Synthesis of Aryltetralin and Dibenzylbutyrolactone Lignans: (±)-Lintetralin, (±)-Phyltetralin, and (±)-Kusunokinin

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Application of a general synthetic pathway for aryltetralin and dibenzylbutyrolactone lignans, starting from the lithium enolate of 3-(3,4-dimethoxybenzyl)butyrolactone (1) led to syntheses of (±)-lintetralin (4), (±)-phyltetralin (5), (±)-isogalcatin (12), and (±)-kusunokinin (13).

RECENT developments of convenient procedures for the preparation of β-benzyl-γ-butyrolactones,[1-5] coupled with improved techniques both for their α-alkylation [6-10] and α-hydroxyalkylation,[11] have led to versatile synthesis routes to lignans. The ready availability of the β-veratrylbutyrolactone (1) provided a suitable starting material for the preparation of a variety of lignans required here for pharmacological and insecticidal evaluation. The synthesis of some representative examples of the aryltetralin and dibenzylbutyrolactone classes are here reported.

The 3,4-dimethoxybenzylbutyrolactone (1) was prepared by a procedure recently communicated (without experimental detail) for the piperonyl analogue.[5] Thus, veratraldehyde was subjected to a Stobbe condensation with dimethyl succinate in methanol containing sodium methoxide to give 3-methoxycarbonyl-4-(3,4-dimethoxyphenyl)but-3-enoic acid (2), which underwent catalytic hydrogenation at atmospheric pressure to produce the corresponding butanoic acid (3). Reduction of the potassium salt of (3) with calcium borohydride [12] gave in 90% yield the required β-veratrylbutyrolactone (1).

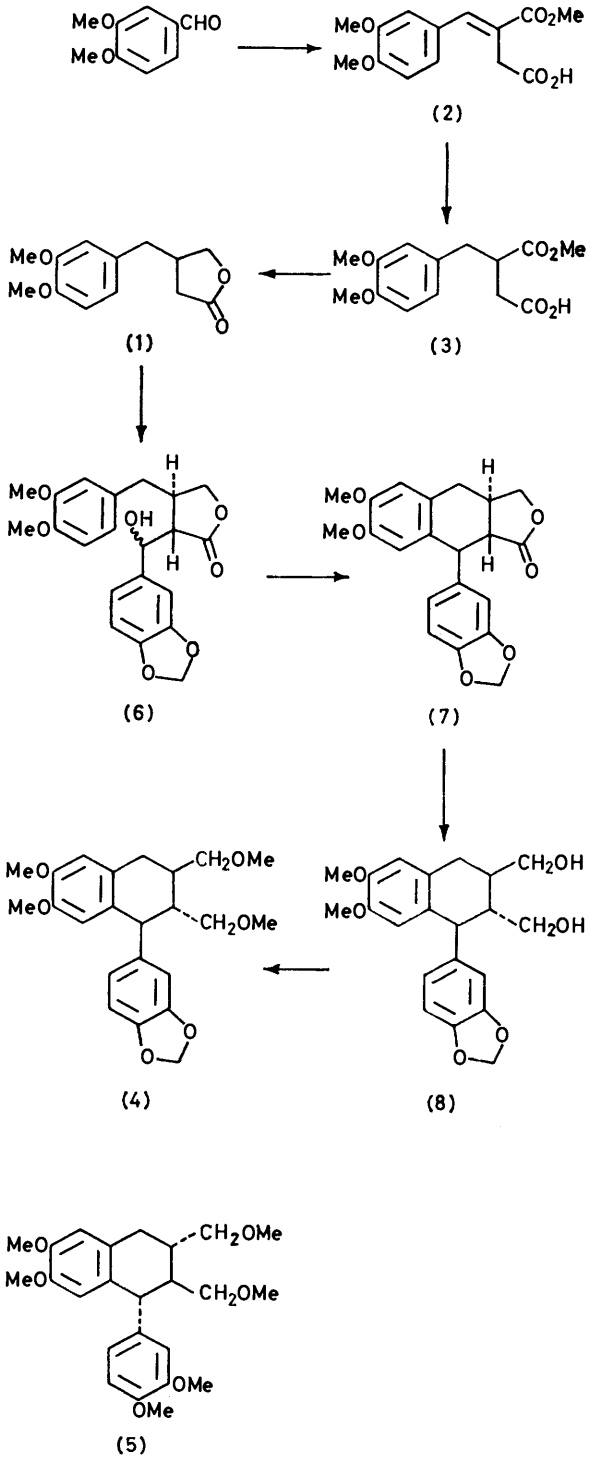
We were first concerned with the synthesis of (±)-lintetralin (4) and (±)-phyltetralin (5). From the leaves of *Phyllanthus niruri* Linn. (Euphorbiaceae), extractives reportedly used in the treatment of jaundice, asthma, and bronchial infections have yielded six lignan products,[13-16] four of which (hypophyllanthin,[13,14] nirtetralin,[15] phyltetralin,[15] and lintetralin [16]) were established as members of the aryltetralin class. Considerable confusion regarding the structures of these products has existed,[17-19] attributable to uncertainty both in the locations of the aryl-ring ether functions and relative configurations of the chiral centres. The conversion described here of (1) into *r*-1-(3,4-methylenedioxyphenyl)-*t*-2,*c*-3-bismethoxymethyl-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (4), *i.e.* the racemic form of the structure which has been tentatively assigned to lintetralin,[16] and spectroscopic comparison with the natural product confirms the proposed formula.

