STUDIES IN THE SYNTHESIS OF CYCLOSTEROID DERIVATIVES AS POTENTIAL AROMATASE INHIBITORS

BY

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ABSTRACT

Breast cancer is a dreaded disease. In North America, it is now second only to lung cancer as the leading cause of cancer death. Breast cancer is well known to respond to hormone manipulation, especially to estrogen level in the body. Aromatase is the key enzyme that controls the endogenous production of estrogen. Traditional ablative surgical procedures can stop the production of estrogen in specific organs but will not prevent peripheral aromatase activity, the major estrogen source in postmenopausal patients. Surgery is therefore not completely effective in removing endogenous estrogen in the treatment of breast cancer. Mechanism-based enzyme inhibitor can effectively prevent estrogen synthesis through aromatase inhibition throughout the body. Such inhibitors are potentially highly selective and effective as enzyme inactivators.

The main objective of this work is to synthesize substituted cyclosteroid derivatives designed as substrates for the aromatase enzyme and able to act as mechanism-based inhibitors. The ultimate goal of this research is to develop drugs for the treatment of estrogen positive breast cancer. In the thesis we propose that certain 19-substituted 1β,19-cycloandrostanes and 5β,19-cycloandrostanes can act as aromatase substrates and, upon hydroxylation at C-19, act as mechanism-based inhibitors of the enzyme. Studies in the

synthesis of saturated C-19 bromo and hydroxy cyclosteroid derivatives, and their unsaturated analogues, are reported in this thesis.

This research began with the synthesis of 19,19-dibromo-5β,19-cycloandrost derivative as described in the chemical literature. Dibromocarbene addition to the steroid 5(10)-double bond, instead of giving a 19,19-dibromo-5β,19-cycloandrosta derivative as reported by Birch in 1964, gave novel insertion, rearrangement and addition products: 19(S)-bromo-9α,19α-cycloandrost derivative, 5β,6β-dibromocyclo-propano-19(S)-bromo-9α,19α-cycloandrost derivative and 19,19-dibromo-5α,19α-cycloandrost derivative.

Reductive cyclization of 19-oxo-androst-4-ene-3,17-dione and 19-oxo-5α-androst-1-ene-3,17-dione by treatment with zinc and aqueous HOAc gave 19(R/S)-hydroxy-5β,19-cycloandrosta-3,17-diones and 19(R/S)-hydroxy-1β,19-cyclo-5α-androsta-3,17-diones. These are the first examples of 19-substituted derivatives of 5β,19-cyclo- and 1β,19-cyclo-5α-steroids to be reported.

The structures of all compounds have been established by ^{1}H and ^{13}C NMR measurements including NOE, COSY, HSQC and HMBC.

The target compounds synthesized during this work are at present awaiting screening for aromatase inhibition.

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INTRODUCTION

I. STATUS OF BREAST CANCER

In North America, breast cancer is now second only to lung cancer as the leading cause of cancer death in premenopausal and postmenopausal women, and first among 40 to 55 year-old women. Approximately 40,000 women die of breast cancer and 100,000 new cases are diagnosed each year in the United States. It is estimated that up to 9% of the adult female population in Canada will develop breast cancer at some point in their life.[1] About 60% of premenopausal and 75% of postmenopausal patients have hormone-dependent cancer as indicated by the presence of estrogen and progesterone receptors in tumour tissues.

Despite the progress that has been made during several decades of intensive research, the molecular basis underlying this disease and the factors that contribute to it are still poorly understood. For example, breast cancer often starts clinically as an estrogen-dependent tumour but may then progress to a more aggressive hormone-independent cancer.[2] Thus treatment at the estrogen dependent stage may curtail its progress to a hormone-independent cancer.

Mammary tumours in animal and in humans are well known to respond to hormone manipulations. There is now ample evidence that tumour growth correlates with the concentration of steroid receptors in tumour tissue. A higher proportion of

postmenopausal, rather than premenopausal, patients have been found to have positive estrogen receptor tumours. It has been estimated that approximately one-third of the breast cancers in women depend upon estrogen for growth.

Traditionally, removal of endogenous estrogens by ovariectomy, adrenalectomy and hypophysectomy has been used to treat women with metastatic breast cancer.[3] However, some morbidity and occasional mortality occurs with these surgical procedures. Furthermore estrogen synthesis by microsomal aromatase takes place not only in the gonads, adrenal and placenta but also in peripheral tissues, such as fat, muscle, liver, brain and breast tissue.[4-7] After menopause, peripheral aromatization increases markedly and becomes the main source of estrogen.[8] Therefore, even after the severe surgical procedures, patients may continue to produce estrogen in significant amounts from peripheral tissues. Thus, the traditional surgical procedures are not a totally effective approach to the removal of endogenous estrogen for the treatment of breast cancer. Drug treatment in contrast with surgery offers advantages, as it is not only economical but desirable in terms of patient comfort.

The fact that approximately one-third of human mammary cancers in women are estrogen dependent has stimulated research into methods of controlling endogenous estrogen production through chemical agents. Aromatase is the enzyme responsible for catalyzing the biochemical transformation of

androgen to estrogen. Because this enzyme is necessary for the conversion of testosterone to estradiol, aromatase inhibition would be a highly effective means of limiting estrogen production in all tissues. Aromatase inhibition would have a minimal effect on other hormonal systems as this conversion occurs as the final steps of steroid hormone biosynthesis.

Research interest has been focused on enzyme inhibitors and inactivators, and several effective compounds have been reported by a number of investigators.[9] In particular, mechanism-based or "suicide" inhibitors offer a potentially selective and effective approach to enzyme inhibition. Such compounds act as substrates for the enzyme but are converted by the normal catalytic mechanism of the enzyme to reactive intermediates, these intermediates can then bind covalently to the active-site of the enzyme causing "irreversibe" loss of activity. The development of aromatase inhibitors has been a matter of considerable interest since the pioneering studies of Schwarzel *et al.* in 1973.[10] The synthesis of potential mechanism-based inhibitors of aromatase is the objective of this thesis.

II. MECHANISM-BASED INHIBITORS

There are several different types of interaction between an enzyme and a substrate. These include weak intermolecular dipole interactions, van der Waals forces, hydrogen bonding and hydrophobic bonding. Any one of these interactions, or a

combination, can play a part in the enzyme substrate binding process. Alternatively a more stable covalent bond at the active-site can produce a stronger enzyme-substrate link. This interaction is usually more permanent than the others and results in prolonged enzyme inactivation. It can also be more highly specific than the other interactions because a mechanism-based inhibitor can only react with a specific enzyme for which it is a substrate.

Any substrate that can reduce the activity of an enzyme is called an enzyme inhibitor. Enzyme inhibitors are classified as two general types, reversible and irreversible inhibitors. Reversible inhibitors can be further divided into three types, (i) competitive inhibitors, (ii) non-competitive inhibitors, (iii) uncompetitive inhibitors. These inhibitors bind through intermolecular interactions and do not form a covalent bond with the enzyme. These enzyme inhibitions are reversible and are, therefore, temporary. Irreversible inhibitors can also be divided into three types, (i) active-site-directed inhibitors (affinity labelling agent), (ii) mechanism-based inhibitors (or suicide inhibitors, or K_{cat} inhibitors),[11-13] (iii) pseudoirreversible inhibitors. These classes of inhibitors form a covalent bond between enzymes and substrate. The first two types of inhibition are essentially irreversible.

Mechanism-based enzyme inhibition is potentially the most selective and effective means of enzyme inactivation. A

mechanism-based inhibitor is an intrinsically unreactive molecule which acts as an enzyme substrate (E--I) and is converted by the enzyme carrying out its normal reaction into a reactive form ($E--I^*$) which then forms a covalent bond with the enzyme at the active-site. The steps involved in this inhibition are represented in **Fig. 1**.

$$E + I \Longleftrightarrow E--I \Longleftrightarrow E--I^* \longrightarrow E-I^*$$

E=enzyme; I=inhibitor; E--I=enzyme inhibitor complex; I^*= electrophilic derivative; $E--I^*$=enzyme electrophile complex; $E-I^*$= covalently bonded enzyme-electrophilic derivative.

Fig. 1 Mechanism-based enzyme inhibition model

The formation of the covalent bond in the $E-I^*$ complex effectively blocks the active-site in an irreversible manner. Because the inhibitor itself must be a specific substrate for the enzyme and capable of undergoing conversion to the reactive form by the enzyme this type of inhibitor can be highly selective. That is, it is a substrate analogue which the enzyme acts upon as if it were a normal substrate. Once the inhibitor binds with the active-site of the enzyme, it will ideally not be released into the solution but will form an irreversible covalent bond. This property enhances its specificity and make it useful in biological systems. The more highly reactive the species formed, the more rapidly is the covalent bond formed and the less possibility there is that it will escape from the active-site of the enzyme, and therefore

the greater is its ability to inactivate the enzyme.[14,15]

Mechanism-based inhibitors offer advantages over active-site directed inhibitors. Firstly, they are more specific because they must be a substrate for a specific enzyme. Secondly, these reagents are generally more stable than active-site directed inhibitors because they are relatively chemically inert prior to enzymic reaction. Furthermore, as the chemically reactive species is generated at the active-site, it can be an exceedingly reactive functionality which can form a strong covalent bond and effectively block the activity of the enzyme. A successfully designed mechanism-based inhibitor should have the following characteristics. Firstly, the molecule must be chemically unreactive. Secondly, it must be a substrate for the target enzyme. Thirdly, it must be converted into a chemically reactive species which must immediately react with the enzyme active-site to form a covalent bond before diffusing into solution. This process offers high selectivity for the target enzyme.

III. AROMATASE INHIBITORS

The steroid hormones are synthesised in the body by many highly specific enzymes.[16] Normal hormone levels can exacerbate diseases such as breast and prostate cancers. While some hormones are associated directly with disease states other syndromes result from production of too much or too little hormone. Alteration of the hormonal status by enzyme

inhibition can be of benefit in a number of disease states, including breast and prostate cancer. Estrogen production from androgen is catalysed by aromatase and is associated directly with breast cancer. In this case, the disease may be controlled by the design of drugs to inhibit this aromatase catalysed reaction so as to lower the estrogen level in the body. Enzyme inhibition is also valuable as a probe to investigate the nature of the active-site, the mechanism of enzyme activity, and the role of certain enzymes and "minor" metabolites.

The mechanism for the conversion of the steroid ring A 4-en-3-one into the aromatic ring has been extensively investigated.[17-19] A comprehensive review of aromatase function, mechanism and biological significance has been published recently.[9] The multistep process is summarized in **Fig. 2**.

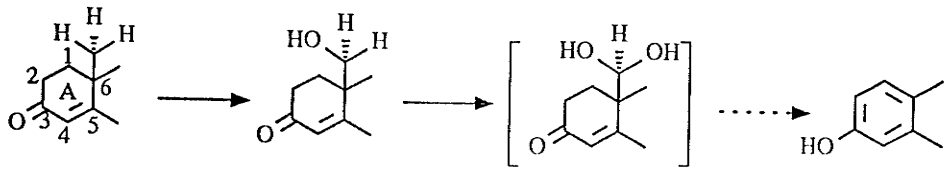


Fig. 2 Aromatase C-19 hydroxylations leading to aromatization

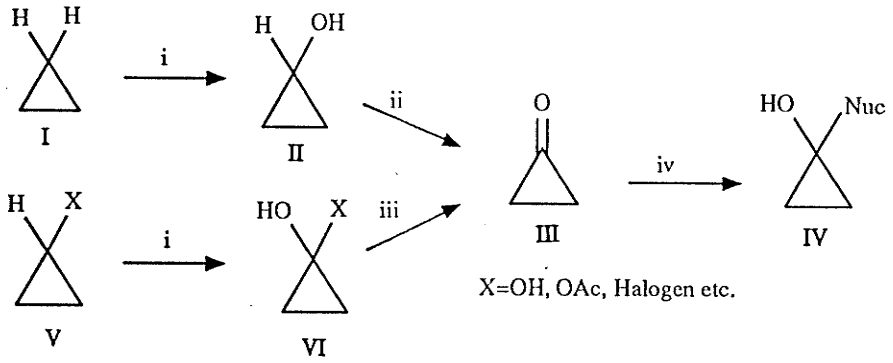
It is generally agreed that the aromatization process in the steroid A-ring begins with two sequential radical oxidations at C-19 for which two equivalents of oxygen and NADPH are required.[20-22] These two oxidative steps are thought to be typical cytochrome P450 type hydroxylations. The final

step of the reaction sequence has not been completely resolved and is still the subject of debate and may involve 1β- or 2β-hydroxylation.

Evaluation of more than one hundred steroids and non-steroidal compounds indicates that C-19 steroids closely related to the natural substances are most effective as inhibitors. Research on the synthesis of steroids derivatives as mechanism-based aromatase inhibitors has been principally based on androstene-3,17-dione substituted at C-19 with a variety of groups. A series of 19-methylsubstituted steroids have been synthesized as aromatase inhibitors. These substituents include epoxide,[23] diazoketone,[24] methylthio,[25] thiiranyl,[26] allenic and acetylenic,[27] difluoromethyl,[28] cyanomethyl[29] and thio[30] groups.

So far, a potent aromatase inhibitor which has been shown to be clinically effective is 4-hydroxyandrost-4-ene-3,17-dione.[16,17] In clinical trials, 4-hydroxyandrost-4-ene-3,17-dione has shown promise in promoting tumor regression in patients with advanced cancer.[18] Recently, 6-methyleneandrost-1,4-diene-3,17-dione, an irreversible aromatase inhibitor, is in Phase II clinical trials for treatment of postmenopausal breast cancer but the exact mechanism is uncertain.[31]

We propose that certain cyclopropano-steroids can act as mechanism-based-inhibitors of steroid enzymes through the general reaction sequence shown in **Fig. 3**.



i, Hydroxylating enzyme; ii, dehydrogenase; iii, spontaneous chemical reaction; iv, active-site nucleophile.

Fig. 3 Proposed mechanism for enzyme inactivation of a cyclopropane ring

In favourable circumstances cyclopropane ring hydroxylation can form a secondary cyclopropanol **II** which on further oxidation by an appropriate oxidoreductase, can yield a cyclopropanone **III** as outlined in **Fig. 3**. The highly electrophilic cyclopropanone[32-34] can rapidly react with a nucleophile at the enzyme active-site to form a covalent bond **(Fig. 3)**. This concept of the cyclopropanol enzyme inhibition is supported by the reported irreversible inhibition of methanol oxidase by cyclopropanol through covalent bond formation[35,36]. Cyclopropanol derivatives e.g. esters, can act as pro-alcohol groups *in vivo*. A modification of this sequence **(Fig. 3)**, applicable to hydroxylating enzymes e.g. aromatase, rather than a dehydrogenase, requires cyclopropane substitution with an electronegative group e.g. F, Cl, Br, or OH, OAc, to spontaneously generate a cyclopropanone after

enzymatic hydroxylation. The use of an unsubstituted cyclopropanosteroid derivative is generally unsuitable because of cyclopropane resistance to metabolic hydroxylation.[37,38] 5β,19-Cycloandrosta-3,17-dione has been shown to be a weak inhibitor of aromatase but the mechanism has not been established.[39]

A newly proposed aromatase active-site model requires that the initial C-10 methyl hydroxylation occurs to a hydrogen atom located over ring A and the alcohol then formed becomes hydrogen bonded to the active-site[40a]. The C-19 Pro-R hydrogen is next enzymatically oxidized to an alcohol.[21,40a] This second hydroxylation step would not be required in our proposed inhibitors as one hydroxyl group (or an equivalent halogen atom) would already be present. Spontaneous loss of H_2O or HX could then occur to generate a carbonyl group (in this case a reactive cyclopropanone). The substances proposed to be synthesized have the required H located in an appropriate space for hydroxylation over ring A. The presence of the C-3 and C-17 carbonyls, able to hydrogen bond to the active-site, is important for receptor attachment.[40a] The cyclopropane ring hydrogens are resistant to metabolic hydroxylation,[37,38] however, the presence of an electronegative substituent appears to make the geminal hydrogen more metabolically reactive. As stated above 5β,19-cycloandrosta-3,17-dione is only a weak inhibitor of aromatase,[39] nevertheless, even weak inhibition indicates that the molecule undergoes receptor attachment.

RESULTS AND DISCUSSION

The conversion of testosterone to estradiol is the final step in the endogenous production of estrogens. As discussed in the introduction, Robinson and Cole[40b] have proposed an aromatase model in which the C-H bond of the 19-methyl group when located over ring A, undergoes hydroxylation by the enzyme. We propose that the Pro-S H in 5β,19-cycloandrostanes is located sufficiently near to the position of the C-H bond of the methyl group to undergo similar hydroxylation provided the steroid molecule is able to act as an enzyme substrate. Furthermore, we propose that 5β,19-cycloandrostane derivatives initially possessing a 19R hydroxyl, or other electro-negative group, can, after hydroxylation followed by loss of H_2O or HX, form a cyclopropanone capable of rapidly reacting with an active-site nucleophile and thereby functioning as a mechanism-based-inhibitor of the aromatase enzyme **(Fig. 3)**. A 19R electronegative substituent is necessary to activate the cyclopropyl C-H bond, which is resistant to metabolic hydroxylation,[37,38] for hydroxylation to occur readily and also to act as a leaving group required to form the highly reactive electrophilic cyclopropanone[33,34] **(Fig. 3)**. Such a compound acting as an enzyme inhibitor may be of clinical usefulness as a therapeutic agent in the treatment of human breast cancer. A mechanism-based enzyme inhibitor of this type is potentially highly selective and effective in enzyme deactivation.

Therefore, in the search for a potential aromatase inhibitor for the treatment of breast cancer, it was necessary to synthesize 19R-mono-substituted-5β,19-cycloandrostane derivatives **(Fig. 4)** and 19S-mono-substituted-1β,19-cyclo-5α-androstane derivative **(Fig. 5)**.

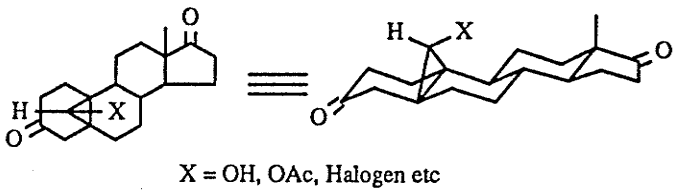


Fig. 4 19-Monosubstituted-5β,19-cycloandrostane derivatives

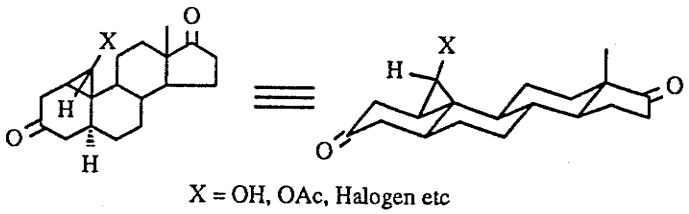
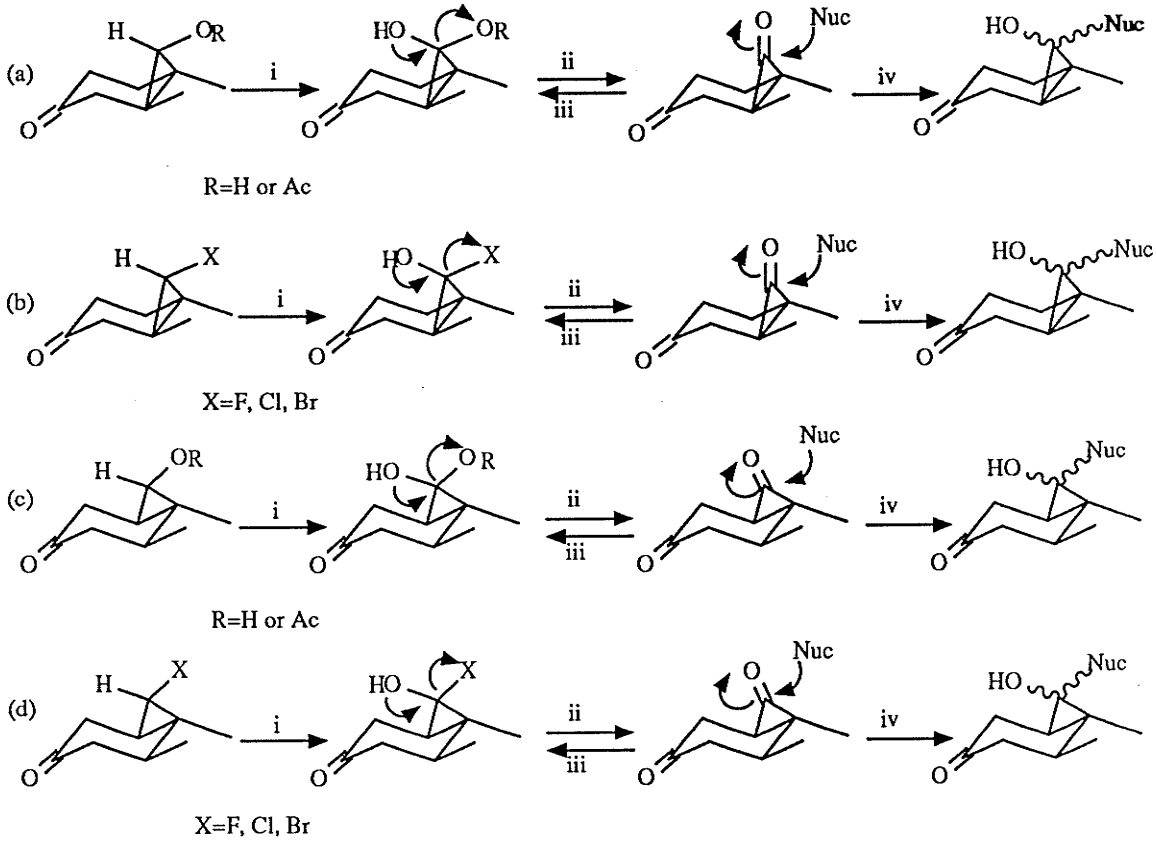


Fig. 5 19-Monosubstituted-1β,19-cycloandrostane derivatives

Enzymatic hydroxylation of these cyclosteroid derivatives could lead to enzyme inhibition as outlined in **Fig. 6**.

Introduction of a C-1 double bond into 5(10)-cyclosteroid **(Fig. 4)** and a C-4 double bond into the 1(10)-cyclosteroid **(Fig. 5)** would yield derivatives even more closely related to the natural substrate androst-4-ene-3,17-dione (androstenedione). This thesis deals principally with the synthesis of



i, enzyme hydroxylation; ii, spontaneous elimination;
iii, spontaneous addition; iv, active-site nucleophile

Fig. 6 Mechanism of enzyme inhibition

19-substituted saturated 5β,19- and 1β,19-cyclosteroids.

The 19-unsubstituted-5β,19-cycloandrostane[41-46] and 1β,19-cycloandrostane[47] derivatives (I-IV) shown in **Fig. 7** have been reported.

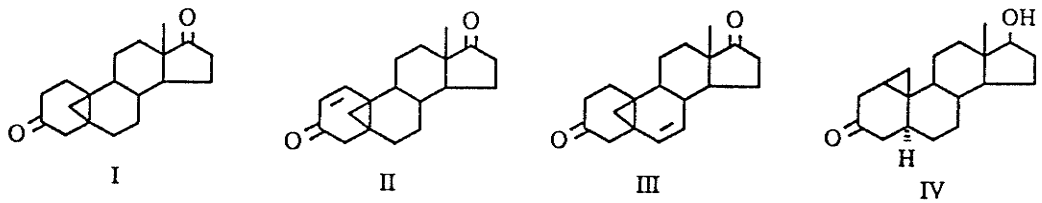


Fig. 7 The synthesized 19-unsubstituted-5β, or 1β,19-cycloandrostane derivatives reported in the literature[41-46]

Part A: Dibromocarbene reaction

I. Review of dibromocarbene reactions with unsaturated steroids

Initial experiments were directed towards the synthesis of 19R-halogenated-5β,19-cycloandrostane derivatives based on the reported synthesis of 19,19-dibromo-5β,19-cycloandrosta-3,17-dione.[48] In 1963, Birch *et al.*[48] treated the steroid 2, 5(10)-diene **I (Fig. 8)** with dibromocarbene, generated from $KOBu^t/Bu^tOH/benzene/CHBr_3$, at 0°C to 10°C. They obtained the mono adduct **II** together with the bisadduct **III** as a minor product. The stereochemistry of the products were not completely established by them at that time. In 1964, they repeated this reaction, employing dibromocarbene generated from $KOBu^t$/dry ether/$CHBr_3$ at -30°C, and were able to isolate the bisadduct **III**[49] in higher yield. The methylene compound **IV**,

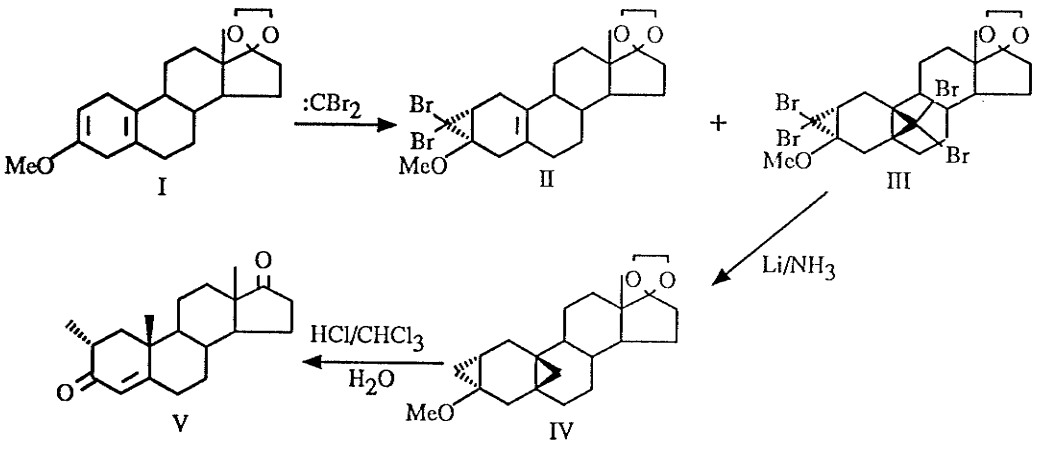


Fig. 8 Synthesis of bis-dibromocarbene adduct by Birch *et al.* in 1963 and 1964

prepared by reductive debromination of the bisadduct **III** with lithium in liquid ammonia, was treated with hydrogen chloride in chloroform, to give 2α-methylandrost-4-ene-3,17-dione **V**, identified by mixed m.p., and optical rotatory dispersion, infrared and ^{1}H NMR spectral comparisons with an authentic sample. Therefore, they concluded that the dibromocarbene addition to the 5(10)-double bond occurred on the β-face and, for steric reasons, that the 2,3-dibromocarbene had added to the α-face. Birch *et al.*[49] predicted β addition to the 5(10)-double bond by analogy with β-epoxide formation. The C-2 methyl group may epimerize during the acid treatment so that no conclusion about the stereochemistry was provided from the 2α-methyl stereochemistry.

