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OXIDATION OF UNACTIVATED CARBON ATOMS OF LUPANE AND FRIEDELANE-TYPE TRITERPENES WITH m-CHLOROPERBENZOIC ACID

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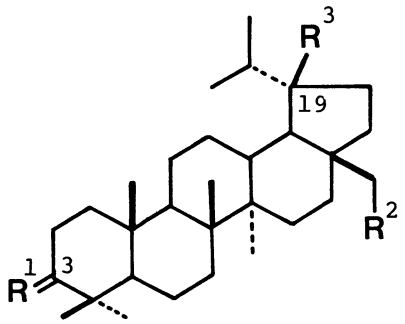
The reaction of lupan-3β,28-diyl diacetate, lupan-3β-yl acetate, and friedelan-3β-yl acetate with m-chloroperbenzoic acid gave their hydroxy or keto derivatives upon oxidation of unactivated carbon atoms.

Efforts to introduce hydroxyl or carbonyl groups into triterpene skeletons have been made for a long time. Remote oxidation applied to triterpenes has been reported by Tanaka and his group using dammarane derivatives,[1] whilst dry ozonization of friedelane and friedelin yielding carbonyl derivatives[2] has been investigated by Takahashi and his co-workers. Although m-chloroperbenzoic acid (mCPBA) has been used for hydroxylation of polycyclic compounds,[3] products are limited to tertiary alcohols. We have examined the reactions of some triterpenes having a lupane or a friedelane skeleton with mCPBA and have found results similar to dry ozonization. In contrast to previous observations, secondary alcohols or carbonyl compounds were produced in these reactions. We now describe our preliminary results of oxidation reactions of some lupane and friedelane derivatives with mCPBA.

Lupane-3β,28-diol (1, 600 mg) was treated with mCPBA in $CHCl_3$ under reflux for 6 h, affording 28-hydroxylupan-3-one (2, 200 mg, 50.2%[4]), an unsaturated ester (3, 20 mg, 4.7%[4]),[5] and a hydroxy ester (4, 35 mg, 7.9%[4])[5] by successive chromatography on Sephadex LH-20 (elution with MeOH-$CHCl_3$) and silica gel (elution with EtOAc-PhH). The second product, 3, showed its molecular ion at m/z 472, IR absorptions at 3450, 1730, and 890 cm^{-1}, and ^1H NMR signals at δ 4.85 (1H, s), 4.65 (1H, s), 3.77 (1H, d, J=11 Hz), 3.66 (3H, s), 3.31 (1H, d, J=11 Hz), and 1.73 (3H, s), the spectra suggesting that the 28-hydroxyl group was intact and that the A-ring was oxidatively cleaved to give the unsaturated methyl ester. The spectral data of 4 were very similar to those of 3, indicating that the 28-OH group remained intact [δ 3.77 (1H, d, J=11 Hz) and 3.31 (1H, d, J=11 Hz)] and that the A-ring was cleaved [δ 3.67 (3H, s), 1.28 (3H, s), and 1.23 (3H, s); IR 3450 and 1730 cm^{-1}]. From these data, the structures of 3 and 4 were assigned to 3,4-seco methyl esters as shown. Since no MeOH was used in the reaction, the esters must be produced during column chromatography on Sephadex LH-20 ($CHCl_3$-MeOH). It is surmised that 1 is oxidized to the ketone (2) followed by Baeyer-Villiger oxidation to give lactone 5, which undergoes acid catalyzed methanolysis during



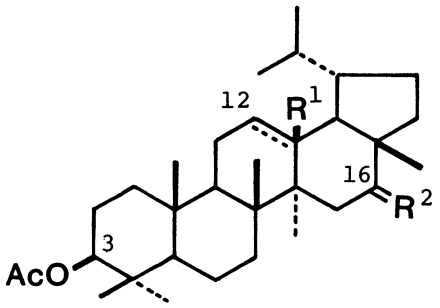
1 R^1=  , R^2=OH, R^3=H

2 R^1=O, R^2=OH, R^3=H

6 R^1=  , R^2=OAc, R^3=H

7 R^1=  , R^2=OAc, R^3=OH

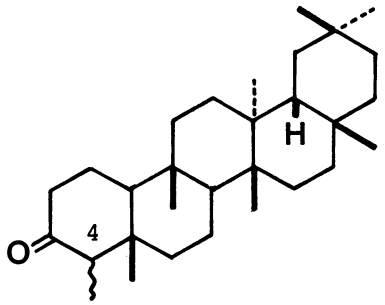
8 R^1=  , R^2=R^3=H



9 R^1=OH, R^2=H_2

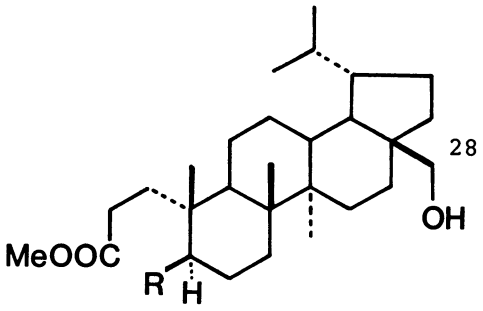
10 R^1=H, R^2= 

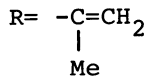
11 R^2=H_2, with Δ^{12} (R^1= none)

