Steroids Related to the Diterpenoid Tumour Inhibitor Aphidicolin

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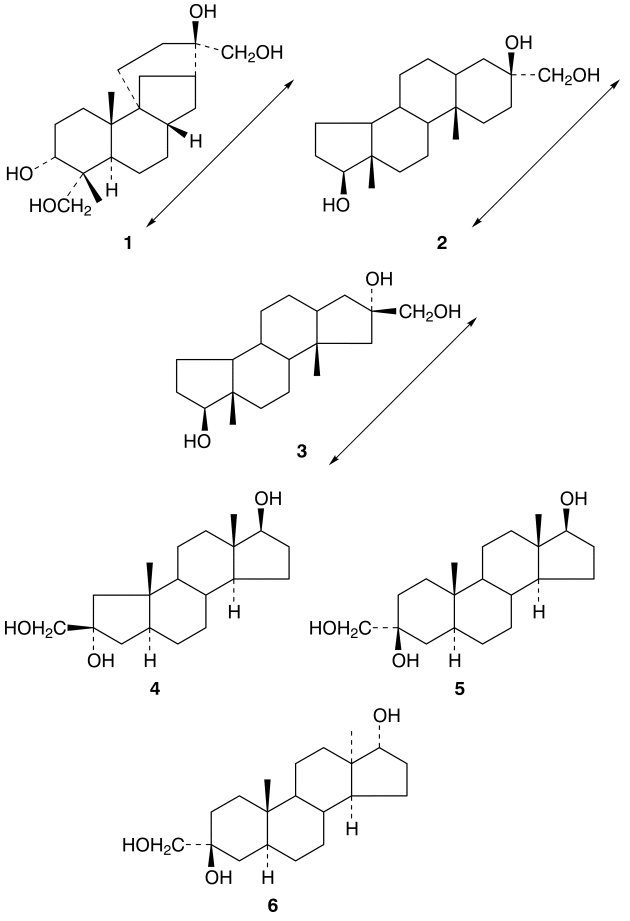
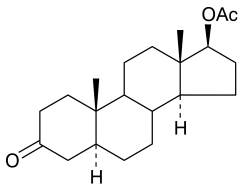
The syntheses of 2α,17β-dihydroxy-2β-hydroxymethyl-A-nor-5α-androstane, 3β,17β-dihydroxy-3α-hydroxymethyl-5α-androstane and 3β,17α-dihydroxy-3α-hydroxymethyl-5α,13α-androstane are described, and the stereochemistry of osmylation of a 3-methylene-5α-androstane is established by X-ray crystallography.

The diterpenoid fungal metabolite aphidicolin (**1**),[1] which is a specific inhibitor of DNA polymerase α,[2] has attracted interest because it shows a potentially useful level of anti-tumour and antiviral activity. Structure–activity studies, which have been restricted by the availability of material, have revealed[3–5] the importance of the distance between the ring A and ring D hydroxy functions. This separation may be mimicked on the readily available steroid skeleton.[6] Molecular models reveal that the superimposition of the C-17 hydroxy group of a steroid over the ring A C-18 hydroxyl group of aphidicolin brings steroidal ring A glycols, such as those based on C-3 of an androstane (**2**) or C-2 of an A-nor steroid (**3**), into juxtaposition with the ring D glycol of aphidicolin. The synthesis of the steroids **4**, **5** and **6** is described in this context.



17β-Acetoxy-5α-androstan-3-one (**7**) was converted into 17β-acetoxy-A-nor-5α-androstan-2-one (**8**),[8] and thence by a Wittig reaction into 17β-acetoxy-2-methylene-A-nor-5α-androstane (**9**). The glycol **10** was obtained by reaction with a catalytic amount of osmium tetraoxide and potassium hexacyanoferrate(III).[9] Nuclear Overhauser enhancement studies established the β-orientation of the hydroxymethyl group. Hydrolysis of the 17β-acetate afforded the triol **4**.



