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Etoposide: a new approach to the synthesis of 4-*O*-(2-amino-2-deoxy-4,6-*O*-ethylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-4-epipodophyllotoxin

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ABSTRACT

Synthesis of 3-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-4,6-*O*-ethylidene-α- (**7α**) and -β-D-glucopyranose (**7β**) and their 3-*O*-chloroacetyl analogues (**11α** and **11β**) are described. Condensation (BF_3-etherate, ethyl acetate, −20°) of **7α** with 4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-4-epipodophyllotoxin (**8**) afforded mainly the β-glycoside **9β** (α,β-ratio 1:9). Condensation of **11αβ** with **8** or the 4′-*O*-chloroacetyl analogue **13** gave mainly the 4-*O*-(2-benzyloxycarbonylamino-3-*O*-chloroacetyl-2-deoxy-4,6-*O*-ethylidene-β-D-glucopyranosyl)-epipodophyllotoxin **12β** or **15β**. Glycosidation of podophyllotoxin (**14**) with **11αβ** (during which the aglycon epimerized at C-4 under the action of BF_3-etherate) afforded α- (**16α**) and β-glycoside (**16β**) in the ratio 1:5. Removal of the chloroacetyl groups from **12β**, its α analogue **12α**, and **15β** gave the 4-*O*-(2-benzyloxycarbonylamino-2-deoxy-4,6-*O*-ethylidene-α- (**17α**) and -β-D-glucopyranosyl)-4′-*O*-demethyl-epipodophyllotoxins (**17β** and **20β**), respectively. Hydrogenolysis of the benzyloxycarbonyl groups then gave 4-*O*-(2-amino-2-deoxy-4,6-*O*-ethylidene-α- (**18α**) and -β-D-glucopyranosyl)-4′-*O*-demethyl-4-epipodophyllotoxin (**18β**). Reductive alkylation of **18β** and **18α** afforded the 2″-deoxy-2″-dimethylamino-etoposide **3** and its α analogue **19α**.

INTRODUCTION

Etoposides[1,2] [4-*O*-(4,6-*O*-alkylidene-β-D-glucopyranosyl)-4′-*O*-demethyl-4-epipodophyllotoxins] constitute an important group of antitumor agents. Etoposide (VP-16, **1**) and Teniposide (VM-26, **2**) are effictive in the treatment of small-cell lung cancers, lymphoma, leukemia, and Karposi's sarcoma[3–5], and 2″-deoxy-2″-dimethylamino-etoposide[6] (DMA-etoposide, **3**) is in clinical trial.

The most difficult steps in the synthesis of etoposides are the glycosidation† and deacylation steps. The glycosidation of epipodophyllotoxin requires[7] a β-glycopyranose donor, and etoposide VP-16 has been synthesised[8,9] from the donors 2,3-di-*O*-acetyl- and 2,3-di-*O*-chloroacetyl-4,6-*O*-ethylidene-β-D-glucopyranose.

DMA-etoposide was synthesised[6,9] by condensation of 4′-*O*-benzyloxycarbonyl-4′-*O*-demethyl-4-epipodophyllotoxin[10] (**8**) with 2,3,4-tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranose[11] in the presence of BF_3-etherate and afforded

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† Epipodophyllotoxin forms the C-4 carbonium ion under the action of BF_3-etherate and the glycosyloxy group is transferred from the donor to this position.

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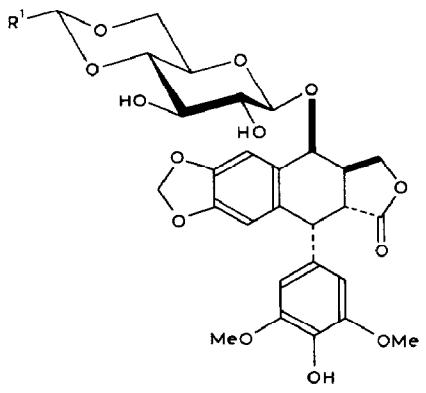
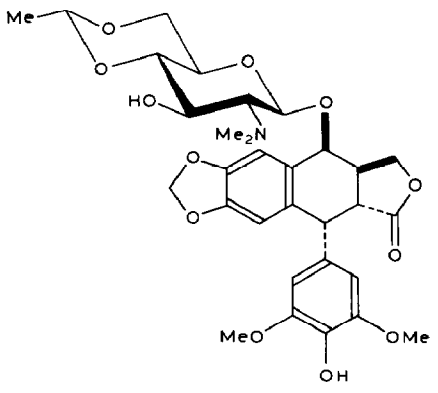


1 R^1 = Me (VP-16)

2 R^1 =  (VM-26)



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a mixture of glycosides with an α,β ratio of 1:5.5, and 4′-*O*-chloroacetyl-4′-*O*-demethyl-4-epipodophyllotoxin (**13**) has been glycosidated[12] using 2-benzyloxycarbonylamino-3-*O*-chloroacetyl-2-deoxy-4,6-*O*-ethylidene-β-D-glucopyranose (**11β**).

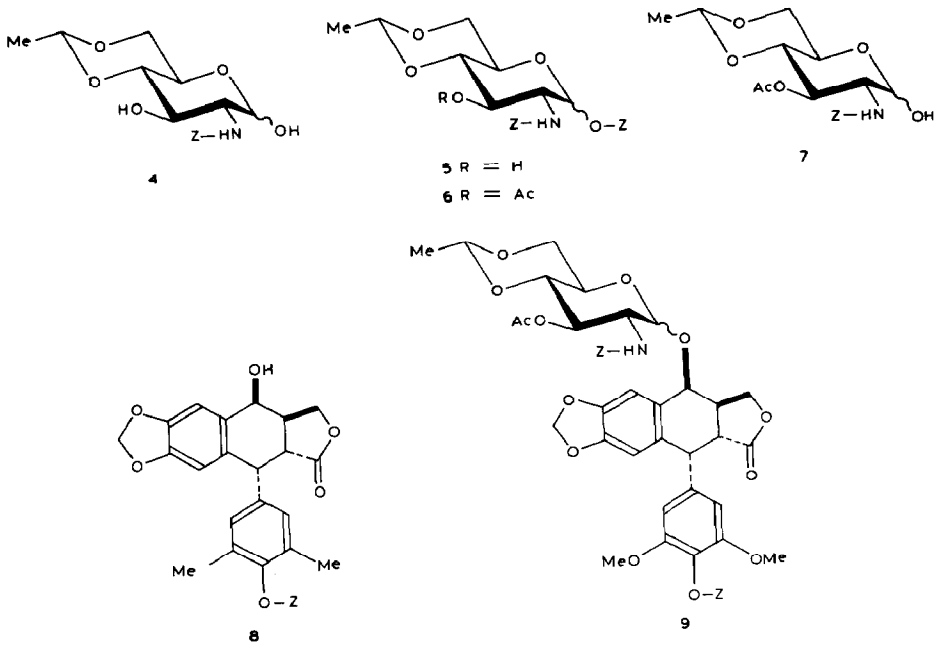
Deacylation[13] of the protected etoposides is complicated by the occurrence of secondary reactions, *i.e.*, epimerization at C-2 (base-catalyzed reaction) and cleavage of the γ-lactone (acid-catalyzed reaction) of the aglycon.

We now report a new method for the glycosidation of epipodophyllotoxins, using derivatives of 2-amino-2-deoxy-α-D-glucopyranose and a simple procedure for removing chloroacetyl groups.

RESULTS AND DISCUSSION

The glycosidation agent **7β** was synthesised from 2-benzyloxycarbonylamino-2-deoxy-4,6-*O*-ethylidene-D-glucopyranose (**4**) as reported[9] but using the acetyl group instead of the chloroacetyl group for protection. Treatment of **4** with benzyloxycarbonyl chloride and sodium hydroxide in aqueous 1,4-dioxane gave the α- (**5α**, 40%) and β-1-*O*-benzyloxycarbonyl (**5β**, 36%) derivatives, each of which was converted (Ac_2O, 1:1 pyridine–dichloromethane) into the 3-acetate (**6α** and **6β**, respectively) in good yield.

