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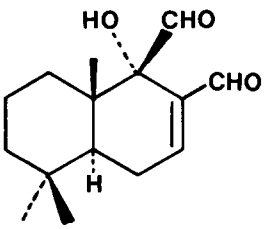
SYNTHESIS OF (±)WARBURGANAL

By Steven V. Ley* and Michael Mahon

(Department of Chemistry, Imperial College, London SW7 2AY.)

SUMMARY: From readily available starting materials a short stereospecific synthesis of the biologically active molecule warburganal (1) has been achieved in 20% overall yield.

Since its isolation in 1976[1] warburganal (1) has been shown to possess a wide spectrum of biological activity including insect antifeeding, plant growth regulation, cytotoxic, antimicrobial, molluscicidal, and anticomplemental properties. For these reasons its synthesis has attracted considerable attention[2].



(1)

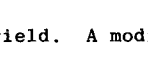
However, the syntheses reported so far are either excessively long, require the extensive use of protecting groups or make use of starting materials which are not readily available.

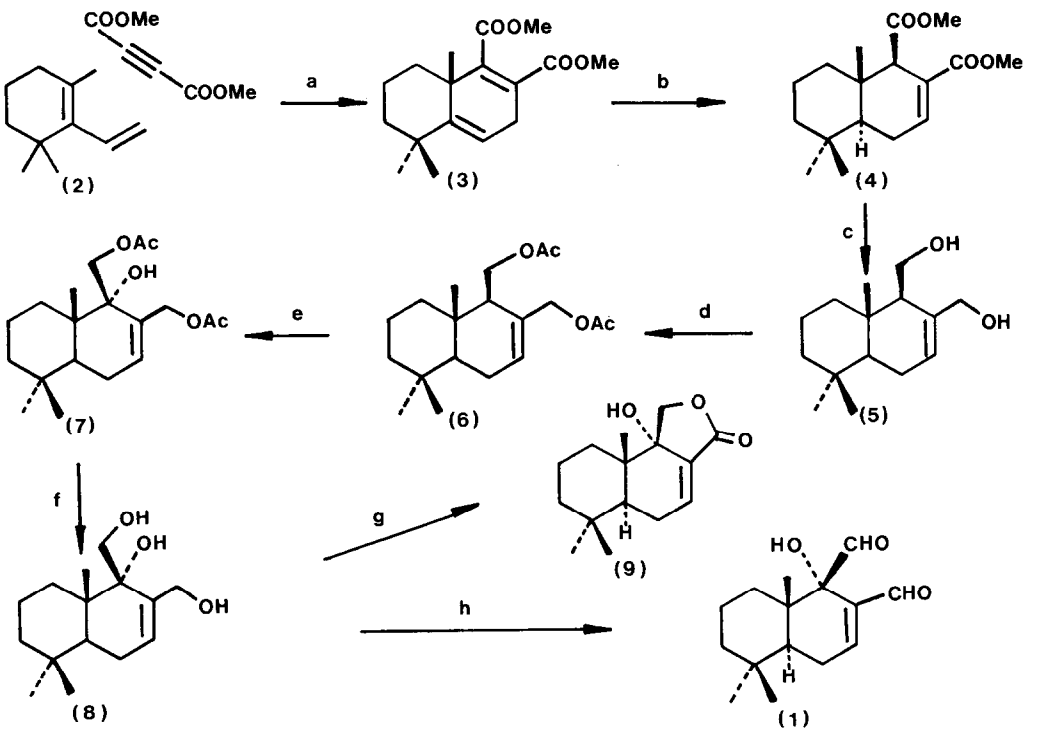
We recently reported[3] a short highly efficient preparation of two other drimane related natural products, polygodial and cinnamolide, and now show that this route can also be applied to warburganal synthesis.

Diels Alder reaction of dimethyl acetylene dicarboxylate with the easily prepared diene (2) gave (3) in 95% yield on a 100 g scale. This adduct was reductively rearranged directly to the diester (4) and converted to the diol (5) in 75% yield as before[3]. This diol now forms the starting point for the present warburganal synthesis.

Quantitative diacetylation of (5) produced (6)† which was then regio- and stereoselectively oxidised by SeO_2 in dioxan at reflux to the desired angular hydroxy diacetate (7) which

was isolated as an oil in 65% yield. Quantitative deprotection of (7) using K_2CO_3/methanol gave the triol (8) m.p. 140-141°C. With this compound to hand, its oxidation by a variety of methods was subsequently studied.

