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A SINGLE POT SYNTHESIS OF 3,4-SECO ACID FROM 4,4-DIMETHYL-3-KETO TRITERPENOID

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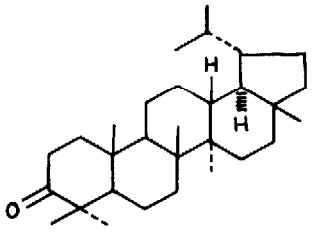
Abstract - Oxidation of 4,4-dimethyl-3-keto triterpenoid with m-CPBA in presence of p-TsOH furnishes 3,4-seco triterpenoid acid whereas 4-mono-methyl-3-keto-triterpenoid affords only the ϵ-lactone under the identical condition.

A large number of 3,4-seco triterpenoid acids have been reported in literature[1] and almost all of them are postulated[2] to have been formed from 3-keto-4,4-dimethyl triterpenoids by Baeyer-Villiger type of oxidation to furnish the ϵ-lactones which ultimately yield the seco acids under some biogenetic conditions. Though Rosenthal et al[3] have shown by pyrolytic method that only the ϵ-lactones derived from 3-keto-4,4-dimethyl steroids could furnish the seco acids of the type A , the isolation of putric acid[4], putranjivic acid[5] and its methyl ester[5] from Putranjiva ruxburghii have shown that some of the plants are capable of synthesising 3,4-seco acids (of type C) even in the absence of gem dimethyl group at C-4 position. Whereas the photochemical oxidation[6] of 3-keto-triterpenoids afford the seco acids of type B in methanol, only the seco acids of the type A have been prepared by Beckmann rearrangement of the oxime derivatives of 3-keto-triterpenoids[7,8].

It is well known that 3-keto-triterpenoids form ϵ-lactones very easily with m-chloroperbenzoic acid (m-CPBA). In order to examine the feasibility of transforming the ketones to the seco acids, we attempted the transformation reaction with m-CPBA in presence of strong acid like p-toluenesulphonic acid (p-TsOH) on lupanone (1) and moretanone (2) as typical representatives of 4,4-dimethyl triterpenoids and friedelin (3) for 4-mono methyl triterpenoids.



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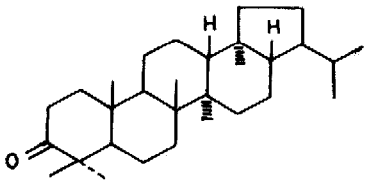

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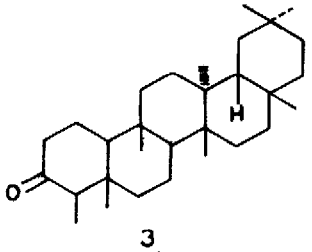

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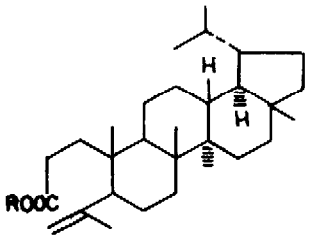
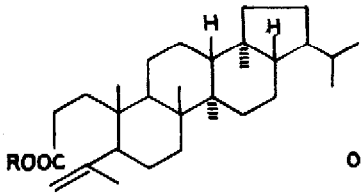


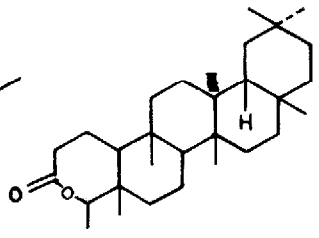
4, R=H

4a, R=CH_3



5, R=H

5a, R=CH_3



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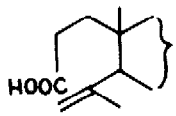
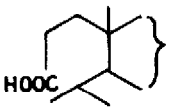
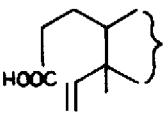


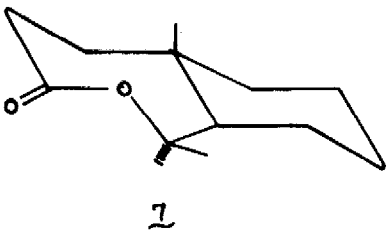
A



B



C



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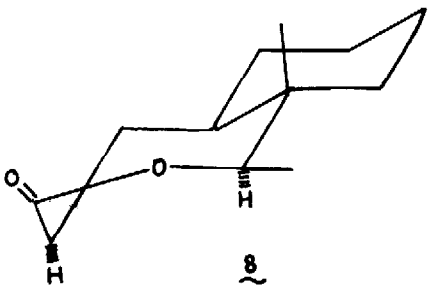

