^6=X_3$
31: $R^1,R^2=$ $-CH_3$, $R^3=OH$, $R^4=R^6=H$, $R^5=X_3$
32: $R^1=R^2=R^3=OH$, $R^4=R^5=H$, $R^6=X_3$
33: $R^1=R^2=R^3=OH$, $R^4=R^6=H$, $R^5=X_3$

Chart 2

(benzyloxycarbonyl)-4:6-*O*-ethylidene-2-methylamino-L-glucopyranoside (**25**). Acylation of **25** with chloroacetyl chloride followed by hydrogenolysis of the *O*-benzyloxycarbonyl group with palladium on carbon afforded a 2-*N*-(benzyloxycarbonyl)-3-*O*-chloroacetyl-2-deoxy-4:6-*O*-ethylidene-2-methylamino-L-glucopyranose (**27**). Condensation of 4′-*O*-chloroacetyl-

Table I. The Antitumor Activities of VP-16-213 (**5**) and Aminoglycosidic Variants of Podophyllotoxin (T/C%)

Dose (μg/mouse)	Compound No.											
	1	**5**	**13**	**16**	**17**	**21**	**28**	**29**	**30**	**31**	**32**	**33**
25	131	184	272	127	85	361	95	84	95	113	96	96
6.25	106	139	133	114	91	133	95	101	101	101	96	96

The T/C values are the percentage ratios of the mean survival of five treated mice to the mean survival of the control group. L-1210 cells (10^6 cells) were inoculated intraperitoneally and the treatment was started on day 1 and continued for 10 d.

4′-*O*-demethyl-1-epipodophyllotoxin (**22**) with **27** by the same procedure as mentioned above gave a mixture of the corresponding α- and β-L-glucopyranosides in a yield of 77%. Removal of protecting groups of the mixture with ethylenediamine followed by hydrogenolysis with palladium on carbon afforded the final products, 1-*O*-(2-deoxy-4:6-*O*-ethylidene-2-methylamino-β-L-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (**30**) and its α-L-isomer (**31**) in yields of 22 and 46%, respectively. On the other hand, 1-*O*-(2-deoxy-2-methylamino-β-L-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (**32**) and its α-L-isomer (**33**) were obtained by acid hydrolysis of **30** and **31**, respectively.

The antitumor activity of the synthesized compounds against leukemia L-1210 in mice appears to be structurally specific and also correlated with the nature of the sugar moiety. Cyclic acetals of 1-*O*-(2-amino-2-deoxy- and 3-amino-3-deoxy-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxins (**13** and **21**) produced a significant survival time increase in the lymphocytic leukemia L-1210 test, while cyclic acetals of the corresponding α-D-glucosides and α- and β-L-glucosides did not show a significant antitumor effect. Compounds **13** and **21** showed superior activity to VP-16-213 (**5**), as shown in Table I.

Experimental

Melting points were determined with a Yamato apparatus and are uncorrected. Infrared (IR) spectra were determined on a Hitachi 260-10 spectrophotometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recoreded with Varian XL-100, Varian EM-390, Bruker WM250 and JEOL GX-400 spectrometers. Chemical shifts were expressed in ppm with tetramethylsilane as an internal standard. The mass spectra were taken with a Hitachi RMU-6M mass spectrometer for electron-impact ionization, a Hitachi RMN-7M for field-desorption (FD) and for secondary ionization (SI), and a JEOL D-300 for fast atom bombardment (FAB).

Typical Experimental Procedures

3,4,6-Tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranose (7)——To a solution of 3,4,6-tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranosyl bromide[39] (1 g) in acetone (3 ml) were added silver carbonate (450 mg) and water (30 μl) at 0 °C, and the mixture was filtered. The filtrate was evaporated to give a solid. The solid was crystallized from a mixture of acetone and diisopropyl ether to give colorless crystals (820 mg, 94%), mp 147—147.5 °C, $[\alpha]_D^{24}$ +31° (c=1.0, $CHCl_3$). IR (KBr): 3430, 3380, 1750, 1700, 1535 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.97, 2.00 and 2.07 (3H, s each, OAc), 4.67 (1H, t, J=8.1 Hz, H-1), 5.12 (2H, s, $COOCH_2$-phenyl), 7.37 (5H, s, phenyl). FAB-MS m/z: 440 $(M+H)^+$, 422 $(M^+ + H - H_2O)$.

