Studies on Lignan Lactone Antitumor Agents. IV. Synthesis of Glycosidic Lignan Variants Related to α-Peltatin

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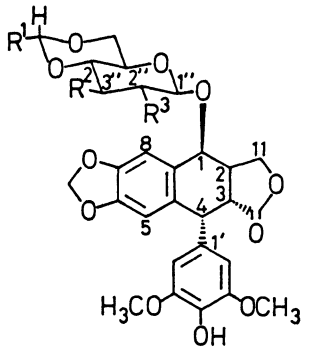
Glycosidic variants of 1-β-hydroxy-α-peltatin and 1-β-hydroxy-8-*O*-methyl-α-peltatin were synthesized by glycosidation of 4′,8-di-*O*-benzyloxycarbonyl-1-β-hydroxy-α-peltatin or 4′-*O*-benzyloxycarbonyl-1-β-hydroxy-8-*O*-methyl-α-peltatin with the corresponding glucopyranose or 2-amino-2-deoxyglucopyranose derivatives. Among synthesized compounds, cyclic acetal of 1-*O*-β-(β-D-glucopyranosyl)-8-*O*-methyl-α-peltatin showed antitumor activity in mice with leukemia L-1210.

The lignan lactone antitumor agents, VP-16-213 (etoposide, **1**) and VM-26 (teniposide, **2**), are used for cancer chemotherapy.[1,2] Due to their clinical efficacy, the synthesis of new active analogues of podophyllotoxin glycoside has been of considerable interest. We have previously reported the syntheses of new active aminoglycosidic variants of podophyllotoxin **3**—**5**, which were found to have the superior activities to **1**.[3,4]