The lithium enolate of (1), prepared by treatment with lithium di-isopropylamide in tetrahydrofuran, reacted with piperonal to give in excellent yield a mixture of the epimeric alcohols (6A and B) in the approximate ratio 1 : 1 (^{1}H n.m.r.), and from which the *erythro* form (6A) could be readily separated by direct crystallization. Pertinent ^{1}H n.m.r. reference data for analogous natural and synthetic products (podorhizol and epipodorhizol) are available for comparison.[3,20] Treatment of the epimer mixture (6) with trifluoroacetic acid at room temperature resulted in smooth cyclization to the aryltetralin lactone (7). Since the isolated yield of this product surpassed 90%, each epimer must dehydrate stereospecifically with reference to formation of the tetralin C-1 chiral site. The assigned *trans*-configurations at C-1, -2, and -3 were consistent with the ^{1}H n.m.r. spectrum, and were confirmed (see later) by conversion of (7) into isogalcatin (12) of established structure. Reduction of the lactone (7) with lithium aluminium hydride gave the diol (8) which on methylation with methyl iodide in dimethyl sulphoxide yielded the corresponding dimethyl ether derivative (4) identified by spectral comparison (^{1}H n.m.r., i.r., and mass) with natural (+)-lintetralin.[16]

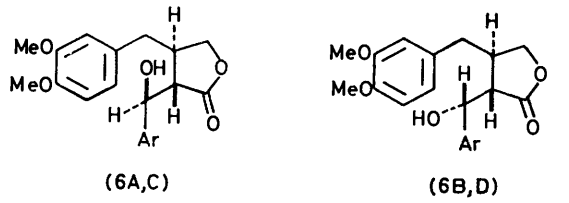
Structures originally proposed [15] for (+)-phyltetralin have recently been shown to be untenable and that the compound should be formulated as (5).[21] This is further supported here by the conversion of the butyrolactone (1) into (±)-phyltetralin (5) by the same procedure. Thus, treatment of (1) with veratraldehyde, followed by cyclization of the epimeric alcohol product (6C and D) with trifluoroacetic acid gave in excellent yield α-retrodendrin dimethyl ether (9).[22-24] Reduction of (9) with lithium aluminium hydride gave the diol, (±)-isolariciresinol dimethyl ether (10),[24-26] which on methylation gave (±)-phyltetralin (5), identified by comparison with the unnatural (−)-enantiomer.[21]

