THE TOTAL SYNTHESIS

OF

LINEAR ANTHRASTEROIDS

by

PETER R. DAVISON

A THESIS SUBMITTED TO THE
COUNCIL FOR NATIONAL ACADEMIC AWARDS
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ABSTRACT

THE TOTAL SYNTHESIS

OF LINEAR ANTHRASTEROIDS

by PETER R. DAVISON

The aim of the project was to synthesize linear anthrasteroid analogues of testosterone, 19-nortestosterone and estradiol.

A total synthesis of (±)-7,11-cyclo-8,9-seco-19-nortestosterone, (±)-7,11-cyclo-8,9-seco estradiol and (±)-1β-t-butoxy-9a,11aβ-dimethyl-1,2,3,3aα,4,4aα,5,8,9,9a,10,10aβ,11,11a-tetradecahydro-7-cyclopent[b]anthracenone was accomplished. The synthesis presented provides a short, direct route to linear anthrasteroid analogues. This compares favourably with the synthesis reported by S. Aoyama and K. Sasaki, which involves complex transformations of steroids.

The synthetic route involved the synthesis of the trans-bicyclic hydrindan, (±)-1β-t-butoxy-7aβ-methyl-3aα,4,7,7a-tetrahydro-5(6H)-indanone, using the synthetic pathway developed by Z.G. Hajos and D.R. Parrish. This intermediate was regiospecifically annulated to give the novel tricyclic enone, (±)-1β-t-butoxy-9aβ-methyl-1,2,3,3aα,4,7,8,8aβ,9,9a-decahydro-6-benz[f]indenone via two different routes. The stereochemistry of the new ring junction was elucidated by using ^1H n.m.r. spectroscopy and the lanthanide shift reagent $Eu(FOD)_3$.

Further regiospecific annulation of the tricyclic enone gave the novel linear tetracyclic compound, (±)-1β-t-butoxy-11aβ-methyl-1,2,3,3aα,4,4aα,5,8,9,9aβ,10,10aβ,11,11a-tetradecahydro-7-cyclopent[b]anthracenone. The t-butyl group of this compound was removed to give (±)-7,11-cyclo-8,9-seco-19-nortestosterone, or the A-ring was aromatized and the t-butyl group cleaved to give (±)-7,11-cyclo-8,9-seco estradiol.

The synthesis of linear anthrasteroid analogues of testosterone was accomplished by regiospecific methylation of the tricyclic enone to give the novel compound (±)-1β-t-butoxy-7,9aβ-dimethyl-1,2,3,3aα,4,7,8,8aβ,9,9a-decahydro-6-benz[f]indenone. Regiospecific annulation of this compound gave a mixture of stereoisomers, (±)-1β-t-butoxy-9aβ,11aβ-dimethyl-1,2,3,3aα,4,4aα,5,8,9,9a,10,10aβ,11,11a-tetradecahydro-7-cyclopent[b]anthracenone and (±)-1β-t-butoxy-9aα,11aβ-dimethyl-1,2,3,3aα,4,4aα,5,8,9,9a,10,10aβ,11,11a-tetradecahydro-7-cyclopent[b]anthracenone.

CONVENTIONS AND ABBREVIATIONS

A broken line: ----- denotes an α-configuration.

A solid tapered line: ◄ denotes a β-configuration.

A wavy line: ~ denotes either an unknown or unspecified configuration.

Me denotes CH_3

Et denotes CH_3CH_2

n-Bu denotes $CH_3CH_2CH_2CH_2$

Bu^t denotes $(CH_3)_3C$

Ph denotes C_6H_5

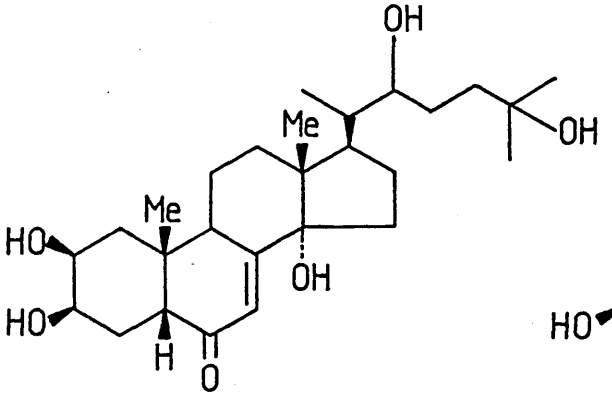
CHAPTER ONE

INTRODUCTION

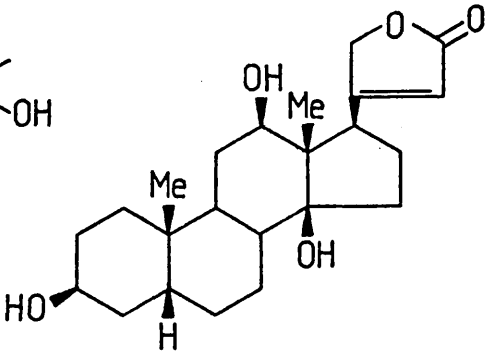
1.1 GENERAL INTRODUCTION

The naturally occurring steroids are a diverse group of compounds, ubiquitous in animals and plants.

They display a wide range of physiological properties, for example[1] ecdysone is required for the moulting process in insects, whilst some cardiac genins , such as digoxigenin, are used clinically as their glycosides, for the treatment of congestive heart failure.

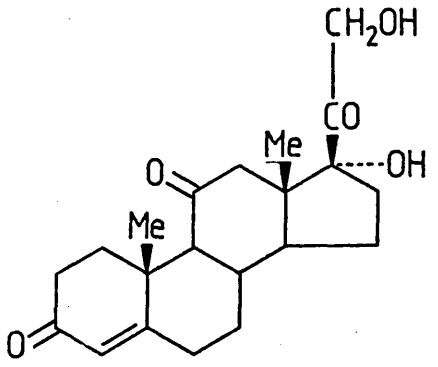


Ecdysone

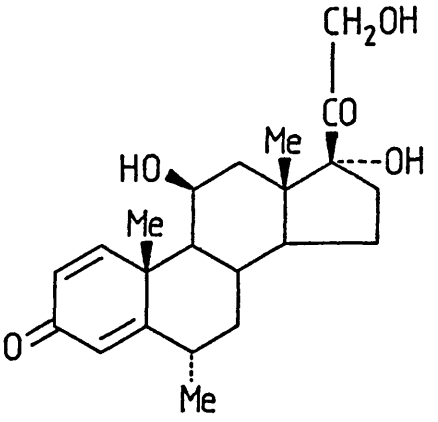


Digoxigenin

The corticosteroids , such as cortisone, are used for the treatment of inflammatory diseases. Indeed, since the demonstration of the anti-arthritic effects of cortisone in 1949, the drug industry has been active in synthesising analogues of cortisone,(for example methyl prednisolone) in an effort to increase its therapeutic usefulness.

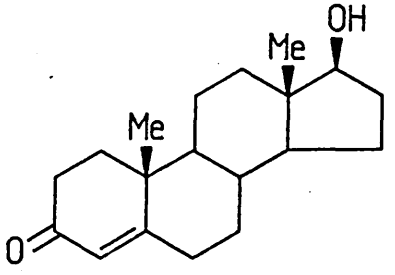


Cortisone

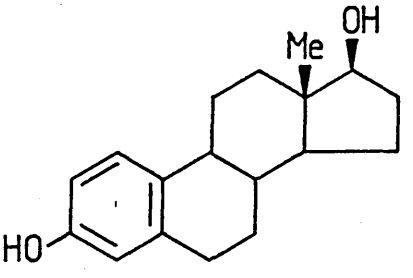


Methylprednisolone

The androgen and estrogen steroids, such as testosterone and estradiol respectively, are examples of steroid hormones which control the growth and development of the reproductive organs in humans. The androgens are used clinically as anabolic agents for the treatment of debilitating diseases, and their muscle building activity has been exploited by athletes.



Testosterone

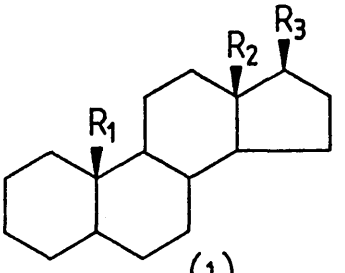


estradiol

Since the recognition of the biological importance of steroids, many synthetic analogues have been prepared with the view to manufacturing therapeutically more potent compounds, dissociated from undesirable side effects. Hence the objective of this study was to prepare linear anthrasteroid analogues of the estrogen and androgen steroids.

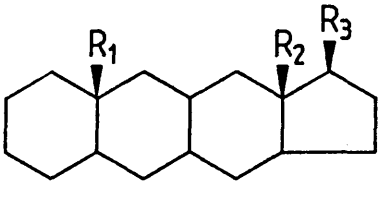
1.2 STRUCTURE AND STEREOCHEMISTRY OF STEROIDS

All the steroids normally possess the tetracyclic cyclopentanoperhydrophenanthrene ring system (1)



(1)

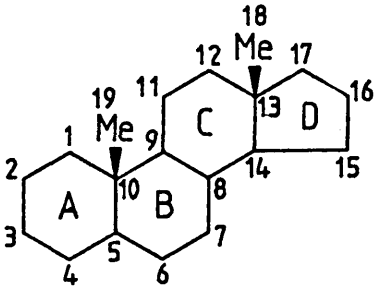
Similarly, the structure of linear anthrasteroids is based on the tetracyclic cyclopentanoperhydro-anthracene ring system (2).



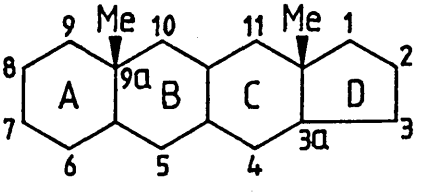
(2)

There are hundreds of known naturally occurring steroids, in addition to many thousands which have subsequently been synthesised. The diversity of this class of compounds is mainly due to the variation of the side chain R_3, whilst R_1 and R_2 are generally angular methyl groups. The side chain R_3 may be absent, or may consist of a carbon chain, a ring or a heteroatom. In addition varying degrees of unsaturation within the skeleton may be present in any of the rings. The presence of additional groups attached at various locations about the ring system provides a plethora of possible structures.

The numbering of the steroid skeleton for 'normal' steroids[2] and linear anthrasteroids is shown in (3) and (4) respectively, with the four rings designated by letter. The numbering of the linear anthrasteroids is based on 1H-cyclopent[b] anthracene, rather than that proposed by Aoyama[3a].



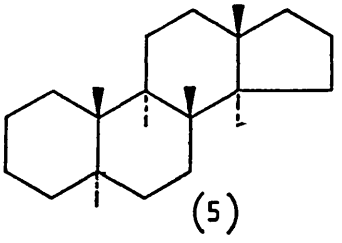
(3)



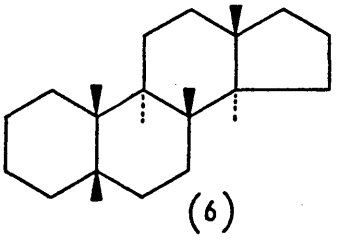
(4)

At nuclear centres of asymmetry, the configuration of attached substituents is denoted by the suffixes α or β. When the orientation of the substituent is below the general plane of the ring, the configuration is designated α, and when above the ring plane, β.

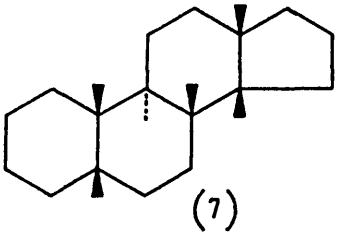
In the basic steroid skeleton, there are six asymmetric centres and consequently $2^6 \div 2$ pairs of enantiomers. Of these, the two most common and important are the 5 α (5) and 5 β (6) systems. The stereochemistry at positions 9, 10, 13 and 14 is fixed as in (5) and (6).. However there are some steroid systems which adopt an abnormal configuration, for example the cardenolides, which possess a cis fused CD ring (7).



(5)



(6)



(7)

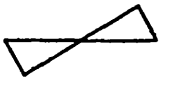
A simple nomenclature readily clarifies the stereochemistry of the above ring junctions, for example (6) is cis-anti-trans-anti-trans, (5) is trans-anti-trans-anti-trans, and finally (7) is cis-anti-trans-syn-cis.

The steroid nucleus is composed of three cyclohexane rings and a terminal cyclopentane ring fused together. To appreciate the stereochemistry of the steroid skeleton, a knowledge and understanding of the conformations of cyclohexane is required.

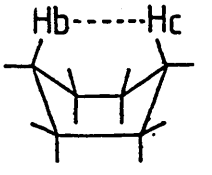
1.2.1 Conformational analysis of cyclohexane[4a]

Cyclohexane may exist in either the rigid chair (8a) or flexible 'skew boat' (9) conformation.

(8a)



(9)



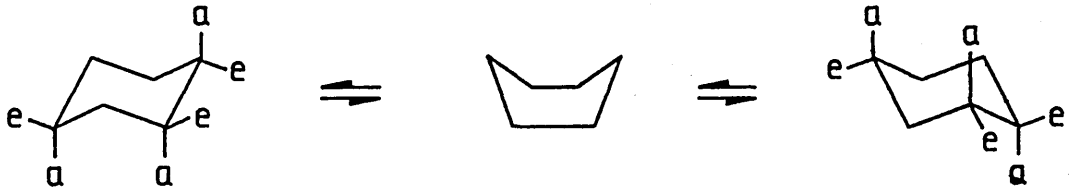
(10)

Analysis demonstrates that in the chair conformation (8a) each bond angle is the stable tetrahedral angle, and the adjacent hydrogen atoms are completely staggered, minimising Van der Waals and torsional strain. This is the most stable conformation of cyclohexane.

The alternative 'skew boat' conformation (9) can be considered to be derived from the boat form (10). The boat conformation (10) is of higher energy than the chair (8a) (by Ca.29KJ/mol), due to bond eclipsing along the sides of the boat producing torsional strain, and steric strain due to unfavourable Van der Waals interaction between the two hydrogen atoms (b and c) occupying the 'bowsprit' and 'flagpole' positions. These unfavourable interactions may be relieved by twisting the appropriate bonds to give the 'skew boat' conformation (9), which is consequently of lower energy (by 7KJ/mol) than the boat (10).

Nevertheless for most cyclohexane systems the skew boat conformation is considered to be unimportant relative to the chair form.

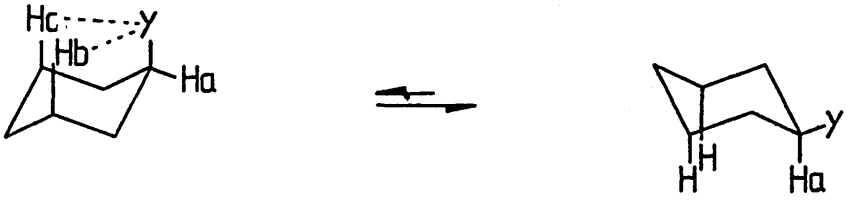
Examination of the chair conformation (8a) reveals that on each carbon atom there are two types of hydrogen-carbon bonds, axial (a) and equatorial (e).



(8a) (10) (8b)

This ring system is not static however, and there is a rapid 'flipping' of the chair conformation, from (8a) through the intermediate boat form (10) to the inverted chair form (8b). As a result of this ring inversion hydrogen atoms at the axial positions in (8a) are moved to equatorial orientations in (8b).

There are two chair conformations possible for mono substituted cyclohexane, (11) and (12). The thermodynamically more stable conformation of these has the substituent (Y) attached by an equatorial bond.



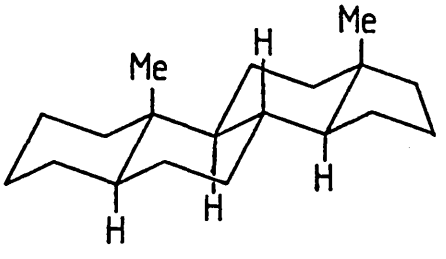
(11) (12)

When the substituent is attached axially (11), there are energetically unfavourable syn-1,3-diaxial interactions between the substituent and the two hydrogen atoms Hb and Hc. These interactions are absent when the substituent is attached equatorially.

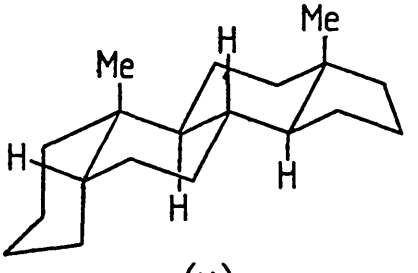
1.2.2 Conformational analysis of Steroids [4b]

Due to the above considerations, the preferred conformation of cyclohexane when fused together to form the steroid skeleton will be the chair conformation.

Thus 5α-androstane (13) and 5β-androstane (14) consist of three chair cyclohexane rings fused together to a terminal cyclopentane ring as shown.



(13)

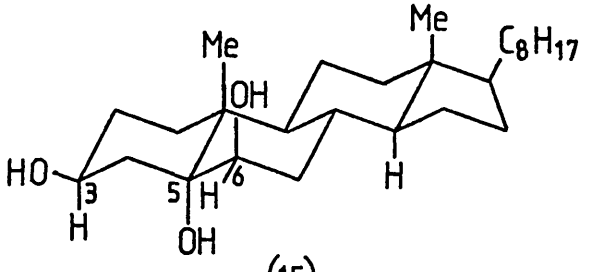


(14)

The B and C rings are locked in this conformation due to their fusion to rings A and D respectively. Although ring A is free to adopt the 'skew boat' conformation, due to the aforementioned reasons the chair conformation is preferred.

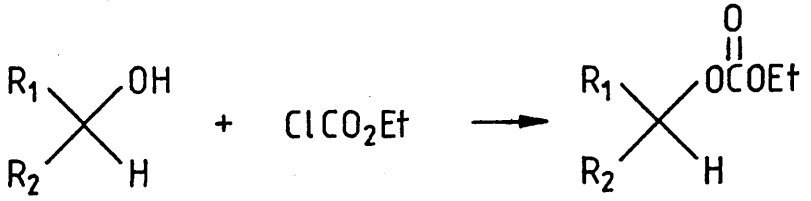
Similarly substituents attached to the steroid nucleus exhibit a stereochemical preference for an equatorial rather than an axial position. Substituents linked by an equatorial bond are also less sterically hindered, and consequently more accessible, than when linked by an axial bond. This manifests itself as a difference in chemical reactivity depending on the substituent's orientation.

Thus in the triol (15), the 3 β-hydroxyl group is equatorial, and the 6 β-hydroxyl group is axial and strongly hindered by 1,3-interaction with the angular methyl group.



(15)

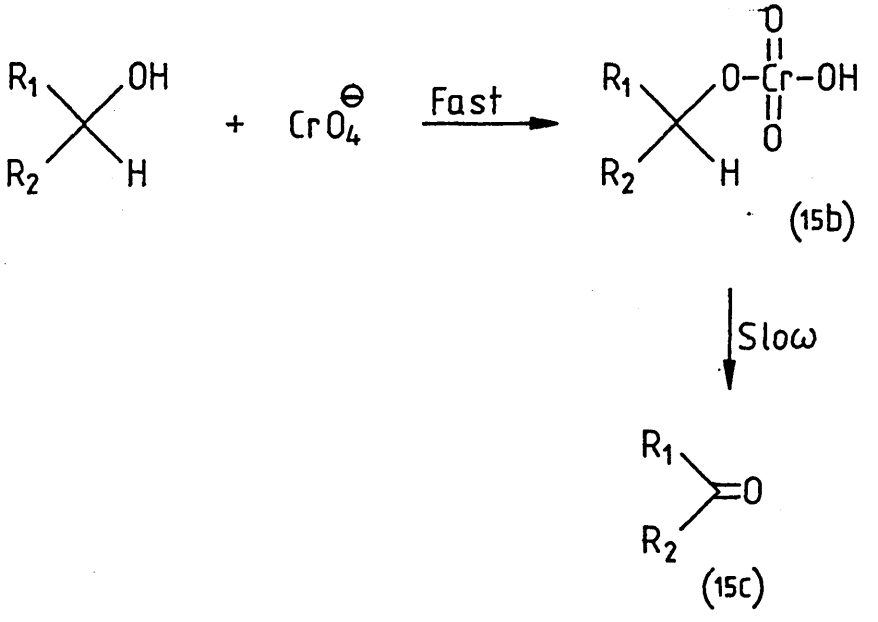
Consequently selective acylation of the 3 β-hydroxyl group,[5] to give the 3-monoacylated derivative, is readily achieved in high yield.



(15a)

However, selective oxidation with chromic acid [6] gives the ketone of the corresponding 6 β-hydroxyl group, whilst retaining the 3 β-hydroxyl group.

This may be explained by considering the mechanism of the oxidation. The initial step involves formation of the chromate ester (15b). This is followed by proton abstraction and subsequent decomposition of the ester (15b) to the product ketone (15c), which is the rate-controlling step of the reaction.



Consequently the accessibility of the proton determines the rate of oxidation, the reaction rate increasing when this proton is equatorial rather than axial. Furthermore, ester formation of the 6 β-hydroxyl group causes steric crowding. This accelerates decomposition of the ester because steric strain is relieved[7] on going from the intermediate (15b) to product (15c).

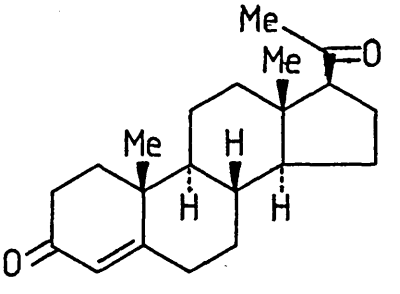
1.3 THE BIOCHEMISTRY OF STEROIDS

1.3.1 Biological Significance of Steroids

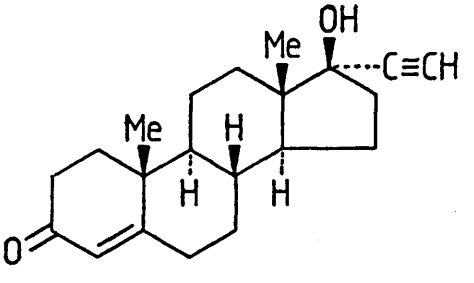
The steroids exhibit a diverse range of biological activities both in plants and animals. Of particular interest are the activities of the progesterone, androgen and oestrogen steroids. Many analogues of these steroids have been synthesised in order to obtain clinically useful compounds, with enhanced therapeutic properties and diminished undesirable side effects, as outlined below[1].

(a) Progesterone Steroids

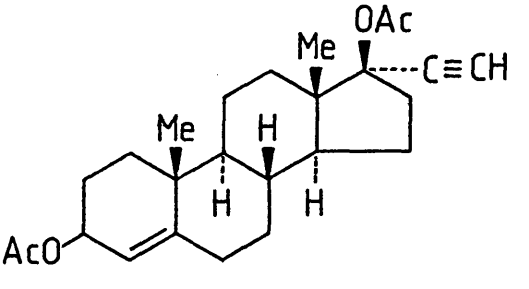
The steroid progesterone is produced by the ovaries, and is associated with the preparation of the uterus for the implantation and maintenance of the fertilised ovum during pregnancy.



Progesterone



Ethisterone



Ethynodiol diacetate

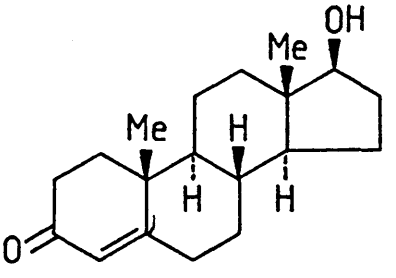
Two synthetic analogues, ethisterone and ethynodiol diacetate are known to exhibit more progestational activity than progesterone. Indeed, ethynodiol diacetate when combined with a small amount of estrogen, is an effective oral contraceptive preparation.

(b) Androgen Steroids

Androgens stimulate the development of the male reproductive organs and secondary sex characteristics.

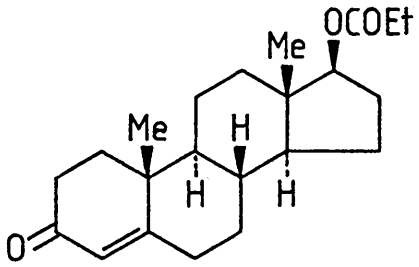
They have been used clinically as anabolic agents to treat debilitating conditions, and their muscle building (myotropic) effect has been exploited.

The most familiar of these steroids is testosterone which occurs naturally in human males.

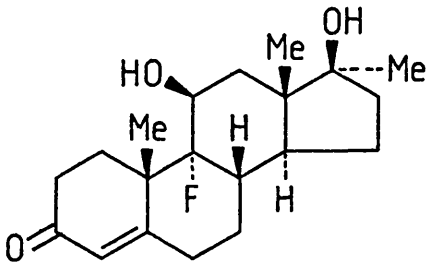


Testosterone

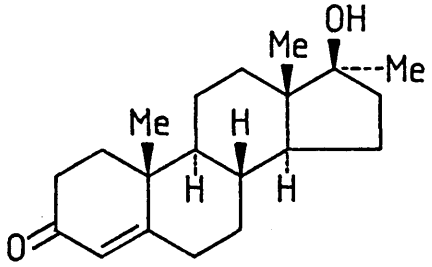
Various analogues have been synthesised in order to dissociate the anabolic activity from the androgenic effect, for example: testosterone propionate, which is used as a long-acting anabolic agent; or fluoxymesterone, which has twenty times the anabolic activity of methyltestosterone; and 19-nortestosterone, which is as myotropic as testosterone propionate, but only one-fifth as androgenic.



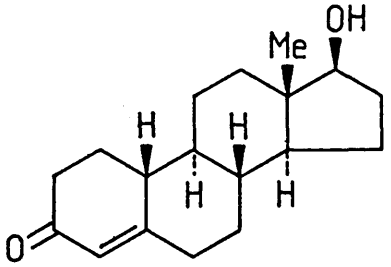
Testosterone propionate



Fluoxymesterone



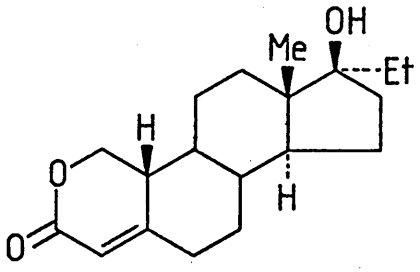
Methyltestosterone



19-nortestosterone

Analogues incorporating heteroatoms within the steroid skeleton, have also been synthesised. For example the 2-oxasteroid Nilevar^{R} was introduced in 1958[8]. This steroid drug exhibits[9] desirable anabolic properties, with minimal androgenic side effects of acne, liver disorders, baldness and reduced sperm production in

men, and the development of masculine sex characteristics in women.

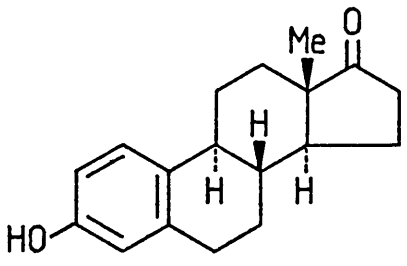


Nilevar^{R}

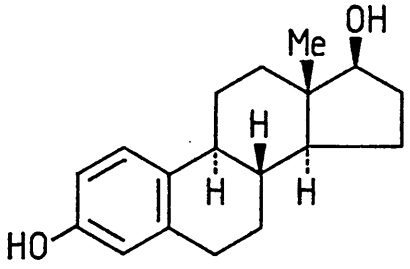
(c) Estrogen Steroids [1]

The steroidal estrogens stimulate the growth and development of female reproductive organs and secondary sex characteristics.

Estrone and estradiol are produced in the ovaries.

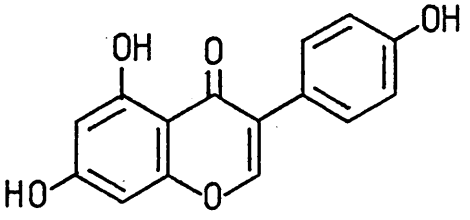


estrone

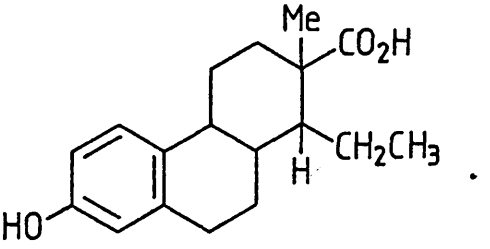


estradiol

Analogues of the estrogens may be structurally quite diverse, yet still display biological activity. Thus (±)-cis-doisynolic acid has high estrogenic activity, even though the ring system is incomplete. Similarly genistein, which is not a member of the steroid class but a flavonoid, displays weak estrogenic activity.



Genistein



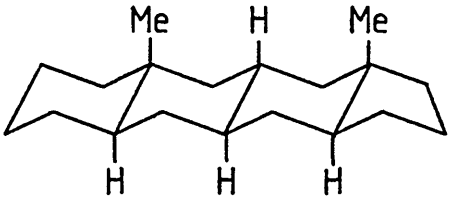
(±)-cis-doisynolic acid

Biological significance of linear anthrasteroids

As shown above, the structure of the synthetic analogues may differ markedly from the naturally occurring steroids, yet still exhibit considerable biological activity. This diversity is highlighted with (±)-cis-doisynolic acid, which is structurally quite different from estrone, yet still exhibits considerable estrogenic activity.

The linear anthrasteroid analogues are structurally quite similar to the steroids (13 and 14, page 10),

when the A/B junction is both trans (16) and cis (17).



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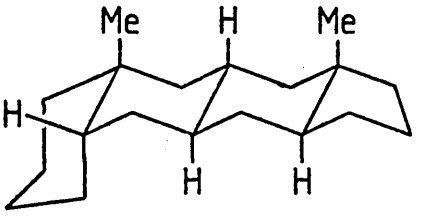


(17)

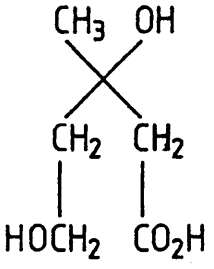
Consequently it was expected that the linear anthrasteroids might be biologically active, and exhibit clinically useful physiological properties. Although limited research has been carried out on these compounds, derivatives of linear anthrasteroids have been shown to exhibit[10] metabolic, hormonal and anti-hormonal properties.

1.3.2. Biosynthesis of Steroids

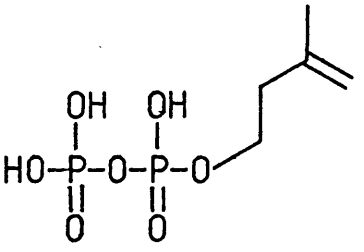
The steroids belong to a vast class of lipid compounds called terpenes, which are characterised by having in common the same biosynthetic pathway.

The biosynthesis[11] involves 3 molecules of acetic acid in a series of c-acylation and aldol addition reactions to give mevalonic acid after reduction. This is phosphorylated and decarboxylated to give isopentenyl

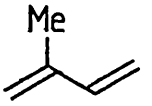
pyrophosphate, the biosynthetic isoprene.



Mevalonic Acid

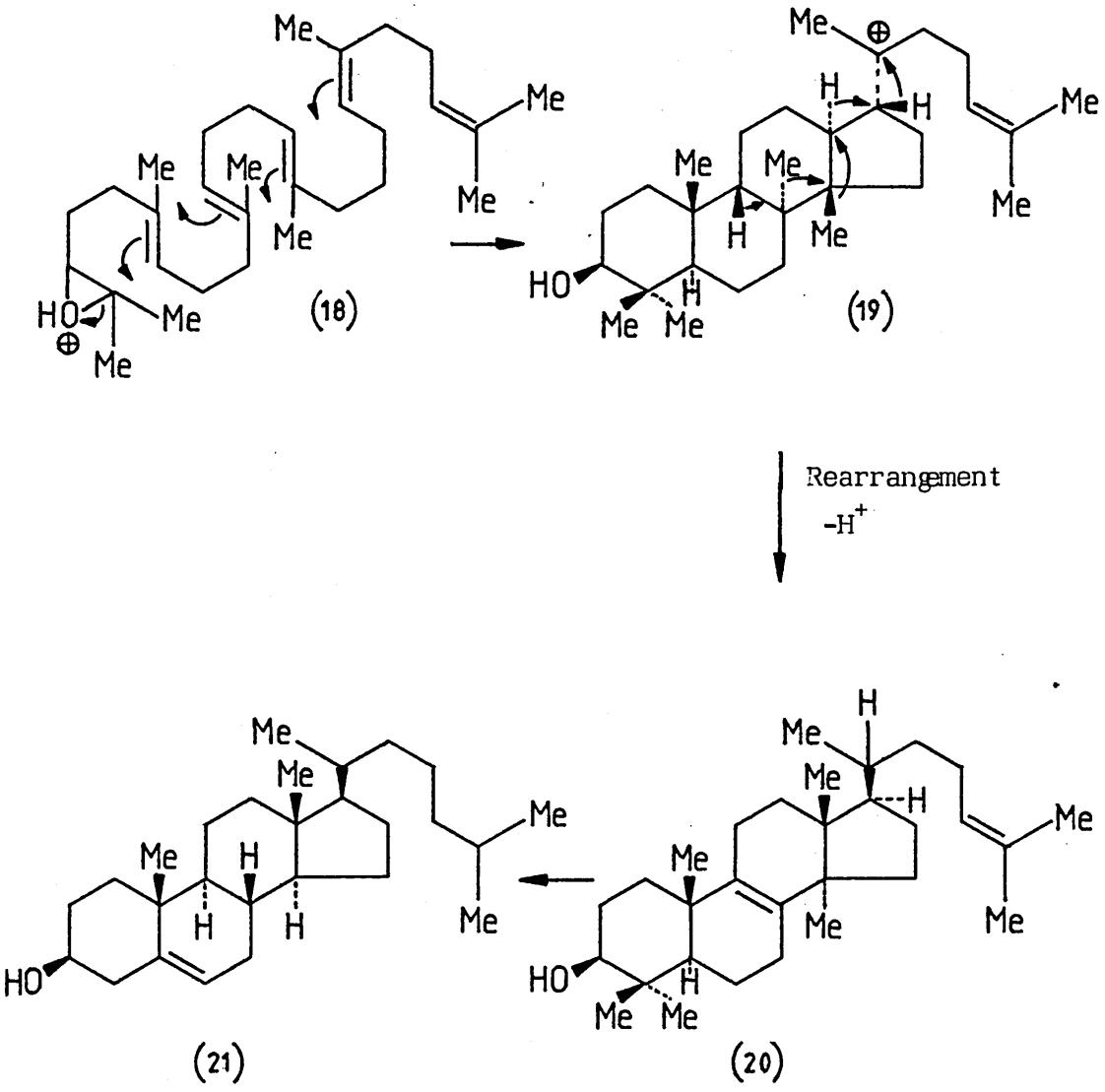


Isopentenyl pyrophosphate



Isoprene

These isoprene units combine to give linear unsaturated hydrocarbons of different length, which are modified to produce terpenes of variable complexity. One such long chain hydrocarbon is squalene, which is modified to biosynthesise terpenes, and undergoes a complex cyclisation as squalene -2,3- oxide (18) to form the steroid skeleton.



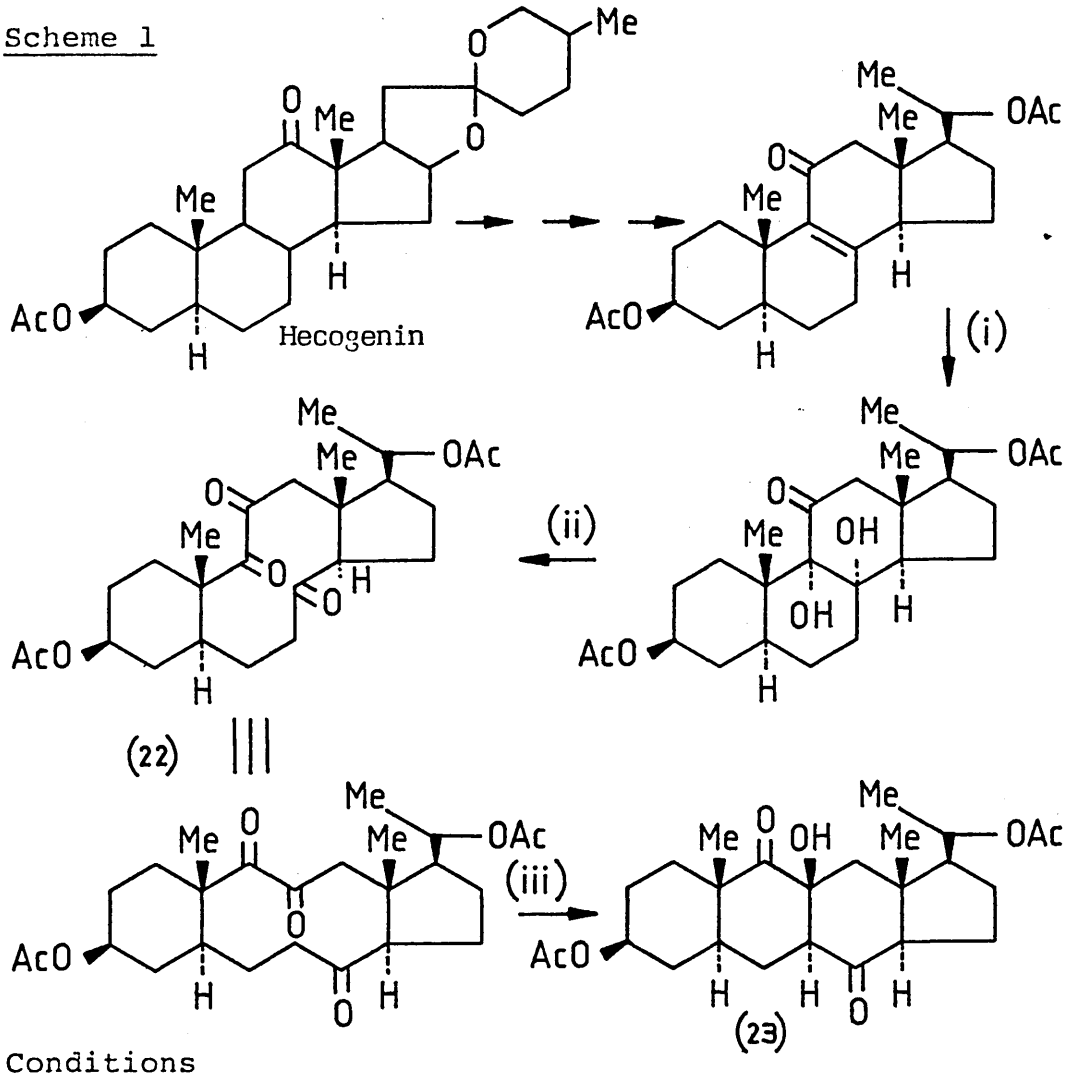
Woodward and Bloch[12] first proposed that squalene cyclises initially to lanosterol(20) after rearrangement.

After various transformations cholesterol (21) is formed. This steroid is present in almost all living organisms, and in animals forms the metabolic pool from which steroid hormones are biosynthesised.

1.4 THE SYNTHESIS OF LINEAR ANTHRASTEROIDS VIA TRANSFORMATIONS OF STEROIDS.

In the late sixties and early seventies, Aoyami and Sasaki developed[3] a method for the transformation of steroids to linear anthrasteroids, as outlined below (scheme 1).

Scheme 1



Conditions

(i) OsO_4;

(ii) $Pb(OAc)_4$;

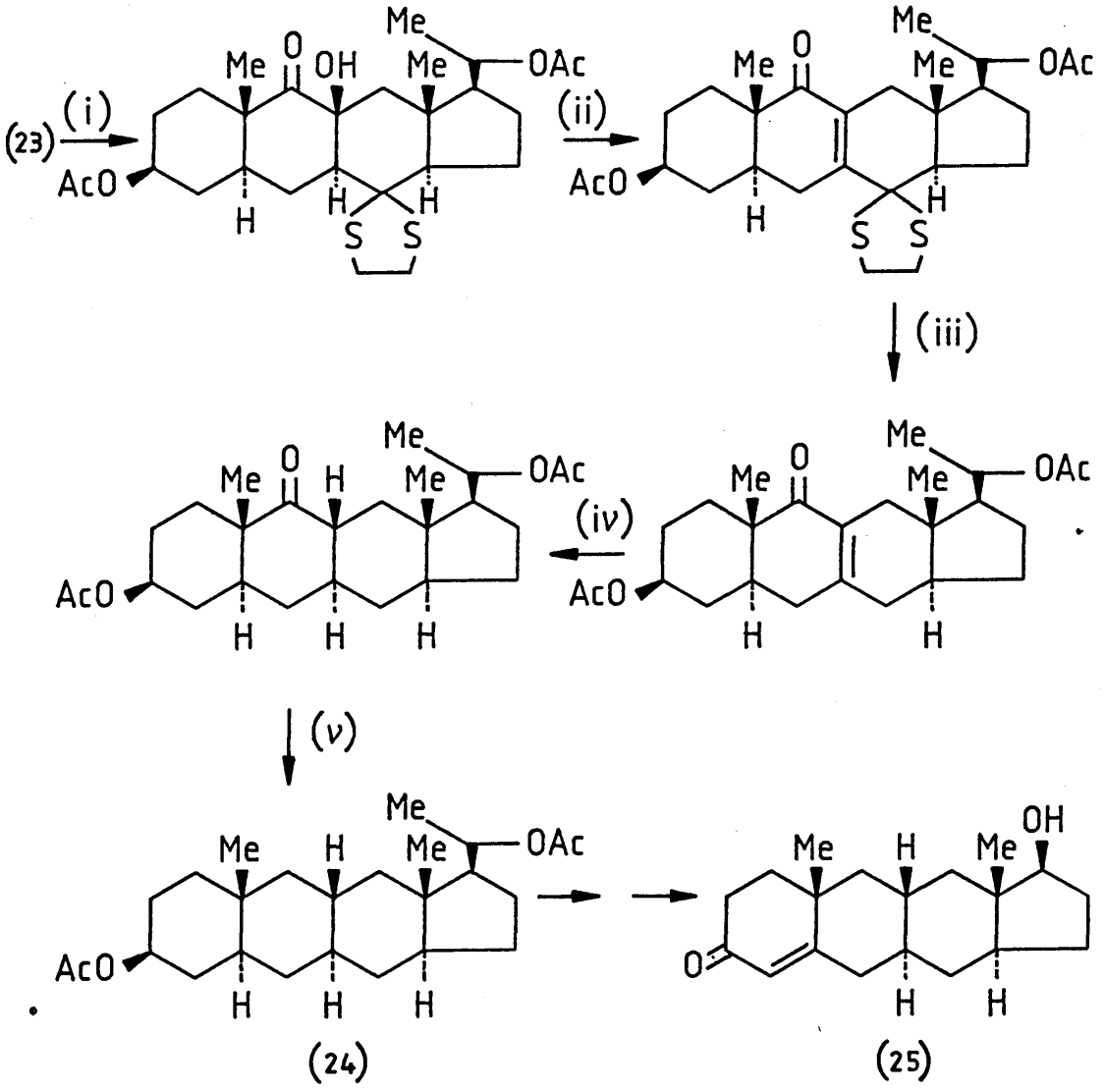
(iii) Al_2O_3

Their route involved the BC Seco steroid intermediate (22), which underwent an aldol condensation to give the linear tetracyclic compound (23).

Although theoretically five condensation products are possible[3a] from the internal cyclisation of (22), most of these form ring systems which are highly strained, and consequently unlikely.

This synthesis was extended[3b] to obtain the tetracyclic compound (24) with the trans-syn-trans-syn-trans stereochemistry, which was transformed in a multistage synthesis to the linear anthrasteroid analogue of testosterone (25), as outlined (scheme2).

Scheme 2



Conditions

(i) $SHCH_2CH_2SH$, BF_3

(ii) $SOCl_2$

(iii) Raney Nickel

(iv) H_2 or Li/NH_3

(v) $H_2N - NH_2$, $H_2N - NH_2 . 2HCl$; KOH

As a practical synthesis of linear anthrasteroids, transformations of normal steroids via the above route suffer from several major disadvantages:

(i) The starting compound is complex and relatively expensive.

(ii) Although the transformation from hecogenin to the linear anthrasteroid (23) is achieved in a reasonable yield and number of steps, conversion of (23) to the target testosterone analogue (25) requires an elaborate interconversion of the functional groups incorporated on the tetracyclic frame.

(iii) The synthesis is inherently inflexible, and adapting this to a branched or combined synthetic route is difficult.

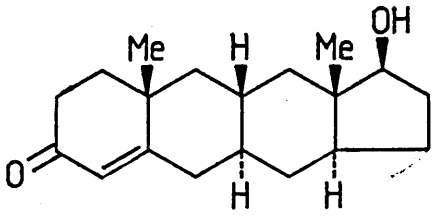
(iv) The stereochemistry of the fused tetracyclic ring system is difficult to elucidate in such a complex molecule.

These disadvantages have stimulated an interest in the total synthesis of linear anthrasteroids. This approach was anticipated to circumvent the problems experienced by the route involving transformations of steroids.

1.5 THE TOTAL SYNTHESIS OF LINEAR ANTHRASTEROIDS

1.5.1 Objectives of this Study

The main objective was to develop strategies for the total synthesis of linear anthrasteroids of general type (28), and specifically the analogues of testosterone (25), 19-nortestosterone (26), and estradiol (27).



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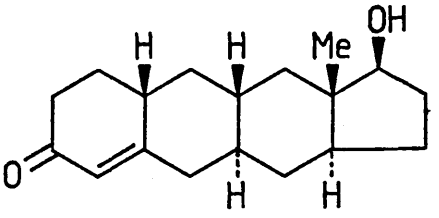
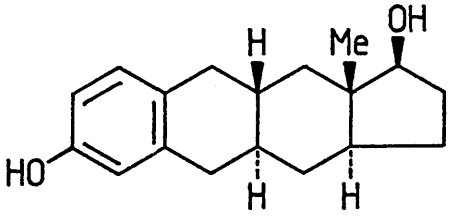
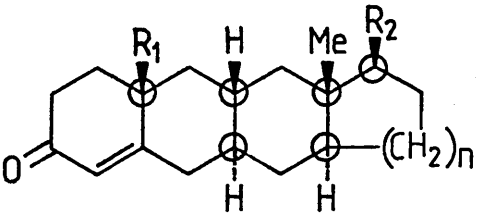


(26)



(27)



(28)

n = 1 or 2
R_1 = Me; H
R_2 = OH; =O

chiral centres: ○

The proposed synthetic route was designed to facilitate sequential ring addition. This allowed elucidation of the stereochemistry of the ring junctions, which was controlled to give the trans-syn-trans-syn-trans configuration. Sufficient flexibility of the route was

sought to allow development of the proposed linear synthesis to a more efficient branched or combined synthesis.

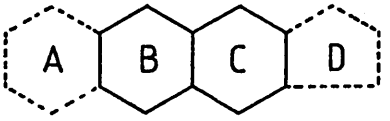
Each of the target compounds (25), (26) and (27) possess several chiral centres, giving the number of stereoisomers each can exist in as 64, 64, and 32 respectively. As steroids usually exhibit biological activity in only one of their isomeric forms, the stereochemical control of each of these centres was essential.

In addition, regiochemical control, particularly of the annulation reactions, was required to avoid product loss and concomitant lowering of overall yield due to the formation of regioisomeric side products.

1.5.2 The Strategies of Total Steroid Synthesis

The synthesis of steroids has enjoyed increased attention since the correct structure of cholesterol was established in 1932. The total synthesis of steroids of increasing complexity has been achieved progressively since this date, with the synthesis of equilenin by Bachmann, Cole and Wilds[13] in 1939, the aromatic steroidal hormones by Johnson et al[14] in 1945, and cortisone by Woodward et al[15] in 1952.

The general strategies used in steroid synthesis usually involve the formation of a bicyclic intermediate, which is annulated to give the remaining rings. This bicyclic fragment may form the AB, BC or CD moiety of the final steroid compound.



The routes involving the AB and CD fragments were considered the best option for the synthesis of linear anthrasteroids. The route from the BC fragment was discounted as this allowed only single, sequential annulations. The routes involving both the AB and CD fragments could be developed to allow bis-annulation[16] i.e. the addition of one ring which contains a second, latent ring. The use of bis-annulating agents allow a combined type synthetic strategy to be used.

An additional advantage offered with the CD fragment is control and elucidation of the stereochemistry of the CD ring junction at an early stage in the synthesis. This is particularly important as the desired trans isomer, when incorporating an angular methyl group, is thermodynamically less stable than the cis isomer[17].

Consequently intermediates were sought which could be used as an AB and CD fragment.

CHAPTER TWO

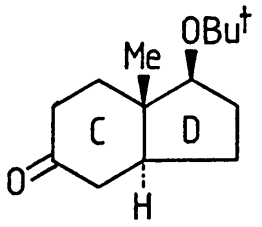
THE SYNTHESIS

OF

BICYCLIC INTERMEDIATES

2.1 INTRODUCTION

A survey of the steroid literature indicated there were several important bicyclic intermediates which might be converted to linear anthrasteroids. Of these, the following compounds were considered particularly important:



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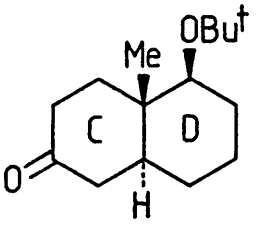

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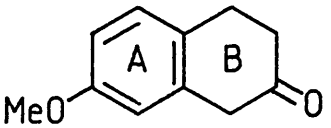


(31)

The rings have been lettered, in accord with steroid terminology, to indicate the position of the above moeities in the envisaged final anthrasteroid.

2.2 THE SYNTHESIS OF THE TRANS-HYDRINDAN INTERMEDIATE (29)

2.2.1 General Approach

As a key intermediate for the synthesis of the anthrasteroid analogues of the androstanes, the

trans-hydrindan bicyclic compound (29), as synthesised by Hajos and Parrish,[18,19] appeared to offer the following major advantages:

(i) The ring junction had the required trans-stereochemistry which is thermodynamically[17,20] less stable than the cis isomer,

(ii) The desired cis relationship of the angular methyl group and alcohol group (protected as a t-butyl ether),

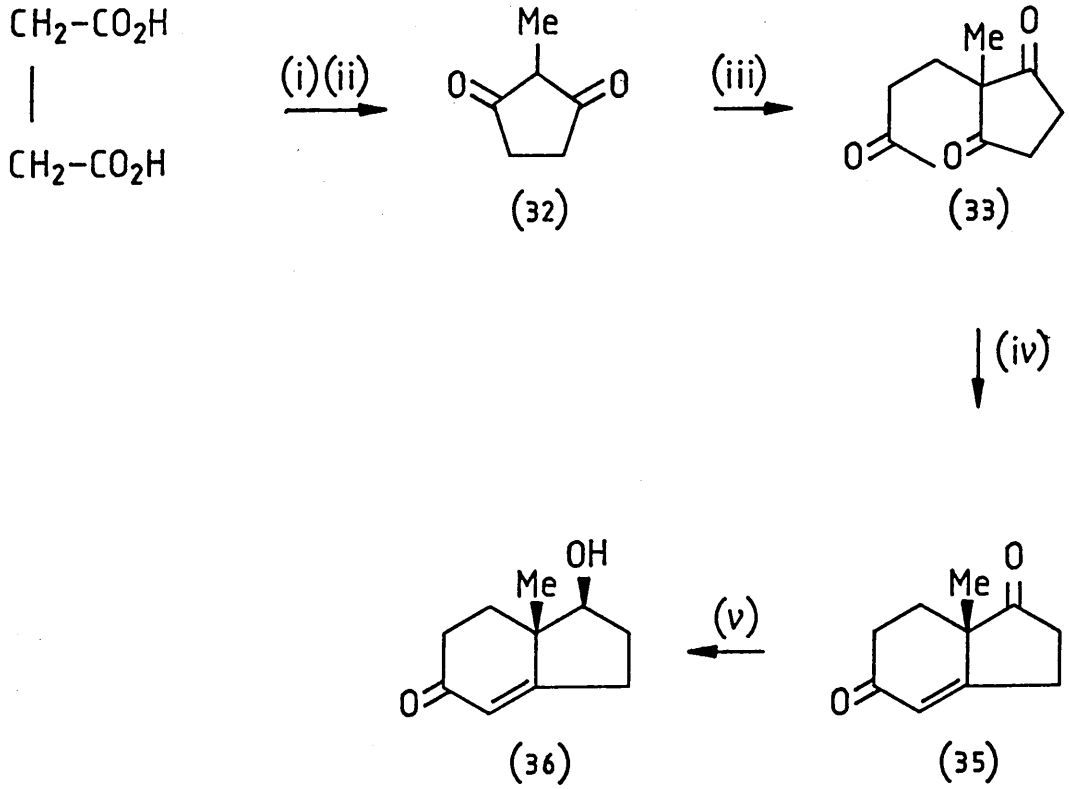
(iii) The ring D is five-membered as desired, circumventing the need for future ring contraction.

2.2.2 The Synthetic Route

The synthetic route used was essentially that developed by Hajos and Parrish,[18,19] and is outlined in schemes 1a and 1b.

Scheme 1a

The first stages of the synthesis gave the bicyclic hydroxy ketone (36) with the stereochemistry as indicated:



Conditions

(i) $AlCl_3$, $MeNO_2$;

(ii) C_2H_5COCl;

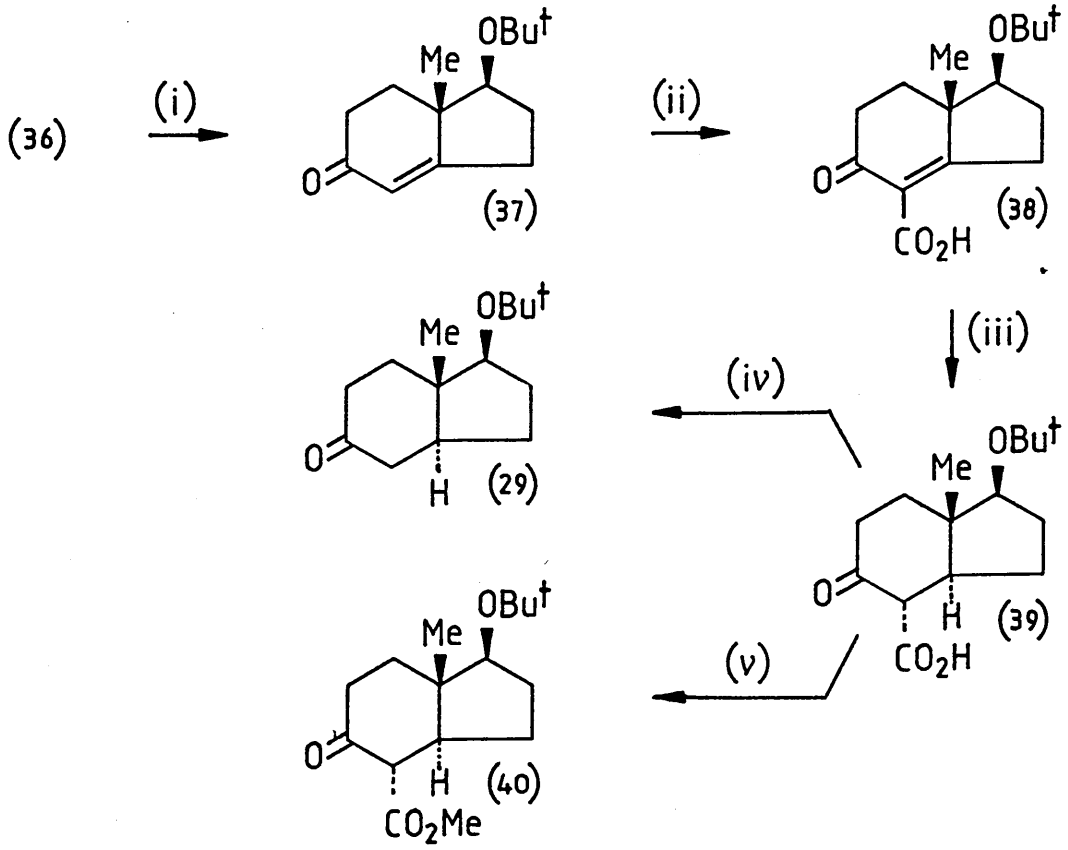
(iii) $H_2C{=}CHCOCH_3$, Water;

(iv) Benzene, pTsOH;

(v) $NaBH_4$, Ethanol

Scheme 1b

The second stage of the synthesis was concerned with achieving the required trans ring junction. This was accomplished to afford the key intermediate (29) in approximately 30% overall yield from succinic acid in seven steps:



Conditions

(i) $(CH_3)_2C=CH_2$, H_3PO_4, BF_3, dichloromethane.

(ii) Magnesium Methyl Carbonate (MMC), dimethylformamide.

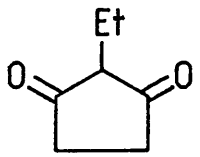
(iii) H_2/Pd, Methanol.

(iv) Toluene, reflux.

(v) CH_2N_2, ether.

The first step in the synthesis of (29) involved the preparation of 2-methyl-1,3-cyclopentanedione (32). The dione (32) has been extensively used in the synthesis of steroids,[21] usually forming the D ring when incorporated into the steroid skeleton.

The dione (32) was prepared in good yield (59%, cf.lit[22] 75%) from succinic acid, propionyl chloride and aluminium chloride. This method was selected instead of that used by Grenda et al [23] (which involved the addition of 2-buten-2-ol acetate to succinic anhydride in nitrobenzene in the presence of aluminium chloride), because the ethyl analogue (41) could also be obtained simply by substituting butyryl chloride for propionyl chloride.



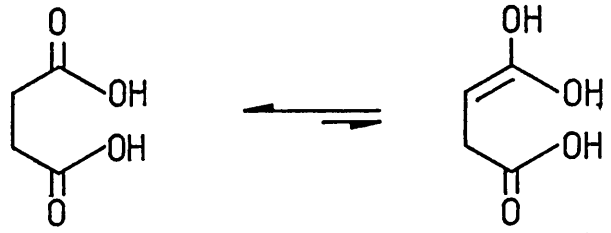
(41)

This consequently offered the flexibility of synthesising linear anthrasteroids with an 18-ethyl as well as an 18-methyl angular group.

