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Oxyfunctionalization of Steroids by Dioxiranes: Site and Stereoselective C_{14} and C_{17} Hydroxylation of Pregnane and Androstane Steroids.

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Abstract: Dimethyldioxirane showed to be site and stereoselective in the C-H oxygen insertion at C_{14} and C_{17} positions of pregnane and androstane steroids. Fine steric control and evidence for the influence of the carbonyl group on the dioxirane reactivity are reported.

Dimethyldioxirane **1** and methyltrifluoromethyldioxirane **2** (scheme), new and powerful oxyfunctionalizing reagents, appear to be very effective for the selective hydroxylation of steroidal carbons.

The reported hydroxylation at the benzylic C_9 of estrone[1], at C_{25} of cholestane derivatives[2] and at C_5 of the bile steroids[3] are significant examples. They suggest a fine control of dioxirane reactivity.

For a better understanding of the stereoelectronic control operating and with the aim of functionalizing other useful steroidal positions, we also submitted some pregnane and androstane steroids to the oxidation by **1**[4].

As reported in the scheme, 5,α-androstan-3,β-ol acetate **3** was selectively oxyfunctionalized at C_{14} to give the corresponding 14,α-hydroxy derivative **9** (50% conv., 85% yield).

The same site- and stereoselective functionalization was observed for pregnanes **5** and **6** which afforded the corresponding 14,α-hydroxy derivatives **11** and **12** (40% conv. , 90% yield).

In the case of 17,β-methyl-5,α-androstan-3,β-ol acetate **4**, we observed the selective and unexpected hydroxylation at C_{17}, **10** being obtained as the only reaction product (50% conv., 90% yield)[5].

The preferential attack of dimethyldioxirane **1** to the C_{14} carbon atom compared to other steroidal tertiary carbon atoms (C_5, C_8, C_9) is explained by the less hindered steric environment as shown by molecular models.

The lack of reactivity of tertiary C_{20}-H bond of **5**, despite the known chemical behaviour of the isopropylic moiety[2], appears to be due to the conformational arrangement of C_{20}-H bond which is shielded by the C_{18} methyl group, as examination of models reveals.

Finer steric controls regulate the reactivity of the C_{17}-H bond. In fact only when the C_{20} position is unsubstituted, as in **4**, the dioxirane approaches the C_{17}-H bond[6]. Therefore the following C-H bond scales of reactivity resulted for steroidal structures: C_{25}-H isopropyl ≈ C_5-Hβ[3] > C_{14}-Hα and C_{17}-H methyl substituted > C_{14}-Hα >> other tertiary positions.

Moreover evidence of the influence of the carbonyl group on the dioxirane reactivity is also reported. Thus, whereas the androstane **3** reacted with **1** to give the C_{14} oxyfunctionalized compound **9**, the

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corresponding 17 keto derivative 7 did not react at all. This chemical behaviour could be due to a carbonyl-dioxirane dipole interaction inhibiting the approach of dioxirane to the C_{14} position.

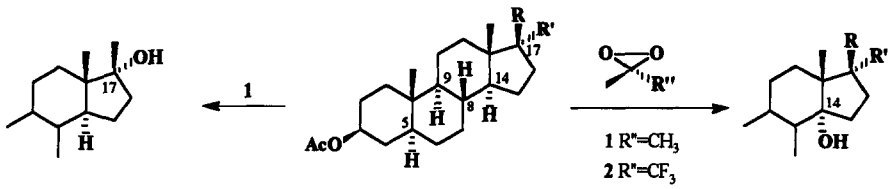
As a matter of fact the 17,β-acetoxy androstane **8** easily reacted with **1** to give the corresponding 14,α-hydroxy derivative **13**[7].

Higher conversions were observed using methyl-trifluoromethyl dioxirane **2** (≈80% conv. at 0°C in 3hrs).

The shown reactivity of **1** with steroidal carbons appears to be very unusual and mimics enzymatic reactions.

With regards to synthetic implications of the C_{14} hydroxy functionalization of steroids, new access to the ecdysonic hormones[8] having the α,C_{14}-OH could result.

