Modes of Methyleneoxy Bridging and Their Effect on Tetrahydronaphthalene Lignan Cytotoxicity

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Received April 15, 2002

Dioxatricyclodecane, oxabicyclooctane, and benzodihydropyran derivatives of α-conidendrin (ACON), podophyllotoxin (PT), and sikkimotoxin (SK) were prepared to learn which methyleneoxy bridging modes and arene and aryl substituents coincided with high cytotoxicity. PT-derived dioxatricyclodecane **14** showed in vitro activity at 10^{-8} M. SK analogue **12** was less active, and ACON analogue **11** was inactive at 10^{-4} M. In vivo intraperitoneal and subcutaneous activities of **14** were observed. In vitro cytotoxicities were higher for oxabicyclooctanes when hydroxymethyl group and methyleneoxy bridge were cis, as in deoxypicropodophyllin analog **20**, rather than trans, as in PT analogue **5**. Acetylation of the hydroxymethyl group of **20** lowered activities, whereas acetylation of **5** increased or lowered activities. Reduction of the hydroxymethyl group of **5** to a methyl group increased cytotoxicities. Molecular dynamics indicated the THN scaffold of benzodihydropyrans was conformationally mobile, but scaffolds of oxabicyclooctanes and dioxatricyclodecanes were immobile. Each of three PT-benzodihydropyrans was less active than its oxabicyclooctane counterpart.

Introduction

Among structural components most important for high cytotoxicity of a tetrahydronaphthalene (THN) lignan are configuration and substitution of the pendant aryl group located at C-4, the benzhydrylic carbon of podophyllotoxin (PT, **1**, Scheme 1). This has been demonstrated[1] through SAR, which was facilitated by oxidative[2] methyleneoxy bridging of PT and dimethyl-α-conidendrin (**2**) through their respective diols **3** and **4** to oxabicyclooctane derivatives **5** and **6**. Succeeding hydrogenolyses were directed through the use of the appropriate reagents to proceed with retention or inversion at C-4 of **5** or **6** and resulted in α- or *β*-stereochemistry for the pendant aryl group as required. Simultaneously, the THN was regenerated in **7** and **8**, and subsequently conformational rigidity of the THN scaffold was restored by dehydration, giving trans-fused oxolane derivatives **9** and **10**, which replaced the original lactones.

The C-4 configuration in PT, its oxabicyclooctane **5**, and the oxabicyclooctane **6** derived from α-conidendrin (ACON) is the same. Conceivably, conformational immobilization of the THN scaffold could be achieved through an oxabicyclooctane just as it is by a trans-fused lactone or oxolane, although molecular models reveal the spacial relation of pendant to fused aromatic rings attached to an oxabicyclooctane scaffold is somewhat different from what it is in the corresponding lactone or oxolane derivatives.[3] These considerations prompted our examination of methyleneoxy-bridging within oxabicyclooctanes and dioxatricyclodecanes and its effect on cytotoxicities. Both bridging modes immobilize the conformation of the THN scaffold. An added incentive for engaging the preparation and cytotoxicity screening of these bridged compounds were future prospects for including additional THN lignans which, initially possessing *β*-pendant-ring stereochemistry, could be converted to α-stereochemistry directly with resulting cytotoxic activation without further hydrogenolyses and oxolane formation. The foregoing prospects have been examined. Additionally, the cytotoxicity of a group of lignans having a conformationally mobile mode of bridging represented by benzodihydropyrans has been compared to the analogous group of conformationally immobilized oxabicyclooctanes.

Results

Chemistry. ACON-derived diol **4**[4] (Scheme 1) was converted directly to dioxatricyclodecane **11** (Scheme 2) in 38% yield by $CuSO_4/K_2S_2O_8$. Using the same oxidant couple, a 36% yield of the sikkimotoxin (SK) analogue **12** was obtained directly from the corresponding diol **13**[1]. However, when this one-step procedure was applied to 9-deoxypodophyllol, **3** (Scheme 1), the dioxatricyclodecane **14** dropped to 0.7% yield. The overall yield of **14** was 29% from a two-step process involving dehydration of podophyllol **15** (Scheme 2) to the known oxabicyclooctane **16**[5] and then treating the latter with the oxidant couple in the usual manner to obtain **14**. However, **14** and oxabicyclooctanes **5** (Scheme 1) and **16** (Scheme 2), all required in smaller amounts for initial cytotoxicity evaluations, could be obtained in the respective yields of 3.7, 44, and 27% from a single oxidation of diol **3** with DDQ. Oxabicyclooctane **5** was converted to its acetate **17** (Scheme 1), which was required for cytotoxicity comparisons. DDQ also converted 9-deoxypicropodophyllol (picroPT) **18** (Scheme 3) to a mixture of the isomeric pair of oxabicyclooctanes **19** and **20** in 10 and 20% yields, respectively. Likewise, DDQ converted SK-based diol **13** to oxabicyclooctanes

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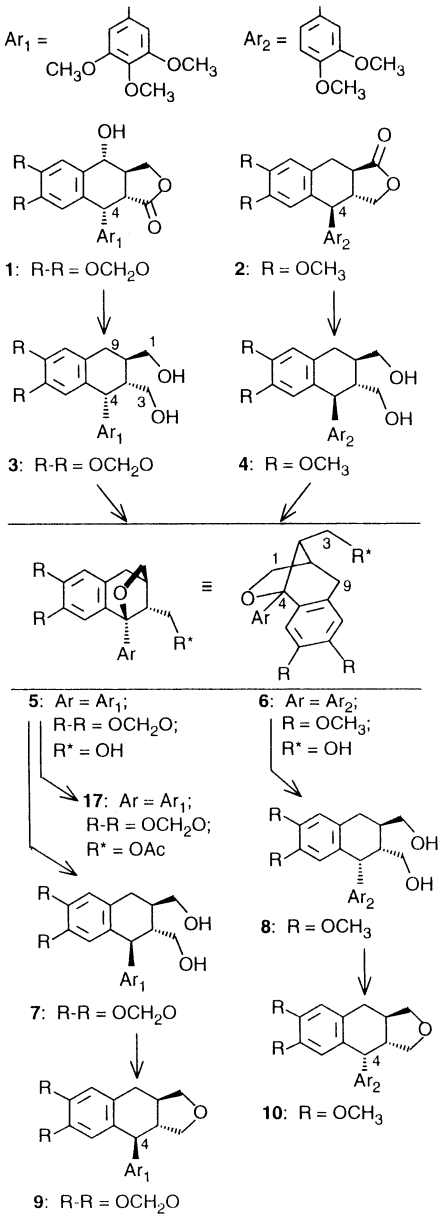
10.1021/jm020158p CCC: $25.00
Published on Web 02/22/2003

Scheme 1

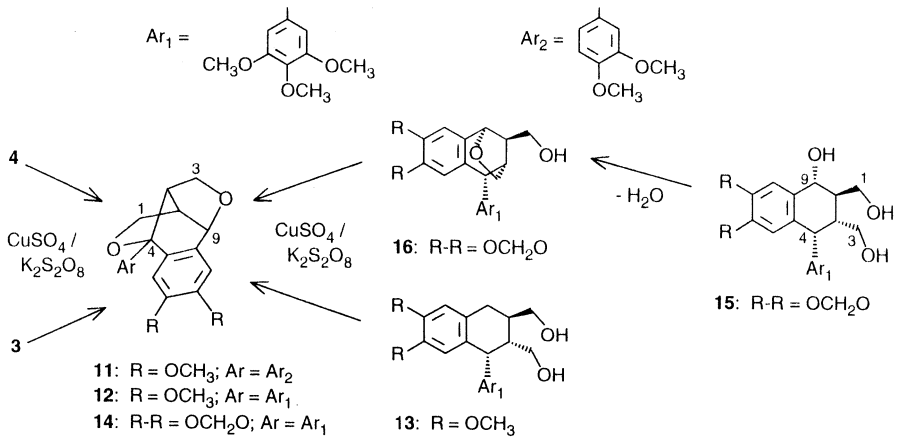


21 and isomeric **22**, in yields of 32% and 43%, respectively. Compound **20** was converted to its acetate **23**. The cytotoxicities of the PT and picroPT acetates would be compared with those of their immediate precursor alcohols. Also, the hydroxymethyl groups of PT-derived **5** and ACON-derived **6** were replaced by methyl groups to learn the influence of both the C-3 hydroxy and acetoxy groups on the cytotoxicity levels of oxabicyclooctanes lacking these more polar groups. Thus, the five-step route summarized in Scheme 4, starting from dimethyl ACON (**2**) and involving the four intermediates **24**−**27**, produced target **28** in 29% overall yield.[6] A similar seven-step sequence started from 9-deoxy PT (**29**, Scheme 4) proceeded through intermediates **30**−**35** and yielded target **36** in 4% overall yield. Relative to the preparation of **28**, the two additional steps leading to **36** included protection and deprotection of the C-1 hydroxyl group, which was required for final methyleneoxy bridging to C-4.

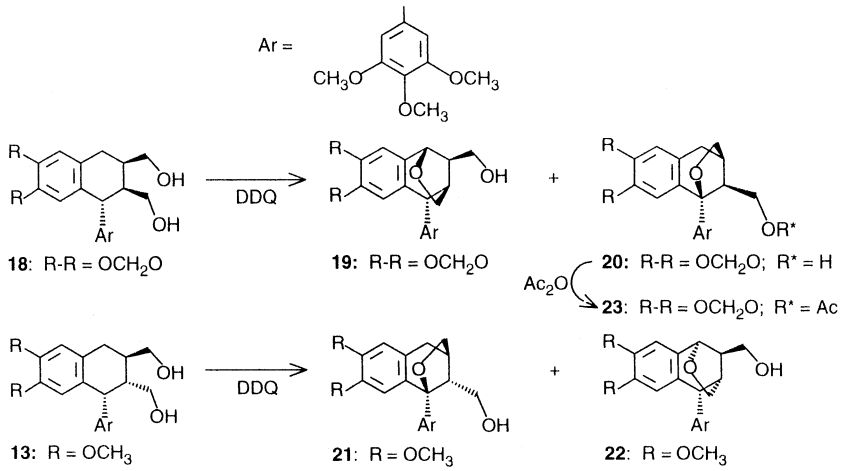
Access to PT and SK benzodihydropyrans was through precursor diols **39** and **42** (Scheme 5). Steps required to obtain diol **39** included Pd/C-catalyzed hydrogenolysis of the C-9 hydroxyl group of 9-epi-4′-demethyl PT (**37**) followed by LAH reduction of the resulting lactone **38**. Preparation of the required SK-based diol **42** involved demethylation at the C-4′ oxygen of 9-deoxysikkimotoxin, **40**, followed by LAH reduction of the resulting lactone **41**. Phenolic diols **39** and **42** were oxidized by sodium metaperiodate[7] (Scheme 6) to their respective *o*-quinones **43** and **44**, which resulted through linking of a C-3 hydroxyl group to a C-2′ position of a pendant, *o*-quinone ring. The intermediate, PT-derived *o*-quinone **43** was isolated and characterized. Subsequent reduction of both quinone intermediates by sodium hydrosulfite in the presence of sodium hydrogen phosphate, followed by treatment with dimethyl sulfate, provided the corresponding PT and SK benzodihydropyrans **45** and **46**. The PT benzodihydropyran alcohol **45** was derivatized as its acetate, **47**, and converted to its methanesulfonate, **48**. The last of these three was treated with sodium iodide and zinc powder to obtain **49**, the product in which the hydroxymethyl group of the precursor **45** had been replaced as a methyl group.

