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Studies on Lignan Lactone Antitumor Agents. II. Synthesis of *N*-Alkylamino- and 2,6-Dideoxy-2-aminoglycosidic Lignan Variants Related to Podophyllotoxin

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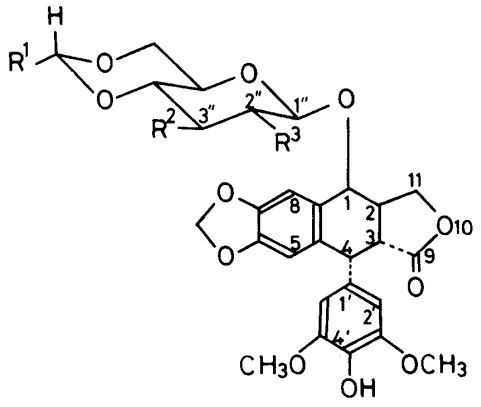
D-(and L-)2,6-Dideoxy-2-aminoglycosidic variants of 4′-*O*-demethyl-1-epipodophyllotoxin were synthesized by glycosidation of 4′-*O*-benzyloxycarbonyl- or 4′-*O*-chloroacetyl-4′-*O*-demethyl-1-epipodophyllotoxin (**6** or **14**) with the corresponding aminosugar derivatives. 1-*O*-(2-Amino-2-deoxy-4:6-*O*-ethylidene-*β*-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (**18**) reacted with aldehydes in the presence of sodium cyanoborohydride, or reacted with *α*,*β*-unsaturated esters, or with *α*,*β*-unsaturated nitriles to yield the corresponding *N*-alkyl analogs. A number of the 4′-*O*-demethyl-1-epipodophyllotoxin *β*-D-aminoglycoside derivatives gave significant survival time increases in mice with leukemia L-1210. In particular, 1-*O*-(2-dimethylamino-2-deoxy-4:6-*O*-ethylidene-*β*-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (**19**) showed superior activity to VP-16-213 (etoposide, **1**).

Keywords——1-*O*-(2-amino-2,6-dideoxy-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin; 1-*O*-(2,6-dideoxy-2-methylamino-L-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin; 1-*O*-(2-*N*-alkyl-2-deoxy-4:6-*O*-ethylidene-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin; 1-*O*-(2-deoxy-2-*N*-dialkyl-4:6-*O*-ethylidene-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin

Systematic chemical modification of the podophyllotoxin glycosides has led to the clinically useful analogues, VP-16-213 (etoposide, **1**) and VM-26 (teniposide, **2**).[1-6] In the preceding article in this issue, we reported the syntheses of 2-amino-D-, 3-amino-D- and 2-methylamino-L-glucosidic variants of podophyllotoxin based on the replacement of the sugar moiety of VP-16-213 with an aminosugar derivative. 2-Amino- and 3-amino-*β*-D-glucosidic variants (**3** and **4**) were found to have superior activity to **1** in the mouse leukemia L-1210 test.



1: VP-16-213 (etoposide); $R^1=CH_3$, $R^2=R^3=OH$

2: VM-26 (teniposide); $R^1=$  , $R^2=R^3=OH$

3: $R^1=CH_3$, $R^2=OH$, $R^3=NH_2$

4: $R^1=CH_3$, $R^2=NH_2$, $R^3=OH$

Fig. 1

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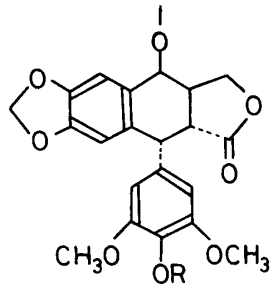
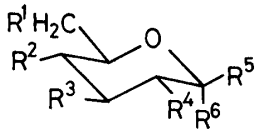
In view of these results, we are interested in further modification of the sugar moiety of **3** and **4**.

