STUDIES IN THE SYNTHESIS OF MECHANISM-BASED STEROID ENZYME INHIBITORS

BY

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ABSTRACT

Metabolic α-hydroxylation of an appropriately located halogen substituted steroid cyclopropane ring can, after spontaneous α-elimination, give a cyclopropanone. This highly electrophilic ring can be attacked by an active-site nucleophile to form a covalent bond thereby inactivating the enzyme. Alternatively a steroid cyclopropanol can be oxidized by a specific steroid dehydrogenase to form a cyclopropanone which can react further in an analogous manner.

This thesis reports on attempts to synthesize both halogen and hydroxy substituted steroid cyclopropane derivatives as potential mechanism-based-inhibitors for 20α- and 20ß-hydroxysteroid dehydrogenase and estrogen synthetase (aromatase), respectively.

The scheme to prepare 19(R and/or S)-bromo-5ß,19-cycloandrostanes required the preparation of 19,19-dibromo-5ß,19-cycloandrostanes, which had been reported in the literature, followed by reduction of one bromine. However this reaction did not give the reported product but instead furnished two different products which have been identified and a mechanism suggested for their formation. These products arise from addition of dibromocarbene to the α-face of the 5(10)-double bond rather than to the ß-face as reported in the literature. This unexpected result required this synthetic approach to be abandoned.

A scheme designed to prepare 20α- and 20ß-hydroxy-17α,21α-cyclopregnanes was then attempted. Wittig reaction of 3ß-(*t*-butyldimethylsiloxy)-5α-androstan-17-one with triethyl phosphonoacetate gave the C-17 unsaturated ester. Attempts to add methylene

to the double bond with Simmons-Smith reagent using Zn-Cu, Zn-Ag, and Sm to prepare the reagent proved unsuccessful. Methylene addition from diazomethane with palladium acetate as catalyst also failed. An alternative approach was then tried. Addition of dihalocarbene generated from $CHBr_3$/NaOH/cetrimide or from thermolysis of CBr_3CO_2Na or CCl_3CO_2Na also did not yield the desired product. Reactions carried out on the non-conjugate allylic alcohol and the corresponding acetate, derived from reduction of the ester function, also gave unsatisfactory results.

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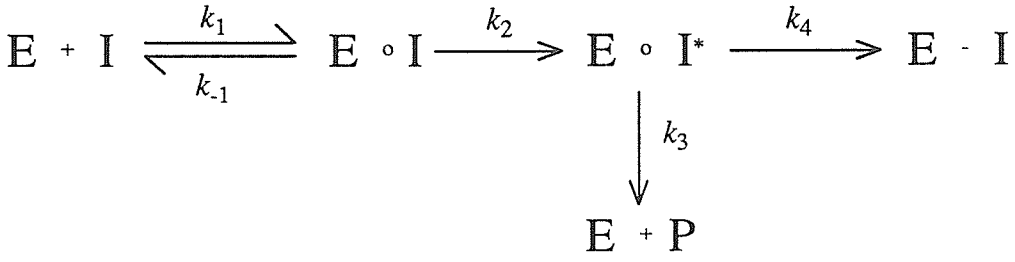
INTRODUCTION

An important method for the inhibition of enzymes is the use of relatively stable compounds which are able to act as enzyme substrates and are converted by the enzyme to a reactive species capable of forming a covalent bond with the target enzyme thus rendering it inactive. These substrates, otherwise known as *mechanism-based enzyme inhibitors* or *suicide substrates*[1-3], have proved extremely valuable in establishing the nature of the enzyme active site. In the first step of the enzymatic process (Scheme 1), the target enzyme can reversibly bind the unactivated substrate to the active site. This equilibrium is governed by the ratio k_1/k_{-1}. Once bound to the active site, the target enzyme is able to convert the inactive substrate into a reactive electrophilic species by carrying out its normal catalytic reaction. This transformation is dependent on the rate constant, k_2. The newly formed reactive electrophilic species may exit the active site, k_3, leaving the enzyme intact. Alternatively, a covalent bond can be formed by attack of an active site nucleophile and the electrophilic substrate, thus rendering the enzyme inactive. This process is controlled by the rate constant k_4. If the step with rate constant k_4 occurs instantaneously and the k_1/k_{-1} equilibrium is rapidly reached, then the rate constant k_2 is described as the *inactivation rate constant* (k_{inact}).[3] Since not all of the activated substrate reacts covalently with the enzyme, the amount of activated substrate that is released for each inactivation, k_3/k_4, is termed the *partition ratio*.[3] Mechanism-based inhibitors can exhibit high selectivity because they are recognized by the enzyme as a substrate. Whereas the normal substrate is released from the active site after the enzymatic reaction,



Scheme 1: Pathway of inactivation for mechanism-based inhibitors.

the activated substrate/enzyme complex should ideally possess a partition ratio of 0. Therefore, enzymes should have a greater affinity for more electrophilic substrates which form a covalent bond; hence, a much lower partition ratio.[1-3] Modification, usually by chemical means, of the functional group(s) on a substrate may or may not allow the substrate to act as an inhibitor. Information gathered from these studies helps to clarify the nature of the structural requirements of the enzyme's active site.

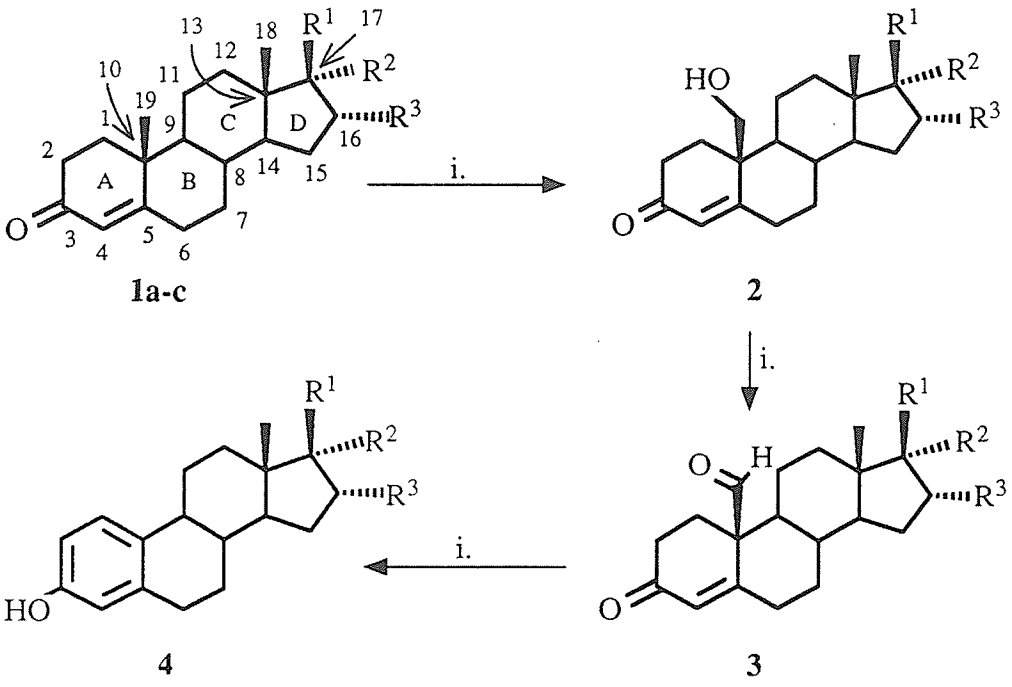
A significant consequence of mechanism-based inhibitors is in the application to drug design. While related means of controlling diseases, such as with affinity labelling agents, can have potential side effects because of their higher chemical reactivity, mechanism-based enzyme inactivators are relatively unreactive compounds. As a consequence, side reactions, i.e. non-specific acylations or alkylations of other biomolecules should be encountered less often. Theoretically, the target enzyme should be the only enzyme to transform the suicide substrate into the reactive species and therefore to react with it covalently. A low partition ratio is of vital importance in drug design, for if the partition ratio is greater than 0, the released activated substrate may react with other proteins or hormones, thus producing undesirable side effects. In this event, the suicide substrate is known as a *metabolically activated inactivator*.[4] On the other hand, the released activated substrate may be hydrolyzed by the aqueous medium or metabolized further to other toxic or non-toxic compounds.

One important class of biological substrates which undergo a multitude of enzyme promoted functional group interconversions are the steroids. Regulation of the enzyme

activity by mechanism-based enzyme inhibitors would allow control of steroid related diseases such as mammary and prostatic cancers by inhibiting the formation of the relevant hormones which exacerbate their growth.

Human mammary carcinoma in women is found to be estrogen dependent in one out of three cases.[5] This finding has stimulated research into ways of regulating the production of estrogen by chemical methods[6,7], thus avoiding surgical removal of the ovaries and adrenal glands. Besides the ovaries and adrenal glands, estrogens are produced in peripheral tissues not affected by surgical removal of the ovaries and adrenal glands, therefore estrogen production is more completely controlled by the inhibition of aromatase. This is particularly important in post-menopausal women where peripheral production is the major estrogen source. The principal enzyme in the conversion of the male sex hormones (androgens) to the female sex hormones (estrogens) is aromatase (estrogen synthetase), a P_{450} monooxygenase enzyme. It would be advantageous to control the aromatase activity since the testosterone/estrogen conversion occurs near the end of the steroid biosynthetic pathway, hence inhibition of the aromatase enzyme would have a minimum effect on other hormonal systems.

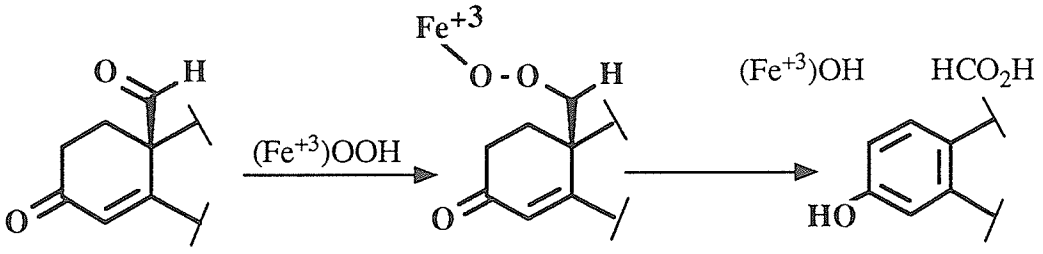
Various facets of the aromatase mechanism for the conversion of the steroid ring A 4-en-3-one system into the aromatic ring have been defined. The presently accepted pathway is outlined in Scheme 2. It is widely acknowledged[8-10] that the aromatization process in ring A begins with two consecutive radical oxidations of the angular C_{19} methyl group which requires two equivalents of O_2 and NADPH. Covey et al[8] have



Scheme 2: Biosynthetic transformation of 4-en-3-one to the aromatic ring.

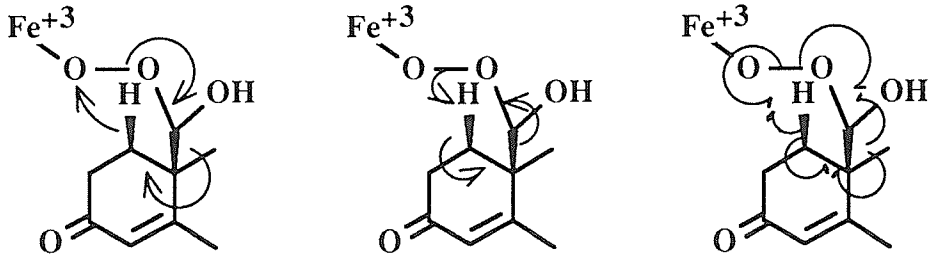
demonstrated that the Pro-R hydrogen is selectively hydroxylated in the second step. However, less is known about the third and final step[8-10]; a third oxidation takes place with the uptake of a third equivalent of O_2 and NADPH.[11] The C_{19} methyl is converted to formic acid and the 1ß-H is lost to the aqueous medium.[12] Removal of the 2ß-H is found to be substrate dependent.[10] Androst-4-ene-3,17-dione-19-al **3c** undergoes highly stereoselective loss of the 2ß-H (11:1), whereas 17ß-hydroxyandrost-4-en-3-one-19-al **3b** losses both the 2α- and 2ß-H in approximately 1:1 ratio. One half of the third equivalent of O_2 consumed is found in the formic acid.[11] Several mechanisms have been advanced for the final step; e.g. 10ß-hydroxy formation[13], hydroxylations at the 2 position[14], 4,5-epoxidation[15], and Bäyer-Villiger type oxygen insertion.[11] Of all proposals, Akhtar's[16] has remained consistent with all known aromatase data and P_{450} mechanistic theory. As shown in Scheme 3, the aldehyde group of **3** undergoes nucleophilic attack by the heme ferric peroxide species. Decomposition of the hydroxyferric peroxide intermediate **4** could follow three different routes (Figure 1) namely, hydride transfer[16] **6**, proton shift[17] **7**, or electron migration[9] **8** to afford the aromatic steroid and formic acid.

Research into aromatase inhibitors centers around derivatives with a functional group at C_{19}; allenic and acetylenic[18], cyanomethyl[19], diazoketone[20], difluromethyl[21], epoxide[22], methylthio[23], 19-thiiranyl[24], and thio.[25] Clinical evaluations of various inhibitors, including the most potent aromatase inhibitor[26,27], 4-hydroxyandrost-4-ene-3,17-dione **9** (Figure 2) showed the most effective inhibitors are those C_{19} steroids which are closely related to the naturally occurring substrates, testosterone **1a** and androst-4-ene-3,17-dione



3 4 5

Scheme 3: Attack of heme ferric peroxide intermediate.



6 7 8

Hydride transfer Proton shift Electron migration

Figure 1: Proposed mechanisms for the decomposition of hydroxy ferric species **4**.

1c. Unlike previous work which centered around substitution of the angular C_{19}, our proposal utilises a cyclopropane ring, bridging C_5 and C_{10}, to act as the latent electrophile (Scheme 4). Hydroxylation of the cyclopropane ring **10** would yield the secondary cyclopropanol **11** which would undergo spontaneous elimination to form the cyclopropanone **12**. This highly reactive intermediate would undergo covalent linkage with a nucleophile at the enzyme's active site **13**. Halogen substituted cyclopropane derivatives can act as Pro-groups.

Part B: Inhibitors of 20α- and 20ß-Hydroxysteroid Dehydrogenase.

A second application of cyclopropanone formation to steroid enzyme inhibition can be in the biotransformation of progesterone to cortisone. In progesterone and cortisone metabolism the 20α-hydroxysteroid dehydrogenase performs an integral role. What purpose the 20ß-hydroxysteroid dehydrogenase metabolites perform[28-30] and the nature of the active site[28,31,32] in both cases are current subjects of research. The 20α-hydroxysteroid dehydrogenase has received more attention because it has been linked to a number of biochemical processes; e.g. enzymatic marker for pre-T and T lymphocytes[33], pregnancy regulation[29,34], and testicular function.[35] Based on the theory of suicide inhibitors, formation of a cyclopropanone at the receptor site can lead to the formation of a covalent bond between the substrate molecule and the enzyme, resulting in irreversible enzyme inhibition. In Scheme 5 enzymatic oxidation of 20α- and 20ß-hydroxy-17,21-cyclopregn-4-en-3-one, **14** and **15** respectively, to the cyclopropanone **16**

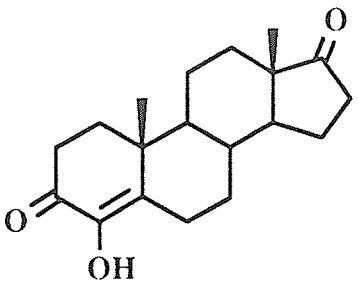


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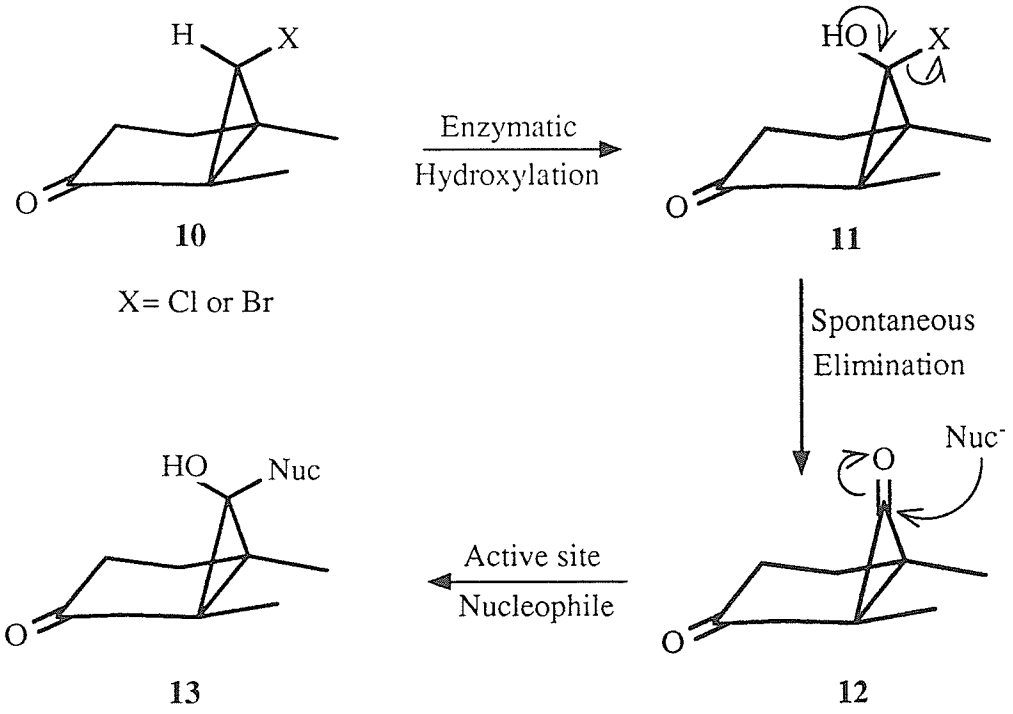
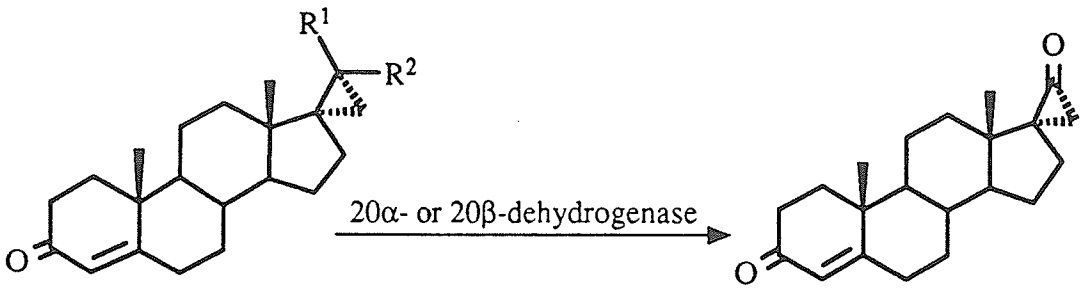
Figure 2: Structure of 4-hydroxyandrost-4-ene-3,17-dione.



Scheme 4: Proposed method of inactivation of aromatase.

would be potentially useful as a means of providing mechanism-based-enzyme inhibitors of both 20α- and 20ß-hydroxysteroid dehydrogenase.



14 R^1=H; R^2=OH

15 R^1=OH; R^2=H

16

Scheme 5: Formation of spirocyclopropanones by 20α- or 20β-dehydrogenase.

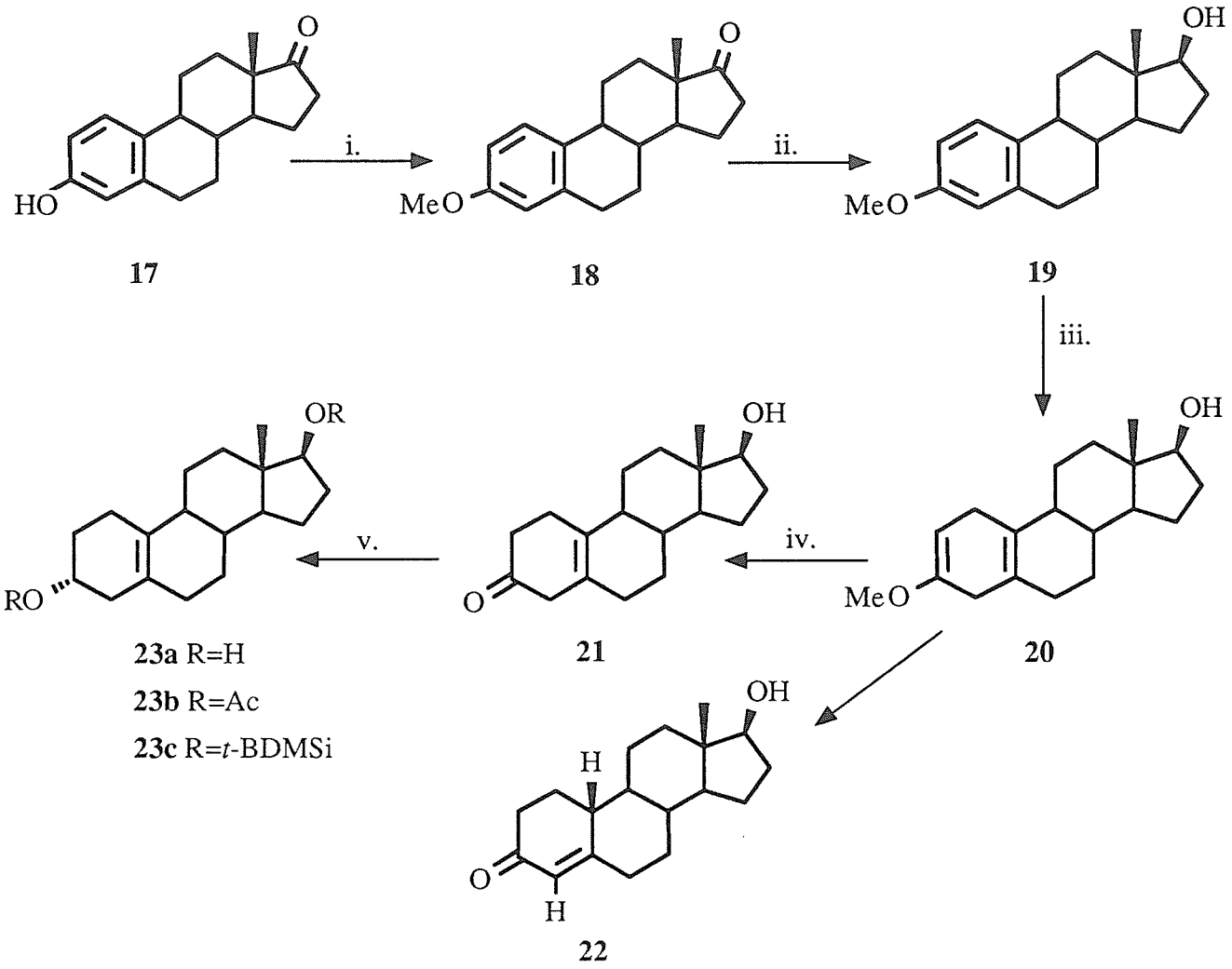
RESULTS AND DISCUSSION

Part A: Synthesis of the 19,19-Dibromo-5ß,19ß-cycloandrostane.

