247. Steroids and Sex Hormons

Part 264[1])

Lewis Acid Catalyzed Reversible [1,5]-Hydride Shift in 3,19-Epoxy-steroids

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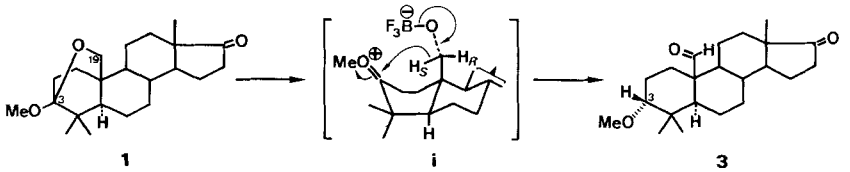
Summary

3β,19-Epoxy-3α-methoxy-steroids *(e.g.* **1**, *Scheme 1)* are converted into the corresponding 3α-methoxy-19-oxo compounds *(e.g.* **3***)* in the presence of boron trifluoride etherate, *via* an intramolecular hydride ion transfer from C(19) to (3) which is shown to be an equilibrium process. By subjecting the specifically deuteriated (19 *S*)- and (19 *R*)-compounds **1b** and **1c** to this reaction it was shown to be highly stereoselective.

In connection with studies directed towards partial synthesis of triterpenoid bitter principles such as limonin [2][2]) and quassin [3][2]) it became necessary to test the stability of the internal acetal grouping in compounds such as **1** *(Scheme 1)* towards *Lewis* acids. On treatment of the 3β,19-epoxy-3α-methoxy-4,4-dimethyl-steroid **1**[3]) with boron trifluoride etherate in benzene solution we found that the 3α-methoxy-19-oxo compound **3**[4]) *(Scheme 1)* was formed in 55% yield, 35% of starting material **1** being apparently recovered.

Scheme 1



[1]) Part 263, s. [1].

[2]) For the structure elucidation of limonin see [4], and of quassin see [5].

[3]) The 5α-steroid **1** was obtained by hydrogenation of the corresponding 5,6-didehydro derivative **2** [6] (see *Table 1*).

[4]) The structure of **3** was confirmed by chemical correlation (see below).

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As demonstrated below, aldehyde **3** results from an *intramolecular* [1,5]-hydride-ion transfer between C(19) and C(3)[5] (see **i** in *Scheme 1*). A similar hydride-ion transfer from C(19) to C(3) has been described earlier by *Wicha & Caspi* [25], who on subjecting **v** *(Scheme 2)* to acetalization conditions, or on reaction of **vi** with base obtained the 19-oxo compounds **vii** and **viii**, respectively[6])[7]).

Scheme 2

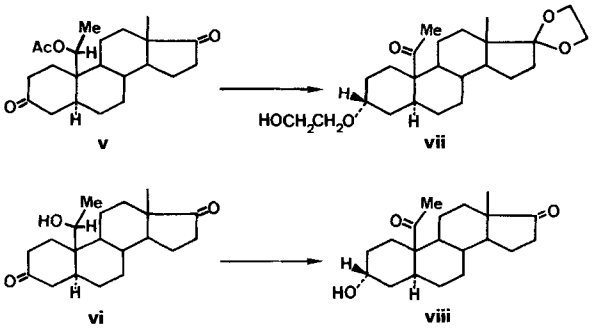
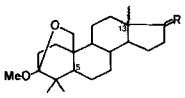
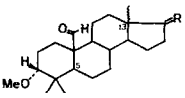


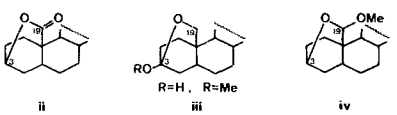
Table 1 summarizes the reactions of further steroid systems with boron trifluoride etherate which have been investigated in this study.

Table 1. *Reaction of 3β,19-epoxy-3α-methoxy-4,4-dimethyl-steroids with boron trifluoride etherate*

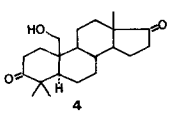
Starting material		Isolated products				
	⇌			+	starting material	
2	13β,5,6-didehydro, R = O	**5**	13β,5,6-didehydro, R = O	6%	**2**	82%
6	13α,5α, R = O	**7**	13α,5α, R = O	27%	**6**	63%
8	13β,5α, R = β – OAc, α – H	**9**	13β,5α, R = β – OAc, α – H	53%	**8**	47%[a])
10	13α,5α, R = β – OAc, α – H	**11**	13α,5α, R = β – OAc, α – H	66%	**10**	33%
12	13α,5α, R = α – OAc, β – H	**13**	13α,5α, R = α – OAc, β – H	45%	**12**	33%

[a]) For the chromatographic separation of **8** and **9** the mixture had to be treated with aqueous acetic acid to hydrolyze the acetal system in **8**.

[5]) The flexibility of ring A in 5α- and Δ^5-steroids facilitates a conformation enabling *intramolecular* interaction involving oxygen functions at C(19) and C(3), *e.g.* the formation of 3β,19-lactones (type **ii**) [7–13] and of 3β,19-acetals (type **iii** and **iv**) [6] [10] [12] and [14–24].



[6]) On treatment of the 19-hydroxy-3-oxo-4,4-dimethyl compound **4** according to the conditions used by *Wicha & Caspi* [25] no reaction occurred.

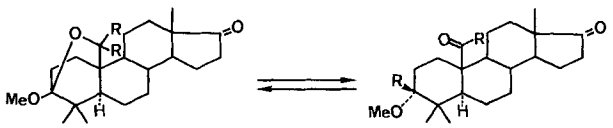


[7]) For further [1,5]-hydride-ion-transfer reactions see *e.g.* [26–28] [4a, (p. 45, III → LII)], and [12].

On further investigation the [1,5]-hydride-ion shift (**1** → **3**, *Scheme 1*) was shown to be an equilibrium reaction (equilibrium constant $K = 1.54 \pm 0.12$; s. below). Moreover, the H_S-transfer from C(19) to C(3) (s. **i**, *Scheme 1*) was found to be highly stereoselective (> 80%, s. below). To our knowledge analogous equilibria have not yet been demonstrated in similar systems. In the reverse reaction the H–C(3) was transferred with more than 80% stereoselectivity to the *si*-face of the C(19)-carbonyl function.

The intramolecular nature of the [1,5]-H-shift. The β-configuration of H–C(3) in product **3** *(Scheme 1)* suggests an *intramolecular* hydride-ion transfer. This was confirmed by an experiment using an 1 : 1 mixture of **1** and the dideuterio-compound **1a**[8]). Mass spectrometric examination of the products showed that only the undeuteriated aldehyde **3** and the 3β,19-dideuteriated aldehyde **3a** could be detected; moreover the reisolated starting material mixture contained only

Scheme 3



1 R = H
1a R = D

3 R = H
3a R = D

undeuteriated **1** and 19,19-dideuteriated **1a**. The absence of any monodeuteriated material proves the *intramolecular* nature of the rearrangement reaction. In a control experiment the 19,19-dideuterio compound **1a** afforded **3a** in pure state.

Equilibrium and selectivity of the [1,5]-hydride-shift. The constant ratio of starting material **1** to product **3** ($1 : 1.54 \pm 0.12$) observed after different reaction times (1, 3, 5, and 7 h) suggested the intramolecular hydride-ion transfer to be an equilibrium process. This was confirmed by treating the aldehyde **3** with boron trifluoride etherate in benzene. After 45 minutes aldehyde **3** and 3β,19-epoxy-3α-methoxy compound **1** *(Scheme 1)* were again isolated in 55 and 36% yield, respectively. In order to obtain information about the time necessary to reach an equilibrium state, with special attention to a possible *selective* hydride-ion transfer from C(19) to C(3), we determined the kinetics[9]) of the hydride shift. The results obtained from ^{1}H-NMR. data are summarized in *Figure 1*, and demonstrate that under the conditions chosen equilibrium was reached after 45 minutes [10]).

In order to test our assumption that one of the two H-atoms at C(19) is transferred preferentially from C(19) to C(3) the specifically deuteriated (19*S*)- and (19*R*)-19-deuterio compounds **1b** and **1c**, respectively[11]), were subjected to standard rearrangement conditions. The deuterium distribution in the products and in the reisolated starting materials were examined by ^{1}H-NMR. spectroscopy

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[8]) For the synthesis of **1a** see below.
[9]) S. exper. part.
[10]) The constant for the forward reaction is $k_1 = 8.91 \cdot 10^{-4}\ s^{-1}$ (reversible first order reaction).
[11]) For the synthesis and the determination of the configuration see below.

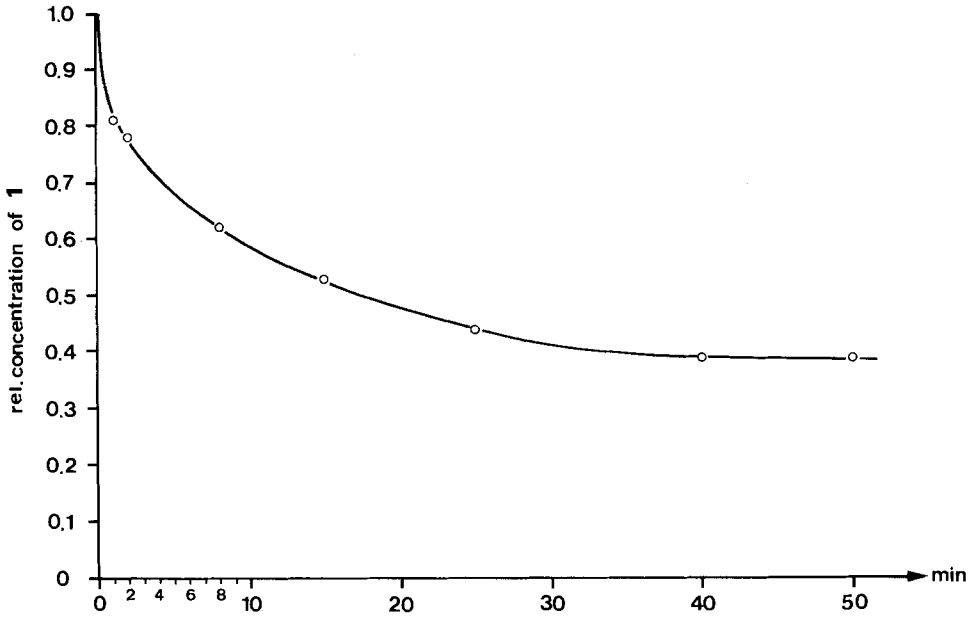
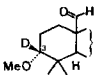
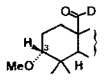
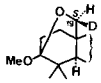
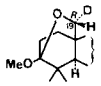


