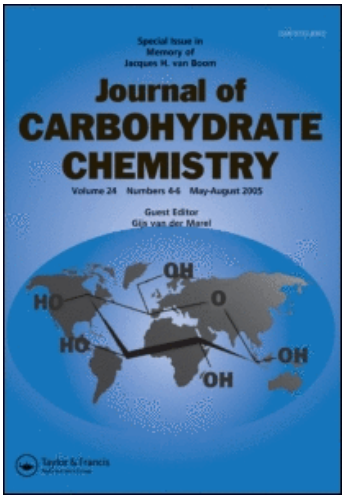

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A NEW APPROACH TO THE SYNTHESIS OF ETOPOSIDE (VP 16)

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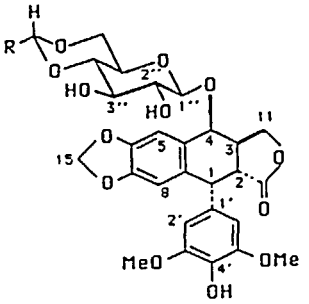
ABSTRACT

The synthesis of the glycosyl donors 2,3-di-*O*-acetyl- and 2,3-di-*O*-chloroacetyl-4,6-*O*-ethylidene-ß-D-glucopyranose (**10β**) and (**11β**) and their use for the glycosidation of 4'-*O*-benzyloxycarbonyl- and 4'-*O*-chloroacetyl-4'-*O*-demethyl-4-epi-podophyllotoxins (**12**) and (**13**) is described. Starting from benzyl β-D-glucopyranoside (**6**), benzyl 2,3-di-*O*-acetyl- and 2,3-di-*O*-chloroacetyl-4,6-*O*-ethylidene-ß-D-glucopyranoside (**8**) and (**9**) were prepared. Hydrogenolysis of the benzyl group in **8** or **9** afforded the β-hydroxy glucopyranose donors **10β** and **11β**. Condensation of **10β** or **11β** with 4'-O-Z-epi-podophyllotoxin **12** in the presence of BF_3-etherate gave selectively the 4-O-(2,3-di-*O*-acetyl- or -2,3-di-*O*-chloroacetyl-4,6-*O*-ethylidene-β-D-glucopyranosyl)-epi-podophyllotoxins **14β** and **15β**, respectively. The β-glycoside **16** was prepared in the same manner starting from **11β** and 4'-*O*-chloroacetyl-epi-podophyllotoxin **13**. By deblocking (Dowex 1X8, 3:2 methanol-chloroform) of the chloroacetyl groups in **15β** and the following hydrogenolysis of the benzyloxycarbonyl group in **17** etoposide **1** was obtained. The deacylation of **16** afforded **1** in a one step procedure.

INTRODUCTION

Etoposides[1] represent an important group of substances among the antitumor chemotherapeutic agents. Two of the substances, Etoposide (VP-16) **1** and Teniposide

(VM-26) **2**, have already proved to be clinically successful for the treatment of small cell lung cancers, lymphoma, leukemia and Karposi's sarcoma.[2]



1: Etoposide (VP-16-213) R = CH_3

2: Teniposide (VM-26) R = 

In the synthesis of etoposides the most difficult and demanding steps are considered to be the glycosidation and deacylation steps. As described by Kuhn et al.,[3,4] glycosidation[4] of epi-podophyllotoxin requires the use of a β-anomeric glucopyranose donor. At C-4 the epi-podophyllotoxin forms a carbonium ion in the presence of BF_3-etherate which is attacked by the hydroxy group of the β-glucopyranose to provide a β-glycosidic linkage. As has been reported 2,3-di-*O*-acetyl- and 2,3-di-*O*-chloroacetyl-4,6-*O*-ethylidene-ß-D-glucopyranose (**10β**)[5] and (**11β**)[7] each proved to be useful donors for glycosidation. A problem in the deacylation of the glycosyl-epi-podophyllotoxin by ethanolysis with a zinc(II) salt catalyst is a concomintant cleavage of the lactone ring which cannot be avoided.[3]

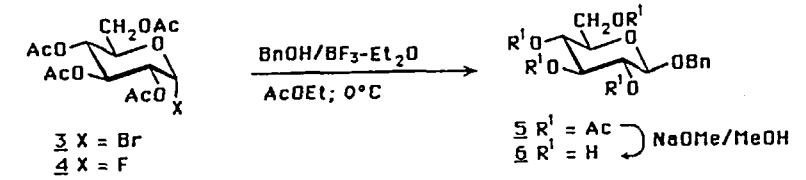
In the present paper we present a new method for the synthesis of the β-glucopyranose donors as well as a simple procedure for the deacylation of chloroacetyl protecting groups.

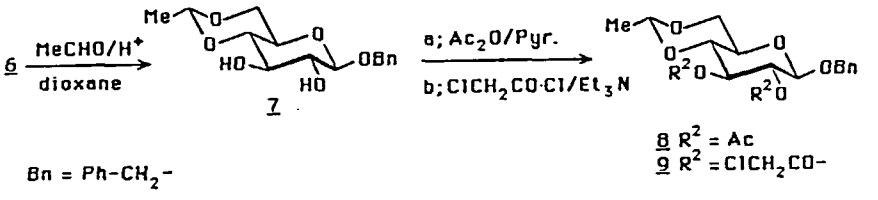
RESULTS AND DISCUSSION

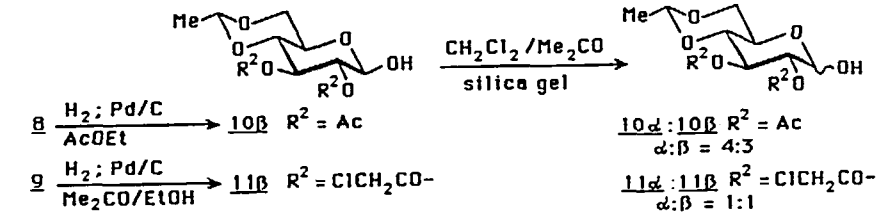
The synthesis of the donors **10β** and **11β** from the corresponding 1-*O*-benzyloxycarbonyl precursors was achieved by means of hydrogenolysis.[5,6] Because there is a simple access of benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**5**)[7,8] it was decided to prepare the β-glucopyranose donors **10β** and **11β** using a procedure in which the β-anomeric position is fixed from the start.

The benzyl glucoside **5** is usually synthesized from acetobromoglucose **3** and benzyl alcohol using mercury or silver salts as the promoter.[8,9] In order to avoid the use of these poisonous and/or expensive salts we employed 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl fluoride (**4**)[9] for the synthesis of **5**. The process of glycosylation in the presence

of BF_3-etherate as the promoter[10] and ethyl acetate as the reaction medium affords **5** in a yield of 76%. When solvents other than acetonitrile or dichloromethane, usually employed for this synthesis, were used[10,11] the glycosylation process led to less consistent results.







