carbinol), 3.05 (m, 1 H, benzyl), 2.25–1.65 (m, 6 H, CH_2), 0.90 and 0.75 (s, 9 H, *t*-Bu), 0.10 (s, 6 H, CH_3).

1-[(*tert*-Butyldimethylsilyl)oxy]-3-(phenylsulfonyl)-5-oxa-*cis*-3-cyclooctene 35. To a vigorously stirred suspension of FeI_2 (Alfa, 401.0 mg, 1.29 mmol) in THF (6.1 mL) at –20 °C was added MeLi (2.30 mL of a 1.69 M solution in ether, 3.89 mmol) slowly. After the mixture was stirred for 15 min, the black ferrate reagent was cooled to –78 °C, a solution of **30** (102.9 mg, 0.261 mmole) in THF (2.0 mL) was added dropwise, and stirring was continued for 20 min. At this time, saturated NH_4Cl (1 mL) was added, and the mixture allowed to warm to room temperature. The organics were extracted into CH_2Cl_2 (3 × 10 mL); washed with saturated $NaHCO_3$ (10 mL) and saturated NaCl (10 mL) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue on silica gel with 30% ethyl acetate/hexane afforded enone **35** as an oil, 65.0 mg, 0.165 mmol, 63% yield: IR 5.84 (C=O), 7.63, 9.00 (sulfone); ^{1}H NMR 7.98 (d of d, 2 H, ortho Ar), 7.75 (t, 1 H, para Ar), 7.70 (d of d, 2 H, meta Ar), 7.22 (d, 1 H, vinyl), 4.52 (m, 1 H, carbinol), 3.35 (d of d, 2 H, O=CCH$_2$C=, J = 18.0 Hz), 2.32 (m, 1 H, CH$_2$C*H*$_2$C=O), 1.85 (m, 4 H, CH_2), 0.87 (s, 9 H, *t*-Bu), 0.05 (s, 6 H, CH_3); ^{13}C NMR: 207.48 (e), 145.11 (o), 138.30 (e), 135.09 (e), 133.75 (o), 129.40 (o), 128.26 (o), 69.36 (o), 41.47 (e), 40.63 (e), 35.64 (e), 25.67 (o), 21.41 (e), 18.09 (e), –4.93 (o), –5.05 (o).

Continued elution afforded **18**, 8.5 mg, 0.0321 mmol, 12% yield, identical (TLC, ^{1}H NMR) with material prepared previously.

***cis*-1,2-Epoxy-5-(methoxymethoxy)-3-(phenylsulfonyl)-3-cyclooctene (38).** To a solution of **28** (92.0 mg, 0.325 mmol), $AgNO_3$ (282.6 mg, 1.66 mmol), and DMF (1.0 mL) was added MOMCl (0.25 mL, 3.29 mmol) dropwise. A white precipitate, presumably AgCl, formed immediately. After 2 h, the mixture was diluted with ether (20 mL) and filtered and the filtrate washed with water (3 × 10 mL) and dried. Evaporation of the solvent and flash chromatography of the residue on silica gel employing a 10–40% ethyl acetate/hexane gradient elution afforded pure **38** as a glass, 105.0 mg, 0.324 mmol, 99% yield: IR 7.63, 8.73 (sulfone); ^{1}H NMR 8.12 (d of d, 2 H, ortho Ar), 7.73 (t, 1 H, para Ar), 7.70 (d of d, 1 H, meta Ar), 7.14 (d, 1 H, vinyl), 4.72 (s, 2 H, OCH_2O), 4.60 (m, 1 H, allylic carbinol), 3.73 (d, 1 H, PhSO$_2$CC*H*O), 3.42 (s, 3 H, CH_3), 3.15 (m, 1 H, CH$_2$C*H*O), 2.18 –1.10 (m, 6 H, CH_2); ^{13}C NMR 145.76 (o) 140.17 (e), 137.02 (e), 133.41 (o), 128.91 (o), 128.43 (o), 95.18 (e), 73.54 (o), 57.07 (o), 55.70 (o), 51.18 (o), 34.26 (e), 27.55 (e), 19.33 (e).

Reaction of 38 with Lithium Dimethylcuprate. The procedure for the reaction of **7** with Me_2CuLi was employed using **38** (33.4 mg, 0.103 mmol) in THF (2.3 mL) at –78 °C for 10 min, to afford 25.5 mg of a mixture of **18** and **39** in a ratio of 9:1 (470-MHz ^{1}H NMR integration).

The regiochemistry of the addition was determined by oxidation of the crude adduct with PCC in CH_2Cl_2, followed by 470-MHz ^{1}H NMR analysis. That the minor vinyl sulfone signal remained as a doublet showed the addition had occurred to the epoxide (to afford **40**), not to the vinyl sulfone.

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Preparation of 2-Substituted Podophyllotoxin Derivatives

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A series of 2-substituted podophyllotoxin derivatives, including 2-methyl-, 2-chloro-, 2-hydroxy-, and 2-bromopodophyllotoxin, were prepared, in order to determine whether nonenolizable podophyllotoxins had enhanced in vivo activity against P388 and L1210 tumor cells. Significant activity against P388 (T/C 156, 40 mg/kg) was observed for 2-chloropodophyllotoxin; under similar conditions, podophyllotoxin was toxic. The corresponding 2-picro isomers were formed as byproducts in the above reactions and were, when tested, inactive against tumors at similar concentrations. An attempt to prepare 2-fluoropodophyllotoxin by reacting podophyllotoxin 4-*O*-THP enolate with $FClO_3$ resulted in a violent explosion, causing serious injury. Extreme caution should be taken when reacting enolates with $FClO_3$.