In order to study the effect of the 4:6-*O*-ethylidene group on antitumor activity, the podophyllotoxin 2-amino-2,6-dideoxy-D- and 2,6-dideoxy-2-methylamino-L-glucoside analogues were synthesized. 3,4-Di-*O*-acetyl-2-benzyloxycarbonylamino-2,6-dideoxy-D-glucopyranose (**5**) was prepared from D-glucosamine in the usual way (8 steps).[7] Condensation of 4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (**6**) with **5** in dichloromethane in the presence of boron trifluoride etherate[8] afforded the corresponding α- and β-D-glucopyranosides (**7** and **8**) in yields of 17 and 75%, respectively. Acetyl groups of **7** and **8** were removed with zinc acetate in methanol under reflux, and the subsequent hydrogenolysis of each isomer with a palladium black catalyst gave the final products, 1-*O*-(2-amino-2,6-dideoxy-α-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (**9**) and its β-isomer (**10**). On the other hand, 3,4-di-*O*-acetyl-2-*N*-(benzyloxycarbonyl)-2,6-dideoxy-2-methylamino-L-glucopyranose (**13**) was prepared from 2-deoxy-2-methylamino-L-glucopyranose.[9] Treatment of 2-*N*-(benzyloxycarbonyl)-2-deoxy-2-methylamino-L-glucopyranose with *p*-toluenesulfonyl chloride in pyridine followed by acetylation with acetic





X_1: R=Z
X_2: R=$COCH_2Cl$
X_3: R=H
6: X_1H
14: X_2H

5: R^1=H, R^2=R^3=OAc, R^4=NHZ, R^5,R^6=H,OH
7: R^1=R^5=H, R^2=R^3=OAc, R^4=NHZ, R^6=X_1
8: R^1=R^6=H, R^2=R^3=OAc, R^4=NHZ, R^5=X_1
9: R^1=R^5=H, R^2=R^3=OH, R^4=NH_2, R^6=X_3
10: R^1=R^6=H, R^2=R^3=OH, R^4=NH_2, R^5=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=O(O)>CH_3, R^3=OH, R^4=NH_2, R^5=X_3, R^6=H
19: R^1,R^2=O(O)>CH_3, R^3=OH, R^4=$N(CH_3)_2$, R^5=X_3, R^6=H
20: R^1,R^2=O(O)>CH_3, R^3=OH, R^4=NHC_2H_5, R^5=X_3, R^6=H
21: R^1,R^2=O(O)>CH_3, R^3=OH, R^4=$N(C_2H_5)_2$, R^5=X_3, R^6=H
22: R^1,R^2=O(O)>CH_3, R^3=OH, R^4=$NH(CH_2)_3CH_3$, R^5=X_3, R^6=H
23: R^1,R^2=O(O)>CH_3, R^3=OH, R^4=$N[(CH_2)_3CH_3]_2$, R^5=X_3, R^6=H
24: R^1,R^2=O(O)>CH_3, R^3=OH, R^4=$NHCH_2CH_2Cl$, R^5=X_3, R^6=H
25: R^1,R^2=O(O)>CH_3, R^3=OH, R^4=$NHCH_2\overset{(R)}{C}H(OH)CH_2OH$, R^5=X_3, R^6=H
26: R^1,R^2=O(O)>CH_3, R^3=OH, R^4=$NHCH_2\overset{(S)}{C}H(OH)CH_2OH$, R^5=X_3, R^6=H
27: R^1,R^2=O(O)>CH_3, R^3=OH, R^4=$NHCH_2CH_2CN$, R^5=X_3, R^6=H
28: R^1,R^2=O(O)>CH_3, R^3=OH, R^4=$NHCH_2CH_2CO_2Et$, R^5=X_3, R^6=H

Chart 1

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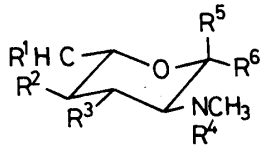