Deacylation of **5** by the method of Zemplén provided benzyl β-D-glucopyranoside (**6**) which could be reacted with acetaldehyde and conc. sulfuric acid as catalyst to provide the 4,6-*O*-ethylidene-glucoside **7** in a yield of 82%. Subsequent acylation of **7** with acetic anhydride-pyridine or chloroacetyl chloride-triethylamine in dichloromethane then yielded the 2,3-di-*O*-acetate **8** or the 2,3-di-*O*-chloroacetate **9**.

The benzyl group in **8** was cleaved hydrogenolytically using 10% Pd/C in ethyl acetate to give the β-anomer **10β** with the optical rotation value of $[\alpha]_D^{23}$ -25.5° (c 0.87, ethyl acetate). For the hydrogenolysis (10% Pd/C) of the benzyl group in **9**, however, 10:1 acetone-ethanol proved to be a suitable reaction medium.[6] Mutarotation of the resulting β-anomer **11β** ($[\alpha]_D^{23}$ -27.5°) proceeds relatively slowly in the reaction medium (see Fig. 1). The ^{1}H-NMR spectra of **10β** or **11β** in acetone-d_6 show the presence of the anomeric β-OH group ($J_{1,2}$= 7.7 Hz) and the intramolecular hydrogen bonding between the hydroxy group and the ring oxygen atom (OH-1: 6.16 ppm, $J_{1,OH}$ = 6.8 Hz, $^4J_{2,OH}$ = 1.0 Hz).

To obtain further data on the speed of mutarotation under the conditions of hydrogenolysis and glycosidation, the changes in optical rotation of **10β** and **11β** were

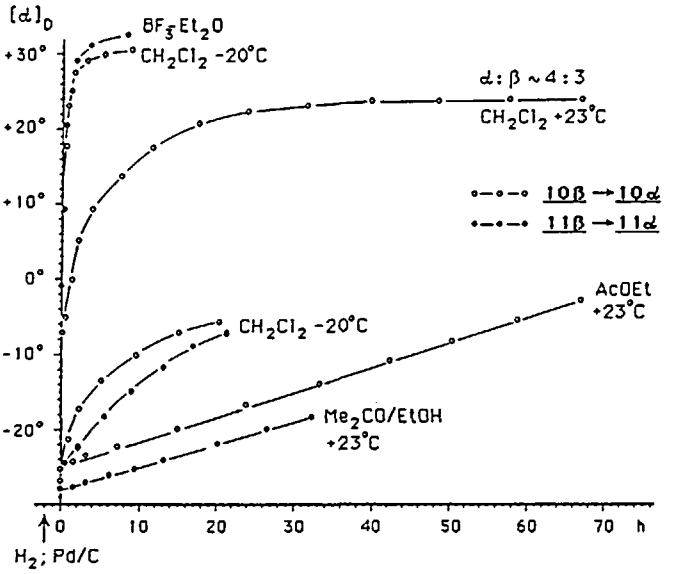
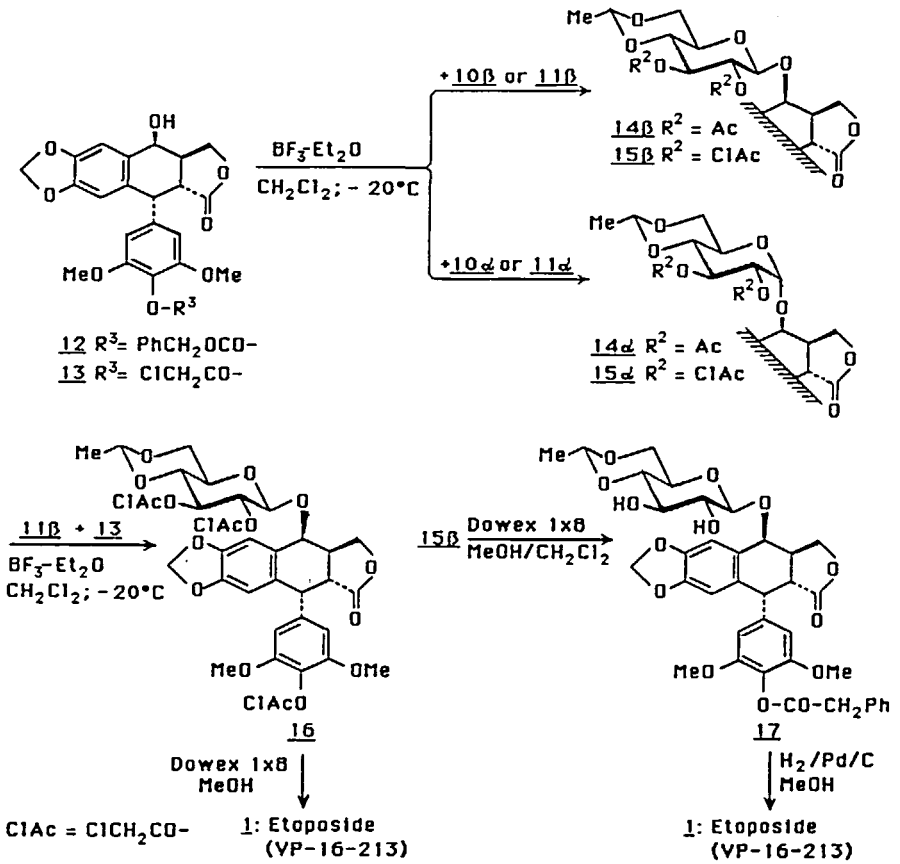


Fig.1. Speed of mutarotation of **10β** → **10α** and **11β** → **11α** under the conditions hydrogenolysis and glycosidation.

measured in different solutions at room temperature and at -20 °C during a period of 67 h (Fig. 1). The measurements showed that under the chosen conditions of hydrogenolysis (ethyl acetate for **10β** and 10:1 acetone-ethanol for **11β**) the mutarotation proceeds linearly with about +0.25°/h. When the β-anomers **10β** or **11β** were dissolved in dichloromethane at -20 °C, the mutarotation proceeded faster (about +2.5°/h). Under the conditions of glycosidation (dichloromethane/BF_3-etherate at -20 °C) the optical rotation value changed exponentially in the first hour and stabilized during the next 1 h ($[a]_D$ about +31°). It can be deduced that due to the influence of BF_3-etherate the equilibrium between α- and β-anomers was achieved. Indeed, when **10β** was chromatographed on silica gel with dichloromethane-acetone, a mixture of the α- and β-anomer (**10α**:**10β** = 4:3; ^1H NMR, $CDCl_3$) was obtained with a comparable optical rotation value ($[\alpha]_D$ = +30.1°). Compound **11β** was likewise converted to the mixture of α- and β-anomer (**11α**:**11β** = 1:1; ^1H NMR, $CDCl_3$) by chromatography on silica gel. The ^1H resonances of the α-anomers **10α** and **11α** were assigned without doubt by means of ^1H NMR, $^1H,^1H$-COSY and $^1H,^{13}C$-COSY spectra of the mixture of α- and β-anomers.

