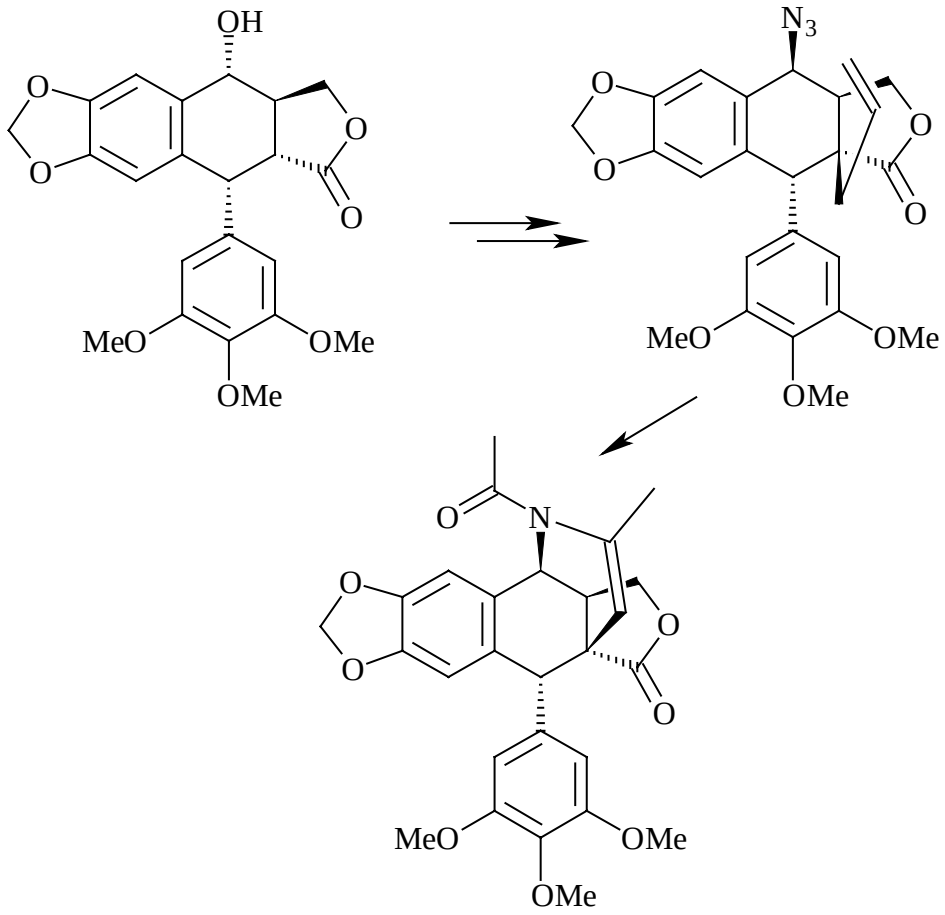
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Synthesis of Sterically Fixed Podophyllotoxins

Hartmut Laatsch*[a], Bernd Peter Ernst[a], and Mathias Noltemeyer[b]

Department of Organic Chemistry, University of Goettingen[a],

Tammannstrasse 2, D-37077 Goettingen

Department of Inorganic Chemistry, University of Goettingen[b]

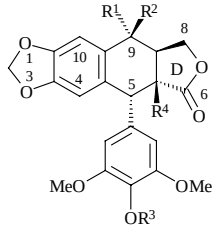
Tammannstrasse 4, D-37077 Goettingen

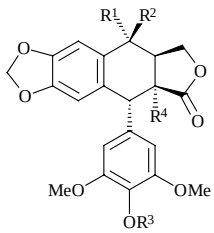
Received October 26, 1995

Key Words: bridged podophyllotoxins / nitrene rearrangement / 5a-alkyl-podophyllotoxin

Podophyllotoxin and epi-podophyllotoxin derivatives (**1**/**2**) with unsaturated side chain at 5a position were obtained by C-alkylation of protected **1**-derivatives. The azide **3a** afforded **4** in quantitative yield at 40-80 °C. With pyridine/acetyl chloride, the latter yielded the rigid epi-podophyllotoxin derivative **7**, whose structure was established by crystal structure analysis. All reported podophyllotoxin derivatives were less cytotoxic than phodophyllotoxin (**1a**) itself.

The cytotoxic podophyllotoxin (**1a**) is deactivated primarily through the opening of the lactone ring[1], but epimerization[2] at C-5a[3] yielding picropodophyllin (**2a**)[4], may also contribute to the rapid loss of biological activity of podophyllotoxin derivatives (a few hours) under physiological conditions. The low residual activity of picropodophyllin (**2a**) can be explained by the **2a** ⇌ **1a** equilibrium which yields up to 2.5 % podophyllotoxin (**1a**) under physiological conditions[4,5]. A minor conformer of **2a** however with a quasi-axial trimethoxyphenyl ring, may also interact with tubuline, due to its similarity with **1a**[6].





1/2	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	1m	1n	1o	1p
	2a						2g	2h	2i	2j	2k	2l	2m	2n	2o	
R^1	OH	H	OX	OH	OY	OZ	OY	OZ	OH	OY	OZ	OH	OY	OZ	OH	OZ
R^2	H	OH	H	H	H	H	H	H	H	H	H	H	H	H	H	H
R^3	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	Z
R^4	H	H	H	Me	H	H	a	a	a	b	b	b	c	c	c	H

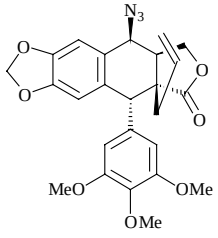
X = THP, 2-tetrahydropyranyl a = $-CH_2CH=CH_2$

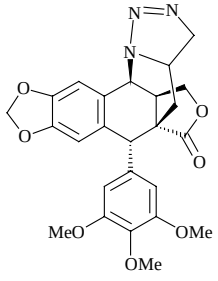
Y = TBDMS, *tert*.-butyl-dimethylsilyl b = $-CH_2CH=CHCH_3$

Z = TBDPS, *tert*.-butyl-diphenylsilyl c = $-CH_2CH=CHPhe$

Stabilization of the podophyllotoxin (**1a**) conformation should therefore have a substantial effect on the duration of its activity. Attempts to effect its stability by the formation of a non-enolizable D-ring, were made until the recent past[7]. However, the vast majority of these changes have resulted in the complete loss of biological activity and gave reason for the assumption that the strained *trans*-lacton ring is essential. Herein we report a new approach to stabilize the *trans*-lacton system by C-5a-alkylation and 5a,9-bridging, whereby the stereochemistry at C-5a of the even more potent *epi*-podophyllotoxin (**1b**) is fixed without changing the conformation of the C-ring substantially. To the best of our knowledge, corresponding derivatives have never been reported, and **1d** is the only 5a-alkylated podophyllotoxin published now[2].

Podopyllotoxin derivatives with an azide group at C-9 react smoothly with alkenes, as we reported recently[8]. Therefore a bridged **1b**-derivative should be accessible by intramolecular [1,3]dipolar cycloaddition of **3a** yielding **4**.





3a

3b: α– instead of ß-azide **4**

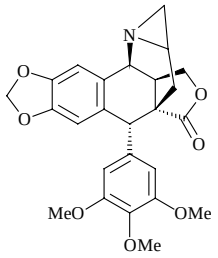
The unsaturated side chain was easily introduced into the starting material by alkylation of 9-O protected **1a**-derivatives. Using potassium hydride, the THP-ether **1c**[9] gave the enolate under mild conditions, which reacted smoothly with alkyl halides. Using this method, alkylation with methyl iodide, followed by cleavage of the THP protective group by pyridinium-*p*-toluolsulfonate, afforded 22.5 % of 5aß-methylpodophyllotoxin (**1d**), which was described previously by Durst et al.[9]. Other isomers or follow-up products could not be obtained by chromatography of the complex reaction mixture on silica gel, corresponding to a thermodynamically directed reaction[2].

Better results were obtained when lithium diisopropylamide was used following Durst´s procedure[2]. This method was also applied successfully to the synthesis of TPDPS- and TBDMS protected podophyllotoxin derivatives: The silyloxy derivatives could be purified and handled easier, due to their lower polarity and higher stability.

In all cases, the alkylation with methyl-, allyl-, crotyl- and cinnamyl halides gave solely C-alkylation products. With increasing size of the incoming substituent, the diastereoselectivity was shifted in favor of the 5aα-configured alkyl picropodophyllins **2h**, **2k**, **2n**. Additionally, an influence of the protective group at C-9 was observed which was opposite to the expectation: In the alkylation of **1a** with allyl iodide, the 5aß-configured **1g** was predominantly formed when using the TBDMS protective group (**1e**); however, when the larger TBDPS group was used, a reverse effect was observed favoring the **2h** configured product. In the alkylations with crotyl- or cinnamyl halides, with both protective groups the formation of the 5aα-configured picropodophyllin products were strongly favored. Differentiation between the podophyllotoxin and the picropodophyllin configuration was made on the basis of ^{1}H nmr shifts for the aromatic A ring protons, and on the value of the 8,8a- and 8´,8a-coupling constants, following Durst´s guidelines[2].

