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A Highly Regio- and Stereoselective Reduction of Steroidal 3′(2*H*)-Furanone

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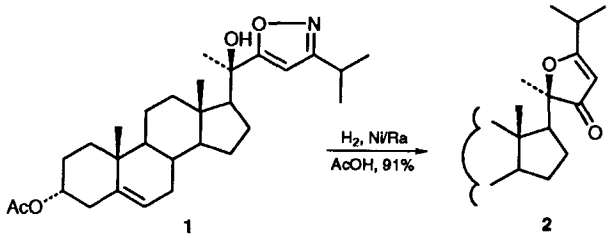
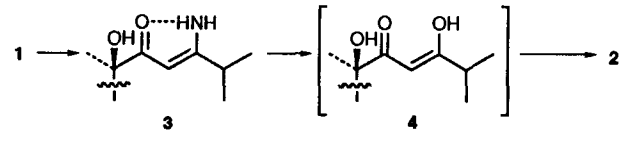
The reduction of steroidal 3′(2*H*)-furanone under the action of complex hydrides yields, regio- and stereoselectively in high yield, the corresponding tetrahydrofuranol, which has value as a potential intermediate in the synthesis of steroids containing polyhydroxylated side chains.

In the course of elaborating the nitrile oxide approach to the construction of polyfunctional steroidal side chains *via* isoxazole derivatives **1**, the adducts of 1,3-dipolar cycloaddition of nitrile oxides to the terminal acetylenes of the homopregnane series,[1] a highly effective reaction involving their direct transformation into steroidal 3′(2*H*)-furanone **2** under catalytic hydrogenation over Raney nickel in acetic acid has been established (Scheme 1).



Scheme 1

Given that the hydrogenation of **1** over Raney nickel in ethanol gives the enaminoketone **3**, which can be transformed into **2** by acid hydrolysis, we supposed that the reaction mechanism in acetic acid involves successive stages of reductive N-O bond rupture, the hydrolysis of the enaminoketone **3** to the corresponding diketone **4** and further intramolecular cyclodehydration of the latter (in its enolic form) to the furanone **2**, Scheme 2.[1]



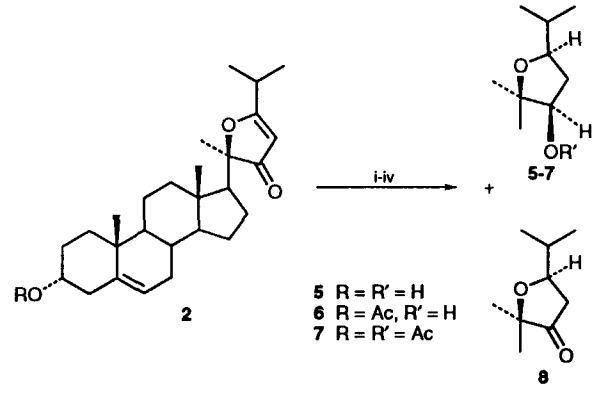
Scheme 2

The 3′(2*H*)-furanone structure is a well-known pharmacophore and a characteristic feature of many biologically active natural products,[2,3] including compounds of the triterpenoid series isolated from the Chinese medicinal herb *Picria fel-Tarrae Lour* and possessing varying biological activity.[4] At the same time, such a structure has never been described for native or synthetic steroids. However, the steroidal 3′(2*H*)-furanone, prepared by us, has value not only as a synthetic analogue of these biologically active compounds, but as a starting material for the construction of steroidal polyfunctionalized (polyhydroxylated) side chains or their intermediates.

To prepare steroidal tetrahydrofuryl alcohol containing the hydroxy function in the 3′-position (22-position according to steroidal nomenclature), the reduction of the furanone **2** under different conditions including complex hydride reduction has been investigated.

This investigation revealed that the reduction of **2** with a large excess of $NaBH_4$ (10 equiv.) in ethanol was highly regio- and stereoselective and gave the only product, the desired alcohol **5**, in 96% yield. In the case of a smaller excess of hydride (2–4 equiv.) it was possible to isolate the intermediate tetrahydrofuranone **8** in poor yield (17%).

Using $LiAlH_4$ as a reductant both 1,4-addition of hydrogen and reduction of 3′-ketone proceeded with larger hindrances resulting in a decrease in the yield of **5** and **8**, but the high regio-and stereoselectivity of the reaction remained, Scheme 3.



Scheme 3 *Reagents and conditions:* i, 10 equiv. $NaBH_4$, EtOH, r.t., 20 h (96% **5**); ii, 2–4 equiv. $NaBH_4$, EtOH, r.t., 20 h (*ca.* 50% **5** and 17% **8**); iii, 10 equiv. $LiAlH_4$, THF, 20 h (*ca.* 50% **5** and 17% **8**); iv, 10 equiv. $LiAlH_4$, Et_2O, 20 h (18% **5** and 75% **8**).