The β-anomers **10β** and **11β** were used for glycosidation of 4'-*O*-benzyloxycarbonyl(Z)- and 4'-*O*-chloroacetyl(ClAc)-epi-podophyllotoxins **12** [3,12] and **13** [6] under essentially the reaction conditions as described (BF_3-etherate, dichloromethane, molecular

sieves 4 Å, at -20 °C).[5,6] The synthesis afforded the β-glycosidically-linked products **14β**, **15β** or **16** in a yield of 70% to 80%. The α-glycosides were produced in trace amounts only. When the mixture of α- and β-anomers **10α/10β** or **11α/11β** was used to glycosidate 4'-*O*-Z-epi-podophylotoxin **12** under the same reaction conditions, a mixture of α- and β-glycosides **14α/14β** or **15α/15β** was obtained in about the same ratio as the starting α- and β-anomer donors.



Deacylation of the protected etoposides is particularly difficult due to the occurrence of secondary reactions, i.e. epimerization at the C-2 atom (base-catalyzed reaction) and cleavage of the γ-lactone (acid-catalyzed reaction) of the epi-podophyllotoxin aglycon.[3] As expected, cleavage of the acetyl protecting groups in **14β** using the described procedure[3] ($ZnCl_2$, methanol, reflux) did not afford **17** in satisfactory purity and yield.

Since similar difficulties with the chloroacetyl-protected[14] derivatives were expected novel cleavage procedures for these protecting groups were of interest. It was observed that dechloroacylation could be performed with ion-exchange resin Dowex 1X8

(mesh size: 20-50; counter-ion: H) in methanol or 3:2 methanol-dichloromethane at room temperature without any considerable formation of secondary products. Deacylation of **15β** with Dowex 1X8 at pH 7 (solution) leads to 4'-O-Z-etoposide **17** within 1 h. Under the above described conditions deacylation of **16** leads directly to etoposide **1**. Since, under these conditions, the O-acetyl protecting groups in the diacetate **14β** are left in tact, this new method should prove useful even for partial deblocking of mixed acylated compounds. When the benzyloxycarbonyl protecting group in **17** is hydrogenolytically cleaved with 10% Pd/C in methanol the substance is completely converted into etoposide **1**.

EXPERIMENTAL

General Procedures. Reactions were carried out at ambient temperature unless otherwise stated. Solutions were concentrated under reduced pressure below 40 °C bath temperature. The phosphate or citrate buffer solutions used to wash the organic phases were prepared as follows: aqueous 0.1M potassium dihydrogen phosphate or 0.1M sodium citrate solutions were adjusted to the corresponding pH value using 0.1N NaOH or 0.1N HCl. Melting points, determined on a Büchi apparatus, are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz, 300 MHz or 400 MHz on a Bruker AC-200, a Bruker AC-300 or a Bruker AM-400 respectively and at 400 MHz also on a Jeol GX-400 NMR spectrometer. Chemical shifts for ^{1}H resonances were recorded relative to tetramethylsilane (0.0). The ^{1}H resonances were routinely assigned by ^{1}H,^{1}H-COSY experiments using the standard pulse sequences of the Bruker Aspect-300 software. Specific rotations were determined with a Perkin-Elmer 241 polarimeter equipped with 10 cm cuvettes. Reactions were monitored by TLC on silica gel plates 60 F 254 (Merck) and the spots were detected by ultraviolet light or by spraying with ethanolic 10% sulfuric acid solution and subsequent heating to 150-200 °C. The glycoside syntheses were performed under an argon or nitrogen cover. Preparative chromatography was performed on silica gel (Merck Kieselgel 60, particle size 0.015-0.040 mm) with the solvent system specified.

Benzyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (5). 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl fluoride (**4**, 60 g, 171 mmol) and benzyl alcohol (20 g, 184.9 mmol) were coevaporated *in vacuo* with toluene (700 mL). The mixture was dissolved in dry ethyl acetate (600 mL), BF_3-etherate (50%, 31 mL) was added at 0 °C and the mixture stirred for 16 h at 0 °C. After addition of triethylamine (25 mL) at 0 °C, the mixture was evaporated *in vacuo*. The residue was dissolved in dichloromethane, washed with citrate buffer (pH 3.5) and aqueous NaCl solution successively. The organic layer was dried (sodium sulfate) and concentrated *in vacuo*. Chromatography of the residue on silica gel (800 g) in 13:1 dichloromethane-ethyl acetate afforded **5** (61.4 g, 82%): mp 100 °C; $[\alpha]_D$ -50.7° (c 1, dichloromethane). Lit.[8,13]: mp 100 °C; $[\alpha]_D$ -53.3° (chloroform), -51° (ethanol).

Benzyl β-D-Glucopyranoside (6). Compound **5** (73.1 g, 167 mmol) was dissolved in dry methanol (500 mL) and deacetylated with a solution of 1M NaOMe in methanol at pH 12. After neutralization with Dowex 50 Wx8 (mesh size: 200-400; counter-ion: Na), the suspension was filtered and the filtrate was than concentrated *in vacuo*. The resulting product (45.1 g) showed one spot on TLC and was used in subsequent steps without further purification: $[\alpha]_D$ -53.0° (c 1, EtOH). Lit.[8]: mp 122 °C; $[\alpha]_D$ -57.6° (c 1.5, MeOH)