11: $R^1=H$, $R^2=R^3=OAc$, $R^4=Z$, R^5,$R^6=H$,OAc
12: $R^1=H$, $R^2=R^3=OAc$, $R^4=Z$, $R^5=R^6=H$,OAc
13: $R^1=H$, $R^2=R^3=OAc$, $R^4=Z$, $R^5=R^6=H$,OH
15: $R^1=R^4=R^5=H$, $R^2=R^3=OH$, $R^6=X_3$
16: $R^1=R^4=R^6=H$, $R^2=R^3=OH$, $R^5=X_3$

Chart 2

TABLE I. The Antitumor Activities of VP-16-213 (**1**) and Aminoglycosidic Variants of Podophyllotoxin (T/C%)

Dose (μg/mouse)	Compound No.															
	1	**3**	**9**	**10**	**15**	**16**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
25	184	272	95	84	82	94	438	143	95	138	113	154	93	107	96	96
6.25	139	133	95	101	88	82	164	107	101	100	94	109	107	93	114	108

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.

anhydride gave the corresponding crude product. Treatment of the product with sodium iodide in *N*,*N*-dimethylformamide afforded 1,3,4-tri-*O*-acetyl-2-*N*-(benzyloxycarbonyl)-2,6-dideoxy-2-methylamino-6-iodo-L-glucopyranose (**11**). The selective hydrogenolysis of **11** with Raney Ni in ethanol gave the corresponding deoxysugar (**12**). Hydrolysis of **12** with a mixture of hydrochloric acid and acetic acid afforded **13**. The syntheses of (2,6-dideoxy-2-methylamino-β-L-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (**15**) and its α-L-isomer (**16**) starting from 4′-*O*-chloroacetyl-4′-*O*-demethyl-1-epipodophyllotoxin (**14**) and **13** were carried out similarly.

In relation to these syntheses, we were interested in the effect of *N*-alkyl substituents of 2-aminosugar analogues on the antitumor activity. *N*-Alkylation was generally achieved by reaction of 1-*O*-(2-amino-2-deoxy-4:6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (**18**)[10] with the corresponding aldehydes in the presence of sodium cyanoborohydride, or by Michael reaction with the corresponding α,β-unsaturated esters or α,β-unsaturated nitriles. In some cases, both mono- and dialkyl derivatives were obtained.

The antitumor activity of the synthesized compounds against mouse leukemia L-1210 is shown in Table I. A number of 1-*O*-(2-*N*-alkyl and 2-*N*-dialkyl-2-deoxy-4:6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxins produced significant survival time increases in the lymphocytic leukemia L-1210 test, while 1-*O*-(2-amino-2,6-dideoxy-D- and 2,6-dideoxy-2-methylamino-L-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin did not show a significant antitumor effect. This indicates that the cyclic acetal group of the sugar moiety is important for the antitumor activity. Among all derivatives synthesized, compound **19** showed the best antitumor activity, and was found to have superior activity to VP-16-213 (etoposide, **1**).

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 recorded 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 (MS) 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).

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Typical Experimental Procedures

3,4-Di-*O*-acetyl-2-benzyloxycarbonylamino-2,6-dideoxy-D-glucopyranose (5)——1,3,4-Tri-*O*-acetyl-2-benzyloxycarbonylamino-2,6-dideoxy-β-D-glucopyranose[11] (500 mg) was dissolved in a mixture of methanol (10 ml), 1 M hydrochloric acid (4 ml) and acetic acid (1 ml), and the mixture was stirred in the refrigerator overnight. Evaporation of the solvent gave an oil, which was subjected to column chromatography on silica gel. Elution with toluene–acetone (5 : 1) and evaporation gave **5** as an oil (277 mg, 62%). IR (KBr): 3420 (br), 1750 (br), 1450 (br) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.16 (3H, d, J=6.9 Hz, CH_3), 1.90 and 2.02 (3H, s each, 2 × OAc), 7.33 (5H, s, phenyl). FAB-MS m/z: 404 (M^+ + Na), 382 $(M+H)^+$, 364.

