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Synthetic Studies on Lignans and Related Compounds. I. Synthesis of 1-Hydroxy-3-hydroxymethyl-4-(3,4-dimethoxyphenyl)-6,7-methylenedioxy-2-naphthoic Acid γ-Lactone

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Synthesis of 1-hydroxy-3-hydroxymethyl-4-(3,4-dimethoxyphenyl)-6,7-methylenedioxy-2-naphthoic acid γ-lactone (I), the structure assigned to diphyllin by T. Murakami in 1961, was carried out by starting from 3,4-dimethoxy-3′,4′-methylenedioxybenzophenone (III) as shown in Chart 1. Cyclization of benzhydrylsuccinic acid (V) derived from III occurred selectively on the benzene ring bearing no bromo group as expected. Non-identity of I with diphyllin was confirmed by comparison of melting points, infrared spectra, thin-layer chromatograms and ferric chloride tests.

In 1961, Murakami and Matsushima[2] isolated diphyllin, a phenolic lignan lactone, from *Diphylleia grayi* and assigned its structure as 1-hydroxy-3-hydroxymethyl-4-(3,4-dimethoxyphenyl)-6,7-methylenedioxy-2-naphthoic acid γ-lactone (I) from spectral studies. Recently, Munakata, *et al.*[3] have found that their justicidin A, a fish poison isolated from *Justicia Hayatai* var. *decumbens*, is identical with the methyl ether (II) of diphyllin. The authors have now synthesized compound I and have found that it is not identical with diphyllin.

A sodium borohydride reduction of 3-bromo-4,5-dimethoxy-3′,4′-methylenedioxybenzophenone (III), prepared, in 54% yield, by the Friedel–Crafts condensation of 5-bromoveratroyl chloride[4] with methylenedioxybenzene,[5] gave a benzhydrol (IV), which was brominated with phosphorous tribromide, subsequently condensed with diethyl sodioacetosuccinate and then hydrolyzed with aqueous caustic soda to give, in 34% yield, a mixture of diastereoisomeric benzhydrylsuccinic acid (V) (characterised as dimethyl ester (VI)). The Stobbe condensation of III with diethyl succinate and subsequent alkaline hydrolysis gave a mixture of isomeric itaconic acid derivative (VII: R=H) (characterized as dimethyl ester (VII: R=CH_3)) in 70% yield. However, catalytic reduction of VII to V was unsuccessful, and sodium amalgam reduction resulted in simultaneous hydrogenolysis of the bromo group, yielding 3′,4′-dimethoxy-3,4-methylenedioxybenzhydrylsuccinic acid (VIII) (characterized as dimethyl ester) as a sole product. The anhydride of V was cyclized with stannic chloride in nitrobenzene to *cis*- and *trans*-tetralonecarboxylic acid (IX) (characterized as methyl esters (Xa, mp 191—193°, 1% yield; Xb, mp 162—163°, 15% yield)). The position of ring closure is evident from absence of *ortho* coupling in aromatic protons of the nuclear magnetic resonance (NMR) spectra as shown in Table I, and the *trans* configuration of Xb is assigned from its larger coupling constant between C_1- and C_2-protons ($J_{1,2}$=6.5 cps) and its higher field chemical shift (5.47τ, *quasi* axial) than those ($J_{1,2}$=4.5 cps; τC_1-H 5.37, *quasi* equatorial) in the *cis* isomer (Xa).[6]

1) Location: *6-5 Toneyama, Toyonaka, Osaka.*
2) T. Murakami and A. Matsushima, *Yakugaku Zasshi*, **81**, 1596 (1961).
3) K. Munakata, S. Marumo, K. Ohta, and Y.-L. Chen, *Tetrahedron Letters*, **1965**, 4167.
4) Prepared from 5-bromoveratric acid (L.C. Laiford and R.P. Perry, *J. Org. Chem.*, **7**, 354 (1942)) by chlorination with thionyl chloride.
5) F. Dallacker and R. Binsack, *Monatsh.*, **92**, 492 (1961).
6) For determination of configuration and conformation of substituents on C_3 and C_4 in tetralone ring system, see the previous paper: Z. Horii, T. Momose, and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **13**, 651 (1965).