Benzyl 4,6-*O*-Ethylidene-β-D-glucopyranoside (7). To a stirred suspension of **6** (45 g, 166 mmol) in dioxane at 10 °C was added acetaldehyde (23 mL) and dropwise conc. H_2SO_4 (1.3 g). The reaction mixture was stirred at room temperature for 16 h, neutralized with a solution of 0.1M sodium methylate in methanol and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (400 mL) and the organic layer was washed with saturated aqueous NaCl solution (150 mL x 3), dried (sodium sulfate) and concentrated *in vacuo*. The residue was crystallized from ether to give **7** (30.5 g, 62%). The remaining syrup was chromatographed on a column of silica gel (150 g) with 1:1:0.1 dichloromethane-ethyl acetate-petroleum ether to give a further amount of **7** (10 g, 20%): mp 162 °C; $[\alpha]_D^{23}$ -79.5° (c 1, ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H, Ph), 4.91 (d, 1H, ^2J = 11.5 Hz, Ph-CH-A), 4.73 (q, 1H, $J_{Me,CH}$ = 5.0 Hz, Me-CH=), 4.60 (d, 1H, ^2J, Ph-CH-B), 4.45 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.18 (dd, 1H, $J_{5,6eq}$ = 4.6 Hz, ^2J = 10.5 Hz, H-6eq), 3.72 (ddd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 9.0 Hz, $J_{3,OH}$ = 2.5 Hz, H-3), 3.59 (dd, 1H, $J_{5,6ax}$ = 9.5 Hz, ^2J, H-6ax), 3.48 (ddd, 1H, $J_{1,2}$, $J_{2,3}$, $J_{2,OH}$ = 3.5 Hz, H-2), 3.35 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 9.0 Hz, H-4), 3.29 (ddd, 1H, $J_{4,5}$, $J_{5,6ax}$, $J_{5,6eq}$, H-5), 3.10 (d, 1H, $J_{3,OH}$, OH-3), 2.88 (br s, 1H, OH-2), 1.38 (d, 3H, $J_{Me,CH}$, CH_3-C=).

Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.72; H, 6.82.

Benzyl 2,3-Di-*O*-acetyl-4,6-ethylidene-β-D-glucopyranoside (8). Compound **7** (4.12 g, 13.90 mmol) was dissolved in 1:1 dichloromethane-pyridine (120 mL) and acetic anhydride (5.3 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 16 h and concentrated *in vacuo*. The residue was dissolved in chloroform (120 mL) and successively washed with phosphate buffer (pH 8, 60 mL x 3), aqueous 0.1N HCl to remove pyridine and saturated NaCl aqueous solution. The organic layer was dried (sodium sulfate) and concentrated *in vacuo*. The resulting product was crystallized from ether-petroleum ether to give **8** (4.75 g, 90%): mp 155 °C; $[\alpha]_D^{23}$ -87° (c 1, chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H, Ph), 5.17 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 5.00 (dd, 1H, $J_{1,2}$ = 7.7 Hz, $J_{2,3}$, H-2), 4.87 (d, 1H, ^2J = 12.0 Hz, Ph-CH-A), 4.68 (q, 1H, $J_{Me,CH}$ = 5.0 Hz, Me-CH=), 4.59 (d, 1H, ^2J, Ph-CH-B), 4.59 (d, 1H, $J_{1,2}$, H-1), 4.21 (dd, 1H, $J_{5,6eq}$ = 4.8 Hz, ^2J = 10.0 Hz, H-6eq), 3.49 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 9.0 Hz, H-4), 3.25 (ddd, 1H, $J_{4,5}$, $J_{5,6ax}$, $J_{5,6eq}$, H-5), 2.06 and 2.00 (2s, 6H, CH_3-CO), 1.32 (d, 3H, $J_{Me,CH}$, CH_3-C=).

Anal. Calcd for $C_{19}H_{24}O_8$: C, 59.99; H, 6.36. Found: C, 59.94; H, 6.38.

Benzyl 2,3-Di-*O*-chloroacetyl-4,6-*O*-ethylidene-β-D-glucopyranoside (9). Compound **7** (25 g, 84.3 mmol) was at first coevaporated with toluene, then dissolved in dry

dichloromethane (400 mL), and dry triethylamine (56 mL) was added. To a stirred mixture at -20 °C was added dropwise a solution of chloroacetyl chloride (20 mL, 252.9 mmol) in dichloromethane (250 mL). After 4 h stirring at -20 °C a further amount of triethylamine (11 mL) and chloroacetyl chloride (7 mL) was added. The reaction mixture was stirred for a further 10 h, filtered, and successively washed with phosphate buffer (pH 8.5, 120 mL x 2) and citrate buffer (pH 5.5, 100 mL). The organic layer was dried (sodium sulfate) and concentrated *in vacuo*. The residue was filtered on a column of silica gel (100 g) with 6:6:1 dichloromethane-petroleum ether-ethyl acetate. The remaining product was crystallized from ether-petroleum ether to give **9** (28.7 g, 76%): mp 105 °C; $[\alpha]_D$ -64.9° (c 1.0, dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H, Ph), 5.25 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 5.06 (dd, 1H, $J_{1,2}$ = 7.7 Hz, $J_{2,3}$, H-2), 4.88 (d, 1H, ^{2}J = 12.0 Hz, Ph-CH-A), 4.69 (q, 1H, $J_{Me,CH}$ = 5.0 Hz, Me-CH=), 4.63 (d, 1H, $J_{1,2}$, H-1), 4.59 (d, 1H ^{2}J, Ph-CH-B), 4.23 (dd, 1H, $J_{5,6eq}$ = 4.5 Hz, ^{2}J 10.5 Hz, H-6eq), 4.08 (d, 1H, ^{2}J = 15.0 Hz, Cl-CH-A), 4.02 (d, 1H, ^{2}J, Cl-CH-B), 3.96 (d, 1H, ^{2}J = 15.0 Hz, Cl-CH-A'), 3.88 (d, 1H, ^{2}J, Cl-CH-B'), 3.60 (dd, 1H, $J_{5,6ax}$ = 10.0 Hz, ^{2}J, H-6ax), 3.54 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 9.5 Hz, H-4), 3.37 (ddd, 1H, $J_{4,5}$, $J_{5,6ax}$, $J_{5,6eq}$, H-5), 1.32 (d, 3H, $J_{Me,CH}$, CH_3-C=).

Anal. Calcd for $C_{19}H_{22}Cl_2O_8$: C, 50.79; H, 4.94; Cl, 15.78. Found: C, 50.83; H, 4.97; Cl, 15.60.