Molecular Modeling. Molecular dynamics (MD) simulations were carried out with dioxatricyclodecane **14**, oxabicyclooctanes **36** and **16**, and benzodihydropyran **45**, which were chosen as representative structures resulting from various modes of methyleneoxy bridging. The trajectories of 400 ps simulations for all structures showed that a single skeletal molecular conformation characterized the dioxatricyclodecanes and each of the

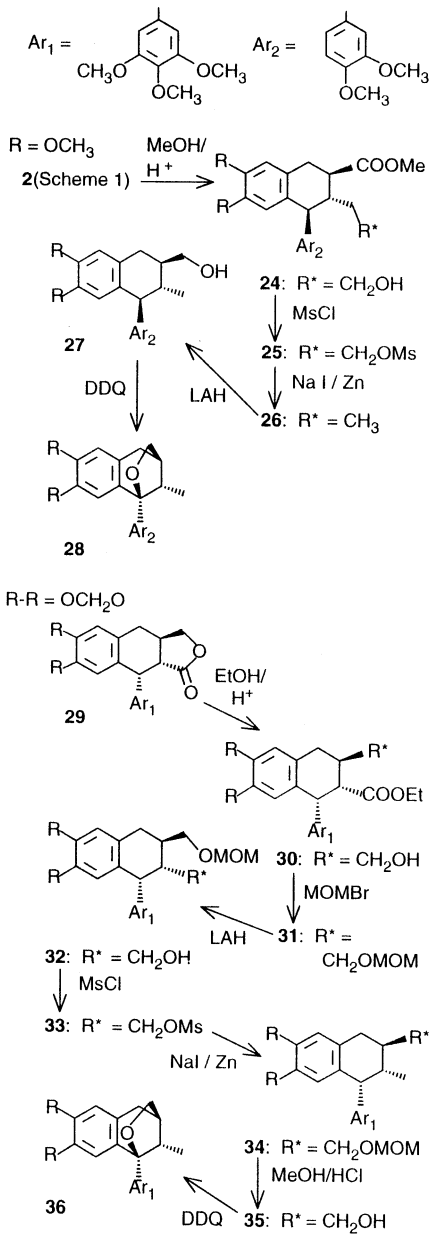
Scheme 2



Scheme 3



Scheme 4



two types of oxabicyclooctanes, whereas the benzodihydropyrans exhibited a high degree of conformational flexibility. The dioxatricyclodecane and oxabicyclooctane conformations were stable and showed little torsional variability. In contrast, the benzodihydropyran skeleton underwent multiple transitions between four conformers, all relatively close in potential energy but exhibiting widely varying torsion angles in the nonaromatic portions of the structure. The minimum-energy conformations of the dioxatricyclodecane and oxabicyclooctane structures and the four benzodihydropyran conformers are illustrated in Figure 1. Comparing these conformational features with the respective cytotoxicity levels could indicate that conformational rigidity in the THN scaffold in these compounds may be among the necessary structural features that determine potential for high levels of cytotoxicity.

Cytotoxicities, SAR, and Discussion. The antiproliferative activities of the eighteen dioxatricyclodecanes, oxabicyclooctanes, and benzodihydropyrans were determined through the National Cancer Institute (NCI), Cancer Drug Discovery and Development program. Each compound was evaluated against approximately 55 cell lines of different tumor origins. The resulting mean graph midpoint (MGM), delta, and range values given in Table 1 allowed a preliminary, general comparison of the 18 compound activities across all cell lines. The MGM is calculated as the average GI_{50} for all tested cell lines. It ranged in value from 10^{-4} to 10^{-8} M and is expressed in Table 1 as log GI_{50}, which had values of >-4 to <-8 M. The PT-derived dioxatricyclodecane, **14**, was generally the most cytotoxic (MGM -7.74 M) of the 18 compounds. Also, **14** had the lowest delta value (0.26), which indicated relatively little difference between this compound's MGM and the log GI_{50} value (<-8.00 M) observed for 49 of the 57 cell lines. However, the relatively high range value (3.37) for **14** pointed to a considerable activity difference in the most and least sensitive of the 57 cell lines. Since cytotoxicity is cell line sensitive, relative activities of the 18 compounds were compared more specifically on the basis of log GI_{50} values given in Table 2. All compounds except **6**, **11**, and **22** were cytotoxic, with log GI_{50} levels between >-4 and <-8 M. Dioxatricyclodecane **14** was the most active of the 18 compounds in all eight cell panels.[8,9] In vivo activities of **5** and **14** were appraised by the NCI fiber assay,[10] which involves the intraperitoneal (IP) and subcutaneous (SC) implanta-

Scheme 5

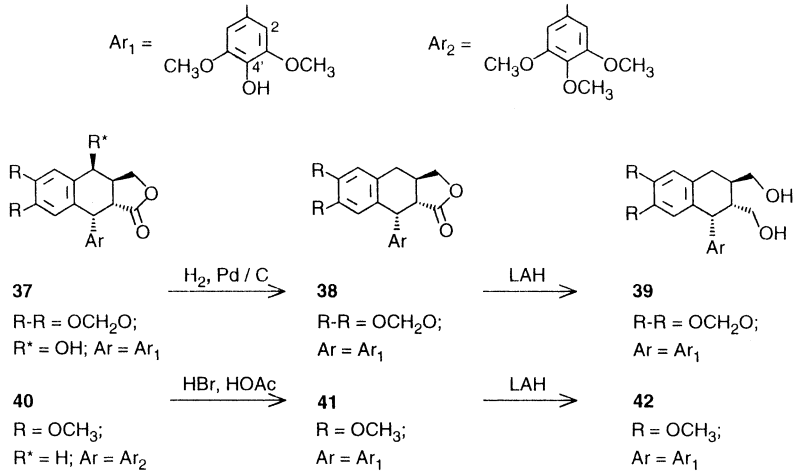


Table 1. Mean Cytotoxicities of Dioxatricyclodecane, Oxabicyclooctane, and Benzodihydropyran Derivatives of THN[a] Lignans toward Human Cancer Cells

	cytotoxicity (log GI_{50}, M)[b]			
compd	MGM[c]	delta[d]	range[e]	cell lines[f,g]
5	−5.39	1.14	2.53	58
6	>−4.00[h]			47
11	>−4.00[h]			51
12	−4.38	0.41	0.79	56
14	−7.74	0.26	3.37[i]	57
16	−4.63	1.15	1.51	53
17	−5.41	0.92	2.33	58
19	−4.49	1.09	1.58	57
20	−4.98	0.73	1.71	56
21	−4.32	0.44	0.76	56
22	>−4.00[h]			
23	−4.91	3.09	4.00	48
28	−5.42	0.49	1.21	56
36	−6.07	1.01	3.08	51
45	−4.51	0.78	1.08	58
46	−4.70	1.01	1.52	58
47	−4.39	0.65	1.03	59
49	−4.42	0.52	0.82	58

[a] Tetrahydronaphthalene. [b] Cytotoxicity values are molar concentrations corresponding to 50% growth inhibition. [c] MGM is the mean graph midpoint for growth inhibition of all human cancer lines successfully tested. [d] Delta is the logarithm difference between the MGM and the most sensitive cell line. [e] Range is the logarithm difference between the log GI_{50} of the most resistant and the most sensitive cell lines. [f] The several cell lines are distributed among nine human cancer cell panels, which include leukemia, melanoma, and nonsmall cell lung, colon, CNS, ovarian, renal, prostrate, and breast cancers. [g] See refs 13 and 14. [h] Cell lines giving log MGM values representing concentrations greater than log MGM −7.74 M are HOP-92 (−4.91), SF-268 (−7.07), MALME-3M (−7.08), SK-MEL-28 (−4.63), OVCAR-4 (−5.94), OVCAR-5 (−4.63), and BT-549 (−7.03). [i] Compound **22** was insufficiently active in the three cell line, one-dose preliminary assay to warrant further testing in the 60 cell line assay.

tion of polyvinylidene fluoride hollow fibers in mice. Each fiber contains the various cancer cell cultures, and generally a minimum of 12 human cancer cell lines are used. Compounds are introduced in solution by the IP route. After termination of the four-day dosing routine, the fibers are evaluated for cell mass. The respective IP and SC scores for **5** were 14 and 2, while the corresponding scores for **14** were 10 and 6. Net cell kill was observed for both compounds.

Replacement of the methylenedioxy group of **14** by two methoxy groups resulted in the sikkimotoxin (SK)-derived **12** and at least a 1000-fold activity loss in the seven cell lines for which activity data had been obtained. A further replacement of the trimethoxyphenyl group of **12** by the dimethoxyphenyl group of ACON-derived **11** resulted in inactivity for all cell lines for the highest concentration level (10^{-4} M) used in routine testing. The same two replacements of fused ring substituents and pendant rings in the oxabicyclooctane series of **5**, **21**, and **6** resulted in a similar stepwise loss of activity.

Table 2 data also reveals that the PT-derived dioxatricyclodecane **14** is more active than its oxabicyclooctane counterpart **5** by factors in excess of 100. However, in MDA-MB-435, **14** is only 30 times more active than **5** for the reason that MDA-MB-435 is much more sensitive than any of the other cell lines to **5**, and to several of the other compounds as well. Oxabicyclooctanes **5** and **20** differ in the stereochemical configuration of their hydroxymethyl groups. Oxabicyclooctane **20** was approximately 8- to 70-times more active than **5** in cell lines HOP-62, HCT-116, UACC-62, and OVCAR-3. However, **20** appeared marginally less active than **5** in SF-539 and DU-145, but was 25-times less active than **5** in MDA-MB-435. Also, MDA-MD-435 was the most sensitive to **5** and the least sensitive to **20** than were any of the other seven cell lines. Of the three additional oxabicyclooctanes, including PT-derived **16**, picropodophyllin-derived **19**, and SK-derived **22**, only diastereomers **16** and **19** were sufficiently active in preliminary screening for subsequent 60 cell line evaluations. These comparisons revealed that activities for both **16** and **19** were at the same low level (log GI_{50} −4.23 to −4.84 M) in seven cell lines. However, the cytotoxicity levels increased for MDA-MB-435, as indicated by log GI_{50} values of −5.41 for **16** and −5.17 for **19**. The hydroxymethyl group and the methyleneoxy bridge have a cis stereochemical relationship in both oxabicyclooctane **19** and its isomer **20**. Activities were lower for **19** than **20** by factors ranging broadly from 6 to 700, except in MDA-MB-435 where activities were virtually the same for both oxabicyclooctanes.