Scheme



10

3 R=R'=H
4 R=CH_3; R'=H
5 R=$CH(CH_3)_2$; R'=H
6 R=CH_2CH_3; R'=H
7 R=R'= O
8 R=OAc, R'=H

9 R=R'=H
11 R=$CH(CH_3)_2$; R'=H
12 R=CH_2CH_2; R'=H
13 R=OAc; R'=H

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2. Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R.; *J. Org. Chem.*, **1992**, *57*, 5052-5054.
3. Bovicelli, P.; Gambacorta, A.; Lupattelli, P.; Mincione, E.; *Tetrah. Lett.*, **1992**, *33*, 7411-7412.
4. As a general procedure 4 eq. of dimethyldioxirane (0.1M solution in acetone) were added to a stirred solution of the substrate in dichlorometane at r.t. and left to react 24 hrs. Evaporation of the solvent gave crude products.
5. **9**: ^{1}H-nmr δ(ppm): 0.81 (6H, bs, C_{18}-H and C_{19}-H), 1.99 (3H, s, CH_3COO), 4.65 (1H, M, C_3-H). ^{13}C-nmr δ(ppm): 38.1 (C_{17}), 44.2 (C_5), 44.9 (C_{13}), 47.1 (C_9), 73.6 (C_3), 84.1 (C_{14}), 170.9 (COO).
10: ^{1}H-nmr δ(ppm): 0.64 (3H, s, C_{18}-H), 0.81 (3H, s, C_{19}-H), 1.16 (3H, s, C_{20}-H), 1.99 (3H, s, CH_3COO), 4.66 (1H, m, C_3-H). ^{13}C-nmr δ(ppm): 44.6 (C_5), 46.6 (C_{13}), 49.8 (C_{14}), 54.0 (C_9), 73.7 (C_3), 82.1 (C_{17}), 170.9 (COO).
11: ^{1}H-nmr δ(ppm): 0.71 (3H, s, C_{18}-H), 0.76 (3H, s, C_{19}-H), 0.80 (6H, d, J=5 Hz, C_{21}-H and C_{22}-H), 1.98 (3H, s, CH_3COO), 4.65 (1H, m, C_3-H). ^{13}C-nmr δ(ppm): 52.8, 53.6 (C_9 and C_{17}), 73.7 (C_3), 85.7 (C_{14}), 170.9 (COO).
12: ^{1}H-nmr δ(ppm): 0.66 (3H, s, C_{18}-H), 0.81 (3H, s, C_{19}-H), 0.92 (3H, t, J=7.3 Hz, C_{21}-H), 1.99 (3H, s, CH_3COO), 4.66 (1H, m, C_3-H). ^{13}C-nmr δ(ppm): 44.6 (C_5), 46.9 (C_{13}), 50.1 (C_{17}), 54.1 (C_9), 73.7 (C_3), 84.3 (C_{14}), 170.9 (COO).
6. A right trajectory for the electrophilic oxygen insertion into a C-H bond of alkanes explaining these fine controls, was recently proposed. Bach, R.D.; Andres, J.L.; Owensby, A.L.; Su, M.D.; McDonall, J.J.W.; *results in press.*
7. **13**: ^{1}H-nmr δ(ppm): 0.79 (3H, s, C_{19}-H), 0.88 (3H, s, C_{18}-H), 2.01 (3H, s) and 2.02 (3H, s) (C_3 and C_{17}), 4.98 (1H, bs, C_3-H), 5.15 (1H, dd, J_1=9 Hz, J_2=6 Hz, C_{17}-H). ^{13}C-nmr δ(ppm): 39.6 (C_5), 46.8 (C_{13}), 47.0 (C_9), 69.9 (C_3), 81.2 (C_{17}), 83.5 (C_{14}), 171.5, 170.9 (C_3 and C_{17}).
8. Slama, K; Romanuk, M.; Sorm, F.; *Insect hormones and bioanalogues*, Springer-Verlag, Wien-N.Y., 1974, *cap. III*, 303-387.

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