Such results can be explained by a specific combination of steric factors and the reactivity of substrate and reductant. This is the reason for the strictly orientated complex hydride anion attack from the sterically less hindered side of the 1,4-position of α,β-unsaturated ketone and then, owing to excess of reagent, on the carbonyl function of the highly reactive **8** (all the known cases of C^{22}-ketone reduction do not have high selectivity).

The spectral and analytical data confirm the struture of **5–8**

perfectly.† The C–22 hydroxy and C–24 isopropyl group configurations were assigned by the study of the differential NOE spectra for the alcohol **5**, its 3-monoacetate **6** and 3,22-diacetate **7**, which were obtained by acetylation of **5** (Ac_2O in pyridine or acetic acid in the presence of $BF_3 \cdot Et_2O$).

The nuclear Overhauser experiments showed a strong interaction between the protons of the C–21 methyl group and the protons at C–22 and C–24. Such an interaction scheme can be realised only for structure **5**.

† Spectroscopic data for **5**: m.p. 200–202 °C (hexane–ether). IR (KBr) ν/cm^{-1} 3420 (O–H); ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 3H, 18–Me), 0.90 (d, 3H, *J* 7.2 Hz, 26 or 27–Me), 1.00 (d, 3H, *J* 7.2 Hz, 26 or 27–Me), 1.04 (s, 3H, 19–Me), 1.27 (s, 3H, 21–Me), 2.33 (m, 1H, C_{25}–H, 2H, C_{23}–H), 3.56 (m, 1H, C_{24}–H, 1H, C_3–H), 4.00 (m, 1H, C_{22}–H), 5.43 (d, 1H, *J* 4.8 Hz, C_6–H).

For **6**: m.p. 182–184 °C (hexane). IR (KBr) ν/cm^{-1} 1257 (–O–C=O), 1720 (C=O), 3440 (O–H); ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3H, 18–Me), 0.87 (d, 3H, *J* 7.2 Hz, 26 or 27–Me), 0.97 (d, 3H, *J* 7.2 Hz, 26 or 27–Me), 1.01 (s, 3H, 19–Me), 1.27 (s, 3H, 21–Me), 2.04 (s, 3H, C_3–OAc), 2.32 (m, 1H, C_{25}–H, 2H, C_{23}–H), 3.49 (m, 1H, C_{24}–H), 3.97 (m, 1H, C_{22}–H), 4.61 (m, 1H, C_3–H), 5.39 (d, 1H, *J* 4.8 Hz, C_6–H).

For **7**: m.p. 90–92 °C (hexane). IR (KBr) ν/cm^{-1} 1240 (–O–C=O), 1735 (C=O); ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3H, 18–Me), 0.87 (d, 3H, *J* 7.2 Hz, 26 or 27–Me), 0.97 (d, 3H, *J* 7.2 Hz, 26 or 27–Me), 1.03 (s, 3H, 19–Me), 1.30 (s, 3H, 21–Me), 2.05 (s, 3H, C_3–OAc), 2.10 (s, 3H, C_{22}–OAc), 2.34 (m, 1H, C_{25}–H, 2H, C_{23}–H), 3.57 (m, 1H, C_{24}–H), 4.65 (m, 1H, C_3–H), 4.97 (tr, 1H, *J* 7.2 Hz, C_{22}–H), 5.43 (d, 1H, *J* 4.8 Hz, C_6–H).

For **8**: IR (KBr) ν /cm^{-1} 1240 (–O–C=O), 1735, 1750 (C=O); ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3H, 18–Me), 0.94 (d, 3H, *J* 7.2 Hz, 26 or 27 Me), 1.01 (s, 3H, 19–Me), 1.03 (d, 3H, *J* 7.2 Hz, 26 or 27–Me), 1.27 (s, 3H, 21–Me), 2.05 (s, 3H, C_3–OAc), 2.33 (m, 2H, C_{23}–H), 3.82 (m, 1H, C_{24}–H), 4.62 (m, 1H, C_3–H), 5.52 (d, 1H, *J* 4.8 Hz, C_6–H).

The highly effective synthetic scheme described: steroidal isoxazole → furanone → tetrahydrofuranol demonstrates the utility of heterocyclic intermediates as efficient tools for the stereoselective construction of a steroidal polyfunctionalized side chain, namely, the formation of hydroxyl-containing chiral centres at C–20 and C–22 which are characteristic of many natural steroids.

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