I. Preparation of the Intermediate, 3α,17ß-Dihydroxyestr-5(10)-ene **23a**.

i. Wilds and Nelson procedure.[36]

Preparation of the proposed aromatase inhibitors began with estrone **17** or estradiol 3-methyl ether **19**. In Scheme 6, estrone **17** was converted to the 3-methyl ether **18** by dimethyl sulphate/KOH at 55°C. The ^{1}H N.M.R. spectrum of the product **18** showed the presence of a new singlet at 3.79 ppm (Table 1); the integration was consistent with three protons. The C_{17}-keto group of estrone 3-methyl ether **18** was reduced with $LiAlH_4$ in THF to give **19** in quantitative yield. The reaction gave almost exclusively the 17ß-alcohol **19**. This is not unexpected because attack on the ß face is sterically blocked by the C_{13} methyl group, hence transfer of the hydride would occur more favourably from the α face. The proton spectrum showed a signal at 3.74 ppm, indicative of the presence of the 17α-H. Dissolving metal reduction of estradiol 3-methyl ether **19** with Na in liquid NH_3 yielded 3-methoxy-17ß-hydroxy-1,4-dihydroestra-2,5(10)-diene **20**. Conversion of the enol ether **20** to the ketone **21** was readily effected by warming the enol ether in a weakly acidic solution of methanolic oxalic acid. T.L.C. of the product showed the presence of two compounds. The less polar product **21** melted at 190-195°C (lit. m.p. 199.8-201°C).[36] The ^{1}H N.M.R. spectrum showed an AB pattern at 2.73 ppm indicative of the presence of the isolated C_4 methylene hydrogens; the AB pattern integrated for two protons. The more polar compound, a by-product of the reaction, showed a singlet



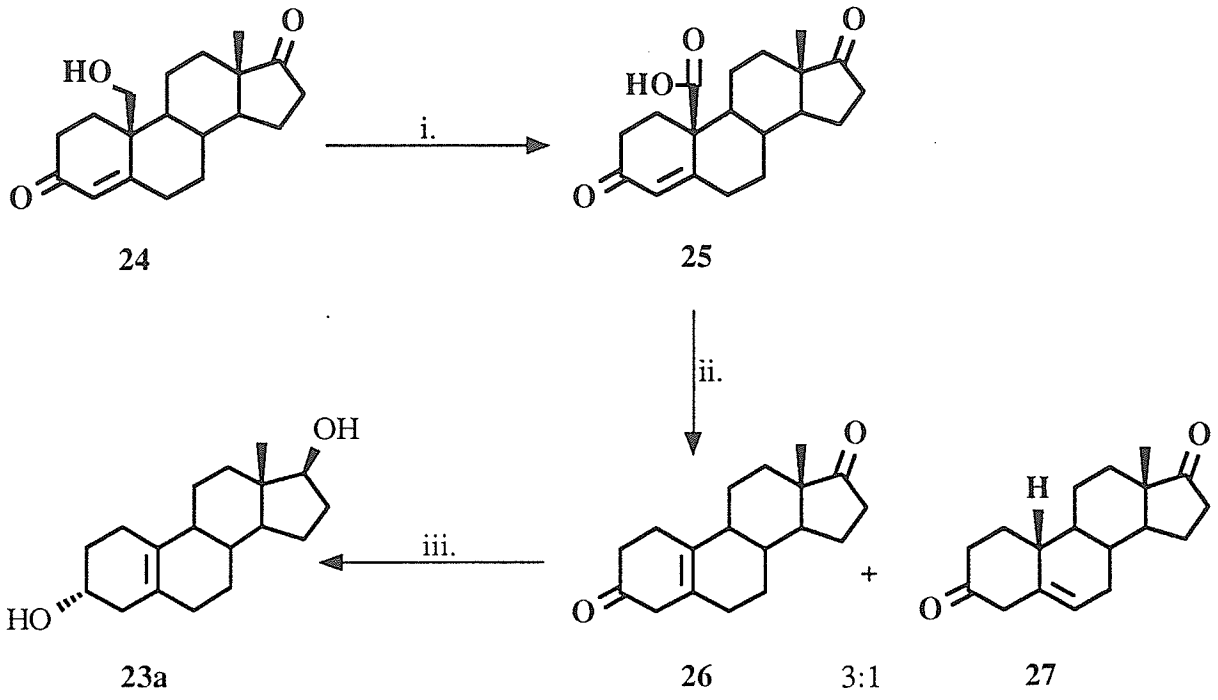
Reagents: i. $(CH_3O)_2SO$, KOH; ii. $LiAlH_4$, THF; iii. Na^O, NH_3, -77°C
iv. $(CO_2H)_2$,MeOH; v. $LiAlH_4$,THF,-77°C.

Scheme 6 : Synthesis of the key intermediate 23 via Birch reduction of estrone.

integrating for one hydrogen at 5.83 ppm, characteristic of an alkenyl proton. Comparison of the proton spectrum of the more polar compound with an authentic spectrum of 17ß-hydroxyestr-4-en-3-one **22** confirmed the structure. Reduction of the 3-keto group in **21** by either $LiAlH_4$ at room temperature[37] or LTBA at -77°C[38b] afforded the 3α-alcohol **23a** in 81% yield. Hartman reported the reduction of the ketone of 17ß-hydroxyestr-5(10)-en-3-one **21**, where he assigned the stereochemistry of the 3-ol as ß.[37] Several years later Levine *et al.* published two papers[38] proving that the 3-ol possessed an α orientation and that Hartman had incorrectly assigned the stereochemistry of the alcohol as ß, thus showing that the 3-ketone is reduced mainly to the 3α-ol.

ii. Kalvoda and Anner procedure.[39]

This method has the advantage of being shorter than the estrogen route, if the starting material, 19-hydroxyandrost-4-ene-3,17-dione **24** is available. In Scheme 7, treatment of **24** with Jone's reagent at room temperature yielded 19-carboxyandrost-4-ene-3,17-dione **25** in good yield. The ^1H N.M.R. spectrum showed a vinylic proton resonance at 5.95 ppm. This was assigned to the C_4 alkenyl proton. The doublet of doublets due to the C_{19} methylene protons at 3.99 ppm in the starting material was absent in the spectrum of the product. The carboxylic acid proton was not observed, perhaps due to proton exchange with trace amounts of acid or water present in the solvent. The C_{13} methyl group resonated at 0.91 ppm. In the ^{13}C N.M.R. spectrum the 3-ketone appeared at 198.95 ppm and the 17-ketone at 220.21 ppm. The C_4 and C_5 alkenyl



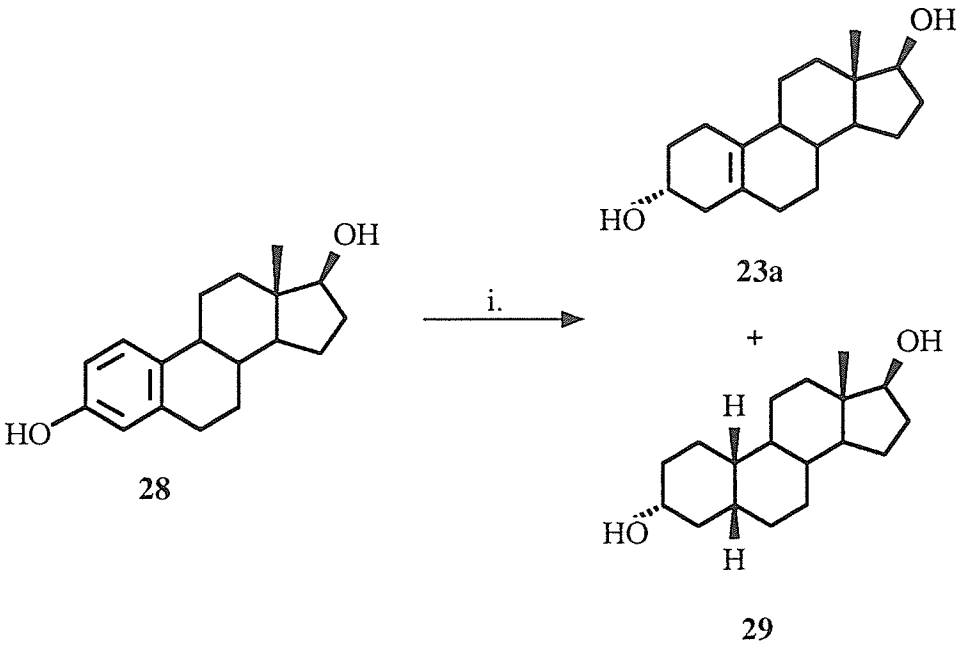
Reagents: i. Jone's Reagent; ii. pyridine, 50°C; iii. $LiAlH_4$,THF,-77°C.

Scheme 7: Synthesis of key intermediate **23** via decarboxylation.

carbons were at 161.96 and 127.12 ppm, respectively, and the acid carbonyl carbon resonated at 175.65 ppm. Decarboxylation of **25** was effected by heating in pyridine which afforded a mixture of estr-5(10)-ene-3,17-dione **26** and estr-5-ene-3,17-dione **27** in a 3:1 ratio.[39] The ^{1}H N.M.R. spectrum of **26** showed the absence of the alkenyl proton and instead an AB pattern (C_4 methylene protons) at 2.80 and 2.69 ppm (J_{AB} 21.0 Hz) was present, which integrated for two protons. The C_{13} methyl groupremained unchanged at 0.90 ppm. The ^{13}C N.M.R. spectrum (Table 2) of **26** was identical with two published spectra of estr-5(10)-ene-3,17-dione.[40a,b] The conversion to the 3α,17ß-diol **23a** was effected by the above mentioned reduction with LTBA or $LiAlH_4$.

iii. Waters and Witkop procedure.[41]

Although not as practical as the two previous procedures in terms of yields and work involved, Witkop's method deserves to be mentioned on the basis of its simplicity. In Scheme 8, 3,17ß-estradiol **28** in ethanol, containing a 4 molar excess of $NaBH_4$, was irradiated with a mercury lamp to yield, upon extensive chromatography, two monomers; 3α,17ß-dihydroxyestr-5(10)-ene **23a** and the A/B cis fused 3α,17ß-dihydroxy-5ß,10ß-estrane **29**. In addition, some polymeric material was isolated, but none of the 3ß-alcohol was detected.



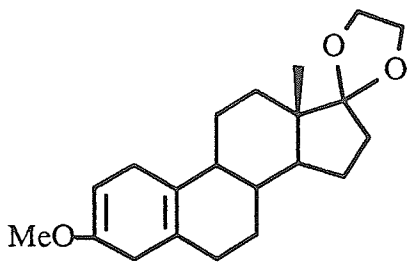
Reagents: i. 4*M* $NaBH_4$,EtOH,Hg lamp.

Scheme 8: Irradiation of 3,17β-estradiol **28.**

II. Review of Dihalocarbene Addition to the 5(10)-Double Bond of Steroids.

The first investigations in the carbene additions to the 5(10)-double bond in steroids was reported by A.J. Birch and co-workers in a series of papers.[42-46] Birch *et al*[42] treated 3-methoxyestra-2,5(10)-diene 17-ethylene ketal **30** with *t*-BuOK/*t*-BuOH (prepared from K and dry *t*-BuOH)/benzene at 0°C followed by the addition of $CHBr_3$ in benzene (Method A) over a 20 minute period (Figure 3). 3-Methoxyestra-3,5(10)-diene 17-ethylene ketal **31** was treated in a similar fashion as follows: resublimed *t*-BuOK in ether, cooled to -20°C, followed by addition of $CHBr_3$ in ether (Method B) over 20 minutes. The crude reaction product from 3-methoxyestra-2,5(10)-diene 17-ketal **30** afforded three fractions, the first fraction gave a "mono-adduct", either **32** or **33** in 41% yield after purification (m.p. 159-161°C); the stereochemistry of addition was not established. The elemental analysis for C and H (bromine was not determined) confirmed the empirical formula for the proposed structure. The second fraction was attributed to a mixture of **32/33** and the bis-dibromocarbene adduct **34**. Attempts at further isolation and purification were not mentioned. The third fraction proved to be a mixture and was identified only as one of the dibromocarbene adducts, namely, **32/33** or **35** (m.p. 155.5-156.5°C) (Figure 3). The crude reaction product from intermediate **31** was isolated and purified to give the dibromocarbene adduct of 1,2-dihydroestrone methyl ether **36** (m.p. 159-161°C) (74% yield).

It was not determined which of the double bonds, the C-2 or the C-5(10), underwent cyclopropanation to give **32** or **33**, nor did Birch make clear which face of ring A



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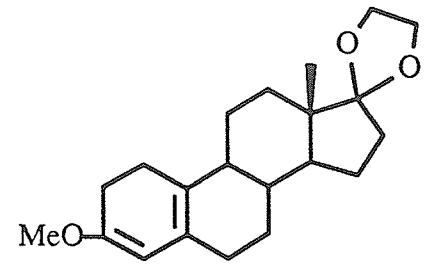

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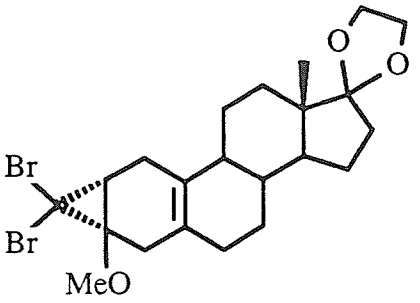

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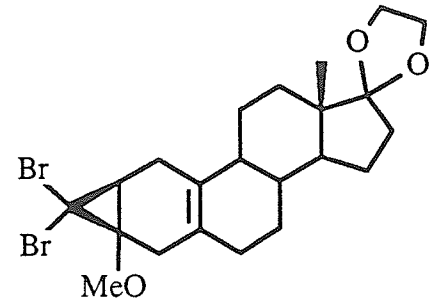

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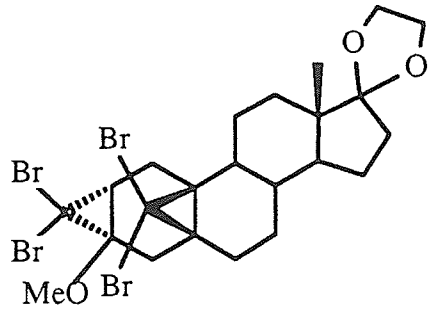

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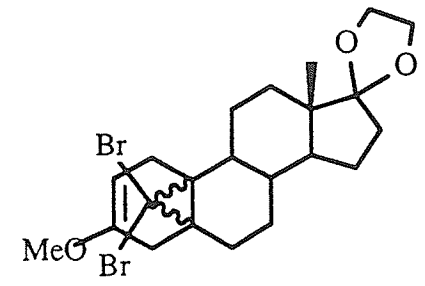

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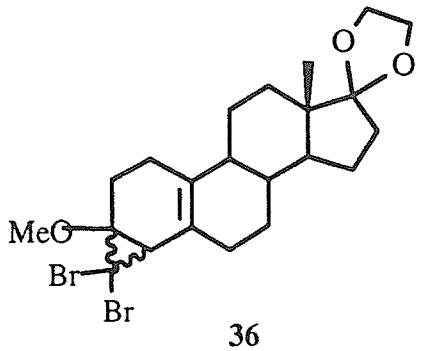

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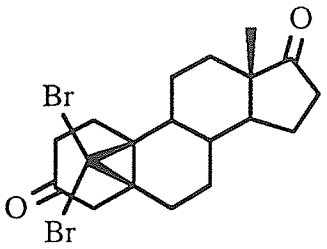
Figure 3: Several dibromocarbene addition products.

underwent attack by dibromocarbene in **30** or **31**. With respect to the question of which double bonds underwent cyclopropanation in **32/33** or **35** and whether α or ß face addition occured, Birch rationalizes the observed regioselectivity of the dibromocarbeneas follows. On the basis of his work with 2,3- and 2,5-dihydroanisole derivatives,[43] Birch stated that the dihalocarbene species reacts mainly "on the double bond carrying the methoxyl group, in accord with the electrophilic reactivity of these reagents..." How is it that the tetrasubstituted 5(10)-double bond possesses a lower electron density relative to the enol ether? The delocalizing effect of the π-system would be expected to lessen the electron density, thereby decreasing the nucleophilicity of the 2,3-double bond. In a subsequent report,[44] treatment of **30** with *t*-BuOK in benzene, cooled to -10°C (Method C), followed by slow addition of excess $CHBr_3$ yielded a mixture of **32/33** and **34**, whereas **34** was previously reported by Birch[42] as only a minor product. The higher yield of **34** in Method C was probably due to the different reaction conditions because **34** can result from further reaction of **32**. In this report the orientation of the 5,19-dibromocyclopropyl ring and 2,3-dibromocyclopropano ring were established as shown in **34**. The 5,19-dibromocyclopropyl ring was concluded to be ß by analogy with the ß-epoxidation of the 5(10)-double bond and reduction of the 5,19-dibromocyclopropyl derivative **37** which afforded the thermodynamically stable 10ß-methyl derivative **38** (Figure 4). It followed for steric reasons that the second dibromocarbene addition was to the α-face of the 2,3-double bond. The stereochemistry of the 2,3-dibromocyclopropano ring was determined by the reduction of **34** with Li/liquid NH_3 to

give 2α-methylandrost-4-ene-3,17-dione **38**. A 2α,3α-cyclopropano ring would give on reduction, a methyl group with the α orientation. However, it was noted by Birch *et al.* that the 2α position is the more stable equatorial configuration, thereby reducing the credibility of the above stereochemical assignment.[44] On the other hand, it is reasonableto assume that if the dibromocarbene species added to the ß face of the 2,3-double bond, it would encounter serious steric hinderance from the 5ß,19ß-dibromocyclopropyl ring. The more favourable situation would have the two dibromocyclopropyl rings trans to each other since this would be the thermodynamically more stable configuration.

In 1966 Birch *et al.*[45] reported the conversion of the normal A ring steroids to the A-homosteroids. In a similar series of reactions to those above, 3-methoxyestra-2,5(10)-diene 17-diethylene ketal **30**, *t*-BuOK, and ether were cooled to -30°C followed by dropwise addition of $CHBr_3$. The reaction mixture gave a combined yield of 75% of three different compounds (Figure 4): Isomer A of **39** (m.p. 154-155°C), Isomer B of **39** (m.p. 180-182°C), and **40** (m.p. 195-196°C). Birch et al. reached the conclusion that Isomer A and Isomer B were the two isomers arising from addition to the top and bottom face of the 2,3-double bond as stated in the following sentence. "The difference is presumably stereochemical and based on direction of addition of the carbene to form the cyclopropane ring."[45] The reactivity of isomers A and B to silver nitrate or silver perchlorate in aqueous acetone yielded the A-homo derivatives. The reaction of Isomer A with aqueous acetone and silver perchlorate at reflux for 30 minutes afforded the



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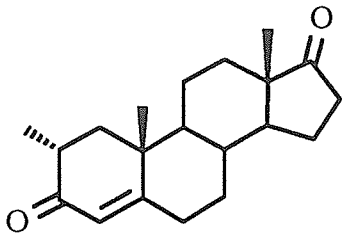

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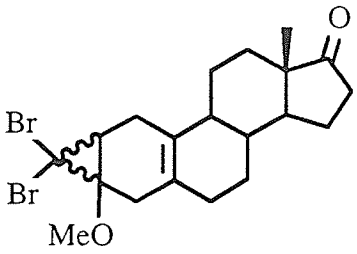

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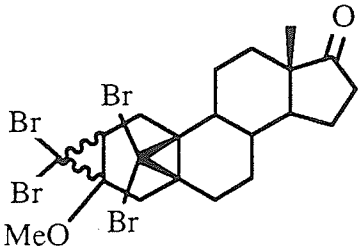

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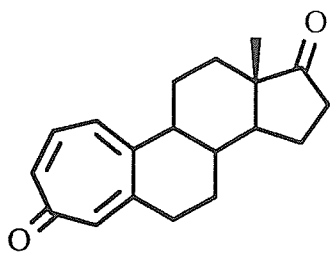
Figure 4: Further examples of dibromocarbene addition products.

tropone **41** (Figure 5). Reaction of Isomer B under the same conditions gave only a marginal amount of **41** after 72 hours. Instead, refluxing Isomer B in pyridine afforded the intermediate **42** which smoothly gave the tropone **41** with silver perchlorate in aqueous acetone or boron trifluoride etherate in formic acid at 0°C. Intermediate **40** possesses the 2,3-cyclopropano ring in the α configuration and reaction with either of thesilver salts gave poor yields as in the case of Isomer B. Nevertheless, refluxing **40** in pyridine gave **43** (m.p. 210-212°C). Reduction of **43** with Li/liquid NH_3 followed by acid hydrolysis of the crude mixture yielded the tropone **44** (m.p. 138-140°C). By comparison of the reaction conditions required for the rearrangement of Isomer B to the tropone **42** and for the conversion of intermediate **40** into the tropone **43**, Isomer B has the 2,3-dibromocyclopropano ring in the α configuration and Isomer A has the 2,3-cyclopropano ring ß.

In their work[44] on the synthesis of non-aromatic steroids Birch and coworkers treated 3,3-dimethoxyestr-5(10)-ene 17-ethylene ketal **45** in *t*-BuOK/ether at -20°C with $CHBr_3$/ether (slow addition). The product was worked up and deketalized to give the 5ß,19ß-(dibromocyclo)estra-3,17-dione **37** in 11% yield. The orientation of the 5(10)-cyclopropyl ring was inferred to be ß based on the previously mentioned rationalisations in which the 19ß-methyl group was formed. Reketalization followed by reduction of the bromines with Li/NH_3 afforded the 5ß,19ß-cycloestra-3,17-dione diethylene ketal **46** (Figure 6).



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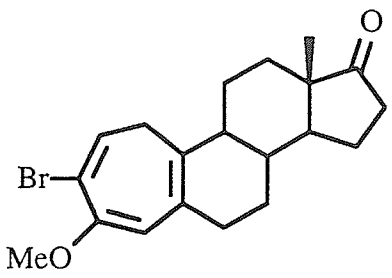

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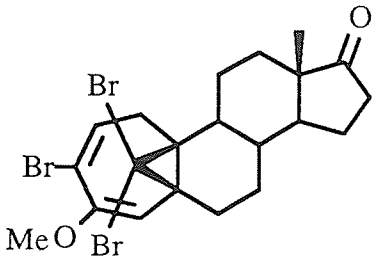

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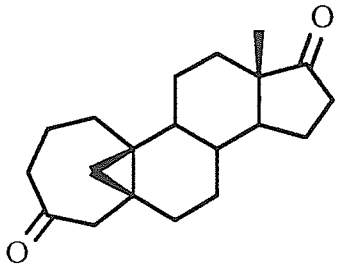

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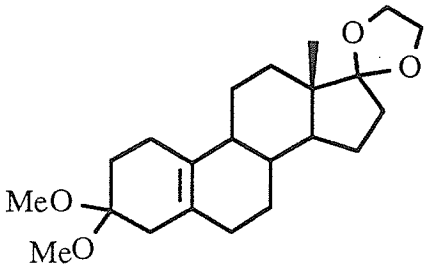

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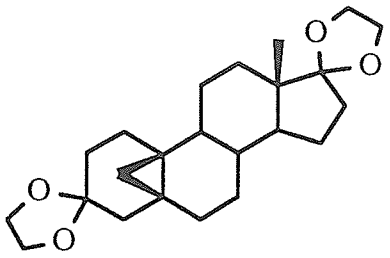
Figure 5: Further examples of dibromocarbene addition products.

In a subsequent paper by Birch *et al.*,[46] addition of the dibromocarbene reagent to the α face of the 5(10)-double bond in 9ß-estr-5(10)-ene-3,17-dione 3,17-diethylene ketal **47** was reported (Figure 6). Treatment of the bisketal **47** (m.p. 128-130°C) with dibromocarbene (K/*t*-BuOH/ether/$CHBr_3$/-28°C) followed by acid hydrolysis gave **48** (m.p. 158-160°C). Reduction of **48** with Li/NH_3 and ring cleavage with dry HCl afforded 9ß-androst-4-ene-3,17-dione **49** (m.p. 125-128°C) and a minor amount of 9ß,10α-androst-4-ene-3,17-dione **50** (m.p. 159-160°C).

Crabbe reported in a review[47] that Cuellar (unpublished work) treated the 5(10)-double bond in **23b** with difluorocarbene generated by thermolytic decomposition of sodium chlorodifluoroacetate in refluxing diglyme to yield a mixture of the α and ß face addition products.

III. Phase Transfer Catalysts.

With the introduction of phase transfer catalysis by several workers[48], heterogeneous reactions became easier and gave higher yields. Templeton et al.[49] formed dibromocarbene under phase transfer catalysis from $CHBr_3$ and NaOH which reacted with the 2,3-double bond of 3,17ß-diacetoxy-5α-androst-2-ene **51** (Figure 6) to give 2α,3α-dibromocyclopropano-3,17ß-diacetoxy-5α-androst-2-ene **52** by α face addition as anticipated.