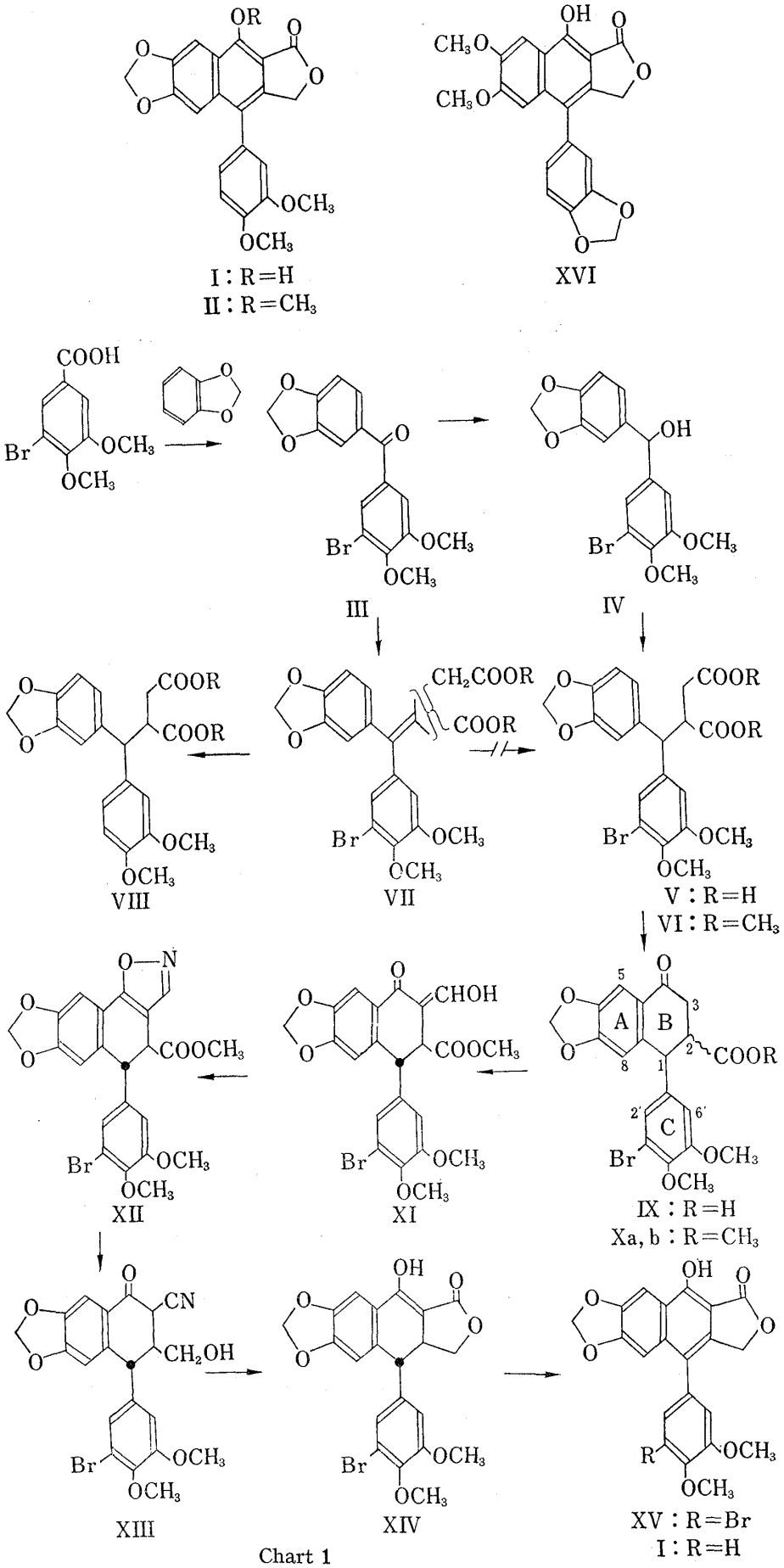


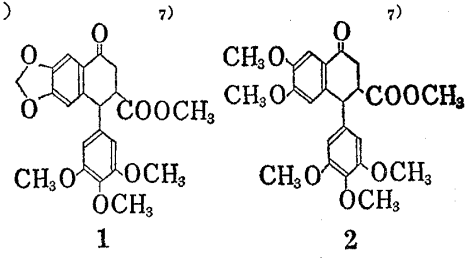
Chart 1

Table I. Benzylic and Aromatic Protons of Isomeric Tetralones ($CDCl_3$) (τ)

