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TOTAL SYNTHESES OF ISODIHYDROFUTOQUINOL A, FUTOQUINOL, AND ISOFUTOQUINOL A AND B

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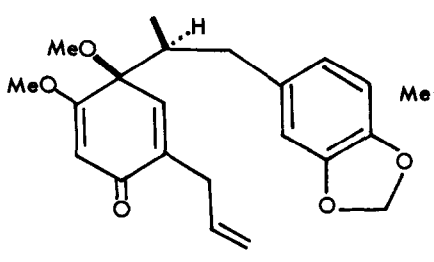
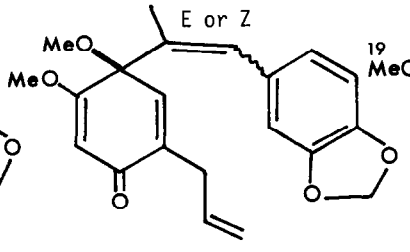
Summary: Isodihydrofutoquinol A has been synthesized starting from 4-benzyloxy-2-methoxyacetophenone, wherein the 2,5-cyclohexadienone moiety has been constructed efficiently by means of electrochemical method. Isodihydrofutoquinol A has been further converted into isofutoquinol A and B through futoquinol. In addition, the stereostructure of isofutoquinol A has been unambiguously determined on the basis of an X-ray crystallographic analysis.

From view point of biological and physiological activities, a number of neolignans with antitumor activity, antifeedant activity against insects and others are attracting increasing attention. In connection with these neolignans, we have synthesized several asatone-type neolignans,[1] denudatins, futoenone and related ones.[2] In the present paper, we wish to describe total syntheses of isodihydrofutoquinol A (1),[3] futoquinol (2),[4] and isofutoquinol A and B (3 and 4)[3] with antifeedant activity against insects, which have been isolated from the leaves of Piper futokadzura Sieb. et Zucc. Particularly, the stereostructure of isofutoquinol A (3) has been determined by means of an X-ray crystallographic analysis. In addition, the stereostructure of isodihydrofutoquinol A, which remains unsettled, is also represented by 1, as discussed later.

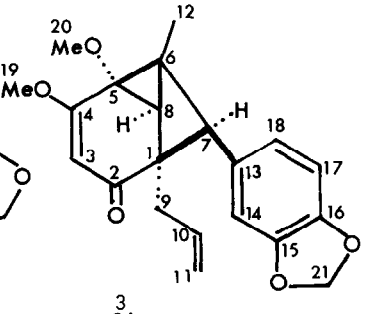
4-Benzyloxy-2-methoxyacetophenone[5] reacted with the thioketal of piperonal in the presence of Bu^nLi in THF under argon (-70 - -20 °C, 1 h) to afford the corresponding condensation



1

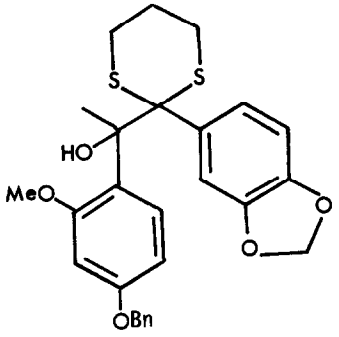


2 (E)
4 (Z)



3

product (5),[6] in 93% yield, which was then treated with excess Raney Ni (W-4) in dioxane (refluxing temp., 20 h) to give rise to a phenol (6),[6] in 78% yield. Furthermore, this compound (6) was readily converted into a desired 2-allylphenol (9),[6] in 2 steps [1) allyl bromide (1 equiv.) - K_2CO_3 (1.5 equiv.)/acetone (refluxing temp., 11 h) (85% yield); 2) 125 °C, 4 h under argon (62% yield)]. After attempted oxidative methoxylation of 7 using TTN, DDQ and others in MeOH, we could succeed in the synthesis of isodihydrofutoquinol A



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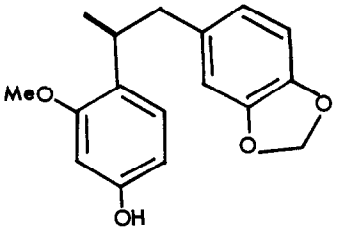

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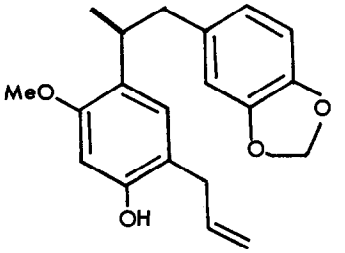