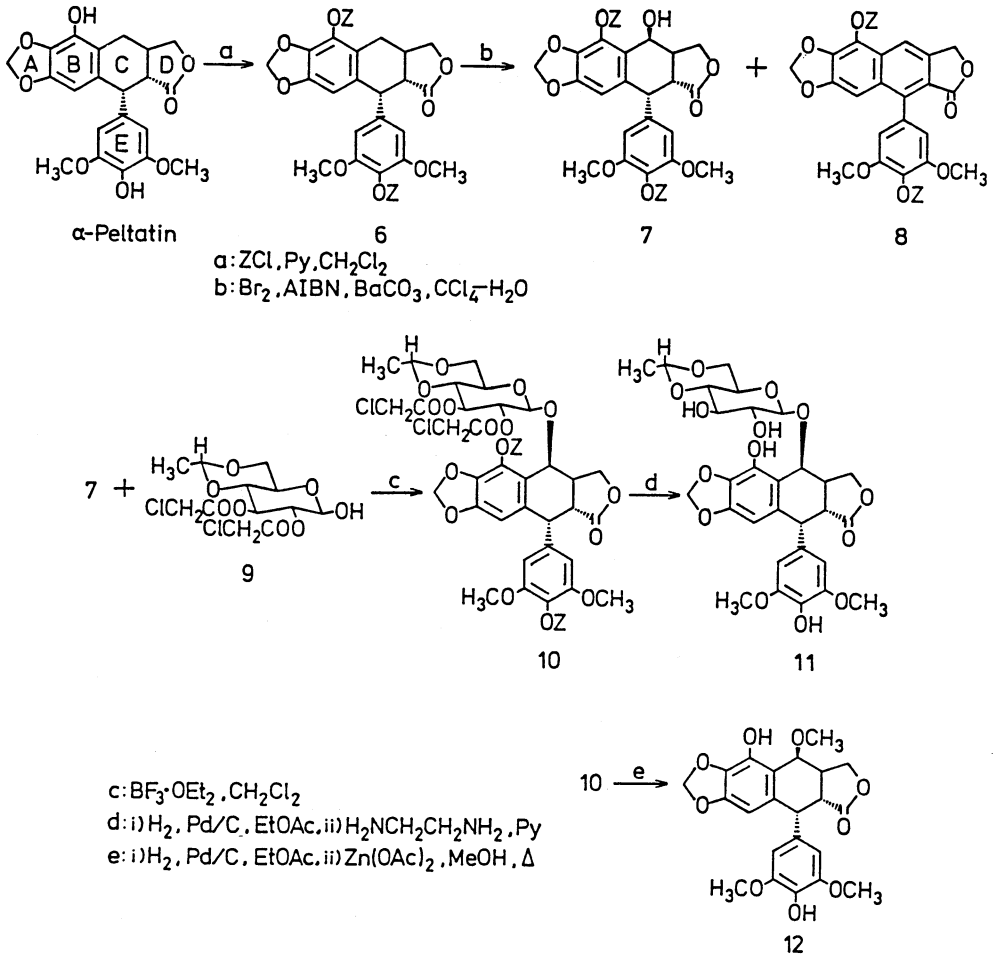
The hitherto-known structural modifications of podophyllotoxin glycoside on sugar or on lignan moiety suggested that the following factors played an important role in increasing the antitumor activity; a) the glucose configuration, b) β-glycosidic linkage, c) 4″,6″-*O*-cyclic acetal group, d) β-configuration at C-1, e) trans-fused lactone and f) 4′-phenolic hydroxyl group. In connection with our interest in investigation on the relationship between structure and antitumor activity among lignan lactone glycosides, we undertook the syntheses of glucosidic analogues of α-peltatin **11**, **17**, and **20**. The starting aglycone, 4′,8-di-*O*-benzyloxycarbonyl-1-β-hydroxy-α-peltatin (**7**) was prepared from α-peltatin.[1] Several methods were examined to introduce 1-β-hydroxyl group by a direct bromine with a hydroxyl group. The bromination at C-1 of α-peltatin by treatment with *N*-bromosuccinimide (NBS) in THF[5] failed, affording the dibrominated product on both of the aromatic ring B and E which was simultaneously demethylated on the ring E. The attempts of bromination of 4′,8-di-*O*-benzyloxycarbonyl-α-peltatin (**6**) with NBS in THF, and with that in the presence of benzoyl peroxide[6] were also unsuccessful. Finally, an introduction of 1-β-hydroxyl group into **6** was successfully carried out by two-step sequences (bromination and hydrolysis) in a one-pot procedure. Treatment of **6** with bromine in a mixture of aqueous barium carbonate solution and carbon tetrachloride in the presence of α,α′-azobis(isobutyronitrile) (AIBN)[7] gave **7** and an aromatized product **8** in a yield of 58 and 10%, respectively. Condensation of **7** with 2,3-di-*O*-chloroacetyl-4,6-*O*-ethylidene-β-D-glucopyranose (**9**)[8] in dichloromethane in the presence of boron trifluoride diethyl etherate[9] afforded 1-*O*-β-(2,3-di-*O*-chloroacetyl-4,6-*O*-ethylidene-β-D-glucopyranosyl)-4′,8-di-*O*-benzyloxycarbonyl-α-peltatin (**10**) as a sole product in a yield of 72%. The reaction was carried out stereoselectively by the same fashion through a benzyl cation at C-1 of the aglycone moiety generated by BF_3 as has been reported in the previous synthesis.[3,4,8,9] The stereochemistry of the glycoside was also controlled by the anomeric configuration of the original pyranose moiety. Removal of protecting groups in **10** by catalytic hydrogenolysis followed by the treatment with ethylenediamine in pyridine yielded 1-*O*-β-(4,6-*O*-ethylidene-β-D-glucopyranosyl)-α-peltatin (**11**).



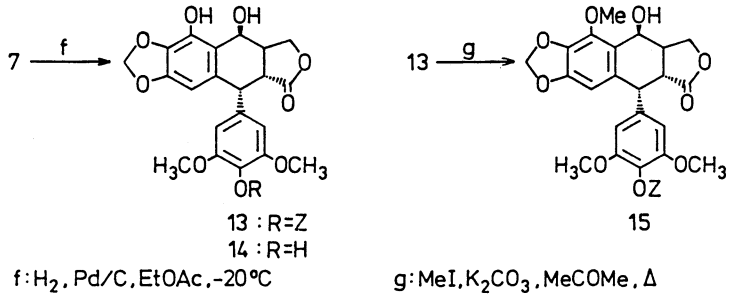
1 : R^1=CH_3, R^2=R^3=OH (Etoposide)
2 : R^1=  , R^2=R^3=OH (Teniposide)
3 : R^1=CH_3, R^2=OH, R^3=NH_2
4 : R^1=CH_3, R^2=NH_2, R^3=OH
5 : R^1=CH_3, R^2=OH, R^3=$N(CH_3)_2$