A mixture of the azides **3a**/**3b** was easily obtained from **1i** via chlorination with thionyl chloride and halogen/azide exchange. The azide **3a** afforded **4** in quantitative yield at 40-80 °C within 1 hour. The product and the starting material were clearly distinguishable by their mass and NMR spectra as well as their chromatographic behaviour. As only **3a** reacted in the cyclo addition, the azide was also used as a diastereomeric mixture and pure **3b** was recovered unchanged.

During our attempts to elucidate the structure of the trizole **4** using a derivative, an unexpected reaction took place which transformed **4** into **7** via rapid rearrangement when using pyridine/acetyl chloride. Corresponding to the formula $C_{27}H_{27}NO_8$ of the product (determined by high resolution ms), **4** was acetylated formally under loss of nitrogen. The ^{1}H NMR spectrum showed the signals of the **1i** skeleton, and changes had occurred as expected only in the 5a-side chain. As no acidic protons were visible, the chemical shift of the acetyl signal (δ = 2.38) pointed to the N-acetylation of a secondary amine. Further interpretation of the ^{1}H and ^{13}C NMR spectra was difficult, as an olefinic proton and a methyl group gave only broad signal groups in various solvents, obviously due to coaleszence phenomena; furthermore, the olefinic proton did not show a correlation signal in the CH-COSY spectrum. Therefore, structure **7** was finally determined by X-ray analysis. It is known that under thermolysis of triazoles, imines as well as aziridines may be formed[10], and **5** or **6** are therefore possibly intermediates of **7**.



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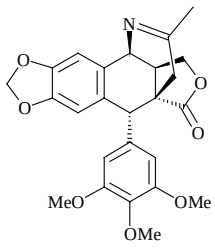

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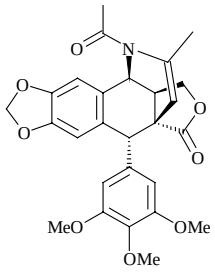

7

As reported by various authors[11], it is merely the conformation of the podophyllotoxins rsp. *epi*-podophyllotoxins which is responsible for the ability to inhibit the tubuline polymerization or to interact with topoisomerase II. Correspondingly, in derivatives with a conformation as in **1a** or **1b**, the cytotoxicity should be high. A close similarity of the C ring conformation of **1d**, **7** and 2'-bromo podophyllotoxin with **1a**/**1b** may be derived by comparison of the X-ray structures[12] as well as from bond lengths and bond angles. The biological activities[13] of **1d** and **7** as well as of the other 5aß-alkyl-podophyllotoxins (**1i**, **1l**, **1o**) presented here, are lower than in podophyllotoxin (**1a**) itself, however. Therefore no attempts were made to cyclize also the 5aß-alkenyl-podophyllotoxins **1l** and **1o**.

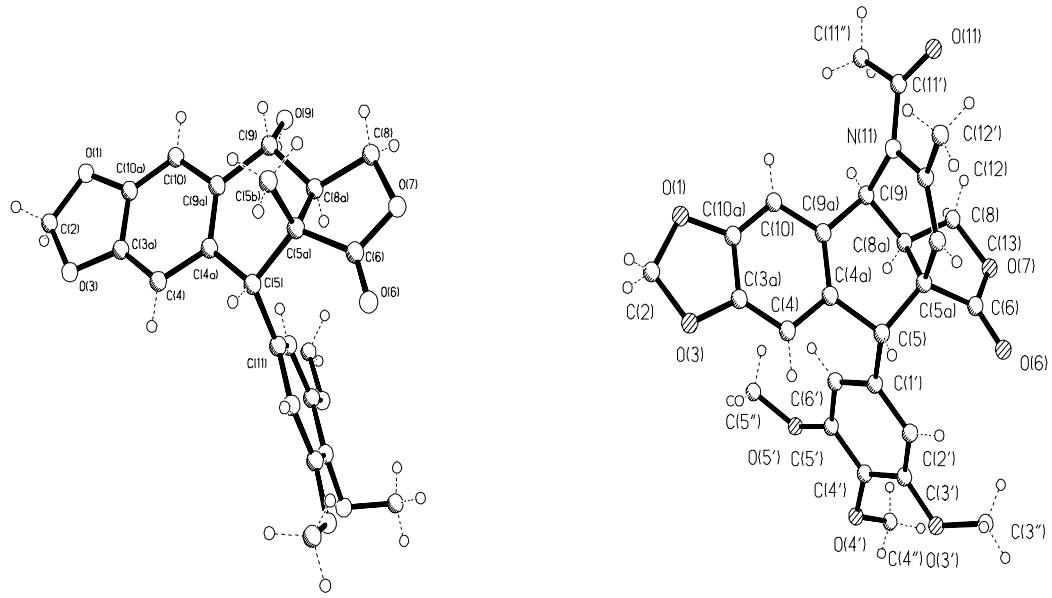

Fig. 1: X-Ray Structure of 5aß-Methyl-podophyllotoxin (**1d**, left) and the bridged *epi*-podophyllotoxin **7**

Certainly the bridge render the interactions with the topoisomerase II more difficult if the enzyme interacts with the *epi*-podophyllotoxin derivative **7** from the bridged ß-side. But as Durst[9] has shown that 5aß-chloro substituted *epi*-podophyllotoxin derivatives are even more active against topoisomerase II than the chlorine-free analogs, the bridge cannot be the only reason for hindered interactions.

Table 1: Cytotoxicity of 5a-alkylated podophyllotoxins and picropodophyllins in a proliferation assay (MTT reduction) in comparison with the activity of **1a**; IC_{50} concentrations are in µg/ml

Substance	L 1210	HT 29	A 549
1a	0.007	0.008	0.008
1d	0.14	0.48	0.27
1i	4.10	5.20	6.80
1l	4.60	5.10	5.60
1o	4.90	5.00	5.80
2i	0.40	1.10	1.40
2l	1.00	1.20	1.40
2o	4.80	5.10	6.70
7	>10	>10	>10

We thank Mr. *R. Machinek* (Göttingen) for detailed NMR measurements, *Dr. D. Hoffmann*, Behringwerke AG (Marburg, Germany) for toxicity measurements and the *Fonds der Chemischen Industrie* for financial support.

Experimental

Material and methods: see previous publication[13]. If not otherwise stated, R_f values were measured using petroleum ether / *tert*.-butyl methyl ether 2:1.

[5R-(5α,5aß,8aα,9α]-5a-Methyl-5,8,8a,9-tetrahydro-5-(3,4,5-trimethoxyphenyl)-furo-[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-on (5aß-Methylpodophyllotoxin, **1d**): a) In a 100 ml three-necked round bottom flask with reflux condenser and septum, a KH-paraffin oil suspension (about 0.5 g KH) was washed in an nitrogen atmosphere with three 10 ml portions of dry pentane. To the residue was added 10 ml of absolute THF followed by dropwise addition addition (5-10 min) of 4.48 g (9 mmol) of **1c**[14] in 50 ml of THF at room temperature. The suspension turned to yellow and then to brown with the development of H_2 gas. After intense stirring for 60 min at room temp., 2.26 g (16 mmol) of MeI was added and the mixture was stirred for an additional 8 h. The reaction mixture was poured into 50 ml of water, the organic layer was separated and dried with Na_2SO_4. After distilling off the solvent, column chromatography (silica gel, *tert*-butyl methyl ether/petroleum ether, 1:1) of the residue gave two fractions with $R_f > 0.50$. *Fraction 1* contained 0.85 g (22.5 %) of THP-protected **1d** ($R_f = 0.60$); *frac-*

tion 2 contained 0.8 g of starting material **1c** (R_f = 0.55).

b) *Cleavage of the THP ether*: 256 mg (0.5 mmol) of the **1d**-THP ether was stirred for 4 h at room temp. with 40 mg of *p*-toluene sulfonic acid in 4 ml of EtOH. The main part of the solvent was distilled off in vacuo and the residue separated by column chromatography on silica gel (25 × 2 cm, *tert*-butyl methyl ether), yielding 189 mg (88.4 %) of **1d** as colorless crystals with m.p. 101-103°C (cit.[2] 92-95), R_f = 0.25. – ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.12 (s, 1 H, 10-H), 6.50 (s, 1 H, 4-H), 6.37 (s, 2 H, 2'-, 6'-H), 6.00, 5.99 (AB, J = 1.3 Hz, 2 H, 2-H_2), 4.71 (dd, $J_{9,8a}$ = 10.5 Hz, $J_{9,OH}$ = 8 Hz, 1 H, 9-H), 4.52 (dd, $J_{8\alpha,8a}$ = 7.3 Hz, $J_{8\alpha,8ß}$ = 8.8 Hz, 1 H, 8α-H), 4.27 (s, 1 H, 5-H), 4.18 (dd, $J_{8\alpha,8ß}$ = 8.8 Hz, $J_{8ß,8a}$ = 11 Hz, 1 H, 8ß-H), 3.81 (s, 3 H, 4'-OCH_3), 3.78 (s, 6 H, 3'-OCH_3, 5'-OCH_3), 2.89 (ddd, $J_{8a,9}$ = 10.5 Hz, $J_{8a,8ß}$ = 11 Hz, $J_{8a,8\alpha}$ = 7.3 Hz, 1 H, 8a-H), 1.87 (d, $J_{9,OH}$ = 8 Hz, 1 H, OH), 1.30 (s, 3 H, -CH_3).

