[Chem. Pharm. Bull. 32(1) 31—37 (1984)]

Biomimetic Synthesis of Podophyllum Lignans

TETSUYA TAKEYA, YUKARI AKABANE, EIICHI KOTANI, and SEISHO TOBINAGA*

Showa College of Pharmaceutical Sciences, Tsurumaki, Setagaya-ku, Tokyo 154, Japan

(Received April 30, 1983)

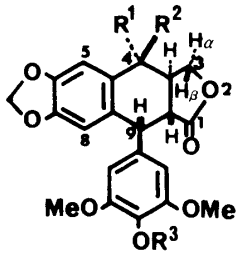
(±)-Isopodophyllotoxone **6a** and the related lactones **8a** and **9a** were synthesized by a biomimetic procedure from the ester **5a** by oxidation with a CrO_3–HBF_4–MeCN reagent system in one step. 4′-Benzyl-isopodophyllotoxone **6b**, 4′-benzyl-picropodophyllone **7b**, and the γ-lactones **8b** and **9b** were also synthesized from the ester **5b** by oxidation with the same reagent system.

Keywords——podophyllum lignan; biomimetic synthesis; chromium trioxide; (±)-isopodophyllotoxone; (±)-picropodophyllone; 4′-benzyl-isopodophyllotoxone; 4′-benzyl-picropodophyllone

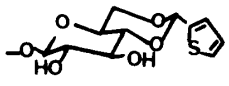
Podophyllum lignans are formed in nature by the oxidative dimerization of cinnamic acids with cinnamyl alcohols,[1] and have a long history as medicinals. This has recently culminated in studies for the development of clinical efficacious synthetic analogues of podophyllotoxin **1a** and epipodophyllotoxin **1b** with the renewed antineoplastic activity, leading to clinical applications of two glycosides VW-26 **1c** and VP-16-213 **1d** in the treatment of lung and bladder cancer.[2] Synthesis of podophyllotoxin **1a** itself has also been a challenging target in view of the stereochemical features: four contiguous chiral centers, and a rigid and strained transfused lactone.[3] The previous synthesis of the aryltetralin lactones **3** and **4** from a doubly unsaturated ester **2** by Diels–Alder reaction by Stevenson and his co-workers is a useful method for the synthesis of podophyllum lignans, but the product lacks the oxygen function at C(4) and it is difficult to obtain the transfused lactone moiety.[4]

In the preceding paper,[5] we reported new reagent systems, CrO_3–HBF_4–MeCN and CrO_3–$HClO_4$–MeCN, with the ability to oxidize 1-aryl-1-propene to give 1-aryltetrahydronaphthalide neo-lignans. Studies on the application of these reagent systems to organic synthesis have been focused on the synthesis of podophyllum lignans, and we found that isopodophyllotoxone **6a** and the related lactones **8a** and **9a** could be synthesized in a biomimetic manner from the ester **5a** by oxidation with these reagent systems in one step.

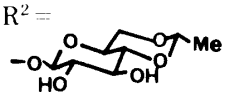
Oxidation of the ester **5a**, mp 118—120 °C, prepared from the corresponding cinnamyl alcohol and cinnamic acid chloride, by the reagent system CrO_3–HBF_4–MeCN at room temperature for 30 s gave (±)-isopodophyllotoxone **6a**,[6] mp 223—225 °C, a γ-lactone **8a**, liq., and a hydroxy-γ-lactone **9a**, mp 175—176 °C, in yields of 6.3, 19, and 7%, respectively. The structure of **8a** was assigned by considering the following chemical transformations and analyses of the ^1H nuclear magnetic resonence (NMR) and ^{13}C NMR spectra. (i) C(9)–H and C(9a)–H may be *cis* because of the coupling constant of 1.95 Hz between these two protons in the ^1H NMR. (ii) C(9a)–H and C(3a)–H may be *trans* because of the coupling constant of 10.25 Hz between these two protons in the ^1H NMR. (iii) The signal of C(8)–OMe, at 3.55 ppm in $CDCl_3$, is observed at higher field than the other –OMe group signals owing to the shielding effect of the phenyl group in the ^1H NMR. (iv) Three doublet signals, 36.75, 42.74, and 49.08 ppm, due to the aliphatic tertiary carbon atoms are observed in the off

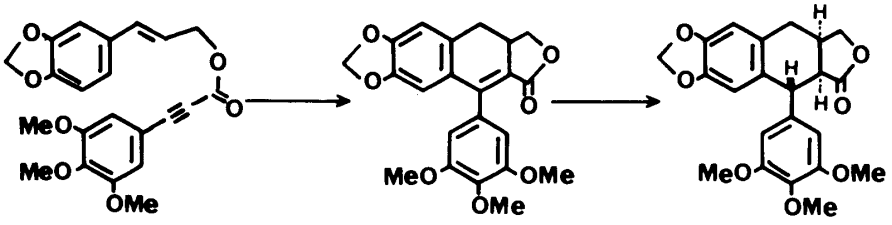


1a : R^1 = OH, R^2 = H, R^3 = Me
1b : R^1 = H, R^2 = OH, R^3 = Me
1c : R^1 = R^3 = H, R^2 =



