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Oxidation of natural targets by dioxiranes. Part 6: on the direct regio- and site-selective oxyfunctionalization of estrone and of 5α-androstane steroid derivatives ☆

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ABSTRACT

Using methyl(trifluoromethyl)dioxirane (**1b**), 3β,6α,17β-triacetoxy-5α-androstane (**6**) could be selectively transformed into its C-14 hydroxy derivative (**7**) and into the valuable C-12 ketone steroid (**8**), in high yields under mild reaction conditions. Similarly, the oxidation of 3α-estrone acetate (**4**) with **1b** was carried out to yield selectively the steroid C-9 hydroxy derivative (**5**). The high regio- and site-selectivity attained demonstrates that the powerful dioxirane **1b** is the reagent of choice to synthesize valuable oxyfunctionalized steroid derivatives.

After our initial investigations,[2] numerous studies have shown that dioxiranes **1**,[3] a class of powerful and versatile oxygen-transfer reagents, serve well in allowing one to achieve the site-selective remote oxyfunctionalization of alkane C–H bonds in several complex natural targets, including steroidal substrates.[2,4]

This appears significant since, in analogy with enzyme-controlled reactions in vitro,[5] the topic of biomimetic synthesis[6] has grown into one of major relevance in organic synthesis.

(**1a**: $R^1 = R^2 = CH_3$; **1b**: $R^1 = CH_3$, $R^2 = CF_3$)

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It is well recognized that the cytochrome P-450 oxidase-dependent systems in mammalian liver can oxidize regio -and stereoselectively unactivated C–H bonds of aliphatic and of aromatic hydrocarbons to give the corresponding hydroxylated compounds. In these transformations, regioselectivity typically results from a particular geometry of the intermediate enzyme/substrate complex, so that its outcome could entirely supplant the characteristic reactivity of the substrate. The *direct* enzymatic oxyfunctionalization of natural targets is rewarding primarily because it can often provide access to physiologically important compounds.[5] Therefore, a variety of oxygen-transfer reagents and methods have been devised to accomplish selectivities that are viable only using enzymes.[7,8] Among these, systems based on manganese(III) porphyrin catalysts, with the bulk oxidant most commonly being PhIO or H_2O_2 have acquired prominence.[7]

To mention one case that is exemplary, Breslow and coworkers[7a] set up to mimic enzyme geometrical control using the natural cytochrome P-450 enzyme as a model, as shown in the example sketched in Chart 1. Thus, the site-selective hydroxylation at the C-9 position of the androstane steroid **2** was elegantly achieved. Preliminarily, these authors synthesized robust fluorinated metalloporphyrin catalysts that retain the natural porphyrin mainstay.[7a] Suitable linkers and attached α-cyclodextrins (α-CD) were employed to produce an artificial binding pocket, so that the porphyrin metal oxo Mn=O group came nearly in van der Waals contact with the axial C9-H hydrogen.

It is seen that the site of the hydroxylation is determined by the particular geometry of the catalyst-substrate complex (**2a**, Chart 1); with 0.1 mol % of the catalyst the C-9 hydroxylated triester was formed in 100% yield, although with only 8% conversion. The selective oxidation produced, after hydrolysis, 5α-androstane-3β,6α,9α,17β-tetraol (**3**).[7a]

In a similar approach, Grieco et al. attached *covalently* a manganese porphyrin to a steroid framework and attained regioselective

☆ See Ref. 1.

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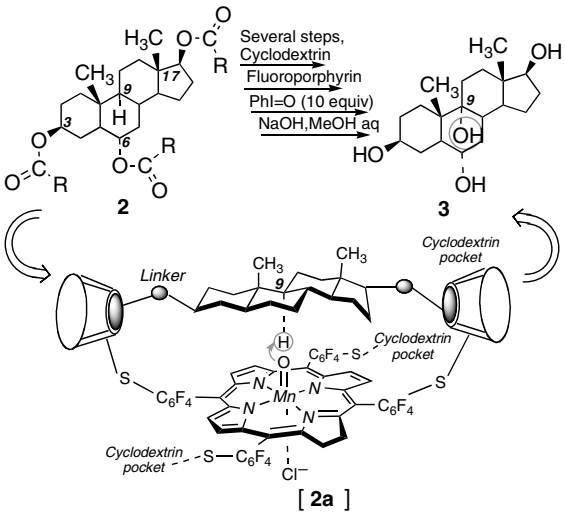


Chart 1. Biomimetic steroid hydroxylation by an artificial P-450 system.