9-*TBDMS-podophyllotoxin* (**1e**): 16.6 g (0.04 mol) of podophyllotoxin (**1a**), 30 ml of DMF, 9.11 g (0.134 mol) of imidazole, and 6.3 g (0.042 mol) of TBDMSCl were stirred for 15 h at room temp. The reaction mixture was diluted with 150 ml of water and extracted with three 100 ml portions of CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and evaporated to dryness in vacuo at 60 °C. The residue was purified by column chromatography on silica gel (6 × 80 cm, CH_2Cl_2). 15.8 g (75 %) of **1e** was obtained as a colorless solid with m.p. 163-64 °C. – ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 6.93 (s, 1 H, 10-H), 6.48 (s, 1 H, 4-H), 6.37 (s, 2 H, 2'-, 6'-H), 5.97, 5.94 (AB, J = 1.3 Hz, 2 H, 2-H_2), 4.80 (d, $J_{9,8a}$ = 8.5 Hz, 1 H, 9-H), 4.57 (d, $J_{5,5a}$ = 4 Hz, 1 H, 5-H), 4.52 (dd, $J_{8\alpha,8a}$ = 6.5 Hz, $J_{8\alpha,ß}$ = 8.5 Hz, 1 H, 8α-H), 4.00 (dd, $J_{8ß,8a}$ = 10.5 Hz, $J_{8\alpha,8ß}$ = 8.5 Hz, 1 H, 8ß-H), 3.82 (s, 3 H, 4'-OCH_3), 3.74 (s, 6 H, 3'-, 5'-OCH_3), 3.00-2.75 (m, 2 H, 5a-H, 8a-H), 0.96 (s, 9 H, -$C(CH_3)_3$), 0.30 (s, 3 H, -CH_3), 0.13 (s, 3 H, CH_3). – $C_{28}H_{36}O_8Si$ (528.7) calcd. C 63.61, H 6.86; found C 63.71, H 6.85.

9-*TBDPS-podophyllotoxin* (**1f**) *and 4´,9-Bis-TBDPS-4´-demethylpotophyllotoxin* (**1p**): 16.58 g (0.04 mol) of podophyllotoxin (**1a**, containing approximately 10 % 4'-demethylpodophyllotoxin), 30 ml of DMF, 9.11 g (0.134 mol) of imidazole and 11.54 g (0.042 mol) of TBDPSCl were mixed and stirred for 15 h at room temp. The mixture was diluted with 150 ml of water and extracted with three 100 ml portions of CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and evaporated to dryness in vacuo at 60 °C. Chromatography (silica gel, column 6 × 80 cm, CH_2Cl_2) gave three fractions with 1.6 g of TBDPSCl in *fraction 2*.

Fraction 1: (R_f = 0.36), 1.26 g of **1p**, faint yellow platelets with m.p. 79-80 °C – ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.78-7.62 (m, 8 H), 7.54-7.23 (m, 12 H), 7.14 (s, 1 H, 10-H), 6.45 (s, 1 H, 4-H), 6.25 (s, 2 H, 2'-, 6'-H), 5.98, 5.94 (AB, J = 1.5 Hz, 2 H, 2-H_2), 4.78 (d, $J_{9,8a}$ = 8.5 Hz, 1 H, 9-H), 4.40 (d, $J_{5,5a}$ = 4.5 Hz, 1 H, 5-H), 3.75 (dd, $J_{8\alpha,8ß}$ = 8.5 Hz, $J_{8\alpha,8a}$ = 8 Hz, 1 H, 8$_\alpha$-H), 3.36 (s, 6 H, 3'-, 5'-OCH_3), 3.05 (dd, $J_{8\alpha,8ß}$ = 8.5 Hz, $J_{8,8a}$ = 10.5 Hz, 1 H, 8ß-H), 2.90-2.67 (m, 1 H, 8a-H), 2.52 (dd, $J_{5,5a}$ = 4.5 Hz, $J_{5a,8a}$ = 14 Hz, 1 H, 5a-H), 1.11, 1.06 (2s, 9 H, -$C(CH_3)_3$). – $C_{53}H_{56}O_8Si_2$ (877.2) calcd. C 72.57, H 6.43; found C 72.82, H 6.70.

Fraction 3: (R_f = 0.16), 21.6 g (82.7 %) of **1f**, colorless crystals with m.p. 118-120 °C. – ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.83-7.66 (m, 4 H), 7.52-7.35 (m, 6 H), 7.18 (s, 1 H, 10-H), 6.48 (s, 1 H, 4-H), 6.44 (s, 2 H, 2'-, 6'-H), 5.99, 5.94 (AB, J = 1.5 Hz, 2 H, 2-H_2), 4.84 (d, $J_{9,8a}$ = 8.5 Hz, 1 H, 9-H), 4.49 (d, $J_{5,5a}$ = 4.5 Hz, 1 H, 5-H), 3.85 (s, 3 H, 4'-OCH_3), 3.84-3.75 (m, 1 H, 8α-H), 3.80 (s, 6 H, 3'-, 5'-OCH_3), 3.09 (dd, $J_{8\alpha,8ß}$ = 8.5 Hz, $J_{8ß,8a}$ = 10.5 Hz, 1 H, 8ß-H), 3.00-2.78 (m, 1 H, 8a-H), 2.60 (dd, $J_{5,5a}$ = 4.5 Hz, $J_{5a,8a}$ = 14 Hz, 1 H, 5a-H), 1.10 (s, 9H, -$C(CH_3)_3$). – $C_{38}H_{40}SiO_8$ (652.8) calcd. C 69.92, H 6.18; found C 69.85, H 6.10.

Synthesis and separation of 5a-alkyl podophyllotoxins – General procedure: In a dry two-necked 100 ml round bottom flask with thermometer and septum, in a nitrogen atmosphere at -78 °C, 10 mmol of a 1.6 M *n*-butyl lithium solution in *n*-hexane was added within 10 min to a stirred solution of 1.16 g (11.5 mmol) of dry diisopropyl amine in 20 ml of dry THF. The mixture was stirred for an additional 30 min at 0°C, cooled again to -78 °C, and within 5 min a solution of 5.28 g (10 mmol) of **1e** or 6.53 g (10 mmol) of **1f** in 10 ml of dry THF was added and stirred for 15 min. Ten equivalents of alkylating reagent were added and the mixture was slowly warmed to room temp. over night. The reaction mixture was concentrated in vacuo, the residue was dissolved in 50 ml of CH_2Cl_2 and the solution extracted with 50 ml of 2 N HCl and 20 ml of sat. $NaHCO_3$ solution. The organic layer was evaporated to dryness and separated by column chromatography (silica gel 4.5 × 90 cm, petroleum ether/*tert*-butyl methyl ether 2:1). Two fractions were obtained: The fraction with a higher R_f contained the 5a,ß-alkyl po-

dophyllotoxins, while that with a lower R_f contained the 5a,α-alkylpicropodophyllins.

5aß-Allyl-9-TBDMS-podophyllotoxin (**1g**) *and 5aα-Allyl-9-TBDMS-picropodophyllin* (**2g**): The reaction of 5.28 g (10 mmol) of **1e** with allyl iodide, following the general procedure stated above, gave 2.89 g (51 %) of **1g** with m.p. 157-58 °C (colorless prisms, R_f = 0.27) and 2.2 g (38.7 %) of **2g** with m.p. 152-53 °C (colorless prisms, R_f = 0.10). – **1g**: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 6.92 (s, 1 H, 10-H), 6.42 (s, 1 H, 4-H), 6.32 (s, 2 H, 2'-, 6'-H), 6.11-5.86 (m, 1 H, -CH=), 5.98 (AB, J = 1.5 Hz, 2 H, 2-H_2), 5.22 (dd, J_{gem} = 1.7 Hz, J_{cis} = 10 Hz, 1 H, Z-3''-H), 5.02 (dd, J_{trans} = 16.5 Hz, J_{gem} = 1.7 Hz, 1 H, E-3''-H), 4.82 (d, $J_{9,8a}$ = 10 Hz, 1 H, 9-H), 4.37 (dd, $J_{8α,8ß}$ = 8.5 Hz, $J_{8α,8a}$ = 7.5 Hz, 1 H, 8α-H), 4.36 (s, 1 H, 5-H), 4.18 (dd, $J_{8α,8ß}$ = 8.5 Hz, $J_{8ß,8a}$ = 11 Hz, 1 H, 8ß-H), 3.80 (s, 3 H, 4'-OCH_3), 3.73 (s, 6 H, 3'-, 5'-OCH_3), 3.16 (ddd, $J_{8a,9}$ = 10 Hz, $J_{8a,8α}$ = 7.5 Hz, $J_{8a8ß}$ = 11 Hz, 1 H, 8a-H), 2.58-2.45, 2.36-2.22 (2 m, 1 H each, -CH_2), 0.94 (s, 9 H, -$C(CH_3)_3$), 0.32, 0.12 (2s, 3 H each, -CH_3). – $C_{31}H_{40}O_8Si$ (568.8) calcd. C 65.47, H 7.09; found C 65.77, H 7.14.

