20. Structural and Configurational Dependence of the Sensory Process in Steroids

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Dedicated to Professor *Holger Erdtman* on the occasion of his 80th birthday

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Summary

Structural modifications of testosterone and 19-nortestosterone have led to the synthesis of over 60 androstane and estrane derivatives whose sensory evaluation has allowed molecular parameters to be established for release of a 'steroid-type' scent. Odor perception with O-containing compounds in both classes has been found to be *regioselective*[1]). Osmophoric groups at C(3) were found to be the most active and specific. Functionality at C(2) is accompanied to a large extent by anosmic defects, and O-containing substituents at C(1) and C(4) appear to affect the receptor membrane in exceptional cases.

A further characteristic of the 'steroid-type' scent is *diastereoselectivity*[1]). The odor intensity of axial 2- and 3-hydroxysteroids is far greater than that of the equatorial epimers, and epimeric hydroxy-groups in the 1-, 4-, and 5-positions lead to almost complete absence of odor. In addition, only steroids with 'normal' ring junctions and configuration were found to be odorants, whereas compounds with *cis*-junctions between rings A and B, or C and D, were found to be practically inactive. Steroids therefore follow the 'triaxial rule of odor sensation'.

The most remarkable feature of our findings with steroid odorants is *enantioselectivity*[1]). Whereas with C_{19}-steroids of the 'natural' enantiomeric series the perception threshold is extremely low (<6 ppb), the corresponding 'unnatural' enantiomers have been found essentially odorless by a panel of 30 persons. This appears to be the first reported instance of a total enantioselective response to an odorant.

Introduction. – In 1944, *Prelog & Ruzicka* isolated 5α-androst-16-en-3α-ol (**2**) and its 3β-epimer **3** from hog testes [1]. Remarkably, the 3α-alcohol **2** was reported

[1]) The term 'regioselective' is currently used for a reaction in which formation of one structural (or positional) isomer is favored over another. For convenience we use 'regioselective', 'diastereoselective' or 'enantioselective' for substrate-receptor interactions in which one positional isomer, diastereoisomer or enantiomer leads to a different sensory response (in quality and/or intensity) than another.

[2] to have a musk-like odor while its diastereoisomer **3** was practically odorless [3]. The extremely intense odor of the corresponding ketone **1** was described as being 'like that of vessels which had been used for storing urine for prolonged periods' [2]. With a steroid A/B-ring *cis*-fusion (5β) both 3α- and 3β-alcohols were found to be practically odorless [3]. Similar results were reported subsequently [2–6], which led to a series of important studies in biochemistry, neurophysiology, endocrinology, sensory studies and general behavioral science in humans and mammals.

An exact analysis of the steroid components in testes of mature hogs showed that the amount of the β-alcohol **3** present was five times that of the α-alcohol **2**. Ketone **1** was found only in small amounts and yet ten times higher than the amount of testosterone. On the other hand ketone **1** and alcohol **2** were the main steroid components in both the parotid and the submaxillary gland; here the β-alcohol **3** constituted only 5% of the total steroid fraction [7]. Other related findings were that 5α-androst-16-en-3-one (**1**) is reduced to the 3α-alcohol in the nasal mucous membrane of sows [8], and that the Δ^{16}-unsaturated C_{19}-steroids **1**, **2**, **3** and **14** have been found to be metabolites of pregnenolone [9].

Ketone **1**, which can accumulate to the extent of 0.5 ppm in fatty tissue in male pigs, has been held responsible for the off-flavor termed 'boar taint' of boiled pork [10], although little if any of this substance is found in female, immature or castrated pigs [10]. Both the ketone **1** and the 3α-alcohol **2** have been identified as hog sex attractants [11]. Following sexual stimulation they are excreted in the boar's saliva from the submaxillary gland, and then stimulate the sow's immobility reflex before copulation [11] [12]. Inhibition of this effect after surgical removal of the sow's olfactory bulb confirms that this stimulation by compounds **1** and **2** is olfactive in nature [13]. In fact, ketone **1** in the form of an aerosol is used for facilitating artificial insemination in pig breeding[2]) [14] [15]. Interestingly, in this series, the epimeric 3β-alcohol **3** still shows 50% of the aphrodisiac activity of alcohol **2**; and 5β-androst-16-en-3-one has been found to be even more effective in animal tests than the 5α-ketone **1** [16].

In humans, C_{19}-steroids with a double bond at C(16) have been identified in urine [17], in armpit perspiration [18], in peripheral plasma and in lipoid tissue [19]. In the urine of both sexes exclusively the 3α-alcohol **2** occurs as a glycoside. In this form it is excreted by males and females at average rates of 1200 and 430 µg per day, respectively, while only a negligible amount if any is excreted by children [18]. In contrast to humans, pig urine contains exclusively the 3β-alcohol **3** [20]. Apocrinal glands of humans contain the sulfate esters of 3α-hydroxy-5α-androstan-17-one and 3β-hydroxyandrost-5-en-17-one which on heating are converted into 5α-androst-2-en-17-one (**49**) and the corresponding 2,5-diene, respectively [21]. The formation of androstane derivatives **1** and **2** in armpit perspiration [19] [22] is probably due to exogenous enzymatic action by certain bacteria [21].

A treatise on the olfactosexual aspect of human behavior has been published over 78 years ago [23]. Armpits and genitals were considered as prime locations for production of a specific scent to which a controlling function in the biological process inherent in human reproduction was ascribed. In this connection the question of the 'likelihood of human pheromones' has been raised [24] [25]. One of the first comprehensive biological interpretation of the 'steroid-type' scent has been published in 1961 [26]. Whether compounds **1** and **2** can serve in any way as chemical signals between the sexes has not been clarified. Animal (chicken comb) tests have failed to indicate any androgenic acitivity for compound **1** [19]. On the other hand topical anti-androgenic activity is claimed for estra-4,16-dien-3-one (**54**) [27] as well as for androstane derivatives **19**, **21** and **22** [28].

The aim of the present work is to ascertain molecular parameters for 'steroid-type' scent release by structural modification of the steroid skeleton. This should provide useful information for understanding the mode of action of this class of odoriferous compounds. To acquire a firm basis for these studies we first reexamined *Prelog*'s compounds **1–3**, **6–8** and **14** and then submitted them to sensory analysis together

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[2]) This product is sold under the trade name *Boar Mate* by *Jeyes* Ltd., Animal Health Division, Norfolk, England.

with the compounds listed in *Schemes 1–5* whose olfactory properties have not previously been reported.

Qualitative sensory testing of compounds *1–65*. – The optically active steroids shown in *Schemes 1–4* belong to the 'natural' enantiomeric series, while those in *Scheme 5* are of the 'unnatural' enantiomeric series[3]). Most of the compounds were perceived by at least one person[4]) (see the *Table*). It should be noted that the description of the odor quality and even more of the odor intensity varied from compound to compound. Cross-adaption experiments indicate that all steroids examined here affect the same olfactory receptor.

The odor profile of steroids in general is less broad than that of odorants belonging to other classes of compounds. Either a urine-sweaty basic note or a musk-like (warm, animal, muscone) note with a basic sandalwood undertone predominates. Both basic notes are known to lead to more or less pronounced anosmia[5]) [30]. For this reason the 'steroid-type' scent has been defined as a 'primary odor' [31]. Parosmia and fatigue[6]) ensued in practically every case to approximately the same extent as previously noted in the case of ambergris-type odorants[7]) [29].

With most steroid derivatives a sex-oriented odor selectivity was observed; this, however, varied within relatively wide limits from one group to another[8]). Furthermore, intensity as perceived for the same compound varied from one observer to another to the extent of up to three orders of magnitude[9]). It thus seems that this class of odorants, like those of the ambergris-type [29], are exceedingly difficult to evaluate; and that the results of testing require very careful scrutiny.

The presence of an O-function seems to be a primary requisite for sensory perception in steroids, thus, 5α-androst-16-ene is odorless. The 3α-alcohols **2**, **7**, **15**

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3) An *ad hoc* panel of 30 to 90 persons was employed for olfactory testing in sessions which were mostly with individuals rather than groups and which took place at irregular intervals between 1974 and 1982 (see the *Table*). The procedure previously reported by us [29] was employed.

4) Classified as odorless by all panel members are the steroids **8**, **10**, **13**, **24**, **27–29**, **33**, **34**, **38**, **40**, **41**, **44**, **46–48**, **53**, **57**, **60–63**, **65**.

5) Each of the test participants failed to detect odor in at least one of the steroid derivatives; and no molecular factor possibly connected with this could be discerned. Six out of 80 persons failed to detect any of the androstane derivatives shown in *Schemes 1–3;* and hence it seems as if they had lacked a steroid acceptor in their receptor membrane. Moreover, the same persons were unable to describe the odors of either sandalwood or civetone.

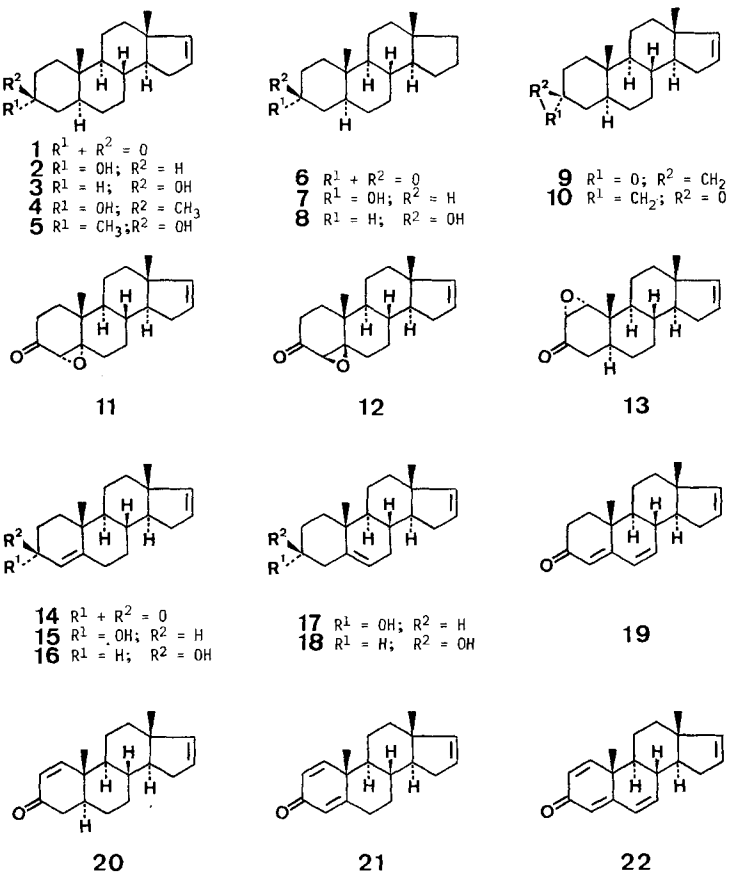
6) For a definition of these terms, see [32].

7) Both with the ambergris and steroid odorants an olfactive after-effect of several hours' duration on the olfactory receptor could be observed. We assume that this is due to a mechanism in which ligands, which at first are not specifically associated with the membrane, take time in finding the appropriate active site and only then form a specific interaction.

8) With one group the distribution of odor perception of compound **2** (see the *Table*) between female (♀) and male (♂) subjects varied only by a maximum of 10% in the course of three tests at different times, although with another panel (12 females and 24 males), we encountered 50% of anosmic defects among female and only 27% among male subjects. This would also appear to account for differences between the present and previously reported results with compound **2** particularly with regard to male participants (46% anosmic cases reported in [33] and 44% in [34]). Compare also the variations of the results obtained for compounds **14** and **23** in the *Table*.

9) Others have regarded this phenomenon as a mere anosmic effect [33].

Scheme 1. *Androstane derivatives with an O-function at C(3)*



and **17** *(Scheme 1)* all have a common muscone-type odor with a sandalwood-like basic note[10]). Several observers also found additional indications of urine-like, sweaty and occasionally ambergris odor. The specific anosmia associated with the 3α-alcohols could be observed in up to 50% of all panel members, depending on the compound but irrespective of the sex of the observer. The saturated derivative **7** not only gave rise to an enhanced anosmic defect but also to a reduced intensity relative to compound **2**; in the former the urine and sweaty components were much less intense than in the latter. Among the 3β-alcohols, compounds **16** and **18** were detected by over 30% of the panel though only 10% found them to be of the same intensity as their diastereoisomers **15** and **17**. Compounds **3** [3] and **8** [35] have been reported as practically odorless, whereas in our investigations **3** was perceived by 10% of the female and 18% of the male participants. With the tertiary alcohols **4** and **5** only 25% of the panel found a 'steroid-type' odor, the urine component being

[10]) Surprisingly six of eight parosmics show the same defect with sandalwood oil.

stronger in the former. The epoxide **9** was found by only a few people to have a 'steroid-type' scent of low intensity, whereas the diastereoisomer **10** was not perceptible.

For ketones **1**, **6**[11]), **11**, **14**, and **19–22** odor profiles similar to the corresponding 3α-alcohols were found[12]), though the sandalwood-like muscone-type odor was less in evidence when compared to the sweaty-urine component. Higher oxidation states in these compounds appear to lead to lower odor intensity and also an increase in anosmia. In the epoxy-ketone **11** tonality and intensity are reminiscent of ketone **1**, whereas the diastereoisomeric epoxy-ketone **12** has only a very weak odor and compound **13** none at all.

Increase in anosmia and decrease in odor intensity were also noticeable in steroids when the 3-oxo-group had been transposed to another position. Among 1-oxo-steroids, compound **30** had the strongest urine-sweaty-type odor; compound **26** was found much weaker in this respect while the α,β-unsaturated ketone **23** was practically odorless. The C(2)-ketones **31** and **34** were detected by less than 20% of the panel. A similar situation was found with 4-oxo-steroids **43**[13]), and **45** as seen from the *Table;* very few subjects found these to have any odor, and none in the case of **46** and of the unsubstituted ketone **38**. The same observation was made with the *cis*-fused C(4)-ketone **41**. Surprisingly, the doubly unsaturated ketones **35** and **42** were highly odoriferous and most panel members noticed a predominant urine-sweaty component. Among alcohols listed in *Scheme 2* only 10% of the panel found any odor with compounds **25**, **32**, **36**, **37** and **39**; and none found any with compounds **24**, **27**, **28**, **33**, **40**, **47** and **48**. 5α-Androst-2-en-17-one (**49**), previously described [3] as having a distinct urine odor, was found only weakly so by a small number of observers. This was also the case with the saturated analog **50** which by some members of the panel was found to be muscone- and sandalwood-like.

C/D-*cis*-compounds **51** and **52** were weakly active, and **52** was more sandalwood/muscone- than urine-like; compound **53** was practically odorless.

The estrane derivatives **54–61** listed in *Scheme 4* showed sensory properties similar to those of corresponding androstane derivatives **1–3**, **14**, **31–33** and **34**, a similarity extending to the lack of odor of equatorial alcohols **57** and **60**. The estrane derivatives, however, caused less anosmic defects and smelt stronger. As observed previously with estra-1,3,5-trien-3-ol and estra-1,3,5,16-tetraen-3-ol [4], aromaticity of ring A in this series leads to complete lack of odor.

Judging from our results with optically active odorants in the decalin series which behave in agreement with our 'triaxial rule of odor sensation' [36] one would expect strong differentiation in odor properties between enantiomers in the steroid series. This expectation was indeed confirmed. Ketone **14** was found to have a strong urine odor with an extraordinarily low (1 ppb) threshold value [33], but in the same panel nobody was able to detect any odor from *ent*-androsta-4,16-dien-

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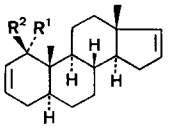
[11]) Ketone **6** showed only 20% of the aphrodisiac activity in hogs when compared to that of the unsaturated ketone **1** [16].

