Synthesis of C-19-Chiral Steroids. Preparation of (19*R*); (19*S*) and (19*RS*)-3β-Hydroxy[19-$^2H_1$,19-$^3H_1$]androst-5-en-17-ones

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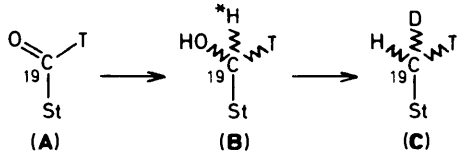
The synthesis of the title compounds by two routes is described. The syntheses were based on the stereoselective reduction of 17,17-ethylenedioxy-3β-methoxy[19-^3H]androst-5-en-19-als to (19*R*)- and (19*S*)-alcohols of high diastereoisomeric purities. The alcohols were converted, with retention, into the 19-iodides without loss of diastereoisomeric purity. The iodides were then hydrogenolysed, with inversion, to 19-chiral products.

For studies of the steric mode of the 'first' C-19 hydroxylation of an androgen by placental aromatase[1,2] in the biosynthesis of estrogens,[3] we required (19*RS*), (19*R*)-, and 19*S*)-3β-hydroxy[19-$^2H_1$,19-$^3H_1$]androst-5-en-17-ones.[4] Details of the first (partial) syntheses of 19-chiral C_{19}-compounds by two routes which are applicable to the syntheses of 19-chiral C_{21}, C_{25}, C_{27}, C_{28}, C_{29}, *etc.* steroids are described herein.

The approach we chose was to reduce an appropriate [19-^{3}H]-aldehyde (A) (T = ^{3}H) to 19-chiral alcohol(s) (B) (*H = ^{1}H or ^{2}H) of high diastereoisomeric purity which, in turn, would be hydrogenolysed without loss of diastereoisomeric purity to the required 19-chiral steroid(s) (C).



(A) (B) (C)

In accordance with this plan, our first objective was to develop a method for the stereoselective reduction of a 19-aldehyde. From the outset, it was obvious that the reduction must proceed at a minimum with a 90% diastereoisomeric selectivity. Assuming that the synthesis of a chiral methyl will proceed in two steps involving the chiral centre (C-19) and that each of the steps will proceed with 90% steric selectivity, the obtained 19-chiral androgen will contain at best *ca.* 81% of *e.g.*, (19*R*)-isomer and *ca.* 19% of (19*S*)-isomer. Should, however, the synthesis require three steps involving the chiral centre (C-19), and again should each step proceed with 90% steric selectivity, the obtained androgen will contain a maximum of *ca.* 72.9%, of *e.g.*, (19*R*)-isomer and *ca.* 27.1% of (19*S*)-isomer.

The projected study of the steric mode of C-19 hydroxylation of a 10β-chiral methyl was based on the premise that, in analogy to previous observations,[5,6] the enzymatic reaction will proceed stereospecifically with a normal kinetic isotope effect $k_H > k_D > k_T$ (D = ^{2}H; T = ^{3}H). It follows, therefore, that a stereospecific 'first' C-19 enzymatic hydroxylation of an optically pure (19*R*)-androgen must yield a mixture containing different amounts of tritiated (19*R*)- and (19*S*)-alcohol. The same applies to the 'optically pure' (19*S*)-substrate except that the ratio of the tritiated (19*R*)- and (19*S*)-alcohol will be reversed. The formation of the mixtures of tritiated 19-alcohols results from the displacement of a hydrogen or deuterium atom by the incoming hydroxy group. Obviously, displacement of a tritium atom will give a 19-alcohol devoid of tritium. The eliminated hydrogen atoms are ultimately exchanged with the protons of the water of the medium. The ratio of the produced alcohols will depend on the isotope effects $k_H > k_D > k_T$.

The products of the aromatization process are: a nontritiated estrogen, tritiated formic acid (TCO_2H), and tritiated water (THO). Based on the distribution of tritium in the formic acid (TCO_2H) and water (THO) derived from (19*R*), (19*S*)-, and (19*RS*)-substrates, the steric mode of C-19 hydroxylation can be deduced.[3] In practice, the synthetically prepared (19*R*)- and (19*S*)-substrate will not be optically pure and each will be a mixture containing a major and a minor amount of the two diastereoisomers. Consequently, the distribution of tritium in the formic acid and water will depend on diastereoisomeric purities of the substrates. Therefore the higher the diastereoisomeric purities of the chiral C_{19}-substrates, the greater will be the differences in the distribution of tritium in TCO_2H and HTO and therefore the interpretation of the steric course of the C-19 hydroxylation will be less ambiguous.

It has been proven, with the use of 19-acetoxy [19-$^2H_1$]-chiral compounds (**1a**) and (**2a**), that the 19-*pro-R* and 19-*pro-S* hydrogens give signals at δ_H 4.49 and 3.97, respectively.[7–9] We decided to utilize this information in exploratory studies of the stereoselectivity of reduction of the 19-aldehyde (**3a**). The required 19-deuteriated aldehyde (**3a**) was prepared from 19-hydroxy-3β-methoxyandrost-5-en-17-one (**1b**; no D) which was oxidized with Jones' reagent and the resulting 19-carboxylic acid (**4a**) was treated with diazomethane. The methyl ester (**4b**) was acetalized and the product (**4c**) was then reduced with $LiAl^2H_4$. The [19-$^2H_2$]-alcohol obtained was oxidized (CrO_3–py) to yield the required deuterio aldehyde (**3a**). To optimize the diastereoisomeric yield of 19-chiral alcohols, various reagents and conditions of reduction of (**3a**) were tested and the results are summarized in Table 1 (entries 1—7). The 19-alcohols were acetylated, the acetal groups were removed, and the resulting [19-$^2H_1$]-19-acetoxy 17-ketones were analysed by proton n.m.r. spectroscopy.

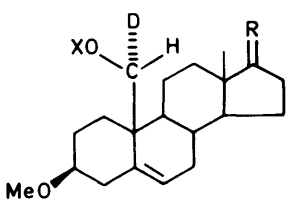
Horse liver alcohol dehydrogenase–NAD–cyclohexanol reduction of the aldehyde (**3a**) (Table 1, entry 7) presumably proceeded with *ca.* 100% diastereoisomeric selectivity. However, the overall yield of the reaction was only of the order of 0.05%, making the approach impractical. In most instances, the reductions with the indicated reagents proceeded with *ca.* 80% steric selectivity (Table 1, entries 2—5). The only results which met our minimal requirements were obtained with Haubenstock's[10] reagent [$Li(Bu_2^tCHO)_3AlH$] (abbreviated as LiA*HA) prepared by treating 1 mol equiv. of $LiAl^*H_4$ with 3 mol equiv. of di-t-butyl ketone. Reduction of the aldehyde (**3a**) with (LiA^1HA) gave a mixture of alcohols consisting of *ca.* 90—95% of (19*R*)-(**1c**) and *ca.* 5—10% of (19*S*)-(**2c**). The products were analysed as (**1a**) and (**2a**) (Table 1, entry 6).

Alternatively, the 19-protiated aldehyde (**3b**), when reduced with the corresponding deuteriated reagents [prepared from $LiAl^2H_4$ (1 mol equiv.) and di-t-butyl ketone (3 mole equiv.)], gave the two alcohols in reverse proportion of isomers *i.e.* (19*S*)-

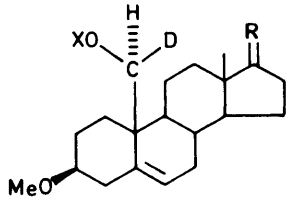
Table 1. Asymmetric reduction of [19*H]-17,17-ethylenedioxy-3β-methoxyandrost-5-en-19-als (**3a**) and (**3b**) (*H = ^{1}H or ^{2}H)

Entry	Reducing agent	Conditions	Alcohol[a] 19*R*	Alcohol[a] 19*S*	Yield (%)
Substrate (**3a**)					
1	$NaBH_4$	CH_3OH, R.T.	60	40	>90
2	$LiAlH_4$	Et_2O or THF–reflux	80	20	>95
3	$LiBu^tO)_3AlH$	THF–reflux	85	15	85
4	$Li(Et_3CO)_3AlH$[b]	THF–reflux	82	18	90
5	Li(isobornylO)$_3$AlH	THF–reflux	80	20	80
6	$(Li(Bu^t{}_2HCO)_3AlH$	THF–reflux	90—95	5—10	95
7	HLAD–NAD^+–cyclohexanol[9]	37 °C, 18 h		~100	0.05
Substrate (**3b**)					
8	NaB^2H_4	CH_3O^2H	40	60	90
9	$LiAl^2H_4$	THF or Et_2O–reflux	20	80	95
10	$LiBu^t{}_2HCO)_3Al^2H$	THF–reflux	5—10	90—95	95
11	$Li(Et_3CO)_3Al^2H$	THF–reflux	20	80	90
12	Li(isobornylO)$_3Al^2H$	THF–reflux	19	81	98
13	Li(−)-*N*-methylephedrine]$_3Al^2H$[c]	THF–reflux	40	60	10

[a] The 19*R* and 19*S* ratios were determined on the derived compounds (**1a**) and **2a**), using ^{1}H and ^{2}H n.m.r. spectroscopy. [b] Lithium [tris(3-ethylpentan-3-yl)oxy]aluminium hydride (S. Krishnamurthy, *J. Org. Chem.*, 1981, **46**, 4628). [c] S. Yamada, M. Kitamoto, and S. Terashima, *Tetrahedron Lett.*, 1976, 3165.