1-*O*-(3,4-Di-*O*-acetyl-2-benzyloxycarbonylamino-2,6-dideoxy-α- and β-D-glucopyranosyl)-4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (7 and 8)——To a solution of a mixture of 4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (360 mg, **6**) and **5** (230 mg) was added dropwise boron trifluoride etherate (0.3 ml) at −18 °C, and the mixture was stirred at −18 °C for 30 min. After being quenched with pyridine (0.3 ml) and added dichloromethane (20 ml), 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 **7** and **8** as solids in yields of 17 and 75%, respectively. Each solid was crystallized from methanol to give colorless crystals.

7: mp 145—147 °C, $[\alpha]_D^{22}$ +61° (c=0.92, $CHCl_3$). IR (KBr): 3450, 1760, 1720, 1605, 1510, 1490, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.15 (3H, d, J=6.5 Hz, CH_3), 1.91 and 2.00 (3H, s each, OAc), 3.70 (6H, s, 2 × OCH_3), 5.99 (2H, s, methylidene), 6.27 (2H, s, H-2′ and 6′), 6.53 (1H, s, H-5), 6.86 (1H, s, H-8). FAB-MS m/z: 920 (M^+ + Na), 898 $(M+H)^+$.

8: mp 136—138 °C, $[\alpha]_D^{22}$ −29° (c=0.96, $CHCl_3$). IR (KBr): 3450, 1770, 1690, 1610, 1510, 1490, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.28 (3H, d, J=6.6 Hz, CH_3), 1.96 and 2.03 (3H, s each, 2 × OAc), 3.70 (6H, s, 2 × OCH_3), 5.88 (2H, d, J=10.8 Hz, methylidene), 6.27 (2H, s, H-2′ and 6′), 6.56 (1H, s, H-5), 6.77 (1H, s, H-8). FAB-MS m/z: 920 (M^+ + Na).

1-*O*-(2-Amino-2,6-dideoxy-α-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (9)——A solution of **7** (60 mg) in. methanol (5 ml) was refluxed in the presence of zinc acetate (15 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. A solution of the solid in a mixture of ethyl acetate (1 ml) and methanol (1 ml) was stirred with palladium black (5 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 **9** (28 mg, 77%), which was recrystallized from methanol, mp 210—213 °C (dec.), $[\alpha]_D^{24}$ +30° (c=1.0, $CHCl_3$–CH_3OH (1 : 1)). IR (KBr): 3400, 2900, 1760, 1610, 1520, 1500, 1485, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, pyridine-d_5) δ: 1.72 (3H, d, J=7.5 Hz, CH_3), 3.77 (6H, s, 2 × OCH_3), 5.00 (1H, d, J=3.8 Hz, H-1), 5.95 (2H, s, methylidene), 6.77 (2H, s, H-2′ and 6′), 7.25 (1H, s, H-8). FAB-MS m/z: 568 (M^+ + Na), 546 $(M+H)^+$, 299.

1,3,4-Tri-*O*-acetyl-2-*N*-(benzyloxycarbonyl)-2,6-dideoxy-2-methylamino-6-iodo-L-glucopyranose (11)——To a solution of 2-*N*-(benzyloxycarbonyl)-2-deoxy-2-methylamino-L-glucopyranose (6.6 g) in pyridine (100 ml) was added *p*-toluenesulfonyl chloride (4.0 g) at −40 °C, and the mixture was allowed to warm from −40 °C to 0 °C under stirring, and further stirred at 0 °C for 3 h. Then acetic anhydride (10 ml) was added at 0 °C, and the whole was allowed to warm from 0 °C to room temperature under stirring. After being quenched with water, the reaction mixture was diluted with chloroform (100 ml). The solution was washed with 10% potassium bisulfate aqueous solution and 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 afforded a crude product (6 g), which was dissolved in *N*,*N*-dimethylformamide (60 ml). To the solution was added sodium iodide (6 g), and the mixture was stirred at 120 °C for 2 h. After being quenched with water, the solution was evaporated to give a solid, which was dissolved in chloroform (100 ml). The solution was washed with water, 10% sodium hydrosulfite aqueous solution and water again, 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 (12 : 1) and evaporation gave **11** as a colorless solid (3.7 g, 33% for 2 steps), $[\alpha]_D^{21}$ −39.5° (c=0.79, $CHCl_3$). IR (KBr): 2950, 1760, 1708, 1375, 1220 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.87 (3H, s, acetyl), 2.03 (6H, s, 2 × acetyl), 2.84 (3H, s, NCH_3), 5.17 (2H, s, CH_2-phenyl), 7.2—7.5 (5H, m, phenyl). SIMS-MS m/z: 564 $(M+H)^+$, 504.

