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Synthesis of Podophyllotoxin Derivatives by Means of Tributyltin Hydride- or Palladium-Mediated Cyclization of α-Benzylidene-β-(*o*-bromobenzyl)-γ-lactones

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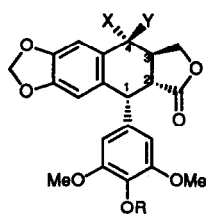
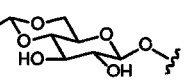
Abstract: Synthesis of podophyllotoxin derivatives based on an aryl radical cyclization of α-benzylidene-β-(*o*-bromobenzyl)-γ-lactones **20** and **21** has been examined. Treatment of a mixture of the alcohols **18a** and **18b** (*ca.* 1:1), prepared from 6-bromopiperonal (**10**) in 7 steps, with methanesulfonyl chloride gave a *ca.* 3:1 mixture of the chlorides **19a** and **19b**, which was treated with DBU to give the (*Z*)- and (*E*)-α-benzylidene-γ-lactones **20** and **21** in 64 and 22% yields, respectively. Thermolysis of the mixture of the sulfoxides **23a** and **23b**, prepared from **18a,b**, afforded the *E*-isomer **21** as a major product. The *Z*-benzylidenelactone **20** when treated with Bu_3SnH in the presence of AIBN gave the 6-*endo-trig* radical cyclization product, (±)-deoxyisopicropodophyllin (**24**), and the 5-*exo-trig* cyclization product **25** in 29 and 49% yields, respectively. The *E*-isomer **21**, however, gave only the 5-*exo* cyclization product **25**. On the other hand, treatment of **20** with $PdCl_2(PPh_3)_3$ gave (±)-γ-apopicropodophyllin (**29**) in 75% yield. Similar treatment of **21** afforded no cyclization product, but, in the presence of sodium formate (H^- source), gave the 5-*exo* cyclization product **25** in 84% yield.

Podophyllotoxin (**1**) and related lignan lactones have received considerable attention due largely to their significant cytotoxic activities.[1] In particular, etoposide (**4**), a semi-synthetic glucoside derived from epipodophyllotoxin (**2**), is currently used for the treatment of many types of human cancers.[2] A number of methods have so far been devised for the construction of this class of molecules and several efforts have culminated in the total synthesis of podophyllotoxin (**1**) and its derivatives.[3,4]

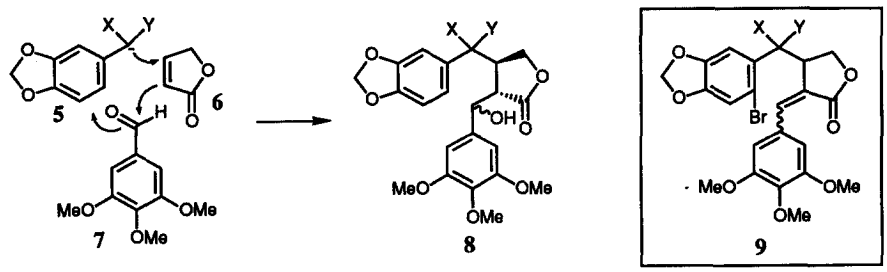


1 : X = OH, Y = H, R = Me
2 : X = H, Y = OH, R = Me
3 : X = Y = H, R = Me
4 : X = R = H, Y =



One of the most frequently employed approaches to podophyllotoxins is based upon the tandem process that consists of successive treatment of the benzylic anions **5** with γ-crotonolactone (**6**) and then with the aldehyde **7**.[5] The resulting alcohols **8**, when treated with acid, undergo an intramolecular aromatic substitution to give podophyllotoxin derivatives. This approach is particularly attractive in terms of the number of steps involved and the *trans*-stereochemistry of the lactone ring of podophyllotoxins. A disadvantage of this procedure is that

the aromatic cyclization of **8** generally leads to the 1,2-*trans* configuration (isopodophyllotoxin-type) rather than the desired 1,2-*cis* configuration (podophyllotoxin-type).[6] From this viewpoint, it seemed to be of interest to investigate the possibility and mode of formation of the C(1)-C(2) bond of podophyllotoxins by means of a tributyltin hydride (Bu_3SnH)-mediated or a palladium-catalyzed reaction (intramolecular Heck reaction) of the α-benzylidene-β-(*o*-bromobenzyl)-γ-lactones **9**. In this paper we report the contrasting behavior of the cyclizations observed with the *E*-lactone **20** and the *Z*-lactone **21**.[7]