1-*O*-(3,4-Di-*O*-acetyl-2-benzyloxycarbonylamino-2,6-dideoxy-α- and β-D-glucopyranosyl)-4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxins (9 and 10)——To a solution of a mixture of 4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (500 mg, **8**) and **7** (620 mg) in dichloromethane (1 ml) was added dropwise boron trifluoride etherate (0.5 ml) at −18 °C, and the mixture was stirred at −18 °C for 30 min, then quenched with pyridine (0.5 ml). Dichloromethane (20 ml) was added, and the solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a solid, which was subjected to column chromatography on silica gel. Elution with toluene–acetone (1:1) and evaporation gave **9** and **10** as solids in yields of 14 and 78%, respectively. Each solid was crystallized from methanol to give the corresponding colorless crystals.

9: mp 145—147 °C, $[\alpha]_D^{21}$ +50° (c=0.92, $CHCl_3$). IR (KBr): 3400, 1780, 1750, 1605, 1555, 1550, 1485, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.89, 1.98 and 2.15 (3H, s each, OAc), 3.68 (6H, s, 2 × OCH_3), 4.68 (1H, d, J=5.6 Hz, H-4), 4.80 (1H, d, J=3.5 Hz, H-1), 5.12 (2H, s, $COOCH_2$-phenyl (?)), 5.27 (2H, s, OCH_2-phenyl (?)), 6.00 (2H, br s,

methylidene), 6.27 (2H, s, H-2′ and 6′), 6.57 (1H, s, H-5), 6.97 (1H, s, H-8), 7.3—7.6 (10H, m, 2 × phenyl). FAB-MS *m/z*: 978 ($M^+ + Na$), 844.

10: mp 180—182 °C, $[\alpha]_D^{21}$ −40° (*c* = 0.92, $CHCl_3$). IR (KBr): 3450, 3400, 1780, 1750, 1540 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.95, 2.02 and 2.13 (3H, s each, OAc), 3.67 (6H, s, 2 × OCH_3), 4.55 (1H, d, *J* = 5.6 Hz, H-4), 5.25 (2H, s, $OC\underline{H}_2$-phenyl (?)), 5.90 (2H, d, *J* = 9 Hz, methylidene), 6.28 (2H, s, H-2′ and 6′), 6.57 (1H, s, H-5), 6.87 (1H, s, H-8), 7.2—7.5 (10H, m, 2 × phenyl). FAB-MS *m/z*: 978 ($M^+ + Na$), 844.

1-*O*-(2-Benzyloxycarbonylamino-2-deoxy-β-D-glucopyranosyl)-4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (11)——A solution of **10** (600 mg) in methanol (5 ml) was refluxed in the presence of zinc acetate (115 mg) for 6 h. After being diluted with dichloromethane (20 ml), the solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave a solid, which was subjected to column chromatography on silica gel. Elution with chloroform–methanol (20 : 1) and evaporation gave a colorless solid (295 mg, 57%), mp 134—136 °C, $[\alpha]_D^{17}$ −57° (*c* = 1.0, $CHCl_3$). IR (KBr): 3450, 1770, 1700, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.62 (6H, s, 2 × OCH_3), 5.23 (2H, s, $COOC\underline{H}_2$-phenyl (?)), 5.78 (2H, br s, methylidene), 6.25 (2H, s, H-2′ and 6′), 6.42 (1H, s, H-5), 6.92 (1H, s, H-8), 7.1—7.6 (10H, m, 2 × phenyl). FAB-MS *m/z*: 830 $(M+H)^+$, 802, 695, 607.

1-*O*-(2-Benzyloxycarbonylamino-2-deoxy-4 : 6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (12)——To a solution of a mixture of **11** (180 mg) and acetaldehyde diethyl acetal in acetonitrile (5 ml) was added *p*-toluenesulfonic acid monohydrate (10 mg), and the mixture was stirred at room temperature for 30 min. After being neutrallized with $NaHCO_3$, the mixture was filtered, and the residue was washed with dichloromethane. The filtrate and washings were combined and evaporated to give a solid. The solid was subjected to column chromatography on silica gel. Elution with chloroform–methanol (50 : 1) and evaporation gave a colorless solid (171 mg, 92%), mp 136—138 °C, $[\alpha]_D^{18}$ −71° (*c* = 0.81, $CHCl_3$). IR (KBr): 3425, 2900, 1770, 1720, 1605, 1510, 1490, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.38 (3H, d, *J* = 5.6 Hz, CH_3), 3.67 (6H, s, 2 × OCH_3), 4.55 (1H, d, *J* = 5.6 Hz, H-4), 4.87 (1H, d, *J* = 3.5 Hz, H-1), 5.06 (2H, s, $COOC\underline{H}_2$-phenyl (?)), 5.26 (2H, s, $OC\underline{H}_2$-phenyl), 5.75 and 5.90 (2H, ABq, *J* = 1 Hz, methylidene), 6.28 (2H, s, H-2′ and 6′), 6.55 (1H, s, H-5), 6.78 (1H, s, H-8), 7.2—7.6 (10H, m, 2 × phenyl). FAB-MS *m/z*: 934 ($M^+ + DMSO + H$), 878 ($M^+ + Na$), 607.

