C-19 Chiral Steroids: the Syntheses of (19*R*)- and (19*S*)-[19-^{3}H,^{2}H,^{1}H]-3β-hydroxyandrost-5-en-17-ones

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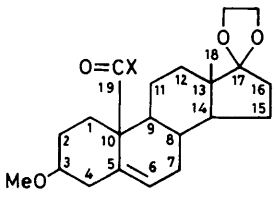
Two syntheses of C-19 chiral steroids are documented by the preparation of (19*R*)- and (19*S*)-[19-^{3}H,^{2}H,^{1}H]-3β-hydroxyandrost-5-en-17-ones (**4**) and (**5**).

The compounds required for studies of estrogen biosynthesis (19*R*)-(**4**) and (19*S*)-(**5**) C_{19}-17-keto steroids (also used in conversion into C_{21}, C_{27}, C_{29} *etc.* steroids)[1] were prepared by two routes, both of which are applicable for the synthesis of other steroids.

The syntheses used 3β,19-dihydroxyandrost-5-en-17-one as a starting material which was converted into the 3-methoxy-19-aldehyde-17-acetal† (**1**). Reduction of the (19-^{2}H)aldehyde[2c] (**1b**) with lithium trialkoxyhydridoaluminate[3] [prepared from $LiAlH_4$ (1 equiv.) and Bu^t_2CO (3 equiv.)] gave the (19*R*)-alcohol (**2a**) in *ca.* 90% yield. The derived 19-acetate (**2b**) showed ^{1}H n.m.r. signals at δ 3.95 (0.9—0.95 atoms ^{1}H) and 4.49 (0.05—0.1; ^{1}H), indicating that the alcohols contain 90—95% of the (19*R*)-[19-^{1}H,^{2}H]-isomer and 5—10% of the (19*S*)-[19-^{1}H,^{2}H]-isomer.[2] Attempted hydrogenolyses of the 19-tosyl and -mesyl esters failed to yield a 10β-methyl moiety.[4] Fortunately the 19-alcohol (**2c**) could be readily converted by treatment with methyltriphenoxyphosphonium iodide (MTPI) in dry dimethylformamide (DMF)[5] (room temperature, 20 h) into the 19-iodide (**3a**) (90% yield) *without loss of diastereoisomeric purity*. We assume that the iodination of the homoallylic alcohol(s)[6] (**2**) proceeds with retention of configuration. The 3β-methoxy compound (**3a**) was converted into the 3β-acetoxy-19-iodide[7] (**3b**); ^{1}H n.m.r. δ 3.28 (0.9—0.95; ^{1}H) and 3.60 (0.05—0.1; ^{1}H). Hydrogenolysis of the 19-iodide (**3a**) with lithium triethylborohydride (Superhydride) gave after oxidation the (19-$^1H_3$)-17-ketone analogous to (**4**).

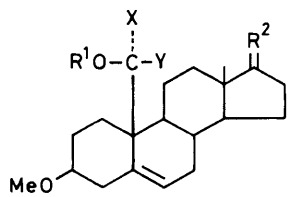
Similarly reduction of (**1a**) with lithium trialkoxydeuterioaluminate [prepared from $LiAl^2H_4$ (1 equiv.) and Bu^t_2CO (3 equiv.)] gave the (19*S*)-[19-^{1}H,^{2}H]-alcohol (**2d**). The derived compound (**2e**) showed δ 3.95 (0.05—0.1; ^{1}H) and 4.49 (0.9—0.95; ^{1}H), Figure 1(a), indicating that (**2d**) contains *ca.* 90—95% of the (19*S*)-[19-^{1}H,^{2}H]-alcohol and *ca.* 5—10% of the (19*R*)-[19-^{1}H,^{2}H]-alcohol. The (19*S*)-hydroxy ketone (**2f**) gave the 19-iodide (**3c**) which was converted into 19-iodo-3-

† All compounds were fully characterized (^{1}H n.m.r., ^{2}H n.m.r., mass spectroscopy *etc.*) and their tritium specific activity determined as needed. The homogeneity of the compounds was assayed by t.l.c., high performance chromatography (Micromeritics-788 dual variable detector) and where applicable radioactive high performance chromatography (Flow-One radioactive detector).



