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Synthetic Approaches to Condensed Aromatic Analogues from Etoposide. Synthesis of A-Ring Pyridazine Picroetoposide

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Abstract: The studies feature the transformation of etoposide **1** into the pivotal intermediate (+)-**19** for the elaboration of pyridazine-fused aromatic systems via a Stille cross-coupling. The synthesis of A-ring pyridazine picroetoposide (+)-**21** has been achieved in 11 steps.

INTRODUCTION

Etoposide **1** is one of the most important anticancer drugs in view of its wide spectrum of activity. In particular, it is effective in the treatment of small-cell lung cancer and germ cell tumors.[1] However, considerations of toxicity (myelosuppression), development of drug resistance, metabolic inactivation, and poor water-solubility are among the reasons for continuing semi-synthetic programs which target analogues of **1** with improved therapeutic efficacy. The last problem was solved with the recent FDA approval of Etopophos® **2**, a prodrug of **1** that is highly water-soluble and preferable for routine clinical use because of its equivalent efficacy and toxicity profile[2] (Figure 1).

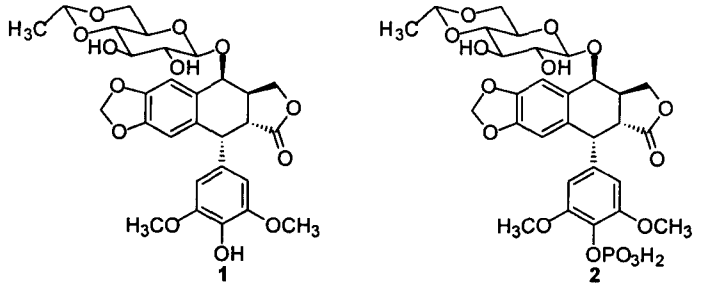

Figure 1

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Regarding the mechanism of action, etoposide is a topoisomerase II inhibitor that induces DNA cleavage by cleavable complex stabilization.[3] Recent important results are: (1) Topo II-etoposide interactions mediate DNA cleavage;[4] (2) The orthoquinone metabolite (VPQ) of **1** is a powerful inhibitor[5] of topoisomerase II, (3) Description of the positional poison model[6] that encompasses the actions of both topo II inhibitors and position-specific topo II poisons such as apurinic sites; (4) Expression of the p53 protein increases the cytotoxicity effect of **1** by inducing G_2-to-M transition;[7] (5) Potential application of the combined topo I and II inhibitors in the clinic.[8] The structure-activity relationship (SAR) of etoposide derivatives has been extensively studied[9] and can be summarized (Figure 2).

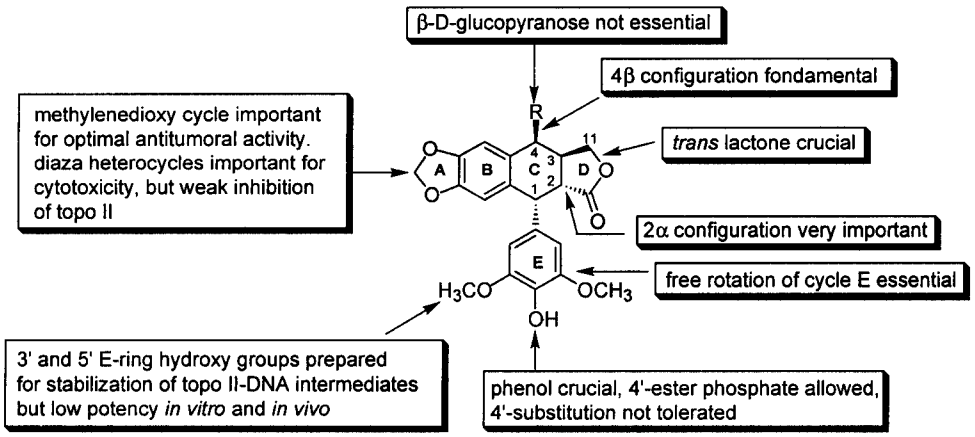


Figure 2

In the absence of the 3-D structure of the topo II active site[10] for conducting rational drug design, two models have been built to provide insight about the key structural parameters required for optimum biological efficacy. First, the composite pharmacophore model[11] based upon various topo II inhibitors that contains three structurally distinct domains: intercalation, groove binding, and variable substituent. Second, the CoMFA model[12] (site receptor model) that represents the 3-D steric and electrostatic fields of a set of superimposed 4'-*O*-demethyl-4-substituted epipodophyllotoxin derivatives. These fields are compatible with stereochemical properties of the DNA backbone. At the time our work began on the exploration of the DNA intercalating domain of the former model, to our knowledge there were no reported studies dealing with this subject. Recently, work[13] notably concerning podophenazine derivatives **3** and **4** has appeared (Figure 3). Interestingly, it has been shown by Lee *et al.*[13] that **3** exhibited an improved cytotoxicity compared to **1** while little effect was observed on topoisomerase II.

We have designed the condensed aromatic derivatives **5** (n = 1, 2, 3) of etoposide **1** that provides : (1) a planar chromophore with two to four fused aromatic rings, as in the case of DNA intercalating agents:[14] Extension of the aromatic surface area should enhance π-stacking interactions[15] in aqueous medium (2) a potential quaternarized aromatic nitrogen needed for an intercalation-based pathway[16] and for water-solubility (Figure 3).

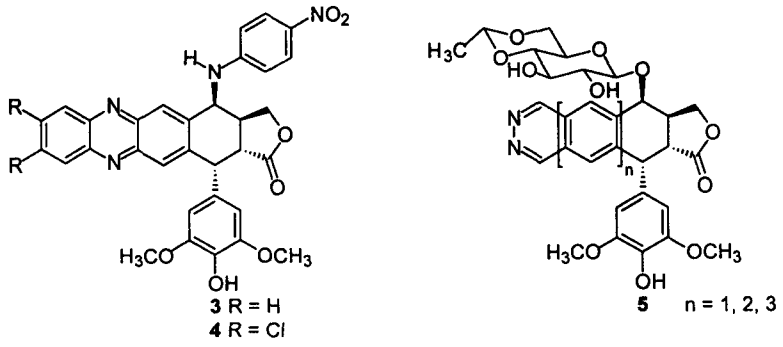
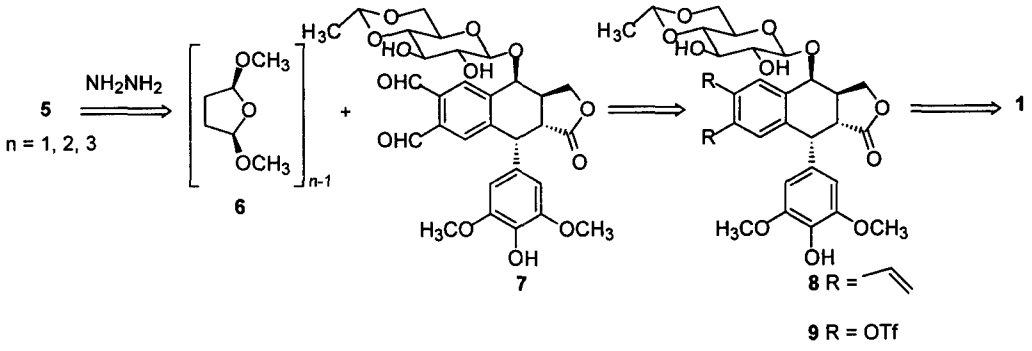


Figure 3

The approach to the targeted diaza etoposide derivatives **5** from etoposide **1** is outlined in retrosynthetic Scheme 1.



