Total Synthesis of (±)-Meridinol, (±)-Epimeridinol, and a Related Cyclolignan

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TOTAL SYNTHESIS OF (±)-MERIDINOL, (±)-EPIMERIDINOL, AND A RELATED CYCLOLIGNAN[1]

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ABSTRACT.—The naturally occurring lignan meridinol [**5**] was synthesized in a racemic form in a convergent manner involving a Grignard reaction on *E*-4-(3,4-methylenedioxybenzylidene)-2,3(2*H*,5*H*)-furandione [**7**]. The hitherto unknown epimeridinol [**11**] and the cyclolignan **15** were also prepared. The structure assignments of the synthesized lignans are determined by their spectroscopic data.

The diverse structures of natural lignans have created an interest which is reflected by the frequently appearing reviews of their chemistry (1–4). Medicinal chemists are especially intrigued by those lignans that display cytotoxicity since these naturally occurring compounds may serve as valuable leads in the search for novel, especially less toxic, antitumor agents (5).

Recently, we have published a novel and simple synthesis of the cyclolignan lactone skeleton of the 1,4-dihydronaphthalene system [**1**] (6). In our approach, Scheme 1, the key precursor **2** was obtained via a regioselective reductive dehydration reaction of 4-benzoyl-2,3(2*H*,5*H*)-furandione [**3**]. Reaction of **2** with benzylmagnesium chloride led to **4** which, upon treatment with polyphosphoric acid, was then converted into **1**.

Recently Amaro-Luis *et al.* (7) reported that the EtOH extract of the leaves and stems of *Zanthoxylum fagara* (a shrub widely distributed over Central and South America, which has been used in indigenous systems of medicine as a sudorific and as a sedative) contains a lignan, namely, (±)-meridinol [**5**]. This compound has an unusual structure which was determined by X-ray analysis of a single crystal as (1*S*,2*R*)-1,2-bis(3,4-methylenedioxybenzyl)-1-hydroxy-γ-butyrolactone.

In continuation of our interest in this field we have envisioned that the key intermediate **4** in our approach towards a total synthesis of cyclolignans would also be suitable for furnishing the skeleton of (±)-meridinol, provided **4** could be hydrogenated. Based on this assumption the total synthesis of (±)-meridinol was contemplated to proceed according to Scheme 2. Thus, 3-hydroxy-4-(3,4-methylenedioxybenzoyl)-2(5*H*)-furanone [**6**] was easily obtained from the commercially available 3,4-methylenedioxyacetophenone by a known procedure (8). Further treatment of **6** with $NaBH_4$ gave (*E*)-4-(3,4-methylenedioxybenzylidene)-2,3(4*H*,5*H*)-furandione [**7**] in 66% yield. However, our attempts to synthesize the methylenedioxy analogue of **4** encountered difficulties with the preparation of piperonylmagnesium chloride [**9**]. The reaction of piperonyl chloride and magnesium turnings did not occur without heating. But heat led directly to the corresponding dimer instead of the desired **9**. Activation by ultrasound (9) had the same effect, and using piperonyl bromide instead of the chloride did not change the results either. Iodine-activated magnesium only gave piperonyl iodide via a Finkelstein reaction. The desired compound **9** finally was prepared by slowly adding a dilute solution of piperonyl chloride to magnesium powder in dry Et_2O without any heating. The reaction of **7** with **9** using the same conditions as employed in our

[1]Part 40 of the series "Substituted γ-Butyrolactones." For part 39 of this series see Hans Zimmer, R. Palmer-Sungail, Douglas Ho, and Adel Amer, *J. Heterocycl. Chem.*, in press.

