Experimental Section

Isolation of Uvarinol (1). The preliminary steps in the purification scheme have been described previously.[2] Continued elution with 1.5 L of 16% ether in benzene and 2.0 L of 32% ether in benzene yielded a 1.15 g fraction from which 195 mg of uvarinol was obtained upon recrystallization from benzene: mp 152–4 °C, $[\alpha]^{20}_{D}$ −16.5 (*c* 1.00, acetone); *m/e* 574.195; calcd for $C_{36}H_{30}O_7$, 574.199; CD spectral data (MeOH), $[\theta]_{350}$ + 4930, $[\theta]_{316}$ + 6090, $[\theta]_{292}$ − 35 300.

Anal. Calcd for $C_{36}H_{30}O_7 \cdot C_6H_6$: C, 77.05; H, 5.58. Found: C, 77.30; H, 5.52.

X-ray Diffraction Study of Uvarinol (1). Small crystals of uvarinol (1) were obtained from slow evaporation of benzene solutions. Preliminary photographs displayed no symmetry other than that required by Friedel's law and thus indicated, when coupled with the known optical activity of uvarinol, the triclinic space group $P1$. Accurate diffractometer determined cell constants were $a = 12.190$ (4), $b = 15.116$ (4), $c = 10.835$ (4) Å, $\alpha = 109.94$ (2), $\beta = 115.31$ (2), and $\gamma = 78.81$ (2)°. We were not able to obtain an accurate density of the crystals at our disposal, but since the elemental analysis indicated one benzene per uvarinol, we assumed that the asymmetric unit contained *two* complexes of composition $C_{36}H_{30}O_7 \cdot C_6H_6$. We tried to recrystallize uvarinol from other solvents but we were only able to prepare the crystals described above. Crystallization from bromobenzene, in an attempt to introduce a heavy atom via the solvate molecule, was unsuccessful. All unique diffraction maxima with $2\theta \le 114°$ were recorded on a computer-controlled four-circle diffractometer, using graphite monochromated Cu Kα (1.54178 Å) radiation. The crystals scattered rather poorly, and of the 4572 unique reflections surveyed only 2682 (58.7%) were judged observed ($F_o^2 \ge 3\sigma(F_o^2)$) after correction for Lorentz–polarization and background effects.

Since the molecular weight of the asymmetric unit of this noncentrosymmetric crystal was in excess of 1300, and the diffraction data were limited at high 2θ values, we anticipated some difficulty in arriving at a trial structure. We were not disappointed. The angular dependence of the structure factors was eliminated as they were converted to normalized structure factors, and a multisolution weighted tangent formula approach was tried.[9] While this did not lead to anything that was interpretable, it did indicate that the chirality, as judged by intensity statistics, was very weak. We observed $\langle |E_h| \rangle_h = 0.8374$ and $\langle |E_h^2 - 1| \rangle_h = 0.9036$, while for the centrosymmetric space group $P\bar{1}$ the values 0.798 and 0.968 are predicted, and for the noncentrosymmetric space group $P1$ the related values are 0.886 and 0.736.[10] Careful inspection of the Patterson synthesis[11] showed that the two complexes in the asymmetric unit might be related by a pseudoinversion center. Following this clue, attempts were made to arrive at a trial structure, using the centrosymmetric space group $P\bar{1}$. Ultimately the following approach was successful. We had noticed in manual phasing attempts that E_{hk3n} were all very large and that E_{300} and E_{600} were strongly correlated with many E_{hk3n}. We reduced all E_{hk3n} to 60% of their calculated values and removed E_{300} and E_{600}. We then assigned signs in the centrosymmetric space group $P\bar{1}$. While the usual figures of merit did not discriminate among the resulting phase sets, a figure of merit based on negative quartets strongly indicated one solution as being reliable.[12] The resulting E synthesis showed 27 chemically sensible atoms which were expanded to 49 reasonable atoms in successive Fourier syntheses. The resulting structure was plausible in its general outlines but unacceptable in many details. The space group was changed to the noncentrosymmetric $P1$, and Fourier refinement was begun again with idealized coordinates of one molecule. Eventually all 98 nonhydrogen atoms were placed. Full-matrix least-squares refinements with isotropic temperature factors for nonhydrogen atoms and no hydrogen atoms have reached a current crystallographic residual of 0.095 for the observed reflections. In view of the limited data available, we terminated refinement at this point. The two independent molecules, excluding C(2) and its attached phenyl ring, are closely related by an inversion center. Additional crystallographic details can be found in the Supplementary Material.