1d : R^1 = R^3 = H, R^2 =





2 3 4

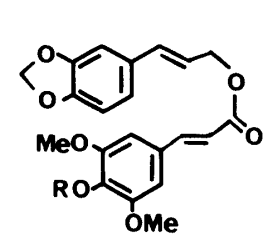
Chart 1

resonance decoupled ^{13}C NMR spectrum. Compound **8a** gave the enol-acetate **10**, mp 144—146 °C, by reaction with Ac_2O–AcONa, and the aromatized compound **11**, mp 218—220 °C, by reaction with $CuCl_2$–LiCl in dimethylformamide (DMF).[7] Compound **10** afforded a decarboxylated product **12a**, liq., on treatment with 10% alcoholic KOH, and **12a** gave the acetate **12b**, liq., on treatment with Ac_2O–pyridine.

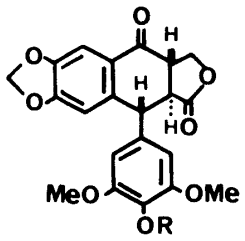
The structure of **9a** was assigned by considering the following chemical transformations and spectral analyses. (i) It has –OH group absorption at 3450 cm^{-1} in the infrared (IR) spectrum. (ii) C(9)–H and C(9a)–H may be *cis* because of the coupling constant of 1.95 ppm between these two protons in the ^1H NMR. (iii) The signal of C(8)–OMe, at 3.59 ppm in $CDCl_3$, is observed at higher field than the other –OMe signals owing to the shielding effect of the phenyl group in the ^1H NMR. (iv) An –OH group proton signal at 4.63 ppm in the ^1H NMR disappeared on adding D_2O. (v) Two doublet signals at 38.30 and 46.67 ppm due to the aliphatic tertiary carbon atoms are observed in the off resonance decoupled ^{13}C NMR. Compound **9a** gave the acetate **9c**, mp 155—157 °C, on reaction with Ac_2O–pyridine, and the aromatized compound **11** on reaction with $SOCl_2$ in pyridine. The structure of **9a** was also confirmed by the hydroxylation of **8a** with oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoO_5·HMPA·pyridine complex)[8] to give **9a** in 90% yield.

The proposed formation process of these oxidation products **6a**, **8a**, and **9a** is shown in Chart 3; the dication **14** is considered to be an important intermediate formed by radical coupling of the bi-radical cation **13**, leading to (±)-isopodophyllotoxone **6a** and the γ-lactones **8a** and **9a**.

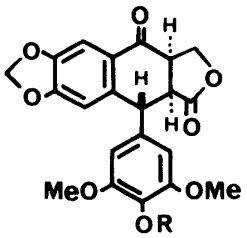
Oxidation of the ester **5b**, mp 110 °C, was also investigated in connection with the less toxic clinically effective compounds **1c** and **1d**. Reaction of **5b** with the same reagent system, CrO_3–HBF_4–MeCN, gave 4′-benzyl-isopodophyllotoxone **6b**, mp 215—217 °C, 4′-benzyl-picropodophyllone **7b**, mp 175—177 °C, a γ-lactone **8b**, liq., and a hydroxy-γ-lactone **9b**, liq., in yields of 3.7, 5, 10.0, and 5.5%, respectively. The structure of **6b** was assigned from the NMR data; there was a coupling constant of 10.99 Hz between C(9)–H and C(9a)–H and one of 15.7 Hz between C(9a)–H and C(3a)–H. The structure of **7b** was assigned similarly from



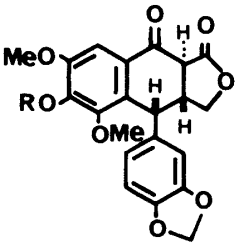
5a : R = Me
5b : R = CH_2Ph



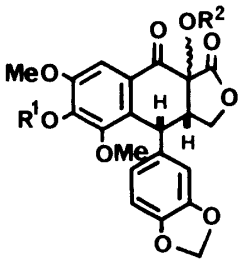
6a : R = Me
6b : R = CH_2Ph
6c : R = H



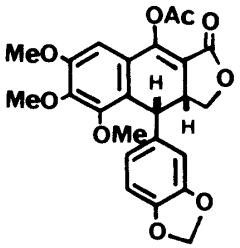
7a : R = Me
7b : R = CH_2Ph
7c : R = H



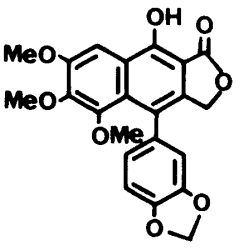
8a : R = Me
8b : R = CH_2Ph



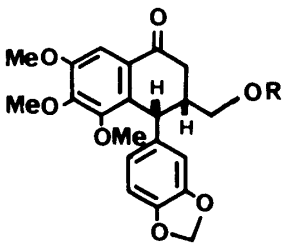
9a : R^1 = Me, R^2 = H
9b : R^1 = CH_2Ph, R^2 = H
9c : R^1 = Me, R^2 = Ac



10



11



12a : R = H
12b : R = Ac

Chart 2

the NMR data; there were coupling constants of 2.44 Hz between C(9)–H and C(9a)–H and 3.41 Hz between C(9a)–H and C(3a)–H.[9] The structures of **8b** and **9b** were elucidated similarly.