A number of years ago, Gensler and co-workers[1,2] attempted the preparation of nonenolizable podophyllotoxins of the type 1. (The numbering for podophyllotoxin is that used in ref 7.) The impetus for this work was the earlier observation that podophyllotoxin (**2**) rapidly isomerized to the biologically inactive picropodophyllotoxin (**3**)[3] when exposed to mild base[4] and the suggestion[5] that podophyllotoxin might be inactivated via such an isomerization. However, in 1980 it was shown that the in vitro deactivation of the clinically used anticancer drug Etoposide (**4**) does not occur via epimerization to the cis-fused lactone but via ring opening to the hydroxy acid **5**.[6]

In addition to the initial attempts by Gensler et al.[1] that produced the undesired cis-fused γ-lactone **6**, several other reports have appeared that describe the preparation of derivatives in which the trans-fused lactone of both podophyllotoxin[2] and Etoposide[7] had been replaced by trans-fused furan, thiolane, thiolanyl sulfone, or cyclo-

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(2) Gensler, W. J.; Murthy, C. D.; Trammell, M. H. *J. Med. Chem.* **1977**, *20*, 635.
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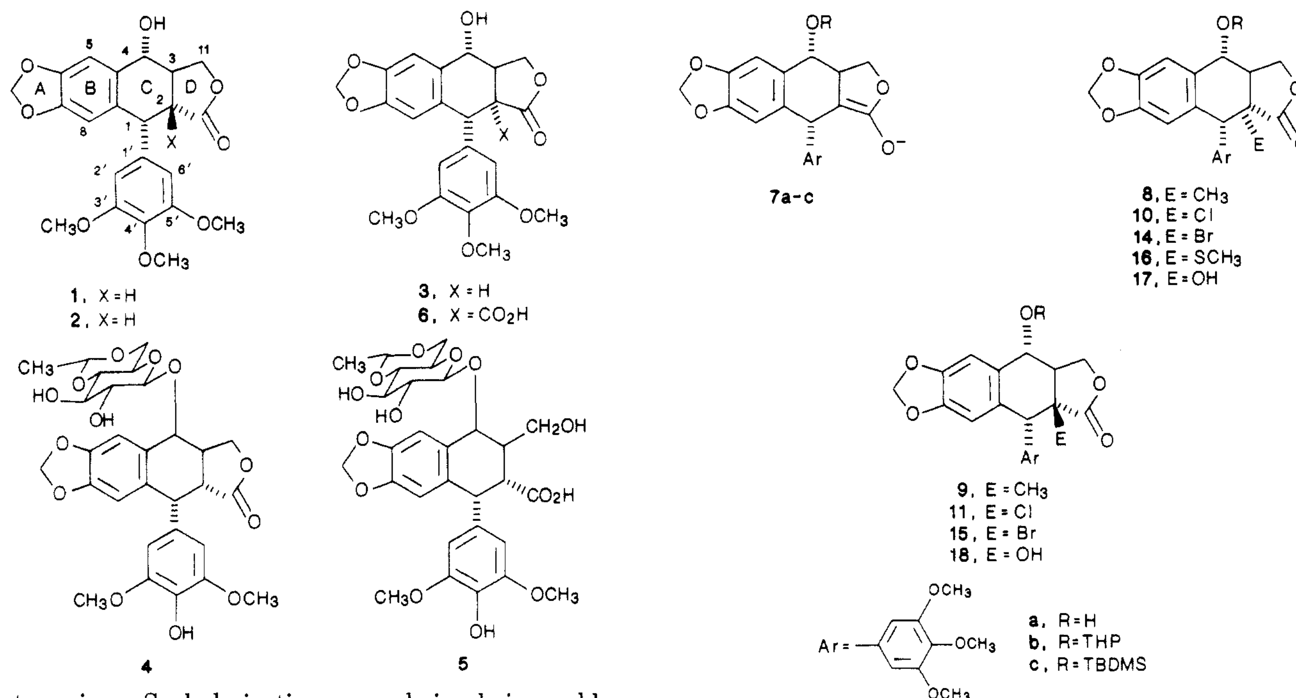

pentane rings. Such derivatives were obviously incapable of isomerizing to the cis-fused analogues of picropodophyllotoxin. All of the compounds in which the lactone ring had been removed, in either the podophyllotoxin or Etoposide series, were considerably less active than the parent compounds.[2,7]

Several years ago,[8] we began a program to prepare a number of podophyllotoxin derivatives in which the trans-fused lactone ring had been retained and isomerization to **3** (X $\neq$ H) via a lactone enolate was no longer possible. We also completed a similar study on both α- and β-peltatins.[9] The results of the latter study will be reported separately.