Fig. 1. *Reaction of* **1** *with* $BF_3 \cdot Et_2O$ *in benzene at 22.7°*

(see *Table 2*). From the product ratio **3b/3c** after 10 min reaction[12]) a clear preference for H_S at C(19) is indicated: In the (19 *S*)-compound **1b**, the deuteride-ion

Table 2. *H-* versus *D-shift in the (19 R)- and (19 S)-19-monodeuterioacetals*

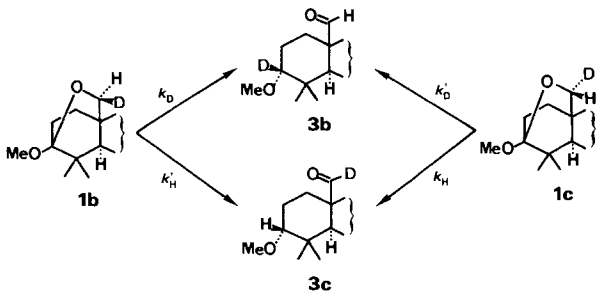
Starting material	Reaction time [min]	 **3b**	 **3c**
 **1b**	10	15	1
 **1c**	10	1	13

is transferred about 1.5 times faster than the hydride despite a retarding isotopic effect. This points to a selectivity due to a specific conformation of the O–H_2C(19) moiety in the intermediate oxonium ion **i**[13]) *(Scheme 1)* which in **1b** delays the H-transfer more than the isotopic effect retards the D-transfer. In the (19 *R*)-compound **1c** the D-transfer as compared to the H-transfer is retarded by both

[12]) Within this time the configuration at C(19) of the reisolated starting material was *not affected*. This indicates that the reverse reaction can be neglected at that stage.

[13]) A similar conformation of O–H_2C(19) was also established in steroids lacking the 4,4-dimethyl group [29].

Scheme 4

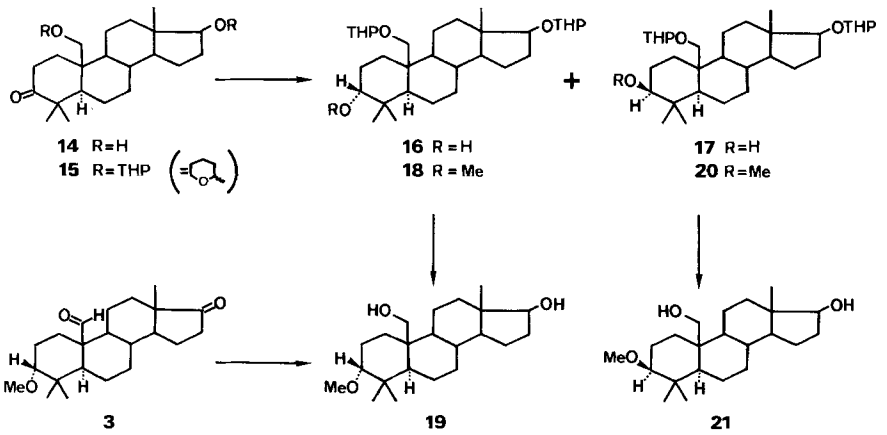


the isotopic effect and the conformational factor mentioned above, giving rise to more than 90% of H-transfer from C(19) to C(3) (s. *Table 2*). From the results shown in *Table 2* and in consideration of the kinetic scheme shown in *Scheme 4*[14]) (within 10 minutes reaction time the reverse reactions can be neglected), the preference of the H_S-shift due to the specific conformation of O–H_2C(19) can be deduced as $k_{H_S} = 4.4\ k_{H_R}$[14]). The isotopic effect can be calculated as $k_H = 2.9\ k_D$[14]).

The same selectivity of the H-transfer in the reverse reaction could be shown by treating the 19-deuterio-19-oxo compound **3c** *(Scheme 4)* under the same rearrangement conditions. After 10 minutes reaction the presence of the (19 *S*)- and the (19 *R*)-compounds, **1b** and **1c**, respectively, could be determined in a 1 : 4 ratio by ^{1}H-NMR. spectroscopy.

Structure of **3**. The structure of aldehyde **3** was confirmed by correlation with compound **19** *(Scheme 5)* which was obtained from **3** by reduction with $NaBH_4$.

Scheme 5



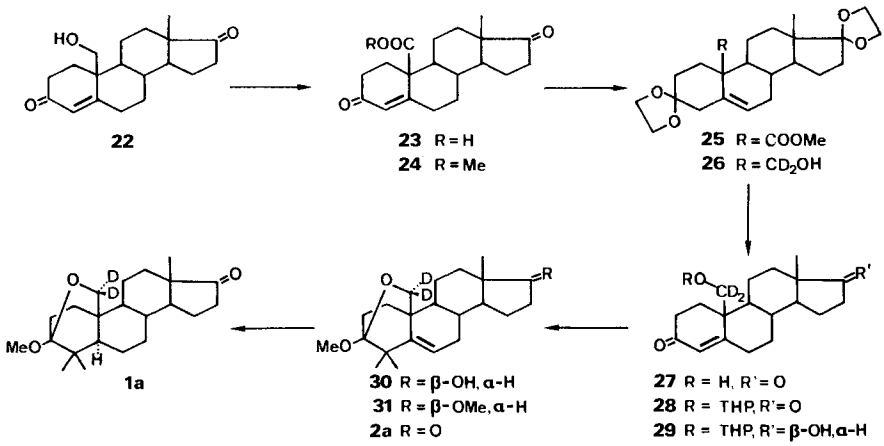
The relay compound **19** has been synthesized previously from **14** [23] *via* hydroxyl protection (→ **15**), reduction with $NaBH_4$ in methanol (→ **16** (8%) + **17** (77%)), methylation of the 3α-hydroxy group (→ **18**), and cleavage of the tetrahydropyranyl

[14]) For this intramolecular competition reaction it can be stated that: $k_D/k'_H = [\mathbf{3b}]/[\mathbf{3c}] = 1.5/1$, and $k'_D/k_H = [\mathbf{3b}]/[\mathbf{3c}] = 1/13$. With $k_H/k'_H = k_D/k'_D$ it follows that $k_{H_S} = 4.4\ k_{H_R}$ and $k_H = 2.9\ k_D$.

groups (THP) (→ **19**). In particular we have confirmed the β-configuration of H–C(3) in **19** by ^{1}H-NMR. spectroscopy (H_β–C(3): *t* at 2.82 ppm, ($J = 2$)). The epimeric compound **21** prepared similarly from **17** by *O*-methylation (→ **20**) and cleavage of the tetrahydropyranyl groups, showed clearly different ^{1}H-NMR. signals (H_α–C(3): *d* × *d* at 2.67 ppm ($J = 12$ and 4)).

Synthesis of **1a**, **1b**, *and* **1c**. The synthesis of the deuteriated compound **1a** was carried out as shown in *Scheme 6*. 19-Hydroxytestosterone (**22**) was oxidized

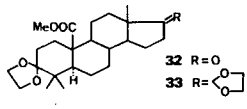
Scheme 6



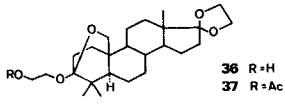
to the acid **23** [30]. Acetalization of the corresponding ester **24** (→ **25** [31]), reduction of the ester function with $LiAlD_4$ (→ **26** [31]), acetal cleavage (→ **27**) and protection of the 19-hydroxy group afforded **28**. Regioselective reduction of the 17-keto group in **28** with lithium tri-*t*-butoxyaluminiumhydride in tetrahydrofuran (→ **29**), dialkylation at C(4) with base and methyl iodide, and tetrahydropyranyl ether cleavage with MeOH/HCl [23] yielded **30**. Oxidation of the 17-hydroxy group (→ **2a**) and hydrogenation of the Δ^5-double bond finally gave **1a**[15]).

The (19 *S*)-19-deuterio compound **1b** and the (19 *R*)-19-deuterio compound **1c** were prepared in the following manner. Treatment of **1** and **1a** *(Scheme 7)* separately with acetic acid/water (→ **4** and **4a**, respectively), acetylation of the 19-hydroxy group (→ **34** and **34a**, respectively), acetalization (→ **35** and **35a**, respectively)[16]) and cleavage of the acetoxy function with $LiAlH_4$ led to the

[15]) Attempts to introduce the two deuterium atoms at C(19) by $LiAlD_4$ reduction of the 4,4-dimethyl compounds **32** and **33** were unsuccessful [32].

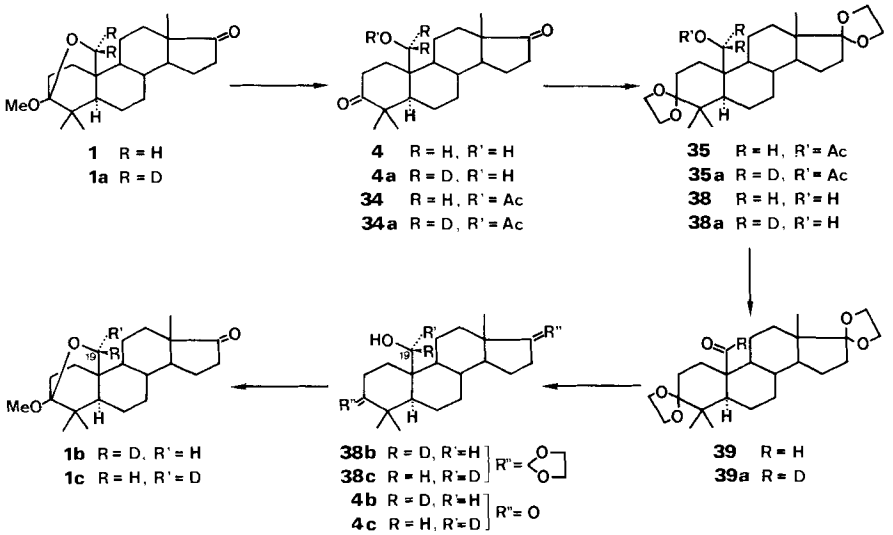


[16]) Direct acetalization of **4** *(Scheme 7)* led to **36**. For further characterization **36** was acetylated (→ **37**).