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Registry No. 1, 66754-55-0.

Supplementary Material Available: Tables I–III listing fractional coordinates, temperature factors, bond distances, and bond angles for uvarinol (8 pages). Ordering information is given on any current masthead page.

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Synthesis of (±)-Machicendiol

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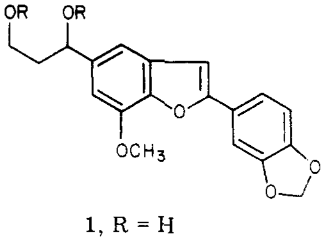
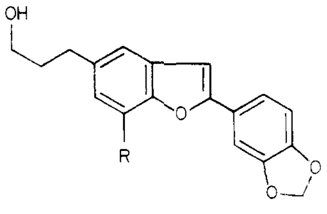
Extracts of *Machilus glaucescens* (Lauraceae) have been used in the treatment of asthma, rheumatism, and ulcers; from the leaves, there has recently been isolated a norlignan, named machicendiol, for which the structure 2-(3,4-methylenedioxyphenyl)-5-(1,3-dihydroxypropyl)-7-methoxybenzofuran (1) was suggested on the basis of spectral data and a partial synthesis from egonol (2).[1] We have recently described syntheses[2] of the congeners egonol



1, R = H
8, R = $COCH_3$



2, R = OCH_3
3, R = H

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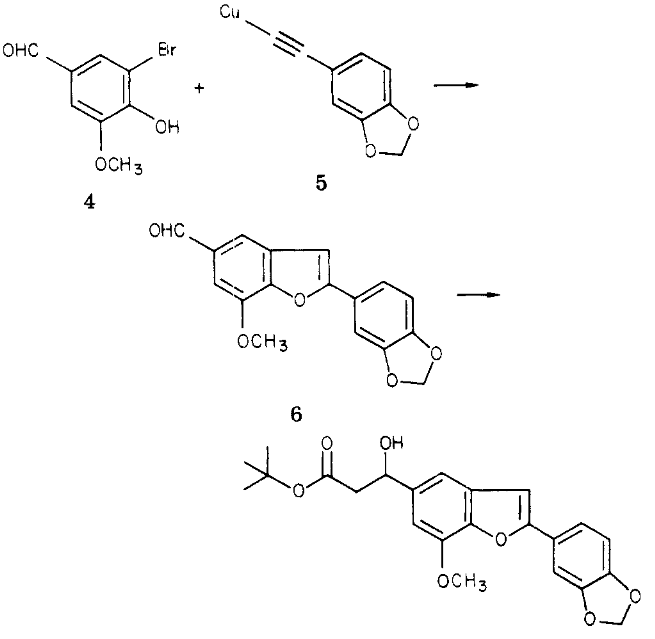
and homoegonol (3) and now report an adaptation of these procedures to a simple synthesis of (±)-machicendiol.

