Stereoselective Glucosidation[1] of Podophyllum Lignans. A New Simple Synthesis of Etoposide

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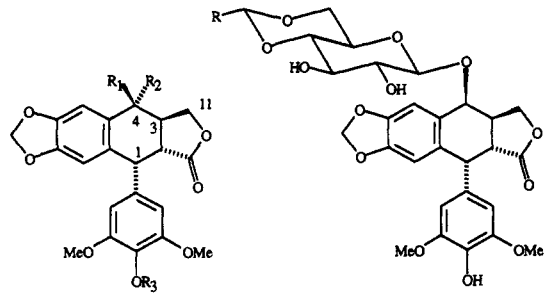
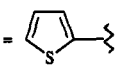
Introduction

The stereoselective formation of *O*-glycosides of podophyllum lignans **1–3** is an important topic in carbohydrate chemistry since a number of these derivatives, including etoposide (**4**) and teniposide (**5**),[2] are clinically useful in the treatment of small-cell lung cancer,[3] testicular cancer,[4]



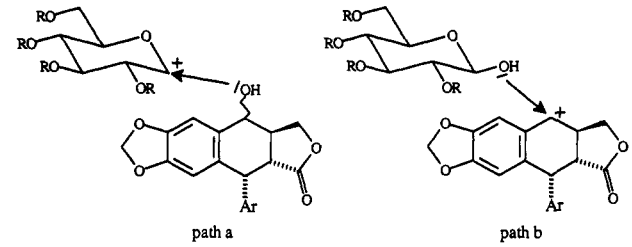
1 R_1 = H; R_2 = OH; R_3 = Me
2 R_1 = OH; R_2 = H; R_3 = Me
3 R_1 = OH; R_2 = R_3 = H

4 R = Me

5 R = 

and leukemia.[5] The formation of the O-glycosidic linkage in these compounds can be accomplished[6,7] by two different strategies (Scheme I). The first one[6] (Scheme I, *path a*) is a Koenigs–Knorr-like coupling of a glucose derivative, bearing a good leaving group at the anomeric carbon, with the hydroxy group of the lignan aglycon. The reaction involves the attack of the hydroxy group of the aglycon on the carboxonium ion formed at the anomeric center of the glycosyl donor under the reaction conditions.

Scheme I



In this case, the anomeric configuration of the *O*-glucoside obtained is independent of that of the glycosyl donor and depends principally upon the ability of the protective group at position 2 of the glycopyranose ring to provide anchimeric assistance to the formed glucopyranoxonium ion. The stereochemistry at C-4 of the aglycon portion of the resulting glycoside is that of the starting lignan.

The second approach[7] (Scheme I, *path b*), first introduced by Kuhn,[7a] involves stereocontrolled attack of a free anomeric hydroxyl group of a glycopyranose derivative on the less-hindered β side of a benzylic cation generated at C-4 of the aglycon by a Lewis acid.

In this case, the stereochemistry of the formed glucosidic linkage is highly dependent upon the anomeric configuration of the glucopyranose donor, and the stereochemistry at C-4 of the resulting glycoside is independent of that of the starting lignan aglycone.

The latter method appears to be more useful in the synthesis of etoposide and its congeners, which all possess a β configuration both at the anomeric carbon and the benzylic carbon of the aglycon moiety.[7a] The problem with this method is the accessibility of glucopyranose donors with the required β configuration and high anomeric purity.