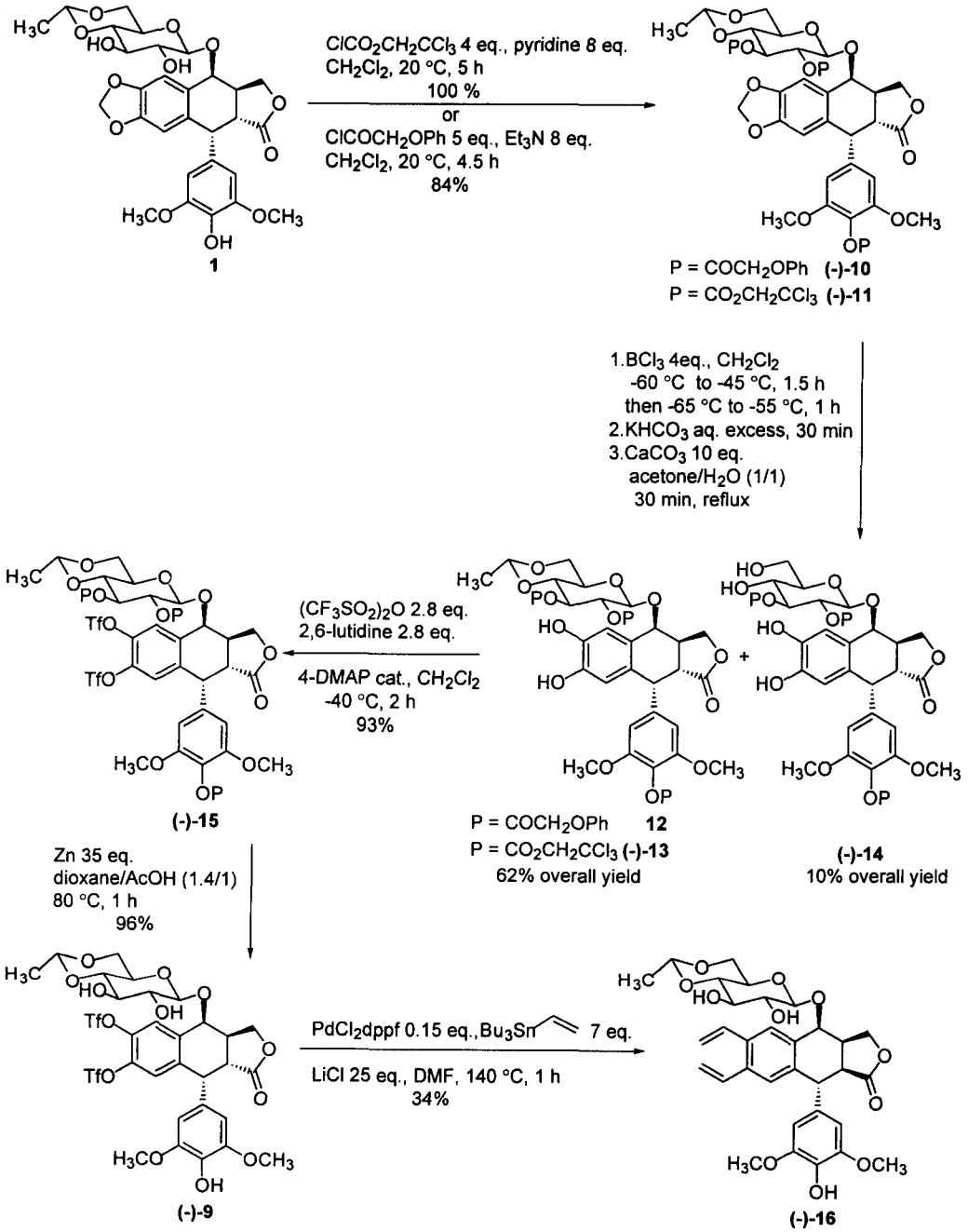
Scheme 1

The construction of condensed benzene systems of **5** (n = 2, 3) could arise by reaction[17] of dialdehyde **7** with appropriate stoechiometric amounts of 2,5-dimethoxytetrahydrofuran **6** yielding the requisite dialdehydes needed for coupling with hydrazine. The dialdehyde functionality of **7** could be introduced by extending the Stille approach used for the synthesis of A-ring pyridazine podophyllotoxin.[18]

We therein fully report on our chemistry leading to the synthesis of the pivotal dialdehyde **19** which presents the *cis*-fused γ-lactone moiety and the subsequent synthesis of A-ring pyridazine picroetoposide **21**.

RESULTS AND DISCUSSION

The synthesis of the bisvinyl key intermediate **16**, epimer of **8** at C-2, required for the preparation of **5** (n = 1, 2, 3) began with the protection of etoposide **1** (Scheme 2).