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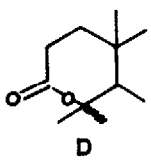
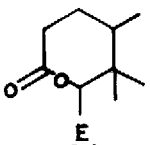


D



E

Whereas 1 and 2 on refluxing with m-CPBA in $CHCl_3$ in presence of p-TsOH furnished the desired 3,4-seco acids - the dihydro derivatives of canaric acid (4) and sebiferic acid (5) respectively, 3 yielded under the identical conditions[9] only the ϵ-lactone (6) and no other products. These observations clearly demonstrate that the C-4 axial methyl and the lactone carbonyl group are under sterical strain in the ϵ-lactones (of type D) derived from 4,4-dimethyl-3-keto triterpenoids (1 / 2) which is releaved by opening of the ring system in situ under the influence of strong acid (p-TsOH). The absence of such a strain makes the ϵ-lactone ring (of type E) comparatively stable in the case of lactones derived from 4-mono-methyl-3-keto triterpenoids (3) where the 4-methyl is equatorially oriented. This could well be visualised by the conformations represented by 7 and 8 . In 7 the 4α-methyl is in proximity to the carbonyl group and the sterical factor coupled with the electromeric effect of the two gem-dimethyl groups help in cleavage of the lactone ring to produce the seco acids ; but the absence of such factors in 8 stabilize the ϵ-lactone in the case of mono methyl or without methyl group at C-4 position of triterpenoids and steroids.

The acids 4 and 5 have been fully characterised as their methyl esters [methyl dihydrocanarate (4a), $C_{31}H_{52}O_2$, m.p. 142-43° , ν_{max}^{nujol} 1730 (-COOMe), 890 (C=CH_2) cm^{-1}; ^1H NMR ($CDCl_3$, δ): 0.76, 0.84, 0.95, 1.09 (4s, 4 x t-Me), 0.77 and 0.86 (2d, 6H, -CH<u>Me</u>$_2$, J = 6.5 Hz), 1.72 (s, =C-Me) 3.68 (s, COOMe), 4.66 and 4.85 (2s, 2H, C=CH_2); MS: m/z 456 [M]$^+$, 442, 441, 426, 413, 177, 81 (base). Methyl dihydrosebiferate (5a), $C_{31}H_{52}O_2$, 129-30°; spectral values similar to that of 4a] and the lactone 6 [friedelolactone $C_{30}H_{50}O_2$, m.p. 272-73°*, ν_{max}^{nujol} 1725 (ϵ-lactone) cm^{-1}; MS: m/z 442 [M]$^+$, 398, 205, 95 (base); ^1H NMR (δ): 0.83, 0.89, 0.95, 0.98, 0.99, 1.00, 1.17 (7s, 7 x t -Me), 1.20 (d, HC-<u>Me</u>, J = 6.5 Hz), 4.21 (q, 1H, CO-O-C<u>H</u>-Me, J = 6.5, 3.5 Hz)] by IR, Mass, ^1H NMR and ^{13}C NMR spectral analysis; the acids 4 and 5 were further confirmed by catalytic hydrogenation (H_2-Pd on charcoal) of 4a and 5a to methyl tetrahydrocanarate[11] and methyl tetrahydrosebiferate[8,12] respectively.

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* Various group of workers have reported the m.p. of friedelolactone (6) as 260-75° (mixture ν :1735 cm^{-1})[10]; 309-12°[14]; 230° (ν : 1740 cm^{-1})[13]; 282° (ν : 1750 cm^{-1})[15]. The m.p. 272-73° may be taken as the correct one as it is spectrally pure (^1H & ^{13}C NMR).

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9. A. Soln. of triterpenoid 1/2/3 (0.3 g) in $CHCl_3$ (75 ml) containing m-CPBA (0.3 g) and p-TsOH (0.05 g) was refluxed for 12 h and kept at room temperature over night. The residue obtained after usual work-up was extracted with ether and separated into neutral and acid parts by usual methods. The acid parts of 1/2 on esterification with CH_2N_2 gave the methyl esters 4a/5a (0.25 g) while that of 3 furnished no methyl ester; the neutral part of 3 afforded the lactone 6 (0.27 g).

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Note: Attempt to carry out Baeyer-Villiger reaction with m-CPBA on 1/2/3 in solid state as per conditions of Toda et al (Ref.: F. Toda, M. Yagi and K. Kiyoshige, J. Chem. Soc., Chem. Commun., 958, 1988) even at the end of 60 d gave back the original ketone showing that no oxidation reaction takes place in the case of triterpenoid ketones.

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