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THE SYNTHESIS AND STRUCTURAL EXAMINATION OF
3 α ,5-CYCLO-5 α -ANDROSTANE STEROIDS

by

Bruce Clark Gibb

A thesis presented in part fulfilment of the requirements for the degree of Doctor of Philosophy of the Council for National Academic Awards.

The Robert Gordon Institute of Technology
in collaboration with the University of Aberdeen
March 1992

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To lost opportunities and new found promises

Acknowledgements

I wish to record my sincere appreciation to my research supervisors, Dr P. J. Cox and Dr S. M. MacManus, of the Pharmacy department of The Robert Gordon Institute of Technology, for the excellent guidance and help they provided. I would also like to express my sincere gratitude to two colleagues from Aberdeen University. My external supervisor, Dr A. B. Turner, for his constructive advice and Dr A. Howie for collecting the X-ray data used in this work.

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I would also like to thank those members of staff who allowed me to undertake this research.

Last, but by no means least, I would like to thank my mother and father for their dedication, support and encouragement over many years.

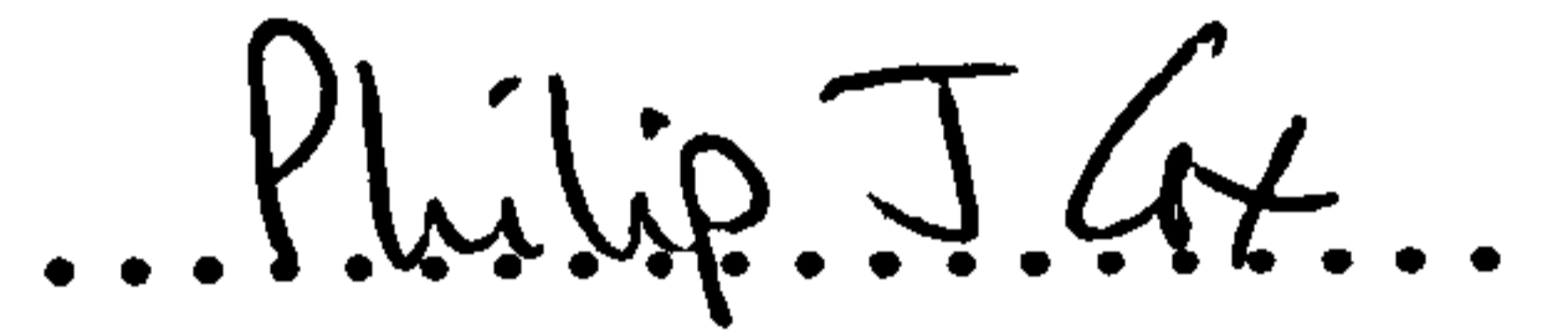
Declaration

All the experimental work described in this thesis was carried out by Bruce C. Gibb in the laboratories of The Robert Gordon Institute of Technology and Aberdeen University.

It has not been accepted in substance or concurrently submitted in candidature for any other degree.

Handwritten signature of Bruce C. Gibb in cursive script, followed by a dotted line.

Candidate

Handwritten signature of Philip J. Cox in cursive script, followed by a dotted line.

Director of Studies

Abstract

Synthesis and Structural Examination of 3 α ,5-Cyclo-5 α -Androstane Steroids.

By Bruce Gibb

The work described in this thesis is based on the synthesis and structural examination of several cyclosteroids.

The σ -aromatic steroid 3 α ,5-cyclo-5 α -androstan-6 β -ol-17-one was used as a lead compound in an attempt to produce, in particular, the 17 α -ethynyl derivative, the 6 β -methyl derivative and the 7 α -hydroxy, 6 β -methyl derivative. Full experimental details of the various routes are provided. X-ray crystallography, along with standard spectroscopic techniques, were utilised in structural determinations. To complement these techniques molecular mechanics were also utilised to predict spectroscopic results and to structurally define the products.

The biological significance of steroids with respect to contraception is outlined and the chemistry of the cyclopropane ring discussed. A critical evaluation of the synthesis of cyclopropane steroids and the alkylation of steroids has been made. The objectives and methodologies behind recent innovations are discussed.

An improved synthesis of the lead compound, from dehydroepiandrosterone, was achieved. The chemical and spectral implications of the introduction of σ -aromaticity into the steroid nucleus is discussed.

The synthesis of the ethynyl derivative, was achieved in increasing yields by four different routes.

Synthesis of the 6 β -methyl derivative was considered via four different pathways. Three of these routes gave the important 6-methylene precursor but insufficient quantities prevented the formation of the desired molecule.

Formation of the 7 α -hydroxy, 6 β -methyl derivative, as well as its 6 β -hydroxy, 7 α -methyl isomer has been accomplished. However, instability of the epoxide precursor resulted in low yields.

Two novel single crystal X-ray structures have been elucidated and X-ray powder diffraction data obtained on a third. Results of the two determinations have been published. The accurate geometrical details of these compounds formed a basis for subsequent molecular mechanics calculations.

Molecular modelling was used to aid product identification, determine theoretical product stability, i.e., potential reaction outcome and to support spectroscopic data.

General Summary.

Synthesis and Structural Examination of 3 α ,5-Cyclo-5 α -Androstane Steroids.

The structurally interesting σ -aromatic steroid 3 α ,5-cyclo-5 α -androstane-6 β -ol-17-one has been used as a lead compound for the synthesis a number of target molecules possessing a cyclopropane ring. The specific target molecules, which it was hoped would possess progestational or anti-progestational activity, were the 17 α -ethynyl derivative, 6 β -methyl derivative and the 7 α -hydroxy, 6 β -methyl derivative. X-ray crystallography, along with standard spectroscopic techniques, were utilised in structural determinations. To complement these techniques molecular mechanics were also utilised to predict spectroscopic results and to structurally define the products.

The structures of two compounds, the starting molecule, dehydroepiandrosterone, and the parent cyclopropane steroid have been successfully elucidated by means of single crystal X-ray crystallography. Results of these two determinations have been published. The accurate geometrical details of these compounds formed a basis for subsequent molecular mechanics calculations.

The synthesis of the parent steroid, from dehydroepiandrosterone (DHEA), was attained by several variations to the classical method. One particular method gave improved yields and was therefore the preferential method of synthesis. The chemical and spectral implications of the introduction of σ -aromaticity into the steroid nucleus is discussed.

The initially intended "direct" synthesis of the first target molecule, the ethynyl derivative, was found under investigation to proceed with relatively low yield. Three alternative routes to this compound were therefore devised and resulted in an improved synthesis of the desired steroid.

For the synthesis of the second target molecule, the 6 β -methyl derivative, protection of the 17-ketone function was a prerequisite. After early results had indicated the fragmentation of the cyclopropane ring, an alternative route, via the dioxalane derivative of DHEA, successfully led to a protected derivative of the parent compound. Yields by this route were low but were improved when an oxathiolane protecting group was used. The reactivity of the 3-C hydroxy group of the DHEA oxathiolane derivative was reduced by a long range effect induced by the protecting group. Molecular mechanics were used in an attempt to interpret of this result. Further conversions of the oxathiolane resulted in the isolation of the important 6-methylene precursor. In an attempt to further increase yields three additional routes to the target molecule were devised and undertaken. The successful synthesis of the novel 6-methylene precursor was achieved by two of these routes. A detailed spectroscopic analysis of the important methylene derivative indicated that the amount of conjugation between the exocyclic methylene group and the cyclopropane ring was approximately half of that found in vinylcyclopropane. Molecular modelling indicated the existence of a repulsive interaction between the 4 α -cyclopropane proton and the methylene group. This

results in the vinylcyclopropane moiety adopting a conformation ill-suited for maximum conjugation. Reduction of the methylene group was not carried out because of insufficient amounts of the precursor.

Formation of the 7α -hydroxy, 6β -methyl derivative, as well as its 6β -hydroxy, 7α -methyl isomer has been accomplished. The 6-ene steroid intermediate to these derivatives was synthesised in higher yields by modifications to the literature technique. This second vinylcyclopropane derivative was shown, by spectroscopic analysis and molecular modelling, to possess greater conjugation than its exocyclic counterpart. Conjugation was less than that found in vinylcyclopropane itself. The epoxide precursor to the target molecule, formed by epoxidation of the 6-ene steroid, was synthesised but found to be exceedingly unstable. Contrary to previously published work, both the α and β -isomers were apparently formed, a result investigated by molecular models. Thus the models showed that the cyclopropane ring can considerably affect reaction at ring B of these steroids by directing reagent attack to the β -face. Based on these models, calculations of the expected ^1H NMR coupling constants between the epoxy protons and their neighbouring protons were made. These results indicated that the epoxide, previously designated as the α -isomer, was most certainly the β -isomer. The accuracy of these models was shown by the modelling of other steroid epoxides, including one whose structure had previously been defined by X-ray crystallography. To avoid protection of the ketone functionality, and hence increase the overall yield of the product, an epoxide

specific organo-copper reagent was utilised for the final step in the process instead of the initially intended Grignard reagent. The two isomers produced were identified by a comparison between the ^1H NMR coupling constants of the proton geminal to the hydroxy group and those predicted by molecular mechanics. In constructing the molecular models of the four possible isomeric products, a relationship between the stability of each isomer and the standard deviation from the mean torsion angle of ring B was noted. Thus it was shown that, as expected, the compounds containing equatorial substituents were the most stable. Results also indicated that products with a hydroxy group at 7-C were more stable than their 6-hydroxy counterparts.

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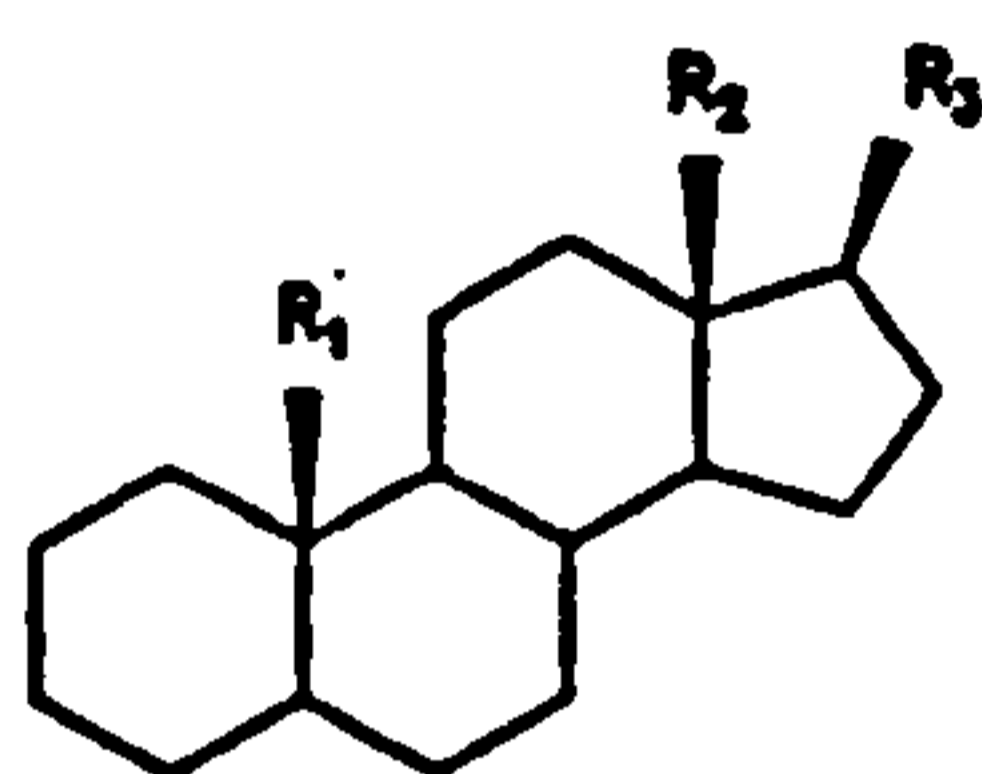
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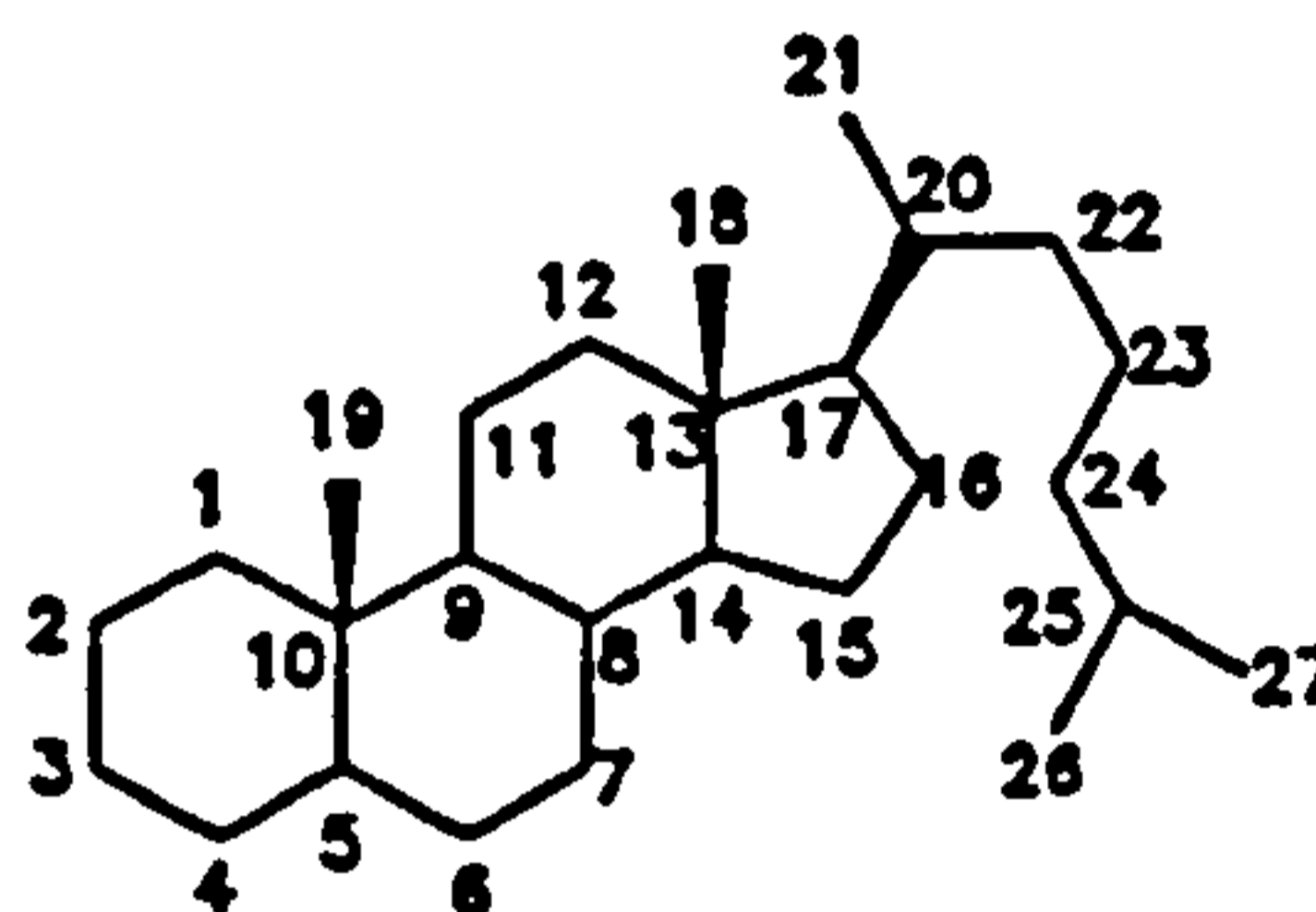
Chapter 1
Introduction

1.1.1 Introduction to steroids.

Steroids are a group of organic compounds that normally possess the characteristic tetracyclic (perhydrocyclopentonephenanthrene) backbone (1). Biologically derived, (section 1.1.4) their occurrence in both animal and plant organisms is considerable, if not unrivalled. Their diversity is such that even outwith living organisms steroids can be isolated in considerable quantities. Thus steroids have been recovered from the ocean sediments, rock formations and shales,

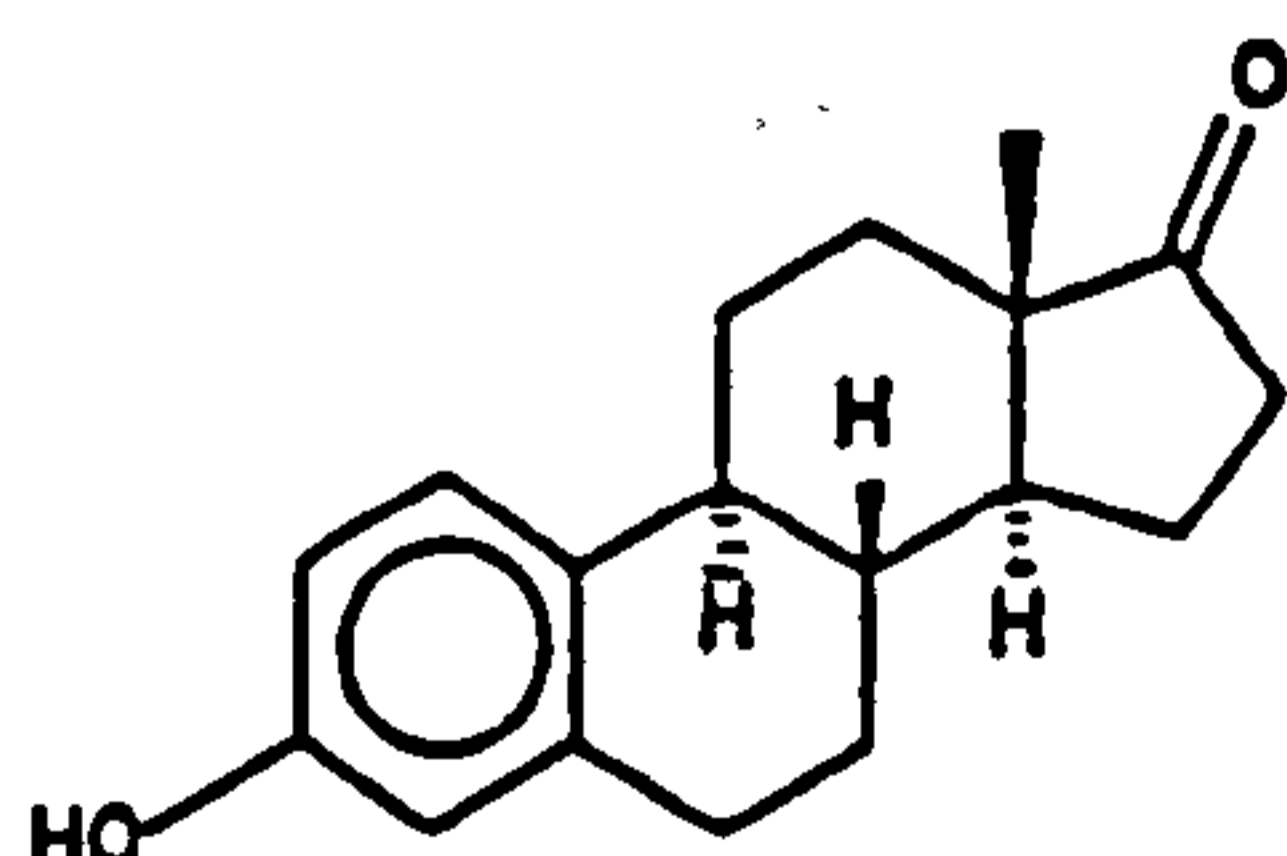


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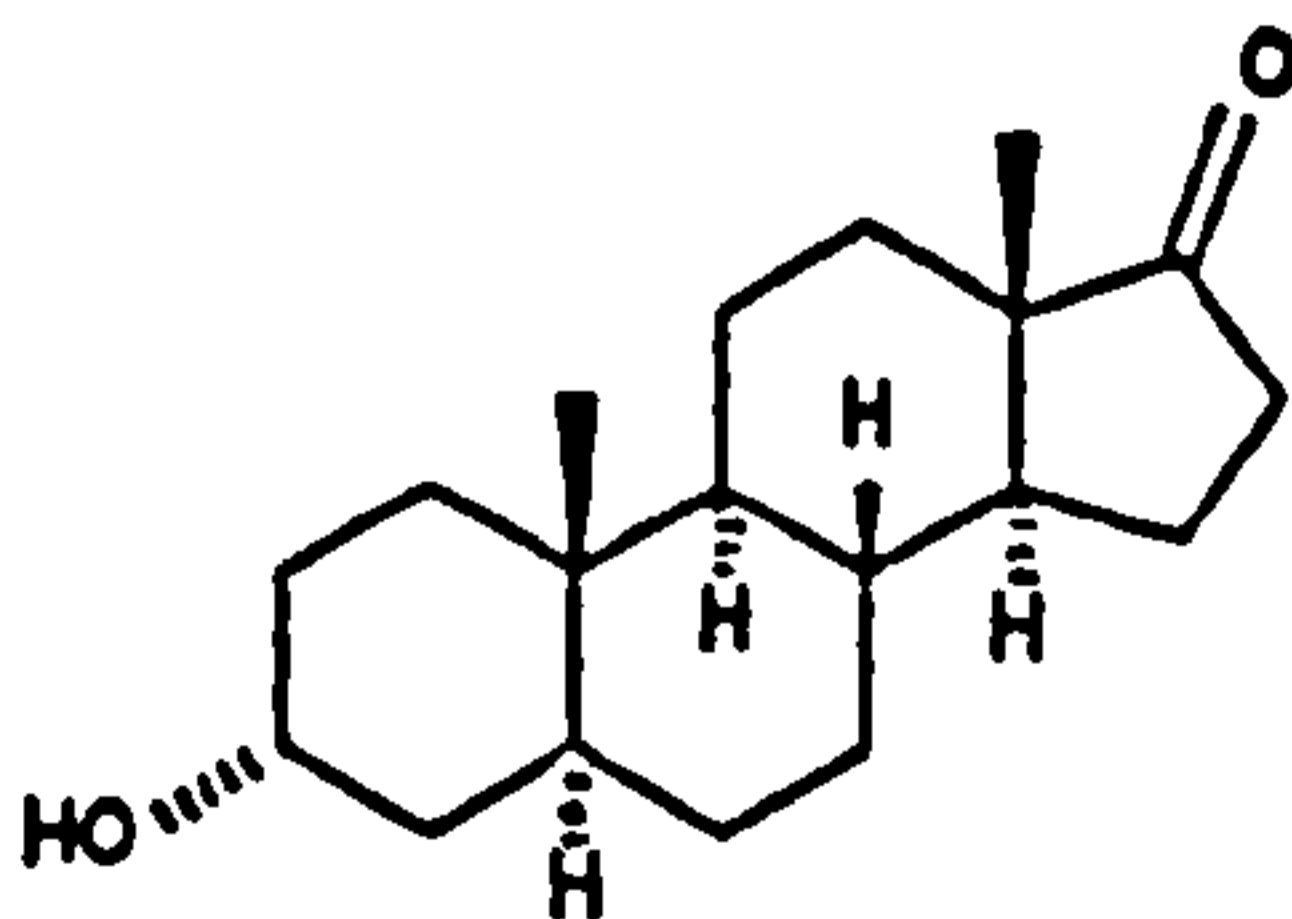


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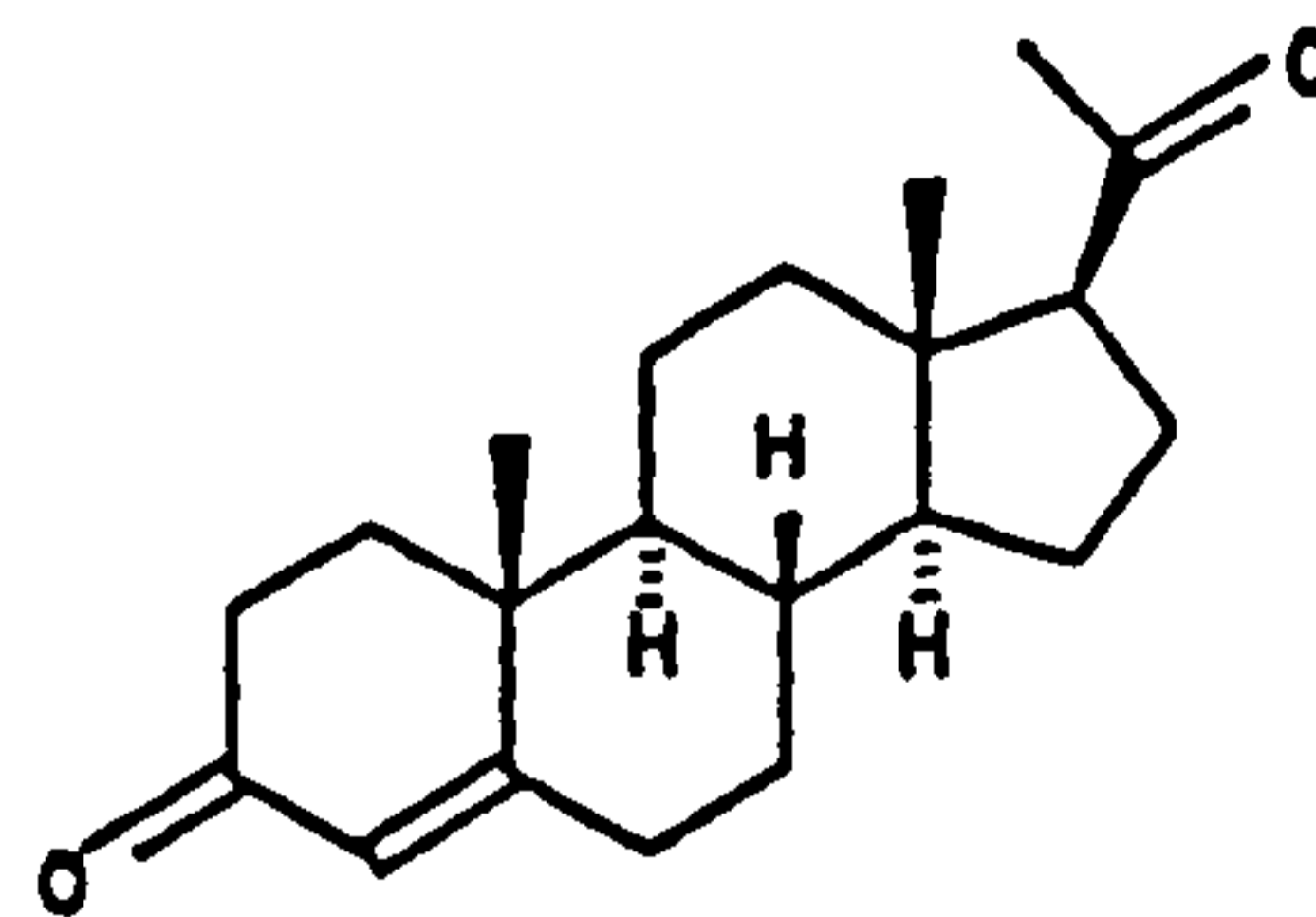
and even as airborne particulates. Their structural variations are primarily due to differences in the side chains R_1 , R_2 and R_3 and secondary to differences in nuclear substitution, degrees of unsaturation and ring junction configurations. R_1 and R_2 are normally methyl groups, therefore the chosen numbering system for these compounds (2) remains constant for any variation of the R_3 sidechain. Amongst the



(3)

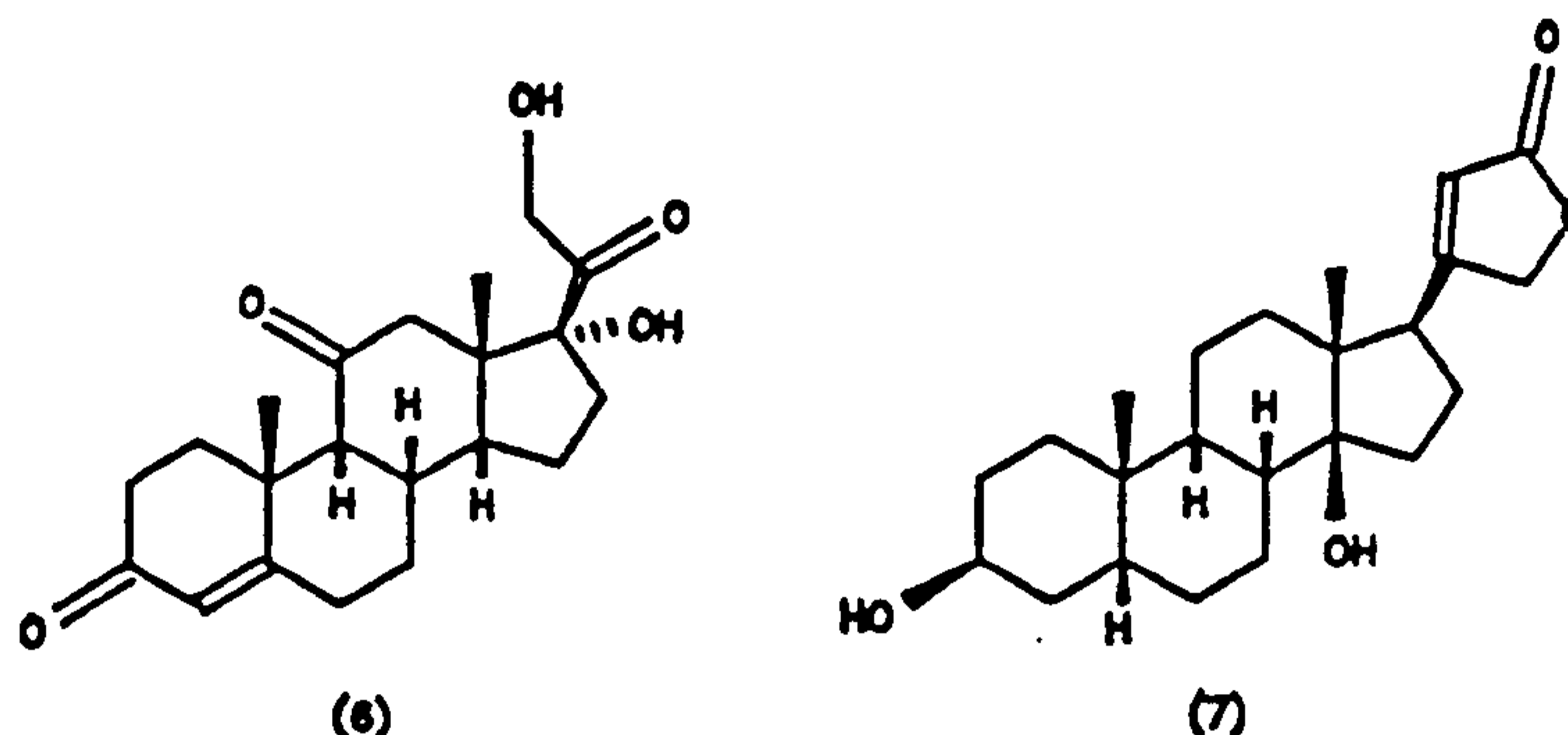


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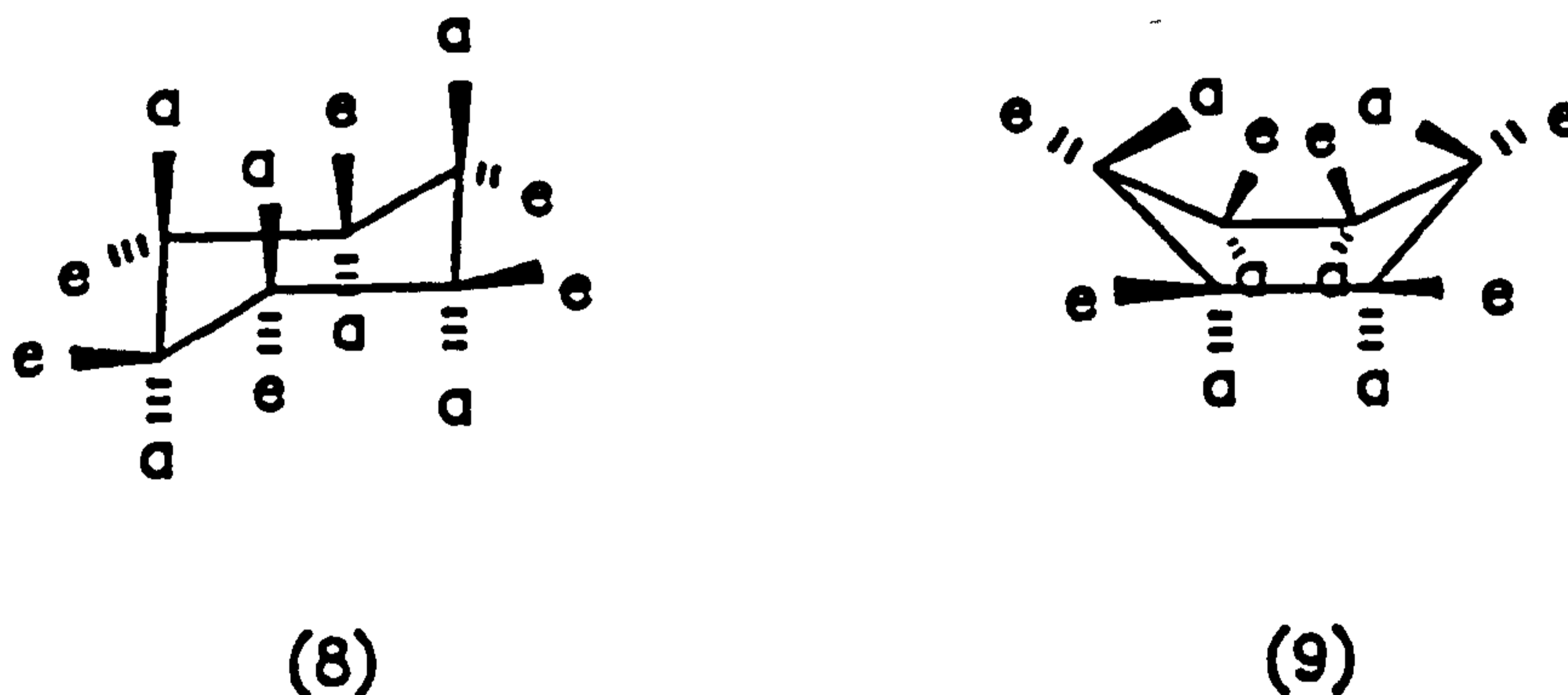
(5)

steroids are compounds of considerable medical importance. These include the sex hormones, such as estrone (3), androsterone (4) and progesterone (5), the adrenocorticoid hormones such as cortisone (6) and the cardiac glycosides (3-C sugar derivatives of steroids such as digitoxigenin (7)).



1.1.2 Conformation and configuration

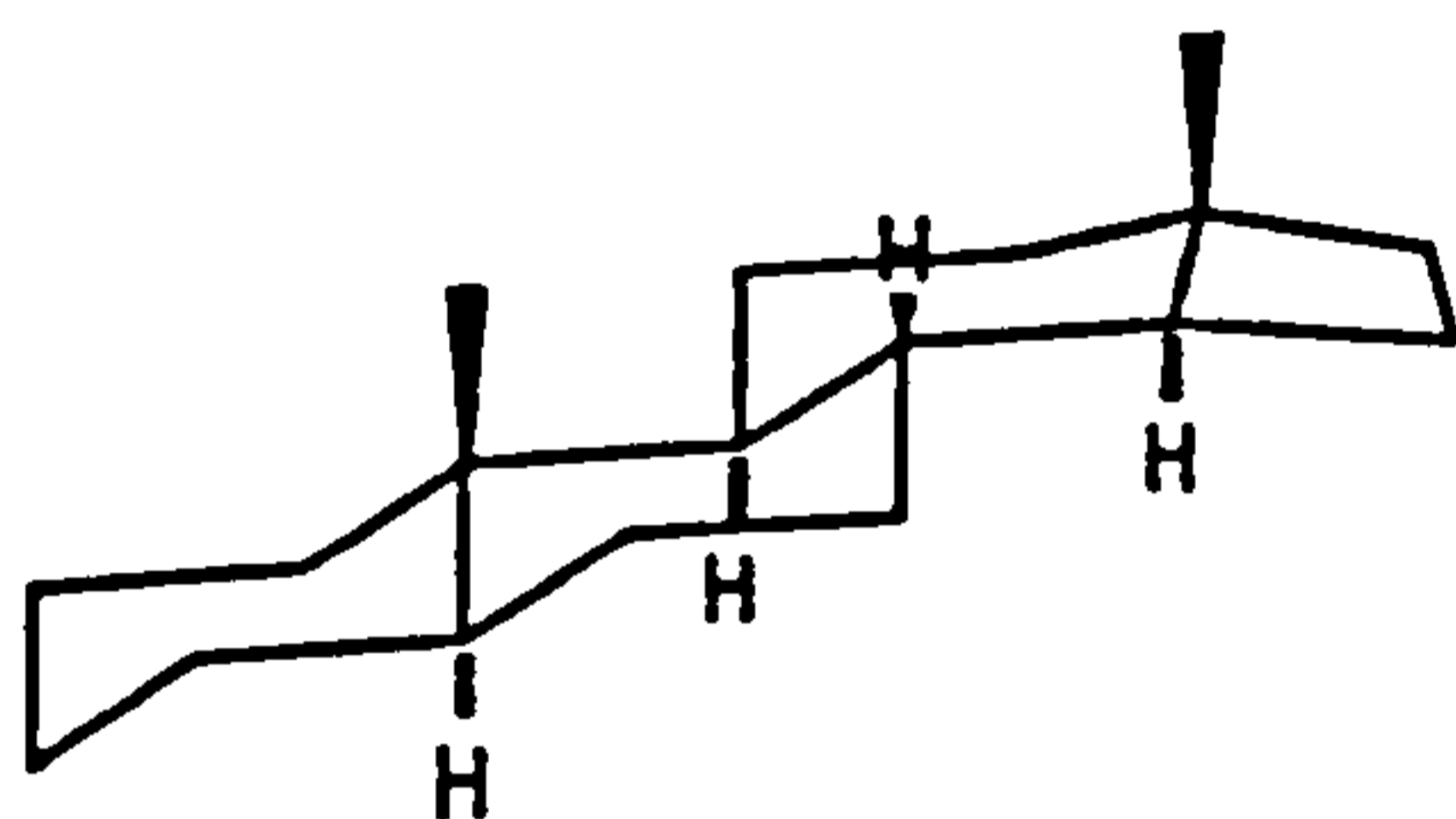
The six carbon atoms of a cyclohexane unit can be considered as either a chair (8) or boat (9) form. As the chair form allows for reduced steric interactions this form



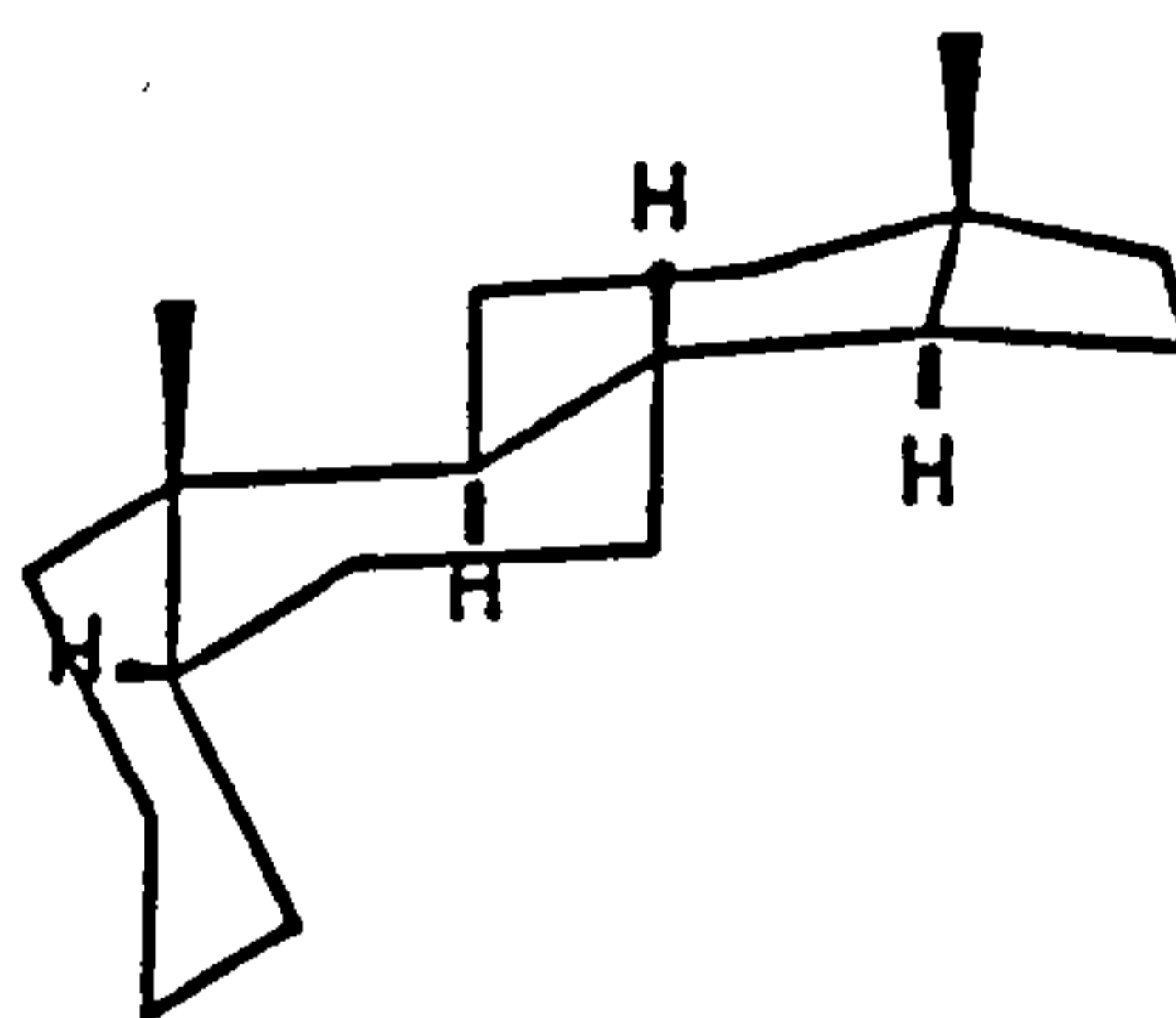
is of lower energy and is therefore the conformation preferred by cyclohexane rings in steroids. In either of the conformations the hydrogens attached to each carbon atom can assume either an equatorial position (e); where the atom lies at 30° to the plane of the ring, or an axial position (a) where the carbon hydrogen is perpendicular to the plane of the ring. For steroids however, it is more convenient to designate the terms α or β to a hydrogen atom or other

substituent to define whether the atom or moiety lies below or above the plane of the steroid, respectively.

The ring junctions of saturated steroids may be either cis or trans, thus giving rise to 6 asymmetric centres (5, 8, 9, 10, 13 and 14-C). Therefore 64 stereoisomeric forms are theoretically possible in the tetracyclic nucleus alone. This range of possibilities is reduced somewhat in nature as all B/C ring junctions in naturally occurring steroids are trans. In the sterols and bile acids the C/D ring junction is also trans but in the plant glycosides this junction is cis. The A/B junction can be either trans, giving the 5 α series (10) or cis giving the 5 β series (11) of compounds.



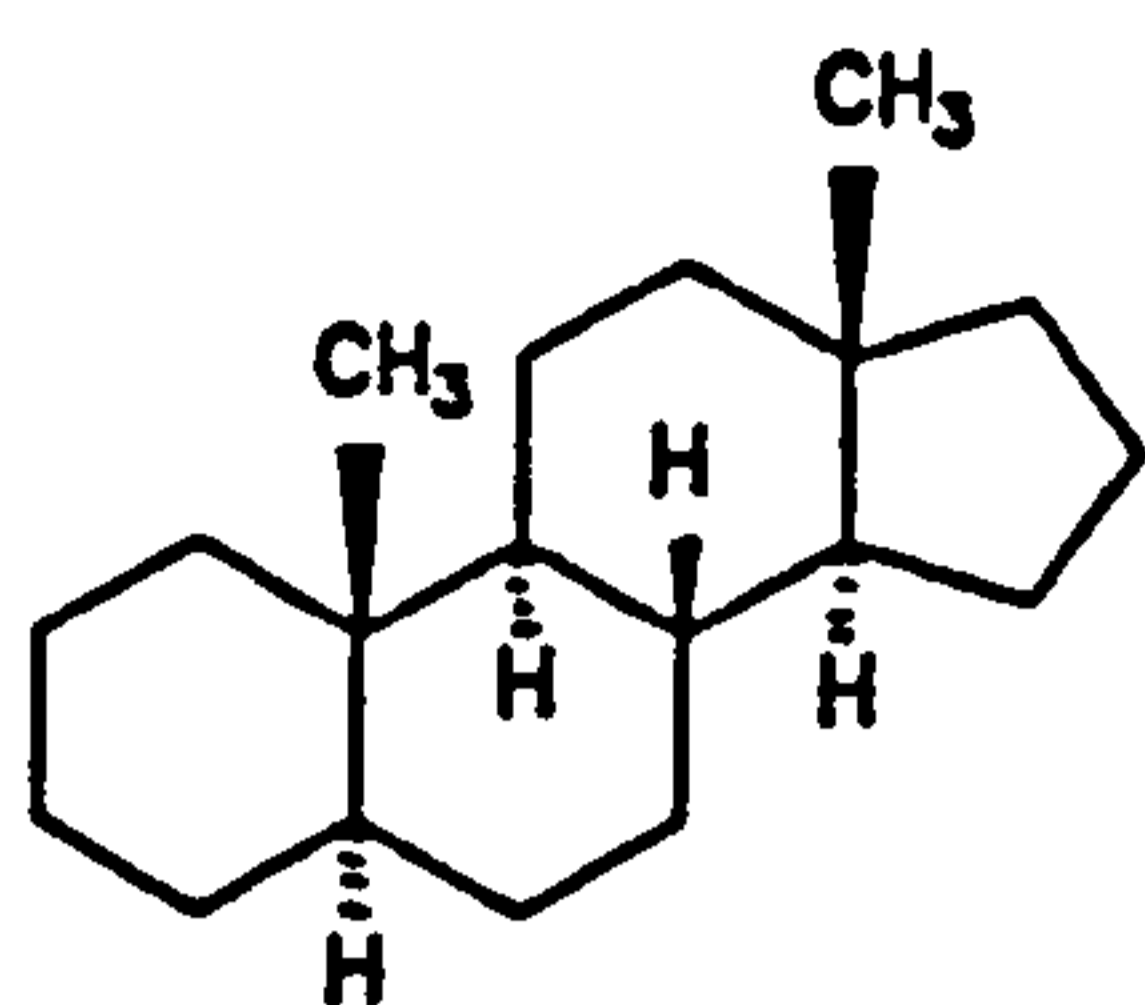
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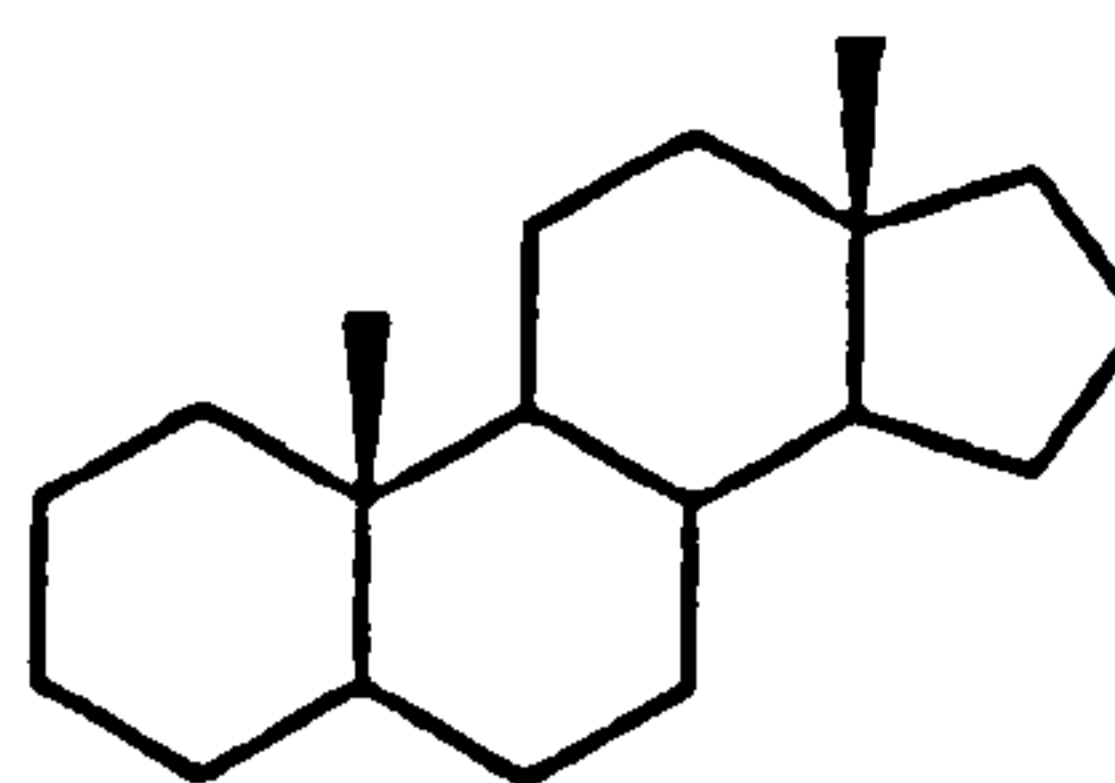
(11)

Most of the biologically important steroids have a trans A/B junction, i.e., they belong to the 5 α series. Because of the immense effect that "backbone" stereochemistry has upon the shape of the molecule, IUPAC rules¹ require the stereochemistry at all backbone carbons to be clearly marked. That is, all hydrogens along the backbone must be drawn. However, as all steroids synthesised in this work are orientated thus: 8 β , 9 α , 10 β , 13 β , and 14 α , (12), the simplified structure (13) will be normally used in this work. Complete structures

will only be drawn where reference is made to molecules that do not possess the above stereochemistry.



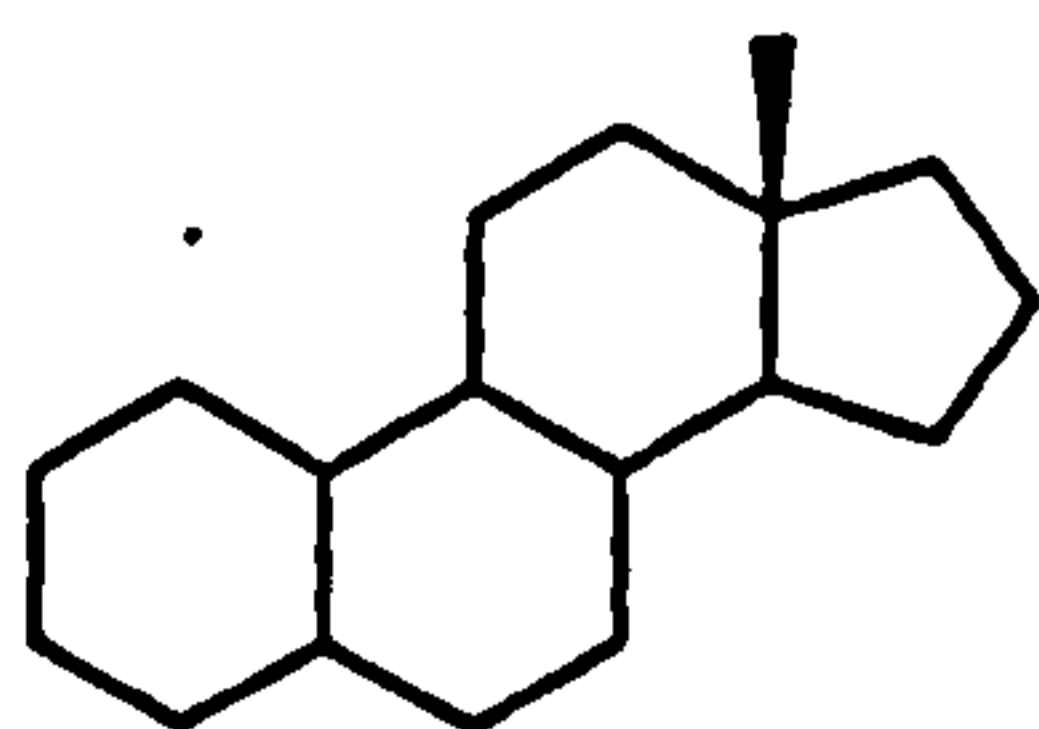
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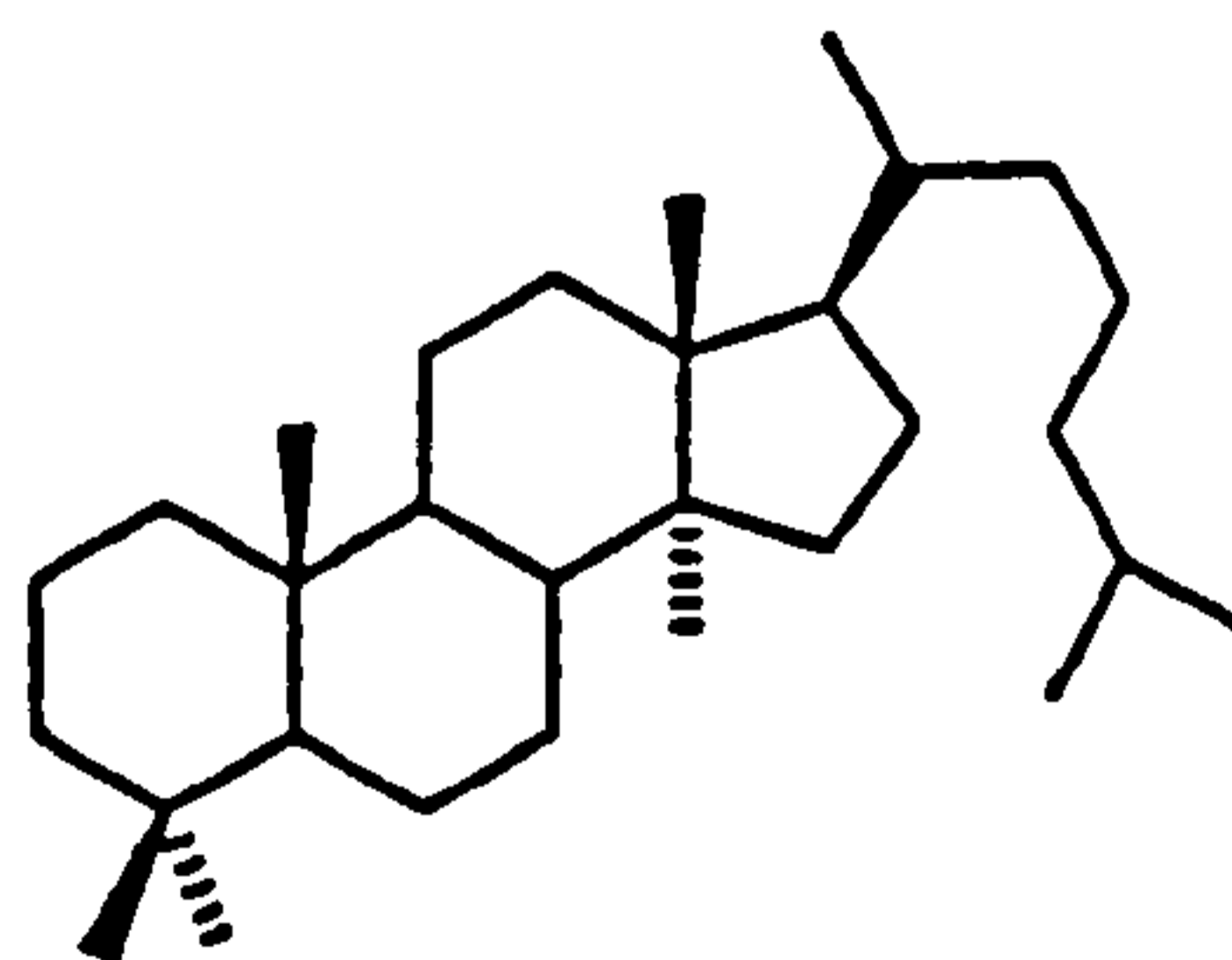
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1.1.3 Classification and nomenclature.

The various steroids, as they were isolated and characterized, were given trivial names based usually on their provenance or their particular pharmacological activity. This resulted in a profusion of names and a rather unsystematic nomenclature which still persists to some extent in the literature. As the various chemical structures of the steroids became known a more rational system of nomenclature, based on a limited number of parent or fundamental compounds, was devised.¹ The parent compounds are therefore ordered in terms of the number of carbon atoms that they possess, from 18 carbon atoms for the estrogen series (parent: estrane (14)) through to the zoosterols (parent: lanostane (15)) which possess 30 carbon atoms. The compounds synthesised in this work all belong to the 19 carbon atom

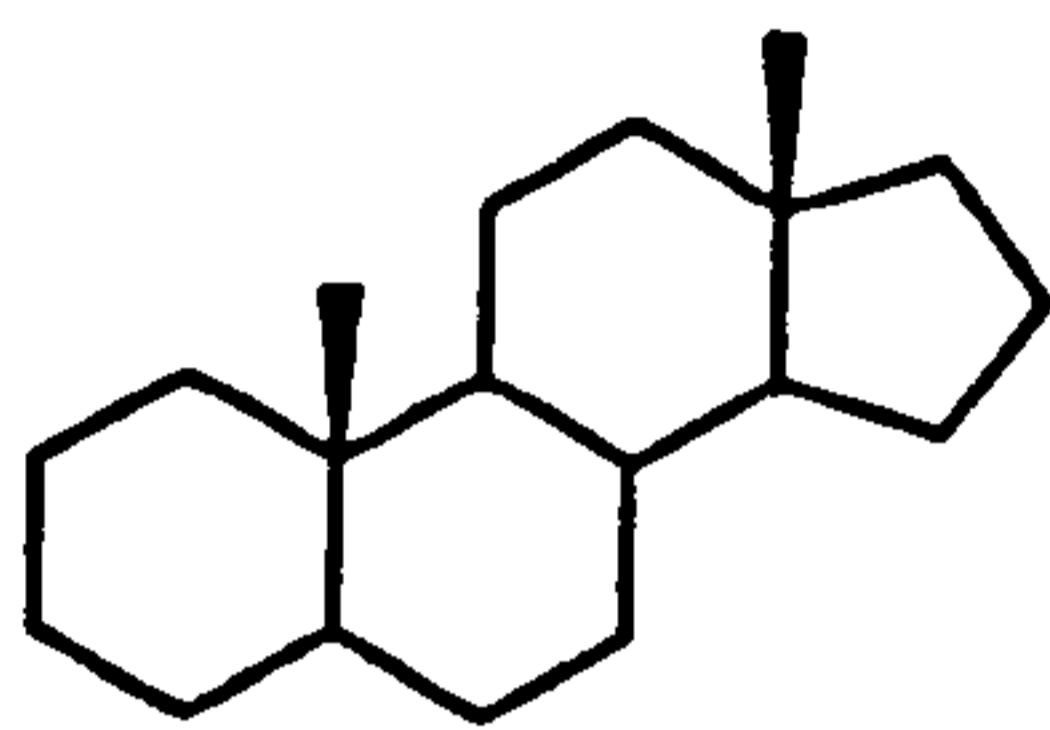


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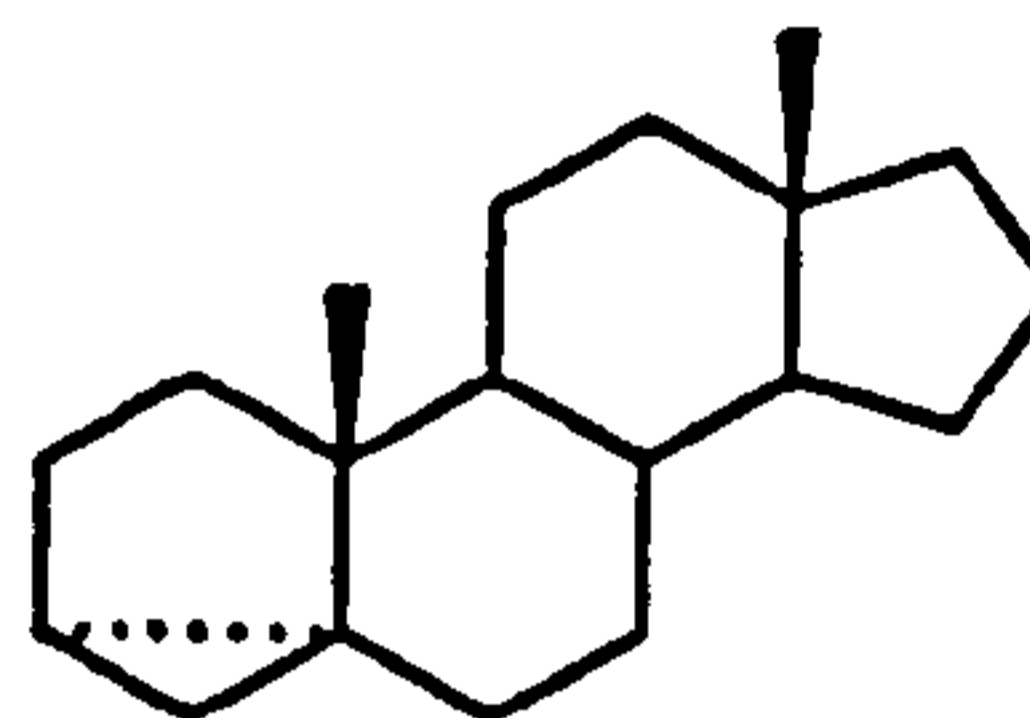


(15)

series the androgens, (parent: androstane (16)). More pertinent to this work, steroids which contain a 3 membered cyclopropane ring within their nuclear structure are commonly known as cyclosteroids. Thus, a more accurate name for the target molecules here are cycloandrostanes. The prefix "cyclo" is also coupled with the appropriate numerals and necessary stereochemical designations to define the position of the cyclopropane ring. Hence all target molecules synthesised here, with the basic structure (17), are designated as belonging to the $3\alpha,5$ -cyclo- 5α -androstanes series. However,



(16)



(17)

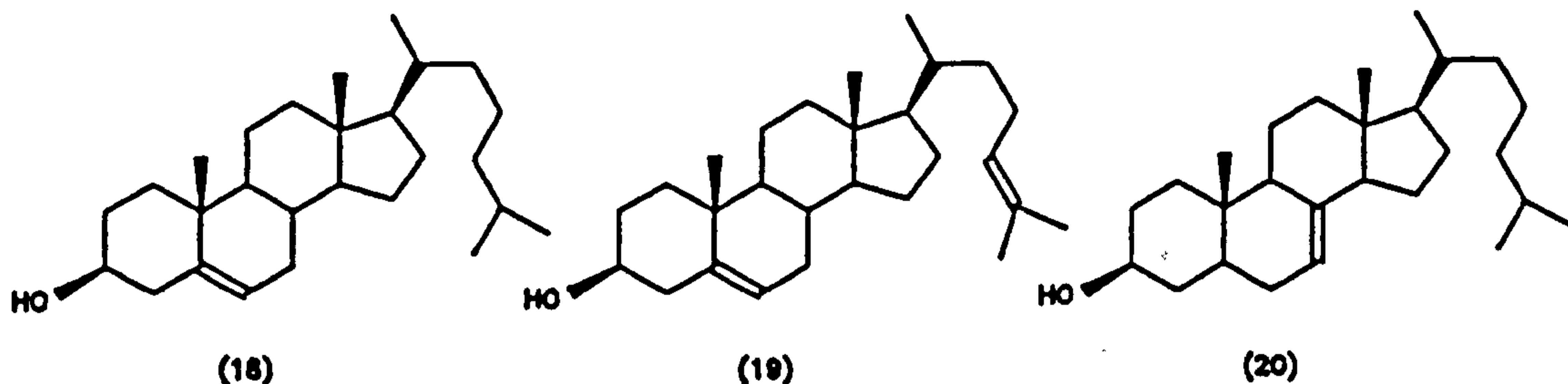
from 1972 onwards Chemical Abstracts has (more correctly) designated this structure as $3\beta,5\alpha$. As the $3\alpha,5\alpha$ terminology is still the most widely used, it is this name that is used in this work.

Structurally intriguing, the cyclosteroids have been subject to intensive synthetic studies. Other such compounds formed thus far include the isomeric series of the title compound; the $3\beta,5$ -cyclo- 5β -steroids, and also both the α and β isomers of the $5,7$ -cyclosteroids. Some of the many cyclopropane steroids synthesised to date are discussed in section 1.4.3

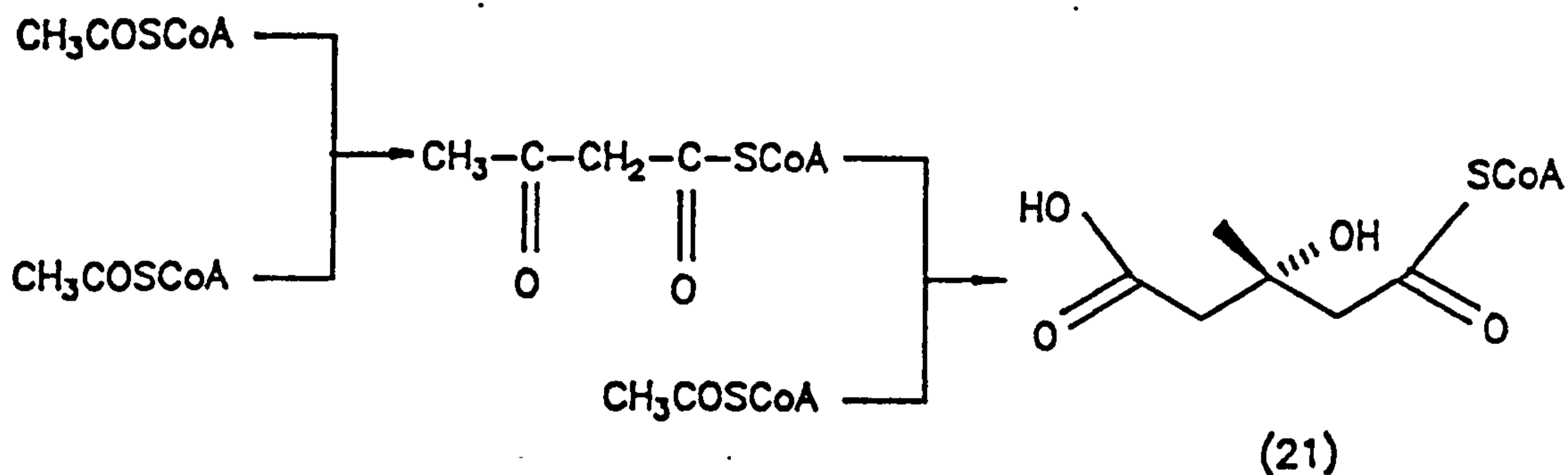
1.1.4 Biosynthesis of steroids.

Biosynthesis of lanosterol.

In animals, cholesterol (18) is believed to be the principle starting molecule for steroid biosynthesis. However, desmosterol (19) and lathosterol (20) also play a significant part. The biochemical reaction which initiates



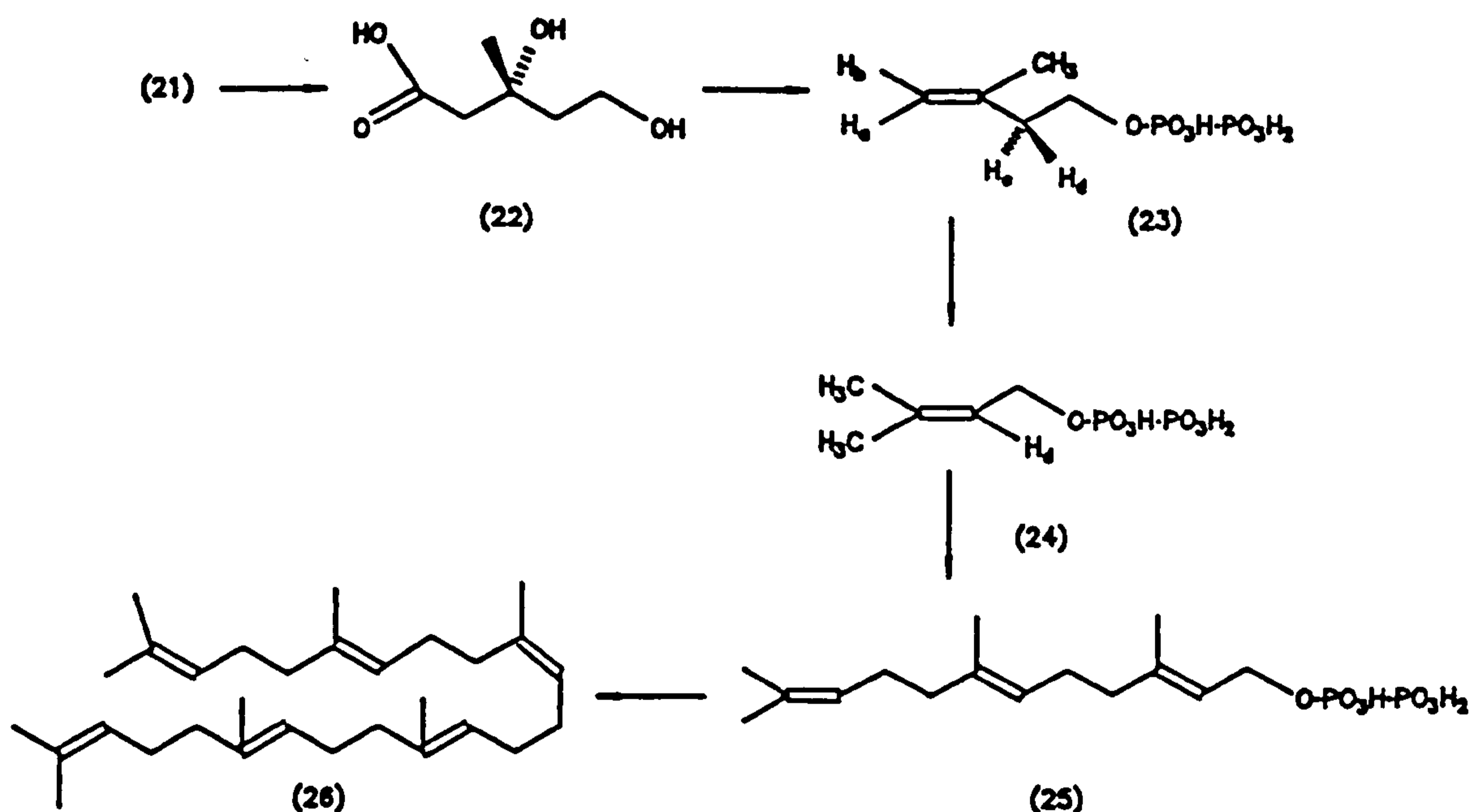
steroid biosynthesis is the enzymatic reduction of S-3-hydroxy-3-methylglutaryl coenzyme-A (21) by 2H transfer from reduced nicotinamide-adenine dinucleotide phosphate (NADPH) to produce R-mevalonic (22) acid. Although other minor pathways do exist, the principle route to the glutarate (21) is by the usual condensation of three molecules of acetate with the aid of coenzyme-A, adenosine triphosphate (ATP) and the enzymes acid coenzyme-A ligase or succinyl coenzyme-A.



The R-mevalonic acid is then converted to the pyrophosphate by a two stage process, ATP being the phosphate donor. This mevalonyl pyrophosphate is then degraded by an anhydrodecar-

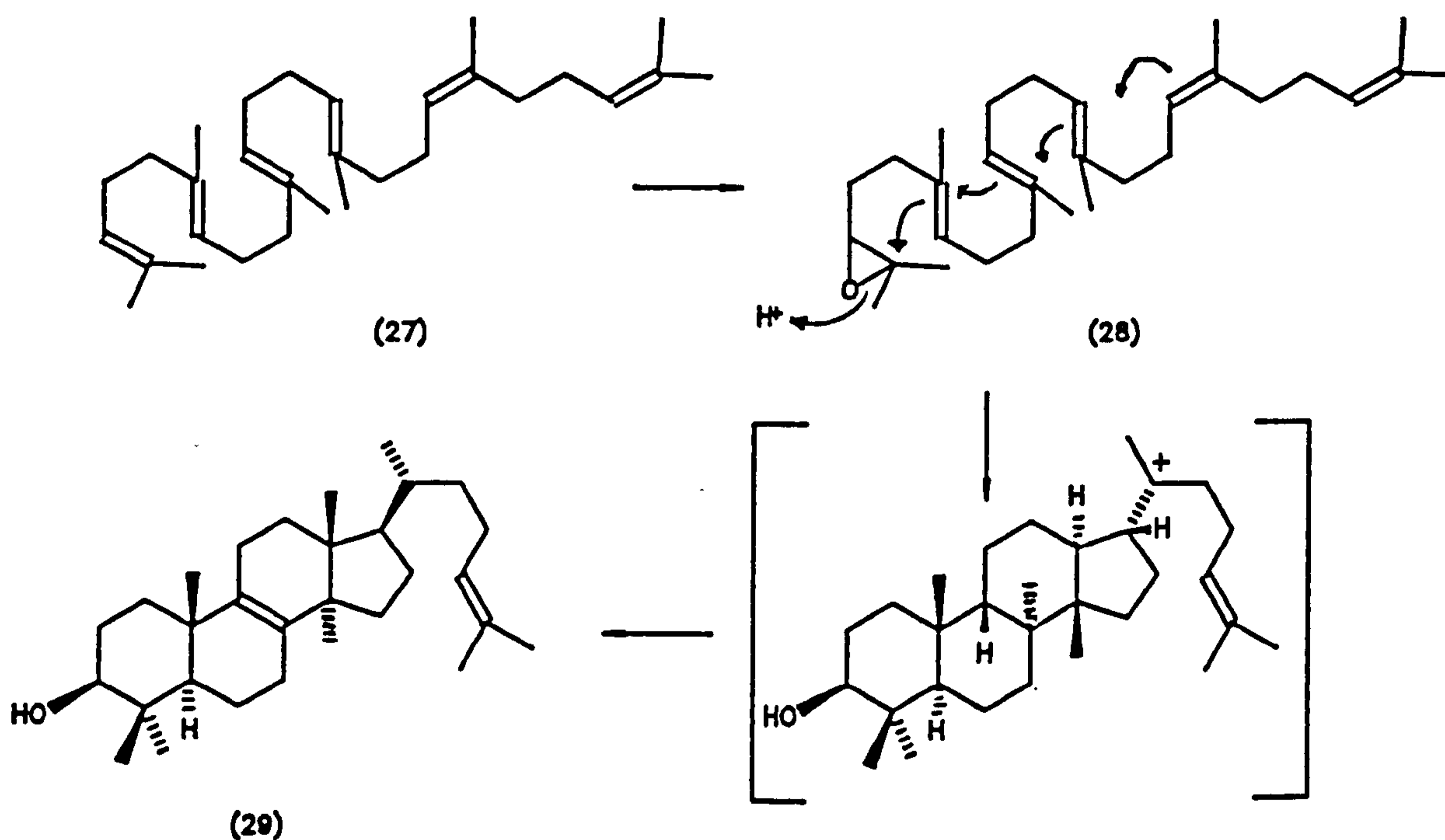
boxylase (with the aid of ATP) to give 3-methyl-3-butenyl pyrophosphate (23), adenosine diphosphate (ADP), inorganic phosphate and carbon dioxide.

Next, the pyrophosphate undergoes a prototropic shift to give 3-methyl-2-butenyl pyrophosphate (24) with the aid of isopentenyl pyrophosphate isomerase. This is one of the few reversible reactions in the series. The shift of a proton is stereospecific, the hydrogen atom H_C being the one eliminated. The effect is to change a compound which has a relatively unreactive phosphoryl group and a nucleophilic double bond to a compound which is a highly reactive electrophilic allyl pyrophosphate.



The enzyme prenyltransferase catalyses the condensation of three molecules of (24) into farnesyl pyrophosphate (25). Two molecules of farnesyl pyrophosphate are then condensed together to form the triterpenoid squalene (26). It is this triterpenoid that is the important precursor in the synthe-

sis of various steroid molecules. How this molecule is rearranged to form the conventional steroid frame work is more easily understood by an alternative view of the molecule (27). Molecular oxygen and reduced triphosopyridine nucleotide (TPNH) are required for the first stage in the cyclisation step and a mono-epoxide, 2,3-oxidosqualene (28) is formed. The enzymatic cyclisation, by 2,3-oxidosqualene cyclase, can be represented as beginning with the uptake of one hydrogen atom and ending with the expulsion of another (28). The enzyme enforces stereospecific rearrangement of the intermediate. Thus, the methyl groups at 8 and 14-C together with the hydrogen atoms at 13 and 17-C undergo a concerted trans-migration. There are two 1,2-methyl shifts, the 8-C methyl going to 14-C and the 14-C methyl group migrating to the 13-C position. The resulting steroid is lanosterol (29).



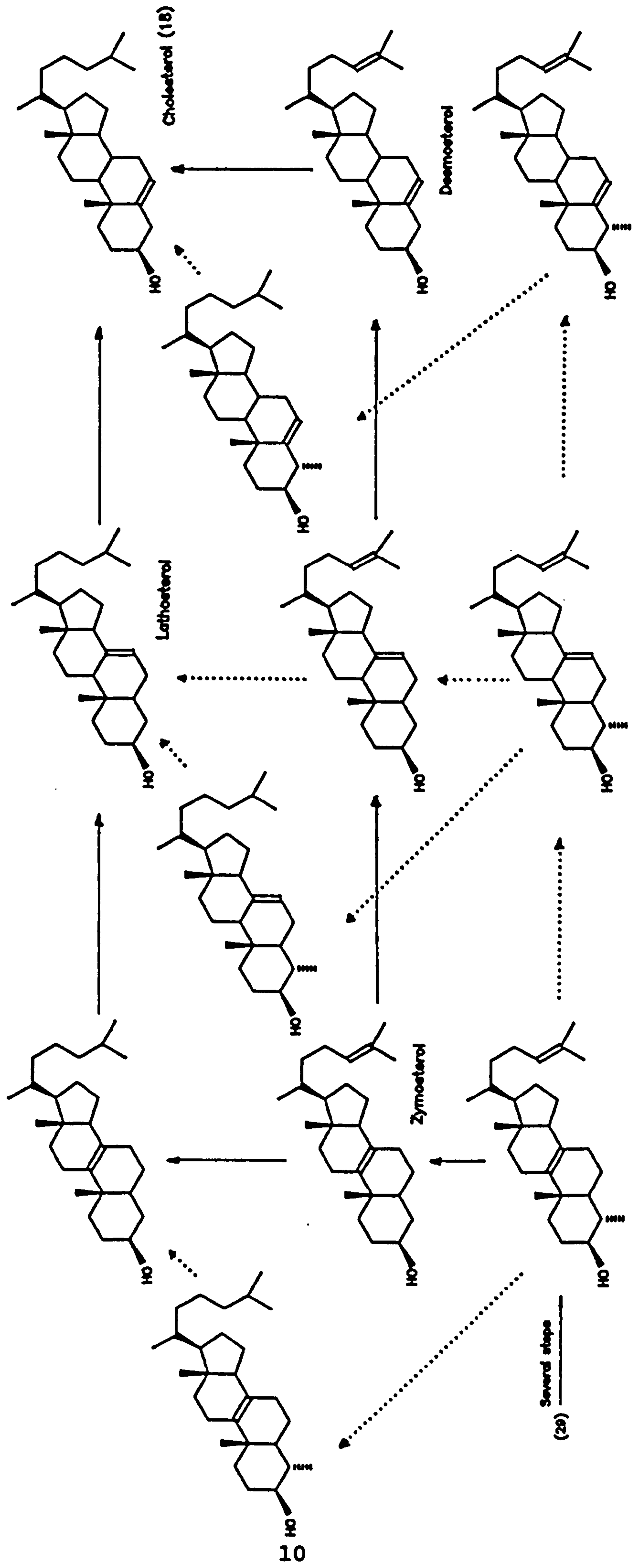


FIGURE 1 Degradation of lanosterol to cholesterol

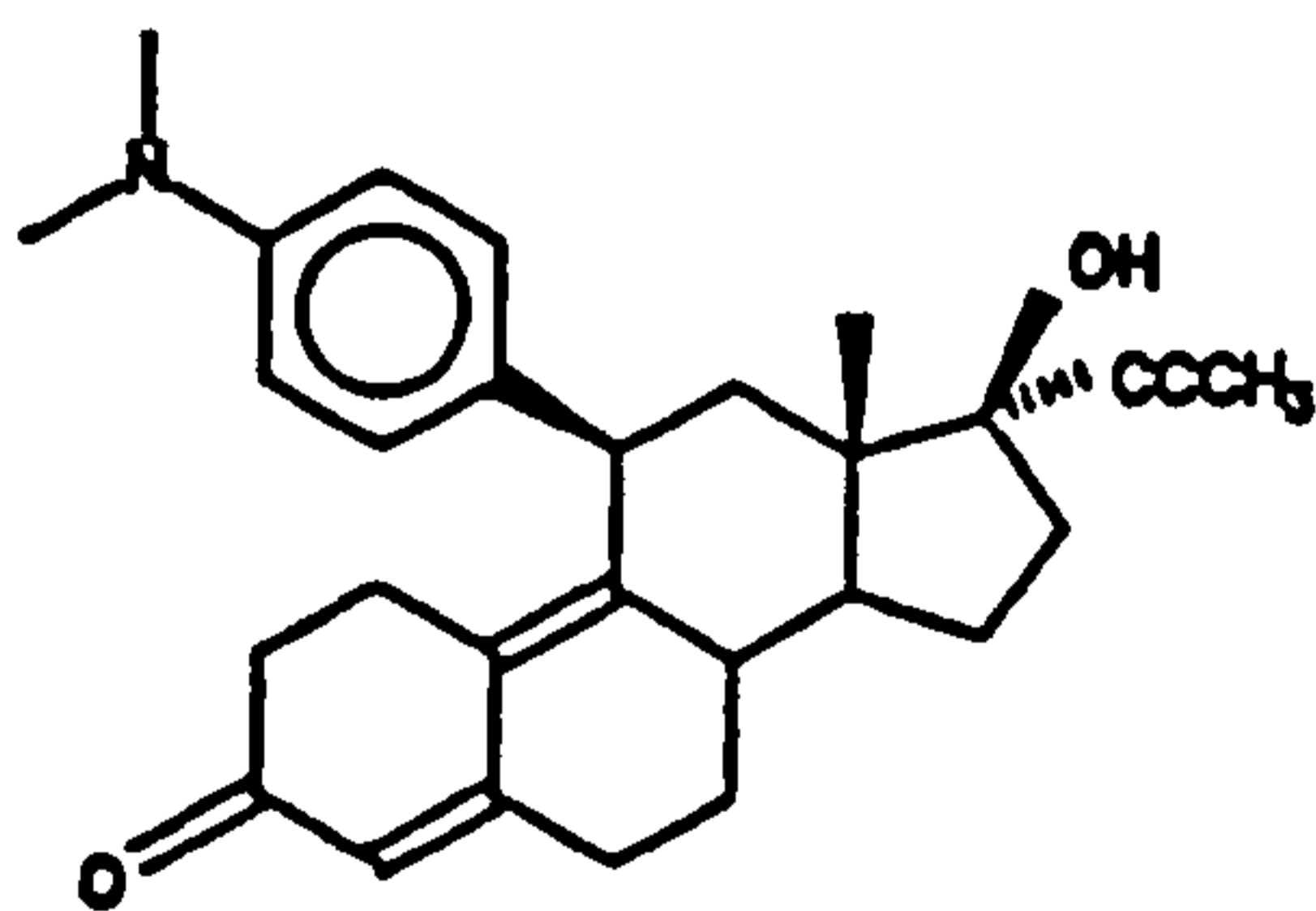
Degradation of Lanosterol to cholesterol.

The general process is shown in Figure 1. The initial steps are the removal of three methyl groups (the gem-dimethyl group at 4-C and the 14 α methyl group), together with the addition of 2H at 24-C and the shift of the ring double bond from 8-C to 5-C. The main pathway to cholesterol is believed to be via zymosterol and desmosterol, i.e., the three methyl groups are removed first, the double bond shifts, and then 2H is added at 24-C. If these reactions occur in a different order, the other intermediates (Figure 1) are produced. An important alternative pathway is via zymosterol and lathosterol. Although a considerable amount of information into these processes has been accumulated many details have still to be determined. As mentioned above, cholesterol is the principle starting molecule for steroid hormone biosynthesis in animals but desmosterol and lathosterol are also utilised in significant quantities. These various conversions make up a vast and complex network of pathways which will not be detailed here but can be readily obtained from the comprehensive literature concerning the subject.

1.2.1 Steroids as chemical contraceptive agents.

The biological activity of steroids is, to say the least, considerable. Paradoxically however, because of the vast structural variations possible, testing is generally restricted to a distinct, targeted domain. Thus the cyclosteroid derivatives discussed in this work were synthesised specifically to evaluate their potential as progesterone agonists or antagonists, i.e., their potential as anti-fertility agents.

The importance of chemical contraceptive agents cannot be under estimated. In a 1974 review of chemical contraception, Bennett² noted that it had taken about 2 million years for the world's population to reach 3 billion. Only a few more years will be needed to increase the population to 6 billion at current growth rates. There is no doubt that the world's increasing population is a major concern, vastly exceeding fuel and food supplies in many parts of the world.² However, important as such agents are, their development has been enormously complicated by not only research cost barriers but also by political and cultural barriers.



(30)

Thus, at present the contraceptive RU 486³ (30) is, in certain cultures, often viewed with the notoriety usually reserved for chemicals such as CFCs or "hard" drugs.

1.2.2 Method of action

Although there is still a considerable amount of detail to be learned about the way in which contraceptives operate, research has provided a considerable amount of information into the general mechanisms involved in specific areas of the female (and male) reproductive system.

The female and male reproductive systems are governed by a family of peptides known as the gonadotropins which are responsible for the control and regulation of ovulation, spermatogenesis, development of sex organs, and maintenance of pregnancy. Figure 2 shows how these gonadotropins regulate ovulation in females. The peptides of particular importance are:-

1) Luteinizing-releasing hormone (gonadotropin-releasing hormone) or LH-RH, (GnRH), a decapeptide with the structure; Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂. Released by the hypothalamus, this simple peptide essentially controls female (and male) reproduction.

2) Luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These are peptides produced in the anterior lobe of the pituitary when stimulated by LH-RH which, in females, regulate the menstrual cycle. The structure, genes, receptors, biological roles, and their regulation (including by negative feedback actions of steroid hormones) have been intensively studied.⁴⁻⁶

Steroids that act as estrogen or progestin agonists are believed to suppress the production of LH or FSH, or both, by a feedback-

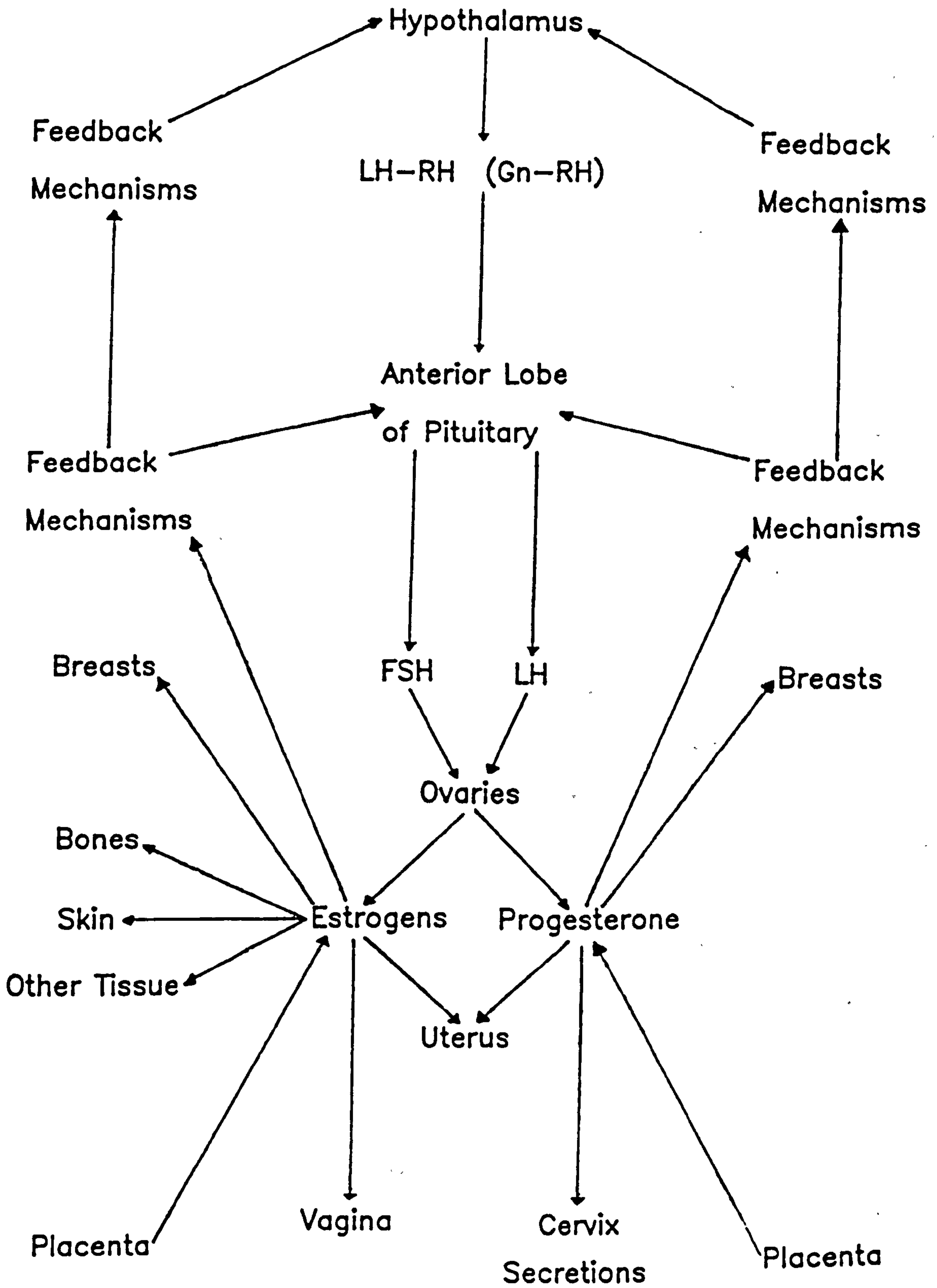
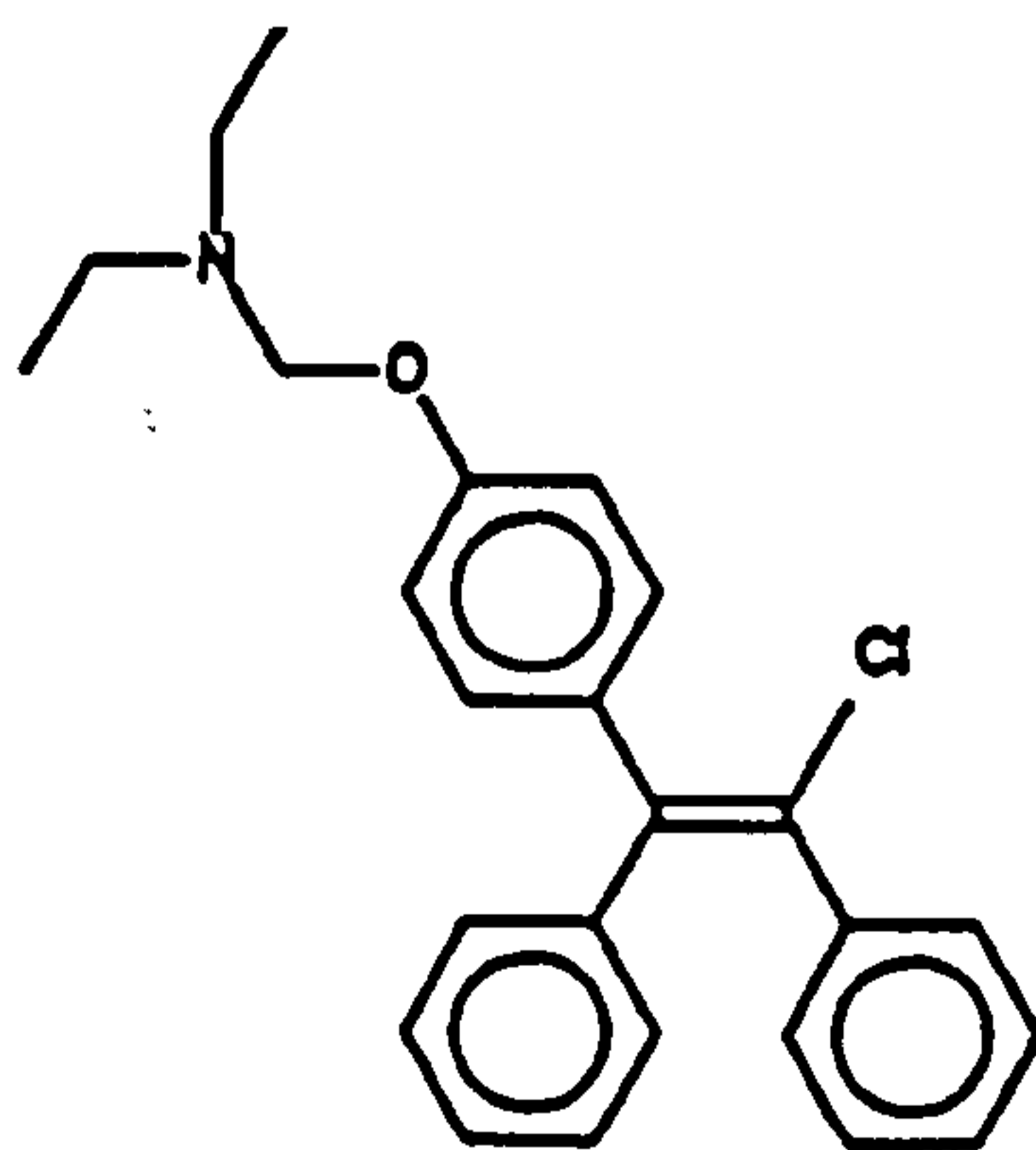


FIGURE 2

Regulation of ovulation in females by LH-RH (Gn-RH)

inhibition process. Without FSH or LH, ovulation is prevented. Thus the process is similar to the natural inhibition of ovulation during pregnancy, caused by the release of estrogens and progesterone from the placenta and ovaries. An additional effect comes from the progestin which causes the cervical mucus to thicken and thus provides a barrier for the passage of sperm through the cervix.

Progesterone antagonists, a completely new drug design approach to oral contraceptives for women, are now receiving considerable attention. The first to be studied in clinical studies is RU 486 [(17 β -hydroxy-11 β -(4-dimethylaminophenyl)-17 α -pro-1-pynyl)-estra-4,9-diene-3-one], (30). This compound acts as an anti-fertility agent by binding to, and hence blocking, the progesterone receptor. When progesterone binds to its receptor, heat shock protein is released from the receptor and thereby opens the progesterone-receptor complex to DNA binding. However, when RU 486 binds to the receptor, heat shock protein is not released; therefore no transcription of the DNA can occur. Alternatively, RU 486 may induce a conformational change in the progesterone receptor so that it does not fit its DNA site. Estrogen

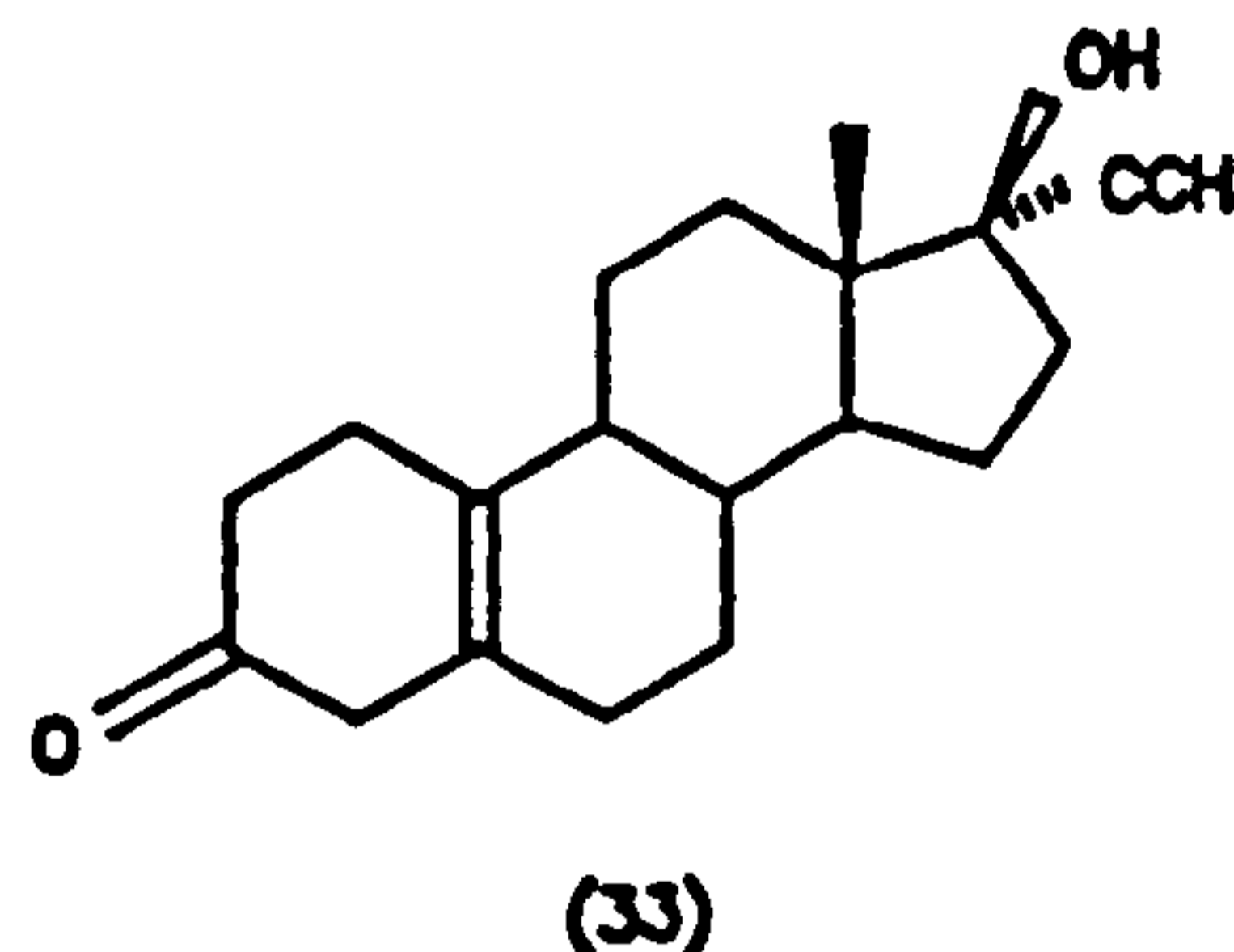
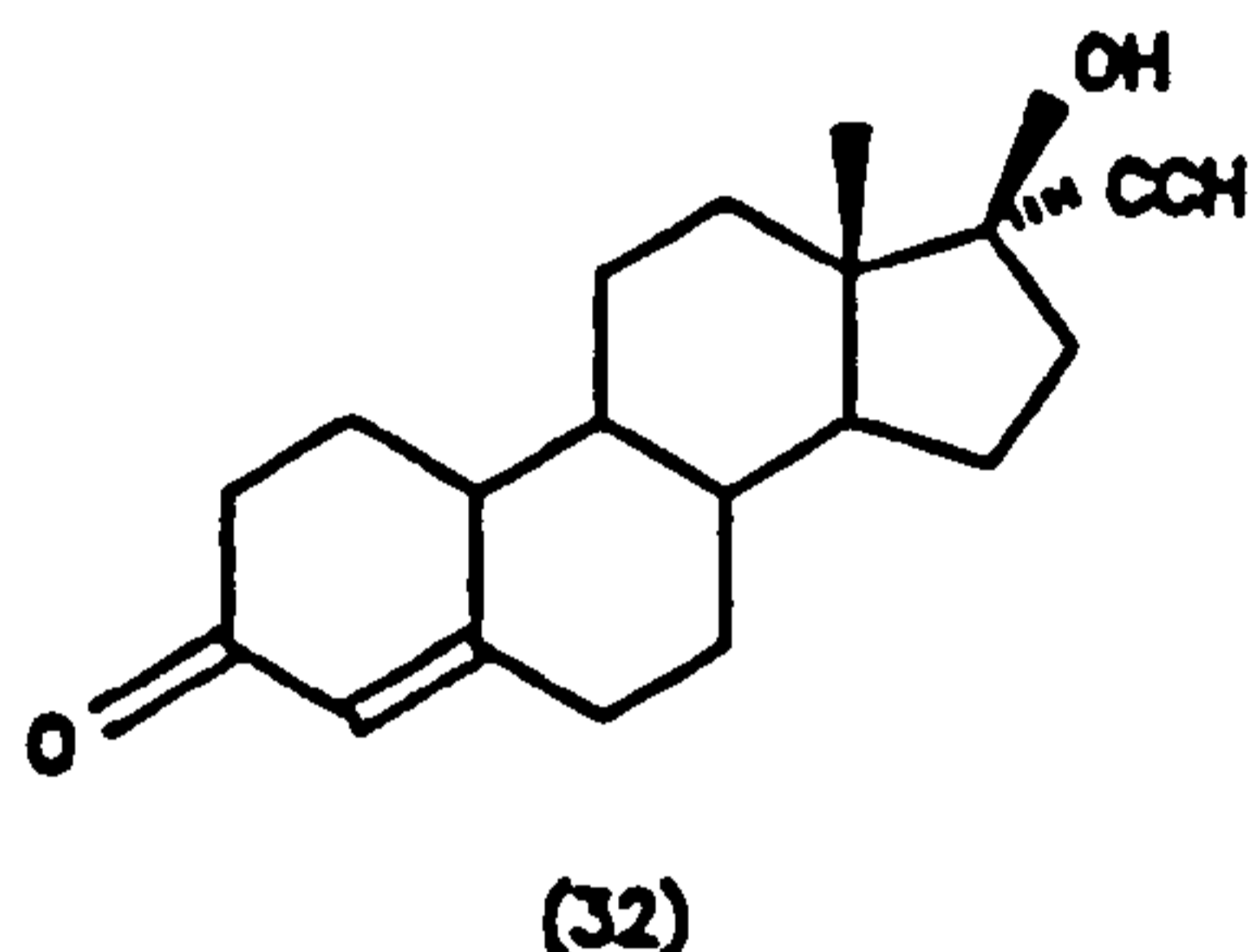


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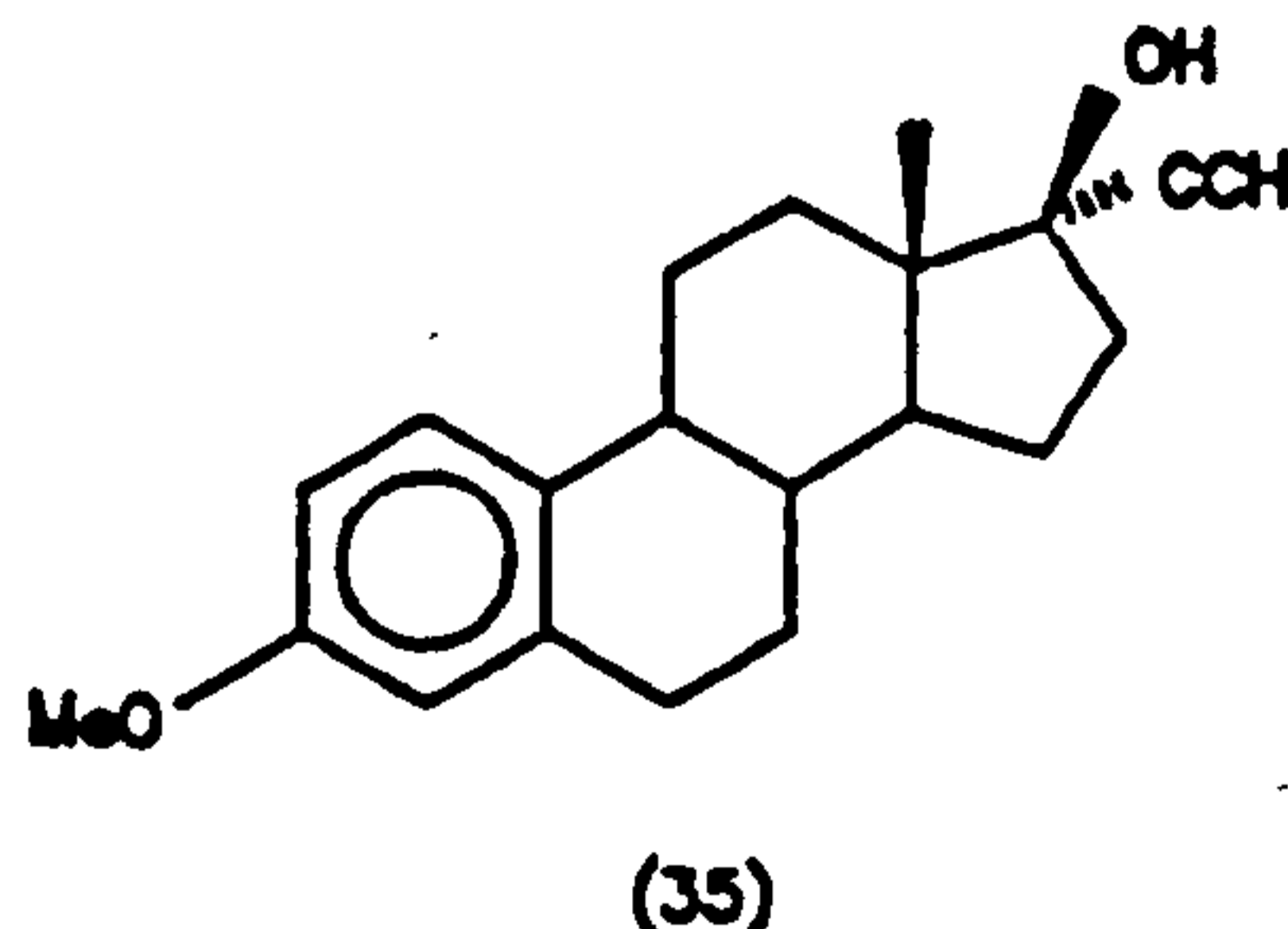
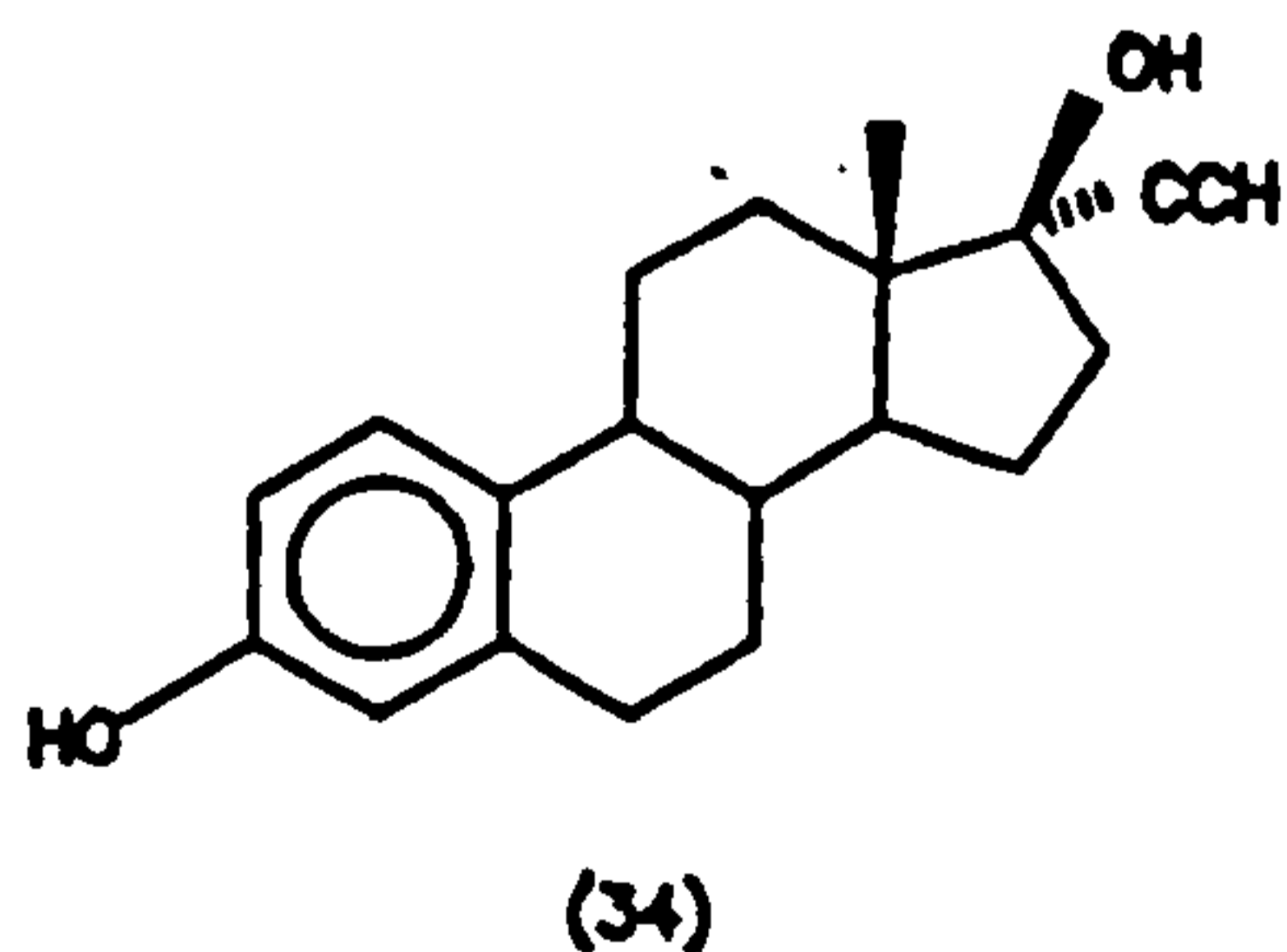
antagonists also operate on the gonadotropin system. Conversely, some of these compounds can increase the level of the peptide LH-RH, and hence increase ovulation, by a blocking of feedback inhibition of ovary-produced estrogens. In this manner such compounds, e.g., Clomiphene (31) are used as fertility agents

1.2.3 Hormonal contraception: a review.

Hormonal contraception was pioneered in the 1950's and was based on the inhibition of ovulation by progesterone.⁷ At the same time Djerassi *et al.*⁸ and Colton⁹ reported the synthesis of two highly ovulation inhibiting compounds, norethindrone (32) and norethynodrel (33). The current oral



contraceptives act as progestin and estrogen agonists and contain mixtures of derivatives of either estrogen, e.g., ethinylestradiol (34), and progesterone, e.g., norethindrone (32) and norethynodrel (33). To this day norethindrone (32)



and norethynodrel (33) remain the most extensively used progestins in oral contraceptives while estrogens such as ethynylestradiol (34) and mestranol (35) make up the bulk of estrogens used.

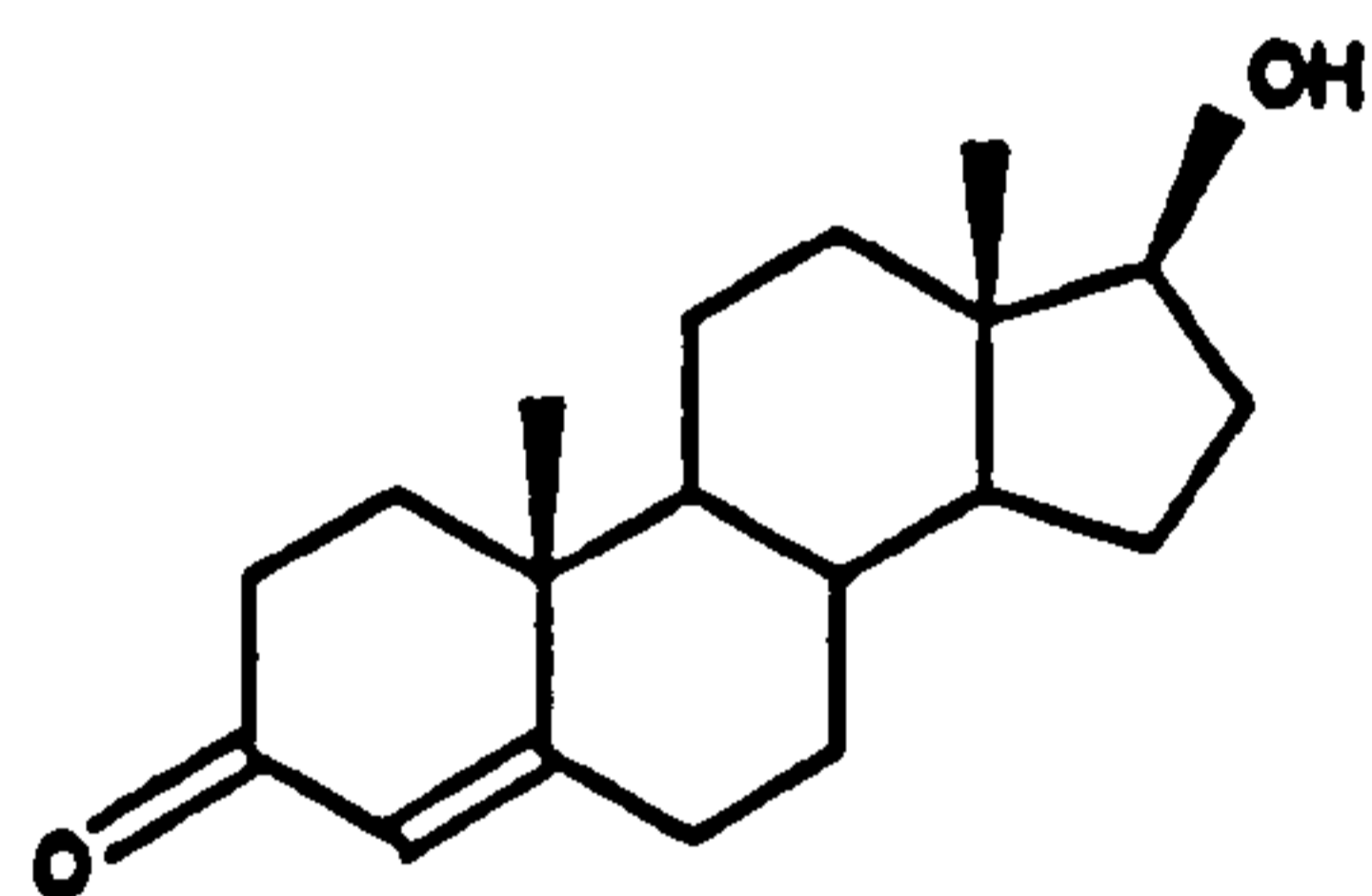
Although any of the considerable number of oral contraceptives available are extremely effective at inhibiting ovulation some side effects are known and the safety of the "pill" has been one of the most intensively discussed subjects in the press. Studies based largely on the early products that contained large doses of estrogen showed an alarming incidence of thromboembolic disease. These studies resulted in the removal of high estrogen dosage contraceptives from the American market, a tendency towards products containing less estrogen and the identification of women who should not take oral contraceptives, e.g., women over 40 years of age and women who are moderate to heavy smokers. The use of the "pill" is also known to increase incidents of cardiovascular death and again a synergistic effect is noted when women smoke. Some common misconceptions, e.g., that oral contraceptives can lead to an increase in incidence of breast cancer have been shown to be false.¹⁰ Indeed, use of the "pill" has shown a decrease in the risk of ovarian cancer.¹¹

Although the incidence of illness or death through the use of chemical contraceptives is small they nevertheless exist and this has meant the continued search for safer products by the development of more powerful contraceptives that can be given in small doses (or less frequently) and possess reduced side effects.

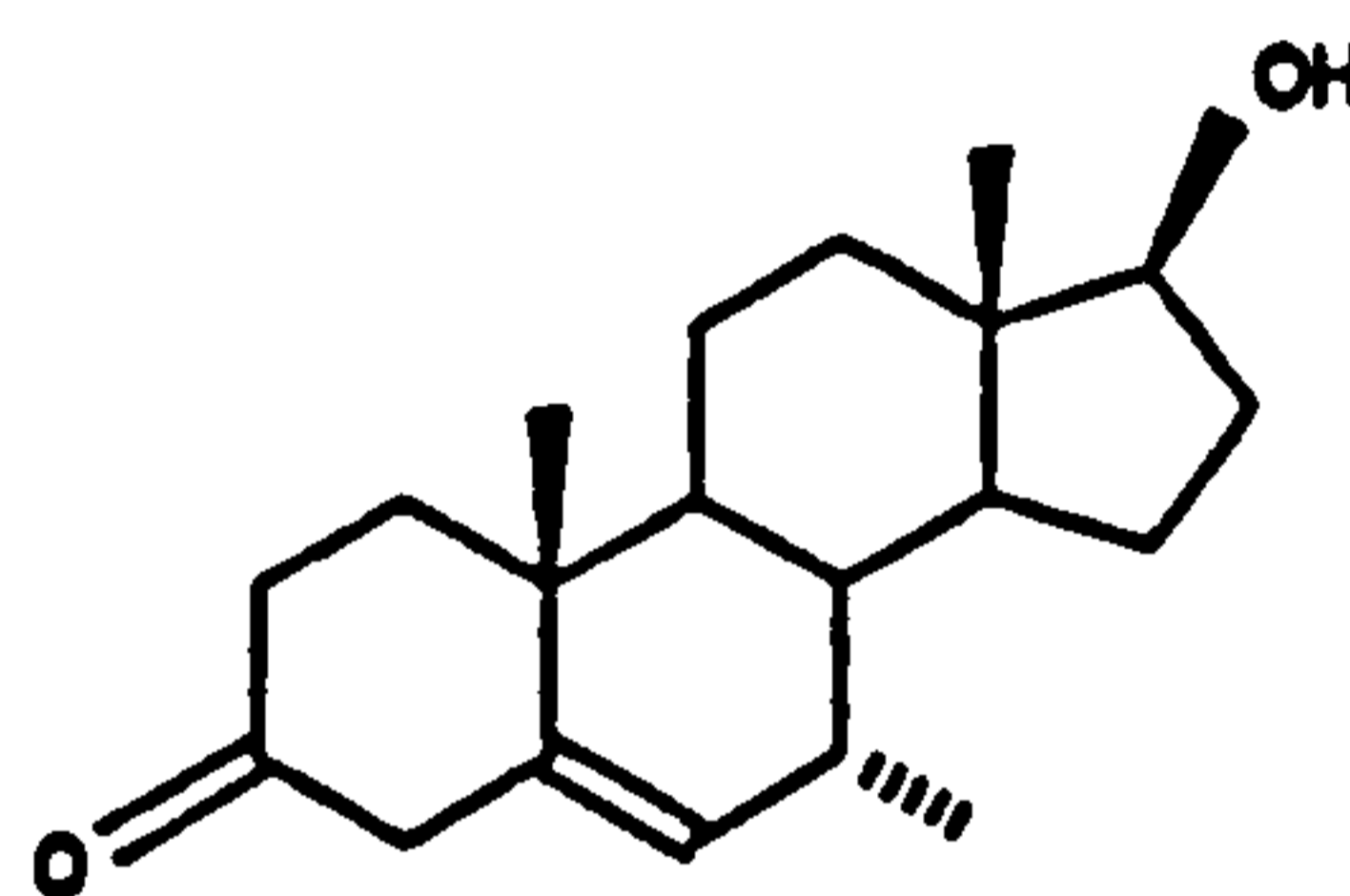
1.2.4 Considerations of steroid receptor binding.

For a recent report into the characterization of the various steroid hormone receptors and the binding of compounds to such sites the reader's attention is directed to the excellent review by Ojasoo *et al.*.¹²

A considerable amount of work has been undertaken in an attempt to map the various steroid-receptor interactions. For example, the uterine progesterone receptor sites have been investigated by synthesising derivatives of a compound showing anti-fertility activity and comparing their relative binding affinities to the protein with their structures as defined by X-ray crystallography. A recent example being the progesterone antagonist steroid R.U. 486 (30) and its derivatives.³ Androgens, such as the principle male sex



(36)

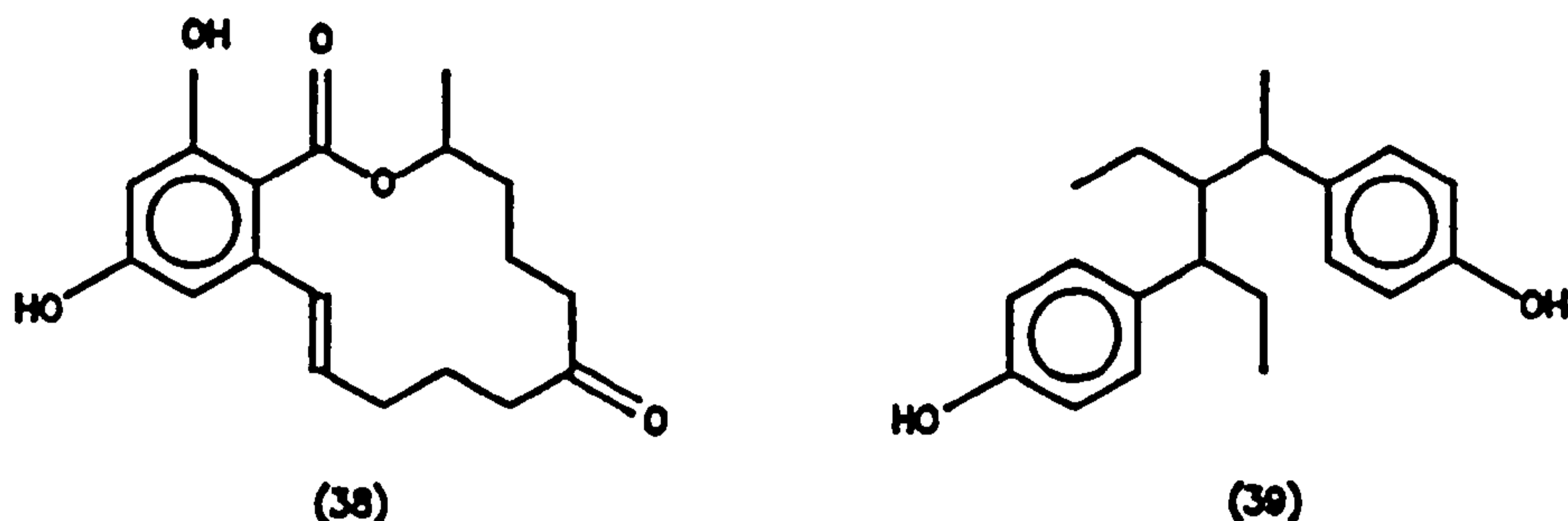


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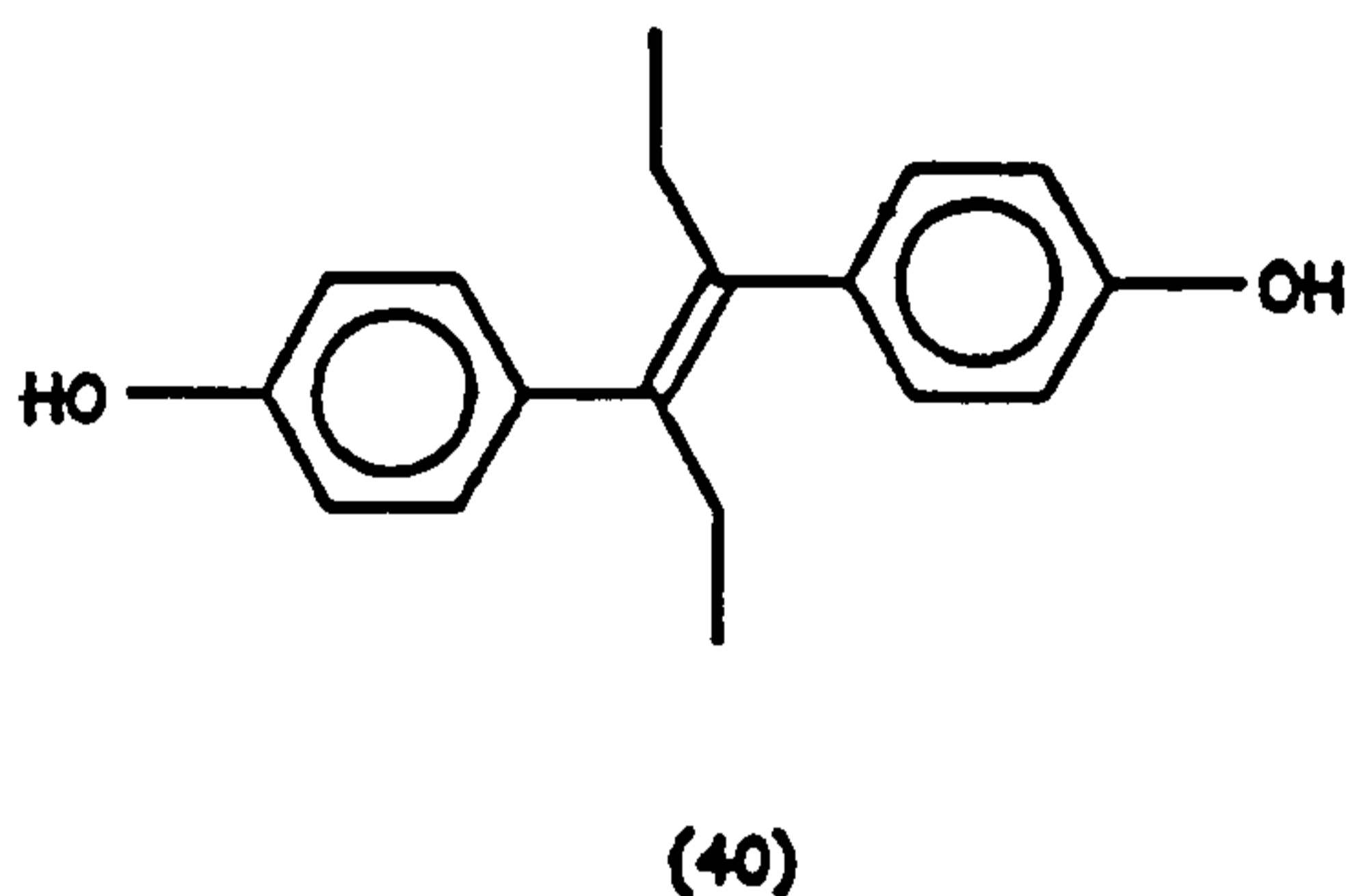
hormone testosterone (36) have also been studied. For example, the testosterone derivative, 17 β -hydroxy-7 α -methylandrost-5-en-3-one (37) has shown to be both anti-estrogenic and anti-progestational¹³ and its molecular conformation has been determined by X-ray crystallography.¹⁴ A review of the stereochemical aspects of receptor binding of steroids was recently presented by Duax.¹⁵

The fact that there are many potent non-steroidal estrogen or progestin agonists, e.g., the plant estrogen

zearalenone (38), indicates that the receptor site is not always (if at all) a tight fit for an agent. However some biologically active non-steroidal compounds such as the estrogen benzestrol (39) can show remarkable structural similarities to the four ring system of steroids. Thus,



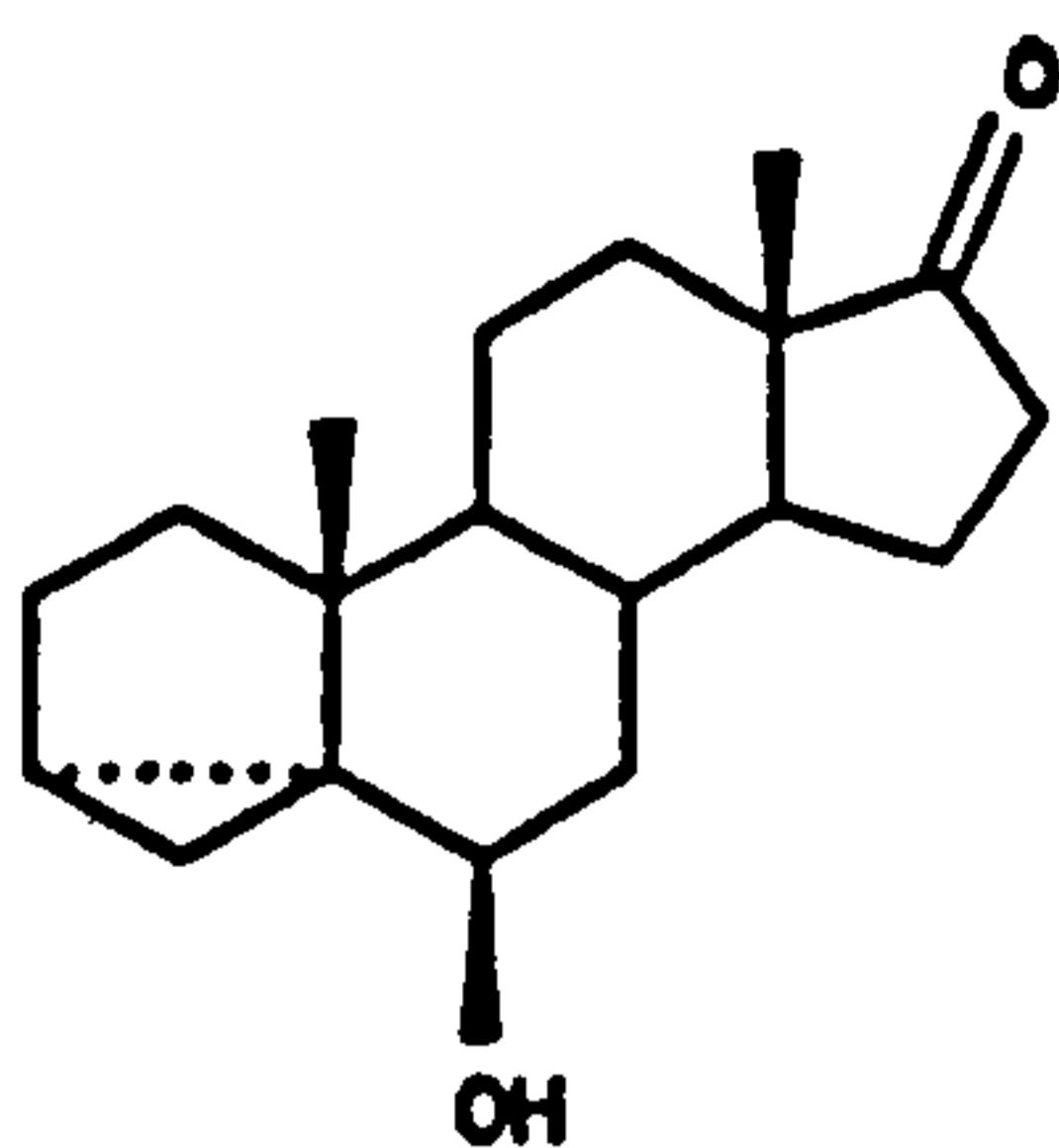
a near identical structural similarity is not a prerequisite for activity. For example, the highly active diethylstilbestrol (40) arises because the distance between the hydroxy groups¹⁶ matches the estradiol/water molecule complex present at the receptor site.



1.3 Rationale for synthetic studies

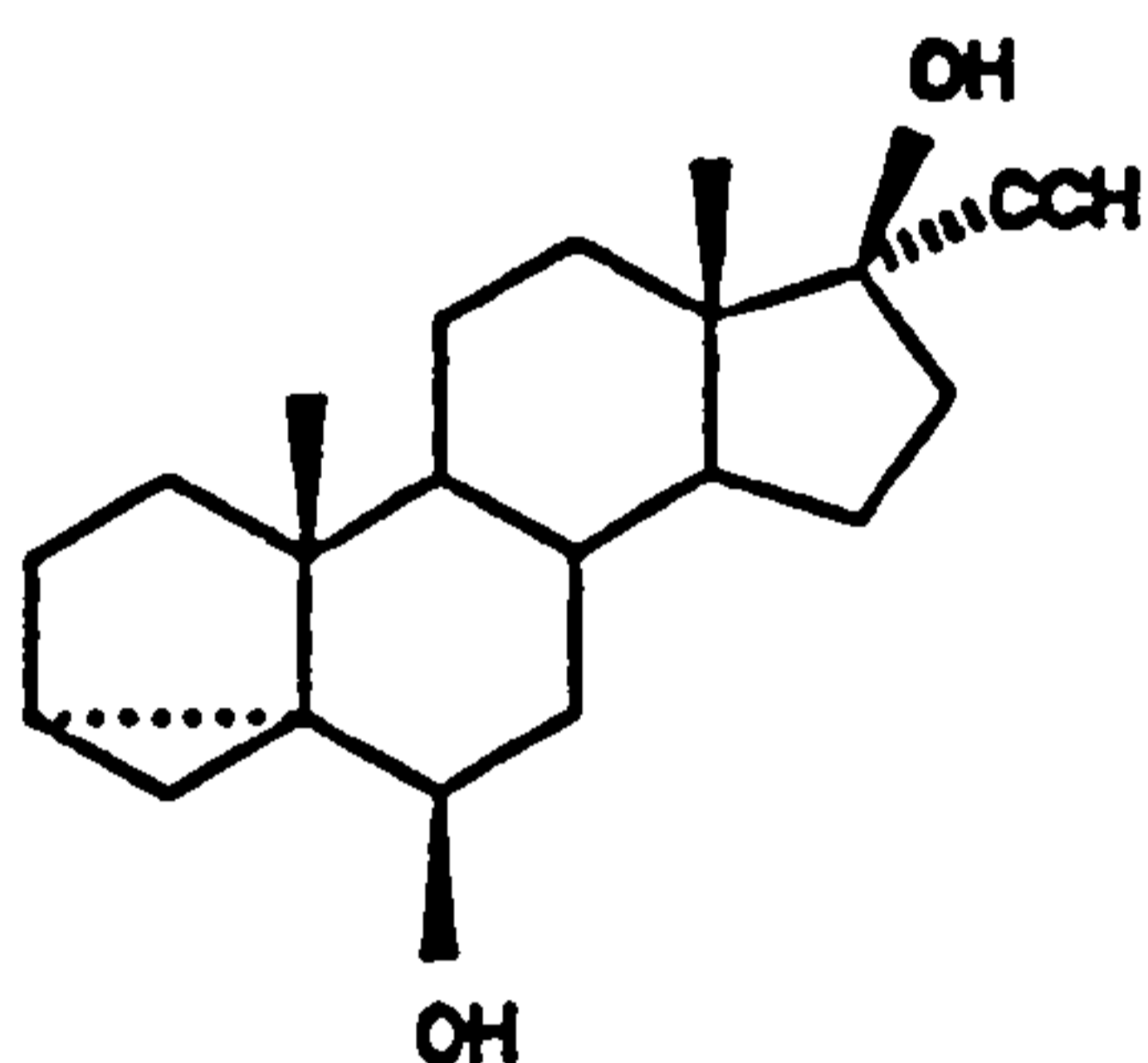
6 β -Hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41) and its effects on male rats have been studied,¹⁷ but its actions on the female reproductive system have not. Previous studies at R.G.I.T. had indicated that this compound possessed progestational or anti-progestational activity, i.e., anti-fertility properties. It was therefore used as a lead compound for the synthesis of a series of 3 α ,5-cyclo-5 α -androstanes in an

attempt to produce compounds possessing female anti-fertility activity. This was the basis of the work carried out here.

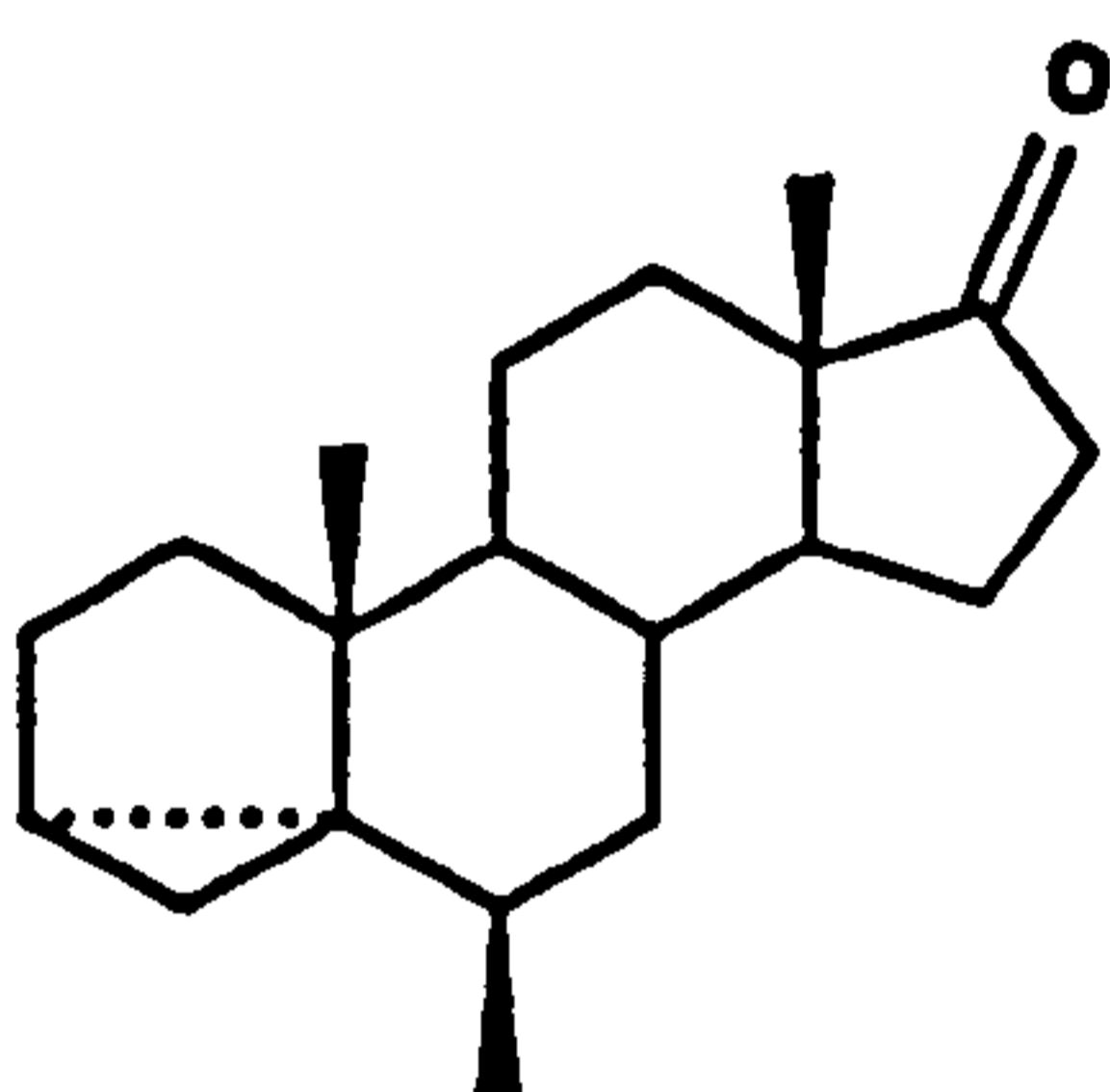


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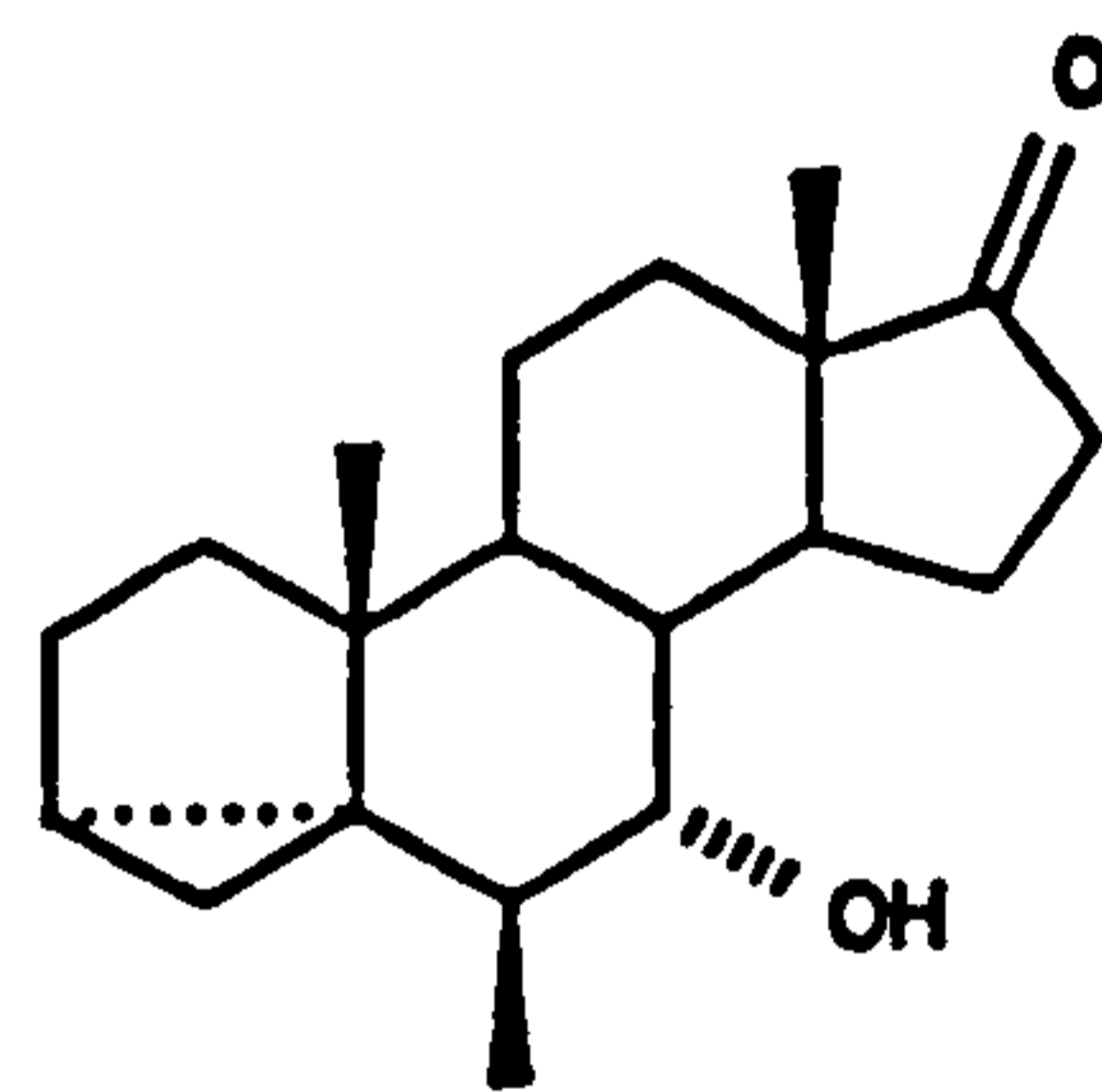
The target compounds were the propargyl alcohol derivative (42), the 6 β -methyl derivative (43), and the 6-methyl 7-hydroxy derivative (44). It was hoped that the synthesis of the compounds would not only produce steroids with notable biological activity but also provide an insight into the



(42)



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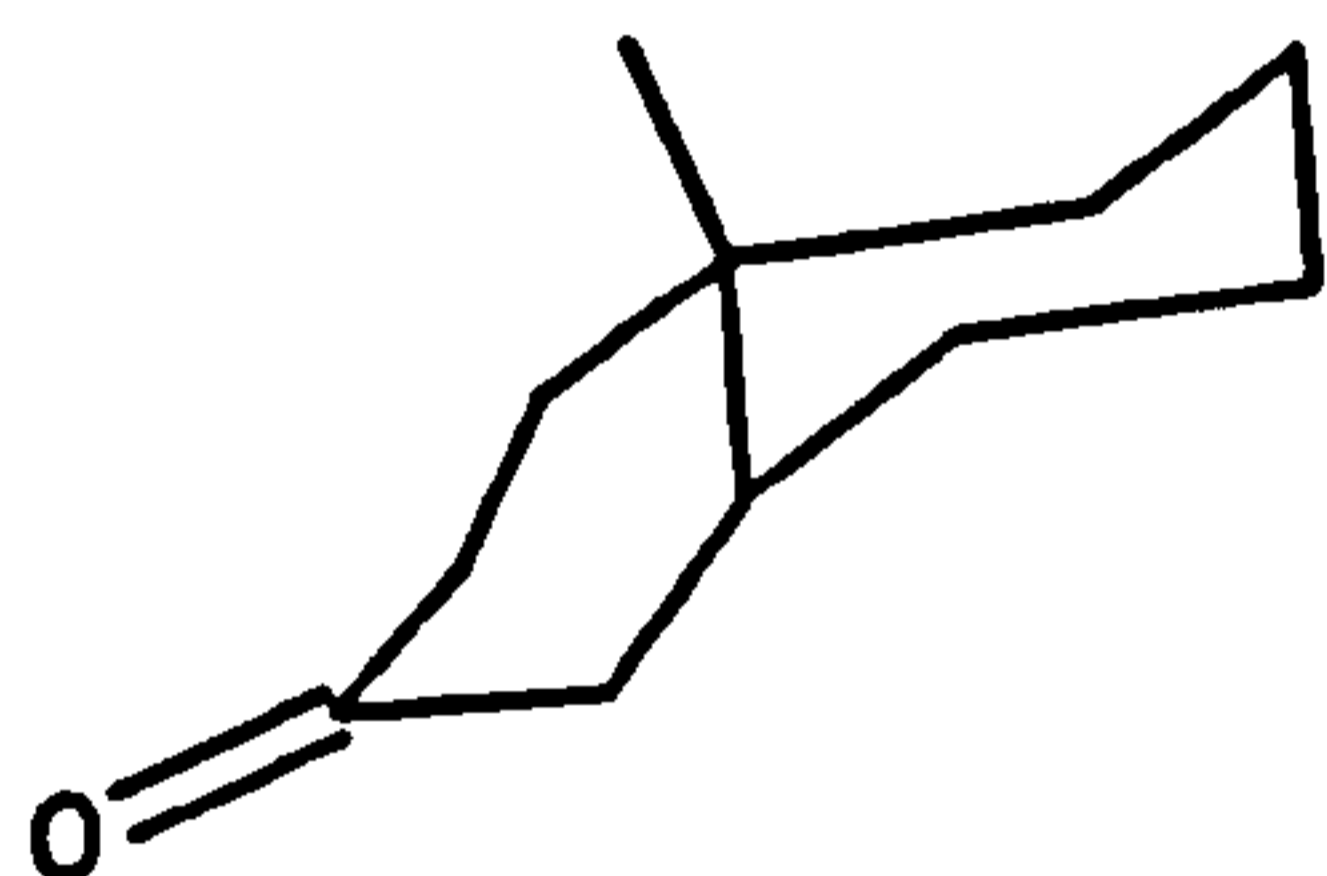


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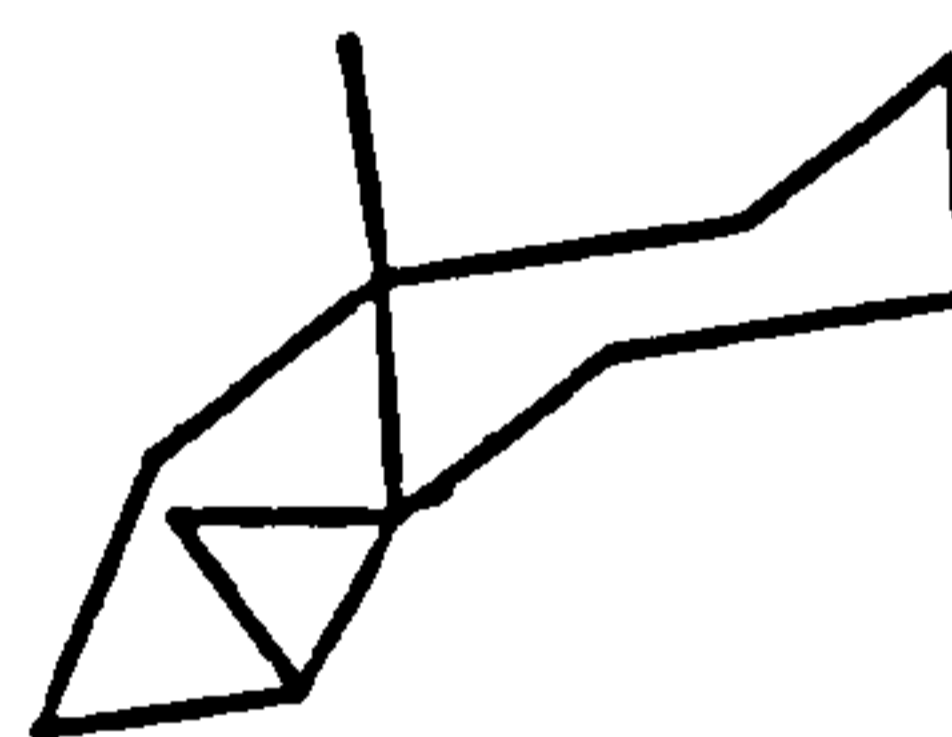
chemical influences and effects of the cyclopropane ring. (It should be noted at this point that if the cyclopropane ring geometry confers any biological activity, then any of the synthesised molecules can do so only if administered by some other means than orally. The acidity of the stomach would most certainly induce addition of HCl to the three membered ring and hence fragment the moiety.)