Scheme 2

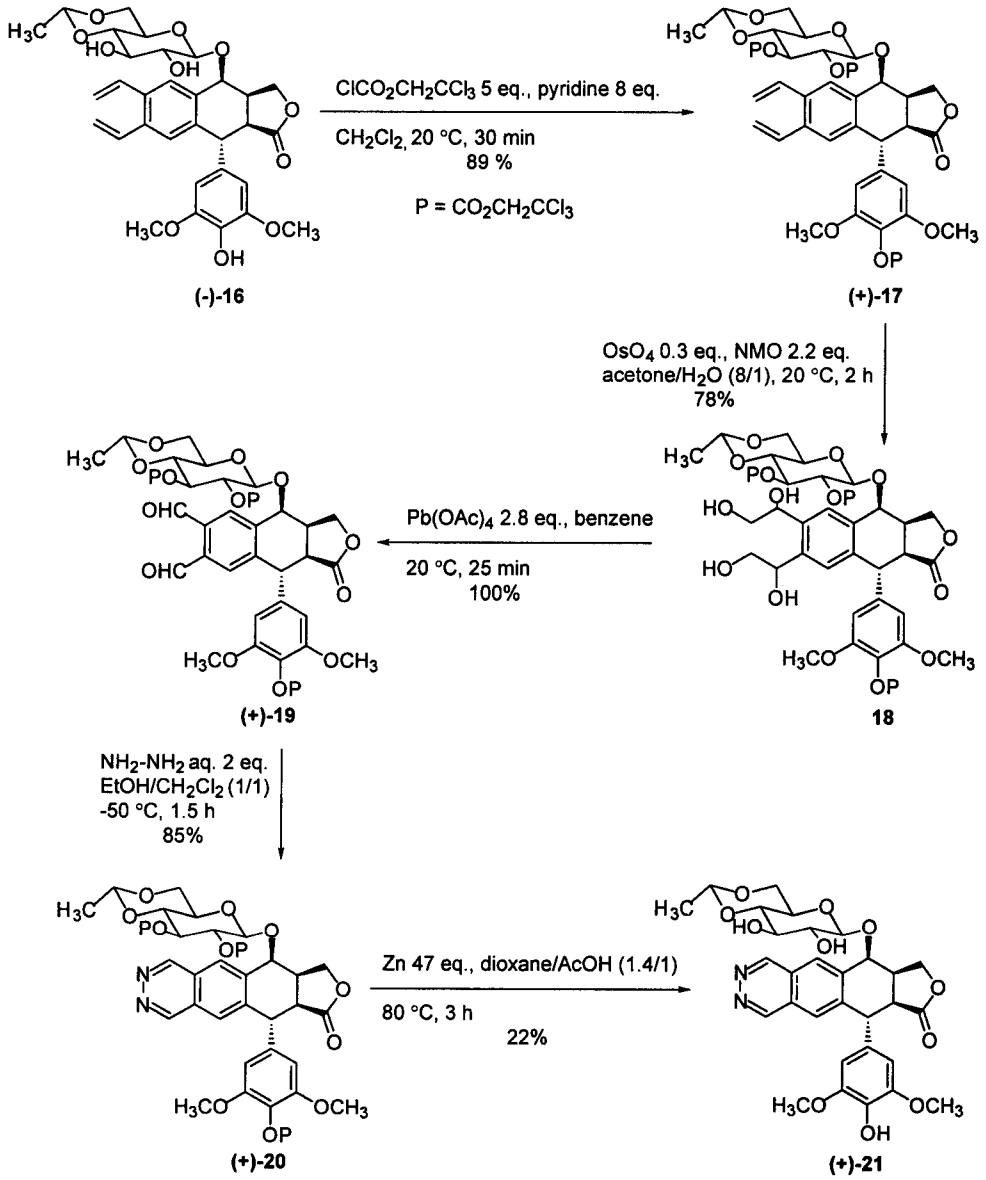
The choice of the protecting group was critical in the success of the formation of the corresponding catechol derivative. Thus, the derivative (-)-**10**, available from protection of etoposide **1** with phenoxyacetyl chloride (84%), was reacted with BCl_3 followed by exposure to $CaCO_3$, under conditions identical to those

established by Kadow and co-workers[19], in the expectation that catechol **12** would result, but this yielded no trace of **12**. All attempts generally led to decomposition of the starting material, formation of 4'-demethoxy epipodophyllotoxin assumed to be induced by BCl_3 cleavage of acetal groups, both resulting from the loss of the sugar moiety and basic cleavage of the 4'-phenoxy acetyl group and, finally, formation of an unidentified non-glycosidic product which lacked ring A. Furthermore, a variety of concentrations, addition times, and reaction temperatures were tried in this process with no success. One conceivable explanation, by examination of Dreiding model, is that the phenoxy acetyl groups sterically hinder the approach of the Lewis acid. Importantly, ^1H NMR analysis revealed the high field shifts and the splits of the methylenedioxy group of (-)-**10** with protons at 5.64 and 5.90 ppm, by comparison with those of (-)-**11** collapsing at 6.02 ppm. It therefore seems likely that the failure for cleaving of **10** to obtain **12** may be also due to electronic effects between the A-ring and the phenoxyacetyl group(s) or π-stacking. Since 2,2,2-trichloroethyl chloroformate had been used as protecting group by Kadow *et al.*[19] for this purpose, the same was done in the synthesis of the subgoal **16**. Thus, we converted quantitatively etoposide **1** into the known derivative (-)-**11**. Treatment of the product (-)-**11** with BCl_3, followed by exposure to $CaCO_3$, effected the cleavage of the A-ring of (-)-**11**, giving the desired catechol (-)-**13** and the byproduct (-)-**14** in 62% and 10% yields, respectively. Conversion of catechol (-)-**13** to bistriflate (-)-**15** (93%), then set the stage for the Stille vinylation[20] which mechanistically proceeds through a sequence involving oxidative addition, transmetallation, *trans-cis* isomerization and reductive elimination. No desired coupling was detected when the protected bistriflate (-)-**15** was allowed to react with 2.2 eq. of tri-*n*-butylvinylstannane in the presence of $Pd(PPh_3)_4$ (LiCl 3 eq., dioxane, 100 °C or DMF, 150 °C) or $PdCl_2(PPh_3)_2$ (PPh_3, DMF, 150 °C). Presumably, extensive decomposition of the sensitive compound (-)-**15** took place due to the competitive oxidative addition between the catalytic system and the halide source.[21] The use of Pd_2dba_3 (LiCl 3 eq., PPh_3, NMP, 25 °C)[22] or $PdCl_2$dppf (LiCl 3 eq., DMF, 25 °C) gave only an unidentified compound which was found to contain one vinyl functionality, as determined by ^1H NMR; purification of the latter proved to be too difficult. Consequently, for simplicity of reaction and purification, we decided to explore the palladium-catalyzed coupling of (-)-**9**. This was prepared from (-)-**15** upon optimized reaction with activated Zn (35 eq) in a mixture of dioxane and acetic acid (1.4/1) at 80 °C (96%) to remove the 2,2,2-trichloroethoxycarbonyl groups. Only decomposition of the starting material was obtained in the Stille coupling of bistriflate (-)-**9** and tri-*n*-butylvinylstannane employing the conditions described by Saá ($PdCl_2(PPh_3)_2$, LiCl, PPh_3, DMF, 100 °C)[23] and successfully applied in the synthesis of 4'-dehydroxy-4'-ethynyl etoposide analogue.[24]

Stille vinylation was further studied with the catalyst $PdCl_2$dppf (dppf = bis(1,1-diphenylphosphino)ferrocene) developed by Hayashi[25] directly under forcing conditions ($Bu_3Sn(C_2H_3)$ 7 eq., LiCl 25 eq., DMF, 140 °C) and closed TLC monitoring. We were pleased to discover that this resulted in formation of picrobisvinyl (-)-**16** (*cis*-lactone) in 34% yield. The *cis* assignment for C and D rings was based upon characteristic ^1H NMR coupling constants[26] (2,3-*cis* configuration from the coupling constants J = 9.8, 5.2 Hz for H-2 and J = 9.4, 1.5 Hz for H-11b).

With bisvinyl *cis*(-)-**16** in hand, all that needed to complete the synthesis of **5** (n = 1) was to extend the chemistry reported by us[18] to the construction of the A-ring pyridazine (Scheme 3). Protection of (-)-**16** with 2,2,2-trichloroethylchloroformate (89%), followed by tetrahydroxylation afforded a mixture of tetraols **18** in 78% overall yield. Oxidative cleavage of **18** was then achieved with $Pb(OAc)_4$ and produced the desired dialdehyde (+)-**19** (quantitative yield).The pyridazine ring was formed by treating (+)-**19** with hydrazine to

give (+)-**20** (85%). Deprotection of the hydroxy groups was again done with activated Zn under acidic conditions to provide the picroetoposide A-ring pyridazine analogue (+)-**21**[27] in low yield (22%).



