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Synthesis of (±)-Pluviatolide and (±)-Isopluviatolide

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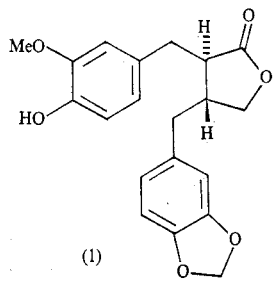
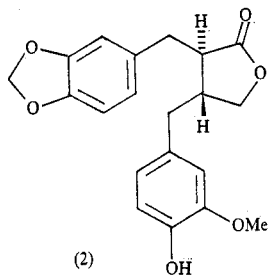
Abstract

The structure 2-(4-hydroxy-3-methoxybenzyl)-3-(3,4-methylenedioxybenzyl)-γ-butyrolactone, proposed for the dibenzylbutyrolactone lignan pluviatolide, is confirmed by an unequivocal synthesis. The isomer, isopluviatolide (2), has also been synthesized.

The dibenzylbutyrolactone lignan (−)-pluviatolide was first reported in this Journal[1] as a constituent of the bark of *Zanthoxylum pluviatile* Hartley (Rutaceae) and more recently has been isolated[2] from the heartwood of *Libocedrus formosana* Florin. The *trans*-configuration of the benzyl groups was indicated by consideration of the ^{1}H n.m.r. spectrum[1] and the absolute 2*R*,3*R*-configuration established.[1,3] The decision in favour of structure (1) for pluviatolide, rather than that in which the aryl groups are interchanged, here designated as isopluviatolide (2), was reached from analysis of the mass spectrum.[1] As part of a program of synthesis of lignans for pharmacological evaluation, we have synthesized both compounds, which incidentally confirms the structure of the natural product.



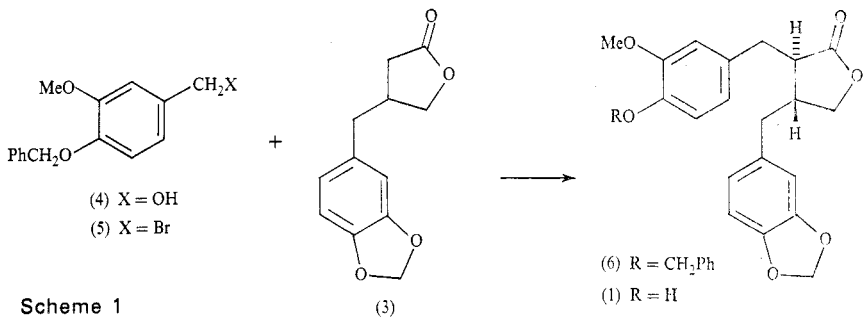
(1)



(2)

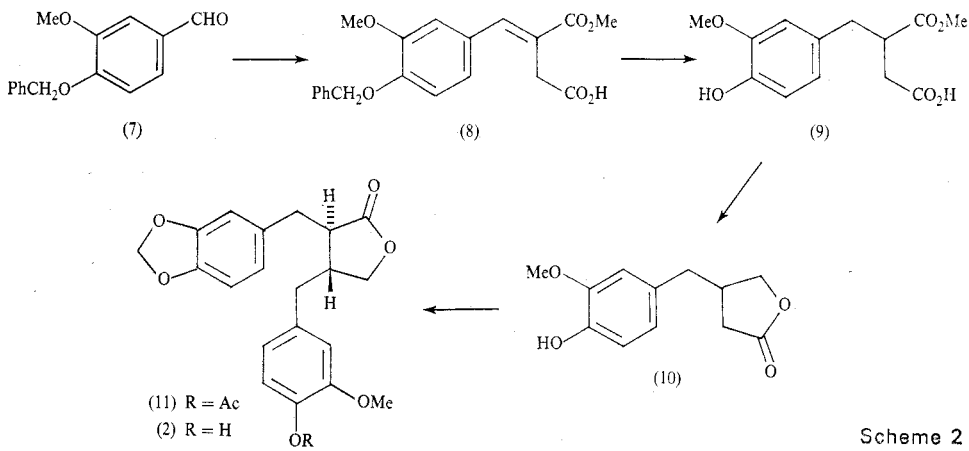
The readily accessible β-piperonyl lactone (3), recently used for the synthesis of the lignans podorhizone[4] and isootobaphenol,[5] yielded the lithium enolate by treatment with lithium diisopropylamide in tetrahydrofuran solution. Reaction of this