The possibility of the lead compound (41), or indeed any of its derivatives, to act as an estrogen agonist (or

antagonist) was considered small because the non-planar nature of the A ring of the steroid would most certainly prevent binding to the estrogen receptor site. The structural requirements of the progesterone receptor site have also been studied in detail by Duax and co-workers.¹⁸ They concluded that the progesterone 4-en-3-one ring A was a key to binding, but apparently only when ring A is in a $1\beta,2\alpha$ half-chair conformation (45) and not the more common $1\alpha,2\beta$ half-chair conformation. There are geometrical similarities between the $1\beta,2\alpha$ half-chair conformation (45) and the general $3\alpha,5$ -cyclo- 5α conformation (46) indicating the possibility of the steroids synthesised in this work acting as progestin agonists or antagonists. However, although



(45)



(46)

structurally suitable, the cyclosteroids synthesised here do not possess the ability to form hydrogen bonds in the region of the 2-C (β -face) area of the molecule, a general prerequisite for good progesterone receptor affinity.¹² Thus, the target compounds of this work may be relatively weak progestins. However, this would not be the only criteria for a potential pharmaceutical product, secondary activities, e.g., anti-estrogenic potency and presence or lack of androgenic activity must also be considered.

The synthesis of so many unnaturally alkylated ster-

oids, although not leading to specific rules, has led to some generalisations concerning how the activity of a steroid can be increased by the alkylation of specific carbon atoms (or indeed by the removal of specific carbon atoms). Note also that similar generalisations have been "derived" for other chemical modifications, such as the introduction of halogen atoms or the conversion of a hydroxy group to its ester derivative (to adjust in vitro solubility), but these modifications are outwith the work here and therefore will not be discussed.

The changes in activity caused by modifications to the carbon framework can occasionally be readily explained but often appear perplexing. For example, the removal of the 19-C angular methyl group generally results in an increase in the estrogenic activity of a steroid. This is not surprising considering what is known about the estrogen receptor site. However, on the other hand the insertion of an alkyl group at atom 6-C has been carried out on numerous occasions and has often led to an increase in the biological activity of a steroid¹⁹⁻²³ while the introduction of an alkyl group to atom 7-C generally causes a decrease in activity.²⁴ One example of the decrease in activity caused by alkylation of atom 7-C highlights the problems associated with the interpretation of results. This modification to testosterone causes a decrease in its anabolic activity, androgenic activity and its ability to act as a competitive inhibitor of the estrogen synthetase.²⁵ Furthermore, as the size of this group increases, the activity of the molecule decreases. However, there does not appear to be a proportional

relationship between the two. Thus this example does not fit the normal "increased hydrophobic chain into a hydrophilic pocket" model. There is obviously a considerable amount of work still to be undertaken to explain such phenomena. One particularly important modification site is atom 17-C. This is because compounds such as the propargyl alcohol (42), synthesised as part of this work, can be orally active since the 17-OH group cannot be metabolised to the corresponding, and generally inactive, 17-one steroid. Furthermore, such hydrophobic 17 α -substituents also tend to increase the relative binding affinity of steroids to the progestin receptor.³ Other modifications to steroid molecules, at atoms 1, 2, 9, 11, and 16-C, also increase their progestational activity.^{26,27}

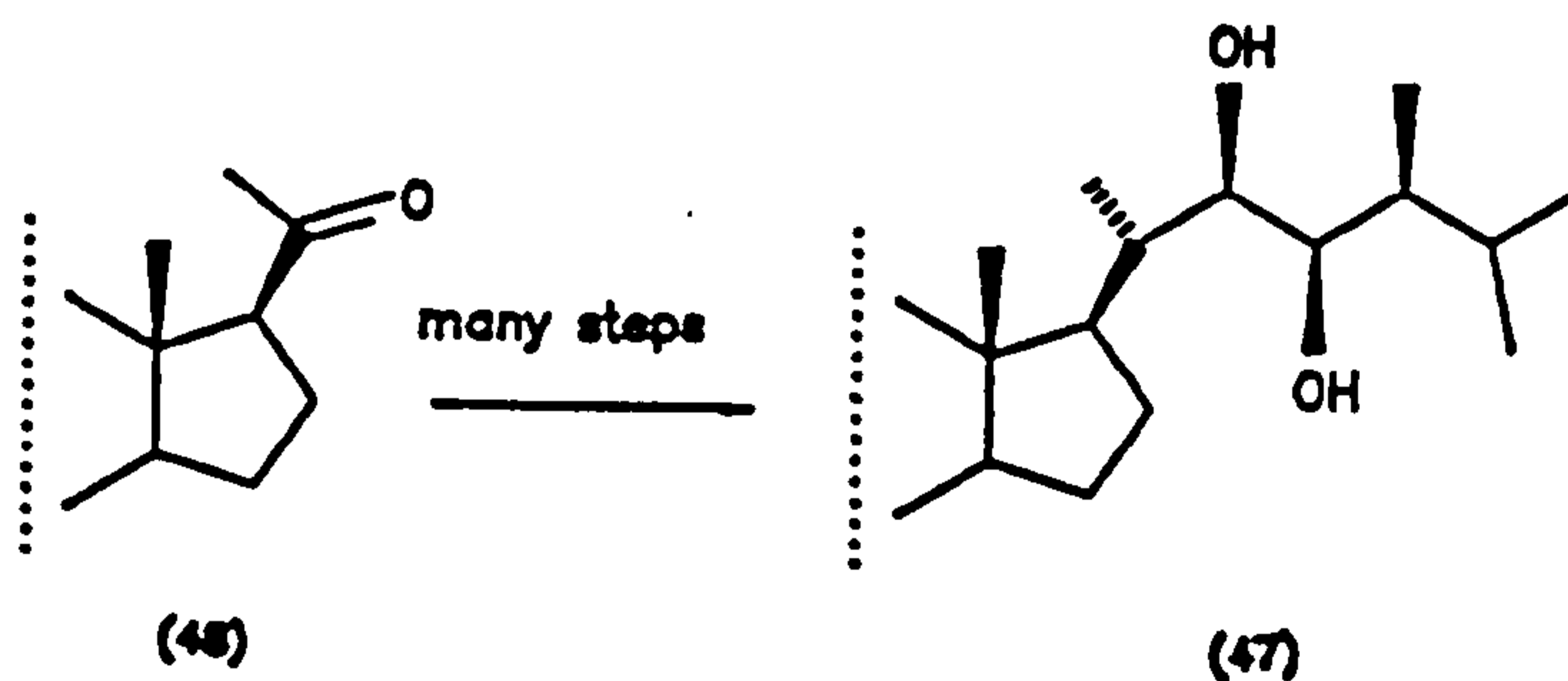
In an effort to explain such binding mechanisms experiments concerning co-crystallisation of steroids with amino acids and nucleic acids have been carried out.²⁸ However, these have provided only limited information. Unfortunately, the best case scenario (where steroids are co-crystallised with protein molecules) is not as yet possible because of the difficulties involved in the isolation of pure stable proteins. Crystallisation of the proteins themselves could also lead to the accurate mapping of the receptor sites. Thus the isolation of stable, crystalline proteins will provide a considerable amount of information into steroid/receptor binding mechanisms and shed light on often bemusing results.

1.4.1 Steroidal alkylations and syntheses of cyclopropane steroids.

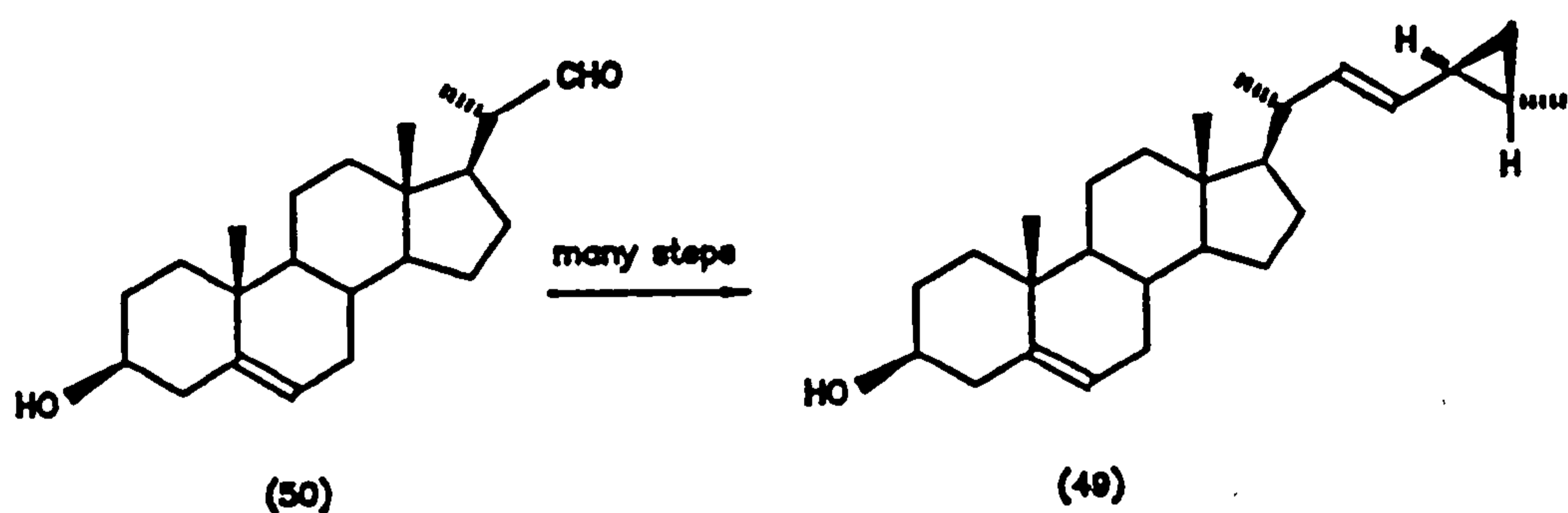
The synthetic work carried out in this research essentially concentrated on the introduction of a cyclopropane ring into the steroid framework and the alkylation of atoms 6 and 7-C. Thus, to supplement the bibliography, developed for the implementation of the various reactions, a further literature search was undertaken. This ascertained the nature of the most recent research concerning the general introduction of cyclopropane moieties into steroids and their alkylation.

1.4.2 Steroidal alkylation.

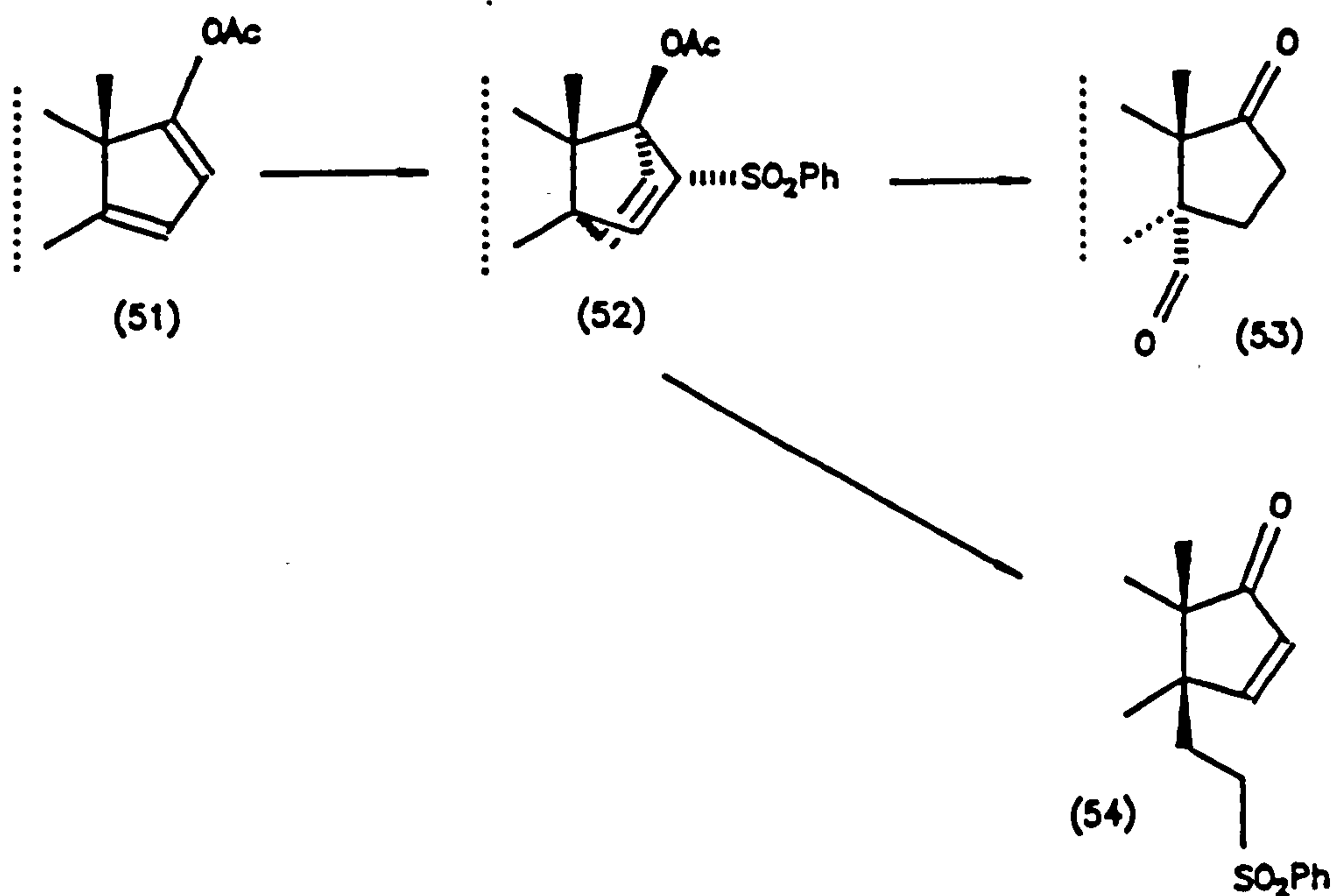
A critical review of steroid syntheses of recent years showed that, with respect to their alkylation, the most prominent area of research has been the stereospecific introduction of various sidechains at 17-C. This has been driven by, among other paradigms, a trend for the isolation of novel marine sterols. Thus, in an attempt to determine the exact configuration of these natural products and provide easy access to compounds possessing potent biological activities a vast amount of research has been undertaken.



Detailing this research is beyond the scope of this work. However, two examples capture the essence and complex nature of recent 17-C sidechain introductions. The formation of the contiguous, four chiral centred brassinolide side chain (47) from a pregnane derivative (48)²⁹ and the synthesis of glaucasterol (49), a soft coral sterol, from (50).³⁰

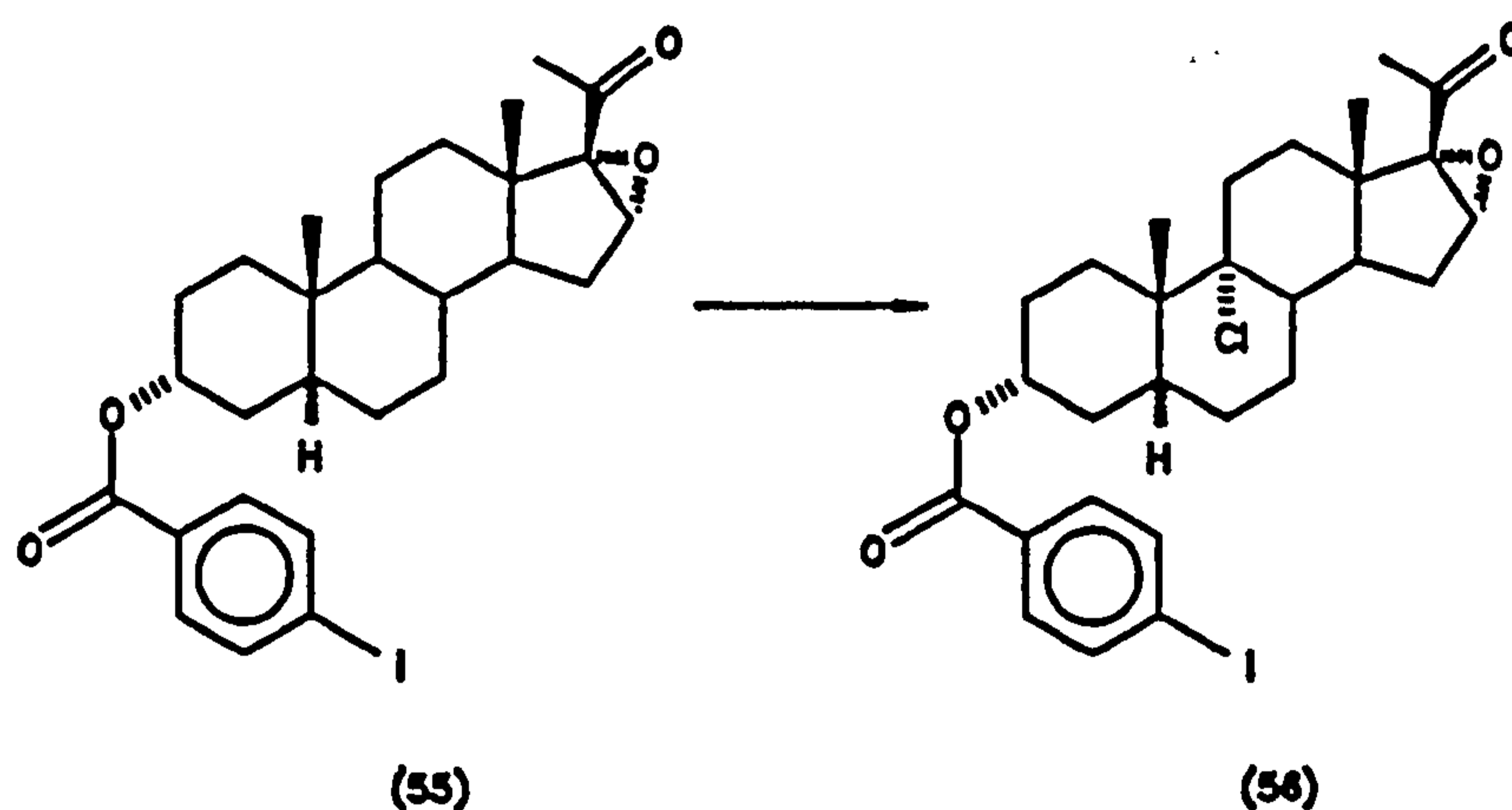


The alkylation of other centres in the steroid nucleus has, compared to the work done at 17-C, been relatively ignored over the last 10 years. This can be attributed to the success of Grignard reagents or other organo metallic reagents in introducing the relatively simple group usually required (expected!). However more novel approaches are frequently developed. One particularly interesting example being the stereospecific carbon-carbon bond formation at 14-



C by cycloaddition of phenyl vinyl sulphone to 14,16-dien-17-yl acetates, e.g., (51). Cleavage of the bridged intermediate (52) gave a variety of products, e.g., (53) and (54).³¹

Related to steroidal alkylation, a considerable amount of work has been undertaken into the functionalisation of saturated carbon atoms by various means. Microbiological hydroxylations are an obvious example, but the work by Breslow³² exemplifies the creative nature of remote functionalisation. Thus, the introduction of a chlorine atom at position 9 α is readily attained by ultra violet irradiation of intermediate (55) in the presence of dichloro-iodobenzene (56).³³ The formation of the 3 α ,5-cyclopropane ring has



of course been used for the direct activation of atoms 5-C,³⁴ 6-C and 19-C.^{35,36}

There are yearly (approximately) reviews covering all aspects of steroid syntheses and reactions including those touched on here. These excellent reports, most recently written by Turner³⁷⁻³⁹ and Elks,⁴⁰⁻⁴³ provides a valuable insight into the field of steroid synthetics.

1.4.3 Introduction of cyclopropane rings:- Some selected examples.

The cyclopropane ring

The most striking feature of the steroids synthesised in this work is the cyclopropane moiety in the A ring of the steroid. The cyclopropane ring, as well as adding interesting chemical features to the compounds, also has a considerable effect on the geometry of the steroid A ring.

Much work into the vast array of chemical reactions associated with the strained⁴⁴ and uniquely bonded cyclopropane ring⁴⁵⁻⁵² has been carried out and was recently summarised by Wong *et al.*⁵³ The σ -aromatic nature^{45,46} or partial sp^2 character^{47-52,54-58} of the 3 membered ring and its induced ring current led to interesting spectral features of the steroids produced, especially when conjugated with π -acceptor moieties such as keto or methylene groups.^{54,55,59-61} The main geometrical effect of the introduction of the cyclopropane ring is to force the A ring of the steroid into the α -phase of the molecule, thus emulating the 5β or cis A/B steroids in conformation (Chapter 5). Reactions of some of the synthesised derivatives did not only show potential participation of the 3 membered ring in that reaction, but also indicated stereochemical influences by the cyclopropane moiety on those modifications carried out at ring B. The bonding and nature of the cyclopropane ring is discussed further in Chapter 2.

The main problem associated with the synthesis of the target steroids was the fragmentation of the cyclopropane

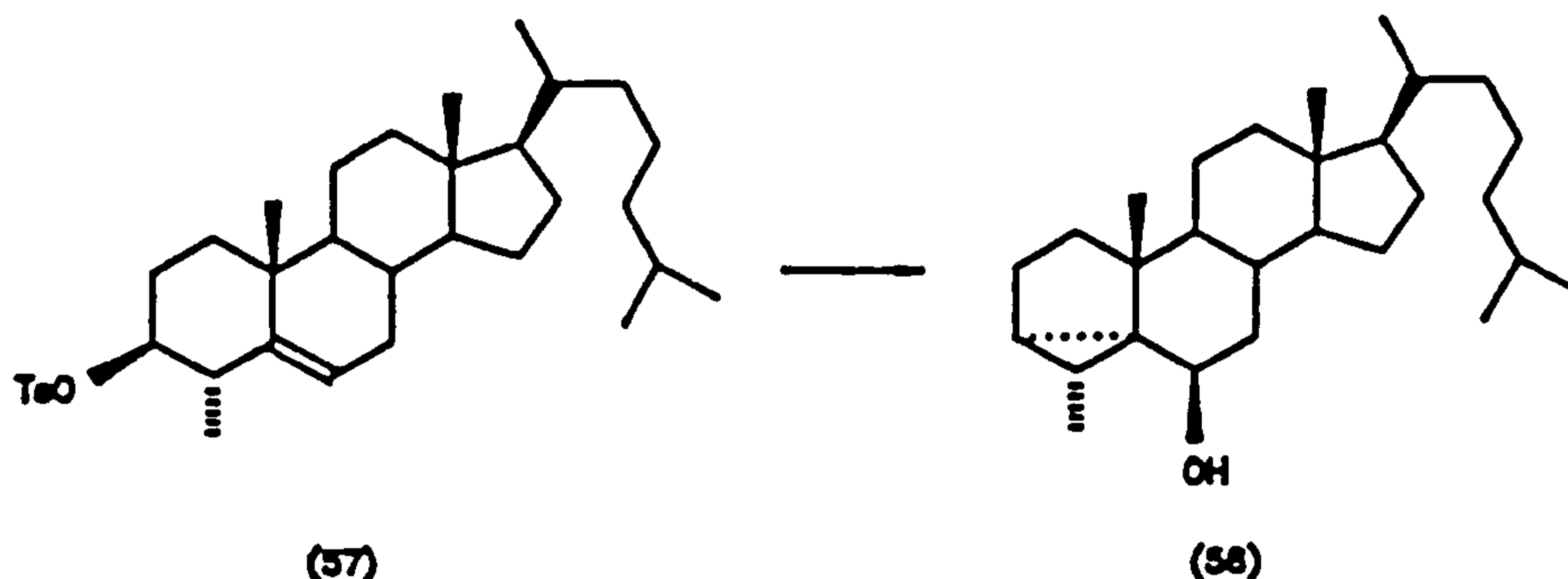
ring during reaction. Where this occurred, procedures were developed where either milder conditions prevented such side reactions occurring, or where this criterion could not be fulfilled, the cyclopropane ring was introduced at a later stage of the synthesis.

Although comparatively rare, compounds containing cyclopropane rings do occur in nature. For example, one of the most unique features of marine sterols is the occurrence of a cyclopropane ring in the 17-C sidechain. The soft coral steroid glaucasterol (49)⁶² is one example. Indeed the parent compound of this work, (41), has been isolated in trace amounts from human urine.^{63,64} However, the vast majority of cyclopropane compounds found in the literature are synthetic in origin. Thus, a considerable number of methods for the introduction of a cyclopropane moiety into a steroid or other molecule exist. The most common methods used for the synthesis of cyclopropane steroids are discussed below. The examples chosen also demonstrate the variety of cyclopropane steroids previously synthesised.

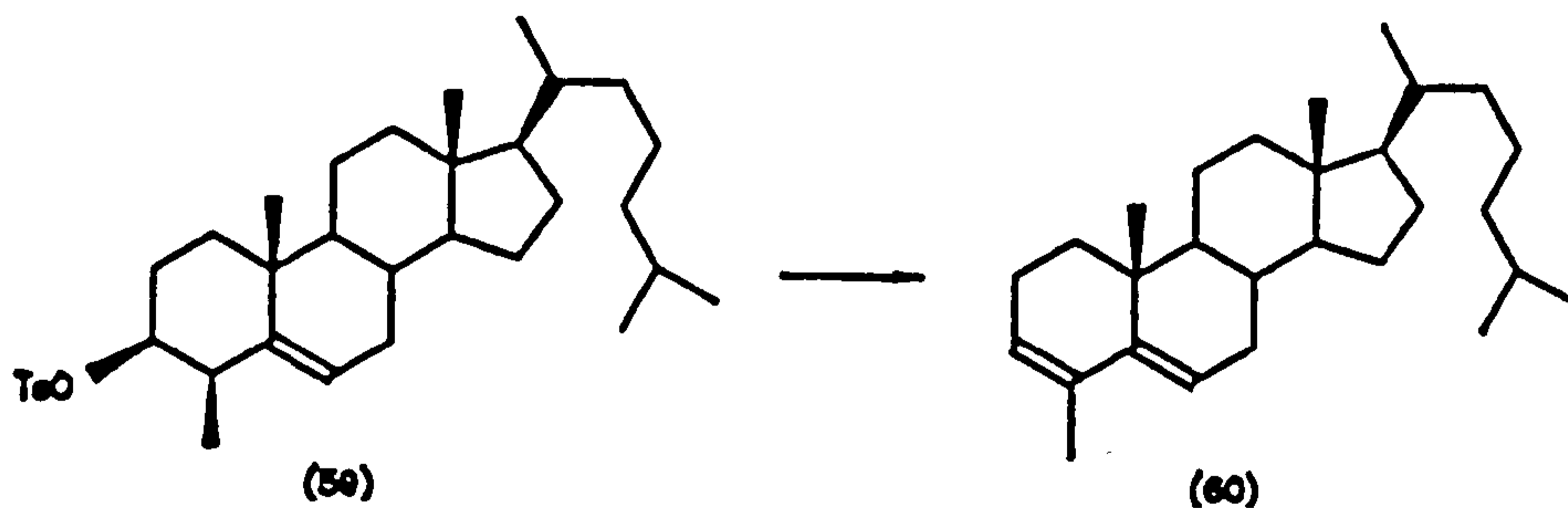
Cyclopropane Steroids.

The rearrangement reaction applied in this work (or variations of it) for the formation of the three membered ring is one of the most common methods utilised in the formation of various cyclosteroids, especially those from the 3 α ,5 series. Consequently, this is one of the most studied methods to date.⁶⁵ For the reaction to proceed to the desired cyclosteroid (Chapter 2) specific geometrical conditions must be met. Thus, for the 3 α ,5 series, rear-

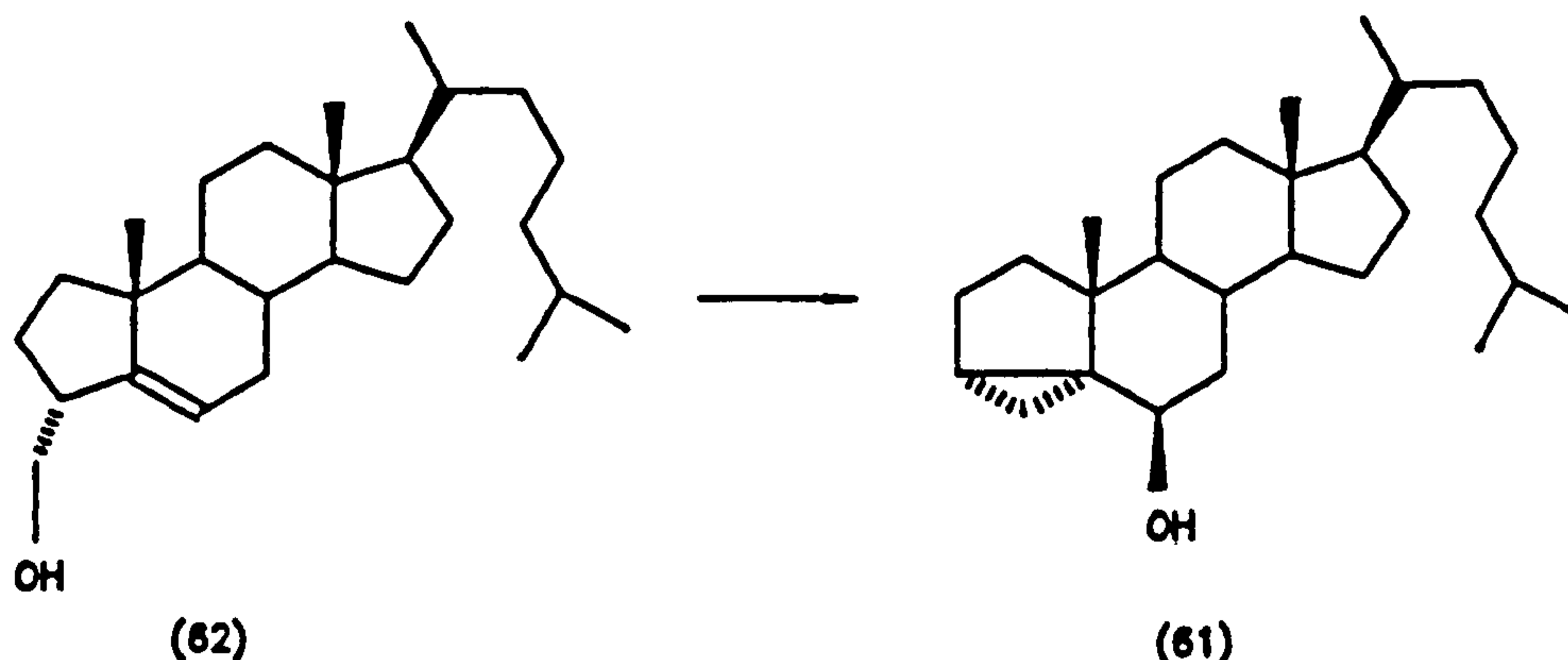
rearrangement only occurs when the 3-C leaving group is β -oriented. Conversely, when the reverse rearrangement of the 6α or 6β -hydroxy- $3\alpha,5$ -cyclosteroids occurs no 3α substituted products are observed. Other substitution patterns effect



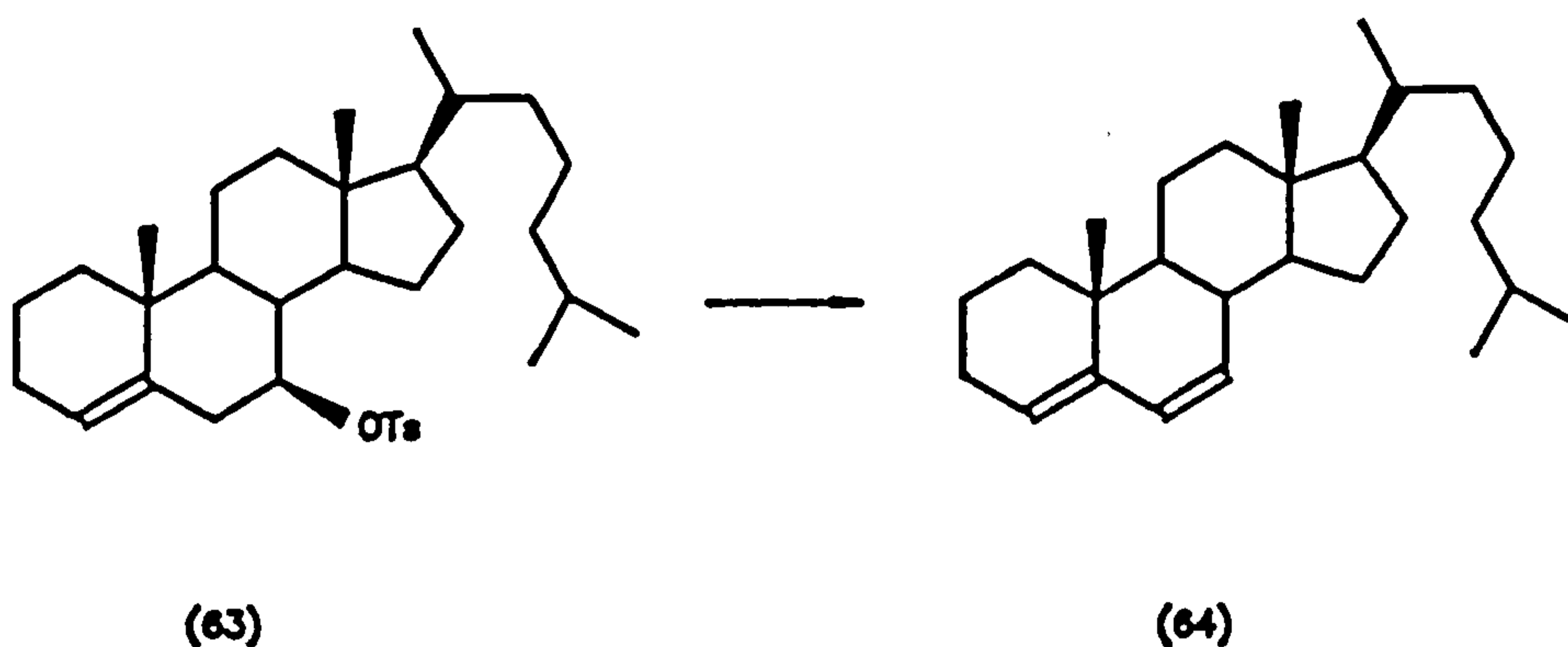
the outcome of solvolysis of 3β -sulphonates. Thus, treatment of 4α -methylcholesteryl tosylate (57) results in the formation of the cyclosteroid (58) while a similar treatment of its 4β -epimer (59) results in the isolation of the diene (60) with no detectable $3\alpha,5$ -cyclosteroid.⁶⁶ In contrast to



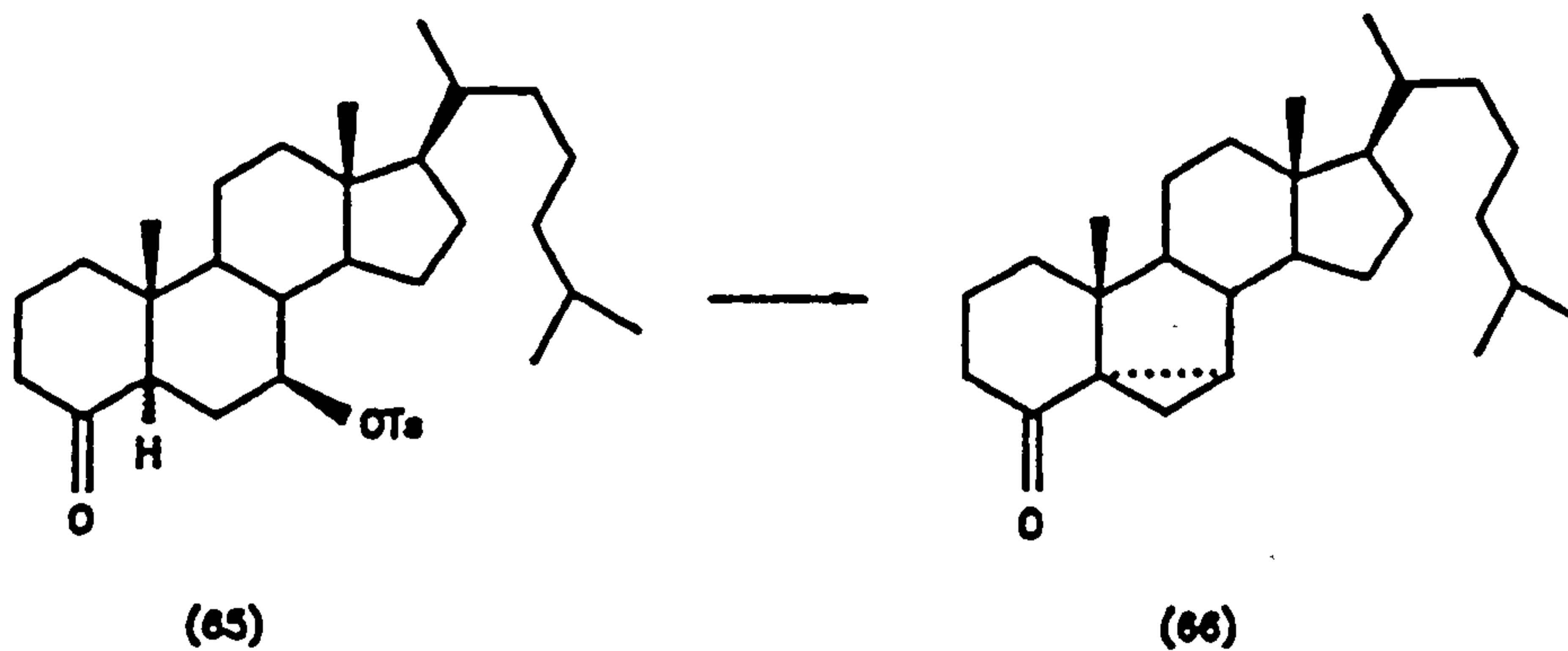
the above, the formation of $3\beta,5$ -cyclosteroid (61) from the A-nor steroid (62) only occurs when the hydroxymethyl group



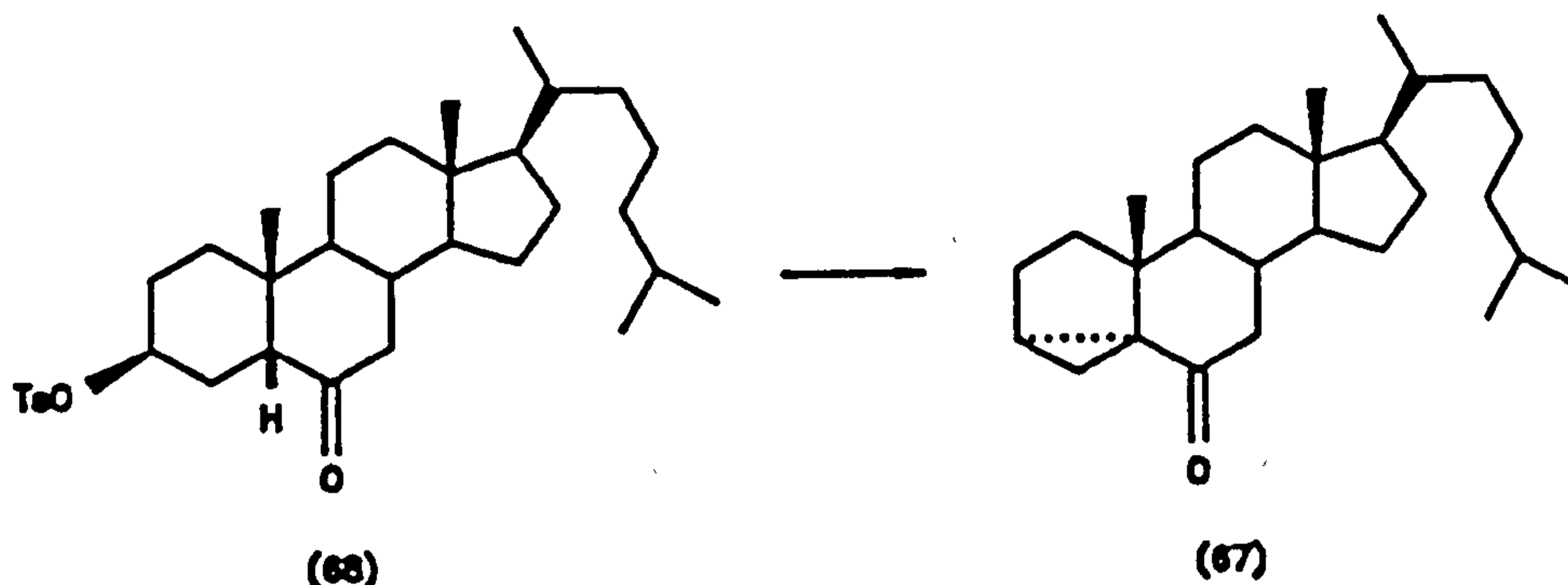
is α -orientated. A β -orientation results in the $3\alpha,5$ -series.⁶⁷ Other geometrical alterations or chemical modifications of the steroid framework also alter the rate of reaction and the yield of the cyclopropane product. The attempted formation of other cyclosteroids by this method again confirms the specific geometrical requirements. Thus, solvolysis of the 7β -tosylate (63) does not lead to the isolation of 5,7-cyclosteroids. The main product being the diene (64).⁶⁸



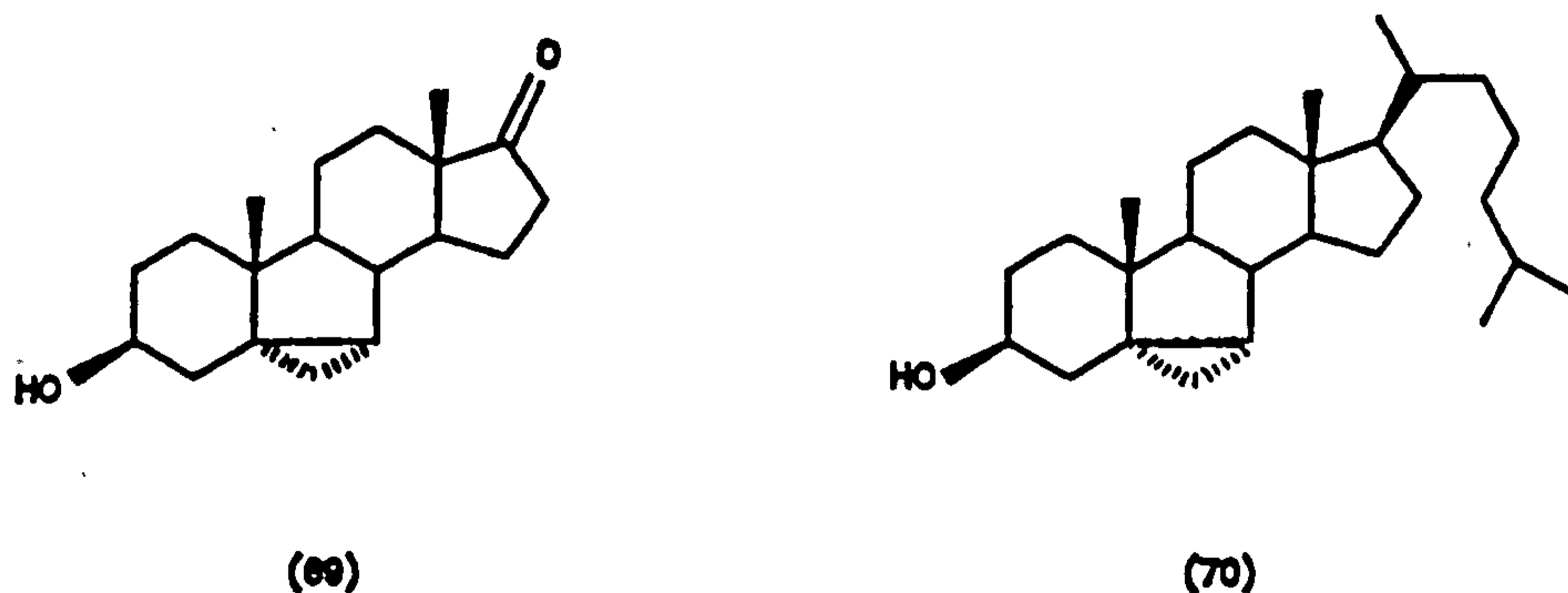
Two variations to the above type of reaction have been utilised in the formation of cyclosteroids. Treatment of the 4-keto-7-tosyl steroid (65) with basified methanol does yield, in contrast to the above, the desired cyclosteroid (66).⁶⁹ Also, direct access to the 6-keto cyclosteroid (67)



is attained by the treatment of the 3-tosylate (68) with tetramethylguanidine or, the phase transfer reagent benzyltrimethylammonium hydroxide, in pyridine. Alternatively, a chlorine atom at 3-C can be used as a leaving group.⁷⁰

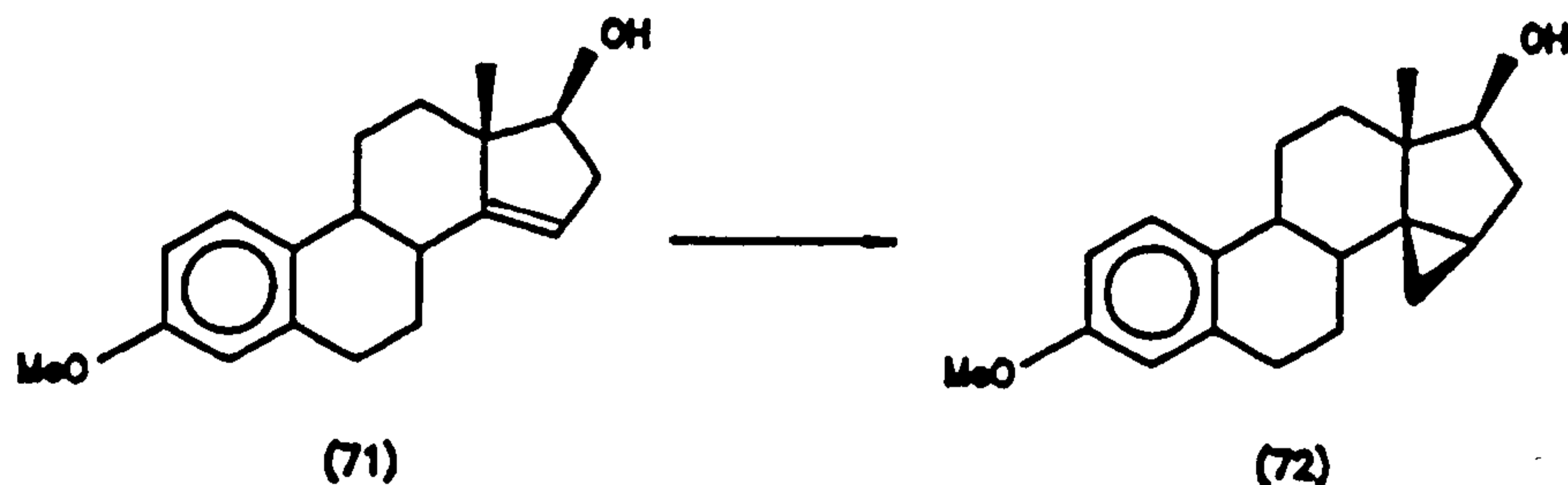


Another particularly important method for the formation of cyclosteroids is by the application of the Simmons-Smith methylenation reaction (methylene iodide and zinc-copper couple).⁷¹ Joska *et al.* used this method for the formation of 5,7 β -cyclosteroids, e.g., (69)⁷² and (70).⁷³ Yields by this method are often low, especially when free hydroxy groups or ketone groups are present in the molecule. However, low yields induced by for example a hydroxy group can be

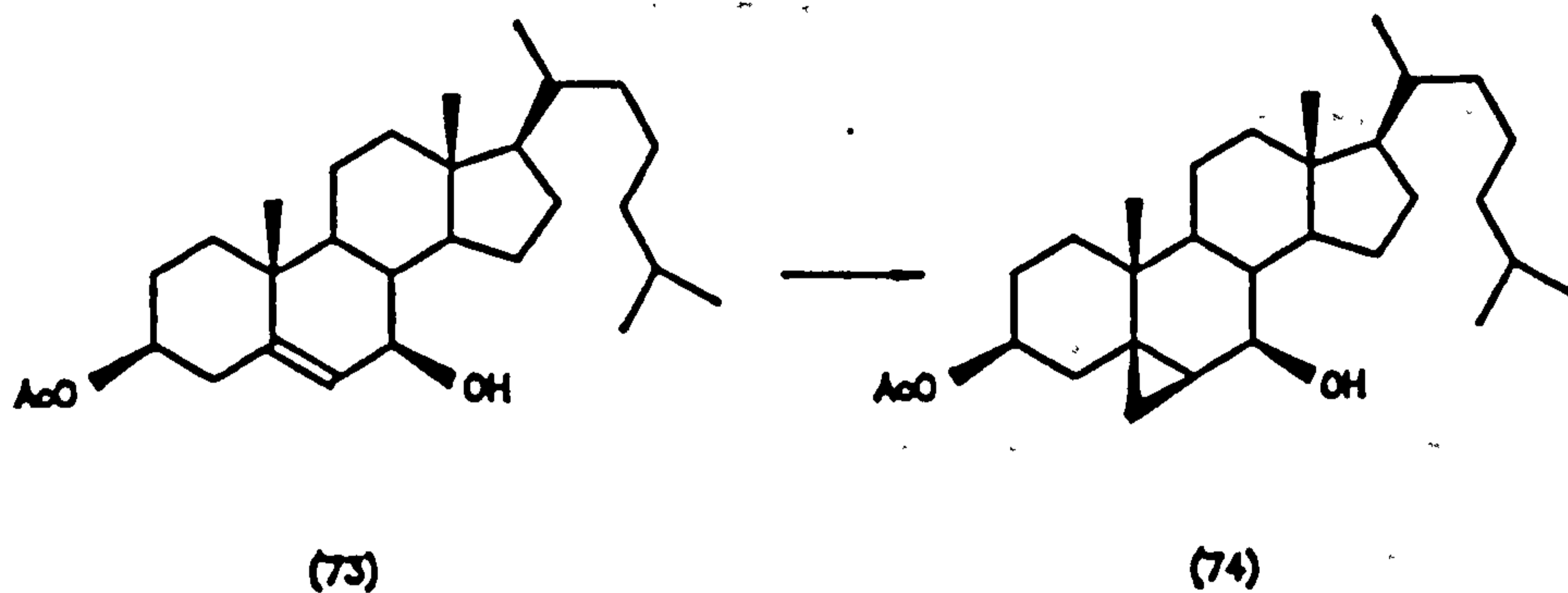


offset when the functional group directs the incoming reagent to form an isomerically pure product. Thus Simmons-Smith cyclopropanation of 17 α and 17 β -hydroxy-14-enes of the androstane and estratriene series, e.g., (71) is controlled by the activating and syn-directing effect of the 17-hydroxy

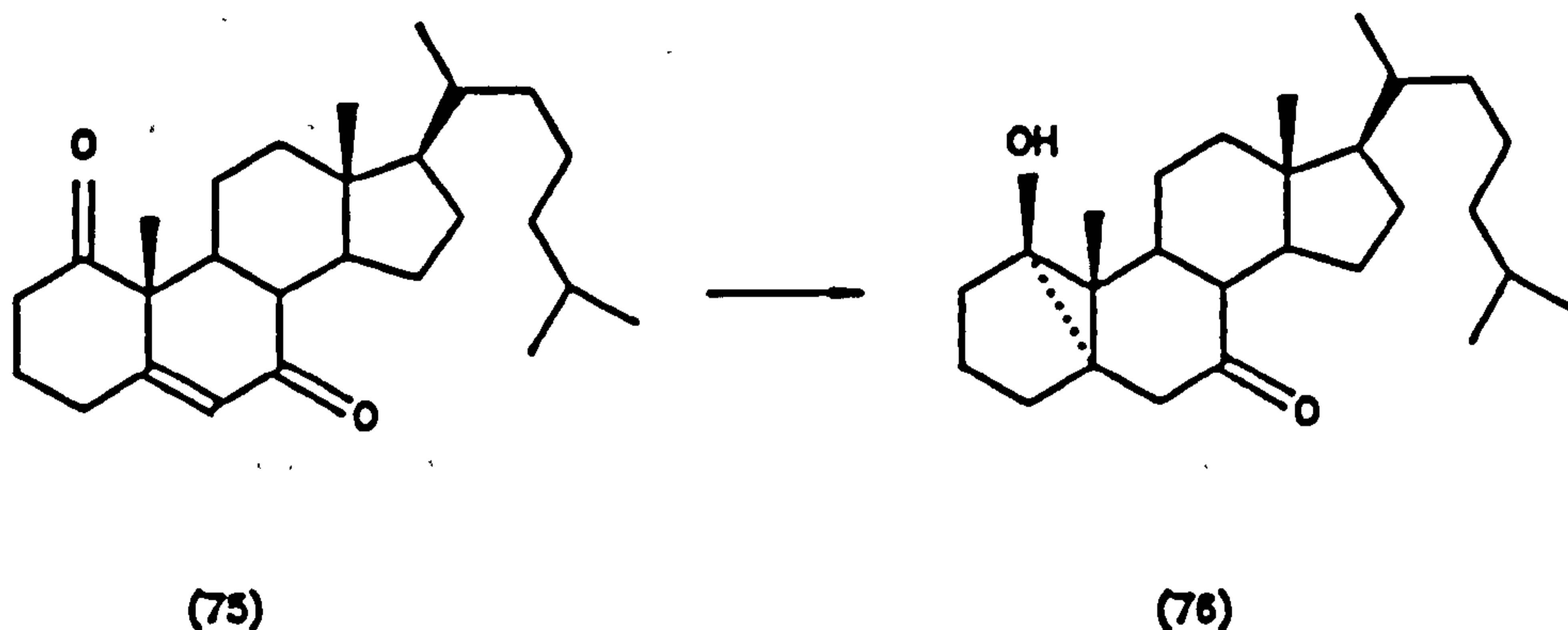
group.⁷⁴ This leads to cyclopropanes in which the 14,15-methylene group and the 17-hydroxy group are *cis* in a stereospecific reaction (72).



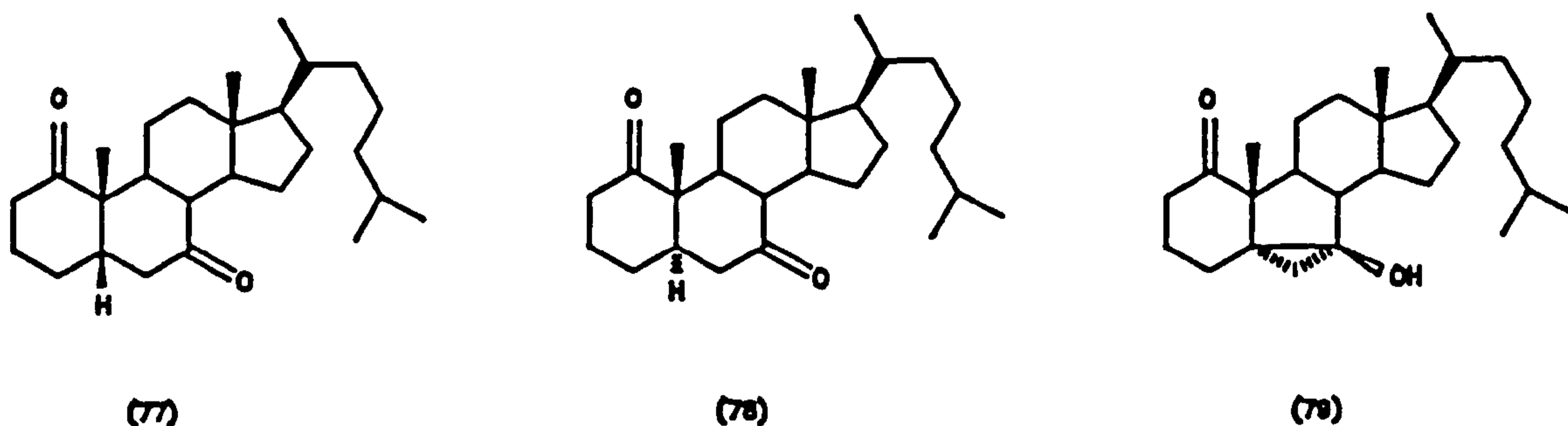
Oxidation to the 17-ketone derivative followed by reduction with diborane or complex metal hydrides results in a trans relationship between the two groups. Likewise, in the cyclopropanation of the epimeric hydroxycholesteryl acetates, e.g., the β -alcohol (73) gives the $5\beta,6\beta$ derivative (74) while the α -isomer gives the $5\alpha,6\alpha$ methylene compound.⁷⁵



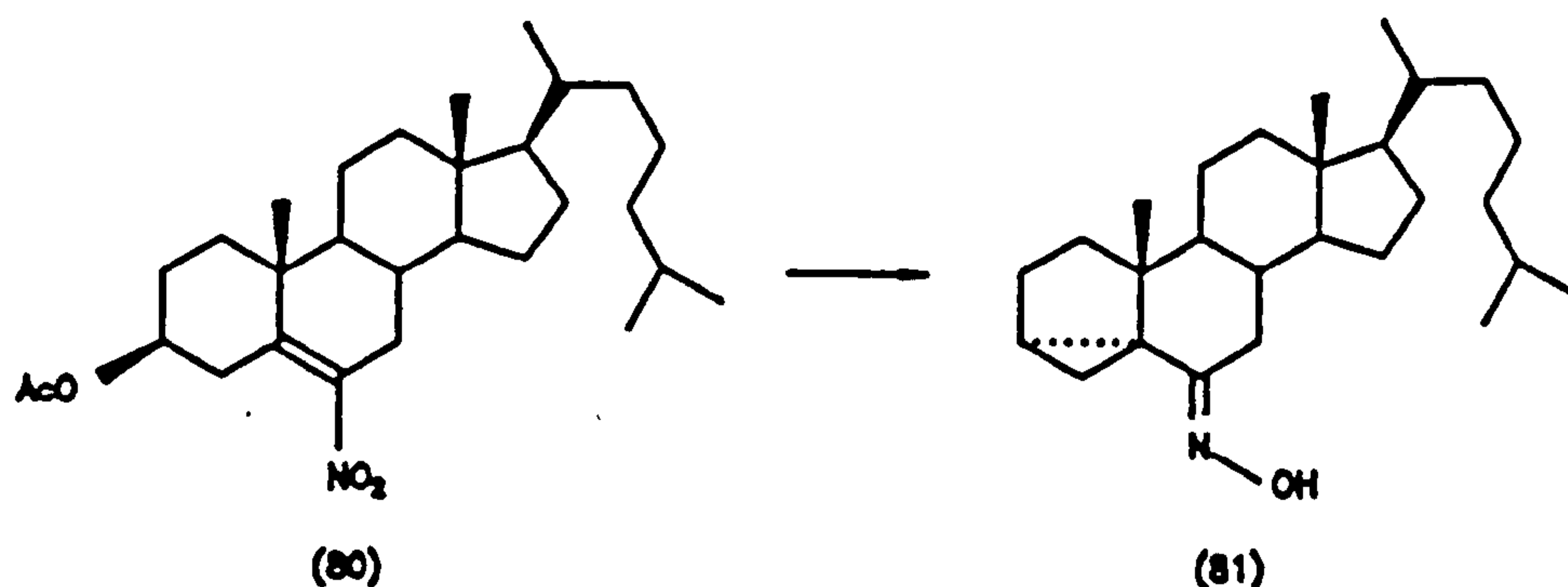
Dissolving metal reductions have also been utilised in the formation of cyclopropane steroids. Thus, cholest-5-en-1,7-dione



(75) when treated with lithium in ammonia/THF gave the 1,5-cyclosteroid (76). When this compound was treated with potassium hydroxide the expected products (77) and (78) were the major products isolated. Surprisingly however, when the steroid was treated with mild base it was converted to the unusual 5,7 β -cyclosteroid (79).⁷⁶

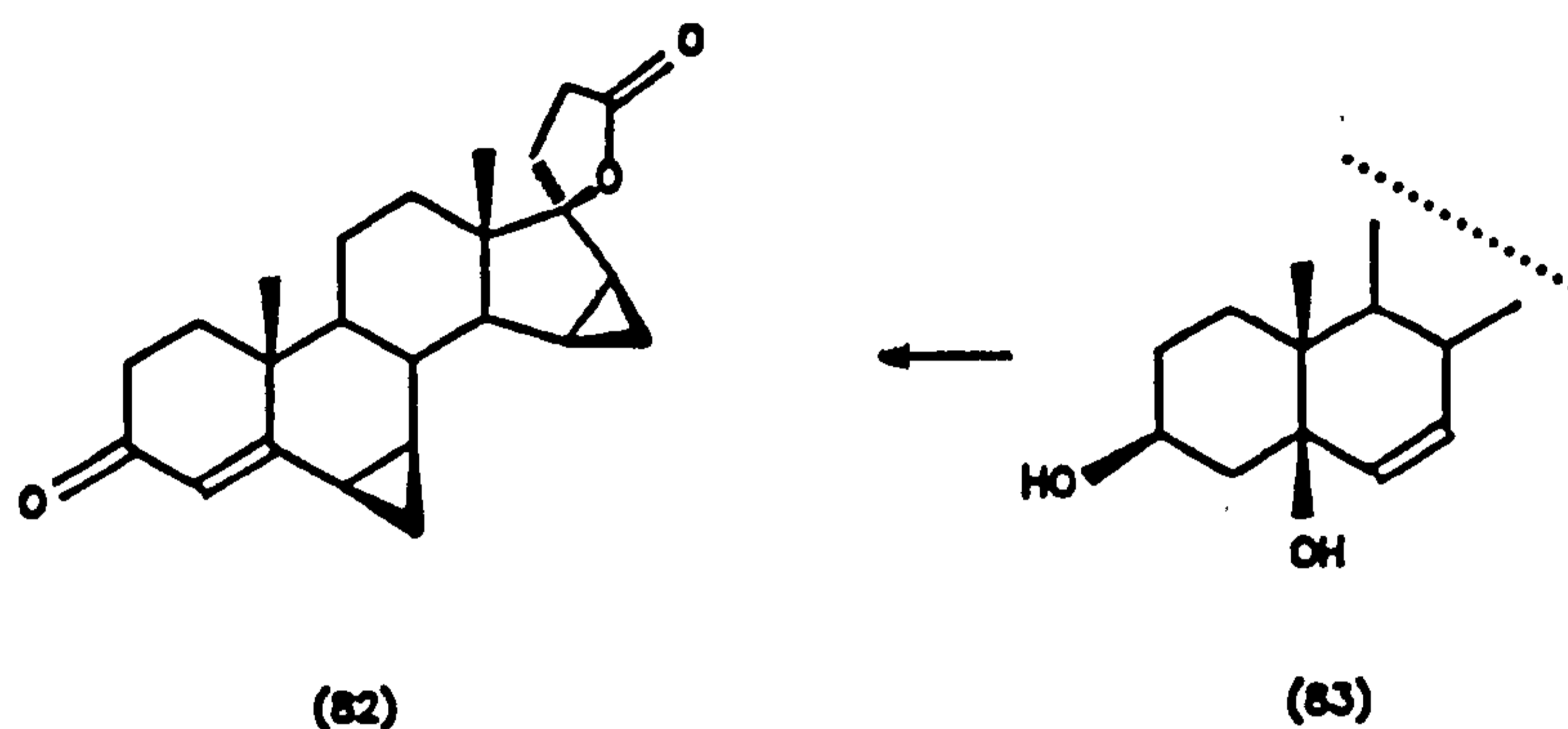


As the above examples show, a sulphonate group is in most cases used as a leaving group although chlorine has also been utilised. One rare example where an acetoxy group is utilised as a leaving group is in the reaction between 3 β -acetoxy-6-nitrocholest-5-ene (80) and dimethylcopper cuprate. The product, the (E)-oxime (81) is thought to be formed via a free radical mechanism. Displacement of the acetate ion may be facilitated by complexation with the copper-lithium species.⁷⁷

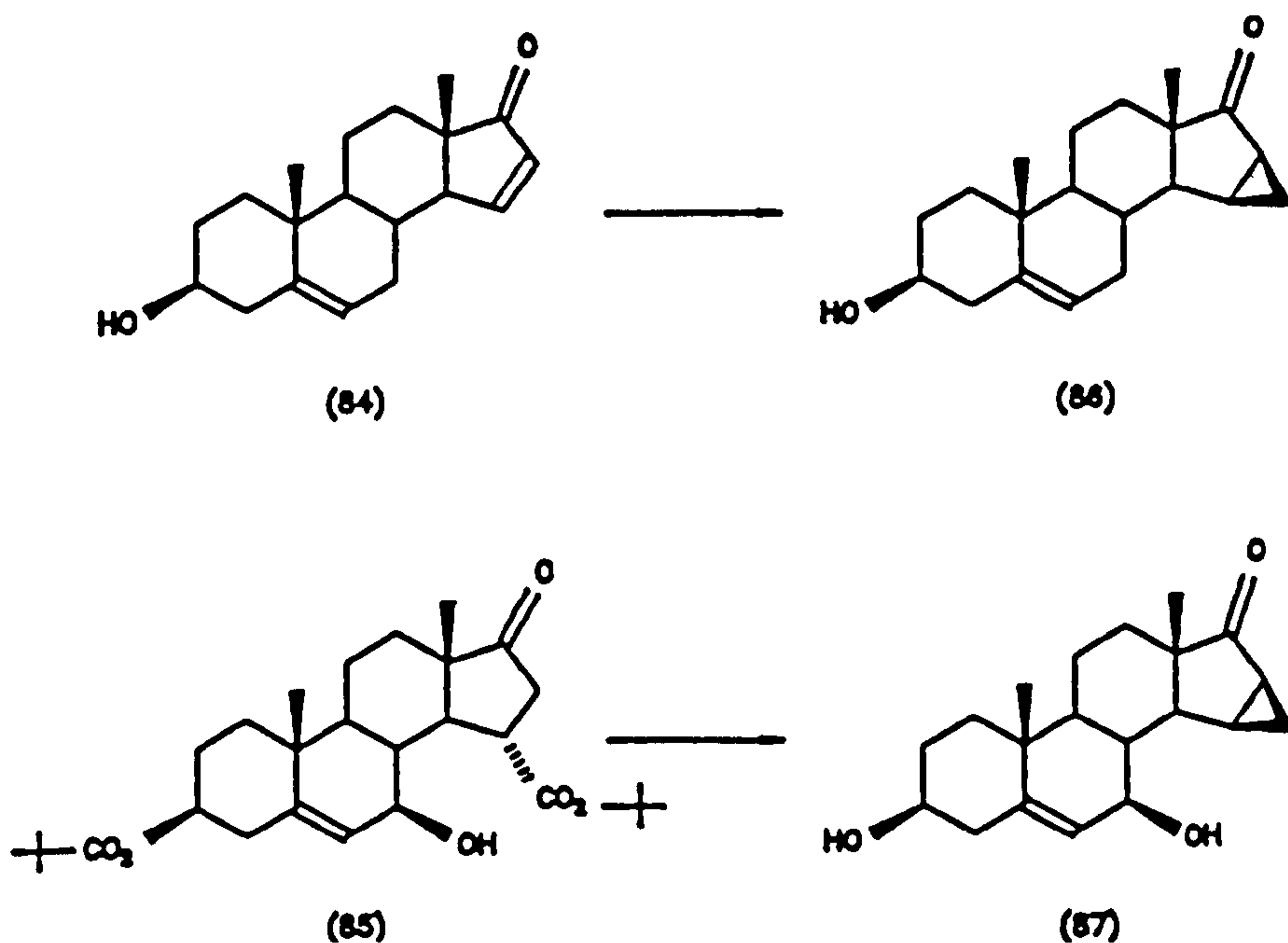


The cyclopropane rings of the anti-aldosterone bis-methylene compound (82) were introduced by two different

techniques.^{78,79} Under Simmons-Smith methylenation conditions (diiodomethane zinc-copper couple) the 6,7 methylene group was introduced. Stereospecificity (β,β) was induced by the 5β -hydroxy group present in the precursor (83).^{79,80} However, the second cyclopropane group was introduced by

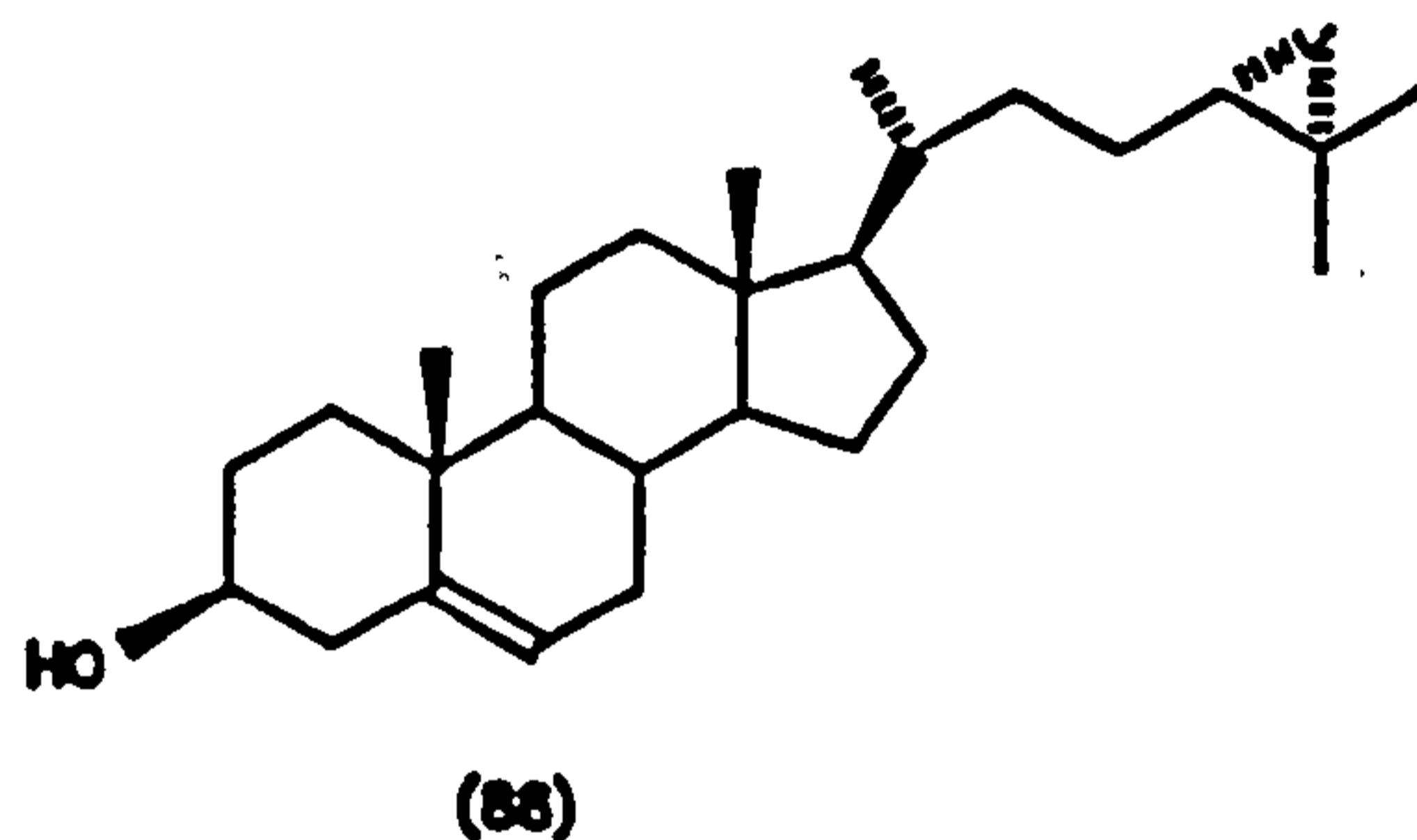


using the less common Corey-methylenation reaction.⁸¹ Thus, either the α,β -unsaturated ketone (84) or the dipivalate (85), when treated with trimethylsulfoxonium iodide in dimethyl sulfoxide (DMSO) containing sodium hydroxide, resulted in the formation of the respective $15\beta,16\beta$ methylene intermediates (86) and (87).



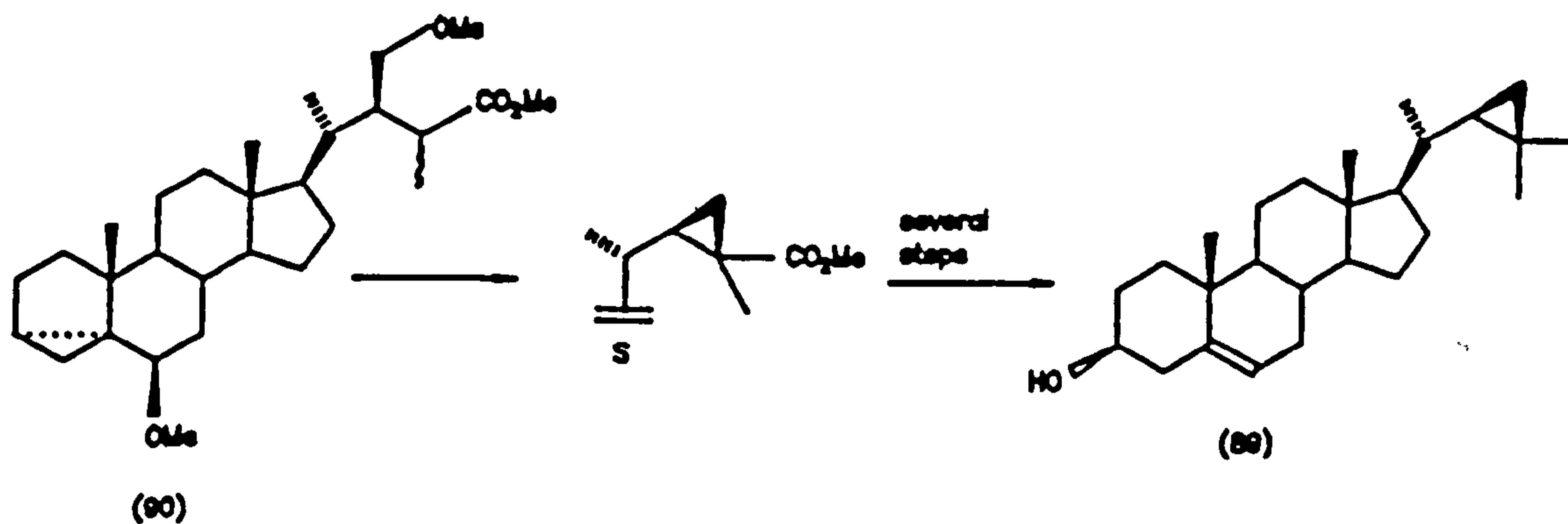
Side chain cyclopropane steroids.

As discussed above, a considerable amount of effort has gone into the stereospecific introduction of 17-C sidechains to the steroid nucleus. The discovery that in the marine environment many sterols possess a cyclopropane ring has led to the speculation that these compounds are intermediates in biomethylation sequences. Consequently, many investigations into the biosyntheses of these steroids, e.g., sormosterol⁸² (88) are being carried out. The possible physiological role of these compounds has also attracted much interest. Thus, a

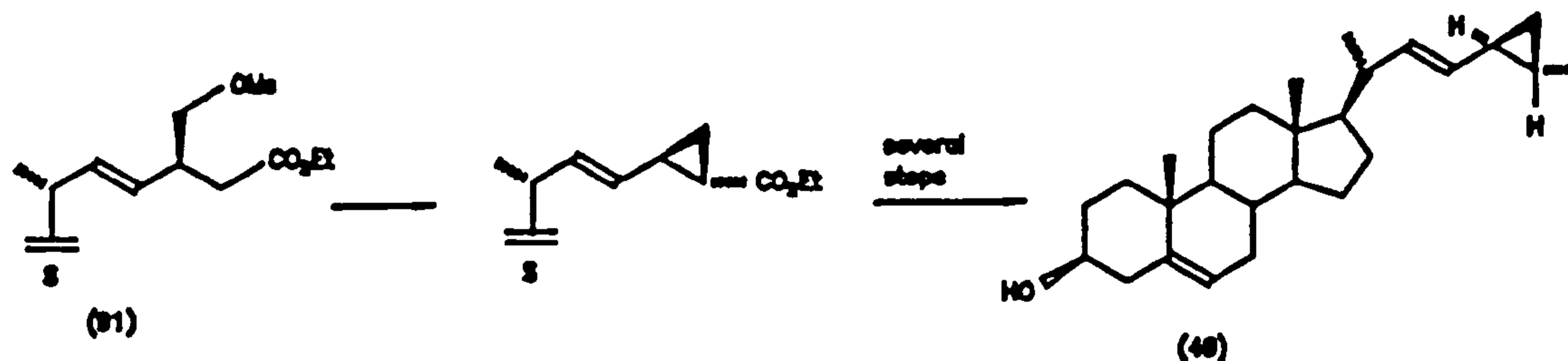


considerable amount of syntheses have been carried out not only to provide access to these novel steroids but also to characterise their configurations.

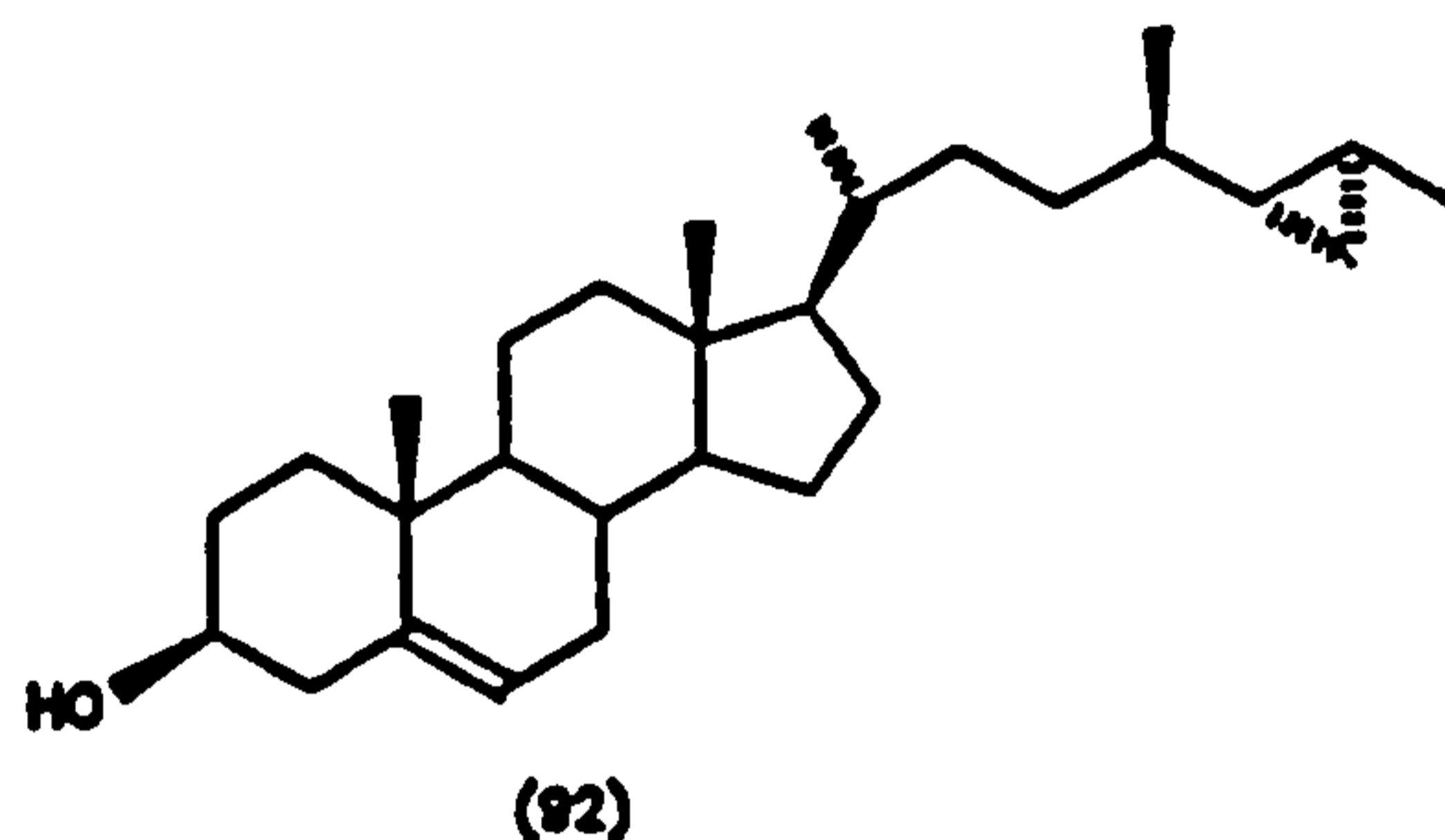
In many of the marine steroids synthesised to date one particular method for the introduction of the cyclopropane



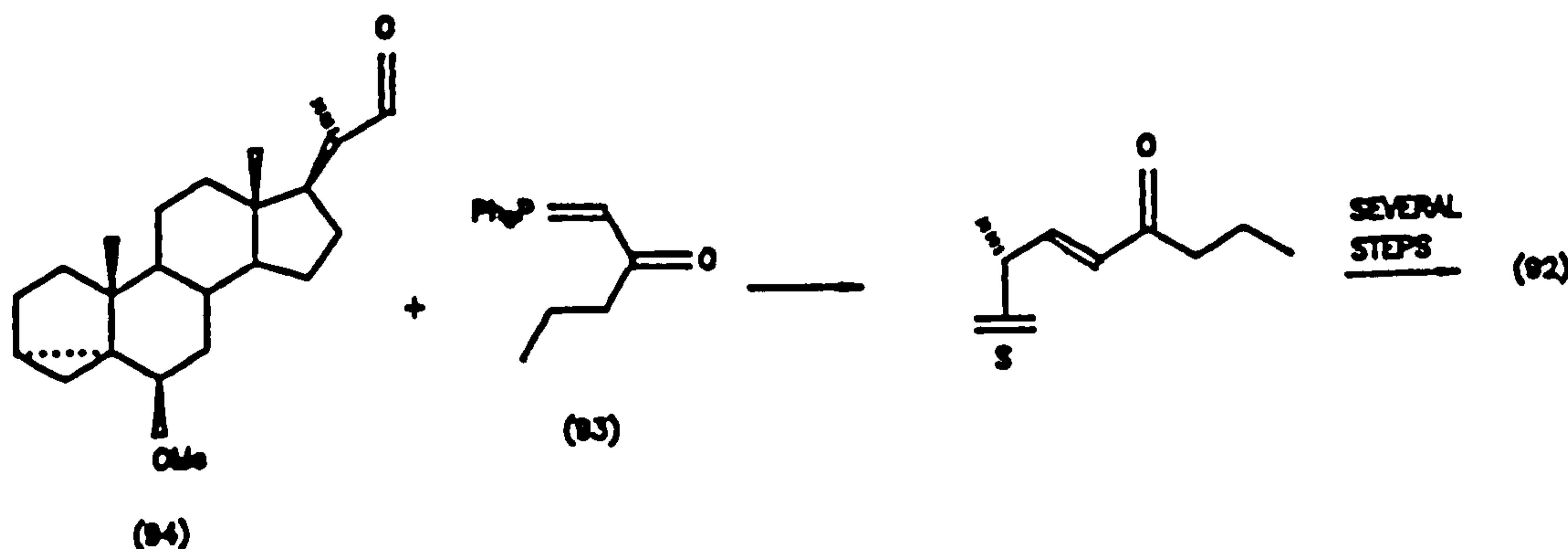
ring has been utilised. Thus the cyclopropane ring of gorgosterol⁸³ (89) was introduced by the treatment of the mesylate (90) with potassium tertiary butoxide as base. Yields were good and only a very small quantity of the 23-C



isomer was isolated.⁸⁴ Another example of this reaction can be found in the synthesis of glaucasterol (49).⁸⁵ Here again the mesylate derivative (91) was the chosen sulphonate. The cyclopropane ring of petrosterol, (92), was also introduced in this manner.⁸⁶



Finally, although not strictly relevant to this discussion (because we are not dealing with the formation of a cyclopropane ring) the marine sterol petrosterol (92) has also



been synthesised by condensation of the phosphorane (93) and the steroid (94).⁸⁷ All four trans isomers were synthesised. However, the product distribution resulting from the acid-catalysed isomerisation of these four diastereomers showed a marked dependence on the relative stereochemistry between the cyclopropane ring and the adjacent chiral centre at 24-C. Thus, an examination of the conformations available to the sidechain led to a rational explanation of this dependence and shed light on hitherto unrecognised subtle stereochemical features operating among aliphatic cyclopropanes.

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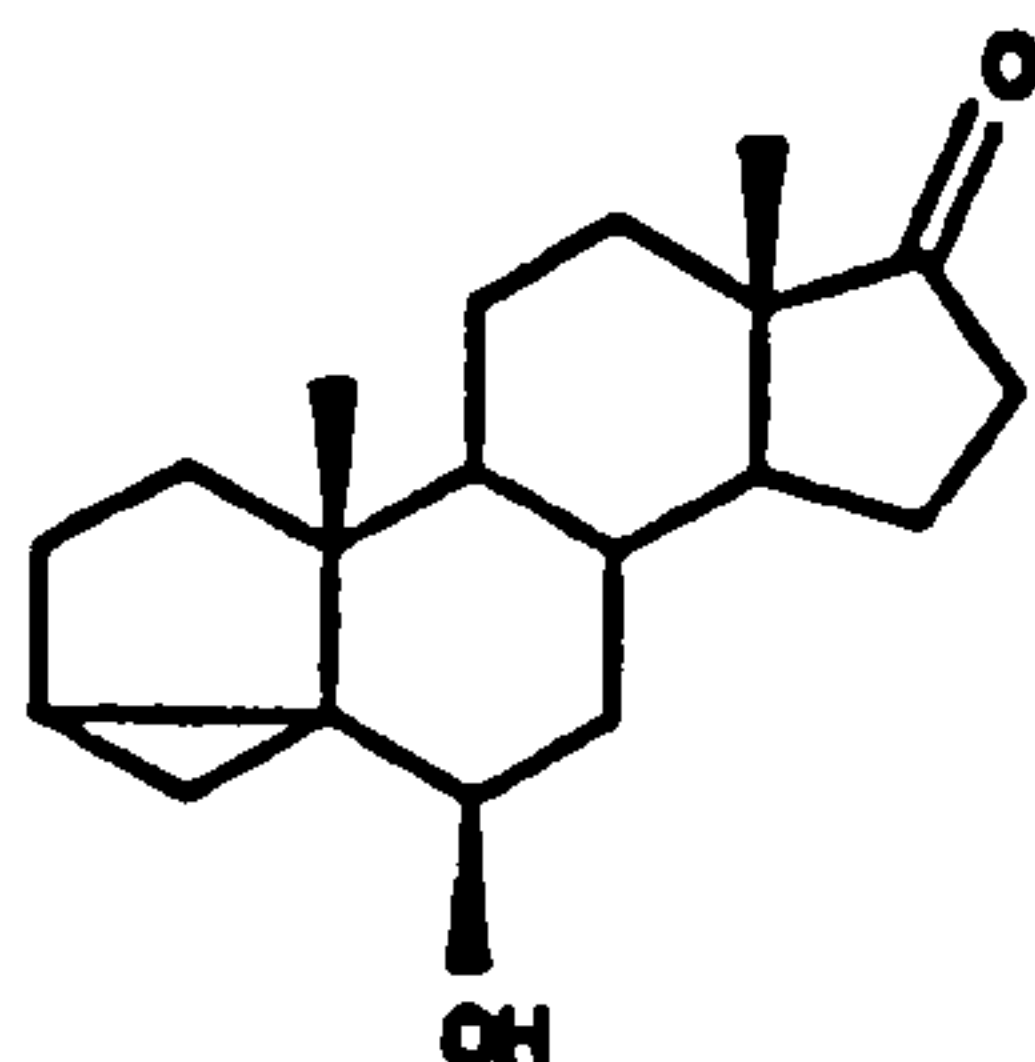
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CHAPTER 2

Formation of 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one and
selected derivatives.

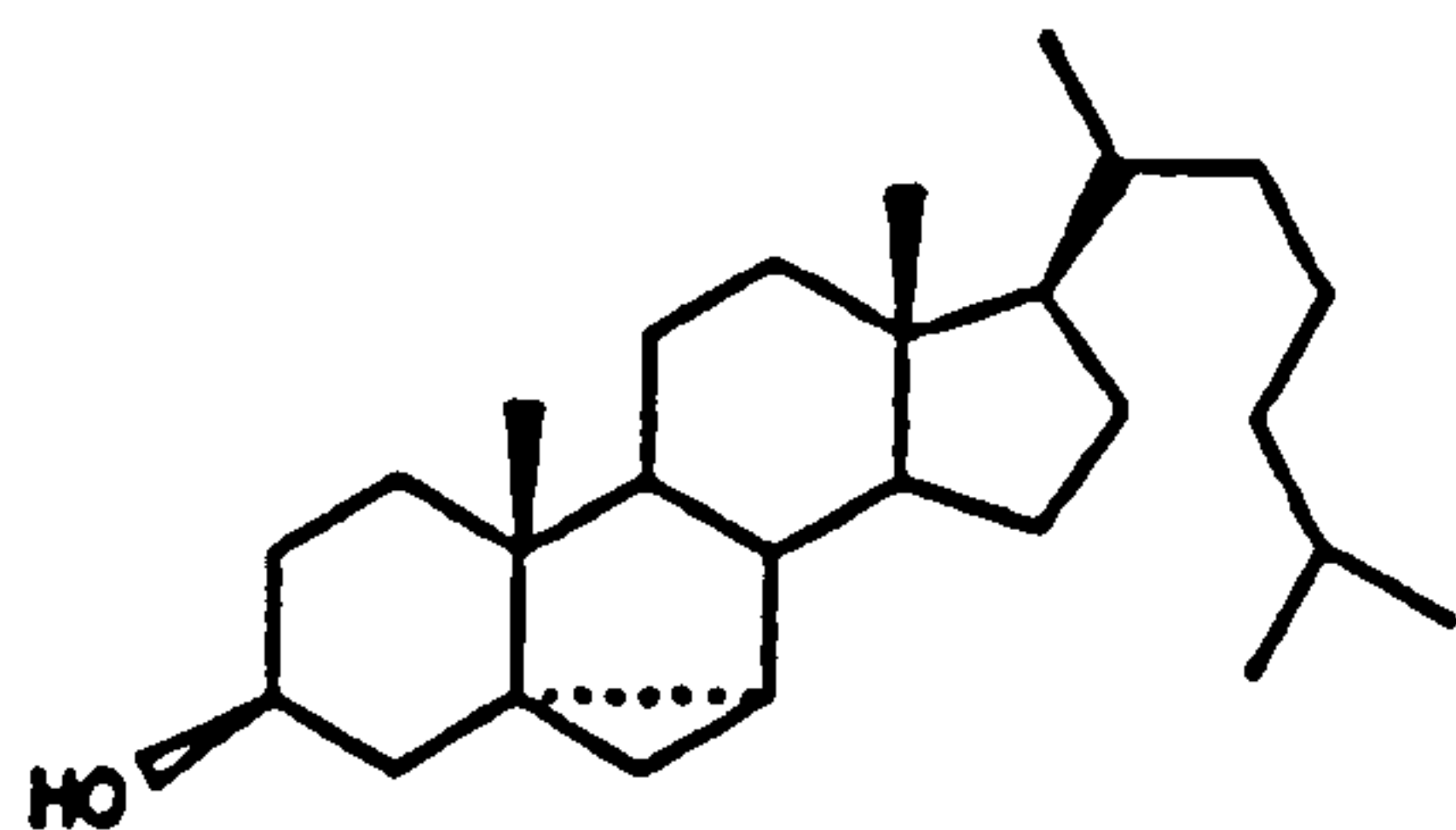
2.1 Introduction.

The title compound (41) is one of many steroids that contain a cyclopropane ring within the steroid nucleus. Most steroids conforming to the above have a cyclopropane ring incorporating carbon atoms 3, 4, and 5, but others, e.g.,

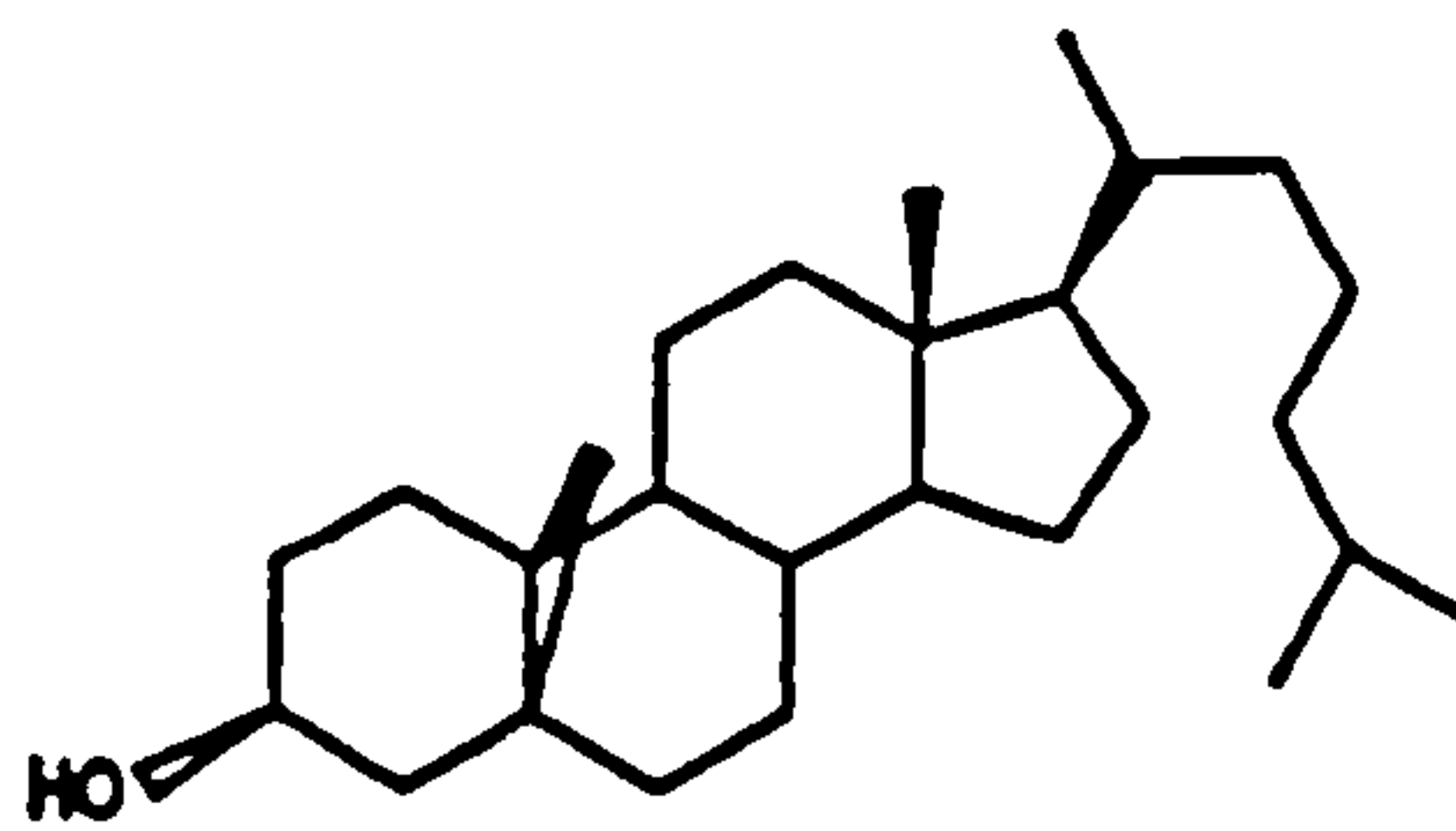


(41)

the 5,7 cyclosteroids (70)¹ and the 5, 19 cyclosteroid (95)² have also been synthesised (Chapter 1). Although first isolated from a synthetic reaction, the title compound (41) has also been isolated from natural sources, originally from human urine.^{3,4} The alcohol (41) was chosen as a lead compound to other steroids because it had, in earlier studies,⁵ shown biological activity. Furthermore, previous work at R.G.I.T. had indicated anti-fertility properties. This was in spite of the 6-C position of the alcohol group which generally reduces the biological activity of steroids.⁶



(70)

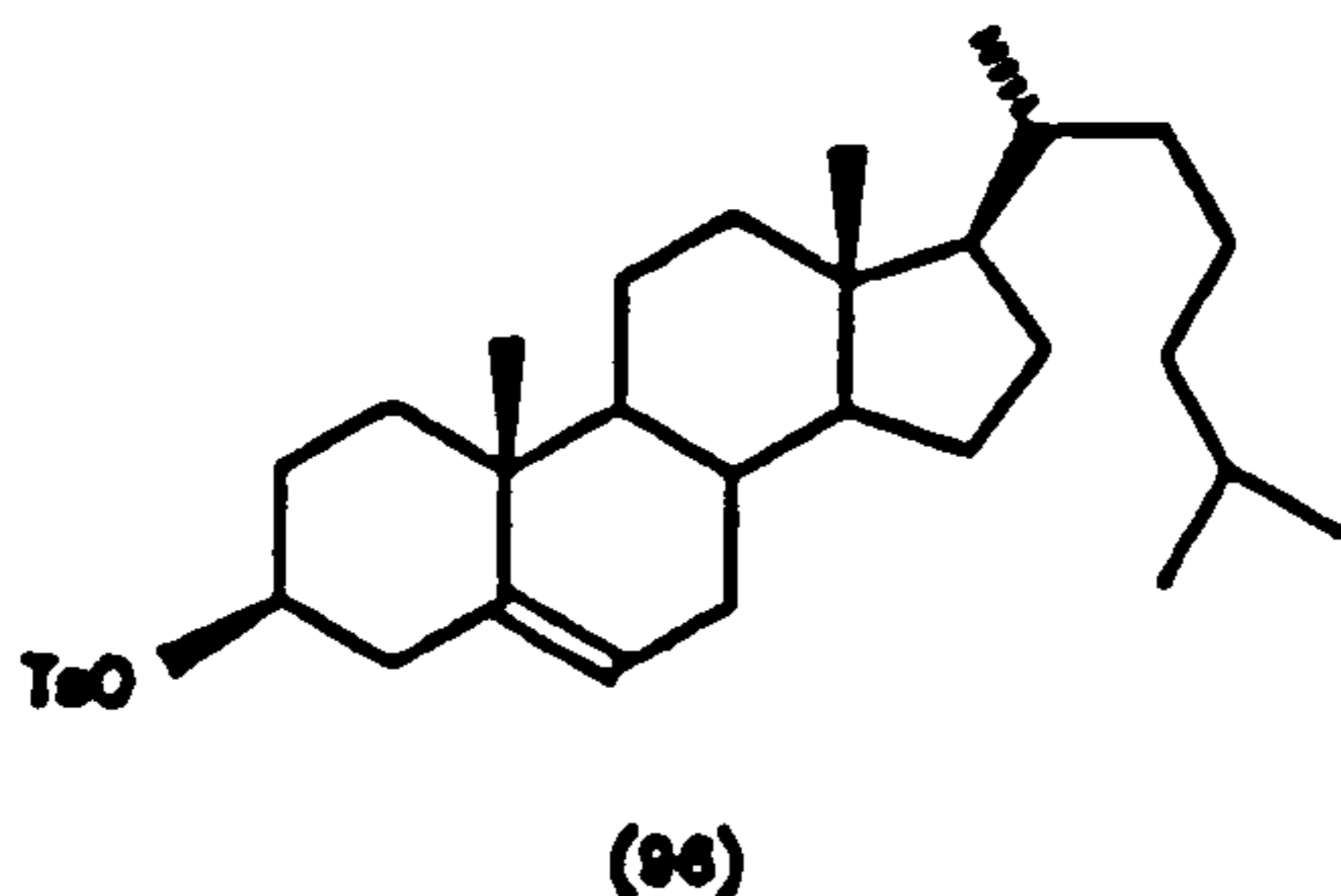


(95)

Other compounds discussed here are the methyl ether (106) of the parent alcohol (41) and the 6-keto steroid (111), both used as intermediates in the formation of the 6-methyl derivative (Chapter 3). The formation of the 17-propargyl derivative (42) by various routes is also discussed.

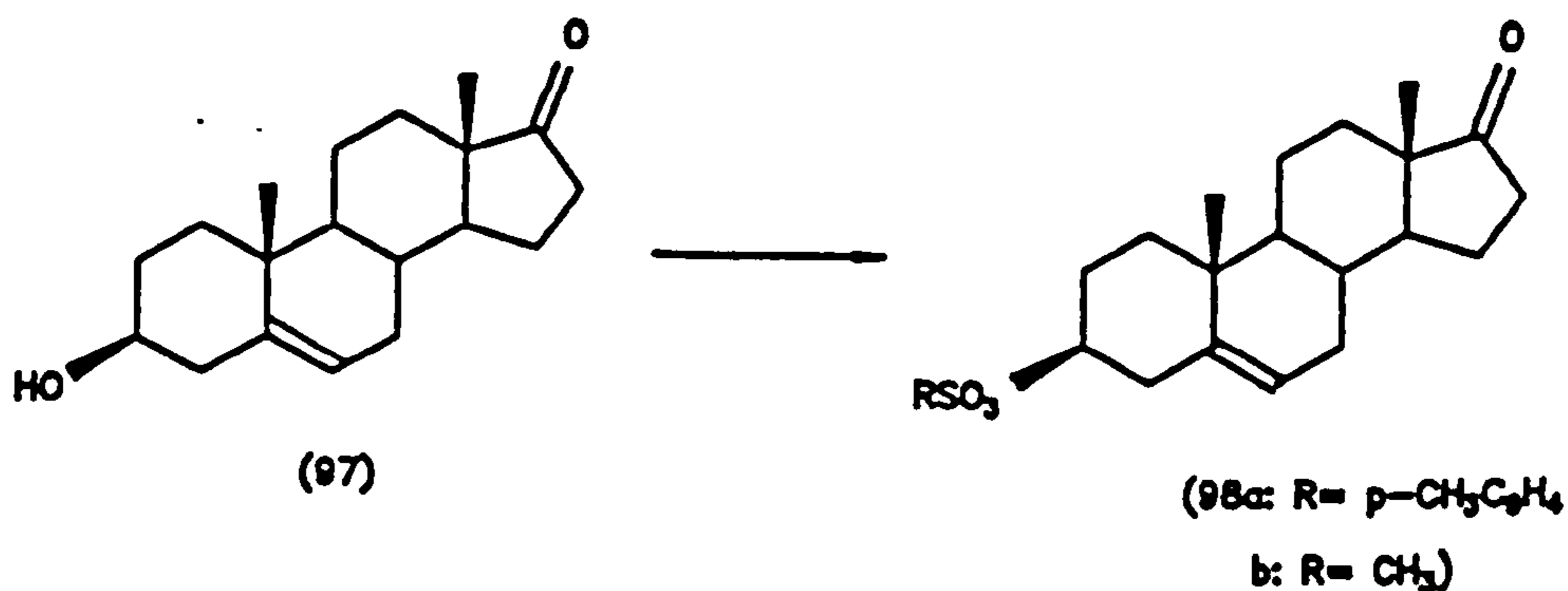
2.2 Formation of 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41).

The parent steroid, 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41)⁷ was prepared via the classical 3,5-cyclosteroid rearrangement originally noted by Stoll⁸ in the solvolysis of cholesteryl p-toluenesulphonate (96).



2.2.1 Formation of 3 β -tosyl-5-androsten-17-one (98a).

The first step, the introduction of a suitable leaving group at 3-C, was carried out by the standard method,^{9,10} i.e., by reacting together in anhydrous pyridine, dehydroepiandrosterone, (DHEA), (97) and p-toluenesulphonyl chloride (TsCl) to yield the sulphonate (98a). The product was readily identified spectroscopically by the appearance of the characteristic two doublets of a para substituted benzene ring in the aromatic region of the ¹H NMR spectrum, corresponding to the tosyl ring and a singlet at $\delta = 2.41$



corresponding to the methyl group of the tosyl moiety. More subtle changes were the downfield shift of the 3-H signal induced by the stronger electron withdrawing properties of the new moiety and the slight downfield shift in the 6-C alkenic proton. In agreement with the above data the IR spectrum showed no hydroxy group absorption and strong aromatic absorption.

Formation of 3 β -mesyl-5-androsten-17-one (98b).

As an alternative to the above, the methyl sulphonate (98b) was formed by reacting DHEA (97) with mesyl chloride under identical conditions. Even though the sulphur atom of the mesylate is less electron deficient than its counterpart in the tosylate molecule this reaction was found to proceed faster than the similar tosylation, most certainly because of its smaller size. Also, by virtue of the physical properties of the sulphonic acid by product, the purity of the resulting sulphonate (98b) was considerably increased. Therefore this method was the preferred route for the formation of a suitable sulphonate.

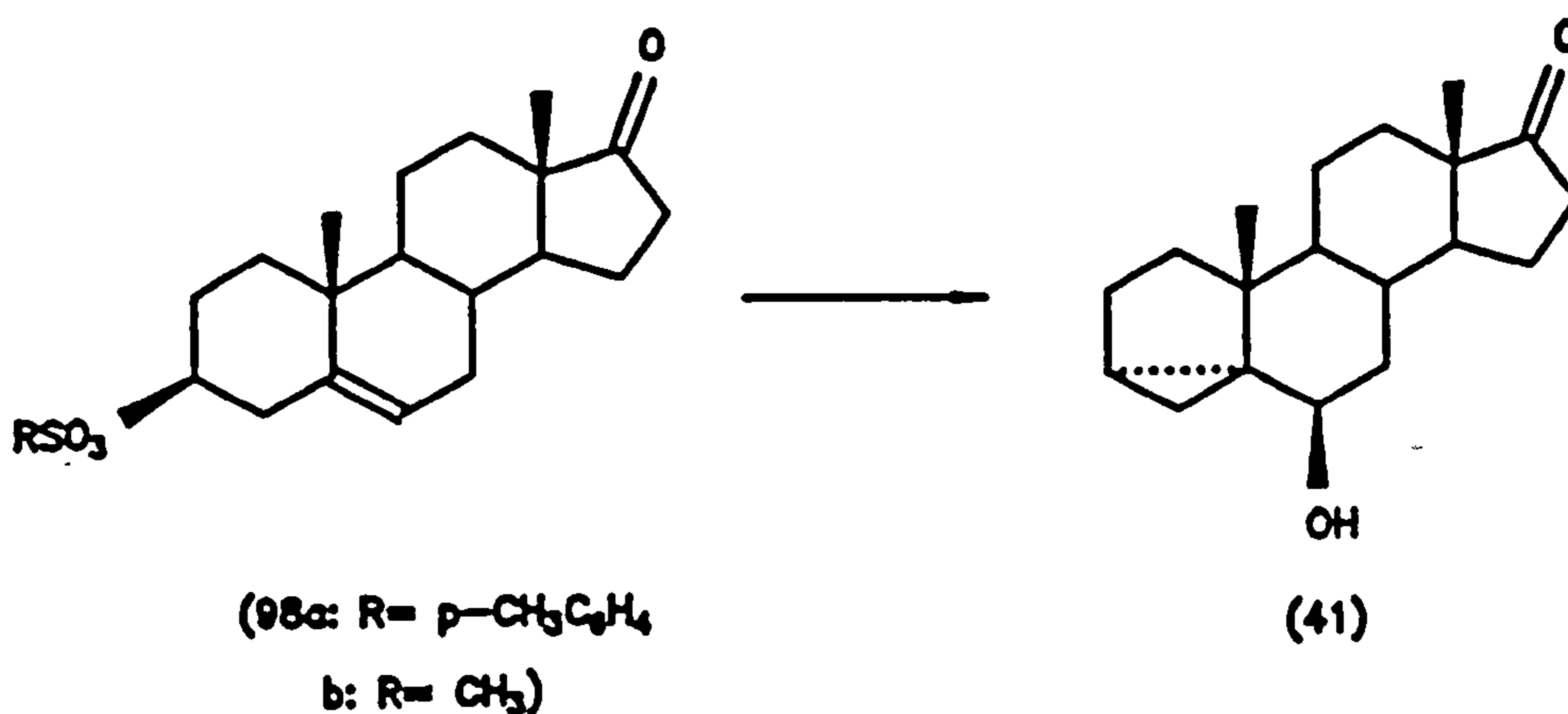
Evidence of product formation was obtained spectroscopically. A notable difference in the ^1H NMR spectrum of the product from its starting material was the addition of a 3H singlet at $\delta = 3.01$ corresponding to the mesyl protons. As with the tosylate more subtle differences lay in the position of the signals attributed to the 3 and 6-H which were both shifted downfield. The IR spectrum of the product did not show absorption due to a hydroxy group but did possess bands corresponding to the sulphonate group.

In variations to the above procedures DHEA was found to be insufficiently soluble in other solvents which readily form the hydrochloride salt (the essential driving force of the reaction) such as triethylamine. Both sulphonating reactions were however successful when a molar equivalent of pyridine was added to a dichloromethane solution of the steroid and the sulphonating agent. The rate of this reaction being increased by heating the mixture.

2.2.2 Hydrolysis and rearrangement of sulphonate esters of DHEA (98a and b).

Formation of 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41).

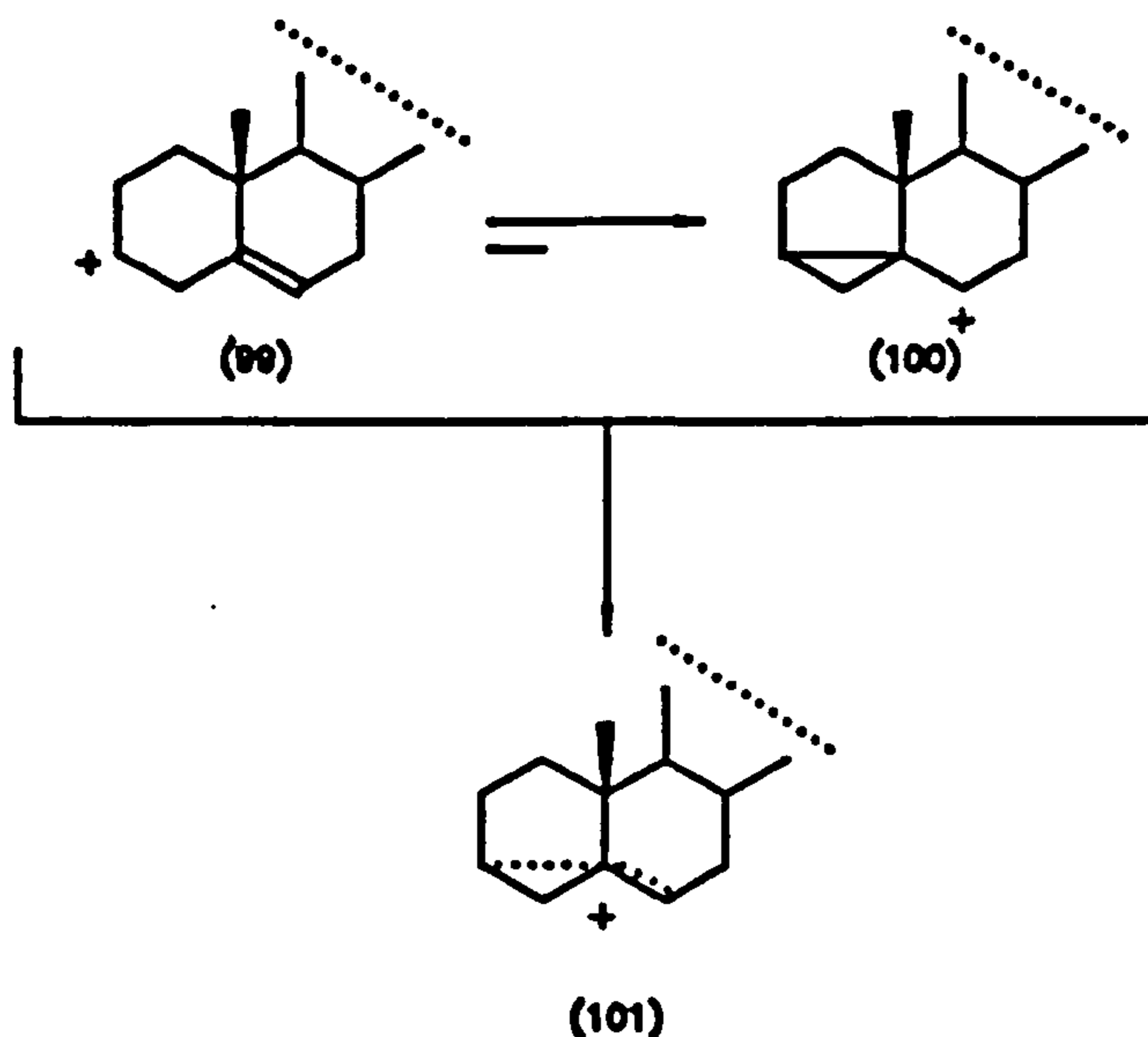
The second step in the formation of the parent cyclosteroid was undertaken using both the above products under a variety of conditions (see below). The product was readily identified by the very high field signals associated with the cyclopropane ring (see later this Chapter) and the



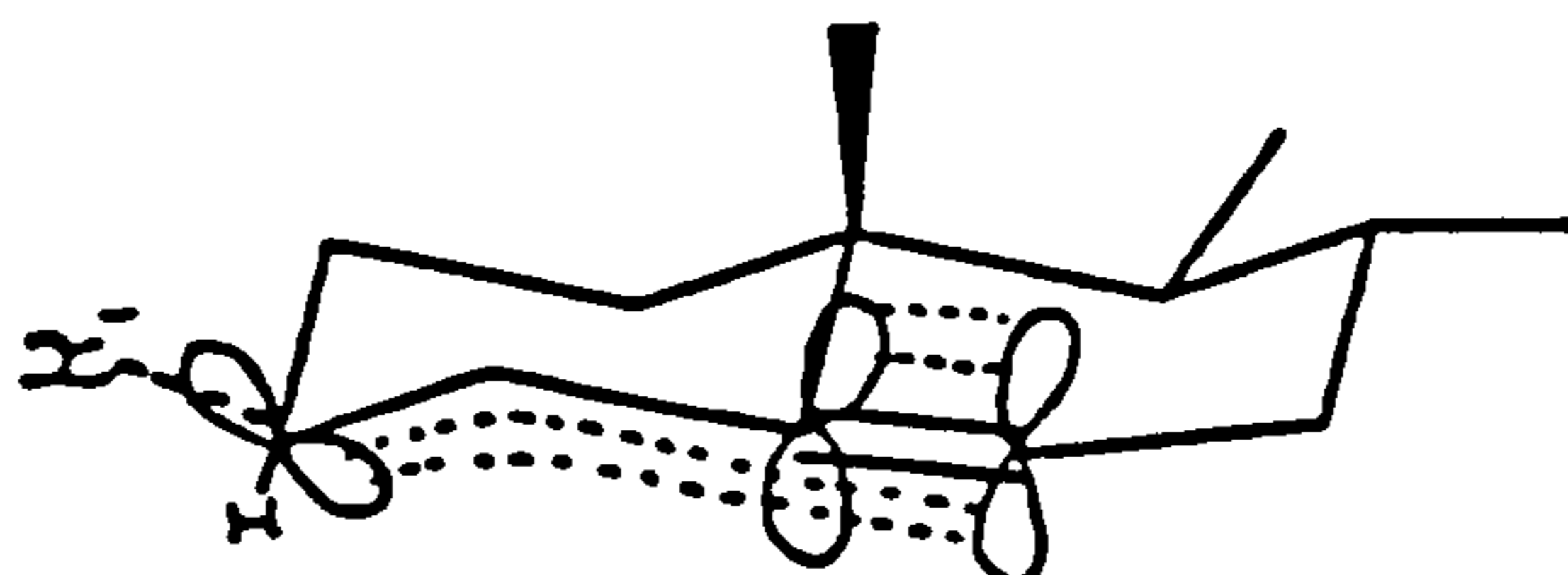
corresponding removal of alkenic absorption. The triplet attributed to the equatorial proton at 6-C, was considerably sharper than the broad signal of the DHEA counterpart (3-H axial) confirming the β -orientation of the 6-alcohol group.¹¹ The distinguishing feature in the IR spectrum of

the product was again attributed to the cyclopropane ring¹²⁻¹⁴; a series of sharp, high frequency C-H stretching bands coupled with the main C-H stretching envelope.

The general reaction mechanism, investigated previously in considerable detail,¹⁵⁻¹⁷ involves the production of the cationic species (99) formed by the loss of the tosylate or the mesylate group which rearranges in the presence of potassium acetate to form ion (100). The intermediate is



normally represented by the non-classical ion (101). This participation of the 5 and 6-C π -electrons in the solvolysis, termed "homo-allylic participation", is regarded as the development of overlap between the π -orbital and the rear lobe of the p-orbital (102) vacant at 3-C.¹⁸ Nucleo-



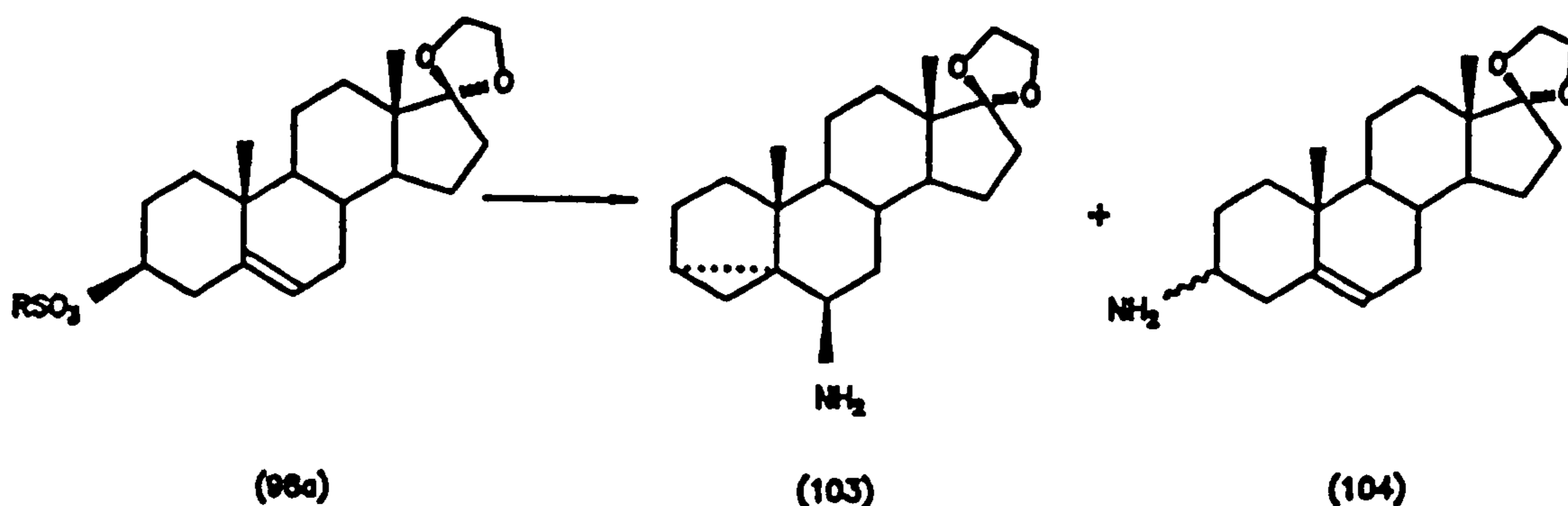
(102)

philic addition to this cation by, for example, hydroxide ion, results, because of an axial attack at the point of maximum overlap of the p-orbitals with the incoming ion, in the formation of the 6β alcohol.¹⁹

The reaction detailed above was attempted by refluxing the steroid tosylate (or mesylate) in a series of aqueous ketones: acetone, butan-2-one and pentan-3-one. These showed that as the reaction temperature was increased the favoured product of solvolysis was the 3-hydroxy steroid (97), i.e., that the cation (99) was the thermodynamically favoured ionic intermediate. Thus when the reaction was carried out in acetone only traces of the 3-C alcohol were found²⁰ but when utilising pentan-3-one the product was a mixture of the desired 3,5-cyclosteroid and the starting material DHEA in a 1:1 ratio. It was also noted that the required reaction time was greater as solvents of increasing molecular weight were used possibly because of the reduced miscibility between the organic solvent and the water. Butan-2-one gave predominantly the desired product in virtually 100% yield if the organic layer was cooled by passing a stream of air over the upper section of the reaction vessel while maintaining gentle reflux of the lower aqueous layer.

The thermodynamic preference for structure (99) was also shown by carrying out the reaction in butan-2-one in a sealed pressure vessel at a temperature of 140°. Under these more extreme conditions DHEA (97) was the only compound recovered. Similar examples in the literature also reflect this dependence. Work by Lee²¹ showed that the yield of 3,5-cyclosteroid when solvolysis of the tosylated steroid is

carried out in methanol, ethanol, 2-propanol and benzyl alcohol²² decreases with the increasing boiling point of the alcohol. Results are attributed to increasing steric effects or decreasing dielectric constants. It was also noted that solvolysis in diols results in the formation of the 3-substituted product, but when carried out in an acetone-diol mixture the 6-substituted β -hydroxy ether is the major product. This dependency is not just observed with alcohols. At 100° for example, the ammonolysis of 3 β substituted compounds gives, as well as the desired 6-substituted steroid (103), an isomeric mixture of the 3 substituted amine (104).²³ Likewise, cyclisation in refluxing acetic anhydride (140°) also gives a mixture of the relevant 3 and 6 substituted acetates.²⁴

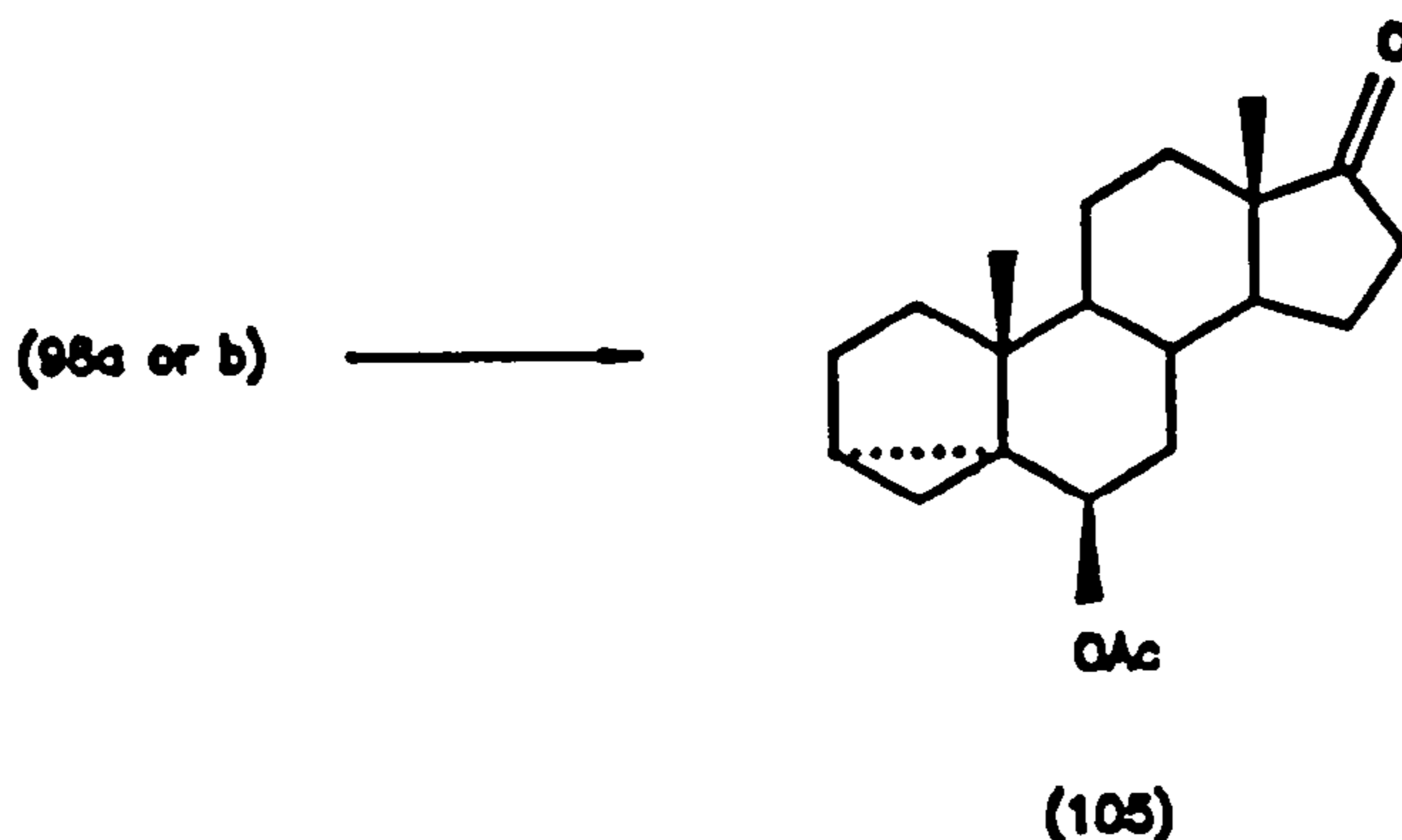


2.2.3 Alternative cyclisation procedures

In an attempt to prevent the removal of a dioxolane protecting group during cyclisation (See Chapter 3), another modification was made to the reaction. By further basifying the aqueous layer (pH 14) in the butan-2-one with a unimolecular amount of sodium hydroxide it was hoped that this would prevent degeneration of the protecting group by the improved removal of the tosylate ions from the organic

layer. When this method was applied to the general, butan-2-one cyclisation reaction, improved product purity was observed. This improvement could also be attained without the presence of potassium acetate but little improvement over the (already high yielding) acetone solvated reaction was detected. Thus the cyclisation of this particular steroid is improved at higher pH.

An earlier method²⁴ for the production of the 6 β -alcohol via the acetate (105), formed by reacting the tosylate steroid (98a or b) with acetic anhydride was also attempted but was abandoned because of the low purity of the product.

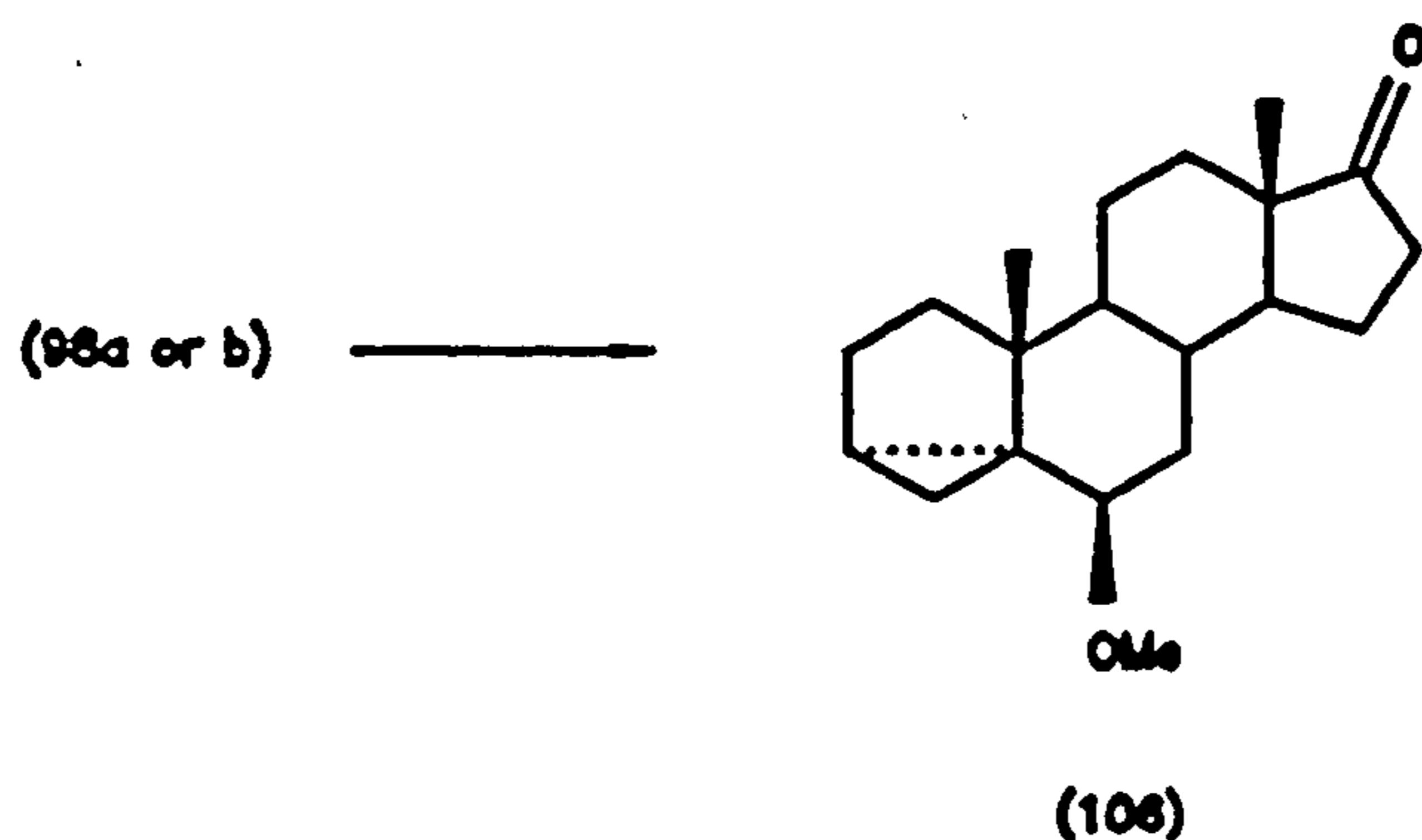


The method of Patel,²⁵ where the tosylate or mesylate (6) is not isolated before cyclisation, gave relatively good results in terms of purity but as noted by the author, a low overall yield (41%). Thus using either acetone or butan-2-one as solvents and either potassium acetate or sodium hydroxide as the buffer were the preferred methods of cyclisation.

2.2.4 Formation of 6 β -methoxy-3 α ,5-cyclo-5 α -androstan-17-one (106).

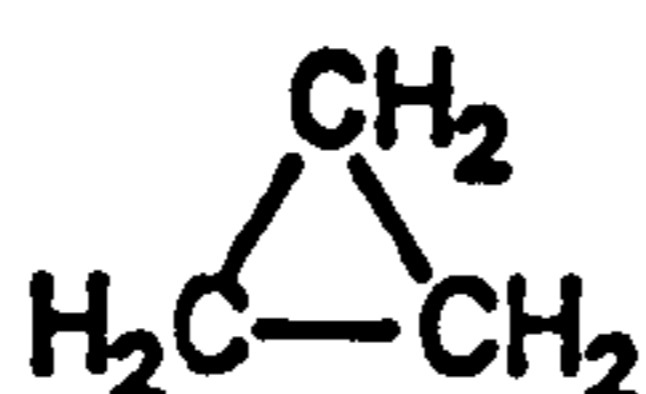
The 6-methoxy derivative (106) was used as an alternative in some reactions where it was considered that the alcohol (41) was too unstable under the utilised conditions. Subsequent formation of the alcohol could then be achieved by the demethylating reagent trimethylsilyl chloride.^{26,27}

The cyclisation of the tosylate (98a) or mesylate (98b) in anhydrous methanol containing potassium acetate gave the desired ether (106). The NMR spectrum of the product showed a prominent 3H methoxy singlet. Evidence of successful cyclisation came from the sharp triplet associated with the 6 α equatorial proton. This, as was expected, was positioned slightly further upfield than the signal from the corresponding atom in the alcohol. As was noted for the alcohol, the signal produced by 6-H in the starting material was "replaced" by highfield cyclopropane absorption.

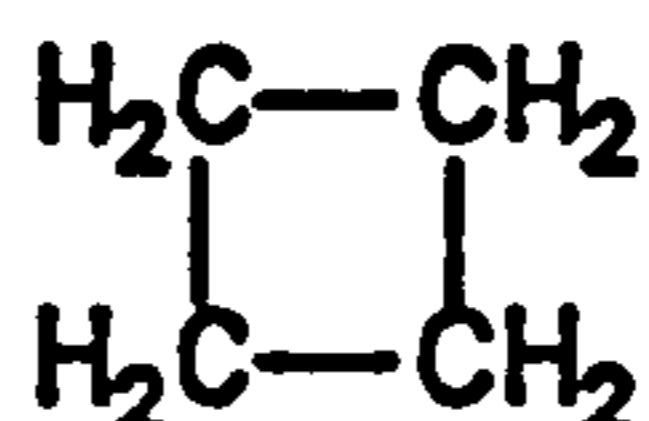


2.2.5 The cyclopropane ring

The cyclopropane ring has, over the last few decades, been subject to intense practical and theoretical investigation and has been discussed many times before (see below). Therefore only a short summary of the moiety's properties and explanations to these, will be discussed here.



(107)



(108)

The peculiar properties of cyclopropane, in particular its ability to interact with π -systems and to stabilise carbonium ions, i.e., its "unique double bond character",²⁸⁻³¹ the observed high field NMR signals, the group's short C-C bond length, and the moiety's reactivity to electrophiles a property not observed in cyclobutane (108) or indeed in any other cyclic alkane, have intrigued chemists for many years. Another unusual property, its relative stability, perhaps best summarises the group's anomalous repertoire of properties.

2.2.6 The cyclopropane ring:- strain.

Formation of a cyclopropane ring requires that three -CH₂- groups must be accommodated into a triangle of atoms where the three C-C-C bond angles are each 60°. This is a considerable deviation from the standard, strain free C sp³ angle of 109.5°. The strain energy of cyclopropane (107), as

conventionally³² defined (conventional strain energy, CSE), is 27.5 kcal mol⁻¹. However, the strain energy calculated using the C-C-C bending force constant estimated from the vibrational spectra of alkanes is considerably greater; 104 kcal mol⁻¹. Moreover, this huge anomaly is only observed for three-membered rings. Thus the strain energy for cyclobutane (108), calculated in the same way; 21.6 kcal mol⁻¹, is less than its CSE value of 26.5 kcal mol⁻¹, the difference being attributed to eclipsing strain. The CSE values for these two cyclic alkanes are thus very similar, as is the energy required for homolytic cleavage (61 and 62.5 kcal mol⁻¹ respectively). From this then, we can conclude that it is erroneous to rationalise the unusual chemical nature of cyclopropane (107), compared to the rather unremarkable chemical repertoire of cyclobutane (108), in terms of its high strain, as is so often the case in standard text books.^{33,34} There is obviously another facet to the cyclopropane ring that facilitates the above properties.

2.2.7 Cyclopropane: a σ -aromatic alkane.

All of the above properties can be explained by the concept of σ -conjugation and σ -aromaticity. Although this principle has been known for many years, it is only recently that its significant chemical implications have been realised. Explanations into the physical,³⁵ electronic³⁶⁻³⁸ and chemical³⁹ properties of derivatives of cyclopropane as well as other, often conveniently ignored, phenomena (such as the pyramidal structure of certain free radicals) can be readily attained by the application of σ -conjugation.³⁵

As the molecular orbitals (MOs) of cyclopropane have been discussed before⁴⁰⁻⁴³ the following resume is confined to only the essential features.

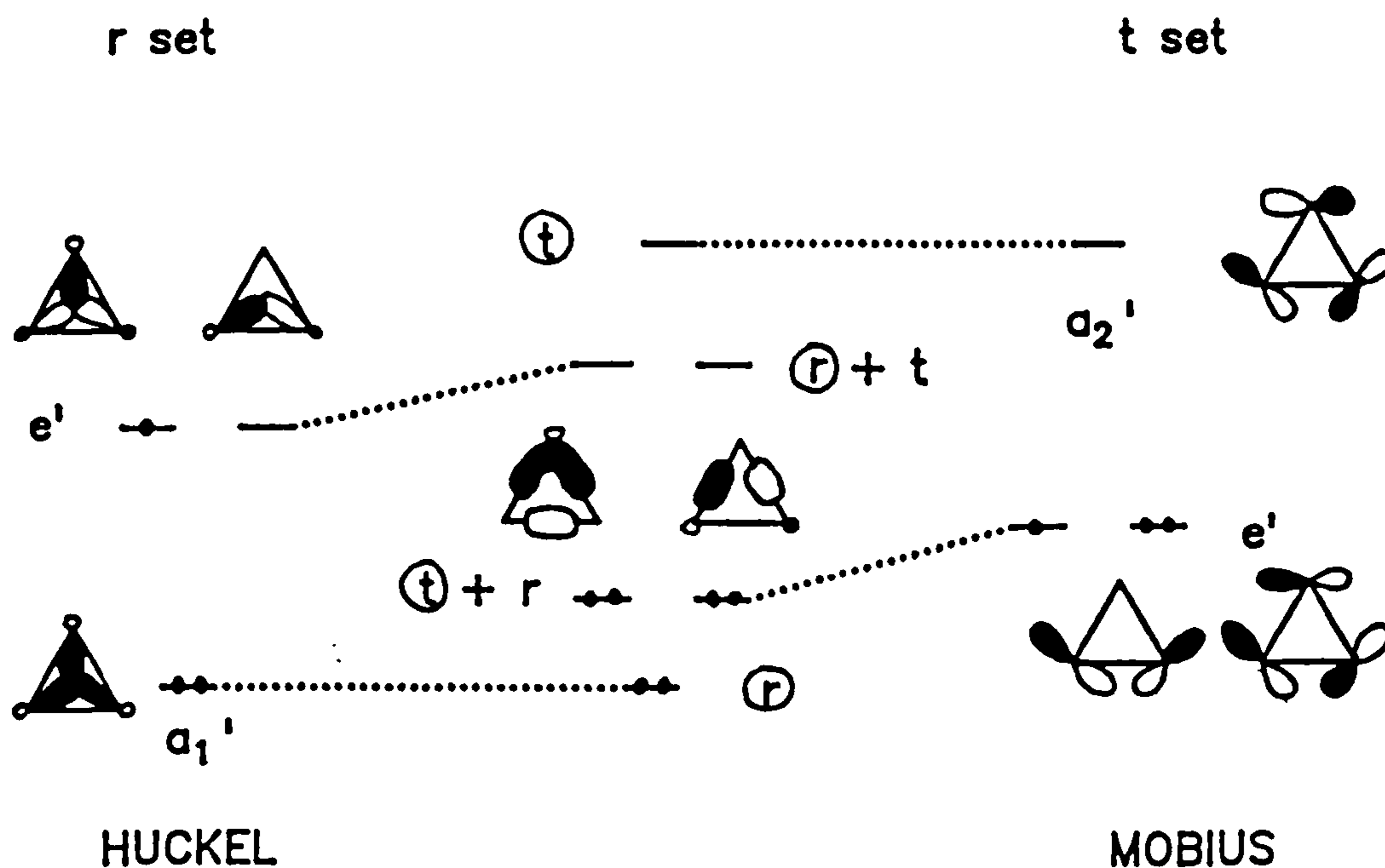


FIGURE 3

Molecular orbitals (MOs) of cyclopropane. The predominant nature of the final MOs, r and t , is indicated by \textcircled{r} and \textcircled{t} respectively

If one considers cyclopropane and other cyclic alkanes to be made up of CH_2 fragments each possessing two singly occupied orbitals (Figure 3), then two sets of MOs can be distinguished: first, the r set (Huckel type system), which consists of linear combinations of radially orientated sp hybrid orbitals (σ), and, secondly, the t set, (Mobius type system) which consists of linear combinations of tangentially orientated p orbitals (π). Mixing of the r and t orbitals which possess the same symmetry yields the final MOs. A closed-shell system is formed with Huckel $(4q + 2)$ "aromatic"

subshells. The mixing of r and t orbitals, apart from improving 1,2 bonding interactions in the ring, cause antibonding interactions across the ring.

Note also that there is always a totally symmetric doubly occupied low lying r MO (a_1' in Figure 3) that stems from the in-phase overlap of all sp^2 orbitals inside the ring. The nature of this orbital changes dramatically with the size of the ring (Figure 4). In the case of cyclopropane it is the "surface" orbital covering the ring surface due to strong overlap of the three sp^2 orbitals in the ring centre. Therefore, due to its unusual topology, cyclopropane differs from all other cycloalkanes; occupation of its "surface orbital" resulting in a three centre two electron bond ($4q + 2$). As these are fully delocalised electrons

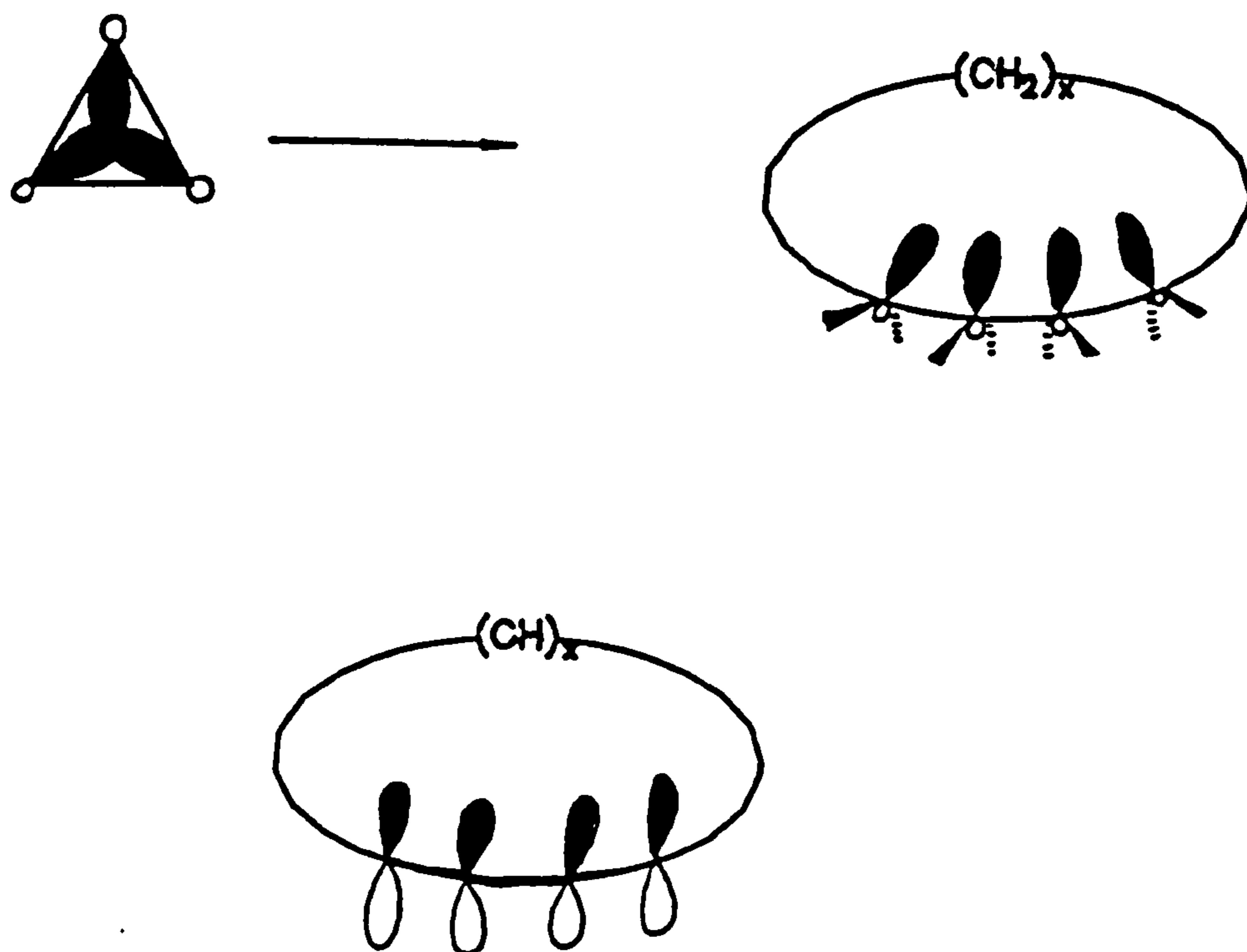


FIGURE 4

Equivalence of the r MOs in a large n-membered ring and the π -MOs of a cyclopolyene

it is justified to term cyclopropane as σ -aromatic. (Delocalisation has been confirmed by calculations³⁷ which estimate that the minimum electron density in the plane of the ring is still 82% of that at the critical bond point, the area of maximum electron density between two atoms. This compares to values of 33% for cyclobutane and 7% for benzene.)

The aromatic stabilisation energy of cyclopropane has been estimated^{35,37,43} to have a value of between 20 and 50 kcal mol⁻¹. Although there are differences in opinion, it is generally believed that cyclopropane is stabilised by its aromaticity to a greater degree than benzene itself (20 kcal mol⁻¹).⁴⁴ The σ -aromaticity then, can be used to explain the huge differences between observed and calculated strain energies. Similarly, the other "anomalies" can be readily explained. The shortness of the cyclopropane bonds is easily understood if they are strengthened by aromaticity. The upfield position of its NMR signals can be understood in terms of diamagnetic shielding due to an aromatic ring

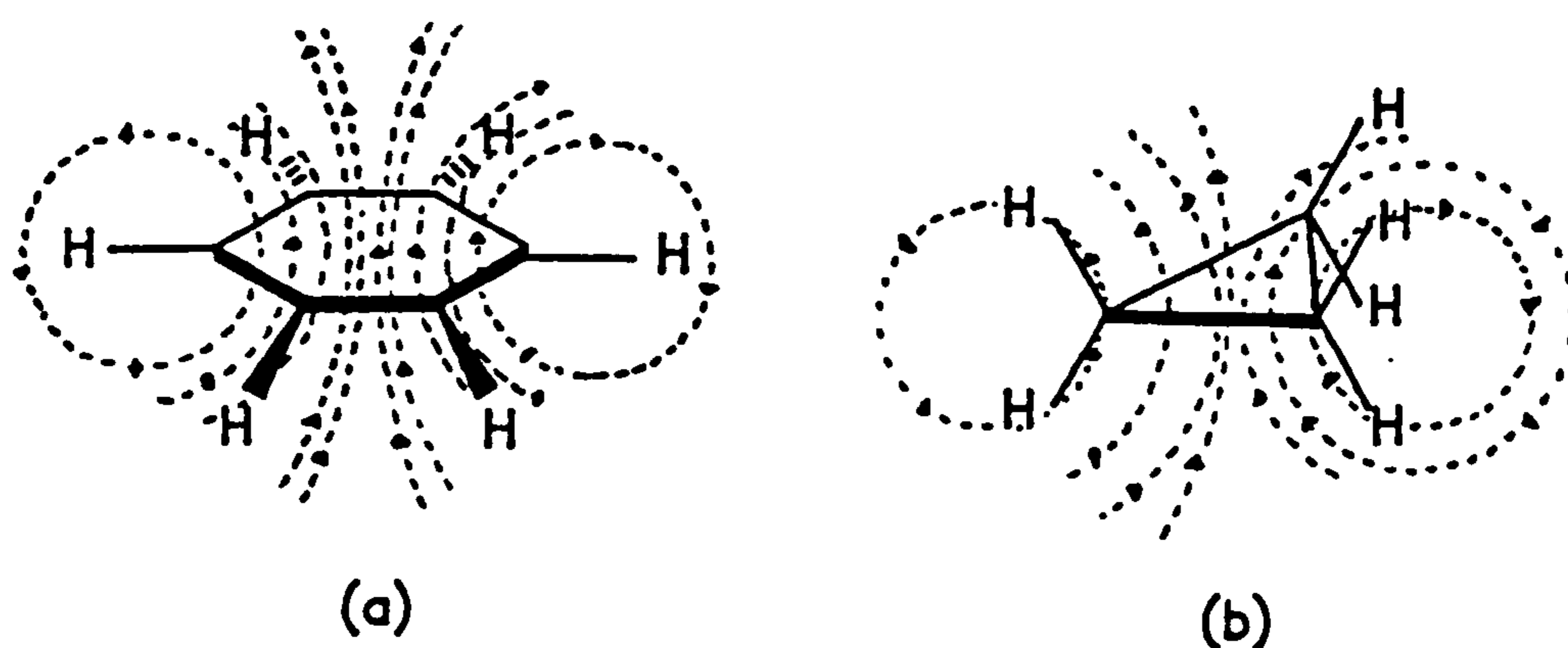
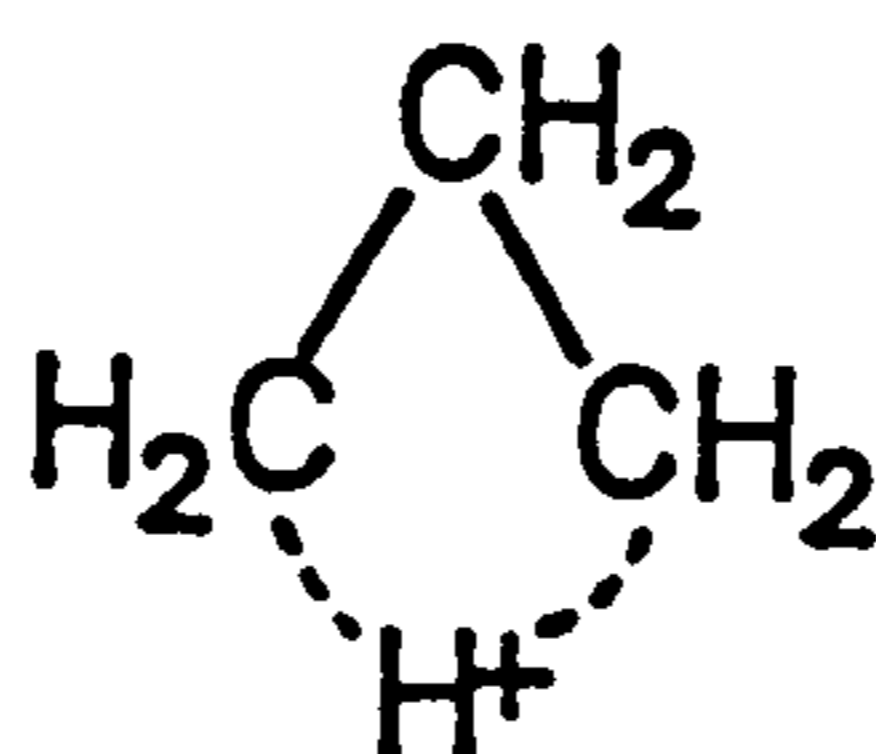


FIGURE 5

Magnetic lines of force in (a) benzene and (b) cyclopropane

current (Figure 5). However, in contrast to benzene, where the ring current leads to a downfield shift because the protons lie in the region where the magnetic lines of force have turned around and consequently reinforce the applied field, the cyclopropane protons lie in the shielded region. Reactions differing markedly from other paraffins (where the ring remains intact), e.g., electrophilic addition are also readily explained.³⁵ The rate determining step involves the formation of a non-classical ion^{45,46}, either "edge protonated cyclopropane" (109) or a π -complex⁴⁷ ($\parallel \rightarrow \text{CH}_3^+$). Such a structure will retain at least a large part of the cyclopropane's initial aromatic stabilisation. The increase in one C-C internuclear distance, will on the other hand, lead to a significant decrease in the real strain energy. Since the strain energy of cyclopropane is very large and since in it is not offset by a corresponding decrease in the σ aromatic stabilisation energy, the net decrease in energy should be large and act as a driving force for the reaction.



