Articles

Comprehensive Synthetic Route to Eight Diastereomeric *Podophyllum* Lignans

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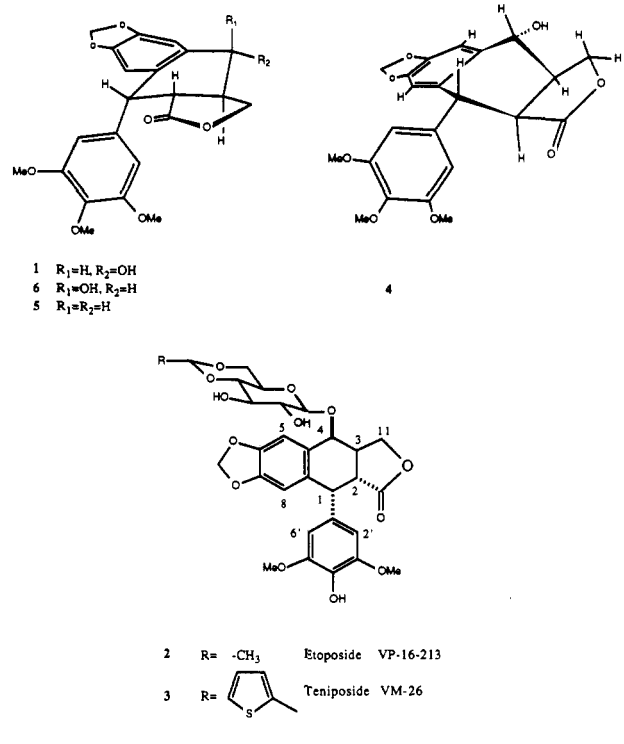
An oxabicyclo compound, **9**, prepared in 47% yield through an isobenzofuran intermediate was converted with excellent regio- and stereocontrol to eight (±)-lignan lactones of the podophyllotoxin series. One of the eight, epiisopicropodophyllin, **36**, the 1,2,3,4-cis isomer, previously unknown, was prepared as its methyl ether, **37**. A comparative study of the ^1H NMR spectra of all eight lactones aided by an X-ray crystal structure of a 2,3-cis lactone, **38**, was used to provide information about the conformations and configurations of these compounds. The abundance of the $[M - H_2O]$ ion in the mass spectra of these lactones is useful in assigning the relative configurations at C-1 and C-3. An unexpected hydrogenation of a benzene ring of a synthetic intermediate by Raney nickel was encountered, and the product was identified by X-ray crystallography.

The aryltetralin lignan lactones isolated from various species of *Podophyllum* (May Apple, American Mandrake) have captured the attention of organic and medicinal chemists for many years.[1] The use of aqueous extracts of these plants in indigenous medicine by North American and Himalayan peoples foreshadowed the discovery in 1946 of the antimitotic properties of podophyllotoxin **1**, the main active constituent, and the development of two semisynthetic drugs etoposide[2] (VP-16-213), **2**, and Teniposide[3] (VM-26), **3**, valuable in cancer chemotherapy today.

Synthetic organic chemists have been attracted to podophyllotoxin for the stereochemical challenge represented by its four contiguous chiral centers, rigid trans lactone and axially locked 1-aryl substituent. The problem is accentuated by facile epimerisation at C-2 to the more stable, flexible cis-lactone picropodophyllin **4**, with even the slightest trace of base. The 1-axial 2,3-trans stereochemistry is essential[4,5] for antimitotic activity, and this fact became another powerful spur for synthetic activity in this area. The early syntheses[6-8] generated much new and interesting chemistry but led to the inactive cis-lactone picropodophyllin **4**, which must be subjected to a rather inefficient C-2 enolate kinetic quenching procedure to obtain some podophyllotoxin. Other syntheses[9-13] elegantly designed to avoid this thermodynamic trap have been devised, and an asymmetric synthesis of (−)-podophyllotoxin has also appeared.[14] Our original researches on the subject disclosed in two brief communications[15,16] delineated a route to (±)-deoxypodophyllotoxin, **5**, (±)-podophyllotoxin, **1**, and (±)-epipodophyllotoxin, **6**. We now provide full details of that work and report its extension to the synthesis of eight enantiomeric pairs of such lignan lactones with virtually complete control of relative stereochemistry.



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(6) Gensler, W. J.; Gatsonis, C. D. *J. Org. Chem.* **1966**, *31*, 4004–4008.
(7) Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 7082–7083. Kende, A. S.; King, M. L.; Curran, D. P. *J. Org. Chem.* **1981**, *46*, 2826–2828.
(8) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, *1*, 271–276.
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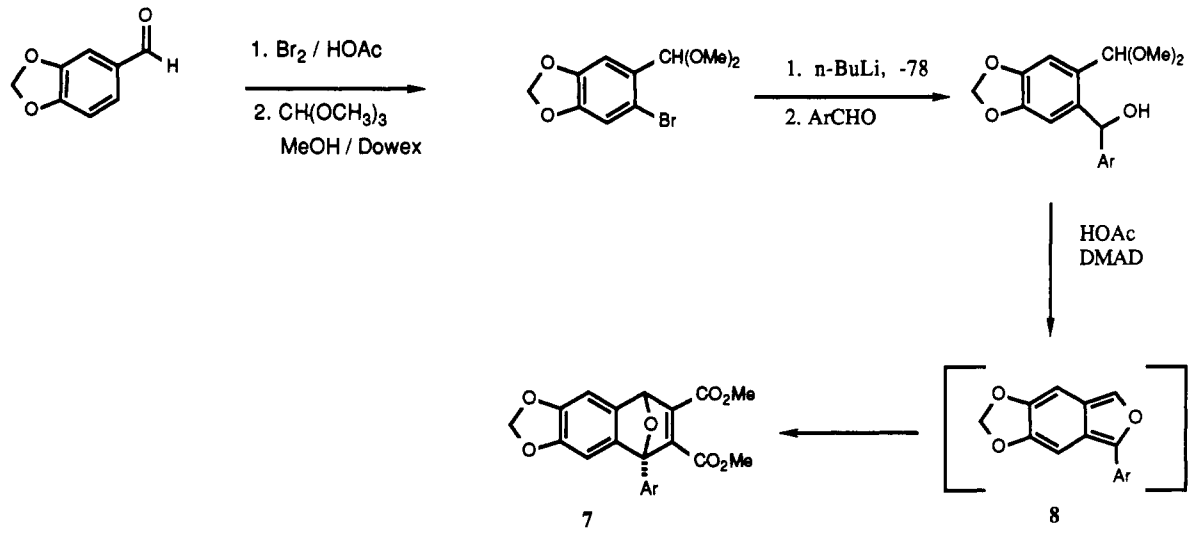
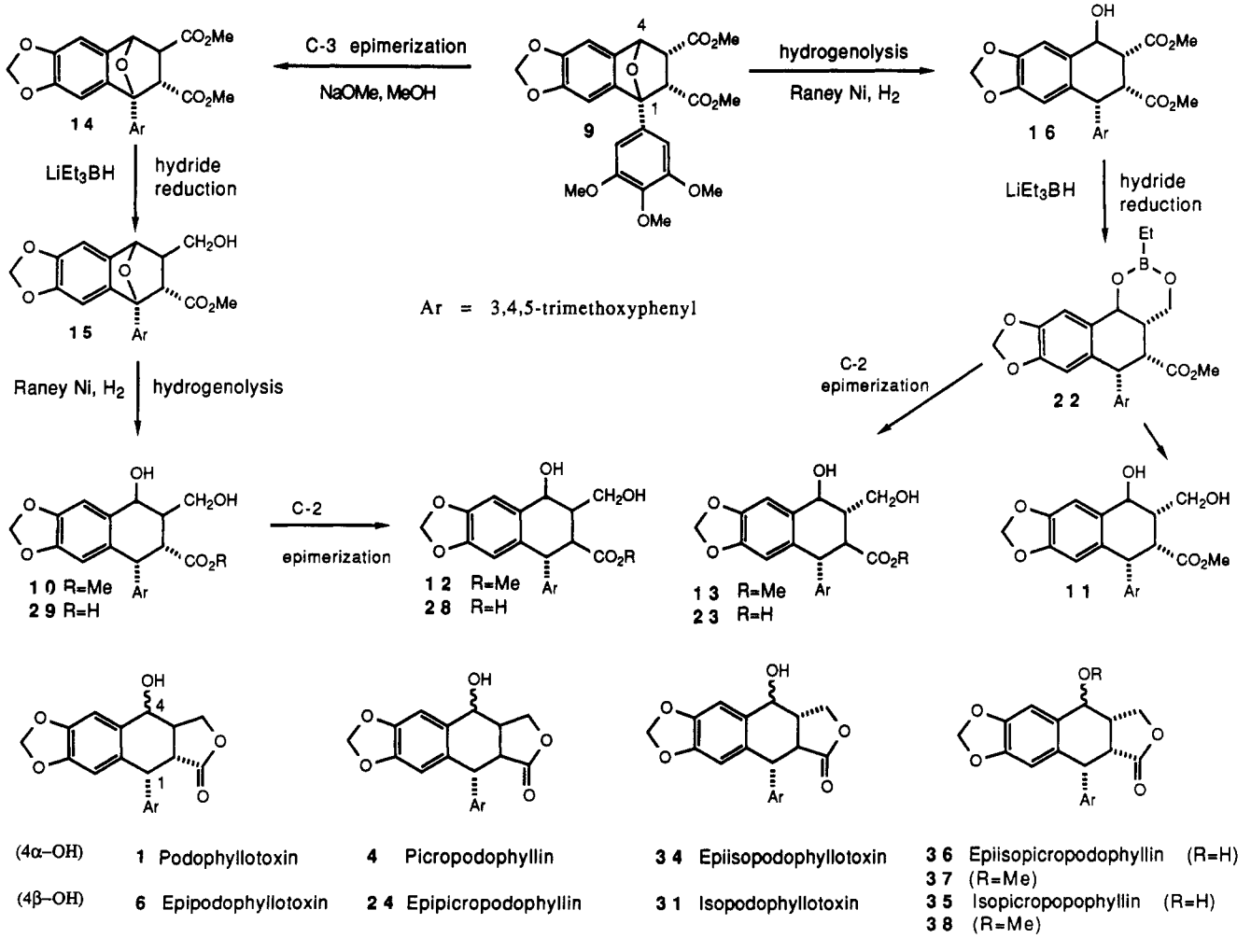
Scheme I



Scheme II



The oxabicyclo adduct **7**, containing all the required carbon and oxygen atoms, was prepared from piperonal in 47% overall yield through the isobenzofuran 8[17,18] as outlined in Scheme I and hydrogenated to the endo diester **9** quantitatively. The 1,4-oxygen bridge of this compound fixes the configuration at these two centers and permits

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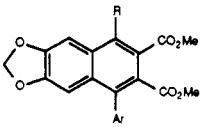
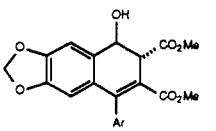
the relative stereochemistry at C-3 to be manipulated by selective epimerization at this site. Hydride reduction of the C-3 ester and Raney nickel hydrogenolysis of the oxygen bridge at C-1 with retention of stereochemistry lead from **9** to either of the epimeric tetralins **10** or **11** at will. Since epimerization at C-2, an enolizable center, is possible in principle, the diastereomers **10–13**, each related to a pair of lignan lactones (epimeric at C-4), should be available from the common oxabicyclo intermediate **9**. These transformations and relationships are outlined in Scheme II; a more detailed account with a discussion of some interesting facets of the reactions employed in the production of **10–13** now follows.

The first step in the conversion of **9** to **10**, the regiospecific epimerization at C-3, is effected with methoxide in methanol at room temperature. The reaction is complete in 30 min and, when repeated with deuteriomethanol (CH_3OD), introduces deuterium cleanly at C-3 of **14**. Prolonging the treatment with methoxide results in slow deuteration at C-2 without epimerization at this site. Enolization at C-3, the less hindered site, must be much faster than at C-2; the less crowded 2,3-trans configuration of **14** quickly results, and once it is formed slow C-3 enolization can proceed. No trace of any other stereoisomer was found under the conditions employed. Hydride reduction of **14** with lithium triethylborohydride (2.2 equiv, 0 °C, THF, 1 h) was also regiospecific with only the less hindered C-3 exo ester being reduced to the alcohol **15** (74% yield). The reduction of the C-3 ester of both **14** and **16** was repeated with super deuteride to obtain the dideuterio alcohols, which were very useful for ^1H NMR monitoring of the stereochemistry of the subsequent tetralins and lactones (vide infra).