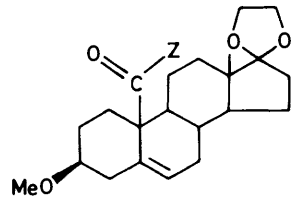


(**1**)

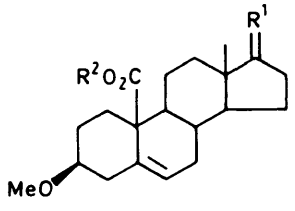


(**2**)

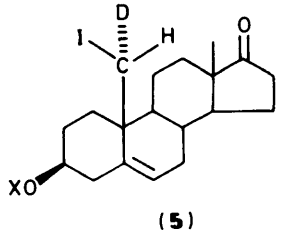
a; X = Ac, R = O
b; X = H, R = O(no 19-D)
c; X = H, R = OCH_2CH_2O
d; X = H, R = O



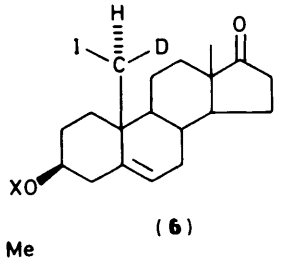
(**3**) **a**; Z = D
b; Z = H
c; Z = T



(**4**) **a**; R^1 = O, R^2 = H
b; R^1 = O, R^2 = Me
c; R^1 = OCH_2CH_2O, R^2 = Me



(**5**)



(**6**)

a; X = Me
b; X = Ac
c; X = H

isomer as major product (Table 1, entry 10). It is worthy of note that reduction of the *deuteriated* aldehyde with a reagent prepared from $LiAlH_4$ and isobornyl alcohol gave a mixture containing *ca.* 80% of (19*R*)- and *ca.* 20% of (19*S*)-alcohol (Table 1, entry 5). Similar reduction of protiated aldehyde with the deuteriated reagent gave the (*R*)- and (*S*)-alcohols in reverse proportion [(19*S*)-alcohol major product] (Table 1, entry 12). Reduction with a reagent prepared from $LiAlH_4$ and (−)-*N*-methylephedrine gave the (19*R*)- and (19*S*)-alcohol in the ratio 2:3 (Table 1, entry 13).

Since the reduction of 19-aldehydes with Haubenstock's reagents proceeded with a (9:1) and up to (19:1)-diastereoisomeric selectivity, we decided on the use of this reagent and prepared the (19*R*)-[19-$^2H_1$]-alcohol (**1c**) (90—95% 19*R*) [from (**3b**) and deuteriated reagent] and (19*S*)-[19-$^2H_1$]-alcohol (**2c**) (90—95% 19*S*) [from (**3a**) and protiated reagent]. The n.m.r. spectrum of compound (**2a**) derived from (**2c**) is shown in Figure 1.

Our next objective was to convert the 19-alcohols into C-19 chiral methyls. To this end, attempts were made to hydrogenolyse the corresponding 19-*p*-tosyl and 19-mesyl esters. Although various metal hydride reagents and conditions were tested, none led to the 10β-methyl product.[11] Under the circumstances, alternative routes of conversion of the 19-alcohols into 19-methyl compounds were explored.

In the context of other studies, we had occasion to use

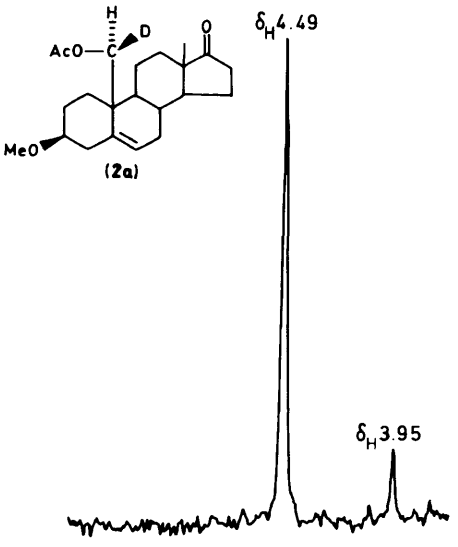


Figure 1.

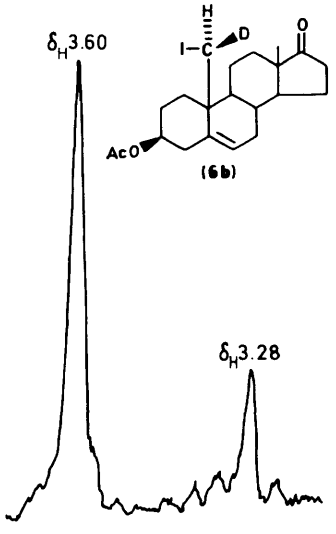


Figure 2.

methyltriphenoxyphosphonium iodide (MTPI)[12] for the conversion of alcohols into iodides.[12,13] Without the assistance of a neighbouring group, the iodination proceeded with inversion of configuration.[13–15] However, retention of configuration was observed when participation of a neighbouring group was involved.[12,16] When (19*S*)-alcohol (**2d**) was treated with MTPI in dimethylformamide (DMF) under N_2, the 19-iodide (**6a**) was obtained in good yield. Treatment of compound (**6a**) with BF_3·diethyl ether in acetic anhydride gave the 3-acetate (**6b**). The ^1H n.m.r. spectrum of compound (**6b**) (Figure 2) showed that the reaction proceeded with complete retention of diastereoisomeric purity. It is apparent that the signals at δ_H 4.49 and 3.95 for compound (**2a**) (Figure 1) are shifted upfield to δ_H 3.60 and 3.28 in the 19-iodide (**6b**) (Figure 2), respectively. No changes in the relative intensities of the signals were observed. In the absence of a C-5(6) double bond, mainly rearranged products were formed.[11] We propose that the iodination of the homoallylic alcohol (**2d**) proceeds with the participation of the C-5(6) double bond and with retention of configuration. When iodide (**6a**) was treated with lithium triethylborohydride ($LiEt_3BH$) (Superhydride) and the product was reoxidized (19-^{2}H)-3β-methoxyandrost-5-en-17-one was obtained. The product gave an n.m.r. spectrum which was identical to that of an authentic sample, except for the lower intensity of the signal for the 10β-methyl hydrogens.