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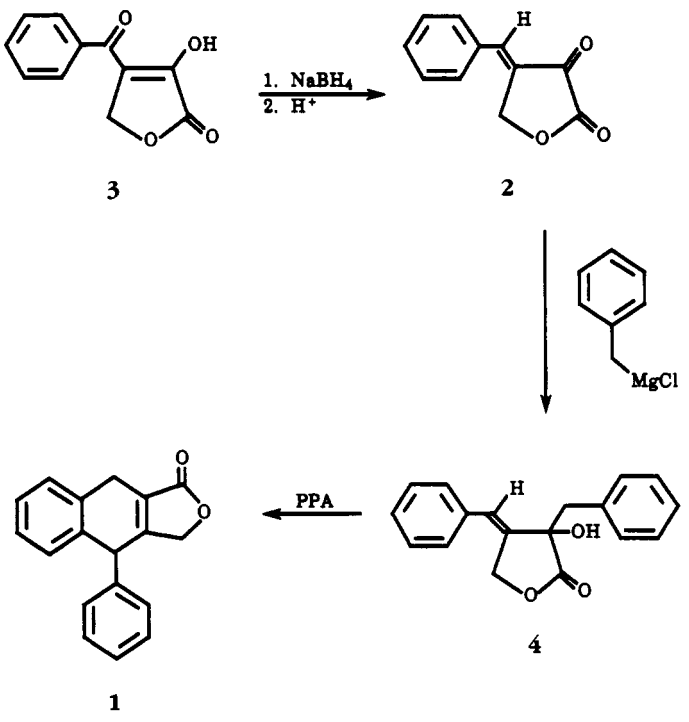
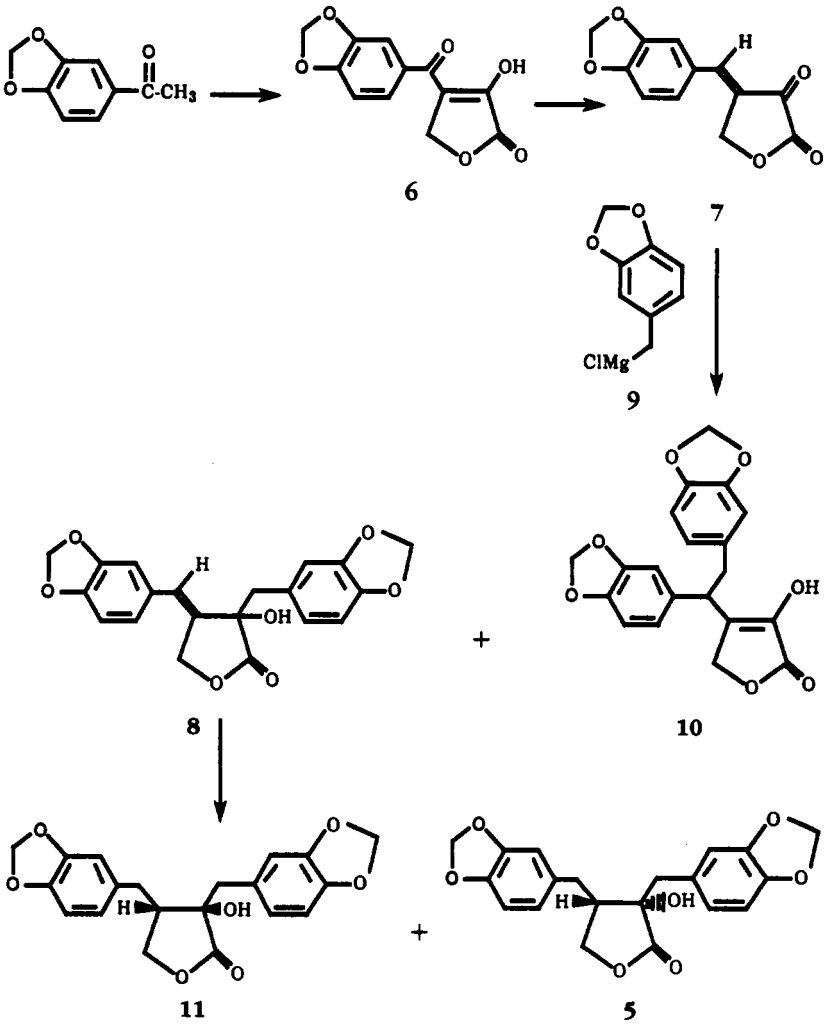