Raney nickel hydrogenolysis of **9** and **15** to **16** and **10**, respectively, was both stereospecific and chemospecific at C-1; it proceeded in excellent yields (75–80%) at atmospheric pressure in refluxing ethanol but only when the freshly prepared W-2 catalyst is used; with older samples of catalyst yields decreased and some undesired byproducts were formed. Four such compounds (**17–20**) were isolated and crystallized in the hydrogenolysis of **9**. Both the naphthalene **17**[18] (13% yield) and naphthol **18**[19] (3.3%) might have arisen from the third compound, **19** (20%), by dehydration and dehydrogenation, respectively. The structure of the latter was evident from the virtual coincidence of its UV spectrum with that[20] of γ-apopodophyllic acid **21** and from its ^1H NMR spectrum. In addition to the presence of the expected signals there was also evidence of restricted rotation about the C_1–C_1' bond, found in the broad absorptions of H-2′ and H-6′ (δ 6.3–6.5) and the C-3′ and C-5′ methoxyl groups (δ 3.8). In carbon tetrachloride–dimethyl sulfoxide (7:3) these resonances are somewhat sharper but improve even more with increasing temperature; at 311 K in the mixed solvent these signals are sharp and coincident at δ 6.35 and 3.8, respectively. Another interesting aspect of these spectra are the chemical shifts and coupling constants of H-3 and H-4. These are 5.05 (H-4, triplet collapses to a doublet with D_2O) and 4.13 (H-3), $J_{3,4}$ = 5.6 Hz in deuteriochloroform, but 4.84 and 3.56, $J_{3,4}$ = 8.7 Hz in the mixed solvent at 311 K. It appears that the dihydronaphthalene system changes conformation with change in the solvent; H-3 and H-4 are more "diequatorial" in chloroform and more "diaxial" in the carbon tetrachloride–dimethyl sulfoxide mixture. Hydrogen bonding of the 4-hydroxyl group to DMSO is probably responsible. The ^1H NMR spectrum of the fourth byproduct (7%) showed the presence of increased aliphatic proton absorption, only two aromatic protons, and the individual signals of the methylenedioxy group well separated from each other at δ 4.89 and 5.21, upfield from their normal position around 6 ppm. These features suggested that the aromatic ring had been hydrogenated, and the structure was established as **20** by X-ray crystallography. The hydrogenation of aromatic rings by W-2 Raney nickel at atmospheric pressure is not common, but a few such hydrogenations have been reported[21] to occur in refluxing isopropyl alcohol.



17 R=H
18 R=OH



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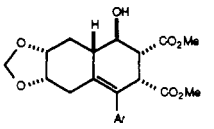

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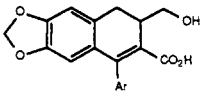

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Ar = 3,4,5-trimethoxyphenyl

Lithium triethylborohydride (or borodeuteride) reduction of **16** at 0 °C in THF was regiospecific; only the C-3 equatorial ester of **16** was reduced, but the product was not the expected diol **11** but the crystalline cyclic ethyl boronate derivative **22** thereof, probably formed by protonolysis of the triethylborane during the workup with acetic acid. The structure of **22** was established by ^1H and ^{11}B NMR, mass spectrometry, and elemental analysis. The ^1H NMR spectrum showed the presence of the *B*-ethyl group (0.77, q, 2 H and 0.95, t, 3 H, J = 7.4 Hz) and that the stereochemistry of the product ($J_{1,2}$ = 6.2, $J_{2,3}$ = 3.7, $J_{3,4}$ = 10.4 Hz) was the same as that of the preceding ester **16** ($J_{1,2}$ = 5.8, $J_{2,3}$ = 3.9, $J_{3,4}$ = 9.7 Hz) and the subsequent tetralin **11** (Figure 2). The ^{11}B signal of **22** was found at 30.4 ppm (BF_3–etherate as external reference) close to the reported ^{11}B signal of similar cyclic boronate esters.[22] Structural proposals for the major ions in the mass spectrum of **22** presented in Scheme III are supported by accurate mass measurements and by the presence of ^{10}B isotope peaks of ca. 20% (relative to ^{11}B) for every boron-containing ion. The formation of cyclic borates in the sodium borohydride reduction of aldoses has been recently observed.[23]

Hydrolysis of the cyclic boronate could be achieved with or without epimerization of the C-2 axial ester as desired. Methyl isopicropodophyllate **11** is obtained in 90% yield with wet methanolic tetrahydrofuran, and methyl isopodophyllate, **13**, or the corresponding acid, isopopodophyllic acid, **23**, is produced when the hydrolytic medium is basic (**13**, NaOMe, MeOH, 81%, **23**, K_2CO_3, MeOH, 95%). Both **11** and **13** were also prepared as the dideuterio derivatives by using lithium borodeuteride in the reduction of **16**. The final stereoisomeric tetralin in the series (**12**) could not be

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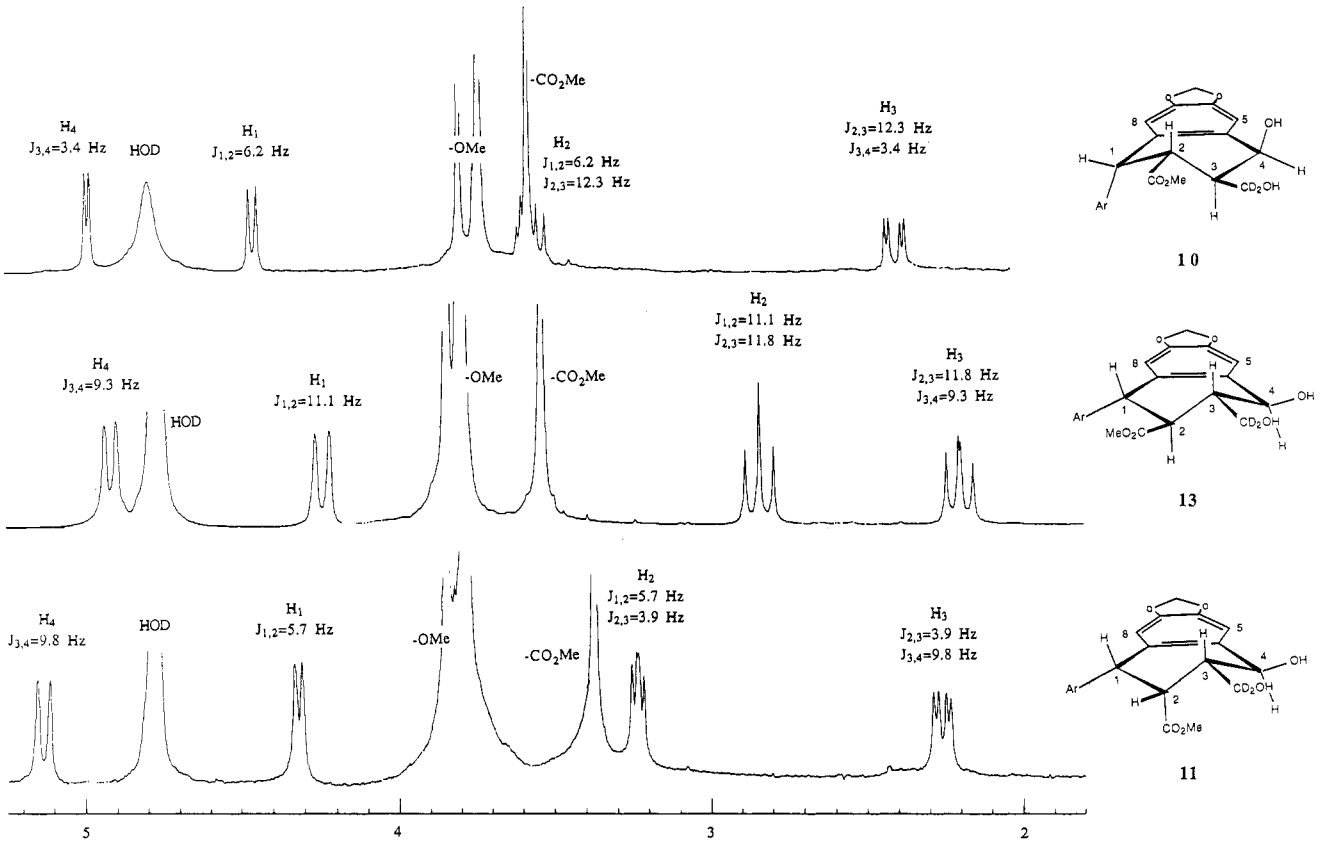
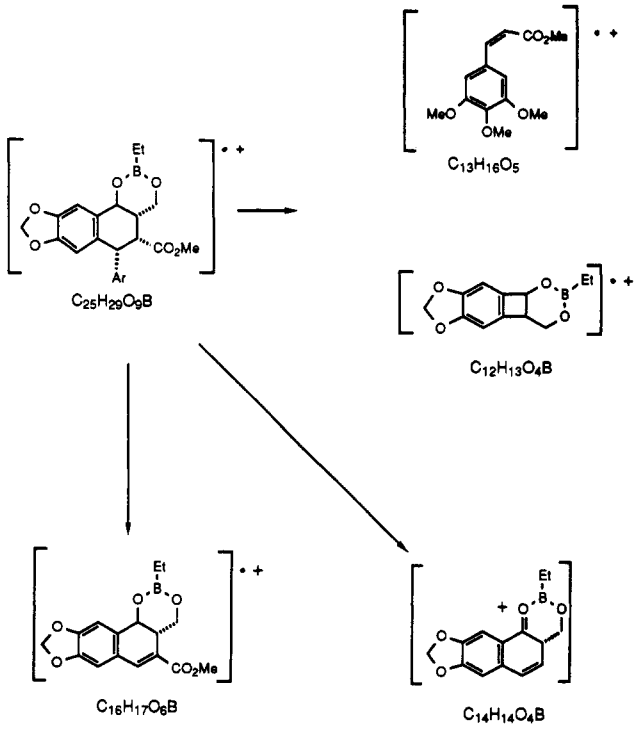


Figure 1. Signals of the aliphatic protons in the NMR spectra of **10**, **11**, and **13** at 250 MHz (in $CDCl_3$ with D_2O added).

Scheme III



obtained by the base-catalyzed epimerization of **10**. Treatment of the latter with methoxide in methanol, for instance, gave a quantitative yield of the C-2 epimeric lactone epipicropodophyllin **24** (23% overall from piperonal), by the initial formation and spontaneous cyclization of **12**.

The aliphatic protons (2–5.2 ppm) of the three tetralins **10**, **11**, and **13** each have chemical shifts and coupling constants, diagnostic of their configuration and conformation. The three spectra, presented in Figure 1, illustrate the value of the dideuterio analogues in this respect and display some interesting differences. The C-2 epimers **11** and **13**, for example, are easily differentiated not only by their coupling constants (all diaxial in **13**) but also by the chemical shifts of the substituent at C-2. Thus the axial ester methyl group in **11** and H-2 in **13** are both found at significantly higher field than their equatorial counterparts. This is a general phenomenon in tetralins with an equatorial aryl substituent at C-1; it has been observed[24] in other instances and is very useful in assigning relative configuration.

The preparation of these tetralins (**10**, **11**, and **13**) in overall yields of 23, 26, and 21%, respectively, from piperonal with complete control of stereochemistry permits the exploration of a practical route to the eight lignan lactones. These experiments are described below.

(±)-Podophyllotoxin (1), (±)-Epipodophyllotoxin (6), (±)-Picropodophyllin (4), and (±)-Epipicropodophyllin (24) from Methyl Epipodophyllate (10). We were able to effect neither the hydrolysis of the C-2 ester nor the direct lactonization of **10** without epimerization at C-2 in spite of many efforts to do so with various reagents and experimental conditions. As already noted, methoxide in methanol caused rapid and quantitative conversion of **10** to **24**. Acidic conditions were also unsatisfactory. Their use produced complex mixtures or resulted in extensive decomposition.