Molecular modeling[11] indicated insignificant differences between the oxabicyclooctane scaffold of **5** and the same scaffold incorporated within the dioxatricyclodecane **14**. This indication coupled to the lower activity of **5** compared with that of **14**, and the variable cell line responses to **5** in relation to those of its diastereomer

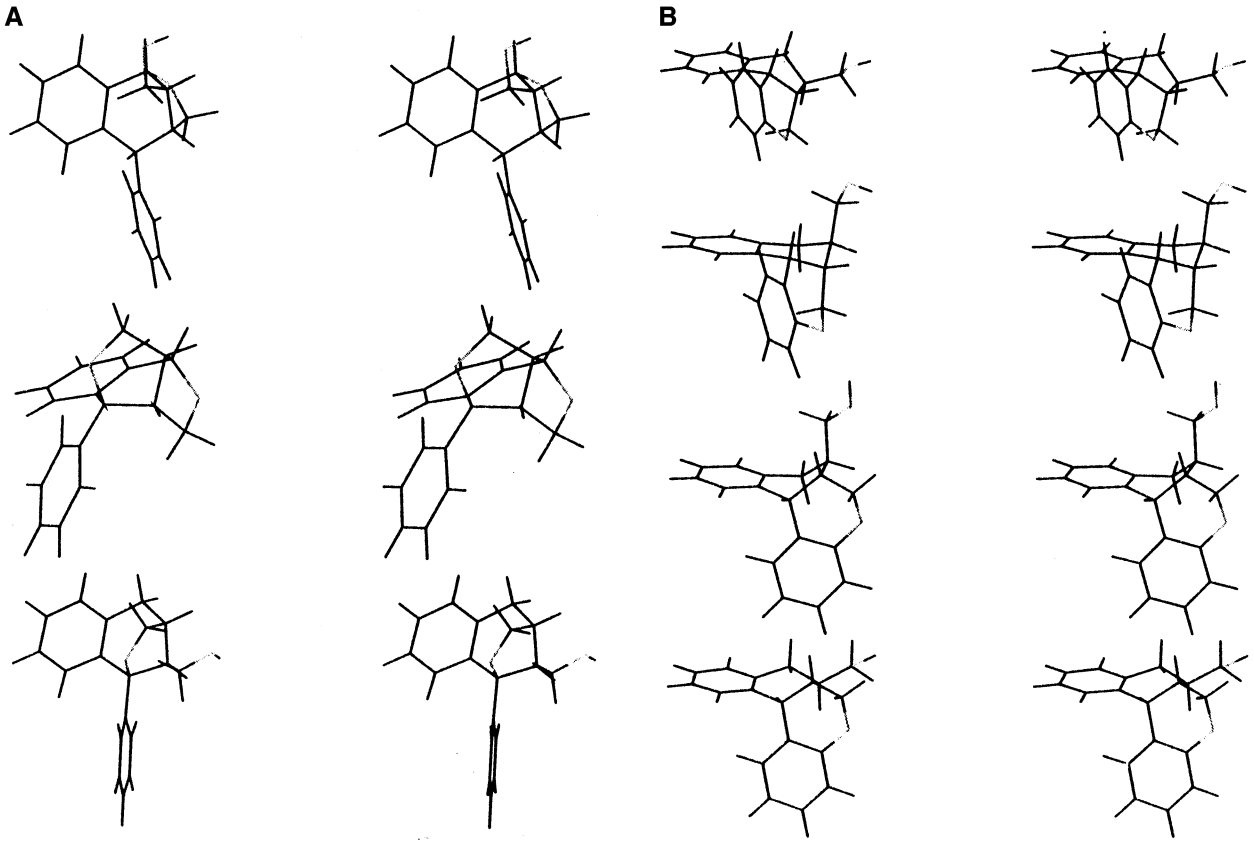
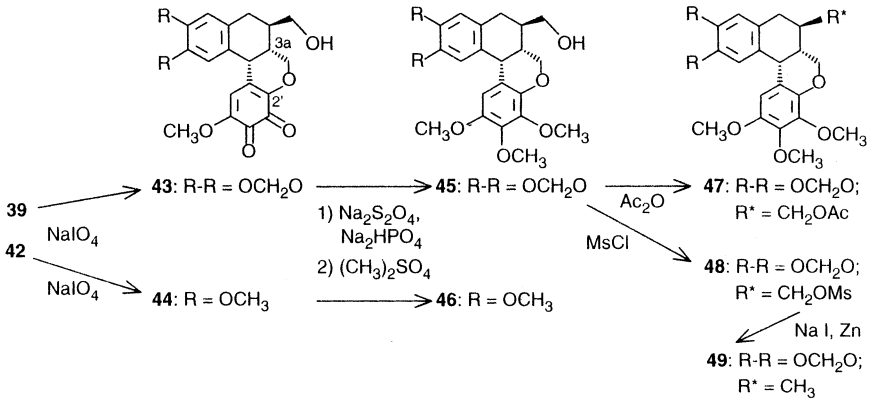


Figure 1. (A) Stereoviews of minimum-energy conformations for three types of methyleneoxy-bridged lignans. Top to bottom: oxabicyclooctane **16**, dioxatricyclodecane **14**, and oxabicyclooctane **5**. (B) Stereoviews of the four minimum energy conformations of benzodihydropyran **45**. Aromatic ring substituents are omitted.

Scheme 6



20, suggested that cytotoxicities could be responding to differing cell line interactions with the hydroxymethyl group, which possibly could function as a hydrogen bond donor or acceptor. The stereochemical relation of the hydroxymethyl group to methyleneoxy bridge is trans in **5**, but cis in **20**. Acetylation of the hydroxymethyl group would allow the resulting ester to function only as a hydrogen bond acceptor. Activities of acetate **17** were only 1.8 times higher or lower than those of its precursor **5** in seven cell lines. In contrast conversion of alcohol **20** to acetate **23** decreased activities by factors ranging from 115 to 316 for HOP-62, HCT-116, and UACC-62, but by only a factor of approximately 5 for SF-539. However, this acetylation also increased activity by a factor of near 4 for MDA-MB-435. Reduction of the hydroxymethyl group of **5** to the methyl group in **36** removed a polar group from the oxabicyclooctane scaffold and increased activity by factors ranging from approximately 4 to 10 in five of the seven cell lines allowing comparison. However, the previously noted inversion of the hydroxymethyl group in **5**, giving **20**, had enhanced activity by greater amounts and in more cell lines than had the reduction of the hydroxymethyl group in **5**. Activity enhancements ranging from 8 (SN12 C) to 66 (MDA-MB-435) resulted from reducing the hydroxymethyl group in ACON-derived **6** to the methyl group of **28**.

The group of benzodihydropyrans **45**, **46**, **47**, and **49** differ structurally from the oxabicyclooctanes in having a more conformationally mobile THN scaffold and a more highly oxygen-substituted aromatic ring. However, these four compounds share with the oxabicyclooctanes the same THN substituents, which include hydroxymethyl, acetoxymethyl, and methyl groups. Overall, the

Table 2. Cytotoxicity of Methyleneoxy-Bridged Tetrahydronaphthalene Lignan Analogues

	cytotoxicity (log GI_{50})							
compd	lung HOP-62	colon HCT-116	CNS SF-539	melanoma UACC-62	ovarian OVCAR-3	renal SN12C	prostate DU-145	breast MDA-MB-435
5	−5.36	−5.54	−5.60	−5.37	−5.84	*a*	−5.58	−6.53
6	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00
11	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	*a*	>−4.00	>−4.00
12	−4.15	−4.55	−4.50	−4.16	−4.52	−4.46	−4.53	−4.71
14[b]	<−8.00	<−8.00	<−8.00	<−8.00	<−8.00	*a*	<−8.00	<−8.00
16	−4.72	−4.53	−4.81	−4.57	−4.84	−4.50	−4.40	−5.41
17	−5.37	−5.63	−5.76	−5.53	−5.67	−5.30	−5.34	−6.33
19	−4.32	−4.52	−4.75	−4.74	−4.62	−4.23	−4.52	−5.17
20	−6.66	−7.36	−5.41	−7.11	−6.74	−5.32	−5.35	−5.13
21	−4.32	−4.52	−4.75	−4.20	−4.62	−4.23	−4.52	−5.17
22[c]								
23	−4.60	−4.86	−4.72	−5.00	*a*	−4.59	*a*	−5.73
28	−5.62	−5.56	−5.71	−5.16	−5.62	−4.92	−5.41	−5.82
36	−6.10	−6.36	d	−6.39	−6.73	−5.27	−6.32	−7.08
45	−4.28	−4.52	−4.68	−4.59	−4.60	−4.35	−4.43	−4.72
46	−4.22	−4.65	−4.61	−4.70	−4.82	−4.60	−4.64	−4.74
47	−4.17	−4.21	−4.24	−4.50	−4.25	−4.39	−4.15	−4.40
49	>−4.12	−4.50	−4.68	−4.52	−4.48	>−4.12	>−4.12	−4.94

[a] This particular cell line was lacking from the cell panel at the time of screening. [b] Etoposide is reported (see ref 8) to give a log GI_{50} value of −5.2 in CAKI-1 (renal). Compounds **14**, **5**, and **46** give the respective log GI_{50} values of <−8.00, −5.24, and −4.60 in this cell line. [c] Compound **22** was insufficiently active in the three cell line, one-dose preliminary assay to warrant further testing in the 60 cell line assay. [d] Two 60-cell line evaluations of compound **36** cytotoxicity resulted in widely divergent results for SF-539. Therefore, the log GI_{50} value was omitted from the table for this particular cell line.

Table 3. Cytotoxicity Comparisons for Benzodihydropyrans **45**, **46**, **47**, and **49** and Their Oxabicyclooctane Analogues **5**, **21**, **17**, and **36**

	cytotoxicity (log GI_{50})			
compound	leukemia SR	lung NCI-322M	CNS SNB-75	ovarian OVCAR-4
45	−5.29	−4.32	−4.37	−4.40
5	−6.23	−5.21	−5.57	−4.63
46	−4.74	−5.06	−5.44	−5.71
21	−4.35	−4.36	*a*	−4.11
47	−4.66	−4.77	−4.61	−4.32
17	−6.12	−5.36	−5.70	−5.37
49	−4.72	>−4.12	−4.91	−4.43
36	−6.83	−5.67	−6.42	−6.42

[a] SNB-75 was lacking from the CNS cell panel when **21** was screened.

four benzodihydropyrans produced were less active than the other types of methyleneoxy-bridged compounds except in cell line MDA-MB-435. The somewhat higher MGM and delta values (Table 1) for **46** pointed to higher sensitivities of other cell lines not included in Table 2. Four such cell lines indicating sensitivities to test compound at concentrations lower than 10^{-5} M were found for **45** and **46**. These cell lines were used in comparing activities (Table 3) of all four benzodihydropyrans to activities of their oxabicyclooctane counterparts. The comparison was deliberately biased in choosing cell lines having the highest sensitivities to the benzodihydropyrans. The pair wise comparison demonstrated consistently higher activities for PT-derived oxabicyclooctanes than PT-derived benzodihydropyrans. However, the SK-derived benzodihydropyran **46** was consistently more active than its oxabicylooctane counterpart, **21**, in three comparisons involving cell lines SR, NCI-322M, and OVCAR-4.

