Notes

Regio- and Stereoselective Epoxidation of Steroidal 1,4-Diene 3-Ones by Dimethyldioxirane: A New Access to A-Norsteroids and to a Class of Estrogen Synthetase Inhibitors

Paolo Bovicelli* and Paolo Lupattelli†

Centro C.N.R. di studio per la Chimica delle Sostanze Organiche Naturali, Dipartimento di Chimica, Università "La Sapienza", P.le A. Moro 5, 00185 Roma, Italy

Enrico Mincione

D.A.B.A.C., Università della Tuscia, V.S. Camillo De Lellis, 01100 Viterbo, Italy

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1,4-Diene 3-one steroidal compounds are generally considered useful starting materials in the synthesis of biologically active molecules and special classes of steroids.[1] To our knowledge, the most common epoxidizing agents are known to show a very low efficiency on this system. 4,5-Epoxy-1-cholesten-3-one may indeed be obtained from 1,4-cholesten-3-one only under particular reaction conditions[2] while epoxidation of the 1,2-double bond is achieved only by multistep procedures.[3] Dioxiranes have shown a very high oxidative power both in situ[4] and in isolated form,[5] since the most commonly employed dioxiranes, dimethyldioxirane (**1**) and methyl(trifluoromethyl)dioxirane, have been employed to perform a variety of synthetic transformations.[6] In previous papers[7] we reported epoxidations of steroidal olefins and oxygen atom insertions by **1** in the C–H σ bonds of steroidal substrates. We noted a very high sensitivity of dioxiranes to stereoelectronic effects which resulted in an unusual and biomimetic site selectivity in the hydroxylation of androstane and pregnane steroids.[7d]

For their wide synthetic applications, we now report on the results of epoxidations of 1,4-diene 3-one systems with dimethyldioxirane (**1**) in isolated form.

1

As we reported earlier,[7a] prednisone acetate (**2**) was readily converted to its 1α,2α-oxirane derivative **3** in 80% yield, while the rest of the reaction mixture was formed by 4,5-epoxides **4** and **5** in the diastereoisomeric ratio β:α = 3:2 (Table 1, entry 1). In this case, dimethyldioxirane showed an unexpectedly high regioselectivity toward the less nucleophilic double bond. We noted that this chemical behavior is general, since the epoxidation of 1,4-androstadiene-3,11,17-trione (**6**) rapidly led to the 1α,2α-oxirane **7** in high yield (entry 2). This high regioselectivity is due exclusively to the presence of the carbonyl moiety at C_{11}.

A complete inversion of the regioselectivity of the epoxidation indeed occurs with 1,4-diene 3-one steroidal compounds, which lack a carbonyl moiety at C_{11}, as reported in Table 1. Compounds **10**, **15**, and **20**[8] afforded the respective 4,5-epoxy derivatives **12**, **17**, and **21**, with a regioselectivity of approximately 80–90% (entries 3, 4, and 5), which is governed by the higher nucleophilicity of the 4,5-double bond; these reactions yielded the thermodynamically more stable β-isomers as the major products.

From a simple examination of Dreiding models we may assume a close dipole–dipole interaction between **1** and the carbonyl moiety at C_{11}, thus favoring the epoxidation of the 1,2-double bond. The C_{11} carbonyl moiety also shows a stereoorienting effect in the reaction, which favors the approach of dimethyldioxirane on the α-face of the dienonic A-ring. In the epoxidations of **10** and **15** (entries 3 and 4), we noted amounts of 1β,2β-epoxides (**14** and **19**, respectively) which were not detectable in the case of compounds **2** and **6** (entries 1 and 2) endowed with the C_{11} carbonyl moiety. A close dipole–dipole interaction forces the dioxirane to align its dipole with that of the carbonyl; thus, the only molecules of dioxirane to reach the 1,2-double bond are those approaching the steroidal α-face, whereas the approach on the β-face of the double bond is forbidden by the C_{19} methyl group. This different dioxirane approach to the 1,2-double bond of compounds **2** and **6**, compared to that of compounds **10**, **15**, and **20**, is the reason for the complete stereoselectivity observed .

As for potential applications in synthesis, the alternative epoxidations of 1,2- or 4,5-double bonds of 1,4-diene 3-one steroidal compounds are particularly telling. 4,5-

* To whom correspondence should be addressed.