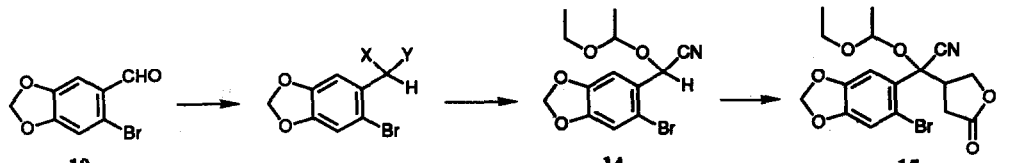


Results and Discussion

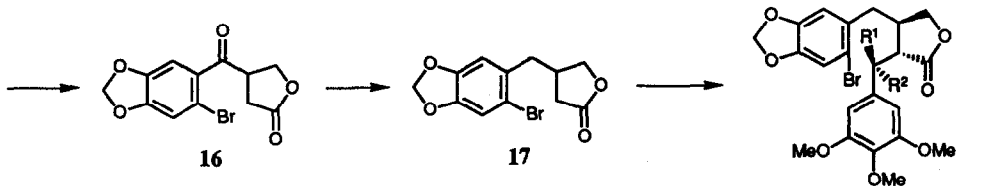
The requisite cyclization precursors **20** and **21** were prepared as follows. Ward and co-workers[8] reported that the carbanion **5** (X = Y = SPh) reacted readily with γ-crotonolactone (**6**) to give quantitatively the desired conjugate addition product. We therefore initiated our investigation by examining the reaction of the lithio derivative of the dithioacetal **11** with γ-crotonolactone (**6**). This, however, resulted in recovery of the starting materials. We found the *O*-ethoxyethyl cyanohydrin **14** to be the best choice for the reaction. The compound **14** was prepared by the reaction sequence which involved treatment of 6-bromopiperonal (**10**)[9] with trimethylsilyl cyanide, hydrolysis of the resultant *O*-TMS cyanohydrin **12**, and reprotection of the cyanohydrin **13** with ethyl vinyl ether. The compound **14** was treated with LDA in the presence of HMPA at -78 °C and the resulting lithio derivative was allowed to react with γ-crotonolactone (**6**) at the same temperature for 2 h and then at -60 °C for 1h to give the desired conjugate addition product **15** in 57% yield. A similar reaction in the absence of HMPA afforded only a 14% yield of **15**.

Deprotection of **15** with 10% HCl gave, in 85% yield, the ketone **16**, which was then reduced by triethylsilane in trifluoroacetic acid[10] to give the lactone **17** in 96% yield. A subsequent aldol reaction of the lithio derivative of **17** with 3,4,5-trimethoxybenzaldehyde (**7**) occurred smoothly to give a *ca.* 1:1 mixture of two diastereoisomeric alcohols **18a** and **18b** in quantitative yield. The stereochemistry of the alcohols **18a** and **18b** depicted in Scheme I was established by a comparison of the ^1H NMR spectra [**18a** : δ 4.81 (d, J = 7.5 Hz, C*H*OH), **18b** : δ 5.26 (d, J = 2.0 Hz, C*H*OH)] with those of the corresponding debrominated derivatives, epipodorhizol [δ 4.81 (d, J = 6.6 Hz)] and podorhizol [δ 5.27 (d, J = 2.2 Hz)].[5a]

Treatment of the mixture of **18a** and **18b** with methanesulfonyl chloride in the presence of triethylamine gave, in 96% yield, a mixture of the chlorides **19a** and **19b** in an approximately 3:1 ratio. The stereochemical assignment of **19a** and **19b** came from a comparison of the coupling constants of the signals due to CHCl (J = 3.9 Hz for **19a** and J = 2.6 Hz for **19b**) with those of the corresponding protons of the alcohols **18a** and **18b**. The mixture of **19a** and **19b** was then treated with DBU to give the (*Z*)-α-benzylidene-β-(*o*-bromobenzyl)-γ-lactone **20** and its *E*-isomer **21** in 64 and 22% yields, respectively. The structures of **20** and **21** were confirmed by their ^1H NMR spectra: the olefinic proton of **20** appeared at δ 6.63 (d, J = 1.7 Hz), whereas the

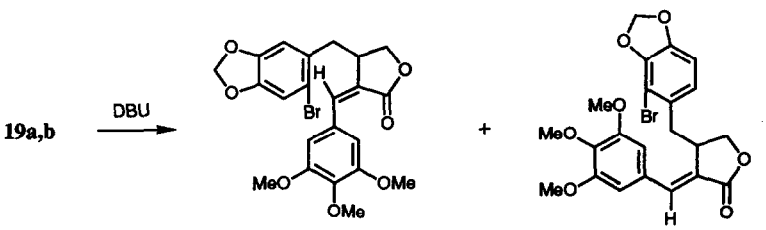


10 **11** : X = Y = SPh
12 : X = $OSiMe_3$, Y = CN
13 : X = OH, Y = CN
14 **15**

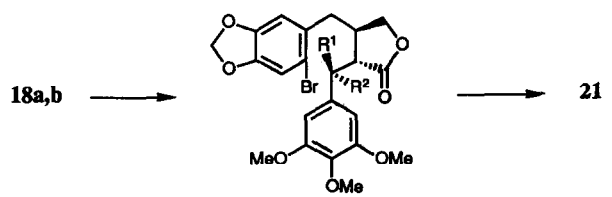


16 **17**

18a : R^1 = H, R^2 = OH
18b : R^1 = OH, R^2 = H
19a : R^1 = H, R^2 = Cl
19b : R^1 = Cl, R^2 = H