(109)

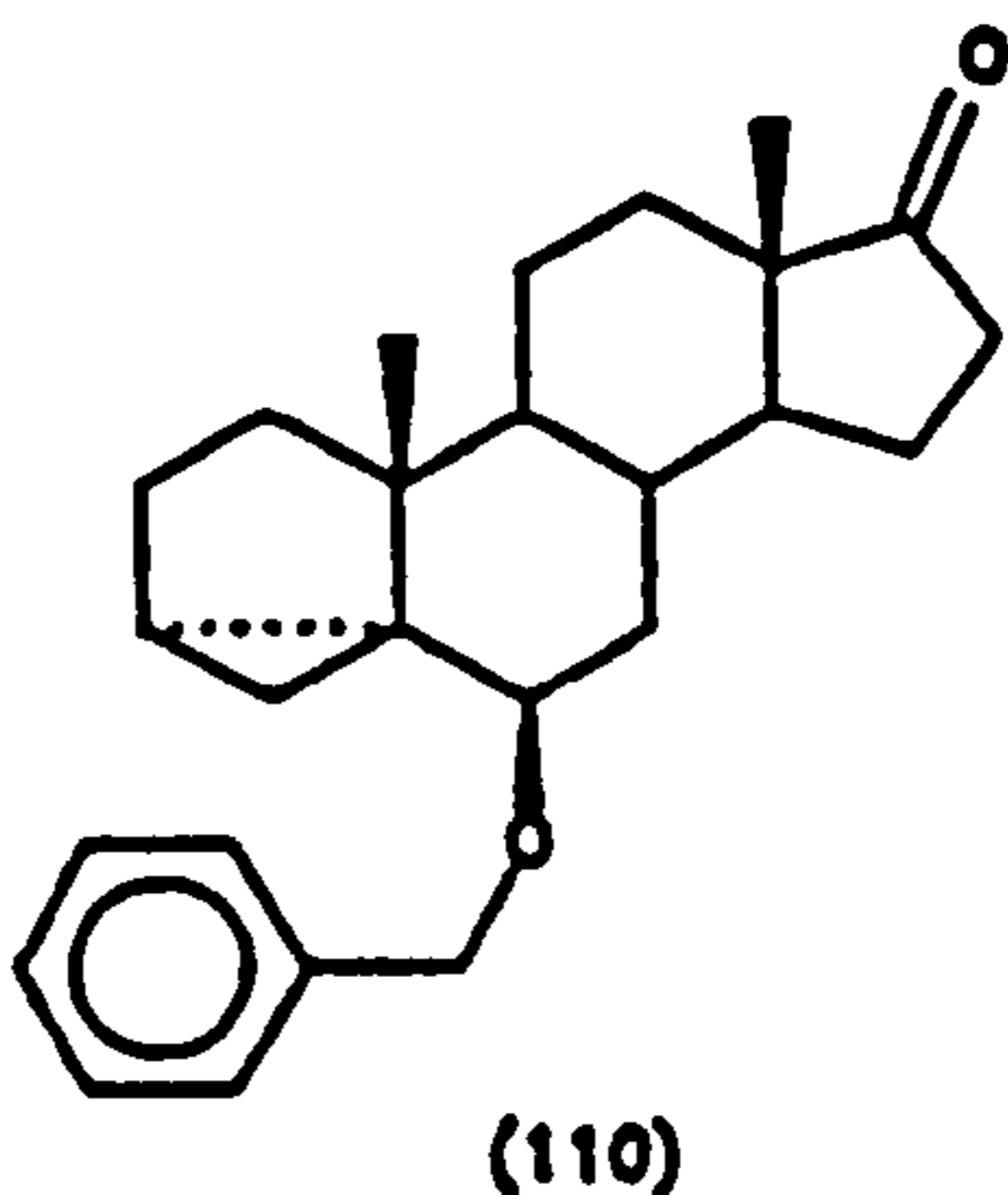
2.2.8 6 β -Hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41):- a σ -aromatic steroid.

The difference between cyclopropane (107) and the cyclopropane moiety of the parent compound (41) is the

effective substitution of the 6 hydrogens for the groups CH_2R , CHR_2 and CHRX ($\text{X} = \text{OH}$). This however should not have a great effect on the stability of the ring as the alkyl groups can only weakly interact with both the σ and π orbitals of the cyclopropane ring.³⁸ The alcohol group has also been calculated to have little effect. However under conditions where the hydroxy proton can be removed (basic) a considerable stabilisation of the cyclopropane ring could occur.⁴⁸ Considering the structure it would seem quite likely that there is, to a small degree, destabilisation induced by increased strain because the cyclopropane ring is fused to ring A, and connected to ring B.

2.2.9 The ^1H NMR spectrum of 6-hydroxy-3 α ,5-cyclo-5 α -andros-
tan-17-one (41).

The most marked feature in the NMR spectrum of the parent steroid and the derivatives formed here is of course the signals attributed to the cyclopropane ring. However, the interpretation of these complex signals is not a simple one even when considering the effects of 6-C substitution (see this work) on the splitting pattern of these signals.



Consider, for example, the splitting pattern of the parent 6β -alcohol's cyclopropane protons (Figure 6). These appear to be split into two sets; a 1H triplet and a set of 4 peaks corresponding to two protons. This type of splitting pattern is observed for all the other steroids synthesised here where there is an β orientated oxygen functionality at 6-C, e.g., all hydroxy, methoxy and 6,7-epoxy steroids. One exception, the 6-benzyloxy derivative²² (110) shows no cyclopropane signals in the expected region. This though can easily be attributed to a downfield shift induced through

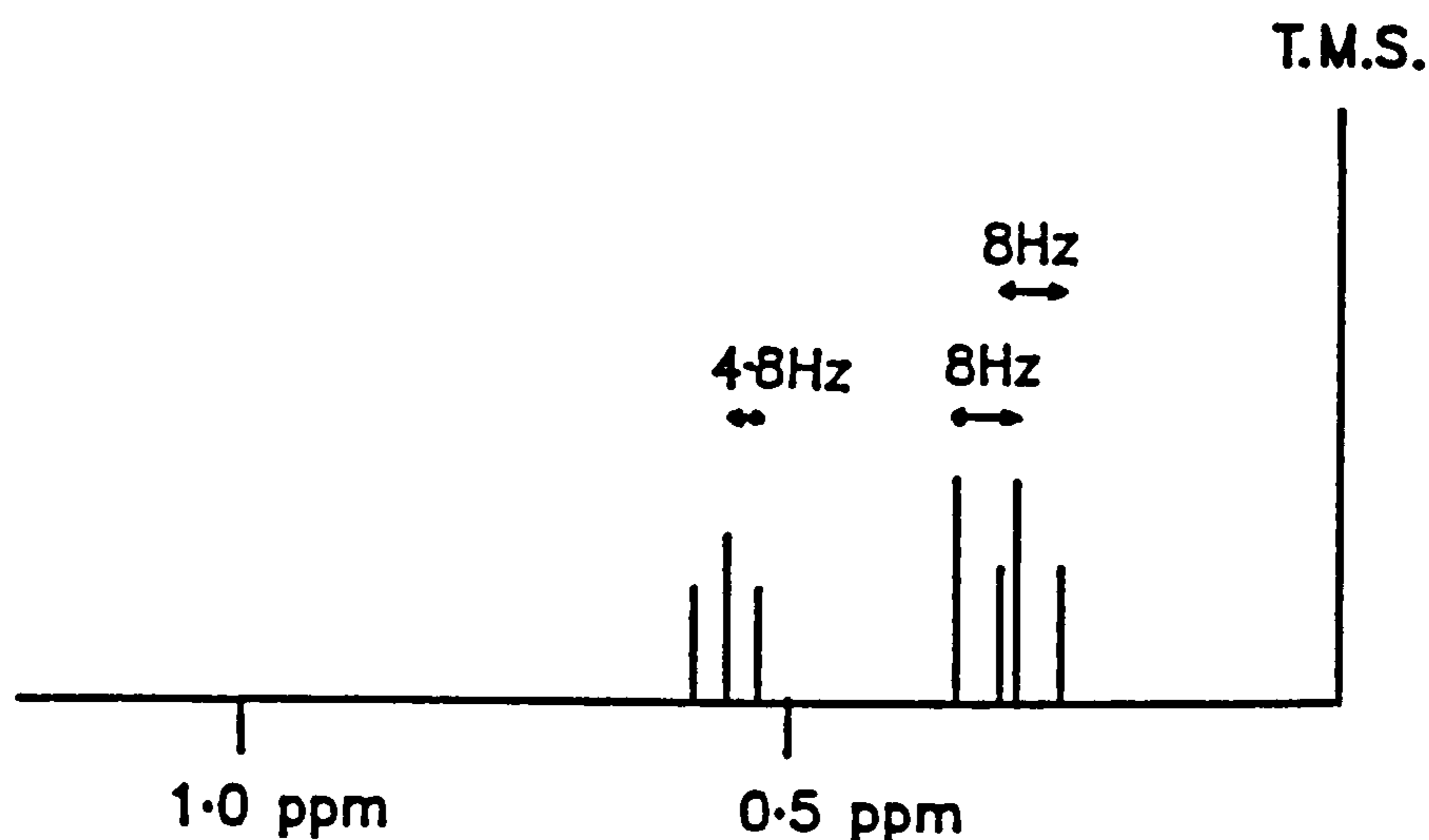


FIGURE 6

Schematic representation of the $^1\text{H.N.M.R.}$
cyclopropane signals of (41)

space, by the aromatic ring, adopting a suitable conformation in solution. Consider the following for the 6β alcohol (41). Firstly, and most obviously, the two sets of peaks mentioned above are readily attributed to the single proton at 3-C and the two protons at 4-C respectively. The 3-H atom appears to be coupled with two protons, either at 2-C or 4-

C to produce the lower field triplet ($J = 4.8\text{Hz}$). The set of four peaks, apparently a pair of overlapping doublets, show non-equivalent protons 4α and 4β coupling with each other ($J = 8.0\text{Hz}$). With this model, there is therefore no observable coupling between the protons at 3 and 4-C, a fact not readily accountable for. Thus, there are no torsion angles between any of the protons which approximate to 90° . There is obviously considerably more to the interpretation of the signals.

In contrast to the above steroids, compounds which do not possess a β functionality, e.g., the 6-substituted ketones, methylenes and 6,7 alkenes all show "simplified" splitting patterns. Both the 6 keto and methylene steroids show only 1H triplets, with the ketone signals occurring slightly further downfield than the methylene signals. This simplified spectrum is relatively easy to interpret. The insertion of the π -system induces a downfield shift for all the cyclopropane protons. This is especially true for the 4-C proton which according to molecular models lies approximately in the plane of the π -system and is correspondingly shifted further downfield, into the main methylene envelope, and is thus unobservable.

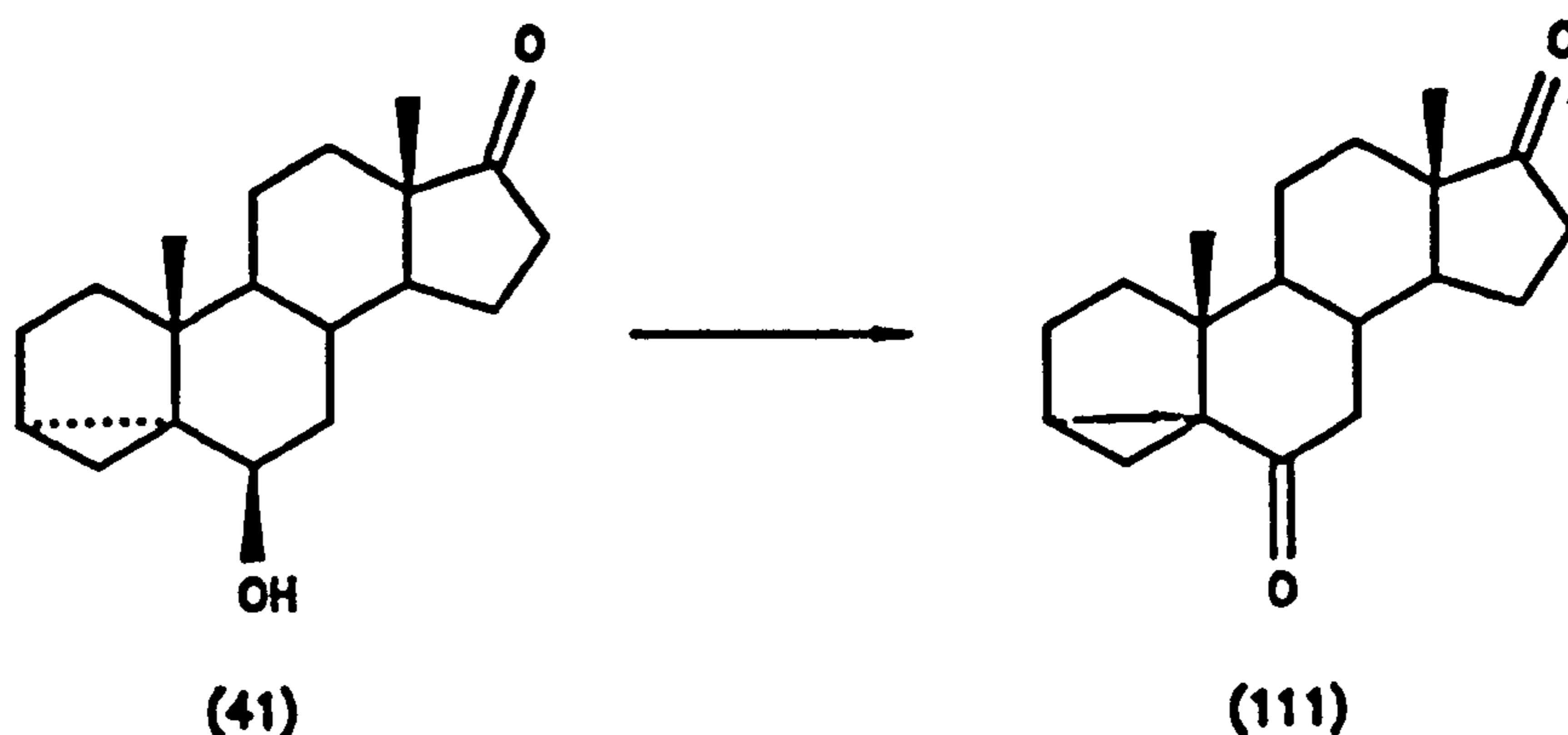
The actual signals of the cyclopropane ring protons are thus full of ambiguities and not easily interpreted, however the σ -aromatic nature of the ring should have effects on other parts of the steroid, e.g., the 2-C protons and the 19-C protons all should be deshielded by the cyclopropane ring. Although, for the 2-C protons, any effect would not be readily observable, the methyl signal is in fact noted^{49,50}

to shift downfield. This small shift can thus be attributed to the σ -aromaticity of the cyclopropane ring.

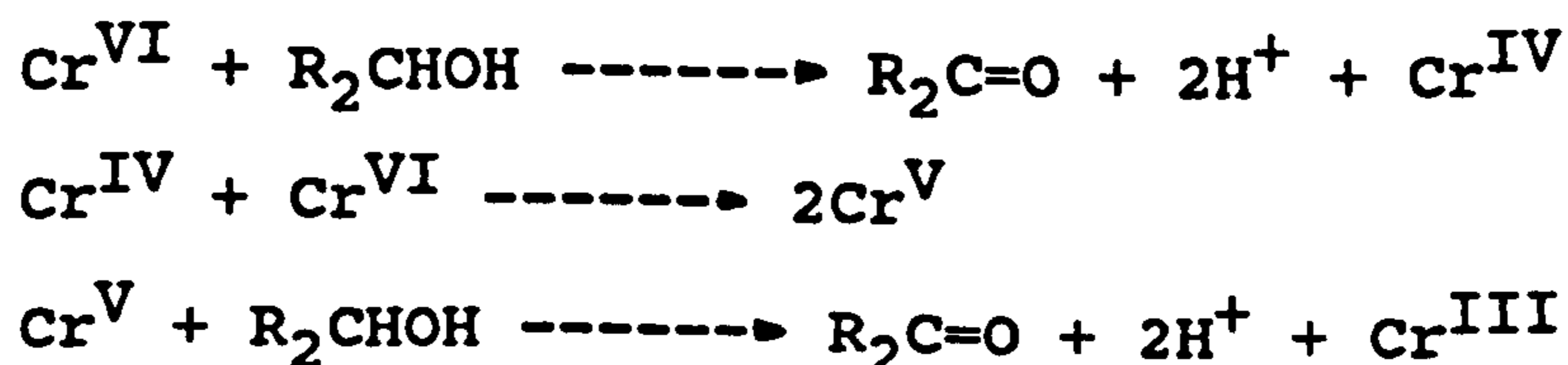
In conclusion the cyclopropane ring, and hence, the series of steroids synthesised here can be justifiably termed σ -aromatic. The introduction of this σ -aromatic ring into the androstane nucleus has little effect on the overall stability of the ring but induces small, detectable changes to non-neighbouring atoms as well as the considerable localised effects. Considering the cyclopropane carbons to be in a hybridised state between sp^2 and sp^3 (and hence possessing a "unique double bond character"²⁸⁻³¹) is a perfectly suitable model for explaining many of its reactions. However σ -aromatic is a more accurate description.

2.3 Formation of 3 α ,5-cyclo-5 α -androstandione (111).

The oxidation of the alcohol (41) was achieved by two methods: with Jones' reagent⁵¹ (CrO₃ in concentrated sulphuric acid) and with Collins' reagent⁵²⁻⁵⁵ (dipyridine CrO₃ complex in dichloromethane). Both these reagents successfully converted the steroid to the pseudo-conjugated system ketone steroid (111) but for overall simplicity and therefore improved yields the Jones' method was, wherever possible, utilised in the synthesis of the various 6-keto steroids produced.



The mechanism of hexavalent chromium oxidation is complex, but it is known that although in each stage of the oxidation of most organic substrates there is a net transfer of two electrons, the oxidising agent normally accepts a total of three electrons. It is therefore evident that intermediate states of chromium are important in the overall process. For the oxidation of a secondary alcohol such as steroid (41) the mechanism may be as follows.



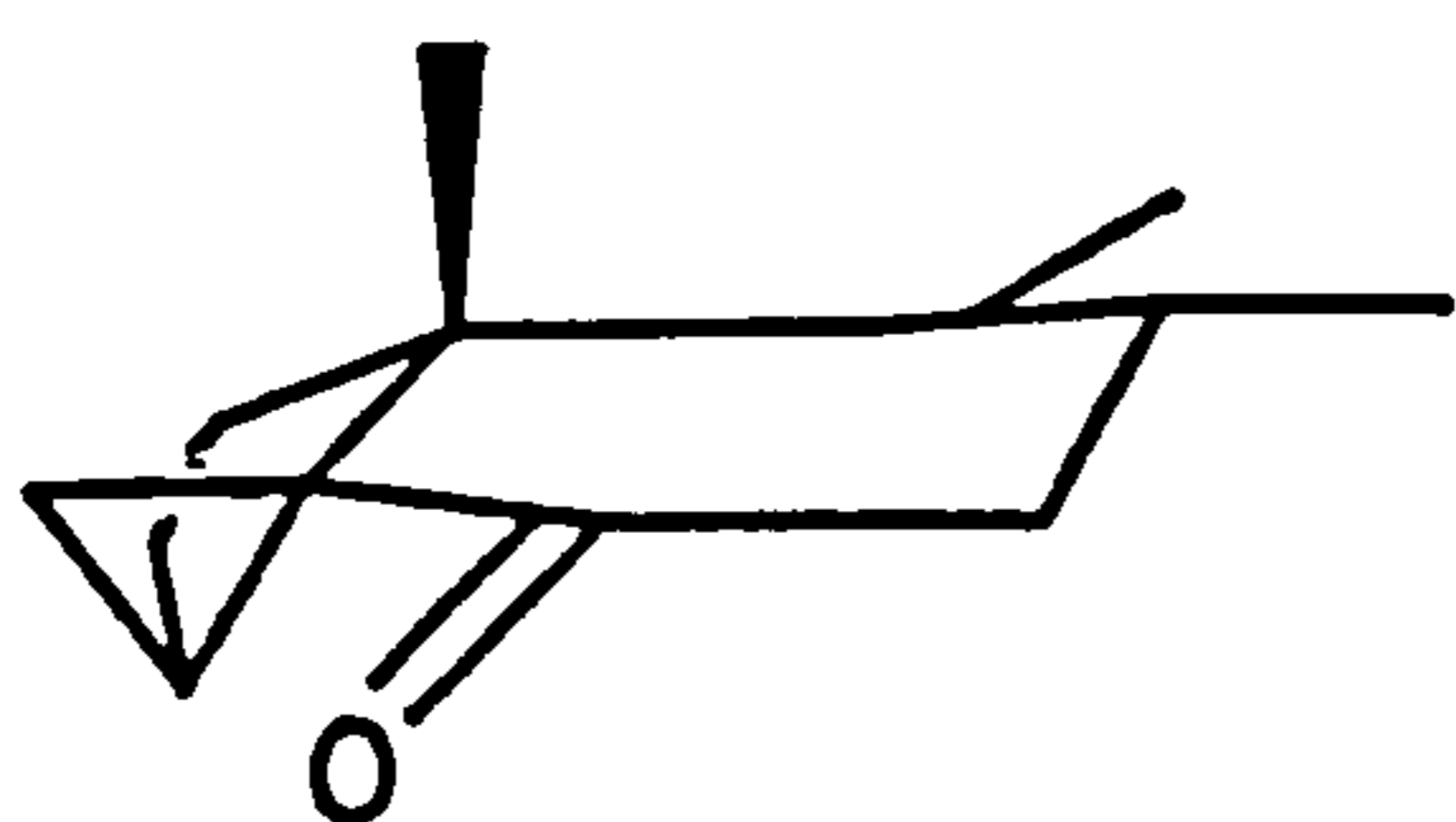
These intermediate valency states of chromium (IV and V) appear to be more powerful oxidising agents than Cr^{VI} and may, as indicated in the equations above, be responsible for up to two thirds of the oxidative process.⁵⁶

The NMR spectrum of the product, as expected, showed no absorption associated with a proton geminal to a hydroxy group. A significant change was also noted in the cyclopropane signals where only a 1H triplet was observed (see below). Removal of hydroxy absorption and a new carbonyl band in the IR spectrum of the product also confirmed conversion. In the mass fragmentation of the product, obvious daughter ions from the parent ion (286) were 271, loss of a methyl group and 258, subsequent loss of carbon monoxide. A weak signal ($m/z = 268$) corresponded to the loss of water; a feature of this cyclopropane ketosteroid previously investigated.⁵⁷

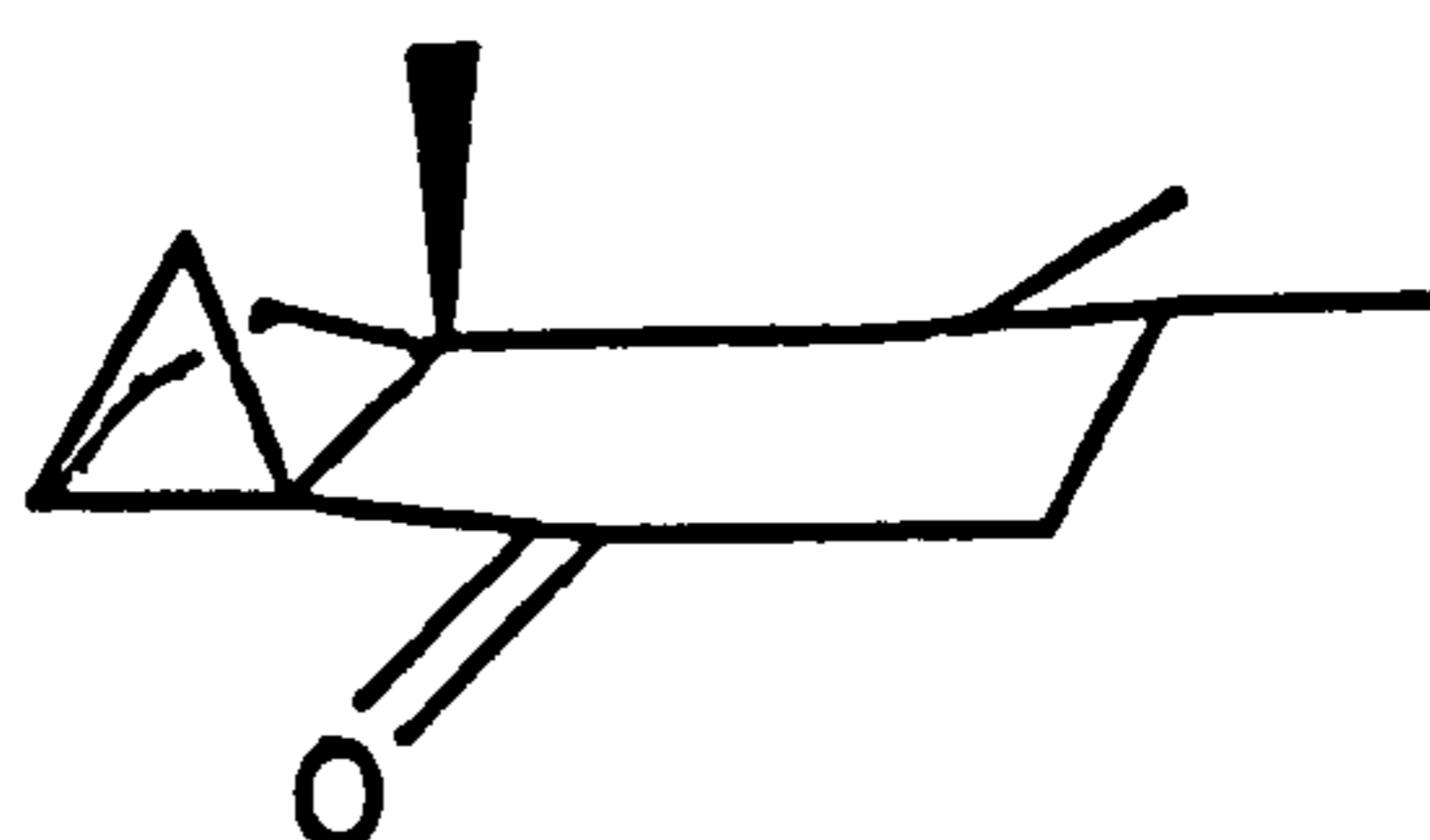
The steroid dione (111) has previously been subject to considerable investigation for its potential biological activity,⁵⁸ its general reactivity⁵⁹⁻⁶¹ and its interesting structure; e.g., Butcher *et al.*⁴⁹ studied the ^1H NMR, IR and UV spectra of the steroid to ascertain its preferred conformation. Although generally agreeing with the presented data the 6-C carbonyl IR signal of the product was noted in this work to occur at 1681 cm^{-1} compared to the value of 1693 cm^{-1} recorded by Butcher.⁴⁹

Butcher noted⁴⁹ that ring B of the steroid can theoretically assume conformations ranging between the extremes of distorted half-chair where carbon atoms 4, 5, 6 and 7 are virtually coplanar with the carbonyl oxygen (112) and an

almost undistorted boat conformation where the carbon 3 atom replaces carbon 4 in the coplanarity sequence (113). The more recent X-ray work of Hanson⁶² on the dione (111) showed that in the crystal phase at least, the B ring approximates to the former structure [C(4)-C(5)-C(6)-O=10°). This explains, the "simplification" of the cyclopropane signals in the NMR spectrum of the product. The 4-H atoms being deshielded to a position where they are obscured by the methylene envelope thus leaving only the 3-H signal



(112)



(113)

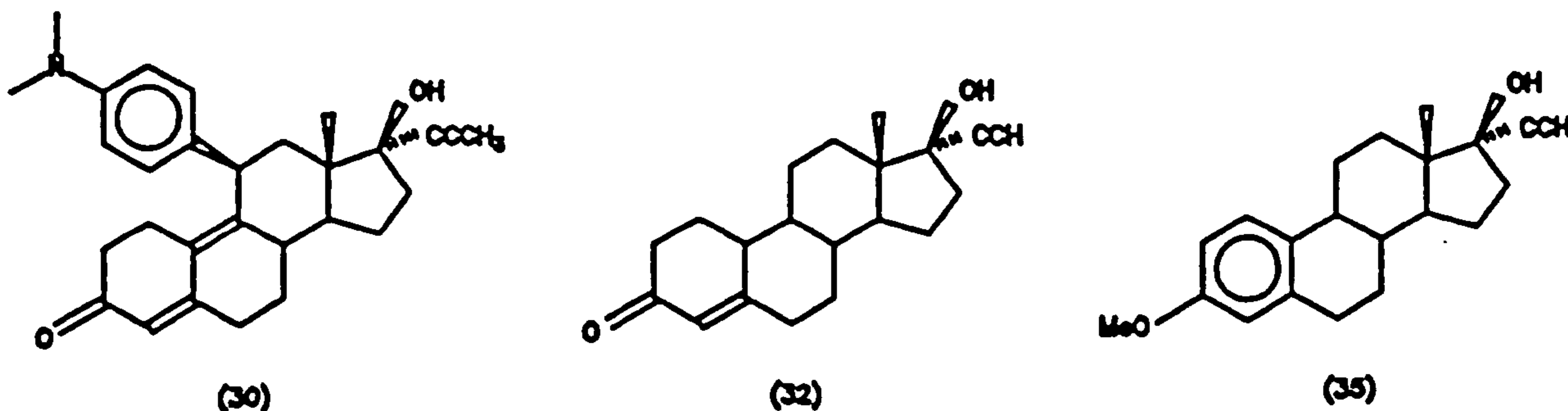
in the "cyclopropane region" as a 1H triplet. This conformation therefore allows for near maximum conjugation between the cyclopropane ring and the ketone group.⁶²

Allan^{28,63} determined that in a cyclopropane compound where the ring is in conjugation with a π -acceptor substituent the vicinal bonds (3-5 and 4-5) are weakened and the distal bond (3-4) is strengthened. Thus vicinal bonds tend to be longer and distal bonds shorter. This however is not the case for steroid (111). The X-ray results obtained by Hanson for the 6,17-diketone steroid where the relevant carbon-carbon bond lengths were determined as: C(3)-C(4)=1.61(4)A, C(3)-C(5)=1.58(4)A and C(4)-C(5)=1.56(3)A, i.e., the exact opposite of that expected. This however, because there is no significant difference between the values, might

be a misrepresentation. A particular effect is not likely to be revealed by one particular study. As it is only when the results of many measurements are analysed that trends become apparent. In terms of the σ -aromaticity of the cyclopropane ring the introduction of a ketone group at the 6-position should, by its nature as a π -attractor, reduce the stability of the ring. However, although the ketone group is potentially the greatest destabilising substituent introduced (in this work) to the steroid its effect should be very small³⁸ even assuming the geometry allows for maximum conjugation.

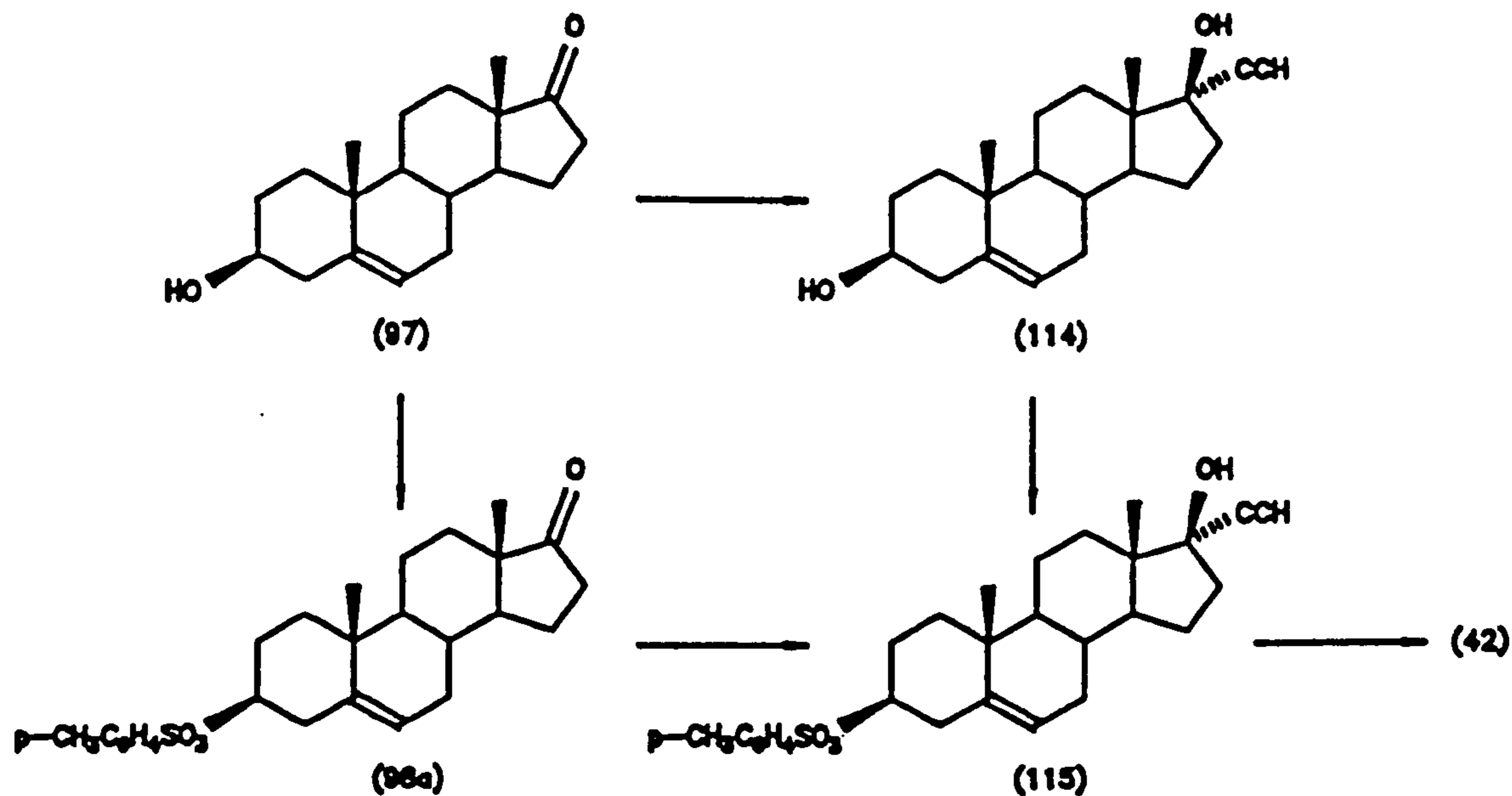
2.4 Formation of 17 α -ethynyl-3 α ,5,cyclo-5 α -androstandane-6 β ,17 β -diol (42).

The insertion of an electron rich functional group at the 17 α position has frequently enhanced the biological activity of a molecule, e.g., its luteoid activity⁶⁴ or its binding affinity to the progestin receptor, for example, the now well known steroid RU 486 (30).⁶⁵ Steroidal propargyl derivatives that have shown high activity include norethindrone (32) and mestranol (35), two of the most popular female contraceptives.⁶⁶ Therefore, the propargyl derivative (42) could be expected to show enhanced activity over that of its parent derivative, the 17-keto steroid (41).

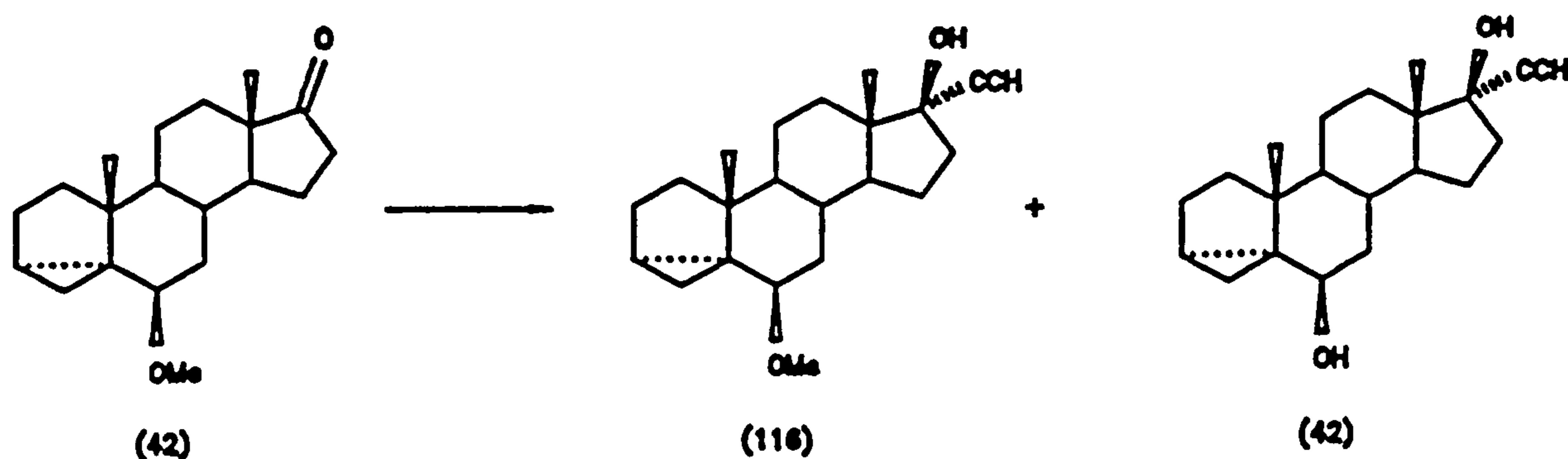


The synthesis of the propargyl derivative was initially undertaken by the direct reaction of the parent steroid (41) with (the now superseded⁶⁷) lithium acetylide but the required reaction time, as measured by the strength of the carbonyl absorption of the crude reaction product, was considerably greater than that stated by Huffman⁶⁸ in the analogous transformation of tricyclic steroid analogues. Thus 72 hours was required before carbonyl absorption of the crude product was absent. The product however, resisted repeated recrystallisation beyond its initially crystallised form of a pale brown, wide melting point solid. Neverthe-

of tosyl chloride to give (115). In fact, it was found that the propargyl alcohol group was so sterically hindered to



the tosyl chloride reagent that even under concentrated conditions with a two fold excess of reagent only the mono-tosylate was isolated. Quantities of this compound, from both sources, were then cyclised to give the desired steroid. Although apparently giving a product of higher purity, the steroid still proved difficult to recrystallise.



The methoxy steroid (106), was also considered as a source of the propargyl derivative (42). Subsequently it was noted that the 6-methoxy derivative (106) underwent propargylation more smoothly than its 6-hydroxy derivative (41) to yield the mono-alcohol (116). Treatment of this steroid with

the versatile reagent trimethylsilyl iodide^{26,27,69-71} yielded the desired diol (42) in low yields. Again however, the product resisted recrystallisation. Further recrystallisation studies with specialised techniques⁷² could be carried out on the compound.

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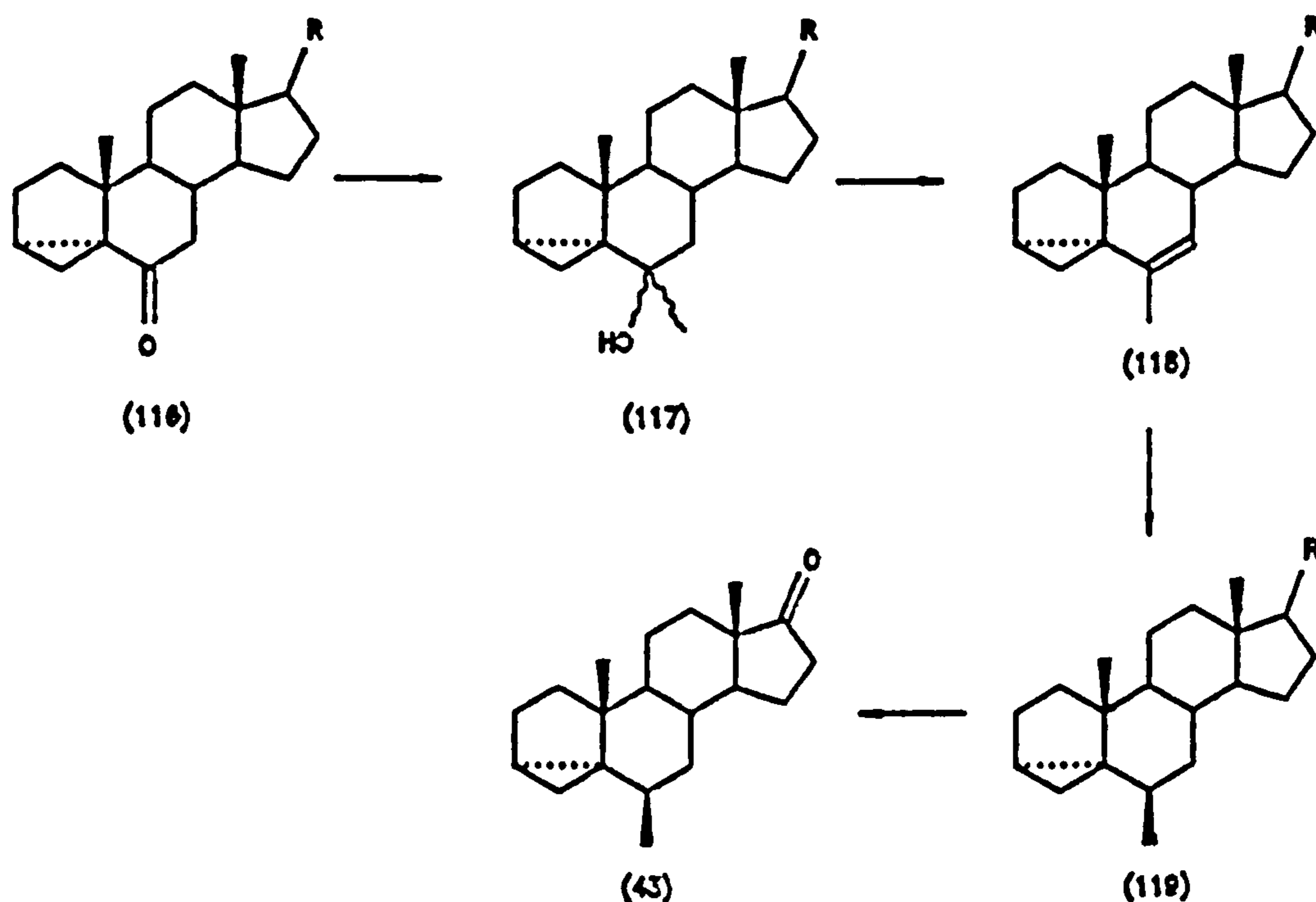
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CHAPTER 3

Formation of 6 β -methyl-3 α ,5-cyclo-5 α -androstan-17-one.

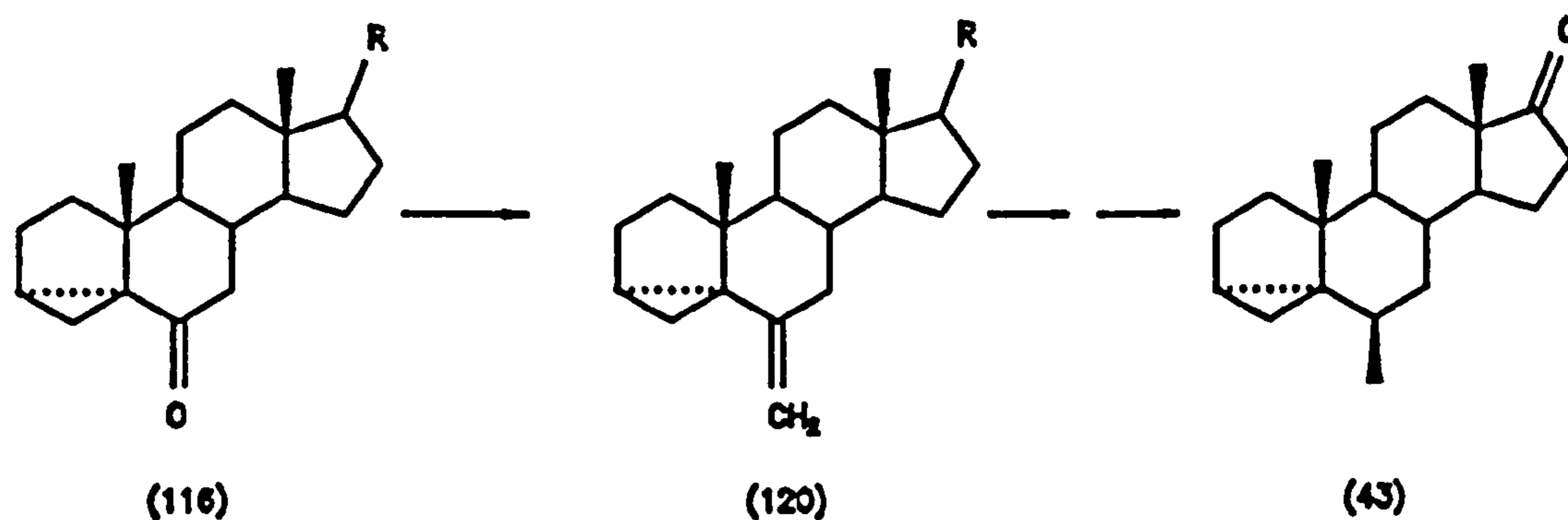
3.1 Introduction

The insertion of a methyl group into the carbon framework can frequently endow a steroid with enhanced biological activity.¹ As a consequence, a considerable amount of work has been performed on the alkylation of steroids, including methylation at the 6-C position.²⁻⁵ The 3,5-cyclopropane ring system had been used as a means of inserting an alkyl group at the 6 and 7-C positions by, for example, reactions between ketone derivatives and Grignard reagents.^{3,4} Subsequently, the cyclopropane ring is fragmented to produce the desired 3-C functionalised steroid. However no attempts have apparently been made to synthesise the 6-methyl cyclosteroid (43).

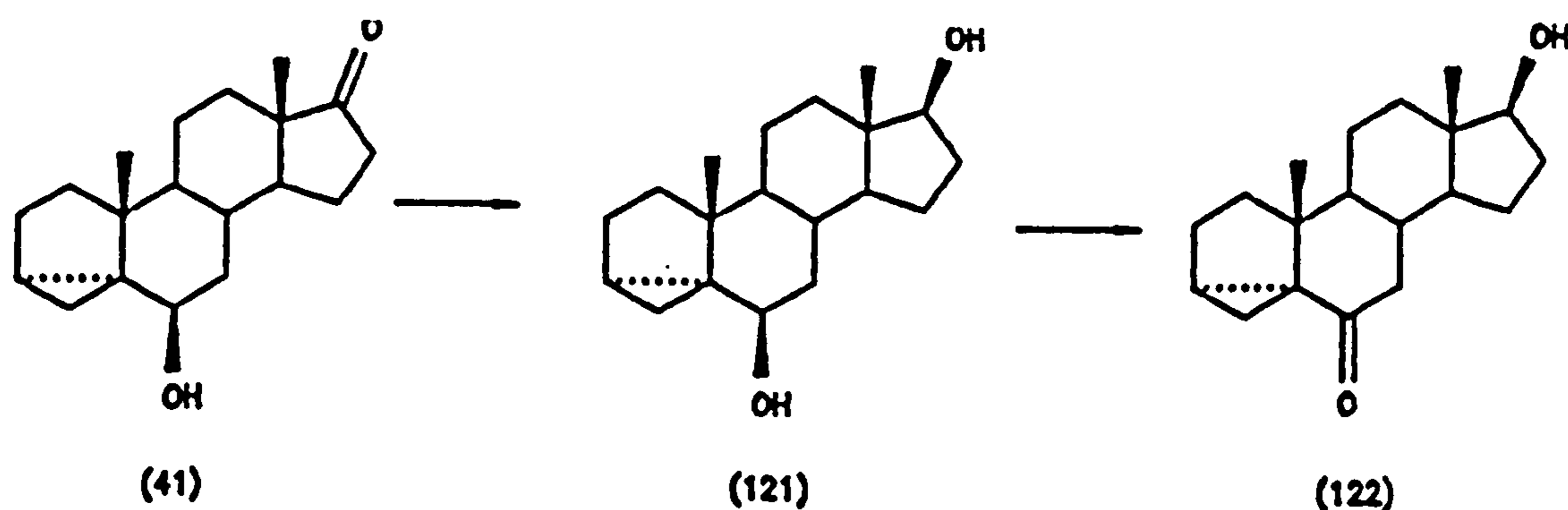


The initially proposed route followed the methodology used in the synthesis of 3-C functionalised 6-C methyl steroids, i.e., by the formation of the ketone derivative

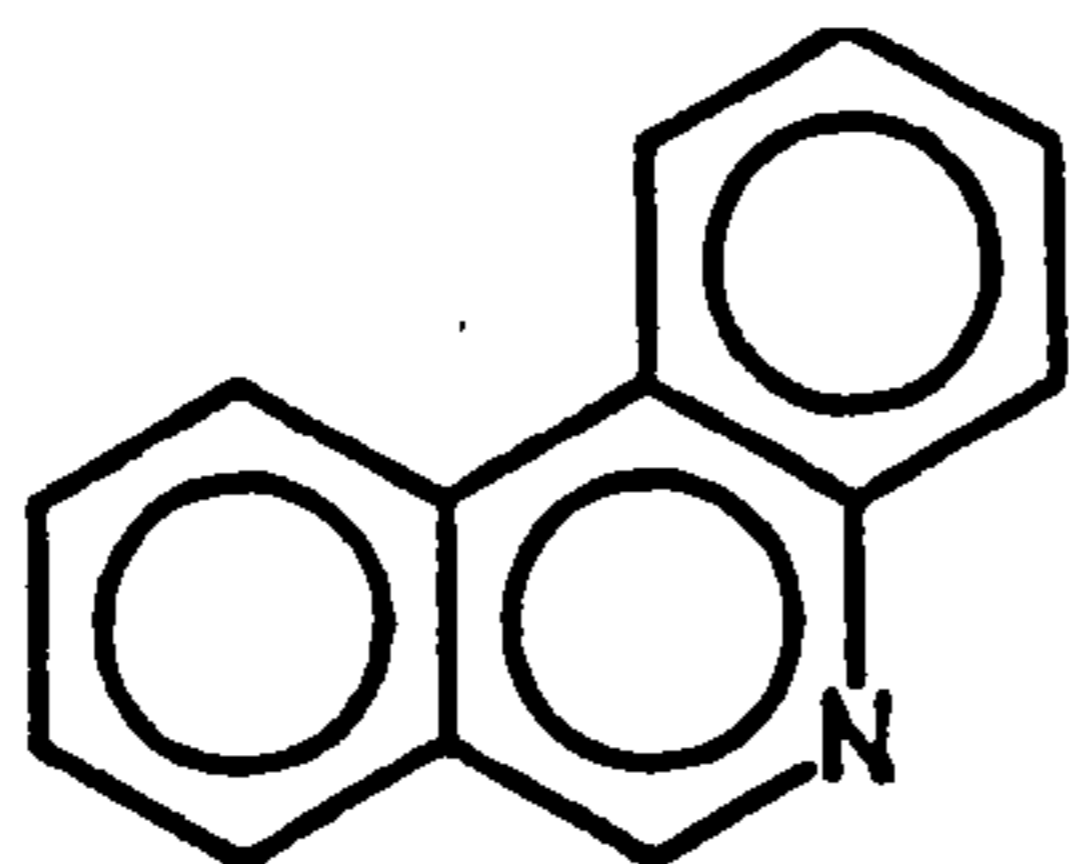
(116: R= protecting group) and reacting it with a methyl Grignard reagent (117). Subsequent dehydration and reduction of the alkene (118), which was potentially unstable to hydrogenation conditions, would lead to the steroid (119). Deprotection would give the desired steroid (43). However, this was superseded by a shorter route devised at a later stage. Thus, the direct conversion of the ketone (116) to the alkene (120) by a Wittig reaction was expected to increase overall yields and was therefore the preferred route.



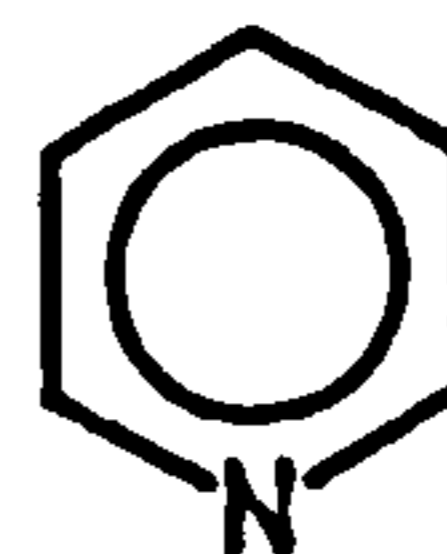
Two different approaches to the formation of 6 β -methyl-3 α ,5-cyclo-5 α -androstan-17-one (43), from the corresponding ketone derivative (116), were considered. Either the 17-C ketone group was to be converted to another functionality, i.e., protected (116: R= protecting group), or reaction conditions were to be investigated which would facilitate



specific reaction at the 6-C position in, for example, the dione (116: R= =O). With respect to the latter option, statistical methods of reaction⁶ such as these usually result in poor yields. In the former case, methods of statistically protecting the 17-keto group were considered, e.g., the reduction of the ketosteroid (41: R= =O) to the diol (121) which could then be specifically oxidised to the 6-keto compound (122) by a bulky oxidant incapable of reaction at 17-C. This could be achieved with a modified Collins reagent (e.g. phenanthridine (123) in the place of pyridine (124)) or by the differential reduction of the dione (111: R= =O) to form the 17-hydroxy steroid (122). However, the

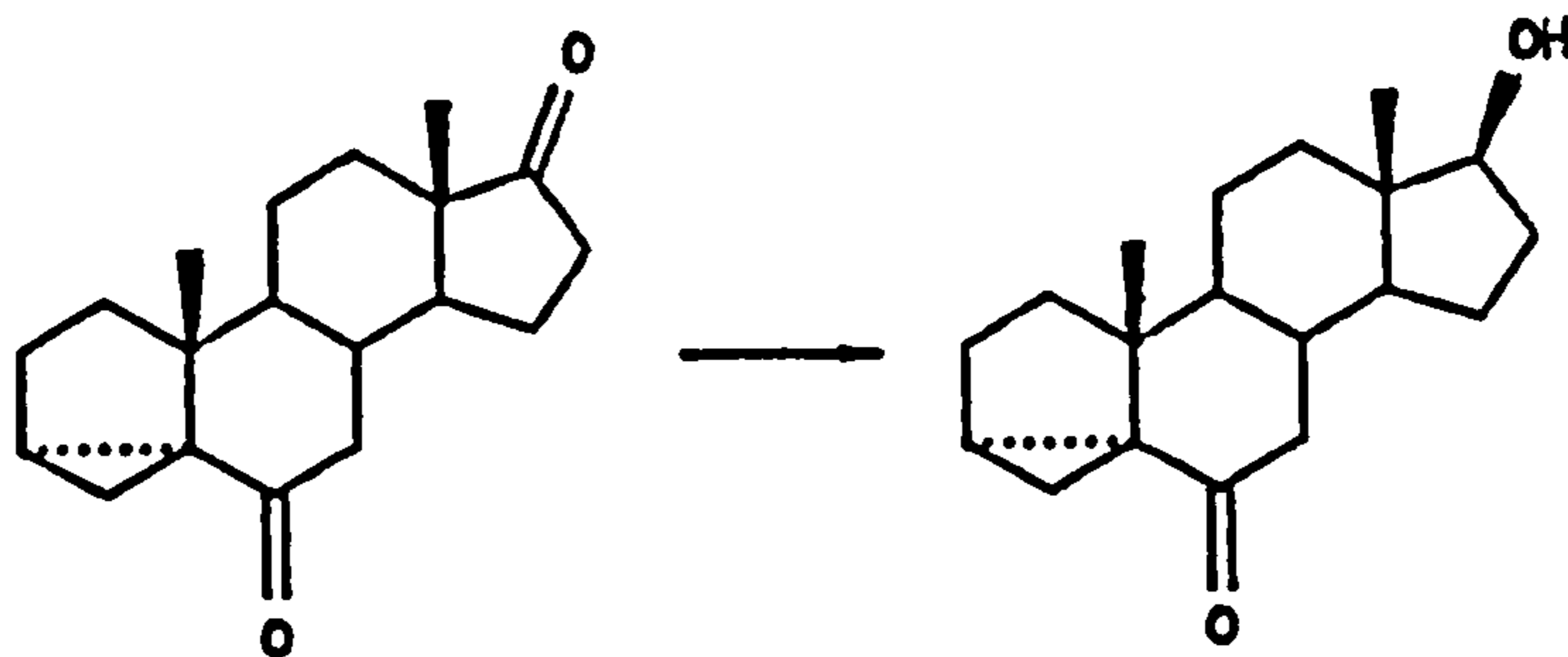


(123)



(124)

limited amount of relevant information and the generally poor yields⁷ discouraged practical investigation. The most common statistical protection methods, i.e., selective dioxolane formation^{8,9} (most recently¹⁰ with the "bulky



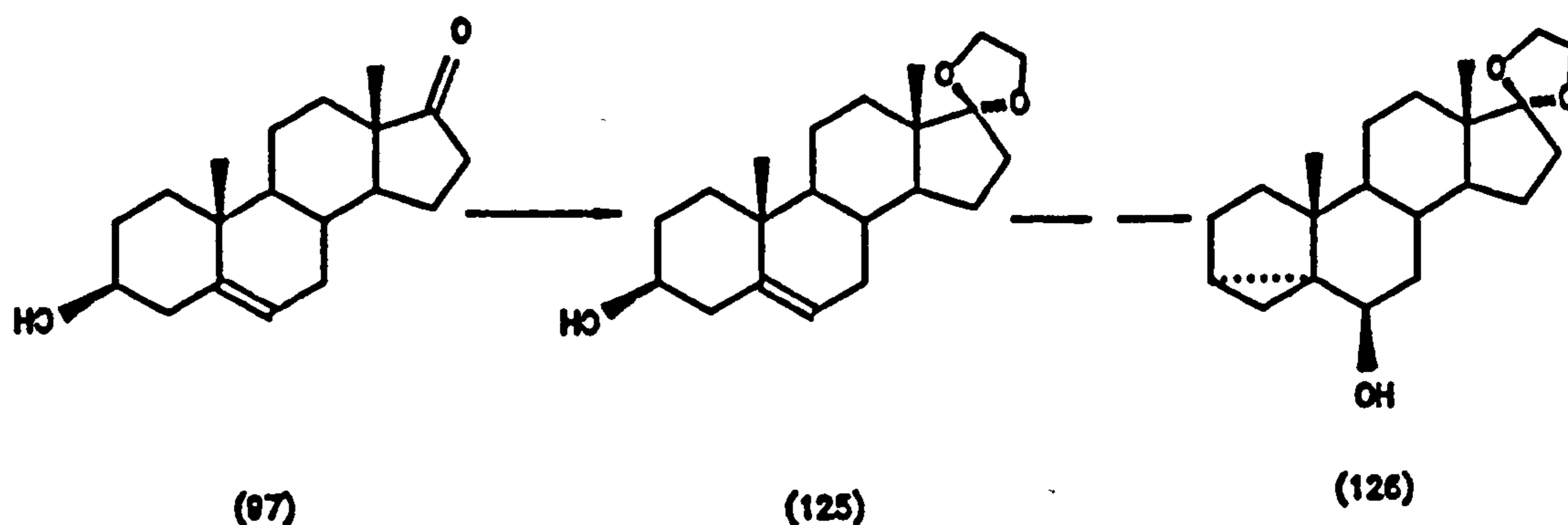
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(122)

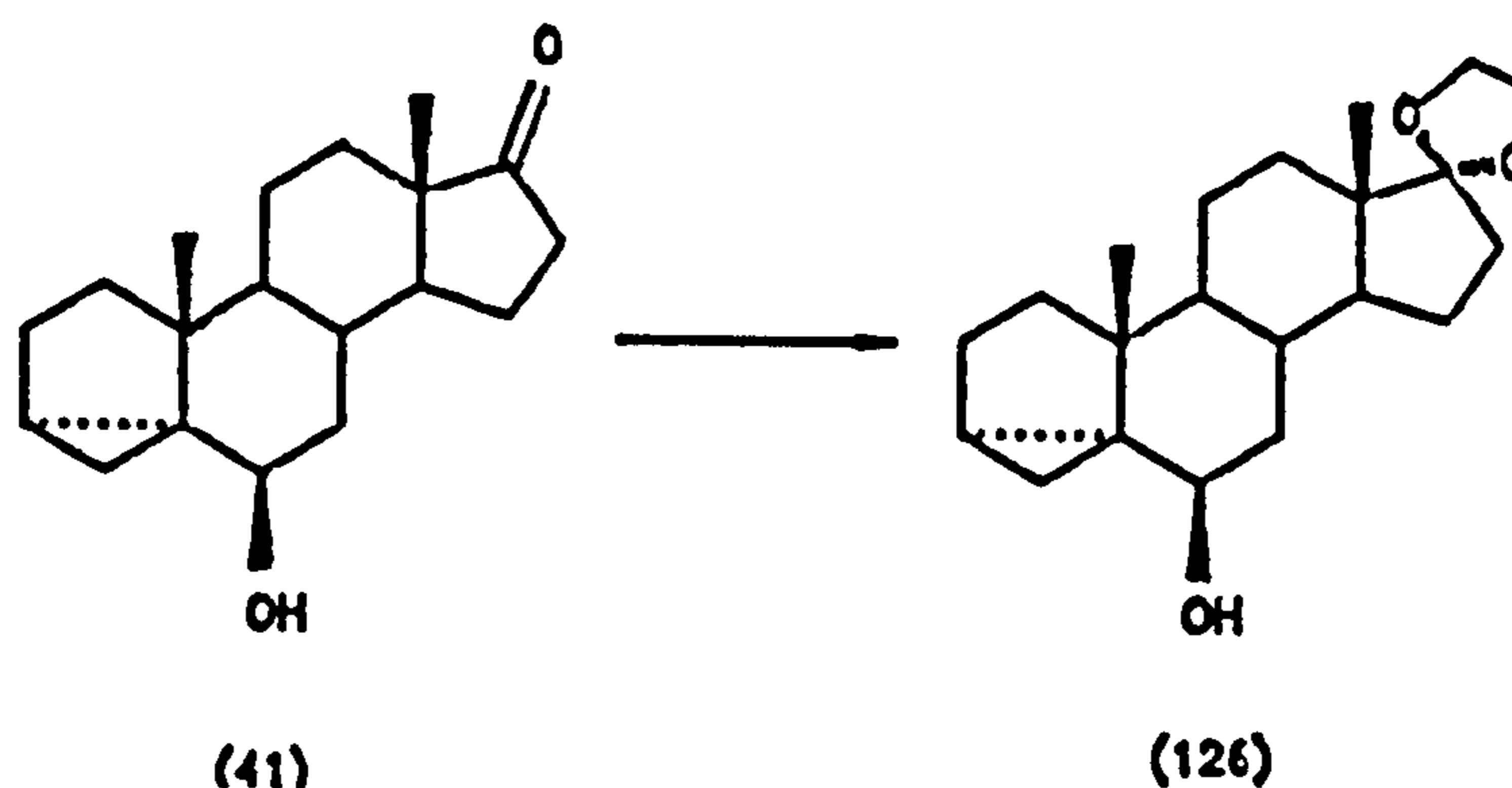
proton" derivative of ethylene glycol, 1,2-bis([trimethylsilyloxy)-ethane), rely on steric hindrance preventing reaction at 17-C, the opposite of that required here. Non-statistical methods were therefore not initially employed.

3.2 Formation of 17-C protected cyclosteroids by direct protection of 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41).

Several studies on the formation of 3,5-cyclosteroids with 17-C dioxolane protecting groups have been performed, notably by Julia.¹¹ Following formation of the 17-C dioxolane

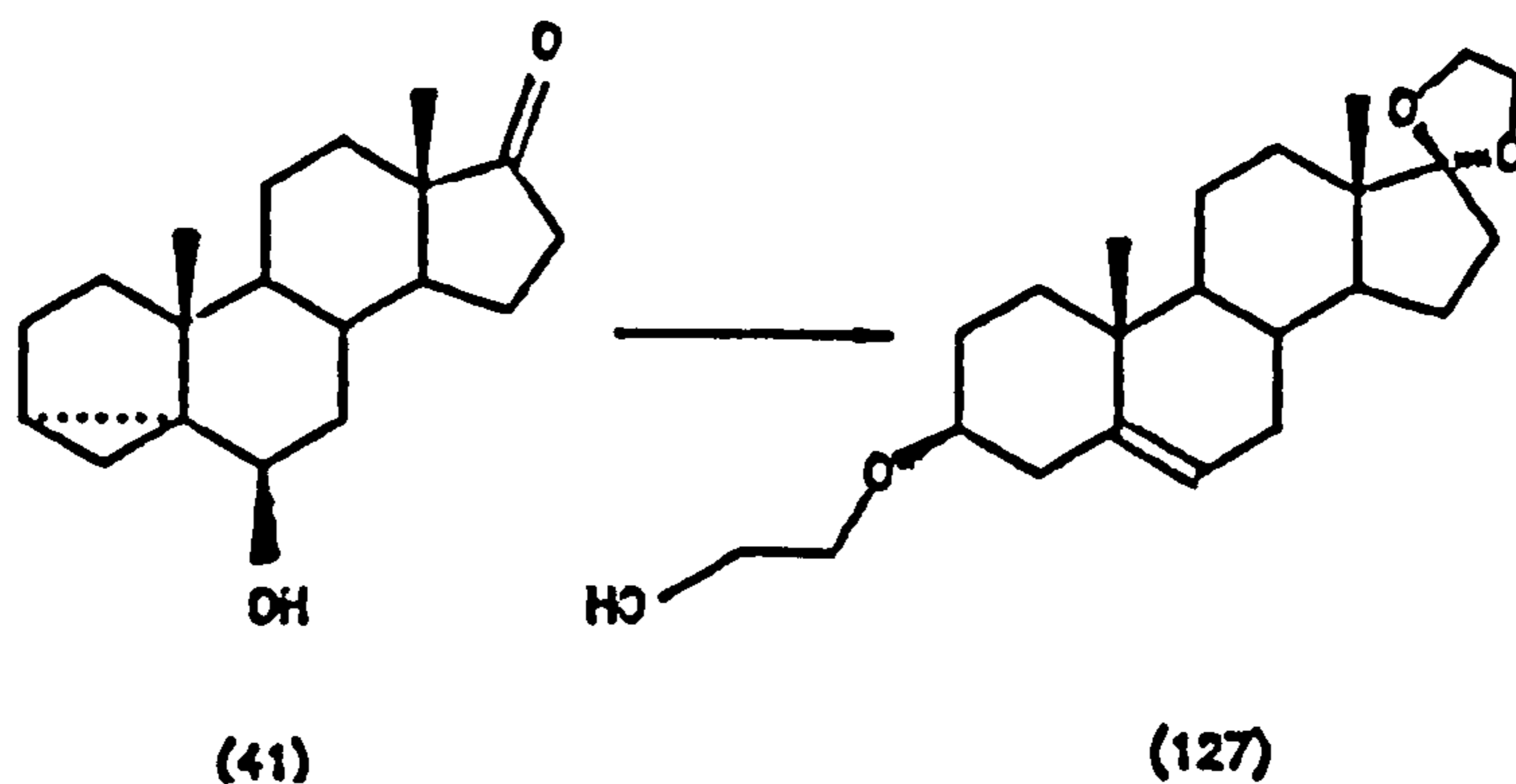


pound (126). However, the synthesis of a dioxolane protected 3,5-cyclosteroid, such as (126), had apparently not been attempted by direct conversion of the cyclosteroid (41) to its dioxolane derivative (126).

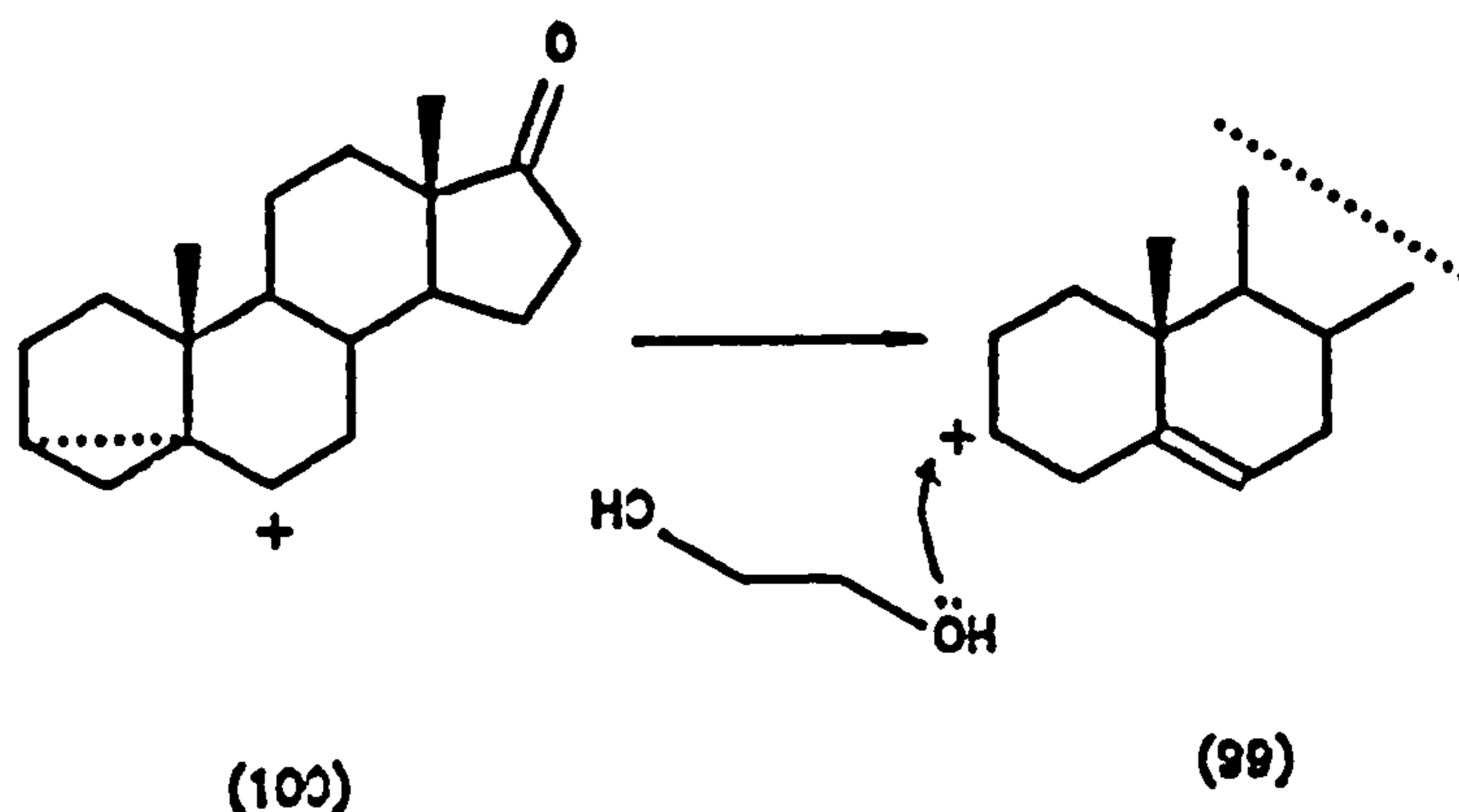


The reaction conditions used were those initially defined by Salmi^{12,13}, i.e., a benzene solution of the steroid was reacted with an excess of ethyl glycol and a catalytic quantity of p-toluene sulphonic acid (PTS). The water formed as a byproduct was azeotropically removed by a cooled Dean-Stark trap. An IR spectrum of the crude reaction

mixture showed that the 3 hours required for the protection of cyclohexanone,¹⁴ or a 20-C ketosteroid¹⁵ was insufficient, i.e., the considerable steric hindrance at 17-C resulted in an increase in the required reaction time.¹⁶ Either a 24 hour reflux or a 18 hour reflux with additional catalyst added after 8 hours was required for total conversion. Thin layer chromatography of the resulting oil, indicated the presence of only one compound which was crystallised to give a white solid whose melting point of 126-128° did not compare well with that of the literature value for the protected cyclosteroid (126) (144-146°).¹¹ The IR spectrum of the product, as expected, showed no carbonyl absorption but a strong ether absorption was present. Confirmation of the presence of the dioxolane group was given by the ¹H NMR spectra which showed a 4H singlet at $\delta=3.87$, however the compound did not show the characteristic high field signals of a cyclopropane moiety, nor the sharp triplet at $\delta= 3.31$ expected for the equatorial 6-H. However, there was a 1H doublet at $\delta= 5.35$ which corresponded to a H-6 alkenic proton, a 4H complex series of peaks centred $\delta= 3.65$ and a broad multiplet centred at $\delta= 3.22$. As the position of this broad multiplet corresponded roughly with that of the 3-H



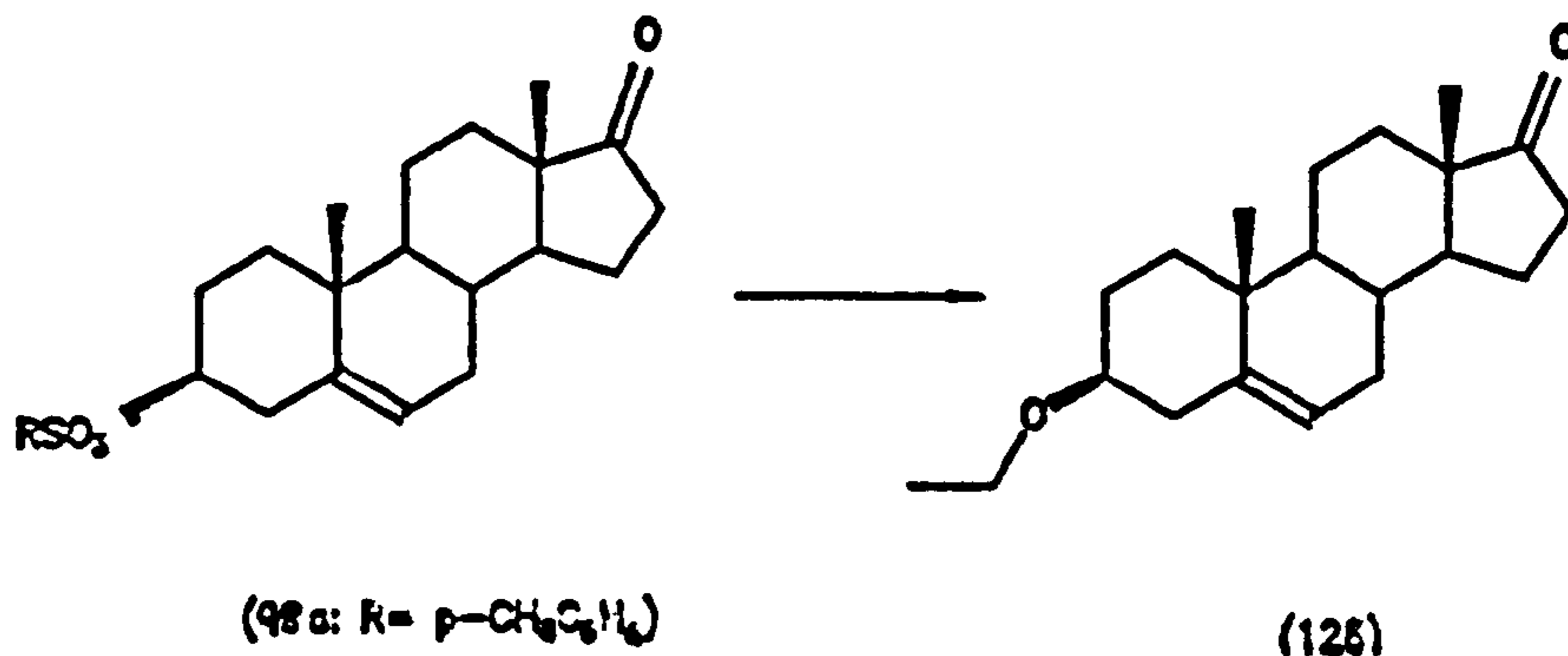
atom of DHEA, but showed a slightly different splitting pattern, it was envisaged that the cyclopropane ring had undergone fragmentation and resulted in the formation of the β -hydroxy ethylether (127) first synthesised (m.pt. 125-128°) by Julia¹¹ by reaction of the tosylate (98a) with ethylene glycol. Protonation of the hydroxy group by the acid forming the good leaving group H_2O^+ at 6-C results in the formation of the 6-C cation (100) and as with all cyclopropane carbocations this system can rearrange¹⁷ in a concerted manner to give the corresponding allyl ion, i.e., the 3-C cation (99). In an apparent release of strain the 3-5 carbon bond is thus broken because it is the bond most geometrically suitable for overlapping with the empty bonding orbitals at 6-C. Nucleophilic attack of the carbocation by ethylene glycol then occurred resulting in the formation



of the β -hydroxy ethylether. This interpretation is supported by several previous studies.¹⁸⁻²⁵ The "reverse reaction", i.e., direct nucleophilic attack on the cyclopropane ring by the ethylene glycol anion followed by rearrangement and loss of the hydroxy group cannot occur as nucleophilic cleavage of cyclopropanes is only possible when electron withdrawing groups are attached directly to the

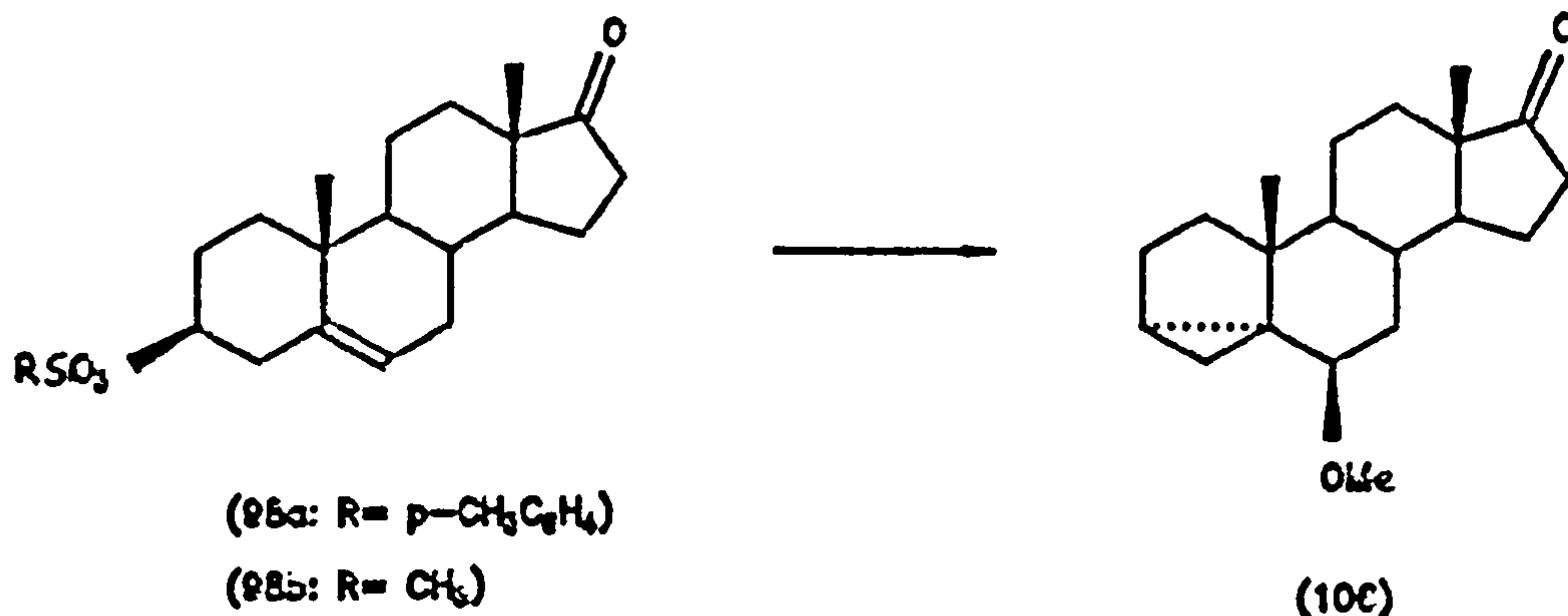
cyclopropane ring.²⁶ A mass fragmentation pattern of the product; molecular ion, $m/z = 346$, and CH analysis confirmed the proposed structure.

As the ^1H NMR spectrum gave limited information concerning the presence of a side chain at 3-C, further conformation was sought via a simple reaction designed to produce a compound which would produce a similar signal corresponding to the 3-H atom. The 3-tosylate (98a), was therefore dissolved in refluxing ethanol (the β' -hydroxy group was assumed not to affect the splitting of the 3-H) to yield the 3-C ethyl ether (128). The product was crystallised directly from the cooled solution, and its ^1H NMR spectrum possessed a splitting pattern identical to that found for the (127), thus confirming the above.

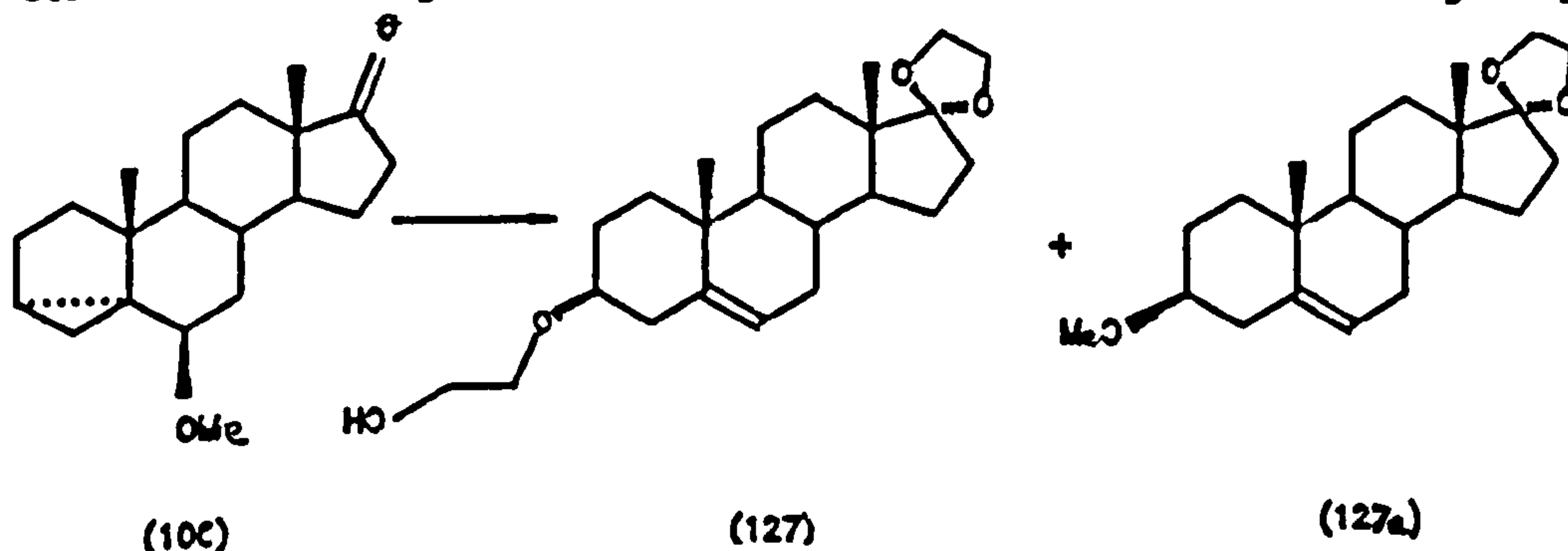


To prevent the rearrangement to the alkene by the attack of ethyl glycol on the latent 3-C carbocation two options were considered. Firstly, the rearrangement could possibly be prevented by the utilisation of a poorer leaving group at 6-C, thus preventing the migration of the C(3)-C(5) bond. Secondly, (as with the initial cyclisation of the tosylate to give the 3,5 cyclosteroid (Chapter 2) where it was noted that the DHEA cation (99) was the thermodynamically preferred structure,) perhaps the use of solvent capable

of the azeotropic removal of water, but at a lower temperature than benzene could prevent fragmentation of the 3-membered ring.



With the first idea in hand, the formation of the 6-methoxy derivative (106) by refluxing the tosylate (98a) in purified and dried methanol in the presence of potassium acetate was undertaken. However, when this compound was treated with ethylene glycol under the conditions used above, the presence of the poorer methoxide leaving group did not prevent the rearrangement of the compound. As was the case with the alcohol (41) the cyclopropane moiety rearranged to give predominantly the β -hydroxy ether (127). However, in this case a small quantity of the 3-C methoxy steroid (128) was also detected by virtue of its prominent OMe ¹H NMR signal. This loss of the functional group at



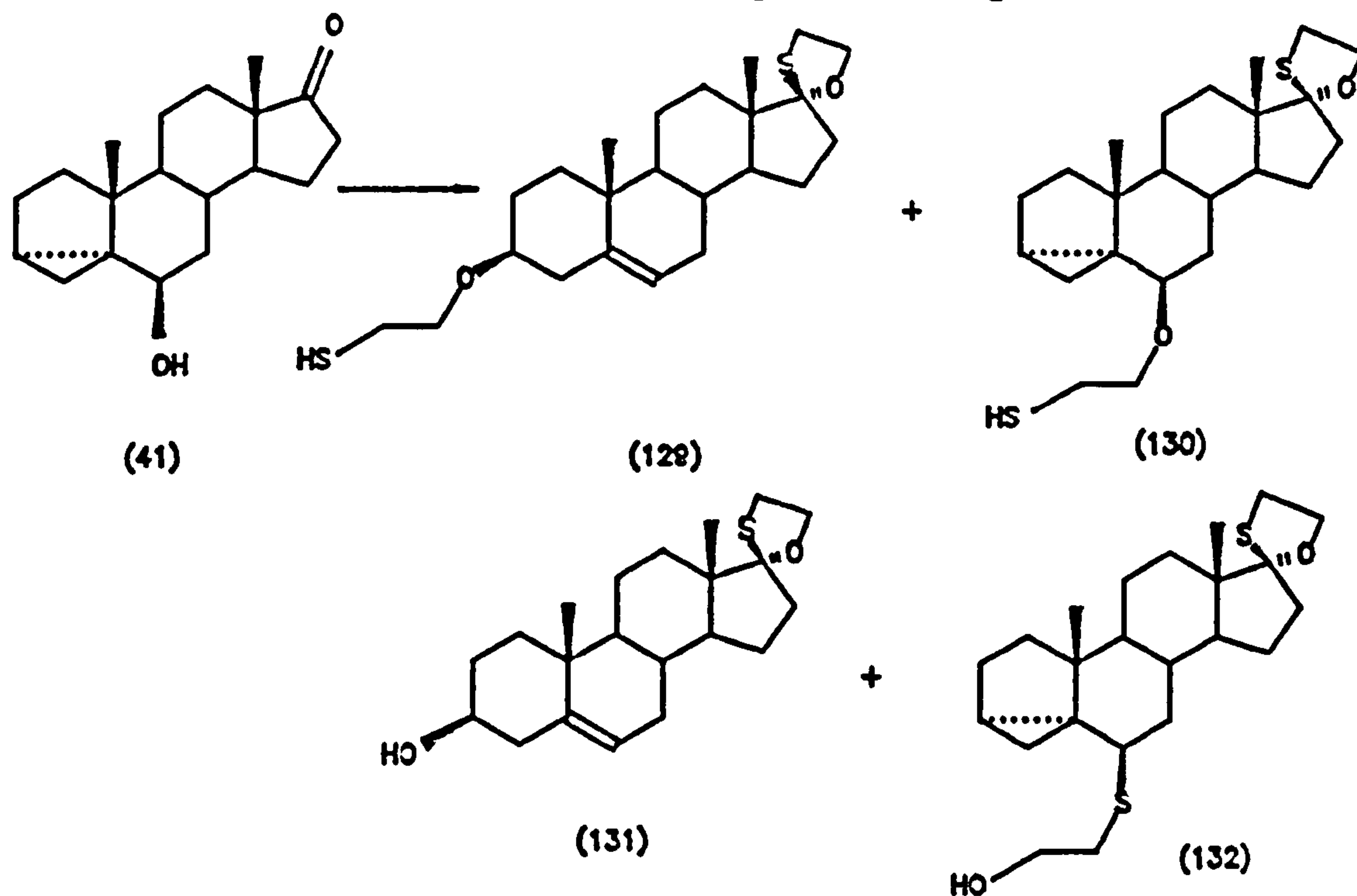
6-C and its subsequent addition at 3-C probably also oc-

curred in the initial experiment with the alcohol but remained undetected.

Attention was then turned to the use of a solvent with a lower boiling point. The reactions, performed in a similar fashion to that used above but with hexane as the solvent and after an increase in reaction time from 18 to 24 hours, successfully converted the keto group to the dioxolane but did not prevent fragmentation of the cyclopropane ring giving either compounds (127) or (127a). A similar reaction but with pentane as a solvent was undertaken (36 hours required) but again this did not prevent the break down of the cyclopropane ring. However, because the alternative solvents used were not as efficient as benzene in the azeotropic remove of water it is very possible that a reduction in the fragmentation of the cyclopropane ring induced by the lowered reaction temperatures may have been masked by the longer reaction time required.

In an attempt to prevent the break-down of the cyclopropane moiety an alternative protecting reagent was chosen to protect the 17-C carbonyl group. The alternative reagent chosen was the more nucleophilic β -mercapto ethanol ($\text{HS}(\text{CH}_2)_2\text{OH}$), which should react more readily with the carbonyl group but not effect fragmentation of the cyclopropane ring. (Direct nucleophilic attack of the ring was not occurring and therefore the increased nucleophilicity of the reaction medium should not increase fragmentation.) The steroid (41) was protected under similar conditions to those used above but required a slightly shorter reaction time (15 hours). The reaction product, a pale yellow oil, was

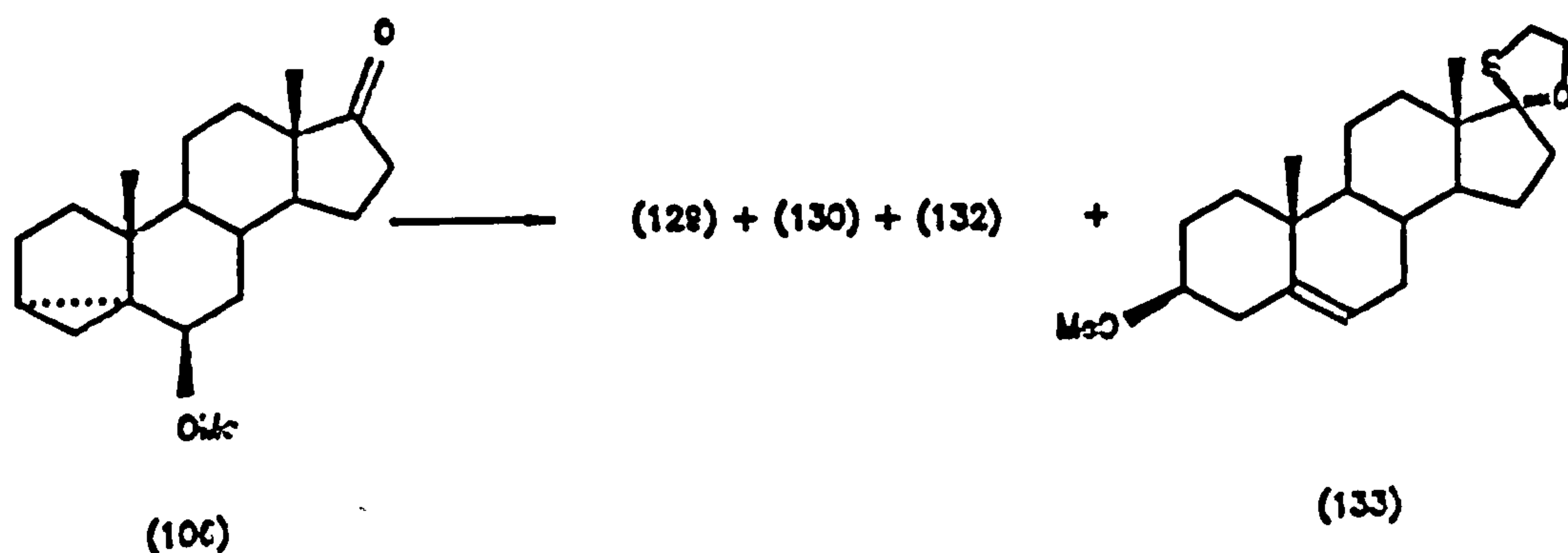
separated by preparative tlc into three fractions, none of which could be crystallised. The ^1H NMR spectra of all these products showed complex M_2X_2 splitting patterns produced by the oxathiolane protection group. The first component removed was a two component mixture (1:1) of the 3β and 6β β -thio ethylether protected steroids (129) and (130). As well as the protecting groups, the ^1H NMR spectra of the compounds showed complex absorption produced by a 3-C or 6-C



sidechain. Neither steroid showed hydroxy group absorption in its IR spectrum. Both these products accounted for approximately 25% of the total weight of the product. The second component, accounting for about 10% of the product weight was assigned as the protected derivative of DHEA (131). The third component isolated, and accounting for slightly over half of the product (60%) was the 6-C β -hydroxy thioethylether compound (132). The ^1H NMR spectrum of component three again showed complex absorption by the side chain, similar to the β -thioethers recovered. However, the 6-

H signal was shifted slightly upfield confirming the presence of the thioether group. Correspondingly, the IR spectrum possessed a strong hydroxy group band.

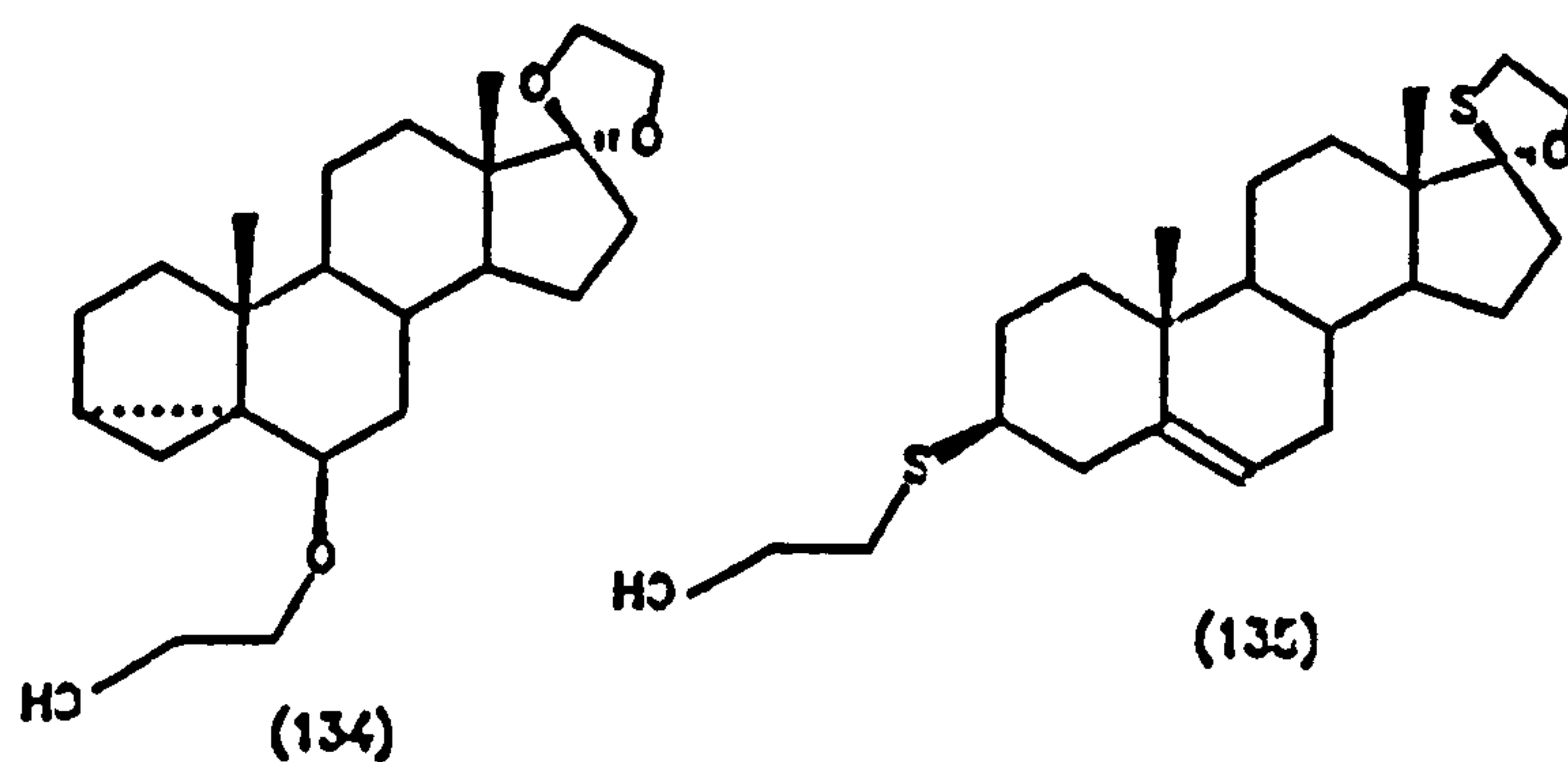
This reaction differed in another way from the ethylene glycol reaction in that by varying the solvent the relative quantities of products would vary. Thus for hexane (reaction time= 24 hours) the ratio of the above products was estimated at 2:1:8 and for the pentane solvated reaction (reaction time= 35 hours) the ratios were 2:1:12. However, the limited solubility of both the steroid and mercapto ethanol in hexane and pentane usually led to the reactants forming a lower, pink layer in the reaction vessel where apparently the majority of the steroid was undergoing reaction in a saturated β -mercapto ethanol environment. An extension to this reaction, the attempted protection of the 6β -methoxy steroid (106) by β -mercapto ethanol, surprisingly produced identical results. The presence of the poorer leaving group



in the molecule made no detectable difference. However by virtue of its prominent ^1H NMR methoxy signal the second component from the reaction mixture was readily identified as the 3β methoxy steroid (133), thus indicating that the second component removed from the reaction between the alcohol (41) and β -mercapto ethanol was, as assumed, the 3β -

alcohol (131).

Several points can be drawn from these results, the most prominent being the increasing amounts of 6-substituted thioether cyclosteroids recovered as the reaction temperature decreased. Thus, although (41) undergoes loss of the 6-hydroxy group a reduced percentage of the molecules rearrange to the thermodynamically more stable delta 5 steroid at the reduced reaction temperatures. Attack by the more nucleophilic thiol moiety of the mercapto ethanol predominately results in the formation of (132). Thermodynamic considerations however do not fully explain the product. The nucleophilicity of the protecting reagent must also play an important role in the mechanism, otherwise the reaction between the steroid and ethylene glycol should also have led to the formation of a 6-substituted steroid, e.g., (134). Furthermore, contrary to the ethylene glycol reactions, a small percentage of a 6-substituted ether, i.e., (130) was recovered, and its yield did not appear to vary considerably as different solvents were used. Both these results can



possibly be attributed to solvent effects where in the case of the reactions solvated with hexane or pentane the reactions are occurring in the "separate" layer of β -mercapto ethanol. Not surprisingly, the methoxy ether (or alcohol)

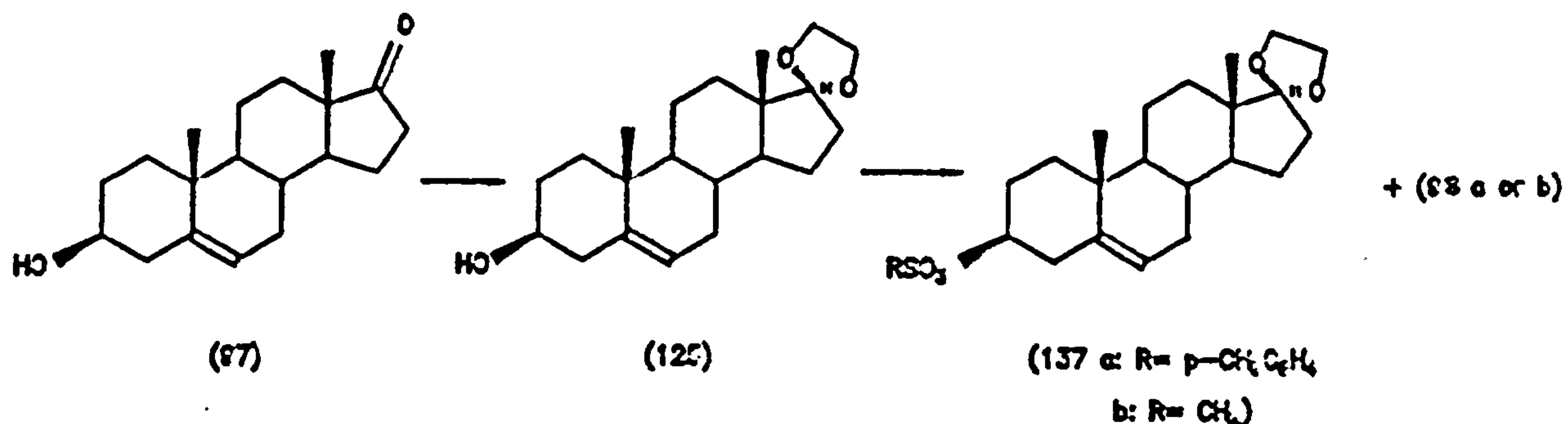
derivative were recovered in the smallest yields; the methoxide ions only being present as a molar equivalent (with respect to the steroid) whereas the β -mercapto ethanol was present in a considerable excess. One possible compound was conspicuous by its absence, namely the 3-substituted β -hydroxy thioether (135). Why did nucleophilic attack of a 3-C carbocation only apparently involve the nucleophilically weaker hydroxy group of the protecting group? Unfortunately, the generally low purity of the above compounds most certainly masked some details of the reaction. However, the results do concur with those of Lee²⁷ in the solvolysis of 3-tosylates with diols and thiols.

Although the differing solubility and nucleophilicity of mercapto ethanol compared to ethylene glycol had a considerable effect on the outcome of the reaction products no real improvement was attained. Therefore, because of the instability of the cyclopropane ring, an alternative route to the protected cyclosteroid was required. Thus, the initial protection of the keto group followed by formation of the cyclopropane ring was attempted.^{11,28-30}

3.3 Formation of 17-C protected cyclosteroids by insertion of a 17-C protection group prior to introduction of the cyclopropane ring.

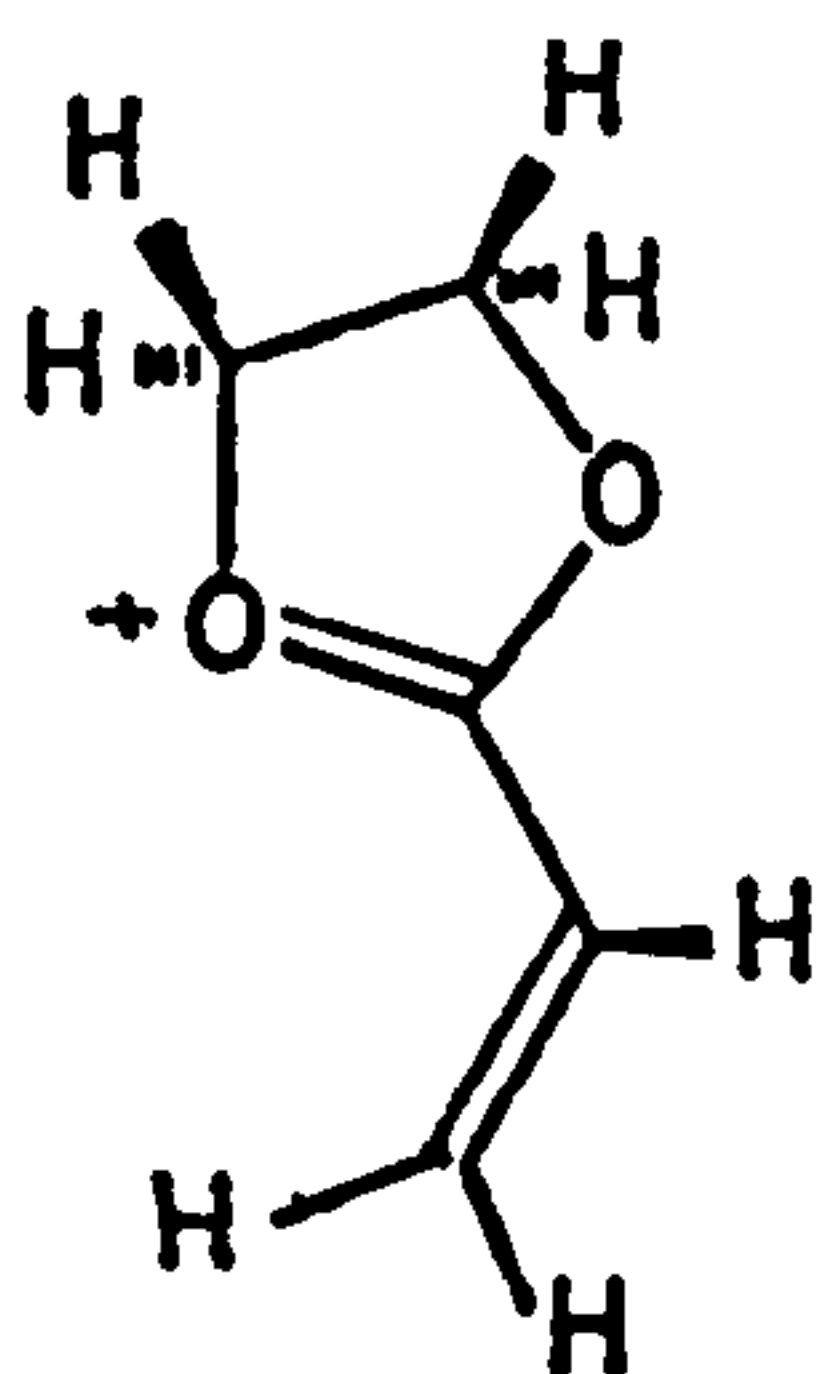
As the direct introduction of a dioxolane or thioxalane group into the $3\alpha,5$ -cyclo- 5α -androstane nucleus was unsuccessful, an alternative route where the protecting group was introduced prior to the insertion of the cyclopropane ring was undertaken. As in the above work, both ethylene glycol

and β -mercapto ethanol were investigated as protection reagents.



3.3.1 Formation of 3 β -hydroxy-5-androsten-17-spiro-2'-(1,3-dioxolane) (125).

Under the conditions employed above for the attempted formation of the protected cyclosteroid (41), DHEA was successfully converted¹¹ to its 17 ketal derivative (125). The ¹H NMR spectrum of the product showed the expected 4H singlet at $\delta = 3.87$ associated with the dioxolane protecting group. The insertion of the β oxygen at 17-C also shifting the 18-methyl signal upfield from $\delta = 0.89$ to 0.84. The IR spectrum, as expected showed a characteristically strong ether band in place of the carbonyl band present in the starting material. The strongest peak in the mass fragmentation pattern ($m/z = 99$) of the product, corresponded to the loss of moiety (136), from the steroid, a common feature of dioxolanes.³¹



(136)

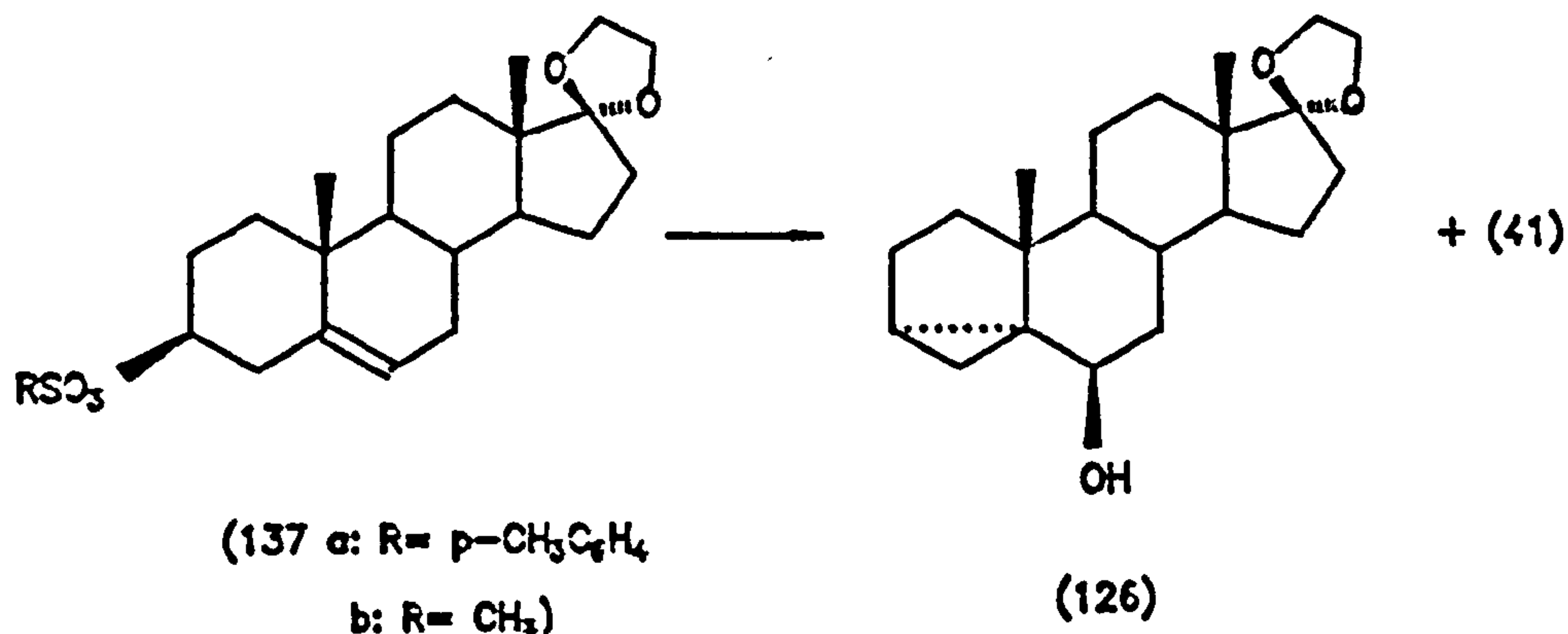
3.3.2 Formation of 3-sulphonate esters of 3 β -hydroxy-5-androsten-17-spiro-2'-(1,3-dioxolane) (137).

After protection of the ketone group, the first step in the formation of the cyclopropane ring was to react the steroid alcohol with p-toluenesulphonyl chloride or methane sulphonyl chloride. The conditions employed in the formation of the tosylate (137a) or mesylate (137b) were identical to those in the corresponding DHEA reactions (see Chapter 2). However, in the isolation of the expected tosylate (137a) a second strongly UV visible compound was isolated. This was shown spectroscopically to be the DHEA tosylate (98a). Approximate 10% of the protected steroid had been converted back to the ketone, most likely by the presence of p-toluenesulphonic acid (the acid frequently used for the deprotection of such compounds) in the tosylating reagent. When the mesylate of the dioxolane (137b) was synthesised no significant improvement was noted. The ^1H NMR and IR spectra of both sulphonates, separated from their corresponding ketones by tlc were unexceptional.

3.3.3 Formation of 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-spiro-2'-(1,3-dioxolane) (126).

The cyclisation of (137b) to give the protected cyclosteroid (126) was carried out under the most favourable conditions for the formation of its 17-ketone derivative (98b), that is, by refluxing the sulphonate in aqueous acetone in the presence of potassium acetate (Chapter 2). Again however, even though an excess of potassium acetate was present, it was found that the protecting group had been

partially removed. The buffering of the reaction with potas-



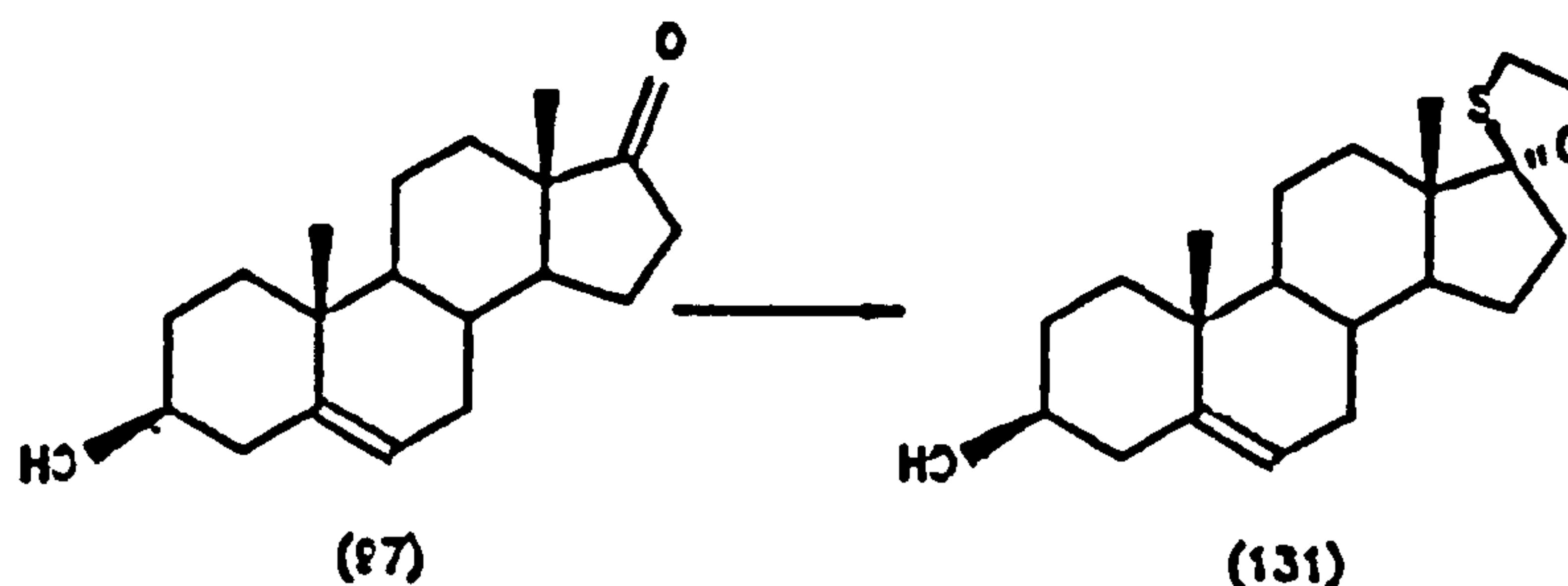
sium acetate did not prevent the acid cleavage of approximately 10% of the dioxolane steroid, a fact not commented on by Julia.¹¹ The desired product (126) was however readily separated by preparative tlc and its ¹H NMR spectrum showed the expected highfield complex signals of the cyclopropane ring (Chapter 2). Confirmation of rearrangement also being found by the absence of an alkenic signal. Also the signal produced by the proton geminal to the hydroxy group appeared as a sharp triplet because of its equatorial position at 6-C instead of the corresponding broad signal of the axial 3-H.

Although these reactions successfully accomplished the incorporation of a protecting group and a cyclopropane ring into the steroid framework, the yields were somewhat reduced because of the breakdown of the dioxolane group. An attempt to improve yields, by for example induced cyclisation under more basic conditions, again resulted in breakdown of the protecting group. However this can be attributed to the more basic conditions³² rather than the presence of the sulphonic acid. Instead the alternative reagent β -mercapto ethanol was used. Djerassi *et al.*³³ had discovered that the oxathiolane protecting group, previously used in the attempted direct synthesis of the oxathiolane cyclosteroid, was surprisingly

more stable in the presence of p-toluenesulphonic acid. Therefore an identical strategy to that used above but with β -mercapto ethanol as the protecting reagent was undertaken to circumvent the preceding problem.

3.3.4 Formation of 3 β -hydroxy-5-androsten-17(S)-spiro-2'-(1,3-oxathiolane) (131).

Because of the problems encountered during initial experimentation with the dioxolane protecting group, the less common oxathiolane protection group, formed by the reaction between the keto group and β -mercapto ethanol was investigated. The oxathiolane group possessed greater stability in the presence of p-toluenesulphonic acid,³³ presumed to be the cause of degradation of the dioxolane protecting group in the two cyclisation steps.

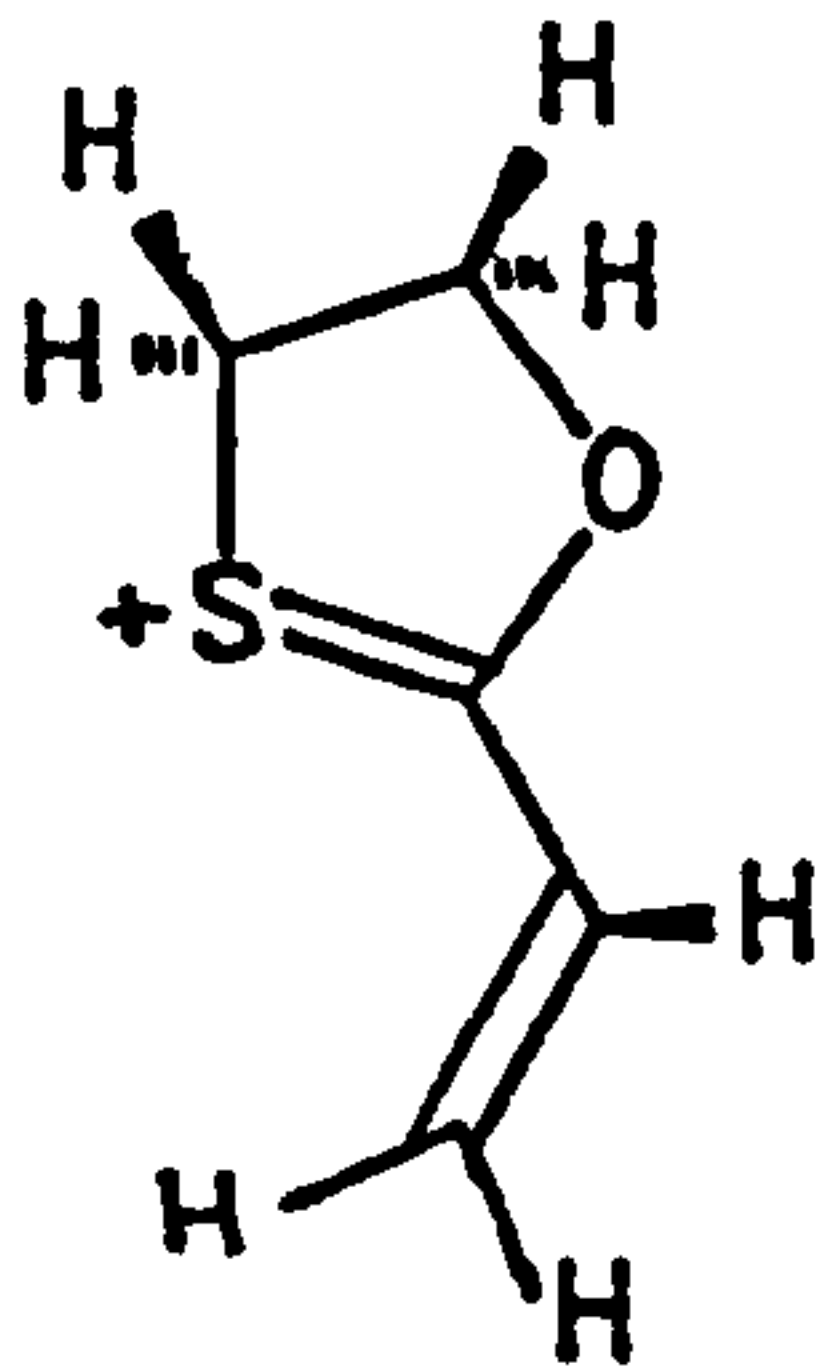


The formation of the oxathiolane steroid (131), see below, was based again on the method of Salmi^{12,13} used by Rosenkranz³⁴ instead of the method of Djerrassi *et al.*³⁵ which resulted in low yields for sterically hindered sites. As before, initial attempts indicated that the time required for total conversion, as found for the formation of the dioxolane derivative (125), was greater than that stated,³⁴ again most certainly because of the steric hindrance around

the 17-C ketone group. An estimation of the conversion was based on the IR spectrum of the product before purification which showed at worst a very weak signal in the carbonyl region. The ketone impurity was suitably removed by two recrystallisations from 70% aqueous acetone or by flash chromatography, necessary for the removal of any remaining mercapto ethanol.

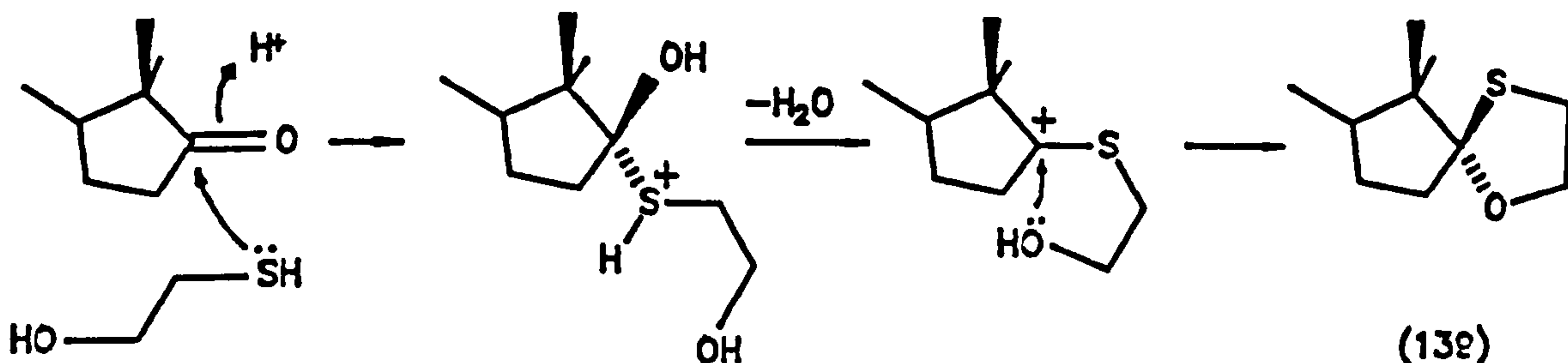
The oxathiolane group was evident from the ^1H NMR spectrum as two complex (M_2X_2) sets of peaks centred at $\delta=4.09$ and 2.86 corresponding to the protons adjacent to the oxygen and sulphur atom respectively. The protecting group also shifted the 18-methyl signal upfield from $\delta=0.89$ to $\delta=0.83$, the singlet indicating the isomeric purity of the product. This was also confirmed by the narrow melting point of the product (Chapter 8). The ^{13}C NMR spectra differed from that of DHEA by three additional signals at $\delta=40$, 70 and 106 corresponding to the carbon atoms α and β to the sulphur in the oxathiolane moiety, and the 17-C chiral carbon respectively. The removal of the carbonyl absorption on the IR spectrum was accompanied by the appearance of strong absorption between $1000\text{-}1100\text{ cm}^{-1}$ associated with the introduction of C-O-C and bonds into the framework. The protecting group was also obvious in the compounds mass fragmentation pattern. In a similar fragmentation to its "sister" compound, the dioxolane derivative (125), the major peak ($m/z=115$), of the spectrum corresponded to moiety (138). Other prominent peaks derived from the parent ion ($m/z=348$) were at 288 (loss of $\text{C}_2\text{H}_4\text{S}$), 270 (loss of water)

and 255 (subsequent loss of a methyl group).



(138)

In the work by Djerassi³³ it was assumed that the regioselective reaction gave the 17(R) compound. However, considering the S_N1 reaction mechanism,³⁶ it seems more likely that after the "formation" of the planar carbocation induced by loss of water, attack by the oxygen occurs from the less hindered α face of the molecule, thus leading to the 17(S) configuration (139). A comparison of the two

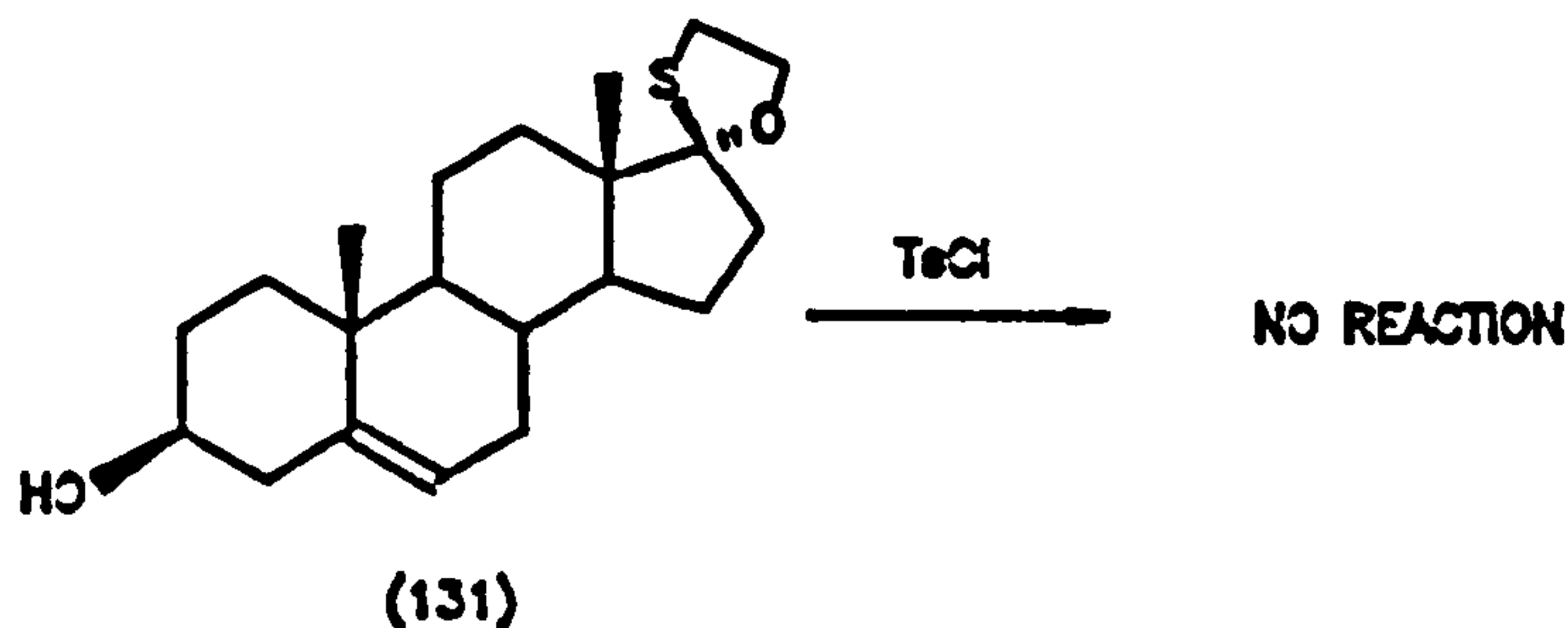


structures (17(R) and 17(S)) with molecular mechanics indicated that although there are slightly greater repulsive forces between the 18-Me group and the β -hetero atom when the steroid possesses the 17(S) configuration, (β -sulphur) the overall energy of the compound is very similar to that of the 17(R) steroid. The only significant difference in the geometry of the compounds being the oxathiolane ring, where the large sulphur atom, close to the methyl group is accom-

modated by the "flipping" of the oxathiolane ring (see Chapter 6).

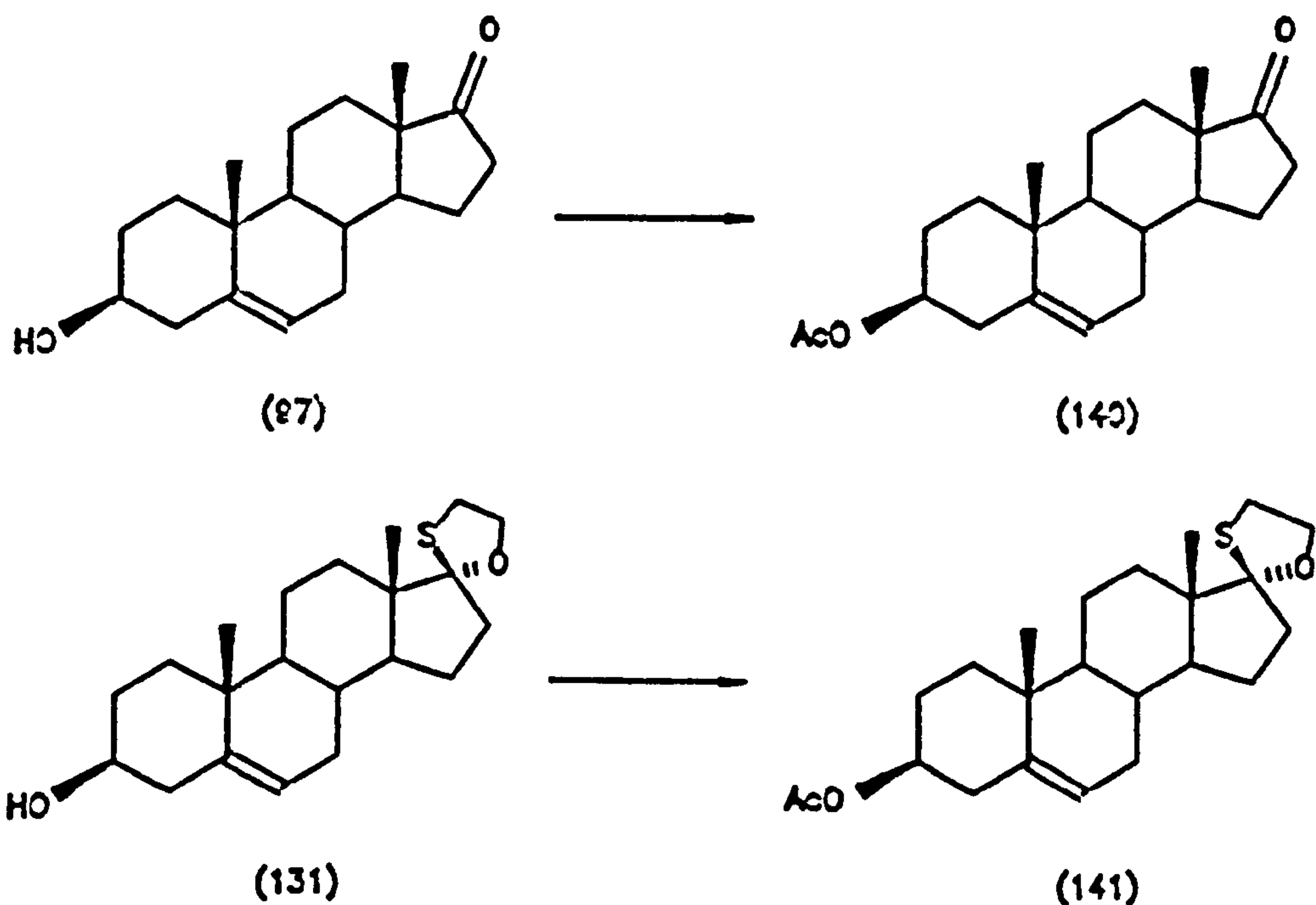
3.3.5 Attempted formation of 3 β -tosyl-5-androsten-17(S)-spiro-2'-(1,3-oxathiolane).

The first step in the formation of the cyclopropane ring of the protected steroid is the conversion of the 3-C alcohol to its sulphonate and this was initially attempted with tosyl chloride (p-toluenesulphonyl chloride). However, under identical conditions to those used in the formation of the DHEA tosylate (Chapter 2), i.e., the dissolution of equimolar amounts of steroid and tosyl chloride in pyridine, only the unreacted steroid (131) and p-toluenesulphonic acid



were recovered. The intended product was isolated by precipitation induced by the addition of water to the pyridine solution. No evidence of formation of the steroidal tosylate was obtained even after the reaction mixture stood for up to one week (cf tosylation of DHEA (97) which required 16 hours). These results were in total contrast to the readily formed dioxolane tosylate formed here and by Julia.¹¹ Several possible sources of interference were therefore examined. The simple possibility of impurities in the particular batch of chemicals was quickly dismissed by a successful

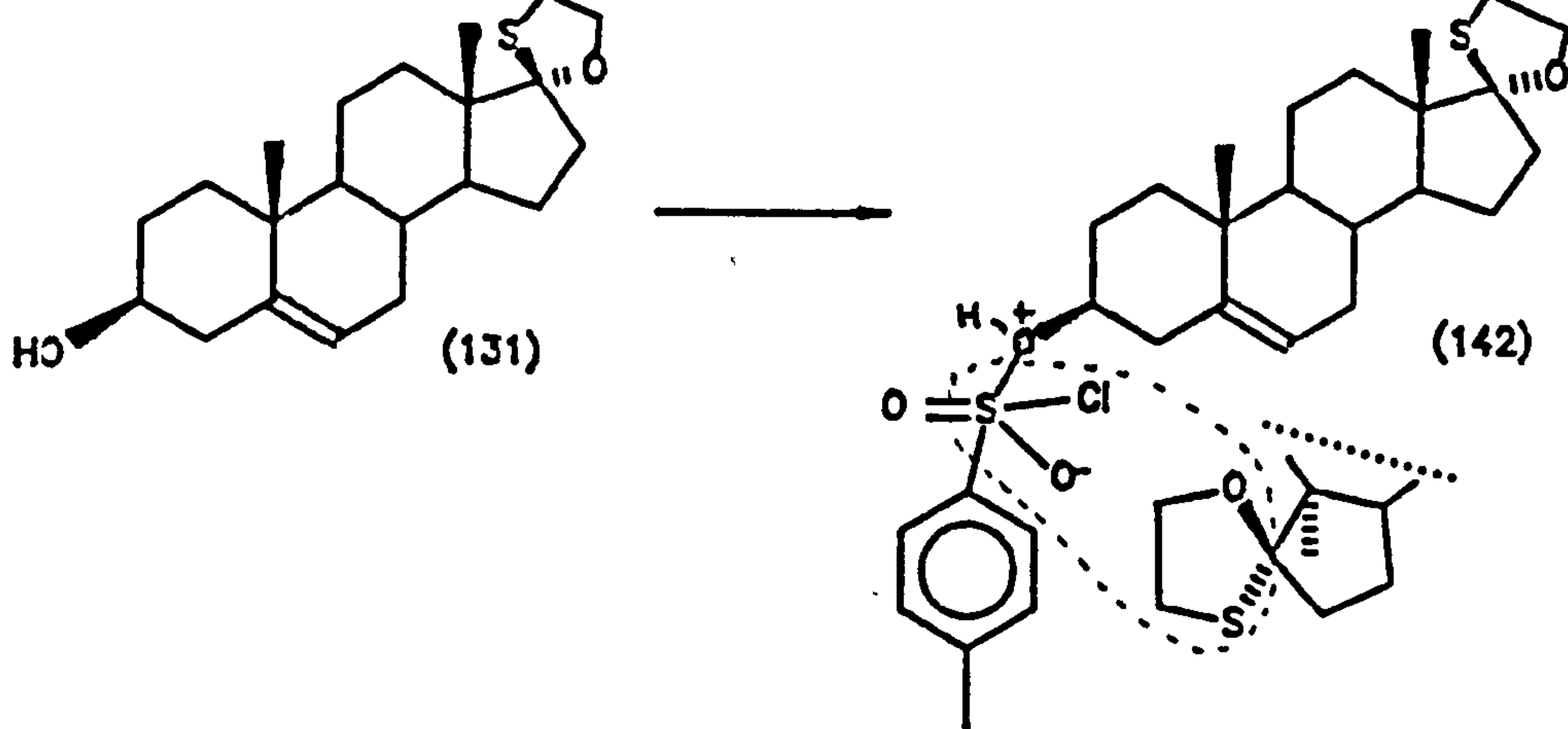
repeat of the reaction on the 17-C ketone and routine spectroscopic analysis of the compounds involved. Another possibility, the presence of water of crystallinity in the steroid was investigated by a series of reactions using excesses of the tosyl chloride (up to five fold). The possibility that the product was unstable in the presence of water was also dismissed by a non-aqueous work-up, only the steroid (131) and tosyl chloride being recovered. The reaction was then performed, based on the technique of Ringold and Djerassi,³⁷ but modified so as to reflux the steroid and the tosyl chloride in a neutral solvent (dichloromethane) and using only a 2 fold excess of pyridine. Unlike the result of the DHEA reaction, (see Chapter 2) only starting materials were recovered. To increase the reaction temperature, chloroform and finally, neat pyridine itself were used as solvents and refluxed over a 24 hour period. These steps however did not facilitate the intended products and at no time was the tosylated steroid recovered.



The apparent inactivity of the 3β -alcohol group by the oxathiolane moiety was also shown when the both DHEA (97) and its 17-oxathiolane derivative (131) were acetylated ((140) and (141)) under identical conditions (pyridine and acetic anhydride). The reaction time required to convert the oxathiolane derivative to the acetate³³ (141) was approximately ten times longer than that for DHEA. Furthermore, as is discussed later in this chapter, the oxathiolane steroid (131) was successfully mesylated at the 3-C position but again at a much reduced rate. Two distinct possibilities for this result were considered. Firstly, that simple steric hindrance, or steric hindrance caused by intermolecular complexing of a reaction intermediate, were responsible. The second (and less likely) possibility was that some form of "electronic deactivation" of the alcohol group, induced by conformational transmission, by the oxathiolane moiety was occurring. Whatever the mechanism, as tosylation of the dioxolane steroid was achieved readily, the reduced reaction rates can be attributed solely to the presence of the sulphur atom.

Deactivation of the 3-hydroxy group by steric effects.

The likelihood that blocking of the alcohol group was by simple steric hindrance was dismissed in the light that the dioxolane steroid (125) was readily tosylated under identical conditions. A study of the oxathiolanes structure with molecular mechanics showed the improbability of the scenario in that the protecting group was a full 12Å distant

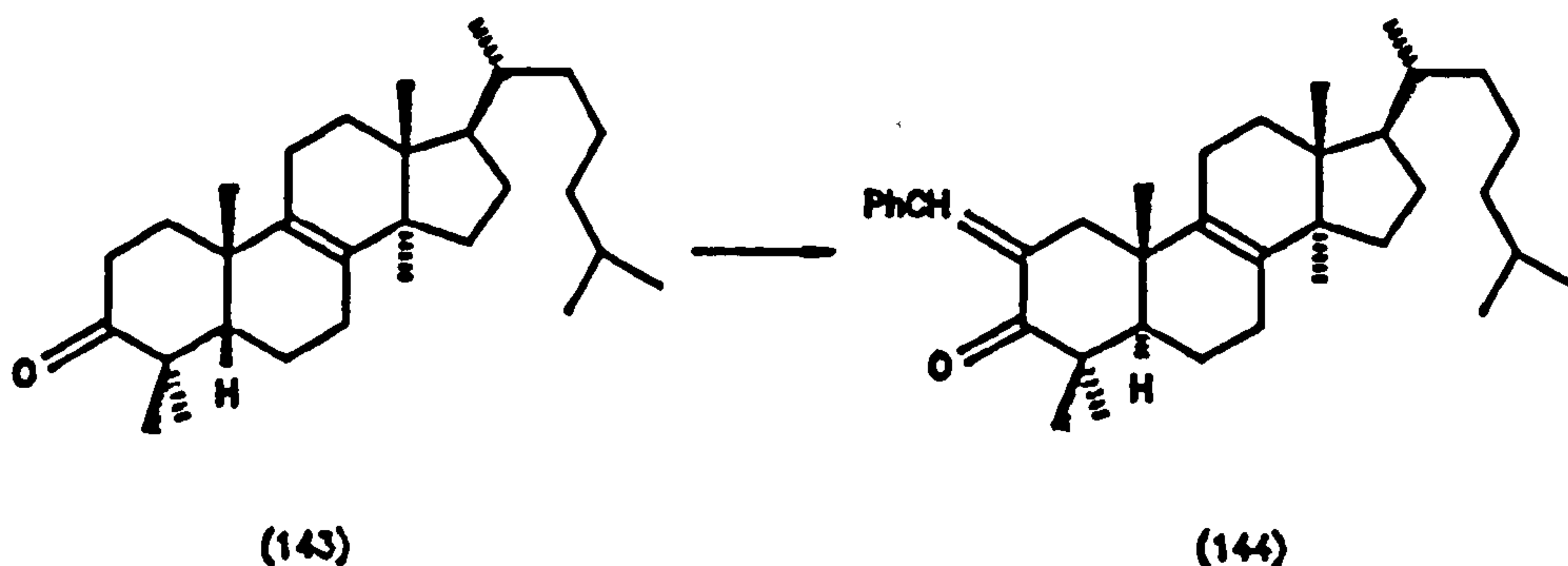


from the reaction centre. Therefore, if the source of inactivity of the alcohol group is to be attributed to steric hindrance it must be via some form of intermolecular complexation occurring before or during the reaction mechanism, e.g., (142), involving either of the reactants and/or the solvent. From the above results it would also appear that this blocking is not absolute, perhaps the geometrical layout of the complex retards the reaction between the mesylate or anhydride but completely restricts the tosylate. However, this is just one possibility. Perhaps the mechanism involved does not require another steroid molecule but is in fact a result of solvent clustering, a combination of the two or some other steric effect.

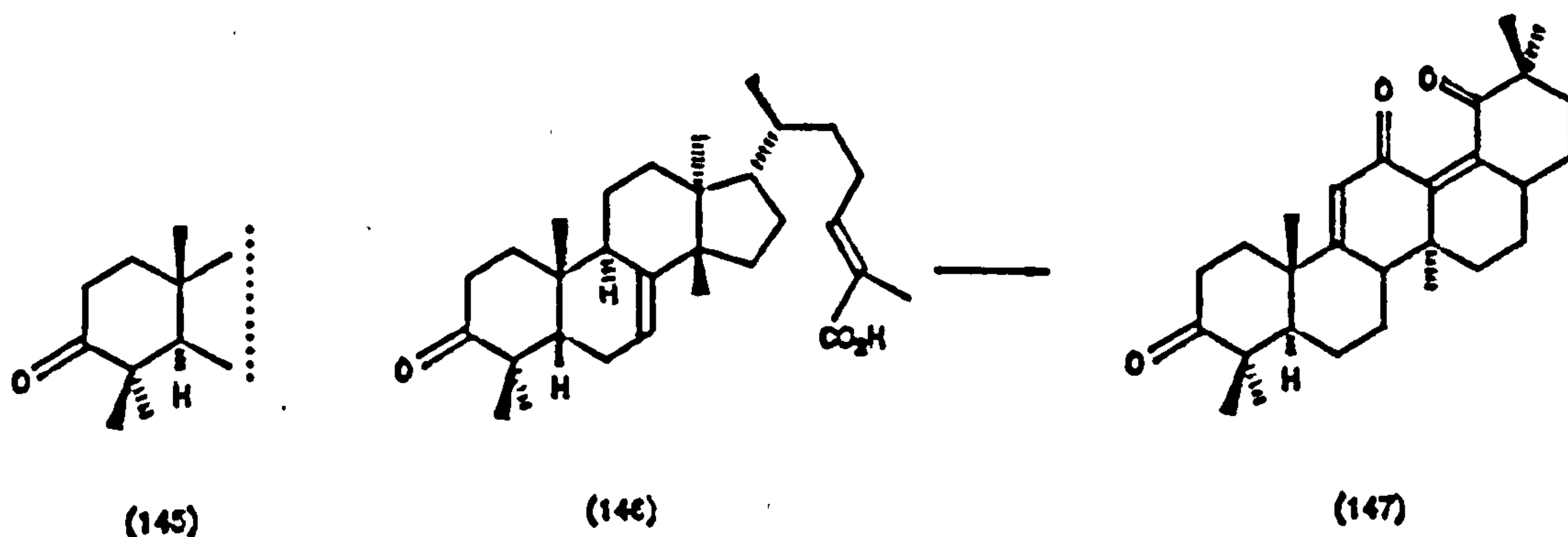
Deactivation of the 3-hydroxy group by a conformational transmission induced electronic effect.

The second possibility, that the alcohol group is somehow deactivated by the oxathiolane group is perhaps less likely, especially since tosyl chloride contains a more electrophilic sulphur atom than mesyl chloride. Past examples of this sort of phenomenon, i.e., the deactivation (or activation) of functional groups in various chemical systems had been reported (see below), including steroidal

alcohols. It was imagined that the deactivation of the 3-C alcohol group might be a form of an inductive effect created or enhanced by the oxathiolane protecting group. Even though it is generally thought that these effects drop off rapidly as the length of saturated carbon chain between substituent group and reaction centre increases, several long range effects across the steroid framework have been reported. It was Barton *et al.*³⁸ who first proposed the conformational transmission effect, (the Barton effect) to describe the differing rates of base catalysed condensations of a series of triterpenoid 3-ketones with benzaldehyde. They found that with respect to lanost-8-enone (143) (rate of reaction =100%, giving 144), other compounds containing the partial



structure (145) underwent the identical reaction at greatly reduced rates, e.g., masticdienonic acid (146) (8%), or



considerably accelerated rates, e.g., β -amyra-9(11),13(18)-diene-3,12,19-trione (147) (344%). No definitive conclusions

were drawn however, the results being described by the author as "probably arising, in main part, from conformational distortion produced by unsaturated substituents (and to a small extent by saturated ones)". It is envisaged that this distortion is transmitted through the saturated molecule by a slight flexing of valance angles and alteration of atomic coordinates. Blickenstaff et al.³⁹ has shown that the reactivity of certain steroidal centres such as the 6-C and the 12-C positions are altered by the substituent at 17-C. For example, selected hydroxy groups are acetylated at differing rates, when reacted under identical conditions of acetic anhydride and pyridine, apparently because of other hydroxy groups present in the steroid. Their results from a number of hydroxy steroids (3, 6, 7 & 12-C), indicated a complex interactive relationship between functional groups present and their degree of activity. Blickenstaff,³⁹ also noted that the presence of a 17-C dioxolane group did not effect the activity of the 6-C alcohol group in the 3,5-cyclosteroid (126). Apart from determining that the observed effects were intramolecular and not intermolecular no definitive explanation was given. It has also been shown⁴⁰ that the rate of addition of bromine across a double bond in the 5 position is not only influenced by a substituent at 3-C, but also at 17-C. Furthermore, Peterson⁴¹ showed that the rate of solvolysis of 3-C tosylates are decreased by electronegative substituents at 17-C. In this case however, the rates of reaction were determined in solvents of low nucleophilicity such as formic acid and trifluoroacetic acid. Also, the 17-C substituents, for example the 17 β -

trifluoro-acetoxy- 17 α -cyano group were highly electronegative. The study indicated that the 6 fold decrease in the rates of reaction were not due to dipole-dipole interactions nor dipole-charge interactions. Instead, partial removal or delocalisation of the negative poles of the dipoles, by hydrogen bonding with the solvent was attributed as the cause. This particular work, although explained in greater detail is however less relevant than the previous examples. It should be noted however that the results obtained in this work differ considerably from all the above examples in one major aspect; that is in the degree of deactivation at the functional site. None of the above cited examples or other works noted such extreme behaviour.

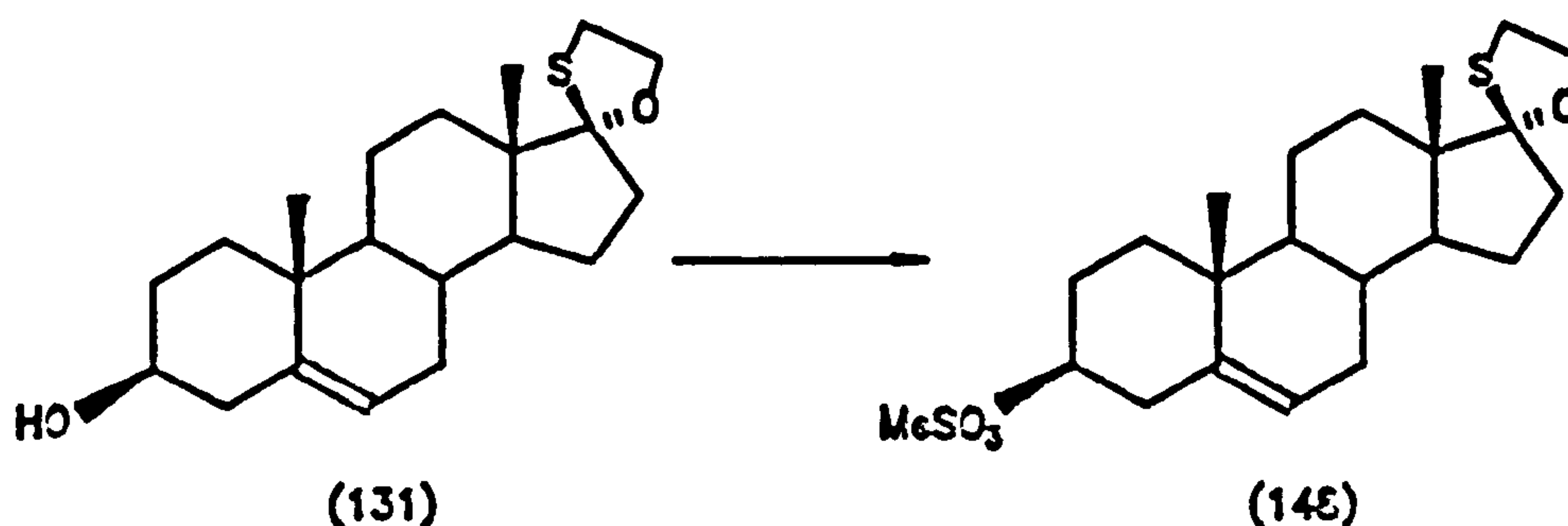
With respect to conformational adjustments, molecular studies on the thioxalane (131) and DHEA (97) have shown that the two structures do not readily differ from one another (Chapter 6). However, if small differences between the compounds is sufficient to cause the observed effect these would not be readily detectable. Indeed, if the cause is novel, a molecular model may be essentially useless as the minimiser would not take that cause into account when defining the structure of the oxathiolane!