4,4-dimethyl-19-hydroxy derivatives **38** and **38a**, respectively. Their oxidation with pyridinium chlorochromate in methylene chloride gave the aldehydes **39** and **39a**,

Scheme 7



respectively. Reduction of **39** with lithium tri-*t*-butoxyaluminiumdeuteride ($Li(t\text{-}BuO)_3AlD$) and of **39a** with lithium tri-*t*-butoxyaluminiumhydride ($Li(t\text{-}BuO)_3AlH$) proceeded stereospecifically (> 95%), from the *si*-face of the aldehyde in each instance, to afford **38b** and **38c**, respectively[17] [18]). Finally acetal cleavage (→ **4b** and **4c**), and treatment with dry methanolic hydrochloric acid led to the (19 *S*)- and (19*R*)-compounds **1b** and **1c**, respectively.

In one of our earlier publications [23] we described pronounced long-range W-coupling of H_S–C(19) with H_α–C(1) and of H_R–C(19) with H_α–C(5) in the oxabicyclo[2.2.2]octane system formed by ring A and the 3β,19-epoxy bridge (s. *Fig. 2*)[19]). In the present work we have used this finding in order to provide proof for the (19 *S*)- and (19-*R*)-configuration of the monodeuteriated compound **1b** and **1c**, respectively. Replacement of H_α–C(5) of **1** with a deuterium atom (s. for instance **1d**)[20]) led to the disappearance of the long-range W-coupling of the higher field H–C(19) signal of **1** (s. *Fig. 2*). Therefore, this signal was assigned to

[17]) Reduction of **39** with $LiAlD_4$ and of **39a** with $LiAlH_4$ proceeded also stereospecifically (90%) from the *si*-face.

[18]) For other reductions of 19-oxo-steroids with deuterium labeled reagents s. *e.g.* [33] [29].

[19]) For similar long-range W-couplings in steroid lacking the 4,4-dimethyl group s. [34].

[20]) The 5α-deuterium atom was introduced by catalytic deuteriation of **2** (D_2, Pd/C, MeOD, RT.). Under these conditions the 5α,6α,7ξ,16ξ-tetradeuterio compound **1d** was obtained. The deuterio positions were deduced from ^{13}C-NMR. spectra. The D-atom at C(16) was exchangeable in aqueous methanolic KOH-solution.

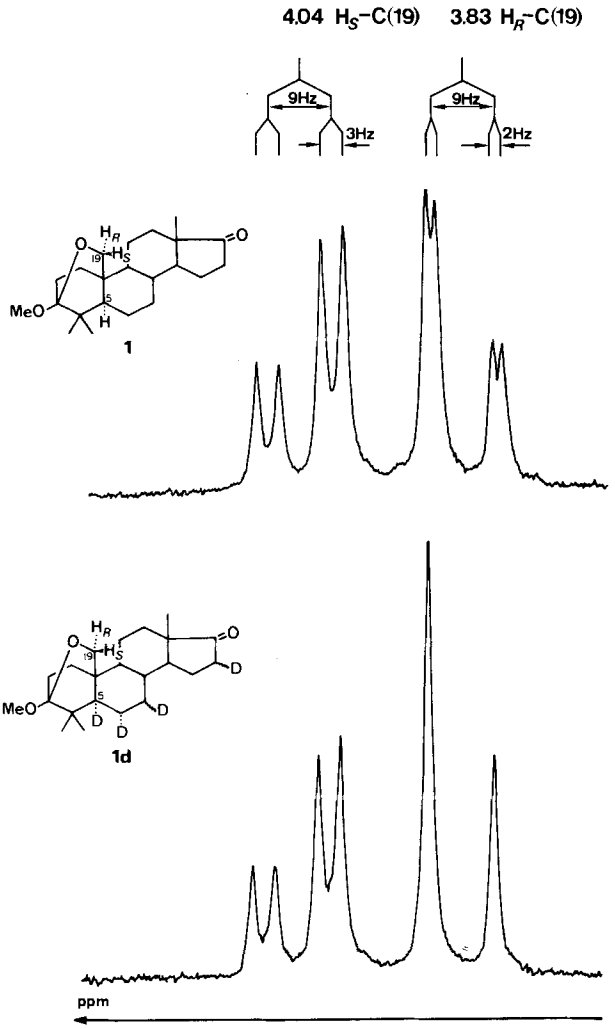


Fig. 2. *^{1}H-NMR. signals (100 MHz, $CDCl_3$) of H–C(19) of* **1** *and* **1d**

H_R–C(19)[21]). Thus, the (19 *S*)- and the (19 *R*)-configuration of **1b** and **1c**, respectively, could be unequivocally determined by ^{1}H-NMR. spectroscopy (s. *Fig. 3*).

[21]) For another determination of the configuration of $^2H^1HC(19)$-systems s. [33].

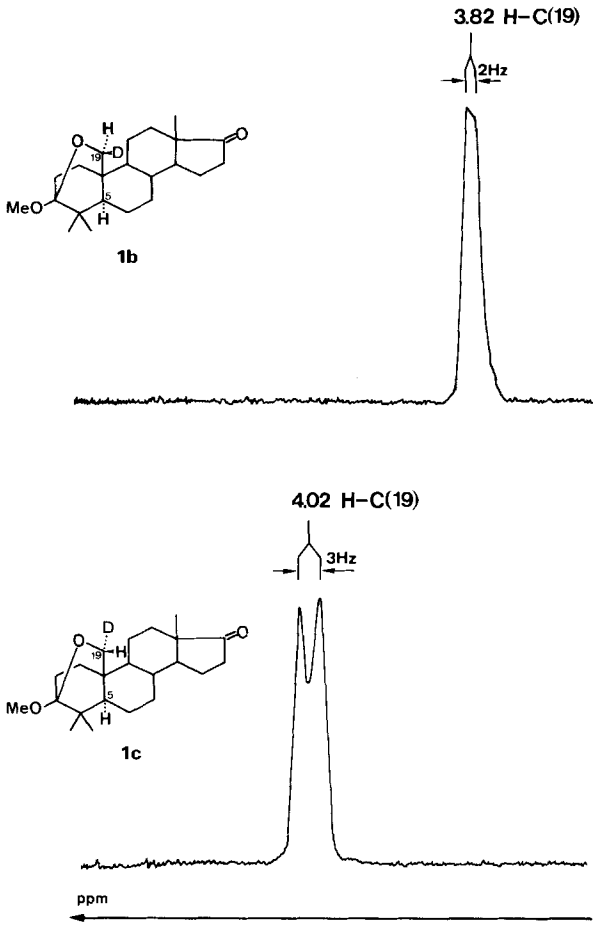


Fig. 3. *^{1}H-NMR. signals (100 MH$_3$, CDCl$_3$) of H–C(19) of* **1b** *and* **1c**

This work was supported by *Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung* and *Ciba-Geigy AG*, Basel.

Experimental Part

General remarks. S. [23].

Synthesis of 3β,19-epoxy-3α-methoxy-4,4-dimethyl-5α-androstan-17-one (**1**). A solution of 1.72 g of the 5,6-didehydro compound **2** [6] in 80 ml of pure ethanol was vigorously stirred at RT. with 400 mg of 5% Pd/C under H_2 for 12 h (checked by TLC, benzene/ethyl acetate 6 : 1). Filtration and solvent removal i.V. gave 1.7 g (98%) of **1**, which after recrystallization from acetone had m.p. 205°, $-[\alpha]_D = +118°$ ($c = 1.30$). – IR.: 1728*s*, 1467*m*, 1452*m*, 1402*w*, 1380*m*, 1370*w*, 1358*w*, 1342*w*, 1330*w*, 1158*m*, 1136*m*, 1120*w*, 1103*m*, 1088*m*, 1072*m*, 1048*s*, 1036*s*, 1005*m*, 987*w*, 955*w*, 921*w*, 895*m*, 868*w*, 830*w*. – ^{1}H-NMR.: 0.82, 0.94 and 0.98 (3 *s*, $H_3C(18)$ and 2 H_3C–C(4)); 3.24 (*s*, CH_3O); 3.83 ($d \times d$, $J = 9$, $J' = 2$, H_R–C(19)); 4.04 ($d \times d$, $J = 9$, $J' = 3$, H_S–C(19)). – ^{13}C-NMR.: 220.19 (*s*, C(17)); 100.49 (*s*, C(3)); 66.59 (*t*, C(19)); 51.98 (*d*, C(5)); 51.32 and 49.66 (2 *d*, C(9) and C(14)); 49.28 (*q2*, CH_3O); 47.51 (*s*, C(13)); 40.76 (*s*, C(10)); 35.69 (*t*, C(16)); 35.45 (*d*, C(8)); 35.03 (*s*, C(4));

31.76 and 31.15 (2 *t*, C(1) and C(12)); 30.32 (*d*, C(7)); 28.14 (*q2*, CH_3–C(4)); 23.98 (*t*, C(6)); 23.27 and 21.03 (2 *t*, C(2) and C(11)); 21.57 (*t*, C(15)); 18.09 (*q2*, CH_3–C(4)); 13.72 (*q2*, C(18)). – MS.: *346* (100, $M^{+\cdot}$), 331 (9), 328 (6), 314 (3), 303 (3), 299 (2), 289 (9), 285 (4), 272 (12), 259 (25), 121 (38), 82 (37).