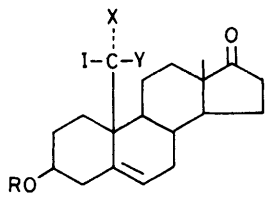
(**1**)

a; X = ^{1}H
b; X = ^{2}H
c; X = ^{3}H



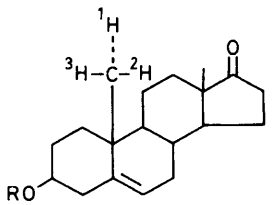
(**2**)

a; R^1 = H, R^2 = $(CH_2O)_2$; X = ^{2}H; Y = ^{1}H
b; R^1 = Ac; R^2 = O; X = ^{2}H; Y = ^{1}H
c; R^1 = H; R^2 = O; X = ^{2}H; Y = ^{1}H
d; R^1 = H; R^2 = $(CH_2O)_2$; X = ^{1}H; Y = ^{2}H
e; R^1 = Ac; R^2 = O; X = ^{1}H; Y = ^{2}H
f; R^1 = H; R^2 = O; X = ^{1}H; Y = ^{2}H
g; R^1 = H; R^2 = $(CH_2O)_2$; X = ^{3}H; Y = ^{1}H
h; R^1 = H; R^2 = O; X = ^{3}H; Y = ^{1}H
i; R^1 = H; R^2 = $(CH_2O)_2$; X = ^{3}H; Y = ^{2}H
j; R^1 = H; R^2 = O; X = ^{3}H; Y = ^{2}H
k; R^1 = H; R^2 = $(CH_2O)_2$; X = ^{2}H; Y = ^{3}H

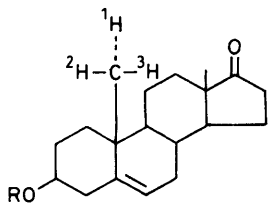


(**3**)

a; R = Me; X = ^{2}H; Y = ^{1}H
b; R = Ac; X = ^{2}H; Y = ^{1}H
c; R = Me; X = ^{1}H; Y = ^{2}H
d; R = Ac; X = ^{1}H; Y = ^{2}H
e; R = Me; X = ^{3}H; Y = ^{1}H
f; R = Me; X = ^{3}H; Y = ^{2}H
g; R = Me; X = ^{2}H; Y = ^{3}H



(19*R*)-(**4**)



(19*S*)-(**5**)