By heating the readily available reactants, 5-bromovanillin (4)[3] and cuprous 3,4-methylenedioxyphenylacetylide (5)[2] in pyridine solution, the required intermediate arylbenzofuranaldehyde (6) was obtained without difficulty. By Rathke's variation of the Reformatsky procedure,[4,5] 6 reacted with *tert*-butyl lithioacetate to afford in good yield the β-hydroxy ester 7. Conversion of 7 to machicendiol (1) was effected by lithium aluminum hydride reduction, and the diol was characterized as the diacetate derivative 8. Identification was confirmed by comparison with solution spectra (NMR, IR, UV) of (−)-machicendiol. The melting point (148–149 °C) given for our synthetic specimen of (±)-machicendiol is notably higher than that previously reported (mp 127 °C) for a specimen obtained from the optically inactive egonol.[1] We attribute this to dimorphism, since the spectra in solution were identical. Furthermore, a (±) form of machicendiol with mp 147 °C and identical spectra has subsequently been isolated by extraction of plant material.[7]



Experimental Section

NMR spectra were determined for solutions in [^{2}H]chloroform (unless otherwise stated) with tetramethylsilane as internal standard, using a Bruker FT 90 MHz instrument.

7-Methoxy-2-(3,4-methylenedioxyphenyl)benzofuran-7-carbaldehyde (6). A solution of 5-bromovanillin (1.22 g) in pyridine (25 mL) was added with stirring to a solution of cuprous 3,4-methylenedioxyphenylacetylide (1.02 g) in the same solvent (40 mL) under nitrogen. The mixture was stirred for 10 min and heated under reflux for 22 h. It was then cooled and diluted with ether (200 mL), and the organic phase was washed successively with brine (100 mL), hydrochloric acid solution (1 N, 3 × 100 mL), and saturated sodium carbonate solution (3 × 50 mL). Evaporation of the dried ($MgSO_4$) extract gave a residue which was dissolved in benzene (ca. 5 mL) and filtered through a column (8 × 2 cm diameter) of alumina. Crystallization from chloroform–methanol gave the benzofuran aldehyde 6 as needles (307 mg): mp 179–180.5 °C; *m/e* 296 (M^+), 267 (M − CHO); NMR δ 4.08 (s, OMe), 6.02 (s, OCH_2O), 6.88 (d, *J* = 8 Hz, H-5′), 6.93 (s, H-3), 7.33 (d, *J* = 2 Hz, H-6), 7.34 (d, *J* = 2 Hz, H-2′), 7.42 (dd, *J* = 8, 2 Hz, H-6′), 7.67 (d, *J* = 2 Hz, H-4), and 9.99 (s, CHO).

Anal. Calcd for $C_{17}H_{12}O_5$: C, 68.91, H, 4.08. Found: C, 68.91; H, 4.32.

***tert*-Butyl 3-Hydroxy-3-[7-methoxy-2-(3,4-methylenedioxyphenyl)benzofuran-5-yl]propanoate (7).** A solution of the aldehyde 6 (159 mg) in tetrahydrofuran (10 mL) was added dropwise over 5 min to a stirred solution of *tert*-butyl lithioacetate[5] (ca. 1.5 mmol) in the same solvent (2.25 mL) at −78 °C under N_2. The mixture was stirred for a further 5 min, and then hydrochloric acid solution (1 N, 5 mL) was added. After the hydrolyzed mixture was allowed to reach room temperature, the organic phase was separated and washed successively with sodium bicarbonate solution, brine, and water. The dried ($MgSO_4$) extract on evaporation yielded a yellow oil, which crystallized from ethyl acetate–light petroleum to yield the ester 7 as rosettes of needles (143 mg): mp 113.5–115 °C; NMR δ 1.42 (s, CMe_3), 2.68 and 2.69 (overlapping d, *J* = 5.5, 7.5 Hz, $-CH_2-$), 3.58 (br, OH), 4.01 (s, OMe), 5.13 (overlapping dd, *J* = ca. 5.5, 7.1 Hz, ArCH), 5.97 (s, OCH_2O), 6.76 (s, H-3), 6.80 (d, *J* = 2 Hz, H-6), 6.85 (d, *J* = 6 Hz, H-5′), 7.08 (d, *J* = 2 Hz, H-4), 7.31 (d, *J* = 2 Hz, H-2′), and 7.40 (dd, *J* = 2, 6 Hz, H-6′).

Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 67.31; H, 6.04.

2-(3,4-Methylenedioxyphenyl)-5-(1,3-dihydroxypropyl)-7-methoxybenzofuran (1). To lithium aluminum hydride (170 mg) in diethyl ether (5 mL) was added a solution of the ester 7 (135 mg) in the same solvent (50 mL) dropwise over 5 min. The mixture was then refluxed for 1 h and cooled; excess reagent was destroyed by addition of ethyl acetate and water. The decanted ether phase was dried ($MgSO_4$) and evaporated, and the residue was crystallized from ethyl acetate–light petroleum to give the product (±)-machicendiol (1) as prisms (47 mg): mp 148–149 °C (lit. for machicendiol, (−) form, mp 127 °C; lit. for (±) form, mp 127 °C[1] and 147 °C[7]); NMR δ [$(CD_3)_2SO$][8] 1.75 (m, appears as 4 lines, *J* = 6 Hz, $2CH_2$), 3.49 (m, $3CH_2OH$), 3.96 (s, OMe), 4.42 (t, *J* = 5 Hz, 3 CH_2OH), 4.74 (m, ArCH), 5.17 (d, *J* = 5 Hz, ArCHOH), 6.09 (s, $-OCH_2O-$), 6.88 (d, *J* = 1 Hz, H-6), 7.03 (d, *J* = 6 Hz, H-5′), 7.11 (d, *J* = 1 Hz, H-4), 7.25 (s, H-3), 7.40 (dd, *J* = 6, 1.5 Hz, H-6′), and 7.44 (d, *J* = 1.5 Hz, H-2′).

Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.93; H, 5.16.

Machicendiol Diacetate (8). Acetic anhydride (2 mL) was added to a solution of machicendiol (1) (128 mg) in pyridine (2 mL); the mixture was stirred at room temperature overnight and then worked up in the usual way. Recrystallization (three times) of the product from methanol yielded the diacetate as prisms: mp 100–101 °C; NMR δ 2.05 (s, OAc), 2.09 (s, OAc), 2.24 (m, $-CH_2-$), 4.06 (s, OMe), 4.09 (t, *J* = ca. 4 Hz, $3CH_2OAc$), 5.92 (t, *J* = ca. 4 Hz, ArCHOAc), 6.01 (s, $-OCH_2O-$), 6.76 (d, *J* = 2 Hz, H-6), 6.80 (s, H-3), 6.86 (d, *J* = 9 Hz, H-5′), 7.14 (d, *J* = 2 Hz, H-4), 7.32 (d, *J* = 2 Hz, H-2′), and 7.40 (dd, *J* = 2, 9 Hz, H-6′).

Anal. Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.63; H, 5.32.

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Registry No. (±)-1, 62306-76-7; 4, 2973-76-4; 5, 58335-53-8; 6, 71798-63-5; (±)-7, 71798-64-6; (±)-8, 62357-40-8; *tert*-butyl lithioacetate, 41850-36-6.

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(6) These spectra were kindly provided by Professor S. K. Talapatra and Dr. Bani Talapatra.

(7) Private communication from Dr. Talapatra.

(8) Comparison of this spectrum with a copy generously provided by the original authors confirmed the identity. We have however interchanged the H-3 and H-4 assignments made in the earlier work.[1] The H-3 signal is a singlet and the H-4 signal a doublet showing meta coupling as expected with H-6. The chemical shift of the H-3 proton (δ 7.25 in Me_2SO) of machicendiol is notably further downfield than the values found[2] for analogues in $CDCl_3$. This shift is solvent related. In $CDCl_3$, the machicendiol H-3 signal is reported[1b] at δ 6.81, i.e., $\Delta(Me_2SO-CDCl_3)$ 0.44. We have also determined the NMR spectra of machicendiol diacetate (8) and egonol (2) in Me_2SO and find corresponding downfield shifts of 0.47 and 0.48, respectively.