

STUDIES IN THE CHEMISTRY OF MEDICINALLY ACTIVE  
STEROIDS: 1,2-CARBONYL TRANSPOSITION IN  
RING-A

by

TALAL HASAN ZEGLAM

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Talal Hasan Zeglam

A thesis submitted to the Faculty of Graduate Studies of  
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## ABSTRACT

1,2-Transposition of ketones in ring-A of the steroid molecule is an important synthetic conversion for the study of metabolism and for the synthesis of steroid derivatives. C-2 and C-4 ketones were required for the identification of metabolites and for use as synthetic intermediates affecting androgenic/anabolic activity.

Vinyl chlorides are shown to be valuable synthetic intermediates in the 1,2-transformation of ketones. In this study the transposition of a steroid C-3 ketone to the C-2 position was carried out through the 2-chloro-2-olefin in which several steps can be combined to give good overall yields. The vinyl chloride can be hydrolysed efficiently to the C-2 ketone with concentrated sulfuric acid. The C-3 ketone was obtained by the thermal rearrangement of the 4-chloro-4,5-epoxides which underwent stereospecific rearrangements. The mechanism of the thermal rearrangement of chloroepoxides is discussed. In addition a synthesis of the diosphenol, 4-androsten-3-one-4,17 $\beta$ -diol 17-acetate, through a novel thermal rearrangement of 3 $\beta$ -hydroxy-4-chloro-4,5-epoxide is described.

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## INTRODUCTION

The transfer of a carbonyl function to an adjacent methylene group, referred to as 1,2-carbonyl transposition, has been the subject of considerable interest in organic synthesis (Scheme 1).

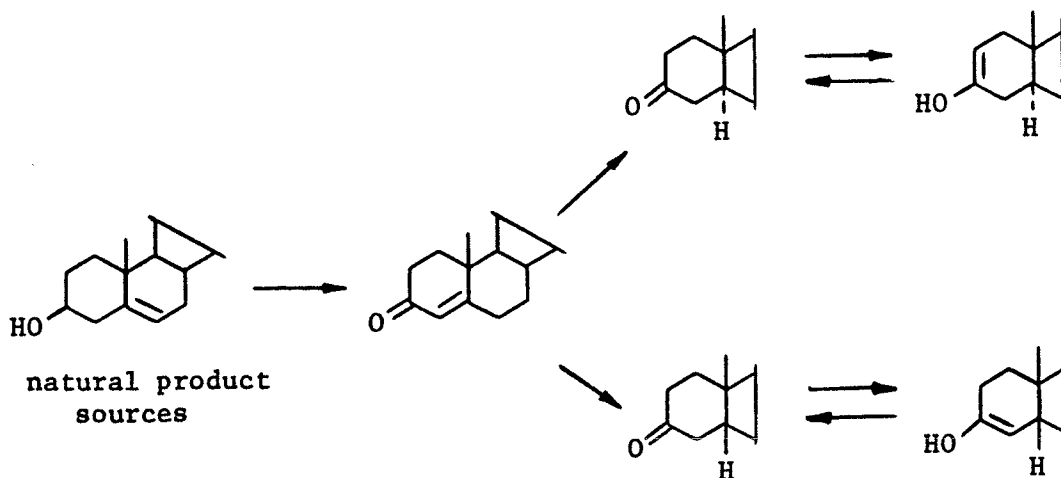


Scheme 1.

This transposition requires a reaction sequence of several steps and efficient conversions with a minimum number of steps is desirable. As the final isomeric product rather than the intermediates is required reaction sequences which can be carried out without isolation of intermediates are useful in minimizing time and maximizing yields. Many synthetic methods have been developed to carry out this transposition and they have been summarized in recent reviews (1-4). The carbonyl group, in its various forms is the most important functional unit in organic synthetic reactions because of its ability to undergo a wide variety of bond forming reactions both at the carbonyl carbon and adjacent sites influenced by its polarity. The carbonyl group acts as a direct electrophilic site for the attack of nucleophiles in the formation of carbon-carbon or carbon-heteroatom bonds. It also plays a role in the formation of enols and enolates which are most useful intermediates in organic synthesis and their nucleophilic properties are extensively used in the formation of carbon-carbon bonds in a number of fundamental reactions.



Alteration of the functional groups in the steroid A-ring has been the subject of extensive studies directed towards the alteration of the biological activities of natural steroid hormones and a number of methods have been developed for the transposition of a steroid C-3 ketone to the C-2 or C-4 position. Transposition of the C-3 ketone to the C-2 position in the  $5\alpha$ -series and in the  $5\beta$ -series gives two possible derivatives each with particular synthetic difficulties. Application of these methods is often dependent on the nature of the functional groups at the C-17 position which may require protection. 1,2-Carbonyl transpositions in the steroid A-ring are limited by the available starting materials which are mainly from plant sources. The most commonly obtainable commercially available starting materials are the steroid 4-en-3-one and the C-3 keto- $5\alpha$ -steroid. The C-3 keto- $5\beta$ -steroid can be readily prepared by hydrogenation of the 4-en-3-one over palladium on  $\text{CaCO}_3$  in pyridine (5) (Scheme 2).



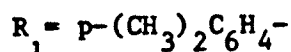
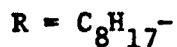
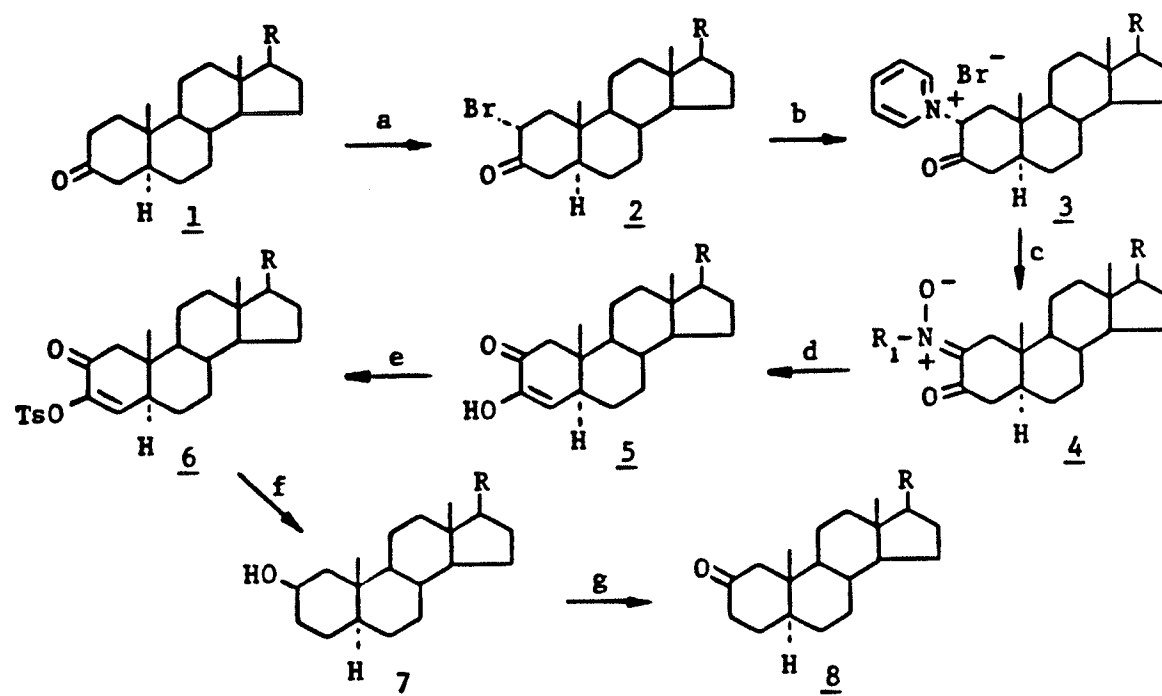
Scheme 2.

A significant property of the saturated steroid C-3 ketone is that in the  $5\alpha$ -series enolization takes place almost exclusively towards the C-2 position (6) and most synthetic methods take advantage of this

property. In the  $5\beta$ -series enolization is towards the C-4 position (7). Most syntheses of the C-4 ketone take advantage of the double bond at C-4 of the unsaturated ketone for functionalization or alternatively the enolization towards C-4 in the  $5\beta$  compounds. The following sections review the methods which have been applied to these transpositions.

#### C-2 to C-3 Steroid Ketone Transposition.

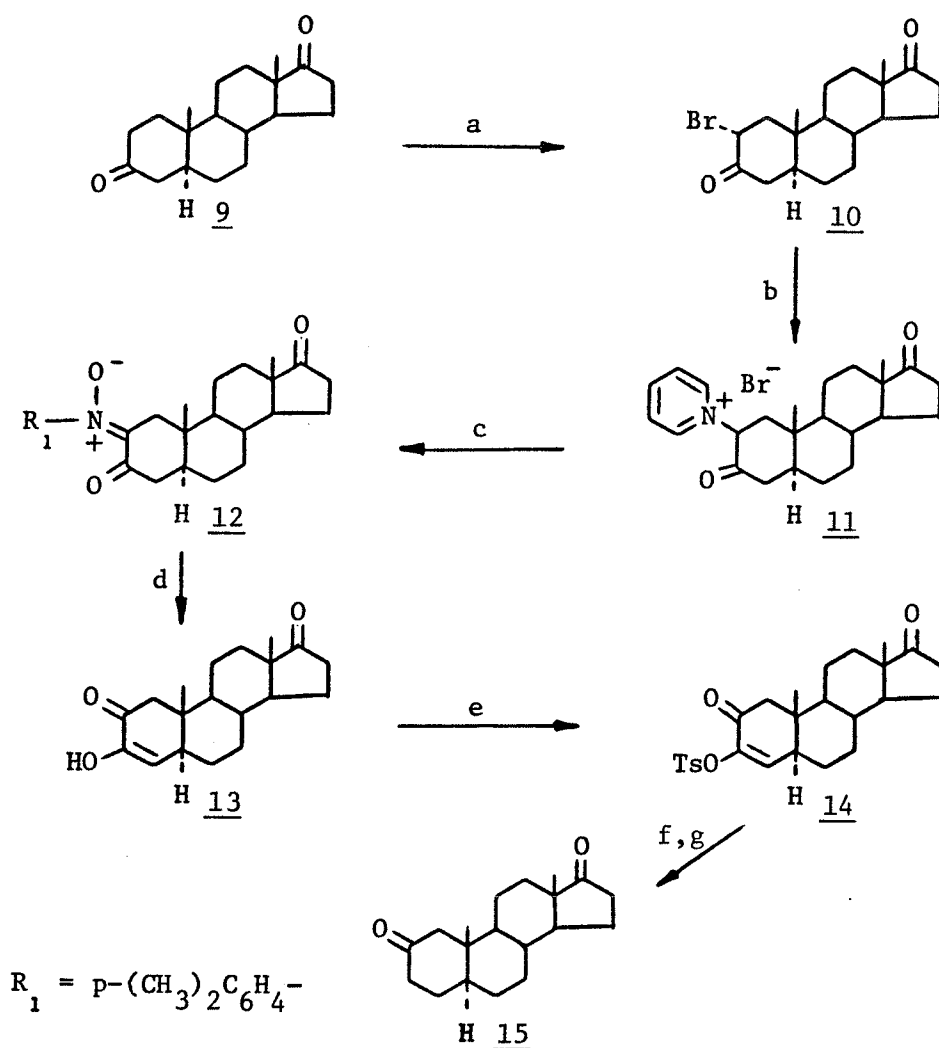
Ruzicka et al. (8) in 1944 developed the first method for the conversion of  $5\alpha$ -cholestan-3-one (1) to  $5\alpha$ -cholestan-2-one (8) (Scheme 3). Bromination of  $5\alpha$ -cholestan-3-one (1) with bromine in acetic acid gave the bromoketone (2), which was converted to its pyridinium salt (3) by heating with pyridine.



Reagents: a)  $Br_2/HOAc$ ; b)  $C_5H_5N$ ; c)  $p-(CH_3)_2C_6H_4NO/CHCl_3/NaOH/EtOH$ ; d) dilute  $HCl$ ; e)  $TsCl/C_5H_5N$ ; f) Raney  $Ni$ ; g)  $CrO_3$

Scheme 3.

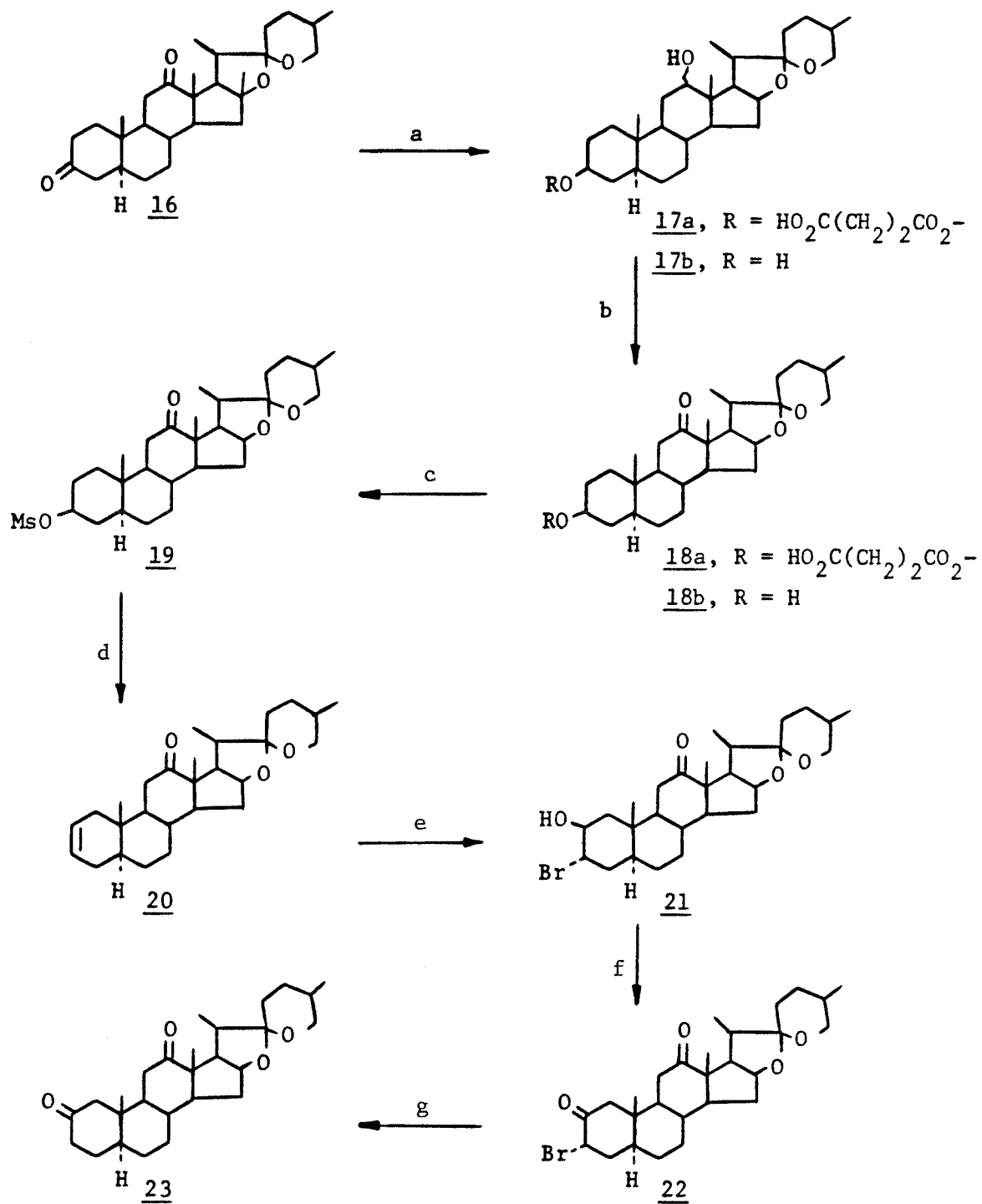
Treatment of 3 with p-nitrosodimethylaniline gave the nitronne (4) which on hydrolysis with dilute hydrochloric acid gave 5 $\alpha$ -cholest-3-en-2-on-3-ol (5). Conversion of 5 to its enol tosylate (6) and subsequent Raney nickel reduction gave the C-2 alcohol (7) which followed by chromium oxidation of the crude product furnished 5 $\alpha$ -cholestan-2-one (8). Djerassi *et al.* (9) used the same sequence described by Ruzicka to prepare 5 $\alpha$ -androstane-2,17-dione (15) from 5 $\alpha$ -androstane-3,17-dione (9) (Scheme 4).



Scheme 4.

Selective bromination of 5 $\alpha$ -androsterone-3,17-dione (9) gave the 2 $\alpha$ -bromo derivative 10 which was reacted as before through 11, 12, 13, 14, to give 5 $\alpha$ -androsterone-2,17-dione (15) although here the overall yield was much lower than that previously obtained in the 5 $\alpha$ -cholestane series.

Another synthesis of the C-2 ketone was reported by Slates and Wendler (10) for the conversion of 22a,5 $\alpha$ -spirosterone-3,12-dione (16) to 22a,5 $\alpha$ -spirosterone-2,12-dione (23) (Scheme 5). The presence of the C-12 ketone required protection which was achieved by reduction to the alcohol (17b), selective acetylation at C-3 (17a) followed by oxidation (18a) and hydrolysis (18b). The 3 $\beta$ -sulfonate ester (19) of the alcohol (18b) was subjected to elimination which gave as the major product the C-2 olefin (20). Addition of hypobromous acid to the C-2 olefin followed by oxidation of the resulting bromohydrin (21) gave the bromoketone (22) which was converted to 22a,5 $\alpha$ -spirosterone-2,12-dione (23) by treatment with zinc and acetic acid. The drawback in this method arises from the non-selectivity in the elimination of the 3 $\beta$ -sulfonate ester (19) where even though the C-2 olefin (20) is the predominant product some C-3 olefin is formed. The purification of this mixture is difficult resulting in a low overall yield. The formation of the C-2 olefin (20) as the major product of elimination has been explained on the basis of its greater stability based on heats of hydrogenation studies (11) and as observed in the enolization of the C-3 keto-5 $\alpha$ -steroids to the C-2 enol (6). 5 $\alpha$ -Androsterone-2-one was prepared from the C-3 ketone by a similar method using the 3 $\beta$ -tosylate which has the same disadvantage as the mesylate (19) (Scheme 4) (12-14). The principle intermediate in these syntheses is the C-2 olefin which in the

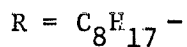
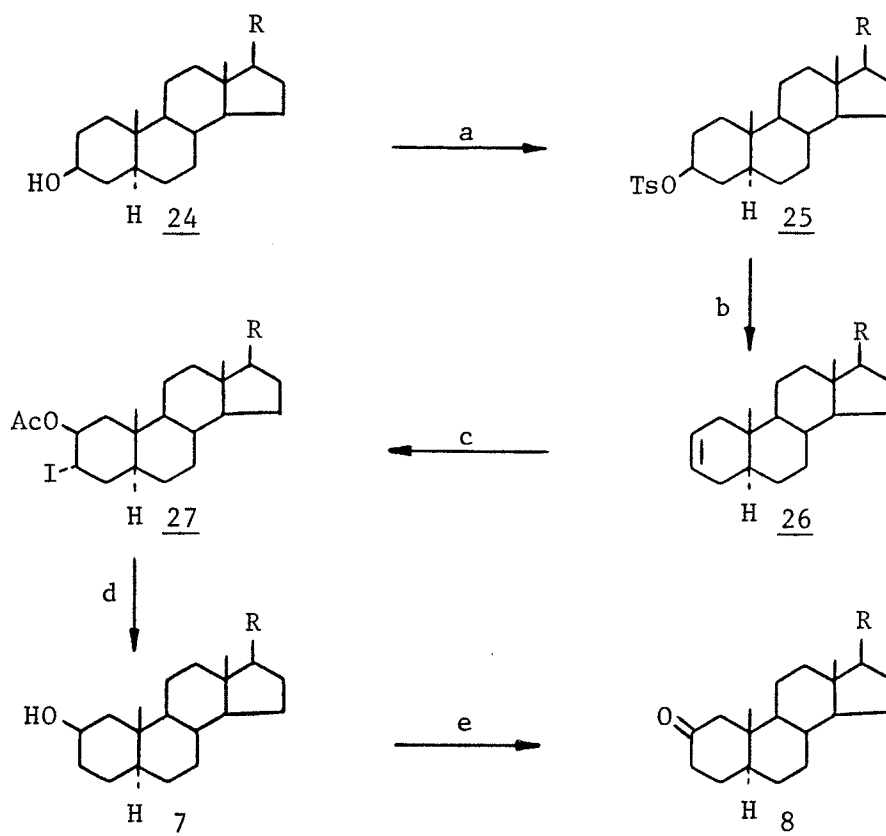


Reagents: a)  $\text{LiAlH}_4/\text{THF}$ ; b)  $(\text{CH}_2\text{CO})_2\text{O}/\text{C}_5\text{H}_5\text{N}$ ;  $\text{CrO}_3/\text{HOAc}$ ;  
 $\text{OH}^-$ ; c)  $\text{MsCl}/\text{C}_5\text{H}_5\text{N}$ ; d)  $\text{NaI}/\text{acetone}$ ; e)  $\text{HOBr}$ ;  
 f)  $\text{CrO}_3/\text{HOAc}$ ; g)  $\text{Zn}/\text{HOAc}$ .

Scheme 5.

synthesis of the analogous C-17 $\beta$ -acetate and benzoate derivatives (12) was prepared either by elimination of the C-3 chloro derivative (which also give some C-3 olefin) or more specifically by bromination of the C-3 ketone, reduction with sodium borohydride to the epimeric alcohols and elimination with zinc in acetic acid (15).

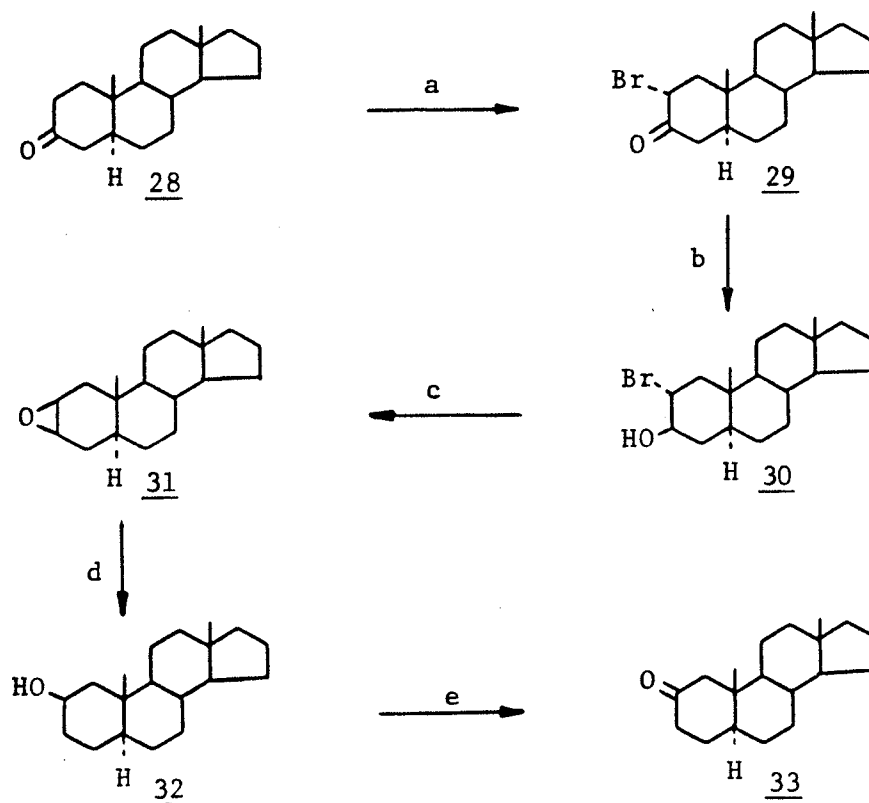
A related synthesis (16) is shown in Scheme 6 where the 3 $\beta$  alcohol (24) is tosylated (25) to give the C-2 olefin (26). Iodoacetate addition to the C-2 olefin (26) gave 27 which was followed by reduction



Reagents: a)  $TsCl/C_5H_5N$ ; b)  $Al_2O_3$  Grade 1; c)  $I_2/KIO_3/HOAc$ ; d)  $LiAlH_4/ether$ ; e) Jones [O].

Scheme 6.

to the 2 $\beta$ -alcohol (7) and oxidation to the C-2 ketone (8). In Scheme 5 formation of the bromohydrin (21) is also not completely regioselective. A third synthesis of steroid C-2 ketones was developed (17) (Scheme 7) which avoids the lack of regioselectivity in elimination of the 3 $\beta$ -tosylate ester (25) (Scheme 6) to form the C-2 olefin.



Reagents: a) Br<sub>2</sub>/HOAc; b) LiAl(t-BuO)<sub>3</sub>H/THF; c) KOH/MeOH; d) LiAlH<sub>4</sub>/ether; e) 8N chromic acid.

Scheme 7.

5 $\alpha$ -Androstan-3-one (28) on bromination gave 2 $\alpha$ -bromo-5 $\alpha$ -androstan-3-one (29) which was reduced with lithium tri-*t*-butoxyaluminum hydride and the resulting 2 $\alpha$ -bromo-5 $\alpha$ -androstan-3 $\beta$ -ol (30) was treated with potassium hydroxide in methanol resulting in the formation of the 2 $\beta$ ,3 $\beta$ -epoxide (31) which with lithium aluminum hydride yielded 5 $\alpha$ -androstan-2 $\beta$ -ol

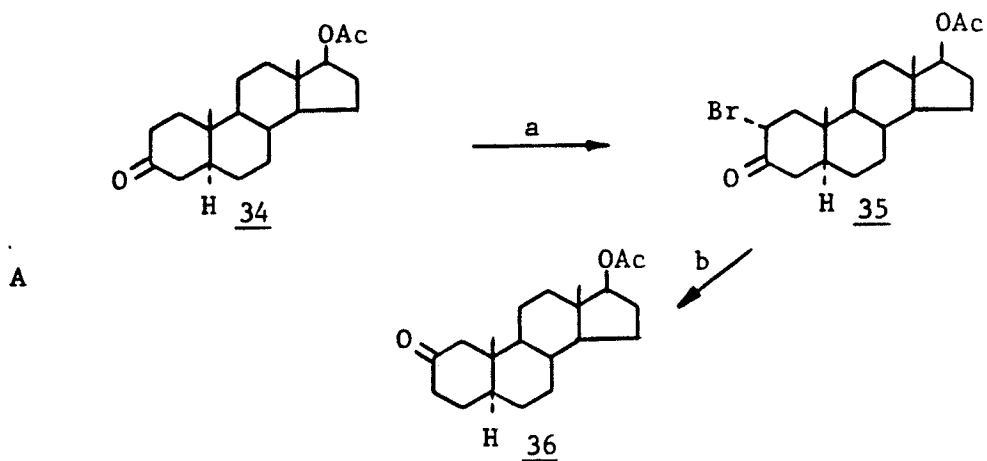
(32). Jones oxidation of 32 afforded 5 $\alpha$ -androstan-2-one (33). Although this procedure removes the problem associated with the sulfonate ester, the reduction of 2 $\alpha$ -bromo-5-androstan-3-one (29) with lithium tri-*t*-butoxyaluminum hydride gave a mixture of the 3 $\alpha$ - and 3 $\beta$ -alcohols, nevertheless, these were not separated but treated with potassium hydroxide in methanol to give predominantly the 2 $\beta$ ,3 $\beta$ -epoxide (31). The overall yield of 5 $\alpha$ -androstan-2-one (33) from 5 $\alpha$ -androstan-3-one (28) was rather low (20%).