In fact, only 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose is easily obtainable from the commercially available 1α-bromo derivative by the action of H_2O and Ag_2CO_3 under controlled reaction conditions;[8] the preparation of other β-glucopyranosyl derivatives is more complex. The preparation of the pure β anomer of 2,3,4,6-tetra-*O*-benzylglucopyranose has not been reported, and the preparations of β anomers of 2,3-protected 4,6-*O*-ethylideneglucopyranoses, which are useful for the synthesis of etoposide since they already possess the acetalic function of the target molecule, involve multistep procedures.[7c,e,f] These procedures require, in the final step, hydrogenolytic regeneration of the β-anomeric hydroxy group from a benzyl or carbobenzyloxy derivative, with the risk of partial anomerization of the β-anomer under the reaction conditions.[7f]

In this paper, we report a new Kuhn-like method for the stereoselective β-O-glucosidation of podophyllotoxin lignans and its application to a simple synthesis of etoposide. The route uses 1β-*O*-trimethylsilyl derivatives of glucopyranosides **6–8**, which are not susceptible to anomerization in solvents and are easily obtainable[9,10] in anomerically pure β form by simple silylation of readily available anomeric mixtures of 1-O-unprotected sugars.

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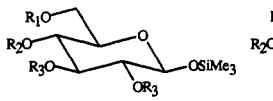
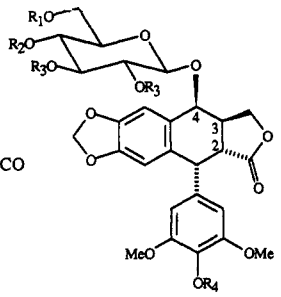
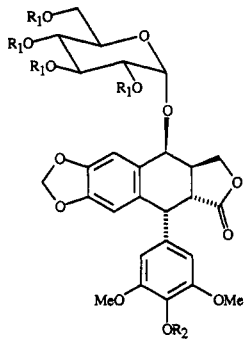


6 $R_1 = R_2 = R_3 = Ac$
7 $R_1 = R_2 = R_3 = Bn$
8 $R_1, R_2 = MeCH<$; $R_3 = Cl_2CHCO$



9 $R_1 = R_2 = R_3 = Ac$; $R_4 = Me$
11 $R_1 = R_2 = R_3 = Ac$; $R_4 = H$
13 $R_1 = R_2 = R_3 = Bn$; $R_4 = Me$
15 $R_1 = R_2 = R_3 = Bn$; $R_4 = H$
17 $R_1, R_2 = MeCH<$; $R_3 = Cl_2CHCO$; $R_4 = H$



10 $R_1 = Ac$; $R_2 = Me$
12 $R_1 = Ac$; $R_2 = H$
14 $R_1 = Bn$; $R_2 = Me$
16 $R_1 = Bn$; $R_2 = H$

Results and Discussion

1-O-trimethylsilylated sugars have already been employed as useful glycosyl donors in Koenigs–Knorr-like O-glycosylations of silylated phenols[11] and silylated alcohols[12] and in the formation of *O*-glycosides with 1,1′-diacetal structures,[13] including 1,1′-coupled disaccharides[13a] and iridoid glucosides.[13d]

In the Koenigs–Knorr-like reactions, O-glycosylation proceeds via an intermediate carbonium ion at the anomeric center of the sugar, which suffers a nucleophilic attack by the aglycon. The stereochemistry at the anomeric center of the formed *O*-glycosides is dependent on the nature of the 2-O-protecting group of the glycosyl donor, the reaction conditions, and the thermodynamic stability of the two anomers.

In the case of 1,1′-diacetal glycosides, complete retention of configuration at the anomeric center is observed under controlled reaction conditions, regardless of the nature of the 2-O-protecting group of the glucosyl donor. This observation suggests that the reaction proceeds through an oxonium ion at the acetal carbon of the aglycon; the oxonium ion undergoes attack by the oxygen atom of the trimethylsilyloxy group of the sugar.

Considering the benzylic nature of the alcoholic group of lignans 1–3 and the easy transformation of the alcohol into a benzylic carbonium ion, we decided to explore the possibility of utilizing 1β-O-trimethylsilylated sugars in a Kuhn-like synthesis of biologically active lignan β-*O*-glucosides. The easy access to anomerically pure 1β-*O*-(trimethylsilyl)glucopyranosyl derivatives circumvents the difficulties connected with preparing anomerically pure β-glucopyranoses containing a free anomeric hydroxyl group.