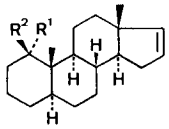
[12]) The *Table* shows that for ketone **1** 34% of the panel were parosmic. With another group comprising 35 persons only 20% (7 in number) showed parosmic defects for ketone **1**, and five of these were parosmic with regard to civetone.

[13]) The corresponding 3α-methyl-derivative could not be prepared.

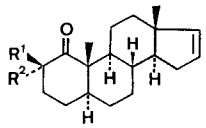
Scheme 2. *Androstane derivatives with O-functions at C(1), C(2), C(4), C(5) and C(17)*



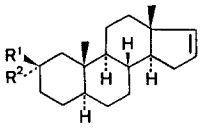
23 $R^1 + R^2 = O$
24 $R^1 = OH$; $R^2 = H$
25 $R^1 = H$; $R^2 = OH$



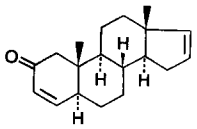
26 $R^1 + R^2 = O$
27 $R^1 = OH$; $R^2 = H$
28 $R^1 = H$; $R^2 = OH$



29 $R^1 = CH_3$; $R^2 = H$
30 $R^1 = H$; $R^2 = CH_3$



31 $R^1 + R^2 = O$
32 $R^1 = OH$; $R^2 = H$
33 $R^1 = H$; $R^2 = OH$



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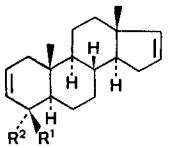
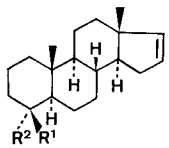
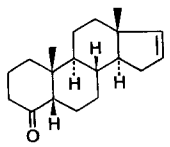


35 $R^1 + R^2 = O$
36 $R^1 = OH$; $R^2 = H$
37 $R^1 = H$; $R^2 = OH$



38 $R^1 + R^2 = O$
39 $R^1 = OH$; $R^2 = H$
40 $R^1 = H$; $R^2 = OH$



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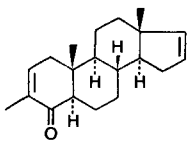

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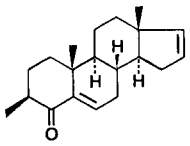

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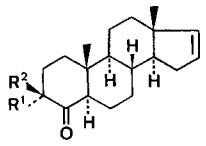
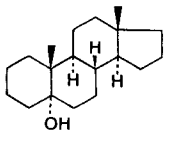


44 $R^1 = CH_3$; $R^2 = H$
45 $R^1 = H$; $R^2 = CH_3$
46 $R^1 = R^2 = CH_3$



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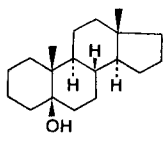

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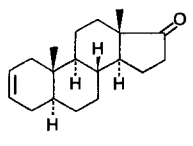

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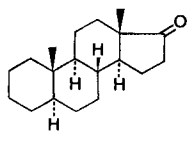

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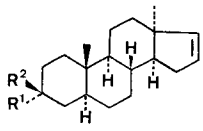
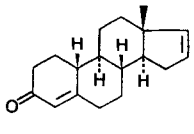
Scheme 3. *5a,13a-Androst-16-ene derivatives* **51–53**



51 $R^1 + R^2 = O$
52 $R^1 = OH$; $R^2 = H$
53 $R^1 = H$; $R^2 = OH$

Scheme 4. *Oxygenated estrane derivatives*



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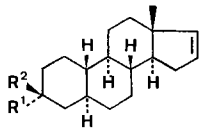
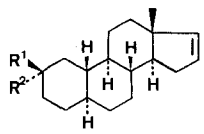
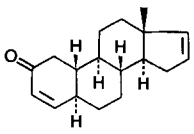


55 $R^1 + R^2 = O$
56 $R^1 = OH$; $R^2 = H$
57 $R^1 = H$; $R^2 = OH$



58 $R^1 + R^2 = O$
59 $R^1 = OH$; $R^2 = H$
60 $R^1 = H$; $R^2 = OH$



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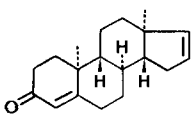
Scheme 5. ent-*Androstane derivatives*



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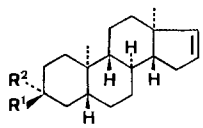


63 $R^1 + R^2 = O$
64 $R^1 = OH$; $R^2 = H$
65 $R^1 = H$; $R^2 = OH$

3-one (**62**) [36]. Similar results were obtained with ring-A-saturated steroids of the 'unnatural' series **63–65**. The equatorial alcohol **65** and the ketone **63** were odorless and only the axial alcohol **64** has an exceedingly weak musk odor[14]) whose lower threshold value was at least six orders of magnitude higher[15]) than that of its enantiomer **2**.

Conclusions concerning receptor activity of steroids and the interaction of geometrical and chemical factors will be discussed after further work[16]).

Syntheses. – Several steroids described in this work are known compounds and have been prepared by literature procedures. For such compounds, only references are given in the *Experimental Part.* In cases, where substantial improvements over known methods were achieved, the procedure is described in detail. A few comments on the synthesis of certain compounds are necessary.

The C_{16}-unsaturated steroids of this work are derived from 17-hydroxy- and 17-oxo-steroids. Although several methods are known for the apparently trivial

[14]) Here the urine note was entirely absent.
[15]) 25% of the panel were able to discern the odor of a 1% solution, and only 10% a 0.1% solution.
[16]) See, *e.g.*, [37].

Table. *Odor sensitivity of human subjects to steroids*[a])

Compound	No. of participants			'Steroid'-scent perception		No or non-typical[b]) odor perception	
	total	♀	♂	♀ (%)	♂ (%)	♀	♂
1	76	17	59	11 (65)	28 (47)	6 (5)	31 (21)
2	89	23	66	21 (91)	50 (76)	2 (1)	16 (8)[c])
2	36	12	24	6 (50)	18 (73)	6 (4)	5 (2)[c])
3	31	9	22	1 (11)	4 (18)	8 (2)	18 (6)
4	36	12	24	3 (25)	6 (25)	9 (3)	18 (4)
5	36	12	24	3 (25)	6 (25)	9 (6)	18 (3)
6	76	17	59	13 (76)	48 (81)	4 (3)	11 (5)
7	76	17	59	11 (65)	36 (61)	6 (6)	23 (13)
9	34	10	24	1 (10)	4 (16)	9 (–)	20 (–)
11	31	10	21	6 (60)	13 (62)	4 (1)	8 (1)
12	31	10	21	2 (20)	3 (14)	8 (–)	18 (–)
14	36	12	24	6 (50)	13 (54)	6 (4)	11 (4)[c])
14	89	23	66	20 (88)	40 (60)	3 (1)	26 (17)[c])
15	36	12	24	7 (58)	22 (92)	5 (4)	2 (2)
16	36	12	24	4 (33)	8 (33)	8 (4)	16 (2)
17	36	12	24	6 (50)	14 (58)	6 (5)	10 (8)
18	36	12	24	5 (42)	8 (33)	7 (5)	16 (9)
19	36	12	24	5 (42)	14 (58)	7 (6)	10 (8)
20	36	12	24	6 (50)	12 (50)	6 (6)	12 (6)
21	31	10	21	5 (42)	10 (48)	5 (3)	11 (3)
22	31	10	21	4 (33)	10 (48)	6 (3)	11 (1)
23	35	12	23	2 (17)	5 (22)	10 (3)	18 (1)[c])
23	32	11	21	1 (9)	1 (5)	10 (1)	20 (3)[c])
25	30	9	21	– (0)	3 (14)	9 (–)	18 (–)
26	32	11	21	4 (36)	10 (48)	7 (2)	11 (1)
30	32	11	21	3 (27)	10 (48)	8 (4)	11 (6)
31	89	23	66	4 (17)	14 (21)	19 (3)	52 (23)
32	89	23	66	5 (22)	4 (6)	18 (12)	62 (24)
35	34	11	23	6 (55)	16 (70)	5 (4)	7 (4)
36	29	8	21	1 (12)	1 (5)	7 (–)	19 (1)
37	29	8	21	1 (12)	2 (10)	7 (1)	19 (–)
39	29	8	21	2 (25)	2 (10)	6 (2)	20 (–)
42	29	9	24	5 (55)	18 (75)	4 (1)	6 (2)
43	29	9	20	1 (11)	2 (10)	8 (2)	18 (2)
45	33	9	24	1 (11)	3 (13)	8 (2)	21 (5)
49	76	17	59	2 (12)	13 (22)	15 (10)	46 (21)
50	76	17	59	4 (24)	12 (20)	13 (9)	47 (23)
51	35	12	23	4 (30)	9 (39)	8 (3)	14 (4)
52	37	12	25	3 (25)	10 (40)	9 (8)	15 (4)
54	89	23	66	20 (87)	42 (64)	3 (–)	24 (15)
55	89	23	66	23 (100)	54 (82)	– (–)	12 (8)
56	89	23	66	18 (78)	49 (74)	5 (3)	17 (12)
58	89	23	66	11 (48)	17 (26)	12 (10)	49 (23)
59	89	23	66	7 (30)	11 (17)	16 (12)	55 (24)
64	29	8	21	2 (25)	5 (24)	6 (–)	16 (–)

[a]) The steroid derivatives listed in the *Table* were chemically pure. Their source and physicochemical data are reported in the *Experimental Part*, and they were submitted to the panel members as 1% solutions in EtOH on smelling strips. The composition of the panel and the method of testing have already been described [29]. Unlike in the earlier work, we have not made any classification about odor strength, but comment on the various sensory properties in the text. The participants were

supplied with a selection of key words, like 'sweaty, musky, urine-like, woody, and ambergris', but they were free to write down any other impressions they had. Compounds, which were not detected by any of the panel members, are not listed in the *Table* (see footnote 4).

[b]) The figures in parentheses refer to the number of participants with a parosmic defect. The 'wrong' answer of these panel members was, in order of frequency, as follows: undefined, fruity, flowery, sweet (mostly vanilla), fresh, hay-like, spicy-peppery, coffee, sulfury, burnt, minty, acid, fatty, incense, tobacco, aniseed, and earthy. Most of the parosmics had trouble with verbal descriptions; this was demonstrated by the varying replies they gave to the same test carried out at different times.

[c]) See footnote 8.

conversion of testosterone (**III**)[17]) into androsta-4,16-dien-3-one (**14**), none of them gives good yields[18]). We found the thermolysis (460°) of the methyl carbonate of testosterone (**IV**) to give the elimination product **14** in 90% yield. The same method gave excellent results also for other steroids with a methyl-carbonate function at C(17), *e.g.* **II** → **1**, **VI** → **20**.

The α,β-unsaturated ketone **34** was synthesized from 5α-androsta-1,16-dien-3-one (**20**) in analogy to a published method [41]. This method gave a low yield (< 10%) for the transformation of enone **14** into enone **35**, a transformation which was accomplished in 31% overall yield using the method of *Hagiwara et al.* [42] (see *Exper. Part*). Several attempts to prepare the 3α-methyl-derivative **44** from **45** by kinetic protonation of the corresponding enolate failed, but direct irradiation of **45** in ether led to a complex mixture, from which **44** could be isolated in 21% yield.

ent-Testosterone (**XXIX**) was synthesized in 15 steps using methods described for the total synthesis of testosterone [43–45]. Special care was taken to ensure the enantiomeric purity of the crucial intermediates **XXVI** [43] and **XXVII** [44] by repeated fractional recrystallization until the m.p. and $[\alpha]_D$-value were constant.

We wish to thank Miss *G. Lingesleben* for valuable assistance in preparing the manuscript and for drawing the formulas.

Experimental Part

(with the valuable collaboration of *A. Chollet-Damerius*, *B. Frei* and *R. Pay*)

General remarks. Melting points (m.p.) were determined in open capillary tubes in an oil bath and are not corrected; for a few (polymorphic) compounds, a second m.p. preceeded by an arrow means that the melt solidified upon further heating and melted again at the second m.p. Specific rotations ($[\alpha]_D$) were measured in $CHCl_3$ at 20° with a *Perkin-Elmer 141* polarimeter, unless otherwise stated. Thin layer chromatography (TLC.) was performed on *F 254* TLC. plates *(Merck)* and preparative column chromatography on silicagel *(Merck)* (0.063–0.2 mm). Gas chromatography (GC.) was carried out on a *Carlo Erba Fractovap 4200* instrument, using one of the three following glass columns (ID = 3 mm): a) l = 1 m, 15% SE 30 on *Chromosorb W*, 60–90 mesh; b) l = 1.1 m, 10% SOMB on *Chromosorb W*, 60–80 mesh; c) l = 1.6 m, 3% *SILAR 5CP* on *Chromosorb Q* (100–120 mesh). Recording of spectra was carried out on the following apparatus: IR.: *Perkin-Elmer 297* and *720* spectrometer; characteristic band positions are given in cm^{-1}; abbreviations: *s* = strong, *m* = medium, *w* = weak,

[17]) Roman numerals are used throughout this work for starting materials and intermediates not submitted to sensory evaluation.

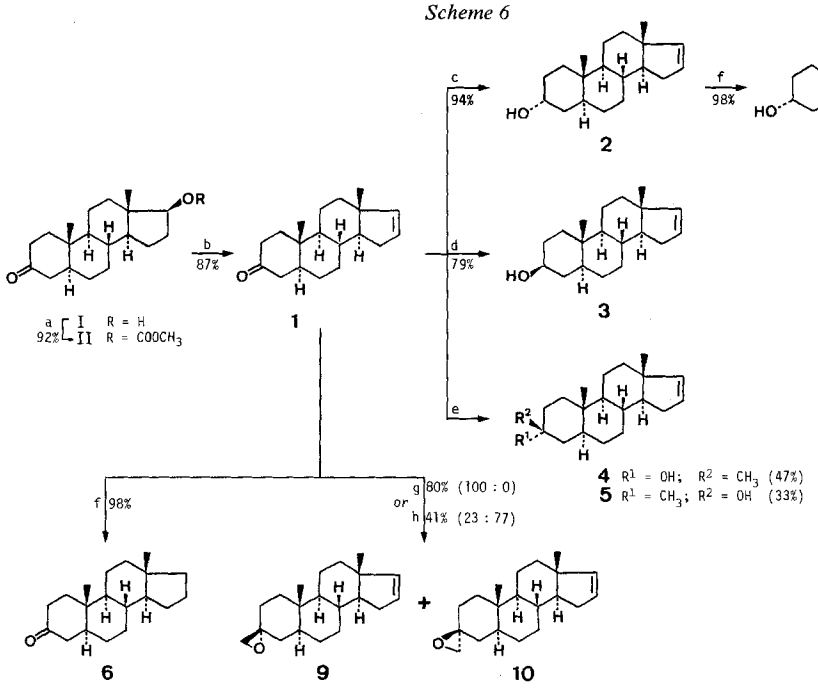
[18]) Androsta-4,16-dien-3-one (**14**) was obtained in unstated yield by thermolysis of testosterone benzoate [3], in 40% yield by pyrolysis of testosterone acetate [38], in 57% yield by treatment of testosterone *p*-toluenesulfonate with tetrabutylammonium acetate in boiling *N*-methylpyrrolidine [39], by treatment of testosterone with a haloimide and sulfur dioxide [40], and in 13% yield by elimination of testosterone methanesulfonate with lithium chloride in DMF [28].

S = shoulder. – ^{1}H-NMR.: *Bruker WH 360* (360 MHz), *Bruker HX 90* (90 MHz) and *Varian EM 360* (60 MHz); measurements were run in $CDCl_3$ with tetramethylsilane as internal standard ($\delta = 0.00$ ppm); abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *qa* = quadruplet, *qi* = quintuplet, *m* = multiplet, br. = broad, *J* = spin-spin coupling constant in Hz, $w_{1/2}$ = half-width in Hz. – MS.: *Atlas CH 4* or *Varian MAT 112*, using electrons of *ca.* 70 eV energy[19]).