Scheme 3

At this stage, there are two significant issues. First, for the time being, use of 2,2,2-trichloroethylchloroformate for the protection of (-)-**16** limits the availability of (+)-**21** and could be also prejudicial for the synthesis of **5** (n = 2,3). This result constrains us to realize the deprotection step earlier or to examine other protecting groups. Second, the crucial inversion of the stereochemistry of **21** at C-2 to form **5** (n = 1) by sequential kinetic deprotonation/protonation requires selective protection of the phenol group at 4'.

Indeed, preliminary results from the etoposide and picroetoposide[28] models showed that deprotonation at C-2 with LDA was inefficient, presumably due to the presence of the more acidic hydrogens of hydroxy groups at the 2", 3" and 4' positions forming the corresponding alkoxy and phenoxy salts with low THF-solubility. This observation is in agreement with the work reported in 1986 by Durst *et al.*[29] regarding the synthesis of 2-chloroetoposide from **1** in a disappointing yield (10%) under identical basic conditions (LDA 4 eq., THF, -78 °C). The approach we were taking was based on the knowledge that the generation of enolates derived from 4'-deshydroxy-4'-substituted etoposide derivatives, in which the 2"- and 3"-hydroxy groups had not been protected, was much more facile and gave the desired *trans* lactone isomers[24] after protonation (AcOH, -78 °C). At this point remains the matter of choosing the protecting group at 4'. Although the benzyloxycarbonyl moiety is well known in podophyllotoxin chemistry, it appeared incompatible[30] with LDA. Selective benzylation[31] of the pyridazine picroetoposide (+)-**21**, deprotonation followed by a kinetically controlled protonation of the lactone enolate with a suitable achiral[32] or chiral[33] proton source, should offer the prospect for formation of the first target pyridazine etoposide **5** (n = 1). In addition, we are presently focusing upon Stille coupling with tri-*n*-butylvinylstannane employing various combinations of Pd/solvent/additive mixtures or alternative organometallic procedure[34] in order to overcome the unwanted epimerization at C-2. The result of all these investigations will be reported in due course.

EXPERIMENTAL SECTION

General Procedures. Reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. All reactions were magnetically stirred and monitored by thin layer chromatography with Merck 0.25 mm silica gel plates (60F-254). Flash chromatography was performed with silica gel (particle size 0.040-0.063 mm) supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Etoposide was obtained from Pierre Fabre Médicament. Melting points were determined on an Electrothermal digital melting point apparatus and are not corrected. Infrared spectra were recorded on a Perkin-Elmer 1710 infrared spectrophotometer. Proton NMR spectra were recorded on a Bruker AM-250 or Bruker AC-300 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Mass spectra (MS) were obtained with a Nermag R10-10C under chemical ionization (CI) or electrospray (ES/MS) conditions. Microanalyses were performed by the "Service d'Analyse du CNRS, Vernaison, France".

4'-*O*-Demethyl-4'-*O*-phenoxyacetyl-4-*O*-[4,6-*O*-ethylidene-2,3-di-*O*-phenoxyacetyl-β-D-glucopyranosyl]-4-epipodophyllotoxin (10). A solution of etoposide **1** (1 g, 1.70 mmol) in dichloromethane (50 mL) and triethylamine (1.9 mL, 13.6 mmol) was treated with phenoxyacetyl chloride (1.17 mL, 8.5 mmol) at ambient temperature. The reaction mixture was stirred for 4.5 h and then quenched with water (50 mL). The organic phase was washed with 1N HCl, brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (cyclohexane/ethyl acetate, 70:30) afforded (-)-**10** (1.42 g, 84% yield): mp 110 -112 °C; $[\alpha]_D^{20}$ -61 (*c* 1.18, $CHCl_3$); IR ($CDCl_3$) 2929, 1777, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32-7.20 and 7.02-6.71 (arom, 15H, 3 PhOCH$_2$CO), 6.78 (s, 1H, H-5), 6.50 (s, 1H, H-8), 6.27 (s, 2H, H-2', H-6'), 5.90 (s, 1H, O-CH$_2$-O), 5.64 (s, 1H, O-CH$_2$-O), 5.37 (t, *J* = 9.2 Hz, 1H, H-3"), 5.05 (dd, *J* = 9.2, 8 Hz, 1H, H-2"), 4.93 (d, *J* = 8 Hz, 1H, H-1"), 4.91 (s, 2H, PhOCH$_2$CO), 4.82 (d, *J* = 3.5 Hz, 1H, H-4), 4.68 (q, *J* = 5 Hz, 1H, H-7"), 4.60 (m, 3H, H-1, PhOCH$_2$CO), 4.40 (m, 2H, H-11b, PhOCH$_2$CO), 4.20

(m, 3H, H-6"ax, H-11a, PhOC$\underline{H}_2$CO), 3.62 (s, 6H, OMe), 3.59 (brt, J = 10 Hz, 1H, H-6"eq), 3.52 (t, J = 9.2 Hz, 1H, H-4"), 3.43 (m, 1H, H-5"), 3.18 (dd, J = 14.2, 5.2 Hz, 1H, H-2), 2.83 (m, 1H, H-3), 1.35 (d, J = 5 Hz, 3H, CH_3); MS (DCI/NH_3) *m/e* 1008 $[M + NH_4]^+$. Anal. Calcd for $C_{53}H_{50}O_{19}$: C, 64.24; H, 5.08. Found: C, 64.08; H, 5.09.

4'-*O*-Demethyl-4'-*O*-(2,2,2-trichloroethoxy)carbonyl-4-*O*-[4,6-*O*-ethylidene-2,3-di-*O*-(2,2,2-trichloroethoxy)carbonyl-β-D-glucopyranosyl]-4-epipodophyllotoxin (11). A solution of etoposide **1** (10.21 g, 17.35 mmol) in dichloromethane (100 mL) and pyridine (11.3 mL, 140 mmol) was treated with 2,2,2-trichloroethylchloroformate (9.55 mL, 69.4 mmol), stirred at ambient temperature for 5 h, quenched with water (100 mL). The organic phase was washed with 2N HCl (20 mL) and brine, dried over $MgSO_4$, filtered, and concentrated (30 °C). Flash chromatography (cyclohexane/ethyl acetate, 75:25, then 60:40) gave (-)-**11** (19.31 g, 100% yield) as a white solid: mp 135-137 °C; $[\alpha]_D^{20}$ -36 (*c* 1.03, $CHCl_3$); IR ($CDCl_3$) 2961, 1776, 1605 cm^{-1}; ^1H NMR (1D + COSY, $CDCl_3$) δ 6.77 (s, 1H, H-5), 6.55 (s, 1H, H-8), 6.26 (s, 2H, H-2', H-6'), 6.02 (s, 2H, O-CH_2-O), 5.17 (m, 1H, H-3"), 4.94 (d, J = 3.2 Hz, 1H, H-4), 4.85 (m, 4H, H-1", H-4", $CO_2C\underline{H}_2CCl_3$), 4.79 (s, 1H, $CO_2C\underline{H}_2CCl_3$), 4.78 (s, 1H, $CO_2C\underline{H}_2CCl_3$), 4.72 (q, J = 5 Hz, 1H, H-7"), 4.64 (s, 2H, $CO_2C\underline{H}_2CCl_3$), 4.59 (d, J = 5.3 Hz, 1H, H-1), 4.40 (dd, J = 10.3, 9 Hz, 1H, H-11b), 4.25 (m, 2H, H-6"eq, H-11a), 3.70 (s, 6H, OMe), 3.64 (brt, J = 10.3 Hz, 1H, H-6"ax), 3.59 (brt, J = 9.4 Hz, 1H, H-4"), 3.43 (m, 1H, H-5"), 3.18 (dd, J = 14.1, 5.3 Hz, 1H, H-2), 2.85 (m, 1H, H-3), 1.35 (d, J = 5 Hz, 3H, CH_3); MS (DCI/NH_3) *m/e* 1132 $[M + NH_4]^+$.