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Table I. Results of O-Glucosidation Reactions

entry	1β-O-silylated sugar	lignan	conditions (catalyst,[a] temp, time)	products (yield);[b] ratio β:α[c]
a	6	1	A, −20 °C, 2 h	9 + 10 (80); 95:5
b	6	1	A, 20 °C, 0.3 h	9 + 10 (80); 40:60
c	6	2	A, −20 °C, 2 h	9 + 10 (77); 95:5
d	6	2	A, 20 °C, 0.3 h	9 + 10 (82); 42:58
e	6	3	A, −20 °C, 2.5 h	11 + 12 (75); 97:3
f	6	3	A, 20 °C, 0.5 h	11 + 12 (76); 34:66
g	7	1	B, −70 °C, 3.5 h	13 + 14 (75); 95:5
h	7	1	B, −20 °C, 0.5 h	13 + 14 (78); 35:65
i	7	1	A, −20 °C, 2.5 h	13 + 14 (75); 40:60
l	7	2	B, −70 °C, 3.5 h	13 + 14 (76); 95:5
m	7	2	B, −20 °C, 0.5 h	13 + 14 (80); 40:60
n	7	2	A, −20 °C, 2.5 h	13 + 14 (76); 42:58
o	7	3	B, −70 °C, 4.5 h	15 + 16 (77); 97:3
p	7	3	B, −20 °C, 1 h	15 + 16 (80); 42:58
q	7	3	A, −20 °C, 3 h	15 + 16 (78); 48:52

[a] Catalyst A: $BF_3{\cdot}Et_2O$, 3 equiv. Catalyst B: TMSOTf, 1 equiv. [b] Yields of the O-glucosidic mixture after flash chromatography. [c] Determined by HPLC.

We first studied the $BF_3{\cdot}Et_2O$-catalyzed reactions of podophyllotoxin (1) and epipodophyllotoxin (2) with 1-*O*-(trimethylsilyl)-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (6)[9] (anomeric purity >98% by ^1H NMR at 500 MHz; prepared in high yield by direct silylation of an anomeric mixture (70:30 α/β) of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose).[14]

Both O-glycosidations occurred in high yields affording similar mixtures of epipodophyllotoxin glucosides **9** and **10**, both of which possess β stereochemistry in C-4. However, the ratio of anomers **9** and **10** was quite dependent upon reaction temperature; in fact, at −20 °C, the β-*O*-glucoside was obtained with very high stereoselection from both substrates, whereas higher temperatures led to increasing percentages of the α-anomer. At 20 °C, the α-anomer was the major product (see Table I, entries a–d), probably because of temperature dependent partial anomerization of the sugar *prior* to glucosidation in the presence of the Lewis acid.

Comparable results were obtained with 4′-demethylepipodophyllotoxin (**3**) (see Table I, entries e and f), which possesses a free phenolic group. This result is remarkable since, in principle, the phenolic group could react with the carbonium ion formed at C-4 of the aglycon and/or with the glucosyl donor, as has been reported for silylated phenols.[11] However, these side reactions did not occur to any significant extent under our reaction conditions.

The O-glucosidation of the same aglycones, **1–3** with 1-*O*-(trimethylsilyl)-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranose (**7**) (anomeric purity >98% by ^1H NMR at 500 MHz), obtainable[10] by silylation of commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (90:10 α/β anomeric mixture), occurred in similar high yields and stereoselectivity when trimethylsilyl trifluoromethanesulfonate (TMSOTf) was used at −70 °C in place of $BF_3{\cdot}Et_2O$ (see Table I, entries g, l and o).

At −20 °C, $BF_3{\cdot}Et_2O$ catalyzes the reaction with poor α/β selectivity (see Table I, entries i, n, and q), and, at lower temperatures, excessively long reaction times are required.