1,3,4-Tri-*O*-acetyl-2-*N*-(benzyloxycarbonyl)-2,6-dideoxy-2-methylamino-L-glucopyranose (12)——A solution of **11** (3.5 g) in ethanol (50 ml) was stirred with Raney Ni (1 g) under a hydrogen stream for 3 h. Raney Ni was removed by filtration, and the residue was washed with ethanol. The filtrate and washings were combined and evaporated to give a solid, which was subjected to column chromatography on silica gel. Elution with toluene–acetone (12 : 1) and evaporation gave a colorless solid (2.4 g, 88%), $[\alpha]_D^{25}$ −43° (c=0.65, $CHCl_3$). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.23 (3H, d, J=6 Hz, CH_3), 1.89 (3H, s, acetyl), 2.02 (6H, s, 2 × acetyl), 2.85 (3H, s, NCH_3), 5.18 (2H, s, CH_2-phenyl) and 7.2—7.5 (5H, m, phenyl). SIMS-MS m/z: 438 $(M+H)^+$, 378, 318.

1-*O*-(2-Dimethylamino-2-deoxy-4 : 6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (19)——To a solution of 1-*O*-(2-amino-2-deoxy-4 : 6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyl-

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lotoxin (**18**) (30 mg) in acetonitrile (0.6 ml) was added 37% aqueous solution of formaldehyde (5 μl) and sodium cyanoborohydride (10 mg), and the mixture was stirred at room temperature for 30 min. After being diluted with dichloromethane (10 ml), the solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a solid, which was subjected to preparative thin-layer chromatography on silica gel developed with chloroform–methanol (7 : 1). The solid obtained was recrystallized from acetone to give colorless crystals of **19** (22 mg, 70%), mp 196—198 °C, $[\alpha]_D^{21}$ −107° (c=0.78, $CHCl_3$). IR (KBr): 3450, 2900 (br), 1775, 1610, 1520, 1505, 1490, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.40 (3H, d, J=5.6 Hz, CH_3), 2.27 (6H, s, $N(CH_3)_2$), 3.76 (6H, s, 2×OCH_3), 4.99 (1H, d, J=3.8 Hz, H-1), 6.02 (2H, s, methylidene), 6.28 (2H, s, H-2′ and 6′), 6.58 (1H, s, H-5), 6.76 (1H, s, H-8). SIMS-MS m/z: 616 $(M+H)^+$, 383, 299, 232.

1-*O*-(2-Chloroethylamino-2-deoxy-4 : 6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (24)——A solution of chloroacetaldehyde diethyl acetal (0.3 ml) in acetone (0.5 ml) was refluxed with 2 M hydrochloric acid (0.2 ml) for 1 h. To the solution thus obtained, a solution of **18** (30 mg) in acetonitrile (1 ml) and sodium cyanoborohydride (15 mg) were added, and the mixture was stirred at room temperature for 20 min. After being neutralized with saturated aqueous sodium bicarbonate and diluted with dichloromethane, the solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a solid, which was subjected to preparative thin-layer chromatography developed with chloroform–methanol (7 : 1). Compound **24** was obtained as a solid in a yield of 42%, mp 195—199 °C (dec.), $[\alpha]_D^{17}$ −77° (c=0.95, $CHCl_3$). IR (KBr): 3450, 2880, 1770, 1610, 1510, 1500, 1480, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.38 (3H, d, J=5.4 Hz, CH_3), 3.77 (6H, s, 2×OCH_3), 4.95 (1H, d, J=3.8 Hz, H-1), 4.99 (2H, br s, methylidene), 6.27 (2H, H-2′ and 6′), 6.57 (1H, s, H-5), 6.83 (1H, s, H-8). SIMS-MS m/z: 650 $(M+H)^+$, 383, 367, 299, 229.