$C_{22}H_{34}O_3$ (346.49) Calc. C 76.26 H 9.89% Found C 76.17 H 9.75%

19,19-Dideuterio-3β,19-epoxy-3α-methoxy-4,4-dimethyl-5α-androstan-17-one (**1a**) was obtained analogously by catalytic hydrogenation of **2a** (s. below). – IR.: 2190*w*, 2090*w*, 1730*s*, 1467*m*, 1452*m*, 1402*w*, 1382*m*, 1372*w*, 1360*w*, 1332*m*, 1164*m*, 1148*m*, 1120*m*, 1092*m*, 1064*m*, 1035*s*, 1020*m*, 1010*m*, 988*w*, 964*w*, 912*w*, 900*w*, 868*m*. – ^{1}H-NMR.: 0.82, 0.94 and 0.98 (3 *s*, H_3C(18) and 2 H_3C–C(4)); 3.24 (*s*, CH_3O). – MS.: *348* (100, $M^{+\cdot}$), 333 (7), 331 (4), 330 (4), 316 (17), 305 (7), 301 (4), 291 (7), 288 (4), 287 (4), 275 (7), 272 (7), 261 (28), 121 (21), 82 (31).

Synthesis of (19S)-19-deuterio-3β,19-epoxy-3α-methoxy-4,4-dimethyl-5α-androstan-17-one (**1b**). A solution of 400 mg of **38b** (s. below) in 30 ml of dioxan was stirred over night with 10 ml of 2N H_2SO_4 at RT. The crude **4b** obtained after the usual work-up was left dissolved in 10 ml of 1.5N anhydrous methanolic HCl at RT. for 5 h. After working up the product was chromatographed on silicagel with cyclohexane/ethyl acetate 2 : 1 giving 298 mg (90%) of **1b**. – IR.: 2160*w*, 1730*s*, 1467*m*, 1450*m*, 1402*w*, 1380*m*, 1370*w*, 1360*w*, 1330*w*, 1158*m*, 1138*m*, 1120*w*, 1102*w*, 1088*m*, 1050*s*, 1038*s*, 1010*m*, 986*w*, 918*w*, 880*w*, 870*w*, 830*w*. – ^{1}H-NMR.: 0.82, 0.94 and 0.98 (3 *s*, H_3C(18) and 2 H_3C–C(4)); 3.24 (*s*, CH_3O); 3.82 (*s*, H_R–C(19)). – MS.: *347* (100, $M^{+\cdot}$), 333 (8), 329 (5), 315 (5), 304 (6), 300 (6), 290 (12), 287 (5), 286 (5), 272 (12), 260 (31), 121 (23), 82 (38).

(19R)-19-Deuterio-3β,19-epoxy-3α-methoxy-4,4-dimethyl-5α-androstan-17-one (**1c**) was obtained from **38c** (s. below) as described for **38b** → **1b**, m.p. 203°$[\alpha]_D = +118°$ ($c = 0.30$). – IR.: 2130*m*, 1730*s*, 1467*m*, 1451*m*, 1402*w*, 1382*m*, 1372*w*, 1360*w*, 1345*w*, 1330*m*, 1290*w*, 1160*s*, 1135*s*, 1120*m*, 1118*s*, 1090*s*, 1052*s*, 1035*s*, 1006*s*, 978*m*, 965*m*, 925*w*, 900*m*, 895*m*, 840*w*, 830*m*. – ^{1}H-NMR.: 0.92, 0.94 and 0.98 (3 *s*, H_3C(18) and 2 H_3C–C(4)); 3.24 (*s*, CH_3O); 4.02 (*d*, $J = 3$, H_S–C(19)). – MS.: *347* (100, $M^{+\cdot}$), 332 (7), 329 (4), 315 (4), 304 (5), 300 (2), 290 (9), 287 (4), 286 (4), 272 (9), 260 (23).

Synthesis of 5α,6α,7ζ,16-tetradeuterio-3β,19-epoxy-3α-methoxy-4,4-dimethylandrostan-17-one (**1d**). A solution of 270 mg of **2** [6] in 20 ml of deuteriomethanol (CH_3OD) was vigorously stirred under deuterium at RT. with 150 mg of 5% Pd/C for 3 h. Filtration and solvent removal was followed by removal of traces of starting material by chromatography on silicagel with benzene/ethyl acetate 19 : 1 to give 250 mg of **1d**. – IR. (CCl_4): 2200–2080 br. 1740*s*, 1468*m*, 1452*m*, 1382*m*, 1372*m*, 1360*m*, 1348*w*, 1334*m*, 1318*w*, 1308*w*, 1262*m*, 1250*w*, 1210*m*, 1195*m*, 1140*s*, 1115*s*, 1098*m*, 1055*s*, 1040*s*, 995*w*, 930*w*, 905*m*. – ^{1}H-NMR.: 0.82, 0.94 and 0.98 (3 *s*, H_3–C(18) and 2 H_3C–C(4)); 3.24 (*s*, CH_3O); 3.83 (*d*, $J = 9$, H_R–C(19)); 4.04 (*d* × *d*, $J = 9$, $J' = 3$, H_S–C(19)). – MS.: 353 (2, D_7), 352 (8, D_6), 351 (28, D_5), *350* (100, D_4), 349 (32, D_3), 348 (5, D_2).

Synthesis of 19,19-dideuterio-3β,19-epoxy-3α-methoxy-4,4-dimethyl-5-androsten-17-one (**2a**). With vigorous stirring 2 ml of 2.37M CrO_3 in 8N H_2SO_4 were added at 0° to a solution of 800 mg of **30** (s. below) in 40 ml of acetone. After 3 min excess reagent was destroyed by adding methanol, the product was isolated by the usual work-up and chromatographed giving 692 mg (87%) of **2a**, m.p. 162°, $[\alpha]_D = +8°$ ($c = 0.92$). – IR.: 2190*w*, 2090*w*, 1730*s*, 1460*m*, 1450*m*, 1432*w*, 1402*w*, 1378*m*, 1372*m*, 1355*w*, 1328*m*, 1286*w*, 1270*w*, 1150*s*, 1138*m*, 1122*w*, 1105*m*, 1088*s*, 1070*m*, 1033*s*, 1006*m*, 998*w*, 990*w*, 965*w*, 922*w*, 912*w*, 887*w*, 870*m*, 840*w*, 828*w*. – ^{1}H-NMR.: 0.85 (*s*, H_3C(18)); 1.07 and 1.10 (2 *s*, 2 H_3C–C(4)); 2.26 (*s*, CH_3O); 5.57 (*d* × *d*, $J = 7$, $J' = 1$, H–C(6)). – MS.: *346* (100, $M^{+\cdot}$), 331 (16), 303 (58), 271 (10), 259 (19), 222 (29), 217 (13).

Synthesis of 3α-methoxy-4,4-dimethyl-17-oxo-5α-androstan-19-al (**3**). Under argon 50 µl of BF_3. Et_2O were added at RT. to a stirred solution of 50 mg of **1** in 2 ml of benzene (freshly distilled from Na). After 50 min 2 ml of aq. $NaHCO_3$-solution were added and the mixture was diluted with ethyl acetate. The organic layer was separated, washed with NaCl-solution, dried ($MgSO_4$) and evaporated. The mixture of **1** and **3** was separated by chromatography (150-fold amount of silicagel, eluent benzene/ethyl acetate 19 : 1) giving 17.5 mg (35%) of **1** and 27.5 mg (55%) of **3**. An analytical sample of **3** was obtained by recrystallisation from acetone, m.p. 176–178°, $[\alpha]_D = +59°$ ($c = 0.97$). – IR.: 2740*w*, 1732*s*, 1700*s*, 1454*m*, 1402*m*, 1388*m*, 1365*m*, 1315*w*, 1100*s*, 1090*s*, 1054*m*, 1038*m*, 1010*m*, 995*w*, 975*w*, 964*w*, 942*w*, 912*m*, 845*m*, 865*w*, 828*w*. – ^{1}H-NMR.: 0.72, 0.75 and 0.96 (3 *s*, H_3C(18) and 2 H_3C–C(4)); 2.78

(*t*, $J = 2$, H–C(3)); 3.26 (*s*, CH_3O); 10.19 (*d*, $J = 1$, H–C(19)). – MS.: 346 (87, $M^{+\cdot}$), 331 (3), 328 (3), 314 (13), *285* (100).

$C_{22}H_{34}O_3$ (346.49) Calc. C 76.26 H 9.89% Found C 75.73 H 9.70%

Kinetics of the hydride-ion transfer. Aliquots were withdrawn from the mixture of 150 mg of **1** and 150 µl of $BF_3 \cdot Et_2O$ in 6 ml of benzene at 22.7° after 1, 2, 8, 15, 25, 40, 50 and 60 min, respectively, and analyzed by ^{1}H-NMR. spectroscopy.

3β,19-Dideuterio-3α-methoxy-4,4-dimethyl-17-oxo-5α-androstan-19-al (**3a**) was obtained from **1a** as described above for **1** → **3**, $[\alpha]_D = +60°$ ($c = 1.10$). – IR.: 2080*m*, 1730*s*, 1688*s*, 1454*m*, 1402*m*, 1388*m*, 1365*m*, 1315*w*, 1110*s*, 1090*m*, 1080*m*, 1015*w*, 1005*m*, 1026*m*, 1000*w*, 985*w*, 968*w*, 945*w*, 905*m*, 885*m*, 865*w*, 830*w*. – ^{1}H-NMR.: 0.72, 0.75 and 0.96 (3 *s*, $H_3C(18)$ and 2 H_3C–C(4)); 3.22 (*s*, CH_3O). – MS.: *348* (100, $M^{+\cdot}$), 333 (3), 330 (3), 316 (15), 286 (85).

Synthesis of 19-Hydroxy-4,4-dimethyl-5α-androstane-3, 17-dione (**4**). A solution of 1.73 g of **1** in 200 ml of acetic acid/H_2O 3 : 1 was stirred at RT. overnight. Evaporation of solvents gave **4** in quantitative yield. An analytical sample was obtained by recrystallisation from acetone, m.p. 176°, $[\alpha]_D = +121°$ ($c = 2.45$). – IR.: 3590*m*, 1730*s*, 1462*m*, 1450*m*, 1440*m*, 1405*m*, 1385*m*, 1372*m*, 1342*w*, 1318*w*, 1290*m*, 1165*m*, 1118*s*, 1100*m*, 1049*s*, 1032*s*, 1008*m*, 976*w*, 960*w*, 920*w*, 900*m*, 868*w*, 830*w*. – ^{1}H-NMR.: 0.81, 0.96 and 1.03 (3 *s*, $H_3C(18)$ and 2 H_3C–C(4)); 3.87 ($d \times d$, $J = 9$, $J' = 2$, H_R–C(19)); 4.02 ($d \times d$, $J = 9$, $J' = 3$, H_S–C(19)). – MS.: *332* (100, $M^{+\cdot}$), 317 (4), 314 (4), 302 (5), 301 (3), 289 (3), 276 (7), 271 (3), 259 (13), 189 (13), 121 (14), 82 (27).