[1] Corrie, J. E. T., Green, G. H., Ritchie, E., and Taylor, W. C., *Aust. J. Chem.*, 1970, **23**, 133.
[2] Wenkert, E., Gottlieb, H. E., Gottlieb, O. R., Pereira, M. O. da S., and Formiga, M. D., *Phytochemistry*, 1976, **15**, 1547.
[3] Nishibe, S., Chiba, M., and Hisada, S., *Yakugaku Zasshi*, 1977, **97**, 1366.
[4] Brown, E., Robin, J. P., and Dhal, R., *J. Chem. Soc., Chem. Commun.*, 1978, 556.
[5] Ganeshpure, P. A., and Stevenson, R., *Org. Prep. Proced. Int.*, 1981, **13**, 323.



Scheme 1

salt (Scheme 1) with the benzyloxymethoxybenzyl bromide (5), obtained easily from the corresponding benzyl alcohol (4), gave (±)-pluviatolide benzyl ether (6) in 72% yield. This product was smoothly debenzylated by catalytic hydrogenolysis to yield (±)-pluviatolide (1), with spectrometric data in excellent agreement with those reported for (−)-pluviatolide.[1]



Scheme 2

The β-vanillylbutyrolactone (10) required for the synthesis of (±)-isopluviatolide (Scheme 2) was prepared by the same general pathway used for the piperonyl analogue (3). *O*-Benzylvanillin (7) was subjected to a Stobbe condensation with dimethyl succinate in methanol containing sodium methoxide to yield the benzylidenesuccinate half ester (8), which on catalytic hydrogenation underwent both addition of hydrogen and debenzylation to give the phenolic derivative (9). Reduction of the dipotassium salt of (9) with calcium borohydride, followed by acidification, gave the desired phenolic lactone (10). For the purpose of alkylation of (10), it was not found necessary to protect the free phenol function. The enolate from lactone (10), produced by addition of slightly more than 2 molar equivalent of lithium diisopropylamide, gave with piperonyl bromide a product that, on acetylation, yielded (±)-isopluviatolide acetate (11) after chromatographic purification. Saponification and acidification of (11) gave (±)-isopluviatolide (2). The mass spectrum of (2) revealed every fragment ion expected, from interpretation similar to that used for pluviatolide (1).[1]

Experimental

Melting points are uncorrected. Analyses were carried out by Galbraith Laboratories (Knoxville, Tennessee). ^{1}H n.m.r. spectra were measured in (D)chloroform solutions.

4-Benzyloxy-3-methoxybenzyl Bromide (5)

A solution of 4-benzyloxy-3-methoxybenzyl alcohol (4) (4 g) in benzene (10 ml) and chloroform (20 ml) was vigorously stirred with concentrated hydrobromic acid (48%, 6 ml) at room temperature for 2 h. More chloroform (30 ml) and water were then added, the layers were separated, and the washed and dried organic phase was evaporated to give the *benzyl bromide* (5) as a solid, which crystallized from ether/light petroleum as long needles (3·8 g) m.p. 70–72° (Found: C, 58·8; H, 5·0. $C_{15}H_{15}BrO_2$ requires C, 58·7; H, 4·9%). ^{1}H n.m.r. 3·93, s, OMe; 4·50, s, $ArCH_2Br$; 5·16, s, $PhCH_2O$; 6·78–6·98, m, H 2,5,6; 7·31–7·52, m, Ph.