20 **21**

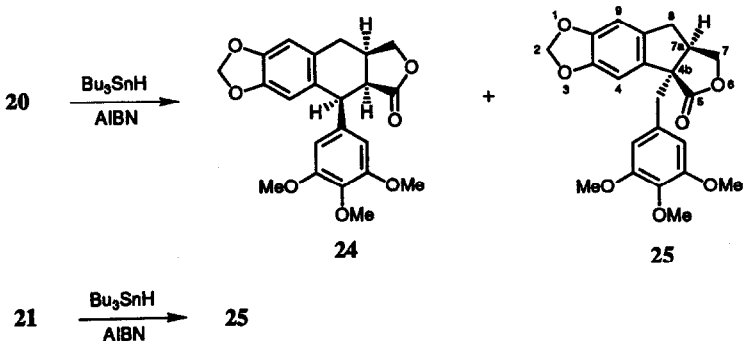


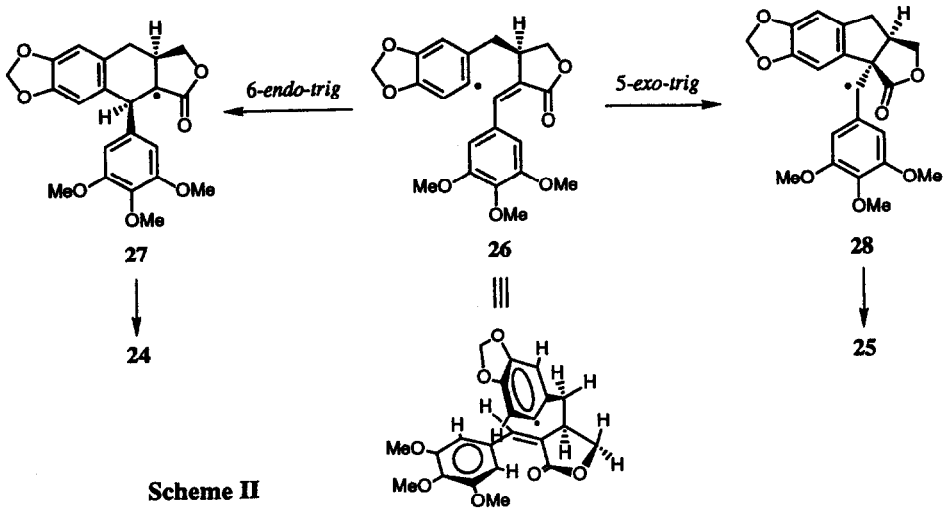
22a : R^1 = H, R^2 = SPh
22b : R^1 = SPh, R^2 = H
23a : R^1 = H, R^2 = S(O)Ph
23b : R^1 = S(O)Ph, R^2 = H

Scheme I

corresponding proton of **21** shifted down-field to δ 7.51 (d, J = 1.6 Hz) due to the deshielding effect of the neighboring lactone carbonyl group. The following procedure enabled us to obtain the *E*- isomer **21** as a major product. Treatment of the mixture of the alcohols **18a** and **18b** with thiophenol in the presence of $HClO_4$ gave, in 94% yield, a mixture of the sulfides **22a** and **22b** in a ratio of *ca.* 3:1. The mixture of **22a,b** was then oxidized with *m*-CPBA and the resulting mixture of the sulfoxides **23a,b** was heated in boiling CCl_4 to give **21** in 43% yield, along with a small quantity of the unchanged sulfoxide (probably **23b**). The difficulty in obtaining the *Z*-isomer **20** from the sulfoxide **23b** may be attributed to the eclipsed interaction between the trimethoxyphenyl group and the lactone carbonyl group in the transition state for the *syn*-elimination of sulfenic acid.

With the requisite α-benzylidene-γ-lactones **20** and **21** in hand, we then examined a cyclization under the Bu_3SnH-mediated conditions. Thus, when the *Z*-isomer **20** was treated with Bu_3SnH in the presence of AIBN in boiling benzene, two cyclization products **24** and **25** were obtained in 29 and 49% yields, respectively. The compound **24** (mp 203-204 °C) was identified as (±)-deoxyisopicropodophyllin (lit. mp 203-204 °C,[11] 208-210 °C[4g]) based on a comparison of the spectral data with those of an authentic sample. The structure of **25**





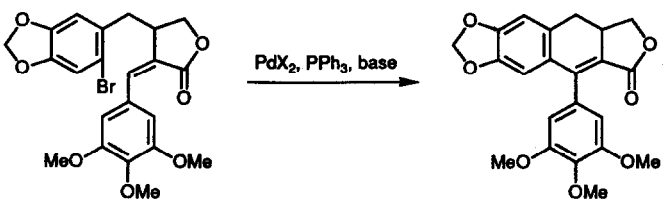
Scheme II

was deduced by examination of the spectroscopic data: the ^{1}H NMR spectrum exhibited an AB quartet (J = 13.7 Hz) at δ 2.96 and 3.23 due to the trimethoxyphenyl-substituted methylene group, and the ^{13}C NMR spectrum showed the presence of one quaternary carbon atom (C-4b) at δ 60.2.

By contrast, the *E*-isomer **21** was found to give only the lactone **25** in 64% yield when treated with Bu_3SnH and AIBN.

It is generally recognized that the *ortho*-3-alkenyl substituted aryl radicals cyclize preferentially in a 5-*exo*-*trig* manner rather than in a 6-*endo*-*trig* manner.[12] This is the case for the *E*-isomer **21** which gives exclusively the 5-*exo* cyclization product **25**. On the other hand, inspection of molecular models indicates that, in the transition state for the 5-*exo* cyclization of the radical **26** derived from the *Z*-isomer **20**, a severe steric repulsion between two aromatic rings becomes evident because they adopt a perpendicular form to each other as shown in Scheme II. Therefore, the 6-*endo*-*trig* cyclization can compete with the 5-*endo*-*trig* cyclization, giving the new radical **27**. The convex attack of Bu_3SnH on the radical center of **27** leads to the observed all *cis* product **24**. The possibility that the radical **27** was formed by a neophyl rearrangement[12a] of the radical **28** was excluded, since the same radical intermediate **28** formed from the *E*-isomer **21** led to only the lactone **25**..