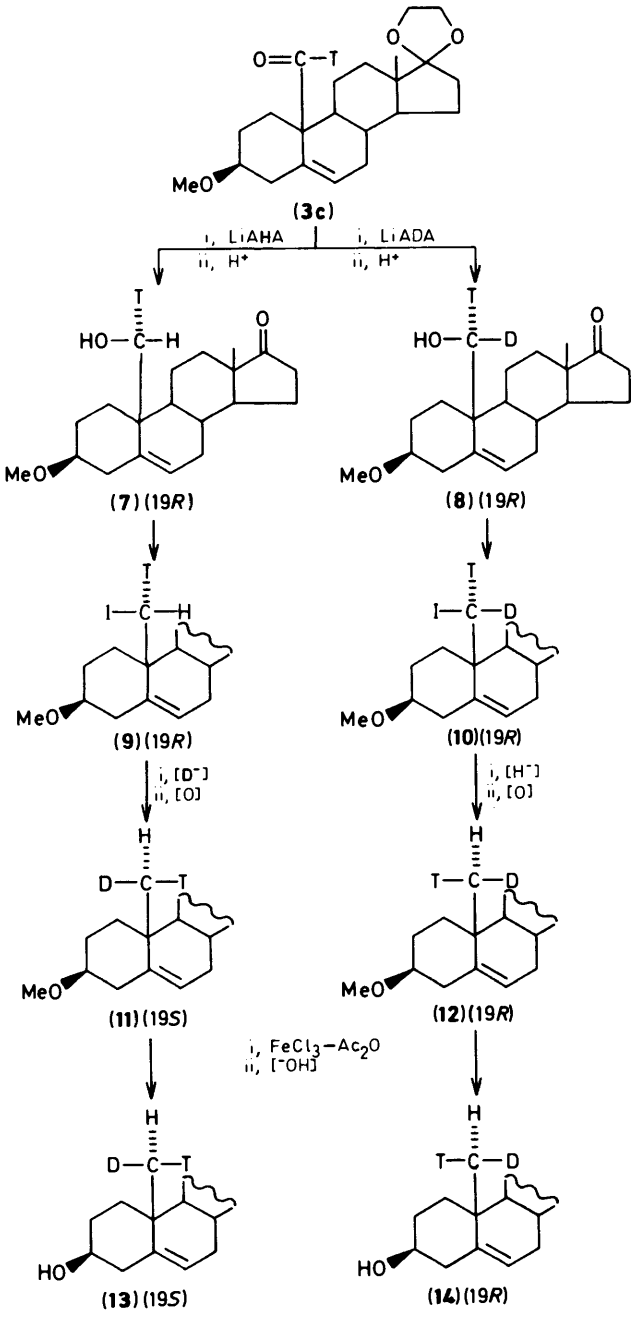
An analogous sequence of reactions was then carried out with the (19*R*)-alcohol (**1d**) to yield the 19-iodide (**5a**) which, in turn, was converted into compound (**5b**). The (19*R*)-acetoxy compound (**1a**) showed signals at δ_H 4.49 (0.05—0.1 ^{1}H) and 3.95 (0.9—0.95 ^{1}H). The iodide (**5b**) derived from alcohol (**1d**) showed signals at δ_H 3.60 (0.05—0.1 ^{1}H) and 3.28 (0.9—0.95 ^{1}H). Here again, the reaction proceeded with complete preservation of the diastereoisomeric purity, as evidenced by lack of changes in the relative intensities of the signals. Hydrogenolysis of the 19-iodide (**5a**), followed by reoxidation of the product, gave 3β-methoxy(19-$^2H_1$)androst-5-en-17-one.

The described sequence of reactions completes a three-step conversion of the 10β-formyl substrate into a 10β-methyl steroid. Unfortunately, at this stage it was not clear whether the sequence was applicable for the preparation of a chiral C-19 methyl. Obviously, the reductions of 19-aldehydes to chiral-19 alcohols proceed with a high degree of diastereoisomeric selectivity as evidenced by n.m.r. spectroscopy. Similarly, the conversions into chiral-19 iodides proceed with preservation of diastereoisomeric purity. In contrast, no information was available on the course of the hydrogenolysis of the 19-iodides. The hydrogenolysis could proceed with retention, inversion, or racemization. Since the steric mode of the hydrogenolysis could not be assessed at this point, we decided to proceed with the syntheses of [19-$^2H_1$,19-$^3H_1$]androgens and to determine the C-19 chiralities of the final products.

The required starting material (**3c**) was prepared *via* $NaBH_4$-[^{3}H] reduction of aldehyde (**3b**) and reoxidation (CrO_3–Py) of the obtained 19-tritiated alcohol. Reduction of aldehyde (**3c**) with protiated Haubenstock's reagent (LiA^1HA) gave, following acid cleavage of the 17-acetal, the (19*R*)-[19-$^3H_1$]-alcohol (**7**) (Scheme 1). Similar reduction of aldehyde (**3c**) with deuteriated Haubenstock's reagent (LiA^2HA) gave, after the removal of the acetal grouping, the (19*R*)-[19-$^2H_1$,19-$^3H_1$]-alcohol (**8**). To simplify discussion, we omit the formation of the minor chiral alcohols (5-10%) accompanying the major products. The alcohols (**7**) and (**8**) were converted by treatment with MTPI into their respective iodides (**9**) and (**10**). Hydrogenolysis of compound (**9**) with deuteriated Superhydride gave, following oxidation, the 17-ketone (**11**). The 3β-methyl ether group of compound (**11**) was cleaved by treatment with $FeCl_3$–Ac_2O–EA (EA = ethyl acetate) and the resulting 3β-acetate was saponified to give compound (**13**). The (19*R*)-[19-$^2H_1$,19-$^3H_1$]-iodide (**10**) (Scheme 1) was hydrogenolysed with protiated Superhydride and processed to give first compound (**12**), and then compound (**14**).

As indicated above, the hydrogenolysis with Superhydride was disturbing since its steric course was unknown; however, the hydrogenolysis with deuteriated Superhydride was of even greater concern, because it could involve a deuterium isotope effect and thus enhance the possibility of racemization. We thought that this potential obstacle could be circumvented if the same reagents were used in each step of the parallel sequence of reactions, particularly if the use of deuteriated Superhydride for hydrogenolysis of the iodides could be avoided.

In the search for an alternative approach, we explored the reduction of the (19-^{2}H)-aldehyde (**3a**) with (*R*)-[^{1}H]- and (*S*)-[^{1}H]-alpineboranes.[17] We were pleased to discover that the reduction with these reagents proceeded with slightly better diastereoisomeric selectivity than with the Haubenstock's reagents. Thus, reduction of compound (**3a**) with (*R*)-[^{1}H]- and (*S*)-[^{1}H]-alpineboranes gave, following the removal of the 17-acetals and acetylation, mixtures of 19-acetates containing 94—96% of (19*S*)-[19-$^2H_1$](**2a**) (Figure 3) and (19*R*)-(19-$^2H_1$)(**1a**) (Figure 3), respectively. Similarly, reduction of the 19-protiated aldehyde (**3b**) with (*S*)-[^{2}H]-alpineborane gave



Scheme. 1

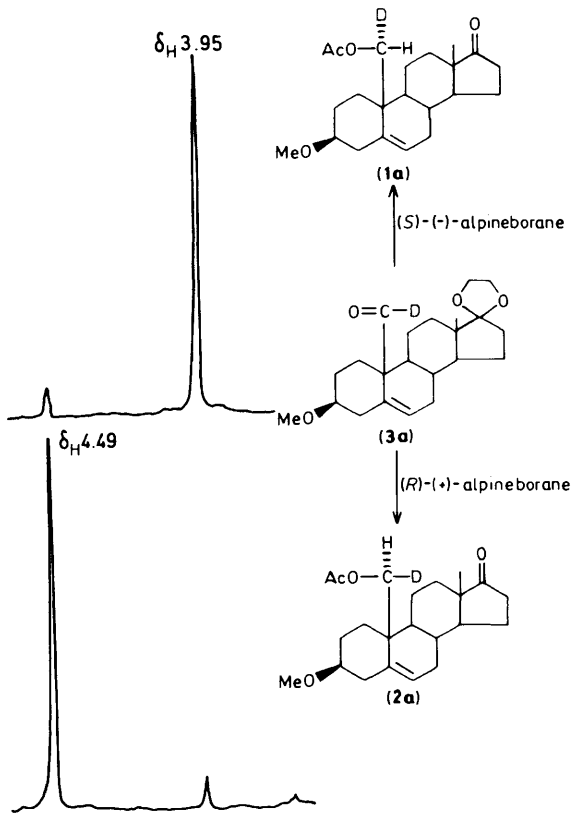


Figure 3.

the (19*S*)-[$^2H_1$]-alcohol (**2c**). These observations provided the basis for the alternative syntheses outlined in Scheme 2.