Abbreviations: aq. = aqueous, RT. = room temperature, PE = petroleum ether (b.p. 50–70°), DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, THF = tetrahydrofuran.

Preparation of compounds *1–10*.

Scheme 6



Reagents: a) $ClCOOCH_3$, pyridine/0°/24 h; b) 480°, 10 m glass column; c) $LiB[CH(CH_3)CH(CH_3)_2]_3H$, THF/−55°; d) $NaBH_4$, THF, MeOH/25°; e) CH_3MgI, ether/30°/1 h; f) H_2/Pd-C, EtOH; g) $(CH_3)_3S^{\oplus}OI^{\ominus}$, NaH, DMF/RT./2 h; h) $(CH_3)_3S^{\oplus}I^{\ominus}$, BuLi, THF/0→25°/3 h.

5α-Androst-16-en-3-one (**1**). A solution of the methyl carbonate **II**[20]) (9.6 g, 27.6 mmol) in toluene (200 ml) was pyrolyzed in a *Pyrex* glass column (l = 10 m, ∅ = 9 mm) at 480° (N_2 stream *ca.* 11 ml/min) at a rate of *ca.* 1 g/h. The crude product (collected in two liquid N_2-cooled traps) was washed with sat. aq. $NaHCO_3$- and NaCl-solution, dried (Na_2SO_4) and evaporated. The residue (7.24 g, 97%) was recrystallized from PE at 0° to give 6.42 g (87%) of **1**. An analytical sample was recrystallized from acetonitrile at RT. M.p. 142–144°, $[\alpha]_D = +35.6°$ (*c* = 1.15) ([2]: m.p. 140–141°, $[\alpha]_D^{17} = +38°$ (*c* = 2.08)). –

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[19]) The mass spectra of all compounds were in agreement with the structures (confirming their molecular weight) and may be obtained on request from the authors.

[20]) *17β-Methoxycarbonyloxy-5α-androstan-3-one* (**II**) was prepared from 17β-hydroxy-5α-androstan-3-one (**I**, *Fluka*) and methyl chloroformate in pyridine in 92% yield. M.p. 84°, $[\alpha]_D = +25.6°$ (*c* = 1.25). – IR. ($CDCl_3$): 1745*s*, 1710*s*, 1450*s*, 1280*s*. – ^{1}H-NMR. (60 MHz): 0.83 (*s*, 3 H); 1.02 (*s*, 3 H); 3.78 (*s*, 3 H); 4.53 (br. *t*, $J \approx 8$, 1 H).

IR. ($CDCl_3$): 1710*s*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.79 (*s*, 3 H); 1.05 (*s*, 3 H); 5.70 (*m*, 1 H); 5.84 (*m*, 1 H).

5α-Androst-16-en-3α-ol (**2**). To a 1 M solution of lithium tris(1,2-dimethylpropyl)hydridoborate (*Aldrich*, 2.5 ml, 2.5 mmol) at −55°, under N_2, was added a solution of ketone **1** (500 mg, 1.84 mmol) in THF (7 ml) and the mixture was allowed to warm up to RT. After 3 h, the mixture was cooled to −55° and hydrolyzed by addition of water (1 ml), followed by EtOH (3 ml). The boranes were oxidized by adding to the mixture at −55° 10% aq. NaOH-solution (5 ml), followed by 30% aq. H_2O_2-solution (3 ml), and stirring for 3 h at RT. Cyclohexane (100 ml) was added and the org. phase washed successively with water, sat. aq. $NaHSO_3$-solution and sat. aq. NaCl-solution; after drying (Na_2SO_4) and evaporation of the solvent, the residue was chromatographed on silica gel (60 g) with toluene/ethyl acetate 2:1. The axial alcohol **2** was eluted first (443 mg, 89%) and the second fraction contained the equatorial alcohol **3** (24 mg, 4.8%). An analytical sample of **2** was recrystallized from PE at 0°. M.p. 142–144°, $[\alpha]_D = +15°$ ($c = 1.33$) ([2]: m.p. 143.5–144°, $[\alpha]_D^{16} = +13.9°$ ($c = 0.94$)). – IR. ($CDCl_3$): 3625*m*, 3450*w*, 1590*w*. – ^{1}H-NMR. (360 MHz): 0.77 (*s*, 3 H); 0.82 (*s*, 3 H); 4.03 (*m*, $w_{1/2} \approx 8$, 1 H); 5.70 (*m*, 1 H); 5.83 (*m*, 1 H).

5α-Androst-16-en-3β-ol (**3**). Ketone **1** (500 mg, 1.84 mmol) was reduced with sodium borohydride (75 mg, 2 mmol) in THF/MeOH 5:1 (18 ml) at RT. (2 h). The crude product was chromatographed on silica gel (60 g) using toluene/ethyl acetate 2:1. After traces of the axial alcohol **2** (9 mg, 2%), the pure equatorial alcohol **3** (388 mg, 77%) was eluted. An analytical sample was recrystallized from MeOH/water. M.p. 124–125°, $[\alpha]_D = +14.2°$ ($c = 1.12$) ([2]: m.p. 125–127°, $[\alpha]_D^{17} = +11.2°$ ($c = 0.76$)). – IR. ($CDCl_3$): 3620*m*, 3430*w*, 1590*w*. – ^{1}H-NMR. (360 MHz): 0.77 (*s*, 3 H); 0.85 (*s*, 3 H); 3.60 ($t \times t$, $J = 11$ and 5, 1 H); 5.70 (*m*, 1 H); 5.84 (*m*, 1 H).

3β-Methyl-5α-androst-16-en-3α-ol (**4**) *and 3α-methyl-5α-androst-16-en-3β-ol* (**5**). The mixture of alcohols **4** and **5**, obtained by treating ketone **1** (545 mg, 2.0 mmol) with an excess of methylmagnesium iodide in ether, was chromatographed on silica gel (50 g) with ether/cyclohexane 2:1. The axial alcohol **4** was eluted first (274 mg, 47%) and was recrystallized from MeOH at −10°. M.p. 74–75°, $[\alpha]_D = +16.5°$ ($c = 1.21$). – IR. ($CDCl_3$): 3620*w*, 3470*w*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.76 (*s*, 3 H); 0.79 (*s*, 3 H); 1.20 (*s*, 3 H); 5.69 (*m*, 1 H); 5.83 (*m*, 1 H).

The equatorial alcohol **5** was eluted in the second fraction (190 mg, 33%) and crystallized in long needles from PE. M.p. 134–136°, $[\alpha]_D = +20.5°$ ($c = 1.17$). – IR. ($CDCl_3$): 3620*w*, 3460*w*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.76 (*s*, 3 H); 0.85 (*s*, 3 H); 1.25 (*s*, 3 H); 5.70 (*m*, 1 H); 5.84 (*m*, 1 H).

5α-Androstan-3-one (**6**) [3]. M.p. 97–98°, $[\alpha]_D = +23.5°$ ($c = 1.3$) ([3]: m.p. 104.5–105.5° (corr.), $[\alpha]_D^{20} = +25.4°$ ($c = 0.71$)). – IR. (KBr): 1710. – ^{1}H-NMR. (90 MHz): 0.73 (*s*, 3 H); 1.02 (*s*, 3 H); 1.9–2.5 (*m*, 4 H).

5α-Androstan-3α-ol (**7**) [2]. M.p. 139–140°, $[\alpha]_D = +2.6°$ ($c = 1.5$) ([2]: m.p. 145–146° (corr.), $[\alpha]_D^{17} = +2°$ ($c = 1.28$)). – IR. (KBr): 3300 br. – ^{1}H-NMR. (90 MHz): 0.70 (*s*, 3 H); 0.79 (*s*, 3 H); 4.05 (*m*, $w_{1/2} \approx 8$, 1 H).

(3R)-Spiro[5α-androst-16-en-3,2′-oxirane] (**9**). To sodium hydride (400 mg, 16.7 mmol) in DMF (20 ml) was added in small portions trimethylsulfoxonium iodide (2.33 g, 10.6 mmol) and the mixture was stirred at RT. After 1 h, ketone **1** (544 mg, 2 mmol) was added. The mixture was stirred for 2 h at RT., then poured into ice-water. The precipitate was removed by filtration, washed with water and dried in vacuum, yielding 459 mg (80%) of pure **9** (by ^{1}H-NMR.).

The pure epoxide **9** was obtained after recrystallization from pentane (at −78°) followed by recrystallization from acetone/water (at RT.), and two recrystallizations from EtOH (at RT.). M.p. 84–85°, $[\alpha]_D = +3.8°$ ($c = 1.05$). – IR. ($CDCl_3$): 1595*w*. – ^{1}H-NMR. (360 MHz): 0.77 (*s*, 3 H); 0.88 (*s*, 3 H); 2.62 (*AB*-system, $J_{AB} = 5$, 2 H); 5.71 (*m*, 1 H); 5.85 (*m*, 1 H).

When epoxid **9** (5 mg, 0.017 mmol) was treated with $LiAlH_4$ (5 mg) in ether (2 ml), an alcohol was obtained which was identical (by TLC. and GC.) with an authentic sample of **4**.

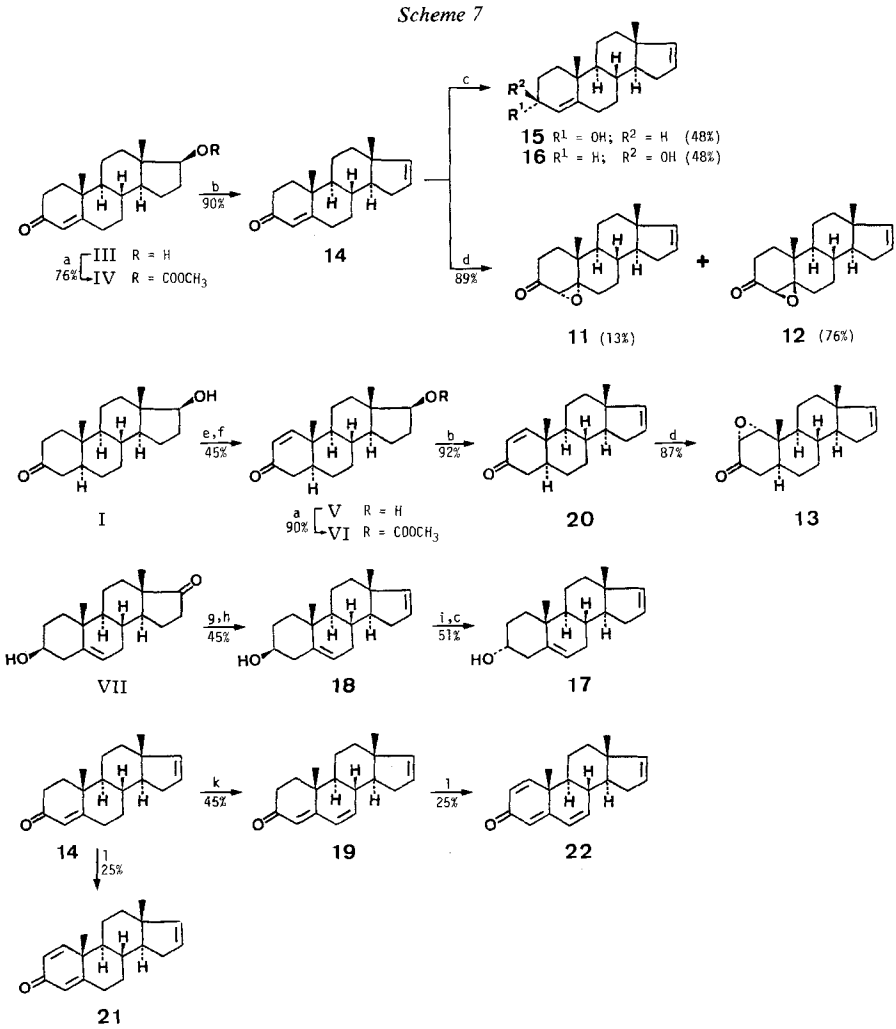
(3S)-Spiro[5α-androst-16-en-3,2′-oxirane] (**10**). A 1.33 M solution of BuLi in THF (1.74 ml, 2.38 mmol) was added dropwise to a stirred suspension of trimethylsulfonium iodide (529 mg, 2.59 mmol) in dry THF (25 ml) at 0° under N_2 and the mixture was stirred for 5 min. Ketone **1** (544 mg, 2 mmol) was added and the suspension was maintained at 0° for 30 min, warmed to 20° for 1 h and stirred for 2 h at RT. The mixture was poured into ice-water, extracted with ether, washed with sat. aq. NaCl-solution, dried (Na_2SO_4), and evaporated in vacuum to give a mixture of **9**, **10** and starting material (500 mg).

Chromatography on 100 g silica gel (cyclohexane/ether 4:1) afforded a first fraction (235 mg, 41%) containing **9** and **10** (ratio 23:77 by ^{1}H-NMR.). Recrystallization from pentane (at $-75°$) and twice from EtOH (at RT.) gave pure **10** (40 mg). (The second chromatographic fraction contained the starting ketone **1** (210 mg, 38%)). M.p. 142–143°, $[\alpha]_D = +5.3°$ ($c = 0.94$). – IR. ($CDCl_3$): 1595*w*. – ^{1}H-NMR. (360 MHz): 0.77 (*s*, 3 H); 0.91 (*s*, 3 H); 2.57 (*AB*-system, $J_{AB} = 5$, 2 H); 5.69 (*m*, 1 H); 5.84 (*m*, 1 H).

A small sample of **10** was reduced with $LiAlH_4$ in ether to give the alcohol **5** (identical with an authentic sample by TLC. and GC.).

Preparation of compounds *11–22*.

Scheme 7



Reagents: a) $ClCOOCH_3$, pyridine, glyme/0°/24 h; b) 460°, glass column; c) $LiB[CH(CH_3)CH(CH_3)_2]_3H$, THF/−55°; d) H_2O_2, KOH, MeOH/0°/24 h; e) (pyrrolidone)$_3HBr_3$, glyme/0°; f) LiBr, Li_2CO_3, DMF/125°/2½ h; g) NH_2-NHTs, toluene/reflux; h) MeLi, THF; i) *Jones* reagent; k) chloranil, *t*-BuOH, AcOH/reflux/3 h; l) 2,3-dichloro-5,6-dicyanobenzoquinone, toluene/80°/15 h.

4a,5α-Epoxyandrost-16-en-3-one (**11**) *and 4β,5β-epoxyandrost-16-en-3-one* (**12**)[21]. To a suspension of androsta-4,16-dien-3-one (**14**) (2.7 g, 10 mmol) in MeOH (100 ml) at −40° was added successively 30% aq. H_2O_2-solution (16 ml) and 10% aq. NaOH-solution (6 ml). The mixture was stirred for 24 h at 0° and extracted with CH_2Cl_2. The crude product (2.8 g, oil) was a mixture of **11** and **12** (1:6) and was recrystallized from PE (30/50) at 0° to give 1.87 g of crystals, m.p. 108–115°, **11/12** (1:9). The mother liquors (830 mg) were chromatographed on silica gel (90 g) with ether/cyclohexane 1:2. The first fraction (164 mg of **12**) was purified by several recrystallizations from PE at 0°, and the second fraction (155 mg of **11**) was recrystallized from acetonitrile at −30°.

Data of **11**. M.p. 86–87°, $[\alpha]_D = -67.4°$ ($c = 0.95$). – IR. ($CDCl_3$): 1710*s*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.80 (*s*, 3 H); 1.09 (*s*, 3 H); 3.05 (*s*, 1 H); 5.72 (*m*, 1 H); 5.86 (*m*, 1 H).

