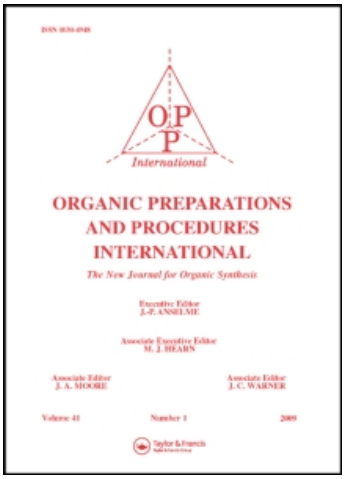

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SYNTHESIS OF (±)-NIRANTHIN

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SYNTHESIS OF (±)-NIRANTHIN

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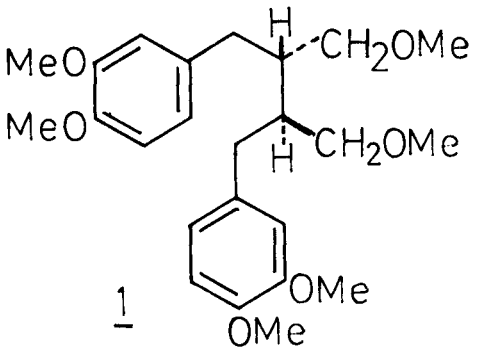
The plant Phyllanthus niruri Linn. (Euphorbiaceae) provides an abundant source for lignans, and six members have been isolated by Ramachandra Row and colleagues.[1-3] Four of these (hypophyllanthin, nirtetralin, phyltetralin and lintetralin) are aryltetralins, whose structures have recently been established by total synthesis,[4] and two (phyllanthin and niranthin) are diarylbutanes. The structure of (+)-phyllanthin[1,5] has been rigorously established as 2S,3S-bis(3',4'-dimethoxybenzyl)-butane-1,4-diol dimethyl ether (1) by interrelating with (-)-eudesmin, and (+)-niranthin is believed to have the constitution 2.[2,6] We now describe a preparation of (±)-nir-



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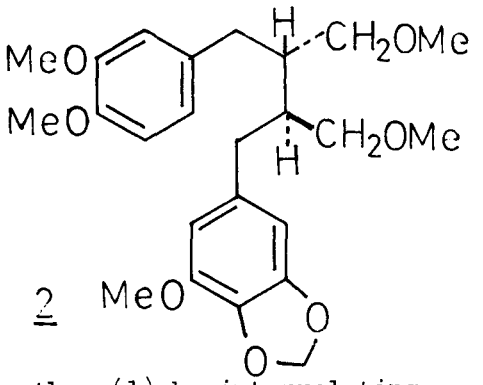
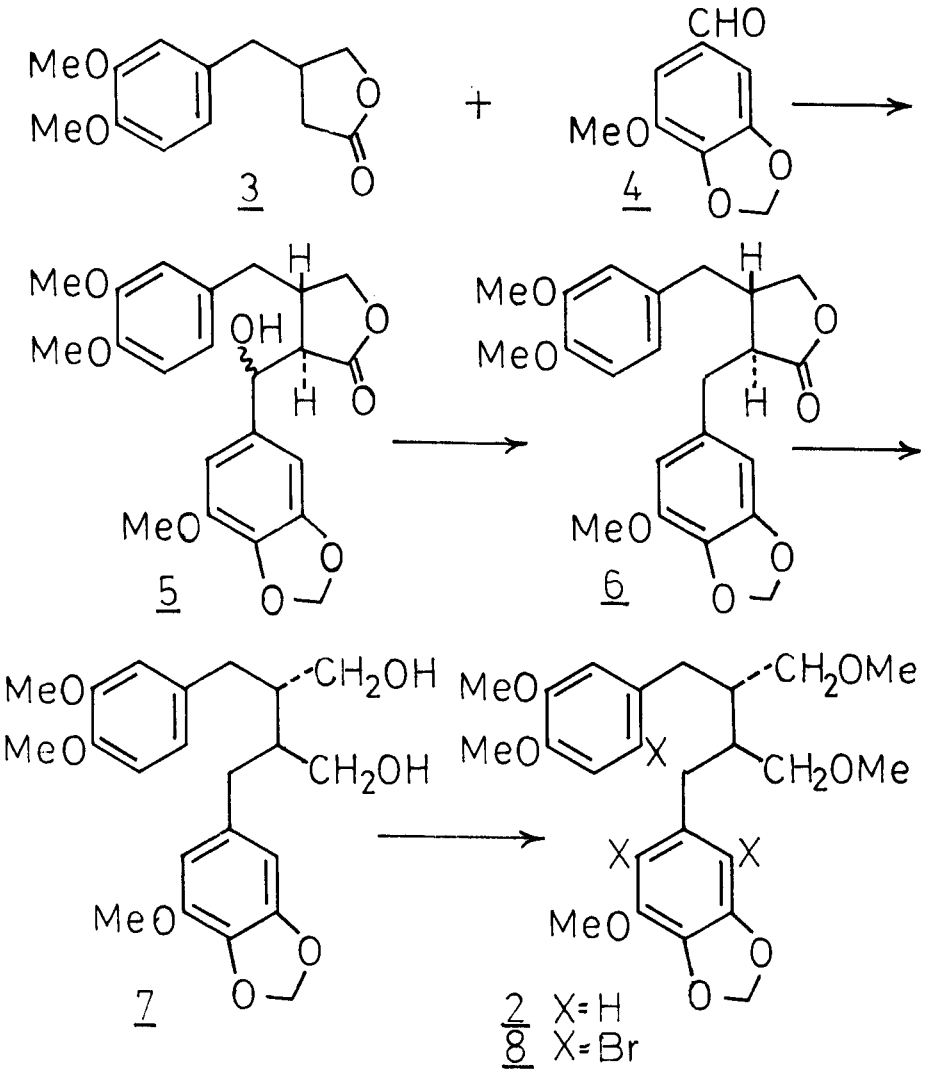