Discussion and Results

The approach we took was based on the knowledge that the enolate **7**, derived from either podophyllotoxin or picropodophyllotoxin, in which the OH group had previously been protected as a tetrahydropyranyl[10] or *tert*-butyldimethylsilyl ether,[11] gave almost a 1:1 mixture of **2** and **3** of kinetic protonation with acetic acid at low temperature. In contrast, the thermodynamic ratio of podo- to picropodophyllotoxin is >97:3.[4] The significant amount of the less stable trans product produced via kinetic protonation has been explained in terms of a greater accessibility of the proton donor to the α face of the enolate.[10]

Our initial studies involved preparation of the alkoxy enolate **7a** (R = Li) via treatment of podophyllotoxin with 2 equiv of LDA at −78 °C in dry THF. Reaction of this enolate with excess methyl iodide, first at −78 °C and then at room temperature for 18 h, furnished in 71% yield a 3:1 mixture of 2-methylpicropodophyllotoxin (**8a**) and 2-methylpodophyllotoxin (**9a**).[12] In contrast, methylation of the 4-*O*-THP enolate **7b** under similar conditions gave, after exposure to aqueous acid to remove the THP group, 19 and 43% yields of **8a** and **9a**, respectively.

The enolates **7a** and **7b** and the 4-*O*-TBDMS enolate **7c** were also reacted successfully with several other electrophilic reagents, including hexachloroethane, bromine, oxygen, and dimethyl disulfide. The results of these reactions are given in Table I. The structures of the various isomers were determined on the basis of their analytical and MS data and, in particular, by comparison of their high-field NMR spectra with those of podo- and picropodophyllotoxin.[7,13] Two important criteria were used in order to distinguish between podo and picro stereochemistry. The first is based on the difference in the chemical shifts of the aromatic protons and the second on the variations in coupling constants, especially $J_{H_3H_{11}}$ and $J_{H_3H_{11'}}$, seen for podo- and picrophyllotoxin, respectively (Tables II and III).

Typically, in podophyllotoxin and derivatives,[7,13] the two aromatic protons on the (methylenedioxy)benzene (B) ring, H_5 and H_8, are downfield from the two proton singlets due to $H_{2'}$ and $H_{6'}$ of the trimethoxyphenyl ring; for podophyllotoxin, the $H_{2'}H_{6'}$ singlet is at δ 6.37, while H_5 and H_8 occur at δ 7.05 and 6.51, respectively. In contrast, for compounds in the picro series,[7,13] the signal for $H_{2'}H_{6'}$ is slightly downfield from either H_8 or both H_8 and H_5; δ 7.05 (H_5), 6.45 ($H_{2'}H_{6'}$), and 6.38 (H_8) in picropodophyllotoxin itself. These trends were clearly observed for all the 2-substituted derivatives assigned either the podo or picro configuration. The assignments were fully corroborated by comparison of some key coupling constants. Key diagnostic differences in coupling constants between the two epimers are observed for H_3H_{11} and $H_3H_{11'}$. In podophyllotoxin, relatively large values of 9.0 and 8.0 Hz, respectively, are found for these two interactions; these decrease to 6.0 and 1.5 Hz for picropodophyllotoxin. The relative position of H_1 in the podo vs. picro compounds bearing electronegative substituents at C_2 was also in agreement with the assignments.

As can be seen from Tables II and III, the major methylation isomer **8a** obtained from the reaction of the alkoxy enolate **7a** with CH_3I showed H_5, H_8, and $H_{2'}H_{6'}$ at δ 6.76, 6.65, and 6.78, respectively, and gave coupling

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Table I. Preparation of 2-Substituted Podo- and Picropodophyllotoxins

enolate	electrophile	podo, %	picro, %
7a	CH_3I	18	53
7b	CH_3I	43	18
7a	CCl_3–CCl_3	24[a]	32[a]
7b	CCl_3–CCl_3	74	
7c	CCl_3–CCl_3	38	
7b	Br_2	35	21
7b	CBr_4	11	33
7b	$PhSO_2Br$	16	32
7b	CH_3SSCH_3		54
7b	O_2	40	40

[a] After conversion to the 4-*O*-Me_3Si derivative.

Table II. Aromatic Proton Chemical Shifts in Podo- and Picropodophyllotoxins

compound	chemical shift, δ H_5	H_7	$H_{2'}H_{6'}$
podophyllotoxin (2)	7.05	6.51	6.37
2-methyl- (**9a**)	7.10	6.48	6.36
2-chloro- (**11a**)	7.09	6.49	6.44
2-chloro-4-*O*-Me_3Si-	6.93	6.49	6.41
2-chloro-4-*O*-TBDMS- (**11c**)	6.94	6.50	6.42
2-bromo- (**15a**)	7.10	6.52	6.42
picropodophyllotoxin (3)	7.05	6.38	6.45
2-methyl- (**8a**)	6.76	6.65	6.78
2-chloro- (**10a**)	6.75	6.61	6.77
2-chloro-4-*O*-Me_3Si- (**12**)	6.65	6.55	6.72
2-bromo- (**14a**)	6.72	6.61	6.81
2-(methylthio)- (**16b**)	6.75	6.72	6.91

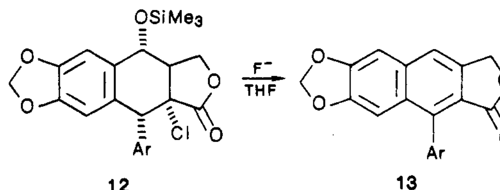
Table III. Coupling Constants (Hertz) in 2-Substituted Podo- and Picropodophyllotoxins

compd	$J_{H_3H_{11'}}$	$J_{H_3H_{11}}$	$J_{H_3H_4}$
2	8.0	9.0	9.1
9a	7.5	10.5	11.0
9c	7.2	11.1	10.4
11a	7.0	9.0	9.5
11c	6.9	10.0	8.8
15a	6.8	9.6	9.0
3	1.5	6.0	8.3
8a	1.4	6.0	7.8
10a	4.6	~0	3.0
12	4.6	~0	2.8
14a	4.8	~0	2.8
16b	4.7	~0	2.6

constants equal to 1.4 and 6.0 Hz for $H_3H_{11'}$ and H_3H_{11}. Thus, **8a** was assigned to the picro series. In contrast, the minor isomer obtained from this reaction showed the three aromatic hydrogen singlets at δ 7.10 (H_5), 6.48 (H_8), and 6.36 ($H_{2'}H_{6'}$). This, together with the 10.5- and 7.5-Hz coupling constants for H_3H_{11} and $H_3H_{11'}$, allowed us to assign to **9a** the podo stereochemistry.