Summary and Conclusions. Podophyllotoxin (PT) and α-conidendrin can be converted through semisynthesis that includes intramolecular methyleneoxy bridging to dioxatricyclodecanes, oxabicyclooctanes, and benzodihydropyrans, including those having the aryl and arene substitution patterns of sikkimotoxin. In vitro cytotoxicities of the PT-derived dioxatricyclodecane **14** were the highest at a log GI_{50} value of <−8 M in most cell lines. In vitro cytotoxicities for the dioxatricyclodecanes and oxabicyclooctanes were lowered through replacement of the methylenedioxy group of the fused aromatic ring by two methoxy groups and were further lowered by replacement of one of two *m*-methoxy groups by hydrogen in the pendant aromatic ring. These results clearly indicated the requirement for particular aromatic substitution patterns in both fused and pendant aromatic rings for highest cytotoxicity of oxabicyclooctanes and dioxatricyclodecanes.

Inversion of the hydroxymethyl group of PT-derived oxabicyclooctane **5** resulted in mixed activity outcomes for its diastereomer, **20**, with some cells becoming more sensitive to **20**, and others less, when compared to **5**. Relevant to the configuration of the hydroxymethyl group in **5** and **20** were the differing activity responses to this group's acetylation. While acetylation of **5** resulted in some very small activity changes, acetylation of **20** lowered some activities by factors of 100 or more. Furthermore, reduction of the hydroxymethyl group of **5** to the methyl group of **36** enhanced activities, although the number of cell lines affected were fewer and the activity increases were smaller than those resulting from inversion of the hydroxymethyl group of **5**. These manifestations of activities responding to hydroxymethyl group manipulation point to this group's interactions with the various cell lines. However, incorporation of the hydroxymethyl group of oxabicyclooctanes **5** or **16** as a second methyleneoxy bridge in dioxatricyclodecane **14** enhanced cytotoxicities by factors of 10 to 1000 and was responsible for the greatest activity enhancement across all cell lines. This result might be attributed to some gain in scaffold rigidity that is provided by double bridging, the absence of the hydroxymethyl group, or a combination of both. Although in vitro activities of dioxatricyclodecane **14** and oxabicyclooctane **5** differed considerably, their in vivo activities were similar.

Activities of the group of oxabicyclooctanes (**5**, **17**, and **36**), which included hydroxymethyl-, acetoxymethyl-, and methyl-substituted members, were higher than those of their benzodihydropyran counterparts, which unlike the oxabicyclooctanes, lacked the measure of immobilization of the THN scaffold, as indicated by molecular dynamics. Also, unlike the dioxatricyclodecanes and oxabicyclooctanes, it was a SK-derivative (**46**) that was the most active of the four-compound series of benzodihydropyrans.

Experimental Section

General. NMR data were obtained from Bruker 300 and 600 spectrometers and recorded in $CDCl_3$ solution, unless indicated otherwise. Chemical shift values (δ) are reported in ppm and in relation to TMS (δ 0.00) and $CDCl_3$ (δ 77.0) for ^1H and ^{13}C NMR, respectively; J values are in hertz (Hz). Quaternary, methine, methylene, and methyl carbons were differentiated by DEPT and when unassigned to a specific carbon are designated within parentheses as 0, 1, 2, and 3 in association with ^{13}C NMR δ values. $^1H-^1H$ correlation and one bond $^1H-^{13}C$ connectivity were determined by COSY and HMQC or HETCOR experiments, respectively, while multiple-bond $^1H-^{13}C$ connectivity was determined by HMBC. HRMS were determined by the Nebraska Center for Mass Spectrometry, University of Nebraska, Lincoln, NE. Preparative TLC was performed using 0.5-mm thickness silica gel plates containing fluorescent indicator and were viewed under 254-nm irradiation. Isocratic and gradient HPLC was determined for each sample submitted for cytotoxicity evaluation. HPLC employed a 5 μm, C18 (2), 250 × 4.60 mm column. Isocratic HPLC used solvents MeOH/H_2O (65/35) for compounds **5**, **6**, **11**, **12**, **14**, **16**, **19**-**23**, **45**, **46**, and **49**, but MeOH/H_2O (80/20) for **17**, **28**, **36**, and **47**. Retention times in minutes are designated t_{RI1} and t_{RI2}, respectively, for the two isocratic solvent systems. A 15-min linear gradient HPLC used CH_3CN/H_2O (50/50−95/5) for compounds **5**, **6**, **11**, **12**, **14**, **16**, **19**-**23**, **45**, **46**, and **49**, but CH_3CN/H_2O (70/30−95/5) for **17**, **28**, **36**, and **47**. Compound retention times are designated t_{RG1} and t_{RG2}, respectively, for the two gradient solvent systems.

Materials. Podophyllotoxin and α-conidendrin were obtained respectively from Toronto Research Chemicals, Inc. (Ontario, Canada) and Raisio Chemicals, Raisio, Finland.

General Reaction, Extraction, and Separation Procedures. Unless indicated otherwise, reactions were conducted under dry N_2, and organic reaction solvents were dried except when a reagent required water as a solvent or the reaction was quenched with water. Product extracts were dried over anhyd $MgSO_4$, and the solvents were removed under vacuum. Products from the residue were separated and purified by silica gel MPLC and/or preparative TLC.

$CuSO_4$/$K_2S_2O_8$ Oxidations of 1,4-Butanediols to Dioxatricyclodecanes: Direct Conversions of Diols 4, 13, and 3, to the Respective Dioxatricyclodecanes 11, 12, and 14. The $CuSO_4$·$5H_2O$ and $K_2S_2O_8$ in H_2O were added together in one portion to the stirred diol in CH_3CN solution. The mixture was heated to reflux for 0.5 h, cooled to 25 °C, diluted with H_2O, and extracted with EtOAc. **Dioxatricyclodecane 11**: Diol **4** (116 mg, 0.3 mmol, 45 mL CH_3CN), $CuSO_4$·$5H_2O$ (75 mg, 0.3 mmol, 5 mL H_2O), and $K_2S_2O_8$ (116 mg, 0.6 mmol, 14 mL H_2O) refluxed 0.5 h gave, after processing and MPLC (CH_2Cl_2/EtOAc, 3:1), 44 mg (38%) **11**: mp 165−166 °C; $[\alpha]^{25}_D$ −6.07° (*c* 2.5, acetone); HPLC t_{RI1} 6.3, t_{RG1} 6.7; ^1H NMR ($CDCl_3$) 7.24−6.90 (br, 2, H-2′, 6′), 6.89 (d, J = 7.72, 1, H-5′), 6.81 (s, 1, H-8), 6.48 (s, 1, H-5), 4.89 (d, J = 5.51, 1, H-9), 4.24 (dd, J = 9.33, 6.33, 1, H-1), 4.11 (dd, J = 9.57, 6.24, 1, H-3), 3.913 (s, 3, OCH_3), 3.906 (s, 6, 2 × OCH_3), 3.84 (d, J = 9.74, 1, H-3), 3.66 (s, 3, OCH_3), 3.52 (d, J = 9.42, 1, H-1), 3.20 (m, 1, H-9a), 2.90 (t, J = 6.10, 1, H-3a); ^1H NMR ($CDCl_3$, 333 K) 7.18 (br, 1) and 7.01 (br, 1) with collapse of 7.24−6.90 observed at 298 K; ^{13}C NMR ($CDCl_3$) 149.36 (0), 149.20 (0), 148.80 (0), 148.38 (0), 133.47 (C-1′), 128.91 (C-4a), 126.87 (C-8a), 118.15 (1), 110.87 (1), 110.56 (1), 109.48 (1), 87.30 (C-4), 80.90 (C-9), 64.25 (C-3), 63.58 (C-1), 56.06 (C-3a), 55.94 (OCH_3), 55.93 (OCH_3), 55.88 (OCH_3), 55.85 (OCH_3), 49.69 (C-9a). HRMS [M^+] Calcd for $C_{22}H_{24}O_6$: 384.1573; Found: 384.1572. **Dioxatricyclodecane 12.** Diol **13** (100 mg, 0.239 mmol, 36 mL CH_3CN), $CuSO_4$·$5H_2O$ (60 mg, 0.239 mmol, 4 mL H_2O), and $K_2S_2O_8$ (129 mg, 0.478 mmol, 11 mL H_2O) refluxed 0.5 h gave, after processing and MPLC, 36 mg (36%) of **12** (glasslike solid): $[\alpha]^{25}_D$ +20.0° (*c* 0.5, $CHCl_3$); HPLC t_{RI1} 6.3, t_{RG1} 7.0; ^1H NMR ($CDCl_3$) 7.13 (br, 1, H-2′ or H-6′), 6.81 (s, 1, H-8), 6.51 (s, 1, H-5), 6.43 (br, 1, H-6′ or 2′), 4.89 (d, J = 5.49, 1, H-9), 4.25 (dd, J = 6.36, 9.35, 1, H-1), 4.10 (dd, J = 6.24, 9.60, 1, H-3), 3.91 (s, 3, OCH_3), 3.88 (s, 6, 2 × OCH_3), 3.83 (d, J = 9.66, 1, H-3), 3.77 (s, 3, OCH_3), 3.67 (s, 3, OCH_3), 3.51 (d, J = 9.25, 1, H-1), 3.20 (ddd, J = 1.19, 5.96, 6.70, 1, H-9a), 2.88 (t, J = 6.14, 1, H-3a); ^{13}C NMR ($CDCl_3$) 153.2 (C-3′, 5′) 149.4 (C-7), 149.3 (C-6), 137.3 (C-4′), 136.4 (C-1′), 128.5 (C-4a), 127.0 (C-8a), 110.8 (C-8), 110.6 (C-5), 103.1 (C-2′, 6′), 87.5 (C-4), 80.8 (C-9), 64.3 (C-3), 63.6 (C-1), 60.8 (OCH_3), 56.1 (C-3a), 56.0 (OCH_3), 55.9 (OCH_3), 55.8 (OCH_3), 49.6 (C-9a); HRMS [M^+ + Na] Calcd for $C_{23}H_{26}O_7Na$: 437.1576; Found: 437.1583. Also formed was oxabicyclooctane **21**: 26 mg (26%); $[\alpha]^{25}_D$ +66.3° (c 0.3, $CHCl_3$). **Dioxatricyclodecane 14**: Diol **3**[1] (2.67 g, 6.63 mmol, 300 mL CH_3CN), $CuSO_4$ ·$5H_2O$ (1.66 g, 6.63 mmol, 100 mL H_2O), and $K_2S_2O_8$ (3.58 g, 13.26 mmol, 100 mL H_2O) heated 0.5 h gave, after processing and MPLC, 20 mg (0.7%) of **14** (crystalline solid from ether): mp 158−160 °C; $[\alpha]^{25}_D$ −5.2° (c 0.59, acetone); HPLC t_{RI1} 9.5, t_{RG1} 8.9; ^1H NMR ($CDCl_3$) 7.08 (br, 1, H-2′ or H-6′), 6.76 (s, 1, H-8), 6.44 (s, 1, H-5), 6.39 (br, 1, H-6′ or H-2′), 5.94 (d, J = 1.39, 1, OCH_2O), 5.92 (d, J = 1.39, 1, OCH_2O), 4.85 (d, J = 5.54, 1, H-9), 4.23 (dd, J = 6.32, 9.36, 1, H-1), 4.12 (dd, J = 9.61, 6.17, 1, H-3), 3.90 (br, 3, OCH_3), 3.88 (br, 4, OCH_3, H-3), 3.77 (br, 3, OCH_3), 3.52 (d, J = 9.35, 1, H-1), 3.20 (m, 1, H-9a), 2.89 (m, 1, H-3a); ^{13}C NMR ($CDCl_3$) 153.23 (C-5′ or C3′), 152.79 (C-3′ or C-5′), 148.07 (C-6 or C-7), 147.62 (C-7 or C-6), 137.28 (C-4′), 136.45 (C-1′), 130.43 (C-8a), 128.24 (C-4a), 108.26 (C-8), 107.96 (C-5), 103.25 (C-2′ or 6′), 102.78 (C-6′ or 2′), 101.20 (OCH_2O), 87.42 (C-4), 80.87 (C-9), 64.40 (C-3), 63.49 (C-1), 60.87 (OCH_3), 56.15 (OCH_3), 55.69 (C-3a), 49.58 (C-9a). HRMS [M^+] Calcd for $C_{22}H_{22}O_7$: 398.1365; Found: 398.1365. The major product from this reaction was oxabicyclooctane **5**: 1.06 g (40%).