Further studies of the reactions between the steroid (131), and the reagents triflyl chloride ($\text{CF}_3\text{SO}_2\text{Cl}$), brosyl chloride ($p\text{-BrC}_6\text{H}_4\text{SO}_2\text{Cl}$), tosyl chloride ($p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$) and mesylchloride ($\text{CH}_3\text{SO}_2\text{Cl}$) could shed some light on whether the observed results were caused by steric or electronic effects by virtue of the sulphonating reagents' size and electrophilicity. From the above limited studies, the idea

that the deactivation of the 3-C hydroxy group is as a result of intermolecular complexation in solution is more germane but without the further studies suggested it is perhaps unwise to judge whether the overriding factors are sterically or electronically based. Indeed, the results may be an effect of σ -conjugation, a phenomenon recently theorised⁴² to be present in all saturates, which is enhanced by the subtle geometrical changes induced by the oxathiolane group.

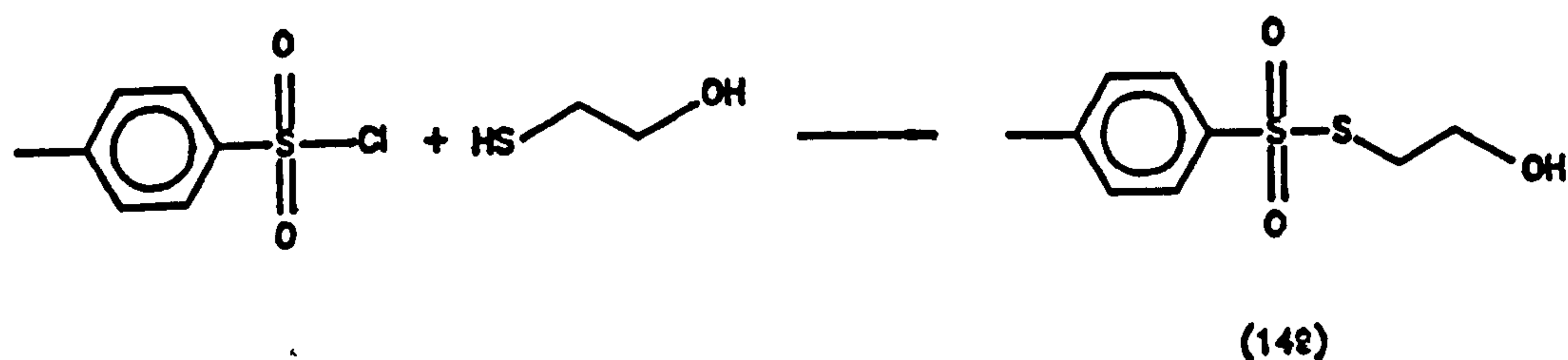
3.3.6 Formation of 3 β -mesyl-5-androsten-17(S)-spiro-2'-(1,3-oxathiolane) (148).

As already mentioned an alternative to the sulphonating agent tosyl chloride is methane sulphonyl chloride (mesyl chloride) which was utilised because of its greater reactivity observed in the mesylation of DHEA. When mesyl chloride



was reacted with the oxathiolane steroid the reaction was found to proceed very slowly. After 24 hours isolation of a small quantity of the reaction mixture gave an off white solid which when subjected to tlc indicated two products. After a total of 48 hours however the reaction was complete with tlc showing no trace of the slower moving starting material. Depending on the particular sample, the product occasionally required recrystallisation to remove traces of

the product of the reaction between β -mercapo ethanol and the mesyl chloride. (The thiol was often present in vary small quantities because small traces did not effect the yields considerably and purification by repeated recrystallisation of (131) or preparative tlc considerably reduced the overall yield.) Because of these losses, incurred during recrystallisation of the starting material, an attempt to chemically alter the impurity (and hence improve purification), by the addition of a small quantity of tosyl chloride was made. This, as discussed, would not react with the thioxalane steroid (131) but any β -mercaptoethanol present would hopefully react to give a product differing considerably in its physical properties (149). However this attempt to form a more easily removable impurity was abandoned because a "pilot" reaction between the thiol and the tosylate (1:1 ratio) did not give a single product (149), but a complex



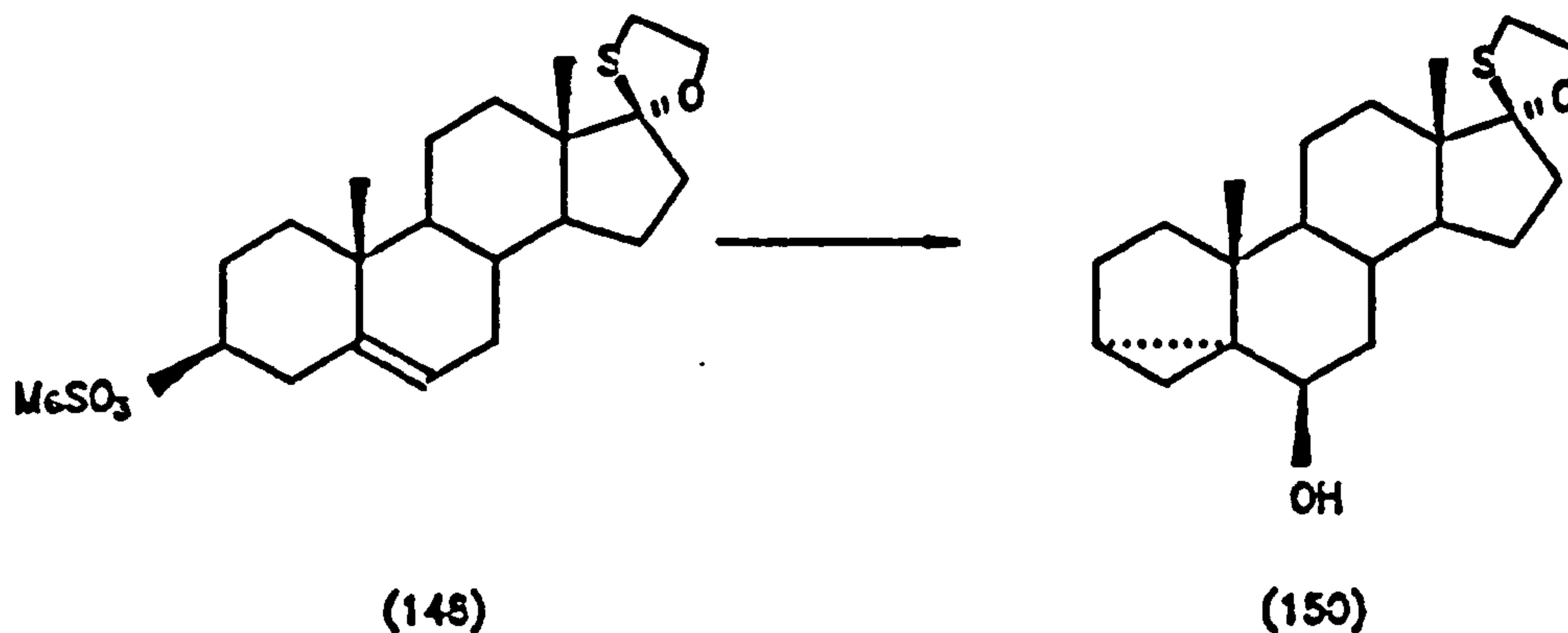
mixture of both mono tosylated, ditosylated and apparently cyclic compounds. This complex mixture, if formed in the steroid solution would therefore be unsuitable for fractional crystallisation experiments and the idea was dropped.

The pure mesylate, an off white solid, was readily identified by spectroscopic techniques. The ¹HNMR spectrum showed a 3H singlet at $\delta = 3.00$ which suggested the successful substitution of the hydroxy hydrogen with a mesylate

group. Indirect evidence was the down field shift of the 1H broad signal associated with the α -hydrogen at 3-C and the 1H doublet, assigned to the delta 5 double bond, to $\delta = 5.43$. The IR spectrum of the product showed no absorption associated with a hydroxy group. Additional strong absorption at 1340 cm^{-1} were allocated to the R-SO₃-R stretching frequencies. A very weak carbonyl signal was also evident in the product but its strength, as was expected, was considerably weaker than in the spectrum of the resultant mesylation product of the dioxolane steroid (137b). As with the other oxathiolanes produced, the compound showed the characteristic loss of the moiety C₅H₇OS, m/z = 115 (138) in its mass fragmentation pattern.

3.3.7 Formation of 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17(S)-spiro-2'- (1,3-oxathiolane) (150).

The sulphonated steroid (148) was cyclised by the preferred cyclisation conditions of aqueous acetone buffered with potassium acetate. Rearrangement predominately occurred but significant traces of the 3 β -hydroxy compound (131) were often present. Flash column chromatography, gave the desired 3,5-cyclosteroid (150).



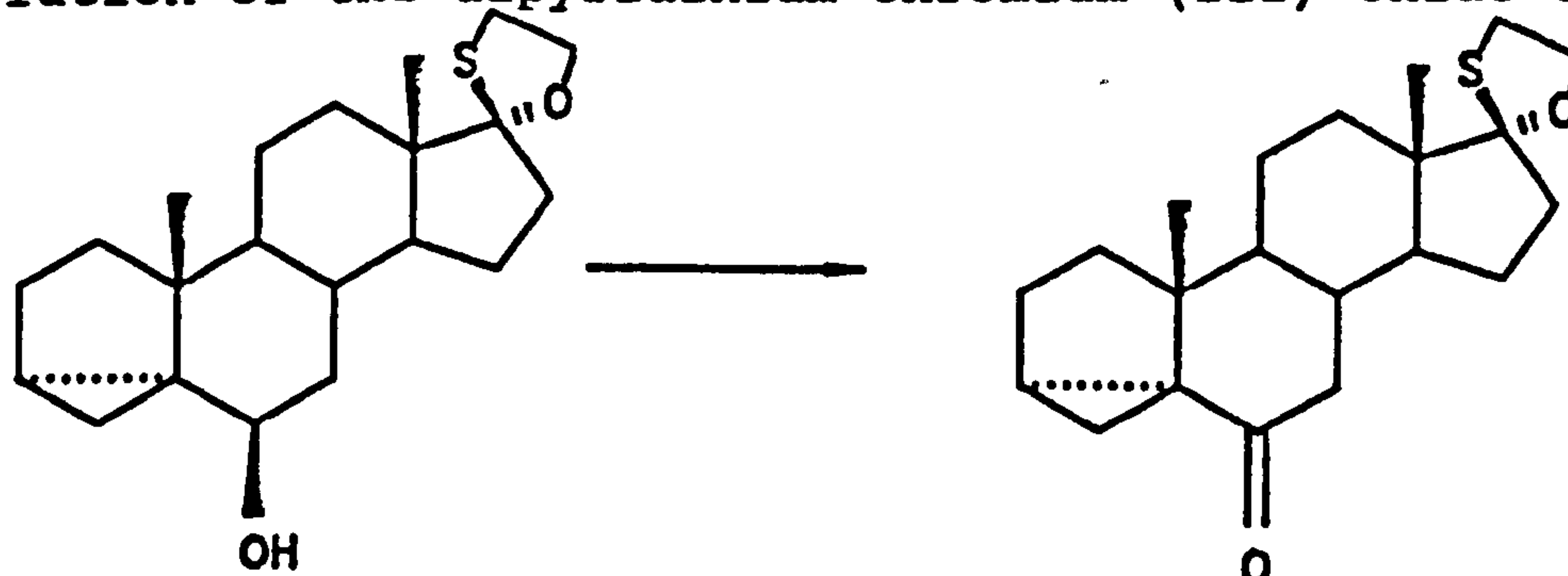
The ¹H NMR of the product showed the expected complex

pair of peaks centred at $\delta = 4.05$ and 2.85 associated with the oxathiolane protecting group. Situated between these two signals was a 1H triplet at $\delta = 3.32$ corresponding to the 6-C equatorial hydrogen. Evidence of the presence of the cyclopropane ring was found in the highfield region as a 5 peak multiplet centred at $\delta = 0.35$. The signals corresponding to the two methyl groups appeared as 3H singlets, with the 19-methyl signal being shifted slightly downfield, by the σ -aromaticity of the cyclopropane ring^{42,43} to $\delta = 1.08$. The axial 6β hydroxy group also causes a downfield shift in this signal.⁴⁴ The IR of the product showed strong OH absorption as well as strong C-O-C absorption. Cyclopropane signals were, in general very difficult to identify in this compound. In the mass fragmentation pattern of this compound, the strongest peak, as with the other oxathiolanes studied, was that with a mass of 115, corresponding to fragment (138). The parent ion ($m/z = 348$) and daughter products; $m/z = 288$, loss of SC_2H_4 , $m/z = 270$, loss of water and $m/z = 254$, subsequent loss of oxygen were also visible.

As very little breakdown of the protecting group occurred over the two steps described above, the method therefore provided an improved route to a 17-C protected 3,5-cyclosteroid.

3.3.8 Formation of 6-oxo-3 α -5-cyclo-5 α -androstande-17(S)-spiro-2'-(1,3-oxathiolane) (151).

The conversion of the 6 β -alcohol to the relevant keto compound (151) was performed using Collins' Reagent,⁴⁵ i.e., a solution of the dipyridinium chromium (III) oxide complex



(150)

(151)

in dichloromethane (for a discussion of chromium III oxidation see Chapter 2). This reagent was formed in a similar manner to the method described by Ratcliffe.⁴⁶ This involved, the careful addition of CrO_3 to a solution of pyridine in dichloromethane. The reverse, i.e., the addition of pyridine to a stirring mixture of chromium trioxide in dichloromethane is not recommended because of the likelihood of fire. After the passage of one hour the steroid was then added to the burgundy coloured mixture as a solution in dichloromethane. The first attempt at this reaction used the recommended⁴⁴ six fold excess excess of reagent, at 25° and a reaction time of 30 minutes for the conversion of bicyclic steroid analogue alcohols to aldehydes or ketones. This resulted in a partial breakdown of the 17-C oxathiolane protection group, which was attributed to the presence of small quantities of chromium trioxide (CrO_3). In an effort to prevent this, the reagent mixture was allowed to settle after being stirred for the 1 hour, and the "clear" burgundy

solution decanted into a clean flask. Degradation of the protecting group was still found to occur however so a series of reactions where the variables, temperature, time and reagent:steroid ratio were independently changed were undertaken. The results of the experiments are shown in Table 1. The % degradation of the protection group was estimated by a comparison of the two IR spectra of the starting material and the product, and comparing the % transmissions of the relevant 17-C carbonyl signals. The % conversion of the 6-alcohol group was estimated by comparing the relevant strengths of the NMR signals of the proton geminal to the hydroxy group. The reaction time for the first set of reactions was a constant 15 minutes.

Table 1

Estimation of percentage degradation of the oxathiolane protecting group during oxidation of 6-hydroxy group in (150).

<u>Ratio, reagent: steroid</u>	<u>% DEGRADATION</u>	<u>% OXIDATION</u>
12:1	30	100
10:1	20	100
8:1	15	100
6:1	10	100
4:1	< 5	80
2:1	0	60

From these results, the 2:1, 6:1 and 12:1 ratios were chosen for the next set of reactions as these represented

the best result (6:1) and the two extremes. On this occasion the contact time of the reactants was adjusted. The results are shown in Table 2.

Table 2

Estimation of percentage degradation of the oxathiolane protecting group during oxidation of 6-hydroxy group in steroid (150) during variation in reaction period.

<u>Reaction time (mins)/ ratio, reagent: steroid</u>	<u>% DEGRADATION</u>	<u>% OXIDATION</u>
15/ 12:1	30	100
8/ 12:1	25	100
4/ 12:1	10	>95
2/ 12:1	< 5	90
30/ 6:1	20	100
15/ 6:1	10	100
8/ 6:1	< 5	100
4/ 6:1	< 5	90
2/ 6:1	0	75
30/ 2:1	20	> 90
20/ 2:1	< 5	75
15/ 2:1	0	60

From these results it became apparent that in agreement with Ratcliffe,⁴⁶ a 6:1 ratio of reactant to alcohol was the most successful combination of reagent and alcohol. However, the reaction time of 30 minutes was too great for this particular system. (Note that although the 12:1 ratio over a 2 minute period also gave good results the reaction time was

considered too short for practical purposes). In a final bid to improve the yield of product even further, a chosen set of reaction conditions, i.e., the results obtained from the reactions utilising a 6:1 ratio were repeated but with the temperature at 0° instead of 25°. These results are shown below in Table 3.

Table 3

Estimation of percentage degradation of the oxathiolane protecting group during oxidation of 6-hydroxy group in steroid (150) during variation in reaction temperature.

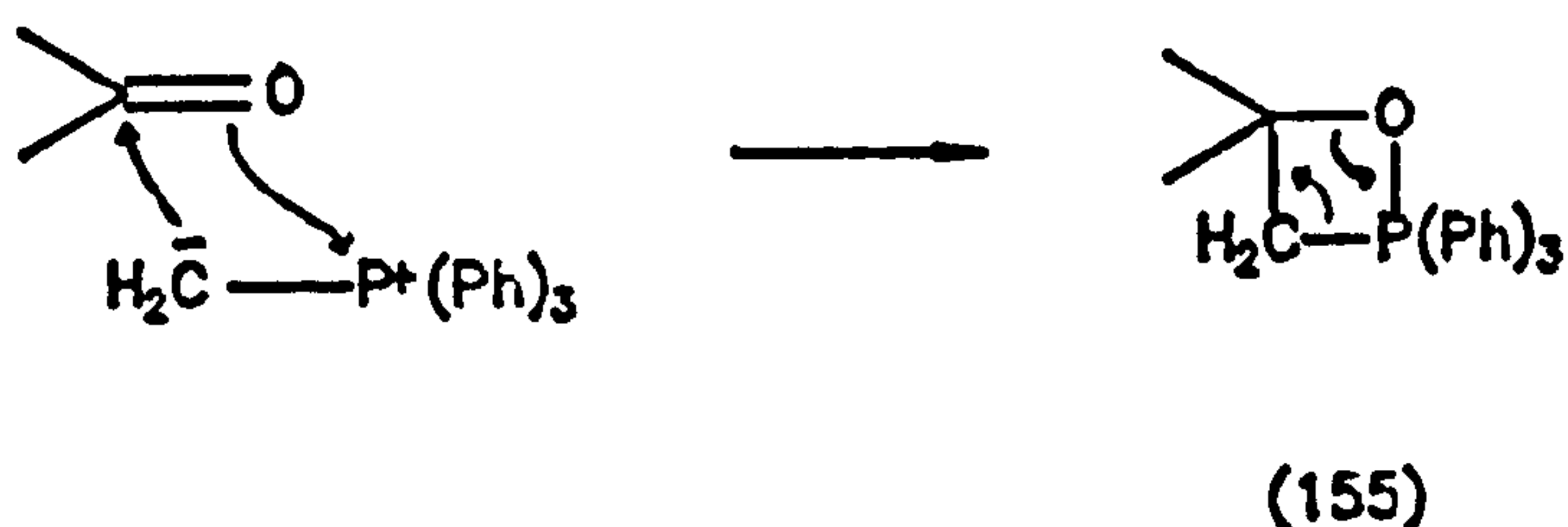
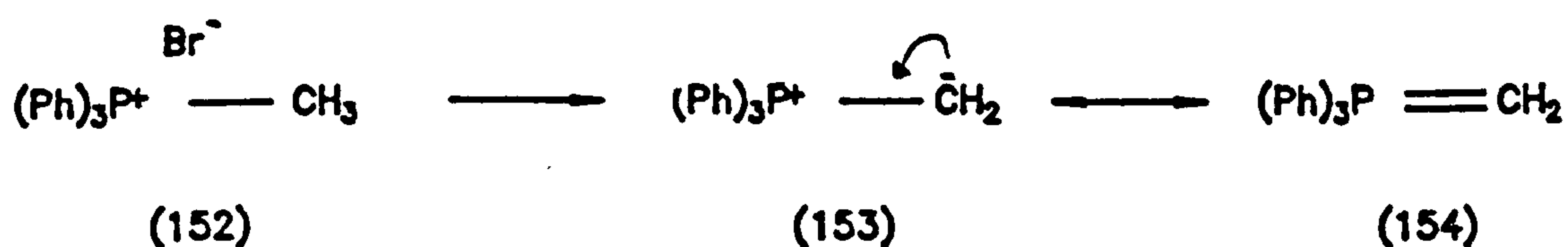
<u>Reaction Time (minutes)/</u> <u>Temperature (°)</u>	<u>% DEGRADATION</u>	<u>%OXIDATION</u>
30/ 0°	10	100
25°	20	100
15/ 0°	< 10	> 95
25°	10	100
8/ 0°	< 5	90
25°	< 5	100
4/ 0°	0	75
25°	< 5	90

From these final results it was clear that the best conditions were a reaction at room temperature with a 6 fold excess of reagent over a period of 8 minutes. After this time the product was worked up in an similar manner used by Ratcliffe.⁴⁶ The clear yellow oil was then subjected to preparative tlc and the pure product isolated as an off white solid and recrystallised as fine, colourless crystals. As well as a trace of the alcohol (150), the only other major product isolated was a small proportion of the dione

(111). The $^1\text{H NMR}$ of the product whilst showing the expected peaks associated with the protecting group possessed no signal between these indicating the removal of the 6-C α hydrogen. Evidence of the conversion of the alcohol to the ketone group was also noted in the position of the absorption signals of the cyclopropane ring protons which were shifted downfield so that only the 3-H cyclopropyl proton were observable. The shifting of the 4-H protons signal into the body of the methylene envelope probably being caused by the approximate planar configuration of the C(4)-C(5)-C(6)-O(6') moiety (Chapter 2). Evidence of conversion was also found in the IR spectrum of the product with the appearance of a strong carbonyl absorption at 1678 cm^{-1} . In contrast to the alcohol, the cyclopropane C-H stretching bands were distinct at 3115 , 3020 and 2990 cm^{-1} . The IR finger print region of the product was generally quite weak apart from the distinctive strong band attributed to the C-O-C bond in the oxathiolane moiety. The mass fragmentation pattern of the compound showed the parent ion ($m/z = 346$) as a weak feature. Obvious daughter products from this ion were $m/z = 318$, corresponding to the loss of carbon monoxide and $m/z = 303$ corresponding to the subsequent loss of a CH_3 group. The loss of carbon monoxide is also indicative of the presence of the 6-C carbonyl group. The strongest ion was again at 115 attributed to fragment (138). Loss of the elements of water, a feature of the mass fragmentation of cyclopropane ketone steroids,⁴⁶ was not a noticeable feature.

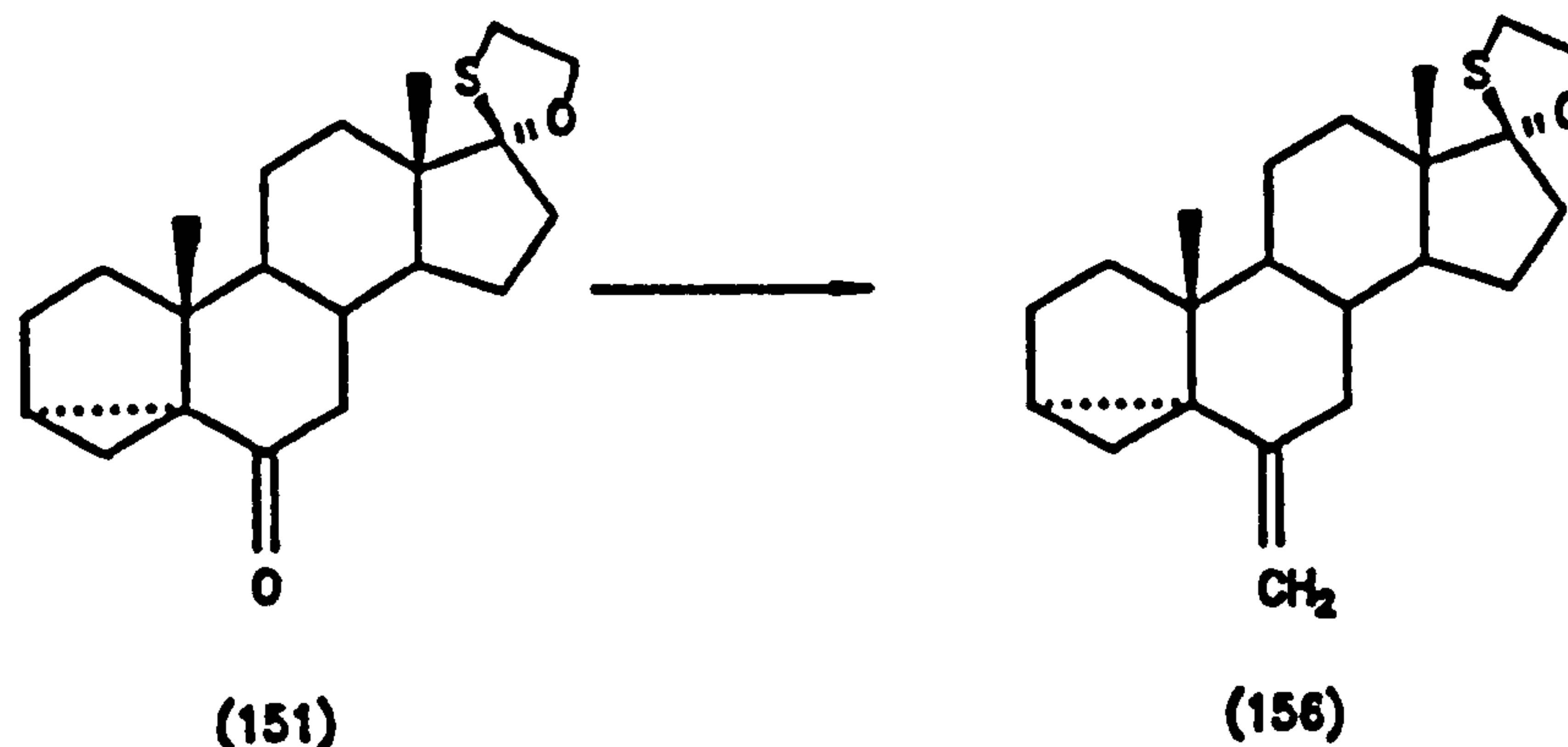
3.3.9 Formation of 6-methylene-3 α ,5-cyclo-5 α -androstande-17(S)-spiro-2'-(1,3-oxathiolane) (156)

The conversion of the ketone to the methylene derivative was attained via a Wittig reaction,⁴⁸ i.e., a reaction between a phosphorus ylide and the carbonyl group. (An ylide is a molecule that has a contributing Lewis structure with opposite charges on adjacent atoms when these atoms have octets of electrons.) The most commonly used method of preparation of a phosphorus ylide is by deprotonation of the phosphonium salt with a strong base. Thus, for the conversion required here, the triphenylphosphonium methylene ylide (153) was formed by the reaction between methyltriphenyl-



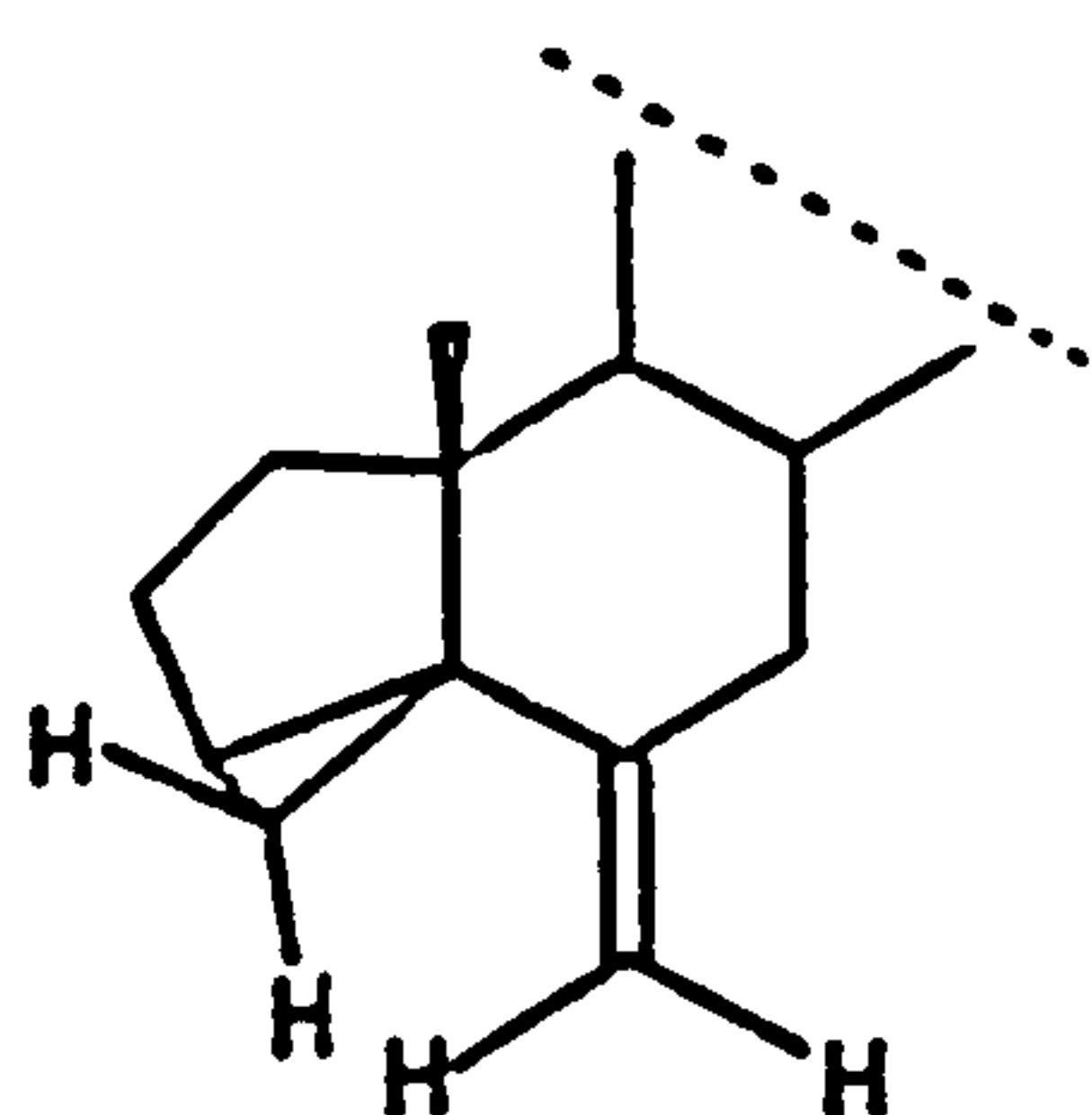
phosphonium bromide (152) and the strong base, *n*-butyllithium. This highly reactive species is generally ascribed to be stabilised by its other resonance form the ylene (154) but NMR studies involving ¹H, ¹³C and ³¹P are consistent with the dipolar form (153), indicating that the ylene form does not make a considerable contribution.⁴⁷ The proposed mechanism⁴⁹⁻⁵¹ of the reaction of an ylide with a ketone or an aldehyde (see below) is initiated with nucleophilic attack at the carbonyl carbon to yield a dipolar intermedi-

ate (a betaine), which because of the strong affinity between oxygen and phosphorus readily forms the four membered dihydrooxaphosphetane intermediate (155). The stronger phosphorus oxygen bond then dictates the breakdown of the intermediate, allowing the elimination of the phosphine oxide, and the formation of the methylene compound.

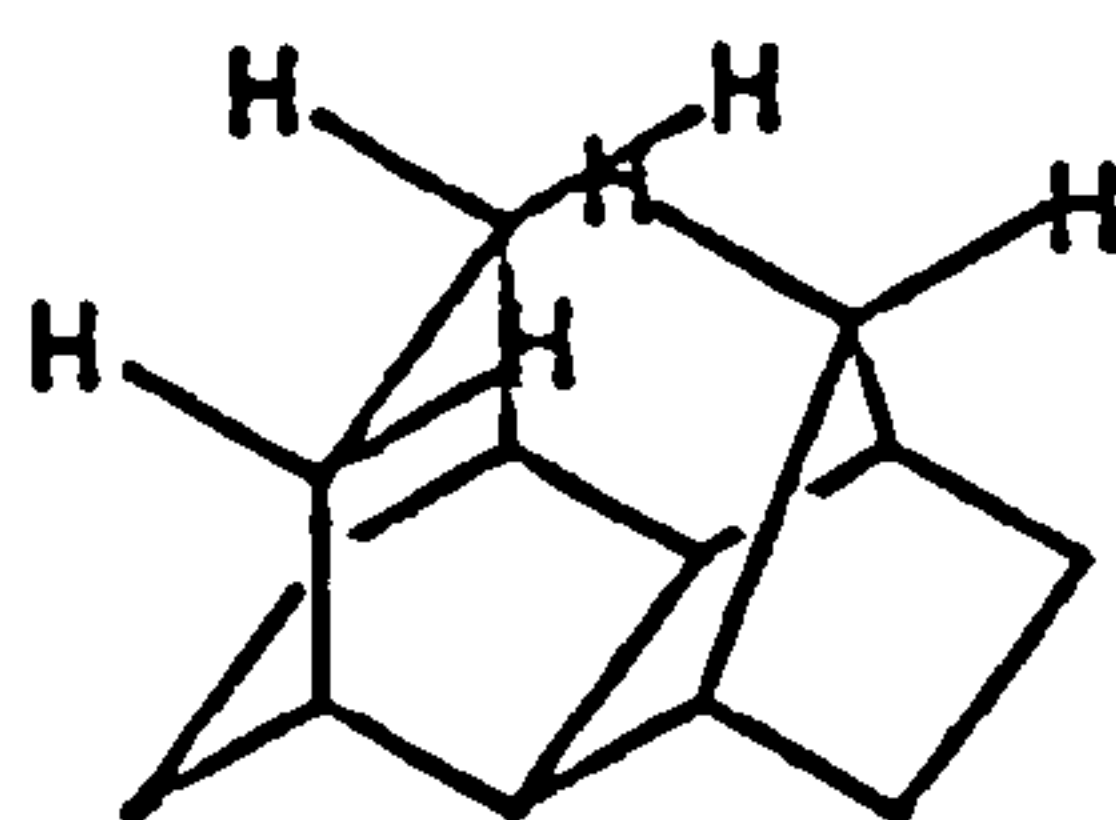


In a slightly modified method to that of Sondheimer,⁵² the steroid (151), was added as an ethereal solution to a 3 fold excess of triphenylphosphine-methylene, formed by the slow addition of triphenylphosphonium bromide to a stirring ethereal solution of n-butyllithium. Workup gave a clear oil which when subjected to preparative tlc give two white solid products. The major product was shown spectroscopically to be the desired 6-methylene derivative (156). The methylene group was evident in the NMR spectrum as a 2H doublet at $\delta=4.63$, similar to the signals attributed to the 7-methylene compound (171).⁵³ Resolution was not sufficient for coupling with the 7-H atoms to be detected. Also present was the complex multiplets associated with the oxathiolane group, identical to those signal in compounds (131), (148), (150) and (151). The presence of the methylene group however, shifted the 19-C methyl group signal upfield so as to coincide with the 18-C methyl signal and produced a 6H singlet

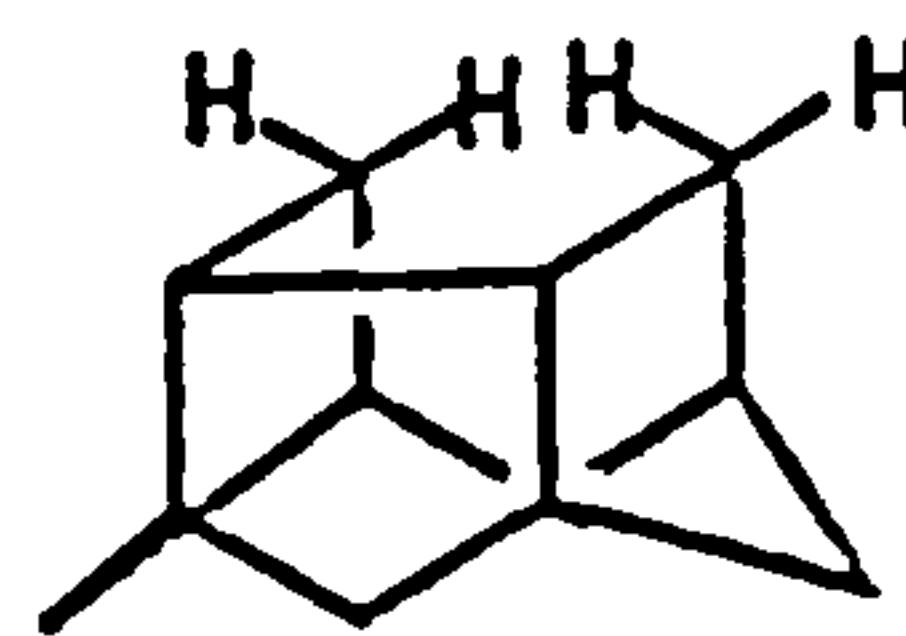
at $\delta = 0.85$. A similar coincidence effect is observed in the NMR spectrum of the delta-6 steroid (185), (see Chapter 4). Finally, the NMR signals produced by the 3-C cyclopropane hydrogen were shifted up field to $\delta = 0.38$ (triplet) indicating the removal of the stronger electron withdrawing carbonyl group but still the approximate planar nature of the cyclopropane and 6-C π -acceptor group. The IR spectrum of the compound showed, as with other cyclopropanes and alkenes, an extended C-H stretching envelope with sharp, well defined bands at 3080, 3065, 3015, 2990, 2985 cm^{-1} . These high frequency vibrations (c.f. 3 α ,5-cyclo-5 α -androst-6-ene-17-one (185)) are probably not only due to the strain involved in the 3 membered ring⁵⁴ or the methylene group, but also because of the interaction between the 4 α -H and the neighbouring methylene 6'-H (157). A similar effect is vividly shown by Kivelson *et al.*⁵⁵ in a study of the IR spectra of various fused bicycloheptanes e.g. (158) and other half caged structures such as (159). In a Drieding model of steroid (156), the distance between the two hydrogens is 1.8A. This distance is however greater when molecular mechanics studies are performed on the structure. These showed that the distance is approximately 2.10A. However, even this distance is considerably less than the normal Van



(157)



(158)

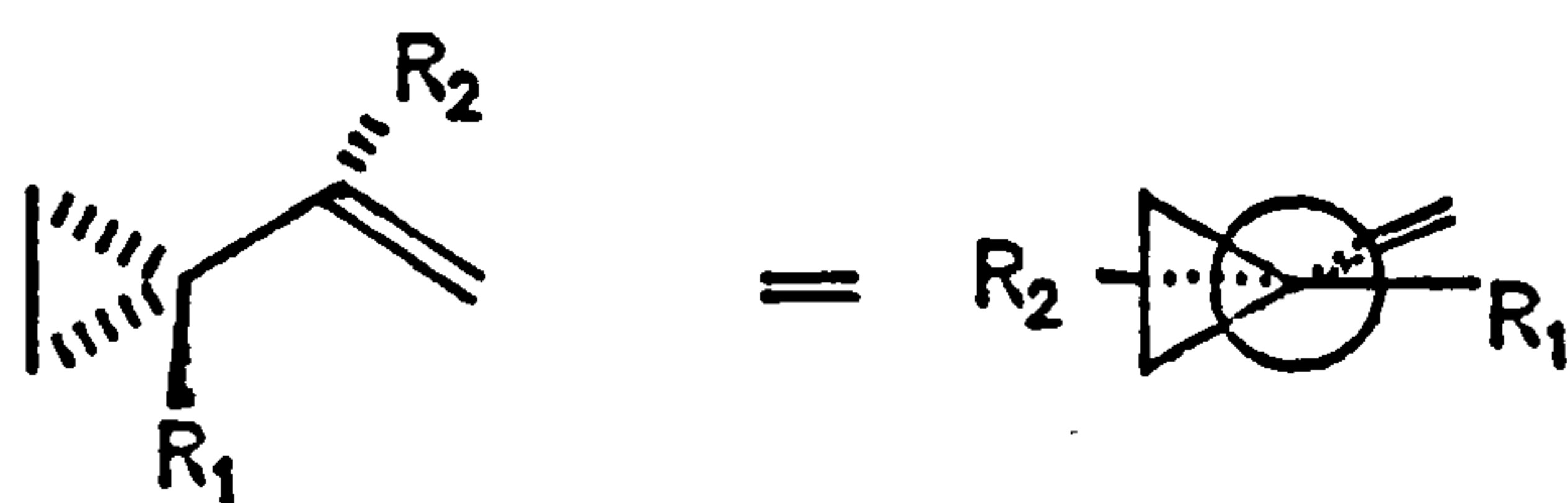


(159)

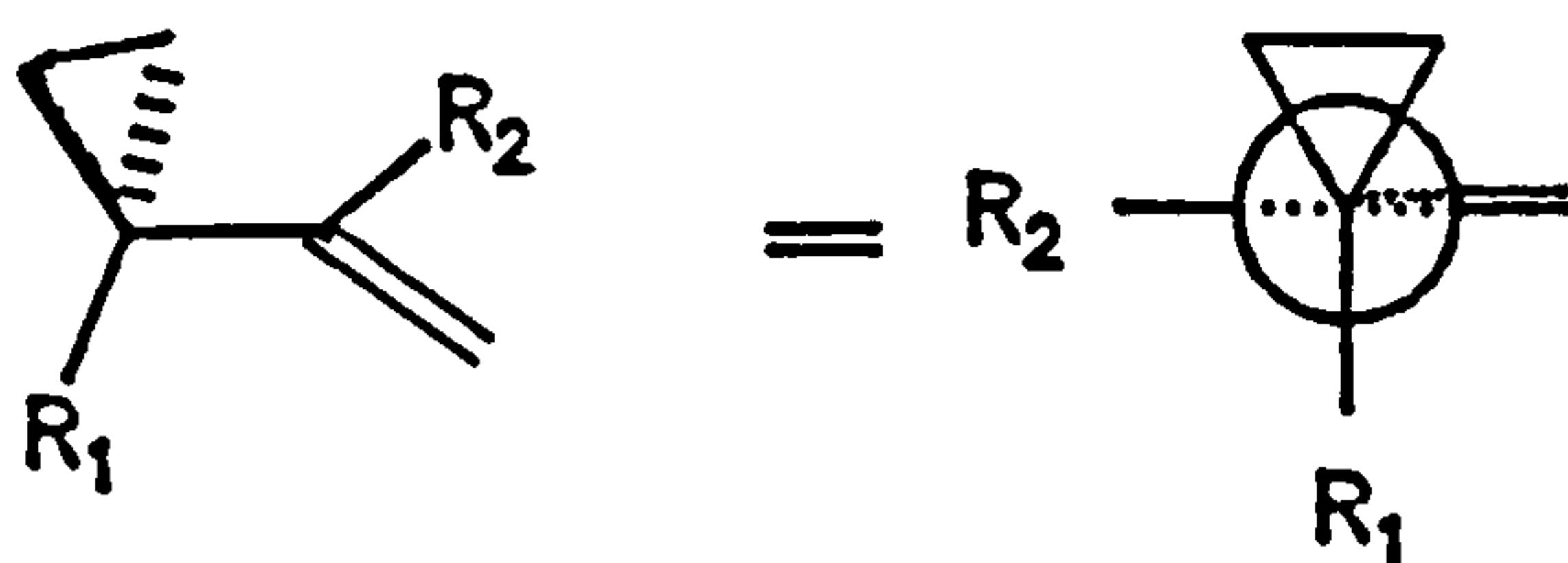
der Waals separation between two adjacent hydrogens (see Chapter 6). In the mass fragmentation pattern of this compound, the major daughter product from the relatively weak parent ion ($m/z = 344$) were found at $m/z = 329$ corresponding to the loss of a methyl group. As with the other steroidal oxathiolanes the major ion, ($m/z = 115$), corresponded to oxathiolane fragment (138).

3.3.10 6-Methylene-3 α ,5-cyclo-5 α -androstane-17(S)-spiro-2'-(1,3-oxathiolane) as a vinyl cyclopropane analogue.

When attached to a π -system, a cyclopropane ring is characterised as a strong π -donor. The interaction of the $3e'$ (r) Walsh (Huckel) orbital (see Chapter 2) with the π -system is maximal when the cyclopropane ring adopts a bisected (160) rather than a symmetric conformation (161) with respect to the adjacent π -system.⁵⁶ With the Walsh⁵⁷ model (see Chapter 2), this conformational requirement is readily

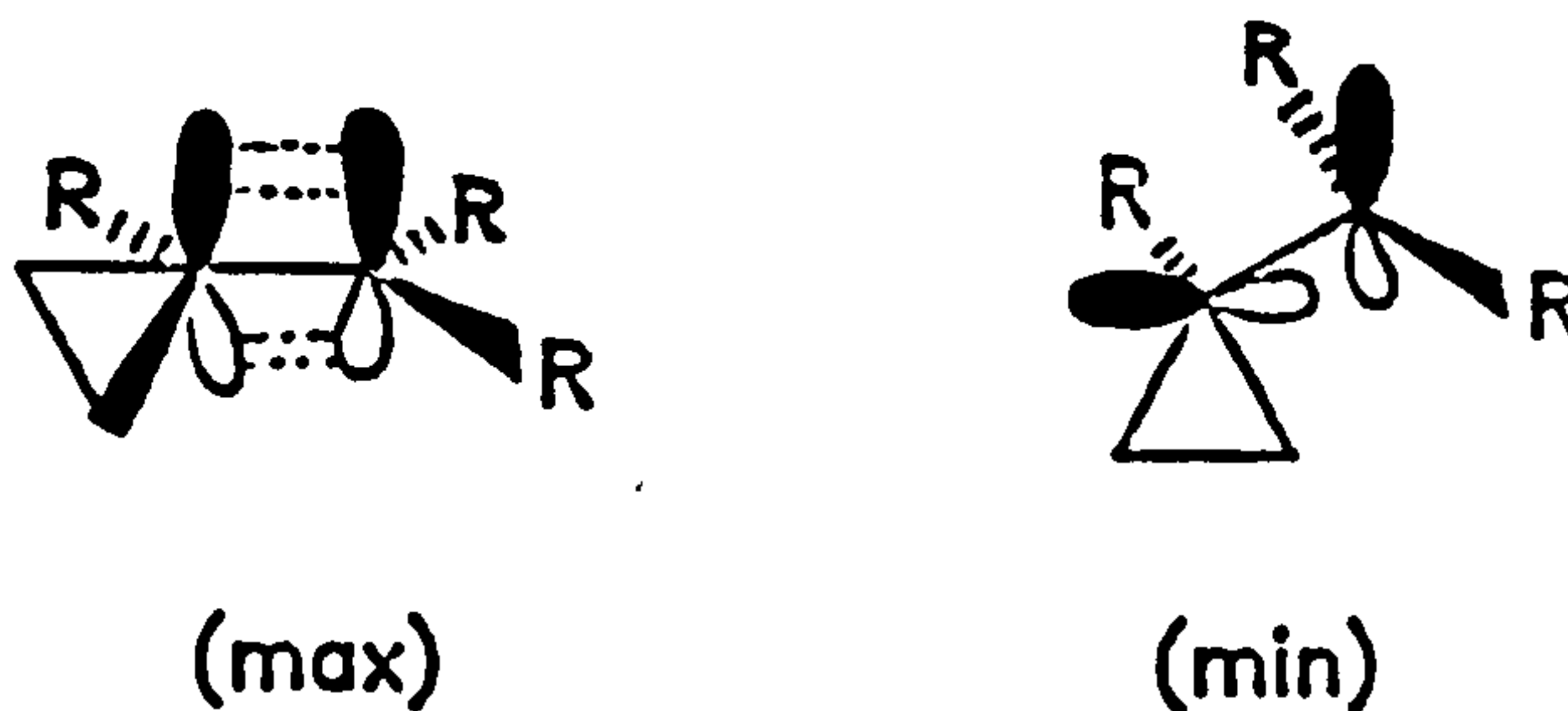


(160)



(161)

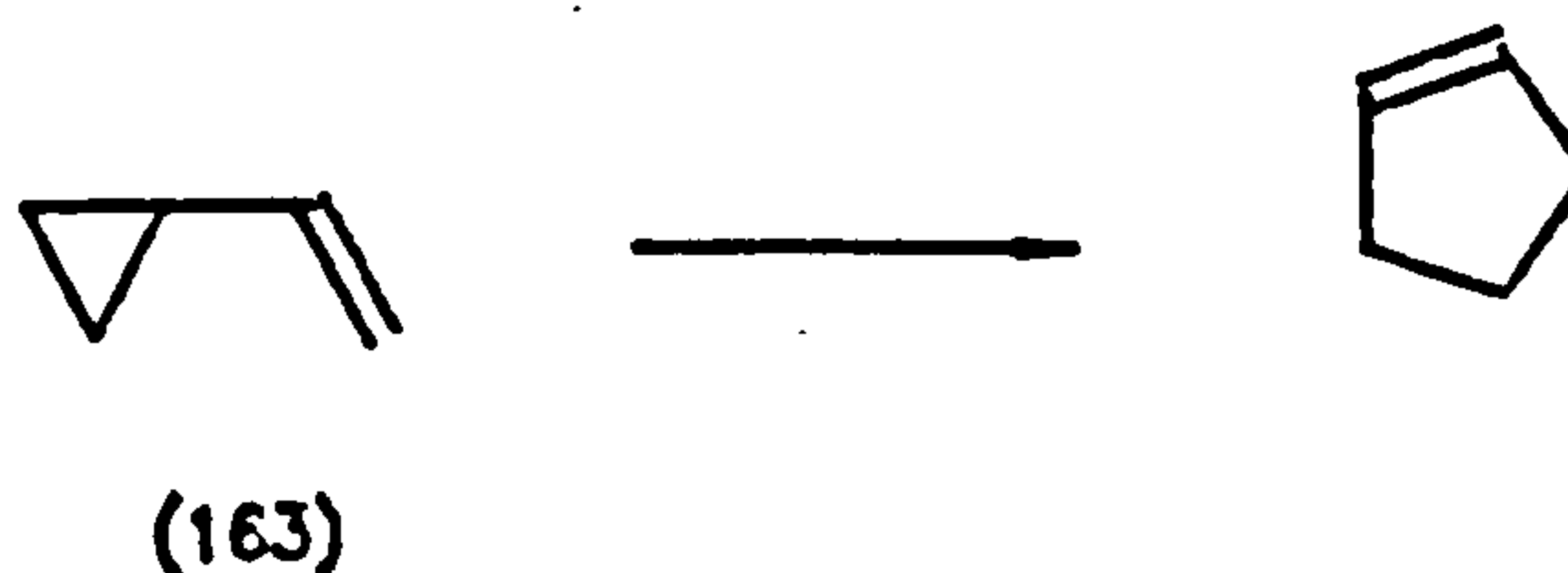
explained by considering the symmetry of the orbitals in a system such as (162). The bisected conformation allows maximum overlap between the p-orbitals of the cyclopropyl carbon and the adjacent π -system. Generally, this conformational



(162)

dependency is assumed⁵⁸⁻⁶³ and used to explain the unusual spectroscopic properties of such π -systems, but a small number of workers^{64,65} have provided evidence to the contrary, describing the cyclopropane ring as a "seat of high electron density whose polarisability is devoid of stereochemical bias".⁶⁵ This can possibly be attributed to the σ -aromatic nature of cyclopropane. Differences in conjugation have been attributed to ring strain⁶⁶ altering the p character of the relevant carbon atoms.⁶⁷

Obviously, the chemical properties of cyclopropanes are greatly altered by conjugation with adjacent pi-systems. Vinylcyclopropane (VCP) (163) undergoes unimolecular rearrangement to yield cyclopentene when heated.⁶⁸⁻⁷¹ The mechanism and stereochemistry of this rearrangement have been

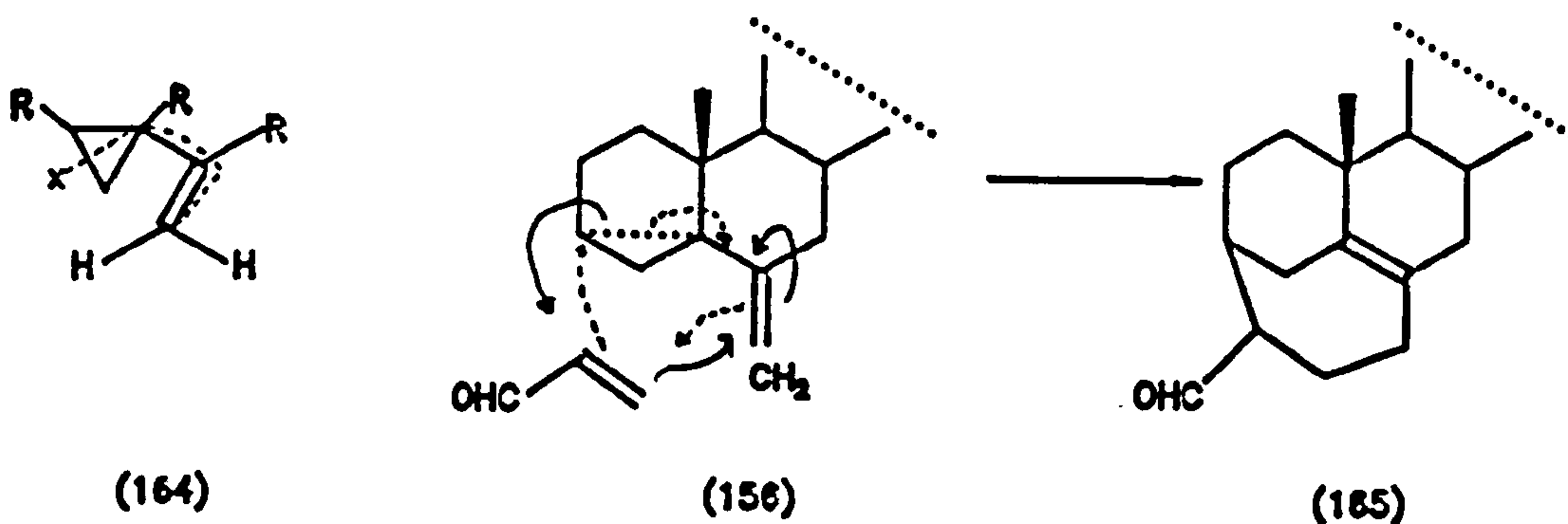


discussed intensively⁷² and the potential of this structurally interesting 6-methylene steroid to undergo a series of reactions (for example, the system X-C(5)-C(6)-C(6'), where X is the mid-point of the C(3)-C(4) bond, possesses a remarkably geometrical similarity to 1,3-butadiene) is worth mentioning (164). Thus, the cyclopropane ring, whether considered as σ -aromatic or to be in the $sp^{2.2}$ hybridised state⁶⁰ can (if it is allowed to assume the correct geometry) conjugate with the vinyl group and thus enable the compound to undergo many interesting reactions.⁵⁸ These include Diels Alder type reactions to yield 5 ring steroid analogues such as the theoretical product (165) of the reaction of (156) with acrolein. This ability is dependent on the ability of the vinyl cyclopropane moiety to conjugate, a property assumed here to be conformationally dependent, and is discussed below.

3.3.11 Conjugation in 6-methylene-3 α ,5-cyclo-5 α -androsterane-17(S)-spiro-2'-(1,3-oxathiolane) (156).

A measure of the degree of overlap of the orbitals of the cyclopropane carbons and the vinyl carbons (and thus the system's ability to conjugate) can be found in the determination of the torsion angle X-C(5)-C(6)-C(6'), where X is the midpoint of the C(3)-C(4) bond (164). Allan⁵⁹ calculated that this angle should be within $\pm 30^\circ$ of the cis (0°) or trans (180°) bisected conformations (162) which allow for maximum overlap and therefore maximum conjugation between a cyclopropane ring and the π -acceptor substituent. Other angular values suggest that conjugation is somewhat reduced

(although still apparent). X-ray crystallography would have provided valuable information concerning possible conjugation, however, suitable crystals were not obtained and therefore molecular mechanics were undertaken as an alternative source of information.



The molecular mechanics model of this compound (see Chapter 6) is however of limited use because the programme does not contain the cyclopropane carbon, either as a σ -aromatic or a $sp^{2.2}$ hybridised atom, in its range of atom types. More importantly, any minimisation will not recognise the potential overlap of cyclopropane orbitals with those of the π -acceptor group; for this quantum mechanics modelling would be required. A model was however created and its structure analysed because it was realised, from a Drieding model, that a considerable non-bonded repulsion may exist between the 4-H and 6'-H. Thus by creating a model with a torsion angle X-C(5)-C(6)-C(6') of 0° (cis-bisected) and reducing, in steps, the structure's overall energy until a minimum was reached, it became apparent that there was a proportional relationship between the separation of the hydrogens at positions 4 and 6' and the energy of the molecule. The minimised structure was attained when the torsion angle X-C(5)-C(6)-C(6') reached 60° . From this it would

therefore seem reasonable to assume that there probably exists in this compound, a conflict between the maximum overlap of the conjugating orbitals and a minimisation of the steric repulsion between the 4 and 6' hydrogens for the molecule to attain a preferred and minimised structure.

As pointed out, the programme in attaining the derived structure, could not take into account the possible overlap of orbitals and therefore resulted in a model based purely on steric hindrance. However, the torsion value obtained (60°) may be considerably reduced by stabilisation derived from increased conjugation. To help ascertain the correct structure and so determine if the system is totally dominated by the steric repulsions or if the overlap of orbitals do contribute to the compound's structure further information must be obtained. Thus the experimental data obtained in this work was compared to those of other structures.

Spectral Evidence of Conjugation

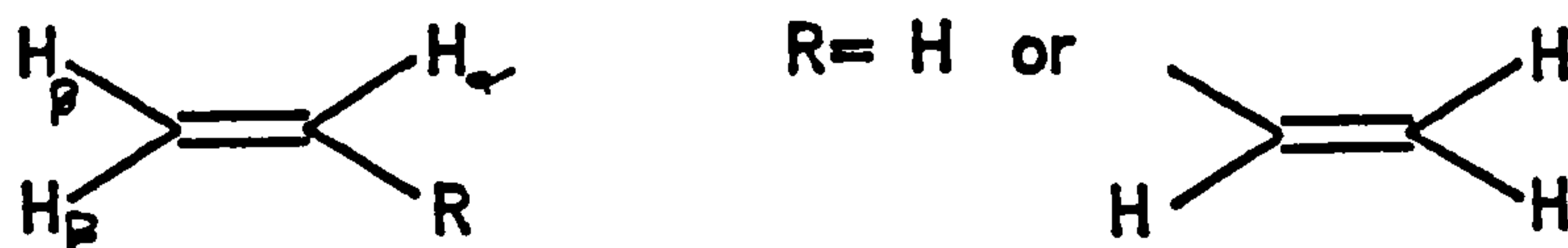
Ultra violet, IR and ^1H NMR spectral data all potentially offer a degree of insight into the system's ability to conjugate.

^1H NMR Spectroscopy.

A considerable amount of NMR work has been undertaken to study the preferred conformations of VCP. However not all of these methods are applicable to the methylene steroid (156). A study of, for example, the temperature dependence of the ^1H NMR spectrum of the compound, in a similar manner to the work of De Mare,⁷³ (who determined a three well

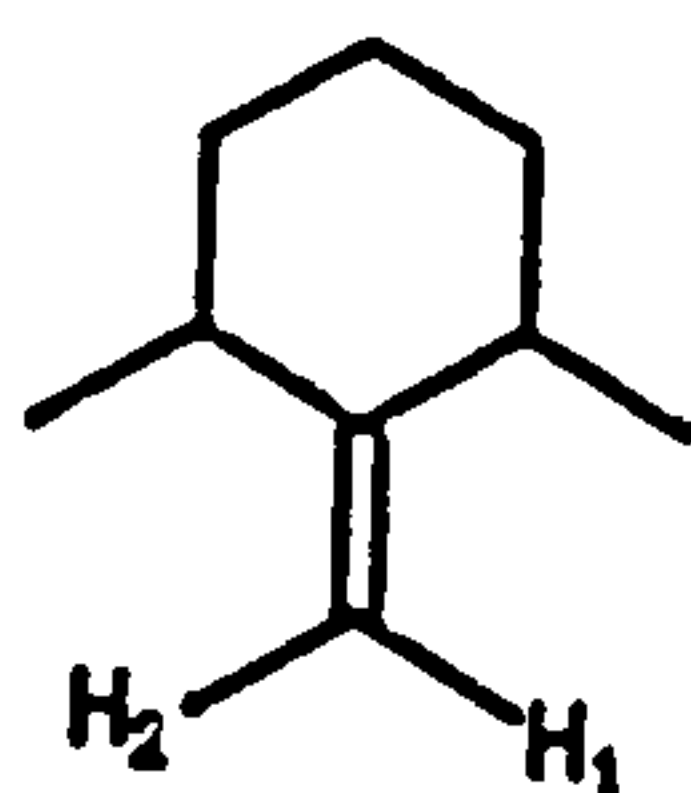
torsion potential and therefore the favoured structure, on the analogous, but free rotating, VCP) would probably yield limited information considering the geometrical restrictions of the system.

However, as the simple example below illustrates, an insight into the degree of conjugation can possibly be gleaned by the actual positions of the methylene signals on the NMR spectrum. The introduction of conjugation creates an upfield shift in the signal associated with the β hydrogen and a downfield shift in the α hydrogen's signal. Thus in structure (166) when $R = H$, both protons H_α and H_β resonate at $\delta = 5.28$. Where $R = CHCH_2$, H_α resonates at $\delta = 6.27$ and H_β resonates at $\delta = 5.06$.⁷⁴ The latter is an example of maximum conjugation. Where this is restricted by structural factors the corresponding shifts in the signals of the α and β hydrogens are diminished. Therefore a simple estimation of

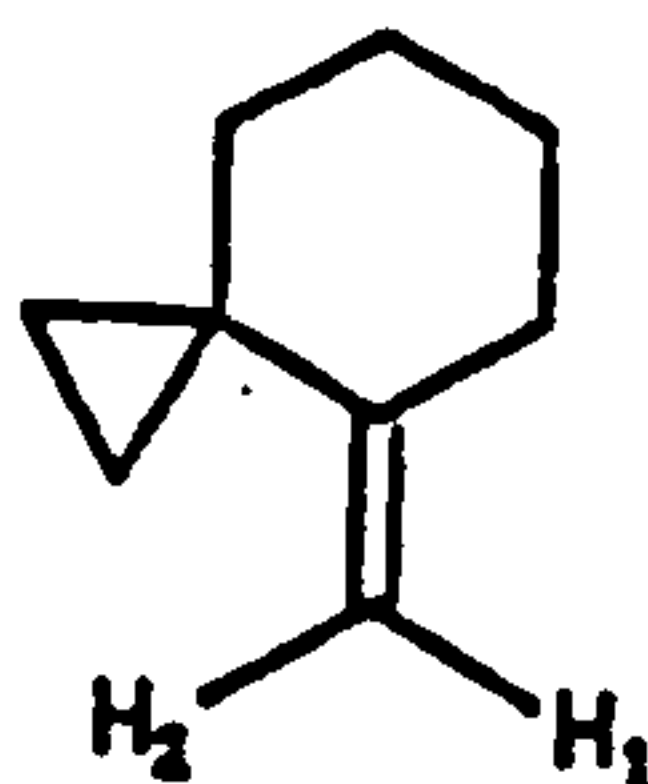


(166)

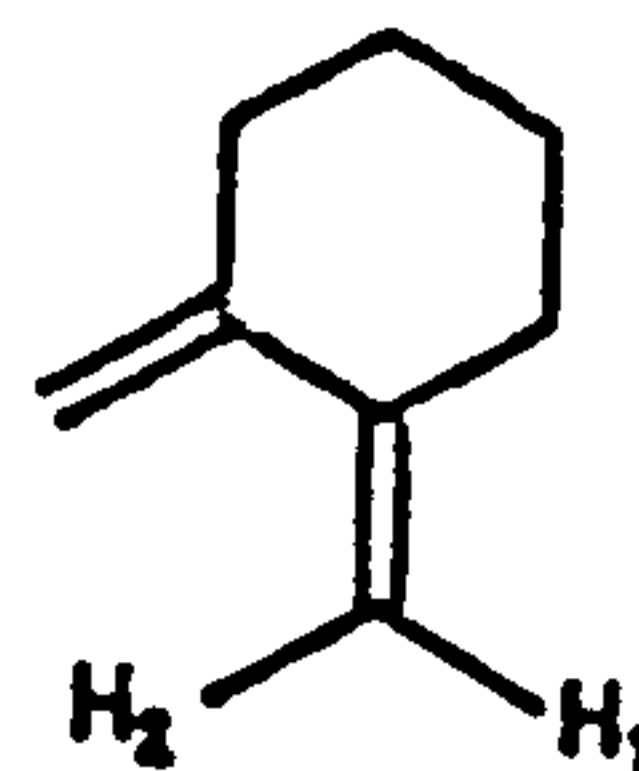
the conjugation could be attained by comparing the chemical shift values of the compound's methylene (β) hydrogens with similar compounds where the cyclopropane ring is substituted with other groups. Analogous steroid structures could not be found for this purpose therefore compounds possessing, 1) a methyl group and 2) a second methylene group, in place of the cyclopropane ring of partial structure (168) were used for comparative purposes. Thus the compounds, 2,6-dimethylmethylene-cyclohexane (167)⁷⁵ and 1,2-dimethylenecyclo-



(167)



(168)



(169)

hexane^{76,77} (169), were compared to the partial structure (168) of the cyclosteroid to give a series of structures of theoretically increasing conjugative ability. The results are shown in Table 4.

Table 4

¹HNMR chemical shifts values of " β -protons" of structures (167), (168) and (169).

<u>Structure</u>	<u>Chemical Shifts of β-protons (ppm)</u>	
	<u>H¹</u>	<u>H²</u>
167	4.51	4.51
168	4.69	4.57
169	4.83	4.55

Note that VCP (163) predominantly (75%) assumes the s-trans conformation⁷⁷ in solution and therefore its NMR data⁷⁹ cannot be compared to those of the steroid (156).

However, these results show that for these types of systems there can be no direct determination of the degree of conjugation based on the chemical shifts of the β -protons because the extremely "tight" s-cis or "homoannular" geometry of the systems (168) and (169) result in the methylene hydrogens experiencing a strong deshielding effect because of their close proximity to the other "half" of the system.

Furthermore, this closeness most certainly enhances the differences between the cyclopropane ring's σ -aromaticity character (see Chapter 2) and the alkene's sp^2 character. It could be said that the vinylcyclopropane system in the steroid does, to a certain degree, emulate conjugated double bonds by an overall deshielding of the methylene hydrogens but this is most certainly a through space effect rather than a direct effect of conjugation. However, it may be possible to circumvent these problems. Molecular models (Chapter 6) indicate that atom H_1 does not lie within the cyclopropane's σ -aromatic deshielding zone and therefore may be used as a more reliable indicator of conjugation. Also as both the conjugation and deshielding ability of an sp^2 atom are derived from that atom's sp^2 character, it is not unreasonable to assume that since the ability of system (168) to conjugate is "hidden" by the inherent deshielding effect of the system an estimation of the conjugation can be inferred from that deshielding effect. Considering the above 1H NMR data this would imply a relative conjugative ability (with respect to the dimethylene system (169) (which is itself not 100% conjugated⁷⁴) of approximately 50%. This compares to the estimated maximum conjugation value for VCP (163) of 71%⁷⁹ where free rotation of the cyclopropane ring pi-acceptor system allows a planar configuration and hence maximum conjugation. In the steroid however, the steric effects between 4-H and 6'-H push the moiety away from the preferred planar configuration leading to a torsion angle X-C(5)-C(6)-C(6') greater than 30° and reduced conjugation.

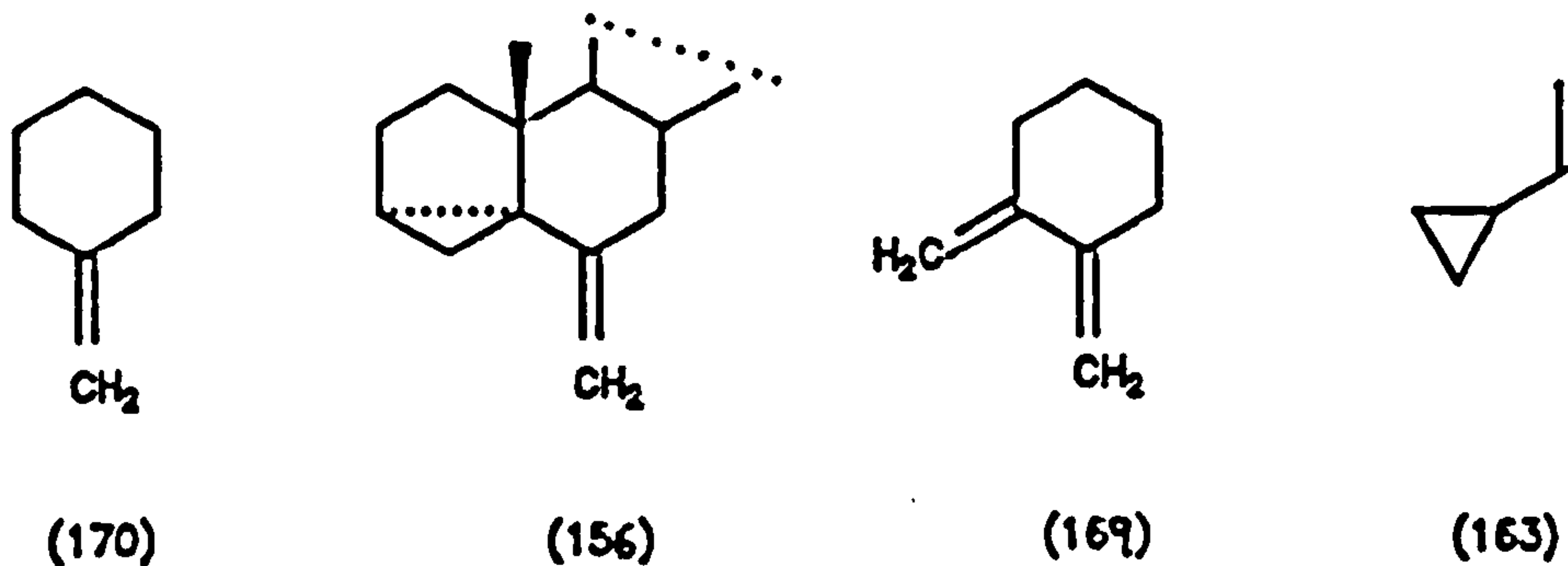
Ultra Violet Spectroscopy.

A comparison of the U.V. spectrum of the steroid with VCP, the non-conjugated methylene cyclohexane (167) and 1,2-dimethylene cyclohexane (169) could not really offer an insight into the amount of conjugation present because of the poor quality of the spectrum. However, even if a suitable spectrum was obtained the extra strain involved in the fused ring system, compared to the strain found in monocycles (e.g., (167) and (169)), would drastically alter the UV spectrum of a group. A search for more suitable model steroids was not successful.

IR Spectroscopy.

A better insight into the conjugation of this system can be found in the IR spectrum of the product as field differences such as in for example, the steroid (156) and VCP (163), have smaller effects on these spectroscopic values. The C=C vibration of the steroid's methylene group occurs at 1642 cm^{-1} . This compares to 1651 cm^{-1} for the non-conjugated methylene cyclohexane⁸⁰ (170), 1639 cm^{-1} for vinylcyclopropane (163)⁸¹ and 1635 cm^{-1} for the dimethylene compound (169).⁸² Thus by this spectroscopic technique, the methylene steroid (156) possesses approximately 50% of the conjugation of the dimethylene compound (169). The data also illustrates the slightly reduced conjugation in the steroid as compared to VCP itself, most certainly because of the repulsive forces between the $4\alpha\text{-H}$ and its neighbouring 6-methylene hydrogen.

The above data would therefore seem to indicate that



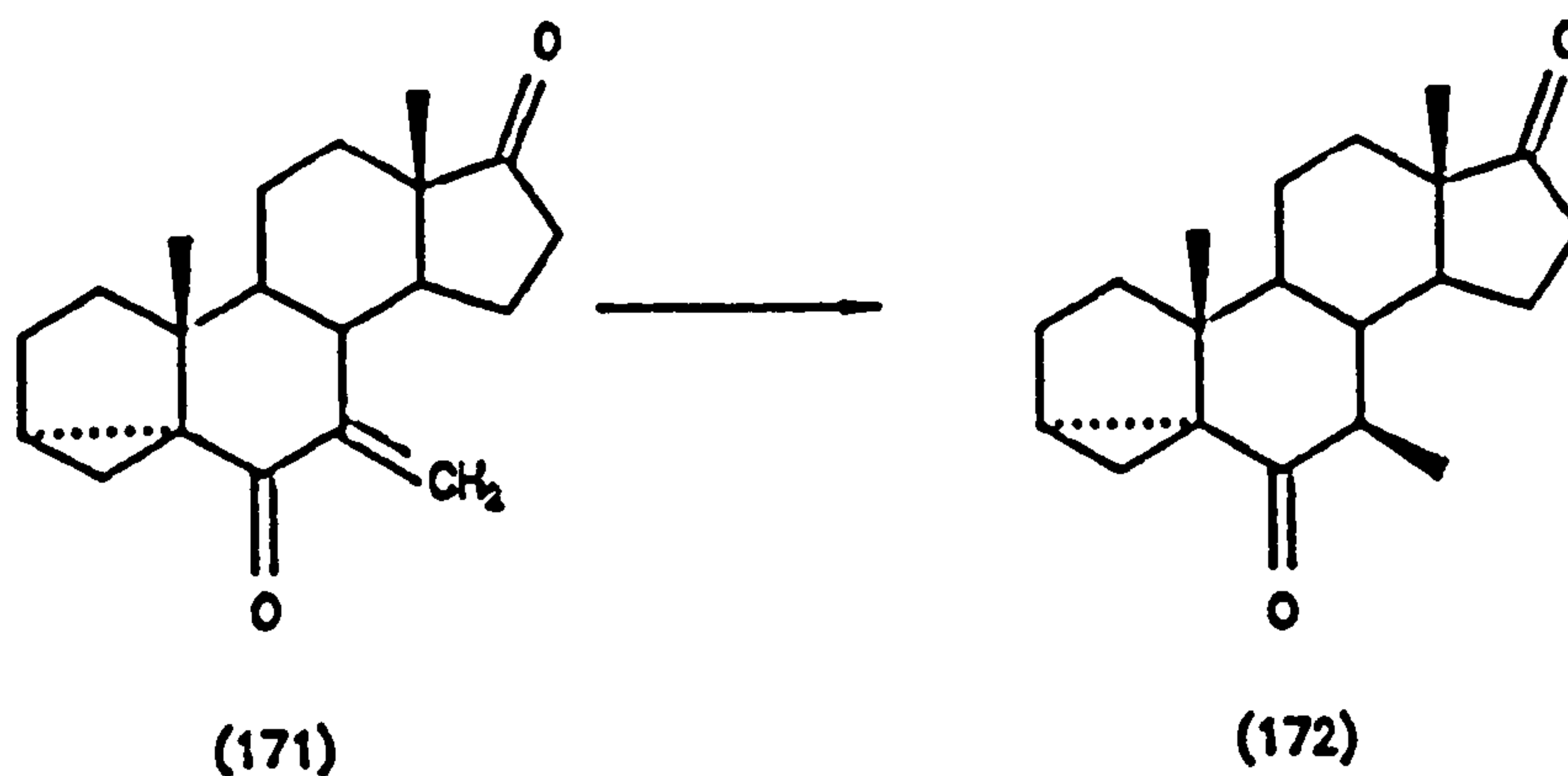
conjugation is present in the molecule, albeit at a slightly reduced level compared to the trans rotamer vinylcyclopropane (163). Thus the steric repulsions between the appropriate methylene and cyclopropane hydrogens appear to predominate over a stabilising effect induced by increased conjugation and result in a geometry similar to that derived from molecular mechanics. Further confirmation of the steroid's conjugative ability could be gleaned from the moiety's ability to undergo thermal rearrangement in a similar fashion to VCP.⁶⁸⁻⁷¹ As mentioned, assuming this donative ability of the cyclopropane ring to the exocyclic methylene group exists, there is a considerable potential for further chemical studies.

Although the formation of the precursor to the target steroid (43) had thus been attained the overall yield, even considering the number of steps, was very poor (18%). This of course does not take into account the reduction of the double bond (see below) and deprotection of the ketone group in (156).

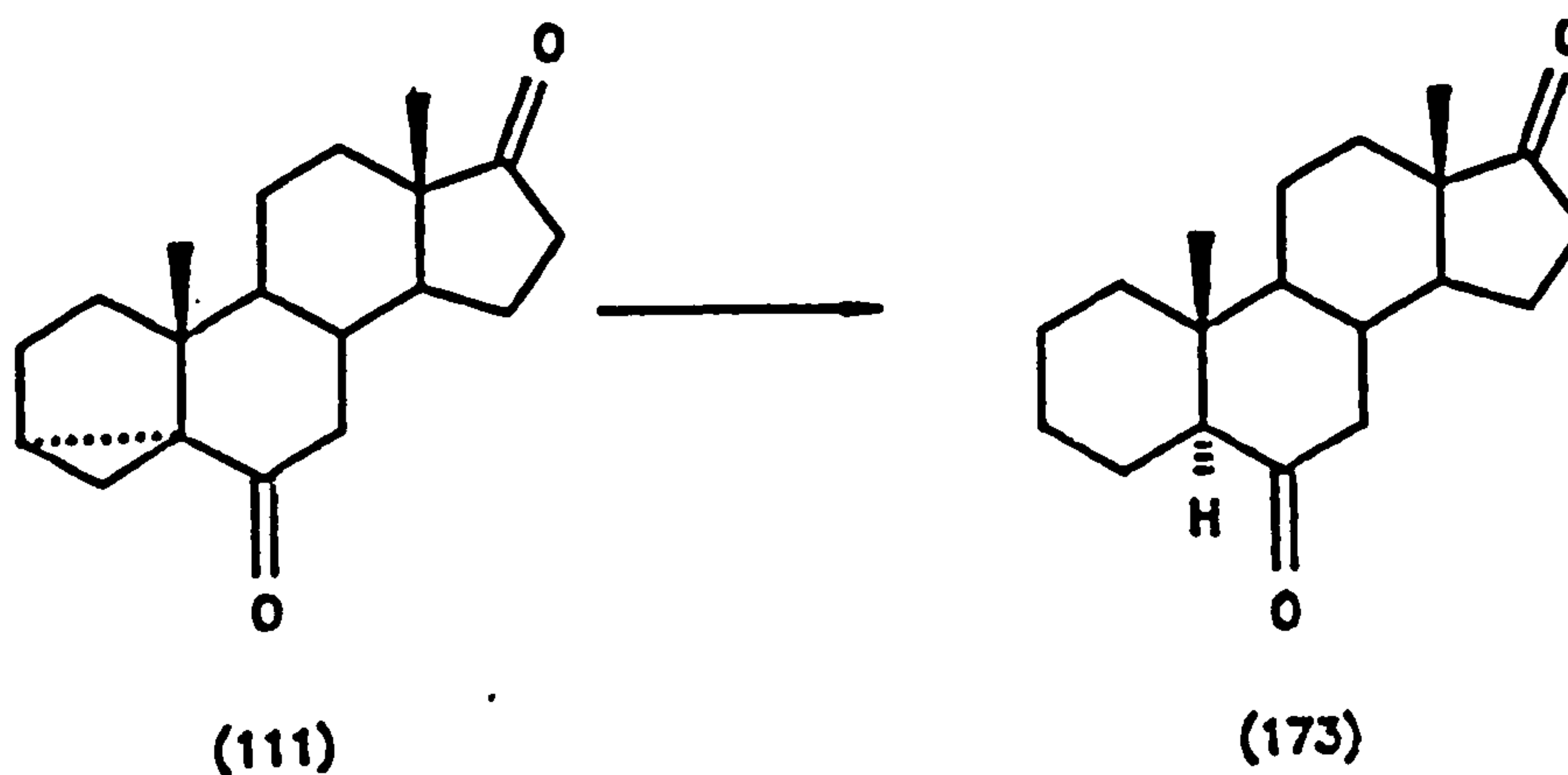
3.3.12 Potential methods for the reduction of 6-methylene-3 α ,5-cyclo-5 α -androstandane-17(S)-spiro-2'-(1,3-oxathiolane) (156).

Cyclopropanes can be cleaved at the least hindered bond by catalytic hydrogenation. This technique can be used in the synthesis of gem dimethyl groups.⁸³⁻⁸⁵

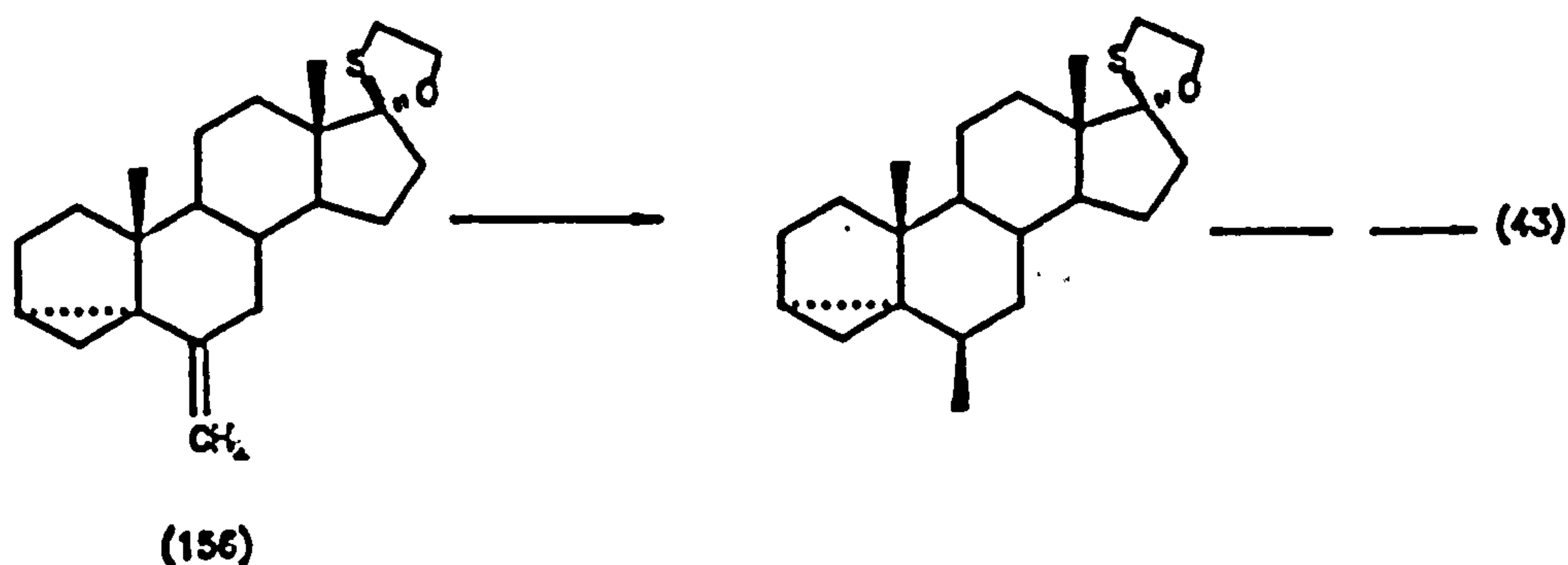
However, although cyclopropane compounds have a tendency to be reduced by standard catalytic reduction methods a few examples where this does not occur and the double bond is selectively reduced have been described. One such example by Burn *et al.*⁵³ was the reduction of 7-methylene-3 α ,5-



cyclo-5 α -androstandane-6,17-dione (171) to its 7 β -methyl derivative (172) by the action of 5% palladium charcoal at room temperature. However, in this particular case the double bond was not in conjugation with the cyclopropane



ring. That said however, catalytic reduction of 3 α ,5-cyclo-5 α -androstan-6-one (111) yields the 5 α -6-one structure (173) because the 3,5 carbon bond is aligned with the π -system of the ketone group.⁸⁶ It has already been shown that this alignment does not exist in the 6-methylene steroid (156) and therefore the propensity of the cyclopropane ring in this system to open is probably decreased. This would therefore appear to be the most suitable method for the



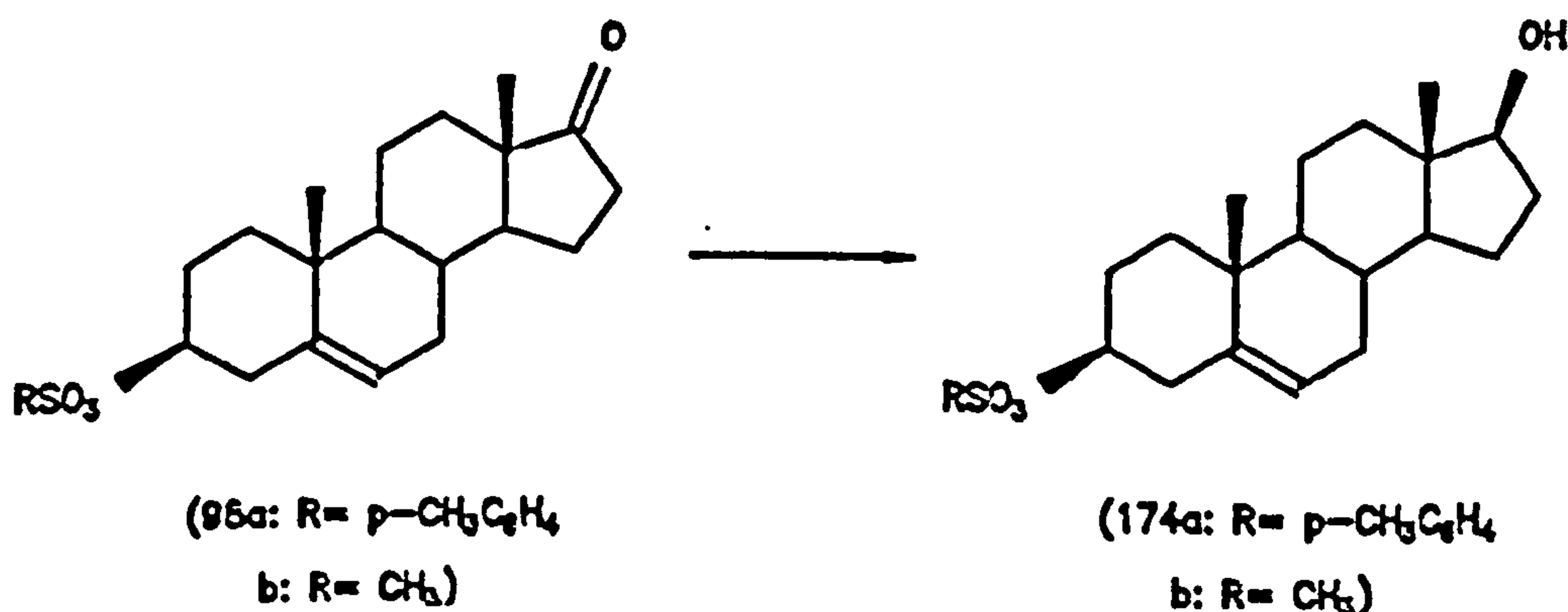
reduction of (156). However, it should be noted that although yields of the above reactions are good, the required deprotection of the 17-ketone group would inevitably result in overall yields of under 10%. Therefore, considering this and the small quantities of the precursor produced a third alternative route to a 6-methylene derivative was utilised (section 3.2.2).

3.4 Formation of a 17-C protected cyclosteroid by insertion of 17-C protecting group prior to introduction of cyclopropane ring:- acetate protection.

Due to the initial difficulties involved in forming a 17-C protected 3,5-cyclosteroid and the rather low yields involved in the oxathiolane series, an alternative approach to a 6-methylene steroid, outlined below, was adopted. The first step in this process, effectively the protection of the carbonyl group by its conversion to an acetate group as used by Labler,⁸⁷ was the formation of the 3-C tosylate or mesylate, a relatively straight forward step utilised in several other aspects of this work.

3.4.1 Formation of 3 β -tosyl-5-androsten-17 β -ol (174a).

The alcohol (174a) was synthesised by the direct reduction of the keto group by two common reducing agents. Initially the method of Labler,⁸⁷ i.e., using sodium borohydride (NaBH₄) with ethanol as the solvent, was chosen. The ethanol contained a small amount of dioxane to increase the solubility of the steroid, as at room temperature the solubility of the steroid (98a) was approximately 0.5g /l. The recommended 30 minute period of reaction was found to be



inadequate and this was increased to 2 hours to ensure complete reduction of the compound.

The more powerful reducing agent, LiAlH_4 , with a tetrahydrofuran/diethyl ether solvent system also gave the required alcohol, in slightly greater yields, after 30 minutes. To prevent the possible reduction^{88,89} or substitution of the tosylate group, the reaction temperature was maintained at -10° over the reaction period. The isolated product was a white solid which recrystallised from acetone as needles. Evidence of the conversion was supported by the appearance of a 1H triplet at $\delta = 3.63$, attributed to the 17-H geminal to the alcohol group, in the compound's ^1H NMR. The formation of the β -alcohol group,⁹⁰ as would be expected because of steric hindrance induced by the 18-methyl group, was shown by the shift of the methyl signal from $\delta = 0.89$ in the case of the ketone (where the methyl group lies in the deshielding zone of the carbonyl group) to $\delta = 0.74$ for the alcohol. Reduction was indicated by the loss of the carbonyl absorption and the appearance of hydroxy absorption in the IR spectrum of the compound.

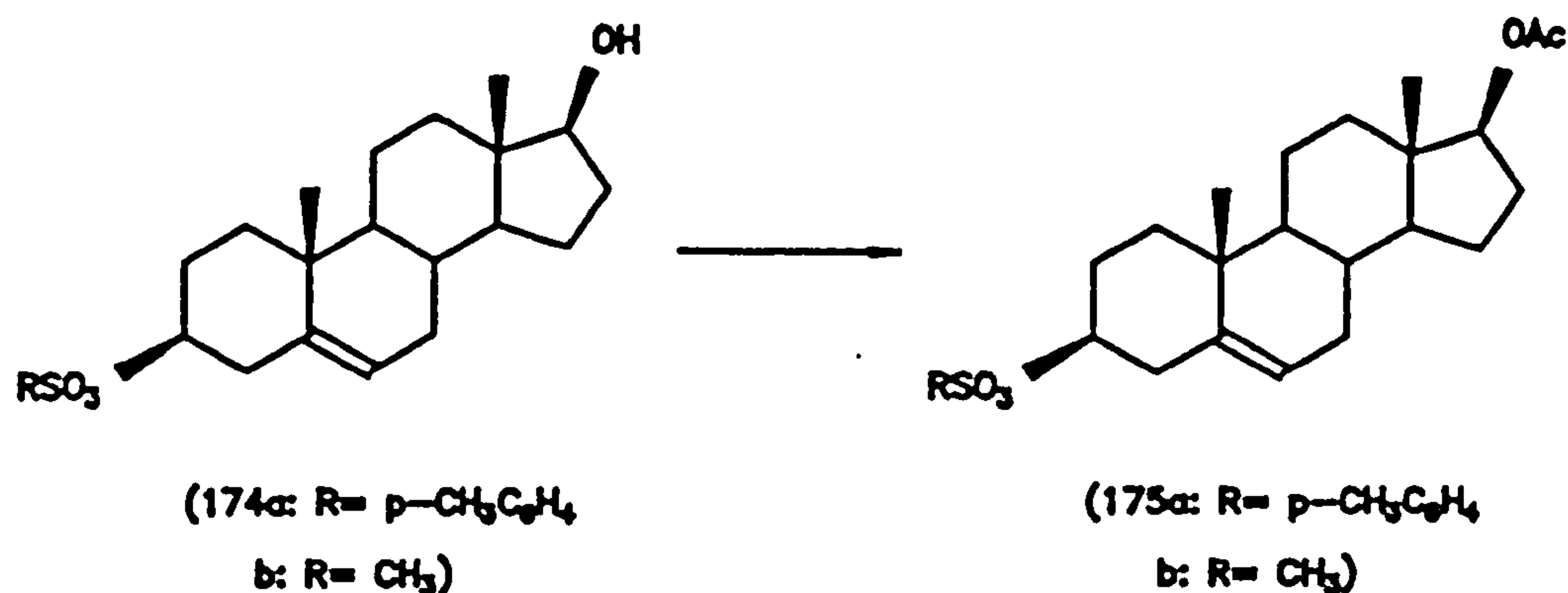
3.4.2 Formation of 3β -mesyl-5-androsten-17 β -ol (174b).

In an identical manner to the formation of (174a), the mesylate was reduced to the alcohol (174b) with lithium aluminium hydride.

3.4.3 Formation of 5 -androsten- $3\beta,17\beta$ -diol-3-tosyl-17-acetate (175a).

Following the procedure of Labler,⁸⁷ the alcohol was converted to the acetate (175a) by reaction in a pyridine

acetic anhydride mixture. This was successful if there was at least a 2:1 ratio of acetic anhydride to steroid (72 hours) but not surprisingly, considerably quicker with a greater excess of acetic anhydride (16 hours). The off white product, isolated by flash chromatography, melted at 118-120°C with decomposition, a trait of all tosylates or mesylates synthesised in this work.



As expected, the ¹H NMR spectrum of this compound was similar to that of its corresponding alcohol. The 17-H signal, as expected occurred further downfield because of the greater electron withdrawing properties of the acetate group. A singlet (3H) corresponding to the acetate methyl group was present at $\delta = 2.02$. The conversion of the alcohol to the acetate caused a shift in the position of the 18-methyl group signal which appeared at $\delta = 0.78$. The presence of the acetate group was evident in the IR spectrum of the product where a strong absorption band at 1720cm^{-1} corresponding to an acetate carbonyl group was present along with an ether linkage absorption at 1030 and 1250cm^{-1} .

A variation to the above procedure, gently heating the reaction mixture at 60°C for an 8 hour period, gave different results. The product crystallised as spirals after the slow addition of cold water to facilitate the decomposition

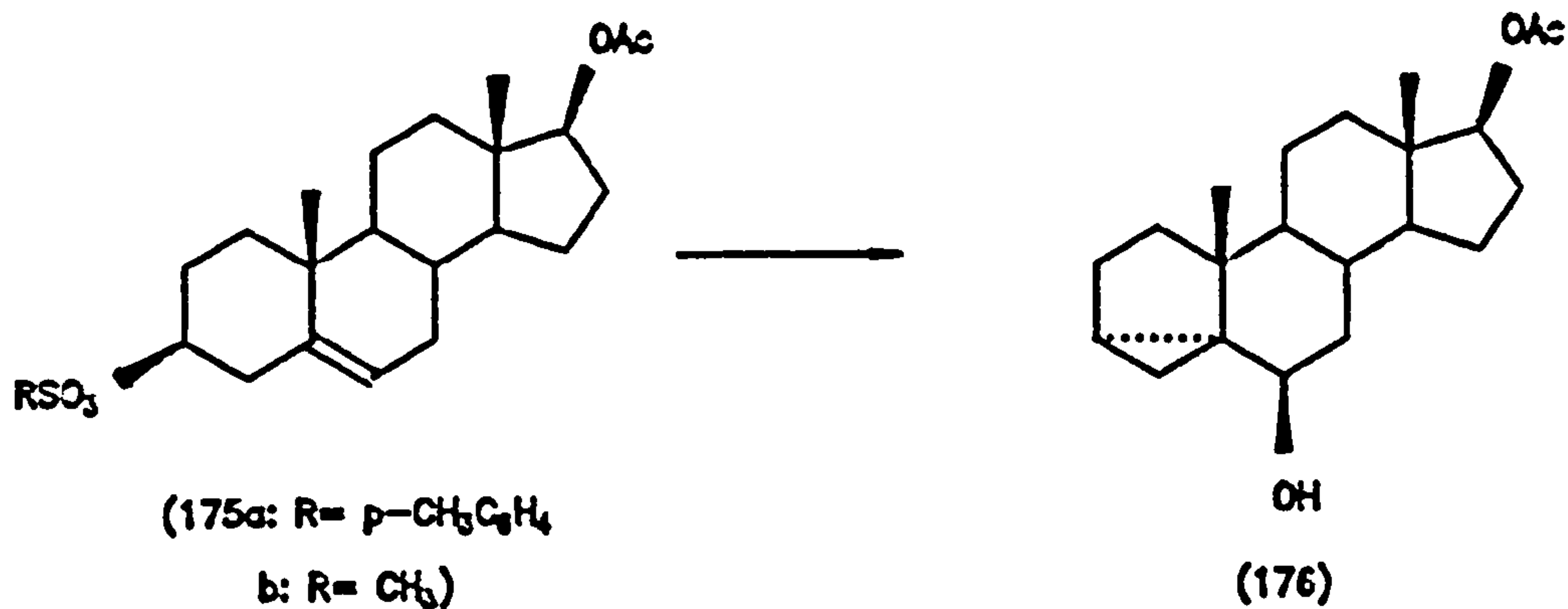
of acetic anhydride and induce crystallisation. However, an ^1H NMR of the product possessed a considerable number of unexpected signals in the aromatic region. Further recrystallisations did not result in any alteration to the NMR spectrum of the compound. In addition to the presence of signals possibly attributed to pyridine, a considerable downfield shift (0.6ppm) of the 17-H signal occurred. The compound was therefore designated as a tosylated steroid-acetate-pyridine complex. Considering the movement in signals from the starting material, complexing most likely occurred at the D-ring, but the exact structure of the compound was not determined. Chemical analysis (C, H, N, & S) agreed with this proposed composition.

3.4.4 Formation of 5-androsten- $3\beta,17\beta$ -diol-3-mesyl-17-acetate (175b).

The alcohol (174b) was converted to the acetate (175b) by identical means to those used for the tosylated steroid (174a).

3.4.5 Formation of $3\alpha,5$ -cyclo- 5α -androstandane- $6\beta,17\beta$ -diol-17-acetate (176).

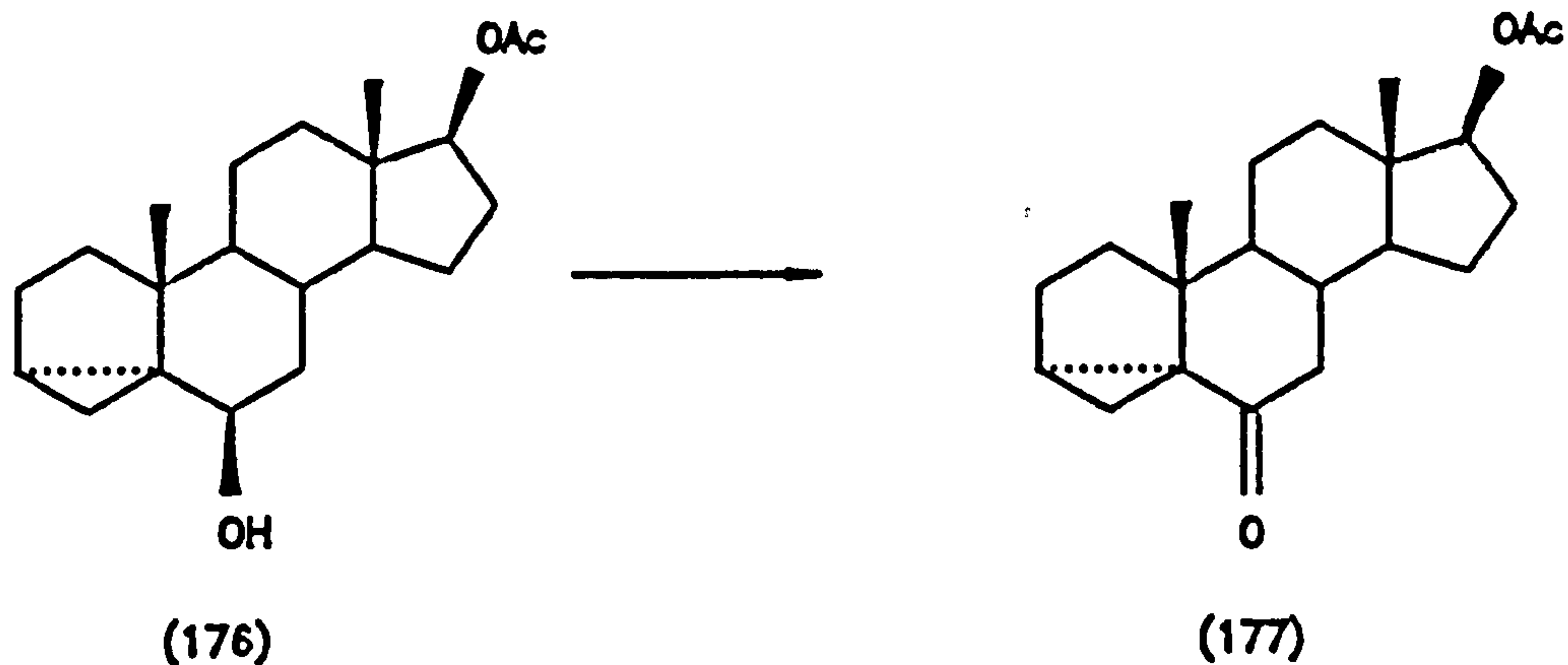
Cyclisation of the sulphonate steroids (175a or b) was undertaken by the acetone solvated method. A 6 hour reflux and the previously described isolation by flash chromatography gave the required cyclosteroid (176). The ^1H NMR of the steroid indicated the successful conversion to the cyclopropane system with the absence of a signal corresponding to an alkenic proton and the highfield absorbance of cyclopropane



protons, i.e., a 7 peak multiplet identical to that of the parent 3,5 cyclosteroid (41). Also in common with the parent compound was a triplet at $\delta = 3.29$ corresponding to the equatorial 6-H. The acetate methyl group signal occurred at $\delta = 2.03$. While the 18-methyl group remained at $\delta = 0.80$, the 19-methyl signal was shifted to $\delta = 1.06$, a reflection of the axial oxygen function at the 6 position⁴⁴ and the σ -aromaticity of the cyclopropane ring^{42,43} (Chapter 2). The IR spectrum of the product showed only one weak band at 3050cm^{-1} corresponding to the cyclopropane ring. Strong absorption bands at 3350 , 1720 and $1285/1020\text{cm}^{-1}$ attributed to OH, C=O and C-O-C functions respectively.

3.4.6 Formation of 17 β -acetoxy-3 α ,5-cyclo-5 α -androstan-6-one (177).

The oxidation of the alcohol (176) was accomplished with Collins reagent.^{45,46} General reaction conditions were identical to those used in the formation of the 17-thioxalane-6-keto steroid (151) (section 3.3.8). The pale brown oil recovered from the reaction medium was then subjected to tlc and the product isolated. Recrystallisation from acetone gave fine plates. The ¹H NMR spectrum of (177)

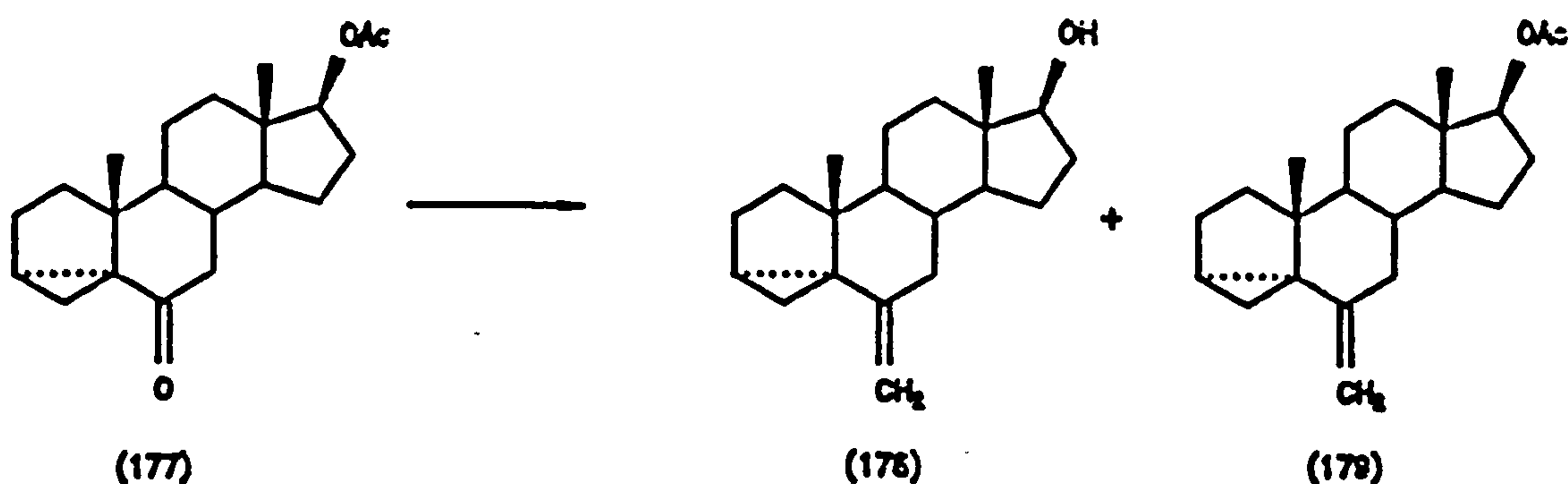


as with the previous alcohol showed a 1H triplet associated with the 17-H geminal to the acetate, a 3H singlet at $\delta=2.01$ corresponding to the acetate group and a 3H singlet at $\delta=0.81$ corresponding to the 18-methyl group. Differences were noted with the 19-methyl group signal and cyclopropane signals. The 19-C methyl group was shifted slightly upfield while the cyclopropane splitting pattern was altered and shifted downfield (Chapter 2 and this chapter, section 3.3.8) in accordance with the conversion of the 6-C functionality from an alcohol to a ketone. As with the IR spectrum of compound (176), the cyclopropane C-H stretching frequencies of the product were not prominent with only one weak band at 3060cm^{-1} . Remaining prominent was the carbonyl absorption at 1730cm^{-1} attributed to the acetate group along side a second new carbonyl signal at 1675cm^{-1} corresponding to six membered ring ketone. Strong absorption associated with the acetate group was also present at 1265 and 1040cm^{-1} .

3.4.7 Formation of 6-methylene-3 α ,5-cyclo-5 α -androstan-17 β -ol (178).

In a similar method^{48,52} to the conversion of the keto

steroid (151) to its 6-methylene derivative (156), compound (177) was reacted with the Wittig⁴⁸ ylide (153) formed by the action of n-butyllithium on methyl triphenylphosphonium bromide. It had been reported by Sondheimer⁵² that an acetate group was susceptible to cleavage under these conditions so the reaction in refluxing dry ethyl ether was extended to 36 hours in a bid to remove the protecting group by hydrolysis. The product, a clear oil, when subjected to



tlc gave three products. The major product, a white solid, was shown by spectroscopic methods to be the desired alcohol (178). The ¹H NMR of this compound showed a doublet (2H) assigned to the 6-C exocyclic methylene group at $\delta = 4.62$. With the loss of the acetate group, the 17-H signal was shifted upfield and as for the 17-alcohol (174) appeared as a triplet. Signals corresponding to the two methyl groups at 18-C and 19-C, in accordance with a β hydroxy group present at 17-C and a 6-methylene group were present at $\delta = 0.86$ and 0.76 respectively. The cyclopropane signals were identical with those of the thioxalane derivative (156). The IR spectrum of this compound possessed an O-H absorption band and no acetate absorption. More prominent than either the alcohol (176) or the ketone (177) were weak, sharp bands associ-

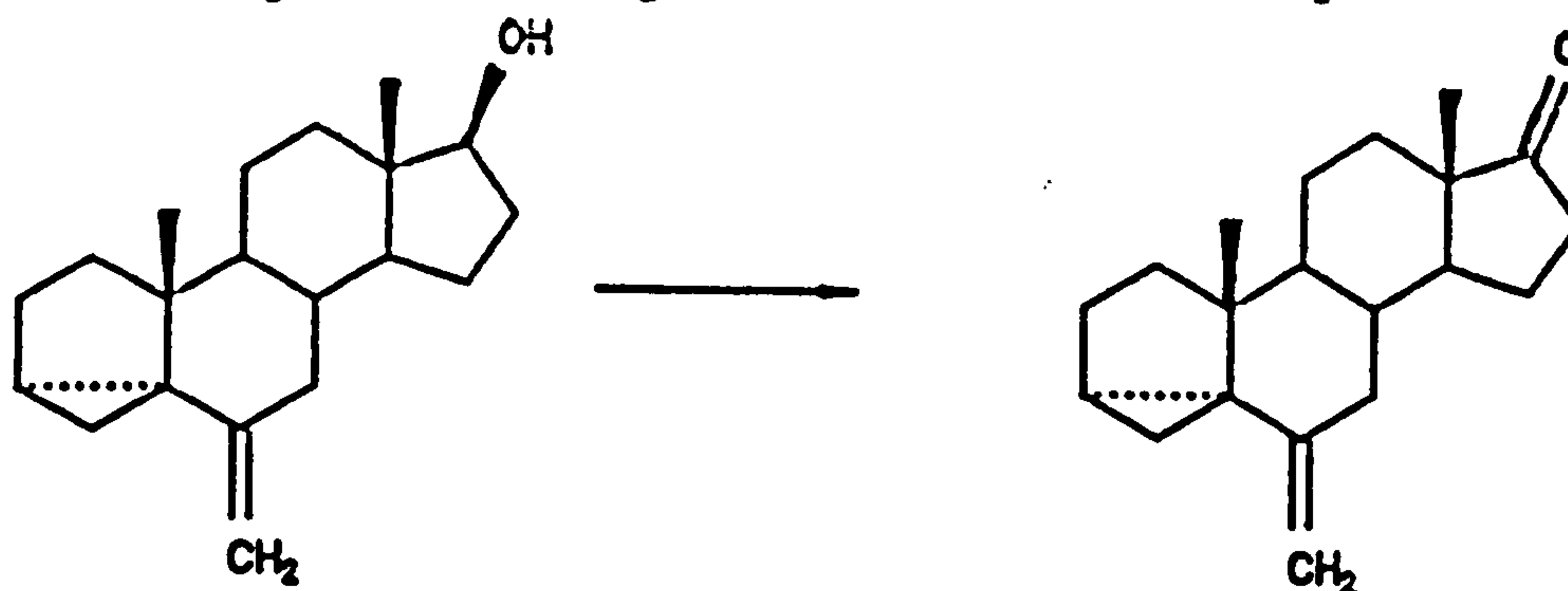
ated with the cyclopropane and methylene groups, which because of their close proximity and partial conjugation are perhaps best considered as one vinyl cyclopropane moiety, at 3090, 3040 and 3020 cm^{-1} . Also associated with this grouping was a methylene C-C band at 1642 cm^{-1} and strong alkenic C-H absorption at 890 cm^{-1} . For a full discussion of this cyclopropane methylene system refer to section 3.3.10 and 3.3.11.

The second compound, accounting for approximately 10% of the product weight was shown to be 6-methylene-3 α ,5-cyclo-5 α -androstan-17 β acetate (179). The ^1H NMR spectrum of this compound showed an identical methylene doublet and a 17-acetate methyl signal, identical with the other acetates. The two other 3H singlets attributed to the 18 and 19-methyl groups occurred at $\delta = 0.86$ and 0.77 . The cyclopropane protons, in an identical pattern to the alcohol (178) absorbed as a triplet at $\delta = 0.41$. The weak, sharp bands in the IR spectrum associated with the cyclopropane and methylene moiety were less prominent as compared to the alcohol, most certainly in this case because of the lower purity of the minor product. A strong acetate ether linkage band and strong carbonyl absorption, at 1250 cm^{-1} and 1730 cm^{-1} respectively, were also present. The carbonyl absorption obscured the methylene signal at 1642 cm^{-1} , but evidence of this group was a strong absorption band at 900 cm^{-1} . The third compound isolated was the unreacted 6-ketone (177).

3.3.8 Formation of 6-methylene-3 α ,5-cyclo-5 α -androstan-17-one (180).

The 17-functional group was converted back to a ketone

group by reacting the alcohol (178) with an excess of Jones reagent.⁹¹ The ¹HNMR spectrum of the product showed no absorption corresponding to the presence of an alcohol group. In other respects the spectrum was identical to the starting material's except for the expected shift in the 18-C methyl signal. The IR spectrum of the product showed strong 5-membered ring keto absorption and no OH absorption.



(178)

(180)

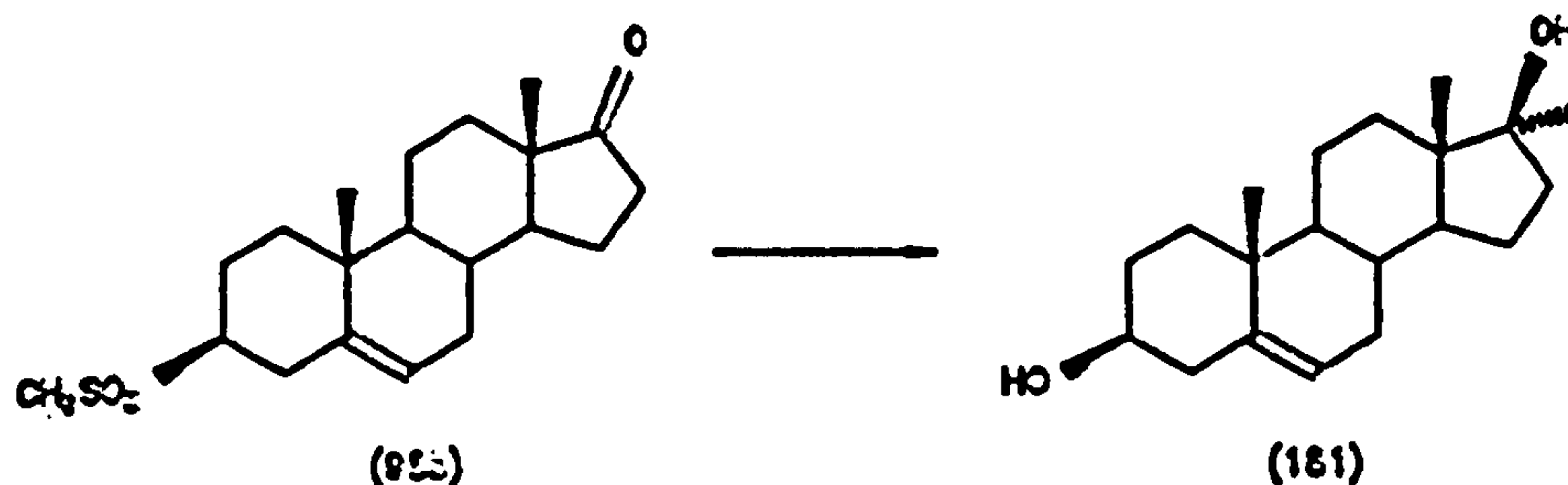
Thus by the above procedure, a 6-methylene steroid, a precursor to the 6-methyl derivative (3) was synthesised in overall yield greater than that obtained in the two alternative syntheses. However, the low yield (23% over 6 steps) prevented the isolation of quantities of the methylene compound suitable for reduction.

3.5 Formation of 6 β -methyl-3 α ,5-cyclo-5 α -androstan-17-one (3) by insertion of 17-C protecting group prior to simultaneous introduction of cyclopropane ring and methyl group

The initially conceived methods for the introduction of the methyl group at the 6-C position (sections 3.2 and 3.3) although successful gave the desired steroid (43) in low yields primarily because of the number of steps required. This prompted the search for alternative, higher yielding, methods for the synthesis of the desired steroid.

Cyclisation with dimethylolithium cuprate.

Cyclisation with dimethylolithium cuprate was attempted because of the noted sulphonyl substituting properties of the reagent.⁹² It was hoped that the relative inertness of the reagent to carbonyl groups would allow direct access to the desired steroid (43) from the mesylate (98b). However,



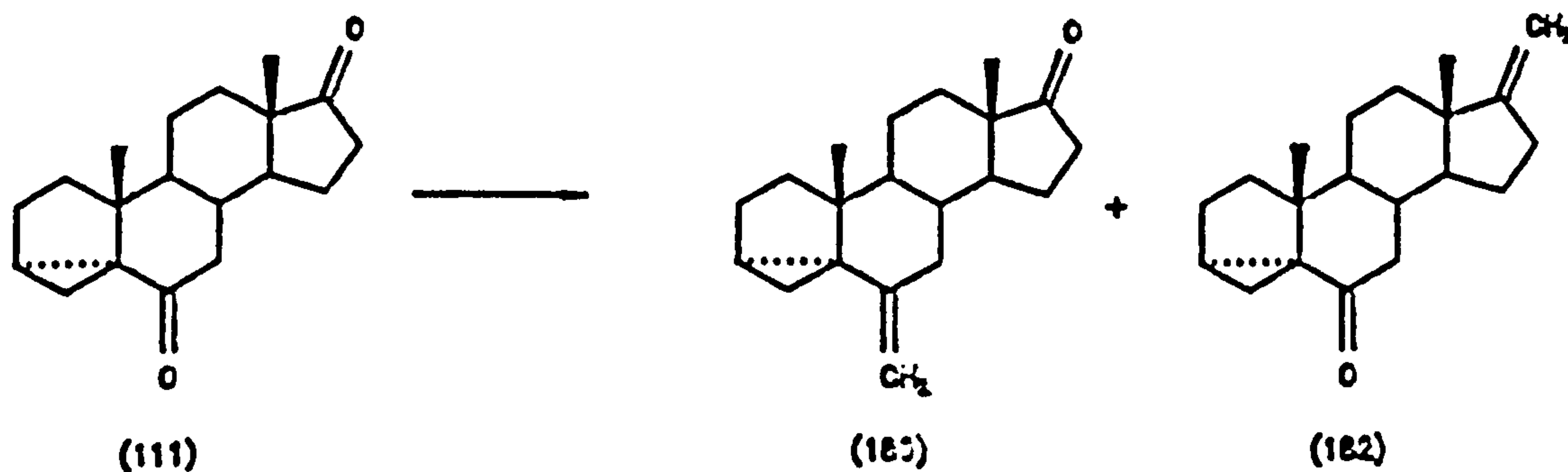
little if any reaction occurred at 3-C over a limited period and a prolonged reaction resulted in (after aqueous work up) the isolation of the potent androgen 17 α -methyl-5-androsten-3 β ,17 β -diol (181). The absence of any form of reaction at 3-C was attributed to the poorer (relative to the tosylate group) leaving group properties of the mesylate moiety.

3.6 Formation of 6 β -methyl-3 α ,5-cyclo-5 α -androstan-17-one (43) via 17-carbonyl steroids.

As an alternative to the use of protecting reagents two methods for the introduction of a 6-methyl group were conceived: the statistical⁶ introduction of a methylene group at the 6-C position of the dione (111) and introduction of a 6 α methyl group with dimethyl lithium copper via a 6-sulphonate.

3.6.1 Selective introduction of a 6-methylene group.

The dione (111) was directly treated with a one molar equivalent of the methylene ylide (153) under identical conditions to those employed in the Wittig⁴⁸ reaction (section 3.3.9) of protected steroids (151) and (177). A tlc of the resulting oil indicated a four component mixture. Separation and purification of the required 6-methylene keto

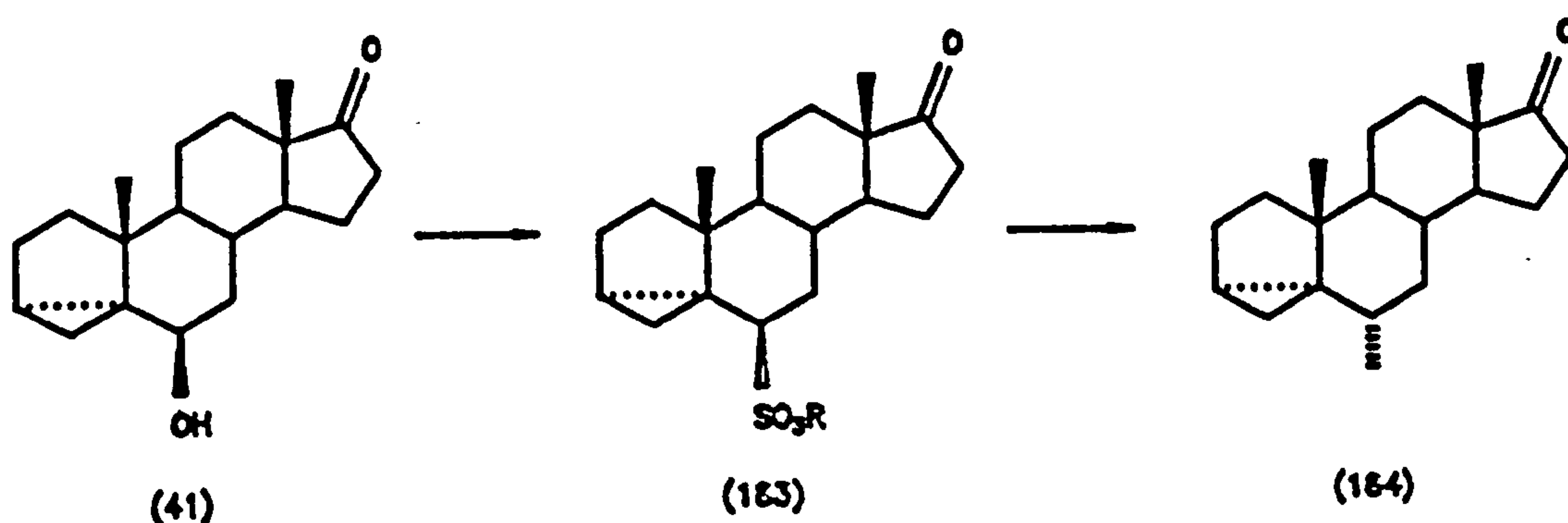


steroid (180), spectroscopically identical to a previous sample (section 3.3.8), was readily achieved but the overall yield was low. The major product of the reaction was the 17-methylene steroid (182) where nucleophilic attack occurred at the considerably more hindered carbonyl group. This is a graphic example of the ability of the cyclopropane ring to

conjugate with the ketone function and deactivate (with respect to nucleophiles) the carbonyl carbon.

3.6.2 "Direct" introduction of a 6-methyl group.

This particular route initially looked very promising, the final target molecule (43) should theoretically be obtained from the readily available 3,5-cyclosteroid parent alcohol (41) via only two reactions, and should not require any form of protection. The alcohol was to be converted to the sulphonate (183) by reacting the steroid under previously described conditions. The sulphonate would then be treated with an alkyl copper reagent⁹² such as dimethyl lithium



cuprate to give, with inversion, the 6 α methyl steroid (184). Although the second stage might have lead to some fragmentation of the cyclopropane ring and hence a small yield, it was hoped that overall yields from DHEA (97) would be much improved. The product could then be compared to the products of hydrogenation of the 6-methylene compounds to readily identify the isomers.

However under further investigation, problems associated with the first stage of the sequence, the conversion of the alcohol to the sulphonate, were identified. Wagner *et al.*⁹³ noted that in the reaction between the 6-alcohol and

p-toluenesulphonic acid the product was not the expected sulphonate but the 3-pyridinium tosylate salt.⁹⁴ The salt is most certainly formed by the rearrangement of the 6-tosylate. The electron withdrawing properties of the tosylate group inducing a partial positive charge at 3-C which is subsequently attacked by the nucleophilic pyridine. The mesylate group however possesses reduced electron withdrawing properties, which it was hoped would prevent rearrangement. Under standard mesylation conditions an intense red coloured precipitate was formed which rapidly disappeared to give a dark brown solution. The product was shown to be a rearranged product, i.e., the pyridinium mesylate salt. This method was therefore abandoned although an extensive investigation might have lead to a successful method, e.g., the use of a leaving group that would not induce rearrangement but could be readily substituted by a methyl group from dimethylolithium cuprate. Use of less nucleophilic solvent could also be investigated.

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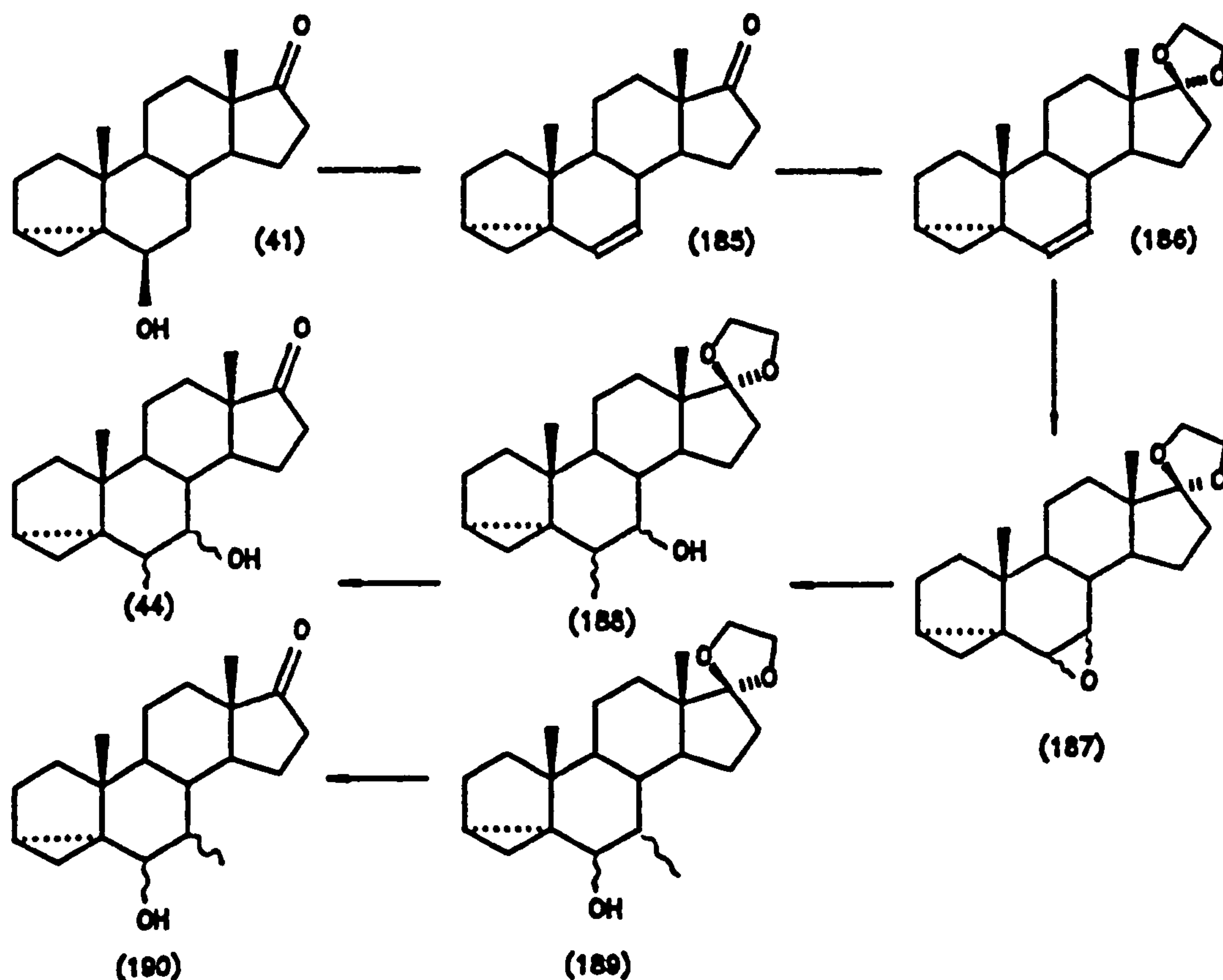
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Chapter 4

Formation of 6 β -methyl-7 α -hydroxy-3 α ,5-cyclo-5 α -
androstan-17-one.

4.1 Introduction

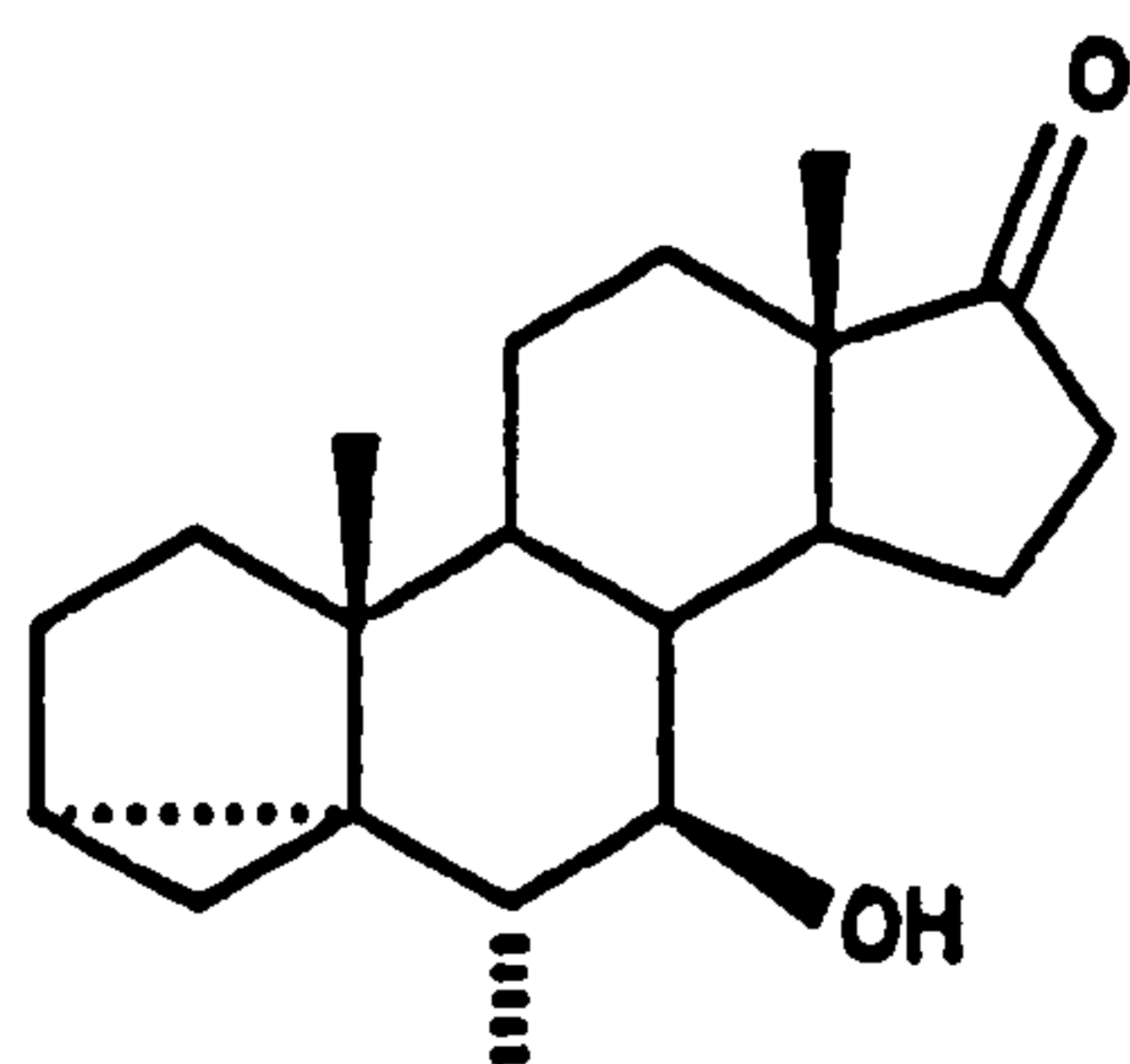
As discussed in Chapter 3, the introduction of a methyl group into the carbon framework of a steroid can frequently enhance its biological activity.¹ It was therefore considered of interest to investigate molecules with a hydroxy group vicinal to the methyl group at 6-C.



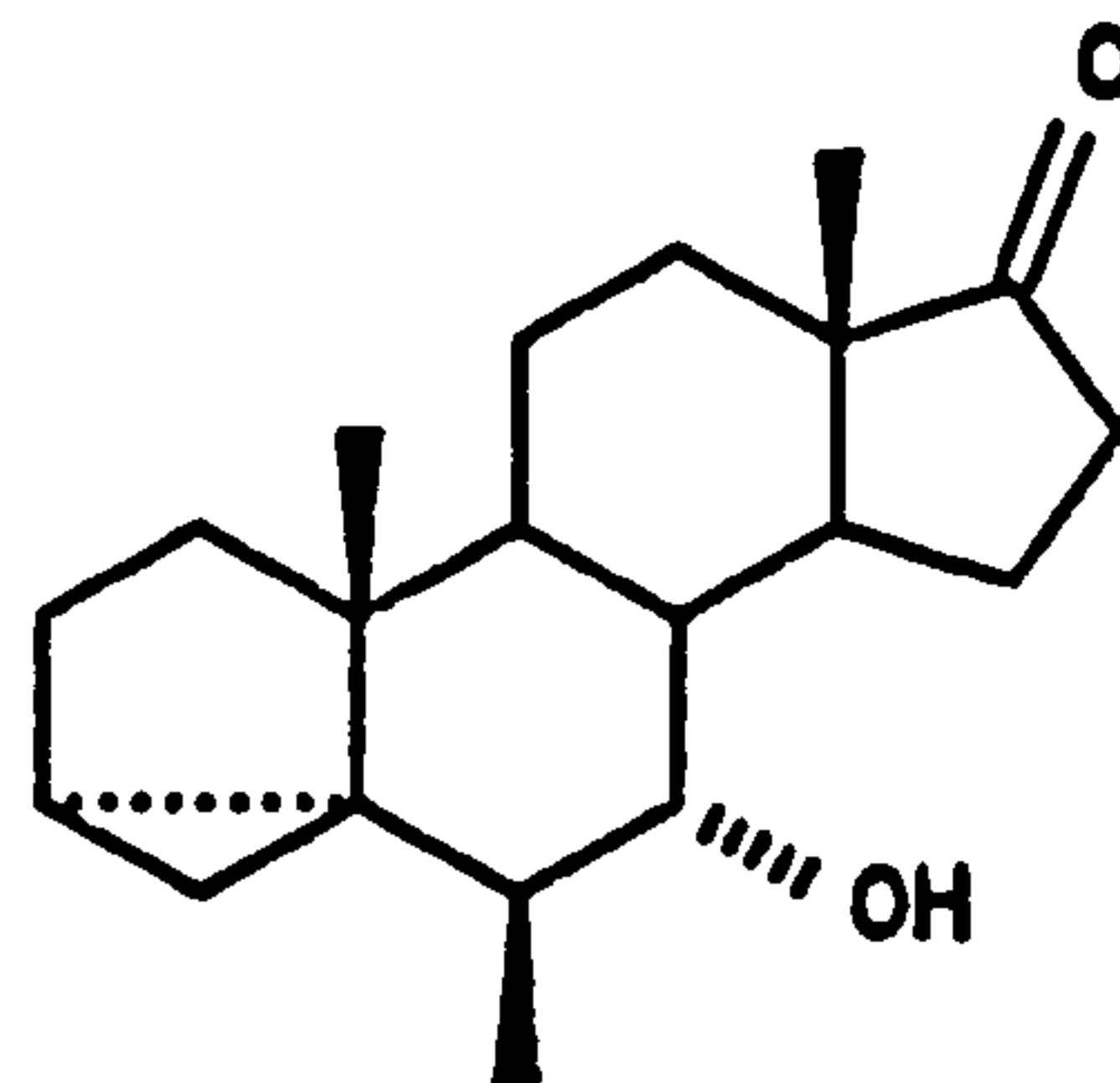
The initial reaction sequence to be undertaken was the dehydration of the alcohol (41) to the delta-6 steroid (185) followed by the protection of its keto group (186). Subsequent epoxidation to form (187), followed by reaction with a Grignard reagent (MeMgCl) should result in the desired target molecules (188) along with the 7-methyl epimers (189). Deprotection would lead to compounds (44) and (190). However, as problems were previously encountered in maintaining the cyclopropane ring during protection of the 17-

ketone group (Chapter 3), [a necessity when using Grignard reagents] this final reaction choice was not definitive.

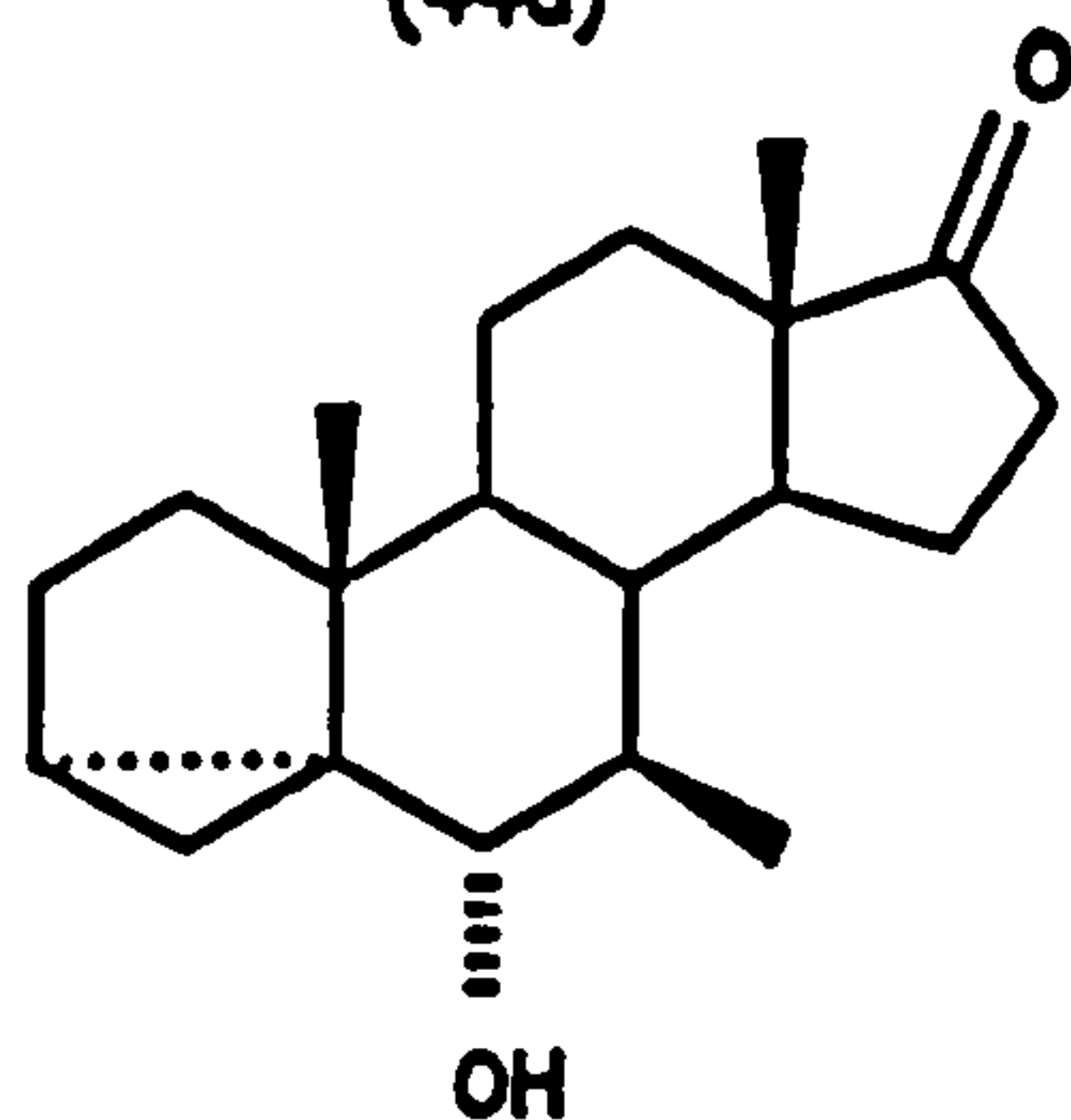
Useful information was hoped to be gleaned from this final step. Thus the introduction of an alkyl group at the 6 position and a hydroxy group at carbon 7 (44a and b) [or its structural isomer (190a or b)] was undertaken not only because of their novel structures and potential activity, but also to investigate if any participation of the cyclopropane ring occurred during reaction of the vital intermediate epoxide and the nucleophilic reagent. A lack of any directing effect on the part of the cyclopropane ring would



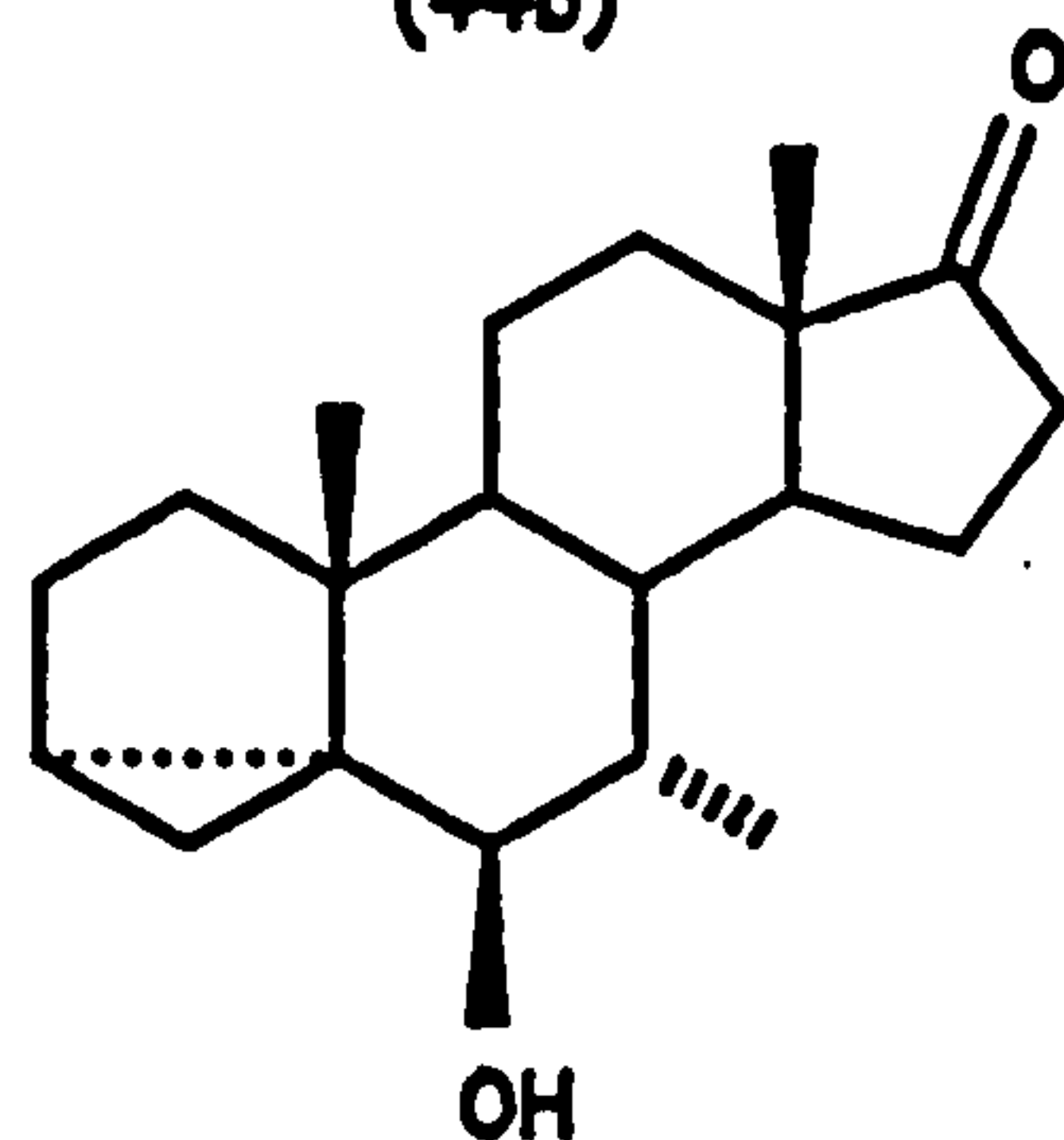
(44a)



(44b)



(190a)

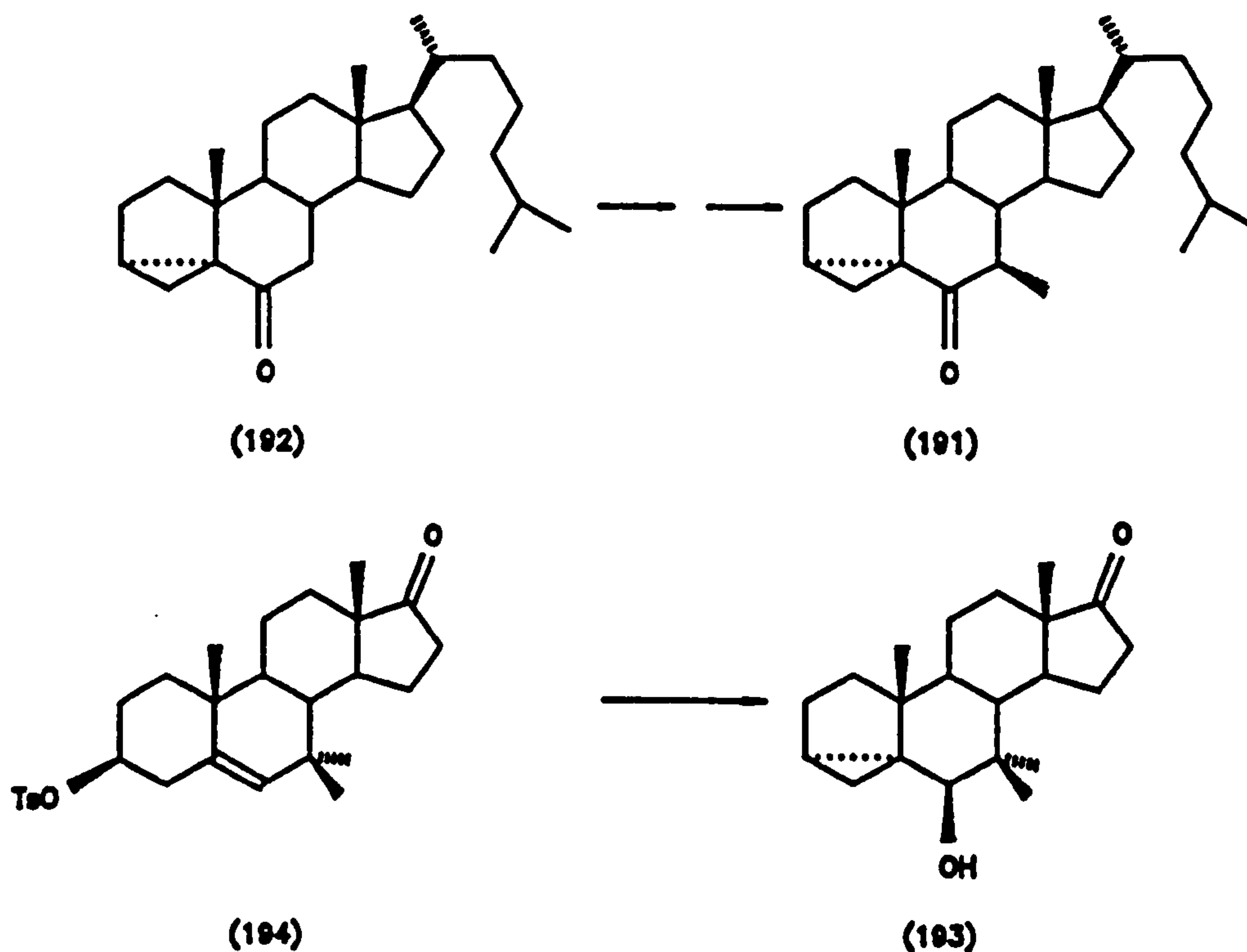


(190b)

probably result in a greater proportion of the 7-methyl isomers (190a or b) [section 4.5]. Although structurally interesting it would not be too unreasonable to assume (considering the deactivating properties of both these 6-hydroxy² and 7-methyl³ groups) that these molecules possess

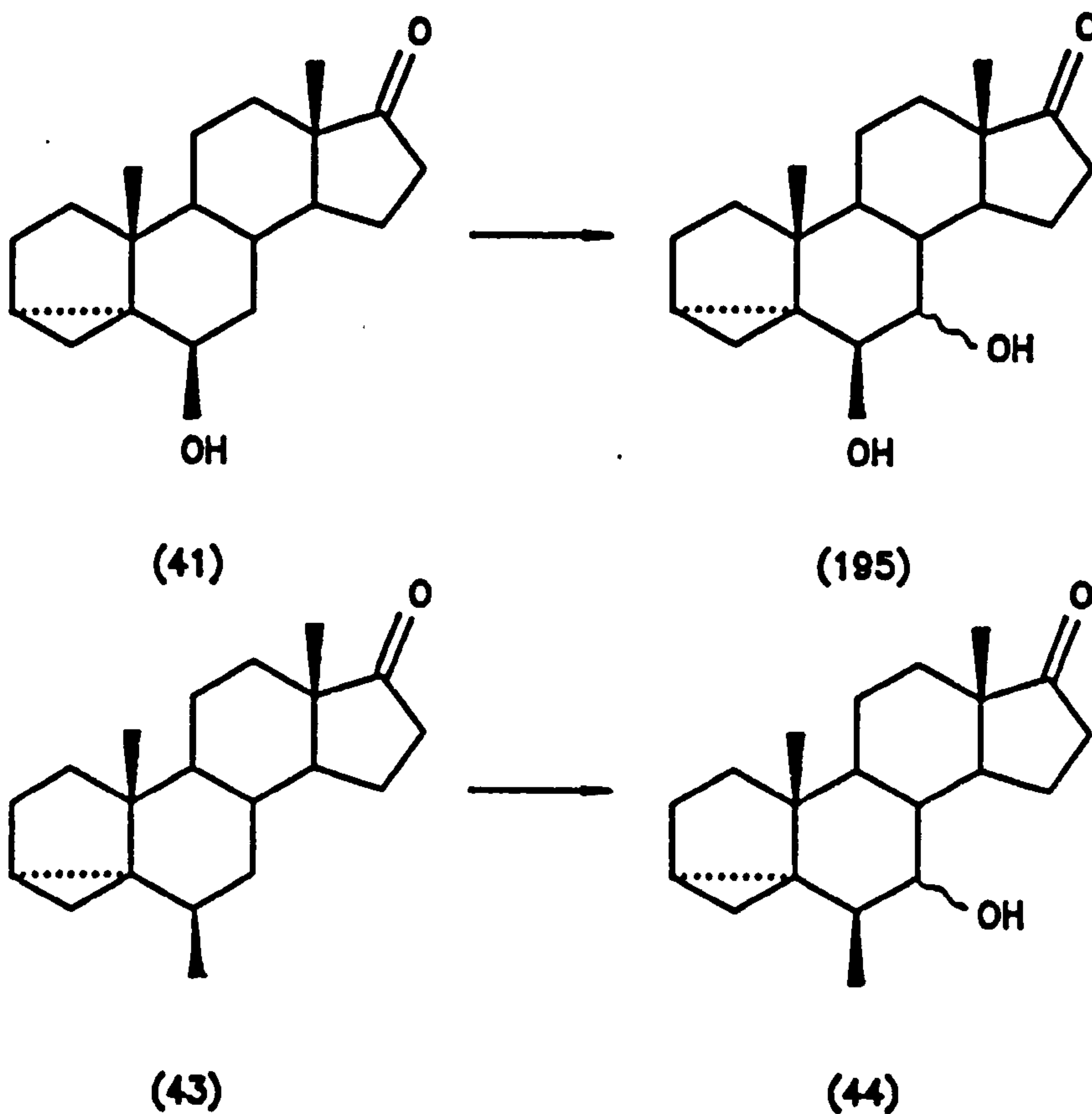
little activity as anti-fertility agents.