SCHEME 1

previous work (6) was monitored by tlc and quenched after disappearance of the starting material. Purification by flash cc of the crude product yielded two compounds which were identified on the basis of their elemental analysis and mass and nmr spectra as **8** and **10**. The most striking feature of the ^{1}H-nmr spectrum of **8** was the appearance of two doublets of doublets of one-proton intensity each at δ 4.31 and 4.84 ppm; these were assigned to the two lactonic methylene protons. A 2D ^{1}H-^{1}H homonuclear-correlated experiment (COSY-SMX) confirmed this assignment. The spectrum showed cross peaks between the lactonic methylene protons and the vinylic proton and enabled us to furnish the complete proton assignments. In contrast the COSY-SMX spectrum of compound **10**, the product of a 1,4-addition of **9** to **7**, did not show any cross peaks between the vinylic region of the spectrum and the lactonic methylene protons. Thus, compounds **8** and **10** could be easily distinguished on the basis of their ^{1}H-nmr spectra.

Hydrogenation of **8** now was the only remaining step before achieving the goal of synthesizing **5**. Subjecting **8** to catalytic hydrogenation using 10% Pd/C gave a product which, according to the tlc results and its ^{1}H-nmr spectra, was identified as a mixture of the two diastereomers **5** and (±)-epimeridinol [**11**], which could be separated by chromatography. These two tertiary alcohols were formed in good yield as essentially a 3:1 mixture in favor of the cis-product **11** as expected from the catalytic hydrogenation mechanistic pathway. (±)-Meridinol was identified by comparison of our spectral data with those published earlier (7), showing that the natural product and **5** were identical. Additionally, the structure assignment was further confirmed by a 2D (COSY) experiment.

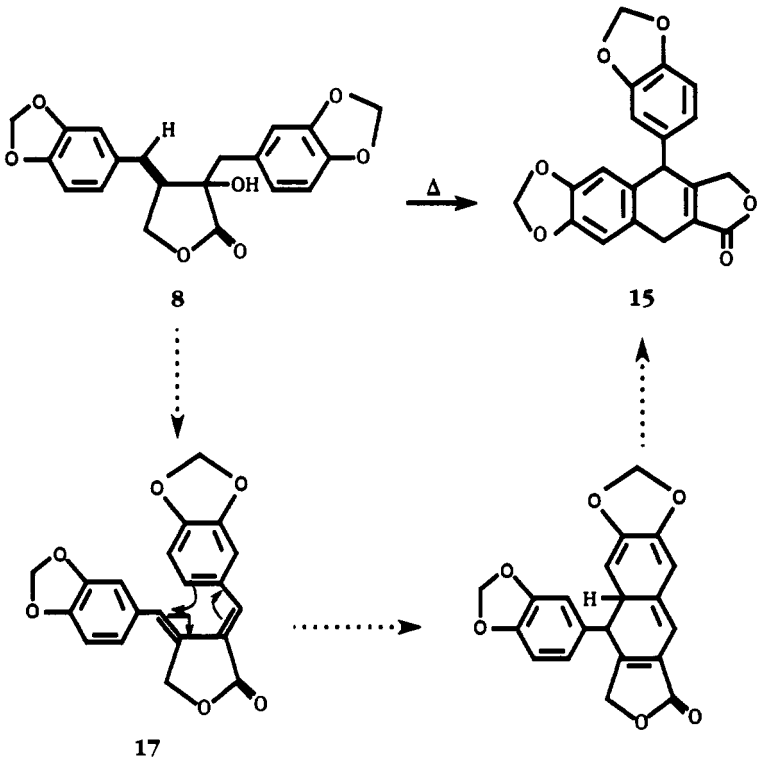
The structure of the previously unknown **11**, whose biological activity might be of considerable interest, was established based on ^{1}H-nmr spectral analysis. Particularly revealing for the structural assignment of this compound was its 2D scalar correlation



SCHEME 2

(COSY) experiment. It showed that the two multiplets of δ 4.20 and 3.90 (1H, each), belonging to the lactonic methylene protons, are coupled to each other. Furthermore these protons exhibited cross peaks with the multiplet at δ 2.90 (3H). Therefore one proton of this signal was assigned to the β proton of the lactone ring, since it exhibited two more cross peaks to the multiplets at δ 3.09 and δ 2.61 (1H). These multiplets must be due to the β-benzylic protons. The remaining two protons of the δ 2.90 multiplet now could readily be assigned to the α-benzylic protons. This assignment for **11** was further corroborated by comparison with spectra of related compounds (9,10).