Again, the starting material was the 19-tritiated aldehyde (**3c**). Reduction of this compound with (*R*)-[^{2}H]alpineborane [18] gave, following removal of the 17-acetal group, (19*S*)-[19-$^2H_1$,19-$^3H_1$](**15**), while reduction with (*S*)-[^{2}H] alpineborane [18] and acid hydrolysis gave (19*R*)-[19-$^2H_1$,19-$^3H_1$](**8**). Both alcohols (**15**) and (**8**) were converted by treatment with MTPI into the respective iodides (**16**) and (**10**). The iodide (**16**) was hydrogenolysed with protiated Superhydride and, following processing described above, gave the required compound (**11**). Hydrogenolysis of iodide (**10**) with protiated Superhydride gave, following similar processing, the isomeric product (**12**). The 3β-ethers (**11**) and (**12**) were cleaved ($FeCl_3$–Ac_2O–EA) and the resulting acetates were saponified to yield alcohols (**13**) and (**14**), respectively. It may be noted that the reductions of aldehyde (**3c**) were carried out with the same reagents of opposite chirality. Identical reagents were used in the subsequent steps of the parallel sequences outlined in Scheme 2.

The synthesis of the (19*RS*)-product was carried out with the use of (*RS*)-alpineborane prepared by mixing equimolar amounts of (*R*)- and (*S*)-alpine borane. Thus, the (19-^{3}H)-aldehyde (**3c**) was reduced with (*RS*)-alpineborane and the 17-acetal group was removed. The resulting (19*RS*)-[19-$^3H_1$]-19-alcohol 17-ketone was converted into the corresponding (19-*RS*)-[19-$^3H_1$]-19-iodide, and this was hydrogenolysed with deuteriated Superhydride. Following reoxidation of the 17-alcohol and cleavage of the 3-methoxy function, the required (19*RS*)-3β-hydroxy[19-$^2H_1$,19-$^3H_1$]androst-5-en-17-one was obtained.

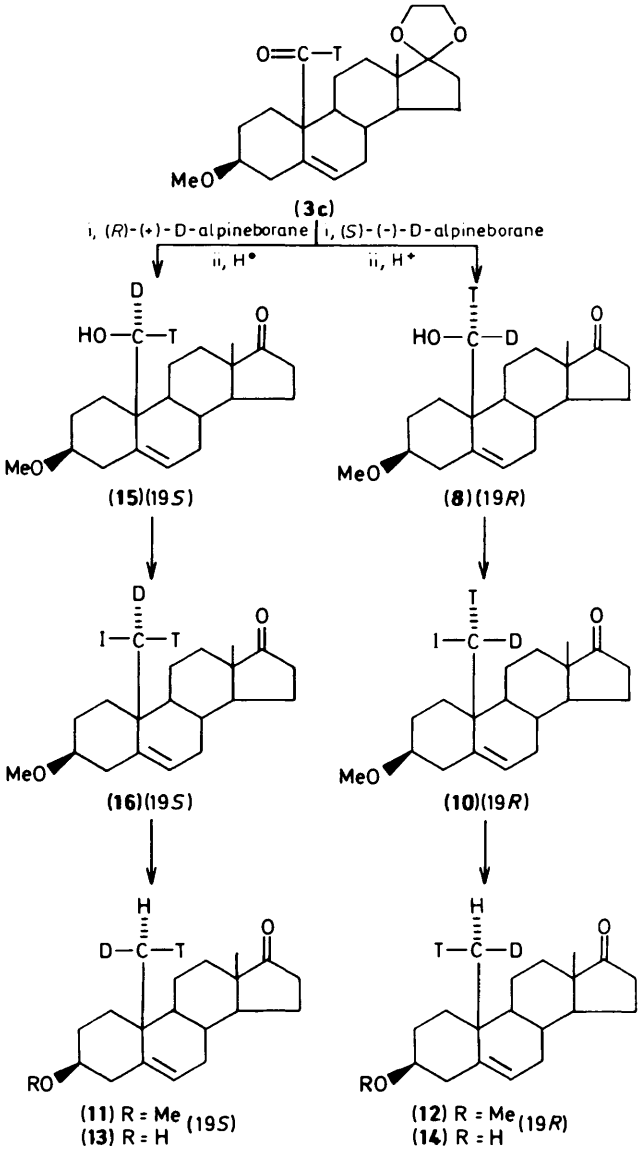
For chirality determination, the products (**11**), (**12**), (**13**), (**14**), and the corresponding (19*RS*)-analogue were converted into the corresponding androst-4-en-3-ones (**15**) and these were treated [19] with SeO_2–H_2O_2 to give secoacid lactones (**16**). The secoacid lactones (**16**) were submitted to Kuhn–Roth oxidation and the resulting samples of chiral acetic acids were isolated by steam distillation. The chirality of the acetic acids was determined by the malate-synthetase–fumarase procedure.[20,21] The (*RS*)-acetic acid and authentic (*S*)-acetic acid were used as references. Details of these investigations are reported elsewhere.[22] The results of chirality determination are summarized in Table 2.

The chiralities of the (19*R*)-(**14**) and (19*S*)-(**13**) obtained *via* the routes outlined in Scheme 1 were $F = 63$ and $F = 33$, respectively.[22] Similarly, the chiralities of the products (**12**)/(**14**) and (**11**)/(**13**) obtained as shown in Scheme 2 were $F = 65$ and $F = 33$, respectively. It is clear that the chiralities of the products obtained by the two routes are essentially the same. To the extent that it is permissible to assume a linear correlation

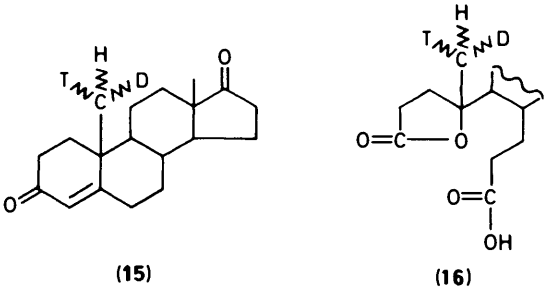
Table 2. Chiral analysis of samples of acetic acid derived from 19-chiral androgens

Entry	Origin of $CHDTCO_2Na$	$^3H/^{14}C$-malate: Initial	$^3H/^{14}C$-malate: Equilibrated with fumarase	*F*-value[a]	Chirality
1	(*RS*)-acetic acid	5.20	2.57	49	Racemic (*RS*)
2	*S*-acetic acid (authentic)	1.45	0.42	29	*S*
3	(19*RS*)-[19-$^2H_1$,19-$^3H_1$]-C_{19}-androgens	3.73	1.88	50	Racemic (*RS*)
4	(19*RS*)-[19-$^2H_1$,19-$^3H_1$]-C_{19}-androgens[b]	6.30	3.08	49	Racemic (*RS*)
5	**(13)** (Scheme 1)	4.15	1.36	33	*S*
6	**(14)** (Scheme 1)	3.11	1.96	63	*R*
7	**(13)** (Scheme 2)	3.85	1.31	34	*S*
8	**(14)** (Scheme 2)	4.45	2.88	65	*R*

[a] $F = \frac{T/^{14}C \text{ (equilibrated malate)}}{T/^{14}C \text{ (initial malate)}} \times 100$. [b] Prepared *via* reduction with (*RS*)-alpineborane.



Scheme 2.



between the *F* value and diastereoisomeric purity, it can be inferred that of the chiral molecules in the (19*R*)-sample, 76% have (19*R*)-methyls and, in the (19*S*)-sample, 79.5% have (19*S*)-methyls. In the modified Kuhn–Roth assay developed in our laboratory, up to 5% of hydrogen atoms of acetic acid are exchanged. It may therefore be assumed that the chiral molecules contained up to 81 and 85% of the corresponding chiral methyls.

Previously, we have indicated that the conversion of the 19-alcohols into 19-iodides apparently proceeds with retention. If indeed the 19-iodides have the indicated chiralities the *F* values indicate that the hydrogenolyses proceed with inversion.

Experimental

M.p.s were taken on a Kofler hot-stage apparatus and are corrected. I.r. spectra were recorded on a Perkin-Elmer 237 spectrophotometer as 5% solutions in $CHCl_3$. ^1H N.m.r. spectra were recorded in C^2HCl_3 on a Varian EM 390 spectrophotometer, using tetramethylsilane as internal reference. Deuterium n.m.r. spectra were recorded at 38.39 MHz on a Bruker WM-250 instrument operating in the FT mode with proton decoupling. Samples for ^2H n.m.r. spectra were dissolved in $CHCl_3$ with C^2HCl_3 as internal standard (δ_D 7.25). Mass spectra were determined on a Nuclide Co. model 12-90-G instrument equipped with a Nuclide DA/CS I.2 data-acquisition system. Silica gel 60HF (254, 366 nm) and Silica gel 60 (70—230 mesh) (E. Merck A. G. Darmstadt, G.F.R.) were used for thin layer and column chromatography, respectively. A Micromeritics h.p.l.c. instrument equipped with model 750 solvent-delivery system and model 788 dual-variable detector was used for h.p.l.c. For h.p.l.c. radiochromatography, a Radiomatic Instrument and Chemical Corporation apparatus Flow-One model was used. (*R*)- and (*S*)-Alpineboranes [0.5M in tetrahydrofuran (THF)] and (^1H)- and (^2H)-Superhydrides (1M in THF) were purchased from Aldrich Chemical Company, Milwaukee, WI.

