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Studies on Lignan Lactone Antitumor Agents. V. 1-*O*-(Aminoethyl) Ether of 4′-*O*-Demethyl-1-epipodophyllotoxin

Hitoshi SAITO, Yoshio NISHIMURA,* Shinichi KONDO, Keiko KOMURO, and Tomio TAKEUCHI
Institute of Microbial Chemistry, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141
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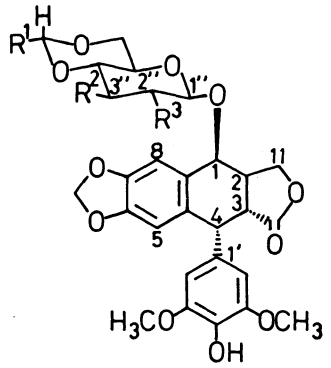
1-*O*-(2-Aminoethyl)-4′-*O*-demethyl-1-epipodophyllotoxin derivatives were synthesized by a stereoselective BF_3-catalyzed coupling of 4′-*O*-benzyloxycarbonyl-1-epipodophyllotoxin with the corresponding 2-aminoethanol derivatives, and with ethylene glycol followed by reductive amination of its aldehyde. Some 1-*O*-(2-aminoethyl) ethers of 4′-*O*-demethyl-1-epipodophyllotoxin prolonged markedly survival periods in mice with leukemia L-1210.

Due to the clinical efficacy and intriguing mechanism of action, the synthetic podophyllotoxin glycosides, VP-16-213 (**1**) and VM-26 (**2**)[1,2] have attracted considerable interest in the synthesis of new active analogues of podophyllotoxin. In the previous paper of this series,[3-5] the systematic chemical modification of podophyllotoxin and α-peltatin based on glycosidation with amino sugar derivatives were reported. 2-Amino-, 3-amino-, and 2-dimethylamino-β-D-glucosidic variants (**3**, **4**, and **5**) were found to have the superior antitumor activity to **1**.

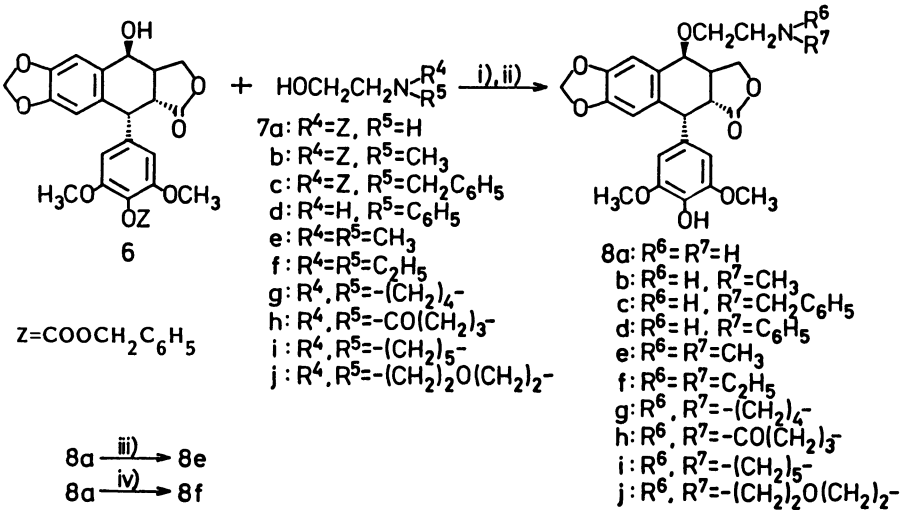
Changes in the 1-*O*-glycosyl group are also interest for simplified structure which might retain the activity of **3**, **4**, and **5**, and be accessible to practical industrialization. The basic amino substituent of the sugar moiety is proved to be important for increasing the activity, but considerable simplification in the sugar structure might be permitted so long as the amino group is retained in the same distance from the linkage at C-1. In the chemical modification of podophyllotoxin glycosides, it also appears that β-configuration at C-1 of aglycone, podophyllotoxin, is indispensable for increasing an antitumor activity and decreasing a toxic side effect.[1]