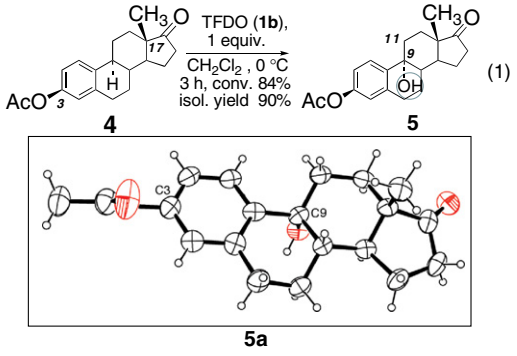
remote hydroxylations, controlled by the distance between the porphyrin metal oxo and a specific C–H site of the substrate.[7c]

Given the remarkable success of ingenious biomimetic methods,[7,8] much past and recent literature suggest that dioxirane oxidation can also be fruitful in the area of site-selective hydroxylation of steroids.[2–4]

We report herein that the reaction of estrone acetate (**4**) with methyl(trifluoromethyl)dioxirane (**1b**, TFDO),[1,9] readily affords the corresponding 9α-hydroxy derivative with excellent conversion and in high yield, under the mild conditions shown in Chart 2 (Eq. 1).

Using just 1.1 equiv of dioxirane **1b** standardized solution,[9] oxidation of substrate **4** was performed on the 80–100 mg scale; the simple procedure merely involved addition of an aliquot of dioxirane solution to the steroid dissolved in CH_2Cl_2 (5–10 mL) at 0 °C. The reaction progress was monitored by GC; product isolation simply entailed solvent removal in vacuo, followed by cold (0 °C) column flash chromatography of the residue, yielding crystalline **5**;[10] this product gave ^1H and ^{13}C NMR, IR, and GC/MS spectral data in full agreement with structure.[10] The stereochemistry was confirmed by single crystal X-ray analysis (ORTEP diagram **5a**, Chart 2).

In an early paper,[2c] we reported that, during the much *slower* (22 h) oxidation of substrate **4** with dimethyldioxirane (**1a**, DDO),[3] the formation of the C-9 hydroxylated steroid **5** could be detected by ^1H NMR in solution. However, **5** could not be isolated in substantial amounts, owing to its facile dehydration into 3-acetoxy-1,3,5(10),9(11)-estratetraen-17-one, its $\Delta^{9,11}$ unsaturated derivative.

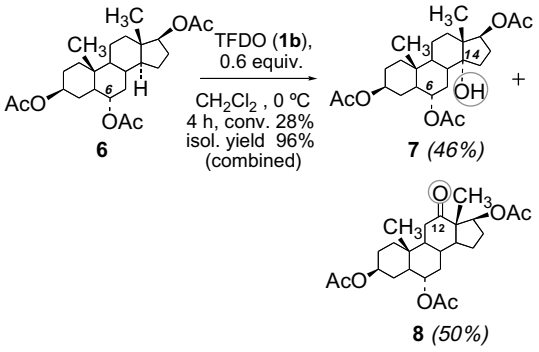


(1)

Chart 2.

Also interesting is the regioselectivities that we were able to attain using the powerful TFDO (**1b**) in the oxidation of 3β,6α,17β-androstane triacetate (**6**).[11]

In a brief communication,[12] it was reported that the reaction of 3β-acetoxyandrostane with DDO (**1a**) results in the exclusive formation of its 14α-hydroxy derivative. In our hands, under the conditions shown in Eq. 2, treatment of androstane triacetate (**6**) with the reactive TFDO results in the carbonyl product **8**[13] derived from selective oxidation at C-12, alongside with the alcohol **7**[14] expected from hydroxylation at the α-C14-H. It is seen that the two oxygenated derivatives are formed in practically equal amounts.