A similar pattern emerged for the 2-chloro derivatives. 2-Chloropodophyllotoxin (**11a**) was obtained as the exclusive product in 74% isolated yield upon treatment of the 4-*O*-THP enolate **7b** with hexachloroethane, followed by hydrolysis of the THP group. The same product could be obtained in 38% yield as its TBDMS ether **11c** after similar chlorination of the enolate **7c**. Compound **11a** showed aromatic peaks at δ 7.09, 6.49, and 6.44 in a 1:1:2 ratio assignable to H_5, H_8, and $H_{2'}$ and $H_{6'}$, respectively. The H_3H_{11} and $H_3H_{11'}$ coupling constants were 9.0 and 7.0 Hz and thus similar to those found for the same protons in podophyllotoxin.

Chlorination of the alkoxy enolate **7a** afforded an inseparable 2:3 mixture of the 2-chloro epimers **10a** and **11a** in 80% yield. These isomers were separated as their trimethylsilyl derivatives and then regenerated by hydrolysis in acetic acid. Desilylation of 2-chloro-4-*O*-(trimethylsilyl)picropodophyllotoxin (**12**) with tetra-*n*-butylammonium fluoride in THF did not lead to **10** but rather to the aromatized lignan lactone **13**, mp 265–268 °C (lit.[14] mp 267–268 °C).



Both **10a** and **12** showed the typical picro aromatic pattern in which the $H_{2'}H_{6'}$ is at lower field than H_8 and/or H_5: δ 6.77 (2 H), 6.75 (1 H), and 6.61 (1 H) for **10a**. The picro stereochemistry places the 2-chloro group anti to H_1 and thus accounts for the ease of aromatization of **12** to **13**, presumably by successive elimination of HCl and H_2O on attempted desilylation of **12** with F^-.

The NMR spectra of **10a** and **12** showed that one of the two H_3H_{11} or $H_3H_{11'}$ coupling constants was very small (not measurable), with the other being near 4.6 Hz (see below). An additional surprising feature for these two compounds and the 2-bromo- or 2-(methylthiopicropodophyllotoxins (see Table III) is the observation of a 2.8-Hz H_3H_4 coupling constant. This is substantially smaller than that observed for picropodophyllotoxin (8.3 Hz) or for the 2-methyl derivative **8a** and suggests that electronegative substituents at C_2 induce a conformational change in ring C when compared to the parent compound **3**.

The 8.3-Hz coupling constant for H_3H_4 in **3** is in agreement with a boat conformation for ring C in which the 1- and 4-substituents both occupy the equatorial positions,[13,15] while the 2–3-Hz coupling constants found for **10a**, **12**, **14a**, and **16b** point to the alternate conformation that places both the C_1-aryl and C_4-substituent axially. Inspection of Dreiding models of such a conformation suggests that H_{11} but not $H_{11'}$ could have a 90° dihedral angle with the C–H_3 bond, thus resulting in a small *J* value.

Brewer and co-workers[13] suggested that the small amount of inhibition of microtubule assembly remaining in picropodophyllotoxin relative to podophyllotoxin is due to the presence of a small amount of an active conformer, one in which the trimethoxyaryl ring, the E ring, occupies a quasi-axial conformation. This places this ring in the same relative orientation as that found in podophyllotoxin. The major conformations indicated for **10a**, **12**, **14a**, and **16a** by their NMR spectra put the E ring in the desirable quasi-axial conformation, and thus, it may be of interest to test and compare the effects of these compounds on microtubule assembly.

The downfield shift of H_1, δ 4.51 vs. 4.79, on going from 2-chloropicro- to 2-chloropodophyllotoxin is expected since in the latter case H_1 is cis to the chlorine atom at C_2 but trans to the neighboring Cl in the picro series. A similar shift from δ 4.55 to 4.91 was noted on going from the 2-bromo picro derivative **14a** to the isomeric podo compound **15a**.

The 4-*O*-THP enolate was reacted at −78 °C with Br_2 and yielded after plate chromatography 35% of the 2-bromo-4-*O*-tetrahydropyranylpodo- (**15b**) and 21% of 2-

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bromo-4-*O*-tetrahydropyranylpicropodophyllotoxin (**14b**). When carbon tetrabromide was used as brominating agent, the yields of the above compounds were 11 and 33% respectively, while benzenesulfonyl bromide produced 11% of podo and 32% picro in addition to 40% of recovered nonbrominated starting material. The 4-*O*-THP group was hydrolyzed after isomer separation to give 2-bromopodophyllotoxin (**14a**), mp 89–93 °C, and 2-bromopicropodophyllotoxin (**15a**), (mp 93–98 °C. The structure assignments were made on the same basis as that for the two chloro derivatives with the aromatic protons for **15a** occurring at δ 7.10 (1 H), 6.52 (1 H), and 6.42 (2 H) and at δ 6.72 (1 H), 6.61 (1 H), and 6.82 (2 H) for **14a** (Tables II and III).