2g: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 6.83 (s, 1 H, 10-H), 6.61 (s, 1 H, 4-H), 6.56 (s, 2 H, 2'-, 6'-H), 5.94, 5.92 (AB, J 1.4 Hz, 2 H, 2-H_2), 5.71-5.46 (m, 1 H, -CH=), 5.13 (dd, J_{gem} = 1.5 Hz, J_{cis} = 10 Hz, 1 H, Z-3''-H, 5.07 (dd, J_{trans} = 16.5 Hz, J_{gem} = 1.5 Hz, 1 H, E-3''-H), 4.67 (d, $J_{9,8a}$ = 5.5 Hz, 1 H, 9-H), 4.38 (dd, $J_{8ß,8α}$ = 9.5 Hz, $J_{8ß,8a}$ = 7.5 Hz, 1 H, H-8ß), 4.12 (s, 1 H, 5-H), 4.11 (dd, $J_{8α,8ß}$ = 9.5 Hz, $J_{8ß,8a}$ = 5 Hz, 1 H, 8α-H), 3.87 (s, 3 H, 4'-OCH_3), 3.83 (s, 6 H, 3'-, 5'-OCH_3), 2.73 (ddd, $J_{9,8a}$ = 5.5 Hz, $J_{8ß,8a}$ = 7.5 Hz, $J_{8α,8a}$ = 5 Hz, 1 H, 8a-H), 2.56-2.41, 2.25-2.08 (2 m, 1 H each, -CH_2), 0.98 (s, 9 H, -$C(CH_3)_3$), 0.23, 0.19 (2s, 3 H each, -CH_3). – $C_{31}H_{40}O_8Si$ (568.8) calcd. C 65.47, H 7.09; found C 65.40, H 7.25.

5aß-Allyl-9-TBDPS-podophyllotoxin (**1h**) and *5aα-allyl-9-TBDPS-picropodophyllin* (**2h**): The reaction of 6.53 g (10 mmol) of **1f** with allyl iodide, following the general procedure stated above, gave 2.4 g (34.6 %) of **1h** with m.p. 83-84 °C (colorless prisms, R_f = 0.23) and 3.3 g (47.6 %) of **2h** with m.p. 75-76 °C (colorless platelets, R_f = 0.19). – **1h**: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.80-7.65 m, 4 H), 7.54-7.32 (m, 6 H), 7.15 (s, 1 H, 10-H), 6.42 (s, 2 H, 2'-, 6'-H), 6.41 (s, 1 H, 4-H), 5.99, 5.95 (AB, ^2J = 1.5 Hz, 2 H, 2-H_2), 5.82-5.60 (m, 1 H, -CH=), 5.04 (dd, J_{gem} = 1.5 Hz, $^3J_{cis}$ = 10 Hz, 1 H, Z-3''-H), 4.88 (d, $J_{9,8a}$ = 9.5 Hz, 1 H, 9-H), 4.80 (dd, $^3J_{trans}$ = 16.5 Hz, $^2J_{gem}$ = 1.5 Hz, 1 H, E-3''-H) 4.28 (s, 1 H, 5-H), 3.84 (s, 3 H, 4'-OCH_3), 3.84-3.75 (m, 1 H, H-8ß), 3.79 (s, 6 H, 3'-, 5'-OCH_3), 3.36-3.10 (m, 2 H, 8α-H, 8a-H), 2.23-1.98 (m, 2 H, -CH_2), 1.10 (s, 9 H, -$C(CH_3)_3$). – $C_{41}H_{44}O_8Si$ (692.9) calcd. C 71.07, H 6.40; found C 71.35, H 6.45.

2h: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.71-7.58 (m, 4 H), 7.51-7.32 (m, 6 H), 6.66 (s, 2 H, 2'-, 6'-H), 6.54, 6.51 (2 s, 1 H each, 10-H, 4-H), 5.91, 5.87 (AB, ^2J = 1.5 Hz, 2 H, 2-H_2), 5.60-5.38 (m, 1 H, -CH=), 5.07 (dd, $^2J_{gem}$ = 1.5 Hz, $^3J_{cis}$ = 10 Hz, 1 H, Z-3''-H), 4.95 (dd, $^3J_{trans}$ = 16.5 Hz, $^2J_{gem}$ = 1.5 Hz, 1 H, E-3''-H), 4.67 (d, $J_{9,8a}$ = 2.6 Hz, 1 H, 9-H), 4.25 (s, 1 H, 5-H), 3.96-3.75 (m, 1 H, H-8ß), 3.84 (s, 3 H, 4'-OCH_3), 3.76 (s, 6 H, 3'-, 5'-OCH_3), 3.34 (dd, $J_{8α,8ß}$ = 9.5 Hz, $J_{8ß,8a}$ = 5 Hz, 1 H, 8α-H), 2.86 (ddd, $J_{9,8a}$ = 2.6 Hz, $J_{8ß,8a}$ = 8 Hz, $J_{8α,8a}$ = 5 Hz, 1 H, 8a-H), 2.50-2.37, 2.26-2.12 (2m, 1 H each, -CH_2), 1.11 (s, 9 H, -$C(CH_3)_3$). – $C_{41}H_{44}O_8Si$ (692.9) calcd. C 71.07, H 6.40; found C 70.99, H 6.35.

5aß-Crotyl-9-TBDMS-podophyllotoxin (**1j**) *and 5aα-Crotyl-9-TBDMS-picropodophyllin* (**2j**): The reaction of 5.28 g (10 mmol) of **1e** with crotyl chloride, following the general procedure stated above, gave 1.48 g (25.4 %) of **1j** with m.p. 69-70 °C (colorless prisms, R_f = 0.30) and 2.94 g (50.5 %) of **2j** with m.p. 112-13 °C (colorless prisms, R_f = 0.20). – **1j**: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 6.92 (s, 1 H, 10-H), 6.41 (s, 1 H, 4-H), 6.32 (s, 2 H, 2'-, 6'-H), 5.96 (AB, ^2J = 1.3 Hz, 2 H, 2-H_2), 5.77-5.30 (m, 1 H, -CH=), 5.40 (dd, $J_{2'',3''}$ = 15 Hz, $J_{3'',4''}$ = 6 Hz, 1 H, 3''-H), 4.83 (d, $J_{9,8a}$ = 10 Hz, 1 H, 9-H), 4.42-4.28 (m, 1 H, 8α-H), 4.32 (s, 1 H, 5-H), 4.25-4.07 (m, 1 H, 8ß-H), 3.80 (s, 3 H, 4'-OCH_3), 3.73 (s, 6 H, 3'-, 5'-OCH_3), 3.14 (ddd, $J_{8a,9}$ = 10 Hz, $J_{8a,8α}$ = 8 Hz, $J_{8aß}$ = 11 Hz, 1 H, 8a-H), 2.57-2.37, 2.32-2.16 (2 m, 1 H each, -CH_2), 1.74 (d, $J_{3'',4''}$ = 6 Hz, 3 H, 4''-CH_3), 0.94 (s, 9 H, -$C(CH_3)_3$), 0.32, 0.11 (2s, 3 H each, -CH_3). – $C_{32}H_{42}O_8Si$ (582.8) calcd. C 65.95, H 7.26; found C 66.28, H 7.55.

2j: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 6.82 (s, 1 H, 10-H), 6.60 (s, 1 H, 4-H), 6.55 (s, 2 H, 2'-, 6'-H), 5.94, 5.91 (AB, ^2J = 1.4 Hz, 2 H, 2-H_2), 5.62-5.36 (m, 1 H, 3''-H), 5.31-5.09 (m, 1 H, 2''-H), 4.67 (d, $J_{9,8a}$ = 5.8 Hz, 1 H, 9-H), 4.35 (dd, $J_{8ß,8α}$ = 9.0 Hz, $J_{8ß,8a}$ = 7.5 Hz, 1 H, H-8ß), 4.11 (dd, $J_{8α,8ß}$ = 9.0 Hz, $J_{8ß,8a}$ = 5 Hz, 1 H, 8α-H), 4.10 (s, 1 H, 5-H), 3.86 (s, 3 H, 4'-OCH_3), 3.82 (s, 6 H, 3'-, 5'-OCH_3), 2.71 (ddd, $J_{9,8a}$ = 5.8 Hz, $J_{8ß,8a}$ = 7.5 Hz, $J_{8α,8a}$ = 5 Hz, 1 H, 8a-H), 2.52-2.33, 2.15-2.00 (2 m, 1 H each, -CH_2), 1.63 (d, $J_{3'',4''}$ = 6 Hz, 3 H, 4''-CH_3), 0.98 (s, 9 H, -$C(CH_3)_3$), 0.23, 0.19 (2s, 3 H each, -

CH_3).. – $C_{32}H_{42}O_8Si$ (582.8) calcd. C 65.95, H 7.26; found C 65.97, H 7.35.