The mechanism of this complex reaction is open to some speculation. Schick et al[22] proposed that the reaction proceeds via the enol ester (32b), which is presumably

formed by the following sequence of reactions:

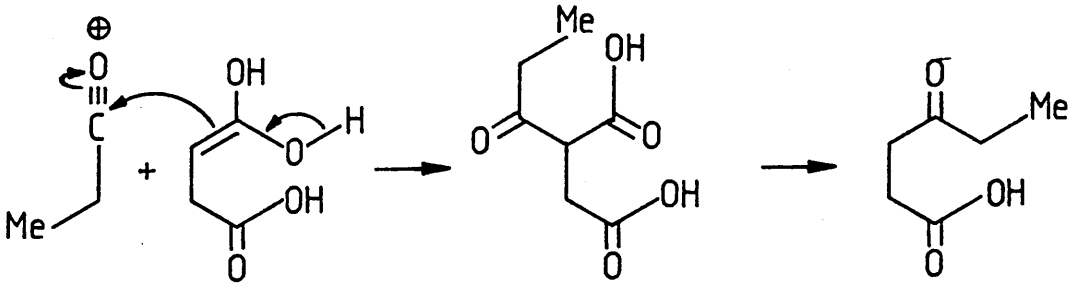
Enolisation of succinic acid initially occurs to give some of the minor tautomer.



Propionyl chloride reacts with aluminium chloride to give the electrophilic acylium ion

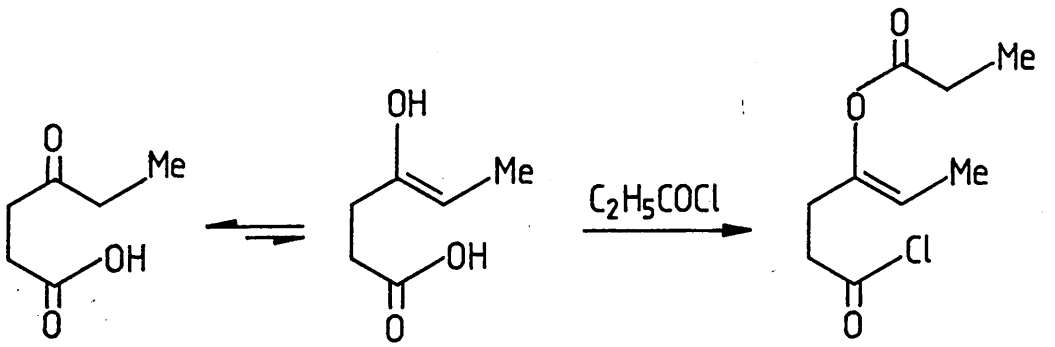
Acylium ion

The enol tautomer of succinic acid undergoes nucleophilic attack on the acylium ion; to give the β -Keto acid adduct which readily decarboxylates to the intermediate (32a)



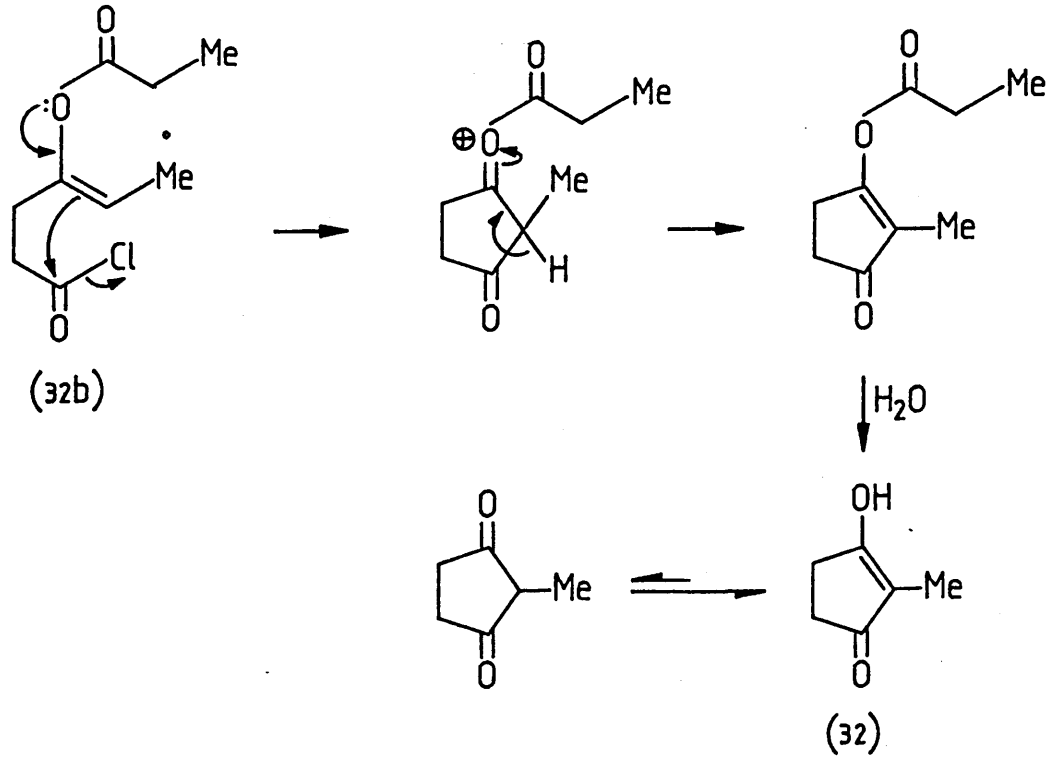
(32a)

Enolisation of (32a), followed by nucleophilic attack of the enol on further propionyl chloride (as its acylium ion) gives, after substitution of the hydroxyl group (of the carboxylic acid) with chlorine, the enol ester intermediate (32b).



(32a) (32b)

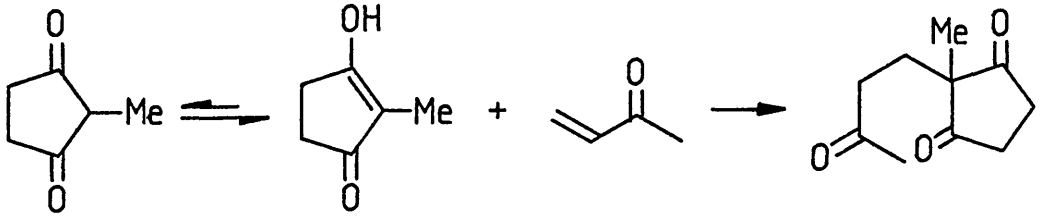
Cyclisation of (32b) probably occurs to eliminate chlorine, followed by facile hydrolytic cleavage of the enol ester on addition of water, to give the product (32).



(32b) (32)

Although the product (32) probably exists mainly as the keto enol tautomer, the naming of this compound, and its representation in this thesis, is based on the minor diketone tautomer.

Treatment of the diketone (32) with methyl vinyl ketone in deionised water[18] gave the adduct 2-(3-oxobutyl)-2-methyl -1,3-cyclopentanedione (33). The yield after distillation (84%) compares favourably with the literature value (87%)[18], and that obtained by Crispin, Vanstone and Whitehurst (54%) [24] in a separate study.

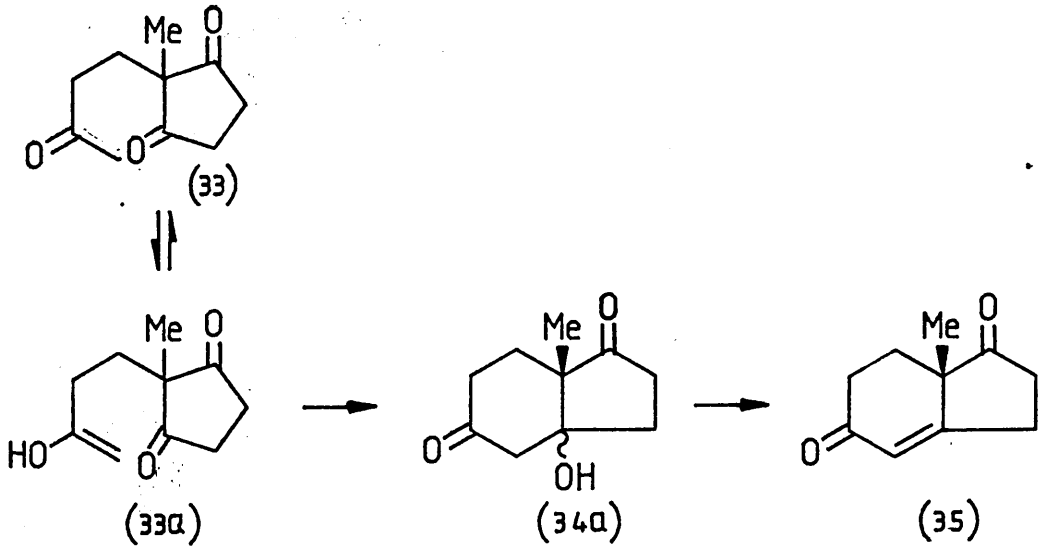


(32) (33)

Conditions given in the literature for Michael reactions between methyl vinyl ketone and cyclic β -diketones consisted of heating the starting materials under reflux in absolute methanol containing a catalytic amount of potassium hydroxide[25,26,27]. Although this afforded a much reduced reaction time (45 mins. [26] instead of 5 days [18]), the reported formation

of bridged cyclic products[18] (34b and 34c, see below) precluded the use of these vigorous conditions.

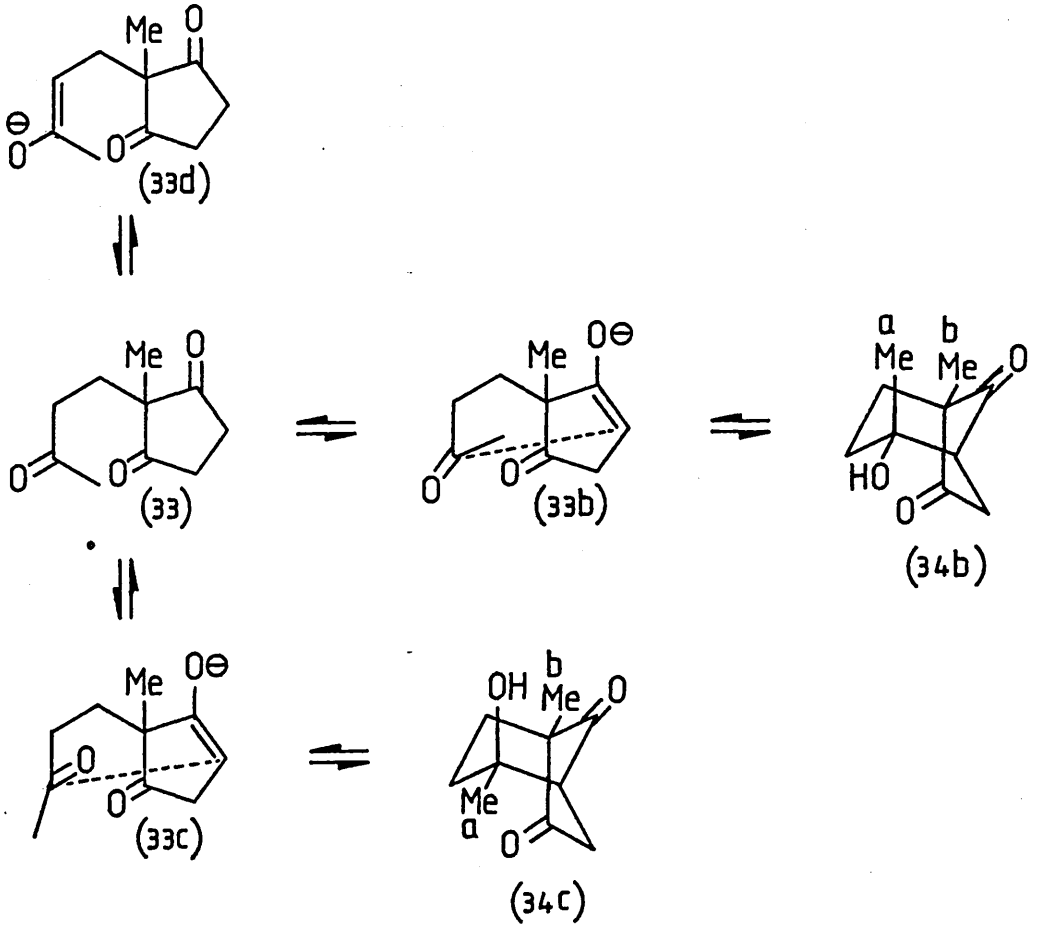
The enone (35) was obtained, by azeotropic removal of the water formed, when the triketone (33) was refluxed in benzene solution containing a catalytic amount of p-toluenesulphonic acid[27].



The reaction proceeds via enolisation of the triketone (33) to the enol (33a), which undergoes cyclisation to the hydroxy ketone (34a). Under the acidic conditions dehydration readily occurs to give the enone (35).

As the initial intramolecular nucleophilic addition of the enol (33a) to either of the cyclic carbonyl groups (at position 1 or 3) is possible, a 50% mixture of isomers, where the angular methyl group is α or β , was obtained.

Although the reaction appears simple, yields of no more than 70% (Cf.lit[27] 83%) were ever realised, even with careful control of temperature and sequential additions of catalyst. Reports in the literature [18,26] suggest that bridged diketones (34b) and (34c) are formed under basic conditions. Thus Hajos and Parrish [18], using piperidinium acetate, observed the formation of the bridged diketone (34b).



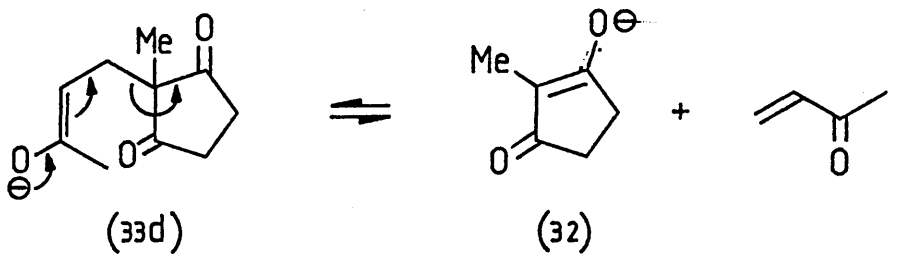
Further, treatment of this isolated product (34b) with piperidine followed by glacial acetic acid gave the epimer (34c), as the major product.

Hajos and Parrish proposed[18] that the reaction proceeds as above, with preferential enolisation of the cyclic ketone (33b and 33c), to the aliphatic ketone (33d). Nucleophilic attack of these cyclic enolates (33b and 33c) subsequently gives the bridged diketones (34b and 34c) respectively. The reactions are all reversible and allow interconversion of (34b) and (34c).

Fortunately these bridged ketones are easily detected as they exhibit markedly different physical characteristics[18] to the desired product (35), with melting points of 115°C (34b) and 158°C (34c), in comparison to 70°C for (35), and with (34b) and (34c) exhibiting a hydroxyl band (Ca.3600 cm^{-1} in $CHCl_3$) by infrared spectroscopy, and two methyl singlets (Ca. δ 1.45 and 1.07 for the a and b methyl groups respectively) by ^1H n.m.r. spectroscopy.

During cyclisations of the triketone (33) under acidic catalysis, the presence of these bridged ketones was never detected.

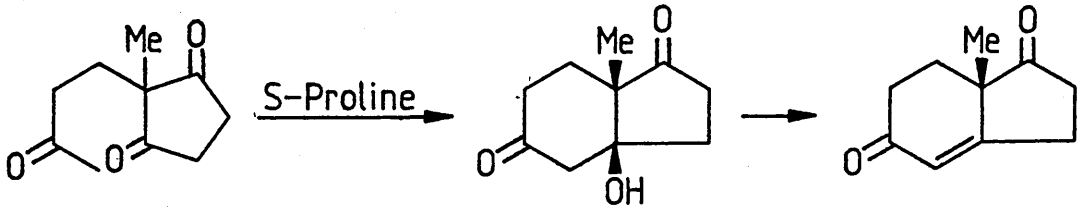
A low yield may be due to the occurrence of a retro-Michael reaction as outlined below:



(33d) (32)

Boyce and Whitehurst [27]. have shown that during the cyclisation of the adduct (33), using either diethylamine-pyridine or thionyl chloride-pyridine as catalyst, enolisation of the side chain carbonyl group to give the enolate (33d) occurs. This undergoes a retro Michael reaction to give the starting dione (32) and methyl vinyl ketone.

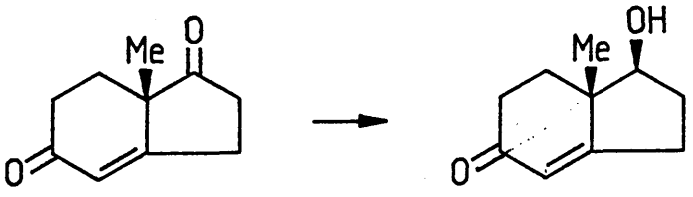
An interesting and important aspect in the cyclisation of the adduct (33), to the optically active bicyclic compound (35d), has been developed[28]. The enone (35d) has been obtained with 97% enantiomeric purity by the use of S-(-)- proline in dimethyl formamide as a chiral catalyst to effect the cyclisation of the triketone (33).



(33) (+)-(34d) (+)-(35d)

Although the synthesis of the chiral enone (35d) and its subsequent annulation to form a stereochemically pure steroid was desirable, the racemic enone (35) was considered a more appropriate building block towards the final linear anthrasteroid as neither stereoisomer could be predicted to be the physiologically active one. Consequently, by synthesising a racemic steroid, any biological activity in either isomer would be detected.

The selective reduction of the 5-membered cyclic ketone (35) was accomplished with sodium borohydride in ethanol at $0^{o}C$.

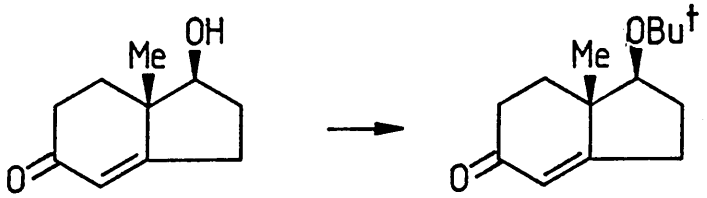


(35) (36)

Boyce and Whitehurst[29] have shown this reduction to be both regio- and stereospecific to afford the racemic β —alcohol (36) in excellent yield.

The infrared spectrum of (36), which exhibited bands at 1650 and 1610 cm^{-1}, corresponding to the cyclic $\alpha\beta$ —unsaturated ketone, confirmed the retention of the enone system. A band at 1740 cm^{-1} corresponding to the 5-membered cyclic ketone group was absent but a band was present at 3420 cm^{-1} due to the hydroxyl group.

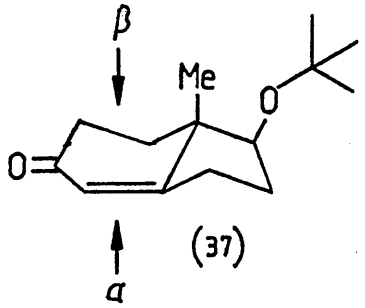
Using a dichloromethane solution of 2-methylpropene and a catalyst of conc. sulphuric acid in a pressure vessel at ambient temperature, the conversion of the alcohol (36) to its t-butyl ether (37), gave poor and erratic yields. A significant improvement in both reproducibility and yield[30] was achieved by carrying out the reaction at -78°C using a mixture of phosphoric acid and boron trifluoride as catalyst.



(36) (37)

The t-butyl ether was chosen as the alcohol protecting group due to its relative ease of formation and removal,[19,20] and its simple ^1H n.m.r. spectrum which consists of a single peak only at δ 1.2.

An additional important advantage of the t-butyl group is the steric hindrance it imposes on reagents approaching the molecule (37) from the β-face.

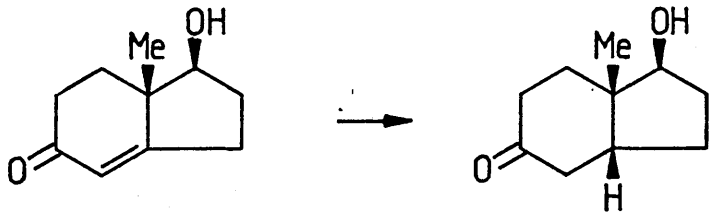


(37)

This stereoselectivity has been exploited to aid the control of the stereochemistry of reduction of the carbon-carbon double bond, as outlined below.

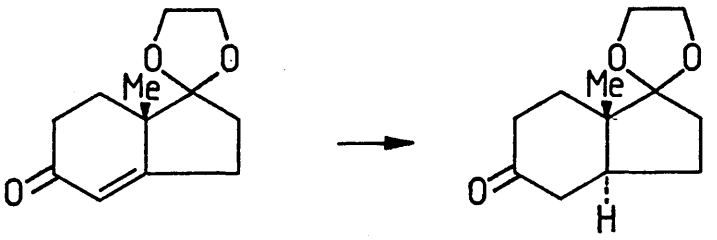
Sterospecific reduction of the enone (36)

One of the major problems in the synthesis of steroids is the attainment of the C/D trans ring junction. Evidence in the literature indicated that lithium-ammonia reduction of bicyclic enones such as (36) gives the cis bicyclic product [32], as exemplified by the reduction of the ketol (36)[29].



(36) (36b)

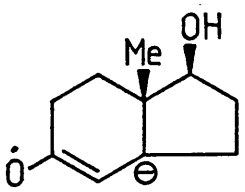
However, Bauduin and Pietrasanta[33] have reported that lithium-ammonia reduction of the acetal (42a) gives the trans product (42b).



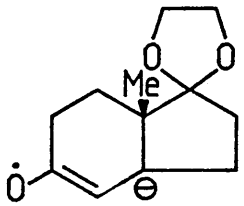
(42a) (42b)

This is surprising, as Stork and Darling[34] have shown that metal-ammonia reductions of bicyclic enones proceed via the thermodynamically most stable

anion-radical intermediate. For the hydrindan compounds, these intermediates (36c and 42c) would be expected to be more stable in the cis- than in the trans- form, with proton addition occurring to give the cis-hydrindan product.



(36c)

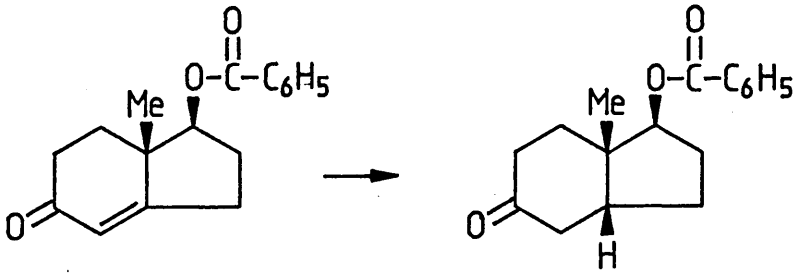


(42c)

Hydrogenation of the carbon-carbon double bond of hydrindans also usually gives the cis product. Although the stereochemical outcome of catalytic hydrogenation is often profoundly influenced by the nature of the substrate, Boyce and Whitehurst[29] were unsuccessful after several attempts in obtaining trans-hydrindan bicyclic compounds, as described below.

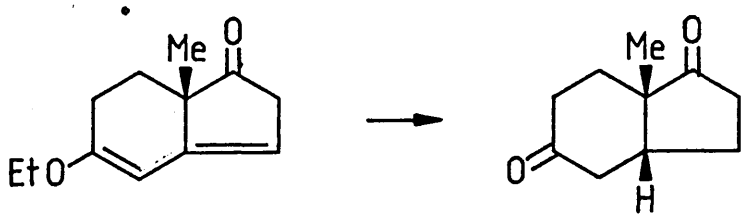
Initial studies on the catalytic reduction of the ketol (36) using 2% palladium strontium carbonate, gave the cis product (36b).

The ketol (36) was then converted to its benzoyl derivative (43a) in the anticipation that such a bulky substituent might promote hydrogen attack at the α-face[35]. However, hydrogenation again gave only the cis compound (43b).



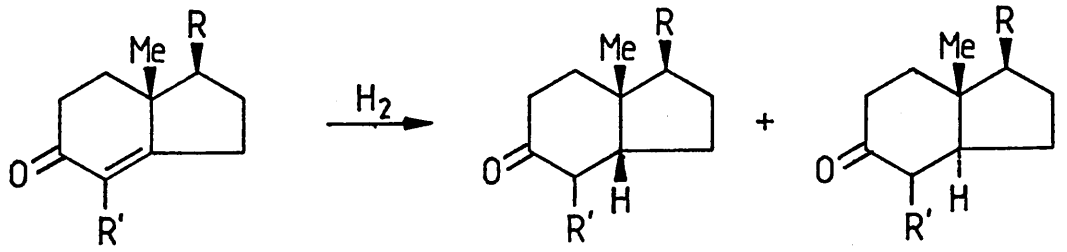
(43a) (43b)

Finally, catalytic hydrogenation of the enol ether (44a), using a palladium or strontium carbonate catalyst, did not change the stereochemical outcome.



(44a) (44b)

Hajos and Parrish[20] also observed that hydrogenation of the hydroxy enone (36) gave predominantly the cis product.



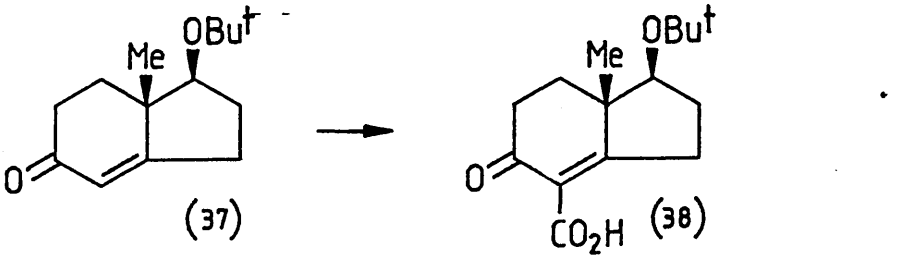
		% isomers	
Compound		Cis	Trans
(36)	R=OH; R' =H	88.5	11.5
(37)	R=OBu^t; R' =H	70	30
(38)	R=OBu^t; R' =CO_2H	6	94

However, incorporation of the bulky t-butoxy group (37) elevated the trans component to 30%. This was further boosted to over 90% trans by incorporation of a carboxylic acid group (38).

From a consideration of the above, the method adopted to obtain the desired trans-hydrindan was that developed by Hajos and Parrish[20]. Although this route involved the addition and removal of the auxiliary carboxylic acid group, which required two extra steps,

an important advantage is that the acid group facilitates confirmation of the trans-fused ring junction by ^{1}H n.m.r.

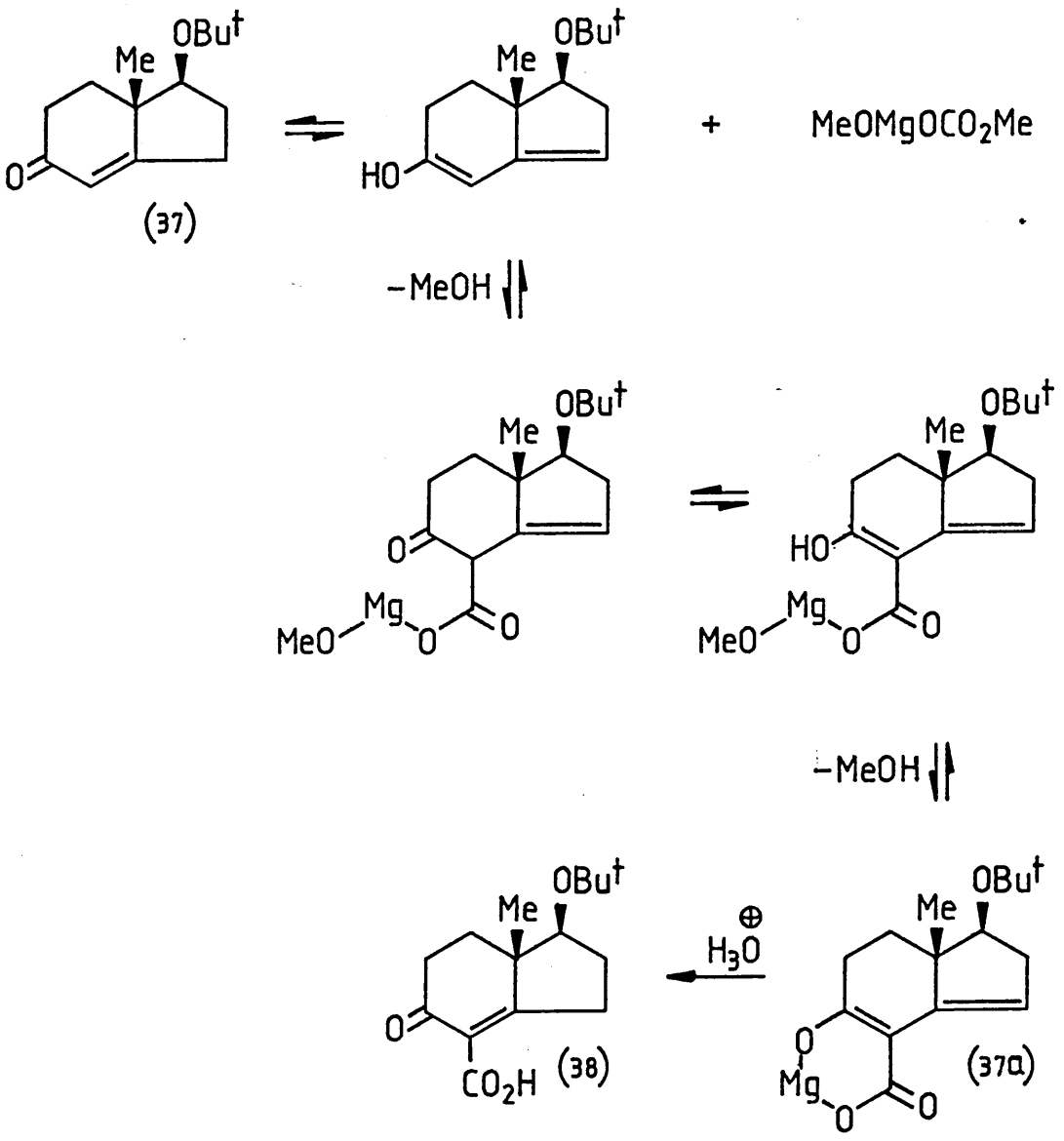
Thus the carboxylic acid group was introduced by treating the t-butyl ether (37) with magnesium methyl carbonate[36] (MMC) in dichloromethane.



Initially, spasmodic yields (20-40%) of the carboxylic acid were obtained. Changing the source of the MMC reagent, extending the reaction time and increasing the purity of the starting material and solvent all had little effect. However, by conducting the reaction in a distillation apparatus, and removing the methanol from the reaction mixture,[37] the yield was elevated to a reproducible 70%.

This compares favourably with the literature yield[20] (36%) of (38) (with recovery of 63% starting butyl ether (37)), using sodium hydride and anhydrous solid carbon dioxide.

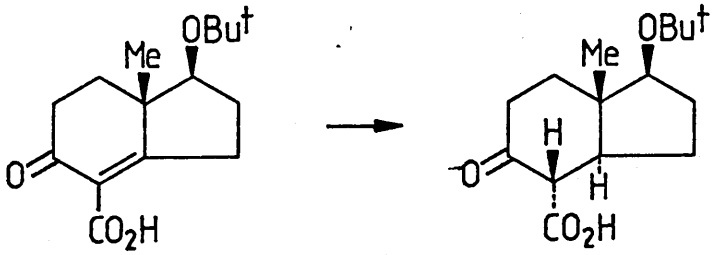
The reaction probably proceeds as follows:



The intermediate (37a) is readily decomposed with aqueous mineral acid to the carboxylic acid (38). Evidently the formation of the intermediate (37a) is an equilibrium reaction[39,40], and the subsequent yield of acid (38) is favoured by removal of methanol from the reaction mixture, with concomitant shift in equilibrium in favour of (37a). In addition, this equilibrium may be favourably influenced[39] by using an excess of MMC reagent.

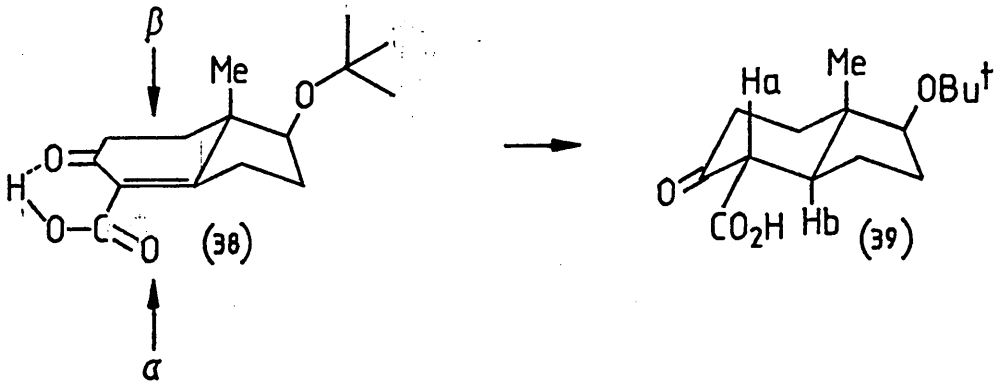
The regiochemistry of the addition of the carboxylic acid group was indicated by ^{1}H n.m.r. as the loss of the vinyl proton signal at δ 5.8.

The carboxylic acid (38) was easily hydrogenated at atmospheric pressure in methanol, using 10% palladium supported on barium sulphate as catalyst[20]. The hydrogenation was conducted at $0^{o}C$, and solvent carefully evaporated at low temperature, to ensure that minimal decarboxylation occurred.



(38) (39)

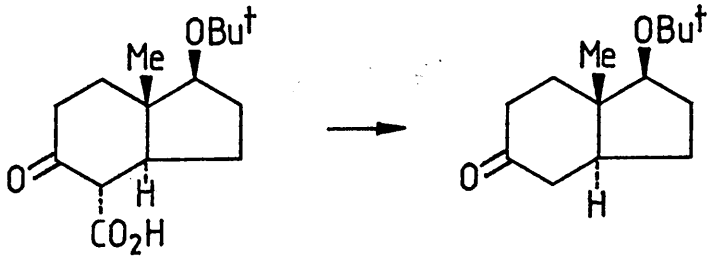
The high ratio of α-attack and subsequently trans-fused C/D rings is considered[20] to be due to the formation of a pseudo β ring (38) by hydrogen bonding of the cyclic carbonyl group and hydroxyl group of the acid. This enhances the rather planar conformation of (38), promoting approach of the catalyst via the α -side, opposite the bulky methyl and t-butoxy substituents.



Evidence for the trans-fusion of the rings was provided by ^{1}H n.m.r. The acidic proton (Ha) of the β-keto acid (39) appeared as a doublet centred at $\delta 3.40$. The large coupling constant between Ha and Hb (13.5Hz)[20] confirmed the trans diaxial relationship of these protons, and subsequently the C/D trans stereochemistry.

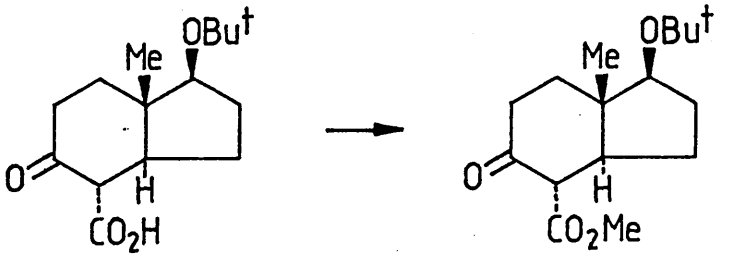
The undesired epimer, with the stereochemistry of the C/D ring junction cis, would have exhibited a coupling constant due to Ha and Hb considerably lower (2-5Hz) than that observed, due to the cis relationship of the axial (Ha) and equatorial (Hb) protons.

The acid was readily decarboxylated by heating under reflux in toluene to provide the trans bicyclic t-butyl ether (29) in high yield (92%). This was considered the key intermediate for annulation to the target linear anthrasteroids.



(39) (29)

The presence of the carboxylic acid group in (39) was considered to be potentially useful in controlling the regiochemistry of further additions to the bicyclic compound.



(39) (40)

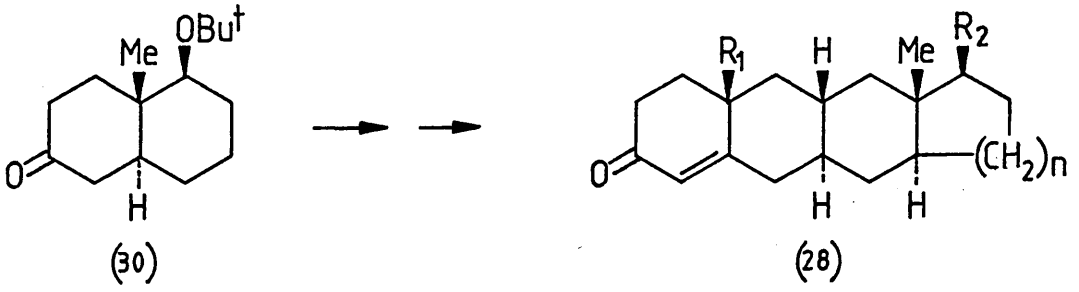
Consequently the methyl ester (40) of the carboxylic acid (39) was prepared by treatment of (39) with diazomethane at 0^{o}C in excellent (93%) yield.

2.3 THE SYNTHESIS OF DECALONE INTERMEDIATES

2.3.1 General Approach

The decalone (30) offered two major advantages as an intermediate:

(i) D-homo linear anthrasteroid analogues, of general type (28), where n=2, could be obtained. These analogues resemble broad spectrum antibiotic tetracyclines, and consequently were anticipated to exhibit interesting biological activity.



(30) (28)

n = 1 or 2
R$_1$ = Me, H
R$_2$ = OH, =O

(ii) The synthesis of the decalone (30) required fewer steps than that of the hydrindan (29) intermediate.

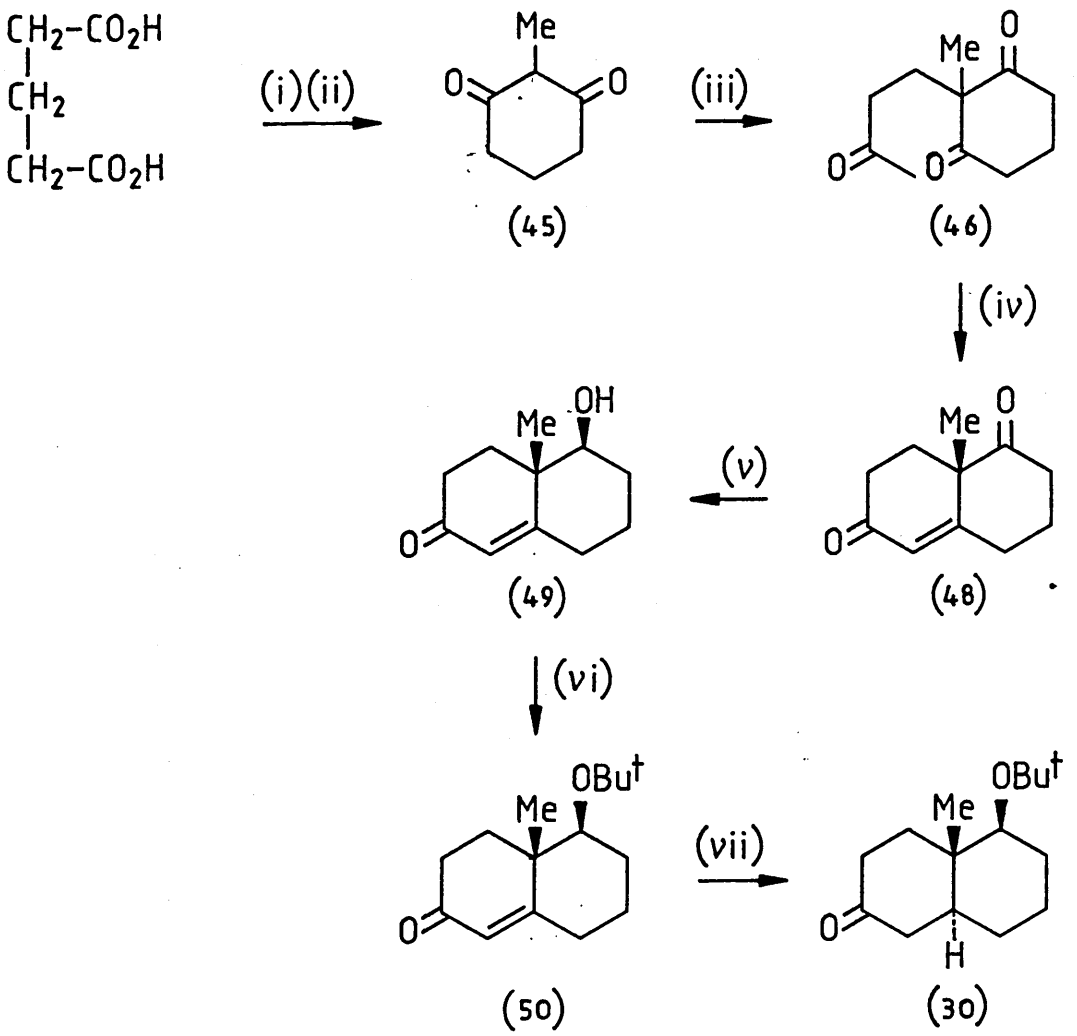
Furthermore, the D-homo series may be transformed to the 5-membered D ring linear anthrasteroids via ring

contraction. Although at first sight this appears as an unnecessary complication, this was envisaged as being required if the synthetic route from the key hydrindan (29) proved difficult.

2.3.2 The Synthetic Route

The synthetic scheme to the key decalone intermediate (30) closely paralleled that to the hydrindan (29), with one notable exception. The desired trans stereochemistry of the ring junction of the bicyclic system was achieved by lithium-ammonia reduction of the enone (50). Consequently the addition and elimination of the auxiliary carboxylic acid group was unnecessary.

Scheme 2



Conditions

(i) $AlCl_3$, $MeNO_2$.

(ii) C_2H_5COCl.

(iii) $H_2C{=}CHCOCH_3$, Water.

(iv) Benzene, pyrrolidine.

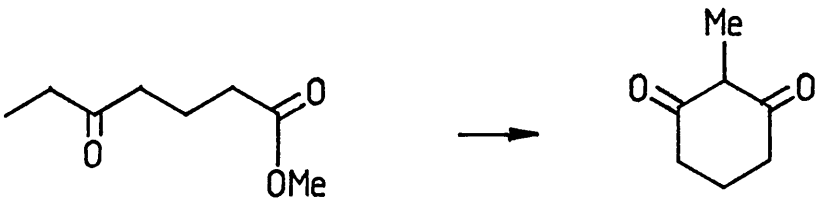
(v) $NaBH_4$, Ethanol.

(vi) $(CH_3)_2C{=}CH_2$, H_3PO_4, BF_3, dichloromethane.

(vii) Li/NH_3.

The key trans decalone intermediate (30) was obtained from glutaric acid in 6 steps and 1.7% overall yield. The Wieland-Miesher Ketone (48) has been utilised extensively in steroid and other syntheses[39], and its preparation from 2-methyl-1,3-cyclohexanedione (45) has been reported[40,41].

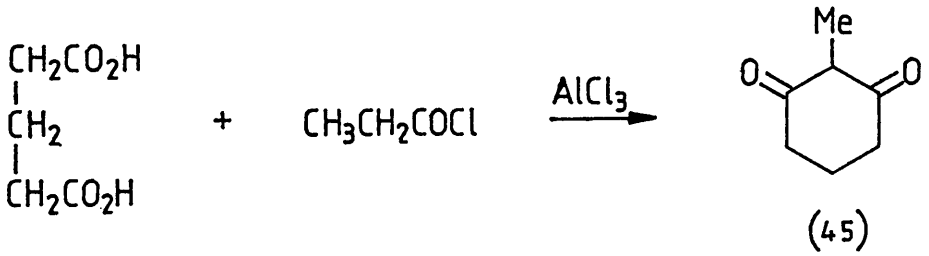
The initial stage involving the preparation of the dione (45) has been accomplished by Swaminathan and Newman[41] in two steps. The first step requires the preparation of methyl 5-oxoheptanoate from γ —carbomethoxybutyryl chloride and ethyl cadmium. The second step involves the internal cyclisation of the keto-ester to give the dione (45) in moderate yield (60%).



(45)

Although the overall yield is acceptable, the two steps required to prepare the dione (45) were considered excessively time consuming.

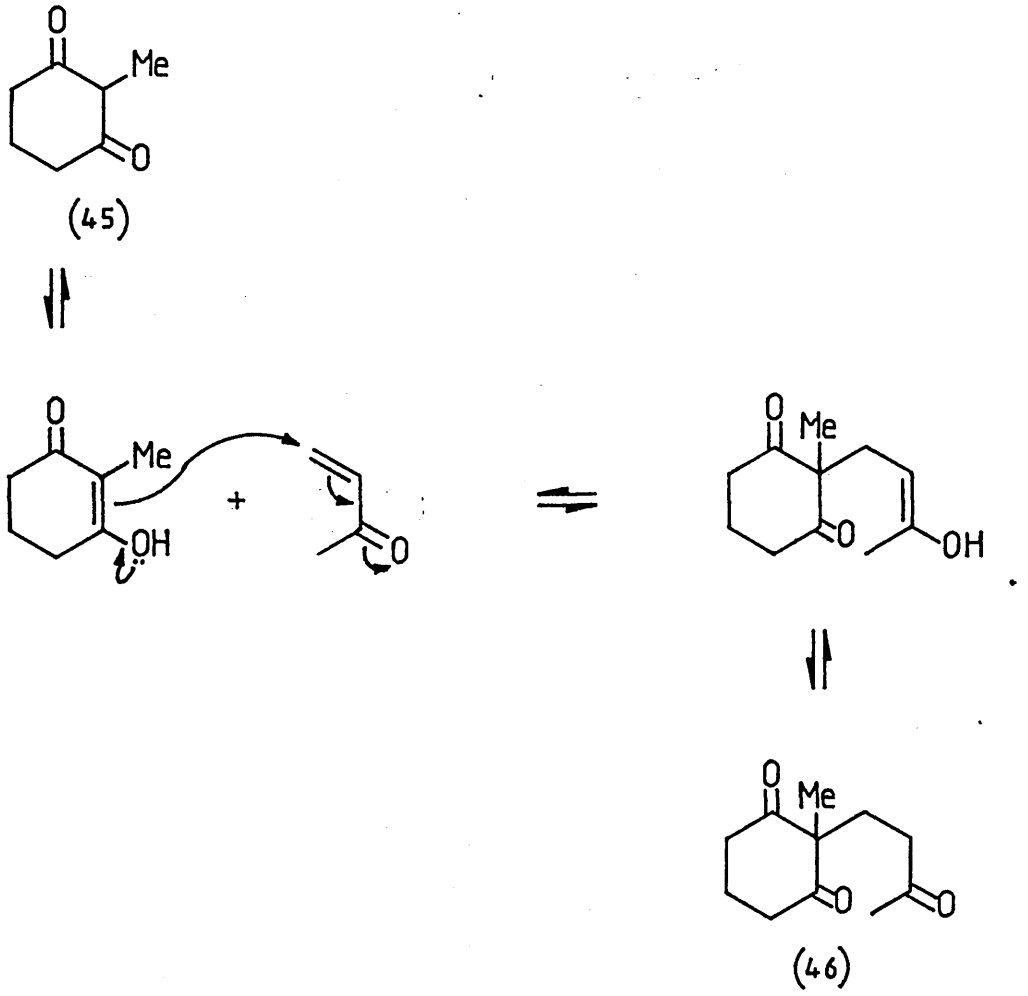
This prompted our attention to the reaction utilised to prepare 2-methyl-1,3-cyclopentanedione (32) (page 34). Using the same conditions as in the synthesis of the cyclopentanedione (32), but substituting glutaric acid for succinic acid, moderate yields (50%) of the cyclohexanedione (45) were obtained.



(45)

The reaction mechanism is presumed to be similar to that proposed for the synthesis of the analogous cyclopentanedione (32).

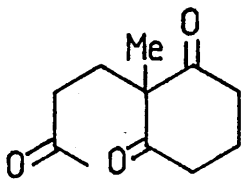
Michael addition of the diketone (45) to methyl vinyl ketone in deionised water afforded the triketone adduct (46). The reaction proceeds via a mechanism which is similar to the cyclopentanedione (32) analogue.



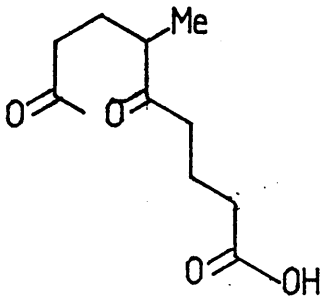
However, although the reactions are similar, the yields of adduct product of 84% (of 33) and 22% (of 46), are in stark contrast.

Other workers have reported low yields of the adduct (46) in the above reaction using various reaction conditions. Thus Swaminathan and Newman[41], employing Triton B as catalyst, have reported a yield of 35%, whereas Wendler, Slates and Tishler[42] have accomplished

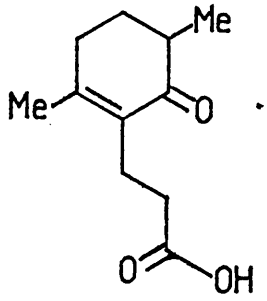
the Michael addition to give (46) in 42% yield, by employing a catalytic amount of triethylamine in aqueous methanol. Although these latter conditions give better yields, even the mild base employed causes the formation of the undesirable acid product[42] (52) in appreciable amounts.



(46)



(51)



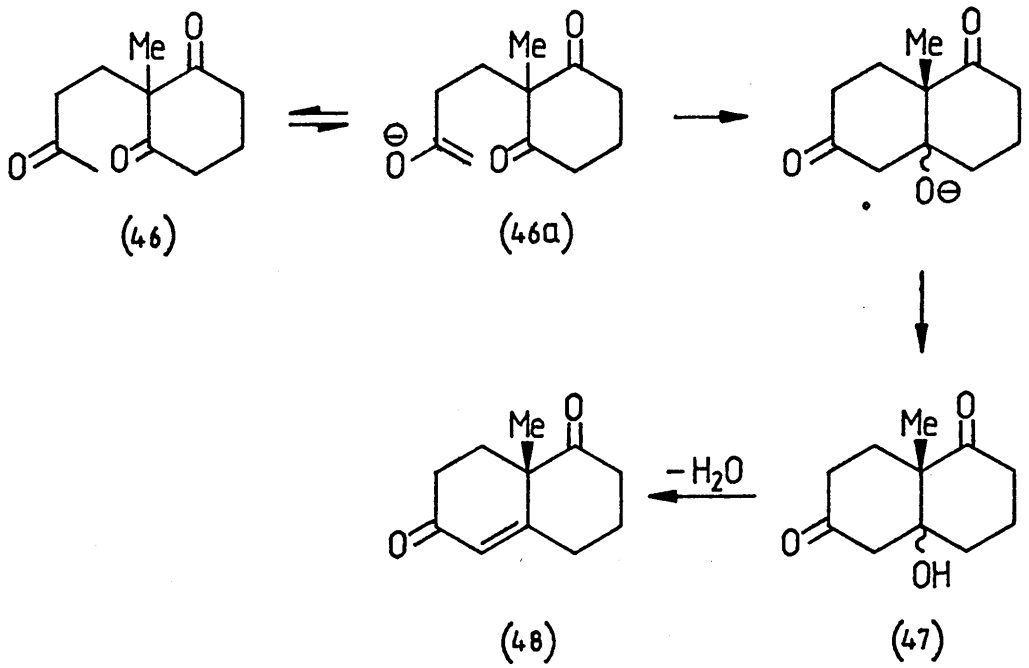
(52)

With 5% aqueous alkali, the triketone is almost instantaneously[42] converted to the acid (52). Although this may account for the poor yields obtained when using basic catalysts, such a transformation seems unlikely under the aqueous conditions employed[18], which are slightly acidic due to the enolic nature of the keto-enol (45).

As in the analogous trione (33) some loss of product may be due to a retro-Michael reaction.

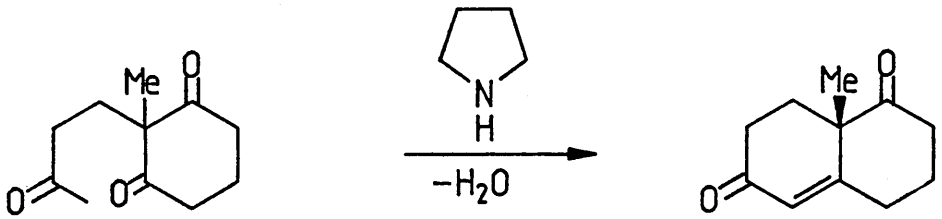
However, none of the above reactions sufficiently explains why the trione (46) should be formed in such poor yield. Indeed, Ruppert, Eder and Wiechert report[43] that the dione (45) reacts with methyl vinyl ketone in water to give the trione (46) in 90% yield after 30 hours.

The cyclisation of the trione (46) to the bicyclic enone (48) follows a similar mechanism to the analogous trione (33), but occurs only with basic catalysts.



Thus the use of p-toluenesulphonic has been reported[27] to give no product, but Swaminathan and Newman[41] have effected cyclisation in 62% yield employing a mixture of pyridine and diethylamine in benzene, which compares favourably with the yield of 40% obtained by Wendler, Slates and Tishler[42] using aluminium t-butoxide catalyst.

Pyrrolidine was used successfully by Ramachandran and Newman[40] to give (48) in over 65% yield, and consequently this catalyst was selected for the cyclisation of the trione (46).

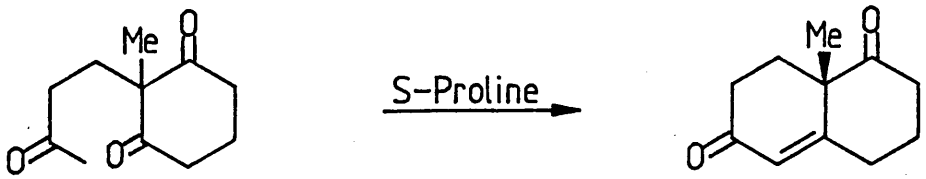


(46) (48)

Initial attempts gave erratic and poor (20%) yields of the bicyclic enone (48), although this was dramatically improved by maintaining the catalyst concentration throughout the duration of the reaction, to give the product (48) in 47% yield.

The bicyclic enone (48) obtained was assumed to be a racemic mixture, by analogy with the cyclisation of (33) in the hydrindan series (page 38).

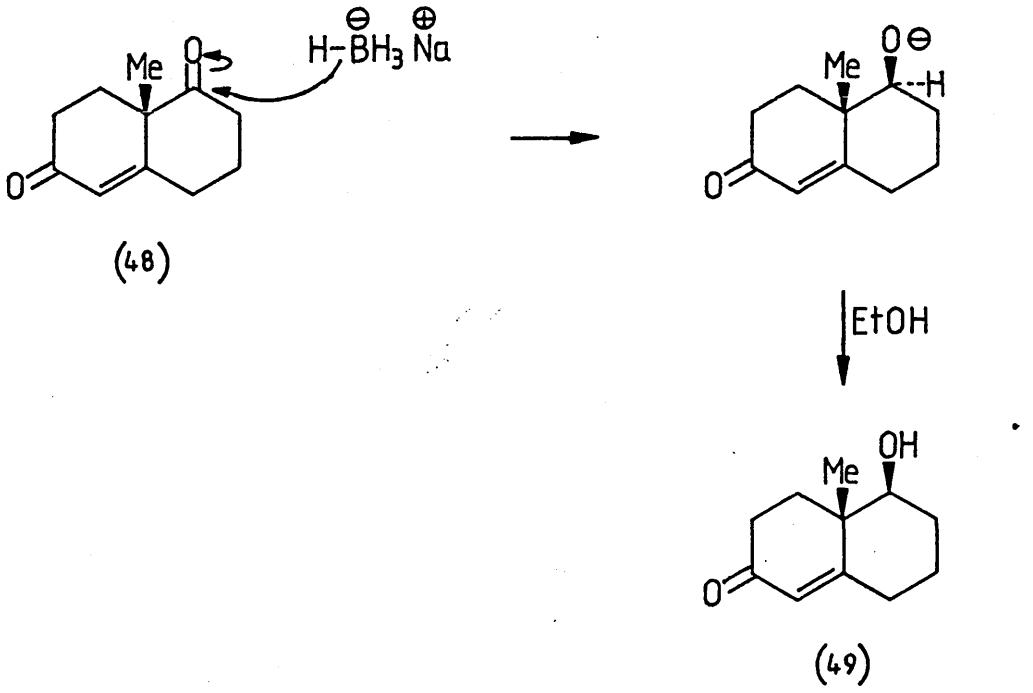
Interestingly, the optically active bicyclic enone (48a) may be obtained by asymmetric induction employing (S)-proline and 1m perchloric acid to afford (S)-8a-methyl-1,2,3,4,6,7,8,8a-octahydro-1,6-naphthalin-dione (48a) in 80% yield, and 68% optical purity[43].



(46) (S)-(48a)

The reasons for using the racemic mixture of (48) in the present study have already been stated.

The unconjugated carbonyl group in (48) was selectively reduced by sodium borohydride to the alcohol (49).

