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SYNTHESIS OF EURYFURAN, VALDIVIOLIDE, AND CONFERTIFOLIN

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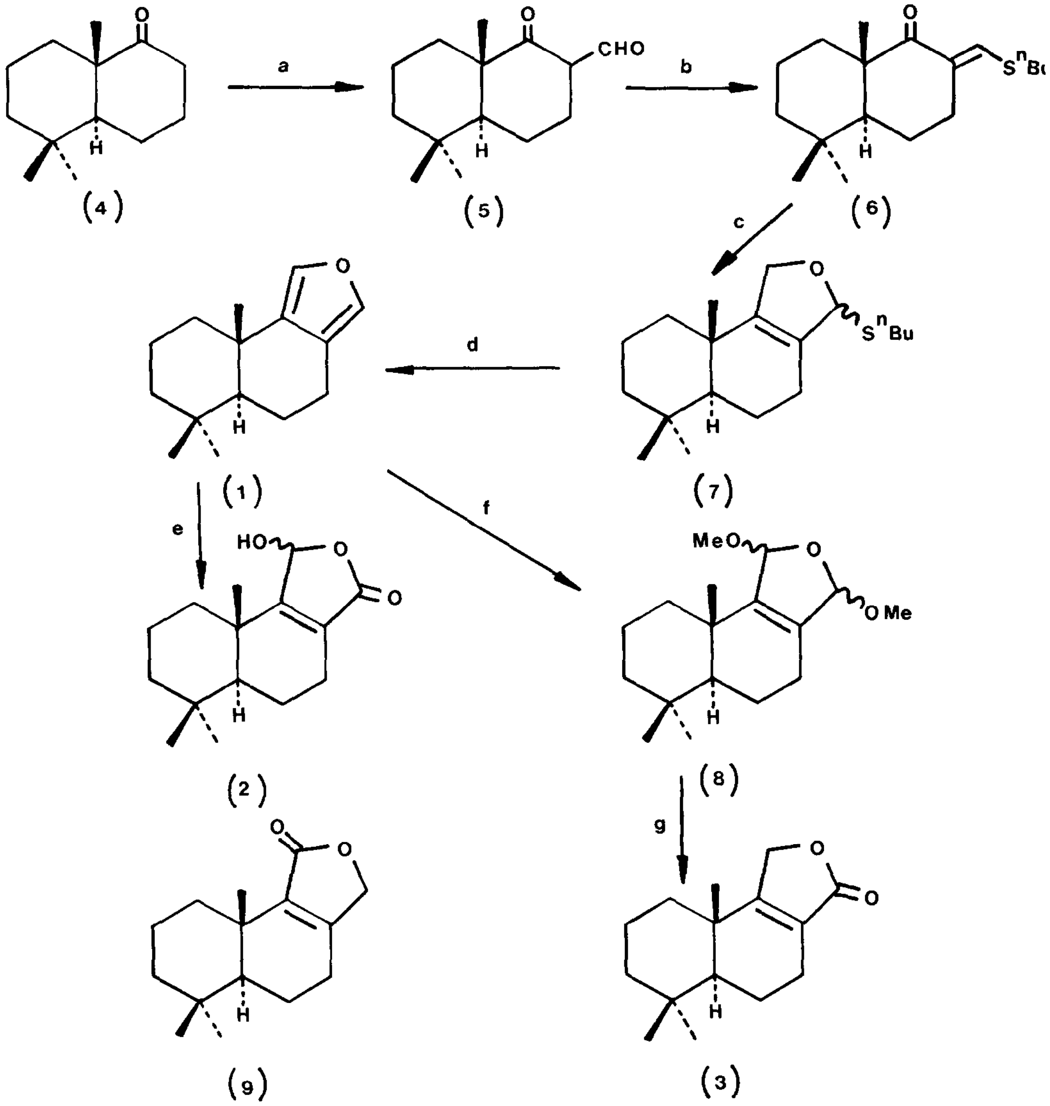
SUMMARY: Starting from 5,5,9-trimethyl-*trans*-1-decalone (4), short and highly efficient syntheses of three drimane natural products, euryfuran (1), valdiviolide (2), and confertifolin (3) have been developed

The biological activity associated with a number of drimane natural products has stimulated considerable recent interest in their synthesis[1]. Here, we report the preparation of euryfuran (1) and show how this molecule can also be used as a precursor for two other natural compounds (2) and (3).

The *trans*-decalone (4)[2] was formylated in the usual way with ethylformate/NaH to give (5)[1e,f,3] after 12 h at room temperature. This compound was subsequently converted to the n-butylthiomethylene derivative (6), m.p. 60-62°C, in 85% overall yield from (4). Treatment of (6) with trimethylsulphonium methylide in dimethoxyethane at -78°C gave the dihydrofuran (7)[4] (*via* rearrangement of the intermediate epoxide) which on standing (35°C, 12 h),or brief treatment with $HgSO_4$, gave euryfuran (1) directly in 70% yield as an oil after flash chromatography. The high field (250 MHz) ^{1}H n.m.r. spectrum of (1) was identical in all respects to the natural product which has been recently isolated from a number of marine sources[1k,5,9,†].