(2)

Substrate **6**[11] was obtained in 40% isolated yield upon treatment with Ac_2O/Py of 3β,6α,17β-trihydroxy andro-stane (**9**);[15] in turn, this triol was synthesized according to a reported procedure,[16] starting with the commercially available 3β-hydroxy-androst-5-en-17-one.

Of course, protection of the secondary CH–OH groups via acetylation is a necessary measure, if one wishes to prevent the facile dioxirane oxidation of the secondary alcohol functionalities to a carbonyl moiety.[3]

The oxidation was performed by the stepwise addition (during 20 min) of aliquots of a standardized TFDO solution to *excess* (ca. 2:1) triacetate **6** (2.4 mmol) in CH_2Cl_2 (90 mL), kept at 0 °C. The reaction was monitored upon following the peroxide titer decay (iodometry) with time;[3] after peroxide consumption (ca. 4 h) and solvent removal in vacuo, careful column chromatography (silica-gel, petroleum ether/Et_2O) of the residue permitted separation of **7** (0.31 mmol) from ketone **8** (0.34 mmol); the unreacted starting material (1.73 mmol) could also be recovered.

A few words are in order about the reaction conditions chosen to perform the oxidation (Eq. 2); in fact, efforts directed at reaction optimization revealed that it is crucial to employ the dioxirane oxidant in substantially lower than the stoichiometric amount in order to avoid overoxidation. Actually, overoxidation of **6** gives complex product mixtures that are difficult to separate.

This problem was well recognized by Iida et al.[4a] during careful studies that involved the oxyfunctionalization of a number of steroids related to the 5β-cholane and 5α-cholestane series by dimethyldioxirane (**1a**). In fact, these authors reported that prolonged exposure of the steroid substrates examined to the usually slow (24–48 h) DDO oxidation results in mixtures of polyoxygenated products.

To our knowledge, steroids **7** and **8** have not been reported previously. In their isolated form, each compound gave spectral data in excellent agreement with structure. For instance, the conversion of substrate **6** C14-H into product **7** C14-OH is easily detected from a change in the related ^1H- and ^{13}C NMR resonances (from δ 1.05 to 5.02, and from δ 50.4 to 89.9, respectively).[14] In parallel, formation of ketone **8** is accompanied by the appearance of a characteristic ^{13}C NMR carbonyl resonance (δ 211.3), and of a new strong C=O stretching band at 1713 cm^{-1} in the IR spectrum.[13] The structure

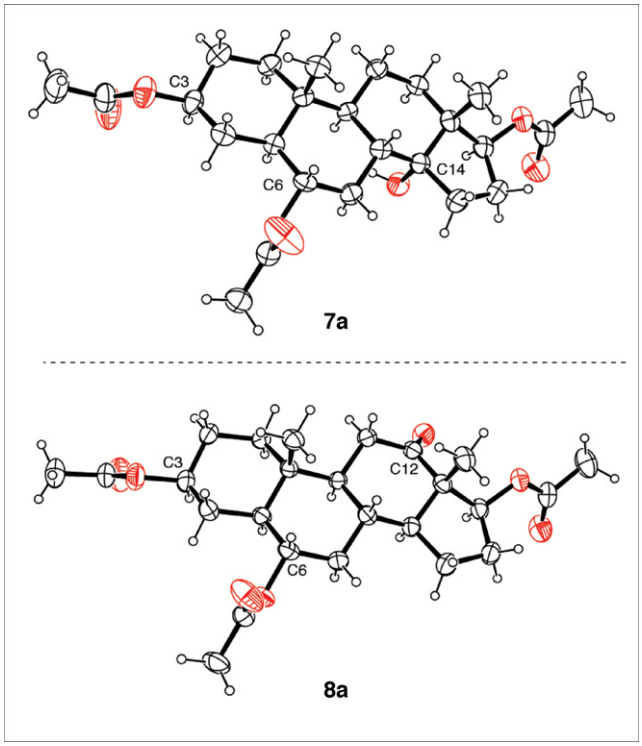


Chart 3. ORTEP view of compounds **7** and **8**.

of both derivatives **7** and **8** became separately established by crystal X-ray analysis (cf., ORTEP diagrams **7a** and **8a**, Chart 3).