1-*O*-(2-Amino-2-deoxy-4 : 6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (13)——A solution of **12** (171 mg) in a mixture of ethyl acetate (2 ml) and methanol (2 ml) was stirred with palladium black (10 mg) under a hydrogen stream for 8 h. The palladium black was filtered off, and washed with methanol and ethyl acetate. The filtrate and washings were combined and evaporated to give a solid. The solid was subjected to column chromatography on silica gel. Elution with chloroform–methanol (30 : 1) gave **12** (88 mg, 75%), which was recrystallized from methanol, mp 201—203 °C, $[\alpha]_D^{21}$ −111° (*c* = 0.85, $CHCl_3$). IR (KBr): 3420, 2990, 2890, 1770, 1610, 1520, 1510, 1490, 1460 cm^{-1}. ^{1}H-NMR (100 MHz, pyridine-d_5) δ: 1.40 (3H, d, *J* = 8.2 Hz, CH_3), 3.78 (6H, s, 2 × OCH_3), 5.09 (1H, d, *J* = 3.8 Hz, H-1), 5.28 (1H, d, *J* = 8.4 Hz, H-1″), 5.96 (2H, s, methylidene), 6.76 (1H, s, H-5), 6.79 (2H, s, H-2′ and 6′), 7.49 (1H, s, H-8′). SIMS-MS *m/z*: 588 $(M+H)^+$, 382, 299, 229.

1-*O*-(2-Amino-2-deoxy-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epopodophyllotoxin (17)——A solution of **11** (80 mg) in a mixture of methanol (1 ml) and water (1 ml) was stirred with palladium black (10 mg) under a hydrogen stream for 5 h. The palladium black was filtered off and washed with methanol and water. The filtrate and washings were combined and evaporated to give a solid. The solid was subjected to preparative thin-layer chromatography on silica gel developed with chloroform–methanol (7 : 1). Compound **17** was obtained as a solid in a yield of 65%, mp 209—212 °C, $[\alpha]_D^{17}$ −75° (*c* = 0.78, CH_3OH). IR (KBr): 3400, 2900, 1760, 1610, 1520, 1505, 1490, 1460 cm^{-1}. ^{1}H-NMR (100 MHz, pyridine-d_5) δ: 3.74 (6H, s, 2 × OCH_3), 5.00 (2H, d, *J* = 8 Hz, H-1″), 5.16 (1H, d, *J* = 4 Hz, H-1), 5.92 (2H, s, methylidene), 6.72 (2H, s, H-2′ and 6′), 6.55 (1H, s, H-5), 7.41 (1H, s, H-8). SIMS-MS *m/z*: 562 $(M+H)^+$, 383, 299, 229.

2-*N*-(Benzyloxycarbonyl)-2-deoxy-2-methylamino-L-glucopyranose (23)——To a solution of 2-deoxy-2-methylamino-L-glucopyranose hydrochloride[40] (23 g) and sodium carbonate (25 g) in a mixture of water (400 ml) and acetone (400 ml) was added dropwise a solution of benzyloxycarbonyl chloride (23 ml) in acetone (25 ml) at 0 °C, and then the mixture was stirred for 1 h. The insoluble inorganic matter was filtered off, and the filtrate was evaporated to give a solid. The solid was taken up in hot ethanol (300 ml), and the insoluble material was removed. Evaporation of the solution gave a solid, which was subjected to column chromatography on silica gel. Elution with chloroform–methanol (8 : 1) and evaporation afforded **23** as a colorless solid (25 g, 76%), $[\alpha]_D^{20}$ −33° (after 1 d) (*c* = 0.61, CH_3OH). IR (KBr): 3380, 2945, 1680, 1028 cm^{-1}. ^{1}H-NMR (90 MHz, pyridine-d_5–D_2O (10 : 1)): 3.20 and 3.30 (totally 3H, s each, NCH_3), 5.19 (2H, s, $C\underline{H}_2$-phenyl) and 7.2—7.6 (5H, m, phenyl). SIMS-MS *m/z*: 328 $(M+H)^+$, 310 $(M^+ - H_2O + H)$.