Hydrogenolysis of **6β** in various solvents (MeOH, EtOH, Me_2CO, EtOAc, or their mixtures) at room temperature showed that the use of 10% Pd–C in ethyl acetate afforded a product with the lowest $[\alpha]_D$ values [−3.0° (*c* 0.5, ethyl acetate) and −4.4° (*c* 0.5, acetonitrile)] and that its mutarotation proceeded relatively slowly [+0.6°/h (*c* 0.5, EtOAc)]. ^{1}H-N.m.r. spectroscopy of this product revealed the α (**7α**, $J_{1,2}$ 3.6 Hz, H-1) and β anomers (**7β**, $J_{1,2}$ 8.2 Hz, H-1) in the ratio 10:1. Hydrogenolysis (10% Pd–C, ethyl acetate) of **6α** afforded a mixture of products, from which 35% of **7α** was isolated with an α:β-ratio of 10:1 (^{1}H-n.m.r. data).



Glycosidation of 4′-*O*-benzyloxycarbonyl-4-epipodophyllotoxin (**8**) with **7β**, under essentially the conditions described[7,9] (BF_3-etherate, dichloromethane, molecular sieves 4 Å, −20°), afforded a mixture of **9α** and **9β** in the ratio 1:15. As expected, similar condensation of **7α** and **8** gave mainly (76%) **9α** with only a trace of **9β**. However, when **7α** and **8** reacted in ethyl acetate with BF_3-etherate (37 equiv.) as the promoter at −20°, surprisingly, a mixture of **9α** and **9β** was obtained in the ratio 1:9.

Because of these results, the synthesis strategy for DMA-etoposide was changed as follows. Reaction of **4** with chloroacetyl chloride in 4:3 dichloromethane–pyridine gave the bis-chloroacetates **10α** and **10β**. Treatment[14] of **10α** and **10β** with silica gel or aminated silica gel (LiChroprep NH_2) in methanol removed the 1-substituent and gave a mixture of **11α** and **11β** that was stable in acid and was purified easily on silica gel. The overall yield of **11α** and **11β** was 83%.

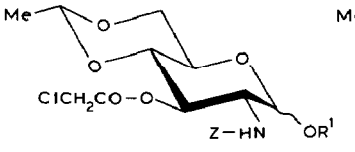
When **11αβ** was dissolved in dichloromethane, mutarotation was complete in ~5 min ($[\alpha]_D$ +31°). The ^{1}H-n.m.r. spectrum (CD_2Cl_2) revealed an α:β-ratio of ~10:1 and **11α** could be crystallized.

In order to obtain further data on mutarotation under the conditions of glycosidation, the optical rotation of **11α** was measured in different solvents in the presence and absence of BF_3-etherate at −20°. For a solution in 1:1 dichloromethane–ethyl acetate, the addition of BF_3-etherate caused an immediate change in $[\alpha]_D^{-20}$ from +31° → +17°. Hence, a new α,ß-equilibrium was achieved. When BF_3 was removed, **11α** was obtained with $[\alpha]_D^{-20}$ +29°.

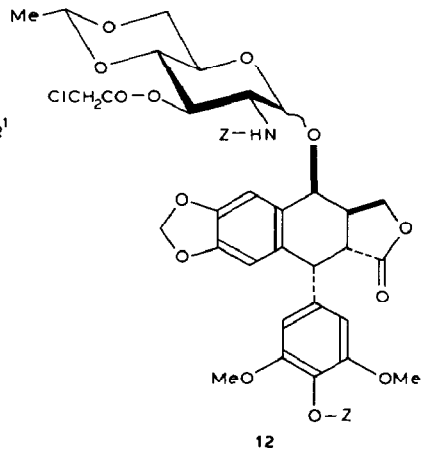
Glycosidation of **8** with **11αβ** ($[\alpha]_D^{-20}$ +29°) under the conditions (BF_3-etherate, molecular sieves 4 Å, −20°) described for the preparation of **9β**, but using 1:1 dichloro-

methane–ethyl acetate as the medium instead of ethyl acetate, afforded a mixture of **12α** and **12β** in the ratio 1:10, from which, after chromatography, 75% of **12β** was obtained. However, the reaction in dichloromethane gave **12α** exclusively.

The new method was applied for the glycosidation of 4′-*O*-chloroacetyl-4′-*O*-demethyl-4-epipodophyllotoxin[11] (**13**) and podophyllotoxin[13] (**14**). Condensation of **11αβ** with **13** in 1:1 dichloromethane–ethyl acetate afforded **15α** (22%) and **15β** (64%) in the ratio[9] 1:2.9. When **11αβ** was used to glycosidate podophyllotoxin **14** under the same reaction conditions, **16α** (14%) and **16β** (73%) were obtained. In the glycosidation process, **14** epimerizes[7] under the action of BF_3-etherate to form the 4-epipodophyllotoxin, and **11α** mutarotates in dichloromethane–ethyl acetate to form **11β**.



10 $R^1 = ClCH_2CO$
11 $R^1 = H$



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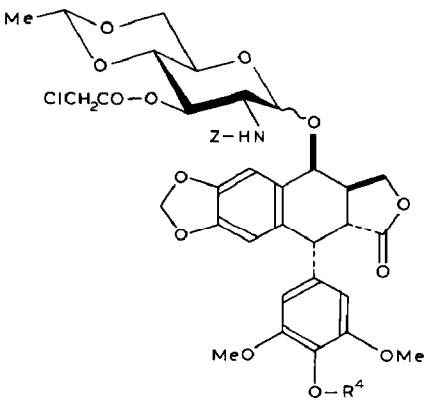
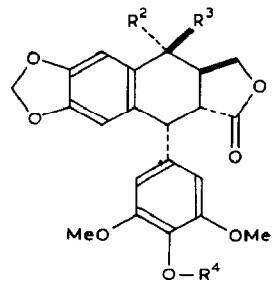


15 $R^4 = ClCH_2CO$
16 $R^4 = Me$

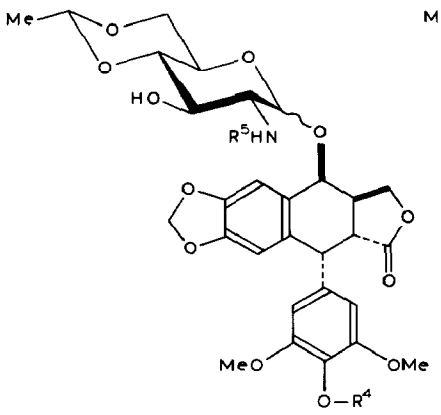


13 $R^2 = H, R^3 = OH, R^4 = ClCH_2CO$
14 $R^2 = OH, R^3 = H, R^4 = Me$

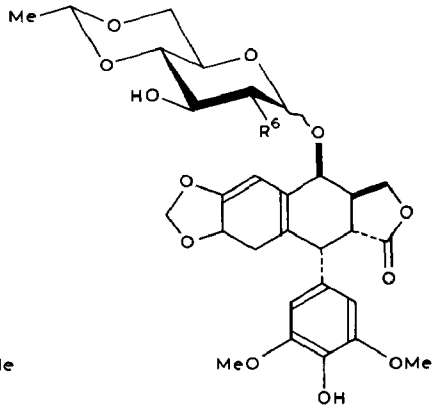
Deprotection[9] of etoposide derivatives is usually effected by *O*-dechloroacetylation with zinc acetate in refluxing methanol and by hydrogenolysis (Pd–C) of the benzyloxycarbonyl groups. *O*-Chloroacetylated etoposides can be deacetylated[15] with Dowex 1-X8 (HO^-) resin in methanol or methanol–dichloromethane without any

considerable formation of secondary products. Thus, **12α** and **12β** were converted into **17α** and **17β**, respectively, within 6–8 h (combined yield 95–96%). The ^{1}H-n.m.r. spectrum of each glycosyl-epipodophyllotoxin contained a typical signal for H-3 (~2.81 p.p.m. ΣJ 36 Hz) of the aglycon. The large $J_{2,3}$ value (14 Hz) is consistent with H-2,3 being trans-diaxial. ^{1}H,^{1}H-COSY experiments were used to assign the resonances of the sugar ring protons in the ^{1}H-n.m.r. spectra. The observed coupling constants ($J_{1'',2''}$ 4.2 Hz for **17α** and $J_{1'',2''}$ 8.2 Hz for **17β**) are characteristic for α and β anomers.

Removal[8] of the benzyloxycarbonyl group from **17α** and **17β** and methylation[9] (CH_2O, $NaCNBH_3$) of the amino group in the products **18α** and **18β**, respectively, gave DMA-etoposide **3** and its α anomer **19α**. Likewise, *O*-dechloroacetylation of **15β** followed by hydrogenolysis of the product **20β** gave 4-*O*-(2-amino-2-deoxy-4,6-*O*-ethylidene-α-D-glucopyranosyl)-4′-*O*-demethyl-4-epipodophyllotoxin (**18α**).