Ketalization of the diol system of **10** with 2,2-dimethoxypropane and *p*-toluenesulfonic acid produced the acetonide **25** in 81% yield with no change in conformation. The coupling constants, $J_{1,2}$ = 6.0, $J_{2,3}$ = 12.5, and $J_{3,4}$ =

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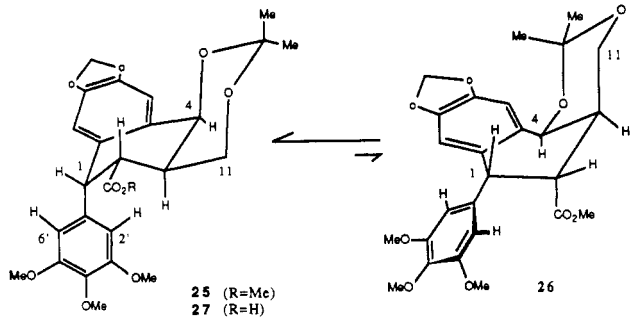
3.7 Hz, were very similar to those found for **10** (Figure 1) rather than those expected for the alternative conformation **26** with the C-2 ester axial. The signals of the acetonide methyl groups (δ 1.32 and 1.57) were unchanged at 183 K (in CD_2Cl_2), but slow rotation about the C_1–C_1' bond was detectable in the progressive broadening and virtual disappearance of the H-2′, H-6′, C-3′, and C-5′ methoxyl signals with decrease in temperature. Similar ^1H NMR studies of podophyllotoxin have been conducted[25] recently with similar results. The absence of any **26** must be due to the intolerable steric interference of the "axial" methyl group of the acetonide with C-5 in this conformation. An important practical consequence of this fact is that the saponification of the C-2 equatorial ester of **25** can now

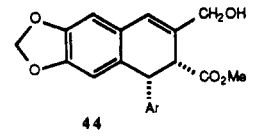


25 (R=Me)
27 (R=H)

26

proceed *without* epimerization to yield the acid **27**. Under identical conditions **10** was hydrolyzed with C-2 epimerization to the 2,3-cis acid **28**. Hydrolysis of the acetonide **25** carried out with dilute hydrochloric acid in aqueous dioxane at room temperature produced a moderate yield of epipodophyllic acid **29** after 24 h. Longer exposure to the same conditions gave an excellent yield of neopodophyllotoxin, **30**. The hydrolysis of the acetonide appears to proceed without participation of the C-2 carboxyl group of **27** (that would require the intervention of a conformation like **26**), and TLC and ^1H NMR monitoring of the reaction do show that **29** is formed initially and that **30** slowly builds up as the reaction progresses. However such participation of the C-2 carboxyl group of **29** in an S_N2 displacement of the protonated 4-hydroxyl group (to form **30**) is no longer prohibited by conformational factors and may well occur since no podophyllic acid (the C-4 epimer of **29**) was detected in our monitoring of the reaction. In any event, stereochemical control at C-4 is available as a result. Since **30** had been previously converted[26] to **1** and podophyllotoxin is easily epimerized[27] at C-2 to picropodophyllin **4**, this completes the synthesis of the C-4 inverted lactones from the tetralin **10**. Lactonization of epipodophyllic acid **29** with dicyclohexyl carbodiimide (DCC) produces epipodophyllotoxin, **6**, which together with **24** makes up the other pair of lactones related to **10**. A recent discovery[13] that **10** can be converted directly to **6** in 81% yield by heating in THF with zinc chloride and 4-Å molecular sieves and to **1** after C-4 epimerization (47%) shortens the route to **1**, **4**, and **6** from methyl epipodophyllate (**10**) and improves the overall yield of these lignans to 11%, 11%, and 19%, respectively, from piperonal.

(±)-Isopodophyllotoxin (31) and (±)-Epiisopodophyllotoxin (34). Isopodophyllic acid (**23**) obtained in 95% yield by decomposition of the cyclic boronate **22** with



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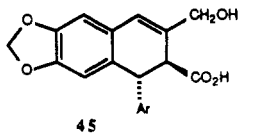

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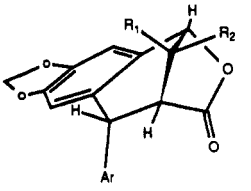

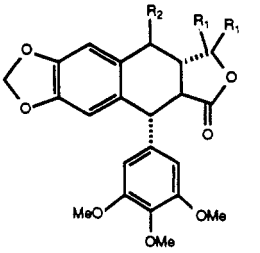

30 (R_1=CH_2OH, R_2=H)
40 (R_1=H, R_2=CH_2OH)
41 (R_1=H, R_2=CH_2OAc)

32 (R_1=D, R_2=OAc)
33 (R_1=H, R_2=OAc)
46 (R_1=R_2=H)

methanolic potassium carbonate was lactonized with DCC to provide **31** in 71% yield (19.5% from piperonal). The melting point of our product (272–3 °C) and the IR absorptions (Nujol) at 1744 (C=O) and 3447 (OH) cm^{-1} are very similar to the previously recorded[27] data (272 °C, 1748, 3448 cm^{-1}) for (±)-isopodophyllotoxin. The ^1H NMR spectra of **31** and its dideuterated derivative revealed the all-trans configuration ($J_{1,2}$ = 11.4, $J_{2,3}$ = 13.7, and $J_{3,4}$ = 10 Hz). The dideuterated acetate **32** was prepared, and its ^1H NMR spectrum observed to be virtually identical with data published[28] for the protonated analogue **33**. The melting points of these compounds were identical, and the carbonyl stretching vibrations in solution IR spectra were found at very similar frequencies. Epimerization of **31** at C-4 to provide epiisopodophyllotoxin (**34**) has already been achieved[29] by a two-step procedure in 36% yield.

(±)-Isopicropodophyllin (35) and (±)-Epiisopicropodophyllin (36). The diol **11** treated with 2 equiv of sodium hydride in THF produced an 85% yield of the cis-lactone isopicropodophyllin (**35**, 22% from piperonal). The dideuterio derivative of **35** was also prepared, and 250-MHz ^1H NMR spectra of both samples were obtained in d_6-DMSO for comparison with published data. Only one discrepancy was found; our spectra showed H-1 as a doublet at δ 4.59 and H-4 at δ 4.64 (a doublet also after D_2O) with $J_{3,4}$ = 7.3 Hz. The earlier 100-MHz data[29] also assigned the signal at δ 4.64 to H-4, but $J_{3,4}$ was reported as 3.0 Hz. Many multiplets between δ 2.7 and 4.75 were left unassigned in the earlier work. The hydroxyl and lactone carbonyl absorptions in the IR spectrum of our sample were very similar to the published[29] values.

The tetralin diol **11** when subjected to acid treatment (dilute aqueous methanolic HCl for 2 days at room temperature) produced the two isomeric lactones **37** and **38** in the ratio 3:1 (98% overall). Comparison of the ^1H NMR spectrum of **38** with that of isopicropodophyllin (**35**) revealed a gross similarity in the chemical shifts and coupling constants, but there were significant differences in the chemical shifts of H-4 (δ 4.78 in **35**, 4.26 in **38**) and the two protons of the C-1 aryl substituent (δ 6.46 in **35** and 6.66 in **38**); the coupling constant $J_{3,4}$ was also reduced from 5.5 (**35**) to 2.9 Hz (**38**). The extra methyl group in **38** was found at δ 3.34. Since the structure of **35** (and its dideuterio analogue) was secured by high-field ^1H NMR measurements, the most likely origin of the difference in the spectra of **35** and **38** appeared to lie in a conformational change of the flexible cis-lactone system of the two com-

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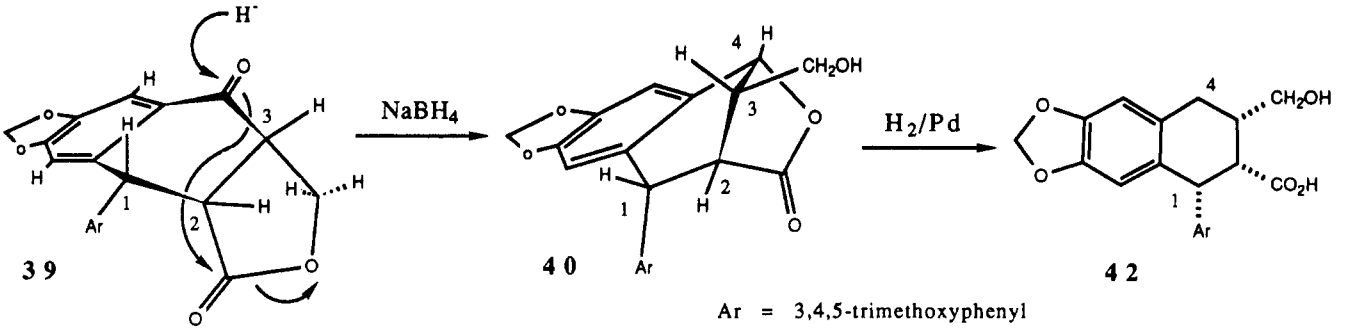
Scheme IV



Ar = 3,4,5-trimethoxyphenyl

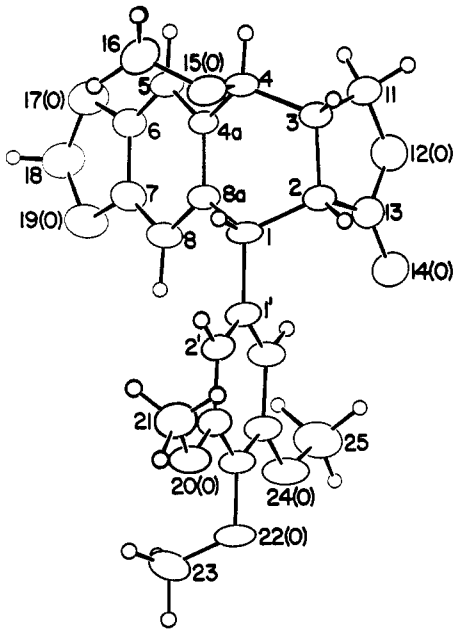


Figure 2. ORTEP diagram of **38**.

pounds caused by methoxy substitution at C-4. An X-ray crystallographic study was therefore undertaken, and it confirmed the structure and conformation of **38**. An ORTEP diagram is presented in Figure 2.

The major product of the reaction of **11** with dilute methanolic hydrochloric acid (74% yield) was assigned the all-cis structure **37**, thus making it the methyl ether of epiisopicropodophyllin (**36**). The preparation of this isomer by borohydride reduction of isopicropodophyllone (**39**) had been reported, but the spectroscopic properties of our methyl ether **37** were very different indeed from those described[30] for **36**. Samples of this compound and its acetate were obtained,[31] and high-field ^{1}H NMR spectra of these compounds clearly demonstrated that they possessed bridged lactone structures **40** and **41** epimeric at C-3 with neopodophyllotoxin[16] (**30**).

The only important difference in the spectra of **40** and **30** is associated with the configurational difference at C-3. In **40** $J_{2,3} \approx J_{3,4} \approx 0$ Hz because these dihedral angles at the bridgehead (C-3) approach 90°. The chemical shifts of H-3 and the CH_2OH group are also predictably affected with the change in configuration at this center. The acetate **41** shows the acetylation shift [$\Delta\nu$($RCH_2OH \rightarrow RCH_2OAc$)] of ca. 0.5 ppm expected for a primary alcohol, a fact in accordance with **40** but not with the secondary alcohol represented by structure **36**.

Table I. Chemical Shifts (δ) of Lactone Methylene Protons (H-11, H-11″) in 2,3-Trans Lactones

compds	H-11 (pseudo-axial)	H-11″ (pseudo-equatorial)	$\Delta\delta$	C-4 substituent and stereochem
1	4.09	4.60	0.51	eq OH
5	3.92	4.45	0.53	
31	4.16	4.73	0.57	eq OH
46	3.90	4.52	0.62	
6	4.35	4.41	0.06	ax. OH
3[32]	4.36	4.54	0.18	ax. OH

The formation of **40** by the borohydride reduction of isopicropodophyllone (**39**) as well as its hydrogenolysis[30] to alcohol acid **42** can be accounted for (Scheme IV) with this structural proposal. Thus it does appear that the all-cis isomer epiisopicropodophyllin (**36**) has not yet been synthesized and probably will be difficult to synthesize because of the proximity of such a C-4α hydroxyl group to the C-2α lactone carbonyl group in this compound.