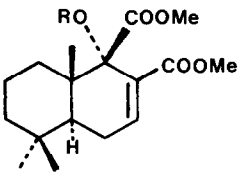
Oxidation of (8) by the Fetizon reagent[4] gave 9-hydroxy-cinnamolide (9), m.p. 175-178°, in excellent yield (98%). However, direct oxidation to warburganal (1) using a number of activated dimethylsulphoxide methods[5] gave variable results. The best procedure was found to be D.M.S.O./trifluoroacetic anhydride[6] which gave (1), identical by n.m.r., t.l.c. and i.r. to the natural product,† in 45% yield. A modified Corey-Kim reagent,  , has been reported[2d] to achieve this transformation but was less successful in our hands. The overall yield to warburganal at this point is 20% from (2) which is an improvement over existing routes.[2]



SCHEME

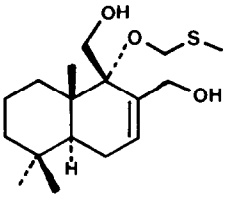
(a) 110°, 22h; (b) H_2, 1 atmos, 10% PdC, dil MeOH, trace H^+; (c) $LiAlH_4$; (d) Ac_2O/Py, RT, 12h; (e) SeO_2, 1.2 eq., dioxan, reflux 1 h; (f) K_2CO_3/MeOH, RT, 10 min; (g) Ag_2CO_3/celite, 5 eq., benzene reflux 20 min; (h) D.M.S.O./T.F.A.A. 6 eq., 0.5h, -50°C then Et_3N 10 eq., -50°C to RT.

In an effort to improve the overall yield of (1), it was attempted to protect the labile tertiary hydroxyl group in (7). However, methylthiomethyl ether[7] formation prior to oxidation failed, although similar protection ($DMSO/Ac_2O$, RT, 120 h) of the hydroxy diester (10) (m.p. 138-140°C) which was prepared in 95% yield by enolate hydroxylation of (4) (LDA, THF, -78° then MoOPH,[8] -78°C to RT), gave (11) in 97% yield (m.p. 126-127°C). Unfortunately all attempts to reduce (11) (or 10) to the protected triol (12) led to the rearranged diol (13)[9] (m.p. 123-124°C).

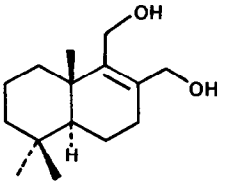


(10) R = H

(11) R = CH_2SCH_3

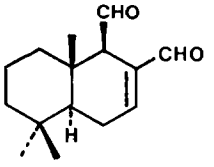


(12)

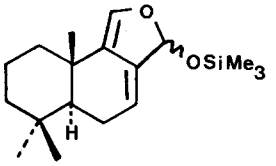


(13)

Finally, we have investigated various possibilities for direct oxidation of polygodial (14) to (1). For example, treatment of the enolate of (14) with MoOPH or O_2 gave only recovered polygodial upon work-up. The lack of reactivity of this enolate must be due to it being present in a cyclized form, i.e. as the lactenolate. In accord with this proposal, work-up of the enolate by treatment with trimethylsilyl chloride gave (15) quantitatively.



(14)



(15)

Attempted conversion of (15) via mCPBA oxidation and treatment with Bu_4NF also failed to provide (1).

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† All new compounds were characterised by spectroscopic methods, acc. mass and/or microanalysis.

‡ We thank Professor I. Kubo, University of California, for a generous sample of the authentic material.

Compound (7) δ after D_2O exch 0.82 (3H, s), 0.91 (3H, s), 0.93 (3H, s), 1.73 (1H, dd, J 5, 12 Hz), 1.91 (1H, dd, J 2, 12, 18 Hz), 2.13 (1H, ddd, J 5, 6, 18 Hz), 3.72 (1H, d, J 11.5 Hz), 3.78 (1H, d, J 11.5 Hz), 4.12 (1H, d, J 12 Hz), 4.31 (1H, d, J 12 Hz), and 5.90 (1H, dd, J 2, 5 Hz).

Compound (9) δ 0.91 (3H, s), 0.97 (3H, s), 0.99 (3H, s), 1.86 (1H, dd, J 5.5, 12 Hz), 2.15 (1H, ddd, J 3.5, 12, 20.5 Hz), 2.45 (1H, ddd, J 5, 5.5, 20.5 Hz), 2.17 (1H, d, J 0.75 Hz -OH), 4.23 (1H, d, J 10 Hz), 4.37 (1H, dd, J 0.75, 10 Hz), and 7.04 (1H, dd, J 3.5, 5 Hz).

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