17 $R^4 = R^5 = Z$
18 $R^4 = R^5 = H$



19α $R^6 = NMe_2$
20β $R^6 = NHZ$

EXPERIMENTAL

General. — Reactions were carried out at ambient temperature unless otherwise stated. Solutions were concentrated under reduced pressure at <40° (bath). Organic solutions were washed with 0.1M potassium dihydrogen phosphate or 0.1M sodium citrate adjusted to the appropriate pH value using 0.1M NaOH or 0.1M HCl. Melting points, determined on a Büchi apparatus, are uncorrected. ^{1}H-N.m.r. spectra were recorded with a Bruker AC-200, AC-300, AM-400, or Jeol GX400 spectrometer, on solutions in $CDCl_3$ (internal Me_4Si) unless stated otherwise. The ^{1}H resonances were assigned by ^{1}H,^{1}H-COSY experiments, using the standard pulse sequences of the Bruker Aspect-300 software. Specific optical rotations were determined with a Perkin–Elmer 241 polarimeter equipped with 10-cm cuvettes, for solutions in $CHCl_3$ at 24°, unless noted otherwise. Reactions were monitored by t.l.c. on Silica Gel 60 F_{254} (Merck) with

detection by u.v. light or by charring with sulfuric acid. Preparative chromatography was performed on Kieselgel 60 (Merck, 0.015–0.040 mm). The glycosidations were performed under argon or nitrogen.

1-O-Benzyloxycarbonyl-2-benzyloxycarbonylamino-2-deoxy-4,6-O-ethylidene-α- (**5α**) *and -β-*D*-glucopyranose*[9] (**5β**). — To a solution of 2-benzyloxycarbonylamino-2-deoxy-4,6-*O*-ethylidene-D-glucopyranose (**4**; 3.00 g, 8.84 mmol) in 2:1 1,4-dioxane–water (300 mL) was added M NaOH (2.3 mL, 0.25 equiv.). To the cooled mixture at 5° was added dropwise a solution of benzyloxycarbonyl chloride in 1,4-dioxane (300 mL) and an approximately equivalent quantity of M NaOH (13.2 mL). The mixture was stirred for 2 h at 5°, then for 30 h at room temperature, filtered, diluted with water (200 mL), and extracted with chloroform (100 mL × 3). The combined extracts were washed with citrate buffer (pH 5.5, 70 mL) and water, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (15:1 chloroform–MeOH) of the residue on silica gel (140 g) gave **5α** (1.70 g, 40%) and **5β** (1.52 g, 36%).

Compound **5α** had m.p. 170°, $[\alpha]_D$ +95° (*c* 1). ^{1}H-N.m.r. data (200 MHz): δ 7.32–7.42 (m, 10 H, 2 Ph), 6.01 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.19 (s, 2 H, PhCH_2), 5.11 (s, 2 H, PhCH_2), 5.05 (d, 1 H, $J_{2,NH}$ 9.0 Hz, NH), 4.72 (q, 1 H, $J_{Me,CH}$ 5.0 Hz, MeC*H*=), 4.10 (dd, 1 H, $J_{5,6e}$ 4.5, $J_{6a,6e}$ 10.0 Hz, H-6), 4.05 (m, 1 H, H-3), 3.83 (ddd, 1 H, $J_{2,3}$ 9.2 Hz, H-2), 3.71 (ddd, 1 H, $J_{4,5}$ 10.0, $J_{5,6a}$ 10.0 Hz, H-5), 3.49 (dd, 1 H, H-6*a*), 3.38 (dd, 1 H, $J_{3,4}$ 10.0 Hz, H-4), 2.79 (d, 1 H, $J_{3,OH}$ 3.0 Hz, HO-3), 1.35 (d, 3 H, *Me*CH=).

Anal. Calc. for $C_{24}H_{27}NO_9$ (473.48): C, 60.88; H, 5.75; N, 2.96. Found: C, 60.67; H, 5.76; N, 2.79.

Compound **5β** had m.p. 155°, $[\alpha]_D$ −19° (*c* 1). ^{1}H-N.m.r. data (90 MHz): δ 7.36–7.30 (m, 10 H, 2 Ph), 5.66 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 1.36 (d, 1 H, $J_{Me,CH}$ 5.0 Hz, *Me*CH=).

Anal. Found: C, 60.81; H, 5.73; N, 2.88.

*3-O-Acetyl-1-O-benzyloxycarbonyl-2-benzyloxycarbonylamino-2-deoxy-4,6-O-ethylidene-α-*D*-glucopyranose* (**6α**). — To a solution of **5α** (1.50 g, 2.90 mmol) in 1:1 dichloromethane–pyridine (30 mL) was added at 0° a solution of acetic anhydride (0.57 g, 3.50 mmol) in dichloromethane (7 mL). The mixture was stirred at 0° to room temperature for 16 h and then concentrated *in vacuo*. A solution of the residue in chloroform (80 mL) was washed with phosphate buffer (pH 8, 30 mL), citrate buffer (pH 5, 30 mL), and water, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (5:5:1 dichloromethane–light petroleum–acetone) of the product on silica gel (50 g) gave **6α** (1.39 g, 93%), m.p. 134–137°, $[\alpha]_D$ +76° (*c* 1). ^{1}H-N.m.r. data (200 MHz): δ 7.3–7.4 (m, 5 H, Ph), 6.02 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.22 (dd, 1 H, $J_{2,3}$ 10.3, $J_{3,4}$ 10.1 Hz, H-3), 5.18 (s, 2 H, PhCH_2), 5.13 (d, 1 H, $J_{A,B}$ 12.0 Hz, PhC*H*A), 5.10 (d, 1 H, $J_{2,NH}$ 9.5 Hz, NH), 5.02 (d, 1 H, PhC*H*B), 4.68 (q, 1 H, $J_{Me,CH}$ 5.0 Hz, MeC*H*=), 4.13 (ddd, 1 H, H-2), 4.12 (dd, 1 H, $J_{5,6e}$ 4.5, $J_{6a,6e}$ 10.3 Hz, H-6*e*), 3.82 (ddd, 1 H, $J_{4,5}$ 9.1, $J_{5,6a}$ 10.0 Hz, H-5), 3.51 (dd, 1 H, H-4), 3.51 (dd, 1 H, H–6*a*), 1.31 (d, 3 H, *Me*CH=).

Anal. Calc. for $C_{26}H_{29}NO_{10}$ (515.52): C, 60.58; H, 5.67; N, 2.72. Found: C, 60.43; H, 5.71; N, 2.65.

3-O-Acetyl-1-O-benzyloxycarbonyl-2-benzyloxycarbonylamino-2-deoxy-4,6-O-ethylidene-β-D-glucopyranose (**6β**). — Acetylation of **5β** (1.5 g, 2.90 mmol), as described for the preparation of **6α**, gave **6β** (1.42 g, 95%), m.p. 112–115°, $[\alpha]_D$ −9° (*c* 1). ^{1}H-N.m.r. data (200 MHz): δ 7.27–7.37 (m, 5 H, Ph), 5.56 (d, 1 H, $J_{1,2}$ 8.7 Hz, H-1), 5.23 (d, 1 H, $J_{A,B}$ 12.0 Hz, PhC*H*A), 5.19 (d, 1 H, $J_{A',B'}$ 12.0 Hz, PhC*H*A'), 5.14 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 10.0 Hz, H-3), 5.13 (d, 1 H, PhC*H*B), 5.07 (d, 1 H, $J_{2,NH}$ 9.8 Hz, NH), 5.03 (d, 1 H, PhC*H*B'), 4.67 (q, 1 H, $J_{Me,CH}$ 5.0 Hz, MeC*H*=), 4.19 (dd, 1 H, $J_{5,6e}$ 3.5, $J_{6a,6e}$ 10.2 Hz, H-6*e*), 3.89 (ddd, 1 H, H-2), 3.56 (ddd, 1 H, $J_{4,5}$ 8.7, $J_{5,6a}$ 10.1 Hz, H-5), 3.50 (dd, 1 H, H-6*a*), 3.50 (dd, 1 H, H-4), 1.32 (d, 3 H, *Me*CH=).

Anal. Calc. for $C_{26}H_{29}NO_{10}$ (515.52): C, 60.58; H, 5.67; N, 2.72. Found: C, 60.60; H, 5.67; N, 2.67.