Galcatin (11) is an aryltetralin lignan of established structure isolated from *Himantandra* species.[27] The name isogalcatin was given to the all-*trans* structural isomer, 6,7-dimethoxy-2,3-dimethyl-1-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene (12) previously synthesized by Adjangba.[28,29] The availability of the intermediate (8) provides a ready access to this latter product and establishes the configuration. Thus, conversion of the diol (8) into the bistoluene-*p*-sulphonate derivative and reduction with lithium aluminium hydride gave isogalcatin (12).

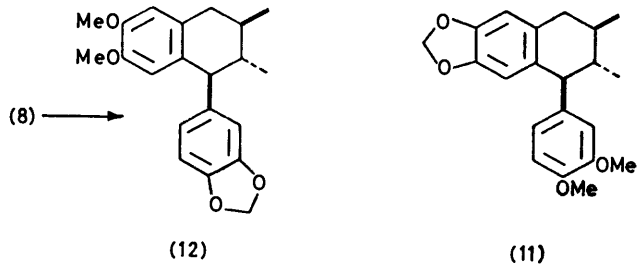
The ready accessibility of hydroxylactones of general structure (6) simplifies synthesis of the dibenzylbutyrolactone lignans, over thirty of which have been reported to occur naturally. This is exemplified here by catalytic hydrogenolysis of the epimeric alcohol mixture (6A, B) to give *trans*-2-piperonyl-3-veratryl-γ-butyrolactone (13),



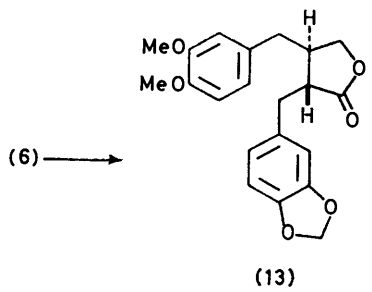
the (—)-form of which has been isolated from *Cinnamomum camphora* Sieb. and named kusunokinin.[30] Since the commonly used procedure for the synthesis of *trans*-dibenzylbutyrolactone lignans involves the reduction of α-benzylidene-β-benzylbutyrolactones and leads to mixtures with predominantly *cis*-disubstituted lactones,[8,31,32] the hydrogenolysis method used here has apparent advantages. In view of the recent reports[33,34] of the

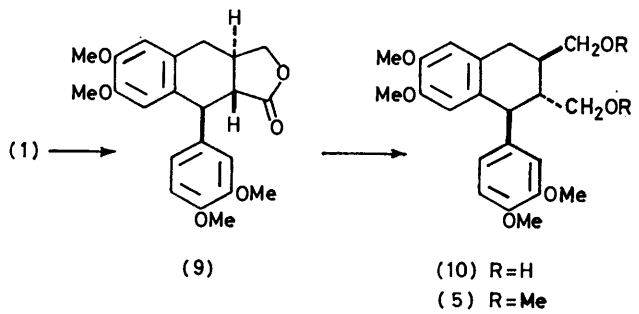


A, B; Ar = 3,4-Methylenedioxyphenyl
C, D; Ar = 3,4-Dimethoxyphenyl



first isolation of lignans from animal sources, and that both *trans*-dibenzylbutyrolactones and the derived (±)-dibenzylbutanediols have been identified, the larger quantities required to address the posed questions of physiological significance should be readily available by this procedure.





EXPERIMENTAL

N.m.r. spectra were determined for solutions in [^{2}H]-chloroform (unless otherwise stated) with tetramethylsilane as internal standard. M.p.s were determined with a Gallen-

kamp apparatus. Column chromatography was performed using silica gel 60 (35—70 mesh, Merck).