The feat of the direct synthesis of the C-12 ketone **8** seems particularly significant. In fact, after the pioneering work by Marples et al.,[16a] it was shown that such steroidal C12=O carbonyl groups can be selectively α-brominated at C-11 easily.[16] This opens the road to the synthesis of a number of valuable C-11 functionalized steroid derivatives that are HIV-1 protease inhibitors, a challenging goal in organic synthesis.[16]

In our case, it is also worthy of note that formation of the 12-oxo compound **8** occurs concurrently with **7**, the product from hydroxylation at the C-14 tertiary carbon. Quite likely, the C-12 ketone derives from the fast consecutive oxidation of the initially formed sec-alcohol C12H–OH.[17] Actually, in dioxirane oxidation of steroids,[2–4] it is rarely observed that ketogenesis from unactivated methylene CH_2 moieties competes efficiently with the amply favored hydroxylation at tertiary C–H's (a common trait of dioxirane O-insertion into alkane bonds).[3,4b,18]

Our results suggest that the presence of an acetoxy function at the C-6 position in the substrate may significantly affect the selectivity of the dioxirane oxyfunctionalization. Clearly, in structurally complex molecules, the electrophilic O-insertion by the dioxirane can be significantly influenced by the particular steric environment or/and by the electron density of the target C–H bonds.[3]

Be the details of the mechanism as they may, we believe that results herein contribute to reinforce the notion that the application of dioxiranes—especially the powerful TFDO (**1b**)—efficiently provides access to useful new steroid derivatives, and this without the need of elaborate multi-step synthetic procedures and/or the application of costly catalysts.

Acknowledgements

Partial support by the Italian Ministry of University and of Scientific Research and by CNR (Italy) is gratefully acknowledged. We thank Dr. C. D. Calvano for her help in running the mass spectra. The files containing the complete crystallographic data for the structures in this Letter are available upon request from the Cambridge Crystallographic Data Centre (12 Union Road, Cambridge, CB2 1EZ, UK; email: deposit@ccdc.cam.ac.uk.): **5a** (no. 691166), triacetate **6** (no. 691164), **7a** (no. 691165), and **8a** (no. 691167).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.042.