3-O-Acetyl-2-benzyloxycarbonylamino-2-deoxy-4,6-O-ethylidene-β-D-glucopyranose (**7β**). — A mixture of **6β** (500 mg, 0.96 mmol), 10% Pd–C (200 mg), and magnesium sulfate (1 g) in ethyl acetate (50 mL) was stirred under hydrogen for 1 h at room temperature, then filtered through Celite, and concentrated *in vacuo* to afford crude **7β** (370 mg, 90%), which was used in the next step without further purification; $[\alpha]_D$ −4.4° (*c* 0.5, acetonitrile), $[\alpha]_D$ −3.0° (*c* 0.5, ethyl acetate). ^{1}H,^{1}H-COSY and ^{1}H-n.m.r. data (400 MHz, $CDCl_3$, α and β anomers 10:1): δ 7.22–7.30 (m, 5 H, Ph), 6.01 (d, 1 H, $J_{1,OH}$ 8.2 Hz, HO-1), 5.42 (d, 1 H, $J_{2,NH}$ 8.2 Hz, NH), 5.07 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 10.0 Hz, H-3), 4.65 (q, 1 H, $J_{Me,CH}$ 5.0 Hz, MeC*H*=), 4.55 (dd, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 4.12 (dd, 1 H, $J_{5,6e}$ 4.7, $J_{6a,6e}$ 10.1 Hz, H-6*e*), 3.56 (m, 1 H, H-2), 3.52 (dd, 1 H, H-6*a*), 3.40 (dd, 1 H, H-4), 3.28 (ddd, 1 H, $J_{4,5}$ 10.0, $J_{5,6a}$ 10.0 Hz, H-5), 1.89 (s, 3 H, Ac), 1.22 (d, 3 H, $J_{Me,CH}$, *Me*C=).

3-O-Acetyl-2-benzyloxycarbonylamino-2-deoxy-4,6-O-ethylidene-α-D-glucopyranose (**7α**). — A solution of **6α** (500 mg, 0.96 mmol) in ethyl acetate (50 mL) was stirred for 1 h under hydrogen (1 atm.) in the presence of 10% Pd–C (200 mg), followed by the usual work-up. Column chromatography (6:1 dichloromethane–acetone) of the product on silica gel (70 g) gave **7α** (128 mg, 35%) as a syrup, $[\alpha]_D$ +28° (*c* 1). ^{1}H-H.m.r. data [400 MHz, $(CD_3)_2CO$]: δ 7.30–7.37 (m, 5 H, Ph), 6.21 (d, 1 H, $J_{1,OH}$ 4.2, $J_{2,OH}$ 1.0 Hz, HO-1), 5.86 (d, 1 H, $J_{2,NH}$ 10.1 Hz, NH), 5.23 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 9.8 Hz, H-3), 5.20 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 5.13 (d, 1 H, $J_{A,B}$ 12.6 Hz, PhC*H*A), 5.02 (d, 1 H, PhC*H*B), 4.75 (q, 1 H, $J_{Me,CH}$ 5.0 Hz, MeC*H*=), 3.98 (dd, 1 H, $J_{5,6e}$ 5.1, $J_{6a,6e}$ 10.1 Hz, H-6*e*), 3.90 (ddd, 1 H, $J_{4,5}$ 9.8, $J_{5,6a}$ 10.1 Hz, H-5), 3.88 (ddd, 1 H, H-2), 3.54 (dd, 1 H, H-6*a*), 3.50 (dd, 1 H, H-4), 1.89 (s, 3 H, Ac), 1.22 (d, 3 H, *Me*C=).

Anal. Calc. for $C_{18}H_{23}NO_8$ (381.39): C, 56.69; H, 6.08; N, 3.67. Found: C, 56.53; H, 6.05; N, 3.53.

4-O-(3-O-Acetyl-2-benzyloxycarbonylamino-2-deoxy-4,6-O-ethylidene-α-D-glucopyranosyl)-4'-O-benzyloxycarbonyl-4'-O-demethyl-4-epipodophyllotoxin (**9α**). — To a mixture of epipodophyllotoxin **8** (280 mg, 0.52 mmol), **7α** (190 mg, 0.50 mmol), and powdered molecular sieves 4 Å (500 mg) in dichloromethane (30 mL) was added 50% BF_3-etherate (0.12 mL, ~1 mmol of BF_3) at −18°. After 3-h stirring, triethylamine (0.2 mL) was added, and the mixture was worked-up, as described for the preparation of **9β**, to afford **9α** (341 mg, 76%) and **9β** (20 mg, 4.5%), α,β-ratio 17:1. Compound **9α** had m.p. 157°, $[\alpha]_D$ +67° (*c* 1). ^{1}H-N.m.r. data (300 MHz): δ 7.38–7.24 (m, 10 H, 2 Ph), 6.79 (s, 1

H, H-5), 6.46 (s, 1 H, H-8), 6.18 (s, 2 H, H-2',6'), 5.92 (s, 1 H, H-15A), 5.92 (s, 1 H, H-15B), 5.33 (d, 1 H, $J_{NH,2''}$ 9.2 Hz, NH), 5.20 (s, 2 H, PhCH_2), 5.06 (d, 1 H, $J_{A,B}$ 12.5 Hz, PhC*H*A), 5.03 (dd, 1 H, $J_{2'',3''}$ 10, $J_{3'',4''}$ 10 Hz, H-3''), 5.02 (d, 1 H, $J_{1'',2''}$ 4.5 Hz, H-1''), 4.99 (d, 1 H, PhC*H*B), 4.62 (d, 1 H, $J_{3,4}$ 3.2 Hz, H-4), 4.61 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 4.61 (q, 1 H, $J_{Me,CH}$ 5.0 Hz, MeC*H*=), 4.13 (dd, 1 H, $J_{A,B}$ 8.5, $J_{3,11A}$ 10.5 Hz, H-11A), 4.00 (dd, 1 H, $J_{6''a,6''e}$ 10, $J_{5'',6''e}$ 4.5 Hz, H-6''*e*), 3.98 (dd, 1 H, $J_{3,11B}$ 8.0 Hz, H-11B), 3.92 (ddd, 1 H, H-2''), 3.61 (s, 6 H, 2 OMe), 3.49 (dd, 1 H, H-6''), 3.43 (m, 1 H, H-5''), 3.39 (dd, 1 H, $J_{4'',5''}$ 10 Hz, H-4''), 3.34 (dd, 1 H, $J_{2,3}$ 14.5 Hz, H-2), 2.75 (m, 1 H, H-3), 1.89 (s, 3 H, Ac), 1.26 (d, 3 H, *Me*C=).

Anal. Calc. for $C_{47}H_{47}NO_{17}$ (897.90): C, 62.87; H, 5.28; N, 1.56; Found: C, 62.81; H, 5.26; N, 1.42.

*4-O-(3-O-Acetyl-2-benzyloxycarbonylamino-2-deoxy-4,6-O-ethylidene-β-*D*-glucopyranosyl)-4'-O-benzyloxycarbonyl-4'-O-demethyl-4-epipodophyllotoxin* (**9β**). — (*a*) To a mixture of **8** (150 mg, 0.28 mmol) and **7β** (140 mg, ~90% pure) and molecular sieves 4 Å (500 mg) in dichloromethane (30 mL) was added 50% BF_3-etherate (0.07 mL, ~0.58 mmol of BF_3) at −18°. After 30-min stirring, dichloromethane (50 mL) and triethylamine (0.2 mL) were added, and the mixture was filtered, washed with 0.1M citrate buffer (50 mL, pH 5) and ice–water (50 mL × 2), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (10:1 dichloromethane–acetone) of the residue on silica gel (65 g) gave **9β** (181 mg, 72%), m.p. 205–207°, $[\alpha]_D$ −44° (*c* 1). ^{1}H-N.m.r. data (300 MHz): δ 7.38–7.19 (m, 10 H, 2 Ph), 6.68 (s, 1 H, H-5), 6.44 (s, 1 H, H-8), 6.18 (s, 2 H, H-2',6'), 5.88 (s, 1 H, H-15A), 5.73 (s, 1 H, H-15B), 5.20 (s, 2 H, PhCH_2), 5.12 (dd, 1 H, $J_{2'',3''}$ 10.0, $J_{3'',4''}$ 9.2 Hz, H-3''), 5.00 (d, 1 H, $J_{A,B}$ 12.5 Hz, PhC*H*A), 4.84 (d, 1 H, PhC*H*B), 4.82 (d, 1 H, $J_{3,4}$ 3.2 Hz, H-4), 4.79 (d, 1 H, $J_{NH,2''}$ 10.0 Hz, NH), 4.69 (d, 1 H, $J_{1'',2''}$ 8.5 Hz, H-1''), 4.69 (q, 1 H, $J_{Me,CH}$ 5.0 Hz, MeC*H*=), 4.45 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 4.41 (dd, 1 H, $J_{A,B}$ 9.0, $J_{3,11A}$ 9.1 Hz, H-11A), 4.18 (dd, 1 H, $J_{3,11B}$ 7.3 Hz, H-11B), 4.15 (dd, 1 H, $J_{6''a,6''e}$ 10.0, $J_{5'',6''e}$ 4.5 Hz, H-6''*e*), 3.60 (s, 6 H, 2 MeO), 3.56 (ddd, 1 H, H-2''), 3.54 (dd, 1 H, $J_{5'',6''a}$ 10.0 Hz, H-6''*a*), 3.40 (dd, 1 H, $J_{4'',5''}$ 9.5 Hz, H-4''), 3.33 (ddd, 1 H, H-5''), 3.19 (dd, 1 H, $J_{2,3}$ 14.3 Hz, H-2), 2.77 (m, 1 H, H-3), 1.97 (s, 3 H, Ac), 1.28 (d, 3 H, *Me*CH=).