1-*O*-(2-Cyanoethylamino-2-deoxy-4 : 6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (27)——To a solution of **17** (25 mg) in a mixture of methanol (1 ml) and acetone (1 ml) was added acrylonitrile (0.5 ml), and the mixture was refluxed for 3 h. Evaporation of the solvent gave a solid, which was dissolved in acetonitrile (1 ml). Then acetaldehyde diethyl acetal (0.5 ml) and *p*-toluenesulfonic acid (2 mg) were added, and the mixture was stirred at room temperature for 1 h. Evaporation of the solvent gave a solid, which was dissolved in dichloromethane. The solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a solid, which was subjected to preparative thin-layer chromatography on silica gel developed with chloroform–methanol (10 : 1). Compound **27** was obtained as a colorless solid in a yield of 63%, mp 232—236 °C, $[\alpha]_D^{19}$ −75° (c=0.92, $CHCl_3$). IR (KBr): 3450, 1765, 1610, 1520, 1510, 1490 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.37 (3H, d, J=5.4 Hz, CH_3), 3.76 (6H, s, 2×OCH_3), 4.88 (1H, d, J=3.8 Hz, H-1), 6.00 (2H, s, methylidene), 6.27 (2H, s, H-2′ and 6′), 6.57 (1H, s, H-5), 6.85 (1H, s, H-8). SIMS-MS m/z: 641 $(M+H)^+$, 383, 367, 309, 229.

1-*O*-[2-Deoxy-2-(ethoxycarbonyl)ethylamino-4 : 6-*O*-ethylidene-β-D-glucopyranosyl]-4′-*O*-demethyl-1-epipodophyllotoxin (28)——To a solution of **17** (20 mg) in methanol (2 ml) was added ethyl acrylate (0.5 ml), and the mixture was stirred at 70 °C for 4 h. Evaporation of the solvent gave a crude product, which was used directly in the next step. The 4 : 6-*O*-ethylidene group of the sugar moiety was introduced in the same manner as described above. Compound **28** was obtained as a colorless solid in a yield of 56%, mp 212—214 °C, $[\alpha]_D^{17}$ −84° (c=1.0, $CHCl_3$). IR (KBr): 3480, 2900, 1770, 1710, 1520, 1490, 1460 cm^{-1}. ^{1}H-NMR (90 MHz, pyridine-d_5) δ: 1.45 (3H, t, J=7.5 Hz, $-CH_2\underline{CH_3}$), 1.38 (3H, d, J=5.4 Hz, CH_3), 3.76 (6H, s, 2×OCH_3), 5.05 (1H, d, J=3.6 Hz, H-1), 6.00 (2H, br s, methylidene), 6.77 (2H, s, H-2′ and 6′), 6.82 (1H, s, H-5) and 7.31 (1H, s, H-8′). SIMS-MS m/z: 688 $(M+H)^+$, 383, 299, 229.

1-*O*-(2-Amino-2,6-dideoxy-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (10)——mp 221—224 °C, $[\alpha]_D^{23}$ −106° (c=1.0, $CHCl_3$). IR (KBr): 3420, 2920, 1765, 1610, 1520, 1510, 1490, 1490 cm^{-1}. ^{1}H-NMR (90 MHz, pyridine-d_5) δ: 1.57 (3H, d, J=5.4 Hz, CH_3), 3.76 (6H, s, 2×OCH_3), 5.07 (1H, d, J=3.8H, H-1), 5.93 (2H, s, methylidene), 6.78 (3H, s, H-5, 2′ and 6′), 7.33 (1H, s, H-8). FAB-MS m/z: 568 $(M^+ + Na)$, 546 $(M+H)^+$, 299.