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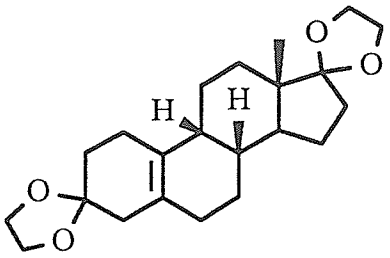

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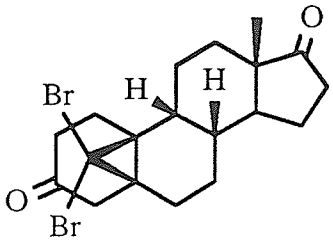

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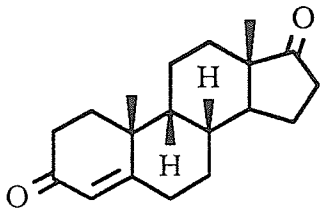

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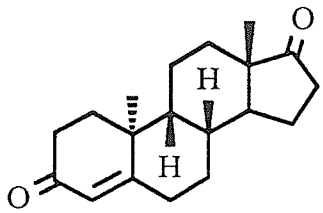

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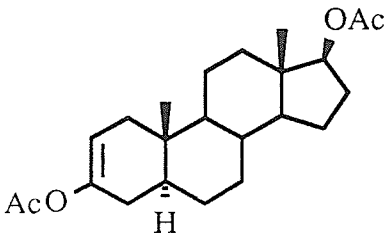

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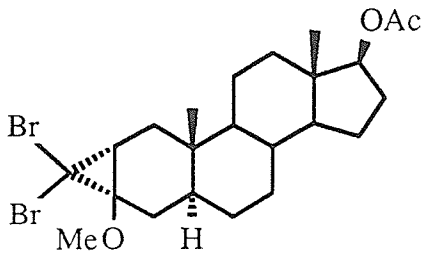

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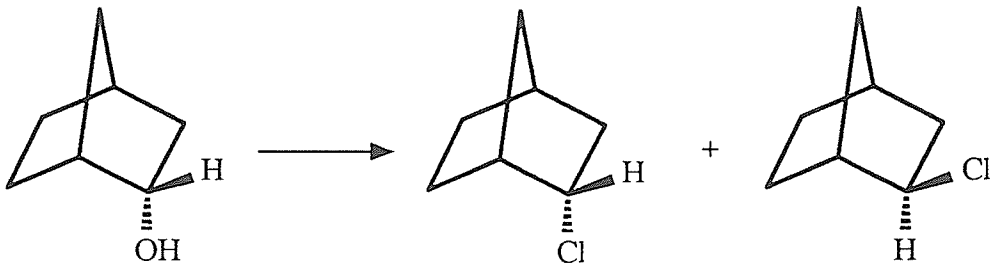
Figure 6: Further examples of dibromocarbene addition products.

IV. Addition of Dihalocarbene to the Steroid 5(10)-Double Bond.

Our initial attempts at addition of a dihalocarbene species to the 5(10)-double bond in 3α,17ß-dihydroxyestr-5(10)-ene **23a**, using phase transfer catalysis, involved no protecting groups for the C_3 and C_{17} hydroxyl groups. The results of these dihalocarbene reactions are summarized in Table 3. In Experiment *1*, reaction of **23a** at 110-120°C with dibromocarbene, produced from 50% aqueous NaOH, cetrimide, and $CHBr_3$, for one hour yielded a crude mixture which on flash chromatography gave several fractions. ^{1}H N.M.R. analysis (Table 4) of the fractions showed two new signals, a singlet at 2.79 ppm and a multiplet at 2.50 ppm. Treatment of **23a** (Experiment *2*) with dibromocarbene generated from 50% aqueous NaOH, cetrimide, $CHBr_3$ at room temperature afforded compound(s) with a higher R_f than the starting material. Flash chromatography yielded two fractions that were again analyzed by ^{1}H N.M.R. The first fraction, *2a* (Table 4), showed the presence of the 3ß-H at 4.03 ppm and the 17α-H at 3.73 ppm. However, there were two new distinguishable signals, a singlet at 2.77 ppm and a sextet at 2.58 ppm. The second fraction, *2b* (Table 4), exhibited a similar spectrum in that the new signals, the singlet (2.77 ppm) and sextet (2.58 ppm) were also present. The 3ß-H was shifted to lower field at 4.06 ppm and 17α-H signal was left unchanged at 3.68 ppm. In both fractions no change in the C_{13} methyl resonance (0.79 ppm) was observed. It can be concluded that the free hydroxyl group(s) have been modified to produce a less polar product (lower R_f). The small downfield shift in the 3ß-H signal indicates a higher degree of deshielding of the proton. Tabushi et al.[50] noted that 2° alcohols can undergo

substitution with halide under carbene conditions. Thus, *endo*-2-norbornyl alcohol **53** (Figure 7) in the presence of $CHCl_3$, NaOH, and a phase transfer catalyst afforded a nearly equal mixture of *exo*- and *endo*-2-chloronorborane, **54** and **55** respectively. Acetylation was therefore chosen to protect the exposed hydroxyl groups. Despite their potential for hydrolysis, acetyl esters have been used successfully in phase transfer catalyzed carbene reactions.[49] A second important function of the 3-acetoxyl group would be to selectively hinder approach to the α-face of the 5(10)-double bond, maximizing ß face addition. The dibromocarbene reaction was repeated on 3α,17ß-diacetoxyestr-5(10)-ene **23b** (Experiment *3*). Dibromocarbene was generated in similar manner and T.L.C. of the reaction products showed a lower R_f than the starting material. However, no deacetylation was evident because the acetoxy methyl groups were both present in the spectrum at 2.03 and 2.05 ppm. As observed in the previous reaction, a singlet at 2.78 and a sextet at 2.59 ppm had been introduced. Repeating the reaction in an air atmosphere (Experiment *4*) gave a product which on work-up afforded a tar. Flash chromatography of the crude tar gave several impure fractions. ^{1}H N.M.R. analysis of the fractions proved inconclusive. The reaction conditions in Experiment *5* were scaled up and the reaction repeated to obtain more product for chromatographic separation. 3α,17ß-Diacetoxyestr-5(10)-ene **23b** was treated with dibromocarbene generated as before from NaOH/cetrimide/$CHBr_3$. After extensive flash chromatography, a non-crystalline product was isolated. ^{1}H N.M.R. showed the presence of the two acetoxy methyls at 2.01 and 2.03 ppm and the C_{13}-methyl was unaltered at 0.81 ppm. The previously noted

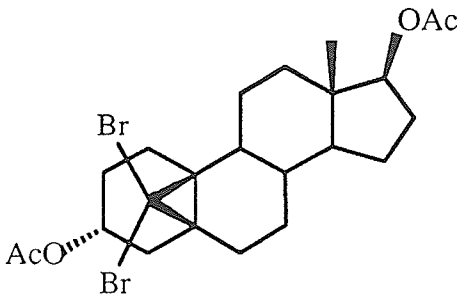


53 **54** **55**

Figure 7: Conversion of 2° alcohols to 2° halides under carbene conditions.

singlet and sextet were observed at 2.76 and 2.57 ppm respectively. The 3ß-H signal was shifted slightly downfield from 4.85 ppm to 5.05 ppm. ^{13}C N.M.R. analysis (Table 5) showed one new quaternary carbon, one less methylene carbon, and one extra methine carbon than required for the anticipated product **56** (Figure 8).

A different approach to generating halocarbenes was utilized using the same starting material (Experiment *6*).[51] Reaction of the starting material with CH_2I_2/CCl_4 and 60% aqueous KOH with tetrabutylammonium hydrogen sulphate ($TBAHSO_4$) as the phase transfer catalyst in glyme at room temperature yielded a more polar product according to T.L.C. The ^1H N.M.R. spectrum showed no signals indicating the presence of the acetoxy protecting groups and there was an absence of the 3ß-H. The 17α-H was still present at 3.66 ppm. An alkenyl proton was observed at 5.82 ppm, indicating that the 5(10)-double bond had shifted or a second double bond had been introduced. Comparison of the ^1H N.M.R. spectrum of an authentic sample of 17ß-hydroxyestr-4-en-3-one **22** showed that they were identical. The removal of the acetyl groups can result from alkali hydrolysis. It is curious that the 3-hydroxy was oxidized preferentially over the 17-hydroxy but this may be due to steric effects. The 5(10)-double bond was shifted into conjugation with the 3-keto group. *t*-Butyldimethylsilyl was then chosen as a protecting group instead of acetyl because it is known to withstand strong alkali and is readily cleaved with fluoride ion under neutral conditions.[52] 3α,17ß-Di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c** was treated with dibromocarbene generated by the earlier method (50% aqueous NaOH, $CHBr_3$, and cetrimide) at room temperature



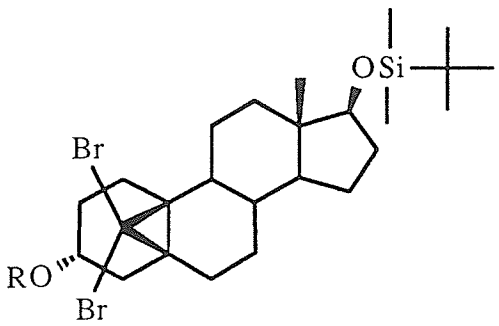
56

Figure 8: Proposed structure for carbene addition product.

(Experiment *7*). The ^{1}H N.M.R. spectrum of the product showed the 3ß-H at 3.96 ppm, a 0.20 ppm shift downfield relative to the starting material whereas the chemical shift of the 17α-H did not change. The characteristic singlet and sextet previously observed were present at 2.75 and 2.54 ppm, respectively. The siloxy protecting groups were not cleaved as indicated by their resonances at 0.01-0.10 ppm for the $Si(CH_3)_2$ and 0.86-0.89 ppm for the $C(CH_3)_3$ groups. Changing the order of addition was carried out to determine whether this would cause any noticeable difference in yields (Experiment *8*), i.e. 3α,17ß-di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c** was dissolved in $CHBr_3$ followed by the addition of cetrimide and 50% aqueous NaOH. Flash chromatography of the crude product afforded 4.2 mg of colourless crystalline material (m.p. 209-211°C). Repeating the reaction on a larger scale was then carried out (Experiment *9*). 3α,17ß-Di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c** was dissolved in $CHBr_3$ followed by the addition of cetrimide and 50% aqueous NaOH. Flash chromatography of the crude reaction material furnished 5.8 mg of colourless crystalline product (m.p. 205-208.5°C). The reaction was repeated again on a larger scale (Experiment *10*) and more product was isolated (m.p. 209.5-212°C). The proton spectrum was similar to the proton spectrum of the product from Experiment 5. The 3ß-H signal was at 4.03 ppm whereas the 17α-H was unchanged at 3.62 ppm. The sextet at 2.55 ppm and the singlet at 2.76 ppm were both present each integrating for one proton, however only one of the *t*-BDMSi protecting groups was accounted for in the spectrum. The shift in the 3α-proton showed that loss of the protecting group had occurred at C_3. The ^{13}C N.M.R. spectrum was also similar

to the spectrum obtained from the product in Experiment *5*; the expected quaternary carbon was observed, along with an extra methine and a methylene signal. This result was not consistent with the anticipated structure **57a** for the carbene addition product (Figure 9). In Experiment *11*, the reaction was repeated and the ^{1}H N.M.R. spectrum of the product **57b** showed the same resonances as observed in the spectrum from Experiment 10: the 3ß-H and 17α-H at 3.96 and 3.62 ppm, respectively, both unchanged; both the sextet and singlet were present at 2.54 and 2.75 ppm, respectively, and integration showed they each represented one proton. Both *t*-BDMSi protecting groups were present as observed from integration of their resonances at the highfield region of the spectrum.

The product isolated from Experiment *10* was reduced with a Zn-Cu couple[53] in EtOH at room temperature (Experiment *12*, see experimental section) to give three different components as detected by T.L.C. The reaction was repeated with zinc dust in EtOH. As only starting material was present after 13 hours, AcOH was added; after 30 minutes three products were observed by T.L.C. (Experiment *13*). Both Experiments *12* and *13* yielded the same three components (T.L.C.) and were therefore combined. Flash chromatography of the combined reaction products afforded the three different compounds. In Table 6, the ^{1}H N.M.R. spectrum of the least polar product **A** showed the 3ß-H had shifted slightly upfield to 3.88 ppm from 4.03 ppm and the 17α-H remained at 3.61 ppm. The sextet present in the starting material was absent and a new singlet at 2.97 ppm was observed as well as a doublet at 2.85 ppm. Both the singlet and doublet



57a R=H

57b R=*t*-BDMSi

Figure 9: Theoretical products from dibromocarbene addition to **23c**.

integrated for one proton each. The proton spectrum of the second product **B** showed the 3ß-H shifted upfield to 3.78 ppm similar to the 3ß-H (3.76 ppm) in 3α,17ß-di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c**. The 17α-H remained unchanged at 3.61 ppm. A singlet integrating for one hydrogen appeared upfield at 3.08 ppm. In the high field region, a triplet and a quartet were observed at 0.41 and 0.30 ppm, respectively, indicative of cyclopropyl hydrogens. The most polar product **C** gave a spectrum different from the other two in that no cyclopropyl resonances were observed and the sextet at 2.50 ppm was present. A singlet (2.90 ppm) and a doublet (2.96 ppm) were observed, both of which integrated for one proton. The 17α-H remained at 3.63 ppm and the 3ß-H came at 3.86 ppm. Jone's oxidation (Experiment *14*) of the product isolated in Experiment *10* yielded one major product. The proton spectrum was devoid of the 3ß and 17α hydrogens. The C_{13} methyl was shifted to lower field (0.94 ppm), consistent with a neighbouring 17-ketone and an AB pattern was present at 2.71 ppm. Pyridinium dichromate (PDC) oxidation in dimethylformamide (DMF) at room temperature (Experiment *15*) of the product obtained in Experiment *10* afforded only starting material based on T.L.C.

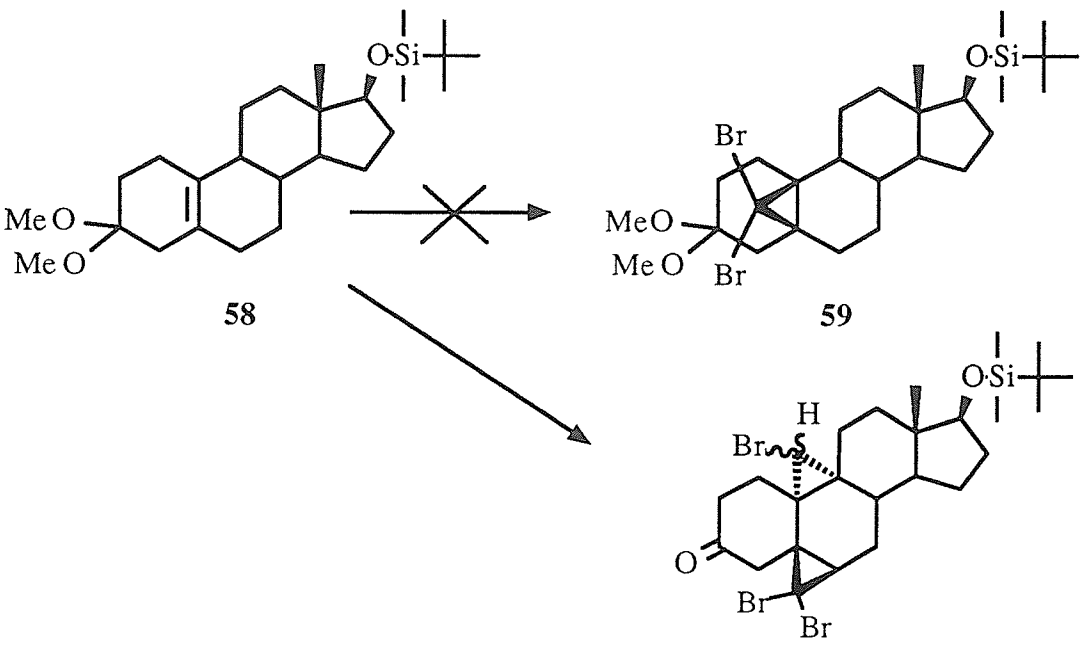
Thermolysis of halogenated salts have been used successfully to generate dihalocarbene for addition of dihalocyclopropane ring to steroid double bonds.[54a] A summary of the reaction conditions employed is given in Table 7. When 3α,17ß-diacetoxyestr-5(10)-ene **23b** was treated with sodium trichloroacetate[54b] in refluxing glyme, b.p. 85°C (Experiment *16*), only unreacted starting material was obtained as

shown by ^{1}H N.M.R. analysis (Table 8). Repeating the reaction (Experiment *17*) with the higher boiling solvent, diglyme (b.p. 162°C), resulted in no reaction. Treatment of the 3α,17ß-diacetoxyestr-5(10)-ene **23b** with dibromocarbene generated from the thermal decomposition of sodium tribromoacetate[54b] in refluxing glyme (Experiment *18*), afforded a more polar compound as observed by its lower R_f value. The ^{1}H N.M.R. spectrum was devoid of both acetoxyl groups and the 3ß-H was absent. The 17α-H was observed at 3.69 ppm and the chemical shift is indicative that indeed the acetyl protecting group has been cleaved. An AB pattern at 2.68 and 2.78 ppm integrating for two hydrogens was assigned to the protons at C_4. The ^{13}C N.M.R. (Table 5) showed the presence of a carbonyl group at 211.31 ppm, characteristic of the non-conjugated keto group at C_3. The ^{1}H and ^{13}C N.M.R. were consistent with 17ß-hydroxyestr-5(10)-en-3-one **21**. It is of interest to note that the effect of the sodium tribromoacetate was to cleave the acetoxyl groups and oxidize the 3-hydroxy to its corresponding ketone. Increasing the amount of sodium tribromoacetate and using diglyme as the solvent also gave an unexpected result (Experiment *19*). Thermolysis of 3α,17ß-diacetoxyestr-5(10)-ene **23b** in refluxing diglyme with sodium tribromoacetate afforded a gum. Flash chromatography of the crude product yielded a colourless fraction. The ^{1}H N.M.R. spectrum of the product showed the acetoxyl protecting groups had been removed. The 3ß-H was conspicuously absent and the 17α-H was shifted upfield by 0.96 ppm to 3.67 ppm. A singlet integrating for one proton at 5.83 ppm corresponding to a vinyl hydrogen was observed, suggesting that

the 5(10)-double bond had shifted. Comparison of the spectrum with an authentic spectrum of 17ß-hydroxyestr-4-en-3-one **22** confirmed the identity of the unknown.

V. Structure of the Unknown Compounds **56**, **57a**, and **57b**.

In similar work from this laboratory,[55] 3,3-dimethoxy-17ß-*t*-butyldimethylsiloxyestr-5(10)-ene **58** (Scheme 9) was treated with dibromocarbene, generated from $CHBr_3$ and 50% aqueous NaOH in the presence of cetyltrimethylammonium bromide, followed by acidic hydrolysis of the ketal. Isolation and purification of the crude product did not yield the anticipated dibromocyclopropyl derivative **59**, but instead a compound tentatively identified as **60** was obtained. The tentative structure for the product rests on the mass spectrometric, ^{1}H and ^{13}C N.M.R. data. The new signals in the proton N.M.R. spectrum of **60** are identical to those observed for the dibromocarbene addition products **23b** and **23c** possessing the acetyl or *t*-butyldimethylsilyl protecting groups described above. With respect to the number of carbon atoms and their types (i.e., quaternary, methine, methylene, and methyl), the ^{13}C N.M.R. spectrum of **60** is consistent with the carbon spectra obtained for the carbene products of **23b** and **23c**. This similarity between the spectra and the fact that the dibromocarbene species was generated by the same procedure as outlined earlier, shows that the products arising from the dibromocarbene addition to **23b**, **23c**, and **58** have identical ring structures. None of the product reported by Birch et al.[44] was obtained.

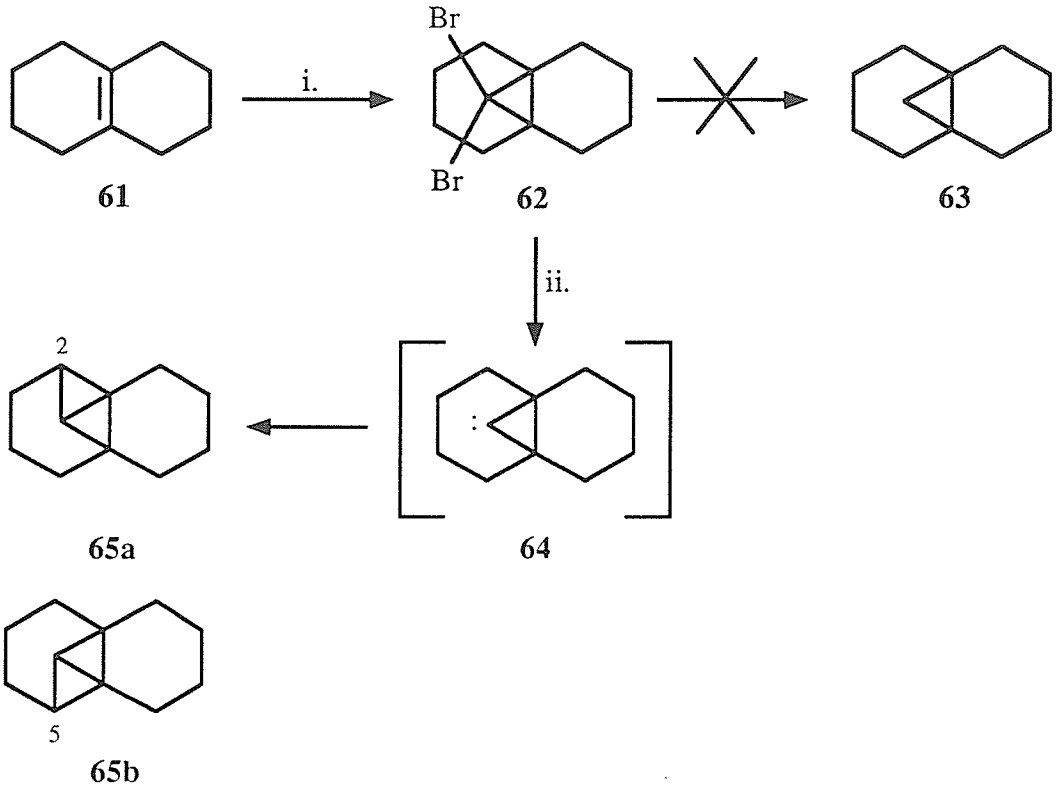


Scheme 9: Theoretical carbene reaction product **59** and actual isolated compound **60**.

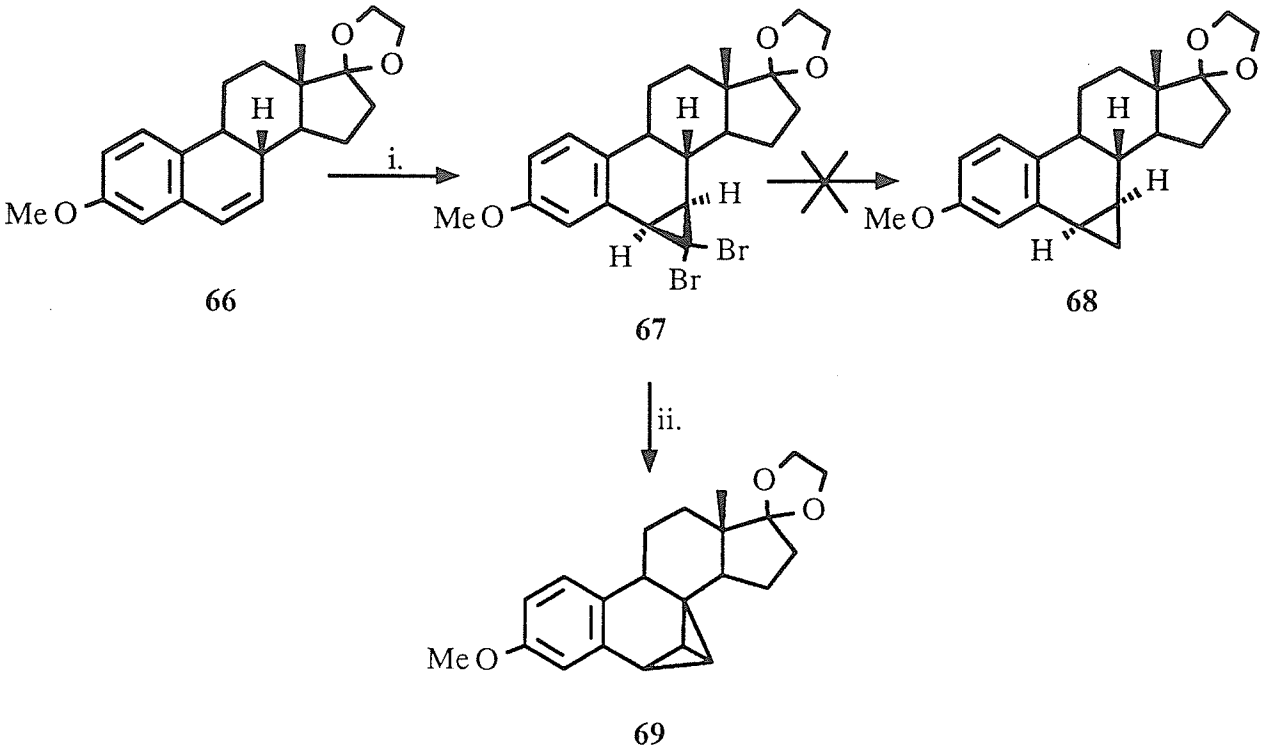
VI. Decomposition/Rearrangement Mechanism.