Treatment of **6b** with CF_3CO_2H at room temperature for 1 d gave 4′-demethyl-isopodophyllotoxone **6c**, mp 220—222 °C, and 4′-demethyl-picropodophyllone **7c**, mp 228—230 °C, in yields of 35 and 31%, respectively. Treatment of **6a** with CF_3CO_2H at room temperature for 2 d gave (±)-picropodophyllone **7a**,[6] mp 200—201 °C, in 80% yield.

Experimental

All melting points are uncorrected. IR spectra were recorded with a Hitachi 260-10 spectrometer, ^1H and ^{13}C NMR spectra with a JEOL JNM-FX 100 spectrometer with tetramethylsilane as an internal standard ($CDCl_3$ or C_6D_6 soln.) and mass spectra (MS) with a JEOL JMS-D 300 spectrometer. Elemental analyses were done by Ms. M. Takeda and Ms. S. Okamura, Kissei Pharmaceutical Company, Matsumoto, Japan. Mallinckrodt silica gel (100 mesh) and Merck Kieselgel 60 F_{254} were used for column chromatography and thin-layer chromatography (TLC), respectively.

3,4-Methylenedioxycinnamyl 3-(3,4,5-Trimethoxyphenyl)acrylate (5a)——A solution of 3,4,5-trimethoxyphenylacrylic acid (23.8 g, 0.1 mol) and thionyl chloride (23.8 g, 0.2 mol) in anhydrous CH_2Cl_2 (250 ml) was refluxed for