This O-glucosidation method was then applied to a new and efficient synthesis of the antitumor agent etoposide (**4**) by means of a reaction between 1-*O*-(trimethylsilyl)-

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4,6-*O*-ethylidene-2,3-di-*O*-(dichloroacetyl)-β-D-glucopyranose (8) and lignan 3, which has an unprotected phenolic group.[7h]

Silylated sugar 8 was prepared in an high anomeric purity (>98% by ^{1}H NMR at 500 MHz) from 4,6-*O*-ethylidene-D-glucopyranose[15] in 70% overall yield. The preparation of 8 required the perchloroacetylation (Cl_2CHCOCl–pyridine) of the free hydroxyl groups, selective hydrolysis (by simple treatment with methanol) of the anomeric hydroxyl to afford an anomeric mixture (α/β 70:30; ^{1}H NMR at 500 MHz) of the corresponding 2,3-di-*O*-dichloroacetates, and silylation of the mixture with chlorotrimethylsilane and triethylamine in dichloromethane. Compound 8 was obtained in pure β form by crystallization of the crude reaction mixture.

O-Glucosidation of lignan 3 with silylated sugar 8 in the presence of BF_3·Et_2O at −20 °C resulted in the formation of the corresponding β-*O*-glucoside (17).

Since the reaction was performed without protecting the phenolic group of 3, the quenching conditions were critical. It was necessary to pour the reaction mixture into ice-cold water under vigorous agitation without any previous neutralization of the Lewis acid with organic or mineral bases. In the presence of base, the formation of undesired byproducts was observed.

Regeneration of the alcoholic groups in positions 2 and 3 of the glycosidic moiety of 17 by simple methanolysis, in presence of zinc acetate at reflux for 90 min, completed the synthesis; etoposide (4) was obtained in 70% total yield from lignan 3.

The stereochemistries of compounds 9, 10, and 13–17 were deducted from the examination of their ^{1}H NMR spectra at 500 MHz. In particular, the configuration at the anomeric center of each product was assigned on the basis of the value of the coupling constant between the anomeric proton and the adjacent glucosidic one. In fact, for the glucopyranosic rings in $^4C_1$ conformation (as evident from the values of the coupling constants of the other glucosidic protons), a high value for this coupling constant (7–10 Hz) indicates an *axial–axial* relationship between these protons, characteristic of a β-configuration of the glucosidic bond; a low value (2–4 Hz) indicates an *equatorial–axial* relationship, characteristic of an α-*O*-glucoside.

The configuration at C-4 of each compound was determined from the value of the coupling constant between the H-3 and H-4 protons. In fact, because of the rigidity conferred on the system by the 2,3-*trans* fusion,[16] these protons in the 4β isomers are in an *axial–equatorial* relationship (J = 3.5 Hz), whereas in the 4α isomers they have an *axial–axial* geometry (J = 9.5–10.0 Hz).[17]

The observed coupling constants between the proton at C-3 and the adjacent protons at C-2 and C-11 ($J_{2,3}$ = 14.0 Hz, $J_{3,11}$ = 10.5 and 7.5–8.0 Hz) show that in no case did epimerization of the lactonic function occur to afford picropodophyllotoxin analogues. In fact, the values are typical[18,19] for the podophyllotoxin series and are quite different from those observed for picropodophyllotoxin ($J_{2,3}$ = 9.0 Hz, $J_{3,11}$ = 6.0 and 1.5 Hz).

In conclusion, our results show that 1β-*O*-(trimethylsilyl)glucosides, easily obtainable in anomerically pure form from anomeric mixture of 1-O-unprotected sugars, provide a new, simple, and convenient approach to the glucosidation of podophyllum lignans including the clinically useful antitumor agent etoposide.