Our attention was next turned to the intramolecular Heck reaction[13] of **20** and **21**. Thus, when the *Z*-isomer **20** was heated in acetonitrile in the presence of $Pd(OAc)_2$ (0.2 equiv.), PPh_3 (0.4 equiv.), and triethylamine (1 equiv.) at 120 °C for 3 h (entry 1 in Table 1), the cyclization product **29** was obtained in 28% yield, along with the recovered starting material **20** (35%). The melting point (252-253 °C) and spectral properties of **29** were identical with those of (±)-γ-apopicropodophyllin (lit. mp 252-253 °C,[14] 251-254 °C[4g]). The results obtained under various conditions by using K_2CO_3 as a base for the reaction are summarized in Table 1. The starting material **20** was consumed at 100 - 110 °C in either DMSO or DMF, but the yields of **29** were not improved (entries 2 and 3). The reaction at 90 °C in DMF was very sluggish (entry 4), whereas the addition of 1.2 equiv.



20 **29**

Table 1. Intramolecular Heck Reaction of 20.

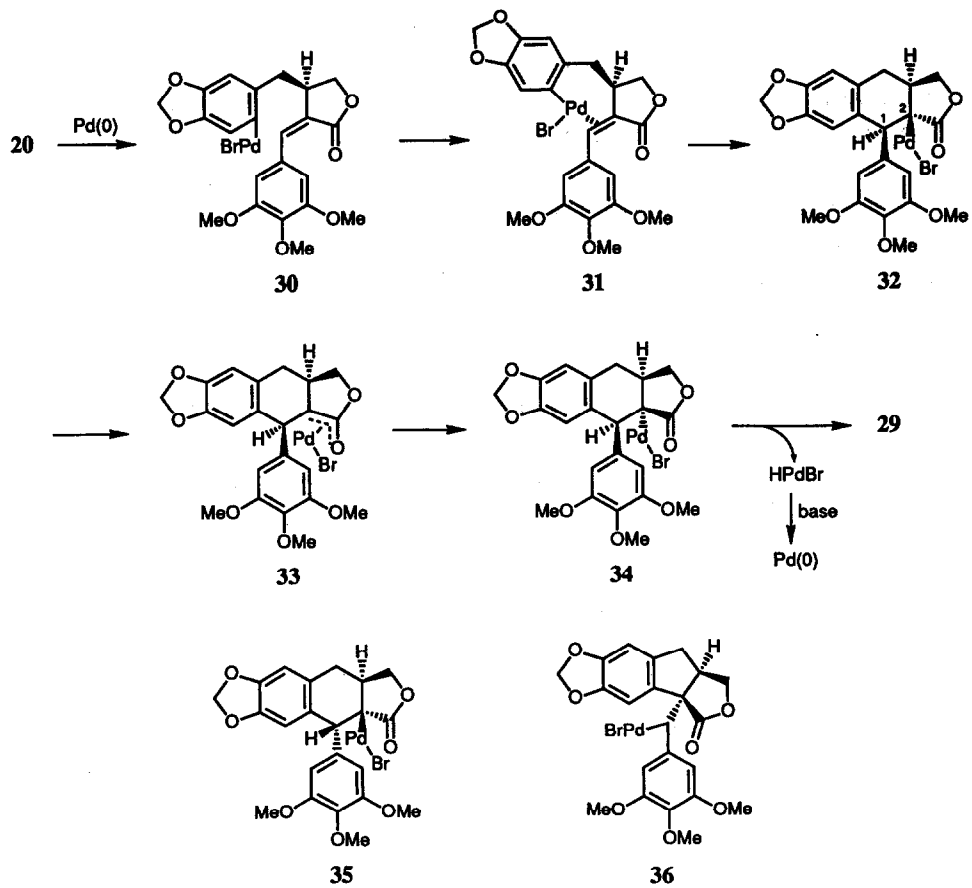
Entry	PdX_2[a)]	Equiv. of PPh_3	Base (equiv.)	Solvent	Temp. °C	Time h	Yield, % 29	Yield, % 20
1	$Pd(OAc)_2$	0.4	Et_3N (1)	CH_3CN	120	3.0	28	36
2	$Pd(OAc)_2$	0.4	K_2CO_3 (2)	DMSO	100	16.0	36	trace
3	$Pd(OAc)_2$	0.4	K_2CO_3 (2)	DMF	110	6.5	35	trace
4	$Pd(OAc)_2$	0.4	K_2CO_3 (2)	DMF	90	3.0	22	60
5	$Pd(OAc)_2$	1.2	K_2CO_3 (2)	DMF	90	4.5	54	9
6	$PdCl_2(PPh_3)_2$	1.2	K_2CO_3 (2)	DMF	90	5.0	75	7

a) 0.2 Equiv. were used.

of PPh_3 gave **29** in 54% yield after 4.5 h (entry 5). The best result was obtained by using $PdCl_2(PPh_3)_2$ as a catalyst in the presence of 1.2 equiv. of PPh_3 in DMF at 90 °C: this gave **29** in 75% yield (conversion yield: 81%) along with a small quantity (7%) of the starting material **20**.

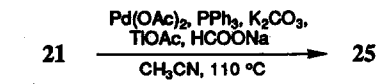
The *E*-isomer **21**, however, resulted in the formation of a complex mixture of products when subjected to the various Heck reaction conditions.

A possible mechanism to account for the formation of **29** from **20** is shown in Scheme III. The oxidative coupling of the bromide **20** with zero-valent palladium gives the σ-complex **30**, which then undergoes the C-C bond coupling at the less hindered site of olefinic bond in a *syn*-addition manner[13] to give the new σ-complex **32** *via* the π-complex **31**. Since a subsequent elimination of palladium and hydrogen atom must proceed in a *syn*-mode,[13] the σ-complex **32** would undergo isomerization to the diastereoisomeric **34** through the intermediacy of the enol complex **33**.[15] This step is then followed by elimination of zero-valent palladium and hydrogen bromide to lead to **29**.