2,3-Di-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucopyranose (10β). Compound **8** (1.0 g, 2.62 mmol) in ethyl acetate (40 mL) was hydrogenolyzed in the presence of 10% Pd/C (1.0 g) at atmospheric pressure and room temperature for 1.5 h. The catalyst was filtered off on magnesium sulfate and washed with ethyl acetate at 0 °C, and the combined filtrates and washings were concentrated *in vacuo* at room temperature. The remaining syrup (0.73 g, 96%) showed one spot on TLC and was used in subsequent steps without further purification: $[\alpha]_D^{23}$ -25.5° (c 0.87, ethyl acetate), -24° (c 0.68, acetone); Lit.[5]: mp 109-111 °C; $[a]_D$ -35.9° (c 1.006, chloroform); ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 6.16 (br d, 1H, $J_{1,OH}$ = 6.8 Hz, $^4J_{2,OH}$ = 1 Hz, OH-1), 5.05 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 9.6 Hz, H-3), 4.77 (dd, 1H, $J_{1,OH}$, $J_{1,2}$ = 7.7 Hz, H-1), 4.67 (dd, 1H, $J_{1,2}$, $J_{2,3}$, ^{4}J, H-2), 4.62 (q, 1H, $J_{Me,CH}$ = 5.0 Hz, Me-CH=), 3.95 (dd, 1H, $J_{5,6eq}$ = 4.3 Hz, ^{2}J = 9.9 Hz, H-6eq), 3.42 (dd, 1H, $J_{5,6ax}$ = 10.0 Hz, ^{2}J, H-6ax), 3.38 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 9.7 Hz, H-4), 3.33 (ddd, 1H, $J_{4,5}$, $J_{5,6ax}$, $J_{5,6eq}$, H-5), 1.85 and 1.84 (2s, 2H, CH_3-CO), 1.09 (d, 1H, $J_{Me,CH}$, CH_3-C=).

Anal. Calcd for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25. Found: C, 49.38; H, 6.25.

***2,3-Di*-O-*acetyl-4,6*-O-*ethylidene*-α,β-D-*glucopyranose* (10α/10α).** Compound **10β** (0.73 g, 2.51 mmol) was chromatographed on a column of silica gel (25 g) with 4:1 dichloromethane-acetone to give product mixture **10α:10β** (4:3): syrup; $[\alpha]_D^{23}$ + 30.1° (c 1, ethyl acetate); *Compound* **10α**: ^{1}H NMR (400 MHz, $(CD_3)_2CO$), δ 6.03 (dd, 1H, $J_{1,OH}$ = 4.6 Hz, $^4J_{2,OH}$ = 1.2 Hz, OH-1), 5.36 (dd, 1H, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 9.9 Hz, H-3), 5.21 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{1,OH}$, H-1), 4.63 (ddd, 1H, $J_{1,2}$, $J_{2,3}$, ^{4}J, H-2), 4.62 (q, 1H, $J_{Me,CH}$ = 5.0 Hz, Me-CH=), 3.87 (dd, 1H, $J_{5,6eq}$ = 4.9 Hz, ^{2}J = 9.9 Hz, H-6eq), 3.80 (ddd, 1H, $J_{4,5}$ = 9.8

Hz, $J_{5,6ax}$ = 9.8 Hz, $J_{5,6eq}$, H-5), 3.41 (dd, 1H, $J_{5,6ax}$, ^2J, H-6ax), 3.39 (dd, 1H, $J_{3,4}$, $J_{4,5}$, H-4), 1.88 and 1.87 (2s, 6H, CH_3-CO),1.09 (d, 3H, $J_{Me,CH}$, CH_3-C=).

2,3-Di-*O*-chloroacetyl-4,6-*O*-ethylidene-β-D-glucopyranose (11β). Compound **9** (25.0 g, 55.6 mmol) in 10:1 acetone-ethanol (660 mL) was hydrogenolyzed in the presence of 10% Pd/C (15.0 g) at atmospheric pressure and room temperature for 1.75 h. The catalyst was filtered off and washed with 10:1 acetone-ethanol at 0 °C, and the filtrate was concentrated *in vacuo* at room temperature. The remaining syrup was coevaporated with toluene to give **11β** (20 g) and was used in subsequent steps without further purification: $[a]_D^{23}$ -27.5° (c 1, 10:1 acetone-ethanol); ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 6.50 (d, 1H, $J_{1,OH}$ = 6.3 Hz, OH-1), 5.32 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 4.99 (dd, 1H, $J_{1,2}$ = 7.6 Hz, $J_{1,OH}$, H-1), 4.91 (dd, 1H, $J_{1,2}$, $J_{2,3}$, H-2), 4.28 (d, 1H, ^2J = 15.0 Hz, Cl-CH-A), 4.27 (d, 1H, ^2J = 15 Hz, Cl-CH-A'), 4.23 (d, 1H, ^2J, Cl-CH-B), 4.22 (d, 1H, ^2J, Cl-CH-B'), 4.11 (dd, 1H, $J_{5,6eq}$ = 4.4 Hz, ^2J = 8.9 Hz, H-6eq), 3.61 (dd, 1H, $J_{5,6ax}$ = 9.6 Hz, ^2J, H-6ax, 3.58 (dd, 1H, $J_{3,4}$, $J_{4,5}$ = 9.5 Hz, H-4), 3.50 (ddd, 1H, $J_{4,5}$, $J_{5,6ax}$, $J_{5,6eq}$, H-5), 1.22 (d, 1H, $J_{Me,CH}$, CH_3-C=).

11β was analyzed after chromatography as a mixture of **11α/11β**.

2,3-Di-*O*-chloroacetyl-4,6-*O*-ethylidene-α- and β-D-glucopyranose (11α/11β). Compound **11β** (1.0 g, 2.78 mmol) was filtered on a column of silica gel (25 g) with 4:1 dichloromethane-acetone to give a mixture of the α- and β-hydroxy compound **11α/11β** (α:β~1:1, 0.96 g, 96%): syrup; $[\alpha]_D^{23}$ +14.7° (c 1, chloroform).

Compound **11α**: ^1H NMR (400 MHz, $(CD_3)_2CO$) d 6.35 (dd, 1H, $J_{1,OH}$ = 3.8 Hz, $^4J_{2,OH}$ = 1.3 Hz, OH-1), 5.57 (dd, 1H, $J_{2,3}$ = 9.8 Hz, $J_{3,4}$ 9.8 Hz, H-3), 5.43 (dd, 1H, $J_{1,2}$ = 3.8 Hz, $J_{1,OH}$, H-1), 4.86 (ddd, 1H, $J_{1,2}$, $J_{2,3}$, ^4J, H-2), 4.77 (q, 1H, $J_{Me,CH}$ = 5.0 Hz, Me-CH=), 4.3-4.2 (m, 2H, $ClCH_2$), 4.03 (dd, 1H, $J_{5,6eq}$ =5.0 Hz, ^2J = 10.1 Hz, H-6eq), 3.96 (ddd, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6ax}$ = 9.5 Hz; $J_{5,6eq}$, H-5), 3.62 (dd, 1H, $J_{5,6ax}$, ^2J, H-6ax), 3.56 (dd, 1H, $J_{3,4}$, $J_{4,5}$, H-4), 1.23 (d, 3H, $J_{Me,CH}$ = 5.0 Hz; CH_3C=).