In the same paper, to avoid introduction of the 2-methyl group, Birch *et al.*[49] treated the steroid 5(10)-double bond of the dimethoxy ketal **I (Fig. 9)** with dibromocarbene generated from KOBu^t/dry ether/$CHBr_3$ at -20°C under nitrogen. They reported a mixture of products which was deketalized by treatment with toluene-p-sulphonic acid in acetone from which the dibromo adduct **II** was isolated in 10% yield. This compound was re-ketalised with ethylene glycol to yield the adduct **III** which was reduced with lithium in liquid ammonia to the methylene compound **IV**. The action of hydrogen chloride in chloroform on compound **IV** gave androst-4-ene-3,17-dione **V** identified by mixed m.p. and infrared spectral comparisions with an authentic specimen. Therefore, they again concluded

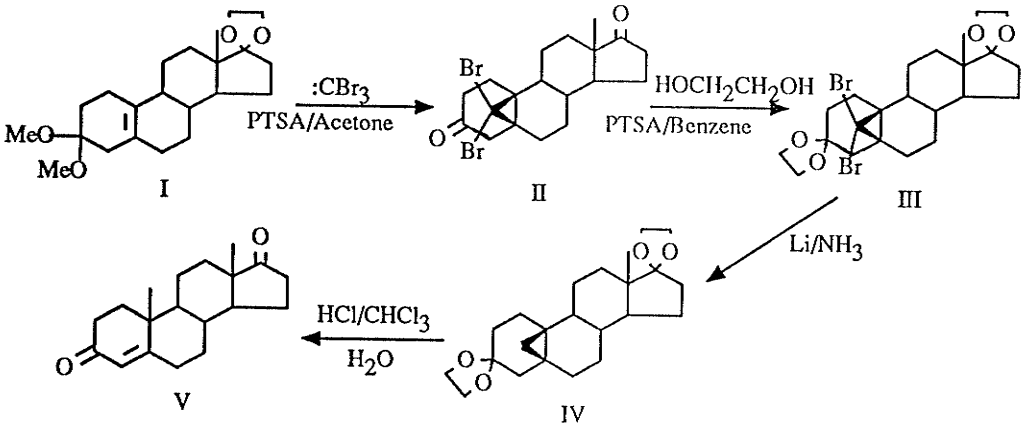


Fig. 9 Synthesis of 19,19-dibromo-5β,19-cyclo-androstanes by Birch *et al* in 1964

that the 5,10-dibromocarbene had added from the β-face.

In 1967, Birch and Rao[50] treated the 9β steroid 5(10)-double bond **I (Fig. 10)** with dibromocarbene, generated from KOBu^t/dry ether/$CHBr_3$ at -28°C under nitrogen, to give a

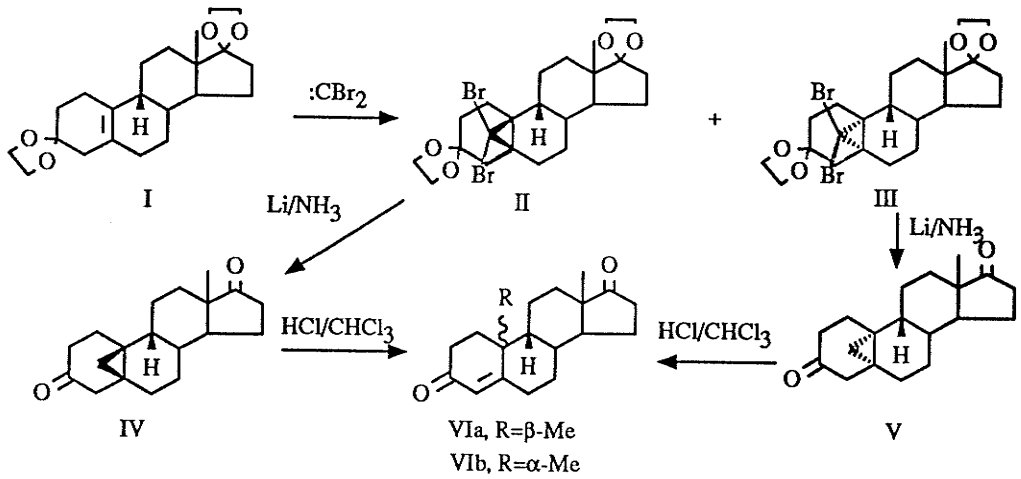


Fig. 10 Synthesis of 19,19-dibromo-5α,19α- and 5β,19-(9β)-cycloandrostanes by Birch and Rao. in 1967

mixture of products **II+III** which had partially lost the ketal groups whose removal was completed by the action of toluene-p-sulphonic acid in acetone, to give the dibromo-compound. This compound was re-ketalised with ethylene glycol to yield the adducts **II+III** and then reduced with lithium in liquid ammonia. Deketalisation by the action of toluene-p-sulphonic acid in acetone gave the methylene compounds **IV+V**. The action of dry hydrogen chloride in chloroform on these compounds gave 9β,10β-androst-4-ene-3,17-dione **VIa** and 9β,10α-androst-4-ene-3,17-dione **VIb** respectively.

In 1975 phase transfer catalysis was introduced for generation of dihalocarbene with CHX_3 and NaOH.[51, 52] Templeton *et al.*[53] obtained the α-face product **II (Fig. 11)** from dibromo-carbene addition, generated under phase transfer catalysis from $CHBr_3$ and NaOH, to the steroid C-2,3 enol ethers and ester **I**. The dibromo steroid **II** was then reduced to the monobromo steroid **III** either by refluxing with zinc-copper couple or by hydrogenation over Raney nickel catalyst. The

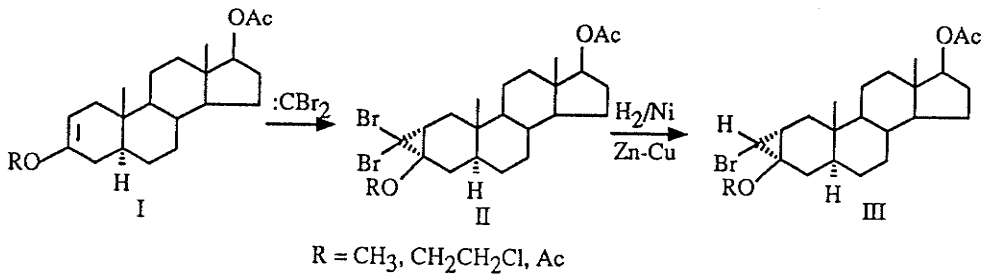


Fig. 11 Dibromocarbene addition to the C-2,3 enol steroid gave α-face product by Templeton *et al.* in 1978

2α,3α-stereochemistry was based on ^{1}H NMR measurements and steric factors.

In this thesis, when the reaction conditions of Birch *et al.*[49] were carefully repeated on 17-tert-butyldimethylsiloxy-estr-5(10)-ene-3-ketal, none of the previously reported β-face addition product, 19,19-dibromo-5β,19-cycloandrosta-3,17-dione, was isolated. However, from this reaction and by using phase transfer catalysis and other methods, the following novel rearrangement and addition products **(Fig. 12)** were obtained: 17β-tert-butyl-dimethylsiloxy-5β,6β-dibromocyclo-propano-19(S)-bromo-9α,19α-cycloandrostan-3-one **I**, 17β-tert-butyl-dimethyl-siloxy-19(S)-bromo-9α,19α-cycloandrost-4-en-3-one **II**, 17β-tert-butyldimethylsiloxy-19,19-dibromo-cyclo-5α,19α-androstan-3-one **III**. These compounds were obtained from dibromocarbene reaction with the three ketals containing a 5(10)-double bond described in the following section.

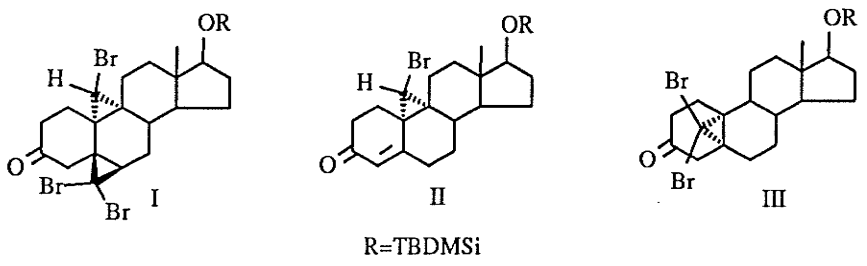


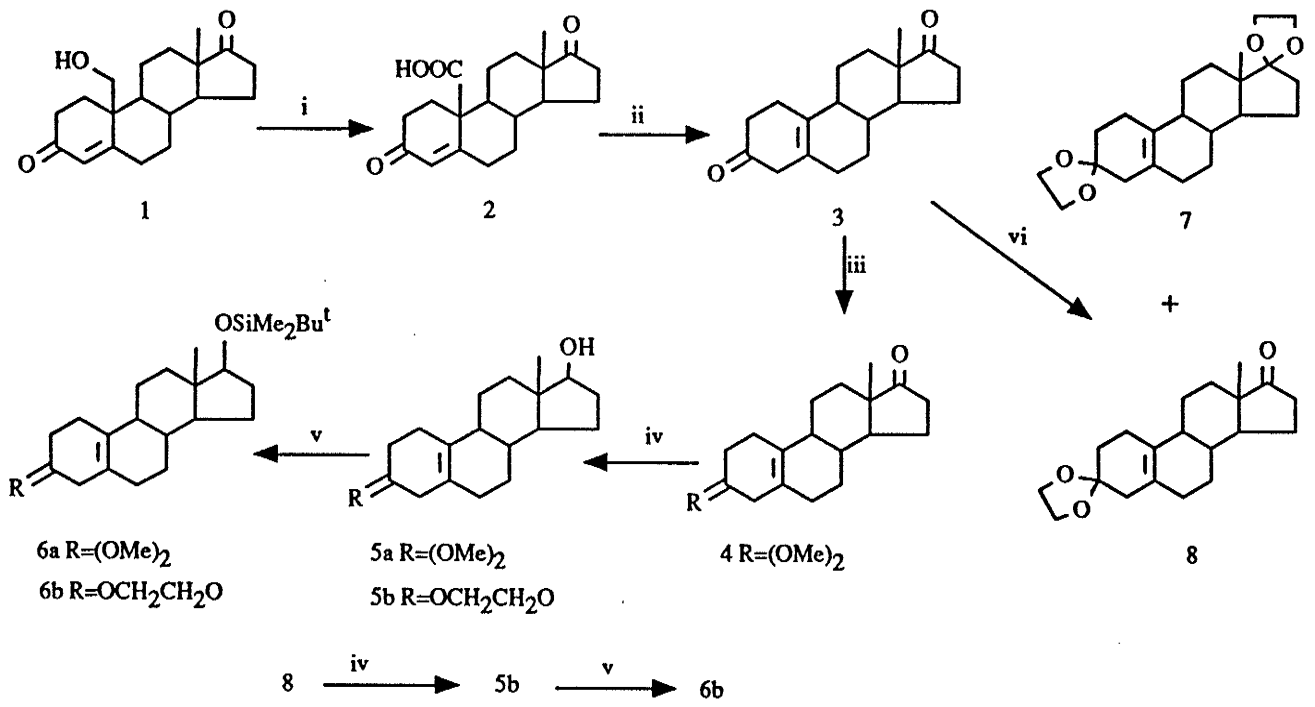
Fig. 12 Novel insertion, rearrangement and addition products from dihalocarbene reaction with 5(10)-unsaturated steroids

II. Synthesis of steroid ketals ***(6a, 6b, 7)*** *containing a 5(10)-double bond.*

i, Synthesis of 17β-tert-butyldimethylsiloxy-3,3-dimethoxy-estr-5(10)-ene **6a**

Synthesis of the ketal **6a**, outlined in **Scheme 1**, was carried out from estr-5(10)-ene-3,17-dione which was prepared as follows using the method of Ueberwasser *et al.*[54] 19-Hydroxy-androst-4-ene-3,17-dione **1** was oxidized by Jones reagent to androst-4-ene-3,17-dion-19-oic acid **2**.[54] The ^{1}H NMR spectrum (see **Table 1**) showed a singlet vinylic proton signal at 5.96 ppm similar to that assigned to the 4-H in the starting material. The AB pattern due to the C-19 methylene protons at 3.96 ppm in the starting material was absent in the product. The ^{13}C NMR spectrum (see **Table 2**) showed a new carbonyl signal at 175.67 ppm, which was assigned to the C-19 carboxylic acid carbonyl, and the absence of the C-19 methylene carbon at 66.10 ppm. Decarboxylation of the acid **2** by heating at 50°C in pyridine afforded estr-5(10)-ene-3,17-dione **3**.[54] The ^{1}H NMR spectrum of the dione **3** showed the absence of a singlet vinylic proton signal and instead an AB pattern at 2.70, 2.81 (J_{AB}=21.2 Hz) was observed which was assigned to the 4-H_2. The ^{13}C NMR spectrum was in agreement with two published spectra of estr-5(10)-ene-3,17-dione.[43, 55]

Estr-5(10)-ene-3,17-dione **3** was selectively ketalised in methanol with malonic acid as catalyst to give 3,3-dimethoxy-estr-5(10)-en-17-one **4** as described by Ueberwasser *et al.*[54]



Scheme 1 *Reagents:* i, Jones reagent; ii, pyridine/50°C; iii, malonic acid/MeOH; iv, $NaBH_4$/MeOH; v, Bu^tMe_2SiCl/imidazole/DMF; vi, $HOCH_2CH_2OH$/PTSA/benzene

The ^{1}H NMR spectrum of the ketal **4** showed two singlets, each of which integrated for three protons, at 3.18, 3.21 ppm, which were assigned to the C-3 dimethoxy protons. The ^{13}C NMR spectrum of the ketal **4** showed two new methyl signals at 48.15, 48.25 ppm which were assigned to the C-3 dimethoxy groups, and one new quaternary carbon signal at 101.13 ppm was assigned to C-3. The absence of a carbonyl carbon in the spectrum of dione **3** was also observed. Sodium borohydride reduction of the ketal **4** in methanol gave 17β-hydroxy-3,3-dimethoxyestr-5(10)-ene **5a**.[54] The ^{1}H NMR spectrum of the alcohol **5a** showed a new triplet signal, for one proton, at 3.60 ppm (J=8.7 Hz) which was assigned to the 17α-H. The ^{13}C NMR spectrum showed a new methine signal at 82.49 ppm which was assigned to C-17 and a loss of a carbonyl at 223.60 ppm from the spectrum of ketal **4**. The alcohol in compound **5a** was protected by tert-butyldimethysilyl chloride and imidazole in DMF to give 17β-tert-butyldimethylsiloxy-3,3-dimethoxyestr-5(10)-ene **6a** which did not crystallize. The ^{1}H NMR spectrum of the silyl ether **6a** showed three new singlet peaks at 0.02, 0.03 and 0.88 ppm which corresponded to the 17β-tert-butyl-dimethylsiloxy group. The ^{13}C NMR spectrum showed a new quaternary carbon at 18.97 ppm and three methyl carbons at -4.54, -4.22 and 26.39 ppm. These signals correspond with the presence of a 17β-tert-butyldimethylsiloxy group. The spectrum of this non-crystalline product did not contain significant extraneous signals and ran as one component on TLC. On this

basis the product was used in further synthetic reactions.

ii, 17β-tert-Butyldimethylsiloxy-3,3-ethylenedioxyestr-5(10)-ene **6b**

Because the 17β-tert-butyldimethylsiloxy-3,3-dimethoxy-estr-5(10)-ene **6a** was not thermally stable and because working with a non-crystalline compound was inconvenient, 17β-tert-butyldimethylsiloxy-3,3-ethylenedioxy-estr-5(10)-ene **6b** was synthesized using the Saha method[56] outlined in **Scheme 1**.

The dione **3** when treated with ethylene glycol in benzene and PTSA as catalyst at 50°C, yields the 3-monoketal **8** as the major product together with the bisketal **7** as a minor product. The ^{1}H NMR spectrum of the monoketal **8** showed new multiplet peaks, which integrated for four protons at 3.97 ppm which were assigned to the 3-ethylenedioxy group. The ^{13}C NMR spectrum of the mono ketal **8** showed that the carbonyl carbon at 207.91 had been lost and a new high field quaternary carbon at 108.18 ppm was observed. Two new methylene carbons at 64.20 and 64.48 ppm which correspond to the 3-ethylenedioxy group were also observed.

Sodium borohydride reduction of the monoketal **8** in methanol gave 17β-hydroxy-3,3-dimethoxyestr-5(10)-ene **5b**.[56] Without further purification, the alcohol in **5b** was protected as the silyl derivative, 17β-tert-butyldimethylsiloxy-3,3-dimethoxyestr-5(10)-ene **6b**, which readily crystallized from ether/methanol. The ^{1}H NMR spectrum of **6b** showed a new triplet signal, which integrated for one proton, at 3.59 ppm (J=8.0

Hz) which was assigned to the 17α-H, and three new singlet peaks at -0.02, 0.01 and 0.88 ppm corresponding to the 17β-tert-butyldimethylsiloxy group. The ^{13}C NMR spectrum showed a new methine signal at 81.76 ppm (C-17), the absence of the C-17 carbonyl carbon at 222.30 ppm, a new quaternary carbon at 18.97 ppm and three methyl carbons at -4.54, -4.22 and 26.39 ppm corresponding to the 17β-tert-butyldimethylsiloxy group. The results of elemental analysis (C, H) also supported structure **6b**.

iii 3,3,17,17-Bis-(ethylenedioxy)estr-5(10)-ene **7**

The dione **3** in benzene was refluxed with an excess of ethylene glycol with PTSA as catalyst employing a Dean-Stark phase separator apparatus for 2 h, to yield the 3,17-bisketal **7**[57,58] as the major product (60-70% yield) together with the 3-monoketal **8** (20-30% yield). Although extending the reflux time did increase the yield of bisketal **7**, a 5,6-double bond isomer, which proved difficult to separate,[57,58] was also formed as shown by the presence of a vinylic proton doublet at 5.46 ppm (J=5.7 Hz) corresponding to 6-H. If the mixture was refluxed for 18 hours, the yield of this by-product, as calculated from the integration of the 6-H in the ^{1}H NMR spectrum, was 25-30%. This result is in agreement with that reported by Djerassi's group.[58]

The ^{1}H NMR spectrum of compound **7** showed a new multiplet peak, integrating for eight protons, at 3.96 ppm which corresponds to the 3,17-bis-ethylenedioxy group. The ^{13}C NMR

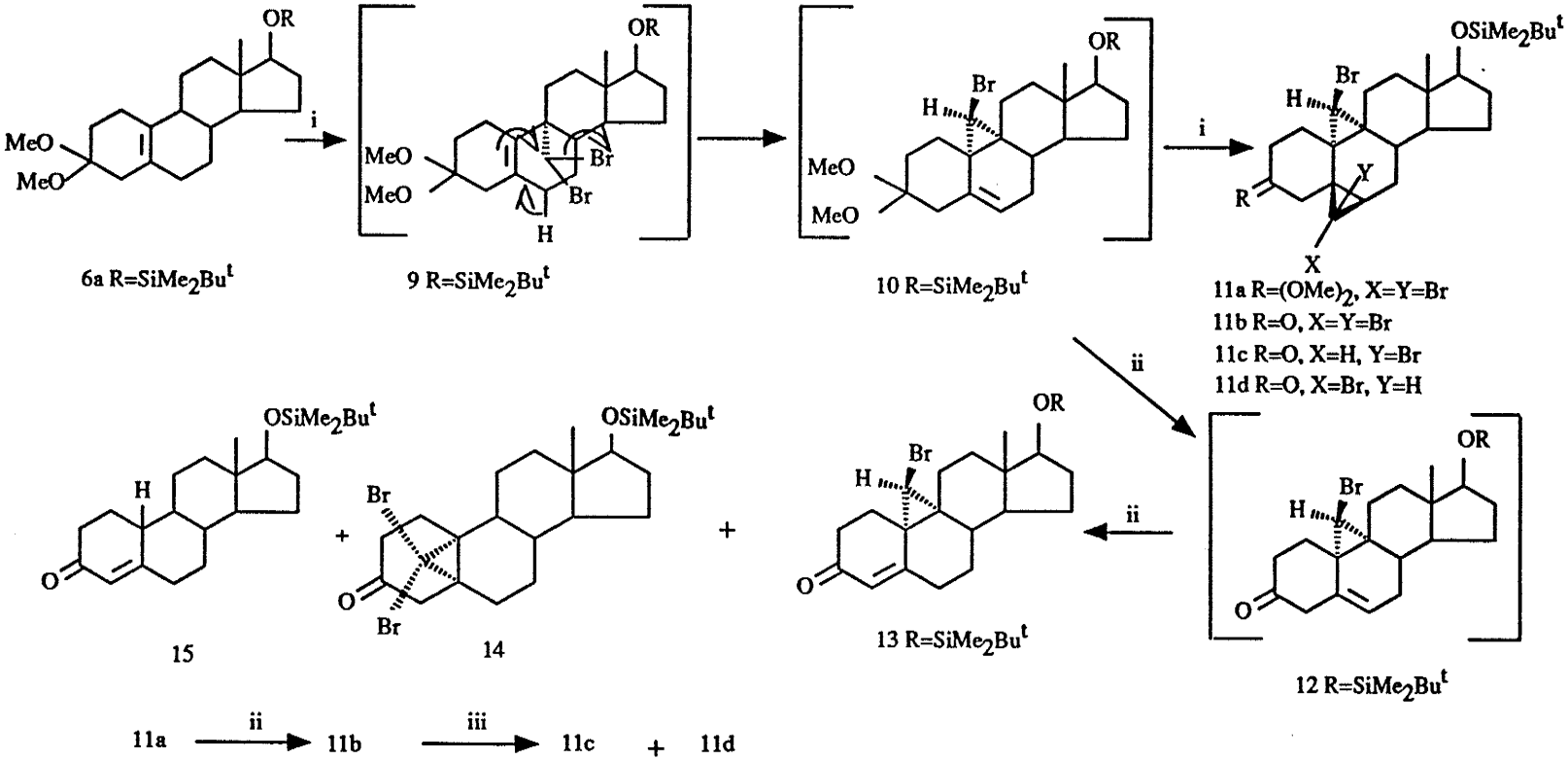
spectrum of compound **7** showed that the two carbonyl carbons (207.91 and 212.50 ppm) had been replaced by two high field signals (108.52 and 119.43 ppm). Four new methylene carbons at 64.20-65.16 ppm, corresponded to the 3,17-bis-ethylenedioxy group.

*III. Dibromocarbene reaction with the steroids 5,10-double bond **6a, 6b and 7***

i. Dibromocarbene reaction with 17β-tert-butyldimethyl-siloxy-3,3-dimethoxyestr-5(10)-ene **6a**

Treatment of the ketal **6a** with dibromocarbene, generated from $CHBr_3$/$KOBu^t$/dry ether at -30°C under an argon atmosphere, gave a mixture of products which had partially lost the ketal group and removal was completed by the action of PTSA in acetone, as described by Birch *et al.*,[48] to give mainly 17β-tert-butyldimethylsiloxy-19(S)-bromo-9α,19α-cycloandrost-4-en-3-one **13** and 17β-tert-butyldimethylsiloxyestr-4-en-3-one **15** (see **Scheme 2**).

The mono bromo derivative **13** clearly did not correspond to the expected 17-tert-butyldimethylsiloxy-19,19-dibromo-5β,19-cycloandrostan-3-one previously reported by Birch *et al.*[49] The ^{1}H NMR spectrum of **13** (see **Table 6**) showed a new singlet peak, integrating for one proton, at 3.37 ppm which corresponds to the C-19 cyclopropyl proton and a singlet vinylic proton signal at 6.18 ppm assigned to 4-H. The ^{13}C NMR spectrum of compound **13** (see **Table 6**) showed a carbonyl carbon



Scheme 2 *Reagents:* i, $CHBr_3$/NaOH/CTAB; ii, PTSA/acetone/water; iii, *n*-Bu_3SnH/AIBN/ether

at 198.83 ppm and the loss of two methoxyl carbons signal in the starting material **6a** which corresponded to the hydrolysis of the 3-ketal. Two ethylene carbons at 126.46 and 162.47 ppm corresponded to a 4,5-double bond. The C-10 signal was shifted to higher field (130.76 ppm to 29.71 ppm) and a new methine signal appearing at 34.21 ppm was assigned to the 19-bromo-cyclopropyl carbon. The homonuclear[59] (COSY) correlation spectrum showed long range (4 bond) coupling between the cyclopropyl proton and 1β-H and 11β-H consistent with the 9,10 location of the cyclopropyl group. These typical "W" configuration couplings also suggested that the cyclopropyl group was on the α face of the steroid. Nuclear Overhauser effect[60] (NOE) measurements observed from the cyclopropyl proton to 7α-H (9.2%), 14-H (3.2%) and 2α-H (0.5%) further confirmed that the cyclopropyl group was located on the α face. Elemental analyses for C, H and Br support the structure.

The ^{1}H NMR spectrum of the unsaturated steroid **15** showed a new singlet peak at 5.74 ppm, integrating for one proton, which was assigned to the 4-vinylic proton. The absence of two singlet peaks at 3.17, 3.20 ppm signalled the loss of the 3,3-dimethoxyl group. The presence of an α,β-conjugated ketone in compound **15** was indicated. The ^{13}C NMR spectrum of compound **15** showed a carbonyl carbon at 198.43 ppm, the loss of two methoxyl carbon signals from the starting material **6a** corresponding to hydrolysis of the 3-ketal, two unsaturated

carbons at 124.83 and 166.51 ppm corresponding to the 4,5-double bond, and the C-10 signal had shifted to higher field from 130.76 ppm to 43.10 ppm. Elemental analysis is in agreement with structure **15**. Compound **15** could be formed directly from the starting material **6a** by ketal hydrolysis and double bond conjugation.

Ketal **6a** was treated with dibromocarbene under phase transfer catalysis $CHBr_3$/NaOH/CTAB (cetyltrimethylammonium bromide) at room temperature in an argon atmosphere to yield 17β-tert-butyldimethylsiloxy-5β,6β-dibromo-cyclopropano-3,3-dimethoxy-19(S)-bromo-9α,19α-cycloandrostane **11a** which after ketal hydrolysis with PTSA gave **11b**. Similarly treatment of ketal **6a** under phase transfer conditions with $CHBr_3$/NaOH/ CTAB followed by ketal hydrolysis with PTSA in acetone gave 17β-tert-butyldimethylsiloxy-5β,6β-dibromocyclopropano-19(S)-bromo-9α,19α-cycloandrostan-3-one **11b**, and 17β-tert-butyl-dimethylsiloxy-19(S)-bromo-9α,19α-cycloandrost-4-en-3-one **13** together with the unsaturated ketone **15**. In a similar reaction the α-face dibromo adduct, 17β-tert-butyldimethyl-siloxy-19,19-dibromocyclo-5α,19α-androstan-3-one **14**, was also isolated (see **Scheme 2**).

The ^{1}H NMR spectrum of the tribromo derivative **11a** showed a new singlet peak, integrating for one proton, at 2.79 ppm which corresponds to the 19-cyclopropyl proton. An AB pattern signal, integrating for two protons, at 1.83, 2.21 ppm (J_{AB}=13.4 Hz) was assigned to the 4-H_2. The ^{13}C NMR spectrum of

compound **11a** showed a new methine carbon signal at 32.80 ppm assigned to the 19-cyclopropyl carbon and a new quaternary carbon signal at 40.79 ppm assigned to 5,6-dibromocyclopropyl carbon. The loss of two quaternary carbons signals at 125.63 and 130.76 ppm from the starting material **6a** was also observed. Elemental analyses for C, H and Br are in agreement with structure **11a**.

The ^{1}H NMR spectrum of the tribromo derivative **11b** (see **Table 3**) showed a new singlet peak, integrating for one proton, at 2.93 ppm which corresponds to the C-19 cyclopropyl proton. An AB pattern, integrating for two protons, at 2.57 and 2.81 ppm (J_{AB}=15.4 Hz) was assigned to the 4-H_2. The ^{13}C NMR spectrum of compound **11b** (see **Table 3**) showed a new methine carbon signal at 32.52 ppm assigned to the C-19 cyclopropyl carbon, a new quaternary carbon signal at 37.71 ppm assigned to 5,6-dibromocyclopropyl carbon, and a carbonyl carbon signal at 207.76 ppm assigned to C-3. The absence of two quaternary carbon signals at 125.63 and 130.76 ppm in the starting material **6a** was also observed.