Surprisingly, reaction of **7b** with dimethyl disulfide gave in 54% yield the picro derivative **16b**, mp 77–78 °C, as the only isolable product. ^{1}H NMR showed aromatic H's at δ 6.91 (2 H), 6.75 (1 H), and 6.72 (1 H), SCH_3 at δ 2.01, and H_1 at δ 4.40; $J_{H_3H_{11'}}$ = 4.7 Hz and $J_{H_3H_4}$ = 2.6 Hz. Similar data were found for the deprotected compound **16a**. Finally, oxygenation of **7b** gave in 64% yield an inseparable mixture of the 2-hydroxy substitution products **17a** and **18a** after removal of the 4-*O*-THP group.

In general, on the basis of the above examples, it can be concluded that reaction of the alkoxy enolate **7a** with electrophiles leads to a larger amount of 2-substituted picro products than are obtained from either the 4-*O*-THP enolate **7b** or the 4-*O*-tBDMS enolate **7c**. Inspection of models of the relatively rigid enolate shows that the 4-alkoxy group is suitably placed to aid in the delivery of the electrophile from the β face, thus resulting in an increase in the picro to podo ratio when compared with the enolates **7b** and **7c** in which the alkoxy group is protected. For these compounds, attack of the electrophile via the more open α face of the enolate seems to be preferred.[10]

Biological Screening. Several of the 2-substituted podo and picro derivatives were tested against leukemia P388 by the Antitumor Division of Bristol Laboratories, Syracuse, NY, using their general testing protocol.[16] The methyl derivatives **8a** and **9a**, 2-chloropodophyllotoxin (**11a**), and the mixture of the 2-hydroxy derivatives **17** and **18** were also tested against leukemia L1210.

The two methyl substitution products were both inactive in either the L1210 or P388 screens, giving T/C 90–100 at dosages ranging from 5 to 120 mg/kg. The 2-SCH_3 picro derivative also showed no activity. The mixture of the two hydroxy compounds **17a** and **18a** was toxic to at least 50% of the test mice at >40 mg/kg dosages. When 20 or 10 mg/kg dosages were administered, no significant increase in the mean survival time was observed. Podophyllotoxin itself is toxic at dosages of 30 mg/kg or above; lower dosages were nontoxic but did not show any significant increase in mean survival times. Finally, 2-chloropodophyllotoxin was found to have significant activity against P388, giving T/C 156 (40 mg/kg) and 122 (20 mg/kg). The bromo derivatives were not tested. The significant activity and lower toxicity of 2-chloropodophyllotoxin as compared to podophyllotoxin has prompted us to attempt the preparation of the 2-chloro derivative of Etoposide. The results will be published when available.

The activity found in 2-chloropodophyllotoxin suggested the possibility that 2-fluoropodophyllotoxin might also be active. An attempt to prepare this compound by treatment of the enolate **7b** with perchloryl fluoride led to a violent explosion, causing serious injury. We urge extreme caution in the use of $FClO_3$ in the fluorination of enolates.

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Experimental Section

NMR spectra were recorded in $CDCl_3$–1% Me_4Si solutions of Varian XL 300 and T-60 spectrometers. MS data were obtained with a VG 7070 mass spectrometer. Melting points are uncorrected. Typical workup refers to partitioning the reaction mixture between water and CH_2Cl_2 and separating and drying the organic phase, followed by evaporation of the solvents.

Reaction of Alkoxy Enolate 7a with CH_3I. Enolate **7a** was prepared by addition of 207 mg (0.5 mmol) of podophyllotoxin (**2**) dissolved in 1 mL of dry THF to a –78 °C solution of 1.0 mmol of LDA [prepared from diisopropylamine and *n*-BuLi (2.5 M in hexane)] in 5 mL of THF. To the yellow solution was added 0.25 mL (excess) of methyl iodide. The solution was warmed to room temperature and stirred for 18 h. Typical workup followed by silica gel column chromatography yielded 112 mg (53%) of **8a** and 40 mg (18%) of **9a**.

Compound **8a**: mp 92–95 °C; IR 1785, 3300–3550 cm^{-1}; MS, *m/e* 428 (M^+) (calcd 428); ^{1}H NMR δ 1.12 (s, 3 H), 2.79 (ddd, *J* = 7.8, 6.0, 1.4 Hz, 1 H), 3.79 (s, 6 H), 3.80 (s, 3 H), 4.23 (s, 1 H), 4.57 (d, *J* = 7.8 Hz, 1 H), 4.42 (m, 2 H), 5.94 (d, *J* = 0.5 Hz, 1 H), 5.96 (d, *J* = 0.5 Hz, 1 H), 6.65 (s, 1 H), 6.76 (s, 1 H), 6.78 (s, 2 H). Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.23; H, 5.84.