Data of **12**. M.p. 114–115° ([28]: 117–118° (from MeOH)), $[\alpha]_D = +143.5°$ ($c = 1.22$). – IR. ($CDCl_3$): 1710*s*, 1590*w*. – ^{1}H-NMR. (360 MHz): 0.79 (*s*, 3 H); 1.19 (*s*, 3 H); 2.99 (*s*, 1 H); 5.71 (*m*, 1 H); 5.85 (*m*, 1 H).

1α,2α-Epoxy-5α-androst-16-en-3-one (**13**). 5α-Androsta-1,16-dien-3-one (**20**) was epoxidized with alkaline H_2O_2 following the standard procedure (*cf.* [46]). The epoxy-ketone **13** was obtained in 87% yield. An analytical sample was recrystallized from PE (30–50°) at 0°. M.p. 174.5–176°, $[\alpha]_D = +127.5°$ ($c = 1.31$). – IR. ($CDCl_3$): 1710*s*, 1590*w*. – ^{1}H-NMR. (360 MHz): 0.80 (*s*, 3 H); 0.93 (*s*, 3 H); 3.23 (*d*, $J = 4$, 1 H); 3.53 (*d*, $J = 4$, 1 H); 5.71 (*m*, 1 H); 5.86 (*m*, 1 H).

Androsta-4,16-dien-3-one (**14**). A solution of the methyl carbonate **IV**[22]) in toluene was pyrolyzed as described for **1**. Recrystallization of the crude product from acetone at RT. gave pure ketone **14** in 90% yield. M.p. 127–129.5°, $[\alpha]_D = +118.9°$ ($c = 1.32$) ([3]: m.p. 131.5–133.5° (hexane), $[\alpha]_D^{16} = +123 \pm 3.5°$ ($c = 1.03$)). – IR. ($CDCl_3$): 3050*w*, 1660*s*, 1615*m*. – ^{1}H-NMR. (360 MHz): 0.82 (*s*, 3 H); 1.22 (*s*, 3 H); 5.70 (*m*, 1 H); 5.73 (*s*, 1 H); 5.84 (*m*, 1 H).

Androsta-4,16-dien-3α-ol (**15**) *and -3β-ol* (**16**). Androsta-4,16-dien-3-one (**14**) was reduced at −55° with lithium tris(1,2-dimethylpropyl)hydridoborate in THF as described for the preparation of **2**. Chromatography on silica gel with CH_2Cl_2/ethyl acetate 9:1 gave pure axial alcohol **15** (48% yield) and pure equatorial alcohol **16** (48% yield). Analytical samples were further purified by recrystallization (from PE at −30° for **15**, from cyclohexane at RT. for **16**).

Data of **15**. M.p. 77–79°, $[\alpha]_D = +120.6°$ ($c = 1.26$). – IR. ($CDCl_3$): 3620*m*, 3440*m* br., 1660*m*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.79 (*s*, 3 H); 1.02 (*s*, 3 H); 4.07 (*m*, $w_{1/2} \approx 10$, 1 H); 5.48 (*d*×*d*, $J = 5$ and 2, 1 H); 5.71 (*m*, 1 H); 5.85 (*m*, 1 H).

Data of **16**. M.p. 116–119°, $[\alpha]_D = +53.9°$ ($c = 1.28$) ([47]: m.p. 116–118°, $[\alpha]_D = +59.3°$ ($c = 0.4$)). – IR. ($CDCl_3$): 3610*m*, 3420*m* br., 3050*m*, 1660*m*, 1590*w*. – ^{1}H-NMR. (360 MHz): 0.78 (*s*, 3 H); 1.08 (*s*, 3 H); 4.15 (*m*, $w_{1/2} \approx 20$, 1 H); 5.30 (*m*, $w_{1/2} \approx 5$, 1 H); 5.71 (*m*, 1 H); 5.85 (*m*, 1 H).

Androsta-5,16-dien-3α-ol (**17**). To a solution of alcohol **18** (545 mg, 2.0 mmol) in acetone (100 ml) at 0° under N_2 was added rapidly *Jones* reagent (1.5 ml, *ca.* 4 mmol). After 5 min, the mixture was poured into a dilute phosphate buffer (pH 7.2, 1200 ml) and extracted with ether. The extracts were washed with sat. aq. NaCl-solution, dried (Na_2SO_4) and evaporated to give mainly androsta-5,16-dien-3-one as an oil (567 mg). The crude product was dissolved in THF (7 ml) and reduced with lithium tris(1,2-dimethylpropyl)hydridoborate at −55° as described for the preparation of **2**. The crude product (530 mg) was chromatographed on silica gel (100 g) with CH_2Cl_2/ethyl acetate 4:1 to give 280 mg (51%) of pure α-alcohol **17** (eluted first) and 13 mg of starting alcohol **18**. A small sample of **17** was recrystallized from acetone/water at RT. M.p. 138°, $[\alpha]_D = -77.5°$ ($c = 1.2$). – IR. ($CDCl_3$): 3580*m*, 3430*m*, 1665*w*, 1590*w*. – ^{1}H-NMR. (360 MHz): 0.80 (*s*, 3 H); 1.06 (*s*, 3 H); 4.02 (*m*, $w_{1/2} \approx 8$, 1 H); 5.44 (*m*, 1 H); 5.72 (*m*, 1 H); 5.86 (*m*, 1 H).

Androsta-5,16-dien-3β-ol (**18**). This compound was prepared in 73% yield by a known procedure [28] from commercial *(Fluka)* 3β-hydroxyandrost-5-en-17-one (**VII**). M.p. 137°, $[\alpha]_D = -71.9°$ ($c = 1.5$) ([48]: m.p. 140–141°, $[\alpha]_D = -68°$). – IR. ($CDCl_3$): 3600*m*, 3420*m* br., 1670*w*, 1590*w*. – ^{1}H-NMR. (360 MHz): 0.80 (*s*, 3 H); 1.05 (*s*, 3 H); 3.53 (*m*, $w_{1/2} \approx 22$, 1 H); 5.38 (*m*, 1 H); 5.72 (*m*, 1 H); 5.86 (*m*, 1 H).

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[21]) The preparation of epoxy-ketone (**12**) by the same method has been described in [28] but the 4α,5α-configuration was erroneously assigned to the major product.

[22]) *17β-Methoxycarbonyloxy-androst-4-en-3-one* (**IV**) was prepared from testosterone (**III**, *Fluka*) with methyl chloroformate/pyridine in 76% yield (after recrystallization from MeOH). M.p. 140–141°, $[\alpha]_D = +95.4°$ ($c = 1.10$). – IR. ($CDCl_3$): 1740*s*, 1665*s*, 1450*s*, 1280*s*. – ^{1}H-NMR. (60 MHz): 0.87 (*s*, 3 H); 1.20 (*s*, 3 H); 3.77 (*s*, 3 H); 4.53 (br. *t*, $J = 8$, 1 H); 5.75 (*s*, 1 H).

Androsta-4,6,16-trien-3-one (**19**). Prepared in 45% yield according to [28]. M.p. 124–126° (from acetone), $[\alpha]_D = +80°$ ($c = 1.25$) ([28]: m.p. 122.5–124° (from heptane)). – IR. ($CDCl_3$): 3040*m*, 1650*s*, 1620*s*, 1590*s*. – ^{1}H-NMR. (360 MHz): 0.85 (*s*, 3 H); 1.14 (*s*, 3 H); 5.60 (*s*, 1 H); 5.76 (*m*, 1 H); 5.91 (*m*, 1 H); 6.14 (*d*×*d*, $J = 10$ and 2, 1 H); 6.20 (*d*×*d*, $J = 10$ and 2.5, 1 H).

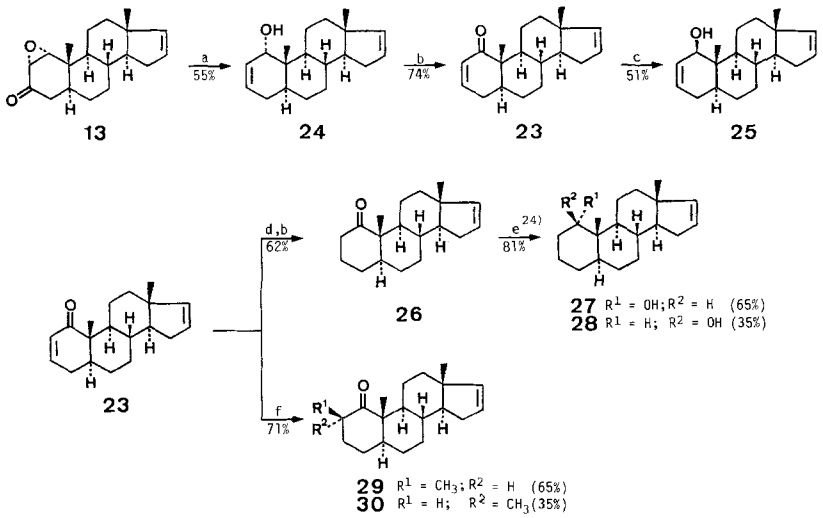
5α-Androsta-1,16-dien-3-one (**20**). 17β-Hydroxy-5α-androst-1-en-3-one (**V**) [49] was converted *via* the methyl carbonate **VI**[23]) into the ketone **20** in over 80% yield. An analytical sample of **20** was recrystallized from PE at 0°. M.p. 96–97°, $[\alpha]_D = +46.5°$ ($c = 1.31$). – IR. ($CDCl_3$): 1675*s*. – ^{1}H-NMR. (360 MHz): 0.80 (*s*, 3 H); 1.05 (*s*, 3 H); 5.71 (*m*, 1 H); 5.85 (*m*, 1 H); 5.86 (*d*, $J = 10$, 1 H); 7.16 (*d*, $J = 10$, 1 H).

Androsta-1,4,16-trien-3-one (**21**) [28]. To a solution of ketone **14** (540 mg, 2 mmol) in dry toluene (20 ml) was added 2,3-dichloro-5,6-dicyanobenzoquinone (1.36 g, 6 mmol) and the mixture was heated overnight at 80° under N_2. The mixture was diluted with ether, washed (diluted aq. NaOH and water), dried (Na_2SO_4) and evaporated. Sublimation (110°/0.5 Torr) of the residue gave 233 mg (43%) of **21**. The product was recrystallized twice from PE. M.p. 121–122°, $[\alpha]_D = \pm 0°$, $[\alpha]_{365} = -301.3°$ ($c = 1.5$) ([28]: m.p. 123–125°). – IR. ($CDCl_3$): 1660*s*, 1625*s*, 1610*s*. – ^{1}H-NMR. (360 MHz): 0.85 (*s*, 3 H); 1.27 (*s*, 3 H); 5.72 (*m*, 1 H); 5.86 (*m*, 1 H); 6.08 (*t*, $J = 1.5$, 1 H); 6.23 (*d*×*d*, $J = 10$ and 2, 1 H); 7.06 (*d*, $J = 10$, 1 H).

Androsta-1,4,6,16-tetraen-3-one (**22**) [28]. Prepared by oxidation of trienone **19** with 2,3-dichloro-5,6-dicyanobenzoquinone under the conditions described for **21**. Sublimation of the crude product at 120°/0.5 Torr gave **22** (25%) which was recrystallized from PE. M.p. 99.5–101°, $[\alpha]_D = +2.8°$ ($c = 1.4$) ([28]: m.p. 100.5–102° (from MeOH)). – IR. ($CDCl_3$): 1655*s*, 1630*m*, 1608*s*. – ^{1}H-NMR. (360 MHz): 0.87 (*s*, 3 H); 1.22 (*s*, 3 H); 5.75 (*m*, 1 H); 5.88 (*m*, 1 H); 6.00 (br. *s*, 1 H); 6.08 (*d*×*d*, $J = 10$ and 2, 1 H); 6.25 (*m*, 2 H); 7.06 (*d*, $J = 10$, 1 H).

Preparation of compounds *23–30*.

Scheme 8



Reagents: a) NH_2NH_2, H_2O/reflux/8 h; b) *Jones* reagent; c) $LiAlH_4$, ether/RT./1 h; d) Li(*sec*-butyl)$_3$BH, THF/−78°→RT.; e) Na, 1-propanol/reflux/1 h; f) Li(*sec*-butyl)$_3$BH, THF/−78°, then CH_3I/→RT.

[23]) *17β-Methoxycarbonyloxy-5α-androst-1-en-3-one* (**VI**). Prepared in 90% yield from hydroxy-ketone **V** [49] with methyl chloroformate in pyridine and recrystallized from ether. M.p. 189–192°, $[\alpha]_D = +42.5°$ ($c = 1.48$). – IR. ($CDCl_3$): 1740*s*, 1670*s*, 1270*s*. – ^{1}H-NMR. (60 MHz): 0.84 (*s*, 3 H); 1.00 (*s*, 3 H); 3.76 (*s*, 3 H); 4.53 (*m*, 1 H); 5.80 (*d*, $J = 10$, 1 H); 7.09 (*d*, $J = 10$, 1 H).

[24]) The reduction of **26** with $LiAlH_4$ in ether leads to a mixture (ratio 85:15) of the alcohols **27** and **28** (89% yield).

5α-Androst-2,16-dien-1-one (**23**). To a solution of the alcohol **24** (1.40 g, 5.13 mmol) in acetone (60 ml) at 0° was added dropwise standard *Jones* reagent and the mixture was stirred at 0° for 15 min. Workup (ether) gave an oil which was chromatographed on silica gel (100 g) with cyclohexane/ether 1:2. The product (1.03 g, 74%) was recrystallized from PE (– 10°). M.p. 69.5°, $[\alpha]_D = +178°$ ($c = 1.23$). – IR. ($CDCl_3$): 1670*s*, 1590*w*. – ^{1}H-NMR. (360 MHz): 0.79 (*s*, 3 H); 1.10 (*s*, 3 H); 5.69 (*m*, 1 H); 5.79 (*t* × *d*, $J = 1.3$ and 10, 1 H); 5.87 (*m*, 1 H); 6.64 (*t* × *d*, $J = 2.6$ and 10, 1 H).

5α-Androsta-2,16-dien-1α-ol (**24**). A suspension of the epoxy-ketone **13** (2.13 g, 7.46 mmol) in 60% aq. hydrazine (70 ml) was heated under reflux for 8 h while N_2 was bubbled through the mixture[25]). After workup (ether), the crude product (oil) was chromatographed on silica gel (200 g) with cyclohexane/ether 1:2 to give 1.12 g (55%) of pure **24**. A small sample was recrystallized from acetone/water (0°). M.p. 86–89°, $[\alpha]_D = +153.9°$ ($c = 1.2$). – IR. ($CDCl_3$): 3610*m*, 3450*w*, 1650*w*, 1590*w*. – ^{1}H-NMR. (360 MHz): 0.76 (*s*, 3 H); 0.78 (*s*, 3 H); 3.70 (br. *d*, $J = 4$, 1 H); 5.70 (*m*, 1 H); 5.84 (*m*, 3 H).

5α-Androsta-2,16-dien-1β-ol (**25**). The ketone **23** was reduced with $LiAlH_4$ in ether (1 h, RT.) to give a mixture of the alcohols **24** and **25** (ratio 39:61 by GC.) in 86% yield. The mixture was separated by chromatography on silica gel with PE/ethyl acetate 9:1. The equatorial alcohol **25** was eluted first and was recrystallized from MeOH. M.p. 87.5–90° (dec.), $[\alpha]_D = +32.6°$ ($c = 0.98$). – IR. ($CDCl_3$): 3620*m*, 1670*w*, 1595*w*. – ^{1}H-NMR. (360 MHz, $CDCl_3 + D_2O$): 0.77 (*s*, 3 H); 0.82 (*s*, 3 H); 3.98 (br. *s*, 1 H); 5.40 (*qa* × *d*, $J \approx 2$ and 10, 1 H); 5.71 (m, 1 H); 5.74 (*m*, 1 H); 5.85 (*m*, 1 H).