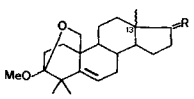
$C_{21}H_{32}O_3$ (332.47) Calc. C 75.86 H 9.70% Found C 76.03 H 9.81%

19,19-Dideuterio-19-hydroxy-4,4-dimethyl-5α-androstane-3,17-dione (**4a**) was obtained from **1a** by the procedure described above for **1** → **4**, m.p. 175°, $[\alpha] = +110°$ ($c = 1.60$). – IR.: 3590*m*, 2190*w*, 2090*w*, 1728*s*, 1700*m*, 1462*m*, 1450*m*, 1440*m*, 1400*m*, 1385*m*, 1368*m*, 1315*m*, 1288*m*, 1165*s*, 1115*s*, 1102*m*, 1075*m*, 1055*s*, 1032*s*, 1018*s*, 1005*s*, 988*m*, 970*w*, 955*m*, 906*w*, 898*w*, 863*m*, 828*w*. – ^{1}H-NMR. (60-MHz): 0.81, 0.96 and 1.03 (3 *s*, $H_3C(18)$ and 2 H_3C–C(4)). – MS.: *334* (100, $M^{+\cdot}$), 319 (7), 316 (7), 302 (17), 301 (13), 291 (4), 283 (9), 276 (9), 273 (7), 261 (20), 216 (11), 189 (24).

(19S)-19-Deuterio-19-hydroxy-4,4-dimethyl-5α-androstane-3,17-dione (**4b**) was obtained from **1b** by the procedure described above for **1** → **4**. – IR.: 3590*m*, 2145*w*, 1730*s*, 1462*m*, 1450*m*, 1440*m*, 1405*m*, 1385*m*, 1372*m*, 1340*w*, 1318*w*, 1290*m*, 1155*m*, 1118*s*, 1100*m*, 1049*s*, 1032*s*, 1008*m*, 930*m*, 956*w*, 918*w*, 885*w*, 868*w*, 830*w*. – ^{1}H-NMR.: 0.81, 0.96 and 1.03 (3 *s*, $H_3C(18)$ and 2 H_3C–C(4)); 3.85 (*s*, H_R–C(19)). – MS.: *333* (100, $M^{+\cdot}$), 318 (5), 315 (5), 302 (17), 301 (12), 290 (5), 283 (8), 276 (12), 260 (17), 189 (24), 121 (27), 82 (56).

(19R)-19-Deuterio-19-hydroxy-4,4-dimethyl-5α-androstane-3,17-dione (**4c**) was obtained from **1c** by the procedure described above for **1** → **4**. – IR.: 3590*m*, 2150*w*, 1730*s*, 1465*m*, 1450*m*, 1403*w*, 1385*w*, 1370*w*, 1340*w*, 1288*w*, 1165*m*, 1116*m*, 1100*m*, 1075*m*, 1050*s*, 1030*m*, 1007*m*, 978*w*, 900*w*, 890*w*, 875*w*.

The aldehydes **5**, **7**, **9**, **11** *and* **13** were prepared as described above for **1** → **3**. *The 5α-steroids* **6**, **8**, **10** *and* **12** were prepared by hydrogenation as described above for **2** → **1** from the corresponding Δ^5-olefins **40**–**43** [6], respectively.



40 13α, R = O
41 13β, R = β-OAc, α-H
42 13α, R = β-OAc, α-H
43 13α, R = α-OAc, β-H

3α-Methoxy-4,4-dimethyl-17-oxo-5-androsten-19-al (**5**). m.p. 131–133°, $[\alpha]_D = -96°$ ($c = 0.80$). – IR.: 2705*w*, 1732*s*, 1708*s*, 1452*m*, 1430*m*, 1402*w*, 1382*m*, 1371*m*, 1362*m*, 1130*w*, 1292*w*, 1155*w*, 1142*w*, 1100*s*, 1085*s*, 1055*m*, 1035*m*, 1020*w*, 1010*w*, 1000*w*, 990*w*, 980*w*, 965*w*, 945*w*, 912*s*, 867*w*. – ^{1}H-NMR.: 0.80, 0.82 and 1.17 (3 *s*, $H_3C(18)$ and 2' H_3C–C(4)); 2.89 (*t*, $J = 3$, H–C(3)); 3.25 (*s*, CH_3O); 5.94 ($d \times d$, $J = 5$, $J' = 2$, H–C(6)); 9.73 (*d*, $J = 1$, H–C(19)). – MS.: 344 (9, $M^{+\cdot}$), 330 (4), 315 (18), *283* (100).

3β,19-Epoxy-3α-methoxy-4,4-dimethyl-5α,13-androstan-17-one (**6**): m.p. 206°, $[\alpha]_D = -34°$ ($c = 1.55$). – IR.: 1730*s*, 1465*m*, 1450*m*, 1435*m*, 1405*w*, 1380*m*, 1375*w*, 1358*w*, 1330*m*, 1312*m*, 1160*m*, 1142*m*, 1135*m*, 1123*m*, 1098*m*, 1075*m*, 1065*m*, 1040*s*, 990*m*, 965*w*, 935*w*, 905*m*, 880*w*, 875*w*. – ^{1}H-NMR.: 0.90, 0.93 and 0.97 (3 *s*, $H_3C(18)$ and 2 H_3C–C(4)); 3.21 (*s*, CH_3O); 3.60 ($d \times d$, $J = 9$, $J' = 1$,

H_R–C(19)); 3.72 ($d \times d$, $J = 9$, $J' = 3$, H_S–C(19)). – MS.: *346* (100, $M^{+\cdot}$), 331 (2), 314 (5), 303 (2), 299 (7), 259 (17), 82 (65).

3α-Methoxy-4,4-dimethyl-17-oxo-5α,13α-androstan-19-al (**7**): m.p. 153–154°, $[\alpha]_D = -84°$ ($c = 1.60$). – IR.: 2735*w*, 1728*s*, 1700*s*, 1468*m*, 1452*m*, 1436*m*, 1405*m*, 1390*m*, 1375*w*, 1365*m*, 1320*m*, 1103*s*, 1090*s*, 1045*m*, 998*w*, 971*w*, 945*w*, 928*w*, 903*m*, 875*w*, 866*w*. – ^{1}H-NMR.: 0.67, 0.92 and 0.94 (3 *s*, $H_3C(18)$ and 2 H_3C–C(4)); 2.78 (*t*, $J = 3$, H–C(3)); 3.26 (*s*, CH_3O); 10.01 (*d*, $J = 1$, H–C(19)). – MS.: 346 (49, $M^{+\cdot}$), 334 (7), 328 (6), 314 (13), 296 (7), *285* (100), 261 (14), 182 (61), 169 (69).

3β,19-Epoxy-3α-methoxy-4,4-dimethyl-5α-androstan-17β-yl acetate (**8**): m.p. 198–200°, $[\alpha]_D = +34°$ ($c = 0.91$). – IR.: 1720*s*, 1465*m*, 1380*m*, 1370*m*, 1358*m*, 1330*m*, 1250*s*, 1156*m*, 1140*s*, 1120*m*, 1102*m*, 1090*m*, 1072*m*, 1030*s*, 1020*s*, 983*m*, 966*w*, 920*w*, 897*m*, 870*w*. – ^{1}H-NMR.: 0.73 (*s*, $H_3C(18)$); 0.93 and 0.97 (2 *s*, 2 H_3C–C(4)); 2.00 (*s*, CH_3COO); 3.23 (*s*, CH_3O); 3.82 ($d \times d$, $J = 8$, $J' = 1$, H_S–C(19)); 4.02 ($d \times d$, $J = 8$, $J' = 3$, H_R–C(19)); 4.56 (*t*, $J = 8$, H–C(17)). – MS.: 390 (60, $M^{+\cdot}$), 330 (26), 315 (8), 303 (11), 274 (16), *43* (100).

3α-Methoxy-4,4-dimethyl-19-oxo-5α-androstan-17β-yl acetate (**9**): m.p. 185–187°, $[\alpha]_D = -10°$ ($c = 1.60$). – IR.: 2740*w*, 1720*s*, 1700*s*, 1458*m*, 1442*m*, 1338*m*, 1370*m*, 1315*w*, 1120*m*, 1102*s*, 1090*s*, 1035*s*, 985*w*, 940*m*, 915*m*, 892*m*, 862*w*. – ^{1}H-NMR.: 0.67, 0.71 and 0.94 (3 *s*, $H_3C(18)$ and 2 H_3C–C(4)); 1.99 (*s*, CH_3COO); 2.77 (*t*, $J = 3$, H–C(3)); 3.25 (*s*, CH_3O); 4.54 (br. *t*, $J = 8$, H–C(17)); 10.20 (*d*, $J = 1$, H–C(19)). – MS.: *390* (100, $M^{+\cdot}$), 358 (11), 345 (8), 330 (51), 329 (66), 269 (57), 43 (49).

$C_{24}H_{38}O_4$ (390.54) Calc. C 73.80 H 9.81% Found C 73.75 H 9.88%

3β,19-Epoxy-3α-methoxy-4,4-dimethyl-5α,13α-androstan-17β-yl acetate (**10**): m.p. 121°, $[\alpha]_D = +24°$ ($c = 0.63$). – IR.: 1720*s*, 1465*m*, 1439*m*, 1375*s*, 1360*m*, 1335*w*, 1255*s*, 1160*s*, 1142*s*, 1138*s*, 1100*s*, 1075*s*, 1043*s*, 980*w*, 955*w*, 900*m*. – ^{1}H-NMR.: 0.85, 0.92 and 0.97 (3 *s*, 2 H_3C–C(4) and H_3C–C(18)); 1.95 (*s*, CH_3COO); 3.20 (*s*, CH_3O); 3.64 ($d \times d$, $J = 8$, $J' = 1$, H_R–C(19)); 3.98 ($d \times d$, $J = 8$, $J' = 3$, H_S–C(19)); 5.77 (br. *d*, $J = 6$, H–C(17)). – MS.: *390* (100, $M^{+\cdot}$), 330 (60), 269 (27), 243 (27), 215 (29), 133 (77), 91 (55), 82 (56), 43 (55).

