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SYNTHESES OF 31-NORPROTOST-24-ENE-3β,20R-DIOL(1)

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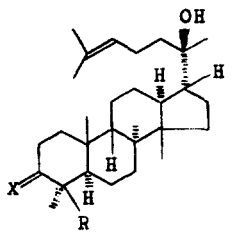
The exact steric requirements for the chain-folding of squalene and the subsequent intermediacy of the cation I during lanosterol biogenesis were first stated by Ruzicka et al. (2,3). In the light of the theories proposed in these papers the structural elucidation of the antibiotic fusidic acid by Arigoni, Godtfredson et al. (4) was of particular importance. This compound is the first reported natural product, having a trans-syn-trans-anti-trans arrangement of the cyclopentanoperhydrophenantrene nucleus, and thus possesses the same stereochemical features as suggested based on hypothetical assumptions for cation I.

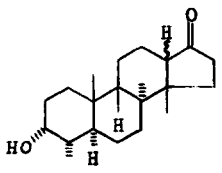
I

It should be noted however that fusidic acid and the related compounds cephalosporin P1 and helvolic acid must be formally derived from a non-classical cation whose chirality at C-20 is opposite to that depicted in I, as stated for sargasterol (3).

From this background the question arises whether a stable equivalent of the cation I exists on the pathway from squalene to lanosterol (5). The most likely candidate for such an intermediate is the alcohol II (6).

This communication describes a synthesis of 31-norprotost-24-ene-3β;20R-diol (III) starting from a degradation product of fusidic acid (7). The route offers several possibilities for appropriate labelling and methylation to the complete protostane skeleton.





II R = CH_3; X = 

III R = H X = 

IV H at C-13 in α position

V H at C-13 in β-position

XV R = H X = 

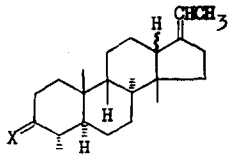
XVI R = H X = =O

As starting material, we used either ketone IV (7) or ketone V (7) which were reacted with ethylidenetriphenylphosphorane in dimethylsulfoxide at 70° (8). Under the reaction conditions equilibration at C-13 takes place (for equilibration constant see (7)), thus leading in both cases to the same mixture of all four possible isomeric structures VI. After oxidation using the procedure of Fenselau and Moffatt (9) followed by ketalization of the formed 3-keto function with ethylene glycol the mixture of the four compounds with structure VII was obtained in an overall yield of 70%.

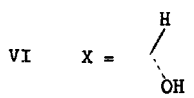
When reacted with diborane in tetrahydrofuran for 12 hours at 0° followed by hydrogen peroxide treatment (8), this mixture gave rise to four alcohols and a compound isomeric with the starting material having a tetrasubstituted double bond. Separation of all compounds was achieved by silica gel column chromatography.

The following transformations deal only with the two less polar alcohols, which were proven to have structures VIII ($C_{25}H_{42}O_3$; m.p. 187-92°, minor component) and IX ($C_{25}H_{42}O_3$; m.p. 156-58°, major component) in the following manner:

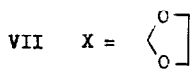
Both alcohols gave rise to the same ketone X ($C_{25}H_{40}O_3$, m.p. 181-83°) when oxidized with chromic acid in pyridine. Attempts to oxidize this ketone with m-chloroperbenzoic acid in methylene chloride failed. Treatment of ketone X with 1N potassium hydroxide in methanol led to the quantitative formation of the isomeric ketone XI (m.p. 149-50°; different R_f on thin layer plates, slight differences in n.m.r.). This ketone was transformed into acetate XII ($C_{25}H_{40}O_4$, m.p. 192-93°) by treatment with 1.1 mole of m-chloroperbenzoic acid in methylene chloride. After saponification of the acetate and hydrolysis of the ketal with acetic acid the keto-alcohol XIII ($C_{21}H_{34}O_2$, m.p. 170-72°) was obtained. The diketone XIV formed after oxidation of XIII (9) was identical in all respects to 4α,8,14-trimethyl-18-nor-5α,8α,9β,13a,14β-androstan-3,17-dione prepared according to Diassi et al. (7).

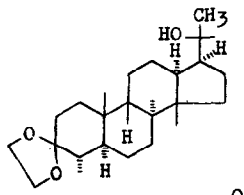


VI X =

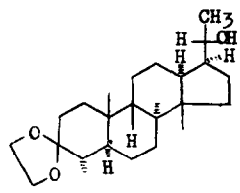


VII X =

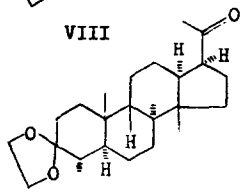




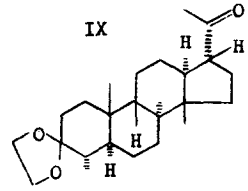
VIII



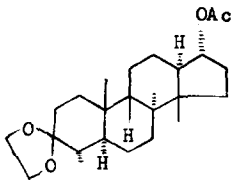
IX



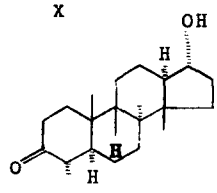
X



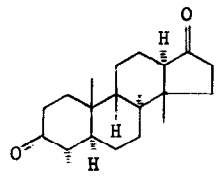
XI



XII



XIII



XIV

The α-orientation of the hydrogen at C-13 being proven it follows that the 17-side chain in VIII, IX and X is β orientated, since hydroboration is proceeding from the less hindered α-side. Base treatment of X then leads to the more stable 17α-orientation as depicted in XI.

Treatment of ketone XI with 4-methylpent-3-enyl-magnesium bromide yielded the alcohol XV ($C_{31}H_{52}O_3$; m.p. 103-06°). According to Crams's rule (10) the predominance of the desired

R-chirality at C-20 can be expected.

Hydrolysis of the ketal grouping at C-3 of XV followed by reduction of ketone XVI with sodium borohydride led to the desired alcohol III ($C_{29}H_{50}O_2$, amorphous product, pure in t.l.c., n.m.r., i.r. and mass spectroscopic data in agreement with structure).

Biosynthetic experiments with III labelled at C-26 or C-27 are currently under way.

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