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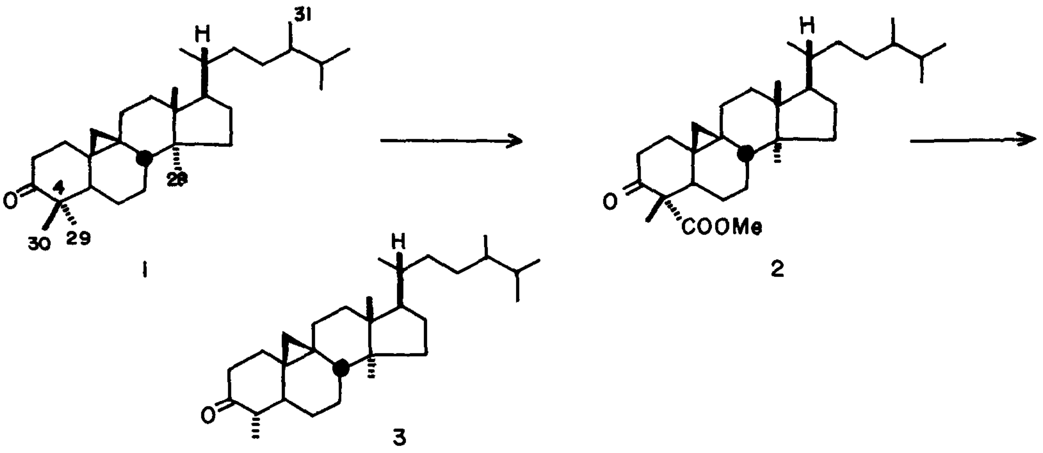
A NOVEL METHOD FOR FUNCTIONALIZATION OF C-4 METHYL IN TRITERPENOIDS. A SYNTHESIS OF CYCLOEUCALANONE[1]

Manoj C. Desai, Chandan Singh, H.P.S. Chawla and Sukh Dev*
Malti-Chem Research Centre, Nandesari, Vadodara, India

Summary: Functionalization of 4α-methyl group in cycloartane-type triterpenoids has been accomplished utilizing, in the key step, photolytic decomposition of an hypoiodite derived from a 3β-hydroxymethyl-4,4-dimethyl precursor. The synthesis of cycloeucalanone from cyclolaudanone is reported.

In connection with our efforts[2] aimed at chemical transformation of cycloartenol/cyclolaudenol into cycloartane-based natural products, we were desirous of developing a general method for selective oxygenation of C-4 methyl, leading finally to 4α-carboxyl/4α-hydroxymethyl functionalities, structural features present in many triterpenoids[3] and steroidal *Buxus* alkaloids.[4,5] Furthermore, these derivatives should eminently lend themselves for transformation into corresponding 4-desmethyl compounds, many of which occur in nature.[3,4] We now describe the conversion of cyclolaudanone (1) into methyl cyclolaudan-3-on-29-oate (2), and eventually into cycloeucalanone (3),[6] by a simple sequence of reactions.[7]



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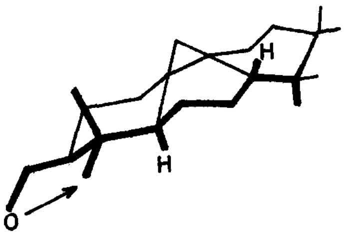
Conceptually, a β-hydroxymethyl function at C-3 on a triterpene skeleton, such as that of cyclolaudane, is geometrically suitably oriented to functionalize either 4α- or 4β-methyl group (4, 5) in a reaction such as photo-decomposition of the derived hypohalite,[8] as the hydroxyl can be so oriented such that the internuclear distance between the oxygen and the concerned methyl carbon falls within the desirable range of 2.5-2.7 A° (Dreiding models).[8] However, situation 4 may be expected to be preferred because of lesser non-bonded interactions.[9] With these reasonable assumptions, the following work was carried out.