3α-Methoxy-4,4-dimethyl-19-oxo-5α,13α-androstan-17β-yl acetate (**11**): m.p. 162°. – IR.: 2740*w*, 1720*s*, 1375*m*, 1315*w*, 1092*s*, 1040*m*, 1025*m*, 978*w*, 962*w*, 940*w*, 908*w*, 885*w*, 865*w*. – ^{1}H-NMR.: 0.70, 0.85 and 0.98 (3 *s*, $H_3C(18)$ and 2 H_3C–C(4)); 1.95 (*s*, CH_3COO); 2.78 (*t*, $J = 3$, H–C(3)); 3.26 (*s*, CH_3O); 4.78 (*m*, H–C(17)); 10.16 (*d*, $J = 1$, H–C(19)). – MS.: 390 (29, $M^{+\cdot}$), 372 (6), 358 (4), 330 (40), 318 (21), 312 (13), 298 (16), 269 (70), *162* (100).

$C_{24}H_{38}O_4$ (390.54) Calc. C 73.80 H 9.81% Found C 73.76 H 9.76%

3β,19-Epoxy-3α-methoxy-4,4-dimethyl-5α,13α-androstan-17α-yl acetate (**12**): m.p. 134–137°, $[\alpha]_D = 6°$ ($c = 1.25$). – IR.: 1725*s*, 1465*m*, 1455*m*, 1440*m*, 1382*m*, 1372*m*, 1360*m*, 1333*w*, 1160*m*, 1145*m*, 1138*m*, 1095*m*, 1075*m*, 1040*s*, 1028*s*, 968*w*, 948*w*, 910*w*, 902*w*, 888*m*. – ^{1}H-NMR.: 0.88, 0.91 and 0.96 (3 *s*, $H_3C(18)$ and 2 H_3C–C(4)); 2.00 (*s*, CH_3COO); 3.22 (*s*, CH_3O); 3.71 ($d \times d$, $J = 10$, $J' = 1$, H_R–C(19)); 3.96 ($d \times d$, $J = 10$, $J' = 3$, H_S–C(19)); 5.00 (*t*, $J = 8$, H–C(17)). – MS.: *390* (100, $M^{+\cdot}$), 330 (16), 315 (8), 303 (10), 287 (6), 274 (10), 248 (20), 82 (55), 43 (60).

3α-Methoxy-4,4-dimethyl-19-oxo-5α,13α-androstan-17α-yl acetate (**13**): m.p. 145–147°, $[\alpha]_D = -48°$ ($c = 1.14$). – IR.: 2740*w*, 1720*s*, 1705*s*, 1460*m*, 1445*m*, 1385*m*, 1378*m*, 1100*s*, 1086*s*, 1058*m*, 1028*m*, 990*w*, 937*m*, 902*m*, 885*w*, 865*w*. – ^{1}H-NMR.: 0.69, 0.87 and 0.94 (3 *s*, $H_3C(18)$ and 2 H_3C–C(4)); 1.97 (*s*, CH_3COO); 2.77 (*t*, $J = 2$, H–C(3)); 3.25 (*s*, CH_3O); 4.89 (*t*, $J = 9$, H–C(17)); 10.08 (*d*, $J = 1$, H–C(19)). – MS.: 390 (26, $M^{+\cdot}$), 273 (6), 358 (5), 330 (11), 329 (11), 269 (50), *162* (100).

Synthesis of 4,4-dimethyl-17β,19-bis(2-tetrahydropyranyloxy)-5α-androstan-3-one (**15**). A solution of 334 mg of **14** [23] and of 210 mg of dihydropyran in 10 ml of dry CH_2Cl_2 containing 38 mg of pyridinium *p*-toluenesulfonate [35] was stirred for 20 h at RT., after which it was diluted with ether and washed twice with half-sat. NaCl-solution. Removal of solvents left 477 mg (95%) of crude **15**. – IR.: 1698*s*, 1465*m*, 1452*m*, 1440*m*, 1384*m*, 1352*m*, 1322*w*, 1276*w*, 1260*w*, 1156*m*, 1136*s*, 1120*s*, 1075*s*, 1060*s*, 1030*s*, 978*m*, 908*m*, 901*m*, 882*w*, 868*m*. – MS.: 502 (2, $M^{+\cdot}$), 419 (6), 418 (17), 402 (2), 400 (2), 388 (2), 386 (2), 345 (2), 335 (14), 334 (25), 317 (5), 316 (5), 304 (17), *85* (100).

Reduction of **15** *to* **16** *and* **17**. A solution of 402 mg of **15** and *ca.* 60 mg of $NaBH_4$ in 10 ml of methanol was stirred at RT. for 1 h. After dilution with ether the organic layer was washed with water, dried ($MgSO_4$) and evaporated. Chromatography with cyclohexane/ethyl acetate 3 : 1 afforded 32 mg (8%) of **16** and 309 mg (77%) of **17**. *4,4-Dimethyl-17β,19-bis(2-tetrahydroxypyranyloxy)-5α-androstan-3α-ol* (**16**): IR.: 3620*m*, 1462*m*, 1448*m*, 1440*m*, 1380*m*, 1360*m*, 1350*m*, 1345*m*, 1320*m*, 1283*m*, 1275*m*,

1260*m*, 1182*m*, 1155*m*, 1145*s*, 118*s*, 1072*s*, 1060*s*, 1025*s*, 978*s*, 944*m*, 910*m*, 895*m*, 880*w*, 865*m*. – MS.: 504 (3, $M^{+\cdot}$), 419 (13), 335 (14), *85* (100). – *4,4-Dimethyl-17β,19-bis(2-tetrahydropyranyloxy)-5α-androstan-3β-ol* (**17**): IR.: 3610*m*, 1465*m*, 1450*m*, 1440*m*, 1380*m*, 1350*m*, 1320*m*, 1275*w*, 1258*m*, 1152*m*, 1136*s*, 1115*s*, 1073*s*, 1060*s*, 1025*s*, 982*s*, 910*m*, 900*m*, 882*w*, 865*m*. – MS.: 504 (1, $M^{+\cdot}$), 419 (6), 401 (5), *85* (100).

Synthesis of 3α-methoxy-4,4-dimethyl-5α-androstane-17β,19-diol (**19**). a) *By methylation of* **16** (→ **18**) *and acetal cleavage.* Under argon 20 mg of NaH (washed with hexane and dried i.V.) were added to a solution of 30 mg of **16** in 2 ml of dry THF. After 5 min stirring at RT. an excess of methyl iodide (0.1 ml) was added. After 3 h ice water was added, and the product extracted with ethyl acetate. The extract was washed with diluted Na_2SO_3- and NaCl-solution, dried ($MgSO_4$) and evaporated. The crude methylated product **18** was treated at RT. with dioxan and 2N H_2SO_4 overnight. After normal work-up and chromatography on silicagel with cyclohexane/ethyl acetate 2 : 1 18 mg (86%) of **19** were obtained.

b) *By $LiAlH_4$ reduction of* **3**. To a solution of 50 mg of **3** in 5 ml of THF 25 mg of $LiAlH_4$ were added at RT. and the mixture was left for 2 h. Normal work-up and chromatography on silicagel with cyclohexane/ethyl acetate 2 : 1 yielded 44 mg (86%) of **19**, m.p. 216–218°, $[\alpha]_D = -36°$ ($c = 1.70$). – IR.: 3618*m*, 1443*m*, 1388*m*, 1378*w*, 1362*m*, 1318*w*, 1102*s*, 1080*s*, 1042*s*, 1012*s*, 937*m*, 910*w*, 888*w*, 862*w*. – ^{1}H-NMR.: 0.75 (*s*, $H_3C(18)$); 0.90 (*s*, 6 H, 2 H_3C–C(4)); 2.82 (*t*, $J = 2$, H–C(3)); 3.27 (*s*, CH_3O); 3.58 (*t*, $J = 8$, H–C(17)); 3.83 and 3.97 (2 *d*, $J = 12$, 2 H–C(19)). – MS.: 350 (< 1, $M^{+\cdot}$), 332 (2), 319 (13), *287* (100), 279 (2), 269 (24), 268 (2), 243 (11).

3β-Methoxy-4,4-dimethyl-5α-androstane-17β,19-diol (**21**) was obtained as described above (**16** → **18** → **19**) by methylation of **17** (→ **20**) and acetal cleavage in 85% yield, m.p. 203°, $[\alpha]_D = +14°$ ($c = 0.85$). – IR.: 3618*m*, 1450*m*, 1443*m*, 1390*m*, 1378*m*, 1360*m*, 1180*m*, 1132*m*, 1090*s*, 1042*s*, 1015*s*, 983*m*, 968*m*, 897*w*, 860*w*. – ^{1}H-NMR.: 0.75, 0.81 and 0.95 (3 *s*, $H_3C(18)$ and 2 H_3C–C(4)); 2.67 ($d \times d$, $J = 12$, $J' = 4$, H–C(3)); 3.32 (*s*, CH_3O); 3.58 (*m*, H–C(17)); 3.92 and 3.96 (2 *d*, $J = 12$, 2 H–C(19)). – MS.: 350 (< 1, $M^{+\cdot}$), 320 (25), 288 (97), *287* (100), 269 (30), 261 (13), 243 (20).