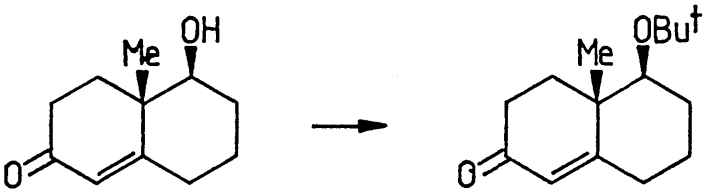


(48)

(49)

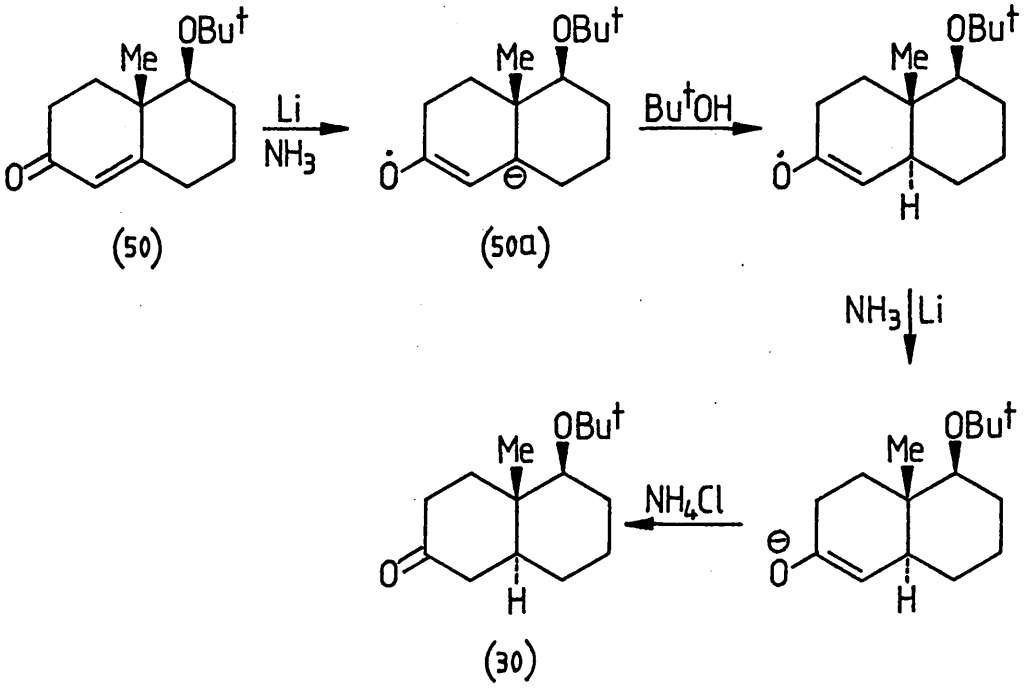
Retention of the C=C double bond was indicated by i.r. spectroscopy, with bands at 1660 and 1620 cm^{-1}. This was corroborated by the observation of a vinylic proton at δ5.90 in ^{1}H.n.m.r. spectroscopy. The borohydride anion was assumed to approach the carbonyl group from the least hindered side, opposite the methyl group[44]. Hydride addition consequently gave the stereoisomer with the hydroxyl group orientated cis to the methyl group.

Protection of the hydroxyl group of (49) was effected by reaction with 2-methylpropene. The t-butyl ether (50) was obtained in a moderate yield (44%) as an oil, which resisted all attempts at crystallization.



(49) (50)

The last reaction to complete the synthesis of (30) involved the lithium-ammonia reduction of the carbon-carbon double bond of the enone (50).



(50) (50a) (30)

The reaction probably proceeds via electron donation to the enone system to give the anion radical (50a), as illustrated above[45]. The stereochemistry of the reduction is dependent on the conformation/ configuration of the anion radical (50a)[34], which for stereoelectronic and steric reasons is most stable in the conformation/configuration which leads to the trans-fused bicyclic ketone (30). Many examples may be found in the steroid literature[46] where lithium-ammonia reduction of the carbon-carbon double bond of enones similar to (30) gives the trans-fused decalin ring junction.

2.4 THE SYNTHESIS OF 2-TETRALONE (31)

2.4.1 General Approach

It was considered that the 2-tetralone (31) offered the following two major advantages as a key intermediate in the synthesis of aromatic steroids.

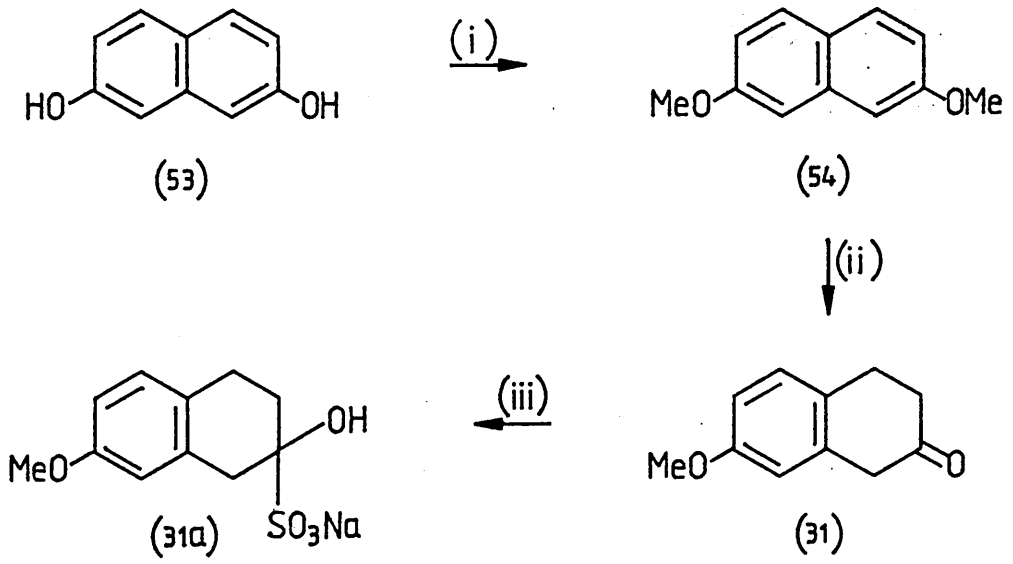
(i) The A ring is already incorporated as an aromatic ring, circumventing the need to aromatise the A ring of the completed steroid skeleton.

(ii) Only two synthetic steps are required to obtain the bicyclic intermediate (31).

2.4.2 The Synthetic Route

The route taken involved methylation of the diol (53), using dimethyl sulphate in aqueous alkali, to the dimethyl ether (54). The ether (54) was reduced using sodium in methanol[47] to give the product 2-tetralone (31) as an oil in moderate yield (49%). This product was identical to authentic sample (by i.r. and ^1H n.m.r. spectroscopy) obtained from the Aldrich Chemical Company.

Scheme 3



Conditions

(i) $NaOH(aq)$, Me_2SO_4.

(ii) Na/Ethanol.

(iii) $NaHSO_3$.

The product 2-tetralone was used immediately, or isolated and stored as its bisulphite adduct (31a).

CHAPTER THREE

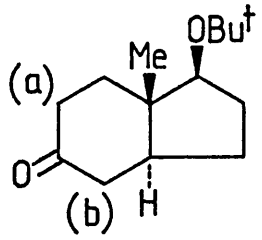
REGIOCHEMICAL CONTROL

OF THE SITE

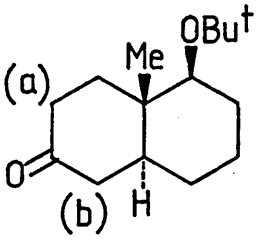
OF ANNULATION

3.1 INTRODUCTION

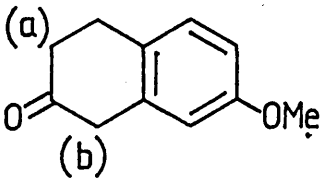
Having achieved the three key bicyclic intermediates (29), (30) and (31), the next problem was to control the position at which they reacted with appropriate annulating reagents, to afford linear tetracyclic compounds.



(29)



(30)



(31)

At this stage, linear anthrasteroid synthesis deviates from 'normal' steroid synthesis in which the position of annulation is site (b). The objective of this study was to restrict the regiochemistry to site (a), facilitating cyclisation via the cyclic ketone group. To achieve this regiochemistry, various strategies were contemplated, of which the main four were:

(i) Use of reaction conditions to direct enolisation of the ketone to position (a).

(ii) Activation of position (a) by the incorporation of various activating groups.

(iii) Blocking of position (b), and subsequent reaction at position (a).

(iv) Use of dianions of β-keto esters to promote reaction at site (a).

Each of these possibilities and their merits are discussed below.

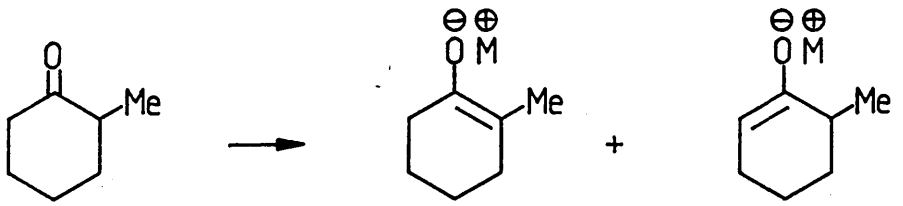
3.2 REGIOSPECIFIC ENOLISATION OF UNSYMMETRICAL KETONES

The enolisation of ketones for C-C bond formation is one of the most versatile and widely used synthetic methods available.

Fortunately, although unsymmetrical ketones can form two regioisomeric enolates, the regiosomer formed can often be controlled to a large degree by judicious choice of reaction conditions[48].

3.2.1 The effect of thermodynamic and kinetic control on the regiochemistry of enolate ion formation

The effect of the reaction conditions on the regiochemistry of ketone enolisation is illustrated with 2-methylcyclohexanone(55), which forms a mixture of the two regioisomers (55a) and (55b), thus:[49].



(55) (55a) (55b)

	Ratios	
Conditions	55a	55b
Thermodynamic control	90	10
Kinetic control	14	86

(This data was obtained from the trapping of the enolate ion as an enol acetate).

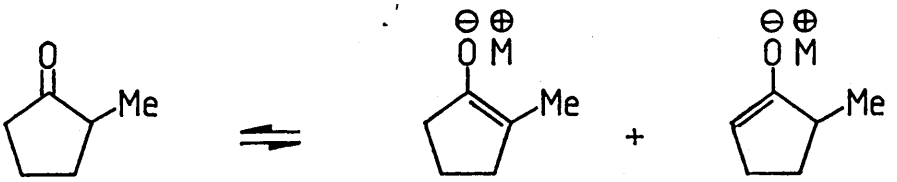
The thermodynamically controlled enolate (55a), in which the double bond is situated to afford optimum stabilisation by conjugation or substitution, is formed under equilibrating conditions (See later).

The alternative kinetically controlled enolate, (55b), is produced by abstraction of the most accessible proton from the starting material, to afford usually the least substituted ketone.

The conditions employed, by choice of base, solvent and temperature, may be selected to manipulate the

regioisomeric enolate as desired[48]. By using protic solvents, high temperatures (room temperature or reflux) and a catalytic amount of a weak base (such as pyrrolidine or diethylamine), 2-methylcyclohexanone(55) enolises to give mainly the thermodynamic isomer (55a). Conversely, by employing an aprotic medium (such as tetrahydrofuran, dimethoxyethane), low temperatures (for example $-78^{o}C$), and an excess of a strong, sterically hindered base (for example lithium diisopropylamide)[50], the most accessible proton is preferentially abstracted giving the kinetic enolate (55b), typically as 85% of the regioisomeric mixture.

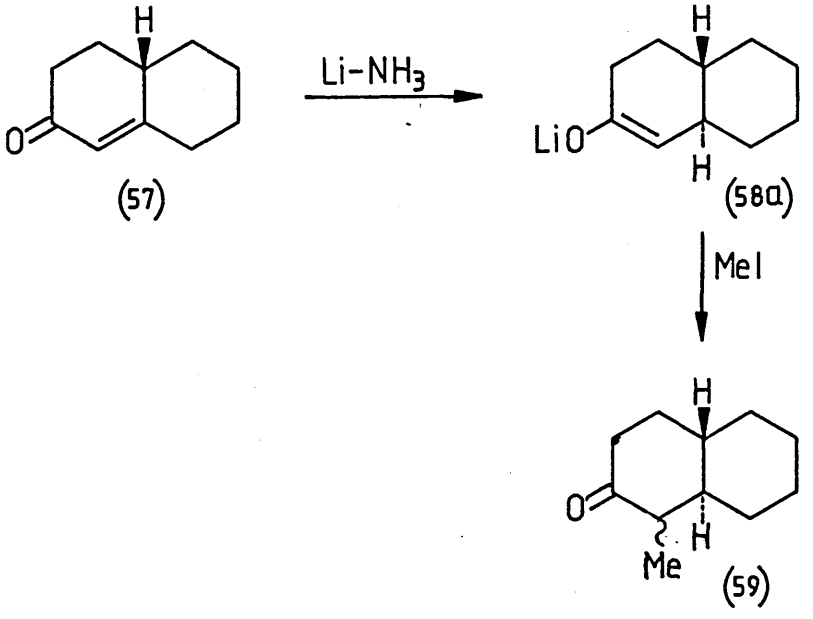
Even the nature of the cation has been shown to exert an influence on the ratio of the regioisomeric enolates[48]. With thermodynamic enolates, as the cation is changed from potassium to lithium, the regioselectivity increases, as illustrated with 2-methylcyclopentanone(56).



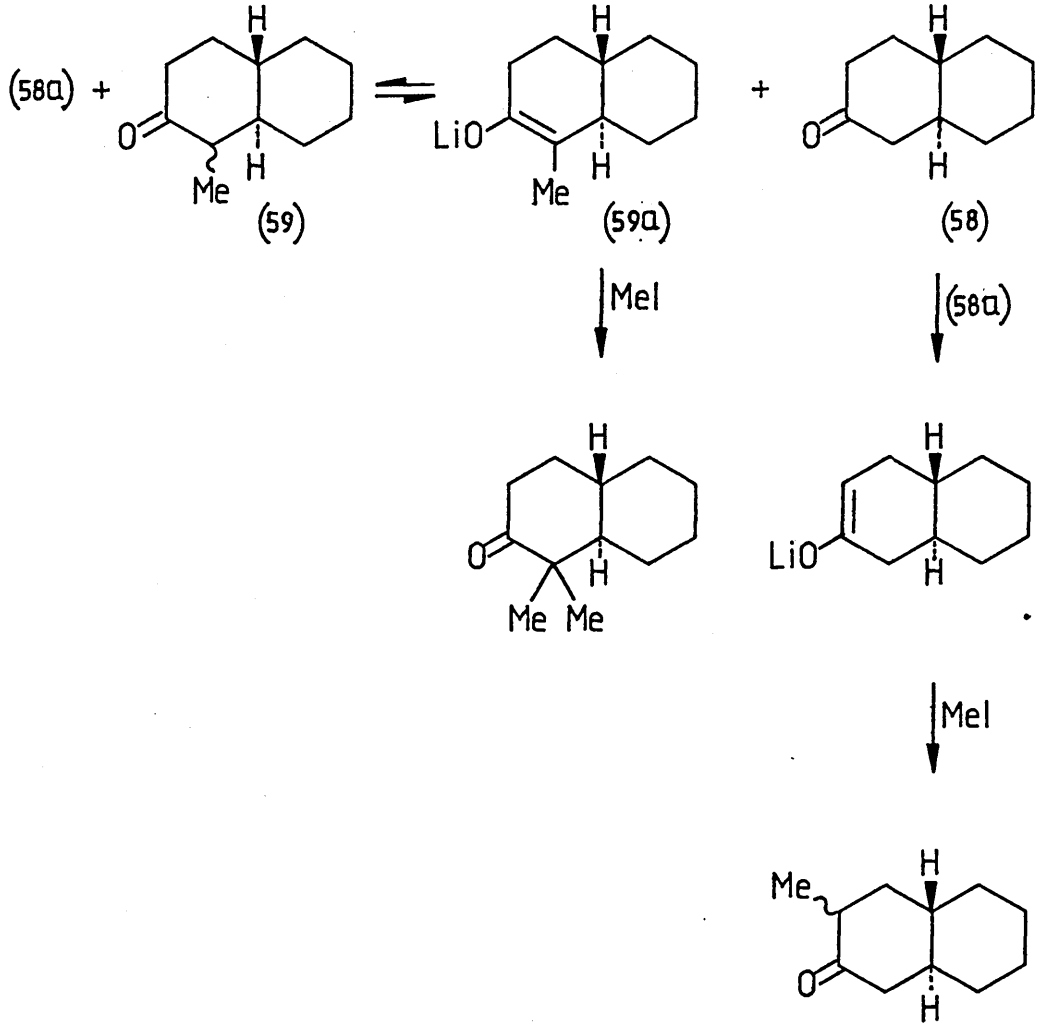
(56) (56a) (56b)

		Ratio	
M		56a	56b
K	cation	80	20
Li	cation	95	5

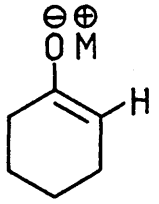
With kinetically generated enolates, a similar pattern emerges, with greater regioselectivity being conferred by the use of cations such as lithium, magnesium, copper, zinc and aluminium. The enolates of these metals equilibrate more slowly than the enolates with sodium and potassium as the counter cation[51,52], because the covalent character of the enolate increases as the associated cation becomes less electropositive. Thus, Stork et al[51] have noted that whilst methylating the anion generated from the lithium-ammonia reduction of 2-octalone (57) with iodomethane, the expected monomethyl compound (59) was formed. By comparison, when using sodium or potassium, mainly polyalkylated material was produced.



Loss of regioselectivity and polyalkylation[53] are considered to occur due to proton transfer from the generated enolate with alkylated ketone product, for example the proton transfer between the enolate (58a) and alkylated product (59). When this equilibration occurs more rapidly than reaction with electrophile [54,55], as with the enolates of sodium and potassium, regiochemical integrity is lost. Lithium enolates equilibrate more slowly with alkylated ketone, and consequently preserve their regioisomeric integrity. This equilibration probably proceeds as follows:



The reason for the effect of the metal cation on the regiochemical integrity of enolates has been studied by Stork et al[53]. These workers, using ^{1}H n.m.r. spectroscopy, observed that the vinyl proton signal of the enolate (60a) of cyclohexanone is shifted upfield as the metal cation is changed from lithium to potassium in glyme, i.e.



M	Chemical Shift (δ) in glyme
Li	4.24
K	3.9

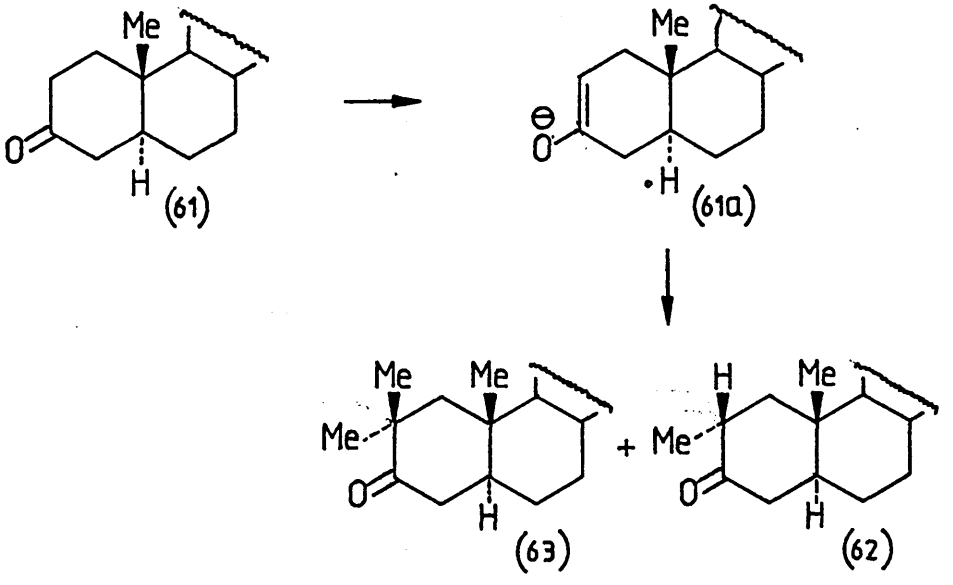
The β-hydrogen atom in the potassium enolate is more shielded than the corresponding hydrogen atom in the lithium derivative. Consequently these workers postulated that the metal-oxygen bond has increased ionic character as the metal changes from lithium to potassium, and that increased ionic character significantly increases base strength. Thus the more basic potassium enolate can more readily abstract a proton from the initially produced alkyl ketone to give a mixture of alkylated and unalkylated enolate derivatives, which leads to polyalkylation and loss of regiospecificity.

Various other countercations have been introduced with a view to increasing regioselectivity of the enolate formed, such as copper[56], diethylaluminium[57] and benzyltrimethylammonium[58] cations. Regioselective α-alkylations of ketones have also been accomplished via[59] potassium enoxytrialkylborate enolate derivatives. However, none of these methods offered any significant advantage for this study over the easily obtainable lithium enolates.

3.2.2 Trapping and regeneration of enolate ions formed under thermodynamically controlled conditions

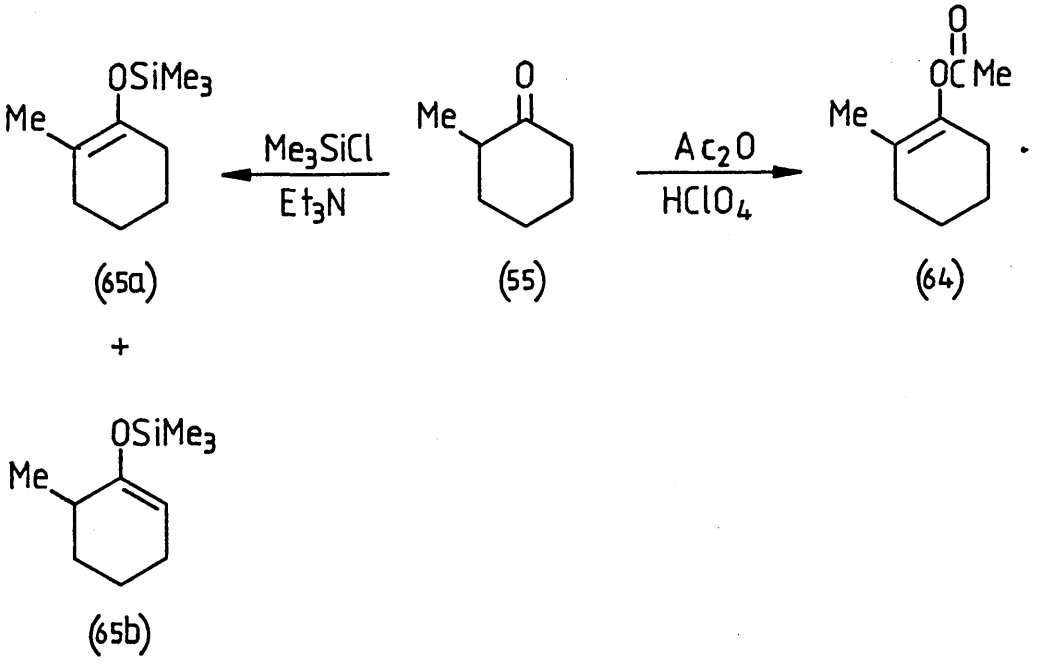
The use of enolates to form C-C single bonds, particularly in the synthesis of steroids, has been widely exploited.

Thermodynamic enolates have been used to effect alkylation, for example[63] the methylation of 5 α - cholestan-3-one (61). This reaction involves generation of the enolate (61a) with potassium t-butoxide in boiling t-butyl alcohol, in the presence of iodomethane, to give mainly the 2-methyl product (62), together with the dimethylated product (63) and starting ketone (61).

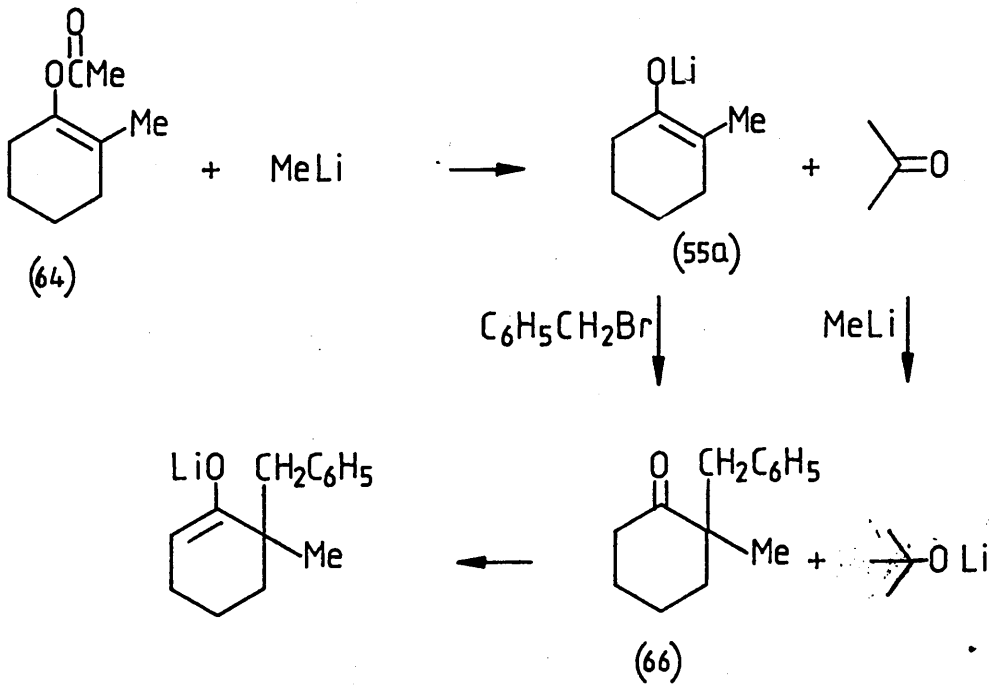


Polyalkylation has been partially overcome by trapping the thermodynamically prepared enolate ions, as

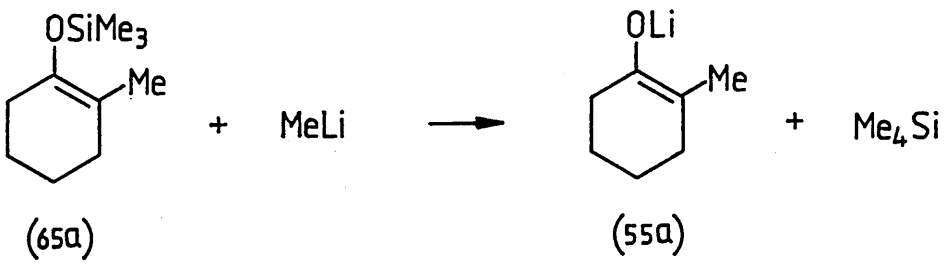
either[50] enol acetates (64) or silyl enol ethers (65) followed by alkylation of the regenerated enolate ion. Although regiochemically pure enol acetates (64) can be obtained, a mixture of isomeric silyl enol ethers (65a and 65b) is often formed, necessitating careful separation (for example[60] by distillation through a spinning band column).



Regeneration of enolate anions (55a) from enol acetates requires two equivalents of methyl lithium. This forms the strong base lithium t-butoxide as a side product, which can induce enolisation of the product ketone (66) leading[50] to loss of regiospecificity and polyalkylation.



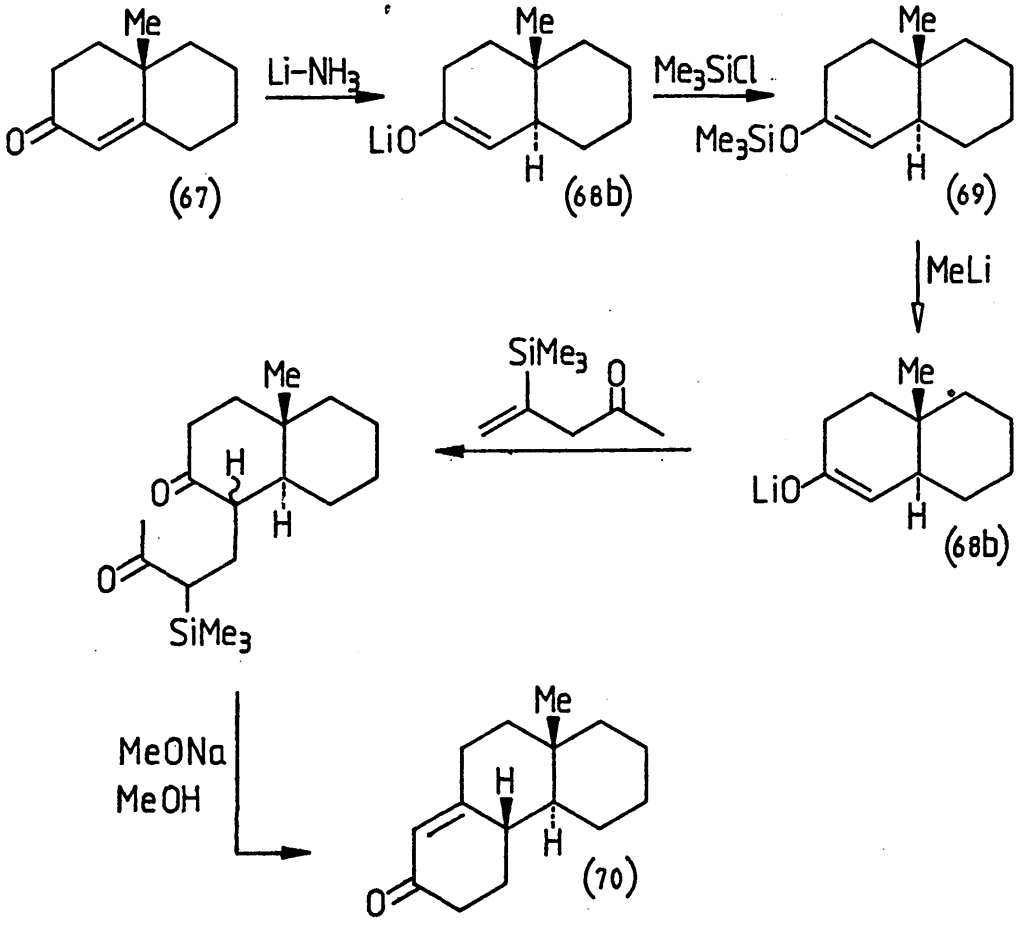
By contrast, cleavage of silyl enol ethers (65a) with one equivalent of methyl lithium results in formation of tetramethyl silane, a relatively inert, volatile side product.



3.2.3 Trapping and regeneration of enolate ions formed under kinetically controlled conditions

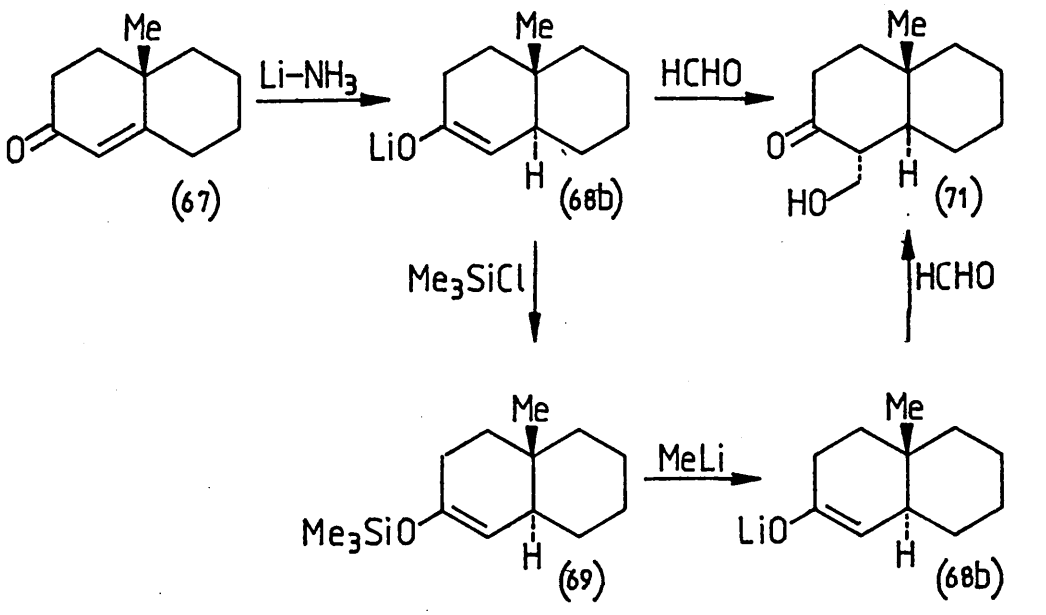
Kinetically controlled regiounstable enolates have been employed by Stork et al[56,57,61] in the synthesis of steroids.

The enolate was usually generated by lithium-ammonia reduction of the corresponding enone, and was subsequently trapped and isolated as its silyl enol ether (69), as illustrated[57] with the enone(67).



Treatment of the silyl enol ether (69) with methyl lithium regenerated the enolate (68b), which subsequently reacted with the annulating reagent in situ to give the tricyclic compound (70).

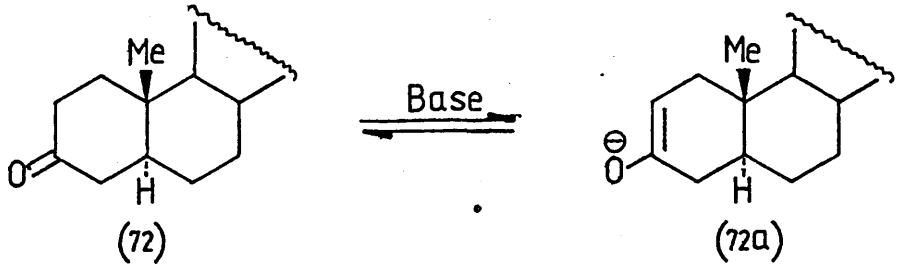
By use of such a trapping procedure an elevation in yield of the final product has been achieved, for example[61] in the condensation of formaldehyde with the enone (67).



Thus the yield of the product (71) was increased from 60%, obtained by direct condensation of formaldehyde with the enolate (68b), to 81% when the intermediate silyl enol ether (69) was employed.

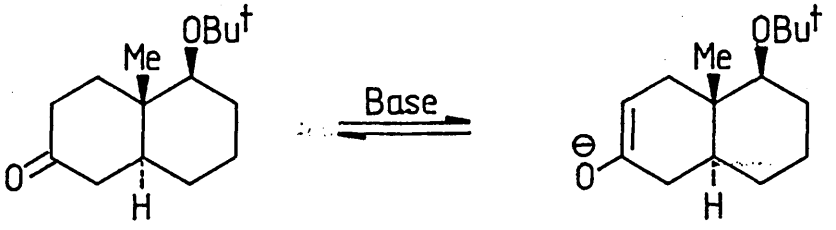
Unfortunately although these kinetically controlled enolates, from lithium-ammonia reduction of the C=C bond, provide an elegant means of effecting annulation, they are not amenable to 'linear anthrasteroid' annulation, because the regiochemistry would lead to the normal steroid system.

However, reports in the literature suggest that the decalin system (72), when incorporating an angular methyl group, forms the enolate (72a) under thermodynamic conditions[48].



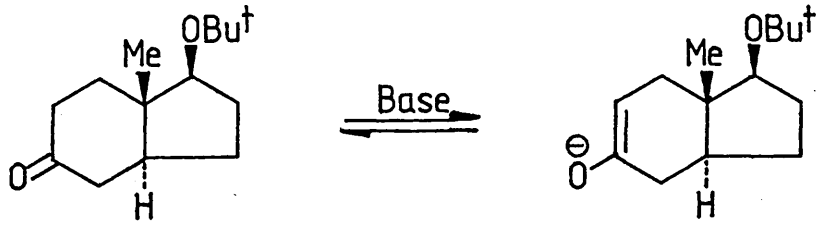
(72) (72a)

Therefore the thermodynamic enolate of the decalin system (30) was expected to give the required regiospecific enolate ion (30a).



(30) (30a)

Furthermore, it was anticipated that the thermodynamic enolate of the hydrindan (29) would give the same regioisomeric enolate ion (29a).



(29) (29a)

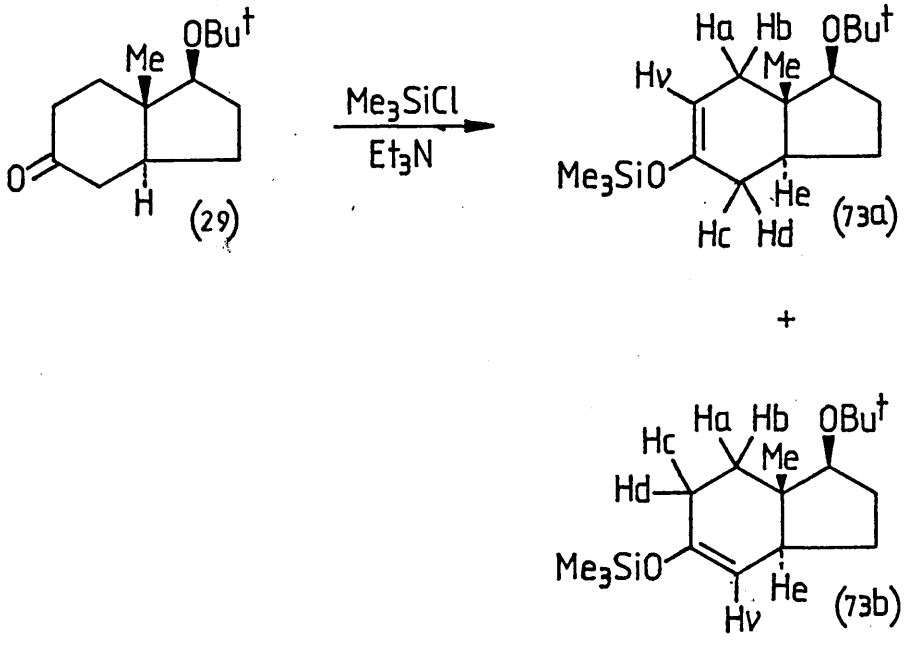
3.2.4 The synthesis of trimethylsilyl enol ethers under thermodynamically controlled conditions.

From the above considerations, trimethylsilyl enol ethers of the cyclic ketones (29) and (30) were selected as intermediates for their annulation.

This trapping sequence also offered the additional benefit of allowing assessment of the homogeneity of the enolisation, and elucidation of the regioisomer formed, by ^{1}H n.m.r. spectroscopy.

The silyl enol ether (73a) was formed by refluxing the hydrindan (29) in dimethylformamide in the presence of triethylamine and chlorotrimethylsilane for 48 hours[62].

Scheme 4



The crude product was chromatographed to give the trimethylsilyl enol ether (73a) in 74% yield. The ^1H n.m.r. spectrum was consistent with that expected for the product, with a resonance at δ 4.85 corresponding to the vinylic proton[53], and a single resonance at δ 0.23 indicating the trimethylsilyl group. Only one vinylic resonance was observed, suggesting that the enol ether was homogenous.

Evidence for the formation of the regioisomer (73a) rather than (73b) was derived from ^1H n.m.r. at 220 MHz. A double resonance spectrum, with irradiation of the olefinic proton, revealed an AB system at δ 1.66 and δ 1.76, with a geminal coupling of 14.5Hz. Irradiation of the low frequency part of this system at δ 1.66 had only a slight effect on the vinylic proton, which resolved to a well defined doublet. Irradiation of the high frequency portion of the AB system at δ 1.76, resulted in collapse of the vinylic doublet to a singlet. This demonstrated that the AB system was coupled to the vinylic proton, and was probably due to the geminal protons Ha and Hb of (73a).

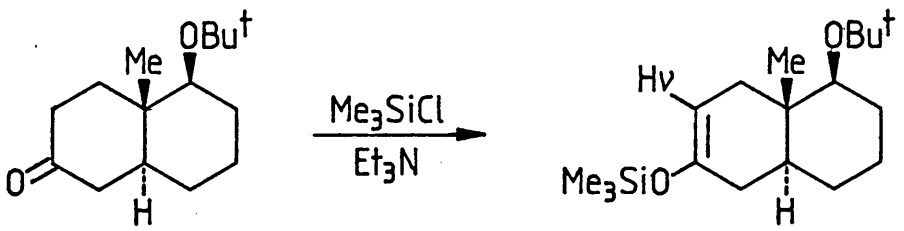
The alternative regioisomer, (73b) would exhibit a vinylically coupled AB system, (corresponding to the protons Hc and Hd), which would be further split by the coupling to the geminal protons Ha and Hb. This would

result in an obscured AB system which was further split and consequently poorly defined, which was not observed.

The assigned regiochemistry was further supported by reaction of (73a) with the annulating reagent to give a compound which was identical to that obtained via a different route. (See later).

The trimethylsilyl enol ether (74a) of the decalin system was formed using the same conditions in 60% yield.

Scheme 5



(30) (74a)

Evidence for the formation of a trimethylsilyl enol ether was provided by ^{1}H n.m.r. spectroscopy with resonances at δ4.90 and δ0.30 being assigned to the single vinylic proton (Hv), and the trimethylsilyl group, respectively. However, no evidence was obtained to support the proposed regiochemistry, as reports in the literature suggest this to be the only regioisomer formed at equilibrium[48,63].

3.3 USE OF ACTIVATING GROUPS

Although the use of activating groups to control regiochemistry is considered a cumbersome technique involving the need for the addition and removal of an auxiliary group, the method offers several major advantages:

(i) Mild reaction conditions may be employed which minimise polyalkylation, and polymerisation of the annulating reagent.

(ii) Methyl vinyl ketone and other simple, readily available annulating reagents may be used, removing the necessity for the synthesis of complex annulating reagents.

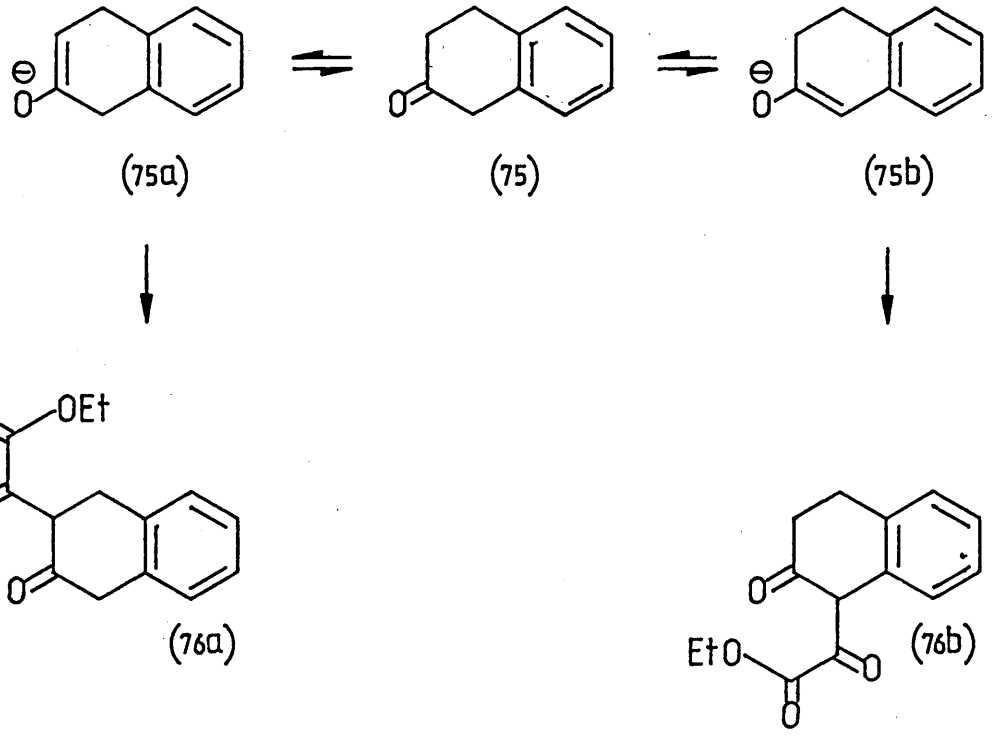
(iii) The activating group may facilitate the elucidation of the regiochemistry of annulation by ^{1}H n.m.r.

The activating groups considered were the glyoxylate ester, carboxylate ester and formyl functional groups.

3.3.1 Regiochemistry of addition of the activating groups

The regiochemistry of the addition of the glyoxylate ester, carboxylate ester and formyl activating groups was initially considered to be dependent on the direction of enolisation of the cyclic ketone group. Thus incorporation of the activating group on to 2-tetralone was expected to occur at the 1-position.

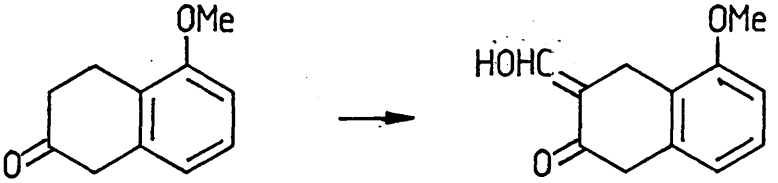
However, a body of evidence in the literature suggests that addition of the activating groups occurs at the 3-position. Thus the condensation of 2-tetralone (75) with diethyl oxalate gives the product (76a)[64].



(75a) (75) (75b)

(76a) (76b)

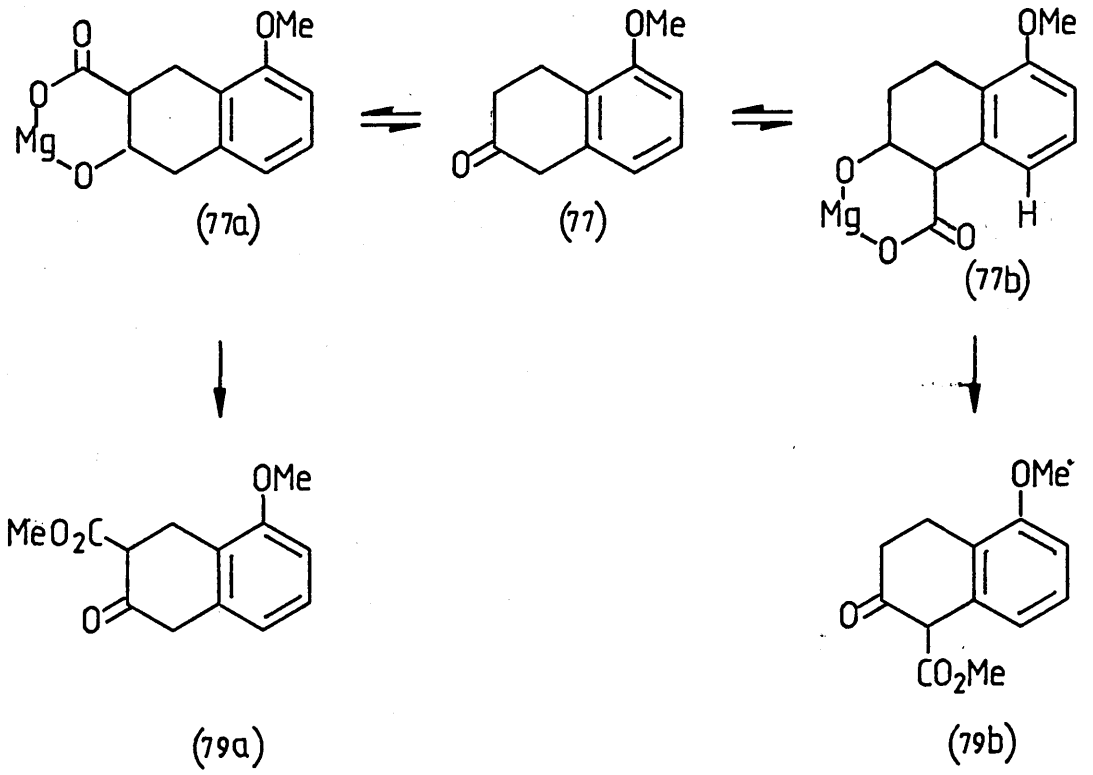
5-methoxy-2-tetralone (77) reacts with ethyl formate to give the 3-hydroxymethylene tetralone (78)[65].



(77) (78)

Addition of a carboxylic acid group to 2-tetralones via magnesium methyl carbonate[65,66,67], also proceeds at

the 3-position, to give the β-ketoester (79a) after acidification and treatment with diazomethane[79].

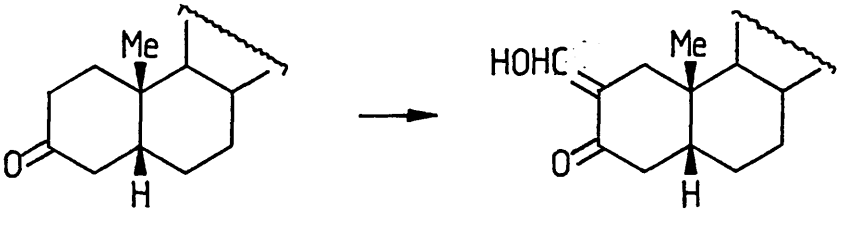


Various positions of substitution of the methoxy group in the aromatic ring are reported not to affect the regiochemistry of the reaction[67].

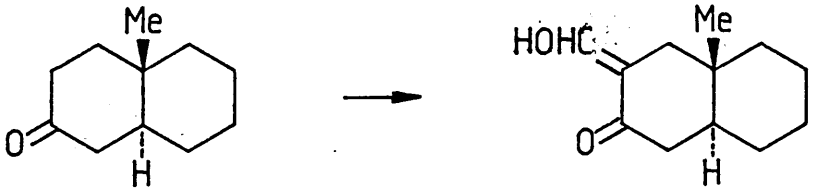
The regiochemical outcome of all these reactions may be explained if addition of the activating groups is subject to steric and thermodynamic control. Consequently when the reaction is at equilibrium the most stable product will be formed irrespective of the

direction of enolisation of the cyclic ketone. This may be illustrated by the reaction of magnesium methyl carbonate with the 2-tetralone (77). The magnesium chelate intermediates (77a) and (77b) are reversibly formed, and at equilibrium the most stable chelate will predominate[66]. Dreiding models indicate that the chelate intermediate (77b) is subject to severe steric interference between the carbonyl group and the hydrogen atom at C-8. This interference is absent in the regioisomeric chelate (77a), which consequently predominates at equilibrium.

Similar steric and thermodynamic control has been observed in the formylation of cis and trans decalin systems. Formylation of the 3-keto steroids (80) of the A/B-cis series using ethyl formate and sodium methoxide in benzene gives the 2-hydroxymethylene product[68] (81), and formylation of the trans decalone (68) gives the 3-hydroxymethylene product (83a)[69].

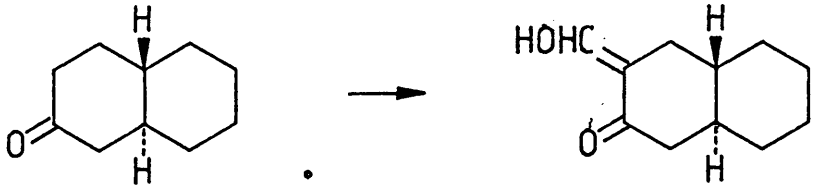


(80) (81)



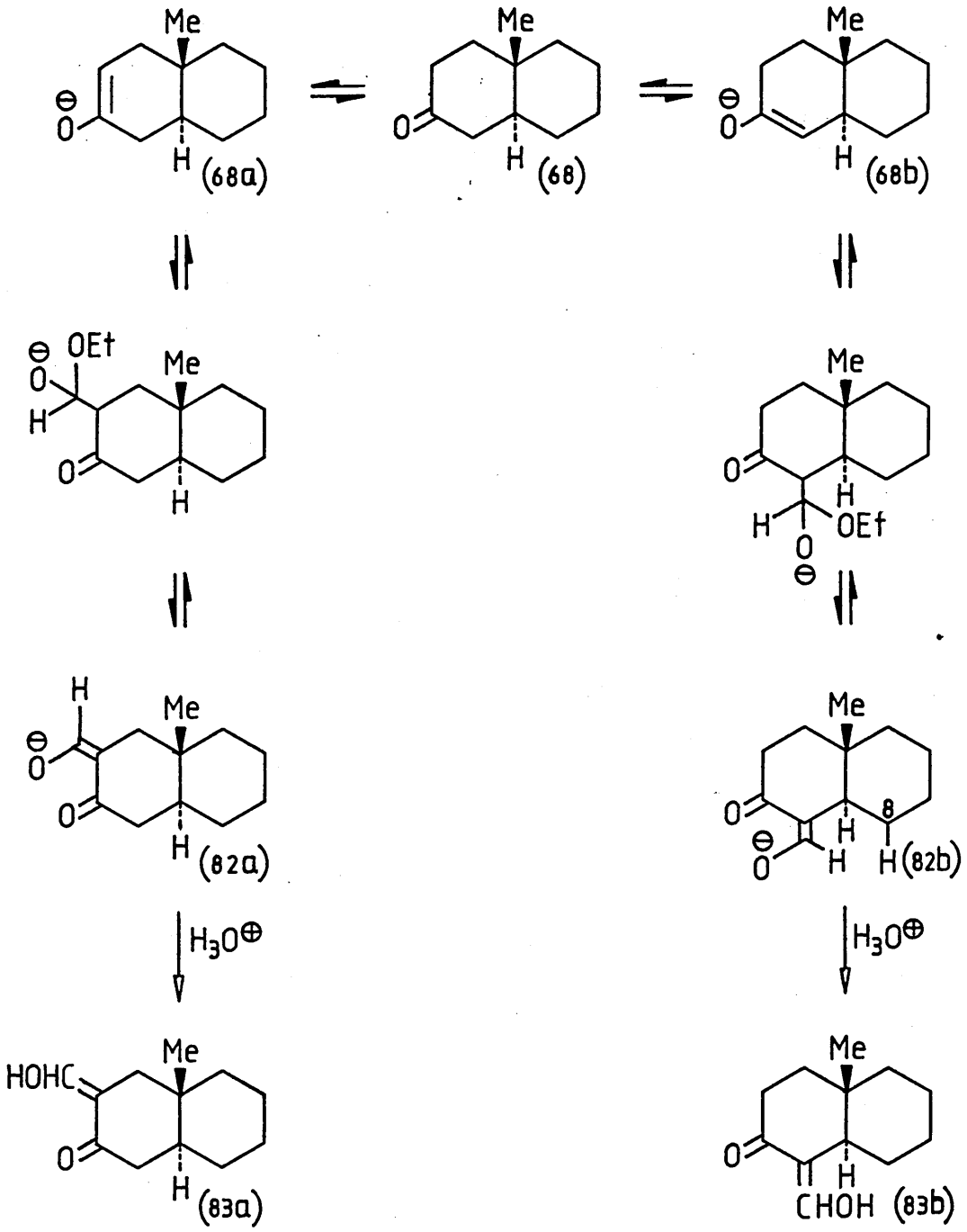
(68) (83a)

Finally, in the absence of the angular methyl group, trans decalone (58) still affords the 3-hydroxymethylene product (84)[70].



(58) (84)

The regiochemical outcome of the above condensations may be rationalised using arguments similar to that used to explain the regiochemistry of addition of 2-tetralone to magnesium methyl carbonate.



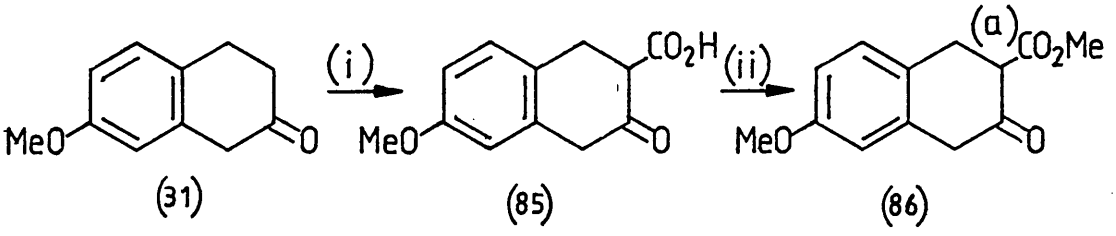
Dreiding models indicate that for the trans decalin system, the conjugate base (82b) of the hydroxymethylene ketone (83b) experiences a type of 1,3-syn diaxial steric interference, but with the equatorial hydrogen atom at position 8. This

interaction is absent in the regioisomeric compound (82a), which is consequently favoured at equilibrium. The regiochemistry of thermodynamically controlled reactions of cis-decalin can be similarly explained.

3.3.2 Synthesis of β-keto ester intermediates

In view of the above, the carboxylation of 7-methoxy-2-tetralone (31) was attempted, the anticipated 3-carbomethoxy adduct (86) offering the possibility of annulation at the (a) position, in the linear anthrasteroid orientation.

Scheme 6



(i) MMC, DMF

(ii) CH_2N_2

Unfortunately, even after repeating the reaction numerous times, on only one occasion was a solid product recovered from the reaction mixture. Furthermore, this compound was isolated in insufficient quantity for unambiguous structural analysis, although

a ^{1}H n.m.r. spectrum of the crude material was consistent with the 3-carboxylic acid product (85).

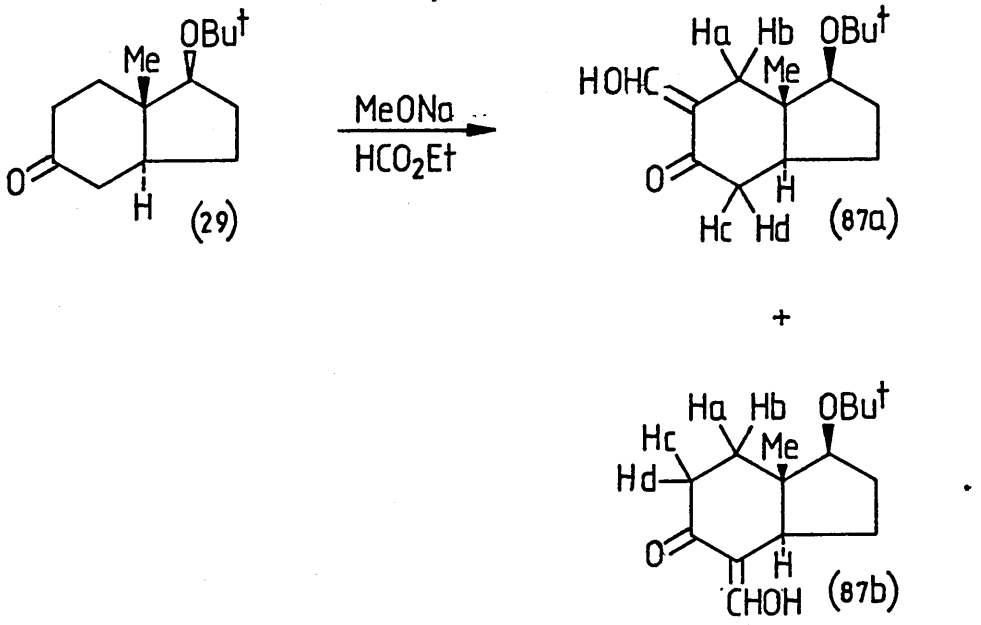
Pelletier et al[65] report that decarboxylation of the β-keto acid readily occurs under the acidic work up conditions. 6-methoxy-2-tetralone gives particularly poor yields[67] of product, and this was assumed to account for the inability to isolate the product (85) in good yield.