5aß-Crotyl-9-TBDPS-podophyllotoxin (**1k**) *and 5aα-Crotyl-9-TBDPS-picropodophyllin* (**2k**): The reaction of 6.53 g (10 mmol) of **1f** with crotyl chloride, following the general procedure stated above, gave 0.9 g (14.6 %) of **1k** with m.p. 77-78 °C (colorless short needles, R_f = 0.27) and 3.57 g (58 %) of **2k** with m.p. 69-70 °C (colorless prisms, R_f = 0.21). – **1k**: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.81-7.63 (m, 4 H), 7.54-7.31 (m, 6 H), 7.16 (s, 1 H, 10-H), 6.42 (s, 2 H, 2'-, 6'-H), 6.41 (s, 1 H, 4-H), 5.98, 5.94 (AB, ^2J = 1.3 Hz, 2 H, 2-H_2), 5.39-5.08 (m, 2 H, -CH=CH-), 4.89 (d, $J_{9,8a}$ = 9.5 Hz, 1 H, 9-H), 4.24 (s, 1 H, 5-H), 3.86-3.68 (m, 1 H, H-8ß), 3.84 (s, 3 H, 4'-OCH_3), 3.79 (s, 6 H, 3'-, 5'-OCH_3), 3.36-3.06 (m, 2 H, 8α-H, 8a-H), 2.17-1.94 (m, 2 H, -CH_2), 1.58 (d, $J_{3",4"}$ = 5 Hz, 3 H, -CH_3), 1.10 (s, 9 H, -$C(CH_3)_3$). – $C_{42}H_{46}O_8Si$ (706.9) calcd. C 71.36, H 6.56; found C 71.44, H 6.45.

2k: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.72-7.57 (m, 4 H), 7.52-7.31 (m, 6 H), 6.64 (s, 2 H, 2'-, 6'-H), 6.53, 6.52 (2 s, 1 H each, 10-H, 4-H), 5.90, 5.86 (AB, ^2J 1.5 Hz, 2 H, 2-H_2), 5.43-5.23, 5.18-5.00 (2 m, 1 H each, -CH=CH-), 4.67 (d, $J_{9,8a}$ = 2.6 Hz, 1 H, 9-H), 4.23 (s, 1 H, 5-H), 3.94-3.70 (m, 1 H, H-8ß), 3.84 (s, 3 H, 4'-OCH_3), 3.75 (s, 6 H, 3'-, 5'-OCH_3), 3.33 (dd, $J_{8α,8ß}$ = 9.5 Hz, $J_{8ß,8a}$ = 5 Hz, 1 H, 8α-H), 2.85 (ddd, $J_{9,8a}$ = 2.6 Hz, $J_{8ß,8a}$ = 8 Hz, $J_{8α,8a}$ = 5 Hz, 1 H, 8a-H), 2.44-2.22, 2.18-2.02 (2 m, 1 H each, -CH_2), 1.60 (d, $J_{3",4"}$ = 6 Hz, -CH_3), 1.11 (s, 9 H, -$C(CH_3)_3$). – $C_{42}H_{46}O_8Si$ (706.9) calcd. C 71.36, H 6.56; found C 71.54, H 6.56.

5aß-Cinnamyl-9-TBDMS-podophyllotoxin (**1m**) a*nd 5aα-Cinnamyl-9-TBDMS-picropodophyllin* (**2m**): The reaction of 5.28 g (10 mmol) of **1e** with *trans*-3-chlor-1-phenyl-1-propene (cinnamyl chloride), following the general procedure stated above, gave 1.75 g (27.1 %) of **1m** with m.p. 64-65 °C (faint yellow flat needles, R_f = 0.29) and 2.85 g (44.2 %) of **2m** with m.p. 168-69 °C (colorless platelets, R_f = 0.19). – **1m**: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.42-7.18 (m, 5 H, ar-H), 6.96 (s, 1 H, 10-H), 6.42 (s, 1 H, 4-H), 6.36-6.27 (m, 2 H, -CH=CH-), 6.33 (s, 2 H, 2'-, 6'-H), 5.99 (AB, ^2J = 0.9 Hz, 2 H, 2-H_2), 4.89 (d, $J_{9,8a}$ = 10.3 Hz, 1 H, 9-H), 4.44-4.30 (m, 1 H, 8α-H), 4.38 (s, 1 H, 5-H), 4.30-4.08 (m, 1 H, 8ß-H), 3.81 (s, 3 H, 4'-OCH_3), 3.73 (s, 6 H, 3'-, 5'-OCH_3), 3.30-3.11 (m, 1 H, 8a-H), 2.74-2.62, 2.54-2.40 (2 m, 1 H each, -CH_2), 0.95 (s, 9 H, -$C(CH_3)_3$), 0.33, 0.10 (2s, 3 H each, -CH_3). – $C_{37}H_{44}O_8Si$ (644.8) calcd. C 68.92, H 6.88; found C 68.97, H 7.05.

2m: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.34-7.16 (m, 5 H, ar-H), 6.83 (s, 1 H, 10-H), 6.63 (s, 1 H, 4-H), 6.59 (s, 2 H, 2'-, 6'-H), 6.36 (d, $J_{2",3"}$ = 16 Hz, 1 H, 3"-H), 6.01-5.83 (m, 1 H, 2"-H), 5.93 (AB, ^2J 1.4 Hz, 2 H, 2-H_2), 4.70 (d, $J_{9,8a}$ = 5.5 Hz, 1 H, 9-H), 4.36 (dd, $J_{8ß,8α}$ = 9.5 Hz, $J_{8ß,8a}$ = 7.5 Hz, 1 H, H-8ß), 4.17 (s, 1 H, 5-H), 4.11 (dd, $J_{8α,8ß}$ = 9.5 Hz, $J_{8α,8a}$ = 5 Hz, 1 H, 8α-H), 3.88 (s, 3 H, 4'-OCH_3), 3.83 (s, 6 H, 3'-, 5'-OCH_3), 2.81 (ddd, $J_{9,8a}$ = 5.5 Hz, $J_{8ß,8a}$ = 7.5 Hz, $J_{8α,8a}$ = 5 Hz, 1 H, 8a-H), 2.69-2.56, 2.42-2.28 (2 m, 1 H each, -CH_2), 0.98 (s, 9 H, -$C(CH_3)_3$), 0.23, 0.19 (2 s, 3 H each, -CH_3). – $C_{37}H_{44}O_8Si$ (644.8) calcd. C 68.92, H 6.88; found C 68.95, H 6.90.

5aß-Cinnamyl-9-TBDPS-podophyllotoxin (**1n**) a*nd 5aα-cinnamyl-9-TBDPS-picropodophyllin* (**2n**): The reaction of 6.53 g (10 mmol) of **1f** with *trans*-3-Chlor-1-phenyl-1-propene (cinnamyl chloride), following the general procedure stated above, gave 0.81 g (10.5 %) of **1n** with m.p. 90-91 °C (colorless prisms, R_f = 0.25) and 5.28 g (68.6 %) of **2n** with m.p. 82-83 °C (colorless prisms, R_f = 0.17). – **2n**: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.80-7.64 (m, 4 H), 7.50-7.16 (m, 7 H, ar-H, 10-H), 6.43 (s, 3 H, 2'-, 6'-H, 4-H), 6.18-5.94 (m, 2 H, -CH=CH-), 6.01, 5.98 (AB, ^2J = 1.5 Hz, 2 H, 2-H_2), 4.94 (d, $J_{9,8a}$ = 9.5 Hz, 1 H, 9-H), 4.30 (s, 1 H, 5-H), 3.87-3.74 (m, 1 H, H-8ß), 3.85 (s, 3 H, 4'-OCH_3), 3.79 (s, 6 H, 3'-, 5'-OCH_3), 3.38-3.18 (m, 2 H, 8α-H, 8a-H), 2.36-2.18 (m, 2 H, -CH_2), 1.11 (s, 9 H, -$C(CH_3)_3$). – $C_{47}H_{48}O_8Si$ calcd. 767.30402. found 767.3043 (HR-MS).

2n: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.68-7.56 (m, 4 H), 7.47-7.11 (m, 11 H), 6.69 (s, 2 H, 2'-, 6'-H), 6.54 (s, 2 H, 10-H, 4-H), 6.11 (d, $J_{2",3"}$ = 16 Hz, 1 H, 3"-H), 5.91, 5.88 (AB, ^2J = 1.5 Hz, 2 H, 2-H_2), 5.86-5.71 (m, 1 H, 2"-H), 4.67 (d, $J_{9,8a}$ = 2.6 Hz, 1 H, 9-H), 4.31 (s, 1 H, 5-H), 3.87 (s, 3 H, 4'-OCH_3), 3.85-3.71 (m, 1 H, H-8ß), 3.77 (s, 6 H, 3'-, 5'-OCH_3), 3.31 (dd, $J_{8α,8ß}$ = 9.5 Hz, $J_{8ß,8a}$ = 5 Hz, 1 H, 8α-H), 2.90 (ddd, $J_{9,8a}$ = 2.6 Hz, $J_{8ß,8a}$ = 8 Hz, $J_{8α,8a}$ = 5 Hz, 1 H, 8a-H), 2.65-2.52, 2.43-2.27 (2 m, 1 H each, -CH_2), 1.12 (s, 9 H, -$C(CH_3)_3$). – $C_{47}H_{48}O_8Si$ (769.0) calcd. C 73.41, H 6.29; found C 73.52, H 6.37.