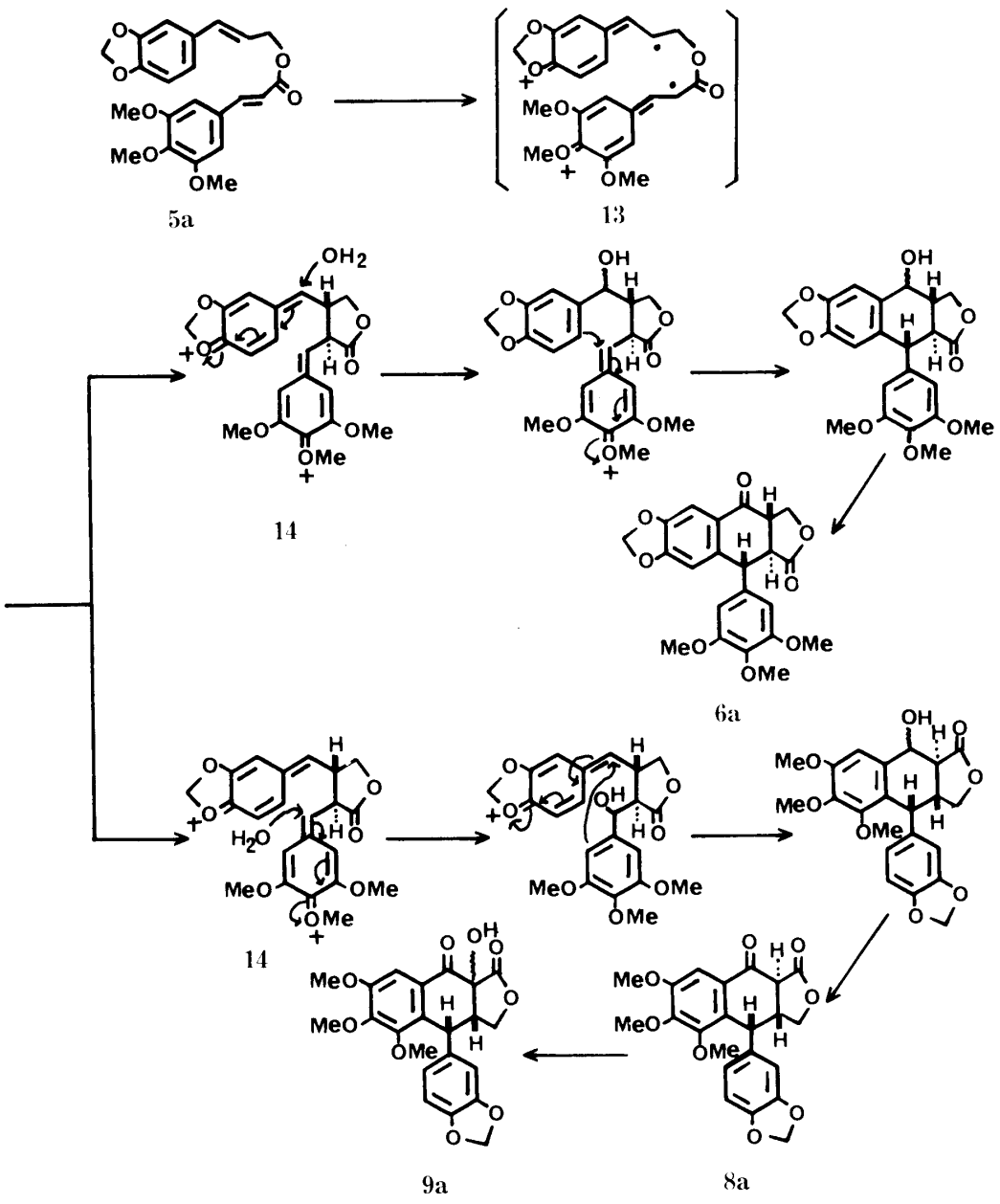


Chart 3

15 min. To the residue obtained by evaporation of the above solution, anhydrous dioxane (200 ml) and a solution of (*Z*)-3,4-methylenedioxycinnamyl alcohol (17.8 g, 0.1 mol) in anhydrous pyridine (30 ml) were added at 0 °C. This mixture was stirred at room temperature for 3 h. The solution was concentrated under a vacuum, the residue was taken up in $CHCl_3$ and the solution was washed with 10% HCl, sat. $NaHCO_3$ and H_2O. The organic residue obtained by evaporation was crystallized from CH_2Cl_2–hexane to yield 28.6 g (72%) of **5a** as colorless crystals, mp 118—120 °C. IR (Nujol) cm^{-1}: 1700, 1630, and 1580. NMR ($CDCl_3$) δ: 3.85 [9H, s, 3×OMe], 4.78 [2H, d, J=6 Hz, –CH=CH–CH_2–], 5.95 [2H, s, OCH_2O], 6.15—6.32 [2H, m, olefinic H], 6.25 [1H, d, J=14 Hz, olefinic H], 6.65—6.90 [5H, m, aromatic H], and 7.50 [1H, d, J=14 Hz, olefinic H]. *Anal.* Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57; *m/e* 398.1366. Found: C, 66.37; H, 5.56; *m/e*, 398.1374.

3,4-Methylenedioxycinnamyl 3-(4-Benzyloxy-3,5-dimethoxyphenyl)acrylate (5b)——Synthesized from 4-benzyloxy-3,5-dimethoxyphenylacrylic acid chloride and (*Z*)-3,4-methylenedioxycinnamyl alcohol in the same manner as described for the synthesis of **5a**. **5b** was obtained in a yield of 70% after recrystallization from CH_2Cl_2–hexane; colorless crystals, mp 110—112 °C. IR (Nujol) cm^{-1}: 1700, 1625, and 1580. NMR ($CDCl_3$) δ: 3.85 [9H, s, 3×OMe], 4.78 [2H, d, J=6 Hz, –CH=CH–CH_2–], 4.95 [2H, s, OCH_2Ph], 5.90 [2H, s, OCH_2O], 6.10—6.30 [2H, m, olefinic H], 6.63—6.85 [5H, m, aromatic H], 6.30 [1H, d, J=16 Hz, olefinic H], 7.15—7.40 [5H, m, aromatic H], and

7.50 [1H, d, J=16 Hz, olefinic H]. *Anal.* Calcd for $C_{28}H_{26}O_7$: C, 70.87; H, 5.52; *m/e* 474.1677. Found: C, 71.05; H, 5.43; *m/e*, 474.1670.

Oxidation of the Ester 5a——A solution prepared by adding 203 ml of MeCN to a mixture of CrO_3 (2.54 g, 0.025 mol) and 42% aqueous HBF_4 (50.8 ml) was added at room temperature to a stirred solution of the ester **5a** (4.6 g, 0.016 mol) in MeCN (150 ml), and the whole was stirred at room temperature for 30 s. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The first elution, with 5% hexane in chloroform, gave 0.9 g (19%) of 1,3,3aα,4,9β,9aβ-hexahydro-6,7,8-trimethoxy-9α-(3,4-methylenedioxyphenyl)-naphtho[2,3-*c*]furan-3,4-dione **8a** as colorless oil. IR (neat) cm^{-1}: 1780, 1680, and 1590. ^1H NMR (C_6D_6) δ: 2.43—2.71 [1H, m, C(9a)–H], 3.27 [3H, s, C(8)–OMe], 3.35, 3.62 [6H, s, 2×OMe], 3.45—3.59 [1H, m, lactone C(1)β-H], 3.50 [1H, d, J=10.25 Hz, C(3a)–H], 3.83 [1H, t, J=8.79 Hz, lactone C(1)α-H], 4.13 [1H, d, J=1.95 Hz, C(9)–H], 5.33 [2H, s, OCH_2O–], 6.18 [1H, dd, J=8.05 and 1.96 Hz, C(6′)–H], 6.30—6.53 [2H, m, C(2′)–H and C(5′)–H], and 7.45 [1H, s, C(5)–H]. ^{13}C NMR ($CDCl_3$) δ: 36.75 (d), 42.74 (d), 49.08 (d), 56.18 (q), 56.42 (q), 61.00 (q), 70.98 (t), 101.22 (t), 106.08 (d), 107.80 (s), 108.61 (d), 120.41 (d), 127.81 (s), 129.57 (s), 136.80 (s), 146.72 (s), 148.24 (s), 148.77 (s), 151.12 (s), 153.35 (s), 170.55 (s), 185.69 (s). *Anal.* Calcd for $C_{22}H_{20}O_8$: *m/e* 412.1158. Found: 412.1163.

