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REGIO- AND STEREOSELECTIVE 1,4-REDUCTIONS OF METHYLATED, CROSS-CONJUGATED STEROIDAL CYCLOHEXADIENONES

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Summary. Regio- and stereoselectivities in conjugate reductions of steroidal 3-oxo-1,4-diene substrates, effected either directly by $Fe(CO)_5$-NaOH-H_2O in methanol solution or in two steps by $NaBH_4$ reduction/Jones oxidation, depend on the substitution pattern of ring A. C(1) and C(2) methylated derivatives furnish Δ^1-products with 5β-stereochemistry, whereas C(4) methylated and unsubstituted steroids both afford Δ^4-derivatives.

Familiar methods for the chemoselective 1,2-reduction of α,β-unsaturated ketones rely on DIBAH,[1] 9-BBN,[2] or $NaBH_4$-$CeCl_3$,[3] while the complementary task, saturation of enone C-C double bonds, may be accomplished by catalytic hydrogenation,[4] dissolving metal reduction,[5] or reagents like $PhCH_2NH_2$-*t*-BuOK,[6] $Fe(CO)_5$-NaOH-H_2O,[7] LiCuHR,[8] KR_3BH,[9] R_3SnH,[10] and Ph_2SiH_2-$Pd(Ph_3P)_4$-$ZnCl_2$,[11] to mention but a few.

In addition, some reagents in the latter category are capable of differentiating between two olefinic sites in steroidal 3-oxo-1,4-diene derivatives in favour of the C(1)-C(2) double bond, I→II.[4b, 5b, 7b, 11a]

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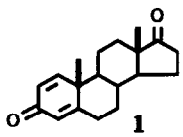
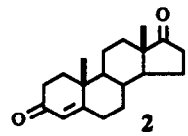
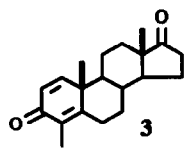
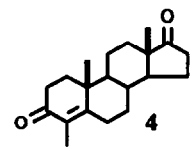
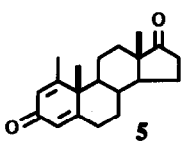
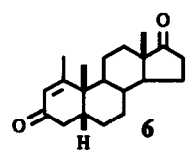
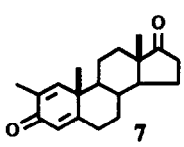
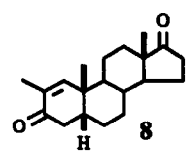
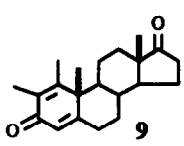
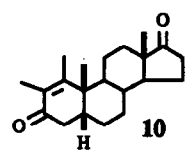
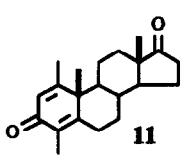
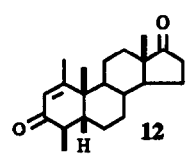
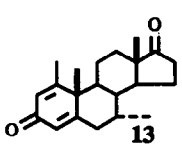
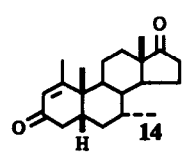
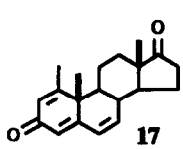
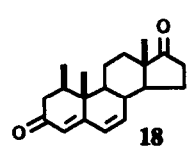
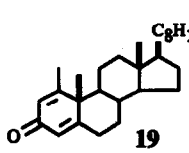
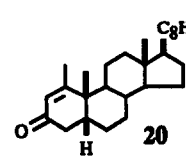
Since the origin of this selectivity is steric in nature, it was of interest to determine whether 1,4-reductions of ring A *substituted* steroidal cyclohexadienones proceed with synthetically useful regio- and stereocontrol. With emphasis on C(1) methylated steroids of pharmacological significance,[12] we demonstrate in this communication that regioselectivity is, in fact, reversed for this class of compounds as well as C(2) methylated analogues.

In exploratory studies, utilizing a number of the aforementioned reagents and the C(1) methylated derivative **5** as substrate, Noyori's procedure[7a] proved to be most satisfactory both with regard to overall efficiency and experimental convenience. For these reasons, the series of steroids listed in the Table was reduced under comparable conditions.

In accordance with previous observations,[7b] androsta-1,4-diene-3,17-dione (**1**) furnished androst-4-ene-

Table. $NaHFe(CO)_4$-Promoted Reduction Of Cross-Conjugated Steroidal Cyclohexadienones

Entry	Substrate	Reaction Conditions; Yield	Product
1	 **1**	50-60°C, 16 h; 85%	 **2**
2	 **3**	50-60°C, 18 h; 82%	 **4**
3	 **5**	50-60°C, 22 h; 95%	 **6**
4	 **7**	50-60°C, 7 days; 25%	 **8**
5	 **9**	22°C, 12 days; 86%	 **10**
6	 **11**	50-60°C, 7 days; 41%	 **12**
7a	 **13**	22°C, 14 days; 48%	 **14**
7b	**15** (7β-Me)	50-60°C, 22 h; 93%	**16** (7β-Me)
8	 **17**	50-60°C, 4 h; 43%	 **18**
9	 **19**	50-60°C, 24 h; 92%	 **20**

3,17-dione (**2**) in 85% yield, along with 10% of over-reduced material, after chromatography on silica gel (Entry 1). The C(4) methylated derivative **3** gave a similar result (Entry 2).