The above data suggests that compound **11b** has two cyclopropyl groups, probably a dibromocyclopropyl at the (5,6) position and a bromocyclopropyl at the (9,10) position. The location of the 9,10-cyclopropyl group was established by the presence of long range (4 bond) "W" couplings between the cyclopropyl proton and 8-H, 1β-H and 11β-H, as seen in the mono bromo derivative **13** discussed above. Furthermore these

protons lacked the usual couplings to the 9α-H and the expected cross peaks were observed in the HMBC spectrum. NOEs were observed from the 19-cyclopropyl proton to the 7α-H (4.5%), 14-H (3.8%) and 4α-H (4.8%) from which it was concluded that the cyclopropyl group was on the α side of the steroid with the hydrogen *endo*. The heteronuclear[61,62] correlation (HSQC) spectrum from the HMBC experiment confirmed the location of the 5,6-cyclopropyl group, but the stereochemistry could not be determined directly from the NMR data. However, reduction products **11c** and **11d** derived from **11b**, which will be discussed later, both have this cyclopropyl group on the β-face, comfirming the β-face configuration. Elemental analysis (C, H, Br) and mass spectrometry are also in agreement with this structure.

The ^{1}H NMR spectrum of compound **14** showed a new AB signal pattern at 2.46 and 2.70 ppm, integrating for two protons, which were assigned to the 4-H_2. The absence of two singlet peaks at 3.17, 3.20 ppm signalled the loss of the 3,3-dimethoxy group. The ^{13}C NMR spectrum of compound **14** showed a carbonyl carbon at 210.36 ppm and the loss of two methoxy signals from the starting material **6a** which was consistent with the hydrolysis of the 3-ketal. A new quaternary carbon signal at 61.24 ppm was assigned to the 19-dibromocyclopropyl carbon and two quaternary carbon signals (5, 10) (125.63 and 130.76 ppm) of the starting material were shifted to higher field (31.28 and 31.37 ppm). The location of the dibromo-

cyclopropyl group was established by comparison with the NMR spectra of 17β-tert-butyldimethylsiloxy-19,19-dichlorocyclo-5α,19α-androstan-3-one the structure of which was established from a HMBC experiment and NOE measurements of its reduction products.[63] Elemental analysis (C, H, Br) also supports the structure.

ii, Tri-n-butyltin hydride reduction of 17β-tert-butyl-dimethylsiloxy-5β,6β-dibromocyclopropano-19(S)-bromo-9α,19α-cycloandrostan-3-one **11b**

Reduction of the tribromo ketone **11b** in dry ether with tri-n-butyltin hydride and azobisisobutyronitrile (AIBN) gave two products identified as the dibromo 5'(R)-isomer **11c** and 5'(S)-isomer **11d**.

The ^{1}H NMR spectrum of compound **11c** (see **Table 4**) showed a new doublet signal, integrating for one proton, at 2.91 ppm (J=4.3 Hz) which was assigned to the 5,6-cyclopropyl proton. The 19-H singlet peak shifted to lower field from 2.93 in **6a** to 3.15 ppm in **11c**. The ^{13}C NMR spectrum of compound **11c** (see **Table 4**) showed a new methine signal at 26.81 ppm and the absence of a quaternary carbon at 37.71 ppm observed in the tribromo derivative **11b**. NOEs were observed from the 9,10-cyclopropyl proton to the 14-H and 7α-H. These results confirm the location of the 19-bromocyclopropyl group on the α face of the steroid, with the hydrogen *endo* and the bromine *exo* i.e. the S-isomer. The 5,6-bromocyclopropyl proton has an NOE to the 4β-H and a *cis* cyclopropyl coupling (J=8.1 Hz) to the 6α-

H, clearly showing that the 5,6-bromocyclopropyl group is on the β face of the steroid with the cyclopropyl proton *exo* i.e. the R-isomer. Elemental analysis (C, H, Br) also supports this structure.

The ^{1}H NMR spectrum of compound **11d** (see **Table 5**) showed a new doublet signal, integrating for one proton, at 2.97 (J=8.1 Hz) which was assigned to the 5,6-cyclopropyl proton. The 19-H singlet peak was shifted to lower field from 2.93 to 3.06 ppm and the 4β-H doublet shifted to higher field from 2.57 to 1.62 ppm. The ^{13}C NMR spectrum of compound **11d** (see **Table 5**) showed a new methine signal at 31.71 ppm and the absence of a quaternary carbon at 37.71 ppm in the tribromo derivative **11b**. NOEs were observed from the 9,10-cyclopropyl proton to the 14-H and 7α-H. These results confirmed the location of the cyclopropyl group on the α face of the steroid, with the hydrogen *endo* and the bromine *exo* i.e. the S-isomer. A strong NOE (12%) was observed from the 5,6-bromocyclopropyl proton to H-8. Therefore, the 5,6-bromocyclopropyl group was located on the β-side of the molecule with the hydrogen *endo* and the bromine *exo*. As further evidence for this conclusion, the coupling patterns indicated that the 6-H was equatorial (and thus α) and had a *trans* cyclopropyl coupling (4.3 Hz) to the 5,6-bromocyclopropyl hydrogen. i.e. the S-isomer. Elemental analysis (C, H, Br) also supports the structure.

iii, The proposed mechanism for the formation of the tribromo derivatives **11a, 11b** and the mono bromo derivative **13**

Scheme 2 shows the proposed formation of **11a, 11b** and **13** through the intermediates **9, 10** and **12**. Dibromocarbene insertion into the 9α C-H bond to give the 9α-$CHBr_2$ intermediate **9**, followed by loss of the 6β-H, either as $H^{\cdot}$ or H^{+}, with concomitant introduction of the 5,6-double bond forms the 19-bromo-9α,19α-cyclo derivative **10** with the less sterically hindered *endo* H. The intermediate **10** on acidic ketal hydrolysis to intermediate **12** followed by double bond conjugation gives the mono bromo derivative **13**. The reaction may be driven by relief of steric strain. This rearrangement is consistent with the observation that no incorporation of deuterium occurred when $CDCl_3$/NaOD was used with phase transfer catalysis.[63] A second dibromocarbene addition to the less sterically hindered β face of the 5,6-double bond in intermediate **10** gives the tribromo derivative **11a** which on acid hydrolysis yields the tribromo ketone **11b**. Reduction of the tribromo ketone **11b** with tri-n-butyltin hydride gave two isomeric products identified as the *endo* (R)-isomer **11c** and the *exo* (S)-isomer **11d**. Initial formation of the 5,6- rather than the 4,5-double bond, shown by formation of the 5,6-dibromocyclopropanyl derivative, is consistent with the greater stability of the 5,6-double bond e.g. preferential 5,6-unsaturated ketal formation from the steroid 4-en-3-one.[64]

Evidence for an initial insertion reaction at the 9α-H

has been obtained by isolation of the 9α-$CHCl_2$ derivative when these reactions were repeated using $CHCl_3$ in place of $CHBr_3$[63].

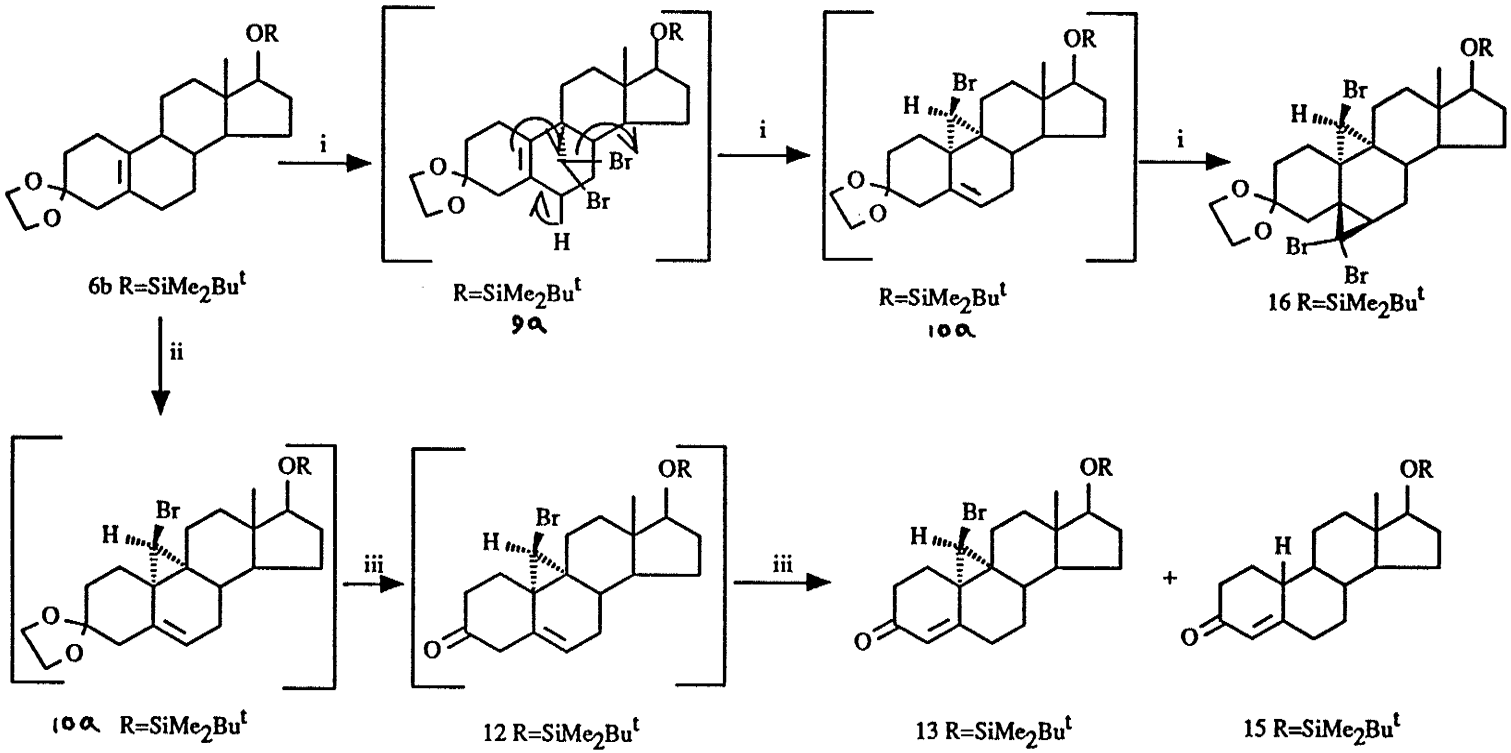
Compounds **11a-11d** (see **Scheme 2**) were first prepared, but not fully characterised, by Professor Ling and repeated to prepare analytically pure samples.

iv. Dibromocarbene reaction with 17β-tert-butyldimethyl-siloxy-3,3-ethylenedioxyestr-5(10)-ene **6b**

Treatment of ketal **6b** with dibromocarbene, generated from $CHBr_3$/$KOBu^t$/dry ether at -30°C under an argon atmosphere, following by deketalisation by the action of PTSA in acetone, as described by Birch *et al.*,[48] gave the mono bromo derivative **13** and the conjugated steroid **15** which were discussed previously. A similar mechanism is proposed in **Scheme 3**.

Treatment of ketal **6b** **(Scheme 3)** with dibromocarbene, generated under phase transfer catalyst condition ($CHBr_3$/NaOH/CTAB), gave mainly the tribromo derivative **16** which refused to hydrolyse under acid treatment. The higher yield of the tribromo derivative **16** is consistent with the addition of a second molecule of dibromocarbene to the intermediate 5,6-double bond which is favoured under the more reactive phase transfer condition to give **16**.

The ^1H NMR spectrum of the tribromo derivative **16** showed a new singlet peak, integrating for one proton, at 2.81 ppm which corresponded to the C-19 cyclopropyl proton. The ^{13}C NMR spectrum of compound **16** showed a new methine carbon signal at 32.48 ppm assigned to the 19-cyclopropyl carbon, a new



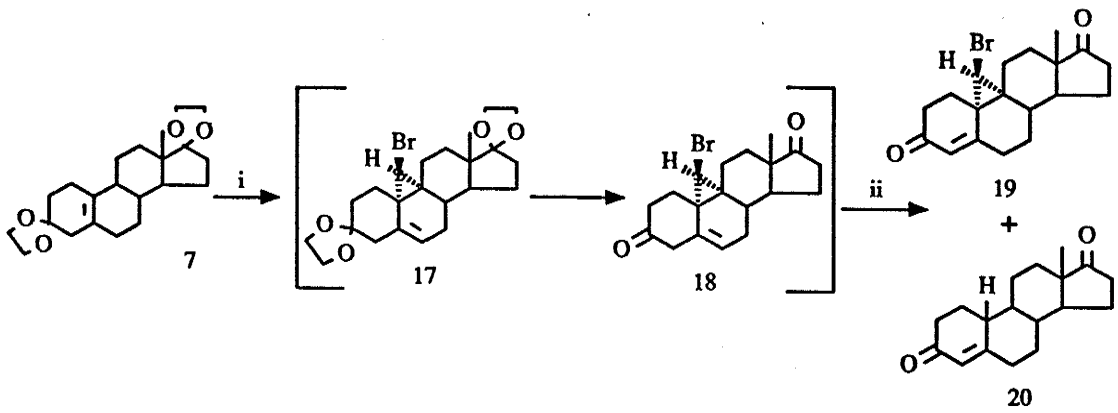
Scheme 3 *Reagents*: i, $CHBr_3$/NaOH/CTAB; ii,$CHBr_3$/t-BuOK/ether; iii, PTSA/acetone

quaternary carbon signal at 40.38 ppm assigned to 5,6-dibromocyclopropyl carbon, and the loss of two quaternary carbons signals at 125.59 and 129.58 ppm from the starting material **6b**. Elemental analysis (C, H, Br) was also in agreement with this structure.

v. Dibromocarbene reaction with 3,3,17,17-bis-(ethylene-dioxy)estr-5(10)-ene **7**

Treatment of ketal **7** **(Scheme 4)** with dibromocarbene, either generated from $CHBr_3/KOBu^t$/dry ether at -30°C or under phase transfer catalyst conditions ($CHBr_3$/NaOH/CTAB), gave mainly the mono bromo derivative **19** and the conjugated ketone **20**.

The ^1H NMR spectrum of the mono bromo derivative **19** showed a new singlet peak, integrating for one proton, at 3.37 ppm which corresponded to the C-19 cyclopropyl proton and a singlet vinylic proton at 5.88 ppm assigned to the 4-H. The ^{13}C NMR spectrum of compound **19** showed two carbonyl carbons at 198.51 and 219.29 ppm and the absence of the four methylene carbon signals which corresponded to the 3,3,17,17-bis-ethylenedioxy groups in the starting material **7**, corresponding to the hydrolysis of the 3,17-ketal. Two ethylene carbons at 126.72 and 161.27 ppm corresponded to the 4,5-double bond. The C-10 signal shifts to high field from 129.49 ppm to 29.88 ppm, and a new methine signal at 33.34 ppm was assigned to the 19-bromocyclopropyl carbon. Elemental analysis (C, H, Br) is in agreement with the structure.



Scheme 4 *Reagents*: i, $CHBr_3$/NaOH/CTAB or $CHBr_3$/t-BuOK/ether; ii, PTSA/acetone

The ^{1}H NMR spectrum of the unsaturated steroid **20** showed a new singlet peak at 5.85 ppm, integrating for one proton, which was assigned to the 4-vinylic proton. The absence of a multiplet at 3.96 ppm corresponded to the loss of the 3,17-bis-ethylenedioxy group. These changes indicated the presence of an α,β-conjugated ketone in compound **20**. The ^{13}C NMR spectrum of compound **20** showed two carbonyl carbon signals at 199.55 ppm and 220.23 ppm, the loss of four methylene carbon signals from the starting material **7** corresponding to hydrolysis of the 3,17-ketal, and two unsaturated carbons at 124.89 and 165.75 ppm corresponding to the 4,5-double bond. The C-10 signal was shifted to higher field from 129.49 ppm to 42.48 ppm. Elemental analysis (C, H) is in agreement with the structure.

Part B: Reductive cyclization of 19-oxo-androst-4-ene-3,17-dione.

I. Review of the synthesis of 19-unsubstituted 5β,19-cyclo-androstane derivatives

The alkali and alkaline earth metals in liquid ammonia have the highest reduction potentials of all chemical reducing agents. In steroid chemistry, metal-ammonia has been used primarily for the reduction of ring A benzenoid compounds to 1,4-dihydro compounds (Birch reduction) and for the reduction of conjugated unsaturated ketones to saturated ketones.

Stork *et al.*[65-67] investigated alkali metal-ammonia reduction of α,β-unsaturated ketones in a series of papers during 1960-1965. However, the mechanism is still the subject of debate. Barton and Robinson[68] proposed a dicarbanion mechanism and Stork and Tsuji[66] a radical-anion mechanism.

In 1965, Stork *et al.*[67] reported that during the course of the metal-ammonia reduction of α,β-unsaturated ketones the β-carbon atom becomes nucleophilic and can attack a suitably placed electrophilic center. They treated 10-hydroxymethyl-$\Delta^{1,9}$-2-octalone tosylate **I** **(Fig. 13)** with lithium in liquid

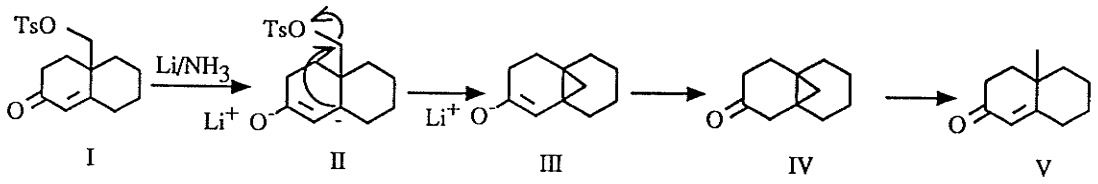


Fig. 13 Reduction of an unsaturated keto tosylate with lithium in ammonia

ammonia and obtained 1,9-cyclopropano-2-octalone **IV**, a product logically arising from displacement of the tosylate on the angular carbon by a carbanion center generated at the β-carbon. Compound **IV** was identified by its transformation on heating with acid (sulfuric acid:acetic acid:water; 1:2:2) into the known 10-methyl-$\Delta^{1,9}$-2-octalone[69] **V**, and characterized by comparision of its 2,4-dinitrophenylhydrazone with an authentic sample.

The synthesis of 19-unsubstituted 5β,19-cycloandrostane derivatives has been extensively investigated by reactions involving 19-hydroxyandrost-4-ene-3,17-dione rearrangement,[41] elimination of a 19-methanesulfonyloxy, p-toluenesufonyloxy or halogen groups with pyridine,[42] KOAc buffer,[70] zinc dust in 50% aqueous acetic acid,[44,71] lithium aluminum hydride,[71] lithium or sodium in liquid ammonia,[71-73] or lithium and biphenyl in THF.[46]

In 1962, Bonet *et al.*[42] reported that they obtained 5β,19-cycloandrost-6-ene-3,17-dione **III** **(Fig. 14)** by refluxing the

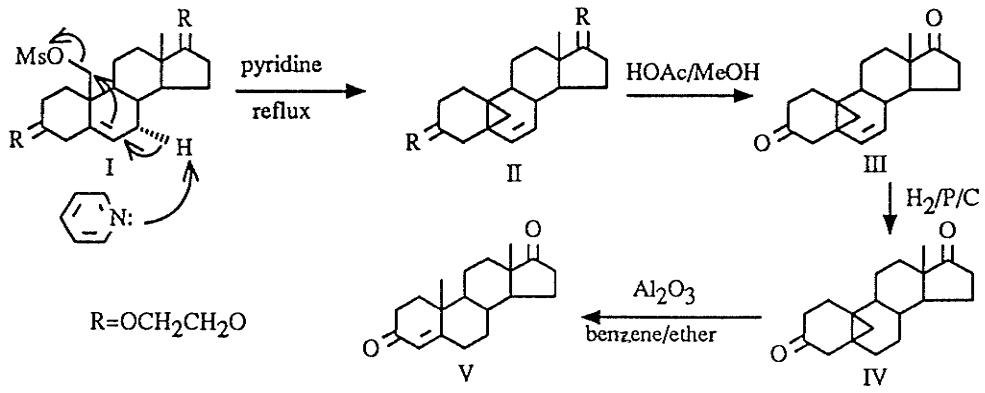


Fig. 14 Rearrangement of the unsaturated keto mesylate in pyridine

methanesulfonate **I** in pyridine followed by deketalisation with HOAc/methanol. Pyridine attack on the allylic 7α-H resulted in *trans* elimination to give the dione **III**. The unsaturated dione **III** was reduced to the saturated dione **IV** by hydrogenation. Dione **IV** was identified by its transformation on neutral Al_2O_3 in benzene-ether to androst-4-ene-3,17-dione **V**.

In 1963, Knox *et al.*[41] reported a remarkable rearrangement when 19-hydroxyandrost-4-ene-3,17-dione **(1)** **(Fig. 15)** was treated with diethyl-(2-chloro-1,1,2-trifluoroethyl)-amine[74] to give 5β,19-cycloandrost-1-ene-3,17-dione **(21)** and 10β-fluoro-5,10-seco-5β-19-cycloandrost-4-ene-3,17-dione.[74] Their proposed mechanism for this transformation is shown in **Fig. 15**.

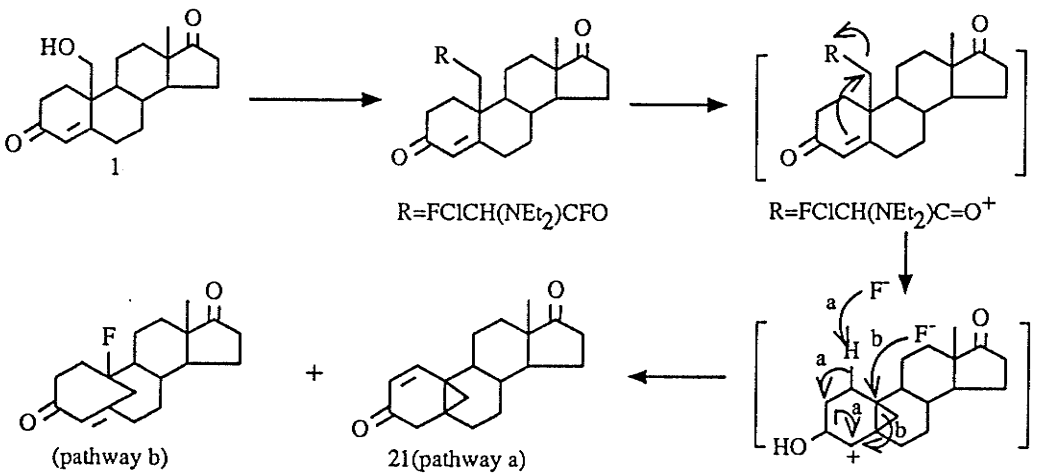


Fig. 15. Synthesis of 5β,19-cycloandrost-1-ene-3,17-dione from a remarkable rearrangement

In 1964, Tadanier and Cole[70] reported that they obtained 3β-methoxy-6α-hydroxy-5β,19-cycloandrostan-17-one **III (Fig. 16)** by acetolysis of the methanesulfonate **I** in aqueous acetone in the presence of potassium acetate buffer, followed by basic hydrolysis of the crude acetate-containing product **II**. Attack of acetate ion at C-6 with cyclization and mesylate elimination gives product **II**. Compound **III** was identified by optical rotation, ultraviolet spectrum and infrared spectrum.

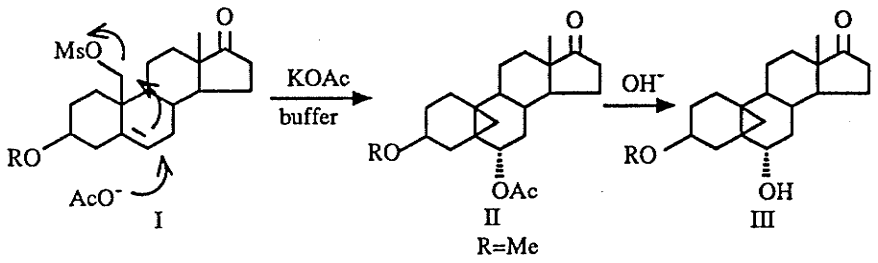


Fig. 16. Rearrangement of the unsaturated keto methylate in aqueous acetone in the presence of KOAc buffer

In 1964, Rakhit and Gut[71] treated 19-hydroxyandrost-4-ene-3,17-dione tosylate **IIa (Fig. 17)** with either zinc dust in 50% aqueous acetic acid under reflux, or lithium in liquid ammonia, followed by oxidation to give 5β,19-cycloandrostane-3,17-dione **III** which was identified by optical rotation, infrared spectrum, ultraviolet spectrum and ^{1}H NMR. They obtained the same product **III** by treating the tosylate **IIa** with lithium aluminum hydride, followed by chromic acid oxidation, or by treatment with sodium borohydride followed by lithium aluminum hydride reduction and oxidation. They

proposed that lithium aluminum hydride first reduced the two carbonyl groups, followed by hydride attack at C-4, causing displacement of the 19-tosyloxy group with concomitant formation of the cyclopropane ring.

In 1965, Knox *et al.*[72] reported that they obtained 5β,19-cycloandrostane-3,17-dione **III**, by exposure of 19-chloroandrost-4-ene-3,17-dione **IIb (Fig. 17)** to lithium in liquid ammonia followed by oxidation. Compound **III** was identified by mixed melting point and infrared spectrum comparison with an authentic sample.

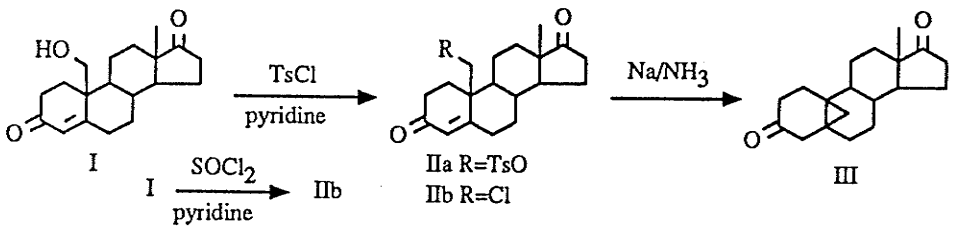


Fig. 17 Synthesis of 5β,19-cycloandrostane-3,17-dione

In 1968, Wieland and Anner[46] attempted to simultaneously synthesize both 5β,19-cycloandrost-1-ene-3,17-dione **XII** and 1β,19-cyclo-androst-4-ene-3,17-dione **V** by treating 19-hydroxy-17,17-ethylenedioxyandrost-1,4-dien-3-one methylate **I (Fig. 18)** with lithium and biphenyl in tetrahydrofuran (THF). They isolated 17,17-ethylenedioxy-5β,19-cycloandrost-1-en-3-one **XI** in only 7% yield together with the rearrangement product, A-homo-19-norandrost-1,5(10)-ene-4,17-dione **VIII**, in 50% yield.