The second chloroform elution gave 0.35 g (7%) of 1,3,3a,4,9β,9aβ-hexahydro-3a-hydroxy-6,7,8-trimethoxy-9α-(3,4-methylenedioxyphenyl)naphtho[2,3-*c*]furan-3,4-dione **9a** as colorless crystals (CH_2Cl_2–hexane), mp 175—176 °C. IR (Nujol) cm^{-1}: 3450, 1775, and 1660. ^1H NMR (C_6D_6–$CDCl_3$) δ: 3.12 [1H, dt, J=8.8 and 2.2 Hz, C(9a)–H], 3.39, 3.41, and 3.69 [9H, s, 3×OMe], 3.56 [1H, t, J=9.03 Hz, lactone C(1)β-H], 4.16 [1H, t, J=9.03 Hz, lactone C(1)α–H], 4.29 [1H, d, J=1.96 Hz, C(9)–H], 4.63 [1H, s, C(3a)–OH], 5.42 [2H, s, OCH_2O], 6.37 [1H, dd, J=8.3 and 1.71 Hz, C(6′)–H], 6.49—6.58 [2H, m, C(2′)–H and C(5′)–H], and 7.20 [1H, s, C(5)–H]. ^{13}C NMR ($CDCl_3$) δ: 38.30 (d), 46.67 (d), 56.19 (q), 60.94 (q), 61.06 (q), 70.16 (t), 76.68 (s), 101.10 (t), 105.97 (d), 2×108.26 (d), 120.94 (d), 126.46 (s), 130.57 (s), 136.44 (s), 146.54 (s), 148.01 (s), 148.01 (s), 151.18 (s), 153.70 (s), 173.14 (s), 190.86 (s). *Aanl.* Calcd for $C_{22}H_{20}O_9$: C, 61.68; H, 4.71; *m/e*, 428.1108. Found: C, 61.88; H, 4.73; *m/e*, 428.1118.

The third elution, with 25% ethyl acetate in chloroform, gave 0.3 g (6.3%) of (±)-isopodophyllotoxone, 1,3,3aβ,4,9β,9aα-hexahydro-6,7-methylenedioxy-9α-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-1,4-dione **6a**, as colorless crystals ($CHCl_3$–ethyl alcohol), mp 223—225 °C.

4-Acetoxy-1,3,9β,9aβ-tetrahydro-6,7,8-trimethoxy-9α-(3,4-methylenedioxyphenyl)naphtho[2,3-*c*]furan-3-one (10)——AcONa (85 mg) was added to a solution of **8a** (1.25 g) in Ac_2O (30 ml), and the mixture was stirred at 80 °C for 8 h. The reaction mixture was poured into ice-water and then extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized from ether to yield 1.3 g (95%) of **10** as colorless crystals, mp 144—146 °C. IR (Nujol) cm^{-1}: 1770, 1710, and 1660. NMR ($CDCl_3$) δ: 2.24 [3H, s, C(4)–OCOMe], 3.51 [3H, s, OMe], 3.80—4.18 [2H, m, C(9a)–H and lactone C(1)β–H], 3.96 [6H, s, 2×OMe], 4.48 [1H, d, J=1.71 Hz, C(9)–H], 4.65 [1H, t, J=6.59 Hz, lactone C(1)α-H], 5.92 [2H, s, OCH_2O], 6.21 [1H, dd, J=1.95 and 8.05 Hz, C(6′)–H], 5.45 [1H, d, J=1.95 Hz, C(2′)–H], 6.62 [1H, d, J=8.05 Hz, C(5′)–H], and 7.53 [1H, s, C(5)–H]. *Anal.* Calcd for $C_{24}H_{22}O_9$: *m/e* 454.1263. Found: 454.1268.

1β,2β,3,4-Tetrahydro-2-hydroxymethyl-6,7,8-trimethoxy-1α-(3,4-methylenedioxyphenyl)-4-oxo-naphthalene (12a)——A solution of **10** (320 mg) in 10% alcoholic KOH (8 ml) was stirred at room temperature for 30 min. The reaction mixture was poured into ice-water, acidified with 10% HCl aq. and then extracted with chloroform. The organic layer was washed with H_2O, dried and concentrated. The residue was subjected to silica gel chromatography. The eluate with 5% ethyl acetate in chloroform, gave 141 mg (52%) of **12a** as an oil. IR (film) cm^{-1}: 3400, 1670, and 1590. ^1H NMR ($CDCl_3$) δ: 1.86 [1H, br s, –OH], 2.21—2.50 [2H, m, C(3)–H and C(2)–H], 2.70 [1H, dd, J=17.8 and 5.86, C(3)–H], 3.55 [2H, d, J=6.83 Hz, $-CH_2OH$], 3.42 [3H, s, C(8)–OMe], 3.83, 3.85 [6H, s, 2×OMe], 4.53 [1H, d, J=1.22 Hz, C(1)–H], 5.84 [2H, s, OCH_2O], 6.38 [1H, dd, J=7.82 and 1.71 Hz, C(6′)–H], 6.51 [1H, d, J=1.71 Hz, C(2′)–H], 6.62 [1H, d, J=7.82 Hz, C(5′)–H], and 7.35 [1H, s, C(5)–H]. *Anal.* Calcd for $C_{21}H_{22}O_7$: *m/e* 386.1365. Found: 386.1350.