Anal. Calc. for $C_{47}H_{47}NO_{17}$ (897.90): C, 62.87; H, 5.28; N, 1.56. Found: C, 62.69; H, 5.29; N, 1.47.

T.l.c. revealed only a trace of **9α**.

(*b*) To a mixture of **8** (1000 mg, 1.87 mmol), **7α** (500 mg, 1.31 mmol), and powdered molecular sieves 4 Å (1.4 g) in dry ethyl acetate (70 mL) was added 50% BF_3-etherate (8.7 mL, ~70 mmol of BF_3) at −18°. After 1-h stirring, triethylamine (10 mL) was added and the mixture was worked-up as described in (*a*) to give **9α** (82 mg, 7%) and **9β** (750 mg), α,β-ratio 1:9.1.

2-Benzyloxycarbonylamino-1,3-di-O-chloroacetyl-2-deoxy-4,6-O-ethylidene-α- (**10α**) *and -β-*D*-glucopyranose* (**10β**). — To a solution of **4** (23.2 g, 68.36 mmol) in 4:3 dichloromethane–pyridine (350 mL) was added dropwise a solution of chloroacetyl chloride (16.4 mL, 23.28 g, 206 mmol) in dichloromethane (50 mL) at −20°. The mixture was stirred for 2 h, diluted with dichloromethane (200 mL), washed with aqueous 5% citric acid until the aqueous layer reached pH 4, dried (Na_2SO_4), and

concentrated *in vacuo*. T.l.c. (1:1 dichloromethane–ethyl acetate) showed the residue (33.4 g) to contain **10α** and **10β** which was used in the subsequent step without further purification. A part of the crude product was purified by preparative t.l.c.

Compound **10α** had m.p. 118–120°, $[\alpha]_D$ +66° (*c* 1). ^{1}H-N.m.r. data (300 MHz): δ 7.4–7.3 (m, 5 H, Ph), 6.20 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 5.28 (dd, 1 H, $J_{2,3}$ 10.4, $J_{3,4}$ 9.6 Hz, H-3), 5.11 (d, 1 H, $J_{A,B}$ 11.5 Hz, PhC*H*A), 5.03 (d, 1 H, PhC*H*B), 5.02 (d, 1 H, $J_{2,NH}$ 9.8 Hz, NH), 4.70 (q, 1 H, $J_{CH,Me}$ 5.0 Hz, MeC*H*=), 4.23 (ddd, 1 H, H-2), 4.15 (s, 2 H, $ClCH_2$), 4.13 (dd, 1 H, $J_{5,6e}$ 4.5, $J_{6a,6e}$ 10.5 Hz, H-6*e*), 4.02 (d, 1 H, $J_{A,B}$ 15.0 Hz, ClCHA), 3.92 (d, 1 H, ClCHB), 3.79 (ddd, 1 H, $J_{4,5}$ 10.0, $J_{5,6a}$ 10.1 Hz, H-5), 3.58 (dd, 1 H, H-4), 3.52 (dd, 1 H, H-6).

Anal. Calc. for $C_{20}H_{23}Cl_2NO_9$ (492.31): C, 48.79; H, 4.71; Cl, 14.40; N, 2.85. Found: C, 48.78; H, 4.72; Cl, 14.49; N, 2.77.

Compound **10β** had m.p. 175–176°, $[\alpha]_D$ −3° (*c* 1). ^{1}H-N.m.r. data (400 MHz): δ 7.32–7.22 (m, 5 H, Ph), 5.69 (d, 1 H, $J_{1,2}$ 8.6 Hz, H-1), 5.17 (dd, 1 H, $J_{2,3}$ 9.4, $J_{3,4}$ 9.2 Hz, H-3), 5.08 (d, 1 H, $J_{2,NH}$ 10.0 Hz, NH), 5.03 (d, 1 H, $J_{A,B}$ 12.2 Hz, PhC*H*A), 4.98 (d, 1 H, PhC*H*B), 4.63 (q, 1 H, $J_{Me,CH}$ 5.1 Hz, MeC*H*=), 4.12 (dd, 1 H, $J_{5,6e}$ 4.2 Hz, H-6*e*), 3.97 (d, 1 H, $J_{A,B}$ 15.0 Hz, ClCHA), 3.95 (d, 1 H, $J_{A,B}$ 15.3 Hz, ClCHA′), 3.93 (ddd, 1 H, H-2), 3.89 (d, 1 H, ClCHB), 3.83 (d, 1 H, ClCHB′), 3.46 (dd, 1 H, $J_{5,6a}$ 10.0, $J_{6a,6e}$ 10.3 Hz, H-6*a*), 3.45 (ddd, 1 H, H-5), 3.45 (dd, 1 H, H-4), 1.26 (d, 3 H, *Me*CH=).

Anal. Calc. for $C_{20}H_{23}Cl_2NO_9$ (492.31): C, 48.79; H, 4.71; Cl, 14.40; N, 2.85. Found: C, 48.74; H, 4.74; Cl, 14.54; N, 2.76.

*2-Benzyloxycarbonylamino-3-*O*-chloroacetyl-2-deoxy-4,6-*O*-ethylidene-α-* (**11α**) *and -β-*D*-glucopyranose* (**11β**). — A solution of crude **10αβ** in methanol (500 mL) was stirred with silica gel (65 g; LiChroprep NH_2; 20–40 mm; Merck) for 3 h at room temperature, then filtered through Celite, and the combined filtrate and washings were concentrated *in vacuo*. A solution of the residue in ethyl acetate was washed with phosphate buffer (pH 7.0), dried (Na_2SO_4), and concentrated *in vacuo*. The residue (30 g) was absorbed on silica gel (80 g), and eluted from a column of silica gel (250 g) with 20:1 dichloromethane–acetone to give **11αβ** (23.6 g, 83%), isolated as a syrup, $[\alpha]_D$ +31° (*c* 1). Recrystallization from dichloromethane–ethyl acetate–light petroleum gave **11α**, m.p. 188–190°, $[\alpha]_D$ +37° (*c* 1, acetone), $[\alpha]_D^{-20}$ +31° (*c* 1, 1:1 dichloromethane–ethyl acetate). ^{1}H-N.m.r. data (400 MHz, CD_2Cl_2): δ 7.30–7.38 (m, 5 H, Ph), 5.27 (dd, 1 H, $J_{2,3}$ 10.1, $J_{3,4}$ 10.0 Hz, H-3), 5.23 (dd, 1 H, $J_{1,2}$ 3.8, $J_{1,OH}$ 4.2 Hz, H-1), 5.23 (d, 1 H, $J_{2,NH}$ 10.0 Hz, NH), 5.09 (d, 1 H, $J_{A,B}$ 12.6 Hz, PhC*H*A), 5.03 (d, 1 H, PhC*H*B), 4.69 (q, 1 H, $J_{Me,CH}$ 5.0 Hz, MeC*H*=), 4.08 (dd, 1 H, $J_{5,6e}$ 5.0, $J_{6a,6e}$ 10.1 Hz, H-6*e*), 4.04 (d, 1 H, $J_{A,B}$ 14.5 Hz, ClCHA), 3.99 (ddd, 1 H, H-2), 3.97 (ddd, 1 H, $J_{4,5}$ 10.0, $J_{5,6a}$ 10.0 Hz, H-5), 3.95 (d, 1 H, ClCHB), 3.53 (dd, 1 H, H-6*a*), 3.51 (dd, 1 H, H-4), 3.29 (dd, 1 H, $J_{1,OH}$ 4.2, $J_{2,OH}$ 1.3 Hz, HO-1), 1.29 (d, 3 H, *Me*CH=); (300 MHz, $CDCl_3$): **11α**, δ 7.38–7.30 (m, 5 H, Ph), 5.32 (dd, 1 H, $J_{2,3}$ 11, $J_{3,4}$ 10 Hz, H-3), 5.26 (d, 1 H, $J_{2,NH}$ 10 Hz, NH), 5.23 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.11 (d, 1 H, $J_{A,B}$ 12 Hz, PhC*H*A), 5.03 (d, 1 H, PhC*H*B), 4.69 (q, 1 H, $J_{Me,CH}$ 5 Hz, MeC*H*=), 4.09 (dd, 1 H, $J_{5,6e}$ 4.7, $J_{6a,6e}$ 10 Hz, H-6*e*), 4.04 (ddd, 1 H, H-2), 4.02 (d, 1 H, $J_{A,B}$ 14.6 Hz, ClCHA), 3.99 (ddd, 1 H, $J_{4,5}$ 10, $J_{5,6a}$ 10 Hz, H-5), 3.92 (d, 1 H, ClCHB), 3.52 (dd, 1 H, H-6*a*), 3.48 (dd, 1 H, H-4), 1.32 (d, 3 H, *Me*CH=); **11β**, δ 7.30–7.38 (m, 5 H,