$C_{22}H_{38}O_3$ (350.52) Calc. C 75.38 H 10.93% Found C 75.37 H 10.98%

Synthesis of 19,19-dideuterio-19-hydroxy-4-androstene-3,17-dione (**27**). To a solution of 1.5 g of **26** [31] in 70 ml of dioxan 15 ml of 2N H_2SO_4 were added and the mixture was stirred at RT. for 5 h. After normal work-up **27** was obtained in quantitative yield, m.p. 159°, $[\alpha]_D = +190°$ ($c = 0.01$). – IR.: 3440 br., 2200*w*, 2080*w*, 1732*s*, 1665*s*, 1620*m*, 1450*m*, 1438*m*, 1405*m*, 1373*m*, 1355*m*, 1338*m*, 1270*m*, 1118*m*, 1045*m*, 1005*m*, 975*m*, 915*w*, 894*w*, 866*m*. – ^{1}H-NMR.: 0.90 (*s*, $H_3C(18)$); 4.93 (*s*, H–C(4)). – MS.: 304 (5, $M^{+\cdot}$), 372 (15), 244 (25), *243* (100), 241 (5.5), 239 (5), 228 (4), 215 (4), 166 (5), 156 (40).

Synthesis of 19,19-dideuterio-19-(2-tetrahydropyranyloxy)-4-androstene-3,17-dione (**28**). A solution of 1.5 g of **27** and of 621 mg of dihydropyran in 20 ml of dry CH_2Cl_2 containing 125 mg of pyridinium *p*-toluenesulfonate [35] was stirred at RT. for 5 h. Then it was diluted with ether and washed twice with half-sat. NaCl-solution. Removal of solvents gave 1.8 g (95%) of crude **28**. – IR.: 2190*w*, 2085*w*, 1735*s*, 1665*s*, 1622*w*, 1465*w*, 1452*m*, 1440*m*, 1405*w*, 1387*w*, 1372*w*, 1353*m*, 1272*w*, 1155*m*, 1122*s*, 1074*m*, 1025*s*, 1010*m*, 970*m*, 900*m*, 868*m*. – MS.: 388 (2, $M^{+\cdot}$), 304 (12), 288 (7), 273 (36), *272* (100), 243 (11), 165 (17), 85 (85).

Synthesis of 19,19-dideuterio-17β-hydroxy-19-(2-tetrahydropyranyloxy)-4-androsten-3-one (**29**). To a solution of 1.5 g of **28** in 50 ml of THF 1 g of $Li[(t\text{-}BuO)_3AlH]$ was added and the mixture stirred at 0° for 1 h and at RT. for 30 min. After addition of *celite*, and of sat. NH_4SO_4-solution to destroy excess reagent, the whole was filtered and the filtrate evaporated. The remaining crude product was chromatographed on silicagel with cyclohexane/ethyl acetate 2 : 1 giving 0.91 g (85%) of **29**. – IR.: 3610*m*, 3450 br., 2190*w*, 2090*w*, 1660*s*, 1620*m*, 1465*w*, 1450*m*, 1380*m*, 1370*m*, 1354*m*, 1335*w*, 1158*m*, 1125*s*, 1100*m*, 1073*m*, 1020*s*, 970*m*, 900*m*, 866*m*. – MS.: 391 (1), 390 (1, $M^{+\cdot}$), 306 (10), *274* (100), 258 (9), 110 (13), 85 (86).

Synthesis of 19,19-dideuterio-3β,19-epoxy-3α-methoxy-4,4-dimethyl-5-androsten-17β-ol (**30**). To a solution of 1.5 g of potassium in 50 ml of abs. *t*-butyl alcohol 2.3 g of **29** in 20 ml of *t*-butyl alcohol were added. After 10 min stirring at RT. 4 ml of methyl iodide in 20 ml of dry benzene were added. After 3 h the mixture was diluted with ether and worked up. The crude product was dissolved in 10 ml dry methanol and left with 20 ml anhydrous sat. methanolic hydrogen chloride at RT. overnight. After work-up the crude product was chromatographed on silicagel with cyclohexane/ethyl

acetate 2 : 1 giving 1.05 (51%) of **30**, m.p. 186°, $[\alpha]_D = -40°$ ($c = 1.40$). – IR.: 3605*m*, 2195*m*, 2095*m*, 2090*m*, 1465*s*, 1452*s*, 1438*m*, 1380*s*, 1358*m*, 1330*s*, 1290*w*, 1180*w*, 1152*s*, 1140*s*, 1108*s*, 1090*s*, 1052*s*, 1025*s*, 1010*s*, 965*w*, 955*w*, 940*w*, 922*w*, 895*w*, 870*s*, 840*m*, 821*w*. – ^{1}H-NMR.: 0.72 (*s*, $H_3C(18)$); 1.06 and 1.09 (2 *s*, 2 $H_3C(4)$); 3.27 (*s*, CH_3O); 3.46–3.74 (*m*, with D_2O *t* at 3.60 ($J = 7$), H–C(17)); 5.54 ($d \times d$, $J = 6$, $J' = 2$, H–C(6)). – MS.: *348* (100, $M^{+\cdot}$), 333 (15), 305 (56), 287 (13), 261 (23).

An additional product isolated from this reaction was *19,19-dideuterio-3β,19-epoxy-4,4-dimethyl-5-androstene-3α,17β-diol dimethyl ether* (**31**; 178 mg), m.p. 134–135°, $[\alpha]_D = -41°$ ($c = 1.31$). – IR.: 2190*w*, 2090*w*, 1465*s*, 1452*s*, 1436*m*, 1380*s*, 1358*m*, 1330*s*, 1178*m*, 1151*s*, 1138*s*, 1100*s*, 1032*s*, 1010*s*, 975*m*, 955*w*, 925*w*, 870*m*, 840*m*. – ^{1}H-NMR.: 0.73 (*s*, $H_3C(18)$); 1.06 and 1.08 (2 *s*, 2 H_3C–C(4)); 3.19 (*t*, $J = 8$, H–C(17)); 3.27 and 3.30 (2 *s*, 2 CH_3O); 5.53 ($d \times d$, $J = 6$, $J' = 2$, H–C(6)). – MS.: *362* (100, $M^{+\cdot}$), 347 (14), 330 (15), 319 (38), 287 (20).

Further products were not identified.

Synthesis of 4,4-dimethyl-3,17-dioxo-5α-androstan-19-yl acetate (**34**). A solution of 3.4 g of **4** in 10 ml of pyridine/acetic anhydride 1 : 1 was kept at 50° overnight. After removal of the solvents i.V. the residue was filtered through silicagel with cyclohexane/ethyl acetate 2 : 1 to give 3.6 g (93%) of pure **34**, m.p. 115°, $[\alpha]_D = +85°$ ($c = 2.7$). – IR.: 1730*s*, 1700*s*, 1450*m*, 1405*m*, 1385*m*, 1372*s*, 1335*w*, 1045*m*, 1038*m*, 1012*w*, 985*w*, 915*w*, 893*w*. – ^{1}H-NMR.: 0.86 (*s*, $H_3C(18)$); 1.05 and 1.10 (2 *s*, 2 H_3C–C(4)); 2.02 (*s*, CH_3COO); 4.26 and 4.41 (2 *d*, $J = 12$, 2 H–C(19)). – MS.: 374 (57, $M^{+\cdot}$), 332 (53), *314* (100), 301 (20).

$C_{23}H_{34}O_4$ (374.50) Calc. C 73.76 H 9.15% Found C 73.66 H 9.14%

19,19-Dideuterio-4,4-dimethyl-3,17-dioxo-5α-androstan-19-yl acetate (**34a**) was obtained from **4a** by the procedure described above for **4** → **34**. – IR.: 1730*s*, 1700*s*, 1450*m*, 1402*w*, 1370*s*, 1255*s*, 1140*w*, 1120*w*, 1105*w*, 1077*m*, 1070*m*, 1032*m*, 1007*w*, 992*w*, 955*w*, 912*w*, 888*w*. – ^{1}H-NMR.: 0.86 (*s*, $H_3C(18)$); 1.05 and 1.10 (2 *s*, 2 H_3C–C(4)); 2.02 (*s*, CH_3COO). – MS.: 376 (49, $M^{+\cdot}$), 334 (43), *316* (100), 301 (21), 283 (15), 273 (10), 43 (28).

Synthesis of 3,3 : 17,17-bis(ethylenedioxy)-4,4-dimethyl-5α-androstan-19-yl acetate (**35**). A mixture of 3.5 g of **34**, 4 g of ethylene glycol and 0.1 g of *p*-toluenesulfonic acid was heated under reflux in 50 ml of benzene for 14 h with removal of water. After work-up and passage of a solution of the crude residue through silicagel using cyclohexane/ethyl acetate 2 : 1 **35** was obtained in quantitative yield as on oil, $[\alpha]_D = -39°$ ($c = 2.30$). – IR.: 1725*s*, 1445*m*, 1388*m*, 1375*m*, 1363*m*, 1308*m*, 1245*s*, 1163*s*, 1140*s*, 1102*s*, 1085*s*, 1060*s*, 1032*s*, 1010*m*, 978*m*, 950*s*, 930*w*, 915*m*, 902*m*. – ^{1}H-NMR.: 0.80, 0.83 and 0.98 (3 *s*, 2 H_3C–C(4) and $H_3C(18)$); 2.03 (*s*, CH_3COO); 3.7–4.2 (*m*, 2 OCH_2CH_2O); 4.27 and 4.46 (2 *d*, $J = 12$, 2 H–C(19)). – MS.: 462 (4, $M^{+\cdot}$), 402 (1), 389 (3), 327 (2), *99* (100).

19,19-Dideuterio-3,3 : 17,17-bis(ethylenedioxy)-4,4-dimethyl-5α-androstan-19-yl acetate (**35a**) was obtained from **34a** by the procedure described above for **34** → **35**. – IR.: 1725*s*, 1450*m*, 1442*m*, 1368*s*, 1305*m*, 1262*s*, 1160*s*, 1145*s*, 1138*s*, 1115*s*, 1100*s*, 1094*s*, 1080*s*, 1050*s*, 1030*s*, 1005*m*, 978*m*, 948*s*, 910*w*, 895*m*. – ^{1}H-NMR. (60 Hz): 0.80, 0.83 and 0.89 (3 *s*, $H_3C(18)$ and 2 H_3C–C(4)); 2.03 (*s*, CH_3COO); 3.7–4.0 (*m*, 2 OCH_2CH_2O). – MS.: 464 (3, $M^{+\cdot}$), 404 (2), 389 (2), 327 (1), *99* (100).