Formation of Dioxatricyclodecane 14 from Oxabicyclooctanes 16 and 5. Podophyllol **15** (185 mg, 0.442 mmol) was dehydrated by the method of Castro et al.[5] giving **16** [153 mg (86.4%), mp 252−257 °C, $[\alpha]^{25}_D$ +18.3° (*c* 2.9, $CHCl_3$)]. A warmed solution of **16** (150 mg, 0.374 mmol) in CH_3CN (55 mL) was cooled to 45 °C, and to it was added a solution of $CuSO_4$·$5H_2O$ (94 mg, 0.374 mmol) in H_2O (6 mL) and $K_2S_2O_8$ (203 mg, 0.749 mmol) in H_2O (18 mL). The resulting mixture was heated to reflux under N_2 for 0.5 h. Processing and MPLC (EtOAc/CH_2Cl_2, 1/10) gave 50 mg (0.125 mmol) of **14** (34% yield) ($[\alpha]^{25}_D$ −28.9° (*c* 3.4, $CHCl_3$)). To a solution of 312 mg (0.779 mmol) of **5** in CH_3CN (115 mL) was added a solution of $CuSO_4$·$5H_2O$ (195 mg, 0.779 mmol) in H_2O (13 mL) and $K_2S_2O_8$ (422 mg, 1.55 mmol) in H_2O (37 mL). The resulting mixture was heated to reflux under N_2 for 0.5 h, cooled to 25 °C, diluted with H_2O (60 mL), processed, and MPLC in the usual manner to obtain 34 mg (11% yield) of **14**.

Formation of Oxabicyclooctane 5 from 9-Deoxypodophyllol 3. A solution of DDQ (597 mg, 2.63 mmol) in 80 mL of CH_2Cl_2 was added to a solution of diol **3** (706 mg, 1.75 mmol) in 200 mL of CH_2Cl_2. The dark blue solution was stirred under N_2 at 25 °C and became progressively lighter in color. TLC indicated the absence of diol **3** (after 5.5 h). The solvent was removed under vacuum, and the residue was dissolved in EtOAc (100 mL). The solution was washed with aq 5% $NaHCO_3$ (120 mL), H_2O (2 × 50 mL), and brine (30 mL). The EtOAc extract was dried. The combined aq layers were extracted with Et_2O. Vacuum removal of solvents from combined extracts left a residue, which by MPLC (EtOAc/CH_2Cl_2, 1/5−1/1) followed by preparative TLC (EtOAc/CH_2Cl_2, 1/1) gave oxabicyclooctane **5** (306 mg, 44%): mp 144−146 °C, $[\alpha]^{25}_D$ +15.2° (*c* 1.2, $CHCl_3$), HPLC t_{RI1} 7.6, t_{RG1} 6.4, Anal. ($C_{22}H_{24}O_7$)

C: calcd, 65.99, found, 65.63; H: calcd, 6.04, found, 6.03; **16** (190 mg, 27%): mp 256−257 °C, $[\alpha]^{25}_D$ +21° (*c* 0.2, dioxane), HPLC t_{RI1} 5.7, t_{RG1} 4.3; and dioxatricyclodecane **14** (26 mg, 3.7%). **Oxabicyclooctane Acetate 17.** Ac_2O (26 mg, 0.255 mmol) in dry THF (0.5 mL) was added to a solution of **5** (51 mg, 0.127 mmol) and DMAP (31 mg, 0.255 mmol) in dry THF (0.5 mL). The resulting solution was stirred under N_2 at 25 °C for 2 h. The liquid was evaporated at reduced pressure. [MPLC] (CH_2Cl_2/EtOAc 15/1) gave 48 mg (85%) of **17**: $[\alpha]^{25}_D$ +67.7° (*c* 0.9, $CHCl_3$); HPLC t_{RI2} 5.7, t_{RG2} 6.4; ^{1}H NMR ($CDCl_3$) 7.14 (br, 1, H-2′ or 6′), 6.64 (s, 1, H-8 or 5), 6.41 (s, 1, H-5 or 8), 6.20 (br, 1, H-6′ or 2′), 5.89 (d, J = 1.28, 1, OCH_2O), 5.84 (d, J = 1.28, 1, OCH_2O), 4.38 (dd, J = 5.36, 11.19, 1, H-3), 4.25 (ddd, J = 2.41, 5.53, 8.06, 1, H-1), 4.17 (t, J = 10.64, 1, H-3), 3.88−3.81 (m, 10, 3 × OCH_3, H-1), 3.20 (dt, J = 2.73, 17.09, 1, H-9), 2.82 (m, 1, H-9a), 2.76 (dd, J = 1.74, 17.37, 1, H-9), 2.46 (m, 1, H-3a), 1.99 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) 170.80 (CO), 147.14 (C-7), 145.69 (C-6), 137.03 (C-1′), 136.07 (C-4′), 132.05 (C-8a), 128.70 (C-4a), 109.00 (C-5 or 8), 107.68 (C-8 or 5), 104.06 (C-2′, 6′), 100.81 (OCH_2O), 72.48 (C-1), 61.81 (C-3), 60.74 (OCH_3), 56.12 (OCH_3), 49.03 (C-3a), 36.82 (C-9a), 33.03 (C-9), 20.70 (CH_3). HRMS [M^+] Calcd for $C_{24}H_{26}O_8$: 442.1628; Found: 442.1623.

Similarly, treatment of 9-deoxysikkimol **13** (164 mg, 0.392 mmol) with DDQ (98 mg, 0.431 mmol) in 80 mL of CH_2Cl_2 gave **21** and **22**. **21**: (53 mg, 33%), $[\alpha]^{25}_D$ + 66.5° (*c* 3.4, $CHCl_3$); HPLC t_{RI1} 4.8, t_{RG1} 4.8; ^{1}H NMR ($CDCl_3$) 7.20 (br, 1, H-2′ or H-6′), 6.68 (s, 1, H-8), 6.47 (s, 1, H-5), 6.21 (br, 1, H-6′ or H-2′), 4.27 (ddd, J = 2.42, 5.69, 8.20, 1, H-1), 3.92 (dd, J = 5.39, 10.90, 1, H-3), 3.88 (s, 6, 2 × OCH_3), 3.86 (s, 3, OCH_3), 3.82 (d, J = 8.27, 1, H-1), 3.74 (s, 3, OCH_3), 3.72 (d, J = 10.57, 1, H-3), 3.62 (s, 3, OCH_3), 3.30 (dt, J = 2.71, 17.04, 1, H-9), 2.90 (m, 1, H-9a), 2.77 (dd, J = 2.18, 17.10, 1, H-9), 2.32 (ddd, J = 4.95, 5.00, 9.52, 1, H-3a), 1.64 (br, 1, OH); ^{13}C NMR ($CDCl_3$) 153.4 (C-3′ or C-5′), 152.0 (C-5′ or C-3′), 148.6 (C-6), 146.9 (C-7), 137.0 (C-1′), 136.8 (C-4′), 131.0 (C-4a), 127.9 (C-8a), 111.9 (C-5), 110.7 (C-8), 104.3 (C-2′ or C-6′), 104.0 (C-6′ or C-2′), 84.1 (C-4), 72.6 (C-1), 60.9 (OCH_3), 60.0 (C-3), 56.2 (OCH_3), 55.9 (OCH_3), 55.8 (OCH_3), 53.2 (C-3a), 36.7 (C-9a), 32.7 (C-9); HRMS [M^+ + Na] Calcd for $C_{23}H_{28}O_7Na$: 439.17327; Found: 439.1737. **22**: (72 mg, 44%), $[\alpha]^{25}_D$ − 8.6° (*c* 1.8, $CHCl_3$); HPLC t_{RI1} 4.1, t_{RG1} 3.7; ^{1}H NMR ($CDCl_3$) 6.68 (s, 1, H-8), 6.61 (s, 1, H-5), 6.37 (s, 2, H-2′, 6′), 4.72 (d, J = 4.78, 1, H-9), 4.45 (d, J = 4.05, 1, H-4), 3.91−3.88 (m, 1, H-3), 3.89 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 3.77 (s, 6, 2 × OCH_3), 3.79−3.73 (m, 1, H-1), 3.72 (s, 3, OCH_3), 3.73−3.68 (m, 2, H-1, 3), 2.76 (sep, J = 4.56, 1, H-3a), 2.69 (dd, J = 4.49, 8.98, 1, H-9a); ^{13}C NMR ($CDCl_3$) 153.1 (C-3′, 5′), 148.8 (C-7), 147.8 (C-6), 138.9 (C-1′), 136.7 (C-4′), 131.1 (C-4a), 128.0 (C-8a), 112.8 (C-5), 110.7 (C-8), 106.6 (C-2′, 6′), 77.7 (C-9), 68.7 (C-3), 60.8 (OCH_3), 60.2 (C-1), 56.2 (OCH_3), 56.1 (OCH_3), 55.8 (OCH_3), 48.1 (C-3a), 47.0 (C-4), 43.3 (C-9a); HRMS [M^+ + Na] Calcd for $C_{23}H_{28}O_7Na$: 439.17323; Found: 439.1731.

Oxabicyclooctane 6. This compound was prepared as previously described and exhibited physical properties, including ^{1}H and ^{13}C NMR, consistent with those reported.[1] Anal. ($C_{22}H_{26}O_6$) C: calcd, 68.38, found, 67.54; H: calcd, 6.78, found, 6.90.