4-(3,4-*Dimethoxyphenyl*)-3-*methoxycarbonylbut*-3-*enoic Acid* (2).—To a solution of sodium methoxide (6.5 g) in methanol (100 ml) heated to reflux were added veratraldehyde (16.6 g) and dimethyl succinate (14.6 g). After heating under reflux for 1½ h, the mixture was cooled, acidified with dilute hydrochloric acid, concentrated under reduced pressure, and extracted with diethyl ether (2 × 100 ml). The ethereal fraction was then re-extracted with aqueous sodium hydrogencarbonate (3 × 50 ml). Acidification with concentrated hydrochloric acid precipitated an oil, which was extracted into chloroform. Evaporation of the washed and dried extract gave a yellowish solid which was boiled with benzene (100 ml), and the mixture was cooled and filtered. One crystallization from methanol yielded the veratrylidene half ester (2) as prisms (13.5 g), m.p. 149—150 °C (lit.,[35] 149—150 °C), δ 3.67 (s, CH_2), 3.88, 3.92, and 3.94 (s, 2 OMe and CO_2Me), 6.86—7.13 (m, 2, 5 and 6-ArH), 7.90 (s, vinyl H), and 9.85br (s, CO_2H).

4-(3,4-*Dimethoxyphenyl*)-3-*methoxycarbonylbutanoic Acid* (3).—Palladium–charcoal (10%; 2.0 g) was suspended in methanol (30 ml) and stirred under hydrogen for 15 min. A solution of (2) (10 g) in methanol (200 ml) was added, and the mixture stirred under hydrogen at atmospheric pressure for 5 h. Filtration and evaporation gave an oil which crystallized from benzene–hexane to give the *veratryl half ester* (3) as prisms (10 g), m.p. 108—109 °C (Found: C, 59.6; H, 6.35. $C_{14}H_{18}O_6$ requires C, 59.6; H, 6.4%), δ 2.50—3.28 (m, H-2, -3, -4), 3.69 (s, CO_2Me), 3.87 (s, 2 ArOMe), 6.70—6.93 (m, 2-, 5-, and 6-ArH), and 10.71br (s, CO_2H). The potassium salt was prepared by addition of aqueous ethanolic potassium hydroxide (*ca.* 40%) to a solution of the acid (3) (10 g) in ethanol (50 ml) until basic to phenolphthalein. Evaporation of solvent gave an oil which changed to a white solid (11.2 g) on vacuum drying.

3-(3,4-*Dimethoxybenzyl*)*butyrolactone* (1).—Powdered anhydrous calcium chloride (3.33 g) was dissolved in anhydrous ethanol (150 ml) and cooled to −10 °C. A solution of sodium borohydride (2.51 g) in the same solvent (150 ml) was added over 10 min, with stirring continued at −10 °C for a further 30 min, followed by a solution of the potassium salt of (3) (9.6 g) in ethanol (50 ml) over 30 min. The mixture was stirred at −10 °C for 3 h and for a further 5 h at room temperature. It was then cooled (ice-bath), diluted with water (50 ml), acidified with 6M-hydrochloric acid and concentrated under reduced pressure. Extraction with diethyl ether and work-up in the usual way gave the lactone (1) as a yellowish oil (6.4 g), collected by vacuum distillation, b.p. 180—185 °C at 2 mmHg (lit.,[1] 220 °C at 6 mmHg), ν 1 780 cm^{-1} (lactone), δ 2.30—2.90 (m, 5 H, H-2, -3, and $ArCH_2$), 3.85 (s, 2 ArOMe), 4.00—4.50 (m, 2 H, H-4), and 6.64—6.80 (m, 2-, 5-, and 6-ArH).