Cleavage of the TBDPS and TBDMS protective groups – general procedure: A solution of 5 mmol of TBDPS or TBDMS ether in 25 ml of dry THF was stirred at room temp. for 4 h with 7.5 mmol of tetrabutyl ammoniumfluorid in the presence of molecular sieves (TLC control). The reaction mixture was concentrated in vacuo to a volume of 10 ml and separated on silica gel (CH_2Cl_2); slower

moving products were eventually eluted with *tert*-butyl methyl ether or separated by flash chromatography (silica gel 3.5 × 20 cm, *tert*-butyl methyl ether). Yields were generally 90-98 %.

2aß-Allyl-podophyllotoxin (**1i**): Cleavage of **1h**, following the general procedure stated above, gave 92.5 % (**1g**: 98 %) of **1i** as a colorless solid with m.p. 217-18 °C. – ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.11 (s, 1 H, 10-H), 6.44 (s, 1 H, 4-H), 6.33 (s, 2 H, 2'-, 6'-H), 6.10-5.86 (m, 1 H, -CH=), 5.98 (s, 2 H, 2-H_2), 5.22 (dd, $^2J_{gem}$ = 1.7 Hz, $^3J_{cis}$ = 10 Hz, 1 H, Z-3''-H), 5.02 (dd, $^3J_{trans}$ = 16.5 Hz, $^2J_{gem}$ = 1.7 Hz, 1 H, E-3''-H), 4.81 (dd, $J_{9,8a}$ = 10.5 Hz, $J_{9,OH}$ = 7 Hz, 1 H, 9-H), 4.46 (dd, $J_{8\alpha,8ß}$ = 8.5 Hz, $J_{8\alpha,8a}$ = 7.5 Hz, 1 H, 8α-H), 4.39 (s, 1 H, 5-H), 4.26 (dd, $J_{8\alpha,8ß}$ = 8.5 Hz, $J_{8ß,8a}$ = 11 Hz, 1 H, 8ß-H), 3.81 (s, 3 H, 4'-OCH_3), 3.75 (s, 6 H, 3'-, 5'-OCH_3), 3.04 (ddd, $J_{8a,9}$ = 10.5 Hz, $J_{8a,8\alpha}$ = 7.5 Hz, $J_{8a8ß}$ = 11 Hz, 1 H, 8a-H), 2.59-2.46, 2.42-2.20 (2m, 1 H each, -CH_2), 2.35 (d, $J_{9,OH}$ = 7.5 Hz, 1 H, OH). – $C_{25}H_{26}O_8$ (454.5) calcd. C 66.07, H 5.76; found C 66.00 H 5.85.

2aα-Allyl-picropodophyllin (**2i**): Cleavage of **2h**, following the general procedure stated above, gave 91 % (**2g**: 95 %) of **2i** as a colorless solid with m.p. 86-88 °C. – ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 6.80 (s, 2 H, 2'-, 6'-H), 6.77 (s, 1 H, 10-H), 6.64 (s, 1 H, 4-H), 5.90, 5.91 (AB, ^2J = 1.4 Hz, 2 H, 2-H_2), 5.76-5.52 (m, 1 H, -CH=), 5.16-4.98 (m, 2 H, Z-3''-H, E-3''-H), 4.87 (dd, $J_{9,8a}$ = 3 Hz, $J_{9,OH}$ = 3.5 Hz, 1 H, 9-H), 4.51 (dd, $J_{8ß,8\alpha}$ = 9.5 Hz, $J_{8ß,8a}$ = 7.5 Hz, 1 H, H-8ß), 4.27 (s, 1 H, 5-H), 4.16 (dd, $J_{8\alpha,8ß}$ = 9.5 Hz, $J_{8ß,8a}$ = 5 Hz, 1 H, 8α-H), 3.83 (s, 3 H, 4'-OCH_3), 3.82 (s, 6 H, 3'-, 5'-OCH_3), 2.92 (ddd, $J_{9,8a}$ = 3 Hz, $J_{8ß,8a}$ = 7.5 Hz, $J_{8\alpha,8a}$ = 5 Hz, 1 H, 8a-H), 2.44 (d, $J_{9,OH}$ = 3.5 Hz, OH), 2.46-2.16 (m, 2 H, -CH_2). – $C_{25}H_{26}O_8$ (454.5) calcd. C 66.07 H 5.76; found C 66.20, H 5.84.

2aß-Crotyl-podophyllotoxin (**1l**): Cleavage of **1j**, following the general procedure stated above, gave 95.5 % (**1k**: 88 %) of **1l** as a colorless solid with m.p. 98-100 °C. – ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.10 (s, 1 H, 10-H), 6.44 (s, 1 H, 4-H), 6.32 (s, 2 H, 2'-, 6'-H), 5.98 (s, 2 H, 2-H_2), 5.68-5.31 (m, 2 H, -CH=CH-), 4.81 (d, $J_{9,8a}$ = 10.5 Hz, 1 H, 9-H), 4.43 (dd, $J_{8\alpha,8ß}$ = 8.5 Hz, $J_{8\alpha,8a}$ = 7.5 Hz, 1 H, 8α-H), 4.36 (s, 1 H, 5-H), 4.25 (dd, $J_{8\alpha,8ß}$ = 8.5 Hz, $J_{8ß,8a}$ = 11 Hz, 1 H, 8ß-H), 3.80 (s, 3 H, 4'-OCH_3), 3.75 (s, 6 H, 3'-, 5'-OCH_3), 3.02 (ddd, $J_{8a,9}$ = 10.5 Hz, $J_{8a,8\alpha}$ = 7.5 Hz, $J_{8a8ß}$ = 11 Hz, 1 H, 8a-H), 2.52-2.37, 2.32-2.15 (2m, 1 H each, -CH_2), 1.72 (d, $J_{3'',4''}$ = 6 Hz, 3 H, 4''-CH_3). – $C_{26}H_{28}O_8$ (468.5) calcd. C 66.65, H 6.02; found C 66.73, H 6.16.

2aα-Crotyl-picropodophyllin (**2l**): Cleavage of **2j**, following the general procedure stated above, gave 94 % (**2k**: 86 %) of **2l** as colorless prisms with m.p. 96-98 °C. – ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 6.79 (s, 2 H, 2'-, 6'-H), 6.77 (s, 1 H, 10-H), 6.65 (s, 1 H, 4-H), 5.91, 5.90 (AB, ^2J = 1.4 Hz, 2 H, 2-H_2), 5.54-5.34, 5.34-5.15 (2m, 1 H each, 3''-H, 2''-H), 4.77 (dd, $J_{9,8a}$ = 3 Hz, $J_{9,OH}$ = 3.5 Hz, 1 H, 9-H), 4.49 (dd, $J_{8ß,8\alpha}$ = 9.5 Hz, $J_{8ß,8a}$ = 7.5 Hz, 1 H, H-8ß), 4.25 (s, 1 H, 5-H), 4.16 (dd, $J_{8\alpha,8ß}$ = 9.5 Hz, $J_{8ß,8a}$ = 3 Hz, 1 H, 8α-H), 3.83 (s, 3 H, 4'-OCH_3), 3.81 (s, 6 H, 3'-, 5'-OCH_3), 2.91 (ddd, $J_{9,8a}$ = 3 Hz, $J_{8ß,8a}$ = 7.5 Hz, $J_{8\alpha,8a}$ = 3 Hz, 1 H, 8a-H), 2.39-2.25, (m, 1 H, 1''-CH_2), 2.29 (d, $J_{9,OH}$ = 3.5 Hz, 1 H, OH), 2.23-2.10 (m, 1 H, 1''-CH_2), 1.64 (d, $J_{3'',4''}$ = 6 Hz, 3 H, 4''-CH_3). – $C_{26}H_{28}O_8$ (468.5) calcd. C 66.66, H 6.02; found C 66.40, H 6.39.