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(8) The isolation of 4β,5β-epoxie **21** is achieved keeping the conversion <50% with reaction times no longer than 24 h. With a total dioxirane/substrate ratio = 9, the main product is 4β,5β-epoxy-25-hydroxy-1-cholesten-3-one (**22**). Worthy note, in this case oxidation of the C^{25}–H moiety precedes epoxidation at the C^1=C^2 double bond of the epoxy enone **21**.

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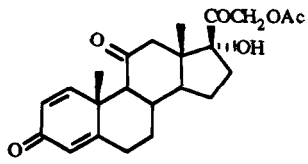
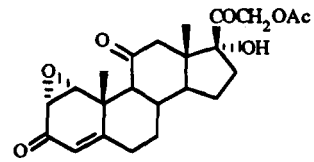
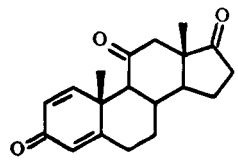
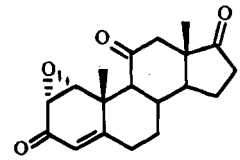
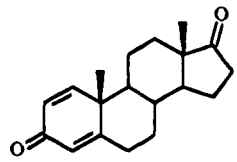
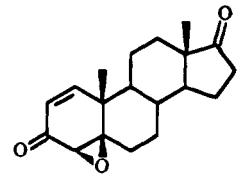
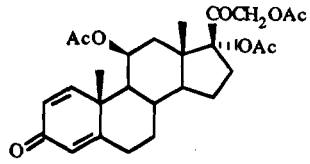
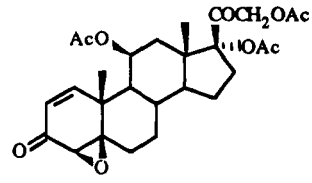
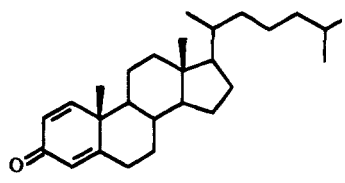
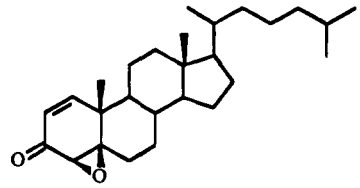
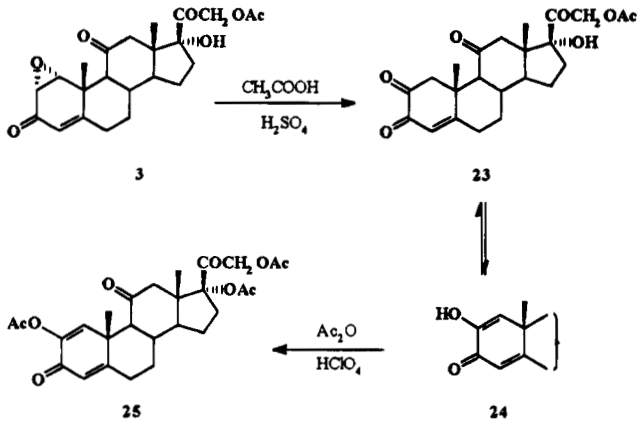
Table 1. Epoxidation of Steroidal 1,4-Diene 3-Ones by Dimethyldioxirane[a]

entry	substrate	reactn time	% conv.[b]	products	% yield
1		20 h	>95		
	2			3	80[c]
				4 4β,5β-epoxide	16[d]
				5 4α,5α-epoxide	4[d]
2		20 h	>95		
	6			7	80[c]
				8 4β,5β-epoxide	15[d]
				9 4α,5α-epoxide	5.0[d]
3		28 h	>92		
	10			12	81[c]
				11 4α,5α-epoxide	12[d]
				13 1α,2α-epoxide	5.8[d]
				14 1β,2β-epoxide	1.2[d]
4		24 h	81		
	15			17	61[d]
				16 4α,5α-epoxide	14[d]
				18 1α,2α-epoxide	21[d]
				19 1β,2β-epoxide	4[d]
5		24 h	50		
	20			21	78[c,e]
6		72 h	>95	22 4β5β-epoxy-25-ol	40[c,f]

[a] Unless noted otherwise, reactions were routinely run with initial dioxirane to substrate molar ratio ca. 3:1 in mixed solvent CH_2Cl_2/acetone (ca. 1:3) for oxidations with **1**. [b] As determined (±2%) by GC. [c] Data refer to yields (±2%) in product isolated after column chromatography and are based on the amount of substrate consumed; products were identified upon their ^1H and ^{13}C NMR spectra. [d] yields determined by ^1H NMR analysis of purified mixture. [e] In the reaction mixture, before separation, GC/MS and ^1H NMR showed small amounts (4-5%) of 1α,2α-epoxy-4-cholesten-3-one and **22**. [f] The reaction was performed by adding three mols of **1** every 24h, after concentration of the reaction mixture.