2-(4-Benzyloxy-3-methoxybenzyl)-3-(3,4-methylenedioxybenzyl)-γ-butyrolactone (6)

A solution of 3-(3,4-methylenedioxybenzyl)-γ-butyrolactone[5] (3) (660 mg) in dry tetrahydrofuran (5 ml) was added to a stirred solution of lithium diisopropylamide (3·5 mmol) [prepared from diisopropylamine (354 mg) and butyllithium (2·5 M, 1·4 ml) in tetrahydrofuran (10 ml)] at −78° under nitrogen. The mixture was stirred at this temperature for 30 min, then warmed to −20°. A solution of the benzyl bromide (5) (921 mg, 3 mmol) in tetrahydrofuran (5 ml) was then added, with stirring at −20° for 30 min and room temperature for 1 h, then poured onto crushed ice. Extraction with ether and workup in the usual way gave a gum, which was chromatographed on silica gel. Elution with benzene gave the *lactone* (6) as a viscous oil (960 mg) (Found: C, 78·4; H, 6·0. $C_{27}H_{26}O_4$ requires C, 78·2; H, 6·3%). ^{1}H n.m.r. 2·30–3·04, m, H 2,3 and $ArCH_2$; 3·78–4·24, m, H 4; 3·89, s, OMe; 5·17 s, $PhCH_2O$; 5·97, s, OCH_2O; 6·43–7·0, m, ArH; 7·37–7·56, m, Ph.

(±)-Pluviatolide (1)

A solution of the lactone (6) (400 mg) in ethyl acetate (20 ml) containing perchloric acid (1 drop) was stirred under hydrogen (1 atm) with palladium–carbon (10%, 50 mg) at room temperature for 3 h. After filtration, the solution was washed with dilute sodium hydrogen carbonate solution and water, then dried and evaporated. The residual oil on t.l.c. purification (silica gel; benzene (80 ml)/ethyl acetate (20 ml)/acetic acid (2 drops)) gave *2-(4-hydroxy-3-methoxybenzyl)-3-(3,4-methylenedioxybenzyl)-γ-butyrolactone* (1) as a glass, which after two recrystallizations from ether afforded the lactone as prisms, m.p. 123° (Found: C, 67·3; H, 5·8. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·7%). $\nu(CHCl_3)$ 1770 (lactone) and 3540 cm^{-1} (phenolic OH). ^{1}H n.m.r. 2·53–2·93, m, H 2,3 and $ArCH_2$; 3·76–4·25, m, H 4; 3·85, s, OMe; 5·53, s, OH; 5·93, s, OCH_2O; 6·41–6·89, m, ArH. Mass spectrum (cf.[1]) *m/e* 356, 221, 220, 194, 162, 137, 135.

3-Methoxycarbonyl-4-(4-hydroxy-3-methoxyphenyl)butanoic Acid (9)

To a solution of sodium methoxide (3·0 g) in methanol (50 ml) heated to reflux were added slowly a solution of *O*-benzylvanillin (7) (12·1 g) and dimethyl succinate (7·3 g) in methanol (15 ml). The mixture was refluxed for 2 h, then cooled, acidified with 6 N hydrochloric acid, and diluted with water. After concentration under reduced pressure, it was extracted with ether, and the ether fraction reextracted with aqueous sodium hydrogen carbonate solution (3 × 50 ml). Acidification of the bicarbonate extract precipitated a gummy solid, which was dissolved in ether. Evaporation of the washed and dried extract yielded the residual benzyloxy butenoic acid (8) as a pale yellow gum (12·1 g). ^{1}H n.m.r. 3·57, s, CH_2CO_2H; 3·85, s, OMe; 3·88, s, OMe; 5·18, s, $PhCH_2O$; 6·84–7·41, m, ArH; 7·86, s, vinyl H.

Without further purification, a solution of (8) (12·9 g) in ethyl acetate (200 ml) was stirred under hydrogen (1 atm) with palladium/carbon (10%, 2·0 g) at room temperature for 2 h. Removal of catalyst and solvent yielded the *vanillyl half ester* (9) as an oil (8·4 g) (Found: $M^{+\cdot}$, 268·0945. $C_{13}H_{16}O_6$ requires $M^{+\cdot}$, 268·0947). ^{1}H n.m.r. 2·28–3·22, m, H 2,3,4; 3·69, s, CO_2Me; 3·87, s, ArOMe; 6·60–6·91, m, ArH. After slow crystallization from hexane, it had m.p. 71–74°.

Potassium salt.—Aqueous ethanolic potassium hydroxide solution (1 N, *c.* 50 ml) was added to a solution of the acid (9) (6·7 g) in ethanol (100 ml). Solvent evaporation and prolonged vacuum drying gave the potassium salt as a white solid.