The identity of our synthetic product **37** was confirmed by hydrogenolysis (H_2/10% Pd–charcoal–acetic acid/50 psi) to the corresponding deoxy-lactone **43** and comparison of the ^{1}H NMR spectrum of this product with the spectrum of an authentic sample.[30,31] In common with the earlier investigators[30] we find this hydrogenolysis to be slow and difficult to carry to completion, probably because the molecule exists in a conformation not particularly suited to approach of the catalyst to the benzylic C-4 ether (conformation C, Figure 3). Attempts to prepare **36** in other ways have not been successful. For example, treating **11** in aqueous dioxane with dilute hydrochloric acid over extended periods at room temperature produces the dehydration product **44**, identified by its ^{1}H NMR spectrum and by the similarity of its UV spectrum[20] to that of α-apopodophyllic acid (**45**).

^{1}H NMR Spectra of the Lignan Lactones. These compounds can be logically divided into two groups for the purpose of NMR examination. The first group, the 2,3-trans lactones made up of **1**, **6**, **31**, and **34**[32] as well as their deoxy analogues[15] **5** and **46**, presents little difficulty in interpretation of the spectra because of the rigidity conferred on the system by the 2,3-trans fusion. The spectra of **1**, **5**, and **6** had been previously examined,[5] and only one aspect of the spectral data deserves further comment. Table I shows the chemical shifts of the protons of the lactone methylene group (H-11, H-11″) for the six compounds. The assignment of the higher field signal to the pseudoaxial proton (H-11), anti to the C-1 aryl substituent of **1**, **5**, and **6**, is based on the 3,11 coupling constants and dihedral angles calculated therefrom[5] and is consistent with the usual chemical shifts of α-methylene protons in five-membered heterocyclic ring systems.[33]

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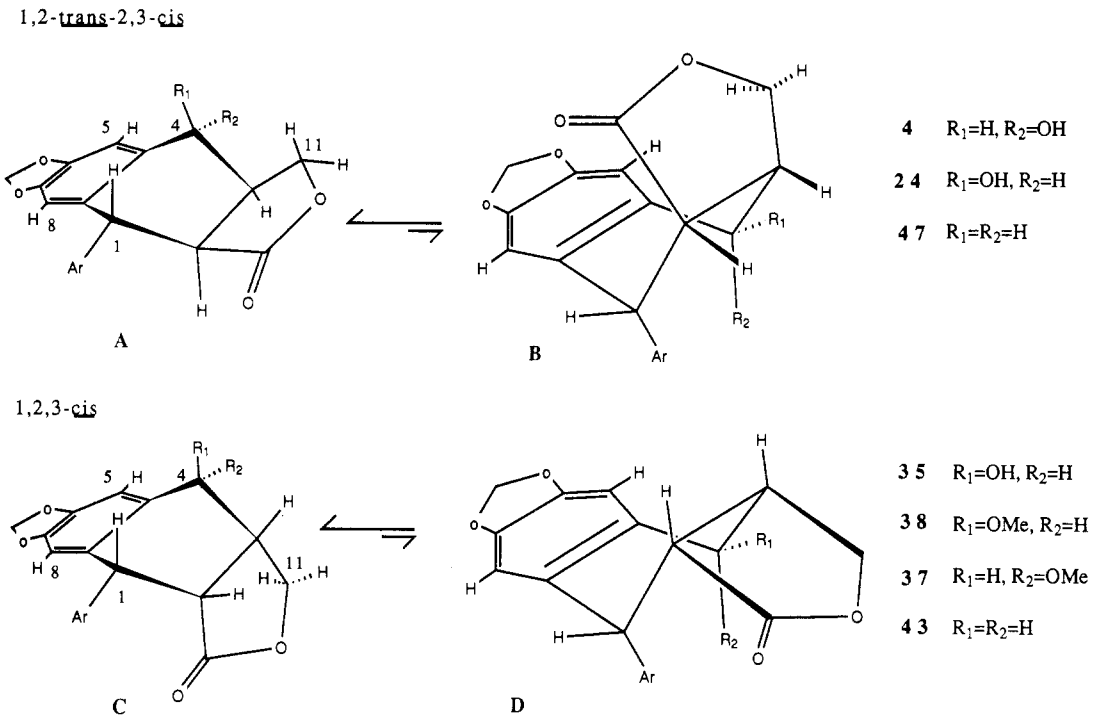

Figure 3. Possible conformations for the 2,3-cis lactones.

Table II. Chemical Shifts (H-1 and H-4), Coupling Constants ($J_{1,2}$ and $J_{3,4}$), and Dihedral Angles ($\phi_{1,2}$ and $\phi_{3,4}$) of *Podophyllum* Cis Lactones from Their ^{1}H NMR Spectra in $CDCl_3$

	δ		J, Hz (ϕ calcd, deg)		
compd	H-1	H-4[a]	1,2	3,4	conformation
4	4.11	4.51 (f)	5.7 (130)	8.3 (147)	A
24	4.44	4.81 (e)	3.7 (123)	5.5 (47)	A
47	4.38	2.49 (f), 2.87 (e)	3.0 (119)	5.3, 6.3 (128, 48)	A
35	4.66	4.78 (e)	5.4 (50)	5.5 (47)	C
38	4.63	4.26 (e)	4.1 (56)	2.9 (60)	C
38 by X-ray			(61.5)	(78.3)	C
37	4.07	4.38 (f)	3.3 (59)	5.8 (46)	C
43	4.41	2.70 (f), 2.98 (e)		5.0, 8.7 (53, 40)	C

[a] f ≡ flagpole hydrogen; e ≡ pseudoequatorial hydrogen.

It is clear from Table I that the chemical shift of the pseudoaxial (H-11) proton is influenced by the presence of an axial oxygen substituent at C-4 (as in **6** and **34**). Neither the lack of a C-4 substituent (**5** and **46**) nor the disposition of the C-1 aryl substituent (axial in **1** and **5**, equatorial in **31** and **46**) affects the value of $\Delta\delta$ to any significant extent. The "1,3-diaxial" relationship of H-11 and the C-4 oxygen substituent prevalent in the final pair of compounds results in a downfield shift of H-11 and an upfield shift of the pseudoequatorial proton H-11″ of about 0.2 ppm each (compare **1** and **6**, **31** and **34**) with a significant net contraction of $\Delta\delta$ in these two cases. Similar deshielding of 1-axial protons by a 3-axial oxygen substituent in steroidal δ-lactones has been reported.[34] It thus appears that in the 2,3-trans-fused *Podophyllum* lactones a small $\Delta\delta$ for the C-11 protons is indicative of the presence of an axial oxygen substituent at C-4.

The lignans of the second group, the 2,3-cis-fused compounds **4**, **24**, **35**, **37**, and **38** together with the two C-4 deoxylactones **43** and **47**,[35] are all flexible compounds whose NMR spectra represent average conformations. Picropodophyllin (**4**) is the only member of the group that had been previously studied,[5,36] and the conclusion was reached that it exists mainly in the boat conformation with the C-1 aryl and C-4 hydroxyl substituents in a quasi-equatorial (nonflagpole) orientations (conformation A, Figure 3). Application of a modified Karplus equation using the experimental value of $J_{1,2}$ supported this conclusion[5] as did NOE enhancements of H-1 and H-2 when the aryl protons at 2′ and 6′ were irradiated.

Our set of seven synthetic cis lactones can be placed in two subgroups according to the configuration at C-1. Thus **4**, **24**, and **47** possess a 1,2-trans 2,3-cis stereochemistry with two possible boat conformations A and B, while **35**, **38**, **37**, and **43** have a 1,2,3-cis arrangment leading to possible boat conformations C and D (Figure 3).

Application of the same modified Karplus equation to the 1,2 and 3,4 couplings ($J_{2,3}$ is not measurable in all cases) in the four C-4 oxygenated examples provides results displayed in Table II, which imply that the major conformations of these compounds are A (**4** and **24**) and C (**35**, **37**, and **38**); in both cases the C-1 aryl substituent seems to control the outcome by choosing the quasi-equatorial rather than the "flagpole" orientation of B and D. The H-1 proton in every case must therefore occupy a flagpole

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(34) Shephard, R. C.; Turner, S. *J. Chem. Soc., Chem. Commun.* **1968**, 77–78.
(35) Deoxypicropodophyllin (**47**) was obtained by the hydrogenolysis of **24** (Pd/HOAc/50 psi).
(36) Ayres, D. C.; Harris, J. A.; Jenkins, P. N.; Phillips, L. *J. Chem. Soc., Perkin Trans 1* **1972**, 1343–1350.

Table III. Chemical Shifts (δ, $CDCl_3$) of C-11 Protons in the 2,3-Cis Lactones

compd	conformation	δ (C-11 protons)[a]	$\Delta\delta$
4	A	4.34, 4.44	0.10
24	A	4.34, 4.36	0.02
47	A	3.98, 4.45	0.47
35	C	3.72, 4.58	0.76
38	C	~3.8, 4.50	0.70
37	C	4.23, 4.27	0.04
43	C	3.49, 4.40	0.91

[a] In these flexible systems the individual signals of H-11 and H-11″ cannot be assigned with confidence.

position. The situation with H-4 is more complex. It is in the flagpole orientation in **4** and **37**, and these signals are at higher field than in **24** and **35** as expected, but the signal due to H-4 in **38** is at an anomalously high field for a C-4 equatorial proton. The X-ray structure of **38** is fortunately available and provides an answer. The presence of a flagpole methoxy group at C-4 in **38** causes sufficient steric compression to widen the H-3, H-4 dihedral angle to 78.3° (calculated as 47° in the C-4 hydroxyl analogue **35** of identical configuration). This is achieved by flattening the boat at C-4 and moving the equatorial hydrogen below the plane of the adjacent benzene ring, thus shifting its resonance upfield in comparison to **35**. Thus the conclusion that the cis lactones exist mainly in boat conformations with pseudoequatorial C-1 aryl substituents (A and C) is supported by ^1H NMR and X-ray crystallography.

The chemical shifts of the C-11 methylene protons in these cis lactones (Table III) revealed that among the C-4 oxygenated compounds the signals were almost coincident except for **35** and **38**. Examination of the conformations A and C (in Figure 3) also reveals that only in **35** and **38** is the C-4 oxygen substituent spatially far removed from the C-11 protons. The implication that the presence of this C-4 oxygen close to the C-11 protons contracts $\Delta\delta$ in the other three examples (**4**, **24**, and **37**), as it did in the trans lactones, cannot be avoided. This conclusion is supported by the fact that the C-11 protons display a large chemical shift difference ($\Delta\delta$) in the C-4 deoxy analogues **47** and **43**. Thus it appears that the combination of a C-type conformation and a C-4 β-hydroxy stereochemistry (i.e., isopicropodophyllin (**35**) is dramatically signalled by the large chemical shift difference of the C-11 protons.

Mass Spectra of the Podophyllum Lignan Lactones. The mass spectra of **1**, **4**, **6**, and **24** have been previously studied,[37] and the observation has been made that the abundance of the [M – H_2O] ion at m/z 396 may bear a relationship to the stereochemistry of the C-4 oxygen substituent. The likelihood of 1,3 and 1,4 but not 1,2 elimination of H_2O (or ROH) in these systems was considered in light of the previous conclusions[38] about the mass spectral elimination of H_2O in cyclohexanol.

The diastereomeric lactones prepared in this study were therefore examined by MS for the m/z 396 ion. We find that this ion is of abundance >10% only in **4** (75%),[37] **6** (11%),[37] **34** (21%),[32] **35** (100), and **38** (100), all examples possessing the C-4 hydroxyl group and C-2 hydrogen cis to each other. The numbers seem to indicate also that such elimination of water is easier in the more flexible cis-lactones **4**, **35**, and **38** than in the rigid trans-compounds **6** and **34**. Particularly noteworthy is the fact that **24**, **31**, and **37**, which possess a 1,4-cis relationship between H-1 and the C-4 oxygen substituent, do not show such an m/z 396 ion of abundance greater than 10%. It appears that in these doubly annelated "cyclohexanols" the 1,4 elimination pathway, which produces formal benzocyclobutane-like structures, is not favored, as might have been expected. Thus the abundance of the m/z 396 ion seems to provide valuable stereochemical information concerning the relative configurations at C-2 and C-4 in the *Podophyllum* lignan lactones.