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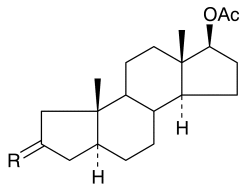
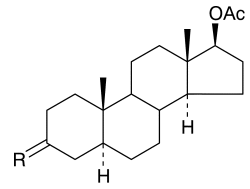
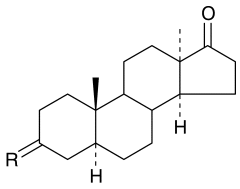


8 R = O
9 R = CH_2
10 R = α-OH, β-CH_2OH

A Wittig reaction with 17β-acetoxy-5α-androstan-3-one (**7**) gave the 3-methylene derivative **11**,[10] which was in turn osmylated and hydrolysed to form the glycol **5**. The stereochemistry at C-3 was established by an X-ray crystal structure of the corresponding diacetate, **12** (Fig. 1). The analogous compound in the 13α-series was prepared *via* 5α,13α-androstane-3,17-dione (**13**).[12] The C-3 and C-17 carbonyl groups differed sufficiently in steric hindrance for a selective Wittig reaction to generate the 3-methylene derivative **14**. The glycol **6** was obtained from this by catalytic osmylation and reduction at C-17.[13]



11 R = CH_2
12 R = α-CH_2OAc, β-OH



13 R = O
14 R = CH_2

The stereochemistry of osmylation of these alkenes has led to the axial hydroxymethyl group with an equatorial tertiary alcohol. This may be rationalized in stereoelectronic terms in which the facial selectivity of reaction is favoured by hyperconjugative interaction between the alkene and the allylic axial C–H bonds.[14]

Crystallographic Data and Structure Determination for **12**.—$C_{24}H_{38}O_5$, M_r 406.5, monoclinic, space group $P2_1$ (no. 4), $a = 6.207(3)$, $b = 11.758(6)$, $c = 15.763(3)$ Å, $\alpha = \gamma = 90°$, $\beta = 98.78(3)°$, $V = 1136.9(8)$ Å^3, $Z = 2$, $D = 1.19$ g cm^{-3}, $F(000)$ 444, monochromated Mo-Kα radiation, $\lambda = 0.71073$ Å, $\mu = 0.08$ mm^{-1} Data were collected for a crystal of size $0.20 \times 0.20 \times 0.05$ mm on an Enraf Nonius CAD4 diffractometer. A total of 2290 reflections were collected for $2 < \theta < 25°$ and $0 < h < 7$, $0 < k < 13$, $-18 < l < 18$. There were 2103 independent reflections and 946 reflections with

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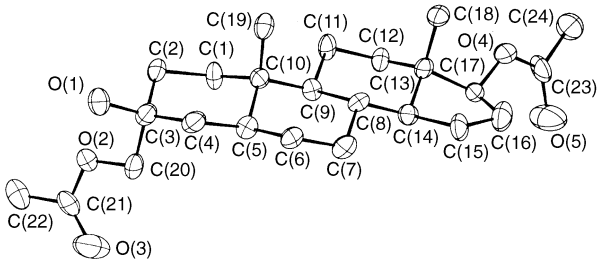

Fig. 1 X-Ray crystal structure of compound **12**

$I > 2\sigma(I)$ which were used in the refinement. There was no crystal decay and no absorption correction was applied. The structure was solved by direct methods using SHELXS-86[15] and SHELXL-93[16] for the structure refinement. 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 $R_1 = 0.0771$, $wR_2 = 0.1705$ and R indices (all data) $R_1 = 0.1863$. $wR_2 = 0.2385$. The goodness of fit on F^2 was 0.964 and the maximum shift/e.s.d. was 0.003.

Tables of atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen atom coordinates and isotropic displacement parameters are given in the Appendix of the full-text paper.

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

References: 16

Appendix: Crystallographic data for **12**

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