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A Highly Regio- and Stereoselective C_5 Oxyfunctionalization of Coprostane Steroids by Dioxiranes: an Improved Access to Progestogen and Androgen Hormones.

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Abstract: *Coprostane steroids are selectively oxyfunctionalized at C_5 by dimethyldioxirane and methyltrifluoromethyldioxirane to give useful intermediates for bioactive compounds.*

Dioxiranes are known to be highly effective oxyfunctionalizing reagents[1]. At present, we are testing the reactivity of these oxidants towards steroidal molecules for the purpose of obtaining useful biological targets.

In this context, we recently reported[2] that estrone was selectively functionalized at C_9 benzylic carbon by dimethyldioxirane **1** to afford 9,α-hydroxy-estrone. Cholestane steroids were also selectively functionalized at C_{25} isopropylic carbon to give intermediates of vitamin D metabolites[3].

We decided to ascertain whether dioxiranes were equally effective in the functionalization of other steroid positions. Consequently, we investigated **1a** and **1b** reactivity towards coprostane steroids, which present the A/B-ring-cis junction and therefore the β-configuration at C_5 hydrogen.

When bile steroid lythocholic acid-3-acetate methyl ester **2** reacted with **1a** (D/S=2:1, solvent $CHCl_3$/acetone, r.t., 24h), this produced a highly regio- and stereoselective oxyfunctionalization at C_5 carbon, whose only product was 5, β-hydroxy derivative **3** (30% conv., 85% isolated yield). When **1b** was employed, as selectivity was unchanged, we noted a considerable rise in conversion (70% conv., 85% isolated yield).

When **1a** (or **1b**) reacted with 5,β-cholanic acid-3,α-12,α-diol-3,12-diacetate methyl ester **5**, we obtained the same regioselectivity, and the only product formed was 5,β-hydroxy derivative **6**[5].

Since C_5 oxyfunctionalization of steroids represents a key step in the conversion of bile acids into androgenic and progestogen hormones[9b], these results therefore appear to be very useful.

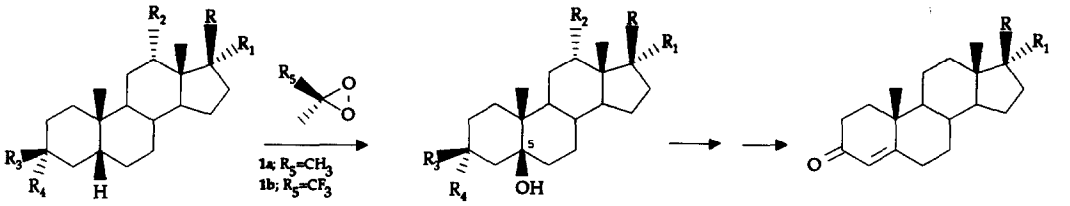
The recovery of unreacted starting material was performed by chromatographic separation, thus enabling us to increase the overall yield.

After this, we deacetylated **3** (K_2CO_3 s.s./CH_3OH 1:9, r.t., 3h), oxidized it at C_3 (PCC in CH_2Cl_2, r.t., 2h) and finally dehydrated it (H_2SO_4 conc., 0-25°C, 1h) to give the enone **4**, an intermediate in progestogen synthesis[9c]. We would also like to point out that compounds such as **6**, which present both C_5 and C_{12} oxyfunctionalized carbons, represent valuable intermediates in cortisonic steroids synthesis starting from cholic acid[9d].

As a further application we oxyfunctionalized 5β-androstan-3α-17β-diacetoxy **7** by **1a** at C_5 (50% conv., 90% isolated yield). This gave **8**, which we then easily converted into the hormone androstenedione **10**.

We also submitted 5,β-cholestan-3,α-ol acetate **11** to **1a**, and achieved simultaneous double oxyfunctionalization at C_5 and C_{25}, to yield 5,β-cholestan-3,α-5,α-25-triol-3-acetate **12**.

SCHEME



2; R=CH(CH$_3$)(CH$_2$)$_2$COOCH$_3$
R$_1$=R$_2$=R$_3$=H; R$_4$=OAc
5; R=CH(CH$_3$)(CH$_2$)$_2$COOCH$_3$
R$_1$=R$_3$=H; R$_2$=R$_4$=OAc
7; R=R$_4$=OAc; R$_1$=R$_2$=R$_3$=H
11; R=CH(CH$_3$)(CH$_2$)$_3$CH(CH$_3$)$_2$
R$_1$=R$_2$=R$_3$=H; R$_4$=OAc