2-Acetoxymethyl-1β,2β,3,4-tetrahydro-6,7,8-trimethoxy-1α-(3,4-methylenedioxyphenyl)-4-oxo-naphthalene (12b)——Anhydrous pyridine (0.5 ml) was added at 0 °C to a solution of **12a** (100 mg) in Ac_2O (1.5 ml) and the mixture was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and then extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and 10% aqueous HCl, then dried and concentrated. The residue was subjected to silica gel chromatography. The eluate with 40% hexane in chloroform, gave 99.8 mg (90%) of **12b** as an oil. IR (film) cm^{-1}: 1730, 1680, and 1590. NMR ($CDCl_3$) δ: 2.03 [3H, s, OCOMe], 2.31—2.85 [3H, m, C(2)–H and C(3)–CH_2], 3.50 [3H, s, C(8)–OMe], 3.92, 3.93 [each 3H, s, 2×OMe], 4.08 [2H, d, J=6.84 Hz, $\underline{CH_2}$–OCOMe], 4.49 [1H, br s, C(1)–H], 5.92 [2H, s, OCH_2O], 6.44 [1H, dd, J=7.82 and 1.7 Hz, C(6′)–H], 6.56 [1H, d, J=1.71 Hz, C(2′)H], 6.70 [1H, d, J=7.82 Hz, C(5′)–H], and 7.44 [1H, s, C(5)–H]. *Anal.* Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65; *m/e* 428.1470. Found: C, 64.56; H, 6.02; *m/e*, 428.1485.

3a-Acetoxy-1,3,3a,4,9β,9aβ-hexahydro-6,7,8-trimethoxy-9α-(methylenedioxyphenyl)naphtho[2,3-*c*]furan-3,4-dione (9c)——**9a** (100 mg) was acetylated with Ac_2O and pyridine at room temperature to give 102 mg (93%) of **9c** as colorless crystals, mp 155—157 °C. IR (Nujol) cm^{-1}: 1780, 1730, 1690, and 1595. NMR ($CDCl_3$) δ: 1.92 [3H, s,

OCOMe], 3.58 [3H, s, C(8)–OMe], 3.65—4.05 [2H, m, C(3a)–H and lactone C(1)β–H], 4.47 [1H, d, J=1.71 Hz, C(9)–H], 4.80 [1H, t, J=13.43, lactone C(1)α–H], 5.91 [2H, s, OCH_2O], 6.40 [1H, dd, J=1.45 and 8.05 Hz, C(6′)–H], 6.50 [1H, d, J=1.45 Hz, C(2′)–H], 6.69 [1H, d, J=8.05 Hz, C(5′)–H], and 7.39 [1H, s, C(5)–H]. *Anal.* Calcd for $C_{24}H_{22}O_{10}$: *m/e* 470.1213. Found 470.1218.

Aromatization of 8a to 11——A solution of $CuCl_2 \cdot 2H_2O$ (135 mg) and LiCl (60 mg) in DMF (3 ml) was heated at 80 °C, and then **8a** (103 mg) was added and the whole was heated at 80 °C for 3 h. The reaction mixture was poured into ice-water and extracted with chloroform. The chloroform layer was washed with 10%HCl, sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 61.5 mg (60%) of 1,3-dihydro-4-hydroxy-6,7,8-trimethoxy-9-(3,4-methylenedioxyphenyl)naphtho[2,3-*c*]furan-3-one **11** as colorless crystals ($CHCl_3$–ether), mp 218—220 °C. IR (Nujol) cm^{-1}: 3400, 1720, 1625, and 1605. NMR ($CDCl_3$) δ: 3.36 [3H, s, C(8)–OMe], 3.94, 4.03 [each 3H, s, 2×OMe], 5.08 [2H, d, J=1.46 Hz, lactone C(1)α–H and β–H], 6.02 [2H, s, OCH_2O], 6.65—6.90 [3H, m, C(2′), C(5′), and C(6′)–H], and 7.52 [1H, s, C(5)–H]. *Anal.* Calcd for $C_{22}H_{18}O_8$: C, 64.39; H, 4.42; *m/e* 410.1003. Found: C, 64.10; H, 4.24; *m/e*, 410.1003.

Aromatization of 9a to 11—$SOCl_2$ (0.12 ml) was added at 0 °C to a solution of **9a** (150 mg) in anhydrous pyridine (1 ml), and the mixture was stirred at room temperature for 30 min. The reaction mixture was worked up and the residue was subjected to silica gel chromatography to give 74.7 mg (52%) of **11** from the chloroform eluate.

Hydroxylation of 8a to 9a——A 15% solution of BuLi in hexane (Merck) (0.51 ml, 1.2 mmol) was added to a solution of **8a** (412 mg, 1 mmol) in dry tetrahydrofuran (THF) (5 ml) under N_2 maintained at −78 °C over a period of 20 s followed by stirring for an additional 20 min. A solution of oxodiperoxy-molybdenum(pyridine)hexamethylphosphoramide $[Mo(O_2)_2O]py \cdot HMPT$[8] (868 mg, 2 mmol) in dry THF (10 ml) was then added, and the whole was stirred at room temperature for 18 h under N_2. The reaction mixture was poured into water and the mixture was extracted with methylene chloride. The organic layer was washed with H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 385 mg (90%) of **9a** as colorless crystals (chloroform–ether), mp 175—176 °C.