Work has been carried out on similar compounds, e.g., (191)⁴ by a Mannich reaction on the 6-ketone (192), or (193), by the cyclisation of the 3-sulphonate (194).⁵ These compounds are readily accessible because introduction of the hydroxy group can be attained by, for example, the cyclisation methodology utilised in this work. However, the formation of the 6-methyl isomers (44), by virtue of the position of the methyl group, provide a whole new series of problems.



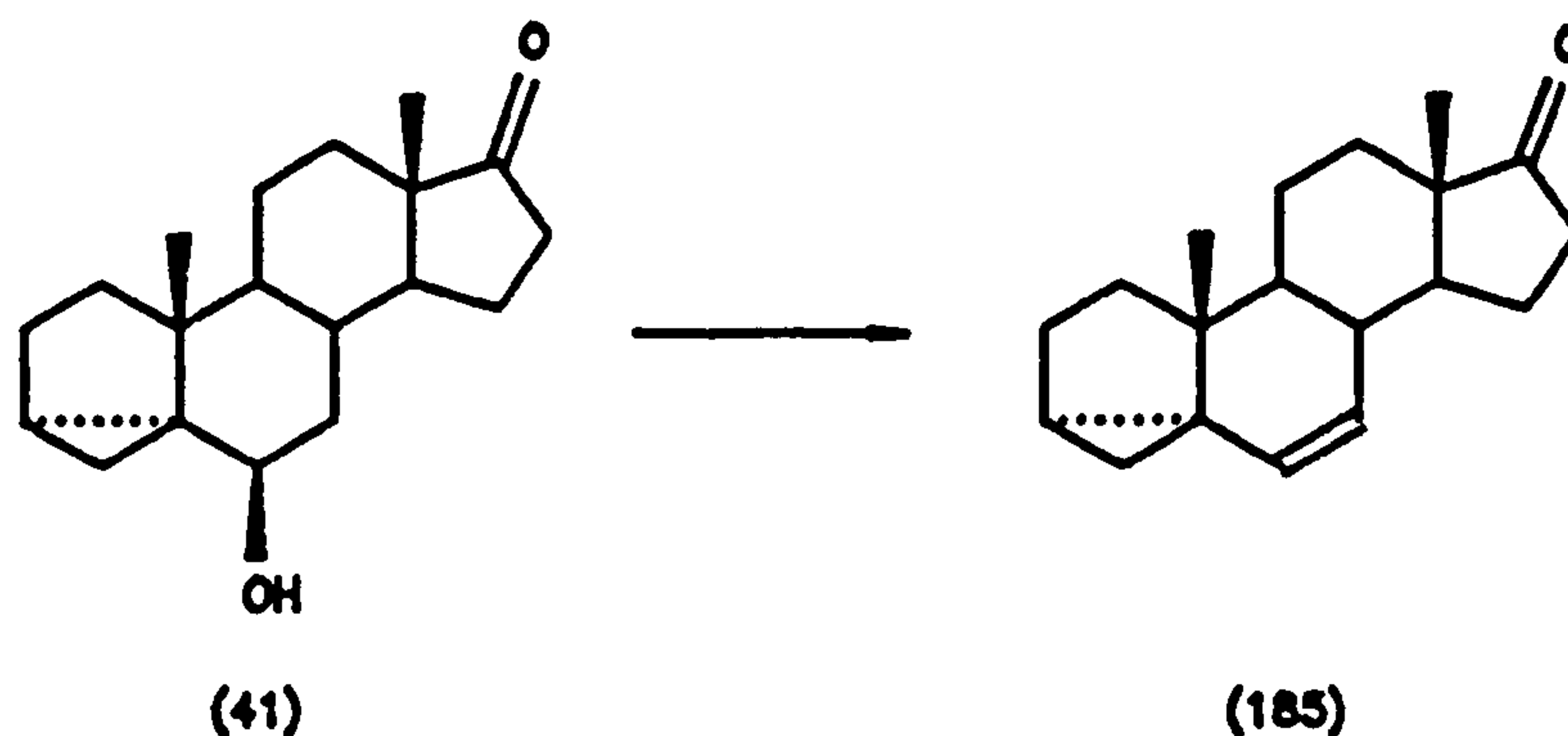
The proposed scheme was considered the most effective route to the target molecule(s), although it later became apparent that another route was available. Thus the biological hydroxylation of the 3,5-cyclosteroid (41)^{6,7} gave small quantities of the 7-hydroxy derivative (195). Therefore the target molecule(s) synthesised here could be available by the biological hydroxylation of the 6-methyl cy-

closteroid (43) (Chapter 3) in conceivably higher yields because of a directing effect induced by the additional methyl group.⁶

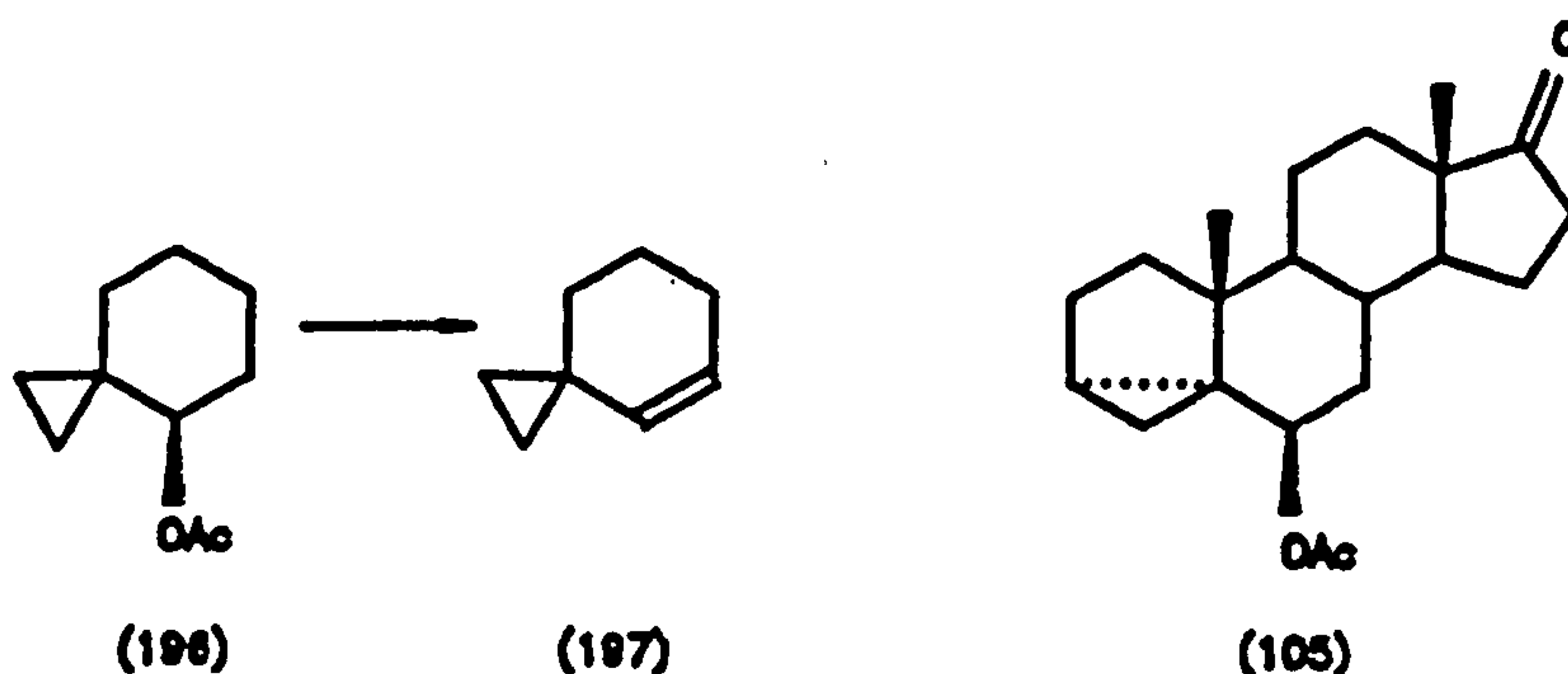


4.2 Formation of $3\alpha,5\text{-cyclo-}5\alpha\text{-androst-6-en-17-one}$ (185).

The first step in the reaction sequence, viz. the conversion of the parent 6β -alcohol (41) to the 6-alkenic steroid (185)⁸ was undertaken by the dehydration over alumina (activated, neutral, Brockman Grade I), of the alcohol (41), in refluxing xylene. Such conversions have been per-



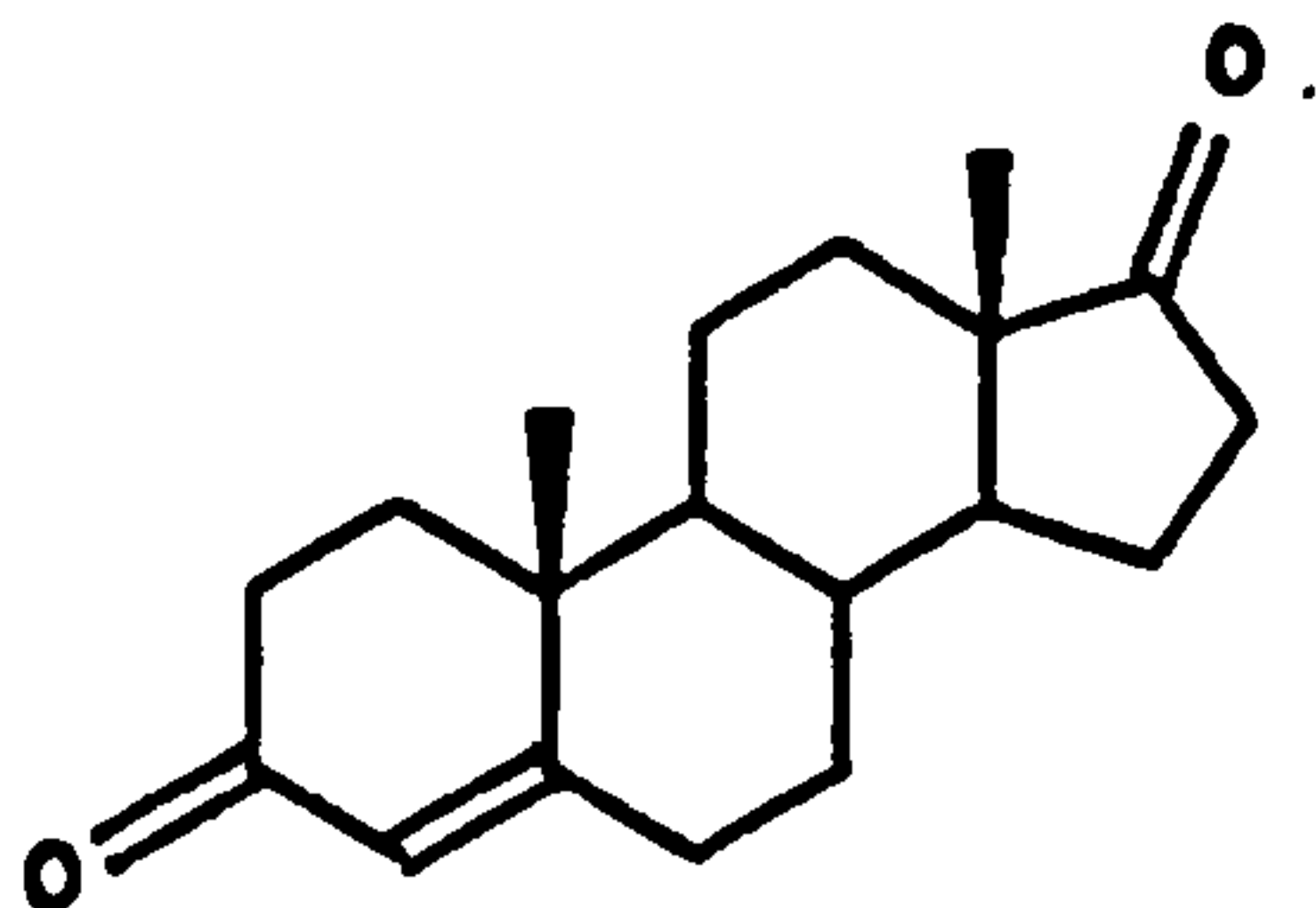
formed by Hanson and Knights⁹ and Riegel *et al.*¹⁰ An alternative synthesis of the steroidal alkene (185) was via the pyrolysis of the 6-acetate (105). Work by Hanack *et al.*¹¹ showed that the pyrolysis of the acetate of spiro-[2,5]-octan-4-ol (196) led to the alkene derivative (197) in exceptional yields. However, as formation of the alcohol (41) was achieved in considerably higher yields than that of the acetate (105), the former dehydration reaction was preferred.



Although a ^1H NMR analysis of the crude reaction product showed that the desired product had been formed it

was apparent that some decomposition of the steroid had occurred. Therefore, to try to reduce this decomposition and ease the isolation of the product from the reaction mixture toluene was chosen as an alternative solvent. This resulted in improved yields as the lower reflux temperature caused less decomposition of the steroid. Also, filtering off the aluminium oxide and washing with chloroform led to a near quantitative return of organic material. Both sets of conditions afforded a pale brown oil, which by tlc, was shown to consist of two major components in a ratio of approximately 4:1. These were successfully separated by preparative tlc or column chromatography. The major component, the required alkene, was recovered as an off white solid which when recrystallised from ethanol gave colourless plates. The successful dehydration was evident from the ^1H NMR spectrum of the compound. Absent from the spectrum, was the signal from the 6-H atom geminal to the hydroxy group in the starting material. New signals, a pair of double doublets (ABX system) in the alkene region of the spectrum, were attributed to the atoms 6-H and 7-H. The coupling between these atoms ($^3\text{J}= 9.6\text{Hz}$), indicated that the dihedral angle between the protons was very small, confirming the cis nature of the alkenic group. Both the 7-H and 6-H atoms were again coupled to the 8-H atom. The vicinal coupling between the protons at 7-C and 8-C ($^3\text{J}= 2.3\text{ Hz}$) was readily observed in most samples but a particularly pure sample, obtained by recrystallisation, was required to detect the smaller coupling ($^4\text{J}= 0.9\text{ Hz}$) between the 6-H and 8-H protons. The position of the double bond resulted in the shielding of the 19-H angular

methyl group, and as a consequence, the angular methyl signals overlapped. Thus a singlet corresponding to 6 protons was present at $\delta = 0.93$. Finally, it was apparent that the complex splitting of the high field signals attributed to the cyclopropane protons had been altered, to a four peak multiplet, by the change at 6-C. The most prominent feature of the IR spectrum of the alkene was the sharp, high frequency C-H stretching bands associated with the cyclopropane and alkene moieties. The alkene function was also evident at 1635 and 735 cm^{-1} , the latter absorption again indicating the cis nature of the alkene.

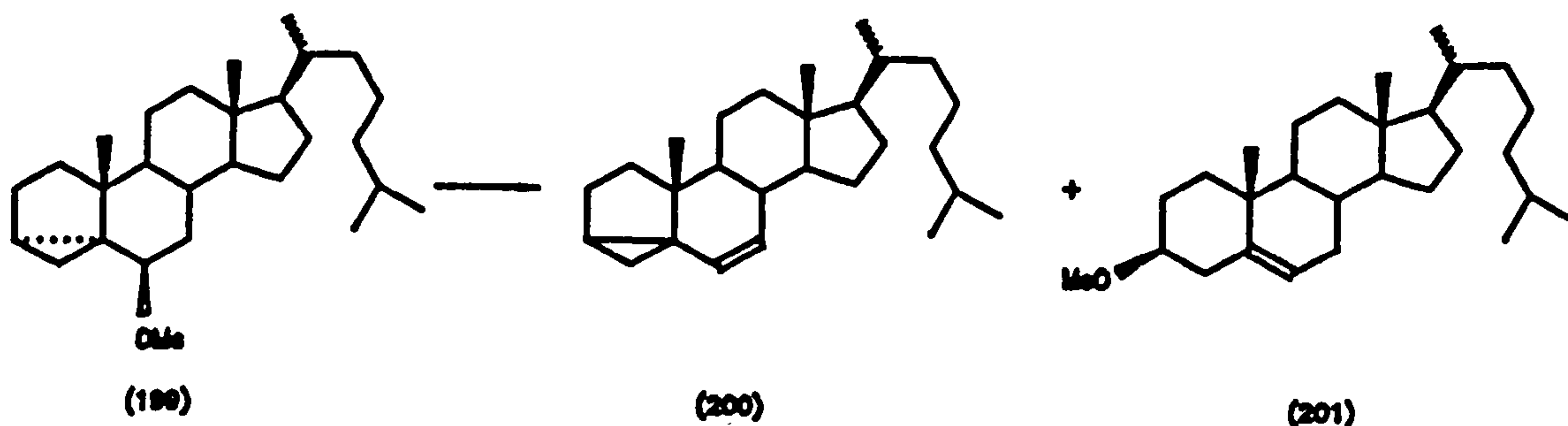


(198)

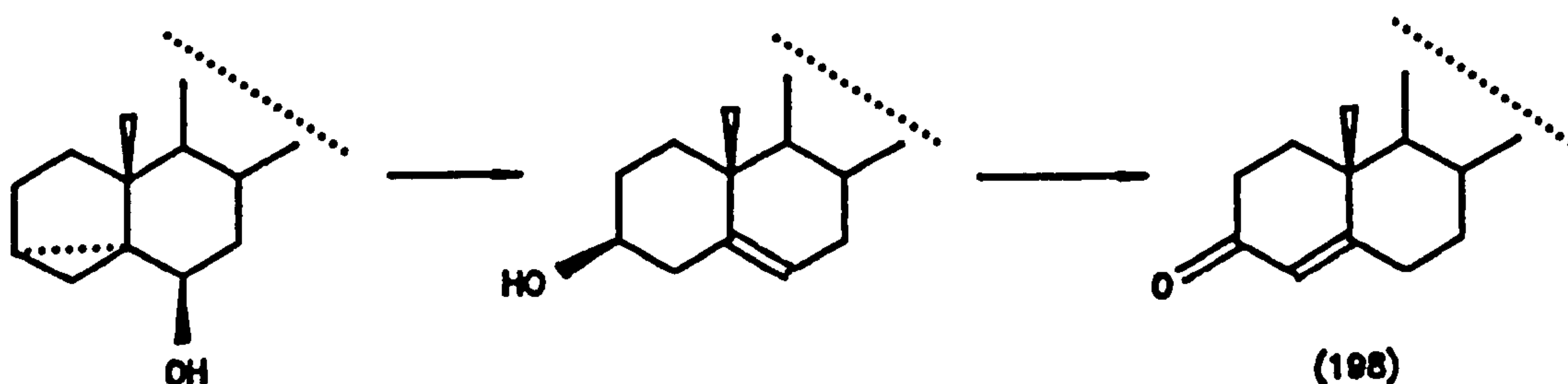
The major side product of the reaction, accounting for 20% of the material recovered, was identified as 4-androstene-3,17-dione (198) by comparison of its melting point and molecular spectra (^1H NMR, IR and UV) with an authentic sample. A trace of a third compound was isolated by column chromatography and shown to be 3 α ,5-cyclo-5 α -androstane-6-17-dione (111).

The side products isolated in this work differed from those obtained by Hanson⁹ who unexceptionally¹² isolated the required 3 α ,5-cyclo-5 α -androst-6-ene-17-one (185) (26%), its 17- α (2%) and β (4%) hydroxy derivatives and 3 α ,5-cyclo-5 α -androstane-6,17-dione (4%). Earlier work by Romeo⁸ and

Riegel *et al.*¹⁰ produced an analogous side product to the major side product obtained here. Thus, treatment of 3 α ,5-cyclo-5 α -cholesteryl methyl ether (199)¹⁰ gave, as well as the expected 6-alkene (200), small quantities of cholesteryl methyl ether (201). It is therefore envisaged that the 6-alcohol, via a similar mechanism, gives the 3 β -alcohol which then undergoes oxidation and rearrangement to form (198). A

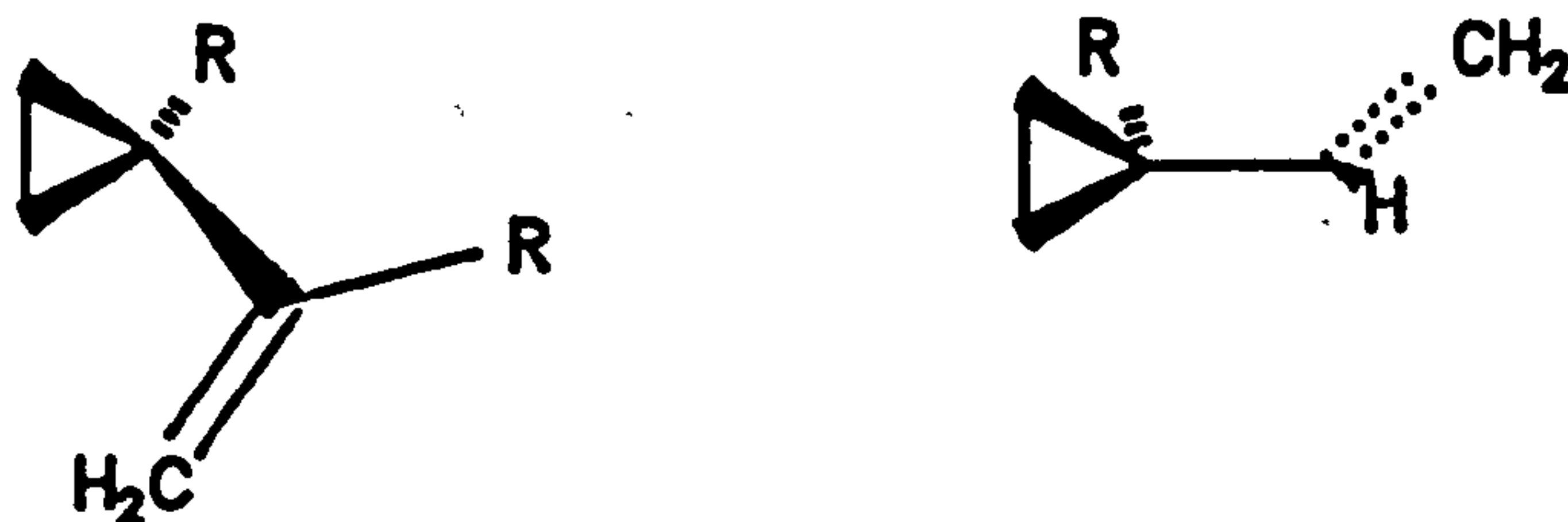


possible mechanism, would involve a 1,4-shift via a aluminum oxide-hydroxide complex and would presumably be intramolecular. However, where the rearranging group from 6-C is a methoxy moiety¹⁰ no subsequent oxidation occurs. The fact that different products were observed can perhaps be attributed to the type of alumina used (as noted in the dehydration of 9 α -hydroxy-4-androstene-3-17-dione¹³). As stated, the alumina utilised for the work carried out here was neutral, but neither of the above authors stated whether they used acidic, neutral, or alkaline alumina.



4.2.1 3 α ,5-Cyclo-5 α -androst-6-en-17-one as a vinylcyclopropane analogue

In Chapter 3 the ability of the cyclopropane ring to conjugate effectively with a π -acceptor group,¹⁴⁻²¹ (in that particular case the exocyclic 6-methylene group) was discussed in terms of whether the structure approached the cis-bisected conformation (torsion angle X-C(5)-C(6)-C(7)=0° where X is the midpoint between 3-C and 4-C, (202)). In the case of the exocyclic methylene steroid (180) it was determined that the conjugation present in the molecule was less than that of vinylcyclopropane (163) because steric repulsion between the methylene hydrogen and the 4-H cyclopropane atoms resulted in the twisting of the cyclopropane moiety away from the ideal cis-bisected conformation. Here (185), we are dealing with a equally ideal trans-bisected conformation.



(202)

Since, in the case of the alkene (185) no similar steric repulsions exist, it is reasonable to assume that the trans bisected (X-C(5)-C(6)-C(7) \approx 180°) system it possesses is more akin to (trans) vinylcyclopropane and therefore possesses a greater degree of conjugation than its exocyclic counterpart. This property, as discussed in Chapter 3, could potentially lead to some unusual chemical properties and rearrangements, e.g., rearrangement induced by thallium (III) ions.²²

4.2.2 Conjugation in 3 α ,5-cyclo-5 α -androst-6-en-17-one.

For maximum overlap between the cyclopropane orbitals and the sp² hybridised bond, and hence maximum conjugation, the torsion angle X-C(5)-C(6)-C(7) must lie within about 30°. ^{17,18} of the trans-bisected conformation (180°). A Drieding model of the steroid (185) indicated that this torsion angle was indeed very close to this value while molecular mechanics (Chapter 6) on the other hand gave a value of 158°. However, as discussed in Chapters 3 and 6, it should be noted that these calculations do not take into account the potential overlap between the cyclopropane orbitals and the sp² hybridised bond which would have a tendency to increase this value closer to 180°. With the lack of any steric repulsions in the steroid (185) the conjugation present in this molecule should be significant, and greater, than that of the methylene steroid (180). Confirmation of this assumption was found in the spectral properties of the steroid and, it is hoped, in the X-ray structure of the steroid which is currently under investigation.

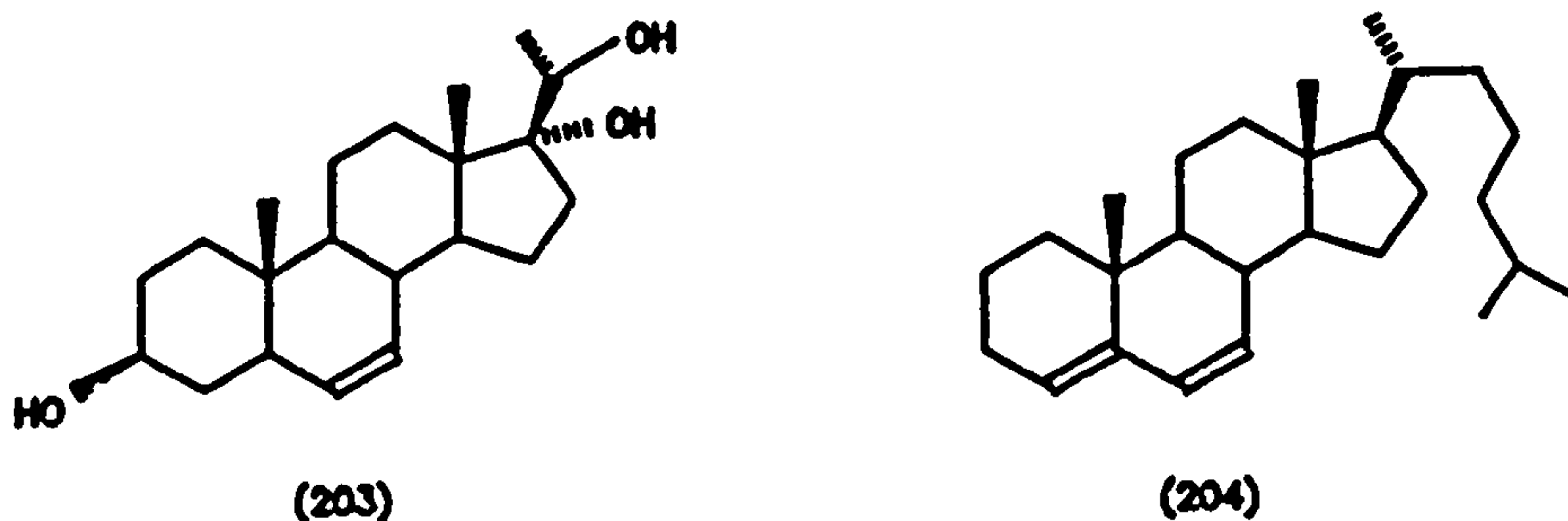
Spectral Evidence of Conjugation

The ¹H NMR, IR and UV spectra of the alkene (185) all potentially offer an insight into the amount of conjugation present in the molecule.

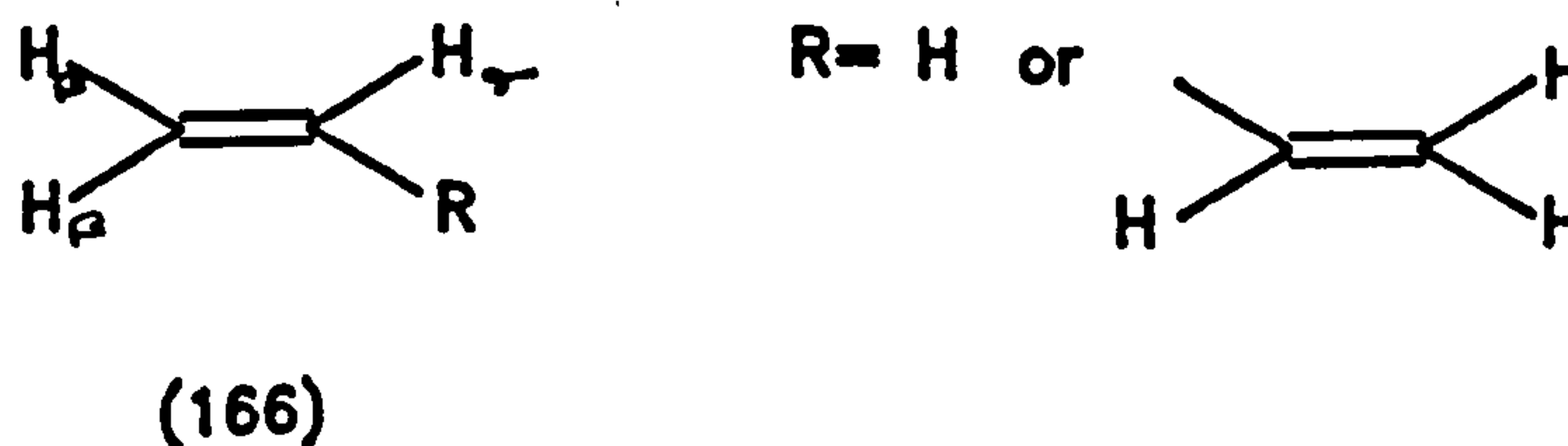
¹H NMR Spectroscopy

As discussed in Chapter 3, difficulties in estimating the degree of conjugation present in (180) arose because of the "tight" cis arrangement of the system. A similar problem

was not anticipated here. However, a literature search for steroids that possessed an isolated delta-6 double bond and/or the 4,6-diene system, used for a comparison with the steroid (185) provided a new set of problems. Although delta-6 or delta-4,6 steroids are comparatively rare, the ^1H NMR data for the steroid (203)²³ and the cholest-4,6-diene (204)²⁴ were available for a comparison of the position of the signal attributed to 6-H. However, because of complications in the spectra no author had attempted the specific



designation of signals. For example, the alkenic signals of the relatively simple alkene (203) do not appear as a singlet as might be expected, but as two doublets at $\delta = 5.26$ and 5.48 . (This splitting is noticed in other delta-6 steroids²⁵ and in cyclohexene itself.²⁶) Furthermore, in the delta-4,6 steroids, the alkenic protons are unresolved and appear as a complex series of absorptions between $\delta = 5.43$ and 5.63 . Thus a comparison with the alkenic signals from the steroid (185), $\delta = 5.59$ and 5.25 (6 and 7-H respectively), is very limited.



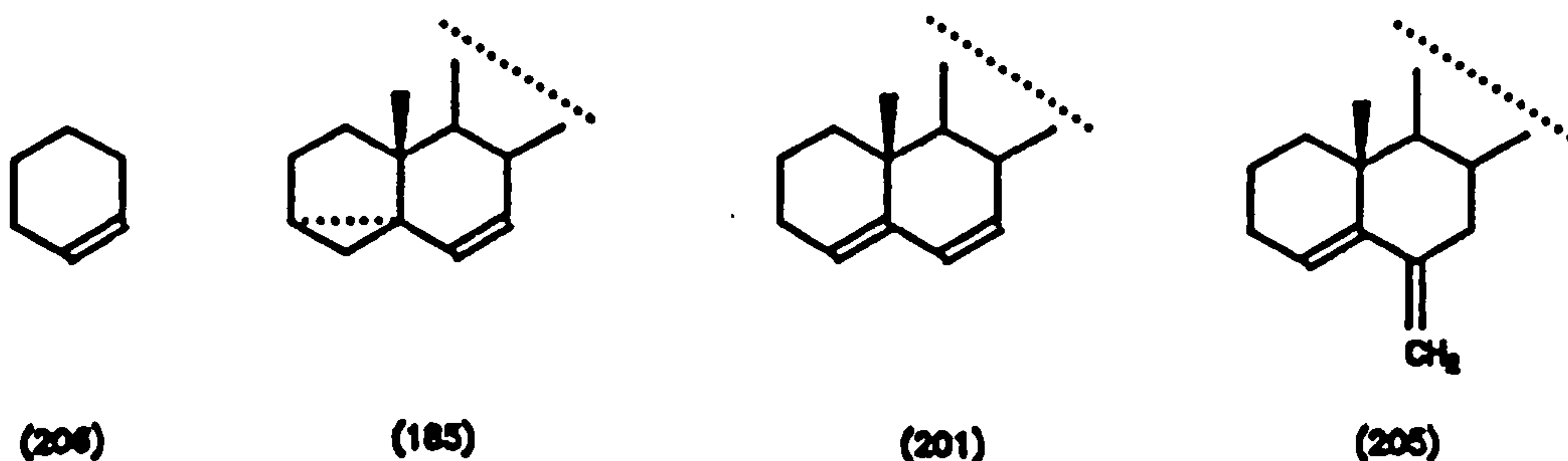
As discussed in Chapter 3, the introduction of a conjugating group into a system such as (166) induces a downfield shift in the α hydrogen's signal. Thus in (166) when R= H, both protons resonate at $\delta= 5.28$. However when R= CHCH₂, H _{α} resonates at $\delta=6.27$. This latter case is an example of maximum conjugation. Where this is restricted by steric factors the corresponding shift is diminished. Therefore, if it is assumed that in the diene (204) the most deshielded proton, whose signal occurs at $\delta= 5.63$, is the 6-H atom, then even without knowing whether the 6-H atom in (203) absorbs at $\delta= 5.26$ or 5.48 it is obvious that there is considerable conjugation in the cyclopropane steroid (185). Even if a small shift in the 6-H signal is due to the proton possibly being situated within the deshielding zone of the σ -aromatic cyclopropane ring (c. f. 19-C, Chapter 2) conjugation is still evident. A simple estimation, direct from these absorption values, indicates a level of conjugation of greater than 50% of that of the diene. This degree of conjugation is also evident when the steroid moiety is compared to vinylcyclopropane (163), where the additional alkyl groups are taken into consideration. However, a comparison between the respective signals of 7-H show that this type of estimation of conjugation is not foolproof. Compared to the non-conjugated alkene (203) and the cyclosteroid (185), the 7-C proton in (204) is deshielded more than anticipated, i.e., here a similar treatment does not work.

It should also be noted that because of the intrinsic differences between the two steroids (185) and (180) a direct comparison between the steroids cannot be made.

However, an indirect comparison can however be made since the diene system (204) is generally assumed to possess greater conjugation²⁷ than the exocyclic counterpart (205). Thus alkene (185) should possess considerably more conjugation than its exocyclic counterpart (180). Although a simplification, the above conclusion is in line with the predictions that steric repulsions in (180) twist the vinylcyclopropane moiety away from the maximum conjugating conformation.

Infra-red Spectroscopy

As mentioned above, data on a non-substituted delta-6 steroid were rather scant. Therefore, a comparison of the C=C stretching frequency of the steroid (185) was made with cyclohexene (206) and the 4,6-diene (204). Thus, for the simple cyclohexene, the double bond absorbs²⁸ at 1649cm^{-1} while absorption by the conjugated diene²⁹ occurs at 1620cm^{-1} . As would be expected, the steroid (185) absorption (1635cm^{-1}) lies approximately midway between these two

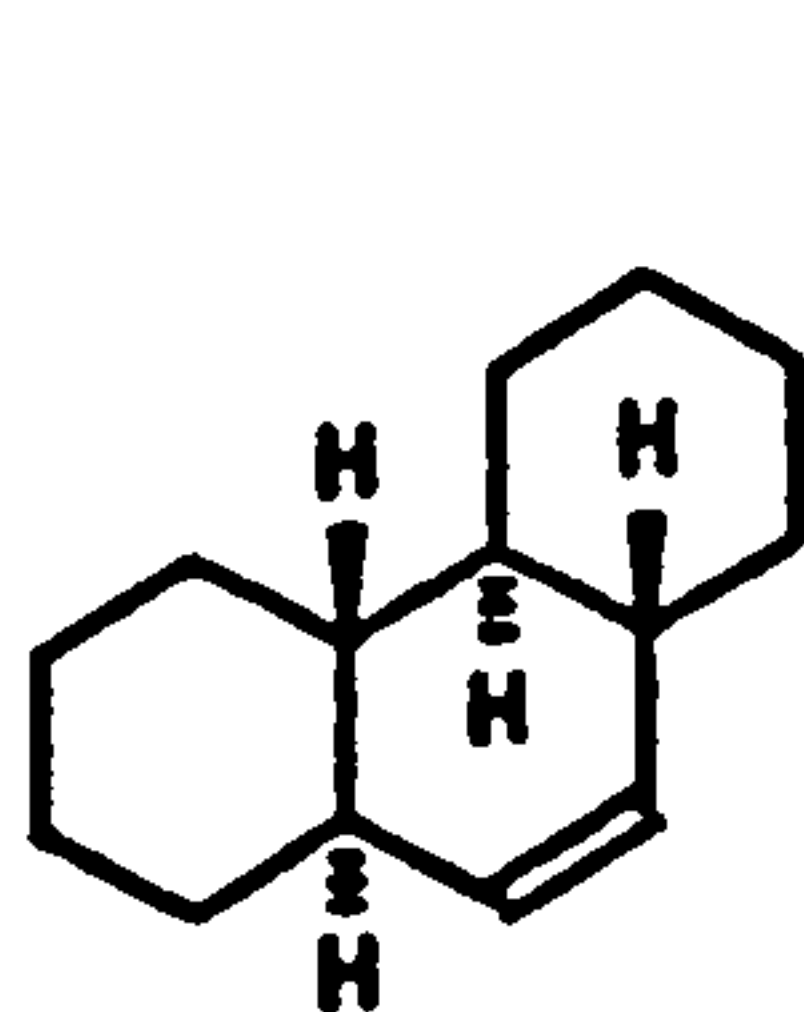


values. For vinylcyclopropane,³⁰ absorption occurs at 1639cm^{-1} but this discrepancy, i.e., that conjugation is apparently greater in the steroid, occurs because double bonds within rings have a tendency to absorb at lower frequencies.²⁸ This shift is generally however not great and

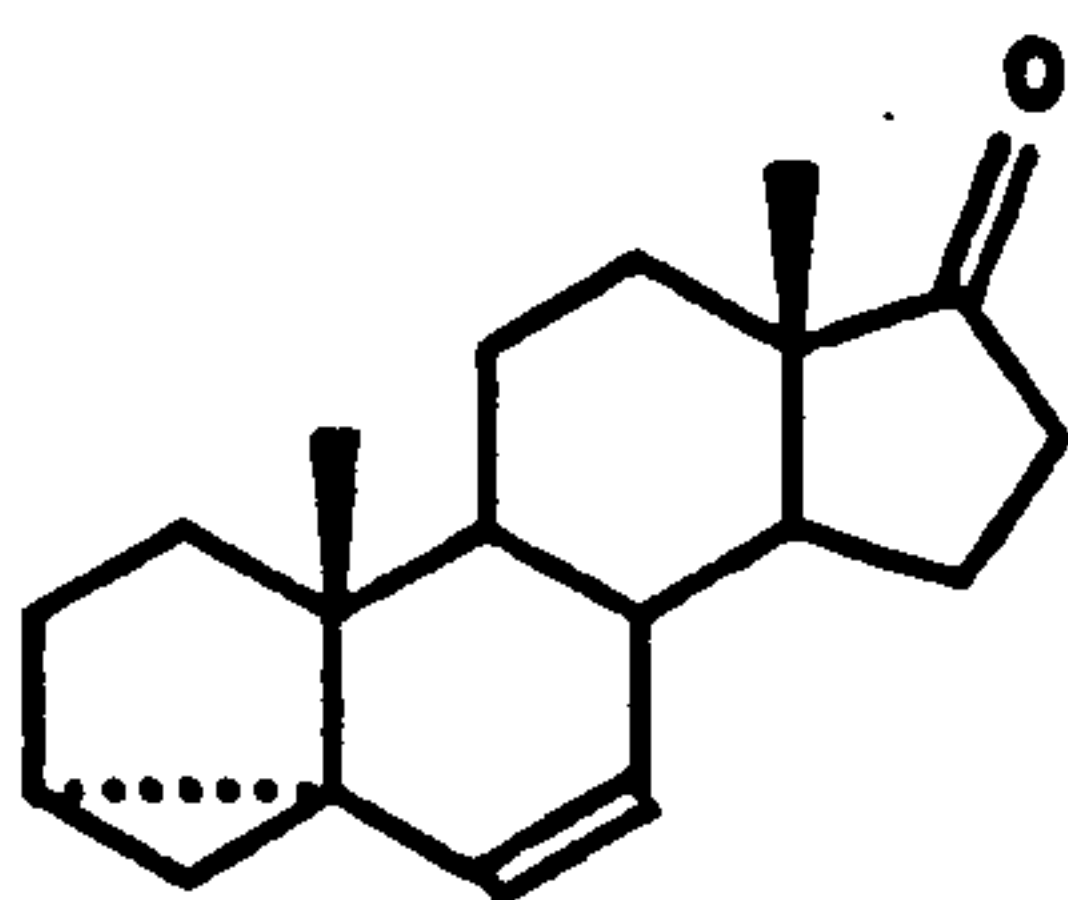
it would therefore be reasonable to assume that the conjugation present in the steroid is comparable with that found in vinylcyclopropane. Since the opposite is true for exocyclic double bonds, i.e., that as the ring size increases the frequency of absorption increases, it would not be justifiable to make an accurate comparison between the two steroids (185) and (180) which have C=C stretching frequencies of 1635 and 1642 cm^{-1} respectively. Indeed, "there are still a number of very interesting anomalies (in conjugation effects on C=C values) which still await an adequate explanation".²⁸ However, if, as above, it is assumed that the system (204) possesses a greater amount of conjugation than its exocyclic counterpart,²⁷ (205) then greater conjugation in (185) can be inferred from the data. Thus unlike the exocyclic steroid (180), compound (185) possesses a similar level of conjugation to that found in vinylcyclopropane (163).

Ultra Violet Spectroscopy

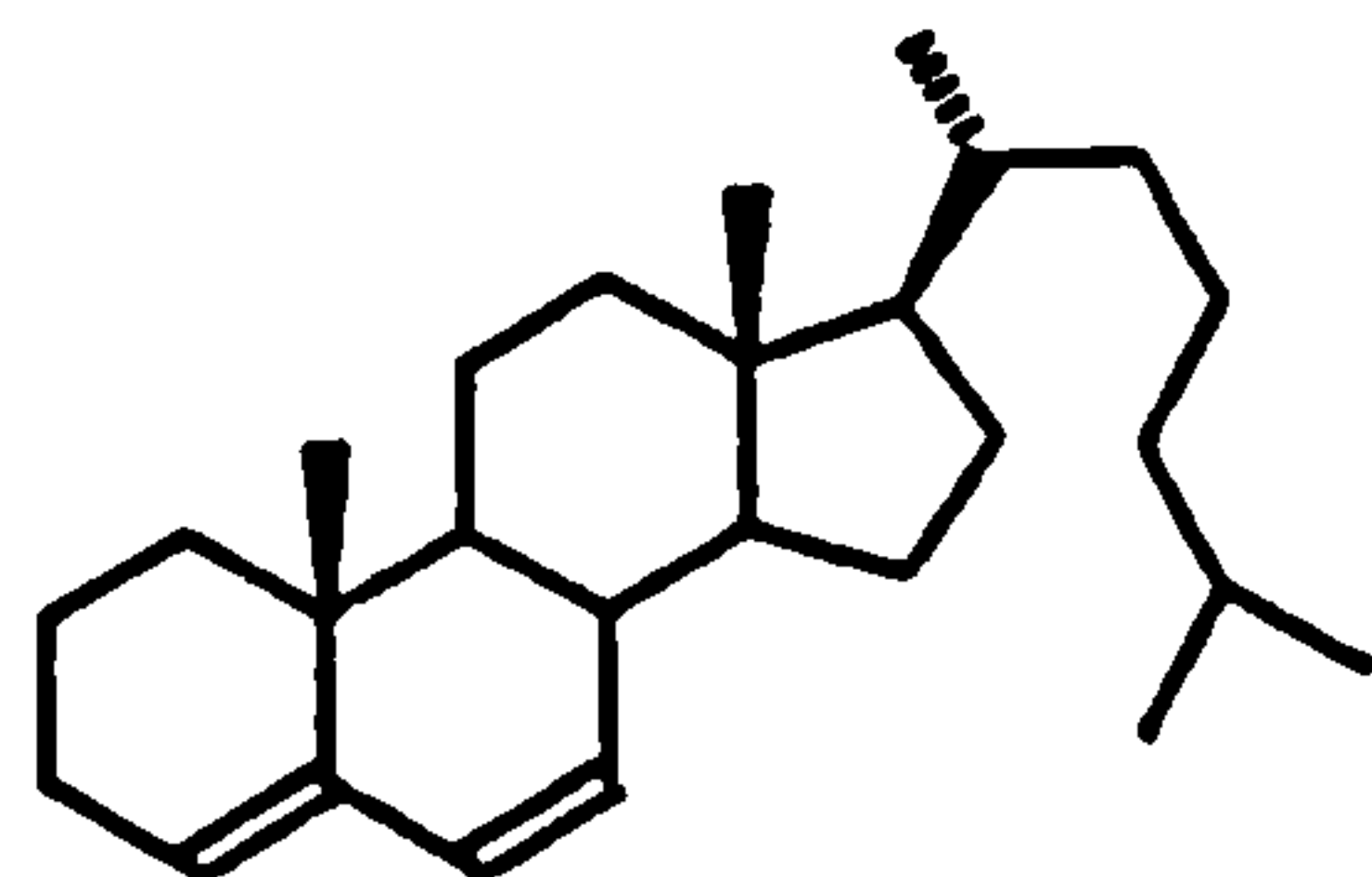
A further indication of conjugation in the steroid can be found in the UV spectrum of the steroid when it is compared to similar structures that possess either a second double bond in the place of the cyclopropane ring, e.g., (204) or a saturated carbon centre, e.g., (207). For the



(207)



(185)



(204)

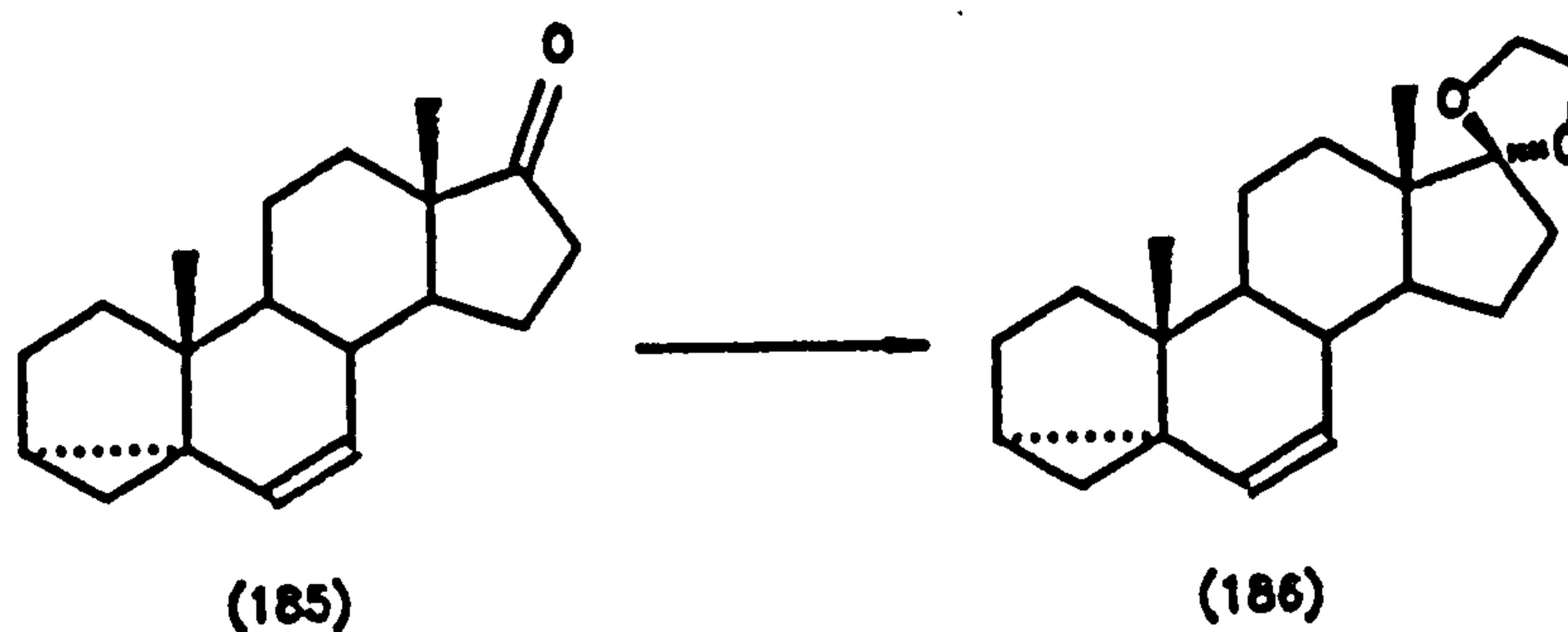
simple alkene (207), the chromophore absorbs at 193nm ($\epsilon = 11000 \text{ l.mol}^{-1}.\text{cm}^{-1}$), 3nm higher than cyclohexene because of the increased amount of strain in the system.³¹ When a double bond is introduced to the structure, as in the case of the conjugated 4,6-diene (204) its λ_{max} is shifted to 235nm ($\epsilon = 19000 \text{ l.mol}^{-1}.\text{cm}^{-1}$).²⁷ In the case of steroid (185), its λ_{max} can be found midway between these two results at 216nm ($\epsilon = 14000 \text{ l.mol}^{-1}.\text{cm}^{-1}$). Although an increase in the amount of strain at the ring junction carbon is created by the presence of the cyclopropane ring any shifting in absorbance maxima is small and cannot account for the whole of the 25nm shift.³² Unfortunately, further estimation of this conjugation cannot be gleaned from a comparison with vinylcyclopropane due of the considerable strain differences between the two systems. Furthermore, a comparison between the UV data of (185) and (180) is not possible because of the vague nature of the UV spectrum of (180) and the intrinsic geometrical differences between them.

The above data would therefore seem to indicate that conjugation is present in this molecule at a level comparable to that of vinylcyclopropane and at a level greater than that found in the exocyclic counterpart (180). However, as the comparison of ^1H NMR and IR data shows, this treatment is at best an approximation which, for the most part, fits reasonably well in these systems. There are most certainly additional complications to be considered if this simplistic approach is to be applied more accurately or indeed to other chemical situations. However, the results indicate the level of conjugation present in (185) is considerable and there-

fore the potential for further chemical studies on this steroid exists.

4.3 Formation of 3 α ,5-cyclo-5 α -androst-6-en-17-spiro-2'-(1,3-dioxolane) (186).

As discussed above, the protection of the ketone group was a prerequisite if the steroid epoxide, formed from the alkene, was to be reacted with a Grignard reagent. Although considerable problems arose in the protection of the 3,5-cycloparent (Chapter 3), similar problems were not anticipated in the protection of the alkene (185) because of the lack of a leaving group at 6-C.



The reaction conditions used were identical to those initially defined by Salmi,³³ i.e., a benzene solution of the steroid was reacted with an excess of ethylene glycol and a catalytic quantity of p-toluene sulphonic acid. The water formed was azeotropically removed by a cooled Dean-Stark apparatus. Isolation of the reaction mixture gave a clear oil which, with the aid of chromatography, was separated into two compounds. The major product, a white solid, was recrystallised from ethanol as fine plates and was shown by spectroscopy to be the required alkene (186). Conversion was evident by the presence of a 4H singlet in the ¹H NMR

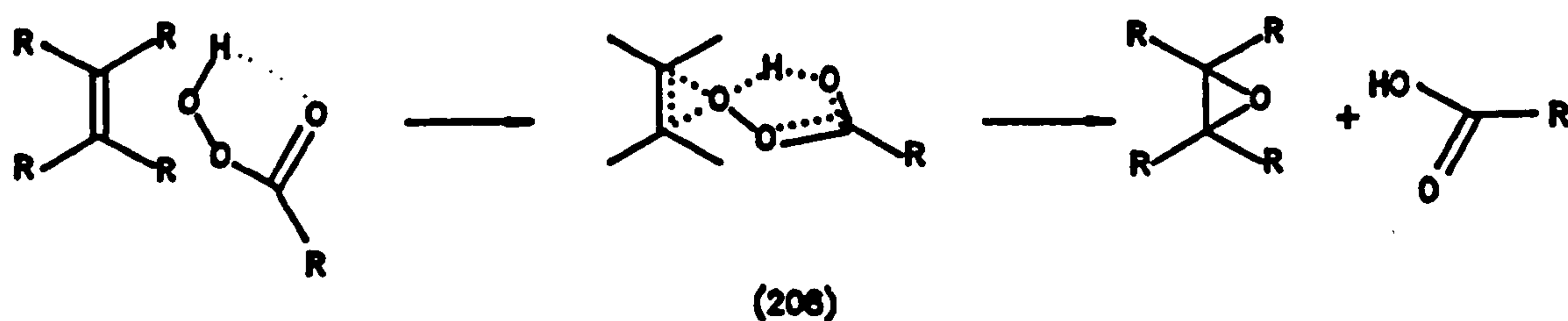
spectrum at $\delta = 3.86$ corresponding to the dioxolane protecting group. Unusually, the signal corresponding to the angular methyl groups, a singlet ($\delta = 0.93$) in the starting alkene, remained a singlet ($\delta = 0.89$) in the product. Conversion was further confirmed in the IR spectrum of the compound which showed no carbonyl absorption but strong ether absorption.

There was spectroscopic evidence to show that the minor product was the starting alkene (185).

Although this product could now be epoxidised to form (187) it was realised, considering the low yield of the epoxidation step,³⁵ that if this step was included in the reaction sequence, the overall yield from DHEA (97) to the epoxide would only be of the order of 5%. Therefore in an attempt to improve overall yields the protection of the carbonyl group was abandoned and the ketone-epoxide (209) reacted with dimethyl lithium cuprate, a reagent more epoxide specific than a Grignard reagent. The nucleophilic ring opening of the oxirane to yield the desired target molecules is discussed in section 4.5.

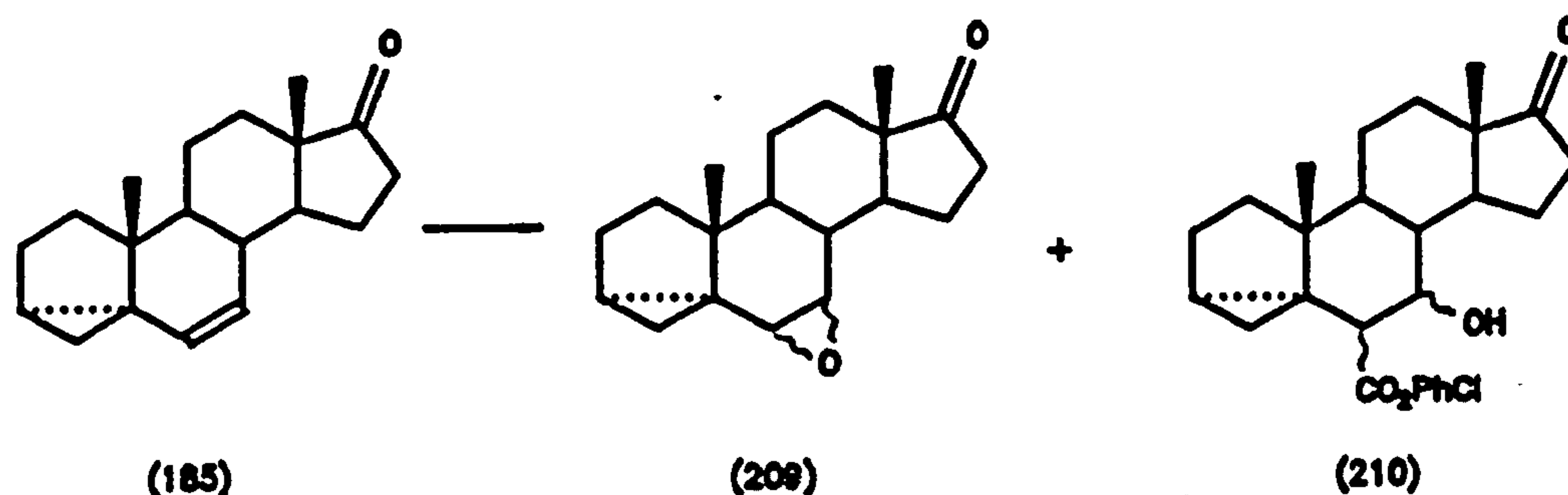
4.4 Formation of 6,7-epoxy-3 α ,5-cyclo-5 α -androstan-17-one (209).

The attack on a carbon double bond by a peracid to form an epoxide is generally believed to be a concerted process.³⁶ The most satisfactory representation of the transition state being shown below (208).³⁷ Belief that the mechanism does not involve ionic intermediates³⁸ is based on the demonstration by Schwartz and Blumberg³⁹ that the reaction rate of the epoxidation process shows no direct relation to the solvent polarity. Reaction rates can, however, be increased when benzene is used as a solvent, e.g., the epoxidation of cyclohexene with perbenzoic acid proceeds 30 times faster than a similar reaction utilising diethyl ether as the solvent.⁴⁰ This is attributed to the benzene allowing the intramolecular hydrogen bond to predominate, thus permitting the molecule to adopt the configuration strongly favoured for reaction. In ether, this intramolecular bonding is greatly reduced by hydrogen bonding with the basic oxygen of the ether.⁴¹



The conversion of the steroid alkene (185) to the epoxide (209) was undertaken by the method used by Hanson *et al.*³⁵ in which the steroid was reacted with *m*-chloroperbenzoic acid (MCPBA) in diethyl ether. Attempts using the

described procedure showed the reaction to be exceptionally variable in its outcome. Often, after the recommended 30 minute period, only starting material was recovered. On other occasions the reaction had apparently proceeded too far with the isolation of hydroxy esters, e.g., (210) a sign of the considerable instability of the epoxide. This property is discussed below.



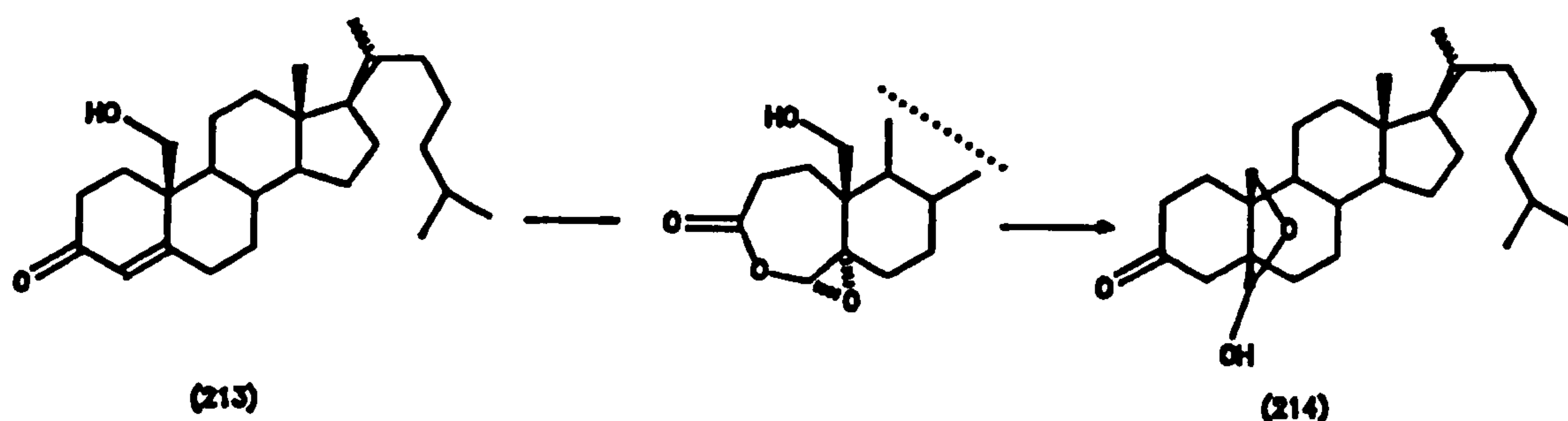
Consider the following: an ester such as (210) is formed when the side product carboxylic acid reacts with the epoxide, a reaction catalysed by mineral acids.^{42,43} However, although this situation arises for reactions performed in formic acid or reaction mixtures that contain a strongly acidic mineral acid, e.g., monopermaleic acid⁴⁴ or peroxytrifluoroacetic acid⁴⁵ it is usually not the case for peracid reagents such as perbenzoic acid and MCPBA when dichloromethane or chloroform are employed as solvents.⁴⁶ Where the epoxidising reagent is a derivative of a strong acid, e.g., peroxytrifluoroacetic acid, anhydrous sodium carbonate (or disodium hydrogen phosphate for reactions that require a longer period⁴⁷) may be used to scavenge the carboxylic acid and prevent the secondary reaction occurring.⁴⁸

However, in the work of Hanson,³⁵ it was noted that

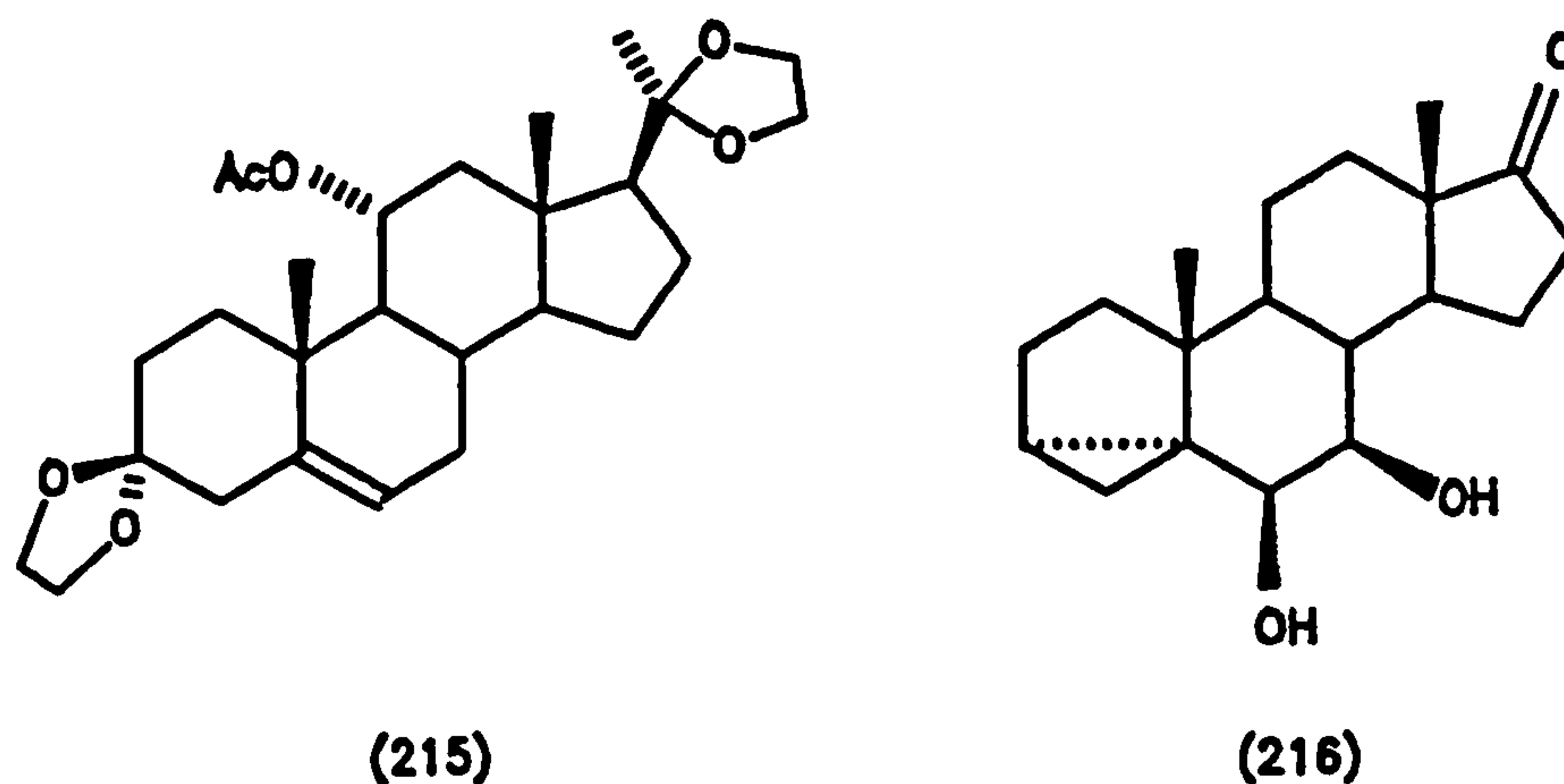
even under the mild conditions (MCPBA, dichloromethane and sodium carbonate) formation of the hydroxy ester still occurred. It is therefore a measure of the epoxide's considerable instability that the oxirane ring fragmented under such mild conditions. The instability, as noted by Hanson,³⁵ is most certainly due to the cyclopropane ring stabilising the incipient carbocation. Products are therefore determined by the nucleophilic components in the reaction medium.

As well as problems with instability, the desired product was also difficult to isolate in a pure state. Already noted³⁵ for its instability during sublimation and chromatography, the product, a clear brown oil, failed to crystallise from various solvent systems including a diethyl ether-petroleum mixture.³⁵ Proton NMR spectra of the crude reaction product was, as noted above, variable. The signals from the epoxidic hydrogens, two doublets ($J = 4.5$ Hz) at $\delta = 2.89$ (6-C) and 3.23 (7-C)³⁶ were never the only signals present that could be attributed to an epoxide. Other signals were found at $\delta = 3.00$ and $\delta = 3.65$. These four signals varied in strength for different samples but the relative strengths of the former pair appeared to predominate. (Note that the above signals were assumed to be pairs because of their similar strengths). A further investigation of possible structural effects governing the possible formation of isomers and the identification of these isomers was therefore undertaken. Unfortunately, in this work, only the signal at $\delta = 3.23$ was ever resolved as a doublet, a crucial factor in the identification of isomers.

rearrangement to form the lactone (214).⁵¹ Other compounds, for example, the equally hindered 5-ene (215) gave an epimeric mixture of α and β -epoxides when reacted with perbenzoic acid.⁵² These examples are accepted to be governed by the steric effects induced by the 19-C methyl group.



However, as mentioned above, a study of the overall shape of any of the 3,5-cyclosteroids either with Drieding models or molecular mechanics shows that the inserted cyclopropane ring causes the A ring to project into the α -phase of the molecule, thus apparently creating as much, if not more steric hindrance than the 19-C methyl group. Corroboration of this hypothesis can be found in the "surprising" formation of the $6\beta,7\beta$ -dihydroxy steroid (216) obtained by the osmylation of the alkene.⁹ The idea that considerable steric effects are induced by the cyclopropane ring is



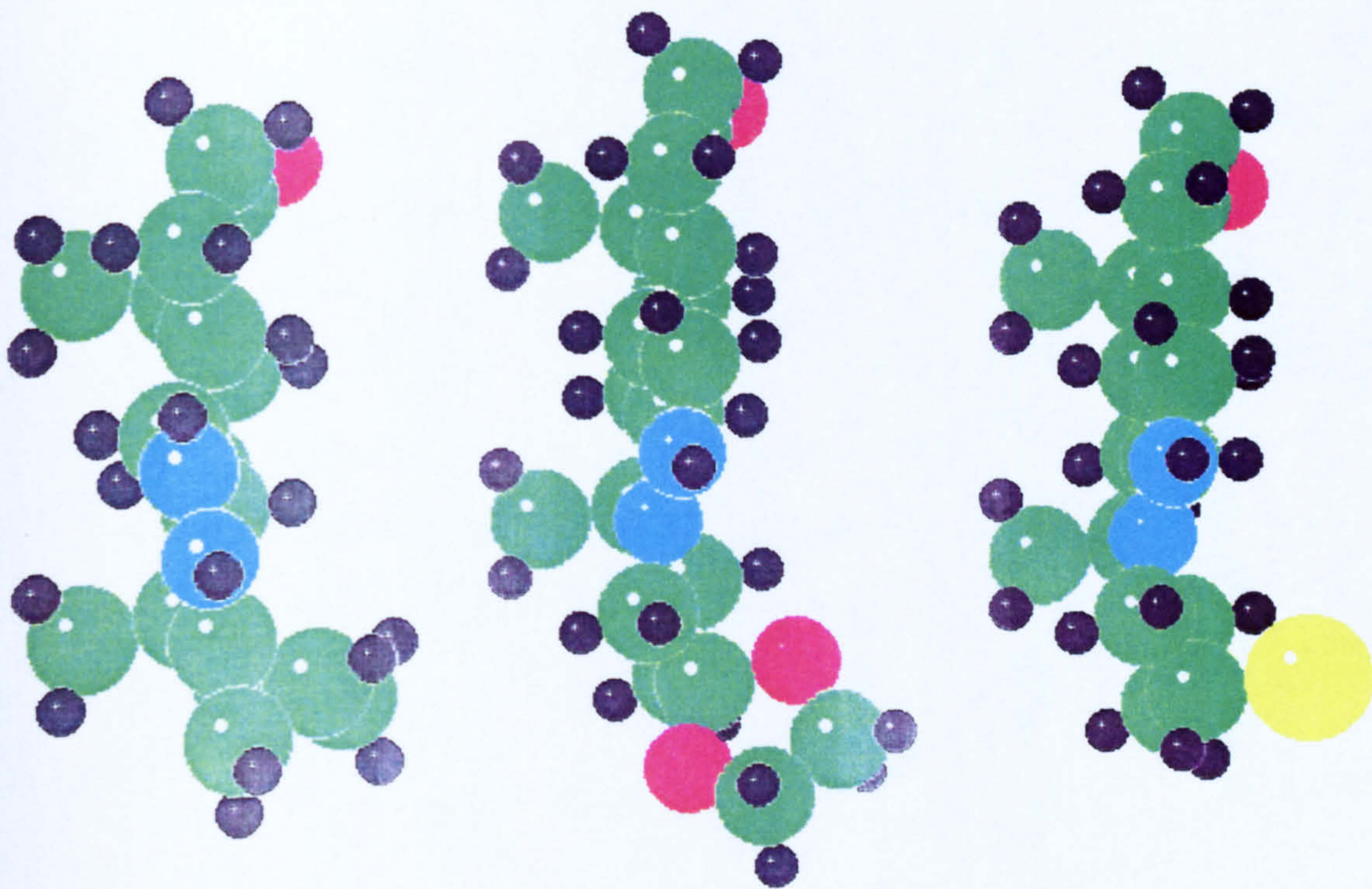
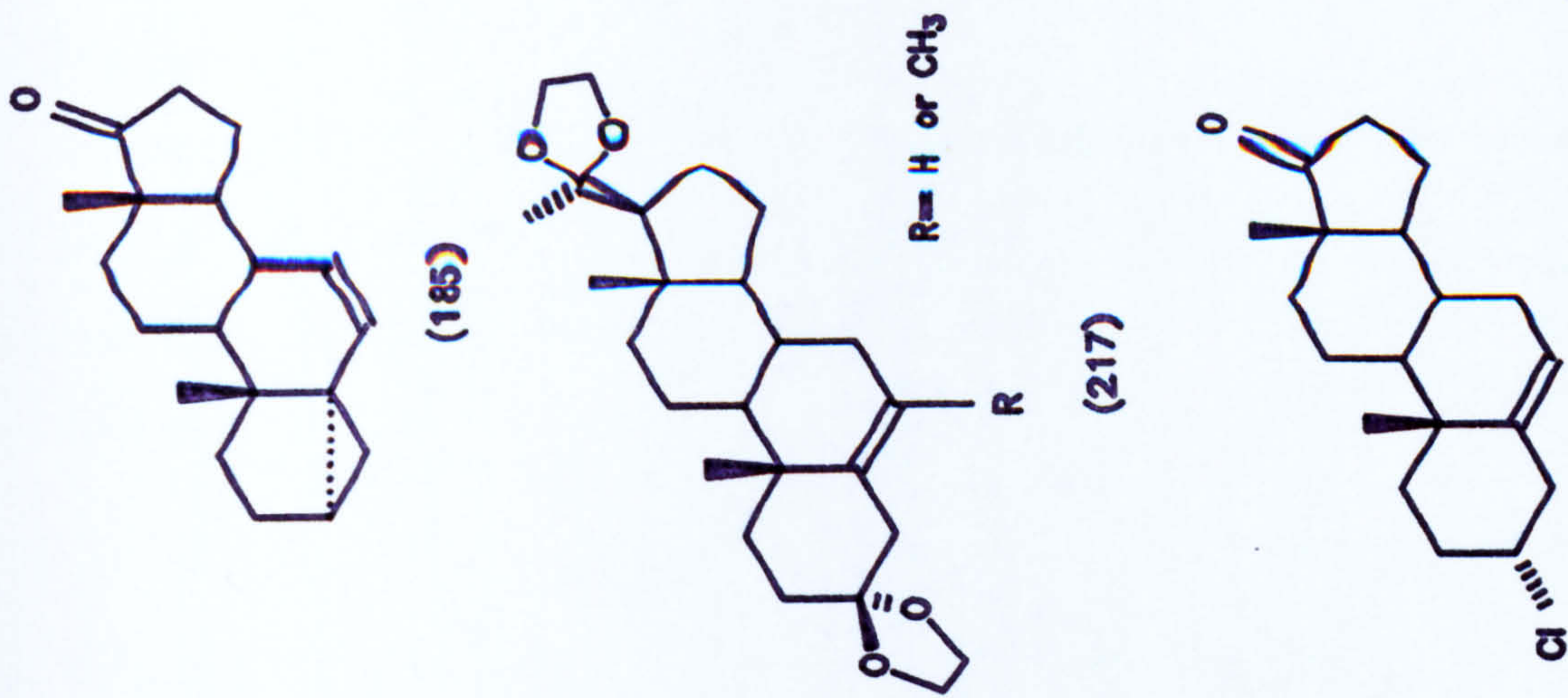
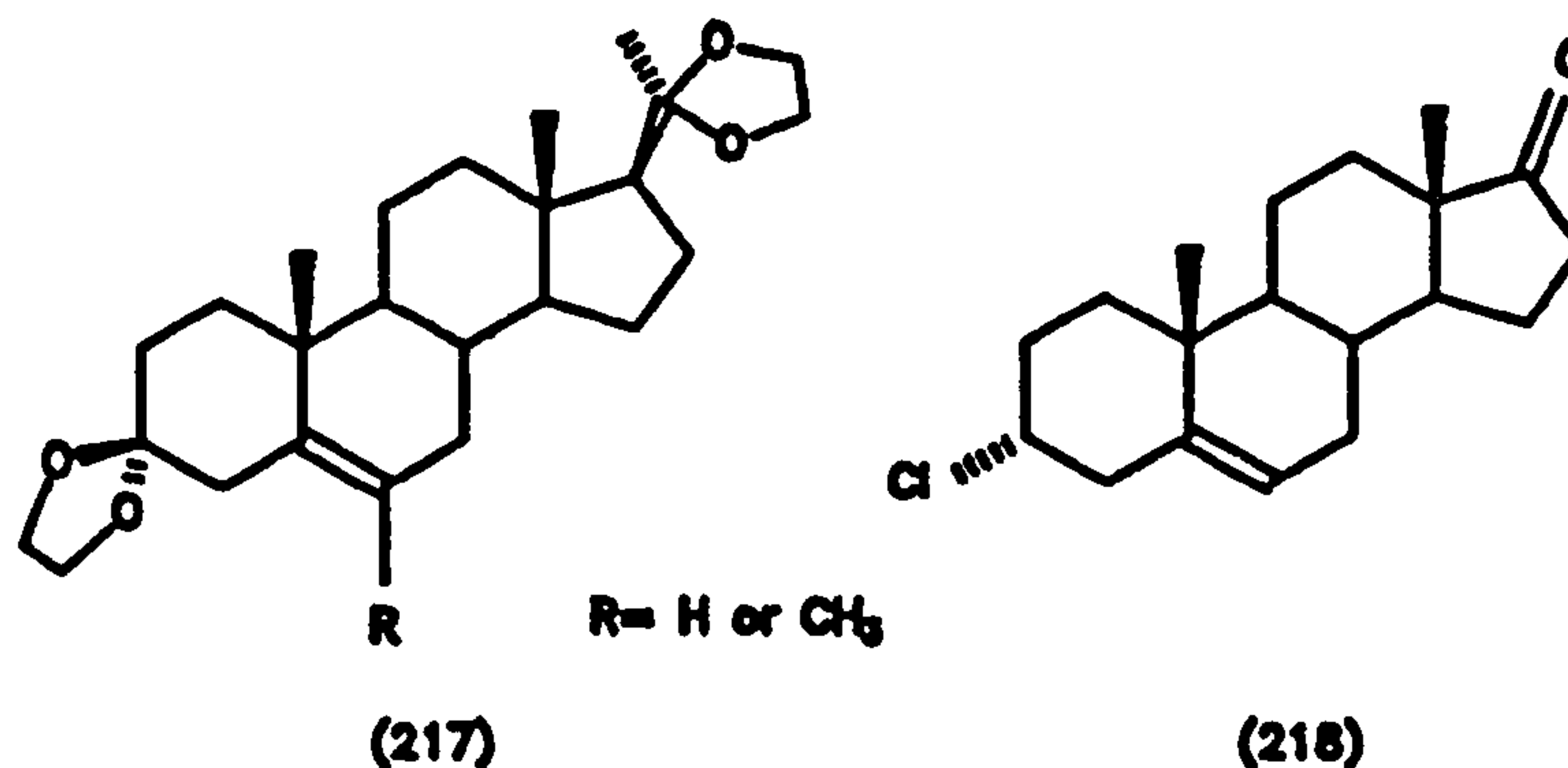


FIGURE 7

Comparison of the "γ-phase protrudents" (and resultant steric hindrance) of steroids (185), (217) and (218)

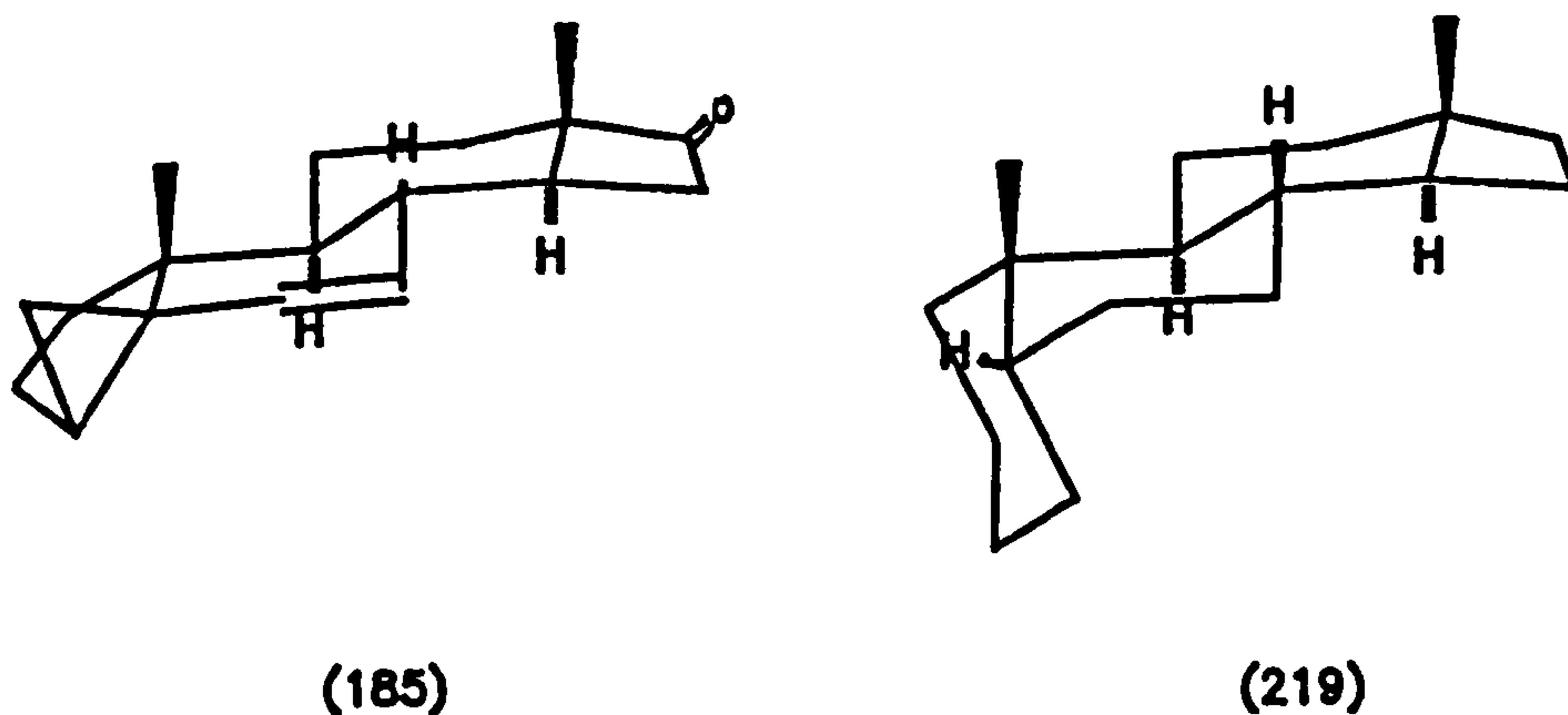
further promoted by a study of other epoxidation reactions involving steric influences by similar " α -phase protrudents".

For example, the epoxidation of the progesterone derivative (217), because of the 3α -oxygen atom, results in the formation of the β -epoxide as the major product.⁵³ Another example⁵⁴ is the



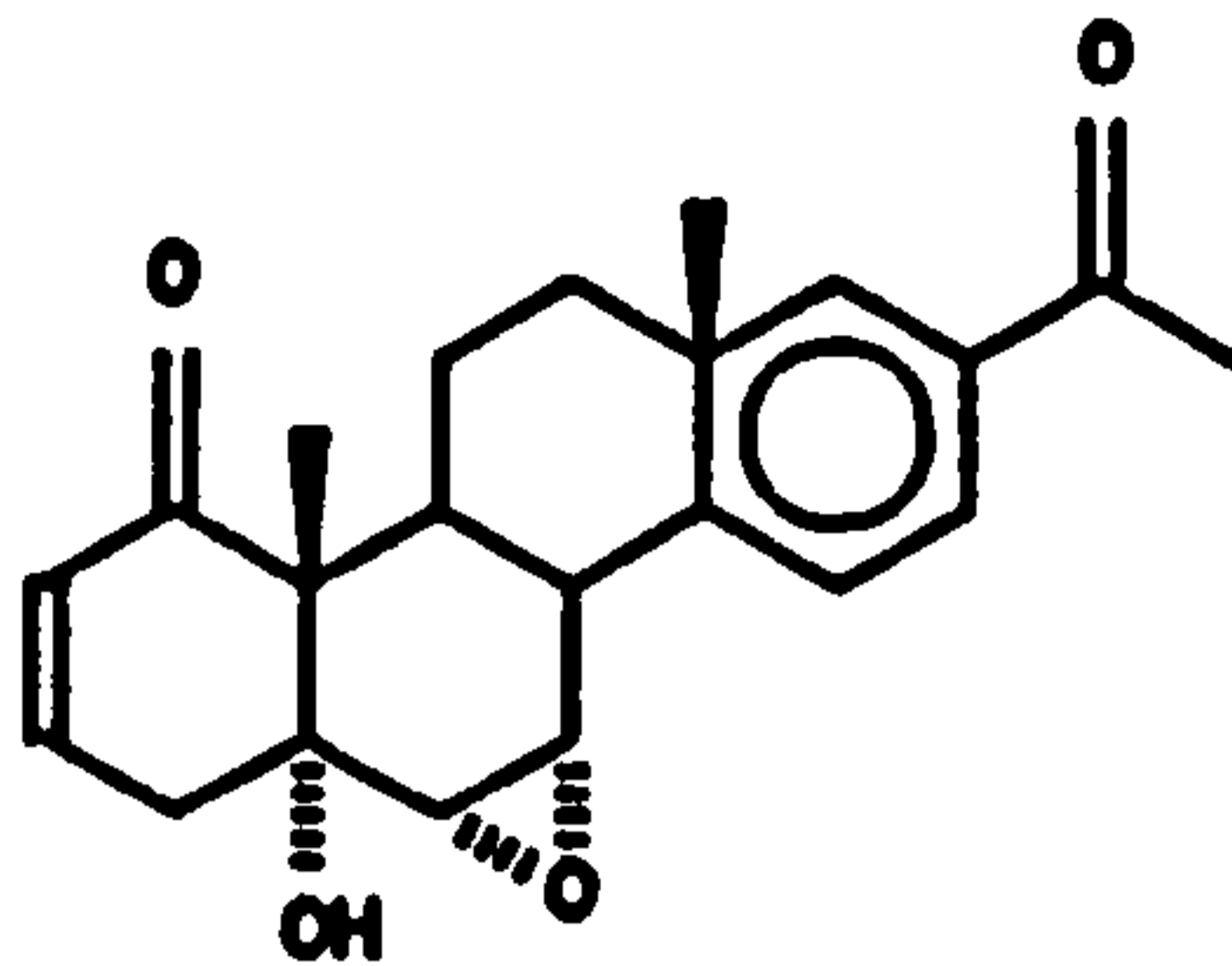
epoxidation of the 3α -chloro DHEA derivative (218), where again steric hindrance (this time by the axial chlorine atom) results in the formation of the β -isomer. If, as in the above examples where the 3-C substituent contribute to the shielding of the α -face it seems very likely that the conformation adopted by the 3,5-cyclosteroid also shields the α -face (Figure 7). Even though we are dealing with non-identical double bonds between the steroid synthesised here (δ -6) and the two examples (217) and (218), (δ -5) it seems likely that the cyclopropane moiety of (185) shields the double bond to a greater extent than the chlorine atom of (218). Furthermore, the notion that the methyl group of the cyclopropane steroids shields the double bond to a greater extent than the cyclopropane moiety is obviously false.

Also note that, the $3\alpha,5$ -cyclo- 5α -steroids structurally emulate the cis bonded A and B rings of the 5β -steroids (219). Epoxidation reactions of the delta 2, 3, and 6 steroids are directed by their non-planar ring system to the β -face.^{55,56} Therefore a similar result might be expected for the steroid (185). From the above we can therefore assume that the epoxidation of (185) is certainly not stereospecific.³⁵



Further searches through the literature for other examples showed that epoxidations at delta-6 were not as well studied as for the other steroid positions. This is perhaps not surprising as a literature search for the previous section showed that the delta-6 steroids have over the years been subject to considerably fewer studies than other steroidal alkenes. This was the case for a search of previous X-ray studies of 6,7-epoxides. Only one epoxide, the naturally occurring compound Nic 10, [($6\alpha,7\alpha$ -epoxy-5-hydroxy-17(13-18)abeo- 5α -pregna-2,13,15,17-tetraene-1,20-dione)] (220),⁵⁷ has to date been investigated and its data entered into the CSSR.⁵⁸

Since the designation of the 6,7 epoxide, defined as



(220)

the α -isomer (209a) by Hanson, was felt to be tenuous, further studies on this compound were carried out. X-ray crystallography was logically considered but it was not possible to grow suitable crystals of the product. Therefore molecular models of the two isomers (209a and b) were constructed in an effort to determine the correct structure. From the relevant dihedral angles of these models (Chapter 6) an estimation of the ^1H NMR coupling constants produced by the epoxidilic protons were made based on the Karplus equation⁵⁹:

$$^3J_{ab} = J^0 \cdot \cos^2\phi - 0.28 \quad (0^\circ \geq \phi \leq 90^\circ)$$

$$^3J_{ab} = J^{180} \cdot \cos^2\phi - 0.28 \quad (90^\circ \geq \phi \leq 180^\circ)$$

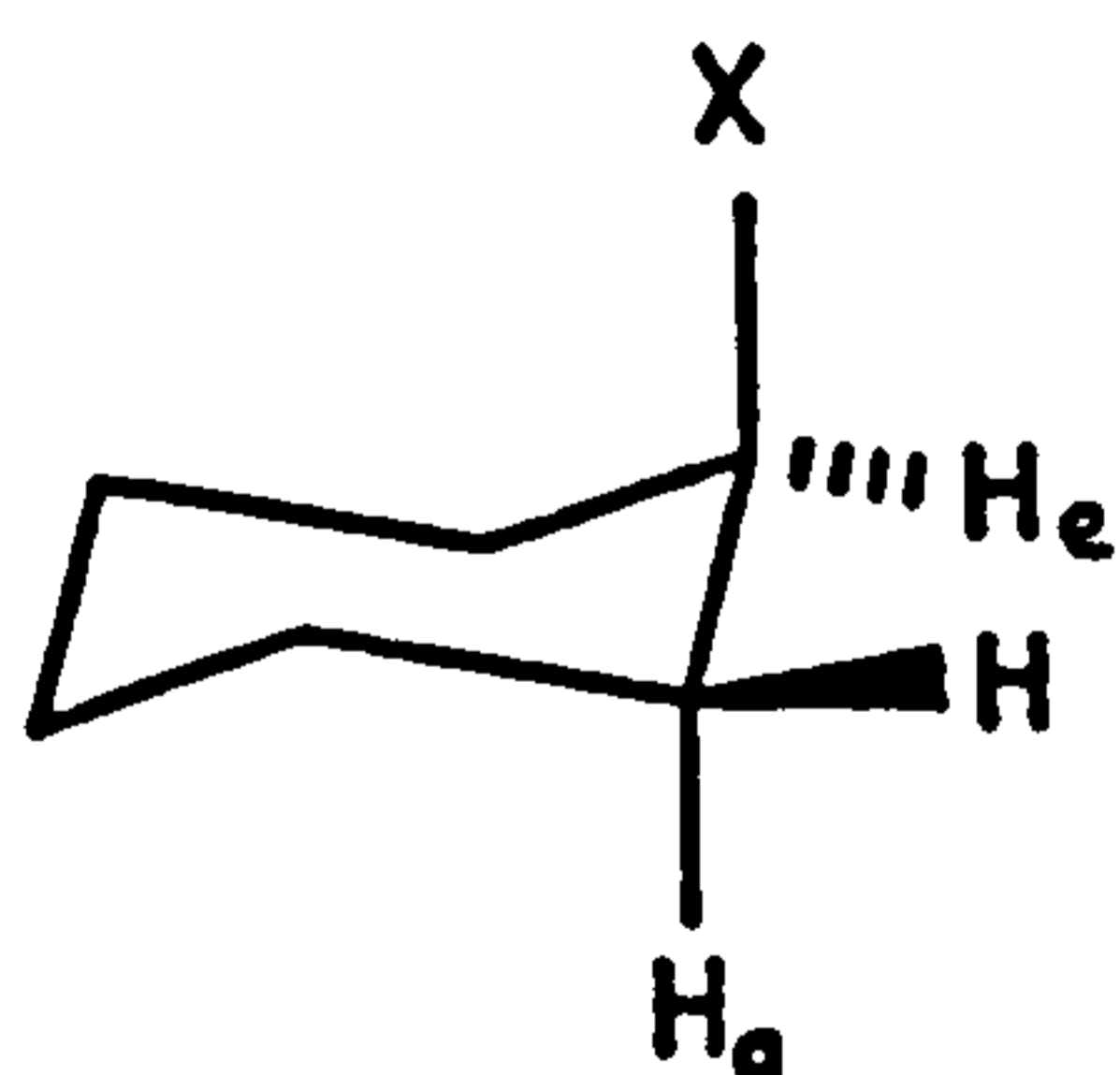
where the constants, J^0 and $J^{180} = 8.5$ and 9.5 respectively and ϕ is the dihedral angle between the two protons. These results are shown below in Table 5.

Table 5

Theoretical ^1H NMR coupling constants of the epoxidilic protons in the two epoxide isomers (209a) and (209b).

<u>STERIOD ISOMER</u>	<u>THEORETICAL COUPLING CONSTANTS, J: (Hz)</u>		
	H6-H7	H7-H6	H7-H8
6 α ,7 α -epoxide	6.7	6.7	4.9
6 β ,7 β -epoxide	4.9	4.9	5.6

When these results were compared to those derived experimentally (two doublets, $J = 4.5 \text{ Hz}^{35}$), it appeared that, with respect to the coupling between the two epoxidilic protons, the model of the β -isomer (209b) was a closer approximation to the product. However, the experimental results showed no coupling between the 7-H and 8-H atoms, and this can be taken to indicate an antiperiplanar relationship between 7 and 8-H. For example, in a rigid system, coupling between two vicinal protons H_a and H_e is reduced, when an electronegative atom is antiperiplanar to one of the

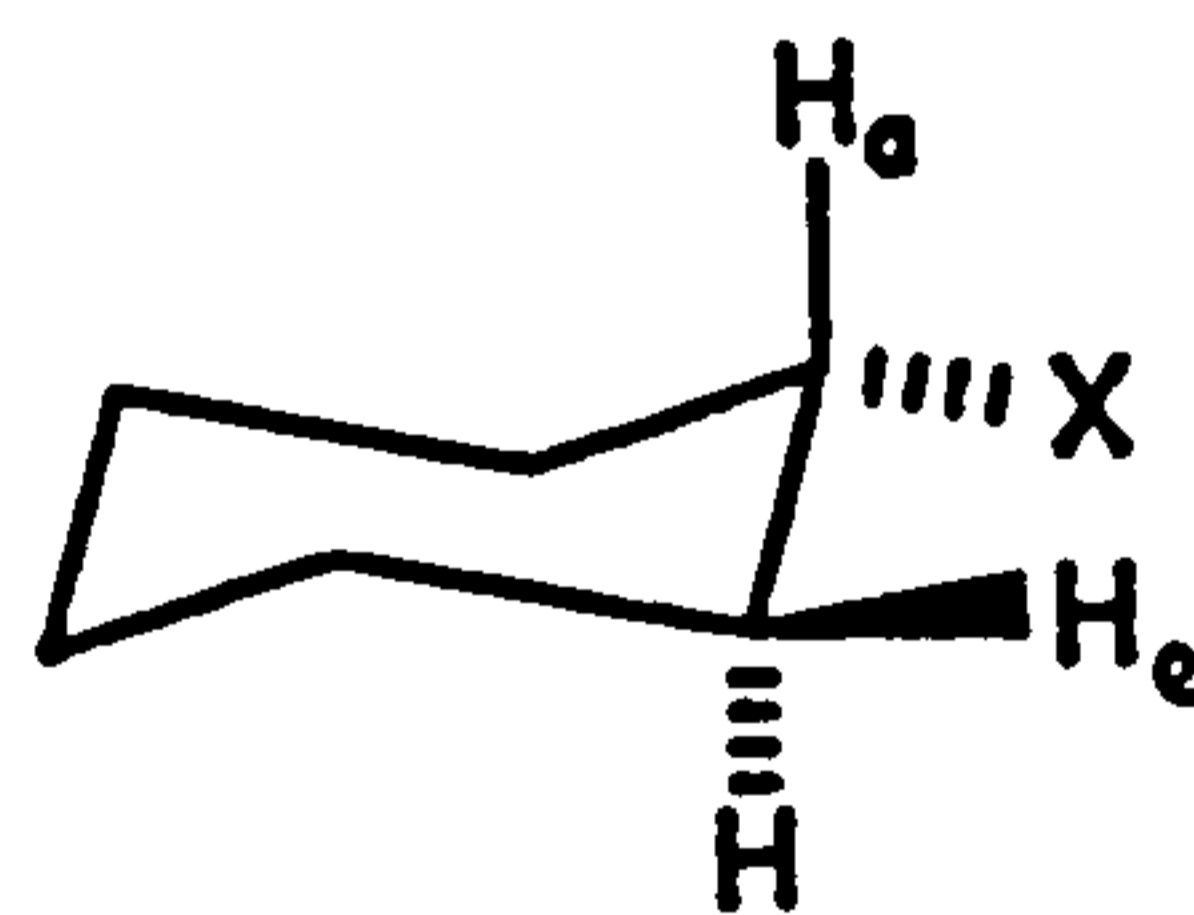


(221)

X = OH

OAc

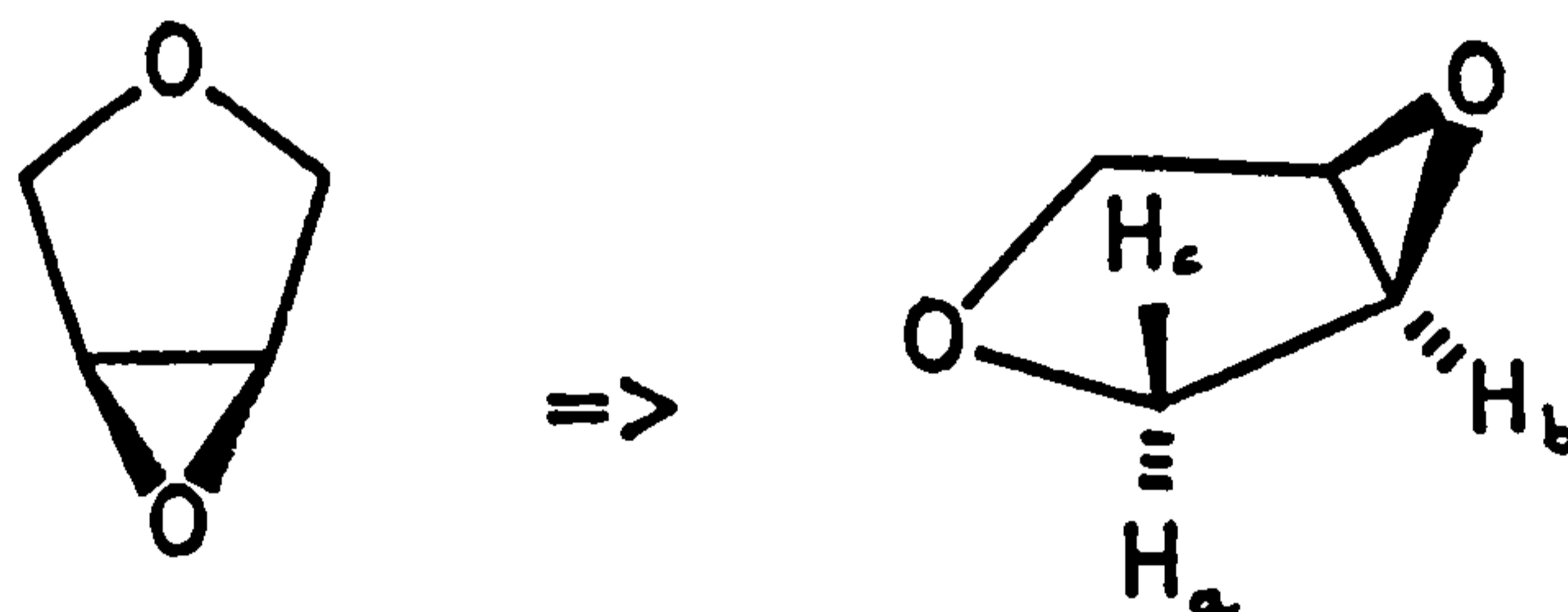
Br



(222)

atoms.²⁷ For the cyclohexane system (221) the coupling constant J_{ae} is only 2.5Hz when X = OH, OAc or Br but 5.5Hz in (222) where the electronegative atom is no longer antiperiplanar. In an extreme case, for example 3,4-epoxytetrahy-

dofuran, (223), which has a plane of symmetry and therefore shows only 3 signals, one anticipated coupling is not observed at all. The dihedral angle between H_b and H_c is close to 90° and therefore it is not really surprising that there is no coupling between them. However, in the case of H_b and H_a the dihedral angle is between 0 and 30° and a coupling constant of between $6-8$ Hz would be expected. No coupling is observed primarily because the electronegative oxygen lies



(223)

antiperiplanar to H_a . Therefore there is a contradiction here. If this is the reason for the lack of observable coupling between $7-H$ and $8-H$ in the steroid epoxide, the epoxidic oxygen must be in the α -position to lie antiperiplanar to the 8β hydrogen, in conflict with that indicated by the molecular mechanics models. Note, however, that it could be said, as indicated in diagram (221) that small amount of coupling should be observed, not none at all, but other effects such as a greater degree of ring strain could play an unknown part.

In an attempt to ascertain whether or not the molecular model was in fact giving a reasonable representation of the product several other steroids, preferably whose structures had been defined by x-ray crystallography, were modelled and these compared to their relevant 1H NMR experimental data.

This, it was hoped, would indicate the accuracy of the models and determine if the lack of 7-H 8-H coupling was caused by a factor other than the presence of an anti-periplanar oxygen atom.

The first compound studied was the naturally occurring aromatic D ring steroid Nic 10 (220) whose X-ray structure had been determined by Begley *et al.*.⁵⁷ The calculated coupling constants (between 6-H, 7-H and 8-H) derived from a molecular model (Karplus equation⁵⁹) and the experimentally obtained results are shown below in Table 6.

Table 6

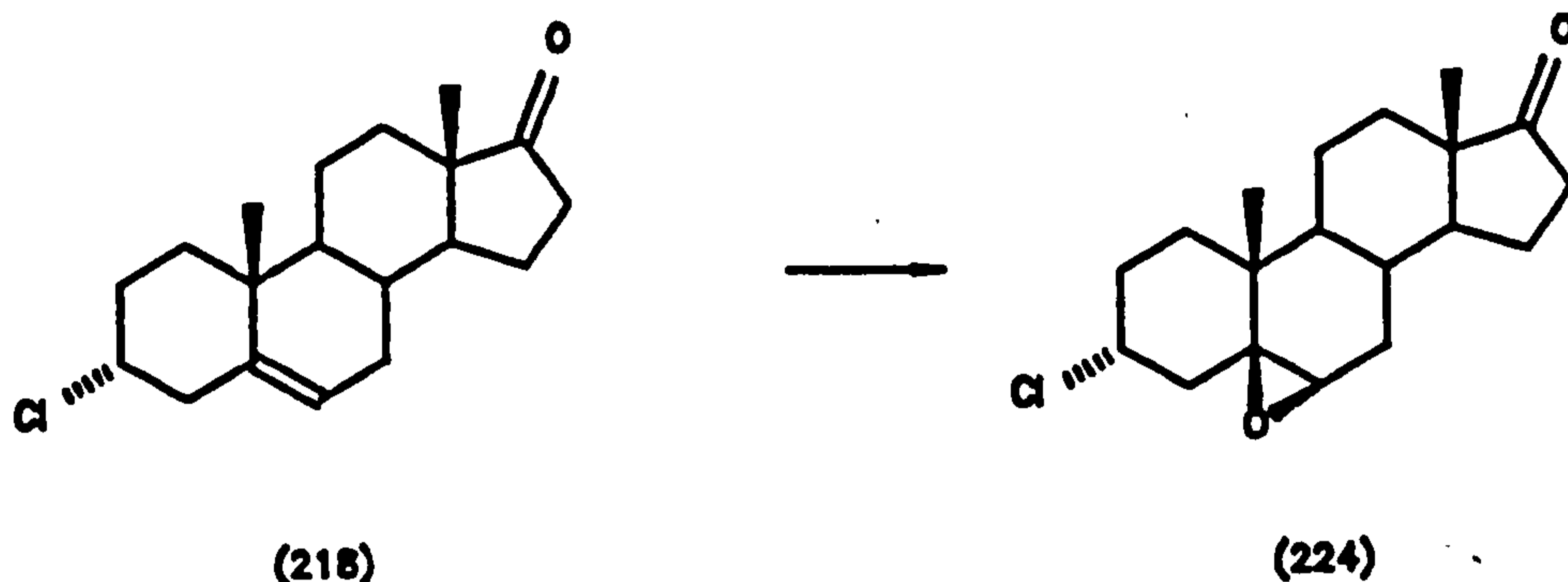
Comparison between theoretical and experimentally derived ¹H NMR coupling constants for Nic 10 (220).

	<u>Coupling Constants, J (Hz)</u>		
	H6-H7	H7-H6	H7-H8
Found	4.0	4.0	2.0
Calculated	4.0	4.0	6.4

It can be seen that from the above results that the model created produced a very accurate estimation of the coupling between the epoxidilic hydrogens. The coupling between the 7 and 8 protons is considerably different, but this can however be explained by the oxygen atom antiperiplanar to 8-H. The observed coupling of 2 Hz indicates that in this system the antiperiplanar oxygen does not cause complete elimination of the coupling between protons at

position 7 and 8. If a similar reduction in the relevant coupling constant of Nic 10 is applied to the α -epoxide (209a) a perhaps small unobserved coupling would be present but an exact value cannot be applied because of the difference in structures. Rather this is taken to indicate that some form of coupling between the 7 and 8 protons should be observed in the 6α - 7α epoxide (209a).

As already mentioned, Nic 10 was the only 6,7-epoxy-steroid that had been subject to an X-ray analysis and registered on the SRC Crystal Structure Search and Retrieval database. However, other steroid epoxide models confirmed the accuracy of the method for estimating the coupling constants of this type of compound. As discussed above, the epoxidation of 3α -chloroandrost-5-en-17-one (218) leads to



the 5β , 6β epoxide (224)⁵⁴ whose experimental coupling constants are shown below, along with the theoretical values derived from the molecular model, in Table 7.

Table 7

Comparison between theoretical and experimentally derived
¹HNMR coupling constants for epoxide (224).

	<u>Coupling Constants, J (Hz)</u>	
	H6 α -H7 α	H6 α -H7 β
Found	3.0	0.0
Calculated	5.0	0.3

Again the model fit is a good approximation. In this example, it is the coupling between protons 6 α and 7 α that would be expected to be reduced because of the antiperiplanar relationship between the oxygen and the 7 α proton. Secondary splitting of the epoxidilic proton's signal, by the 7 β proton, would be virtually undetectable.

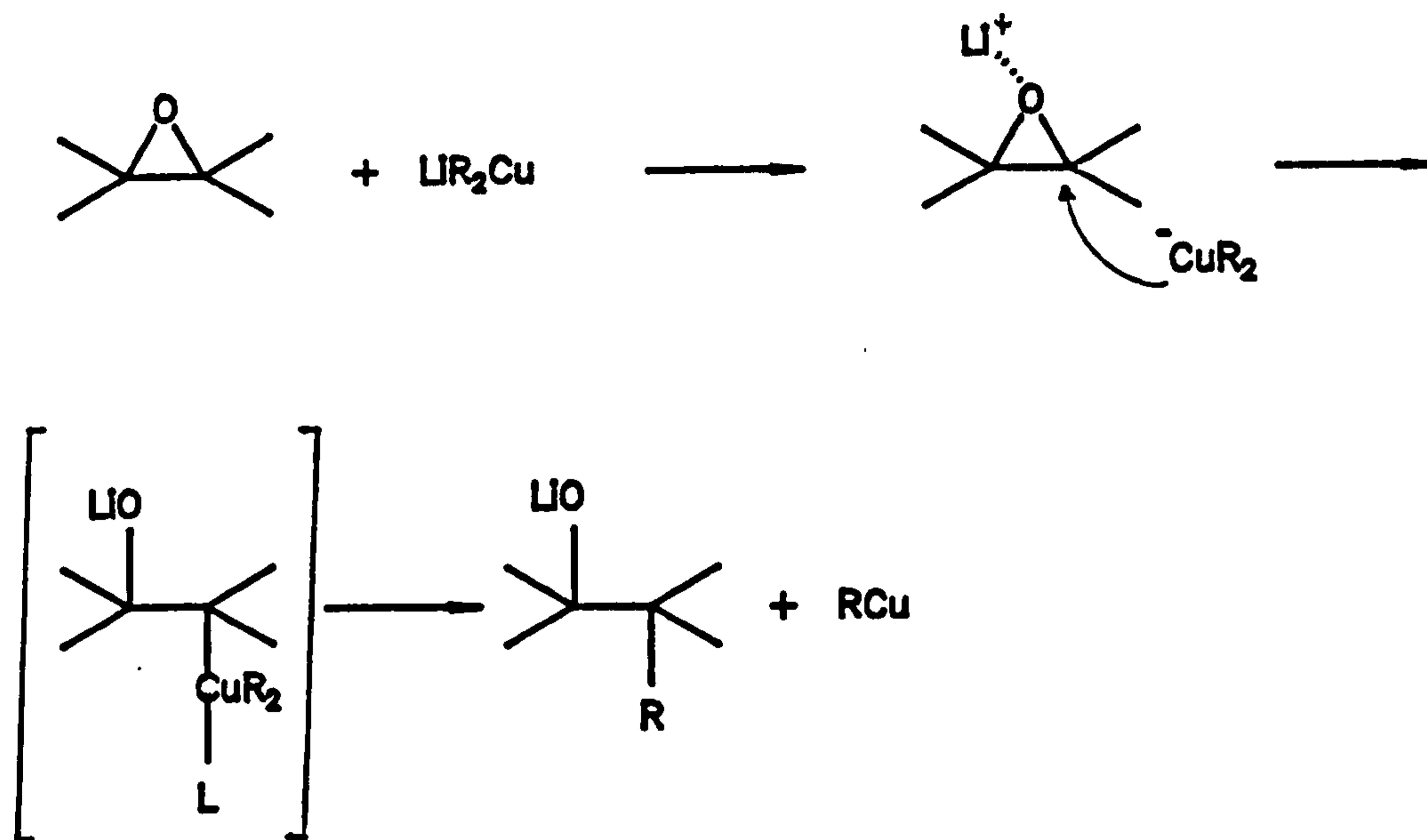
In conclusion, these above examples show that accurate models of various steroid epoxides can be produced with the molecular mechanics utilised here. However problems are encountered with the steroid central to the discussion; (185). The molecular model of the 6 β ,7 β -epoxide (209b), with respect to epoxidilic proton coupling, fits reasonably well with data quoted by Hanson³⁵, but also predicts (an unobserved³⁵) coupling between atoms 7 and 8-H (J= 5.6Hz). For the 6 α ,7 α -epoxide (209a) the predicted coupling between the epoxidilic protons are not consistent with those quoted³⁵ nor is an expected 2Hz coupling between atoms 7 and 8-H. The work carried out here indicated that a varying epimeric mixture was the most likely outcome of the reaction but

difficulty in separation, because of the instability of the products, prevented the determination of coupling constants. Thus no comparison to the molecular models or to Hansons data can be made.³⁵

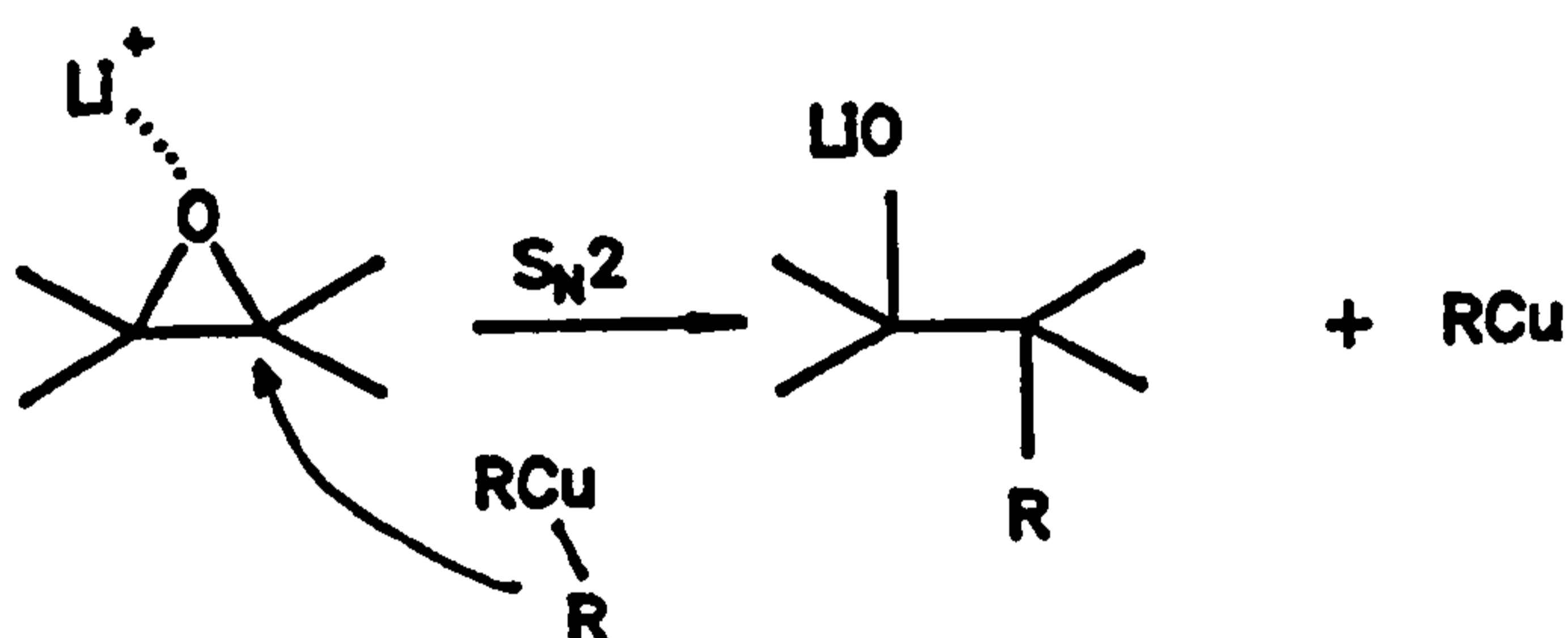
In view of the problems encountered in this work it was decided that no further attempts at purifying the unstable epoxide would be attempted and that the product, after removal of the peracid and carboxylic acid, would be reacted directly with dimethyl lithium cuprate. The stable products could then be separated, and by virtue of their configuration, used to identify the stereochemistry of the epoxide.

4.5 Formation of 6β -methyl- 7α -hydroxy- $3\alpha,5$ -cyclo- 5α -androstane-17-one (44).

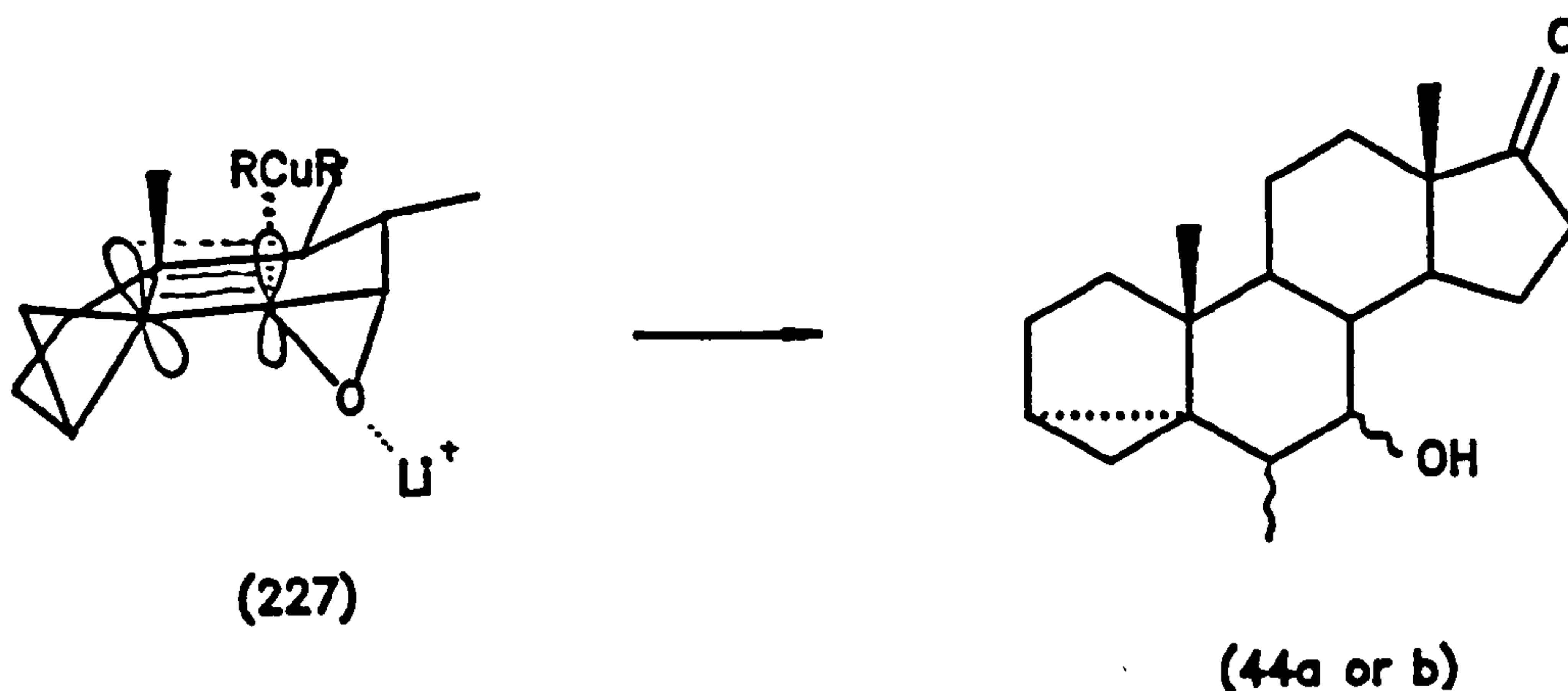
The nucleophilic ring opening of oxiranes by organometallic reagents is a useful synthetic method which has been limited in scope by competing reactions arising from either the Lewis acidity or basicity of the reagent. However, dimethyl lithium cuprate⁶⁰ and other lithium cuprate reagents⁶¹ have been shown⁶²⁻⁶⁴ to largely circumvent these side reactions which are encountered with other organometallic reagents such as Grignard reagents. Equally as important for this work is the relative inert nature of organocuprates to carbonyl groups. Thus, although Grignard reagents were initially proposed for the oxirane ring opening, dimethyl lithium cuprate was chosen as a more suitable reagent because increased yields could be expected by the omission of two steps in the reaction sequence and by the more specific nature of the reagent.^{63,64}



The reaction between a simple oxirane and dimethyl-lithium cuprate is envisaged to proceed by one of two mechanisms (225 and 226). Lithium ion assistance is suggested by the fact that diethyl ether is a better solvent than tetrahydrofuran⁶² as the oxirane competes effectively with the ether for the lithium ion. The reagent's attack on the epoxide ring via an S_N2 mechanism results in the introduction of a methyl group on the less hindered carbon atom.

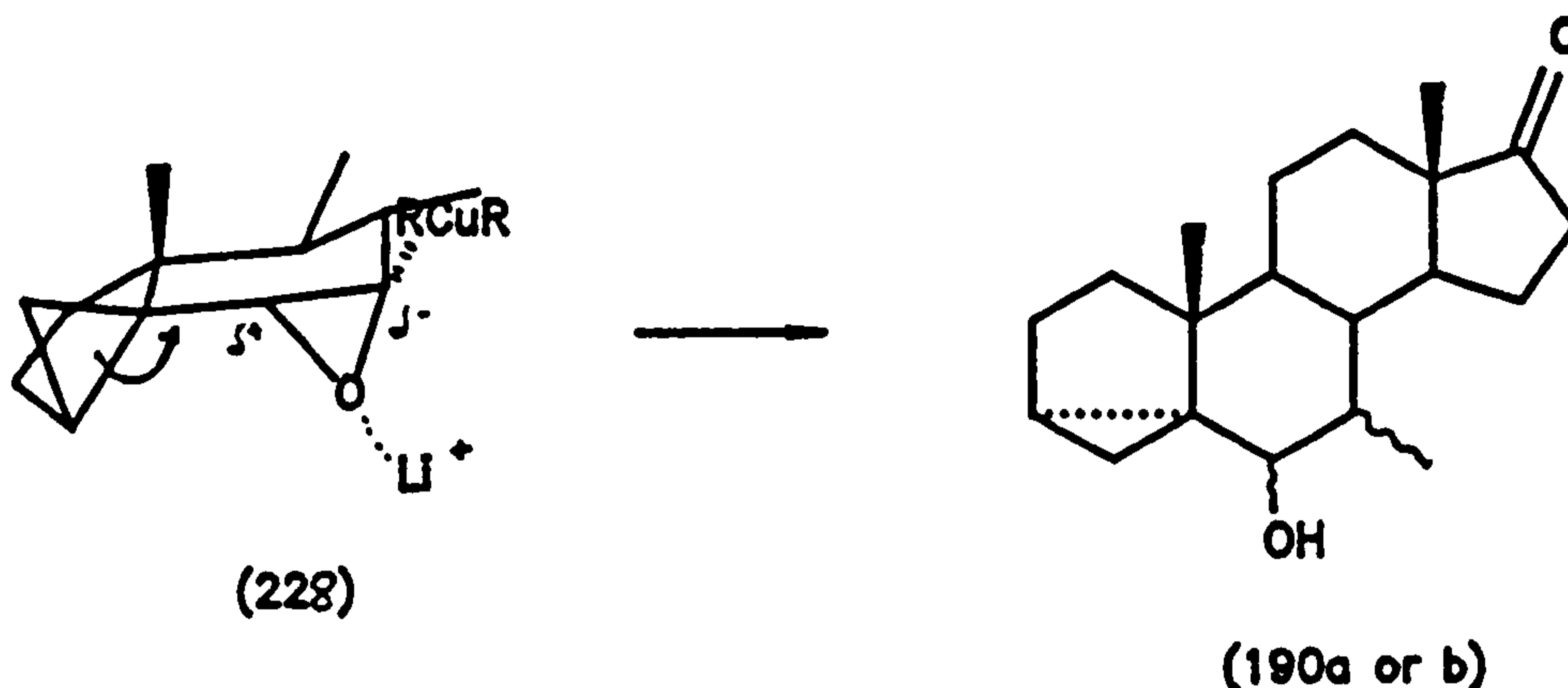


the reacting epoxide. For example, if the epoxide is in the α -configuration (209a) then attack from the β -phase will be influenced by the 19-methyl group. From models, it would appear that both positions 6 and 7 are more or less equally hindered by this group and therefore for this steroid no

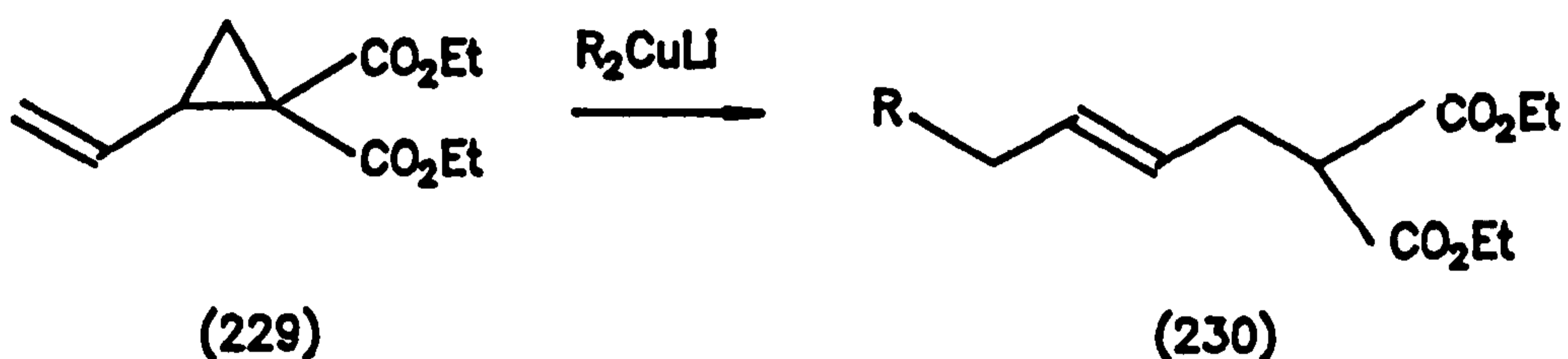


real preference should be noted. The use of the fairly bulky copper reagent, instead of the smaller Grignard reagent, might however favour attack at the 7 position. If the epoxide is in the β -configuration (209b) then attack from the α -phase is more likely to occur at the 7 position because of the greater steric hindrance induced by the cyclopropane ring. Thus considering only steric effects results would be expected to show a higher yield of the 7-methyl derivative. However, for this steroid one other complicating factor must be taken into account; the possible (electronic) directing effect of the cyclopropane ring. In the transition state of an S_N2 mechanism the carbon undergoing reaction changes from the sp^3 hybridised state to sp^2 hybridised state and therefore possesses a p-orbital which forms partial bonds with both the incoming and outgoing moieties (227). This entire group of atoms carries a negative charge which adjacent p-orbitals, in this particular case the cyclopropane orbitals (Chapter 2), can stabilise. This will result in a bias towards formation of 6-methyl derivatives (44) which will, to an unknown degree, cancel out any of the steric effects discussed above. Alternatively, if the cyclopropane ring acts only in its capacity as an electron donator then a

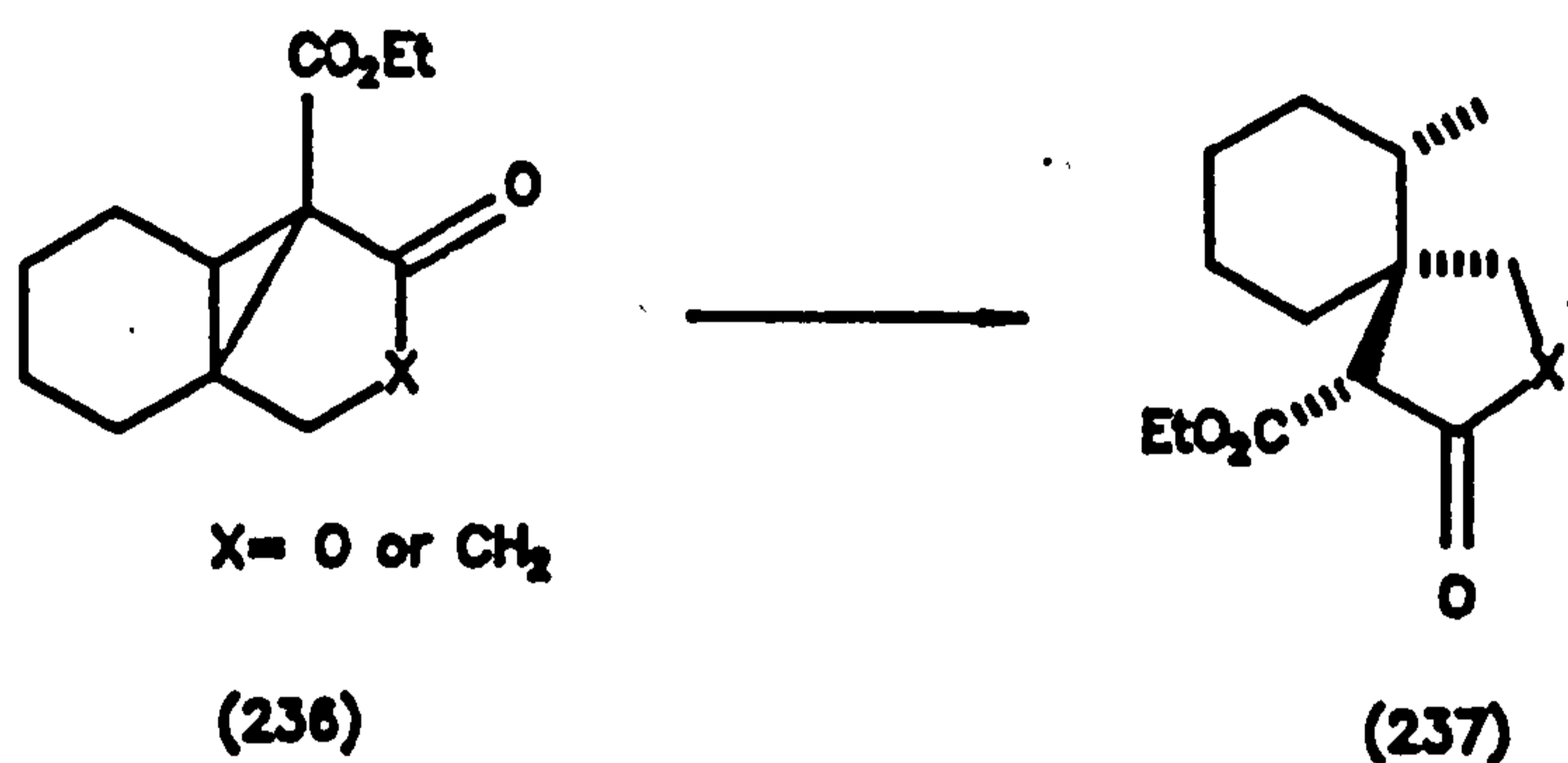
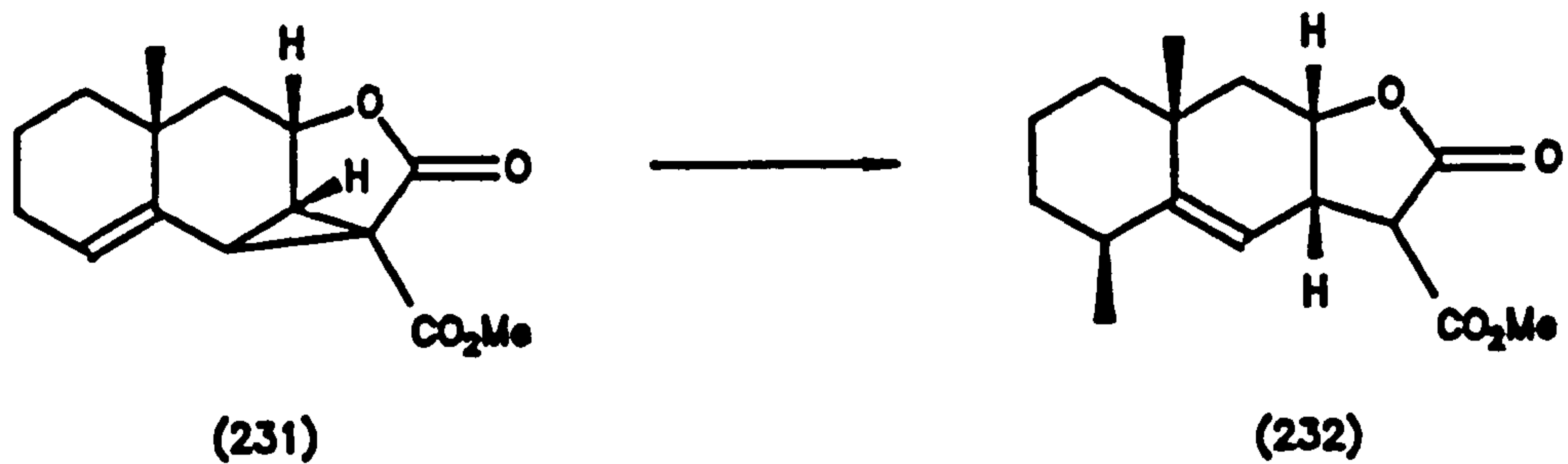
transition state at 7-C would be stabilised (228) and formation of the 7-methyl derivative (190) accentuated. A similar effect to this latter possibility has been noted in the hydroboration of vinylcyclopropane.⁶⁵



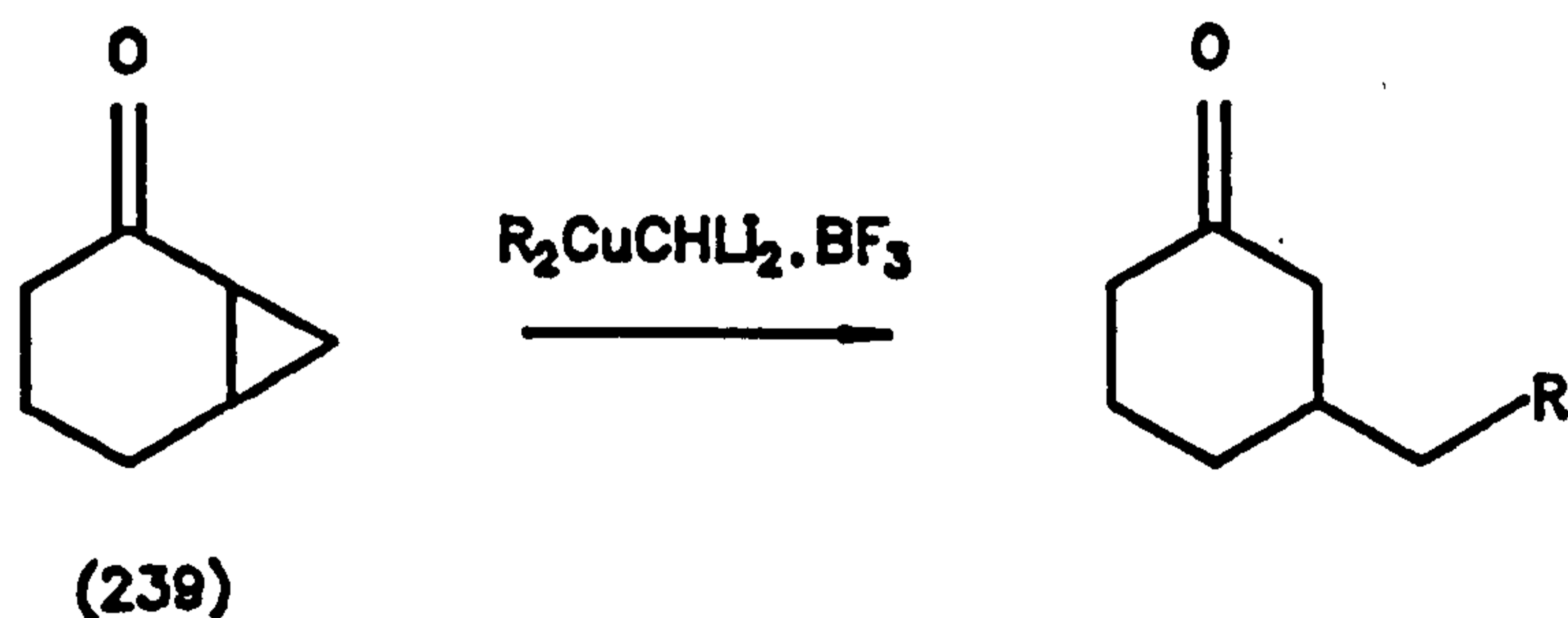
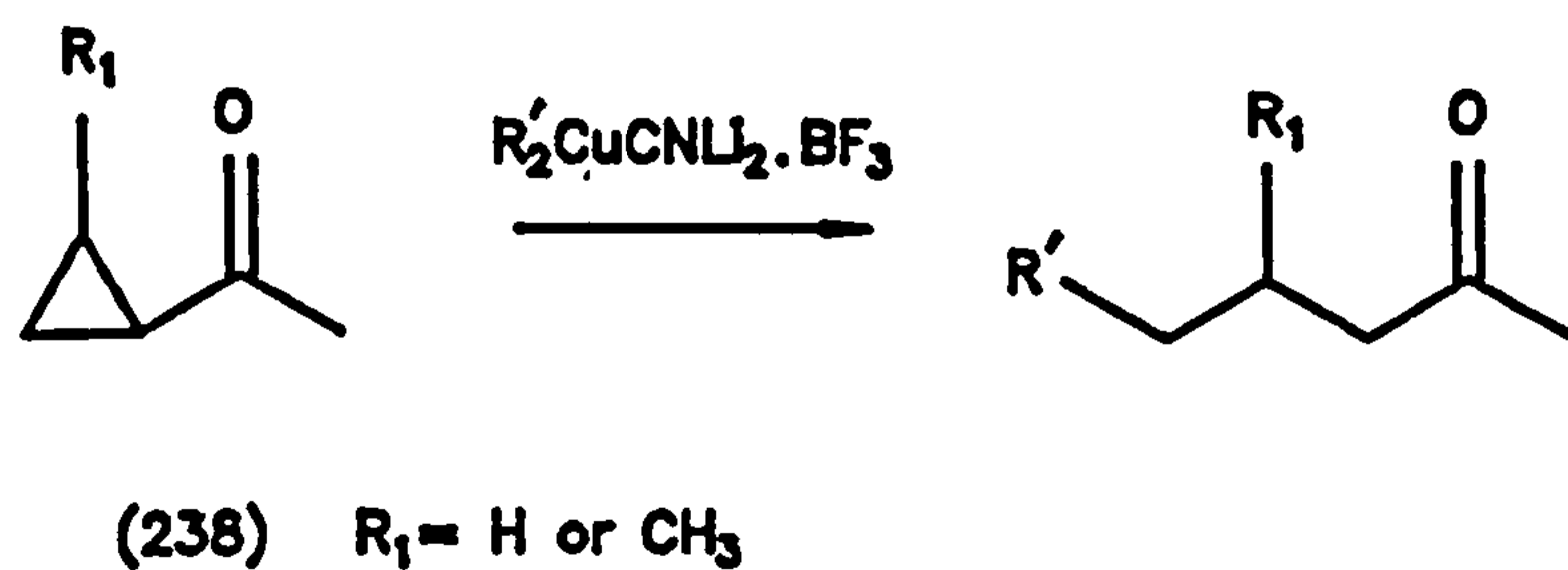
Dimethyl lithium cuprate, as potentially with other organometallic reagents, can react with cyclopropanes in such a manner as to cause ring fragmentation. However, this undesired side reaction usually only occurs to any great degree when the cyclopropane ring is activated. For example, compound (229) rapidly undergoes 1,7-addition⁶⁶ because of the activating properties of the ester groups (230). Likewise,



(231) undergoes ring opening under similar conditions to form the tricyclic compound (232).⁶⁷ Cyclopropyl carbonyls, e.g., highly strained (234) or strained and activated (236) can also react with dimethyl lithium cuprate to give (235)⁶⁸ and (237)⁶⁹ respectively. Similarly, cyclopropyl ketones such as (238) undergo 1,5 addition at the less substituted



carbon with the complex cuprate $R_2CuCNLi_2 \cdot BF_3$ ⁷⁰ but, related to this work, the yield is reduced to 5% when the cyclopropane ring is fused to another ring (239).⁷⁰



Ignoring the possible formation of rearranged products but considering just those desired and the uncertainty of the exact configuration of the epoxide(s) produced in the previous step it seemed prudent, with molecular mechanics, to construct models of the four possible isomers which could then be used to identify the products of reaction. This in turn would give valuable information into the opening of the oxirane ring and details of the configuration of the epoxide reactant(s).

The construction of the models of the four isomers, (44a,b) and (190a,b), as well as indicating the relative stabilities of the compounds (Chapter 6), allowed the calculation of the dihedral angles between the proton geminal to the hydroxy group and its neighbouring protons. Using the Karplus equation⁵⁹ would thus allow the prediction of the relevant protons coupling constants. The results are shown below in Table 8.

Table 8

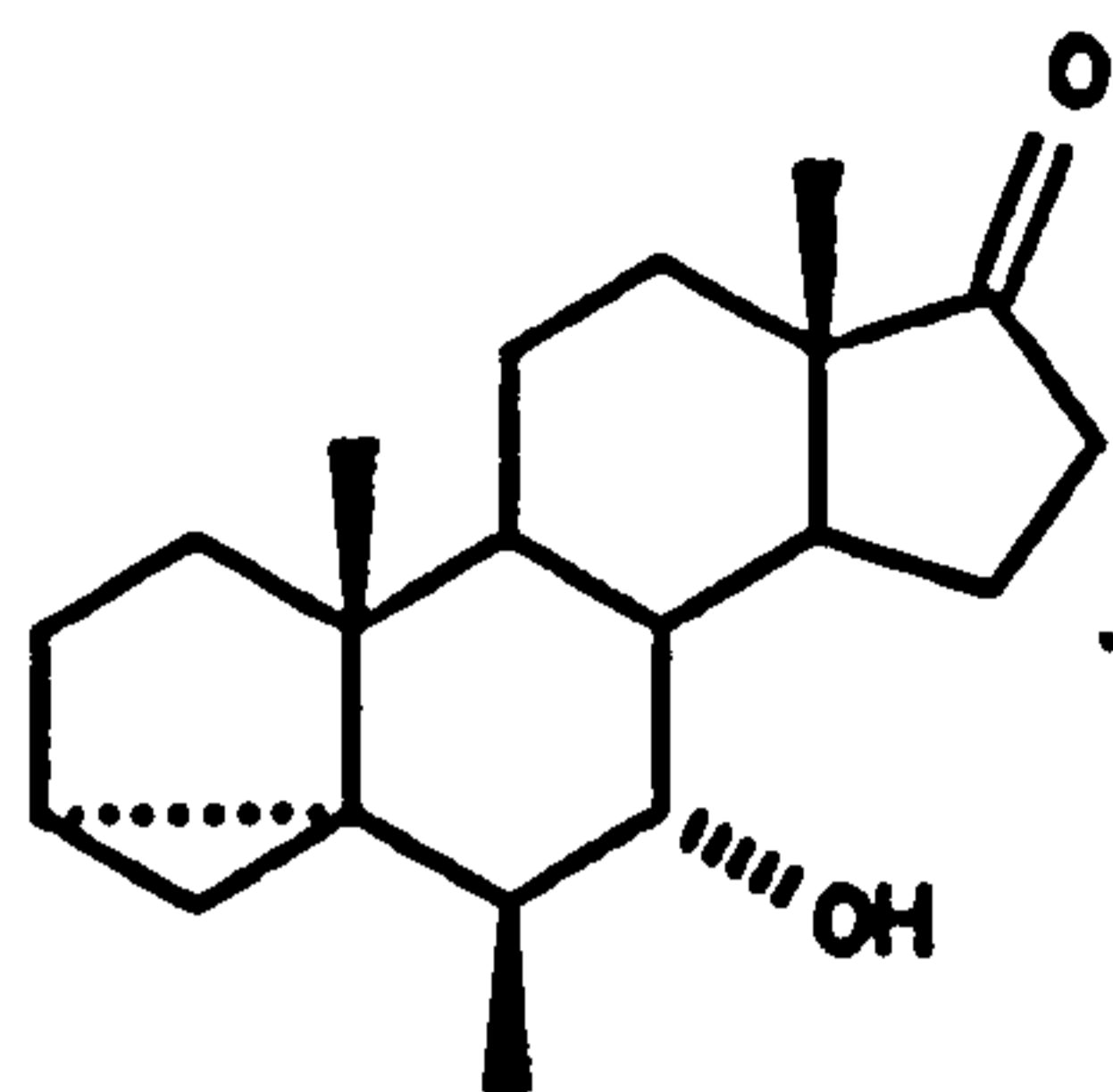
Theoretical ¹H NMR coupling constants of the proton geminal to the hydroxy group in the four isomers (44a and b) and (190a and b).

<u>STEROID ISOMER</u>	<u>DIHEDRAL ANGLES BETWEEN H GEMINAL TO OH GROUP AND NEIGHBOURING H'S.</u>	<u>CALCULATED COUPLING CONSTANTS (J)</u>
6 α -Me, 7 β -OH (44a)	175° (6-H), 179° (8-H)	9.1, 9.2 Hz
6 β -Me, 7 α -OH (44b)	67° (6-H), 56° (8-H)	1.0, 2.4 Hz
6 α -OH, 7 β -Me (190a)	178° (7-H)	9.2 Hz
6 β -OH, 7 α -Me (190b)	66° (7-H)	1.1 Hz

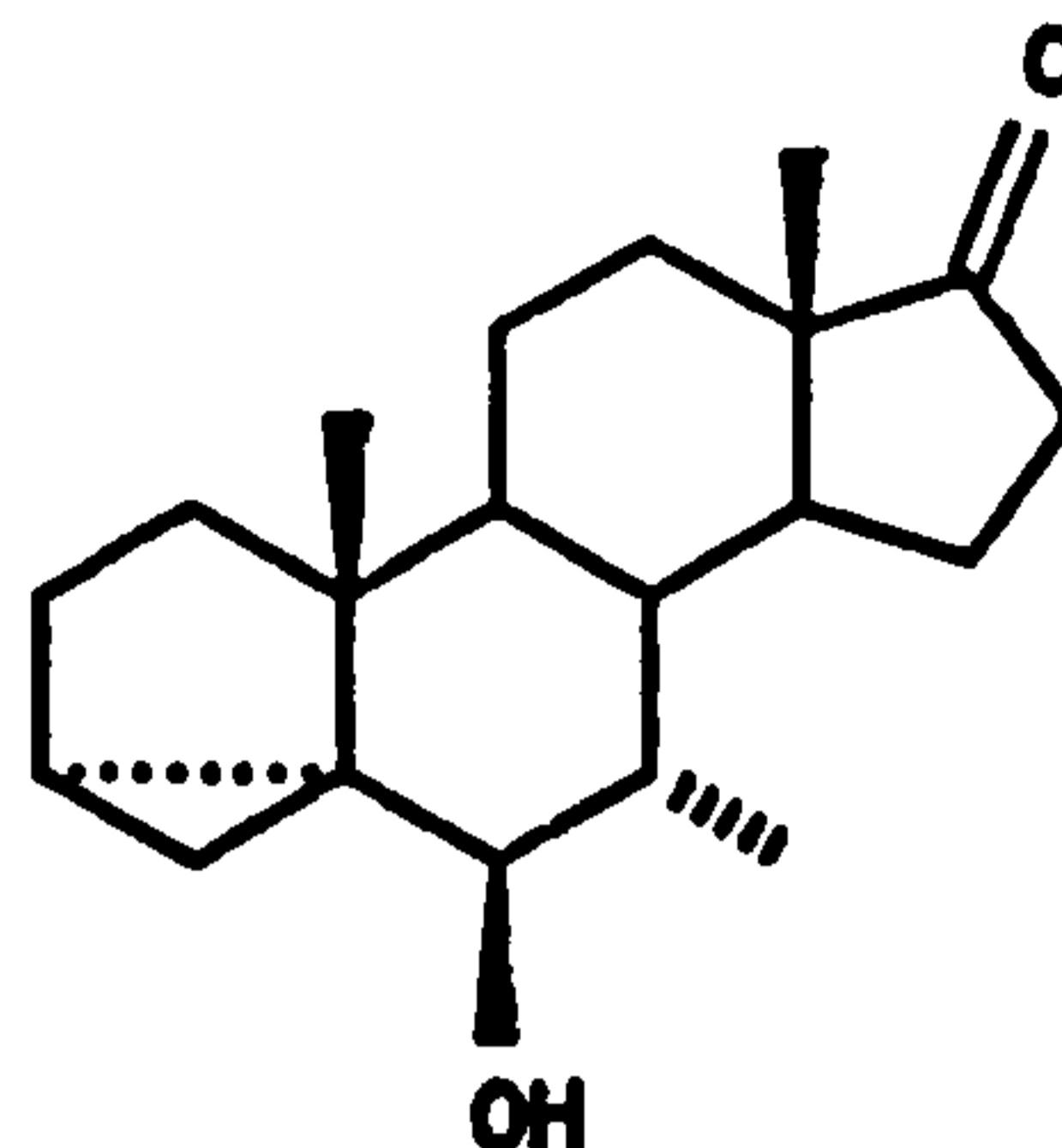
Therefore, for 7-hydroxy derivatives a double doublet (or possibly a triplet) would be expected for the signal from the 7-H atom with the two isomers being readily distinguished by large or small couplings. For the corresponding 6-hydroxy steroids the 6-H atom would appear as a doublet with the two isomers again being readily distinguished by the observed coupling constant.