Liquid scintillation counting was performed on a Packard (TRI-CARB, Model 3330) spectrometer in Liquifluor.

17,17-*Ethylenedioxy*-3β-*methoxy*[19-^2H]*androst*-5-*en*-19-*al* (**3a**).—The required starting material 3β,19-dihydroxyandrost-

5-en-17-one (4.0 g) was acetylated [py (15 ml); Ac_2O (8 ml)] to give the 3,19-diacetate, m.p. 102—104 °C (95%). A portion of the 3,19-diacetate (3.7 g) was dissolved in MeOH (70 ml), then water (2 ml) and $KHCO_3$ (1.5 g) were added. The mixture was stirred at ambient temperature (1.5 h) and water (100 ml) was added. The product was recovered with diethyl ether and processed in the usual way (3.6 g). The residue was purified by column chromatography (EA–hexane) to give 19-acetoxy-3β-hydroxyandrost-5-en-17-one (2.75 g, 85%), m.p. 121—123 °C; δ_H 2.05 (s, 3 H, 19-OAc), 3.96 (d, 1 H, 19-H, *J* 12 Hz), and 4.50 (d, 1 H, 19 H, *J* 12 Hz).

The 19-acetoxy-3β-hydroxy product (2.38 g) was dissolved in dioxane (20 ml) containing 70% $HClO_4$ (5 drops), then trimethyl orthoformate (9.81 ml) was added dropwise (15 min). After a further 10 min, the reaction was terminated with saturated aqueous $NaHCO_3$ (50 ml) and the mixture was extracted with diethyl ether. Work-up of the extract gave the crude 3β-methoxy-19-acetate (2.44 g) which was purified by column chromatography (EA–hexane) to give homogeneous material (1.89 g, 76%), δ_H 2.02 (s, 3 H, 19-OAc), 3.33 (s, 3 H, 3β-OMe), 3.94 (d, 1 H, 19-H, *J* 12 Hz), and 4.49 (d, 1 H, 19-H, *J* 12 Hz).

Acetalization of the 3β-methoxy acetate 17-ketone (1.69 g) [dry benzene (200 ml), toluene-*p*-sulphonic acid (200 mg), ethylene glycol (10 ml), reflux 16 h under a Dean–Stark water separator] gave, after work-up, the 19-acetoxy-3β-methoxy-17-ethylenedioxy compound (1.8 g), δ_H 2.02 (s, 3 H, 19-OAc), 3.33 (s, 3 H, 3β-OMe), 3.86 (m, 4 H, 17-OCH_2CH_2O), 3.94 (d, 1 H, 19-H, *J* 12 Hz), and 4.49 (d, 1 H, 19-H, *J* 12 Hz).

Treatment of the 19-acetoxy-17-acetal (1.135 g) with $LiAlH_4$ (0.5 g) in dry diethyl ether (50 ml) at reflux (2 h) gave 19-hydroxy-3βmethoxy-17-acetal (900 mg), m.p. 176—177 °C; δ_H 3.34 (s, 3 H, 3β-OMe) and 3.72 (d, 1 H, 19-H, *J* 6 Hz); the other doublet is hidden under the multiplet of (OCH_2CH_2O), δ_H 3.88 (m, 17-OCH_2CH_2O). The mass spectrum of the corresponding 19-(dimethyl-t-butylsilyl) ether showed ions at *m/z* 476 (M^+, $C_{28}H_{48}O_4Si$), 444 ($M^+ - 32$), 419 ($M^+ - C_4H_9$), 387, and 344.

The 19-hydroxy-3-methoxy-17-acetal (0.737 g) was dissolved in dry CH_2Cl_2 (10 ml) and the solution was added to a stirred mixture of CrO_3 (1.26 g), dry pyridine (2.04 g), and dry CH_2Cl_2 (30 ml). After the mixture had been stirred for 30 min, the liquid was decanted from the tarry residue and the residue was washed several times with diethyl ether (50 ml). The extracts and the decanted solution were combined and concentrated, and the residue was taken up in diethyl ether. The ether-insoluble solid was removed by filtration and, following the usual work-up and chromatography, 17,17-ethylenedioxy-3β-methoxyandrost-5-en-19-al (0.63 g) was obtained, m.p. 130—132 °C; δ_H 0.77 (s, 3 H, 13β-Me), 3.33 (s, 3β-OMe), 3.70 (m, 17-OCH_2CH_2O), and 9.7 (s, 1 H, 19-CHO).

Alternatively, oxidation of 17,17-ethylenedioxy-3β-methoxyandrost-5-en-19-ol (3.6 g) in acetone (40 ml) at −5 °C with Jones' reagent (8 ml) for 80 min gave [after removal of partly formed aldehyde (2.0 g)] the 17-oxo-10β-carboxylic acid (1.4 g, 37%). The acid was treated with diazomethane and, following column chromatography, the 19-methyl ester 17-ketone was obtained (1.25 g), m.p. 98—101 °C; δ_H 3.33 (3β-OMe) and 3.7 (s, 3 H, 19-CO_2Me).

The 19-methyl ester 17-ketone (0.6 g) was converted into the corresponding 17-acetal (0.582 g) [ethylene glycol (2 ml), dry benzene (100 ml), toluene-*p*-sulphonic acid (15 mg), Dean–Stark water separator]. The 19-methyl ester 17-ethylene dioxide showed δ_H 3.32 (s, 3β-OMe), 3.7 (s, 19-CO_2Me), and 3.88 (m, 17-OCH_2CH_2O).

Reduction of the 3β-methoxy-19-methyl ester 17-acetal (650 mg) with $LiAl^2H_4$ (100 mg) in THF (10 ml) under reflux (4 h) gave the 17,17-ethylenedioxy-3β-methoxy[19-$^2H_2$]androst-5-en-19-ol (550 mg), δ_H 3.4 (s, 3β-OMe), 3.94 (m, 17-OCH_2-CH_2O). The mass spectrum of the derived 19-(dimethyl-t-butylsilyl) ether exhibited ions at 478 (M^+, $C_{28}H_{46}D_2O_4Si$), 446 ($M^+ - 32$), 421 ($M^+ - C_4H_9$), 389, and 346. The m.s. indicates that products contain at least 98% 19-D_2. Oxidation of the 19-dideuterio alcohol (500 mg) with Collins' reagent (as described above for the 10-CH_2OH compound) gave 17,17-ethylenedioxy-3β-methoxy[19-^{2}H]androst-5-en-19-al (**3a**) (400 mg), m.p. 132 °C; δ_H 0.77 (s, 13β-Me), 3.33 (s, 3β-OMe), 3.7 (m, 4 H, 17-OCH_2CH_2O), and 5.84 (m, 1 H, 6-H). No signal for a proton of an aldehyde was detected, indicating a *ca.* 99—100% incorporation of deuterium at C-19.

(19S)-17,17-*Ethylenedioxy*-3β-*methoxy*[19-$^2H_1$]*androst*-5-*en*-19-*ol* (**2c**).—*(General procedure for reduction with Haubenstock's reagent).* A dry round-bottom flask (50 ml) equipped with a magnetic stirrer, reflux condenser, and a balanced (pressure-equalized) addition funnel was flushed with dry N_2. The flask was charged with a solution of $LiAl^2H_4$ (0.0336 g, 0.8 mmol) in dry diethyl ether (2 ml) (distilled once from $LiAlH_4$ and twice from $LiAl^2H_4$) and with di-t-butyl ketone (0.3449 g, 2.42 mmol). The mixture was stirred for 30 min at ambient temperature under N_2. Then, a solution of 17,17-ethylenedioxy-3β-methoxyandrost-5-en-19-al (**3b**) (180 mg, 0.5 mmol) in dry diethyl ether (12 ml) was added dropwise from the addition funnel. The mixture was refluxed under N_2 for 3.5 h, cooled, and water was added. The ethereal solution was separated and the aqueous phase was extracted with diethyl ether, then acidified (10% H_2SO_4), and again extracted with diethyl ether. The combined extract was washed sequentially with 2% H_2SO_4, water, saturated aqueous $NaHCO_3$, and brine, and dried ($MgSO_4$). The ether was removed under reduced pressure and the product was chromatographed on a column of silica gel (10 g). Elution with ethyl acetate–hexane (1 : 1) gave compound (**2c**) (168 mg), $\nu_{max.}$ (KBr) 3 440 and 1 660 cm^{-1}; δ_H 0.87 (s, 3 H, 13β-Me), 3.31 (s, 3 H, 3β-OMe), 3.77 [(s, 0.9—0.95 H, 19-*H*^{2}HOH) (0.05—0.1 H buried under OMe signal)], 3.83 (m, 4 H, 17-OCH_2CH_2O), and 5.69 (m, 1 H, 6-H).