Two similar syntheses of the C-2 ketone were reported in the 5 $\alpha$ -cholestan-3-one series (18,19). The only difference in these two syntheses from that shown in Scheme 7 was the method of epoxide ring opening to give C-3 substituted derivatives, namely 5 $\alpha$ -cholestan-2-on-3 $\beta$ -ol acetate (18) and 3 $\beta$ -methyl-5 $\alpha$ -cholestan-2-one (19).

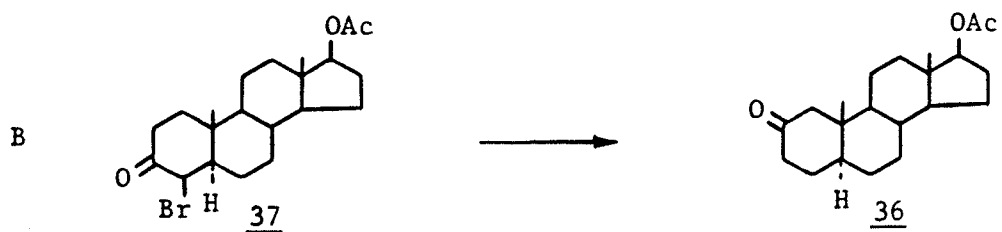
Bromination of 5 $\alpha$ -androstan-3-on-17 $\beta$ -ol acetate (34) (Scheme 8A) gave the bromoketone (35) which has been reported (20) to react with *n*-propyl mercaptan on refluxing to produce 5 $\alpha$ -androstan-2-on-17 $\beta$ -ol acetate (36). A multistep rearrangement has been postulated for the formation of this product (36) in 41% yield which was separated from the C-3 ketone also formed in 49% yield by the selective formation of the C-3 bisulfite addition product.

Reaction with *n*-propyl mercaptan also produced 5 $\alpha$ -androstan-2-on-17 $\beta$ -ol acetate (36) from 4 $\alpha$ -bromo-5 $\alpha$ -androstan-3-on-17 $\beta$ -ol acetate (37) (Scheme 8B) but the yield was only 12% (21).





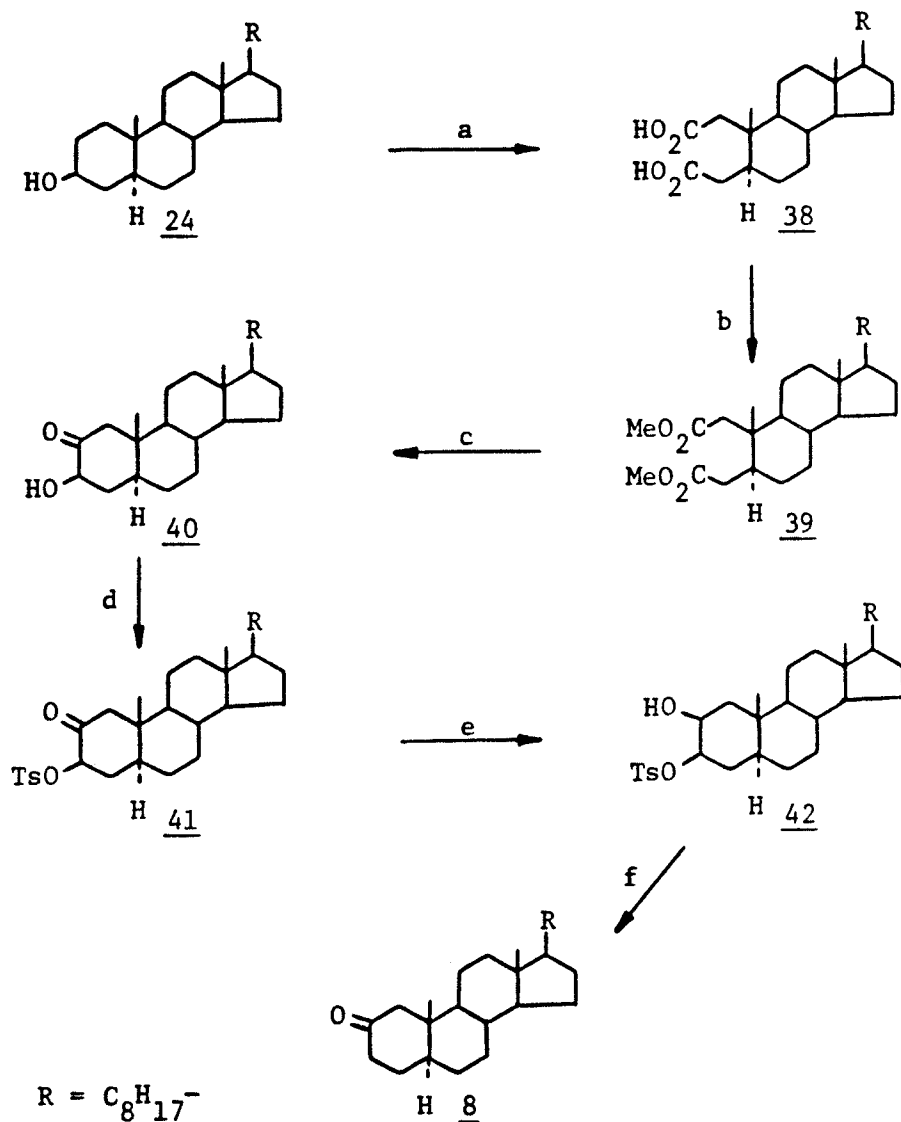
Reagents: a)  $\text{Br}_2/\text{HOAc}$ ; b)  $n\text{-PrSH}, \text{Ac}_2\text{O}/\text{C}_5\text{H}_5\text{N}$ .



Reagent:  $n\text{-PrSH}, \text{Ac}_2\text{O}/\text{C}_5\text{H}_5\text{N}$ .

Scheme 8 A & B.

Another approach for C-3 to C-2 ketone transposition was reported by Sheehan and Erman (22) as shown in Scheme 9.

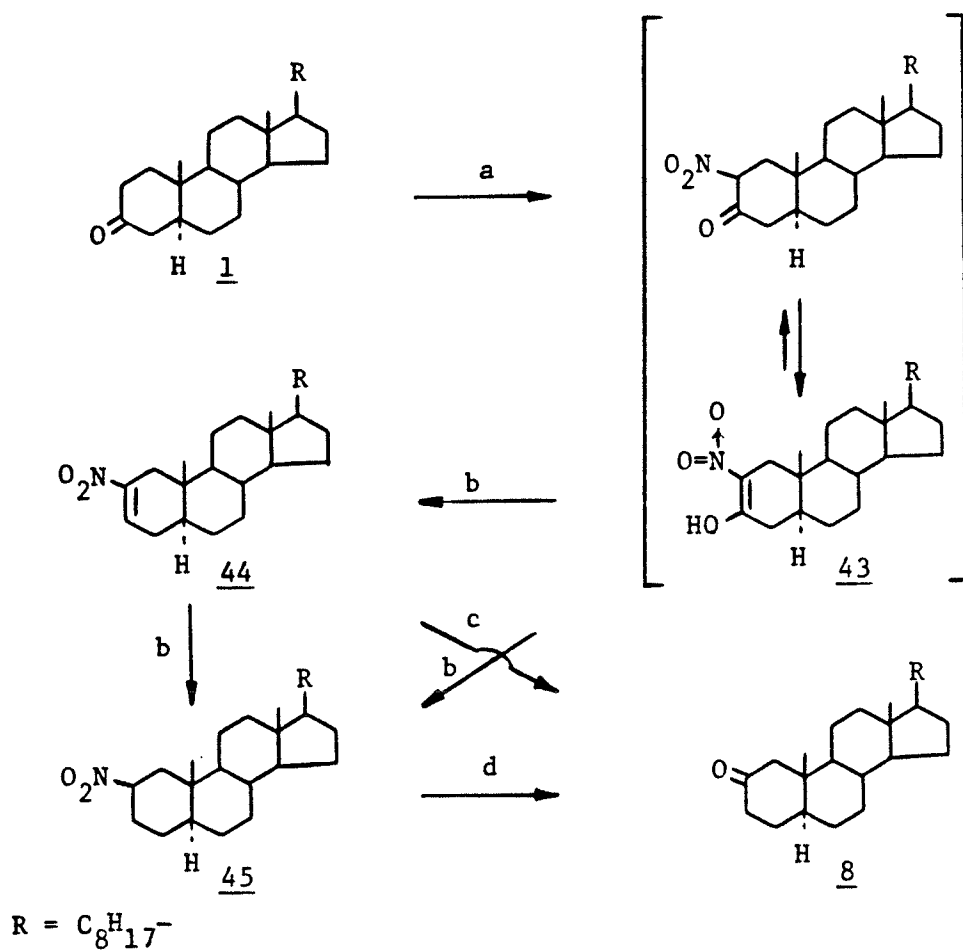


Reagents: a)  $\text{CrO}_3/\text{HOAc}$ ; b)  $\text{CH}_2\text{N}_2$ ; c)  $\text{Na}/\text{NH}_3/\text{ether}$ ,  $\text{H}_3\text{O}^+$ ; d)  $\text{TsCl}/\text{C}_5\text{H}_5\text{N}$ ; e)  $\text{NaBH}_4/\text{MeOH}$ ; f) collidine.

Scheme 9.

Starting from 5 $\alpha$ -cholestan-3 $\beta$ -ol (24) oxidation with chromium oxide in acetic acid afforded 2,3-secocholestane-2,3-dioic acid (38) and this was treated with diazomethane to give 2,3-secocholestane-2,3-dioic acid dimethyl ester (39). Acyloin condensation using sodium metal in liquid ammonia afforded a mixture from which 5 $\alpha$ -cholestan-2-on-3 $\beta$ -ol (40) was isolated by chromatography. Formation of the tosylate ester (41), subsequent reduction with sodium borohydride (42) and treatment with collidine gave 5 $\alpha$ -cholestan-2-one (8). The ketone is apparently formed by initial elimination of p-toluene sulfonic acid to give the C-2 enol. Although the overall yield was 41%, this method employed rather extreme conditions of oxidative cleavage and reductive recyclization which limits its use in the presence of other functional groups sensitive to oxidation, reduction or strong base treatment.

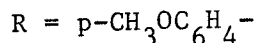
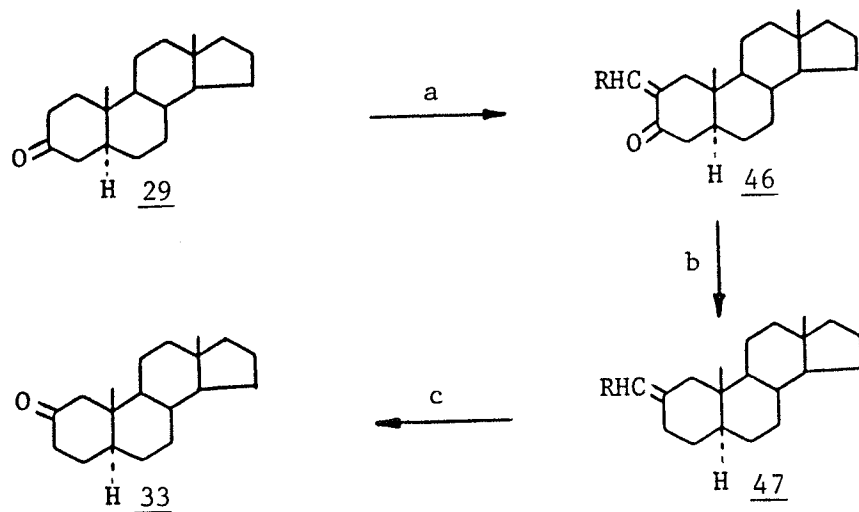
Transposition of a C-3 ketone to C-2 via the 2-nitroketone (43) was investigated with 5 $\alpha$ -cholestan-3-one (4) by Hassner *et al.* (23) (Scheme 10). The method involved nitration of 5 $\alpha$ -cholestan-3-one (1) with an alkyl nitrate in the presence of potassium t-butoxide which gave regiospecific nitration to form 2-nitro-5 $\alpha$ -cholestan-3-one (43). This compound exists predominantly in the highly hydrogen-bonded enol form (43). Sodium borohydride reduction of 43 led to 2-nitro-5 $\alpha$ -cholest-2-ene (44) in low yield (2 $\alpha$ -nitrocholestan-3 $\beta$ -ol was a major by-product). 2-Nitro-5 $\alpha$ -cholest-2-ene (44) was converted to 5 $\alpha$ -cholestan-2-one either in one step by reaction with zinc and acetic acid or in two steps by sodium borohydride reduction followed by alkaline hydrolysis of 45.



Reagents: a)  $t\text{-BuONO}_2/t\text{-BuOK}$ ; b)  $\text{NaBH}_4/\text{ether}$ ; c)  $\text{Zn}/\text{HOAc}$ ; d)  $\text{KOH}/\text{EtOH}, \text{HCl}$ .

Scheme 10.

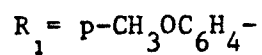
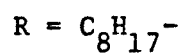
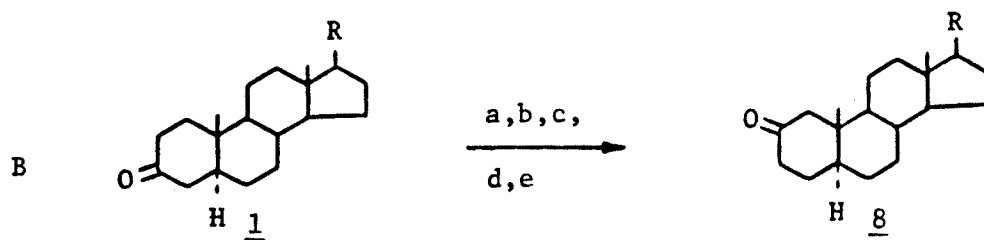
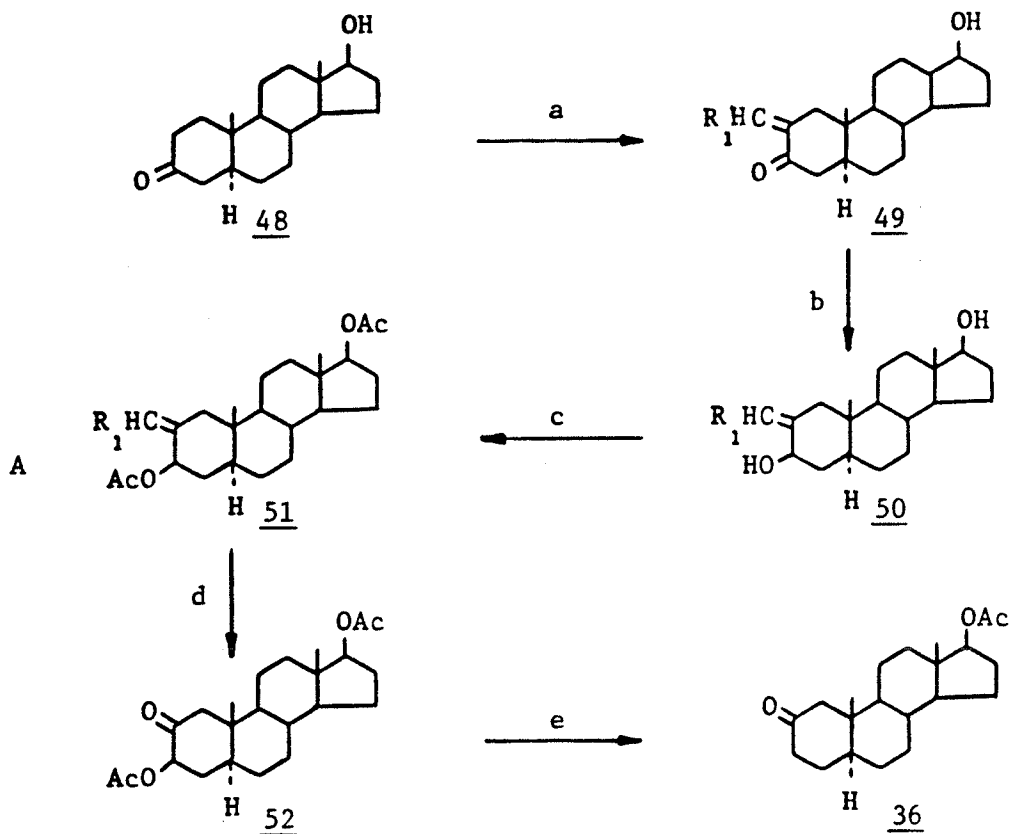
In 1967 Fetizon *et al.* (24) prepared 5 $\alpha$ -androstan-2-one (33) (Scheme 11) in a three steps synthesis by condensation of p-anisaldehyde with 5 $\alpha$ -androstan-3-one (29) at C-2 followed by reduction with lithium aluminum hydride and aluminum chloride at C-3 (46) to give the hydrocarbon (47); ozonolysis of 47 afforded 5 $\alpha$ -androstan-2-one (33). This reduction gave by-products and a low overall yield of about 19% was obtained.



Reagents: a)  $p\text{-CH}_3\text{OC}_6\text{H}_4\text{CHO/KOH/EtOH}$ ; b)  $\text{LiAlH}_4/\text{AlCl}_3$  (1:3); c)  $\text{O}_3/\text{C}_5\text{H}_5\text{N/EtOH}$ .

Scheme 11.

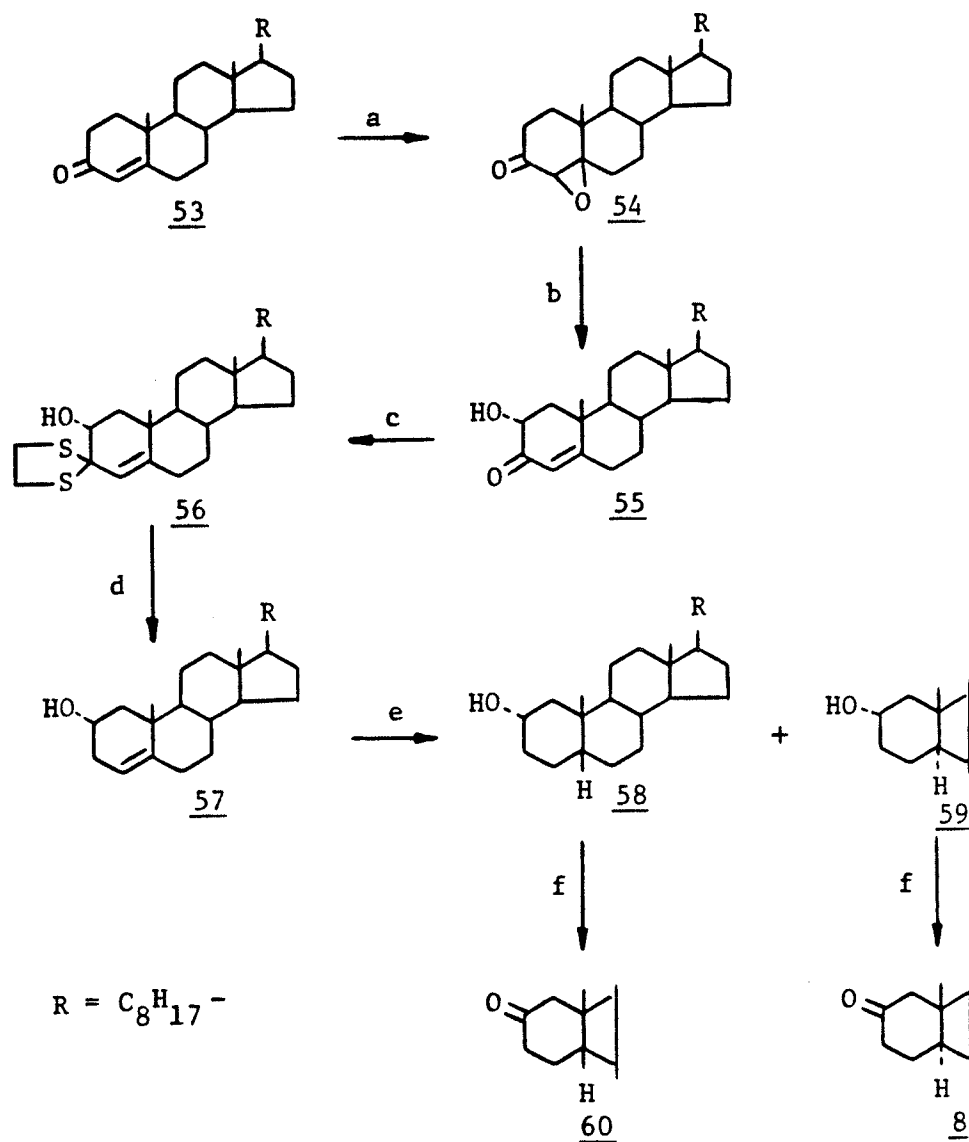
A modification of this method requiring five steps as shown in Scheme 12 was reported by Bridgeman *et al.* (25). Condensation of the C-3 ketone (48) with p-anisaldehyde and reduction of the product (49) (Scheme 12A) to the alcohol (50), acetylation (51), ozonolysis (52) and removal of the acetate gave 5 $\alpha$ -androstan-2-on-17 $\beta$ -ol acetate (36) in an overall yield of 43%. This procedure has also been applied to 5 $\alpha$ -cholestan-3-one (1) (Scheme 12B) to give 5 $\alpha$ -cholestan-2-one (8).



Reagents: a)  $p-CH_3OC_6H_4CHO/KOH/EtOH$ ; b)  $NaBH_4/THF/MeOH$ ; c)  $Ac_2O/C_5H_5N$ ; d)  $O_3$ ; e)  $Zn/HOAc$ .

Scheme 12 A & B.

In 1965 the synthesis of 5 $\beta$ -cholestan-2-one (60) (Scheme 13) from 4-cholesten-3-one (53) was reported (26).



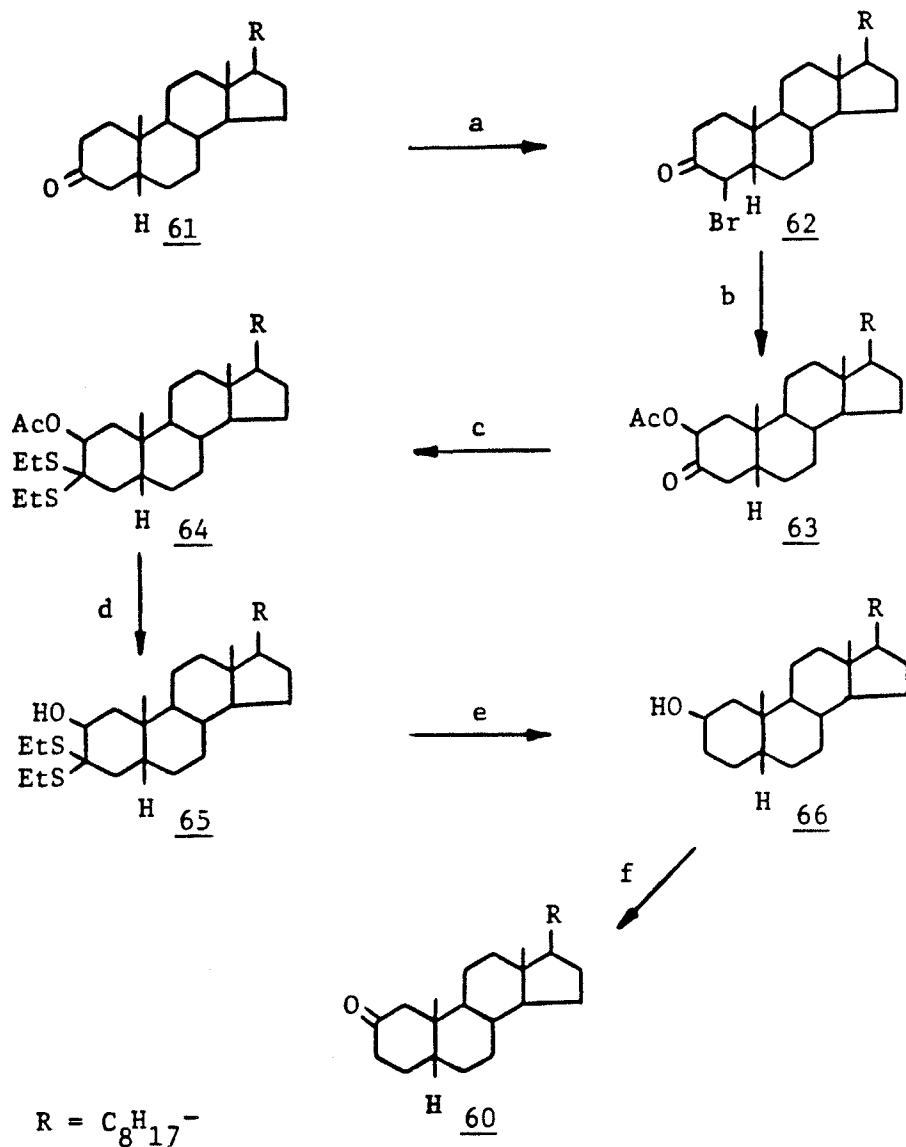
Reagents: a) NaOH/H<sub>2</sub>O<sub>2</sub>; b) H<sub>2</sub>SO<sub>4</sub>/aq. acetone; c) (CH<sub>2</sub>SH)<sub>2</sub>/Et<sub>2</sub>O.BF<sub>3</sub>.HOAc; d) Raney Ni(W2)/MeOH; e) Pt/HOAc; f) Jones [O].

Scheme 13.

This synthesis involved epoxidation of the C-4 olefin of 54 and abnormal ring opening in sulfuric acid/aqueous acetone to give 4-en-3-on-2 $\alpha$ -ol (55), then condensation with ethanedithiol in boron trifluoride etherate in acetic acid to give the ethylene thioketal (56) and desulfurization with Raney nickel in methanol to give the 4-en-2 $\alpha$ -ol (57) which followed by hydrogenation using platinum catalyst in acetic acid afforded, on chromatography, 5 $\beta$ - and 5 $\alpha$ -cholestan-2 $\alpha$ -ol (58 and 59 respectively). Jones oxidation gave their corresponding 2-ketone derivatives, 5 $\beta$ -cholestan-2-one (60) and its 5 $\alpha$ -isomer (8) (Scheme 13). This method gave an overall yield of 28.5% because of side products.