4'-*O*-Demethyl-4'-*O*-(2,2,2-trichloroethoxy)carbonyl-4-*O*-[4,6-*O*-ethylidene-2,3-di-*O*-(2,2,2-trichloroethoxy)carbonyl-β-D-glucopyranosyl]-6,7-di-*O*-demethylene-4-epipodophyllotoxin (13), and 4'-*O*-Demethyl-4'-*O*-(2,2,2-trichloroethoxy)carbonyl-4-*O*-[2,3-di-*O*-(2,2,2-trichloroethoxy)carbonyl-β-D-glucopyranosyl]-6,7-di-*O*-demethylene-4-epipodophyllotoxin (14). A solution of 1N BCl_3 (75.6 mL, 75.6 mmol) in dichloromethane (115 mL) was cooled to -60 °C, and compound (-)-**11** (21.11 g, 18.9 mmol) in dichloromethane (115 mL) was added dropwise over 30 min. The reaction mixture was warmed to -45 °C over 1 h, cooled again to -65 °C, then allowed to warm to -55 °C over 1 h. This mixture was poured onto a precooled saturated aqueous $KHCO_3$ solution (200 mL), stirred for 30 min, and extracted with dichloromethane (3 x 100 mL). The organic phase was washed with brine (200 mL) to pH = 7, dried over $MgSO_4$, filtered and concentrated (30 °C), affording 24.4 g of the corresponding boronate compound. This crude extract was dissolved in a mixture of acetone (70 mL) and water (70 mL), and $CaCO_3$ (18.9 g, 189 mmol) was added. The reaction mixture was refluxed for 30 min, then cooled to ambient temperature, filtered, and finally acidified with 2N HCl (20 mL) to pH = 1. After extraction with ethyl acetate (3 x 100 mL), the combined organic phases were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated (30 °C). Flash chromatography (cyclohexane/ethyl acetate, 65:35 then 50:50) provided successively (-)-**13** (13 g, 62% yield) as a white solid and (-)-**14** (2 g, 10%) as a foam.

(-)-**13**: mp 149-151 °C; $[\alpha]_D^{20}$ -49 (*c* 1.03, $CHCl_3$); IR ($CDCl_3$) 3549, 2938, 1775, 1608 cm^{-1}; ^1H NMR (1D + COSY, $CDCl_3$) δ 6.86 (s, 1H, H-5), 6.56 (s, 1H, H-8), 6.24 (s, 2H, H-2', H-6'), 5.11 (m, 1H, H-3"), 4.90 (d, J = 3.1 Hz, 1H, H-4), 4.53-4.85 (m, 10H, H-1, H-1", H-2", H-7", 3 $CO_2C\underline{H}_2CCl_3$), 4.40 (dd, J = 10.3, 9 Hz, 1H, H-11b), 4.25 (m, 2H, H-6"eq, H-11a), 3.71 (m, 1H, H-6"ax), 3.69 (s, 6H, OMe), 3.58 (brt, J = 9.8 Hz, 1H, H-4"), 3.43 (m, 1H, H-5"), 3.20 (dd, J = 14, 5.1 Hz, 1H, H-2), 2.82 (m, 1H, H-3), 1.33 (d, J = 4.9 Hz, 3H, CH_3); MS (ES/MS) *m/e* 1123, 1124, 1126, 1128 $[M + Na]^+$. Anal. Calcd for $C_{37}H_{35}O_{19}Cl_9$: C, 40.30; H, 3.20. Found: C, 40.17; H, 3.19.

(-)-**14**: $[\alpha]_D^{20}$ -41.7 (*c* 1, $CHCl_3$); IR ($CDCl_3$) 3700-3200, 2970, 1775, 1607 cm^{-1}; ^1H NMR (1D + COSY, $CDCl_3$) δ 6.98 (s, 1H, H-5), 6.63 (s, 1H, H-8), 6.26 (s, 2H, H-2', H-6'), 5.08 (d, *J* = 2.7 Hz, 1H, H-4), 4.96 (brt, *J* = 9.3 Hz, 1H, H-3"), 4.87 (m, 1H, H-2"), 4.87-4.65 (m, 6H, $CO_2C\underline{H}_2CCl_3$), 4.61-4.56 (m, 2H, H-1, H-1"), 4.40 (brt, *J* = 9.8 Hz, 1H, H-11b), 4.29 (brt, *J* = 8.1 Hz, 1H, H-11a), 4.05 (brd, *J* = 11.8 Hz, 1H, H-6"eq), 3.88 (dd, *J* = 11.8, 6.2 Hz, 1H, H-6"ax), 3.77 (brt, *J* = 9.3 Hz, 1H, H-4"), 3.68 (s, 6H, OMe), 3.48 (m, 1H, H-5"), 3.18 (dd, *J* = 13.9, 5.2 Hz, 1H, H-2), 2.90 (m, 1H, H-3), 1.85 (brs, 2H, OH); MS (FAB) *m/e* 1094, 1096, 1097, 1098, 1099, 1100, 1101, 1102 $[M + Na]^+$.