Here we wish to present the synthesis of 1-*O*-(aminoethyl)-4′-*O*-demethyl-1-epipodophyllotoxin derivatives (**8a—8j** and **12k—12m**) having a β-configuration at C-1, and their biological activities. Acid-catalyzed coupling using boron trifluoride diethyl etherate, as a key step, was successfully used in these syntheses. The synthesis was achieved by the following three methods. Condensation of 4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (**6**) with 2-(benzyloxycarbonylamino)ethanol analogues (**7a**, **7b**, and **7c**) in dichloromethane in the presence of $BF_3 \cdot OEt_2$,[6,7] followed by removal of the masking groups gave the corresponding 1-*O*-(2-aminoethyl)-4′-*O*-demethyl-1-epipodophyllotoxins (**8a**, **8b** and **8c**), respectively, in good yields. Compound **8a** was further transformed into dimethylamino and diethylamino derivatives **8e** and **8f** upon a reductive amination with the corresponding aldehydes using sodium cyanotrihydroborate.[8] Alternative BF_3-catalyzed coupling was successfully accomplished when **6** was added into a solution of 2-(phenylamino)-ethanol (**7d**) and 2-(dialkylamino)ethanol analogues (**7e—7j**) with $BF_3 \cdot OEt_2$ in dichloromethane. Thus, 1-*O*-[2-(phenylamino)ethyl]-4′-*O*-demethyl-1-epipodophyllotoxin (**8d**) and 1-*O*-[2-(dialkylamino)ethyl]-4′-*O*-demethyl-1-epipodophyllotoxins (**8e—8j**) were synthesized by one step in excellent yields. BF_3-catalyzed coupling in dichloromethane was also successful in a formation of an ether bond with ethylene glycol, and 1-*O*-(2-hydroxyethyl)-4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (**9**) was obtained in an excellent yield. Compound **9** was converted to an aldehyde **10** by Swern oxidation, and the successive reduction with the corresponding alkylamines **11c**, **11f**, and **11k—12m** by sodium cyanotrihydroborate gave 1-*O*-[2-(alkylamino)ethyl]-4′-*O*-demethyl-1-epipodophyl-

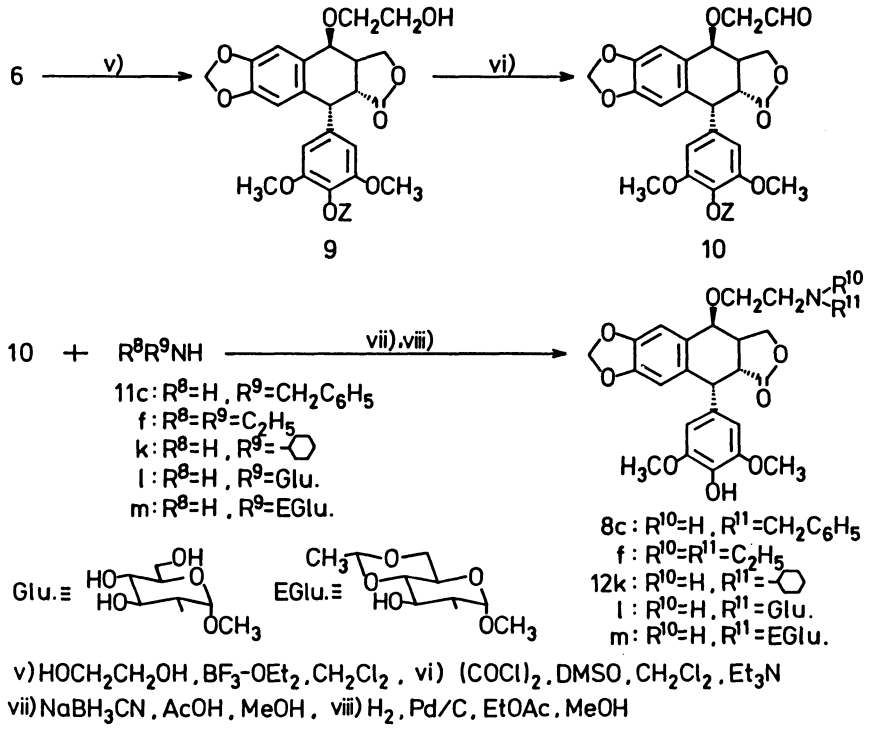


1 : R^1=CH_3, R^2=R^3=OH (Etoposide)
2 : R^1= , R^2=R^3=OH (Teniposide)
3 : R^1=CH_3, R^2=OH, R^3=NH_2
4 : R^1=CH_3, R^2=NH_2, R^3=OH
5 : R^1=CH_3, R^2=OH, R^3=$N(CH_3)_2$

Fig. 1.