Scheme 1



Epoxy-1-androstene-3,17-diones **11** and **12** in fact represent key intermediates[9] to the 4-amino 1,4-diene 3-one derivative, one of the most active estrogen synthetase inhibitors.[10] Alternatively 1α,2α-epoxides **3** and **7** may be key intermediates in the synthesis of A-norsteroids, with the Pfister route[3] via photochemical ring contraction of epoxy enones.

Moreover, epoxy enone **3** was readily transformed into 2,3-diketo derivative **23** by acidic cleavage of the oxirane ring (Scheme 1). This intermediate may easily be transformed either into A-norcorticoids, via benzylic ring contraction[11] of its more stable enolic derivative **24**, or into heterocyclic steroids with high pharmacological activity, as with azasteroids.[12]

Experimental Section

Equipment. Melting points were not corrected. The ^1H and ^{13}C NMR spectra were recorded on a 200-MHz spectrometer. Mass spectra were run employing a mass selective detector connected to a gas chromatograph. The GLC analyses were performed on a gas chromatograph equipped with a 25 m × 0.11 μm film thickness capillary column.

Materials. Commercial androsta-1,4-diene-3,11,17-trione (**6**) and androsta-1,4-diene-3,7-dione (**10**) were used without further purification. Cholesta-1,4-dien-3-one (**20**) [mp 111–112 °C][13] was synthesized by a literature procedure[14] from commercial 4-cholesten-3-one. 21-Acetoxy-17α-hydroxy-1,4-pregnadiene-3,11,20-trione (**2**) [mp 219–220 °C][7a] was obtained upon treatment with Ac_2O/Py of commercial 17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione. 11β,17α,21-Triacetoxy-1,4-pregnadiene-3,20-dione (**15**) [mp 99–103 °C][15] was prepared according to the literature procedure[16] from commercial 11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate.

All starting materials gave satisfactory ^1H and/or ^{13}C NMR spectra. Solutions of dimethyldioxirane in acetone were obtained as described in the literature.[5a,17] Minor products were identified by comparing the ^1H NMR data with those reported in the literature for analogous compounds.[18]

Dioxirane Reaction with Steroids 2, 6, 10, 15, and 20. An aliquot of a standarized[5c,17,19] cold solution of dimethyldioxirane (ca. 0.09 M in acetone) was rapidly added to a stirred solution of the steroidal substrate (100–150 mg) in CH_2Cl_2 (4–6 mL) kept by a thermostat at room temperature (ca. 20 °C), with a dioxirane:substrate molar ratio of from 2.5:1 to 3.5:1. The reaction was carried out to a suitable conversion point (GC or TLC monitoring), by adding further dioxirane aliquots when necessary; the product isolation was then achieved by removal of the solvent in vacuo which was followed by column flash chromatography (silica gel, *n*-hexane/AcOEt).

21-Acetoxy-1α,2α-epoxy-17α-hydroxy-4-pregnene-1,11,-20-trione (3): 100 mg from 120 mg of **2**, yield 80%; mp and ^1H and ^{13}C NMR in agreement with literature values.[7a]

21-Acetoxy-4,5-epoxy-17α-hydroxy-1-pregnene-3,11,20-trione 4 and **5**, as a mixture of 4β,5β-epoxide and 4α,5α-epoxide (ratio β:α = 4:1), were detected in the ^1H NMR spectra of the reaction mixture: ^1H NMR (200 MHz, $CDCl_3$) δ 3.20 (d, J = 2.0 Hz, 0.8 H), 3.32 (d, J = 2.0 Hz, 0.2 H), 4.62 (d, J = 18 Hz, 1 H), 5.16 (d, J = 18 Hz, 1 H), 5.78 (brs, $W_{1/2}$ = 5.6 Hz, 1 H), 7.14 (d, J = 10.6 Hz, 0.8 H), 7.16 (d, J = 10.6 Hz, 0.2 H).