2aß-Cinnamyl-podophyllotoxin (**1o**): Cleavage of **1m**, following the general procedure stated above, gave 91 % (**1n**: 88 %) of **1o** as colorless a solid with m.p. 153-55 °C. – ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.42-7.19 (m, 5 H, arom.-H), 7.14 (s, 1 H, 10-H), 6.46 (s, 1 H, 4-H), 6.39-6.28 (m, 2 H, -CH=CH-), 6.32 (s, 2 H, 2'-, 6'-H), 6.00, 5.99 (AB, ^2J = 1.3 Hz, 2 H, 2-H_2), 4.87 (d, $J_{9,8a}$ = 10.5 Hz, 1 H, 9-H), 4.48 (dd, $J_{8\alpha,8ß}$ = 8.5 Hz, $J_{8\alpha,8a}$ = 7.5 Hz, 1 H, 8α-H), 4.42 (s, 1 H, 5-H), 4.39 (dd, $J_{8\alpha,8ß}$ = 8.5 Hz, $J_{8\alpha,8a}$ = 11 Hz, 1 H, 8ß-H), 3.80 (s, 3 H, 4'-OCH_3), 3.74 (s, 6 H, 3'-, 5'-OCH_3), 3.07 (ddd, $J_{9,8a}$ = 10.5 Hz, $J_{8ß,8a}$ = 7.5 Hz, $J_{8\alpha,8a}$ = 11 Hz, 1 H, 8a-H), 2.74-2.61, 2.52-2.39 (2m, 1 H each, -CH_2). – $C_{31}H_{30}O_8$ (530.6) calcd. C 70.18, H 5.69; found C 70.11, H 5.82.

2aα-Cinnamyl-picropodophyllin (**2o**): Cleavage of **2m**, following the general procedure stated above, gave 95 % (**2n**: 92 %) of **2o** as a colorless solid with m.p. 113-15 °C. – ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.26 (mc, 5 H), 6.83 (s, 2 H, 2'-, 6'-H), 6.77 (s, 1 H, 10-H), 6.66 (s, 1 H, 4-H), 6.28 (d, $J_{2'',3''}$ = 15 Hz, 1 H, 3''-H), 6.03-5.86 (m, 1 H, 2''-H), 5.91, 5.89 (AB, ^2J = 1.4 Hz, 2 H, 2-H_2), 4.79 (d, $J_{9,8a}$ = 2.5 Hz, 1 H, 9-H), 4.50 (dd, $J_{8ß,8\alpha}$ = 9.5 Hz, $J_{8ß,8a}$ = 7.5 Hz, 1 H, H-8ß), 4.31 (s, 1 H, 5-H), 4.18 (dd, $J_{8\alpha,8ß}$ = 9.5 Hz, $J_{8\alpha,8a}$ = 3 Hz, 1 H, 8α-H), 3.84 (s, 3 H, 4'-OCH_3), 3.79 (s, 6 H, 3'-, 5'-OCH_3), 2.98 (ddd, $J_{9,8a}$ = 2.5 Hz, $J_{8ß,8a}$ = 7.5 Hz, $J_{8\alpha,8a}$ = 3 Hz, 1 H, 8a-H), 2.61-2.35 (m, 2 H, -CH_2). – $C_{31}H_{30}O_8$ (530.6) calcd. C 70.18, H 5.69; found C 70.09, H 5.71.

*2ß-Allyl-9ß-azido-9-desoxypodophyllotoxin (**3a**) and 2ß-Allyl-9α-azido-9-desoxypodophyllotoxin (**3b**)*: In a 100 ml round bottom flask, 2.0 g (4.4 mmol) of **1i** was dissolved in 20 ml of CH_2Cl_2; 4 ml of $SOCl_2$ was then added and the mixture was

stirred for 30 min at room temp. in a nitrogen atmosphere. Finally, all volatile components were distilled off in a vacuum at 50 °C. The oily product was triturated two times with 20 ml of toluene and again evaporated to dryness in vacuo at 50 °C. The dry residue was dissolved in 20 ml of toluene, followed by the sequential addition of 2.86 g (44 mmol) of NaN_3 and 3.39 g (1 mmol) of tetrabutylammonium hydrogensulfate (neutralized with 2 N NaOH). The suspension was stirred vigorously for 30 h at room temp. The organic layer was separated and the aqueous residue extracted with two 10 ml portions of hot toluene. The solution was evaporated i. vacuo to dryness and the residue was purified by column chromatography (4 × 20, CH_2Cl_2/petroleum ether 1 : 1), giving 1.62 g (76.8 %) of **3a**/**3b** (1.6 : 1). – **3a**: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 6.95 (s, 1 H, 10-H), 6.54 (s, 1 H, 4-H), 6.22 (s, 2 H, 2'-, 6'-H), 6.26-5.92 (m, 1 H, 2''-H), 6.05 (s, 2 H, 2-H_2), 5.26 (dd, $^2J_{gem}$ = 1.7 Hz, $^3J_{cis}$ = 10 Hz, 1 H, Z-3''-H, 5.06 (dd, $^3J_{trans}$ = 16.5 Hz, $^2J_{gem}$ = 1.7 Hz, 1 H, E-3''-H), 4.95 (d, $J_{9,8a}$ = 5 Hz, 1 H, 9-H), 4.58-4.20 (m, 2 H, 8α-H, 8ß-H), 4.49 (s, 1 H, 5-H), 3.81 (s, 3 H, 4'-OCH_3), 3.77 (s, 6 H, 3'-, 5'-OCH_3), 3.26-3.08 (m, 1 H, 8a-H), 2.71-2.52, 2.44-2.26 (2 m, 1 H each, -CH_2). – $C_{25}H_{25}N_3O_7$ calcd. 479.16925, found 479.16922 (HR-MS, from the mixture).

3b: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.10 (s, 1 H, 10-H), 6.53 (s, 1 H, 4-H), 6.36 (s, 2 H, 2'-, 6'-H), 6.12-5.90 (m, 1 H, 2''-H), 6.06, 6.05 (AB, J = 1.3 Hz, 2 H, 2-H_2), 5.27 (dd, $^2J_{gem}$ = 1.7 Hz, $^3J_{cis}$ = 10 Hz, 1 H, Z-3''-H, 5.06 (dd, $^3J_{trans}$ = 16.5 Hz, $^2J_{gem}$ = 1.7 Hz, 1 H, E-3''-H), 4.52 (dd, $J_{8α,8ß}$ = 8 Hz, $J_{8α,8a}$ = 7.5 Hz, 1 H, 8α-H), 4.42 (s, 1 H, 5-H), 4.34 (d, $J_{9,8a}$ = 10.5 Hz, 1 H, 9-H), 4.27 (dd, $J_{8α,8ß}$ = 8 Hz, $J_{8ß,8a}$ = 11 Hz, 1 H, 8ß-H), 3.84 (s, 3 H, 4'-OCH_3), 3.77 (s, 6 H, 3'-, 5'-OCH_3), 3.23 (ddd, $J_{8a,9}$ = 10.5 Hz, $J_{8a,8α}$ = 7.5 Hz, $J_{8aßß}$ = 11 Hz, 1 H, 8a-H), 2.60-2.46, 2.36-2.20 (2 m, 1 H each, -CH_2).

(5R,5aR,8aR,9S)-11-Acetyl-11-aza-5-(3,4,5-trimethoxyphenyl)-12-methyl-6-oxo-dioxolo-[4,5:1,2]benzo[5,6-g]furo[3,4-j]bicyclonona-12-en (**7**): A solution of 32 mg (0.06 mmol) of **3a** in 5 ml of toluene was heated to 80 °C for 8 h in a nitrogen atmosphere to obtain quantitatively **4**. – ^{1}H-NMR ($CDCl_3$): δ = 6.68 (s, 1 H, 10-H), 6.48 (s, 1 H, 4-H), 6.30 (s, 2 H, 2´, 6´-H), 5.94, 5.92 (AB, J = 1.3 Hz, 2 H, 2-H_2), 4.98 (s br, 1 H, 9-H), 4.43 (s, 1 H, 5-H), 4.25 (m, 1 H, 8αβ-H), 3.75 (m, 1 H, 8αβ-H), 3.80 (s, 3 H, 4´-OMe), 3.73 (s, 6 H, 3´-, 5´-OMe), 3.08 (m, 1 H, 8a-H), 1.62, 1.60 (AB, 2 H, CH_2), 1.5-1.2 (m, 2 H), 0.85 (m, 1 H).