Preparation of (R)-[^{2}H]*Alpineborane and* (S)-[^{2}H]*Alpineborane.*[18]—*Deuterio*-9-BBN.* The deuteriated alpineboranes were prepared following a slight modification of the procedure of Midland and Greer.[18]

A flame-dried round-bottom flask, equipped with a condenser and a side arm sealed with a septum, was flushed with argon. A balloon was mounted on the condenser and the assembly was kept under a slight positive pressure of argon. A 1M solution of trideuterioborane (B^2H_3) in THF (25 ml; 25 mmol) was injected from a syringe *via* the septum. The flask was cooled in an ice-bath and then cyclo-octa-1,5-diene (3.06 ml, 25 mmol) was added dropwise to the stirred solution. At the completion of the addition, the mixture was gently refluxed for 1.5 h. The n.m.r. spectrum of an aliquot of the solution indicated that all of the cyclo-octadiene was converted into [9-^{2}H]-9-BBN. The [9-^{2}H]-9-BBN solution was used for the preparation of (*R*)- and (*S*)-deuterioalpineboranes.

(S)-[^{2}H]*Alpineborane.* To a stirred (under argon) 1M solution of [9-^{2}H]-9-BBN in THF (12.5 ml; 12.5 mmol) was added a solution of (−)-α-pinene (α_D −42°; 2.1 ml, 14 mmol) in THF (10 ml). The mixture was gently refluxed (4 h) in an atmosphere of argon. After cooling, the resulting solution was transferred (with a syringe) into a 25 ml volumetric flask (flushed with argon and sealed with a septum) and made up to volume (25 ml) with THF to give a 0.5M solution of (*S*)-[^{2}H]alpineborane. The solution could be stored in the refrigerator for 2—3 weeks without appreciable decomposition.

* 9-BBN = 9-borabicyclo[3.3.1]nonane.

(R)-[^{2}H]*Alpineborane*. The (*R*)-[^{2}H]alpineborane-^{2}H was prepared in the similar way, using (+)-α-pinene ([α] 47.1°).

Reduction of 19-Aldehydes with Alpineboranes (General Procedure).—The following procedure (adjusted to scale) was used in reduction experiments with alpineboranes.

To a 0.5M solution of (*S*)-[^{2}H]alpineborane (4 ml) (stirred under a slightly positive pressure of argon) was added a solution of 17,17-ethylenedioxy-3β-methoxyandrost-5-en-19-al (**3b**) (60 mg) in THF (3 ml). The mixture was gently refluxed (24 h), then cooled, and acetaldehyde (1 ml) was added and the mixture was stirred (15 min). The solvent was removed under reduced pressure and α-pinene was removed under reduced pressure (oil pump). The residue was dissolved in diethyl ether (20 ml), ethaneolamine (1 ml) was added, and the mixture was filtered through a short column of silica gel. The column was eluted with diethyl ether; the filtrate was washed with water, dried (Na_2SO_4), and the solvent was removed. The product was purified by preparative t.l.c. [silica gel; hexane–EA (2:1)] to give the (19*S*)-alcohol [94—96% (19*S*)]. Hydrolysis of the acetal (HCl in aqueous dioxane) was followed by acetylation to give (19*S*)-19-acetoxy-3β-methoxy[19-$^2H_1$]androst-5-en-17-one (**2a**), δ_H 4.49 (0.94—0.96 H) and 3.95 (0.04—0.06 H); δ_D 4.48 (0.04 ^{2}H) and 3.98 (0.96 ^{2}H).

Similar reduction of 19-aldehyde (**3b**) with (*R*)-[^{2}H]alpineborane gave the (19*R*)-[19-$^2H_1$]-alcohol (**1c**) which, following the removal of the acetal group and acetylation, furnished the (19*R*)-[19-$^2H_1$]-acetate (**1a**), δ_D 4.48 (0.95 ^{2}H) and 3.98 (0.05 ^{2}H).

(19S)-19-*Hydroxy*-3β-*methoxy*[19-$^2H_1$]*androst*-5-*en*-17-*one* (**2d**).—A solution of compound (**2c**) (145 mg) in 0.4M-methanolic hydrochloric acid (15 ml) was heated in a water-bath (15 min) and then stored at room temperature (30 min). Most of the solvent was removed under reduced pressure, then saturated aqueous $NaHCO_3$ (10 ml) was added and the product was recovered with EA. Following the usual work-up, the title product (**2d**) (125 mg) was obtained. Purification by t.l.c. [silica gel; EA–hexane (1:1)] gave a homogeneous sample of the ketone (**2d**), m.p. 147—148 °C; δ_H 0.93 (s, 3 H, 13β-Me), 3.34 (s, 3 H, 3β-OMe), 3.65 [s, 0.05—0.1 H, 19-*H*D(OH)], 3.85 [s, 0.9—0.95 H, 19-*H*D(OH)], and 5.79 (m, 1 H, 6-H).

(19S)-19-*Acetoxy*-3β-*methoxy*[19-$^2H_1$]*androst*-5-*en*-17-*one* (**2a**).—Acetylation of compound (**2d**) (100 mg) [py (1 ml) and Ac_2O (0.3 ml), 16 h, room temp.] gave, after the usual work-up, the acetate (**2a**) (95 mg), δ_H 0.89 (s, 3 H, 13β-Me), 2.02 (s, 3 H, 19-OAc), 3.34 (s, 3 H, 3β-OMe), 3.95 [s, 0.05—0.1 H, 19-*H*D(OAc)], 4.49 [s, 0.9—0.95 H, 19-*H*D(OAc)], and 5.64 (m, 1 H, 6-H).

(19S)-19-*Iodo*-3β-*methoxy*[19-$^2H_1$]*androst*-5-*en*-17-*one* (**6a**).—A solution of compound (**2d**) (100 mg) in dry DMF (10 ml) was stirred under nitrogen and then methyl triphenoxyphosphonium iodide (230 mg; 30% excess) was added. The mixture was stirred at room temperature (20 h) and the reaction was terminated with brine. The product was recovered with diethyl ether; the extract was washed successively with 5% aqueous sodium thiosulphate and with water, dried, and concentrated to give a residue (340 mg). Preparative t.l.c. [silica gel; EA–hexane (1:9)] gave the homogeneous 19-iodide (**6a**) (130 mg), δ_H 3.35 (s, 3 H, 3β-OMe), 3.28 (0.05—0.1 H, CHDI, partly superimposed on the 3β-OMe signal), 3.6 (s, 0.9—0.95 H, 19-HDI), and 5.69 (m, 1 H, 6-H).

(19S)-3β-*Acetoxy*-19-*iodo*[19-$^2H_1$]*androst*-5-*en*-17-*one* (**6b**).—A solution of the (19*S*)-3β-methoxy 19-iodide (**6a**) (100 mg) in acetic anhydride–diethyl ether (4:1) (10 ml) was cooled in an ice-bath (0 °C), then freshly redistilled boron trifluoride–diethyl ether (0.7 ml) was added. The mixture was stored at 0 °C for 15 h and then poured on ice–water. After *ca.* 6 h, the product was extracted with diethyl ether, and the extract was washed (aqueous $NaHCO_3$, water), dried, and concentrated (75 mg). The crude residue was purified by t.l.c. [silica gel; EA–hexane (1:1)] to yield homogeneous acetate (**6b**) (65 mg, *ca.* 60%), δ_H 0.98 (s, 13β-Me), 2.02 (s, 3 H, 3β-OAc), 3.60 (s, 0.9—0.95 H, 19-HDI), 3.28 (s, 0.05—0.1 H, 19-HDI), 4.61 (m, 1 H, 3α-H), and 5.72 (m, 1 H, 6-H).