It was reported[56] that 9,10-octalin **61**, a highly strained bicyclo system, was treated with $CHBr_3$ in a stirred slurry of *t*-BuOK in dry pentane at -10°C (Scheme 10). The product isolated was the expected 11,11-dibromotricyclo-[4.4.1.$0^{1,6}$]-undecane **62**. Removal of the bromines with ethereal methyllithium at -80°C did not yield the expected tricyclo-[4.4.1.$0^{1,6}$]-undecane **63**, but instead the insertion product **65a** was isolated as the major product (78%). It was theorized that reduction of the bromines afforded the carbene intermediate **64** which inserted itself into the neighbouring C_2-H bond. Gas chromatographic analysis claimed this product, **65a**, to be 98% pure, thus implying that the insertion was directed mainly towards a C_2-H bond. Why was none of the C_5-H insertion product **65b** observed? Examination of the structures reveal that they are indeed enantiomers, of one another. However, they are chemically equivalent, thus, spectroscopic (N.M.R., M.S., and I.R.) techniques and gas chromatography would not distinguish between the two isomers.

In another example[57], 3-methoxyestra-1,3,5(10),6-tetraen-3-one 17-ethylene ketal **66** was treated with $PhHgCBr_3$ in refluxing cyclohexane to yield the dibromocyclopropano product **67** (Scheme 11). When reduction of the bromines with ethereal methyllithium at -70°C was carried out, the product isolated was not the anticipated cyclopropano steroid **68**, instead the insertion product **69** was obtained in 56% yield. The remaining products were attributed to sterically non-homogeneous carbene-solvent insertion products.



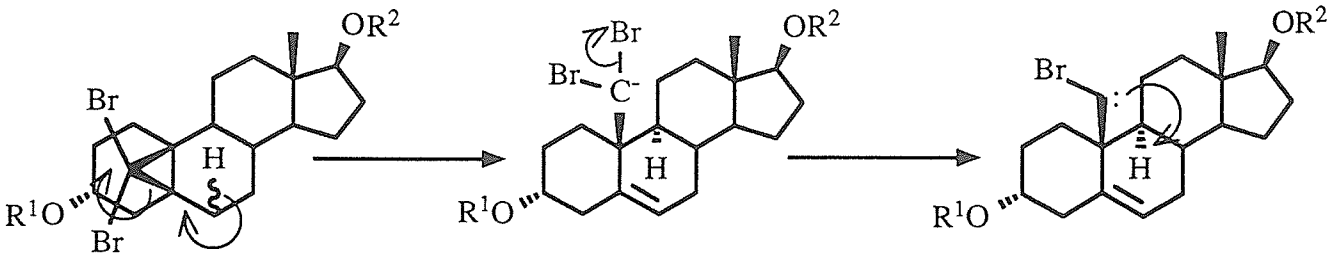
Reagents: i. $CHBr_3$,*t*-BuOK, pentane,-10°C; ii. CH_3Li, ether,-80°C.
Scheme 10: Synthesis of novel carbene insertion product.



Reagents: i. $PhHgCBr_3$, cyclohexane, reflux; ii. CH_3Li, ether, -70 °C.

Scheme 11: Formation of the carbene insertion product **69**.

Based on these examples of carbene insertion reactions, a rationalization for the observed products is advanced. Formation of the dicyclopropyl steroid begins with the 5ß,19ß-dibromocyclopropylsteroids **56**, **57a**, and/or **57b**. The highly strained bridgehead 5,19-dibromocyclopropyl ring undergoes opening by breaking either the C_5-C_{19} bond with simultaneous loss of either 4ß- or 6ß-axial protons (Scheme 12a) or the C_{10}-C_{19} bond with a concomitant loss of either the 1α- or 9α-axial protons (Scheme 12b). The result would be a total of four possible intermediates of which two can be rejected on the grounds that the double bond migrated to the A ring. In Scheme 12a, loss of bromide **70** from the intermediate **71** would give a carbene species unable to undergo intramolecular insertion into the 9α-H bond and produce the product isolated. In Scheme 12b, the C_{10}-C_{19} bond undergoes cleavage along with simultaneous loss of the C_9 proton and the transitory intermediate **72** is obtained. Elimination of bromide from **72**, followed by insertion of the newly formed carbene into the C_6-H axial bond gives **73** which would yield the intermediate **74**. Addition of the second dibromocarbene would take place from approach to the ß-face of the 5-alkene. The final product **75** has the required orientation, however the regiochemistry of the two cyclopropyl rings is incorrect. An alternative route is by addition of the initial dibromocarbene to the bottom face of the 5(10)-double bond to give the 5α,19α-dibromocyclopropyl derivatives **76**, **77a**, and/or **77b**. The cyclopropyl ring can undergo opening via the C_5-C_{19} or C_{10}-C_{19} bonds as shown in Scheme 12c and Scheme 12d respectively. In Scheme 12c, rupture of the C_5-C_{19} bond and loss of a C_8 proton would result in the formation of the negatively charged species **78**. **78** undergoes

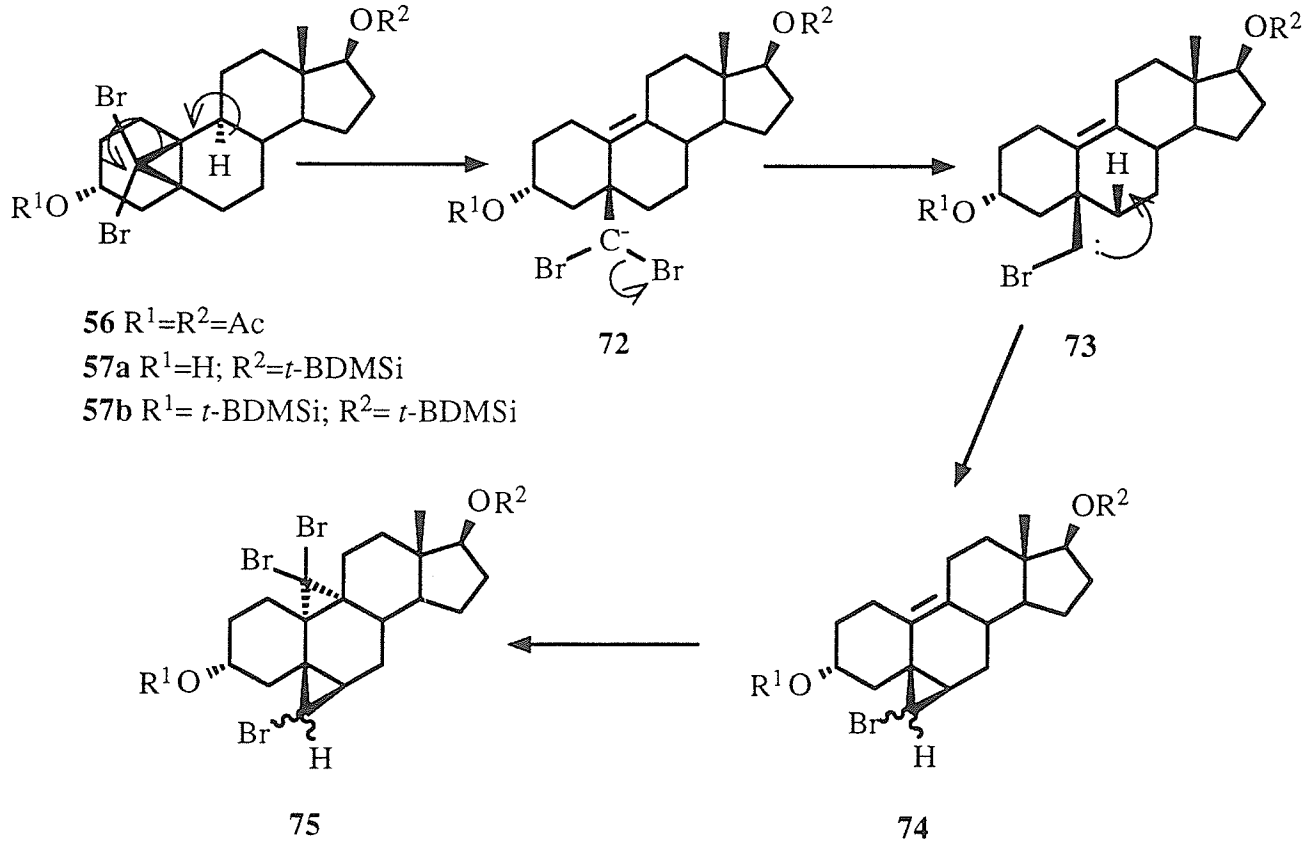


56 $R^1=R^2=COCH_3$ **70** **71**

57a $R^1=H$; $R^2=t$-BDMSi

57b $R^1=t$-BDMSi; $R^2=t$-BDMSi

Scheme 12a: Improbable rearrangement via carbene insertion into the 9α-H bond.



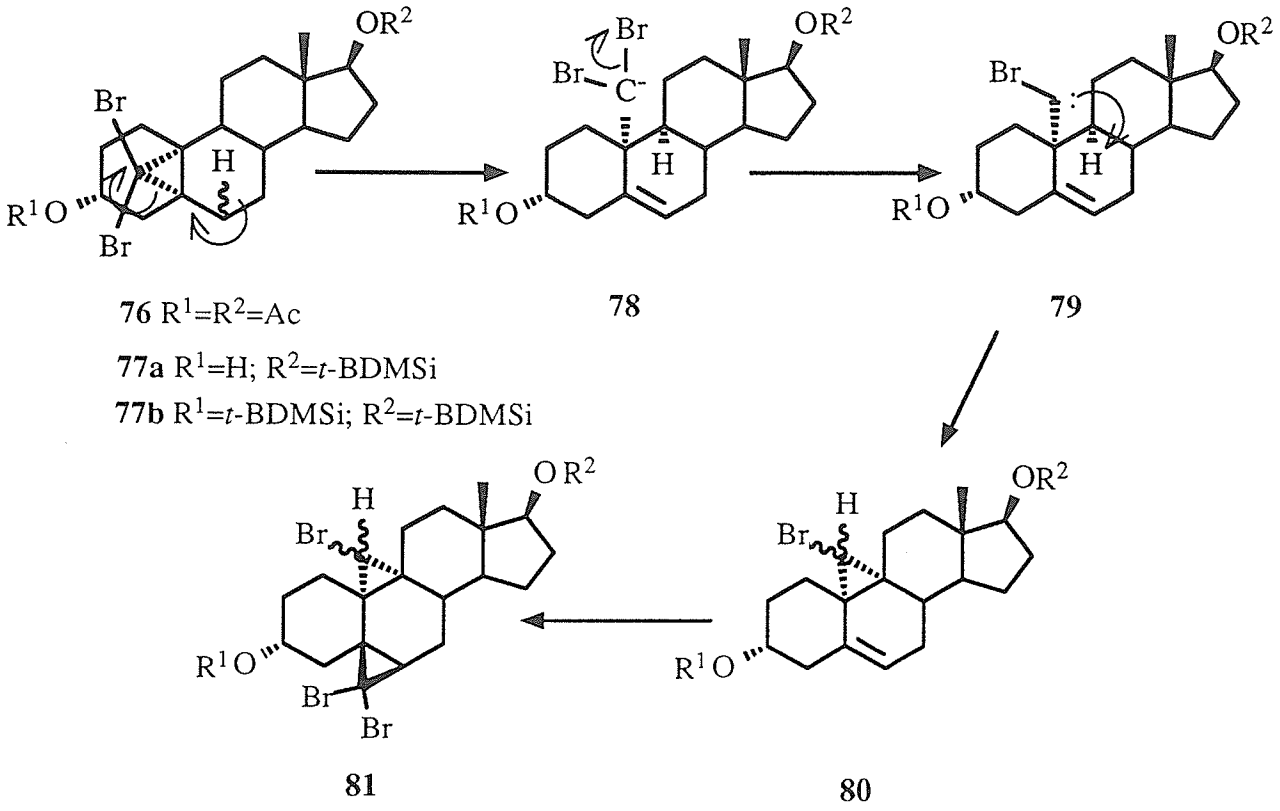
56 $R^1=R^2=Ac$ **72** **73**

57a $R^1=H$; $R^2=t$-BDMSi

57b $R^1=t$-BDMSi; $R^2=t$-BDMSi

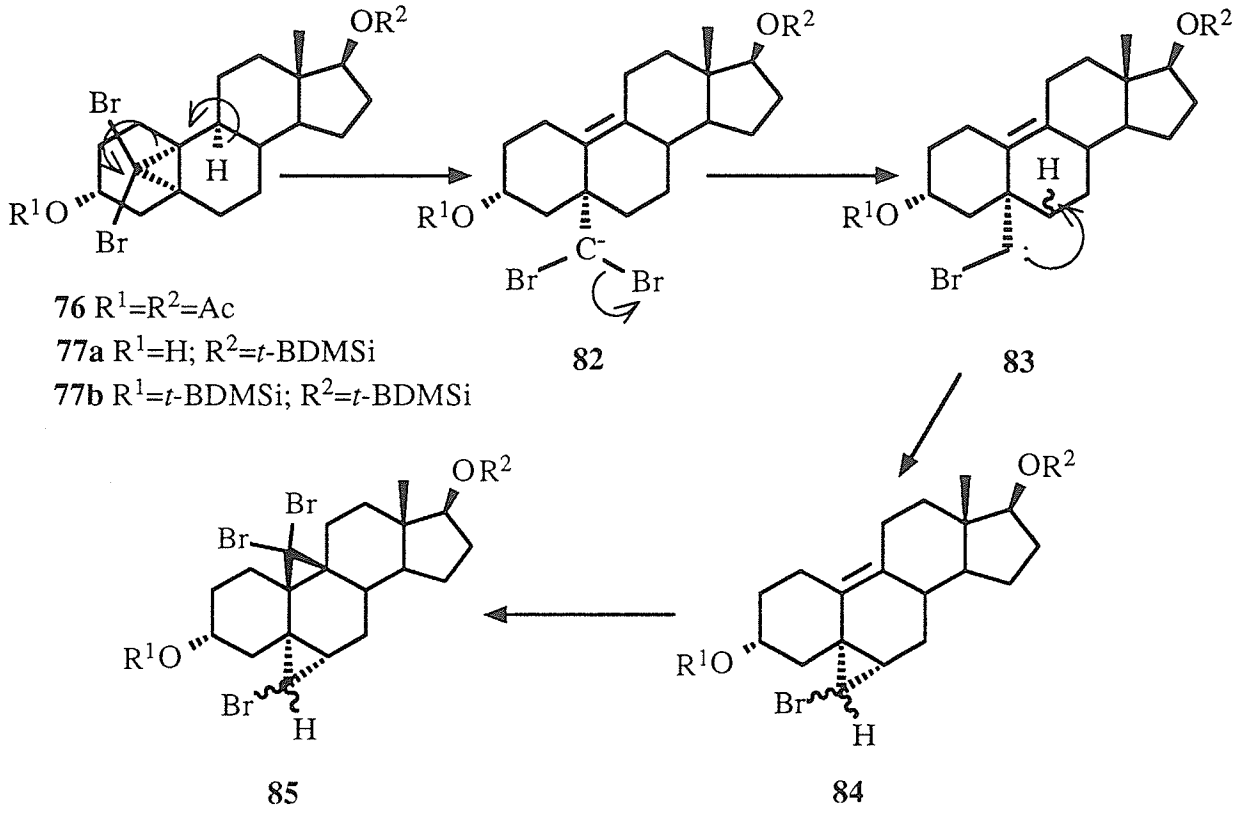
75 **74**

Scheme 12b: Rearrangement pathway via cleavage of the C_{10}-C_{19} bond.



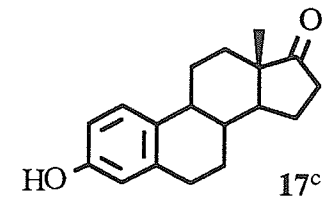
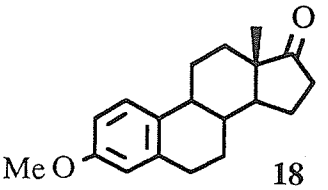
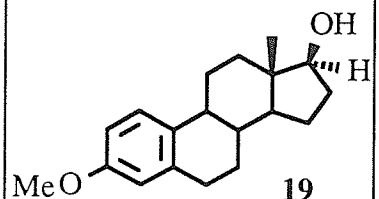
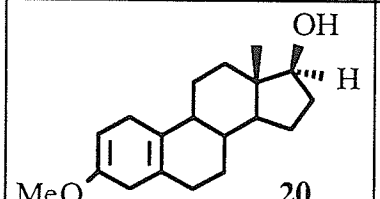
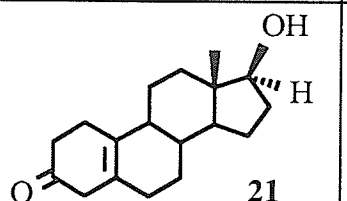
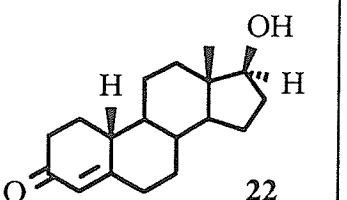
Scheme 12c: Rearrangement pathway via cleavage of the C_5-C_{19} bond.

loss of bromide ion to give the carbene intermediate, **79**, which inserts itself into the C_9-H bond **80**. Formation of the 5,6-cyclopropano ring would occur by addition of the dibromocarbene species to the ß-face of the 5-alkene **81**, a known ß addition[58a,h] which is augmented by the steric effect of the 9α,19α-bromocyclopropyl ring. The final structure is consistent with the isolated product; both the 9,19-cyclopropyl and the 5,6-cyclopropano rings incorporate the required regio- and stereochemistry. Scheme 12d affords a product, **85**, in which the structure possesses both the incorrect regio- and stereochemistry. If Scheme 12c were the route by which the product **81** was formed, then attack of the dibromocarbene species to the 5(10)-double bond must be α, a conclusion which is in contradiction with the literature.[42-46] As mentioned previously, Birch et al. claimed to have obtained the 5ß,19ß-dibromocyclopropyl derivative. Repeating the experiment did not give the 5ß,19ß-dibromocyclopropyl derivative.[55] It should be mentioned that the carbene species **73**, **79**, and **83** can theoretically undergo insertion into several other C-H bonds, for example C_1-H, C_2-H, or C_4-H. These can be ruled out as possible pathways on the basis that the products resulting from these alternative insertions lack the required number of cyclopropyl rings and the types of carbons that should be present in the structure as indicated by the ^{13}C N.M.R. data.



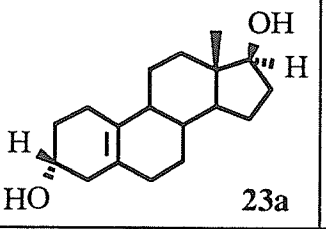
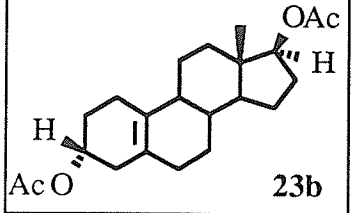
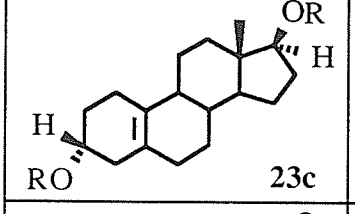
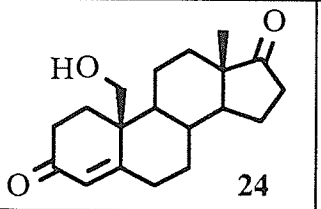
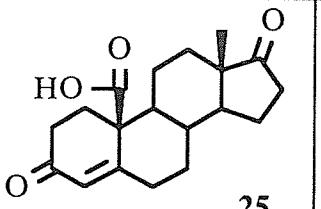
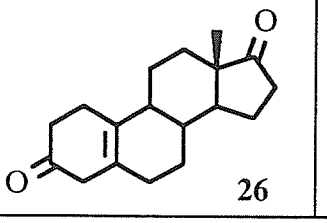
Scheme 12d: Rearrangement pathway via cleavage of the C_{10}-C_{19} bond.

Table 1: Compilation of ^{1}H N.M.R. data of estrane starting materials and intermediates.[a,b]

Steroid	3β-H	17α-H	C_{13}-CH_3	Other
 **17**[c]			0.82,s	HO-: 8.99,s C_1-H: 7.04,d (*J* 8.4) C_2-H: 6.51,dd (*J* 2.6, 8.4 Hz) C_4-H: 6.45,d (*J* 2.5 Hz)
 **18**			0.92,s	$C\underline{H_3}O$-: 3.79,s C_1-H: 7.21,d (*J* 8.5 Hz) C_2-H: 6.73,dd (*J* 2.8, 8.6 Hz) C_4-H: 6.65,d (*J* 2.7 Hz)
 **19**		3.74,t	0.79,s	$C\underline{H_3}O$-: 3.78,s C_1-H: 7.21,d (*J* 8.6 Hz) C_2-H: 6.71,dd (*J* 2.8, 8.6 Hz) C_4-H: 6.63,d (*J* 2.7 Hz)
 **20**		3.67,t (*J* 8.5 Hz)	0.81,s	$C\underline{H_3}O$-: 3.49,s C_2-H: 5.83,s
 **21**		3.69,t (*J* 8.4 Hz)	0.77,s	C_4-H_2: 2.68, 2.78, dd (J_{AB} 21 Hz)
 **22**		3.67,t (*J* 8.5 Hz)	0.81,s	C_4-H: 5.83,s

[a]For solutions in $CDCl_3$ (TMS internal standard) recorded on a Bruker AM300 instrument.
[b]Abbreviations used s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublets, sxt=sextet, m=multiplet, and bm=broad multiplet. [c]in DMSO-d_6.

Table 1: continuation...

Steroid[a]	3β-H	17α-H	C_{13}-CH_3	Other
 **23a**	3.83,bm	3.68,t (J 8.3 Hz)	0.76,s	
 **23b**	4.85,m	4.63,t (J 7.7 Hz)	0.81,s	$C\underline{H_3}CO$-: 2.04,s
 **23c**	3.76,m	3.69,t (J 8.2 Hz)	0.73,s	$Si(C\underline{H_3})_2$: 0.007,s 0.015,s $Si(C\underline{H_3})_2$: 0.069,s 0.070,s $SiC(C\underline{H_3})_3$ (2x): 0.88,s 0.90,s
 **24**			0.91,s	C_{19}-H_2: 3.92,4.06,dd (J_{AB} 8.2 Hz) C_4-H: 5.93,s
 **25**			0.91,s	C_4-H: 5.95,s
 **26**			0.90,s	C_4-H_2: 2.69, 2.80,dd (J_{AB} 21 Hz)

[a] R=*t*-BDMSi.

Table 2: ^{13}C N.M.R. shifts for estrane starting materials.[a]

Steroid	**17**[b]	**17**[c]	**18**	**18**[c]	**19**	**19**[60a,b]	**20**	**21**
Carbon								
1	125.89	126.9	126.29	127.3	126.28	126.1	35.50	25.12
2	112.65	113.5	111.55	112.5	111.44	111.2	124.57	39.08
3	154.86	155.8	157.56	158.9	157.41	157.2	199.86	211.28
4	114.81	115.9	113.87	114.7	113.80	113.6	36.43	44.65
5	136.95	138.2	137.70	138.4	137.93	137.7	166.57	126.40
6	31.26	30.2	29.67	30.3	29.82	29.7	30.71	39.10
7	26.02	27.4	26.57	27.3	27.26	27.1	26.16	27.45
8	37.87	39.3	38.40	39.4	38.87	38.7	40.52	39.10
9	43.33	45.0	43.99	45.0	43.96	43.8	46.17	46.17
10	129.76	131.9	132.00	133.2	132.60	132.5	135.97	131.01
11	25.45	26.4	25.95	26.6	26.33	26.2	26.62	26.44
12	28.93	32.5	31.61	32.4	36.74	36.7	36.52	36.98
13	47.21	48.3	48.00	48.3	43.27	43.2	43.03	43.56
14	49.48	51.1	50.43	51.1	50.06	49.9	49.76	49.69
15	21.03	22.2	21.60	22.0	23.15	23.1	23.22	23.00
16	35.23	35.9	35.87	35.9	30.62	30.4	30.71	30.70
17	219.44	219.3	220.74	219.1	81.90	81.6	81.71	81.48
18	13.42	13.9	13.87	13.8	11.06	11.1	11.29	11.29
CH_3O-			55.21	55.3	55.20	55.0	50.87	

[a]For solutions in $CDCl_3$ (TMS internal standard) recorded on a Bruker AM300 instrument. [b]in DMSO-d_6. [c]in dioxane.[59]

Table 2: continuation...