More recently another approach was reported (27) for the synthesis of 5 $\beta$ -cholestan-2-one (60) (Scheme 14) from 5 $\beta$ -cholestan-3-one (61). The synthetic pathways involved bromination (63), acetolysis (63) with potassium acetate and acetic acid, condensation with ethyl mercaptan to give the diethyl mercaptal (64), hydrolysis and desulfurization of 65 with Raney nickel to give 5 $\beta$ -cholest-2 $\beta$ -ol (66) which on oxidation with chromic acid and acetic acid gave 5 $\beta$ -cholestan-2-one (60).

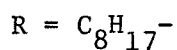
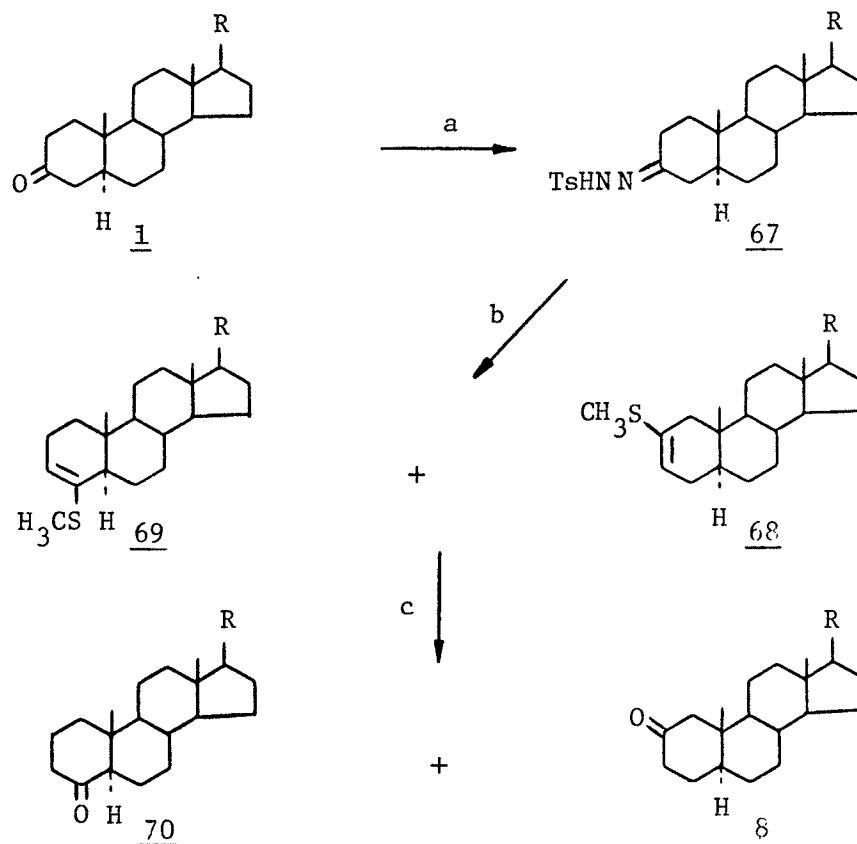




Reagents: a)  $Br_2/HOAc$ ; b)  $HOAc/KOAc$ ; c)  $CH_3CH_2SH/HCl$  gas; d)  $NaOH/MeOH$ ; e)  $Raney\ Ni/MeOH/(CH_3)_2C=O$ ; f)  $CrO_3/HOAc$ .

Scheme 14.

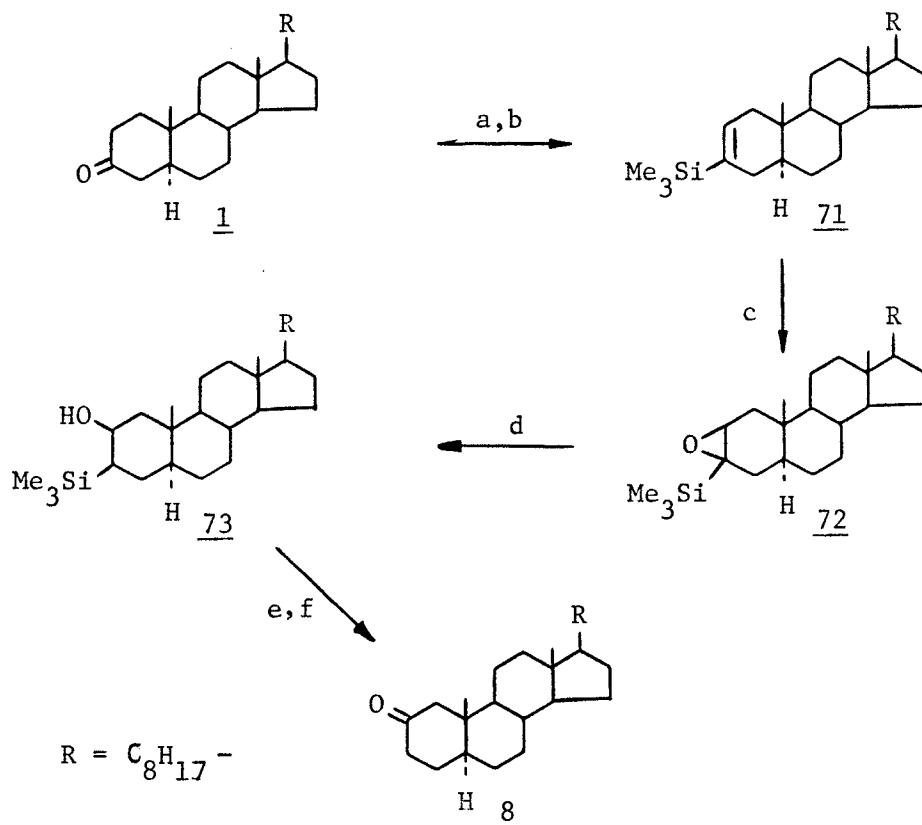
A recent general method for 1,2-carbonyl transposition has been reported (28) (Scheme 15), however, it is not of particular value in transposition of the C-2 ketone in steroids because it lacks regiospecificity. In this method a ketone tosylhydrazone (67) was converted to the enol thioethers (68, 69) by treatment with n-butyl lithium followed by dimethyldisulfide. Hydrolysis of the thioethers (68, 69) to the corresponding ketones was performed with mercuric chloride in hot aqueous acetonitrile (8, 70). The C-2 and C-4 ketones were obtained in the ratio of 2:1.



Reagents: a) TsHNNH<sub>2</sub>; b) n-BuLi, (CH<sub>3</sub>S)<sub>2</sub>; c) HgCl<sub>2</sub>, CH<sub>3</sub>CN.

Scheme 15.

Another procedure describing the carbonyl transposition from a C-3 ketone to a C-2 ketone via a vinylsilane intermediate has been reported recently by Fristad *et al.* (29). Starting with 5 $\alpha$ -cholestan-3-one (1) (Scheme 16) which was treated with tosylhydrazide and then with alkyl lithium to give the C-2 vinylsilane (71). Epoxidation of (71) gave the epoxysilane (72). Epoxide ring opening of (72) was achieved by hydride reduction using lithium aluminum hydride in ether to give the  $\beta$ -silyl alcohol (73). Oxidation of the resulting  $\beta$ -silyl alcohol (73) and hydrolytic desilication gave 5 $\alpha$ -cholestan-2-one (8).



Reagents: a)  $\text{C}_6\text{H}_5\text{SO}_2\text{NHNH}_2$ ; b)  $n\text{-BuLi}, (\text{CH}_3)_3\text{SiCl}$ ;  
 c) *m*-chloroperbenzoic acid; d)  $\text{LiAlH}_4$ /  
 ether; e)  $\text{Na}_2\text{Cr}_2\text{O}_7/\text{conc. H}_2\text{SO}_4$  (Brown  
 oxidation); f)  $\text{F}^-$ .

Scheme 16.

In this method the resulting C-2 ketone was obtained in very low yield (9%) indicating the disadvantage of the sequence as a promising technique for this transformation.

The yields obtained from the Schemes outlined are summarized in Table 1. As shown above methods which work well on, for example, 5 $\alpha$ -cholestan-3-one (23%) (Scheme 3) may not be as useful in more substituted compounds such as 5 $\alpha$ -androstane-3,17-dione (4%). Scheme 6 gave the highest yield (62%) whereas Schemes 4 and 16 gave very low yields (4%).

TABLE 1

Synthesis of steroid C-2 ketone from the C-3 ketone

<u>C-2 Ketone</u>	<u>Scheme</u>	<u>No of Steps</u>	<u>Overall Yield %</u>
5 $\alpha$ -cholestan-2-one	2	7	23
5 $\alpha$ -androstona-2,17-dione	4	6	4
22 $\alpha$ -5 $\alpha$ -spirostane-2,12-dione	5	7	34
5 $\alpha$ -androstan-2-on-17 $\beta$ -ol benzoate	5	7	9 <sup>a</sup>
5 $\alpha$ -androstan-2-on-17 $\beta$ -ol acetate	5	6	44 <sup>a</sup>
5 $\alpha$ -cholestan-2-one	6	5	62
5 $\alpha$ -androstan-2-one	7	5	20
5 $\alpha$ -cholestan-2-on-3 $\beta$ -ol acetate	7	5	10
3 $\alpha$ -methyl-5 $\alpha$ -cholestan-2-one	7	7	20
5 $\alpha$ -cholestan-2-one	8	6	41 <sup>b</sup>
5 $\alpha$ -androstan-2-on-17 $\beta$ -ol acetate	9	2	41 <sup>b</sup>
5 $\alpha$ -androstan-2-on-17 $\beta$ -ol acetate	9	2	12 <sup>c</sup>
5 $\alpha$ -cholestan-2-one	10	3	24
5 $\alpha$ -cholestan-2-one	10	4	17
5 $\alpha$ -androstan-2-one	11	3	19
5 $\alpha$ -androstan-2-on-17 $\beta$ -ol acetate	12	5	43
5 $\alpha$ -cholestan-2-one	12	5	43
5 $\beta$ -cholestan-2-one	13	6	15
5 $\alpha$ -cholestan-2-one	13	6	7
5 $\beta$ -cholestan-2-one	14	6	29
5 $\alpha$ -cholestan-2-one	15	3	18
5 $\alpha$ -cholestan-2-one	15	3	12
5 $\alpha$ -cholestan-2-one	16	5	4

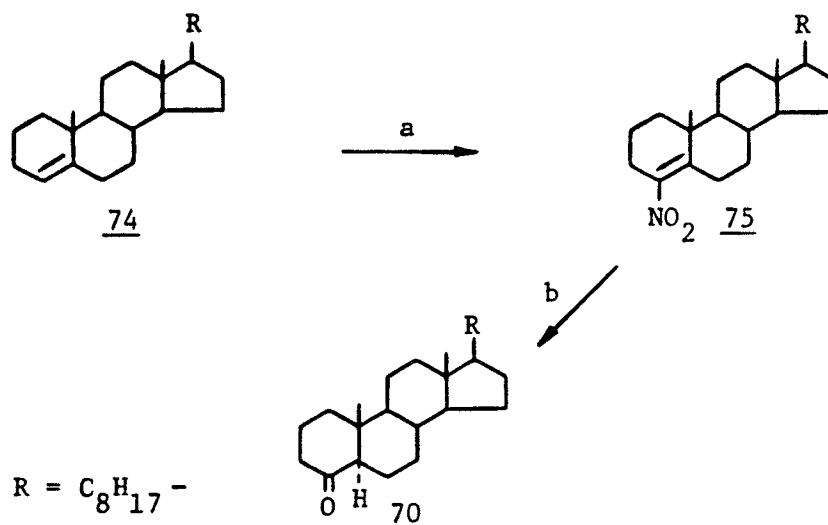
<sup>a</sup> with isolation of intermediates.

<sup>b</sup> calculated from C-2 bromo compound.

<sup>c</sup> calculated from C-4 bromo compound.

### C-3 to C-4 Steroid Ketone Transposition

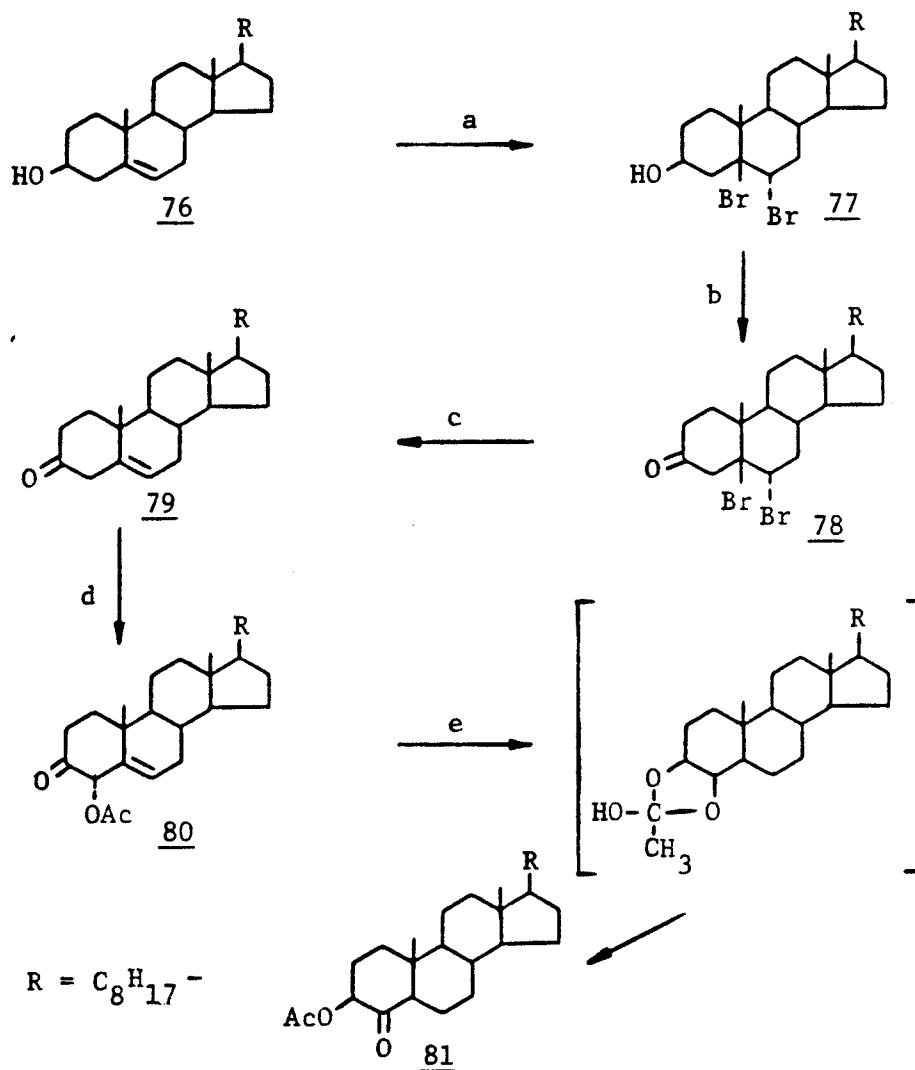
In the early 1920's the transposition of the C-3 ketone to the C-4 ketone in steroids was investigated by Windaus (30) (Scheme 17). Cholest-4-ene (74) on nitration with nitric acid gave 4-nitro-4-cholestene (75) which on reduction with zinc and acetic acid afforded 5 $\alpha$ -cholestan-4-one (70). However this method gave a low yield and the product was contaminated with cholest-4-en-3-one and cholest-4-en-6-one (31).



Reagents: a) HOAc/HNO<sub>3</sub>; b) Zinc/HOAc.

Scheme 17.

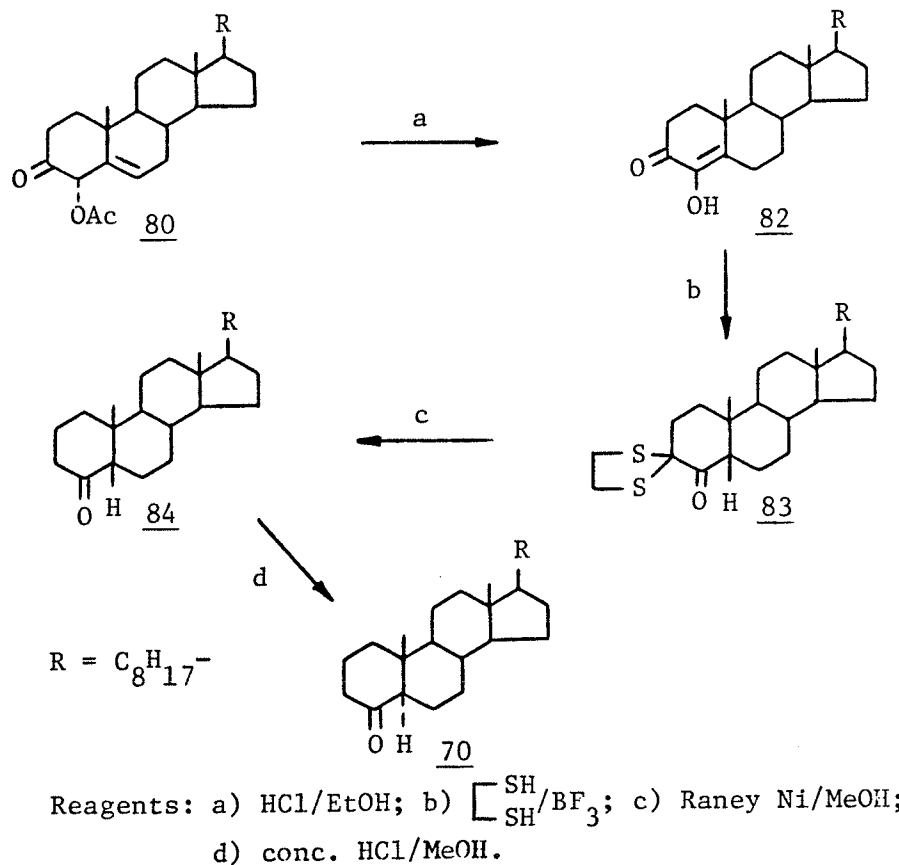
Fieser and Stevenson (32) reported the synthesis of cholest-5-en-4-on-3 $\beta$ -ol acetate (81) (Scheme 18A) from cholest-5-en-3 $\beta$ -ol (76). This procedure involved the bromination of the C-5 olefin (76) followed by oxidation of the C-3 $\beta$  alcohol (77) to give the C-3 ketone (78) which is readily debrominated to the cholest-5-en-3-one (79) using zinc and acetic acid. Oxidation of cholest-5-en-3-one (79) with lead tetraacetate occurs at the C-4 position giving cholest-5-en-3-one-4 $\alpha$ -ol acetate (80) which was isomerized to cholest-5-en-4-on-3 $\beta$ -ol acetate (81) on contact with alumina. This method also provided only a low yield of the final product.



Reagents: a)  $\text{Br}_2/\text{HOAc}$ ; b)  $\text{Na}_2\text{Cr}_2\text{O}_7/\text{HOAc}$ ; c)  $\text{Zn}/\text{HOAc}$ ;  
 d)  $\text{Pb}(\text{OAc})_4/\text{C}_6\text{H}_6/\text{HOAc}$ ; e)  $\text{Al}_2\text{O}_3$ .

Scheme 18 A.

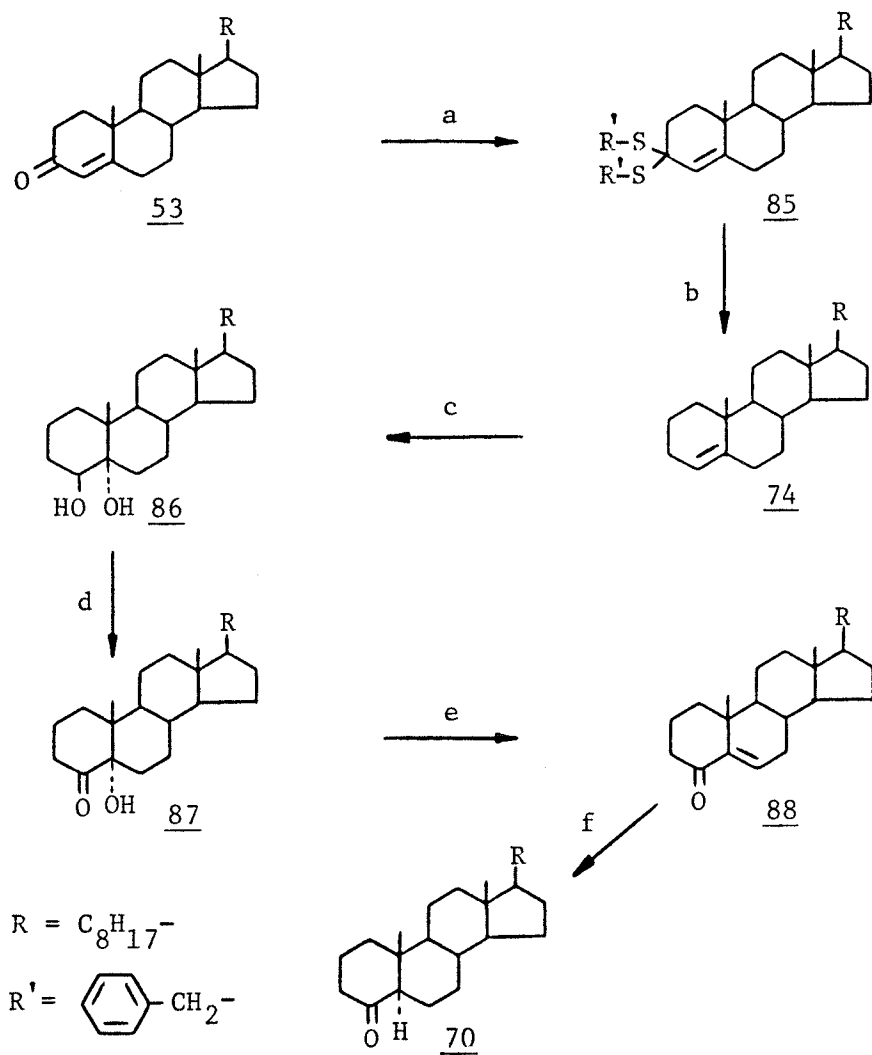
The same group (33) attempted another route starting with the same sequence for the synthesis of cholest-5-en-4-on-3 $\beta$ -ol acetate (80) (Scheme 18B). Treatment of 80 with hydrochloric acid in ethanol gave cholest-4-en-3-on-4-ol (82). Treatment of this product (82) with excess ethanedithiol in the presence of boron trifluoride etherate led to the formation of the ethylene thioketal (83) which after desulfurization with Raney nickel afforded 5 $\beta$ -cholestan-4-one (84). Isomerization of 84 with concentrated hydrochloric acid in methanol gave 5 $\alpha$ -cholestan-4-one (70). This multi-step procedure results in a low overall yield, although it is useful for obtaining both the 5 $\beta$ - and 5 $\alpha$ -cholestan-4-one isomers.



Scheme 18 B.



Another attempt was made by Jones *et al.* (34) to utilize the C-4 olefin of cholest-4-ene (74) (Scheme 19).



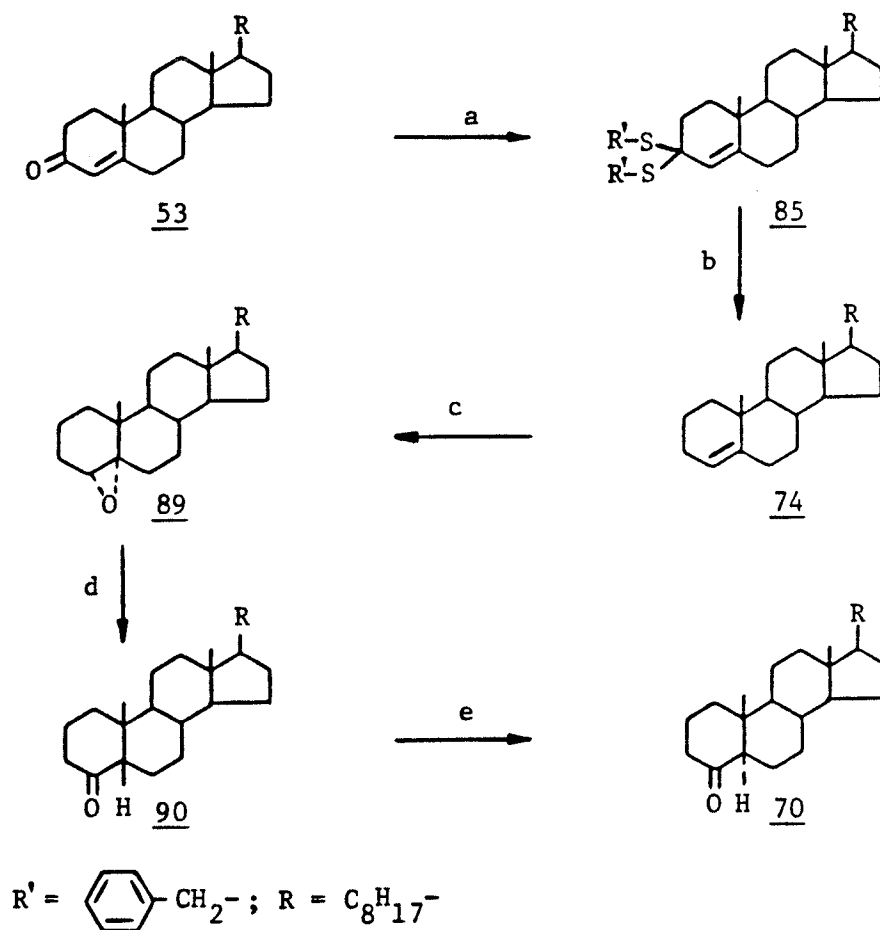
Reagents: a)  $C_7H_8SH/HClO_4$ ; b) Raney Ni/ $C_6H_6$ ; c)  $OsO_4/Et_2O/C_5H_5N, LiAlH_4$ ; d)  $CrO_3/HOAc$ ; e)  $SOCl_2/C_5H_5N$ ; f) Raney Ni/ $EtOH$ /trace  $HCOOH$ .

Scheme 19.

Cholest-4-ene (74) was prepared from cholest-4-en-3-one (53) by treatment with benzylthiol to give the benzylmercaptal (85) which with Raney nickel afforded the intermediate product 74. Hydroxylation of

cholest-4-ene (74) with osmium tetroxide gave cholestane-4 $\beta$ ,5 $\alpha$ -diol (86). Oxidation of cholestane-4 $\beta$ ,5 $\alpha$ -diol with chromium trioxide in acetic acid furnished cholestan-4-on-5 $\alpha$ -ol (87). This was readily dehydrated with thionyl chloride in pyridine to cholest-5-en-4-one (88). Reduction of cholest-5-en-4-one (88) with Raney nickel in ethanol containing a trace of formic acid gave cholestan-4-one (70). This multi-step method gave a good overall yield.

A related synthesis through epoxidation of the C-4 olefin rather than hydroxylation has also been demonstrated (35) (Scheme 20).