Oxidation of the Ester 5b——A solution which was prepared by adding MeCN (26.4 ml) to a mixture of CrO_3 (330 mg, 3.3 mmol) and 42% aq. HBF_4 (6.6 ml) was added at room temperature to a stirred solution of the ester **5b** (708 mg, 1.5 mmol) in MeCN (18 ml), and the whole was stirred at room temperature for 30 s. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. Elution with 10% hexane in chloroform gave 73.3 mg (10.05%) of 7-benzyloxy-1,3,3aα,4,9β,9aβ-hexahydro-6,8-dimethoxy-9α-(3,4-methylenedioxyphenyl)naphtho[2,3-*c*]furan-3,4-dione **8b** as a colorless oil. IR (film) cm^{-1}: 1770, 1670, and 1580. NMR ($CDCl_3$) δ: 3.23—3.60 [1H, m C(2)–H], 3.55 [3H, s, C(8)–OMe], 3.91[3H, s, C(6)–OMe], 3.90 [2H, m, C(3)–H and lactone C(1)β–H], 4.45 [1H, br s, C(9)–H], 4.42 [1H, t, J=8.3 Hz, lactone C(1)α–H], 5.14 [2H, s, OCH_2Ph], 5.91 [2H, s, OCH_2O], 6.38 [1H, dd, J=7.81 and 1.71 Hz, C(6′)–H], 6.48 [1H, d, J=1.71 Hz, C(2′)–H], 6.68 [1H, d, J=7.81 Hz, C(5′)–H], 7.25—7.38 [5H, m, aromatic H], and 7.42 [1H, s, C(5)–H]. *Anal.* Calcd for $C_{28}H_{24}O_8$: *m/e* 488.1470. Found: 488.1452.

The subsequent chloroform eluate gave 36.6 mg (5.02%) of 9α-(4-benzyloxy-3,5-dimethoxyphenyl)-1,3,3aα,9β,9α-hexahydro-6,7-methylenedioxynaphtho[2,3-*c*]furan-1,4-dione **7b** as colorless crystals, mp 175—177 °C (chloroform–ether). IR (Nujol) cm^{-1}: 1770, 1660, and 1590. NMR ($CDCl_3$) δ: 3.30 [1H, d, J=3.41 Hz, C(9a)–H], 3.28—3.32 [1H, m, C(3a)–H], 3.73 [6H, s, 2×OMe], 4.27—4.43 [1H, m, lactone C(3)β–H], 4.70 [1H, d, J=2.44 Hz, C(9a)–H], 4.76 [1H, d, J=9.28 Hz, lactone C(3)α–H], 4.95 [2H, s, OCH_2Ph], 6.04 [2H, s, OCH_2O], 6.23 [2H, s, C(2′)–H and C(6′)–H], 6.69 [1H, s, C(8)–H], 7.27—7.49 [5H, m, aromatic H], and 7.52 [1H, s, C(5)–H]. *Anal.* Calcd for $C_{28}H_{24}O_8$: *m/e* 488.1470. Found: 488.1485.

Further chloroform elution gave 41.4 mg (5.5%) of 7-benzyloxy-1,3,3a,4,9β,9aβ-hexahydro-3a-hydroxy-6,8-dimethoxy-9α-(3,4-methylenedioxyphenyl)naphtho[2,3-*c*]furan-3,4-dione **9b** as a colorless oil. IR (film) cm^{-1}: 1780, 1670, and 1585. NMR ($CDCl_3$) δ: 3.37 [1H, dt, J=9.03 and 2.2 Hz, C(9a)–H], 3.86 [1H, t, J=9.03 Hz, lactone C(1)β–H], 3.59 [3H, s, C(8)–OMe], 3.90 [3H, s, C(6)–OMe], 4.47 [1H, d, J=2.2 Hz, C(9)–H], 4.73 [1H, t, J=9.03 Hz, lactone C(1)α–H], 5.14 [2H, s, OCH_2Ph], 5.89 [2H, dd, J=8.06 and 1.71 Hz, C(6′)–H], 6.51 [1H, d, J=1.71 Hz, C(2′)–H], 6.60 [1H, d, J=8.06 Hz, C(5′)–H], and 7.30—7.45 [6H, m, C(5)–H and aromatic H]. *Anal.* Calcd for $C_{28}H_{24}O_9$: *m/e* 504.1422. Found: 504.1442.

The fourth elution, with 25% ethyl acetate in chloroform, gave 27 mg (3.7%) of 9α-(4-benzyloxy-3,5-dimethoxyphenyl)-1,3,3aβ,4,9β,9aα-hexahydro-6,7-methylenedioxynaphtho[2,3-*c*]furan-1,4-dione **6b** as colorless crystals (chloroform–ether), mp 215—217 °C. IR (Nujol) cm^{-1}: 1780, 1690, and 1590. NMR ($CDCl_3$) δ: 3.04 [1H, dd, J=15.7 and 10.98 Hz, C(9a)–H], 3.25—3.58 [1H, m, C(3a)–H], 3.77 [6H, s, 2×OMe], 4.21 [1H, d, J=10.99 Hz, C(9)–H], 4.42 [1H, t, J=9.52 Hz, lactone C(3)α–H], 4.64 [1H, dd, J=9.52 and 9.03 Hz, lactone C(3)β–H], 5.02 [2H, s, OCH_2Ph], 6.02 [2H, s, OCH_2O], 6.37 [3H, s, C(8), C(2′), and C(6′)–H], 7.30—7.43 [5H, m, aromatic H], and 7.45 [1H, s, C(5)–H]. *Anal.* Calcd for $C_{28}H_{24}O_8$: C, 68.84; H, 4.95; *m/e* 488.1470. Found: C, 69.09; H, 4.91; *m/e*, 488.1480.