Anal. Calcd for $C_{12}H_{16}Cl_2O_8$: C, 40.13; H, 4.49. Found: C, 40.03; H, 4.53.

4'-*O*-Benzyloxycarbonyl-4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucopyranosyl)-4'-*O*-demethyl-4-epi-podophyllotoxin (14β). A cooled (-20 °C) solution of 4'-*O*-benzyloxycarbonyl-4'-*O*-demethyl-4-epi-podophyllotoxin (**12**, 164 mg, 0.31 mmol) and BF_3-etherate (50%, 0.39 mL) were added to the mixture of **10β** (90 mg, 0.31 mmol) and powdered molecular sieves 4 Å (200 mg) at -20 °C. After stirring for 1 h at -18 °C, triethylamine (0.43 mL) and dichloromethane (20 mL) were added. The mixture was stirred for 5 min at -18 °C, filtered and the filtrate was washed successively with citrate buffer (pH 5.5, 20 mL) and saturated NaCl aqueous solution (20 mL). The organic layer was dried (sodium sulfate) and concentrated *in vacuo*. The remaining product was chromatographed on a column of silica gel (65 g) with 5:5:1 dichloromethane-petroleum ether-ethyl acetate to give **14β** (192 mg, 77 %): mp 228 °C; $[\alpha]_D$ -58.2° (c 1, chloroform). Lit.[5]: mp 230°C; $[a]_D$ -60.4°(c 1.054, chloroform); ^1H NMR (300 MHz, $CDCl_3$) δ

7.44-7.32 (m, 5H, Ph), 6.78 (s, 1H, H-5), 6.54 (s, 1H, H-8), 6.26 (s, 2H, H-2' and H-6'), 6.01 (d, 1H, J =1.0 Hz, H-15-A), 5.99 (d, 1H, J = 1.0 Hz, H-15-B), 5.26 (s, 2H, Ph-CH_2), 5.22 (dd, 1H, $J_{2'',3''}$ = 9.0 Hz, $J_{3'',4''}$ = 9.5 Hz, H-3''), 4.92 (dd, 1H, $J_{1'',2''}$ = 7.5 Hz, $J_{2'',3''}$, H-2''), 4.84 (d, 1H, $J_{3,4}$ = 3.3 Hz, H-4), 4.80 (d, 1H, $J_{1'',2''}$, H-1''), 4.70 (q, 1H, $J_{Me,CH}$ = 5.0 Hz, Me-CH=), 4.61 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1), 4.40 (dd,1H, $J_{3,11a}$ = 10.5 Hz, ^2J = 9.0 Hz, H-11-A), 4.23 (dd, 1H, $J_{3,11b}$ = 7.5 Hz, ^2J, H-11-B), 4.20 (dd, 1H, $J_{5'',6''_{eq}}$ = 4.5 Hz, ^2J = 10.3 Hz, H-6''eq), 3.67 (s, 6H, OMe), 3.59 (dd, 1H, $J_{5'',6''_{ax}}$ = 9.7 Hz, ^2J, H-6''ax), 3.47 (dd, 1H, $J_{3'',4''}$, $J_{4'',5''}$ = 9.0 Hz, H-4''), 3.38 (ddd, 1H, $J_{4'',5''}$, $J_{5'',6''ax}$, $J_{5'',6''eq}$, H-5''), 3.17 (dd, 1H, $J_{1,2}$, $J_{2,3}$ = 14.5 Hz, H-2), 2.84 (m, 1H, ΣJ = 36 Hz, H-3), 2.06 and 1.84 (2s, 6H, Ac), 1.35 (d, 3H, $J_{Me,CH}$, CH_3C=).

4'-*O*-Benzyloxycarbonyl-4-*O*-(2,3-di-O-acetyl-4,6-*O*-ethylidene-α- and -β-D-glucopyranosyl)-4'-*O*-demethyl-4-epi-podophyllotoxin (14α and 14β). A mixture of compounds **10α/10β** (72 mg, 0.25 mmol) and epi-podophyllotoxin **12** (133 mg, 0.25 mmol) were dissolved in dichloromethane (20 mL). After addition of powdered molecular sieves 4 Å (200 mg), BF_3-etherate (50%, 0.31 mL) was added at -20 °C. The mixture was stirred for 1 h at -20 °C. Work-up and chromatography as described for the preparation of compound **14β** resulted in compounds **14α** (95 mg, 47%) and **14β** (70 mg, 35%); *Compound* **14α**: mp 136 °C; [α] +49.5° (c 1, chloroform); ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.32 (m, 5H, Ph), 6.89 (s,1H, H-5), 6.54 (s, 1H, H-8), 6.28 (s, 2H, h-2' and H-6'), 6.01 (d, 1H, ^2J = 1.2 Hz, H-15-A), 5.08 (d, 1H, ^2J, H-15-B),5.36 (dd, 1H, $J_{2'',3''}$ = 10.0 Hz, $J_{3'',4''}$ = 9.5 Hz, H-3''), 5.26 (s, 2H, Ph-CH_2), 5.19 (d, 1H, $J_{1'',2''}$ = 4.0 Hz, H-1''), 4.97 (dd, 1H, $J_{1'',2''}$, $J_{2'',3''}$, H-2''), 4.70 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1), 4.68 (d, 1H, $J_{3,4}$ = 3.1 Hz, H-4), 4.63 (q, 1H, $J_{Me,CH}$ = 5.0 Hz, Me-CH=), 4.32 (dd, 1H, $J_{3,11a}$ = 10.5 Hz, ^2J = 8.0 Hz, H-11-A), 4.26 (dd, 1H, $J_{3,11b}$ = 8.0 Hz, ^2J, H-11-B), 4.02 (dd,1H, $J_{5'',6''_{eq}}$ = 2.8 Hz, ^2J = 9.0 Hz, H-6''eq), 3.68 (s, 6H, MeO), 3.51 (dd, 1H, $J_{5'',6''_{ax}}$ = 10.0 Hz, ^2J, H-6''ax), 3.51 (m, 1H, H-5''), 3.49 (dd,1H, $J_{1,2}$, $J_{2,3}$ = 14.5 Hz, H-2), 3.42 (dd,1H, $J_{3'',4''}$, $J_{4'',5''}$ = 10.0 Hz, H-4''), 2.86 (m, 1H, ΣJ = 36.2 Hz, H-3), 2.10 (s, 3H, Ac), 2.06 (s, 3H, Ac), 1.29 (d, 3H, $J_{Me,CH}$, CH_3-C=).

Anal. Calcd for $C_{41}H_{42}O_{17}$: C, 61.04; H, 5.25. Found: C, 61.09; H, 5.27.