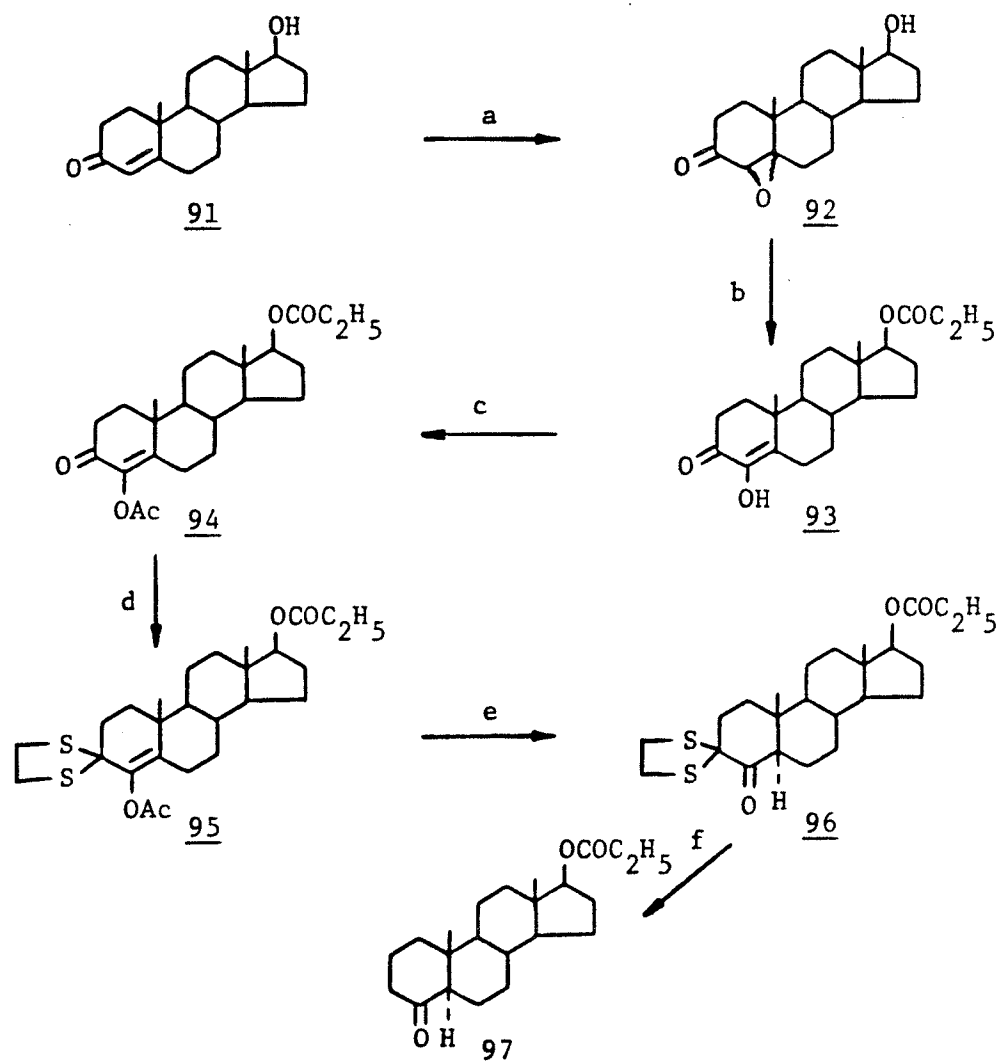


Reagents: a)  $C_7H_8SH/HClO_4$ ; b) Raney Ni/ $C_6H_6$ ;  
 c) perbenzoic acid/ $C_6H_6$ ; d)  $BF_3 \cdot Et_2O$ /  
 $C_6H_6$ ; e)  $Al_2O_3$ .

Scheme 20.

The reaction of boron trifluoride etherate with the epoxide (89) within a few minutes gave the  $5\beta$ -C-4 ketone (90). Acid treatment of  $5\beta$ -cholestan-4-one (90) gave the isomer  $5\alpha$ -cholestan-4-one (70). This method gave a good yield and it is useful for obtaining both the  $5\alpha$ - and  $5\beta$ -isomers.

A different approach has been made by Heusler *et al.* (36) for transposition of the carbonyl group of the  $\alpha,\beta$ -unsaturated ketone (91) to the C-4 ketone in the androstane series (Scheme 21).

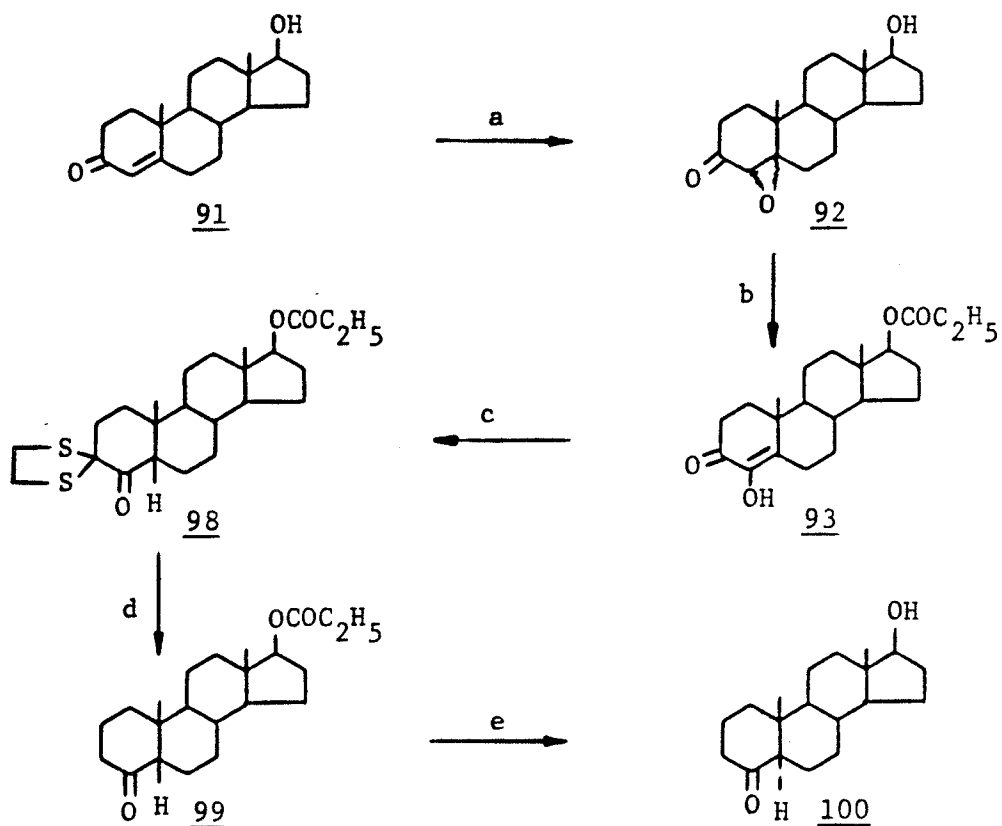


Reagents: a)  $\text{H}_2\text{O}_2/\text{KOH}/\text{MeOH}$ ; b)  $\text{EtCO}_2\text{H}/\text{conc. H}_2\text{SO}_4$ ;  
 c)  $\text{C}_5\text{H}_5\text{N}/\text{Ac}_2\text{O}$ ; d)  $(\text{CH}_2\text{SH})_2/\text{Et}_2\text{O}\cdot\text{BF}_3$ ; e)  
 $\text{MeOH}/\text{K}_2\text{CO}_3/\text{H}_2\text{O}$ ,  $(\text{EtCO})_2\text{O}/\text{C}_5\text{H}_5\text{N}$ ; f) Raney  
 Ni/EtOH.

Scheme 21.

Starting with propionic acid in concentrated sulfuric acid treatment of the epoxide (92) led to epoxide ring opening to the diosphenol (93) which was acetylated with acetic anhydride in pyridine to give 4-androstan-3-one-4,17 $\beta$ -diol 3-acetate 17-propionate (94). This compound was treated with ethanedithiol in boron trifluoride etherate to give the thioketal (95). Compound 95 was refluxed with potassium carbonate and the isolated product was treated with propionic anhydride in pyridine to give 3,3-ethylenedithio-5 $\alpha$ -androstan-4-on-17 $\beta$ -ol propionate (96). Desulfurization of 96 with Raney nickel furnished 5 $\alpha$ -androstan-4-on-17 $\beta$ -ol propionate (97). The overall yield was low and the synthesis involved many steps.

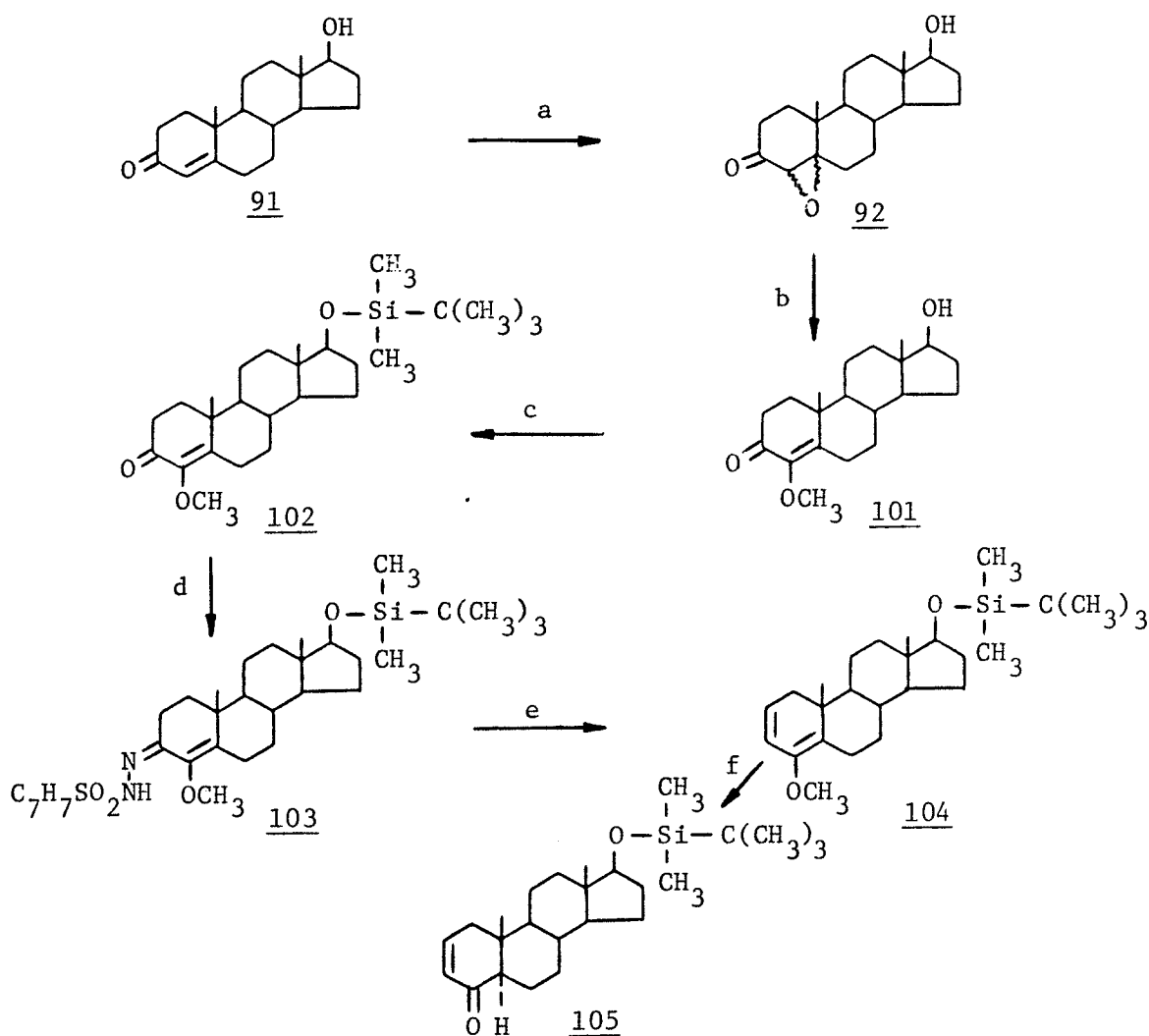
In 1963, Heusler *et al.* (37) provided a shorter route starting with the same compound (91) (Scheme 22) to give compound 92, the diosphenol (93) was treated with ethanedithiol in boron trifluoride etherate to give 3,3-ethylenedithio-5 $\beta$ -androstan-4-on-17 $\beta$ -ol propionate (98). This thioketal (98) reacted with Raney nickel to give 5 $\beta$ -androstan-4-on-17 $\beta$ -ol propionate (99) which on treatment with sodium hydroxide in methanol gave the C-5 epimer, 5 $\alpha$ -androstan-4-on-17 $\beta$ -ol (100). The overall yield was the same as the previous method (Scheme 21) but this method has the advantage that both the 5 $\beta$ - and 5 $\alpha$ -isomers are obtained in fewer steps.



Reagents a)  $\text{H}_2\text{O}_2/\text{KOH}/\text{MeOH}$ ; b)  $\text{EtCO}_2\text{H}/\text{conc. H}_2\text{SO}_4$ ; c)  $(\text{CH}_2\text{SH})_2/\text{BF}_3 \cdot \text{Et}_2\text{O}$ ; d) Raney Ni/EtOH; e)  $\text{NaOH}/\text{MeOH}/\text{H}_2\text{O}$ .

Scheme 22.

More recently Patel and Reusch (38) reported another approach to carbonyl transposition from the C-3 ketone to the C-4 ketone which involves an  $\alpha$  keto enol ether intermediate. Starting with testosterone (91) (Scheme 23) treatment with 30% hydrogen peroxide and sodium hydroxide in methanol gave a mixture of epoxides (92) which were opened to give the enol ether (101). The C-17 hydroxyl group was protected as the tert-butyl-dimethylsilyl derivative (102). The C-17 hydroxyl group was protected as the tert-butyl-dimethylsilyl derivative (102).

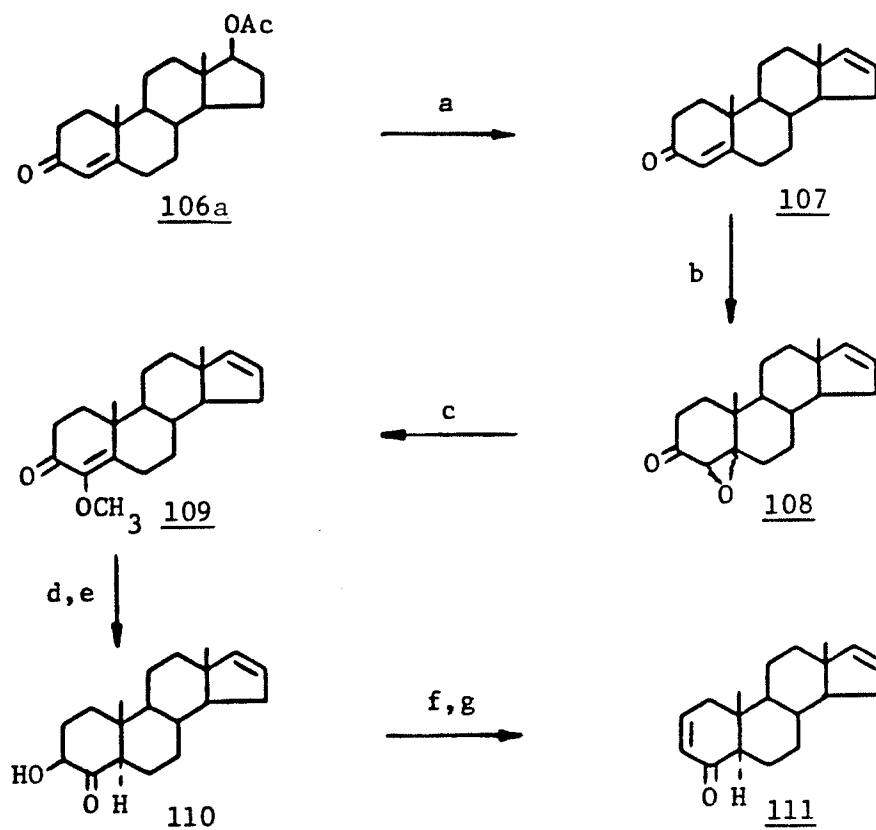


Reagents: a) 30%  $H_2O_2$ /10% NaOH/ MeOH; b) KOH or  $NaOCH_3/CH_3OH$ ;  
 c)  $t-Bu(CH_3)_2SiCl/DMF$ ; d)  $C_7H_7SO_2NHNH_2/EtOH$ ; e)  
 $MeLi/(Et)_2O$ ; f) 5% HCl/THF.

Scheme 23.

Treatment of 102 with p-toluenesulfonyl hydrazide gave the hydrazone (103) which on treatment with methyl lithium in ether gave the vinyl ether (104). Subsequent hydrolysis of 104 furnished the transposed ketone (105). This route is particularly useful in the cholestane series which does not require protection at the C-17 position. The overall yield for Scheme 23 was 60%.

Recently Ohloff *et al.* (39) described a modified procedure (Scheme 24) which was closely related to the Patel and Reusch method (Scheme 23).



Reagents: a)  $460^{\circ}\text{C}$ , glass column; b)  $\text{H}_2\text{O}_2/\text{KOH}/\text{MeOH}$ ;  
 c)  $\text{KOH}/\text{MeOH}$ ; d)  $\text{LiAlH}_4/\text{ether}$ ; e)  $\text{HCl}/\text{acetone}$ ;  
 f)  $\text{PBr}_3/\text{CCl}_4$ ; g)  $\text{LiBr}/\text{Li}_2\text{CO}_3/\text{DMF}$ .

Scheme 24.

Testosterone methyl carbonate (106a) (Scheme 24) was pyrolyzed at  $460^{\circ}$  to give androst-4,16-dien-3-one (107). Epoxidation of 107 with hydrogen peroxide and potassium hydroxide gave a mixture of epoxides (108) which was treated as such with potassium hydroxide in methanol to give the enol ether (109). This compound was reduced with lithium aluminum hydride followed by acid hydrolysis of the enol ether which gave  $5\alpha$ -androst-16-en-4-on-3 $\beta$ -ol (110). Further treatment of 110 with phosphorous tribromide followed by lithium bromide and lithium carbonate in dimethyl formamide gives the  $\alpha,\beta$ -unsaturated ketone (111). The overall yield for carbonyl transposition from the C-3 to the C-4 ketone i.e., from compound 106 to compound 111 was about 46%.

Table 2 illustrates the overall yield for each Scheme which shows the variety of methods used for the transposition from the C-3 ketone to the C-4 ketone. The low yields are generally obtained because of the formation of by-products and/or the type of the reagent used. For example, the  $5\alpha$ -cholesten-4-on-3 $\beta$ -ol acetate was obtained in only 4% overall yield in Scheme 18A because of the low yield efficiency of the alumina rearrangement.



TABLE 2

Synthesis of steroid C-4 ketone from the 4-en-3-one

<u>C-2 Ketone</u>	<u>Scheme</u>	<u>No. of Steps</u>	<u>Overall Yield %</u>
5 $\alpha$ -cholestan-4-one	17	3	low
5 $\alpha$ -cholesten-4-on-3 $\beta$ -ol acetate	18A	5	4
5 $\beta$ -cholestan-4-one	18B	7	10
5 $\alpha$ -cholestan-4-one	18B	8	9
5 $\alpha$ -cholestan-4-one	19	6	40 <sup>a</sup>
5 $\beta$ -cholestan-4-one	20	2	18 <sup>a</sup>
5 $\alpha$ -cholestan-4-one	20	3	16 <sup>a</sup>
5 $\alpha$ -androstan-4-on-17 $\beta$ -ol propionate	21	6	32
5 $\beta$ -androstan-4-on-17 $\beta$ -ol propionate	22	4	36
5 $\alpha$ -androstan-4-on-17 $\beta$ -ol propionate	22	5	32
5 $\alpha$ -androst-2-en-4-on-17 $\beta$ -ol tert-butyl- dimethylsilyl ether	23	6	60
5 $\alpha$ -androst-2,16-dien-4-one	24	5	28

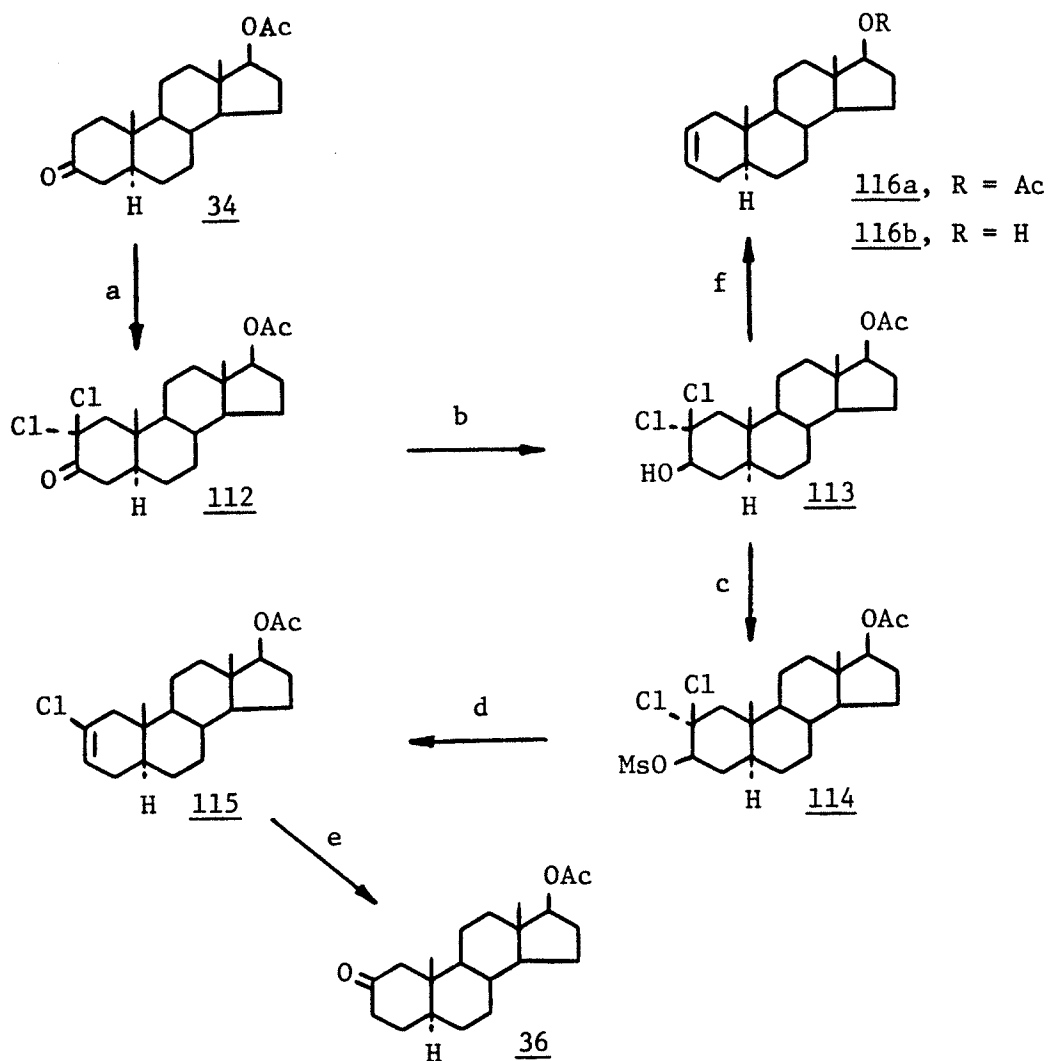
<sup>a</sup>calculated from the C-4 olefin

## RESULTS AND DISCUSSION

### Synthesis of a C-2 steroid ketone

The chlorination product of 5 $\alpha$ -androstan-3-on-17 $\beta$ -ol acetate (112) (Scheme 25) showed a molecular ion cluster at m/z, 400, 402, 404 in the mass spectrum consistent with the addition of two chlorine atoms together with ions corresponding to loss of, chlorine, hydrochloric acid and acetic acid. The  $^1\text{H}$  NMR (Table 3) shows the chemical shift of the C-10 methyl group at 1.21 ppm compared with 1.03 ppm in the starting ketone (34). The downfield shift of 0.17 ppm is consistent with a 1,3 diaxial interaction between the axial substituted chlorine at C-2 and the C-10 methyl group. The spectrum also shows two pairs of doublets at 2.31 and 3.05 ppm ( $J = 15$  Hz) which are assigned to the 1 $\beta$ -proton and 1 $\alpha$ -proton respectively. These protons are downfield of the methylene envelope because of the anisotropic effect of the adjacent C-2 chlorine atoms. The infrared spectrum gives evidence for the C-3 ketone at 1725  $\text{cm}^{-1}$  which is shifted from 1710  $\text{cm}^{-1}$  in the starting ketone (34) because of the adjacent chlorine atoms (40-42); a second absorption at 1745  $\text{cm}^{-1}$  is assigned to the carbonyl group of the C-17 acetate; a strong ester C-O stretching vibration is present at 1255  $\text{cm}^{-1}$ . These results established the chlorination product as 2,2-dichloro-5 $\alpha$ -androstan-3-on-17 $\beta$ -ol acetate (112).

Reduction of (112) with sodium borohydride gave a product (113) which showed two major components on TLC consistent with the expected formation of the 3 $\alpha$ - and 3 $\beta$ -alcohols. Recrystallization gave the major product which on examination of its absorption in the infrared spectrum showed loss of the carbonyl absorption at 1725  $\text{cm}^{-1}$  assigned to the ketone and the appearance of hydroxyl absorption at 3595  $\text{cm}^{-1}$ . The  $^1\text{H}$



Reagents: a)  $\text{Cl}_2/\text{HOAc}$ ; b)  $\text{NaBH}_4/\text{EtOH}$ ; c)  $\text{MsCl}/\text{C}_5\text{H}_5\text{N}$ ;  
 d)  $\text{Zn}/\text{HOAc}$ ; e)  $\text{conc. H}_2\text{SO}_4$ ; f)  $\text{Zn}(\text{Cu})$  or  
 $\text{Zn}/\text{HOAc}$ .

Scheme 25.