3.3.3 Synthesis of α-hydroxymethylene ketone intermediates.

By analogy to the above it was anticipated that formylation of the hydrindan(29) would occur at the (a) position, thus activating the bicyclic compound (29) towards linear anthrasteroid annulation.

This was accomplished by treating the ketone(29) with sodium methoxide and ethyl formate in benzene[71] to give the hydroxymethylene ketone (87a) as an oil in excellent (98%) yield. (Scheme 7). This compares favourably with the yield (50%) of hydroxymethylene ketone product obtained whilst using sodium hydride as base[68,72].

Scheme 7



Spectral analysis of the product was consistent with the hydroxymethylene compound (87a), with the infrared spectrum indicating the α-hydroxymethylene ketone moeity with bands at 1640 and 1590 cm^{-1}. The ^1H n.m.r. spectrum in chloroform exhibited two characteristic doublets at δ14.7 and δ8.60, corresponding to the hydroxyl proton and methylene proton, of the hydroxymethylene group, respectively. Irradiation at δ 14.7 resulted in collapse of the doublet at δ8.60 to a singlet, indicating that the two protons were coupled, with a coupling constant of 3Hz.

Further doublets were evident at δ14.3 and δ7.45, probably corresponding to the hydroxyl and methylene protons respectively of the corresponding regioisomeric hydroxymethylene ketone (87b). A 9Hz coupling constant was observed for these protons, which, by integration, indicated the regioisomer (87b) to be present in less than 10%.

Evidence for the proposed regioisomer (87a) rather than the alternative hydroxymethylene ketone (87b) was provided by a ^{1}H n.m.r. spectrum at 220MHz. This spectrum, when obtained from a solution of (87a) in deuterated benzene, revealed an AB system at δ2.05 and δ2.35, with a geminal coupling constant of 14 Hz. This was only consistent with the regioisomer (87a) and was attributed to the two protons Ha and Hb. In addition, a second AB system was observed corresponding to the methylene protons Hc and Hd. A portion of this AB system was evident at δ2.45 as a doublet of doublets, with a geminal coupling constant of 18Hz, and a weaker secondary coupling constant of 5Hz. These signals were attributed to the equatorial proton Hc.

The alternative regioisomer would be expected to exhibit two AB systems, with their geminal couplings, which would be further split due to mutual coupling of the adjacent methylene groups. This would produce a

more complex and poorly defined spectrum.

3.4 USE OF BLOCKING GROUPS

Although the use of blocking groups to control the regiochemical site at which ketones will react is considered a cumbersome strategy, requiring the addition and removal of an auxiliary group, such a method does offer notable advantages:

(i) Although dialkylation in addition to mono-alkylation may still occur at the free site, any alkylation at the undesired position is completely prevented.

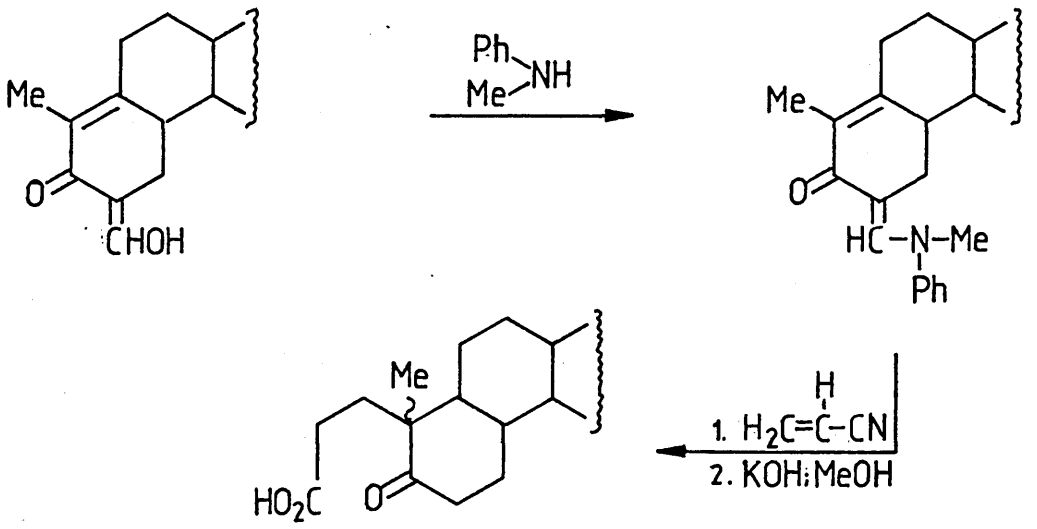
(ii) The blocking group may be further exploited by conversion to a group required in the target molecule. For example, the thioether group may be used as such a latently functional group. (See later).

3.4.1 General survey of blocking groups

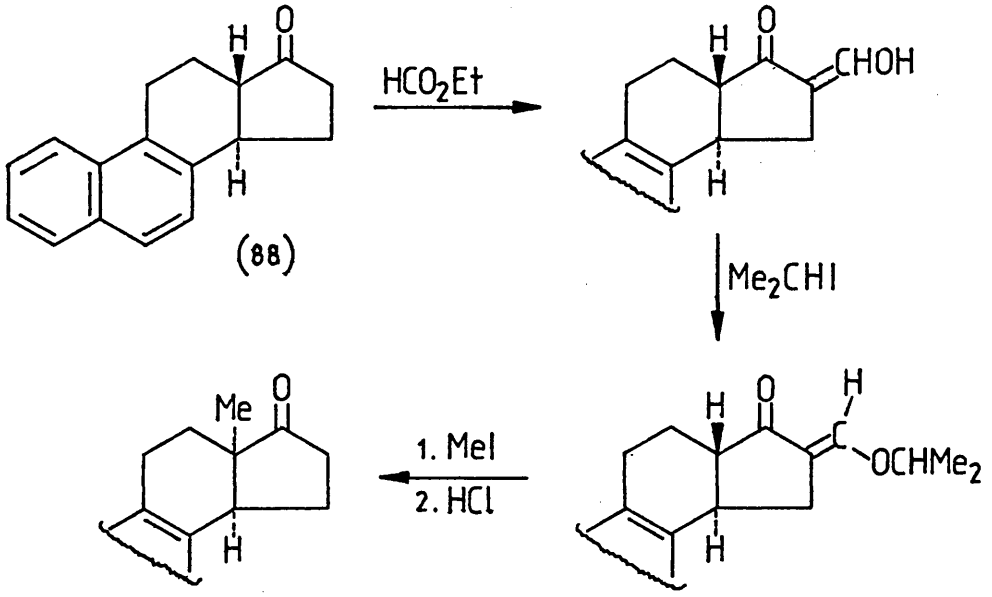
Various blocking groups are available which have been used successfully to control the regiochemistry of reactions, for example the methylanilinomethylene, isopropoxymethylene and n-butyl thiomethylene blocking groups.

The methylanilinomethylene group was used by Woodward et al[15], in their initial synthesis of steroids, for

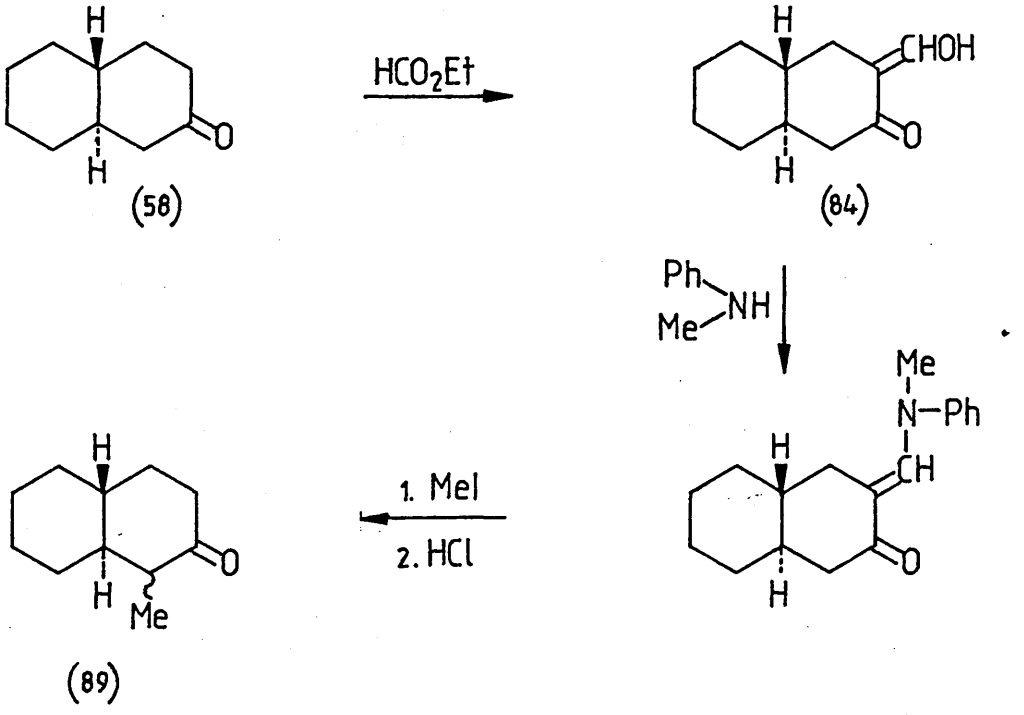
the regiospecific introduction of the A ring.



The isopropoxymethylene group has been used by Johnson and Posvic[73] for the introduction of an angular methyl group in the norequilenin derivative (88).

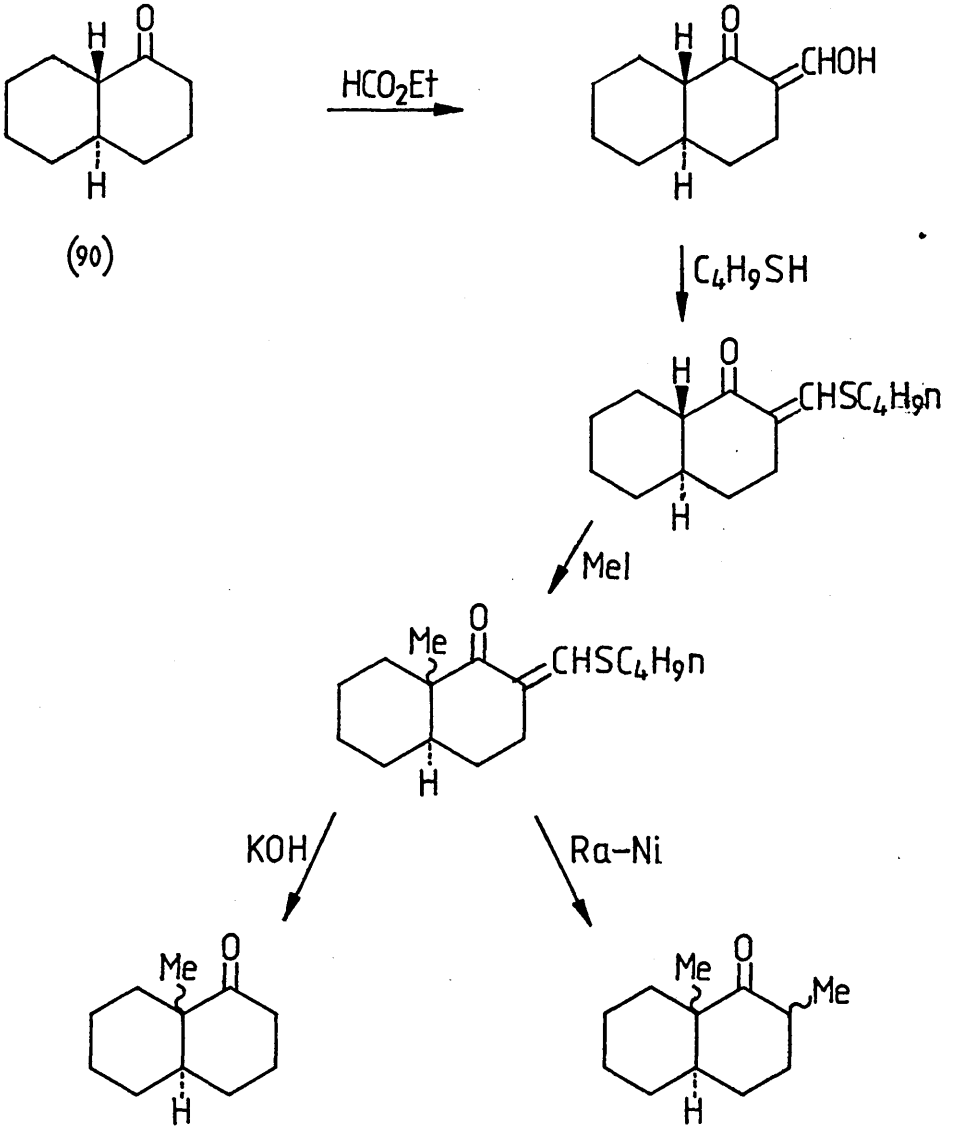


This group has also been used by Pinder and Robinson[70] to allow regiospecific alkylation of trans-2-decalone (58) to give 1-methyl-trans-2-decalone (89)



The last group, n-butylthiomethylene ketones, have been developed by Ireland and Marshall[74] for various regiospecific alkylations, including the introduction of an angular methyl group to 1-decalone (90). This blocking group offers the additional advantage that the auxiliary group may be cleaved after alkylation under either mild acid or basic conditions. Thus the appropriate removal procedure may be used which is

compatible with acid or base labile groups within the product. Furthermore, the butylthiomethylene moiety may be easily reduced with Raney nickel to a methyl group[74], thereby exploiting the latent functionality of this blocking group.

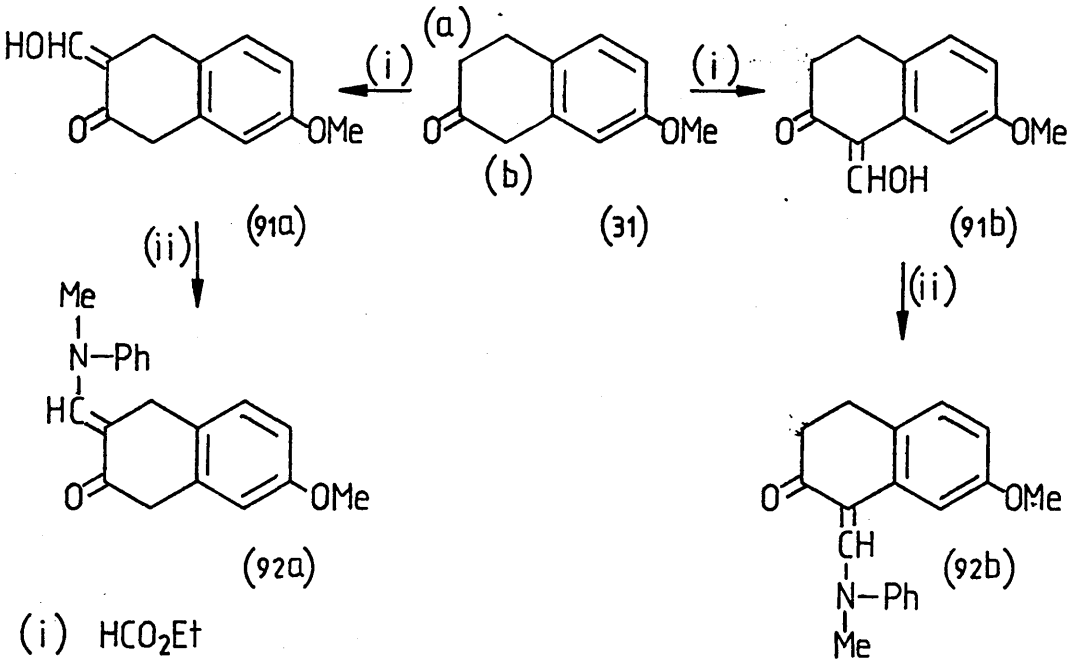


3.4.2 Synthesis of compounds blocked with the methylanilinomethylene group

All the aforementioned blocking groups involve the initial formation of a hydroxymethylene ketone, and the regiochemistry of the intermediate determines the vacant site at which the desired annulation will occur.

Initially it was assumed that ethyl formate would react with 2-tetralone (31) in benzene in the presence of sodium methoxide to give the desired regioisomer (91b), which could be blocked by treatment with N-methylaniline to give the product (92b). This would prevent reaction at the (b) position, and allow annulation to proceed via the free (a) site only.

Scheme 8



However, evidence in the literature[65] suggests that reaction of 2-tetralone with ethyl formate proceeds at the (a) site, despite the direction of enolisation of (31) being towards the (b) position at thermodynamic equilibrium.

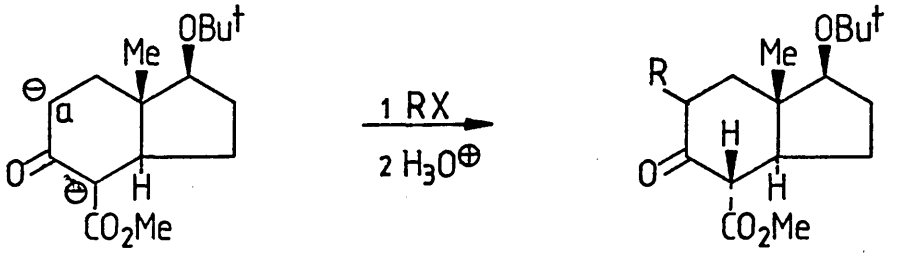
The 2-tetralone (31) reacted with ethyl formate in benzene under basic conditions to give the hydroxymethylene ketone (91a/b) as an oil in only poor (40%) yield. Although infrared spectral evidence supported the expected hydroxymethylene product, with bands at 1660 and 1620 cm^{-1} corresponding to a α-hydroxymethylene ketone and aromatic ring, the ^1H

n.m.r. spectrum was ambiguous, and although mainly consistent with product, the particular regioisomer could not be ascertained.

Coupling of the adduct (91a/b) with N-methylaniline, to afford the methylanilinomethylene (92a/b) proved unsuccessful. As evidence in the literature cited above suggested that the alternative hydroxymethylene regioisomer (91a) was probably the product obtained, this synthetic scheme was abandoned.

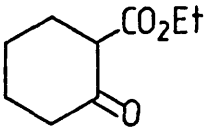
3.5 THE USE OF DIANIONS OF β-KETO ESTERS

The use of dianions of β-keto esters was envisaged as an elegant method of controlling the regiochemistry of annulation of the hydrindan (40) by exploiting the carboxylic acid group which had already been incorporated. The dianion of the β-keto ester (40) was expected to react with electrophiles at the (a) position, as shown:



(40)

As the authentic β-keto ester material (40) was relatively precious, initial studies to assess the feasibility of this method were conducted on the model β-keto ester compound, ethyl 2-oxocyclohexane carboxylate (93).



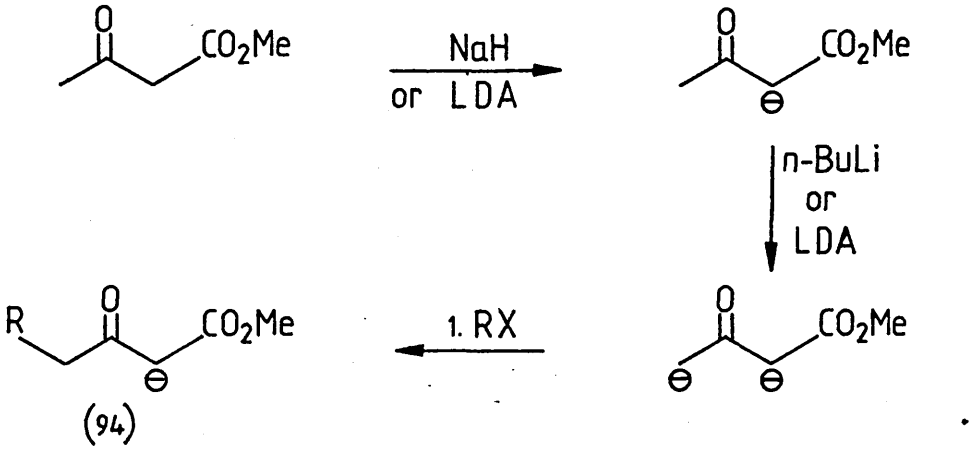
(93)

3.5.1 Generation and reaction of dianions

The dianions of β-keto esters, and their reaction at the γ-position with electrophiles, has been reported [75,76,77] as a synthetically useful reaction for the regioselective formation of C-C bonds.

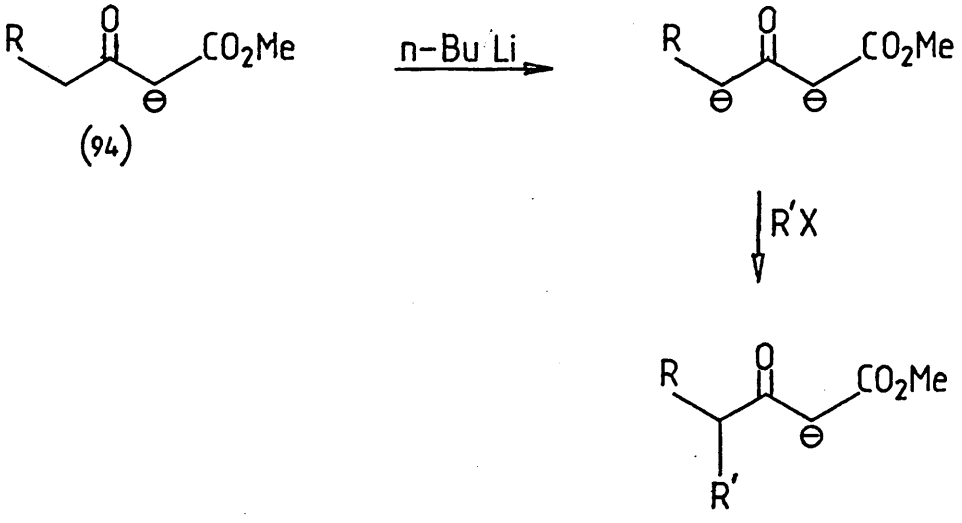
The conditions for the generation of the dianions usually involve treating the β-keto ester with two equivalents of lithium diisopropylamide (LDA)[75,77], or forming the mono anion with sodium hydride or lithium diisopropylamide followed by the addition of 1 equivalent of n-butyl lithium to generate the dianion[76,77].

The dianions are alkylated at the γ-position by treatment with the appropriate alkyl halide.



(94)

The synthetic utility of the reaction may be extended by generating the dianion of the γ-alkylated β-keto ester (94), and reacting this with further alkyl halide to effect dialkylation[77].



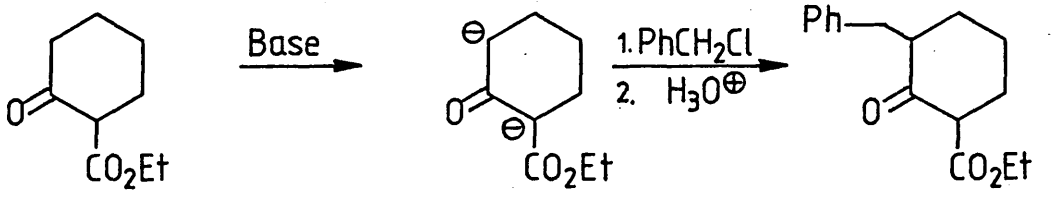
(94)

The alkylation is reported to be free of competing alkylation at the α-position. This is possibly due to the greater reactivity of β-keto ester dianions compared to their monoanions[77].

3.5.2 Attempted alkylation of the dianion of ethyl 2-oxocyclohexane carboxylate

Initial studies on the alkylation of the dianion of the β-keto ester (93) used benzyl chloride as the alkylating agent. This halide was chosen because of its reactivity, compared to saturated alkyl chlorides, and the relatively simple ^1H n.m.r. spectrum expected of the alkylated product (95). In addition, benzyl chloride has been used successfully for the alkylation of the dianions of β-keto aldehydes[78], β-keto amides[79] and β-keto esters[76,77].

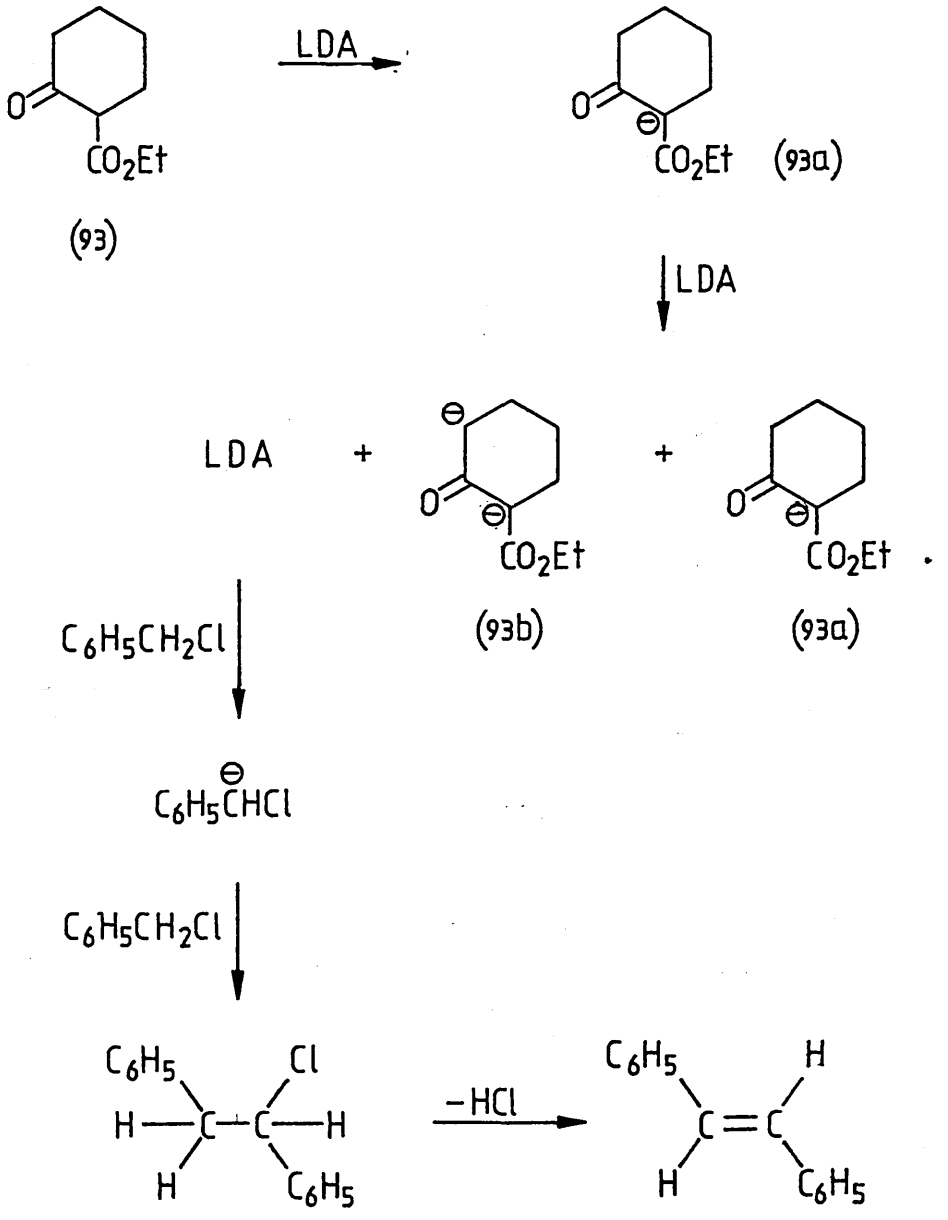
Scheme 9



(93) (93b) (95)

The dianion (93b) was generated by treating the β-keto ester (93) with 2 equivalents of lithium diisopropylamide. However, addition of benzyl chloride to this dianion gave a mixture of products. Vacuum distillation of the reaction mixture gave the β-keto ester (93) 1-chloro-1,2-diphenyl ethane, and trans stilbene, with no product (95) evident. Even on repeating the reaction using 1 equivalent of lithium diisopropylamide followed by 1 equivalent of n-butyl lithium; or 1 equivalent of sodium hydride followed by 1 equivalent of n-butyl lithium to generate the dianion, a similar product mixture was obtained.

A plausible explanation for the formation of trans stilbene rather than the expected product (95) is that dianion formation of the β-keto ester is incomplete. Consequently an excess of base is present on addition of the alkylating agent, and proton abstraction from the benzyl chloride occurs. The anion generated undergoes nucleophilic subsitution of further benzyl chloride to give 1-chloro-1,2-diphenylethane, which undergoes 1,2 elimination of hydrogen chloride to give trans stilbene.



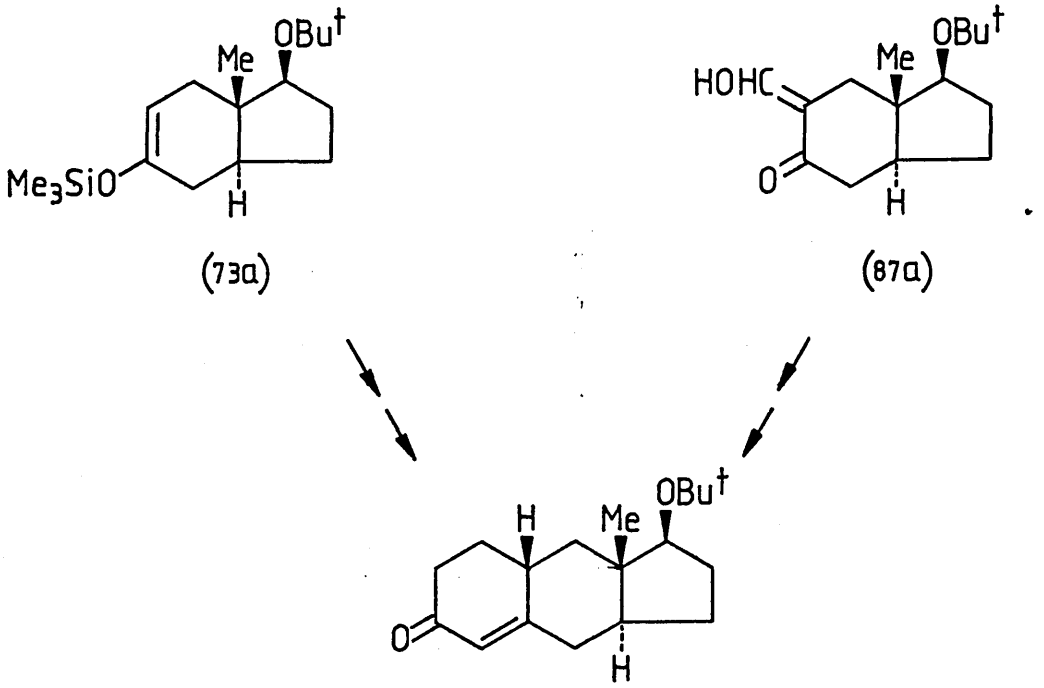
This explanation is supported by Wolfe et al[80], who similarly explain the formation of trans stilbene from the alkylation of the dianion of ethyl acetoacetate (formed from 2 equivalents of potassium amide in liquid ammonia) with benzyl chloride.

CHAPTER FOUR

ANNULATION OF BICYCLIC COMPOUNDS

4.1 INTRODUCTION

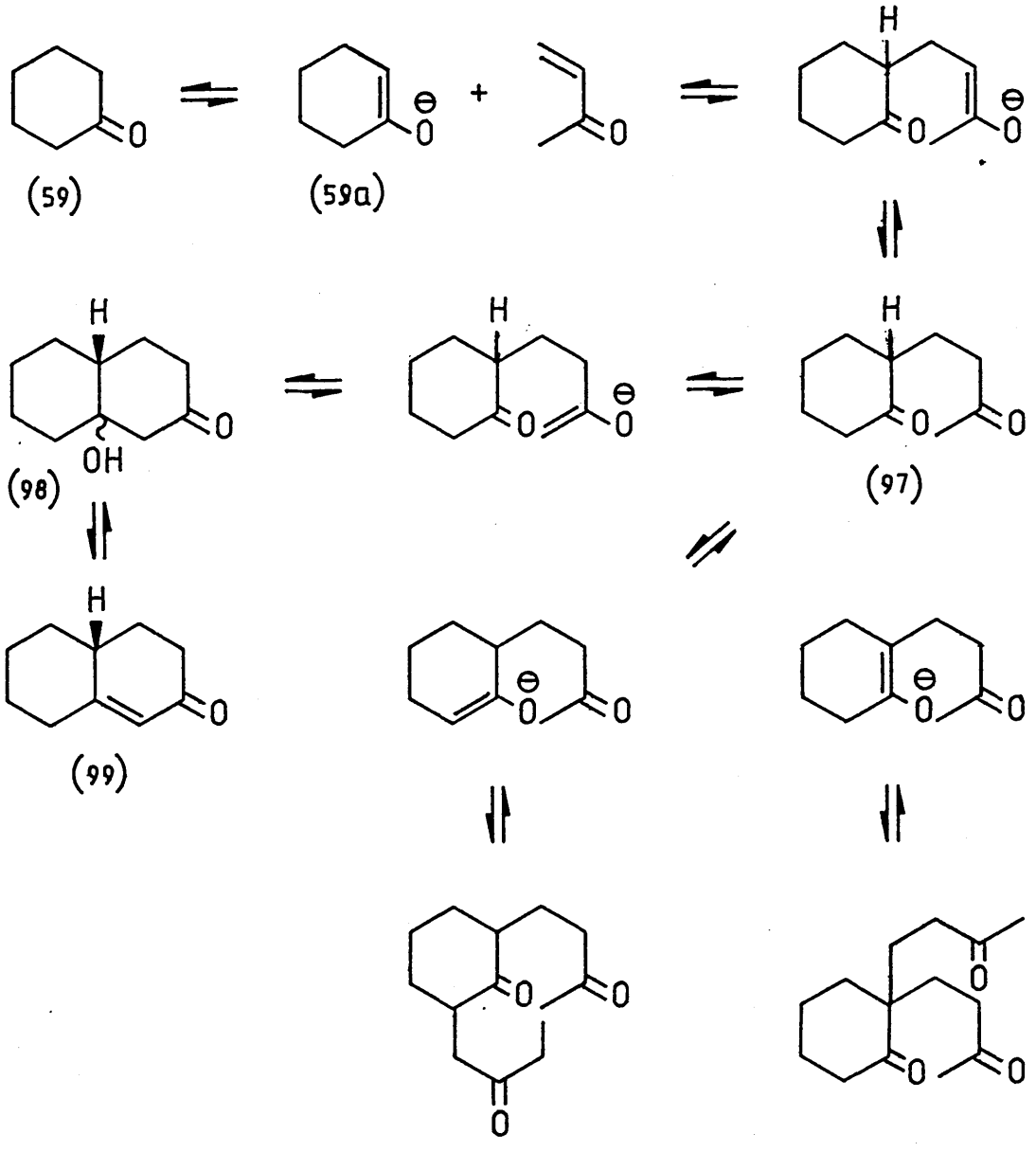
Having achieved the synthesis of the bicyclic compounds (73a) and (87a), the next consideration was regiospecific and stereospecific annulation to give the tricyclic compound (96).



The initial problem of regio-annulation was solved by utilising the regiochemically pure silyl enol ether (73a) and hydroxymethylene ketone (87a). However, stereochemical control, to give the configuration as indicated in (96), was more difficult to achieve.

4.1.1 The Robinson Annulation

The Robinson annulation has been used extensively in the synthesis of steroids to effect ring addition[21]. This annulation usually involves the Michael addition of an enolate anion (59a) to methyl vinyl ketone, followed by aldol-type ring closure to the hydroxy ketone (98) and dehydration to the product enone (99) [81,82], as follows:



Although in principle a simple reaction, various side reactions and problems arise due to the similarity in pKa of the protons α to the carbonyl group of the starting ketone (59), adduct ketone (97) and product ketone (99). This may result in proton transfer between ketones[81], which manifests itself as a loss of regiospecificity of starting ketone (if proton transfer is considerably faster than Michael addition), poly-alkylation of the cyclic ketone and polymerisation of methyl vinyl ketone.

There are two distinct ways in which these problems can be overcome:

(i) The use of various annulating reagents incorporating functional groups which avoid most of the difficulties mentioned above.

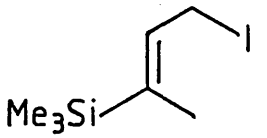
(ii) The use of activated ketones with pKa values considerably less than those of simple ketones (for example hydroxymethylene ketones).

Each of these strategies are discussed below.

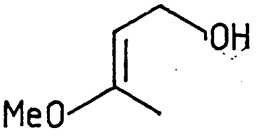
4.2 GENERAL SURVEY OF ANNULATING REAGENTS

Many annulating reagents have been developed which avoid the problems associated with methyl vinyl ketone[81,82], for example the trimethylsilyl iodides (100)[83], hemiacetal vinylogues (101)[84], γ-halotiglates

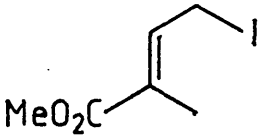
(102)[85] and trimethylsilyl vinyl ketones (103)[86].



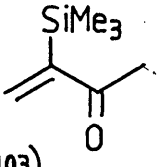
(100)



(101)

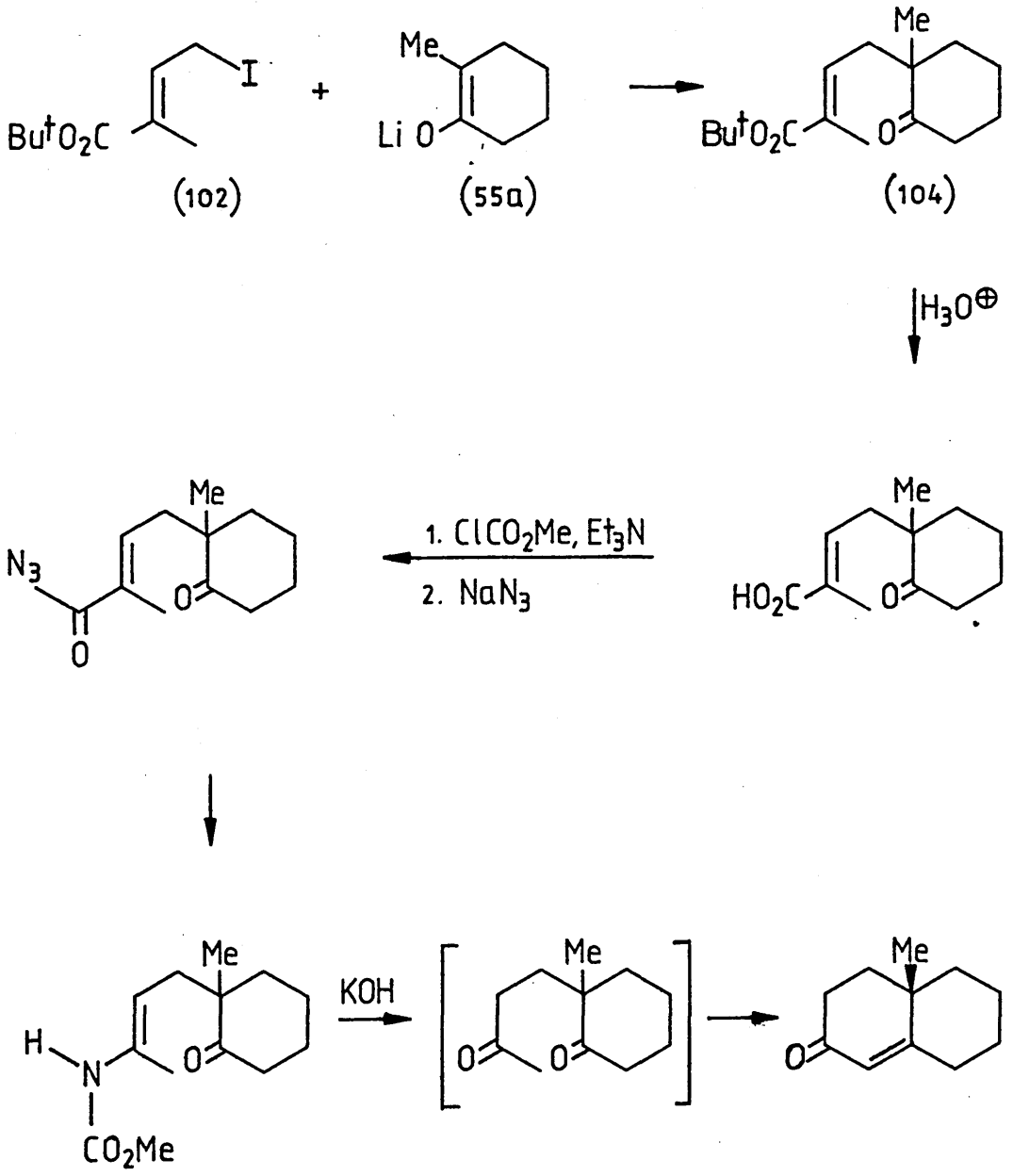


(102)



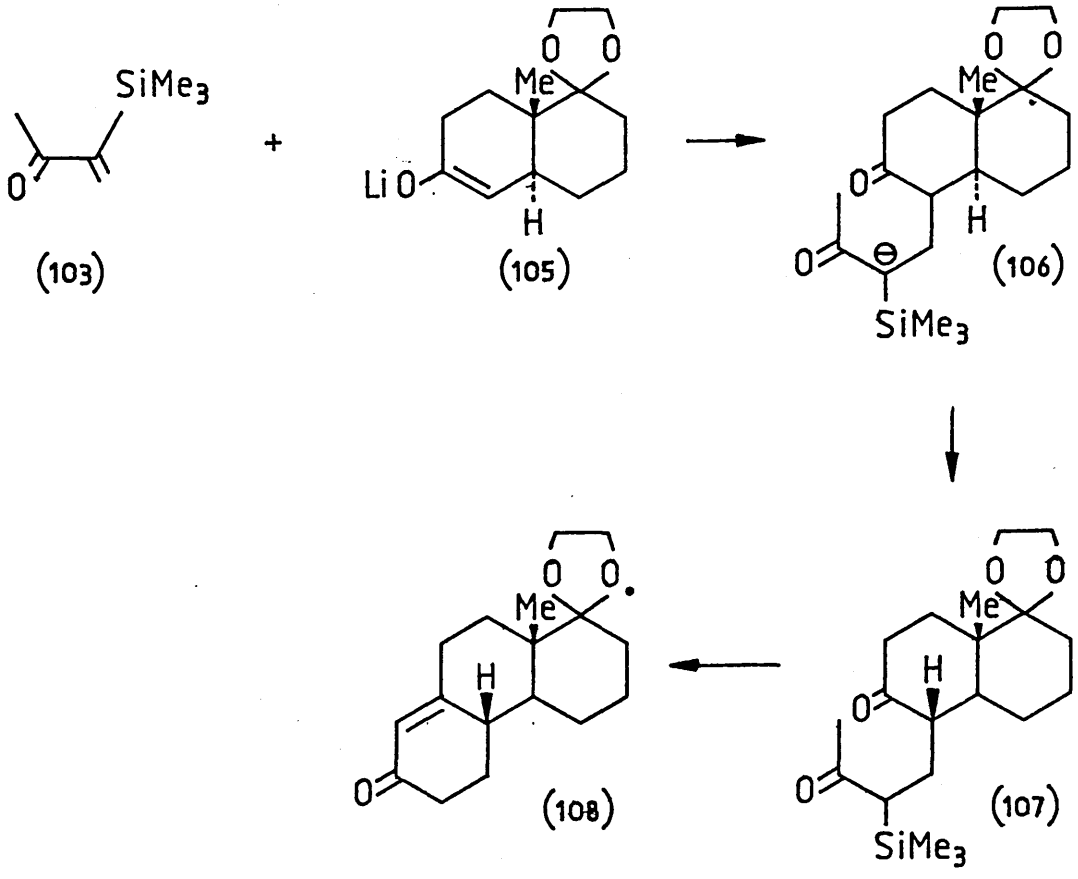
(103)

The first three reagents (100), (101) and (102) contain a latent carbonyl function which requires unmasking on completion of the initial alkylation reaction. Thus the γ-halotiglate (102) [85b] reacts readily with the lithium enolate (55a) of 2-methylcyclohexanone to give the adduct (104). The carbonyl function is unmasked under mild, non acidic conditions using the Weinstock-modified Curtius degradation reaction, as shown:



Although the γ-halotiglates offer the advantages of high reactivity with lithium enolates, which reduces the problems arising from proton transfer, the number of reactions required to unmask the carbonyl function is a major disadvantage.

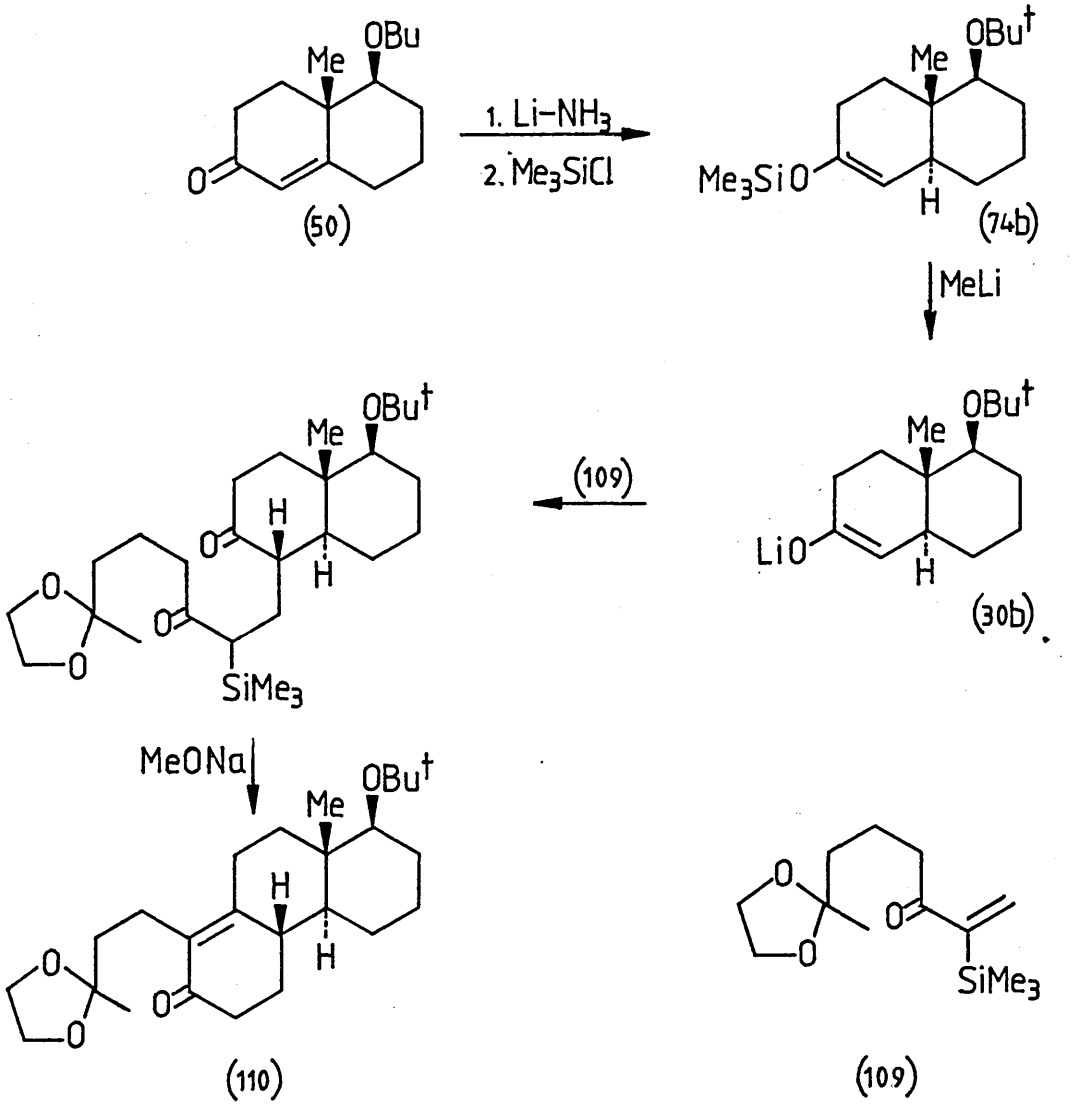
The trimethylsilyl vinyl ketones (103) were introduced by Stork and Ganem[86] as methyl vinyl ketone equivalent synthons. These annulating reagents have been used by Stork et al[57] and Boeckman[56,87] to effect ring addition to a number of enolates. Thus the regiounstable enolate (105) reacts with trimethylsilyl vinyl ketone to give the adduct (107), which is cyclised using 5% sodium methoxide in methanol as shown[57].



An advantage of the trimethylsilyl vinyl ketone reagents is that the trimethylsilyl moiety is cleaved under the cyclisation conditions, obviating the need

for additional reactions to remove the modifying group. Furthermore, the trimethylsilyl group helps to stabilise the initially formed carbanion adduct (106), the vacant 3d orbitals of silicon allowing back bonding from the filled 2p orbitals on the adjacent carbanion[88]. Thus loss of regiospecificity by acid (ketone)/base (enolate anion) reactions and further alkylation leading to polyalkylated material, are considerably reduced (see page 115).

Stork and Singh[57] have extended the synthetic utility of the trimethylsilyl vinyl ketones and developed the bis-annulating reagent (109). They report that annulation of the lithium enolate (30b) with this reagent gives the tricyclic compound (110) in 74% yield.

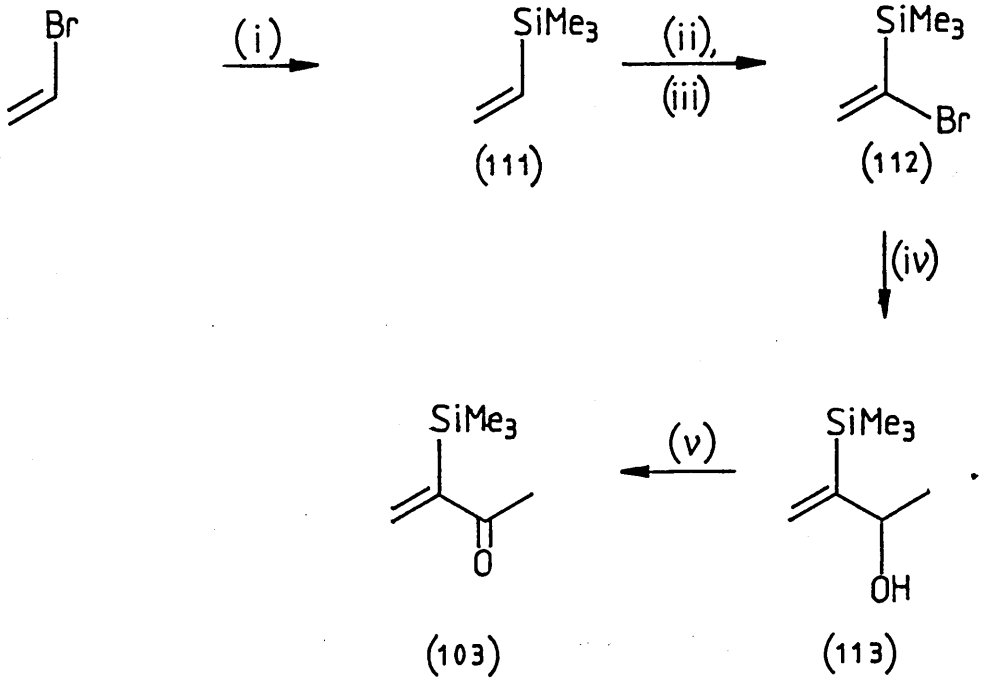


In view of the above, the α-trimethylsilyl vinyl ketone (103) was selected as the annulating reagent, and was prepared by the method of Boeckman et al[89].

4.2.1 Synthesis of 3-Trimethylsilyl-3-buten-2-one (103)

The synthesis of the annulating reagent was accomplished in four steps as follows:

Scheme 10



Conditions

(i) Mg/THF; Me_3SiCl;

(ii) Br_2;

(iii) Et_2NH, reflux;

(iv) Mg/THF; CH_3CHO;

(v) CrO_3, Acetone.

The initial step involved the reaction of vinyl magnesium bromide with trimethylsilyl chloride to give the vinyltrimethylsilane (111). This product was immiscible with water, and traces of tetrahydrofuran solvent and starting material were expected to be

removed by washing the distilled product with water. However, the boiling points of product (111), solvent (THF) and trimethylsilyl chloride were all close, and attempts to separate the product from the reaction mixture by fractional distillation, followed by washing the distillate with water, proved unsuccessful.

The distillate was found to be miscible with water due to the large amounts of solvent (THF) present. Replacement of THF by 1,2-dimethoxyethane gave the desired product, but only in poor yield. However, repetition of the reaction with tetrahydrofuran as solvent, and collecting the product from fractional distillation of the stirred reaction mixture, gave a distillate which was immiscible with water, and which afforded vinyltrimethylsilane (111) in good yield (73%).

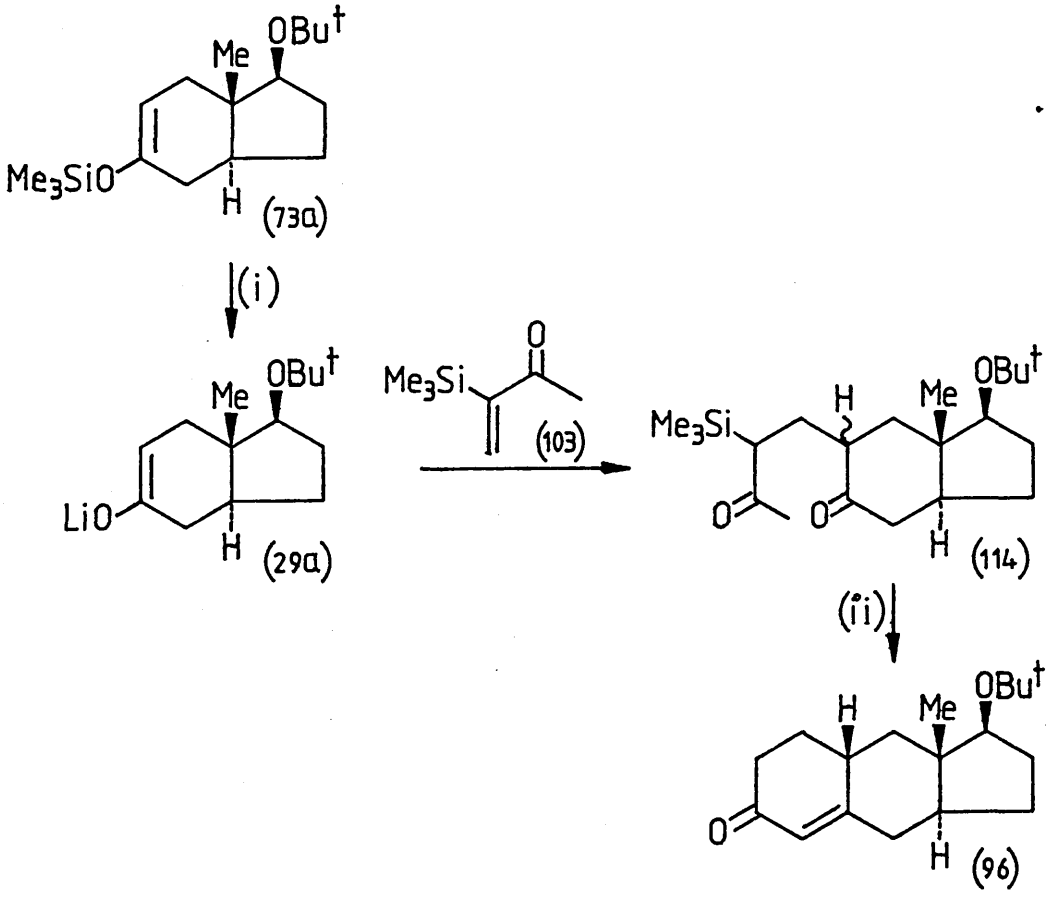
Addition of bromine to (111) followed by dehydrobromination with refluxing diethylamine gave the intermediate 1-bromo-1-trimethylsilylethene (112). This readily reacted via its Grignard reagent with acetaldehyde to form the alcohol (113), which was oxidised using Jones reagent to the product 3-trimethylsilyl-3-buten-2-one(103). After purification of the product by distillation, the pale yellow liquid was stored under nitrogen at $4^{o}C$, and found to be

unchanged (by ^1H n.m.r. spectrum) after several months.

4.3 ANNULATION OF THE TRIMETHYLSILYL ENOL ETHER (73a) USING 3-TRIMETHYLSILYL-3-BUTEN-2-ONE (103)

The proposed synthesis of the tricyclic enone (96) from the trimethysilyl enol ether (73a) was as follows:

Scheme 11



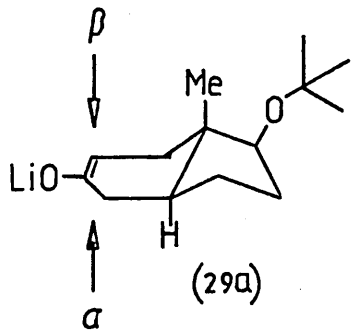
Conditions

(i) MeLi, Tetrahydrofuran;;

(ii) 5% NaOMe, methanol.