4'-*O*-Benzyloxycarbonyl-4-*O*-(2,3-di-*O*-chloroacetyl-4,6-*O*-ethylidene-β-D-glucopyranosyl)-4'-*O*-demethyl-4-epi-podophyllotoxin (15β). A cooled (-20 °C) solution of epipodophyllotoxin **12** (28.8 g, 53.9 mmol) and BF_3-etherate (50%, 57.6 mL) in dichloromethane (1200 mL) was added to a mixture of compound **11β** (23.7 g, 65.99 mmol) and powdered molecular sieves 4 Å (25 g) at -20 °C. The reaction mixture was stirred for 2.5 h at -20 °C. Triethylamine (60 mL) was poured into the stirred mixture at -20 °C and filtered off. The filtrate was washed successively with citrate buffer (pH 5.5, 300 mL x 3) and ice-cooled water. The organic layer was dried (sodium sulfate) and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel (600 g) with 3:1:1 diethyl ether-petroleum ether-dichloromethane to afford compound **15**, which

was recrystallized from dichloromethane-ether-petroleum ether to give **15β** (36.7 g, 78%): mp 152 °C; $[\alpha]_D$ -48.2° (c 1, chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.32 (m, 5H, Ph), 6.73 (s, 1H, H-5), 6.55 (s, 1H, H-8), 6.25 (s, 2H, H-2' and H-6'), 6.02 (d, 1H, ^{2}J 1.0 Hz, H-15-A), 6.01 (d, 1H, ^{2}J, H-15-B), 5.30 (dd, 1H, $J_{2'',3''}$ = 9.0 Hz, $J_{3'',4''}$ = 10.2 Hz, H-3''), 5.25 (s, 2H, Ph-CH_2), 4.98 (dd, 1H, $J_{1'',2''}$ 7.7 Hz, $J_{2'',3''}$, H-2''), 4.87 (d, 1H, $J_{1'',2''}$, H-1''), 4.84 (d, 1H, $J_{3,4}$ = 3.2 Hz, H-4), 4.70 (q, 1H, $J_{Me,CH}$ = 5.0 Hz, Me-CH=), 4.61 (d, 1H, $J_{1,2}$ = 5.3 Hz, H-1), 4.38 (dd, 1H, $J_{3,11a}$ = 10.5 Hz, ^{2}J = 8.5 Hz, H-11-A), 4.23 (dd, 1H, $J_{3,11b}$ = 7.5 Hz, ^{2}J, H-11-B), 4.22, (dd, 1H, $J_{5'',6''eq}$ = 4.5 Hz, ^{2}J = 10.5 Hz, H-6''), 4.08 (d, 1H, ^{2}J = 15.0 Hz, Cl-CH-A), 4.02 (d, 1H, ^{2}J, Cl-CH-B), 3.86 (d, 1H, ^{2}J, Cl-CH-A'), 3.72 (d, 1H, ^{2}J, Cl-CH-B'), 3.66 (s, 6H, MeO), 3.60 (dd, 1H, $J_{5'',6''ax}$ = 10.0 Hz, ^{2}J, H-6''ax), 3.52 (dd, 1H, $J_{3'',4''}$, $J_{4'',5''}$ = 9.0 Hz, H-4''), 3.43 (ddd, 1H, $J_{4'',5''}$, $J_{5'',6''ax}$, $J_{5'',6''eq}$, H-5''), 3.20 (dd, 1H, $J_{1,2}$ = 5.0 Hz, $J_{2,3}$ = 14.2 Hz, H-2), 2.85 (m, 1H, ΣJ = 36.1 Hz, H-3), 1.35 (d, 3H, $J_{Me,CH}$, CH_3-C=).

Anal. Calcd for $C_{41}H_{40}Cl_2O_{17}$: C, 56.24; H, 4.60; Cl, 8.10. Found C, 56.39; H, 4.62.

4'-*O*-Benzyloxycarbonyl-4-*O*-(2,3-di-*O*-chloroacetyl-4,6-*O*-ethylidene-α- *and* **-β-D-glucopyranosyl)-4'-*O*-demethyl-4-epipodophyllotoxin (15α** and **15β).** Epi-podophyllotoxin **12** (530 mg, 0.99 mmol) and a mixture of **11α/11β** (α:β=1:1, 360 mg, 1 mmol) were dissolved in dichloromethane (30 mL). After addition of powdered molecular sieves (1 g), BF_3-etherate (50%, 0.9 mL) was added at -20 °C and the mixture was stirred for 2 h at -20 °C. Work-up and chromatography as described for the preparation of compound **15β** resulted in compounds **15α** (400 mg, 45.8%) and **15β** (361 mg, 41.3%): *Compound* **15α**: mp 136 °C; $[\alpha]_D$ + 49.5° (c 1, chloroform); ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.44-7.32 (m, 5H, Ph), 6.28 (s, 1H, H-5), 6.55 (s, 1H, H-8), 6.27 (s, 2H, H-2' and H-6'), 6.01 (d, 1H, ^{2}J = 15.0 Hz, H-15-A), 5.99 (d, 1H, ^{2}J, H-15-B), 5.42 (dd, 1H, $J_{2'',3''}$ = 10.0 Hz, $J_{3'',4''}$ = 9.0 Hz, H-3''), 5.26 (d, 1H, $J_{1'',2''}$ = 3.7 Hz, H-1''), 5.25 (s, 2H, Ph-CH_2), 5.08 (dd, 1H, $J_{1'',2''}$; $J_{2'',3''}$, H-2''), 4.72 (d, 1H, $J_{3,4}$ =3.0 Hz, H-4), 4.71 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1), 4.64 (q, 1H, $J_{Me,CH}$ = 5.0 Hz, Me-CH=), 4.26 (d, 1H, $J_{3,11a}$ = 10.5 Hz, H-11-A), 4.26 (d, 1H, $J_{3,11b}$ = 8.0 Hz, H-11-B), 4.11 (d, 1H, ^{2}J = 15.0 Hz, Cl-CH-A), 4.03 (d, 1H, ^{2}J, Cl-CH-B), 4.03 (s, 2H, Cl-CH_2), 3.98 (dd, 1H, $J_{5'',6''eq}$ = 4.5 Hz, ^{2}J 10.0 Hz, H-6''eq),3.68 (s, 6H, MeO), 3.64 (dd, 1H, $J_{5'',6''ax}$ = 10.0 Hz, ^{2}J, H-6''ax), 3.52 (ddd, $J_{4'',5''}$ = 10.0 Hz, $J_{5'',6''ax}$, $J_{5'',6''eq}$, H-5''), 3.49 (dd, 1H, $J_{3'',4''}$, $J_{4'',5''}$, H-4''), 3.46 (dd, 1H, $J_{1,2}$, $J_{2,3}$ =14.0 Hz, H-2), 2.88 (m, 1H, ΣJ = 36.0 Hz, H-3), 1.29 (d, 3H, $J_{Me,CH}$, CH_3-C=).