a; R = Me
b; R = H

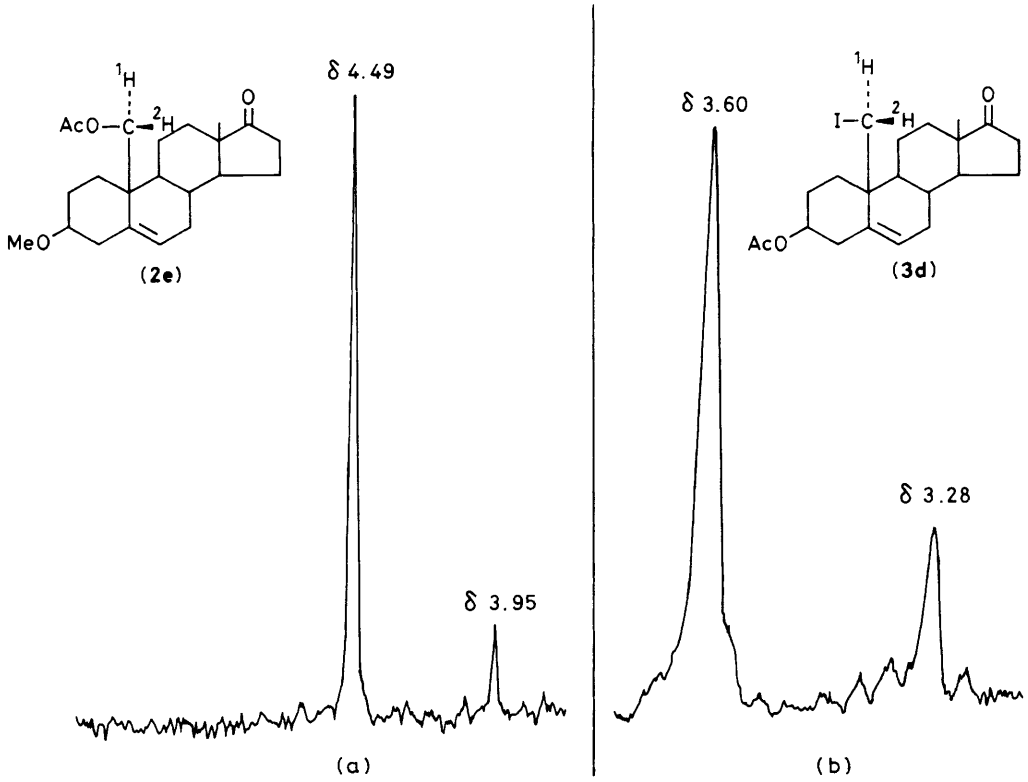


Figure 1. ^{1}H N.m.r. spectra of (a) compound (**2e**) and (b) compound (**3d**).

acetate (**3d**): n.m.r. δ 3.28 (0.05—0.1; ^{1}H) and 3.60 (0.9—0.95; ^{1}H), Figure 1(b). The iodide (**3c**) was hydrogenolysed with Superhydride to the 10β-methyl compound (75—80%).

Based on these observations, the syntheses of 19-chiral analogues were undertaken. Reduction of (19-^{1}H)aldehyde (**1a**) in EtOH with (^{3}H)$NaBH_4$ (100 mCi) and reoxidation[8] of the resulting (19*RS*)-(19-^{1}H,^{3}H)-alcohol yielded the (19-^{3}H)aldehyde (**1c**) (55 mCi).

Aliquots of (**1c**) were reduced with lithium trialkoxyhydrido(or deuterio)aluminates[2] to yield (19*R*)-[19-^{1}H,^{3}H]-19-hydroxy (**2g**) or (19*R*)-[19-^{2}H,^{3}H]-19-hydroxy (**2i**) compounds respectively. The 17-keto-(19*R*)-alcohols (**2h**) and (**2j**) were converted (MTPI-DMF) into the corresponding (19-^{1}H,-^{3}H)-19-iodide (**3e**) and (19-^{2}H,^{3}H)-19-iodide (**3f**).

Compound (**3f**) (13 mCi) was hydrogenolysed [(^{1}H)-Superhydride–THF] to give, after reoxidation, (19*R*)-[19-^{3}H,^{2}H,^{1}H]-(**4a**) (11.2 mCi; 86% yield). Cleavage of the methoxy moiety[7] of (**4a**) and saponification gave the required (19*R*)-[19-^{3}H,^{2}H,^{1}H]-3β-hydroxyandrost-5-en-17-one (**4b**). For C-19 chirality determination, the obtained (**4**) was converted into androst-4-ene-3,17-dione, treated with SeO_2–H_2O_2[9] and oxidised by the Kuhn–Roth procedure.‡ The resulting acetic acid was analysed for chirality by the malate-synthetase fumarase procedure[10,11] and showed[11] $F = 63$ for (19*R*)-chirality of (**4**). Treatment of (**3e**) with (^{2}H)-Superhydride gave after analogous processing (19*S*)-(**5b**), $F = 33$.

Alternatively, reduction of (19-^{2}H)aldehyde (**1b**) with (^{1}H)-(*R*)-alpine borane (Aldrich Co., Milwaukee, WI, U.S.A.) gave the (19*S*)-[19-^{1}H,^{2}H]-alcohol [94—96%; (19*S*)-(**2e**)] and reduction of (**1b**) with (^{1}H)-(*S*)-alpine borane gave (19*R*)-[19-^{1}H,^{2}H]-alcohol [94—96%; (19*R*)-(**2b**)], Figure 2. Similarly, reduction of (**1a**) with deuterio (*S*)-alpine borane gave the (19*S*)-[19-^{1}H,^{2}H]-alcohol [94—96%; (19*S*)-(**2e**)].