Formation of Dioxatricyclodecane 12 from Oxabicyclooctane 21. Oxabicyclooctane **21** (53 mg, 0.127 mmol) dissolved in acetonitrile (20 mL) was refluxed with $CuSO_4 \cdot 5H_2O$ (34 mg, 0.134 mmol) in H_2O (2 mL) and $K_2S_2O_8$ (73 mg, 0.269 mmol) in water (6 mL) for 0.5 h to give 28 mg of oxatricyclooctane **12** (53%); $[\alpha]^{25}_D$ +21.6° (*c* 1.3, $CHCl_3$).

Formation of Dioxatricyclodecane 12 from Oxabicyclooctane 22. Oxabicyclooctane **22** (70 mg, 0.168 mmol, 28 mL CH_3CN) was oxidized by $CuSO_4 \cdot 5H_2O$ (43 mg, 0.168 mmol, 3 mL of H_2O) and $K_2S_2O_8$ (91 mg, 0.336 mmol, 9 mL of H_2O), 43 mg of dioxatricyclodecane **12** was obtained (60%); $[\alpha]^{25}_D$ +19.6° (*c* 3.4, $CHCl_3$).

Formation of Oxabicyclooctanes 19 and 20 from 9-Deoxypicropodophyllol 18. DDQ (85 mg, 0.372 mmol) and **18**[12] (100 mg, 0.248 mmol) in CH_2Cl_2 (120 mL) solution were heated to reflux under N_2 for 22 h to give **19**[5] (10 mg, 10%) and **20** (20 mg, 20%) which were separated by MPLC (CH_2Cl_2/EtOAc, 1/1) followed by preparative TLC (CH_2Cl_2/EtOAc, 1/1). **19**: mp 71−72 °C (glasslike solid); $[\alpha]^{25}_D$ +88.5° (*c* 1.1, $CHCl_3$); HPLC t_{RI1} 6.6, t_{RG1} 5.2; ^{1}H NMR ($CDCl_3$) 6.71 (s, 1, H-8), 6.49 (s, 1, H-5), 6.20 (s, 2, H-2′, 6′), 5.96 (d, J = 1.19, 1, OCH_2O), 5.90 (d, J = 1.20, 1, OCH_2O), 4.75 (s, 1, H-9), 4.10 (br, 1, H-4), 4.06 (dd, J = 8.63, 5.94, 1, H-3), 3.83 (s, 3, OCH_3), 3.76 (s, 6, 2 × OCH_3), 3.71 (d, J = 8.69, 1, H-3), 3.59 (dd, J = 8.91, 10.50, 1, H-1), 3.47 (dd, J = 5.78, 10.68, 1, H-1), 2.48 (d, J = 5.56, 1, H-3a), 2.47 (dd, J = 5.88, 8.69, 1, H-9a); ^{13}C NMR ($CDCl_3$) 153.0 (C-3′, 5′), 147.6 (C-7), 146.4 (C-6), 140.4 (C-1′), 136.6 (C-4′), 133.8 (C-4a), 129.1 (C-8a), 110.9 (C-8), 107.7 (C-5), 106.0 (C-2′, 6′), 101.0 (OCH_2O), 78.1 (C-9), 71.0 (C-3), 62.5 (C-1), 60.8 (OCH_3), 56.1 (OCH_3), 53.6 (C-3a), 45.0 (C-4), 43.9 (C-9a); HRMS [M^+] Calcd for $C_{22}H_{24}O_7$: 400.1522; Found: 400.1521. **20**: mp 84−86 °C (glasslike solid); $[\alpha]^{25}_D$ −23.7° (*c* 0.9, $CHCl_3$); HPLC t_{RI1} 8.4, t_{RG1} 6.5; ^{1}H NMR ($CDCl_3$) 7.03 (s, 1, H-2′), 6.64 (s, 1, H-8), 6.25 (s, 1, H-6′), 6.11 (s, 1, H-5), 5.87 (s, 1, OCH_2O), 5.83 (s, 1, OCH_2O), 4.23 (t, J = 6.95, 1, H-1), 3.90 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 3.77 (t, J = 4.06, 1, H-1), 3.75 (s, 3, OCH_3), 3.48 (dd, J = 5.21, 11.27, 1, H-3), 3.34 (dd, J = 7.30, 11.20, 1, H-3), 3.25 (d, J = 15.65, 1, H-9), 2.90 (d, J = 15.65, 1, H-9), 2.88 (m, 1, H-9a), 2.58 (t, J = 6.20, 1, H-3a), 1.49 (br, 1, OH); ^{13}C NMR ($CDCl_3$) 153.1 (C-3′ or 5′), 153.0 (C-5′ or 3′), 147.1 (C-6), 145.7 (C-7), 137.0 (C-4′), 136.3 (C-4a), 135.1 (C-1′), 128.3 (C-8a), 109.0 (C-8), 107.3 (C-5), 104.6 (C-2′) 104.0 (C-6′), 100.9 (OCH_2O), 86.4 (C-4), 71.5 (C-1), 62.3 (C-3), 60.9 (OCH_3), 56.2 (OCH_3), 56.1 (OCH_3), 52.7 (C-3a), 38.5 (C-9), 37.5 (C-9a); HRMS [M^+] Calcd for $C_{22}H_{24}O_7$: 400.1522; Found: 400.1534.

Oxabicyclooctane Acetate 23. Ac_2O (24 mg, 0.231 mmol) in dry THF (0.5 mL) was added dropwise to **20** (42 mg, 0.105 mmol) and DMAP (26 mg, 0.210 mmol) in dry THF (1.0 mL), and the resulting solution was stirred under N_2 for 2 h. The solvent was evaporated at reduced pressure to dryness, and the residue was dissolved in ether (20 mL). The solution was washed with 5% aq $NaHCO_3$ (2 × 3 mL), 1 N aq HCl (5 × 3 mL), H_2O (3 mL) and brine (3 mL) then dried (anhyd $MgSO_4$). Evaporation of solution at reduced pressure and MPLC of the residue ($CHCl_2$/EtOAc, 10/1) gave **23** (35 mg, 75%). **23**: $[\alpha]^{25}_D$ −27.0° (*c* 2.3, $CHCl_3$); HPLC t_{RI1} 18.9, t_{RG1} 11.7; ^{1}H NMR ($CDCl_3$) 6.99 (d, J = 1.82, 1, H-2′), 6.63 (s, 1, H-8), 6.27 (d, J = 1.82, 1, H-6′), 6.09 (s, 1, H-5), 5.87 (d, J = 1.37, 1, OCH_2O), 5.84 (d, J = 1.37, 1, OCH_2O), 4.26 (dt, J = 2.24, 8.34, 1, H-1), 3.94−3.88 (m, 1, H-1), 3.90 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 3.82−3.75 (m, 1, H-3), 3.76 (s, 3, OCH_3), 3.71 (dd, J = 10.18, 11.36, 1, H-3), 3.23 (d, J = 16.56, 1, H-9), 2.90 (dd, J = 2.43, 16.71, 1, H-9), 2.84−2.76 (m, 2, H-3a, 9a), 2.00 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) 170.94 (CO), 152.89 (C-3′ or 5′), 152.77 (C-5′ or 3′), 147.04 (C-7 or 6), 145.60 (C-6 or 7), 136.70 (C-4′), 136.05 (C-4a), 134.58 (C-1′), 127.80 (C-8a), 108.75 (C-8), 107.27 (C-5), 104.56 (C-2′), 103.72 (C-6′), 100.80 (OCH_2O), 85.89 (C-4), 70.97 (C-1), 63.40 (C-3), 60.81 (OCH_3), 56.07 (OCH_3), 55.98 (OCH_3), 44.29 (C-3a), 37.97 (C-9), 36.91 (C-9a), 20.80 (CH_3); HRMS [M^+] Calcd for $C_{24}H_{26}O_8$: 442.1628; Found: 442.1624.

Preparation of 4′-Demethyldeoxypodophyllotoxin, 38. 4′-Demethyl-9-epipodophyllotoxin (**37**) (200 mg, 0.50 mmol) in 15 mL of glacial HOAc at 95 °C was stirred 5.5 h under H_2 (1 atm) with 200 mg of Pd/C (10%). After the catalyst was filtered off and the solvent was removed in a vacuum, the residue was recrystallized from CH_3OH/THF to give **38**,[13] 120 mg (62%).

4′-Demethyl-9-deoxypodophyllol 39 by Reduction of 4′-Demethyldeoxypodophyllotoxin 38. 4′-Demethyldeoxypodophylotoxin **38** (400 mg, 1.04 mmol) in 35 mL of dry THF was treated with $LiAlH_4$ (320 mg, 8.32 mmol) gave **39** (333 mg, 82%).

Formation of Benzodihydropyran 45. A solution of diol **39** (100 mg, 0.258 mmol) in $(CH_3)_2CO$ (20 mL) was added to a stirred solution of $NaIO_4$ (124 mg, 0.568 mmol) in H_2O (40 mL), and stirring was continued at 25 °C for 6 h. Brine (10 mL) was added, and the mixture was extracted with $CHCl_3$ (5 × 30 mL). The combined organic phase was washed with H_2O (2 × 20 mL), dried over $MgSO_4$, and evaporated to dryness. Preparative TLC of one-third of the residue gave red solid quinone (15 mg) **43**: ^{1}H NMR ($CDCl_3$) 6.62 (s, 1, H-8), 6.38 (s,

1, H-5), 5.88 (d, J = 1.41, 1, OCH_2O), 5.84 (d, J = 1.42, 1, OCH_2O), 5.77 (s, 1, H-6′), 4.16 (ddd, J = 1.91, 4.07, 10.98, 1, H-3), 3.80 (s, 3, OCH_3), 3.78−3.72 (m, 3, H-1, 4), 3.52 (t, J = 11.50, 1, H-3), 2.67 (dd, J = 5.13, 14.46, 1, H-9), 2.46 (dd, J = 10.94, 14.32, 1, H-9), 2.26 (dt, J = 4.86, 16.80, 1, H-3a), 1.86−1.68 (br, 1, OH), 1.40−1.34 (m, 1, H-9a); ^{13}C NMR ($CDCl_3$) 176.2 (C-5′), 175.7 (C-4′), 167.7 (C-2′), 153.5 (C-3′), 146.3 (C-6), 146.0 (C-7), 130.6 (C-4a), 129.9 (C-8a), 108.9 (C-1′), 108.6 (C-5), 108.0 (C-8), 106.8 (C-6′), 100.7 (OCH_2O), 69.8 (C-3), 66.1 (C-1), 56.1 (OCH_3), 38.6 (C-9a), 34.1 (C-3a), 31.0 (C-4), 30.4 (C-9); HRMS [M^+] Calcd for $C_{20}H_{20}O_7$ (reduced form): 372.1209; Found: 372.1210. The remaining 2/3 of the residue was redissolved in $CHCl_3$ (30 mL) and stirred with aq (15 mL) $Na_2S_2O_4$ (164 mg, 0.80 mmol) and Na_2HPO_4 (60 mg, 0.42 mmol) for 0.5 h following a known method.[14] The $CHCl_3$ phase was separated, and the aq phase was extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ phase was dried over $MgSO_4$. Evaporation of the $CHCl_3$ gave a residue, which was methylated with $(CH_3)_2SO_4$ to afford **45** (21 mg, three-step yield from 4′-demethyl-9-deoxypodophyllol, **39**, 30%). **45**: $[\alpha]^{25}_D$ −126.6° (*c* 4.6, $CHCl_3$); HPLC t_{RI1} 5.5, t_{RG1} 4.7; ^{1}H NMR ($CDCl_3$) 6.67 (s, 1, H-8), 6.29 (s, 1, H-5), 6.21 (s, 1, H-6′), 5.86 (s, 2, OCH_2O), 3.87 (s, 3, OCH_3), 3.87−3.83 (m, 2, H-3, 4), 3.83 (s, 6, 2 × OCH_3), 3.83−3.76 (m, 2, H-1), 3.26 (d, J = 10.44, 11.76, 1, H-3), 2.75 (dd, J = 4.99, 13.97, 1, H-9), 2.54 (dd, J = 12.10, 13.53, 1, H-9), 2.20−2.16 (m, 1, H-3a), 1.65−1.25 (m, 1, H-9a); ^{13}C NMR ($CDCl_3$) 153.4 (C-5′), 151.9 (C-3′), 150.6 (C-2′), 146.0 (C-7), 145.6 (C-6), 135.4 (C-4′), 133.3 (C-4a), 130.3 (C-8a), 108.8 (C-5), 107.8 (C-8), 107.4 (C-1′), 100.5 (OCH_2O), 95.7 (C-6′), 67.1 (C-3), 66.6 (C-1), 60.94 (OCH_3), 60.91 (OCH_3), 55.8 (OCH_3), 39.6 (C-9a), 34.6 (C-3a), 33.2 (C-4), 31.2 (C-9); HRMS [M^+] Calcd for $C_{22}H_{24}O_7$: 400.1522; Found: 400.1531.