The less polar podo isomer **9a**: mp 101–103 °C; MS, M^+ *m/e* 428 (calcd 428); IR (γ-lactone carbonyl) 1780 cm^{-1}; ^{1}H NMR δ 1.32 (s, 3 H), 2.89 (ddd, 7.5, 10.5, 11.0 Hz, 1 H), 3.75 (s, 6 H), 3.81 (s, 3 H), 4.17 (dd, *J* = 9.0, 10.5 Hz, 1 H), 4.26 (s, 1 H), 4.51 (dd, *J* = 7.5, 9.0 Hz, 1 H) 4.70 (d, *J* = 11.0 Hz, 1 H), 5.97 (d, *J* = 0.5 Hz, 1 H), 5.98 (d, *J* = 0.5 Hz, 1 H), 6.36 (s, 2 H), 6.48 (s, 1 H), 7.10 (s, 1 H). Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.39; H, 5.61.

Reaction of Alkoxy Enolate 7a with CCl_3–CCl_3. Enolate **7a** (0.5 mmol) prepared as above was reacted with 500 mg (~2 mmol) of CCl_3–CCl_3 at –78 °C for 30 min and then at 0 °C for 1 h. Typical workup afforded 180 mg (80%) of a beige powder, which was shown to be an inseparable mixture of **10a** and **11a**. This mixture (153 mg, 0.34 mmol) was combined with 67 mg (0.85 mmol) of pyridine and 82 mg (0.74 mmol) of trimethylsilyl chloride in 10 mL of CH_2Cl_2 for 3 h. Workup followed by plate chromatography gave, after three developments, two components: 4-*O*-(trimethylsilyl)-2-chloropodophyllotoxin (20 mg, 24%) and 4-*O*-(trimethylsilyl)-2-chloropicropodophyllotoxin (34 mg, 32%) as clear colorless oils. The former compound showed the following: MS, *m/e* 520 (M^+) and 522 (M^+ + 2); ^{1}H NMR δ 0.26 (s, 9 H), 3.12 (ddd, *J* = 9.9, 9.1, 7.1 Hz, 1 H), 3.75 (s, 6 H)8 3.80 (s, 3 H), 4.29 (dd, *J* = 9.9, 8.6 Hz, 1 H), 4.38 (dd, *J* = 8.6, 7.1 Hz, 1 H), 4.75 (s, 1 H), 4.96 (d, *J* = 9.1 Hz, 1 H), 5.97 (s, 1 H), 5.98 (s, 1 H), 6.41 (s, 2 H), 6.49 (s, 1 H), 6.93 (s, 1 H). The latter more polar isomer showed the following: MS, *m/e* 520 (M^+) and (M^+ + 2); ^{1}H NMR δ 0.27 (s, 9 H), 3.01 (d, *J* = 9.3 Hz), 4.43 (s, 1 H), 4.80 (dd, *J* = 9.3, 4.6 Hz, 1 H), 4.85 (d, *J* = 2.8 Hz, 1 H), 5.91 (s, 1 H), 5.92 (s, 1 H), 6.55 (s, 1 H), 6.65 (s, 1 H), 6.72 (s, 2 H).

The above 4-*O*-Me_3Si derivatives were desilylated in 4:1 acetic acid–H_2O at room temperature to afford compounds **11a** and **10a** in 84 and 73% yields, respectively. The 2-chloro podo derivative thus obtained was identical with that obtained via chlorination of the enolate **7b** followed by hydrolysis. Picro compound **10a**: mp 99–104 °C; ^{1}H NMR δ 2.30 (br s, 1 H), 3.17 (dd, *J* = 4.6, 3.0 Hz, 1 H), 3.83 (s, 9 H), 4.49 (d, *J* = 9.3 Hz, 1 H), 4.51 (s, 1 H), 4.84 (dd, *J* = 9.3, 4.6 Hz, 1 H), 4.90 (br s, 1 H), 5.93 (s, 1 H), 5.94 (s, 1 H), 6.61 (s, 1 H), 6.75 (s, 1 H) 6.77 (s, 2 H). Anal. Calcd for $C_{22}H_{21}ClO_8$: C, 58.86; H, 4.72. Found: C, 58.72; H, 4.91.

Attempted desilylation of the 2-chloro picro derivative **12** with TBAF in dry THF at room temperature for 1 h afforded in 51% yield the naphthalene lignan lactone **13**.

Reactions of 4-*O*-THP Enolate 7b. (i) With CH_3I. The tetrahydropyranyl ether of podophyllotoxin was prepared in 85% yield according to Gensler.[10] This compound (400 mg, 0.8 mmol) was dissolved in 1 mL of dry THF and added to a –78 °C solution of 0.84 mmol of LDA in 10 mL of THF. The reaction mixture was stirred for 10 min and then treated with 0.5 mL (excess) of CH_3I. The solution was allowed to warm to room temperature and kept for a further 18 h. The usual workup afforded the crude methylation product, which was refluxed in 10 mL of 5% HCl–

THF (1:9) for 4 h. Workup afforded a yellow foam from which 20 mg (6%) of picropodophyllotoxin, 60 mg (18%) of **8a**, and 145 mg (43%) of **9a** could be isolated via column chromatography. All compounds gave NMR spectra identical with those isolated earlier.