3,4-Di-*O*-acetyl-2′-*N*-(benzyloxycarbonyl)-2,6-dideoxy-2-methylamino-L-glucopyranose (13)——$[\alpha]_D^{20}$ −35.4° (after 1 d) (c=1.0, $CHCl_3$). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.23 (3H, d, J=6 Hz, CH_3), 1.92 (3H, s, acetyl), 2.02 (6H, s, 2× acetyl), 2.93 (3H, s, NCH_3), 5.17 (2H, s, $C\underline{H}_2$-phenyl), 7.2—7.5 (5H, m, phenyl). SIMS-MS m/z: 396 $(M+H)^+$, 378 $(M^+ + H - H_2O)$, 318.

1-*O*-(2,6-Dideoxy-2-methylamino-β- and α-L-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (15 and 16)——**15**: mp 212—220 °C (dec.), $[\alpha]_D^{22}$ −45° (c=0.47, CH_3OH). IR (KBr): 3475, 2903, 1762, 1615, 1486, 1238 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$–pyridine-d_5 (5 : 1)) δ: 1.45 (3H, d, J=6 Hz, CH_3), 2.57 (3H, s, NCH_3), 3.73 (6H, s, 2×OCH_3), 5.00 (1H, d, J=3 Hz, H-1), 5.93 (2H, m, methylidene), 6.34 (2H, s, H-2′ and 6′), 6.52 (1H, s, H-5), 7.23 (1H, s, H-8). FAB-MS m/z: 560 $(M+H)^+$, 383.

16: mp 166—170 °C, $[\alpha]_D^{23}$ −119° (c=0.50, CH_3OH). IR (KBr): 3420, 2910, 1773, 1615, 1490, 1238, 1040 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.37 (3H, d, J=6 Hz, CH_3), 2.12 (3H, s, NCH_3), 3.77 (6H, s, 2×OCH_3), 4.65 (1H, d, J=5.5 Hz, H-4), 4.86 (1H, d, J=3 Hz, H-1), 5.17 (1H, d, J=4 Hz, H-1″), 6.00 (2H, s, methylidene), 6.25 (2H, s, H-2′ and 6′), 6.60 (1H, s, H-5), 6.94 (1H, s, H-8). FAB-MS m/z: 560 $(M+H)^+$, 383.

1-*O*-(2-Ethylamino-2-deoxy-4 : 6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (20)——mp 234—238 °C (dec.), $[\alpha]_D^{27}$ −90° (c=1.0, $CHCl_3$). IR (KBr): 3400, 2900, 1760 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.90 (3H, t, J=7.2 Hz, $-CH_2\underline{CH_3}$), 1.38 (3H, d, J=5.6 Hz, CH_3), 3.77 (6H, s, 2×OCH_3), 4.95 (1H, d, J=3.8 Hz, H-1), 5.97 (2H, br s, methylidene), 6.27 (2H, s, H-2′ and 6′), 6.57 (1H, s, H-5), 6.83 (1H, s, H-8). SIMS-MS m/z: 616

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$(M+H)^+$, 383, 299, 229.

1-*O*-(2-Diethylamino-2-deoxy-4 : 6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-1-epipodophyllotoxin (21) ——mp 148—150 °C, $[\alpha]_D^{27}$ −93° (*c* = 0.69, $CHCl_3$). IR (KBr): 3420, 2920, 1760 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.95 (6H, t, *J* = 7.2 Hz, $N(CH_2CH_3)_2$), 1.40 (3H, d, *J* = 5.4 Hz, CH_3), 3.77 (6H, s, 2 × OCH_3), 4.99 (1H, d, *J* = 3.7 Hz, H-1), 6.02 (2H, s, methylidene), 6.25 (2H, s, H-2′ and 6′), 6.62 (1H, s, H-5), 6.75 (1H, s, H-8). SIMS-MS *m/z*: 644 $(M+H)^+$, 383, 299, 260, 229.