The existence of cyclolignans, such as konyanin [**12**] (11), justicidin E [**13**] (12), and helioxanthin [**14**] (13), could be taken as a reasonable assumption that "(±)-dihydrojusticidin E" [**15**] and "(±)-isodihydrojusticidin E" [**16**] also might occur, though they have not as yet been discovered as natural products. It is interesting to note that the intramolecular cyclization of **8** occurred by simply heating it at 130° and 1 torr for 3 days (Scheme 3). Purification of the crude reaction mixture gave **15** in 40% yield. The ^{1}H-nmr spectrum confirmed the orientation of the methylenedioxy group by the



SCHEME 3

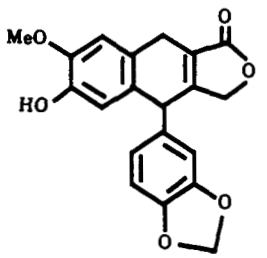
absence of a ^3J coupling for H-5 and H-8 as shown by a 2D (COSY) experiment. This is exactly the same pattern as was reported earlier for the methyl ether of **12** (11).

Formation of **15** is thought to proceed via a sequence as outlined in Scheme 3. The reaction sequence is initiated by thermal dehydration of **8** to **17**, which undergoes a [4+2] intramolecular cycloaddition followed by a 1,3-sigmatropic shift.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's were determined on a Mel-Temp melting point apparatus and are uncorrected. Analytical tlc was performed using an ascending technique with EM Si gel 60 F_{254} precoated on plastic sheets. Ir spectra were obtained on a Perkin-Elmer model 599 spectrometer and were calibrated against the 1601 cm^{-1} band of polystyrene. Nmr spectra were recorded on a Bruker AC-250 instrument with TMS as internal standard. Flash chromatography was conducted with Si gel 60, 230–400 mesh ASTM under a positive pressure of N_2. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

3-Hydroxy-4-(3,4-methylenedioxybenzoyl)-2(5H)-furanone [**6**].—A 2-liter three-necked round-bottom flask equipped with a heavy-duty stirrer, thermometer, and 250 ml pressure-equalized addition funnel, was charged with NaOMe (6 g, 0.111 mol) and dry Et_2O (100 ml). The suspension was cooled to 0–5°, and a mixture of 3,4-methylenedioxyacetophenone (18.2 g, 0.111 mol), diethyl oxalate (16.2 g, 0.111 mol), and dry Et_2O (100 ml) was added in small portions with stirring over a period of 30 min while maintaining the temperature at 5–10°. The temperature mixture was maintained at 20° for 3 h. The mixture was hydrolyzed by adding 100 ml of H_2O followed by addition of a 37% aqueous formaldehyde (9.0 g, 0.111 mol) solution. Vigorous stirring for 5–10 min caused all solid materials to dissolve, and two layers formed which had to be separated immediately. The organic layer was further washed with 25 ml H_2O, and the combined aqueous layers were cooled to 5° and acidified with concentrated HCl (7 ml). The precipitate was collected, dried, and recrystallized from iPrOH (16 g, 58% yield): mp 200–201°; ^1H nmr δ [$(CD_3)_2SO$] 5.02 (s, 2H, CH_2OCO), 6.15 (s, 2H, OCH_2O), 7.00, 7.36, 7.52 (d, s, d, 3H, ArH), 11.7 (bs, 1H, D_2O exchangeable); ^{13}C nmr δ [$(CD_3)_2SO$] 68.1, 102.1 107.8, 108.5, 122.0, 125.8, 131.2, 143.5, 147.5, 151.7, 169.7, 187.3;



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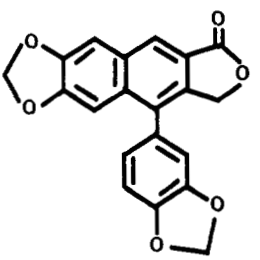