2

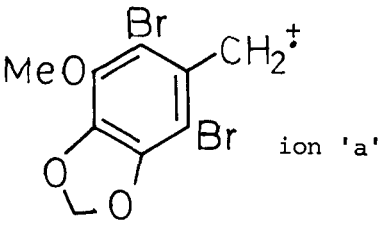
anthin, the sole remaining member for which no synthesis has been reported.

The ready availability of 3-(3,4-dimethoxybenzyl)butyrolactone (3)[7,8] and 3-methoxy-4,5-methylenedioxybenzaldehyde (4)[9,10] at hand from other projects,[8,10] governed the chosen synthesis pathway. The lithium enolate of 3, prepared by

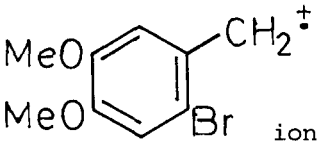


the action of lithium diisopropylamide in tetrahydrofuran, reacted with aldehyde 4 to give in excellent yield, the expected mixture of epimeric alcohols (5),[8,11-13] catalytic hydrogenolysis[14] of which yielded 2-(3-methoxy-4,5-methylenedioxybenzyl)-3-(3,4-dimethoxybenzyl)butyrolactone (6). Reduction of 6 with lithium aluminium hydride gave the diol 7, which without purification, was methylated (MeI, NaH, DMSO) to yield (±)-niranthin (2).

Since a specimen of natural (+)-niranthin was unavailable for comparison, the synthetic product was further characterized by bromination. The natural product yielded a tribromo derivative, which was assigned structure 8 on the basis of the pmr spectrum. We find that the synthetic niranthin also yields a tribromo product whose structure 8 is confirmed by the mass spectrum, which in addition to revealing the M^+



ion 'a'



ion 'b'

isotope cluster ($C_{24}H_{29}O_7Br_3$) gives the expected cleavage ions, ion 'a' ($C_9H_7O_3Br_2$) and ion 'b' ($C_9H_{10}O_2Br$).

EXPERIMENTAL

trans-2-(3-Methoxy-4,5-methylenedioxy-α-hydroxybenzyl)-3-(3,4-dimethoxybenzyl)-γ-butyrolactones (5). – n-Butyllithium (2.55 M, 1.17 ml) was added to a stirred solution of tetrahydrofuran (3 ml) at 0° under nitrogen, followed by diisopropylamine (0.42 ml) added dropwise over 5 min. The mixture was then cooled to -78°, with stirring for 10 min. and a solution of the lactone[8] (3)(472 mg) in tetrahydrofuran (5 ml) added dropwise over 5 min., with stirring for a further 15 min. The aldehyde[10] (4)(350 mg) in tetrahydrofuran (5 ml) was then added over 5 min., with stirring for an additional 30 min. at -78°, after which hydrochloric acid (1 N, 5 ml) was added, and the mixture allowed to warm to room temp. The layers were separated, and the aqueous phase extracted with ethyl acetate. The combined organic extracts were washed and dried in the usual way, and on evaporation yielded the epimeric hydroxybenzyl lactones (5) as a pale yellow oil (790 mg), δ ($CDCl_3$) 4.75 (d, J = 10 Hz) and 5.18 (d, J = 3 Hz) corresponding to the ArCHOH protons in approximately equal integrated intensity, and used without attempted separation or further purification.

trans-2-(3-Methoxy-4,5-methylenedioxybenzyl)-3-(3,4-dimethoxybenzyl)-butyrolactone (6). – A solution of the lactones (5) (780 mg) in ethyl acetate (60 ml) was stirred under hydrogen

with palladium-carbon (10%, 800 mg) overnight. A further 1.3 g of catalyst was then added and reaction continued for 36 hr. Removal of catalyst and solvent gave a residual oil (480 mg), and extraction of the filtered catalyst (Soxhlet) with chloroform yielded a further 250 mg of oil product. Chromatography of these residues on silica gel (40 g) with chloroform (500 ml) yielded as the initial eluate[14] the lactone (6) as an oil (250 mg), δ ($CDCl_3$) 2.2-3.2 (m, 6H, H-2 and 3, two $ArCH_2$), 3.84 (s, 9H, three OMe), 3.9-4.4 (m, 2H, $-CH_2O$), 5.89 (s, 2H, $-OCH_2O-$), 6.28 (s, 2H, H-2′ and 6′) and 6.42-6.84 (m, 3H, H-2″,5″ and 6″).