1-*O*-[2-(*n*-Butylamino)-2-deoxy-4 : 6-*O*-ethylidene-β-D-glucopyranosyl]-4′-*O*-demethyl-1-epipodophyllotoxin (22) ——mp 143—145 °C, $[\alpha]_D^{17}$ −67° (*c* = 1.0, $CHCl_3$). IR (KBr): 3450, 2930, 2870, 1780 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.38 (3H, d, *J* = 5.4 Hz, CH_3), 3.77 (6H, s, 2 × OCH_3), 4.92 (1H, d, *J* = 3.8 Hz, H-1), 6.00 (2H, br s, methylidene), 6.27 (2H, s, H-2′ and 6′), 6.57 (1H, s, H-5), 6.84 (1H, s, H-8). SIMS-MS *m/z*: 644 $(M+H)^+$, 383, 299, 260, 229.

1-*O*-[2-Di(*n*-butylamino)-2-deoxy-4 : 6-*O*-ethylidene-β-D-glucopyranosyl]-4′-*O*-demethyl-1-epipodophyllotoxin (23)——mp 128—129 °C, $[\alpha]_D^{27}$ −65° (*c* = 0.75, $CHCl_3$). IR (KBr): 3430, 2930, 2870, 1780 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.40 (3H, d, *J* = 5.4 Hz, CH_3), 3.77 (6H, s, 2 × OCH_3), 4.96 (1H, d, *J* = 3.8 Hz, H-1), 6.00 (2H, s, methylidene), 6.25 (2H, s, H-2′ and 6′), 6.62 (1H, s, H-5), 6.75 (1H, s, H-8). SIMS-MS *m/z*: 700 $(M+H)^+$, 383, 316, 229.

1-*O*-[2-Deoxy-2-((2*R*,3)-dihydroxypropyl)amino-4 : 6-*O*-ethylidene-β-D-glucopyranosyl]-4′-*O*-demethyl-1-epipodophyllotoxin (25)——mp 160—163 °C, $[\alpha]_D^{21}$ −81° (*c* = 1.0, $CHCl_3$–CH_3OH (1 : 1)). IR (KBr): 3440, 2910, 1770, 1620, 1520, 1505, 1490 cm^{-1}. ^{1}H-NMR (90 MHz, pyridine-d_5) δ: 1.38 (3H, d, *J* = 5.4 Hz, CH_3), 3.73 (6H, s, 2 × OCH_3), 5.07 (1H, d, *J* = 3.8 Hz, H-1), 6.00 (1H, d, *J* = 5.7 Hz, methylidene), 6.75 (3H, br s, H-5, 2′ and 6′), 7.35 (1H, s, H-8). SIMS-MS *m/z*: 662 $(M+H)^+$, 383, 299, 229.

1-*O*-[2-Deoxy-2-((2*S*,1)-dihydroxypropyl)amino-4:6-*O*-ethylidene-β-D-glucopyranosyl]-4′-*O*-demethyl-1-epipodophyllotoxin (26)——mp 159—161 °C, $[\alpha]_D^{22}$ −93° (*c* = 0.95, $CHCl_3$–CH_3OH (1 : 1)). IR (KBr): 3450, 2900, 1770, 1620, 1520, 1510, 1490 cm^{-1}. ^{1}H-NMR (90 MHz, pyridine-d_5) δ: 1.40 (3H, d, *J* = 5.4 Hz, CH_3), 3.75 (6H, s, 2 × OCH_3), 5.10 (1H, d, *J* = 3.8 Hz, H-1), 5.97 (1H, s, methylidene), 6.73 (3H, br s, H-5, 2′ and 6′), 7.30 (1H, s, H-8). SIMS-MS *m/z*: 662 $(M+H)^+$, 383, 299, 229.

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