Scheme III

The differing behavior of **20** and **21** toward the palladium-catalyzed reaction may be explained by considering the stereochemical requirements in the transition state for the formation of the σ-complex of type **32**. The C-C bond coupling of the π-complex **31** formed from **20** proceeds so as to form the 1,2-*trans* σ-complex **32** in which the trimethoxyphenyl group occupies the relatively stable *quasi*-equatorial conformation. However, the corresponding C-C bond coupling of the π-complex derived from the *E*-isomer **21** must give the sterically disfavored 1,2-*cis* σ-complex **35** in which the trimethoxyphenyl group is *quasi*-axial. It can therefore be presumed that the *E*-isomer **21** gives the five-membered σ-complex **36** and then decomposes under the reaction conditions employed, since it has no β-hydrogen atom required for elimination of the palladium. Indeed, treatment of **21** with $Pd(OAc)_2$ and K_2CO_3 in the presence of sodium formate (a hydride source) and TlOAc[16] in acetonitrile at 110 °C gave the lactone **25** in high yield (84%).



(±)-γ-Apopicropodophyllin (**29**) herein obtained has already been converted into (±)-deoxypodophyllotoxin (**3**) by Yamaguchi and co-workers.[4g]

Finally, the compound **25** was tested for growth inhibitory effects against various carcinoma cells such as Lu-99, LY-1, DLD-1, and P388 cell lines, but no remarkable effect was observed.

Experimental

Meling points are uncorrected. IR spectra were recorded on a JASCO A-100 spectrophotometer. ^1H and ^{13}C NMR spectra were measured on a JEOL JNM-PMX 60 or a Varian XL-300 spectrometer using tetramethylsilane as an internal standard. Exact mass (MS) determinations were obtained on a Hitachi M-80 instrument operating at 20 eV. All solvents for the Heck reaction were degassed by freeze-pump-thaw cycle procedure. Column chromatography was performed on silica gel 60 PF_{254} (Nacalai Tesque) under pressure.

2-(2-Bromo-4,5-methylenedioxyphenyl)-2-(trimethylsilyloxy)acetonitrile (12). To a solution of 6-bromopiperonal (**10**)[9] (5.0 g, 2.18 mmol) in CH_2Cl_2 (50 ml) containing ZnI_2 (5 mg) was added trimethylsilyl cyanide (3.49 ml, 2.62 mmol) at 0 °C, and the mixture was stirred at the same temperature for 30 min and then at room temperature for 5 min. Water (20 ml) was added to the reaction mixture and the organic layer was separated, dried ($MgSO_4$), and concentrated *in vacuo* to give **12** (7.08 g, 99%) as an oil: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.24 (9H, s), 5.60 (1H, s), 5.96 (2H, s), 6.92 (1H, s), 7.10 (1H, s). This compound was used immediately in the next stage.

2-(2-Bromo-4,5-methylenedioxyphenyl)-2-hydroxyacetonitrile (13). To a solution of **12** (5.52 g, 16.2 mmol) in THF (20 ml) was added 5% HCl (1 ml) at 0 °C and the mixture was stirred at the same temperature for 1.5 h. Water (40 ml) was added to the reaction mixture and the whole was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated *in vacuo* to give **13** (4.58 g, quant.) as colorless crystals: ^1H NMR ($CDCl_3$, 60 MHz) δ 4.00 (1H, br s), 5.72 (1H, d, J = 5.5 Hz), 6.00 (2H, s), 6.96 (1H, s), 7.15 (1H, s). This compound was used immediately in the next stage.

2-(2-Bromo-4,5-methylenedioxyphenyl)-2-(1-ethoxyethoxy)acetonitrile (14). To a solution of **13** (3.0 g, 11.8 mmol) in ethyl vinyl ether (40 ml) was added 5% HCl (1.5 ml) and the mixture was heated under reflux for 5.5 h. After completion of the reaction, the whole was concentrated *in vacuo* and the residue was chromatographed on silica gel (hexane-AcOEt, 4:1) to give **14** (3.11 g, 81%) as an oil: ^1H NMR ($CDCl_3$, 60 MHz) δ 1.0-1.5 (6H, m), 3.3-3.8 (2H, m), 4.7-5.2 (1H, m), 5.65 (1/2H, s), 5.76 (1/2H, s), 5.99 (2H, s), 6.97 (1H, s), 7.12 (1H, s). *Anal.* Calcd for $C_{13}H_{14}BrNO_4 \cdot 1/2H_2O$: C, 46.31; H, 4.48; N, 4.15. Found: C, 46.70; H, 4.32; N, 3.92.

4-[2-Bromo-4,5-methylenedioxy-α-cyano-α-(1-ethoxyethoxy)benzyl]dihydro-2(3*H*)-furanone (15). To a solution of LDA, prepared from diisopropylamine (0.47 ml, 3.36 mmol) and *n*-butyllithium (1.6 M in hexane, 2.15 ml, 3.36 mmol), in dry THF (7 ml) were added successively a solution of

14 (1.0 g, 3.05 mmol) in THF (5 ml), HMPA (0.53 ml, 3.05 mmol), and γ-crotonolactone (**7**) (256 mg, 3.05 mmol) at -78 °C, and the mixture was stirred at the same temperature for 2 h and then at -60 °C for 1 h. A saturated NH_4Cl solution (15 ml) was added and the whole was extracted with CH_2Cl_2. The exract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane-AcOEt, 2:1) to give **15** (716 mg, 57%) as an oil: IR (CCl_4) ν 1790 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.8-1.6 (6H, m), 2.3-2.9 (2H, m), 3.2-3.8 (2H, m), 3.9-5.3 (4H, m), 6.0-6.15 (2H, m), 7.1-7.2 (1H, m), 7.3-7.45 (1H, m). *Anal.* Calcd for $C_{17}H_{18}BrNO_6 \cdot H_2O$: C, 47.45; H, 4.68; N, 3.26. Found: C, 47.84; H, 4.52; N, 3.28.