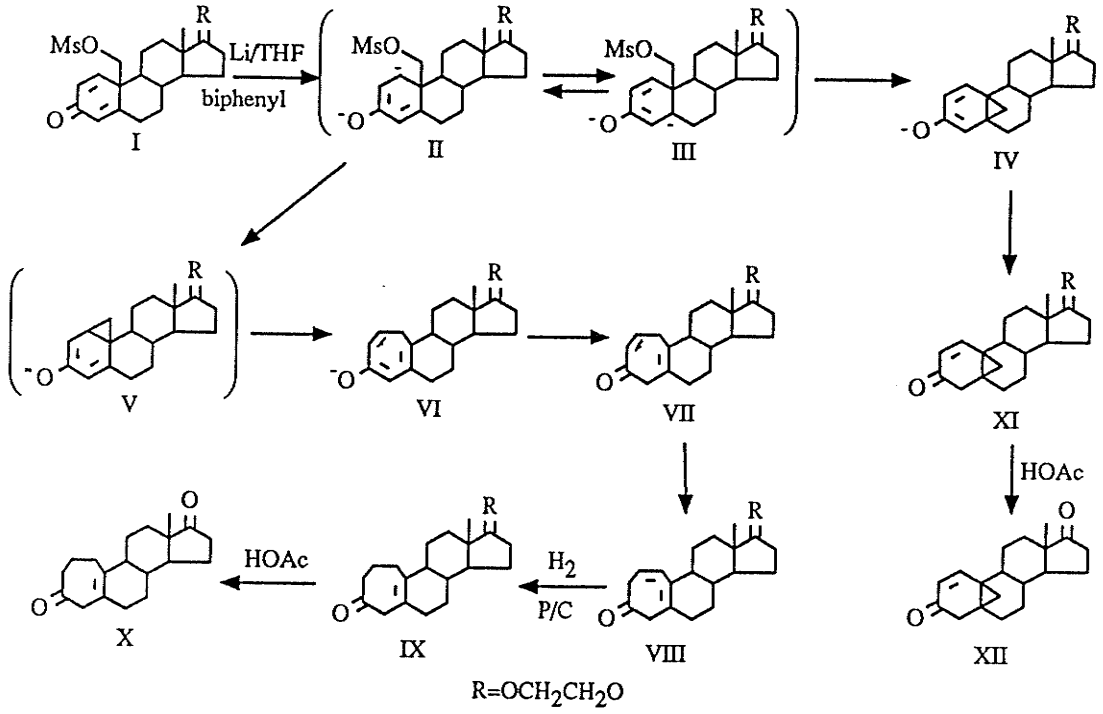


Fig. 18 Synthesis and mechanism of formation of 5β,19-cycloandrost-1-ene-3,17-dione and A-homo-19-norandrost-1,5(10)-ene-4,17-dione

Compound **XI** was identified by its transformation on treatment with acetic acid to the known 5β,19-cycloandrost-1-ene-3,17-dione[41] **XII**. The structure of the rearrangement product was established by its hydrogenation to compound **IX** following deketalisation to the known A-homo-19-norandrost-5(10)-ene-4,17-dione[75] **X**. This result is in agreement with reduction of cross-conjugated 1,4-enones to the 4-en-3-ones as the major product.[76-78]

A proposed mechanism for these transformations is shown

in **Fig. 18**. The mesylate **I** was reduced by lithium and biphenyl in THF to dianion **II** and **III**. Dianion **II** attacked the electrophilic C-19 to give intermediate **V** which was unstable and rearranged via **VI** and **VII** to the more stable product **VIII**. Dianion **III** attacked the electrophilic C-19 to give intermediate **IV** which, on acidic ketal hydrolysis, gave the known compound **XII**.[41]

In 1979, to prepare C-19 deuterium labelled steroids, Dyer and Harrow[73] treated the methyl ester **I (Fig. 19)** with

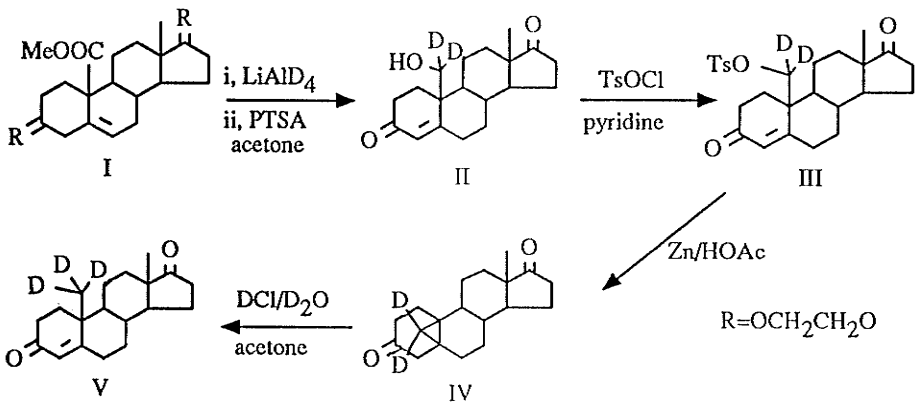


Fig. 19 The preparation of 19-d_2-steroids through Zn/HOAc reduction of a 19-d_2-tosylate

lithium aluminium deuteride in THF, followed by ketal hydrolysis with boiling aqueous acetone containing PTSA, to give the alcohol **II**. The alcohol **II** on reaction with p-toluenesulfonyl chloride in pyridine gave 19-d_2-19-p-toluene-sulfonyloxyandrost-4-ene-3,17-dione **III**. The tosylate **III** was treated with zinc dust in boiling aqueous acetic acid to give 5β,19-d_2-cycloandrostane-3,17-dione **IV** in 79% yield, which on

heating under reflux with deuterium chloride in deuterium oxide underwent ring opening to give **V**.

In 1981, Holland and Taylor[44] treated 17-benzyloxy-19-hydroxyandrost-4-ene-3,17-dione tosylate **I (Fig. 20)** with zinc dust in 50% acetic acid under reflux to give 17-benzyloxy-5β,19-cycloandrostane-3,17-dione **II** in 41% yield, which after

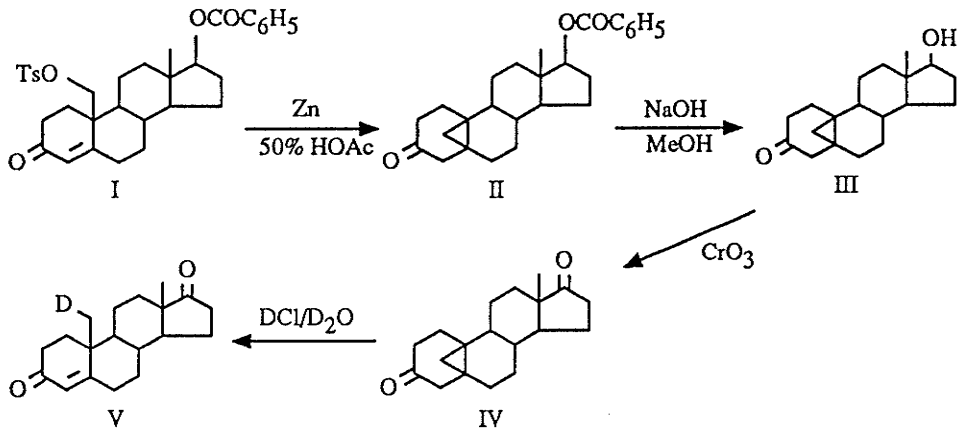


Fig. 20 The preparation of 19-deuterated steroids through ring opening of a 19-d_2-5β,19-cycloandrostane-3,17-dione

hydroxylation and oxidation gave the dione **IV**. The dione **IV**, on reflux with deuterium chloride in deuterium oxide,[73] underwent ring opening to afford 19-deuterioandrost-4-ene-3,17-dione **V** consistent in physical and spectral properties with an authentic sample of unlabelled material.

II. The synthesis of 5β,19-cycloandrost-1-ene-3,17-dione ***21***

We repeated the synthesis of 5β,19-cycloandrost-1-ene-3,17-dione **21** by treatment of 19-hydroxyandrost-4-ene-3,17-dione **1** with diethyl-(2-chloro-1,1,2-trifluoroethyl)-amine as described by Knox *et al.*[41] **(Fig. 15)**. The ^{1}H NMR spectrum (see **Table 7**) of the cyclopropyl enone **21** as expected showed an AB pattern at 0.37, 1.17 ppm (J_{AB}=4.3 Hz) assigned to the two *geminal* protons at 19-H_2; an AB pattern at 2.50, 2.85 ppm (J_{AB}=8.4 Hz) assigned to the protons at 4-H_2 and two doublet signals at 5.76, 7.28 ppm (J=10.2 Hz) assigned to the two vinylic protons at 1-H and 2-H. The ^{1}H NMR spectrum was in agreement with the published spectrum.[41] The ^{13}C NMR spectrum was assigned by 2-D analysis (see **Table 7**), and was similar to the published spectrum of 5β,19-cycloandrostane-3,17-dione.[43] Because the melting point obtained (m.p. 184-186°C) was appreciably higher than the published value (m.p. 173-175°C), the elemental analysis (H, C) was carried out and proved to be in agreement with the accepted structure.

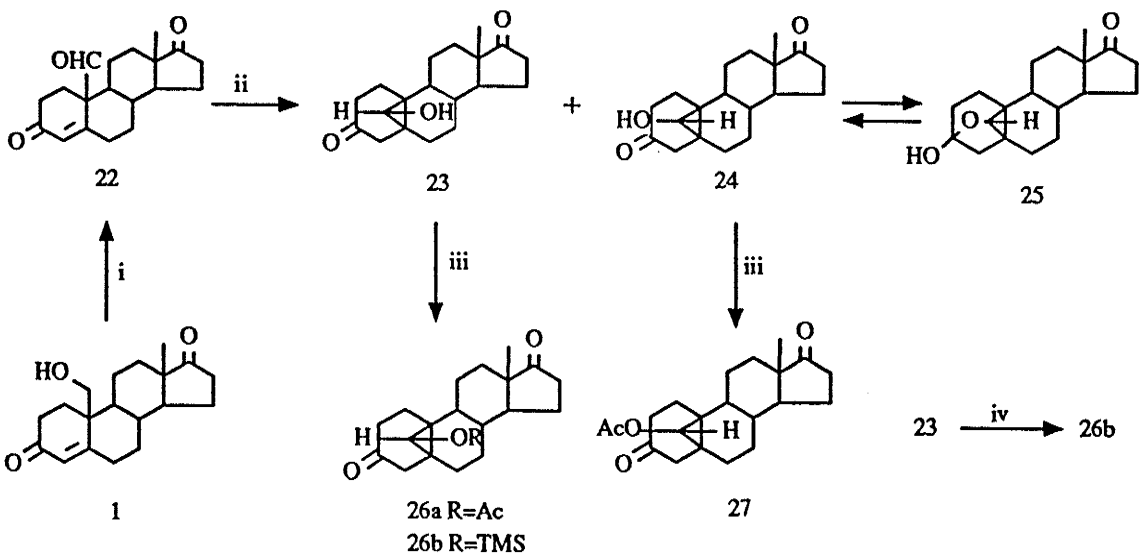
III. Synthesis of 19(R/S)-hydroxy-5β,19-cyclo-androstane-3,17-dione derivatives

i, The synthesis of 19(R)-hydroxy-5β,19-cycloandrostane-3,17-dione **23** and its derivatives **26a** and **26b**.

The synthesis of compounds **23, 26a, 26b** and **27** is outlined in **Scheme 5**. Pyridinium chlorochromate oxidation[79] of the 19-hydroxy alcohol **1** gave a quantitive yield of the

aldehyde **22**.[80] The ^{1}H NMR spectrum (see **Table 1**) of the aldehyde **22** showed a singlet vinylic proton signal at 5.93 ppm similar to that assigned to the 4-H in the starting material. A new singlet signal, which integrated for one proton, at 9.88 ppm was assigned to the C-19 aldehyde proton. The AB pattern for the C-19 methylene protons at 3.96 ppm in the spectrum of the starting material was absent in the product spectrum. The ^{13}C NMR spectrum (see **Table 2**) showed a new carbonyl signal at 200.71 ppm which was assigned to the C-19 aldehyde carbon and the absence of the methylene carbon at 66.10 ppm assigned to C-19 in the starting material.

Reduction of the aldehyde **22** with zinc dust in 50% aqueous HOAc afforded 19(R)-hydroxy-5β,19-cycloandrostane-3,17-dione **23** as the major product and a trace amount of the S-isomer **24** in equilibrium with its hemiketal tautomer, 3-hydroxy-3β,19-oxido-5β,19-cycloandrostan-17-one **25**, as indicated in the ^{1}H NMR spectrum of the mother liquor. A similar keto-alcohol/hemiketal equilibrium between 19-hydroxy-5α-androstane-3,17-dione and 3α-hydroxy-3β,19-oxido-5α-androstan-17-one, has been reported.[72] The ^{1}H NMR spectrum (see **Table 8**) of the 19(R)-hydroxy isomer **23** showed the absence of a singlet vinylic proton signal and instead exhibited an AB pattern at 2.31, 2.49 ppm (J_{AB}=17.1 Hz) which was assigned to the 4-H_2; a new singlet at 3.30 ppm was assigned to the C-19 cyclopropyl proton. The C-19 aldehyde proton signal was absent. The location of the 5,10-cyclopropyl group was



Scheme 5 *Reagents:* i, PDC/CH_2Cl_2; ii, Zn/50% AcOH; iii, Ac_2O/pyridine; iv, TMS-imidazole/CH_2Cl_2

established by the presence of a long range (4 bond) "W" coupling between the cyclopropyl proton with H-9 and H-6α. NOEs were observed from the cyclopropyl proton to H-4β, H-2β and H-1β, which confirmed the location of the cyclopropyl proton as lying on the β-face over ring A. The ^{13}C NMR spectrum assigned by a 2-D analysis experiment (see **Table 8**) showed a new methine carbon signal at 63.40 ppm assigned to the cyclopropyl carbon and the loss of two ethylene carbon signal at 127.53 and 160.35 ppm observed in the starting material. The ^{13}C NMR spectrum is similar to the published spectrum of 5β,19-cycloandrostane-3,17-dione **(20)**.[43] Elemental analysis (C, H) was in agreement with this structure.

The alcohol **23** was treated with Ac_2O and DMAP in CH_2Cl_2 to afford the acetate **26a**. The ^1H NMR spectrum of the acetate **26a** showed a new singlet signal at 2.15 ppm which integrated for three protons corresponding to the C-19 acetoxy group. The AB pattern assigned for the 4-H_2 in the alcohol **23** was replaced by a singlet signal at 2.54 ppm, which integrated for two protons. The ^{13}C NMR spectrum of the acetate **26a** showed a new methyl signal at 20.93 ppm and a new carbonyl carbon at 170.57 ppm which corresponded to the C-19 acetoxy group. The results of elemental analysis (C, H) were in agreement with the acetate.

The alcohol **23** was treated with trimethylsilyl chloride-imidazole in CH_2Cl_2 to afford the non-crystalline silyl ether **26b**. The TMSi derivatives rather than the TBDMSi derivatives

were employed because they frequently separate better on TLC.[81] The ^{1}H NMR spectrum of the silyl ether **26b** showed a new multiplet at 0.16 ppm which integrated for nine protons and corresponded to the C-19 trimethylsilyloxy group. The ^{13}C NMR spectrum of the silyl ether **26b** showed a new methyl signal at -0.26 ppm corresponding to the trimethylsilyloxy group at C-19. The results of elemental analysis (C, H) were in agreement with structure **26b**.

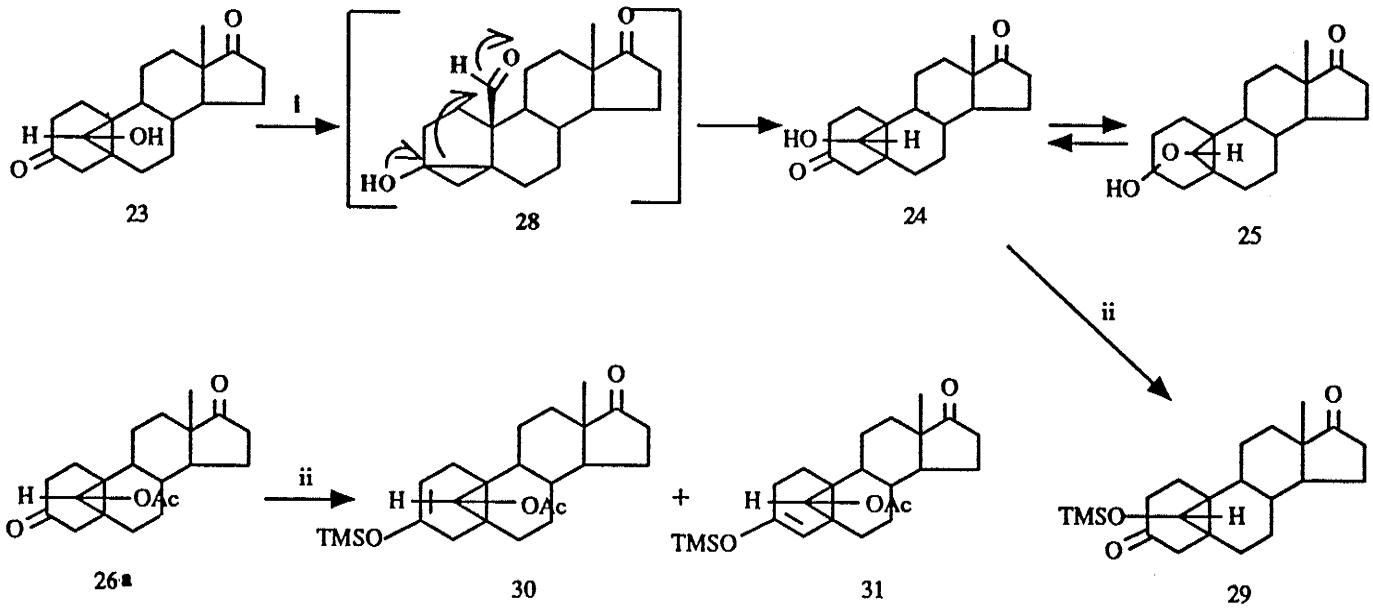
ii, The synthesis of 19(S)-hydroxy-5β,19-cycloandrostane-3,17-dione acetate **27** and the trimethylsilyl ether **29**

19(R)-Hydroxy-5β,19-cycloandrostane-3,17-dione **23** was obtained by zinc dust reduction of the aldehyde **22** in 50% aqueous HOAc as described above. A trace amount of the S-isomer **24** and its tautomeric hemiketal, 3-hydroxy-3β,19-oxido-5β,19-cycloandrostan-17-one **25**, was obtained as an equilibrium mixture from the mother liquor. The R-isomer **23** was readily crystallized from the reaction product and the mother liquor treated with Ac_2O and DMAP in CH_2Cl_2 to afford, after chromatographic separation, the non-crystalline acetate **27**. The ^{1}H NMR spectrum (see **Table 9**) of the S-isomer acetate **27** showed a new singlet signal at 2.08 ppm which integrated for three protons and corresponded to the C-19 acetoxy group; the AB pattern assigned for the 4-H_2 was shifted to 2.25, 2.38 ppm (J=16.5 Hz). The observation of NOEs from 19-H to 7-βH, 8-βH and 12-βH confirms the location of the cyclopropyl proton over ring B. The ^{13}C NMR spectrum of the acetate **27** was assigned by 2-D

analysis (see **Table 9**) and showed a new methyl signal at 20.53 ppm and a new carbonyl carbon at 171.14 ppm which corresponded to the C-19 acetoxy group.

The alcohol **23** (R-isomer) was treated with 0.5 M KOH in methanol to afford a crystalline equilibrium mixture of the S-isomer alcohol **24** and its tautomeric hemiketal **25** with its ^{1}H and ^{13}C NMR corresponding to that observed in the mother liquor discussed above[82]. This epimerization would not be expected to occur through S_N1 or S_N2 displacement at C-19 and it was proposed[82] that compound **28** is an intermediate (see **Scheme 6**). The mixture was then treated with trimethysilyl chloride-imidazole in CH_2Cl_2 to afford the crystalline silyl ether **29**. The ^{1}H NMR spectrum of the silyl ether **29** showed a new singlet at 0.16 ppm which integrated for nine protons and corresponded to the C-19 trimethylsilyloxy group. The AB pattern assigned to the 4-H_2 was shifted to 2.09, 2.53 ppm (J=16.3 Hz). The ^{13}C NMR spectrum of the silyl ether **29** showed a new methyl signal at -0.35 ppm corresponding to the C-19 trimethylsilyloxy group. Similar rearrangements have been studied in detail by Reusch's group.[83,84]

As we desired to introduce a C-1 double bond into the R-isomer, it was of value to know the direction of enolization of the C-3 ketone in the 5β,19-cycloandrostane. Therefore, the acetate **26a** was treated with trimethylsilyl triflate (TMSOTf) in DMF. This reaction yielded a less polar product as shown by TLC. ^{1}H NMR of the total reaction product showed it to be a

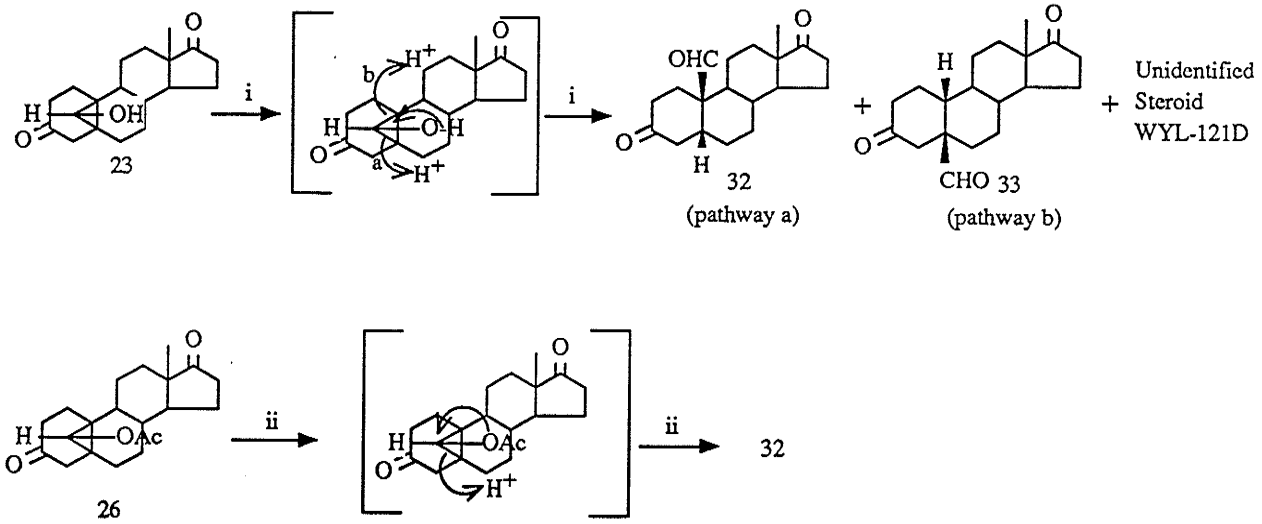


Scheme 6 *Reagents:* i, 0.5 M KOH/MeOH; ii, TMS-imidazole/Et_3N/DMF

mixture of 57% enol **30** and 43% enol **31** as calculated from the ^{1}H NMR spectrum by comparision of the vinylic 2-H **30** and 4-H **31** signals (see **Scheme 6**).

iii. Synthesis of 19-oxo-5β-androstane-3,17-dione **32**, 5β-estrane-3,17-dione 5β-aldehyde **33** and an unidentified steroid **WYL-121D**.

In an attempt to synthesize 19(R)-chloro-5β,19-cyclo-androstane-3,17-dione from the 19(R)-alcohol **23** through S_N1[85] or S_N2[86] substitution, several methods proved unsuccessful. The 19(R)-alcohol **23** was treated with concentrated HCl in CH_2Cl_2 to give 19-oxo-5β-androstane-3,17-dione **32** and an unidentified steroid **WYL-121D** as the major products together with a trace amount of non-crystalline 5β-estrane-3,17-dione 5β-aldehyde **33** (**Scheme 7**). The structure of the aldehyde **32** was established based on HSQC and COSY experiments. The observation of NOEs between the aldehyde proton and the 5-H and 1-βH confirms the β-face stereochemistry. The ^{1}H NMR spectrum of the aldehyde **32** showed a new singlet signal at 9.62 ppm which integrated for one proton and corresponded to the 19-aldehyde proton; the AB pattern assigned to the 4-H_2 at 2.31, 2.49 ppm (J=17.2 Hz) and the cyclopropyl proton signal at 3.30 ppm in the starting 19(R)-alcohol **23** were absent in the aldehyde **32**. The ^{13}C NMR spectrum of the aldehyde **32** showed a new carbonyl carbon signal at 204.51 ppm which corresponded to the C-19 aldehyde carbon. The results of elemental analysis (C, H) supported this conclusion. No further work was carried out on this



Scheme 7 *Reagents:* i, HCl/CH_2Cl_2 or PTSA/acetone; ii, DDQ/benzene or $[C_6H_5Se(O)]_2O$/benzene

compound (**WYL-121D**), mp: 246-250°C (Found: C, 77.45, H, 8.49), and the structure was not established.

Preliminary attempts to introduce a double bond into ring A using small scale experiments monitored by TLC under UV did not indicate the formation of a conjugated ketone. For example, treatment of the acetate **26a** with either 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[87-88] or benzeneseleninic acid anhydride[89] in benzene under reflux resulted in ring opening to afford the aldehyde **32** established by NMR spectral comparison **(Scheme 7)**.

Part C: Reductive cyclization of 19-oxo-androst-1-ene-3,17-dione.

I. Review of the synthesis of 1β,19-cyclo-5α-androstane derivatives

The synthesis of 19-unsubstituted 1β,19-cyclo-5α-androstane derivatives have been reported.[46,47] In 1970, to synthesize 1β,19-cyclo-5α-androstane-3,17-dione, Wieland and Anner[47] treated 17-acetoxy-19-hydroxy-5α-androst-1-en-3-one mesylate **II (Fig. 21)**, obtained from the saturated mesylate **I** by bromination followed by dehydrobromination, with lithium and biphenyl in THF to give 17-acetoxy-1β,19-cyclo-5α-androstan-3-one **III**. The structure of the product **III** was established by its infrared spectrum, ^{1}H NMR and elemental analysis.