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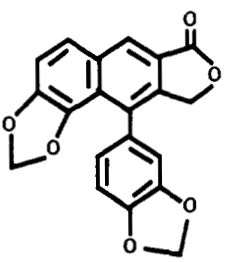

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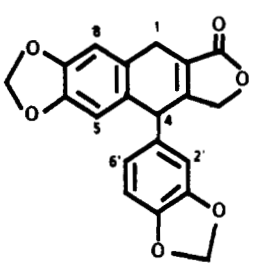

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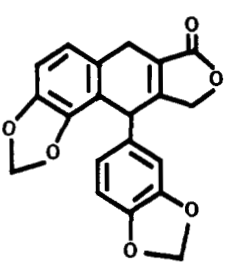

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eims *m/z* $[M]^+$ 248, 149 (100); ir (KBr) 3400, 1765 cm^{-1}. *Anal.* calcd for $C_{12}H_8O_6$, C 58.07, H 3.25; found C 57.87, H 3.50.

(3E)-*4-(3.4-Methylenedioxybenzylidine)-2.3(4H.5H)-furandione* [**7**].—A suspension of **6** (6 g, 2.4 mmol) in distilled H_2O (50 ml) was treated with $NaBH_4$ (0.11 g, 2.9 mmol). The mixture was stirred for 1.5 h, then acidified with concentrated HCl (8 ml). After 1 h, the formed precipitate was filtered off and recrystallized from iPrOH or C_6H_6 (0.37 g, 66% yield): mp 238°; ^{1}H nmr δ [$(CD_3)_2SO$] 5.53 (d, 2H, CH_2OCO), 6.15 (s, 2H, OCH_2O), 6.78–7.25 (m, 3H, ArH), 8.26 (t, 1H, -CH=C); ^{13}C nmr δ [$(CD_3)_2SO$] 68.53, 102.19, 109.19, 110.10, 125.40, 127.38, 129.02, 137.47, 148.35, 150.60, 162.11, 180.37; eims *m/z* $[M]^+$ 232, 160 (100); ir (KBr) 1788, 1718, 1630 cm^{-1}. *Anal.* calcd for $C_{12}H_8O_5$, C 62.07, H 3.47; found C 62.07, H 3.44.

*Formation of (±) 3-hydroxy-*E*-4-(3.4-methylenedioxyphenylmethylene)-3-(3.4-methylenedioxyphenylmethyl)-3.4-dihydro-2(5H)-furanone* [**8**] *and 4-{1.2-bis(3.4-methylenedioxyphenylethyl}-3-hydroxy-2(5H)-furanone* [**10**].—To a cold solution at −16° of **7** (1.16 g, 5 mmol) in dry THF (50 ml), piperonylmagnesium chloride (5 mmol) was added over a period of 10 min while stirring under an N_2 atmosphere. After 30 min the reaction mixture was heated slowly to 40° and kept there for 1 h. Then it was poured onto H_2O, acidified by 10% HCl, and extracted with $CHCl_3$. Evaporation of the dried organic phase gave a yellow oil which was chromatographed on Si gel and eluted with Et_2O-petroleum ether (2:1) to yield **8** as a waxy solid (0.57 g, 31% yield): ^{1}H nmr δ ($CDCl_3$) 3.00 (d, J=12.8 Hz, 1H), 3.18 (d, J=12.8 Hz, 1H), 3.65 (s, 1H, D_2O exchangeable), 4.31 (dd, J=2.0 and 13.6 Hz, 1H), 4.85 (dd, J=2.0 and 13.6 Hz, 1H), 5.91 (d, 2H), 5.96 (s, 2H), 6.52–6.81 (m, 7H); ^{13}C nmr δ ($CDCl_3$) 46.8, 69.2, 76.2, 77.2, 101.0, 101.3, 108.2, 108.6, 110.3,