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10. *3-Acetoxy-9α-hydroxy-1,3,5(10)-estratrien-17-one* (**5**): white solid (mp 161–163 °C, lit.[2c] 162–164 °C); column chromatography (silicagel, petroleum ether/ethyl acetate 1:1) yields **5** (purity > 98%, GC); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45 (d, *J* = 8.5 Hz 1H), 6.83 (d, *J* = 8 Hz, 1H), 6.78 (s, 1H), 2.83 (br, 2H), 2.45–1.20 (m, 12H), 2.21 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 220.55, 169.54, 149.75, 139.03, 138.30, 126.40, 122.12, 119.36, 69.81, 47.54, 42.92, 40.99, 35.80, 32.02, 29.26, 27.50, 21.32, 21.04, 19.83, 12.80. ORTEP diagram **5a**: CCDC No. 691166; salient crystallo-graphic data: $C_{20}H_{24}O_4{\cdot}H_2O$, M_T = 344.39 g mol^{-1}, orthorhombic, space group: $P2_12_12_1$, *a* = 13.803(2), *b* = 8.020(1), *c* = 16.416(3) Å, α = β = γ = 90°; cell volume = 1817.3(5) Å^3, *Z* = 4, *T* = 293(2) K, ρ_c = 1.259 g cm^{-3}, μ = 0.090 mm^{-1}, ϑ range = 5.08–27.53°. The SHELXL-97 program was employed for refinement.
11. *3β,6α,17β-Triacetoxy- 5α-androstane* (**6**): white solid (mp 154–156 °C). ^{1}H- and ^{13}C NMR data in agreement with literature (Chambers, V.E.M.; Denny, W.A.; Evans, J.M.; Jones, E.R.H.; Kasal, A.; Meakins, G.D.; Pragnell, J. *J. Chem. Soc. Perkin I* **1973**, 1500). Crystal structure: present work, CCDC No. 691164.
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13. *3β,6α,17β-Triacetoxy-5α-androstan-12-one* (**8**): white solid mp 180–183 °C; column chromatography (silicagel, petroleum ether/Et_2O 2:3) affords **8** (purity > 98%, GC); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.08 (broad t, *J* = 7.5 Hz, 1H), 4.72 (td, *J* = 11 Hz, *J* = 4 Hz, 1H), 4.65 (quintet, *J* = 6.5 Hz, 1H), 2.44–2.07 (m, 3H), 2.03–2.02 (s, 9H), 1.95–1.20 (m, 15H), 0.98 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 211.34, 170.79, 170.43, 170.39, 74.36, 72.47, 71.39, 55.45, 54.69, 50.42, 48.15, 37.40, 36.83, 36.39, 34.09, 28.32, 26.84, 22.75, 22.31, 21.32, 21.16, 21.04, 14.02, 12.85, 12.07; IR (KBr pellet): 2936, 1730, 1713, 1454, 1383, 1250, 1048, 1024, 902, 803 cm^{-1}; $[\alpha]_D$ +88.3 (*c* = 0.72, $CHCl_3$). GC–MS (EI 70 eV, SIM scan mode) *m*/*z* 448.0354 (M$^+$); calcd for $C_{25}H_{36}O_7$: *m*/*z* 448.2461. ORTEP diagram **8a**: CCDC No. 691167; salient crystallographic data: $C_{25}H_{36}O_7$, M_T = 448.54 g mol^{-1}, orthorhombic, space group: $P2_12_12_1$, *a* = 11.523(3), *b* = 12.072(5), *c* = 18.288(9) Å, α = β = γ = 90°; cell volume = 2544.0(18) Å^3, *Z* = 4, *T* = 293(2) K, ρ_c = 1.171 g cm^{-3}, μ = 0.085 mm^{-1}, ϑ range = 5.02–27.54°. The SHELXL-97 employed for refinement.
14. *3β,6α,17β-Triacetoxy-5α-androstan-14a-ol* (**7**): white solid (mp 160–163 °C); column chromatography (silicagel, petroleum ether/Et_2O 2:3) gives **7** (purity > 98%, GC); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.21–4.60 (m, 3H), 2.40–2.30 (m, 2H), 2.10 (s, 9H), 1.89–1.10 (m, 18H), 0.93 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$,

125 MHz): δ 171.16, 170.90, 170.53, 82.83, 80.89, 72.91, 72.19, 48.12, 46.90, 46.30, 37.00, 36.90, 36.56, 32.47, 31.82, 29.06, 28.31, 27.08, 26.84, 21.39, 21.24, 21.18, 19.60, 15.98, 13.01; IR (KBr pellet): 3567, 2955, 1734, 1653, 1473, 1457, 1375, 1252, 1031, 804 cm^{-1}. $[\alpha]_D$ 55.6 (c = 0.14, $CHCl_3$); GC–MS (EI 70 eV, SIM scan mode) m/z 450.1727 (M^+); calcd for $C_{25}H_{38}O_7$: m/z 450.2618. ORTEP diagram **7a**: CCDC No. 691165; salient crystallographic data: $C_{25}H_{38}O_7$, M_T = 450.55 g mol^{-1}, orthorhombic, space group: $P2_12_12_1$, a = 11.508(2), b = 11.916(2), c = 18.560(3) Å, $\alpha = \beta = \gamma = 90°$; cell volume = 2545.1(6) $Å^3$, Z = 4, T = 293(2) K, ρ_c = 1.176 g cm^{-3}, μ = 0.085 mm^{-1}, ϑ range = 5.04–27.50°. Refinement by SHELXL-97.

15. *5α-Androstane-3β,6α,17β-triol* (**9**): white solid (mp 231–233 °C, lit. 232–234 °C); spectral data in agreement with literature. (De Munari, S.; Cerri, A.; Gobbini, M.; Almirante, N.; Banfi, L.; Carzana, G.; Ferrari, P.; Marazzi, G.; Micheletti, R.; Schiavone, A.; Sputore, S.; Torri, M.; Zappavigna, M. P.; Melloni, P. *J. Med. Chem.* **2003**, *46*, 3644).
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