Experimental Section

General. All melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-500 instrument in $CDCl_3$ and are reported in δ units relative to $CHCl_3$ fixed at 7.24 ppm. Optical rotations were recorded with a Perkin-Elmer 141 spectropolarimeter, $[\alpha]^t_D$ values are given in degrees. TLC was performed on precoated silica gel G plates (Merck, HF_{254}); spots were visualized by spraying with 70% sulfuric acid and heating. Column chromatographies were performed by Still's method (flash chromatography).[20]

HPLC analyses were performed on a Jasco twinkle pump system and on a Uvidec 100 II. The analyses were carried out on a reverse-phase Lichrosorb C-18 column (3 μm; 4 × 250 mm; Merck), with the solvent mixtures reported; the flow rate was 1 mL min^{-1}, and detection was performed at 254 nm.

Usual workup refers to washing the organic layer with water, drying it over Na_2SO_4, and evaporating the solvent under reduced pressure.

Materials. Podophyllotoxin (1) (99%) was obtained from Aldrich Chemical Co. Epipodophyllotoxin (2),[21] 4′-demethylepipodophyllotoxin (3),[22] 1-*O*-(trimethylsilyl)-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranose (7),[10] 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose,[14] and 4,6-*O*-ethylidene-D-glucopyranose[15] were synthesized as described in the literature.

Preparation of 1-*O*-(Trimethylsilyl)-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (6). To a stirred solution of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose[14] (34.8 g, 0.1 mol, anomeric mixture α/β, 70:30) in dichloromethane (130 mL) containing triethylamine (20.8 mL, 0.15 mol) was added chlorotrimethylsilane (15.2 mL, 0.12 mol) dropwise at room temperature. After being stirred for 2 h, the mixture was filtered through a pad of Celite and worked up to afford a residue that was crystallized to afford silyl derivative 6 in 85% yield as a single (^{1}H NMR, 500 MHz) β-anomer: mp 104–105 °C (from diisopropyl ether); $[\alpha]^{23}_D$ −7.1° ($CHCl_3$, *c* 1) [lit.[13b] mp 104.7 °C; $[\alpha]^{20}_D$ −6.8° ($CHCl_3$, *c* 1)]; ^{1}H NMR (500 MHz) δ 0.12 (s, 9 H, Si-CH_3), 1.96, 1.98, 1.99, and 2.03 (4 × s, 12 H, 4 × OCOCH_3), 3.67 (ddd, J = 2.1, 5.6, 9.8 Hz, 1 H, H-5), 4.09 (dd, J = 2.1, 12.6 Hz, 1 H, H-6a), 4.17 (dd, J = 5.6, 12.6 Hz, 1 H, H-6b), 4.71 (d, J = 7.7 Hz, 1 H, H-1), 4.87 (dd, J = 7.7, 9.8 Hz, 1 H, H-2), 5.01 (dd, J = 9.8, 9.8 Hz, 1 H, H-4), 5.15 (dd, J = 9.8, 9.8 Hz, 1 H, H-3). Solutions of 6 in $CHCl_3$ or CH_2Cl_2 showed unchanged optical rotations after 6 days standing at 25 °C.

Preparation of 1-*O*-(Trimethylsilyl)-4,6-*O*-ethylidene-2,3-di-*O*-(dichloroacetyl)-β-D-glucopyranose (8). A solution of dichloroacetyl chloride (31.7 mL, 0.33 mol) in dichloromethane (50 mL) was added dropwise to a stirred suspension of 4,6-*O*-ethylidene-D-glucopyranose (20.6 g, 0.1 mol, anomeric mixture α/β, 90:10) in dichloromethane (400 mL) containing pyridine (55 mL) at −20 °C. The mixture was stirred for 2 h at 0 °C and then was poured into an ice-cold solution of HCl (500 mL, 1.3 M). The organic layer was washed with an aqueous $NaHCO_3$ solution and water and dried.