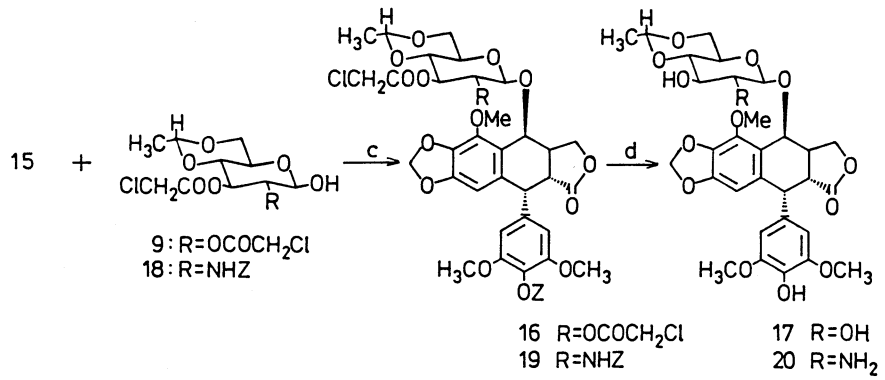
Fig. 1.

Compound **11** showed no antitumor activity against mouse leukemia L-1210 (Table 1). Compound **10** was transformed into 1-β-methoxy-α-peltatin (**12**) having no antitumor activity under the conditions employed in the synthesis of podophyllotoxin glycoside[8] to remove chloroacetyl group [$Zn(OAc)_2$, CH_3OH, reflux]. These results suggested that the glycosidic bond was easily hydrolyzed by the electronic effect of the neighbouring hydroxyl group at C-8.[10] In order to improve its stability, we undertook the synthesis of the methylated compound at C-8, 1-*O*-β-(4,6-*O*-ethylidene-β-D-glucopyranosyl)-8-*O*-methyl-α-peltatin (**17**). Catalytic hydrogenolysis of **7** with 10% palladium on carbon in



Scheme 1.





Scheme 2.

Table 1. The Antitumor Activities of α-Peltatin Analogues (T/C%)

Dose (μg/mouse)	Compound No.			
	11	**12**	**17**	**20**
25	105	128	156	119
6.25	117	103	100	95

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.

ethyl acetate at −20 °C gave 4′-*O*-benzyloxycarbonyl-1-β-hydroxy-α-peltatin (**13**) and 1-β-hydroxy-α-peltatin (**14**) in 70 and 25% yield, respectively. When the same catalytic hydrogenolysis was carried out at room temperature, **14** was obtained as a sole product. Compound **13** was methylated with methyl iodide in the presence of potassium carbonate in acetone to afford quantitatively 4′-*O*-benzyloxycarbonyl-1-β-hydroxy-8-*O*-methyl-α-peltatin (**15**). Condensation of **15** with **9** followed by removal of protecting groups by the same procedure as mentioned above gave **17** in a good yield. Compound **17** was found to have the superior antitumor activity to **11**.

In relation to these syntheses, we were interested in the replacement of the sugar moiety of **17** with an amino sugar. Condensation of **15** with 2-benzyloxycarbonylamino-3-*O*-chloroacetyl-4,6-*O*-ethylidene-β-D-glucopyranose (**18**)[8] and a successive deprotection of the masking groups were carried out by the similar sequences described above to afford 1-*O*-β-(2-amino-2-deoxy-4,6-*O*-ethylidene-β-D-glucopyranosyl)-8-*O*-methyl-α-peltatin (**20**) in an excellent yield. Compound **20** showed no antitumor activity (Table 1). 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. ^{1}H 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 were taken by a Hitachi RMN-7M for field-desorption (FD) and a Jeol D-300 for fast atom bombardment (FAB). Natural α-peltatin was provided by Nippon Kayaku Co., Ltd.