TABLE 3

<sup>1</sup>H NMR SPECTRA OF SOME ANDROSTANE DERIVATIVES<sup>a</sup>

Compound	C-13CH <sub>3</sub>	C-10CH <sub>3</sub>	17β-OAc	3ξ-OAc	17α-H	3ξ-H
5α-androstan-2-on-17β-ol acetate (36)	0.78	0.76	2.03		4.60,dd, J=7&9 Hz	
2,2-dichloro-5α-androstan-3-on-17β-ol acetate (112)	0.81	1.21	2.03		4.59,dd, J=7.4&8.8 Hz	2.31,d,J=15.2 Hz (1αH); 3.05,d,J=15.2 Hz (1βH)
2,2-dichloro-5α-androstan-3β,17β-diol 17-acetate (113)	0.79	1.05	2.03		4.59,dd, J=7&9 Hz	3.86,dd, J=8&15 Hz 2.04,d,J=15 Hz (1αH); 2.87,d,J=15 Hz (1βH)
2,2-dichloro-5α-androstan-3β,17β-diol 3-mesylate 17-acetate (114)	0.78	1.08	2.03		4.59,dd, J=7&9 Hz	4.80,dd, J=6,10 Hz 2.08,d,J=15 Hz (1αH); 2.88, d,J=15 Hz (1βH); 3.18 (CH <sub>3</sub> SO <sub>3</sub> ); 5.73,m, (C-3H)
2-chloro-5α-androst-2-en-17β-ol acetate (115)	(0.81)	(0.79)	2.03		4.59,dd, J=7.4&8.8 Hz	
5α-androst-2-en-17β-ol acetate (116a)	(0.81)	(0.78)	2.03		4.59,dd, J=7&9 Hz	5.58,m, (C-2H & C-3H)
4-chloro-4-androsten-3-on-17β-ol acetate (120)	0.84	1.24	2.04		4.61,dd, J=7&9 Hz	
4-chloro-4-androstene-3β,17β-diol 17-acetate (121)	0.81	1.10	2.03		4.58,dd, J=7.3&8.9 Hz	4.15,m,
4-chloro-4-androstene-3β,17β-diol diacetate (123)	0.81	1.12	2.03	2.10	4.59,dd, J=7&9 Hz	5.39,m,
4α-chloro-4,5-oxido-5β-androstane-3β,17β-diol 17-acetate (124)	0.81	1.04	2.05		4.60,dd, J=7&9 Hz	4.30,dd, J=3.1&5.4 Hz
4β-chloro-4,5-oxido-5α-androstane-3α,17β-diol 17-acetate (125) <sup>b</sup>	0.81	1.12	2.03		4.60,dd, J=7,9 Hz	4.06,t, J=8.5 Hz
4-androsten-3-one-4,17β-diol diacetate (126)	0.84	1.25	2.04		4.60,dd, J=7.3,8.8 Hz	2.23 (C-4 OAc)
4-androsten-3-one-4,17β-diol 17-acetate (127)	0.83	1.18	2.04		4.60,dd, J=7.3,8.9 Hz	6.06 (C-4 OH)
4α-chloro-4,5-oxido-5β-androstane-3β,17β-diol diacetate (128)	0.82	1.06	2.05	2.17	4.61,dd, J=7.7&9.2 Hz	5.49,dd, J=3.9&5.8 Hz
4β-chloro-4,5-oxido-5α-androstane-3β,17β-diol diacetate (129)	0.81	1.14	2.03	2.12	4.60,dd, J=7&9 Hz	5.25,t, J=8.5 Hz
5-chloro-5α-androstan-4-one-3β,17β-diol diacetate (130)	0.78	0.96	2.04	2.16	4.63,dd, J=7.5&10 Hz	6.18,dd, J=8&12 Hz

.....continued.

Compound	C-13CH <sub>3</sub>	C-10CH <sub>3</sub>	17β-OAc	3ξ-OAc	17α-H	3ξ-H
5α-androstan-4-one-3β,17β-diol diacetate (131)	(0.78)	(0.76)	2.03	2.14	4.60,dd, J=7&9 Hz	5.16,dd, J=7&10 Hz
3ξ,4-dichloro-4-androsten-17β-ol acetate (132)	0.82	1.07	2.04			4.58,m, (3ξH & 17αH)
4α-chloro-4,5-oxido-5β-androstane-3β,17β-diol 3-mesylate 17-acetate(133) <sup>c</sup>	0.82	1.06	2.05		4.60,dd, J=7,9 Hz	5.27, J=3.3,5.5 Hz 3.21 (CH <sub>3</sub> SO <sub>3</sub> )
5-chloro-5α-androstan-4-one-3β,17β-diol 3-mesylate 17-acetate (134)	0.79	0.97	2.04		4.62,dd, J=7.8,9.1 Hz	6.06,dd, J=8.5,11.2 Hz 3.19 (CH <sub>3</sub> SO <sub>3</sub> )
5β-androstan-4-one-5,17β-diol diacetate (135)	0.76	1.12	2.02	2.08	4.55,dd, J=7.8&9.2 Hz	
3β-chloro-5β-androstan-4-one-5,17β-diol diacetate (138)	0.77	1.20	2.03	2.09	4.56,dd, J=7.8&9.1 Hz	5.12,t, J=3.3 Hz 2.48,octet, J=2.2,4.4&13.7 Hz
3α-chloro-5β-androstan-4-one-5,17β-diol diacetate (139)	0.76	1.14	2.02	2.09	4.55,dd, J=7&9 Hz	4.61,dd, J=6.5&12 Hz
(S)-5-spiroandrost-1(10)-en-4-one-3β,17β-diol diacetate (140)	0.80	1.81	2.04	2.16	4.58,dd, J=7.1&9.1 Hz	5.36,dd, J=8&11.9 Hz 5.50,d, J=5.8 Hz <sup>d</sup> 2.40,m(2αH) 2.65,m(2βH)

<sup>a</sup>Spectra were recorded on either a Bruker WH90 or a Bruker AM300 instrument in chloroform-d; enclosed values in a row are interchangeable.

<sup>b</sup>From reaction product mixture of 5α- and 5β-epoxides. <sup>c</sup>From epoxide product mixture. <sup>d</sup>dd,J=2.5&6 Hz after allylic decoupling.

NMR spectrum shows the C-10 methyl group at 1.05 ppm compared with 1.21 ppm in the 2,2-dichloroketone (112) (Table 3). This upfield shift of 0.16 ppm is in agreement with reduction of the C-3 ketone to the 3 $\alpha$ - or 3 $\beta$ -alcohol (43). The chemical shift of the C-3 proton is deshielded by the hydroxyl group (44) and appears at 3.86 ppm as a doublet of doublets ( $J = 8$  and  $15$  Hz). Axial-axial coupling ( $J = 8-14$  Hz) are larger than axial-equatorial ( $J = 1-7$  Hz) and equatorial-equatorial ( $J = 1-7$  Hz) coupling as expected from their dihedral angles (43). The couplings observed in the alcohol are in excellent agreement with the 3 $\beta$ -equatorial alcohol (3 $\alpha$ -axial hydrogen) and the stereochemistry is assigned on this basis. Reduction with sodium borohydride of the steroid A-ring C-3 ketone system is known to give the 3 $\beta$ -alcohol (equatorial) as the major product (45) whereas introduction of  $\alpha$ -halogens (Cl, Br) increases the proportion of the 3 $\alpha$ -alcohol (axial) (46-48). This assignment is further supported by the C-3 proton coupling constants of the sulfonate ester (114) ( $J = 6$  and  $10$  Hz, Table 3). The mass spectrum of the 2,2-dichloroalcohol (113) shows an ion cluster at 402, 404, 406, corresponding to the molecular ion and fragment ions indicating loss of chlorine, acetic acid, acetic acid and methyl radical.

The C-3 mesylate (114) shows a weak molecular ion cluster at  $m/z$  480, 482, and 484 in the mass spectrum and the loss of the neutral fragments of acetic acid, acetic acid and a methyl radical, and acetic acid and methane-sulfonic acid which arise from the molecular ion. The  $^1\text{H}$  NMR spectrum shows the methyl peak of the C-3 mesylate (114) with a chemical shift downfield at 3.18 ppm. The C-3 proton is shifted further downfield than the C-3 proton of the 2,2-dichloroalcohol (113) because

of the greater deshielding effect of the mesyl group. The infrared shows no hydroxyl absorption and there is evidence for the sulfonate (S=O) symmetric stretch at  $1175\text{ cm}^{-1}$ , asymmetric stretch at  $1340\text{ cm}^{-1}$  and (S-O) stretch at  $970\text{ cm}^{-1}$ .

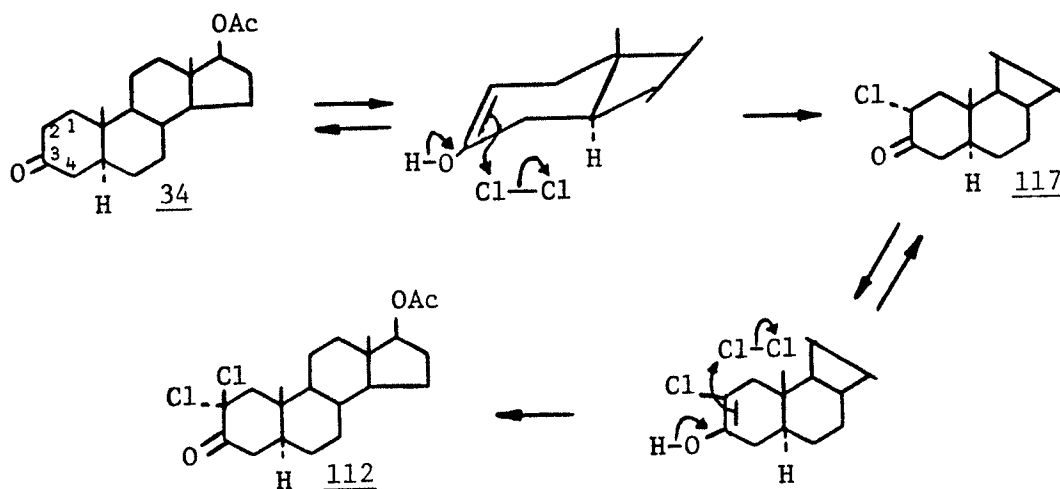
Treatment of the mesylate (114) with zinc and acetic acid gives the vinyl chloride (115) identified on the basis of the following spectral evidence. The infrared vinylic C-H stretching vibration is observed at  $3020\text{ cm}^{-1}$  as well as the C=C stretching absorption at  $1660\text{ cm}^{-1}$ . The  $^1\text{H}$  NMR spectrum shows an olefinic C-3 proton as an unresolved multiplet at 5.73 ppm which is significantly downfield of the chemical shift of the C-2 and C-3 protons in the non-chlorinated compound (Table 3, 116a) in agreement with the effect of the chlorine substituted. The mass spectrum shows molecular ion clusters at  $m/z$  350 and 352, 290 and 292, and 275 and 277 corresponding to the molecular ion with loss of acetic acid and methyl fragments. A strong fragment at  $m/z$  262 corresponds to the retro-Diels Alder fragmentation of ring A characteristic of the C-2 double bond (49) and establishing it at that position. Weaker fragments show loss of chlorine and hydrochloric acid. Loss of chlorine has been reported for other vinyl chlorides (50).

TLC and  $^1\text{H}$  NMR showed the presence of some non-chlorinated olefin (116a) (<10% in  $^1\text{H}$  NMR) accompanied by some hydrolysis of the C-17 acetate (116b). The structures of these compounds were established by comparison of their properties with authentic samples prepared previously (51).

Treatment of the vinyl chloride (115) with concentrated sulfuric acid gave the C-2 ketone (36) whose mp is consistent with the published value (12). The  $^1\text{H}$  NMR spectrum shows the expected small shielding

(-0.03 ppm) of the C-10 methyl group (43). Further evidence for the structure lies in the carbonyl absorptions in the infrared spectrum which shows a carbonyl stretching vibration at  $1720\text{ cm}^{-1}$  assigned to the C-2 ketone together with a band at  $1732\text{ cm}^{-1}$  for the C-17 acetate.

Treatment of 5 $\alpha$ -androstan-3-one-17 $\beta$ -ol acetate (34) with two moles of chlorine in acetic acid rapidly gives the 2,2-dichloroketone (112), as expected from the predominant formation of the C-2 enol (6,52) as shown in Scheme 26.

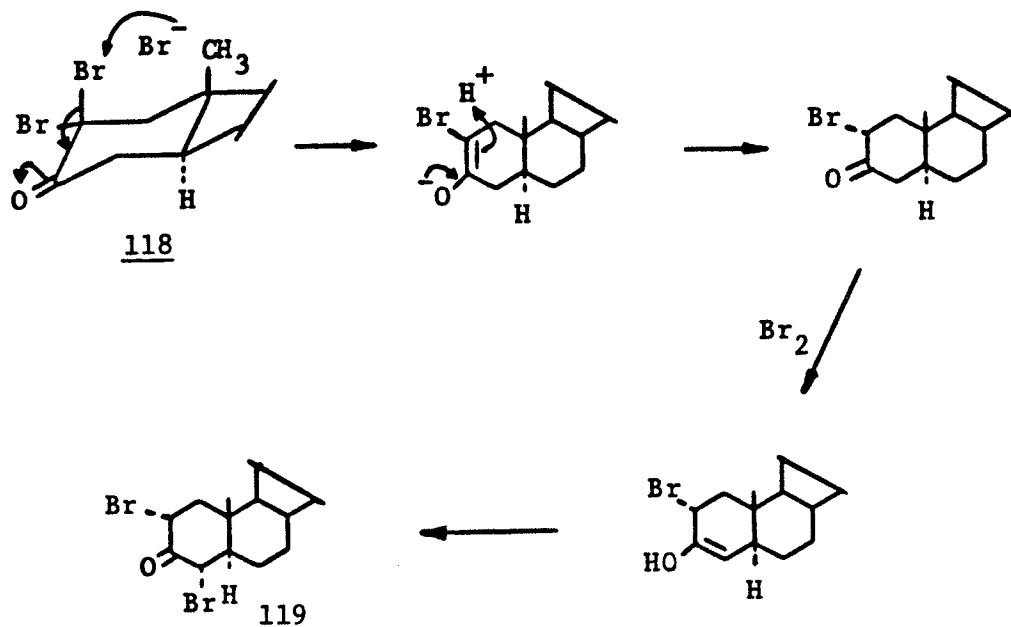


Scheme 26.

Initial formation of the monochloroketone (117) can be observed on TLC. The  $^1\text{H}$  NMR spectrum shows two downfield protons as doublets which can be assigned to the C-1 $\alpha$  (axial) and C-2 $\beta$  (equatorial) protons. The 2,2-dichloroketone (112) shows no rearrangement product (52,53), namely the 2,4-dichloroketone compared with the 2,2-dibromoketone (118) which rearranges to the 2,4-dibromoketone (119) (54) as shown in Scheme 27. The product of halogenation is the 2,2-dichloroketone (112) unlike the



2,2-dibromoketone (118) where the 1,3-diaxial interaction with the C-10CH<sub>3</sub> group leads to the thermodynamically more stable 2,4-dibromoketone (119). This rearrangement also reflects the weak reducing ability of Br<sup>-</sup> ion to attack the bromine atom at C-2 compared with Cl<sup>-</sup> ion which does not catalyse the rearrangement.



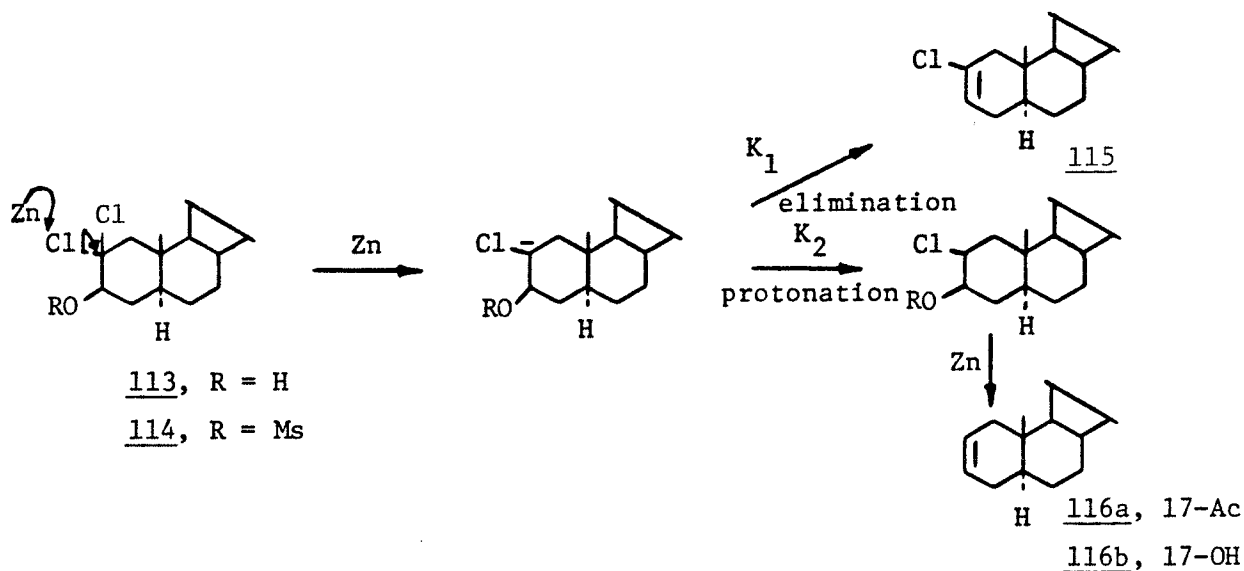
Scheme 27.

Chlorination and bromination of the C-3 ketone has been shown to occur from the  $\alpha$ -face as a result of steric hindrance of the C-10CH<sub>3</sub> group rather than to follow the expected stereoelectronic control favouring the formation of the axial bromoketone (55,56). Halogenation of steroid C-3 ketones has been extensively studied (56-58).

Reduction of the 2,2-dichloroketone (112) with sodium borohydride gave a mixture of two components by TLC of the epimeric 3 $\alpha$ - and 3 $\beta$ -alcohols (3 $\alpha$ :3 $\beta$ ; 1:9 by HPLC) from which the 3 $\beta$ -alcohol (113) (Scheme 27, R=Ms) can be obtained by crystallization. The configuration of the

C-3 alcohol is established by the chemical shift of the C-3H in the  $^1\text{H}$  NMR spectrum.

Mesylation of the mixture to give 114, R=Ms (Scheme 28) followed by treatment with zinc in acetic acid gave a crude product which on filtration through alumina readily separated the less polar components which consisted of mainly 2-chloro-5 $\alpha$ -androst-2-en-17 $\beta$ -ol acetate (115). This product also contained some (10%) of the non-chlorinated olefin (116a and 116b). The presence of the non-chlorinated olefin could occur in a trivial way as a result of incomplete chlorination giving some monochloro olefin (115) or through loss of a chlorine atom during borohydride reduction as is known to occur with  $\alpha$ -bromoketones (59). These possibilities have been ruled out and it is probable that reduction occurs through initial reductive loss by zinc of one chlorine to give the monochloro olefin (115) as shown in Scheme 28 and discussed below.

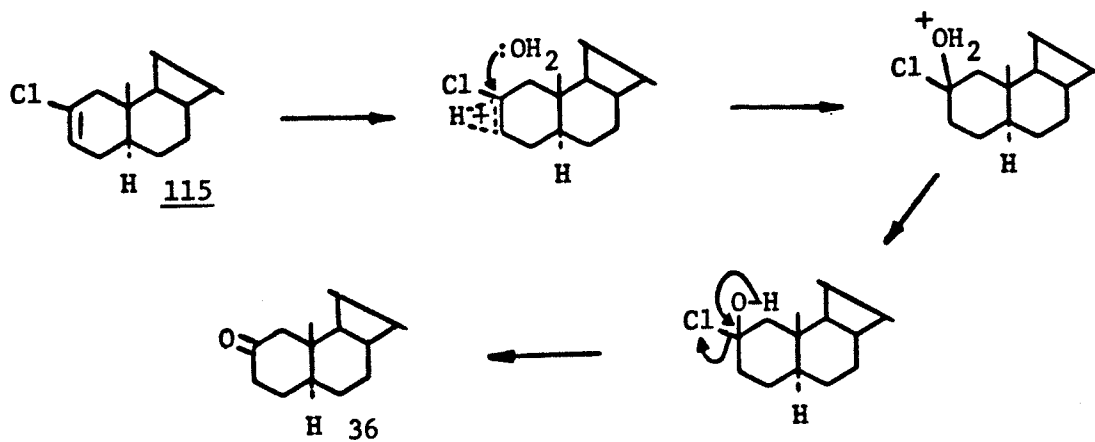


Scheme 28.

The elimination of a chlorine atom by zinc is thought (60) to occur through the formation of a carbanion intermediate which in this case is stabilized by the inductive effect of the chlorine atom. Most probably the initial attack of the zinc is on the more accessible equatorial C-2 chlorine atom causing elimination of the axial chlorine. The carbanion can either displace the C-3 mesylate to form the monochloro olefin (115) or be protonated to give the monochloro mesylate. The monochloro mesylate can then further react to give the non-chlorinated olefin. This explanation is supported by the fact that when the dichloroalcohols (113, R=H) are treated with zinc in acetic acid or zinc-copper couple the non-chlorinated olefin (116a) is obtained as the major product together with some hydrolysis of the C-17 acetate (116b) and 25% vinyl chloride (115). As mesylate is a good leaving group compared with hydroxyl the relative rate of elimination ( $K_1$ ) is greater than protonation ( $K_2$ ) whereas the rates are reversed when the hydroxyl group is present.

The vinyl chloride itself is stable to these reaction conditions (zinc in acetic acid) which is consistent with that reported for other vinyl chlorides (60). Vinyl chlorides are less nucleophilic than the unsubstituted olefin because of the strong inductive effect of the chlorine.

Several methods (61-68) are available for the conversion of vinyl chlorides into the corresponding ketones. This C-2 chloro olefin (115) is readily hydrolysed with concentrated sulfuric acid at 0 C<sup>o</sup> to the ketone (65) as shown in Scheme 29.



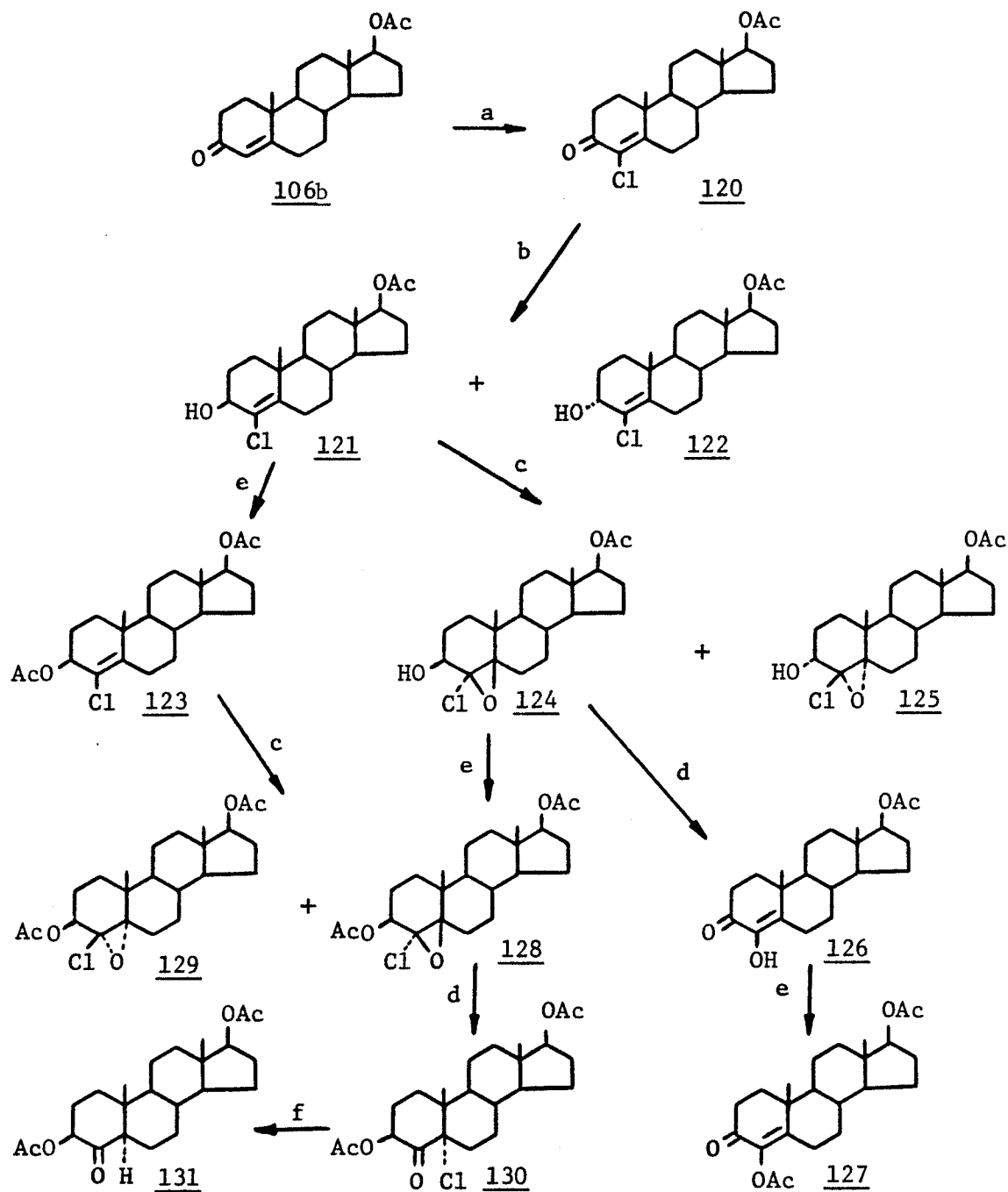
Scheme 29.

The C-2 chloro olefin (115) shows a higher melting point (123-123.5 C<sup>o</sup>) than that reported earlier (90-92 C<sup>o</sup>) (12). The earlier preparation was based on phosphorous pentachloride treatment of the C-2 ketone and the earlier workers (12) suggested that although it appeared to be homogeneous that it may have been a mixture of the C-1 and C-2 olefins. In our preparation there is no reason to expect an isomeric mixture and the higher and sharper melting point obtained is consistent with their suggestion that their sample was a mixture. The C-2 chloro olefin (115) can be prepared in 86% overall yield without isolation of intermediate products in the first four steps. The melting point of the C-2 ketone (36) was consistent with that reported previously (12). The overall synthesis is shown in Scheme 25.

### Synthesis of a C-4 steroid ketone

The chlorination product of testosterone acetate (106b) (Scheme 30) with sulfuryl chloride gave 4-chlorotestosterone acetate (120) which showed a melting point consistent with that reported earlier (69). Examination of the  $^1\text{H}$  NMR spectrum showed the chemical shift of the C-13 methyl and the C-10 methyl groups to be in agreement with the expected values. There was no evidence for a C-4 vinylic proton consistent with the presence of the C-4 substituted chlorine atom. The infrared spectrum shows a C-3 carbonyl stretching vibration at  $1685\text{ cm}^{-1}$  and olefinic absorption at  $1588\text{ cm}^{-1}$  with a carbonyl group at  $1730\text{ cm}^{-1}$  for the  $17\beta$ -acetate. Reduction with lithium tri-*t*-butoxyaluminum hydride gave a product with two components on TLC corresponding to the  $3\alpha$ - and  $3\beta$ -alcohol (122, 121); crystallization gave the major product which showed a molecular ion cluster at  $m/z$  366, 368 in its mass spectrum. Chlorine and hydrogen chloride were lost from the molecular ion giving rise to fragment ions at  $m/z$  333, 332. The  $^1\text{H}$  NMR spectrum shows the chemical shift of the C-3 proton downfield from the methylene envelope as an unresolved multiplet. The stereochemistry of the C-3 alcohol was assigned the equatorial configuration based on the C-3 proton ( $W_{1/2} = 15\text{ Hz}$ ) which is in agreement with the value published for the analogous C-3 allylic alcohol (39). Reduction of the unsubstituted  $\alpha,\beta$ -unsaturated ketone with lithium tri-*t*-butoxyaluminum hydride is known to give the  $3\beta$ -alcohol as the major product (70). The infrared spectrum shows free hydroxyl group stretching absorption at  $3600\text{ cm}^{-1}$  and a weak absorption at  $1640\text{ cm}^{-1}$  corresponding to the C-4 olefinic stretch absorption.