2-*N*-(Benzyloxycarbonyl)-2-deoxy-2-methylamino-4 : 6-*O*-ethylidene-L-glucopyranose (24)——A suspension of 2-*N*-(benzyloxycarbonyl)-2-deoxy-2-methylamino-L-glucose (**23**, 1 g) in paracetaldehyde (1.5 ml) was treated with conc. sulfuric acid (50 μl), and the mixture was stirred at room temperature for 3 h. The mixture was directly subjected to column chromatography on silica gel. Elution with chloroform–methanol (20 : 1) and evaporation gave a colorless solid (650 mg, 60%), $[\alpha]_D^{20}$ −18° (after 1 d) (*c* = 0.39, CH_3OH). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.36 (3H, d, *J* = 5 Hz, CH_3), 3.02 and 3.06 (totally 3H, s each, NCH_3), 5.15 (2H, s, $C\underline{H}_2$-phenyl), 7.2—7.5 (5H, m, phenyl). SIMS-MS *m/z*: 354 $(M+H)^+$, 336 $(M^+ - H_2O + H)$.

Benzyloxycarbonyl 2-*N*-(Benzyloxycarbonyl)-2-deoxy-2-methylamino-4 : 6-*O*-ethylidene-L-glucopyranoside (25) ——To a solution of **24** (600 mg) and benzyloxycarbonyl chloride (0.3 ml) in dioxane (6 ml) was added dropwise a 30% sodium hydroxide aqueous solution (0.4 ml), and the mixture was stirred at room temperature for 30 min. After being diluted with dichloromethane (20 ml), the solution was washed with water, dried over Na_2SO_4, and filtered. The filtrate was evaporated to give a solid, which was subjected to column chromatography on silica gel. Elution with toluene–acetone (9 : 1) and evaporation gave a colorless solid (360 mg, 43%), $[\alpha]_D^{24}$ −0.7° (c=0.44, CH_3OH). IR (KBr): 3450, 2890, 1761, 1697, 1260, 1090 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.33 (3H, d, J=5 Hz, –O–CH(C$\underline{H}_3$)O–), 2.97 (3H, s, N-Me), 4.70 (1H, q, J=5 Hz, –O–C$\underline{H}$(CH$_3$)–O–), 5.14 (4H, s, 2×C$\underline{H}_2$-phenyl), 7.1—7.6 (10H, m, 2×phenyl). SIMS-MS m/z: 488 $(M+H)^+$, 426, 354, 336.

Benzyloxycarbonyl 2-*N*-(Benzyloxycarbonyl)-3-*O*-chloroacetyl-2-deoxy-4 : 6-*O*-ethylidene-2-methylamino-L-glucopyranoside (26)——To a solution of **25** (530 mg) in a mixture of dichloromethane (5 ml) and pyridine (150 μl) was added dropwise chloroacetyl chloride (120 μl) at 0 °C, and then the mixture was stirred at 0 °C for 1 h. The solution was washed with water, dried over Na_2SO_4, and filtered. The filtrate was evaporated to give a solid, which was subjected to column chromatography on silica gel. Elution with toluene–acetone (9 : 1) and evaporation gave **26** as a colorless solid (555 mg, 93%), $[\alpha]_D^{24}$ +11° (c=0.35, CH_3OH). IR (KBr): 2960, 2890, 1764, 1703, 1262, 1102 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.29 (3H, d, J=5 Hz, –O–CH(C$\underline{H}_3$)–O–), 2.90 (3H, s, N–CH$_3$), 3.90 (2H, s, ClCH$_2$), 4.63 (1H, q, J=5 Hz, –O–C$\underline{H}$(CH$_3$)–O–), 5.14 (4H, s, 2×C$\underline{H}_2$-phenyl), 7.1—7.6 (10H, m, 2×phenyl). FD-MS m/z: 563 (M^+), 565.