5α-Androst-16-en-1-one (**26**). To a stirred solution of ketone **23** (270 mg, 1 mmol) in THF (5 ml) at – 78°, under N_2, was added lithium tri(*sec*-butyl)hydridoborate (*Fluka pract.*, 1 ml of a 1 M solution in THF) and the mixture was allowed to warm to RT. After 1 h, the mixture was cooled to 0° and water (5 ml), 10% aq. NaOH-solution (7 ml), 35% aq. H_2O_2-solution (4.5 ml) were added in succession. After 30 min at RT. the product was extracted with cyclohexane, washed (water, aq. $NaHSO_3$-solution, sat. aq. NaCl-solution), dried (Na_2SO_4) and the solvent evaporated. The crude product (containing some alcohols) was oxidized with *Jones* reagent in acetone (0°) to give 263 mg of crude **26**. Column chromatography on silica gel (30 g) with toluene/ethyl acetate 9:1 gave 169 mg (62%) of pure **26**. M.p. 58.5–60° (from PE), $[\alpha]_D = +156.2°$ ($c = 1.05$). – IR. ($CDCl_3$): 1705*s*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.76 (*s*, 3 H); 1.19 (*s*, 3 H); 2.72 (*m*, 1 H); 5.69 (*m*, 1 H); 5.87 (*m*, 1 H).

5α-Androst-16-en-1α-ol (**27**) *and -1β-ol* (**28**)[24]. To a boiling solution of ketone **26** (217 mg, 0.79 mmol) in 1-propanol (100 ml), under N_2, was added with stirring sodium in small pieces (2 g, 87 mmol) during 45 min. The mixture was heated under reflux for 15 min. After workup (ether), the crude product was chromatographed on silica gel (20 g) with CH_2Cl_2/toluene 1:1 to give 175 mg (81%) of a mixture (ratio 65:35) of alcohols **27** and **28**. They were separated by three successive column chromatographies on silica gel (50 g, desactivated with 10% water) using CH_2Cl_2/cyclohexane 2:1. The equatorial alcohol **28** was eluted first.

Data of **27**. M.p. 109° (from PE), $[\alpha]_D = +32°$ ($c = 1.03$). – IR. ($CDCl_3$): 3630*m*, 3450*w* br., 1595*w*. – ^{1}H-NMR. (360 MHz, $CDCl_3 + D_2O$): 0.75 (*s*, 3 H); 0.82 (*s*, 3 H); 3.76 (*t*, $J = 2$, 1 H); 5.70 (*m*, 1 H); 5.82 (*m*, 1 H).

Data of **28**. M.p. 105–106° (from $MeOH/H_2O$), $[\alpha]_D = 0°$, $[\alpha]_{436}^{20} = -6.1°$ ($c = 0.82$); $[\alpha]_{365}^{20} = -24.4°$ ($c = 0.82$). – IR. ($CDCl_3$): 3620*w*, 1595*w*. – ^{1}H-NMR. (360 MHz, $CDCl_3 + D_2O$): 0.76 (*s*, 3 H); 0.82 (*s*, 3 H); 3.39 (*d* × *d*, $J = 11$ and 5, 1 H); 5.67 (*m*, 1 H); 5.82 (*m*, 1 H).

2β-Methyl- (**29**) *and 2α-methyl-5α-androst-16-en-1-one* (**30**). To a stirred solution of ketone **23** (239 mg, 0.88 mmol) in THF (5 ml) at – 78°, under N_2, was added lithium tri(*sec*-butyl)hydridoborate (*Fluka pract.*, 0.9 ml of a 1 M solution in THF). After 1 h, MeI (71.6 µl, 1.15 mmol) was added and the mixture was allowed to warm to RT. (1 h). Workup (ether) gave an oily residue which was chromatographed on silica gel (40 g) with toluene/ethyl acetate 9:1 to give a mixture of **29** and **30** (180 mg, 71%, ratio 24:76 by GC. on a 12 m capillary column *OV-101*). The mixture was partly separated by repeated chromatography on silica gel (desactivated with 5% H_2O) using toluene/CH_2Cl_2 4:1 → 1:1. **30** (eluted first) was obtained pure after two recrystallizations from MeOH, but **29** (*ca.* 90% pure) did not crystallize.

Data of **29**. $[\alpha]_D = -105°$ ($c = 0.6$). – IR. ($CDCl_3$): 1695*s*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.77 (*s*, 3 H); 0.96 (*d*, $J = 6.5$, 3 H); 1.03 (*s*, 3 H); 2.77 (*qa* × *d* × *d*, $J = 6.5$, 11.5 and 7, 1 H); 5.68 (*m*, 1 H); 5.84 (*m*, 1 H).

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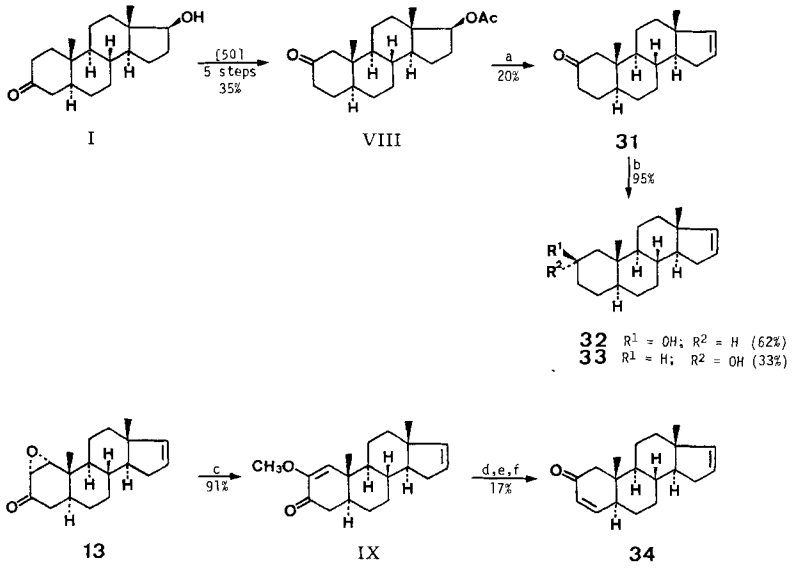
[25]) Traces of oxygen, probably by the formation of diimide, caused partial reduction of the double bond at C(16).

Data of **30**. M.p. 111–112.5°, $[\alpha]_D = +144°$ ($c = 1.02$). – IR. ($CDCl_3$): 1705*s*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.76 (*s*, 3 H); 0.93 (*d*, $J = 6.5$, 3 H); 1.17 (*s*, 3 H); 2.82 (*qa*×*d*×*d*, $J = 6$, 13 and 6.5, 1 H); 5.69 (*m*, 1 H); 5.87 (*m*, 1 H).

Preparation of compounds *31–34*.

Scheme 9



Reagents: a) 540°, glass column; b) $LiAlH_4$, ether; c) KOH, MeOH/reflux/24 h; d) NH_2NHTs, MeOH/reflux/4 h; e) MeLi, ether/reflux/1.5 h; f) HCl, acetone/RT./10 min.

5α-Androst-16-en-2-one (**31**). A solution of 17β-acetoxy-5α-androstan-2-one (**VIII**) [50] (12.0 g, 36.1 mmol) in toluene (25 ml) was pyrolyzed at 540°/70 Torr in a *Pyrex* tube (length 1 m, ID 15 mm, packed with quartz pieces) in an Ar-atmosphere. The pyrolysate (7.8 g) was chromatographed on silica gel (350 g) with CH_2Cl_2 and the homogenous fractions were recrystallized twice from MeOH to give 1.96 g of pure **31** (20%). M.p. 93–93.5°, $[\alpha]_D = +57.1°$ ($c = 1.0$). – IR. ($CHCl_3$): 1700*s*, 1580*w*. – ^{1}H-NMR. (90 MHz): 0.76 (*s*, 3 H); 0.80 (*s*, 3 H); 5.80 (*m*, 2 H).

5α-Androst-16-en-2β-ol (**32**) *and -2α-ol* (**33**). The ketone **31** was reduced with lithium aluminium hydride in ether (1 h, 20°) to give a mixture of the alcohols **32** and **33** (ratio 2:1), which were separated by chromatography on silica gel with CH_2Cl_2. The axial alcohol **32** was eluted first (yield 62%) and recrystallized from MeOH. M.p. 115–116.5°, $[\alpha]_D = +27.7°$ ($c = 1.0$). – IR. ($CHCl_3$): 3650*m*, 3500 br., 1585*w*. – ^{1}H-NMR. (90 MHz): 0.76 (*s*, 3 H); 1.07 (*s*, 3 H); 4.15 (*m*, $w_{1/2} \approx 10$, 1 H); 5.79 (*m*, 2 H).

The second fraction from the chromatography gave 33% of the equatorial alcohol **33** which was recrystallized from MeOH. M.p. 126–127°, $[\alpha]_D = +17.3°$ ($c = 1.0$). – IR. ($CHCl_3$): 3650*m*, 3500 br., 1585*w*. – ^{1}H-NMR. (90 MHz): 0.76 (*s*, 3 H); 0.83 (*s*, 3 H); 3.78 (*m*, $w_{1/2} \approx 28$, 1 H); 5.79 (*m*, 2 H).

5α-Androsta-3,16-dien-2-one (**34**). – *2-Methoxy-5α-androsta-1,16-dien-3-one* (**IX**). A solution of the epoxy-ketone **13** (825 mg, 2.9 mmol) in 1% *(w/v)* methanolic KOH (57 ml) was stirred under reflux for 24 h under N_2. The mixture was diluted with toluene, washed (sat. $NaHCO_3$- and sat. aq. NaCl-solution), dried (Na_2SO_4) and evaporated. The residue (900 mg) was chromatographed on silica gel (90 g) with cyclohexane/ethyl acetate 1:1 to give pure **IX** (800 mg, 91%). M.p. 86.5° (from ethyl acetate), $[\alpha]_D = +41.7°$ ($c = 0.91$). – IR. ($CDCl_3$): 1690*s*, 1620*s*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.80

(*s*, 3 H); 1.07 (*s*, 3 H); 2.32 (*d*×*d*, *J* = 18 and 4, 1 H); 2.47 (*d*×*d*, *J* = 18 and 14, 1 H); 3.58 (*s*, 3 H); 5.72 (*m*, 1 H); 5.87 (*m*, 1 H); 6.04 (*s*, 1 H).

A solution of **IX** (300 mg, 1 mmol) and tosylhydrazine (279 mg, 1.5 mmol) in MeOH (10 ml) under N_2 was heated at reflux for 4 h. The solvent was evaporated and the crude tosylhydrazone was dissolved in dry ether (20 ml). MeLi (2 ml of a 1.6 M solution in ether, 3.2 mmol) was added and the mixture was heated under reflux for 1.5 h. After workup (ether), the crude oily 2-methoxy-5α-androsta-1,3,16-triene (300 mg) was dissolved in acetone (3 ml) containing 3 drops of conc. aq. HCl. The mixture was stirred at RT. for 10 min and poured into cold sat. aq. $NaHCO_3$-solution. Workup (ether) gave an oil (250 mg) which was chromatographed on silica gel (25 g) with toluene/ethyl acetate 9:1. A crystalline homogenous fraction (47 mg, 17%) of **34** was obtained. M.p. 96–98° (from PE), $[\alpha]_D = +113°$ ($c = 0.77$). – IR. ($CDCl_3$): 1670*s*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.76 (*s*, 3 H); 0.92 (*s*, 3 H); 2.08 (*d*, *J* = 16, 1 H); 2.55 (*d*, *J* = 16, 1 H); 5.71 (*m*, 1 H); 5.86 (*m*, 1 H); 5.97 (*d*×*d*×*d*, *J* = 10, 3 and 1, 1 H); 6.58 (*d*×*d*, *J* = 10 and 2, 1 H).

Preparation of compounds *35–46* (see *Scheme 10*). – *5α-Androsta-2,16-dien-4-one* (**35**). – *4-Methoxy-androsta-4,16-dien-3-one* (**X**). A solution of the crude mixture of epoxy-ketones **11** and **12** (ratio *ca.* 1:6, 2.86 g, 10 mmol) and KOH (2.0 g, 36 mmol) in MeOH (200 ml) was heated under reflux in a N_2-atmosphere for 40 h. After usual workup (ether), the crude product was sublimed at 140°/0.5 Torr (24 h) to give 1.79 g (60%) of **X** as a yellowish solid. A small sample was recrystallized from MeOH and PE. M.p. 100–101.5°, $[\alpha]_D = +10.4°$ ($c = 1.48$). – IR. ($CDCl_3$): 1670*s*. – ^{1}H-NMR. (60 MHz): 0.80 (*s*, 3 H); 1.22 (*s*, 3 H); 3.58 (*s*, 3 H); 5.76 (*m*, 2 H).

3β-Hydroxy-5α-androst-16-en-4-one (**XI**). *Cf.* [42]. A solution of the methoxy-ketone **X** (1.77 g, 5.9 mmol) in ether (50 ml) was added at RT. to a slurry of $LiAlH_4$ (225 mg, 5.9 mmol) in ether (50 ml). After 30 min the mixture was cooled to 10° and acetone (100 ml) was added, followed by the addition of conc. HCl (3 ml). The mixture was stirred at RT. for 2 h and after workup with ether, the crude product (1.9 g) was chromatographed on silica gel (110 g) with toluene/ethyl acetate 2:1 to give 1.61 g (95%) of a mixture of two isomers (*ca.* 4:1 by GC.). The main product **XI** was obtained pure after two recrystallizations from PE. M.p. 139.5–141°, $[\alpha]_D = +16.9°$ ($c = 1.2$). – IR. ($CDCl_3$): 3500*m*, 1715*s*, 1595*w*. – ^{1}H-NMR. (360 MHz, $CDCl_3 + D_2O$): 0.76 (*s*, 3 H); 0.77 (*s*, 3 H); 4.11 (*d*×*d*, *J* = 11 and 8, 1 H); 5.72 (*m*, 1 H); 5.85 (*m*, 1 H).

The 5β-configuration is tentatively assigned (by NMR.) to the minor isomer of the above mixture.

A solution of PBr_3 (1.02 g, 3.8 mmol) in CCl_4 (20 ml) was added at RT. to a solution of the above 4:1-mixture of **XI** (1.03 g, 3.58 mmol) in CCl_4 (20 ml). After stirring for 3 h at RT., the mixture was diluted with ether, washed neutral ($NaHCO_3$- and sat. aq. NaCl-solution), dried (Na_2SO_4) and evaporated. The crude bromide (1.22 g, 97%) was dissolved in DMF (30 ml), LiBr (1.73 g, 20 mmol) and Li_2CO_3 (1.47 g, 20 mmol) were added, and the mixture was heated to reflux for 2 h. After workup (ether), the crude product was chromatographed on silicagel (90 g) with CH_2Cl_2 to give 598 mg (62%) of pure ketone **35**. M.p. 82–84° (from acetone/H_2O), $[\alpha]_D = +46°$ ($c = 1.41$). – IR. ($CDCl_3$): 1675*s*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.76 (*s*, 3 H); 0.89 (*s*, 3 H); 5.72 (*m*, 1 H); 5.86 (*m*, 1 H); 6.00 (*d*×*d*, *J* = 10 and 3, 1 H); 6.80 (*d*×*d*×*d*, *J* = 10, 6 and 2.5, 1 H).

