Total Synthesis of C-Nor-D-Homo-steroids

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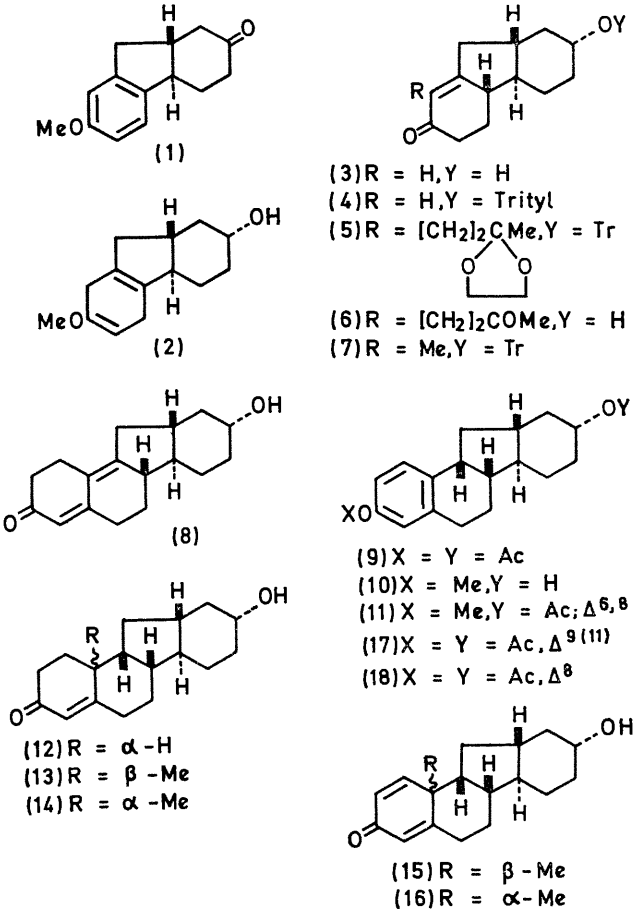
Summary A 7-step total synthesis of 9β,10α- and 9β,10β-C-nor-D-homo-steroids and related substances is reported.

WE report an efficient synthesis of C-nor-D-homo-steroids from readily available fluorene derivatives, which for the first time constructs this system in as few as seven steps.[1] Reduction of the *trans*-ketone methyl ether (**1**)[2] dissolved in tetrahydrofuran–ethanol with 1·16 M-Li in NH_3 gave in 70% yield the enol ether (**2**),† m.p. 135—136° which was hydrolysed quantitatively with 0·2N-HCl in ethanol at 20° to the αβ-unsaturated ketone (**3**), m.p. 126—127°, and converted in boiling pyridine into its 17-trityl ether, m.p. 172—174°. Alkylation of the anion of (**4**), (NaH, glyme) with 1-iodo-3,3-ethylenedioxybutane at 80°‡ afforded the acetal (**5**) (50%), m.p. 120—122°, which was hydrolysed with 95% acetic acid to the hydroxy-diketone (**6**) (76%), m.p. 104—105°. Cyclization of the latter with 0·1N-sodium methoxide in boiling methanol produced the tetracyclic dienone (**8**) in 78% yield; m.p. 179—180°. Aromatization of (**8**) was achieved in two ways. Heating with acetic anhydride, acetyl chloride, and pyridine at 80° gave the phenolic diacetate (**9**), m.p. 90·5—91·5° (70%), from which the 3-methyl ether (**10**), m.p. 103—104°, was prepared by hydrolysis with $NaHCO_3$ followed by methylation. Alternatively, (**8**) was isomerized to (**10**) with 10% Pd/C in boiling ethanol followed by methylation. Extended reaction (50 hr.) led to the naphthol characterized as the methyl ether acetate (**11**), m.p. 176—177°.



Only one series of enantiomers is shown.