2-*N*-(Benzyloxycarbonyl)-3-*O*-chloroacetyl-2-deoxy-2-methylamino-4 : 6-*O*-ethylidene-L-glucopyranose (27)—— A solution of **26** (525 mg) in acetone (30 ml) was stirred with 10% palladium on carbon (60 mg) at −15 °C under a hydrogen stream for 2 h. The palladium was filtered off, and the filtrate was evaporated to give **27** as a solid (373 mg, 93%), $[\alpha]_D^{26}$ +23° (after 1 d) (c=0.64, CH_3OH). IR (KBr): 3310, 1755, 1685, 1335, 1192, 1090 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.31 (3H, d, J=5 Hz, –O–CH(C$\underline{H}_3$)–O–), 2.92 and 2.95 (totally 3H, s each, N–CH$_3$), 3.93 (2H, s, ClCH$_2$), 4.68 (1H, q, J=5 Hz, –O–C$\underline{H}$(CH$_3$)–O–), 5.15 (2H, s, OC$\underline{H}_2$-phenyl), 7.2—7.6 (5H, m, phenyl). SIMS-MS m/z: 430 $(M-H)^+$, 432, 386, 322.

1-*O*-(2-Benzyloxycarbonylamino-2-deoxy-α-D-glucopyranosyl)-4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (14)—— mp 134—137 °C, $[\alpha]_D^{18}$ +75° (c=1.0, CH_3OH). IR (KBr): 3430, 1770, 1700, 1605, 1510 cm^{-1}. ^{1}H-NMR (90 MHz, Py-d_5) δ: 3.60 (6H, s, 2×OCH$_3$), 5.93 (2H, br s, methylidene), 6.63 (3H, s, H-5, 2′ and 6′), 7.2—7.8 (11H, m, 2×phenyl and H-8). FAB-MS m/z: 908 $(M^+ + H + DMSO)$, 830 $(M+H)^+$, 812, 607.

1-*O*-(2-Benzyloxycarbonylamino-2-deoxy-4 : 6-*O*-ethylidene-α-D-glucopyranosyl)-4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (15)——mp 146—148 °C, $[\alpha]_D^{17}$ +65° (c=0.7, $CHCl_3$). IR (KBr): 3450, 2920, 1780, 1705, 1605, 1510, 1490, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.30 (3H, d, J=5.4 Hz, CH$_3$), 3.68 (6H, s, 2×OCH$_3$), 5.97 (2H, br s, methylidene), 6.27 (2H, s, H-2′ and 6′), 6.50 (1H, s, H-5), 6.9 (1H, s, H-8), 7.2—7.6 (10H, m, 2×phenyl). FAB-MS m/z: 934 $(M^+ + H + DMSO)$, 878 $(M^+ + Na)$, 607.

1-*O*-(2-Amino-2-deoxy-4 : 6-*O*-ethylidene-α-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (16)——mp 225—227 °C, $[\alpha]_D^{21}$ +25° (c=0.83, $CHCl_3$). IR (KBr): 3420, 2990, 2900, 1770, 1610, 1520, 1510, 1490, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.33 (3H, d, J=5.4 Hz, CH$_3$), 5.77 (6H, s, 2×OCH$_3$), 5.00 (1H, d, J=3.8 Hz, H-1), 5.98 (2H, s, methylidene), 6.29 (2H, s, H-2′ and 6′), 6.52 (1H, s, H-5), 6.86 (1H, s, H-8). SIMS-MS m/z: 588 $(M+H)^+$, 383, 299, 229.

2,4,6-Tri-*O*-acetyl-3-benzyloxycarbonylamino-3-deoxy-β-D-glucopyranose (18)——mp 154—156 °C, $[\alpha]_D^{21}$ 0° (c=1.0, $CHCl_3$). IR (KBr): 3420, 3325, 2950, 1750, 1700, 1550 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.90, 1.97 and 2.05 (3H, s each, OAc), 4.75 (1H, d, J=7.8 Hz, H-1), 4.92 (1H, t, J=10.5 Hz, H-4), 5.09 (2H, s, COOC$\underline{H}_2$-phenyl), 7.35 (5H, s, phenyl). FAB-MS m/z: 462 $(M^+ + Na)$, 440 $(M+H)^+$, 422.