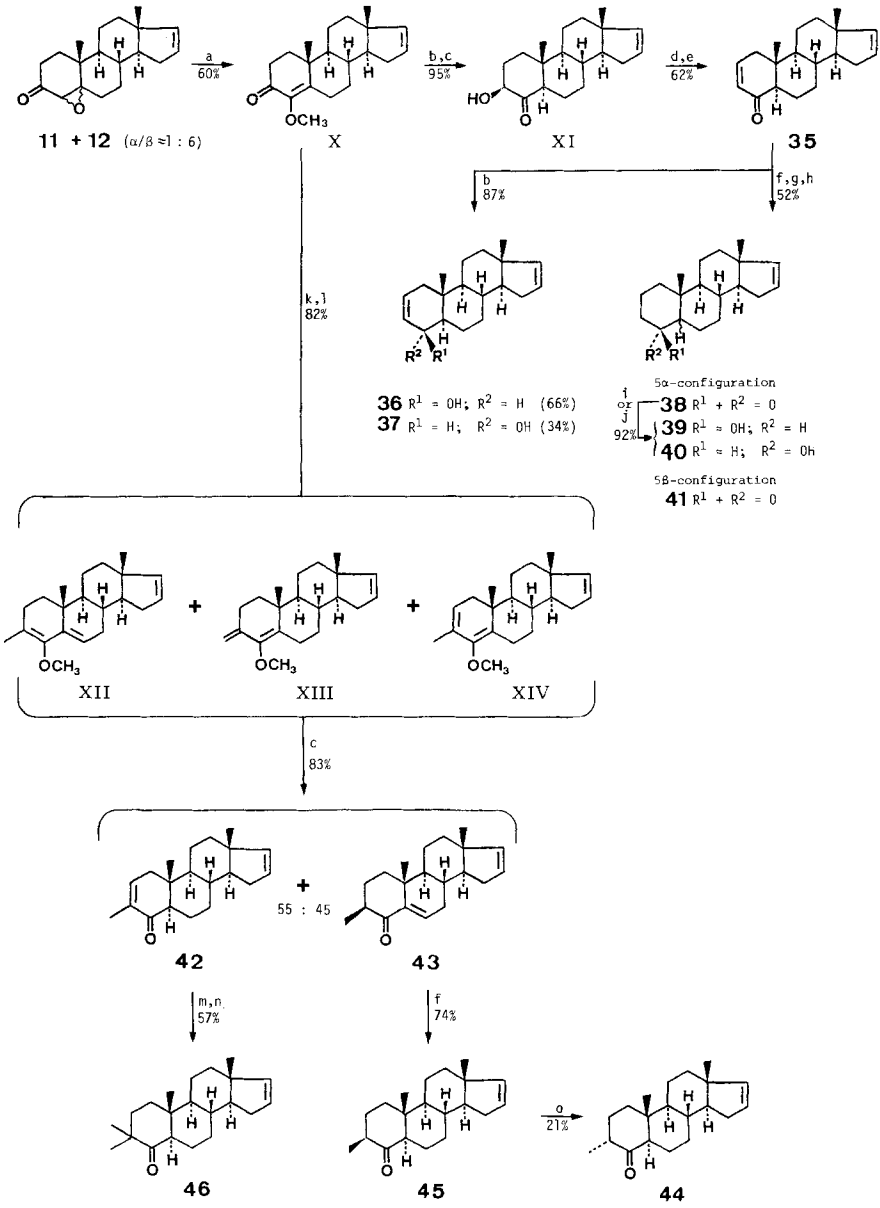
5α-Androsta-2,16-dien-4β-ol (**36**) *and -4α-ol* (**37**). Reduction of ketone **35** (220 mg) with $LiAlH_4$ in ether by the standard method gave a mixture of the alcohols **36** and **37** (ratio 66:34, yield 87%) which were separated on silica gel (50 g) with CH_2Cl_2/ethyl acetate 9:1. The axial alcohol **36** was eluted first.

Data of **36**. M.p. 99–100° (from PE), $[\alpha]_D = +138.7°$ ($c = 1.11$). – IR. ($CDCl_3$): 3630*m*, 1660*w*, 1595*w*. – ^{1}H-NMR. (360 MHz, $CDCl_3 + D_2O$): 0.76 (*s*, 3 H); 0.98 (*s*, 3 H); 3.96 (*m*, $w_{1/2} \approx 10$, 1 H); 5.71 (*m*, 1 H); 5.84 (*m*, 3 H).

Data of **37**. M.p. 118–120° (from PE), $[\alpha]_D = -4.5°$ ($c = 0.89$). – IR. ($CDCl_3$): 3600*m*, 3440*m* br., 1660*w*, 1595*w*. – ^{1}H-NMR. (360 MHz, $CDCl_3 + D_2O$): 0.76 (*s*, 3 H); 0.84 (*s*, 3 H); 3.79 (br. *d*, *J* = 6, 1 H); 5.70 (*m*, 3 H); 5.85 (*m*, 1 H).

5α-Androst-16-en-4-one (**38**) *and 5β-androst-16-en-4-one* (**41**). To a solution of Li (120 mg, 17 mmol) in liq. NH_3 (50 ml) at −34° was added a solution of **35** (300 mg, 1.1 mmol) and *t*-BuOH (90 mg, 1.2 mmol) in ether/THF (1:1, 10 ml) and the mixture was stirred for 1 h. After workup (ether), an oil (298 mg) was obtained which was directly oxidized in acetone solution (15 ml) at 0° with *Jones*

Scheme 10



Reagents: a) KOH, MeOH/65°/40 h; b) $LiAlH_4$, ether/RT./30 min; c) HCl, acetone/RT./2–3 h; d) PBr_3, CCl_4/RT./3 h; e) LiBr, Li_2CO_3, DMF/reflux/2 h; f) Li, liq. NH_3, *t*-BuOH, THF, ether; g) *Jones* reagent, acetone/0°/10 min; h) KOH, MeOH/65°/2 h; i) $NaBH_4$, THF, MeOH/RT./1 h; j) Na, 2-propanol/reflux/1 h; k) MeMgI, ether; l) $POCl_3$, pyridine/0°; m) LiB(*sec*-butyl)$_3$H, THF/−50°; n) MeI; o) hν (> 300 nm), ether/RT./2 h.

reagent (0.5 ml) for 10 min. After workup (ether), the crude product (280 mg) was heated to reflux with 0.4N methanolic KOH-solution (20 ml) for 2 h. The mixture was poured into sat. $NaHCO_3$-solution to give, after workup with ether, a mixture of **38** and **41** (268 mg, ratio 92:8 by GC.). Repeated chromatography on silica gel with toluene/ethyl acetate 19:1 and CH_2Cl_2 allowed the isomers to be separated (**41** was eluted first).

Data of **38**. M.p. 118–119° (from acetone/H_2O), $[\alpha]_D = +29.5°$ ($c = 1.12$). – IR. ($CDCl_3$): 3060*w*, 1710*s*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.76 (*s*, 3 H); 0.78 (*s*, 3 H); 5.71 (*m*, 1 H); 5.85 (*m*, 1 H).

Data of **41**. M.p. 116–117° (from acetone/H_2O), $[\alpha]_D = +21°$ ($c = 1.10$). – IR. ($CDCl_3$): 3060*w*, 1700*s*. – ^{1}H-NMR. (360 MHz): 0.75 (*s*, 3 H); 1.15 (*s*, 3 H); 5.67 (*m*, 1 H); 5.79 (*m*, 1 H).

5α-Androst-16-en-4β-ol (**39**). Reduction of the ketone **38** with $NaBH_4$ in THF/MeOH 9:1 by the standard procedure gave a mixture of the epimers **39** and **40** (ratio 95:5, 92% yield), which was separated by chromatography on silica gel with CH_2Cl_2/ethyl acetate 9:1. The main product **39** was recrystallized from acetone/water. M.p. 92–94°, $[\alpha]_D = +23.2°$ ($c = 0.82$). – IR. ($CDCl_3$): 3630*m*, 1595*w*. – ^{1}H-NMR. (360 MHz, $CDCl_3 + D_2O$): 0.75 (*s*, 3 H); 1.06 (*s*, 3 H); 3.81 (*m*, $w_{1/2} \approx 7$, 1 H); 5.70 (*m*, 1 H); 5.84 (*m*, 1 H).

5α-Androst-16-en-4α-ol (**40**). The ketone **38** was reduced with Na in 2-propanol as described for alcohol **27**. The mixture of **39** and **40** (ratio 1:9), yield 69%, was separated by chromatography as described for **39** and the main product **40** was recrystallized from acetone/water. M.p. 141–142°, $[\alpha]_D = -12.4°$ ($c = 1.13$). – IR. ($CDCl_3$): 3620*w*, 3450*w* br., 1595*w*. – ^{1}H-NMR. (360 MHz, $CDCl_3 + D_2O$): 0.75 (*s*, 3 H); 0.83 (*s*, 3 H); 3.45 (*t* × *d*, $J = 11$ and 4.5, 1 H); 5.70 (*m*, 1 H); 5.84 (*m*, 1 H).

5β-Androst-16-en-4-one (**41**). See the preparation of compound **38**.

3-Methyl-5α-androsta-2,16-dien-4-one (**42**) *and 3β-methylandrosta-5,16-dien-4-one* (**43**). A solution of the methoxy-ketone **X** (3.0 g, 10 mmol) in ether (30 ml) was added at RT. to a solution of methylmagnesium iodide (34 mmol, prepared from Mg (800 mg, 34 mmol) and MeI (2.2 ml, 35.5 mmol)) in ether (100 ml). The mixture was heated under reflux for 1 h, cooled (ice), hydrolyzed with NH_4Cl-solution and extracted with ether to give a mixture of epimeric 4-methoxy-3-methylandrosta-4,16-dien-3-ols (3.0 g, 95%, oil).

To a solution of the above crude alcohols (750 mg, 2.4 mmol) in pyridine (15 ml) at 0° under N_2 was slowly added phosphorus oxychloride (4.2 g, 27.5 mmol) and the mixture was stirred at RT. for 1 h. Workup (ether/water) gave a mixture of the enol ethers **XII**[26]), **XIII**, and **XIV** (ratio 32:44:24) (700 mg) which was dissolved in acetone (50 ml). Conc. aq. HCl (5 drops) was added and the solution was stirred at RT. for 3 h. After workup, the crude mixture of the α,β-unsaturated ketones **42** and **43** (ratio 55:45 by GC.) was separated by chromatography on silica gel with toluene. The first fraction (317 mg, 47%) was pure ketone **42** and was recrystallized from MeOH (−30°). M.p. 63–65°, $[\alpha]_D = +77.7°$ ($c = 1.35$). – IR. ($CDCl_3$): 1665*s*. – ^{1}H-NMR. (360 MHz): 0.76 (*s*, 3 H); 0.86 (*s*, 3 H); 1.76 (*t*, $J = 1.2$, 3 H); 5.71 (*m*, 1 H); 5.85 (*m*, 1 H); 6.53 (*m*, 1 H).

The second fraction (237 mg, 36%) was recrystallized from PE (−30°) to give pure ketone **43**. M.p. 92°, $[\alpha]_D = -53.3°$ ($c = 0.92$). – IR. ($CDCl_3$): 1680*s*, 1630*s*. – ^{1}H-NMR. (360 MHz): 0.80 (*s*, 3 H); 0.97 (*s*, 3 H); 1.11 (*d*, $J = 6$, 3 H); 5.73 (*m*, 1 H); 5.86 (*m*, 1 H); 6.29 (*d* × *d*, $J = 5$ and 2, 1 H).

3α-Methyl-5α-androst-16-en-4-one (**44**). A solution of the 3β-methyl ketone **45** (286 mg, 1 mmol) in ether (120 ml) was irradiated (*Pyrex* filter) with a medium-pressure Hg-lamp (125 W) at 20° for 2 h, while N_2 was bubbled through the solution. The solvent was distilled and the residue chromatographed on silica gel (60 g) with CH_2Cl_2. After a fraction containing starting material **45** (54 mg), a fraction (50 mg, 21% based on consumed **45**) was obtained which crystallized spontaneously. It was recrystallized from PE to give pure **44**. M.p. 119–120°, $[\alpha]_D = -18°$ ($c = 1.0$). – IR. ($CDCl_3$): 1710*s*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.76 (*s*, 3 H); 0.79 (*s*, 3 H); 1.21 (*d*, $J = 7$, 3 H); 2.36 (*d* × *d*, $J = 12$ and 4, 1 H); 2.48 (br. *qi*, $J \approx 7$, 1 H); 5.71 (*m*, 1 H); 5.85 (*m*, 1 H).

3β-Methyl-5α-androst-16-en-4-one (**45**). Li (240 mg, 34.6 mmol) was dissolved in liq. NH_3 (60 ml) at −34°. A solution of the ketone **43** (600 mg, 2.1 mmol) and *t*-BuOH (180 mg, 2.4 mmol) in THF/ether 1:1 (10 ml) was added and the mixture stirred at −34° for 1 h. Ammonium chloride (2 g) was added and the NH_3 evaporated. After workup (ether), the crude product (oil) was chromatographed on silica

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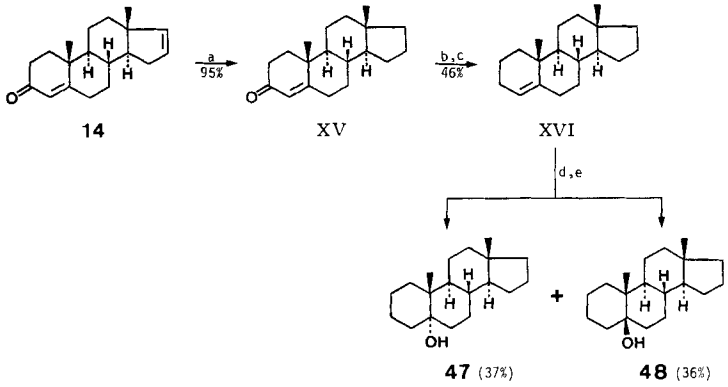
[26]) Enol ether **XII** was obtained as the main product in 60% yield if the crude 4-methoxy-3-methylandrosta-4,16-dien-3-ols were dehydrated with pyridinium *p*-toluenesulfonate in MeOH (1 h reflux). Hydrolysis of pure **XII** with aq. HCl-solution in acetone gave ketone **43** in 80% yield.

gel with toluene/ethyl acetate 19:1 to give 442 mg (74%) of pure ketone **45**. M.p. (from PE) 88–89.5°, $[\alpha]_D = +35.5°$ ($c = 1.41$). – IR. ($CDCl_3$): 1710*s*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.73 (*s*, 3 H); 0.76 (*s*, 3 H); 0.99 (*d*, $J = 6$, 3 H); 2.37 (*m*, 1 H); 5.70 (*m*, 1 H); 5.84 (*m*, 1 H).

3,3-Dimethyl-5α-androst-16-en-4-one (**46**). To a solution of ketone **42** (214 mg, 0.75 mmol) in THF (10 ml) at $-50°$ under N_2 was added a 1M solution of lithium tri(*sec*-butyl)hydridoborate in THF (1 ml, 1 mmol). After 1 h at $-50°$, MeI (228 mg, 1.6 mmol) was added and the mixture was allowed to reach RT. and stirred for 90 min. The mixture was diluted with PE (20 ml), cooled to $-30°$ and 10% aq. NaOH-solution (3.5 ml) was added, followed by 30% aq. H_2O_2-solution (2.5 ml). The two-phase system was vigorously stirred at RT. for 30 min. After workup (cyclohexane) the crude product was chromatographed on silica gel (50 g) with CH_2Cl_2 to give 129 mg (57%) of **46**. M.p. (from PE): 144–145.5°, $[\alpha]_D = -16.7°$ ($c = 1.20$). – IR. ($CDCl_3$): 1700*s*, 1595*w*. – ^{1}H-NMR. (360 MHz): 0.72 (*s*, 3 H); 0.75 (*s*, 3 H); 1.02 (*s*, 3 H); 1.18 (*s*, 3 H); 2.40 (*d* × *d*, $J = 12$ and 3.5, 1 H); 5.71 (*m*, 1 H); 5.85 (*m*, 1 H).

Preparation of compounds *47* and *48*.

Scheme 11



Reagents: a) $H_2/(Ph_3P)_3RhCl$, EtOH/RT./4 h; b) HS-CH_2CH_2-SH, AcOH, $BF_3 \cdot Et_2O$/RT./2 days; c) *Raney*-Ni, MeOH; d) *m*-Cl-$C_6H_4CO_3H$, $CHCl_3$/20°/1 h; e) $LiAlH_4$, dioxane/reflux/4 h.