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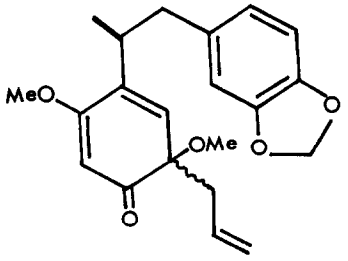

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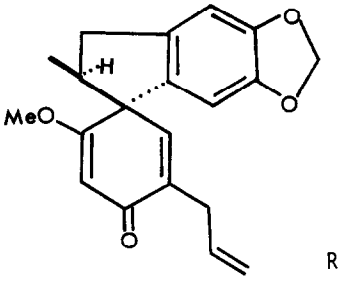

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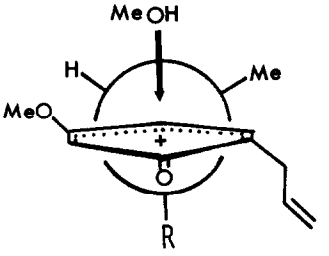

R : 3,4-methylenedioxybenzyl

[A]

(1) by means of electrochemical method: when electrolyzed at a constant current [10 mA (+900 - 1090 mV vs. SCE); ca. 1.8 F/mol][7] in THF - MeOH (1 : 1), the phenol (7) was converted into isodihydrofutoquinol A (1),[8] a dienone (8),[6,9] and a spiro compound (9),[6] in 51, 15, and 2.3% yields, respectively. However, any amount of isodihydrofutoquinol B[3] could not be detected. As seen in [A],[10] clearly, the electrogenerated cation [A] is expected to be attacked by the solvent molecule (MeOH) from the upside, resulting in the formation of 1 selectively.

Isodihydrofutoquinol A (1) so far obtained was oxidized with DDQ (1.7 equiv.) in benzene under argon (refluxing temp., 1 day) to afford futoquinol (2),[11] in 72% yield. In this case, DDQ oxidation was superior to electrochemical one. Finally, futoquinol (2) was subjected to photochemical reaction in hexane using a high pressure Hg lamp (100 W) (room temp., 18 h) giving rise to isofutoquinol A and B[12] (3 and 4) in 67 and 16% yields, respectively. The synthetic sample of the former was completely identical with natural isofutoquinol A (3) in all respects (mixed melting point, IR and ^{1}H NMR spectra). Finally,

the stereostructure of isofutoquinol A (3) was unambiguously determined by means of an X-ray crystallographic analysis, as follows.

CRTSTAL DATA: $C_{21}H_{22}O_5$, MW 354.4, triclinic, $P\bar{1}$, a = 9.653(2), b = 12.474(2), c = 8.182(1) Å, α = 91.30(2), β = 97.79(1), γ = 109.15(1)°, Z = 2, V = 919.8(3) Å^3, D_x = 1.28, D_m = 1.26 g·cm^{-3}, μ(Mo K$_\alpha$) = 0.085 mm^{-1}.

The X-ray intensities up to 2θ = 55° were measured on a Rigaku AFC-5 four-circle diffractometer with graphite-monochromatized Mo K$_\alpha$ radiation. The structure was solved by direct methods and refined by block-diagonal least squares. All the hydrogen atoms were found from difference synthesis. Final R was 0.04 for 2336 unique reflections.[13] An ORTEP drawing is shown in Fig. 1.[14] The C(1)-C(7) bond distance is 1.606(3) Å, longer by 0.08 Å than the other C-C bonds in the cyclobutane ring. This may be due to a strain in a 3-4-6 fused ring structure.

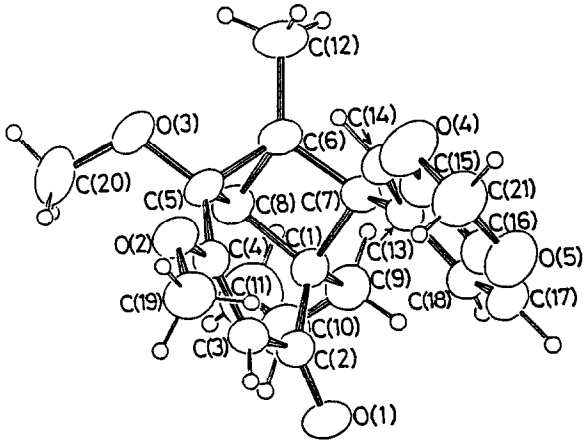

Fig. 1 A computer generated ORTEP drawing of the molecule 3.