(ii) With CCl_3–CCl_3. To 0.5 mmol of enolate **7b** prepared as above was added 178 mg (0.74 mmol) of hexachloroethane. The reaction mixture was allowed to warm slowly to room temperature and stirred for a further 18 h. Workup, followed by hydrolysis of the 4-*O*-THP group as in the case of the 2-methyl derivatives above, afforded after column chromatography 164 mg (74%) of **11a**: mp 106–110 °C; IR 3300–3350 (br), 1785 (s) cm^{-1}; ^1H NMR 2.79 (d, J = 7.0 Hz, 1 H), 3.07 (ddd, J = 7.0, 9.0, 9.5 Hz, 1 H), 3.77 (s, 6 H), 3.84 (s, 3 H), 4.26–4.65 (m, 2 H), 4.79 (s, 1 H), 4.98 (dd, J = 7.0, 9.5 Hz, 1 H), 5.97 (d, J = 0.5 Hz, 1 H), 5.99 (s, J = 0.5 Hz, 1 H), 6.44 (s, 2 H), 6.49 (s, 1 H), 7.09 (s, 1 H); MS, *m/e* 448 (M^+), 450 (M^+ + 2). Anal. Calcd for $C_{22}H_{21}ClO_8$: C, 58.86; H, 4.72. Found: C, 59.03; H, 4.98.

(iii) With Br_2. Enolate **7b** in THF at −78 °C prepared from 1 mmol of 4-*O*-tetrahydropyranylpodophyllotoxin as above was reacted with 1.2 mmol of Br_2 at −78 °C for 15 min and then at room temperature for 15 min. The usual workup followed by plate chromatography (ethyl acetate–hexanes, 1:3) afforded **15b** [201 mg, 35%; mp 86–89 °C] and **14b** [124 mg, 21%; mp 82–85 °C] as their THP derivatives.

(iv) With Carbon Tetrabromide. Enolate **7b** (0.40 mmol) prepared as above was allowed to react with CBr_4 for 2.5 days at room temperature. Usual workup, followed by plate chromatography, afforded 26 mg (11%) of the THP derivative of **14** and 76 mg (33%) of the THP derivative of **15**.

(v) With Benzenesulfonyl Bromide. Enolate **7b** (0.5 mmol) in THF at −78 °C was reacted with 0.5 mmol of $PhSO_2Br$ for 15 min at −78 °C and then for 2 h at room temperature. Workup, followed by plate and chromatography, gave 47 mg (16%) of **14** (THP), 93 mg (32%) of **15** (THP), and 101 mg of recovered podophyllotoxin THP.

Hydrolysis of 2-Bromo-4-*O*-tetrahydropyranylpodophyllotoxin. The THP derivative (82 mg) was hydrolyzed by refluxing it in 10 mL of 10% HCl–THF (1:9) for 2 h. Usual workup, followed by preparative TLC, afforded 38 mg (51%) of 2-bromopodophyllotoxin (**15a**) as a beige powder: mp 89–93 °C; ^1H NMR δ 2.43 (d, J = 7.0 Hz, 1 H), ddd, J = 9.6, 9.0, 6.8 Hz, 1 H), 3.75 (s, 6 H), 3.81 (s, 3 H), 4.25 (dd, J = 9.6, 8.8 Hz, 1 H), 4.56 (dd, J = 8.8, 6.8 Hz, 1 H), 4.91 (s, 1 H), 4.92 (dd, J = 9.0, 7.0 H z, 1 H), 5.99 (d, J = 0.5 Hz, 1 H), 6.01 (d, J = 0.5 Hz, 1 H), 6.42 (s, 2 H), 6.52 (s, 1 H), 7.10 (s, 1 H). Anal. Calcd for $C_{22}H_{21}BrO_8$: C, 53.47; H, 4.29. Found: C, 53.85; H, 4.41.

Hydrolysis of 2-Bromo-4-*O*-tetrahydropyranylpicropodophyllotoxin. Hydrolysis of the THP was carried out as above to yield 60% of 2-bromopicropodophyllotoxin (**14a**), mp 93–98 °C dec, as a beige powder: ^1H NMR δ 2.57 (br s, OH), 3.22 (dd, J = 4.8, 2.4 Hz, 1 H), 3.83 (s, 9 H), 4.47 (d, J = 9.4 Hz, 1 H), 4.55 (s, 1 H), 4.81 (dd, J = 9.4, 4.8 Hz, 1 H), 4.94 (br s, 1 H), 5.91 (d, J = 0.5, 1 H), 5.93 (d, J = 0.5 Hz, 1 H), 6.61 (s, 1 H), 6.72 (s, 1 H), 6.81 (s, 2 H); MS, *m/e* 394 (M^+ − HBr − H_2O). Anal. Calcd for $C_{22}H_{21}O_8Br$: C, 53.53; H, 4.29. Found: C, 53.82; H, 5.67. The compound has limited thermal stability.

(vi) With Dimethyl Disulfide. To enolate **7b** (1.00 mmol) in 5 mL of THF at −78 °C was added an excess (1 mL) of dimethyl disulfide. The solution was stirred at −78 °C for 2 h, allowed to warm to room temperature, and stirred for a further 2 h. Normal workup, followed by chromatography, afforded 295 mg (54%) of the 4-*O*-THP ether of 2-(methylthio)picropodophyllotoxin: mp 72–75 °C; MS, *m/e* 544 (M^+) (calcd 544).

Hydrolysis of the above product (99 mg, 0.18 mmol) in 10 mL of 5% HCl–THF (1:9) at reflux for 1 h afforded after workup and chromatography 58 mg (70%) of **16** as a beige solid: mp 97–101 °C; ^1H NMR δ 2.01 (s, 3 H), 2.12 (d, J = 5.0 Hz, 1 H), 2.88 (dd, J = 4.6, 2.6 Hz, 1 H), 3.84 (s, 9 H), 4.37 (d, J = 10.0 Hz, 1 H), 4.40 (s, 1 H), 4.83–4.85 (m, 2 H), 5.91 (s, 1 H), 5.93 (s, 1 H), 6.72 (s, 1 H), 6.75 (s, 1 H), 6.91 (s, 2 H) ; MS *m/e* 460 (M^+ (calcd 460), exact mass calcd 460.1192, found 460.1188.