Anal. Calcd. for $C_{22}H_{24}O_7$: m/e 400·15220. Found: m/e 400·15307.

(±)-Niranthin (2). – A solution of the lactone (6)(175 mg) in tetrahydrofuran (20 ml) was added dropwise to a suspension of lithium aluminium hydride (100 mg) in the same solvent (10 ml) and the mixture stirred at room temp. for 3 hr. Excess reagent was decomposed by addition of ethyl acetate, and the decanted organic layer washed, dried and evaporated to yield the diol (7) as a colorless oil (111 mg), δ ($CDCl_3$) 1.7-2.0 (m, CH), 2.4-2.8 (m, two $ArCH_2$), 3.3-3.9 (m, CH_2OH), 3.82 (s, three OMe), 5.86 (s, $-OCH_2O-$), 6.28 (br.s, H-2′ and 6′) and 6.60-6.76 (m, H-2″,5″ and 6″).

A sodium hydride-oil suspension (57%, 0.9 g) was washed four times with pentane, covered with dimethylsulphoxide and added portionwise to a solution of the diol (7)(110 mg) and

methyl iodide (0.27 ml) in dimethylsulphoxide (10 ml). More methyl iodide (0.25 ml) was added, the mixture stirred at room temp for 1 hr. and the process repeated. Water (15 ml) was then carefully added, and the reaction worked up via ether extraction. The residual oil obtained from the washed and dried extract was dissolved in light petroleum and chromatographed on alumina (11 x 1 cm. dia.). After elution with the same solvent (200 ml), light petroleum-methylene chloride (200 ml) eluted 2-(3',4'-dimethoxybenzyl)-3-(3"-methoxy-4",5"-methylenedioxybenzyl)-butane-1,4-diol dimethyl ether [(±)-niranthin] (2) as fine needles, mp 89.5-90° (from hexane), δ ($CDCl_3$) 1.84-2.16 (m, CH), 2.60 (d, J = 8 Hz, $ArCH_2$), 3.30 (s, CH_2OMe), 3.34 (br.s, CH_2OMe), 3.80 (s, ArOMe), 3.83 (s, ArOMe), 3.84 (s, ArOMe), 5.89 (s, $-OCH_2O-$), 6.24 and 6.29 (each d, J = 1 Hz, H-2' and 6') and 6.56-6.76 (m, H-2", 5" and 6").

Anal. Calcd. for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46

Found: C, 66.63; H, 7.49%

(±)Tribromoniranthin. – A solution of bromine (64 mg) in chloroform (5 ml) was added to a solution of (±)-niranthin (40 mg) in chloroform (5 ml) over 10 min, and stirred at room temp. for 1 hr. The mixture was washed with dilute sodium sulphite, water, dried and evaporated to give a residual oil, purified by preparative t.l.c. (Whatman, silica gel, chloroform, R_f 0.4). Crystallization from methanol gave 2-(2'-

bromo-4′,5′-dimethoxybenzyl)-3-(2″,6″-dibromo-3″-methoxy-4″, 5″-methylenedioxybenzyl)-butane-1,4-diol dimethyl ether (8) as needles, mp 119.5-120°, δ ($CDCl_3$)1.9-2.4 (m, CH), 2.82 (d, J = 7 Hz, $ArCH_2$), 3.06 (d, J = 7 Hz, $ArCH_2$), 3.28 (s, CH_2OMe), 3.33 (s, CH_2OMe), 3.2-3.6 (m, CH_2OMe), 3.78 (s, ArOMe), 3.82 (s, ArOMe), 3.98 (s, ArOMe), 6.00 (s, $-OCH_2O-$), 6.68 (s, H-6′) and 6.92 (s, H-3′). Mass spectrum: m/e 672, 670,668 and 666 (M^+, $C_{24}H_{29}O_7Br_3$), 325,323,321 (ion 'a', $C_9H_7O_3Br_2$) and 231,229 (ion 'b', $C_9H_{10}O_2Br$).

Anal. Calcd. for $C_{24}H_{29}O_7Br_3$: C, 43.07; H, 4.37

Found: C, 43.26; H, 4.41%

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14. The epimeric benzylic alcohols hydrogenolyze at different rates, and the epimer (δ 5.18, J = 3 Hz) could be recovered partly unchanged in subsequent fractions.

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