3-(4-Hydroxy-3-methoxybenzyl)-γ-butyrolactone (10)

Powdered anhydrous calcium chloride (4·1 g) was dissolved in anhydrous ethanol (100 ml) and cooled to −10°. A suspension of sodium borohydride (2·8 g) in the same solvent (100 ml) was added over 20 min with stirring, followed by a solution of the dipotassium salt of (9) (8·65 g) in ethanol (70 ml) over 15 min. The mixture was stirred at −10° for 2 h and at room temperature for 24 h. It was then cooled, diluted with water, acidified with dilute hydrochloric acid and concentrated under reduced pressure. Extraction with ether and workup in the usual way gave a residual oil which was distilled at 165–170°/2 mm to give the *lactone* (10) as an oil (2·5 g) which crystallized from ether/light petroleum as short needles, m.p. 88–90° (Found: C, 64·8; H, 6·2. $C_{12}H_{14}O_4$ requires C, 64·8; H, 6·4%). *ν*(KBr) 1760 (lactone) and 3385 cm^{-1} (phenolic OH). ^1H n.m.r. 2·12–3·13 m, H 2,3 and $ArCH_2$; 3·88, s, OMe; 3·95–4·42 m, H 4; 5·53, s, OH; 6·61, d, *J* 2 Hz, H 2; 6·66, dd, *J* 8, 2 Hz, H 6; 6·86, d, *J* 8 Hz, H 5.

trans-*2-(3,4-Methylenedioxybenzyl)-3-(4-acetoxy-3-methoxybenzyl)-γ-butyrolactone (11)*

A solution of lithium diisopropylamide (8 mmol), prepared from diisopropylamine (808 mg) and butyllithium (2·5 M, 3·2 ml) in tetrahydrofuran (15 ml) at −78° under nitrogen was warmed to −20° and a solution of the lactone (10) (775 mg, 3·5 mmol) in tetrahydrofuran (5 ml) injected. The mixture was stirred at −20° for 15 min, then a solution of piperonyl bromide (753 mg, 3·5 mmol) in tetrahydrofuran (5 ml) added with continued stirring at −20° for 30 min and at room temperature for 30 min. It was then cooled (ice-bath), acidified with dilute hydrochloric acid, diluted with water and extracted with ether. Evaporation of the washed and dried extract yielded a viscous gum (1·25 g) which was dissolved in pyridine (3 ml) and acetic anhydride (3 ml) and allowed to stand at room temperature for 4 h. The usual workup gave an oil (1·2 g) which was chromatographed on silica gel (10 g). Elution with benzene/ether (96 : 4) gave the *dibenzyl lactone* (11) as an oil, which crystallized from methanol as glistening prisms, m.p. 125° (Found: C, 66·4; H, 5·8. $C_{22}H_{22}O_7$ requires C, 66·3; H, 5·6%). *ν*(KBr) 1755 (acetate) and 1770 cm^{-1} (lactone). ^1H n.m.r. 2·28, s, OAc; 2·40–3·02, m, H 2,3 and $ArCH_2$; 3·75–4·25, m, H 4; 3·79, s, OMe; 5·92, s, OCH_2O; 6·53–7·0, m, ArH.

(±)-*Isopluviatolide (2)*

The acetate (11) (180 mg) was added to a solution of sodium hydroxide (200 mg) in methanol (15 ml) and water (5 ml) and the mixture refluxed for 2 h. The solution was then concentrated, and acidified with 10% sulfuric acid. Workup by ether/benzene extraction and evaporation yielded an oil, which was dissolved in benzene and chromatographed on silica gel to yield *2-(3,4-methylenedioxybenzyl)-3-(4-hydroxy-3-methoxybenzyl)-γ-butyrolactone* (2) as a glossy solid (Found: C, 67·2; H, 6·0. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·7%). *ν*($CHCl_3$) 1770 (lactone) and 3535 cm^{-1} (phenolic OH). ^1H n.m.r. 2·53–2·90 m, H 2,3 and $ArCH_2$; 3·78–4·24, m, H 4; 3·84, s, OMe; 5·51, s, 1H, OH; 5·93, s, OCH_2O; 6·47–6·86, m, ArH. Mass spectrum *m/e* 356, 219, 218, 192, 164, 137, 135.

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