After cooling to room temp., 0.047 g (0.06 mmol) of acetyl chloride and 0.047 g (0.06 mmol) of pyridine were added to the crude **4**. After standing for 15 min, the reaction mixture was concentrated in vacuo and the oily residue was separated by preparative TLC on silica gel (20 × 20 cm, *tert*-butyl methyl ether). From its solution in CH_2Cl_2, 30 mg (91 %) of **7** were precipitated by petroleum ether as a colorless solid with m.p. 203-4 °C. – ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 6.87 (s, 1 H, 10-H), 6.44 (s, 1 H, 4-H), 6.28 (s, 2 H, 2'-, 6'-H), 6.00-5.82 (s broad, 1 H, =CH-), 5.95, 5.92 (AB, ^2J = 1.3 Hz, 2 H, 2-H_2), 4.87 (dd, J_1 = J_2 = 1 Hz, 1 H, 9-H), 4.40 (s, 1 H, 5-H), 4.25 (dd, $J_{8α,8ß}$ = 8 Hz, $J_{8αß,8a}$ = 8 Hz, 1 H, 8αß-H), 3.83-3.76 (m, 1 H, 8αß-H), 3.78 (s, 3 H, 4'-OCH_3), 3.73 (s, 6 H, 3'-OCH_3, 5'-O-CH_3), 3.08 (mc, 1 H, 8a-H), 2.35 (s, 3 H, -CH_3), 1.99 (s, 3 H, -CH_3). – ^{1}H-NMR (C_6D_6, 500 MHz): δ = 7.15 (s, 1 H, 10-H), 7.08-6.93 (s broad, 1 H, =CH-), 6.63 (s, 2 H, 2'-, 6'-H), 6.43 (s, 1 H, 4-H), 5.25, 5.19 (AB, ^2J = 1.3 Hz, 2 H, 2-H_2), 4.70 (s, 1 H, 9-H), 4.41 (s, 1 H, 5-H), 3.77 (s, 3 H, 4'-OCH_3), 3.60-3.48 (m, 2 H, 8αß-H), 3.54 (s, 6 H, 3'-OCH_3, 5'-O-CH_3), 2.95 (mc, 1 H, 8a-H), 1.72 (s, 3 H, -CH_3), 1.53 (s broad, 3 H, -CH_3). – ^{13}C-NMR ($CDCl_3$, 125.7 MHz): δ = 174.8 (O-*C*=O), 169.6 (N-*C*=O) 152.6 (3'-, 5'-*C*-OCH_3), 148.1 147.2 (C-11a, C-1'), 137.3 (*C*-10a), 134.2, 132.1, 128.0 (*C*-4a, *C*-4', *C*-3a), 111.1 (*C*-9), 109.9 (*C*-10), 108.6 (*C*-4, *C*-2',-6'), 101.4 (O-*C*H_2-O), 67.3 (-*C*H_2-O-CO), 60.7 (O*C*H_3-4'), 56.1 (O*C*H_3-3',-5'), 52.0 (*C*-5), 48.1 (*C*-5a), 35.3 (*C*-8a), 25.2 (CO-*C*H_3), 23.2 (CH_3). – $C_{27}H_{27}NO_8$ (493.5) calcd. C 65.71, H 5.51, N 2.84; found C 65.62, H 5.73, N 2.90.

Further details on the crystal structure investigation are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshausen 2, (FRG) on quoting the depository number CSD 380088 (**1d**) or CSD 380089 (**7**), the names of the authors, and the journal citation.

Table 2: X-Ray data of the podophyllotoxin derivatives **1d** and **7**

Structure	**1d**	**7**
Empirical formula	C_{23} H_{24} O_8	C_{27} H_{27} N O_8
Formula weight	428.42	493.50
Temperature	293(2) K	293(2) K
Wavelength	0.71072 A	0.71073 A
Crystal system	trigonal	orthorhombic
Space group	P3(2)21	P2(1)2(1)2(1)
Unit cell dimensions	a = 12.848(6) A, α = 90°	a = 10.3810(10) A, α = 90°
	b = 12.848(6) A, ß = 90°	b = 15.1330(10) A, ß = 90°
	c = 22.197(11) A, γ = 120°	c = 16.131(2) A, γ = 90°
Volume	3173(3) A^3	2534.1(4) A^3
Z	6	4
Density (calculated)	1.345 Mg/m^3	1.294 Mg/m^3
Absorption coefficient	0.102 mm^{-1}	0.096 mm^{-1}
F(000)	1356	1040
Crystal size	0.50 x 0.20 x 0.20 mm	1.00 x 0.20 x 0.20 mm
Theta range for data collection	3.66° to 22.49°	3.56° to 22.49°
Index ranges	-11<h<11, -13<k<13, -8<l<23	-3<h<11, -16<k<16, -17<l<17
Reflections collected	2970	2787
Independent reflections	2725 [R(int) = 0.0933]	2480 [R(int) = 0.0200]
Refinement method	Full-matrix, least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	2704 / 0 / 284	2475 / 0 / 330
Goodness-of-fit on F^2	1.180	1.073
Final R indices [I>2sigma(I)]	R1 = 0.0635, wR2 = 0.1128	R1 = 0.0473, wR2 = 0.1042
R indices (all data)	R1 = 0.1074, wR2 = 0.1566	R1 = 0.0627, wR2 = 0.1236
Absolute structure parameter	2(3)	-3(2)
Largest diff. peak and hole	0.297 and -0.185 $e \cdot A^{-3}$	0.254 and -0.166 $e.A^{-3}$

Table 3. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for **1d**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	64(5)	7511(5)	6858(2)	89(2)
C(2)	-24(9)	7840(10)	7459(4)	106(3)
O(3)	836(5)	7747(5)	7824(2)	86(2)
C(3A)	1393(6)	7321(7)	7438(3)	60(2)
C(4)	2281(5)	7086(6)	7580(3)	49(2)
C(4A)	2764(5)	6705(5)	7115(3)	44(2)
C(5)	3825(5)	6546(5)	7284(2)	43(2)
C(5A)	4503(5)	6626(6)	6704(2)	47(2)
C(5B)	5259(6)	7969(5)	6514(3)	58(2)
C(6)	5419(6)	6207(6)	6718(3)	56(2)
O(6)	6151(4)	6335(4)	7090(2)	64(1)
O(7)	5397(4)	5677(4)	6181(2)	65(1)
C(8)	4463(6)	5649(7)	5789(3)	60(2)
C(8A)	3633(6)	5790(6)	6229(2)	49(2)
C(9)	2825(6)	6241(6)	6006(2)	51(2)
O(9)	1905(4)	5383(4)	5618(2)	68(1)
C(9A)	2306(5)	6582(5)	6533(2)	45(2)
C(10)	1386(6)	6836(6)	6407(3)	54(2)
C(10A)	950(6)	7197(6)	6868(3)	58(2)
C(11)	3458(5)	5424(6)	7668(2)	46(2)
C(12)	4241(5)	5497(6)	8120(2)	46(2)
C(13)	3999(7)	4522(6)	8478(2)	51(2)
C(14)	2960(6)	3441(6)	8378(3)	52(2)
C(15)	2155(6)	3347(6)	7931(3)	52(2)
C(16)	2407(6)	4340(6)	7581(2)	50(2)
O(13)	4711(4)	4551(4)	8939(2)	63(1)
O(14)	2675(4)	2482(4)	8763(2)	72(1)
O(15)	1153(4)	2241(4)	7881(2)	71(1)
C(13')	5725(6)	5683(7)	9083(3)	69(2)
C(14')	2778(9)	1540(8)	8511(4)	109(3)
C(15')	243(7)	2073(7)	7462(3)	85(3)

Table 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for **7**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	-114(4)	9237(2)	1604(2)	75(1)
C(2)	-1127(7)	8658(4)	1380(3)	82(2)
O(3)	-1677(4)	8298(2)	2114(2)	80(1)
C(3A)	-897(5)	8584(3)	2753(3)	56(1)
C(4)	-979(5)	8375(3)	3573(3)	53(1)
C(4A)	-36(5)	8746(3)	4104(3)	45(1)
C(5)	-78(5)	8448(2)	5016(2)	44(1)
C(5A)	748(5)	9106(3)	5510(3)	45(1)
C(6)	1055(6)	8904(3)	6407(3)	57(1)
O(7)	2296(4)	9130(2)	6570(2)	71(1)
C(8)	2894(5)	9502(3)	5833(3)	62(1)
C(8A)	2068(5)	9180(3)	5119(3)	47(1)
C(9)	1915(5)	9751(3)	4348(3)	48(1)
C(9A)	881(5)	9323(3)	3799(3)	43(1)
C(10)	911(5)	9533(3)	2944(3)	53(1)
C(10A)	21(6)	9146(3)	2448(3)	54(1)
N(11)	1572(4)	10660(2)	4591(2)	49(1)
C(12)	485(5)	10716(3)	5138(3)	58(1)
C(13)	87(5)	10000(3)	5520(3)	54(1)
C(11')	2369(6)	11376(3)	4471(3)	61(1)
O(11)	2265(4)	12047(2)	4876(3)	86(1)
C(11")	3401(6)	11306(4)	3816(3)	79(2)
C(12')	-262(6)	11570(3)	5173(4)	89(2)
O(6)	352(4)	8635(2)	6945(2)	72(1)
C(1')	332(5)	7483(3)	5110(3)	42(1)
C(2')	-23(6)	7029(3)	5825(3)	55(1)
C(3')	319(5)	6151(3)	5931(3)	52(1)
C(4')	995(5)	5697(3)	5321(3)	51(1)
C(5')	1344(5)	6158(3)	4604(3)	47(1)
C(6')	1022(5)	7041(3)	4502(3)	44(1)
O(3')	-30(4)	5667(2)	6612(2)	76(1)
O(4')	1238(4)	4809(2)	5360(2)	74(1)
O(5')	2013(4)	5678(2)	4026(2)	63(1)
C(3")	-409(9)	6132(4)	7336(3)	107(3)
C(4")	2082(7)	4512(4)	5998(4)	98(2)
C(5")	2069(7)	6012(4)	3201(3)	78(2)

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