Scheme 1.



Scheme 2.

Table 1. The Antitumor Activities of **1**, **5**, and 1-*O*-(2-Aminoethyl) Ethers of 4′-*O*-Demethyl-1-epipodophyllotoxin (T/C%)

Dose (μg/mouse)	Compound No.														
	1	**5**	**8a**	**8b**	**8c**	**8d**	**8e**	**8f**	**8g**	**8h**	**8i**	**8j**	**12k**	**12l**	**12m**
25	184	438	130	188	139	109	270	139	72	113	145	172	108	95	102
6.25	139	164	162	271	108	103	141	108	72	104	133	135	108	95	102

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

lotoxins (**8c**, **8f**, and **12k—12m**) in good overall yields. Condensations in all cases were carried out stereoselectively by the same fashion through a benzyl cation at C-1 generated by $BF_3 \cdot OEt_2$ as has been reported in a previous synthesis.[4,6,9]

Synthesized compounds **8a—8j** and **12k—12m**, compared with **1** and **5**, were screened for antitumor activities using lymphocytic leukemia L-1210 in mice. Test results are shown in Table 1. Compounds **8a**, **8b**, **8e**, **8i**, and **8j** produced a good survival time increase in mice with leukemia L-1210. Interestingly, prototypal structures such as **8b** and **8e** showed a significant antitumor activity alongside **1** and **5**. These results suggest further elaboration of the amino side chain to optimize their structures. Further study for antitumor activity of synthesized compounds is in progress.

Experimental

General Methods. Melting points were determined with a Yamato apparatus and were uncorrected. IR spectra were determined on a Hitachi Model 260-10 and Jasco IR-810 spectrophotometers. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. ^1H NMR spectra were recorded with Varian EM-390, Jeol GX-270 and Jeol GX-400 spectrometers. Chemical shifts are expressed in δ values (ppm) with tetramethylsilane as an internal standard. The mass spectra was taken by a Jeol D-300 for fast atom bombardment (FAB).

1-*O*-(2-Aminoethyl)-4′-*O*-demethyl-1-epipodophyllotoxin (8a). To a solution of a mixture of **6** (320 mg) and 2-(benzyloxycarbonylamino)ethanol (142 mg) in dichloromethane (8 ml) was added $BF_3 \cdot OEt_2$ (200 μl) at −10 °C, and the mixture was stirred at −10 °C for 1 h. After being quenched with pyridine (200 μl), the solution was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a solid. The solid was dissolved in ethyl acetate–methanol (1:1, 30 ml), and the solution was stirred under atmosphere of hydrogen in the presence of 10% Pd/C (40 mg) at room temperature for 1 h. After removal of catalyst, the solvent was evaporated to afford a solid. The solid was chromatographed on a column of silica gel with chloroform–methanol (4:1) to give a solid of **8a** (191 mg, 72%). The solid was recrystallized from methanol to give a crystal of **8a**: mp 182—184 °C; $[\alpha]_D^{23}$ −46° (*c* 0.4, MeOH); IR (KBr) 1775, 1760, 1483 1230, and 1110 cm^{-1}; ^1H NMR (C_5D_5N, 270 MHz) δ=3.18 (3H m, H-2 and $-OCH_2C\underline{H}_2N-$), 3.58 (1H dd, *J*=5 and 14 Hz, H-3), 3.71 (6H s, 2×OCH_3), 3.84 and 3.98 (1H each m, $-OC\underline{H}_2CH_2N-$), 4.39 (1H t, *J*=8 Hz, H-11), 4.51 (1H dd, *J*=8 and 11 Hz, H-11), 4.62 (1H d, *J*=3.0 Hz, H-1), 4.76 (1H d, *J*=5 Hz, H-4), 5.98 (2H d, methylene), 6.66 (2H s, H-2′ and 6′), 6.74 (1H s, H-5), and 7.15 (1H s, H-8); MS (FAB) *m/z* 444 (M^++H) and 383.