However, when the crude epoxide was treated with dimethylolithium cuprate it became obvious that the problems encountered in the previous step were not overcome. Thus a complex mixture of products was recovered which was not fully separated by flash chromatography. Yields were also low, such that, during the many attempts of this reaction only on two separate occasions were the targeted compounds identified along with compounds derived from the fragmentation of the epoxide.³⁵ Thus, by ¹H NMR analysis, two different products possessing a cyclopropane ring, a third methyl group and a hydroxy group were detected. Both the products showed poorly resolved absorptions at $\delta = 3.68$ and 3.83 indicative of protons geminal to hydroxy groups. The first of these two compounds also possessed cyclopropane absorption as a triplet at $\delta = 0.4$. Only two signals attributed to the methyl groups were observed, the higher (and broader) field signal corresponding to 6 protons. The second compound also possessed cyclopropane absorption but this time virtually identical to the splitting pattern found in the parent cyclosteroid (41). Three methyl signals were readily observable. Comparing the molecular mechanics calculations and the observed sharpness of the signals from the atoms adjacent to

the hydroxy groups indicated that the products were the 7α -hydroxy, 6β -methyl (44b) and the 6β -hydroxy, 7α -methyl (190b) derivatives respectively. This is further substantiated by the similarities between the splitting patterns of



(44b)



(190b)

the cyclopropane protons absorptions in the parent 6β -hydroxy cyclosteroid (41) and the second compound isolated (190b). The differences in position between the two signals caused by the proton geminal to the hydroxy group can be accounted for by the substitution of a neighbouring hydrogen atom for a methyl group.

Several points can be drawn from these results. With respect to a directing effect induced by the cyclopropane ring; with both 6 and 7-methyl products isolated from different reactions it is impossible to say whether or not there is a prevailing influence during the reaction. Also, although the molecular mechanics calculations (Chapter 6) indicate that the above two products are the least stable among the four possible isomers (44a and b) (190a and b), no conclusions can be drawn again because of the limited results and the possibly small differences in overall energy of the conformers. Finally, although there is room for improvement in the formation and isolation of these steroid derivatives the reaction products indicate that the epoxida-

tion of the alkene (185) does not occur selectively from the α -phase of the molecule. Thus, the presence in the A-ring of the cyclopropane ring has a dramatic effect on the product determination of reactions occurring at ring-B.

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Chapter 5
X-ray Studies

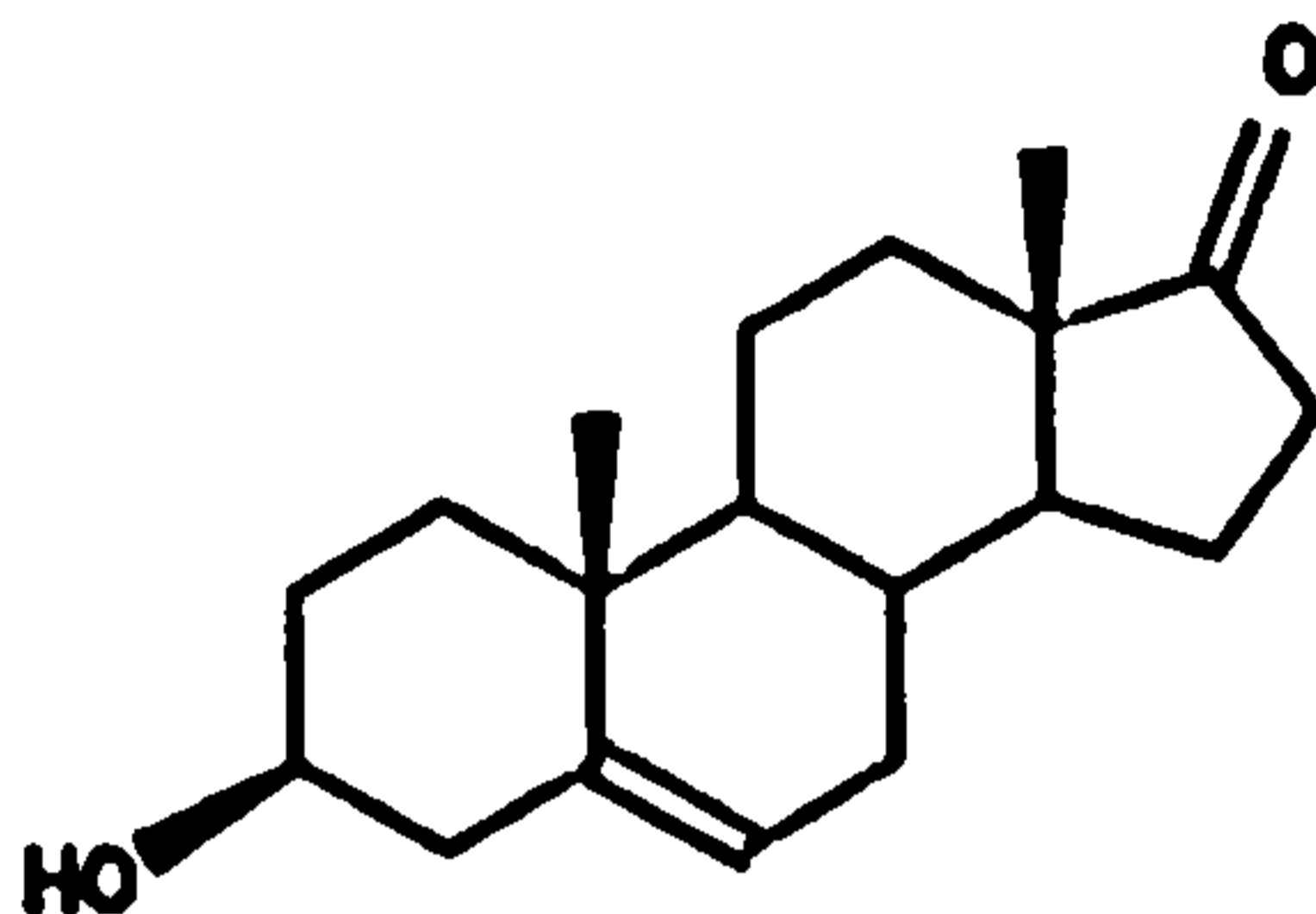
5.1 Introduction.

X-ray crystallography has for some time now provided details of the conformations of various chemical structures in the solid state. It has often been assumed that there could be no relationship between the conformation of molecules in crystals and their preferred conformations in solution, however, it is now clear from studies of many families of compounds that the X-ray technique can be a powerful tool in our understanding of drug action and for designing new drugs.¹ This is perhaps especially true for steroids because of their rigid carbon framework.² The presence of only weak forces of attraction in both the crystal lattice and the receptor site means that conformations are generally very similar and of low energy. The measurement of coupling constants derived from ¹H NMR spectroscopic analysis of steroids in solutions has provided further confirmation. For example, from the X-ray studies carried out in this work, C(14)-C(15)-C(16)-C(17) torsion angles of DHEA (97) and the 3,5-cyclosteroid (41) were calculated to be 22.6° and 23.8° respectively (this compares to the values of 15.8° (DHEA) and 18.6° (3,5-cyclosteroid) obtained from molecular modelling). From ¹H NMR spectroscopic experiments³ a value of approximately 20° has been calculated for this torsion angle. In short, the steroid conformation observed in steroid crystals can be assumed to be the same or very similar to that at a receptor.

5.2 Discussion.

5.2.1 3 β -Hydroxy-5-androsten-17-one, DHEA (97).

Although structurally unexceptional, it was a surprise, considering the importance of DHEA as a precursor, to find that it had not previously been subjected to an X-ray analysis. As a result of an X-ray study⁴ the asymmetric unit of



(97)

the compound (97) was found to contain two steroid molecules with similar conformations together with two water molecules. Extensive hydrogen bonding was present but fine details were obscured due to the difficulty in locating water hydrogen atoms accurately. The ring conformations of DHEA are A: chair, B: 8 β ,9 α half chair, C: chair, D: C14 α -envelope (Figure 8). The atomic co-ordinates (& temperature factors), bond lengths, valence angles, ring torsion angles and structure factors of 3 β -hydroxy-5-androsten-17-one (97) are listed in Tables 10-14 respectively.

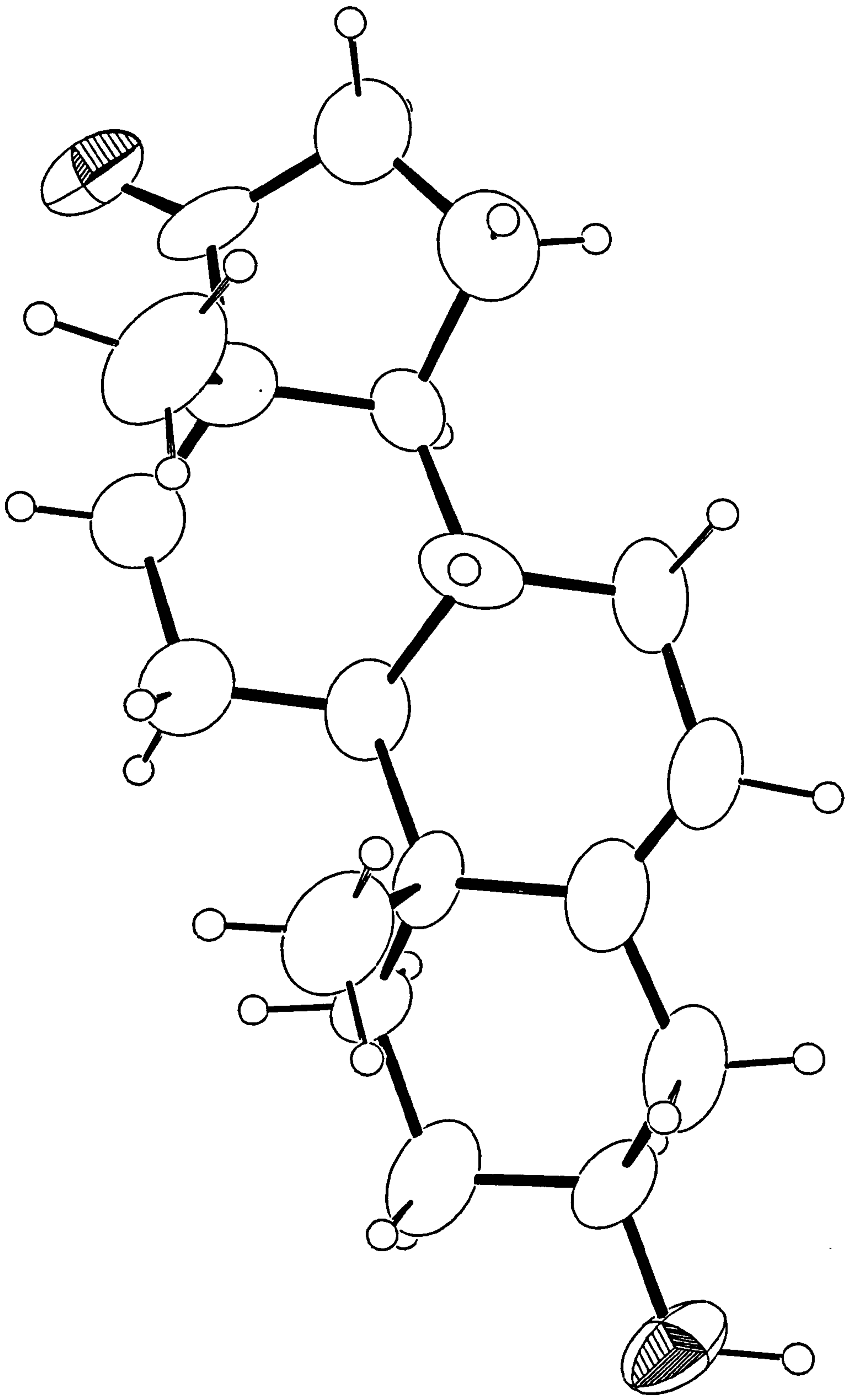
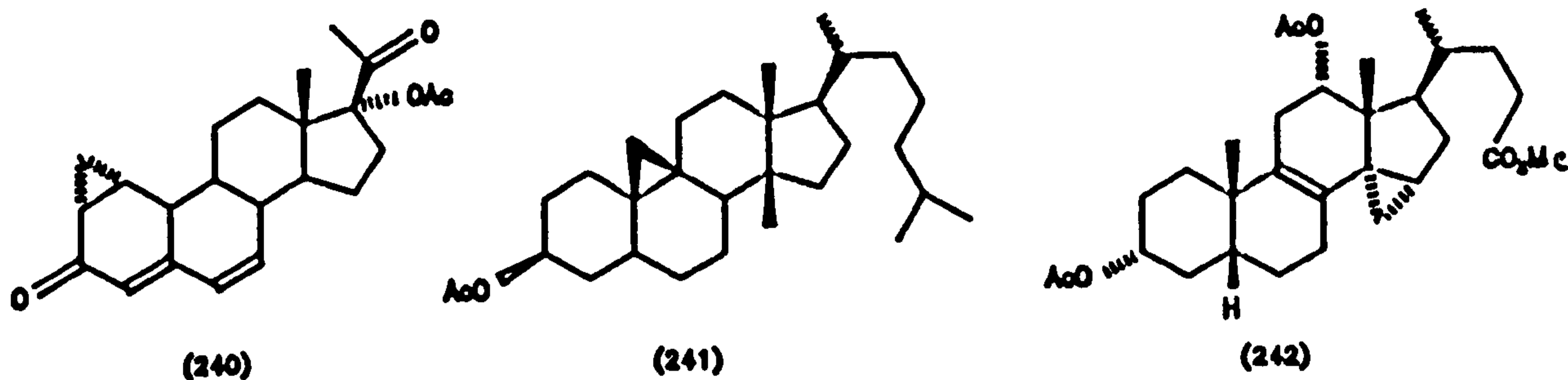


FIGURE 8

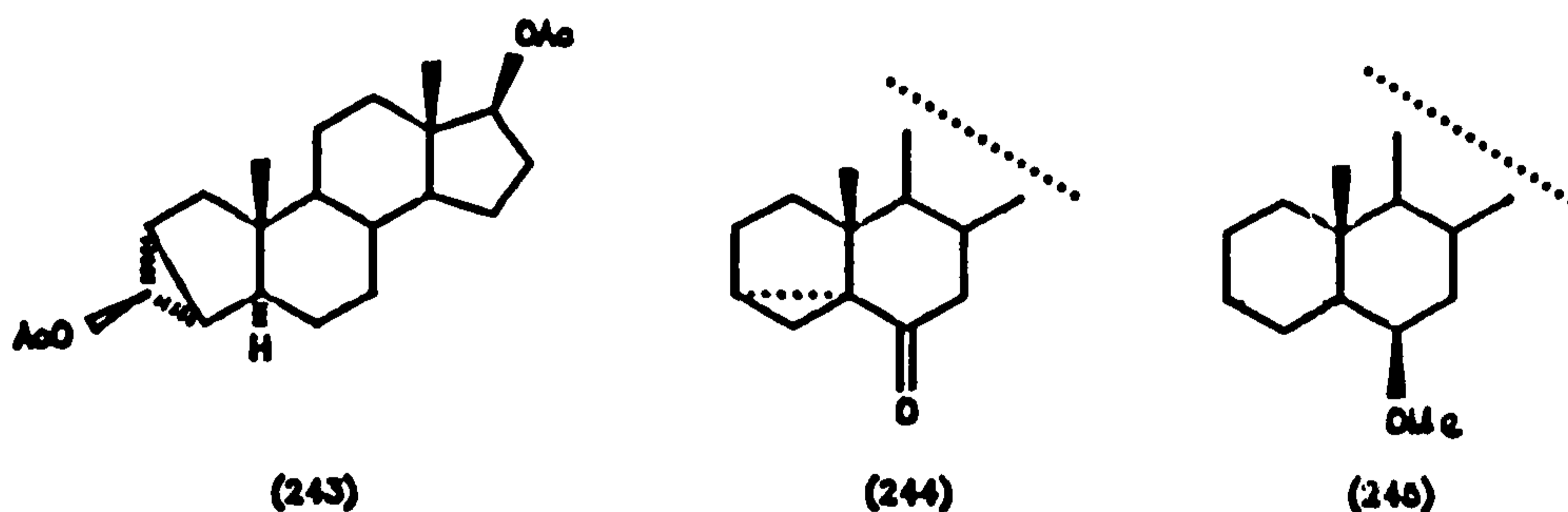
"Normal" view of 3 β -hydroxy-5-androsten-17-one (97).

5.2.2 6 β -Hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41).

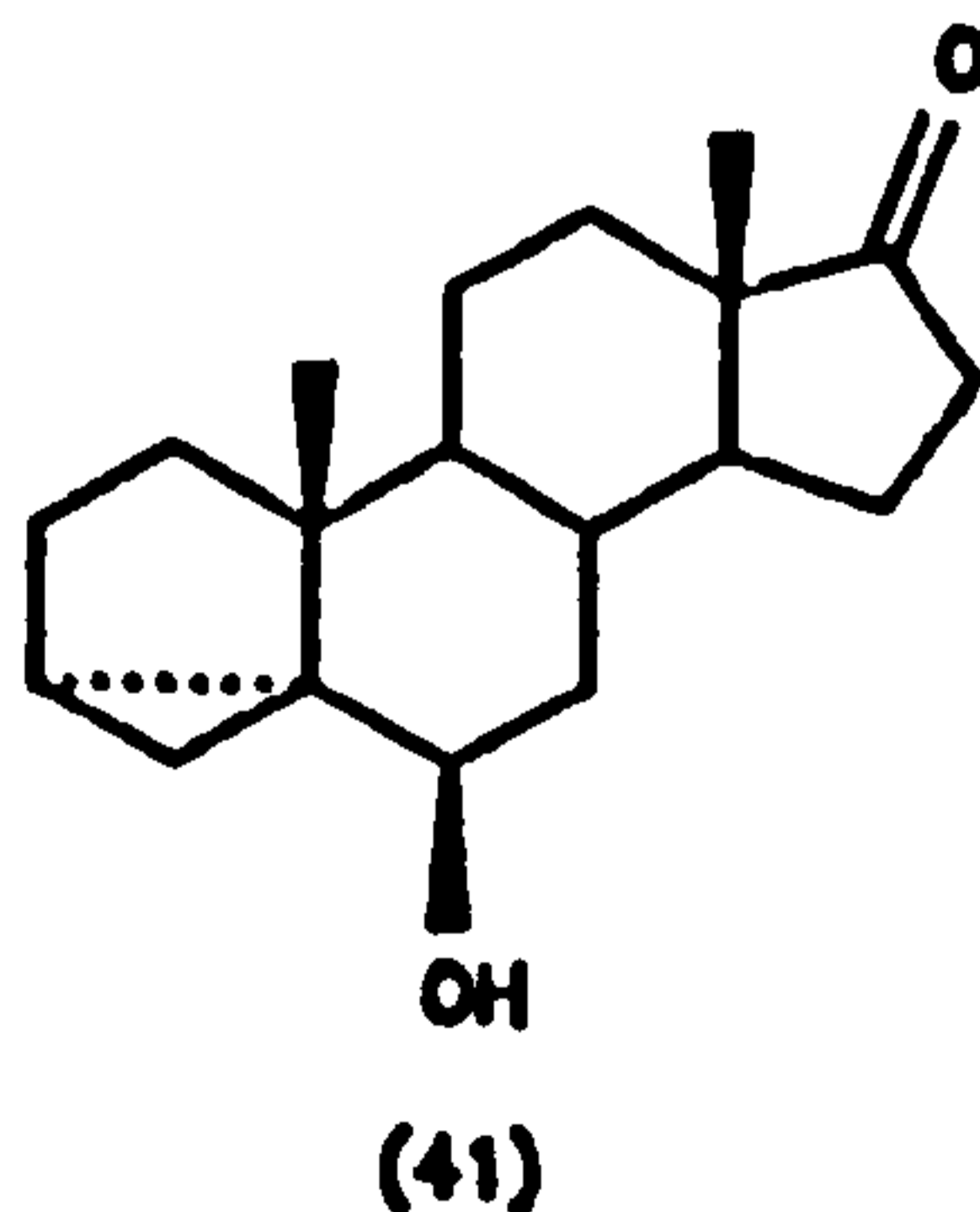
Although several other cyclosteroid derivatives have been studied by X-ray crystallography, e.g. (240)⁵, (241),⁶ (242)⁷ and (243)⁸, 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41) is one of only a few 3 α ,5-cyclo-5 α -steroids to be



studied by single crystal X-ray diffractometry.⁹ These include compounds with the 6-keto (244),¹⁰⁻¹² and 6-methoxy functionality (245).¹³ Analysis of the ketone structure indicates that the compound adopts such a conformation so as



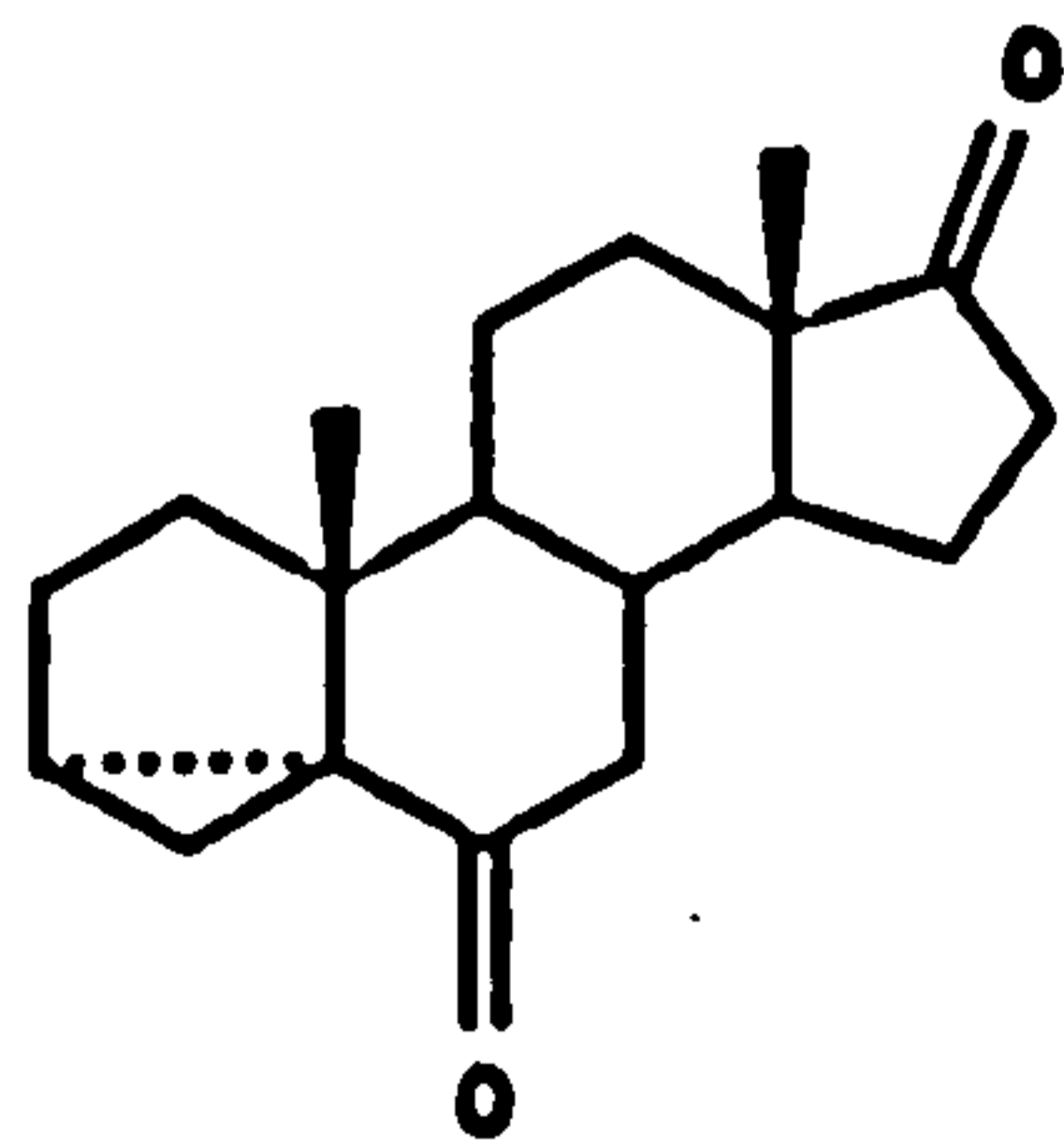
to allow maximum conjugation between the cyclopropane ring and the ketone moiety.¹⁰⁻¹²



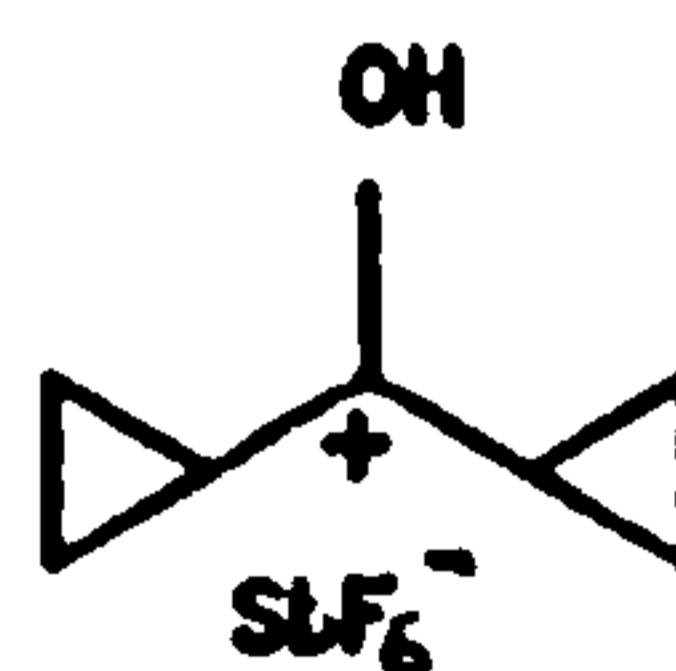
The atomic co-ordinates (& temperature factors), bond lengths, valance angles, ring torsion angles and structure factors of 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41) are listed in Tables 15-19 respectively.

The most prominent feature of the steroid (41) is the cyclopropane ring and the geometry and orientation of the three membered ring were accurately defined by the X-ray analysis. Thus, prediction of steric influences during reaction, for close analogues of the compound, are possible.

The planar cyclopropane ring has valancy angles {C(3)-C(4)-C(5), C(3)-C(5)-C(4) and C(4)-C(5)-C(3)} of 61.0(7), 59.3(7) and 59.7(7) $^\circ$ respectively. The presence of the cyclopropane ring, which lies predominantly in the α -phase of the molecule results in the associated 5-membered ring also adopting an α -phase orientation. Thus the steroid structurally emulates the cis or 5 β family of steroids. This most certainly results in significant protection of the α -face of rings A and B, an important factor when considering probable reaction products. Simultaneously, the cyclopropane ring and the C(19) methyl group would, because of their β (relative to the 5-membered A ring) orientation, most certainly direct reaction at C(1) and C(2) to the α -phase. Thus the X-ray structure of the cyclosteroid predicts retarded reaction rates at these two carbon



(111)



(240)

atoms. The electron donating effect of the cyclopropane ring is noticeable in the B ring (half chair) of the steroid with the relatively short C(5)-C(6) bond. Not surprisingly, the dione (111)¹⁰ and more so the cyclopropylcarbiny l cation (246)¹⁴ exhibit similar, but greater, reductions in their relative bond lengths. The remaining rings of the steroid, C: half chair and D: 14 α envelope are unexceptional (Figure 9).

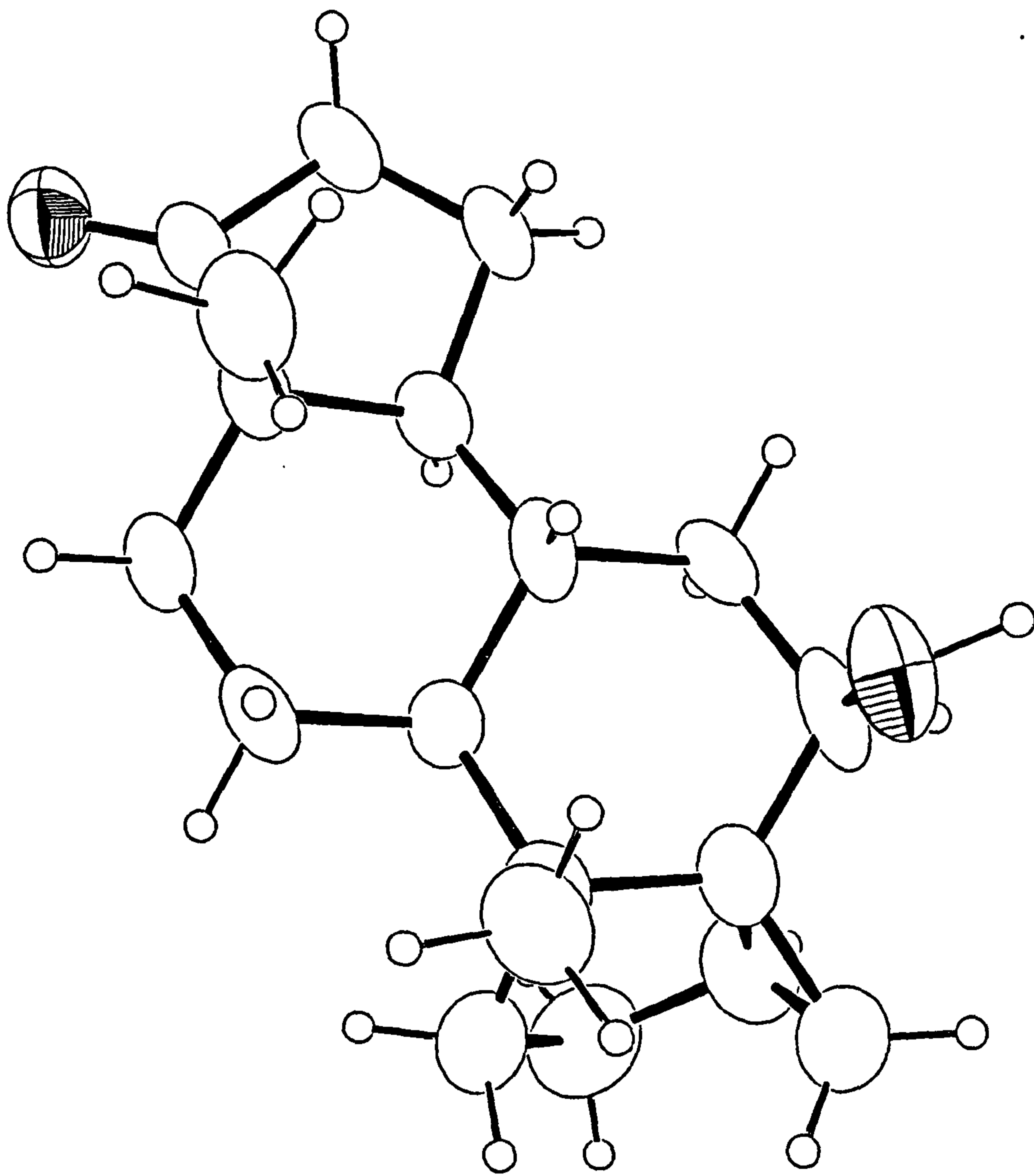
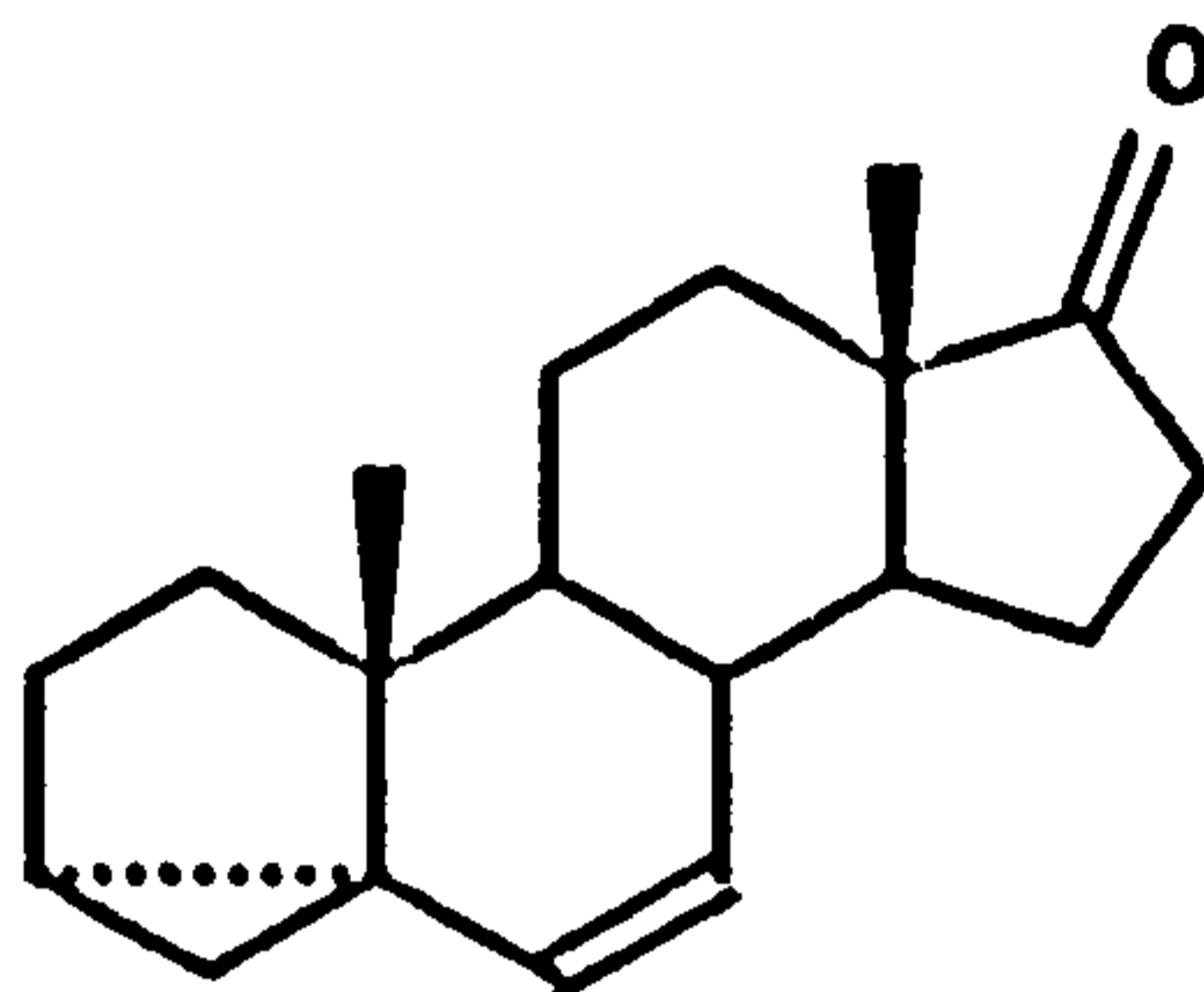


FIGURE 9

"Normal" view of 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41).

5.2.3 X-ray powder diffraction analysis of 3 α ,5-cyclo-5 α -androst-6-en-17-one (185).

Suitably large crystals of the alkene (185) proved surprisingly difficult to grow. However, batches of small crystals were readily grown and these were subjected to powder diffraction analysis. The "d" values for the eight



(185)

strongest peaks (calculated from Bragg's law) are shown below in Table 9. Thus the data for this compound can be entered into the Powder Diffraction File of organic and organometallic phases.¹⁵ More recently suitable crystals for single crystal analysis have been obtained. An analysis should provide information concerning the conjugation present in the vinylcyclopropane moiety.

Table 9

Calculated "d" values for eight strongest peaks derived from powder diffraction data of compound (185).

<u>Peak</u>	<u>Intensity</u>	<u>2θ</u>	<u>θ</u>	<u>sin θ</u>	<u>d</u>
1	100	15.03	7.52	0.13	5.88
2	21	13.50	6.75	0.12	6.53
3	13	16.05	8.02	0.14	5.51
4	10	14.00	7.00	0.12	6.32
5	8	17.58	8.79	0.15	5.04
6	8	16.73	8.36	0.14	5.32
7	6	19.79	9.90	0.17	4.48
8	5	26.79	13.40	0.23	3.32

5.3 Experimental.

Data for both structures were collected on a Nicolet P3 automated diffractometer using a graphite monochromator. The structures were determined with MITHRIL¹⁶ and completed with SHELX76.¹⁷ Molecular geometries were generated by the GX package.¹⁸

3 β -Hydroxy-5-androsten-17-one (DHEA) (97) Monohydrate.

$C_{19}H_{28}O_2 \cdot H_2O$, $M_r = 288$, orthorhombic, $P2_12_12_1$ (No 19), $a = 22.545(7)$, $b = 22.673(22)$, $c = 6.819(2)$ Å. $V = 3485.6$ Å³, $Z = 8$, $D_x = 1.17$ gcm⁻³, Mo $K\alpha$, $\lambda = 0.71069$ Å, $\mu = 0.43$ cm⁻¹, $F(000) = 1344$, $T = 293$ K, $R = 0.071$ for 1308 observed reflections.

A colourless crystal, 1.40x 0.20x 0.20 mm was used. Cell dimensions were obtained from the setting angles of 12 independent reflexions with $2\theta < 20^\circ$. The data were corrected for Lorentz and polarization effects, but not for absorption. A total of 2738 unique intensities were measured with $2\theta \leq 50^\circ$ from ω - 2θ scans; 1308 reflections had $F > 5\sigma(F)$. Range of hkl: $0 \leq h \leq 24$, $0 \leq k \leq 23$, $0 \leq l \leq 8$. Two reference reflexions monitored periodically showed no significant variation in intensity. In determination of the structure, blocked full-matrix least-squares calculations on F with anisotropic thermal parameters for C and O atoms and isotropic thermal parameters for H atoms converged at $R = 0.071$. Each hydrated steroid molecule was refined in alternate cycles of least-squares calculations such that the total number of parameters was 423. Units weights were used. The position of the hydroxy and water hydrogen atoms, which were associated with high error, were refined but the remaining

hydrogen atoms were allowed to ride on their attached atoms. All C-H and O-H bond distances were constrained to 1.00(2) Å and the hydrogen atoms were given one of four common temperature factors (methyl and non-methyl in molecule A and B). Atomic scattering factors from SHELX.¹⁷ Final $\Delta/\sigma \leq 0.5$, $\rho_{\max} = 0.1$, $\rho_{\min} = -0.1 \text{ e \AA}^{-3}$.

The atomic co-ordinates (& temperature factors), bond lengths, valency angles, ring torsion angles and structure factors of 3 β -hydroxy-5-androstan-17-one (97) are listed in Tables 10-14 respectively.

5.3.2 6 β -Hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41).

$\text{C}_{19}\text{H}_{28}\text{O}_2$, $M_r = 288$, orthorhombic, $P222_1$ (No. 20), $a = 11.041(22)$, $b = 9.591(17)$, $c = 31.210(25)$ Å. $V = 3305.0 \text{ \AA}^3$, $Z = 8$, $D_x = 1.16 \text{ g cm}^{-3}$, Mo $K\alpha$, $\lambda = 0.71069$ Å, $\mu = 0.39 \text{ cm}^{-1}$, $F(000) = 1264$, $T = 293\text{K}$, $R = 0.062$ for 776 unique reflections.

A colourless crystal, 0.64x 0.65x 0.08 mm was used. Cell dimensions were obtained from the setting angles of 12 independent reflexions with $2\theta \approx 20^\circ$. The data were corrected for Lorentz and polarization effects, but not for absorption. A total of 2028 unique intensities were measured with $2\theta \leq 50^\circ$ from $\omega - 2\theta$ scans; 1308 reflections had $F > 5\sigma(F)$. The small number of intensities above background level were due to the very thin, weakly diffracting crystal. Range of hkl: $0 \leq h \leq 14$, $0 \leq k \leq 12$, $0 \leq l \leq 44$. Two reference reflexions monitored periodically showed no significant variation in intensity. In the determination of the structure, blocked full-matrix least-squares calculations on F with anisotropic thermal parameters for C and O atoms and common isotropic

thermal parameters for methyl and non-methyl H atoms converged at $R = 0.062$, $wR = 0.046$. The hydroxy hydrogen atom was freely refined but the remaining hydrogen atoms were allowed to ride on their attached atoms. Atomic scattering factors from SHELX.¹⁷ Final $\Delta/\sigma < 0.03$, final $\rho_{\max} = 0.06$, $\rho_{\min} = -0.8e \text{ \AA}^{-3}$.

The atomic co-ordinates (& temperature factors), bond lengths, valency angles, ring torsion angles and structure factors of 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41) are listed in Tables 15-19 respectively.

5.3.2 Powder diffraction analysis: Experimental.

Crystals of the alkene (185) were ground in a mortar and pestle, by hand, so as to reduce the possibility of any phase changes occurring. A layer of the powder was then mounted on a slide backed by a piece of translucent adhesive tape.

The sample was then rotated through an angle of $2\theta = 45^\circ$ at a rate of $2\theta^\circ$ per minute (Cu K_α , $\lambda = 1.5418 \text{ \AA}$) and the collected data processed.¹⁹

TABLE 10

FRACTIONAL ATOMIC COORDINATES AND ISOTROPIC TEMPERATURE FACTORS (ANGSTROM SQUARED), WITH STANDARD DEVIATIONS IN THE LEAST SIGNIFICANT DIGITS IN PARENTHESES. FOR ANISOTROPIC ATOMS, THE EQUIVALENT ISOTROPIC TEMPERATURE FACTORS ARE SHOWN. (97)

	X/A	Y/B	Z/C	U
O(1)	. 8917(4)	-. 4164(4)	-. 4426(14)	. 067
O(2)	. 7201(5)	-. 0058(4)	. 1760(13)	. 066
O(3)	. 9922(4)	. 0278(4)	-. 0789(13)	. 070
O(21)	. 9499(5)	. 0781(5)	. 2629(15)	. 075
O(22)	. 8339(6)	. 5457(5)	. 2117(16)	. 102
O(23)	. 9108(5)	. 0310(7)	. 6129(16)	. 126
C(1)	. 7896(6)	-. 2932(5)	-. 3047(19)	. 053
C(2)	. 8086(6)	-. 3553(7)	-. 3651(21)	. 072
C(3)	. 8741(5)	-. 3589(6)	-. 4010(18)	. 048
C(4)	. 9106(6)	-. 3323(7)	-. 2353(18)	. 062
C(5)	. 8884(6)	-. 2722(7)	-. 1737(17)	. 051
C(6)	. 9262(6)	-. 2301(7)	-. 1683(17)	. 052
C(7)	. 9117(5)	-. 1664(6)	-. 1107(19)	. 056
C(8)	. 8526(6)	-. 1647(5)	-. 0029(17)	. 043
C(9)	. 8053(5)	-. 2008(6)	-. 1019(18)	. 047
C(10)	. 8259(5)	-. 2656(6)	-. 1290(15)	. 038
C(11)	. 7427(6)	-. 1937(6)	-. 0236(21)	. 064
C(12)	. 7256(6)	-. 1292(5)	. 0145(21)	. 060
C(13)	. 7720(6)	-. 0982(6)	. 1311(18)	. 048
C(14)	. 8321(5)	-. 1026(5)	. 0365(17)	. 040
C(15)	. 8712(6)	-. 0579(6)	. 1410(20)	. 071
C(16)	. 8262(6)	-. 0070(7)	. 1709(21)	. 068
C(17)	. 7657(7)	-. 0342(5)	. 1627(18)	. 048
C(18)	. 7716(7)	-. 1237(7)	. 3504(20)	. 086
C(19)	. 8085(7)	-. 3030(6)	. 0575(20)	. 077
C(21)	. 9307(6)	. 2362(7)	. 4018(16)	. 062
C(22)	. 9565(7)	. 1750(7)	. 4089(19)	. 078
C(23)	. 9240(6)	. 1349(7)	. 2607(18)	. 053
C(24)	. 9362(7)	. 1624(7)	. 0521(17)	. 064
C(25)	. 9145(6)	. 2231(7)	. 0444(18)	. 054
C(26)	. 8762(6)	. 2398(7)	-. 0967(19)	. 057
C(27)	. 8530(6)	. 3014(6)	-. 1275(18)	. 057
C(28)	. 8885(6)	. 3495(6)	-. 0116(18)	. 051
C(29)	. 9016(6)	. 3245(6)	. 1973(16)	. 050
C(30)	. 9392(6)	. 2678(6)	. 1942(17)	. 052
C(31)	. 9312(7)	. 3751(6)	. 3282(18)	. 063
C(32)	. 8937(7)	. 4307(7)	. 3354(19)	. 068
C(33)	. 8855(8)	. 4532(6)	. 1204(21)	. 063
C(34)	. 8513(6)	. 4036(6)	. 0124(17)	. 053
C(35)	. 8265(8)	. 4356(7)	-. 1682(21)	. 083
C(36)	. 8039(8)	. 4942(7)	-. 0887(20)	. 087
C(37)	. 8427(8)	. 5021(8)	. 1017(21)	. 074
C(38)	. 9445(7)	. 4762(7)	. 0337(21)	. 101
C(39)	1. 0051(5)	. 2798(7)	. 1542(20)	. 075

(contd.)

	X/A	Y/B	Z/C	U
H(1)	. 9356(13)	-. 4220(46)	-. 4600(158)	. 048(8)
H(1A)	. 7945(6)	-. 2668(5)	-. 4211(19)	. 048(8)
H(1B)	. 7468(6)	-. 2946(5)	-. 2661(19)	. 048(8)
H(2A)	. 7872(6)	-. 3667(7)	-. 4879(21)	. 048(8)
H(2B)	. 7979(6)	-. 3833(7)	-. 2576(21)	. 048(8)
H(3)	. 8826(5)	-. 3342(6)	-. 5191(18)	. 048(8)
H(4A)	. 9527(6)	-. 3285(7)	-. 2793(18)	. 048(8)
H(4B)	. 9085(6)	-. 3594(7)	-. 1198(18)	. 048(8)
H(6)	. 9680(6)	-. 2393(7)	-. 2056(17)	. 048(8)
H(7A)	. 9094(5)	-. 1413(6)	-. 2309(19)	. 048(8)
H(7B)	. 9435(5)	-. 1511(6)	-. 0222(19)	. 048(8)
H(8)	. 8597(6)	-. 1838(5)	. 1273(17)	. 048(8)
H(9)	. 8008(5)	-. 1834(6)	-. 2360(18)	. 048(8)
H(11A)	. 7144(6)	-. 2107(6)	-. 1211(21)	. 048(8)
H(11B)	. 7395(6)	-. 2158(6)	. 1029(21)	. 048(8)
H(12A)	. 6872(6)	-. 1281(5)	. 0879(21)	. 048(8)
H(12B)	. 7208(6)	-. 1086(5)	-. 1142(21)	. 048(8)
H(14)	. 8328(5)	-. 0905(5)	-. 1045(17)	. 048(8)
H(15A)	. 8857(6)	-. 0736(6)	. 2694(20)	. 048(8)
H(15B)	. 9058(6)	-. 0457(6)	. 0588(20)	. 048(8)
H(16A)	. 8309(6)	. 0227(7)	. 0637(21)	. 048(8)
H(16B)	. 8326(6)	. 0125(7)	. 3007(21)	. 048(8)
H(18A)	. 7754(7)	-. 1676(7)	. 3461(20)	. 11(2)
H(18B)	. 7335(7)	-. 1128(7)	. 4164(20)	. 11(2)
H(18C)	. 8056(7)	-. 1066(7)	. 4255(20)	. 11(2)
H(19A)	. 7653(7)	-. 2979(6)	. 0848(20)	. 11(2)
H(19B)	. 8320(7)	-. 2890(6)	. 1729(20)	. 11(2)
H(19C)	. 8172(7)	-. 3456(6)	. 0332(20)	. 11(2)
H(21)	. 920(5)	. 046(5)	. 248(22)	. 09(1)
H(21A)	. 8872(6)	. 2336(7)	. 4300(16)	. 09(1)
H(21B)	. 9504(6)	. 2607(7)	. 5050(16)	. 09(1)
H(22A)	. 9996(7)	. 1767(7)	. 3746(19)	. 09(1)
H(22B)	. 9518(7)	. 1584(7)	. 5440(19)	. 09(1)
H(23)	. 8808(6)	. 1321(7)	. 2926(18)	. 09(1)
H(23A)	. 8691(19)	. 0255(50)	. 6580(187)	. 09(1)
H(23B)	. 937(4)	. 000(4)	. 670(18)	. 09(1)
H(24A)	. 9156(7)	. 1382(7)	-. 0500(17)	. 09(1)
H(24B)	. 9799(7)	. 1621(7)	. 0267(17)	. 09(1)
H(26)	. 8619(6)	. 2085(7)	-. 1886(19)	. 09(1)
H(27A)	. 8555(6)	. 3109(6)	-. 2705(18)	. 09(1)
H(27B)	. 8106(6)	. 3027(6)	-. 0845(18)	. 09(1)
H(28)	. 9258(6)	. 3593(6)	-. 0841(18)	. 09(1)
H(29)	. 8629(6)	. 3127(6)	. 2571(16)	. 09(1)
H(31A)	. 9710(7)	. 3850(6)	. 2721(18)	. 09(1)

(contd.)

	X/A	Y/B	Z/C	U
H(31B)	. 9363(7)	. 3598(6)	. 4648(18)	. 09(1)
H(32A)	. 8542(7)	. 4217(7)	. 3952(19)	. 09(1)
H(32B)	. 9144(7)	. 4614(7)	. 4156(19)	. 09(1)
H(34)	. 8175(6)	. 3847(6)	. 0832(17)	. 09(1)
H(35A)	. 7934(8)	. 4125(7)	-. 2282(21)	. 09(1)
H(35B)	. 8584(8)	. 4420(7)	-. 2682(21)	. 09(1)
H(36A)	. 8115(8)	. 5267(7)	-. 1845(20)	. 09(1)
H(36B)	. 7605(8)	. 4923(7)	-. 0587(20)	. 09(1)
H(38A)	. 9752(7)	. 4445(7)	. 0420(21)	. 11(3)
H(38B)	. 9582(7)	. 5116(7)	. 1086(21)	. 11(3)
H(38C)	. 9381(7)	. 4872(7)	-. 1067(21)	. 11(3)
H(39A)	1. 0205(5)	. 3085(7)	. 2532(20)	. 11(3)
H(39B)	1. 0101(5)	. 2966(7)	. 0196(20)	. 11(3)
H(39C)	1. 0278(5)	. 2420(7)	. 1645(20)	. 11(3)

TABLE 10 (contd.)

VIBRATION PARAMETERS (ANGSTROM SQUARED) IN THE EXPRESSION:

$$-2(\text{PI SQUARED})(\text{U11}((\text{H. A}^*)\text{SQUARED}) + \text{U22}((\text{K. B}^*)\text{SQUARED}) + \text{U33}((\text{L. C}^*)\text{SQUARED}) + 2. \text{U12. H. K. A}^*. \text{B}^* + 2. \text{U13. H. L. A}^*. \text{C}^* + 2. \text{U23. K. L. B}^*. \text{C}^*)$$

	U11	U22	U33	U12	U13	U23
O(1)	. 078(7)	. 067(7)	. 057(6)	. 026(6)	-. 006(6)	-. 032(6)
O(2)	. 094(8)	. 056(6)	. 049(6)	. 017(7)	. 016(6)	-. 010(6)
O(3)	. 075(7)	. 090(8)	. 046(6)	-. 009(6)	-. 003(6)	-. 007(6)
O(21)	. 107(9)	. 065(9)	. 053(6)	. 011(7)	. 003(7)	. 001(6)
O(22)	. 15(1)	. 10(1)	. 06(1)	. 01(1)	-. 02(1)	-. 01(1)
O(23)	. 10(1)	. 22(2)	. 05(1)	. 01(1)	. 00(1)	. 05(1)
C(1)	. 052(9)	. 044(9)	. 064(10)	. 010(7)	. 007(8)	-. 010(8)
C(2)	. 06(1)	. 11(1)	. 05(1)	. 02(1)	-. 01(1)	-. 02(1)
C(3)	. 052(9)	. 061(10)	. 030(7)	. 020(7)	-. 003(7)	-. 014(7)
C(4)	. 048(9)	. 111(13)	. 026(7)	. 016(9)	. 001(7)	-. 003(8)
C(5)	. 05(1)	. 09(1)	. 01(1)	. 01(1)	-. 01(1)	. 00(1)
C(6)	. 037(8)	. 087(13)	. 033(7)	. 018(9)	-. 007(7)	. 003(9)
C(7)	. 038(8)	. 090(13)	. 039(8)	. 004(8)	-. 004(7)	. 015(8)
C(8)	. 08(1)	. 03(1)	. 02(1)	-. 02(1)	. 00(1)	. 02(1)
C(9)	. 050(9)	. 059(10)	. 033(7)	. 011(7)	-. 005(7)	. 022(8)
C(10)	. 033(8)	. 060(10)	. 022(7)	. 018(7)	-. 004(6)	. 011(7)
C(11)	. 06(1)	. 07(1)	. 06(1)	. 00(1)	. 00(1)	-. 01(1)
C(12)	. 06(1)	. 06(1)	. 06(1)	. 01(1)	. 00(1)	. 01(1)
C(13)	. 07(1)	. 04(1)	. 04(1)	. 01(1)	. 00(1)	. 01(1)
C(14)	. 040(8)	. 052(10)	. 028(7)	-. 008(7)	-. 001(6)	. 006(6)
C(15)	. 07(1)	. 11(1)	. 04(1)	-. 01(1)	. 00(1)	. 00(1)
C(16)	. 07(1)	. 09(1)	. 05(1)	. 00(1)	. 00(1)	. 00(1)

(contd.)

	U11	U22	U33	U12	U13	U23
C(17)	.07(1)	.04(1)	.04(1)	.03(1)	-.01(1)	-.01(1)
C(18)	.11(1)	.10(1)	.05(1)	.03(1)	.02(1)	.01(1)
C(19)	.09(1)	.07(1)	.06(1)	.02(1)	.03(1)	.03(1)
C(21)	.049(9)	.119(15)	.016(6)	.010(10)	-.006(7)	-.012(8)
C(22)	.10(1)	.11(1)	.03(1)	.03(1)	.00(1)	.00(1)
C(23)	.045(9)	.080(12)	.035(8)	-.010(8)	-.001(7)	-.008(8)
C(24)	.08(1)	.08(1)	.03(1)	.00(1)	-.02(1)	-.01(1)
C(25)	.06(1)	.07(1)	.03(1)	.01(1)	.00(1)	-.01(1)
C(26)	.06(1)	.08(1)	.04(1)	.01(1)	-.01(1)	.00(1)
C(27)	.07(1)	.07(1)	.03(1)	-.01(1)	.00(1)	-.01(1)
C(28)	.054(9)	.068(11)	.032(7)	.005(8)	-.012(7)	-.002(8)
C(29)	.07(1)	.06(1)	.02(1)	-.01(1)	.00(1)	.00(1)
C(30)	.07(1)	.06(1)	.03(1)	-.01(1)	.01(1)	-.02(1)
C(31)	.09(1)	.07(1)	.03(1)	.01(1)	.01(1)	.00(1)
C(32)	.09(1)	.08(1)	.03(1)	-.01(1)	-.01(1)	.00(1)
C(33)	.11(1)	.03(1)	.05(1)	-.03(1)	-.01(1)	.00(1)
C(34)	.07(1)	.06(1)	.02(1)	-.01(1)	.00(1)	.01(1)
C(35)	.14(2)	.06(1)	.04(1)	.00(1)	.01(1)	.00(1)
C(36)	.15(2)	.06(1)	.05(1)	-.01(1)	-.03(1)	.02(1)
C(37)	.12(2)	.07(1)	.04(1)	-.04(1)	-.01(1)	.01(1)
C(38)	.14(2)	.10(1)	.06(1)	-.07(1)	.02(1)	.00(1)
C(39)	.046(9)	.123(14)	.058(10)	.000(9)	.015(9)	-.023(10)

TABLE 11

BOND LENGTHS (A), WITH E.S.D.'S, OF DHEA (97)

D(1) - C(3)	1.39(2)	O(2) - C(17)	1.22(2)
O(21) - C(23)	1.42(2)	O(22) - C(37)	1.26(3)
C(1) - C(2)	1.53(2)	C(1) - C(10)	1.58(2)
C(2) - C(3)	1.50(2)	C(3) - C(4)	1.52(2)
C(4) - C(5)	1.51(3)	C(5) - C(6)	1.28(3)
C(5) - C(10)	1.45(2)	C(6) - C(7)	1.53(3)
C(7) - C(8)	1.52(2)	C(8) - C(9)	1.50(2)
C(8) - C(14)	1.51(2)	C(9) - C(10)	1.55(2)
C(9) - C(11)	1.52(2)	C(10) - C(19)	1.58(2)
C(11) - C(12)	1.53(2)	C(12) - C(13)	1.49(2)
C(13) - C(14)	1.50(2)	C(13) - C(17)	1.47(2)
C(13) - C(18)	1.60(2)	C(14) - C(15)	1.52(2)
C(15) - C(16)	1.55(3)	C(16) - C(17)	1.50(3)
C(21) - C(22)	1.51(3)	C(21) - C(30)	1.60(2)
C(22) - C(23)	1.54(3)	C(23) - C(24)	1.58(2)
C(24) - C(25)	1.46(3)	C(25) - C(26)	1.35(2)
C(25) - C(30)	1.54(2)	C(26) - C(27)	1.51(2)
C(27) - C(28)	1.57(2)	C(28) - C(29)	1.56(2)
C(28) - C(34)	1.49(2)	C(29) - C(30)	1.54(2)
C(29) - C(31)	1.60(2)	C(30) - C(39)	1.54(2)
C(31) - C(32)	1.52(3)	C(32) - C(33)	1.56(2)
C(33) - C(34)	1.55(2)	C(33) - C(37)	1.47(3)
C(33) - C(38)	1.54(3)	C(34) - C(35)	1.54(2)
C(35) - C(36)	1.52(3)	C(36) - C(37)	1.58(3)

TABLE 12

VALENCY ANGLES (°), WITH E.S.D.'S, OF DHEA (97)

C(2) -	C(1) -	C(10)	115. 1(11)	C(1) -	C(2) -	C(3)	111. 8(12)
O(1) -	C(3) -	C(2)	111. 5(11)	O(1) -	C(3) -	C(4)	111. 7(11)
C(2) -	C(3) -	C(4)	112. 9(11)	C(3) -	C(4) -	C(5)	112. 7(11)
C(4) -	C(5) -	C(6)	117. 4(13)	C(4) -	C(5) -	C(10)	118. 3(13)
C(6) -	C(5) -	C(10)	124. 2(15)	C(5) -	C(6) -	C(7)	124. 7(13)
C(6) -	C(7) -	C(8)	109. 6(11)	C(7) -	C(8) -	C(9)	112. 9(10)
C(7) -	C(8) -	C(14)	112. 2(11)	C(9) -	C(8) -	C(14)	111. 8(11)
C(8) -	C(9) -	C(10)	110. 9(10)	C(8) -	C(9) -	C(11)	116. 3(11)
C(10) -	C(9) -	C(11)	114. 8(11)	C(1) -	C(10) -	C(5)	107. 6(10)
C(1) -	C(10) -	C(9)	108. 1(10)	C(1) -	C(10) -	C(19)	105. 7(10)
C(5) -	C(10) -	C(9)	114. 4(12)	C(5) -	C(10) -	C(19)	110. 8(11)
C(9) -	C(10) -	C(19)	109. 8(10)	C(9) -	C(11) -	C(12)	113. 2(11)
C(11) -	C(12) -	C(13)	111. 4(11)	C(12) -	C(13) -	C(14)	111. 8(11)
C(12) -	C(13) -	C(17)	118. 4(12)	C(12) -	C(13) -	C(18)	108. 8(12)
C(14) -	C(13) -	C(17)	102. 5(11)	C(14) -	C(13) -	C(18)	112. 4(11)
C(17) -	C(13) -	C(18)	102. 6(11)	C(8) -	C(14) -	C(13)	114. 5(11)
C(8) -	C(14) -	C(15)	122. 0(11)	C(13) -	C(14) -	C(15)	106. 0(11)
C(14) -	C(15) -	C(16)	100. 3(11)	C(15) -	C(16) -	C(17)	106. 6(12)
O(2) -	C(17) -	C(13)	127. 8(14)	O(2) -	C(17) -	C(16)	123. 4(12)
C(13) -	C(17) -	C(16)	108. 8(13)	C(22) -	C(21) -	C(30)	113. 3(11)
C(21) -	C(22) -	C(23)	109. 7(12)	O(21) -	C(23) -	C(22)	109. 4(12)
O(21) -	C(23) -	C(24)	107. 3(11)	C(22) -	C(23) -	C(24)	106. 0(12)
C(23) -	C(24) -	C(25)	110. 2(12)	C(24) -	C(25) -	C(26)	120. 3(13)
C(24) -	C(25) -	C(30)	118. 3(12)	C(26) -	C(25) -	C(30)	121. 3(14)

(contd.)

C(25) - C(26) - C(27)	C(26) - C(27) - C(28)	125. 6(13)	113. 5(11)
C(27) - C(28) - C(29)	C(27) - C(28) - C(34)	107. 7(11)	110. 0(11)
C(29) - C(28) - C(34)	C(28) - C(29) - C(30)	107. 7(11)	113. 3(10)
C(28) - C(29) - C(31)	C(30) - C(29) - C(31)	109. 2(11)	112. 1(11)
C(21) - C(30) - C(25)	C(21) - C(30) - C(29)	104. 4(11)	107. 2(11)
C(21) - C(30) - C(39)	C(25) - C(30) - C(29)	110. 6(11)	111. 1(11)
C(25) - C(30) - C(39)	C(29) - C(30) - C(39)	110. 4(11)	112. 8(12)
C(29) - C(31) - C(32)	C(31) - C(32) - C(33)	112. 3(12)	107. 9(11)
C(32) - C(33) - C(34)	C(32) - C(33) - C(37)	105. 5(12)	113. 8(13)
C(32) - C(33) - C(38)	C(34) - C(33) - C(37)	111. 6(13)	100. 3(13)
C(34) - C(33) - C(38)	C(37) - C(33) - C(38)	119. 4(12)	106. 1(13)
C(28) - C(34) - C(33)	C(28) - C(34) - C(35)	111. 7(12)	120. 3(11)
C(33) - C(34) - C(35)	C(34) - C(35) - C(36)	102. 6(11)	104. 4(12)
C(35) - C(36) - C(37)	O(22) - C(37) - C(33)	101. 9(13)	130. 0(15)
O(22) - C(37) - C(36)	C(33) - C(37) - C(36)	119. 6(15)	110. 4(13)

TABLE 13

TORSION ANGLES (°), WITH E.S.D.'S, OF DHEA (97)

C(10) - C(1) - C(2) - C(3)	-51.6(12)	C(2) - C(1) - C(10) - C(5)	50.1(12)
C(2) - C(1) - C(10) - C(9)	174.2(15)	C(2) - C(1) - C(10) - C(19)	-68.3(12)
C(1) - C(2) - C(3) - O(1)	173.9(16)	C(1) - C(2) - C(3) - C(4)	49.2(12)
O(1) - C(3) - C(4) - C(5)	-174.3(16)	C(2) - C(3) - C(4) - C(5)	-47.7(12)
C(3) - C(4) - C(5) - C(6)	-127.5(17)	C(3) - C(4) - C(5) - C(10)	51.1(13)
C(4) - C(5) - C(6) - C(7)	179.6(21)	C(4) - C(5) - C(10) - C(1)	-49.9(12)
C(4) - C(5) - C(10) - C(9)	-170.1(17)	C(4) - C(5) - C(10) - C(19)	65.2(13)
C(6) - C(5) - C(10) - C(1)	128.6(18)	C(10) - C(6) - C(7)	1.1(13)
C(6) - C(5) - C(10) - C(9)	8.4(14)	C(6) - C(5) - C(10) - C(19)	-116.3(18)
C(5) - C(6) - C(7) - C(8)	17.3(14)	C(6) - C(7) - C(8) - C(9)	-45.6(12)
C(6) - C(7) - C(8) - C(14)	-173.1(15)	C(7) - C(8) - C(9) - C(10)	55.9(11)
C(7) - C(8) - C(9) - C(11)	-170.4(16)	C(7) - C(8) - C(14) - C(13)	176.2(15)
C(7) - C(8) - C(14) - C(15)	-53.8(13)	C(14) - C(8) - C(9) - C(10)	-176.4(14)
C(14) - C(8) - C(9) - C(11)	-42.7(12)	C(9) - C(8) - C(14) - C(13)	48.1(12)
C(9) - C(8) - C(14) - C(15)	178.2(16)	C(8) - C(9) - C(10) - C(1)	-156.2(13)
C(8) - C(9) - C(10) - C(5)	-36.3(11)	C(8) - C(9) - C(10) - C(19)	89.0(12)
C(8) - C(9) - C(11) - C(12)	44.1(12)	C(11) - C(9) - C(10) - C(1)	69.4(12)
C(11) - C(9) - C(10) - C(5)	-170.7(16)	C(10) - C(9) - C(11) - C(12)	176.0(16)
C(11) - C(9) - C(10) - C(19)	-45.4(12)	C(9) - C(11) - C(12) - C(13)	-49.2(12)
C(11) - C(12) - C(13) - C(14)	54.8(12)	C(11) - C(12) - C(13) - C(17)	173.5(17)
C(11) - C(12) - C(13) - C(18)	-70.0(13)	C(12) - C(13) - C(14) - C(8)	-55.7(12)
C(12) - C(13) - C(14) - C(15)	166.9(15)	C(12) - C(13) - C(17) - O(2)	31.1(14)
C(12) - C(13) - C(17) - C(16)	-147.2(17)	C(14) - C(13) - C(17) - O(2)	154.6(19)
C(17) - C(13) - C(14) - C(8)	176.3(14)	C(17) - C(13) - C(14) - C(15)	39.0(11)

(contd.)

C(14) - C(13)	- C(17)	- C(16)	-23. 7(11)	C(18) - C(13)	- C(14)	- C(14)	- C(8)	67. 1(12)
C(18) - C(13)	- C(14)	- C(15)	-70. 4(12)	C(18) - C(13)	- C(17)	- C(17)	- O(2)	-88. 7(17)
C(18) - C(13)	- C(17)	- C(16)	93. 0(13)	C(8) - C(14)	- C(15)	- C(15)	- C(16)	-171. 5(15)
C(13) - C(14)	- C(15)	- C(16)	-38. 0(11)	C(14) - C(15)	- C(16)	- C(16)	- C(17)	22. 6(11)
C(15) - C(16)	- C(17)	- O(2)	-178. 0(19)	C(15) - C(16)	- C(17)	- C(17)	- C(13)	. 4(11)
C(30) - C(21)	- C(22)	- C(23)	-62. 9(13)	C(22) - C(21)	- C(30)	- C(30)	- C(25)	52. 3(13)
C(22) - C(21)	- C(30)	- C(29)	170. 2(16)	C(22) - C(21)	- C(30)	- C(30)	- C(39)	-66. 4(13)
C(21) - C(22)	- C(23)	- O(21)	177. 8(16)	C(21) - C(22)	- C(23)	- C(23)	- C(24)	62. 4(13)
O(21) - C(23)	- C(24)	- C(25)	-175. 7(16)	C(22) - C(23)	- C(24)	- C(24)	- C(25)	-58. 9(13)
C(23) - C(24)	- C(25)	- C(26)	-125. 4(18)	C(23) - C(24)	- C(25)	- C(25)	- C(30)	58. 0(13)
C(24) - C(25)	- C(26)	- C(27)	-176. 6(22)	C(24) - C(25)	- C(30)	- C(30)	- C(21)	-51. 5(13)
C(24) - C(25)	- C(30)	- C(29)	-166. 7(17)	C(24) - C(25)	- C(30)	- C(30)	- C(39)	67. 5(14)
C(26) - C(25)	- C(30)	- C(21)	131. 9(17)	C(30) - C(25)	- C(26)	- C(26)	- C(27)	- 1(13)
C(26) - C(25)	- C(30)	- C(29)	16. 7(13)	C(26) - C(25)	- C(30)	- C(30)	- C(39)	-109. 1(17)
C(25) - C(26)	- C(27)	- C(28)	13. 9(14)	C(26) - C(27)	- C(28)	- C(28)	- C(29)	-41. 9(12)
C(26) - C(27)	- C(28)	- C(34)	-159. 0(15)	C(27) - C(28)	- C(29)	- C(29)	- C(30)	60. 7(12)
C(27) - C(28)	- C(29)	- C(31)	-173. 7(14)	C(27) - C(28)	- C(34)	- C(34)	- C(33)	-178. 1(15)
C(27) - C(28)	- C(34)	- C(35)	-57. 7(13)	C(34) - C(28)	- C(29)	- C(29)	- C(30)	179. 3(15)
C(34) - C(28)	- C(29)	- C(31)	-55. 1(12)	C(29) - C(28)	- C(34)	- C(34)	- C(33)	64. 8(12)
C(29) - C(28)	- C(34)	- C(35)	-174. 8(17)	C(28) - C(29)	- C(30)	- C(30)	- C(21)	-161. 4(15)
C(28) - C(29)	- C(30)	- C(25)	-47. 8(12)	C(28) - C(29)	- C(30)	- C(30)	- C(39)	76. 7(13)
C(28) - C(29)	- C(31)	- C(32)	54. 9(12)	C(31) - C(29)	- C(30)	- C(30)	- C(21)	74. 6(12)
C(31) - C(29)	- C(30)	- C(25)	-171. 9(15)	C(30) - C(29)	- C(31)	- C(31)	- C(32)	-178. 8(16)
C(31) - C(29)	- C(30)	- C(39)	-47. 4(12)	C(29) - C(31)	- C(32)	- C(32)	- C(33)	-58. 9(13)

(contd.)

C(31) - C(32)	-	C(33)	-	C(34)	62. 6(13)	C(31) - C(32)	-	C(33)	-	C(37)	171. 5(18)
C(31) - C(32)	-	C(33)	-	C(38)	-68. 5(14)	C(32) - C(33)	-	C(34)	-	C(28)	-68. 4(13)
C(32) - C(33)	-	C(34)	-	C(35)	161. 4(14)	C(32) - C(33)	-	C(37)	-	0(22)	39. 2(18)
C(32) - C(33)	-	C(37)	-	C(36)	-140. 3(18)	C(34) - C(33)	-	C(37)	-	0(22)	151. 3(22)
C(37) - C(33)	-	C(34)	-	C(28)	173. 2(16)	C(37) - C(33)	-	C(34)	-	C(35)	43. 0(13)
C(34) - C(33)	-	C(37)	-	C(36)	-28. 2(13)	C(38) - C(33)	-	C(34)	-	C(28)	58. 0(14)
C(38) - C(33)	-	C(34)	-	C(35)	-72. 2(15)	C(38) - C(33)	-	C(37)	-	0(22)	-83. 9(20)
C(38) - C(33)	-	C(37)	-	C(36)	96. 7(15)	C(28) - C(34)	-	C(35)	-	C(36)	-167. 8(17)
C(33) - C(34)	-	C(35)	-	C(36)	-43. 1(12)	C(34) - C(35)	-	C(36)	-	C(37)	24. 8(12)
C(35) - C(36)	-	C(37)	-	0(22)	-176. 9(20)	C(35) - C(36)	-	C(37)	-	C(33)	2. 6(13)

TABLE 14

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR C19H28O2.H2O (97)

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	
2	0	0	422	508	4	3	0	296	318	13	5	0	183	146	2	8	0	216	215	
4	0	0	1437	1543	5	3	0	536	610	14	5	0	105	85	3	8	0	234	228	
6	0	0	886	954	6	3	0	606	618	15	5	0	102	100	4	8	0	408	383	
8	0	0	481	497	7	3	0	422	430	16	5	0	147	195	5	8	0	718	730	
10	0	0	370	373	8	3	0	118	91	17	5	0	175	192	6	8	0	202	197	
12	0	0	346	361	9	3	0	223	229	18	5	0	103	105	7	8	0	208	226	
14	0	0	137	140	10	3	0	210	205	0	6	0	653	677	8	8	0	367	369	
16	0	0	126	125	11	3	0	549	538	2	6	0	333	350	9	8	0	306	303	
18	0	0	200	199	12	3	0	283	275	4	6	0	332	369	11	8	0	159	180	
2	1	0	156	138	13	3	0	98	83	5	6	0	263	254	12	8	0	126	113	
3	1	0	913	976	16	3	0	136	134	7	6	0	122	118	13	8	0	333	331	
4	1	0	1859	1969	0	4	0	742	751	8	6	0	153	161	14	8	0	279	277	
5	1	0	1440	1509	2	4	0	153	161	10	6	0	166	181	15	8	0	172	200	
6	1	0	155	166	3	4	0	729	750	11	6	0	199	196	18	8	0	133	161	
7	1	0	104	146	4	4	0	274	280	12	6	0	121	116	20	8	0	295	262	
8	1	0	139	178	5	4	0	171	187	13	6	0	136	132	1	9	0	334	390	
9	1	0	198	196	6	4	0	584	581	14	6	0	110	122	2	9	0	288	309	
12	1	0	616	601	7	4	0	413	421	15	6	0	235	226	3	9	0	203	227	
15	1	0	261	281	8	4	0	158	125	16	6	0	121	119	4	9	0	454	428	
21	1	0	174	180	9	4	0	98	118	18	6	0	178	195	6	9	0	234	204	
0	2	0	255	334	10	4	0	141	138	19	6	0	110	85	7	9	0	365	350	
1	2	0	114	45	11	4	0	307	296	20	6	0	120	113	8	9	0	543	524	
2	2	0	580	671	12	4	0	207	203	1	7	0	523	541	9	9	0	194	211	
3	2	0	734	775	13	4	0	169	158	3	7	0	333	330	11	9	0	185	170	
4	2	0	96	90	16	4	0	155	173	4	7	0	269	251	12	9	0	106	112	
5	2	0	162	173	17	4	0	161	144	5	7	0	291	291	13	9	0	281	273	
6	2	0	634	642	19	4	0	151	147	6	7	0	78	37	16	9	0	145	129	
7	2	0	681	727	1	5	0	162	153	10	7	0	166	186	17	9	0	132	91	
8	2	0	269	245	2	5	0	459	489	12	7	0	241	255	18	9	0	125	89	
10	2	0	145	157	3	5	0	491	537	14	7	0	127	141	19	9	0	137	156	
11	2	0	85	69	4	5	0	268	253	15	7	0	132	136	20	9	0	164	152	
13	2	0	239	250	5	5	0	171	188	16	7	0	214	213	21	9	0	110	110	
14	2	0	155	154	6	5	0	77	100											
16	2	0	212	208																
18	2	0	213																	
2	3	0	242																	

(contd.)

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR C19H28O2.H2O

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
15	13	0	200	186	2	0	1	1920	1852	15	2	1	151	163	0	5	1	101	72	3	7	1	271	281
16	13	0	114	113	3	0	1	734	778	0	3	1	388	368	1	5	1	760	823	4	7	1	276	256
0	14	0	229	228	4	0	1	697	725	1	3	1	938	946	2	5	1	447	457	5	7	1	272	295
1	14	0	198	246	5	0	1	191	194	2	3	1	606	599	3	5	1	379	342	6	7	1	198	206
2	14	0	111	126	6	0	1	375	378	3	3	1	782	792	4	5	1	384	382	7	7	1	501	547
4	14	0	118	112	8	0	1	735	759	5	3	1	467	463	4	5	1	295	278	8	7	1	172	152
5	14	0	229	220	13	0	1	259	252	6	3	1	162	124	6	5	1	360	355	9	7	1	355	372
8	14	0	113	132	17	0	1	283	276	7	3	1	422	409	7	5	1	153	160	10	7	1	291	288
9	14	0	97	86	0	1	1	344	355	8	5	1	156	160	8	5	1	290	277	11	7	1	295	286
10	14	0	199	179	1	1	1	917	844	9	3	1	464	483	9	5	1	132	112	12	7	1	148	144
11	14	0	108	125	2	1	1	716	678	10	3	1	296	297	10	5	1	129	137	13	7	1	95	107
12	14	0	136	133	3	1	1	1596	1601	11	3	1	210	195	13	5	1	209	187	15	7	1	123	110
13	14	0	195	210	4	1	1	556	584	12	3	1	144	138	14	5	1	97	120	16	7	1	114	80
3	15	0	115	83	5	1	1	885	904	14	3	1	159	182	15	5	1	181	202	17	7	1	120	99
6	15	0	129	132	6	1	1	367	394	15	3	1	176	175	17	5	1	184	193	18	7	1	245	246
12	15	0	145	129	7	1	1	397	379	16	3	1	162	164	19	5	1	109	102	20	7	1	127	136
15	15	0	129	141	8	1	1	525	529	17	3	1	195	187	1	6	1	378	384	0	8	1	116	114
18	15	0	115	41	9	1	1	879	891	24	3	1	102	65	2	6	1	596	599	1	8	1	201	221
2	16	0	165	224	10	1	1	290	289	0	4	1	206	202	3	6	1	248	257	2	8	1	146	142
7	16	0	121	101	11	1	1	174	210	1	4	1	326	319	4	6	1	335	350	3	8	1	370	367
9	16	0	179	172	12	1	1	265	255	2	4	1	614	631	5	6	1	500	534	4	8	1	225	218
11	16	0	113	117	14	1	1	165	171	3	4	1	260	268	6	6	1	377	387	5	8	1	150	136
2	17	0	129	183	0	2	1	947	896	4	4	1	304	291	7	6	1	432	443	6	8	1	260	244
12	17	0	152	143	1	2	1	1803	1730	5	4	1	103	95	8	6	1	548	549	7	8	1	313	299
13	17	0	147	148	2	2	1	603	574	6	4	1	444	440	9	6	1	219	206	8	8	1	194	185
14	17	0	147	146	3	2	1	1304	1295	7	4	1	505	481	10	6	1	329	334	9	8	1	341	351
4	18	0	128	143	4	2	1	332	348	8	4	1	316	321	11	6	1	233	241	10	8	1	99	83
9	18	0	108	70	5	2	1	473	510	9	4	1	355	336	12	6	1	144	119	11	8	1	235	236
11	18	0	128	128	6	2	1	690	708	10	4	1	127	167	13	6	1	174	179	12	8	1	126	105
6	19	0	222	226	7	2	1	367	387	11	4	1	171	191	15	6	1	99	112	13	8	1	242	250
8	19	0	117	151	8	2	1	836	858	12	4	1	119	126	17	6	1	100	89	15	8	1	126	138
1	20	0	144	124	9	2	1	316	325	13	4	1	93	99	18	6	1	134	128	16	8	1	146	161
2	20	0	305	304	10	2	1	481	476	14	4	1	161	179	22	6	1	125	131	18	8	1	148	131
3	20	0	123	125	11	2	1	99	133	18	4	1	141	172	0	7	1	148	151	21	8	1	117	93
6	20	0	127	180	12	2	1	230	222	19	4	1	126	116	1	7	1	286	301	1	9	1	232	246
1	0	1	776	710	13	2	1	200	187	21	4	1	115	115	2	7	1	335	363	2	9	1	94	96

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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR C19H28O2. H2O

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
3	9	1	345	342	10	11	1	179	158	7	14	1	132	139	2	0	2	112	117
4	9	1	457	454	11	11	1	115	133	9	14	1	192	180	3	0	2	461	389
5	9	1	213	232	13	11	1	127	146	10	14	1	214	205	4	0	2	109	105
6	9	1	254	260	14	11	1	231	214	11	14	1	163	157	5	0	2	287	269
7	9	1	81	82	15	11	1	148	170	0	15	1	267	309	6	0	2	257	248
8	9	1	156	184	17	11	1	168	184	4	15	1	90	110	7	0	2	295	281
11	9	1	213	244	22	11	1	115	62	5	15	1	167	180	8	0	2	371	374
12	9	1	322	335	23	11	1	117	71	6	15	1	99	95	9	0	2	80	78
13	9	1	161	161	3	12	1	104	108	8	15	1	153	118	10	0	2	83	71
14	9	1	175	162	4	12	1	261	274	10	15	1	115	54	11	0	2	82	65
16	9	1	284	249	5	12	1	103	88	13	15	1	249	238	17	0	2	140	156
17	9	1	118	139	6	12	1	181	176	15	15	1	117	108	0	1	2	202	180
0	10	1	618	609	8	12	1	165	160	1	16	1	162	163	1	1	2	131	104
2	10	1	124	113	9	12	1	161	146	4	16	1	107	104	2	1	2	626	574
3	10	1	306	303	10	12	1	107	91	5	16	1	202	191	3	1	2	563	509
4	10	1	680	659	11	12	1	189	185	11	16	1	129	149	4	1	2	233	185
5	10	1	281	264	12	12	1	259	255	12	16	1	157	182	5	1	2	307	301
6	10	1	280	289	13	12	1	147	164	14	16	1	156	138	6	1	2	449	436
7	10	1	182	177	14	12	1	203	200	4	17	1	130	125	7	1	2	298	304
8	10	1	225	216	16	12	1	142	141	5	17	1	193	190	8	1	2	371	356
9	10	1	173	175	17	12	1	111	91	7	17	1	112	113	10	1	2	210	210
10	10	1	265	259	19	12	1	126	108	8	17	1	152	157	11	1	2	466	465
11	10	1	179	189	2	13	1	274	265	10	17	1	125	131	13	1	2	259	260
13	10	1	208	226	3	13	1	173	189	1	18	1	127	153	20	1	2	110	105
15	10	1	121	124	5	13	1	253	268	2	18	1	222	227	0	2	2	233	226
16	10	1	163	144	8	13	1	126	125	5	18	1	164	136	1	2	2	1228	1166
18	10	1	105	111	9	13	1	110	118	6	18	1	136	143	2	2	2	1019	929
0	11	1	115	125	10	13	1	204	180	7	18	1	198	176	3	2	2	700	691
1	11	1	270	291	11	13	1	135	149	3	19	1	120	130	4	2	2	176	179
2	11	1	398	380	12	13	1	258	275	4	19	1	175	197	5	2	2	195	205
3	11	1	300	277	14	13	1	121	108	12	19	1	110	82	6	2	2	110	121
4	11	1	224	209	16	13	1	102	115	2	20	1	136	152	7	2	2	379	373
5	11	1	256	234	3	14	1	319	323	1	21	1	143	134	8	2	2	244	265
6	11	1	202	233	4	14	1	127	122	3	21	1	162	176	9	2	2	472	470
7	11	1	103	79	5	14	1	183	181	0	0	2	227	210	10	2	2	338	336
8	11	1	251	247	6	14	1	203	195	1	0	2	408	400	12	2	2	142	121

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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR C19H28O2. H2O

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
0	5	2	310	305	3	7	2	194	190	12	9	2	166	181	4	12	2	261	278
1	5	2	148	162	4	7	2	495	497	14	9	2	228	233	6	12	2	182	149
2	5	2	511	491	5	7	2	674	661	15	9	2	225	231	9	12	2	125	143
3	5	2	707	724	6	7	2	412	407	16	9	2	201	202	14	12	2	153	145
4	5	2	338	326	7	7	2	415	395	19	9	2	139	107	15	12	2	120	113
5	5	2	170	177	8	7	2	358	356	0	10	2	200	186	6	17	2	217	226
6	5	2	263	260	9	7	2	224	215	1	10	2	154	138	2	13	2	181	219
7	5	2	409	384	10	7	2	253	219	2	10	2	184	184	3	13	2	202	217
8	5	2	217	214	13	7	2	95	87	3	10	2	239	219	4	13	2	233	249
9	5	2	247	232	14	7	2	171	153	4	10	2	136	127	5	13	2	188	193
11	5	2	100	78	16	7	2	146	142	5	10	2	136	143	6	13	2	135	164
12	5	2	89	89	17	7	2	131	86	6	10	2	216	219	9	13	2	121	115
13	5	2	105	129	0	8	2	197	203	8	10	2	145	119	10	13	2	178	220
14	5	2	154	157	1	8	2	218	221	9	10	2	94	130	14	13	2	120	140
16	5	2	220	200	2	8	2	182	162	11	10	2	133	135	0	14	2	159	150
19	5	2	135	136	3	8	2	313	312	12	10	2	278	264	2	14	2	153	153
0	6	2	424	417	4	8	2	265	231	13	10	2	251	261	3	14	2	168	160
1	6	2	542	484	5	8	2	414	437	16	10	2	130	140	4	14	2	216	231
2	6	2	349	339	6	8	2	112	94	17	10	2	136	153	5	14	2	93	86
3	6	2	152	146	7	8	2	352	360	18	10	2	103	106	6	14	2	175	188
4	6	2	446	428	10	8	2	176	168	0	11	2	181	205	7	14	2	109	105
5	6	2	303	292	11	8	2	170	138	1	11	2	273	249	8	14	2	111	133
6	6	2	148	132	16	8	2	135	131	2	11	2	178	199	10	14	2	109	103
7	6	2	200	201	18	8	2	108	84	3	11	2	135	106	11	14	2	152	144
8	6	2	102	114	19	8	2	148	121	4	11	2	176	181	1	15	2	107	118
10	6	2	386	386	22	8	2	111	88	5	11	2	186	192	2	15	2	250	262
11	6	2	202	202	23	8	2	118	53	6	11	2	143	124	3	15	2	272	293
12	6	2	180	197	0	9	2	156	128	7	11	2	122	143	4	15	2	119	102
14	6	2	150	150	1	9	2	260	245	10	11	2	132	103	9	15	2	172	143
15	6	2	96	81	2	9	2	491	458	12	11	2	162	146	2	16	2	396	409
16	6	2	257	236	3	9	2	167	194	13	11	2	184	249	3	16	2	176	188
18	6	2	155	178	4	9	2	91	88	14	11	2	189	203	4	16	2	262	257
19	6	2	147	179	5	9	2	199	202	16	11	2	113	102	5	16	2	115	111
0	7	2	224	234	7	9	2	174	169	17	11	2	109	86	7	16	2	238	235
1	7	2	414	401	10	9	2	110	105	0	12	2	148	155	14	16	2	125	107
2	7	2	131	132	11	9	2	170	171	3	12	2	156	153	15	16	2	116	106

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR C19H28O2. H2O

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
2	1	3	470	441	8	3	3	358	358	13	5	3	204	199	4	8	3	80	66
3	1	3	146	137	9	3	3	245	266	14	5	3	130	70	5	8	3	232	205
4	1	3	660	654	10	3	3	131	155	0	6	3	272	250	6	8	3	129	121
6	1	3	400	385	11	3	3	188	211	1	6	3	591	539	7	8	3	113	109
7	1	3	137	123	12	3	3	148	135	2	6	3	488	475	9	8	3	128	142
8	1	3	154	161	13	3	3	104	110	3	6	3	179	171	11	8	3	123	100
9	1	3	140	130	14	3	3	137	116	5	6	3	179	188	13	8	3	232	219
10	1	3	203	170	20	3	3	144	151	6	6	3	223	206	14	8	3	144	127
11	1	3	153	149	0	4	3	1568	1534	7	6	3	96	102	15	8	3	141	132
12	1	3	85	87	1	4	3	113	108	8	6	3	261	263	23	8	3	115	66
14	1	3	115	115	2	4	3	767	717	9	6	3	235	238	0	9	3	264	253
15	1	3	107	101	3	4	3	351	340	10	6	3	114	135	3	9	3	99	121
20	1	3	111	117	4	4	3	266	247	11	6	3	238	246	4	9	3	111	125
0	2	3	424	377	5	4	3	450	437	13	6	3	153	169	6	9	3	96	108
1	2	3	247	218	6	4	3	346	330	14	6	3	192	185	7	9	3	206	206
3	2	3	498	467	7	4	3	273	274	15	6	3	158	169	8	9	3	241	219
4	2	3	516	464	8	4	3	433	408	17	6	3	114	88	9	9	3	227	225
5	2	3	222	181	9	4	3	317	311	18	6	3	155	146	10	9	3	110	89
6	2	3	154	144	10	4	3	236	281	20	6	3	113	78	11	9	3	121	118
7	2	3	308	326	14	4	3	97	112	0	7	3	78	36	12	9	3	156	164
8	2	3	288	285	15	4	3	143	105	1	7	3	266	254	13	9	3	127	137
9	2	3	228	245	16	4	3	97	122	2	7	3	97	110	0	10	3	302	299
11	2	3	255	251	18	4	3	110	126	4	7	3	356	325	2	10	3	115	108
13	2	3	117	138	0	5	3	721	689	5	7	3	178	158	3	10	3	221	200
16	2	3	111	94	1	5	3	391	352	6	7	3	217	218	4	10	3	148	142
17	2	3	113	134	2	5	3	475	439	7	7	3	188	166	5	10	3	153	129
20	2	3	104	113	3	5	3	109	82	9	7	3	205	212	7	10	3	109	106
0	3	3	542	489	4	5	3	222	225	10	7	3	189	196	8	10	3	108	91
1	3	3	111	98	5	5	3	155	165	11	7	3	237	247	10	10	3	93	79
2	3	3	332	316	6	5	3	164	170	13	7	3	166	156	12	10	3	157	147
3	3	3	228	207	7	5	3	145	148	14	7	3	281	268	13	10	3	108	108
4	3	3	372	369	8	5	3	145	148	15	7	3	170	144	17	10	3	104	95
5	3	3	536	528	9	5	3	279	269	17	7	3	169	151	22	10	3	137	107
6	3	3	220	182	10	5	3	96	98	0	8	3	126	97	1	11	3	188	208
7	3	3	354	350	11	5	3	143	141	1	8	3	169	151	2	11	3	89	84
					12	5	3	208	198	2	8	3	209	204	7	11	3	108	106

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR C19H28O2.H2O

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H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
9	14	3	108	96	4	22	3	118	78	12	2	4	115	84	6	5	4	303	290
10	14	3	139	151	9	23	3	122	97	13	2	4	178	188	7	5	4	98	100
11	14	3	164	156	0	0	4	553	566	16	2	4	105	107	8	5	4	270	271
12	14	3	118	84	2	0	4	220	216	0	3	4	365	338	9	5	4	258	265
0	15	3	211	210	3	0	4	572	562	1	3	4	388	379	10	5	4	143	132
1	15	3	196	179	3	0	4	130	108	3	3	4	100	84	11	5	4	99	78
2	15	3	110	100	5	0	4	144	150	4	3	4	190	200	12	5	4	108	117
3	15	3	114	111	6	0	4	112	98	5	3	4	122	104	14	5	4	102	77
6	15	3	270	262	7	0	4	102	94	6	3	4	96	96	15	5	4	192	220
7	15	3	141	124	8	0	4	131	138	21	5	4	121	144	21	5	4	119	79
10	15	3	193	198	9	0	4	279	265	0	6	4	200	210	0	6	4	101	76
11	15	3	145	129	10	0	4	110	105	10	3	4	267	280	1	6	4	307	352
13	15	3	126	114	13	0	4	146	166	11	3	4	192	182	3	6	4	325	319
18	15	3	108	69	16	0	4	426	447	12	3	4	323	320	4	6	4	123	123
1	16	3	107	101	0	1	4	316	312	14	3	4	110	131	6	6	4	184	193
2	16	3	314	327	1	2	4	163	144	17	3	4	115	128	7	6	4	276	276
3	16	3	148	163	2	3	4	85	77	0	4	4	713	696	8	6	4	199	195
4	16	3	113	94	3	4	4	88	85	10	4	4	426	405	10	6	4	123	126
5	16	3	236	236	4	5	4	246	226	1	4	4	345	343	11	6	4	183	181
6	16	3	270	244	5	6	4	185	161	2	4	4	199	214	13	6	4	236	229
7	16	3	227	230	6	7	4	197	198	3	4	4	290	293	13	6	4	124	138
8	16	3	192	211	7	8	4	259	284	4	4	4	91	95	17	6	4	131	145
2	17	3	134	121	8	9	4	111	133	1	7	4	144	122	1	7	4	266	268
3	17	3	165	184	9	15	4	135	117	6	4	4	136	131	2	7	4	205	211
5	17	3	120	133	15	17	4	145	146	7	4	4	191	194	3	7	4	212	205
6	17	3	221	236	17	18	4	124	119	10	4	4	239	223	4	7	4	127	116
7	17	3	118	112	18	0	4	80	79	11	4	4	195	200	5	7	4	127	110
10	17	3	107	68	0	1	4	203	185	12	4	4	234	248	7	7	4	121	130
1	18	3	233	208	1	2	4	186	193	8	7	4	169	176	8	7	4	113	120
3	18	3	135	137	2	3	4	278	284	17	4	4	105	86	9	7	4	144	134
5	18	3	136	143	3	4	4	197	189	10	7	4	136	121	12	7	4	110	105
12	18	3	128	121	6	6	4	261	253	13	7	4	127	160	13	7	4	155	153
13	19	3	110	76	7	7	4	434	414	1	5	4	304	297	14	7	4	200	225
0	20	3	171	175	8	8	4	316	320	2	5	4	413	380	14	7	4	143	180
1	21	3	100	61	9	9	4	111	121	17	7	4	229	244	17	7	4	149	168
5	21	3	121	85	10	10	4	99	112	0	8	4	280	284	1	8	4	112	141

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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR C19H28O2.H2O

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
8	13	4	123	135	0	2	5	316	316	8	5	5	260	287	11	9	5	236	245
1	14	4	182	173	1	2	5	164	169	9	5	5	159	154	0	10	5	161	163
2	14	4	193	183	3	2	5	194	209	10	5	5	125	158	2	10	5	197	205
3	14	4	318	307	4	2	5	297	304	11	5	5	129	139	3	10	5	96	87
4	14	4	145	152	6	2	5	236	233	12	5	5	144	132	4	10	5	159	163
6	14	4	202	210	9	2	5	119	130	14	5	5	173	168	5	10	5	125	114
7	14	4	136	152	11	2	5	97	88	0	6	5	110	138	7	10	5	126	130
0	15	4	115	116	20	2	5	114	77	2	6	5	93	112	3	11	5	113	119
1	15	4	127	173	0	3	5	205	244	3	6	5	114	139	4	11	5	128	140
2	15	4	164	158	1	3	5	193	219	4	6	5	125	117	7	11	5	190	203
3	15	4	178	149	2	3	5	124	138	5	6	5	175	165	12	11	5	127	123
7	15	4	158	158	3	3	5	205	217	6	6	5	167	150	13	11	5	106	95
0	16	4	106	111	4	3	5	328	357	10	6	5	140	138	16	11	5	127	133
3	16	4	106	79	5	3	5	272	278	11	6	5	119	143	0	12	5	195	188
4	16	4	223	239	7	3	5	112	110	12	6	5	142	131	2	12	5	215	199
6	16	4	121	124	8	3	5	195	213	14	6	5	131	124	3	12	5	133	108
9	16	4	126	126	9	3	5	177	190	15	6	5	103	92	4	12	5	165	159
5	19	4	105	84	10	3	5	216	209	2	7	5	115	133	5	12	5	102	100
1	0	5	139	150	11	3	5	148	164	3	7	5	113	102	11	12	5	116	123
2	0	5	241	234	13	3	5	127	121	4	7	5	166	164	2	13	5	157	152
3	0	5	119	129	14	3	5	114	91	6	7	5	178	190	4	13	5	140	131
4	0	5	283	289	15	3	5	106	97	7	7	5	134	112	5	13	5	160	162
6	0	5	182	201	2	4	5	115	119	9	7	5	179	186	6	13	5	160	164
7	0	5	144	159	3	4	5	140	111	10	7	5	125	142	8	13	5	106	119
9	0	5	448	471	4	4	5	385	410	11	7	5	132	145	9	13	5	122	132
10	0	5	152	164	5	4	5	186	190	14	7	5	137	103	13	13	5	114	106
11	0	5	109	100	6	4	5	220	217	3	8	5	96	99	1	14	5	111	107
2	1	5	169	162	7	4	5	260	293	4	8	5	155	174	5	14	5	153	163
3	1	5	97	83	8	4	5	228	221	5	8	5	175	180	6	14	5	166	147
4	1	5	335	364	9	4	5	153	141	0	9	5	217	220	7	14	5	130	139
5	1	5	189	195	10	4	5	223	217	1	9	5	138	126	3	15	5	119	96
7	1	5	132	122	12	4	5	144	137	2	9	5	112	138	6	15	5	111	47
8	1	5	288	305	2	5	5	139	150	3	9	5	171	145	2	16	5	132	148
9	1	5	176	191	3	5	5	173	185	6	9	5	121	127	5	16	5	105	130
10	1	5	136	142	6	5	5	116	87	8	9	5	105	74	0	0	6	117	131
11	1	5	99	107	7	5	5	98	103	9	9	5	115	121	1	0	6	219	205

(contd.)

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR C19H28O2.H2O

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC					
2	7	6	120	124	3	10	6	127	137	2	12	6	134	121	4	1	7	118	112	0	8	7	131	125
3	7	6	101	119	5	10	6	136	128	3	12	6	184	176	7	1	7	157	159	8	8	7	107	56
7	7	6	107	98	13	10	6	144	147	6	12	6	138	136	0	2	7	108	140	6	9	7	114	160
8	7	6	130	141	14	10	6	132	115	7	12	6	125	113	1	2	7	113	126	7	9	7	124	158
9	7	6	129	108	6	11	6	120	119	10	12	6	106	104	8	2	7	101	105	4	11	7	114	126
12	7	6	121	115	8	11	6	175	169	6	13	6	105	55	8	3	7	112	115	2	12	7	112	69
4	8	6	137	138	9	11	6	111	90	1	14	6	117	114	3	5	7	145	180	4	0	8	110	88
8	8	6	189	200	12	11	6	144	144	1	0	7	112	137	11	5	7	116	80	0	1	8	176	205
2	9	6	149	135	0	12	6	112	77	2	0	7	117	117	7	6	7	130	138	1	1	8	106	101
7	9	6	140	153	1	12	6	121	82	6	0	7	142	141										

TABLE 15

FRACTIONAL ATOMIC COORDINATES AND ISOTROPIC TEMPERATURE FACTORS (ANGSTROM SQUARED), WITH STANDARD DEVIATIONS IN THE LEAST SIGNIFICANT DIGITS IN PARENTHESES. FOR ANISOTROPIC ATOMS, THE EQUIVALENT ISOTROPIC TEMPERATURE FACTORS ARE SHOWN. (41)

	X/A	Y/B	Z/C	U
O(1)	. 1579(6)	. 5260(6)	. 5590(2)	. 067
O(2)	. 3043(5)	-. 2567(6)	. 5939(2)	. 067
C(1)	. 3246(8)	-. 0115(9)	. 7189(3)	. 068
C(2)	. 2033(9)	-. 0745(10)	. 7340(3)	. 082
C(3)	. 1801(9)	-. 1932(11)	. 7028(4)	. 071
C(4)	. 2816(9)	-. 2897(10)	. 6954(3)	. 084
C(5)	. 2577(8)	-. 1731(10)	. 6647(3)	. 051
C(6)	. 2082(8)	-. 2103(9)	. 6217(3)	. 057
C(7)	. 1451(7)	-. 0834(8)	. 6017(3)	. 044
C(8)	. 2248(7)	. 0441(8)	. 6003(3)	. 042
C(9)	. 2704(7)	. 0838(8)	. 6458(3)	. 039
C(10)	. 3305(8)	-. 0373(9)	. 6704(3)	. 047
C(11)	. 3465(7)	. 2159(8)	. 6449(3)	. 046
C(12)	. 2828(7)	. 3400(8)	. 6236(3)	. 045
C(13)	. 2375(7)	. 2992(9)	. 5794(3)	. 043
C(14)	. 1591(8)	. 1706(8)	. 5830(3)	. 043
C(15)	. 0930(7)	. 1634(9)	. 5393(3)	. 050
C(16)	. 0627(7)	. 3180(9)	. 5318(3)	. 055
C(17)	. 1522(8)	. 4002(9)	. 5574(3)	. 046
C(18)	. 4633(6)	-. 0596(9)	. 6559(3)	. 067
C(19)	. 3444(7)	. 2830(10)	. 5470(3)	. 069
H(1A)	. 3939(8)	-. 0584(9)	. 7336(3)	. 056(5)
H(1B)	. 3269(8)	. 0908(9)	. 7250(3)	. 056(5)
H(2)	. 275(6)	-. 338(5)	. 577(2)	. 056(5)
H(2A)	. 1369(9)	-. 0038(10)	. 7323(3)	. 056(5)
H(2B)	. 2101(9)	-. 1099(10)	. 7640(3)	. 056(5)
H(3A)	. 0929(9)	-. 2103(11)	. 7097(4)	. 056(5)
H(4A)	. 3548(9)	-. 2868(10)	. 7142(3)	. 056(5)
H(4B)	. 2652(9)	-. 3882(10)	. 6867(3)	. 056(5)
H(6A)	. 1482(8)	-. 2875(9)	. 6253(3)	. 056(5)
H(7A)	. 0713(7)	-. 0612(8)	. 6190(3)	. 056(5)
H(7B)	. 1206(7)	-. 1077(8)	. 5718(3)	. 056(5)
H(8A)	. 2935(7)	. 0193(8)	. 5809(3)	. 056(5)
H(9A)	. 1964(7)	. 1044(8)	. 6632(3)	. 056(5)
H(11A)	. 3668(7)	. 2423(8)	. 6751(3)	. 056(5)
H(11B)	. 4228(7)	. 1960(8)	. 6288(3)	. 056(5)
H(12A)	. 3414(7)	. 4189(8)	. 6208(3)	. 056(5)
H(12B)	. 2127(7)	. 3698(8)	. 6417(3)	. 056(5)
H(14A)	. 0962(8)	. 1741(8)	. 6061(3)	. 056(5)
H(15A)	. 0180(7)	. 1053(9)	. 5411(3)	. 056(5)
H(15B)	. 1471(7)	. 1258(9)	. 5164(3)	. 056(5)
H(16A)	-. 0216(7)	. 3386(9)	. 5416(3)	. 056(5)

(contd.)

	X/A	Y/B	Z/C	U
H(16B)	. 0705(7)	. 3410(9)	. 5007(3)	. 056(5)
H(18A)	. 4652(6)	-. 0765(9)	. 6243(3)	. 06(1)
H(18B)	. 4984(6)	-. 1419(9)	. 6711(3)	. 06(1)
H(18C)	. 5120(6)	. 0254(9)	. 6628(3)	. 06(1)
H(19A)	. 4058(7)	. 2171(10)	. 5591(3)	. 06(1)
H(19B)	. 3830(7)	. 3759(10)	. 5420(3)	. 06(1)
H(19C)	. 3130(7)	. 2453(10)	. 5193(3)	. 06(1)

TABLE 15 (contd.)

VIBRATION PARAMETERS (ANGSTROM SQUARED) IN THE EXPRESSION:

$$-2(\text{PI SQUARED})(U11((\text{H. A}^*)\text{SQUARED}) + U22((\text{K. B}^*)\text{SQUARED}) + U33((\text{L. C}^*)\text{SQUARED}) + 2. U12. \text{H. K. A}^*. \text{B}^* + 2. U13. \text{H. L. A}^*. \text{C}^* + 2. U23. \text{K. L. B}^*. \text{C}^*)$$

	U11	U22	U33	U12	U13	U23
O(1)	.081(4)	.045(4)	.077(5)	-.002(5)	-.023(4)	-.003(4)
O(2)	.057(4)	.059(4)	.084(6)	-.016(4)	.016(4)	-.026(5)
C(1)	.073(8)	.050(6)	.080(9)	.004(6)	-.012(7)	.000(6)
C(2)	.10(1)	.08(1)	.07(1)	.00(1)	.03(1)	.01(1)
C(3)	.066(8)	.077(8)	.070(9)	-.016(7)	.012(7)	-.007(7)
C(4)	.11(1)	.06(1)	.09(1)	-.03(1)	-.03(1)	.01(1)
C(5)	.044(6)	.046(6)	.063(9)	-.001(5)	.003(6)	-.013(6)
C(6)	.044(6)	.053(6)	.075(9)	-.025(6)	.008(6)	-.030(6)
C(7)	.039(5)	.055(6)	.039(7)	-.013(5)	-.003(5)	-.014(5)
C(8)	.031(5)	.039(5)	.058(7)	-.014(5)	.008(5)	-.013(6)
C(9)	.029(5)	.036(5)	.053(7)	.003(4)	.000(5)	-.004(5)
C(10)	.049(6)	.050(6)	.043(6)	.003(6)	.008(5)	-.010(6)
C(11)	.030(4)	.054(6)	.055(7)	-.013(5)	-.007(5)	-.015(5)
C(12)	.032(5)	.043(5)	.060(9)	-.011(5)	-.002(5)	-.010(6)
C(13)	.037(5)	.043(6)	.048(7)	-.009(5)	.005(5)	-.012(5)
C(14)	.039(5)	.048(6)	.041(7)	-.012(5)	.006(5)	-.007(5)
C(15)	.052(6)	.050(6)	.049(8)	-.020(5)	-.003(5)	-.017(6)
C(16)	.049(6)	.066(7)	.051(7)	-.020(5)	-.012(5)	-.011(6)
C(17)	.045(6)	.048(6)	.045(7)	-.012(6)	-.001(5)	-.010(6)
C(18)	.037(6)	.074(8)	.089(8)	.004(5)	-.007(5)	-.014(7)
C(19)	.056(6)	.076(7)	.075(8)	-.029(6)	.021(6)	-.013(7)

TABLE 16

BOND LENGTHS (Å), WITH E.S.D.'S, OF (41)

O(1) - C(17)	1.21(2)	O(2) - C(6)	1.44(2)
C(1) - C(2)	1.54(2)	C(1) - C(10)	1.53(2)
C(2) - C(3)	1.52(2)	C(3) - C(4)	1.47(2)
C(3) - C(5)	1.48(2)	C(4) - C(5)	1.50(2)
C(5) - C(6)	1.49(2)	C(5) - C(10)	1.54(2)
C(6) - C(7)	1.54(2)	C(7) - C(8)	1.51(2)
C(8) - C(9)	1.56(2)	C(8) - C(14)	1.51(2)
C(9) - C(10)	1.54(2)	C(9) - C(11)	1.52(2)
C(10) - C(18)	1.55(2)	C(11) - C(12)	1.53(2)
C(12) - C(13)	1.52(2)	C(13) - C(14)	1.51(2)
C(13) - C(17)	1.51(2)	C(13) - C(19)	1.56(2)
C(14) - C(15)	1.55(2)	C(15) - C(16)	1.54(2)
C(16) - C(17)	1.50(2)		

TABLE 17

VALENCY ANGLES (°), WITH E.S.D.'S, OF (41)

C(2) -	C(1) -	C(10)	106. 0(8)	C(1) -	C(2) -	C(3)	104. 1(8)
C(2) -	C(3) -	C(4)	116. 3(9)	C(2) -	C(3) -	C(5)	108. 7(9)
C(4) -	C(3) -	C(5)	61. 0(7)	C(3) -	C(4) -	C(5)	59. 7(7)
C(3) -	C(5) -	C(4)	59. 3(7)	C(3) -	C(5) -	C(6)	118. 6(8)
C(3) -	C(5) -	C(10)	108. 6(9)	C(4) -	C(5) -	C(6)	117. 5(9)
C(4) -	C(5) -	C(10)	117. 8(9)	C(6) -	C(5) -	C(10)	119. 8(9)
O(2) -	C(6) -	C(5)	110. 2(7)	O(2) -	C(6) -	C(7)	109. 5(8)
C(5) -	C(6) -	C(7)	110. 0(8)	C(6) -	C(7) -	C(8)	113. 0(7)
C(7) -	C(8) -	C(9)	111. 2(8)	C(7) -	C(8) -	C(14)	112. 4(7)
C(9) -	C(8) -	C(14)	106. 5(7)	C(8) -	C(9) -	C(10)	114. 2(7)
C(8) -	C(9) -	C(11)	111. 5(8)	C(10) -	C(9) -	C(11)	113. 5(7)
C(1) -	C(10) -	C(5)	103. 2(8)	C(1) -	C(10) -	C(9)	110. 5(8)
C(1) -	C(10) -	C(18)	110. 6(8)	C(5) -	C(10) -	C(9)	110. 8(7)
C(5) -	C(10) -	C(18)	110. 1(7)	C(9) -	C(10) -	C(18)	111. 4(8)
C(9) -	C(11) -	C(12)	113. 6(7)	C(11) -	C(12) -	C(13)	110. 2(7)
C(12) -	C(13) -	C(14)	109. 3(8)	C(12) -	C(13) -	C(17)	116. 8(8)
C(12) -	C(13) -	C(19)	111. 4(7)	C(14) -	C(13) -	C(17)	101. 5(7)
C(14) -	C(13) -	C(19)	113. 6(8)	C(17) -	C(13) -	C(19)	104. 0(8)
C(8) -	C(14) -	C(13)	114. 0(7)	C(8) -	C(14) -	C(15)	120. 3(7)
C(13) -	C(14) -	C(15)	103. 9(7)	C(14) -	C(15) -	C(16)	101. 2(7)
C(15) -	C(16) -	C(17)	106. 5(7)	O(1) -	C(17) -	C(13)	125. 9(9)
O(1) -	C(17) -	C(16)	125. 6(9)	C(13) -	C(17) -	C(16)	108. 4(8)

TABLE 18

TORSION ANGLES (°), WITH E.S.D'S, OF (41)

C(10) -	C(1) -	C(2) -	C(3)	29. 4(8)	C(2) -	C(1) -	C(10) -	C(5)	-29. 9(8)
C(2) -	C(1) -	C(10) -	C(9)	88. 6(9)	C(2) -	C(1) -	C(10) -	C(18)	-147. 6(10)
C(1) -	C(2) -	C(3) -	C(4)	49. 0(10)	C(1) -	C(2) -	C(3) -	C(5)	-17. 1(8)
C(2) -	C(3) -	C(4) -	C(5)	-97. 7(10)	C(2) -	C(3) -	C(5) -	C(4)	110. 4(10)
C(2) -	C(3) -	C(5) -	C(6)	-143. 0(12)	C(2) -	C(3) -	C(5) -	C(10)	-1. 5(8)
C(4) -	C(3) -	C(5) -	C(4)	. 0(7)	C(5) -	C(3) -	C(4) -	C(5)	. 0(7)
C(4) -	C(3) -	C(5) -	C(6)	106. 7(11)	C(4) -	C(3) -	C(5) -	C(10)	-111. 8(9)
C(3) -	C(4) -	C(5) -	C(3)	. 0(7)	C(3) -	C(4) -	C(5) -	C(6)	-108. 6(11)
C(3) -	C(4) -	C(5) -	C(10)	96. 2(10)	C(3) -	C(5) -	C(6) -	0(2)	-148. 9(12)
C(3) -	C(5) -	C(6) -	C(7)	90. 2(11)	C(3) -	C(5) -	C(10) -	C(1)	19. 5(8)
C(3) -	C(5) -	C(10) -	C(9)	-98. 8(10)	C(3) -	C(5) -	C(10) -	C(18)	137. 5(10)
C(4) -	C(5) -	C(6) -	0(2)	-80. 7(10)	C(4) -	C(5) -	C(6) -	C(7)	158. 4(12)
C(4) -	C(5) -	C(10) -	C(1)	-45. 0(9)	C(4) -	C(5) -	C(10) -	C(9)	-163. 3(12)
C(4) -	C(5) -	C(10) -	C(18)	73. 1(10)	C(10) -	C(5) -	C(6) -	0(2)	73. 9(10)
C(6) -	C(5) -	C(10) -	C(1)	160. 5(11)	C(10) -	C(5) -	C(6) -	C(7)	-46. 9(9)
C(6) -	C(5) -	C(10) -	C(9)	42. 1(9)	C(6) -	C(5) -	C(10) -	C(18)	-81. 5(10)
0(2) -	C(6) -	C(7) -	C(8)	-67. 9(8)	C(5) -	C(6) -	C(7) -	C(8)	53. 4(8)
C(6) -	C(7) -	C(8) -	C(9)	-57. 1(8)	C(6) -	C(7) -	C(8) -	C(14)	-176. 4(10)
C(7) -	C(8) -	C(9) -	C(10)	52. 1(8)	C(7) -	C(8) -	C(9) -	C(11)	-177. 6(10)
C(7) -	C(8) -	C(14) -	C(13)	-177. 6(10)	C(7) -	C(8) -	C(14) -	C(15)	-53. 3(8)
C(14) -	C(8) -	C(9) -	C(10)	174. 9(10)	C(14) -	C(8) -	C(9) -	C(11)	-54. 8(8)
C(9) -	C(8) -	C(14) -	C(13)	60. 4(8)	C(9) -	C(8) -	C(14) -	C(15)	-175. 2(10)
C(8) -	C(9) -	C(10) -	C(1)	-156. 4(10)	C(8) -	C(9) -	C(10) -	C(5)	-42. 7(8)

(contd.)

C(8) - C(9) - C(10) - C(18)
C(11) - C(9) - C(10) - C(1)
C(10) - C(9) - C(11) - C(12)
C(9) - C(11) - C(12) - C(13)
C(11) - C(12) - C(13) - C(17)
C(12) - C(13) - C(14) - C(8)
C(12) - C(13) - C(17) - 0(1)
C(14) - C(13) - C(17) - 0(1)
C(17) - C(13) - C(14) - C(15)
C(19) - C(13) - C(14) - C(8)
C(19) - C(13) - C(17) - 0(1)
C(8) - C(14) - C(15) - C(16)
C(14) - C(15) - C(16) - C(17)
C(15) - C(16) - C(17) - C(13)

80. 2(9)
74. 3(9)
-175. 4(10)
-53. 0(8)
168. 7(11)
-61. 7(8)
37. 2(10)
155. 9(12)
41. 7(7)
63. 4(8)
-86. 0(11)
-169. 9(10)
23. 8(7)
1. 3(7)

C(8) - C(9) - C(11) - C(12)
C(11) - C(9) - C(10) - C(5)
C(11) - C(9) - C(10) - C(18)
C(11) - C(12) - C(13) - C(14)
C(11) - C(12) - C(13) - C(19)
C(12) - C(13) - C(14) - C(15)
C(12) - C(13) - C(17) - C(16)
C(17) - C(13) - C(14) - C(8)
C(14) - C(13) - C(17) - C(16)
C(19) - C(13) - C(14) - C(15)
C(19) - C(13) - C(17) - C(16)
C(13) - C(14) - C(15) - C(16)
C(15) - C(16) - C(17) - 0(1)

54. 0(8)
-171. 9(10)
-49. 1(8)
54. 3(8)
-72. 0(8)
165. 6(9)
-145. 3(11)
174. 4(10)
-26. 6(8)
-69. 3(8)
91. 5(9)
-40. 9(7)
178. 8(13)

TABLE 19

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR C19H28O2 (41)

PAGE 1

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
2	0	0	4341	4313	6	8	0	136	136	5	9	1	147	128	7	7	2	120	139	1	7	3	289	281
6	0	0	668	652	3	9	0	211	195	2	0	2	867	856	2	8	2	491	498	3	7	3	175	173
8	0	0	171	191	2	0	1	1048	1060	4	0	2	778	780	4	8	2	386	412	5	7	3	122	143
10	0	0	326	345	4	0	1	324	317	6	0	2	98	75	12	8	2	165	139	0	8	3	423	421
1	1	0	703	687	6	0	1	374	384	10	0	2	118	126	2	0	3	1551	1560	2	8	3	165	189
3	1	0	204	197	1	1	1	546	557	1	1	2	224	235	6	0	3	338	330	4	8	3	236	207
5	1	0	176	161	3	1	1	585	578	8	0	3	560	547	8	0	3	110	94	6	8	3	129	102
7	1	0	280	276	5	1	1	315	305	5	1	2	164	180	1	1	3	1888	1890	5	11	3	137	71
9	1	0	295	316	7	1	1	125	134	7	1	2	219	223	3	1	3	98	114	0	0	4	2129	2192
0	2	0	1030	1062	0	2	1	1107	1156	9	1	2	188	195	5	1	3	246	246	2	0	4	1570	1563
2	2	0	742	738	2	2	1	686	706	11	1	2	214	207	7	1	3	387	401	4	0	4	835	827
4	2	0	166	186	4	2	1	861	862	0	2	2	865	906	9	1	3	183	188	8	0	4	153	206
6	2	0	364	339	6	2	1	199	198	2	2	2	116	147	11	1	3	143	170	10	0	4	152	142
8	2	0	111	107	8	2	1	123	167	4	2	2	220	229	2	2	3	370	361	1	1	4	1806	1823
1	3	0	843	862	1	3	1	283	310	8	2	2	147	183	4	2	3	432	424	3	1	4	434	439
3	3	0	1439	1440	3	3	1	478	479	1	3	2	470	484	8	2	3	255	263	5	1	4	233	225
5	3	0	511	519	5	3	1	537	529	3	3	2	1108	1079	1	3	3	167	185	9	1	4	127	122
7	3	0	125	123	7	3	1	200	193	5	3	2	480	482	3	3	3	120	109	11	1	4	174	188
9	3	0	156	170	9	3	1	193	177	7	3	2	248	276	5	3	3	143	154	0	2	4	500	493
0	4	0	649	635	0	4	1	174	169	9	3	2	270	275	11	3	3	140	133	2	2	4	993	993
2	4	0	539	563	2	4	1	805	806	11	3	2	171	189	0	4	3	514	499	4	2	4	328	320
4	4	0	119	118	4	4	1	682	633	13	3	2	124	73	2	4	3	785	782	6	2	4	254	254
6	4	0	319	335	6	4	1	403	416	0	4	2	224	227	4	4	3	824	804	8	2	4	176	164
8	4	0	176	165	8	4	1	264	263	2	4	2	320	328	6	4	3	319	329	1	3	4	126	151
1	5	0	104	106	1	5	1	163	178	4	4	2	260	265	8	4	3	198	224	3	3	4	150	205
5	5	0	190	197	5	5	1	253	242	6	4	2	354	355	10	4	3	137	185	5	3	4	207	199
7	5	0	159	172	7	5	1	119	128	1	5	2	485	498	1	5	3	426	429	7	3	4	317	307
0	6	0	110	107	0	6	1	105	95	3	5	2	282	276	3	5	3	210	198	0	4	4	175	150
6	6	0	110	103	2	6	1	315	323	5	5	2	191	175	5	5	3	349	366	2	4	4	681	680
12	6	0	142	107	1	7	1	115	122	7	5	2	318	341	7	5	3	368	360	4	4	4	229	209
3	7	0	263	267	5	7	1	117	59	9	5	2	135	139	9	5	3	191	204	6	4	4	224	225
5	7	0	258	229	0	8	1	137	100	0	6	2	169	150	0	6	3	268	267	8	4	4	377	377
7	7	0	113	5	2	8	1	152	185	2	6	2	157	144	2	6	3	207	207	10	4	4	174	173
13	7	0	139	71	4	8	1	130	105	6	6	2	193	196	4	6	3	224	217	1	5	4	314	305
0	8	0	414	416	1	9	1	173	179	8	6	2	171	174	6	6	3	209	213	3	5	4	125	93
4	8	0	132	132	3	9	1	195	171	5	7	2	161	150	8	6	3	131	104	5	5	4	276	305

(contd.)

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR C19H28O2

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
7	5	4	338	326	4	6	5	247	254	0	6	6	139	136	8	4	7	144	137	9	3	8	232	280
9	5	4	133	119	1	7	5	196	201	2	6	6	233	214	10	4	7	187	187	0	4	8	308	307
0	6	4	291	289	3	7	5	163	199	4	6	6	260	250	1	5	7	222	235	2	4	8	334	316
2	6	4	266	259	5	7	5	167	151	6	6	6	131	103	3	5	7	183	174	4	4	8	276	232
4	6	4	315	313	7	7	5	149	141	1	7	6	342	346	7	5	7	263	266	6	4	8	162	160
1	7	4	425	417	0	8	5	600	609	3	7	6	209	225	9	5	7	201	178	8	4	8	412	446
3	7	4	135	173	2	8	5	296	323	5	7	6	279	273	0	6	7	195	184	1	5	8	333	331
5	7	4	224	233	4	8	5	177	181	0	8	6	148	115	4	6	7	147	103	3	5	8	343	319
0	8	4	166	163	10	8	5	149	151	4	8	6	133	98	1	7	7	367	372	5	5	8	255	255
2	8	4	137	153	3	9	5	159	145	6	8	6	163	148	3	7	7	138	148	7	5	8	251	237
1	9	4	146	149	0	0	6	952	968	1	9	6	154	135	5	7	7	154	91	9	5	8	181	187
2	0	5	719	730	2	0	6	1206	1188	6	12	6	171	137	7	7	7	154	179	0	6	8	291	281
4	0	5	635	626	4	0	6	536	523	2	0	7	1202	1195	2	8	7	184	227	2	6	8	146	153
6	0	5	227	230	6	0	6	298	305	4	0	7	504	503	4	8	7	206	244	4	6	8	143	130
8	0	5	191	205	14	0	6	146	99	8	0	7	278	276	6	8	7	152	130	1	7	8	411	425
12	0	5	148	184	1	1	6	706	739	12	0	7	174	227	1	9	7	232	227	3	7	8	312	331
1	1	5	751	743	3	1	6	861	842	14	0	7	148	197	5	9	7	169	106	4	8	8	130	107
3	1	5	393	397	5	1	6	384	380	1	1	7	587	610	0	0	8	872	887	1	9	8	120	131
5	1	5	274	271	7	1	6	148	154	3	1	7	310	302	4	0	8	583	569	2	0	9	130	140
7	1	5	260	264	0	2	6	179	180	5	1	7	178	172	6	0	8	390	404	6	0	9	171	168
2	2	5	908	889	2	2	6	167	172	7	1	7	284	296	10	0	8	194	224	10	0	9	138	147
4	2	5	353	348	4	2	6	357	348	9	1	7	260	277	12	0	8	186	210	1	1	9	863	878
10	2	5	153	148	6	2	6	339	329	2	2	7	429	421	1	1	8	1255	1255	3	1	9	1174	1156
1	3	5	367	356	8	2	6	121	111	4	2	7	118	85	3	1	8	983	943	5	1	9	1004	1001
3	3	5	548	529	1	3	6	505	528	6	2	7	222	215	5	1	8	524	510	7	1	9	170	171
5	3	5	506	491	3	3	6	640	604	8	2	7	128	89	7	1	8	270	290	11	1	9	147	171
7	3	5	315	323	5	3	6	219	221	10	2	7	227	225	9	1	8	232	245	13	1	9	161	143
9	3	5	125	124	7	3	6	172	161	1	3	7	624	629	0	2	8	164	160	0	2	9	317	323
2	4	5	557	575	9	3	6	206	210	3	3	7	842	827	2	2	8	447	437	2	2	9	345	352
4	4	5	292	284	0	4	6	333	333	5	3	7	282	281	4	2	8	390	371	4	2	9	371	354
6	4	5	353	361	2	4	6	310	322	7	3	7	347	345	6	2	8	344	343	6	2	9	310	291
8	4	5	170	177	4	4	6	357	329	9	3	7	204	216	8	2	8	158	145	8	2	9	265	270
10	4	5	160	202	6	4	6	234	236	0	4	7	195	225	1	3	8	577	578	1	3	9	686	678
1	5	5	507	504	1	5	6	181	173	2	4	7	258	252	3	3	8	544	538	3	3	9	383	361
3	5	5	220	190	7	5	6	139	181	4	4	7	381	367	5	3	8	124	106	5	3	9	179	165
5	5	5	133	127	9	5	6	122	149	6	4	7	216	254	7	3	8	460	458	7	3	9	235	273

(contd.)

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR C19H28O2

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
0	4	9	98	91	5	3	10	211	207	10	2	11	143	111	3	3	12	388	405	0	4	13	283	285
2	4	9	103	121	9	3	10	129	144	1	3	11	296	295	2	4	13	229	216	2	4	13	212	202
8	4	9	127	100	0	4	10	363	327	5	3	11	211	199	7	3	12	341	335	4	4	13	311	301
1	5	9	122	149	2	4	10	328	345	7	3	11	285	302	9	3	12	241	274	6	4	13	340	348
3	5	9	222	215	4	4	10	444	434	4	4	11	210	225	4	4	12	264	259	1	5	13	155	104
5	5	9	155	163	6	4	10	292	290	6	4	11	216	217	3	4	12	339	321	3	5	13	318	349
7	5	9	211	211	8	4	10	123	107	2	4	11	167	169	5	5	13	257	240	5	5	13	311	328
0	6	9	154	118	10	4	10	127	142	4	4	11	253	269	3	5	12	309	306	7	5	13	149	170
2	6	9	212	208	1	5	10	119	121	6	4	11	325	314	5	5	12	234	241	0	6	13	120	146
12	6	9	152	90	3	5	10	174	136	8	4	11	282	296	7	5	12	154	158	4	6	13	214	214
1	7	9	178	174	5	5	10	375	370	3	5	11	337	333	0	6	12	198	177	8	6	13	112	58
7	7	9	128	132	7	5	10	217	234	5	5	11	271	259	2	6	12	187	183	10	6	13	170	163
0	8	9	207	210	2	6	10	283	283	4	6	11	365	392	4	6	12	146	67	1	7	13	180	182
2	8	9	245	247	4	6	10	128	122	6	6	11	214	224	8	6	12	189	201	3	7	13	269	263
4	8	9	216	232	6	6	10	134	71	1	7	11	212	179	10	6	12	183	164	3	7	13	146	154
6	8	9	132	119	1	7	10	184	240	3	7	11	230	253	1	7	12	350	339	7	7	13	142	79
8	8	9	130	73	3	7	10	165	189	5	7	11	204	214	5	7	12	160	166	2	7	13	347	329
10	8	9	156	136	6	8	10	137	132	4	8	11	139	134	2	8	12	124	140	6	8	13	182	172
1	9	9	198	173	8	8	10	185	186	1	9	11	207	217	8	8	12	172	173	10	9	13	124	135
0	0	10	641	646	1	9	10	159	160	3	9	11	163	201	1	9	12	238	259	3	9	13	492	479
2	0	10	649	667	3	9	10	140	91	0	0	12	303	316	2	9	13	399	386	5	9	13	172	160
4	0	10	248	250	4	12	10	174	119	2	0	12	334	340	4	0	13	332	303	9	1	14	140	153
10	0	10	232	238	4	0	11	174	81	4	0	12	460	463	6	0	13	162	169	11	1	14	152	150
1	1	10	852	821	6	0	11	216	212	8	0	12	188	203	1	1	13	720	816	0	2	14	126	92
3	1	10	739	712	8	0	11	178	173	10	0	12	177	166	3	1	13	726	683	2	2	14	262	240
5	1	10	487	478	10	0	11	181	182	1	1	12	902	838	5	1	13	393	397	4	2	14	112	89
7	1	10	118	104	12	0	11	211	214	3	1	12	361	363	7	1	13	304	312	8	2	14	183	211
11	1	10	223	222	14	0	11	152	145	5	1	12	373	368	2	2	13	120	119	1	3	14	265	268
0	2	10	662	679	1	1	11	362	301	7	1	12	140	171	4	2	13	190	156	0	4	14	134	176
2	2	10	484	468	3	1	11	370	361	9	1	12	126	126	6	2	13	175	191	4	4	14	294	288
4	2	10	281	287	5	1	11	575	563	0	2	12	514	525	10	2	13	130	146	3	5	14	259	268
6	2	10	187	206	7	1	11	143	129	2	2	12	149	151	1	3	13	248	288	5	5	14	280	260
8	2	10	260	252	2	2	11	144	144	4	2	12	301	275	3	3	13	402	380	7	5	14	251	265
10	2	10	137	166	4	2	11	241	144	8	2	12	212	217	1	3	13	108	75	4	4	14	159	146
14	2	10	137	85	6	2	11	454	435	10	2	12	113	114	7	3	13	131	139	6	6	14	303	301
3	3	10	270	266	8	2	11	379	398	1	3	12	362	358	9	3	13	163	155	1	7	14	183	189

(contd.)

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR C19H28O2

H	K	L	10FO	1OFC	H	K	L	10FO	1OFC	H	K	L	10FO	1OFC	H	K	L	10FO	1OFC	H	K	L	10FO	1OFC
5	7	14	222	246	8	8	15	126	76	5	3	17	269	284	3	7	18	172	182	1	7	20	227	274
11	7	14	138	122	1	9	15	180	179	7	3	17	114	102	0	8	18	132	117	3	7	20	122	69
3	9	14	173	147	0	0	16	652	652	2	4	17	202	180	3	9	18	131	85	4	10	20	139	75
7	9	14	132	100	4	4	16	128	139	4	4	17	208	211	6	10	18	158	90	3	1	21	156	137
9	9	14	139	137	3	5	16	433	429	3	5	17	175	199	4	0	19	148	143	5	1	21	157	164
0	10	14	143	140	5	5	16	163	176	5	5	17	300	329	7	1	19	310	305	7	1	21	174	167
1	11	14	144	134	7	5	16	226	240	7	5	17	126	131	7	1	19	321	334	2	2	21	489	493
2	0	15	139	138	2	6	16	207	175	2	6	17	231	262	9	1	19	149	151	4	2	21	508	510
4	0	15	430	434	4	4	16	263	260	4	6	17	227	219	0	2	19	522	545	6	2	21	197	193
8	0	15	278	292	6	6	16	147	160	6	6	17	198	197	2	2	19	455	451	3	3	21	143	137
10	0	15	157	157	8	8	16	193	209	1	2	17	161	122	4	4	19	203	189	2	4	21	149	166
1	1	15	998	1008	1	5	16	278	279	2	7	17	139	143	6	6	19	144	133	4	4	21	145	155
3	1	15	347	347	5	3	16	193	162	7	9	17	146	68	3	3	19	183	183	6	4	21	115	85
5	1	15	306	307	7	7	16	179	180	0	0	18	238	213	5	3	19	246	241	1	5	21	255	250
7	1	15	128	119	2	4	16	225	231	4	4	18	273	281	7	3	19	149	165	3	5	21	175	190
0	2	15	425	425	6	6	16	194	99	6	6	18	307	320	1	5	19	173	138	0	6	21	242	302
2	4	15	404	390	1	5	16	150	151	3	3	18	394	399	3	5	19	175	153	2	6	21	205	226
4	2	15	363	358	3	3	16	206	200	7	7	18	239	214	5	5	19	182	187	1	7	21	139	156
6	6	15	314	317	5	5	16	168	165	9	9	18	195	199	0	6	19	125	96	3	7	21	136	164
8	2	15	172	163	2	6	16	255	259	0	2	18	892	899	2	6	19	182	216	1	9	21	134	97
10	2	15	143	143	4	4	16	269	256	2	2	18	319	330	0	0	20	221	227	0	10	21	157	140
1	3	15	160	173	12	6	16	137	109	4	4	18	232	232	4	0	20	143	147	2	10	21	140	90
3	3	15	274	298	1	7	16	125	130	6	6	18	242	261	6	6	20	161	173	0	0	22	122	144
5	7	15	291	302	6	8	16	121	81	1	3	18	273	291	3	3	20	118	161	4	0	22	135	141
7	3	15	291	304	7	9	16	187	150	3	3	18	331	304	5	1	20	108	64	4	4	22	341	333
11	3	15	120	65	0	12	16	160	70	5	3	18	159	161	4	4	20	274	262	3	3	22	121	140
2	4	15	283	287	2	0	17	111	132	9	3	18	128	144	6	4	20	351	352	5	3	22	147	168
4	4	15	292	285	4	0	17	356	356	4	4	18	117	92	8	2	20	168	163	1	5	22	176	187
6	4	15	368	358	1	1	17	316	412	6	4	18	173	212	3	3	20	152	165	2	6	22	156	186
3	5	15	213	231	5	4	17	177	182	8	4	18	123	49	5	5	20	141	115	10	6	22	141	79
5	5	15	193	218	7	7	17	215	202	1	3	18	162	185	2	4	20	169	194	2	0	23	228	234
7	4	15	207	211	9	9	17	152	151	3	5	18	318	318	4	4	20	155	160	4	0	23	274	288
4	6	15	206	221	2	2	17	261	238	2	6	18	193	216	12	4	20	139	64	3	3	23	139	118
6	6	15	135	100	4	4	17	161	163	4	6	18	187	220	7	5	20	148	140	5	1	23	244	272
3	7	15	134	143	6	6	17	161	209	6	6	18	188	194	0	0	20	344	365	7	1	23	143	131
0	8	15	194	188	8	8	17	195	173	8	8	18	131	117	10	2	20	258	252	4	2	23	357	365

(contd.)

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR C19H28O2

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC					
6	2	23	154	196	1	3	24	128	160	5	3	25	135	78	0	6	26	161	178	5	1	29	137	80
3	3	23	149	91	3	3	24	201	246	2	6	25	134	173	8	8	26	149	67	0	2	29	216	243
5	3	23	207	217	5	3	24	153	145	6	6	25	146	117	4	0	27	216	201	0	10	29	154	85
0	4	23	233	241	3	5	24	124	143	2	8	25	127	33	4	2	27	199	214	5	3	30	130	113
2	4	23	178	178	0	6	24	321	344	4	0	26	182	194	6	2	27	146	128	7	5	31	150	95
0	6	23	303	310	2	6	24	184	204	6	0	26	213	226	5	3	27	126	119	3	7	33	138	57
2	6	23	153	198	4	6	24	172	160	3	1	26	262	247	0	6	27	128	152	8	0	35	141	68
4	6	23	131	55	8	6	24	128	47	0	2	26	261	254	0	0	28	149	119	9	1	35	134	52
1	7	23	177	155	5	7	24	122	54	0	4	26	156	167	2	0	28	178	194	4	6	37	142	32
0	2	24	453	466	3	1	25	184	182	1	5	26	164	142	1	1	28	220	263	4	4	40	157	61
4	2	24	158	138	3	3	25	168	165	3	5	26	136	124	5	3	28	123	130	0	0	44	207	152
6	2	24	160	158																				

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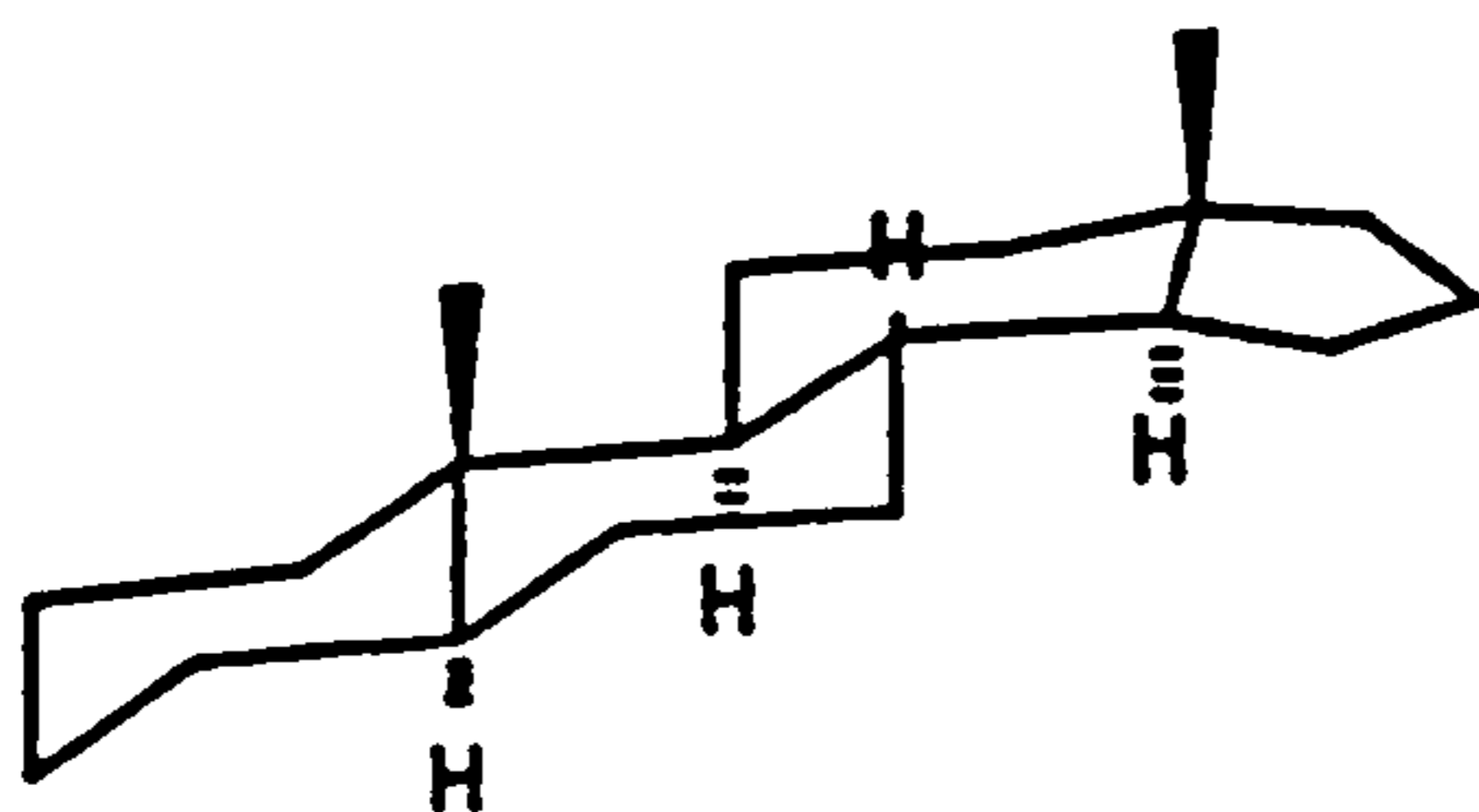
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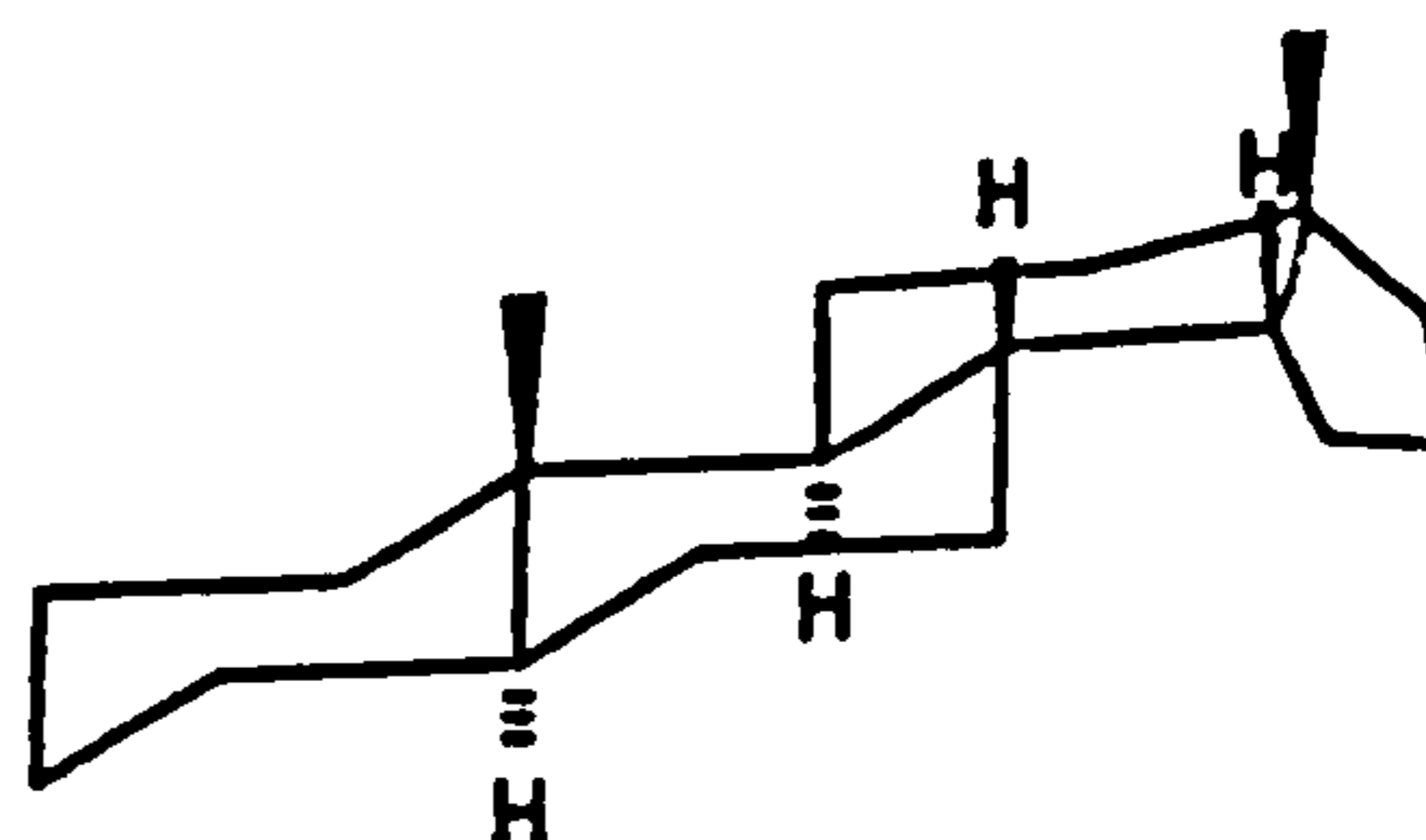
Chapter 6
Molecular Mechanics Calculations

6.1 Introduction.

Although molecular mechanics calculations can deal with much larger molecules than quantum mechanical calculations their application to macro-molecules has been limited. However, further down the scale, a significant amount of work has been carried out on relatively large molecules such as steroids. For this particular class of compound several molecular mechanics calculations have been published, and the geometries obtained usually show good agreement with X-ray structural data.¹⁻³ The molecular models usually show the β -phase convex conformation of the steroids as seen in X-ray studies, a feature not readily detected from a Drieding model.⁴ Results from molecular mechanics calculations also confirm that the most common stereochemistry, 5α , 8β , 9α , 14α , (247), (a kinetic product resulting from the cyclisation of squalene) is not the most thermodynamically stable configuration. Rather the 5α , 8β , 9α , 14β configuration (248) is the most stable, although the presence of a 17-C sidechain tends to stabilise the 14α isomer.⁵ The reader is directed to "Molecular Mechanics" by Burkert and Allinger¹ for a comprehensive review of molecular mechanics calculations and their application to steroids.



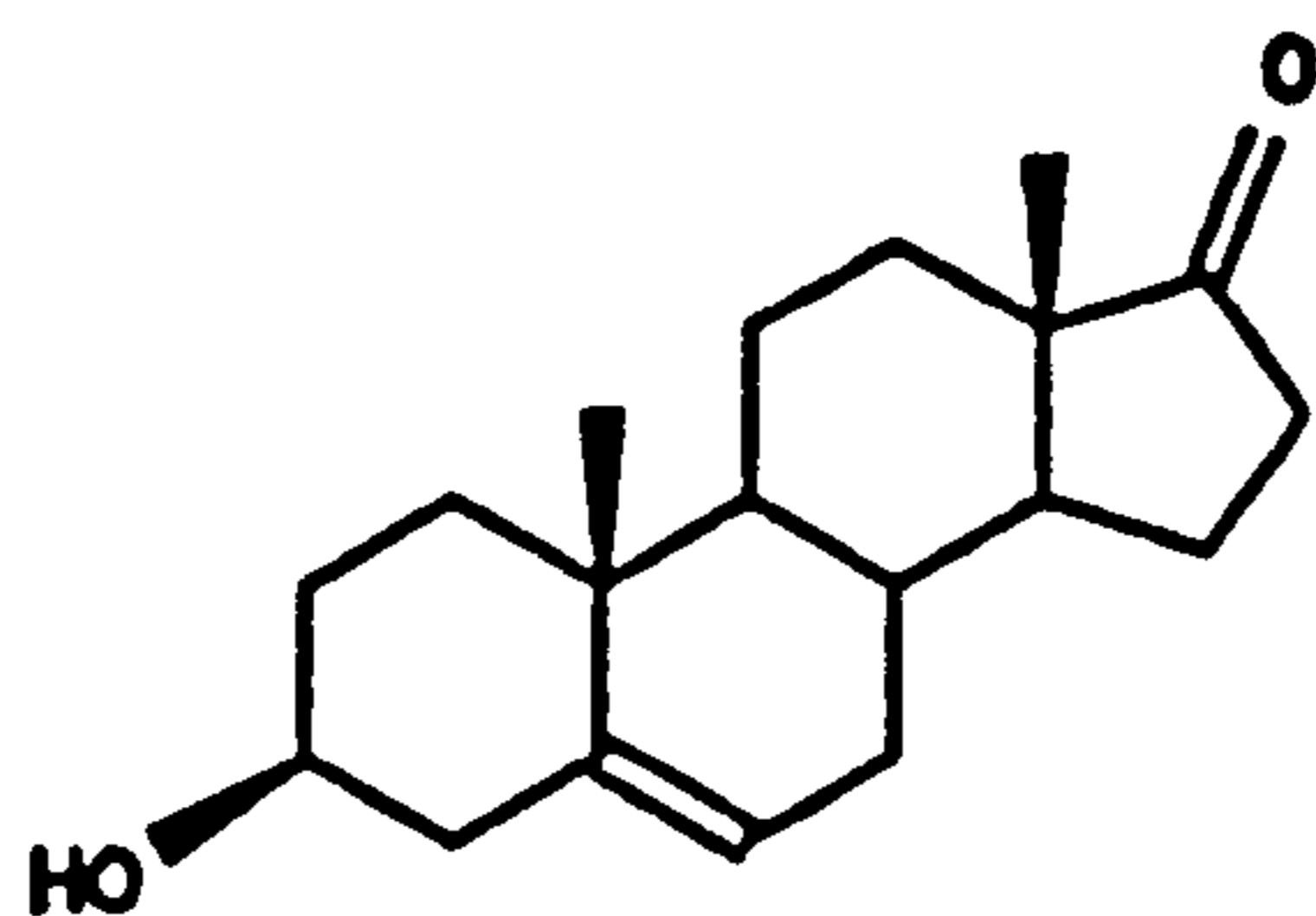
(247)



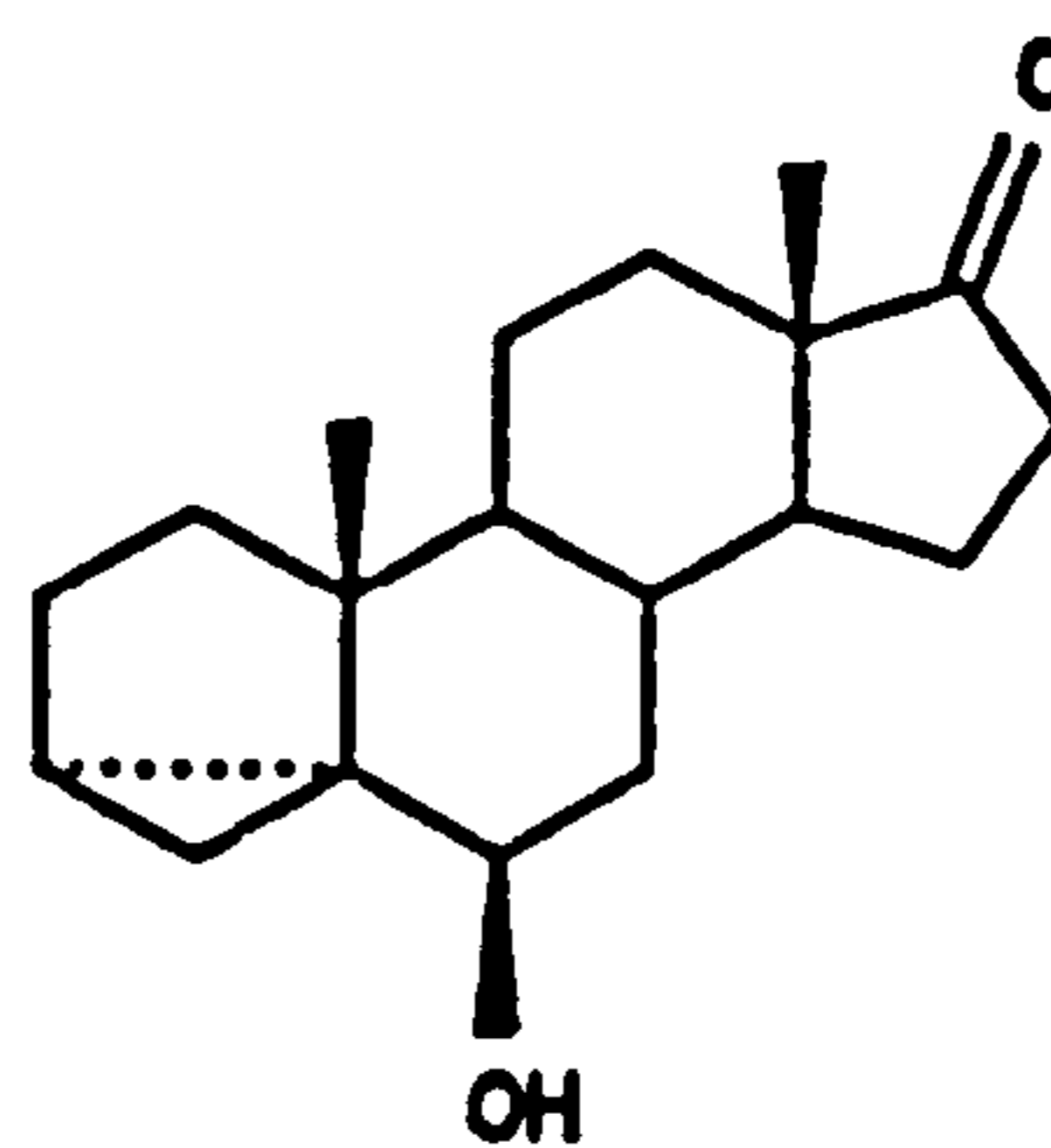
(248)

The molecular mechanics package used in this work was the PC version of the Chemmod^R system by U-micro which utilised a force field developed by White and Bovill.⁶

The compounds that were studied were those that were deemed to be of particular structural interest in the synthetic work. Wherever possible the models were constructed from the atomic co-ordinates of dehydroepiandrosterone (97) or the parent 3,5 cyclosteroid (41) whose structures were determined from single crystal X-ray crystallographic work (Chapter 5). Several starting models were employed in an effort to determine if the Newton-Raphson minimiser was indeed finding a global minimum molecular potential energy conformation and not coming to rest on, for example, a local energy minimum.¹ The Chemmod molecular modelling system was found to be restrictive in several areas and these are highlighted in the following pages where they have arisen. All molecular diagrams in this chapter are based on energy minimised structures.