4'-*O*-Demethyl-4'-*O*-(2,2,2-trichloroethoxy)carbonyl-4-*O*-[4,6-*O*-ethylidene-2,3-di-*O*-(2,2,2-trichloroethoxy)carbonyl-β-D-glucopyranosyl]-6,7-di-*O*-demethylene-6,7-di-*O*-trifluoromethylsulfonyl-4-epipodophyllotoxin (15). A solution of catechol (-)-**13** (13 g, 11.8 mmol) and 4-DMAP (0.432 g, 3.5 mmol) in dichloromethane (410 mL) was cooled to -40 °C, and 2,6-lutidine (3.85 mL, 33 mmol) and triflic anhydride (5.55 mL, 33 mmol) were successively added dropwise. The reaction mixture was stirred for 2 h, quenched with water (200 mL), acidified with 2N HCl to pH = 1, and extracted with dichloromethane (2 x 100 mL). The organic phase was washed with brine (2 x 200 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (cyclohexane/ethyl acetate, 75:25) afforded (-)-**15** (15 g, 93% yield) as a white solid: mp 136-138 °C; $[\alpha]_D^{20}$ -36 (*c* 0.74, $CHCl_3$); IR ($CDCl_3$) 2936, 1779, 1607 cm^{-1}; ^1H NMR (1D + COSY, $CDCl_3$) δ 7.60 (s, 1H, H-5), 7.30 (s, 1H, H-8), 6.14 (s, 2H, H-2', H-6'), 5.31-4.62 (m, 12H, H-1, H-4, H-1", H-2", H-3", H-7", 3 $CO_2C\underline{H}_2CCl_3$), 4.45 (brt, *J* = 9 Hz, 1H, H-11b), 4.33 (brt, *J* = 9 Hz, 1H, H-11a), 4.26 (dd, *J* = 10, 4.2 Hz, 1H, H-6"eq), 3.66 (s, 6H, OMe), 3.61-3.52 (m, 3H, H-4", H-5", H-6"ax), 3.25 (dd, *J* = 14, 5.2 Hz, 1H, H-2), 2.90 (m, 1H, H-3), 1.36 (d, *J* = 5 Hz, 3H, CH_3); MS (ES/MS) *m/e* 1386, 1388, 1390, 1392 $[M + Na]^+$. Anal. Calcd for $C_{39}H_{33}O_{23}S_2Cl_9F_6$: C, 34.27; H, 2.43. Found: C, 34.39; H, 2.45.

4'-*O*-Demethyl-4-*O*-(4,6-*O*-ethylidene-β-D-glucopyranosyl)-6,7-di-*O*-demethylene-6,7-di-*O*-trifluoromethylsulfonyl-4-epipodophyllotoxin (9). A solution of bistriflate (-)-**15** (15 g, 11 mmol) in dioxane (200 mL) and acetic acid (140 mL) was treated with activated Zn (25.1 g, 384 mmol). The reaction mixture was stirred at 80 °C for 1 h and then recooled to ambient temperature, and diluted with toluene (100 mL). After filtration and concentration, the crude was redissolved in toluene (50 mL) and dichloromethane (50 mL), and concentrated. Flash chromatography (cyclohexane/ethyl acetate, 1:2) furnished (-)-**9** (8.9 g, 96% yield): mp 155-157 °C; $[\alpha]_D^{20}$ -63 (*c* 0.40, $CHCl_3$); IR ($CDCl_3$) 3690-3600, 1776, 1604 cm^{-1}; ^1H NMR (1D + COSY, $CDCl_3$) δ 7.62 (s, 1H, H-5), 7.26 (s, 1H, H-8), 6.15 (s, 2H, H-2', H-6'), 5.04 (d, *J* = 3.5 Hz, 1H, H-4), 4.80 (d, *J* = 5.2 Hz, 1H, H-1), 4.75 (q, H = 5 Hz, 1H, H-7"), 4.65 (d, *J* = 7.6 Hz, 1H, H-1"), 4.47 (dd, *J* = 10.5, 8.7 Hz, 1H, H-11b), 4.27 (brt, *J* = 8.7 Hz, 1H, H-11a), 4.10 (dd, *J* = 9.8, 4 Hz, 1H, H-6"eq), 3.70 (m, 1H, H-3"), 3.66 (s, 6H, OMe), 3.58 (brt, *J* = 9.8 Hz, 1H, H-6"ax), 3.46 (brt, *J* = 8.3 Hz, 1H, H-2"), 3.35 (m, 2H, H-4", H-5"), 3.30 (dd, *J* = 14.4, 5.2 Hz, 1H, H-2), 2.90 (m, 1H, H-3), 1.40 (d, *J* = 5 Hz, 3H, CH_3); MS (ES/MS) *m/e* 841 $[M + H]^+$, 863 $[M + Na]^+$. Anal. Calcd for $C_{30}H_{30}O_{17}S_2F_6$: C, 42.86; H, 3.60. Found: C, 42.71; H, 3.62.

4'-*O*-Demethyl-4-*O*-(4,6-*O*-ethylidene-β-D-glucopyranosyl)-6,7-demethylenedioxy-6,7-diethenyl-4-epipicropodophyllin (16). A solution of bistriflate (-)-**9** (480 mg, 0.57 mmol) in DMF (25 mL) was treated with $PdCl_2$dppf (93 mg, 0.11 mmol), LiCl (603 mg, 14.22 mmol), tri-*n*-butylvinylstannane (1.16 mL 3.97 mmol) and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol at ambient temperature. The reaction mixture was heated to 140 °C for 40 min, cooled to ambient temperature, and then quenched with

water (100 mL) and saturated aqueous KF (20 mL). After filtration and extraction with ether, the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (gradient elution, dichloromethane → dichloromethane/acetone, 95:5 then 80:20) gave (-)-**16** (116 mg, 34% yield) as a white solid: mp 221-223 °C; $[\alpha]_D^{20}$ -71 (*c* 0.79, $CHCl_3$); IR ($CDCl_3$) 3587, 3545, 2927, 1776, 1621, 1604 cm^{-1}; ^1H NMR (1D + COSY, $CDCl_3$) δ 7.38 (s, 1H, H-5), 7.00 (s, 1H, H-8), 6.98 (dd, J_{trans} = 17.5, J_{cis} = 11 Hz, 1H, vinyl), 6.90 (dd, J_{trans} = 17.5, J_{cis} = 11.1 Hz, 1H, vinyl), 6.50 (s, 2H, H-2', H-6'), 5.60 (d, J_{trans} = 17.5 Hz, 1H, vinyl), 5.39 (d, J_{trans} = 17.5 Hz, 1H, vinyl), 5.35 (d, J_{cis} = 11 Hz, 1H, vinyl), 5.28 (d, J_{cis} = 11 Hz, 1H, vinyl), 5.05 (d, *J* = 2.7 Hz, 1H, H-4), 4.72 (q, *J* = 5 Hz, 1H, H-7"), 4.58 (dd, *J* = 9.4, 1.5 Hz, 1H, H-11b), 4.55 (dd, *J* = 9.4, 6.7 Hz, 1H, H-11a), 4.31 (d, *J* = 5.0 Hz, 1H, H-1), 4.14 (dd, *J* = 10.3, 4.9 Hz, 1H, H-6"eq), 3.92 (d, *J* = 7.6 Hz, 1H, H-1"), 3.75 (s, 6H, OMe), 3.65-3.53 (m, 2H, H-3", H-6"ax), 3.46 (m, 1H, H-2"), 3.33 (brt, *J* = 9.2 Hz, 1H, H-4"), 3.20 (dd, *J* = 9.8, 5.2 Hz, 1H, H-2), 3.10 (td, *J* = 9.8, 4.9 Hz, 1H, H-5"), 2.97 (m, 1H, H-3), 1.35 (d, *J* = 5 Hz, 3H, CH_3); MS (DCI/NH_3) *m/e* 614 $[M + NH_4]^+$. Anal. Calcd for $C_{32}H_{36}O_{11}$: C, 64.42; H, 6.08. Found: C, 64.66; H, 6.10.