Compound	C_1–H	C_5–H	C_8–H	$C_{2'}$–H	$C_{6'}$–H
Xa	5.37 d. J=4.5 cps	2.47 s.	3.43 s.	3.31 d. J=2.5 cps	3.54 d. J=2.5 cps
Xb	5.47 d. J=6.5 cps	2.47 s.	3.58 s.	3.14 d. J=2.5 cps	3.39 d. J=2.5 cps
1[a] *cis*	5.31 d. J=4.5 cps	2.45 s.	3.37 s.	3.81 s. (2H)	
trans	5.46 d. J=6.5 cps	2.47 s.	3.53 s.	3.65 s. (2H)	
2[a] *cis*	5.28 d. J=4.5 cps	2.38 s.	3.37 s.	3.80 s. (2H)	
trans	5.38 d. J=6.5 cps	2.39 s.	3.50 s.	3.66 s. (2H)	

s.: singlet; d.: doublet

a) 7)



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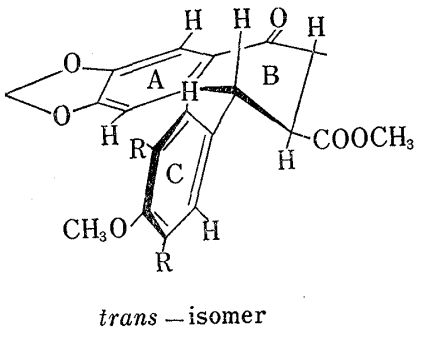
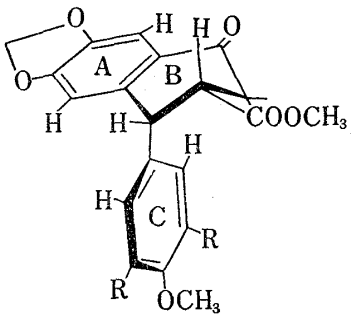


trans—isomer



cis—isomer

Fig. 1. Conformation of Tetralones

Favorable conformation of both tetralones (Xa, Xb) and analogous tetralones found in the literature[7] is shown in Fig. 1. The high field shifts of $C_{2'}$- and $C_{6'}$-H in the *cis* isomer can be attributed to the anisotropic shielding effect of ring A, and of C_8–H in the *trans* isomer to that of ring C.

The *trans* ester (Xb) was condensed with methyl formate to give, in 90% yield, the hydroxymethylene derivative (XI), which gave an isoxazole (XII) in 85% yield on treatment with hydroxylamine hydrochloride in boiling acetic acid. A lithium aluminum hydride reduction of XII at −60° and subsequent treatment with sodium ethoxide afforded, in 41% yield, an α-cyanotetralone (XIII), ν_{max} (KBr) 3401 (OH), 2232 (C≡N), 1672 (C=O) cm^{-1}, which showed a negative ferric chloride test and was recovered unchanged on bromination owing probably to *quasi axial* conformation (*cis*$_{2,3}$-configuration) of the cyano group.

7) E. Schreier, *Helv. Chim. Acta*, **46**, 75 (1963).

On treatment with hydrogen chloride in absolute ethanol, XIII gave, in 61% yield, a γ-lactone (XIV), ν_{max} (KBr) 3367 (OH), 1776 (C=O), 1661 (C=O) cm^{-1}, which showed a green coloration on ferric chloride test and was considered to have an enolized structure. Dehydrogenation of XIV with selenium dioxide in boiling acetic acid gave, in 67% yield, a naphthol (XV), ν_{max} (KBr) 3344 (OH), 1727 (C=O) cm^{-1}, which was hydrogenated over Raney nickel in dimethylformamide in the presence of potassium hydroxide to give the debromonaphthol (I), mp 272—275°, ν_{max} (KBr) 3368 (OH), 1724 (C=O), a positive $FeCl_3$ test (green in EtOH), in quantitative yield. The melting point, thin-layer chromatogram and infrared (IR) spectrum of I are quite different from those of diphyllin (reported:[2] mp 291°, ν_{max} (Nujol) 3220, 1709 cm^{-1}, a negative $FeCl_3$ test), suggesting that the structure (I) assigned to diphyllin should be reinvestigated.