[Evaporation of an aliquot of this solution gave crude 4,6-*O*-ethylidene-1,2,3-tri-*O*-(dichloroacetyl)-α-D-glucopyranose, as a syrup, with a high anomeric purity (>97%): ^{1}H NMR (500 MHz) δ 1.32 (d, J = 5.0 Hz, 3 H, CH_3CH), 3.54 (dd, J = 10.5, 10.5 Hz, 1 H, H-6a), 3.63 (dd, J = 9.8, 9.8 Hz, 1 H, H-4), 3.95 (ddd, J = 4.9, 9.8, 10.5 Hz, 1 H, H-5), 4.18 (dd, J = 4.9, 10.5 Hz, 1 H, H-6b),

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4.71 (q, J = 5.0 Hz, 1 H, CH_3CH), 5.24 (dd, J = 4.2, 9.8 Hz, 1 H, H-2), 5.61 (dd, J = 9.8, 9.8 Hz, 1 H, H-3), 5.86 (s, 1 H, Cl_2CHCO), 5.94 (s, 1 H, Cl_2CHCO), 6.03 (s, 1 H, Cl_2CHCO), 6.41 (d, J = 4.2 Hz, 1 H, H-1).]

The bulk of the solution was treated with methanol (50 mL) and stirred at 20 °C for 20 h. After this time, usual workup afforded crude 4,6-*O*-ethylidene-2,3-di-*O*-(dichloroacetyl)-D-glucopyranose (36.4 g) as an anomeric mixture (α/β, 70:30); its ^{1}H NMR (500 MHz) spectrum showed signals for the α-anomer at δ 1.31 (d, J = 5.0 Hz, 3 H, CH_3CH), 3.51–3.55 (overlapping, 2 H, H-6a and H-4), 4.06 (ddd, J = 5.0, 9.5, 9.5 Hz, 1 H, H-5), 4.13 (dd, J = 5.0, 10.5 Hz, 1 H, H-6b), 4.69 (q, J = 5.0 Hz, 1 H, CH_3CH), 4.98 (dd, J = 3.5, 9.5 Hz, 1 H, H-2), 5.50 (d, J = 3.5 Hz, 1 H, H-1), 5.64 (dd, J = 9.5, 9.5 Hz, 1 H, H-3), 5.93 (s, 1 H, Cl_2CHCO), 5.94 (s, 1 H, Cl_2CHCO). Signals attributable to the β-anomer were observed at δ 1.30 (d, J = 5.0 Hz, 3 H, CH_3CH), 3.46 (ddd, J = 5.0, 9.5, 9.5 Hz, 1 H, H-5), 3.56–3.60 (overlapping, 2 H, H-6a and H-4), 4.21 (dd, J = 5.0, 10.5 Hz, 1 H, H-6b), 4.68 (q, J = 5.0 Hz, 1 H, CH_3CH), 4.89 (d, J = 8.0 Hz, 1 H, H-1), 5.00 (dd, J = 8.0, 9.5 Hz, 1 H, H-2), 5.37 (dd, J = 9.5, 9.5 Hz, 1 H, H-3), 5.92 (s, 1 H, Cl_2CHCO), 5.93 (s, 1 H, Cl_2CHCO).

The crude anomeric sugar mixture obtained was dissolved in dichloromethane (200 mL) containing triethylamine (22.2 mL, 0.16 mol), and chlorotrimethylsilane (15.2 mL, 0.12 mol) in dichloromethane (50 mL) was added dropwise at room temperature. After stirring at room temperature for 2 h, the mixture was filtered through a pad of Celite and worked up to afford, after crystallization silyl derivative 8 (34.9 g, 70% yield from 4,6-*O*-ethylidene-D-glucopyranose) as a single (^{1}H NMR, 500 MHz) β-anomer: mp 115–116 °C; (from hexane–diisopropyl ether); $[\alpha]^{23}_D$ –34.2° ($CHCl_3$, c 1); ^{1}H NMR (500 MHz) δ 0.13 (s, 9 H, $SiCH_3$), 1.29 (d, J = 5.0 Hz, 3 H, CH_3CH), 3.41 (ddd, J = 5.0, 9.5, 9.5 Hz, 1 H, H-5), 3.54 (dd, J = 9.5, 9.5 Hz, 1 H, H-4), 3.57 (dd, J = 9.5, 10.0 Hz, 1 H, H-6a), 4.16 (dd, J = 5.0, 10.0 Hz, 1 H, H-6b), 4.67 (q, J = 5.0 Hz, 1 H, CH_3CH), 4.85 (d, J = 7.5 Hz, 1 H, H-1), 4.99 (dd, J = 7.5, 9.5 Hz, 1 H, H-2), 5.32 (dd, J = 9.5, 9.5 Hz, 1 H, H-3), 5.89 (s, 1 H, Cl_2CHCO), 5.91 (s, 1 H, Cl_2CHCO). Anal. Calcd for $C_{15}H_{22}O_8SiCl_4$: C, 36.02; H, 4.43. Found: C, 36.15; H, 4.37.