4′,8-Di-*O*-benzyloxycarbonyl-α-peltatin (6). To a solution of α-peltatin (800 mg) in dichloromethane (5 ml) containing pyridine (400 mg) was added a solution of benzyloxycarbonyl chloride (800 mg) in dichloromethane (1 ml) at 0 °C, and the mixture was stirred for 1 h. The solution was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a solid. The solid was subjected to column chromatography on silica gel. Elution with acetone-toluene (1 : 19) gave **6** (1.1 g, 82%), which was recrystallized from methanol: mp 98—99 °C; $[\alpha]_D^{24}$ −90° (*c* 0.69, $CHCl_3$); IR (KBr) 1770, 1602, 1240, and 1128 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ=2.40 (1H dd, *J*=5 and 15 Hz, H-1), 2.65 (1H m, H-2), 2.72 (1H dd, *J*=4.7 and 13.7 Hz, H-3), 3.01 (1H dd, *J*=5 and 15 Hz, H-1), 3.69 (6H s, 2×OCH_3), 3.87 (1H t, *J*=9 Hz, H-11), 4.43 (1H dd, *J*=6.6 and 9 Hz, H-11), 4.64 (1H d, *J*=4.7 Hz, H-4), 5.26 and 5.31 (2H each s, 2×$C\underline{H}_2$Ph), 6.01 (2H s, methylene), 6.36 (2H s, H-2′ and 6′), 6.50 (1H s, H-5) and 7.3—7.5 (10H m, 2×Ph); MS (FAB) *m/z* 669 (M^+ +H), 533, and 381.

4′,8-Di-*O*-benzyloxycarbonyl-1-β-hydroxy-α-peltatin (7). To a suspension of **6** (334 mg), AIBN (200 mg) and $BaCO_3$ (500 mg) in a mixture of water (5 ml) and carbon tetrachloride (30 ml) was added bromine (33 μl), and the mixture was stirred at room temperature for 2 h. After evaporation, the mixture was dissolved in a mixture of acetone (30 ml) and water (1 ml), and the solution was stirred at 40 °C for 2 h. The insoluble matter was filtered off, and the filtrate was evaporated to give an oil. The oil was chromatographed on silica gel with the solvent system of acetone-toluene (1 : 5) to give solids of **7** (200 mg, 58%) and **8** (33 mg, 10%). Each solid was recrystallized from ethanol. **7**: mp 105—106 °C. $[\alpha]_D^{23}$ −78° (*c* 0.46, $CHCl_3$); IR (KBr) 1772, 1602, 1482, 1240, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ=2.72 (1H m, H-2), 3.32 (1H dd, *J*=5 and 14 Hz, H-3), 3.68 (6H s, 2×OCH_3), 4.37 (2H m, H-11), 4.66 (1H d, *J*=5 Hz, H-4), 5.02 (1H d, *J*=3.4 Hz, H-1), 5.26 and 5.33 (2H each s, 2×$C\underline{H}_2$Ph), 6.04 and 6.06 (2H each d, *J*=1.3 Hz, ethylidene), 6.29 (2H s, H-2′ and 6′), 6.52 (1H s, H-5) and 7.3—7.5 (10H m, 2×Ph); MS (FD) *m/z* 684 (M^+), 640, 599, and 550. **8**: mp 215—216 °C; $[\alpha]_D^{23}$ 0° (*c* 0.5, $CHCl_3$); IR (KBr) 1788, 1615, 1280, and 1228 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ=3.79 (6H s, 2×OCH_3), 5.33 (2H s, $C\underline{H}_2$Ph), 5.36 (2H s, H-11), 5.38 (2H s, $C\underline{H}_2$Ph), 6.15 (2H s, methylene), 6.55 (2H s, H-2′ and 6′), 7.08 (1H s, H-5), 7.3—7.5 (10H m, 2×Ph), and 7.81 (1H s, H-1); MS (FD) *m/z* 664 (M^+) and 529.

1-*O*-β-(2,3-*O*-Chloroacetyl-4,6-*O*-ethylidene-β-D-glucopyranosyl)-4′,8-di-*O*-benzyloxycarbonyl-α-peltatin (10). To a solution of a mixture of **7** (200 mg) and 2,3-di-*O*-chloroacetyl-4,6-*O*-ethylidene-β-D-glucose (130 mg, **9**) in dichloromethane (5 ml) was added dropwise boron trifluoride etherate (200 μl) at −20 °C, and the mixture was stirred at −20 °C for 1.5 h, then quenched with pyridine (200 μl). 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 (9 : 1) gave a solid of **10** (214 mg, 72%), which was recrystallized from ethanol: mp 116—117 °C, $[\alpha]_D^{23}$ −81° (*c* 0.55, $CHCl_3$); IR (KBr) 1772 and 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ=1.34 (3H d, *J*=5 Hz, CH_3 of ethylidene), 3.66 (6H s, 2×OCH_3), 6.1 (2H s, methylene), 6.23 (2H s, H-2′ and 6′), 6.50 (1H s, H-5), and 7.2—7.6 (10H m, 2×Ph); MS (FAB) *m/z* 1025 (M^+ +H) and 890.