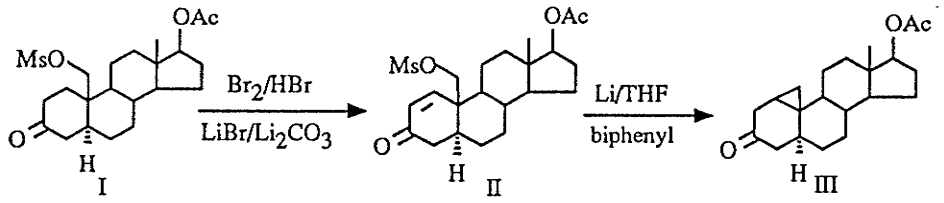


Fig. 21 Synthesis of 1β,19-cyclo-5α-androstane-3,17-dione

*II Attempted synthesis of 19-hydroxy-1β and 5β,19-cycloandrostanes together: estrone derivatives **36, 37***

An attempt to synthesis both 19-hydroxy-1β,19-cyclo-5α-androst-4-ene-3,17-dione **V** and 19-hydroxy-5β,19-cyclo-androst-

1-ene-3,17-dione **VI**, via radicals or dianions **III** and **IV (Fig. 22)**, through treatment of 19-oxo-androst-1,4-diene-3,17-dione **II**,[90] obtained from pyridinium dichromate (PDC) oxidation of the 19-hydroxy diene **I**, with zinc dust and aqueous acetic acid was unsuccessful and resulted in the formation of estrone. This is because the 19-hydroxy and 19-oxo-androst-1,4-diene-3,17-dione readily undergo aromatization to yield the aromatic system of estrone.[90]

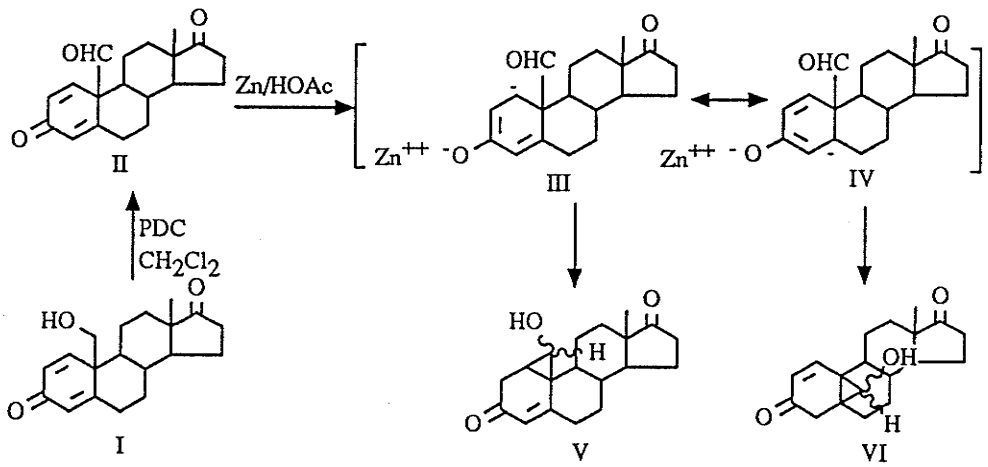
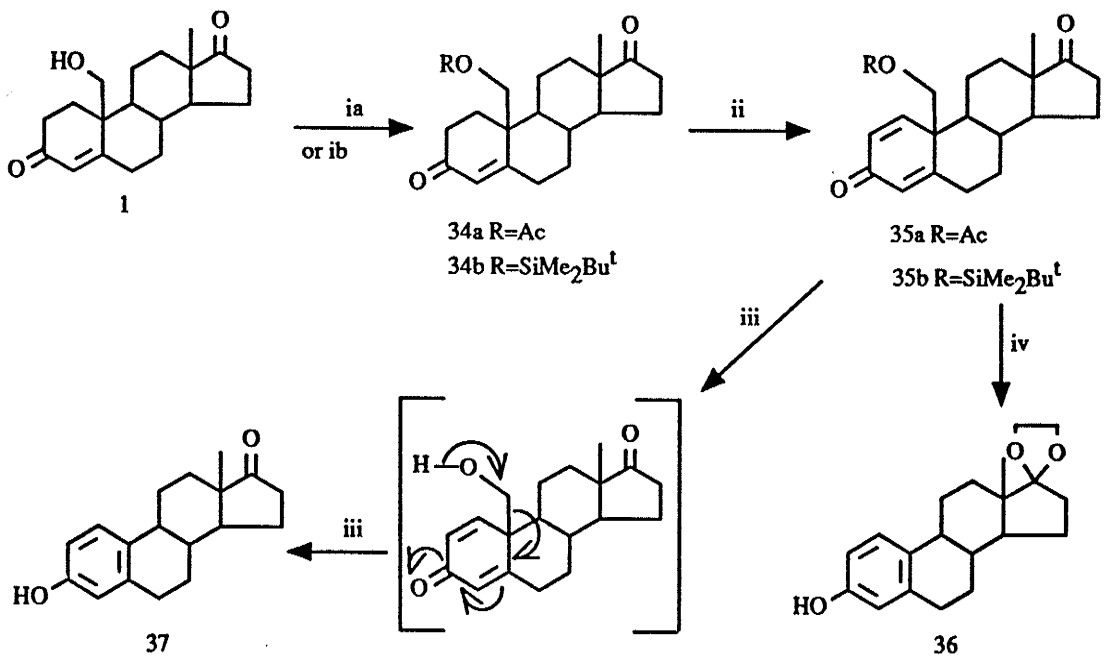


Fig. 22 Proposed mechanism for the synthesis of 19-hydroxy-1β,19-cyclo-5α-androst-1-ene-**V** and 19-hydroxy-5β,19-cycloandrost-4-ene-3,17-dione **VI**

19-Hydroxyandrost-4-ene-3,17-dione **1** was acetylated with acetic anhydryde and DMAP in CH_2Cl_2 to afford the acetate **34a**[72,91] (see **Scheme 8**). The ^1H NMR spectrum of the acetate **34a** showed a new singlet at 2.02 ppm which integrated for three protons corresponding to the C-19 acetoxy group. This acetate **34a** has been reported as non-crystalline[91] and later with a low



Scheme 8 *Reagents:* i, Ac_2O/DMAP/CH_2Cl_2, i, $BuMe_2SiCl$/imidazole/DMF; ii, $[C_6H_5Se(O)]_2O$/$NaHCO_3$/benzene; iii, 5% KOH/CH_3OH or Bu_4NF /THF; iv, $HOCH_2CH_2OH$/PTSA/benzene

melting point[72a]. In our preparation the non-crystalline acetate, which was pure by TLC and ^1H NMR, was used. The ^{13}C NMR spectrum of the acetate **34a** showed a new methyl signal at 20.88 ppm and a new carbonyl carbon at 170.50 ppm corresponded to the introduction of C-19 acetoxy group. The acetate **34a** was treated with benzeneseleninic acid anhydride (SBA)[89,92] and $NaHCO_3$ in benzene to afford the diene **35a**. The ^1H NMR spectrum of the diene **35a** showed that the AB pattern corresponding to 19-H_2 in the acetate **34a** was shifted to 4.42, 4.64 ppm (J_{AB}=10.9 Hz); the 4-H signal in the spectrum of the acetate **34a** was shifted to lower field at 6.21 ppm; two new doublet signals at 6.36 and 7.07 ppm (J=10.2 Hz) assigned to 1-H, 2-H corresponding to the introduction of the 1,2-double bond. The ^{13}C NMR spectrum of the diene **35a** showed two new vinylic methine signals at 130.46, 151.05 ppm corresponding to the 1,2 vinylic carbons. A similar compound, 17-tetrahydropyranyloxy-19-acetoxyandrost-1,4-dien-3-one, has been recently reported.[89] Elemental analysis (C, H) supported the structure.

Treatment of the diene **35a** with 5% KOH/MeOH at room temperature did not afford the expected 19-hydroxyandrost-1,4-diene-3,17-dione but yielded estrone **37** indentified by comparision of the melting point, ^1H and ^{13}C NMR spectra with published data.[93] An attempt to protect the C-3 ketone in the diene **35a** as the ethylenedioxy ketal before hydrolysis, by reflux with ethylene glycol and PTSA in benzene, resulted in the formation of 17,17-ethylenedioxyestrone **36** whose structure

was established by ^{1}H, ^{13}C NMR and elemental analysis. This provided further evidence that 19-hydroxyandrost-1,4-diene-3,17-dione was unstable and underwent aromatization spontaneously to give estrone as outlined in **Scheme 8**.

Treatment of 19-hydroxyandrost-4-ene-3,17-dione **1** with tert-butyldimethylsilyl chloride and imidazole in DMF afforded the silyl ether **34b** (see **Scheme 8**). The ^{1}H NMR spectrum of the silyl ether **34b** showed new signals at 0.04, 0.05 and 0.86 ppm corresponding to the C-19 tert-butyldimethylsilyoxy group. The ^{13}C NMR spectrum of the silyl ether **34b** showed three new methyl signals at -4.48, -4.81 and 25.84 ppm and a new quaternary carbon signal at 18.07 ppm corresponding to the C-19 tert-butyldimethylsilyoxy group. Elemental analysis (C, H) also supported formation of the silyl ether.

The silyl ether **34b** was treated with benzene-seleninic acid anhydride (BSA)[89,92] and $NaHCO_3$ in benzene to afford the 1,4-dienone silyl ether **35b**. The ^{1}H NMR spectrum of the 1,4-dienone silyl ether **35b** showed that the 4-H signal in the silyl ether **34b** was shifted to lower field at 6.15 ppm. Two new doublet signals at 6.33 ppm and 7.09 ppm (J=10.2 Hz,), assigned to the C-1,2 vinylic carbon corresponded to the introduction of the 1,2-double bond. The ^{13}C NMR spectrum of the 1,4-dienone silyl ether **35b** showed two new vinylic methine signals at 129.99 and 186.40 ppm, in agreement with the introduction of the 1,2-double bond. Elemental analysis (C, H) supported the conclusion.

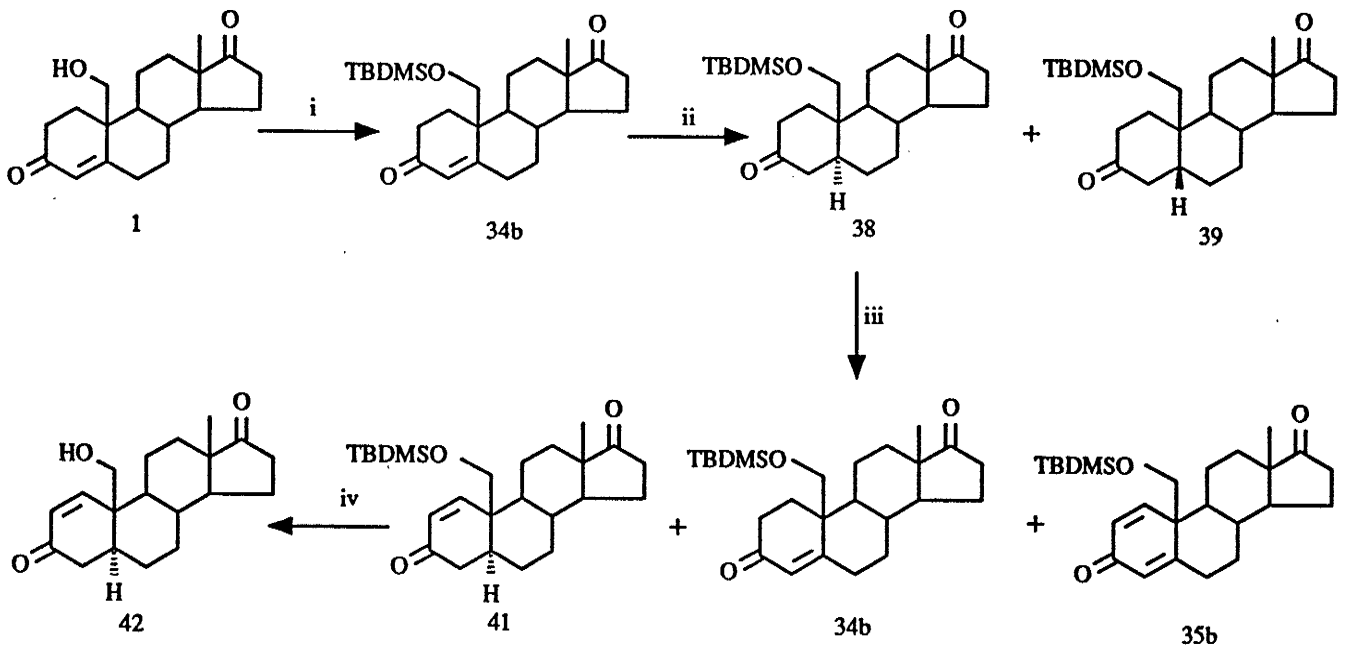
Desilylation of the 1,4-dienone silyl ether **35b**, by treatment with tertrabutylammonium fluoride in THF, did not give the expected 19-hydroxyandrost-1,4-diene-3,17-dione but instead yielded estrone **37**. Attempts to protect the ketone of the silyl ether 1,4-dienone **35b** as the ethylenedioxy ketal before hydrolysis again resulted in the formation of 17,17-ethylene-dioxyestrone **36 (Scheme 8)** as discussed above. Due to the instability of 19-hydroxyandrosta-1,4-diene-3,17-dione, this approach was abandoned.

*III Synthesis of 19-hydroxyandrost-1-ene-3,17-dione **42** and 2β,19-oxido-5α-androstane-3,17-dione **40***

i, Synthesis of 19-hydroxyandrost-1-ene-3,17-dione **42**

The synthesis of 19-hydroxyandrost-1-ene-3,17-dione **42** starting with 19-hydroxyandrost-4-ene-3,17-dione **1** was carried out as outlined in **Scheme 9**. Because hydrogenation of the 19-alcohol **1** gave the 5β-isomer as the major product,[72] the alcohol **1** was protected with the bulky tert-butyldimethylsilyl group to favour α-face addition of hydrogen. Treatment of the alcohol **1** with tert-butyl-dimethylsilyl chloride and imidazole in dimethyforamide afforded the silyl ether **34b**. Catalyzed hydrogenation[72] of the silyl ether **34b** on 5% Palladium on charcoal afforded the 5α-isomer **38** as the major product together with the 5β-isomer **39**.

The ^{1}H NMR spectrum, recorded on a Bruker AMX 500 spectrometer, of the 5α-isomer **38** showed that the vinylic



1 34b 38 39 42 41 34b 35b

Scheme 9 *Reagents*: i, TBDMSCl/imidazole/DMF; ii, H_2/Pd/C; iii, $[C_6H_5Se(O)]_2O$/$NaHCO_3$ /benzene; iv, n-Bu_4NF/THF

singlet signal assigned to the 4-H in the starting silyl ether **34b** was absent and a new multiplet signal, at 1.67 ppm, was assigned to the 5α-H. The 5α-stereochemistry was established by the observation of two axial couplings between the 5-H and 4β-H, 6β-H, i.e. the 5α-H, in the H/C correlation spectrum (HSQC). The ^{13}C NMR spectrum of the 5α-isomer **38** showed the absence of the two vinylic carbons at 126.02 and 163.49 ppm in the silyl ether **34b** spectrum. The quaternary C-5 in the silyl ether **34b** was replaced by a methine carbon and shifted to higher field at 46.23 ppm. Elemental analysis (C, H) was in agreement with the saturated structure.

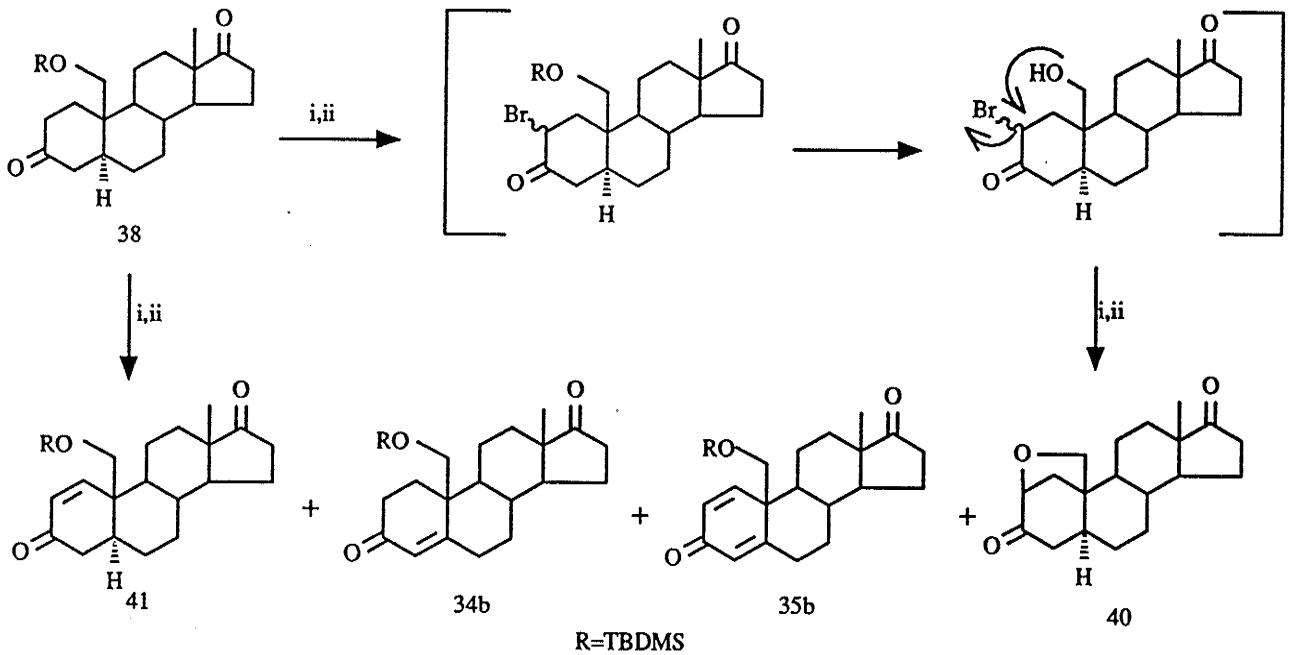
The ^{1}H NMR spectrum, recorded on a Bruker AMX 500 spectrometer, of the 5β-isomer **39** showed that the vinylic singlet signal assigned to the 4-H in the silyl ether **34b** was absent; the AB pattern assigned to the 19-CH_2 shifted to 3.60 and 3.81 ppm; a new multiplet signal, at 2.26 ppm was assigned to the 5β-H. The stereochemistry of the 5β-isomer was established by the observation, from the H/C correlation spectrum (HSQC), that 5-H has only one axial coupling to the 4α-H and no axial coupling to the 6β-H, i.e., the 5β-H. The ^{13}C NMR spectrum of the 5β-isomer **39** showed the absence of the two vinylic carbons at 126.02 and 163.49 ppm observed in the silyl ether **34b** spectrum. The quaternary C-5 signal in the silyl ether **34b** was replaced by a methine carbon and shifted to higher field at 36.38 ppm. Elemental analysis (C, H) was in agreement with the structure.

Introduction of a conjugated double bond into ring A of the 5α-isomer was carried out by refluxing the 5α-isomer with benzeneseleninic acid anhydride (BSA)[89,92] and $NaHCO_3$ in benzene to afford the silyl ether **41** 1-en-3-one (*ca.* 40%) together with silyl ether **34b** 4-en-3-one (*ca.* 35%) and 1,4-dienone silyl ether **35a** (*ca.* 25%) identical with the compounds prepared previously. The ^1H NMR spectrum of the silyl ether **41** showed two new doublet vinylic proton signals at 6.01 and 6.98 ppm (J=10.2 Hz), corresponding to the 1-H and 2-H respectively, which confirmed the introduction of the C-1,2 double bond. The specific AB pattern corresponding to the 19-CH_2 was shifted to 3.74 and 3.98 ppm. The ^{13}C NMR spectrum of the silyl ether **41** showed two new vinylic carbon signals at 130.27 and 152.54 ppm corresponding to the C-1,2 double bond. The result of elemental analysis (C, H) supported the structure.

Desilylation of the silyl ether **41** by treatment with tetrabutylammonium fluoride in THF afforded the 19-hydroxy 1-en-3-one **42**. The ^1H NMR spectrum of the 19-hydroxy 1-en-3-one **42** showed that the signals at 0.02 and 0.86 ppm in **41** which corresponded to the presence of the tert-butyldimethylsilyl group, were absent. Two doublet vinylic proton signals at 6.11 and 7.01 ppm (J=10.2 Hz) were similar to those assigned to the C-1,2 vinylic protons in the silyl ether **41**. The ^{13}C NMR spectrum and elemental analysis (C, H) result were in agreement with the 1-en-3-one structure **42**.

ii, Synthesis of 2β,19-oxido-5α-androstane-3,17-dione **40**

Attempts to improve the yield of the silyl ether **41** by treatment of the 5α-isomer **38** with Br_2/HBr/HOAc, followed by dehydrobromination[47] with LiBr/Li_2CO_3, gave the silyl ether 1-en-3-one **41** (*ca.* 30%), the silyl ether 4-en-3-one **34b** (*ca.* 20%) and the silyl ether 1,4-dienone **35b** (*ca.* 20%) as discussed above, together with another by-product, identified as 2β,19-oxido-5α-androstane-3,17-dione[94] **40** (*ca.* 30%). The ether **40** was probably formed from displacement of the C-2α bromine by the 19-hydroxyl group derived from hydrolysis of the silyl ether. The proposed mechanism is outlined in **Scheme 10**. Obviously this by-product lowered the yield of the silyl ether **41**. The ^{1}H NMR of the by-product **40** showed the specific AB pattern corresponding to the 19-CH_2 in the 5α-isomer **38** shifted to 3.89 and 4.06 ppm (J_{AB}=8.4 Hz) and a new doublet signal at 4.14 ppm (J 7.1 Hz) which corresponded to the 2-αH. The H/C correlation spectrum (HSQC) showed the 1-αH and 1-βH coupled to only the 2-αH which confirmed the presence of 2β,19-oxido bridge. 4-βH and 6-βH both showed axial coupling to the 5-H which further confirmed the 5α stereochemistry. The ^{13}C NMR spectrum and elemental analysis (C, H) were in agreement with compound **40**.

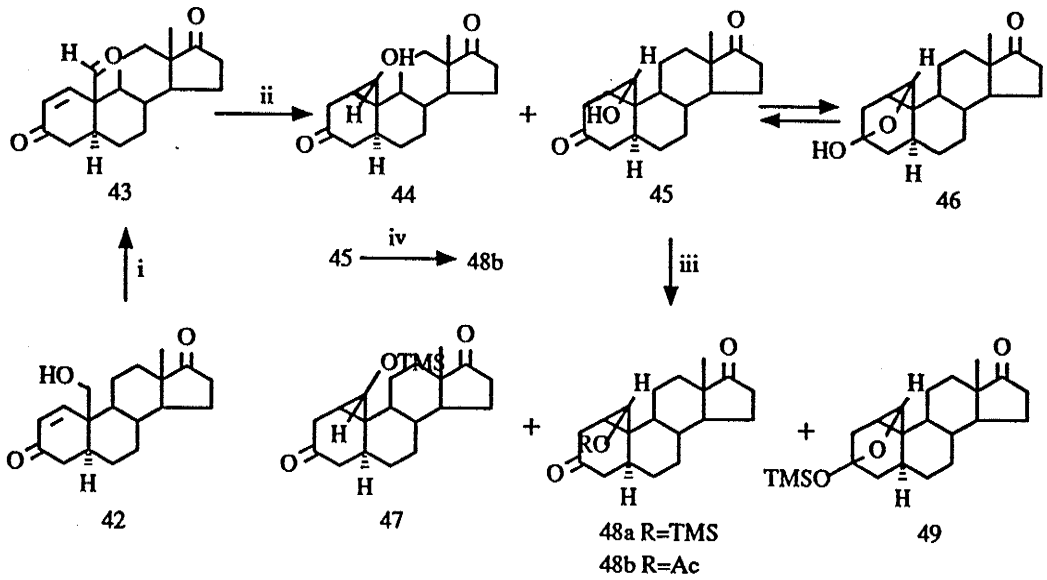


Scheme 10 *Reagents*: i, Br_2/HBr/HOAc; ii, LiBr/Li_2CO_3

IV. Synthesis of 19(R/S)-hydroxy-1β,19-cyclo-androstane-3,17-dione and 3α-hydroxy-3β,19-oxido-1β,19-cyclo-5α-androstan-17-one derivatives

The synthesis of compounds **47, 48a, 48b** and **49** is outlined in **Scheme 11**. Pyridinium chlorochromate oxidation[79] of the 19-hydroxy-1-en-3-one **42** gave a quantitive yield of the aldehyde **43**. The ^{1}H NMR spectrum (see **Table 1**) of the aldehyde **43** showed two doublet vinylic proton signals at 6.23 and 7.00 ppm (J=10.2 Hz) similar to those assigned to the C-1,2 vinylic proton in the 19-hydroxy-1-en-3-one **42**. A new singlet signal, which integrated for one proton, at 9.93 ppm was assigned to the C-19 aldehyde proton. The AB pattern for the C-19 methylene protons at 3.74 and 3.98 ppm (J_{AB}=11.5 Hz) in the spectrum of the 19-hydroxy-1-en-3-one **42** was absent in the product spectrum. The ^{13}C NMR spectrum (see **Table 2**) showed a new carbonyl signal at 201.27 ppm, which was assigned to the C-19 aldehyde carbon, and the absence of the methylene carbon at 66.10 ppm assigned to C-19 in the 19-hydroxy-1-en-3-one **42**. The result of elemental analysis (C, H) was in agreement with the aldehyde **43** structure.

Reduction of the aldehyde **43** with zinc dust in 50% aqueous HOAc afforded a crystalline product which was identified as a mixture of 19(R)-hydroxy-1β,19-cyclo-5α-androstane-3,17-dione **45** and its hemiketal tautomer, 3-hydroxy-3β,19-oxido-1β,19-cyclo-5α-androstan-17-one **46**. a small fraction perhaps corresponding to the S-isomer **44** was



Scheme 11 *Reagents:* i, PDC/CH_2Cl_2; ii, Zn/50%AcOH, iii, TMS-imidazole/DMF iv, Ac_2O/DMAP/pyridine

also indicated in the ^{1}H NMR spectrum of the mixture **(45, 46)**. An analogous keto-alcohol/hemiketal equilibrium for 19-hydroxy-5α-androstane-3,17-dione and 3α-hydroxy-3β,19-oxido-5α-androstan-17-one has been reported.[72] Elemental analysis (C, H) of the tautomeric mixture **(45, 46)** was in agreement with the molecular formula.

Acetylation of the mixture **(45, 46)** by treatment with acetic acid anhydride and DMAP in CH_2Cl_2 afforded 19(R)-hydroxy-1β,19-cyclo-5α-androstane-3,17-dione acetate **48b**. No hemiketal acetate was isolated. COSY and HSQC spectra, recorded on a Bruker AMX 500 spectrometer, allowed a complete NMR assignment (see **Table 10**). The ^{1}H NMR spectrum of the acetate **48b** showed a singlet at 2.03 ppm corresponding to the acetate group. A doublet at 4.31 ppm (J=7.5 Hz) was assigned to the C-19 cyclopropyl proton. The observation of a strong NOE from 19-H to 11-βH and 8-H confirmed the location of the cyclopropyl ring on the β-face with the 19-H *exo*. The *cis* coupling (J=7.5 Hz) between the 19-H and 1-αH also agreed with the 19(R)-acetate stereochemistry. The ^{13}C NMR spectrum of the acetate **48b** and elemental analysis (C, H) were in agreement with the structure of the acetate **48b**.

In order to isolate the 19(S)-isomer, the aldehyde **43** was treated with Zn/HOAc and the crude product treated directly with trimethylsilyl chloride-imidazole in CH_2Cl_2. On chromatographic separation the product afforded three crystalline fractions which were identified as the 19(S)-silyl

ether **47**, the 19(R)-silyl ether **48a** and the hemiketal silyl ether **49**.