Androst-4-en-3-one (**XV**). A solution of androsta-4,16-dien-3-one (**14**, 1.0 g) in EtOH (50 ml) was hydrogenated at RT. in the presence of chloro-*tris*(triphenylphosphine)rhodium (50 mg) until no more H_2 was absorbed (4 h). The solution was filtered through neutral alumina (30 g) and evaporated to give 1.0 g of ketone **XV**. $[\alpha]_D = +111.3°$ ($c = 6.9$). – IR. ($CDCl_3$): 1655*s*. – ^{1}H-NMR. (60 MHz): 0.77 (*s*, 3 H); 1.20 (*s*, 3 H); 5.7 (*s*, 1 H).

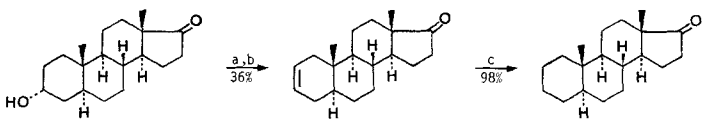
Androst-4-ene (**XVI**). To a solution of the ketone **XV** (3.0 g, 11 mmol) and 1,2-ethanedithiol (5 ml) in acetic acid (60 ml) at 60° was added boron trifluoride etherate (3 ml) and the solution was stirred for 2 days at RT. The solvent was distilled *in vacuo* and the residue dissolved in MeOH (50 ml). The solution was stirred with *Raney*-Ni (20 g) for 20 h, filtered, and concentrated. Chromatography of the residue on neutral alumina with PE gave 1.3 g (46%) of pure **XVI**. M.p. 49–54°, $[\alpha]_D = +68°$ ($c = 10$). – IR. ($CDCl_3$): 815*m*. – ^{1}H-NMR. (60 MHz): 0.72 (*s*, 3 H); 1.0 (*s*, 3 H); 5.27 (*m*, 1 H).

5α-Androstan-5-ol (**47**) *and 5β-androstan-5-ol* (**48**). A solution of 4-androstene (**XVI**, 258 mg, 1 mmol) and *m*-chloroperbenzoic acid (210 mg, 85%, *Aldrich*) in $CHCl_3$ (10 ml) was stirred at RT. for 1 h. The solution was washed with aq. $NaHCO_3$-solution and filtered through a small amount of silica gel. The crude mixture of epoxides (280 mg, ratio *ca.* 45:55 by GC.) and lithium aluminium hydride (100 mg) in dioxane (20 ml) was heated under reflux for 4 h. The mixture was cooled, poured on ice-cold aq. HCl and worked up with ether. The mixture of **47** and **48** was separated on silica gel with PE/ether 9:1. The first fraction (100 mg, 36%) was pure alcohol **48**. M.p. 76–78°, $[\alpha]_D = -10.6°$ ($c = 10$). – IR. (liq.): 3480. – ^{1}H-NMR. (60 MHz): 0.70 (*s*, 3 H); 0.97 (*s*, 3 H).

The second fraction (102 mg, 37%) was pure alcohol **47**. M.p. 60.5–62°, $[\alpha]_D = +11.03°$ ($c = 10$). – IR. (liq.): 3500*m*. – ^{1}H-NMR. (60 MHz): 0.70 (*s*, 3 H); 0.92 (*s*, 3 H).

Preparation of compounds *49* and *50*.

Scheme 12



XVII **49** **50**

Reagents: a) TsCl, pyridine; b) K-O-C$(CH_3)_3$, DMSO/20°/4 h; c) H_2, Pd/C, EtOH.

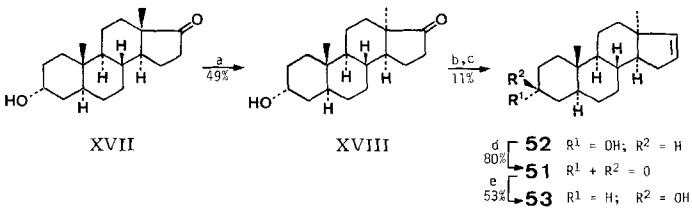
5α-Androst-2-en-17-one (**49**) [3]. 3α-Hydroxy-5α-androstan-17-one (**XVII**, androsterone, *Sigma Chem. Co.*) was converted into the *p*-toluenesulfonate [51] in 81% yield after recrystallization of the crude product from acetone/hexane. M.p. 153–153.5° (decomp.) ([51]: 149–150°), $[\alpha]_D = +59.3°$ ($c = 1.3$).

The *p*-toluenesulfonate (1.5 g, 3.38 mmol) was stirred at RT. with potassium *t*-butoxide (1.68 g, 15 mmol) in DMSO (30 ml) for 4 h. The mixture was diluted with water and extracted with ether. The crude product was chromatographed on alumina (50 g, activity II, neutral) with hexane/ether 1:1 to yield 407 mg (44.2%) of pure ketone **49**. M.p. (from EtOH/water) 99–101°, $[\alpha]_D = +142.1°$ ($c = 1.3$) ([3]: m.p. 104.5–105.5° (corr.); $[\alpha]_D = +146°$ (±9°) ($c = 0.4$, EtOH)). – IR. (KBr): 1740*s*, 1650*w*. – ^{1}H-NMR. (90 MHz): 0.82 (*s*, 3 H); 0.91 (*s*, 3 H); 5.65 (br. *s*, 2 H).

5α-Androstan-17-one (**50**). Catalytic hydrogenation of **49** over Pd/C (10%) in EtOH gave ketone **50** in quantitative yield. M.p. 116–116.5° (from aq. EtOH-solution), $[\alpha]_D = +94.1°$ ($c = 1.5$) ([52]: m.p. 119.5–120.5°, $[\alpha]_D^{16} = +87.8°$ ($c = 0.8$)). – IR. (KBr): 1740*s*. – ^{1}H-NMR. (90 MHz): 0.84 (*s*, 3 H); 0.89 (*s*, 3 H).

Preparation of compounds *51–53*.

Scheme 13



XVII XVIII **52** R^1 = OH; R^2 = H; **51** $R^1 + R^2$ = O; **53** R^1 = H; R^2 = OH

Reagents: a) *hν*, ether/9 h; b) NH_2NHTs, EtOH/reflux/18 h; c) CH_3Li, ether/RT./18 h; d) *Jones* reagent; e) $LiAlH_4$/ether.

3α-Hydroxy-5α,13α-androstan-17-one (**XVIII**) [53]. A solution of androsterone (**XVII**; 2.0 g, 6.8 mmol) in ether (300 ml) was irradiated (*Pyrex* filter) under a stream of N_2, with a 125-W medium-pressure Hg-lamp for 9 h. The mixture of **XVII** and **XVIII** (ratio *ca.* 3:2 by GC.) was separated by chromatography on silica gel (200 g) with ethyl acetate/cyclohexane 1:1. The first compound eluted was the 13α-ketone **XVIII** (990 mg, 49%). M.p. 156–157° (from ether/pentane), $[\alpha]_D = -100.2°$ ($c = 10.4$) ([53]: m.p. 145–146°, $[\alpha]_D^{22} = -99.7°$ ($c = 0.71$, EtOH)). – IR. ($CDCl_3$): 3640*w*, 3475*w*, 1730*s*. – ^{1}H-NMR. (60 MHz): 0.60 (*s*, 3 H); 0.96 (*s*, 3 H); 1.94 (*s*, 1 H, OH); 4.03 (*m*, 1 H).

The second compound eluted was starting material **XVII** (916 mg, 46%).

5α,13α-Androst-16-en-3-one (**51**). Oxidation of alcohol **52** with *Jones* reagent (acetone, 0°, 5 min) gave a crude product which was chromatographed on silica gel with ether/cyclohexane 1:1 to give pure ketone **51** in 80% yield. M.p. 120–122° (from PE), $[\alpha]_D = -86.8°$ ($c = 8.5$). – IR. ($CDCl_3$): 1700*s*. – ^{1}H-NMR. (60 MHz): 0.88 (*s*, 3 H); 0.91 (*s*, 3 H); 5.48 (*m*, 2 H).

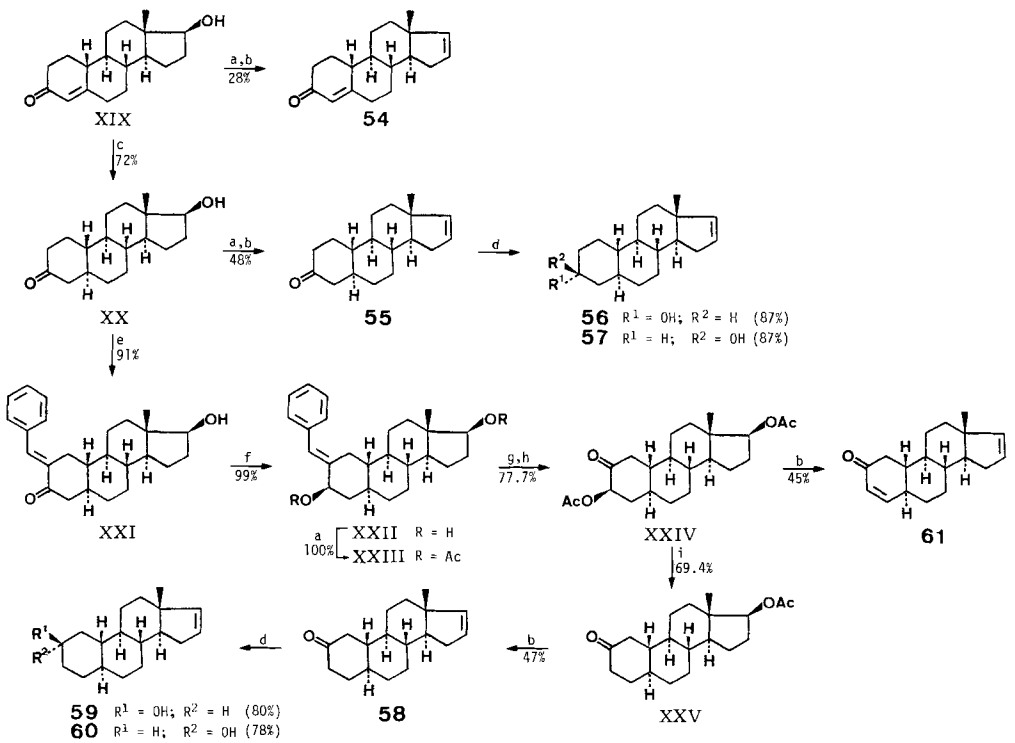
5α,13α-Androst-16-en-3α-ol (**52**). A mixture of the 13α-ketone **XVIII** (1.394 g, 4.8 mmol) and tosylhydrazine (890 mg, 4.8 mmol) in EtOH (40 ml) was heated under reflux for 18 h. The mixture was evaporated to dryness and chromatographed on silica gel (150 g) with ethyl acetate/cyclohexane 1:1. The first fraction was starting ketone **XVIII** (530 mg, 38%) and the second fraction was the desired

tosylhydrazone (657 mg, 30%). To a solution of this crude tosylhydrazone (630 mg, 1.37 mmol) in ether (50 ml) at 0° under N_2 was added dropwise MeLi (4 ml of a 1.6M solution in ether, 6.4 mmol). The mixture was stirred at RT. for 18 h. After workup (ether) the crude product was chromatographed on silica gel (40 g) with ethyl acetate/cyclohexane 1:1 to give 140 mg (37%) of alcohol **52**. M.p. 120–121° (from PE), $[\alpha]_D = -108.8°$ ($c = 7.43$). – IR. ($CDCl_3$): 3650*w*. – ^{1}H-NMR. (60 MHz): 0.63 (*s*, 3 H); 0.90 (*s*, 3 H); 4.03 (*m*, 1 H); 5.48 (*m*, 2 H).

5α,13α-Androst-16-en-3β-ol (**53**). Reduction of ketone **51** with $LiAlH_4$ in ether (RT., 1 h) gave a mixture of **52** and **53** (ratio 1:9) which was separated by chromatography on silica gel with ethyl acetate/cyclohexane 1:1. The pure equatorial alcohol **53** was obtained in 53% yield. M.p. 92–94° (from PE), $[\alpha]_D = -93.1°$ ($c = 1.15$). – IR. ($CDCl_3$): 3610*m*, 3430*w*. – ^{1}H-NMR. (60 MHz): 0.68 (*s*, 3 H); 0.91 (*s*, 3 H); 3.60 (*m*, 1 H); 5.48 (*m*, 2 H).

Preparation of compounds *54–61*.

Scheme 14



Reagents: a) Ac_2O, pyridine; b) 540°; c) Li, NH_3; d) LiB(*sec*-butyl)$_3$H, THF/0°/1 h or $LiAlH_4$, ether; e) PhCHO, KOH, EtOH/RT./3 days; f) $NaBH_4$, THF, MeOH/RT./3 h; g) O_3, AcOEt, MeOH/–78°; h) Zn, AcOH/30°/40 min; i) Zn, AcOH/reflux/2 h.

Estra-4,16-dien-3-one (**54**) [27]. 19-Nortestosterone (**XIX**) *(Chemical Dynamics Corp.)* was converted into the known acetate [54] with acetanhydride and pyridine. A solution of this acetate (4.8 g, 15.17 mmol) in toluene (10 ml) was pyrolyzed at 540° (200 Torr, slow N_2-stream) in a glass tube packed with quartz pieces. Chromatography of the crude pyrolysate (3.1 g) on silica gel (150 g) with CH_2Cl_2 gave 1.1 g (28%) of the homogenous oily ketone **54**; $[\alpha]_D = +57.9°$ ($c = 1$) ([27]: m.p. 71–73°). – IR. ($CHCl_3$): 1660*s*, 1615*m*, 1585*w*. – ^{1}H-NMR. (90 MHz): 0.84 (*s*, 3 H); 5.82 (*m*, 2 H); 5.87 (br. *s*, 1 H).

5α-Estr-16-en-3-one (**55**). A solution of 17β-acetoxy-5α-estran-3-one [55] (8.0 g, 25.1 mmol) in octane/acetone 10:1 (22 ml) was pyrolyzed at 550° (200 Torr, slow N_2-stream). Chromatography of the

crude product (5.4 g) on silica gel (600 g) with CH_2Cl_2 and recrystallization of the homogenous fractions from PE gave 3.13 g (48.3%) of the pure ketone **55**. M.p. 51–54°, $[\alpha]_D = +72.8°$ ($c = 1.0$). – IR. ($CHCl_3$): 1705*s*, 1585*w*. – ^{1}H-NMR. (90 MHz): 0.79 (*s*, 3 H); 5.71 (*m*, 1 H); 5.87 (*m*, 1 H).

5α-Estr-16-en-3α-ol (**56**). L-Selectride (lithium tri(*sec*-butyl)hydridoborate, 4 ml of a 1M solution in THF, 4 mmol) was added dropwise at 0° to a solution of ketone **55** (800 mg, 3.10 mmol) in dry ether (5 ml). After stirring for 1 h at 0°, water was added (10 ml). The boranes were oxidized by adding 10% aq. NaOH-solution (5 ml), followed by 30% aq. H_2O_2-solution (3 ml) and stirring for 3 h at RT. After workup (ether), the crude product (790 mg, *ca.* 9:1 mixture of **56** and **57**) was chromatographed on silica gel with CH_2Cl_2 to give 700 mg (87%) of pure alcohol **56**. M.p. 119–120° → 123–124° (from PE), $[\alpha]_D = +40.6°$ ($c = 1.0$). – IR. ($CHCl_3$): 3640*m*, 3500 br., 1585*w*. – ^{1}H-NMR. (90 MHz): 0.78 (*s*, 3 H); 4.09 (*m*, $w_{1/2} \approx 8$, 1 H); 5.71 (*m*, 1 H); 5.87 (*m*, 1 H).