1-*O*-[2-(Dimethylamino)ethyl]-4′-*O*-demethyl-1-epipodophyllotoxin (8e). To a solution of 2-(dimethylamino)-ethanol (30 mg) in dichloromethane (1 ml) was added $BF_3 \cdot OEt_2$ (110 μl) at −15 °C and the mixture was stirred at −15 °C for 10 min. Then to the mixture was added dropwise a solution of **6** (108 mg) in dichloromethane (1 ml) at −15 °C, and the mixture was stirred at −15 °C for 30 min. The similar work-up and purification to those used for preparation of **8a** were used (43% overall yield).

From **8a**: To a solution of **8a** (88 mg) in methanol (3 ml) was added 37% aqueous solution of formaldehyde (50 μl) and sodium cyanoborohydride (30 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 (4:1). A solid of **8e** was obtained in a yield of 90%. The solid was recrystallized from methanol to give a crystal of **8e**: 195—197 °C; $[\alpha]_D^{22}$ −57° (*c* 0.5, MeOH); IR (KBr) 1760, 1483, 1227, 1108, and 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=2.27 (6H s, 2×NCH_3), 2.53 (2H t, *J*=6 Hz, $-OCH_2C\underline{H}_2N-$), 2.87 (1H m, H-2), 3.39 (1H dd, *J*=5.1 and 14 Hz, H-3), 3.61 and 3.80 (1H each m, $-OC\underline{H}_2CH_2N-$), 3.77 (6H s, 2×OCH_3), 4.35 (2H m, H-11), 4.45 (1H d, *J*=3.4 Hz, H-1), 4.59 (1H d, *J*=5.1 Hz, H-4), 5.95 and 5.99 (2H ABq, *J*=1.5 Hz, methylene), 6.26 (2H s, H-2′ and 6′), 6.54 (1H s, H-5), and 6.84 (1H s, H-8); MS (FAB) *m/z* 472 (M^++H) and 383.

1-*O*-(2-Hydroxyethyl)-4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-1-epipodophyllotoxin (9). To a solution of **6** (1 g) and ethylene glycol (0.2 ml) in dichloromethane (15 ml) was added dropwise a solution of $BF_3 \cdot OEt_2$ (0.6 ml) in dichloromethane (1 ml) at −15 °C, and the mixture was stirred at −15 °C for 2 h. After being quenched with pyridine (0.6 ml), the solution was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a solid, which was subjected to column chromatography on silica gel. Elution with toluene–acetone (5:1) gave **9** (980 mg, 90%), which was recrystallized from methanol: mp 182—183 °C; $[\alpha]_D^{22}$ −51° (*c* 0.66, $CHCl_3$); IR (KBr) 1770, 1602, 1482, 1234, and 1125 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=2.88 (1H m, H-2), 3.40 (1H dd, *J*=14 and 5.1 Hz, H-3), 3.68 (6H s, 2×OCH_3), 4.51 (1H, d, *J*=3 Hz, H-1), 4.64 (1H d, *J*=5.1 Hz H-4), 5.26 (2H s, $OC\underline{H}_2Ph$), 6.28 (2H s, H-2′ and 6′), 6.55 (1H s, H-5), 6.85 (1H s, H-8), and 7.15—7.45 (5H, Ph); MS (FAB) *m/z* 579 (M^++H), 517, and 443.