Benzodihydropyran Acetate 47. Ac_2O (33 mg, 0.32 mmol) in dry THF (0.5 mL) was added to **45** (64 mg, 0.16 mmol) and DMAP (39 mg, 0.32 mmol) in THF (1 mL). The resulting solution was stirred under N_2 at 25 °C for 2 h. The residue from evaporation of THF at reduced pressure was dissolved in ether (30 mL). The mixture was washed with aq $NaHCO_3$ (5%) (2 × 5 mL), 1 N HCl (2 × 5 mL), water (5 mL), and brine (5 mL). The organic phase was dried (anhyd $MgSO_4$). The ether was evaporated at reduced pressure. MPLC (CH_2Cl_2/EtOAc, 20/1) gave pure **47** (60 mg, 85%): $[\alpha]^{25}_D$ −122.2° (*c* 1.04, $CHCl_3$); HPLC t_{RI2} 9.4, t_{RG2} 8.5; ^{1}H NMR ($CDCl_3$) 6.67 (s, 1, H-8), 6.29 (s, 1, H-5), 6.22 (s, 1, H-6′), 5.87 (s, 2, OCH_2O), 4.24−4.17 (m, 2, H-1), 3.88 (s, 3, OCH_3), 3.93−3.86 (m, 1, H-4), 3.86−3.82 (m, 1, H-3), 3.84 (s, 6, 2 × OCH_3), 3.25 (dd, J = 10.78, 11.63, 1, H-3), 2.70 (dd, J = 4.99, 14.02, 1, H-9), 2.54 (dd, J = 11.97, 13.81, 1, H-9), 2.23−2.18 (m, 1, H-3a), 2.10 (s, 3, CH_3), 1.43−1.38 (m, 1, H-9a); ^{13}C NMR ($CDCl_3$) 171.1 (CO), 153.4 (C-5′), 151.9 (C-3′), 150.4 (C-2′), 146.1 (C-7), 145.6 (C-6), 135.4 (C-4′), 133.0 (C-4a), 129.7 (C-8a), 108.8 (C-5), 107.7 (C-8), 107.1 (C-1′), 100.6 (OCH_2O), 95.6 (C-6′), 67.6 (C-1), 66.8 (C-3), 60.9 (OCH_3), 55.8 (OCH_3), 36.3 (C-9a), 34.8 (C-3a), 33.0 (C-4), 31.2 (C-9), 20.9 (CH_3); HRMS [M^+] Calcd for $C_{24}H_{26}O_8$: 442.1628; Found: 442.1631.

Benzodihydropyran 49 through Mesylation of Alcohol 45 Giving 48. Alcohol **45** (162 mg, 0.40 mmol) was treated with MsCl (66 mg, 0.57 mmol) in CH_2Cl_2 (5 mL) under N_2 and at 0 °C for 2 h in the presence of Et_3N (58 mg, 0.57 mmol). Mesylate **48** (193 mg, 99.7%) was obtained after the standard workup procedure. Reductive cleavage[15] of mesylate **48** giving **49**. A mixture of mesylate **48** (95 mg, 0.20 mmol), NaI (150 mg, 1.0 mmol), zinc powder (131 mg, 2.0 mmol), and glyme (5 mL) was heated to reflux under N_2 for 3 h. Standard processing of the reaction mixture followed by MPLC (CH_2Cl_2/EtOAc 20/1) gave **49** (52 mg, 68%) and unconverted **48** (12 mg, 13%). **49**: mp 152−154 °C; $[\alpha]^{25}_D$ −175.0° (*c* 0.7, $CHCl_3$); HPLC t_{RI1} 18.3, t_{RG1} 12.9; ^{1}H NMR ($CDCl_3$) 6.64 (s, 1, H-8), 6.31 (s, 1, H-5), 6.21 (s, 1, H-6′), 5.85 (s, 2, OCH_2O), 3.90 (d, J = 5.57, 1, H-4), 3.88 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), 3.82 (dd, J = 1.62, 4.01, 1, H-3), 3.22 (t, J = 11.23, 1, H-3), 2.61 (dd, J = 4.87, 14.09, 1, H-9), 2.47 (dd, J = 11.33, 13.93, 1, H-9), 2.02 (m, 1, H-3a), 1.23 (d, J = 6.67, 3, H-1), 1.13 (m, 1, H-9a); ^{13}C NMR ($CDCl_3$) 153.28 (C-5′), 152.03 (C-3′), 150.63 (C-2′), 145.80 (C-7), 145.40 (C-6), 135.36 (C-4′), 132.76 (C-4a), 131.35 (C-8a), 108.82 (C-5), 107.58 (C-1′), 107.52 (C-8), 100.46 (OCH_2O), 95.65 (C-6′), 66.83 (C-3), 60.93 (OCH_3), 60.89 (OCH_3), 55.81 (OCH_3), 39.22 (C-3a), 36.51 (C-9), 32.88 (C-4), 31.57 (C-9a), 21.55 (C-1); HRMS [M^+] Calcd for $C_{22}H_{24}O_5$: 384.1573; Found: 384.1580.

Preparation of 4′-Demethyl-9-deoxysikkimotoxin, 41. According to a known procedure,[10] treating 9-deoxysikkimotoxin **40** (550 mg, 1.33 mmol) with 30% HBr−HOAc (3 mL) in CH_2ClCH_2Cl (25 mL) for 13.7 h gave **41** (338 mg, 64%).

Preparation of 4′-Demethyl-9-deoxysikkimol, 42. Treating 4′-demethyl-9-deoxysikkimotoxin (**41**, 338 mg, 0.844 mmol) in dry THF (25 mL) with $LiAlH_4$ (257 mg, 6.752 mmol) gave **42** (210 mg, 62%).

Formation of Benzodihydropyran 46. A solution of diol **42** (208 mg, 0.514 mmol) and $NaIO_4$ (242 mg, 1.131 mmol) in $(CH_3)_2CO/H_2O$ (40/80 mL) was stirred at 25 °C for 9 h. Processing the reaction mixture in the manner previously described for conversion of **39** to **43** followed by MPLC (CH_2Cl_2/EtOAc, 1/1) gave red, solid quinone (100 mg, 50%) **44**: ^{1}H NMR ($CDCl_3$) 6.59 (s, 1, H-8), 6.40 (s, 1, H-5), 5.75 (s, 1, H-6′), 4.16 (d, J = 9.07, 1, H-3), 3.96 (br, 1, OH), 3.78 (s, 3, OCH_3), 3.77 (s, 3, OCH_3), 3.69 (s, 3, OCH_3), 3.82−3.52 (m, 4, H-1, 3, 4), 2.65 (dd, J = 5.51, 15.22, 1, H-9), 2.44 (dd, J = 8.84, 15.08, 1, H-9), 2.32−2.24 (m, 1, H-3a), 1.53−1.48 (m, 1, H-9a); ^{13}C NMR ($CDCl_3$) 176.2 (C-5′), 175.9 (C-4′), 167.9 (C-2′), 153.3 (C-3′), 147.6 (C-6), 147.5 (C-7), 129.0 (C-4a), 128.0 (C-8a), 112.0 (C-8), 111.4 (C-5), 109.5 (C-1′), 106.9 (C-6′), 69.8 (C-3), 65.5 (C-1), 56.2 (OCH_3), 56.0 (OCH_3), 55.9 (OCH_3), 37.7 (C-9a), 33.3 (C-3a), 30.0 (C-4), 29.2 (C-9). The quinone **44** (100 mg, 0.259 mmol) in $CHCl_3$ (30 mL) and an aq solution of $Na_2S_2O_4$ (477 mg, 2.329 mmol) and Na_2HPO_4 (184 mg, 1.295 mmol) in H_2O (8 mL) were stirred rapidly for 0.5 h. The resulting catechol was methylated in $(CH_3)_2CO$ (30 mL) with dimethyl sulfate (300 mg, 2.38 mmol) gave **46** (60 mg, 56%): $[\alpha]^{25}_D$ −242.3° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 6.70 (s, 1, H-8), 6.36 (s, 1, H-5), 6.22 (s, 1, H-6′), 3.90 (d, J = 5.44, 1, H-4), 3.87 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), 3.82 (m, 1, H-3), 3.81 (s, 3, OCH_3), 3.81−3.68 (m, 2, H-1), 3.68 (s, 3, OCH_3), 3.29 (t, J = 11.18, 1, H-3), 2.76 (dd, J = 5.15, 14.18, 1, H-9), 2.56 (dd, J = 11.25, 13.96, 1, H-9), 2.22 (m, 1, H-3a), 1.72 (br, 1, OH), 1.35 (m, 1, H-9a); ^{13}C NMR ($CDCl_3$) 152.1 (C-5′), 150.9 (C-3′), 149.5 (C-2′), 146.1 (C-7 or 6), 146.0 (C-6 or 7), 134.1 (C-4′), 130.5 (C-4a), 127.8 (C-8a), 110.9 (C-5), 109.7 (C-8), 106.5 (C-1′), 94.6 (C-6′), 66.1 (C-3), 65.4 (C-1), 59.8 (OCH_3), 59.7 (OCH_3), 54.9 (OCH_3), 54.7 (OCH_3), 54.6 (OCH_3), 38.3 (C-9a), 33.3 (C-3a), 31.5 (C-4), 29.4 (C-9); HRMS [M^+ + Li] Calcd for $C_{23}H_{28}O_7Li$: 423.1995; Found: 423.2001.