1α,2α-Epoxy-4-androstene-3,11,17-trione (7): 126 mg from 150 mg of **6**, yield 80%. After recrystallization from *n*-hexane–ether: mp 233–235 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (s, 3 H), 1.46 (s, 3 H), 3.37 (dd, 1 H, J = 3.9 and 2 Hz), 4.26 (d, 1 H, J = 3.9 Hz), 5.70 (br, 1 H); $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$) δ 14.58, 18.54, 21.39, 29.51, 30.89, 32.02, 35.76, 40.12, 49.41, 49.88, 50.12, 55.01, 58.87, 60.41, 60.46, 121.05, 169.44, 199.88, 207.75, 216.66. Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.58; H, 7.06. Found: C, 72.61; H, 7.10.

4,5-Epoxy-1-androstene-3,11,17-trione 8 and **9**, as a mixture of 4α,5α-epoxide and 4β,5β-epoxide (ratio β:α = 3:1), were detected in the ^1H NMR spectra of the reaction mixture: ^1H NMR (200 MHz, $CDCl_3$) δ 3.20 (d, J = 2.0 Hz, 0.75 H), 3.32 (d, J = 2.0 Hz, 0.25 H), 5.79 (brs, $W_{1/2}$ = 5.6 Hz, 1 H), 7.11 (d, J = 10.6 Hz).

4α,5α-Epoxy-1-androstene-3,17-dione (11) was detected in the ^1H NMR spectra of the mixture with **5** (ratio 1:1): ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (s, 3 H), 1.17 (s, 3 H), 3.30 (s, 1 H, J = 2.0 Hz), 5.79 (dd, 1 H, J = 10.7 and 2.0 Hz), 6.70 (d, 1 H, J = 10.7 Hz).

4β,5β-Epoxy-1-androstene-3,17-dione (12): 104 mg from 130 mg of **10**, yield 80%. After recrystallization from *n*-hexane–ether: mp 248–250 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (s, 3 H), 1.30 (s, 3 H), 3.20 (d, 1 H, J = 2.0 Hz), 5.83 (dd, 1 H, J = 10.7 and 2.0 Hz), 6.49 (d, 1 H, J = 10.7 Hz); $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$) δ 13.49–15.99, 21.35, 21.55, 28.59, 29.69, 30.86, 34.56, 35.33, 42.21–47.32, 50.23, 53.91, 62.20, 66.81, 123.53, 155.09, 195.91, 220.12; MS (70 eV) m/z 300 (M^+), 285 (M^+ – 15). Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.96; H, 8.06. Found: C, 75.99; H, 8.09.

1,2-Epoxy-4-androstene-3,17-dione 13 and **14**, as a mixture of 1α,2α-epoxide and 1β,2β-epoxide (ratio α:β = 5.8:1.2), were detected in the ^1H NMR spectra of the reaction mixture: ^1H NMR (200 MHz, $CDCl_3$) δ 3.28 (brs, 0.17 H), 3.35 (brs, 0.83 H), 3.47 (d, J = 3.7 Hz, 0.83 H), 3.60 (d, J = 4.0 Hz, 0.17 H).

The epoxides **16**, **17**, **18**, and **19** were characterized by ^1H NMR of the crude from reaction of **15** with **1**.

4α,5α-Epoxy-11β,17α,21-triacetoxy-1-pregnene-3,20-dione (16): ^1H NMR (200 MHz, $CDCl_3$) δ. 3.29 (d, J = 2.0 Hz, 0.14 H), 5.80 (dd, J = 10.6 and 2.0 Hz, 0.14 H), 6.59 (d, J = 10.6 Hz, 0.14 H).

4β,5β-Epoxy-11β,17α,21-triacetoxy-1-pregnene-3,20-dione (17): ^1H NMR (200 MHz, $CDCl_3$) δ 3.23 (d, J = 2.0 Hz, 0.61 H), 5.88 (dd, J = 10.6 and 2.0 Hz, 0.61 H), 6.41 (d, J = 10.6 Hz, 0.61 H).

1α,2α-Epoxy-11β,17α,21-triacetoxy-4-pregnene-3,20-dione (18): ^1H NMR (200 MHz, $CDCl_3$) δ 3.29 (dd, J = 3.9 and 2.0 Hz, 0.21 H), 3.45 (d, J = 3.9 Hz, 0.21 H), 5.61 (brs, 0.21 H).

1β,2β-Epoxy-11β,17α,21-triacetoxy-4-pregnene-3,20-trione (19): ^1H NMR (200 MHz, $CDCl_3$) δ 3.35 (dd, J = 4.0 and 2.0 Hz, 0.04 H), 3.57 (d, J = 3.9 Hz, 0.04 H), 5.62 (brs, 0.04 H).