The C-3 acetate (123) shows the same melting point as reported previously (71). 4-Chloroandrost-4-ene- $3\beta,17\beta$ -diol diacetate (123) has



Reagents: a)  $\text{SO}_2\text{Cl}_2/\text{C}_5\text{H}_5\text{N}$ ; b)  $\text{LiAl}(\text{OC}(\text{CH}_3)_3)_3\text{H}/\text{THF}$ ; c)  $m\text{-ClC}_6\text{H}_4\text{O}_3\text{H}/\text{CH}_2\text{Cl}_2$ ; d)  $190\text{-}200\text{ C}^\circ$ ; e)  $\text{Ac}_2\text{O}/\text{C}_5\text{H}_5\text{N}$ ; f)  $\text{Zn}/\text{Cu}/\text{EtOH}$ .

Scheme 30.

been previously prepared by microbial reduction of 4-chloro-4-androstene-3,17-dione (71). Although the melting point obtained here is in agreement with the published value the  $^1\text{H}$  NMR data previously reported is clearly incorrect. Our results show the chemical shift of the C-3 proton at 5.39 ppm as a broad multiplet moved downfield because of the deshielding effect of the C-3 acetoxy function (44). The chemical shift of the C-3 proton is significantly greater (+1.24 ppm) than the chemical shift of the C-3 proton in compound 123 indicative of the substituted acetyl group at this position. The chemical shift of the C-3 acetate appeared at 2.10 ppm compared to the chemical shift of the C-17 acetate at 2.03 ppm.

Epoxidation of the  $3\beta$ -alcohol (121) with *m*-chloroperbenzoic acid gave the  $5\beta$ -epoxyalcohol (124) as the major product which showed a chemical shift of the C-3 proton at 4.30 ppm ( $J = 3.1$  and  $5.4$  Hz) as a doublet of doublets. The stereochemistry of the C-3 hydroxyl group was assigned by the coupling constant of this downfield proton which corresponds to a pseudoaxial proton undergoing axial-equatorial coupling. The  $^1\text{H}$  NMR spectrum of the epoxidation reaction mixture showed by subtraction of the spectrum of the purified  $5\beta$ -epoxyalcohol (124) the presence of the  $5\alpha$ -epoxyalcohol (125) in the proportion 125:124; 1:3. The infrared spectrum of 124 shows free hydroxyl stretching absorption at  $3594\text{ cm}^{-1}$  and no olefinic absorption. Pyrolysis of the  $5\beta$ -epoxyalcohol (124) at  $200\text{ C}^\circ$  for 10 min gave an unexpected product which showed a positive ferric chloride test (72) and was identified as the diosphenol (126) which together with its diacetate (127) were characterized by comparison with published data [ mp, IR,  $^1\text{H}$  NMR ] (73,74). The mechanism of this thermal rearrangement is discussed

later. Examination of the  $^1\text{H}$  NMR spectrum of (127) showed the chemical shift of the C-4 acetate protons peak appeared at 2.23 ppm downfield compared to the C-17 acetate protons peak at 2.04 ppm. Evidence from its infrared spectrum shows a band corresponding to the carbonyl stretch absorption of the C-4 acetate at  $1758\text{ cm}^{-1}$  and in the double bond region at  $1630\text{ cm}^{-1}$  a strong absorption indicative of a (C=C) stretching vibration which suggests that the group in the ring-A is an enol acetate. The 5 $\beta$ -epoxyacetate (128) shows the C-3 proton shifted further downfield at 5.49 as a doublet of doublets compared with the C-3 proton of the 5 $\beta$ -epoxyalcohol (124) at 4.30ppm. Epoxidation of the C-3 acetate (123) gave the 5 $\alpha$ -epoxyacetate (129) (Scheme 30) which shows the chemical shift of the C-3 proton as a triplet at 5.25 ppm. The stereochemistry of these two epoxides (128, 129) can be assigned from the coupling constant of their C-3 proton. The C-3 proton of the epoxy acetate (128) has a coupling constant ( $J= 3.9$  and  $5.8$  Hz) and ( $W_{1/2} = 3.9 + 5.8 = 9.7$  Hz) indicating the C-3 proton is in an equatorial configuration and the 4,5-oxido group will therefore be in an axial configuration. The other 5 $\alpha$ -epoxyacetate (129) has a coupling constant ( $J= 8.5$  Hz) and ( $W_{1/2} = 8.5 \times 2 = 17$  Hz) which is assigned to the axial proton making the 4,5-oxido group in the  $\alpha$ -configuration. The pyrolysis product (130) of the 5 $\beta$ -epoxyacetate (128) showed a molecular ion cluster at  $m/z$  424, 426 in its mass spectrum. Fragments at  $m/z$  389 and  $m/z$  382 and 384 corresponds to loss of chlorine and ketene, respectively. The mass spectrum also shows signals at  $m/z$  373; 364 and 366; 328; and 313 which indicate loss of hydrogen chloride and methyl group; acetic acid; acetic acid and hydrogen chloride; acetic acid, hydrogen chloride and methyl group respectively. The  $^1\text{H}$  NMR spectrum

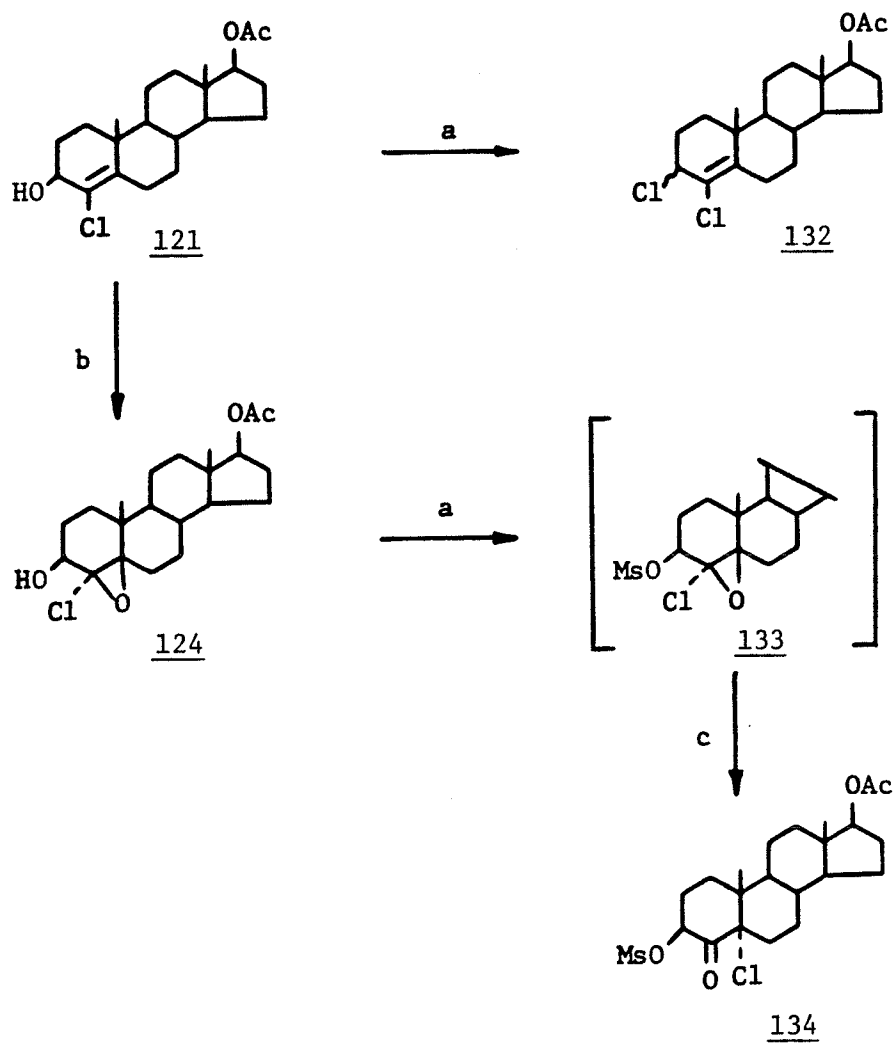


shows the chemical shift of the C-3 proton at 6.18 ppm as a doublet of doublets. This proton is strongly deshielded by the 1,3-diaxial relationship to the 5 $\alpha$ -chlorine. The coupling constant of this proton ( $J = 8$  and  $12$  Hz) which undergoes an axial-equatorial and an axial-axial coupling proves that the acetate group at C-3 is equatorial. The chemical shift of the C-3 acetate appeared at 2.16 ppm and the C-17 acetate at 2.04 ppm. Data published in the cholestane series for a compound similarly substituted in ring-A are in agreement with these results (75). The infrared spectrum shows the C-4 keto group stretching absorption band at  $1755\text{ cm}^{-1}$ . The carbonyl groups of the C-3 and C-17 diacetate appeared together at  $1735\text{ cm}^{-1}$ . The (C-O) stretching vibration of C-17 acetate at  $1230\text{ cm}^{-1}$  and for C-3 acetate at  $1245\text{ cm}^{-1}$ . The above spectra are in complete agreement with the proposed structure.

Treatment of the 5 $\alpha$ -chloroketone (130) with zinc-copper couple gave a dechlorinated product (131) (Scheme 30) which indicated a molecular ion at  $m/z$  390. The fragment ion at  $m/z$  348 corresponds to loss of ketene ( $\text{CH}_2\text{C}=\text{O}$ ) which can arise from an acetate group and also another fragment at  $m/z$  330 corresponding to loss of acetic acid. Examination of the  $^1\text{H}$  NMR spectrum (Table 3) shows a chemical shift of the C-3 proton at 5.16 ppm as a doublet of doublets and a coupling constant ( $J = 7$  and  $10$  Hz). Axial-equatorial and an axial-axial coupling with the C-2 protons allows the assignment of the stereochemistry of the C-3 acetate as equatorial. The acetate methyl chemical shift appears at 2.14 ppm compared to the C-17 acetate protons at 2.03 ppm. The infrared spectrum shows the C-4 carbonyl stretching absorption band at  $1760\text{ cm}^{-1}$  and the carbonyl group of the C-3 and C-17 acetate appeared together at  $1738\text{ cm}^{-1}$ . This zinc reduction product supports the structure of the 5 $\alpha$ -chloroderivative (130).

Treatment of the alcohol (121) with mesyl chloride in pyridine for (1.45 hr.) gave a single product on TLC. This product has been identified as 3 $\xi$ ,4-chloro-4-androsten-17 $\beta$ -ol acetate (132) (Scheme 31) on the basis of the following evidence: the infrared spectrum shows no hydroxyl absorption, no methanesulfonate bands but showed weak olefin absorption 1630  $\text{cm}^{-1}$ ; the mass spectrum showed highest mass signals at m/z 384, 386, 388 corresponding to the presence of two chlorine atoms with loss of fragments corresponding to chlorine, hydrogen chloride and acetic acid;  $^1\text{H}$  NMR spectrum shows a multiplet 4.58 ppm overlapping with the C-17 $\alpha$ -proton, and the absence of the methanesulfonate protons. The result can be rationalized in terms of the formation of the allylic cation and addition of chloride ion.

Mesylation of the 5 $\beta$ -epoxyalcohol (124) gave a product which showed two components on TLC which on heating was converted to one of the components. The  $^1\text{H}$  NMR spectrum of the reaction mixture compared with that of the purified single product corresponded to the expected pyrolysis product (134). The epoxymesylate (133) appears to undergo thermal rearrangement more easily than the 5 $\beta$ -epoxy acetate (128) which could be isolated under the same conditions.



Reagents: a)  $\text{CH}_3\text{SO}_2\text{Cl}/\text{C}_5\text{H}_5\text{N}$ ; b)  $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}/\text{CH}_2\text{Cl}_2$ ;  
 c)  $190\text{-}200\text{ }^\circ\text{C}$ .

Scheme 31.

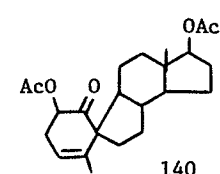
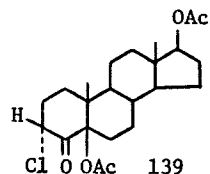
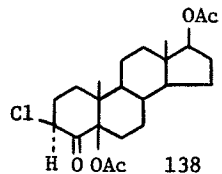
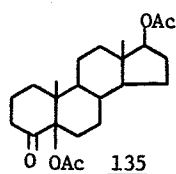
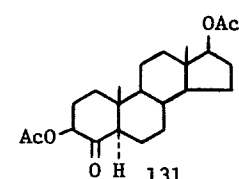
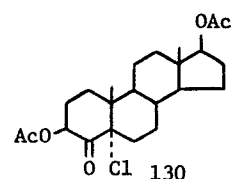
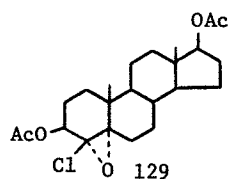
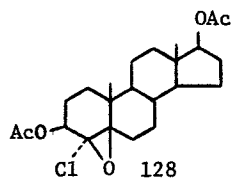
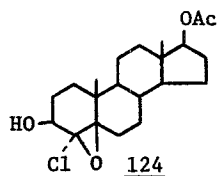
Whereas pyrolysis of the 5 $\beta$ -epoxide (128) led to the expected thermal rearrangement product in high yield, similar pyrolysis of the 5 $\alpha$ -epoxide (129) did not lead to a simple rearrangement product as expected on the basis of the proposed  $\alpha$ -ketocarbenium ion intermediate (42,76). Pyrolysis of the 5 $\alpha$ -epoxide (129) gave a mixture containing three major components on TLC and on HPLC. HPLC separation gave these three as crystalline compounds with a fourth minor component obtained crystalline from column chromatography. The remaining substances were not obtained in a completely pure form. Two of the crystalline products contained chlorine in their elemental analysis and mass spectra while the remaining two had lost the elements of hydrogen chloride and showed unsaturated carbon atoms in the  $^{13}\text{C}$  NMR (Table 4). The chlorine containing compounds showed a molecular weight isomeric with the 5 $\alpha$ -epoxide (129). The  $^1\text{H}$  NMR showed a downfield proton coupling which indicated an equatorial proton (5.12,t, J = 3.3 Hz) in one and an axial proton (4.61, dd, J = 6.5 and 12 Hz) in the other suggesting a pair of C-3 epimers. An equatorial C-3 proton may arise through formation of a 5 $\beta$ -derivative as conversion from the 5 $\alpha$ - to the 5 $\beta$ -structure reverses the initial C-3 axial proton in the 5 $\alpha$ -epoxide (129) (see Scheme 32), and if a 5 $\beta$ -derivative were formed there would be a severe 1,3-diaxial interaction between an axial group at C-3 and the 5 $\beta$  substituent. This interaction would favour epimerization (through the enol) to give the C-3 axial proton thereby leading to a pair of C-3 epimers.

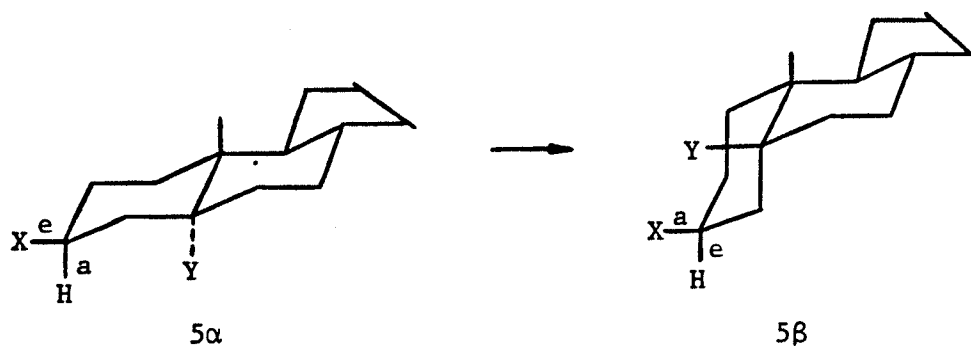
Treatment of the compound containing the C-3 axial proton with zinc-copper couple gave two main products; 5 $\alpha$ -androstan-4-one-3 $\beta$ ,17 $\beta$ -diol diacetate (131) (Scheme 33) was identified by comparison with the properties (mp, IR, MS,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR) of the previously obtained

TABLE 4

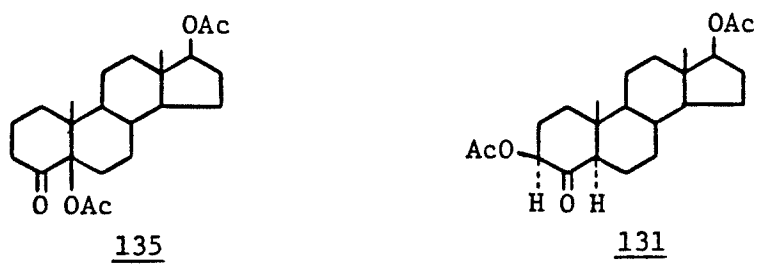
 $^{13}\text{C}$  NMR SPECTRA OF ANDROSTAN-17 $\beta$ -OL ACETATE DERIVATIVES

C	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	3 COCH <sub>3</sub>	3 COCH <sub>3</sub>	17 COCH <sub>3</sub>	17 COCH <sub>3</sub>
124	26.0	27.1	73.4	88.2	74.9	26.7	29.4	35.0	48.1	37.7	21.1	36.8	42.8	50.5	23.7	27.7	82.7	12.2	18.8			21.3	171.3
128	26.6	24.2	74.7	85.2	72.7	29.1	29.4	35.1	49.1	37.4	21.2	36.8	42.8	50.4	23.7	27.7	82.7	12.2	18.4	21.3	170.4	21.3	171.3
129	[28.2]	(24.1)	68.7	87.1	73.6	[28.6]	(25.9)	34.9	50.2	37.2	20.5	36.8	42.8	50.2	23.6	27.7	82.8	12.3	17.2	21.3	169.9	21.3	171.3
130	30.8	27.4	72.3	200.4	81.7	28.8	25.0	34.4	45.6	44.7	21.3	37.0	43.0	50.3	23.5	27.7	82.7	12.4	16.5	20.8	170.0	21.3	171.2
131	36.1	28.6	76.3	205.7	57.5	20.2	30.0	34.9	54.4	(42.9)	21.4	37.0	(42.8)	50.6	23.6	27.7	82.8	12.3	13.9	20.9	170.3	21.3	171.4
135	30.8	21.9	39.8	208.4	87.7	27.5	26.0	33.8	41.8	45.7	20.3	36.8	42.6	50.7	23.6	27.7	82.8	12.2	17.8	21.5	170.1	21.3	171.3
138	(26.4)	(25.1)	73.4	198.6		(32.5)	(29.3)	34.1	45.8	44.2	21.5	36.8	42.5	50.7	23.6	27.7	82.5	12.1	18.2	21.3	170.0	21.3	171.2
139	(27.0)	(27.3)	62.0	199.4	88.6	[30.5]	[33.3]	33.7	41.6	45.5	20.3	36.6	42.6	50.5	23.6	27.7	82.7	12.2	17.5	[21.4]	170.2	[21.3]	171.2
140	121.2	(30.4)	73.7	206.6	61.4	(30.8)	(31.4)	45.6	58.2	138.3	24.1	37.0	44.0	51.0	23.3	28.1	82.3	12.9	22.3	20.9	170.4	21.3	171.2





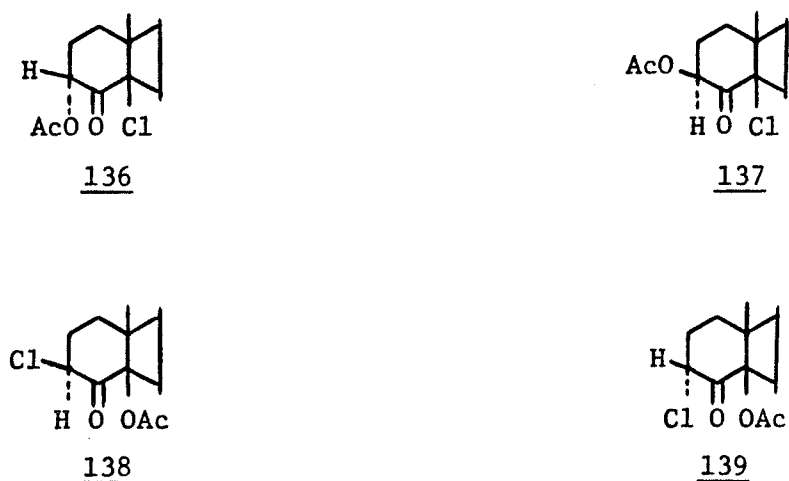
Scheme 32.



Products obtained from 138 by treatment with zinc-copper couple.

Scheme 33.

product from zinc copper couple treatment of the 5 $\alpha$ -chloroderivative (130) and 5 $\beta$ -androstan-4-one-5,17 $\beta$ -diol diacetate (135); this compound showed no downfield methine proton corresponding to a secondary acetate and the  $^{13}\text{C}$  NMR shows one more methylene carbon, one less methine proton and one more quaternary proton. [The  $^1\text{H}$  NMR chemical shift of the C-10 methyl protons 1.12 ppm is somewhat upfield of that obtained from substituent additivity relationships (43) or by comparison with 5 $\beta$ -cholestan-4-on-5-ol (1.03 ppm) (77). This lack of additivity may be attributed to interactions between the functions because of their proximity]. Because zinc-copper couple treatment gave both the 3 $\beta$ - and 5 $\beta$ -acetates it does not establish the initial site of the acetate or chlorine function although it does show that they are in the  $\alpha,\alpha$ -positions. Furthermore the products establish that no rearrangement of the carbon skeleton has occurred. These results suggest two pairs of epimers (Scheme 34) but does not exclude one from each pair.

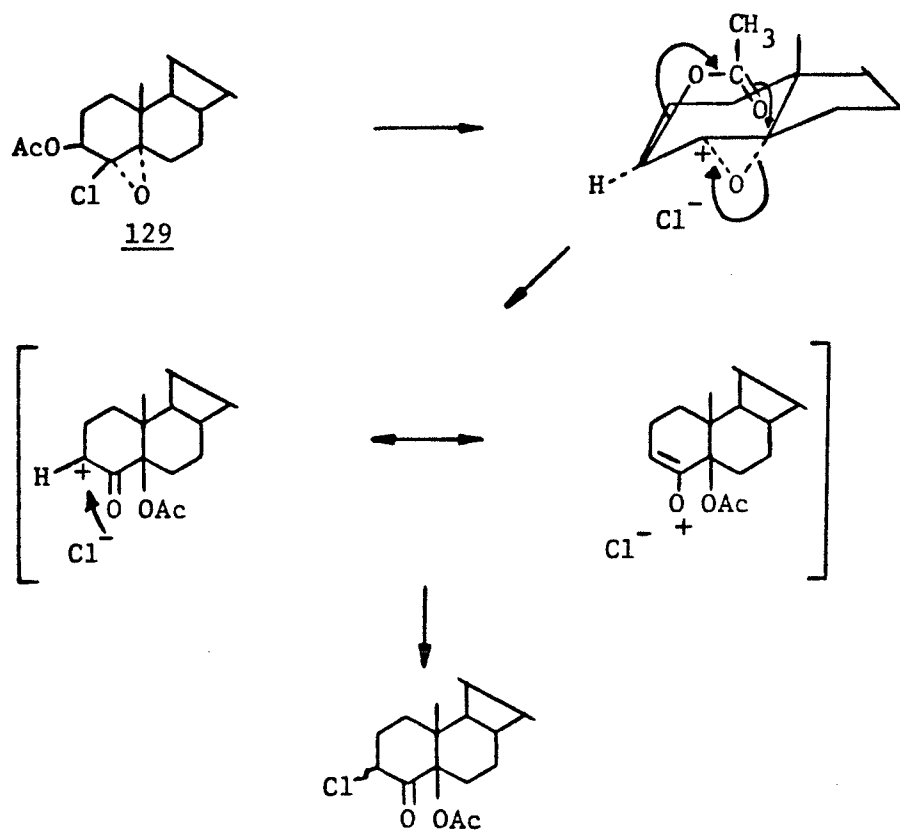


Scheme 34.

The C-3 axial hydrogen in the 5 $\beta$ -chloro derivative (136) would be

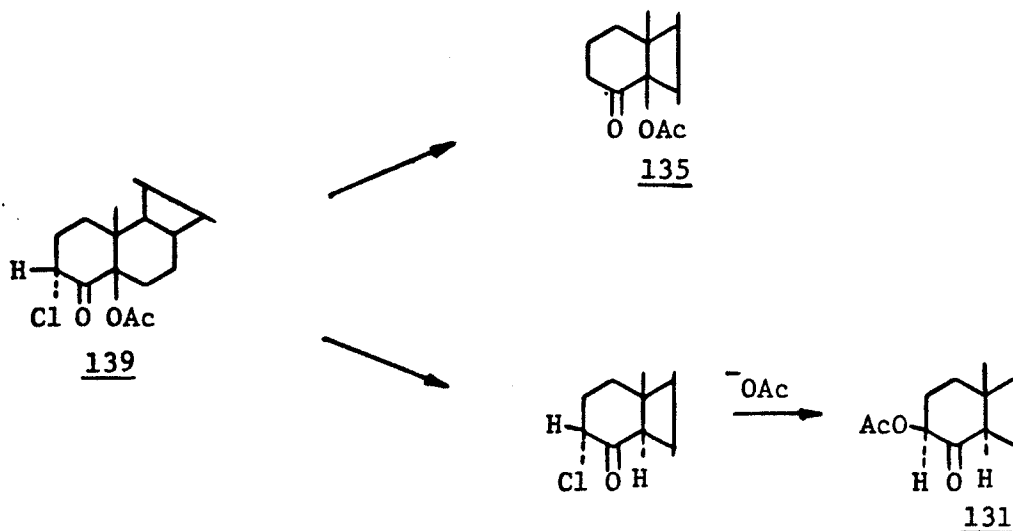
expected to resonate at about 6.18 ppm as it is in a 1,3-diaxial relationship to the 5 $\beta$ -chlorine (137) analogous to that relationship in the 5 $\alpha$ -chloro compound (130). The C-3 proton absorbs at 4.16 ppm which is more compatible with the chemical shift of a methine proton on a carbon attached to a chlorine atom; the equivalent 1,3-diaxial 5 $\beta$ -acetate interaction is about 0.1 ppm (78). The C-3 hydrogen in the epimeric compound (137) resonates at 5.12 ppm. The chemical shift of the C-10 methyl group is consistent between the 5 $\beta$ -acetate (135), the 3 $\beta$ -chloro-5 $\beta$ -acetate (138) and the 3 $\alpha$ -chloro-5 $\beta$ -acetate (139); the small differences being attributed to the C-3 chlorine. Similarly the  $^{13}\text{C}$  NMR spectra are internally consistent for these three compounds. [Again additivity rules (79-81) are of less predictive value because of the mutual interaction between the adjacent group]. The  $^{13}\text{C}$  NMR fit for the isomeric 5 $\beta$ -chloro derivatives is in poorer agreement although as both chlorine and acetoxy have similar effects on the  $^{13}\text{C}$  NMR spectrum the direction of change is parallel. As the 5 $\alpha$ - and 5 $\beta$ -epoxides (129, 128) give different products on thermal rearrangement the proposed (76,77)  $\alpha$ -ketocarbenium ion-chlorine ion pair (see below) which should lead to the same rearrangement products is less likely than an intermediate which retains stereochemical control. A mechanism is proposed for the rearrangement in Scheme 35.