Formation of Oxabicyclooctane 36 from 9-Deoxypodophyllotoxin. Ethanolysis of 9-Deoxypodophyllotoxin **29. 29** (530 mg, 1.33 mmol) in 30 mL of absolute EtOH and 10 drops of concentrated H_2SO_4 was heated to reflux for 2 h after which the reaction mixture was cooled to 25 °C and the EtOH was evaporated. The residue was dissolved in EtOAc (40 mL) and successively washed with 5% aq $NaHCO_3$ (5 mL), water (10 mL), and brine (5 mL). The organic phase was dried ($MgSO_4$). Evaporation of the solvent and MPLC of the residue (eluting first with CH_2Cl_2/EtOAc, 10/1, then EtOAc) gave **30** (140 mg, 24%) and starting **29** (389 mg, 73%). **Hydroxyl Group Protection of 30**. DIPEA (643 mg, 4.96 mmol) dissolved in CH_2Cl_2 (1 mL) was added to an ice-cooled solution of **30** (552 mg, 1.24 mmol) in CH_2Cl_2 (10 mL). After stirring the resulting solution under N_2 for 10 min, a solution of $BrCH_2OCH_3$ (689 mg, 90%, 4.96 mmol) in CH_2Cl_2 (4 mL) was added dropwise over 5 min, after which time stirring under N_2 continued for 7 h. Solvent was removed at reduced pressure below 30 °C, and the residue was dissolved in EtOAc (40 mL). The EtOAc solution was washed with H_2O (2 × 5 mL) and brine (5 mL), and the organic phase was dried (anhyd $MgSO_4$). Reduced pressure solvent evaporation gave a residue, which was purified by MPLC (CH_2Cl_2/EtOAc, 5/1) to give **31** (589 mg, 97%). **Ester Reduction in 31.** Ester **31** (617 mg, 1.26 mmol) in dry THF was stirred with $LiAlH_4$ (252 mg, 6.31 mmol) for 4.5 h. The residue obtained after standard workup was purified

by MPLC (CH_2Cl_2/EtOAc, 1/1) to obtain **32** (494 mg, 88%). **Mesylation of Alcohol 32 Giving 33**. MsCl (234 mg, 2.04 mmol) dissolved in CH_2Cl_2 (1 mL) was added dropwise to an ice-cooled solution of **32** (455 mg, 1.02 mmol) and triethylamine (310 mg, 3.06 mmol) in CH_2Cl_2 (7 mL). The resulting mixture was stirred under N_2 at 0 °C for 1.5 h. Water was added and the organic phase separated. The aq phase was extracted with $CHCl_3$ (3 × 5 mL), and the combined organic phase was dried (anhyd $MgSO_4$). Evaporation of the solvent at reduced pressure and below 30 °C gave **33** (520 mg, 97%), which was used in the next step without further purification. **Reductive Cleavage[15] of Mesylate 33 Giving 34**. A mixture of **33** (510 mg, 0.97 mmol), NaI (730 mg, 4.86 mmol), and zinc powder (636 mg, 9.72 mmol) in glyme (10 mL) was refluxed under N_2 for 3 h. The mixture was filtered to remove excess NaI and zinc. The filtrate was added to water and then extracted with EtOAc (3 × 30 mL). The combined EtOAc extract was washed with brine and dried (anhyd Mg SO_4), and EtOAc was evaporated at reduced pressure. The residue was separated by MPLC (CH_2Cl_2/EtOAc 10/1) to obtain **34** (238 mg, 57%) and unconverted **33** (50 mg, 10%). **Deprotection in 34 Giving 35**. A mixture of **34** (238 mg, 0.55 mmol), aq HCl (37%, 10 drops), and MeOH (10 mL) was refluxed under N_2 for 1 h and then cooled to 25 °C. The MeOH was evaporated at reduced pressure, and the residue was dissolved in EtOAc (25 mL). The solution was washed with 5%, aq $NaHCO_3$ (6 mL), H_2O (5 mL), and brine. The organic phase was dried (anhyd $MgSO_4$). The EtOAc was evaporated at reduced pressure, and alcohol **35** (170 mg, 80%) was separated from the residue by MPLC (CH_2Cl_2/EtOAc 5/1). **Methyleneoxy Bridging in 35 Giving 36.** Employing the standard DDQ oxidation procedure described above, alcohol **35** (156 mg, 0.40 mmol) was treated with DDQ (110 mg, 0.48 mm) in CH_2Cl_2 (30 mL) for 4.5 h. MPLC (CH_2Cl_2/EtOAc 15/1) gave **36** (60 mg, 39%). **36**: $[\alpha]^{25}_D$ + 10.5° (*c* 1.0, $CHCl_3$); HPLC t_{RI2} 7.6, t_{RG2} 8.4; ^{1}H NMR ($CDCl_3$) 7.15 (br, 1, H-2′ or 6′), 6.64 (s, 1, H-8), 6.38 (s, 1, H-5), 6.27 (br, 1, H-6′ or 2′), 5.88 (d, J = 1.42, 1, OCH_2O), 5.83 (d, J = 1.42, 1, OCH_2O), 4.21 (ddd, J = 2.42, 5.54, 8.07, 1, H-1), 3.89 (s, 3, OCH_3), 3.95−3.74 (m, 7, 2 × OCH_3, H-1), 3.20 (dt, J = 2.79, 17.03, 1, H-9), 2.73 (dd, J = 2.21, 17.04, 1, H-9), 2.55 (m, 1, H-9a), 2.17 (m, 1, H-3a), 1.16 (d, J = 6.93, 3, H-3); ^{13}C NMR ($CDCl_3$) 153.18 (C-3′ or 5′), 152.51 (C-5′ or 3′), 146.84 (C-7), 145.67 (C-6), 137.12 (C-1′), 136.89 (C-4′), 132.93 (C-8a), 128.80 (C-4a), 108.96 (C-5), 108.12 (C-8), 104.53 (C-2′ or 6′), 103.75 (C-6′ or 2′), 100.78 (OCH_2O), 85.43 (C-4), 72.25 (C-1), 60.88 (OCH_3), 56.18 (OCH_3), 44.81 (C-9a), 39.97 (C-3a), 32.21 (C-9), 11.21 (C-3); HRMS [M^+] Calcd for $C_{22}H_{24}O_6$: 384.1573; Found: 384.1577.

Formation of Oxabicyclooctane 28 from Dimethyl-α-conidendrin, 2. Methanolysis of 2. 2 (204 mg, 0.53 mmol) in 24 mL of absolute MeOH and 5 drops of concentrated H_2SO_4 was heated to reflux for 24 h and then processed in the manner used for the conversion of 9-deoxypodophyllotoxin to **30**. Obtained **24** (98 mg, 44%) and recovered **2** (104 mg, 51%). **Mesylation of Alcohol 24 Giving 25.** MsCl (129 mg, 1.12 mmol) dissolved in CH_2Cl_2 (2 mL) was added dropwise to an ice-cooled solution of alcohol **24** (234 mg, 0.56 mmol) and triethylamine (114 mg, 1.12 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred under N_2 at 0 °C for 2.5 h. Subsequent processing of the mixture in the manner used in the conversion of **32** to **33** gave **25** (268 mg, 96%), which was used without further purification. **Reductive Cleavage of Mesylate 25 Giving 26.** A mixture of **25** (258 mg, 0.52 mmol), NaI (391 mg, 2.61 mmol), Zn powder (171 mg, 2.61 mmol), and glyme (15 mL) was heated to reflux under N_2 for 4 h. Subsequent processing of the mixture in the manner used in the conversion of **33** to **34** gave **26** (155 mg, 74%) and recovered **25** (24 mg, 9%) from MPLC (CH_2Cl_2/EtOAc, 10/1). **Reduction of Ester 26 to 27.** Ester **26** (153 mg, 0.382 mmol) in 7 mL of dry THF and $LiAlH_4$ (73 mg, 1.910 mmol) was stirred for 14 h followed by processing in the normal manner as noted above gave **27** (130 mg, 91%). **Methyleneoxy Bridging in 27 Giving 28.** **27** (120 mg, 0.322 mmol) treated with DDQ (88 mg, 0.387 mmol) in CH_2Cl_2 in the manner indicated above gave **28** (67 mg, 56%) and an aromatized aldehyde as minor product (13 mg, 11%). **28**: $[\alpha]^{25}_D$ +50.6° (*c* 1.8, $CHCl_3$); HPLC t_{RI2} 6.0, t_{RG2} 7.2; ^{1}H NMR ($CDCl_3$) 7.48 (br, 1, H-5′), 6.87 (br, 1, H-6′), 6.66 (s, 1, H-8), 6.64 (br, 1, H-2′), 6.43 (s, 1, H-5), 4.22 (ddd, J = 2.28, 5.65, 8.01, 1, H-1), 3.90 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 3.76 (d, J = 8.10, 1, H-1), 3.97−3.74 (br, 3, OCH_3), 3.59 (s, 3, OCH_3), 3.21 (dt, J = 2.70, 16.89, 1, H-9), 2.71 (dd, J = 2.03, 16.91, 1, H-9), 2.57 (m, 1, H-9a), 2.12 (m, 1, H-3a), 1.08 (d, J = 6.88, 3, H-3); ^{13}C NMR ($CDCl_3$) 148.10 (C-3′), 147.57 (0), 146.70 (0), 133.90 (C-1′), 131.53 (C-4a), 127.36 (C-8a), 119.14 (C-6′), 111.71 (C-5), 110.84 (C-8), 109.90 (C-2′, 5′), 85.10 (C-4), 72.13 (C-1), 55.76 (OCH_3), 55.74 (OCH_3), 55.60 (OCH_3), 45.28 (C-9a), 39.72 (C-3a), 32.74 (C-9), 10.74 (C-3). HRMS [M^+] Calcd for $C_{22}H_{26}O_5$: 370.1780; Found: 370.1779.

Molecular Modeling. Initial structural models of all compounds were constructed using Alchemy (versions II and 2000)[11] or Chem3D (version 3.5.1)[16] molecular modeling programs. Atomic charges were computed from a Mulliken population analysis using the Gaussian94 program.[17] Final minimum-energy structures were computed with the Discover (version 2.9.5) program[18] using its built-in Amber force field. Molecular dynamics (MD) simulations were also carried out with the Discover-Amber combination. All MD simulations were run at 300 K (NVT conditions) for a duration of 400 ps (after an initial equilibration period of 5 ps) using a time-step of 1 fs. Preliminary MD runs comparing fully substituted molecules with their skeletal equivalents, which were devoid of substituents on the two aromatic rings but contained all other substituents, showed no measurable differences. Consequently, all MD results are reported for the unsubstituted (skeletal) molecules.

Acknowledgment. This work was supported by the McIntire-Stennis USDA-CREES program and SUNY-ESF. Determination of high-resolution mass spectra by the Nebraska Center for Mass Spectrometry, University of Nebraska, Lincoln, NE is also acknowledged. Compounds were evaluated for cytotoxic activities through the Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institute of Health, Bethesda, MD.

Supporting Information Available: HPLC data for compounds **5**, **6**, **11**, **12**, **14**, **16**, **17**, **19**−**23**, **28**, **36**, **45**, **46**, **47**, and **49**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM020158P