trans-3-(3,4-*Dimethoxybenzyl*)-2-(3,4-*methylenedioxy*-α-*hydroxybenzyl*)*butyrolactone* (6).—A solution of the butyrolactone (1) (2.36 g, 10 mmol) in dry tetrahydrofuran (10 ml) was injected into a stirred solution of lithium di-isopropylamide (12 mmol) [from di-isopropylamine (1.21 g) and n-butyl-lithium (2.56M; 4.7 ml)] in tetrahydrofuran (30 ml) at −78 °C under nitrogen. The mixture was stirred at this temperature for 30 min, then warmed to −20 °C. A solution of piperonal (1.50 g, 10 mmol) in tetrahydrofuran (10 ml) was injected with stirring at −20 °C for 1 h, followed by acidification with dilute hydrochloric acid and extraction with ethyl acetate (2 × 50 ml). Evaporation of the washed and dried extract gave the epimeric hydroxybenzyl-lactones (6) as a pale yellow solid (3.5 g), δ 5.23 [d, *J* 2.5 Hz, ArC*H*OH, corresponding to (6A)] and 4.78 [d, *J* 7.5 Hz, ArC*H*OH, corresponding to (6B)]. Crystallization from ethyl acetate gave a solid (1.32 g), m.p. 158—159 °C, which on two further recrystallizations from ethyl acetate–light petroleum gave the erythro-*isomer* (6A), m.p. 160—161 °C (Found: C, 65.3; H, 5.8. $C_{21}H_{22}O_7$ requires C, 65.3; H, 5.7%), δ($CDCl_3$–H_2O) 2.16—2.95 (m, $ArCH_2$, H-2 and -3), 3.81 (s, OMe), 3.85 (s, OMe), 3.92—4.45 (m, CH_2O), 5.25 (d, *J* 2.5 Hz, ArC*H*OH), 5.97 (s, OCH_2O), and 6.34—6.86 (m, 6 ArH). The crystallization mother-liquors were evaporated and chromatographed on silica gel; elution with benzene–ethyl acetate (97 : 3 v/v) gave the threo-*isomer* (6B) as a glass (1.48 g), δ 2.15—2.70 (m, $ArCH_2$, H-2 and -3), 3.84 (s, 3- and 4-OMe), 3.95—4.23 (m, CH_2O), 4.78 (d, *J* 7.5 Hz, ArC*H*OH), 5.96 (s, CCH_2O), and 6.36—6.92 (m, 6 ArH).

c-3-*Hydroxymethyl*-6,7-*dimethoxy*-r-1-(3,4-*methylenedioxyphenyl*)-1,2,3,4-*tetrahydronaphthalene*-t-2-*carbolactone* (7).—To a stirred solution of trifluoroacetic acid (14 ml) in dichloromethane (126 ml) at room temperature under nitrogen was added a solution of the epimeric lactones (6) (2.7 g) in the same solvent (20 ml). Evaporation after stirring for 3 h yielded a residual solid, which crystallized from chloroform–methanol to give the *all*-trans-*lactone* (7) as needles (2.34 g), m.p. 223—224 °C (Found: C, 68.1; H, 5.45. $C_{21}H_{20}O_6$ requires C, 68.5; H, 5.5%), δ 2.45—2.64 (m, H-2 and -3), 2.91—2.98br (d, H-4), 3.63 (s, 7-OMe), 3.86 (s, 6-OMe), 3.96—4.15 (m, CH_2O), 4.43—4.60 (m, H-1), 5.93 (s, OCH_2O), 6.33 (s, H-8), 6.61 (s, H-5), and 6.62—6.77 (m, H-2, -5 and -6 of phenyl).