General Procedure for O-Glucosidation. To a cooled (see Table I for temperature), stirred mixture of 1β-O-trimethylsilylated sugar **6** or **7** (5.2 mmol) and lignan 1, 2, or 3 (4 mmol) in dichloromethane (100 mL for lignan 1 or 2; 300 mL for lignan 3), an acid catalyst (1.47 mL, 12 mmol, of BF_3-Et_2O or 0.77 mL, 4 mmol, of TMSOTf) was added under argon. The resulting mixture was then stirred for the time required at the appropriate temperature (see Table I). Then the reaction mixture was worked up to afford, after flash chromatography (eluting with dichloromethane–acetone 100:10 v/v for compounds **9**–**12** and 100:3 v/v for compounds **13**–**15**), the O-glucosidic fraction.

(i) 1-*O*-(Trimethylsilyl)-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**6**) and podophyllotoxin (1) or epipodophyllotoxin (2) afforded an O-glucosidic mixture of 4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)epipodophyllotoxin (**9**) and 4-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)epipodophyllotoxin (**10**) (reaction conditions and yields are reported in Table I).

Compound 9: mp 201–203 °C (from MeOH); $[\alpha]^{23}_D$ –59.1° ($CHCl_3$, c 1) [lit.[7a] mp 202–204 °C; $[\alpha]^{21}_D$ –58.9° ($CHCl_3$, c 0.612)]; HPLC, t_R 26.3 min (eluting system CH_3CN–AcOH–H_2O 57:1:72 v/v/v).

Compound 10: mp 239–241 °C (from MeOH); $[\alpha]^{23}_D$ +49.5° ($CHCl_3$, c 1) [lit.[7a]] mp 238–241 °C; $[\alpha]^{21}_D$ +48.7° ($CHCl_3$, c 0.565)]; HPLC, t_R 24.5 min (eluting system CH_3CN–AcOH–H_2O 57:1:72 v/v/v).

(ii) Compound **6** and 4′-demethylepipodophyllotoxin (**3**) afforded an O-glucosidic mixture of 4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4′-demethylepipodophyllotoxin (**11**) and 4-(2,3,-4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-4′-demethylepipodophyllotoxin (**12**) (reaction conditions and yields are reported in Table I).

Compound 11: mp 224–226 °C (from MeOH); $[\alpha]^{23}_D$ –62.8° ($CHCl_3$, c 1) [lit.[7b] mp 228–230 °C; $[\alpha]^{22}_D$ –63.8° ($CHCl_3$, c 1.019)]; HPLC, t_R 29.2 min (eluting system CH_3CN–AcOH–H_2O 45:1:72 v/v/v).

Compound 12, a glass, shows the same physicochemical properties described previously;[7h] HPLC, t_R 26.4 min (eluting system CH_3CN–AcOH–H_2O 45:1:72 v/v/v).

(iii) 1-*O*-(Trimethylsilyl)-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranose (**7**) and podophyllotoxin (1) or epipodophyllotoxin (2) afforded an O-glucosidic mixture of 4-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)epipodophyllotoxin (**13**) and 4-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)epipodophyllotoxin (**14**) (reaction conditions and yields are reported in Table I), which were separable by column chromatography (eluting with hexane–AcOEt, 65:35 v/v).