(19R)-17,17-*Ethylenedioxy*-3β-*methoxy*[19-$^2H_1$]*androst*-5-*en*-17-*one* (**1c**).—Treatment of the 19-deutorio aldehyde (**3a**) with the trialkoxyaluminium hydride prepared from $LiAl^1H_4$ (1 mmol equiv.) and di-t-butyl ketone (3 mmol equiv.), as described for the preparation of compound (**2c**), gave the title product (90%), admixed with a minor amount of (19*S*)-alcohol (**2c**). The product had δ_H 0.87 (s, 3 H, 13β-Me), 3.31 (s, 3 H, 3β-OMe), and 3.77 [s, 0.05—0.1 H, 19C*H*D(OAc)] (the remaining 0.9—0.95 H signal is buried under that of OMe).

(19R)-19-*Hydroxy*-3β-*methoxy*[19-$^2H_1$]*androst*-5-*en*-17-*one* (**1d**).—The acetal alcohol (**1c**) was dissolved in 0.4M methanolic hydrochloric acid and processed as described for the preparation of compound (**2d**) to give the (19*R*)-isomer (**1d**), δ_H 3.34 (s, 3β-OMe), 3.65 [s, 0.9—0.95 H, 19-*H*D(OH)], 3.85 [s, 0.05—0.1 H, 19-*H*D(OH)], and 5.79 (m, 1 H, 6-H).

(19R)-19-*Acetoxy*-3β-*methoxy*[19-$^2H_1$]*androst*-5-*en*-17-*one* (**1a**).—Acetylation of alcohol (**1d**) (py–Ac_2O) gave the acetate (**1a**), δ_H 0.89 (s, 3 H, 13β-Me), 2.02 (s, 3 H, 19-OAc), 3.34 (s, 3 H, 3β-OMe), 3.95 [s, 0.9—0.95 H, 19-*H*D(OAc)], 4.49 [s, 0.05—0.1 H, 19-HD(OAc)], and 5.64 (m, 1 H, 6-H).

(19R)-19-*Iodo*-3β-*methoxy*[19-$^2H_1$]*androst*-5-*en*-17-*one* (**5a**).—Iodination of alcohol (**1d**) was carried out as described for the preparation of compound (**6a**). The obtained (19*R*)-isomer (**5a**) showed δ_H 3.35 (s, 3β-OMe), 3.6 (s, 0.05—0.1 H, 19-HDI), 3.28 (0.9—0.95 H, 19-HDI), and 5.69 (m, 1 H, 6-H).

(19R)-3β-*Acetoxy*-19-*iodo*[19-$^2H_1$]*androst*-5-*en*-17-*one* (**5b**).—Cleavage of the methoxy group of the ether (**5a**) with BF_3·diethyl ether–Ac_2O [for details see preparation of (19*S*)-isomer (**6b**)] gave the 3β-acetate (**5b**), δ_H 2.02 (s, 3β-OAc), 3.28 (s, 0.9—0.95 H, 19-HDI), 3.60 (s, 0.05—0.1 H, 19-HDI), and 5.72 (m, 1 H, 6-H).

3β-*Methoxy*[19-$^2H_1$]*androst*-5-*en*-17-*one from* (19S)-*Iodide* (**6a**) *and* (19R)-*Iodide* (**5a**).—To a solution of the (19*S*)-iodide (**6a**) (90 mg, 0.209 mmol) in dry THF (5 ml) (stirred under N_2) was added a 1M solution of $LiEt_3BH$ in THF (0.88 ml) and the mixture was refluxed under N_2 (10 h). After the mixture had cooled (ice-bath), the reaction was terminated by dropwise addition of water, and the mixture was poured on ice–water (50 ml). The product was recovered with EA and the extract was washed, dried, and concentrated. The product was purified by t.l.c. (silica gel; EA–hexane (3:7)] to give homogeneous 3β-methoxy[19-$^2H_1$]androst-5-en-17β-ol (59 mg, 91%), δ_H 0.76 (s, 3 H, 13β-Me), 1.02 (br s, 2 H, 19-H_2D), 3.35 (s, 3 H, 3β-OMe), and 5.35 (m, 1 H, 6-H).

Treatment of an acetone solution of the 17β-alcohol with Jones' reagent yielded 3β-methoxy[19-$^2H_1$]androst-5-en-17-one, the ^{1}H n.m.r. spectrum of which was identical in all respects with that of an authentic sample, except that the 10β-methyl signal showed a lower intensity.

The (19*R*)-iodide (**5a**) was processed in an identical manner to give the title compound.

17,17-*Ethylenedioxy*-3β-*methoxy*[19-^{3}H]*androst*-5-*en*-19-*al* (**3c**).—To a vial containing (^{3}H) $NaBH_4$ (100 mCi; *ca.* 0.34 mg; 9.0 μmol) were added sequentially the 19-protiated aldehyde (**3b**) (25 mg, 69 μmol) and ethanolic sodium hydroxide [ethanol (1 ml) and 0.01M-NaOH (0.06 ml)]. The reaction mixture was stored (8 h) at room temp., then water (1 ml) was added and the product was extracted several times with EA. The extract was washed with saline and concentrated. Analytical t.l.c. indicated the presence of the 19-alcohol and of some unchanged starting material. The crude residue was dissolved in dry CH_2Cl_2 and treated with Collins' reagent (30 min), and the required [19-^{3}H]-aldehyde was recovered with diethyl ether. Removal of the solvent gave the crude aldehyde, which was purified by column chromatography on silica gel. Homogeneous compound (**3c**) (55 mCi) was eluted with EA–hexane (1:5). T.l.c.-autoradiography and h.p.l.c. with a radioactive-flow detector confirmed the homogeneity of the product.

(19R)-19-*Hydroxy*-3β-*methoxy*[19-$^3H_1$]*androst*-5-*en*-17-*one* (**7**).—The [19-^{3}H]-aldehyde (**3c**) (575 mg, 1.6 mmol; 27 mCi) was treated with the lithium trialkoxyaluminium hydride prepared from $LiAlH_4$ (160 mg, 4.2 mmol) and di-t-butyl ketone (1.688 g, 11.9 mmol), as described for the preparation of compound (**2c**). The resulting (19*R*)-[19-$^3H_1$]-alcohol 17-acetal was hydrolysed with methanolic hydrochloric acid to give, after the usual chromotographic fractionation, the alcohol (**7**) (23.24 mCi; 86% yield).

(19R)-19-*Hydroxy*-3β-*methoxy*[19-$^2H_1$,19-$^3H_1$]*androst*-5-*en*-17-*one* (**8**).—*A*. Reduction of aldehyde (**3c**) (585 mg, 1.63 mmol; 27 mCi) with the lithium trialkoxyaluminium deuteride prepared from $LiAl^2H_4$ (176.4 mg, 4.2 mmol) and di-t-butyl ketone (1.874 g, 13.2 mmol) gave, following the usual work-up, the (19*R*)-[19-$^2H_1$, 19-$^3H_1$]-alcohol 17-acetal The acetal group was then hydrolysed (methanolic hydrochloric acid) to yield, after chromatographic purification, the (19*R*)-[19-$^2H_1$,19-$^3H_1$]-alcohol (**8**) (23 mCi; 87% yield).

B. The [19-^{3}H]-aldehyde (**3c**) (2.5 mCi; 15 mg) in THF was treated with a THF solution of (*S*)-deuterioalpineborane (4 ml; 0.5M solution) at reflux under argon. The progress of the reduction was monitored by h.p.l.c. with a radioactive-flow detector. After 24 h (although some aldehyde remained) the reaction was terminated and the mixture processed. Following acid-catalysed cleavage of the acetal group and preparative t.l.c. on silica gel [hexane–EA (2:1)], the (19*R*)-[19-$^2H_1$,19-$^3H_1$]-alcohol (**8**) (7 mg; 1.1 mCi) was obtained, δ_D ($CHCl_3$) 3.58 (19-^{2}H).