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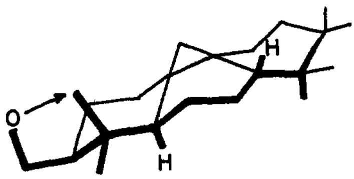

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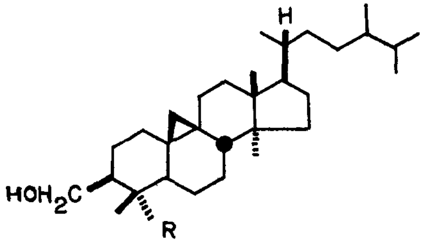
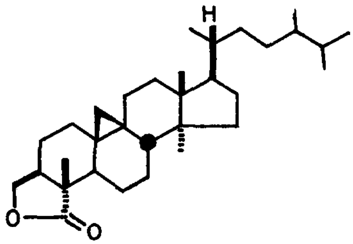
Cyclolaudanone (1) on exposure to methylenetriphenylphosphorane (THF, 27°, 0.5 hr) gave in 84% yield the required 3-methylenecyclolaudane[10] (m.p. 100-102°. IR: C=CH$_2$ 1640, 896 cm^{-1}. PMR: C=CH$_2$, two 1H broad singlets, 4.55, 4.62 ppm). Hydroboration [9-borabicyclo(3.3.1)nonane,[11] THF, reflux, 2 hr], followed by oxidation with H_2O_2/NaOH furnished a mixture of two alcohols (86%; 85:15) which were separated by column chromatography (SiO_2-II). The major isomer (m.p. 153-55°. IR: OH 3615 cm^{-1}. PMR: CH_2OH, 1H, m, 3.18-3.49 ppm; 1H, m, 3.73-3.98 ppm) was considered, in view of the expected preferential attack by the hydroborating reagent from the less hindered α-face, to be the desired 6. This was confirmed by the PMR spectrum of the derived aldehyde.[12] Reaction of alcohol 6 with Pb(OAc)$_4$-I$_2$ in cyclohexane, under irradiation from a tungsten lamp (100 watt, 2 hr), followed by oxidation with Jones' reagent, furnished a product, from which lactone 7 was obtained in 35-50% yield: m.p. 205-208°; IR, C=O 1779 cm^{-1}; PMR: OCH_2 (2H, m, 3.78-4.28 ppm), cyclopropane CH_2 (1H, d, 0.18 ppm, J= 4 Hz; second 1H signal is presumably under other down-field signals). That the lactone 7 has indeed the structure



6: R = Me
8: R = COOMe



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shown follows from the ^{13}C-NMR spectrum of the derived (alkaline hydrolysis, followed by esterification with CH_2N_2) hydroxy ester 8 (m.p. 165-167°. IR: OH 3610 cm^{-1}; C=O 1720 cm^{-1}; C-O 1245 cm^{-1}. PMR: $C\underline{H}_2OH$, 2H, d, 3.46 ppm, J = 8 Hz; COO$\underline{Me}$, 3H, s, 3.71 ppm). In the ^{13}C-NMR spectrum of 8, the presence of a signal at 10.34 ppm is taken as a proof for the presence of a 4β-methyl carbon atom: in 3β-hydroxy-triterpenoids carrying 4,4-dimethyl groups, 4β-methyl carbon atom signal occurs comparatively upfield (14.00 - 16.00 ppm)[13] due to γ-effect[14] from C-2, C-6 and C-10; a 4α-ester group in place of 4α-methyl causes a further upfield shift[15] of ~5.0 ppm.

Oxidation of the hydroxy ester (8) with Collins reagent[16] smoothly furnished the corresponding aldehyde ester (m.p. 115-119°. IR: CHO 2710, 1728 cm^{-1}. PMR: $C\underline{H}O$, 1H, s, 9.46 ppm). This was converted into the enamine with piperidine in benzene soln in presence of 5A°-type molecular sieves[17] and directly oxidized further with $Na_2Cr_2O_7$-AcOH (0-5°, 24 hr) to furnish the desired β-keto ester 2 in an overall yield of 50% from the hydroxy ester 8.