1-*O*-(2,4,6-Tri-*O*-acetyl-3-benzyloxycarbonylamino-3-deoxy-β-D-glucopyranosyl)-4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (19)——mp 251—254 °C, $[\alpha]_D^{19}$ −40° (c=0.9, $CHCl_3$). IR (KBr): 3420, 1755, 1730, 1605, 1540, 1510, 1490, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.77, 1.90 and 2.10 (3H, s each, OAc), 3.67 (6H, s, 2×OCH$_3$), 5.06 (2H, s, COOC$\underline{H}_2$-phenyl), 5.23 (2H, s, OC$\underline{H}_2$-phenyl), 6.0 (2H, s, methylidene), 6.28 (2H, s, H-2′ and 6′), 6.57 (1H, s, H-5), 6.87 (1H, s, H-8), 7.2—7.6 (10H, m, 2×phenyl). FAB-MS m/z: 1034 $(M^+ + H + DMSO)$, 978 $(M^+ + Na)$.

1-*O*-(2-*O*-Acetyl-3-benzyloxycarbonylamino-3-deoxy-4 : 6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (20)——mp 140—143 °C, $[\alpha]_D^{25}$ −36° (c=0.85, $CHCl_3$). IR (KBr): 3400, 2940, 2870, 1770, 1750, 1600, 1510, 1485, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.32 (3H, d, J=5.4 Hz, CH$_3$), 1.73 (3H, s, OAc), 3.68 (6H, s, 2×OCH$_3$), 5.10 (2H, s, COOC$\underline{H}_2$-phenyl), 5.28 (2H, s, OC$\underline{H}_2$-phenyl), 5.98 (2H, s, methylidene), 6.28 (2H, s, H-2′ and 6′), 6.53 (1H, s, H-5), 6.78 (1H, s, H-8), 7.2—7.5 (10H, m, 2×phenyl). FAB-MS m/z: 920 $(M^+ + Na)$, 786, 607.

1-*O*-(3-Amino-3-deoxy-4 : 6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (21)——mp 233—235 °C, $[\alpha]_D^{23}$ −95° (c=0.98, CH_3OH). IR (KBr): 3420, 2980, 2900, 1770, 1610, 1520, 1505, 1490, 1460, 1420 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.35 (3H, d, J=5.4 Hz, CH$_3$), 3.77 (6H, s, 2×OCH$_3$), 4.90 (1H, d, J=3.8 Hz, H-1), 5.97 (2H, br s, methylidene), 6.27 (2H, s, H-2′ and 6′), 6.55 (1H, s, H-5), 6.85 (1H, s, H-8). SIMS-MS m/z: 588 $(M+H)^+$, 383, 299, 229.

1-*O*-[2-*N*-(Benzyloxycarbonyl)-2-deoxy-4 : 6-*O*-ethylidene-2-methylamino-β- and α-L-glucopyranosyl]-4′-*O*-demethyl-1-epipodophyllotoxin (28 and 29)——**28**: mp 158—161 °C, $[\alpha]_D^{24}$ −19° (c=0.5; $CHCl_3$). IR (KBr): 3450, 2955, 2900, 1775, 1695, 1613, 1485, 1120 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.37 (3H, d, J=5 Hz, –OCH(C$\underline{H}_3$)O–), 3.04 (3H, s, NCH_3), 3.75 (6H, s, 2×OCH_3), 5.12 (2H, s, C$\underline{H}_2$-phenyl), 5.95 (2H, br s, methylidene), 6.27 (2H, s, H-2′ and 6′), 6.50 (1H, s, H-5), 6.99 (1H, s, H-8), 7.25—7.5 (5H, m, phenyl). SIMS-MS m/z: 736 $(M+H)^+$, 735, 473, 383.

29: mp 220—222 °C, $[\alpha]_D^{24}$ −141° (c=0.51, $CHCl_3$). IR (KBr): 3440, 2930, 2900, 1776, 1688, 1486, 1115 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.37 (3H, d, J=5 Hz, –OCH(C$\underline{H}_3$)O–), 2.71 (3H, s, NCH_3), 3.75 (6H, s, 2×OCH_3), 5.11 (2H, s, C$\underline{H}_2$-phenyl), 5.97 (2H, br s, methylidene), 6.25 (2H, s, H-2′ and 6′), 6.55 (1H, s, H-5), 6.78 (1H, s, H-8), 7.2—7.5 (5H). SIMS-MS m/z: 736 $(M+H)^+$, 735, 473, 383.