(97)

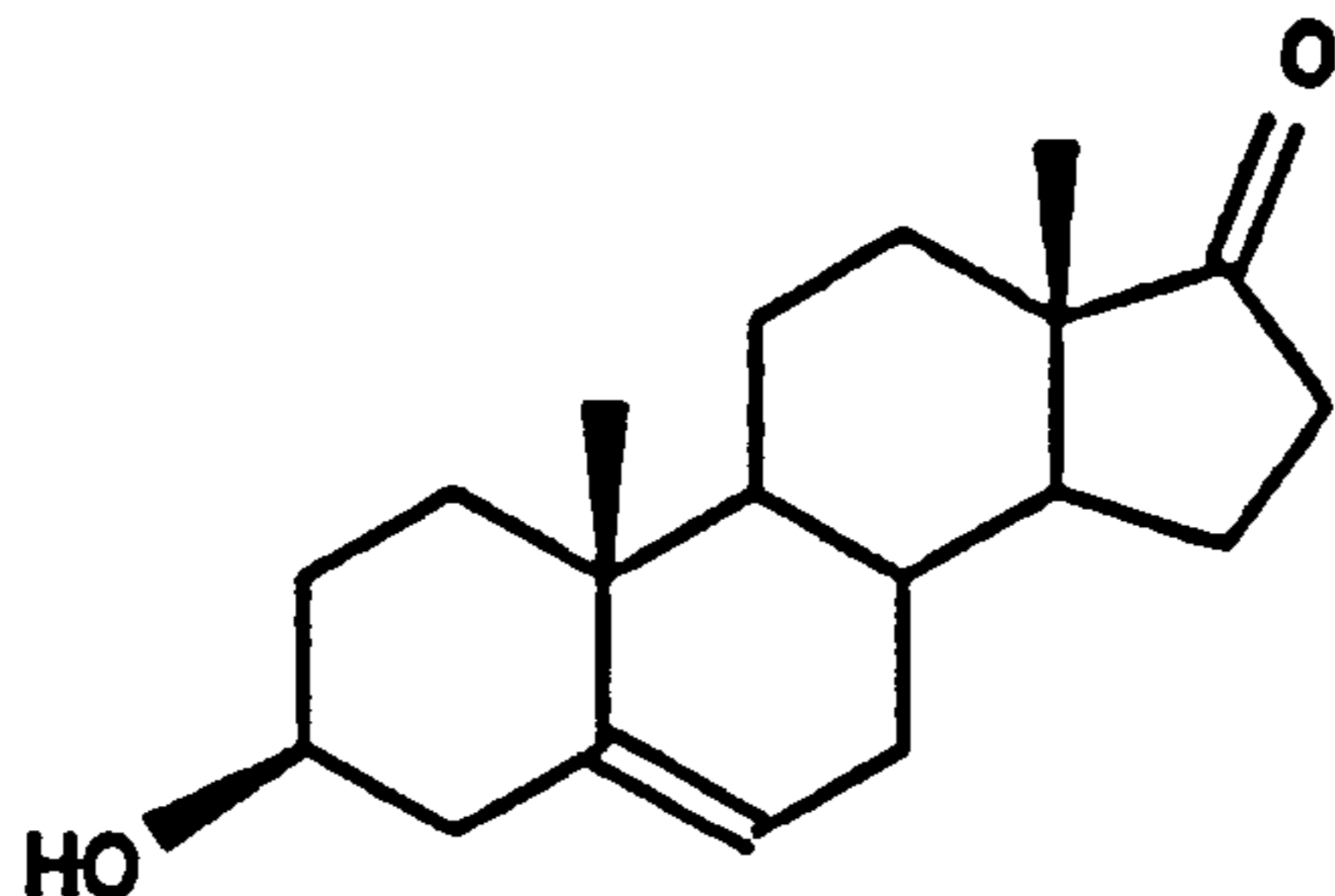


(41)

6.2 Molecular Mechanics of Compounds Studied by X-Ray Crystallography

6.2.1 3 β -Hydroxy-5-androsten-17-one (97).

The bond lengths, bond angles and torsion angles of dehydroepiandrosterone (97) from the X-ray data and the



(97)

molecular model are compared below in Tables 20, 21, and 22. Figures 10 and 11 show DHEA (97) from the "normal" prospective and a lengthways view (methyl groups to rear).

TABLE 20

COMPARISON OF BOND LENGTHS (Å) DERIVED FROM X-RAY STUDIES
(average e.s.d.= 0.02Å) AND MOLECULAR MECHANICS STUDIES FOR
DEHYDROEPIANDROSTERONE (97).

	<u>X-ray</u>	<u>MM</u>		<u>X-ray</u>	<u>MM</u>
C(1)-C(2)	1.52	1.55	C(9)-C(10)	1.56	1.58
C(1)-C(10)	1.59	1.56	C(9)-C(11)	1.53	1.57
C(2)-C(3)	1.51	1.55	C(10)-C(19)	1.57	1.56
C(3)-O(1)	1.29	1.44	C(11)-C(12)	1.53	1.56
C(3)-C(4)	1.53	1.55	C(12)-C(13)	1.51	1.56
C(4)-C(5)	1.51	1.54	C(13)-C(14)	1.50	1.56
C(5)-C(6)	1.35	1.43	C(13)-C(17)	1.48	1.53
C(5)-C(10)	1.45	1.54	C(13)-C(18)	1.61	1.56
C(6)-C(7)	1.54	1.52	C(14)-C(15)	1.52	1.55
C(7)-C(8)	1.52	1.55	C(15)-C(16)	1.55	1.55
C(8)-C(9)	1.50	1.56	C(16)-C(17)	1.49	1.53
C(8)-C(14)	1.52	1.56	C(17)-O(2)	1.22	1.21

TABLE 21

COMPARISON OF VALENCY ANGLES (°) DERIVED FROM X-RAY STUDIES
(average e.s.d.= 1.1°) AND MOLECULAR MECHANICS STUDIES FOR
DEHYDROEPIANDROSTERONE (97).

	<u>X-ray</u>	<u>MM</u>		<u>X-ray</u>	<u>MM</u>
C1-C2-C3	111.7	112.0	C8-C14-C13	114.3	114.0
C1-C10-C5	107.6	107.3	C8-C14-C15	121.4	121.3
C1-C10-C9	108.0	110.8	C9-C8-C14	111.1	112.2
C1-C10-C19	105.8	109.2	C9-C10-C19	110.7	111.7
C2-C1-C10	114.8	116.6	C9-C11-C12	112.0	116.4
C2-C3-O1	113.8	113.1	C10-C9-C11	113.3	115.9
C2-C3-C4	113.0	111.1	C11-C12-C13	110.9	111.6
O1-C3-C4	109.7	113.1	C12-C13-C14	111.6	107.0
C3-C4-C5	112.3	113.4	C12-C13-C17	118.3	117.1
C4-C5-C6	116.3	119.1	C12-C13-C18	109.0	111.2
C4-C5-C10	118.9	118.4	C13-C14-C15	106.4	104.4
C5-C6-C7	123.4	124.7	C13-C17-O2	127.0	124.1
C5-C10-C9	114.0	111.4	C13-C17-C16	108.7	110.9
C5-C10-C19	110.4	106.3	C14-C13-C17	102.2	98.6
C6-C5-C10	124.8	122.5	C14-C13-C18	113.2	116.0
C6-C7-C8	110.1	114.9	C14-C15-C16	100.0	104.2
C7-C8-C9	112.6	111.8	C15-C16-C17	106.8	103.8
C7-C8-C14	112.1	111.7	C16-C17-O2	124.3	123.8
C8-C9-C10	110.7	114.1	C17-C13-C18	102.3	106.7
C8-C9-C11	116.5	113.2			

TABLE 22

COMPARISON OF RING TORSION ANGLES (°) DERIVED FROM X-RAY STUDIES (average e.s.d.= 1.6°) AND MOLECULAR MECHANICS STUDIES FOR DEHYDROEPIANDROSTERONE (97).

<u>RING A</u>	<u>X-ray</u>	<u>MM</u>
C(1)-C(2)-C(3)-C(4)	49.2	52.4
C(2)-C(3)-C(4)-C(5)	-47.7	-50.4
C(3)-C(4)-C(5)-C(10)	51.1	50.2
C(4)-C(5)-C(10)-C(1)	-49.9	-46.9
C(5)-C(10)-C(1)-C(2)	50.1	48.6
C(10)-C(1)-C(2)-C(3)	-51.6	-54.4
<u>RING B</u>	<u>X-ray</u>	<u>MM</u>
C(5)-C(6)-C(7)-C(8)	17.3	15.3
C(6)-C(7)-C(8)-C(9)	-45.6	-42.4
C(7)-C(8)-C(9)-C(10)	55.9	55.7
C(8)-C(9)-C(10)-C(5)	-36.3	-40.1
C(9)-C(10)-C(5)-C(6)	8.4	11.8
C(10)-C(5)-C(6)-C(7)	1.1	0.7

<u>RING C</u>	<u>X-ray</u>	<u>MM</u>
C(8)-C(9)-C(11)-C(12)	44.1	42.0
C(9)-C(11)-C(12)-C(13)	-49.2	-50.8
C(11)-C(12)-C(13)-C(14)	54.8	58.1
C(12)-C(13)-C(14)-C(8)	-55.7	-61.6
C(13)-C(14)-C(8)-C(9)	48.1	55.0
C(14)-C(8)-C(9)-C(11)	-42.7	-42.7

<u>RING D</u>	<u>X-ray</u>	<u>MM</u>
C(13)-C(14)-C(15)-C(16)	-38.0	-37.3
C(14)-C(15)-C(16)-C(17)	22.6	15.8
C(15)-C(16)-C(17)-C(13)	0.4	11.4
C(16)-C(17)-C(13)-C(14)	-23.7	-33.1
C(17)-C(13)-C(14)-C(15)	39.0	42.2

One of the differences between the model and the X-ray structure was in the determination of the C(3)-O(1), C(5)-C(10) and C(5)-C(6) bond lengths. The greater values in the molecular model probably arise because the model is of an isolated molecule and is therefore not subject to crystal packing forces. Rings B and D, where sp^2 character exists, were affected the most with a change of bond angles and torsion angles resulting in small but significant changes in geometry. The twisting of the original B ring geometry of a slightly distorted half-chair with C(8) out of the plane is reduced so that the plane through C(10)-C(5)-C(6)-C(7) is now virtually planar (to within 0.7°). Changes in the other torsion angles result in an effective shifting of C(7) into

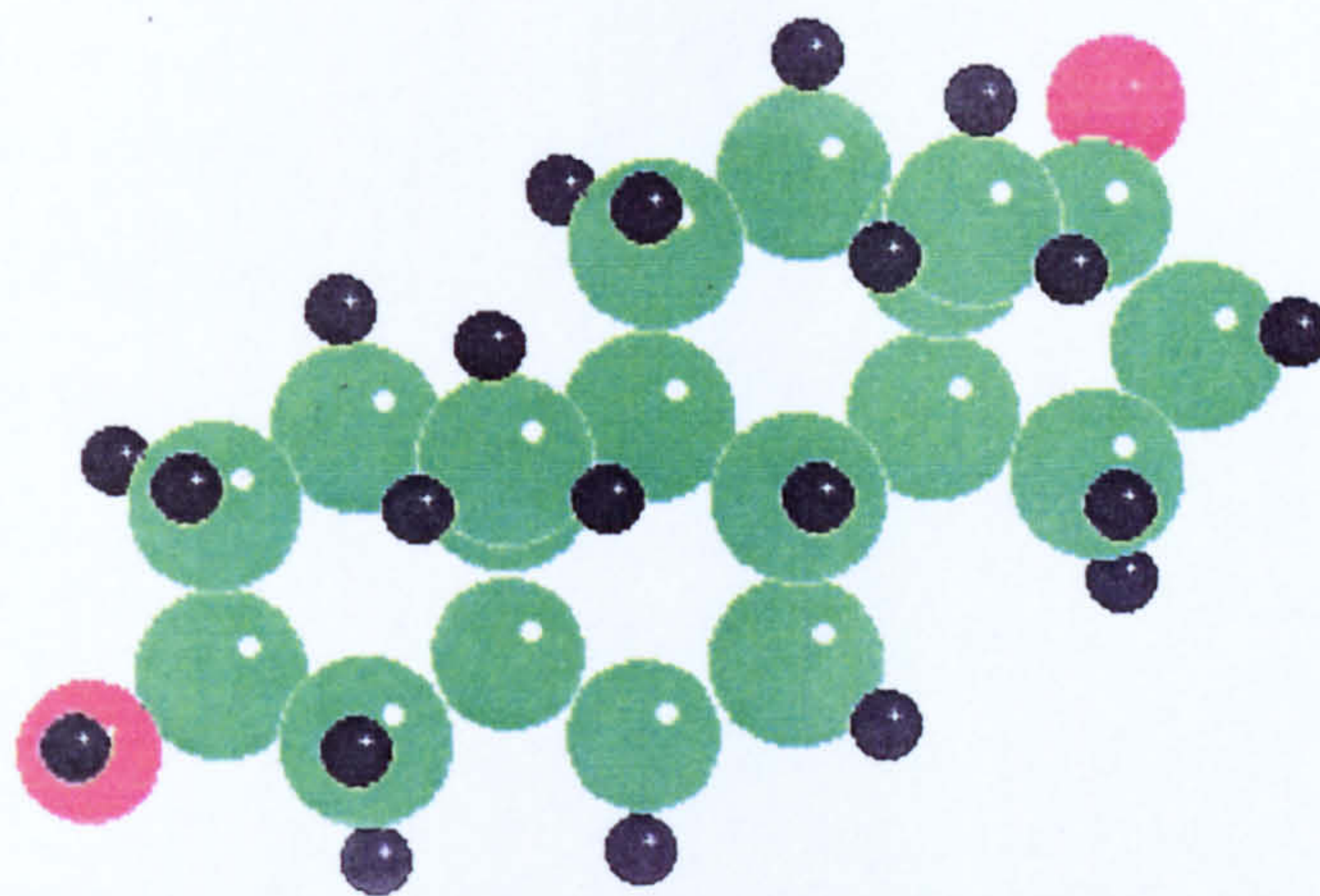


FIGURE 10 "Normal" perspective of dehydroepiandrosterone (97)

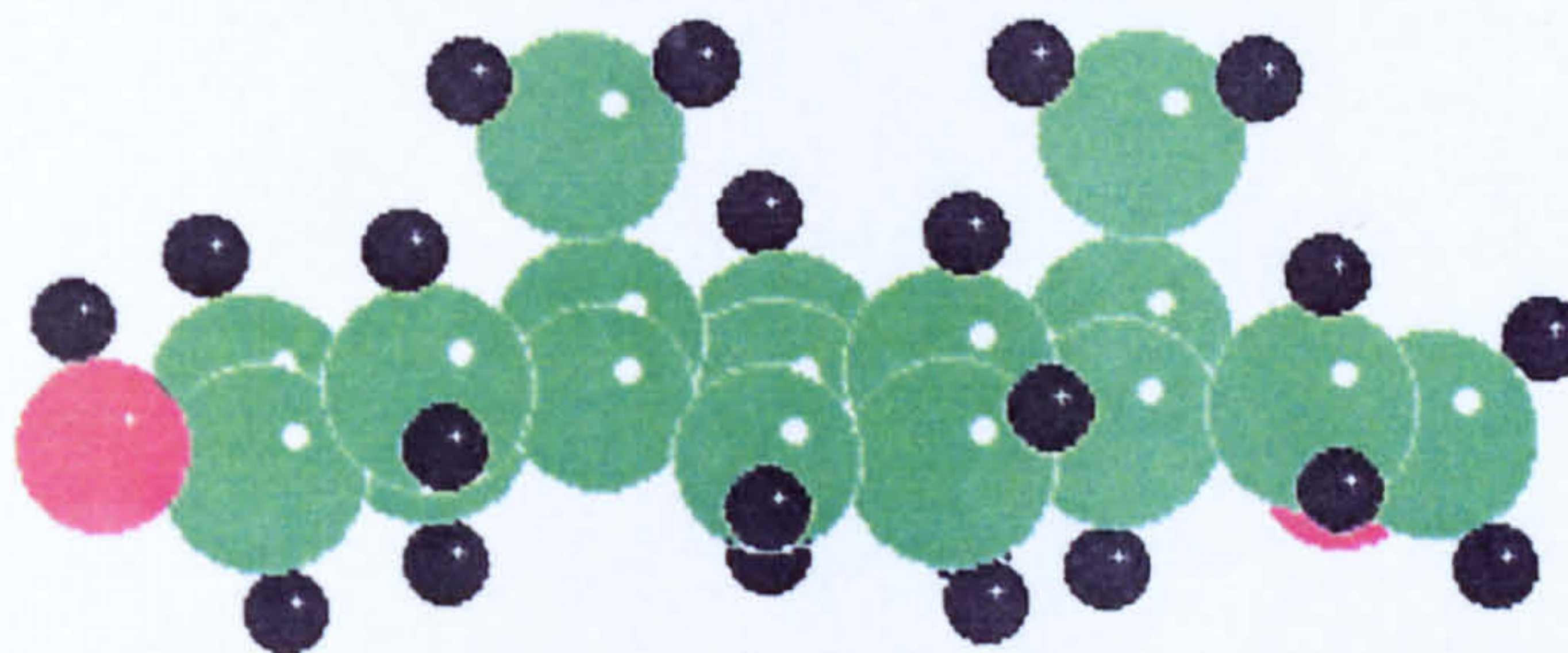


FIGURE 11

"Lengthways" perspective (methyl groups to rear) of dehydroepiandrosterone (97)

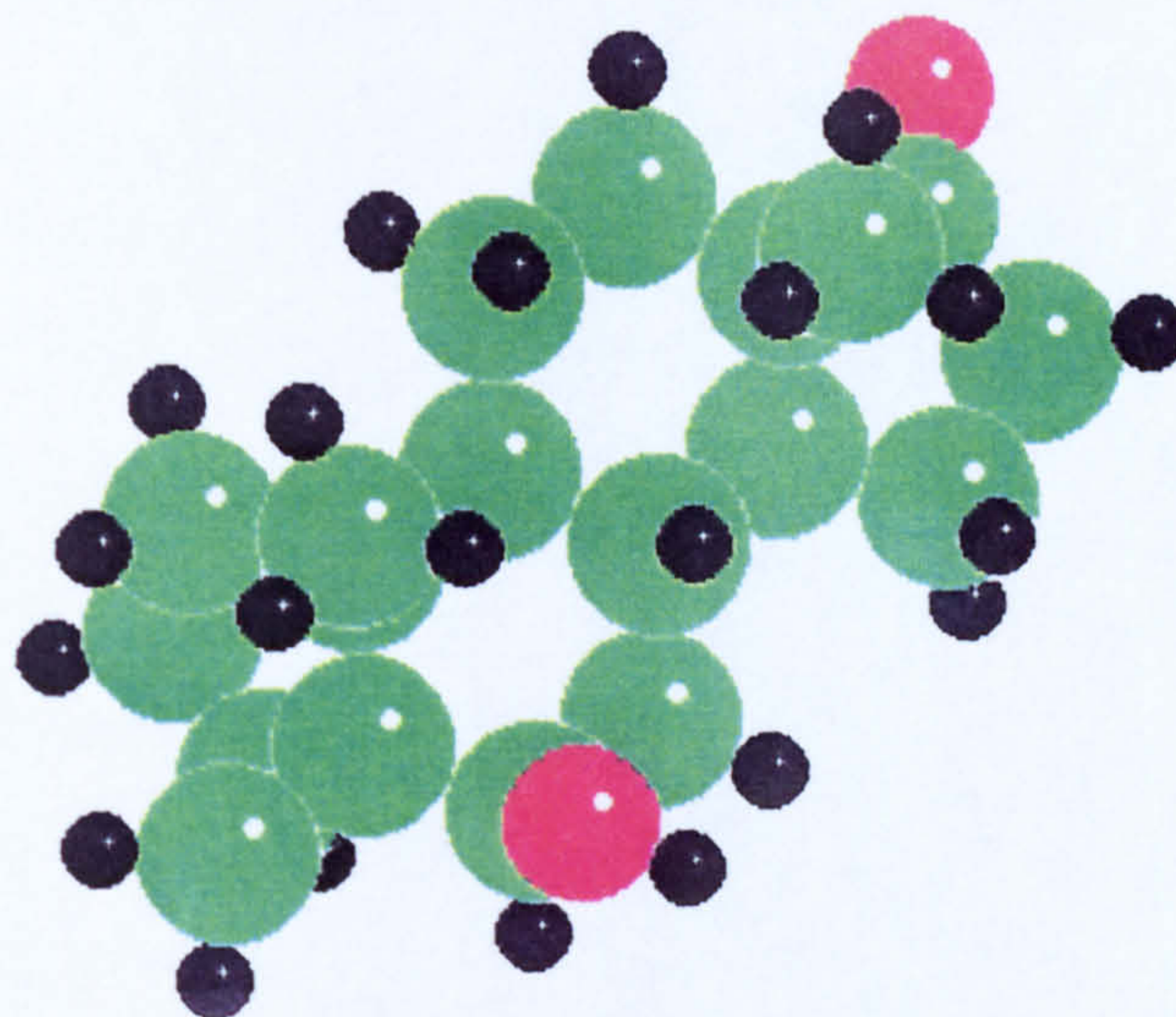


FIGURE 12

"Normal" perspective of 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41)

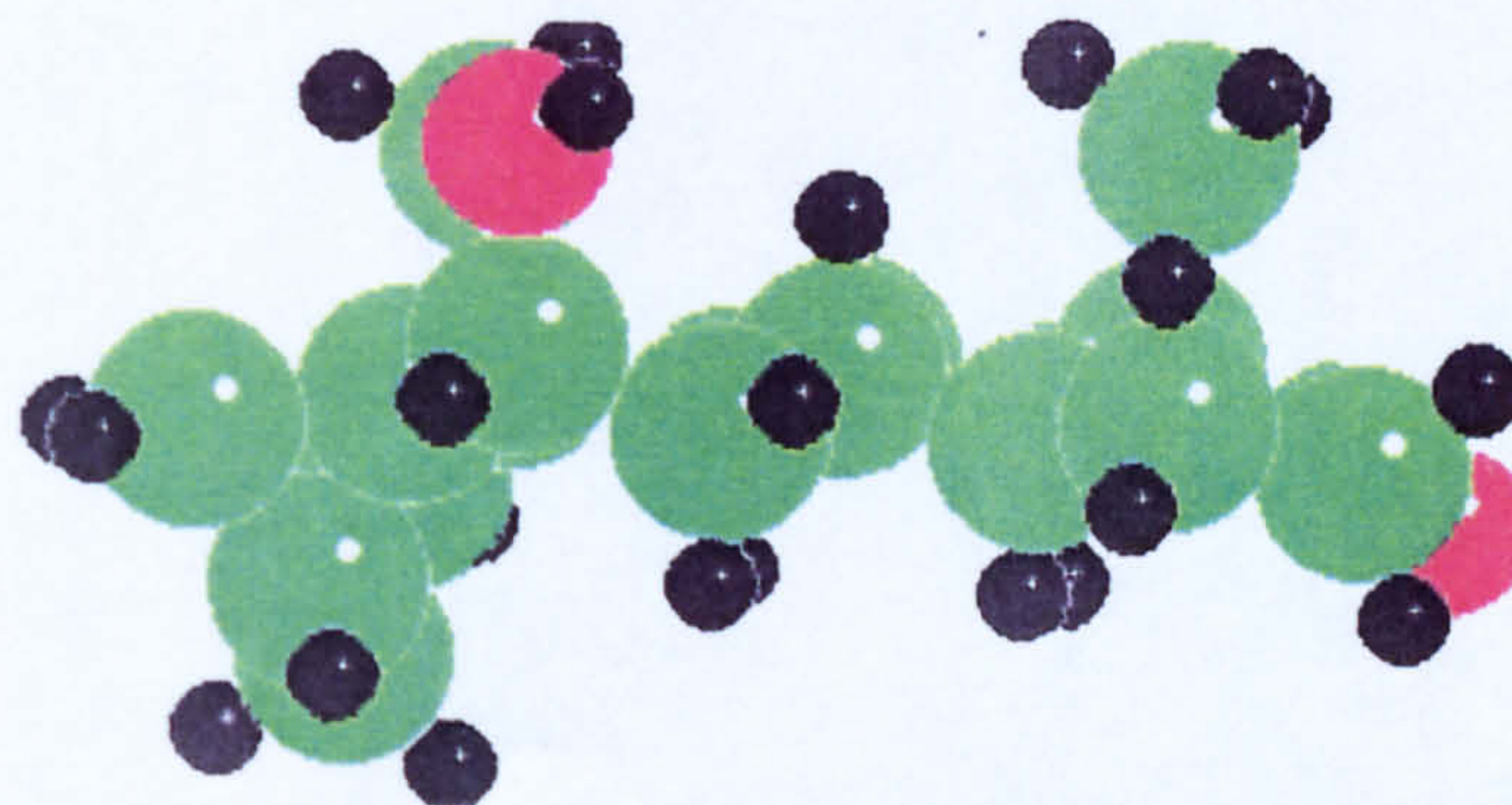


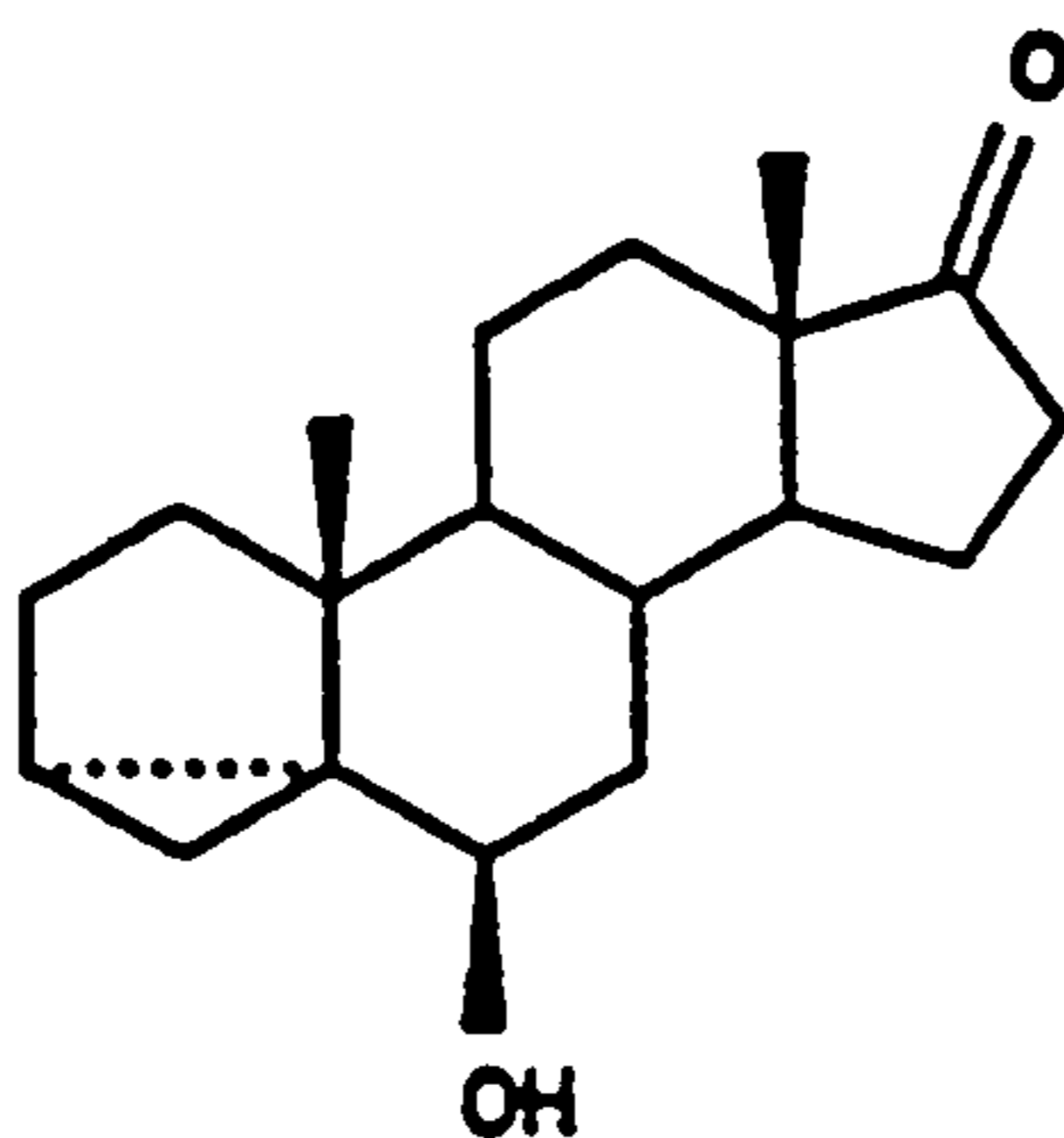
FIGURE 13

"Lengthways" perspective (methyl groups to rear) of 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41)

the α -plane and hence reduced distortion from the half-chair configuration. Deviation from the 14α envelope configuration of the D ring was due to the movement of the C(17) keto group into the α -plane. Overall however, general changes were small.

6.2.2 6β -Hydroxy- $3\alpha,5$ -cyclo- 5α -androstan-17-one (41).

As mentioned in section 6.1, the programme was severely limited in some calculations. One of the major limitations of the modelling system used was its inability to perform calculations on the cyclopropane ring carbons. Indeed force fields capable of handling cyclopropane rings are relatively rare. Attempts to treat the cyclopropane ring with force fields suitable for open chains have been undertaken^{7,8} but have not worked well. Alternatively, force fields with additional parameters have been quite successful^{8,9} but are still not as good as those for simple alkanes. The treatment of more complex cyclopropane compounds, especially those where the cyclopropane ring is fused to another ring, results in compounds with a multitude of various strains that are, at best, very difficult to work with.¹



(41)

As it was only possible to treat the cyclopropane ring

keep the bonds between these three atoms at constant values (those derived from the X-ray data) and to allow the ring to ride freely as an integral unit. The bond lengths, bond angles and torsion angles of compound (41) from the X-ray analysis and the molecular model were compared and are shown below in Tables 23, 24 and 25. Figures 12 and 13 show the 3,5-cyclosteroid from the "normal" prospective and a lengthways view (methyl groups to rear).

TABLE 23

COMPARISON OF BOND LENGTHS (Å) DERIVED FROM X-RAY STUDIES (average e.s.d.= 0.02Å) AND MOLECULAR MECHANICS STUDIES FOR 6β-HYDROXY-3α,5-CYCLO-5α-ANDROSTAN-17-ONE (41).

	<u>X-ray</u>	<u>MM</u>		<u>X-ray</u>	<u>MM</u>
C(1)-C(2)	1.54	1.55	C(9)-C(10)	1.54	1.57
C(1)-C(10)	1.53	1.56	C(9)-C(11)	1.52	1.56
C(2)-C(3)	1.52	1.54	C(10)-C(19)	1.55	1.56
C(3)-C(4)	1.47	--- a	C(11)-C(12)	1.52	1.56
C(3)-C(5)	1.47	--- a	C(12)-C(13)	1.52	1.56
C(4)-C(5)	1.50	--- a	C(13)-C(14)	1.51	1.56
C(5)-C(6)	1.49	1.57	C(13)-C(17)	1.52	1.53
C(5)-C(10)	1.54	1.58	C(13)-C(18)	1.56	1.56
C(6)-C(7)	1.54	1.55	C(14)-C(15)	1.55	1.55
C(6)-O(1)	1.44	1.44	C(15)-C(16)	1.54	1.55
C(7)-C(8)	1.51	1.55	C(16)-C(17)	1.50	1.53
C(8)-C(9)	1.56	1.56	C(17)-O(2)	1.21	1.21
C(8)-C(14)	1.51	1.56			

^acyclopropane bond lengths constrained.

TABLE 24

COMPARISON OF VALENCY ANGLES (°) DERIVED FROM X-RAY STUDIES (average e.s.d.= 0.9°) AND MOLECULAR MECHANICS STUDIES FOR 6 β -HYDROXY-3 α ,5-CYCLO-5 α -ANDROSTAN-17-ONE (41).

	<u>X-ray</u>	<u>MM</u>		<u>X-ray</u>	<u>MM</u>
C1-C2-C3	104.1	104.0	C7-C8-C14	112.4	113.0
C1-C10-C5	103.2	100.9	C8-C9-C10	114.2	115.0
C1-C10-C9	110.5	111.0	C8-C9-C11	111.5	111.4
C1-C10-C19	110.6	110.3	C8-C14-C13	114.0	112.8
C2-C1-C10	106.0	105.7	C8-C14-C15	120.3	122.2
C2-C3-C4	116.3	118.1	C9-C8-C14	106.5	110.7
C2-C3-C5	108.7	108.6	C9-C10-C19	111.4	112.2
C3-C4-C5	59.7	--- a	C9-C11-C12	113.6	114.8
C3-C5-C4	59.3	--- a	C10-C9-C11	113.5	115.8
C3-C5-C6	118.6	118.7	C11-C12-C13	110.2	112.0
C3-C5-C10	108.6	108.4	C12-C13-C14	109.3	107.6
C4-C3-C5	61.0	--- a	C12-C13-C17	116.8	117.2
C4-C5-C6	117.5	118.3	C12-C13-C18	111.4	110.9
C4-C5-C10	117.8	124.9	C13-C14-C15	103.9	104.6
C5-C6-O1	110.2	108.8	C13-C17-O2	125.9	124.0
C5-C6-C7	110.0	111.5	C13-C17-C16	108.4	111.0
C5-C10-C9	110.8	113.5	C14-C13-C17	101.5	98.5
C5-C10-C19	110.1	108.3	C14-C13-C18	113.6	116.1
C6-C5-C10	119.8	114.0	C14-C15-C16	101.2	103.6
C6-C7-C8	113.0	111.4	C15-C16-C17	106.5	104.1
C7-C6-O1	107.5	113.6	C16-C17-O2	125.6	123.4
C7-C8-C9	111.2	111.3	C17-C13-C18	104.0	106.3

TABLE 25

COMPARISON OF RING TORSION ANGLES (°) DERIVED FROM X-RAY STUDIES (average e.s.d. = 0.9°) AND MOLECULAR MECHANICS STUDIES FOR 6 β -HYDROXY-3 α ,5-CYCLO-5 α -ANDROSTAN-17-ONE (41).

<u>RING A</u>	<u>X-ray</u>	<u>MM</u>
C(1)-C(2)-C(3)-C(4)	49.0	52.6
C(1)-C(2)-C(3)-C(5)	-17.2	-14.5
C(2)-C(3)-C(4)-C(5)	-97.7	-97.0
C(2)-C(3)-C(5)-C(10)	-1.5	-7.6
C(3)-C(4)-C(5)-C(10)	96.2	91.8
C(3)-C(5)-C(10)-C(1)	19.5	26.2
C(4)-C(5)-C(10)-C(1)	-45.0	-38.5
C(5)-C(10)-C(1)-C(2)	-29.9	-34.9
C(10)-C(1)-C(2)-C(3)	29.4	31.3
<u>RING B</u>	<u>X-ray</u>	<u>MM</u>
C(5)-C(6)-C(7)-C(8)	53.4	58.3
C(6)-C(7)-C(8)-C(9)	-57.1	-57.6
C(7)-C(8)-C(9)-C(10)	52.1	49.7
C(8)-C(9)-C(10)-C(5)	-42.7	-42.0
C(9)-C(10)-C(5)-C(6)	42.1	42.1
C(10)-C(5)-C(6)-C(7)	-46.9	-50.5

<u>RING C</u>	<u>X-ray</u>	<u>MM</u>
C(8)-C(9)-C(11)-C(12)	54.0	47.7
C(9)-C(11)-C(12)-C(13)	-53.0	-52.0
C(11)-C(12)-C(13)-C(14)	54.3	56.2
C(12)-C(13)-C(14)-C(8)	-61.7	-60.0
C(13)-C(14)-C(8)-C(9)	60.4	58.6
C(14)-C(8)-C(9)-C(11)	-54.8	-49.6

<u>RING D</u>	<u>X-ray</u>	<u>MM</u>
C(13)-C(14)-C(15)-C(16)	-40.9	-38.8
C(14)-C(15)-C(16)-C(17)	23.8	18.6
C(15)-C(16)-C(17)-C(13)	1.3	8.9
C(16)-C(17)-C(13)-C(14)	-26.6	-30.9
C(17)-C(13)-C(14)-C(15)	41.7	41.8

One of the obvious results in the table of bond lengths is the difference in the length of the C(5)-C(6) bond. The X-ray study (indicating the "partial sp^2 " character of the cyclopropane ring) gives a shorter bond length. Thus the major weakness of the molecular mechanics model is evident here because the programme, in treating the three cyclopropane carbons as sp^3 hybridised, has calculated this bond to be longer by assuming no movement of electrons occurs.

The torsion angles of the A ring show greater deviation from the planar nature of the 5 membered [C(1)-C(2)-C(3)-C(5)-C(10)] ring (noted in a Drieding model) than those in the X-ray structure. Bond angles C(2)-C(3)-C(4) and C(4)-C(5)-C(10), i.e., those defining the relationship between the cyclopropane and cyclopentane rings, were increased. As

was noted in the case of the D ring of DHEA, torsion angles were adjusted, i.e., the pushing of the C(17) atom out of the plane distorting the 14α envelope. Changes elsewhere were small.

The accuracy of the model was indicated by the theoretical estimation of the coupling between 6-H and its neighbouring protons. The dihedral angles between the 6α -hydrogen and its vicinal 7-hydrogens were measured at 54.3° and 58.4° which gives, using the Karplus equation:^{10,11}

$${}^3J_{ab} = J^0 \cdot \cos^2\phi - 0.28 \quad (0^\circ \geq \phi \leq 90^\circ)$$

$${}^3J_{ab} = J^{180} \cdot \cos^2\phi - 0.28 \quad (90^\circ \geq \phi \leq 180^\circ)$$

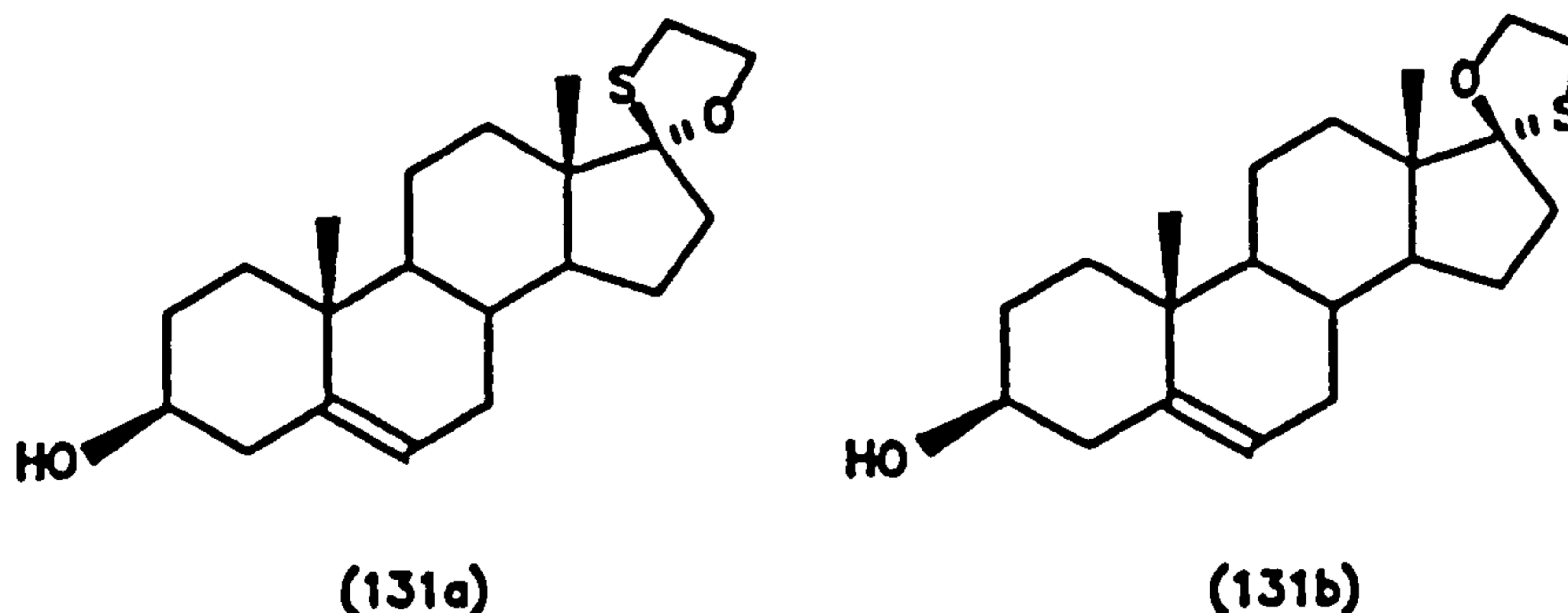
where the constants, J^0 and $J^{180} = 8.5$ and 9.5 respectively and ϕ is the dihedral angle between the two protons, an estimated coupling constants of $2.5 \text{ Hz} \pm 0.5\text{Hz}$. This compares very favourably with the observed triplet ($J = 2.7\text{Hz}$). As this relatively simple example shows, the clarification of a structure can be achieved by predicting ${}^1\text{H}$ NMR coupling constants. Therefore this technique was utilised on other, more complex examples to help predict or elucidate their structure.

6.3 Molecular modelling investigations of structurally interesting steroids related to the synthetic studies.

Several compounds, detailed below, were investigated by molecular mechanics in attempts to gain further details of their structure. Information gained was used for a variety of purposes.

6.3.1 3β -Hydroxy-5-androstene-17-spiro-2'-(1,3-oxathiolane) (131). R or S configuration?

By study of the reaction mechanism for the formation of the oxathiolane (Section 3.3.4) it was concluded that the 17(S) configuration (131a) was the product of this apparently regioselective reaction. However, because of a potentially large repelling force between the β -orientated sulphur



atom and the C(18) methyl group in the S-isomer it was considered that the product of reaction may in fact have the 17(R) configuration (131b). Thus although attack at C(17) by the hydroxy group may, by steric effects, be directed to form the S-isomer, the (potentially) lower energy of the R-isomer may direct the reaction to this product via a higher energy intermediate. To determine the exact structures of the two isomers and hence examine the steric differences between (131a) and (131b) the two models were gener-

ated, and their energies minimised. A comparison of the geometrical data of the two compounds is presented below in Tables 26, 27 and 28. Not surprisingly, data from rings A and B were virtually identical and therefore have been omitted.

TABLE 26

COMPARISON OF BOND LENGTHS (Å) DERIVED FROM MOLECULAR MECHANICS STUDIES FOR THE 17R AND 17S OXATHIOLANE STEROIDS (131a and b).

	<u>17R</u>	<u>17S</u>		<u>17R</u>	<u>17S</u>
C(11)-C(12)	1.556	1.556	C(16)-C(17)	1.563	1.563
C(12)-C(13)	1.561	1.563	C(17)-O(2)	1.440	1.441
C(13)-C(14)	1.558	1.561	C(17)-S(1)	1.837	1.836
C(13)-C(17)	1.573	1.573	S(1)-C(20)	1.801	1.796
C(13)-C(18)	1.569	1.566	C(20)-C(21)	1.544	1.545
C(14)-C(15)	1.548	1.546	C(9)-C(11)	1.566	1.565
C(15)-C(16)	1.554	1.553	C(21)-O(2)	1.433	1.431

TABLE 27

COMPARISON OF THE VALENCY ANGLES (°) DERIVED FROM MOLECULAR MECHANICS STUDIES OF THE 17R AND 17S OXATHIOLANE STEROIDS (131a and b).

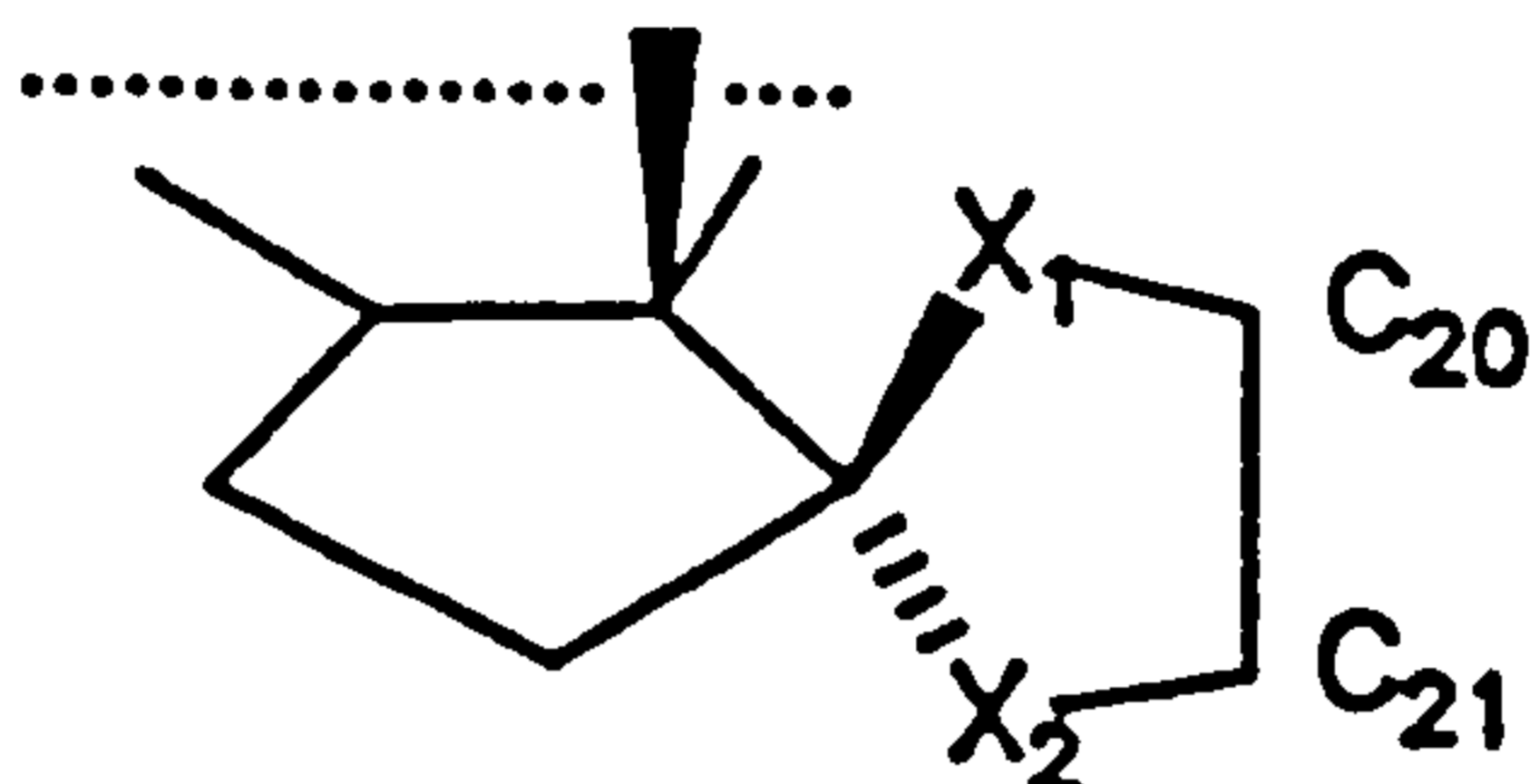
	<u>17R</u>	<u>17S</u>		<u>17R</u>	<u>17S</u>
C8-C9-C11	112.5	112.2	C13-C17-C16	102.6	102.8
C8-C14-C13	115.7	116.1	C14-C13-C17	102.1	101.6
C8-C14-C15	119.5	119.4	C14-C13-C18	113.1	113.4
C9-C8-C14	112.7	112.4	C14-C15-C16	104.2	103.5
C9-C10-C19	111.4	111.4	C15-C16-C17	108.5	108.6
C9-C11-C12	116.0	116.0	C16-C17-O2	110.5	109.2
C10-C9-C11	115.7	115.8	C16-C17-S1	109.0	110.2
C11-C12-C13	113.5	113.6	C17-C13-C18	108.6	109.7
C12-C13-C14	106.1	105.1	O2-C17-S1	105.9	105.1
C12-C13-C17	118.5	117.6	C17-S1-C20	91.2	91.6
C12-C13-C18	111.4	109.4	C17-O2-C21	114.3	113.8
C13-C14-C15	103.9	103.9	C20-C21-O2	111.7	112.3
C13-C17-O2	112.2	110.0	C21-C20-S1	103.9	102.7
C13-C17-S1	117.4	119.3			

TABLE 28

COMPARISON OF THE RING TORSION ANGLES (°) DERIVED FROM MOLECULAR MECHANICS STUDIES OF THE 17R AND 17S OXATHIOLANE STEROIDS, (131a and b).

<u>RING C</u>	<u>17R</u>	<u>17S</u>
C(8)-C(9)-C(11)-C(12)	41.9	42.3
C(9)-C(11)-C(12)-C(13)	-51.0	-51.0
C(11)-C(12)-C(13)-C(14)	55.8	56.2
C(12)-C(13)-C(14)-C(8)	-58.3	-59.0
C(13)-C(14)-C(8)-C(9)	53.0	53.9
C(14)-C(8)-C(9)-C(11)	-41.4	-41.6
<u>RING D</u>	<u>17R</u>	<u>17S</u>
C(13)-C(14)-C(15)-C(16)	-30.6	-34.2
C(14)-C(15)-C(16)-C(17)	5.9	10.6
C(15)-C(16)-C(17)-C(13)	20.7	16.7
C(16)-C(17)-C(13)-C(14)	-39.0	-37.0
C(17)-C(13)-C(14)-C(15)	20.7	44.8

Table 29 shows the values of the torsion angles of the oxathiolane ring and the torsion angles defining the geometry of attachment of the oxathiolane ring (ring E) to the D ring of the steroid. In the Table, X(1) and X(2) represent a sulphur atom and a oxygen atom respectively in the case of the 17S isomer. The opposite is true for the R isomer (Figure 14).



(131a: 17(S), $X_1 = S$, $X_2 = O$)

(131b: 17(R), $X_1 = O$, $X_2 = S$)

FIGURE 14

Numbering used for Table 29

TABLE 29

COMPARISON OF THE TORSION ANGLES (°) OF THE OXATHIOLANE RING DERIVED FROM MOLECULAR MECHANICS STUDIES OF THE 17R AND 17S OXATHIOLANE STEROIDS (131).

<u>RING E. (OXATHIOLANE RING)</u>	<u>17R</u>	<u>17S</u>
C(17)-X(1)-C(20)-C(21)	2.0	-33.5
X(1)-C(20)-C(21)-X(2)	-25.2	26.5
C(20)-C(21)-X(2)-C(17)	31.7	-2.1
C(21)-X(2)-C(17)-X(1)	-31.7	-23.0
X(2)-C(17)-X(1)-C(20)	21.8	33.8
C(13)-C(17)-X(1)-C(20)	-107.3	-90.2
C(13)-C(17)-X(2)-C(21)	94.2	106.6
C(14)-C(13)-C(17)-X(1)	-157.1	-159.2
C(14)-C(13)-C(17)-X(2)	80.3	79.2
C(15)-C(16)-C(17)-X(1)	139.9	144.9
C(15)-C(16)-C(17)-X(2)	-104.1	-100.2
C(16)-C(17)-X(1)-C(20)	139.7	151.2
C(16)-C(17)-X(2)-C(21)	-150.6	-141.2

As already stated, examination of the two isomers (131) showed that changes in configuration at the 17-position had no effect on the A and B rings. However, the above data also shows that there is very little geometrical difference between rings C and D of the two isomers. The two structures, constructed from the DHEA (97) model by identical means and minimised to the same degree showed that the final energy value of the 17S configuration was only 4.5% greater than that of the 17R steroid. Figures 15 and 16 show the two

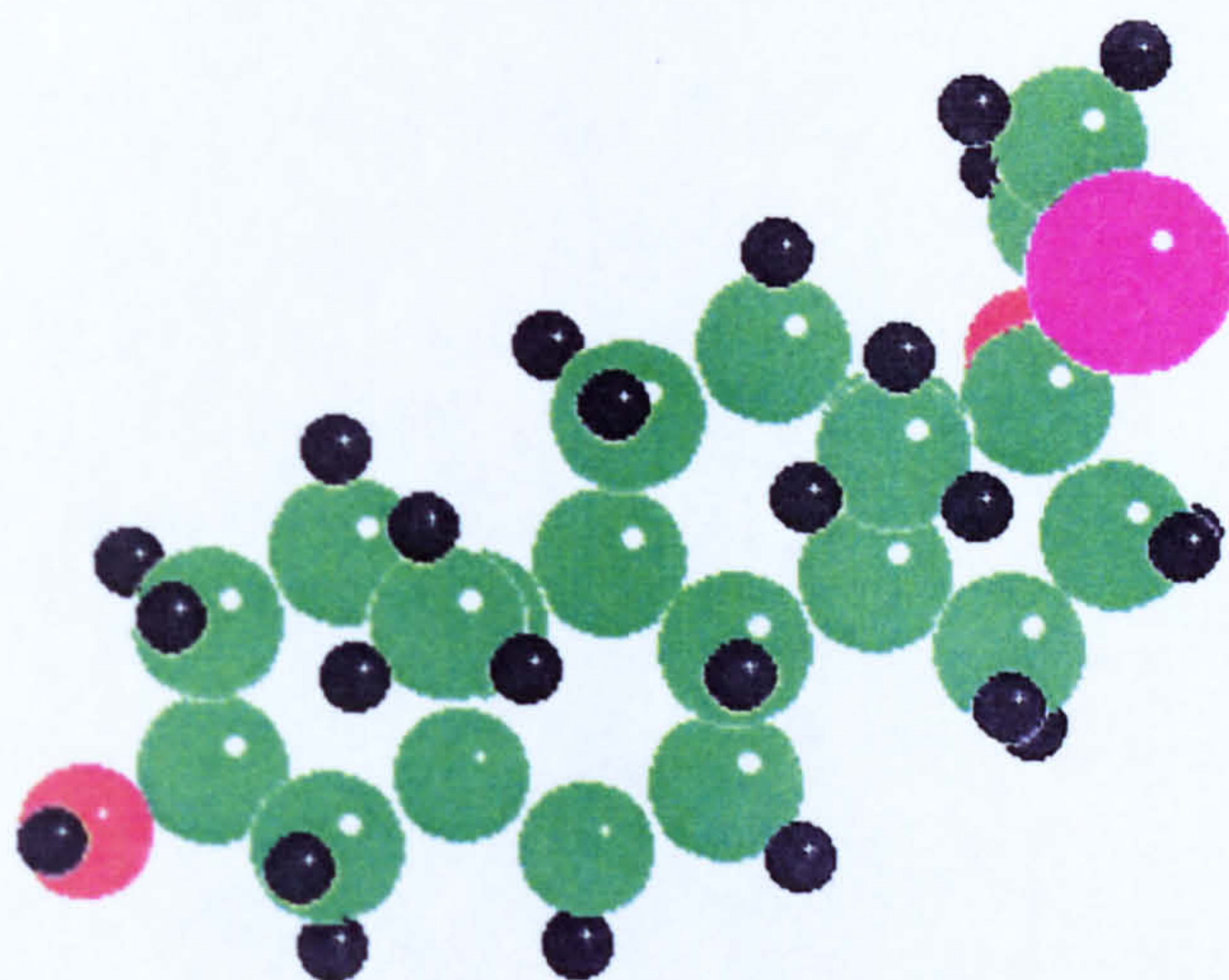


FIGURE 15

"Normal" perspective of 3β-hydroxy-androst-5-en-17(S)-spiro-2'-(1,3-oxathiolane) (131a)

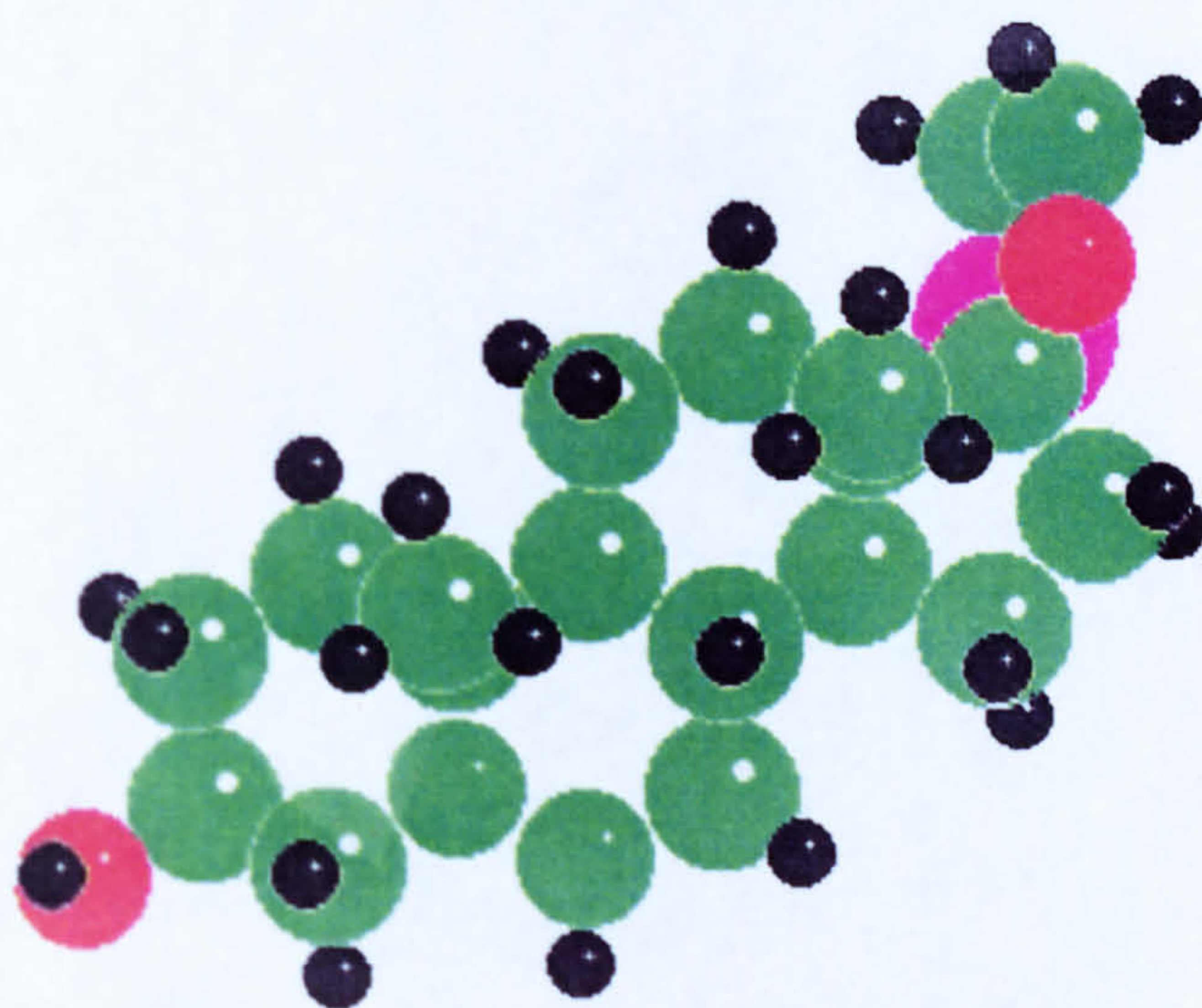


FIGURE 16

"Normal" perspective of 3β-hydroxy-androst-5-en-17(R)-spiro-2'-(1,3-oxathiolane) (131b)

isomers from the "normal prospective". Thus there is no great difference between the two structures in terms of overall energy and therefore no reason to presume that the regioselective product is the R-isomer. Further confirmation can be gleaned from a more detailed study of the oxathiolane ring in the two isomers.

The only significant difference between the two steroids epimers' lies with the two oxathiolane rings where the rings of each epimer are "mirror images" of each other. Table 30, where the torsion angles are arranged under the same type of bond instead of their geometrical orientation, gives a clearer picture than Table 29. The unnumbered carbons represent the respective oxathiolane carbons of each epimer.

TABLE 30

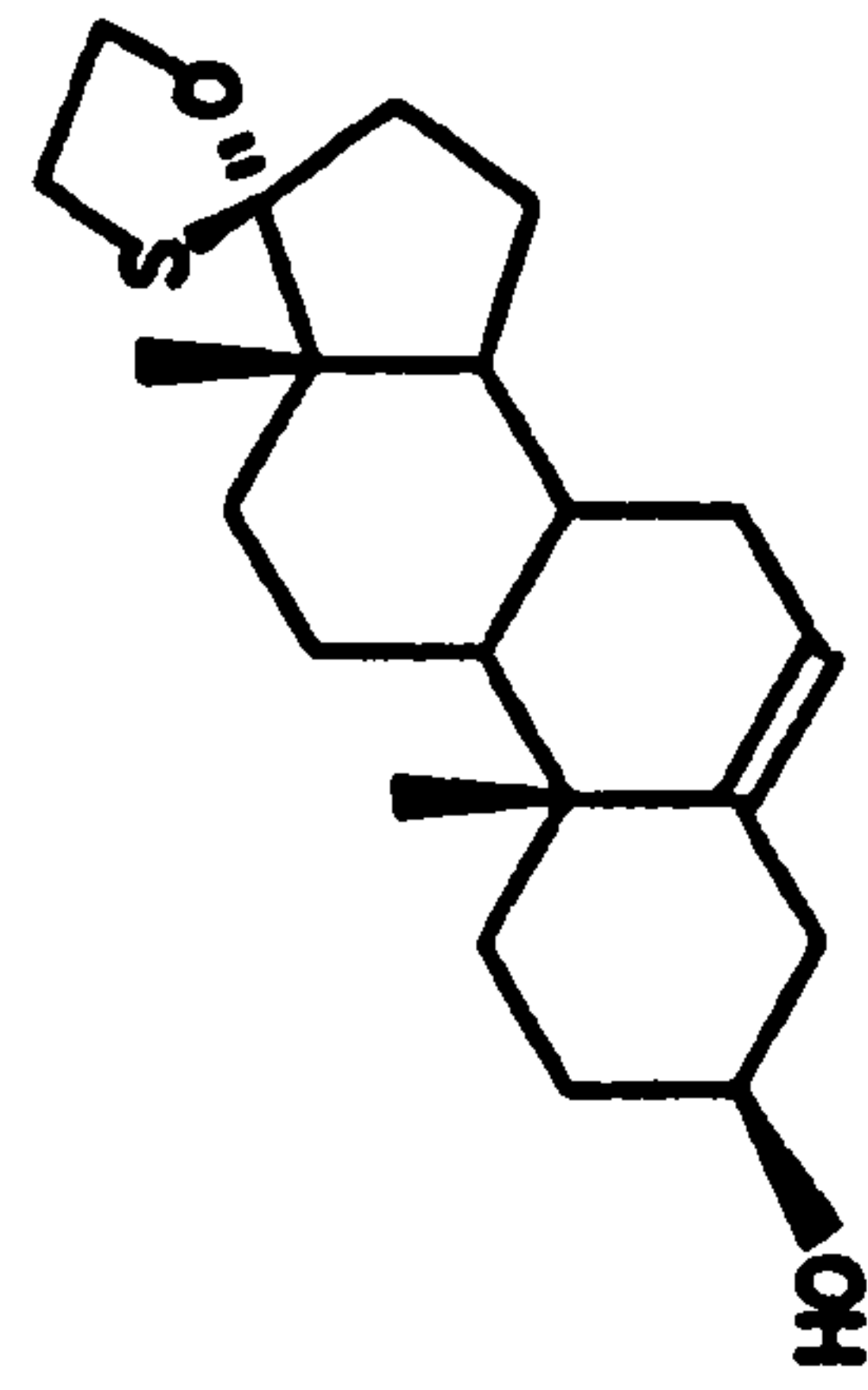
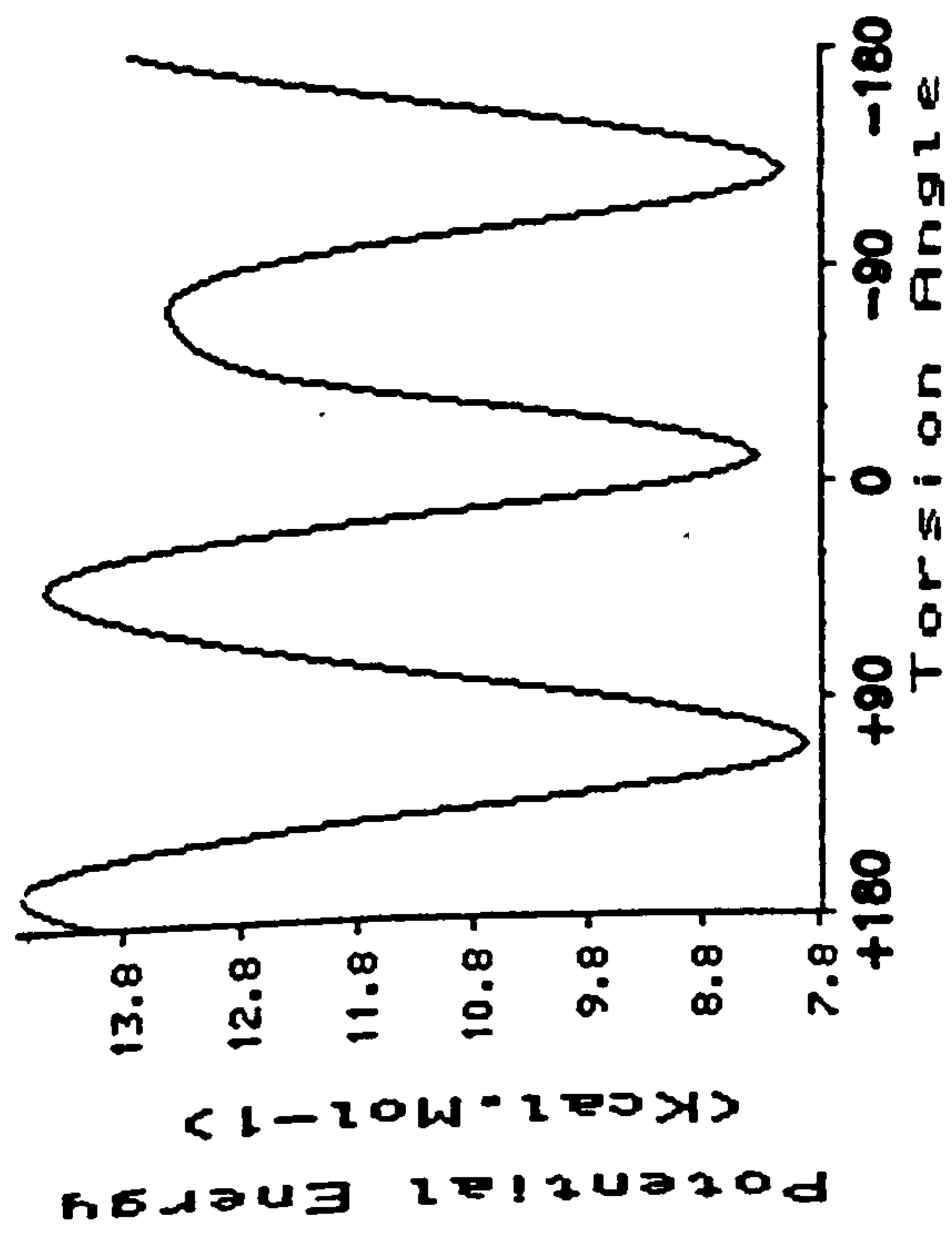
ALTERNATIVE COMPARISON OF THE OXATHIOLANE RING TORSION ANGLES (°) OF THE 17R AND 17S OXATHIOLANE STEROIDS, (131).

<u>TORSION ANGLE</u>	<u>17R</u>	<u>17S</u>
C(17)-S-C-C	31.7	-33.5
S-C-C-O	-25.2	26.5
C-C-O-C(17)	2.0	-2.1
C-O-C(17)-S	21.8	-23.0
O-C(17)-S-C	-31.7	33.8

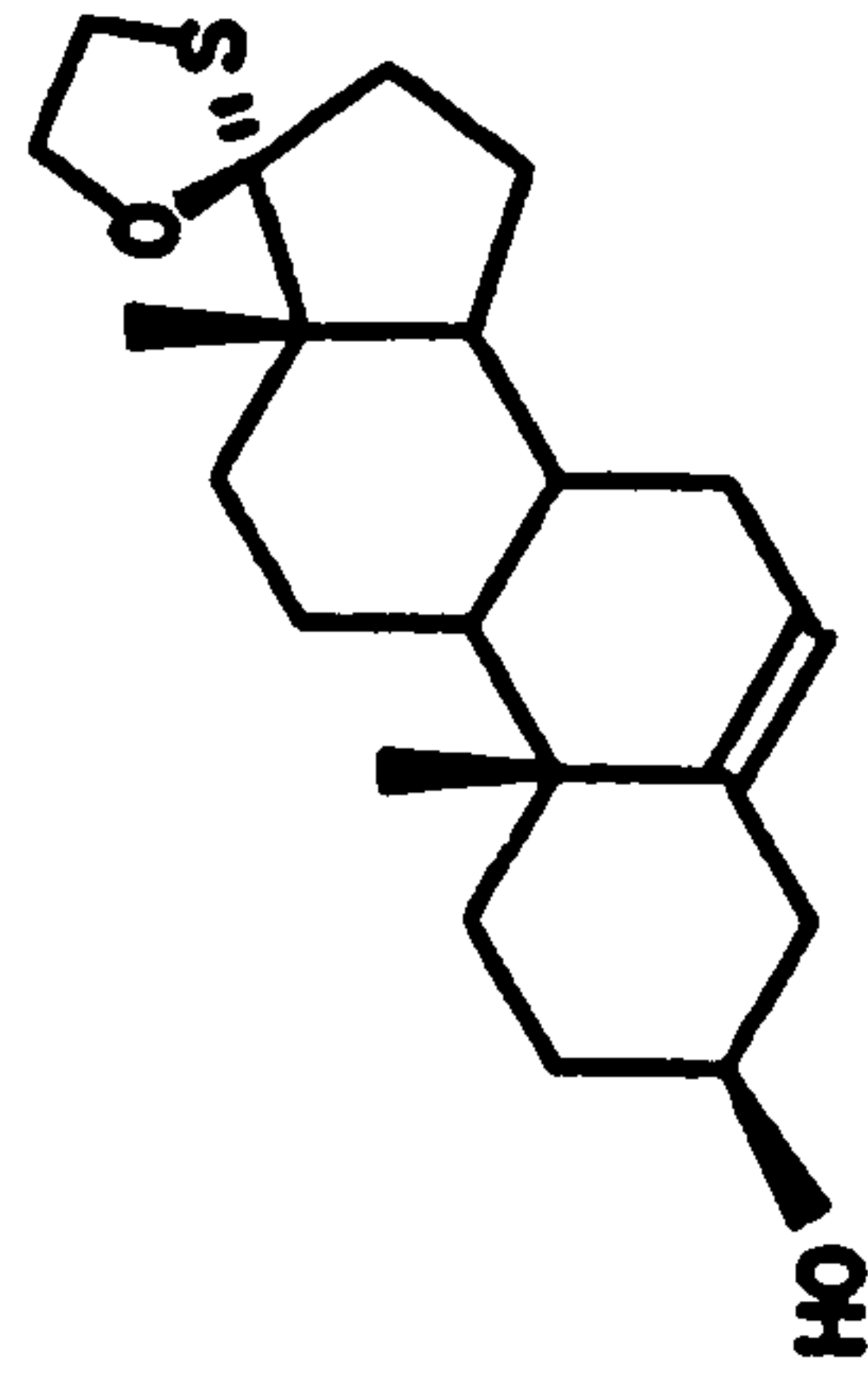
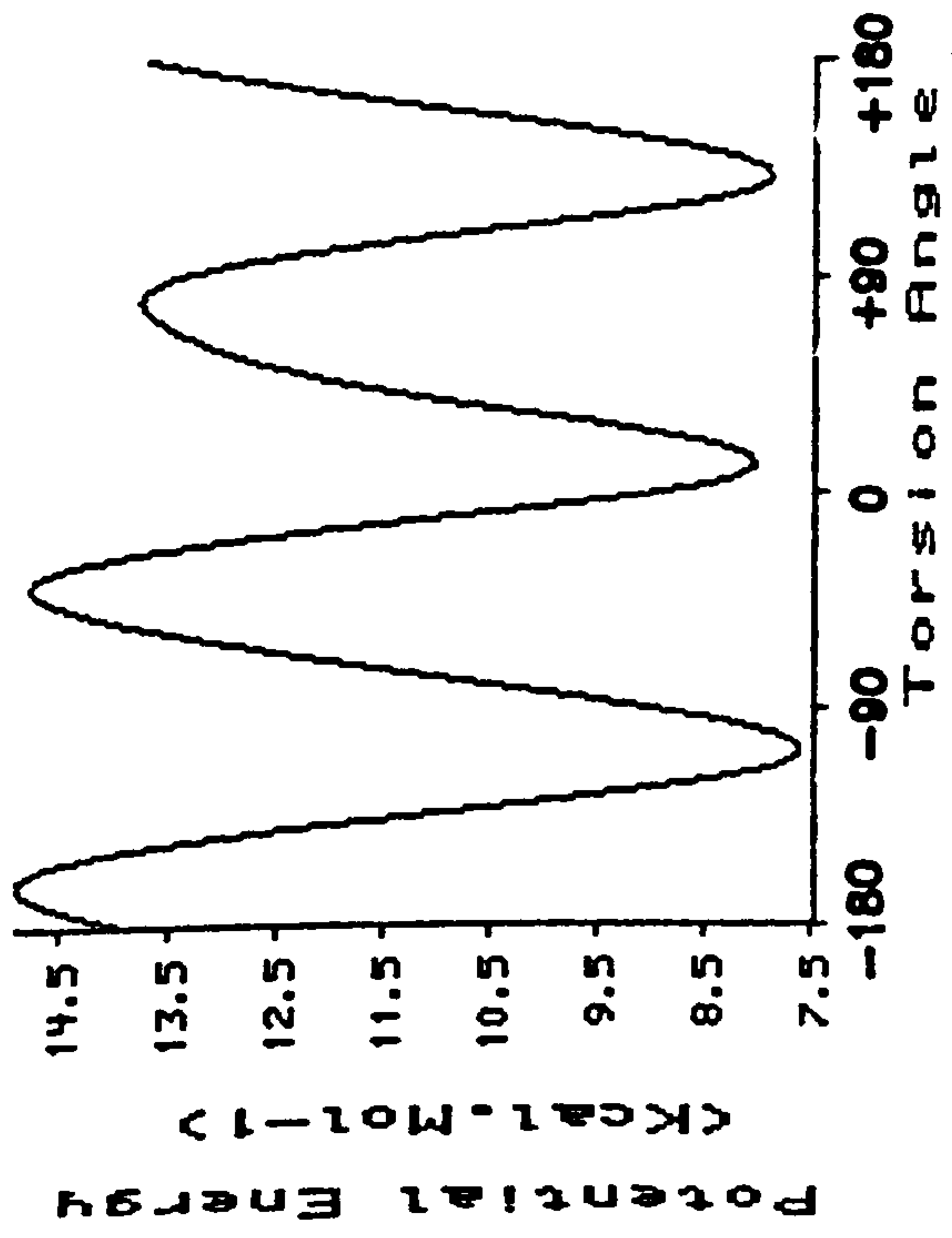
As indicated by the data, the oxathiolane ring of the 17S isomer is more distorted than the oxathiolane ring of the 17R isomer. This distortion is also seen in the steroid

framework, e.g., the angle C(17)-C(13)-C(18) increases from 102.6° for DHEA to 108.6° for the R-isomer (131b) and to 109.7° for the S-isomer (131a). However, these changes, as indicated above, do not significantly add to the overall energy of the molecule and can therefore easily accommodate the sulphur atom into the β -position. This is further supported by comparing the strengths of the interaction between the oxathiolane and C(18) methyl groups of the two epimers. Thus a plot of potential energy verses rotation of torsion angle C(14)-C(13)-C(18)-H led to a measurement of the repulsive force on the hydrogen atom's closest approach (Figure 17). For the 17S compound the increase in energy as the methyl hydrogen reached its closest point to the heteroatom was only 2% more than that for the 17R steroid. This information and that given above lead to the conclusion that there is, with respect to an energetically favoured structure, essentially no difference between the two compounds and that the reaction would not be affected by the introduction of the sulphur atom into the β -position. This is used to support the postulate of the formation of the 17S isomer by the mechanism given in Chapter 3.

Note however that the molecular mechanics models do potentially offer a more definitive identification of the isomeric product by an analysis of the splitting patterns of the ^1H NMR signals of the product. Because of the two forms of the oxathiolane ring the dihedral angles between the 4 protons of the ring differ (Table 31) and would therefore lead to differing splitting patterns. However, the differences between the theoretical splitting patterns



(131a)



(131b)

FIGURE 17

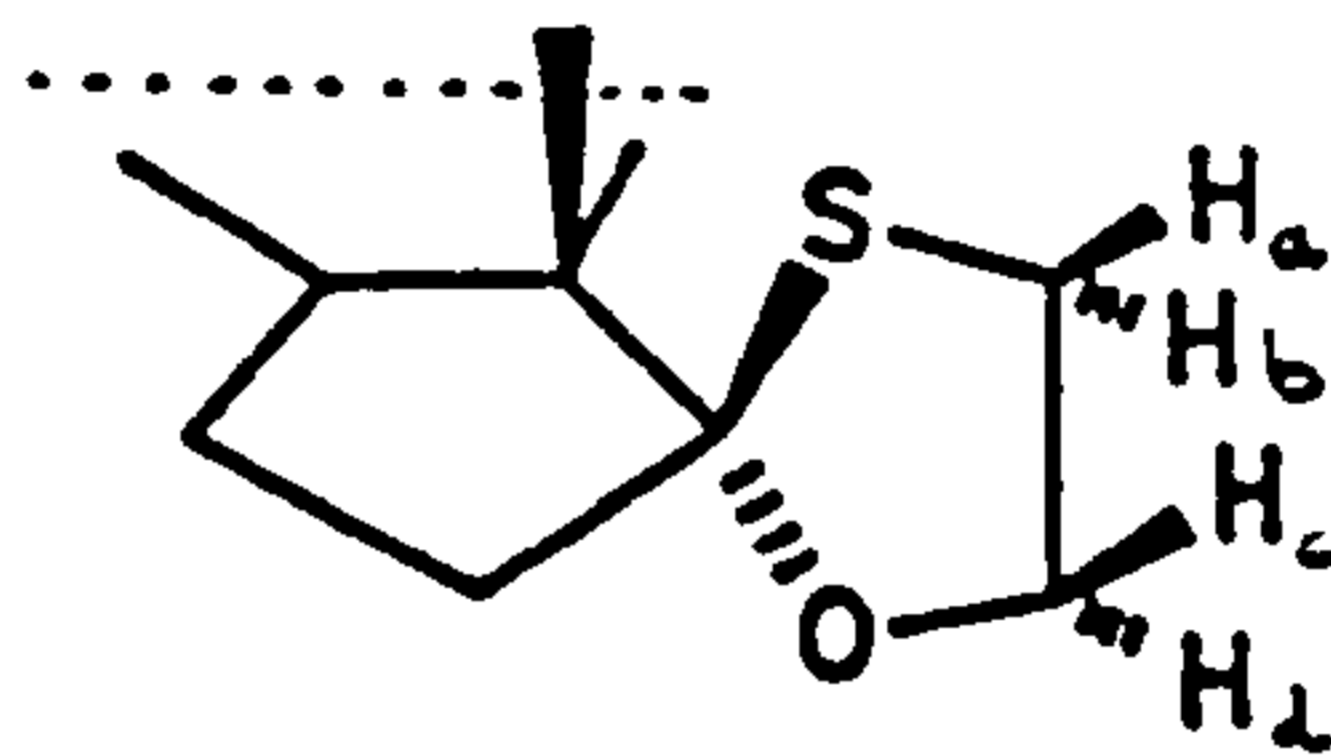
Potential energy graphs obtained by the rotation of the 18-C methyl groups of compounds (131a and b)

resulting from these differences are too small to be distinguished readily on the instrument used and certain identification would most certainly involve considerable experimentation on a more powerful instrument.

TABLE 31

DIHEDRAL ANGLES ($^{\circ}$) BETWEEN THE OXATHIOLANE PROTONS OF THE TWO POSSIBLE ISOMERS (131).

<u>DIHEDRAL ANGLE</u>	<u>17R</u>	<u>17S</u>
θ_{ac}	31.8	35.0
θ_{ad}	32.2	29.9
θ_{bc}	72.1	85.5
θ_{bd}	28.9	29.6



6.3.2 3β -Hydroxy-5-androstene-17(S)-spiro-2'-(1,3-oxathiolane) (131a). A comparison of conformational features with DHEA (97).

In Chapter 3 it was noted that the oxathiolane steroid (131a) would not undergo tosylation at the C(3) hydroxy group. It was also observed that the mesylation or acetylation of the above group occurred at a considerably slower rate than for a similar reaction with DHEA (97). In relation to this, the two respective compounds were compared to ascertain if the oxathiolane group conferred any structural changes to the main steroid framework and was thus experiencing a form of the Barton effect¹² (Chapter 3). The complete results showed that the A and B rings of the two compounds were almost identical. However, as noted in Tables 32, 33 and 34, slight alterations to the C ring and considerable alterations to the D ring (due to the change in hybridisation of atom C(17)) were noted.

TABLE 32

COMPARISON OF BOND LENGTHS (Å) DERIVED FROM MOLECULAR MECHANICS STUDIES FOR DEHYDROEPIANDOSTERONE AND ITS 17S-OXATHIOLANE COMPOUND.

	<u>DHEA</u>	<u>17S</u>		<u>DHEA</u>	<u>17S</u>
C(11)-C(12)	1.556	1.556	C(16)-C(17)	1.526	1.563
C(12)-C(13)	1.556	1.563	C(17)-O(2)	1.212	1.440
C(13)-C(14)	1.557	1.561	C(17)-S(1)	--	1.836
C(13)-C(17)	1.529	1.573	S(1)-C(20)	--	1.796
C(13)-C(18)	1.562	1.566	C(20)-C(21)	--	1.545
C(14)-C(15)	1.552	1.546	C(9)-C(11)	1.568	1.565
C(15)-C(16)	1.554	1.553	C(21)-O(2)	--	1.433

TABLE 33

COMPARISON OF THE VALENCY ANGLES (°) DERIVED FROM MOLECULAR MECHANICS STUDIES OF DEHYDROEPIANDROSTERONE AND THE 17S-OXATHIOLANE COMPOUND.

	<u>DHEA</u>	<u>17S</u>		<u>DHEA</u>	<u>17S</u>
C8-C9-C11	113.2	112.2	C13-C17-C16	110.9	102.8
C8-C14-C13	114.0	116.1	C14-C13-C17	98.6	101.6
C8-C14-C15	121.3	119.4	C14-C13-C18	116.0	113.4
C9-C8-C14	112.2	112.4	C14-C15-C16	104.2	103.5
C9-C10-C19	111.7	111.4	C15-C16-C17	103.8	108.6
C9-C11-C12	116.4	116.0	C16-C17-O2	123.8	109.2
C10-C9-C11	115.9	115.8	C16-C17-S1	---	110.2
C11-C12-C13	111.6	113.6	C17-C13-C18	106.7	109.7
C12-C13-C14	107.0	105.1	O2-C17-S1	---	105.1
C12-C13-C17	117.1	117.6	C17-S1-C20	---	91.6
C12-C13-C18	111.2	109.4	C17-O2-C21	---	113.8
C13-C14-C15	104.4	103.9	C20-C21-O2	---	112.3
C13-C17-O2	124.1	110.0	C21-C20-S1	---	102.7
C13-C17-S1	---	119.3			

TABLE 34

COMPARISON OF THE RING TORSION ANGLES (°) DERIVED FROM MOLECULAR MECHANICS STUDIES OF DEHYDROEPIANDROSTERONE AND ITS 17S OXATHIOLANE COMPOUND.

<u>RING C</u>	<u>DHEA</u>	<u>17S</u>
C(8)-C(9)-C(11)-C(12)	40.6	42.3
C(9)-C(8)-C(14)-C(13)	53.9	53.9
C(9)-C(11)-C(12)-C(13)	-50.3	-51.0
C(11)-C(12)-C(13)-C(14)	58.1	56.2
C(12)-C(13)-C(14)-C(8)	-61.6	-59.0
C(14)-C(8)-C(9)-C(11)	-40.8	-41.6

<u>RING D</u>	<u>DHEA</u>	<u>17S</u>
C(13)-C(14)-C(15)-C(16)	-37.8	-34.2
C(14)-C(13)-C(17)-C(16)	-32.0	-37.0
C(14)-C(15)-C(16)-C(17)	17.1	10.9
C(15)-C(16)-C(17)-C(13)	9.9	16.7
C(17)-C(13)-C(14)-C(15)	41.8	44.8

RING E (OXATHIOLANE RING)

C(17)-S(1)-C(20)-C(21)	-33.5
S(1)-C(20)-C(21)-O(2)	26.5
C(17)-O(2)-C(21)-C(20)	-2.1
S(1)-C(17)-O(2)-C(21)	-23.0
O(2)-C(17)-S(1)-C(20)	33.8

The information given above readily shows the alteration of the D ring induced by the conversion of the C(17) atom from an sp^2 to an sp^3 hybridised state. Although changes in the conformation of the C ring are noticeable with the alteration at C(17) these changes are not significant. Since no difference was observed between the A and B rings of the two compounds it would appear that the noted reduced rates of reaction cannot be explained by geometrical alterations leading to some form of Barton effect¹² (Chapter 3).

6.3.3 6-Methylene-3 α ,5-cyclo-5 α -androstan-17-one (180).

Conformation dependence by conjugation or by the 4-H/6'-H interaction?

When constructed from a Drieding model, the 6-methylene derivatives synthesised, e.g., (180) (Chapter 3) appeared to be of interest. It was noted that there may be a repulsive interaction between the C(4) cyclopropane protons and the relevant C(6') methylene proton because of their close proximity (157). This would have an effect on the geometry and hence on the level of conjugation between the cyclopropane and the exo-cyclic methylene group. There is effectively therefore a compromise here between maximum conjugation and minimum interaction which will determine the geometry of the steroid (the reader is directed to Chapter 3, for a detailed explanation of this). Although the modelling system used cannot refine cyclopropane carbon positions (and hence any conjugation present in the molecule), a molecular mechanics model was constructed to investigate the proton

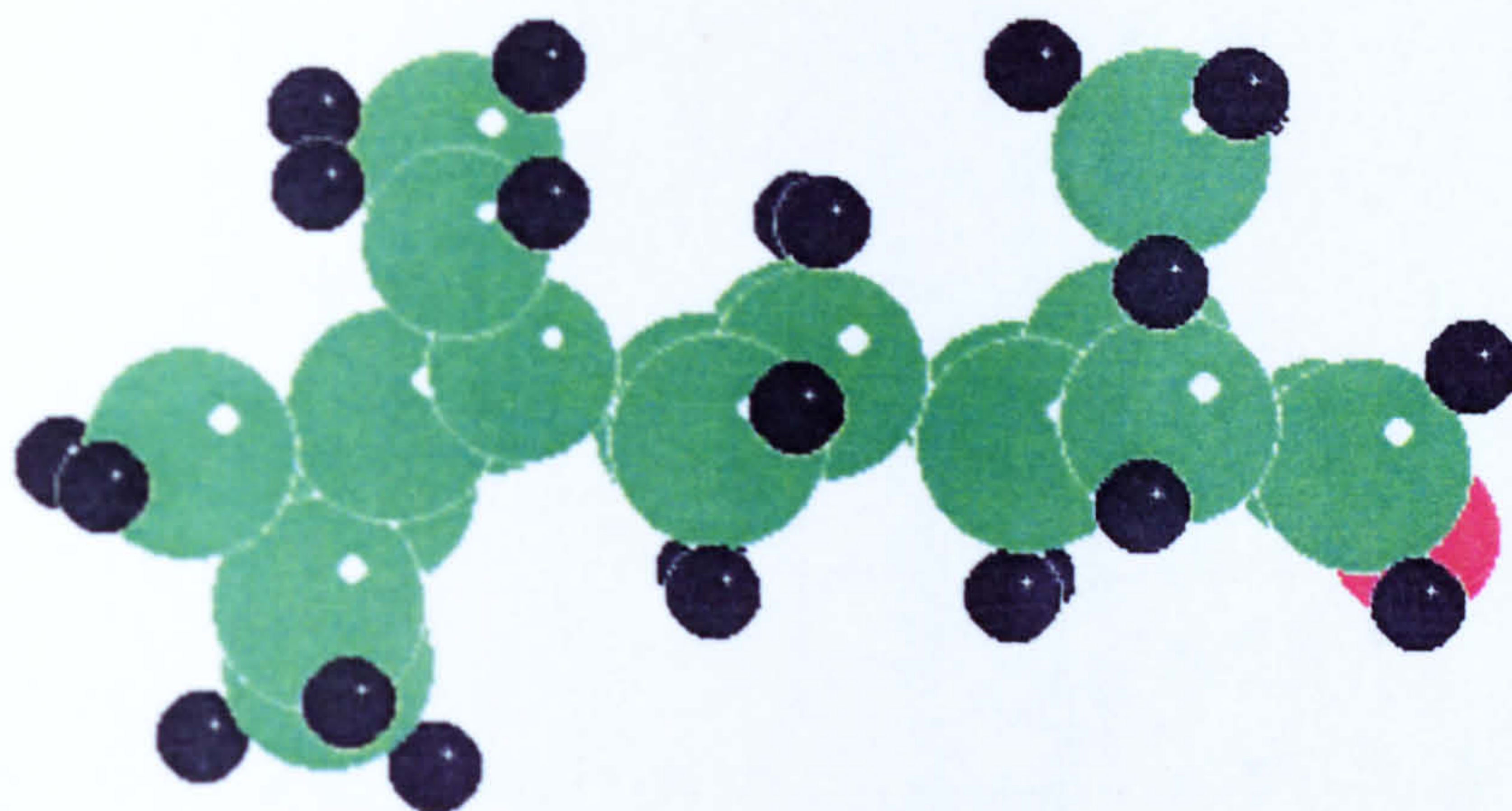
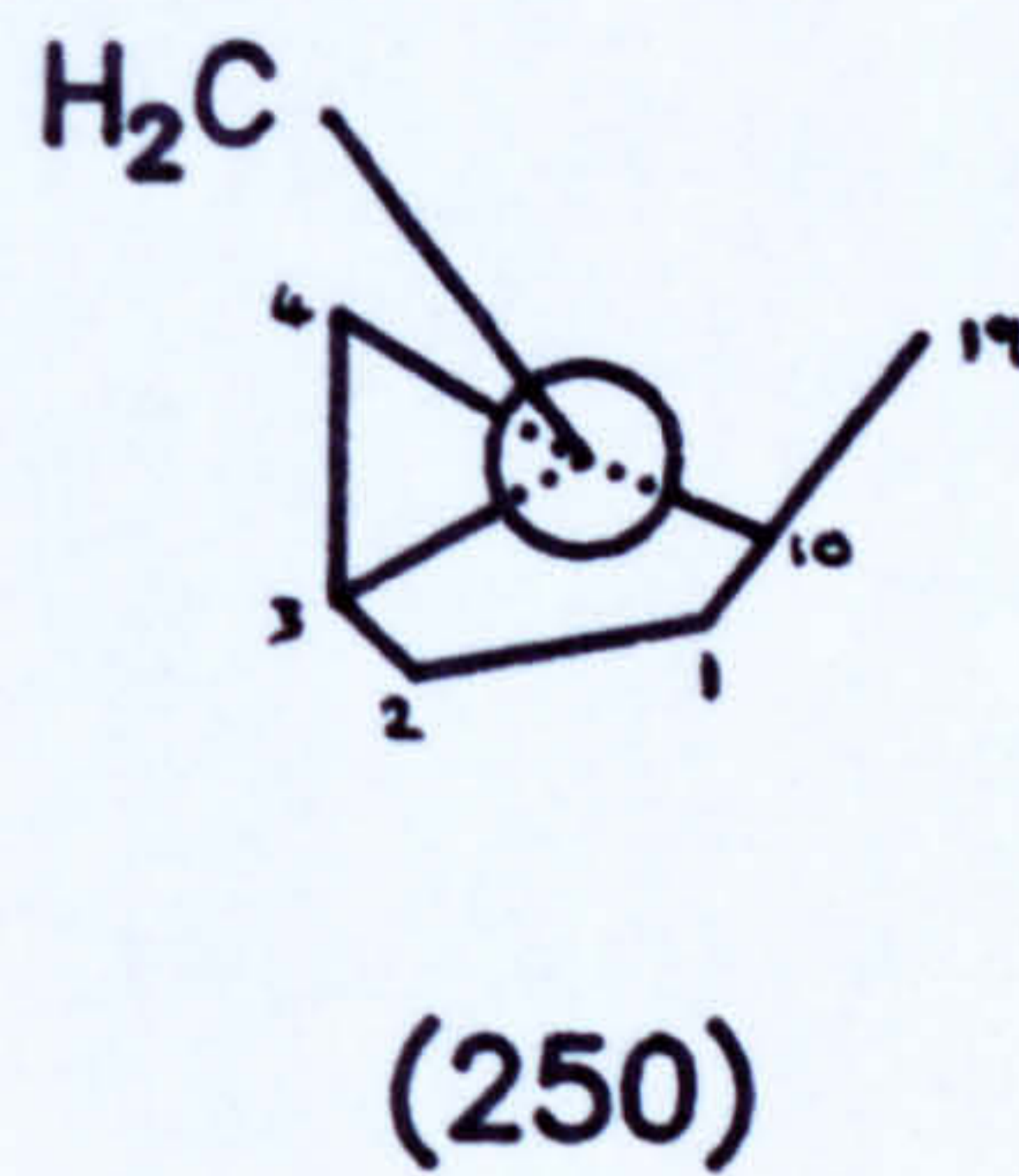
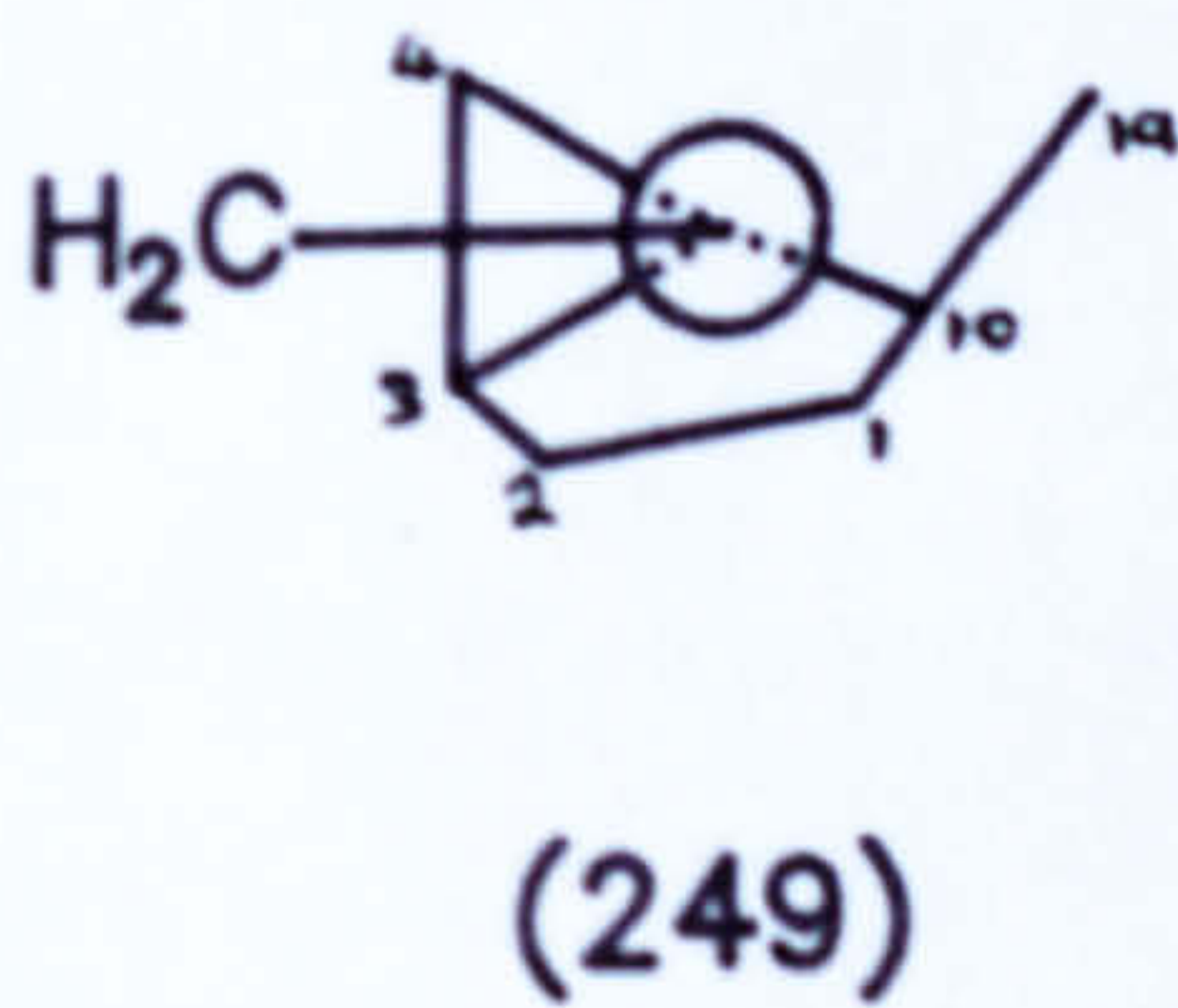
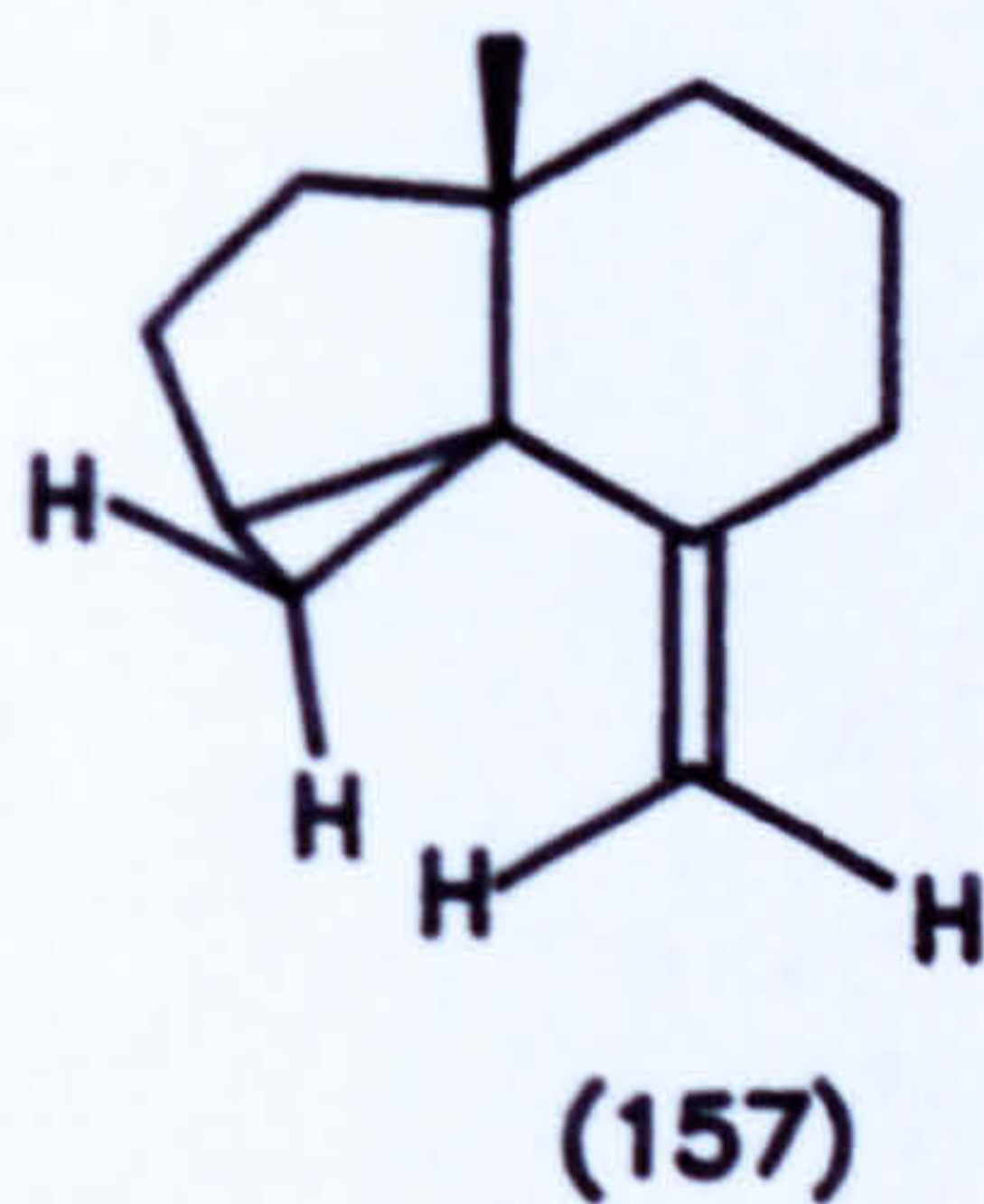


FIGURE 18

"Lengthways" perspective (methyl groups to rear) of 6-methylene-
3,5-cyclo-5 α -androstan-17-one (180)



interaction and determine its effects on the conjugation. The model was constructed from the parent 3,5-cyclosteroid (41) by the transforming of C(6) into a sp^2 carbon and attaching a methylene group. The torsion angle C(4)-C(5)-C(6)-C(6') was, before minimisation, set at 30° , i.e., $X-C(5)-C(6)-C(6') = 0^\circ$ [where X is the midpoint between C(3) and C(4)] (249), the value that would theoretically allow maximum conjugation, and also that indicated by a Drieding model. A comparison between the parent cyclosteroid (41) and its (minimised) methylene derivative (Figure 18) was made and is presented below in Tables 35, 36 and 37. As no changes were expected, nor indeed found, in the C and D rings their relevant data have been omitted.

TABLE 35

COMPARISON OF BOND LENGTHS (Å) DERIVED FROM MOLECULAR MECHANICS STUDIES OF $3\alpha,5$ -CYCLO- 5α -ANDROSTAN- 6β -OL-17-ONE, AND 6 -METHYLENE- $3\alpha,5$ -CYCLO- 5α -ANDROSTAN-17-ONE.

	<u>PARENT</u>	<u>METHLYENE</u>		<u>PARENT</u>	<u>METHYLENE</u>
C(1)-C(2)	1.548	1.548	C(6)-C(7)	1.550	1.526
C(1)-C(10)	1.564	1.564	C(6)-C(6')	---	1.342
C(2)-C(3)	1.545	1.545	C(7)-C(8)	1.553	1.553
C(3)-C(4)	1.471	--- ^a	C(8)-C(9)	1.560	1.567
C(3)-C(5)	1.477	--- ^a	C(8)-C(14)	1.559	1.561
C(4)-C(5)	1.496	--- ^a	C(9)-C(10)	1.574	1.543
C(5)-C(6)	1.573	1.549	C(9)-C(11)	1.565	1.578
C(5)-C(10)	1.578	1.579	C(10)-C(19)	1.559	1.558

^acyclopropane bond lengths constrained.

TABLE 36

COMPARISON OF VALENCY ANGLES (°) DERIVED FROM MOLECULAR MECHANICS STUDIES OF 3 α ,5-CYCLO-5 α -ANDROSTAN-6 β -OL-17-ONE AND 6-METHYLENE-3 α ,5-CYCLO-5 α -ANDROSTANE.

	<u>PARENT</u>	<u>METHYLENE</u>		<u>PARENT</u>	<u>METHYLENE</u>
C1-C2-C3	104.0	104.0	C4-C5-C10	124.9	124.9
C1-C10-C5	100.9	100.8	C5-C6-C6'	---	120.4
C1-C10-C9	111.0	110.7	C5-C6-C7	111.5	117.6
C1-C10-C19	110.3	110.9	C5-C10-C9	113.5	114.6
C2-C1-C10	105.7	105.5	C5-C10-C19	108.3	107.1
C2-C3-C4	118.1	117.7	C6-C5-C10	114.0	111.7
C2-C3-C5	108.6	108.6	C6-C7-C8	111.4	110.2
C3-C4-C5	59.4	--- a	C7-C6-C6'	---	122.0
C3-C5-C4	59.0	--- a	C7-C8-C9	111.3	111.0
C3-C5-C6	118.7	117.0	C7-C8-C14	113.0	112.6
C3-C5-C10	108.4	108.3	C8-C9-C10	115.0	115.0
C4-C3-C5	61.6	--- a	C8-C9-C11	111.4	111.4
C4-C5-C6	118.3	121.7	C10-C9-C11	115.8	116.0

^aCyclopropane ring constrained

TABLE 37

COMPARISON OF RING TORSION ANGLES (°) DERIVED FROM MOLECULAR MECHANICS STUDIES OF 3 α ,5-CYCLO-5 α -ANDROSTAN-6 β -OL-17-ONE AND 6-METHYLENE-3 α ,5-CYCLO-5 α -ANDROSTAN-17-ONE.

<u>RING A</u>	<u>PARENT</u>	<u>METHYLENE</u>
C(1)-C(2)-C(3)-C(4)	52.6	52.7
C(1)-C(2)-C(3)-C(5)	-14.5	-14.4
C(2)-C(3)-C(4)-C(5)	-97.0	-97.5
C(2)-C(3)-C(5)-C(10)	-7.6	-8.3
C(3)-C(4)-C(5)-C(10)	91.8	91.5
C(3)-C(5)-C(10)-C(1)	26.2	27.1
C(4)-C(5)-C(10)-C(1)	-38.5	-37.4
C(5)-C(10)-C(1)-C(2)	-34.9	-35.7
C(10)-C(1)-C(2)-C(3)	31.3	31.7
<u>RING B</u>	<u>PARENT</u>	<u>METHYLENE</u>
C(5)-C(6)-C(7)-C(8)	58.3	55.8
C(6)-C(7)-C(8)-C(9)	-57.6	-55.4
C(6')-C(6)-C(5)-C(10)	---	132.5
C(6')-C(6)-C(7)-C(8)	---	-123.3
C(7)-C(8)-C(9)-C(10)	49.7	51.0
C(8)-C(9)-C(10)-C(5)	-42.0	-42.9
C(9)-C(10)-C(5)-C(6)	42.1	38.4
C(10)-C(5)-C(6)-C(7)	-50.5	-46.7

The introduction of the methylene group, as the above tables show, had little effect on the geometry of the A ring. The change in geometry in the B ring, as would be

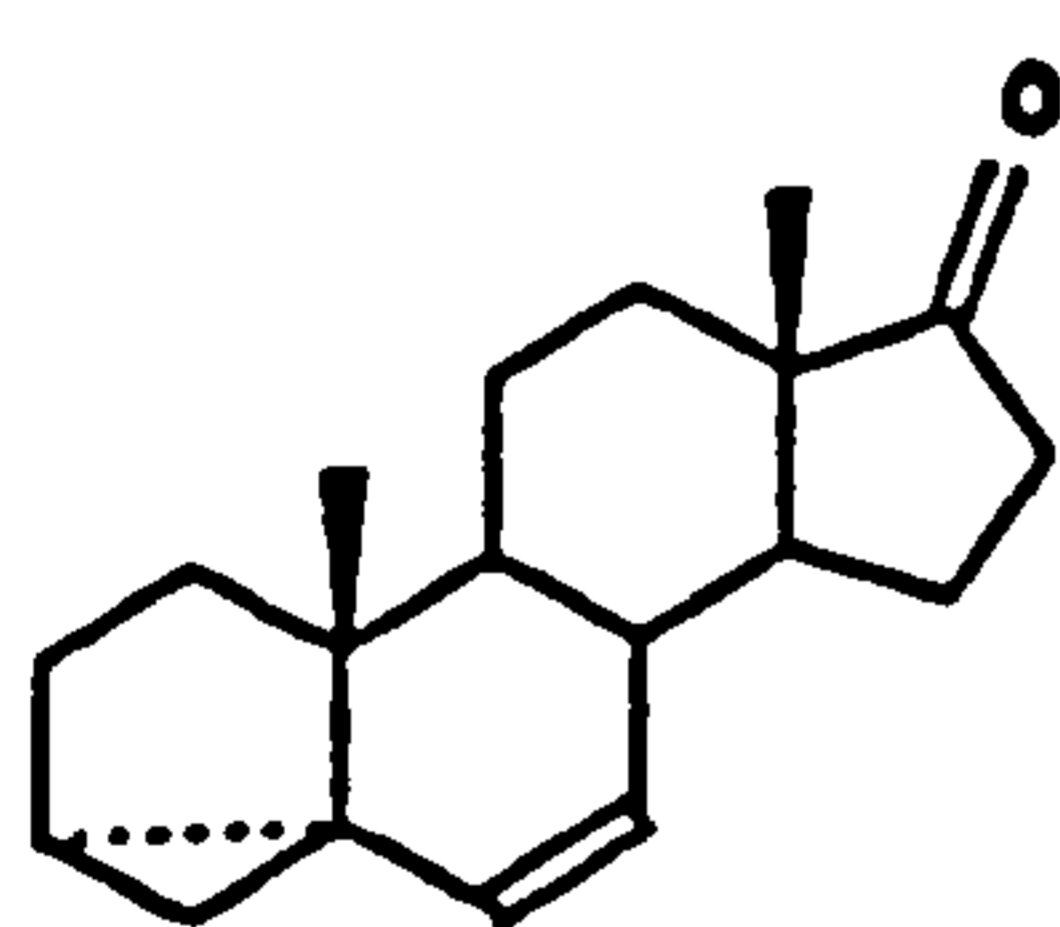
expected, is more pronounced. As well as the obvious shortening of the C(5)-C(6) and C(6)-C(7) bonds, the torsion angles change to allow the B ring to adopt a chair conformation. This results in the methylene hydrogens, which appear virtually in the plane of the steroid framework in a Drieding model, moving out of the plane and away from the cyclopropane hydrogens. So much so that the methylene hydrogens become the most β -orientated hydrogens in the structure with the exception of the methyl protons (Figure 18). Thus the torsion angle C(4)-C(5)-C(6)-C(6') [X-C(5)-C(6)-C(6')] was adjusted to -42° [-72°] (250).

This movement was shown to be as a result of the interaction between the two protons in question by repeating the minimisation and observing each step in the minimisation process. Thus, for each step the methylene group was pushed further out of the plane of the B ring and the overall energy of the steroid was reduced by approximately 30%.

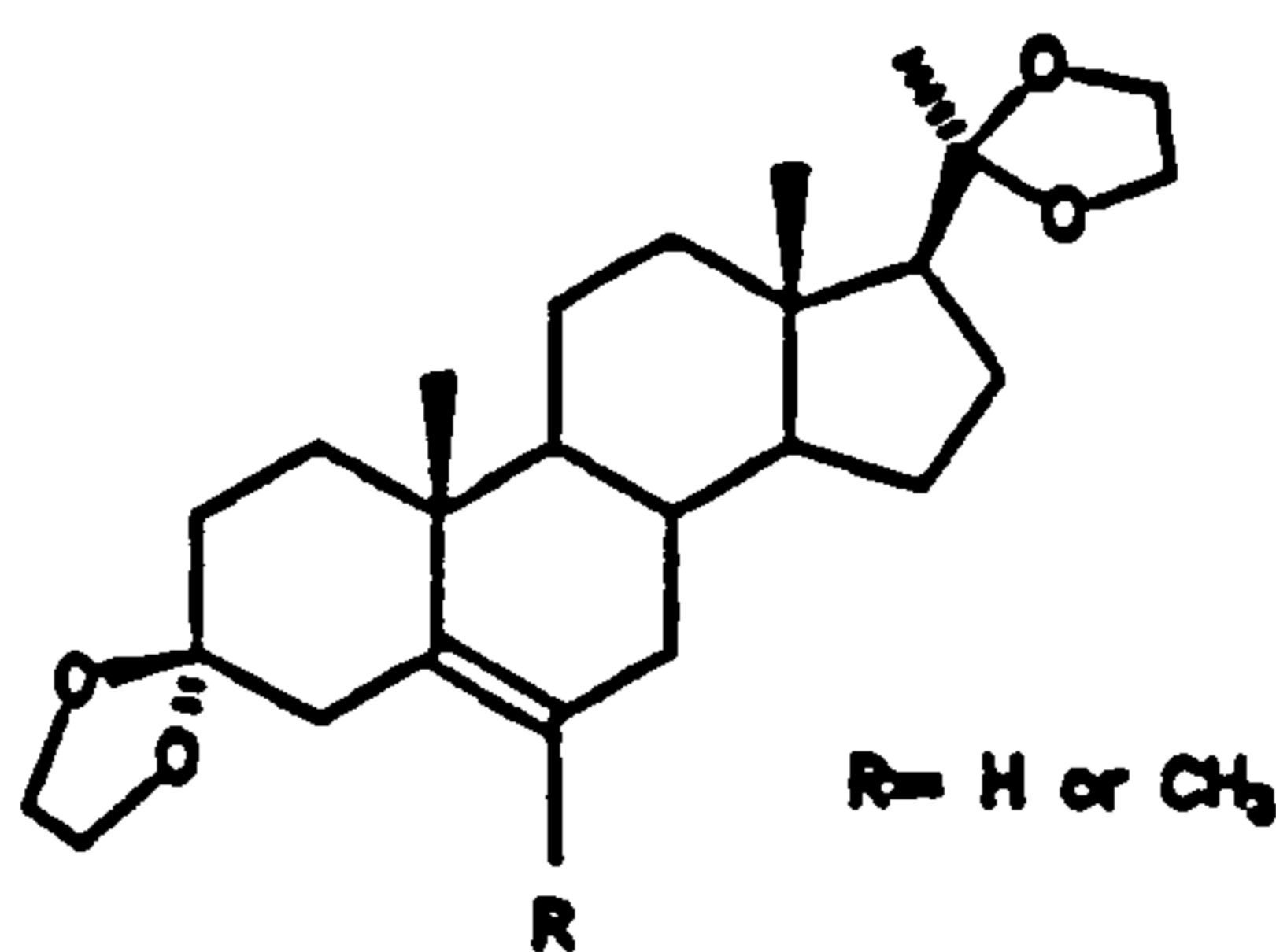
However, the modelling system, as already discussed, cannot perform calculations for cyclopropane carbons. The above result is therefore based purely on steric considerations, i.e., the conjugation present between the cyclopropane ring and the exocyclic methylene group has not been taken into account. As the minimised model stands (torsion angle X-C(5)-C(6)-C(6') = 72°) very little conjugation will be present. The true structure would be between the original model and its minimised alternative because of the stabilising effect from an increased level of conjugation.

6.3.4 3 α ,5-Cyclo-5 α -androst-6-en-17-one (185).

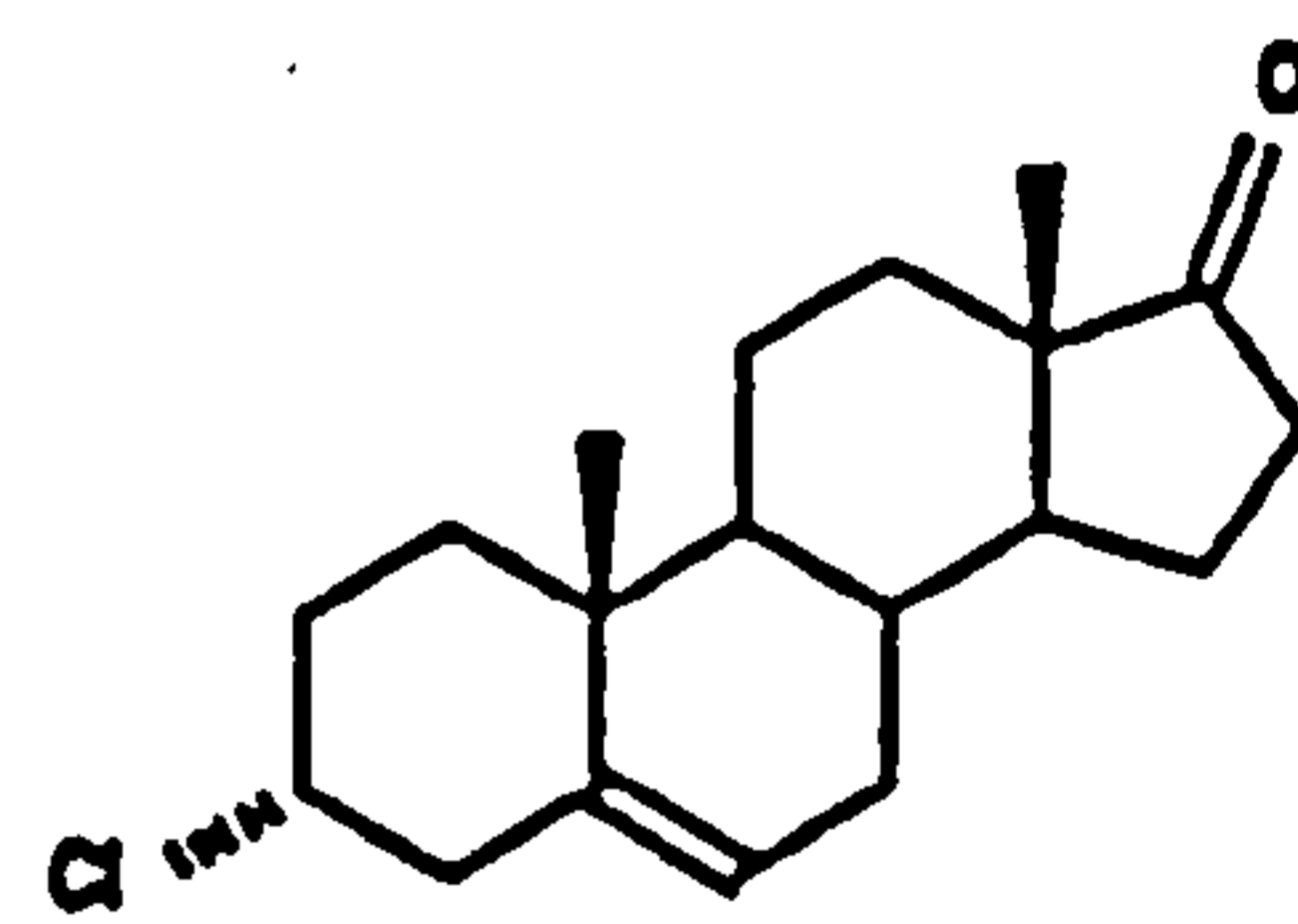
A molecular model of the title compound (185) was constructed along with the models of steroids (217) and (218) in order to estimate and compare the amounts of steric hindrance around the double bond of each steroid. Although the comparison is between delta-5 steroids and the delta-6 steroid (185) it would still appear (Figs 19-24) that the delta-6 double bond in (185) is as hindered from the α -phase as that of the chloro compound (217) but perhaps slightly less hindered than the dioxolane (218). From the "end-on view" the more complete blocking of the A ring in (185) is evident. Both views of (185) (Fig 19 and 20) show that the A ring provides considerably more hindrance than the 19-methyl group. Therefore as steroids (217) and (218) both yield the β -epoxide on reaction with *m*-chloroperbenzoic acid,^{13,14} the models here would indicate that the steroid (185) does likewise or possibly forms an epimeric mixture. It is false to assume that under epoxidation conditions the α -isomer is formed exclusively.¹⁵



(185)



(217)



(218)

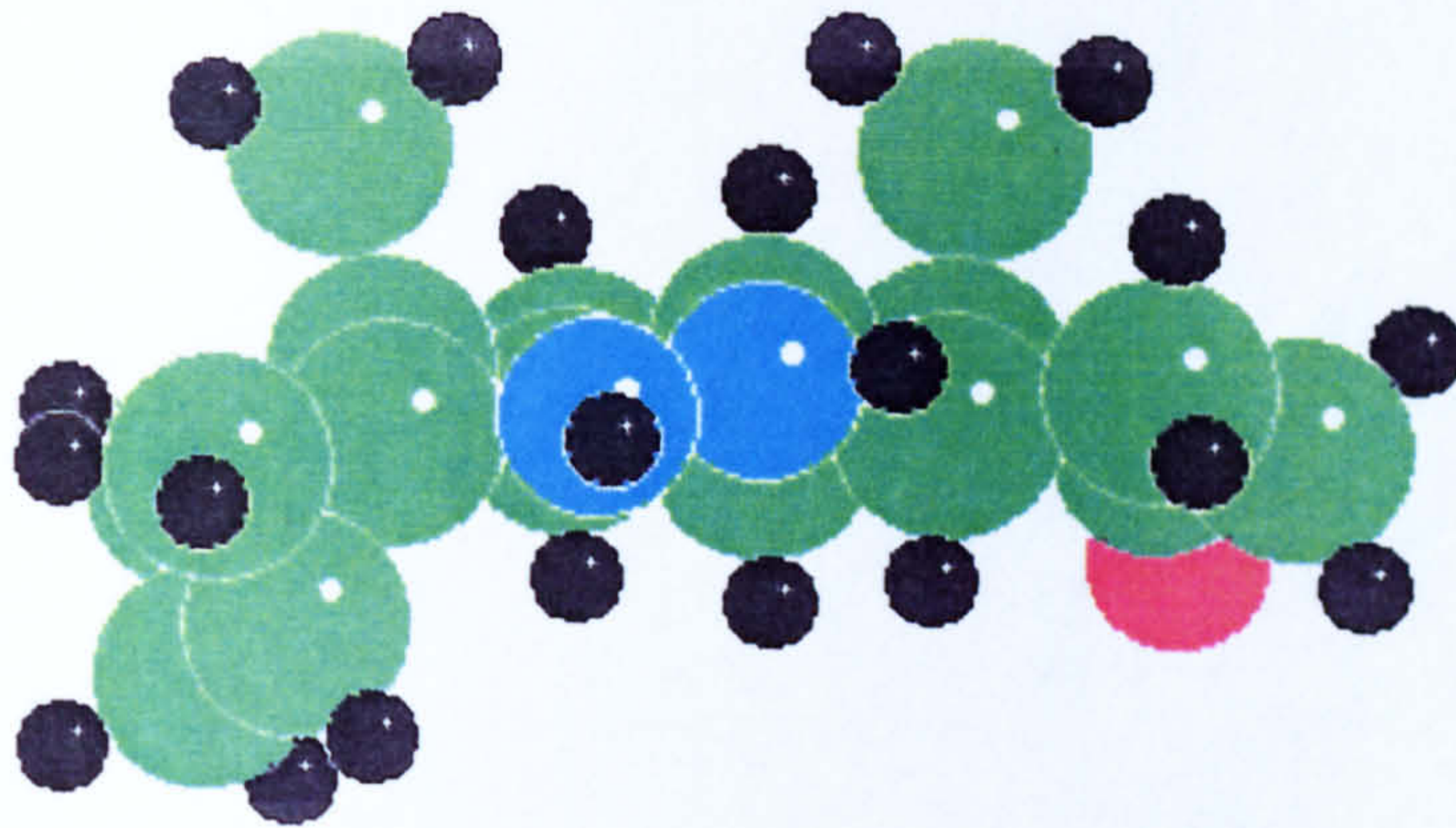


FIGURE 19
 "Lengthways" perspective (methyl groups to rear) of 3 α ,5-cyclo-5 α -androst-6-en-17-one (185)

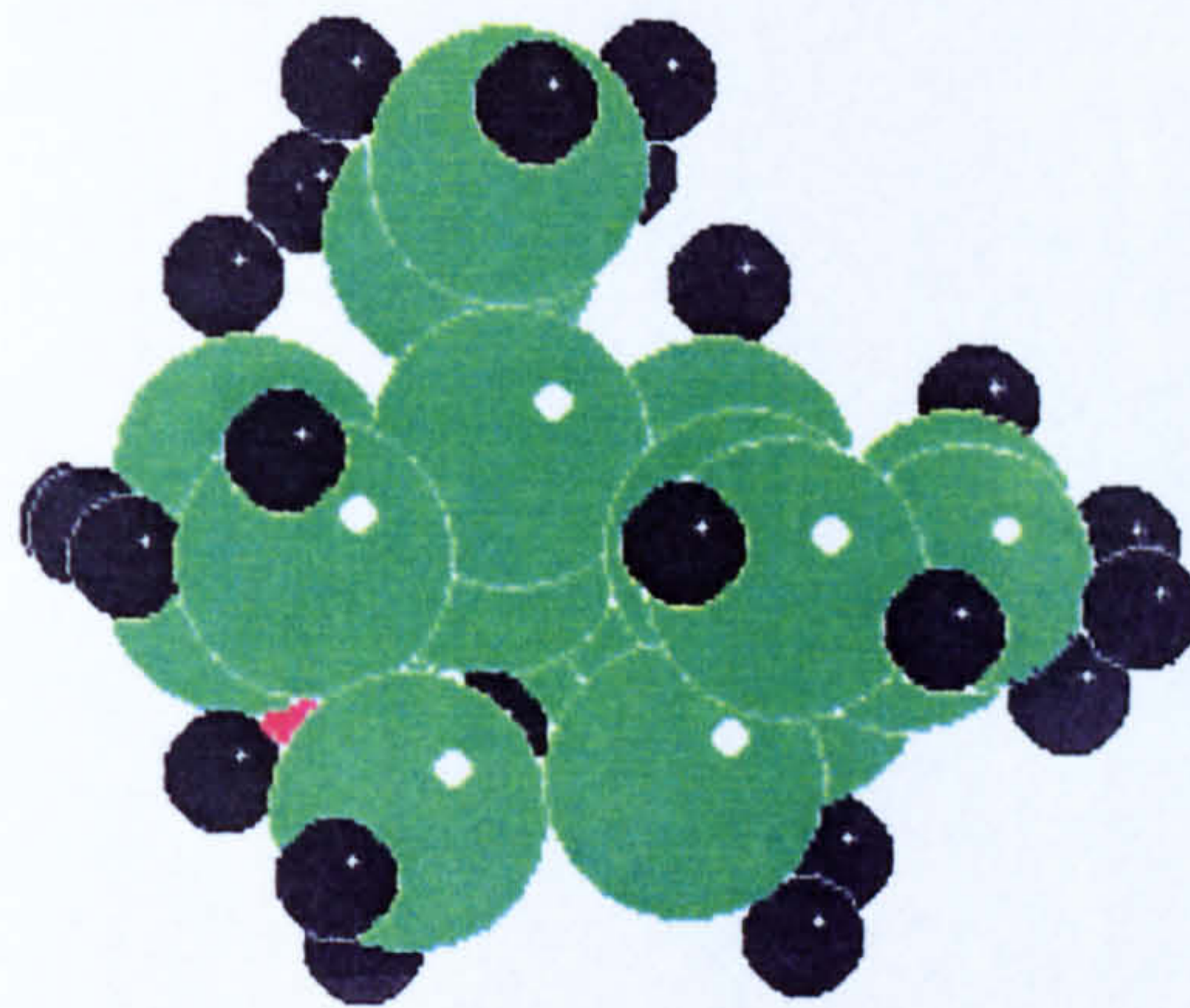


FIGURE 20
 "End on" perspective of 3 α ,5-cyclo-5 α -androst-6-en-17-one (185)

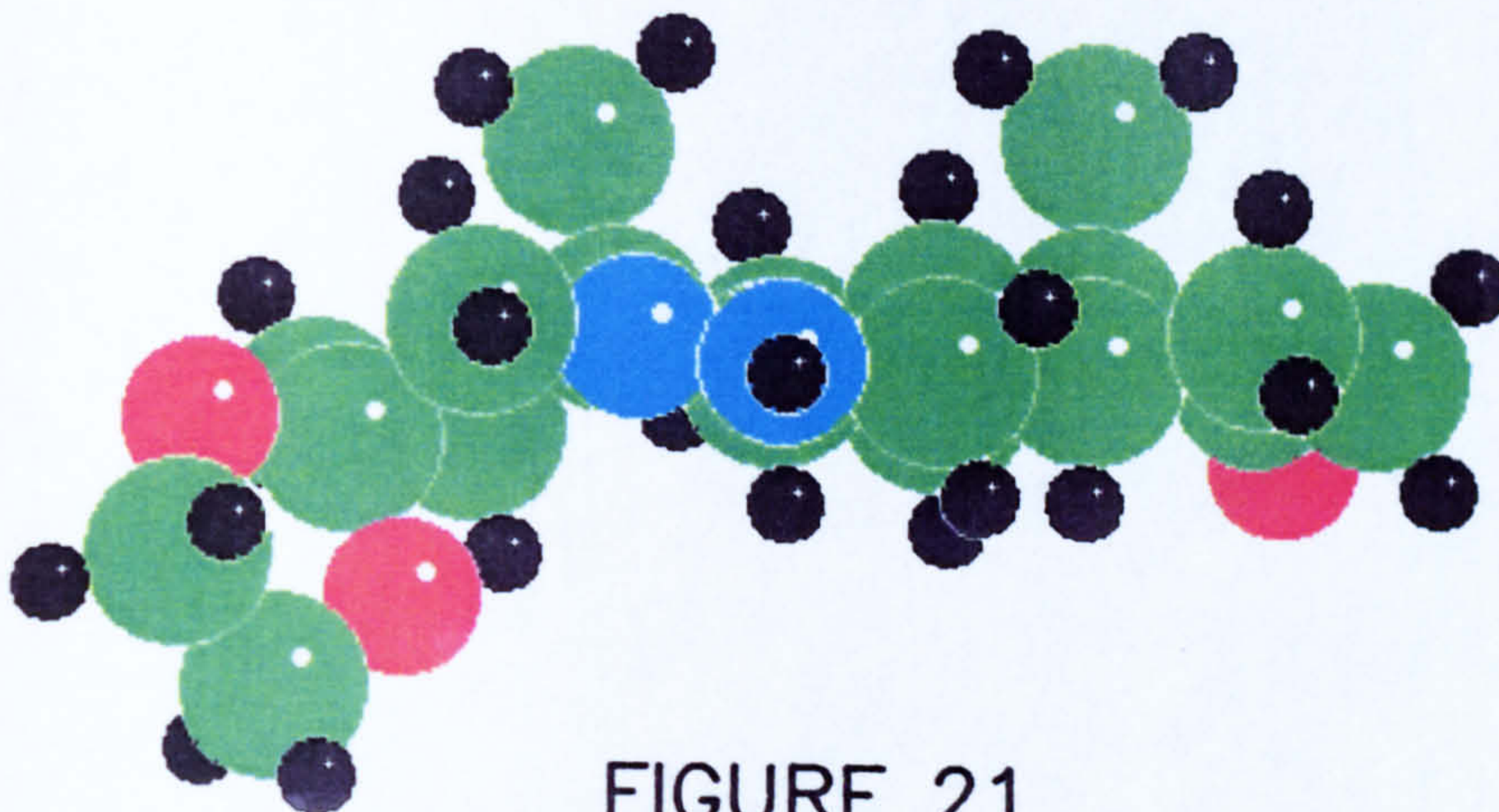


FIGURE 21
 "Lengthways" perspective (methyl groups to rear) of progesterone derivative (217)

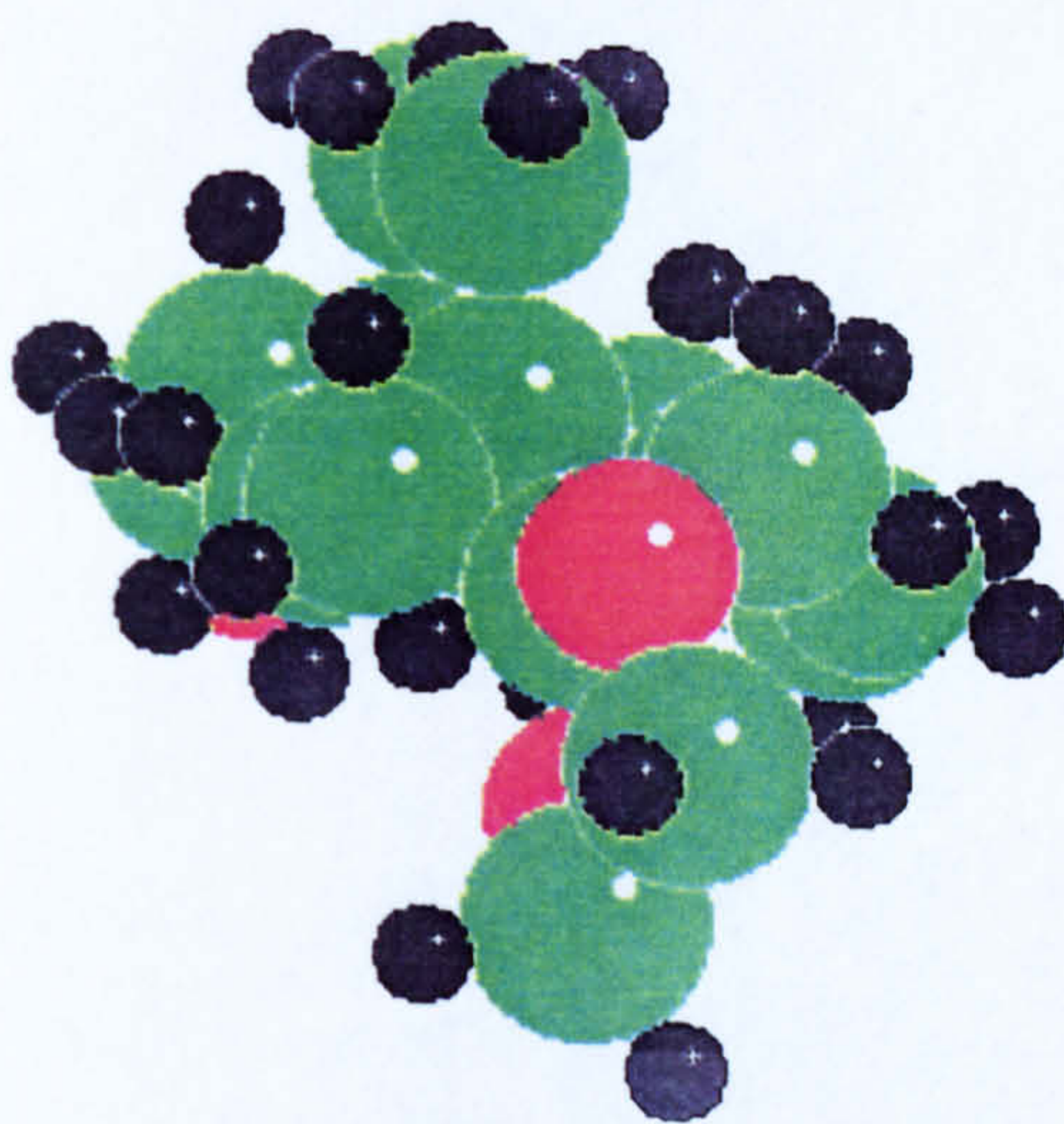


FIGURE 22

"End on" perspective of progesterone derivative (217)

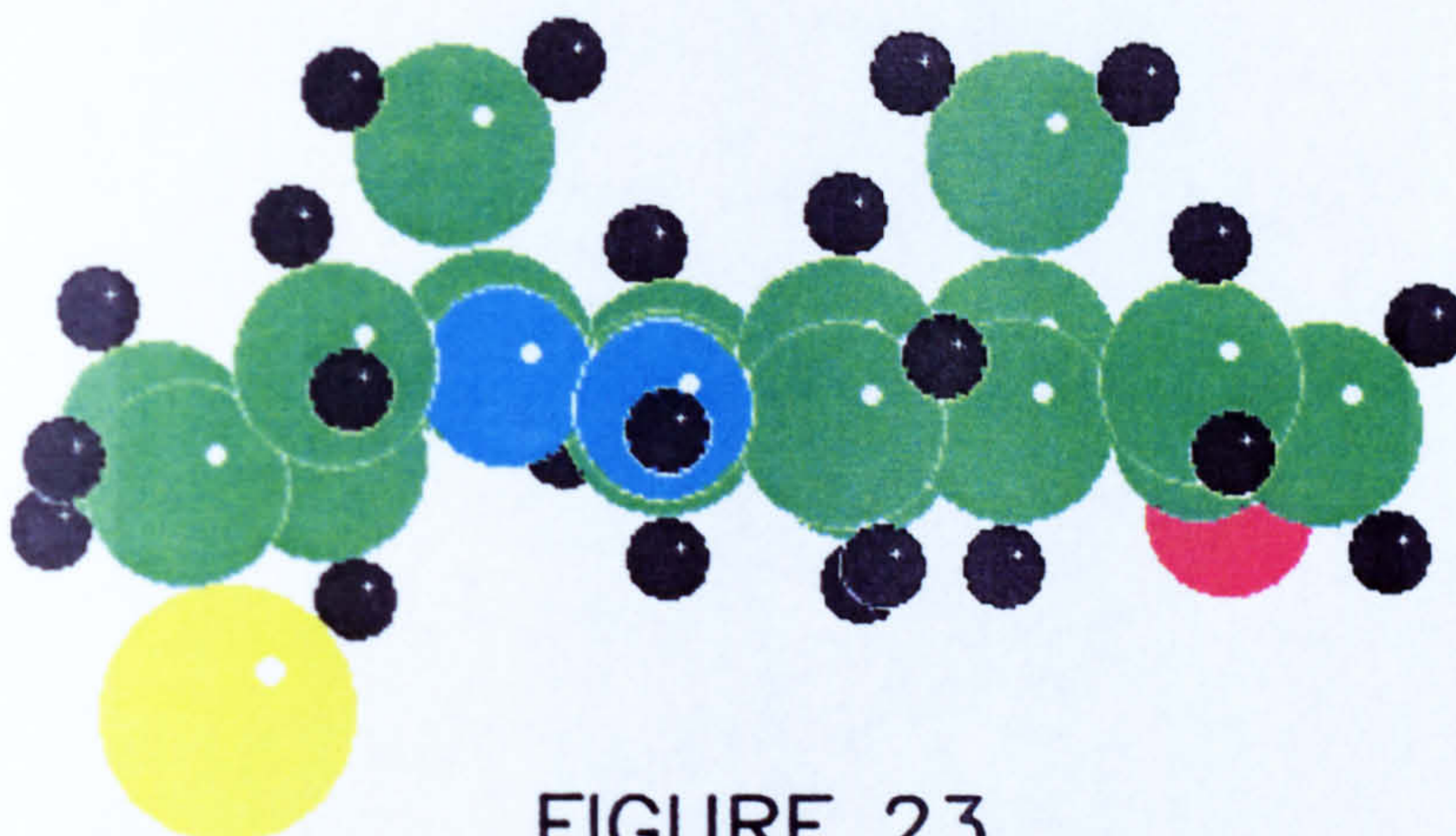


FIGURE 23

"Lengthways" perspective (methyl groups to rear) of dehydroepiandrosterone derivative (218)

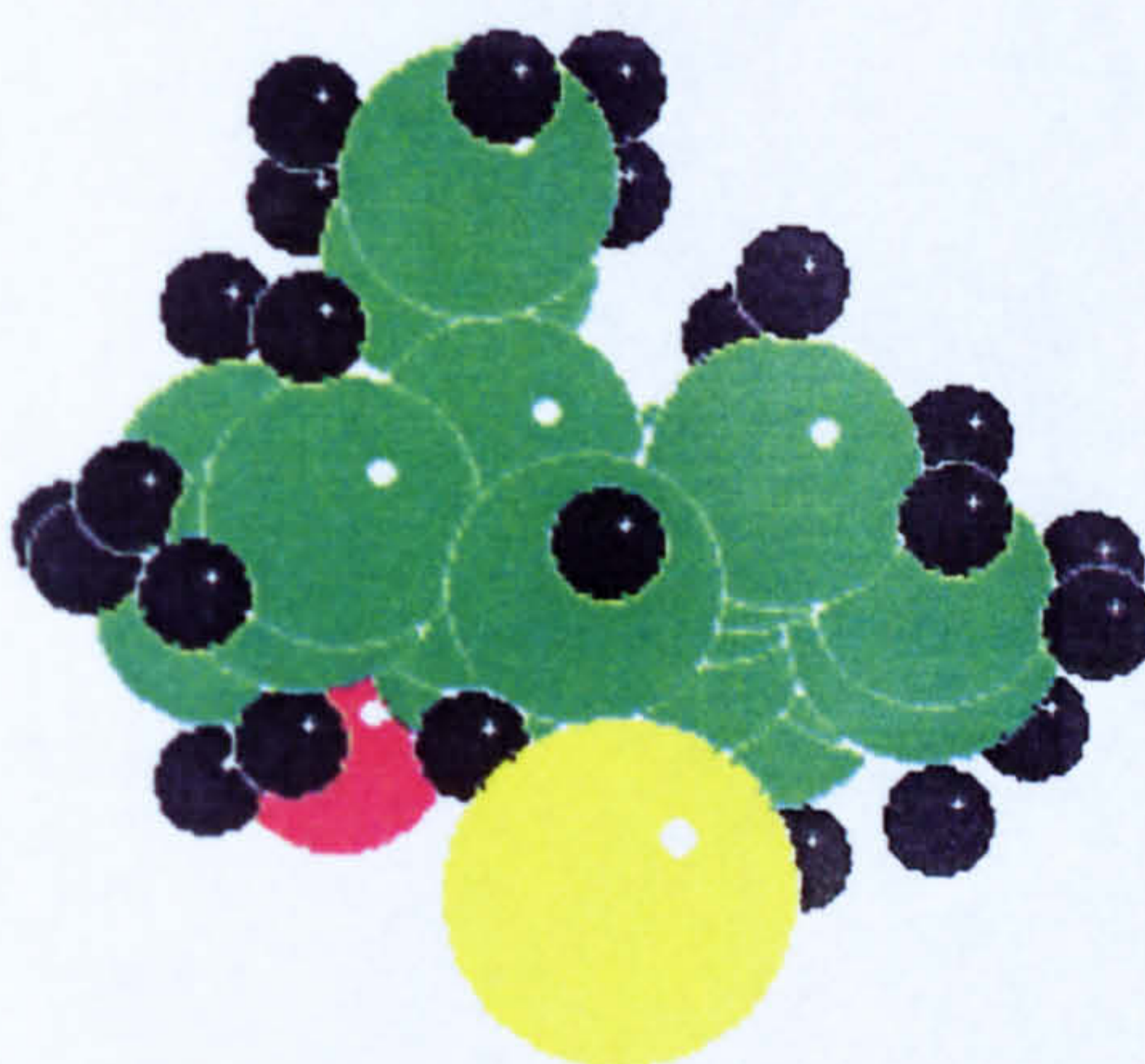


FIGURE 24

"End on" perspective of dehydroepiandrosterone derivative (218)

6.3.5 6,7-Epoxy-3 α ,5-cyclo-5 α -androstan-17-one (209).

The modelling of the 6,7 epoxide (209) was originally undertaken to help predict the likely outcome of the reaction between it and dimethyl lithium cuprate (Chapter 4). Thus, nucleophilic ring opening is initiated by attack on the least hindered carbon (assuming no electronic effects induced by the cyclopropane ring) which could potentially be identified from the model. However, from the model of the 6 α ,7 α epoxide (209a) it became clear that the predicted ^1H NMR signals from the epoxidilic hydrogens did not match the data recorded by Hanson et al.¹⁵ As experimental and theoretical results indicated an isomeric mixture of epoxides the β -epoxide was also constructed (209b) and the two structures (Figures 25 and 26) compared. Table 38 shows the calculated torsion angles for both isomers.

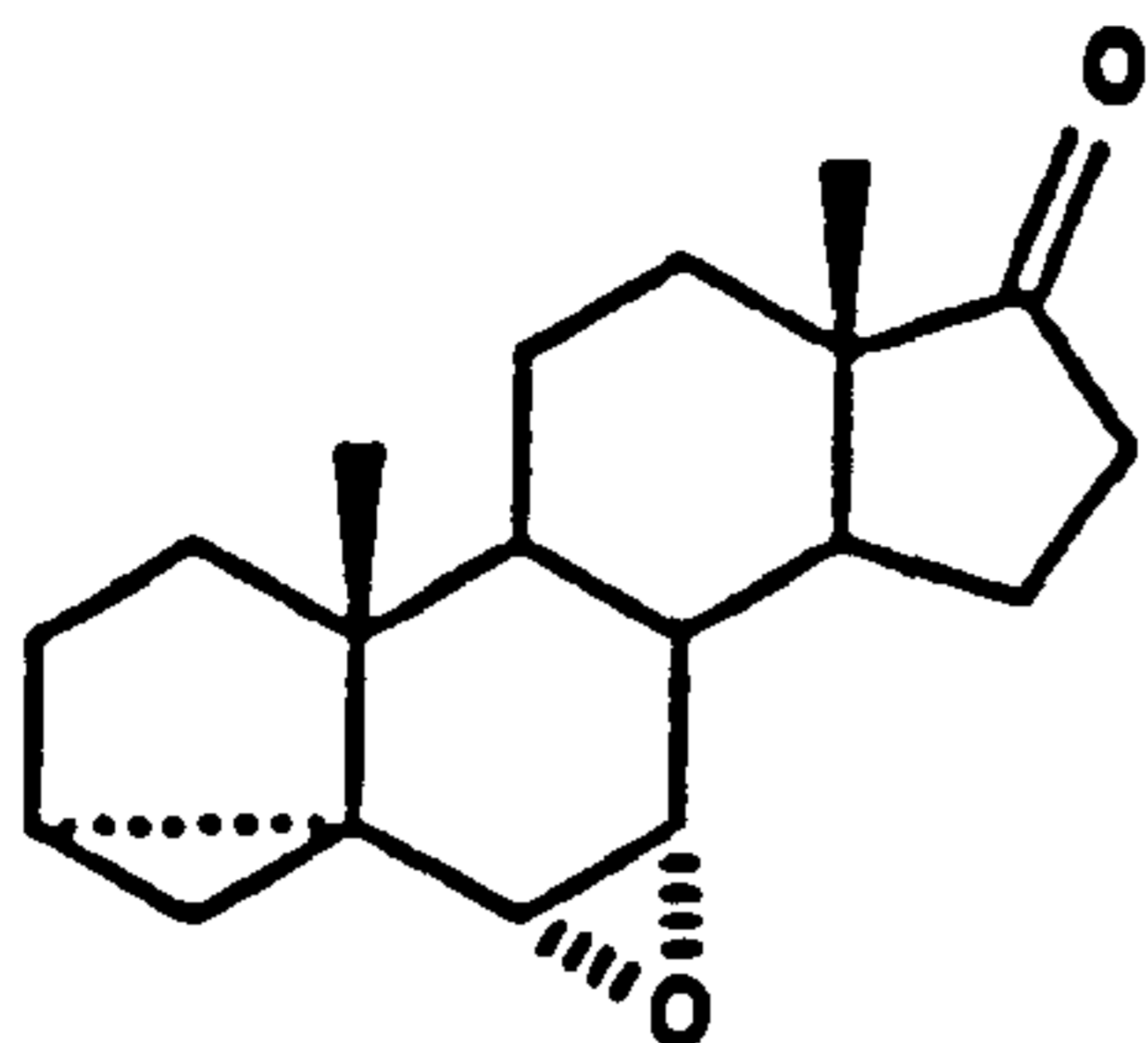
TABLE 38

COMPARISON OF THE DIHEDRAL ANGLES ($^\circ$) BETWEEN THE EPOXIDILIC PROTONS, AND BETWEEN THE EPOXIDILIC PROTONS AND H-8 FOR THE α AND β -EPOXIDE ISOMERS (209a) AND (209b).