Steroid	**22**	**22**[d]	**23a**	**23b**	**23c**	**24**	**24**[e]	**25**
Carbon								
1	26.61	27.0	26.65	26.38	27.25	33.40	33.6	33.71
2	36.52	36.6	32.47	28.62	33.00	34.81	35.0	34.77
3	199.86	198.6	67.98	70.91	68.88	199.81	199.6	198.95
4	124.56	124.8	40.21	37.27	40.80	126.90	127.3	127.12
5	166.59	166.2	125.89	125.63	126.42	166.40	165.5	161.86
6	35.49	35.6	30.93	30.77	31.10	33.40	33.6	32.56
7	30.45	31.3	25.19	25.00	25.19	31.64	31.9	31.36
8	40.51	41.0	39.12	38.78	39.18	35.84	36.1	35.55
9	49.60	49.2	46.56	46.36	46.79	54.00	54.3	53.68
10	42.61	42.9	129.78	129.77	129.70	43.81	43.9	50.56
11	26.15	26.6	26.72	26.56	26.67	20.85	21.0	21.98
12	36.43	37.1	37.12	36.22	37.58	30.89	31.0	29.97
13	43.03	43.4	43.62	43.24	43.97	47.58	47.7	47.60
14	49.76	48.9	49.85	49.56	49.46	51.21	51.5	50.93
15	23.21	23.6	23.08	23.16	23.19	21.67	21.8	21.64
16	30.70	30.7	30.75	27.68	30.90	35.68	35.8	35.71
17	81.69	81.4	81.97	82.80	81.80	220.21	220.0	220.21
18	11.07	11.4	11.35	12.33	11.64	13.82	13.9	13.90
19						65.82	66.1	175.5

[d]in dioxane.[61] [e]in $CDCl_3$/DMSO-d_6.[40]

Table 2: continuation...

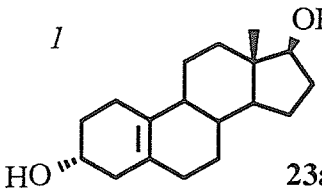
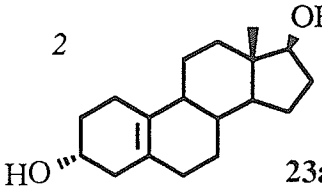
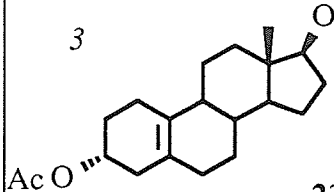
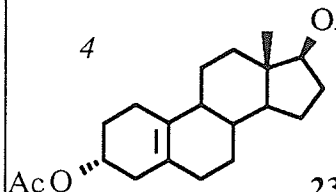
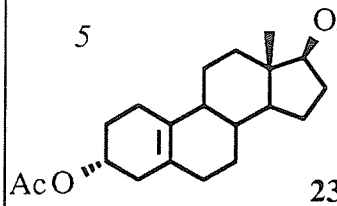
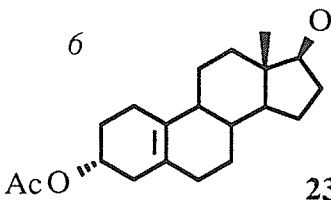
Steroid	22	22	23a	23b	23c	24	24	25
Carbon								
3α-$\underline{C}OCH_3$				171.22				
3α-$CO\underline{C}H_3$				21.50[1]				
17ß-$\underline{C}OCH_3$				170.81				
17ß-$CO\underline{C}H_3$				21.23[1]				
3α-$Si(\underline{C}H_3)_2$					-4.50			
3α-$Si\underline{C}(CH_3)_3$					18.29			
3α-$SiC(\underline{C}H_3)_3$					25.99			
17ß-$Si(\underline{C}H_3)_2$					(-4.45 & -4.77)			
17ß-$Si\underline{C}(CH_3)_3$					18.13			
17ß-$SiC(\underline{C}H_3)_3$					25.90			

[1] values within a column can be interchanged.

Table 2: continuation...

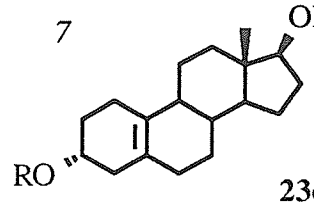
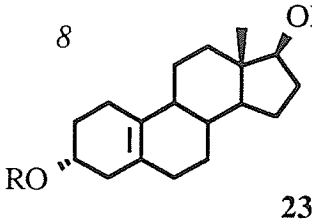
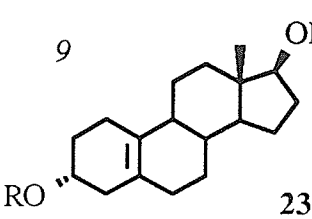
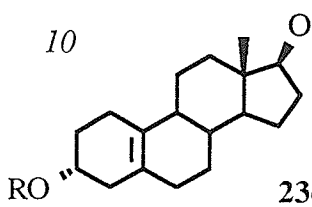
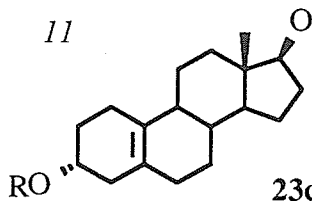
Steroid	**26**	**26**^{40a}	**26**^{40b}
Carbon			
1	24.73	25.0	24.9
2	39.00	39.1	39.0
3	210.82	210.4	210.5
4	44.59	44.7	44.6
5	126.65	127.0	126.8
6	31.82	32.2	32.0
7	27.41	27.7	27.5
8	38.63	38.9	38.8
9	46.17	46.5	46.3
10	130.67	130.9	130.8
11	25.72	26.0	25.9
12	30.56	30.8	30.7
13	48.22	48.3	48.3
14	50.03	50.4	50.3
15	21.43	21.6	21.5
16	35.83	35.9	35.8
17	220.72	220.1	220.1
18	14.06	14.1	14.0
19			

Table 3: Summary of various dibromocarbene reactions and conditions.

Experiment/Steroid	Reagents [a]		°C	Time	Comments
1  **23a**	cetrimide $CHBr_3$ 50% NaOH	0.46 25.3 0.8 ml	110-120	1 hr.	-argon atmosphere -two major spots with greater R_f.
2  **23a**	cetrimide $CHBr_3$ 50% NaOH	0.30 25.3 0.8 ml	r.t.	3.5 hrs.	-argon atmosphere -two major spots with greater R_f.
3  **23b**	cetrimide $CHBr_3$ 50% NaOH	0.45 25.0 0.8 ml	r.t.	2 hrs.	-argon atmosphere -two major spots with greater R_f.
4  **23b**	cetrimide $CHBr_3$ 50% NaOH	0.29 22.3 0.8 ml	r.t.	3 hrs.	-air
5  **23b**	cetrimide $CHBr_3$ 50% NaOH	0.24 24.0 5 ml	r.t.	4 hrs.	-argon atmosphere -product (120 mg)
6  **23b**	$TBAHSO_4$ CCl_4 60% KOH glyme	0.47 1 µl 1 ml 1 ml	r.t.	40 min.	-argon atmosphere -product (8 mg)

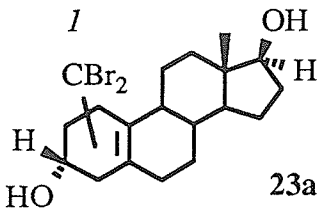
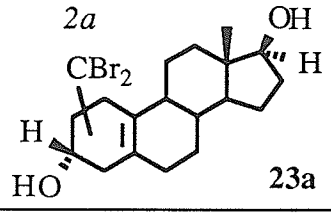
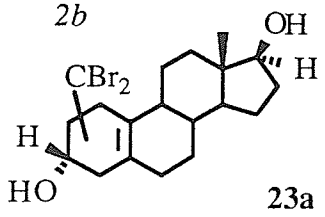
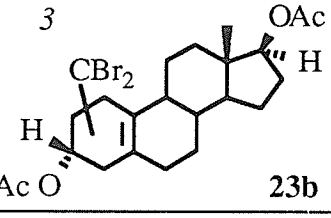
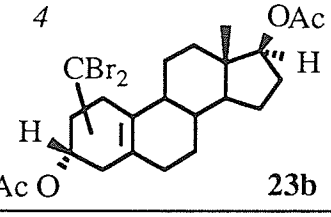
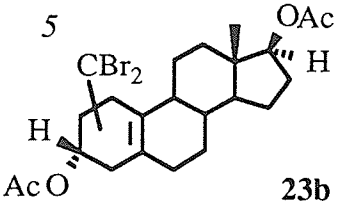
[a]mol ratio.

Table 3: continuation...

Experiment/Steroid[a]	Reagents[b]		°C	Time	Comments
7  **23c**	cetrimide $CHBr_3$ 50% NaOH ether	1.44 170 2 ml 2 ml	r.t.	2.5 hrs.	-argon atmosphere.
8  **23c**	cetrimide $CHBr_3$ 50% NaOH	0.64 133 2 ml	r.t.	7 hrs.	-argon atmosphere. -product (4.2 mg). -m.p. 209-211°C.
9  **23c**	cetrimide $CHBr_3$ 50% NaOH	0.30 65 1 ml	r.t.	7 hrs.	-argon atmosphere. -product (5.8 mg). -m.p. 205-208.5°C.
10  **23c**	cetrimide $CHBr_3$ 50% NaOH	0.49 77 5 ml	r.t.	12 hrs.	-argon atmosphere. -product (60 mg). -m.p. 209.5-212°C.
11  **23c**	cetrimide $CHBr_3$ 50% NaOH	0.45 72 2 ml	r.t.	5 hrs.	-argon atmosphere. -product (76 mg).

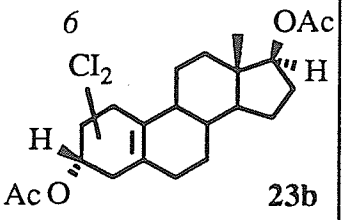
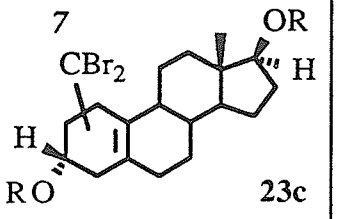
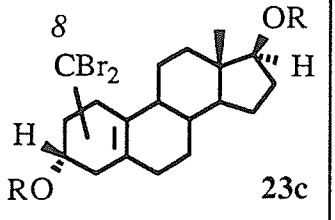
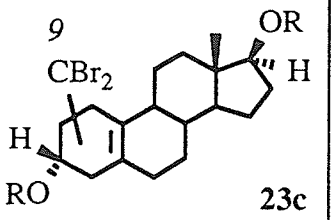
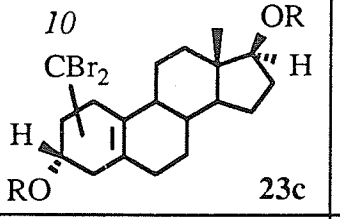
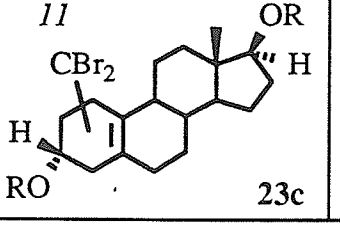
[a]R=*t*-BDMSi. [b]mol ratio.

Table 4: ^{1}H N.M.R. shifts of dibromocarbene reaction products.[a,b]

Experiment/Steroid	3β-H	17α-H	C_{13}-CH_3	Other
1  **23a**	4.34,m	3.73,t	0.79,s	2.79,s; 2.58,m
2a  **23a**	4.03,m	3.73,t (*J* 7.7 Hz)	0.79,s	2.77,s; 2.58,sxt
2b  **23a**	3.82,m	3.68,t (*J* 8.5 Hz)	0.79,s	2.77,s; 2.58,sxt
3  **23b**	5.07,bm	4.66,t (*J* 7.3 Hz)	0.84,s	$C\underline{H_3}CO$- (2x): 2.03,s 2.05,s 2.78,s; 2.59,sxt
4  **23b**	——	——	——	-spectrum proved inconclusive.
5  **23b**	5.03,m	4.63,t (*J* 7.4 Hz)	0.81,s	$C\underline{H_3}CO$- (2x): 2.01,s 2.03,s 2.76,s; 2.57,sxt

[a]For solutions in $CDCl_3$ (TMS internal standard) recorded on a Bruker AM300 instrument. [b]The abbreviations used s=singlet, d=doublet, t=triplet, q=quartet, sxt=sextet, m=multiplet, and bm=broad multiplet.

Table 4: continuation...

Experiment/Steroid[a]	3β-H	17α-H	C_{13}-CH_3	Other
6  **23b**		3.66,t (*J* 8.5 Hz)	0.81,s	5.82,s
7  **23c**	3.96,m	3.62,t (*J* 7.7 Hz)	0.74,s	$Si(C\underline{H}_3)_2$: 0.008,s; 0.017,s $Si(C\underline{H}_3)_2$: 0.071,s; 0.10 $SiC(C\underline{H}_3)_3$: 0.87,s; 0.90,s 2.54,m; 2.75,s
8  **23c**	——	——	——	-pmr spectrum was not acquired.
9  **23c**	——	——	——	-pmr spectrum was not acquired.
10  **23c**	4.03,m	3.62,t (*J* 7.5 Hz)	0.74,s	$Si(C\underline{H}_3)_2$: 0.008,s; 0.017,s $SiC(C\underline{H}_3)_3$: 0.87,s 2.55,m; 2.76,s
11  **23c**	3.96,m	3.62,t	0.74,s	$Si(C\underline{H}_3)_2$: 0.006,s; 0.014,s $Si(C\underline{H}_3)_2$: 0.096,s; 0.11,s $SiC(C\underline{H}_3)_3$: 0.87,s; 0.89,s 2.54,m; 2.75,s

[a]R=*t*-BDMSi.

Table 5 : ^{13}C N.M.R. shifts for carbene reaction products.[a]

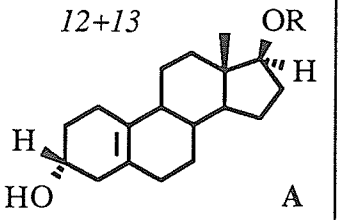
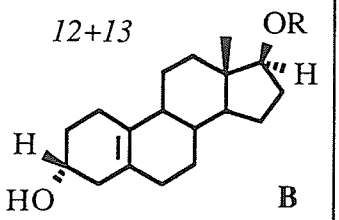
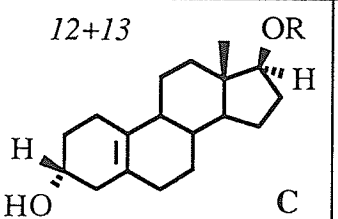
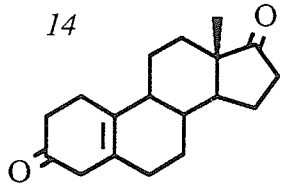
Steroid	**21**	**56**	**57**	**60**	**A**
Carbon					
1	25.12	23.54	23.83	24.49	24.87
2	39.08	27.56	32.84	39.13	33.05
3	211.31	70.27	68.15	207.76	68.15
4	44.65	40.00	43.70	48.31	40.90
5	126.39	38.28	39.34	39.13	26.26
6		34.35	34.50	33.95	27.59[2]
7	27.45	21.87	21.97	21.94	22.34
8	39.10	29.72	30.03	30.08	32.33
9	46.17	33.12[1]	33.32[1]	29.51	31.49[1]
10	131.00	29.96[1]	31.31[1]	32.39	29.49[1]
11	26.44	24.48	24.72	25.04	24.93
12	36.98	34.48	34.70	34.77	34.83
13	43.56	43.23	44.02	44.05	43.65
14	49.68	48.96	48.84	48.81	48.35
15	23.00	22.68	22.76	22.75	23.03
16	30.69	28.95	30.96	30.93	30.85
17	81.82	82.14	81.25	81.15	81.31
18	11.29	12.22	11.51	11.51	11.20
19		32.13	32.72	32.52	33.53
20		31.23	29.97		28.00[2]

[a]For solutions in $CDCl_3$ (TMS internal standard) recorded on a Bruker AM300 instrument. [1,2] values can be interchanged within a column.

Table 5: continuation...

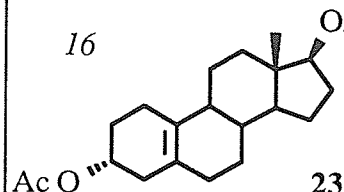
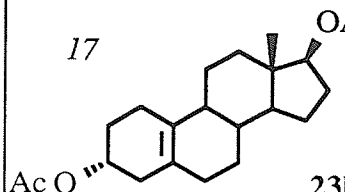
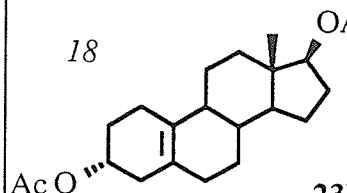
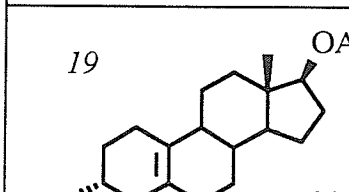
Steroid	**56**	**57**	**A**
Carbon			
3α-$\underline{C}OCH_3$	171.06		
3α-$CO\underline{C}H_3$	21.33		
17ß-$\underline{C}OCH_3$	170.26		
17ß-$CO\underline{C}H_3$	21.13		
3α-$Si(\underline{C}H_3)_2$			
3α-$Si\underline{C}(CH_3)_3$			
3α-$SiC(\underline{C}H_3)_3$			
17ß-$Si(\underline{C}H_3)_2$		-4.44	-4.44
		-4.74	-4.74
17ß-$Si\underline{C}(CH_3)_3$		18.09	18.08
17ß-$SiC(\underline{C}H_3)_3$		25.86	25.85

Table 6: ^{1}H N.M.R. chemical shifts of reduction and oxidation products.[a,b]

Experiment/Steroid[c]	3β-H	17α-H	C_{13}-CH_3	Other
12+13  A	3.88,m	3.61,t (*J* 7.6 Hz)	0.75,s	$Si(C\underline{H}_3)_2$: 0.004,s 0.012,s $SiC(C\underline{H}_3)_3$: 0.87,s 2.85,d (*J* 4.0 Hz) 2.97,s
12+13  B	3.78,m	3.61,t	0.75,s	$Si(C\underline{H}_3)_2$: 0.005,s 0.015,s $SiC(C\underline{H}_3)_3$: 0.87,s 0.30,dd (*J* 4.6, 8.7 Hz) 0.41,t (*J* 4.5 Hz) 0.65,m; 3.08,s
12+13  C	3.86,bm	3.63,t	0.76,s	$Si(C\underline{H}_3)_2$: 0.012,s 0.022,s $SiC(C\underline{H}_3)_3$: 0.89,s 2.50,sxt; 2.90,s 2.94,d (*J* 4.6 Hz)
14 			0.94,s	2.59, 2.83,dd (J_{AB} 15 Hz) 2.95,s

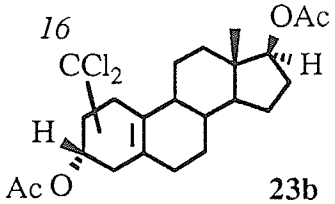
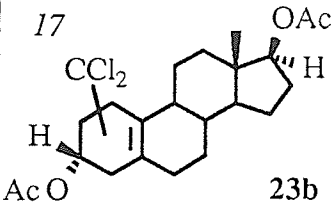
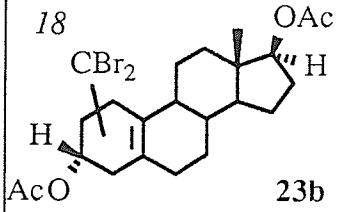
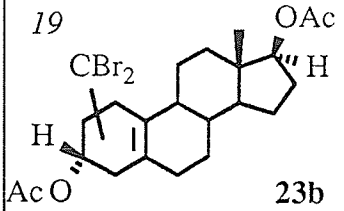
[a]For solutions in $CDCl_3$ (TMS internal standard) recorded on a Bruker AM300 instrument. [b]The abbreviations used s=singlet, d=doublet, dd=doublet of doublets, t=triplet, q=quartet, sxt=sextet, m=multiplet, bm=broad multiplet. [c]R=*t*-BDMSi.

Table 7: Summary of carbene reactions derived from thermolysis of halogenated sodium acetate salts.

Experiment/Steroid	Reagents[a]	°C	Time	Comments
16  **23b**	CCl_3CO_2Na 1.8 glyme 300 µL	100	1 hr.	-argon atmosphere. -starting material recovered.
17  **23b**	CCl_3CO_2Na 15 diglyme 450 µL	125	4 hrs.	-argon atmosphere. -starting material recovered.
18  **23b**	CBr_3CO_2Na 2.2 glyme 5 mL	reflux	2 hrs.	-argon atmosphere. -flame dried glassware. -product (17 mg).
19  **23b**	CBr_3CO_2Na 4.0 diglyme 7 mL	reflux	1.5 hrs.	-argon atmosphere. -flame dried glassware. -product (17 mg).

[a] mol ratio.

Table 8: ^{1}H N.M.R. data of carbene reaction products derived from thermolysis of halogenated sodium acetate salts.[a,b]

Experiment/Steroid	3β-H	17α-H	C_{13}-CH_3	Other
16  **23b**	4.86,bm	4.64,t (*J* 7.8 Hz)	0.81,s	CH_3CO-: 2.04,s
17  **23b**	4.86,bm	4.63,t (*J* 7.8 Hz)	0.81,s	CH_3CO-: 2.04,s
18  **23b**		3.69,t (*J* 8.4 Hz)	0.77,s	C_4-H_2: 2.68, 2.78,dd (J_{AB} 21 Hz)
19  **23b**		3.67,t (*J* 8.5 Hz)	0.81,s	C_4-H: 5.83,s

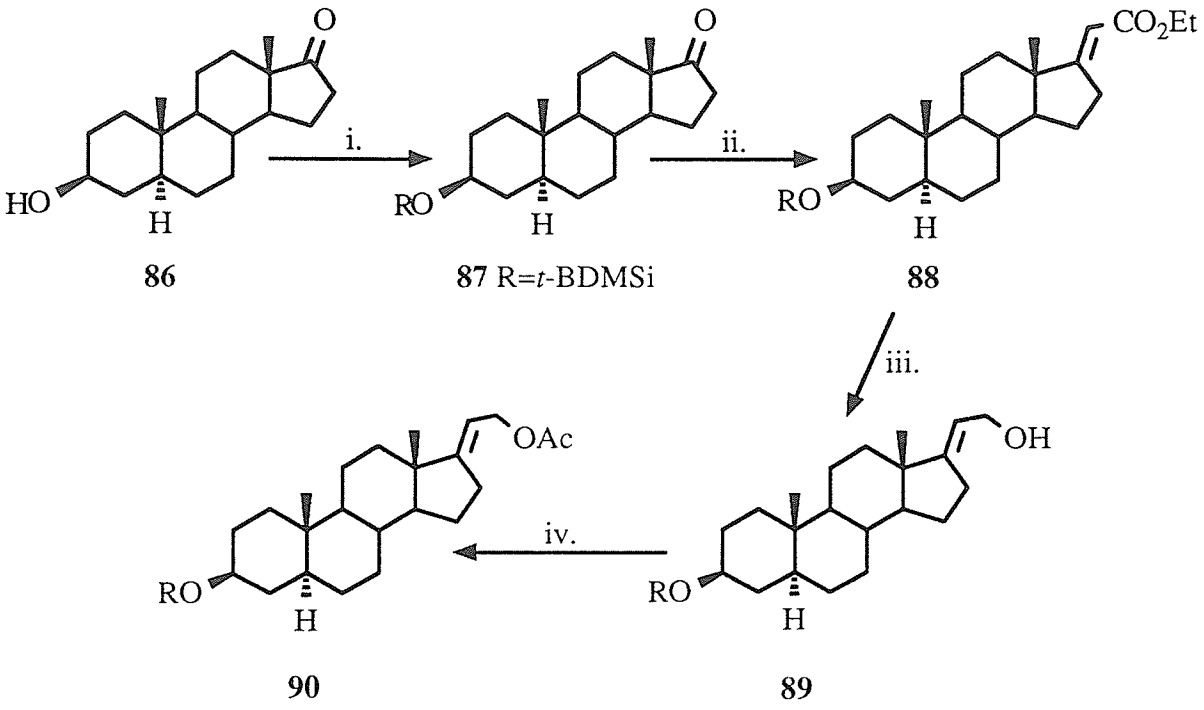
[a]For solutions in $CDCl_3$ (TMS internal standard) recorded on a Bruker AM300 instrument. [b]The abbreviations used s=singlet, d= doublet, dd=doublet of doublets, t=triplet, q=quartet, sxt=sextet, m=multiplet, and bm=broad multiplet.