Compound 13: an amorphous solid, $[\alpha]^{23}_D$ –29.4° ($CHCl_3$, c 1); HPLC, t_R 15.6 min (eluting system MeOH–H_2O 90:10 v/v). Anal. Calcd for $C_{56}H_{56}O_{13}$: C, 71.78; H, 6.02. Found: C, 71.91; H, 5.95.

Compound 14: mp 185–186 °C (from MeOH); $[\alpha]^{23}_D$ +30.8° ($CHCl_3$, c 1); HPLC, t_R 14.8 min (eluting MeOH–H_2O 90:10 v/v). Anal. Calcd for $C_{56}H_{56}O_{13}$: C, 71.78; H, 6.02. Found: C, 71.59; H, 6.15.

(iv) Compound **7** and 4′-demethylepipodophyllotoxin (**3**) afforded an O-glucosidic mixture of 4-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-4′-demethylepipodophyllotoxin (**15**) and 4-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-4′-demethylepipodophylloxotin (**16**) (reaction conditions and yields are reported in Table I), which were separable by column chromatography eluting with hexane–AcOEt 50:50 v/v).

Compound 15: an amorphous solid, $[\alpha]^{23}_D$ –20.7° ($CHCl_3$, c 1); HPLC, t_R 27.9 min (eluting system MeOH–H_2O 86:14 v/v). Anal. Calcd for $C_{55}H_{54}O_{13}$: C, 71.57; H, 5.90. Found: C, 71.45; H, 5.82.

Compound 16: mp 166–167 °C (from MeOH); $[\alpha]^{23}_D$ +28.8° ($CHCl_3$, c 1); HPLC, t_R 26.7 min (eluting system MeOH–H_2O 86:14 v/v). Anal. Calcd for $C_{55}H_{54}O_{13}$: C, 71.57; H, 5.90. Found: C, 71.62; H, 5.79.

Synthesis of Etoposide (4). BF_3-Et_2O (0.92 L, 7.5 mol) was added to a stirred suspension of lignan **3** (1.0 kg, 2.5 mol) and 1β-O-trimethylsilylated sugar **8** (1.5 kg, 3 mol) in dichloromethane (100 L), at –20 °C, under nitrogen. The mixture was stirred for 8 h at –20 °C and then for 30 min at –10 °C. The reaction mixture was then rapidly poured into ice-cold water (100 L) and worked up to afford the crude 4-(4,6-*O*-ethylidene-2,3-di-*O*-(dichloroacetyl)-β-D-glucopyranosyl)-4′-demethylepipodophyllotoxin (**17**), which was directly used in the next step.

[An analytical sample of compound **17** was obtained by chromatographic purification (silica gel): mp 243–244 °C (from ethyl acetate); $[\alpha]^{22}_D$ –66.5° ($CHCl_3$, c 1). Anal. Calcd for $C_{33}H_{32}O_{15}Cl_4$: C, 48.91; H, 3.98. Found: C, 48.69; H, 4.01.]

Crude compound **17** in methanol (15 L) containing zinc acetate dihydrate (0.9 kg, 4.1 mol) was refluxed for 90 min. The resulting suspension was concentrated under reduced pressure to a 7 L final volume and then diluted with H_2O (10 L), dichloromethane (20 L), and acetic acid (0.5 L). Usual workup and crystallization afforded etoposide (**4**) (1.03 kg, 70% yield): mp 261–263 °C dec (crystallized first from ethyl acetate and then from ethanol); $[\alpha]^{23}_D$ –108° ($CHCl_3$, c 1) [lit.[7f] mp 254–256 °C; $[\alpha]^{20}_D$ –109.6° ($CHCl_3$, c 1)]. ^{1}H NMR spectrum was identical with that reported.[23]

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Supplementary Material Available: ^{1}H NMR (500 MHz) spectral data for compounds **9**, **10**, **13**–**17** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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