Ph), 5.26 (d, 1 H, NH), 5.11 (dd, 1 H, $J_{2,3}$ 10.1, $J_{3,4}$ 10.0 Hz, H-3), 4.70 (d, 1 H, H-1), 4.69 (q, 1 H, $J_{Me,CH}$ 5.0 Hz, MeC*H*=), 4.17 (dd, 1 H, $J_{5,6e}$ 5.0, $J_{6a,6e}$ 9.8 Hz, H-6*e*), 3.67 (ddd, 1 H, $J_{1,2}$ 8.2, $J_{2,3}$ 10.0, $J_{2,NH}$ 10.0 Hz, H-2), 3.57 (dd, 1 H, $J_{5,6a}$ 10.1 Hz, H-6*a*), 3.52 (dd, 1 H, H-4), 3.37 (ddd, 1 H, $J_{4,5}$ 10.0 Hz, H-5), 1.29 (d, 3 H, *Me*CH=).

Anal. Calc. for $C_{18}H_{22}ClNO_8$ (415.83): C, 51.99; H, 5.33; Cl, 8.53; N, 3.37. Found: C, 51.73; H, 5.33; N, 3.31.

4'-O-Benzyloxycarbonyl-4-O-(2-benzyloxycarbonylamino-3-O-chloroacetyl-2-deoxy-4,6-O-ethylidene-α-D-glucopyranosyl)-4'-O-demethyl-4-epipodophyllotoxin (**12α**). — To a stirred mixture of **8** (610 mg, 1.14 mmol), **11α** (450 mg, 1.08 mmol), and powdered molecular sieves 4 Å (1.0 g) in dichloromethane (80 mL) was added dropwise 50% BF_3-etherate (1.4 mL, ~11.62 mmol of BF_3) at −18°. After work-up, as described for the preparation of **9α**, column chromatography (10:1 dichloromethane–acetone) afforded **12α** (815 mg, 81%), m.p. 137–142°, $[\alpha]_D$ +50.5° (*c* 1). ^{1}H-N.m.r. data (300 MHz): δ 7.44–7.30 (m, 10 H, 2 Ph), 6.82 (s, 1 H, H-5), 6.52 (s, 1 H, H-8), 6.24 (s, 2 H, H-2',6'), 6.00 (d, 1 H, H-15A), 5.98 (d, 1 H, H-15B), 5.26 (s, 2 H, PhCH_2), 5.13 (d, 1 H, $J_{2'',NH}$ 8.2 Hz, NH), 5.12 (d, 1 H, $J_{A,B}$ 12.5 Hz, PhC*H*A), 5.11 (dd, 1 H, $J_{2'',3''}$ 10.0, $J_{3'',4''}$ 10.0 Hz, H-3''), 5.09 (d, 1 H, $J_{1'',2''}$ 4.5 Hz, H-1''), 5.07 (d, 1 H, PhC*H*B), 4.71 (d, 1 H, $J_{3,4}$ 3.2 Hz, H-4), 4.68 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 4.66 (q, 1 H, $J_{3,11A}$ 10.1, $J_{A,B}$ 9.2 Hz, H-11A), 4.08 (dd, 1 H, $J_{3,11B}$ 7.8 Hz, H-11B), 4.08 (dd, 1 H, H-6''*e*), 4.06 (ddd, 1 H, H-2''), 3.99 (d, 1 H, $J_{A,B}$ 15.0 Hz, ClCHA), 3.91 (d, 1 H, ClCHB), 3.67 (s, 6 H, MeO-3',5'), 3.53 (dd, 1 H, H-6''*a*), 3.50 (dd, 1 H, H-4''), 3.50 (ddd, 1 H, H-5''), 3.39 (dd, 1 H, $J_{2,3}$ 14.3 Hz, H-2), 2.83 (m, 1 H, H-3), 1.29 (d, 3 H, $J_{Me,CH}$ 5.0 Hz, *Me*CH=).

Anal. Calc. for $C_{47}H_{46}ClNO_{17}$ (932.34): C, 60.55; H, 4.97; Cl, 3.80; N, 1.50. Found: C, 60.49; H, 4.98; N, 1.47.

4'-O-Benzyloxycarbonyl-4-O-(2-benzyloxycarbonylamino-3-O-chloroacetyl-2-deoxy-4,6-O-ethylidene-β-D-glucopyranosyl)-4'-O-demethyl-4-epipodophyllotoxin (**12β**). — To a stirred mixture of **8** (13.0 g, 24.32 mmol), **11αβ** (10.11 g, 24.32 mmol), and molecular sieves 4 Å (23 g) in 1:1 dichloromethane–ethyl acetate (300 mL) was added 50% BF_3-etherate (80 mL, ~66.4 mmol) at −18°. After 4 h, more **8** (1.3 g, 2.43 mmol) was added, the mixture was stirred for 6 h at −18°, triethylamine (80 mL) and ethyl acetate (150 mL) were added, and the suspension was filtered through Celite. The combined filtrate and washings were concentrated *in vacuo*. A solution of the residue in dichloromethane was washed with citrate buffer (pH 5, 200 mL × 2) and ice–water (200 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (15:1 dichloromethane–acetone) of the residue gave **12α** (1.7 g, 7.5%) and **12β** (17.0 g, 75%), m.p. 142°, $[\alpha]_D$ −41° (*c* 1). ^{1}H-N.m.r. data (300 MHz): δ 7.30–7.44 (m, 10 H, 2 Ph), 6.74 (s, 1 H, H-5), 6.50 (s, 1 H, H-8), 6.24 (s, 2 H, H-2',6'), 5.93 (s, 1 H, H-15A), 5.76 (s, 1 H, H-15B), 5.33 (dd, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 10 Hz, H-3'), 5.26 (s, 2 H, PhCH_2), 5.05 (s, 1 H, $J_{A,B}$ 12.5 Hz, PhC*H*A), 4.93 (s, 1 H, PhC*H*B), 4.89 (d, 1 H, $J_{1'',2''}$ 7.5 Hz, H-1''), 4.89 (d, 1 H, $J_{3,4}$ 3.2 Hz, H-4), 3.89 (d, 1 H, $J_{2'',NH}$ 9.5 Hz, NH), 4.70 (q, 1 H, $J_{Me,CH}$ 5 Hz, MeC*H*=), 4.52 (d, 1 H, $J_{1,2}$ 5.3 Hz, H-1), 4.45 (dd, 1 H, $J_{A,B}$ 9, $J_{3,11A}$ 10.0 Hz, H-11A), 4.24 (dd, 1 H, $J_{3,11B}$ 7.3 Hz, H-11B), 4.22 (d, 1 H, $J_{5'',6''e}$ 4.5, $J_{6''a,6''e}$ 10.5 Hz, H-6''*e*), 4.06 (d, 1 H, $J_{A,B}$ 15.0 Hz, ClCHA), 3.99 (d, 1 H, ClCHB), 3.60 (dd, 1 H, $J_{5'',6''a}$ 10.2 Hz, H-6''*a*), 3.66 (s, 6 H,

MeO-3′,5′), 3.60 (dd, 1 H, $J_{4'',5''}$ 9.3 Hz, H-4″), 3.42 (ddd, 1 H, H-5″), 3.23 (dd, 1 H, $J_{2,3}$ 14 Hz, H-2), 2.83 (m, 1 H, H-3), 1.34 (s, 3 H, *Me*CH=).