After completion of this work, Govindachari, *et al.*[8] reported an isolation of diphyllin from *Cleistanthus collinus* (Roxb.) Benth. & Hook. f. and proposed a revised structure (XVI) based on the fact that controlled oxidation of diphyllin gave 6-(3,4-methylenedioxybenzoyl) veratric acid. Non-identity of our synthetic I with natural diphyllin would provide an additional support to the revision. Synthesis of XVI and its comparison with natural diphyllin will be reported in another paper.

Experimental[9]

3-Bromo-4,5-dimethoxy-3′,4′-methylenedioxybenzophenone (III)——A mixture of 5-bromoveratric acid (150 g) and $SOCl_2$ (126 ml) was refluxed for 2 hr and $SOCl_2$ was removed under reduced pressure to give the acid chloride as a solid. To a cooled and stirred solution of the chloride in dry $CHCl_2CHCl_2$ (200 ml) was added $SnCl_4$ (148.2 g) over 20 min, and to this was added a solution of methylenedi oxybenzene(75.6 g) in dry $CHCl_2CHCl_2$ (300 ml) over 30 min. The mixture was stirred at room temperature for 6 hr, poured onto cracked ice, made strongly alkaline with 20% NaOH and subjected to steam distillation. The remaining brown solid was collected, washed with H_2O, 10% HCl and H_2O, dried in an open air and dissolved in benzene (600 ml). The benzene solution was filtered and evaporated to give 140 g of a crystalline solid. Three recrystallizations from EtOH gave 111 g (54%) of III as colorless needles, mp 115—116°, which was converted into crystals of a quite different IR spectrum on crystallization from acetone and regenerated on EtOH recrystallization. *Anal.* Calcd. for $C_{16}H_{13}O_5Br$: C, 52.62; H, 3.59. Found: C, 52.34; H, 3.68. IR ν_{max}^{KBr} cm^{-1}: 1647 (C=O).

3-Bromo-4,5-dimethoxy-3′,4′-methylenedioxybenzhydrol (IV)——To an ice cooled solution of $NaBH_4$ (7.3 g) in MeOH (350 ml) was added a solution of III (93 g) in tetrahydrofuran (200 ml), and the mixture was stirred at room temperature for 3 hr, poured into satd. NaCl (1 liter) after removal of 300 ml of the solvent under reduced pressure, and extracted with ether (200 ml × 4). The extract was washed with satd. NaCl, dried over anhyd. Na_2SO_4 and evaporated to give 98 g of a viscous oil, which crystallized on trituration with ether to give 98 g (96%) of IV as colorless crystals, mp 90—92°. Recrystallization from benzene–cyclohexane gave an analytical sample, mp 92—93°. *Anal.* Calcd. for $C_{16}H_{15}O_5Br$: C, 52.33; H, 4.12. Found: C, 52.86; H, 4.17. IR ν_{max}^{KBr} cm^{-1}: 3401 (OH).

3-Bromo-4,5-dimethoxy-3′,4′-methylenedioxybenzhydrylsuccinic Acid (V)——To an ice cooled and stirred solution of PBr_3 (30 g) in dry CCl_4 (60 ml) was added a solution of IV (30 g) in dry CCl_4 (250 ml) over 4 hr, and the mixture was allowed to stand overnight and poured into ice water (1 liter). The CCl_4 layer was separated, washed with 10% AcONa and H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 35 g of a viscous oil.