Exposure of 2 to NaCN in hexamethylphosphoric triamide (80°, 4 hr) resulted[18] in hydrolysis followed by concomittant decarboxylation to furnish the known[6] cycloeucalanone (3) in 81% yield: m.p. 109-110°, $[\alpha]_D$ + 49.7° ($CHCl_3$). (Lit.[6]: m.p. 107-108°, $[\alpha]_D$ + 49.0°)

References and Notes

1. MRC Communication No. 20.

2. Chandan Singh and Sukh Dev, *Tetrahedron* *33*, 817, 1053 (1977).

3. See e.g.: T.K. Devon and A.I. Scott, *Handbook of Naturally Occurring Compounds*, vol. II, pp. 281-384. Academic Press, New York (1972).

4. See e.g.: J. Tomko and Z. Voticky in *The Alkaloids* (Editor: R.H.F. Manske), vol. XIV, p. 32. Academic Press, New York (1973).

5. The earlier C-4 configuration for the hydroxymethyl group in many *Buxus* alkaloids[4] has since been proved to be 4α: M. Sangare, F. Khuong-Huu, D. Herlem, A. Milliet, B. Septe, G. Berenger and G. Lukacs, *Tetrahedron Letters* 1791 (1975); J. Guilhem, *ibid.* 2937 (1975).

6. J.S.G. Cox, F.E. King and T.J. King, *J. Chem. Soc.* 1384 (1956); 514 (1959).

7. Though recently, functionalization of 4-methyl groups in lanostane or 4,4-dimethyl cholestane/androstane derivatives has been reported along lines quite distinct from the present approach, the methods are either not selective or furnish only poor yields: J.A. Nelson, S. Chou and T.A. Spencer, *J. Am. Chem. Soc.* *97*, 648 (1975); A.J. Jones, P.F. Alewood, M. Benn and J. Wong, *Tetrahedron Letters* 1655 (1976); M.R. Czarny, B.W. Benson and T.A. Spencer, *J. Org. Chem.* *42*, 556 (1977); J.M. Midgley, J.E. Parkin and W.H. Whalley, *J. Chem. Soc. Perkin I*, 834 (1977).

8. See e.g.: K. Heusler and J. Kalvoda in *Organic Reactions in Steroid Chemistry* (Editors: J. Fried and J.A. Edwards), *Vol. II, p. 237. Van Nostrand Reinhold,* New York (1972).

9. From an examination of Dreiding models, it is clear that **4** has one less 1,3-diaxial-type of interaction and the C-OH (of CH_2OH group) is flanked by a 'small' (hydrogen atom) and a 'large' group (C-4) on the adjacent carbon atom (C-3), in contrast to **5** in which these groups are 'medium' (C-2) and 'large' (C-4).

10. Satisfactory elemental analysis were obtained for all new compounds.

11. C.G. Scouten and H.C. Brown, *J. Org. Chem.* *38*, 4092 (1973).

12. G.W. Buchanan, J.B. Stothers and S.T. Wu, *Canad. J. Chem.* *45*, 2955 (1967).

13. Replacement of 3β-hydroxyl by 3β-hydroxymethyl group should have only a little effect (Ref. 14, pp. 58, 142).

14. J.B. Stothers, *Carbon-13 NMR Spectroscopy*, p. 65. Academic Press, New York (1972)

15. See e.g.: F.W. Wehrli and T. Nishida, *Progress in the Chemistry of Organic Natural Products*, *36*, 1 (1979).

16. J.C. Collins, W.W. Hess and F.J. Frank, *Tetrahedron Letters*, 3363 (1968); R. Ratcliffe and R. Rodehorst, *J. Org. Chem.* *35, 4000 (1970)*.

17. L.F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Vol. I, p. 703 John Wiley, New York (1967).

18. P. Muller and B. Siegfried, *Tetrahedron Letters*, 3565 (1973).

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