3β,19-Epoxy-3α-(2'-hydroxyethoxy)-4,4-dimethyl-5α-androstan-17-one ethylene acetal (**36**) was obtained in quantitative yield from **4** by the procedure described above **34** → **35**, m.p. 143–144°, $[\alpha]_D = +12°$ ($c = 1.025$). – IR.: 3590*w*, 3400*m*, 1468*m*, 1442*m*, 1385*m*, 1360*w*, 1345*w*, 1331*w*, 1308*m*, 1280*w*, 1165*s*, 1145*m*, 1132*m*, 1120*m*, 1105*s*, 1090*s*, 1058*s*, 1040*s*, 1015*s*, 988*m*, 955*m*, 930*w*, 912*w*, 902*w*, 885*m*. – ^{1}H-NMR.: 0.78 (*s*, $H_3C(18)$); 0.94 and 0.99 (2 *s*, 2 H_3C–C(4)); 2.92 (*m*, HO, exchangeable with D_2O); 3.40–3.94 (*m*, 2 H–C(1'), 2 H–C(2'), OCH_2CH_2O, and H_R–C(19)); 4.04 ($d \times d$, $J = 9$, $J' = 3$, H_S–C(19)). – MS.: 420 (80, $M^{+\cdot}$), 405 (2), 375 (3), 358 (9), *99* (100).

Acetylation of **36** gave *3β,19-epoxy-3α-(2'-acetoxyethoxy)-4,4-dimethyl-5α-androstan-17-one ethylene acetal* (**37**), m.p. 76–79°, $[\alpha]_D = +15°$ ($c = 1.85$). – IR.: 1730*s*, 1470*m*, 1455*m*, 1442*m*, 1378*m*, 1362*m*, 1345*w*, 1330*w*, 1310*m*, 1168*s*, 1145*m*, 1105*s*, 1056*s*, 1038*s*, 1020*s*, 988*w*, 955*m*, 912*w*, 890*w*. – ^{1}H-NMR.: 0.79 (*s*, $H_3C(18)$); 0.91 and 0.97 (2 *s*, 2 H_3C–C(4)); 2.02 (*s*, CH_3COO); 3.48–3.92 (*m*, H_R–C(19), 2 H–C(1'), and OCH_2CH_2O); 4.02 ($d \times d$, $J = 8$, $J' = 3$, H_S–C(19)); 4.15 (*t*, 2 H–C(2')). – MS.: 462 (28, $M^{+\cdot}$), 400 (6), 99 (91), *87* (100).

Synthesis of 19-hydroxy-4,4-dimethyl-5α-androstane-3,17-dione bis(ethylene acetal) (**38**). To a solution of 3.5 g of **35** in 50 ml of dry ether were added 300 mg of $LiAlH_4$, and the mixture was kept at RT. for 15 min. Normal work-up gave **38** in quantiative yield, m.p. 195°, $[\alpha]_D = -35°$ ($c = 2.20$). – IR.: 3620*m*, 3560–3360 br., 1470*m*, 1455*m*, 1443*m*, 1385*m*, 1380*m*, 1365*w*, 1345*w*, 1308*m*, 1282*w*,

1168*m*, 1150*s*, 1140*s*, 1100*s*, 1085*s*, 1060*s*, 1032*s*, 1020*m*, 1005*m*, 980*m*, 950*s*, 925*w*, 912*m*, 900*m*. – ^{1}H-NMR.: 0.82, 0.84 and 0.99 (3 *s*, 2 H_3C–C(4) and H_3C(18)); 3.7–4.1 (*m*, $w_{1/2}$ = 12, 2 H–C(19) and 2 OCH_2CH_2O). – MS.: 420 (7, M^+·), 390 (5), 389 (5), 358 (5), *99* (100).

$C_{25}H_{40}O_5$ (420.57) Calc. C 71.39 H 9.59% Found C 71.41 H 9.63%

19,19-Odeuterio-19-hydroxy-4,4-dimethyl-5α-androstane-3,17-dione bis(ethylene acetal) (**38a**) was obtained from **35a** by the procedure described above for **35** → **38**, m.p. 190°, $[\alpha]_D = -34°$ (*c* = 1.72). – IR.: 3630*m*, 2220*w*, 2110*w*, 1454*m*, 1442*m*, 1378*m*, 1360*w*, 1342*w*, 1305*m*, 1278*m*, 1360*w*, 1342*w*, 1305*m*, 1278*m*, 1160*m*, 1134*m*, 1098*s*, 1085*s*, 1050*s*, 1030*m*, 1002*m*, 976*m*, 946*m*, 910*m*, 892*m*. – ^{1}H-NMR.: 0.82, 0.84 and 0.99 (3 *s*, 2 H_3C–C(4) and H_3C(18)); 3.7–4.1 (*m*, $w_{1/2}$ = 12, 2 OCH_2CH_2O). – MS.: 422 (10, M^+·), 390 (5), 389 (5), 360 (18), 327 (10), *99* (100).

Synthesis of (19S)-19-deuterio-19-hydroxy-4,4-dimethyl-5α-androstane-3,17-dione bis(ethylene acetal) (**38b**). At 15° and under argon 2.65 g of *t*-butyl alcohol were added during 15 min to 0.5 g of $LiAlD_4$ in 15 ml of dry THF. The mixture was stirred at RT. overnight, then 500 mg of **39** (s. below) in 10 ml of dry THF were added. After 5 h normal work-up gave **38b** in quantitative yield, m.p. 192°, $[\alpha]_D = -35°$ (*c* = 1.0). – IR.: 3620*m*, 3560–3360 br., 2190*w*, 1468*m*, 1455*m*, 1443*m*, 1385*m*, 1362*m*, 1355*w*, 1345*w*, 1308*m*, 1282*w*, 1168*m*, 1148*s*, 1138*s*, 1100*s*, 1085*s*, 1055*s*, 1032*s*, 1005*m*, 980*m*, 950*s*, 925*w*, 912*m*, 900*m*. – ^{1}H-NMR.: 0.82, 0.84 and 0.99 (3 *s*, 2 H_3C–C(4) and H_3C(18)); 3.7–4.1 (*m*, $w_{1/2}$ = 12, H_R–C(19) and 2 OCH_2CH_2O). – MS.: 421 (11, M^+·), 390 (2), 389 (2), 359 (2), *99* (100).

Synthesis of (19R)-19-deuterio-19-hydroxy-4,4-dimethyl-5α-androstane-3,17-dione bis(ethylene acetal) (**38c**). At RT. and under argon 500 mg of $Li[(t\text{-}BuO)_3AlH]$ were added to 500 mg of **39a** (s. below) in THF. After 5 h normal work-up gave **38c** in quantitative yield, m.p. 191°, $[\alpha]_D = -28°$ (*c* = 4.38). – IR.: 3630*m*, 2170*w*, 1475*m*, 1452*m*, 1442*m*, 1385*m*, 1378*m*, 1360*w*, 1345*w*, 1308*m*, 1280*m*, 1161*m*, 1138*m*, 1100*s*, 1080*s*, 1060*s*, 1032*s*, 1005*m*, 980*m*, 948*m*, 911*m*, 895*m*. – ^{1}H-NMR.: 0.82, 0.84 and 0.99 (3 *s*, H_3C–C(4) and H_3C(18)); 3.7–4.1 (*m*, $w_{1/2}$ = 12, H_S–C(19) and 2 OCH_2CH_2O). – MS.: 421 (25, M^+·), 390 (9), 389 (9), 359 (9), 327 (7), 305 (6), *99* (100).

Synthesis of 3,3 : 17,17-bis(ethylenedioxy)-4,4-dimethyl-5α-androstan-19-al (**39**). To a suspension of 1 g of pyridinium chlorochromate in 15 ml of CH_2Cl_2 1 g of **38** in 10 ml of CH_2Cl_2 was added with vigorous stirring at RT. After 30 min the mixture was diluted with ethyl acetate (50 ml), washed with Na_2CO_3 and NaCl-solution, dried ($MgSO_4$) and the solvent removed. Recrystallisation from acetone gave 680 mg (68%) of **39**, m.p. 187–189°, $[\alpha]_D = +8°$ (*c* = 0.80). – IR.: 2740*w*, 1702*s*, 1468*m*, 1456*m*, 1402*w*, 1385*m*, 1363*w*, 1348*w*, 1310*m*, 1282*w*, 1165*s*, 1140*s*, 1100*s*, 1082*s*, 1052*s*, 1032*s*, 1008*s*, 980*m*, 950*s*, 925*w*, 912*m*, 902*s*. – ^{1}H-NMR.: 0.73, 0.81 and 0.85 (3 *s*, H_3C(18) and 2 H_3C–C(4)); 3.74–3.98 (*m*, 2 OCH_2CH_2O); 10.18 (*d*, *J* = 1, H–C(19)). – MS.: 418 (10, M^+·), 390 (24), 375 (7), 356 (5), 347 (5), 328 (5), 285 (10), *99* (100), 87 (48), 86 (33).

$C_{25}H_{38}O_5$ (418.55) Calc. C 71.74 H 9.15% Found C 71.63 H 9.14%

3,3 : 17,17-Bis(ethylenedioxy)-19-deuterio-4,4-dimethyl-5α-androstan-19-al (**39a**) was obtained from **38b** by the procedure described above for **38** → **39**, m.p. 195–197°, $[\alpha]_D = +2°$ (*c* = 2.2). – IR.: 2080*w*, 1690*s*, 1383*m*, 1362*w*, 1308*m*, 1280*w*, 1162*m*, 1150*m*, 1140*m*, 1098*s*, 1085*m*, 1060*m*, 1045*s*, 1020*w*, 1005*m*, 978*m*, 949*m*, 923*w*, 912*m*, 895*m*. – ^{1}H-NMR.: 0.73, 0.80 and 0.85 (3 *s*, H_3C(18) and 2 H_3C–C(4)); 3.7–4.0 (*m*, 2 OCH_2CH_2O). – MS.: 419 (4, M^+·), 391 (11), 376 (3), 357 (3), 348 (4), 286 (4), *95* (100).

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