That hydride delivery onto C(1) methylated steroids **5** and **19** (Entry 3; 9 (C_8H_{17}: cholesterol side-chain)) had occurred exclusively on the β-face at C(5) to afford **6** in 95% and **20** in 92% yield, respectively, followed readily from the corresponding ^1H NMR spectra (300 MHz; $CDCl_3$). In both instances, this structural assignment is firmly based on the presence of an allylic methyl group (**6**: δ 2.02 ppm (d, J= 1.1 Hz); **20**: δ 2.00 ppm (d, J= 1.2 Hz)) and the resonance of the axial α-proton at C(4) (**6**: δ 2.79 ppm (dd, J= 18.4, 13.8 Hz); **20**: δ 2.82 ppm (dd, J= 17.6, 13.0 Hz)). Interestingly, a methyl group located at C(2) also blocks reduction of the C(1)-C(2) olefinic bond (Entry 4). The dismal yield (25%) in this example is largely a consequence of a low conversion; 60% of starting material was recovered unchanged.

In order to further define the scope and limitations of the current reaction, four examples with an additional methyl group at a characteristic position of the steroid backbone were also investigated. The 1,2-dimethyl derivative **9** was converted into **10** in 86% yield during 12 days at room temperature. Slow but preferential reduction of the tetrasubstituted enone double bond was observed with substrate **11**, resulting in a 41% yield of **12** and 52% recovery of starting material **11** after 7 days of reaction at 50-60°C. Severe steric interactions in the transition-state, caused by the axial methyl group at C(7) and the incipient axial bond at C(5), are believed to be responsible for the slow transformation of **13** into **14** (22°C, 14 days, 48%; 46% recovery of **13**). Higher reaction temperatures (50-60°C) led to appreciable over-reduction, providing a lower yield (< 40%) of the desired product **14**. The 7β-methyl derivative **15**, on the other hand, reacted smoothly to give **16** in 93% yield. As demonstrated by the example in Entry 8, a methyl group at C(1) does not always impede reduction of a C(1)-C(2) double bond. At 70% conversion under the reaction conditions indicated, 1β-methylandrosta-4,6-diene-3,17-dione (**18**) was isolated in 43% yield, along with 20% of recovered starting material, and a small amount of 1β-methylandrost-4-ene-3,17-dione. The latter compound formed the main product on longer reaction periods (10-18 h).

In an effort to secure a better yield of **8**, recourse was made to a two-step reduction-oxidation procedure, which had already been used for the regiocontrolled conversion of 17β-hydroxyandrosta-1,4-dien-3-one into 17β-hydroxyandrost-4-en-3-one (testosterone).[13] Contrary to our expectation, exposure of **7** to an excess of $NaBH_4$ in aqueous methanol (0-22°C, 4 h), followed by Jones oxidation of the crude product, proved to be inferior to the reduction method (Entry 4) described above. Analogous transformations with substrates **5** and **13**, however, provided enone derivatives **6** and **14** in acceptable 70% and 67% overall yield, respectively.

In conclusion, a methyl substituent at C(1) or C(2) in 3-oxo-1,4-diene steroid derivatives directs hydride attack with exceptional selectivity to the 5β-position, in contrast to C(1)/C(2) unsubstituted examples where reduction on the α-face at C(1) is preferred.[4b, 11a] This finding considerably improves the availability of ring A methylated steroid analogues, which are not readily obtained by alternate methods.[14]

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References and Notes

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14. Representative $NaHFe(CO)_4$-promoted reduction procedure. A Schlenk flask equipped with a stirring bar was flushed with argon and subsequently charged with deoxygenated methanol (30 mL), water (1.6 mL), and NaOH (600 mg, 15 mmol). This solution was stirred until the base had dissolved. Pentacarbonyliron (5.880 g, 30 mmol) was then added, followed by **5** (895 mg, 3 mmol), after an additional stirring period of 10 min. The flask was immersed into an oil bath and stirring of the reaction mixture under an atmosphere of argon was continued for 22 h at 50-60°C. The resulting dark-red solution was poured into a mixture consisting of ice-water (200 mL), sulfuric acid (100 mL, 1 molar), and CH_2Cl_2 (100 mL). After being vigorously stirred for 1 h, the organic layer was separated, washed with bicarbonate solution and water, and dried over anhydrous Na_2SO_4. The green solution was transferred onto a silica gel column, from which the colored iron species were eluted first with CH_2Cl_2, followed by **6** (856 mg, 95%), after switching to the solvent system CH_2Cl_2-EtOAc (1:1).
Physical data for selected reduction products are as follows. **6**: mp 200-201°C (ethyl acetate), $[\alpha]_D^{22}$ +187.2° (c 0.51); **8**: mp 170-171°C (acetone-hexane), $[\alpha]_D^{22}$ +191.4° (c 0.50); **10**: mp 140-141°C (acetone-hexane), $[\alpha]_D^{22}$ +205.4° (c 0.52); **12**: mp 231-235°C (acetone-hexane), $[\alpha]_D^{22}$ +183.8° (c 0.50); **14**: mp 142-144°C (acetone-hexane), $[\alpha]_D^{22}$ +147.8° (c 0.50); **16**: mp 150-151°C (acetone-hexane), $[\alpha]_D^{22}$ +224.6° (c 0.51); **18**: mp 169-170°C (acetone-hexane), $[\alpha]_D^{22}$ +231.8° (c 0.51); **20**: mp 138-139°C (hexane), $[\alpha]_D^{22}$ +102.8° (c 0.50). All $[\alpha]_D^{22}$-values were recorded in $CHCl_3$.

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