RESULTS AND DISCUSSION

Part B: Addition of Methylene to the 17(20)-Double Bond of Steroids.

I. Synthesis of the 17(20)-Pregnenes.

Scheme 13 outlines our synthetic scheme for potential inhibitors for 20α- and 20ß-steroid dehydrogenase starting from 3ß-hydroxy-5α-androst-17-one **86**. Treatment of 3ß-hydroxy-5α-androst-17-one **86** with imidazole and *t*-butyldimethylsilyl chloride in DMF afforded 3ß-(*t*-butyldimethylsiloxy)-5α-androst-17-one **87** in very high yield.[62] In Table 9, the ^{1}H N.M.R. spectrum of the product showed the 3α-H resonating at 3.54 ppm, unchanged from the alcohol (3.59 ppm). The C_{18} and C_{19} methyl protons resonated at 0.82 and 0.85 ppm, respectively. An AB spectral pattern at 2.04 and 2.43 ppm was assigned to the C_{16} protons. The silyl methyl groups showed as a singlet at 0.05 ppm and the *t*-butyl methyl protons were observed as a singlet at 0.88 ppm. Wittig reaction[63] with 3ß-(*t*-butyldimethylsiloxy)-5α-androst-17-one **87** using triethyl phosphonoacetate in EtOH/THF and 5% NaOEt under an argon atmosphere yielded the (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17-en-21-oate **88**. The ^{1}H N.M.R spectrum showed the presence of one alkenyl hydrogen at 5.51 ppm. A quartet at 4.14 ppm indicated the presence of the ethyl ester. The 3α-H remained unchanged at 3.55 ppm showing that the silyl ether was intact. A small shift upfield to 0.80 and 0.82 ppm was observed for both the C_{18} and C_{19} methyl protons, respectively. (*E*)-Ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17-en-21-oate **88** was readily reduced to 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17-ene **89** with $LiAlH_4$ in THF. The ^{1}H N.M.R. spectrum of the product showed



86 **87** R=*t*-BDMSi **88**

90 **89**

Reagents: i. imidazole,DMF,*t*-BuDMSiCl; ii. 5% NaOEt,triethyl phosphonoacetate; iii. $LiAlH_4$,THF,r.t.; iv. $(AcO)_2$,py.

Scheme 13: Synthesis of the 17(20)-pregnene intermediates.

the 3α-H proton again remained unchanged, whereas the C_{18} methyl protons were shifted further upfield to 0.75 ppm. The signal at 5.22 ppm indicated that the alkenyl proton had also moved upfield. The multiplet at 4.53 ppm which integrated for two hydrogens was assigned to the C_{22} protons. The 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17-ene **89** was readily acetylated with pyridine and acetic anhydride to give the 3ß-(*t*-butyldimethylsiloxy)-21-acetoxy-5α-pregn-17-ene **90**. The ^{1}H N.M.R. spectrum showed that the signals remained the same with the exception of the addition of the acetoxy methyl protons which were observed at 2.05 ppm.

II. Attempted Synthesis of a 17,20-Cyclopropano Steroid.

i. Simmons-Smith methylenation.

Introduction of a 17,20-cyclopropano group to the 17(20)-double bond **91** (Figure 10) proved to be unsuccessful. Several methods of generating a carbeneoid type species were utilized. Initial experiments employed the Zn-Cu couple described by Templeton et al[64] to generate the Simmons-Smith reagent[65] ($IZnCH_2I$). Varying the quantity of reagents and the reaction time resulted in crude material consisting of starting material and several less polar compounds, according to T.L.C. Table 11 summarizes these findings. Only starting material was recovered from reaction of (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88** (Experiment *20*). When the higher boiling ether, THF, was used as a solvent in place of diethyl ether, again only starting material was recovered from the reaction (Experiment *21*). The resonance effect of the

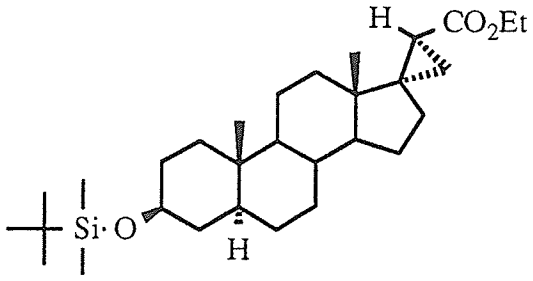


Figure 10: Sturcture of key 17α,22α-cyclopropano derivative **91**.

conjugated ester decreases the electron density on the double bond, thus rendering the double bond less reactive. An allylic alcohol is known to assist in Simmons-Smith methylenation through coordination with the zinc giving intramolecular assistance. Therefore, 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17-ene **89** was chosen as the starting material. In Experiment *22*, 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89** was added to a suspension of Zn-Cu couple/CH_2I_2 in ether and refluxed for 3 hours. A 3 fold excess of CH_2I_2 was used and the reaction furnished a non-crystalline product. Flash chromatography of the crude product yielded several fractions, each with several compounds of similar polarity. High field signals in the ^{1}H N.M.R. spectrum of these fractions revealed that a cyclopropano derivative was present in trace quantities. An interesting observation was noted; the cyclopropyl signals were present in the spectra of the less polar fractions as well as the more polar fractions. It was thought that increasing the amount of CH_2I_2 would afford more of the product exhibiting the cyclopropyl signals. In Experiment *23*, 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89** was treated in similar fashion with the exception that an 86 fold excess of CH_2I_2 was employed. After 2 hours, no starting material was detected by T.L.C. and less polar compounds were present. Work up of the reaction furnished a crude product, which when analyzed by ^{1}H N.M.R., showed only a trace amount of the desired 17,22-cyclopropano derivative ($<1\%$) as indicated by the signals in the cyclopropyl region. It appeared that increasing the amount of CH_2I_2 resulted in no substantial increase in product. 3ß-(*t*-Butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89** was again

refluxed in a mixture of Zn-Cu couple and CH_2I_2 and ether (Experiment *24*). T.L.C. of the reaction mixture after 6 hours revealed the presence of less polar products and no starting material. The reaction was worked-up and flash chromatography yielded a colourless product. ^{1}H N.M.R. analysis showed the product was approximately 17% starting material as indicated by the integration of the 20-alkenyl proton. The 3α-H appeared at 3.54 ppm as an unresolved signal. Only trace amounts of the 17,22-cyclopropano derivative were present in the sample as shown by the resonances in the cyclopropyl region. The previous reaction was again repeated using an 84 fold excess of CH_2I_2 (Experiment *25*). T.L.C. showed no starting material after 2.5 hours. Work-up of the reaction followed by flash chromatography afforded a colourless product. The ^{1}H N.M.R. spectrum of the product was similar to the spectrum obtained for the product isolated from Experiment *24*. As previously observed, only trace amounts of the cyclopropano derivative could be detected as shown by the weak signals in the cyclopropyl region. There was less of the unreacted starting material present as shown by the weaker signal for the 21-alkenyl proton. The quantities of Zn-Cu couple and CH_2I_2 were reduced in hope of increasing the yield of the cyclopropano derivative and decreasing the amount of side products which seemed to be omnipresent (Experiment *26*). Again only polar by-products were obtained as shown by T.L.C. Flash chromatography yielded a non-crystalline product of which the ^{1}H N.M.R. spectrum did not indicate any cyclopropyl hydrogens to be present. A blank reaction was carried out to determine whether CH_2I_2 was responsible for the side products (Experiment *27*). 3ß-(*t*-

Butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89** was refluxed in an ethereal suspension of the Zn-Cu couple in the absence of CH_2I_2. T.L.C. of the crude product showed only starting material was present. This result indicated that the CH_2I_2 reagent was involved in modifying the starting material to furnish the polar products that were obtained in previous Simmons-Smith reactions. Therefore in the last experiment, a lesser amount of the Zn-Cu couple and CH_2I_2 were used and the volume of ether was reduced 2.5 fold. Work-up of the reaction again afforded a non-crystalline product. The ^1H N.M.R. spectrum of the product did not show any high field signals indicating that no cyclopropane product was present.

ii. Modified Simmons-Smith methylenation.

A modification of the original Zn-Cu couple was used to determine whether more of the cyclopropano derivative, which has been present in several fractions in some experiments, could be formed in a larger quantity. A report describing a modification of the Simmons-Smith reagent appeared in 1972.[66] Instead of activating the Zn with Cu as was done previously, Ag was used in place of the Cu, resulting in a more reactive couple (Method A). The results are summarized in Table 13. In Experiment *29*, (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)pregn-17-en-21-oate **88** was added to an ethereal solution of the Zn-Ag couple/CH_2I_2 reagent and refluxed for 7 hours, after which T.L.C. showed only starting material present. The reaction was allowed to continue at room temperature for an additional 17 hours. T.L.C. still showed only starting material. A conjugated

double bond is relatively unreactive and despite a 107 fold excess of the CH_2I_2 reagent no product was obtained. An alternative method[67] (Method B) to prepare the modified Simmons-Smith was then utilized. The advantage of Method B was that it required no acetic acid. Residual acetic acid from the preparation of the couple would not be beneficial in the Simmons-Smith reaction. Utilizing this new Zn-Ag couple[67], this modified Simmons-Smith reaction was repeated (Experiment *30*). To an ethereal solution of the Zn-Ag couple/CH_2I_2 reagent was added 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89**. The mixture was refluxed for 4.5 hours, after which T.L.C. showed the presence of several less polar compounds. Work-up of the reaction afforded a non-crystalline product, which on the basis of the T.L.C., was not analyzed further. The Simmons-Smith reaction was also carried out on the acetylated derivative **90** (Experiment *31*). Addition of an ethereal solution of 3ß-(*t*-butyldimethylsiloxy)-21-acetoxy-5α-pregn-17-ene **90** to a suspension of the Zn-Ag couple (Method B) and CH_2I_2 in ether afforded only starting material after 9 hours under reflux.

iii. Samarium methylenation.

It was reported[68] that a methylene group had been added to an ester using samarium in place of zinc to give the cyclopropano ring in yields varying from 9-71%. Since a double bond is more reactive to methylenation, it was reasonable to attempt this reaction on **90**. In Experiment *32*, 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17-ene **90** was added to a suspension of Sm powder/CH_2I_2 in THF and stirred for 1 hour at -

77°C followed by stirring for 19 hours at room temperature. Following this procedure, a less polar compound was detected on T.L.C. The absence of appropriate high field resonances in the ^{1}H N.M.R. spectrum indicated that the desired cyclopropano ring was not achieved. After the lack of success with the Simmons-Smith reaction, several alternative methylene addition reactions were investigated to determine whether formation of the 17,22-cyclopropano ring was possible.

iv. Diazomethane/$Pd(OAc)_2$ methylenation.

Addition of diazomethane to a double bond is an alternative method for introducing a cyclopropano ring. In Experiment *33*, diazomethane (prepared from the Aldrich Diazomethane Kit),[69] palladium acetate, and (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17-en-21-oate **88** were reacted at 5°C. After 3 hours stirring, T.L.C. of the mixture showed only starting material. Repeating the reaction at room temperature and using 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89** gave a similar result (Experiment *34*).

v. Dihalocarbene addition.

The strategy of using dihalocarbenes followed by reduction of the halogens to give the cyclopropyl ring is a known procedure.[44] The disadvantage of to this approach is that the transient carbene, generated from the reduction of the halides, can insert itself into a nearby C-H bond.[56] A phase transfer catalyzed reaction was reported in the addition

of dichlorocarbene to a α,ß-unsaturated ester in 77% yield.[70a,b] This precedent appeared very encouraging for our work. In Experiment *35*, (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88** in ether was treated with $CHBr_3$, 50% aqueous NaOH, and cetrimide and stirred for 20 hours at room temperature. T.L.C. showed the starting material in largest quantity along with some polar products. Work-up of the reaction afforded a non-crystalline product. Because of the small quantity of starting material used and the number of different compounds present in the crude product, flash chromatography was not carried out.

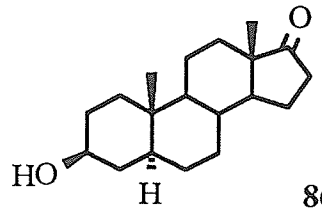
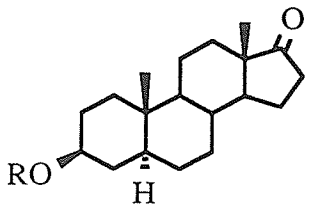
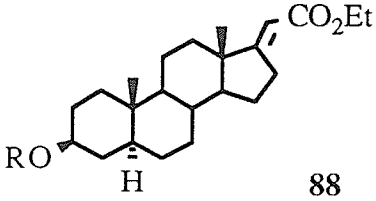
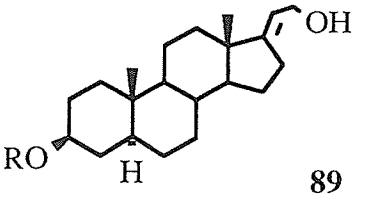
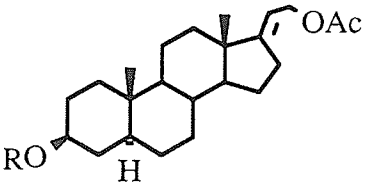
An alternative procedure to forming a dihalocarbene species is the thermolysis of halogenated acetate salts.[54a] The advantage in this method over the haloform/alkali procedure is that only the solvent and halogenated acetate salt are present, thus minimizing the potential for unwanted side reactions. In Experiment *36*, (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88** was treated with sodium trichloroacetate[54b] in diglyme at 160°C. After 4.5 hours of reaction, only starting material was observed by T.L.C. The reaction was repeated using sodium tribromoacetate[54b] in refluxing glyme (Experiment *37*) but after 4.5 hours, T.L.C. showed only starting material.

vi. Trimethylsulphoxonium iodide methylenation.

In a final attempt,[71] (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88** was treated with trimethylsulphoxonium iodide, DMSO, and NaH at 96°C for 5 hours after which time only starting material was present according to T.L.C.

The unsuccessful addition of methylene to a double bond such as the one in **89**, is unusual. Approach of the carbenoid would be expected to occur from the α-face as the ß face of the alkene is blocked by the axial C_{13} methyl group. The presence of an allylic hydroxyl group to assist the reaction makes this procedure more attractive. The Simmons-Smith reagent did not cleave the *t*-BDMSi protecting group. The conditions required for Simmons-Smith reactions are not drastic, and therefore potential side reactions resulting from temperature effects or reagents are usually not encountered. However, by-products resulting from insertion of the solvent to form the ether and dimerization have been previously reported.[64] This can account for the polar products isolated from the reaction mixtures.

Table 9: Compilation of ^{1}H N.M.R. data of androstane and 17(20)-pregnene starting materials and intermediates.[a,b]

Steroid[c]	3α-H	C_{10}-CH_3	C_{13}-CH_3	Other
 **86**	3.59,m	0.85,s	0.82,s	16α-H: 2.04,q (*J* 8.9, 10.1 Hz) 16β-H: 2.43,q (*J* 9.0, 9.9 Hz)
 **87**	3.54,m	0.85,s	0.82,s	16α-H: 2.04,q (*J* 8.7, 10.2 Hz) 16β-H: 2.43,q (*J* 9.0, 9.9 Hz) $Si(C\underline{H}_3)_2$: 0.05,s $SiC(C\underline{H}_3)_3$: 0.88,s
 **88**	3.55,m	0.82,s	0.80,s	C_{20}-H: 5.51,t (*J* 2.3 Hz) C_{22}-H: 4.14,q (*J* 7.1 Hz) $Si(C\underline{H}_3)_2$: 0.05,s $SiC(C\underline{H}_3)_3$: 0.88,s
 **89**	3.55,m	0.82,s	0.80,s	C_{20}-H: 5.22,m C_{22}-H: 4.10,m $Si(C\underline{H}_3)_2$: 0.05,s $SiC(C\underline{H}_3)_3$: 0.88,s
 **90**	3.55,m	0.82,s	0.76,s	C_{20}-H: 5.15,m C_{22}-H: 4.53,m $C\underline{H}_3CO$-: 2.05,s $Si(C\underline{H}_3)_2$: 0.05,s $SiC(C\underline{H}_3)_3$: 0.88,s

[a]For solutions in $CDCl_3$ (TMS internal standard) recorded on a Bruker AM300 instrument. [b] Abbreviations used s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, [c]R=*t*-BDMSi.

Table 10: ^{13}C N.M.R. shifts for androstane and 17(20)-pregnene starting materials.[a]

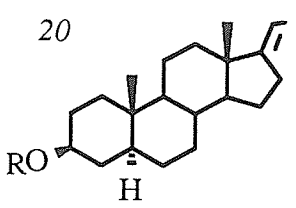
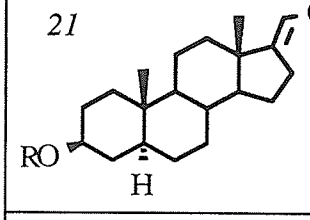
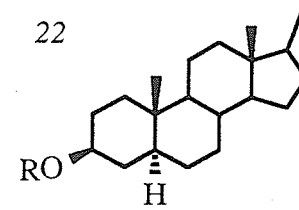
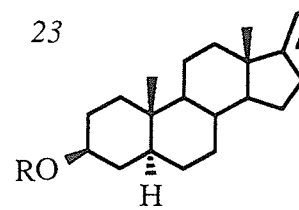
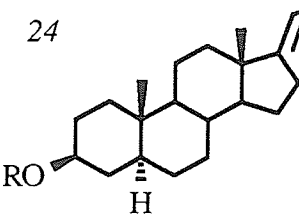
Steroid	**86**[72]	**86**	**87**	**88**	**89**	**90**
Carbon						
1	36.9	36.95	37.16	37.20	37.23	37.24
2	31.4	31.46	31.62	31.94	31.97	31.96
3	70.9	71.14	72.00	72.08	72.13	72.12
4	38.0	38.09	38.63	38.65	38.70	38.69
5	44.8	44.86	45.05	45.04	45.10	45.09
6	28.4	28.40	28.49	28.65	26.17	26.34
7	30.9	30.90	30.99	30.43	28.72	28.71
8	35.0	35.08	35.10	35.26	35.37	35.34
9	54.4	54.46	54.59	54.56	54.83	54.77
10	35.6	35.65	35.70	35.65	35.68	35.67
11	20.5	20.52	20.52	21.14	21.15	21.13
12	31.6	31.58	31.91	32.00	32.04	32.01
13	47.7	47.79	47.83	46.34	44.10	44.32
14	51.4	51.44	51.49	53.61	54.22	54.11
15	21.8	21.79	21.82	24.38	24.24	24.20
16	35.8	35.84	35.87	35.44	35.90	35.77
17	220.8	221.23	221.29	167.47	156.07	158.39
18	13.8	13.83	13.83	18.52	18.80	18.28
19	12.3	12.31	12.37	12.40	12.41	12.40
20				108.38	115.27	110.39
21				176.55	60.42	62.37

[a]For solutions in $CDCl_3$ (TMS internal standard) recorded on a Bruker AM300 instrument.

Table 10: continued...

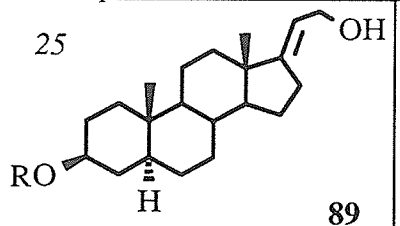
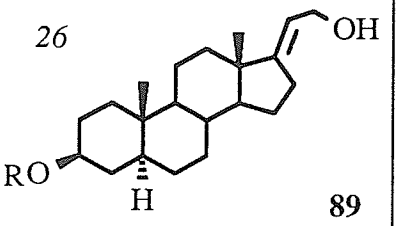
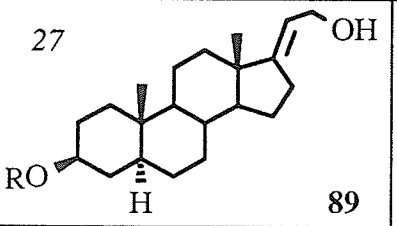
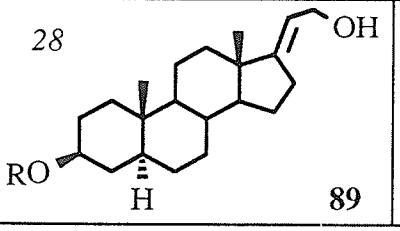
Steroid	**86**	**86**	**87**	**88**	**89**	**90**
Carbon						
3ß-Si($\underline{C}H_3$)$_2$			-4.53	-4.54	-4.54	-4.55
3ß-Si$\underline{C}$(CH_3)$_3$			18.27	18.28	18.29	18.28
3ß-SiC($\underline{C}H_3$)$_3$			25.95	25.96	25.97	25.96
O$\underline{C}H_2CH_3$				59.46		
O$CH_3\underline{C}H_3$				14.41		
O$\underline{C}OCH_3$						171.10
OCO$\underline{C}H_3$						15.28

Table 11: Summary of Simmons-Smith reactions on some 17(20)-pregnenes.

Experiment/Steroid[a]	Reagents[b]	°C	Time	Comments
20  **88**	Zn-Cu 16.6 CH_2I_2 13.5 ether 20 mL	reflux	6 hrs.	-starting material recovered.
21  **88**	Zn-Cu 10.6 CH_2I_2 10.8 ether/THF (40/50 mL)	reflux	11 hrs.	-starting material recovered.
22  **89**	Zn-Cu 4.9 CH_2I_2 2.8 ether 51 mL	reflux	3 hrs.	-several products detected by T.L.C.
23  **89**	Zn-Cu 132 CH_2I_2 86 ether 20 ml	reflux	2 hrs.	-flame dried glassware. -less polar products on T.L.C.
24  **89**	Zn-Cu 132 CH_2I_2 86 ether 15 mL	reflux	6 hrs.	-flame dried glassware. -less polar products.

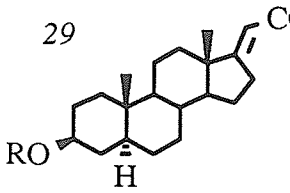
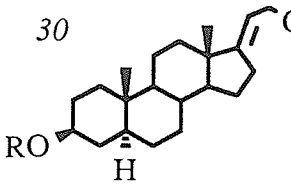
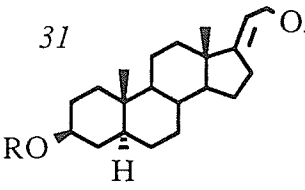
[a]R=*t*-BDMSi. [b]mol ratio.

Table 11: continuation...

Experiment/Steroid[a]	Reagents[b]	°C	Time	Comments
25  **89**	Zn-Cu 130 CH_2I_2 84.3 ether 15 mL	reflux	2.5 hrs.	-flame dried glassware. -less polar compound.
26  **89**	Zn-Cu 31 CH_2I_2 21.5 ether 15 mL	reflux	8.5 hrs.	-flame dried glassware. -less polar compound.
27  **89**	Zn-Cu 132 CH_2I_2 0 ether 2 mL	reflux	5 hrs.	-flame dried glassware. -flushed with Ar.
28  **89**	Zn-Cu 5.3 CH_2I_2 5.2 ether 6 mL	reflux	3 hrs.	-flame dried glassware. -less polar products.

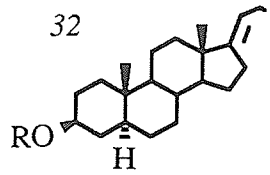
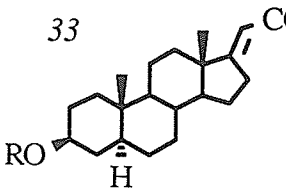
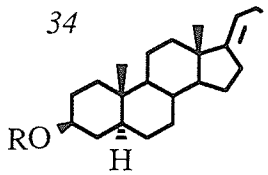
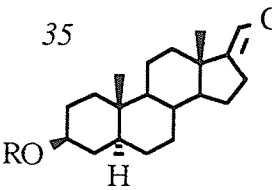
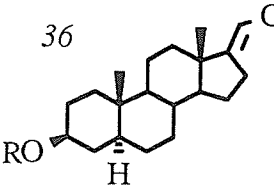
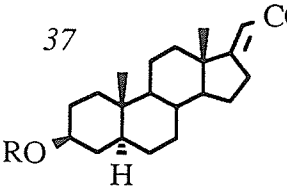
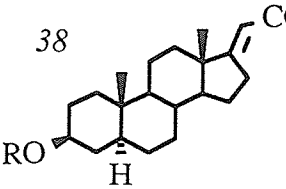
[a]R=*t*-BDMSi. [b]mol ratio.