4-(2-Bromo-4,5-methylenedioxybenzoyl)dihydro-2(3*H*)-furanone (16). To a solution of **15** (1.14 g, 3.63 mmol) in THF (5 ml) was added 3N HCl (6 ml), and the mixture was stirred at room temperature for 4.5 h. Ethyl ether (15 ml) was added to the reaction mixture and the whole was neutralized with saturated $NaHCO_3$ solution. The organic layer was separated, dried ($MgSO_4$), and concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane-AcOEt, 2:1) to give **16** (757 mg, 88%): mp 121-123 °C (from hexane-AcOEt): IR ($CHCl_3$) ν 1780, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.7-2.9 (2H, m), 4.3-4.6 (3H, m), 6.02 (2H, s), 6.90 (1H, s), 7.04 (1H, s). *Anal.* Calcd for $C_{12}H_9BrO_5$: C, 46.03; H, 2.90. Found: C, 46.13; H, 2.88.

4-(2-Bromo-4,5-methylenedioxybenzyl)dihydro-2(3*H*)-furanone (17). Triethylsilane (0.1 ml, 0.64 mmol) was added to a solution of **16** (100 mg, 0.32 mmol) in trifluoroacetic acid (0.5 ml), and the mixture was stirred overnight at 45 °C. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and the whole was extracted with ethyl acetate. The extract was dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane-AcOEt, 2;1) to give **17** (92 mg, 96%): mp 99-100 °C (hexane-AcOEt); IR ($CHCl_3$) ν 1770 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.32 (1H, dd, J = 17.6, 8.1 Hz), 2.60 (1H, dd, J = 17.6, 8.0 Hz), 2.80-2.84 (2H, m), 2.86-2.99 (1H, m), 4.07 (1H, dd, J = 9.2, 6.1 Hz), 4.34 (1H, dd, J = 9.2, 6.9 Hz), 5.98 (2H, s), 6.66 (1H, s), 7.01 (1H, s). *Anal.* Calcd for $C_{12}H_{11}BrO_4$: C, 48.19; H, 3.71. Found: C, 48.15; H, 3.64.

***trans*-4-(2-Bromo-4,5-methylenedioxybenzyl)-3-(3,4,5-trimethoxy-α-hydroxybenzyl)dihydro-2(3*H*)-furanones (18a and 18b).** To a solution of LDA, prepared from diisopropylamine (0.2 ml, 1.41 mmol) and *n*-butyllithium (1.6 M in hexane, 0.9 ml, 1.41 mmol), in dry THF (8 ml) was added a solution of **17** (382 mg, 1.28 mmol) at -78 °C. After 5 min, a solution of 3,4,5-trimethoxybenzaldehyde (**7**) (251 mg, 1.28 mmol) in dry THF (2 ml) was added and the mixture was further stirred for 2 h. A saturated NH_4Cl solution was added to the reaction mixture and the whole was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel (hexane-AcOEt, 1:1) to give a mixture of the *threo* isomer **18a** and the *erythro* isomer **18b** (631 mg, quant.) as colorless crystals, whose ^1H NMR spectrum showed the ratio of **18a** and **18b** to be *ca.* 1:1: IR ($CHCl_3$) ν 3520, 1755 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55-1.70 (0.5H, br), 2.42-2.74 (4H, m), 2.87-3.00 (0.5H, m), 3.81, 3.83, 3.87 (total 9H, both s), 3.94-4.16 (1.5H, m), 4.46 (0.5H, dd, J = 8.9, 7.8 Hz), 4.81 (0.5H, d, J = 7.5 Hz, C*H*OH for **18a**), 5.26 (0.5H, d, J = 2.0 Hz, C*H*OH for **18b**), 5.95, 5.97 (1H, ABq, J = 1.5 Hz), 5.96 (1H, s), 6.29 (0.5H, s), 6.41 (1.5H, s), 6.63 (1H, s), 6.79 (0.5H, s), 6.90 (0.5H, s). *Anal.* Calcd for $C_{22}H_{23}BrO_8$: C, 53.35; H, 4.68. Found: C, 53.77; H, 4.47.