To a suspension of NaH (58% in oil, 4.55 g) in dry toluene (100 ml) was added diethyl acetosuccinate (21.1 g), and the suspension was stirred at room temperature for 40 min. To this was added a solution of the bromide prepared above in dry toluene (90 ml), and the mixture was stirred at 120—130° (bath temp.) for 14 hr and poured into conc. HCl–ice. The organic layer was separated, washed with satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 27.5 g of a dark red paste, which was refluxed with 20% KOH (60 ml) for 5 hr. The hydrolysate was shaken with ether (20 ml × 2), acidified with conc. HCl and extracted with AcOEt. The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 16 g (42%) of V as a glass. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O).

8) T.R. Govindachari, S.S. Sathe, N. Viswanathan, B.R. Pai, and M. Srinivasan, *Tetrahedron Letters*, **1967**, 3517.

9) All melting points and boiling points are uncorrected. NMR spectra were taken on Hitachi H-6013 spectrometer with Me_4Si as the internal standard.

Treatment of the glass with CH_2N_2 in ether gave dimethyl ester (VI) as a colorless oil, bp 240—245° (0.005 mmHg). *Anal.* Calcd. for $C_{22}H_{23}O_8Br$; C, 53.34; H, 4.68. Found: C, 54.05; H, 4.64. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1729 (C=O).

Stobbe Condensation of III (Dimethyl 3-Bromo-4,5-dimethoxy-3′,4′-methylenedioxybenzhydrylidenesuccinate (VII))——To an ice cooled and stirred solution of III (23 g) in diethyl succinate (64.5 g) was added NaH (58% in oil, 8 g) portion-wise, and to this suspension was added anhyd. EtOH (1 ml) dropwise over 30 min. The mixture became viscous under evolution of heat. Dry benzene (60 ml) was added to the mixture, followed by 6 hr's stirring. A mixture of AcOH (16 ml) and AcOEt (160 ml) was added to the mixture, and the mixture was poured into 5% HCl (300 ml). The aqueous layer was sparated and extracted with AcOEt (50 ml×2). The combined organic layer was shaken with satd. $NaHCO_3$ until no more acidic component was extracted. The $NaHCO_3$ extract was shaken with ether (50 ml×2), acidified with conc·HCl and extracted with AcOEt (100 ml×3). The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was hydrolysed with 10% KOH to give 20.5 g (70%) of the itaconic acid (VII) as a glassy solid. IR ν_{max}^{Nujol} cm^{-1}: 1700, 1670 (C=O).

Treatment of VII with CH_2N_2 gave dimethyl ester as a colorless glass, bp 260° (0.15 mmHg). *Anal.* Calcd. for $C_{22}H_{21}O_8Br$: C, 53.56; H, 4.29. Found: C, 53.95; H, 4.39. IR $\nu_{max}^{ccl_4}$ cm^{-1}: 1739, 1709 (C=O).

Sodium Amalgam Reduction of VII (Dimethyl 3,4-Dimethoxy-3′,4′-methylenedioxybenzhydrylsuccinate (VIII))——To a stirred solution of VII (2 g) in satd. $NaHCO_3$ (100 ml) was added 4% Na–Hg (20 g) over 1 hr, and the mixture was stirred for an addtional 1.5 hr, during which time CO_2 was led into the mixture. After removal of Hg by decantation, the aqueous layer was acidified with conc. HCl and extracted with ether (20 ml×3). The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 1.8 g of a glass, which showed a negative Beilstein test and was esterified with CH_2N_2 in ether to give 1.8 g of VIII as a colorless viscous oil, bp 215—220° (0.005 mmHg). *Anal.* Calcd. for $C_{22}H_{24}O_8$: C, 63.77; H, 5.84. Found: C, 63.45; H, 5.81. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (C=O).

Methyl *cis*- and *trans*-1-(3-Bromo-4,5-dimethoxyphenyl)-6,7-methylenedioxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (Xa and Xb)——A solution of V (16 g) in AcCl (35 ml) was refluxed for 2 hr. After removal of AcCl, the residue was dissolved in benzene (200 ml), and the solution was washed with satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 13.2 g (86.5%) of the anhydride as a pale yellow glass. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1860, 1785 (C=O).