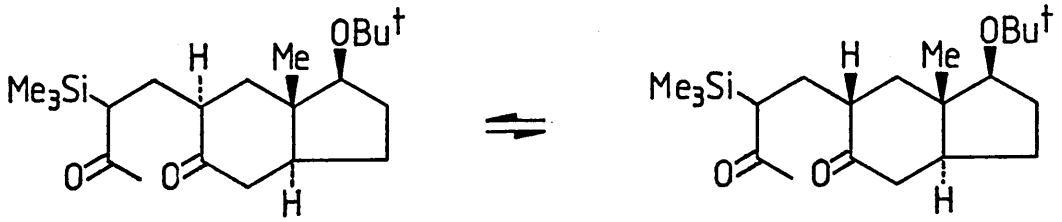
The regiochemistry of addition of annulating reagent (103) was expected to be controlled by generating, under non-equilibrating conditions[50,57], the lithium enolate (29a) from the trimethylsilyl enol ether (73a). However, the stereochemistry of addition, and subsequently the configuration of the new ring junction, was subject to less control.

Evidence in the literature[90] suggests that, in the absence of substantial steric hindrance to attack from one side of an enolate anion, alkylation proceeds to give approximately equal amounts of axial and equatorial alkylated product. Dreiding models of the enolate ion (29a) indicated that preferential attack via the α-face would probably occur, due to steric shielding of the β-face by the angular methyl group, and, to a lesser extent, by the t-butoxy group. By employing the bulky α-trimethylsilyl vinyl ketone annulating agent, it was anticipated that any selectivity for α-attack induced by this steric hindrance would be maximised.

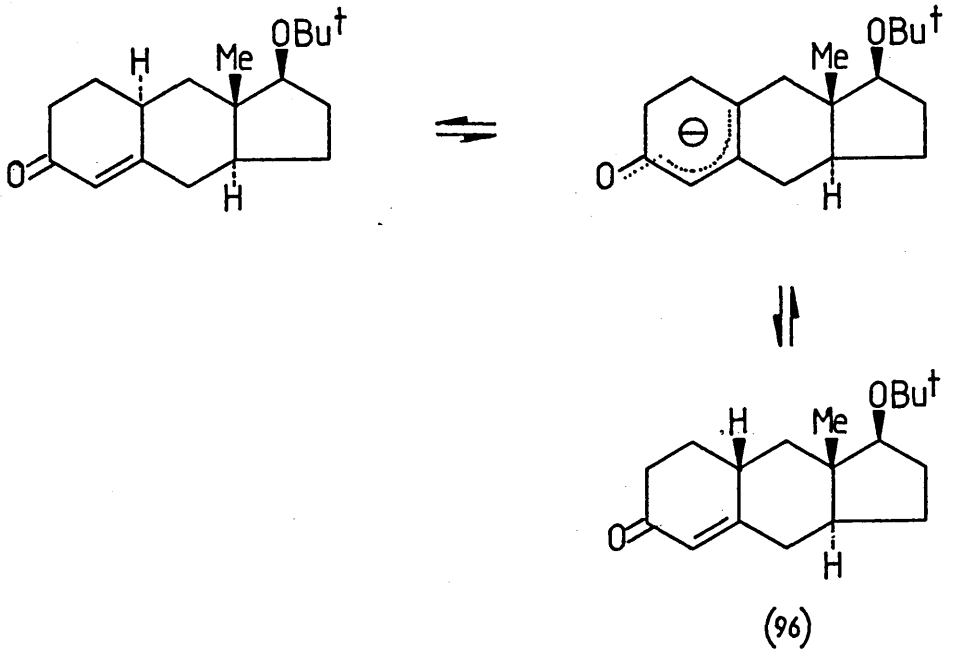


(29a)

However, if a mixture of stereoisomers was obtained, epimerisation was expected to occur under the basic cyclisation conditions to give the desired stereoisomer.



Even if aldol cyclisation occurred faster than epimerisation, there is evidence in the literature[87] that the product can be epimerised under the basic conditions employed, to give the required stereochemistry.



(96)

4.3.1. Synthesis of the tricyclic enone (96) from the trimethylsilyl enol ether (73a)

The synthesis of the tricyclic enone (96) was accomplished in two steps with an overall yield of 15% from the silyl enol ether (73a), as outlined in scheme 11.

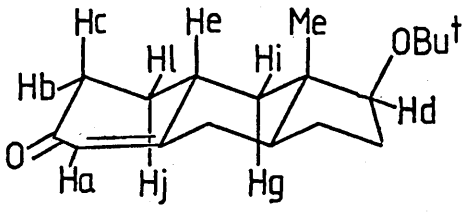
The first step involved treatment of the silyl enol ether (73a) with methyllithium under aprotic, non-equilibrating conditions. This generated the lithium enolate (29a), which reacted with a slight excess of the annulating reagent (103) to give a mixture of three products (using t.l.c.). Spectroscopic analysis was consistent with the presence of the expected product (114). The infrared spectrum showed the two carbonyl functions at 1710 and 1690cm^{-1}, whilst

a ^{1}H n.m.r. spectrum indicated the side chain methyl group at δ 2.10, the t-butyl group at δ 1.12, the angular methyl group at δ 0.70 and the trimethylsilyl group at δ 0.08. The mixture could not be separated by column chromatography, and was subsequently used without further purification.

The adduct (114) was cyclised with 5% sodium methoxcide in methanol to give the tricyclic enone (96) in only 16% yield after column chromatography. The spectroscopic properties were consistent with the enone structure (96). The infrared spectrum showed the enone system with bands at 1668 and 1610cm^{-1}, whilst the ^{1}H n.m.r. spectrum indicated the vinyl proton at δ 5.85, the t-butyl group at δ1.10 and the angular methyl group at δ 0.85. However, elucidation of the stereochemistry of the B/C ring junction required the use of ^{1}H n.m.r. spectroscopy with lanthanide shift reagents, as outlined below.

4.3.2 The use of ^{1}H n.m.r. Spectroscopy to elucidate the stereochemistry of the B/C ring junction of (96)

The stereochemistry of the He proton in the tricyclic enone (96) was determined from the following ^{1}H n.m.r. study using the lanthanide shift reagent $Eu(FOD)_3$. This work was conducted at Glaxo Group Research, Ware.



(96)

The 250 MHz ^1H n.m.r. spectrum of the enone (96) was not particularly informative, although the following assignments could be made:

1) The vinyl proton Ha as a singlet at δ 5.85.
2) The proton Hd as a triplet at δ 3.40.
3) The t-butyl group as a singlet at δ 1.10.
4) The angular methyl group as a singlet at δ 0.85.
5) The spectrum was complex from δ 2.6 to δ 1.0.

Expanding the scale to 10 Hz/cm resolved the downfield end of the complex part of the spectrum, and a very broad partially obscured singlet became apparent at δ 2.55. This was assigned as the angular proton He.

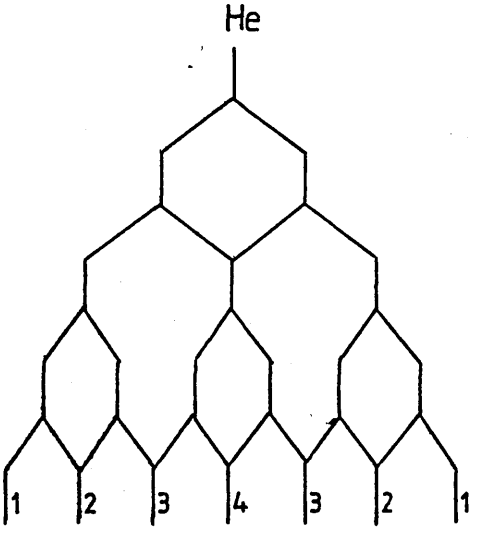
In order to resolve this proton further, $Eu(FOD)_3$ was added. Chelation of this reagent with the carbonyl

oxygen atom rather than the t-butyl ether oxygen atom occurred. This was indicated by the large shift downfield of the vinylic proton Ha, but the Hd proton, and the nuclei of the t-butyl and angular methyl groups, remained relatively static. The spectrum was re-assigned as follows:

1) The vinyl proton Ha as a broad singlet at δ 7.55.
2) The methylene protons Hb and Hc, as a double doublet at δ 4.4 to 4.0.
3) The Hd proton as a triplet at δ 3.55.
4) The angular proton He as a broad singlet at δ 2.8.
5) The Hj proton as a quadruplet at δ 2.25.
6) The t-butyl group as a singlet at δ 1.2.
7) The angular methyl group as a singlet at δ 0.95.

Irradiation of the vinylic proton at 4736.4Hz caused resolution of the broad singlet at δ 2.8 to a definite overlapped septet. This splitting pattern may be rationalised as the coupling of the axial proton, He, to two adjacent trans diaxial protons Hj and Hg, with a coupling constant of 11Hz, and to two adjacent equatorial protons, Hi and Hl, with a weaker coupling constant of 5Hz.

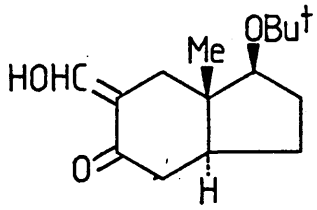
This is illustrated diagrammatically:



The splitting pattern observed is that illustrated, with seven peaks equally spaced with intensities of 1234321. The converse stereochemistry, where He is α, would be expected to give a different splitting pattern. Thus the stereochemistry of the B/C ring junction is as indicated (96).

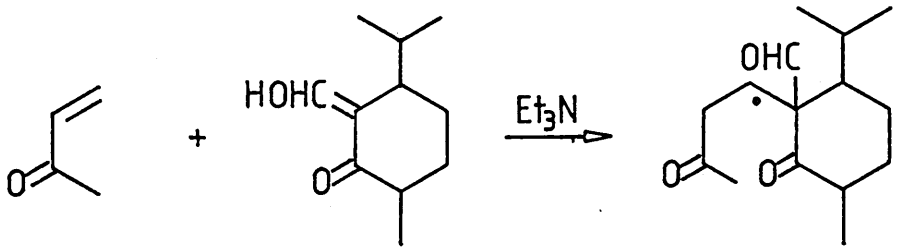
4.4 ANNULATION OF α-HYDROXYMETHYLENE KETONES USING METHYL VINYL KETONE

It was anticipated that due to the mild conditions required to effect regiospecific enolisation of the activated α-hydroxymethylene ketone (87a), methyl vinyl ketone could be used as the annulating reagent.



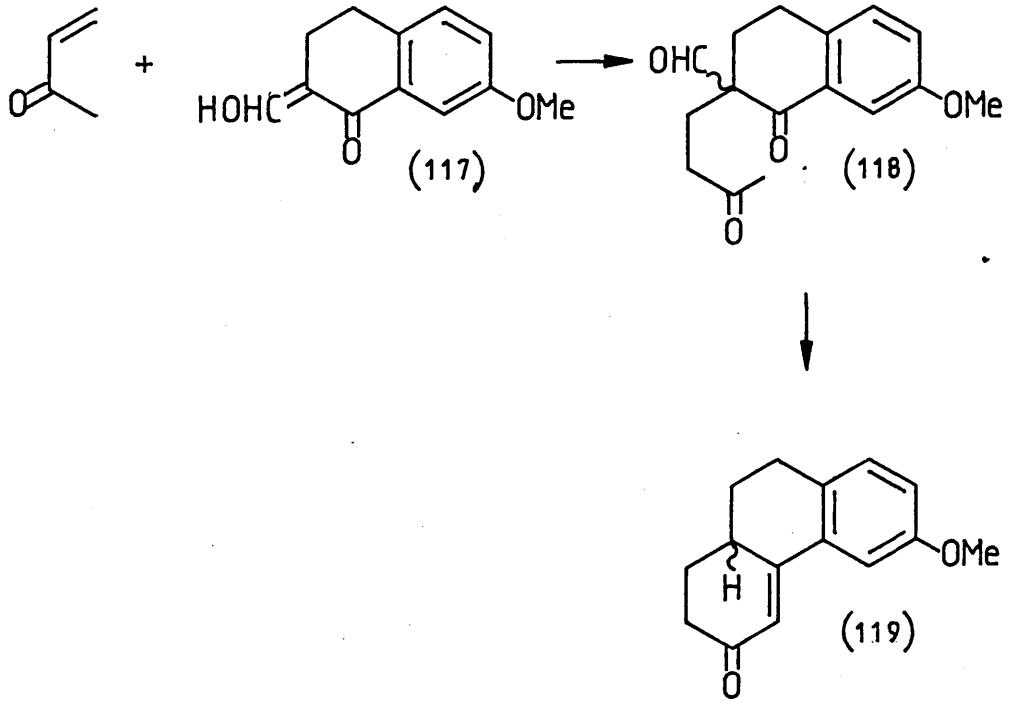
(87a)

Indeed, addition of activated α-hydroxymethylene ketones to methyl vinyl ketone have been reported to proceed in good yield[71,91,92], without significant interference from polyalkylation or polymerisation of annulating reagent. For example, Corey and Nozoe report[91] that the α-hydroxymethylene carvomenthone (115) reacts with methyl vinyl ketone in the presence of triethylamine, to give the adduct (116) in 71% yield after three days at ambient temperature.



(115) (116)

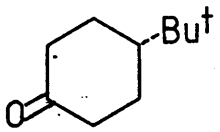
Turner et al[71] report a similar high yield for the addition of the α-hydroxymethylene ketone (117) to methyl vinyl ketone, in the presence of triethylamine after three days at ambient temperature.



The adduct (118) was cyclised and the formyl group removed by treatment with potassium hydroxide (2%) in aqueous methanol at reflux. Although the regiochemistry of annulation is dictated by the regiochemistry of the α-hydroxymethylene ketone, the stereochemistry of the ring junction is subject to less control, as discussed later.

4.4.1 Synthesis of Bicyclic Model Compounds

In order to conserve the precious hydrindan intermediate (29), the model system 4-t-butylcyclohexanone (120) was used to optimise the annulation conditions.

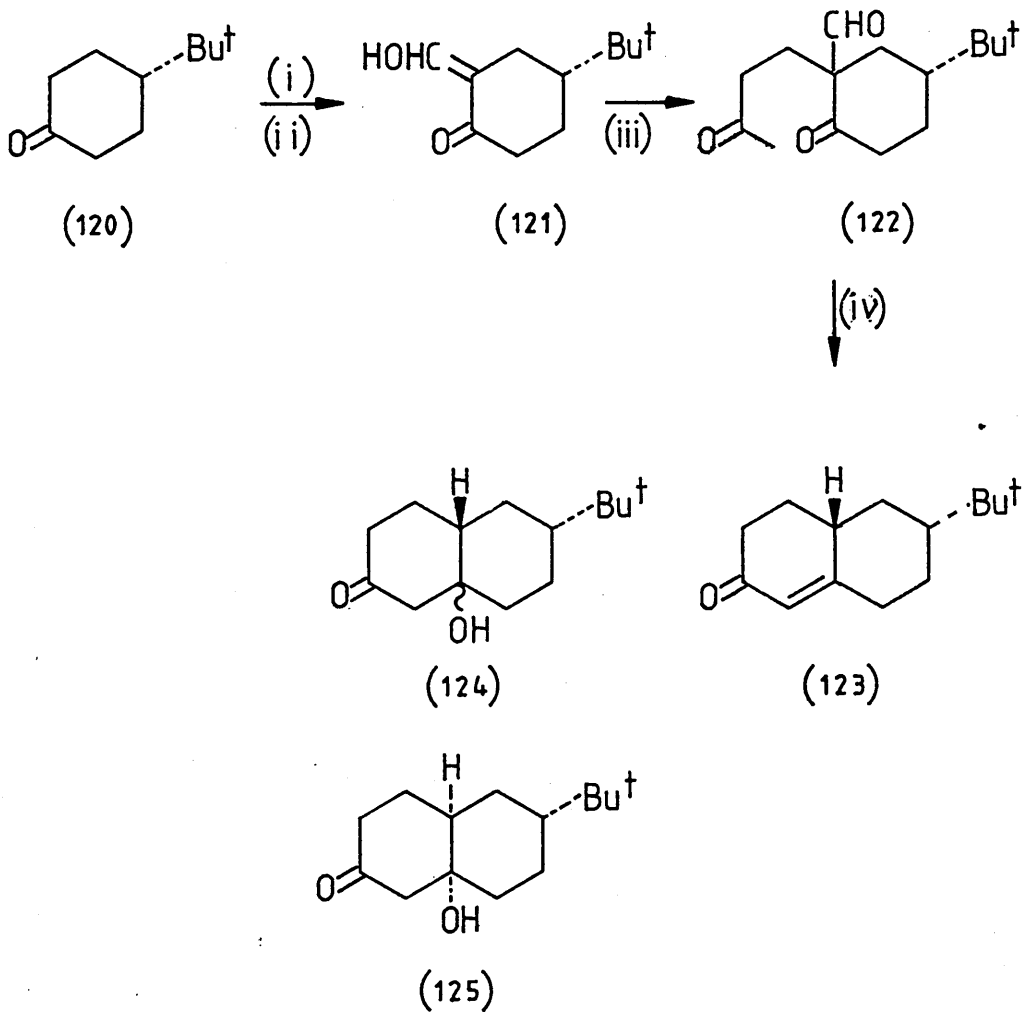


(120)

This compound was chosen as the stereochemistry of the annulation reaction was of interest. The bulky t-butyl substituent is known to impart conformational preference to the cyclohexane ring[90,93,94], thereby allowing examination of the stereochemical outcome of the annulation reaction.

The bicyclic enone (123) was obtained from the 4-t-butylcyclohexanone (120) in 3 steps, as outlined:

Scheme 12



Conditions

(i) NaOMe, HCO_2Et; benzene.

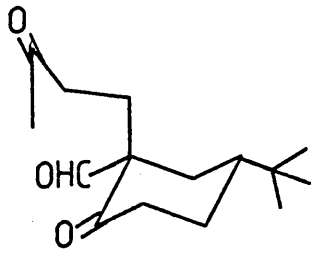
(ii) H_3O^+.

(iii) $H_2C{=}CHCOCH_3$, Et_3N.

(iv) KOH (1% W/W); water and methanol (1:1 v/v).

The formylation of the 4-t-butylcyclohexanone occurred readily in excellent yield (96%) to give the α-hydroxymethylene ketone (121).

Initial attempts to form the adduct (122), from the addition of the activated ketone (121) to methyl vinyl ketone using potassium hydroxide in methanol as catalyst[95], failed. A solid product was obtained whose infrared spectrum exhibited a hydroxyl group at 3400cm^{-1}, but indicated no carbonyl groups. However, using triethylamine as catalyst gave the product (115) in 65% yield as a yellow oil after three hours at room temperature. Infrared and ^{1}H n.m.r. spectra were consistent with the product. The stereochemistry was assumed to be as indicated. Axial alkylation would be expected in the absence of sterically hindering groups, and the presence of the formyl group at the α-position of alkylation[90,94].



(122)

The formyl proton exhibited two singlet peaks in the ^1H n.m.r. spectrum at δ 9.70 and δ 9.45, in a ratio of approximately 7:1. These resonances probably correspond to the two stereoisomers possible from addition, with the δ 9.70 resonance corresponding to the equatorial and δ 9.45 to the axial formyl groups.

Reaction conditions had to be selected which removed the formyl group before cyclisation to give the bicyclic enone (123) with the indicated stereochemistry. Pilot studies were conducted on the cyclisation of the adduct (122), using variable concentrations of potassium hydroxide (0.25, 0.5, 1 and 2% w/w) over different reaction times (5 hours and 18 hours), in a mixture of methanol and water (1:1, v/v), and assaying the product mixture by t.l.c. This study suggested that the mildest conditions consistent with product formation were those using potassium hydroxide (1% w/w) at ambient temperature over 5 hours. Lower concentrations of base (0.25% w/w) failed to effect any detectable cyclisation.

The adduct (122) (scheme 12) was subsequently cyclised to give the bicyclic enone (123) as a yellow oil in 43% yield. The spectral properties were consistent with this product, with the enone system exhibiting characteristic infrared peaks at 1670 and 1620cm^{-1}, and

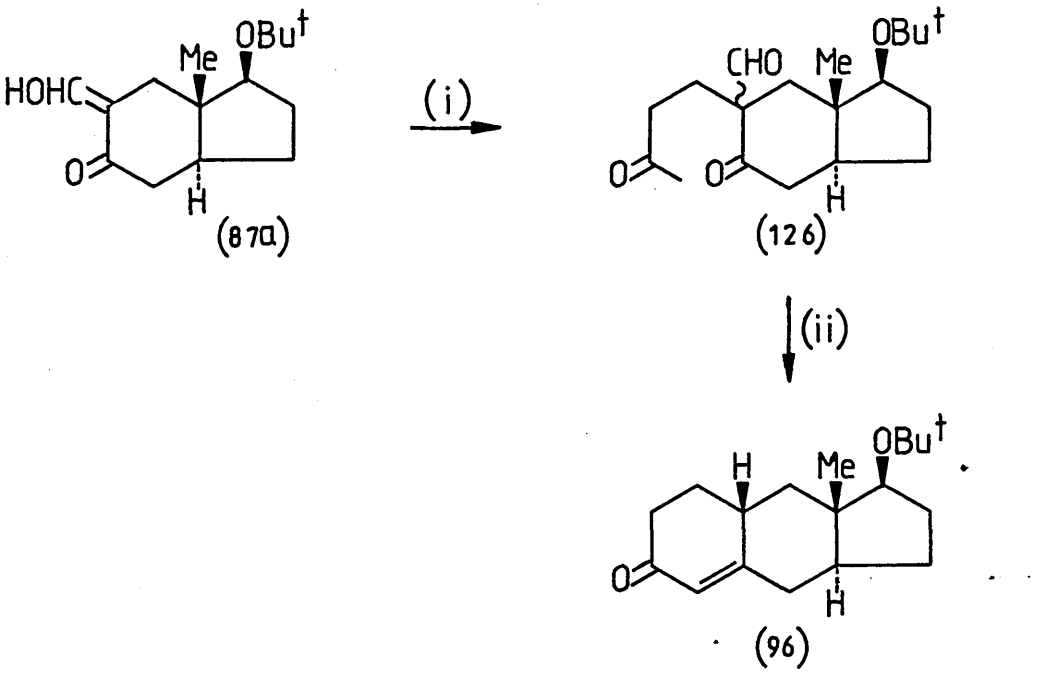
^{1}H n.m.r. indicating the presence of a vinylic proton at δ 5.80. However, the stereochemistry of the ring junction was not determined. This was assumed to be as indicated, which is the expected product if formyl cleavage occurs prior to cyclisation, or epimerisation of the angular proton of the enone (123) takes place under the basic reaction conditions (see page 126).

Two other products were obtained (124) and (125) in a total yield of 14%. These were expected to be hydroxy ketone intermediates from their spectra. Their stereochemistry was assumed to be as indicated.

4.4.2 Synthesis of the tricyclic enone (96) from the α-hydroxy methylene ketone (87a)

The synthesis of the tricyclic enone (96) was accomplished in 2 steps, with an overall yield of 50%, from the α-hydroxymethylene ketone (87a) as shown.

Scheme 13



Conditions

(i) $H_2C{=}CHCOCH_3$; Et_3N.

(ii) KOH (1% w/w); water, methanol (1:1 v/v).

The α-hydroxymethylene ketone (87a) reacted with methyl vinyl ketone to give the adduct (126) as a foam in good yield (78%). As with the model system (scheme 12), the stereochemistry of addition was uncertain, and probably unimportant at this stage. However, the

^1H n.m.r. of the adduct (126) indicated one stereoisomer, as only one resonance was observed at δ 9.45 due to the aldehyde proton.

The cyclisation of (126) gave the enone (96) in good yield (65%), with the stereochemistry as indicated. This was proven by showing the product to be identical (by mixed m.p., i.r. and ^1H n.m.r. spectroscopy), with that obtained via the trimethylsilyl enol ether (73a) (scheme 11).

Comparison of the two routes (schemes 11 and 13) for the synthesis of the tricyclic enone (96) showed that the annulation sequence using the activating hydroxymethylene group (scheme 13) offered the highest overall yield.

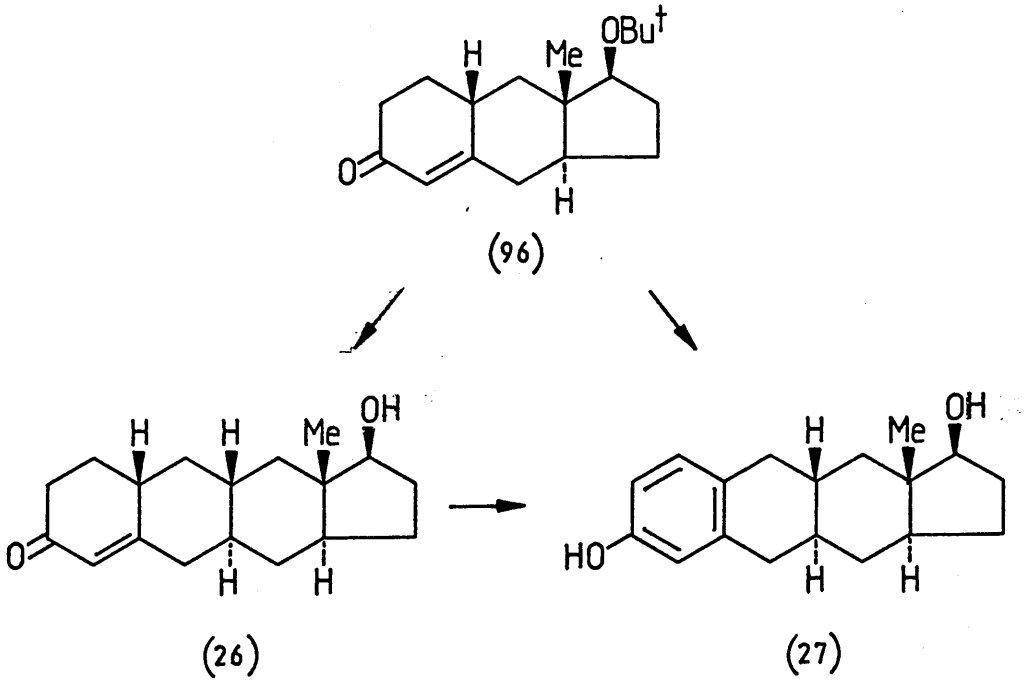
CHAPTER FIVE

SYNTHESIS OF LINEAR ANTHRASTEROID ANALOGUES OF 19-NORTESTOSTERONE AND ESTRADIOL

5.1 INTRODUCTION

The synthesis of the key tricyclic enone (96) had been accomplished in an overall yield, from 2-methyl-1,3-cyclopentanedione (32), of 14.7% over ten steps.

Completion of the synthesis to give the linear anthrasteroid analogue of 19-nortestosterone (26) required annulation of the tricyclic enone (96), and the removal of the t-butyl protecting group to reveal the alcohol group. It was envisaged that the addition of the fourth ring would be accomplished by application of the 'formyl annulation' sequence (cf. scheme 13)



Various strategies were considered for the synthesis of the linear anthrasteroid analogue of estradiol (27). These included annulation of the tricyclic enone (96) with appropriate functional groups to facilitate aromatization of the fourth ring, or aromatization of ring A of the linear tetracyclic enone (26). These strategies will be discussed in section 5.3.

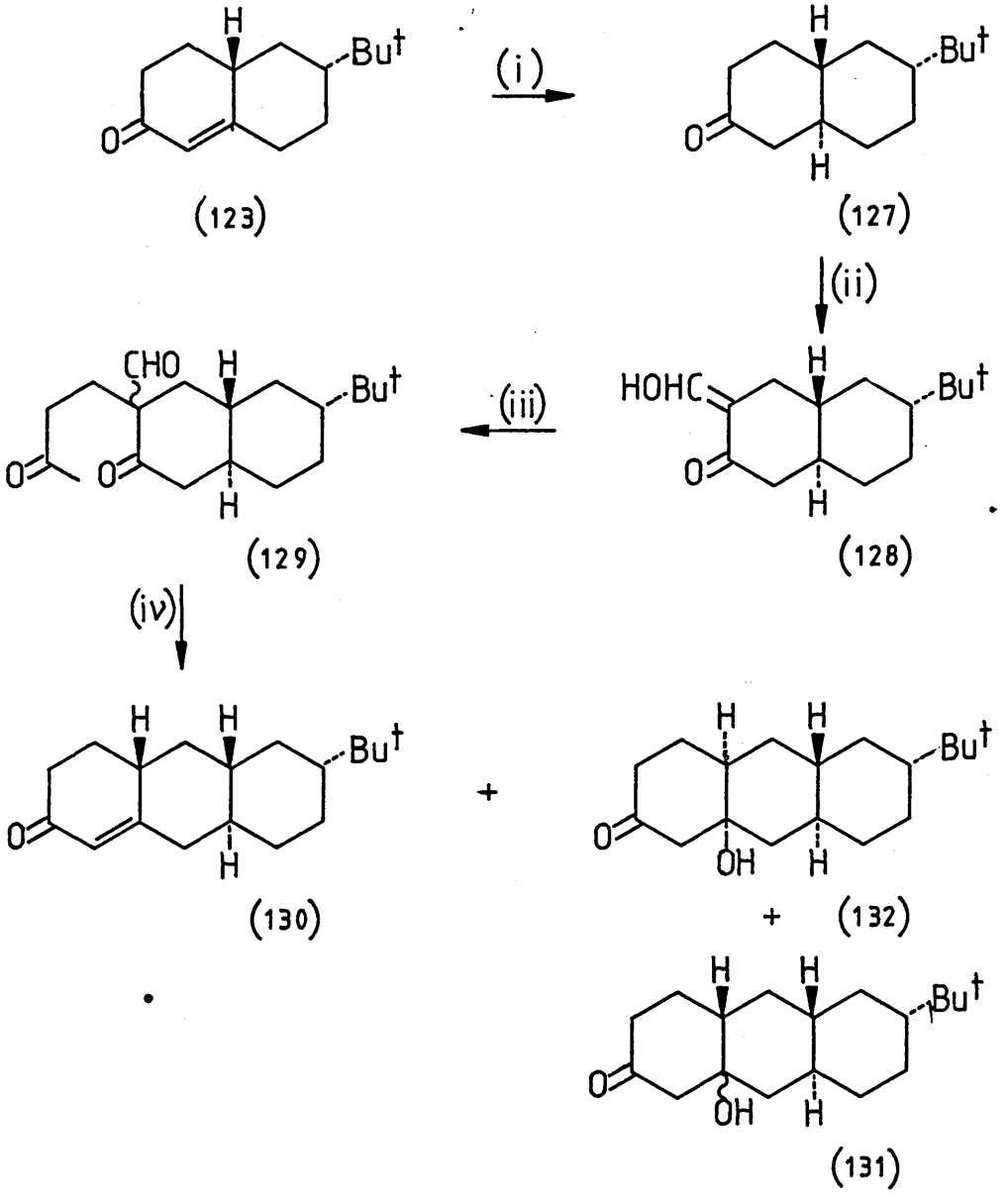
5.2 LINEAR ANTHRASTEROID ANALOGUES OF 19-NORTESTOSTERONE

At this stage, conservation of the limited stock of tricyclic enone (96) was important, so the model bicyclic enone (123) was employed to assess the annulation sequence.

5.2.1 Synthesis of tricyclic model compounds

Annulation of the bicyclic model compound (123) was effected with methyl vinyl ketone to give the tricyclic enone (130) as follows:

Scheme 14



Conditions

(i) Li/NH_3

(ii) NaOMe, HCO_2Et, benzene

(iii) $H_2C=CHCOCH_3$, Et_3N

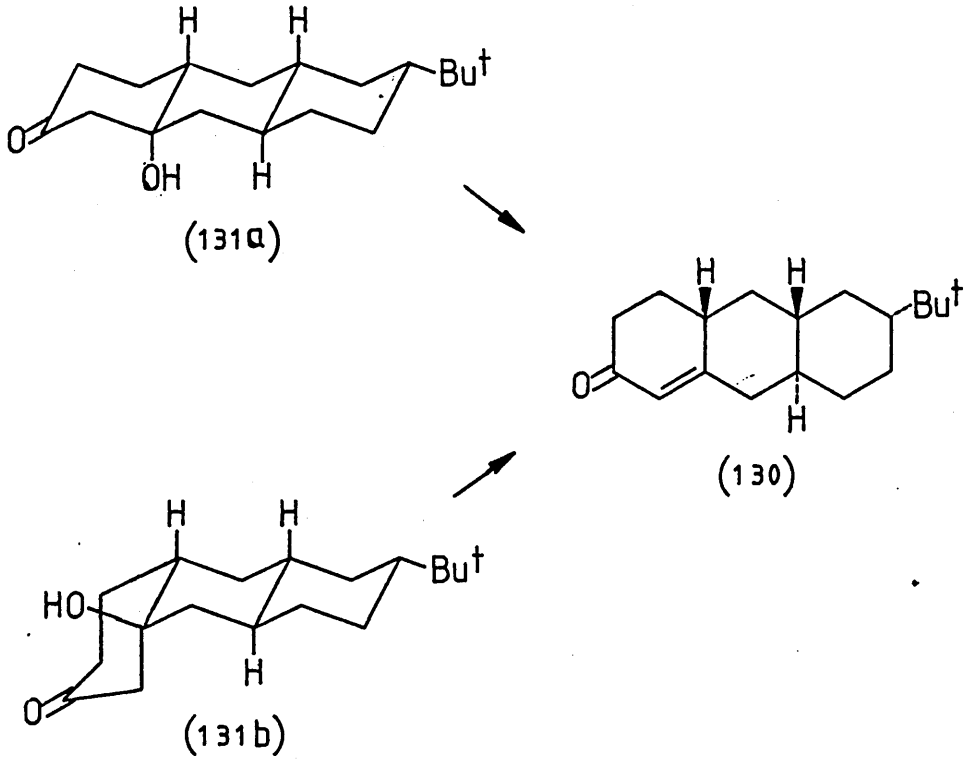
(iv) KOH (1% W/W), water, methanol (1:1 v/v)

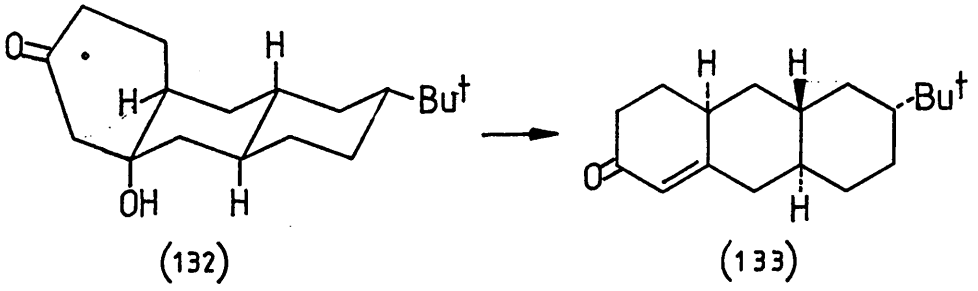
The bicyclic enone (123) was reduced to the trans bicyclic ketone (127) in high yield using lithium in liquid ammonia. The stereochemistry was assumed (see page 67). Formylation to the hydroxymethylene ketone (128) again occurred in good yield (88%). The regiochemistry of addition was assumed to be as indicated, in view of the overwhelming supporting evidence in the literature (see section 3.3.1). Addition of the α-hydroxymethylene ketone (128) to methyl vinyl ketone was accomplished in 83% yield to give a yellow oil. The ^{1}H n.m.r. spectrum of the product (129) indicated two peaks at δ 9.67 and 9.45, in a 7:1 ratio, which were assigned as the the aldehyde proton of the two stereoisomers of (129).

Cyclisation of the adduct (129) employing the conditions as previously established, surprisingly gave a very poor yield (17%) of the tricyclic enone (130). Further chromatography of the reaction mixture led to the isolation of two other products in substantial amounts, which were identified as hydroxy ketone intermediates (131) (m.p.201-202^{o}C) and (132) (m.p.291.5-293.5^{o}C). Significantly two hydroxy ketones were also isolated in small amounts from cyclisation of the model Michael adduct (122) to the bicyclic enone (123) (see scheme 12).

The stereochemistry of both the hydroxy ketones (131) and (132) was uncertain. However, dehydration of (131) readily occurred in refluxing benzene in the presence of para-toluenesulphonic acid to give the tricyclic enone (130) (by i.r.,t.l.c.,mixed m.p.) in 64% yield. This provided an overall yield of 34% for the cyclisation of the adduct (129) to the tricyclic enone (130). Dehydration of the hydroxy ketone (132) gave an enone which was not identical to the tricyclic enone (130) by t.l.c.

This may be explained by considering the reaction of the α-hydroxymethylene ketone (128) with methyl vinyl ketone. The Michael adduct formed by equatorial addition of the annulating reagent could cyclise to give the hydroxy ketones (131a) and (131b), as indicated below. Both of these hydroxy ketones would be expected to undergo dehydration to the tricyclic enone (130). However, the Michael adduct formed by axial addition of methyl vinyl ketone to the α-hydroxymethylene ketone (128) could cyclise to give the hydroxy ketone (132) only. Dehydration of this hydroxy ketone would be expected to give the stereoisomeric enone (133).





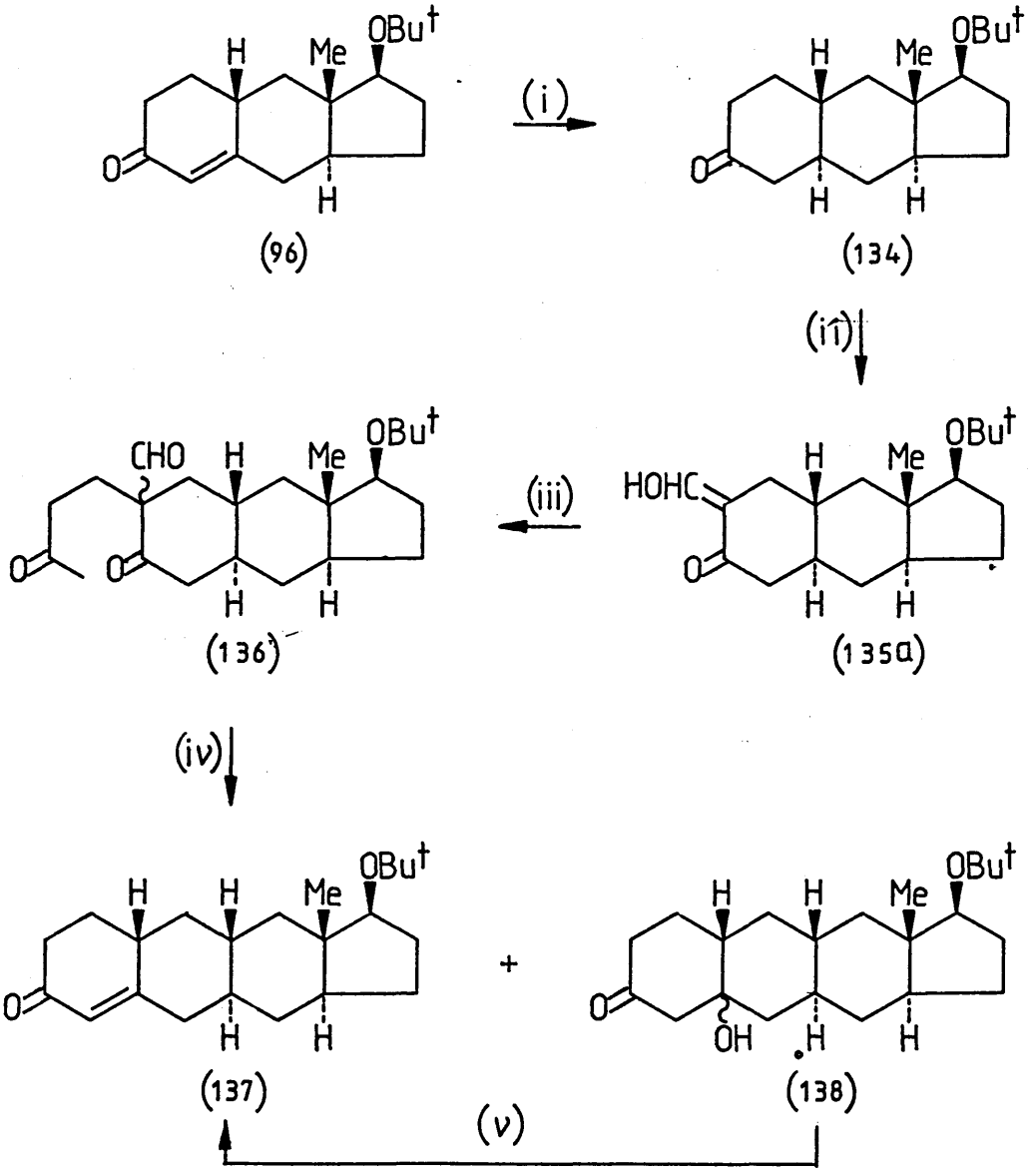
The occurrence of similar β-hydroxy ketone intermediates from the cyclisation of Michael adducts have been reported in the literature[84,96]. These intermediates have been dehydrated to the corresponding

enones either by treatment of the hydroxy ketone with potassium hydroxide (8%) in ethanol at 20°C,[96] or by heating under reflux with an aqueous solution of hydrochloric acid (3 M)[84].

5.2.2 Synthesis of linear anthrasteroid analogues of 19-nortestosterone

The series of reactions described previously (scheme 14) were used for the synthesis of the linear anthrasteroid analogue of 19-nortestosterone (26) as outlined (scheme 15).

Scheme 15



Conditions

(i) Li/NH_3

(ii) HCO_2Et; NaOMe; benzene

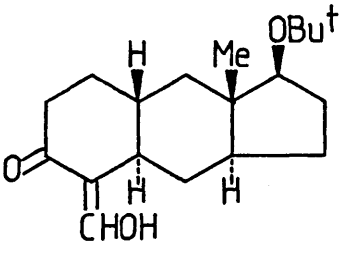
(iii) $H_2C=CHCOCH_3$, Et_3N

(iv) KOH (1% w/w), water, methanol (1:1 v/v)

(v) pTsOH; benzene, reflux

The tricyclic enone (96) was reduced using lithium in liquid ammonia to give the saturated ketone (134) in 60% yield. The stereochemistry of the reduction was assumed to give the trans fused ring junction (see page 67). Formylation of the tricyclic ketone (134) gave the α-hydroxymethylene ketone (135a) in 93% yield. The regiochemistry of this reaction was assumed to be as indicated, in view of the supporting body of evidence in the literature (see section 3.3.1). The ^1H n.m.r. of the product (135a) indicated peaks at δ 14.3 and 8.55, corresponding to the vinylic and hydroxyl protons of the hydroxymethylene moeity.

In contrast to the bicyclic hydroxymethylene ketone (87) (scheme 7) analogue, other signals indicating the presence of the regioisomeric tricyclic hydroxymethylene ketone (135b) were absent.



(135b)

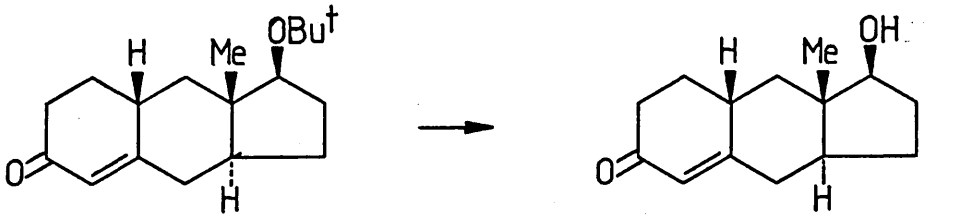
Michael addition of the tricyclic hydroxymethylene ketone (135a) to methyl vinyl ketone gave the adduct (136) in 79% yield.

Cyclisation of the Michael adduct (136) to the enone (137) was achieved, but in only 20% yield. Further chromatography of the reaction mixture led to the isolation of a hydroxy ketone (138), which was obtained in 39% yield, as a solid (m.p. 214-216^{o}C). This hydroxy ketone was dehydrated by heating under reflux with p-toluenesulphonic acid in benzene to give the tetracyclic enone (137) (by i.r.,mixed m.p.,^{1}H n.m.r.). This provided an overall yield for the cyclisation of (136) to the tetracyclic enone (137) of 43%.

The cyclisation of the Michael adduct (136) closely resembles the cyclisation of the adduct (129) in the model system (scheme 14). However, only one β-hydroxy ketone intermediate (138) was recovered in a significant amount from the cyclisation of the Michael adduct (136).

The final step in the synthesis of the target compound (26), involving removal of the t-butyl group to reveal the alcohol group, proved problematic. Initial attempts to cleave the t-butyl ether by heating with dilute hydrochloric acid[15] gave a poor yield (47%) of

product (26). This prompted the use of the tricyclic butyl ether (96) as a model system, to assess the three different sets of reaction conditions considered to effect cleavage of the t-butyl ether group.

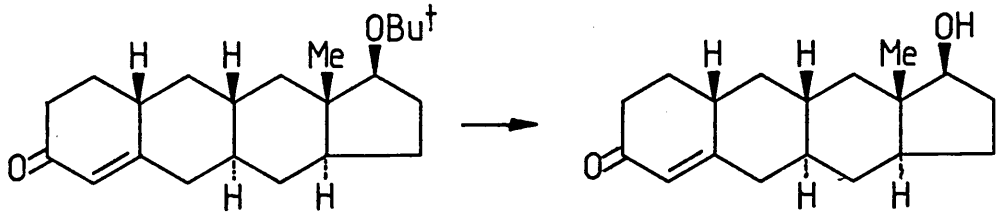


(96) (139)

Hydrolysis of the t-butyl ether group of (96) with aqueous alcoholic hydrochloric acid[15] at 80°C gave the alcohol (139) in only 48% yield. A better yield (56%) was achieved when the t-butyl ether (96) was treated with the chlorotrimethylsilane/sodium iodide reagent[97,98] at room temperature. However, the best yield (74%) of (139) was obtained by stirring the t-butyl ether (96) in trifluoroacetic acid overnight at ambient temperature, followed by alkaline hydrolysis[99].

Hydrolysis of the t-butyl ether of the tetracyclic compound (137) was similarly accomplished using trifluoroacetic acid to give the tetracyclic

alcohol(26) in good (73%) yield.

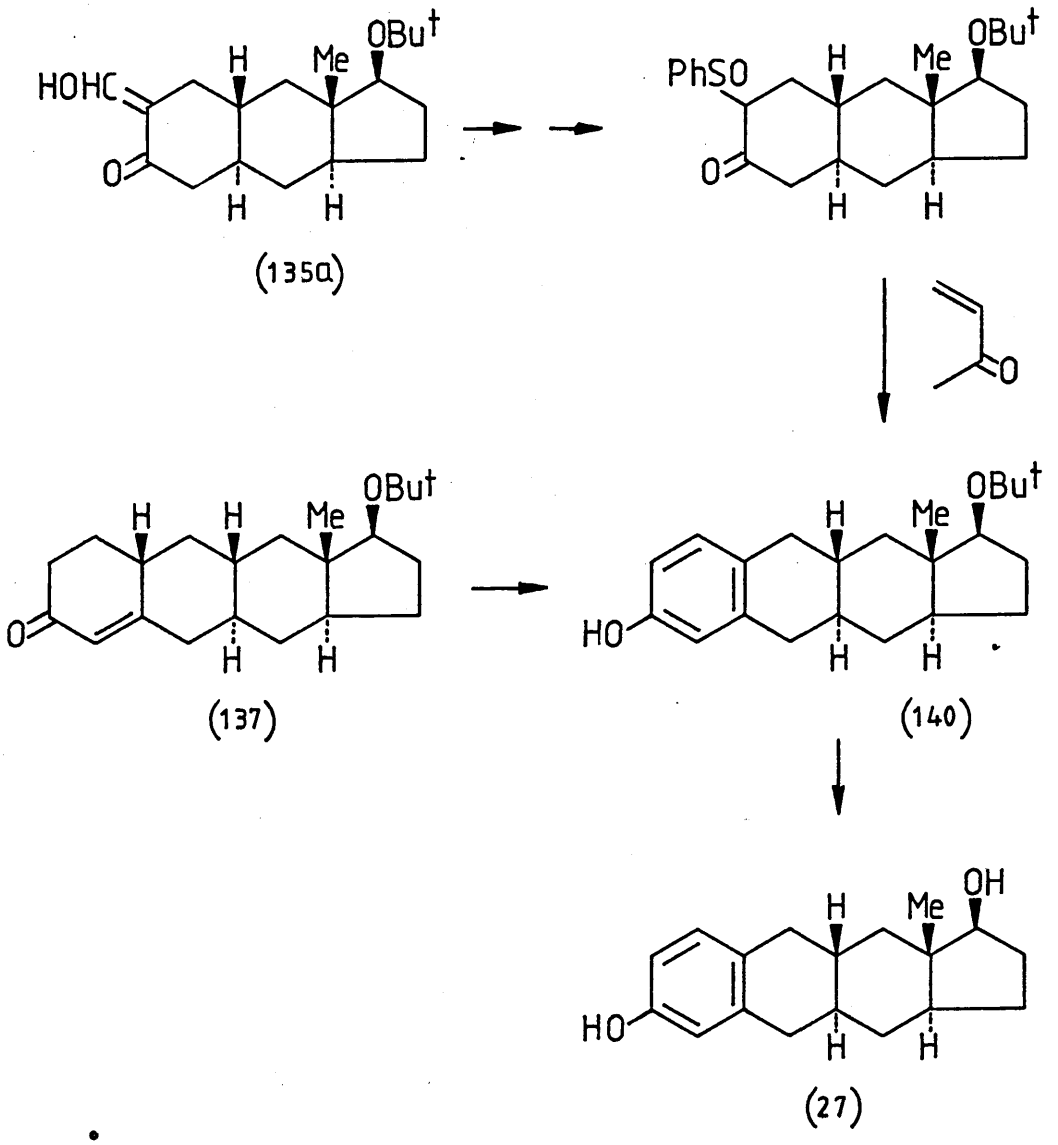


(137) (26)

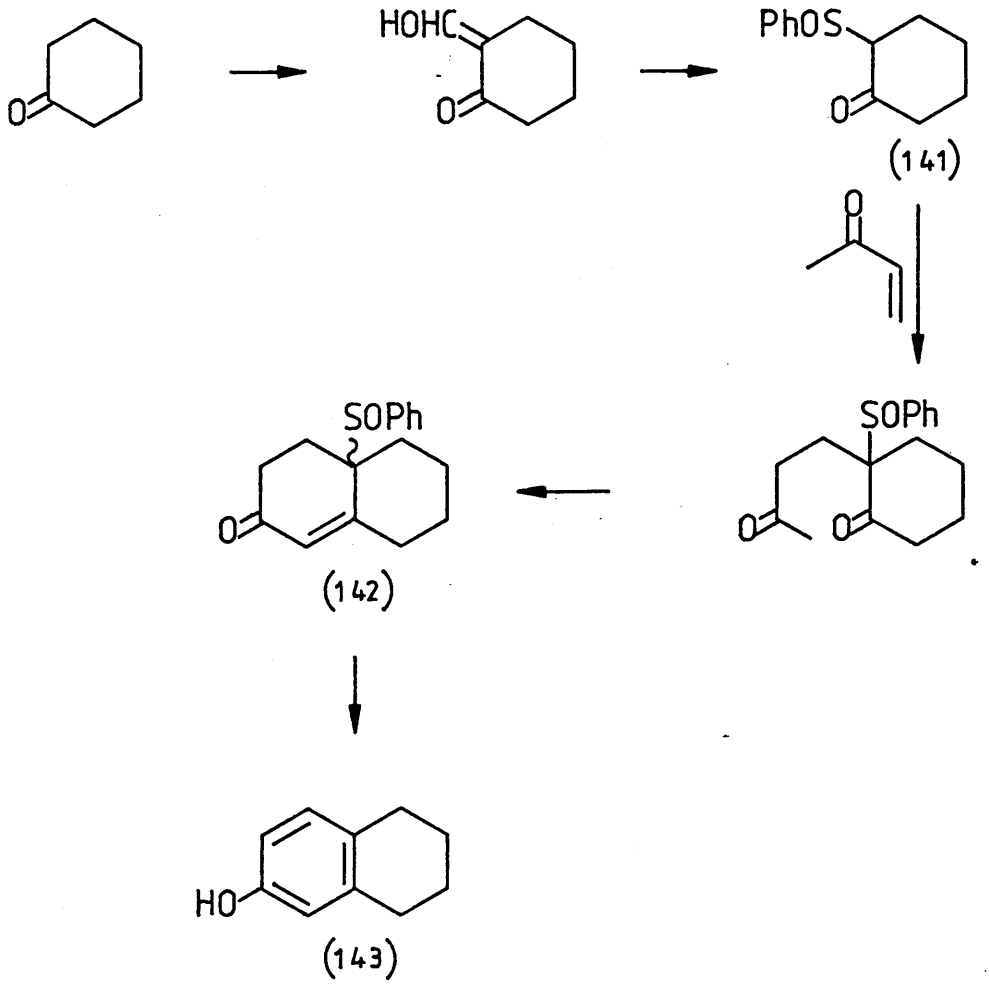
Thus the target linear anthrasteroid analogue (26) of 19-nortestosterone has been synthesised in 15 steps in an overall yield of 2% from 2-methyl-1,3-cyclopentanedione (32).

5.3 LINEAR ANTHRASTEROID ANALOGUES OF ESTRADIOL

Two main strategies were considered for the synthesis of the linear anthrasteroid analogue (27) of estradiol. These were the aromatization of ring A in the tetracyclic enone (137), or phenol annulation of the tricyclic compound (135a) as described below.



The phenol annulation of β-keto sulphoxides has been reported in the literature[100]. Thus 2-(phenylsulphinyl) cyclohexanone (141) reacts with methyl vinyl ketone in methanol at 0-25^{o}C in the presence of sodium methoxide to form the expected bicyclic enone (142), which then eliminates phenylsulphenic acid to give the annulated phenol (143).

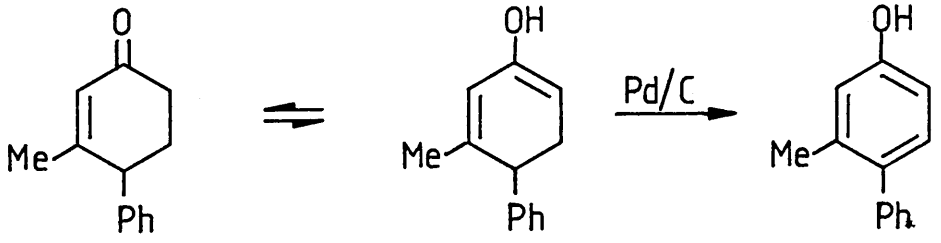


The addition of the phenyl sulphoxide group (141) may be accomplished by reaction of phenyl thiosulphonate with α-hydroxymethylene ketones under basic conditions, followed by facile peroxide oxidation of the sulphur group[101].

Although this is an elegant method for the introduction

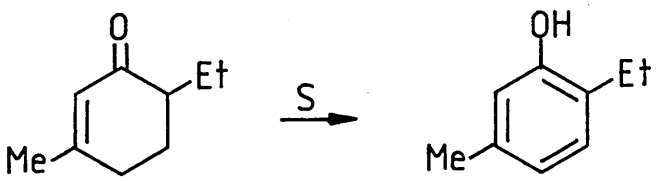
of aromatic rings, this strategy requires several reactions for the addition and oxidation of the sulphur groups. Consequently the strategy of aromatization of enones was considered.

The dehydrogenation of cyclic enones with palladium[102] have been known for sometime. Thus Ross and Levine[95] used this method to aromatize the enone (144).



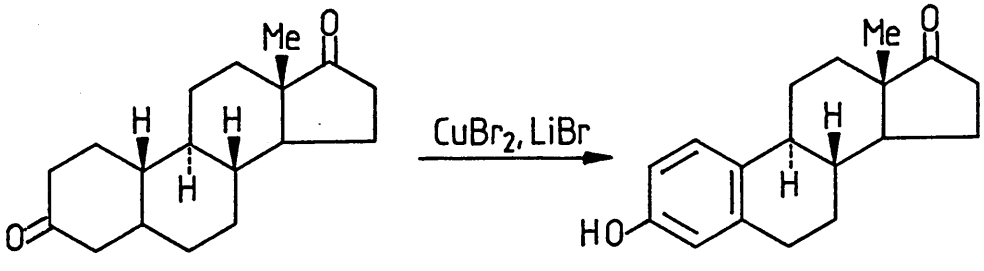
(144) (145)

Although the phenol (145) was obtained in 53% yield, vigorous reaction conditions (heating at 180°C for 3 hours) were required. These workers have also used sulphur to aromatize the enone (146), but although milder reaction conditions were employed, the yield (26%) of phenol (147) obtained was poor. Consequently this method was not considered further.



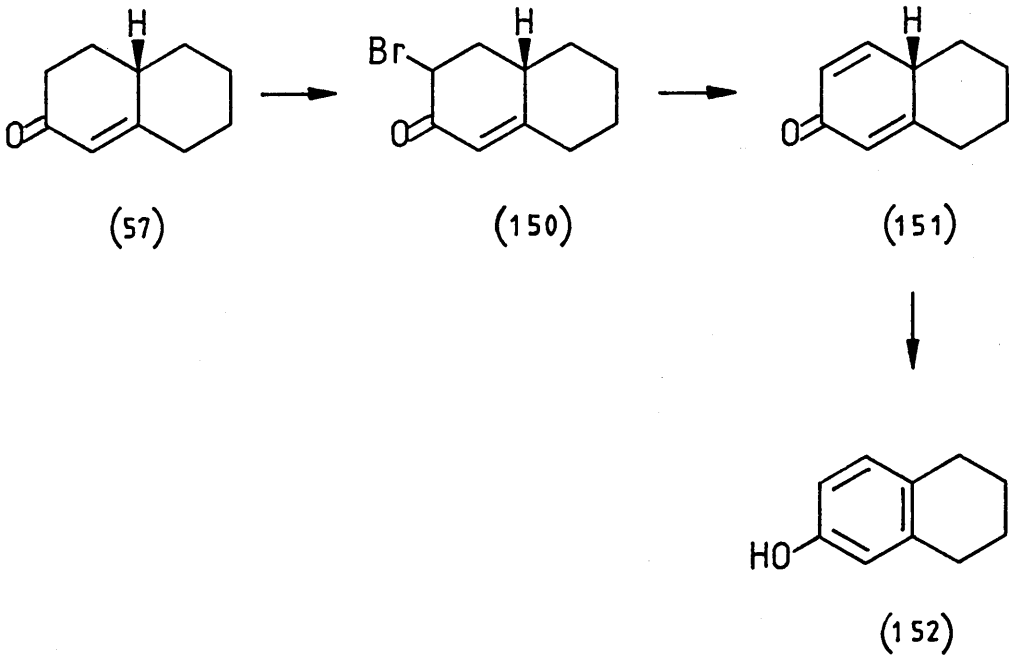
(146) (147)

Bondon et al[103] have reported an aromatization reaction which gave phenols from cyclic enones, in tricyclic and steroidal tetracyclic fused ring systems, in yields of 75-85%. For example, the steroid (148) was aromatized at ring A to give the phenol (149) in 85% yield, with conservation of the stereochemistry about the adjoining rings.