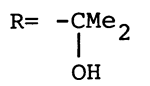


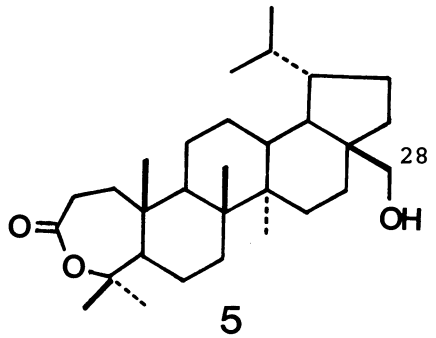
13 4β-Me

14 4α-Me



3 R= 

4 R= 



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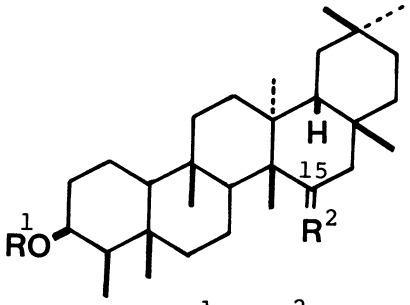
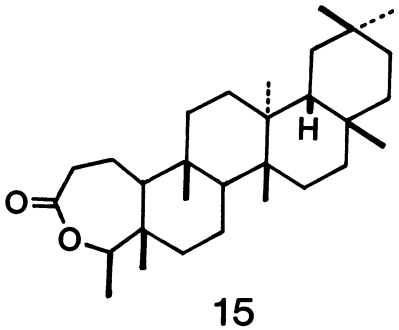


12 R^1=H, R^2=H_2

16 R^1=Ac, R^2=H_2

17 R^1=Ac, R^2=O



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separation to afford the hydroxy ester (4) which is then dehydrated to 3. Indeed, 5 gave 3 and 4 on chromatography under the same conditions.

When the reaction mixture was washed with aq. Na_2SO_3, aq. $NaHCO_3$, and brine, successively, it yielded the ketone (2, 50.2%[4]) and the lactone(5, 20.2%[4])[m/z 458 (M^+); IR 3450 and 1715 cm^{-1}; δ 3.77 (1H, d, J=11 Hz), 3.32 (1H, d, J=11 Hz), 2.63 (1H, td, J=13 and 4 Hz), and 2.49 (1H, ddd, J=13, 6, and 3.5 Hz) by chromatographic separation on silica gel (EtOAc-PhH). As the esters 3 and 4 were not produced in this case, this procedure was adopted as the standard work-up thereafter.

Lupane-3β,28-diyl diacetate (6, 270 mg) was allowed to react with mCPBA in the same manner, yielding 19β-hydroxylupane-3β,28-diyl diacetate (7, 30 mg)[6] in 83.2% yield based on consumed 6 (235 mg of 6 were recovered), which was previously obtained by dry ozonization of 6 by Suokas and Hase (500 mg of 6 gave ca. 50 mg of 7)[6]. The C-28 acetoxyl group seems to play an important role in the oxidation of the C-19 position, as 7 was produced in high yields in both reactions.

Lupan-3β-yl acetate (8, 470 mg), however, gave two hydroxylated products, a hydroxy acetate (9, 20 mg, 20.4%[4]) and 16β-hydroxylupan-3β-yl acetate (10, 5 mg, 5.1%[4]). Product 9 was a tertiary alcohol [IR 3500 cm^{-1}; δ_C 85.8 (s, C-13) and 81.0 (d, C-3)] which was dehydrated ($POCl_3$/Py) to an unsaturated acetate (11),[8] whose mass spectrum showed the molecular ion at m/z 468 and a characteristic peak at m/z 218 due to retro Diels-Alder fragmentation of the C-ring. As 11 was identical with the known lup-12-en-3β-yl acetate,[8] 9 must be formulated as 13β-hydroxylupan-3β-yl acetate.

Friedelan-3β-ol (12, 200 mg) afforded friedelin (13, 85 mg, 42.7%[4]), 4-epi-friedelin (14, 19 mg, 9.5%[4]),[9] and a lactone (15, 42 mg, 20.3%[4]). The lactone was identical with that derived from friedelin *via* Baeyer-Villiger oxidation. The structure of 14 was established to be 4-epifriedelin, because treatment of 14 with KOH in MeOH yielded friedelin (13) quantitatively. Although the mechanism is still unclear, we suspect that fission of the C-3, C-4 bond could occur during the reaction followed by recyclization to friedelin and 4-epifriedelin.

Reaction of friedelan-3β-yl acetate (16, 100 mg) with mCPBA was next carried out to give a keto acetate (17, 2 mg, 12.9%[4]).[5] The structure of 17 was deduced from the spectral data [m/z 484 (M^+); IR 1730 and 1695 cm^{-1}; δ 4.89 (1H, m), 2.50 (1H, d, J=18 Hz), 2.16 (1H, d, J=18 Hz), and 2.04 (3H, s)] to be 15-oxofriedelan-3β-yl acetate. This was confirmed by conversion to the known friedelane-3,15-dione.[2]

These results clearly indicate that when the compound has a hydroxyl group in their A-ring, oxidation leading to the corresponding ketone predominates, sometimes followed by Baeyer-Villiger oxidation, while in the case of the acetates, oxidation occurs at an unactivated carbon atom to yield a secondary or tertiary alcohol or a ketone. Although at the present stage, the reaction site is not predictable enough and the mechanism has not been rationalized, these reactions would be convenient entries to polycyclic natural products oxygenated at unactivated carbons. Other applications are currently under way.

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4) Yields shown indicate isolation yields based on the unchanged starting material.
5) Satisfactory spectral data including high resolution mass spectra were obtained for all new compounds. ^{1}H and ^{13}C NMR spectra were measured on a JEOL GX-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer in $CDCl_3$.
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