1-*O*-(2-Oxoethyl)-4′-*O*-demethyl-1-epipodophyllotoxin (10). A solution of dichloromethane (0.5 ml) and dimethyl sulfoxide (120 μl) was added to a stirred solution of dichloromethane (2 ml) and oxallyl dichloride (70 μl) at −60 °C. To the solution was added a solution of **9** (360 mg) in dichloromethane (2 ml) within 5 min, and the mixture was stirred at −60 °C for 15 min. Triethylamine (0.4 ml) was added and the reaction mixture was stirred for 5 min and then allowed to warm to room temperature. After being quenched with water, the mixture was extracted with dichloromethane (10 ml). The organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$. The filtered solution was evaporated to give a solid, which was subjected to a column chromatography on silica gel. Elution with toluene–acetone (2:1) gave a solid of **10** (250 mg, 69%). The solid was crystallized from methanol: mp 96—98 °C; $[\alpha]_D^{22}$ −57 ° (*c* 0.48, $CHCl_3$); IR (KBr) 1770, 1602, 1482, 1235, and 1127 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=3.67 (6H s, 2×OCH_3), 5.26 (2H s, $OC\underline{H}_2Ph$), 5.98 (2H s, methylene), 6.28 (2H s, H-2′ and 6′), 6.59 (1H s, H-8), 7.25—7.50 (5H broad s, Ph), and 9.66 (1H s, CHO); MS (FAB) *m/z* 599 (M^++Na) and 517.

Methyl 2-Amino-2-deoxy-4,6-*O*-ethylidene-α-D-glucopyranoside (11m). To a suspension of methyl 2-benzyloxy-

carbonylamino-2-deoxy-α-D-glucopyranoside (100 mg) and acetaldehyde diethyl acetal (0.3 ml) in dichloromethane (5 ml) was added *p*-toluenesulfonic acid (5 mg) at room temperature, and the mixture was stirred for 2 h. The solution was washed with a saturated $NaHCO_3$ solution and water, and dried over $MgSO_4$. Evaporation of the filtered solution gave a solid, which was crystallized from methanol to give a crystal of methyl 2-benzyloxycarbonylamino-2-deoxy-4,6-*O*-ethylidene-α-D-glucopyranoside (**13**) (88 mg, 81%): mp 176—177 °C; $[\alpha]_D^{22}$ +65° (*c* 0.5, $CHCl_3$). Compound **13** (70 mg) was dissolved in ethanol (5 ml), and the solution was stirred under atmosphere of hydrogen in the presence of 10% Pd/C (10 mg) at room temperature for 1 h. After removal of catalyst, the solvent was evaporated to afford solid. The solid was subjected to a next step without purification.

13: IR (KBr) 1693, 1542, 1280, and 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=1.36 (3H d, CH_3 of ethylidene), 3.34 (3H s, OCH_3), 5.13 (2H s, OCH_2Ph), and 7.3—7.5 (5H m, Ph); MS (FAB) *m/z* 354 (M^++H) and 322.

1-*O*-[2-(Cyclohexylamino)ethyl]-4′-*O*-demethyl-1-epipodophyllotoxin (12k). A solution of cyclohexylamine (20 mg) and sodium cyanoborohydride (10 mg) in methanol (2 ml) was adjusted pH value to 4—5 with acetic acid, and to the solution was added **10** (58 mg), and then the mixture was stirred at room temperature for 1 h. After dilution with chloroform (10 ml), the mixture was washed with a saturated $NaHCO_3$ solution and water, and dried over $MgSO_4$. Evaporation of the solvent gave a solid, which was dissolved in ethyl acetate–methanol (1:1). The mixture was stirred under atmosphere of hydrogen in the presence of 10% Pd/C (10 mg) at room temperature for 1 h. After removal of catalyst, evaporation of the solvent gave a solid. The solid was subjected to preparative thin-layer chromatography on silica gel with chloroform–methanol (4:1) to give a solid of **12k** (34 mg, 64%). The solid was recrystallized from methanol to give a crystal of **12k**: mp 169—171 °C; $[\alpha]_D^{22}$ −57° (*c* 0.5, $CHCl_3$); IR (KBr) 2935, 1765, 1482, 1228, and 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=1.0—2.0 (10H m, methylene protons of cyclohexyl), 2.45 (1H m, methine proton of cyclohexyl), 2.83 (2H t, *J*=5 Hz, $-OCH_2C\underline{H}_2N-$), 3.40 (1H dd, *J*=5 and 14 Hz, H-3), 3.77 (6H s, 2×OCH_3), 4.34 (2H d, *J*=9 Hz, H-11), 4.46 (1H d, *J*=3 Hz, H-1), 4.60 (1H d, *J*=5 Hz, H-4), 5.97 (2H m, methylene), 6.28 (2H s, H-2′ and 6′), and 6.55 (1H s, H-5); MS (FAB) *m/z* 526 (M^++H) and 383.