5α-Estr-16-en-3β-ol (**57**). A solution of the ketone **55** (800 mg, 3.10 mmol) in dry ether (5 ml) was added dropwise at RT. to a slurry of $LiAlH_4$ (38 mg, 1 mmol) in ether (3 ml). After 1 h, the mixture was hydrolyzed with 10% aq. H_2SO_4. After workup (ether), the crude product (802 mg, 9:1-mixture of **57** and **56**) was chromatographed on silica gel with CH_2Cl_2. A small fraction of **56** (70 mg) was eluted first, followed by the main fraction of **57** (705 mg, 87%). M.p. 113–115°, $[\alpha]_D = +36.3°$ ($c = 1.0$). – IR. ($CHCl_3$): 3640*m*, 3500 br., 1585*w*. – ^{1}H-NMR. (90 MHz): 0.78 (*s*, 3 H); 3.60 (*m*, $w_{1/2} \approx 20$, 1 H); 5.71 (*m*, 1 H); 5.87 (*m*, 1 H).

5α-Estr-16-en-2-one (**58**). – *2-Benzylidene-17β-hydroxy-5α-estran-3-one* (**XXI**). *Cf.* [50]. A solution of 17β-hydroxy-5α-estran-3-one (**XX**, 15.4 g, 55.8 mmol) [56], benzaldehyde[27]) (15.4 g, 145 mmol) and KOH (3.2 g, 56.9 mmol) in EtOH/water 95:5 (450 ml) was stirred in the dark for 3 days at 20°. The crystals were filtered, washed with EtOH, and dried in vacuum. Yield 18.5 g (91.1%). M.p. 214–217° (dec.) (from CH_2Cl_2/EtOH), $[\alpha]_D = -36.9°$ ($c = 1$). – IR. ($CHCl_3$): 3640 br., 1675*s*, 1595*s*, 1570*m*. – ^{1}H-NMR. (90 MHz): 0.76 (*s*, 3 H); 2.66 (*d*×*d*, $J = 17$ and 3.5, 1 H); 3.36 (*d*×*d*, $J = 16$ and 4, 1 H); 3.69 (br. *t*, $J = 8$, 1 H); 7.42 (*m*, 6 H).

2-Benzylidene-5α-estrane-3β,17β-diol (**XXII**). *Cf.* [50]. A solution of the hydroxy-ketone **XXI** (18.9 g, 51.9 mmol) in THF/MeOH 3:1 (600 ml) was stirred with $NaBH_4$ (1.3 g, 34.3 mmol) at 20° for 3 h. The bulk of the solvents was distilled and replaced by ether. The solution was washed with water, dried (Na_2SO_4) and evaporated to give 18.8 g (99%) of the crude diol **XXII**. A small sample was recrystallized from acetone/hexane. M.p. 110–114° → 168–169°, $[\alpha]_D = +95.4°$ ($c = 1$). – IR. ($CHCl_3$): 3640*m*, 3500 br., 1600*w*. – ^{1}H-NMR. (90 MHz): 0.76 (*s*, 3 H); 3.23 (*d*×*d*, $J = 13$ and *ca.* 2, 1 H); 3.64 (br. *t*, $J = 8$, 1 H); 4.22 (*m*, $w_{1/2} \approx 18$, 1 H); 6.60 (br. *s*, 1 H); 7.28 (*m*, 5 H).

3β,17β-Diacetoxy-2-benzylidene-5α-estrane (**XXIII**). *Cf.* [50]. The crude diol **XXII** (18.6 g, 50.8 mmol) was dissolved in a (1:1)-mixture of acetic anhydride/pyridine (400 ml) and left overnight at 20°. Evaporation of the reagents gave the solid crude acetate in quantitative yield. A small sample was recrystallized from MeOH. M.p. 154–155°, $[\alpha]_D = +44.4°$ ($c = 1$). – IR. ($CHCl_3$): 1725*s*, 1250*s*. – ^{1}H-NMR. (90 MHz): 0.80 (*s*, 3 H); 2.06 and 2.19 (2×*s*, 6 H); 3.23 (br. *d*, $J \approx 14$, 1 H); 4.60 (br. *t*, $J \approx 8$, 1 H); 5.38 (*m*, 1 H); 6.40 (br. *s*, 1 H); 7.29 (*m*, 5 H).

3β,17β-Diacetoxy-5α-estran-2-one (**XXIV**). *Cf.* [50]. A solution of the crude diacetate **XXIII** (22.6 g, 50.2 mmol) in MeOH/ethyl acetate 8:3 was ozonized at −78° until a blue color persisted (1 h). Ar was passed through the solution for 20 min, acetic acid (150 ml) was added and the solution was warmed to +30°. Zinc dust (80 g) was added within 20 min to the stirred solution which was maintained at 30–35° by cooling. After 20 min, the solution was filtered, the filtrate evaporated and the residue treated with CH_2Cl_2/water. The org. phase was washed with aq. $NaHCO_3$-solution, dried (Na_2SO_4) and evaporated. Recrystallization of the residue from acetone/pentane afforded 14.7 g (77.7%) of pure ketodiester **XXIV**. M.p. 194.5–195.5°, $[\alpha]_D = +62.7°$ ($c = 1.0$). – IR. ($CHCl_3$): 1720*s*, 1700 S, 1245*s*. – ^{1}H-NMR. (90 MHz): 0.80 (*s*, 3 H); 2.04 and 2.16 (2×*s*, 6 H); 2.72 (*d*×*d*, $J = 13$ and 3.5, 1 H); 4.62 (*d*×*d*, $J = 9$ and 7, 1 H); 5.23 (*d*×*d*, $J = 12$ and 7, 1 H).

17β-Acetoxy-5α-estran-2-one (**XXV**). *Cf.* [50]. Zinc dust (150 g) was added to a stirred solution of the diacetate **XXIV** (15.5 g, 41.2 mmol) in glacial acetic acid (600 ml) at RT., and the mixture was boiled under reflux for 2 h. The mixture was filtered, the zinc washed with acetone, and the combined filtrates evaporated in vacuum. The residue was taken up in ether (500 ml) and washed with 10% aq.

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[27]) When 4-methoxybenzaldehyde (*cf.* [50]) was employed, the corresponding 2-(4-methoxybenzylidene)-derivative of **XX** did not crystallize from the reaction mixture.

HCl, aq. $NaHCO_3$-solution and water. The crude product (15.0 g) was recrystallized from ether/PE to give 9.1 g (69.4%) of keto-acetate **XXV**. M.p. 133–135°, $[\alpha]_D = +29.4°$ ($c = 0.9$). – IR. ($CHCl_3$): 1720 S, 1710*s*, 1255*s*. – ^{1}H-NMR. (90 MHz): 0.80 (*s*, 3 H); 2.04 (*s*, 3 H); 2.59 (br. *d*, $J \approx 15$, 1 H); 4.61 (*d*×*d*, $J = 8$ and 7, 1 H).

A solution of the acetate **XXV** (14.3 g, 44.9 mmol) in toluene (20 ml) was pyrolyzed at 540° and 200 Torr. Chromatography of the crude pyrolysate on silica gel with CH_2Cl_2 gave 5.5 g (47%) of pure ketone **58**. M.p. 79–80° (from PE), $[\alpha]_D = +73.5°$ ($c = 1.0$). – IR. ($CHCl_3$): 1700*s*, 1585*w*. – ^{1}H-NMR. (90 MHz): 0.76 (*s*, 3 H); 2.60 (br. *d*, $J \approx 14$, 1 H); 5.71 (*m*, 1 H); 5.87 (*m*, 1 H).

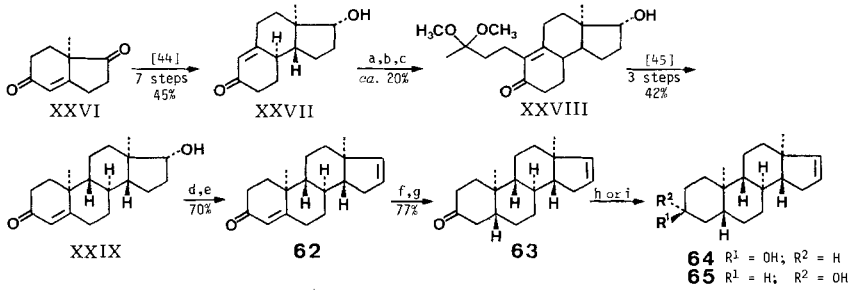
5α-Estr-16-en-2β-ol (**59**). The ketone **58** (1.0 g, 3.87 mmol) was reduced with L-Selectride as described for **56**. The crude product contained *ca.* 85% of the axial alcohol **59** and was chromatographed on silica gel (150 g) with CH_2Cl_2 to give 802 mg (80%) of pure alcohol **59**. M.p. 109–110° (from PE), $[\alpha]_D = +45.7°$ ($c = 1.0$). – IR. ($CHCl_3$): 3650*m*, 3500 br., 1585*w*. – ^{1}H-NMR. (90 MHz): 0.78 (*s*, 3 H); 4.16 (*m*, $w_{1/2} \approx 7$, 1 H); 5.71 (*m*, 1 H); 5.87 (*m*, 1 H).

5α-Estr-16-en-2α-ol (**60**). The ketone **58** (600 mg, 2.33 mmol) was reduced with $LiAlH_4$ in ether as described for **57**. After chromatography of the crude product (600 mg, **60**/**59** ≈ 95:5) on silica gel with CH_2Cl_2, the pure equatorial alcohol **60** (470 mg, 78%) was obtained. M.p. 125–126° (from PE), $[\alpha]_D = +47.3°$ ($c = 1.0$). – IR. ($CHCl_3$): 3640*m*, 3500 br., 1585*w*. – ^{1}H-NMR. (90 MHz): 0.78 (*s*, 3 H); 3.60 (br. *m*, $w_{1/2} \approx 20$, 1 H); 5.71 (*m*, 1 H); 5.87 (*m*, 1 H).

5α-Estra-3,16-dien-2-one (**61**). Pyrolysis of the diacetate **XXIV** under conditions described for **58** gave the unsaturated ketone **61** in 45% yield. M.p. 139–140° (from MeOH), $[\alpha]_D = +112.9°$ ($c = 0.8$). – IR. ($CHCl_3$): 1665*s*, 1640 S, 1585*w*. – ^{1}H-NMR. (90 MHz): 0.76 (*s*, 3 H); 2.71 (*d*×*d*, $J = 16$ and 3, 1 H); 5.71 (*m*, 1 H); 5.87 (*m*, partly overlapping, 1 H); 5.97 (*d*×*d*, partly overlapping, $J = 10$ and 2, 1 H); 6.76 (*d*×*d*, $J = 10$ and *ca.* 1, 1 H).

Preparation of compounds *62–65*.

Scheme 15



Reagents: a) 1,3-dichloro-2-butene, *t*-BuOK, DME/0°/20 h; b) conc. H_2SO_4, CH_2Cl_2/−15°/30 min; c) $HC(OCH_3)_3$, MeOH, *p*-TsOH, RT./4 h; d) $ClCOOCH_3$, pyridine/0°/24 h; e) 480°, 10 m glass column; f) Li, NH_3 liq., *t*-BuOH; g) *Jones* reagent; h) $LiB[CH(CH_3)CH(CH_3)_2]_3H$, THF/−55°; i) $NaBH_4$, THF, MeOH/25°.

(6R)-6-Methyl-bicyclo[4.3.0]non-1-ene-3,7-dione (**XXVI**). *Cf.* [43]. The optically pure diketone **XXVI** was prepared following [43b] using (*R*)-proline instead of (*S*)-proline. The product was recrystallized several times from ether until the m.p. and $[\alpha]_D$ value were constant. M.p. 65.8–66.8°, $[\alpha]_D = -370°$ ($c = 1.5$, benzene) ([43b]: m.p. 66–66.5°, $[\alpha]_D = +367°$ ($c = 1.0$, benzene) for the enantiomer of **XXVI**).

ent-*Des-A-17β-hydroxyestr-9-en-5-one* (**XXVII**). *Cf.* [44]. This compound was synthesized in 7 steps, starting from **XXVI** following the method described for the enantiomer [44]. M.p. 108–111° (from acetone), $[\alpha]_D = +39.5°$ ($c = 10$) ([44]: m.p. 113–114°, $[\alpha]_D^{23} = -44.5°$ ($c = 1.0$) for the enantiomer).

ent-*Testosterone* (**XXIX**). *Cf.* [45]. The optically pure ketone **XXVII** was converted to the ketal **XXVIII** by a standard sequence (*cf.* [44]). The crude ketal, by a known method [45], was transformed to crude **XXIX** ($[\alpha]_D = -115°$) which showed the same spectra (^{1}H-NMR., IR.) as testosterone (**III**) ($[\alpha]_D = +125°$).

ent-*Androsta-4,16-dien-3-one* (**62**). The crude *ent*-testosterone **XXIX** (2.2 g, 7.63 mmol) was converted into the corresponding methyl carbonate (2.6 g, 98%)[22]) which was pyrolyzed as described for **1**. The crude product (1.6 g) was chromatographed on silica gel (430 g) with PE → ether to give 1.5 g (70%) of slightly impure **62**. Recrystallization (5 times) from ether/pentane gave 320 mg of pure, odorless **62**. M.p. 130–132°, $[\alpha]_D = -125°$ ($c = 3.5$) ([3]: m.p. 131.5–133.5° (hexane), $[\alpha]_D^{16} = +123 \pm 3.5°$ ($c = 1.03$) for the enantiomer **13**). The spectral data (IR., ^{1}H-NMR.) were identical with those of **13**.

Evaporation of the combined mother-liquors gave slightly impure **62** (1.1 g) which was used for the next step.

ent-5α-*Androst-16-en-3-one* (**63**). To a stirred solution of Li (60 mg, 8.65 mmol) in dry liq. NH_3 (100 ml) at −34° was added dropwise a solution of the α,β-unsaturated ketone **62** (202 mg, 0.748 mmol) and *t*-BuOH (70 mg, 0.946 mmol) in THF/ether (1:1, 5 ml). The mixture was stirred at −34° for 1 h and MeOH was slowly added until the blue color disappeared. Another portion of Li was added (60 mg) and the blue solution was stirred for 1 h. NH_4Cl was added to discharge the blue color, the NH_3 was allowed to evaporate and the mixture was dissolved in ether/water. The org. phase was washed neutral, and the solvant evaporated. The crude product (200 mg, mainly alcohols **64** and **65**) was dissolved in acetone (10 ml) and oxidized with standard *Jones* reagent (1.4 ml). After workup (ether), the product was chromatographed on silica gel with cyclohexane/ethyl acetate 4:1 to give 182 mg (77%) of almost pure **63**. Recrystallization from pentane gave 112 mg odorless **63**. M.p. 140–141°, $[\alpha]_D = -38.5°$ ($c = 1.0$) ([2]: m.p. 140–141°, $[\alpha]_D^{17} = +38°$ ($c = 2.08$) for the enantiomer **1**). – Same spectra as **1**.

ent-5α-*Androst-16-en-3α-ol* (**64**). The axial alcohol **64** was obtained from **63** by the method described for the enantiomer **2**. M.p. 131–132.5° (from pentane), $[\alpha]_D = -14.8°$ ($c = 0.2$) ([2]: m.p. 143.5–144°, $[\alpha]_D^{16} = +13.9°$ ($c = 0.94$) for **2**). – Same spectra as **2**.

ent-5α-*Androst-16-en-3β-ol* (**65**). The equatorial alcohol **65** was prepared from **63** by the method described for the enantiomer **3**. M.p. 118–119° (from pentane), $[\alpha]_D = -12.6°$ ($c = 1.1$) ([2]: m.p. 125–127°, $[\alpha]_D^{17} = +11.2°$ ($c = 0.76$) for **3**). – Same spectra as **3**.

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