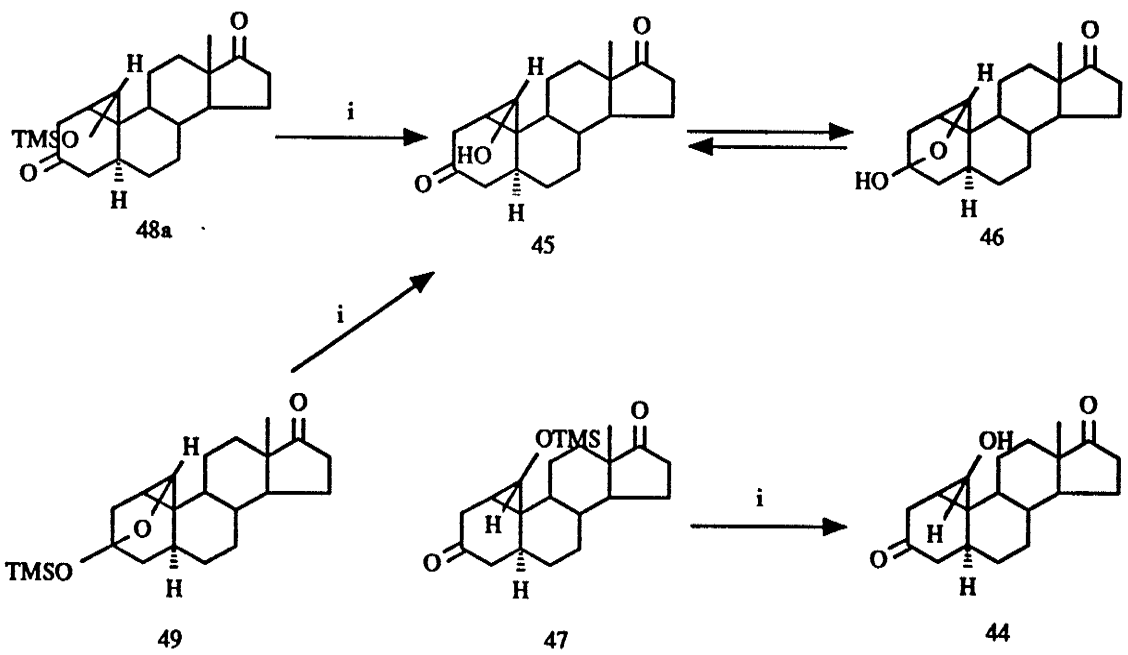
The ^{1}H NMR spectrum of the 19(S)-silyl ether **47** showed a signal at 0.16 ppm which integrated for nine protons and corresponded to the C-19 trimethylsilyloxy group; a doublet signal at 3.33 ppm (J=3.1 Hz), intergrated for one proton, and corresponded to the C-19 cyclopropyl proton. The *trans* coupling (J=3.1 Hz) between the 19-H and 1-αH confirms the 19(S) stereochemistry, i.e. the 19-H *endo*. The ^{13}C NMR spectrum of the 19(S) silyl ether **47** showed a methyl signal at -0.27 ppm corresponding to the trimethylsilyloxy group at C-19; a methine carbon signal at 55.51 ppm was assigned to the cyclopropyl carbon. Elemental analysis (C, H) was in agreement with the product.

The ^{1}H NMR spectrum of the 19(R)-silyl ether **48a** is similar to the 19(R)-acetate **48b** spectrum. A signal at 0.15 ppm, which integrated for nine protons, corresponded to the C-19 trimethylsilyloxy group and a doublet signal at 3.49 ppm (J=7.03 Hz), intergrating for one proton, corresponded to the C-19 cyclopropyl proton. The *cis* coupling (J=7.0 Hz) between the 19-H and 1-αH confirmed the 19(R) stereochemistry, i.e. 19-H *exo*. The ^{13}C NMR spectrum of the 19(R) silyl ether **48a** showed a methyl signal at -0.27 ppm corresponding to the trimethyl-silyloxy group at C-19. A methine carbon signal at 54.74 ppm was assigned to the cyclopropyl carbon. Elemental analysis (C, H) was in agreement with the product.

The ^{1}H NMR spectrum of the hemiketal silyl ether **49**, recorded on a Bruker AMX 500 spectrometer, showed a signal at 0.16 ppm which integrated for nine protons and corresponded to the C-19 trimethylsilyloxy group. A a doublet of doublets at 2.44 ppm (J=9.0, 19.2 Hz) was assigned to the 16-βH and a doublet at 4.02 ppm (J=5.6 Hz), intergrating for one proton and corresponded to the C-19 cyclopropyl proton. The *cis* coupling (J=5.6 Hz) between the 19-H and 1-αH confirmed the 19(R) stereochemistry, i.e. the 19-H *exo*. The axial coupling between 5-H and the 4-βH and 6-βH confirmed the C-5 stereochemistry, i.e. the 5-αH. The ^{13}C NMR spectrum of the hemiketal silyl ether **49** showed a signal at -0.27 ppm corresponding to the trimethylsilyloxy group at C-19. A methine carbon signal at 60.47 ppm was assigned to the cyclopropyl carbon and a quaternary carbon signal at 104.29 ppm corresponded to the hemiketal carbon, i.e. C-3. Elemental analysis (C, H) was in agreement with the hemiketal structure.

Attempts to obtain the alcohols **45** and **46** by hydrolysis of the silyl ethers **48a** and **49** was unsuccessful. Hydrolysis of both the 19(R)-silyl ether **48a** and the hemiketal silyl ether **49**, by treatment with K_2CO_3/MeOH[95] or tetrabutylammonium fluoride,[96] gave the equilibrium mixture of 19(R)-alcohol **45** and its tautomeric hemiketal **46** (see **Scheme 12**). Hydrolysis of the 19(S)-silyl ether **47** gave as expected a more polar product as shown on TLC. However, because of the low yield of the 19(S)-alcohol **44**, insufficient material was obtained for NMR

and elemental analysis.



Scheme 12 *Reagents:* i, n-Bu_4NF/THF or K_2CO_3/MeOH

Experimental

Reactions were monitored by TLC which was carried out in the following solvent systems on silica gel (Merck type 60H): acetone/light petroleum ether (35-60°C) (P.E.), diethyl ether/P.E., ethyl acetate/P.E.; compounds were visualized by dipping the plates in 5% sulphuric acid/ethanol followed by heating on a hot-plate at *ca*. 120°C.

Melting points were determined on either an Electrothermal or Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed by Mr. W. Baldeo, School of Pharmacy, University of London, England or the Guelph Chemical Laboratories Ltd., Guelph, Ontario, Canada.

^{1}H and ^{13}C NMR spectra are reported in Tables 1 and 2. ^{1}H and ^{13}C NMR spectra of the key compounds are reported in Tables 3-10. Survey spectra were obtained on a Bruker AM300 instrument while two dimensional and NOE spectra were recorded on a Bruker AMX500 spectrometer. Samples were measured as approximate 50 mM solutions in $CDCl_3$ in 5 mm sample tubes. The residual $CHCl_3$ peak in the solvent (δ_C=77.0 ppm, δ_H=7.26 ppm) was used as the internal reference for both proton and carbon spectra. Sample temperature was controlled at 300°K for all spectra. Carbon spectra were classified as to multiplicity with the DEPT technique.[60]

Homonuclear correlation (COSY) spectra,[59] were recorded with an F_1 time domain of 256 points. Zero filling yielded a

1024 (real) by 1024(real) matrix after transformation. A 45° mixing pulse was employed, and spectra were displayed and plotted in the magnitude mode.

Heteronuclear correlation spectra were recorded with the proton detected single quantum coherence (HSQC) experiment,[61] with an F_2 time domain of 4096 points and an F_1 time domain of 256 points. Zero filling in F_1 and F_2 resulted in a 4096(real) by 512(real) matrix after transformation.

Proton detected multiple bond heteronuclear correlation (HMBC) spectra[62] were recorded with a low pass J filter to suppress correlations due to the one bond couplings. The matrix dimensions were the same as for the HSQC spectra.

Difference NOE experiments were performed with a spectral width of *ca*. 2500 Hz and a real frequency domain data size of 32K points, resulting in a digital resolution of 0.08 Hz per point. Frequency list cycling was employed to distribute long-term changes in homogeneity equally among all spectra. Multiplets were irradiated by stepping the decoupler frequency between each line of the multiplet at 200 ms intervals, and each multiplet was irradiated for a total of 5 s. The irradiating field strength (calculated from the 90° pulse length and expressed as $\gamma B_2/2\pi$) was *ca*. 7 Hz. At least 512 transients (32 transients per irradiation point with 16 loops through the frequency list) were acquired for each irradiation point in order to ensure adequate signal-to-noise ratio and cancellation of non-enhanced peaks. A control spectrum

subtracted from each spectrum, and NOE values were determined by careful integration of the resulting difference spectrum. Using these techniques, NOE enhancements of less than 1% could be easily observed.

Androst-4-ene-3,17-dion-19-oic acid **(2)**

To a stirred solution of 19-hydroxyandrost-4-ene-3,17-dione **1** (10.00 g, 33.07 mmol) in acetone (150 mL), maintained at 10-15°C in an ice-bath, was added Jones reagent (30 mL) (prepare from 27 g CrO_3 and 23 mL concentrated sulfuric acid, then diluted to 100 mL with water) dropwise over 30 min. Isopropanol (15 mL) was added to destroy excess reagent and the mixture extracted with benzene (350 mL) and the organic layer washed with water and 43% w/v aqueous $(NH_4)_2SO_4$ as described by Uberwasser *et al.*[54] Evaporation of the solvent gave a residue which was stirred with saturated aqueous $NaHCO_3$ (100 mL) for 30 min. The aqueous layer was washed with EtOAc and the EtOAc back extracted with aqueous $NaHCO_3$ (20 mL) and the combined water layers acidified with 10% HCl to give on filtration, androst-4-ene-3,17-dion-19-oic acid **2** (7.30 g, 23.07 mmol, 69.8%), m.p. 145-147°C (decomp.) (lit.,[54] m.p. 146°C).

Estr-5(10)-ene-3,17-dione **(3)**

Androst-4-ene-3,17-dion-19-oic acid **2** (1.00 g, 3.16 mmol) in pyridine (1 mL) was heated with stirring at 50°C for 1 h,[54] when it was poured into ice-water and filtered to give the unsaturated dione **3** (700 mg, 2.57mmol, 81.3%), m.p. 140-145°C

(from benzene/P.E.) (lit.,[43,54] m.p. 144-146°C) as described by Uberwasser *et al.*[54].

3,3-Dimethoxyestr-5(10)-en-17-one **(4)**

A solution of estr-5(10)-ene-3,17-dione **3** (6.00 g, 22.03 mmol) and malonic acid (3.00 g) in MeOH (90 mL) was stirred for 19 h, cooled in an ice bath, adjusted to pH 8 with saturated aqueous $NaHCO_3$ and filtered to give 3,3-dimethoxyestr-5(10)-en-17-one **4** (5.10 g, 16.01 mmol, 72.7%) m.p. 114-117°C (lit.,[54] m.p. 115-116°C).

17β-Hydroxy-3,3-dimethoxyestr-5(10)-ene **(5a)**

To a solution of 3,3-dimethoxyestr-5(10)-en-17-one **4** (5.50 g, 17.16 mmol) in MeOH (50 mL) was added $NaBH_4$ (1.30 g, 34.36 mmol) and the mixture stirred for 1 h. The reaction mixture was poured into ice water and extracted with diethyl ether. The diethyl ether layer was washed with brine, water, dried over Na_2SO_4, and evaporated to give the 17-alcohol **5a** (5.20 g, 16.23 mmol, 94.6%), m.p. 90-95°C (from Et_2O/P.E.). Recrystallization gave m.p. 110-112°C (lit.,[54] m.p. 112-113°C).

17β-Hydroxy-3,3-ethylenedioxyestr-5(10)-ene **(5b)**

A solution of 3,3-ethylenedioxyestr-5(10)-en-17-one **8** (4.00 g, 12.64 mmol) in methanol (50 mL) was stirred with $NaBH_4$ (2.00 g, 56.87 mmol) at room temperature for 1 h, poured into water and extracted with diethyl ether. The diethyl ether layer was washed with water, dried over Na_2SO_4, and evaporated to give a gum which after flash chromatography, on elution with 20% EtOAc/P.E., gave the non-crystalline ketal **5b** (3.20

g, 10.05 mmol, 79.5%) which was used without further purification.

17β-tert-Butyldimethylsiloxy-3,3-dimethoxyestr-5(10)-ene **(6a)**

To imidazole (1.40 g, 20.56 mmol) in DMF (40 mL) was added 17β-hydroxy-3,3-dimethoxyestr-5(10)-ene **5a** (1.60 g, 4.99 mmol) and Bu^tMe_2SiCl (1.50 g, 10.00 mmol) and the mixture stirred at 50°C for 1 h. This was then poured into water, extracted with diethyl ether, and the organic layer washed with brine, water and dried over Na_2SO_4. Evaporation gave a residue which on flash chromatography on elution with 5% diethyl ether/P.E. gave non-crystalline fractions of dimethoxy ketal **6a** (1.70 g, 3.92 mmol, 78.6%). It was used without further purification.

17β-tert-Butyldimethylsiloxy-3,3-ethylenedioxyestr-5(10)-ene **(6b)**

A solution of 17β-hydroxy-3,3-ethylenedioxyestr-5(10)-ene **5b** (4.00 g, 12.56 mmol) in DMF (150 mL) was stirred with imidazole (1.50 g, 10.00 mmol) and *tert*-butyldimethylsilyl chloride (3.00 g, 19.90 mmol) at 50°C for 2 h. Water was added and the mixture was extracted with CH_2Cl_2, which was washed with water, dried over Na_2SO_4 and evaporated to give the ketal **6b** (3.76 g, 8.69 mmol, 69.2%), m.p. 126-127°C (from Et_2O/MeOH) (Found: C, 72.08; H, 10.38. $C_{26}H_{44}O_3Si$ requires C, 72.17; H, 10.25%).

3,3,17,17-Bis(ethylenedioxy)estr-5(10)-ene **(7)** and *3,3-ethylenedioxyestr-5(10)-en-17-one* **(8)**

A solution of estr-5(10)-ene-3,17-dione **3** (3.00 g, 11.01 mmol), PTSA (125 mg, 0.66 mmol) and ethylene glycol (42 mL) in benzene (160 mL) was refluxed in a Dean-Stark apparatus to remove water for 2 h. The organic layer was washed with aqueous $NaHCO_3$, water, dried over Na_2SO_4, and evaporated to give a residue which was flash chromatographed. Elution with 20% EtOAc/P.E., gave the diketal **7** (2.55 g, 7.11 mmol, 64.6%), m.p. 84-86°C (from mrthanol) (lit.,[57] 79-80°C) and the mono ketal **8** (586 mg, 1.85 mmol, 16.8%), m.p. 122-125°C (from benzene/P.E.) (lit.,[56] 130-131°C).

17β-tert-Butyldimethylsiloxy-5β,6β-dibromocyclopropano-3,3-dimethoxy-19(S)-bromo-9α,19α-cycloandrost-5(10)-ene **(11a)**

To a solution of 17β-*tert*-butyldimethylsiloxy-3,3-dimethoxyestr-5(10)-ene **6a** (1.10 g, 2.54 mmol) in bromoform (5 mL) was added CTAB (200 mg) and 50% aqueous NaOH (5 mL) and the mixture stirred vigorously at room temperature in an argon atmosphere for 18 h. The reaction mixture was diluted with diethyl ether and the diethyl ether layer washed with 3% HCl to give a residue which on flash chromatography, on elution with 4% Et_2O/P.E., yielded the tribromo derivative **11a** (650 mg, 0.93 mmol, 36.7%), m.p. 148-152°C (from Et_2O/P.E.) (Found: C, 48.53; H, 6.57; Br, 34.08. $C_{28}H_{45}O_3Br_3Si$ requires C, 48.22; H, 6.50; Br, 34.37%).

17β-tert-Butyldimethylsiloxy-5β,6β-dibromocyclopropano-19(S)-bromo-9α,19α-cycloandrost-3-one **(11b)**

A solution of 17β-*tert*-butyldimethylsiloxy-5β,6β-dibromocyclopropano-3,3-dimethoxy-19(S)-bromo-9α,19α-cycloandrost-5(10)-ene **11a** (300 mg, 0.43 mmol) in acetone (10 mL) was stirred with 3% HCl (1 mL) at room temperature for 30 minutes. The solution was adjusted to pH 8 with aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water, dried over Na_2SO_4 and evaporated to give a residue which was flash chromatographed. Elution with 5% EtOAc/P.E. gave the tribromo ketone **11b** (200 mg, 0.31 mmol, 72.1%), m.p. 217-218°C (from Et_2O-P.E.) (Found: C, 47.81; H, 5.99; Br, 36.45. $C_{26}H_{39}Br_3O_2Si$ requires C, 47.94; H, 6.03; Br, 36.80%).

17β-tert-Butyldimethylsiloxy-5β,6β-dibromocyclopropano-19(S)-bromo-9α,19α-cycloandrost-3-one **(11b)** and *17β-tert-butyldimethylsiloxy-19(S)-bromo-9α,19α-cycloandrost-4-en-3-one* **(13)**

To a solution of 17β-*tert*-butyldimethylsiloxy-3,3-dimethoxyestr-5(10)-ene **6a** (1.10 g, 2.54 mmol) in bromoform (5 mL) was added CTAB (200 mg), 50% NaOH (5 mL) and the mixture stirred vigorously in an argon atmosphere for 18 h. Et_2O extraction and evaporation gave a residue which was stirred with aqueous 3% HCl (3.5 mL) in acetone (35 mL) at room temperature for 30 minutes. The mixture was then adjusted to pH 8 with aqueous $NaHCO_3$ and extracted with CH_2Cl_2, which was

washed with water, dried over Na_2SO_4 and evaporated to give a residue which was flash chromatographed. Elution with 5% acetone/P.E. gave the tribromo derivative **11b** (215 mg, 0.33 mmol, 13.0%), m.p. 210-215°C (from CH_2Cl_2/Et_2O) (see above) and the monobromo derivative **13** (53 mg, 0.11 mmol, 4.3%), m.p. 182-185°C (from CH_2Cl_2/Et_2O) (Found: C, 62.40; H, 8.08; Br, 16.35. $C_{25}H_{39}BrO_2Si$ requires C, 62.61; H, 8.20; Br, 16.66%).

17β-tert-Butyldimethylsiloxy-5β,6β-dibromocyclopropano-19(S)-bromo-9α,19α-cycloandrost-3-one **(11b)** and *17β-tert-butyldimethylsiloxy-19,19-dibromocyclo-5α,19α-androstan-3-one* **(14)**

To a solution of 17β-*tert*-butyldimethylsiloxy-3,3-dimethoxyestr-5(10)-ene **6a** (1.45 g, 3.34 mmol) in bromoform (5 mL) was added CTAB (300 mg), 50% aqueous NaOH (5 mL) and the mixture stirred vigorously in an argon atmosphere for 48 h. The mixture was diluted with Et_2O and the organic layer washed with 3% HCl, brine and water. Evaporation gave a residue which was passed through silica gel in 5% Et_2O-P.E. to remove excess bromoform. The steroid fractions (1.13 g) were evaporated and dissolved in acetone (30 mL), stirred with PTSA (150 mg) at room temperature for 1 h, diluted with water and extracted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$, water, and dried over Na_2SO_4. Evaporation gave a residue which on flash chromatography on elution with 8% acetone/P.E., yielded the tribromo derivative **11b** (300 mg, 0.46 mmol, 13.8%), m.p. 217-218°C (from CH_2Cl_2/Et_2O) (see above) and the 19,19-dibromo adduct **14** (21 mg, 0.037 mmol, 1.1%), m.p. 173-

176°C (from CH_2Cl_2/Et_2O) (Found: C, 53.80; H, 6.99; Br, 28.80. $C_{25}H_{40}Br_2O_2Si$ requires C, 53.57; H, 7.19; Br, 28.51%).

17β-tert-Butyldimethylsiloxy-5β,6β-(R)-bromocyclopropano-19(S)-bromo-9α,19α-cycloandrost-3-one **(11c)** and *17β-tert-butyldimethylsiloxy-5β,6β-(S)-bromocyclopropano-19(S)-bromo-9α,19α-cycloandrost-3-one* **(11d)**

To a solution of 17β-*tert*-butyldimethylsiloxy-5β,6β-dibromocyclopropano-19(S)-bromo-9α,19α-cycloandrost-3-one **(11b)** (250 mg, 0.38 mmol) in dry Et_2O (15 mL) containing azobisiso-butyronitrile (AIBN) (2 mg) under argon at 0°C was added slowly tri-n-butyltin hydride (150 mg) in Et_2O (15 mL) and the mixture was stirred at room temperature for 2 h. TLC showed that reduction was complete. Evaporation gave a residue which was flash chromatographed and on elution with 2% acetone/P.E. gave the (R)-isomer **11c** (48 mg, 0.08 mmol, 21.1%), m.p. 200-203°C (from Et_2O/MeOH), (Found: C, 54.2; H, 7.2; Br, 28.1. $C_{26}H_{40}Br_2O_2Si$ requires C, 54.55; H, 7.0; Br, 27.9%) and the (S)-isomer **11d** (72 mg, 0.13 mmol, 34.2%), m.p. 155-158°C (from Et_2O/MeOH), (Found: C, 54.55; H, 7.1; Br, 27.8. $C_{26}H_{40}Br_2O_2Si$ requires C, 54.55; H, 7.0; Br, 27.9%).

17β-tert-Butyldimethylsiloxy-19(S)-bromo-9α,19α-cycloandrost-4-en-3-one **(13)** and *17β-tert-butyldimethylsiloxyestr-4-en-3-one* **(15)**

A solution of 17β-*tert*-butyldimethylsiloxy-3,3-ethylenedioxyestr-5(10)-ene **(6b)** (500 mg, 1.15 mmol) in dried Et_2O (15 mL) was stirred with $KOBu^t$ [prepared by dissolving K

metal (500 mg, 12.82 mmol) in dry Bu^tOH, evaporating excess alcohol under reduced pressure and drying the residue at 150°C for 1 h] at -30°C while $CHBr_3$ (3.5 mL, 39.48 mmol) in dry Et_2O (15 mL) was added dropwise over 2 h. The mixture was stirred for a further 22 h when it was poured into water and extracted with Et_2O, washed with brine and water, dried over Na_2SO_4 and evaporated to give a residue which was stirred with PTSA (300 mg) in acetone (30 mL) at room temperature for 2 h. Water was added and the mixture extracted with CH_2Cl_2, washed with aqueous $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to give the mono bromo derivative **13** (65 mg, 0.14 mmol, 12.2%), m.p. 182-185°C (from CH_2Cl_2/Et_2O) and the unsaturated ketone **15** (45 mg, 0.12 mmol, 10.4%), m.p. 134-136°C (from Et_2O/MeOH) (Found: C, 74.0; H, 10.5. $C_{24}H_{40}O_2Si$ requires C, 74.2; H, 10.4%).

17β-tert-Butyldimethylsiloxy-5β,6β-dibromocyclopropano-3,3-ethylenedioxy-19(S)-bromo-9α,19α-cycloandrostane **(16)**

17*β-tert*-Butyldimethylsiloxy-3,3-ethylenedioxyestr-5(10)-ene **(6b)** (200 mg, 0.46 mmol) was stirred vigorously with $CHBr_3$ (1 mL), 50% NaOH (1 mL) and CTAB (40 mg) in an argon atmosphere for 18 h, worked up as for **11a**, evaporated to give a residue which was stirred with PTSA (120 mg, 63.08 mmol) in acetone (15 mL) at room temperature for 2 h. This was worked up as described for **13** to give the tribromo derivative **16** (40 mg, 0.06 mmol, 13.0%), m.p. 245-248°C (from Et_2O/CH_2Cl_2) (Found: C, 46.82; H, 6.19; Br, 33.25. $C_{28}H_{43}Br_3O_3Si.1.5\ H_2O$

requires C, 46.55; H, 6.42; Br, 33.18%).

19(S)-Bromo-9α,19α-cycloandrost-4-ene-3,17-dione **(19)** and *estr-4-ene-3,17-dione* **(20)**

The diketal **7** (1.00 g, 2.79 mmol) and solid $KOBu^t$ [prepared as described from K metal (1.00 g, 25.64 mmol) above for **13** and sublimed] in dry Et_2O (30 mL) was treated with $CHBr_3$ (6.7 mL, 75.58 mmol) followed by treatment with acetone (50 mL) containing PTSA (500 mg, 2.63 mmol) as described for the preparation of compound **13**. Flash chromatography on elution with 40% EtOAc/P.E. gave the dione **20** (213 mg, 0.78 mmol, 28%), m.p. 170-172°C (from CH_2Cl_2/Et_2O) (lit.,[97] m.p. 171-173°C) and the mono bromo derivative **19** (161 mg, 0.44 mmol, 15.8%), m.p. 239-240°C (from CH_2Cl_2/Et_2O) (Found: C, 62.57; H, 6.09; Br, 21.73. $C_{19}H_{23}BrO_2$ requires C, 62.82; H, 6.38; Br, 21.99%).

When the above dibromocarbene reaction was carried out on the diketal **7** (468 mg, 1.31 mmol) for 2 h as reported by Birch *et al.*[49] the unsaturated ketone **20** (53 mg, 0.19 mmol, 14.5%), m.p. 166-170°C and the mono bromo derivative **19** (28 mg, 0.08 mmol, 6.1%), m.p. 235-240°C were obtained.

5β,19-Cycloandrost-1-ene-3,17-dione **(21)**

To 19-hydroxyandrost-4-ene-3,17-dione **1** (500 mg, 1.65 mmol) in acetonitrile (5 mL) was added diethyl-[2-chloro-1,1,2-trifluoroethyl]-amine as described by Knox *et al.*[41] The mixture was refluxed under argon for 1 h, poured into water, extracted with diethyl ether and the diethyl ether layer washed with water and dried over Na_2SO_4. Evaporation gave a gum

which was flash chromatographed and on elution with 20% acetone/P.E. gave fractions (236 mg) which yielded the unsaturated 5β,19-cyclo compound **21** (120 mg, 0.42 mmol, 25.5%) m.p. 184-186°C (from CH_2Cl_2/diethyl ether) (lit.,[41] m.p. 173-175°C). Because the m.p. was substantially higher than the literature value elemental analysis was carried out (Found: C, 79.96; H, 8.73. $C_{19}H_{24}O_2$ required: C, 80.24; H, 8.51%).

19-Oxo-androst-4-ene-3,17-dione **(22)**

19-Hydroxyandrost-4-ene-3,17-dione **1** (5.00 g, 16.53 mmol) and PDC (10.00 g, 26.58 mmol) was dissolved in CH_2Cl_2 (30 mL) and the mixture was stirred at room temperature overnight. Diethyl ether (100 mL) was added and the supernatant was filtered through Celite to remove traces of chromium compounds. Evaporation gave a gum which was flash chromatographed. Elution with 30% acetone/P.E., gave the aldehyde **22**, (3.02 g, 10.06 mmol, 60.9%), m.p. 132-134°C (lit.[80] m.p. 129-133°C).

19(R)-Hydroxy-5β,19-cycloandrostane-3,17-dione **(23)**

19-Oxo-androst-4-ene-3,17-dione **22** (500 mg, 1.67 mmol) was dissolved in 50% aqueous HOAc (10 mL). Zn powder (2.50 g, 38.24 mmol) was added and the mixture stirred at room temperature for 3 h, filtered to remove excess Zn, poured into water, extracted with CH_2Cl_2, washed with saturated $NaHCO_3$ and water, and dried over Na_2SO_4. Evaporation gave a gum which was recrystallized to give the cyclopropanol **23** (230 mg, 0.76 mmol, 45.5%), m.p. 161-164°C (from CH_2Cl_2/diethyl ether)

(Found: C, 75.38; H, 8.80. $C_{19}H_{26}O_3$ required: C, 75.46; H, 8.67%).

19(R)-Hydroxy-5β,19-cycloandrostane-3,17-dione **(23)**, *19(S)-hydroxy-5β,19-cycloandrostane-3,17-dione* **(24)** and *3α-hydroxy-3β,19-oxido-5β,19-cycloandrostan-17-one* **(25)**

19-Oxo-androst-4-ene-3,17-dione **22** (8.00 g, 26.65 mmol) was dissolved in 50% aqueous HOAc (160 mL) and Zn powder (40 g, 61.19 mmol) added. The mixture was stirred at room temperature for 3 h and filtered to remove excess Zn, poured into water, extracted with CH_2Cl_2, washed with saturated $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to give a gum which was crystallized to give the cyclopropanol **23** (5.00 g, 16.53 mmol, 62.0%), m.p. 160-167°C, (from CH_2Cl_2/diethyl ether) the mother liquor was flash chromatographed and on elution with 80% Et_2O/P.E. gave fractions which on crystallization gave **23** (390 mg, 1.29 mmol, 4.8%), m.p. 160-165°C (from CH_2Cl_2/diethyl ether) and a mixture of compound **24** and **25** (135 mg, 0.45 mmol, 1.7%) m.p. 155-159°C (from CH_2Cl_2/Et_2O/P.E.) as shown by ^1H NMR spectrum.