8b: **8b** was obtained from **6** (0.6 mmol) and 2-benzyloxycarbonyl-2-(methylamino)ethanol (0.7 mmol) by the similar procedure for the preparation of **8a** (yield 73%): mp 182 °C (crystallized from ethanol); $[\alpha]_D^{23}$ −60° (*c* 0.5, MeOH); IR (KBr) 1775, 1480, 1328, 1227 and 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=2.45 (3H s, NCH_3), 2.77 (2H m, $OCH_2C\underline{H}_2N$), 2.87 (1H m, H-2), 3.37 (1H dd, *J*=5.4 and 14 Hz, H-3), 3.64 and 3.82 (1H each m, $-OC\underline{H}_2CH_2N-$), 3.76 (6H s, 2×OCH_3), 4.34 (2H d, *J*=9 Hz, H-11), 4.45 (1H d, *J*=3.4 Hz, H-1), 4.76 (1H d, *J*=5.4 Hz, H-4), 5.97 (2H d, methylene), 6.26 (2H s, H-2′ and 6′), 6.54 (1H s, H-5), and 6.81 (1H s, H-8); MS (FAB) *m/z* 458 (M^++H) and 383.

8c: **8c** was obtained from **6** (0.6 mmol) and 2-benzyloxycarbonyl-2-(benzylamino)ethanol (0.7 mmol) by the similar procedure for the preparation of **8a** (yield 70%). **8c** was also prepared from **10** (0.1 mmol) and benzylamine (0.2 mmol) by the similar procedure for the preparation of **12k** (yield 75%): mp 146—148 °C (recrystallized from methanol); $[\alpha]_D^{22}$ −51° (*c* 0.5, $CHCl_3$); IR (KBr) 1763, 1482, 1228, and 1108 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=2.82 (2H t, *J*=5 Hz, $-OCH_2C\underline{H}_2N-$), 3.10 (1H m, H-2), 3.36 (1H dd, *J*=5 and 14 Hz, H-3), 3.75 (6H s, 2×OCH_3), 3.81 (2H s, $OC\underline{H}_2Ph$), 4.32 (2H d, *J*=9 Hz, H-11), 4.43 (1H d, *J*=3 Hz, H-1), 4.59 (1H d, *J*=5 Hz, H-4), 5.95 (2H m, methylene), 6.26 (2H s, H-2′ and 6′), 6.53 (1H s, H-5), and 6.81 (1H s, H-8); MS (FAB) *m/z* 534 (M^++H) and 383.

8d: **8d** was obtained from **6** (0.2 mmol) and 2-(phenylamino)ethanol (0.3 mmol) by the similar procedure for the preparation of **8e** from **6** (yield 67%): mp 157—158 °C (recrystallized from methanol); $[\alpha]_D^{20}$ −60° (*c* 0.4, $CHCl_3$); IR (KBr) 1779, 1619, 1520, 1498, 1240, and 1121 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=2.87 (1H m, H-2), 3.35 (3H m, H-3 and $-OCH_2C\underline{H}_2N-$), 3.73 and 3.87 (1H each m, $-OC\underline{H}_2CH_2N-$), 3.76 (6H s, 2×OCH_3), 4.30 (2H m, H-11), 4.45 (1H d, *J*=3.4 Hz, H-1), 4.61 (1H d, *J*=5 Hz, H-4), 5.40 (1H broad s, 4′-OH), 5.97 and 5.99 (2H ABq, *J*=1.3 Hz, methylene), 6.25 (2H s, H-2′ and 6′), 6.56 (1H s, H-5), 6.61, 6.74 and 7.19 (2H, 1H and 2H each m, Ph), and 6.77 (1H s, H-8); MS (FAB) *m/z* 520 (M^++H) and 383.