The authors wish to thank Dr. K. Matsui (Ohtsuka Pharmaceutical Co. Ltd.) for the authentic samples of futoquinol and isofutoquinol A as well as for the IR and ^{1}H NMR spectra of isofutoqinol B. They are also indebted to the Asahi Glass Foundation for Industrial Technology for financial support.

REFERENCES AND NOTES

1. A. Nishiyama, H. Eto, Y. Terada, M. Iguchi, and S. Yamamura, Chem. Pharm. Bull., 31, 2820 (1983).
2. Y. Shizuri and S. Yamamura, Tetrahedron Lett., 24, 5011 (1983).
3. K. Matsui and K. Munakata, Tetrahedron Lett., 1976, 4371.
4. S. Takahashi and A. Ogiso, Chem. Pharm. Bull., 18, 100 (1970).
5. L. Jurd and L. A. Rolle, J. Am. Chem. Soc., 80, 5527 (1958).
6. The spectral data for the new compounds were in accord with the structures assigned, and only selected data are cited: 5: mp 179 - 181 °C; $C_{27}H_{28}O_5S_2$ [m/z 478.1261(M^+ - 18)]; IR (film) 3480 cm^{-1}; δ($CDCl_3$) 1.97(3H, s), 3.30(3H, s), 5.00(2H, s), 5.46(1H, br.s, OH), and 5.90(2H, s). 6 as a colorless oil: $C_{17}H_{18}O_4$ [m/z 286.1195(M^+)]; IR (film) 3400 cm^{-1};

δ ($CDCl_3$) 1.12(3H, d, J= 6.5Hz), 2.48(1H, dd, J= 13, 9Hz), 2.83(1H, dd, J= 13, 6Hz), 3.28(1H, m), 3.70(3H, s), and 5.82(2H, s). 7: mp 74 - 75 °C; $C_{20}H_{22}O_4$ [m/z 326.1508 (M^+)]; δ ($CDCl_3$) 3.30(2H, br.d, J= 6.5Hz), 4.9 - 5.2(2H, complex, overlapped with OH signal), 5.8 - 6.25(1H, m), 6.34(1H, s), 6.45 - 6.7(3H, complex), and 6.82(1H, s). 8 as a colorless oil: $C_{21}H_{24}O_5$ [m/z 356.1639(M^+)]; IR (film) 1655, 1645sh., 1565, 1500sh., and 1485 cm^{-1}; δ ($CDCl_3$) 1.10(3H, d, J= 6.5Hz), 2.37(2H, d, J= 7Hz), 2.4 - 3.2(3H, complex), 2.98(3H, s), 3.2 - 3.5(1H, m), 3.78(3H, s), 4.95(1H, br.d, J= 15.5Hz), 4.98 (1H, br.d, J= 10Hz), 5.3 - 5.7(1H, m), 5.88(2H, s), 6.01(1H, s), and 6.5 - 6.7(3H, complex). 9 as a colorless oil: $C_{20}H_{20}O_4$ [m/z 324.1348(M^+)]; IR (film) 1655, 1625, 1600, 1500, and 1475 cm^{-1}; δ ($CDCl_3$) 0.94(3H, d, J= 7Hz), 2.65 - 3.25(5H, complex), 3.68 (3H, s), 4.85 - 5.15(2H, m), 5.80(1H, s), 5.89(2H, s), 5.5 - 6.0(1H, m, overlapped with 3 protons), 6.25(2H, br.s), and 6.71(1H, s).

7. A glassy carbon beaker and a platinum wire tip were used as an anode and a cathode, respectively.
8. The IR and ^1H NMR spectral data of the synthetic compound were completely identical with those of natural isodihydrofutoquinol A cited in ref. 3.
9. Another stereoisomer of 9 has been also obtained as a minor product (~1% yield).
10. The most favorable conformation of the electrogenerated cation must be depicted as [A] on the basis of the same reason as discussed in the following reference: G. J. McGarvey and J. M. Williams, J. Am. Chem. Soc., 107, 1435 (1985).
11. The synthetic dienone was identical with an authentic sample of futoquinol in all respects (mass, IR and ^1H NMR spectra).
12. The synthetic compound was proved to be identical with isofutoquinol B by direct comparison of their IR and ^1H NMR spectra.
13. Full details of X-ray crystal structure determination will be published separately.
14. Tables of atomic parameters, bond lengths and bond angles have been deposited with the Cambridge Crystallographic Data Centre.

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