1-*O*-β-(4,6-*O*-Ethylidene-β-D-glucopyranosyl)-α-peltatin (11). A solution of **10** (180 mg) in ethyl acetate (10 ml) was stirred with 10% Pd/C (10 mg) under atmosphere of hydrogen at room temperature for 2 h. The catalyst was filtered off, and the filtrate was evaporated to give a solid (100 mg). The solid was dissolved in pyridine (1 ml), and to the solution was added ethylenediamine (25 μl) at 0 °C, and then the mixture was stirred at 0 °C for 1.5 h. The mixture was di-

luted with chloroform (30 ml), and washed with 5% aqueous $KHSO_4$ solution and water. The chloroform solution was dried over Na_2SO_4, and evaporated to give a solid. The solid was chromatographed on silica gel with the solvent system of toluene-acetone (2:1) to afford a solid of **11** (72 mg, 68%). The solid was recrystallized from chloroform: mp 208—209 °C (decomp); $[\alpha]_D^{25}$ −96° (*c* 0.3, CH_3OH); IR (KBr) 1758, 1625, 1482, and 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=1.44 (3H d, *J*=5 Hz, CH_3 of ethylidene), 3.26 (1H m, H-2), 3.55 (1H dd, *J*=5 and 14 Hz, H-3), 3.69 (2H m, H-4″ and 5″), 3.75 (6H s, 2×OCH_3), 4.04 (1H t, *J*=8 Hz, H-2″), 4.32 (1H t, *J*=8 Hz, H-3″), 4.38 (1H t, *J*=8 Hz, H-11), 4.80 (1H dd, *J*=9 and 11 Hz, H-11), 4.88 (1H d, *J*=5 Hz, H-4), 4.91 (1H q, *J*=5 Hz, CH of ethylidene), 5.74 (1H d, *J*=3.5 Hz, H-1), 5.76 (1H d, *J*=8 Hz, H-1″), 5.84 and 5.91 (2H ABq, *J*=1 Hz, methylene), 6.45 (1H s, H-5), and 6.86 (2H s, H-2′ and 6′); MS (FD) *m/z* 604 (M^+) and 398.

1-β-Methoxy-α-peltatin (12). A solution of debenzyloxycarbonylated compound of **10** (54 mg) in methanol (5 ml) was refluxed in the presence of zinc acetate (25 mg) for 4 h. After being diluted with chloroform (10 ml), the solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave a solid, which was subjected to preparative thin-layer chromatography on silica gel developed with chloroform-methanol (1:5). Compound **12** was obtained as a solid in a yield of 66%. **12** was recrystallized from acetone to give a colorless crystal: mp 209—211 °C (decomp); $[\alpha]_D^{20}$ −92° (*c* 0.57, $CHCl_3$); IR (KBr) 1772, 1630, 1518, 1478, 1217, 1113 and 1062 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.70 (1H m, H-2), 3.28 (1H dd, *J*=5 and 14 Hz, H-3), 3.53 (3H s, OCH_3), 3.78 (6H s, 2×OCH_3), 4.35 (2H m, H-11), 4.60 (1H d, *J*=5 Hz, H-11), 4.86 (1H d, *J*=3 Hz, H-1), 5.40 (1H s, OH), 5.61 (1H s, OH), 5.96 (2H m, methylene), 6.22 (1H s, H-5), and 6.28 (2H s, H-2′ and 6′); MS (FD) *m/z* 430 (M^+).

