Stereospecific Introduction of a C-17 Side Chain in a 14β-Hydroxy-steroid; *X*-Ray Crystal Structures of Two Epimeric 17-Ethynyl-17-hydroxy-14β-hydroxy-steroids

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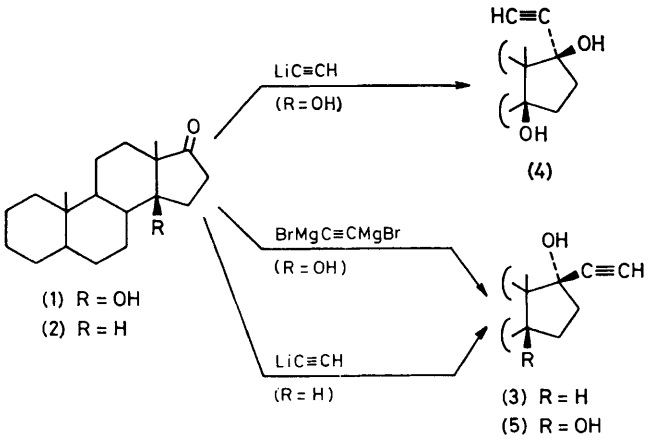
Summary Stereospecific introduction of a C-17 side chain in a 14β-hydroxy-steroid was carried out using acetylenic lithium or Grignard reagents; unequivocal proof of the structures of the two products was derived from single-crystal *X*-ray analyses.

IN the course of our studies on cardenolide syntheses[1] the key intermediate 14β-hydroxyandrostan-17-one (**1**) was prepared with the *trans* A/B ring junction (5α-H).[2] A corresponding intermediate with cardenolide configuration (3β-OH, 5β-H) was also prepared.[2] There have been few investigations of the reactivities of C-17 ketones in the 14β-steroid series, though it is known that Li–C≡CH reacts with 14β-androstan-17-one (**2**) to give only 17α-hydroxy-14β-pregn-20-yne (**3**).[3] These reactions of 14β-H-steroids might be due to a stereospecific approach of the carbanion from the less crowded β-face of the D ring because of the shape of the molecule.

Surprisingly, when the hydroxy-ketone (**1**) was submitted to the action of LiC≡CH in tetrahydrofuran (THF), the sole isolated product was 14β,17β-dihydroxy-17α-pregn-20-yne (**4**), m.p. 166—168 °C (pentane–ether); $[\alpha]_D^{23}$ −17° (*c* 0·5, $CHCl_3$); ν_{max} (CCl_4) 3602, 3536, and 3320 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0·78 (3H, s, 10-Me), 1·1 (3H, s, 13-Me), and 2·47 (1H, s, ≡CH), which has the opposite configuration to that of (**3**) at C-17.



However, the stereoselective introduction of the 17β side chain of the cardenolides could be achieved by the use of BrMgC≡CMgBr in THF; compound (**1**) reacted with this Grignard reagent to give only 14β,17α-dihydroxypregn-20-yne (**5**), m.p. 170—172 °C; $[\alpha]_D^{22}$ −19·4° (*c* 1, $CHCl_3$); ν_{max} (CCl_4) 3610, 3580, and 330 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0·78 (3H, s, 10-Me), 1·18 (3H, s, 13-Me), and 2·78 (1H, s, ≡CH).

It should be noted that both (**4**) and (**5**), when treated with Ag_2CO_3–Celite,[4] gave the starting hydroxy-ketone (**1**), thus excluding molecular rearrangements at C-13 and C-17.

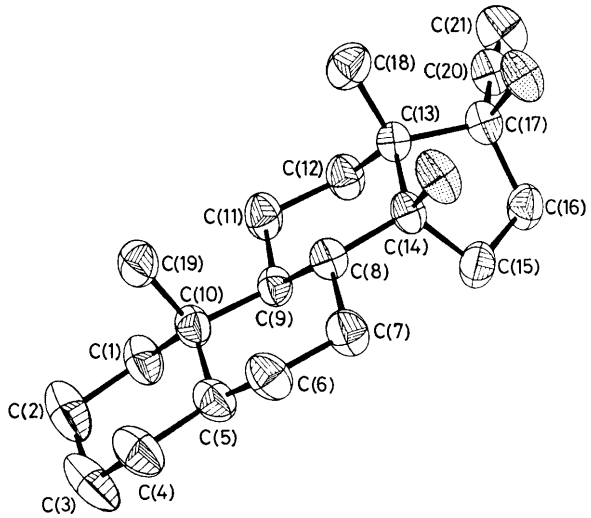


FIGURE. ORTEP view of (**4**), with 50% probability thermal ellipsoids.

From spectroscopic (i.r., ^1H and ^{13}C n.m.r.) and chemical data [(**4**) resists the usual specific reagents for diols] it was not possible to determine the configuration at C-17 of the two epimers (**4**) and (**5**), and so an *X*-ray structure determination was necessary. Compounds (**4**) and (**5**) both crystallize in the monoclinic system, space group $P2_1$ ($Z = 2$), with the following parameters: (**4**): $a = 7{\cdot}438(4)$, $b = 8{\cdot}595(5)$, $c = 14{\cdot}681(5)$ Å; $\beta = 98{\cdot}9(1)°$; (**5**): $a = 6{\cdot}445(3)$, $b = 23{\cdot}500(7)$, $c = 7{\cdot}080(4)$ Å; $\beta = 112{\cdot}6(1)°$. Using a Philips PW 1100 four-circle diffractometer with graphite-monochromatized Cu-K_α radiation ($\lambda = 1{\cdot}5418$ Å), 1542 and 1144 reflections with $I \geqslant 2\sigma(I)$ were collected for (**4**) and (**5**), respectively. The two structures were solved by the multisolution technique.[5]† Hydrogen atoms were introduced at their theoretical positions with an isotropic thermal factor equal to that of the bonded carbon atom. In the final steps of the refinement, the methyl hydrogens were located on Fourier-difference syntheses. The non-hydrogen atoms were anisotropically refined to $R = 3{\cdot}9\%$ for (**4**) and 7·8% for (**5**). An ORTEP view of (**4**) is depicted in the Figure.

It is thus possible to select the stereochemistry of the C-17 side chain in 14β-hydroxy-steroids.

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† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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