(148) (149)

The mild conditions used involved heating the enone at 80°C for 1 hour with two equivalents of copper (II) bromide and one equivalent of lithium bromide. The mechanism of the reaction appears to involve α-bromination of the ketone [104,105] to give the intermediate (150). Dehydrobromination occurs to produce the dienone (151), which subsequently enolises to the phenol (152).

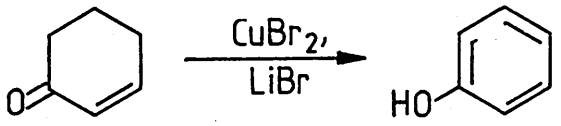


(57) (150) (151) (152)

In view of the above, the conditions of Bondon et al were tried on various model enone compounds before application on the precious tetracyclic enone (137).

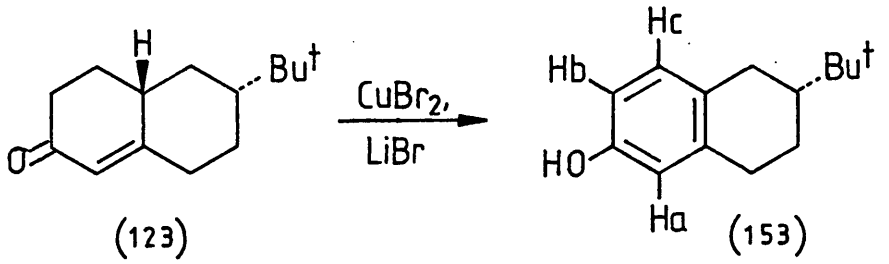
5.3.1 Synthesis of model phenolic compounds

Cyclohexanone was aromatized by heating at 80°C with two equivalents of copper (II) bromide and one equivalent of lithium bromide in dimethylformamide to give phenol in 59% yield.



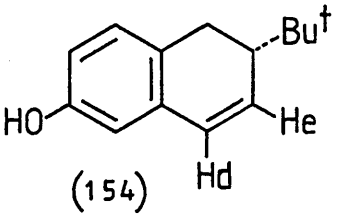
Aromatization of the model bicyclic enone (123) using these conditions was also accomplished to give the phenol (153) in 69% yield. The infrared spectrum of the product exhibited a peak at 3400cm^{-1}, corresponding to the aromatic hydroxyl group, and absorption peaks at 1620 and 1590cm^{-1} due to the aromatic ring. The ^{1}H n.m.r. spectrum exhibited a doublet at δ 6.90 with a coupling constant of 8Hz, which was assigned to the

Hc proton, and a doublet and broad singlet at δ 6.55, which were assigned to the Ha and Hb protons.



(123) (153)

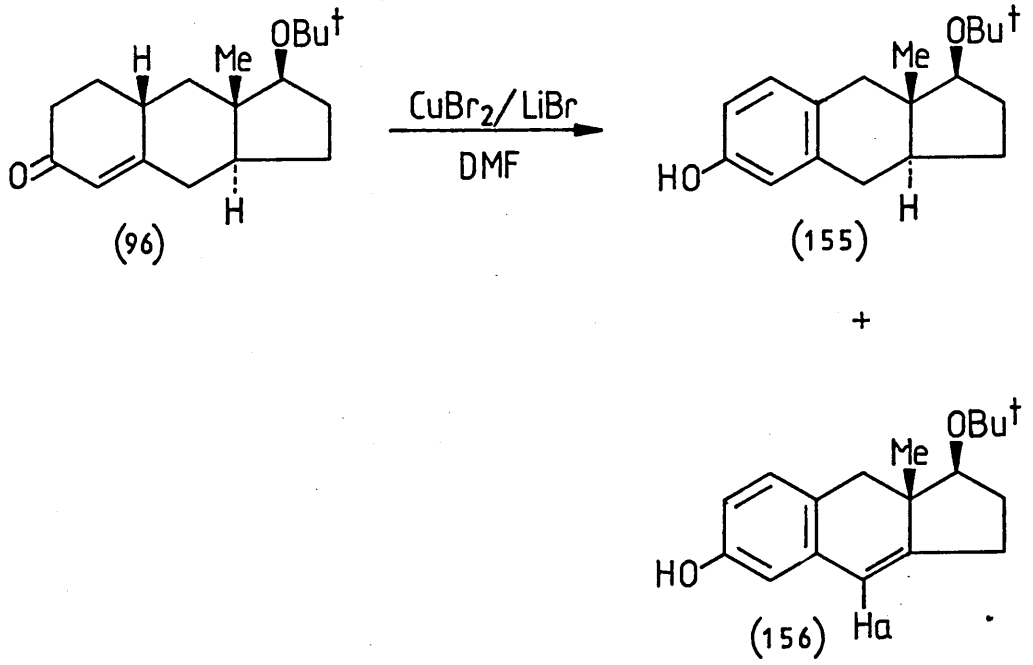
+



(154)

However, the ^{1}H n.m.r. spectrum of the crude reaction mixture indicated the presence of (154) (Ca 15% by integration). A doublet at δ 6.35, with a coupling constant of 8Hz, was assigned to the Hd proton, and a multiplet at δ 5.95 was assigned to the He proton of (154).

Similarly, when the tricyclic enone (96) was aromatized under similar conditions the phenol (155) was obtained in 63% yield, but the ^{1}H n.m.r. of the crude product revealed the presence (Ca. 25% by integration) of the corresponding conjugated phenol (156).

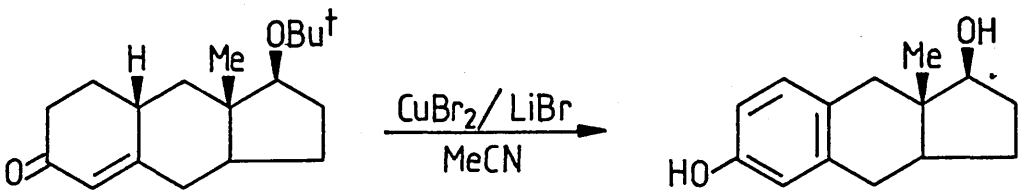


The vinylic proton (Ha) of (156) exhibited a signal at δ 6.1, whilst signals at δ 1.26 and δ 1.17, corresponding to the t-butyl and methyl groups respectively, were also present in the expected intensities and chemical shifts.

From the above, it would appear that bromination and dehydrobromination has occurred in the adjacent fused ring, with concomitant introduction of an additional double bond in conjugation with the phenolic ring. These conditions have been used by Yuan[106] for the aromatization of the A ring in steroids, but no mention was made as to the introduction of further double bonds

in adjacent rings.

When the aromatization of the tricyclic enone (96) was repeated under the same conditions, but using acetonitrile as the solvent, the t-butyl group was surprisingly cleaved. This gave the diol (157) as a solid (m.p. 207-210°C dec.) in 84% yield.



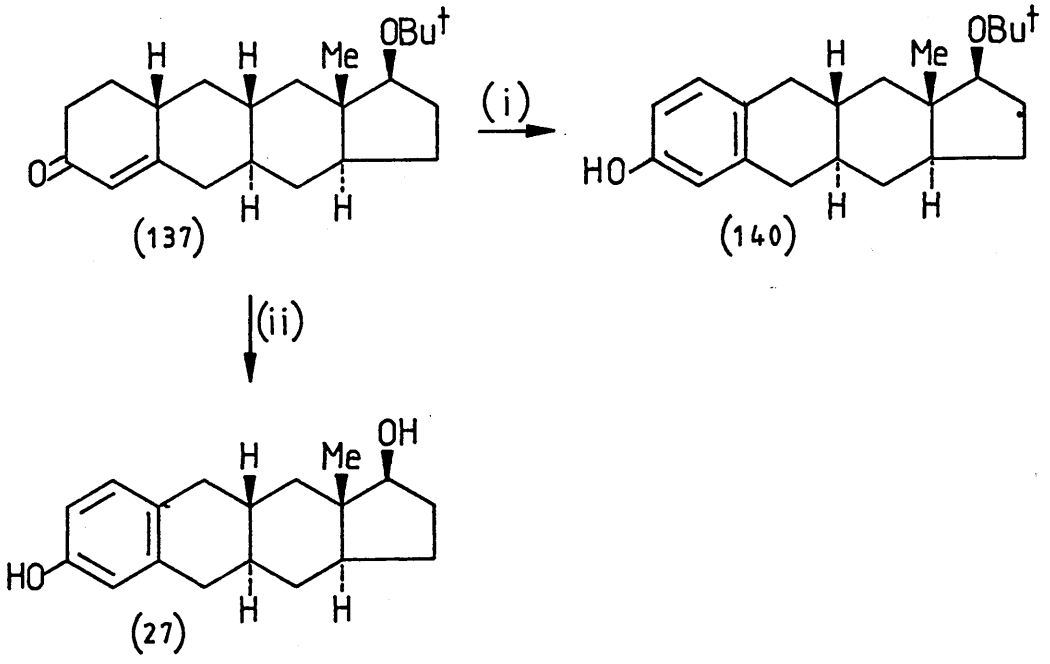
(96) (157)

The infrared spectrum of the product (157) exhibited peaks at 3450 and 3200 cm^{-1}, corresponding to the aliphatic and aromatic hydroxyl groups, and peaks at 1620 and 1590 cm^{-1}, due to the aromatic ring. The ^1H n.m.r. spectrum exhibited signals due to three protons at δ 6.90 and δ 6.55, corresponding to the aromatic protons. The signal due to the t-butyl group was absent, which confirmed that cleavage of the t-butyl ether had occurred.

5.3.2 Synthesis of Linear anthrasteroid analogues of estradiol

The aromatization conditions, as described previously (5.3.1), were applied to the tetracyclic enone (137) (Scheme 16).

Scheme 16



Conditions

(i) $CuBr_2$; LiBr; dimethylformamide; 80°C; 1 hour

(ii) $CuBr_2$; LiBr; acetonitrite; 82°C; 1 hour.

When using dimethylformamide as solvent, the tetracyclic enone (137) was converted to the phenol (140) in 59% yield. The infrared spectrum of the product indicated the aromatic hydroxyl group as a broad peak at 3350 cm^{-1}, and the presence of the aromatic ring with peaks at 1620 and 1590 cm^{-1}. The ^{1}H n.m.r. spectrum exhibited peaks at δ 6.90 and 6.55, corresponding to the aromatic protons, and similar to that obtained from the tricyclic phenol (155).

Changing the solvent to acetonitrile again resulted in aromatization of the tetracyclic enone, but with cleavage of the t-butyl ether group to give the tetracyclic diol (27) as a solid (m.p. 253-256°C dec) in 54% yield. The reaction is similar to that used to give the model tricyclic diol (157), and the spectral data paralleled that of the tricyclic diol (157). Thus the infrared spectrum of (27) exhibited peaks at 3450 and a broad peak at 3200 cm^{-1}, corresponding to the aliphatic and aromatic hydroxyl groups. The aromatic ring was indicated by infrared peaks at 1620 and 1590 cm^{-1}. Unfortunately due to poor solubility of the product in a variety of deuterated solvents (including acetone and chloroform) only a poorly defined ^{1}H n.m.r. spectrum was obtained. This was consistent with the product (27), with the aromatic protons at δ 6.90 and 6.55, with a splitting pattern expected for the

substituted phenol and identical to that of the corresponding tricyclic diol (157). The angular methyl group was present at δ 0.78, and the t-butyl group was absent.

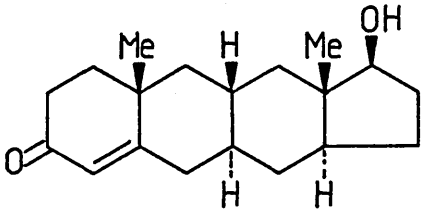
Thus the total synthesis of the target linear anthrasteroid analogue of estradiol (27) has been achieved in 15 steps in an overall yield of 1.5% from (32).

CHAPTER SIX

SYNTHESIS OF LINEAR ANTHRASTEROID ANALOGUES OF TESTOSTERONE

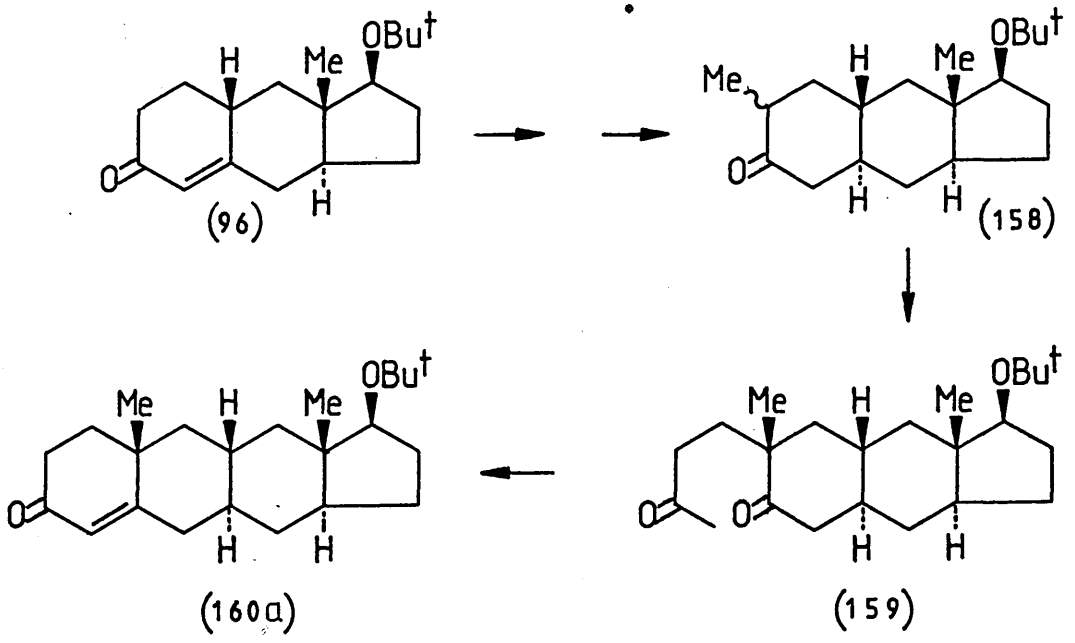
6.1 INTRODUCTION

The synthesis of the linear anthrasteroid analogue of testosterone (25) posed more difficult problems of regiochemistry and stereochemistry than the synthesis of the 19-nortestosterone analogue (26) (Chapter 5), due to the additional angular methyl group.



(25)

Consequently not only was introduction of the methyl group required to be regiospecific, but subsequent annulation to give the tetracyclic enone (160a) had to be both regiospecific and stereospecific, as outlined below.

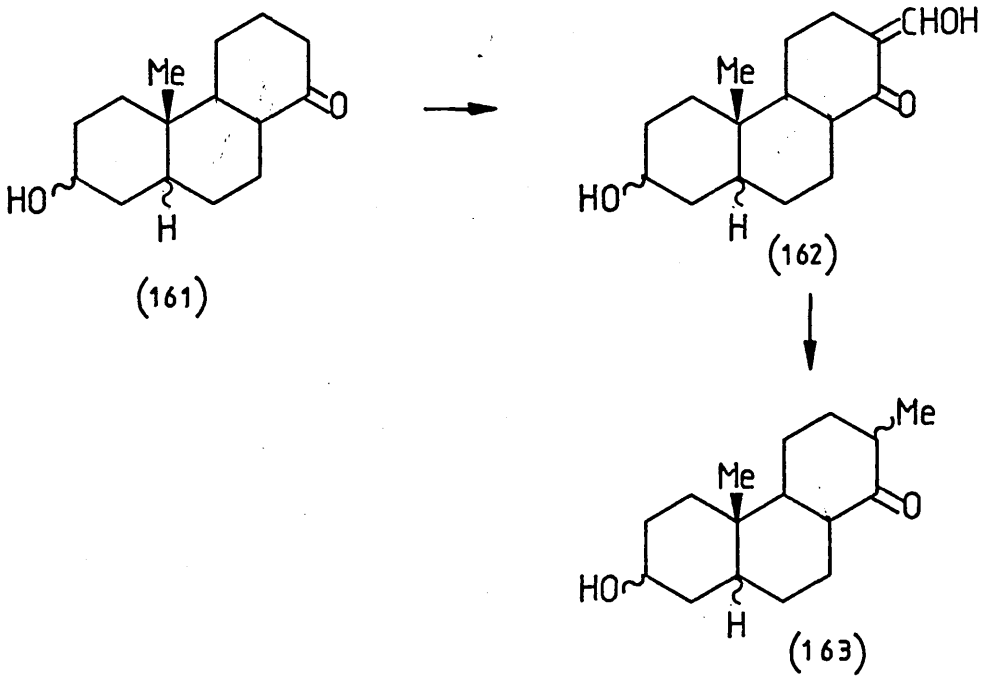


Although the regiochemistry of addition of the annulating reagent was envisaged not to be a problem, as enolates generated under thermodynamic conditions usually react at the most substituted position (Chapter 3), the stereochemistry of the angular methyl group was more difficult to control. This stereochemistry is determined by the stereochemistry of the intermediate (159), which cyclises to give the enone (160a). Unlike the 19-nortestosterone analogue (137), the tetracyclic enone (160a) does not possess an angular proton which can be epimerised.

The literature was surveyed for methods of introducing the methyl group regiospecifically, and for the regiospecific annulation of the tricyclic ketone (158), as described below.

6.2 INTRODUCTION OF THE METHYL SUBSTITUENT

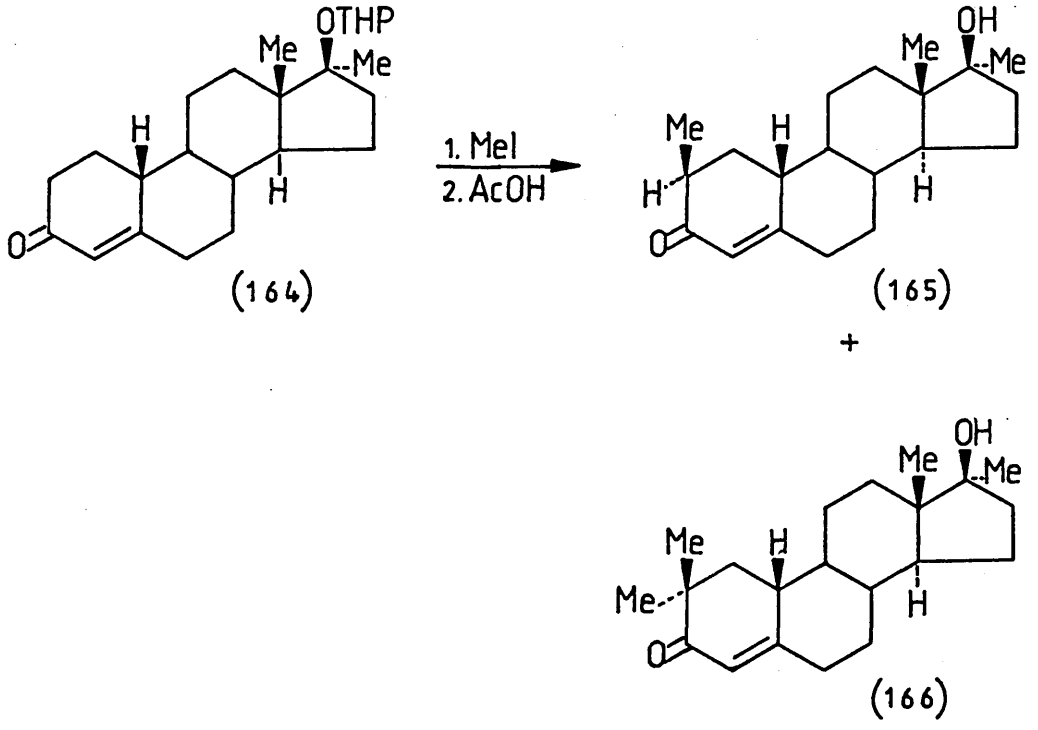
Two strategies were considered for the introduction of the methyl group. The first of these methods involved methylation of an activated ketone, such as an α-hydroxymethylene ketone. This approach has been used by Cornforth and Robinson[107] for the regiospecific methylation of the ketone (161).



Although methylation of the α-hydroxymethylene ketone (162) occurs under mildly basic conditions (potassium carbonate in the presence of iodomethane), the yield of product is diminished by competing O-alkylation. The addition and removal of the hydroxymethylene activating group was also considered a disadvantage. This attracted attention to the second strategy for the introduction of the methyl group.

The regiospecific methylation of conjugated polycyclic ketones under kinetically controlled conditions has been shown by Nedelec et al[108] to proceed in good

yield. By careful control of reaction conditions (slow addition of 1.9 equivalents of potassium t-butoxide in tetrahydrofuran to a solution of the conjugated polycyclic ketone and 14 equivalents of methyl iodide, in tetrahydrofuran at -78°C) these workers have alkylated the enone (164) to give the methylated enone (165) in 67% yield. Less than 10% of the alternative dimethylated product (166) was detected. Increasing the base used to 5.8 equivalents resulted in an increase of the dimethylated product (166) obtained to 66% yield.



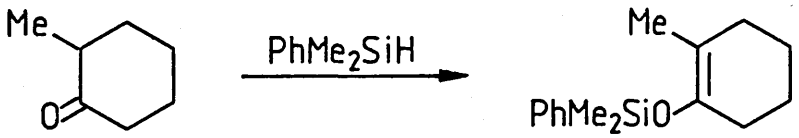
(164) (165) (166)

This method offered the advantage of requiring only one step to regiospecifically introduce the methyl substituent, and was consequently employed to this effect. (See 6.4 and 6.5).

6.3 REGIOSPECIFIC ANNULATION OF α-METHYL SUBSTITUTED KETONES

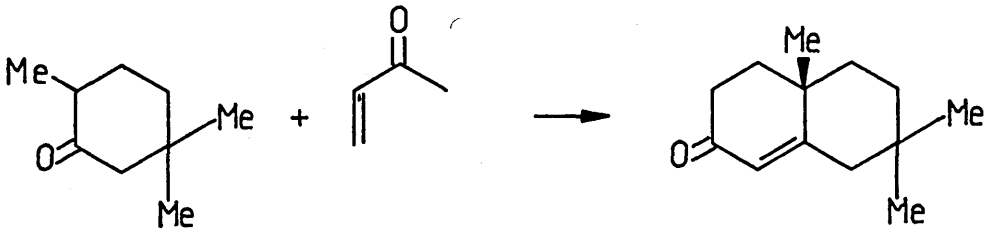
Two main strategies were contemplated to effect regiospecific addition of the annulating reagent. The first involved trapping of the enolate as a silyl enol ether, and subsequent regeneration of the enolate and reaction of this with annulating reagent. The second involved generation of the enolate under thermodynamically controlled conditions, and reaction of this with the appropriate annulating reagent.

The silyl enol ethers derived from dehydrogenative silylation of ketones have been reported[109] to give high regioselectivity. Thus 2-methylcyclohexanone and dimethylphenylsilane, in the presence of a catalytic amount of dicobalt octacarbonyl and pyridine, readily forms the silyl enol ether (167) in high yield (89%) and regioisomeric purity (92%).



(55) (167)

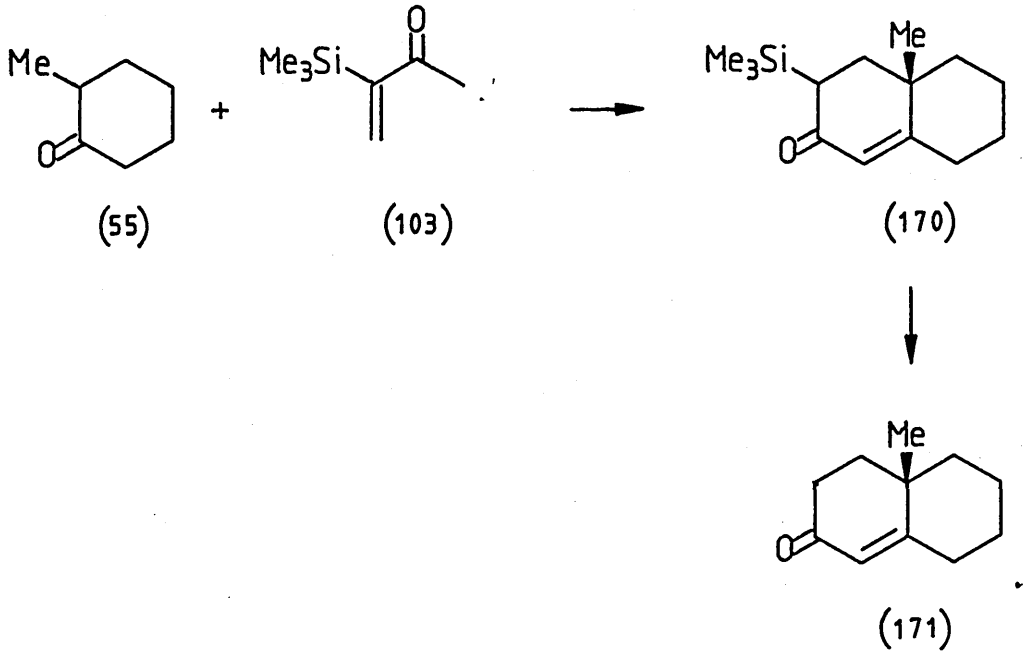
However, experience with silyl enol ethers suggests that the subsequent annulation reaction may proceed in poor yield (see 4.3). The second strategy, involving generation of the enolate under thermodynamically controlled conditions and direct reaction with an annulating reagent, offered the advantage that fewer steps were required, but using methyl vinyl ketone as annulating reagent usually results in a poor yield of product, and polymerisation. However, the annulation of 2,5,5-trimethylcyclohexanone (168) with methyl vinyl ketone under acidic conditions has been reported[110] to give the enone (169) in 60% yield.



(168) (169)

Unfortunately, the reaction conditions involved heating under reflux a solution of (168) with methyl vinyl ketone and conc.sulphuric acid for 16 hours. These conditions were considered too severe.

The use of the trimethylsilyl vinyl ketone (103) annulating reagent, as used by Stork and Ganem[86], was therefore considered. These workers have annulated 2-methylcyclohexanone using this reagent and a catalytic amount of potassium t-butoxide in t-butyl alcohol. Under these thermodynamic conditions, the expected enone (171) was produced. The trimethylsilane group was readily cleaved by treating the enone (170) with sodium hydroxide in isopropyl alcohol to give the bicyclic enone in 60% yield from 2-methylcyclohexanone (by V.P.C.).



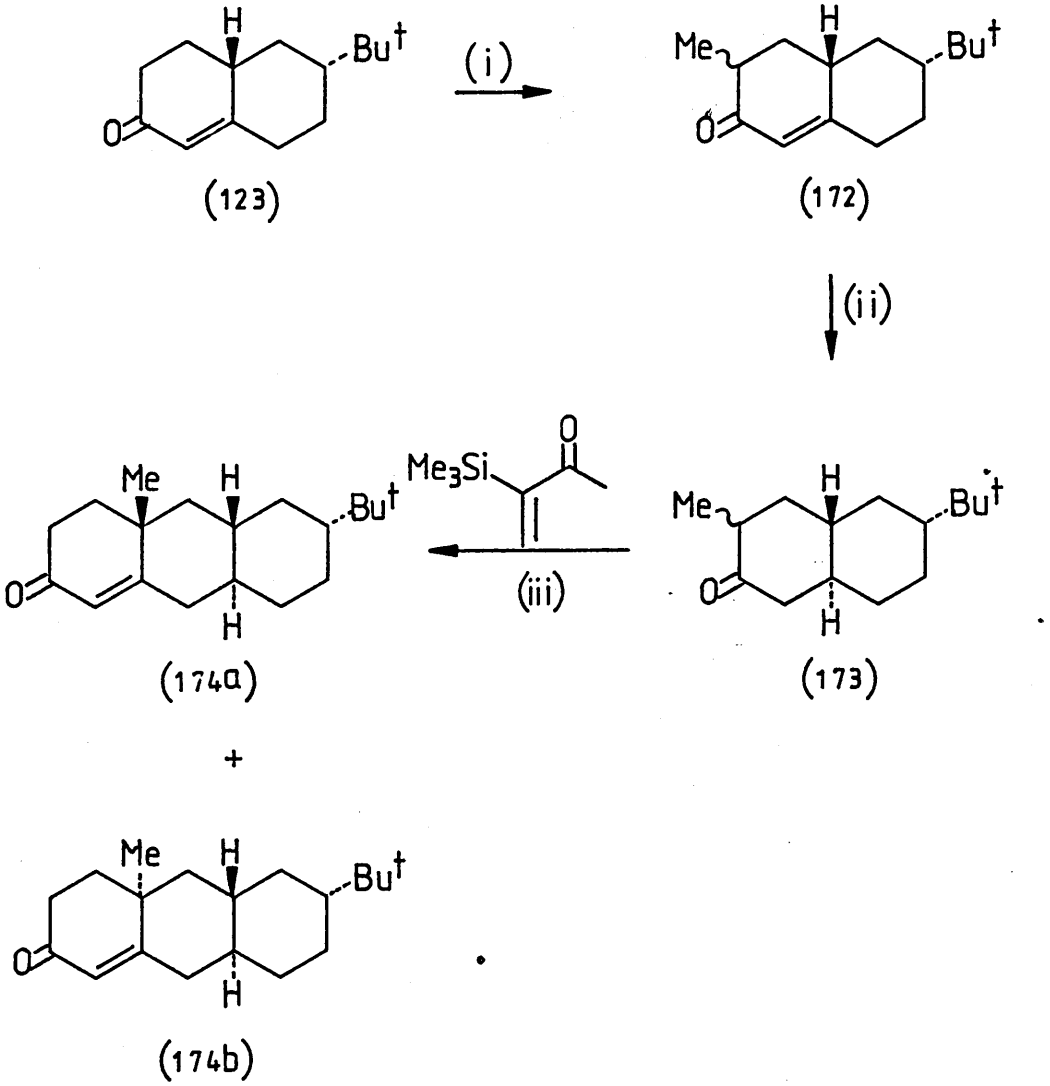
(55) (103) (170) (171)

Due to the mildness of the reaction conditions, the availability of the annulating reagent (103) and the yield of product, the conditions of Stork and Ganem were used to effect annulation.

6.4 SYNTHESIS OF TRICYCLIC MODEL COMPOUNDS INCORPORATING AN ANGULAR METHYL GROUP

The model bicyclic enone (123) was used to optimise the reaction conditions for the methylation and subsequent annulation reaction, as outlined in scheme 17.

Scheme 17



Conditions

(i) MeI(14 equivalents); Bu^tOK (1.4 equivalents); t-butyl alcohol.

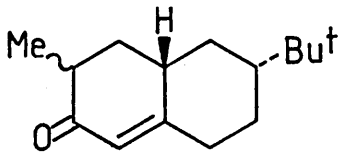
(ii) Li/NH_3.

(iii) Bu^tOK; t-butyl alcohol.

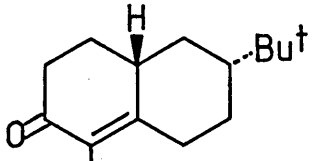
The bicyclic enone (123) was methylated by addition of 1.4 equivalents of potassium t-butoxide in tetrahydrofuran to a solution of (123) and 14 equivalents of iodomethane, in tetrahydrofuran at -78°C. The progress of the reaction was monitored by t.l.c. and the addition of base was stopped when the product (172) was the major component. The product was obtained as an oil in 40% yield. The infrared spectrum exhibited peaks at 1675 and 1630 cm^{-1}, indicating the presence of the conjugated enone system, whilst ^1H n.m.r. confirmed the presence of a methyl group, exhibited as a doublet centred at δ 1.22 with a coupling constant of 7.5 Hz. A broad singlet at δ 5.75 indicated the presence of the vinylic proton.

Several plausible alternative regioisomeric products are possible from the methylation reaction. However, most of these are incompatible with the observed spectra and may be ruled out. Thus (176) would not exhibit the characteristic peaks of a conjugated enone system in infrared spectroscopy, whilst (175) would not exhibit a vinylic proton in ^1H n.m.r.spectroscopy.

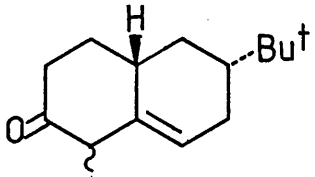
The regioisomer (177) could be discounted from the spectral evidence after removal of the double bond (see later).



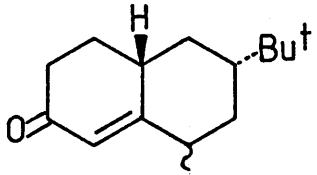
(172)



(175)



(176)

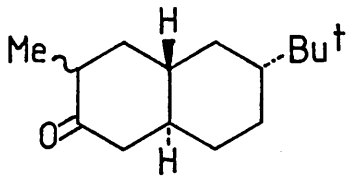


(177)

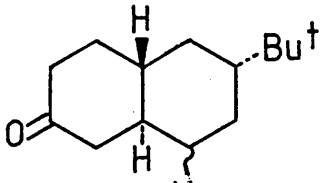
Improvement in the rather poor yield was attempted by using lithium diisopropylamide as base. Unfortunately this gave the lower yield of only 22%.

The carbon-carbon double bond was reduced by lithium-ammonia reduction to give the saturated bicyclic ketone (173) in 46% yield. The ^{1}H n.m.r. spectrum of the product indicated the methyl group as a doublet at δ 1.20. On removal of the double bond, the signals due to the methyl group have moved downfield from δ 1.12 to δ 1.20. This spectrum

confirms that the regiochemistry of methylation is as indicated in (172). The alternative regioisomer (178), obtained from reduction of the enone (177), would exhibit a methyl signal which would be expected to shift dramatically upfield on removal of the carbon-carbon double bond.



(173)



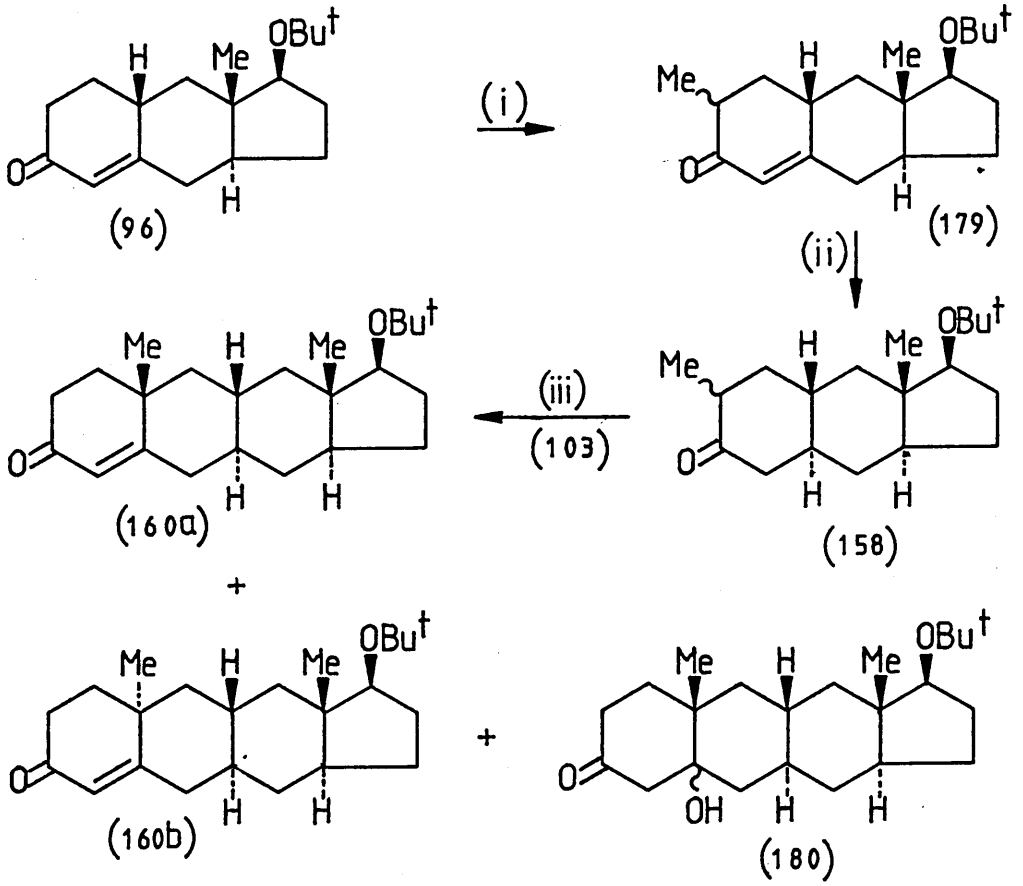
(178)

The bicyclic ketone (173) was annulated using α-trimethylsilyl vinyl ketone (103) as annulating reagent, and potassium t-butoxide as base in t-butyl alcohol. The product was obtained as a colourless oil in poor yield (20%). The infrared spectrum indicated the enone system with peaks at 1670 and 1620 cm^{-1}, whilst the ^1H n.m.r. spectrum suggested that the product consisted of an equal mixture of the isomers (174a) and (174b). Two signals were evident at δ 5.85 and 5.70, which by integration were due to one proton. These signals were assumed to be due to the vinylic protons of (174a) and (174b).

6.5 SYNTHESIS OF LINEAR ANTHRASTEROID ANALOGUES OF TESTOSTERONE

The above sequence of reactions (methylation, reduction and annulation) were applied to the tricyclic enone (96).

Scheme 18



Conditions

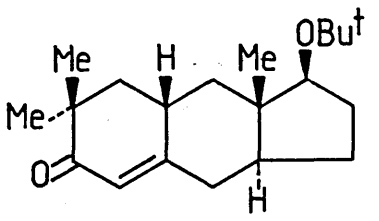
(i) MeI(14equivalents), Bu^tOK(1.18 equivalents); t-butyl alcohol.

(ii) Li/NH_3.

(iii) Bu^tOK; t-butyl alcohol.

The mono methylation of the enone (96) was accomplished by the careful addition of potassium t-butoxide in t-butyl alcohol to a solution of the enone and iodomethane in t-butyl alcohol. The progress of the reaction was monitored by t.l.c., and the addition of the base was stopped when the substrate (96) could not be detected. By careful addition of the base, the product (179) was obtained in 70% yield as a solid after chromatography. The infrared spectrum of an analytical sample indicated the integrity of the enone system, with peaks at 1665 and 1620 cm^{-1}. The ^1H n.m.r. spectrum indicated the presence of a vinylic proton at δ 5.75, and the methyl substituent as a doublet centred at δ 1.15, with a coupling constant of 7.5Hz.

The solid dialkylated product (181) was also obtained in 1.6% yield. The infrared spectrum of this product was as expected, with peaks at 1670 and 1625 cm^{-1} corresponding to the enone system. The ^1H n.m.r. spectrum indicated the two methyl groups as a singlet at δ 1.10, with an integration corresponding to six protons, and the vinylic proton as a singlet at δ 5.73.



(181)

The carbon-carbon double bond of the enone (179) was reduced by lithium-ammonia reduction to give the saturated tricyclic ketone (158) in 57% yield. The ^{1}H n.m.r. spectrum of this product indicated the methyl group as a doublet at δ 1.20. As in the model compound (scheme 17), removal of the double bond has caused the signals due to the methyl group to move downfield by 0.05 p.p.m.

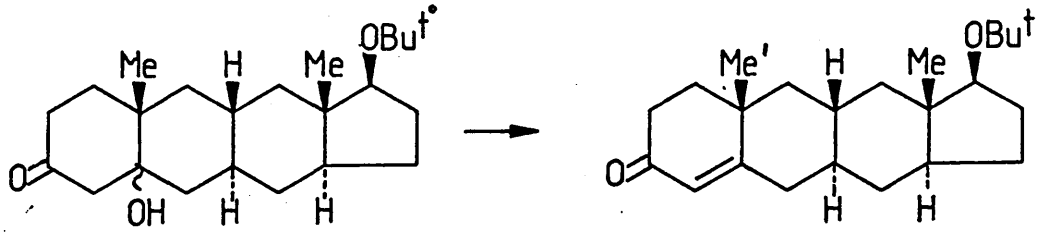
The infrared and ^{1}H n.m.r. spectra of the enone (179) and saturated ketone (158) are similar to the spectra obtained from the analogous model enone (172) and ketone (173) (scheme 17). As in the model system, a variety of regioisomeric products are possible from the methylation of the tricyclic enone (96). By using a similar argument which was used to confirm the regiochemistry of the methylation of the model system, the regioisomer obtained from methylation of the tricyclic enone was established to be as indicated.

Annulation was accomplished by treatment of the tricyclic ketone (158) with the annulating reagent α-trimethylsilyl vinyl ketone (103) in t-butyl alcohol, in the presence of a catalytic amount of potassium t-butoxide. A poor yield (22%) of an oily solid was obtained after chromatography. The ^1H n.m.r. of this product indicated two signals at δ 5.85 and 5.70, which together integrated to one proton. These signals were assigned as the vinylic proton of the two stereoisomers (160a) and (160b), which were present in equal amounts.

The stereoisomeric mixture was crystallized from petroleum spirit 40/60 to give a colourless solid (m.p. 97-102^{o}C). The infrared spectrum of this solid product exhibited peaks at 1675 and 1620 cm^{-1}, corresponding to the conjugated enone system. Significantly, the ^1H n.m.r. spectrum indicated only one signal at δ 5.70, corresponding to the vinylic proton, and indicated the presence of only one of the stereoisomers. This isomer was arbitrarily assigned as the (160a) isomer, in which the methyl group is β as a consequence of equatorial addition of the annulating reagent.

Continued chromatography of the crude product gave a hydroxy ketone (180) as a white solid after recrystallization (m.p. 181-183.5°C). This was the major component by weight from the crude product. Similar hydroxy ketone intermediates from the Robinson annulation have been reported earlier (Chapters 4 and 5). The insolubility of these intermediates in the reaction solvent may account for their occurrence[111].

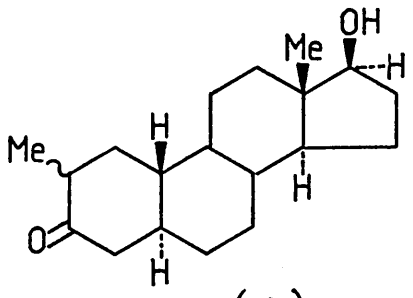
The hydroxy ketone (180) was dehydrated by heating under reflux a solution in benzene containing p-toluenesulphonic acid. The solid product was recrystallized several times to give a pure product (m.p. 112-113.5°C), which was identical to the enone isomer (160a) by infrared and ^{1}H n.m.r. spectroscopy (in $CDCl_3$ and C_6D_6).



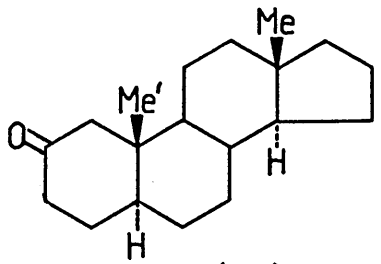
(180) (160a)

Unfortunately there was insufficient time to unequivocally determine the stereochemistry of the tetracyclic enone (160a). However, tentative support for the proposed assignment was provided by solvent effects in ^{1}H n.m.r. spectroscopy.

Changing the solvent from deuterated chloroform to deuterated benzene in ^{1}H n.m.r. spectroscopy may markedly affect the chemical shift of methyl groups adjacent to a carbonyl group[111,112]. The change in chemical shift is indicative of the orientation of the methyl group. Thus in the ketone (182)[110], when the methyl group at C-2 is axial, changing the solvent from chloroform to benzene caused the resonance due to this methyl group to move upfield (by Ca.0.1 to 0.3 ppm). Conversely, when this methyl group is equatorial, a small downfield shift (Ca.0.05-0.1 ppm) is observed.



(182)



(183)

This effect is also experienced by angular methyl groups which are more remote from the ketone group, for example the axial methyl group indicated (Me′) in 5 -androstan-2-one (183)[113]. This methyl group is shifted from δ 0.75 to 0.59 when the solvent is changed from deuterated chloroform to deuterated benzene.

A similar shift in the resonance due to the angular methyl group (Me′) of the tetracyclic enone (160a) was observed. This methyl group was shifted from δ 1.25 to 0.95 when the deuterated solvent was changed from chloroform to benzene.

Although this chemical shift induced by benzene suggests that the methyl group (Me′) is axial as proposed, the result should be treated with caution. The enone system of (160) is similar, but not identical, to the ketone system of (182) and (183), with regard to the proximity of the methyl group in question. Consequently the effects of changing solvent can be predicted with less certainty.

CHAPTER SEVEN

EXPERIMENTAL

7.1 GENERAL NOTES

Proton nuclear magnetic resonance (^{1}H n.m.r.) spectra were obtained on one or more of the following instruments: Jeol-C-60 (60 Mz); Hitachi-Perkin Elmer R-600 ft. (60 MHz); Bruker spectrospin WP 80 (80 MHz); Varian EM 390 (90 MHz); Perkin Elmer R34 (220 MHz); Bruker Spectrospin WM 250 (250 MHz); Bruker Spectrospin WM 400 (400 MHz). Chemical shifts are quoted in parts per million (ppm). Tetramethylsilane was added as an internal standard, its resonance being assigned a value of zero ppm on the δ scale. All spectra were obtained using deuterated chloroform ($CDCl_3$) as solvent unless otherwise stated. The multiplicities are reported using the following abbreviations: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; b, broad and J, apparent coupling constant in Hz.

Infrared (I.r.) spectra were obtained on a Pye-Unicam SP 200 grating infrared spectrometer. Samples were in the form of thin liquid films or a 1% dispersion in potassium bromide (KBr.), or a suspension in nujol. The infrared figures quoted are frequency maxima (ν max) in reciprocal wavenumbers (cm^{-1}).

Mass spectral (m.s.) data were obtained on a AEI MS9, Kratos MS 80 or MS 30 instruments. Samples were

introduced by direct insertion probe and ionised by electron impact at 24 or 70 electron volts (eV). Some spectra have been obtained by using chemical ionization with methane. Only the strongest and/or structurally most important peaks are quoted.

The microanalyses were performed by the analytical department of Glaxo Group Research (Ware) Ltd., Ware, Herts., or by Elemental Microanalysis Ltd., Amberley, Beaworthy, Devon.

Thin layer chromatograms (T.l.c.) were obtained using Merck "5734" plastic backed chromatography plates with incorporated fluorescent indicator. Compounds were visualised by quenching of fluorescence upon irradiation with ultra-violet light (254nm), iodine vapour adsorption and the use of one or more of the following spray reagents; molybdophosphonic acid (MPA), iodoplatinic acid (IPA), basic potassium permanganate ($KMnO_4$), 2,4-dinitrophenylhydrazine (DNP).

Short column chromatography[114] was performed using Merck "7734" (70-230 mesh) silica gel. Flash chromatography[115] was performed using Merck "9385" 40-63 μM (230-400 mesh) silica gel 60. Solvents for chromatography were distilled prior to use. The petrol used for column chromatography was the fraction of

petroleum spirit boiling between 40-60°C.

Melting points are uncorrected.

Anhydrous reactions were run using megnetic stirring under a positive pressure of dry nitrogen, dry glassware being obtained by flame drying and then cooling under a stream of nitrogen. All reaction temperatures were measured externally. All solvents for anhydrous reactions were distilled as follows: diethyl ether from lithium aluminium hydride; tetrahydrofuran from potassium; dichloromethane, t-butyl alcohol, dimethylformamide and triethylamine from calcium hydride; diisopropylamine was dried over and distilled from calcium hydride and then stored under nitrogen over 3A° molecular sieves. n-Butyl lithium was used as a solution in hexane, stored under argon, and standardized prior to use against diphenyl acetic acid.

7.2 EXPERIMENTAL METHODS

The experimental methods have been presented in the order in which they appear in the text. The chapter and section number have been included to aid location of any particular method.

CHAPTER TWO

2.2.2

2-Methyl-1,3-Cyclopentanedione (32)[22]

Finely ground succinic acid (32 g, 0.27 mol) was added cautiously (over 50 mins.) to a stirred solution of aluminium chloride (108 g, 0.81 mol) in dry nitromethane (110 ml) under nitrogen. After the vigorous evolution of hydrogen chloride abated, freshly distilled propionyl chloride (70 mls, 0.81 mol) was added dropwise (over 45 mins) and the solution stirred at 80°C for 4 hr.

The dark red solution was cooled to -10°C, and crushed ice (220 g) added at a rate to maintain the solution temperature below 10°C. The resulting brown slurry was left at -10°C for 2 hr, filtered under vacuum, and washed successively with aqueous sodium chloride solution (10% w/w) and toluene.

A crystalline product (from water) was obtained in good yield (17.9 g, 59%), m.p. 212-215°C (Lit. m.p. 214-216°C[22] and 212-214°C[23])

$\underline{\nu}$max.(KBr): 2670 (intramolecularly hydrogen bonded OH) 1580 (β-hydroxy,$\alpha\beta$ – unsaturated C=O) cm^{-1}.

2-Methyl-2-(3-oxobutyl)-1,3-Cyclopentanedione (33)[18]

To a suspension of the dione (32) (80.4 g, 0.72 mol) in deionised water (150 ml) was added freshly distilled 3-butene-2-one (130 ml, 1.6 mol) all at once, and the mixture mechanically stirred for 5 days under nitrogen at ambient temperature.

The viscous solution was extracted with benzene (4 x 70 ml), which was combined and treated with sodium sulphate, magnesium sulphate and charcoal. After filtration the solids were extracted with boiling benzene (100 ml), and the combined benzene extracts evaporated. The residue (244 g) was fractionally distilled (105-110°C, 0.3-0.5 mmHg)[18] to afford the triketone (33) (219 g, 84%) as a pale yellow oil.

$\underline{\nu}$max (thin film): 1770 (5 ring cyclic C=O) and 1720 cm^{-1} (chain C=O)

δ (60 MHz): 3.0-1.8 (Total 8H, m, $COCH_2CH_2CO$ and $COCH_2CH_2$) 2.16 (3H, s, CH_3CO), 1.25 (3H, s, CH_3C).

(±)-7a-methyl-7,7a-dihydro-1,5(6H)-indandione (35)[27]

The trione (33) (23.5 g, 0.13 mol) and p-toluenesulphonic acid monohydrate (0.4 g) in dry benzene (300 ml) were heated under reflux using a water jacket cooled Dean-Stark water separator. After 2 hr. and 4 hr. further portions of the acid catalyst (0.4 g) were added, and the solution heated under reflux until the theoretical amount of water was collected (Ca. 2.3 mls, 7 hr). The reaction mixture was washed with aqueous saturated sodium hydrogen carbonate solution (1 x 10 ml), water (1 x 5 ml), dried ($MgSO_4$) and evaporated in vacuo to leave an oily, orange residue which crystallized on standing over 0.5 hr. at room temperature. Trituration with cold ether gave the dione (35), (14.89 g, 70%) as white crystals, m.p. 69-71°C (Lit.[27] m.p. 72-73°C).

νmax (nujol): 1740 (saturated C=O), 1650 and 1610 cm^{-1} (unsaturated C=O)

δ (90 MHz): 5.95 (1H, s, vinylic proton), 3.0-1.7 (8H, complex), 1.3 (3H, s, 7a-CH_3).

(±)-1β-hydroxy-7aβ-methyl-7,7a-dihydro-5(6H)-indanone (36) [19,116]

To a chilled (0°C) solution of indandione (35) (57.7 g, 0.35 mol) in absolute ethanol (300 ml) was added dropwise a solution of sodium borohydride (3.87 g, 0.10 mol, 1.16 equivalent) in absolute ethanol (270 ml). The progress of the reaction was monitored by t.l.c. (petroleum spirit-ethyl acetate 1:1, v/v) and when all the dione (35) (Rf: 0.63) was reduced to the alcohol (4) (Rf: 0.46), addition of the reagent was stopped. The rate of addition was controlled so as to maintain the internal temperature between 0 and 5°C (Ca 1 hr.).

The reaction mixture was cooled (-10°C) and hydrochloric acid (2 M) added dropwise until the solution was acidic (pH 2). The solvent was evaporated (40°C) and the aqueous residue extracted with ethyl acetate (4 x 50 ml). The combined extracts were washed with water (2 x 30 ml), dried ($MgSO_4$) and evaporated to leave a viscous orange oil (36) (57.4 g, 98%).

νmax (liquid film): 3420 (OH), 1660 and 1620 cm^{-1} (α β-unsaturated C=O).

δ (80 MHz): 5.80 (1H, s, vinylic proton), 3.50 (1H, dd, 1α-H), 2.90-1.55 (8H, complex), 1.13 (3H, s, 7β $-CH_3$).

(±)-1β-t-butoxy-7aβ-methyl-7,7a-dihydro-5(6H)-indanone (37)[30]

a) Using phosphoric acid, boron trifluoride as catalyst

The alcohol (36) (24.4 g, 0.11 mol) in dry dichloromethane (250 ml) was stirred and cooled to -78°C under nitrogen. To this was added phosphoric acid (2.5 ml) (prepared by dissolving 2.4 g of phosporus pentoxide in 8.2 mls of 85% phosphoric acid), 47% boron trifluoride etherate (6.1 ml) and liquid isobutylene (130 ml, 1.4 mol). The mixture was stirred for 2 hr. at -78°C and then overnight at ambient temperature. T.l.c. analysis (petroleum spirit-ethyl acetate 8:1, v/v) indicated the product (37) at Rf: 0.75 as the major component.

The reaction mixture was poured into ammonium hydroxide (2 M, 250 ml) and the product extracted with dichloromethane. The dried ($MgSO_4$) extracts were evaporated to yield an orange oil which partly crystallized on cooling (0°C, 0.5 hr.) to give an oily solid (30.0 g, 94%).

νmax (nujol): 1670 and 1640 ($\alpha\beta$ - unsaturated C=O), 1375, 1190 and 1080 cm^{-1}

δ(60 MHz): 5.8 (1H, s, vinylic proton), 3.4 (1H, dd, 1 α-H), 2.90-1.55 (8H, complex), 1.18 (9H, s, $-OBu^t$), 1.10 (3H, s, 7aβ-CH_3).

(b) Using Conc. Sulphuric Acid as Catalyst

A solution of the alcohol (36) (3.48 g, 15.7 mmol) in dichloromethane (25 ml) containing conc. sulphuric acid (0.2 ml) and 2-methyl propene (18.6 ml, 200 mmol) was shaken in a pressure vessel at ambient temperature over 4 days.

The reaction mixture was washed with water (2 x 5 ml), dried ($MgSO_4$), and the solvent removed under vacuum to give an orange oil (2.14 g, 47%). This was identical to the product obtained above (by i.r., ^1H n.m.r. and t.l.c.)

(±)-1β-t-Butoxy-7aβ-methyl-5,6,7,7a-tetrahydro-5-oxo-4-indancarboxylic acid (38)[19,20]

To the t-butyl ether (37) (6.02 g, 27.1 mmol) was added magnesium methyl carbonate (MMC) (2.3 M, 120 ml, 10.2 equivalent) in dimethylformamide. The reaction vessel, equipped for distillation, was placed in an oil bath (preheated to 120°C) and the mixture stirred under a nitrogen flow. The internal temperature (110°C) was maintained for 2.5 hr. during which Ca.20 ml of distillate was collected. T.l.c. (dichloromethane -ethyl acetate 8:1, v/v) indicated product only to be

present.

The solution was chilled (0°C), poured into a mixture of ice and conc.hydrochloric acid (40 ml), and extracted with benzene (3 x 30 ml). This was then extracted with sodium carbonate solution (15% w/w, 3 x 30 ml), and the combined basic extracts acidified carefully with cold (0°C) dil. hydrochloric acid. This aqueous phase was extracted with benzene (3 x 30 ml), dried ($MgSO_4$) and evaporated to give, after trituration with cold (0°C) ether-petroleum spirit (1:1) the acid (38) (5.07 g, 70%) as a white solid, m.p. 154-157°C (dec). (lit[20] m.p. 159.5°C dec).

νmax (KBr): 1725 (acid C=O), 1630 and 1610 ($\alpha\beta$-unsaturated cyclic C=O), 1480, 1460 and 1100 cm^{-1}.

δ (90 MHz): 3.67 (1H, dd, 1α-H), 3.3-2.5 (4H, m, 6-H_2 and/or 3-H_2), 2.2-1.6 (4H, m, 2-H_2 and 7-H_2), 1.18 (12 H, s, -OBu^t and 7aβ-CH_3).

(±)-1β-t-butoxy-7aβ-methyl-3aα,4β,5,6,7,7a-hexahydro-5-oxo-4-indancarboxylic acid (39)[20]

The unsaturated β-keto acid (38) (5.02 g, 22.6 mmol) was dissolved im methanol (320 ml) and hydrogenated in the presence of 10% palladium on barium sulphate (820

mg) at 1 atmosphere pressure and 0°C. The theoretical amount of hydrogen was consumed in 2 hr, and when no further uptake occurred over Ca.1 hr, the reduction was terminated.

The solution was vacuum filtered (hyflo supercell) and solvent evaporated (water bath below 0°C) to produce, after trituration with petroleum spirit, a white solid (4.31 g, 85%) m.p. 106-108°C dec. (lit.[20] m.p. 114-114.5°C dec).

νmax (KBr): 3450 br (OH) 1730 (acid C=O), 1705 cm^{-1} (cyclic C=O).