4'-*O*-Demethyl-4'-*O*-(2,2,2-trichloroethoxy)carbonyl-4-*O*-[4,6-*O*-ethylidene-2,3-di-*O*-(2,2,2-trichloroethoxy)carbonyl-β-D-glucopyranosyl]-6,7-demethylenedioxy-6,7-diethenyl-4-epipicropodophyllin (17). A solution of bisvinyl (-)-**16** (111 mg, 0.186 mmol) in dichloromethane (5 mL) and pyridine (121 μL, 1.5 mmol) was treated with 2,2,2-trichloroethylchloroformate (129 μL, 0.937 mmol). The reaction mixture was stirred for 30 min at ambient temperature and then quenched with 1N HCl to pH 1-2. The organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (cyclohexane/ethyl acetate, 80:20 then 70:30) afforded (+)-**17** (186 mg, 89% yield) as a white solid: mp 150-152 °C; $[\alpha]_D^{20}$ +12 (*c* 1.06, $CHCl_3$); IR ($CDCl_3$) 2928, 1776, 1609 cm^{-1}; ^1H NMR (1D + COSY, $CDCl_3$) δ 7.40 (s, 1H, H-5), 7.03 (s, 1H, H-8), 6.99 (dd, J_{trans} = 17.5, J_{cis} = 11.1 Hz, 1H, vinyl), 6.92 (dd, J_{trans} = 17.5, J_{cis} = 11.1 Hz, 1H, vinyl), 6.50 (s, 2H, H-2', H-6'), 5.66 (d, J_{trans} = 17.5 Hz, 1H, vinyl), 5.44 (d, J_{trans} = 17.5 Hz, 1H, vinyl), 5.39 (d, J_{cis} = 11.1 Hz, 1H, vinyl), 5.33 (d, J_{cis} = 11.1 Hz, 1H, vinyl), 5.04 (m, 4H, H-3", H-4, $CO_2C\underline{H}_2CCl_3$), 4.90 (s, 2H, $CO_2C\underline{H}_2CCl_3$), 4.78 (d, *J* = 11.9 Hz, 1H, $CO_2C\underline{H}_2CCl_3$), 4.70 (m, 3H, H-2", H-7", $CO_2C\underline{H}_2CCl_3$), 4.45 (m, 2H, H-11a, H-11b), 4.39 (d, *J* = 7.4 Hz, 1H, H-1"), 4.31 (d, *J* = 5.2 Hz, 1H, H-1), 4.21 (dd, *J* = 9.8, 4.9 Hz, 1H, H-6"eq), 3.80 (s, 6H, OMe), 3.62 (brt, *J* = 10.2 Hz, 1H, H-6"ax), 3.57 (brt, *J* = 9.3 Hz, 1H, H-4"), 3.30 (dd, *J* =10.5, 5.2 Hz, 1H, H-2), 3.27 (m, 1H, H-5"), 3.11 (m, 1H, H-3), 1.31 (d, *J* = 5 Hz, 3H, CH_3); MS (DCI/NH_3) *m/e* 1136, 1138, 1140, 1142, 1144 $[M + NH_4]^+$.

4'-*O*-Demethyl-4'-*O*-(2,2,2-trichloroethoxy)carbonyl-4-*O*-[4,6-*O*-ethylidene-2,3-di-*O*-(2,2,2-trichloroethoxy)carbonyl-β-D-glucopyranosyl]-6,7-demethylenedioxy-6,7-di-(1,2-hydroxyethyl)-4-epipicropodophyllin (18). A solution of bisvinyl (+)-**17** (256 mg, 0.228 mmol) and N-methylmorpholine-N-oxide (58.7 mg, 0.501 mmol) in acetone (16 mL) and water (2 mL) was cooled to 0 °C, and catalytic OsO_4 (850 μL of a 2.5 wt % solution in *t*.BuOH, 0.068 mmol) was added dropwise. The ice bath was removed, and the reaction mixture was stirred for 2 h and then partitioned between saturated aqueous $NaHSO_3$ and ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (cyclohexane/ethyl acetate, 30:70) provided an uncharacterized mixture of tetrahydroxy lactones **18** (211 mg, 78% yield); MS (ES/MS) *m/e* 1210, 1211, 1213, 1218, 1219 $[M + Na]^+$.

4'-*O*-Demethyl-4'-*O*-(2,2,2-trichloroethoxy)carbonyl-4-*O*-[4,6-*O*-ethylidene-2,3-di-*O*-(2,2,2-trichloroethoxy)carbonyl-β-D-glucopyranosyl]-6,7-demethylenedioxy-6,7-dicarboxyaldehyde-4-epipicropodophyllin (19). A solution of tetraols **18** (211 mg, 0.177 mmol) in benzene (10 mL) was treated with lead tetraacetate (225 mg, 0.507 mmol) at ambient temperature. The reaction mixture was stirred for 25 min, diluted with benzene, filtered, and concentrated. Flash chromatography (cyclohexane/ethyl acetate, 1:1) furnished (+)-**19** (198 mg, quantitative yield): mp 151-153 °C; $[\alpha]_D^{20}$ +15 (*c* 1.03, $CHCl_3$); IR ($CDCl_3$) 2963, 1775, 1704, 1607 cm^{-1}; ^1H NMR (1D + COSY, $CDCl_3$) δ 10.66 (s, 1H, C<u>H</u>O) 10.35 (s, 1H, C<u>H</u>O), 8.00 (s, 1H, H-5), 7.65 (s, 1H, H-8), 6.41 (s, 2H, H-2', H-6'), 5.10-5.01 (m, 4H, H-2", H-3", H-4, $CO_2C\underline{H}_2CCl_3$), 4.90 (s, 2H, $CO_2C\underline{H}_2CCl_3$), 4.86 (d, *J* = 12.2 Hz, 1H, $CO_2C\underline{H}_2CCl_3$), 4.79 (d, *J* = 11.6 Hz, 1H, $CO_2C\underline{H}_2CCl_3$), 4.71 (d, *J* = 11.6 Hz, 1H, $CO_2C\underline{H}_2CCl_3$), 4.70 (q, *J* = 5 Hz, 1H, H-7"), 4.55 (d, *J* = 4.3 Hz, 1H, H-1), 4.47-4.41 (m, 3H, H-11a, H-11b, H-1"), 4.25 (dd, *J* = 10.5, 4.9 Hz, 1H, H-6"eq), 3.79 (s, 6H, OMe), 3.65-3.54 (m, 2H, H-4", H-6"ax), 3.44 (dd, *J* = 10.6, 4.3 Hz, 1H, H-2), 3.38-3.22 (m, 2H, H-3, H-5"), 1.31 (d, *J* = 5 Hz, 3H, CH_3); MS (DCI/NH_3) *m/e* 1140, 1142, 1144, 1146, 1148 $[M + NH_4]^+$.

