The Stereochemistry of Epoxidation of Steroidal 4,6-Dienes

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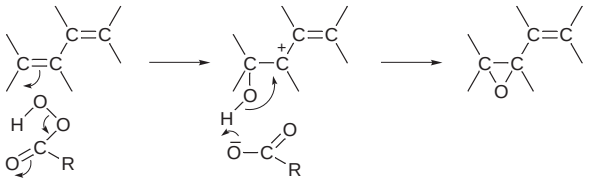
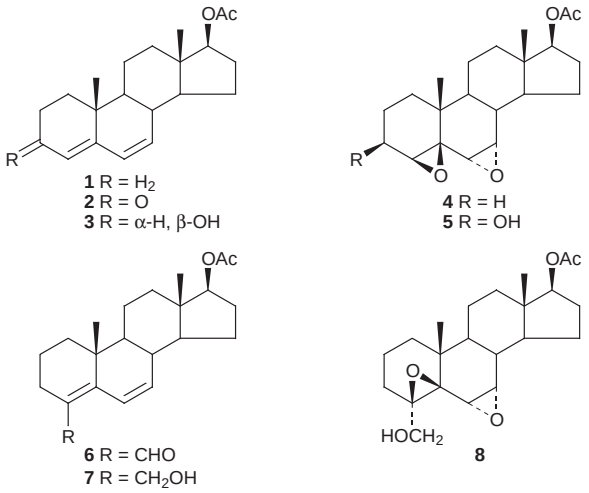
The epoxidation of some androsta-4,6-dienes with *m*-chloroperbenzoic acid has been shown to give the 4β,5β;6α,7α-diepoxides, the stereochemistry can be rationalized in terms of the directing effect of one epoxide on the facial selectivity of the second epoxidation.

Whilst the balance between the various stereoelectronic factors that control the stereochemistry of epoxidation of steroidal alkenes has been thoroughly investigated,[1,2] apart from ergosterol[3] and lumisterol[4] in which the 5,6-double bond is attacked preferentially, there have been relatively few studies of the epoxidation of conjugated steroidal dienes. A number of features may affect the stereochemistry of the reaction. The initial axial attack on the diene involves an interaction between the π-HOMO of the alkene and the σ* LUMO of the O–O bond of the peracid.[5] The peracid may be directed to the α-face of the steroid by unfavourable interactions with the C-10 angular methyl group on the β-face. Allylic interactions between the adjacent double-bond and the intermediate in the epoxidation might favour a particular site of attack by stabilizing an adjacent carbocationic intermediate (Scheme 1). Once the initial epoxide has been formed, the stereochemistry of the second epoxidation may, in part, be determined by a repulsive interaction between the non-bonding electrons of the epoxide oxygen and the π-electrons of the alkene. This would lead to a higher electron density on the face of the alkene that is *trans* to the first epoxide. Hence attack on the second double bond by the peracid might be directed to take place *trans* to the first epoxide. Thus in determining the overall stereochemistry of diepoxidation of a diene, there could be a balance between this effect, the steric directing effect of the angular methyl group and other neighbouring group effects. In this paper we report the epoxidation of some androsta-4,6-dienes.[8] Initial attack by a peracid should be directed to a pseudo-axial site on the face opposite to the C-10 methyl group and at the terminus of the diene. This position is C-7α and it would lead in the first instance to the 6α,7α-epoxide. The α-oriented epoxide would in turn direct the second epoxidation to the β-face of the 4,5-double bond leading to the 4β,5β;6α,7α-diepoxide. This would contrast with the epoxidation of an isolated 4,5-double bond which gives the 4α,5α-epoxide as the major product.[9]



Scheme 1

Epoxidation of 17β-acetoxyandrosta-4,6-diene **1**[8] with *m*-chloroperbenzoic acid gave a single diepoxide **4** in 82% yield. The stereochemistry of this was established by X-ray crystallography (Fig. 1). Reduction of 17β-acetoxy-androsta-4,6-dien-3-one 2 gave the 3β-alcohol 3.[10] The epoxidation of this diene gave a diepoxide **5** in 64% yield. The diepoxide was assigned the 4β,5β;6α,7α- stereochemistry on the basis of ^{1}H NMR experiments.



Treatment of 17β-acetoxyandrosta-4,6-diene **1** with *N*-formylmorpholine under modified Vilsmeier–Haack conditions[11] gave 17β-acetoxy-4-formylandrosta-4,6-diene **6**. Reduction of the aldehyde gave 17β-acetoxy-4-hydroxymethylandrosta-4,6-diene **7**. The ^{1}H NMR spectrum of the corresponding diepoxide showed that it possessed the 4β,5β;6α,7α-stereochemistry.

The stereochemistry of each of these epoxidations has followed the same pattern in which it is possible that epoxidation of the 6,7-double bond from the less hindered α-face has directed epoxidation of the 4,5-alkene to the β-face despite the steric hinderance of the transannular axial methyl group at C-10.

Crystallographic Data and Structure Determination for Compound **4**.—$C_{21}H_{30}O_4$, $M_r = 346.5$, monoclinic, space group $P2_1$ (no. 4), $a = 11.918(4)$, $b = 6.066(5)$, $c = 14.093(2)$ Å, $\beta = 113.06(2)^0$; $V = 937.4(8)$ Å^3, $Z = 2$, $D_c = 1.23$ g cm^{-3}, $F(000) = 376$, monochromated Mo-Kα radiation ($\lambda = 0.71071$ Å), $\mu = 0.67$mm^{-1} Data were collected using a crystal size, *ca.* $0.20 \times 0.10 \times 0.10$ mm on an Enraf-Nonius CAD4 diffractometer. A total of 1606 reflections were collected for $2 < \theta < 60^\circ$ and $0 < h < 13$, $0 < k < 6$ and

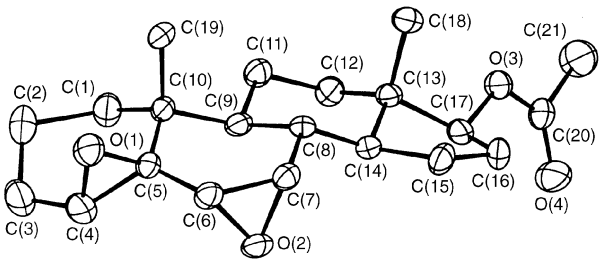


Fig. 1 X-Ray crystal structure of compound **4**

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$-15 < l < 14$. 1323 Reflections with $I > 2\sigma(I)$ were used in the refinement. There was no crystal decay and no absorption corrections was applied.

The structure was solved by direct methods using SHELXS-86[12] and refined using SHELXL-93.[13] The non-hydrogen atoms were refined anisotropically by full matrix least squares. Hydrogen atoms were included in riding mode with $U_{iso} = 1.2U_{eq}$(C) or $1.5U_{eq}$(C) for methyl groups. The final R indices were $R_1 = 0.050$, $wR_2 = 0.123$ and R indices (all data) $R_1 = 0.60$ and $wR_2 - 0.133$. The goodness-of-fit on F^2 was 1.037 and the maximum shift to esd was 0.001.

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Techniques used: IR and ^{1}H NMR spectroscopy, X-ray crystallography

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Appendix: Crystallographic data for compound **4**

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