Anal. Calc. for $C_{47}H_{46}ClNO_{17}$ (932.34): C, 60.55; H, 4.97; Cl, 3.80; N, 1.50. Found: C, 60.64; H, 4.99; N, 1.37.

4-O-(2-Benzyloxycarbonylamino-3-O-chloroacetyl-2-deoxy-4,6-O-ethylidene-α-(**15α**) *and -β-*D*-glucopyranosyl)-4′-O-chloroacetyl-4′-O-demethyl-4-epipodophyllotoxin* (**15β**). — Condensation[9] of **13** with **11αβ**, as described for the preparation of **12β**, gave **15α** (22%), m.p. 153°, $[\alpha]_D$ +45.5° (*c* 1), and **15β** (64%), m.p. 153–155°, $[\alpha]_D$ −37° (*c* 1).

4-O-(2-Benzyloxycarbonylamino-3-O-chloroacetyl-2-deoxy-4,6-O-ethylidene-α-(**16α**) *and -β-*D*-glucopyranosyl)-4-epipodophyllotoxin* (**16β**). — To a mixture of podophyllotoxin (**14**, 1.00 g, 2.41 mmol), **11αβ** (1.00 g, 2.41 mmol), and powdered molecular sieves 4 Å (2 g) was added 50% BF_3-etherate (8.5 mL, ~70 mmol of BF_3) at −18°. The mixture was stirred for 20 h, then treated with triethylamine (10 mL), and worked-up as described for preparation of **12α**. Column chromatography (10:1 dichloromethane–acetone) of the product on silica gel (100 g) gave **16α** (0.33 g, 14%), and **16β** (1.42 g, 73%).

Compound **16α** had m.p. 254°, $[\alpha]_D$ +50.5° (*c* 1). ^{1}H-N.m.r. data (300 MHz): δ 7.37–7.33 (m, 5 H, Ph), 6.82 (s, 1 H, H-5), 6.53 (s, 1 H, H-8), 5.99 (bs, 2 H, H-15A,B), 5.17 (dd, 1 H, $J_{2'',3''}$ 9.5, $J_{3'',4''}$ 9.5 Hz, H-3″), 5.13 (d, 1 H, $J_{2'',NH}$ 9 Hz, NH), 5.10 (s, 2 H, PhCH_2), 5.07 (d, 1 H, $J_{1'',2''}$ 4.2 Hz, H-1″), 4.72 (d, 1 H, $J_{3,4}$ 2.7 Hz, H-4), 4.66 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 4.66 (q, 1 H, $J_{CH,Me}$ 5.0 Hz, MeC*H*=), 4.17 (dd, 1 H, $J_{3,11A}$ 10.5, $J_{A,B}$ 8.5 Hz, H-11A), 4.10 (dd, 1 H, $J_{3,11B}$ 7.3 Hz, H-11B), 4.08 (dd, 1 H, $J_{5'',6''}$ 4.5, $J_{6''a,6''e}$ 10.0 Hz, H-6″*e*), 4.06 (m, 1 H, H-2″), 4.00 (d, 1 H, $J_{A,B}$ 14.5 Hz, ClCHA), 3.91 (d, 1 H, ClCHB), 3.80 (s, 3 H, MeO-4′), 3.73 (s, 6 H, MeO-3′,5′), 3.51 (dd, 1 H, H-6″*a*), 3.51 (dd, 1 H, H-4″), 3.50 (m, 1 H, H-5″), 3.39 (dd, 1 H, $J_{2,3}$ 14.0 Hz, H-2), 2.88 (m, 1 H, Σ*J* 36.1 Hz, H-3), 1.29 (d, 3 H, *Me*CH=).

Anal. Calc. for $C_{40}H_{42}ClNO_{15}$ (812.23): C, 59.15; H, 5.21; N, 1.72. Found: C, 59.27; H, 5.24; N, 1.63.

Compound **16β** had m.p. 221°, $[\alpha]_D$ −40° (*c* 1). ^{1}H-N.m.r. data (300 MHz): δ 7.36–7.26 (m, 5 H, Ph), 6.74 (s, 1 H, H-5), 6.51 (s, 1 H, H-8), 6.21 (s, 2 H, H-2′,6′), 5.95 (s, 1 H, H-15A), 5.79 (s, 1 H, H-15B), 5.30 (dd, 1 H, $J_{2'',3''}$ 10.0, $J_{3'',4''}$ 9.1 Hz, H-3″), 5.07 (d, 1 H, $J_{A,B}$ 12.5 Hz, PhC*H*A), 4.94 (d, 1 H, PhC*H*B), 4.90 (d, 1 H, $J_{3,4}$ 3.1 Hz, H-4), 4.86 (d, 1 H, $J_{1'',2''}$ 7.9 Hz, H-1″), 4.83 (d, 1 H, $J_{2'',NH}$ 9.0 Hz, NH), 4.71 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 4.71 (q, 1 H, $J_{Me,CH}$ 5.0 Hz, MeC*H*=), 4.45 (dd, 1 H, $J_{3,11A}$ 11.0, $J_{A,B}$ 8.5 Hz, H-11A), 4.25 (dd, 1 H, $J_{3,11B}$ 7.1 Hz, H-11B), 4.23 (dd, 1 H, $J_{5'',6''e}$ 4.0, $J_{6''a,6''e}$ 10.0 Hz, H-6″*e*), 4.06 (d, 1 H, $J_{A,B}$ 15.0 Hz, ClCHA), 3.99 (d, 1 H, ClCHB), 3.79 (s, 3 H, MeO-4′), 3.73 (s, 6 H, MeO-3′,5′), 3.60 (dd, 1 H, $J_{5'',6''a}$ 10.0 Hz, H-6″*a*), 3.60 (m, 1 H, H-2″), 3.48 (dd, 1 H, $J_{4'',5''}$ 9.2 Hz, H-4″), 3.43 (m, 1 H, H-5″), 3.22 (dd, 1 H, $J_{2,3}$ 14.1 Hz, H-2), 2.88 (m, 1 H, Σ*J* 36 Hz, H-3), 1.34 (d, 3 H, *Me*CH=).

Anal. Found: C, 59.17; H, 5.23; N, 1.70.

*4′-O-Benzyloxycarbonyl-4-O-(2-benzyloxycarbonylamino-2-deoxy-4,6-O-ethylidene-α-*D*-glucopyranosyl)-4′-O-demethyl-4-epipodophyllotoxin* (**17α**). — To a solution of **12α** (500 mg, 0.53 mmol) in methanol (25 mL) was added Dowex 1-X8 (HO^-) resin

(800 mg). After 6 h, the mixture was worked-up, and the product was purified, as described for preparation of **17β**, to give **17α** (435 mg, 96%), m.p. 155°, $[\alpha]_D$ +75° (*c* 1, methanol); lit.[11] m.p. 146–148°, $[\alpha]_D$ +65° (*c* 0.7).