Table 12: Summary of modified Simmons-Smith reactions on some 17(20)-pregnenes.

Experiment/Steroid[a]	Reagents[b]	°C	Time	Comments
29  **88**	Zn-Ag 235 CH_2I_2 107 ether 30 mL	reflux r.t.	7 hrs. 17 hrs.	-starting material recovered.
30  **89**	Zn-Ag 10 CH_2I_2 3.1 ether 8 mL	reflux	4.5 hrs.	-argon atmosphere. -less polar products (T.L.C.).
31  **90**	Zn-Ag 14 CH_2I_2 4.1 ether 12 mL	reflux	9 hrs.	-argon atmosphere. -starting material recovered.

[a]R=*t*-BDMSi. [b]mol ratio.

Table 13: Summary of various carbene reactions on some 17(20)-pregnenes.

Experiment/Steroid[a]	Reagents[b]		°C	Time	Comments
32  **89**	Sm CH_2I_2 THF	8 10 4 mL	-77 r.t	1 hr. 19 hrs.	-flame dried glassware. -faster moving spot.
33  **88**	CH_2N_2 $Pd(OAc)_2$ ether	10 0.40 8 mL	5	3 hrs.	-starting material recovered.
34  **89**	CH_2N_2 $Pd(OAc)_2$ ether	16 0.19 7 mL	r.t.	2 hrs.	-starting material recovered.
35  **88**	$CHBr_3$ cetrimide 50% NaOH ether	114 0.16 2 mL 2 mL	r.t.	20 hrs.	-more polar products.
36  **88**	CCl_3CO_2Na diglyme	13 4 mL	160	4.5 hrs.	-starting material recovered.
37  **88**	CBr_3CO_2Na glyme	19 4 mL	reflux	4.5 hrs.	-starting material recovered.
38  **88**	TMSI NaH DMSO	2.1 9 3 mL	96	5 hrs.	-starting material recovered.

[a]R=*t*-BDMSi.[b]mol ratio.

CONCLUSIONS

Part A

The synthesis of 19,19-dibromo-5ß,19-cycloandrostane derivatives as reported in the literature could not be repeated. Carbene reaction on **23a** afforded more polar compounds, indicating that the 3 and 17-hydroxyl groups have been modified to yield less polar compounds. Using the acetyl (**23b**) and silyl (**23c**) protecting groups afforded three different cyclopropano derivatives **56**, **57a**, and **57b** were obtained and their structures established by comparison of their ^{1}H and ^{13}C N.M.R. spectra with analogous compounds isolated in larger quantities in this laboratory. A mechanism has been suggested for their formation. The formation of these novel cyclopropano derivatives can be rationalized as resulting from carbene addition to the 5(10)-double bond, followed by rearrangement or possibly through initial carbene insertion into the adjacent C_9-H bond. The addition of a second dibromocarbene occurs to the 5,6-double bond, formed as a result of the initial rearrangement. The carbon-hydrogen sigma bond insertion reaction appears to be similar in energy to double bond addition, thus allowing competition to occur. In 3-methylcyclohex-1-ene competition between dichlorocarbene addition to the double bond and insertion into the C_3-H bond has been observed.[73] Generally whether addition to the 5(10)-double bond, or other steroid double bonds, occured to the α or ß face of the molecule has been described to steric differences.

Part B

Synthesis of 17,20-unsaturated compounds **88**, **89**, and **90** was carried out and attempts were made to add CH_2, CBr_2, or CCl_2 to the 17,20-double bond using the following methods: 1. the Simmons-Smith reagent formed with (i) Zn-Cu couple, (ii) Zn-Ag couple, and (iii) Samarium. 2. Diazomethane/$Pd(OAc)_2$. 3. $CHBr_3$/NaOH/cetrimide. 4. Thermolysis of CBr_3CO_2Na and CCl_3CO_2Na. Methods 3 and 4 required reduction of the halogens to give the desired hydrocarbon. Reduction of the ester in **88** was carried out because the non-conjugated double bond is more reactive to electrophilic reagents and because the allylic alcohol has been shown to be more reactive with the Simmons-Smith reagent through alcohol coordination.

The unsuccessful addition of methylene to a double bond such as the one in **89**, is unusual. Approach of the carbenoid would be expected to occur from the α-face as the ß-face of the alkene is blocked by the axial C_{13} methyl group. The presence of an allylic hydroxyl group to assist the reaction makes this procedure more attractive. Never-the-less, steric factors may be great enough to inhibit reaction.

None of these latter reactions gave the desired compound although traces of cyclopropane addition were observed in the ^1H N.M.R. of reaction products resulting from using the Simmons-Smith reagent.

EXPERIMENTAL

Instruments

Melting point determinations were performed on a microscope equipped Koffler hot stage and are uncorrected. N.M.R. samples were recorded in $CDCl_3$ using TMS as an internal standard. The ^1H N.M.R. spectra were recorded on a Bruker AM300 (300MHz) instrument at the Department of Chemistry, University of Manitoba. ^{13}C N.M.R. spectra were also recorded on the Bruker AM300 instrument, implementing the polarization transfer spectroscopy technique[74a,b] to determine the number the numbers of attached hydrogen atoms.

Elemental analyses were completed by Mr. W. Baldeo at the Microanalytical Laboratory, School of Pharmacy, University of London, England.

Materials

Flash chromatography[75] was carried out with silica gel (pH 7.1, moisture content 7.5%, particle size distribution 20-45 microns, Terochem Laboratories Ltd.). T.L.C. was carried out on precoated silica gel GHLF plates (250 microns thickness, Analtech 25). Eluents for both flash chromatography and T.L.C. were varying mixtures of ethyl acetate (10-40%)-petroleum ether (bp 30-60°C). Visualization of the T.L.C. plates was achieved by dipping in 5-8% v/v sulphuric acid and ethanol, followed by heating on a hot plate to produce a characteristic colour.

The following table lists the sources of the materials used.

Table 14: Source of starting materials

Reagents	Source
tribromoacetic acid	Aldrich, Milwaukee, WI.
trichloroacetic acid	Aldrich, Milwaukee, WI.
copper acetate	BDH, Poole, England
palladium acetate	Alfa Products, MA.
silver acetate	BDH, Poole, England
cetrimide	Aldrich, Milwaukee, WI.
t-butyldimethylsilyl chloride	Sigma Chemical Co., St.Louis, MO.
$CHBr_3$	Mallinckrodt, Paris, KN.
$CDCl_3$	Aldrich, Milwaukee, WI.
CH_2I_2	Aldrich, Milwaukee, WI.
Zn dust	Mallinckrodt, Paris, KN.
lithium aluminum hydride	Aldrich, Milwaukee, WI.
litium tri-*t*-butylaluminum hydride	Aldrich, Milwaukee, WI.
sodium hydride	Aldrich, Milwaukee, WI.
imidazole	Fischer, New Jersey
trimethylsulphoxonium iodide	Aldrich, Milwaukee, WI.
triethyl phosphonoacetate	Aldrich, Milwaukee, WI.
samarium powder	Aldrich, Milwaukee, WI.
dimethyl sulphate	Aldrich, Milwaukee, WI.
tetrabutylammonium hydrogen sulphate	Aldrich, Milwaukee, WI.
Steroids	
Estrone	Biosynth OSS, Holland
3-Methoxyestradiol	Sigma Chemical Co., St.Louis, MO.
3ß-Hydroxy-5α-androstan-17-one	Biosynth OSS, Holland

For work-up of the reactions, the following reagents were used:

a) 1M Hydrochloric acid.
b) Saturated aqueous solution of sodium hydrogen carbonate (10% w/v).
c) Saturated aqueous solution of sodium chloride (brine).
d) Anhydrous sodium sulfate.

All organic solvents were reagent grade or better.

Methods

Part A

Preparation of estrone 3-methyl ether **18**:[36]

Estrone **17** (500 mg) was dissolved in 1M KOH/MeOH (150 mL) at 50°C. A dropping funnel was charged with a 1:1 solution of dimethyl sulphate/MeOH (10 mL) and the solution added over a period of 15 minutes. After 45 minutes, T.L.C. (25% ethyl acetate/petroleum ether) showed the major component to be unreacted estrone. Dimethyl sulphate (10 mL) and MeOH (10 mL) was again added dropwise over a period of 30 minutes. MeOH (10 mL) was added to the dropping funnel to wash out any remaining dimethyl sulphate. After 90 minutes, T.L.C. showed the major product to be the estrone 3-methyl ether **18** along with a minor amount of unreacted estrone. Dimethyl sulphate (10 mL) in MeOH (10 mL) was added a second time. After 3 hours, T.L.C. still showed the presence of starting material. KOH (2.1 g) was added and the temperature was increased to 50°C. The reaction was filtered to remove K_2SO_4. The filtrate was concentrated and water (200 mL) was added. The reaction was diluted with water and the product extracted with CH_2Cl_2. The organic portion was washed with water, saturated $NaHCO_3$, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* yielded a gum. Two crystallizations from CH_2Cl_2/acetone afforded estrone 3-methyl ether (207 mg), m.p. 155-160°C. (lit. m.p. 163-167°C)[36] See Tables 1 and 2 for the ^1H and ^{13}C N.M.R. data.

Preparation of estradiol 3-methyl ether **19**:[36]

Estrone 3-methyl ether **18** (4.55 g) was dissolved in freshly distilled tetrahydrofuran (200 mL). To this solution was added $LiAlH_4$ (641 mg) and the solution brought to reflux. After 30 minutes, T.L.C. (25% ethyl acetate/petroleum ether) of the reaction showed no starting material. The reaction was quenched by dilution with water (50 mL). Excess solvent was evaporated to 50 mL, diluted with water, and the product extracted with CH_2Cl_2. The organic portion was washed successfully with 5% aqueous HCl, water, and dried over Na_2SO_4. Evaporation *in vacuo* of the solvent gave an oily residue. Crystallization from CH_2Cl_2 yielded estradiol 3-methyl ether **19** (3.27g), m.p. 115-118°C (lit. m.p. 118-119°C).[36]

Preparation of 3-methoxy-17ß-hydroxy-1,4-dihydro-estra-2,5(10)-diene **20**:[36]

Ammonia (500 mL) was redistilled into a 1L 3-necked flask that had been cooled to -77°C (dry ice/acetone bath). With stirring, lithium metal (3.1 g) was added in small portions. To this solution was added 3-methoxy-17ß-estradiol **19** (3.03 g) in anhydrous ether (200 mL). The mixture was stirred for 5 minutes, where upon anhydrous EtOH (35 mL) was added dropwise over a 20 minute period. Upon completion of the addition of EtOH, the NH_3 was allowed to evaporate overnight. Cold water was added carefully and the aqueous solution was extracted with ether. The organic layer was washed with Claisen alkali, water, brine, and dried over Na_2SO_4. Crystallization of the crude product

from CH_2Cl_2/hexane gave 3-methoxy-17ß-hydroxy-1,4-dihydroestra-2,5(10)-diene **20** (2.54g) in 83% yield, m.p. 112-115°C. (lit. m.p. 105-113°C)[36]

Preparation of 17ß-hydroxyestr-5(10)-en-3-one **21**:[36]

3-Methoxy-17ß-hydroxy-1,4-dihydroestra-2,5(10)-diene **20** (2.5 g) was dissolved in MeOH (220 mL). To this solution was added a solution of oxalic acid dihydrate (3.30 g) in water (43 mL) and stirred. The temperature was maintained at 55°C for 40 minutes when the T.L.C. (25% ethyl acetate/hexane) showed no starting material. The solution was evaporated *in vacuo* to a manageable volume and washed with ether. The organic layer was washed twice with saturated $NaHCO_3$, water, brine, and dried over Na_2SO_4. Flash chromatography yielded the 17ß-hydroxyestr-5(10)-en-3-one **21** (2.03 g), m.p. 190-195°C. (lit. m.p. 199.8-201°C)[36]

Preparation of 3α,17ß-dihydroxyestr-5(10)-ene **23a**:[37]

17ß-Hydroxyestr-5(10)-en-3-one **21** (2.03 g) was dissolved in tetrahydrofuran (100 mL). To this was added $LiAlH_4$ (540 mg) and an additional volume of tetrahydrofuran (100 mL). After 90 minutes, T.L.C. (50% ethyl acetate/petroleum ether) showed the presence of starting material. $LiAlH_4$ (340 mg) was added. The reaction was stopped after 2 hours when T.L.C. showed no further change in starting material. The solution was concentrated, diluted with an excess of 5% HCl (to give a positive litmus test), and extracted with ether. The ether layer was washed with water, saturated $NaHCO_3$, water,

brine (twice), and dried over Na_2SO_4. Evaporation *in vacuo* gave an oily product (2.12 g). Flash chromatography yielded of the crude product yielded 3α,17ß-dihydroxyestr-5(10)-ene **23a**, m.p. 200-205 °C. (lit. m.p. 208-209.4°C)[37]

Preparation of 3α,17ß-diacetoxyestr-5(10)-ene **23b**:[37]

3α,17ß-Dihydroxyestr-5(10)-ene **23a** (820 mg) was added to a 2:1 pyridine/acetic anhydride solution (75 mL) and stirred overnight. The reaction was diluted with water and extracted with ether. The organic layer was washed with water, 1M HCl, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded an oily residue. Crystallization from CH_2Cl_2/MeOH gave long fine needles of 3α,17ß-diacetoxy-estr-5(10)-ene **23b**, m.p. 115-118°C. (lit. m.p. 120.6-121.4°C)[37]

Preparation of 3α,17ß-di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c**:[64]

3α,17ß-Dihydroxyestr-5(10)-ene **23a** (9 mg) and dimethylformamide (2 mL) was added to a flame dried 3-neck 25 mL pear shaped flask. Argon was flushed through the system for 10 minutes. To this solution was added imidazole (19 mg) and *t*-butyldimethylsilyl chloride (30 mg). After 11 hours, T.L.C. (30% ethyl acetate/petroleum ether) of the reaction showed that only one of the hydroxyl groups were derivatized. A second portion of imidazole (92 mg) and *t*-butyldimethylsilyl chloride (107 mg) were added. One hour later the reaction was complete as observed by T.L.C.. The reaction was diluted with water and extracted with CH_2Cl_2. The organic layer was washed twice with 5% HCl,

twice with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded 13 mg of non-crystalline product. Yield 80%. m.p. 129-130°C.

Preparation of 19-carboxyandrost-4-ene-3,17-dione **25**:[39]

To a 1 L flat bottom flask was added 19-hydroxyandrost-4-ene-3,17-dione **24** (10.0 g) and acetone (400 mL). This was stirred until a clear solution was obtained. Jone's reagent (100 mL) was added dropwise until a red colour was obtained. After 4 hours, T.L.C. (30% ethyl acetate/petroleum ether) showed only product as the major component. The reaction was quenched by adding an excess of MeOH, and the solution was filtered through Celite. The filtrate was concentrated, diluted with an excess of water, and extracted with CH_2Cl_2. The organic layer was washed with 5% HCl, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a non-crystalline product (8.0 g). decomp. 145°C (lit. decomp. 146°C).[39]

Preparation of estr-5(10)-ene-3,17-dione **26**:[39]

A solution of freshly distilled pyridine (12 mL) and 19-carboxyandrost-4-ene-3,17-dione **25** (1.00 g) was stirred for 1.5 hours at 60°C. T.L.C. (30% ethyl acetate/petroleum ether) showed no starting material. The solution was diluted with 5% HCl and extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a tan gum (904 mg). The crude

product was purified by flash chromatography to give estra-5(10)-en-3,17-dione **26** (386 mg). m.p. 142-145°C (lit. m.p. 144-146°C)[39]

Preparation of 3α,17ß-dihydroxyestr-5(10)-ene **23a**:

$LiAlH_4$ (1.44 g) and freshly distilled tetrahydrofuran (100 mL) were added to a 500 mL flat bottom flask and immersed in an acetone/dry ice bath. To this solution was added dropwise, estr-5(10)-en-3,17-dione **26** (5.18 g) in freshly distilled tetrahydrofuran (170 mL) over 35 minutes. After 1 hour, T.L.C. (40% ethyl acetate/petroleum ether) showed no starting material. The reaction was warmed to room temperature, and the excess reagent was destroyed by adding aqueous NaOH and an equal volume of water. The reaction mixture was then neutralized with 5% HCl and extracted with CH_2Cl_2. The organic portion was washed with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded 4.25 g of crude product. m.p. 194-197°C (lit. m.p. 199.8-201°C)[36]

Preparation of sodium trichloro- and tribromoacetate salts.[54b]

Trichloroacetic acid (5.00 g) was dissolved in anhydrous MeOH (50 mL) and neutalized to the phenolphthalein end point with 5% sodium methoxide (w/v) solution. $CHCl_3$ was then added to precipitate the sodium trichloroacetate. The salt was collected by filtration and dried *in vacuo*.

Preparation of the Zn-Cu couple:[53]

Zn dust (1 g) and cupric acetate (62 mg) were thoroughly homogenized. The mixture was then added to a boiling solution of AcOH (10 mL). Immediately, a second volume of cold AcOH (10 mL) was added and the suspension was filtered. The Zn-Cu couple was washed with ether until the odour of AcOH could not be detected.

Experiment *1*: Carbene reaction on 3α,17ß-dihydroxyestr-5(10)-ene **23a**:

A three-necked 25 mL pear shape flask was flushed with argon for 10 minutes. 3α,17ß-Dihydroxyestr-5(10)-ene **23a** (25 mg), cetrimide (15 mg), and $CHCl_3$ (200 μL) were added and the mixture stirred. 50% Aqueous NaOH (800 μL) was added dropwise. The heterogeneous mixture was refluxed at 110-120°C for 1 hour. T.L.C. (25% ethyl acetate/petroleum ether) showed the presence of two less polar compounds. The reaction was cooled to room temperature, diluted with brine, and neutralized with 0.5M H_2SO_4. The product was extracted with CH_2Cl_2 which was filtered through silica gel. The filtrate was washed once with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a dark tar which was flash chromatographed using a (column i.d. 10 mm, eluent 25% ethyl acetate/hexane). The fractions collected were submitted for N.M.R. analysis which showed the presence of new signals (Table 4).

Experiment *2*: Carbene reaction on 3α,17ß-dihydroxyestr-5(10)-ene **23a**:

A three-necked 25 mL pear shaped flask was flushed with argon for 10 minutes. 3α,17ß-Dihydroxyestr-5(10)-ene **23a** (25 mg), cetrimide (10 mg), and $CHCl_3$ (200 μL) were added and dissolved prior to the dropwise addition of 50% aqueous NaOH (800 μL). The reaction proceeded at room temperature for 3.5 hrs after which time T.L.C. (50% ethyl acetate/petroleum ether) showed no starting material, but instead the presence of less polar compounds. The reaction was neutralized with 0.5M H_2SO_4 and extracted with CH_2Cl_2. The organic layer was washed with water, saturated $NaHCO_3$, water, brine, and dried over H_2SO_4. Evaporation *in vacuo* yielded a dark gum. The gum was redissolved in CH_2Cl_2 and filtered through silica gel. The filtrate was concentrated and flash chromatographed (column i.d. 5 mm, eluent 25% ethyl acetate/petroleum ether). The fractions were submitted for ^1H N.M.R., which showed two new signals.

Experiment *3*: Carbene reaction of 3α,17ß-diacetoxyestr-5(10)-ene **23b**:

A 25 mL pear shaped flask was flushed with argon for 10 minutes. 3α,17ß-Diacetoxyestr-5(10)-ene **23b** (33 mg), cetrimide (10 mg), and $CHBr_3$ (200 μL) were added and dissolved prior to dropwise addition of 50% aqueous NaOH (800 mL). After vigorous stirring for 2 hours at room temperature, T.L.C. (25% ethyl acetate/petroleum ether) showed no starting material. The reaction was quenched with brine, neutralized with 0.5M H_2SO_4, and extracted with CH_2Cl_2. The organic layer was washed with water, saturated $NaHCO_3$, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* yielded

a dark gum. The gum was reconstituted in CH_2Cl_2 and flash chromatographed (column i.d. 5 mm, eluent 15% ethyl acetate/petroleum ether). Fractions were collected and submitted for ^1H N.M.R. analysis which showed the identical two signals that were present in both spectra from Experiments *1* and *2*.

Experiment *4*: Carbene reaction of 3α,17ß-diacetoxyestr-5(10)-ene **23b**:

A solution of cetrimide (11 mg) in $CHCl_3$ (200 μL) was added dropwise to a suspension of 3α,17ß-diacetoxyestr-5(10)-ene **23b** (37 mg) in 50% aqueous NaOH (800 μL). The reaction proceeded at room temperature. After 3 hours, T.L.C. (15% ethyl acetate/petroleum ether) showed no starting material. The reaction was diluted with brine (10 mL) and 1N H_2SO_4 (10 mL). The crude product was extracted with CH_2Cl_2. The organic portion was washed with saturated $NaHCO_3$, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a tan gum. This was reconstituted in CH_2Cl_2 and flash chromatographed (column i.d. 5 mm, eluent 15% ethyl acetate/petroleum ether) to give several fractions. ^1H N.M.R. analysis of the fractions gave no definite interpretation.

Experiment *5*: Carbene reaction on 3α,17ß-diacetoxyestr-5(10)-ene **23b**:

A 25 mL pear shaped flask was flushed with argon for 10 minutes. 50% Aqueous NaOH (5 mL) was added dropwise to a solution of 3α,17ß-diacetoxyestr-5(10)-ene **23b** (206 mg) and cetrimide (50 mg) in $CHBr_3$ (1.2 mL). After 4 hours, T.L.C. (20% ether/petroleum

ether) showed no starting material present. The mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a dark gum. The gum was reconstituted in CH_2Cl_2 and flash chromatographed twice (column i.d. 20 mm, eluent 20% ether/petroleum ether). A non-crystalline product (120 mg) corresponding to one spot on T.L.C. was collected.

Experiment *6*: Carbene reaction on 3α,17ß-diacetoxyestr-5(10)-ene **23b**:

To an argon evacuated 3-necked 25 mL pear shaped flask was added: glyme (1 mL), 3α,17ß-diacetoxyestr-5(10)-ene **23b** (49 mg), tetrabutylammonium hydrogen sulphate (23 mg), 60% aqueous KOH (1 mL), and CCl_4 (1 μL). The mixture was stirred vigorously. After 10 minutes, T.L.C. (25% ethyl acetate/petroleum ether) showed no starting present, instead a more polar product was detected. The reaction was diluted with CH_2Cl_2. The organic layer was washed twice with water, twice with 5% HCl, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* yielded a dark yellow liquid. Flash chromatography (column i.d. 10 mm, eluent 25% ethyl acetate/petroleum ether), followed by crystallization from ether/acetone afforded product (8 mg). ^{1}H N.M.R. spectrum of the product was identical with the spectrum of an authentic sample of 17ß-hydroxyestr-4-en-3-one **22**.

Experiment *7*: Carbene reaction on 3α,17ß-di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c**:

To an argon flushed 3-neck 25 mL pear shaped flask was charged 3α,17ß-di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c** (44 mg), ether (2 mL), cetrimide (37 mg), and 50% aqueous NaOH (1 mL). $CHBr_3$ (131 mg) was added dropwise. After 1.5 hours no product was detected by T.L.C. (5% benzene/petroleum ether). $CHBr_3$ (1 mL) and 50% aqueous NaOH (1 mL) was added. After 2.5 hours T.L.C. showed the presence of product. The reaction was stopped by addition of 5% HCl and extracted with CH_2Cl_2. The organic layer was washed with 5% HCl, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* yielded a non-crystalline product. ^1H N.M.R. analysis of the product showed two new signals at 2.54 and 2.75 ppm.

Experiment *8*: Carbene reaction on 3α,17ß-di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c**:

Into a 3-necked 25 mL pear shaped flask was added 3α,17ß-di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c** (54 mg), cetrimide (20 mg), and $CHBr_3$ (1 mL). 50% Aqueous NaOH (1 mL) was added dropwise. After 3 hours, T.L.C. (5% benzene/petroleum ether) showed starting material present. A second portion of 50% aqueous NaOH (1 mL) was added. After 7 hours, T.L.C. showed only one spot as product with no starting material present. The reaction was diluted with 5% HCl and extracted with CH_2Cl_2. The organic layer was washed with 5% HCl, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a dark coloured liquid. Flash chromatography (column i.d. 10 mm, eluent 5% benzene/petroleum ether) furnished a product (4 mg).

Crystallization from ether/petroleum ether yielded a white crystalline compound, m.p. 209-211°C.