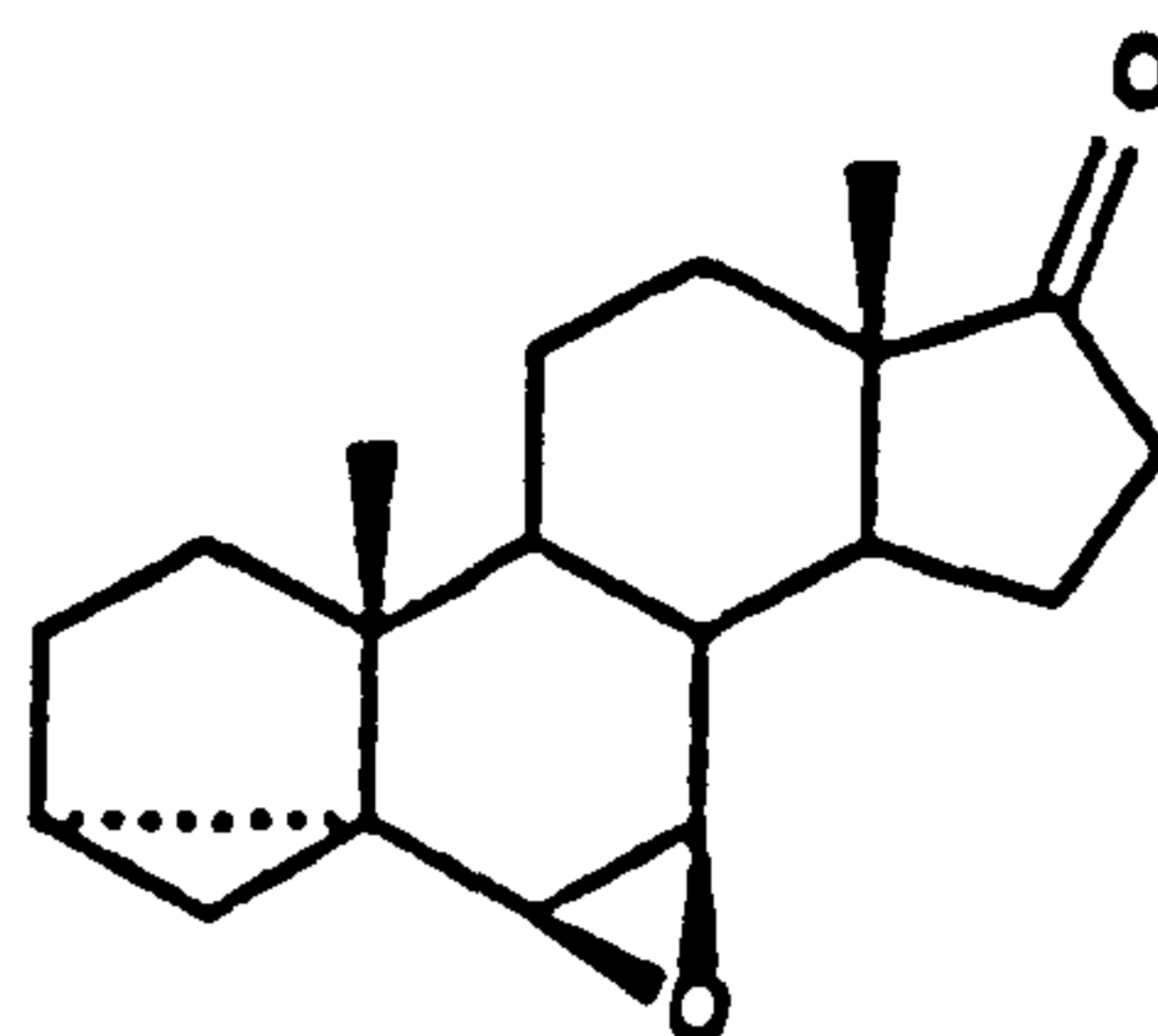
<u>Steroid isomer</u>	<u>H6-C6-C7-H7</u>	<u>H7-C7-C8-H8</u>
6 α ,7 α -epoxide	25.3	39.0
6 β ,7 β -epoxide	38.9	141.6

With the Karplus equation¹⁰ these results indicate that in the case of the α -isomer, the C(6) proton's signal would appear as a doublet ($J= 6.7$ Hz) and the C(7) proton as a

double doublet ($J= 6.7$ and 4.9 Hz). Its corresponding isomer should show a doublet for the C(6) proton ($J= 4.9$ Hz) and a double doublet ($J= 4.9$ and 5.6 Hz). These results are compared with those measured experimentally (Chapter 4).



(209a)



(209b)

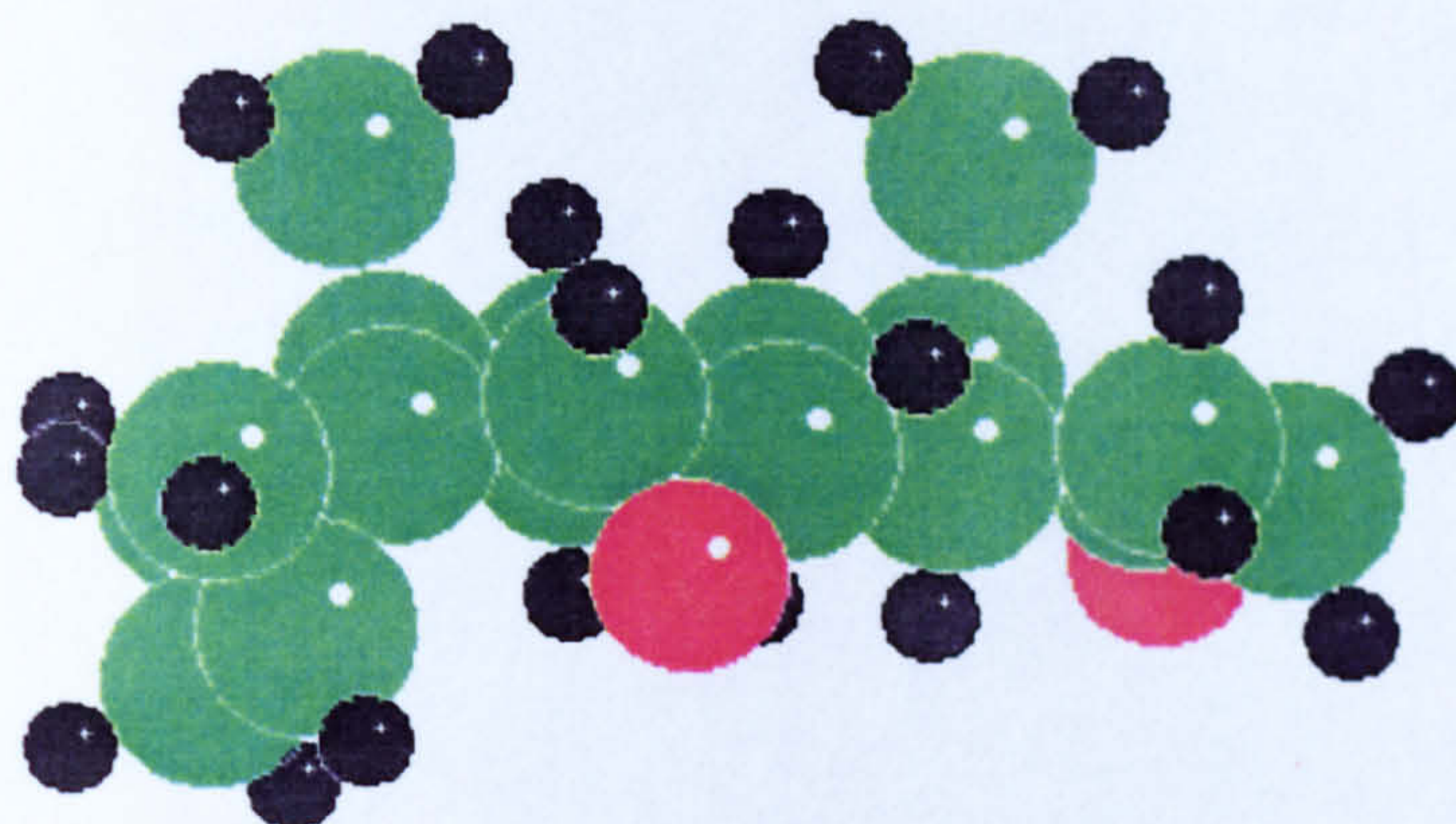


FIGURE 25

"Lengthways" perspective (methyl groups to rear) of 6 α ,7 α -epoxy-3 α ,5-cyclo-5 α -androstan-17-one (209a)

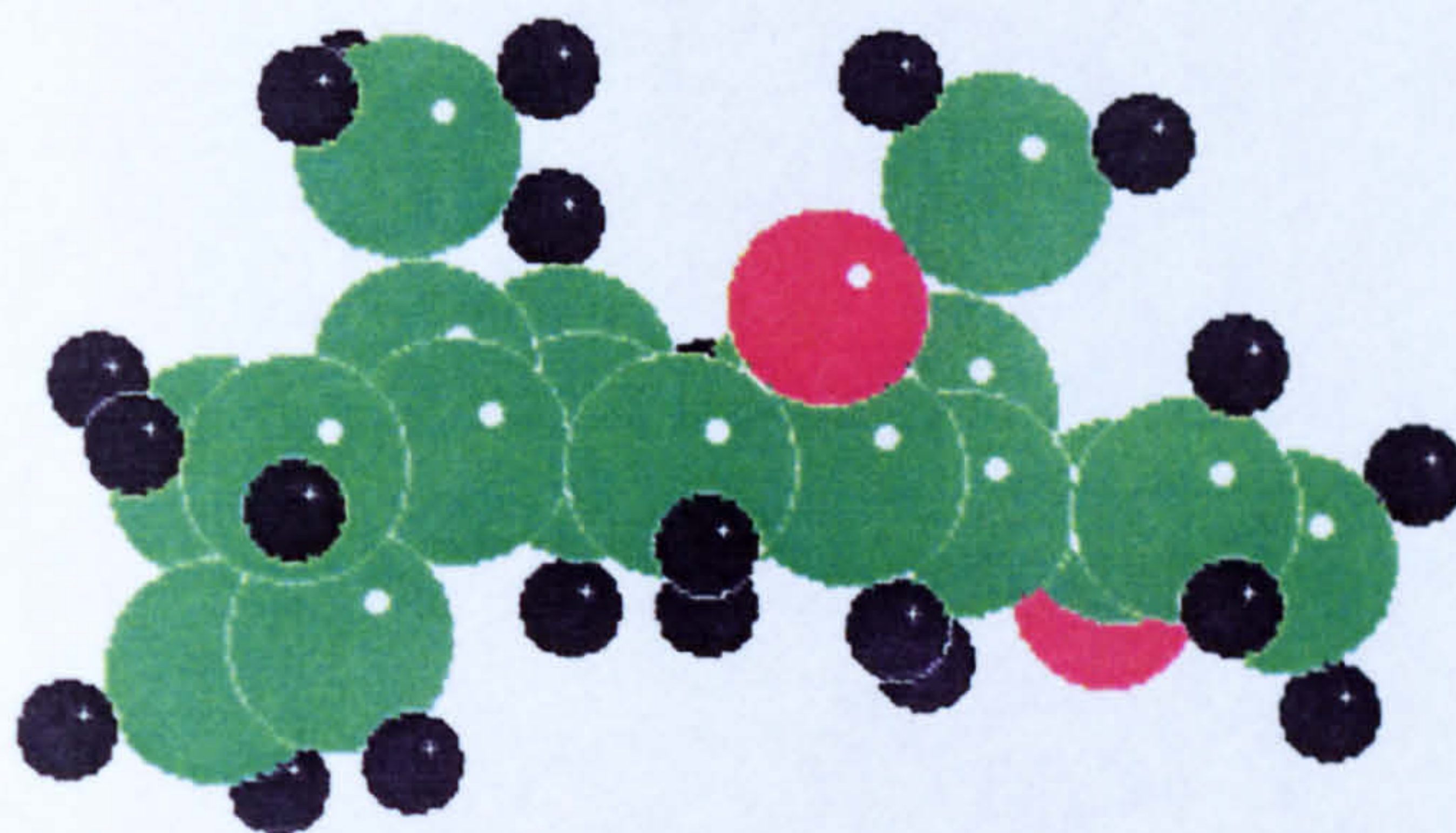
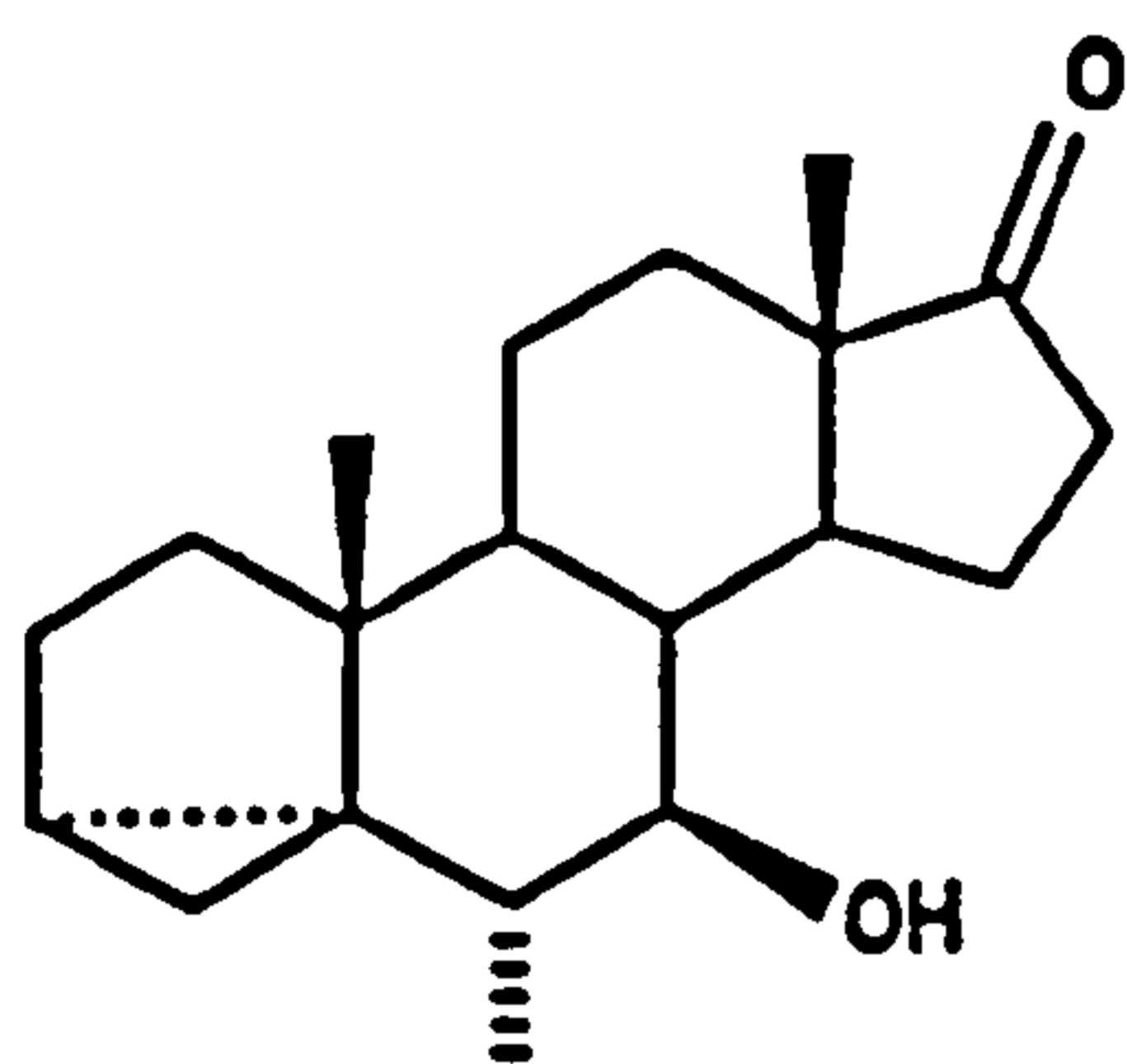


FIGURE 26

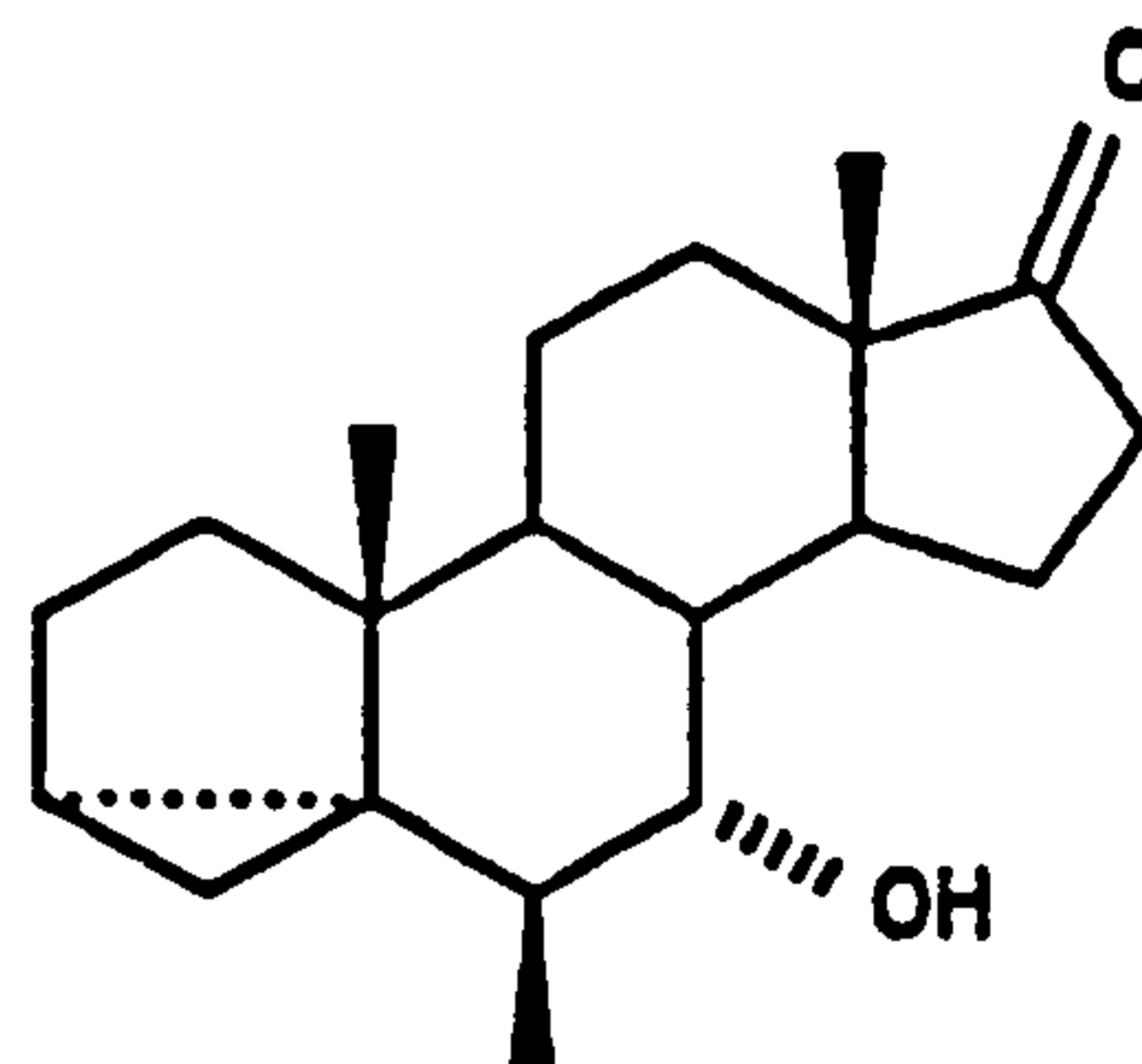
"Lengthways" perspective (methyl groups to rear) of 6 β ,7 β -epoxy-3 α ,5-cyclo-5 α -androstan-17-one (209b)

6.3.6 The four possible isomeric products of reaction between the two 6,7-epoxy-3 α ,5-cyclo-5 α -androstan-17-one isomers (209a and 209b) and dimethylolithium cuprate.

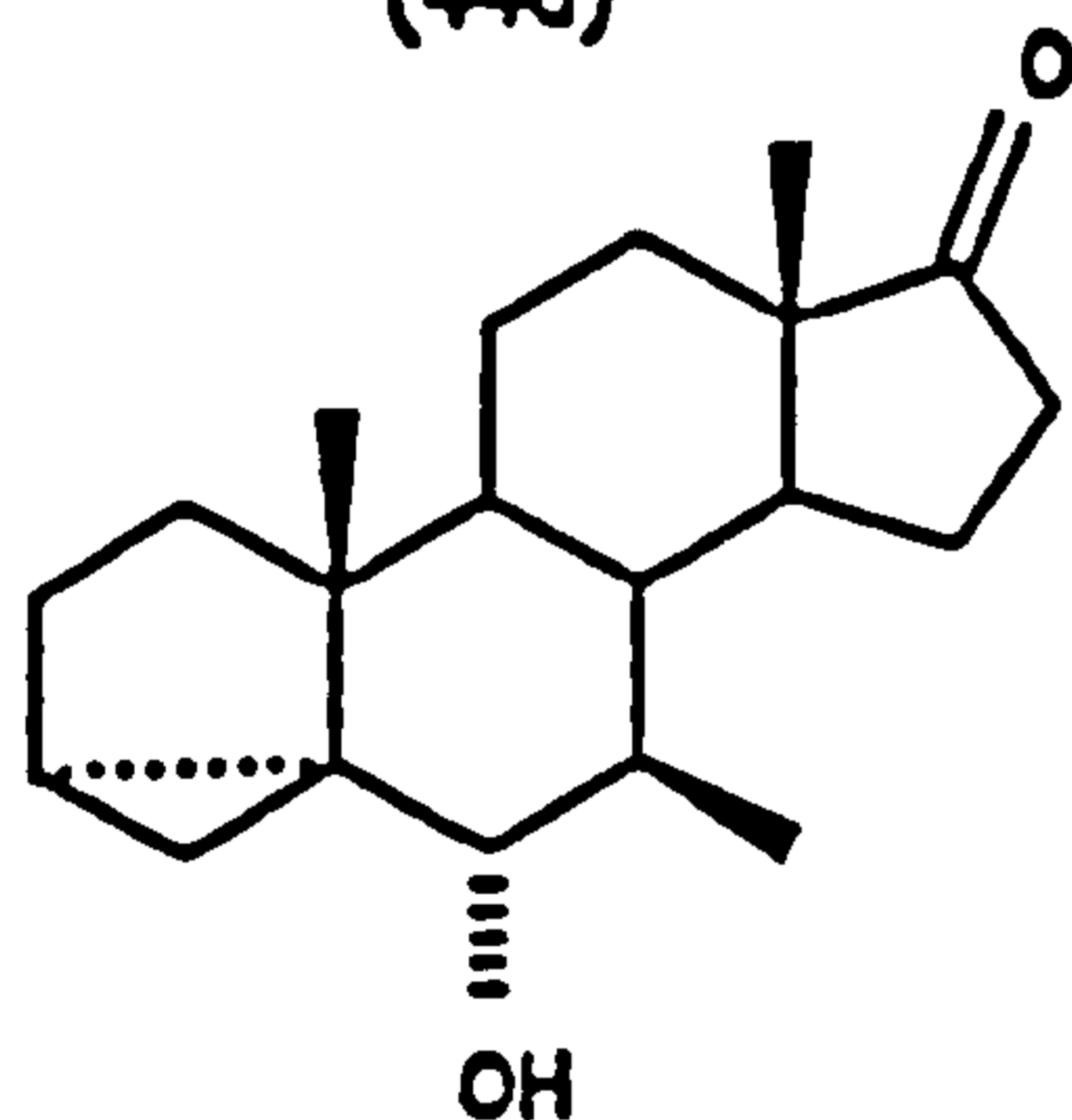
As discussed in section 6.2.5, in any S_N2 nucleophilic reaction, attack of an epoxide by dimethylolithium cuprate occurs at the less hindered carbon atom (1° > 2° > 3°). As in this particular example both carbons are secondary carbons, steric hindrance induced by another part of the molecule will determine the outcome of the reaction, especially where the reagent contains a bulky metal atom, e.g., copper. However, for this steroid participation of the cyclopropane



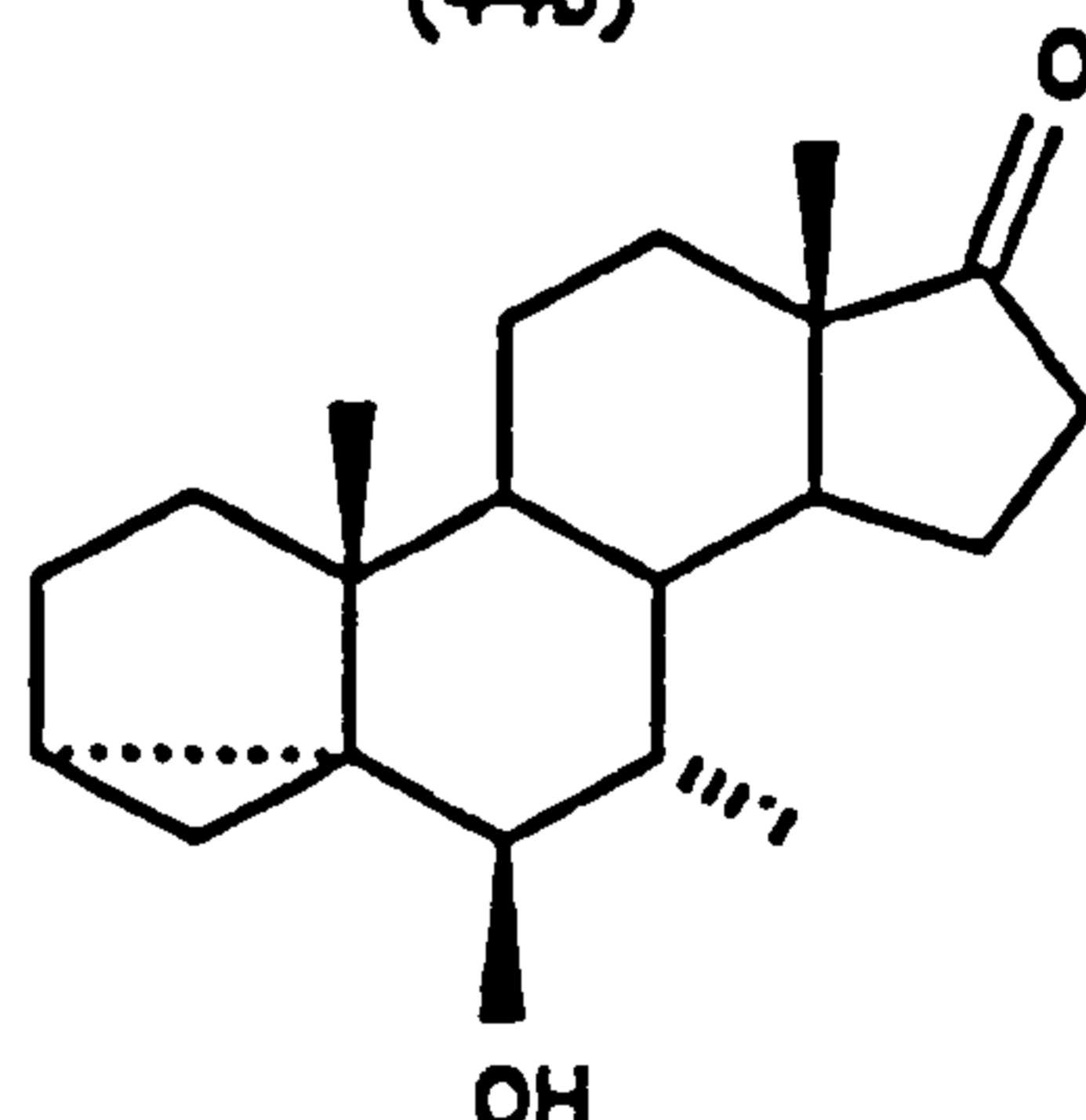
(44a)



(44b)



(190a)



(190b)

ring must also be considered. To aid identification of the possible products, 6 α (β)-methyl-3 α ,5-cyclo-5 α -androstan-7 α (β)-ol-17-one (44a, (44b)) or 7 α (β)-methyl-3 α ,5-cyclo-5 α -androstan-6 α (β)-ol-17-one (190a, (190b)), molecular models were constructed to investigate their geometrical differ-



FIGURE 27

"Lengthways" perspective of 7β -hydroxy- 6γ -methyl- $3\alpha,5$ -cyclo- 5α -androstan-17-one (44a)

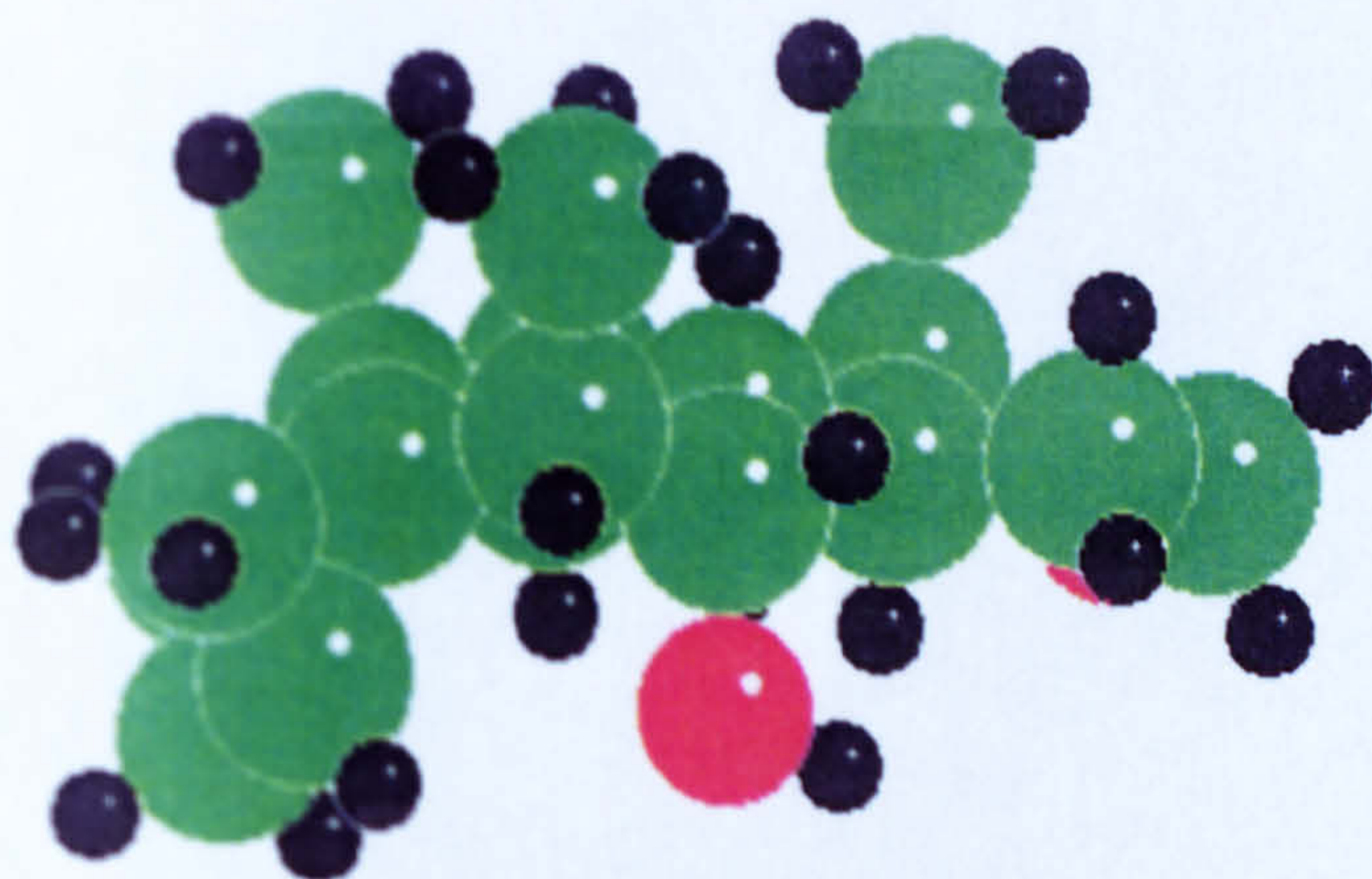


FIGURE 28

"Lengthways" perspective of 7α -hydroxy- 6β -methyl- $3\alpha,5$ -cyclo- 5α -androstan-17-one (44b)

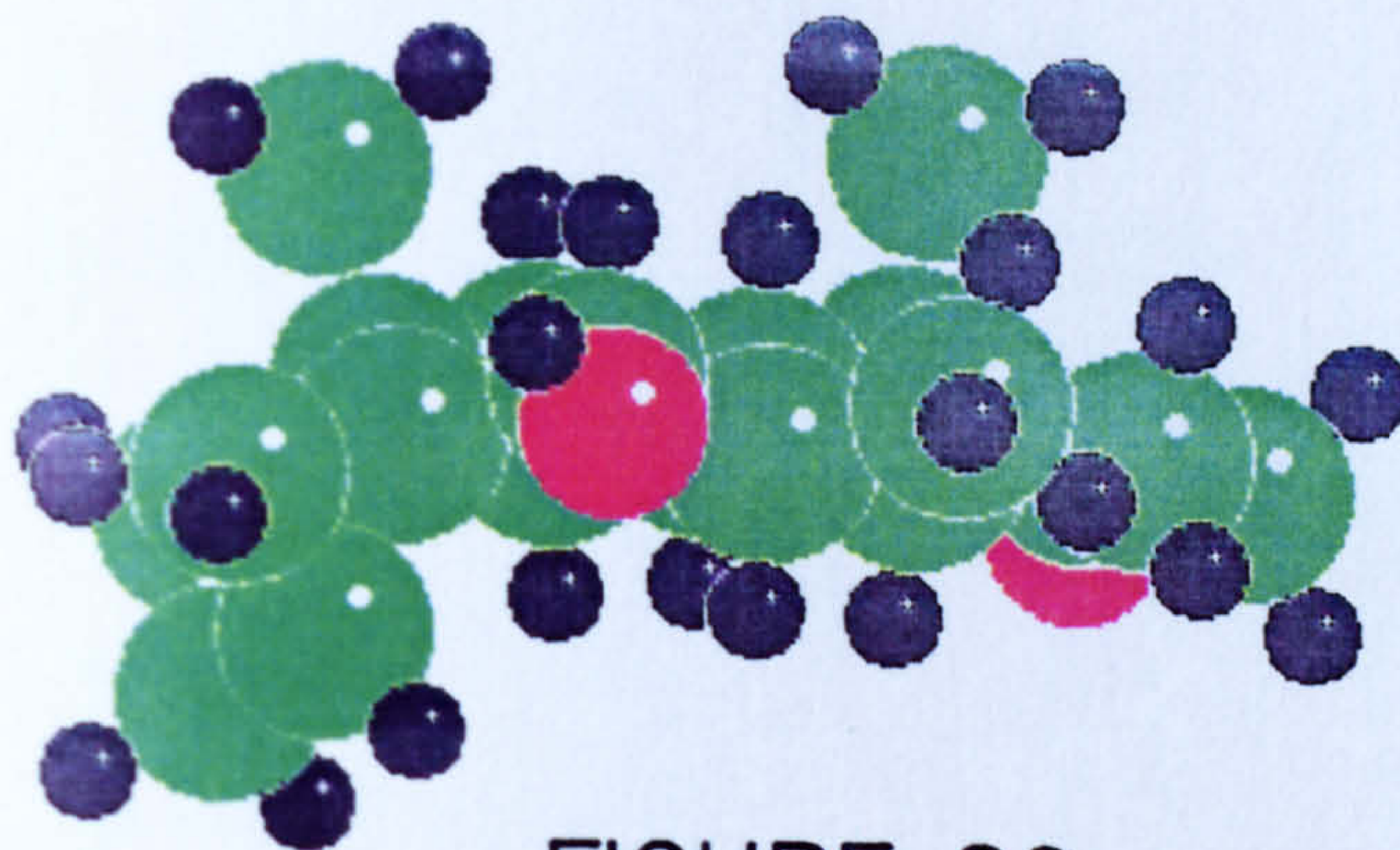


FIGURE 29

"Lengthways" perspective of 6α -hydroxy- 7β -methyl- $3\alpha,5$ -cyclo- 5α -androstan-17-one (190a)

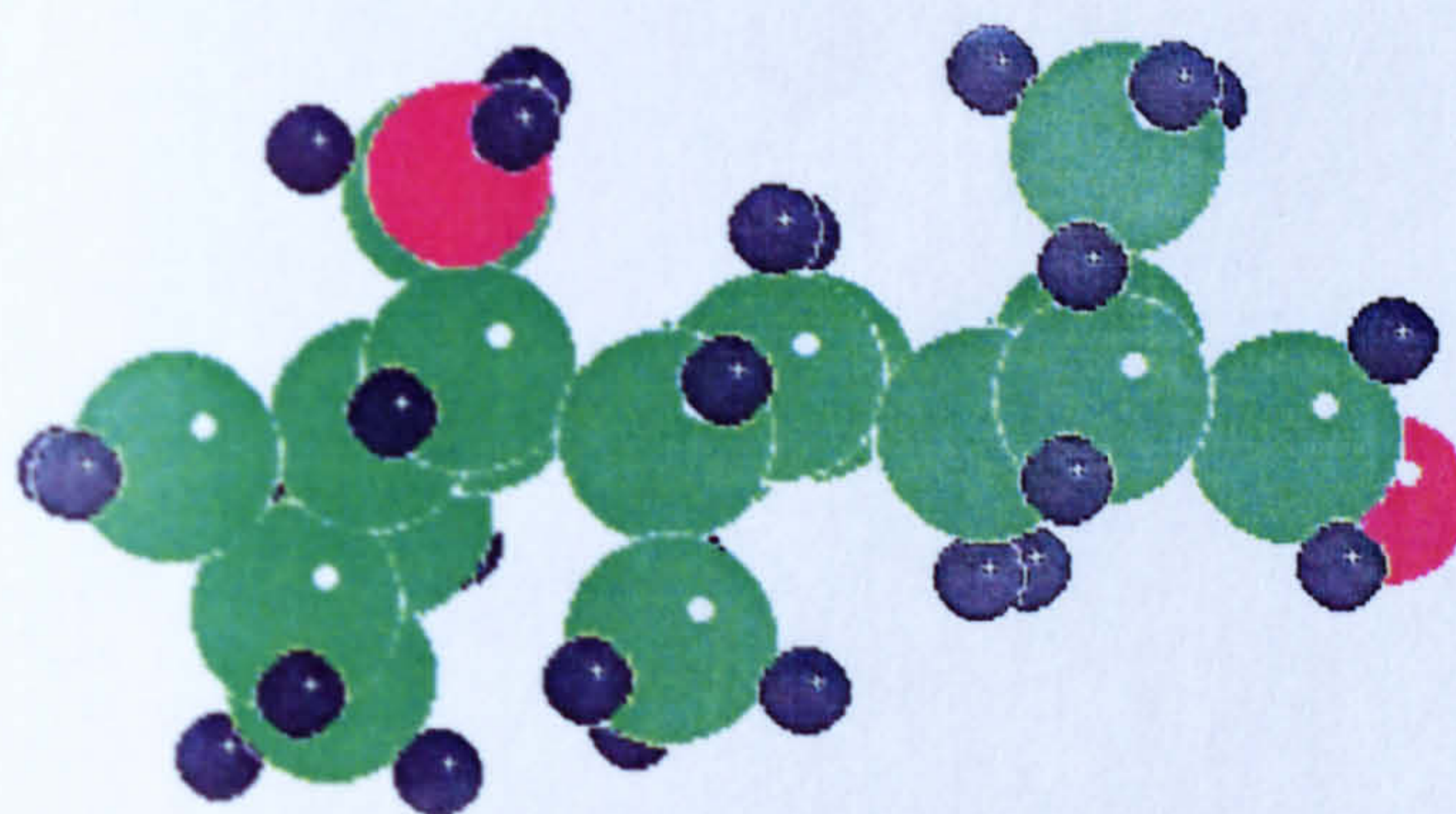


FIGURE 30

"Lengthways" perspective of 6β -hydroxy- 7α -methyl- $3\alpha,5$ -cyclo- 5α -androstan-17-one (190b)

ences. Tables 39, 40 and 41 compares rings A and B of the four compounds with the parent cyclosteroid (41). Figures 27-30 show the four isomers and the orientation of their substituents.

TABLE 39

COMPARISON OF BOND LENGTHS (Å) DERIVED FROM MOLECULAR MECHANICS OF COMPOUNDS (44a), (44b), (190a) AND (190b) WITH 6β-HYDROXY-3α,5-CYCLO-5α-ANDROSTAN-17-ONE (41).

<u>Bond</u>	<u>Parent</u>	<u>(44a)</u>	<u>(44b)</u>	<u>(190a)</u>	<u>(190b)</u>
C(1)-C(2)	1.548	1.546	1.564	1.548	1.548
C(1)-C(10)	1.564	1.546	1.564	1.565	1.563
C(2)-C(3)	1.545	1.544	1.544	1.544	1.544
C(3)-C(4)	1.471 ^a	--- a	--- a	--- a	--- a
C(3)-C(5)	1.477 ^a	--- a	--- a	--- a	--- a
C(4)-C(5)	1.496 ^a	--- a	--- a	--- a	--- a
C(5)-C(6)	1.573	1.576	1.577	1.572	1.572
C(5)-C(10)	1.578	1.581	1.580	1.573	1.579
C(6)-C(7)	1.550	1.557	1.555	1.561	1.558
C(7)-C(8)	1.553	1.560	1.559	1.569	1.561
C(8)-C(9)	1.560	1.568	1.566	1.574	1.567
C(9)-C(10)	1.574	1.575	1.576	1.576	1.576

^acyclopropane ring constrained.

TABLE 40

COMPARISON OF VALENCY ANGLES (°) DERIVED FROM MOLECULAR MECHANICS OF COMPOUNDS (44a), (44b), (190a) AND (190b) WITH 6 β -HYDROXY-3 α ,5-CYCLO-5 α ANDROSTAN-17-ONE (41).

<u>Bond angle</u>	<u>(41)</u>	<u>(44a)</u>	<u>(44b)</u>	<u>(190a)</u>	<u>(190b)</u>
C1-C2-C3	104.0	103.7	103.6	108.6	104.1
C1-C10-C5	100.9	101.3	100.6	100.3	100.6
C1-C10-C9	111.0	110.8	111.1	111.5	111.1
C2-C1-C10	105.7	105.6	106.0	105.8	105.8
C2-C3-C4	118.1	117.8	118.0	116.2	118.1
C2-C3-C5	108.6	109.3	109.0	108.8	108.3
C3-C4-C5	59.4	--- ^a	--- ^a	--- ^a	--- ^a
C3-C5-C4	59.0	--- ^a	--- ^a	--- ^a	--- ^a
C3-C5-C6	118.7	119.5	118.1	119.8	119.2
C3-C5-C10	108.4	107.7	108.0	108.1	108.9
C4-C3-C5	61.6	--- ^a	--- ^a	--- ^a	--- ^a
C4-C5-C6	118.3	120.4	118.4	119.6	119.2
C4-C5-C10	124.9	123.4	125.4	125.8	124.7
C5-C6-C7	111.5	113.6	112.4	113.9	112.8
C5-C10-C9	113.5	114.0	113.7	113.5	114.0
C6-C5-C10	114.0	113.5	113.9	112.0	113.1
C6-C7-C8	111.4	111.8	111.0	111.3	109.6
C7-C8-C9	111.3	111.5	112.0	111.8	112.5
C8-C9-C10	115.0	115.4	115.2	117.3	115.0

^aCyclopropane ring constrained.

TABLE 41

COMPARISON OF TORSION ANGLES (°) DERIVED FROM MOLECULAR MECHANICS OF COMPOUNDS (44a), (44b), (190a) AND (190b) WITH 6 β -HYDROXY-3 α ,5-CYCLO-5 α -ANDROSTAN-17-ONE (41).

<u>Ring A</u>	<u>Parent</u>	<u>(44a)</u>	<u>(44b)</u>	<u>(190a)</u>	<u>(190b)</u>
C1-C2-C3-C4	52.6	52.3	53.5	54.6	51.9
C1-C2-C3-C5	-14.5	-15.0	-13.8	-12.4	-15.1
C2-C3-C4-C5	-97.0	-98.1	-97.6	-98.0	-96.6
C2-C3-C5-C10	-7.6	-7.0	-8.8	-10.8	-7.1
C3-C4-C5-C10	91.8	91.6	90.9	90.7	92.4
C3-C5-C10-C1	26.2	25.8	27.2	28.9	25.8
C4-C5-C10-C1	-38.5	-38.3	-37.1	-35.4	-39.0
C5-C10-C1-C2	-34.9	-35.1	-35.7	-36.5	-34.8
C10-C1-C2-C3	31.3	31.6	31.3	31.0	31.7
<u>Ring B</u>	<u>Parent</u>	<u>(44a)</u>	<u>(44b)</u>	<u>(190a)</u>	<u>(190b)</u>
C5-C6-C7-C8	58.3	55.2	57.2	57.1	58.8
C6-C7-C8-C9	-57.6	-54.9	-56.4	-50.8	-56.8
C7-C8-C9-C10	49.7	49.6	49.2	44.6	48.9
C8-C9-C10-C5	-42.0	-43.1	-41.6	-41.5	-40.9
C9-C10-C5-C6	42.1	41.5	41.7	44.0	41.8
C10-C5-C6-C7	-50.5	-48.2	-50.1	-53.4	-51.8

As would be expected, the greater influences by the methyl and hydroxy group are noted for the B ring of the steroid. In all four compounds this ring has a chair conformation which can yield valuable information about the strain involved in the system. Consider the following. In the chair conformation of cyclohexane all six torsion angles are, when the signs are ignored, equal. Thus, in the minimum energy conformation, the standard deviation (σ_{n-1}) from the average torsion angle value is zero. However, when strain is introduced into the system by, for example, the substitution of a hydrogen atom by an alkyl group, this strain produces a distortion in the conformation of the ring which in turn results in an increase in the standard deviation from the average torsion angle. For the four isomers (44a), (44b), (190a) and (190b) the B rings experience identical amounts of strain due to the coupling with rings A and C. Therefore any increase in strain can be attributed to the substituents present and this will be observed by calculating the standard deviation from the average torsion value. Thus, for this and other similar systems we have a method for estimating strain by noting the (most readily detectable) out of plane bending. For the four isomers (44a), (44b), (190a) and (190b) the standard deviation from the average torsion value were calculated at 5.7, 6.8, 6.1 and 7.5 respectively. Thus the equatorial isomers (44a) and (190a) show, as would be expected, that they are the least strained compounds by virtue of the standard deviation from their torsion angles. In contrast, the more strained derivatives (44b) and (190b), with axial substituents, show greater standard deviations

from the mean. Another important fact can be drawn from these results, i.e., that the derivatives where the hydroxy group is situated at carbon 6 are apparently less stable than those where the hydroxy group is situated at carbon 7. Apparently there is a greater interaction between the cyclopropane moiety and a hydroxy group at this position than there is for a methyl group. If therefore both epoxide isomers are being produced in the previous step and the stability of the products influence the outcome of the reaction, i.e., we neglect any possible electronic influences by the cyclopropane ring, we could expect to see greater quantities of the 6 α -methyl compound (44a) than its 7 α -methyl counterpart (190b). Likewise we would expect to see greater quantities of the 7 β -methyl compound (190a) than the 6 β derivative (44b). The ratio between these two product pairs is dependent on molar ratio of the epoxide isomers.

The construction of the models also allows the estimation of the coupling constants of the proton geminal to the hydroxy group and thus product identification. Shown below in Table 42 are the torsion angles between the proton geminal to the hydroxy group and its neighbouring proton.

TABLE 42

ESTIMATION OF TORSION ANGLES (°) BETWEEN COUPLING PROTONS FOR POSSIBLE REACTION PRODUCTS (44a), (44b), (190a) AND (190b).

<u>COMPOUND</u>	<u>ϕ-(HO)CH-CH(CH₃)</u>	<u>ϕ-(HO)CH-C(8)H</u>
(44a): 6 α -Me, 7 β -OH	174.8	179.0
(44b): 6 β -Me, 7 α -OH	67.5	55.9
(190a): 6 α -OH, 7 β -Me	177.8	--- ^a
(190b): 6 β -OH, 7 α -Me	65.8	--- ^a

^aNo coupling between H(6) and H(8).

Thus, by the Karplus equation,¹⁰ the 6 α -methyl derivative (44a) should show a broad double doublet (or triplet), $J= 9.2$ and 9.1Hz , while the 6 β -methyl isomer (44b) should show a sharp double doublet (or triplet), $J= 1.0$ and 2.4Hz . In a similar manner, the 7 α and β -methyl steroids (190a) and (190b) should both show a broad and sharp ($J= 9.2$ and 1.1Hz respectively) doublet. By these means the products of reaction between the epoxide (15 or 16) and dimethyl lithium cuprate were thus readily identified.

- 1). "Molecular Mechanics", Burkert, U.; Allinger, N. L., American Chemical Society, New York. 1987.
- 2). Schneider, H. J.; Gschwendtner, W., Weigand, E. F., J. Am. Chem. Soc., 1979, 101, 7195.
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- 5). Van Horn, A. R.; Djerassi, C., J. Am. Chem. Soc., 1967, 89, 651.
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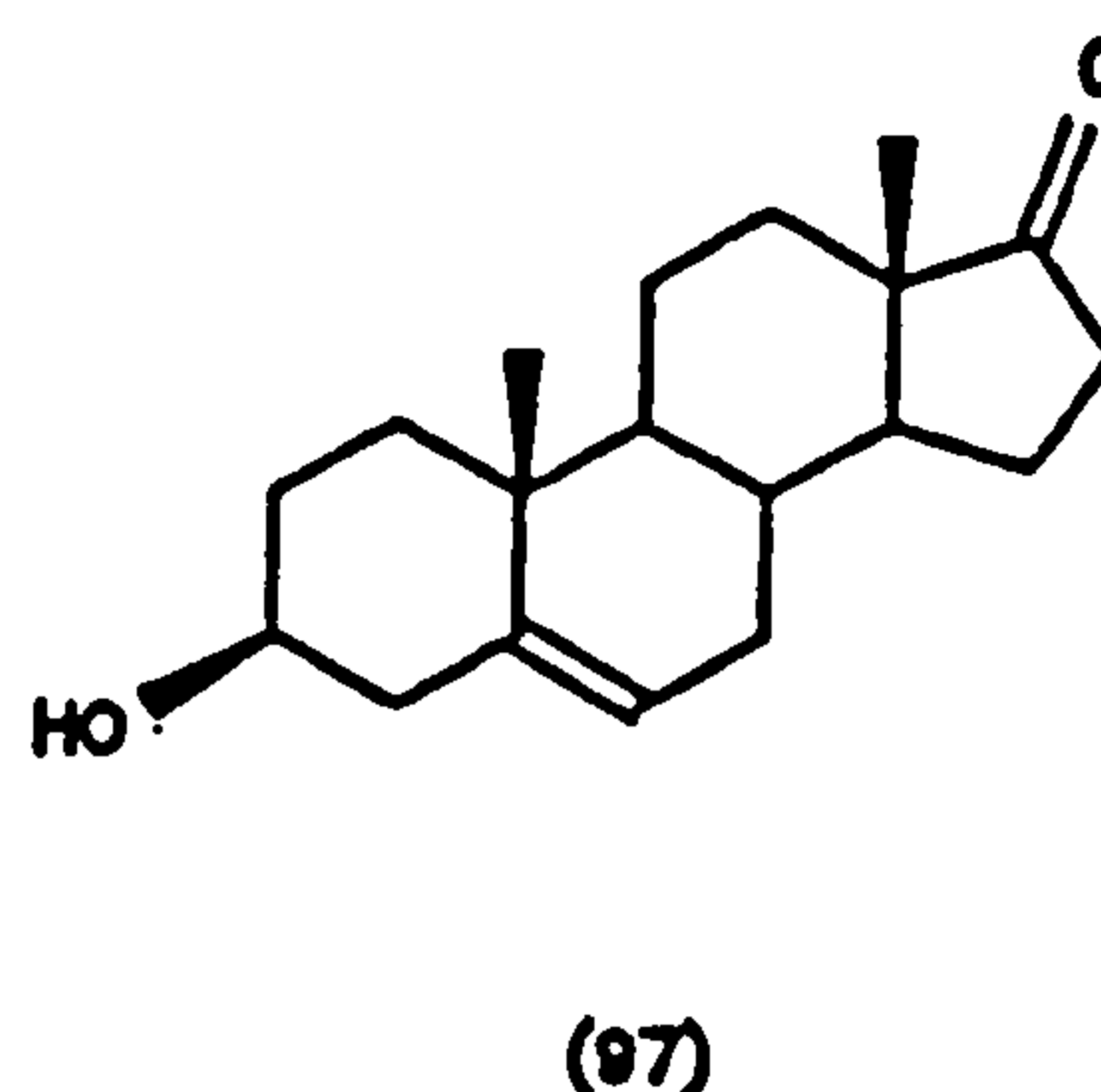
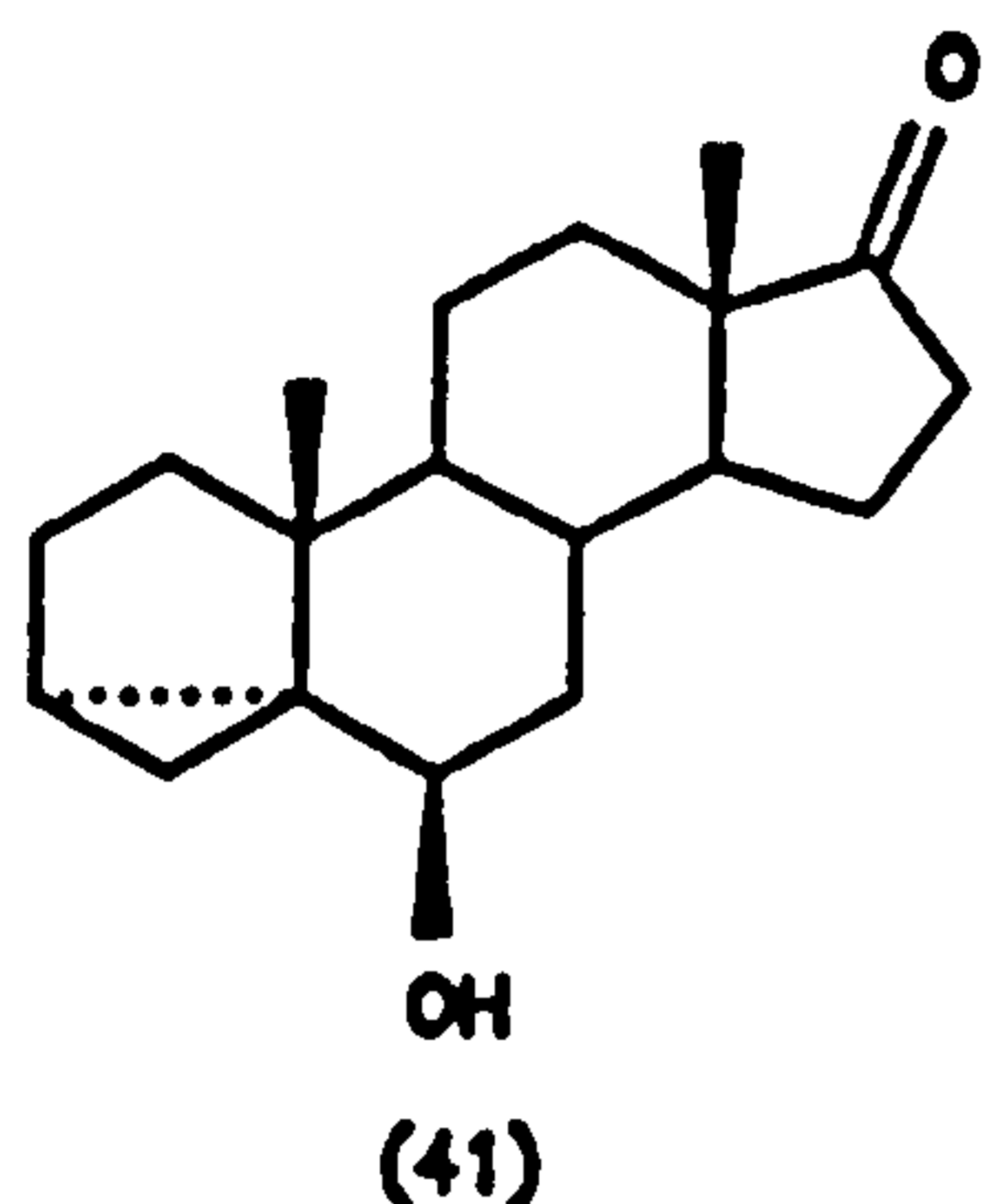
- 11). "Organic Spectroscopy", Brown, D. W.; Floyd, A. J.; Sainsbury, M., John Wiley and Sons Ltd, Chichester.1988.
- 12). Barton, D. H. R.; Head, A. J.: May, P. J., J Chem. Soc., 1957, 935.
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- 14). Hanson, J. R.; Truneh, A, J. Chem. Soc. Perkin Trans. I, 1988, 2001.
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Chapter 7

Biological testing and suggestions for future work.

7.1 Biological testing.

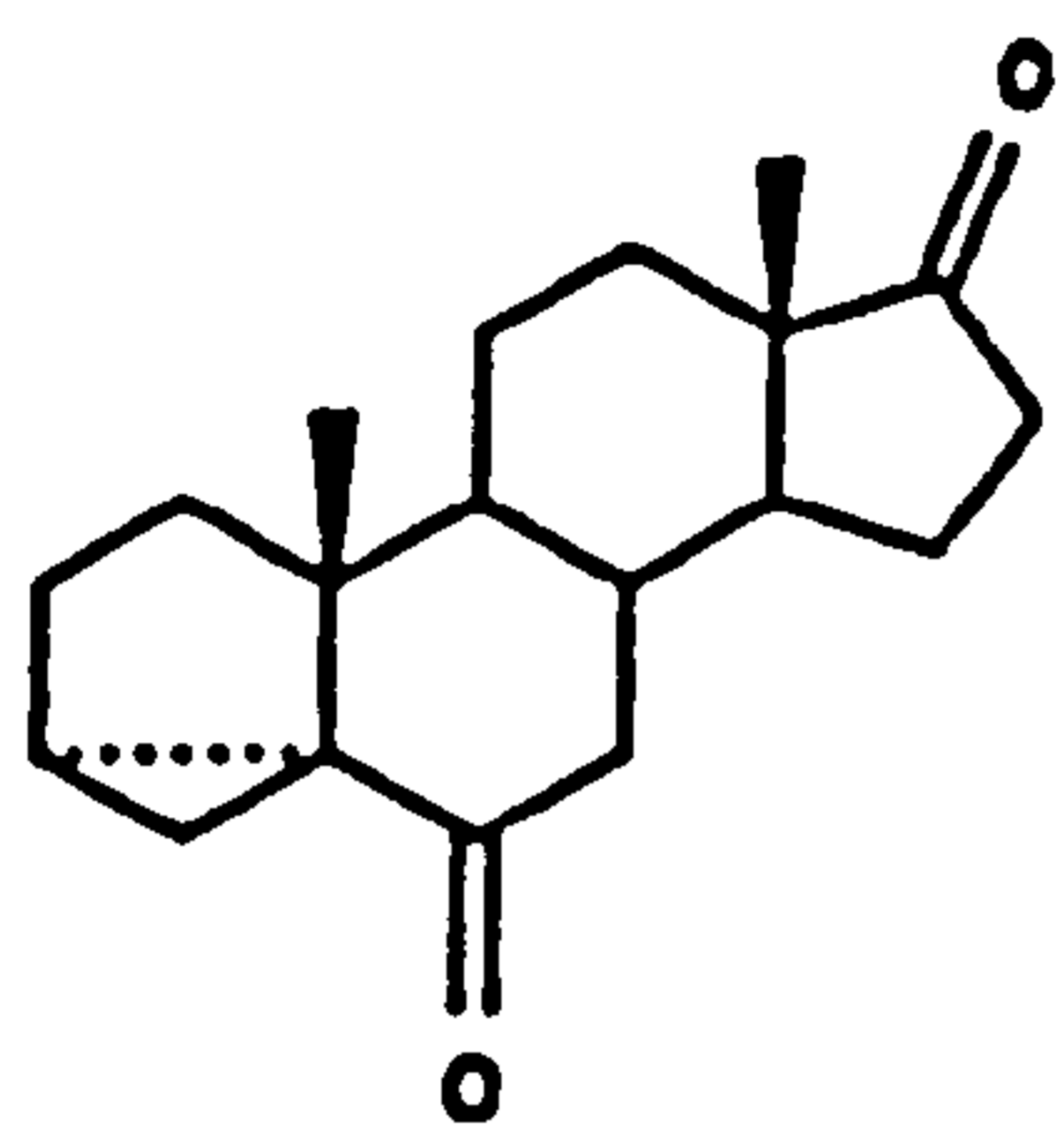
The aim of this work was to synthesise a variety of steroid molecules based on the parent cyclosteroid (41) which had previously been shown to possess anti-fertility properties. However, a subsequent test of this compound contradicted this result, i.e., that the steroid showed no anti-fertility properties. Therefore, it was proposed that



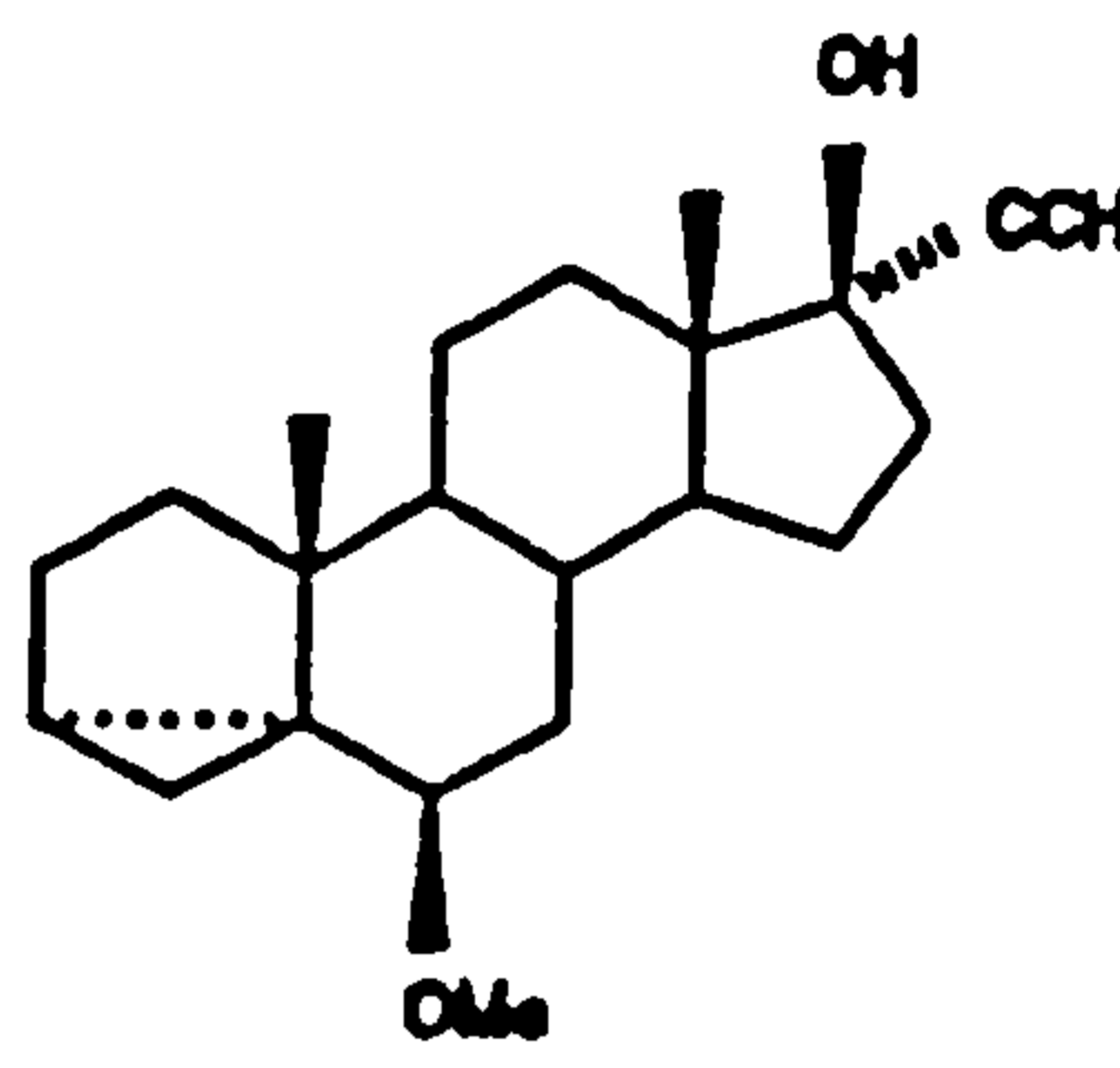
the activity originally noted arose from some impurity in the initial sample. The variety of syntheses of the parent steroid had indicated that often small quantities of DHEA (97) were present either because of incomplete sulphonation of the starting material or incomplete rearrangement in the second step of the synthesis of (41). Therefore DHEA, as a trace impurity, was considered the most likely cause of the noted biological activity. However, the subsequent testing of this compound indicated that it too possessed no anti-fertility activity. Thus, the originally noted activity of the sample must have been, if a simple experimental error is assumed not to have occurred, derived from either one of two possibilities. Firstly, the activity may be induced by another impurity in the sample. However, considering the knowledge of the reactions used in the synthesis of (41) this seems very unlikely. The second possibility is that

both steroids, (41) and (97), were present and that a synergistic effect was responsible for the activity. However, testing to evaluate such an effect was not undertaken.

Although the above results were disappointing several of the derivatives synthesised were also tested. However, because of frequently low yields or difficulty in isolating some of the products in the pure state testing was limited. Neither of the two steroids that were tested, (111) and (116), possessed any degree of biological activity.



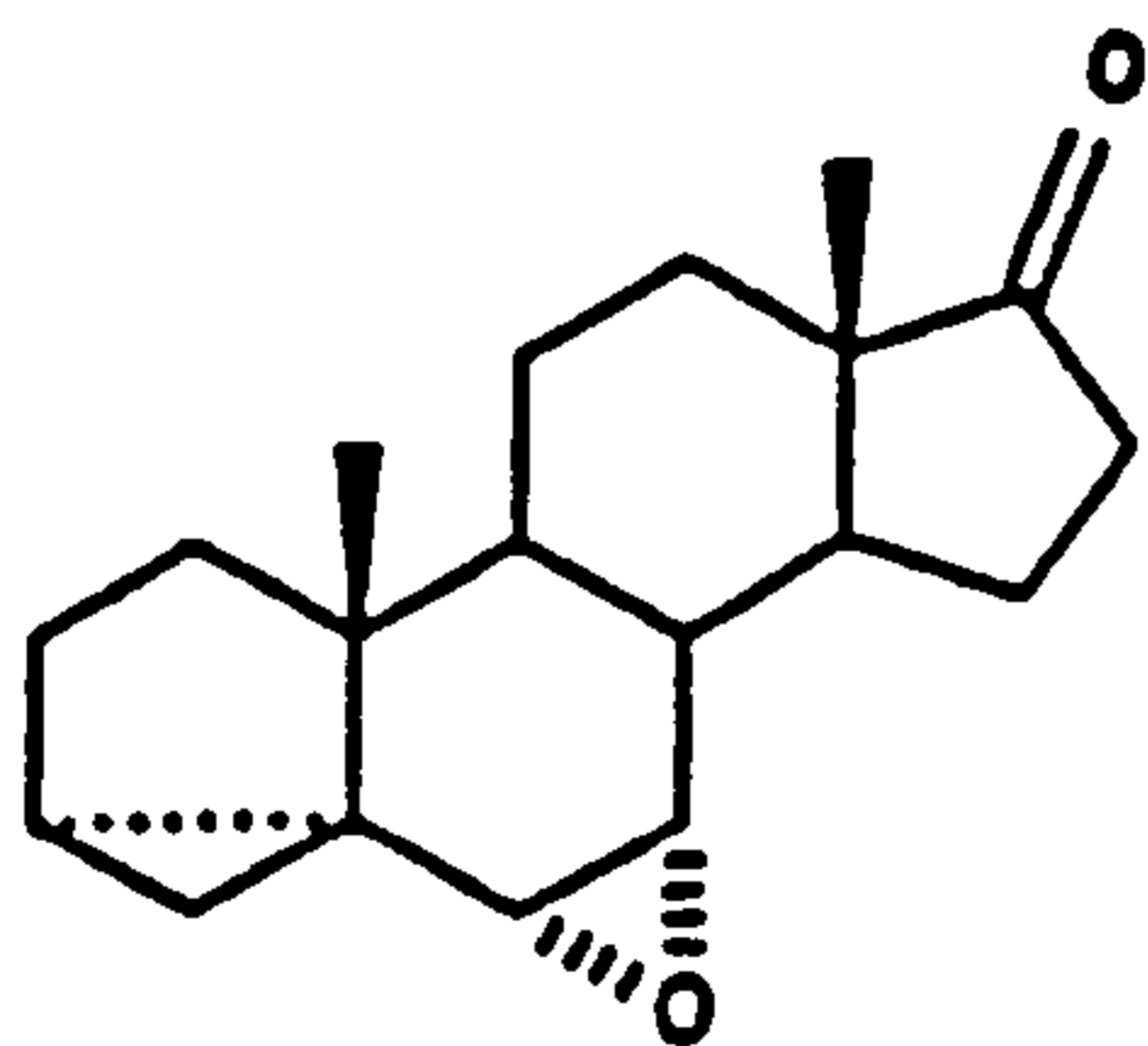
(111)



(116)

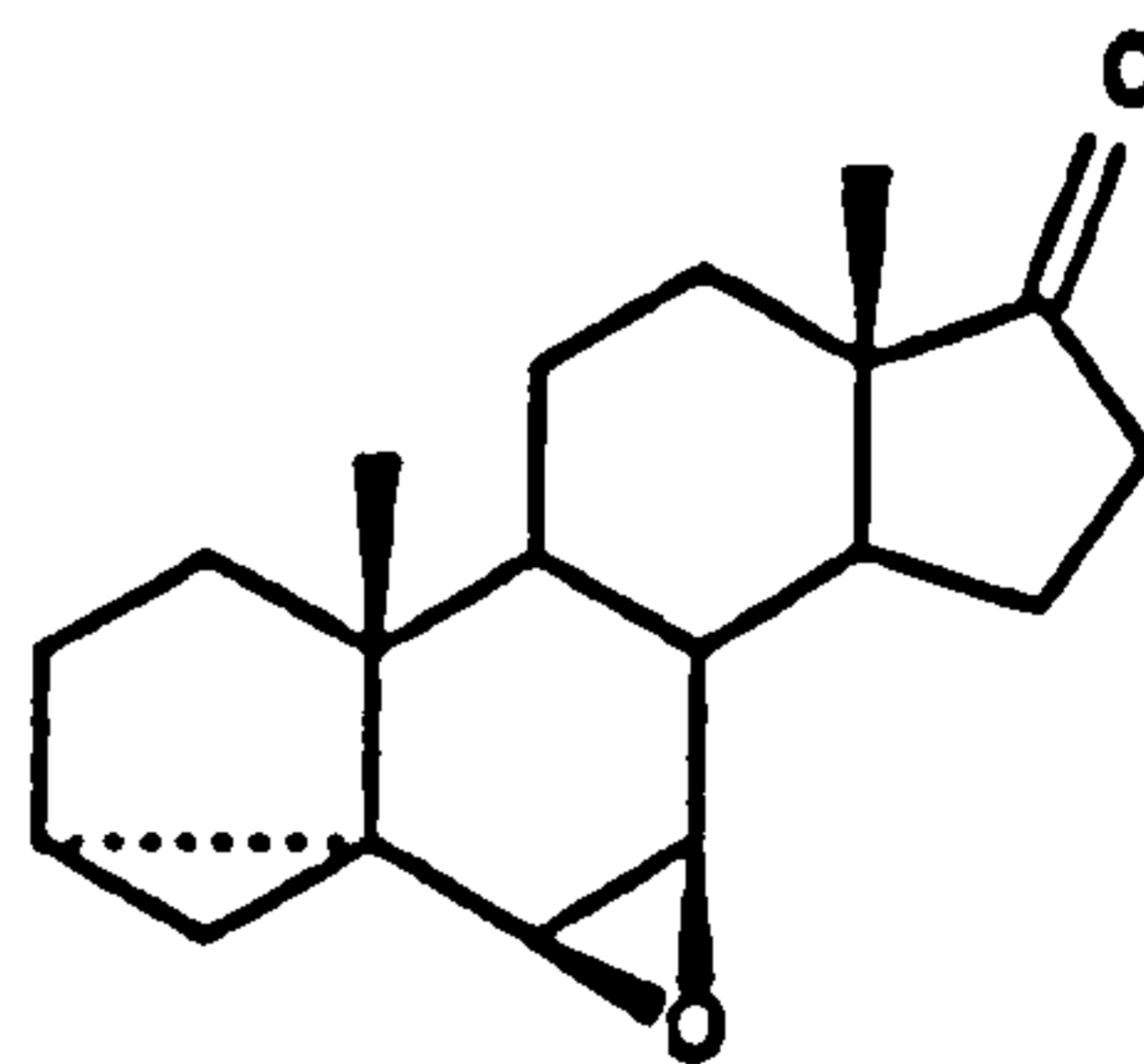
7.2 Suggestions for further work.

It was apparent from early on in the work that one of the major problems associated with the isolation of the desired target molecules was the presence of the cyclopropane ring in the target molecules. For example, in the protection of the 17-C carbonyl group fragmentation of the three membered ring was a considerable problem. However,



(209a)

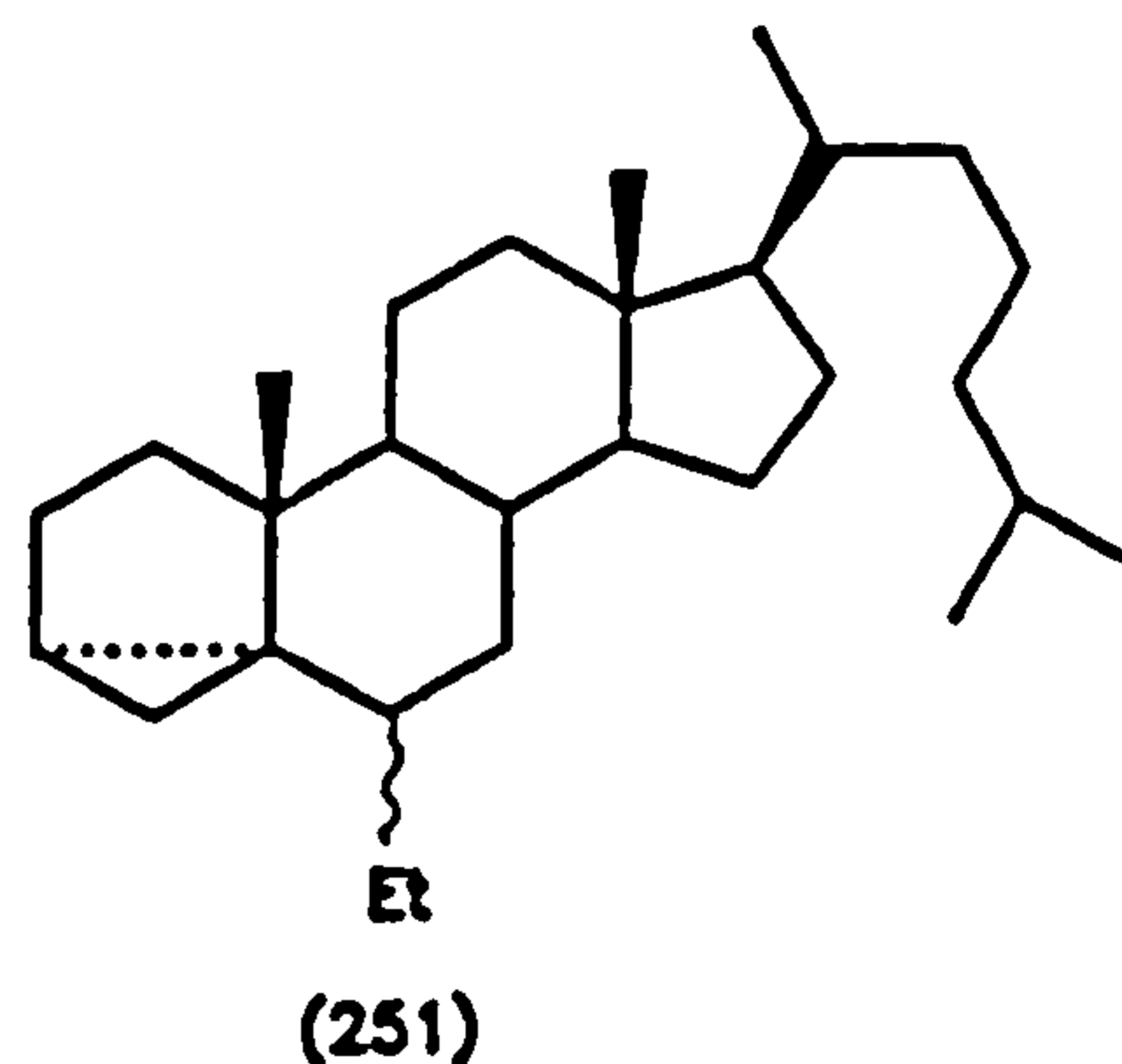
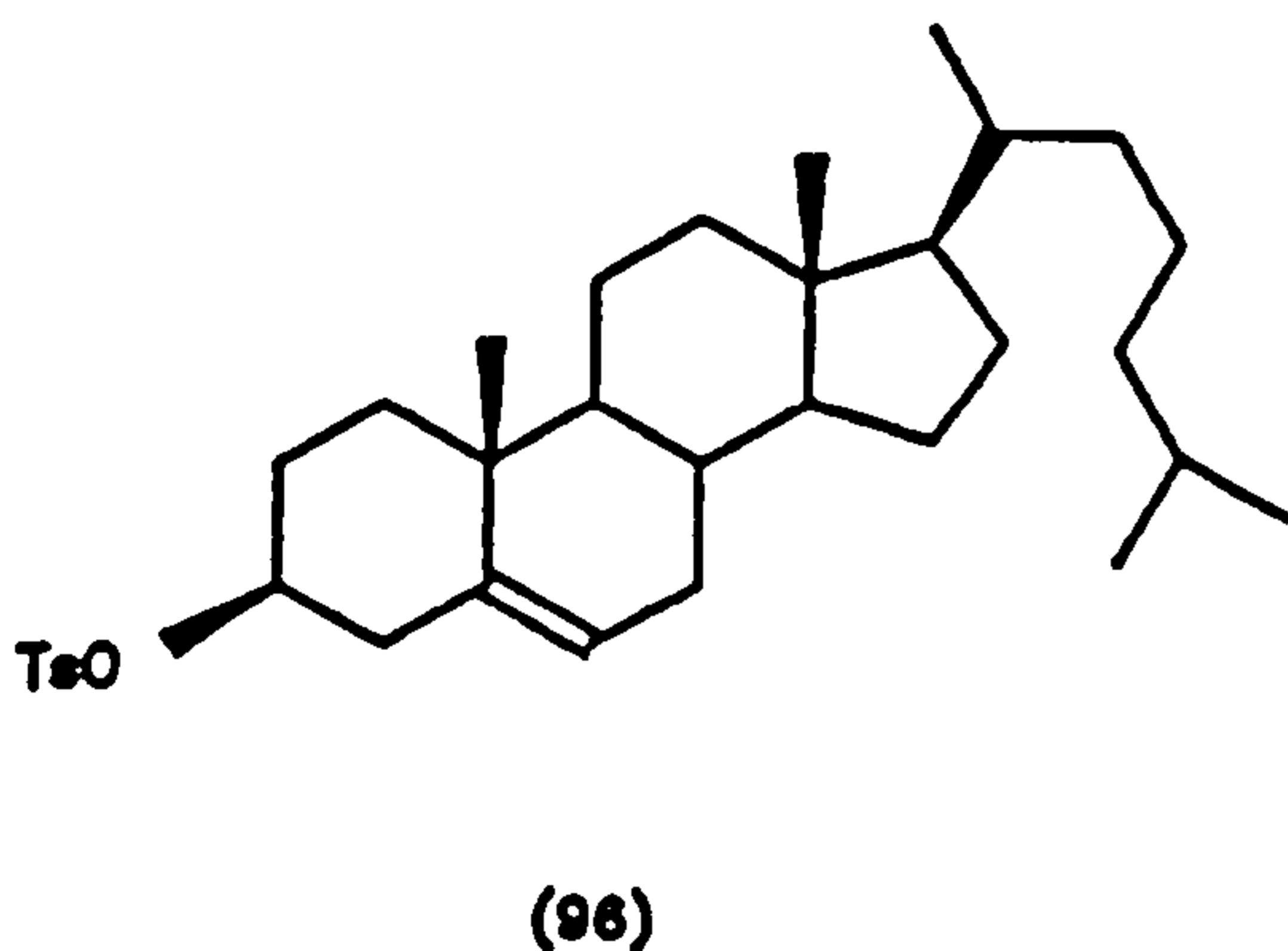
+



(209b)

problems did not only arise with the stability of the cyclo-

propane ring but also because of its effect on other functional groups in the molecule. Two specific examples being the activation of a neighbouring epoxide group, e.g., compounds (209a and b), which resulted in considerable instability, and the deactivation of the 6-C ketone group in (111) which prevented selective methylenation at 6-C. Both these phenomena had considerable influence on overall "route suitability." Future work could therefore be based on the premise that the cyclopropane ring be introduced during the final stages of a route in the synthesis of such compounds. However, this represents an entirely different strategy to that used here. Modifications to those strategies utilised in this work were discussed in the introductions to chapters 3 and 4 and will therefore not be commented upon here. However, in the latter stages of this work one particular method came to light which holds considerable potential for future work. Thus, the treatment of the cholesteryl tosylate (96) with triethyl aluminium resulted in, among other products, the isolation of 6 (α and β) ethyl substituted cyclopropane derivatives (251).¹ This represents a combination of the two approaches outlined above and potentially offers rapid access to the desired steroidal systems.



Another major problem associated with the work undertaken was in the purification of the various intermediates. Thus the application of preparative tlc, column chromatography and flash chromatography often failed to separate the reaction mixtures into the various components. In several cases, irreversible binding was also found to occur to a certain degree. With respect to future work, it would therefore be worth considering the application of more sophisticated means of separation such as preparative high performance liquid chromatography (hplc). Alternatively, further studies into flash chromatographic separation could be carried out using more complex and/or gradient solvent systems and investigations into different silica types.

- 1). Tolsmkov, G. A., Izv. Akad Nauk. SSSR Ser. Khim., 1983, 6, 1452.

CHAPTER 8
EXPERIMENTAL

8.1 Introduction.

8.1.1 Instrumentation.

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded on a Nicolet 5ZDX FTIR spectrometer either as a Nujol suspension or as a neat liquid film. The ultraviolet spectra were recorded on a Cecil CE588 spectrometer. The mass spectra were recorded on a A.E.I. MS 10 low resolution instrument. The ^1H and ^{13}C NMR spectra were determined with a Varian FT 80A spectrometer. Elemental analysis were performed on a Perkin Elmer 240 analyser.

8.1.2 Abbreviations.

The following abbreviations are used in the following sections:

m.pt.: - melting point.

$^1\text{H}/^{13}\text{C}$ NMR: - proton or carbon nuclear magnetic resonance spectroscopy respectively.

s: singlet, d: doublet, t: triplet, m: multiplet, bs: broad singlet, bm: broad multiplet.

IR: - infrared spectroscopy.

UV: - ultraviolet spectroscopy.

8.2 Syntheses from Chapter 2.

3 β -Hydroxy-5-androsten-17-one (Dehydroepiandrosterone) (97).

The starting material, Dehydroepiandrosterone (97), DHEA, was obtained from Aldrich Chem Co. m.pt.= 149-151°. ¹H NMR (δ): 0.89 (3H, s, 18-H), 1.05 (3H, s, 19-H), 3.44 (1H, bm, 3-H), 5.37 (1H, d, J= 2.4Hz, 6-H). ¹³C NMR (δ): 145.09 (5-C), 124.68 (6-C), 75.37 (3-C). IR ν_{\max} (cm⁻¹): 3450, 3025, 1730, 1665. CH analysis, calculated for C₁₉H₂₈O₂, C= 78.99%, H= 9.73%. Found, C= 79.16%, H= 9.72%.

Sulphonation reactions.

3 β -Tosyl-5-androsten-17-one (98a).

Method 1.

Dehydroepiandrosterone (DHEA) (97) was converted to its 3 β tosylate by the method described by Butenandt and Suranyi,¹ and Johns.² The steroid, (1g, 3.47 mmoles) was dissolved in 10 ml of anhydrous pyridine. To this stirring solution was added p-toluenesulphonyl chloride (0.67g, 3.52 mmoles). During dissolution and for a period thereafter of 30 minutes, an increase in the solution temperature was noted. The reaction mixture was then allowed to stand at room temperature for 16 hours. After this period the pyridine hydrochloride salt had precipitated out of solution. 10ml of cold (0°) distilled water was added to allow dissolution of the salt and cause complete precipitation of the steroid product. The slightly off white solid was then filtered, washed further with cold distilled water and dried

by vacuum. (1.37g, 90%) m.pt 151°. [lit= 151°¹]. ¹H NMR (δ): 0.84 (3H, s, 18-H), 0.97 (3H, s, 19-H), 2.41 (3H, s, tosyl Me-H), 4.30 (1H bm, 3-H), 5.45 (1H, d, J= 3.2Hz, 6-H), 7.31 (2H, d, J= 9.6Hz, aromatic-H), 7.80 (2H, d, J= 9.6Hz, aromatic-H). ¹³C NMR. (δ): 143.03 (5-C), 133.65 (aromatic-C, β to S), 131.49 (aromatic-C α to S), 126.64 (6-C), 85.86 (3-C). IR ν_{max} (cm⁻¹): 3080, 1740, 1675, 1605, 1360, 1090.

Method 2.

Dehydroepiandrosterone (97), (0.5g, 1.74 mmoles), tosyl chloride (0.32g, 1.74 mmoles) and anhydrous pyridine (0.27g, 3.46 mmoles) were dissolved in 50 ml dichloromethane. The reaction mixture was then refluxed overnight. After cooling, the solution was diluted with 100 ml chloroform and washed with 3 portions (100ml) of 5% HCl, 5% NaHCO₃ and distilled water. The organic layer was then dried with anhydrous magnesium sulphate. Removal of the solvent under reduced pressure gave the desired tosylate (98a), (0.68g, 90%), identical to the above in all respects.

3β-Mesyl-5-androsten-17-one (98b).

Method 1

In an identical manner to the formation of the tosylate, methanesulphonyl chloride (0.4g, 3.49 mmoles) was added to a stirring solution of anhydrous pyridine (10ml) containing 3β-hydroxy-5-androstene-17-one (97), an increase in solution temperature was noted. The reaction mixture was allowed to stand overnight. After this time the pyridine hydrochloride salt had precipitated out of solution. The

addition of 10ml cold distilled water caused the dissolution of the salt and the complete precipitation of the required steroid. The product, an off white solid was washed with cold distilled water and vacuum dried. (1.20g, 95%), m.pt 149-150° [lit= 149-151°³]. ¹H NMR. (δ): 0.88 (3H, s, 18-H), 1.05 (3H, s, 19-H), 3.01 (3H, s, mesyl-H), 4.45 (1H bm, 3-H), 5.45 (1H, d, J= 4.2Hz, 6-H). IR ν_{\max} (cm⁻¹): 3050, 3025, 1735, 1675, 1370, 1080, 740.

Method 2

Methanesulphonyl chloride (0.4g, 3.49 mmoles) was added to a dichloromethane solution (100ml) containing anhydrous pyridine (0.28g, 3.49 mmoles) and 3 β -hydroxy-5-androsten-17-one (97) (1.0g 3.46 mmoles). The reaction mixture was refluxed overnight. After cooling the pyridine solution was washed with 3 portions (50ml) of 5% HCl, 5% Na₂CO₃ and cold, distilled water. Drying of the organic layer and removal of the solvent gave the desired mesylate (98b) spectroscopically identical to the above.

Cyclisation reactions.

6 β -Hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41).

The 3 β -tosylate (98a) or mesylate (98b) were converted to the 3,5-cyclo-5 α -androstan-17-one (41) by several methods. The most successful being the aqueous acetone solvolysis method based loosely on the method of Johns² and Kosower;⁴ a variety of solvents were used. Other cyclisations attempted were based on the methods of Patel⁵ and that of Ringold and Djerassi.⁶

Method 1.

To a solution of the tosylate (1g, 2.26 mmoles) or the mesylate (1g, 2.73 mmoles) in 100ml acetone was added 30ml of distilled water containing 1g of potassium acetate (KOAc). This mixture was then heated under reflux for 6 hours. After cooling, the solution was extracted with 5x 50ml portions of dichloromethane (CH_2Cl_2). The organic layer was then dried with magnesium sulphate and the solvent removed under reduced pressure. The product, a white solid was recrystallised from 70% acetone or saturated aqueous butan-2-one as colourless plates. (0.52/ 0.63g, 80%) m.pt= 136-138°. [lit= 138-140°¹]. ¹H NMR (δ): 0.27 (1H, d, J= 8Hz, 4-H), 0.32 (1H, d J= 8Hz, 4-H), 0.55 (1H, t, J= 4.8 Hz, 3-H), 0.92 (3H, s, 18-H), 1.09 (3H, s, 19-H), 3.31 (1H, t, J= 2.7 Hz, 6-H). ¹³C NMR (δ): 77.20 (6-H). IR ν_{max} (cm^{-1}): 3450, 3060, 3012, 2997, 1735. CH analysis, calculated for $\text{C}_{19}\text{H}_{28}\text{O}_2$, C= 79.20%, H= 9.72%. Found, C= 79.16%, H= 9.72%.

Method 2.

The tosylated steroid (98a) (1g, 2.26 mmoles) or mesylated steroid (98b) (1g, 2.73 mmoles) was dissolved in 55ml of butan-2-one. To this was added a solution of potassium acetate, (1g, 10.2 mmoles), in 20ml distilled water. This two phase mixture was refluxed for 8 hours. After cooling the two layers were separated and the aqueous layer washed with 5 portions (20ml) of diethyl ether. The two organic layers were then combined and dried with anhydrous magnesium sulphate. Evaporation of the solvent under reduced pressure

gave a white crystalline solid. Thin layer chromatography (tlc) indicated small and varying amount of secondary minor product (0%-25%). Recrystallisation from a saturated aqueous butan-2-one gave the desired 3,5-cyclosteroid (41) as colourless plates (0.48/ 0.58g, 75%) and DHEA (97) (0.09/ 0.1g, 13%), needle crystals. Spectroscopic data of both compounds were identical to those cited above.

Method 3.

The tosylate (98a) (200mg, 0.45 mmoles) or the mesylate (98b) (200mg, 0.55 mmoles) were dissolved in 100ml of pentan-3-one. To this was added a solution of potassium acetate (399mg, 4.08 mmoles) in 100ml of distilled water. This two phase mixture was refluxed for 8 hours and the product isolated in the usual manner (see Method 2, above). Thin layer chromatography indicated a small and varying amount of a minor product. Recrystallisation from 70% acetone solution gave the desired 3,5-cyclosteroid (41) (91/ 110mg, 70%) as plate crystals, and DHEA (97) (26/ 30mg, 20%) as a residual gum. Spectroscopic data of both compounds were identical to those cited above.

Method 4

A two phase reaction mixture identical to that of method 2 was placed in a sealed reaction vessel which was heated to 140°C for a period of 8 hours. After this time the vessel was cooled in iced water. The flask contents were then extracted with dichloromethane (CH₂Cl₂). The resulting solution was washed with 5% NaHCO₃ and distilled water,

dried with magnesium sulphate and decolourised with activated charcoal. Removal of the solvent under reduced pressure gave a white solid which afforded DHEA (97) as colourless needle crystals (0.55g, 71%) when recrystallised from 70% acetone. The spectroscopic data of the product are cited above.

Method 5.

A solution of potassium acetate (1g, 10.1 mmoles) and sodium hydroxide (120mg 3.00 mmoles) in 50ml distilled water was added to a solution of the tosylate (98a) (1g, 2.26 mmoles) or mesylate (98b) (1g, 2.73 mmoles) dissolved in 100ml acetone. The solution was refluxed for 6 hours. Isolation by the usual method gave a white solid which recrystallised from 70% acetone as the desired 3,5-cyclosteroid (41), plates, (0.52/ 0.63g, 80%).

Method 6.

A solution of potassium acetate (1g, 10.1 mmoles) and sodium hydroxide (120mg 3.00 mmoles) in 50ml distilled water was added to a solution of the tosylate (98a) (1g, 2.26 mmoles) or mesylate (98b) (1g, 2.73 mmoles) dissolved in 100ml butan-2-one. This two phase mixture was refluxed for 8 hours. Isolation by the usual method gave a white solid which recrystallised from 70% acetone as the desired 3,5-cyclosteroid (41), plates (0.48/ 0.59g, 75%).

Method 7.

Distilled water (50ml) containing sodium hydroxide (1g, 1.02 mmoles) was added to a solution of the tosylate (98a),

(1g, 2.26 mmoles) or mesylate (1g, 2.73 mmoles) in 100ml acetone. The reaction mixture was then refluxed for 6 hours. The product, worked up in the usual manner give a white crystalline solid. Recrystallisation from 70% acetone gave the required 3,5-cyclosteroid (41) (0.59/ 0.70g, 70%) as colourless plates. Spectroscopic data of the product were identical to that cited above.

6 β -Methoxy-3 α ,5-cyclo-5 α -androstan-17-one (106).

Formation of the methyl ether derivative was via the 3 β -tosyl steroid (98a). 5g (1.13 mmoles) of the steroid (98a) and 2g (2.04 mmoles) of potassium acetate were dissolved in 400ml of purified and dried methanol. Refluxing of the solution allowed full dissolution of the mixture and reflux was then maintained for 6 hours. After this period the solution was cooled and the solvent removed under reduced pressure. The resulting slurry was taken up in chloroform and washed with 5x 100ml distilled water. Drying of the solvent followed by its removal under reduced pressure gave a clear glass. (2.7g, 80%). Crystallisation from 50% aqueous methanol gave fine needles m.pt= 102-105° [lit⁷ 104-105°]. ¹H NMR (δ): 0.49, (3H, m, 3 and 4-H), 0.92 (3H, s, 18-H), 1.05 (3H, s, 19-H), 2.84 (1H, t, J= 1.6Hz, 6-H), 3.36 (3H, s, methoxy-H). IR ν_{\max} (cm⁻¹): 3058, 1735, 1090.

Oxidation reactions.

Oxidation to the 6-ketone system was attained by two methods. Both Jones' and Collins' reagents successfully oxidising the 6 β -alcohol in high yield.

Method 1

3,5-Cyclo-5 α -androstane-6,17-dione (111).

Jones' reagent, was freshly made by dissolving chromium trioxide (CrO₃, 26.72g, 26.7 mmoles) in concentrated sulphuric acid (H₂SO₄, 23ml). This solution was made up to 100ml by the slow addition of cold distilled water.

In an analogous method to that of Djerassi *et al.*,⁸ the alcohol (41) (500mg, 1.74 mmoles) was dissolved in 20ml of purified acetone. Jones' Reagent was then added drop-wise and with stirring until no further green precipitate was produced and a permanent orange colour predominated (3ml). The reaction temperature was maintained at 0° during the addition of the reagent and for a further 0.5 hours. The reaction mixture was then poured into a separating funnel containing distilled water (100ml), chloroform and a trace of propan-2-ol. After vigorous agitation the layers were allowed to separate and stand for 5 minutes. Isolation of the organic layer, followed by drying, decolourising and removal of the solvent under reduced pressure gave a yellow solid. Thin layer chromatography (tlc) indicated a small amount of secondary product spectroscopically identical to 4-androstene-3,17-dione. The pale yellow solid, recrystallised from 70% aqueous acetone gave colourless needles (0.41g, 85%). m.pt= 182-183° [lit= 182-183°¹]. ¹H NMR (δ):

0.75 (1H, t, J= 4.0Hz, 3-H), 0.92 (3H, s, 18-H), 1.04 (3H, s, 19-H). ^{13}C NMR (δ): 145.09, C-5, 124.68, C-6, 75.37, C(3). IR ν_{max} (cm^{-1}): 3093, 3022, 1732, 1681. CH analysis, calculated for $\text{C}_{19}\text{H}_{26}\text{O}_2$, C= 79.72%, H= 9.09%. Found C= 79.18%, H= 9.39%. MS: m/z= 286 (80%) [molecular ion], 271 (30%), 136 (100%).

Method 2

3 α ,5-Cyclo-5 α -androstane-6,17-dione (111).

The Collins' reagent⁹ was freshly prepared by the addition of chromium trioxide (CrO_3 , 0.52g, 5.21 mmoles) to a stirring solution of pyridine (0.82g, 10.5 mmoles) in 50ml purified dichloromethane. The reaction mixture was stirred at room temperature for 1 hour. In an analogous method to Ratcliffe,¹⁰ the steroid (41), (250mg, 0.87 mmoles), as a solution in 30 ml purified dichloromethane, was added to the stirring solution of Collins reagent. After a period of one hour the solvent was decanted and washed with 5% sodium hydroxide (NaOH) until no further decolourisation of the organic layer occurred. The gum on the surface of the reaction vessel was then dissolved in 100ml 5% NaOH and extracted with 3x 50ml CH_2Cl_2 . The organic layers were then combined and further washed with consecutive 50ml portions of 5% NaOH, 5% HCl, 5% NaHCO_3 , 5% NaCl and distilled water until each of the aqueous solution failed to decolourise the organic layer further. The solvent was then dried with anhydrous magnesium sulphate and decolourised with activated charcoal. Removal of the solvent under reduced pressure gave the desired 3,5-cyclosteroid dione (111) as an off white

solid. Recrystallisation from 70% acetone gave colourless needles (0.39g, 80%). Spectroscopic data were identical with that cited above.

17 α -ethynyl-3 α ,5-cyclo-5 α -androstandane-6 β ,17 β -diol (42).

The propargyl alcohol was synthesised by four routes.

These were:-

- 1). The direct propargylation of the cyclosteroid (41).
- 2). Propargylation of DHEA followed by insertion of the cyclopropane ring.
- 3). Propargylation of the tosylate of DHEA followed by cyclisation.
- 4). Propargylation of the 6-methoxy steroid (106) followed by its conversion to the alcohol (42).

Route I

17 α -Ethynyl-3 α ,5-cyclo-5 α -androstandane-6 β ,17 β -diol (42).

Propargylation of the parent 3,5-cyclosteroid was based on the method of propargylation used by Huffman and Arapakos.¹¹ Under a nitrogen atmosphere, a 60ml solution of sodium dried 1,4-dioxane was saturated with acetylene gas. To this solution was added, with stirring, 6g of lithium acetylide ethylenediamine complex and, cautiously, a 20ml portion of the anhydrous 1,4-dioxane containing 1g (3.47 mmoles) of the keto steroid (41). During this period and for an additional 30 minutes, acetylene gas was bubbled through the solution. The reaction, monitored by infra red spectroscopy, was complete after a period of 5 days at room temperature. After this time, a 20% aqueous solution of ammonium

chloride was slowly added, while maintaining vigorous agitation, until no further evolution of gas occurred. This mixture was then extracted with diethyl ether until the ether extracts were clear. The organic layer was then dried with magnesium sulphate and decolourised with activated charcoal. Removal of the solvent gave a pale brown oil. Preparative thin layer chromatography (mobile phase toluene, chloroform, methanol (3:2:1)) gave one major product which was isolated as a pale brown solid (0.38g, 40%). m.pt= 75-81°. ^1H NMR. (δ): 0.27 (1H, d, J= 8Hz, 4-H), 0.32 (1H, d, J= 8Hz, 4-H), 0.55 (1H, t, J= 4.8Hz, 3-H), 0.86 (3H, s, 18-H), 1.07 (3H, s 19-H), 2.49 (1H, s, alkynic-H), 3.32, (1H, t, J= 2.4 Hz, 6-H). IR ν_{max} (cm^{-1}): 3580, 3460, 3270, 2110. CH analysis, calculated for, $\text{C}_{21}\text{H}_{30}\text{O}_2$: C= 80.75%, H= 9.95%. Found, C= 81.10%, H= 10.23%.

Route II

17 α -Ethylnyl-5-androstene-3 β ,17 β -diol (114).

The propargyl derivative (114) of DHEA was synthesised under identical conditions to those used for the direct synthesis of compound (42). The product (114) was isolated by preparative thin layer chromatography (tlc) using a toluene, chloroform and methanol mobile phase (3:2:1) as an off-white solid. (0.80g, 80%) m.pt= 229-230°. [lit= 240-242.¹²] ^1H NMR (δ): 0.85 (3H, s, 18-H), 1.01 (3H, s 19-H), 2.49 (1H, s, alkynic-H), 3.50 (1H, bm, 3-H), 5.37 (1H, d, J= 2.4Hz, 6-H). IR ν_{max} (cm^{-1}): 3575, 3440, 3270, 2110, 1675. CH analysis, calc for, C= 80.25, H= 9.55. Found, C= 81.09, H= 9.61.

3 β -Tosyl-17 α -ethynyl-5-androsten-17 β -ol (115), Method 1.

The 3-C tosylate was synthesised under identical conditions to the synthesis of the DHEA tosylate (98a). The product, purified by preparative tlc (3:1 toluene ethyl acetate) was an off white solid (0.59g, 80%). m.pt= 143° (with decomposition). ¹H NMR (δ): 0.84 (3H, s, 18-H), 0.99 (3H, s, 19-H), 2.43 (3H, s, tosyl methyl-H), 2.53 (1H, s, alkynic-H), 4.56 (1H, bm, 3-H), 5.31 (1H, d, J=3.2Hz, 6-H), 7.33 (2H, d, J= 9.6Hz, aromatic-H), 7.81 (2H, d, J= 9.6Hz, aromatic-H). IR ν_{\max} (cm⁻¹): 3400, 3100, 2110, 1665, 1605, 1340, 1080.

Method 2.

The 3-C tosylate was synthesised under identical conditions to the method described in method 1 but a second molar equivalent of tosyl chloride was added to the reaction mixture. The product, (115) spectroscopically identical in all respects to that cited above was recovered as an off white solid (0.60g, 80%).

17 α -Ethynyl-3 α ,5-cyclo-5 α -androstane-6 β ,17 β -diol (42).

The cyclisation of the 3-C tosylate, to give the 3,5-cyclosteroid propargyl alcohol (42) was attained by an identical method to that used to give the 3,5-cyclosteroid parent (41), (Method 1). The product was purified by preparative tlc (3:2:1 toluene, chloroform, methanol) giving an off white solid, (0.25g, 70%) spectroscopically identical to that cited above.

Route III.

3 β -Tosyl-5-androsten-17-one (98a).

Details of the synthesis of the tosylated DHEA (98a) and the compounds analytical data are described earlier in this Chapter.

3 β -Tosyl-17 α -ethynyl-5-androsten-17 β -ol (115).

Propargylation of the tosylated steroid was carried out under identical conditions to those used in the propargylation of the parent 3,5-cyclosteroid (Route I) and DHEA (Route II). Preparative tlc (3:1 toluene, ethyl acetate) gave an off white solid. m.pt= 139-141° with decomposition. Spectroscopic data of this product were identical to that cited above.

17 α -Ethynyl-3 α ,5-cyclo-5 α -androstane-6 β ,17 β -diol (42).

The cyclisation of the C(3) tosylate, propargyl alcohol was carried out under the standard conditions previously mentioned. The product, spectroscopically identical that previously cited was isolated in an identical manner.

Route IV.

6 β -Methoxy-17 α -ethynyl-3 α ,5-cyclo-5 α -androstan-17 β -ol (116).

Synthesis of (116) from the 6-methoxy steroid (106) was attained using identical conditions to the propargylation of the parent 3,5-cyclosteroid alcohol (41). The product of reaction was a pale oil. Preparative tlc gave an off white creamy solid that resisted crystallisation. ^1H NMR (δ): 0.47 (3H, m, 3 and 4-H), 0.92 (3H, s, 18-H), 1.05 (3H, s, 19-H),

2.48 (1H, s, alkynic-H), 2.83 (1H, t, J= 1.6Hz, 6-H), 3.36 (3H, s, methoxy-H). IR ν_{\max} (cm⁻¹): 3058, 1735, 1090. Chemical analysis, calculated for C₂₁H₃₀O₂: C= 80.01%, H= 9.74%. Found, C= 80.39%, H= 9.75%.

17 α -Ethyanyl-3 α ,5-cyclo-5 α -androstande-6 β ,17 β -diol (42).

Under a nitrogen atmosphere, the methoxy steroid (116), 0.25g (0.76 mmoles) was dissolved in 30ml dry chloroform containing 1.98 (0.99 mmoles) trimethylsilyl iodide. This solution was then refluxed for 24 hours. The reaction mixture was washed with 5% Na₂S₂O₅, NaHCO₃ and NaCl. Removal of the solvent gave a clear oil. Thin layer chromatography indicated the presence of three compound in an approximately a 1:1:1 mixture. Separation by preparative tlc gave the parent 3,5-cyclosteroid alcohol (41), 6 β -methoxy-17 α -ethynyl-3 α ,5-cyclo-5 α -androstan-17 β -ol (116) and 17 α -ethynyl-3 α -cyclo-5 α -androstande-6 β ,17 β -diol (42). Spectroscopic details of t products are cited above.

8.3 Syntheses from Chapter 3. Formation of 6 β -Methyl-3 α ,5-cyclo-5 α -androstan-17-one (43).

Syntheses from section 3.2.

6 β -Hydroxy-3 α ,5-Cyclo-5 α -androstan-6 β -17-spiro-2'-(1,3-dioxolane) (126)

The attempted formation of the protected steroid was attempted via either the well documented method of Salmi¹³ or by similar means but using unconventional solvents such as hexane or pentane. In these cases the volume of solvent used was fifty times greater than that stated below for benzene. However the product described below was shown to be solvent independent. The 3,5-cyclosteroid (41) (5g, 17.36 mmoles), 3.10g ethylene glycol (50 mmoles) and 0.25g p-toluene sulphonic acid [PTS] (1.45 mmoles) were dissolved in 200ml of benzene and the round bottomed flask fitted with a modified Dean/Stark trap possessing a second condenser to cool the condensate.¹⁴ After refluxing for 16 hours the solution was cooled, diluted to 400ml with diethyl ether and washed with five, 100ml portions of 5% NaHCO₃ solution and distilled water. The organic phase was then dried, decolourised and the solvent removed under reduced pressure. The product, a white solid, was shown to be virtually pure by tlc, a very small amount of a second product being present. The two products were separated by recrystallisation from 70% aqueous acetone:

Major product, 3 β -(β -hydroxyethoxy)-5-androstene-17-spiro-2'-(1,3-dioxolane), (127), colourless plates, (4.2g, 65%). m.pt= 126-128° [lit= 125-128°¹⁵]. ¹H NMR (δ): 0.86

(3H, s, 18-H), 1.01 (3H, s, 19-H), 3.22 (1H, bm 3-H), 3.65 (4H, m, β -hydroxyethoxy sidechain), 3.87 (4H, s, dioxolane-H), 5.35 (1H, d, $J=4.2\text{Hz}$, 6-H). ^{13}C NMR (δ): 62.2, 64.5, 65.2, 69.0, 70.4, 119.5. IR ν_{max} (cm^{-1}): 3420, 1665, 1050. MS m/z : 367(5%) [molecular ion], 270(10%), 155(35%), 99(100%), 91(75%). CH analysis, calculated for $\text{C}_{21}\text{H}_{32}\text{O}_3$, C=79.84%, H=7.26%. Found, C=79.82%, H=7.06%.

Evaporation of the recrystallising medium gave 3β -hydroxy-5-androsten-17-spiro-2'-(1,3-dioxolane), (125), as a gum, (0.44g, 7%). ^1H NMR (δ): 0.86 (3H, s, 18-H), 1.01 (3H, s, 19-H), 3.46 (1H, bm 3-H), 3.87 (4H, s, dioxolane-H), 5.34 (d, $J=3.2\text{Hz}$, 6-H). IR ν_{max} (cm^{-1}): 3350, 1735, 1665, 1020.

3β -Ethoxy-5-androsten-17-one (128).

To 20ml of refluxing ethanol was added 200mg (4.54×10^{-4} moles) of the tosylated steroid (98a). Heating was then maintained for a further 10 minutes. After this period, the solution was allowed to cool slowly by wrapping the flask in tin foil and placing it in a refrigerator. Complete cooling resulted in the crystallisation of 122mg (85%) of the desired ether as fine needles. m.pt= 128-130 °. ^1H NMR (δ): 0.88 (3H, s, 18-H), 1.03 (3H, s, 19-H), 1.19 (3H, t, $J=7.2\text{Hz}$, ethylether methyl-H) 3.18 (1H, bm 3-H), 3.53 (2H, q, $J=7.2\text{Hz}$, ethylether methylene-H), 5.37 (1H, d, $J=4.0\text{Hz}$, 6-H). IR ν_{max} (cm^{-1}): 3420, 1735, 1665, 1050.

6 β -Methoxy-3 α ,5-cyclo-5 α -androstandane-17-spiro-2'-(1,3-dioxolane).

The reaction was carried out by the method described for the reaction of the 6 β -alcohol (41) (see above). Again the three solvent systems were investigated but the product yields were identical in all cases. The two products were separated by crystallisation from 70% aqueous acetone:

Major product, 3 β -(β -hydroxy ethoxy)-5-androsten-17-spiro-2'-(1,3-dioxolane) (127), colourless plates (0.9g, 70%), compound was spectroscopically identical to previous sample.

Evaporation of the recrystallising medium gave 3 β -methoxy-5-androsten-17-spiro-2'-(1,3-dioxolane) (128) as a gum. ^1H NMR (δ): 0.84 (3H, s, 18-H), 1.02 (3H, s, 19-H), 3.20 (1H, bm 3-H), 3.42 (3H, s, methoxy-H) 3.87 (4H, s, dioxolane-H), 5.34 (1H, d, J= 3.2 Hz, 6-H). IR ν_{max} (cm^{-1}): 3350, 1665, 1020.

6 β -Hydroxy-3 α ,5-cyclo-5 α -androstandane-17(S)-spiro-2'-(1,3-oxathiolane) (150).

Formation of the protected steroid was via a slightly modified method to that of Djerassi *et al.*¹⁶ and Salmi,¹³ i.e., the addition of a further quantity of p-toluenesulphonic acid mid-way through the reaction. Similar reactions but using the unconventional solvents hexane or pentane. In these cases the volume of solvent is 50 times greater than those stated below for benzene. 5g of the 3,5-cyclosteroid (41) (17.36 mmoles), 3.90g β -mercapto ethanol (50 mmoles) and 0.25g p-toluene sulphonic acid [PTS] (1.45 mmoles) were

dissolved in 200ml of benzene and the round bottomed flask fitted with a modified Dean/Stark trap possessing a second condenser to cool the condensate.¹⁴ After refluxing for 16 hours a further 0.15g of PTS was added and the reflux continued for a further 24 hours. The solution was then diluted to 400ml with ether and washed with five, 100ml portions of 5% NaHCO₃ solution and 10, 100ml portions of distilled water. The organic phase was then dried and decolourised and the solvent removed under reduced pressure to give a pale brown oil. Preparative tlc gave three components all of which failed to recrystallise. The ratio (by weight) of components (1:2:3) varied, depending on the solvent used. Approximate ratios for benzene hexane and pentane as solvents were 2:1:5, 2:1:6 and 2:1:12 respectively:

Component 1, assigned as inseparable mixture of 3 β -(β -thiol ethoxy)-5-androsten-17(S)-spiro-2'-(1,3-oxathiolane) (129) and 6 β -(β -thiol ethoxy)-3 α ,5-cyclo-5 α -androstane-17(S)-spiro-2'-(1,3-oxathiolane) (130). ¹H NMR (δ): 0.48 (1H, m, 3 or 4-H), 0.89, 1.02 (3H, s, 18-H), 0.92, 1.05 (3H, s, 19-H), 2.53 (2H, m, methylene H, α to sulphur, β -thiol ethoxy sidechain), 2.88 (3H, bm, (M₂X₂ + 3-H or 6-H), 4-H oxathiolane moiety), 3.69 (2H, m, methylene H α to oxygen, β -thiol ethoxy sidechain), 4.10 (2H, m, (M₂X₂), 5-H oxathiolane moiety), 5.33 (0.5H, d, J= 2.4Hz, 6-H). IR ν_{\max} (cm⁻¹): 2530, 1670, 1080, 770.

Component 2, assigned as 3 β -hydroxy-5-androsten-17(S)-spiro-2'-(1,3-oxathiolane) (131). ¹H NMR (δ): 0.83 (3H, s, 18-H), 1.00 (3H, s, 19-H), 2.91 (2H, bm, (M₂X₂), 4-H oxathiolane moiety), 3.41 (1H, bm, 3-H), 3.99, 4.04 (2H, m,

(M₂X₂), 5-H oxathiolane moiety), 5.34 (1H, d, J= 3.2Hz, 6-H). IR ν_{\max} (cm⁻¹): 1665, 1090, 1060, 730.

Component 3, assigned as 6 β -(β -thio ethoxy)-3 α ,5-cyclo-5 α -androstane-17(S)-spiro-2'-(1,3-oxathiolane) (132). ¹H NMR (δ): 0.50 (1H, m, 3 or 4-H), 0.83 (3H, s, 18-H), 1.06 (3H, s, 19-H), 2.60 (2H, m, methylene α to sulphur, β -hydroxy thio ethyl ether sidechain), 2.91 (2H, bm, (M₂X₂), 4-H oxathiolane moiety), 3.12 (1H, s, 6-H), 3.62 (2H, bm, methylene H α to oxygen atom, β -hydroxy thioether sidechain), 3.99, 4.01, 4.08, 4.15 (2H, m, (M₂X₂), 5-H oxathiolane moiety), 5.34 (1H, d, J= 4.2Hz, 6-H). IR ν_{\max} (cm⁻¹): 3400, 1665, 1090, 1060, 755.

6 β -Methoxy-3 α ,5-cyclo-5 α -androstane-17(S)-spiro-2'-(1,3-oxathiolane).

The formation of the 6-methoxyoxathiolane protected steroid was attempted by the three methods used in the attempted protection of the 6 β -alcohol derivative (see above). Yields of the products were identical to the results from the 6 β -alcohol reaction:

Component 1, assigned as inseparable mixture of 3 β -(β -thio ethoxy)-5-androsten-17(S)-spiro-2'-(1,3-oxathiolane) (129) and 6 β -(β -thio ethoxy)-3 α ,5-cyclo-5 α -androstane-17(S)-spiro-2'-(1,3-oxathi-olane) (130). Spectroscopically identical to previous sample.

Component 2, assigned as 6 β -methoxy-5-androsten-17(S)-spiro-2'-(1,3-oxathiolane) (133). ¹H NMR (δ): 0.83 (3H, s, 18-H), 1.00 (3H, s, 19-H), 2.90 (2H, bm, (M₂X₂), 4-H oxathi-olane moiety), 3.17 (1H, bm, 6-H), 3.35 (3H, s, methoxy-H)

4.04 (2H, m, (M₂X₂), 5-H oxathiolane moiety), 5.34 (1H, d, J= 2.4Hz, 6-H). IR ν_{\max} (cm⁻¹): 1650, 1090, 1060, 730.

Component 3, assigned as 6 β -(β -hydroxy thioethyl ether)-3 α ,5-cyclo-5 α -androstane-17(S)-spiro-2'-(1,3-oxathiolane) (132). Spectroscopically identical to previous sample.

Syntheses from section 3.3

3 β -Hydroxy-5-androsten-17-spiro-2'-(1,3-dioxolane) (125).

The synthesis of the protected derivative of DHEA was carried out under identical conditions to those used in the attempted protection of the 3,5-cyclosteroid (41). The product, isolated as a white solid was recrystallised from 70% aqueous acetone as colourless plates, (4.61g, 80%). m.pt= 166-168° [165-166°¹⁷] ¹H NMR (δ): 0.84 (3H, s, 18-H), 1.01 (3H, s, 19-H), 3.50 (1H, bm, 3-H), 3.87 (4H, s, dioxolane-H), 5.36 (1H, d, J= 2.4Hz, 6-H). IR ν_{\max} (cm⁻¹): 3350, 1665, 1020.

3 β -Tosyl-5-androsten-17-spiro-2'-(1,3-dioxolane) (137a).

Formation of the tosylate derivative was in an identical manner to the synthesis of the DHEA tosylate (98a). Isolation gave an off white solid which tlc showed as comprising of two products in the approximate ratio of 10:1. These two compounds were readily separated by preparative tlc:

Major component, 3 β -tosyl-5-androsten-17-spiro-2'-(1,3-dioxolane) (137a) (2.80g, 70%). m.pt= 138-141°C. [lit= 139-141°¹⁵]. ¹H NMR (δ): 0.86 (3H, s, 18-H), 1.01 (3H, s, 19-H), 2.41 (3H, s, tosyl Me-H), 3.89 (4H, s, dioxolane-H),

4.32 (1H, bm, 3-H), 5.35 (J= 4.2 Hz, 6-H), 7.30, (2H, d, J= 8.6Hz, aromatic-H), 7.80 (2H, d, J= 8.6Hz, aromatic-H). IR ν_{\max} (cm⁻¹): 1670, 1605, 1350, 1030.

Minor component, (0.25g) 3 β -tosyl-5-androsten-17-one (98a). Identical to previously produced sample.

6 β -Hydroxy-3 α ,5-Cyclo-5 α -androstane-17-spiro-2'-(1,3-dioxolane) (126).

The protected, tosylated steroid (137a) was cyclised under identical conditions to those employed in the acetone solvated cyclisation of the DHEA tosylate (98a). Thin layer chromatography showed the presence of two products in the off white solid which were readily separated by preparative tlc:

Major product, (1.41g, 70%), 6 β -hydroxy-3 α ,5-cyclo-5 α -androstane-17-spiro-2'-(1,3-dioxolane) (126). m.pt= 144-146° [lit= 144-146°¹⁸]. ¹H NMR (δ): 0.27 (1H, d, J= 8Hz, 4-H), 0.33 (1H, d, J= 8Hz, 4-H), 0.55 (1H, t, J= 4.8Hz, 3-H), 0.86 (3H, s, 18-H), 1.05 (3H, s, 19-H), 3.30 (1H, t, J= 2.4Hz, 6-H), 3.80 (4H, s, dioxolane-H). IR ν_{\max} (cm⁻¹): 3060, 3010, 1050.

Minor component, isolated as a gum from recrystallisation medium, 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (41) (0.29g). Identical to previously isolated sample.

3 β -Mesyl-5-androsten-17-spiro-2'-(1,3-dioxolane) (137b).

Mesylation of the protected steroid (126) was carried out in an identical manner to the mesylation of DHEA (97). Two compounds (10:1) were detected and separated by tlc:

Major component, 3 β -mesyl-5-androsten-17-spiro-2'-(1,3-dioxolane) (137b), (2.84g, 71%). m.pt= 165-167°. ¹H NMR (δ): 0.86 (3H, s, 18-H), 1.03 (3H, s, 19-H), 3.00 (3H, s, mesyl-H), 3.87 (4H, s, dioxolane-H), 5.43 (1H, d, J= 4.2 Hz, 6-H). IR ν_{\max} (cm⁻¹): 1670, 1360, 1140, 1050.

Minor component, (0.35g), 3 β -mesyl-5-androsten-17-one (97b). Identical to previously synthesised sample.

6 β -Hydroxy-3 α ,5-Cyclo-5 α -androstan-17-spiro-2'-(1,3-dioxolane) (126).

Cyclisation of the steroid mesylate was accomplished under the same conditions used in the acetone solvated cyclisation of DHEA.

The white solid product was shown by tlc to consist of two compounds which were separated by tlc:

Major product, 6 β -hydroxy-3 α ,5-cyclo-5 α -androstan-17-spiro-2'-(1,3-dioxolane) (126), (1.50g, 75%). Identical to previously synthesised sample.

Minor component, (0.22g), 6 β -hydroxy-3 α ,5-cycloandrostan-17-one (41). Identical to previously synthesised sample.

3 β -Hydroxy-5-androsten-17(S)-spiro-2'-(1,3-oxathiolane) (131).

Formation of the oxathiolane derivative of DHEA was undertaken in an identical procedure to that used in the attempted direct synthesis of compound (150) where benzene was used as solvent. The product was isolated as a white solid by flash column chromatography of the crude reaction slurry (5.37g: 80%). m.pt= 148-150° [lit= 151-153°¹⁹]. ¹H

NMR (δ): 0.83 (3H, s, 18-H), 1.02 (3H, s, 19-H), 2.86 (2H, m, (M₂X₂), oxathiolane moiety 4-H), 3.53 (1H, bm, 3-H), 4.09 (2H, m, (M₂X₂), oxathiolane moiety 5-H), 5.35 (1H, d, J=4.2Hz, 6-H). ¹³C NMR (δ): 40 (oxathiolane moiety 5-C), 70 (oxathiolane moiety 4-C), 72 (3-C), 106 (17-C), 122 (6-C), 142 (5-C). IR ν_{\max} (cm⁻¹): 3380, 1670, 1085, 740. CH analysis, calc for, C= 68.90%, H=9.10%, Found, 69.23%, H=9.19%. MS m/z: 348 (25%) [molecular ion], 288 (40%), 270 (50%), 255 (30%), 244 (15%), 213 (15%), 145 (20%), 115 (100%).

3 β -Tosyl-5-androsten-17(S)-spiro-2'-(1,3-oxathiolane).

Formation of the tosylated oxathiolane steroid was initially undertaken in an identical procedure to that used in the tosylation of DHEA (97). Three further adaptations were also investigated.

Method 1.

The reaction was carried out under identical conditions to the tosylation of DHEA (97). The product, a pale brown solid was crystallised direct from solution by the addition of iced water. Thin layer chromatography indicated two compounds which were readily separated by preparative tlc utilising toluene/ ethyl acetate (3:1) as a mobile phase:

Major compound, DHEA, spectroscopically identical to starting material.

Minor compound, p-toluenesulphonic acid. Identical to an authentic sample.

Method 2.

This method was identical to method I but a five fold excess of tosylchloride was employed. The product was worked up in the usual manner and resulted in the isolation of the starting steroid (131) and p-toluenesulphonyl chloride.

Method 3

By identical means to the tosylation of DHEA where dichloromethane was used as a solvent (method 2), the thioxalane (131) was treated with an equimolar amount of tosyl chloride under reflux. The product showed no sign of tosylation having occurred.

Method 4.

The conditions employed were identical to those used in both method I and II but the reaction mixtures were warmed to 40° or 60° in an oil bath or allowed to reflux. All six reactions again resulted in the isolation of starting material.

Method 5.

All the above methods were repeated but a non-aqueous workup was employed. Removal of the solvent under reduced pressure at room temperature, followed by preparative tlc resulted in the isolation of the two starting materials.

3β-Mesyl-5-androsten-17(S)-spiro-2'-(1,3-oxathiolane) (148).

In a similar manner to the formation of the mesylate (98b), 1g of the oxathiolane (2.87 mmoles) was dissolved in 10ml of anhydrous pyridine. To this solution was added 0.34g

of methanesulphonyl chloride (2.97 mmoles) and the mixture allowed to stand at room temperature for 48 hours. After this period 20 ml of 50% acetone solution was added to the solution and the precipitate filtered off. Vacuum drying at 40° gave a white solid. (0.96g: yield= 75%). m.pt= 147-148°. ^1H NMR (δ): 0.83 (3H, s, 18-H), 1.03 (3H, s, 19-H), 2.85 (2H, m, (M_2X_2), oxathiolane moiety 4-H), 3.00 (3H, s, mesylate-H), 4.05 (2H, m, (M_2X_2), oxathiolane moiety 5-H), 4.50 (1H, bm, 3-H), 5.43 (1H, d $J= 4.2\text{Hz}$, 6-H). IR ν_{max} (cm^{-1}): 3050, 3025, 1675, 1340, 1090, 780.

Reaction between tosyl chloride and β -mercapto ethanol.

p-Toluenesulphonyl chloride (1g, 5.25 mmoles) and an equimolar amount of β -mercapto ethanol (0.41g) were dissolved in 5ml of pyridine. This mixture was then stirred overnight. removal of the solvent under reduced pressure gave a brown oil consisting of a complex mixture of products. Partial separation by preparative tlc gave three fractions:

Fraction 1, 2-tosyl- β -mercaptoethanol (149). ^1H NMR (δ): 2.32 (3H, s, tosyl Me-H), 2.86 (2H, t, $J= 5.6\text{Hz}$, 1-H), 3.83 (2H, t, $J= 5.6\text{Hz}$, 2-H), 7.10 (2H, d, $J= 8.0$, aromatic-H), 7.62 (2H, d, $J= 8\text{Hz}$, aromatic-H). IR ν_{max} (cm^{-1}): 3420, 1600, 1150, 820.

Fractions 2 and 3 were tentatively assigned as inseparable mixtures of ditosylates and cyclised products.

6 β -Hydroxy-3 α ,5-Cyclo-5 α -androstande-17(S)-spiro-2'-(1,3-oxathiolane) (150).

Cyclisation was attained by an identical method to that used in the formation of the parent 3,5 cyclosteroid (41). Purification of the resulting oil with flash chromatography (mobile phase toluene/ ethyl acetate, 3:1) gave the desired steroid (150) as a colourless glass, (1.29g, 80%). ^1H NMR (δ): 0.28 (1H, d, $J= 8\text{Hz}$, 4-H), 0.34 (1H, d, $J= 8\text{Hz}$, 4-H), 0.57 (1H, t, 4.8Hz, 3-H), 0.85 (3H, s, 18-H), 1.08 (3H, s, 19-H), 2.85 (2H, m, (M_2X_2), oxathiolane moiety 4-H), 3.32 (1H, t, $J= 2.4\text{Hz}$, 6-H), 4.05 (2H, m, oxathiolane moiety 5-H). IR ν_{max} (cm^{-1}): 3420, 3070, 1080, 1035. CH analysis, calc for, C= 72.41% H= 9.19%. Found C= 72.83% H= 9.23%. MS m/z : 348 (10%) [molecular ion], 288 (25%), 270 (30%), 254 (20%), 115 (100%).

6-oxo-3 α ,5-Cyclo-5 α -androstande-17(S)-spiro-2'-(1,3-oxathiolane) (151).

The oxidation of the 6 β alcohol to the relevant ketone with Collins' reagent¹⁰ was carried out in an identical procedure to that used for the oxidation of the parent alcohol (41) to the ketone (111). Drying the organic extract with anhydrous magnesium sulphate, decolourising with charcoal and evaporation of the solvent gave a clear yellow oil. Preparative tlc utilising a 3:1 toluene ethyl acetate mobile phase yielded two pale yellow solids:

The major product, was recrystallised from 70% acetone as colourless needles. Major product, (0.32g, 65%), 6-oxo-3 α ,5-cyclo-5 α -androstande-17(S)-spiro-2'-(1,3-oxathiolane)

(151). m.pt 148-150°. ¹H NMR (δ): 0.74 (1H, t, J= 4.0Hz, 3-H), 0.87 (3H, s, 18-H), 1.01 (3H, s, 19-H), 2.86 (2H, m, (M₂X₂) oxathiolane moiety 4-H), 4.06 (2H, m, (M₂X₂) oxathiolane moiety 5-H). IR ν_{max} (cm⁻¹): 3115, 3020, 2990, 1678, 1070, 805. MS m/z: 346 (1%) [molecular ion], 287 (20%), 115, (100%).

Minor product, (30mg), 3α,5-cyclo-5α-androstane-6-17-dione (111). Data cited above.

6-Methylene-3α,5-cyclo-5α-androstane-17(S)-spiro-2'-(1,3-oxathiolane (156).

Synthesis of the 6-methylene derivative, from the 6-keto steroid, was carried out using similar methods to that of Wittig²⁰ and Sondheimer.²¹ Under a nitrogen atmosphere, 1ml of a 1.6M ethereal solution of n-butyl lithium (1.59 mmoles) was added slowly and with stirring to a suspension of 0.52g methyltriphenylphosphonium bromide (CH₃P(Ph)₃Br (1.44 mmoles) in 50ml sodium dried diethyl ether. This yellow solution was then stirred at room temperature for 4 hours. 100mg of the steroid (0.29 mmoles) dissolved in 20ml of sodium dried ether was then slowly added and this mixture was refluxed, with the exclusion of oxygen, for 16 hours. After this period the precipitate was filtered off and washed with ether. The combined solutions were washed with aqueous solutions of 5% HCl, 5% NaHCO₃ and water before drying with magnesium sulphate. Decolourising and removal of the solvent under vacuum gave a brown oil. Preparative tlc using 3:1 toluene: ethyl acetate as the mobile phase resulted in the isolation of two products:

Major component, 6-methylene-3 α ,5-cyclo-5 α -androstane-17(S)-spiro-2'-(1,3-oxathiolane) (156), (66mg, 66%). m.pt=133-136°. ¹H NMR (δ): 0.38 (1H, t, J= 5.6Hz, 3-H), 0.85 (6H, s, 18 and 19-H), 2.85 (2H, m, (M₂X₂), oxathiolane moiety 4-H), 4.03 (2H, m, oxathiolane moiety 5-H), 4.63 (2H, d, J= 5.6Hz, 6'-H). IR ν_{\max} (cm⁻¹): 3080, 3065, 3015, 2990, 2985, 1642. MS m/z: 344 (2%) [molecular ion], 277 (10%), 115 (100%).

Minor component, 3 α ,5-cyclo-5 α -androstan-6-one-17(S)-spiro-2'-(1,3-oxathiolane (151) (20mg).

Syntheses from section 3.4.

The reaction conditions for the synthesis of 3 β -mesyl-5-androsten-17-ol (or the 3 β tosylate), its corresponding 17 β -acetate, 3 α ,5-cyclo-5 α -androstane-6 β ,17 β -diol-17-acetate and 17 β -acetoxy-3 α ,5-cyclo-5 α -androstan-6-one were based on the work of Labler and Sorm.²²

3 β -Tosyl-5-androsten-17-one (98a).

The formation of this compound is discussed elsewhere in this chapter.

5-Androsten-3 β ,17 β -diol-3-tosylate (174a).

1g of lithium aluminiumhydride (LiAlH₄, 26.3 mmoles) as a slurry in 100ml of sodium dried diethyl ether was slowly added, with stirring to a solution of the tosylated steroid (98a), 3.76g (8.51 mmoles) in 100ml sodium dried tetrahydrofuran. After a period of 3 hours 50ml of ice cold distilled water were carefully added and the mixture stirred for 30 minutes. The organic layer was then separated off and the aqueous layer washed with 2x 50ml portions of diethyl ether. The organic layers were then combined, dried with magnesium sulphate and the solvent removed under reduced pressure. The desired alcohol, a creamy white solid, gave colourless crystals, (3.13g, 83%), after recrystallisation from anhydrous acetone. m.pt= 138-140° (with decomposition), [lit 145-147°²²]. ¹H NMR (δ): 0.74 (3H, s, 18-H), 0.98 (3H, s, 19-H), 2.44 (3H, s, tosyl-H), 3.63, (H, t, J= 8.0Hz, 17-H), 4.36 (1H, bm, 3-H), 5.42 (1H, d, J= 2.4Hz, 6-H), 7.32

(2H, d, J= 8.8Hz, aromatic-H), 7.84 (2H, d, J= 8.8Hz, aromatic-H). IR ν_{\max} (cm^{-1}): 3380, 1680, 1605, 1350, 1170, 640.

3 β -Mesyl-5-androsten-17-one (98b).

The formation of this compound is discussed elsewhere in this chapter.

5-Androsten-3 β ,17 β -diol-3-mesylate (174b).

The reduction of the keto group of the mesylate (98b) was achieved by an identical procedure to that used for the tosylate, that is, with a three molar excess of LiAlH_4 (see above). The alcohol, a creamy white solid, gave colourless crystals, (2.46g, 83%) after recrystallisation from acetone. m.pt= 135-138°, (with decomposition). ^1H NMR (δ): 0.74 (3H, s, 18-H), 1.05 (3H, s, 19-H), 3.02 (3H, s, mesyl-H), 3.67 (1H, t, J= 7.2 Hz, 17-H), 4.43 (1H, bm, 3-H), 5.45 (1H, d, J= 4.8 Hz, 6-H). IR ν_{\max} (cm^{-1}): 3330, 3025, 3005, 1665, 1350, 1170, 950.

5-Androstene-3 β ,17 β -diol-3-tosylate-17-acetate (175).

The steroid alcohol (174), 1g (2.25 mmoles) was dissolved in a mixture of acetic anhydride (5ml) and pyridine (15ml) and the mixture stirred over a 12 hour period. After this time 10ml of iced distilled water was added to the reaction mixture. This was then stirred for an additional 30 minutes at which point the solution was extracted with 5x 50ml portions of CHCl_3 . The organic layer was then separated and washed repeatedly with 5% HCl and 5% NaHCO_3 solutions. Drying of the solvent with magnesium sulphate and removal of

the solvent under reduced pressure gave a white solid which recrystallised as long needles, (1.01g, 92%), from a 70% acetone solution. m.pt= 118-120° [lit= 119-121°²²]. ¹H NMR (δ): 0.78 (3H, s, 18-H), 0.97 (3H, s, 19-H), 2.02 (3H, s, acetate-H), 2.44 (3H, s, tosyl-H), 4.40 (1H, bm, 3-H), 4.59 (1H, t, J= 7.2 Hz, 17-H), 5.44 (1H, d, J= 4.8 Hz, 6-H), 7.34, (2H, d, J= 8.0, aromatic-H), 7.84 (2H, d, J= 8.0Hz, aromatic-H). IR ν_{\max} (cm⁻¹): 1720, 1675, 1600, 1250, 1030, 640.

5-Androstene-3 β ,17 β -diol-3-mesylate-17-acetate (175b).

The steroid alcohol (174b), 1g (2.72 mmoles) was converted to its 17 β -acetate under identical conditions to those used for the tosylate. The product a white solid recrystallised as long needles (1.06g, 95%), from anhydrous acetone. m.pt= 150-152°. ¹H NMR (δ): 0.78 (3H, s, 18-H), 1.05 (3H, s, 19-H), 2.00 (3H, s, acetate-H), 3.04 (3H, s, mesyl-H), 4.44 (1H, bm, 3-H), 4.62, (1H, t, J= 7.2Hz, 17-H), 5.45 (1H, d, J= 4.8 Hz, 6-H). IR ν_{\max} (cm⁻¹): 3330, 3025, 3005, 1725, 1665, 1350, 1070.

3 α ,5-Cyclo-5 α -androstane-6 β ,17 β -diol-17-acetate (176).

The cyclisation of the mesylate (175b) or tosylate (175a) was undertaken by method 1 of the cyclisation reactions attempted. 1g of the steroid (2.05/ 2.43 mmoles) was dissolved in 100ml of acetone. To this solution was added 1g (10.20 mmoles) potassium acetate in 20ml distilled water and the resulting aqueous solution refluxed for 6 hours. After cooling a further 20ml of distilled water was added and the

solution temperature lowered. The product, as colourless crystals, was collected by filtration and dried. (0.54g 80% (mesylate)/ 0.68g 85%(tosylate)). m.pt= 131-132° [lit= 130-132°²²]. ¹H NMR (δ): 0.29 (1H, d, J= 8Hz, 4-H) 0.35 (1H, d, J= 8Hz, 4-H), 0.56 (1H, t, J= 4.8Hz, 3-H), 0.84 (3H, s, 18-H), 1.06 (3H, s, 19-H), 2.03 (3H, s, acetate-H), 3.29 (1H, t, J= 2.4 Hz, 6-H), 4.61 (1H, t, J= 7.2Hz, 17-H). IR ν_{\max} (cm⁻¹): 3350, 3050, 1720, 1285, 1020.

17β-Acetoxy-3α,5-cyclo-5α-androstan-6-one (177).

The oxidation of the 6β-alcohol (176) was undertaken in an identical procedure to that used in the oxidation of steroid alcohol (150). Reaction between the steroid (1g, 3.03 mmoles) and the six fold excess of Collins' reagent¹⁰ gave, after removal of the solvent, a clear or pale yellow glass. Crystallisation from acetone afforded colourless plates (0.68g 68%). m.pt= 113-114° [lit= 114°²²]. ¹H NMR (δ): 0.69 (1H, t, J= 4.8 Hz, 3-H), 0.81 (3H, s, 18,-H), 1.00 (3H, s, 19-H), 2.01 (3H, s, acetate-H), 4.61 (1H, t, J= 7.2Hz, 17-H). IR ν_{\max} (cm⁻¹): 3060, 1730, 1675, 1265, 1040.

6-Methylene-3α,5-cyclo-5α-androstan-17β-ol (178).

Synthesis of the methylene derivative was undertaken in an identical fashion to the 6-methylene steroid (156). The reaction between the steroid (250mg) and a four fold excess of the Wittig reagent gave, after removal of the solvent under reduced pressure, a pale yellow oil. Preparative tlc successfully separated two products:

Major component, 6-methylene-3 α ,5-cyclo-5 α -androstan-17 β -ol (178), (175mg, 70%) as a white solid. m.pt= 139-141°. ¹H NMR (δ): 0.41, (1H, t, J= 4.6 Hz, 3-H), 0.77 (3H, s, 18-H), 0.86 (3H, s, 19-H), 3.66 (1H, t, J= 7.2 Hz, 17-H), 4.64 (2H, d, J= 5.6Hz, 6'-H). IR ν_{\max} (cm⁻¹): 3380, 3090, 3042, 3020, 1650, 890. CH analysis, calculated for C₂₀H₃₀O: C= 83.92%, H= 10.49%. Found C= 83.22%, H= 10.49%.

Minor component 6-methylene-3 α ,5-cyclo-5 α -androstan-17 β -yl acetate (179), (40mg, 16%) as a pale brown gum. ¹H NMR (δ): 0.41, (1H, t, J= 4.6Hz, 3-H), 0.77 (3H, s, 18-H), 0.86 (3H, s, 19-H), 2.02 (3H, s, acetate-H), 4.60 (1H, t, J= 8.0Hz, 17-H), 4.63 (2H, d, J= 5.6Hz, 6'-H). IR ν_{\max} (cm⁻¹): 3090, 3020, 1730, 1645, 1250, 900.

6-Methylene-3 α ,5-cyclo-5 α -androstan-17-one (180).

In an identical manner to the Jones' oxidation of DHEA (97), 100mg (3.49x mmoles) of steroid alcohol (179) was oxidised to the 17-ketone compound. Removal of the solvent under reduced pressure gave a clear glass which failed to crystallise (76mg, 77%) ¹H NMR (δ): 0.41, (1H, t, J= 4.8Hz, 3-H), 0.86 (3H, s, 18-H), 0.90 (3H, s, 19-H), 4.64 (2H, d, J= 5.6Hz, 6'-H). IR ν_{\max} (cm⁻¹): 3085, 3040, 3020, 1735, 1650, 890.

Syntheses from section 3.5

6 β -methyl-3 α ,5-cyclo-5 α -androstan-17-one

On the basis of the sulphonate substituting properties of dimethyl lithium cuprate²³ and the use of trialkyl aluminium for simultaneous cyclisation and alkylation of 6-C in 3-C sulphonates,²⁴ the reaction between the 3-C mesylate and dimethyl lithium cuprate was investigated.

A five fold (1.53 mmoles) excess of dimethyl lithium cuprate was formed under a dry nitrogen atmosphere by the addition of 0.29g copper iodide to 33.7mg methyl lithium in 100ml anhydrous diethyl ether. The yellow precipitate thus formed was stirred at room temperature for 30 minutes. After this period the steroid, 100mg (3.07 mmoles), was added as a solution in 50ml anhydrous diethyl ether resulting in a white precipitate. The reaction mixture was then continuously stirred for 12 hours. Decomposition of the excess of the reagent was facilitated by the slow addition of a saturated solution of ammonium chloride. The two phase mixture was then stirred for an additional 2 hours. The organic layer was then removed and the aqueous layer washed with 3x 100ml diethyl ether. The combined organic layers were then dried with anhydrous magnesium sulphate and the solvent removed. Column chromatography of the resulting oil, on silica gel with toluene/ ethyl acetate (3:1) as eluent, resulted in the isolation of two white solids:

Major component, 17 α -methylandrosta-5-ene-3 β , 17 β -diol (70mg) (181), m.pt. 207-210° [lit= 212°²⁵]. ¹H NMR (δ): 0.80 (3H, s, 18-H), 0.96 (3H, s, 18-H), 1.15 (3H, s, 17-H), 3.44 (1H, bm, 3-H), 5.37 (1H, d, J= 2.4Hz, 6-H). IR ν_{\max}

(cm^{-1}): 3400, 1640.

Minor component, 3 β -hydroxy-5-androsten-17-one (20mg) (97).

Syntheses from section 3.6

Attempted synthesis of the 6-methylene derivative (180) was undertaken in an identical fashion^{20,21} to the 17-protected methylene steroids (156) and (178). The reaction between the dione (500mg) and a four fold excess of Wittig reagent, gave after removal of the solvent under reduced pressure, an off white solid. Column chromatography on silica gel using toluene/ethyl acetate (3:1) as eluent gave three products:

17-methylene-3 α ,5-cyclo-5 α -androstan-6-one (182) as an off white solid (300mg). m.pt.= 135-141°. ¹H NMR (δ): 0.75 (1H, t, J= 4.8Hz, 3-H), 1.02 (3H, s, 18-H), 0.87 (3H, s, 18-H), 4.50 (2H, bs, 17'-H). IR ν_{max} (cm^{-1}): 3075, 3010, 1680.

6-methylene-3 α ,5-cyclo-5 α -androstan-17-one (180) as a colourless oil (80mg). ¹H NMR (δ): 0.40 (1H, t, J= 4.8Hz, 3-H), 0.86 (3H, s, 18-H), 0.90 (3H, s, 18-H), 4.64 (2H, d, J= 5.6Hz, 6'-H). IR ν_{max} (cm^{-1}): 3085, 3040, 3020, 1735, 1645, 890.

3 α ,5-cyclo-5 α -androstan-6,17-dione (111), (50mg). m.pt.= 181-183° [lit= 182-183°] ¹H NMR (δ): 0.75 (1H, t, J= 4.8Hz, 3-H), 0.92 (3H, s, 18-H), 1.04 (3H, s, 19-H). IR ν_{max} (cm^{-1}): 3090, 3015, 1735, 1680.

Synthesis of 6 β -methyl-7 α -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (44).

8.4 Synthesis from chapter 4.

3 α ,5-Cyclo-5 α -androst-6-en-17-one (185).

In an analogous manner to Cambie *et al.*²⁸ unpurified steroid alcohol (41) (4g, 1.74×10^{-2} moles) was dissolved in 150ml toluene and to this solution was added 15g neutral alumunium oxide and this mixture refluxed overnight. The addition of boiling sticks as well as anti-bumping granules was necessary to avoid excessive bumping. After this period the mixture was cooled and alumina removed by filtration. The alumina was then washed for a period of 1 hour with dichloromethane. Combining the organic solutions, decolourising with charcoal and removal of the solvent gave an oily, brown solid. Column chromatography on silica gel with toluene/ ethyl acetate as eluent gave three compounds the first two of which were in sufficient quantities for recrystallisation from neat ethanol:

Major product, 3 α ,5-cyclo-5 α -androst-6-en-17-one (185), (2.72g, 59%) m.pt= 136-137°, [lit= 136-137°²⁷]. ¹H NMR (δ): 0.44 (1 or 2H, m, 3 or 4-H), 0.93 (6H, s, 18 and 19-H), 5.25 (1H, dd, J= 9.6 and 2.3 Hz, 7-H), 5.57 (1H, dd, J= 9.6 and 0.9 Hz, 6-H). IR ν_{\max} (cm⁻¹): 3062, 3022, 3000, 1735, 1635, 735. UV (nm), 216 (14000).

4-androsten-3,17-dione, (0.42g) (198). m.pt= 169-171°. [lit= 170-171°²⁵] ¹H NMR (δ): 0.92 (3H, s, 18-H), 1.21 (3H, s, 19-H), 5.75 (1H, s, 4-H). IR ν_{\max} (cm⁻¹): 1740, 1675, 1620, UV (nm), 239.5

3 α ,5-cyclo-5 α -androstane-6,17-dione, (0.33g) (111).

m.pt= 179-182° [lit= 182-183°¹]. ¹HNMR (δ): 0.75, (1H, t, J= 4.0Hz), 3-H), 0.92 (3H, s, 18-H), 1.04 (3H, s, 19-H). IR ν_{max} (cm⁻¹): 3093, 3022, 1732, 1681.

3α,5-Cyclo-5α-androstan-6-en-17-dioxolane (186).

In a similar manner to the attempted formation of the dioxolane derivative (125) 0.5g (1.84 mmoles) of the steroid, 5.1g (82.2 mmoles) ethylene glycol and 100mg of p-toluenesulphonic acid were dissolved in 100ml benzene. The flask was fitted with a modified Dean/Stark apparatus and the solution refluxed for 16 hours. After cooling, the benzene was diluted with 100ml diethyl ether and washed with 10x 100ml, 5% NaHCO₃. The organic layer was then dried and the solvent removed under reduced pressure to give a clear oil. Preparative tlc utilising a 3:1 ratio of toluene and ethyl acetate as the mobile phase produced only one major product as a colourless glass.

3α,5-cyclo-5α-androstan-6-ene-17,17-dioxolane (186). ¹H NMR (δ): 0.36 (1 or 3H, m, 3 and 4-H), 0.89 (6H, s, 18 and 19-H), 3.86 (4H, s, dioxolane-H), 5.19 (1H, d, J= 9.6Hz, 7-H), 5.54 (1H, d, J= 9.6Hz, 6-H). IR ν_{max} (cm⁻¹): 3065, 3040, 1645, 1120, 1050.

6α,7α-Epoxy-3α,5-cyclo-5α-androstan-17-one (209).

The epoxidation of 3α,5-cyclo-5α-androst-6-en-17-one was based on the method used by Cambie *et al.*²⁸ The steroid, 3α,5-cyclo-5α-androstan-6-en-17-one (800mg, 2.94 mmoles) in 30ml sodium dried ether was treated with m-chloroperbenzoic acid (1.26g, 7.35 mmoles) at 0° for 30 minutes.

After this period the solution was diluted with a further 50ml of diethyl ether and then washed rapidly with ice cold 50ml portions of 2% ferrous sulphate, water, 5% sodium hydrogen carbonate and water. The organic layer was then dried with anhydrous magnesium sulphate and the solvent removed under reduced pressure to yield a pale brown oil. Spectroscopic data varied from sample to sample but the ^1H NMR spectrum consistently showed signals at (δ): 0.38, (3H, m, 3 and 4-H), 2.89, 3.00, 3.23 3.65 (bs, 6 and 7H).

Because isolation proved extremely difficult the oily product was treated instantaneously with dimethyl lithium cuprate.

6 β -methyl-7 α -hydroxy-3 α ,5-cyclo-5 α -androstan-17-one (44).

The oil obtained from the epoxidation of the alkene (185) (0.8g, 2.80 mmoles), as a solution in anhydrous diethyl ether (50ml) was added slowly to a five fold excess of dimethyl lithium cuprate²³ in 100ml anhydrous ether prepared by the addition of 20ml, 1.4 M solution methyl lithium (0.62g) to 80ml anhydrous ether containing 2.66g copper (I) iodide. As expected, the addition of one molar equivalent of methyl lithium resulted in a yellow precipitate. The addition of a second equivalent resulted in the desired colourless/ pale brown oil. The reaction mixture was then stirred for 14 hours. After this period 80ml of a saturated solution of ammonium chloride was added and the solution stirred for a further 2 hours. The layers were then separated and the aqueous layer washed with three portions of diethyl ether (50ml). The organic phases were then combined and the sol-

vent removed under reduced pressure to yield an olive green gum. Flash chromatography utilising a mobile phase of ethyl acetate and toluene (3:1) resulted in the collection of five pale brown oily fractions. Thin layer chromatography and ^1H NMR spectroscopy showed limited separation had been attained but identified the presence of two of the desired products:

6β -methyl- 7α -hydroxy- $3\alpha,5$ -cyclo- 5α -androstan-17-one (44b), 40mg. ^1H NMR (δ): 0.40 (3H, t, cyclopropyl), 0.91 (6H, bs, $6'$ and 18-H), 0.97 (3H, s, 19-H), 3.68 (1H, 7-H). IR ν_{max} (cm^{-1}): 3480, 1735.

7α -methyl- 6β -hydroxy- $3\alpha,5$ -cyclo- 5α -androstan-17-one (190b), 40mg. ^1H NMR (δ): 0.30 (2H, m, 4-H) 0.50 (1H, m, 3-H), 0.88 (3H, s, 18-H), 1.09 (3H, s, 19-H), 1.18 (3H, bs, $7'-\text{H}$), 3.83 (1H, 6-H). IR ν_{max} (cm^{-1}): 3530, 1735.

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Appendix

Publications

"Structure of 3β -hydroxy-5-androsten-17-one (DHEA) monohydrate." Acta Cryst., 1990, C46, 334.

"Crystal and Molecular Structure of 6β -hydroxy- $3\alpha,5$ -cyclo- 5α -androstan-17-one." J. Cryst. & Spec. Res., 1990, 20(5), 415.

Postgraduate studies.

Additional Courses

The following courses at Aberdeen University and The Robert Gordon Institute of Technology have been attended:

- 1). Chemical Crystallography (3rd year undergraduate course).
- 2). Organic Synthesis (4th year undergraduate course).
- 3). Radiation Hazards Course.
- 4). Biologically Active Steroids (4th year undergraduate course).

Conferences

The 19th Scottish regional meeting (December 1990) of the Royal Society of Chemistry- Perkin Division was attended. Posters presentations were made at the Chemistry Postgraduate Summer School, Scottish College of Textiles, 1988 and the British Crystallographic Association, Spring Meeting, Exeter University, April 1990. In addition a number of seminars at Aberdeen University and The Robert Gordon Institute of Technology were presented and/or attended.