(vii) With Oxygen. Dry oxygen was bubbled through 1 mmol of enolate **7b** in 10 mL of THF at −78 °C. The solution was warmed to room temperature, and workup was carried out in the usual manner to afford a yellowish foam, which was purified by chromatography to yield 350 mg (80%) of a 1:1 mixture of **17** and **18** as a colorless powder: IR 3300–3350 (br), 1775 (s) cm^{-1}; ^1H NMR δ 2.60–3.33 (m, 2 H), 3.74 and 3.74 (2 s, 6 H), 3.83 and 3.87 (2 s, 3 H), 4.25 (m, 3 H), 5.96 (br s, 2 H), 6.38 and 6.46 (2 s, 2 H), 6.34 and 6.49 (2 s, 1 H), 7.04 and 7.10 (2 s, 1 H); MS, *m/e* 430 (M^+). Anal. Calcd for $C_{22}H_{22}O_9$: C, 61.53; H, 4.93. Found: C, 61.59; H, 5.08.

Preparation of 4-*O*-(*tert*-Butyldimethylsilyl)picropodophyllotoxin. Podophyllotoxin was converted to picropodophyllotoxin in 79% yield by heating with sodium acetate in aqueous ethanol for 18 h.[11] The product thus obtained was dissolved in dry DMF (7 mL/g) containing 2 equiv each of imidazole and *tert*-butyldimethylsilyl chloride. This solution was heated for 3 h, cooled to room temperature, and stored overnight. Workup afforded the desired product in 90% yield after recrystallization from CH_2Cl_2–hexane.

Preparation of Enolate 7c and Reaction with CH_3I. 4-*O*-(*tert*-Butyldimethylsilyl)picropodophyllotoxin (206 mg, 0.39 mmol) was added to 5 mL of dry THF at −78 °C containing 0.39 mmol of LDA. After 15 min, excess (1 mL) of CH_3I was added, and the solution was stirred for a further 15 min at −78 °C followed by warming to room temperature. The crude product obtained after normal workup was separated by plate chromatography into two components, the podo derivative **9c** (66 mg, 31%) and the picro compound **8c** (67 mg, 32%).

Compound **9c**: mp 44–48 °C; ^1H NMR δ 0.11 (s, 3 H), 0.30 (s, 3 H), 0.94 (s, 9 H), 1.31 (s, 3 H), 3.02 (ddd, J = 11.1, 10.4, 7.2 Hz, 1 H), 3.74 (s, 6 H), 3.81 (s, 3 H), 4.08 (dd, J = 11.1, 8.2 Hz, 1 H), 4.24 (s, 1 H), 4.42 (dd, J = 8.2, 7.2 Hz, 1 H), 4.71 (d, J = 10.4 Hz, 1 H), 5.95 (d, J = 1.2 Hz, 1 H), 5.97 (d, J = 1.2 Hz, 1 H), 6.37 (s, 2 H), 6.46 (s, 1 H), 6.92 (s, 1 H). Desilylation of **9c** afforded **9a**, identical with the sample prepared from **7b** and CH_3I followed by hydrolysis.

Picro derivative **8c**: mp 55–59 °C; ^1H NMR δ 0.19 (s, 3 H), 0.22 (s, 3 H), 0.96 (s, 9 H), 1.14 (s, 3 H), 2.53 (ddd, J = 6.4, 5.3, 4.1 Hz, 1 H), 3.82 (s, 6 H), 3.85 (s, 3 H), 4.10 (s, 1 H), 4.23 (dd, J = 9.9, 4.1 Hz, 1 H), 4.48 (dd, J = 9.9, 6.4 Hz, 1 H), 4.68 (d, J = 5.3 Hz, 1 H), 5.91 (J = 1.2 Hz, 1 H), 5.93 (d, J = 1.2 Hz, 1 H), 6.52 (s, 1 H), 6.56 (s, 2 H), 6.80 (s, 1 H); MS, *m/e* calcd (M^+) 542, found 542.

Reaction of Enolate 7c with Hexachloroethane. Enolate **7c** (0.39 mmol) prepared in THF at −78 °C in the usual manner was allowed to react with excess hexachloroethane (0.79 g) for 15 min at −78 °C and then for 18 h at room temperature. Workup followed by plate chromatography, afforded 83 mg (38%) of 2-chloro-4-*O*-(*tert*-butyldimethylsilyl)podophyllotoxin (**11c**): ^1H NMR δ 0.13 (s, 3 H), 0.33 (s, 3 H), 0.94 (s, 9 H), 3.14 (ddd, J = 10.0, 8.8, 6.9 Hz, 1 H), 3.74 (s, 6 H), 3.81 (s, 3 H), 4.29 (dd, J = 10.0, 8.3 Hz, 1 H), 4.50 (dd, J = 8.3, 6.9 Hz, 1 H), 4.74 (s, 1 H), 4.95 (d, J = 8.8 Hz, 1 H), 5.97 (d, J = 1.3 Hz, 1 H) 6.00 (d, J = 1.3 Hz, 1 H), 6.42 (s, 2 H), 6.50 (s, 1 H), 6.94 (s, 1 H). The compound was desilylated to **11a**.

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