Anal. Calcd for $C_{41}H_{40}Cl_2O_{17}$: C, 56,24; H, 4.60; Cl, 8.10. Found: C, 56.13; H, 4.61.

4'-*O*-Chloroacetyl-4-*O*-(2,3-di-*O*-chloroacetyl-4,6-*O*-ethylidene-β-D-gluco-pyranosyl)-4'-*O*-demethyl-4-epi-podophyllotoxin (16). A cooled (-20 °C) solution of 4'-*O*-chloroacetyl-4'-*O*-demethyl-4-epi-podophyllotoxin **13** (2.57 g, 5.4 mmol) and BF_3-etherate (50 %, 5.8 mL) in dichloromethane (120 mL) was added to a mixture of compound **11β** (2.22 g, 6.2 mmol) and powdered molecular sieves 4 Å (2.5 g) at -20 °C.

After 3 h stirring, the mixture was worked up as described for the preparation of the compound **15β**. The resulting product was chromatographed on a column of silica gel (50 g) with 35:1 dichloromethane-acetone to give **16** (3.22 g, 73%): mp 241-243 °C; $[\alpha]_D$ -63.9° (c 1, chloroform); Lit.[6]: mp 244-246 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 1H, H-5), 6.57 (s, 1H, H-8), 6.26 (s, 2H, H-2' and H-6'), 6.04 (d, 1H, J = 1.2 Hz, H-15-A), 6.01 (d, 1H, J = 1.2 Hz, H-15-B), 5.31 (dd, 1H, $J_{2'',3''}$ = 9.5 Hz, $J_{3'',4''}$ = 9.5 Hz, H-3''), 4.99 (dd, 1H, $J_{1'',2''}$ =7.6 Hz, H-2''), 4.87 (d, 1H, $J_{1'',2''}$, H-1''), 4.85 (d, 1H, $J_{3,4}$ = 3.2 Hz, H-4), 4.70 (q, 1H, $J_{Me,CH}$ = 5.0 Hz, Me-CH=), 4.62 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1), 4.38 (dd, 1H, $J_{3,11a}$ = 10.7 Hz, ^{2}J =8.8 Hz, H-11-A), 4.34 (s, 2H, Cl-CH_2), 4.24 (dd, 1H, $J_{3,11b}$ = 7.6 Hz, ^{2}J, H-11-B), 4.22 (dd, 1H, $J_{5'',6''eq}$= 4.4 Hz, ^{2}J = 10.1 Hz, H-6''eq), 4.08 (d, 1H, ^{2}J = 14.5 Hz, Cl-CH-A), 4.03 (d, 1H, ^{2}J, Cl-CH-B), 3.86 (d, 1H, ^{2}J = 14.5 Hz, Cl-CH-A'), 3.72 (d, 1H, ^{2}J, Cl-CH-B'), 3.67 (s, 6H, Ph-OMe), 3.60 (dd, 1H, $J_{5'',6''ax}$ = 10.1 Hz, ^{2}J, H-6''ax), 3.53 (dd, 1H, $J_{3'',4''}$, $J_{4'',5''}$ = 9.0 Hz, H-4''), 3.43 (ddd, 1H, $J_{4'',5''}$, $J_{5'',6''ax}$, $J_{5'',6''eq}$, H-5''), 3.20 (dd, 1H, $J_{1,2}$, $J_{2,3}$ = 13.9 Hz, H-2), 2.85 (m, 1H, ΣJ =36 Hz, H-3), 1.35 (d, 1H, $J_{Me,CH}$, CH_3-C=).

Anal. Calcd for $C_{35}H_{35}Cl_3O_{16}$: C, 51.39; H, 4.31; Cl, 13.00. Found: C, 51.45; H, 4.29.

4'-*O*-Benzyloxycarbonyl-4-*O*-(4,6-*O*-ethylidene-β-D-glucopyranosyl)-4'-*O*-demethyl-4-epi-podophyllotoxin (17). Compound **15β** (10.72 g, 12.2 mmol) was dissolved in 3:2 methanol-dichloromethane (750 mL) and stirred with Dowex 1X8 (22.6 g; mesh size: 20-50 pract.; counter ion: H; Serva) for 1 h at room temperature. The resin was filtered off and washed with methanol, and the combined filtrate and washings were concentrated *in vacuo*. The residue was dissolved in dichloromethane (250 mL) and washed successively with phosphate buffer (pH 7.5, 70 mL) and saturated NaCl aqueous solution. The organic layer was dried (sodium sulfate) and concentrated *in vacuo*. The residue was crystallized from ethyl acetate-petroleum ether to give **17** (8.37 g, 95%): mp 162 °C; $[\alpha]_D$ -79.5° (c 1, chloroform); Lit.[5]: mp 156-157 °C; $[\alpha]_D$ -84.6° (c 1.04, chloroform).

4-*O*-(4,6-*O*-Ethylidene-β-D-glucopyranosyl)-4'-*O*-demethyl-4-epi-podophyllotoxin (1). *A*; *starting from* **17:** Compound **17** (9.7 g, 13.4 mmol) in methanol (160 mL) was hydrogenolyzed in the presence of 10% Pd/C (5 g) at atmospheric pressure and room temperature for 40 min. The catalyst was filtered off on a Celite pad, washed with methanol, and then the filtrate was concentrated *in vacuo*. The residue was crystallized from methanol-dichloromethane-hexane to give **1** (7.17 g, 91%): mp 254-256 °C; $[\alpha]_D^{23}$ -109,6° (c 1, chloroform); Lit.[5]: mp 253-255 °C; $[\alpha]_D$ -111.0° (c 1.046, chloroform); Lit.[6]: 259-262 °C. *B*; *starting from* **16**: Compound **16** (3.50 g, 4.28 mmol) was dissolved in 3:2 methanol-dichloromethane (80 mL) and Dowex 1X8 (8.0 g) was added. The mixture was stirred for 1 h at room temperature. After filtration of the resin and washing with methanol, the combined filtrate and washings were concentrated *in vacuo*. The residue

was dissolved in 20:1 dichloromethane-methanol (25 mL) and washed with phosphate buffer (pH 7, 10 mL). The organic layer was dried (sodium sulfate) and concentrated *in vacuo*. The residue was crystallized from methanol-dichloromethane-hexane to give **1** (2.24 g, 89%): mp 254-257 °C; $[\alpha]_D$ 108.9° (c 1, chloroform).

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