Steroidal Aphidicolin Analogues Derived from Pregnenolone

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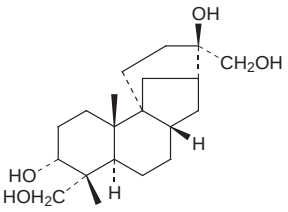
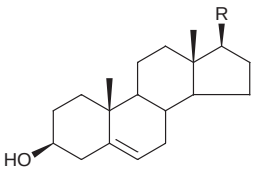
The conversion of pregnenolone into the 3β,5α-, 3α,5α-, 4β,5α-, 3α,4α-, 3α,4β- and 3α,4α-dihydroxy derivatives of 17β-hydroxymethyl-5α-androstane as steroidal analogues of the diterpenoid DNA polymerase α inhibitor, aphidicolin, is described.

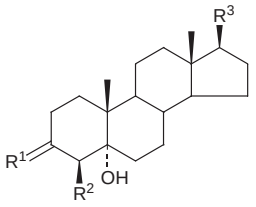
The steroid hormones exert their biological activity by binding to steroid receptors which also have a nucleic acid binding domain. This binding may result in the initiation of nucleic acid biosynthesis.[1] The diterpenoid aphidicolin **1**[2] has attracted considerable interest because it is a specific inhibitor of DNA polymerase α.[3,4] Although aphidicolin is relatively inaccessible, the limited structure–activity studies that have been carried out suggest that the activity may be related to the separation between the hydroxy groups on the A and D rings of aphidicolin.[5] There is a formal similarity between the rings A, B and C of aphidicolin and the steroid framework and hence we have examined the possibility of mimicking the separation of these hydroxy groups on the more readily available steroids with the object of producing steroid hormone analogues of aphidicolin.[6,7] Molecular modelling studies reveal that the superimposition of a steroidal 17-hydroxymethyl substituent onto the 17-hydroxymethyl group of aphidicolin brings steroidal ring A alcohols within the orbit of those of aphidicolin. The preparation of a series of 17-hydroxymethyl steroids from the readily available pregnenolone **2** forms the subject of this paper.

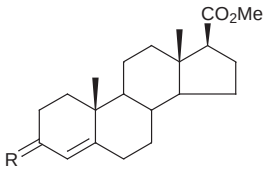


1



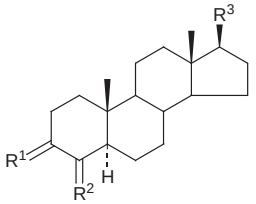
2 R = COMe
3 R = CO_2Me
4 5α, 6α-epoxy, R = CO_2Me

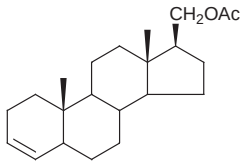




5 R^1 = α-H, β-OH; R^2 = H; R^3 = CH_2OH
6 R^1 = α-OH, β-H; R^2 = H; R^3 = CH_2OH
9 R^1 = H_2; R^2 = OH; R^3 = CO_2Me
10 R^1 = H_2; R^2 = OH; R^3 = CH_2OH

7 R = O
8 R = H_2





11 R^1 = α-H, β-OH; R^2 = α-OH, β-H; R^3 = CH_2OH
12 R^1 = α-H, β-OH; R^2 = α-OH, β-H; R^3 = CO_2Me
15 R^1 = α-OH, β-H; R^2 = α-H, β-OH; R^3 = CH_2OAc
16 R^1 = α-OH, β-H; R^2 = α-H, β-OH; R^3 = CH_2OH
17 R^1 = R^2 = α-OH, β-H; R^3 = CH_2OAc
18 R^1 = R^2 = α-OH, β-H; R^3 = CH_2OH

13 3,4-ene
14 3α,4α-epoxy

The 17β-hydroxymethyl group was generated by oxidation of pregnenolone **2** with sodium hypobromite to form the 17-carboxylic acid[8,9] and methylation with caesium fluoride and methyl iodide in dimethylformamide to generate the methyl ester **3**.[10,11] Reduction of the 17β-carbomethoxy group was carried out at appropriate stages in the subsequent sequences.

Epoxidation of 17β-carbomethoxyandrost-5-en-3β-ol **3** with *m*-chloroperbenzoic acid gave the 5α,6α-epoxide **4** which was reduced with lithium aluminium hydride to form the triol, 3β,5α-dihydroxy-17β-hydroxymethylandrostane **5**. Inversion of the 3β-hydroxy group by the Mitsunobu procedure, was carried out with monochloroacetic acid as the nucleophile.[11] Hydrolysis of the bis(monochloroacetate) with aqueous potassium carbonate gave 3α,5α-dihydroxy-17β-hydroxymethylandrostane.

17β-Carbomethoxyandrost-5-en-3β-ol **3** was oxidized to the unsaturated ketone, 17β-carbomethoxyandrost-4-en-3-one **7**, using the Meerwein–Ponndorf procedure.[12] Reduction with sodium tetrahydroborate in trifluoroacetic acid–acetic acid–acetonitrile[13] gave 17β-carbomethoxyandrost-4-ene **8**. Epoxidation of this and hydrolysis of the epoxide with aqueous periodic acid gave the, 4β,5α-diol **9**. Reduction of the 17β-ester with lithium aluminium hydride gave 4β,5α-dihydroxy-17β-hydroxymethylandrostane **10**.

Hydroboration of the unsaturated ketone **7** gave 3β,4α-dihydroxy-17β-hydroxymethyl-5α-androstane **11** and the corresponding 17β-carbomethoxy ester **12**. Although reduction of 17β-carbomethoxyandrost-4-en-3-one **7** with boron trifluoride etherate–sodium borohydride in diglyme followed by treatment with acetic anhydride[15] gave 17β-acetoxymethyl-5α-androst-3-ene **13** directly, a better yield of the 3-ene was obtained by carrying out the reaction in a stepwise sequence *via* 3β-acetoxy-17β-carbomethoxyandrost-4-ene. Epoxidation of the 3-ene **13** gave the 3α,4α-epoxide **14**. This epoxide was hydrolysed with aqueous periodic acid to the diaxial 3α,4β-diol and then with aqueous potassium carbonate to give 3α,4β-dihydroxy-17β-hydroxymethyl-5α-androstane **16**. Catalytic osmylation of the 3-ene using potassium hexacyanoferrate(III) as the co-oxidant[16] gave the 3α,4α-diol **17** from which 3α,4α-dihydroxy-17β-hydroxymethyl-5α-androstane **18** was obtained by hydrolysis with aqueous potassium carbonate.

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Techniques used: IR, ^{1}H NMR spectroscopy, chromatography

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