t-2,c-3-*Bishydroxymethyl*-6,7-*dimethoxy*-r-1-(3,4-*methylenedioxyphenyl*)-1,2,3,4-*tetrahydrophthalene* (8).—To a stirred suspension of lithium aluminium hydride (1 g) in tetrahydrofuran (30 ml) was added dropwise a solution of lactone (7) (1.3 g) in the same solvent (40 ml) over 15 min under nitrogen. The mixture was stirred at room temperature for 3 h, then ethyl acetate (10 ml) and saturated aqueous ammonium chloride cautiously added. Extraction with chloroform and evaporation of the washed and dried extract gave a gum, which crystallized from benzene. Recrystallization from ethyl acetate–light petroleum gave the *diol* (8) as fine needles (1.15 g), m.p. 135—136 °C (Found: C, 67.7; H, 6.7. $C_{21}H_{24}O_6$ requires C, 67.7; H, 6.5%), δ 1.60—2.20 (m, H-2 and -3), 2.69—2.79 (m, H-4), 2.93br (s, 2 OH), 3.39—3.80 (m, H-1 and 3- and 4-CH_2OH), 3.60 (s, 7-OMe), 3.83 (s, 6-OMe), 5.92 (s, OCH_2O), and 6.21—6.90 (m, 5 ArH).

(±)-*Lintetralin* (4).—Methyl iodide (800 mg) was added to a stirred solution of the diol (8) (200 mg) in dry dimethyl sulphoxide (20 ml). Sodium hydride (1.2 g; 57% dispersion in oil) was washed twice with dry diethyl ether, and added portionwise to the solution over 20 min, followed by more methyl iodide (0.5 ml). After being stirred at room temperature for 2.5 h, the mixture was cooled to 0 °C, and methanol (5 ml) added. Isolation of the product by acidification with dilute hydrochloric acid, extraction with diethyl ether, and evaporation of the washed and dried extract gave a residual oil, which was chromatographed on silica gel. Elution with benzene–ethyl acetate (9 : 1 v/v) eluted an oil which crystallized from hexane to yield 6,7-*dimethoxy*-t-2,c-3-*bismethoxymethyl*-r-1-(3,4-*methylenedioxyphenyl*)-1,2,3,4-*tetrahydronaphthalene* (4) as clusters of needles (182 mg), m.p. 87—88 °C (Found: C, 69.1; H, 7.2. $C_{23}H_{28}O_6$

requires C, 69.0; H, 7.2%), δ 1.5—2.3 (m, H-2 and -3), 2.82br (d, H-4), 3.0—3.5 (m, 2- and 3-CH_2OMe), 3.27 and 3.36 (s, 2- and 3-CH_2OMe), 3.62 (s, 7-OMe), 3.84 (s, 6-OMe), 3.99 (d, *J* 11 Hz, H-1), 5.93 (s, OCH_2O), 6.24 (s, H-8), 6.58 (s, H-5), 6.59 (d, *J* 1.5 Hz, *H*-2 of phenyl), 6.63 (dd, *J* 7.5 and 1.5 Hz, H-6 of phenyl), and 6.75 (d, *J* 7.5 Hz, H-5 of phenyl), identical with that of natural lintetralin (kindly supplied by Dr. R. S. Ward, University College, Swansea).

r-1-(3,4-*Dimethoxyphenyl*)-c-3-*hydroxymethyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydronaphthalene*-t-2-*carbolactone* (9) *'α-Retrodendrin Dimethyl Ether.'*—A solution of the butyrolactone (1) was treated as for the preparation of (6A, B) except that piperonal was replaced by veratraldehyde, to give the *trans*-3-(3,4-dimethoxybenzyl)-2-(3,4-dimethoxy-α-hydroxybenzyl)butyrolactones (6C, D) as a light yellow solid (95%), δ 5.27 (d, *J* 2.5 Hz) and 4.88 (d, *J* 7 Hz). A solution of this product (2.2 g) in dichloromethane (15 ml) was added dropwise over 15 min to a stirred solution of trifluoroacetic acid (11 ml) in the same solvent (100 ml) at room temperature under nitrogen. Removal of solvents after stirring for a further 3 h gave a solid, which crystallized from chloroform–methanol as clusters of fine needles (1.93 g), m.p. 190—191 °C (lit.,[24] 190—191 °C), δ 2.45—2.67 (m, H-2 and -3), 2.92—3.02 (m, H-4), 3.63 (s, 7-OMe), 3.85 (s, 6-OMe), 3.90 (s, 3- and 4-OMe), 3.96—4.23 (m, CH_2O), 4.47—4.62 (m, H-1), and 6.39—6.85 (m, 5 ArH).