4′-O-Benzyloxycarbonyl-1-β-hydroxy-α-peltatin (13). A solution of **7** (200 mg) in ethyl acetate (20 ml) was stirred under atmosphere of hydrogen in the presence of 10% Pd/C (10 mg) at −20 °C for 1 h. Catalyst was removed by filtration, and the filtrate was evaporated to give a solid. The solid was subjected to preparative thin-layer chromatography on silica gel developed with toluene-acetone (4:1). Compound **13** and 1-β-hydroxy-α-peltatin (**14**) were obtained as solids in yields of 70 and 25%, respectively. Each solid was recrystallized from methanol. **13**: mp 172—174 °C; $[\alpha]_D^{20}$ −55° (*c* 0.34, $CHCl_3$); IR (KBr) 1780, 1618, 1268, and 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=2.75 (1H m, H-2), 3.25 (1H dd, *J*=5 and 14 Hz, H-3), 3.69 (6H s, 2×OCH_3), 4.36 (1H t, *J*=8 Hz, H-11), 4.47 (1H dd, *J*=8 and 11 Hz, H-11), 4.63 (1H d, *J*=5 Hz, H-4), 5.21 (1H d, *J*=4.3 Hz, H-1), 5.26 (2H s, $C\underline{H}_2Ph$), 5.98 (2H s, methylene), 6.24 (1H s, H-5), 6.34 (2H s, H-2′ and 6′) and 7.3—7.5 (5H m, Ph); MS (FD) *m/z* 550 (M^+), 532 and 398. **14**: mp 212—214 °C; $[\alpha]_D^{20}$ −74° (*c* 0.25, $CHCl_3$); IR (KBr) 1778, 1615, and 1110 cm^{-1}; ^1H NMR ($CDCl_3$ 270 MHz) δ=2.77 (1H m, H-2), 3.23 (1H dd, *J*=4.7 and 14 Hz, H-3), 3.78 (6H s, 2×OCH_3), 4.34 (1H t, *J*=8 Hz, H-11), 4.46 (1H dd, *J*=8 and 11 Hz, H-11), 4.61 (1H d, *J*=4.7 Hz, H-4), 5.23 (1H broad s, H-1), 5.99 (2H s, methylene), 6.26 (1H s, H-5), and 6.32 (2H s, H-2′ and 6′), MS (FD) *m/z* 416 (M^+) and 398.

4′-O-Benzyloxycarbonyl-1-β-hydroxy-8-O-methyl-α-peltatin (15). A solution of **13** (168 mg) in acetone (5 ml) was refluxed with methyl iodide (150 μl) in the presence of potassium carbonate (140 mg) for 1 h, and the mixture was further refluxed with an additional methyl iodide (100 μl) for 1 h. Evaporation of the solvent gave an solid, which was dissolved in chloroform. The solution was washed with water, dried over Na_2SO_4, and filtered. The solvent was evaporated to give a solid. The solid was subjected to preparative thin-layer chromatography on silica gel developed with toluene-acetone (2:1). Compound **16** was obtained as a solid (174 mg) quantitatively. The solid was recrystallized from methanol: mp 107—108 °C $[\alpha]_D^{27}$ −57° (*c* 0.55, $CHCl_3$); IR (KBr) 1770, 1256, 1218, and 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=2.72 (1H m, H-2), 3.27 (1H dd, *J*=5 and 14 Hz, H-3), 3.70 (6H s, 2×OCH_3), 4.17 (3H s, OCH_3), 4.40 (2H m, H-11), 4.62 (1H d, *J*=5 Hz, H-4), 5.15 (1H d, *J*=3.5 Hz, H-1), 5.26 (2H s, $C\underline{H}_2Ph$), 5.95 (2H s, methylene), 6.29 (1H s, H-5), 6.37 (2H s, H-2′ and 6′), and 7.3—7.5 (5H m, Ph); MS (FAB) *m/z* 565 (M^++H), 547 and 429.

1-O-β-(2,3-Di-O-chloroacetyl-4,6-O-ethylidene-β-D-glucopyranosyl)-4′-O-benzyloxycarbonyl-8-O-methyl-α-peltatin (16). Procedure used was similar to that used for the preparation of **10** from **7** and **9** (78% yield). **16**: mp 129—130 °C; $[\alpha]_D^{23}$ −63° (*c* 0.53, $CHCl_3$); IR (KBr) 1775, 1480, 1258, 1206, and 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=1.35 (3H d, *J*=5 Hz, CH_3 of ethylidene), 2.73 (1H m, H-2), 3.67 (6H s, 2×OCH_3), 4.16 (3H s, OCH_3), 5.96 (2H s, methylene), 6.29 (3H s, H-5, 2′ and 6′), and 7.3—7.5 (5H m, Ph); MS (FAB) *m/z* 905 (M^+ +H), 770, and 547.