8f: **8f** was obtained from **6** (0.2 mmol) and 2-(diethylamino)ethanol (0.3 mmol) by the similar procedure for the preparation of **8e** from **6**, and from **8c** (0.2 mmol) by the similar procedure for the preparation of **8e** from **8a** in yields of 80 and 88%, respectively. **8f** was also prepared from **10** (0.1 mmol) and diethylamine (0.2 mmol) by the similar procedure for the preparation of **12k** (yield 69%): mp 196—198 °C (recrystallized from methanol); $[\alpha]_D^{22}$ −73° (*c* 0.5, $CHCl_3$); IR (KBr) 1760, 1482, 1228, and 1110 cm^{-1}; ^1H NMR ($CDCl_3$ 90 MHz) δ=1.05 (6H t, *J*=7 Hz, 2×$-NCH_2C\underline{H}_3$), 2.62 (4H q, *J*=7 Hz, 2×$NC\underline{H}_2CH_3$), 2.70 (2H t, *J*=6 Hz, $-OCH_2C\underline{H}_2N-$), 2.90 (1H m, H-2), 3.37 (1H dd, *J*=5 and 14 Hz, H-3), 3.77 (6H s, 2×OCH_3), 4.36 (2H d, *J*=9 Hz, H-11), 4.47 (1H d, *J*=3 Hz, H-1), 4.60 (1H d, *J*=5 Hz, H-4), 5.98 (2H m, methylene), 6.27 (2H s, H-2′ and 6′), 6.54 (1H s, H-5), and 6.86 (1H s, H-8); MS (FAB) *m/z* 500 (M^++H) and 383.

8g: **8g** was obtained from **6** (0.2 mmol) and 2-(cyclopentylamino)ethanol (0.3 mmol) by the similar procedure for the preparation of **8e** from **6** (yield 81%): mp 227—228 °C (recrystallized from methanol); $[\alpha]_D^{22}$ −48° (*c* 0.5, MeOH); IR (KBr) 1758, 1610, 1482, 1225, 1108, and 1080 cm^{-1}; ^1H NMR ($CDCl_3/C_5D_5N$=2/1, 270 MHz) δ=1.8—2.0 and 2.9—3.4 (4H and 8H each m, H-2, H-3 and pyrrolidine), 3.68 (6H s, 2×OCH_3), 3.96 and 4.06 (1H each m, $-OC\underline{H}_2CH_2N-$), 4.31 (2H m, H-11), 4.59 (1H d, *J*=3.8 Hz, H-1), 5.92 (2H s, methylene), 6.36 (2H s, H-2′ and 6′), 6.59 (1H s, H-5), and 6.97 (1H s, H-8); MS (FAB) *m/z* 498 (M^++H) and 383.

8h: **8h** was obtained from **6** (0.2 mmol) and 2-(2-hydroxyethyl)pyrrolidone (0.3 mmol) by the similar procedure for the preparation of **8e** from **6** (yield 91%): mp 212—214 °C (recrystallized from ethanol); $[\alpha]_D^{22}$ −82° (*c* 0.8, $CHCl_3$); IR (KBr) 1762, 1682, 1610, 1480, 1220, and 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.99 (2H m, $-NCOCH_2C\underline{H}_2-$), 2.38 (2H t, *J*=8 Hz, $-NCOC\underline{H}_2CH_2-$), 2.89 (1H m, H-2), 3.77 (6H s, 2×OCH_3), 4.29 (2H m, H-11), 4.47 (1H d, *J*=3 Hz, H-1), 4.60 (1H d, *J*=5.1 Hz, H-4), 5.40 (1H s, 4′-OH), 5.98 and 6.00 (2H ABq, *J*=1.3 Hz, methylene), 6.24 (2H s, H-2′ and 6′), 6.56 (1H s, H-5), and 6.77 (1H s, H-8); MS (FAB) *m/z*

512 (M^++H) and 383.