***trans*-4-(2-Bromo-4,5-methylenedioxybenzyl)-3-(α-chloro-3,4,5-trimethoxybenzyl)dihydro-2(3*H*)-furanones (19a and 19b).** Methanesulfonyl chloride (291 mg, 2.54 mmol) was added to a solution of the mixture of **18a** and **18b** (631 mg, 1.27 mmol) in CH_2Cl_2 (10 ml) containing triethylamine (0.35 ml, 2.54 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. Water (5 ml) was added to the reaction mixture and the organic layer was separated and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (hexane-AcOEt, 1:1) to give a mixture of the *threo* isomer **19a** and the *erythro* isomer **19b** (625 mg, 96%) as an oil, whose ^1H NMR spectrum showed the ratio of **19a** and **19b** to be *ca.* 3:1: IR ($CHCl_3$) ν 1765 cm^{-1}; ^1H NMR ($CDCl_3$,300 MHz) δ 2.58 (0.25H, dd, J = 13.5, 9.9 Hz), 2.74 (0.25H, dd, J = 13.5, 6.0 Hz), 2.82 (0.75H, dd, J = 13.2, 8.5 Hz), 2.91-3.13 (2.75H, m), 3.79 (0.75H, dd, J = 9.3, 7.3 Hz), 3.81, 3.84, 3.85, 3.86, 3.87 (total 9H, both s), 3.90 (0.75H, dd, J = 9.3, 5.8 Hz), 4.11 (0.25H, dd, J = 9.2, 3.8 Hz), 4.53 (0.25H, dd, J = 9.2, 7.8 Hz), 5.30 (0.75H, d, J = 3.9 Hz, CHCl for **19a**), 5.48 (0.25H, d, J = 2.6 Hz, CHCl for **19b**), 5.98 (2H, s), 6.25 (0.25H, s), 6.47 (0.5H, s), 6.64 (0.75H, s), 6.69 (1.5H, s), 6.79 (0.25H, s), 7.01 (0.75H, s). Exact MS *m/z*: Calcd for $C_{22}H_{22}BrClO_7$: 512.0236. Found: 512.0244.

(*Z*)- and (*E*)-4-(2-Bromo-4,5-methylenedioxybenzyl)-3-(3,4,5-trimethoxybenzylidene)dihydro-2(3*H*)-furanones (20 and 21). To a solution of the mixture of **19a** and **19b** (565 mg, 1.1 mmol) in acetonitrile (10 ml) was added DBU (167 mg, 1.1 mmol), and the mixture was stirred at room temperature for 5 h. Water (20 ml) was added to the reaction mixture and the whole was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane-AcOEt, 2:1). The first eluate gave **20** (334 mg, 64%): mp 149-150 °C (from hexane-AcOEt): IR

($CHCl_3$) ν 1740, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.92 (1H, dd, *J* = 13.9, 9.0 Hz), 3.04 (1H, dd, *J* = 13.9, 6.8 Hz), 3.41-3.52 (1H, m), 3.89 (9H, s), 4.17 (1H, dd, *J* = 9.0, 3.5 Hz), 4.34 (1H, dd, *J* = 9.0, 6.9 Hz), 5.97, 5.98 (1H each, ABq, *J* = 1.8 Hz), 6.63 (1H, d, *J* = 1.7 Hz), 6.69 (1H, s), 7.05 (1H, s), 7.26 (2H, s). *Anal.* Calcd for $C_{22}H_{21}BrO_7$: C, 55.36; H, 4.43. Found: C, 55.07; H, 4.42.

The second eluate gave **21** (115 mg, 22%): mp 156-157 °C (from hexane -AcOEt); IR ($CHCl_3$) ν 1745, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.79 (1H, dd, *J* = 13.8, 8.8 Hz), 3.00 (1H, dd, *J* = 13.8, 6.6 Hz), 3.86 (3H, s), 3.87 (6H, s), 3.99-4.11 (1H, m), 4.27 (1H, dd, *J* = 9.2, 1.2 Hz), 4.40 (1H, dd, *J* = 9.2, 6.6 Hz), 5.82, 5.89 (1H each, ABq, *J* = 1.4 Hz), 6.46 (1H, s), 6.56 (2H, s), 6.80 (1H, s), 7.51 (1H, d, *J* = 1.6 Hz). *Anal.* Calcd for $C_{22}H_{21}BrO_7$: C, 55.36; H, 4.43. Found: C, 55.27; H, 4.41.

***trans*-4-(2-Bromo-4,5-methylenedioxybenzyl)-3-[3,4,5-trimethoxy-α-(phenylthio)benzyl]-dihydro-2(3*H*)-furanones (22a and 22b).** To a solution of the mixture of **18a** and **18b** (42 mg, 0.08 mmol) in ethyl acetate (1 ml) were added successively thiophenol (0.02 ml, 0.16 mmol) and two drops of $HClO_4$, and the mixture was stirred at room temperature for 5 h. Water (5 ml) was added to the reaction mixture and the organic layer was separated, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane-AcOEt) to give a mixture of the *threo* isomer **22a** and the *erythro* isomer **22b** (47 mg, 94%) as colorless crystals, whose ^{1}H NMR spectrum showed the ratio of **22a** and **22b** to be *ca.* 3:1: IR ($CHCl_3$) ν 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) : 2.59-2.80 (1.25H, m), 2.90-3.02 (2H, m), 3.11 (0.75H, dd, *J* = 13.1, 6.5 Hz), 3.59 (0.75H, dd, *J* = 9.0, 6.9 Hz), 3.78-3.87 (9.75H, m), 4.03 (0.25H, dd, *J* = 9.0, 3.8 Hz), 4.41 (0.25H, *J* = 9.0, 7.3 Hz), 4.56 (0.25H, d, *J* = 3.5 Hz, SCH for **22b**), 4.82 (0.75H, d, *J* = 2.9 Hz, SCH for **22a**), 5.96-5.98 (2H, m), 6.34 (0.25H, s), 6.59 (0.5H, s), 6.60 (0.75H, s), 6.70 (1.5H, s), 6.86 (0.25H, s), 6.99 (0.75H, s), 7.20-7.34 (5H, s). *Anal.* Calcd for $C_{22}H_{27}BrO_7S$: C, 57.25; H, 4.63. Found: C, 56.98; H, 4.69.

