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SYNTHETIC AND STEREOCHEMICAL STUDIES RELATED TO TRANS-CLERODANE DITERPENOIDS AND CONGENERS

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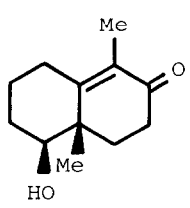
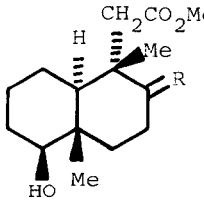
Summary: *Synthesis of a key trans-clerodane diterpenoid intermediate 6, which is also a degradation product of ilimaquinone, is described. In view of a discrepancy in our earlier work on correlation of the stereochemistry of keto-ester (5), with that of avarol, the present studies have also been useful in re-establishing our previous conclusions.*

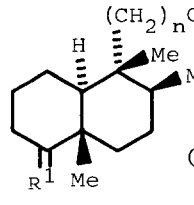
Recently we reported[1] a total synthesis of avarol based on a flexible methodology of potential applicability to structural analogues. The utility of this approach to the synthesis of a key trans-clerodane diterpenoid intermediate 6, which is also a degradation product of ilimaquinone, is presently described. Further, during our synthesis of avarol, one of the intermediates was transformed to the keto-ester (5) with a view to defining the stereochemistry of the secondary methyl function in that series. This was based on our mistaken assumption that ester (5) is a degradation product of ilimaquinone[2]. However it is evident from a recent publication[3] that the above degradation product is not 5 but a higher homologue 7, and further that ilimaquinone can be oxidised to olefinic esters (6) and (8). The present synthesis of 6 has also been useful in providing an alternative evidence for our earlier conclusions on the stereochemistry of avarol and its intermediates.



(1)



(2): R=O
(3): R=CH_2
(4a): R=βMe; αH
(4b): R=αMe; βH



(5): R^1=O; R^2=Me; n=1
(6): R^1=CH_2; R^2=Me; n=1
(6a): R^1=CH_2; R^2=H; n=1
(7): R^1=O; R^2=Me; n=2
(8): R^1=CH_2; R^2=Me; n=2

The hydroxy enone (1) was subjected to reductive alkylation according to our earlier procedure[1], by treatment of 1 with lithium (Ca.4 g atoms) in liq. NH_3 (distilled over lithium) and then reacting the resulting enolate with ethyl bromoacetate. There was vigorous reaction during the rapid addition of this alkylating agent also (cf. our Experimental[1]). The resulting product was hydrolysed, re-esterified (CH_2N_2) and then purified by extensive column chromatography (silica gel) to afford methyl ester (2)[4], in about 50% yield. Wittig olefination of 2 with methylenetriphenylphosphorane ($NaH/DMSO/Ph_3\overset{+}{P}CH_3I^-$) under the conditions employed earlier[1] led mostly to undesired products, evidently due to the presence of the ester function. Several variations in the experimental conditions (temperature and time of reaction) failed to provide 3 in an appreciable yield. However, 3 could be finally obtained (50% yield) by the slow addition of a salt-free solution of the ylide (2 equiv.) in benzene, to a solution of 2 in benzene (70-72°C for 3.5 hrs). Catalytic hydrogenation (10% Pd-C/DMF) of purified 3 afforded a mixture of corresponding methyl epimers, (4a) and (4b), in a ratio of Ca. 4:1, respectively (GLC). These epimers were separated through column chromatography (silica gel) to afford 4a, m.p. 87.5-88.5°C and 4b, m.p. 66-68°C. Oxidation of 4a with PCC gave 5[4], m.p. 74-75°C, almost quantitatively, which on reaction with methylenetriphenylphosphorane under the above salt-free conditions gave 6[4], in about 50% yield. The corresponding acid[4] (6a), m.p. 138-139°C was found to be identical with an optical isomer obtained from ilimaquinone[3].

The above keto-ester (5) was found to be identical to the compound obtained earlier[1] by us through RuO_4-oxidation of an intermediate of avarol, thus re-establishing our earlier stereochemical conclusions.

We thank Prof. D.J. Faulkner of Scripps Institute of Oceanography, La Jolla, California, for comparison of our sample of 6a with the authentic compound and Prof. U.R.Ghatak of this department for helpful discussions.

REFERENCES AND NOTES

1 A.S. Sarma and P. Chattopadhyay, *J.Org.Chem.*, 47, 1727 (1982)

2 We had inadvertently overlooked the discrepancy in the data reported for this degradation product (cf.Ref.3). As we were unable to compare our ester (5), derived from the avarol intermediate, with ilimaquinone oxidation product, we could only base our stereochemical conclusions on the partial ^1H NMR and IR spectral data reported. We regret to have made definitive conclusions on the basis of such inadequate data/ cf. our correction: *J.Org.Chem.*, 47, 5427 (1982) /

3 B. Sullivan and D.J. Faulkner, *Tetrahedron Letters*, 23, 907 (1982)

4 All new compounds gave expected elemental analyses and spectral data; ^1H NMR of 5 (60 MHz, CCl_4): δ 0.85 (s,tert-Me), 0.89 (partially overlapping d, sec-Me), 1.1 (s, tert-Me) and 3.58 (s, -COOMe); of 6 (100MHz, $CDCl_3$): δ0.76 (s,tert-Me), 0.89 (d,J=6Hz, sec-Me), 1.01 (s,tert-Me), 3.59 (s, COOMe) and 4.47 (d,J= 1.5Hz, vinyl CH_2); of 6a (360MHz, $CDCl_3$): δ0.79 (s,tert-Me), 0.91 (d,J=6.7Hz , sec.-Me), 1.04 (s, tert-Me), and 4.31 (vinyl CH_2).

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