δ (90 MHz): 3.53 (1H, dd, 1α-H), 3.40 (1H, d, $J_{3a\alpha,4\beta}$ = 13.5 Hz; 4β-H), 2.7-1.3 (9H, complex), 1.14 (9H, s, $-OBu^t$), 1.03 (3H, s, 7aβ-CH_3).

^{1}H n.m.r. indicated a 91% trans [(90 MHz) 3.40, d, $J_{3a\alpha,4\beta}$ = 13.5 Hz; 4β-H] and 9% cis [3.16, d, $J_{3a\beta,4\beta}$ = 5 Hz; 4β-H] isomer ratio.

(±)-1β-t-butoxy-7aβ-methyl-3aα,4 .,7,7a-tetrahydro-5(6H)-indanone (29)

The acid (39) (4.41 g, 16.5 mmol) in dry toluene (180 ml) was refluxed under nitrogen (Ca. 1.5 hr). T.l.c. (petroleum spirit-ethyl acetate 4:1, v/v) indicated a product (Rf: 0.37, yellow DNP) as the major component.

The solvent was evaporated to leave a brown solid residue, which on chromatography over silica (40-63 μm) with petroleum spirit-ethyl acetate (4:1, v/v) as eluant afforded the product (3.39 g, 92%) as a white solid, m.p. 25-28°C.

ν_{max} (melt): 1715 (cyclic C=O), 1195 and 1060 cm^{-1}.

δ (90 MHz): 3.37 (1H, dd, 1α-H), 2.50-1.30 (11H, complex), 1.12 (9H, s, $-OBu^t$), 1.07 (3H, s, 7a-CH_3)

M.s. Found: 224 (M+).

(±)-1β-t-butoxy-7aβ-methyl-3aα,4β,5,6,7,7a-hexahydro-5-oxo-4-indancarboxylic acid methyl ester (40)[20]

To a solution of the carboxylic acid (39) (0.90 g, 3.36 mmol) in dry ether (30 ml) at 0°C was added a solution (20 ml) of diazomethane in ether (0.21 mmol/ml) dropwise with stirring.

After 20 min. the solvent was removed in vacuo to give the product as a white, powdery solid (0.87g, 92%). An analytical sample (from ether-petroleum spirit) gave a white powder, m.p. 112-114°C (lit m.p. 112.5-113.5°C)[20].

νmax (KBr): 1750 (C=O of ester), 1710 cm^{-1} (cyclic C=O)

δ (80 MHz): 3.70 (3H, s, $-CO_2CH_3$), 1.15 (9H, s, $-OBu^t$), 1.0 (3H, s, 7aβ-CH_3).

2-methyl-1,3-cylohexanedione (45)[41]

Finely ground glutaric acid (10 g, 0.08 mol) was added cautiously (over Ca 20 mins) to a stirred solution of aluminium chloride (32 g, 0.24 mol) in dry nitromethane (36 ml) under nitrogen. After the rapid evolution of hydrogen chloride abated, freshly distilled propionyl chloride (21 ml, 0.24 mol) was added dropwise (over Ca 15 mins) and the solution stirred at 80°C for 4 hr. The dark red solution was cooled (-10°C), and crushed ice (72 g) added at a rate to maintain the solution temperature below 10°C. The brown slurry was left at -10°C for 2 hr, filtered under vacuum, and washed successively with sodium chloride solution (10% w/w) and toluene. Recrystallization from water afforded a crystalline product as spindles, (4.9 g, 51%) m.p. 207-209°C (cf. lit[41] m.p. 207-210°C).

νmax (KBr): 2670 (intramolecularly hydrogen bonded OH), 1580 cm^{-1} (β-hydroxy,$\alpha\beta$-unsaturated C=O).

2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (46)[41]

To a suspension of the dione (45) (30 g, 0.24 mol) in deionised water (60 ml) was added freshly distilled 3-buten-2-one (45 ml, 0.54 mol) all at once, and the mixture mechanically stirred for 5 days under nitrogen at ambient temperature. The solution rapidly became viscous, and after 5 days, a substantial quantity of polymer had formed.

The solution was extracted with dichloromethane (4 x 20 ml) which was treated with magnesium sulphate and charcoal (Ca. 0.5 g). After filtration the solids were extracted with boiling dichloromethane (30 ml) and the combined dichloromethane extracts evaporated. The orange residual oil was fractionally distilled (140-150°C at 0.4 mmHg)[41] to afford the triketone (20.1 g, 22%) as a clear yellow oil.

νmax (liquid film): 1720 cm^{-1} (cyclic and acyclic C=O).

δ (60 MHz): 2.17 (3H, s, $COCH_3$), 1.30 (3H, s, 2-CH_3), 2.9-1.1 (10H, complex).

(±)-8a-methyl-1,2,3,4,6,7,8,8a-octahydro-1,6-naphthalenedione (48)[41]

To a stirred solution of the trione (46) (17.1 g, 87

mmol) in dry benzene (70 ml) was added freshly distilled pyrrolidine (0.7 ml). The resultant red solution was heated under reflux under nitrogen, and water produced from the condensation azeotropically distilled off. After 1 hr, a further aliquot (0.7 ml) of pyrrolidine was added, and the dark red solution left refluxing for a further 2 hr, when 2.3 ml of water had collected.

The solution was cooled to ambient temperature, washed with hydrochloric acid (10% v/v, 3 x 10 ml), water (2.x 10 ml), and dried ($MgSO_4$). The solvents were removed under vacuum to leave a yellow oil, which after cooling (4°C, 12 hr), and 'seeding' with authentic material finally crystallized out to a yellow solid. Trituration with cold (0°C) diethyl ether afforded the product (48) as a white powdery solid (7.3 g, 47%), m.p. 47-49°C (cf.lit[41], 47-50°C).

νmax (KBr): 1720 (saturated cyclic C=O), 1660 and 1620cm^{-1} ($\alpha\beta$-unsaturated C=O),

δ (60 MHz): 5.90 (1H, s, vinylic proton), 3.0-1.2 (10H, complex), 1.50 (3H, s, $\alpha\beta$-CH_3).

(±)-5β-hydroxy-4aβ-methyl-2,3,4,4a,5,6,7,8-octahydro-2-naphthalenone (49)[44]

To a cooled (0°C) solution of the dione (48) (10.96 g, 61.6 mmol) in absolute ethanol (70 ml) was added dropwise sodium borohydride (0.68 g, 17.9 mmol, 1.16 equivalents) in absolute ethanol (50 ml). Reaction progress was monitored by t.l.c. (Petroleum spirit ethyl acetate 1:1, v/v) and when all the dione (48) (Rf: 0.60) was reduced to the alcohol (49) (Rf: 0.42), addition of the reagent was ceased. The rate of addition was controlled so as to maintain the internal temperature between 0°C and 5°C (Ca. 10 min).

The reaction mixture was cooled (-10°C) and hydrochloric acid (2 M) added dropwise until the solution was acidic (pH 2). The volatile solvent (ethanol) was evaporated (50°C) and the aqueous residue extracted with ethyl acetate (3 x 40 ml). The combined extracts were washed with water (1 x 20 ml), saturated brine (1 x 20 ml), dried ($MgSO_4$) and evaporated to yield a clear, yellow oil which was subjected to high vacuum (15 mmHg, 1 hr) to afford the alcohol (49) (10.73 g, 97%).

ν max (liquid film): 3470 (OH), 1660 and 1620.cm^{-1} (α β-unsaturated cyclic C=O).

δ (60 MHz): 5.70 (1H, brs, vinylic proton), 3.5 (1H, dd, 5α-H), 1.18 (3H, s, 4aβ-CH_3).

(±)-5β-t-butoxy-4aβ-methyl-2,3,4,4a,5,6,7,8-octahydro-2-naphthalenone (50)

The alcohol (49) (10.37. g, 5.76 mmol) in dried dichloromethane (100 ml) was stirred and cooled to approximately -78°C under nitrogen. To this was added phosphoric acid (1.5 ml) (prepared by dissolving 1.6 g P_2O_5 in 5.5 mls of 85% phosphoric acid), followed successively by boron trifluoride etherate (47% w/w .4 ml) and liquid isobutylene (80 ml, 86 mmol). The mixture was stirred for 3 hr at -78°C, when t.l.c. analysis (petroleum spirit-ethyl acetate 8:1, v/v) indicated a mixture of starting material and product as the major component. This mixture was left stirring overnight at ambient temperature.

The reaction mixture was poured into ammonium hydroxide (2 M 150 ml) and the product extracted with dichloromethane (3 x 50 ml). The dried ($MgSO_4$) extracts were evaporated to yield an orange oil, which by t.l.c. consisted mainly of starting alcohol and the butylated product (50).

Chromatography over silica (70-230 mesh), with petroleum spirit-ethyl acetate (8:1, v/v) as eluant gave the product as an oil (3.68 g, 44%), which

resisted crystallization.

νmax (thin film): 1660 and 1620 ($\alpha\beta$-unsaturated cyclic C=O) 1070 cm^{-1} (C-O-Bu^t).

δ (60 MHz): 5.70 (1H, brs, vinylic proton), 3.45 (1H, dd, 5α-H), 1.20 (12H, s, 4aβ-CH_3 and -OBu^t).

M.s. Found: 236 (M^+).

(±)-5β-t-butoxy-4aβ-methyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-2-naphthalenone (30)

To a solution of refluxing dry ammonia (130 ml) and lithium (180 mg, 26 mmol), was added slowly, dropwise, (Ca. 30 mins) a solution of the enone (50) (2.17 g, 9.7 mmol) in dry THF (40 ml), containing dried t-butyl alcohol (0.52 g, 7.0 mmol). The solution was stirred for a further 1 hr, t.l.c. (Petroleum spirit-ethyl acetate 1:1, v/v) indicated product (R.f: 0.82, yellow DNP), as the major component with some residual starting material (rf: 0.72; UV, orange DNP).

Excess saturated ammonium chloride solution was added cautiously, and the mixture warmed (40°C) under a vigorous nitrogen flow to expel the ammonia. The product was extracted with ether (3 x 25 ml), washed with brine (1 x 10 ml), dried ($MgSO_4$) and evaporated to

afford a yellow oil. Chromatography over silica (40-63 μm) using petroleum spirit-ethyl acetate (1:1, v/v) as eluant gave the product as a clear colourless oil (162 mg, 74%) which eventually solidified on storage at 4°C over 24 hours to give a crystalline solid, mp 55-61°C.

νmax (KBr): 1720 (cyclic C=O), 1460, 1370, 1200 and 1080 cm^{-1}.

δ (60 MHz): 3.35 (1H, m, 1α-H), 1.15 (12H, s, 4aβ-CH_3 and -OBu^t).

M.s. Found: M^+, 238.1927 (24%)

$C_{15}H_{26}O_2$ requires M, 238.1933.

2.4.2.

2,7-Dimethoxynaphthalene (54)

To a cooled (0°C) mechanically stirred solution of 2,7-dihydroxynaphthalene (28 g, 0.18 mol) in water (200 ml) containing sodium hydroxide (16.8 g, 0.42 mol) was added dimethyl sulphate (50 ml, 0.53 mol) over 0.5 hr. After a further 0.5 hr the solution was heated (60°C) for 1 hr, when a precipitate of product as fawn particles gradually formed.

The cooled reaction mixture was filtered under vacuum, and the solids washed successively with sodium

hydroxide (2 M) and water. The brown solid was recrystallized (from ethanol) to give the product as a fine, fawn coloured solid (21.8 g), m.p. 137-140°C. Further crystallization from the mother liquors gave additional product (3.9 g, total 25.7 g, 78%). This was identical to authentic product from Aldrich Chemical Company (by i.r. and m.p.).

νmax (KBr): 1630, 1620 and 1520 (aromatic ring), 1480, 1400 and 1030 cm^{-1}.

δ(60 MHz): 7.85 (2H, d, $J_{3H,4H}$ and $J_{5H,6H}$ = 10 Hz; 4-H and 5-H), 7.40-7.00 (Total 4H: d, 3-H and 6-H: s, 1-H and 8-H overlapped) 4.00 (6H, s, 2-OMe and 7-OMe).

7-methoxy-1,2,3,4-tetrahydro-2-naphthalenone (31)

To a refluxing solution of dimethoxynaphthalene (54) (21.7 g, 0.12 mol) in dried methanol (240 ml), was added sodium (22 g, 0.96 mol) under an atmosphere of nitrogen. The heating was continued until all the sodium dissolved (approx. 20 mins), when the solution was cooled to ambient temperature.

The mixture was diluted with water (200 ml), followed by the rapid addition of conc. hydrochloric acid (200 ml), and the resultant solution heated on a steam bath (15 min). After cooling, the aqueous mixture was

extracted with ether (3 x 50 ml), and the combined organic extracts washed with water (2 x 20 ml). Treatment of this organic phase with an excess of saturated sodium hydrogen sulphite over 2 hr produced an orange precipitate, which after vacuum filtration and trituration with cold ($0^{o}C$) petroleum spirit-ether (1:1, v/v) afforded the product sodium sulphite complex as colourless crystals (15.7 g, 49%).

νmax(KBr): 3480br (OH), 3040 (Aryl-H stretch), 1615, 1590, and 1510 (aromatic ring), 1170 and 1050 cm^{-1}. .

The sulphite adduct was decomposed to give the product ketone (31) by treating the sodium salt (31a) (4.52 g) in water (45 ml) with aqueous sodium carbonate (1 M) at $0^{o}C$. After 15 min. the product was extracted with ether (3 x 20 ml), and the combined organic extracts washed successively with water (1 x 10 ml), brine (1 x 10 ml), and dried ($MgSO_4$). Evaporation of solvent gave a yellow oil, which after vacuum distillation ($124^{o}C$/1.25 mmHg) afforded a colourless oil (2.17 g, 76%), purple with alcoholic alkali, and identical to authentic sample (Aldrich Chemical Co. Ltd., by i.r.).

νmax (thin film): 1720 (saturated C=O), 1620, 1590 and 1575 (aromatic ring), 1260, 1060 and 1040 cm^{-1}.

δ(60 MHz): 7.45 (1H, d, $J_{6H,5H}$ = 10 Hz; 5-H), 7.2-6.9 (Total 2H: d, 6-H, and 8-H overlapped), 3.95 (3H, s, 7-OMe), 3.83 (2H, brs, 1-H_2), 3.15-2.75 (4H, complex).

CHAPTER THREE

3.2.4

(±)-1β-t-butoxy-7aβ-methyl-6-trimethylsiloxy-3aα,4,7,7a-tetrahydroindan (73a)

To a solution of freshly distilled chlorotrimethyl silane (2.62 g, 24.0 mmol), and anhydrous triethylamine (4.85 g, 48.0 mmol) in dry dimethylformamide (20 ml), was added the trans-hydrindan (29) (4.47 g, 20.0 mmol) in dry dimethylformamide (5 ml). The resulting mixture, from which a pale yellow solid continually precipitated (presumably triethylamine hydrochloride) was stirred under nitrogen at reflux for 48 hr. T.l.c. (petroleum spirit-ethyl acetate 40:1, v/v) indicated product as the major component (Rf: 0.43, $KMnO_4$).

The reaction mixture was cooled (0°C), diluted with diethyl ether (100 ml) and washed with cold (0°C) aqueous sodium bicarbonate (10% w/w, 2 x 20 ml), water (1 x 10 ml), saturated brine (1 x 5 ml), dried, ($MgSO_4$) and concentrated to afford an orange oil, which on chromatography over silica (70-230 mesh) employing

petroleum spirit-ethyl acetate (40:1, v/v) as eluant gave the product as a clear, colourless oil (4.40 g, 74%).

νmax (neat): 1655 ($C=C-OSiMe_3$), 1365, 1250, 1190, 1140, 1065, 905, 890 and 850 cm^{-1}.

δ(80 MHz): 4.85 (1H, m, vinylic proton), 3.50 (1H, m, 1α-H), 1.20 (9H, s, $-OBu^t$), 0.80 (3H, s, 7aβ-CH_3), 0.23 (9H, s, $-OSiMe_3$).

M.s. Found: 296.2188 (13%)

$C_{17}H_{32}O_2Si$ requires 296.2172.

($\pm$)-1β-t-butoxy-8aβ-methyl-6-trimethylsiloxy-1,2,3,4,4a α,5,8,8a-octahydronaphthalene (74a)

To a solution of freshly distilled chlorotrimethyl silane (0.20 g), 1.84 mmol), and anhydrous triethylamine (0.36 g, 3.56 mmol) in dry dimethyl formamide (4 ml), was added the trans-decalone (30) (340 mg, 1.43 mmol) in dry dimethylformamide (3 mls). The resulting mixture, from which a pale yellow solid continually precipitated (presumably triethylamine hydrochloride) was stirred under nitrogen at reflux for 48 hr. T.l.c. (petroleum spirit-ethyl acetate 45:1, v/v) indicated product (Rf: 0.37, $KMnO_4$) plus numerous other components to be present.

The reaction mixture was cooled ($0^{o}C$), diluted with ether (30 ml), and washed with cold ($0^{o}C$) aqueous sodium bicarbonate (2 x 10 ml), water (1 x 5 ml) saturated brine (1 x 5 ml), and dried ($MgSO_4$). Evaporation of solvent gave an orange oil, which on chromatography over silica (70-230 mesh) employing petroleum spirit-ethyl acetate (45:1, v/v) as eluant gave the product as a colourless oil (242 mg, 60%), one spot by t.l.c..

νmax (thin film): 1655 ($C=C-OSiMe_3$), 1250 and 1070 cm^{-1}.

δ(60 MHz): 4.90 (1H, m, vinylic proton), 3.25 (1H, m, 9-H), 1.32 (9H, s, $-OBu^t$), 0.93 (3H, s, 8aβ-CH_3), 0.30 (9H, s, $-OSiMe_3$).

M.s. Found: 310.2346 (15%)
$C_{18}H_{34}O_2Si$ requires 310.2328.

3.3.2

6-methoxy-3-oxo-1,2,3,4-tetrahydro-2-naphthalene-carboxylic acid (85)

To a solution of the 2-tetralone (31) (870 mg, 4.9 mmol) in dried dimethylformamide (20 ml), was added magnesium methyl carbonate (2.3 M, 22 ml, 10.3

equivalents), in dried dimethylformamide (8 ml). The reaction vessel, equipped for distillation, was heated (oil bath at Ca. 120°C) whilst stirring under a moderate nitrogen flow for 5 hr. T.l.c. (petroleum spirit-ethyl acetate 8:1, v/v) indicated starting material plus one other component, whose t.l.c. characteristics were consistent with product (Rf: 0.05).

The reaction mixture was cooled (Ca. -10°C), and carefully poured into precooled (Ca -10°C) hydrochloric acid solution (10% v/v, 10 ml) with vigorous stirring. The resultant precipitate was filtered, washed with water, followed by cold acetone. Unfortunately, washing with acetone also removed the solid, leaving insufficient for unambiguous analysis. A crude ^{1}H n.m.r. spectrum contained peaks consistent with product in the enol form.

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$\underline{\delta}$(60MHz): 7.4-6.7 (4H, m, 5-H, 6-H, 8-H and C=C-OH), 3.85 (3H, s, 8-OMe), 3.60 (2H, d, 4-H_2) 3.0 (2H, d, 1-H_2).

3.3.3

(±)-1β-t-butoxy-6-hydroxymethylene-7aβ-methyl-3aα,4,7,7a-tetrahydro-5(6H)-indanone (87a)

A) Using Sodium hydride as base

Sodium hydride (50% dispersion in oil) (0.43 g, 8.91 mmol) was washed with petrol (3 x 10 ml) under nitrogen. Freshly distilled and dried (over K_2CO_3) ethyl formate (6.5 ml, 80 mmol) was added cautiously, and to this stirred suspension was added indanone (29) (0.50 g, 2.0 mmol) in dimethoxy ethane (5 ml), slowly dropwise, (Ca. 10 mins), followed by absolute ethanol (0.1 ml). After 2 hr t.l.c. (petroleum spirit-ethyl acetate (10:1, v/v) indicated product (Rf: 0.30, UV, orange/red DNP) as the major component, with no starting material (Rf: 0.24, yellow DNP) detected. The reaction mixture (50% w/w. 5 ml) acidified with hydrochloric acid (2 M,Ca. 10 ml) separated and the aqueous layer extracted with diethylether (3 x 10 ml). The combined organic layers were washed successively with water (2 x 10 ml), saturated brine solution (1 x 10 ml), and dried ($MgSO_4$). Evaporation of solvent yielded an orange oil (0.63 g) which on chromatography over silica (40-63 m) with petroleum spirit-ethyl acetate (10:1, v/v), as eluant afforded the product (0.28 g, 50%) as a yellow oil.

νmax (liquid film):1640 and 1590 (α-hydroxymethylene ketone), 1370 1190 and 1070 cm^{-1} (t-butyl ether).

δ(90 MHz): 14.7 (1H, d, $J_{CH,OH}$ = 3 Hz; -OH) 8.60 (1H, d, $J_{CH,OH}$ = 3Hz; -CHOH) 3.52 (1H, dd, 1α-H) 2.60-1.00 (9H, complex), 1.14 (9H, s, $-OBu^t$), 0.70 (3H, s, 7a $-CH_3$).

δ(250 MHz) (C_6D_6): 8.30 (1H, d, $J_{CH,OH}$ = 3 Hz; CHOH), 3.15 (1H, dd, 1α-H), 2.40-1.00 (total 9H; complex), 1.05 (9H, s, $-OBu^t$), 0.60 (3H, s, 7aβ-CH_3).

M.s: Found: M^+,252.1741 (20%)

$C_{15}H_{24}O_3$ requires M, 252.1725.

B) Using sodium methoxide as base

Sodium methoxide (2.16 g, 40 mmol) was freshly prepared by adding super dry methanol (30 ml) to sodium (0.92 g, 40 mmol) under nitrogen. When all the sodium had dissolved (Ca. 0.5 hr) the solvent was removed by distillation under nitrogen until dry. To this was added dry benzene (21 ml), followed after 10 mins. by dry ethyl formate (5 ml, 62 mmol). After 0.5 hr, the stirred mixture was cooled (0^oC), and the indanone (29) (2.04 g, 9.11 mmol) in benzene (30 ml) was added slowly dropwise (Ca. 0.5 hr). After a further 0.5 hr, the mixture was warmed to ambient temperature over 2 hr. T.l.c. (petroleum spirit-ethyl acetate 10:1, v/v)

indicated product (Rf: 0.30, UV, orange DNP) as the major component. The reaction mixture was shaken with cold ($0^{o}C$) sulphuric acid (2 M, 50 ml), separated, and the aqueous layer extracted with benzene (3 x 20 ml). The combined organic extracts were washed successively with water (2 x 20 ml), saturated sodium chloride solution (1 x 20 ml), and dried ($MgSO_4$). Evaporation of solvent, and subjection of the residue to high vacuum (20 mmHg, 2 hr), yielded the product as an orange oil (2.24 g, 98%), sufficiently pure for use in subsequent reactions (by t.l.c.) Chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (10:1, v/v) as eluant gave an analytical sample, identical to that above (t.l.c., ^{1}H n.m.r., i.r.)

3.4.2

1-hydroxymethylene-7-methoxy-1,2,3,4,-tetrahydro-2-naphthalenone (91b)

To freshly prepared sodium methoxide (74 mmol) (from 1.72 g sodium) under dry benzene (45 ml) in an atmosphere of nitrogen was added freshly distilled, dried (over K_2CO_3) ethyl formate (8 ml, 99 mmol) in a thin stream whilst stirring. After 0.5 hr at ambient temperature, a solution of the tetralone (2.97 g, 16.9 mmol) in dry benzene (40 ml) was added gradually (over

15 min.). The mixture was stirred for a further period (1-2 hr), when it darkened to an opaque, black colour. This was left overnight under nitrogen.

A phosphate buffer solution [prepared by adding 45 ml of KH_2PO_4 (0.7 M) to 363 ml of $Na_2HPO_4.7H_2O$, (0.7 M)] was added with ice cooling, and the aqueous layer (Ca.pH 8) extracted with ether (3 x 40 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to give an oil, which after vacuum distillation (130°C/0.2 mmHg) afforded a yellow oil (1.37 g, 40%).

νmax (thin film): 1660 and 1620 (α-hydroxymethylene ketone and aromatic ring), 1515 (aromatic ring) 1270 and 1210 cm^{-1}.

δ(60 MHz): 8.55 (1H, brs, =CH-OH), 7.25 (1H, d, $J_{H6,H5}$ = 10 Hz; 5-H), 7.05-6.15 (3H, m, 6-H, 8-H and CH-OH), 3.83 (3H, s, 7-OMe), 3.1-2.4 (remainder)

^1H n.m.r. gave only an equivocal spectrum, from which the regiochemistry could not be determined.

1-methylanilinomethylene-7-methoxy-1,2,3,4-tetrahydro-2-naphthalenone (92b)

To a solution of the hydroxymethylene compound (1.07 g,

5.2 mmol) in methanol (20 ml) was added N-methylaniline (5.8 ml, 54 mmol) at ambient temperature. After standing for 24 hr, the yellow solution gradually darkened to a deep red colour. Evaporation of solvent gave an orange oil, which resisted attempts at crystallization (using ether, petroleum spirit-ether, methanol-chloroform and methanol). ^{1}H n.m.r. and i.r. spectra of the crude product were ambiguous

3.5.2

Attempted alkylation of the dianion of Ethyl 2-oxocyclohexanecarboxylate (93)

A) Using 1 equivalent of LDPA and 1 equivalent of n-BuLi as base

To a solution of diisopropylamine (2.25 ml, 16.0 mmol) in dry distilled tetrahydrofuran (50 ml) at -78°C was added slowly dropwise n-butyl lithium (1.60 m, 14 ml, 14.9 mmol), followed after 15 min. by dropwise addition of ethyl 2-oxocyclohexanecarboxylate (2.53 g, 14.9 mmol). The solution was allowed to warm to room temperature (over 15 min), then recooled to -78°C, and n-butyl lithium (1.60 M, 14 ml, 14.9 mmol) added slowly dropwise. After 0.5 hr, benzyl chloride (2.02 g, 15.9 mmol) was added, and the solution left stirring for a further 2 hr at ambient temperature.

The reaction mixture was quenched with conc. hydrochloric acid (5 ml), water (50 ml), and the aqueous layer extracted with ether (3 x 30 ml). The combined organic extracts were washed with saturated brine (2 x 20 ml), and dried ($MgSO_4$). Evaporation of solvent gave a white solid after trituration with cold ether, whose ^1H n.m.r. and i.r. spectra were identical to those of trans stilbene. Vacuum distillation (80°C/1.5 mmHg) of the resultant filtrates afforded a colourless oil whose ^1H n.m.r. was consistent with a mixture of 1-chloro-1,2-diphenyl ethane and starting β-keto ester. Further vacuum distillation (120°C/1.5 mmHg) afforded pure 1-chloro-1,2-diphenylethane (i.r identical to authentic sample).

δ (60 MHz): 7.30 (5H, s, 1-phenyl), 7.20 (5H, s, 2-phenyl), 5.05 (1H, dd, 1-H), 2.35 (2H, d, 2-H_2.).

B) Using 1 equivalent of NaH and 1 equivalent of n-BuLi as base

To a suspension of sodium hydride (50% dispersion in oil) (0.95 g, 19.6 mmol) in dry tetrahydrofuran (50 ml) was added dropwise the ethyl carboxylate (93) (3.33 g, 19.6 mmol). The solution was stirred for 3 hours at ambient temperature, then cooled to -78°C and n-butyl lithium (1.06 M, 18.5 ml, 19.6 mmol) added slowly dropwise. After 0.25 hr, benzyl chloride (2.67 g, 21

mmol) was added, and the solution left stirring for a further 2 hr. at ambient temperature.

Work up as above gave a similar mixture of products.

C) Using 2 equivalents of lithium diisopropylamide as base

To a solution of diisopropylamine (5.4 ml, 38.4 mmol) in dry tetrahydrofuran (50 ml) at -78°C was added slowly dropwise n-butyl lithium (1.06 m, 34 ml; 36 mmol), followed after 15 min. by dropwise addition of the ethyl carboxylate (93). The solution was warmed to room temperature, and benzyl chloride (6.45 g, 38.0 mmol) was added, and the solution stirred for a further 2 hr. Work up as above gave a similar mixture of products.

CHAPTER FOUR

4.2.1

1. Vinyltrimethylsilane (111)[89]

To a suspension of magnesium turnings (25.4 g, 1.0 mol) in dry tetrahydrofuran (700 ml), was added a crystal of iodine and vinyl bromide (72 ml, 1.0 mol) in dry tetrahydrofuran (200 ml) slowly, under an atmosphere of nitrogen. After refluxing the mixture of 1 hr, freshly distilled trimethylsilyl chloride (126 ml, 1.0 mol) was

added slowly at reflux (over 45 min) and the mixture refluxed for a further 3 hr.

The solution was filtered, and the clear reaction mixture was stirred and distilled (range 50-60°C collected) through a 12" Vigreux column. The distillate was washed with water (10 x 100 ml) to remove solvent, to give the product as a colourless liquid (60.2 g, 73%).

νmax (thin film): 1650 cm^{-1}.

δ(90 MHz): 6.1-5.6 (3H, m, 1-H and 2-H_2), 0.1 (9H, s, -$SiMe_3$).

1-Bromo-1-trimethylsilyl ethene (112)[89]

Bromine (9 ml, 0.17 mol) was added dropwise (over 0.5 hr) to 1-trimethylsilyl ethene (15.8 g, 0.16 mol) at -78°C. Dry diethylamine (100 ml) was added carefully to the clear red solution, and the mixture refluxed overnight under an atmosphere of nitrogen.

The reaction mixture was diluted with ether (200 ml), and washed with hydrochloric acid (10% v/v, 4 x 20 ml), brine (1 x 20 ml), and dried (sodium sulphate). After removal of solvent by distillation, the mixture was distilled under vacuum (70°C/130 mmHg) and the product

collected as a clear, colourless liquid (3.71 g, 13%).

νmax (thin film): 1600 (C=C), 1250, 920 and 850 cm^{-1}.

δ(60 MHz): 6.1-5.9 (2H, m, vinylic protons), 0.02 (9H, s, $-SiMe_3$).

3-Trimethylsilyl-3-butene-2-ol (113)[89]

To a suspension of magnesium turnings (0.41 g, 16.1 mmol) in dry tetrahydrofuran (10 ml) under a nitrogen atmosphere was added sufficient 1,2-dibromoethane (0.5 ml) to start the solvent refluxing, and 1-bromo-1-trimethylsilyl ethene (112) (2.17 g, 12.1 mmol) was added at a rate to maintain reflux.

The mixture was then refluxed for 2 hr. when acetaldehyde (1.21 g, 27.5 mmol) in dry tetrahydrofuran (5 ml) was added. The solution was refluxed for a further 1 hr. The solvent was removed by distillation, the residue diluted with ether (30 ml), and the undissolved solids removed by filtration. The solid residue was extracted with ether, and the combined organic fractions were washed with hydrochloric acid (2 M, 1 x 20 ml), water (1 x 20 ml), brine (1 x 20 ml), and dried ($MgSO_4$). The solvent was removed by distillation, and the residue distilled under vacuum

(70°C/100 mmHg) to give the product as a clear, yellow oil (1.07 g, 61%).

νmax (thin film): 3450 cm^{-1} (-OH)

δ(60 MHz): 6.05 and 5.60 (2H, m, vinylic protons), 4.65 (1H, m, 2-H), 2.10 (1H, s, -OH), 1.45 (3H, d, $-CH_3$), 0.25 (9H, s, $-OSiMe_3$).

3-Trimethylsilyl-3-butene-2-one (103)[89]

To the allylic alcohol (112) (1.57 g, 10.9 mmol) in acetone (30 ml) at 0°C was added dropwise a standard solution of Jones reagent (3.0 ml) until the reddish chromium (VI) colour persisted. Excess reagent was destroyed with isopropanol to a green end point.

The reaction mixture was diluted with ether (200 ml) and water (100 ml), and the aqueous layer extracted with further ether (3 x 40 ml). The combined organic extracts were washed with brine (2 x 40 ml) dried ($MgSO_4$) and solvent removed by distillation. The residual liquid was distilled under vacuum (55°C/90 mmHg) to give the product as a clear liquid (1.03 g, 67%).

νmax (thin film): 1680 (unsaturated C=O), 1280 and 1260 cm^{-1}.

δ (60 MHz): 6.15 and 5.80 (2H, m, vinylic protons), 1.95 (3H, s, $-COCH_3$) -0.2 (9H, s, $-SiMe_3$).

4.3.1

(±)-1β-t-butoxy-7aβ-methyl-6(3-oxo-2-trimethylsilyl-butyl)-3aα,4,7,7a-tetrahydro-5(6H)-indanone (114)

To a stirred solution of ethereal methyl lithium (1.2 equivalents, 1.90 ml) in dry dimethoxyethane (10 ml) under nitrogen was added slowly dropwise the silyl enol ether (73a) (0.75 g, 2.53 mmol) in dry dimethoxyethane (10 ml). After 1 hr. t.l.c. (petroleum spirit-ethyl acetate 6:1, v/v) indicated that no silyl enol ether remained. The mixture was cooled (-78°C), and α-trimethylsilyl vinyl ketone (0.46 g, 3.24 mmol) in dry dimethoxy ethane (5 ml) was added rapidly. After 10 min the solution was allowed to warm to ambient temperature.

The reaction mixture was diluted with dimethoxyethane (30 ml), washed successively with saturated ammonium chloride (1 x 30 ml), saturated brine (1 x 20 ml) and dried ($MgSO_4$). The residual oil was chromatographed over silica (70-230 mesh) employing petroleum spirit-ethyl acetate (6:1, v/v) as eluant, affording an oil (0.86 g, 93%) which by t.l.c. consisted of three components which proved difficult to separate by

further chromatography.

This mixture was subsequently used without further purification.

νmax (thin film): 1710 (cyclic C=O), 1690 cm^{-1} (acyclic C=O).

δ(60 MHz): 3.40 (1H, m, 1-H), 2.10 (3H, s, CH_3-C=O), 1.12 (9H, s, -OBu^t), 0.70 (3H, s, 7aβ-CH_3), 0.08 (9H, s, -$SiMe_3$).

(±)-1β-t-butoxy-9aβ-methyl-1,2,3,3aα,4,7,8,8aβ,9,9a-decahydro-6-benz[f]indenone (96).

A solution of 5% sodium methoxide and the adduct (114) (0.83 g, 2.27 mmol) in dry methanol (15 ml) was stirred at reflux under nitrogen for 4 hr. T.l.c. (petroleum spirit-ethyl acetate 8:1, v/v) indicated product (Rf: 0.27, UV, orange DNP) together with numerous other components (yellow DNP).

The reaction mixture was diluted with ether (50 ml), cooled in ice and washed successively with cold (0°C) water (2 x 20 ml), and saturated brine (1 x 20 ml). The aqueous washings were back extracted with ether (2 x 20 ml) and the combined organic extracts dried ($MgSO_4$), and concentrated to yield an orange, oily solid.

Chromatography over silica (70-230 mesh) employing petroleum spirit-ethyl acetate (6:1, v/v) as eluant gave the product as an oily, crystalline solid (100 mg, 16%). Further chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (2.5:1, v/v) as eluant afforded the product as a solid, m.p. 85-88°C. This was identical to the tricyclic compound obtained via the formylation sequence (i.r., n.m.r. mixed m.p.).

4.4.1

(±)-2-hydroxymethylene-4-t-butylcyclohexanone (121) [72]

A) Using sodium methoxide as base

Freshly distilled (from P_2O5) and dried (K_2CO_3) ethyl formate (27 ml, 0.33 mol) was added rapidly to freshly prepared sodium methoxide (0.21 mol) (from 4.8 g sodium and excess super dry methanol) under dry benzene (50 ml) in a nitrogen atmosphere at ambient temperature. After 0.5 hr t-butyl cyclohexanone (120) (10.07 g, 65 mmol) in dry benzene (120 ml) was added dropwise (over 1.5 hr) to the ice cooled stirred slurry. After addition the reaction mixture was allowed to warm to ambient temperature over 2 hr, when t.l.c. (petroleum spirit-ehtyl acetate (10:1, v/v) indicated product (Rf: 0.37, UV, orange DNP) only, with no starting material detected (Rf: 0.26, yellow DNP).

The reaction mixture was shaken with cold (0°C) hydrochloric acid (2 M, 200 ml), and the organic layer washed successively with water (2 x 20 ml), saturated brine (1 x 10 ml), and dried ($MgSO_4$). Evaporation of solvent gave a clear, orange-tinted oil which crystallized on cooling over 12 hr, to afford a crystalline solid (11.44 g, 96%), m.p. 37-42°C. after subjection to high vacuum.

An analytical sample from chromatography over silica (40-63 μM) employing petroleum spirit-ethyl acetate (10:1, v/v) gave a crystalline solid, m.p. 40-43°C.

νmax (nujol): 1640 and 1590 (α-hydroxymethylene ketone), 1350 and 1230 cm^{-1}.

δ (90 MHz): 14.4 (1H, brs, =CH-OH), 8.60 (1H, brs, =CHOH), 2.6-1.0 (7H, complex), 0.90 (3H, s, Bu^t).

M.s. Found: M^+, 182.1316 (20%); $(M-C_4H_9)^+$, 125.0600.

$C_{11}H_{18}O_2$ requires M, 182.1307; $(M-C_4H_9)$, 125.0603.

B) Using NaH as base.

Sodium hydride (8.8 g, 0.18 mol) as 50% dispersion in oil), was washed with petrol (3 x 10 ml) under nitrogen. Freshly distilled dried (over K_2CO_3) ethyl formate

(140 ml, 1.72 mol) was added cautiously whilst stirring to form a slurry. The t-butyl cyclohexanone (7.37 g, 48 mmol) in dried dimethoxy ethane (90 ml) was added slowly dropwise (Ca. 0.5 hr), to form a yellow slurry. Absolute ethanol (0.9 ml, 16 mmol) was added, and the mixture stirred at ambient temperature for a further 5 hr. T.l.c. (petroleum spirit-ethyl acetate 10:1, v/v) indicated product (Rf: 0.37, UV, orange DNP) with no starting material detected (Rf: 0.26, yellow DNP), but with minor impurities present.

The reaction mixture was poured into saturated ammonium chloride solution (50% w/w 100 ml), acidified with hydrochloric acid (2 M, Ca. 150 ml), the layers separated and the aqueous layer extracted with ether (3 x 50 ml). The combined organic extracts were washed successively with water (2 x 20 ml), saturated brine (1 x 20 ml), dried ($MgSO_4$) and solvent evaporated to give an orange oil. Chromatography over silica (40-63 μM), employing petroleum spirit-ethyl acetate (10:1, v/v) as eluant gave the product as a viscous orange oil (5.85 g, 56%), one spot by t.l.c., identical to the above (by t.l.c. i.r. and ^1H n.m.r. spectroscopy).

(±)-5-t-butyl-1-(3-oxobutyl)-2-oxocyclohexanecarbaldehyde (122)

Freshly distilled and dried (over K_2CO_3) methyl vinyl

ketone (4.86 g, 69 mmol), was added to the hydroxymethylene ketone (121) (8.71 g, 48 mmol) under nitrogen. Freshly distilled triethylamine (Ca. 0.1 ml) was added dropwise to the stirred solution, followed at hourly intervals by further portions of base (Ca. 0.1 ml). After a total of 3 hr, t.l.c. (petroleum spirit-ethyl acetate 2:1, v/v) indicated product (Rf: 0.31, yellow DNP), with an impurity (Rf: 0.40, orange DNP), and no starting material detected (Rf: 0.53, UV, orange DNP).

The reaction mixture was diluted with ether (20 ml), and washed successively with hydrochloric acid (2 M, 2 x 5 ml), water (1 x 3 ml), saturated brine (1 x 3 ml), and dried ($MgSO_4$). Evaporation of solvent gave an orange oil, which after chromatography over silica (40-63 μM) employing petroleum spirit-ethyl acetate (2:1, v/v) as eluant, afforded a clear yellow oil (7.89 g, 65%), one spot pure by t.l.c.

νmax (thin film): 2720 (CHO-C-H stretch), 1720 to 1700 br.(HC=O, Cyclic C=O and acyclic C=O overlapped), 1370 and 1170 cm^{-1}.

δ (90 MHz): 9.70 and 9.45 (1H, 2 x s in 7:1 ratio respectively, CHO of 2 isomers).2.10 (3H, s, $COCH_3$), 0.92 (9H, s, $-OBu^t$).

M.s. Found: M^+, 252.1725 (0.27%).

$C_{15}H_{24}O_3$ requires M, 252.1725.

Reaction of the α-hydroxymethylene ketone (121) with methyl vinyl ketone employing potassium hydroxide as a base

To a stirred solution of the α-hydroxymethylene ketone (121) (0.31 g, 1.7 mmol) in freshly distilled and dried (over K_2CO_3) methyl vinyl ketone (0.17 g, 2.5 mmol) was added a solution of potassium hydroxide (0.83 mg) in absolute ethanol (0.8 ml). After 24 hr the homogenous solution had precipitated a paste. T.l.c. (petroleum spirit-ethyl acetate 2:1, v/v) indicated two main components (Rf: 0.33 and 0.30), with no starting material detected. The solid was filtered and washed with ice cold ether, to give a colourless solid, m.p. 87-90°C. i.r. and ^1H n.m.r. indicated that this was not the desired product (37).

ν max (nujol): 3400, 1140, 1000cm^{-1} carbonyl absorption absent.

(±)-6-t-butyl-2,3,4,4aβ,5,6β,7,8-octahydro-2-naphthalenone (123)

To a solution of the adduct (122) (1.02 g, 4.0 mmol) in ethanol (9 ml), was added a solution of potassium hydroxide (1% w/w in methanol-water 1:1, 64 ml). The

homogenous yellow solution was stirred under nitrogen for 5 hr at ambient temperature, when a small amount of precipitate was apparent. T.l.c. (petroleum spirit-ethyl acetate 2.5:1, v/v) indicated the presence of product (Rf: 0.34, UV, orange DNP), and two other major components (Rf: 0.24 and 0.1, yellow DNP)

The reaction mixture was extracted with dichloromethane (7 x 40 ml), the combined organic extracts washed successively with water (2 x 20 ml) and saturated brine (1 x 20 ml). The combined organic extracts were dried ($MgSO_4$), and the solvent evaporated to give a yellow oil (0.84 g). Chromatography over silica (40-63 μM) with petroleum spirit-ethyl acetate (2.5:1, v/v) as eluant gave the product as a yellow oil (0.36 g, 43%).

νmax (thin film): 1670 (conjugated C=O), 1620 (conjugated C=C), 1360 and 1260 cm^{-1}

δ(90 MHz): 5.80 (1H, brs, vinylic proton), 2.60-0.70 (remainder), 0.88 (9H, s, $-Bu^t$).

Microanalysis Found: C, 81.6; H, 10.86%

$C_{14}H_{22}O$ requires C, 81.55; H, 10.68%

M.s. Found: M^+, 206.1672 (35%); $(M-CH_3)^+$, 191.1433; $(M-C_2H_4)^+$, 178.1356.
$C_{14}H_{22}O$ requires M, 206.1671; $(M-CH_3)$, 191.1436; $(M-C_2H_4)$, 178.1358.

Further elution gave a colourless solid (0.10 g), m.p. 164-169°C, one spot pure by t.l.c. (Rf: 0.24). The spectral data was consistent with the hydroxy ketone intermediate (124).

νmax (nujol): 3360br(-OH), 1705 (cyclic saturated C=O) cm^{-1}.

δ(90 MHz) 2.35-0.9 (15H, complex), 0.85 (9H, s, $-Bu^t$)

M.s. Found: M^+, 224.1766 (100%); $(M-CH_3)^+$, 209.1530; $(M-H_2O-CH_3)^+$, 191.1426.
$C_{14}H_{24}O_2$ requires M, 224.1776; $(M-CH_3)$, 209.1541; $(M-H_2O-CH_3)$, 191.1435.

Finally continued elution gave a second hydroxy ketone (125) as a colourless solid, (56 mg), m.p. 105-109°C, one spot pure by t.l.c. (Rf: 0.1).

νmax (nujol) 3440br(-OH), 1705 (saturated C=O), 1380, 1370 and 1000 cm^{-1}.

δ (90 MHz) 2.60-0.90 (15H, complex), 0.85 (9H, s -Bu^t).

M.s. Found: M^+, 224.1766 (100%)

$C_{14}H_{24}O_2$ requires M,224.1776.

This spectrum was similar to that above.

4.4.2

(±)-1β-t-butoxy-7aβ-methyl-5-oxo-6-(3-oxobutyl)-3aα,4,5,6,7,7a-hexahydro-6-indancarbaldehyde (126)

Freshly distilled methyl vinyl ketone (0.95 g, 13.6 mmol) was added to the β-keto aldehyde (87a) (1.79 g, 7.10 mmol) under nitrogen. To this stirred homogenous solution was added distilled triethylamine (0.3 ml) dropwise, followed after 1.5 hr by a further portion of amine (0.2 ml). After 3.5 hr, t.l.c. (petroleum spirit-ethyl acetate 2:1, v/v) indicated product (Rf: 0.31, yellow DNP) as the major component, with a minor impurity present whose t.l.c. characteristics were consistent with starting material (Rf: 0.51, UV, orange DNP). The solution was diluted with dichloromethane, and the volatile liquids evaporated to leave an orange oily residue. Chromatography over silica (40-63 μm) with petroleum spirit-ethyl acetate (2:1, v/v) as eluant afforded the product (1.78 g, 78%) as an oily colourless solid, homogenous by t.l.c.

νmax (nujol): 1715, 1710 and 1700 cm^{-1} (CHO, cyclic and acyclic C=O).

δ(250 MHz): 9.48 (1H, s, CHO), 3.40 (1H, dd, 1α-H), 2.13 (3H, s, $COCH_3$), 1.15 (9H, s, $-OBu^t$), 0.75 (3H, s, 7aβ-CH_3).

M.s. [C.I.M.S.] Found: $(M+H)^+$, 323.2247 (10%).
$C_{19}H_{30}O_4$ requires (M+H) 323.2222.

(±)-1β-t-butoxy-9aβ-methyl-1,2,3,3aα,4,7,8,8aβ,9,9a-decahydro-6-benz[f]indenone (96)

To a solution of the adduct (126); (5.74 g, 17.8 mmol) in ethanol (37 ml), was added a solution of potassium hydroxide (1% w/w) in methanol-water (1:1, v/v, 290 ml). The homogenous yellow solution was stirred under nitrogen for 5 hr at ambient temperature. T.l.c. (petroleum spirit-ethyl acetate 2.5:1, v/v) indicated product as the major component (Rf: 0.42, UV active, orange DNP), with minor impurities (Rf: 0.56, yellow DNP; 0.26, yellow DNP). The reaction mixture was extracted with dichloromethane (7 x 60 ml) and the combined organic extracts were washed with water (2 x 20 ml) and saturated sodium chloride solution (1 x 20 ml). The combined organic extracts were dried ($MgSO_4$), and the solvent evaporated to leave an orange oily residue (4.50 g).

Chromatography over silica (40-63 μm) with petroleum spirit-ethyl acetate (2.5:1, v/v) as eluant gave the product as a colourless solid (3.18 g, 65%), m.p. 76-82°C. An analytical sample (from light petroleum spirit) gave colourless crystals, m.p. 88-88.5°C.

νmax (nujol): 1668 and 1610 (cyclic $\alpha\beta$-unsaturated C=O), 1060 cm^{-1}.

δ (90 MHz): 5.85 (1H, brs, vinylic proton), 3.40 (1H, dd, 1α-H), 1.10 (9H, s, $-OBu^t$), 0.85 (3H, s, 9aβ-CH_3).

Microanalysis Found: C,78.06; H,10.47%.
$C_{18}H_{28}O_2$ requires C,78.21; H,10.21%.

M.s. [C.I.M.S.] Found: $(M+H)^+$, 277.2163 (100%)
$(M+H-C_4H_8)^+$, 221.1532; $(M+H-HO-CMe_3)^+$, 203.1436.
$C_{18}H_{28}O_2$ requires (M+H), 277.2167;
$(M+H-C_4H_8)$, 221.1541; $(M+H-HO-CMe_3)$, 203.1436.

CHAPTER FIVE

5.2.1

($\pm$)-6α-t-butyl-1,2,3,4,4aβ,5,6,7,8,8aα-decahydro-2-naphthalenone (127)

To a solution of refluxing dry ammonia (50 ml) and

lithium (107 mg, 15.6 mmol) was added slowly dropwise (Ca 10 min) a solution of the enone (123) (1.008 g, 4.9 mmol) in dry (over 4A molecular sieves for 24 hr) ether (30 ml), containing dried t-butanol (288 mg, 3.8 mmol). The solution was stirred for a further 15 min when t.l.c. (petroleum spirit-ethyl acetate 5:1, v/v) indicated predominantly product (Rf: 0.35, yellow DNP), with minor impurities (Rf: 0.1, blue by M.P.A.).

Excess saturated ammonium chloride solution was added cautiously, the mixture heated (40°C) under a vigorous nitrogen flow to expel ammonia, and the product extracted with ether (3 x 20 ml). The combined extracts were washed successively with water (2 x 20 ml), brine (1 x 20 ml), dried ($MgSO_4$) and solvent evaporated to yield a paste. Chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (5:1, v/v) as eluant gave the product as an off-white powdery solid (807 mg, 79%), m.p. 53-55°C.

νmax (nujol): 1720 (unsaturated C=O), 1380 and 1370 cm^{-1}.

δ (90 MHz): 2.40-1.00 (complex), 0.90 (9H, s, $-Bu^t$).

Microanalysis: Found: C,80.45; H,11.42%.

$C_{14}H_{24}O$ requires C,80.71; H,11.61%.

M.s. Found: M^+, 208.1834 (60%).

$C_{14}H_{24}O$ requires M, 208.1827.

(±)-6α-t-butyl-3-hydroxymethylene-1,2,3,4,4aβ,5,6,7,8,8aα-decahydro-2-naphthalenone (128)

To freshly prepared sodium methoxide (10.4 mmol) (from 0.24 g sodium with excess super dry methanol), under dry benzene (6 ml) in a nitrogen atmosphere, was added freshly distilled (from P_2O_5) and dried (over K_2CO_3) ethyl formate (1.4 ml, 17.1 mmol) at ambient temperature. After 0.5 hr the decalone (127) (504 mg, 2.4 mmol) in dry benzene (10 ml) was added dropwise (over 15 min) to the ice cooled stirred slurry. After addition the reaction mixture was allowed to warm to ambient temperature over 2 hr, when t.l.c. (petroleum spirit-ethyl acetate 10:1, v/v) indicated product (Rf: 0.39, UV, orange DNP) as the major component, with no starting material detected.

The reaction mixture was shaken with cold (0°C) hydrochloric acid (2 M, 10 ml), and the organic layer washed successively with water (2 x 5 ml), saturated brine (1 x 5 ml), and dried ($MgSO_4$). Evaporation of solvent gave an orange oil, which on chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (10:1, v/v) as eluant afforded the product (128) as an oily crystalline orange solid (490 mg,

86%), one spot by t.l.c.

νmax (nujol): 1640 and 1590 (α-hydroxymethylene ketone), 1360 and 1230 cm^{-1}.

δ (90 MHz): 14.50 (1H, d, $J_{\underline{CH},OH}$ = 3 Hz; -OH), 8.65 (1H, d, $J_{CH,\underline{OH}}$ = 3 Hz; C$\underline{H}$OH), 2.6-0.7 (complex), 0.85 (9H, s, $-Bu^t$).

M.s. Found: M^+, 236.1775 (26%)

$C_{15}H_{24}O_2$ requires 236.1775.

(±)-7α-t-butyl-3-oxo-2-(3-oxobutyl)-1,2,3,4,4aα,5,6,7,8,8aβ-decahydro-2-naphthalenecarbaldehyde (129)

Freshly distilled and dried (over K_2CO_3) methyl vinyl ketone (0.24 g, 3.4 mmol) was added to the β-keto aldehyde (128) (386 mg, 1.6 mmol) under nitrogen. Distilled triethylamine (0.2 ml) was added dropwise, followed after 2 hr by a further portion of amine (0.1 ml). After a total of 3 hr t.l.c. (petroleum spirit-ethyl acetate 2:1, v/v) indicated product (Rf: 0.30, yellow DNP) plus other impurities.

The reaction mixture was diluted with ether (20 ml), and washed successively with hydrochloric acid (2 M 2 x 5 ml), water (1 x 3 ml) saturated brine (1 x 3 ml) and dried ($MgSO_4$). Evaporation of solvent gave an orange

oil, which after chromatography over silica (40-63 μM) employing petroleum spirit-ethyl acetate (2:1, v/v) as eluant gave a clear yellow oil, (414 mg, 83%), one spot by t.l.c..

νmax (liquid film): 2750 (CHO, C-H stretch), 1720 br to 1700 (HC=O, cyclic C=O and acyclic C=O overlapped), 1370 and 1170 cm^{-1}.

δ(90 MHz): 9.67 and 9.45 (1H, 2 x s in 7:1 ratio respectively, CHO of 2 isomers), 2.10 (3H, s, $COCH_3$),. 0.92 (9H, s, $-Bu^t$).

M.s. Found: M^+, 306.4294.
$C_{19}H_{30}O_3$ requires M,306.4291.

(±)-7α-t-butyl-2,3,4,4aβ,5,5aβ,6,7,8,9,9aβ,10-dodecahydro-2-anthracenone (130).

To a solution of the adduct (129) (415 mg, 1.36 mmol) in ethanol (3 ml), was added a solution of potassium hydroxide (2% w/w in methanol-water, 1:1 v/v, 22 ml) and the mixture stirred under nitrogen, at ambient temperature. After 1 hr an extensive precipitate of colourless solid had formed from the pale yellow solution, which persisted throughout the course of the reaction. After 5 hr t.l.c. (petroleum spirit-ethyl acetate (2.5:1, v/v) indicated the presence of product

(Rf: 0.35, UV, orange DNP) and two other major components (Rf: 0.24 and 0.1, yellow DNP).

The reaction mixture was extracted with dichloromethane (4 x 10 ml), the combined organic extracts washed successively with water (2 x 5 ml), and saturated brine (1 x 5 ml). The organic phase was dried ($MgSO_4$), and the solvent evaporated to give a white solid (322 mg). Chromatography over silica (40-63 μm) with petroleum spirit-ethyl acetate (2.5:1, v/v) as eluant gave the product as a yellow tinted solid (61 mg, 17%), m.p. 86-88.5°C.

νmax (nujol): 1665 (conjugated C=O), 1625cm^{-1} (conjugated C=C).

δ (90 MHz): 5.80 (1H, brs, vinylic proton) 2.6-0.7 (complex), 0.80 (9H, s, $-Bu^t$).

Microanlysis Found: C,81.52; H,10.83%.
$C_{18}H_{28}O$ requires C,83.02; H,10.84% (best available).

M.s. Found: M^+, 260.2147 (78%); $(M-C_2H_4)^+$, 232.1822.
$C_{18}H_{28}O$ requires M, 260.2147; $(M-C_2H_4)$, 232.1827.

Further elution gave the hydroxy ketone (131) (149 mg) as a white solid, m.p. 201-202°C, one spot pure by

t.l.c. (Rf: 0.24).

νmax (nujol): 3370 br (-OH), 1705 cm^{-1} (unsaturated C=O).

δ(90 MHz): 2.4-0.7 (complex), 0.85 (9H, s, $-Bu^t$).

M.s. Found: M^+, 278.2272 (65%).
$C_{18}H_{30}O_2$ requires M, 278.2246. The spectra was similar to that of the hydroxy ketone (132) below.

Finally, continued elution afforded the hydroxy ketone (132) (108 mg) as a colourless solid, m.p. 291.5-293.5°C. This was one spot pure by t.l.c. (Rf: 0.1).

νmax (nujol): 3440 br (OH), 1705 cm^{-1} (saturated C=O).

δ(90 MHz): 2.65-0.7 (complex), 0.85 (9H, s, $-Bu^t$).

M.s. Found: M^+, 278.2257 (65%); $(M-H_2O)^+$, 260.2144;
$C_{18}H_{30}O_2$ requires M, 278.2247; $(M-H_2O)$, 260.2140;

Dehydration of the keto-alcohol (131) to the enone (130)

A stirred suspension of the hydroxy ketone (131) (47 mg) in dry benzene (30 ml), containing

p-toluenesulphonic acid (catalytic) was azeotropically refluxed under nitrogen using a water jacket-cooled Dean-Stark water separator. After 1.5 hr t.l.c. (petroleum spirit-ethyl acetate 2.5:1, v/v) indicated the enone (130) with minor impurities.

The cooled, clear reaction mixture was washed with sodium bicarbonate (15% w/w; 2 x 5 ml), water (2 x 5 ml), saturated brine (1 x 5 ml) and dried ($MgSO_4$). Evaporation of solvent yielded a solid, which after chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (2.5:1, v/v) as eluant afforded a crystalline solid (32 mg, 64%) identical to the enone (130) (by i.r., mixed m.p., t.l.c.).

Dehydration of the keto-alcohol (132)

A stirred suspension of the hydroxy ketone (132) (42 mg) in dry benzene (30 ml), containing para-toluenesulphonic acid (catalytic) was azeotropically refluxed under nitrogen . After 1.5 hr t.l.c. (petroleum spirit-ethyl acetate 2.5:1, v/v) indicated an enone (Rf: 0.30, UV, orange DNP) which was not identical to the enone (130) (Rf: 0.35).
The reaction mixture was discarded.