Preparation of 21 by Thermolysis of the Sulfoxides 23a and 23b. *m*-CPBA (146 mg, 0.68 mmol) was added portionwise to a solution of the mixture of **22a** and **22b** (400 mg, 0.68 mmol) in CH_2Cl_2 (10 ml) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction mixture was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated *in vacuo*. The residue containing the sulfoxides **23a,b** was dissolved in CCl_4 (5 ml) and the mixture was heated under reflux in the presence of a small quantity of K_2CO_3 for 1.5 h. The reaction mixture was washed with water, dried ($MgSO_4$), and concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane-AcOEt, 2:1) to give **21** (140 mg, 43%), whose physical data were identical with those of the compound obtained above from the chlorides **19a,b**.

Bu_3SnH-Mediated Reaction of 20. A mixture of Bu_3SnH (0.06 ml, 0.21 mmol) and AIBN (3 mg, 0.019 mmol) in dry benzene (20 ml) was added dropwise to a boiling solution of **20** (90 mg, 0.19 mmol) in dry benzene (20 ml) over a period of 3 h, and the mixture was further refluxed for 30 min. The solvent was evaporated off, diethyl ether (5 ml) and 10% KF solution were added to the residue, and the mixture was stirred vigorously for 1 h. The organic layer was separated, dried ($MgSO_4$), and concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane-AcOEt, 2:1). The first eluate gave 4b,7,7a,8-tetrahydro-4b-(3,4,5-trimethoxybenzyl)-5*H*-furo[3',4':1,2]indeno[5,6-*d*]-1,3-dioxol-5-one (**25**) (37 mg, 49%): mp 69-70 °C (from diethyl ether); IR ($CHCl_3$) ν 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Hz) δ 2.50 (1H, d, *J* = 16.2 Hz, one of H-8), 2.61 (1H, d, *J* = 16.2, 6.8 Hz, one of H-8), 2.96 (1H, d, *J* = 13.7 Hz), 3.09-3.18 (1H, m, H-7a), 3.23 (1H, d, *J* = 13.7 Hz), 3.68 (1H, dd, *J* = 9.1, 8.1 Hz, one of H-7), 3.74 (6H, s), 3.81 (3H, s), 4.35 (1H, t, *J* = 9.1 Hz, one of H-7), 5.97 (2H, s), 6.21 (2H, s), 6.61 (1H, s), 7.01 (1H, s); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 35.8, 42.4, 43.1 (C-7a), 56.0, 60.2 (C-4b), 60.9, 101.5 (C-2), 104.4, 105.4, 106.6, 132.0, 133.9, 134.6, 147.8, 148.8, 152.9, 178.6 (C-5); MS *m/z* 398 (M^+), 181 (3,4,5-trimethoxybenzyl$^+$). *Anal.* Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.38. Found: C, 66.32; H, 5.57.

The second eluate gave (±)-deoxyisopicropodophyllin (**24**) (21 mg, 29%): mp 203-204 °C (from hexane-CH_2Cl_2) (lit. mp 203-204 °C,[11] 208-210 °C[4g]); IR ($CHCl_3$) ν 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.70 (1H, dd, *J* = 15.7, 5.0 Hz), 2.97 (1H, dd, *J* = 15.6, 8.5 Hz), 3.10-3.25 (2H, m), 3.50 (1H, dd, *J* = 8.9, 7.9 Hz), 3.77 (6H, s), 3.83 (3H, s), 4.37-4.45 (2H, m), 5.96 (2H, s), 6.50 (2H, s), 6.65 (1H, s), 6.74 (1H, s).

Bu_3SnH-Mediated Reaction of 21. A mixture of Bu_3SnH (0.03 ml, 0.1 mmol) and AIBN (1 mg, 0.009 mmol) in dry benzene (10 ml) was added dropwise to a boiling solution of **21** (43 mg, 0.09 mmol) in dry benzene (10 ml), and the mixture was refluxed for 11.5 h. A similar work-up to that described above for the reaction of **20** gave **25** (23 mg, 64%), whose physical data were identical with those of the compound obtained from **20**.

(±)-γ-Apopicropodophyllin (29). A mixture of **20** (100 mg, 0.21 mmol), $PdCl_2(PPh_3)_2$ (29 mg, 0.04 mmol), PPh_3 (66 mg, 0.25 mmol), and K_2CO_3 (58 mg, 0.42 mmol) in DMF (2 ml) was heated at 90 °C for 5 h under an argon atmosphere. Water (10 ml) was added to the reaction mixture and the whole was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel (hexane-AcOEt, 1:1). The first eluate gave the starting material **20** (7 mg, 7%).

The second eluate gave **29** (62 mg, 75%): mp 252-253 °C (from hexane-CH_2Cl_2) (lit. mp 252-253 °C,[14] 251-254 °C[4g]); IR ($CHCl_3$) ν 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.82 (1H, dd, J = 14.9, 0.9 Hz), 2.94 (1H, dd, J = 14.9, 6.6 Hz), 3.31-3.47 (1H, m), 3.84 (6H, s), 3.92 (3H, s), 4.01 (1H, t, J = 8.8 Hz), 4.70 (1H, t, J = 8.8 Hz), 5.97 (2H, s), 6.52 (3H, s), 6.79 (1H, s). *Anal.* Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.40; H, 5.04.

Formation of 25 by Heck Reaction of 21. A mixture of **21** (45 mg, 0.09 mmol), $Pd(OAc)_2$ (4 mg, 0.02 mmol), PPh_3 (9 mg, 0.04 mmol), K_2CO_3 (25 mg, 0.19 mmol), TlOAc (49 mg, 0.19 mmol), sodium formate (9 mg, 0.14 mmol) in acetonitrile (1.5 ml) was heated in a sealed tube at 110 °C for 3 h. A similar work-up to that described above gave **25** (32 mg, 84%).

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