To an ice cooled and stirred solution of $SnCl_4$ (15 g) in dry nitrobenzene (70 ml) was added a solution of the anhydride (10 g) in dry nitrobenzene (100 ml) over 20 min and the mixture was stirred for 6 hr at room temperature and poured into 5N HCl (100 ml). The nitrobenzene layer was shaken with 5 N HCl (100 ml×3) and extracted with satd. $NaHCO_3$ (100 ml×5). The alkaline layer was shaken with ether (50 ml×2), acidified with conc. HCl and extracted with AcOEt (50 ml×3). The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 5 g of the acid, which was esterified with CH_2N_2 in ether to 4.7 g of a glass. Column chromatography on alumina in benzene gave recovered VI as the first fraction, 1.55 g (15%) of Xb, colorless needles, mp 162—163°, as the second and 0.1 g (1%) of Xa, colorless needles, mp 191—192°, as the third after recrystallization from MeOH. *Anal.* Calcd. for $C_{21}H_{19}O_7Br$: C, 54.44; H, 4.13. Found: for Xa: C, 54.72; H, 4.07; for Xb: C, 54.73; H, 4.12. IR ν_{max}^{KBr} cm^{-1}: 1733, 1658 (C=O) for Xa; 1724, 1669 (C=O) for Xb. NMR ($CDCl_3$) τ: 6.33 (3H, singlet), 6.28 (3H, singlet), 6.20 (3H, singlet), 5.37 (1H, doublet, J=4.5 cps, C_1–H), 3.98 (2H, singlet, $-OCH_2O-$) for Xa; τ: 6.39 (3H, singlet), 6.19 (3H, singlet), 6.16 (3H, singlet), 5.47 (1H, doublet, J=6.5 cps, C_1–H), 3.97 (2H, singlet, $-OCH_2O-$) for Xb.

Methyl *trans*-1-(3-Bromo-4,5-dimethoxyphenyl)-3-hydroxymethylene-6,7-methylenedioxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (XI)——To a suspension of NaH (58% in oil, 1.65 g) in dry benzene (60 ml) was added anhyd. MeOH (0.82 g),and the suspension was stirred at room temperature for 3 hr under N_2. To this was added methyl formate (4.96 g) and subsequently a solution of Xb (3.83 g) in dry benzene (40 ml) over 1 hr, and the mixture was stirred at room temperature for 6 hr under N_2 and allowed to stand overnight. The mixture was poured into ice water (100 ml) and shaken thoroughly. The benzene layer was shaken with 1% NaOH (50 ml×2), and the combined alkaline layer was shaken with ether (30 ml×2) and poured into 1% H_2SO_4 (250 ml). The deposited pink solid was collected, washed with H_2O and dried to give 3.66 g (90%) of XI. Recrystallization from cyclohexane gave an analytical sample as an amorphous solid, mp 157—160°. *Anal.* Calcd. for $C_{22}H_{19}O_8Br$: C, 53.78; H, 3.90. Found: C, 53.99; H, 3.89. IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O), 1626, 1608.

***trans*-3,4-Dihydro-3-methoxycarbonyl-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-methylenedioxynaphth[2,1-*d*]isoxazole (XII)**——A mixture of XI (4.14 g), $H_2NOH·HCl$ (1.76 g) and AcOH (30 ml) was refluxed for 30 min and poured into ice water (60 ml). The deposited pink solid was collected, washed with H_2O and dried to give 3.5 g (85%) of XII. Recrystallization from MeOH–benzene gave an analytical sample as an amorphous powder, mp 183—186°. *Anal.* Calcd. for $C_{22}H_{18}O_7NBr$: C, 54.11; H, 3.72; N, 2.87. Found: C, 53.72; H, 3.71; N, 2.81. IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O), 1633 (C=N).

***trans*-3,4,2-Cyano-3-hydroxymethyl-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydro-1(2*H*)-naphthalenone (XIII)**——A suspension of $LiAlH_4$ (4 g) in dry ether (150 ml) was cooled to −60°, and to this was added a solution of XII (3.5 g) in dry tetrahydrofuran (70 ml) over 1.5 hr. The mixture was stirred at −60° for 4.5 hr, and to this was added AcOEt (30 ml) and subsequently dil. HCl (100 ml).