4'-*O*-Demethyl-4'-*O*-(2,2,2-trichloroethoxy)carbonyl-4-*O*-[4,6-*O*-ethylidene-2,3-di-*O*-(2,2,2-trichloroethoxy)carbonyl-β-D-glucopyranosyl]-4-epipicropodopyridazine (20). A solution of dialdehyde (+)-**19** (192 mg, 0.17 mmol) in dichloromethane (10 mL) and ethanol (10 mL) was cooled to -50 °C, and hydrazine monohydrate (660 μL of a 2.5% v/v solution in ethanol, 0.34 mmol) was added dropwise. The reaction mixture was stirred for 1.5 h at -50 °C, quenched with water, and extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (cyclohexane/ethyl acetate, 1:1) gave (+)-**20** (163 mg, 85% yield): mp 189-191 °C; $[\alpha]_D^{20}$ +45 (*c* 1, $CHCl_3$); IR ($CDCl_3$) 2927, 1778, 1607 cm^{-1}; ^1H NMR (1D + COSY, $CDCl_3$) δ 9.58 (s, 1H, N=C<u>H</u>), 9.52 (s, 1H, N=C-<u>H</u>), 7.97 (s, 1H, H-5), 7.64 (s, 1H, H-8), 6.48 (s, 2H, H-2', H-6'), 5.21 (d, *J* = 4.5 Hz, 1H, H-4), 5.07 (brt, *J* = 9.5 Hz, 1H, H-3"), 5.02 (brt, *J* = 9.5 Hz, 1H, H-2"), 4.91 (s, 3H, $CO_2C\underline{H}_2CCl_3$), 4.81-4.71 (m, 4H, H-7", $CO_2C\underline{H}_2CCl_3$), 4.63 (d, *J* = 5.2 Hz, 1H, H-1), 4.54 (d, *J* = 7.3 Hz, 1H, H-1"), 4.45 (d, *J* = 5.5 Hz, 2H, H-11a, H-11b), 4.24 (dd, *J* = 10.5, 4.9 Hz, 1H, H-6"eq), 3.79 (s, 6H, OMe), 3.67-3.57 (m, 2H, H-4", H-6"ax), 3.53 (dd, *J* = 10.5, 5,2 Hz, 1H, H-2), 3.34 (m, 1H, H-5"), 3.30 (m, 1H, H-3), 1.31 (d, *J* = 5 Hz, 3H, CH_3); MS (DCI/NH_3)*m/e* 1119, 1121, 1123, 1125, 1127 $[M + H]^+$.

4'-*O*-Demethyl-4-*O*-(4,6-*O*-ethylidene-β-D-glucopyranosyl)-4-epipicropodopyridazine (21). A solution of pyridazine (+)-**20** (93.2 mg, 0.076 mmol) in dioxane (1.4 mL) and acetic acid (1 mL) was treated with activated Zn (233 mg, 3.56 mmol), and the resultant solution was heated to 80 °C for 3 h. The reaction mixture was diluted with ethyl acetate, filtered, and concentrated azeotropically with toluene. The crude was partitioned between water and ethyl acetate, and the organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (cyclohexane/acetone, 1:7) afforded (+)-**21** (10 mg, 22% yield) as an amorphous solid: $[\alpha]_D^{20}$ +14 (*c* 0.51, $CHCl_3$); IR ($CDCl_3$) 3649, 3596, 3536, 3296, 2928, 1729, 1618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.50 (s, 1H, N=C<u>H</u>), 9.40 (s, 1H, N=C<u>H</u>), 8.02 (s, 1H, H-5), 7.53 (s, 1H, H-8), 6.47 (s, 2H, H-2', H-6'), 5.60 (brs, 1H, OH), 5.21 (d, *J* = 3.6 Hz, 1H, H-4), 4.73 (q, *J* = 5.0 Hz, 1H, H-7"), 4.67 (d, *J* = 5.4 Hz, 1H, H-1), 4.54 (m, 2H, H-11a, H-11b), 4.17 (m, 2H, H-1", H-6"), 3.84 (s, 7H, OMe, H-1"), 3.70-3.50 (m, 3H, H-2", H-3", H-6"), 3.47 (dd, *J* = 10.3, 5.4 Hz, 1H, H-2), 3.37 (t, *J* = 9.2 Hz, 1H, H-4"), 3.20 (m, 2H, H-3, H-5"), 1.35 (d, *J* = 5 Hz, 3H, CH_3); HRMS (DCI/CH_4) calcd for $C_{30}H_{33}N_2O_{11}$ $[M + H]^+$: 597.2084. Found: 597.2078.

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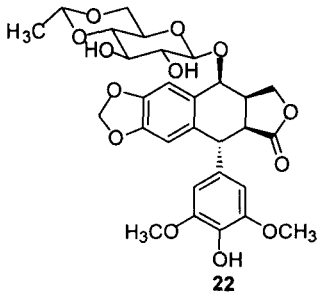
27. With regard to the *in vivo* antitumor activity, compounds **9**, **16**, and **21** were inactive against P388 murine leukemia at the doses tested (40 mg/kg/one shot).
28. Treatment of etoposide **1** with TBAF (1.6 eq.) in THF at 20 °C for 48 h afforded picroetoposide **22** in 87%.



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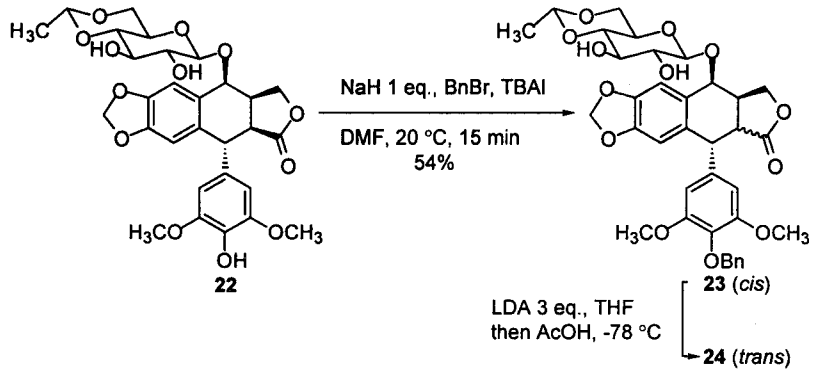
30. When treated with LDA (3 eq.) in THF at -78 °C, 4'-*O*-benzyloxycarbonyl-4'-demethyl etoposide afforded a mixture of uncharacterized compounds as well as the complete disappearance of the benzyloxycarbonyl group.
31. Indeed, brief experimentation indicated that selective benzylation of picroetoposide **22** at 4' was realized (NaH 1 eq., BnBr, TBAI, DMF, 20 °C, 15 min) in 54% yield. Deprotonation of the benzyl derivative **23**, followed by protonation in an identical manner to that of ref. 1, produced approximately a 1:4 ratio of recovered starting material and the desired *trans* lactone isomer **24**. Furthermore, monobenzylation of etoposide **1** with NaH furnished a 1:4 mixture of 4'-*O*-benzyl 4'-*O*-demethyl picroetoposide **23** and 4'-*O*-benzyl-4'-*O*-demethyl etoposide **24** in 70% overall yield.



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