19(S)-Hydroxy-5β,19-cycloandrostane-3,17-dione **(24)** and *3α-hydroxy-3β,19-oxido-5β,19-cycloandrostan-17-one* **(25)**

19(R)-Hydroxy-5β,19-cycloandrostane-3,17-dione **23** (150 mg, 0.50 mmol) was dissolved in 0.5 M KOH/methanol (10 mL) and stirred at room temperature for 1 h, CH_2Cl_2 added and the CH_2Cl_2 washed with water and evaporated to give a gum which was crystallized twice from CH_2Cl_2/diethyl ether/P.E. to give a

mixture of the ketone and hemiketal **24** and **25** (63 mg, 0.21 mmol, 42.0%), m.p. 160-165°C (from CH_2Cl_2/Et_2O/P.E.) (Found: C, 73.42; H, 8.69. $C_{19}H_{26}O_3.1/2H_2O$ required: C, 73.28; H, 8.74%).

19(R)-Hydroxy-5β,19-cycloandrostane-3,17-dione acetate **(26a)**

19(R)-Hydroxy-5β,19-cycloandrostane-3,17-dione **23** (200 mg, 0.66 mmol) was dissolved in CH_2Cl_2 (10 mL), and 4-dimethylamino-pyridine (50 mg) and Ac_2O (1 mL) added. The mixture was stirred at room temperature for 1 h. Water (10 mL) was added, and the mixture extracted with CH_2Cl_2, which was washed with saturated $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to give a gum which was crystallized to give the cyclopropanol acetate **26a** (100 mg, 0.29 mmol, 43.9%), m.p. 180-183°C (from CH_2Cl_2/diethyl ether) (Found: C, 72.98; H, 8.46. $C_{21}H_{28}O_4$ required: C, 73.23; H, 8.19%).

19(R)-Trimethylsiloxy-5β,19-cycloandrostane-3,17-dione **(26b)**

To a solution of compound **23** (150 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) was added 1.0 M trimethylsilyl chloride-imidazole in CH_2Cl_2 (0.5 mL) and the mixture stirred at room temperature for 2 h, poured into water, extracted with CH_2Cl_2, and the organic layer washed with water, dried over Na_2SO_4 and evaporated to give the the non-crystalline cyclopropanol trimethylsilyl ether **26b** (74 mg, 0.20 mmol, 40%). m.p. 96-98°C (from diethyl ether/P.E.) (Found: C, 70.61; H, 9.22. $C_{22}H_{34}O_3Si$ required: C, 70.54; H, 9.15%).

19(S)-Hydroxy-5β,19-cycloandrostane-3,17-dione acetate **(27)**

The mother liquor of the mixture of **24** and **25** (100 mg,

0.33 mmol) was dissolved in pyridine (1 mL), Ac_2O (1 mL) was added, and the mixture stirred at room temperature for 1 h. The mixture was poured into water, extracted with CH_2Cl_2 and the CH_2Cl_2 washed with water, dried over Na_2SO_4 and evaporated to give a gum which was flash chromatographed and on elution with 25% acetone/P.E. gave the non-crystalline cyclopropanol acetate **27** (80 mg, 0.23 mmol, 69.7%).

19(S)-Trimethylsiloxy-5β,19-cycloandrostane-3,17-dione **(29)**

To a solution of a mixture of compounds **24** and **25** (75 mg, 0.25 mmol) in CH_2Cl_2 (2 mL) was added 1.0 M trimethylsilyl chloride-imidazole in CH_2Cl_2 (0.2 mL) and the mixture stirred at room temperature for 2 h, poured into water, extracted with CH_2Cl_2, which was washed with water, dried over Na_2SO_4 and evaporated to give the cyclopropanol silyl ether **29** (32 mg, 0.09 mmol, 36%), m.p. 122-125°C (from diethyl ether/P.E.) (Found: C, 70.55; H, 9.28. $C_{22}H_{34}O_3Si$ required: C, 70.54, H, 9.15%).

3-Trimethylsiloxy-19(R)-hydroxy-5β,19-cycloandrost-2-en-17-one **(30)** and *3-trimethylsiloxy-19(R)-hydroxy-5β,19-cycloandrost-3-en-17-one* **(31)**

To 19(R)-hydroxy-5β,19-cycloandrostane-3,17-dione acetate **26a** (50 mg, 0.15 mmol) in DMF (1 mL) was added triethylamine (1 mL) and TMSOTf (60 μl) and the mixture stirred at room temperature for 15 minutes. TLC showed one less polar component and no starting material. The mixture was poured into water, extracted with CH_2Cl_2, which was washed with water,

dried over Na_2SO_4, and evaporated to give a crude product which was flash chromatographed and on elution with 10% acetone/P.E. gave a non-crystalline mixture of compounds **30** and **31** (15 mg, 0.04 mmol, 26.7%).

19-Oxo-5(β)-androstane-3,17-dione **(32)** and *5β-oxo-19(β)-androstane-3,17-dione* **(33)**

19(R)-Hydroxy-5β,19-cycloandrostane-3,17-dione **23** (1.00 g, 3.31 mmol) was dissolved in CH_2Cl_2 (10 mL), concentrated HCl (36.5%, 7 mL) added and the mixture stirred at room temperature for 3 h, poured into water, extracted with CH_2Cl_2, which was washed with water, dried over Na_2SO_4, and evaporated to give a gum which was flash chromatographed and on elution with 20% acetone/P.E. gave three factions: **A**, the non-crystalline compound **33** (12 mg, 0.04 mmol, 1.2%); **B**, compound **32**, (241 mg, 0.80 mmol, 24.2%) recrystallized to give 190 mg, m.p. 141-144°C (from CH_2Cl_2/diethyl ether) (Found: C, 75.64; H, 8.85. $C_{19}H_{26}O_3$ required C, 75.46; H, 8.67%); **C**, unidentified steroid **WYL-121D** (86 mg), crystallized from CH_2Cl_2/ diethyl ether to give 64 mg, m.p. 246-250°C (Found: C, 77.45; H, 8.49).

19-Oxo-5β-androstane-3,17-dione **(32)**

With 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ):

A solution of 19(R)-hydroxy-5β,19-cycloandrostane-3,17-dione 19-acetate **26a** (60 mg, 0.17 mmol) in benzene (5 mL) was refluxed with DDQ (60 mg) under an argon atmosphere overnight (monitored by TLC, no significant reaction after 4 hrs). The

reaction mixture was poured into water, extracted with CH_2Cl_2, and dried over Na_2SO_4 to give a crude residue which was flash chromatographed and eluted with 20% acetone/P.E. to give compound **32** (15 mg, 0.05 mmol, 29.4%) (based on TLC and ^1H NMR comparisons).

With benzeneseleninic acid anhydride:

A solution of the cyclopropanol acetate **26a** (60 mg, 0.17 mmol) in benzene (5 mL) containing benzeneseleninic acid anhydride (60 mg) and $NaHCO_3$ (60 mg) was refluxed in an argon atmosphere for 4 hrs. The reaction mixture was poured into water, extracted with CH_2Cl_2, and dried over Na_2SO_4 to give a crude residue which was flash chromatographed and eluted with 20% acetone/P.E. to give compound **32** (15 mg, 0.05 mmol, 29.4%).

19-Hydroxyandrost-4-ene-3,17-dione acetate **(34a)** and *19-hydroxyandrosta-2,4-diene-3,17-dione acetate* **(35a)**

To 19-hydroxyandrost-4-ene-3,17-dione **1** (1.00 g, 3.31 mmol) in CH_2Cl_2 (30 mL) was added DMAP (200 mg) and Ac_2O (5 mL) and the mixture stirred at room temperature for 2 h when TLC indicated that the reaction was complete. The mixture was poured into water, extracted with CH_2Cl_2, washed with saturated $NaHCO_3$, water, dried over Na_2SO_4 and evaporated to give a non-crystalline product **34a** (985 mg, 2.86 mmol, 86.4%) which indicated one component on TLC (lit.[72a] m.p.52-53°C and 81-82°C). [The acetate **34a** has also been reported in ref.[91] which includes elemental analysis (C, H), as a non-crystalline

compound.].

The product **34a** was then refluxed with benzeneseleninic acid anhydride (1.00 g,) and $NaHCO_3$ (1.00 g) in benzene (30 mL) under an argon atmosphere overnight. The mixture was cooled to room temperature and washed with aqueous 0.1 M sodium phosphate buffer (pH 7.1) and diluted with CH_2Cl_2 as described by Cole and Robinson.[89] The aqueous phase was further extracted with CH_2Cl_2 and the organic phase combined and washed with water, dried over Na_2SO_4, and evaporated to give a gum which was flash chromatographed and on elution with 30% acetone/P.E. to give product **35a** (340 mg, 0.99 mmol, 34.6%), m.p. 151-153°C (from CH_2Cl_2/diethyl ether) (Found: C, 73.47; H, 7.68. $C_{21}H_{26}O_4$ required C, 73.66; H, 7.65%) and the starting material **34a** (300 mg).

19-tert-Butyldimethylsiloxyandrost-4-ene-3,17-dione **(34b)**

To a solution of 19-hydroxyandrost-4-ene-3,17-dione **1** (7.00 g, 23.15 mmol) in DMF (50 mL) was added imidazole (2.0 g) and *tert*-butyldimethylsilyl chloride (4.0 g, 26.54 mmol)and the mixture refluxed for 2 h. After cooling to room temperature, water (30 mL) was added and the mixture extracted with diethyl ether, washed with brine and water, dried over Na_2SO_4, and evaporated to give the *tert*-butylsilyl diethyl ether **34b** (5.60 g, 13.44 mmol, 58.1%), m.p. 161-162°C (from CH_2Cl_2/diethyl ether) (Found: C, 71.87; H, 9.70. $C_{25}H_{40}O_3Si$ required C, 72.06; H, 9.68%).

19-tert-Butyldimethylsiloxyandrosta-2,4-diene-3,17-dione **(35b)**

19-*tert*-Butyldimethylsiloxyandrost-4-ene-3,17-dione **34b** (500 mg, 1.20 mmol) was refluxed with benzeneseleninic acid anhydride (500 mg, 1.39 mmol) and $NaHCO_3$ (500 mg) in benzene (20 mL) under an argon atmosphere for 20 hrs. The mixture was cooled to room temperature and washed with aqueous 0.1 M sodium phosphate buffer (pH 7.1) and diluted with CH_2Cl_2.[89] The aqueous phase was further extracted with CH_2Cl_2 and the combined organic phase was washed with water, dried over Na_2SO_4 and evaporated to give a gum which was flash chromatographed and on elution with 10% acetone/P.E. gave product **35b** (131 mg, 0.32 mmol, 26.7%), m.p. 160-163°C (from CH_2Cl_2/diethyl ether) and **34b** (150 mg), m.p. 154-157°C (from CH_2Cl_2/diethyl ether) (Found: C, 72.23; H, 9.29. $C_{25}H_{38}O_3$ required C, 72.41; H, 9.24%).

17,17-Ethylenedioxyestra-1,3,5(10)-trien-3-ol **(36)**

To17β-*tert*-butyldimethylsilylandrost-2,4-ene-3,17-dione **35b** (60 mg, 0.14 mmol) in benzene (4 mL) was added PTSA (5 mg) and ethylene glycol (1 mL) and the mixture refluxed for 1 h. This was poured into water and extracted with CH_2Cl_2 which was washed with water, dried over Na_2SO_4 and evaporated to give a crude product which was flash chromatographed. Elution with 10% acetone/P.E. gave product **36** (40 mg, 0.12 mmol, 85.7%), m.p. 164-167°C (from diethyl ether) (Found: C, 77.24; H, 8.12. $C_{21}H_{26}O_3$ requires C, 77.27; H, 8.03%).

To 19-hydroxyandrosta-2,4-diene-3,17-dione acetate **35a**

(30 mg, 0.09 mmol) in benzene (4 mL) was added PTSA (5 mg) and ethylene glycol (1 mL) and the mixture refluxed for 1 h, poured into water, extracted with CH_2Cl_2, which was washed with water, dried over Na_2SO_4 and evaporated to give a crude product which was flash chromatographed, and on elution with 10% acetone/P.E. gave the non-crystalline ketal **36** (20 mg, 0.06 mmol, 66.7%).

Estra-1,3,5(10)-trien-17-one-3-ol (estrone) **(37)**

From NaOH:

To 19-hydroxyandrost-2,4-ene-3,17-dione acetate **35a** (30 mg, 0.09 mmol) in methanol (2 mL) was added 10% NaOH (1 mL) and the mixture stirred at room temperature for 2 h. The mixture was poured into water, extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated to give estrone **37** (18 mg, 0.07 mmol, 77.8%), m.p. 257-260°C (from CH_2Cl_2/diethyl ether) (lit.[93b] m.p. 258-260°C).

From tetrabutylammonium fluoride:

To 19-*tert*-Butyldimethylsiloxyandrost-2,4-ene-3,17-dione **35b** (10 mg, 0.02 mmol) in THF (2 mL) was added tetrabutylammonium fluoride (7 mg). The mixture was stirred at room temperature for 1 h to give estrone **37** based on TLC and ^{1}H NMR comparison with an authentic sample.

19-tert-Butyldimethylsiloxy-5α-androstane-3,17-dione **(38)** and *19-tert-butyldimethylsiloxy-5β-androstane-3,17-dione* **(39)**

A solution of 19-*tert*-butyldimethylsiloxy-androst-4-ene-3,17-dione **34b** (2.0 g, 4.80 mmol) in ethyl acetate (30 mL) was

stirred with 10% palladium charcoal (200 mg) in a hydrogen atmosphere at atmospheric pressure overnight. The solution was filtered to get rid of the catalyst and evaporated at reduced pressure to yield a crude product which was crystallized from CH_2Cl_2/diethyl ether to give the 5α product **38** (1.0 g, 2.39 mmol, 49.8%), m.p. 133-135°C (Found: C, 71.31; H, 10.19. $C_{25}H_{42}O_3Si$ required C, 71.71; H, 10.11%).

The mother liquor was flash chromatographed and on elution with 10% acetone/P.E. gave **38** (662 mg), m.p. 134-135°C and the 5β product **39** (158 mg, 0.38 mmol, 7.9%), m.p. 151-153°C (Found: C, 71.72; H, 10.28. $C_{25}H_{42}O_3Si$ required C, 71.71; H, 10.11%).

19-tert-Butyldimethylsiloxyandrost-4-ene-3,17-dione **(34b)**, *19-tert-butyldimethylsiloxyandrosta-2,4-diene-3,17-dione* **(35b)** *19-tert-butyldimethylsiloxy-5α-androst-1-ene-3,17-dione* **(41)**

19-*tert*-Butyldimethylsiloxy-5α-androstane-3,17-dione **38** (2.00 g, 4.78 mmol) was refluxed with benzeneseleninic acid anhydride (1.60 g) and $NaHCO_3$ (1.50 g) in benzene (80 mL) under an argon atmosphere for 2 h. The mixture was cooled to room temperature and washed with aqueous 0.1 M sodium phosphate buffer (pH 7.1) and diluted with CH_2Cl_2.[89] The aqueous phase was further extracted with CH_2Cl_2, and the combined organic phase washed with water, dried over Na_2SO_4 and evaporated to give a gum which was flash chromatographed and on elution with 10% acetone/P.E. gave the C-2 olefin **41** (860 mg, 2.06 mmol, 43.1%), m.p. 143-145°C (from CH_2Cl_2/diethyl

ether), the C-4 olefin **34b** (380 mg, 0.91 mmol, 19.0%), m.p. 155-158°C (from CH_2Cl_2/diethyl ether) and C-1,4 diene **35b** (424 mg, 1.02 mmol, 21.3%), m.p. 155-158°C (from CH_2Cl_2/diethyl ether).

2β,19-Oxido-5α-androstane-3,17-dione **(40)** and *19-tert-butyldimethylsiloxy-5α-androst-1-ene-3,17-dione* **(41)**

To a stirred solution of 19-*tert*-butyldimethylsiloxy-5α-androstane-3,17-dione **38** (1.00 g, 2.39 mmol) in HOAc (10 mL) containing HBr (0.05 mL) was added benzyltrimethylammonium tribromide (1.24 g) in portions and stirring continued at room temperature until the bromine colour disappeared (about 5 minutes). The mixture was poured into water, extracted with CH_2Cl_2 which was washed with water, dried over Na_2SO_4 and evaporated to give a crude product. This was refluxed with LiBr (2.5 g) and Li_2CO_3 (2.5 g) in DMF (30 mL) for 5 h, poured into water, extracted with CH_2Cl_2, which was washed with water, dried over Na_2SO_4 and evaporated at reduced pressure to give a crude product. Flash chromatography, on elution with 20% EtOAc/P.E., gave the C-1 olefin **41** (141 mg, 0.34 mmol, 14.2%), m.p. 139-141°C (from CH_2Cl_2/diethyl ether) (Found: C, 72.27; H, 9.69. CHOSi requires C, 72.08; H, 9.68%), and the cyclic ether **40**, (400 mg, 1.32 mmol, 55.2%), m.p. 143-146°C (from diethyl ether/P.E.) (Found: C, 75.33; H, 8.70. $C_{19}H_{26}O_3$ requires C, 75.46; H, 8.67%) and two minor products corrresponding to **34b** and **35b** based on TLC comparison.

19-Hydroxy-5α-androst-1-ene-3,17-dione **(42)**

To 19-*tert*-butyldimethylsiloxy-5α-androst-1-ene-3,17-dione **41** (500 mg, 1.20 mmol) in THF (25 mL) was added tetrabutylammonium fluoride (530 mg) and the mixture stirred at room temperature for 1 h, poured into water, extracted with CH_2Cl_2, which was washed with water, dried over Na_2SO_4 followed by evaporation at reduced pressure to yield a crude product. This was flash chromatographed and on elution with 25% acetone/P.E. gave the C-1 olefin **42** (300 mg, 0.99 mmol, 82.5%), m.p. 200-202°C (from CH_2Cl_2/diethyl ether) (Found: C, 75.15; H, 8.95. $C_{19}H_{26}O_3$ required: C, 75.46; H, 8.67%).

19-Oxo-5α-androst-1-ene-3,17-dione **(43)**

19-Hydroxy-5α-androst-1-ene-3,17-dione **42** (735 mg, 2.43 mmol) and PDC (1.0 g) was dissolved in CH_2Cl_2 (50 mL) and the mixture stirred at room temperature for 2 h. Diethyl ether (50 mL) was added and the diethyl ether filtered through Celite to remove traces of chromium compounds. Evaporation of the solvent gave a gum which was flash chromatographed and on elution with 30% acetone/P.E. gave the aldehyde **43** (603 mg, 2.00 mmol, 82.3%), m.p. 148-150°C (from CH_2Cl_2/diethyl ether) (Found: C, 75.75; H, 8.02. $C_{19}H_{24}O_3$ required: C, 75.97; H, 8.05%).

19(S)-Hydroxy-1β,19-cyclo-5α-androstane-3,17-dione **(44)**

A solution of 19(S)-trimethylsiloxy-1β,19-cyclo-5α-androstane-3,17-dione **47** (2 mg, 0.01 mmol) in methanol (0.3 mL) was stirred with K_2CO_3 (2 mg) at room temperature for 30

minutes. TLC indicated no starting material and formation of a more polar substance corresponding to compound **44**.

19(S)-Hydroxy-1β,19-cyclo-5α-androstane-3,17-dione **(44)**, *19(R)-hydroxy-1β,19-cyclo-5α-androstane-3,17-dione* **(45)** and *3α-hydroxy-3β,19-oxido-1β,19-cyclo-5α-androstan-17-one* **(46)**

19-Oxo-5α-androst-1-ene-3,17-dione **43** (100 mg, 0.33 mmol) was dissolved in 50% aqueous HOAc (5 mL) and Zn powder (300 mg, 4.59 mmol) added. The mixture was stirred at room temperature for 1 h, filtered to remove excess Zn, poured into water, extracted with CH_2Cl_2, washed with water, saturated $NaHCO_3$, dried over Na_2SO_4 and evaporated to give a gum which was crystallized to yield a mixture of the ketone and hemiketal **45** and **46** (50 mg, 0.17 mmol, 51.5%), m.p. 186-189°C (from CH_2Cl_2/diethyl ether) (Found: C, 75.27; H, 8.52. $C_{19}H_{23}O_3$ required: C, 75.46; H, 8.67%). The ^1H NMR of the mother liquor showed signals corresponding to the isomer **44**.

19(R)-Hydroxy-1β,19-cyclo-5α-androstane-3,17-dione **(45)** and *3α-hydroxy-3β,19-oxido-1β,19-cyclo-5α-androstan-17-one* **(46)**

A solution of 19(R)-trimethylsiloxy-1β,19-cyclo-5α-androstane-3,17-dione **48a** (15 mg, 0.04 mmol) in methanol (1 mL) was stirred with K_2CO_3 (15 mg) at room temperature for 30 minute, poured into water, extracted with CH_2Cl_2, filtered through a filter paper to remove finely dispersed water droplets, evaporated to give the crude product (13 mg) which was crystallized (from CH_2Cl_2/diethyl ether), to give a mixture of the *endo*-cyclopropanol and hemiketal **45** and **46** (7.6 mg,

0.03 mmol, 75.0%), m.p. 187-190°C as determined by ^{1}H NMR.

A solution of 3α-trimethylsiloxy-3β,19-oxido-(5α)-1β,19-cycloandrostane-3,17-dione **49** (74 mg, 0.20 mmol) in methanol (5 mL) was stirred with K_2CO_3 (74 mg) at room temperature for 30 minute, poured into water, extracted with CH_2Cl_2, filtered through filter paper to remove traces of water and evaporated to give a crude product (68 mg) which was recrystallized to give a mixture of compounds **45** and **46** (32 mg, 0.11 mmol, 55%), m.p. 187-190°C (from CH_2Cl_2/diethyl ether) as shown by ^{1}H NMR.

19(S)-Trimethylsiloxy-1β,19-cyclo-5α-androstane-3,17-dione **(47)**, *19(R)-trimethylsiloxy-1β,19-cyclo-5α-androstane-3,17-dione* **(48a)** and *3α-trimethylsiloxy-3β,19-oxido-1β,19-cyclo-5α-androstan-17-one* **(49)**

19-Oxo-5α-androst-1-ene-3,17-dione **43** (600 mg, 2.00 mmol) was dissolved in 50% HOAc (30 mL) and Zn powder (3.00 g, 45.89 mmol) added. The mixture was stirred at room temperature for 2 h, filtered to remove excess Zn, poured into water, extracted with CH_2Cl_2, washed with saturated $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to give a gum which was crystallized from CH_2Cl_2/diethyl ether to give a mixture of the ketone and hemiketal **45** and **46**, (372 mg, 1.23 mmol, 61.5%), m.p. 184-189°C. The residue from the mother liquor (254 mg, 0.84 mmol) was dissolved in CH_2Cl_2 (5 mL) and stirred with 97% N-(trimethylsilyl)imidazole (1 mL) for 30 minutes, poured into water, extracted with CH_2Cl_2, which was washed with water, dried over Na_2SO_4 and evaporated at reduced pressure to give

a crude product. This was flash chromatographed and on elution with 5% acetone/P.E. followed by 10% acetone/P.E. gave (i) the ketal silyl diethyl ether **49** (50 mg, 0.13 mmol, 15.5%), m.p. 115-118°C (from CH_2Cl_2/diethyl ether) (Found: C, 70.36; H, 8.97. $C_{22}H_{34}O_3Si$ required: C,70.54, H,9.15%), (ii) the *endo*-cyclopropanol silyl diethyl ether **48a** (147 mg, 0.39 mmol, 46.4%), m.p. 110-113°C (from diethyl ether/P.E.) (Found: C, 70.16; H, 9.38. $C_{22}H_{34}O_3Si$ required: C, 70.54, H, 9.15%) and (iii) the *exo*-cyclopropanol silyl diethyl ether **47** (15 mg, 0.04 mmol, 4.7%), m.p. 140-142°C (from CH_2Cl_2/diethyl ether) (Found: C, 70.32; H, 9.09. $C_{22}H_{34}O_3Si$ required: C, 70.54, H, 9.15%).