Photooxygenation of (1) in the presence of 2,6-lutidine[6] gave valdiviolide (2), m.p 160-168°C, as a 2.1 mixture of 11α:11β hydroxy isomers in 90% yield. The authentic natural material, isolated from *Drimys winteri*[7‡], was shown to have specifically the 11α configuration. The formation of (2) from (1) was expected on mechanistic grounds in that the initial attack of singlet oxygen should lead predominantly to the α-endoperoxide, by addition to the least hindered face, which then, on removal of the more exposed methine proton at C-12, collapses to (2).



(a) HCO$_2$Et, NaH, benzene, RT, 12 h; (b) nBuSH, *p*TSA, benzene, 2h, Δ, (c) $(CH_3)_2\overset{+}{S}-\overset{-}{C}H_2$, $-78^{\circ}C$, 10 min; (d) $35^{\circ}C$, 12 h or HgSO$_4$, 1 eq, DME, RT, 10 min, (e) O$_2$, hν, eosin, $25^{\circ}C$, 4h, 300 watt quartz iodine lamp, ^{t}BuOH : 2,6-lutidine, 2 : 1; (f) Br$_2$, MeOH, $0^{\circ}C$, 30 min; (g) 10% HCl in acetone, RT, 30 min.

Oxidation of euryfuran (1) with bromine in methanol gave (8) in 92% yield as a mixture of all possible isomers. Treatment of (8) with 10% hydrochloric acid gave confertifolin (3), m p. 120-123°C, in 75% yield, again identical to the natural product[8‡]. Also isolated from this reaction was a small amount (10%) of the other regioisomer, i.e. isodrimenin (9). The formation of (3) from (8) is rationalised as a facile 1,4-elimination of methanol *via* loss of the more accessible proton and sterically more congested methoxyl group. Further reactions of (1) will be reported in full at a later date.

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REFERENCES

1. S.P. Tanis and K. Nakanishi, J. Am. Chem. Soc., 1979, 101, 4398; (b) A. Ohsuka and A. Matsukawa, Chem. Lett., 1979, 635, (c) T. Nakata, H. Akita, T. Naito, and T. Oishi, J. Am. Chem. Soc., 1979, 101, 4400; (d) A Kimura and S. Isoe, 22nd Symposium on the Chemistry of Natural Products, Fukuoka 1979, 198; (e) A.S. Kende and T J. Blacklock, Tetrahedron Lett., 1980, 3119; (f) D.J. Goldsmith and H.S. Kezar III, Tetrahedron Lett., 1980, 3543; (g) S.C. Howell, S.V. Ley, M. Mahon, and P.A. Worthington, J. Chem. Soc. Chem. Commun., 1981, 507; (h) M. Jallali-Naini, G. Boussac, P. Lemaitre, M. Larcheveque, D. Guillerm, and J-Y. Lallemand, Tetrahedron Lett., 1981, 2995; (i) L.P.J. Burton and J.D. White, J. Am. Chem. Soc., 1981, 103, 3226; (j) S.V. Ley and M. Mahon, Tetrahedron Lett , 1981, in press; (k) H. Akita, T. Naito, and T Oishi, Chem. Lett., 1979, 1365, (l) T. Naito, T. Nakata, H. Akita, and T. Oishi, Chem. Lett., 1980, 445.

2 D.L Snitman, M-Y. Tsai, D.S. Watt, C.L. Edwards, and P.L. Stotter, J Org Chem., 1979, 44, 2838

3. N. Ototani, T. Kato, and Y. Kitahara, Bull. Chem. Soc. Jap., 1967, 40, 1730

4. M.E. Garst and T.A. Spencer, J. Am. Chem. Soc., 1973, 95, 250.

5. (a) M.S. Henderson, R McCrindle, and D. McMaster, Can. J. Chem., 1973, 51, 1346; (b) Y. Asakawa and T. Takemoto, Experientia, 1979, 35, 1420; (c) T. Nakano and M.A. Maillo , Syn. Commun., 1981, 11, 463.

6. E.J. Corey, D.N. Crouse, and J.E. Anderson, J. Org. Chem., 1975, 40, 2140.

7. H.H. Appel, R.P.M. Bond, and K.H. Overton, Tetrahedron, 1963, 19, 635.

8. H.H. Appel, J.D. Connolly, K.H. Overton, and R.P.M. Bond, J. Chem. Soc., 1960, 4685

9. G. Cimino, S. De Rosa, S. De Stefano, and G. Sodano, Tetrahedron Lett., 1981, 1271.

NOTES

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250 MHz ^{1}H n.m.r. ($CDCl_3$)

Euryfuran: 0.91 (3H, s), 0.94 (3H, s), 1.21 (3H, s), 1.2-2.0 (9H, m), 2.5 (1H,dddd, J 2, 7. 11.5, and 16 Hz), 2.77 (1H, dddd, J 1, 1.5, 6.5, and 16 Hz), 7.05 (1H, dd, J 2,2 Hz), 7.07 (1H, d, J 2 Hz).

Valdiviolide: 0.91 (3H, s), 0.92 (3H, s), 1.25 (3H, s), 1.1-2.0 (9H, m), 2.13 (1H, m), 2.38 (1H, m), 3.95 (1H, brs -OH), 6.09 (1H, m).

Confertifolin: 0.92 (3H, s), 0.96 (3H, s), 1.17 (3H, s), 1.1-2.0 (9H, m), 2.15 (1H, m), 2.4 (1H, m), 4.65 (1H, ddd, J 2, 3.5, and 17.5 Hz), 4.75 (1H, ddd, J 3, 3, and 17.5 Hz).

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