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Experimental Section

General Techniques. All compounds synthesized in this study are racemates. Many of them had been previously prepared as single enantiomers by interconversions of naturally occurring materials. In such cases elemental analyses have not been obtained, but the compounds have been purified by chromatography and crystallization and characterized by ^1H NMR and mass spectrometry. All spectra obtained in these instances indicated that these materials were more than 95% pure.

Dimethyl 1,4-Epoxy-1,2,3,4-tetrahydro-6,7-(methylenedioxy)-1-(1,2-*cis*)-(3′,4′,5′-trimethoxyphenyl)-2,3-*cis*-naphthalenedicarboxylate (9). The adduct **7** (4.550 g) in EtOAc (30 mL, dried over anhydrous K_2CO_3) with 10% Pd/C (30 mg) was hydrogenated at 50 psi for 6 h. The reaction mixture was filtered through a Whatman glass microfiber filter, and upon removal of the solvent in vacuo a quantitative yield of **9** was obtained. The product was recrystallized from ether: mp 151–153 °C; IR ($CHCl_3$) 1738 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) δ 3.58 (s, 6 H, 2 × CO_2Me), 3.74 (d, 1 H, $J_{2,3}$ = 10.6 Hz, H_2), 3.86 (s, 6 H, 3′,5′-OMe), 3.88 (s, 3 H, 4′-OMe), 3.93 (dd, 1 H, $J_{3,4}$ = 4.8 Hz, H_3), 5.54 (d, 1 H, H_4), 5.95, 5.97 (ABq, J_{AB} = 1.4 Hz, 2 H, OCH_2O), 6.63 (s, 1 H, H_8), 6.85 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.86 (s, 1 H, H_5); MS (EI) m/z (rel int) 472 (M^+, 0.4), 454 ($M^+ - H_2O$, 13), 328 (85), 413 (49), 113 (61). Anal. Calcd for $C_{24}H_{24}O_{10}$: C, 61.02; H, 5.12. Found: C, 61.37; H, 5.26.

Dimethyl 1,4-Epoxy-1,2,3,4-Tetrahydro-6,7-(methylenedioxy)-1-(1,2-*cis*)-(3′,4′,5′-trimethoxyphenyl)-2,3-*trans*-naphthalenedicarboxylate (14). The cis-diester **9** (0.625 g, 1.324 mmol) was dissolved in MeOH (30 mL), sodium methoxide in methanol added, and the solution stirred for 2 h at 25 °C. The reaction mixture was treated with dry ice and water (20 mL), the MeOH removed in vacuo, more water added, and the solution extracted with CH_2Cl_2 (3 × 10 mL). After drying (Na_2SO_4) and removal of the solvent, the crude product was recrystallized from ether to give **14** (0.563g, 90%): mp 164 °C; IR ($CHCl_3$) 1732 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) δ 3.23 (d, 1 H, $J_{2,3}$ = 3.9, $J_{3,4}$ = 0 Hz, H_3), 3.56 (s, 3 H, CO_2Me), 3.80 (s, 3 H, CO_2Me), 3.88 (s, 6 H, 3′,5′-OMe), 3.89 (s, 3 H, 4′-OMe), 4.11 (d, 1 H, H_2), 5.67 (s, 1 H, H_4), 5.99, 5.96 (ABq, J_{AB} = 1.4 Hz, 2 H, OCH_2O), 6.50 (s, 1 H, H_8), 6.89 (s, 1 H, H_5), 6.99 (s, 2 H, $H_{2'}$, $H_{6'}$); MS (EI) m/z (rel int) 328 (85), 313 (78), 113 (65). Anal. Calcd for $C_{24}H_{24}O_{10}$: C, 61.02; H, 5.12. Found: C, 60.76; H, 5.27.

Methyl 1,4-Epoxy-3-*exo*-(hydroxymethyl)-6,7-(methylenedioxy)-1-(1,2-*cis*)-(3′,4′,5′-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2-*endo*-carboxylate (15). The diester **14** (0.1052 g, 0.223 mmol) was dissolved in dry THF (15 mL) and cooled to 0 °C. Lithium triethylborohydride (1 M, 2.2 equiv) was added, and after stirring for 1 h at 0 °C, dilute acetic acid (50% aqueous) was added until the yellow color disappeared. The solution was quickly poured into a separatory funnel containing a mixture of CH_2Cl_2 and water (50% v/v, 20 mL) and shaken, and the organic layer poured over anhydrous K_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined extracts were dried for 1 h. After removal of the solvent in vacuo and recrystallization from ether, 0.073 g of **15** was isolated (74%): mp 160 °C; IR ($CHCl_3$) 3500 (br, OH), 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.46 (m, 1 H, H_3), 3.23 (d, 1 H, $J_{2,3}$ = 4.0 Hz, H_2), 3.56 (s, 3 H, CO_2Me), 3.87 (s, 6 H, 3′,5′-OMe), 3.88 (s, 3 H, 4′-OMe), 3.85–3.90 (H_{11} obscured by 4′-OMe), 3.96 (dd, 1 H, $J_{3,11''}$ = 6.1, $J_{11,11''}$ = 10.5 Hz, $H_{11''}$), 5.27 (s, 1 H, $J_{3,4}$ = 0 Hz, H_4), 5.97, 5.94 (ABq, $J_{AB} \leq$ 1.4 Hz, 2 H, OCH_2O), 6.53 (s, 1 H, H_8), 6.84 (s, 1 H, H_5), 6.93 (s, 2 H, $H_{2'}$, $H_{6'}$); MS (EI) m/z (rel int) 444 (M^+, 2), 396 (4), 328 (47), 313 (28), 113 (28). Anal. Calcd for $C_{23}H_{24}O_9$: C, 62.16; H, 5.44. Found: C, 62.48; H, 5.50.

Methyl Epipodophyllate (10). The alcohol **15** (0.526 g, 1.1844 mmol) was dissolved in ethanol, freshly prepared W-2 Raney Ni added, and the suspension stirred at 25 °C in an atmosphere of hydrogen for 4 h. The catalyst was filtered through a Whatman glass microfiber filter, and the solvent was removed in vacuo. The residue was recrystallized from ether to give **10** (0.407 g 77%): mp 217 °C; IR (Nujol) 3492, 3370 (OH), 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 250 MHz) δ 2.40 (m, 1 H, $J_{2,3}$ = 12.3, H_3), 3.55–3.65 (H_2, obscured by CO_2Me), 3.57 (s, 3 H, CO_2Me), 3.73 (s, 6 H, 3′,5′-OMe), 3.79 (s, 3 H, 4′-OMe), 3.95 (dd, 1 H, $J_{3,11}$ = 3.1, $J_{11,11''}$ = 11.0 Hz, H_{11}), 4.02 (dd, 1 H, $J_{3,11''}$ = 5.5, $H_{11''}$), 4.45 (d, 1 H, $J_{1,2}$ = 6.2 Hz, H_1), 4.98 (d, 1 H, $J_{3,4}$ = 3.4 Hz, H_4), 5.94, 5.93 (ABq, J_{AB} = 1.2 Hz, 2 H, OCH_2O), 6.05 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.41 (s, 1 H, H_8), 6.82 (s, 1 H, H_5): MS (EI) *m/z* (rel int) 446 (M^+, 2), 414 (M^+ – MeOH, 100), 398 (19), 351 (19), 339 (27). Anal. Calcd for $C_{23}H_{26}O_9$: C, 61.88; H, 5.87. Found: C, 61.78; H, 5.89.

Methyl Epipodophyllate 4,11-Acetonide (25). The diol **10** (0.326 g, 0.7039 mmol) was stirred at 25 °C with *p*-TsOH (50 mg) in 2,2-dimethoxypropane (10 mL). When the reaction was completed (~4 h by TLC), powdered K_2CO_3 was added, and the mixture was stirred for 1 h. After removal of the excess dimethoxypropane in vacuo, water was added, and the organic material extracted with ether (3 × 25 mL). The extracts were dried (Na_2SO_4), and after removal of the solvent, the residue was crystallized from ether/hexane to give **25** (0.278 g, 81%): mp 175 °C; IR ($CHCl_3$) 1734 cm^{-1} (C=O); ^1H NMR (CD_2Cl_2, 250 MHz) δ 1.32 (s, 3 H, Me), 1.57 (s, 3 H, Me), 2.26 (m, 1 H, H_3), 3.59 (s, 3 H, CO_2Me), 3.64 (dd, 1 H, $J_{1,2}$ = 6.0, $J_{2,3}$ = 12.5 Hz, H_2), 3.70 (s, 6 H, 3′,5′-OMe), 3.71 (s, 3 H, 4′-OMe), 3.86 (dd, 1 H, $J_{3,11}$ = 3.1, $J_{11,11''}$ = 12.5 Hz, H_{11}), 4.15 (dd, 1 H, $J_{3,11''}$ = 4.4, $H_{11''}$), 4.45 (d, 1 H, H_1), 4.95 (d, 1 H, $J_{3,4}$ = 3.7 Hz, H_4), 5.92, 5.90 (ABq, J_{AB} = 1.3 Hz, 2 H, OCH_2O), 6.05 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.39 (s, 1 H, H_8), 6.73 (s, 1 H, H_5); MS (EI) *m/z* (rel int) 486 (M^+, 12), 398 (86), 410 (25), 324 (26), 339 (100), 365 (25). Anal. Calcd for $C_{26}H_{30}O_9$: C, 64.19; H, 6.22. Found: C, 64.09; H, 6.42.

Epipodophyllic Acid 4,11-Acetonide (27). The acetonide **25** (0.234 g) in dioxane (15 mL) was refluxed with dilute sodium hydroxide (2 M, 2 mL) and water (3 mL) for 6 h. The dioxane was removed in vacuo, and the residue diluted with water and extracted with ether (25 mL). The aqueous layer was cooled to 0 °C, acidified with concentrated HCl, and extracted with EtOAc (3 × 25 mL). The combined EtOAc extracts were washed with water and dried (Na_2SO_4). Removal of the solvent and recrystallization from ether gave **27** (0.175 g, 71%): mp 190 °C; IR (Nujol) 3432 (br, *COOH*), 1695 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 250 MHz), δ 1.40 (s, 3 H, Me), 1.61 (s, 3 H, Me), 2.28 (m, 1 H, H_3), 3.70 (s, 6 H, 3′,5′-OMe), 3.64–3.70 (partially obscured by OMe, H_2), 3.79 (s, 3 H, 4′-OMe), 3.84 (dd, 1 H, $J_{3,11}$ = 3.3, $J_{11,11''}$ = 12.5 Hz, H_{11}), 4.16 (dd, 1 H, $J_{3,11''}$ = 4.8, $H_{11''}$), 4.49 (d, 1 H, $J_{1,2}$ = 5.7 Hz, H_1), 4.95 (d, 1 H, $J_{3,4}$ = 3.7 Hz, H_4), 5.94, 5.95 (ABq, J_{AB} ≤ 1.4 Hz, 2 H, OCH_2O), 6.11 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.42 (s, 1 H, H_8), 6.74 (s, 1 H, H_5); MS (EI) *m/z* (rel int) 472 (M^+, 32), 414 (84), 396 (51), 384 (34), 365 (25), 351 (26), 339 (100), 365 (25). Anal. Calcd for $C_{25}H_{28}O_9$: C, 63.55; H, 5.97. Found: C, 63.09; H, 5.85.

Epipodophyllic Acid (29). The acetonide **27** (0.234 g) in dioxane (15 mL) was stirred with dilute hydrochloric acid (2 M, 5 drops) at 25 °C for 24 h. Water was added, and the dioxane was removed in vacuo. The residue was extracted with EtOAc (3 × 50 mL). The combined EtOAc extracts were washed with water and then dried (Na_2SO_4). Removal of the solvent and recrystallization from ether/MeOH yielded **29** (0.182 g, 58%); mp 186 °C; IR (KBr) 1690 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 250 MHz) δ 2.17 (m, 1 H, H_3), 3.11 (dd, 1 H, $J_{1,2}$ = 6.2, $J_{2,3}$ = 11.7 Hz, H_2), 3.58 (s, 3 H, 4′-OMe), 3.5–3.7 (H_{11} and $H_{11''}$ obscured by 4′-OMe), 3.62 (s, 6 H, 3′,5′-OMe), 4.33 (d, 1 H, H_1), 4.75 (d, 1 H, $J_{3,4}$ = 2.6 Hz, H_4), 5.90 (s, 2 H, OCH_2O), 6.13 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.35 (s, 1 H, H_8), 6.84 (s, 1 H, H_5); MS (EI) *m/z* (rel int) 414 ($M^+ - H_2O$, 100), 396 (31), 384 (34), 365 (20), 351 (12), 339 (31), 337 (15).