Experiment *9*: Carbene reaction on 3α,17ß-di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c**:

To a pear shaped 25 mL flask (flushed with argon) was added 3α,17ß-di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c** (110 mg), cetrimide (19 mg), $CHBr_3$ (1 mL), and 50% aqueous NaOH (1 mL). The whole mixture was stirred vigorously. After 7 hours, T.L.C. (5% benzene/petroleum ether) showed no starting material. The reaction was diluted with 5% HCl and washed with CH_2Cl_2. The organic layer was separated, washed with 5% HCl, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a dark gum. The gum was reconstituted in CH_2Cl_2 and filtered through silica gel. Crystallization from CH_2Cl_2/MeOH yielded product (6 mg), m.p. 205-208.5°C.

Experiment *10*: Carbene reaction on 3α,17ß-di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c**:

To a 2-necked 100 mL pear shaped flask was added 3α,17ß-di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c** (372 mg), cetrimide (106 mg), and $CHBr_3$ (2 mL). 50% Aqueous NaOH (1 mL) was added and the mixture was stirred vigorously. After 3 hours a second portion of 50% aqueous NaOH (2 mL) was added. After 3 hours and 40 minutes, $CHBr_3$ (1 mL) was added. After 7 hours, $CHBr_3$ (1 mL) was added. After 8 hours, 50% aqueous NaOH (1 mL) was added. After 12 hours, T.L.C. (5% benzene/petroleum ether) showed product along with by-products. The reaction was diluted with CH_2Cl_2 and

washed with 5% HCl. The organic layer was washed with 5% HCl, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a gum. The gum was reconstituted in CH_2Cl_2 and filtered through silica gel. The filtrate was evaporated and the residue was crystallized from ether/petroleum ether to give a tan product (378 mg). This was followed by flash chromotagraphy (column i.d. 10 mm, eluent 20% ethyl acetate/petroleum ether) which gave product (60 mg). Three crystallization from CH_2Cl_2/MeOH afforded a crystalline compound, m.p. 209.5-212°C.

Experiment *11*: Carbene reaction on 3α,17ß-di-(*t*-butyldimethylsiloxy)estr-5(10)-ene **23c**:

To a two necked 100 mL pear shaped flask was added 3α,17ß-di-(*t*-butyldimethylsiloxy)estr-5(10)-ene (200 mg), cetrimide (52 mg), $CHBr_3$ (2 mL), and 50% aqueous NaOH (2 mL). The heterogeneous solution was stirred for 5 hours at room temperature, after which T.L.C. showed the presence of a product with the same R_f as the starting material. The reaction was diluted with ether and washed twice with 5% HCl, water (until neutral), brine, and dried over Na_2SO_4. All the aqueous washings were combined and extracted with CH_2Cl_2 and washed as before. Evaporation *in vacuo* of the ether and CH_2Cl_2 fractions furnished 428 mg of crude product. Flash chromatography (column i.d. 10 mm, eluent petroleum ether) afforded a colourless product (76 mg). ^1H N.M.R. analysis of the product showed two new signals at 2.55 and 2.76 ppm.

Experiment *12*: Zn-Cu couple reduction of product from Experiment *10*:

To a flame dried pear shaped 3-necked 25 mL flask was added a suspension of Zn-Cu couple in ethanol, followed by the product from Experiment *10* (13 mg). An argon tube was attached and the mixture stirred at room temperature. After 1 hour, T.L.C. (20% ethyl acetate/petroleum ether) showed 3 products and no starting material. The reaction mixture was filtered to remove the couple. The filtrate was diluted with water, and extracted with CH_2Cl_2. The organic phase was washed with 5% HCl, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* yielded a non-crystalline product. The product was combined with the crude product from Experiment *13* and flash chromatographed. See following experiment.

Experiment *13*: Zn reduction of product from Experiment *10*:

To a 25 mL pear shaped flask was added product from Experiment 10 (8 mg), Zn dust (131 mg), and ethanol (1 mL). A few drops of CH_2Cl_2 were added to solubilize the starting material. The mixture was stirred for 13 hours; only starting material was detected. AcOH (269 mg) was added. After 0.5 hours, T.L.C. (25% ethyl acetate/petroleum ether) showed three products. The reaction was stopped by filtering the mixture. The filtrate was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a gum. The crude product from the Zn-Cu reduction (Experiment *12*) and the Zn dust/AcOH reduction (Experiment *13*) were pooled (12 mg) and flash

chromatographed (column i.d. 5 mm, eluent 25% ethyl acetate/petroleum ether). Three compounds were isolated; **A** (5 mg), **B** (2 mg), and **C** (2 mg).

Experiment *14*: Jone's Oxidation of the product from Experiment *10*:

To a pear shaped 25 mL flask was added a solution of the product from Experiment 10 (12 mg) in acetone (1 mL). Jone's Reagent was added dropwise until a red colour persisted. After 10 minutes, T.L.C. (15% ethyl acetate/petroleum ether) showed two spots. After 0.5 hours, the slower moving spot was the major component. The reaction was quenched immediately with MeOH. The solution was diluted with CH_2Cl_2, and the organic layer washed with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a gum. Flash chromatography (column i.d. 5 mm, eluent 25% ethyl acetate/petroleum ether) yielded a crystalline product (6 mg).

Experiment *15*: Pyridinium dichromate oxidation of the product from Experiment *10*:

To a flame dried pear-shaped 25 mL flask was added the product from Experiment *10* (9 mg), dimethylformamide (1 mL), and pyridinium dichromate (21 mg). The whole mixture was stirred. T.L.C. (25% ethyl acetate/petroleum ether) over hourly intervals showed no product present. After 20 hours, pyridinium trifluoroacetate (13 mg) was added. After a total of 26 hours, only starting material was detected by T.L.C. The reaction was diluted with water, extracted with CH_2Cl_2, washed with water, brine, and

dried over Na_2SO_4. Evaporation *in vacuo* yielded a non-crystalline product which was found to be starting material by T.L.C.

Experiment *16*: Carbene reaction on 3α,17ß-diacetoxyestr-5(10)-ene **23b**:

To an argon evacuated 3-necked 25 mL pear shaped flask was added 3α,17ß-diacetoxyestr-5(10)-ene **23b** (11 mg), sodium trichloroacetate (10 mg), and glyme (300 μL). The solution was refluxed at 100°C under argon for 1 hour. T.L.C. (10% ethyl acetate/petroleum ether) showed no starting material present. The reaction was diluted with water and washed with CH_2Cl_2. The organic portion was washed with water, brine, and dried over Na_2SO_4. The crude product (10 mg) was analyzed by ^1H N.M.R., the spectrum of which was identical to the spectrum of the starting material.

Experiment *17*: Carbene reaction on 3α,17ß-diacetoxyestr-5(10)-ene **23b**:

3α,17ß-Diacetoxyestr-5(10)-ene **23b** (10 mg), sodium trichloroacetate (40 mg), and diglyme (300 μL) was dissolved in an argon evacuated 3-necked 25 mL pear shaped flask. The solution was heated to 130°C for 1 hour. After 1.25 hours, sodium trichloroacetate (21 mg) was added. After 2 hours, a second portion of sodium trichloroacetate (21 mg) was added. T.L.C. (5% ethyl acetate/petroleum ether) showed starting material present. The reaction was diluted with water and washed with CH_2Cl_2. The organic portion was washed with water, brine, and dried over Na_2SO_4. The crude

product (6 mg) was analyzed by ^{1}H N.M.R., the spectrum of which was identical to the spectrum of the starting material.

Experiment *18*: Carbene reaction on 3α,17ß-diacetoxyestr-5(10)-ene **23b**:

All glassware was flame dried and cooled to room temperature under argon in a dessicator. To a 3-necked 25 mL pear shaped flask was added a solution of the 3α,17ß-diacetoxyestr-5(10)-ene **23b** (54 mg) in glyme (2 mL). The solution was brought to reflux before adding sodium tribromoacetate (104 mg) in one portion. T.L.C. (25% ethyl acetate/petroleum ether) immediately after the introduction of the salt showed no starting material present. After 2 hours a second more polar spot was seen on the T.L.C. plate. The reaction was stopped by diluting with brine. The product was extracted three times with CH_2Cl_2. The combined organic fractions were washed twice with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded yellow crystals. Flash chromatography (column i.d. 5 mm, eluent 35% ethyl acetate/petroleum ether) of the crude product afforded non-crystalline material (17 mg). The ^{1}H and ^{13}C N.M.R. spectra of the product were identical to the spectra of an authentic sample of 17ß-hydroxyestr-5(10)-en-3-one **21**.

Experiment *19*: Carbene reaction on 3α,17ß-diacetoxyestr-5(10)-ene **23b**:

Using flame dried glassware, a 3-necked 25 mL pear shaped flask was equipped with a condenser and an argon inlet tube. 3α,17ß-Diacetoxyestr-5(10)-ene **23b** (56 mg) and

diglyme (4 mL) were added and the solution was brought to reflux. The reaction vessel was covered with tin foil. Sodium tribromoacetate (200 mg) in diglyme (6 mL) was added dropwise. The temperature of the oil bath was maintained between 100-120°C. After 1.5 hours, T.L.C. (25% ethyl acetate/petroleum ether) showed no starting material present. The reaction was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a dark gum. Flash chromatography (column i.d. 10 mm, eluent 25% ethyl acetate/petroleum ether) yielded a crystalline product (17 mg). The ^1H N.M.R. spectrum of the product showed it to be identical to an authentic spectrum of 17ß-hydroxyestr-4-en-3-one **22**.

Part B

Preparation of 3ß-(*t*-butyldimethylsiloxy)-5α-androst-17-one **87**:[62]

To an argon flushed 3-necked 100 mL round bottom flask was added 3ß-hydroxy-5α-androst-17-one **86** (5.00 g), dimethylformamide (35 mL), imidazole (3.00 g), *t*-butyldimethylsilyl chloride (3.29 g), and the mixture stirred at room temperature. After two hours, dimethylformamide (25 mL) was added to solubilize the white gelatinous mass. The reaction was allowed to proceed overnight when T.L.C. (20% ethyl acetate/ petroleum ether) showed the presence of starting material. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a viscous residue which

crystallized from CH_2Cl_2/MeOH to yield 3ß-(*t*-butyldimethylsiloxy)-5α-androst-17-one **87**, m.p. 164-166°C.

Preparation of (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88**:[63]

3ß-(*t*-Butyldimethylsiloxy)-5α-androst-17-one **87** (1.29 g) in freshly distilled tetrahydrofuran (10 mL) was mixed with a solution of triethyl phosphonoacetate (6.4 mL) in EtOH (distilled from Mg and I_2) (10 mL). A dropping funnel was charged with EtOH (10 mL) and Na metal (1.75 g) and allowed to react until no sodium remained. The NaOEt solution was added dropwise to the refluxing steroidal solution. After 3 hours reflux, T.L.C. (20% ethyl acetate/petroleum ether) indicated no starting material. The reaction was concentrated, diluted with water, and extracted with ether. The organic layer was washed with water, 1M HCl, water, brine, and dried over Na_2SO_4. Crystallization from ether/MeOH afforded (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88** (591 mg), m.p. 112-114°C (lit. m.p. 118°C).[63]

Preparation of 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89**:

To a 250 mL flat bottom flask was added (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88** (1.85 g), ether (100 mL), and $LiAlH_4$ (743 mg). The reaction proceeded at room temperature with stirring. After 1.5 hours, T.L.C. (5% ethyl acetate/petroleum ether) showed no starting material. The reaction was diluted with water, acidified with 12M HCl, and extracted with ether. The organic layer was washed

twice with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a gum. A portion was crystallized from ether/MeOH which gave 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89**, m.p. 125-126°C. Calculated C 74.94%, H 11.18%. Found C 74.75%, H 11.24%.

Preparation of 3ß-(*t*-butyldimethylsiloxy)-21-acetoxy-5α-pregn-17(20)-ene **90**:

3ß-(*t*-Butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89** (103 mg) was dissolved in a 2:1 solution of acetic anhydride/pyridine (3 mL) and stirred at room temperature. T.L.C. (20% ethyl acetate/petroleum ether) showed no starting material after 30 minutes. The reaction was diluted with ice water and the product extracted with CH_2Cl_2. The organic layer was washed thrice with 5% HCl, twice with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* gave 3ß-(*t*-butyldimethylsiloxy)-21-acetoxy-5α-pregn-17(20)-ene **90**, m.p. 119-121°C.

Preparation of the Zn-Cu couple:[64]

$Cu(OAc)_2 \cdot H_2O$ (56 mg) was added to a flame dried test tube which was placed in an oil bath (150 °C). Glacial acetic acid (2 mL) was added with stirring. To the boiling acetic acid/$Cu(OAc)_2 \cdot H_2O$ solution was added Zn dust (982 mg). Immediately the black Zn-Cu couple precipitated and was filtered and washed with ether (6x20 mL) until no odour of acetic acid could be detected.

Preparation of Zn-Ag couple:

Method A[66]

To a flame dried 2-necked 100 mL pear shaped flask was added silver acetate (22 mg) and acetic acid (5 mL). This was heated until all the silver acetate dissolved. To this solution was added Zn dust (3.42 g) in one portion. The black couple was washed with acetic acid (5 mL) and ether (5x50 mL) until no acetic acid could not be detected.

Method B[67]

10% Aqueous HCl (10 mL) was added to Zn dust (1.5 g) and stirred for 4-5 minutes at room temperature, after which, the Zn was allowed to settle and the supernatant was decanted. The residue was washed with acetone (10 mL) and ether (10 mL). A suspension of silver acetate (60 mg) in boiling glacial acetic acid (10 mL) was added and the mixture stirred for approximately 1 minute. The liquid was decanted and the Zn-Ag couple was washed with glacial acetic acid (5 mL) and ether (4x10 mL). After drying under a stream of N_2 gas, the couple was used immediately for the modified Simmons-Smith reactions.

For each of the methods used: Simmons-Smith, Modified Simmons-Smith, and Samarium/CH_2I_2, and for each of the substrates **88**, **89**, and **90**, a typical experiment is given.

Experiments *20*-21: Simmons-Smith reaction on (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88**:

(Experiment *20*) To a flask containing the Zn-Cu couple[64] (1.00 g) was added CH_2I_2 (1 mL) in ether (10 mL) and the heterogenous mixture refluxed for 30 minutes. (*E*)-Ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88** (438 mg) in ether (10 mL) was added under reflux. After 6 hours, T.L.C. (20% ethyl acetate/petroleum ether) showed only the presence of starting material. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water, brine, and dried over Na_2SO_4 to yield the crude product. T.L.C. of the crude product indicated only starting material. Experiment *21* was carried out in a similar manner as described in Table 11.

Experiments *22-28*: Simmons-Smith reaction on 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89**:

(Experiment *22*) Argon was flushed through a 3-necked 100 mL round bottom flask and a suspension of Zn-Cu couple[64] (991 mg) in ether (50 mL) was added followed by a solution of CH_2I_2 (700 μL) in ether (1 mL). The reaction mixture was refluxed for 30 minutes followed by the addition of 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89** (1.34 g) and ether (150 mL). Ether was added periodically to maintain constant volume. After 3 hours reflux, T.L.C. (2% ethyl acetate/petroleum ether) showed no starting material present. The reaction was diluted with water and acidified with 12M HCl. The organic layer was separated and washed twice with water, brine,

and dried over Na_2SO_4. Evaporation *in vacuo* gave a gum. Flash chromatography (column i.d. 10 mm, eluent 10% ethyl acetate/petroleum ether) gave products which were found to be impure as shown by ^1H N.M.R. and could not be separated or flash chromatographed. Experiments *23-28* were carried out in a similar manner as described in Table 11.

Experiment *29*: Modified Simmons-Smith reactions on (*E*)-ethyl 3ß-(*t*-butyldimethyl-siloxy)-5α-pregn-17-en-21-oate **88**:

CH_2I_2 (6.42 g) was added dropwise to an ethereal suspension (20 mL) of the Zn-Ag couple (Method A) (3.43 g) and the mixture was refluxed for 1 hour. (*E*)-Ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17-en-21-oate **88** (106 mg) in ether (10 mL) was then added dropwise. The mixture was refluxed for 7 hours followed by stirring overnight at room temperature. After 24 hours, T.L.C. (20% ethyl acetate/petroleum ether) showed the product to have the same R_f value as starting material. The reaction flask was immersed in a cold ice water bath and pyridine (15 mL) was added dropwise with vigorous stirring. The precipitate was filtered and the filtrate was evaporated *in vacuo*. The residue was reconstituted in CH_2Cl_2 and washed with 5% HCl, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* afforded a non-crystalline product. T.L.C of the product indicated only starting material.

Experiment *30*: Modified Simmons-Smith reaction on 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89**:

Under argon, a flame dried 3-necked 25 ml pear shaped flask was charged with Zn-Ag couple (106 mg) (Method B). A solution of distilled ether (5 mL) and CH_2I_2 (133 mg) was added dropwise over 20 minutes. 3ß-(*t*-Butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89** (70 mg) in distilled ether (3 mL) was added and the mixture was refluxed for 4.5 hours. The reaction was quenched by adding pyridine (10 mL) and ice water (10 mL). The product was extracted with CH_2Cl_2. The organic layer was separated and washed with 5% HCl, dilute $Na_2S_2O_3$, water, brine, and dried over Na_2SO_4. T.L.C. (20% ethyl acetate/petroleum ether) showed the presence of several less polar products and for this reason the ^1H N.M.R. spectrum was not obtained.

Experiment *31*: Modified Simmons-Smith reaction on 3ß-(*t*-butyldimethylsiloxy)-21-acetoxy-5α-pregn-17(20)-ene **90**:

To a flame dried three-necked 25 ml pear shaped flask was added the Zn-Ag couple (97 mg) (Method B) and freshly distilled ether (5 mL). CH_2I_2 (116 mg) in distilled ether (2 mL) was added dropwise and stirred for 1.5 hours under argon. 3ß-(*t*-Butyldimethylsiloxy)-21-acetoxy-5α-pregn-17(20)-ene **90** (50 mg) in distilled ether (5 mL) was added dropwise and the whole mixture was refluxed. After 9 hours, T.L.C. (20% ethyl acetate/petroleum ether) showed the presence of a product with the same R_f as the starting material. Pyridine (12 ml) was added and stirred overnight in an ice bath. The

organic layer was washed with 5% HCl, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* gave a colourless product. T.L.C. indicated only starting material.

Experiment *32*: Reaction of samarium/CH_2I_2[68] on 3ß-(*t*-Butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89**:

To a flame dried 3-necked 25 mL pear shaped flask was added flamed dried samarium powder (69 mg) and freshly distilled THF (2 mL). The flask was flushed with argon and cooled to -77°C (dry ice/acetone). 3ß-(*t*-Butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89** (50 mg) and a solution of CH_2I_2 (129 mg) in distilled tetrahydrofuran (2 mL) was added. The mixture was stirred for 1 hour at -77°C, after which the reaction vessel was removed and warmed to room temperature. A second portion of samarium powder (70 mg) was added. After 3 hours, T.L.C. (25% ethyl acetate/petroleum ether) showed the presence of a less polar product. After 4 hours, CH_2I_2 (50 μL) was added. Through out the course of the reaction the volume of THF was maintained at 4 ml. After 20 hrs., the reaction was diluted with water and the product was extracted with CH_2Cl_2. The organic layer was washed with 5% HCl, brine, and dried over Na_2SO_4. Evaporation *in vacuo* gave a non-crystalline product. None of the desired cyclopropano derivative was obtained as indicated by the absence of resonances in the highfield region of the ^1H N.M.R. spectrum.

Experiment *33*: Reaction of diazomethane[69] on (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88**:

To a 100 mL pear shaped flask was added (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88** (53 mg), ether (8 mL), $Pd(OAc)_2$ (5 mg) and the mixture was stirred. The temperature was maintained at 5°C. Upon dropwise addition of CH_2N_2 (1 mL), the solution turned dark brown. T.L.C. (4% ethyl acetate/petroleum ether) showed no product present. The ice bath was removed and the solution was warmed to room temperature. After 50 minutes, no product was observed by T.L.C. and CH_2N_2 (4 mL) and $Pd(OAc)_2$ (5 mg) were added. After 3 hours, the reaction was diluted with water and extracted with CH_2Cl_2. The organic layer was separated and washed with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* gave a crystalline product. T.L.C. of the product showed only starting material.

Experiment *34*: Reaction of diazomethane[69] on 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89**:

To a 50 mL pear shaped flask was added 3ß-(*t*-butyldimethylsiloxy)-21-hydroxy-5α-pregn-17(20)-ene **89** (50 mg), ether (7 mL), and $Pd(OAc)_2$ (5 mg). CH_2N_2 (1 mL) was added dropwise. The reaction was stirred at room temperature. After 10 minutes, T.L.C. (20% ethyl acetate/petroleum ether) showed only starting material. After 50 minutes CH_2N_2 (2 mL) was added. T.L.C. showed only one compound with the same R_f as the starting material. After 65 minutes, CH_2N_2 (5 mL) was added and the reaction

mixture stirred. After 2 hours, T.L.C. showed only starting material present. The reaction was diluted with water and the product was extracted with CH_2Cl_2. The organic layer was washed with 5% HCl, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* gave starting material as indicated by T.L.C.

Experiment *35*: Carbene reaction on (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17-en-21-oate **88**:

To a 3-necked 25 mL pear shaped flask was added (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17-en-21-oate **88** (50 mg) in ether (2 mL) and 50% aqueous NaOH (1 mL). Cetrimide (6 mg) and $CHBr_3$ (50 μL) were added and the whole mixture was stirred for 1 hour, after which T.L.C. (5% ethyl acetate/petroleum) showed only starting material. A second portion of $CHBr_3$ (500 μL) was added. After 2 hours, T.L.C. showed no presence of product and a second portion of cetrimide (10 mg) was added. After 18 hours, T.L.C. showed the presence of starting material and more polar products. A second portion of 50% aqueous NaOH (1 mL) and a third portion of $CHBr_3$ (500 μL) was then added. After 20 hours, the reaction was diluted with brine and extracted with CH_2Cl_2. The organic layer was washed with water, 5% HCl, brine, and dried over Na_2SO_4. Evaporation *in vacuo* furnished a non-crystalline product. T.L.C of the product showed the presence of several less polar compounds that were not separated due to the small quantity of starting material used.

Experiment *36*: Carbene reaction on (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17-en-21-oate **88**:

To a flame dried 3-necked 25 mL pear shaped flask was added (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17-en-21-oate **88** (50 mg) in diglyme (2 mL). The flask was flushed with argon, immersed in an oil bath and heated to reflux (160°C). A solution of sodium trichloroacetate (103 mg) in diglyme (2 mL) was added. Immediately a white solid precipitated out of solution. After 3 hours, sodium trichloroacetate (50 mg) was added. After 4.5 hours, a third portion of trichloroacetate (103 mg) was added. T.L.C. (5% ethyl acetate/petroleum ether) showed the presence of starting material. The reaction was stopped by diluting with water. The product was extracted with CH_2Cl_2. The organic layer was washed with 5% HCl, water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* gave a non-crystalline product, which was identified by T.L.C. as starting material.

Experiment *37*: Carbene reaction on (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88**:

To a flame dried 3-neck 25 mL pear shaped flask was added (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88** (50 mg) and glyme (1 mL). The solution was refluxed and sodium tribromoacetate (175 mg) was added, upon which the reaction turned dark brown. A second portion of glyme (1 mL) was added. After 30 minutes, T.L.C. (5% ethyl acetate/petroleum ether) showed the presence (1-5%) of a

more polar compound. After 1.5 hours, sodium tribromoacetate (475 mg) and glyme (2 mL) was added. After 4.5 hours, no significant amount of product had been formed according to T.L.C. (4% ethyl acetate/petroleum ether). The reaction was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* gave a non-crystalline product, which was identified as starting material by T.L.C.

Experiment *38*: Reaction of trimethylsulphoxonium iodide/NaH[71] on (*E*)-ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88**:

To an argon evacuated flame dried 3-necked 25 mL pear shaped flask was added a solution of trimethylsulphoxonium iodide (179 mg) in dimethylsulphoxide (3 mL). To this was added NaH (27 mg). (*E*)-Ethyl 3ß-(*t*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate **88** (292 mg) was added and heated to 96°C. After 4 hours no product was detected by T.L.C. (20% ethyl acetate/petroleum ether). More trimethylsulphoxonium iodide (TMSI) (101 mg) and NaH (103 mg) were added. After five hours, only starting material was detected by T.L.C. The reaction was diluted with water and extracted with ether. The organic layer was washed with water, brine, and dried over Na_2SO_4. Evaporation *in vacuo* yielded a non-crystalline product, which was again identified as starting material by T.L.C.

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