4'-O-Benzyloxycarbonyl-4-O-(2-benzyloxycarbonylamino-2-deoxy-4,6-O-ethylidene-β-D-glucopyranosyl)-4'-O-demethyl-4-epipodophyllotoxin (**17β**). — To a solution of **12β** (14.0 g, 15.01 mmol) in methanol (500 mL) was added Dowex 1-X8 (HO^-) resin (20 g). The mixture was stirred for 8 h at room temperature and filtered, and the resin was washed with methanol (150 mL). The combined filtrate and washings were concentrated *in vacuo*, and a solution of the residue in dichloromethane (400 mL) was washed with phosphate buffer (pH 7, 100 mL × 2), dried (Na_2SO_4), and concentrated *in vacuo*. The product crystallized from ethyl acetate–di-isopropyl ether to give **17β** (12.20 g, 95%), m.p. 155°, $[\alpha]_D$ −69° (*c* 1); lit.[11] m.p. 136–138°, $[\alpha]_D$ −71° (*c* 0.81). ^{1}H-N.m.r. data (300 MHz, H–D change): δ 7.36–7.24 (m, 10 H, 2 Ph), 6.29 (s, 1 H, H-5), 6.46 (s, 1 H, H-8), 6.31 (s, 2 H, H-2',6'), 5.86 (s, 1 H, H-15A), 5.70 (s, 1 H, H-15B), 5.18 (s, 2 H, PhCH_2), 4.97 (d, 1 H, $J_{A,B}$ 12.5 Hz, PhC*H*A), 4.93 (d, 1 H, $J_{3,4}$ 3.1 Hz, H-4), 4.86 (d, 1 H, PhC*H*B), 4.76 (q, 1 H, $J_{Me,CH}$ 5.0 Hz, MeC*H*=), 4.75 (d, 1 H, $J_{1'',2''}$ 8.2 Hz, H-1''), 4.52 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 4.45 (dd, 1 H, $J_{3,11A}$ 9.8, $J_{A,B}$ 9.1 Hz, H-11A), 4.24 (dd, 1 H, $J_{3,11B}$ 7.3 Hz, H-11B), 4.13 (dd, 1 H, $J_{5'',6''e}$ 4.3, $J_{6''a,6''e}$ 10.2 Hz, H-6''*e*), 3.69 (dd, 1 H, $J_{2'',3''}$ 9.0, $J_{3'',4''}$ 9.2 Hz, H-3''), 3.58 (dd, 1 H, $J_{5'',6''a}$ 10 Hz, H-6''*a*), 3.39 (dd, 1 H, H-2''), 3.38 (dd, 1 H, $J_{4'',5''}$ 10.5 Hz, H-4''), 3.28 (m, 1 H, H-5''), 2.81 (m, 1 H, Σ*J* 36 Hz, H-3), 1.31 (d, 3 H, *Me*CH=).

Anal. Calc. for $C_{45}H_{45}NO_{16}$ (855.86): C, 63.15; H, 5.30; N, 1.64. Found: C, 63.24; H, 5.32; N, 1.57.

4-O-(2-Amino-2-deoxy-4,6-O-ethylidene-α-D-glucopyranosyl)-4'-O-demethyl-4-epipodophyllotoxin (**18α**). — Compound **17α** (400 mg, 0.46 mmol) was treated, as described for the preparation of **18β**, to give **18α** (243 mg, 90%), m.p. 224°, $[\alpha]_D$ +25° (*c* 0.5); lit.[11] m.p. 225–227°, $[\alpha]_D$ +25° (*c* 0.83).

4-O-(2-Amino-2-deoxy-4,6-O-ethylidene-β-D-glucopyranosyl)-4'-O-demethyl-4-epipodophyllotoxin (**18β**). — A solution of **17β** (10.0 g, 11.68 mmol) in methanol (200 mL) was stirred for 3 h under hydrogen (1 atm.) in the presence of 10% Pd–C (2.5 g), then filtered through Celite, the filter pad was washed, and the combined filtrate and washings were concentrated *in vacuo*. Column chromatography (10:1 dichloromethane–methanol) of the residue on silica gel (100 g) gave **18β** (6.17 g, 90%), m.p. 218–220° (dec.), $[\alpha]_D$ −115° (*c* 1, methanol); lit.[11] m.p. 201–203°, $[\alpha]_D$ −111° (*c* 0.85).

4'-O-Demethyl-4-O-(2-deoxy-2-dimethylamino-4,6-O-ethylidene-β-D-glucopyranosyl)-4-epipodophyllotoxin (**3**). — To a solution of **18β** (5.0 g, 8.51 mmol) in methanol (100 mL) were added sodium cyanoborohydride (2.14 g, 34.04 mmol) and aqueous formaldehyde (37%, 8 mL). The mixture was stirred for 1 h at room temperature, then concentrated *in vacuo*. Column chromatography (10:1 dichloromethane–methanol) of the residue on silica gel (90 g) afforded **3** (4.45 g, 87%), m.p. 196–198°, $[\alpha]_D$ −104° (*c* 1); lit.[6] m.p. 196–198°, $[\alpha]_D$ −107° (*c* 0.78).

4'-O-Demethyl-4-O-(2-deoxy-2-dimethylamino-4,6-O-ethylidene-α-D-glucopyranosyl)-4-epipodophyllotoxin (**19α**). — Compound **18α** (120 mg, 0.20 mmol) was sub-

jected to reductive alkylation, as described for the preparation of **3**, to give **19α** (104 mg, 85%), m.p. 270–273°, $[\alpha]_D$ +17.4° (*c* 1). ^{1}H-N.m.r. data (400 MHz): δ 6.75 (s, 1 H, H-5), 6.51 (s, 1 H, H-8), 6.25 (s, 2 H, H-2′,6′), 5.99 (d, 1 H, $J_{A,B}$ 1.0 Hz, H-15A), 5.98 (d, 1 H, H-15B), 4.91 (d, 1 H, $J_{3,4}$ 3.5 Hz, H-4), 4.89 (dd, 1 H, $J_{3,11A}$ 10.5, $J_{A,B}$ 9.0 Hz, H-11A), 4.72 (d, 1 H, $J_{1'',2''}$ 3.5 Hz, H-1″), 4.71 (q, 1 H, $J_{Me,CH}$ 5.0 Hz, MeC*H*=), 4.63 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 4.28 (dd, 1 H, $J_{3,11B}$ 7.5 Hz, H-11B), 4.12 (dd, 1 H, $J_{5'',6''e}$ 4.5, $J_{6''a,6''e}$ 10.0 Hz, H-6″*e*), 4.10 (dd, 1 H, $J_{2'',3''}$ 10.0, $J_{3'',4''}$ 9.1 Hz, H-3″), 3.77 (s, 6 H, MeO-3′,5′), 3.54 (dd, 1 H, $J_{5'',6''a}$ 10.0 Hz, H-6″*a*), 3.48 (ddd, 1 H, $J_{4'',5''}$ 10.0 Hz, H-5″), 3.36 (dd, 1 H, $J_{2,3}$ 14.2 Hz, H-2), 3.30 (dd, 1 H, H-4″), 2.89 (m, 1 H, ΣJ 35.5 Hz, H-3), 2.74 (dd, 1 H, H-2″), 2.56 (s, 6 H, NMe_2), 1.34 (d, 3 H, *Me*CH=).

Anal. Calc. for $C_{31}H_{37}NO_{12}$ (615.64): C, 60.48; H, 6.06; N, 2.28. Found: C, 60.53; H, 6.03; N, 2.17.

*4-O-(2-Benzyloxycarbonylamino-2-deoxy-4,6-O-ethylidene-β-*D*-glucopyranosyl)-4′-O-demethyl-4-epipodophyllotoxin* (**20β**). — Compound **15β** was deprotected, as described for the preparation of **17α**, to give **20β**, m.p. 143–145° $[\alpha]_D$ −74° (*c* 1). ^{1}H-N.m.r. data (400 MHz): δ 7.2–7.3 (m, 5 H, Ph), 6.698 (s, 1 H, H-5), 6.45 (s, 1 H, H-8), 6.19 (s, 2 H, H-2′,6′), 5.84 (s, 1 H, H-15A), 5.65 (bs. 1 H, H-15B), 4.97 (s, 2 H, PhCH_2),4.89 (d, 1 H, $J_{1'',2''}$ 7.6 Hz, H-1″), 4.79 (d, 1 H, $J_{3,4}$ 3.8 Hz, H-4), 4.68 (q, 1 H, $J_{CH,Me}$ 5.0 Hz, MeC*H*=), 4.49 (d, 1 H, $J_{1,2}$ 5.1 Hz, H-1), 4.38 (dd, 1 H, $J_{3,11A}$ 10.0, $J_{A,B}$ 9.0 Hz, H-11A), 4.27 (s, 2 H, $ClCH_2$), 4.16 (dd, 1 H, $J_{3,11B}$, 7.4 Hz, H-11B), 4.11 (dd, 1 H, $J_{5'',6''e}$ 4.6, $J_{6''a,6''e}$ 10.6 Hz, H-6″*e*), 3.60 (s, 6 H, MeO-3′,5′), 3.51 (dd, 1 H, $J_{5'',6''a}$ 9.6 Hz, H-6″*a*), 3.29 (ddd, 1 H, $J_{4'',5''}$ 9.3 Hz, H-5), 3.25 (dd, 1 H, $J_{3'',4''}$ 9.5 Hz, H-4″), 3.15 (dd, 1 H, $J_{2,3}$ 13.9 Hz, H-2), 3.15 (dd, 1 H, H-2″), 2.76 (m, 1 H, ΣJ 35.6 Hz, H-3), 1.32 (d, 1 H, *Me*CH=).

Anal. Calc. for $C_{37}H_{39}NO_{14}$ (721.72): C, 61.58, H, 5.45. Found: C, 61.67, H, 5.47.

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