1-*O*-(2-Deoxy-4 : 6-*O*-ethylidene-2-methylamino-β-L-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (30)——mp 184—185 °C, $[\alpha]_D^{21}$ −42° (c=0.34, $CHCl_3$). IR (KBr): 3440, 2875, 1770, 1616, 1482, 1230, 1100 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.38 (3H, d, J=5 Hz, –OCH(C$\underline{H}_3$)O–), 2.46 (1H, dd, J=8, 10 Hz, H-2″), 2.55 (3H, s, NCH_3), 2.88 (1H, m, H-2), 3.29 (1H, dd, J=5, 14 Hz, H-3 overlapped with H-4″ and 5″), 3.54 (1H, t, J=10 Hz, H-3″), 3.69 (1H, t, J=10 Hz, H-6″), 3.77 (6H, s, 2×OCH_3), 4.22 (1H, dd, J=4, 10 Hz, H-6″), 4.33 (1H, d, J=8 Hz, H-1″), 4.35 (1H, t, J=8 Hz, H-11), 4.61 (1H, d, J=5 Hz, H-4), 4.70 (1H, dd, J=8, 11 Hz, H-11), 4.77 (1H, q, J=5 Hz, –OC$\underline{H}$(CH$_3$)O–), 4.94 (1H, d, J=3 Hz, H-1), 5.94 and 5.99 (1H, ABq, J=1 Hz, methylidene), 6.28 (2H, s, H-2′ and 6′), 6.50 (1H, s, H-5), 6.99 (1H, s, H-8). SIMS-MS m/z: 602 $(M+H)^+$, 383, 299, 229.

1-*O*-(2-Deoxy-4 : 6-*O*-ethylidene-2-methylamino-α-L-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (31)——mp 205—207 °C, $[\alpha]_D^{21}$ −156° (c=0.48, $CHCl_3$). IR (KBr): 3425, 2900, 1776, 1613, 1485, 1115 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.40 (3H, d, J=5 Hz, –OCH(C$\underline{H}_3$)O–), 2.13 (3H, s, NCH_3), 2.54 (1H, dd, J=4, 10 Hz, H-2″), 3.00 (1H, m, H-2), 3.38 (2H, m, H-3 and 4″), 3.52 (1H, m, H-5″), 3.62 (2H, m, H-3″ and 6″), 3.77 (6H, s, 2×OCH_3), 4.16 (1H, dd, J=5, 10 Hz, H-6″), 4.37 (2H, m, H-11), 4.65 (1H, d, J=5.5 Hz, H-4), 4.79 (1H, q, J=5 Hz, –OC$\underline{H}$(CH$_3$)O–), 4.85 (1H, d, J=3 Hz, H-1), 5.20 (1H, d, J=4 Hz, H-1″), 5.99 and 6.00 (2H, ABq, J=1 Hz, methylidene), 6.22 (2H, s, H-2′ and 6′), 6.60 (1H, s, H-5), 6.86 (1H, s, H-8). SIMS-MS m/z: 602 $(M-H)^+$, 383, 299, 229.

1-*O*-(2-Deoxy-2-methylamino-β-L-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (32)——mp 181—185 °C, $[\alpha]_D^{20}$ −53° (c=0.32, CH_3OH). ^{1}H-NMR (90 MHz, $CDCl_3$–pyridine-d_5 (10 : 1)) δ: 2.53 (3H, s, NCH_3), 3.73 (6H, s, 2×OCH_3), 4.63 (1H, d, J=5 Hz, H-4), 4.99 (1H, d, J=3 Hz, H-1), 5.87 and 5.97 (totally 2H, br s each, methylidene), 6.33 (2H, s, H-2′ and 6′), 6.51 (1H, s, H-5), 7.22 (1H, s, H-8). FAB-MS m/z: 576 $(M+H)^+$, 383.

1-*O*-(2-Deoxy-2-methylamino-α-L-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (33)——mp 220—226 °C (dec.), $[\alpha]_D^{23}$ −125° (c=0.26, CH_3OH). ^{1}H-NMR (90 MHz, $CDCl_3$–pyridine-d_5 (10 : 1)) δ: 2.16 (3H, s, N–CH_3), 3.72 (6H, s, 2×OCH_3), 4.66 (1H, d, J=5 Hz, H-4), 4.97 (1H, d, J=3 Hz, H-1), 5.27 (1H, d, J=4 Hz, H-1″), 5.93 (2H, s, methylidene), 6.32 (2H, s, H-2″ and 6′), 6.62 (1H, s, H-5), 7.02 (1H, s, H-8). FAB-MS m/z: 576 $(M+H)^+$, 383.

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