Epipodophyllotoxin (6). Epipodophyllic acid **29** (0.343 g) was dissolved in dry THF (20 mL) and stirred with dicyclohexyl carbodiimide (DCC, 1.1 equiv). When the reaction was complete (~4 h by TLC), the mixture was quenched with dilute aqueous acetic acid (50%) and stirred for another hour. The solvent was removed in vacuo, and a solution of $NaHCO_3$ (20 mL) was added. The aqueous solution was extracted with CH_2Cl_2 (3 × 15 mL), and the combined extracts were dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was chromatographed (EtOAc:hexane, 1:1) to remove the remaining dicyclohexylurea to give **6** (0.280 g, 85%), which was recrystallized from ether: mp 211 °C; IR ($CHCl_3$) 1780 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.84 (m, 1 H, H_3), 3.29 (dd, 1 H, $J_{1,2}$ = 4.9, $J_{2,3}$ = 14.0 Hz, H_2), 3.74 (s, 6 H, 3′,5′-OMe), 3.81 (s, 3 H, 4′-OMe), 4.38 and 4.35 (AB component of an ABX system, 2 H, $J_{11,11''}$ = 8.5, $J_{3,11}$ = 4.8, $J_{3,11''}$ = 7.3 Hz, H_{11}, $H_{11''}$), 4.86 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H_1), 4.61 (d, 1 H, $J_{3,4}$ = 3.3 Hz, H_4), 6.00, 5.97 (ABq, J_{AB} ≤ 1.2 Hz, 2 H, OCH_2O), 6.28 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.55 (s, 1 H, H_8) 6.87 (s, 1 H, H_5).

Neopodophyllotoxin (30). The acetonide **27** (0.0252 g, 0.5830 mmol) dissolved in dioxane (15 mL) was treated with dilute hydrochloric acid (2 M, 5 drops) and stirred at 25 °C for 48 h. Water was added, and the dioxane was removed in vacuo. The residue was extracted with EtOAc (3 × 5 mL), and the combined extracts were washed (H_2O, 25 mL) and dried (Na_2SO_4). Removal of the solvent and recrystallization from ether gave **30**: mp 230–31 °C (0.030 g, 95%); ^1H NMR ($CDCl_3$, 250 MHz) δ 3.01 (t, 1 H, $J_{1,2}$ = 4.6, $J_{2,3}$ = 4.6 Hz, H_2), 3.14 (m, 1 H, H_3), 3.65 (dd, 1 H, $J_{3,11}$ = 7.6, $J_{11,11''}$ = 10.8 Hz, H_{11}), 3.7 ($H_{11''}$ partially obscured by 3′,5′-OMe), 3.78 (s, 6 H, 3′,5′-OMe), 3.85 (s, 3 H, 4′-OMe), 4.27 (d, 1 H, H_1), 5.17 (d, 1 H, $J_{3,4}$ = 4.9 Hz, H_4), 5.97, 5.95 (ABq, J_{AB} = 1.3 Hz, 2 H, OCH_2O), 6.27 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.49 (s, 1 H, H_8), 6.74 (s, 1 H, H_5). This ^1H NMR spectrum was identical with a spectrum of (–)-neopodophyllotoxin published earlier.[26]

Dimethyl 4-(3,4-*trans*)-Hydroxy-6,7-(methylenedioxy)-1-(1,2-*cis*)-(3′,4′,5′-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2,3-*cis*-dicarboxylate (16). A solution of the oxabicyclo endo diester **9** (4.74 g, 10.04 mmol) in ethanol (200 mL) was refluxed for 3 h under an atmosphere of hydrogen with freshly prepared W-2 Raney Ni, cooled, and filtered through a Whatman glass microfiber filter. The ethanol was removed in vacuo to leave a white foam which was recrystallized from ether to give **16** (3.45 g 73%). Note: depending on the freshness of the Raney Ni the yield varied between 85 and 60%; mp 174–175 °C, IR ($CHCl_3$) 3588 (br, OH), 1739 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 250 MHz) δ 3.03 (dd, 1 H, $J_{2,3}$ = 3.9, $J_{3,4}$ = 9.7 Hz, H_3), 3.35 (s, 3 H, CO_2Me), 3.55 (dd, 1 H, H_2), 3.77 (s, 3 H, CO_2Me), 3.79 (s, 6 H, 3′,5′-OMe), 3.85 (s, 3 H, 4′-OMe), 4.37 (d, 1 H, $J_{1,2}$ = 5.8 Hz, H_1), 5.54 (t, d with addition of D_2O, 1 H, $J_{3,4}$ = 9.7 Hz, H_4), 5.93, 5.90 (ABq, 2 H, J_{AB} ≤ 1.4 Hz, OCH_2O), 6.38 (s, 3 H, H_8, $H_{2'}$, $H_{6'}$), 7.17 (s, 1 H, H_5); MS (EI) *m/z* (rel int) 474 (M^+, 68), 456 ($M^+ - H_2O$, 100), 454 (34), 425 (12), 424 (16), 414 (14), 396 (52), 363 (61), 312 (32), 306 (64), 252 (57), 247 (68), 246 (31). Anal. Calcd for $C_{24}H_{26}O_{10}$: C, 60.75; H, 5.52. Found: C, 60.77; H, 5.13.

Dimethyl 4-(3,4-*trans*)-Hydroxy-6,7-(methylenedioxy)-1-(3′,4′,5′-trimethoxyphenyl)-3,4-dihydronaphthalene-2,3-dicarboxylate (19). The dihydronaphthalene **19** was a byproduct in the hydrogenolysis of **9** that was separated from the mother liquor by chromatography on silica gel (75:25 EtOAc:hexane) and recrystallized from ether/CH_2Cl_2: mp 133–134 °C; IR (Nujol) 3460 (OH), 1731 and 1721 cm^{-1} (C=O); λ(EtOH/max) 330 (log ϵ = 3.63), 203 (log ϵ = 4.44); ^1H NMR ($CDCl_3$, 250 MHz) δ 2.05 (d, 1 H, OH), 3.51 (s, 3 H, CO_2Me), 3.71 (s, 3 H, CO_2Me), 3.83 (br s, 6 H, 3′,5′-OMe), 3.92 (s, 3 H, 4′-OMe), 4.15 (d, 1 H, $J_{3,4}$ = 5.5 Hz, H_3), 5.06 (t, d with addition of D_2O, 1 H, H_4), 5.97 (s, 2 H, OCH_2O), 6.34 (br s, 1 H, $H_{2'}$), 6.40 (s, 1 H, H_8), 6.44 (br s, 1 H, $H_{6'}$), 6.96 (s, 1 H, H_5); MS (EI) *m/z* (rel int) 472 (M^+, 2), 454 ($M^+ - H_2O$, 100), 439 (24), 423 (12). Anal. Calcd for $C_{24}H_{24}O_{10}$: C, 61.02; H, 5.12. Found: C, 60.89; H, 5.67.

Dimethyl 4-(3,4-*trans*)-Hydroxy-6,7-(methylenedioxy)-1-(3′,4′,5′-trimethoxyphenyl)-2,3,4,4a,5,6,7,8-octahydro-2-naphthalene-2,3-*cis*-dicarboxylate (20). The octahydronaphthalene **20** was produced as a byproduct in the hydrogenolysis of **9** that was separated from the mother liquor by chromatography on silica gel (75:25, EtOAc:hexane) and recrystallized from ether/CH_2Cl_2: mp 150 °C; IR (KBr) 3378 (OH), 1741 cm^{-1} (C=O); ^1H NMR δ 1.72 (m, 1 H, H_5), 2.12–2.46 (m, 2 H, H_8, H_{4a}), 2.42 (m, 1 H, $H_{5'}$), 2.81 (q, 1 H, $H_{8'}$), 2.91 (dd, 1 H, H_3), 3.50 (s, 3 H, CO_2Me), 3.75 (s, 3 H, CO_2Me), 3.85 (s, 9 H, 3′,4′,5′-OMe), 3.90 (d, 1 H, H_2), 4.08 (m, 1 H, H_7), 4.17–4.29 (m, 2 H, H_4, H_6), 4.89 (s, 1 H, OCH_2O), 5.21 (s, 1 H, OCH_2O), 6.44 (s, 2 H, $H_{2'}$, $H_{6'}$); coupling constants (hertz) $J_{2,3}$ = 5.8, $J_{3,4}$ = 10.6, $J_{4a,5}$ = 10.5, $J_{4a,5'}$ = 4.6, $J_{5',6}$ = 7.8, $J_{5,6}$ ~ 10.5, $J_{5,5'}$ = 14.2, $J_{6,7}$ ~ 4, $J_{7,8}$ = 3.8, $J_{7,8'}$ = 3.3, $J_{8,8'}$ = 15.6; MS (EI) *m/z* (rel int) 478 (M^+, 100), 355 (11), 295 (17), 270 (11), 252 (11).

X-ray Crystal Data for 20. $C_{24}H_{30}O_{10}$, mol wt = 478.501, trigonal, a = 18.940 (5) Å, α = 115.72 (2)°, V = 3541 (2) Å^3, space group $R3$, Z = 6, ρ_c = 1.346 g cm^{-1}, $F(000)$ = 1524, T = 294 ± 1 K, λ = 0.710 69 Å, μ(Mo Kα) = 1.132 cm^{-1}.

Data were collected from a crystal of dimensions 0.28 × 0.32 × 0.33 mm mounted on a Syntex $P2_1$ diffractometer by the θ–2θ method ($2\theta \leq 45°$). From 3140 unique measured reflections, 1851 with $I \geq 3\sigma(I)$ were considered, observed, and used in the structure solution and refinement. The structure was solved by direct methods (MULTAN80) and refined by full-matrix least-squares methods to final R and R_w values of 0.041 and 0.047, respectively.

2-(2,3-*cis*)-Carbomethoxy-4-(3,4-*trans*)-hydroxy-3-(hydroxymethyl)-6,7-(methylenedioxy)-1-(1,2-*cis*)-(3′,4′,5′-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene 4,11-(Ethylboronate) (22). A solution of **16** (1.042 g, 2.20 mmol) in dry THF (40 mL) was cooled to 0 °C under a nitrogen atmosphere, and $LiB(Et)_3H$ (3.3 equiv) was added. After 1 h dilute aqueous acetic acid (50%) was added until the yellow color disappeared. Water (30 mL) was added, the mixture was extracted with methylene chloride (4 × 20 mL), and the combined extracts were dried (K_2CO_3) for 1 h. The solvent was removed to leave a yellowish solid. Recrystallization from ether gave **22** (0.924 g, 87%): mp 193–194 °C; IR ($CHCl_3$) 1726 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.77 (q, 2 H, J = 7.4 Hz, BCH_2CH_3), 0.95 (t, 3 H, BCH_2CH_3), 2.35 (m, 1 H, H_3), 3.19 (dd, 1 H, $J_{1,2}$ = 6.2, $J_{2,3}$ = 3.7 Hz, H_2), 3.34 (s, 3 H, CO_2Me), 3.79 (s, 7 H, 3′,5′-OMe, H_{11} obscured by 3′,5′-OMe), 3.85 (s, 3 H, 4′-OMe), 4.03 (dd, 1 H, $J_{11,11''}$ = 10.9, $J_{3,11''}$ = 4.4 Hz, $H_{11''}$), 4.38 (d, 1 H, $J_{1,2}$ = 6.2 Hz, H_1), 5.42 (d, 1 H, $J_{3,4}$ = 10.4 Hz, H_4), 5.94, 5.90 (ABq, $J_{AB} \leq$ 1.4 Hz, 2 H, OCH_2O), 6.38 (s, 3 H, H_8, $H_{2'}$, $H_{6'}$), 7.21 (s, 1 H, H_5); ^{11}B NMR ($CDCl_3$, 250 MHz, external reference BF_3:OEt_2) δ 30.4; MS (EI) m/z (rel int) 484 (M^+, 15), 316 (18), 257 (42), 252 (39), 231 (13); high-resolution mass spectrum: calcd for $C_{25}H_{29}O_9B$, 484.1905; found, 484.1905; calcd for $C_{16}H_{17}O_6B$, 316.1118; found, 316.1127; calcd for $C_{14}H_{14}O_4B$, 257.098 54; found, 257.099 04; calcd for $C_{15}H_{13}O_3B$, 252.099 81; found, 252.100 71; calcd for $C_{17}H_{12}O_1$, 232.090 69; found, 232.091 59. Anal. Calcd for $C_{25}H_{29}O_9B$: C, 61.96; H, 6.04. Found: C, 61.93 H, 6.22.