122.9, 123.4, 126.2, 126.7, 129.0, 133.7, 147.5, 148.0, 177.8; eims *m/z* [M]$^+$ 368, 135 (100). *Anal.* calcd for $C_{20}H_{16}O_7$, C 65.21, H 4.38; found C 65.10, H 4.36. Continued column elution gave **10** as a waxy solid (0.52 g, 28% yield): ^{1}H nmr δ ($CDCl_3$) 3.09 (m, 1H), 3.30 (m, 1H), 3.79 (t, J=8 Hz, 1H), 4.40 (d, J=16.1 Hz, 1H), 4.56 (d, J=16.1 Hz, 1H), 5.91 (m, 4H), 6.54–6.76 (m, 6H), 7.44 (s, 1H D_2O exchangeable); eims *m/z* [M]$^+$ 368, 135 (100); ir (KBr) 3328, 1741 cm^{-1}. *Anal.* calcd for $C_{20}H_{16}O_7$, C 65.21, H 4.38; found C 65.18, H 4.39.

Formation of (±)-meridinol [**5**] *and (±)-epimeridinol* [**11**].—Compound **8** (78 mg, 0.2 mmol) was dissolved in EtOAc (20 ml), and 10% Pd/C (50 mg) was added. The mixture was subjected to H_2 at low pressure (40 psi) for 12 h. Filtration followed by evaporation of the organic solvent gave a yellow oil which was purified using hplc [stationary phase Si gel; mobile phase EtOAc–*n*-C_6H_{14} (1:3)] to give **11** and **5** as waxy solids. Compound **11** (60% yield): ^{1}H nmr δ ($CDCl_3$) 2.61 (m, 1H), 2.77 (s, 1H, D_2O exchangeable), 2.84–2.98 (m, 3H), 3.09 (dd, J=6.0 and 16 Hz, 1H), 3.90 (m, 1H), 4.20 (m, 1H), 5.95 (s, 4H), 6.60–6.78 (m, 6H); ^{13}C nmr δ ($CDCl_3$) 32.07, 38.11, 48.06, 69.32, 75.69, 101.06, 108.32, 108.52, 108.69, 110.63, 121.34, 123.53, 126.73, 131.43, 146.45, 147.15, 147.77, 148.02, 177.54; ir (KBr) 3542, 1778 cm^{-1}; hrms *m/z* [M]$^+$ 370.1038 (calcd for $C_{20}H_{18}O_7$, 370.1052). Compound **5** (20% yield): ^{1}H nmr δ ($CDCl_3$) 2.46–2.50 (m, 2H), 2.52 (s, 1H, D_2O exchangeable), 2.89–2.94 (m, 2H), 2.89–2.94 (m, 2H), 3.05 (d, J=13.6 Hz, 1H), 4.01–4.03 (m, 2H), 5.94 (s, 2H), 5.95 (s, 2H), 6.57–6.77 (m, 6H); eims *m/z* [M]$^+$ 370 (100); hrms *m/z* 370.1088 (calcd for $C_{20}H_{18}O_7$, 370.1052).

3-Hydroxymethyl-4-(3,4-methylenedioxyphenyl)-(6,7-methylenedioxy)-1,4-dihydronaphthalene-2-carboxylic acid lactone [**15**].—The lactone **8** (0.5 g, 1.4 mmol) was heated for 3 days under vacuum (1 torr) at 130°. The resulting gummy product was recrystallized from CCl_4 and iPrOH (39% yield): mp 227–228°; ^{1}H nmr δ ($CDCl_3$) 3.64 (m, 2H), 4.49 (dt, J=2.3 and 17.0 Hz, 1H), 4.74 (m, 2H), 5.93 (m, 4H), 6.44 (d, J=1.6 Hz, 1H), 6.49 (s, 1H), 6.63 (dd, J=1.6 and 7.9 Hz, 1H), 6.73 (s, 1H), 6.76 (d, J=7.9 Hz, 1H); ^{13}C-nmr δ ($CDCl_3$) 25.53, 45.57, 70.92, 101.23, 101.29, 108.23, 108.52, 108.81, 121.39, 123.75, 124.80, 128.18, 135.98, 147.10, 148.47, 160.20, 173.24; eims *m/z* [M]$^+$ 350; ir (KBr) 1754 cm^{-1}. *Anal.* calcd for $C_{20}H_{14}O_6$, C 68.57, H 4.03; found C 68.32, H 4.23.

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