8i: **8i** was obtained from **6** (0.2 mmol) and 1-piperidineethanol (0.3 mmol) by the similar procedure for the preparation of **8e** from **6** (yield 73%): mp 199—200 °C (recrystallized from methanol); $[\alpha]_D^{23}$ −73° (*c* 0.4, $CHCl_3$); IR (KBr) 1772, 1481, 1237, 1223, and 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.4—1.65 (6H m, piperidine), 2.45 (4H t, *J*=4 Hz, 2×-NCH_2- of piperidine), 2.56 (2H t, *J*=6 Hz, -$OCH_2C\underline{H}_2N$-), 2.85 (1H m, H-2), 3.37 (1H dd, *J*=5.1 and 14 Hz, H-3), 3.76 (6H s, 2×OCH_3), 4.35 (2H m, H-11), 4.45 (1H d, *J*=3.0 Hz, H-1), 4.60 (1H d, *J*=5.1 Hz, H-4), 5.40 (1H s, 4′-OH), 5.95 and 5.98 (2H ABq, *J*=1.3 Hz, methylene), 6.26 (2H s, H-2′ and 6′), 6.53 (1H s, H-5), and 6.88 (1H s, H-8); MS (FAB) *m/z* 512 (M^++H).

8j: **8j** was obtained from **6** (0.2 mmol) and 4-(2-hydroxyethyl)morpholine (0.3 mmol) by the similar procedure for the preparation of **8e** from **6** (yield 80%): mp 220—224°C (recrystallized from methanol); $[\alpha]_D^{23}$ −73° (*c* 0.5, $CHCl_3$); IR (KBr) 1774, 1480, 1230, and 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=2.4—2.7 (6H m, -$OCH_2C\underline{H}_2N$- and 2×-NCH_2- of morpholine), 2.92 (1H m, H-2), 3.40 (1H dd, *J*=5 and 14 Hz, H-3), 3.77 (6H s, 2×OCH_3), 4.46 (1H d, *J*=3 Hz, H-1), 4.63 (1H d, *J*=5 Hz, H-4), 6.00 (2H broad s, methylene), 6.30 (2H s, H-2′ and 6′), 6.56 (1H s, H-5), and 6.89 (1H s, H-8); MS (FAB) *m/z* 514 (M^++H) and 383.

12l: **12l** was obtained from **10** (0.1 mmol) and methyl 2-amino-2-deoxy-α-D-glucopyranoside (0.2 mmol) by the similar procedure for the preparation of **12k** (yield 73% based on **10**): mp 178—180 °C (recrystallized from methanol); $[\alpha]_D^{23}$ +14° (*c* 0.5, MeOH); IR (KBr) 1763, 1482, 1230, and 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=3.36 and 3.76 (3H and 6H each s, 3×OCH_3), 4.33 (2H d, *J*=9 Hz, H-11), 4.46 (1H d, *J*=3 Hz, H-1), 4.60 (1H d, *J*=5 Hz, H-4), 5.86 (1H d, *J*=3 Hz, H-1 of glucopyranoside), 5.97 (2H broad s, methylene), 6.26 (2H s, H-2′ and 6′), 6.56 (1H s, H-5), and 6.81 (1H s, H-8); MS (FAB) *m/z* 620 (M^++H) and 383.

12m: **12m** was obtained from **10** (0.1 mmol) and methyl 2-amino-2-deoxy-4,6-*O*-ethylidene-α-D-glucopyranoside (0.2 mmol) by the similar procedure for the preparation of **12k** (yield 59% based on **10**): mp 179—181 °C (recrystallized from methanol); $[\alpha]_D^{22}$ +7° (*c* 0.5, $CHCl_3$); IR (KBr) 1762, 1482, 1228, and 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=1.36 (3H d, *J*=5 Hz, CH_3 of ethylidene), 3.36 and 3.76 (3H and 6H each s, 3×OCH_3), 4.35 (2H d, *J*=9 Hz, H-11), 4.46 (1H d, *J*=3 Hz, H-1), 4.61 (1H d, *J*=5 Hz, H-4), 5.98 (2H m, methylene), 6.27 (2H s, H-2′ and 6′), 6.56 (1H s, H-5), and 6.81 (1H s, H-8); MS (FAB) *m/z* 646 (M^++H) and 607 and 515.

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