4β,5β-Epoxy-1-cholesten-3-one[8] (21): 61 mg from 150 mg of **20**, yield 78%. After recrystallization from petroleum ether–acetone: mp 113–115 °C; ^1H NMR (200 MHz, $CDCl_3$) δ

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0.68 (s, 3 H), 0.83 (d, J = 6.6 Hz, 6 H), 0.86 (d, J = 6.3 Hz, 3 H), 1.28 (s, 3 H), 3.19 (d, J = 2.0 Hz, 1 H), 5.83 (dd, J = 10.6 Hz and 2.0 Hz), 6.51 (d, J = 10.6 Hz, 1 H); $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$) δ 11.74, 16.01, 18.41, 22.06, 22.37, 22.63, 23.65, 24.04, 27.75, 27.84, 29.81, 30.00, 35.00, 35.59, 35.95, 39.18, 39.35, 42.29, 53.95, 55.26, 56.04, 62.34, 67.17, 123.20, 156.10, 196.39. Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.34; H, 10.67. Found: C, 81.36; H, 10.67.

4β,5β-Epoxy-25-hydroxy-1-cholesten-3-one[8] (22): 62 mg from 150 mg of **20**, yield 40%; oil; ^1H NMR (200 MHz, $CDCl_3$) δ 0.67 (s, 3 H), 0.88 (d, J = 6.3 Hz), 1.18 (s, 6 H), 1.27 (s, 3 H), 3.19 (d, J = 2.0 Hz), 5.83 (dd, J = 10.6 and 2.0 Hz), 6.51 (d, J = 10.6 Hz, 1 H); $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$) δ 11.75–12, 16.00, 18.39, 20.64, 22.07, 24.03, 27.77, 29.08, 29.18, 29.81, 30.00, 35.02, 35.56, 36.24, 39.20, 42.33, 44.26, 53.96, 55.28, 56.02, 62.35 (C^2), 67.17, 71.10, 123.22, 156.08, 196.42.

2,17α,21-Triacetoxy-1,4-pregnadiene-3,11,20-trione (25). A mixture of **3** (80 mg, 0.19 mmol), glacial acetic acid (4 mL), and sulfuric acid (0.05 mL) was stirred at 60 °C for 4 h. The acidic reaction mixture was cooled at 0–5 °C, neutralized with sodium bicarbonate solution, and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate, and the solvent was evaporated in vacuo. After rapid filtration over silica gel, 61 mg (77%) of oil product was obtained. ^1H NMR analysis resulted in a mixture of **24** and **23** (ratio 3:2): ^{H} NMR (200 MHz, $CDCl_3$) δ 0.66 (s, 3 H), 1.42 (s, 3 H), 2.14 (s, 3 H), 4.62 (d, J = 17.6 Hz), 5.90 (d, J = 17.6 Hz), 6.17 (s, 0.4 H), 6.24 (s, 0.6 Hz), 6.93 (s, 0.6 H).

After being dissolved in 3 mL of chloroform, the crude product was acetylated by treatment with 0.6 mL of acetic anhydride and 0.05 mL of 70% perchloric acid at room temperature for 2 h. The product was then neutralized with sodium bicarbonate solution, extracted with ethyl acetate, and dried over sodium sulfate and the solvent was finally evaporated in vacuo to give 60 mg of **25**: oil: ^1H NMR (200 MHz, $CDCl_3$) δ 0.74 (s, 3 H), 1.47 (s, 3 H), 2.10, 2.15, 2.24 (3s, 9 H), 4.66 (d, J = 16.7 Hz, 1 H), 4.78 (d, J = 16.7 Hz, 1 H), 6.13 (s, 1 H), 7.34 (s, 1 H); $\{^1H\}^{13}C$ NMR (50 MHz, $CDCl_3$) δ 14.73–15.08, 18.91, 20.24, 20.92, 23.25, 30.76, 31.60, 33.30, 35.43, 43.04, 49.32, 49.77, 50.36, 60.25, 65.78, 66.90, 93.14, 124.53, 140.73, 145.15, 166.17, 169.02, 170.54, 170.82, 198.63, 208.01.

Supplementary Material Available: 200-MHz ^1H NMR of **4** and **5** (mixture), **7**, **8** and **9** (mixture), **5** and **11** (mixture), **12**, **13** and **14** (mixture), **16–19** (mixture), **21**, **22**, **23** and **24** (mixture), and **25**, and 50-MHz $\{^1H\}^{13}C$ NMR of the isolated compounds **7**, **12**, **21**, **22**, and **25** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.