3; R=CH(CH$_3$)(CH$_2$)$_2$COOCH$_3$
R$_1$=R$_2$=R$_3$=H; R$_4$=OAc
6; R=CH(CH$_3$)(CH$_2$)$_2$COOCH$_3$
R$_1$=R$_3$=H; R$_2$=R$_4$=OAc
8; R=R$_4$=OAc; R$_1$=R$_2$=R$_3$=H
9; R=R$_1$=O; R$_2$=H; R$_3$=R$_4$=O
12; R=CH(CH$_3$)(CH$_2$)$_3$COH(CH$_3$)$_2$
R$_1$=R$_2$=R$_3$=H; R$_4$=OAc

4; R=CH(CH$_3$)(CH$_2$)$_2$COOCH$_3$
R$_1$=H
10; R=R$_1$=O

The C_5 oxyfunctionalization of coprostane steroids by dioxiranes is clearly due to the favoured steric environment at this position; the attack on C_{25} isopropylic carbon once again demonstrates the electrophilicity of dioxiranes.

We may conclude by suggesting that the steroselective introduction of the β-hydroxyl moiety on C_5 steroidic carbon may also allow a new entry to cardiac-active and ecdysonic compounds[10].

References and Notes

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2) P.Bovicelli, P.Lupattelli, E.Mincione, T.Prencipe, R.Curci, J. Org. Chem., **57**, 2182 (1992).
3) P.Bovicelli, P.Lupattelli, E.Mincione, T.Prencipe, R.Curci, J. Org. Chem., (1992) in press.
4) For a representative oxidation of steroids with dioxiranes see ref. (2).
5) **3**: m.p.=167-168°C from Hexane/Et$_2$O; ^{1}H-NMR δ: 0.61 (3H, s, C$_{18}$-H), 0.87 (3H, s, C$_{19}$-H), 0.89 (3H, d., J=6Hz, C$_{21}$-H), 2.00 (3H, s, CH$_3$COO), 3.64 (3H, s, OCH$_3$), 5.05 (1H, t.t., J$_1$=11.1, J$_2$=4.7, C$_3$-H). The observed C$_{19}$ methyl chemical shift is consistent with a ß-configuration of C$_5$-OH[6]. ^{13}C-NMR δ: 71.41 (C$_3$), 75.34 (C$_5$), 170.80 (CH$_3$COO), 175.02 (C$_{24}$). **4**: m.p.=123-126°C from Hexane/Et$_2$O; ^{1}H-NMR spectrum agrees with literature data[7]. **6**; m.p.=127-128°C from Hexane/Et$_2$O; ^{1}H-NMR δ: 0.69 (3H, s, C$_{18}$-H), 0.77 (3H, d, J=6Hz, C$_{21}$-H), 0.84 (3H, s, C$_{19}$-H), 1.99 (3H, s, CH$_3$COO-C$_3$), 2.07 (3H, s, CH$_3$COO-C$_{12}$), 3.63 (3H, s, OCH$_3$), 5.03 (1H, tt, J$_1$=11.1Hz, J$_2$=4.7Hz, C$_3$-H), 5.07 (1H, m, C$_{12}$-H). ^{13}C-NMR δ: 71.17 (C$_3$), 75.14 (C$_5$), 75.56 (COOC$_{24}$), 170.63, 170.70 (COO-C$_3$ + COO-C$_{12}$), 174.84 (C$_{24}$). **8**; m.p.=220°-222°C from Hexane/Et$_2$O (lit.[6] m.p.=221-224°C); ^{1}H-NMR spectrum agrees with literature data[6]. **9**: m.p.=180-183°C from Hexane/Et$_2$O (lit.[8] m.p.=183-186°C). **10**; m.p.=171-173°C (lit.[9a] 173-174°C). **12**; ^{1}H-NMR δ: 0.61 (3H, s, C$_{18}$-H), 0.87 (3H, s, C$_{19}$-H), 0.88 (3H, d, J=6.5Hz, C$_{21}$-H), 1.19 (6H, s, C$_{26}$-H + C$_{27}$-H), 2.00 (3H, s, CH$_3$COO), 5.05 (1H, m, C$_3$-H). ^{13}C-NMR δ: 71.09 (C$_{25}$), 71.41 (C$_3$), 75.40 (C$_5$), 170.78 (CH$_3$COO).
6) J.P.Begue, J. Org. Chem., **47**, 4268 (1982).
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9) a) L.F.Fieser and M.Fieser, Steroids, Reinhold Publishing Corporation N.Y. p. 519 (1959); b) *ibid.* p. 545 and following; c) *ibid.* p. 546; d) *ibid.* p. 651 and following.
10) It is known that oxyfunctionalization of saturated carbon atoms by dioxiranes proceeds with retention of configuration[1].

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