Epimeric halogen products were obtained in other thermal rearrangements of haloepoxides (82,84).

The formation of the  $3\beta$ -acetoxy derivative (131) from zinc-copper couple reduction of 139 may arise from acetate ion (from  $\text{Zn}(\text{OAc})_2$ ) from the zinc-copper couple displacement of the axial chlorine atom if reductive removal of the  $5\beta$ -acetate (135) occurs first as shown in Scheme 36.

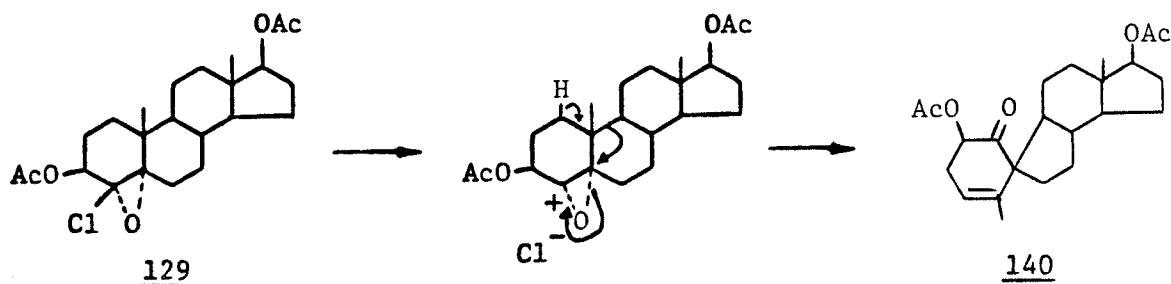


Scheme 36.

The major olefinic compound contained no chlorine as determined from elemental analysis and the mass spectrum. This compound has been identified as (S)-5-spiroandrost-1(10)-en-4-one-3 $\beta$ ,17 $\beta$ -diol diacetate (140) on the following evidence:  $^1\text{H}$  NMR homonuclear shift correlation spectra show that the C-1 vinylic proton is coupled with two protons which appear as multiplets at 2.40 and 2.65 ppm and are assigned to the C-2 methylene protons. A further coupling is observed with protons of the C-10 methyl group at 1.81 ppm which exhibits allylic coupling. The relationship between the C-1 vinylic proton and the 3 $\alpha$ -hydrogen is shown by the coupling of the 3 $\alpha$ -hydrogen with the same protons at 2.40 and 2.65 ppm which were coupled with the vinylic proton. The coupling constants of the 3 $\alpha$ -proton ( $J = 8$  and  $11.9$  Hz) clearly distinguish it an axial proton establishing the substance as the 3 $\beta$ -acetate.

Decoupling experiments show that irradiation of the C-10 methyl group at 1.81 ppm resolves the doublet observed for the C-1 vinyl proton into a doublet of doublets by removing the allylic coupling. Decoupling

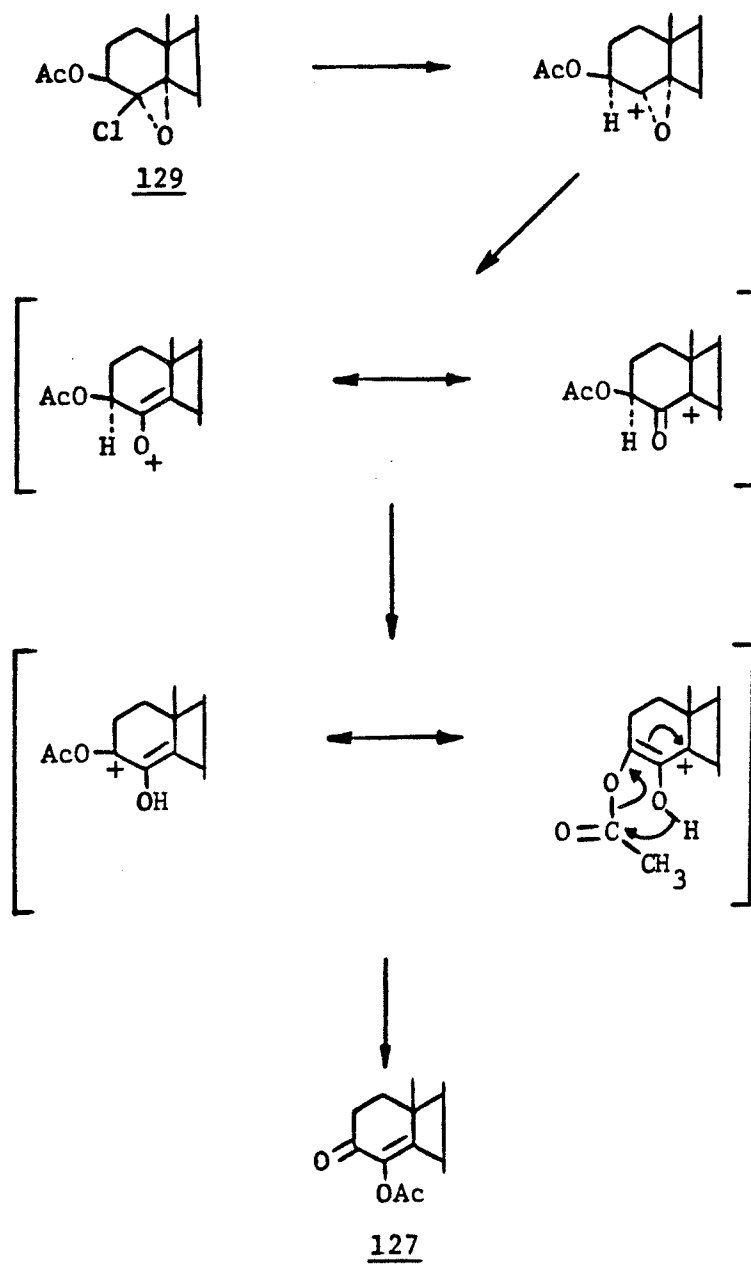
of the C-1 vinyl proton produces simplification of the proton at 2.65 ppm. The  $^{13}\text{C}$  NMR showed the presence of unsaturated carbon atoms and the atoms have been assigned as shown in Table 3 and is consistent with the structure. A proposed mechanism is shown in Scheme 37 for the formation of this compound.



Scheme 37.

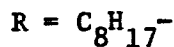
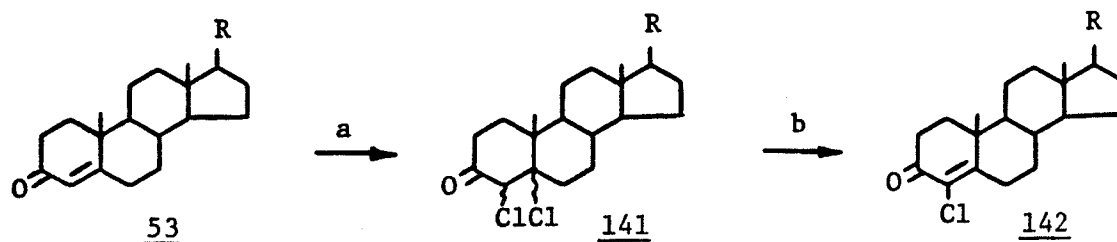
Related rearrangements have been demonstrated (85).

A second unsaturated compound has been identified as 4-androsten-3-one-4,17 $\beta$ -diol diacetate (127) by comparison of its properties (mp, TLC, IR,  $^1\text{H}$  NMR) with the material identified earlier. A mechanism is proposed in Scheme 38.



Scheme 38.

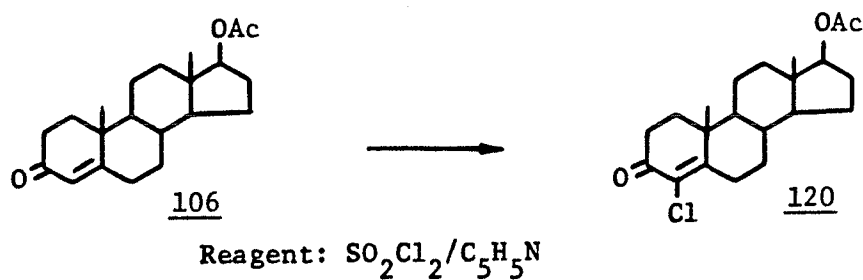
4-Chloro-4-en-3-oxo-steroids were first synthesized by Kirk (86), Camerino (72) and Ringold (87) in 1956. Kirk has shown that treatment of the C-4-unsaturated-3-ketosteroid (53) (Scheme 39) with chlorine in the presence of propionic acid led to the 4 $\xi$ ,5 $\xi$ -dichloro-3-ketosteroid (141) and dehydrochlorination with pyridine gave 4-chloro-4-en-3-oxo-steroid (142).



Reagents: a)  $Cl_2/CH_3CH_2COOH$ ; b)  $C_5H_5N$ .

Scheme 39.

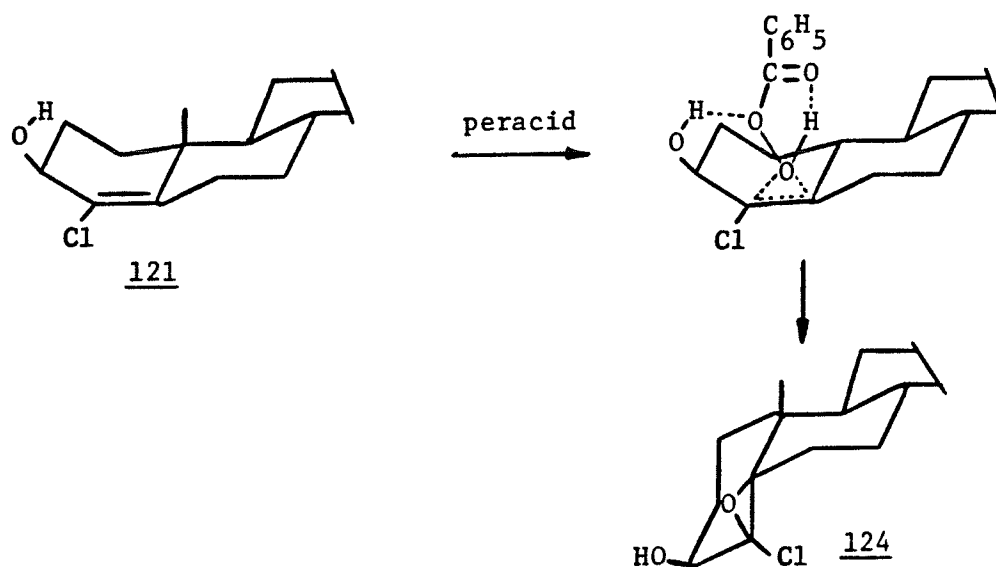
This procedure gives a low yield of the product. A better result was obtained by Mori (69) when he treated testosterone acetate (106) (Scheme 40) with sulfuryl chloride instead of chlorine (86). This reagent converted directly testosterone acetate (106) into 4-chloro-4-en-3-oxo-steroid (120) in the presence of pyridine.



Reagent:  $SO_2Cl_2/C_5H_5N$

Scheme 40.

4-Chlorotestosterone acetate (120) (Scheme 32) was prepared by the Mori method (69). This compound was reduced with lithium tri-*t*-butoxy-aluminium hydride to give a mixture of the 3 $\alpha$ - and 3 $\beta$ -alcohols (122, 121) (Scheme 30). The major product was the 3 $\beta$ -alcohol (121) (by TLC) and the ratio of 3 $\beta$ - to 3 $\alpha$ -alcohol was 9.3:0.7 (by HPLC). Epoxidation with *m*-chloroperbenzoic acid gave a mixture of the 5 $\alpha$ - and 5 $\beta$ -epoxides (129, 128). The 5 $\beta$ -epoxide (128) was the major product (5 $\alpha$ :5 $\beta$ ; 1:4 by HPLC). This major product was obtained by the directive effect of the C-3 hydroxyl group which has been suggested to arise from hydrogen bonding between the hydroxyl group and the attacking peracid (88,89). The optimum geometry for this epoxidation transition state is illustrated in Scheme 41.

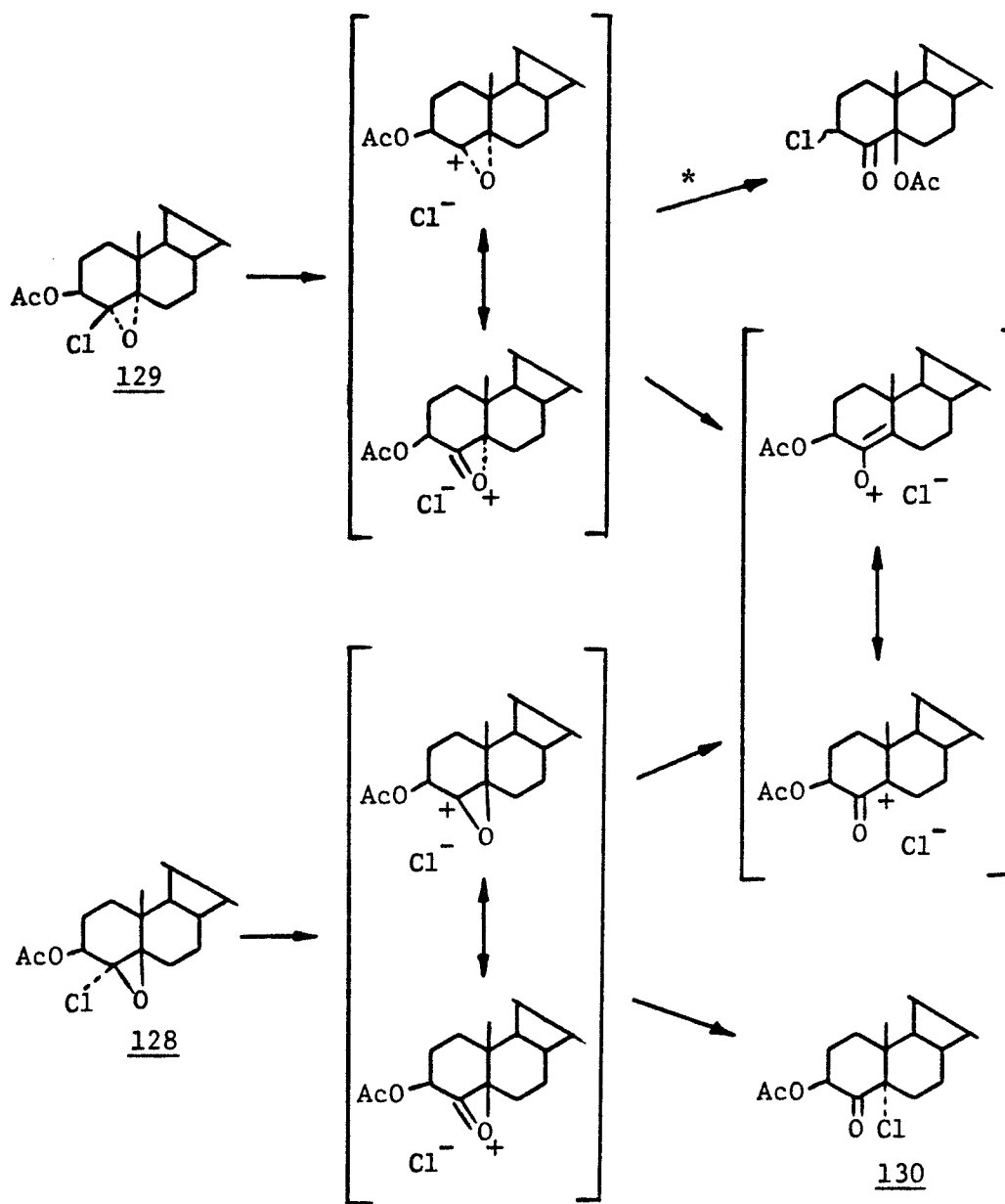


Scheme 41.

This observation was supported by the fact that when epoxidation of the C-4 olefin 3 $\beta$ -acetate (123) (Scheme 30) was carried out it gave a mixture of epoxides in the reversed ratio (5 $\alpha$ :5 $\beta$ ; 3:2 by HPLC) (129, 128).

It has been generally accepted since the initial postulate of McDonald and Tabor in 1967 that thermal rearrangement of chloroepoxides proceeds through an  $\alpha$ -ketocarbenium ion-chloride ion pair (42,76). More recently McDonald and Cousins (90) have concluded that the thermal rearrangement of chloroepoxides proceed by disrotatory  $C_{\beta}$ -O bond opening to an  $\alpha$ -ketocarbenium ion-chloride ion pair to account most readily for their kinetic data and for the stereochemistry of the C-Cl bond formed. Whereas a common  $\alpha$ -ketocarbenium ion intermediate from both 1-chloro-cis-and-trans-4-methyl-cyclohexene oxide accounts for the formation of the same  $\alpha$ -chloroketone from both, in contrast pyrolysis of the  $\alpha$ -epoxide (129) and  $\beta$ -epoxide (128) (see Scheme 42) gave difference epimeric  $\alpha$ -chloroketones from each, therefore, a common reactive intermediate from both the  $\alpha$ - and  $\beta$ -epoxide cannot be involved and the rearrangement, in this case, requires an intermediate which retains stereochemical preference. Denny et al. (82) erroneously depict the oxiranyl cation and the  $\alpha$ -ketocarbenium ion as resonance structures.

McDonald and Cousins (90) have provided evidence that the rate limiting step in the rearrangements of the chloroepoxides studied does not involve the formation of an oxiranyl cation-chloride ion pair and has favoured the  $\alpha$ -ketocarbenium ion-chloride ion pair formed by disrotatory  $C_{\beta}$ -O bond opening as the intermediate leading to the observed products. These results do not prove that an oxiranyl cation chloride ion pair is not an intermediate. Both the  $\alpha$ -epoxide (129) and  $\beta$ -epoxide (128) are able to undergo disrotary  $C_{\beta}$ -O bond opening to the same  $\alpha$ -ketocarbenium ion which would lead to the formation of the same  $\alpha$ -chloroketone from both the  $\alpha$ - and  $\beta$ -epoxides. The epimeric  $\alpha$ -chloroketones obtained on thermal rearrangement of the  $\alpha$ -epoxide (129) and  $\beta$ -epoxide (128) can best be accounted for by addition of chloride ion



\* see also Scheme 32.

Scheme 42.

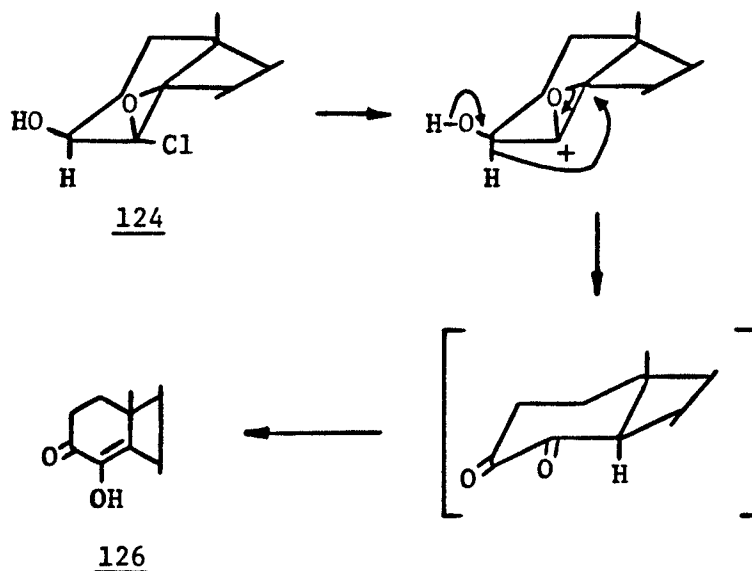


to an oxiranyl cation intermediate (see Scheme 42) which would result in stereospecific addition of chloride ion to give the observed products. Other intermediates requiring stereospecific addition of chloride ion such as a chloronium ion or other concerted mechanism have been ruled out in extensive studies by McDonald et al (91-93). Although formation of the oxiranyl cation intermediate may not be the rate limiting step in the formation of an  $\alpha$ -ketocarbenium ion in the cases studied by McDonald, in this steroid example chloride addition to an oxiranyl cation best accounts for the stereochemistry of the  $\alpha$ -chloroketones formed.

A stereospecific intermediate is consistent with the observation that the  $\beta$ -epoxide (128) rearranges quantitatively (as does the  $3\beta$ -mesylate (133) whereas the  $\alpha$ -epoxide (129) rearranges with the formation of several products. Besides the  $3\beta$ -chloroketone (138) (31%) the epimeric  $3\alpha$ -chloroketone (139) (34%) is obtained. Together 65% of the rearrangement product results from stereospecific rearrangement of the  $5\alpha$ -epoxide (129) which is favourably oriented for migration of the bond whereas in the  $5\beta$ -epoxide an unfavourable cis relationship exists. Examination of the stereochemistry of the  $5\beta$ -epoxide (128) shows that approach of chloride ion to C-5 leads to epoxide ring opening and a trans ring junction with inversion of the pseudoaxial  $3\beta$ -acetate to the equatorial configuration. Three 1,3-diaxial hydrogen interactions are encountered on approach of chloride ion to C-5 to give the axial chloride product. Alternatively, in the  $5\alpha$ -epoxide, the approach of chloride ion to C-5 encounter two 1,3-diaxial hydrogen and one, more

severe, 1,3-diaxial methyl interaction which leads to the more strained cis ring junction with an axial chloride. The energetically less favoured addition of chloride to the  $\beta$ -face, therefore, allows competing reactions to occur. This difference in reactivity between the steroid  $5\alpha$ - and  $5\beta$ -epoxides would not be predicted if a common intermediate were involved.

The novel thermal rearrangement which occurs with the  $5\beta$ -epoxide (124) leads quantitatively to the diosphenol (126) (Scheme 43). This rearrangement apparently proceeds through initial formation of the oxiranyl cation intermediate (or in this case possibly the 2-keto-carbenium ion) which undergoes proton loss at the  $3\beta$ -alcohol and a 1,3-hydride shift of the pseudo-axial C- $3\alpha$ H to the axial C- $5\alpha$ -position. The resulting 3,4-diketone then enolizes to the unsaturated ketone.



Scheme 43.

## EXPERIMENTAL

### Instruments

Melting points (mp) were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Perkin-Elmer Model 237 Infrared spectrophotometer either as a KBr disc or in  $\text{CCl}_4$  solution as indicated below. Proton magnetic resonance ( $^1\text{H}$  NMR) spectra were recorded using deuteriochloroform ( $\text{CDCl}_3$ ) as the solvent and tetramethylsilane (TMS) as the internal standard using the following instruments: a. Bruker WH (90 MHz) for compounds of the C-2 ketone synthesis and some synthetic compounds of C-4 ketone synthesis; b. Bruker AM (300 MHz) for compounds of the C-4 ketone synthesis, recorded at the Department of Chemistry, University of Manitoba, Winnipeg, Manitoba. The following designations are used in characterizing  $^1\text{H}$  NMR signals: singlet (s), doublet (d), triplet (t), doublet of doublet (dd), multiplet (m) and width at half height ( $W_{1/2}$ ). Carbon-13 magnetic resonance ( $^{13}\text{C}$  NMR) spectra were recorded on a Bruker AM 300 using the polarization transfer spectroscopy technique (94,95) in  $\text{CDCl}_3$  (77.1 ppm peak as the internal standard).  $^1\text{H}$  and  $^{13}\text{C}$  NMR data are reported in Tables 3 and 4 respectively. Mass spectra (MS) were recorded on a Finnigan Quadrupole Model 1015 mass spectrophotometer at 70 eV using the direct probe method at the Department of Chemistry, University of Manitoba. Elemental analyses were performed by Mr. W. Baldeo at the Microanalytical Laboratory, School of Pharmacy, University of London, England or Guelph Chemical Laboratories Ltd. Guelph, Ontario. High pressure liquid chromatography (HPLC) was carried out on a Waters Scientific Ltd. M45G solvent delivery system with U6K Universal liquid chromatogram injector using RCM-100 radial Compression Separation System

(RCSS), and with  $\mu$ -Porasil column (10 $\mu$ ) (7.8 mm x 30 cm) and RCSS silica guard pak. The detector used was R 401 refractive index detector-differential refractometer. The sample solution injected has a concentration of about 50  $\mu$ g/ $\mu$ L in 10% v/v ethyl acetate/hexane (filtered and degassed) and the flow rate was 1.5 mL/min unless stated otherwise. The standards and their retention times (RT) were as follows: 2,2-dichloro-5 $\alpha$ -androstan-3 $\alpha$ ,17 $\beta$ -diol 17-acetate (7.5 min), 2,2-dichloro-5 $\alpha$ -androstan-3 $\beta$ ,17 $\beta$ -diol 17-acetate (8.5 min), 4-chloro-4-androstene-3 $\beta$ ,17 $\beta$ -diol 17-acetate (10 min), 4-chloro-4-androstene-3 $\alpha$ ,17 $\beta$ -diol 17-acetate (11.4 min), 4 $\beta$ -chloro-4,5-oxido-5 $\alpha$ -androstan-3 $\beta$ ,17 $\beta$ -diol diacetate (24.6 min), 4 $\alpha$ -chloro-4,5-oxido-5 $\beta$ -androstan-3 $\beta$ ,17 $\beta$ -diol diacetate (33.2 min), 5-chloro-5 $\alpha$ -androstan-4-one-3 $\beta$ ,17 $\beta$ -diol diacetate (17.1 min)\*, 3 $\alpha$ -chloro-5 $\beta$ -androstan-4-one-3,17 $\beta$ -diol diacetate (19.4 min) 3 $\beta$ -chloro-5 $\beta$ -androstan-4-one-5,17 $\beta$ -diol diacetate (26.8 min), (S)-5-spiroandrost-1(10)-en-4-one-3 $\alpha$ ,17 $\beta$ -diol diacetate (23.0 min) (\*Flow rate 1.9 mL/min).