The 11,11″-dideuterio analogue was prepared in the same way by using lithium triethylborodeuteride as the reducing agent.

Methyl Isopicropodophyllate (11). A solution of the boronate **22** (0.766 g, 1.583 mmol) in MeOH/THF (20 mL, 1:1) was stirred for 12 h with water (2 mL). The solvent was removed in vacuo, EtOAc (40 mL) added, the organic phase washed (H_2O, 4 × 20 mL), and the solvent removed to leave **11**, which was recrystallized from ether/CH_2Cl_2 (0.635 g, 90%): mp 202–204 °C; IR (KBr) 3409 (br, OH), 1728 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.27 (m, 1 H, H_3), 3.24 (dd, 1 H, $J_{1,2}$ = 5.7, $J_{2,3}$ = 3.9 Hz, H_2), 3.37 (s, 3 H, CO_2Me), 3.78 (s, 6 H, 3′,5′-OMe), 3.80–3.85 (H_{11} obscured by 3′,5′-OMe and 4′-OMe), 3.85 (s, 3 H, 4′-OMe), 3.93 (dd, 1 H, $J_{11,11''}$ = 10.9, $J_{3,11''}$ = 7.4 Hz, $H_{11''}$), 4.32 (d, 1 H, H_1), 5.14 (d, 1 H, $J_{3,4}$ = 9.8 Hz, H_4), 5.93, 5.90 (ABq, 2 H, J_{AB} = 1.4 Hz, OCH_2O), 6.36 (s, 3 H, H_8, $H_{2'}$, $H_{6'}$), 7.11 (s, 1 H, H_5); MS (EI) m/z (rel int) 446 (M^+, 5), 442 (88), 428 ($M^+ - H_2O$, 32), 414 (77), 410 (37), 397 (30), 396 (100), 352 (25), 351 (98), 320 (17), 312 (12), 246 (17), 215 (56), 168 (56). Anal. Calcd for $C_{23}H_{26}O_9$: C, 61.88; H, 5.87. Found: C, 61.82; H, 5.79.

Isopicropodophyllin (35). A solution of methyl isopicropodophyllate (11, 0.0632 g, 0.1363 mmol) in dry THF (25 mL) was treated with NaH (2 equiv) for 1 h at 25 °C under a nitrogen atmosphere. Dry ice and water (15 mL) were added, the volume was reduced to approximately 15 mL, and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. The product was recrystallized from CH_2Cl_2/MeOH to give **35** (0.0498 g, 85%): mp 191–192 °C; IR (KBr) 3429 (OH), 1756 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.03 (m, 1 H, H_3), 3.27 (dd, 1 H, $J_{1,2}$ = 5.4, $J_{2,3}$ = 10.7 Hz, H_2), 3.72 (dd, 1 H, $J_{11,11''}$ = 9.0, $J_{3,11}$ = 6.9 Hz, H_{11}) 3.76 (s, 6 H, 3′,5′-OMe), 3.83 (s, 3 H, 4′-OMe), 4.58 (t, 1 H, $J_{3,11''}$ = 9.0 Hz, $H_{11''}$), 4.66 (d, 1 H, H_1), 4.78 (t, d with addition of D_2O, 1 H, $J_{3,4}$ = 5.5 Hz, H_4), 5.99 (s, 2 H, OCH_2O), 6.46 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.69 (s, 1 H, H_8), 7.10 (s, 1 H, H_5); MS (EI) m/z (rel int) 414 (M^+, 80), 396 (100), 246 (21), 181 (26), 168 (42).

Methyl Isopodophyllate (13) (The 11,11″-Dideuterio Analogue). The 11,11″-dideuterio boronate (0.113 g, 0.234 mmol) was dissolved in methanol (30 mL), methanolic sodium methoxide added, and the solution stirred for 1 h at 25 °C. Dry ice and water (20 mL) were added, the volume was reduced in vacuo to approximately 20 mL, and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were dried (Na_2SO_4), and the solvent was removed. The crude product was recrystallized from ether to give **13** (0.0922 g, 81%); mp 167–169 °C; IR (KBr) 3429 (br, OH), 1730 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.02 (dd, 1 H, $J_{2,3}$ = 11.8, $J_{3,4}$ = 9.3, Hz, H_3), 2.84 (dd, 1 H, $J_{1,2}$ = 11.1, H_2), 3.54 (s, 3 H, CO_2Me), 3.79 (s, 6 H, 3′,5′-OMe), 3.84 (s, 3 H, 4′-OMe), 4.25 (d, 1 H, H_1), 4.92 (t, d with addition of D_2O, 1 H, $J_{3,4}$ = 9.3 Hz, H_4), 5.93, 5.91 (ABq, $J_{AB} \leq$ 1.4 Hz, 2 H, OCH_2O), 6.19 (s, 1 H, H_8), 6.28 (s, 2 H, $H_{2'}$, $H_{6'}$), 7.09 (s, 1 H, H_5); MS (EI) m/e (rel int) 448 (M^+, 0.7), 416 (100), 398 (9), 168 (14).

Isopodophyllic Acid (23). Potassium carbonate (0.3 g) was added to a solution of the boronate **22** (0.507 g, 1.1334 mmol) in methanol (30 mL). After the solution stirred for 4 h at 25 °C, the methanol was removed in vacuo, water (20 mL) was added, and the aqueous solution was acidified with concentrated HCl. The resulting precipitate was filtered, washed with water, and recrystallized from MeOH/CH_2Cl_2 to give **23** (0.467 g, 95%): mp 219–220 °C; IR (KBr) 3386 (br) and 3260 (br, C*OOH*, OH), 1694 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6, 250 MHz) δ 1.84 (m, 1 H, H_3), 2.84 (dd, 1 H, $J_{1,2}$ = 10.9, $J_{2,3}$ = 11.3 Hz, H_2), 3.44 (dd, 1 H, $J_{11,11''}$ = 10.0, $J_{3,11}$ = 3.5 Hz, H_{11}) 3.61 (s, 3 H, 4′-OMe), 3.65 (s, 6 H, 3′,5′-OMe), 3.77 (dd, 1 H, $J_{3,11''}$ = 3.1 Hz, $H_{11''}$), 4.07 (d, 1 H, H_1), 4.63 (t, d with addition of D_2O, 1 H, $J_{3,4}$ = 9.6 Hz, H_4), 5.89 (s, 2 H, OCH_2O), 6.03 (s, 1 H, H_8), 6.38 (s, 2 H, $H_{2'}$, $H_{6'}$), 7.00 (s, 1 H, H_5) 12.0 (br s, 1 H COOH); MS (EI) m/z (rel int) 414 ($M^+ - H_2O$, 5), 396 (3), 168 (6), 57 (7), 43 (100). This is an unstable compound and did not provide acceptable elemental analysis results.

Isopodophyllotoxin (31). Isopodophyllic acid (**23**, 0.490 g, 1.1435 mmol) was dissolved in dry dioxane (10 mL) and stirred with DCC (1.1 equiv, 0.260 g). When the reaction was completed (~4 h by TLC; a precipitate also formed), the dioxane was removed in vacuo, methanol and chloroform were added, and the mixture was dissolved by warming on a steam bath. Isopodophyllotoxin was then crystallized from the solution (0.3293 g, 69%); mp 272–273 °C; IR (KBr) 3447 (br, OH), 1744 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6, 250 MHz) δ 2.5 (m, 1 H, partially obscured by DMSO, H_3), 3.14 (dd, 1 H, $J_{1,2}$ = 11.4, $J_{2,3}$ = 13.7 Hz, H_2), 3.62 (s, 3 H, 4′-OMe), 3.68 (s, 6 H, 3′,5′-OMe), 4.00 (d, 1 H, H_1), 4.13 (dd, 1 H, $J_{11,11''}$ = 8.7, $J_{3,11}$ = 10.4 Hz, H_{11}), 4.49 (dd, 1 H, $J_{3,11''}$ = 7.6 Hz, $H_{11''}$), 4.81 (t, d with addition of D_2O, 1 H, $J_{3,4}$ = 10.0 Hz, H_4), 5.89, 5.87 (ABq, $J_{AB} \leq$ 1.4 Hz, 2 H, OCH_2O), 6.12 (s, 1 H, H_8), 6.47 (s, 2 H, $H_{2'}$, $H_{6'}$), 7.01 (s, 1 H, H_5); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.49–2.93 (m, 2 H, H_2, H_3), 3.81 (s, 6 H, 3′,5′-OMe), 3.85 (s, 3 H, 4′-OMe), 4.07 (d, 1 H, $J_{1,2}$ = 10.6 Hz, H_1), 4.16 (dd, 1 H, $J_{11,11''}$ = 8.8, $J_{3,11}$ = 10.1 Hz, H_{11}), 4.73 (dd, 1 H, $J_{3,11''}$ = 6.2 Hz, $H_{11''}$), 4.49 (t, d with addition of D_2O, 1 H, $J_{3,4}$ = 9.2 Hz, H_4), 5.94, 5.93 (ABq, J_{AB} = 1.4 Hz, 2 H, OCH_2O), 6.33 (s, 1 H, H_8), 6.37 (s, 2 H, $H_{2'}$, $H_{6'}$), 7.11 (s, 1 H, H_5); MS (EI) m/z (rel int) 414 (M^+, 5), 396 (3), 57 (6), 43 (100), 42 (32), 41 (28).

11,11″-Dideuterioisopodophyllotoxin 4-Acetate (32). A suspension of dideuterioisopodophyllotoxin (0.046 g, 0.1098 mmol) in CH_2Cl_2 (10 mL) was treated with DMAP (0.4 equiv), imidazole (1.2 equiv), and acetic anhydride (1 mL). After 2 h the clear solution was washed once with aqueous $NaHCO_3$ and twice with water (20 mL). The volume was reduced over a steam bath, and MeOH added; crystals formed on standing (0.042 g, 83%): mp 273–274 °C; IR ($CHCl_3$), 1783 (C=O), 1736 cm^{-1} (Ac, C=O); ^{1}H NMR (d_5-pyridine, 250 MHz) δ 2.17 (s, 3 H, $OCOCH_3$), 2.90 (dd, 1 H, $J_{2,3}$ = 14.1, $J_{3,4}$ = 10.0, Hz, H_3), 3.6 (obscured by 3′,5′-OMe, H_2), 3.67 (s, 6 H, 3′,5′-OMe), 3.87 (s, 3 H, 4′-OMe), 4.38 (d, 1 H, $J_{1,2}$ = 11.4 Hz, H_1), 5.97, 5.93 (dd, 2 H, OCH_2O), 6.40 (d, 1 H, H_4), 6.65 (s, 1 H, H_8), 6.88 (s, 2 H, $H_{2'}$, $H_{6'}$), 7.05 (s, 1 H, H_5); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.23 (s, 3 H, $OCOCH_3$), 2.8 (m, 1 H, $J_{2,3}$ = 14.1, $J_{3,4}$ = 10.0, Hz, H_3), 2.7 (m, 1 H, $J_{1,2}$ = 10.8, $J_{2,3}$ = 14.1, Hz, H_2), 3.82 (s, 6 H, 3′,5′-OMe), 3.85 (s, 3 H, 4′-OMe), 4.08 (d, 1 H, $J_{1,2}$ = 10.8 Hz, H_1), 5.94, 5.93 (ABq, J_{AB} = 1.3 Hz, 2 H, OCH_2O), 6.11 (d, 1 H, $J_{3,4}$ = 10.0 Hz, H_4), 6.33 (s, 1 H, H_8), 6.37 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.71 (s, 1 H, H_5).