19(R)-Hydroxy-1β,19-cyclo-5α-androstane-3,17-dione acetate **(48b)**

To a solution of 19(R)-Hydroxy-1β,19-cyclo-5α-androstane-3,17-dione **(45)** and 3α-hydroxy-3β,19-oxido-1β,19-cyclo-5α-androstan-17-one **(46)** mixture (80 mg, 0.26 mmol) in Ac_2O (5 mL) was added 4-dimethylaminopyridine (DMAP) (30 mg) and the mixture stirred at room temperature for 1 h. It was then poured into water, extracted with CH_2Cl_2, and the organic layer washed with water, dried over Na_2SO_4 and evaporated at reduced pressure to give a crude product which was flash chromatographed and on elution with 20% acetone/P.E. gave the acetate **48b** (36 mg, 0.10 mmol, 3.8%), m.p. 161-163°C (from CH_2Cl_2/diethyl ether) (Found: C, 72.30; H, 8.22. $C_{21}H_{28}O_4.1/4\ H_2O$ required: C,72.28, H,8.16%)

Table 1 ^{1}H NMR Chemical Shifts (J in Hz)[a] (...continued)

Compound	13-Me	17α-H	$SiMe_2$	CMe_3	Others
1	0.92				5.96 (s, 4-H); 3.94, 4.07 (d J_{AB} 10.3, 19-H)
2	0.92				5.96 (s, 4-H)
3	0.91				2.70, 2.81 (d, J_{AB} 21.2, 4-H_2)
4	0.90				3.18, 3.21 (s, 2xOCH_3)
5a[b]	0.75	3.60 (t, J 8.7)			3.18, 3.20 (s, 2xOCH_3)
6a[b]	0.74	3.64 (dd, J 7.6, 8.4)	0.02, 0.03	0.88	3.17, 3.20 (s, 2xOCH_3)
6b	0.71	3.59 (t, J 8.0)	-0.02, 0.01	0.88	3.96 (m, -OCH_2CH_2O-)
7	0.85				3.96 (m, -OCH_2CH_2O-)
8	0.88				3.97 (m, -OCH_2CH_2O-)
11a[c]	0.74	3.61 (t, J. 8.5)	0.01, 0.02	0.87	3.25 (s, 2xOCH_3); 2.79 (s, 19-H); 1.83, 2.21 (d, J_{AB} 13.4, 4-H_2); 2.52, (m, 2α-H)
11b[c]	0.76	3.65 (dd, J 7.6, 8.9)	0.01, 0.02	0.88	2.93 (s, 19-H); 2.81 (d, J 15.4, 4α-H); 2.57 (d, J 15.4, 4β-H)

Table 1 ^{1}H NMR Chemical Shifts (J in Hz)[a] (...continued)

Compound	13-Me	17α-H	$SiMe_2$	CMe_3	Others
11c[c]	0.78	3.65 (t, J 8.6)	0.01, 0.02	0.88	3.15 (s, 19-H); 2.91 (d, J 4.3, 20-H); 2.81 (d, J 15.3, 4α-H); 2.56 (m, 2α-H); 2.48 (m, 2β-H); 2.38 (dd, J 2.0, 15.4, 4β-H)
11d[c]	0.78	3.65 (dd, J 7.6, 8.7)	0.01, 0.02	0.88	3.06 (s, 19-H); 2.97 (d, J 8.1, 20-H); 2.92 (d, J 14.5, 4α-H); 2.63 (m, 2β-H); 2.54 (m, 8β-H); 2.45 (m, 2α-H); 2.34 (m, 1β-H); 1.62 (d, J 14.5, 4β-H)
13[c]	0.83	3.66 (t, J 8.6)	0.02, 0.03	0.89	3.37 (s, 19-H); 2.66 (m, 2α-H); 6.18 (s, 4-H)
14	0.73	3.58 (t, J 8.2)	0.00, 0.01	0.88	2.70 (d, J 16.4, 4α-H); 2.61 (ddd, J 1.7, 6.0, 14.8, 1β-H); 2.46 (d, J 16.4, 4β-H)
15[b]	0.87	3.73 (t, J 7.4)	0.06, 0.07	0.90	5.74 (s, 4-H),
16	0.75	3.62 (t, J 8.5)	0.01, 0.02	0.87	4.10 (m, $-OCH_2CH_2O-$); 2.81 (s, 19-H); 2.60 (m, 2α-H)
19	1.00				5.88 (s, 4-H); 3.37 (s, 19-H)

Table 1 ^{1}H NMR Chemical Shifts (J in Hz)[a] (...continued)

Compound	13-Me	19-H	$SiMe_3$	Others
20	0.94			5.85 (s, 4-H)
21[c]	0.92	0.35, 1.16 (d, J_{AB} 4.4)		2.10 (m, 11α-H + 16β-H); 2.46 (dd, J 8.0, 18.4, 16β-H); 2.50, 2.85 (d, J_{AB} 8.4, 4-H_2); 5.76 (d, J 10.2, 1-H); 7.28 (d, J 10.2, 2-H)
22	0.83	9.88 (s)		5.93 (s, 4-H)
23[c]	0.90	3.30 (s)		2.31 (d, J 17.2, 4β-H); 2.40 (dd, J 10.3, 19.2, 16β-H); 2.49 (d, J 17.1, 4α-H)
26a[c]	0.91	4.03 (s)		2.14 (s, $COCH_3$); 2.46 (dd, J 8.3, 19.2 16β-H); 2.54 (s, 4-H)
26b	0.87	3.12 (s)	0.16	2.31 (d, J 16.9, 4β-H); 2.50 (d, J 16.4, 4α-H)
27[c]	0.92	3.88 (s)		2.07 (m, 16α-H); 2.08 (s, $COCH_3$); 2.25 (d, J 16.4, 4β-H); 2.38 (d, J 16.6, 4α-H); 2.44 (dd, J 8.9, 19.6, 16β-H)
29	0.92	3.15 (s)	0.17	2.09 (d, J 16.3, 4β-H); 2.45 (dd, J 8.3, 19.2, 16β-H); 2.53 (d, J 16.3, 4α-H)
32[c]	0.98	9.63 (s)		2.49 (dd, J 8.2, 19.1, 16β-H); 2.65 (dd, J 13.7, 14.6, 4α-H)

Table 1 ^{1}H NMR Chemical Shifts (J in Hz)[a] (...continued)

Compound	13-Me	19-H	$COCH_3$	Others
34a	0.92	4.19, 4.68 (d, J_{AB} 11.3)	2.02	5.93 (s, 4-H)
34b	0.92	3.90 (dd, J 10.5, 12.5)		0.04, 0.05 (m, $SiMe_2$); 0.86 (m, CMe_3); 5.87 (s, 4-H)
35a	0.95	4.42, 4.64 (d, J_{AB} 10.9)	1.93	6.21 (s, 4-H); 6.36 (dd, J 1.9, 8.72, 2-H); 7.07 (d, J 10.2, 1-H)
35b	0.95	3.86, 4.00 (d, J_{AB} 9.6)		-0.01, 0.00 (m, $SiMe_2$); 0.80 (m, CMe_3); 6.15 (s, 4-H); 6.33 (dd, J 1.9, 10.2, 2-H); 7.09 (d, J 10.2, 1-H)
36	0.88			2.79 (m, 6-H); 3.91 (m, 17-OCH_2CH_2O-); 4.86 (s, 3-OH); 6.55 (d, J 2.6, 4-H); 6.62 (dd, J 2.6, 8.3, 2-H); 7.15 (d, J 8.4, 1-H)
37	0.91			2.51 (dd, J 8.2, 18.3, 16β-H); 2.85 (m, 6-H); 4.80 (s, 3-OH); 6.58 (d, J 2.6, 4-H); 6.64 (dd, J 2.7, 8.4, 2-H); 7.15 (d, J 8.4, 1-H)
38[c]	0.90	3.91, 3.97 (d, J_{AB} 10.8)		0.08, 0.10 (m, $SiMe_2$); 0.89 (s, CMe_3); 1.67 (m, 5α-H); 2.07 (m, 16α-H); 2.45 (m, 16β-H + 4β-H)

Table 1 ^{1}H NMR Chemical Shifts (J in Hz)[a] (...continued)

Compound	13-Me	19-H	$SiMe_3$	Others
39[c]	0.90	3.60, 3.81 (d, J_{AB} 9.7)		0.05, 0.05 (m, $SiMe_2$); 0.89 (s, CMe_3); 2.26 (m, 5β-H); 2.47 (dd, J 8.6, 19.0, 16β-H); 2.63 (dd, J 14.6, 14.6, 4β-H)
40[c]	0.83	3.89, 4.06 (d, J_{AB} 8.4)		2.08 (m, 16α-H); 2.18 (dd, J 4.6, 14.6, 4α-H); 2.40 (t, J 12.5, 4β-H); 2.43 (m, 16β-H); 2.53 (dd, J 7.4, 12.5, 1α-H); 4.14 (d, J 7.1, 2-H)
41	0.90	3.74, 3.98 (d, J_{AB} 10.6)		0.01, 0.03 (m, $SiMe_2$); 0.87 (m, CMe_3); 2.47 (dd, J 8.5, 19.0, 16β-H); 2.70 (dd, J 14.2, 17.8, 4β-H); 6.01 (d, J 10.3, 2-H); 6.98 (d, J 10.2, 1-H)
42	0.92	3.83, 4.11 (d, J_{AB} 11.5)		2.25 (dd, J 4.7, 17.8, 4α-H); 2.45 (dd, J J 8.7, 19.1, 16β-H); 2.77 (dd, J 14.4, 18.0, 4β-H); 6.11 (d, J 10.2, 2-H); 7.01 (d, J 10.2, 1-H)
43	0.96	9.93 (s)		6.23 (d, J 10.2, 2-H); 7.00 (d, J 10.2, 1-H)
47	0.87	3.33 (d, J 3.1)	0.15	2.46 (dd, J 8.7, 18.8, 16β-H); 2.58 (d, J 5.2, 2β-H); 2.65 (dd, J 1.7, 19.4, 2α-H)

Table 1 ^{1}H NMR Chemical Shifts (J in Hz)[a]

Compound	13-Me	19-H	$SiMe_3$	Others
48a	0.87	3.49 (d, J 7.0)	0.14	2.47 (dd, J 8.7, 18.7, 16β-H); 2.54 (d, J (d, J 2.3, 2β-H); 2.59 (dd, J 4.9, 18.4, 2α-H)
48b[c]	0.90	4.31 (d, 7.5)		2.03 (s, $COCH_3$); 2.43 (dd, J 8.7, 18.7, J 16β-H); 2.54 (d, J 17.5, 2β-H); 2.64 (dd, J 5.1, 17.5, 2α-H)
49[c]	0.84	4.02 (d, J 5.6)	0.15	1.72 (dd, J 2.6, 4.4, 12β-H); 1.87 (d, J 11.7, 2β-H); 1.92 (t, J 11.0, 4α-H); 2.44 (dd, J 9.0, 19.2, 16β-H)

[a]For solution in $CDCl_3$ ($SiMe_4$ internal standard) unless otherwise indicated on a Bruker AM300 instrument. [b]In CD_3OD. [c]Determined by 2-D analysis on a Bruker AMX500 instrument.

Table 2 ^{13}C NMR Chemical Shifts[a] (...continued)

	Compound δ (ppm)								
Carbon	**1**	**2**	**3**[h]	**4**[b,g]	**5a**[b,g]	**6a**[c,b,g]	**6b**[c,d]	**7**[d]	**8**[d]
1	33.6	33.71	24.80	25.85	26.22	26.24	23.15	22.18	25.88
2	35.0	34.76	38.97	36.71	38.36	38.86	37.58	34.32	35.84
3	199.6	199.03	207.91	101.13	101.17	101.20	108.32	108.52	108.18
4	127.3	127.07	44.67	40.35	40.35	40.36	40.70	40.68	40.67
5	165.6	161.97	126.66	125.98	125.62	125.63	125.59	125.62	125.92
6	33.6	32.54	32.39	31.73	31.89	31.91	31.40	31.37	31.90
7	31.9	31.35	27.54	27.10	27.85	27.86	26.62	26.36	30.63
8	36.1	35.53	38.66	39.92	40.46	40.54	38.93	39.09	38.40
9	54.3	53.66	46.24	47.63	47.70	47.78	46.52	46.02	46.35
10	43.9	50.56	130.60	130.37	130.71	130.76	129.58	129.49	129.09
11	21.0	21.64	25.93	26.20	26.31	26.24	26.07	26.06	26.02
12	31.0	29.96	30.60	29.96	30.78	30.00	30.85	30.79	30.63
13	47.1	47.60	47.98	48.15	44.65	45.07	43.90	46.46	48.29
14	51.5	50.91	49.98	51.44	51.09	50.69	49.56	49.20	50.24
15	21.8	21.97	21.43	22.37	23.92	24.15	25.15	24.90	21.41
16	35.8	35.71	35.61	33.10	27.98	32.18	31.06	31.16	31.28
17	220.0	220.25	217.50	223.60	82.49	83.20	81.76	119.43	222.30
18	13.9	13.89	13.98	14.50	11.90	12.17	11.60	14.54	14.08
19	66.1	175.67							

Table 2 ^{13}C NMR Chemical Shifts[a] (...continued)

	Compound δ (ppm)								
Carbon	**11a**[b,c]	**11b**[c,j]	**11c**[c,j]	**11d**[c,j]	**13**[c,j]	**14**[c,j]	**15**[c]	**16**[c,d]	**19**[j]
1	24.61	24.49	25.97	25.46	26.86	25.58	27.49	24.66	26.85
2	40.25	39.13	39.22	39.21	35.44	37.20	37.08	34.73	35.37
3	100.10	207.76	208.36	209.08	198.83	210.36	198.43	108.30	198.51
4	48.79	48.31	45.78	49.90	126.41	48.06	124.83	41.23	126.72
5	33.94	32.40	27.33	25.51	162.47	31.28[k]	166.51	33.42	161.27
6	34.70	33.95	27.63	21.27	29.60	28.30	35.88	34.33	29.60
7	22.04	21.94	22.17	21.87	21.03	25.92	31.58	21.98	21.19
8	29.78	30.08	32.24	31.85	36.50	35.48	41.21	29.81	36.00
9	33.45	33.96	32.06	33.17	33.61	41.82	50.09	31.54	33.34
10	30.75	29.51	29.15	28.44	29.71	31.37[k]	43.10	30.31	29.88
11	24.61	25.04	25.24	25.20	24.33	25.24	26.84	23.21	23.91
12	34.76	34.77	34.85	34.96	34.95	36.80	37.69	34.73	35.66
13	43.89	44.05	43.68	43.94	43.77	43.28	44.13	43.90	47.93
14	48.79	48.81	48.31	49.00	48.30	50.56	50.64	48.82	49.02
15	22.73	22.75	23.01	22.81	22.88	23.51	23.95	22.72	20.45
16	30.93	30.93	30.84	30.96	30.91	30.69	31.58	30.94	29.37
17	81.25	81.15	81.39	81.29	81.31	81.43	82.45	81.24	219.29
18	11.42	11.51	11.20	11.47	11.17	11.51	11.78	11.43	13.64
19	32.80	32.52	32.92	32.65	34.21	61.24		32.48	33.34
5′	40.79	37.71	26.81	31.71				40.38	

Table 2 ^{13}C NMR Chemical Shifts[a] (...continued)

	Compound δ (ppm)								
Carbon	**20**	**21**	**22**	**23**[j]	**26a**[e]	**26b**[f]	**27** [e,j]	**29**[f]	**32**[j]
1	25.75	156.18	34.09	27.61	22.47	27.31	23.12	20.88	28.31
2	36.49	124.35	29.61	36.28	36.21	36.41	36.37	36.16	35.39
3	199.55	196.67	197.54	212.31	210.59	212.38	212.02	214.01	209.72
4	124.89	44.91	127.53	47.89	47.20	48.21	43.10	42.86	41.49
5	165.75	21.82	160.35	21.19	21.14	20.75	24.44	23.24	37.62
6	35.26	32.68	33.67	25.71	26.60[k]	26.31	31.68	31.59	27.38
7	29.91	25.53	31.41	26.23	25.87[k]	26.40	25.70	26.08	24.58
8	39.93	35.82	36.38	36.83	36.82	36.73	35.79	36.06	35.78
9	49.56	44.11	53.54	46.47	46.32	46.54	45.53	47.80	39.92
10	42.48	27.98	54.97	25.33	24.75	24.61	27.92	28.77	50.36
11	26.65	24.75	21.09	24.23	23.79	23.42	24.10	24.65	20.59
12	31.34	31.47	30.27	32.20	31.97	32.13	31.48	32.17	31.81
13	47.70	48.29	47.32	48.68	48.45	48.67	48.26	48.22	47.80
14	50.19	49.95	50.91	51.16	50.92	51.07	50.26	50.26	51.44
15	21.66	21.63	21.57	21.62	21.62	21.54	21.51	21.55	21.68
16	35.73	35.69	35.58	35.63	35.74	35.81	35.69	35.73	35.78
17	220.23	220.14	219.51	221.22	220.40	221.22	221.66	220.36	220.41
18	13.82	14.14	13.65	14.35	14.11	14.08	14.14	14.14	13.71
19		31.31	200.71	63.40	64.21	64.05	62.13	60.37	204.51

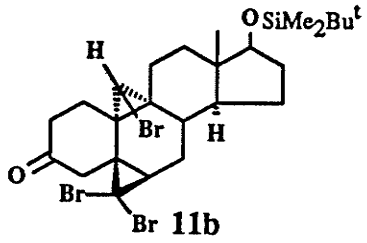
Table 2 ^{13}C NMR Chemical Shifts[a] (...continued)

	Compound δ (ppm)								
Carbon	**34a**[e]	**34b**[c]	**35a**[e]	**35b**[c]	**36**[d]	**37**	**38**[c,j]	**39**[c,j]	**40**[j]
1	32.84	33.29	151.05	152.45	126.48	126.9	33.96	31.16	41.28
2	34.51	34.69	130.46	129.99	112.62	113.5	38.64	36.91	81.45
3	198.99	199.65	185.89	186.40	153.29	155.8	211.91	212.84	209.57
4	126.87	126.02	126.73	126.03	115.23	115.9	44.86	42.06	42.42
5	164.82	167.25	163.49	165.54	138.28	138.2	46.23	36.38	44.67
6	33.49	33.58	32.37[k]	32.23	29.62	30.2	28.32	24.49	29.71
7	31.53	30.79[k]	31.48	31.63	26.93	27.4	30.66[k]	25.90	30.08
8	35.67	35.93	35.66	35.71	39.54	39.3	35.51	35.21	37.75
9	54.02	54.07	52.86	52.27	43.60	45.0	54.33	41.59	46.04
10	41.82	43.60	47.56[l]	49.58[k]	132.73	131.9	39.54	39.22	47.41
11	20.78	20.96[l]	22.63	22.60	26.16	26.4	21.72[l]	20.59	20.65
12	30.85	31.73[k]	32.40[k]	32.81	30.75	32.5	31.93[k]	32.04	31.19
13	47.41	47.59	47.69[l]	47.70[k]	46.18	48.3	47.79	47.77	47.66
14	51.09	51.34	50.84	50.97	49.36	51.1	51.66	51.92	51.30
15	21.57	21.71[l]	21.83	21.87	22.37	22.2	21.78[l]	21.71	21.70
16	35.56	35.71	35.51	35.60	34.24	35.9	35.79	35.83	35.74
17	219.64	220.10	219.14	219.62	119.50	219.3	220.72	220.47	220.12
18	13.73	13.89	13.85	13.96	14.36	13.9	13.92	13.91	13.59
19	66.49	65.81	63.48	64.34			60.87	65.19	67.43

Table 2 ^{13}C NMR Chemical Shifts[a]

	Compound δ (ppm)						
Carbon	**41**[c]	**42**	**43**	**47**[f,j]	**48a**[f,j]	**48b**[e,j]	**49**[f,j]
1	130.27	131.13	132.14	19.93	17.66	17.41	19.28
2	153.46	152.54	147.24	35.98[k]	35.08	34.73	36.27
3	200.17	200.16	197.54	209.98	211.99	210.10	104.29
4	41.68	41.70	41.24	43.80	44.47	43.96	42.79
5	44.35	44.31	45.14	38.24	38.56	38.02	38.67
6	27.37	27.25	28.18	32.97	32.52	32.68	35.75
7	30.36[k]	30.34[k]	31.59[k]	31.36[l]	30.83	30.68	30.30
8	35.77	35.60	36.09	39.01	39.48	39.10	39.14
9	52.05	51.85	51.43	46.49	46.52	46.22	44.69
10	43.37	43.68	55.40	29.12	26.05	26.93	25.17
11	21.16[l]	21.16[l]	21.30[l]	21.82	21.69[k]	21.57	21.46
12	31.80[k]	31.71[k]	30.03[k]	31.71[l]	31.08	31.02	31.27
13	47.88	47.79	47.79	47.86	47.54	47.54	47.61
14	50.23	50.16	48.92	51.54	50.97	50.95	50.68
15	21.69[l]	21.67[l]	21.62[l]	22.82	21.81[k]	21.63	21.62
16	35.75	35.72	35.66	37.37[k]	35.86	35.80	35.82
17	220.27	220.22	219.89	221.29	220.57	220.28	220.79
18	14.10	13.98	13.92	13.38	13.59	13.68	13.62
19	62.06	61.39	201.27	55.51	54.74	56.93	60.47

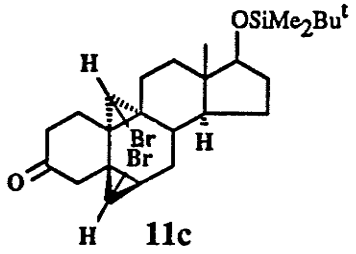
[a]For solutions in $CDCl_3$ ($SiMe_4$ internal standard) on a Bruker AM300 instrument unless otherwise indicated. [b]The methoxy ketal signals occurs at ca. 48.15s and 48.25s ($\underline{C}H_3O$). [c]The tert-butyldimethylsiloxy group occurs at ca. -4.48s and 4.81s ($Si\underline{Me}_2$), 18.07 ($\underline{C}Me_3$) and 25.84 ($C\underline{Me}_3$). [d]The glycol ketal signals occur at ca. 64.21s and 64.47s ($O\underline{C}H_2\underline{C}H_2O$). [e]The acetyl group signals occur at ca. 20.65 ($CO\underline{C}H_3$) and 170.67 ($\underline{C}OCH_3$). [f]The trimethylsiloxy group signals occur at ca. -0.26 ($Si\underline{Me}_4$). [g]In CD_3OD. [h]In C_6D_6. [i]In d_6-Acetone. [j]Determined by 2-D analysis on a Bruker AMX500 instrument. [k,l]Numbers in columns are interchangeable.



11b

Carbon	δC(ppm)	δHα	H	δHβ
1	24.49	1.98		2.37
2	39.13	2.68		2.57
3	207.76	----		----
4	48.31	2.81		2.57
5	32.40	----		----
6	33.95	1.46		----
7	21.94	1.31		2.10
8	30.08	----		2.60
9	33.76	----		----
10	29.51	----		----
11	25.04	1.56		1.72
12	34.77	1.24		1.64
13	44.05	----		----
14	48.81	1.13		----
15	22.75	1.47		1.32
16	30.93	1.92		1.46
17	81.15	3.64		----
18	11.51	----		0.76
19	32.52		2.94	
20	37.71		----	
Si-CH_3	-4.79		0.01	
Si-CH_3	-4.47		0.02	
Si-Bu^t	18.06/25.82		0.88	

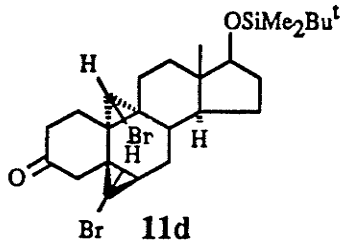
Table 3. ^1H and ^{13}C NMR assignments for compound 11b from H/C correlation via HSQC, AMX500, $CDCl_3$



11c

Carbon	δC(ppm)	δHα	H	δHβ
1	25.46	1.98		2.34
2	39.21	2.63		2.45
3	209.08	----		----
4	49.90	2.92		1.62
5	25.50	----		----
6	21.27	0.92		----
7	21.87	1.40		1.87
8	31.85	----		2.54
9	33.17	----		----
10	28.44	----		----
11	25.20	1.61		1.72
12	34.96	1.24		1.53
13	43.94	----		----
14	49.00	1.16		----
15	22.81	1.47		1.32
16	30.96	1.91		1.44
17	81.29	3.65		----
18	11.47	----		0.78
19	32.65		3.06	
20	31.71		2.97	
Si-CH_3	-4.48		0.02	
Si-CH_3	-4.81		0.03	
Si-Bu^t	18.07/25.84		0.88	

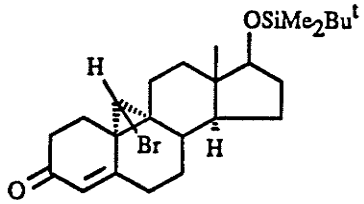
Table 4. ^1H and ^{13}C NMR assignments for compound 11c from H/C correlation via HSQC, AMX500, $CDCl_3$



11d

Carbon	δC(ppm)	δHα	H	δHβ
1	25.97	2.06		2.02
2	39.22	2.56		2.48
3	208.36	----		----
4	45.78	2.81		2.38
5	27.33	----		----
6	27.63	1.04		----
7	22.17	1.17		1.87
8	32.24	----		1.64
9	32.06	----		----
10	29.15	----		----
11	25.24	1.65		1.63
12	34.85	1.17		1.64
13	43.68	----		----
14	48.31	1.17		----
15	23.01	1.50		1.29
16	30.84	1.92		1.45
17	81.39	3.63		----
18	11.20	----		0.77
19	32.92		3.12	
20	26.81		2.91	
Si-CH_3	-4.48		0.01	
Si-CH_3	-4.81		0.02	
Si-Bu^t	18.05/25.81		0.88	

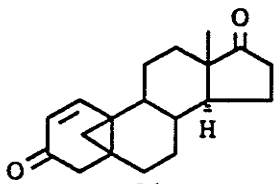
Table 5. ^1H and ^{13}C NMR assignments for compound 11d from H/C correlation via HSQC, AMX500, $CDCl_3$



13

Carbon	δC(ppm)	δHα	H	δHβ
1	26.86	2.07		2.18
2	35.44	2.66		2.39
3	198.83	----		----
4	126.41		6.18	
5	162.47	----		----
6	29.60	2.42		2.27
7	21.03	0.98		1.48
8	36.50	----		2.83
9	33.61	----		----
10	29.71	----		----
11	24.33	1.64		1.83
12	34.95	1.23		1.72
13	43.77	----		----
14	48.30	1.23		----
15	22.88	1.53		1.32
16	30.91	1.93		1.47
17	81.31	3.66		----
18	11.17	----		0.83
19	33.61		3.37	
Si-CH_3	-4.45		0.02	
Si-CH_3	-4.78		0.03	
Si-Bu^t	18.18/25.83		0.88	

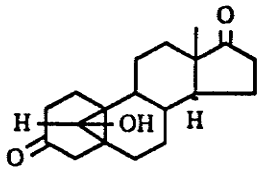
Table 6. ^1H and ^{13}C NMR assignments for compound 13 from H/C correlation via HSQC, AMX500, $CDCl_3$



21

Carbon	δC(ppm)	δHα	H	δHβ
1	156.18		7.28	
2	124.37		5.76	
3	196.69	----		----
4	44.90	2.46		2.89
5	21.81	----		----
6	32.66	1.88		1.88
7	25.10	0.96		1.51
8	35.81	----		1.08
9	44.09	1.40		----
10	27.95	----		----
11	24.73	2.07		1.36
12	31.46	1.41		1.90
13	48.27	----		----
14	49.94	1.39		----
15	21.60	1.92		1.51
16	35.70	2.08		2.45
17	220.18	----		----
18	14.12	----		0.90
19	33.31	0.35(A ring)		1.16(B ring)

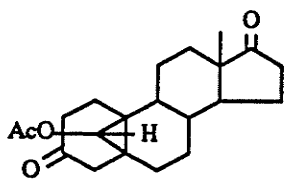
Table 7. ^{1}H and ^{13}C NMR assignments for compound 21 from H/C correlation via HSQC, AMX500, $CDCl_3$



23

Carbon	δC(ppm)	δHα	H	δHβ
1	27.61	1.99		1.78
2	36.28	2.24		2.10
3	212.31	----		----
4	47.89	2.49		2.31
5	21.19	----		----
6	25.71	1.65		1.82
7	26.23	0.80		1.50
8	36.83	----		1.70
9	46.47	1.17		----
10	25.33	----		----
11	24.23	1.89		1.53
12	32.20	1.29		1.83
13	48.68	----		----
14	51.16	1.32		----
15	21.62	1.89		1.50
16	35.63	2.03		2.40
17	221.22	----		----
18	14.35	----		0.90
19	63.40		3.30	

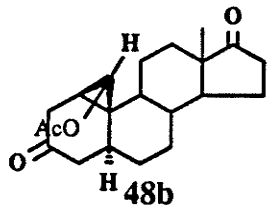
Table 8 ^{1}H and ^{13}C NMR assignments for compound 23 from H/C correlation via HSQC, AMX500, $CDCl_3$



27

Carbon	δC(ppm)	δHα	H	δHβ
1	23.12	1.98		1.84
2	36.37	2.23		2.23
3	212.02	----		----
4	43.10	2.38		2.25
5	24.44	----		----
6	31.68	1.89		1.89
7	25.70	0.82		1.50
8	35.79	----		0.99
9	45.53	1.17		----
10	27.92	----		----
11	24.10	1.87		1.48
12	31.48	1.34		1.89
13	48.26	----		----
14	50.26	1.31		----
15	21.51	1.49		1.90
16	35.69	2.07		2.44
17	221.66	----		----
18	14.14	----		0.92
19	62.13		3.88	
OAc	20.53/171.14		2.08	

Table 9 ^{1}H and ^{13}C NMR assignments for compound 27 from H/C correlation via HSQC, AMX500, $CDCl_3$



48b

Carbon	δC(ppm)	δHα	H	δHβ
1	17.31	1.60		----
2	34.64	2.64		2.55
3	210.08	----		----
4	43.87	2.33		2.19
5	37.93	2.37		----
6	32.59	1.74		1.33
7	30.59	1.14		1.95
8	39.01	----		1.66
9	46.14	1.30		----
10	26.84	----		----
11	21.48	1.30		0.98
12	30.94	1.24		1.80
13	47.45	----		----
14	50.87	1.32		----
15	21.54	1.96		1.54
16	35.70	2.08		2.45
17	220.26	----		----
18	13.57	----		0.89
19	56.85		4.31	
OAc	20.68/171.19		2.03	

Table 10 ^{1}H and ^{13}C NMR assignments for compound 48b from H/C correlation via HSQC, AMX500, $CDCl_3$

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