(±)-*Isolariciresinol Dimethyl Ether* (10).—The lactone (9) was reduced with lithium aluminium hydride [as for the preparation of (8)] to yield (10), m.p. 156—157 °C (91%) after one crystallization from methanol (lit. m.p., 155—158,[25] 161—164 °C [26]).

(±)-*Phyltetralin* (5).—The diol (10) was methylated with methyl iodide, as for (±)-lintetralin (4). Crystallization of the product from diethyl ether–hexane gave (±)-phyltetralin as fine needles, m.p. 97—98 °C (83%) (Found: C, 69.3; H, 7.8. $C_{24}H_{32}O_6$ requires C, 69.2; H, 7.7%), δ 1.5—2.3 (m, H-2 and -3), 2.84br (d, H-4), 3.0—3.5 (m, 2- and 3-CH_2OMe), 3.27 and 3.36 (s, 2- and 3-CH_2OMe), 3.59 (s, 7-OMe), 3.80, 3.84, and 3.88 (3 × ArOMe), 3.99 (d, *J* 10 Hz, H-1), 6.23 (s, H-8), 6.61br (s, H-5 and H-2 of phenyl), 6.67 (dd, *J* 8 and 2 Hz, H-6 of phenyl), and 6.82 (d, *J* 8 Hz, H-5 of phenyl).

Isogalcatin (12).—To a solution of toluene-*p*-sulphonyl chloride (600 mg) in dry pyridine (5 ml) at 0 °C was added the diol (8) (225 mg) and the mixture stirred at 0 °C for 2 h. It was then diluted with water, allowed to stand for 1 h, and then extracted with chloroform. Evaporation of the washed and dried extract gave an oil which was dissolved in tetrahydrofuran (20 ml) and added dropwise to a suspension of lithium aluminium hydride (200 mg) in the same solvent (25 ml) under nitrogen. Work-up in the usual way gave an oil which was chromatographed on silica gel. Elution with benzene–ethyl acetate (99 : 1 v/v) gave an oil, which on crystallization from diethyl ether–light petroleum gave isogalcatin (12) as rhombs (65 mg), m.p. 135—136 °C (lit.,[28] 137—138 °C), δ 0.88 (d, *J* 6 Hz, 2-Me), 1.07 (d, *J* 6 Hz, 3-Me), 1.22—1.70 (m, H-2 and -3), 2.58—2.70 (m, H-4), 3.43 (d, *J* 8.5 Hz, H-1), 3.60 (s, 7-OMe), 3.84 (s, 8-OMe), 5.93 (s, OCH_2O), and 6.18—6.80 (m, 5 ArH).

(±)-*Kusunokinin* (13).—A solution of the epimeric lactones (6) (300 mg) in ethanol (25 ml) was added to a suspension of palladium–carbon (10%; 100 mg) in ethanol (20 ml) and the mixture was stirred under hydrogen for 24 h. Filtration and evaporation gave an oil containing starting material. The hydrogenation was repeated with fresh catalyst, then the product chromatographed on silica gel and eluted with benzene–ethyl acetate (95 : 5 v/v) to give trans-3-(3,4-*dimethoxybenzyl*)-2-(3,4-*methylenedioxybenzyl*)*butyrolactone* as a glass (215 mg) (Found: C, 68.2; H, 5.9. $C_{21}H_{22}O_6$ requires C, 68.1; H, 6.0%), δ 2.42—2.94 (m, 6 H, H-2, -3, and $ArCH_2$), 3.82 (s, OMe), 3.85 (s, OMe), 3.90—4.24 (m, CH_2O), 5.92 (s, OCH_2O), and 6.49—6.82 (m, 6 ArH).

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