(19S)-19-*Hydroxy*-3β-*methoxy*[19-$^2H_1$,19-$^3H_1$]*androst*-5-*en*-17-*one* (**15**).—Reduction (under N_2) of [19-^{3}H]-aldehyde (**3c**) (8.3 mCi) with (*R*)-deuterioalpineborane at reflux (36 h) and processing of the reaction mixture as described above gave the (19*S*)-[19-$^2H_1$,19-$^3H_1$]-19-alcohol 17-acetal (5.8 mCi). H.p.l.c.-radiochromatographic analysis of the ratio of the alcohol:aldehyde indicated that the yield of the alcohol was *ca.* 85%. Following hydrolysis of the acetal group and chromatography (3 mCi), the [19-$^2H_1$,19-$^3H_1$]-alcohol 17-ketone (**15**) was obtained (2.7 mCi).

(19R)-19-*Iodo*-3β-*methoxy*[19-$^3H_1$]*androst*-5-*en*-17-*one* (**9**).—To a solution of the (19*R*)-[19-$^3H_1$]-alcohol (**7**) (*ca.* 14 mCi) in dry DMF (3 ml) was added MTPI (450 mg), and the mixture was stirred under N_2 at room temperature (20 h). The reaction was terminated with saturated brine and the product was recovered with diethyl ether. Processing of the extract in the manner described above gave, following chromatographic purification of the residue, the (19*R*)-[19-$^3H_1$]-19-iodide (**9**) (13 mCi).

(19R)-19-*Iodo*-3β-*methoxy*[19-$^2H_1$,19-$^3H_1$]*androst*-5-*en*-17-*one* (**10**).—*A*. The (19*R*)-alcohol (**8**) (*ca.* 14 mCi) was treated with MTPI (212 mg) in dry DMF (5 ml) under N_2. After the usual work-up and chromatography on silica gel, the (19*R*)-[19-$^2H_1$,19-$^3H_1$]-iodide (**10**) (*ca.* 13 mCi) was obtained.

B. Similarly, reaction of the (19*R*)-[19-$^2H_1$,19-$^3H_1$]-alcohol (**8**) (prepared as in Scheme 2) (1 mCi) with MTPI (110 mg) gave the (19*R*)-[19-$^2H_1$,19-$^3H_1$]-iodide (**10**) (0.7 mCi).

(19S)-19-*Iodo*-3β-*methoxy*[19-$^2H_1$,19-$^3H_1$]*androst*-5-*en*-17-*one* (**16**).—Treatment of the (19*S*)-19-$^2H_1$,19-$^3H_1$]-alcohol (**15**) (3 mCi) with MTPI (112 mg) gave the (19*S*)-[19-$^2H_1$,19-$^3H_1$]-iodide (**16**) (2.58 mCi).

(19S)-3β-*Methoxy*[19-$^2H_1$,19-$^3H_1$]*androst*-5-*en*-17-*one* (**11**).—*A*. To a solution of the (19*R*)-[19-$^3H_1$]-iodide (**9**) (13 mCi) in dry THF (10 ml) was added a 1M solution of $LiEt_3B^2H$ (Superdeuteride) in THF (5 ml), and the mixture was refluxed (12 h) under N_2. The 17-alchohol produced was oxidized with Jones' reagent to give, after chromatographic purification on a silica gel column, the (19*S*)-[19-$^2H_1$,19-$^3H_1$]-3β-methoxy ketone (**11**) (*ca.* 11 mCi).

B. Reaction of the (19*S*)-[19-$^2H_1$,19-$^3H_1$]-19-iodide (**16**) (1.5 mCi) with $LiEt_3BH$ gave, after reoxidation of the 17-alcohol, the (19*S*)-[19-$^2H_1$,19-$^3H_1$]-3β-methoxy ketone (**11**).

(19R)-3β-*Methoxy*[19-$^2H_1$,19-$^3H_1$]*androst*-5-*en*-17-*one* (**12**).—*A*. Treatment of the (19*R*)-iodide (**10**) (13 mCi) with 1M-$LiEt_3BH$ (5 ml) gave the 17β-hydroxy product, which was oxidized and processed in the conventional manner to give compound (**12**) (11.22 mCi).

B. Hydrogenolysis of the (19*R*)-iodide (**10**) (from Scheme 2) (0.5 mCi) with $LiEt_3BH$ gave, after reoxidation and chromatographic purification, the title compound (**12**) (0.29 mCi).

(19R)- and (19S)-3β-*Hydroxy*[19-$^2H_1$,19-$^3H_1$]*androst*-5-*en*-17-*one* (**14**) and (**13**) (*General Procedure*).—To a solution of (19*R*)- or (19*S*)-3β-methoxy[19-$^2H_1$,19-$^3H_1$]androst-5-en-17-one (**12**) or (**11**) in a 1:1 mixture of acetic anhydride and ethyl acetate (1 ml) was added anhydrous iron(III) chloride (1—2 mg), and the mixture was stirred for 2—3 h at ambient temperature. Water was then added and the solution was stored at room temperature for several hours. The product was recovered with EA, and the extract was washed successively with water, aqueous $NaHCO_3$, and water, dried, and concentrated to yield the corresponding 3-acetate. The acetate was dissolved in 5% methanolic KOH (2—5 ml) and the solution was stirred (3—4 h) at room temperature under nitrogen. The product was recovered in the conventional manner and was purified by column chromatography on silica with mixtures of hexane–EA as eluant.

Immediately prior to use, each compound was purified by h.p.l.c. on an Altech silica column (4.5 mm × 20 cm; 10μ particle size; 5% propan-2-ol in iso-octane). Usually, a single peak (radioactive) was observed.

Reduction of 17,17-*Ethylenedioxy*-3β-*methoxy*[19-^{2}H]-*androst*-5-*en*-19-*al* (**3a**) *with Protiated* (*R*)- *and* (*S*)-*Alpineboranes*.—Reduction of the aldehyde (**3a**) with (*R*)-alpineborane gave the (19*S*)-17,17-ethylenedioxy[19-$^2H_1$]androsten-19-ol (**2c**), which was converted as above into compound (**2a**), δ_H 4.49 (0.94—0.96 ^{1}H) and 3.95 (0.04—0.06 ^{1}H) (Figure 3).

Similarly, reduction of the [19-^{2}H]-aldehyde (**3a**) with (*S*)-alpineborane gave, after processing, the (19*R*)-[$^2H_1$]-19-acetoxy ketone (**1a**), δ_H 4.49 (0.04—0.06 ^{1}H) and 3.95 (0.94—0.96 ^{1}H) (Figure 3).

(19RS)-3β-*Methoxy*[19-$^2H_1$,19-$^3H_1$]*androst-5-en*-17-*one* [(**11**) + (**12**)].—A dry round-bottom flask equipped with a reflux condenser and a side arm closed with a septum was flushed with argon. The assembly was kept under a positive pressure of argon and charged with [19-^{3}H]-aldehyde (**3c**) (20 mg; 550 μCi). A mixture of (*R*)-alpineborane (0.5M) in THF) (3 ml) and (*S*)-alpineborane (0.5M in THF) (3 ml) was then injected from a syringe *via* the septum. The resulting solution was refluxed under argon (40 h), and processed as described above. The 17-acetal (19*RS*)-alcohol thus obtained was hydrolysed in 0.4M-methanolic HCl (3 ml) and processed to yield (19*RS*)-19-hydroxy-3β-methoxy[19-$^3H_1$]androst-5-en-17-one (14.5 mg; 270 μCi). The 19-hydroxy 17-ketone was dissolved in DMF (5 ml), then MTPI (100 mg) was added and the mixture was stirred (24 h) at room temp. under argon. Following the conventional work-up, the (19*RS*)-[19-$^3H_1$]-19-iodide (185 μCi) was recovered. The 19-iodide was treated with a solution of deuteriosuperhydride (1M in THF) (5 ml) and the mixture was refluxed (16 h) under argon. The recovered product was dissolved in acetone and oxidized with Jones' reagent. The resulting 3β-methoxy 17-ketone was purified by t.l.c. [silica gel; hexane–EA (2:1)] to yield homogeneous (19*RS*)-3β-methoxy[19-$^2H_1$,19-$^3H_1$]androst-5-en-17-one (**11**/**12**) (7.2 mg; 142 μCi), $\delta_D(CCl_4)$ 1.1, m.s. 303 (M^+), 271 ($M - 32$), 255, and 232.

The methoxy group was cleaved ($FeCl_3$–Ac_2O–EA) to give, after saponification, (19*RS*)-3β-hydroxy[19-$^2H_1$,19-$^3H_1$]-androst-5-en-17-one (**13**)/(**14**).

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