The required *deuteriated* (*R*)- and (*S*)-alpine boranes were prepared by treating deuteriated 9-borabicyclo[3.3.1]nonane with (+)- and (−)-α-pinenes, respectively.[12] Reduction of the (19-^{3}H)aldehyde (**1c**) with deuteriated (*R*)- and deuteriated (*S*)-alpine boranes gave the (19*S*)-[19-^{2}H,^{3}H]-19-alcohol (**2k**) and (19*R*)-[19-^{2}H,^{3}H]-19-alcohol (**2i**). Treatment of (19*S*)-(**2k**) and (19*R*)-(**2i**) with MTPI–DMF and removal of the acetals gave the corresponding (19-^{2}H,^{3}H)-19-iodide (**3g**) and (19-^{2}H,^{3}H)-19-iodide (**3f**). The iodides (**3g**) and (**3f**) were first treated with (^{1}H)-Superhydride and then oxidised to yield (19*S*)-[19-^{3}H,^{2}H,^{1}H]-(**5a**) and (19*R*)-[19-^{3}H,^{2}H,^{1}H]-(**4a**) which in turn were converted into (**5b**) and (**4b**). Aliquots of (**5b**) and (**4b**) were processed as described above and samples of acetic acid obtained were analysed for chirality. The acetic acid derived from (19*S*)-(**5b**) showed $F = 33$ and that obtained from (19*R*)-(**4b**) had $F = 65$.

Assuming a linear correlation of F and diastereoisomeric purity it is estimated[11,13] from the F values that each of the (19*R*)-(**4**) and (19*S*)-(**5**) compounds contained *ca.* 76 and 79.5% of the respective chiral methyl. Considering that up to 5% of a hydrogen atom of acetic acid is exchanged in Kuhn–Roth oxidation‡ it may be inferred that the samples contained up to 81 and 85% of the corresponding 19-chiral methyls. These results indicate that on average the three reactions of the synthetic sequence proceeded with a 90—95% diastereoisomeric selectivity.

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‡ The Kuhn–Roth oxidations were carried out in sealed vials at room temperature (72 h) with shaking. Usually up to 5% of a hydrogen atom was exchanged when products from ref. 9 were used.

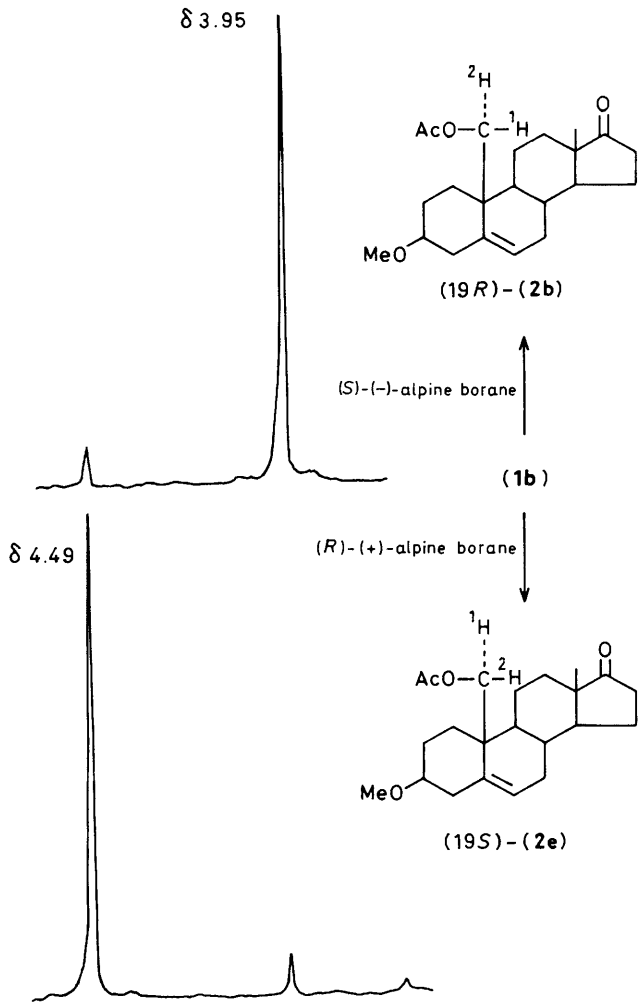

Figure 2. ^{1}H N.m.r. spectra of the compounds (**2b**) and (**2e**) obtained from (**1b**).

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