Epipicropodophyllic Acid (28). The diol **10** (0.16 g) was refluxed in dioxane (10 mL) with water (3 mL) and 2 N NaOH (2 mL) for 4 h. Water was added, the dioxane removed in vacuo, and the aqueous solution washed with ether (25 mL), cooled to

0 °C, and acidified with concentrated HCl. The acidified aqueous solution was extracted with EtOAc (3 × 20 mL), the combined extracts were dried (Na_2SO_4), the solvent was evaporated, and the residue was crystallized from ether (0.1041 g, 63%): mp 187–188 °C; IR (KBr) 1700 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 250 MHz) δ 2.40–2.50 (H_3, obscured by DMSO), 3.02 (dd, 1 H, $J_{1,2}$ = 8.0, $J_{2,3}$ = 3.2 Hz, H_2), 3.43 (dd, 1 H, $J_{11,11''}$ = 10.6, $J_{3,11}$ = 5.9 Hz, H_{11}), 3.61 (s, 3 H, 4′-OMe), 3.67 (s, 6 H, 3′,5′-OMe), 3.65–3.70 ($H_{11''}$, obscured by 3′,5′-OMe), 4.28 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H_1), 4.91 (t, d with addition of D_2O, 1 H, $J_{3,4}$ = 5.0 Hz, H_4), 5.92, 5.91 (ABq, J_{AB} = 1.4 Hz, 2 H, OCH_2O), 6.27 (s, 1 H, H_8), 6.34 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.94 (s, 1 H, H_5), 12.1 (br s, 1 H, COOH); MS (EI) *m/z* (rel int) 414 ($M^+ - H_2O$, 31), 245 (13), 181 (8), 43 (100). This was an unstable compound and did not provide acceptable elemental analysis results.

Epipicropodophyllin (24). Methyl epipodophyllate (**10**, 0.032 g) was dissolved in methanol (20 mL), and sodium methoxide in methanol added and stirred for 3 h at 25 °C. Dry ice and water (10 mL) were added. The volume was reduced in vacuo to approximately 10 mL, and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were dried (Na_2SO_4), and the solvent was removed. The crude product was recrystallized from ether to give **24** (0.0283 g, 96%): mp 188–190 °C; IR ($CHCl_3$) 1762 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 250 MHz) δ 3.16 (m, 1 H, H_3), 3.44 (dd, 1 H, $J_{1,2}$ = 3.7, $J_{2,3}$ = 10.4 Hz, H_2), 3.78 (s, 6 H, 3′,5′-OMe), 3.83 (s, 3 H, 4′-OMe), 4.35 (H_{11} and $H_{11''}$ are separated by approximately 2 Hz, AB component of an ABX system, $J_{3,11}$ = ~4.4, $J_{3,11''}$ = ~7.2, Hz), 4.44 (d, 1 H, H_1), 4.81 (d, 1 H, $J_{3,4}$ = 5.5 Hz, H_4), 5.98, 5.95 (ABq, $J_{AB} \leq$ 1.4 Hz, 2 H, OCH_2O), 6.35 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.60 (s, 1 H, H_8), 7.01 (s, 1 H, H_5); MS (EI) *m/z* (rel int) 414 (M^+, 1), 58 (3), 57 (6), 43 (100), 42 (32), 41 (35). The (+) isomer had been previously prepared[39] by epimerization of epipodophyllotoxin.

4-*O*-Methylepiisopicropodophyllin (37) and 4-*O*-Methylisopicropodophyllin (38). Methyl isopicropodophyllate (**11**, 0.074 g) was dissolved in MeOH (30 mL) over a steam bath and cooled, and dilute hydrochloric acid (4 drops, 5%) was added. After this stirred for 2 days (a precipitate had formed after 1 day) at ambient temperature, water was added, the precipitate was filtered, and washed with water. The ^1H NMR spectrum of this material showed the presence of **37** and **38**. The crude product was recrystallized from CH_2Cl_2/MeOH to give **37** (0.057 g, 74%), and the mother liquor, upon concentration and crystallization from CH_2Cl_2/MeOH, gave **38** (0.017 g, 24%). **37**: mp 242–243 °C; IR (Nujol) 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 250 MHz) δ 3.5 (m, 2 H, H_2, H_3), 3.59 (s, 3 H, OMe), 3.86 (s, 6 H, 3′,5′-OMe), 3.89 (s, 3 H, 4′-OMe), 4.07 (d, 1 H, $J_{1,2}$ = 3.3 Hz, H_1), 4.23 and 4.27 (AB component of an ABX system, 1 H, $J_{3,11}$ = 7.7, $J_{3,11''}$ = 3.8 Hz, H_{11}, $H_{11''}$), 4.38 (d, 1 H, $J_{3,4}$ = 5.8 Hz, H_4), 5.93, 5.92 (ABq, J_{AB} = 1.2 Hz, 2 H, OCH_2O), 6.54 (s, 1 H, H_8), 6.90 (s, 2 H, $H_{2'}$, $H_{6'}$), 7.03 (s, 1 H, H_5); MS (EI) *m/z* (rel int) 428 (M^+, 100), 396 (10), 312 (50), 313 (28), 297 (17), 282 (17); high-resolution mass spectrum calcd for $C_{23}H_{24}O_8$, 428.147 12; found, 428.146 72. Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.46; H, 5.65. Found: C, 64.42, H, 5.89. **38**: mp 164–165 °C; IR ($CHCl_3$) 1767 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 250 MHz) δ 3.23 (m, 1 H, partially obscured by H_2, H_3), 3.29 (partially obscured by OMe and H_3, H_2), 3.34 (s, 3 H, OMe), 3.81 (s, 6 H, 3′,5′-OMe), 3.86 (s, 3 H, 4′-OMe), 4.26 (d, 1 H, $J_{3,4}$ = 2.9 Hz, H_4), 3.75–3.80 (H_{11} obscured by 3′,5′-OMe), 4.50 (dd, 1 H, $J_{3,11''}$ = 7.4, $J_{11,11''}$ = 8.0 Hz, $H_{11''}$), 4.63 (d, 1 H, $J_{1,2}$ = 4.1 Hz, H_1), 5.97 (s, 2 H, OCH_2O), 6.66 (s, 3 H, $H_{2'}$, $H_{6'}$, H_8), 6.96 (s, 1 H, H_5).

X-ray Crystal Data for 38. $C_{23}H_{24}O_8$, mol wt = 428.443, monoclinic, a = 25.794 (5), b = 8.406 (2), c = 21.785 (5) Å, β = 115.95 (2)°, V = 4247 (2) $Å^3$, space group $C2/c$, Z = 8, ρ_c = 1.340 g cm^{-1}, $F(000)$ = 1808, T = 294 ± 1 K, λ = 0.710 69 Å, μ(Mo Kα) = 1.096 cm^{-1}.

Data were collected from a crystal of dimensions 0.30 × 0.30 × 0.36 mm mounted on a Syntex $P2_1$ diffractometer by the θ–2θ method ($2\theta \leq 45°$). From 2790 unique measured reflections, 1488 with $I \geq 3\sigma(I)$ were considered, observed, and used in the structure solution and refinement. The structure was solved by direct methods (MULTAN80) and refined by full-matrix least-squares methods to final R and R_w values of 0.034 and 0.037, respectively.

Methyl 3-(Hydroxymethyl)-6,7-(methylenedioxy)-1-(1,2-*cis*)-(3′,4′,5′-trimethoxyphenyl)-1,2-dihydronaphthalene-2-carboxylate (44). A solution of **11** (20.2 mg) in dioxane (20 mL) and 2 N HCl (5 drops) was stirred for 3 days at 25 °C. The solvent was removed in vacuo, water was added, and the mixture was extracted with CH_2Cl_2. The ^1H NMR spectrum of the crude product showed the two compounds **44** and **11** in an approximately 1:1 ratio. These were separated by chromatography on silica gel (3:1, EtOAc:hexane), and **44** was isolated (8.9 mg, 46%): mp 153–4 °C; UV λ(EtOH/max) 308 (log ε = 4.16); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.13 (t, 1 H, removed with the addition of D_2O, OH) 3.53 (s, 3 H, CO_2Me), 3.71 (d, 1 H, $J_{11,11''}$ = 7.3 Hz, H_{11}), 3.75–3.80 (H_2 partially obscured by 3′,5′-OMe) 3.80 (s, 6 H, 3′,5′-OMe), 3.84 (s, 3 H, 4′-OMe), 4.26 (d, 1 H, $J_{1,2}$ = 5.83 Hz, H_1), 4.36 (d, 1 H, $H_{11''}$), 5.92 (s, 2 H, OCH_2O), 6.50 (s, 3 H), 6.54 (s, 1 H), 6.67 (s, 1 H); MS (EI) *m/z* (rel int) 428 (M^+, 26), 396 (100), 365 (6), 352 (10), 351 (43), 339 (12), 320 (12).

4-Deoxyisopicropodophyllin (43). 4-*O*-Methylepiisopicropodophyllin (**37**, 0.0219 g) in HOAc (10 mL) and EtOAc (5 mL) with trifluoroacetic acid (5 drops) and 10% Pd/C (10 mg) was hydrogenated at 50 psi for 5 days. The workup was the same as for deoxypicropodophyllin (below) except that purification was accomplished on a preparative 1000-μm chromatography plate (60:40 EtOAc:hexane) to give **43**: mp 198–9 °C (0.0146 g, 71%); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.70 (dd, 1 H, J_{gem} = 15.5, $J_{3,4}$ = 5.5 Hz, H_4), 2.97 (dd, 1 H, $J_{3,4'}$ = 8.4 Hz, $H_{4'}$), 3.10–3.19 (m, 2 H, H_2, H_3), 3.49 (t, 1 H, $J_{11,11''}$ = 8.5, $J_{3,11}$ = 8.5 Hz, H_{11}), 3.77 (s, 6 H, 3′,5′-OMe), 3.83 (s, 3 H, 4′-OMe), 4.36–4.45 (m, 2 H, $H_{11''}$, H_1), 5.95 (s, 2 H, OCH_2O), 6.50 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.65 (s, 1 H, H_8), 6.7 (s, 1 H, H_5).

4-Deoxypicropodophyllin (47). Epipicropodophyllin (0.0543 g) in HOAc (15 mL) with 10% Pd/C (10 mg) was hydrogenated at 50 psi for 24 h. The reaction mixture was filtered through a Whatman glass microfiber filter, water added (10 mL), and the volume reduced to approximately 5 mL. Saturated $NaHCO_3$ was added to neutralize the acid, the solution was extracted with CH_2Cl_2 (3 × 10 mL), the combined extracts were dried (Na_2SO_4), and the solvent were removed in vacuo. Recrystallization from ether gave **47** (0.0457 g, 88%): mp 169–171 °C (lit.[40] 169.5–171 °C for the (+) isomer), lost crystalline structure at 149 °C; IR ($CHCl_3$) 1763 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz), 2.50 (dd, 1 H, J_{gem} = 5.3, $J_{4,4'}$ = 15.2 Hz, H_4), 2.87 (dd, 1 H, $J_{3,4'}$ = 6.3, $H_{4'}$), 3.02 (m, 1 H, $J_{3,11}$ = 3.1, $J_{3,11''}$ = 7.3, $J_{2,3}$ = 9.5 Hz, H_3), 3.34 (dd, 1 H, $J_{1,2}$ = 3.0, H_2), 3.78 (s, 6 H, 3′,5′-OMe), 3.83 (s, 3 H, 4′-OMe), 3.98 (dd, 1 H, $J_{11,11''}$ = 9.2 Hz, H_{11}), 4.38 (d, H_1), 4.45 (dd, 1 H, $J_{11,11''}$ = 9.2 Hz, $H_{11''}$), 5.92, 5.95 (ABq, J_{AB} = 1.4 Hz, 2 H, OCH_2O), 6.34 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.59 (s, 1 H, H_8), 6.67 (s, 1 H, H_5).

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Supplementary Material Available: Atomic coordinates, anisotropic thermal parameters, and bond lengths and angles for **20** and **38** (10 pages). Ordering information is given on any current masthead page.

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