Reaction of 6b with CF_3CO_2H——CF_3CO_2H (2 ml) was added at 0 °C to **6b** (60 mg), and the solution was allowed to stand at room temperature for 24 h. The reaction mixture was then poured into ice-water and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, dried and concentrated. The residue was

subjected to silica gel chromatography. Elution with 5% ethyl acetate in chloroform gave 15.2 mg (31%) of (±)-4′-demethyl-picropodophyllone, 1,3,3aα,4,9β,9aα-hexahydro-9α-(4-hydroxy-3,5-dimethoxyphenyl)-6,7-methylenedioxynaphtho[2,3-*c*]furan-1,4-dione **7c**, as colorless crystals (chloroform), mp 228—230 °C. IR (Nujol) cm^{-1}: 3450, 1770, 1665, and 1610. NMR ($CDCl_3$) δ: 3.29 [1H, d, J=3.42 Hz, C(9a)–H], 3.27—3.30 [1H, m, C(3a)–H], 3.78 [6H, s, 2×OMe], 4.27—4.40 [1H, m, lactone C(3)β–H], 4.42 [1H, br s, –OH], 4.70 [1H, d, J=2.93 Hz, C(9)–H], 4.76 [1H, d, J=9.03 Hz, lactone C(3)α–H], 6.04 [2H, s, OCH_2O], 6.24 [2H, s, C(2′) and C(6′)–H], 6.68 [1H, s, C(8)–H], and 7.50 [1H, s, C(5)–H]. *Anal.* Calcd for $C_{21}H_{18}O_8$: *m/e* 398.1001. Found: 398.1001.

Subsequent elution with 25% ethyl acetate in chloroform, gave 17.1 mg (35%) of (±)-4′-demethyl-isopodophyllotoxone, 1,3,3aβ,4,9,9aα-hexahydro-9α-(4-hydroxy-3,5-dimethoxyphenyl)-6,7-methylenedioxynaphtho[2,3-*c*]furan-1,4-dione **6c** as colorless crystals (chloroform), mp 220—222 °C. IR (Nujol) cm^{-1}: 1780, 1680, and 1610. NMR ($CDCl_3$) δ: 3.03 [1H, dd, J=15.8 and 11.23 Hz, C(9a)–H], 3.2—3.61 [1H, m, C(3a)–H], 3.85 [6H, s, 2×OMe], 4.20 [1H, d, J=11.23 Hz, C(1)–H], 4.42 [1H, t, J=9.28 Hz, lactone C(3)α–H], 4.57 [1H, s, –OH], 4.63 [1H, dd, J=9.28 and 9.03 Hz, lactone C(3)β–H], 6.02 [2H, s, OCH_2O], 6.40 [2H, s, C(2′) and C(6′)–H], 7.25 [1H, s, C(8)–H], and 7.45 [1H, s, C(5)–H]. *Anal.* Calcd for $C_{21}H_{18}O_8$: *m/e* 398.1002. Found: 398.1004.

Isomerization of (±)-Isopodophyllotoxone (6a) to (±)-Picropodophylone (7a)——CF_3CO_2H (2 ml) was added at 0 °C to **6a** 60 mg, and the mixture was allowed to stand at room temperature for 48 h. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized twice from benzene to yield 48 mg (80%) of (±)-picropodophyllone, 1,3,3aα,4,9β,9aα-hexahydro-9α-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxynaphtho[2,3-*c*]-furan-1,4-dione **7a** as colorless crystals, mp 200—201 °C.

References and Notes

1) C. B. S. Rao (ed.), "Chemistry of Lignans," Andhra University Press, 1978.
2) I. Jardine, *Med. Chem.*, **16**, 319 (1980).
3) R. S. Ward, *Chem. Soc. Rev.*, **11**, 75 (1982).
4) E. Block and R. Stevenson, *Chem. Ind.* (London), **1970**, 894; *J. Org. Chem.*, **36**, 3453 (1971); F. Kohen, I. Maclean, and R. Stevenson, *J. Chem. Soc.*, (*C*), **1966**, 1775.
5) T. Takeya, H. Matsumoto, E. Kotani, and S. Tobinaga, *Chem. Pharm. Bull.*, **31**, 4364 (1983).
6) W. S. Murphy and S. Wattanasin, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 271.
7) E. M. Kosowere and W. J. Cole, G. -S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963).
8) H. Mimoun, I. Seree de Roch, L. Sajus, *Bull. Soc. Chim. Fr.*, **1969**, 1481.
9) D. C. Ayres and J. A. Harris, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 1343.