#### Materials

Thin-layer chromatography (TLC) was carried out on Analtech 25 precoated silica gel GHLF plates 0.25 mm thickness using one of the following liquid phases: a. 10% ethyl acetate/petroleum ether; b. 25% ethyl acetate/petroleum ether 60° to 90°C; and c. 2% acetone/dichloromethane. The TLC plates were viewed under an ultraviolet (U.V.) source and/or spraying with a 4% v/v solution of concentrated sulfuric acid in 95% ethanol followed by heating at approximately 100°C in an oven for 5 to 10 minutes to produce a color ( $R_f$  data are given in Table 5). Column chromatography was carried out with alumina (Brockmann activity II aluminum oxide for chromatographic adsorption analysis, BDH Chemicals Ltd.). (neutral alumina ethyl acetate treated alumina prepared by

TABLE 5

R<sub>f</sub> VALUE OF ANDROSTANE DERIVATIVES ON PRE-COATED SILICA GEL TLC PLATES IN TWO SOLVENT SYSTEMS  
 (Plates were viewed under U.V. light and sprayed with 4% EtOH in conc. sulfuric acid and heated 100-110°C for 5 min. to develop a color).

Compound	R <sub>f</sub> (25% EtOAc/PE)		R <sub>f</sub> (2% Acetone/CH <sub>2</sub> Cl <sub>2</sub> )	
	Silica gel <sup>a</sup>	U.V. <sup>b</sup>	Silica gel <sup>a</sup>	U.V. <sup>b</sup>
5α-androstan-2-one-17β-ol acetate (36)	0.23 (brown)	-		
2,2-dichloro-5α-androstan-3-on-17β-ol acetate (112)	0.32 (reddish)	-		
2,2-dichloro-5α-androstan-3β,17β-diol 17-acetate (113)	0.21 (purple)	-		
2,2-dichloro-5α-androstan-3β,17β-diol 3-mesyate 17-acetate (114)	0.20 (purple)	-		
2-chloro-5α-androst-2-en-17β-ol acetate (115)	0.53 (brown)	-		
5α-androst-2-en-17β-ol acetate (116a)	0.56 (blue)	-		
4-chloro-4-androsten-3-on-17β-ol acetate (120)			0.38 (blue)	+
4-chloro-4-androstene-3β,17β-diol 17-acetate (121)	0.21 (pink)	-		
4-chloro-4-androstene-3β,17β-diol diacetate (123)	0.34 (purple)	-		
4α-chloro-4,5-oxido-5β-androstane-3β,17β-diol 17-acetate (124)	0.11 (blue)	-		
4β-chloro-4,5-oxido-5α-androstane-3β,17β-diol 17-acetate (125)	0.17 (brown)	-		
4-androsten-3-one-4,17β-diol diacetate (126)	0.15 (greenish)	+		
4-androsten-3-one-4,17β-diol 17-acetate (127)			0.36 (blue)	+
4α-chloro-4,5-oxido-5β-androstane-3β,17β-diol diacetate (128)	0.29 (greenish)	-		
4β-chloro-4,5-oxido-5α-androstane-3β,17β-diol diacetate (129)	0.31 (brown)	-		
5-chloro-5α-androstan-4-one-3β,17β-diol diacetate (130)	0.26 (blue)	-		
5α-androstan-4-one-3β,17β-diol diacetate (131)	0.18 (pink)	-		
3ξ,4-dichloro-4-androsten-17β-ol acetate (132)	0.75 (reddish)	-		
4α-chloro-4,5-oxido-5β-androstane-3β,17β-diol 3-mesyate 17-acetate (133)	0.16 (violet)	-		
5-chloro-5α-androstan-4-one-3β,17β-diol 3-mesyate 17-acetate (134)	0.17 (reddish)	-		
5β-androstan-4-one-5,17β-diol diacetate (135)	0.29 (pink)	-		
3β-chloro-5β-androstan-4-one-5,17β-diol diacetate (138)	0.36 (grey)	-		
3α-chloro-5β-androstan-4-one-5,17β-diol diacetate (139)	0.20 (blue)	-		
(S)-5-spiroandrost-2(10)-en-4-one-3β,17β-diol 17-acetate (140)	0.40 (orange)	-		

<sup>a</sup>Analtech 25 Silica Gel GHLF

<sup>b</sup>Long wave-length

immersing the alumina in ethyl acetate, stirring and letting the mixture stand for at least 2 days with occasional shaking, filtering and drying at 80°C (96)), or silica gel (Merck Silica Gel 60H for TLC from BDH Chemicals Ltd.).

#### Methods

##### 2,2-Dichloro-5 $\alpha$ -androstan-3-on-17 $\beta$ -ol acetate (112)

To 5 $\alpha$ -androstan-3-on-17 $\beta$ -ol acetate (34) (18.9 g) in glacial acetic acid (300 ml) containing conc. hydrochloric acid (3 drops) was added, dropwise at a rate to maintain a colorless solution, chlorine (8.0 g) in glacial acetic acid (100 ml). After addition over 10-15 min the reaction was allowed to stand for a further 10 min and poured into ice-water. The resulting white precipitate was filtered, washed with water and dissolved in dichloromethane. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated at reduced pressure below 25° to yield a crystalline residue (23.5 g), which on recrystallization from dichloromethane/methanol at room temperature gave 2,2-dichloro-5 $\alpha$ -androstan-3-on-17 $\beta$ -ol acetate, mp 166-168°; IR  $\nu_{\max}$  (CCl<sub>4</sub>), 1736 (17 $\beta$ -OAc and C-3 C=O) cm<sup>-1</sup>;

Anal. C, 58.13; H, 6.57; C<sub>19</sub>H<sub>26</sub>O<sub>3</sub>Cl<sub>2</sub> · ½ CH<sub>2</sub>Cl<sub>2</sub> requires C, 58.18; H, 7.04.

This compound decomposed on heating so that complete removal of solvent was not achieved.

##### 2,2-Dichloro-5 $\alpha$ -androstan-3 $\beta$ ,17 $\beta$ -diol 17-acetate (113)

To a stirred mixture of 2,2-dichloro-5 $\beta$ -androstan-3-on-17 $\beta$ -ol acetate (11.4 g) in ethanol (250 ml) was added sodium borohydride (1.06 g). After 30 min the reaction was carefully poured into ice-water containing excess dilute sulfuric acid. The reaction was extracted with dichloromethane which was washed with water, dried over anhydrous sodium

sulfate, and evaporated at reduced pressure to give a crude product (11 g) (3 $\alpha$ :3 $\beta$ ;1:9 by HPLC). Recrystallization from dichloromethane/methanol gave 2,2-dichloro-5 $\alpha$ -androstane-3 $\beta$ ,17 $\beta$ -diol 17-acetate (5.3 g), mp 165-167°C; IR  $\nu_{\max}$  (CCl<sub>4</sub>) 3595 (OH), 1738 (17 $\beta$ -OAc) cm<sup>-1</sup>; MS m/z: 402, 404, 406 (M<sup>+</sup>).

Anal. C, 62.50; H, 7.98; Cl 17.61; C<sub>21</sub>H<sub>32</sub>O<sub>3</sub>Cl<sub>2</sub> requires C, 62.53; H, 8.00; Cl, 17.58.

2,2-Dichloro-5 $\alpha$ -androstane-3 $\beta$ ,17 $\beta$ -diol 3-methanesulfonate 17-acetate (114)

2,2-Dichloro-5 $\beta$ -androstane-3 $\beta$ ,17 $\beta$ -diol 17-acetate (113) (4.2 g) was dissolved in pyridine (50 ml) and methanesulfonyl chloride (5 ml) added to the cooled solution. After standing at room temperature overnight the mixture was poured into excess cold water and extracted with dichloromethane. The organic layer was separated and washed with water, dried over anhydrous sodium sulfate and evaporated at reduced pressure at room temperature to yield a crude product (5.7 g). Recrystallization from dichloromethane/methanol gave the mesylate (114) (3.4 g) mp 196-200°; further recrystallization gave mp 229-230°C; IR  $\nu_{\max}$  (KBr) 1735 (17 $\beta$ -OAc), 1340 and 1175 (S=O), 970 (S-O) cm<sup>-1</sup>; MS m/z: 480, 482, 484 (M<sup>+</sup>), 420, 422 (M<sup>+</sup>-HOAc).

Anal. C, 54.77; H, 7.14; Cl, 14.70; S, 6.41; C<sub>22</sub>H<sub>34</sub>O<sub>5</sub>Cl<sub>2</sub>S requires C, 54.88; H, 7.12; Cl, 14.73; S, 6.66.

2-Chloro-5 $\alpha$ -androst-2-en-17 $\beta$ -ol acetate (115)

The steroid mesylate (114) (3.0 g) was added to a mechanically stirred mixture of zinc dust (75 g) in glacial acetic acid (125 ml). After 1 hr the reaction was poured into cold water and extracted with ether. The ether layer was washed with water, excess aqueous sodium

bicarbonate, brine, dried over anhydrous sodium sulfate to give 2-chloro-5 $\alpha$ -androst-2-en-17 $\beta$ -ol acetate (2.2 g). Recrystallization from ether/methanol yielded the vinyl chloride (115), (1.2 g), mp 123-123.5° (lit. (12) mp 90-92°C); IR  $\nu_{\max}$  (CCl<sub>4</sub>) 1734 (17 $\beta$ -OAc), 1660 (olefin), 1240 (C-O) cm<sup>-1</sup>; MS m/z: 350, 352 (M<sup>+</sup>), 262 (M<sup>+</sup>-C<sub>4</sub>H<sub>5</sub>Cl).

Preparation from 5 $\alpha$ -androstan-3-on-17 $\beta$ -ol acetate (2.4 g) without isolation of intermediates gave after treatment with zinc in acetic acid followed by filtration through neutral alumina in 10% benzene/hexane the vinyl chloride (115) (2.18 g), mp 117-120°C.

Treatment of 2-chloro-5 $\alpha$ -androst-2-en-17 $\beta$ -ol acetate (115) with zinc-copper couple.

The vinyl chloride (115) (150 mg) in ethanol (25 ml) was heated under reflux with 2% zinc-copper couple (3 g) (97) for 8 hrs. TLC showed no change. The reaction mixture was diluted with water and extracted with ether to give on recrystallization from dichloromethane/methanol the vinyl chloride (115) (81 mg) mp 118-120°; mixture mp was undepressed and IR (CCl<sub>4</sub>) was identical with the starting material.

Treatment of 2,2-dichloro-5 $\alpha$ -androstan-3 $\beta$ ,17 $\beta$ -diol 17-acetate (113) with zinc-copper couple.

To a stirred solution of 113 (537 mg) in ethanol (30 ml) was added zinc-copper couple (3 g) (97). After 8 hrs under reflux the mixture was poured into water and extracted with ether to give a product which contain a mixture (116a:116b; 3:1 by <sup>1</sup>H NMR comparison of the olefinic protons). Chromatography over ethyl acetate washed alumina with benzene/hexane mixtures gave 5 $\alpha$ -androst-2-en-17 $\beta$ -ol acetate (116a) (312 mg), mp 90-93°C (lit. (12) mp 96°C) and 5 $\alpha$ -androst-2-en-17 $\beta$ -ol (116b) (87.5 mg), mp 161-163°C (lit. (12) mp 165°C). Mixture mp and IR



( $\text{CCl}_4$ ) spectrum were in agreement with an authentic sample. A similar result was obtained by treatment of (113) with zinc and acetic acid.

5 $\alpha$ -Androstan-2-on-17 $\beta$ -ol acetate (36)

2-Chloro-5 $\alpha$ -androst-2-en-17 $\beta$ -ol acetate (115) (150 mg) was added to stirred and cooled (ice-bath) concentrated sulfuric acid (10 ml). After 1 hr the reaction mixture was poured onto crushed ice and extracted with ether. The ether extract was washed with water and excess sodium hydrogen carbonate solution to give a crystalline residue which after passing through neutral alumina in hexane/benzene mixtures gave a residue (138 mg) mp 147-9°C. (lit. (12) mp 149-150°C); IR  $\nu_{\text{max}}$  (KBr), 1732 (17 $\beta$ -OAc), 1720 (C-3 ketone), 1245 (C-0)  $\text{cm}^{-1}$ .

4-Chlorotestosterone acetate (120)

4-Chlorotestosterone acetate (120) mp 228-231°C (lit. (69) mp 228-230°C) was prepared from testosterone acetate (106) by the method of Mori (69). IR  $\nu_{\text{max}}$  (KBr) 1730 (17 $\beta$ -OAc), 1685 (C-3 C=O), 1588 (C-4 C=C-Cl)  $\text{cm}^{-1}$ ;

4-Chloro-4-androstene-3 $\beta$ ,17 $\beta$ -diol 17-acetate (121)

4-Chlorotestosterone acetate (120) (2 g) and lithium tri-*t*-butoxy-aluminium hydride (3.36 g) were dissolved in freshly distilled tetrahydrofuran (100 ml) in an ice-bath under argon and stirred for 3 hrs at which time no starting material remained by TLC (2% v/v acetone/dichloromethane). The reaction mixture was poured into saturated sodium hydrogen carbonate (100 ml) and extracted with dichloromethane. The organic layer was washed thoroughly with water, dried over anhydrous sodium sulfate and evaporated to give a crystalline residue which showed one major and one minor component on TLC (2% v/v acetone/dichloromethane) (3 $\alpha$ :3 $\beta$ ; 0.7:9.3 by HPLC). Recrystallization from dichloromethane/

ethyl acetate gave the 3 $\beta$ -alcohol (1.73 g) mp 169-173°C. Four recrystallizations gave an analytical sample mp 172-4°C. IR  $\nu_{\max}$  (CCl<sub>4</sub>): 3600 (OH), 1737 (17 $\beta$ -OAc) cm<sup>-1</sup>; ppm; MS m/z: 368, 366 (M<sup>+</sup>), 332 (M<sup>+</sup>-HCl).

Anal. C, 68.50; H, 8.68; Cl 9.73, C<sub>21</sub>H<sub>31</sub>O<sub>3</sub>Cl requires C, 68.74; H, 8.52; Cl, 9.66.

4-Chloro-4-androstene-3 $\beta$ ,17 $\beta$ -diol diacetate (123)

4-Chloro-4-androstene-3 $\beta$ ,17 $\beta$ -diol 17-acetate (121) (400 mg) was dissolved in dry pyridine (4 ml) and acetic anhydride (2 ml) added, after standing at room temperature overnight, dilution with ice-water, acidification and ether extraction the residue was recrystallized from dichloromethane/methanol to give the diacetate (315 mg) mp 145-147°C; (lit. (71) mp 145-147°C); MS m/z: 408, 410 (M<sup>+</sup>), 348, 350 (M<sup>+</sup>-HOAc).

4 $\alpha$ -Chloro-4,5-oxido-5 $\beta$ -androstane-3 $\beta$ ,17 $\beta$ -diol 17-acetate (124).

To 4-chloro-4-androstene-3 $\beta$ ,17 $\beta$ -diol 17-acetate (121) (250 mg) in dichloromethane (50 ml) was added 85% w/w m-chloroperbenzoic acid (275 mg) and the solution allowed to stand at room temperature until no starting material remained by TLC (18 hrs). The organic layer was washed thoroughly with saturated aqueous 10% w/v sodium sulfite, excess 5% w/v aqueous sodium carbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure at room temperature to give a crystalline residue on addition of ether and showing two components on TLC (5 $\alpha$ :5 $\beta$ -epoxides; 1:4 by HPLC). Recrystallization from dichloromethane/ethyl acetate gave the 5 $\beta$ -epoxyalcohol (124) (200 mg) mp 130-133°C (this compound was unstable at room temperature); <sup>1</sup>H NMR of the reaction mixture showed by difference the 5 $\alpha$ -epoxy alcohol (125).

4-Androsten-3-one-4,17 $\beta$ -diol 17-acetate (126)

A flask containing 4 $\alpha$ -chloro-4,5-oxido-5 $\beta$ -androstane-3 $\beta$ ,17 $\beta$ -diol 17-acetate (124) (200 mg) attached to a water pump was immersed in an oil bath preheated to 200°C and the temperature maintained at 190–200°C until effervescence ceased (10 min). The residue was recrystallized from dichloromethane/ methanol to give 126 (111 mg) mp 191–2°C (lit. (74) mp 194–195°C); IR  $\nu_{\max}$  (KBr): 3420 (OH), 1737 (17 $\beta$ -OAc), 1668 (C-3 ketone), 1639 (C-4 double bond)  $\text{cm}^{-1}$ ; MS m/z: 346 ( $M^+$ ).

Preparation from 4-chlorotestosterone acetate (120) (7.5g) without isolation of intermediates gave (126) (3g) m.p. 182–187°C.

4-Androsten-3-one-4,17 $\beta$ -diol diacetate (127)

The diosphenol 126 (500 mg) was dissolved in dry pyridine (5 ml) and acetic anhydride (2.5 ml) was added. After standing at room temperature overnight the reaction mixture was poured into ice-water, acidified and extracted with ether to give the diacetate (127) 232 mg, mp 168–169 °C, (lit. (73) mp 170–172°C); IR  $\nu_{\max}$  (KBr) 1758 (4-OAc), 1730 (17 $\beta$ -OAc), 1685 (C-3 C=O), 1630 (C=C-OAc)  $\text{cm}^{-1}$ .

4 $\alpha$ -Chloro-4,5-oxido-5 $\beta$ -androstane-3 $\beta$ ,17 $\beta$ -diol diacetate (128)

4 $\alpha$ -Chloro-4,5-oxido-5 $\beta$ -androstane-3 $\beta$ ,17 $\beta$ -diol 17-acetate (124) (253 mg) was dissolved in dry pyridine (2.5 ml) and acetic anhydride (1.25 ml) added. After 3 hr at room temperature TLC showed no (124) and the reaction was diluted with ice-water, acidified and extracted with dichloromethane. The product was crystallized from cyclohexane to give 128 (228 mg) mp 121–3°C, further recrystallization gave mp 123–125°C. Anal. C,65.02; H,7.90; Cl,8.62,  $C_{23}H_{33}O_5Cl$  requires C,65.01; H,7.83; Cl,8.34.

5-Chloro-5 $\alpha$ -androstane-4-one-3 $\beta$ ,17 $\beta$ -diol diacetate (130)

A flask containing the chloroepoxide diacetate (128) (8.2 g) attached to a water pump was immersed in a preheated oil bath (200°C) maintained at 190-200°C for 10 min. The crystalline residue was recrystallized from dichloromethane/methanol to give the 5 $\alpha$ -chloroderivative (130) (72 mg), m.p. 172-3°C (analytical sample mp 173-173.5°C); IR  $\nu_{\max}$  (KBr) 1755 (C-4 C=O), 1735 (ester carbonyls)  $\text{cm}^{-1}$ ; MS m/z: 424, 426 ( $\text{M}^+$ ).

Anal. C, 65.00; H, 7.84; Cl, 8.48,  $\text{C}_{23}\text{H}_{33}\text{O}_5\text{Cl}$  requires C, 65.01; H, 7.83; Cl, 8.34.

Preparation from 4-chlorotestosterone acetate (120) (1.8 g) without isolation of intermediates gave 128 (760 mg), mp 165-168°C.

5 $\alpha$ -Androstane-4-one-3 $\beta$ ,17 $\beta$ -diol diacetate (131)

5-Chloro-5 $\alpha$ -androstane-4-one-3 $\beta$ ,17 $\beta$ -diol diacetate (130) (518 mg) was dissolved in ethanol (25 ml) and 2% zinc-copper couple (97) (5 g) added. After stirring for 5 min at room temperature the reaction mixture was filtered and the filtrate evaporated to dryness. Chromatography of the crude product over neutral alumina in benzene/hexane mixtures gave (131) (154 mg) mp 137-9°C IR  $\nu_{\max}$  ( $\text{CCl}_4$ ) 1745 (17 $\beta$ -OAc), 1720 (C-3 C=O)  $\text{cm}^{-1}$ ; MS/mz: 390 ( $\text{M}^+$ ).

Anal. C, 70.52; H, 8.72,  $\text{C}_{23}\text{H}_{34}\text{O}_5$  requires C, 70.74; H, 8.78.

4 $\beta$ -Chloro-4,5-oxido-5 $\alpha$ -androstane-3 $\beta$ ,17 $\beta$ -diol diacetate (129)

4-Chloro-4-androstene-3 $\beta$ ,17 $\beta$ -diol diacetate (123) (1 g) was dissolved in dichloromethane (50 ml) and 85% w/w m-chloroperbenzoic acid (987 mg) was added at room temperature. After standing overnight TLC showed no starting material and formation of two products (5 $\alpha$ :5 $\beta$ -epoxides; 3:2 by HPLC). The reaction mixture was washed thoroughly with

excess 100% sodium sulfite solution, 5% sodium carbonate solution and water to give, after evaporation of the solvent at reduced pressure, a crystalline product. Several recrystallizations from dichloromethane/methanol gave the epoxide (129) (381 mg) mp 158-160°C.

Anal. C, 64.98; H, 8.12; Cl 8.08,  $C_{23}H_{35}O_5Cl$  requires C, 65.01; H, 7.83; Cl, 8.34.

3 $\xi$ ,4-Dichloro-4-androsten-17 $\beta$ -ol acetate (132)

To 4-Chloro-4-androstene-3,17-diol 17-acetate (121) (500 mg) in pyridine (6 ml) was added mesyl chloride (0.6 ml) at 0°C, after 1.15 hr TLC shows no starting material and one new component, dilution with ice-water, ether extraction, acidification and washing with water, brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give a crystalline residue on addition of ether. Recrystallization from ether/methanol gave (150 mg) mp 138-141°C; IR  $\nu_{max}$  (KBr) 1733 (17 $\beta$ -OAc), 1630 (C-4 C=C-Cl)  $cm^{-1}$ ; MS m/z: 384, 386, 388 ( $M^+$ ).

4 $\alpha$ -Chloro-4,5-oxido-5 $\beta$ -androstan-3 $\beta$ ,17 $\beta$ -diol 3-mesylate 17-acetate (133) and 5-chloro-5 $\alpha$ -androstan-4-one-3 $\beta$ ,17 $\beta$ -diol 3-mesylate 17-acetate (134).

To flask containing 4 $\alpha$ -chloro-4,5-oxido-5 $\beta$ -androstan-3 $\beta$ ,17 $\beta$ -diol 17-acetate (128) (300 mg) and mesyl chloride (0.5 ml) was added. After standing at room temperature overnight the reaction mixture was poured into ice-water, extracted with ether, acidified, washed with water, brine, dried and evaporated under reduced pressure to give a crystalline residue which showed two spots on TLC of similar  $R_f$  (25% v/v ethyl acetate/hexane). The crystalline crude product was collected in a flask and pyrolyzed in a preheated oil bath at 200°C and the temperature maintained at 190-200°C for 10 min. The residue showed one component

on TLC. Crystallization from dichloromethane/ methanol gave mp 211-212°C; IR  $\nu_{\max}$  (KBr) 1740 (17 $\beta$ -OAc), 1725 (C-4 ketone), 1360 and 1175 (S=O), 1000-800 (S-O, several strong bands)  $\text{cm}^{-1}$ ; MS m/z: 460, 462 ( $\text{M}^+$ ), 400 ( $\text{M}^+$ -HOAc) 409 [ $\text{M}^+$ -( $\text{CH}_3$ +HCl)].

Anal. C, 57.25; H, 7.55; Cl, 7.60; S, 7.34;  $\text{C}_{22}\text{H}_{33}\text{O}_6\text{ClS}$  requires C, 57.31; H, 7.22; Cl, 7.69; S, 6.95.

Pyrolysis of 4 $\beta$ -chloro-4,5-oxido-5 $\alpha$ -androstane-3 $\beta$ ,17 $\beta$ -diol diacetate (129)

A flask containing the chloroepoxide (129) (40 mg) attached to a water pump was immersed in a preheated oil bath (200°C) maintained at 190-200°C for 10 min. The crude product showed four components on TLC and on HPLC with several by-products. The three major components were collected from HPLC and showed the following properties:

(i) 3 $\alpha$ -Chloro-5 $\beta$ -androstane-5,17 $\beta$ -diol diacetate (139)

The crystalline product (13.6 mg) was recrystallized from dichloromethane/methanol to give mp 235-236.5°C; MS m/z: 424, 426 ( $\text{M}^+$ ), 389 ( $\text{M}^+$ -Cl), 364 ( $\text{M}^+$ -HOAc), Anal. C, 65.07; H, 7.77; Cl, 8.60,  $\text{C}_{23}\text{H}_{30}\text{O}_5\text{Cl}$  requires C, 64.97; H, 7.78; Cl, 8.58.

(ii) 3 $\beta$ -Chloro-5 $\beta$ -androstane-5,17 $\beta$ -diol diacetate (138)

Crystalline product (12.4 mg) gave mp 136-137°C (from dichloromethane/ methanol); MS m/z: 424, 426 ( $\text{M}^+$ ), 389 ( $\text{M}^+$ -Cl), 364 ( $\text{M}^+$ -HOAc).

Anal. C, 64.65; H, 7.82;  $\text{C}_{23}\text{H}_{30}\text{O}_5\text{Cl}$  requires C, 65.07; H, 7.83.

(iii) (S)-5-Spiroandrost-1(10)-en-4-one-3 $\beta$ ,17 $\beta$ -diol diacetate (140)

Crystalline product (7 mg), mp 193-194.5°C (from dichloromethane/ methanol); IR  $\nu_{\max}$  (KBr) 1758 (C-4 C=O), 1730 (ester carbonyls)  $\text{cm}^{-1}$ ; MS m/z: 328 ( $\text{M}^+$ ), 268 ( $\text{M}^+$ -HOAc), 253 [ $\text{M}^+$ -(HOAc +  $\text{CH}_3$ )].

Anal. C, 71.25; H, 8.19,  $C_{23}H_{32}O_5$  requires C, 71.11; H, 8.30.

4-Androstan-3-one-4,17 $\beta$ -diol diacetate (127)

This substance was obtained (<1%) by column chromatography ( $SiO_2$ ) in a separate reaction. The crystalline product, mp 168-169 °C (from dichloromethane/methanol) showed identical mp, IR,  $^1H$  NMR as for the sample prepared previously from 126.

Treatment of 3 $\alpha$ -chloro-5 $\beta$ -androstan-5,17 $\beta$ -diol diacetate (139) with zinc-copper couple

The 3 $\alpha$ -chloro-5 $\beta$ -androstan-5,17 $\beta$ -diol diacetate (139) (36 mg) in ethanol (10 ml) was heated under reflux with 2% zinc-copper couple (400 mg) (97) for 45 min. TLC showed no starting material and the formation of two new components. The reaction mixture was diluted with water and extracted with dichloromethane to give a product which was separated on HPLC.

(i) 5 $\beta$ -Androstan-4-one-5,17 $\beta$ -diol diacetate (135)

Crystalline product (11.2 mg) was recrystallized from dichloromethane/methanol to give mp 204-206°C; MS m/z: 390 ( $M^+$ ), 330 ( $M^+$ -HOAc), 315 [ $M^+$ -(HOAc +  $CH_3$ )].

(ii) 5 $\alpha$ -Androstan-4-one-3 $\beta$ ,17 $\beta$ -diol diacetate (131)

Crystalline product (5.7 mg); showed identical, mp,  $^1H$  NMR,  $^{13}C$  NMR as the sample prepared previously from 130.

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