1-O-β-(4,6-O-Ethylidene-β-D-glucopyranosyl)-8-O-methyl-α-peltatin (17). Procedures used were similar to those used for the preparation of **11** from **10** (69% yield). **17**: mp 221—222 °C; $[\alpha]_D^{23}$ −91° (*c* 0.54, $CHCl_3$); IR (KBr) 1777, 1618, 1220 and 1118 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz), δ=1.39 (3H d, *J*=5 Hz, CH_3 of ethylidene), 2.53 (1H broad s, 2″-OH), 2.70 (1H broad s, 3″-OH), 2.75 (1H m, H-2), 3.19 (1H dd, *J*=5.5 and 14 Hz, H-3), 3.38 (1H t, *J*=8 Hz, H-2″), 3.55 (1H m, H-6″), 3.77 (6H s, 2×OCH_3), 4.14 (3H s, OCH_3), 4.17 (1H dd, *J*=8 and 9 Hz, H-11), 4.46 (1H dd, *J*=9 and 11 Hz, H-11), 4.58 (1H d, *J*=5.5 Hz, H-4), 4.75 (1H q, *J*=5 Hz, CH of ethylidene), 4.84 (1H d, *J*=8 Hz, H-1″), 5.15 (1H d, *J*=3.5 Hz, H-1), 5.40 (1H s, 4′-OH), 5.94 and 5.96 (2H ABq, *J*=1.5 Hz, methylene), 6.26 (1H s, H-5), and 6.26 (2H s, H-2′ and 6′), MS (FAB) *m/z* 618 (M^+) and 413.

1-O-β-(2-Benzyloxycarbonylamino-3-chloroacetyl-2-deoxy-4,6-O-ethylidene-β-D-glucopyranosyl)-4′-O-benzyloxycarbonyl-8-O-methyl-α-peltatin (19). Procedure used was similar to that used for the preparation of **10** from **7** and **9** (92% yield). **19**: mp 219—220 °C; $[\alpha]_D^{18}$ −53° (*c* 0.52, $CHCl_3$); IR (KBr) 1790, 1775, 1700, 1246, 1211, and 1132 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=1.33 (3H d, *J*=5 Hz, CH_3 of ethylidene), 2.73 (1H m, H-2), 3.67 (6H s, 2×OCH_3), 4.31 (3H s, OCH_3), 5.62 and 5.86 (1H each s, methylene), 6.24 (1H s, H-5), 6.29 (2H s, H-2′ and 6′) and 7.2—7.5 (10 H m, 2×Ph); MS (FAB) *m/z* 984 (M^+ +Na), 828, and 547.

1-O-β-(2-Amino-2-deoxy-4,6-O-ethylidene-β-D-glucopyranosyl)-8-O-methyl-α-peltatin (20). A solution of **19** (40 mg) in a mixture of dichloromethane (2 ml) and pyridine (1 ml) was stirred in the presence of ethylenediamine (30 μl) at 0 °C for 2 h. The mixture was diluted with chloroform (5 ml), and the solution was washed with 5% aqueous $KHSO_4$ solution and water. The chloroform layer was dried over Na_2SO_4, and filtered. The solvent was evaporated to give a crude solid (40 mg). The solid was dissolved in ethyl acetate-ethanol (3:2, 2 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 a solid, which was subjected to preparative thin-layer chromatography on silica gel developed with chloroform-methanol (9 : 1). Compound **20** was obtained as a solid in a yield of 66%. The solid was recrystallized from methanol: mp 215—220 °C (decomp); $[\alpha]_D^{20}$ −82° (*c* 0.84, $CHCl_3$); IR (KBr) 1778, 1615, 1480, and 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.38 (3H d, *J*=5 Hz, CH_3 of ethylidene), 2.61 (1H dd, *J*=8 and 10 Hz, H-2″), 2.74 (1H m, H-2), 3.22 (1H dd, *J*=5.5 and 14 Hz, H-3), 3.77 (6H s, 2×OCH_3), 4.13 (3H s, OCH_3), 4.16 (1H dd, *J*=8 and 9 Hz, H-11), 4.45 (1H dd, *J*=9 and 11 Hz, H-11), 4.58 (1H d, *J*=5.5 Hz, H-4), 4.75 (1H d, *J*=8 Hz, H-1″), 4.75 (1H q, *J*=5 Hz, CH of ethylidene), 5.14 (1H d, *J*=3.5 Hz, H-1), 5.94 and 5.96 (2H, ABq, *J*=1.5 Hz, methylene), and 6.26 (3H s, H-5, 2′ and 6′); MS (FAB) *m/z* 618 (M^+ +H) and 413.

References

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