The organic layer was separated, and the aqueous layer was extracted with AcOEt (20 ml × 2). The combined organic layer was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 3.7 g of an oily material, which could not be purified even by column chromatography on silica gel in $CHCl_3$. The reduction product was dissolved in anhyd. EtOH (30 ml), and the solution was mixed with a solution of Na (1 g) in anhyd. EtOH (30 ml) and stirred at room temperature for 2 hr. The mixture was diluted with ether (150 ml) and shaken with H_2O (200 ml) and subsequently with 5% KOH (50 ml × 3). The aqueous layer and alkaline layer were combined, shaken with ether (50 ml), acidified with dil. HCl and extracted with AcOEt (50 ml × 3). The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 2.33 g of a glass, which was triturated with $CHCl_3$ (10 ml) to afford 1.52 g (41%) of XIII. Recrystallization from benzene gave an analytical sample as colorless needles, mp 205—208°. *Anal.* Calcd. for $C_{21}H_{18}O_6NBr$: C, 54.80; H, 3.94; N, 3.04. Found: C, 54.82; H, 3.80; N, 2.97. IR ν_{max}^{KBr} cm^{-1}: 3401 (OH), 2232 (CN), 1672 (C=O).

***trans*-3-Hydroxymethyl-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-methylenedioxy-1-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid γ-Lactone (XIV)**——An ice cooled solution of XIII (600 mg) in anhyd. EtOH (40 ml) was saturated with dry HCl, allowed to stand overnight at room temperature, poured into satd. NaCl (150 ml) and extracted with AcOEt (30 ml × 3). The extract was washed with satd. $NaHCO_3$ and H_2O, dried over anhyd. $MgSO_4$ and evaporated to give 600 mg of an oily material, which was purified by column chromatography on silica gel in $CHCl_3$ to give 390 mg (64%) of XIV as colorless micro needles, mp 199—201° (EtOH). *Anal.* Calcd. for $C_{21}H_{17}O_7Br$: C, 54.68; H, 3.71. Found: C, 54.52; H, 3.62. IR ν_{max}^{KBr} cm^{-1}: 3367 (OH), 1776 (C=O), 1661 (C=O); $\nu_{max}^{CHCl_3}$ cm^{-1}: 1782, 1709, 1668 (C=O).

1-Hydroxy-3-hydroxymethyl-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-methylenedioxy-2-naphthoic Acid γ-Lactone (XV)——A mixture of XIV (130 mg), SeO_2 (40 mg) and AcOH[10] (8 ml) was refluxed for 2 hr, allowed to stand overnight at room temperature, poured into H_2O (50 ml) and extracted with AcOEt (10 ml × 3). The extract was washed with satd. $NaHCO_3$ and H_2O, dried over anhyd. $MgSO_4$ and evaporated. The residual oily material was purified by column chromatography on silica gel in $CHCl_3$ to give 87 mg (67%) of XV as colorless crystals, mp 165—168° (benzene–hexane). *Anal.* Calcd. for $C_{21}H_{15}O_7Br$: C, 54.92; H, 3.29. Found: C, 54.97; H, 3.05. IR ν_{max}^{KBr} cm^{-1}: 3344 (OH), 1727 (C=O).

1-Hydroxy-3-hydroxymethyl-4-(3,4-dimethoxyphenyl)-6,7-methylenedioxy-2-naphthoic Acid γ-Lactone (I) A suspension consisting of Raney nickel (1 g), KOH (80 mg) and MeOH (5 ml) was shaken in an atmosphere of H_2, and to this was added a solution of XV (63 mg) in dimethylformamide (20 ml). The suspension was shaken in H_2 until no more H_2 was consumed, and then filtered. The filtrate was evaporated, and the residual solid was washed with 10% HCl and H_2O, dried and recrystallized from AcOH to give 50 mg (96%) of I as colorless micro needles, mp 272—275°. *Anal.* Calcd. for $C_{21}H_{16}O_7$: C, 66.31; H, 4.24. Found: C, 65.95; H, 4.05. IR ν_{max}^{KBr} cm^{-1}: 3333 (OH), 1724 (C=O).

The IR spectrum of I was not identical with that of diphyllin kindly provided by Professor T. Murakami.

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10) Distilled over SeO_2.