Reductive methylation[3] of (**5**) with Li–NH_3 and methyl iodide provided a mixture whose n.m.r. spectrum showed tertiary methyl signals at 71, 66, and 60 Hz in the ratio 1 : 8 : 2. The mixture was separated by t.l.c. into two fractions containing the 66 Hz and the 60 Hz product, respectively. They were deacetalized and cyclized separately, as described above, to furnish from the former a mixture of (**12**) (m.p. 164—165°) and (**13**) (m.p. 164—165°), and from the latter compound (**14**), (m.p. 144—145° and 151—152°). Dehydrogenation of (**12**) with acetone-dried cells of *Arthrobacter simplex*[4] containing a steroid 1,2-dehydrogenase induced with testosterone, and 2-methyl-1,4-naphthaquinone as a hydrogen acceptor, followed by acetylation, yielded the phenolic acetate (**9**) showing that rings B and C are *cis*-fused. This establishes the stereochemistry of (**12**) at all centres but C-10, which will be discussed below. In order to ascertain the stereochemistry at C-9, (**13**) and (**14**) were subjected to the dehydrogenase from *A. simplex* yielding, respectively, (**15**), m.p. 197—198°, $[\alpha]_D$ −118° ($CHCl_3$); and (**16**), m.p. 191—192°, $[\alpha]_D$ −4·2° ($CHCl_3$), their optical activity demonstrating discrimination by the enzyme for one of the two enantiomers. Reductive aromatization of (**15**) and (**16**) by the Dryden procedure,[5] yielded after acetylation the diacetate (**9**), m.p. 64—65°, whose n.m.r. spectra and i.r. spectra in CCl_4 solution were identical with those for racemic (**9**), but whose $[\alpha]_D$ values and o.r.d. and c.d. curves showed that they were optical antipodes. The material derived from (**15**) had $[\alpha]_D$ −40° ($CHCl_3$) and showed a negative Cotton effect.¶

Thus, the three products, (**12**), (**13**), and (**14**) derived in the reductive methylation of (**5**) all possess rings B and C in *cis*-fusion, leaving only the relative configuration at C-10 to be determined. Contradictory conclusions as to this last point based on chemical-shift comparisons for the

† All products gave correct analytical figures and satisfactory spectroscopic data.

‡ Prepared by E. L. Brown by addition of HI to methyl vinyl ketone in chloroform followed by exchange dioxolanation.

§ The stereochemistry at C-9 (BC-*cis*-fusion) in (**9**) and (**10**) is clearly indicated by a 1-proton quartet at τ 6·70 *J* 9Hz, which is not found in the spectrum of the corresponding BC-*trans*-fused compounds. Thus, etiojerva-1,3,5(10)-trien-3-ol-17-one (*cf.* S. M. Kupchan, A. W. By, and M. S. Flom, *J. Org. Chem.*, 1968, **33**, 911, and earlier papers; W. F. Johns and I. Laos, *ibid.*, 1965, **30**, 123 and 4220; H. Mitsuhashi and N. Kawahara, *Tetrahedron*, 1965, **21**, 1215; T. Masamune and K. Orito, *ibid.*, 1969, **25**, 4551, and earlier papers) shows no benzylic H below τ 7·20. We thank Professor S. M. Kupchan for a tracing of the n.m.r. spectrum of this compound.

¶ These and other o.r.d. and c.d. data to be reported separately establish the absolute configuration of all enzymatically resolved products and permit the conclusion that the dehydrogenase preferentially attacks the antipode possessing 10*R*-chirality.

10-methyl signals in (**13**) and (**14**)[6] which favoured reversal of the two structures, and the demonstrated preference of the dehydrogenase for the antipode possessing 10*R*-chirality, predicting the structures as shown, prompted a three-dimensional *X*-ray structure analysis of (**14**). This was carried out employing 1111 observed reflections on the triclinic crystal with $a = 14{\cdot}45$, $b = 9{\cdot}98$, $c = 7{\cdot}04$, $\alpha = 103{\cdot}5$, $\beta = 122{\cdot}3$, and $\gamma = 61{\cdot}6°$. The phase problem of the centric $P\bar{1}$ space group was determined by direct methods[7] and the structure was refined by least-squares and difference-map techniques. The result confirms the relative stereochemistry of all centres as previously assigned and firmly establishes that of C-10 as shown in both (**13**) (the major product) and (**14**). The relative configuration of the C-10 hydrogen in the 19-nor-derivative (**12**) has been assigned as *anti*, since (**9**) derived by enzymatic dehydrogenation of (**12**) possesses a positive Cotton effect, as in the case of (**14**).

Enzymatic dehydrogenation of the dienone (**8**) gave, after acetylation, a 67% yield of the styryl derivatives (**17**) and (**18**) in a 2:1 ratio, which could be separated by fractional crystallization. The less soluble isomer (**17**) had m.p. 164—166°; hydrogenation gave exclusively (**9**). Compound (**18**) had m.p. 132—134°, and its n.m.r. spectrum indicated the absence of vinyl protons. Neither (**17**) nor (**18**) was optically active, most likely a consequence of the lack of dissymmetry of the substrate (**8**) at C-10. The potential of (**17**) for the introduction of oxygen at C-11 and subsequent conversion into 10β-methyl-9α-C-nor-D-homo-steroids[8] is readily apparent.

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