5.2.2

(±)-1β-t-butoxy-9aβ-methyl-1,2,3,3aα,4,4aα,5,7,8,8aβ,9,9a-dodecahydro-6-benz[f]indenone (134)

To a solution of refluxing dry ammonia (60 ml) and lithium (70 mg, 10 mmol) was added slowly dropwise (Ca 10 min) a solution of the enone (96) (0.89 g, 3.22 mmol), in dry ether (30 ml), containing dried t-butanol (200 mg, 2.70 mmol). The solution was stirred for a further 10 min; t.l.c. (petroleum spirit-ethyl acetate 5:1, v/v) indicated predominantly product (Rf: 0.45, yellow DNP), with minor impurities (Rf: 0.25, UV, orange DNP, 0.18, blue by MPA). Excess saturated ammonium chloride solution was added cautiously, the mixture heated (30-40°C) under a vigorous nitrogen flow to expel ammonia, and the product extracted with ether (3 x 20 ml). The combined extracts were washed successively with water (2 x 20 ml), saturated sodium chloride solution (1 x 20 ml) dried ($MgSO_4$) and evaporated to afford an orange oil (840 mg). Chromatography over silica (40-63 μm) using petroleum spirit-ethyl acetate (5:1, v/v) as eluant gave the product as a colourless oil (540 mg, 60%), which solidified over 0.5 hr at ambient temperature. An analytical sample (from light petroleum spirit) afforded a colourless crystalline solid, m.p. 64-65°C.

νmax (nujol): 1725 (cyclic C=O), 1375, 1200 and 1070 cm^{-1}

δ (60 MHz): 3.30 (1H, dd, 1α -H), 2.60-1.00 (17H, complex), 1.10 (9H, s, $-Obu^t$), 0.75 (3H, s, 9aβ-CH_3).

Microanalysis Found: C, 77.15; H, 10.97%.

$C_{18}H_{30}O_2$ requires C, 77.65; H, 10.86%.

(±)-1β-t-butoxy-7-hydroxymethylene-9aβ-methyl-1,2,3, 3aα,4,4aα,5,7,8,8aβ,9,9a-dodecahydro-6-benz[f]indenone (135a)

Sodium methoxide (1.46 g, 27.0 mmol), was freshly prepared by adding super dry methanol (20 ml) to sodium (0.62 g, 27.0 mmol) under nitrogen. When all the sodium had dissolved (Ca. 0.5 hr) the solvent was removed by distillation under a vigorous nitrogen flow until dry. To this was added dry benzene (15 ml), followed after 10 min. by dry ethyl formate (3.5 ml), 43.4 mmol). After 0.5 hr the stirred suspension was cooled (0°C), and the saturated ketone (134) (1.32 g, 4.31 mmol) in benzene (20 ml) was added slowly dropwise (0.5 hr), to form an orange solution. After a further 0.5 hr, the mixture was warmed to ambient temperature (over 1.25 hr). T.l.c. (petroleum spirit-ethyl acetate 10:1, v/v) indicated product (Rf: 0.32, UV, orange DNP) only.

The reaction mixture was shaken with cold ($0^{o}C$) dil. sulphuric acid (40 ml) (Ca. 5 min), separated, and the aqueous layer extracted with benzene (3 x 20 ml). The combined organic extracts were washed successively with water (2 x 20 ml), saturated sodium chloride solution (1 x 10 ml) and dried ($MgSO_4$). Evaporation of solvent, and subjection of the residue to high vacuum (20 mmHg, 1 hr) yielded the product as an orange oil (1.97 g, 93%). An analytical sample was prepared by chromatography over silica (40-63 μm) with petroleum spirit-ethyl acetate (10:1, v/v) as eluant, to afford an orange oil, homogenous by t.l.c.

νmax (liquid film): 1640 and 1590 (α-hydroxymethylene ketone), 1370 1190 and 1070 cm^{-1}.

δ(60 MHz): 14.3 (1H, brs, -OH), 8.55 (1H, brs, CHOH), 3.35 (1H, m, 1α-H), 1.10 (9H, s, $-OBu^{t}$), 0.70 (3H, s, 9aβ-CH_3).

M.s. Found: M^{+}, 306.2180.
$C_{19}H_{30}O_3$ requires M, 306.2195.

(±)-1β-t-butoxy-9aβ-methyl-6-oxo-7-(3-oxobutyl)-2,3,3aα,4,4aα,5,6,7,8,8aβ,9,9a-dodecahydro-7(H)-benz[f]-indenecarbaldehyde (136)

Freshly distilled methyl vinyl ketone (990 mg, 142

mmol) was added to the hydroxymethylene ketone (135a) (1.88 g, 6.14 mmol) under nitrogen. To this stirred homogenous solution was added triethylamine (0.3 ml), dropwise, followed after 2 hr. by a further portion of amine (0.2 ml). After 4 hr, t.l.c. (petroleum spirit-ethyl acetate 2:1, v/v) indicated product (Rf: 0.37, yellow DNP) as the major component, together with 4 minor impurities (Rf: 0.56, 0.49, 0.24 and 0.01).

The solution was diluted with dichloromethane, and the volatile component liquid evaporated under vacuum to leave an orange oil (2.30 g). Chromatography over silica (40-63 μm) afforded the product (1.81 g, 79%) as a yellow foam after subjection to high vacuum (20 mmHg,2 hr).

νmax (nujol): 1720 br, 1700 (CHO, cyclic C=O and acyclic C=O), 1385, 1195 and 1065 cm^{-1}.

δ (60 MHz): 9.40 (1H, s, CHO), 3.30 (1H, dd, 1α-H), 2.10 (3H, s, $COCH_3$), 1.10 (9H, s, $-OBu^t$), 0.80 (3H, s, 9aβ-CH_3).

M.s. Found: M^+, 376.2600 (0.06%).

$C_{23}H_{36}O_4$ requires M, 376.2613.

(±)-1β-t-butoxy-11aβ-methyl-1,2,3,3aα,4,4aα,5,8,9,9aβ,10,10aβ,11,11a-tetradecahydro-7-cyclopent[b]anthracenone (137)

To a solution of the adduct (136) (1.76 g), 4.68) mmol) in ethanol (10 ml) under nitrogen was added a solution of potassium hydroxide (2% w/w in 1:1, v/v, methanol-water 80 ml). An immediate white precipitate was formed, which persisted throughout the course of the reaction. The heterogenous yellow solution was stirred for 7.5 hr at ambient temperature, t.l.c. (petroleum spirit-ethyl acetate 2.5:1, v/v) indicated product (Rf: 0.40, UV, orange DNP) together with two other major components (Rf: 0.24, yellow then orange with DNP, blue by MPA; 0.10 yellow DNP, blue by MPA).

The reaction mixture was extracted with dichloromethane (7 x 30 ml) and the combined organic extracts washed with saturated sodium chloride solution (2 x 20 ml).

The combined organic extracts were dried ($MgSO_4$) and evaporated to leave an orange oily residue (1.53 g). Chromatography over silica (40-63 μm) with petroleum spirit-ethyl acetate (2.5:1, v/v) as eluant afforded the product as a colourless solid (0.31 g, 20%). An analytical sample (from petroleum spirit 40/60) gave colourless crystals, m.p. 123-124.5°C.

νmax(KBr): 1680 and 1625 (unsaturated cyclic C=O), 1370, 1200 and 1065 cm^{-1}.

δ(80 MHz): 5.82 (1H, brs, vinylic proton), 3.37.(1H, dd, 1α-H), 1.15 (9H, s, $-OBu^t$), 0.78 (3H, s, 11aβ-CH_3).

M.s. Found: M^+, 330.2573 (2%).
$C_{22}H_{34}O_2$ requires M, 330.2588.

Further elution afforded 0.64 g of the hydroxy ketone (138), (Rf: 0.24), as a solid. An analytical sample (from methanol) gave colourless crystals,m.p.214-216°C.

νmax(KBr): 3450 (OH), 1710 (cyclic C=O), 1370, 1195 and 1060 cm^{-1}.

δ(80 MHz): 3.39 (1H, dd, 1α-H), 1.15 (9H, s, $-OBu^t$), 0.75 (3H, s, 11aβ-CH_3).

M.s. Found: M^+, 348.2670 (0.5%).
$C_{22}H_{36}O_3$ requires 348.2676.

Dehydration of the hydroxy ketone (138) to the enone (137)

A stirred suspension of the hydroxy ketone (570 mg, 1.64 mmol) in dry benzene (50 ml) with para-toluene sulphonic acid (catalytic) was azeotropically refluxed

under nitrogen using a water jacket-cooled Dean-Stark water separator. After 1.5 hr t.l.c. (petroleum spirit-ethyl acetate 2.5:1, v/v) indicated product with minor impurities.

The cooled, clear reaction mixture was washed with sodium bicarbonate (15% w/w, 2 x 10 ml), water (1 x 10 ml), saturated brine (1 x 10 ml), and dried ($MgSO_4$). Evaporation of solvent yielded 0.61g of an oily solid, which on chromatography over silica (40-63 μm) with petroleum spirit-ethyl acetate (2.5:1, v/v) as eluant afforded the enone (137) as a crystalline solid (310 mg, 57%). An analytical sample (from petroleum spirit 40/60) was identical (mixed m.p., i.r., n.m.r.) with authentic sample.

(±)-1β-hydroxy-11aβ-methyl-1,2,3,3aα,4,4aα,5,8,9,9aβ,10,10aβ,11,11a-tetradecahydro-7-cyclopent[b]anthracenone (26)

A) Deprotection of the t-butyl ether (137) using trifluoroacetic acid.

A solution of the tetracyclic ether (137) (100 mg, 030 mmol) in trifluoroacetic acid (6 ml) was stirred at ambient temperature overnight under nitrogen. T.l.c. (petroleum spirit-ethyl acetate 2:1, v/v) indicated one component only.

The dark brown reaction mixture was diluted with ether (20 ml) and washed successively with sodium hydroxide (2 M, 4 x 20 ml), until alkaline. The organic layer was shaken vigorously (10 min) with methanol-sodium hydroxide (2 M, 1:1, v/v, 24 ml), the layers separated, the aqueous layer extracted with ether (3 x 10 ml), and the combined organic extracts washed with brine (2 x 10 ml), dried ($MgSO_4$), and concentrated to yield a yellow paste (75 mg). T.l.c. indicated product as the major component (Rf: 0.45, UV, $KMnO_4$). Chromatography over silica (40-63 μm) with petroleum spirit-ethyl acetate (1:3,v/v) as eluant realised the product (61 mg, 73%) as a white solid, m.p. 168-171°C.

νmax(KBr): 3550 (OH), 1665 (conjugated C=O), 1620 (conjugated C=C), 1330, 1255 and 1205 cm^{-1}.

δ(80 MHz): 5.81 (1H, s, vinylic proton), 3.70 (1H, dd, 1α-H), 0.80 (3H, s, 11aβ-CH_3).

Microanalysis: Found: C,78.10; H,9.67%

$C_{18}H_{26}O_2$ requires C,78.79;H,9.55% (best available).

M.s. Found: M^+, 274.1950

$C_{18}H_{26}O_2$ requires M, 274.1933.

B) Deprotection of the t-butyl ether using hydrochloric acid

To a stirred solution of the butyl ether (137) (46 mg, 0.14 mmol), in ethanol (1.0 ml) was added hydrochloric acid (2 M) (1.0 ml) and the solution heated at 80°C under nitrogen for 2.5 hr. T.l.c. (petroleum spirit-ethyl acetate 1:4, v/v), indicated product (Rf: 0.31, UV, $KMnO_4$) and other components.

The reaction mixture was cooled to ambient temperature and diluted with ether (20 ml) and water (15 ml). The aqueous phase was extracted with ether (3 x 10 ml), and the combined organic extracts washed successively with water (3 x 5 ml), saturated brine (1 x 5 ml), and dried ($MgSO_4$). Evaporation of solvent gave an oil which on chromatography over silica (40-63 μm) using petroleum spirit-ethyl acetate (1:2, v/v) as eluant gave the product as a clear colourless oil (18 mg, 47%), which crystallized on treatment with ice cold ether to a white solid, m.p. 164-168°C. This was identical with the authentic material (mixed m.p., i.r.).

(±)-1β-hydroxy-9aβ-methyl-1,2,3,3aα,4,7,8,8aβ,9,9a-decahydro-6-benz[f]indenone (139)

A) Using trifluoroacetic acid

A solution of the t-butyl ether (96) (48 mg, 0.17 mmol) in trifluoroacetic acid (3 ml) was stirred at ambient

temperature overnight in a nitrogen atmosphere. T.l.c. (petroleum spirit-ethyl acetate 2:1, v/v) indicated one component only.

The dark brown reaction mixture was diluted with ether (101), and washed successively with sodium hydroxide (2 M, 3 x 10 ml), until alkaline. The organic layer was shaken vigorously (10 min) with methanol-sodium hydroxide (2 M, 1:1, 12 ml), the layers separated, the aqueous layer extracted with ether (4 x 5 ml), and the combined organic extracts washed with saturated brine (2 x 5 ml). The organic layer was dried ($MgSO_4$) and concentrated to yield a white powdery solid (31 mg), m.p. 141-150°C, which on chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (1:4, v/v) as eluant afforded the product alcohol (139) as a white solid (27 mg, 74%, m.p. 151-153.5°C.

νmax(KBr): 3450 (OH), 1650 (conjugated C=O), 1620 (conjugated C=C), 1370, 1330, 1260 and 1050 cm^{-1}.

δ(60 MHz): 5.85 (1H, brs, vinylic proton), 3.75 (1H, t, 1α-H), 2.5-0.8 (15H, complex), 0.90 (3H, S, 9aβ-CH3)

Microanalysis: Found: C, 74.66; H,9.04%.

$C_{14}H_{20}O_2$ requires C, 76.32; H,9.15 (best available).

M.s. Found: M^+, 220.1459 (96%);

$C_{14}H_{20}O_2$ requires M, 220.1463.

B) Using hydrochloric acid

To a stirred solution of the tricyclic t-butyl ether (96) (44 mg, 0.16 mmol), in ethanol (1.0 ml) was added hydrochloric acid (2 M, 1.0 ml) and the solution heated at 80°C under nitrogen for 2.5 hr. T.l.c. (petroleum spirit-ethyl acetate 1:4, v/v) indicated product (Rf: 0.31, UV) and other components to be present.

The reaction mixture was cooled to ambient temperature and diluted with ether (20 ml) and water (15 ml). The aqueous phase was extracted with ether (3 x 10 ml), and the combined organic extracts washed successively with water (3 x 5 ml), saturated brine (1 x 5 ml), and dried ($MgSO_4$). Evaporation of solvent gave a yellow oil (30 mg), which on chromatography over silica (40-63 μm) using petroleum spirit-ethyl acetate (1:4, v/v) as eluant gave the product as a colourless powdery solid (16 mg, 48%), m.p. 137-147°C. An analytical sample (from diethyl ether) had m.p. 144-150°C, which was idential to authentic product (i.r., mixed m.p., t.l.c.).

C) Using trimethylsilyl chloride and sodium iodide

To a homogenous yellow solution of the tricyclic

t-butyl ether (96) (45 mg, 0.16 mmol) in methyl cyanide (3 ml) containing sodium iodide (8.0 mg, 0.33 mmol) was added freshly distilled trimethylsilyl chloride (0.04 ml, 0.32 mmol). The mixture was left for 5 hr at ambient temperature under nitrogen, when t.l.c. (petroleum spirit-ethyl acetate 1:2, v/v) indicated numerous components to be present.

The reaction mixture was diluted with ether (30 ml), and washed successively with sodium thiosulphate (1 x 10 ml), water (1 x 5 ml) saturated brine (1 x 5 ml), and dried ($MgSO_4$). Evaporation of solvent gave a yellow oil (38 mg), which after chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (1:4, v/v) as eluant afforded the product alcohol (139) as a white powdery solid (19 mg, 56%) m.p. 136-144°C. This was identical to authentic product (i.r., t.l.c.).

5.3.1.

Phenol

A solution of cyclohexenone (300 mg, 3.13 mmol) in dried dimethylformamide (20 ml) was added to a stirred dark green solution of copper (II) bromide (1.39 g, 6.23 mmol) and lithium bromide (270 mg, 3.1 mmol) in dried dimethylformamide (15 ml) at 80°C under nitrogen.

After approx. 15 min. the solution changed from dark green to an opaque orange, brown colour. The solution was heated for a further period (1 hr), then allowed to cool to ambient temperature.

The reaction mixture was diluted with ether (50 ml), and water (30 ml), and the resultant flocculent precipitate filtered under vacuum through hyflo supercell. The solids were washed liberally with ether, the aqueous layer extracted with ether (3 x 20 ml), and the combined organic extracts washed with water (2 x 10 ml). The organic layer was extracted with sodium hydroxide (2 M, 3 x 10 ml), and the combined alkaline extracts cooled ($0^{o}C$), and carefully acidified with cold ($0^{o}C$) hydrochloric acid (2 M). This was extracted with dichloromethane (3 x 20 ml), and the combined organic extracts washed successively with water (2 x 10 ml), saturated brine (1 x 10 ml), and dried ($MgSO_4$). Evaporation of the solvent gave an orange oil (247 mg), which on chromatography over silica (40-63 μm) employing ethyl acetate as eluant gave a yellow oil (172 mg, 59%), one spot pure by t.l.c. (ethyl acetate) (Rf: 0.38, UV). Crystallization occurred after fridge storage (2 hr, $4^{o}C$), giving colourless spindles, m.p. 37-39^{o}C, after tituration with cold ($0^{o}C$) petroleum spirit. This was identical by t.l.c. and i.r. to commercially available authentic

product (m.p. 39-40°C).

νmax(melt): 3400br (aromatic OH), 1600, 1510 and 1480 (aromatic ring), 1210, 750 and 680 cm^{-1}.

Evaporation of solvent from the neutral extractions gave a yellow oil (77 mg, 26% of starting material) which by t.l.c. (ethyl acetate) (Rf: 0.36, UV, orange by DNP), and i.r. was consistent with starting material.

(±)-6α-t-butyl-5,6,7,8-tetrahydro-2-naphthalenol (153)

A solution of the enone (123) (200 mg, 1.03 mmol), in dried dimethylformamide (8 ml) was added to a stirred dark green solution of copper (II) bromide (480 mg, 2.15 mmol) and lithium bromide (90 mg, 1.03 mmol) in dried dimethylformamide (8 ml) at 80°C under nitrogen. After approximately 0.5 hr, the solution changed from opaque dark green to a deep red colour, and t.l.c. (petroleum spirit-ethyl acetate-triethylamine 5:5:1, v/v) indicated product (Rf: 0.35, UV) and impurities (Rf: 0.61, 0.55 and 0.21). The solution was heated for a further period (1 hr), then allowed to cool to ambient temperature.

The reaction mixture was diluted with ether (50 ml), and water (30 ml), and the resultant flocculent

precipitate filtered under vacuum through hyflo supercell. The solids were liberally washed with ether, and the aqueous layer extracted with ether (3 x 15 ml). The combined organic extracts were washed successively with water (2 x 10 ml), saturated brine (1 x 10 ml), and dried ($MgSO_4$). Evaporation of solvent gave an orange oil, which on chromatography over silica (40-63 μm) using petroleum spirit-ethyl acetate-triethylamine (5:5:1, v/v) as eluant afforded a colourless oil (136 mg, 69%), one spot pure by t.l.c.

νmax (thin film): 3400br (aromatic OH), 1620 and 1510 (aromatic ring), 1460, 1370, 1280, 1220 and 1150 cm^{-1}.

δ (220 MHz): 6.90(1H, d, $J_{3H,4H}$ = 8 Hz; 4-H), 6.55 (Total 2 H: d, 1-H; and brs, 3-H, overlapped), 5.45 (1H, brs, aromatic OH), 2.8-1.0 (7H, complex), 0.90 (9H, s, $-Bu^t$).

M.s. Found: M^+, 204.1514 (42%).
$C_{14}H_{20}O$, requires M, 204.1514.

A small amount (maximum 15% from n.m.r. integration) of the impurity (154) was discernable in the product, prior to chromatography, from ^1H n.m.r. with the following impurity peaks assigned.

δ (220 MHz). 6.35 (1H, d, $J_{7H,8H}$ = 8 Hz; 8-H), 5.95 (1H, m, 7-H).

(±)-1β-t-butoxy-9aβ-methyl-2,3,3aα,4,9,9a-hexahydro-6-(1H)-benz[f]indenol (155)

A solution of the enone (96) (67 mg, 0.24 mmol) in dried dimethylformamide (2 ml) was added to a stirred dark green solution of copper (II) bromide (117 mg, 0.52 mmol) and lithium bromide (25 mg, 0.29 mmol) in dried dimethylformamide (3 ml) at 80°C under nitrogen. After approximately 0.5 hr the solution changed from, opaque dark green to a clear yellow colour, and t.l.c. (petroleum spirit-ethyl acetate-triethylamine 5:5:1, v/v) indicated product (Rf: 0.35, UV) and other impurities. The solution was heated for a total of 1 hr, then allowed to cool to ambient temperature.

The reaction mixture was diluted with ether (20 ml), and water (10 ml), and the resultant flocculent precipitate filtered under vacuum through hyflo supercell. The solids were washed liberally with ether and the aqueous layer extracted with ether (3 x 10 ml). The combined organic extracts were washed successively with water (2 x 5 ml), saturated brine (1 x 5 ml), and dried ($MgSO_4$). Evaporation of solvent gave a yellow oily solid, which on trituration with cold (0°C) dichloromethane afforded the crude product as white

crystals, (42 mg, 63%) m.p. 180-190°C. ^1H n.m.r. indicated this to be a mixture of the product (155), with the impurity (156) present at about 25% (by integration).

δ(80 MHz): 6.90 (1H, d, $J_{7H,8H}$ = 8 Hz; 8-H), 6.55 (2H: d, 7-H and 1H, s, 5-H), 6.1 (Ca. 1H, s, 4-H from 156), 3.8-3.3 (complex, 1α-H from 155 and 156), 1.26 (Ca. 9H, s, $-OBu^t$ of 156), 1.20 (9H, s, $-OBu^t$ of 155), 1.12 (Ca. 3H, s, 9a $-CH_3$ of 156), 0.70 (3H, s, 9a $-CH_3$ of 155).

An analytical sample (from dichloromethane) gave a colourless solid, m.p. 188-192°C.

νmax(KBr). 3350 br (aromatic OH), 3300 (aryl C-H stretch), 1620 and 1520 (aromatic ring), 1450, 1210 and 1050 cm^{-1}.

δ(80 MHz) 6.90 (1H, d, $J_{7H,8H}$ = 8 Hz; 8-H), 6.55 (2H, d, 7-H and brs, 5-H overlapped), 3.50 (1H, dd, 1α-H), 1.20 (9H, s, $-OBu^t$), 0.70 (3H, s, 9aβ-CH_3).

M.s. Found: M^+, 274.1926 (10%).

$C_{18}H_{26}O_2$ requires M, 274.1932.

(±)-9aβ-methyl-2,3,3aα,4,9,9a-hexahydro-1,6(1H)-benz-[f]indendiol (157)

A solution of the enone (96) (61 mg, 0.22 mmol), in dried methyl cyanide (3 ml) was added to a stirred dark green solution of copper (II) bromide (98 mg, 0.44 mmol) and lithium bromide (19 mg, 0.22 mmol) in dried methyl cyanide (3 ml) at reflux under nitrogen. After approximately 10 min. the solution changed from dark green, through yellow to a clear, light orange colour. After a total of 1 hr t.l.c. (petroleum spirit-ethyl acetate 1:2, v/v) indicated product (Rf: 0.46, UV, $KMnO_4$) with impurities (Rf: 0.40 and Rf: 0.25).

After cooling the solution to ambient temperature the reaction mixture was diluted with ether (30 ml) and water (15 ml). The aqueous layer was extracted with ether (3 x 5 ml), and the combined organic extractions washed successively with water (2 x 5 ml), saturated brine (1 x 10 ml), and dried ($MgSO_4$). Evaporation of solvent afforded a yellow paste (62 mg), which after chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (1:2, v/v) as eluant gave a white powdery solid (51 mg, 84%), m.p. 197-204°C dec. An analytical sample (from dichloromethane) gave a colourless, powdery solid, m.p. 207-210°C dec., one spot pure by t.l.c.

νmax(KBr): 3450, 3200 br (aliphatic and phenolic OH), 1620 and 1520 (aromatic ring), 1480, 1460, 1240 and 1045 cm^{-1}.

δ(80 MHz): 6.90 (1H, d, $J_{7H,8H}$ = 8 Hz; 8-H), 6.55 (total 2H: d, 7-H and 6.50 brs, 5-H, overlapped), 3.85 (1H, dd, 1α-H), 2.9-0.9 (complex), 0.75 (3H, s, 9aβ-CH_3).

M.s. Found: M^+, 218.1308 (75%).
$C_{14}H_{18}O_2$ requires M, 218.1307.

(±)-1β-t-butoxy-11aβ-methyl-2,3,3aα,4,4aα,5,10,10aβ,11,11a-decahydro-7(1H)-cyclopent[b]anthracenol (140)

A solution of the enone (137) (183 mg, 0.55 mmol) in dried dimethylformamide (5 ml) was added to a stirred dark green solution of copper (II) bromide (250 mg, 1.12 mmol) and lithium bromide (48 mg, 0.55 mmol) in dried dimethylformamide (5 ml) at 80% under nitrogen. After approximately 0.5 hr the solution changed from opaque dark green to a clear yellow colour, and t.l.c. (petroleum spirit-ethyl acetate 7:2, v/v) indicated product (Rf: 0.28, UV, $KMnO_4$) and impurities (Rf: 0.52 and Rf: 0.21). The solution was heated for a further period (1 hr), then allowed to cool to ambient temperature.

The reaction mixture was diluted with ether (30 ml), and water (15 ml), and the resultant flocculent precipitate filtered under vacuum through hyflo supercell. The solids were washed liberally with ether and the aqueous layer extracted with ether (3 x 10 ml). The combined organic extracts were washed successively with water (2 x 5 ml), saturated brine (1 x 5 ml), and dried ($MgSO_4$). Evaporation of solvent gave a yellow oil, which on chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (7:2, v/v) as eluant afforded a yellow oily crystalline solid (125 mg), which after trituration with cold (0^oC) dichloromethane afforded a white powdery solid (107 mg, 59%), m.p. 206-215^oC.

Further chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate-triethylamine (5:4:1, v/v) as eluant gave an analytical sample of white, powdery product, m.p. 221-223^oC.

νmax(KBr): 3350 br (aromatic OH), 3030 (Aryl C-H stretch), 1620 and 1520 (aromatic ring), 1445, 1205 and 1050 cm^{-1}.

δ (80 MHz) [$(CD_3)_2CO$]: 7.85 (1H, s, aromatic OH), 6.90 (1H, d, $J_{8H,9H}$ = 8 Hz, 9-H), 6.55 (2H: d, 8-H and brs 6-H overlapped), 3.45 (1H, dd, 1α-H), 1.15 (9H, s, $-OBu^t$), 0.75 (3H, s, 11aβ-CH_3).

M.s. Found: M^+, 328.2396 (9%); $(M-H_2)^+$, 326.2246.
$C_{22}H_{32}O_2$ requires M, 328.2402 ($M-H_2$), 326.2246.

Microanalysis Found: C,79.08, H,9.78.
$C_{22}H_{32}O_2$ requires C,80.44, H,9.82% (best available).

($\pm$)-11aβ-methyl-2,3,3aα,4,4aα,5,10,10aβ,11,11a-deca-hydro-1,7(1H)-cyclopent[b]anthracendiol (27)

A solution of the enone (137) (116 mg, 0.35 mmol), in dried methyl cyanide (5 ml) was added to a stirred dark green solution of copper (II) bromide (164 mg, 0.74 mmol) and lithium bromide (30 mg, 0.34 mmol) in dried methyl cyanide (5 ml) at reflux under nitrogen. After approximately 15 min. the solution changed from dark green, through yellow green to an orange colour. After a total of 1 hr, t.l.c. (petroleum spirit-ethyl acetate 1:2, v/v) indicated product (Rf: 0.50, UV, $KMnO_4$) and impurities at the origin.

After cooling the solution to ambient temperature the reaction mixture was diluted with ether (40 ml) and water 20 ml). The aqueous layer was extracted with

ether (3 x 10 ml), and the combined organic extractions washed successively with water (2 x 10 ml), saturated brine (1 x 10 ml), and dried ($MgSO_4$). Evaporation of solvent afforded a yellow powdery solid (97 mg), m.p. 233-241°C dec., which after chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (1:1, v/v) as eluant gave a colourless powdery solid, (52 mg, 54%), m.p. 252-255°C dec. An analytical sample (from acetone) gave a colourless powdery solid, m.p. 253-256°C dec., one spot pure by t.l.c. (petroleum spirit-ethyl acetate 1:1, v/v).

νmax(KBr) 3450, 3200 br (aliphatic and aromatic OH), 1620 and 1520 (aromatic ring), 1460, 1440, 1240 and 1040 cm^{-1}.

δ(80 MHz) (CD_3OD) (only partially soluble): 7.30 (1H, s, aromatic OH), 6.90 (1H, d, $J_{8H,9H}$ = 8 Hz; 9-H), 6.55 (total 2H: d, 8-H and brs, 6-H, overlapped), 0.78 (3H, s, 11aβ-CH_3).

M.s. Found: M^+, 272.1767 (100%); $(M-H_2)^+$, 270.1616, $(M-H_2O)^+$, 254.1661, $(M-C_2H_4O)^+$, 228.1522.
$C_{18}H_{24}O_2$ requires M, 272.1776; $(M-H_2)$, 270.1620; $(M-H_2O)$, 254.1670; $(M-C_2H_4O)$, 228.1514.

6.4

(±)-6α-t-butyl-3-methyl-2,3,4,4aβ,5,6,7,8-octahydro-2-napthalenone (172).

A) Methylation using potassium t-butoxide as base

To a stirred solution of the enone (123) (1.73 g, 8.40 mmol) in dry tetrahydrofuran (15 ml) under nitrogen was added iodomethane (7.5 ml, 120 mmol). The solution was cooled (-78°C), and a solution of potassium t-butoxide (1.80 g, 16.0 mmol) in dry tetrahydrofuran (20 ml) was added slowly, dropwise, whilst monitoring progress of the reaction by t.l.c. (petroleum spirit-ethyl acetate 6:1, v/v). Addition of the base ceased (Ca. 15 ml, 1.4 equivalents added), when t.l.c. indicated the major component to be the product (172) (Rf: 0.35, UV, yellow DNP), with the presence of traces only of starting material (Rf: 0.25, UV, orange DNP), and other product (Rf: 0.47, UV, not detected by DNP)

The reaction mixture was diluted with water (20 ml), and extracted with ether (3 x 10 ml). The combined organic extracts were washed with water (2 x 5 ml), brine (1 x 5 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil (1.60 g), which on

chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (6:1, v/v) as eluant afforded the product as a yellow oil (0.74 g, 40%).

$\underline{\nu max}$ (thin film): 1675 (conjugated C=O), 1630 cm^{-1} (conjugated C=C),

$\underline{\delta}$ (220 MHz): 5.75 (1H, s, vinylic proton), 1.12 (3H, d, $J_{3Me,3H}$ = 7.5 Hz; 3-CH_3), 0.88 (9H, s, -Bu^t).

M.s. Found: M^+, 220.1822 (11%)

$C_{15}H_{24}O$ requires 220.1827.

B) Methylation using lithium diisopropylamide as base

To a stirred and cooled (-78°C) solution of diisopropylamine (0.16 ml, 1.16 mmol) in dry tetrahydrofuran (5 ml) was added n-butyl lithium (0.8 ml, 1.16 mmol) over approx. 5 min. After a further 10 mins. the enone (123) (200 mg, 0.97 mmol) in dry tetrahydrofuran (5 ml), was added slowly, dropwise, to the solution containing lithium diisopropylamide. After 0.5 hr, this solution was added slowly dropwise to a stirred solution of iodomethane (1.7 ml, 27 mmol) in dry tetrahydrofuran (5 ml) at -78°C. After a further 0.5 hr t.l.c. (petroleum spirit-ethyl acetate 6:1, v/v) indicated product (172) (Rf: 0.35, UV, yellow DNP) with assumed dialkylated side product (Rf: 0.47, UV,

undetected by DNP) as the major components.

The reaction mixture was diluted with water (20 ml), and extracted with ether (5 x 10 ml). The combined organic extracts were washed with water (2 x 5 ml), brine (1 x 5 ml), and dried ($MgSO_4$). Evaporation of solvent gave a yellow oil which after chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (6:1, v/v) as eluant afforded the product (172) (46 mg, 22%), which was identical to that obtained by using potassium t-butoxide as base (t.l.c., i.r.).

(±)-6α-t-butyl-3-methyl-1,2,3,4,4aβ,5,6,7,8,8aα-decahydro-2-naphthalenone (173)

To a solution of refluxing dry ammonia (100 ml) and lithium (137 mg, 19.6 mmol) under nitrogen, was added slowly, dropwise, (Ca. 10 min) a solution of the enone (172) (1.27 g, 5.8 mmol) in dry ether (20 ml), containing dried t-butyl alcohol (327 mg, 4.42 mmol). The solution was stirred for a further 15 min; t.l.c. (petroleum spirit-ethyl acetate 7:1, v/v) indicated predominantly product (Rf: 0.38, yellow DNP).

Excess ammonium chloride (Ca. 2 g) was added cautiously, and the resultant paste dissolved in water. The mixture was gently warmed (30°C) under a vigorous nitrogen flow to expel the ammonia, and the product

extracted with ether (3 x 20 ml). The combined extracts were washed successively with water (2 x 20 ml), saturated brine (1 x 20 ml), dried ($MgSO_4$) and evaporated to yield a yellow oil (127 mg). Chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (7:1, v/v) as eluant gave the product as a yellow oil (63 mg, 46%).

νmax (thin film): 1710 (cyclic C=O), 1470, 1450, 1370 and 1240 cm^{-1}.

δ(220 MHz): 1.20 (3H, d, $J_{3Me,3H}$ = 7.5 Hz; 3-CH_3), 0.82 (9H, s, -Bu^t).

M.s. Found: M^+, 222.1988 (26%).
$C_{15}H_{26}O$, requires M, 222.1984.

(±)-7α-t-butyl-4a-methyl-2,3,4,4a,5,5aβ,6,7,8,9,9aα,10-dodecahydro-2-anthracenone (174)

To a stirred solution of the α-methyl ketone (173) (68 mg, 0.31 mmol), in dry t-butyl alcohol (3 ml) under nitrogen was added a catalytic amount of potassium t-butoxide. After 15 min, trimethylsilyl vinyl ketone (103) (67 mg, 0.41 mmol) in dry t-butyl alcohol (2 ml) was canulated into the reaction mixture (over 10 min). After 2 hr, t.l.c. (petroleum spirit-ethyl acetate 3:1, v/v) indicated product (Rf: 0.38, UV, orange DNP), with

numerous other components (Rf: 0.55, 0.50, 0.32 and 0.17).

The reaction mixture was diluted with ether (30 ml), washed successively with water (2 x 3 ml), and saturated brine (1 x 3 ml), dried ($MgSO_4$) and evaporated to afford a yellow oil (97 mg). Chromatography over silica (40-63 μm), employing petroleum spirit-ethyl acetate (3:1, v/v) afforded a colourless oil (17 mg, 20%), one spot by t.l.c., which ^1H n.m.r. indicated to be a mixture of isomers.

νmax (thin film): 1670 (conjugated C=O), 1620 (conjugated C=C), 1460, 1370 and 1250 cm^{-1}.

δ(220 MHz): 5.85 and 5.70 (1H, 2 x s, vinylic proton) 1.25 (3H, s, 4a-CH_3) 0.82 (9H, s, -Bu^t).

M.s. Found: M^+, 274.2292 (18%)

$C_{19}H_{30}O$ requires M, 274.2297.

6.5

(±)-1β-t-butoxy-7,9aβ-dimethyl-1,2,3,3aα,4,7,8,8aβ,9,9a-decahydro-6-benz[f]indenone (179)

To a stirred solution of the enone (96) (1.45 g, 5.25 mmol) in dry tetrahydrofuran (10 ml) under nitrogen was

added iodomethane (5 ml, 80 mmol). The solution was cooled (-78°C), and a solution of potassium t-butoxide (1.16 g, 10.3 mmol) in dry tetrahydrofuran (25 ml) was added slowly dropwise, whilst continually monitoring progress of the reaction by t.l.c. (petroleum spirit-ethyl acetate 6:1, v/v). Addition of the base was ceased (Ca. 15 ml, 1.18 equivalents added), when t.l.c. indicated the major component to be the product (20) (Rf: 0.37, UV, yellow DNP), with the presence of traces only of starting material (Rf: 0.27, UV, orange DNP), and dialkylated product (183) (Rf: 0.47, UV, not detected by DNP).

The reaction mixture was diluted with water (30 ml) and extracted with ether (3 x 30 ml). The combined organic extractions were washed with brine (2 x 10 ml), dried ($MgSO_4$) and concentrated to afford a yellow oil (1.51 g). Chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (6:1, v/v) as eluant afforded the product as a crystalline solid (1.07 g, 70%), m.p. 93-98°C. An analytical sample (from petroleum spirit 40/60) had m.p. 101-102°C.

ν max(KBr): 1665 and 1620 ($\alpha\beta$-unsaturated C=O), 1470, 1365, 1260, 1200 and 1060 cm^{-1}.

δ (80 MHz): 5.75 (1H, s, vinylic proton), 3.40 (1H, dd, 1α-H), 1.15 (9H, s, $-OBu^t$), 1.19 and 1.10 (3H, d, $J_{7Me,7H'}$ = 7.5 Hz, 7-CH_3) 0.90 (3H, s, 9aβ-CH_3).

Microanalysis Found: C,78.17; H,10.39%

$C_{19}H_{30}O_2$ requires C,78.57; H,10.41%.

Initial elution gave the dialkylated product (183) (26 mg), m.p. 88-108°C. An analytical sample (from petroleum spirit 40/60) had m.p. 111-115°C.

νmax(KBr): 1670 and 1625 ($\alpha\beta$-unsaturated C=O), 1480, 1370, 1200 and 1060 cm^{-1}.

δ (60 MHz): 5.73 (1H, s, vinylic proton), 3.40 (1H, dd, 1α-H), 1.15 (9H, s, $-OBu^t$), 1.10 (6H, s, 7α-CH_3 and 7β-CH_3), 0.87 (3H, s, 9aβ-CH_3).

M.s. Found: M^+, 304.2396 (0.4%). $(M-C_4H_8)^+$, 248.1774; $(M-C_4H_9)^+$, 247.1679.

$C_{20}H_{32}O_2$ requires M, 304.2402; $(M-C_4H_8)$, 248.1776; $(M-C_4H_9)$, 247.1698.

(±)-1β-t-butoxy-7,9aβ-dimethyl-1,2,3,3aα,4,4aβ,5,7,8,8aβ,9,9a-dodecahydro-6-benz[f]indenone (158)

To a solution of refluxing dry ammonia (70 ml) and lithium (170 mg, 24.3 mmol) under nitrogen, was added

slowly dropwise (Ca. 15 min) a solution of the enone (179) (1.04 g, 3.60 mmol) in dry ether (30 ml), containing dried t-butyl alcohol (210 mg, 2.84 mmol). The solution was then stirred for a further 10 min; t.l.c. (petroleum spirit-ethyl acetate 7:1, v/v) indicated predominantly product (Rf: 0.40, yellow DNP).

Excess ammonium chloride (Ca. 2 g) was added cautiously, and the resultant paste dissolved in water. The mixture was heated (30-40°C) under a vigorous nitrogen flow to expel ammonia, and the product extracted with ether (3 x 20 ml). The combined extracts were washed successively with water (2 x 20 ml), saturated brine (1 x 20 ml), dried ($MgSO_4$) and evaporated to yield a solid (995 mg), m.p. 78-91°C. Chromatography over silica (40-63 μm) employing petroleum spirit-ethyl acetate (7:1, v/v) as eluant gave the product as a powdery solid (597 mg, 57%), m.p. 93-98°C. An analytical sample (from petroleum spirit 40/60) had m.p. 104-105.5°C.

ν max(KBr): 1710 (cyclic saturated C=O) 1470, 1370, 1190 and 1060 cm^{-1}.

δ (80 MHz): 3.40 (1H, dd, 1α-H), 1.25 (total 1.5H, half of 7-CH_3 doublet), 1.15 (total 10.5H; 9H, s, -OBu^t and 1.5H, half of 7-CH_3 doublet), 0.80 (3H, s, 9aβ-CH_3).

Microanalysis Found: C,78.84; H,11.19%.

$C_{19}H_{32}O_2$ requires C,78.03; H,11.03% (best available).

M.s. Found: M^+, 292.2378;

$C_{19}H_{32}O_2$ requires M,292.2402.

(±)-1β-t-butoxy-9a,11aβ-dimethyl-1,2,3aα,4,4aα,5,8,9,9a,10,10aβ,11,11a-tetradecahydro-7-cyclopent[b]anthracenone (160)

To a stirred solution of the α-methyl ketone (180) (127 mg, 0.441 mmol) in dry t-butyl alcohol (6 ml) under nitrogen, was added a catalytic amount of potassium t-butoxide. After 0.5 hr, α-trimethylsilyl vinyl ketone (72 mg, 0.441 mmol) in dry t-butyl alcohol (4 ml) was canulated into the reaction mixture (over 10 min). After 3 hr t.l.c. (petroleum spirit-ethyl acetate 6:1, v/v) indicated product (Rf: 0.27, UV, orange DNP), with other components (Rf: 0.45, yellow DNP; Rf: 0.21 and Rf: 0.16, $KMnO_4$).

The reaction mixture was diluted with ether (70 ml), washed successively with water (3 x 20 ml), and saturated brine (1 x 20 ml), dried ($MgSo_4$) and evaporated to afford a paste (170 mg). Chromatography over silica (40-63 μm), employing petroleum spirit-ethyl acetate as eluant (6:1, v/v) gave an oily white solid, one spot by t.l.c., (33 mg, 22%), which ^1H

n.m.r. indicated to be a mixture of isomers.

$\underline{\delta}$ (80 MHz) ($CDCl_3$): 5.85 and 5.70 (1H, 2 x s, vinylic proton), 3.35 (1H, dd, 1α-H), 1.25 (3H, s, 9a-CH_3), 1.15 (9H, s, -OBu^t), 0.80 (3H, s, 11aβ-CH_3).

$\underline{\delta}$ (80 MHz), (C_6D_6): 5.95 and 5.85 (1H, 2 x s, vinylic proton), 3.35 (1H, dd, 1α-H), 1.15 (9H, s -OBu^t), 0.95 (Ca. 1.5 H, s, approximately half of 9a-CH_3), 0.82 (3H, s, 11aβ-CH_3).

An analytical sample (from petroleum spirit 40/60) gave a white solid, m.p. 97-102°C.

$\underline{\nu}$max(KBr): 1675 (conjugated C=O), 1620 (conjugated C=C) 1370, 1190 and 1060 cm^{-1}.

$\underline{\delta}$ (80 MHz) ($CDCl_3$): 5.70 (1H, s, vinylic proton), 3.35 (1H, dd, 1α-H), 1.25 (3H, s, 9aβ-CH_3), 1.15 (9H, s, -OBu^t), 0.80 (3H, s, 11aβ-CH_3).

$\underline{\delta}$ (80 MHz) (C_6D_6): 5.85 (1H, s, vinylic proton, 3.35 (1H, dd, 1α-H), 1.15 (9H, s, -OBu^t), 0.95 (3H, s, 9aβ -CH_3), 0.82 (3H, s, 11aβ-CH_3).

M.s. Found: M^+, 344.2729 (0.8%); $(M-C_4H_8)^+$, 288.2097; $(M-C_4H_9)^+$, 287.2042.

$C_{23}H_{36}O_2$ requires M, 344.2715; $(M-C_4H_8)$, 288.2090; $(M-C_4H_9)$, 287.2011.

Further elution afforded the hydroxy ketone, (182) (77 mg), as a white solid. An analytical sample (from ether/petroleum spirit 40/60), gave a white powdery solid, m.p. 181-183.5°C.

νmax(KBr): 3500 (br OH), 1700 (cyclic C=O) 1370, 1190 and 1060 cm^{-1}

δ(80 MHz) ($CDCl_3$): 3.35 (1H, dd, 1α-H), 1.20 (3H, s, 9a-CH_3), 1.15 (9H, s, -OBu^t), 0.75 (3H, s, 11aβ-CH_3).

δ(80 MHz) (C_6D_6): 3.35 (1H, dd, 1α-H), 1.15 (9H, s, -OBu^t), 0.92 (3H, s, 9a-CH_3), 0.83 (3H, s, 11aβ-CH_3).

M.s. Found: M^+, 362.2818 (0.5%); $(M-C_4H_8)^+$, 306.2217; $(M-C_4H_9)^+$, 305.2145.

$C_{23}H_{38}O_3$ requires M,363.2820; $(M-C_4H_8)$, 306.2194; $(M-C_4H_9)$, 305.2117.

Dehydration of the keto-alcohol (180) to the enone (160a)

A stirred solution of the keto-alcohol (182) (111 mg)

(0.31 mmol), in dry benzene (50 ml), with p-toluenesulphonic acid (catalytic) was azeotropically refluxed under nitrogen using a water jacket cooled Dean-Stark water separator. After 1 hr, t.l.c. (petroleum spirit-ethyl acetate 3:1, v/v) indicated the enone as the major component (Rf: 0.38).

After cooling the reaction mixture to ambient temperature the solution was washed with aqueous sodium bicarbonate (15% w/w, 2 x 10 ml), water (1 x 10 ml), saturated brine (1 x 10 ml), and dried ($MgSO_4$). Evaporation of solvent gave a clear, yellow oil (76 mg), which after chromatography over silica (40-63 μm) with petroleum spirit-ethyl acetate (3:1, v/v) as eluant afforded an enone (48 mg, 46%) as an oil which crystallized at ambient temperature over 0.5 hr.

An analytical sample (recrystallized several times from petroleum spirit 40/60) gave a colourless crystalline solid, m.p. 112-113.5°C, which was identical to (181a) by i.r., ^1H n.m.r. and t.l.c.

Preparation of Magnesium Methyl Carbonate

To magnesium turnings (15.9 g, 0.66 mol) was added a small portion of anhydrous methanol (50 ml) and iodine. After the reaction started, the remainder of the methanol (200 ml) was added. After hydrogen evolution

ceased, the solvent was removed by distillation and dry dimethylformamide (250 ml) was added to the residual solid magnesium methoxide. Dry carbon dioxide gas was bubbled through the mixture, and the dissolution of the gas was accompanied by an exothermic reaction with the suspended magnesium methoxide to form a solution (Ca. 3 hr).

Residual methanol was removed by distillation under a stream of carbon dioxide, and the solution was cooled to ambient temperature under carbon dioxide to ensure saturation.

The molarity of the reagent was calculated by treating a known small volume with excess sulphuric acid (1 M), and titrating the mixture with sodium hydroxide (2 M) to determine the unreacted sulphuric acid.

REFERENCES

1. "Steroid Biochemistry", E. Heftmann, Academic Press Inc., 1970.
2. "Steroids", L.F. Fieser, M. Fieser, Reinhold Publishing Corp., 1959, 1.

3a. S. Aoyama, K. Sasaki, Chem.Pharm.Bull., 1970, 18, 481.

b. ibid, 1310.

c. ibid, 1971, 19, 2776.

d. ibid, 896.

4a. "Conformational Analysis", E.L. Eliel, J. Wiley & Sons, 1966, 36.

b. ibid, 256.

5. L.F. Fieser, J.E. Herz, M.W. Klohs, M.A. Romero, T. Utne, J.Amer.Chem.Soc., 1952, 74, 3309.
6. B. Ellis, V. Petrow, J.Chem.Soc., 1939, 1078.
7. "Some Modern Methods of Organic Synthesis"., W. Carruthers, C.U.P., 1971.
8. F.B. Colton, L.N. Nysted, B. Riegel, A.L. Raymond, J. Amer.Chem.Soc., 1959, 79, 1123.
9. A.A. Frimer, J. Hameiri-Buch, S. Ripshtos, P. Gilinsky-Sharon, Tetrahedron, 1986, 42, 5693.
10. S. Aoyama, Chem.Abs., 1970, 72, 380.
11. "Organic Chemistry"., J.B. Hendrickson, D.J. Cram, G.S. Hammond, McGraw-Hill, 1970, 1070.

12. R.B. Woodward, K. Bloch, J.Amer.Chem.Soc., 1953, 75, 2023.

13a. W.E. Bachmann, W. Cole, A.L. Wilds, J.Amer.Chem.Soc., 1939, 61, 974.

b. ibid, 1940, 62, 62.

14a. W.W. Johnson, J.W. Petersen, C.D. Gutsche, J. Amer. Chem.Soc., 1945, 67, 2274.

b. W.S. Johnson, R.G. Christiansen, J. Amer. Chem. Soc., 1951, 73, 5511.

15. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, W.M. McLamore, J. Amer.Chem.Soc., 1952, 74, 4223.

16. S. Danishefsky, P. Cain, A. Nagel, J.Amer.Chem.Soc., 1975, 97, 380.

17. "Concepts of Organic Synthesis"., B.P. Mundy, Marcel Dekker Inc., 1979, 22.

18. Z.G. Hajos, D.R. Parrish, J.Org.Chem, 1974, 39, 1612.

19. R.A. Micheli, Z.G. Hajos, N. Cohen, D.R. Parrish, L.A. Portland, W. Sciamanna, M .A. Scott, P.A. Wehrli, J.Org.Chem., 1975, 40, 675.

20. Z.G. Hajos, D.R. Parrish, J.Org.Chem., 1973, 38, 3239.

21. "Total Synthesis of Steroids"., A.A. Akhrem, Y.A. Titov, I.P.S.T. Press, 1967.

22. H. Schick, G. Lehmann, G. Hilgetag, Chem.Ber., 1969, 3238.

23. V.J. Grenda, G.W. Lindberg, N.L. Wendler, S.H. Pines, J.Chem.Soc., 1967, 32, 1236.

24. D.J. Crispin, A.E. Vanstone, J.S. Whitehurst, J.Chem.Soc., 1970, (C) 10.

25. J.N. Gardner, B.A. Anderson, E.P. Oliveto, J.Org.Chem., 1969, 34, 107.

26. T.A. Spencer, K.K. Schmiegel, K.L. Williamson. J.Amer.Chem.Soc., 1963, 85, 3785.

27. C.B.C. Boyce, J.S. Whitehurst, J.Chem.Soc., 1959, 2022.

28. Z.G. Hajos, D.R. Parrish, J.Org.Chem., 1974, 39, 1615.

29. C.B.C. Boyce, J.S. Whitehurst, J.Chem.Soc., 1960, 4547.

30. Z.G. Hajos, R.A. Micheli, D.R. Parrish, E.P. Oliveto, J.Org.Chem., 1967, 32, 3008.

31. H.C. Beyerman, G.J. Meiszwolf, J.Chem.Soc., 1963, 755.

32. D.H.R. Barton, C.H. Robinson, J.Chem.Soc., 1954, 3045.

33. G. Bauduin, Y. Pietrasanta, Tetrahedron, 1973, 29, 4225.

34. G. Stork, S.D. Darling, J.Amer.Chem.Soc., 1964, 86, 1761.

35. R.P. Linstead, W.E. Doering, S.B. Davis, P. Levine, R.R. Whetstone, J.Amer.Chem.Soc., 1942, 64, 1985.

36. S.N. Balasubrahmanyam, M. Balasubramanian, Org.Synth., 1969, 49, 56.

37. H.L. Finkbeiner, M. Stiles, J.Amer.Chem.Soc., 1963, 85, 676.

38. M. Stiles, J.Amer.Chem.Soc., 1959, 81, 2598.

39a. P.A. Grieco, S. Ferrino, T. Oguri, J.Org.Chem., 1979, 44, 2594.

b. M.S. Newman, A.B. Mekler, J.Amer.Chem.Soc., 1960, 82, 4039.

40. S. Ramachandran, M.S. Newman, Org.Synth., 1961, 41, 38.

41. S. Swaminathan, M.S. Newman, Tetrahedron, 1958, 2, 88.

42. N.L. Wendler, H.L. Slates, M. Tishler, J.Amer.Chem.Soc., 1957, 73, 3816.

43. J. Ruppert, V. Eder, R. Wiechert, Chem Ber., 1973, 3636.

44. J.D. Cocker, T.G. Halsall, J.Chem.Soc., 1957, 3441.

45. "Some Modern Methods of Organic Synthesis", W. Carruthers, C.U.P., 1971, 246.

46. "Steroid Reactions", Ed.C. Djerassi, Holden-Day, 1963, 299.

47. J.W. Cornforth, R.H. Cornforth, R. Robinson, J.Chem.Soc., 1942, 689.

48. J. d'Angelo, Tetrahedron Rep., 1976, 32, 2979.

49. D. Caine, B.J.L. Huff, Tetrahedron Lett., 1966, 39, 4695.

50. H.O. House, M. Gall, H.D. Olmstead, J.Org.Chem., 1971, 36, 2361.

51. G. Stork, P. Rosen, N. Goldman, R.V. Coombs, J. Tsuji, J.Amer.Chem.Soc., 1965, 87, 275.

52. E.S. Binkley, C.H. Heathcock, J.Org.Chem., 1975, 40, 2156.

53. G. Stork, P.F. Hudrlik, J.Amer.Chem.Soc., 1968, 90, 4464.

54. G. Stork, P. Rosen, N.L. Goldman, J.Amer.Chem. Soc., 1961, 83, 2965.

55. D. Caine, J.Org.Chem., 1964, 29, 1868.

56. R.K. Boeckman Jr., J.Amer.Chem.Soc., 1974, 96, 6179.

57. G. Stork, J. Singh, J.Amer.Chem.Soc., 1974, 96, 6181.

58. I. Kuwajima, E. Nakamura, J.Amer.Chem.Soc., 1975, 97, 3257.

59. E. Negishi, M.J. Idacavage, Tetrahedron Lett., 1979, 845.

60. G. Stork, P.F. Hudrlik, J.Amer.Chem.Soc., 1968, 90, 4462.

61. G. Stork, J. d'Angelo, J.Amer.Chem.Soc., 1974, 96, 7114.

62. H.O. House, L.J. Czuba, M.Gall, H.D. Olmstead, J.Org.Chem., 1969, 34, 2324.

63a. Y. Mazur, F. Sondheimer, J.Amer.Chem.Soc., 1958, 80, 5220.

63b. ibid, 6296.

64. M.D. Soller, R.A. Stewart, G.L. Smith, J.Amer.Chem.Soc., 1952, 74, 1556.

65 S.W. Pelletier, R.L. Chappell, P.C. Parthasarathy, N. Lewin, J.Org.Chem., 1966, 31, 1747.

66. S.W. Pelletier, P.C. Parthasarathy, Tetrahedron Lett., 1964, 2, 103.

67. J.A. Beres, J.G. Cannon, Synth.Comm., 1979, 9, 819.

68. R.O. Clinton, R.L. Clarke, F.W. Stonner, A.J. Manson, K.F. Jennings, D.K. Phillips, J.Org.Chem., 1962, 27, 2800.

69. B. Gaspert, T.G. Halsall, D. Willis, J.Chem.Soc., 1958, 624.

70. A.R. Pinder, Sir R. Robinson, J.Chem.Soc., 1952, 1224.

71. R.B. Turner, D.E. Nettleton Jr., R.Ferebee, J.Amer.Chem.Soc., 1956, 78, 5923.

72. E.J. Corey, D.E. Cane, J.Org.Chem., 1971, 36, 3070.

73. W.S. Johnson, H. Posvic, J.Amer.Chem.Soc., 1947, 69, 1361.

74. R.E. Ireland, J.A. Marshall, J.Org.Chem., 1962, 27, 1615.

75. N.S. Narasimhan, R. Ammanamanchi, J.Org.Chem., 1983, 48, 3945.

76. L. Weiler, J.Amer.Chem.Soc., 1970, 92, 6702.

77. S.N. Huckin, L. Weiler, J.Amer.Chem.Soc., 1974, 96, 1082.

78. T.M. Harris, C.R. Hauser, J.Amer.Chem.Soc., 1962, 84, 1750.

79. J.W. Hubbard, T.M. Harris, Tetrahedron Lett., 1978, 4601.

80. J.F. Wolfe, T.M. Harris, C.R. Hauser, J.Org.Chem., 1964, 29, 3249.

81. M.E. Jung, Tetrahedron Rep., 1976, 32, 3.

82. R.E. Gawley, Synthesis, 1976, 777.

83. G. Stork, M.E. Jung, J.Amer.Chem.Soc., 1974, 96, 3682.

84. P. Duhamel , L. Hennequin, J.M. Poirier, G. Tavel, C. Vottero, Tetrahedron, 1986, 42, 4777.

85a. P.L. Stotter, K.A. Hill, Tetrahedron Lett., 1975, 21, 1679.

b. P.L. Stotter, K.A. Hill, J.Amer.Chem.Soc., 1974, 96, 6524.

86. G. Stork, B. Ganem, J.Amer.Chem.Soc., 1973, 95, 6152.

87. R.K. Boeckman Jr., J.Amer.Chem.Soc., 1973, 95, 6868.

88. E.W. Colvin, Chem.Soc.Rev., 1978, 7, 15.

89. R.K. Boeckman Jr., D.M. Blum, B. Ganem, N. Halvey, Org.Synth., 1978, 58, 152.

90. H.O. House, M.J. Umen, J.Org.Chem., 1973, 38, 1000.

91. E.J. Corey, S. Nozoe, J.Amer.Chem.Soc., 1965, 87, 5728.

92. F. Fringuelli, A. Taticchi, E. Wenkert, J.M. Bernassau, W. Klyne, D.N. Kirk, J.Chem.Soc., Perkin Trans. 1, 1980, 176.

93. S. Winstein, N.J. Holness, J.Org.Chem., 1955, 77, 5562.

94. M.E. Kuehne, J.Org.Chem., 1970, 35, 171.

95. N.C. Ross, R. Levine, J.Org.Chem., 1964, 29, 2341.

96. F.E. Ziegler, K.J. Hwang, J.Org.Chem., 1983, 48, 3349.

97. T. Morita, Y.O. Kamoto, H. Sakurai, J.Chem.Soc., Perkin Trans.1, 1978, 874.

98. G.W. Olah, S.C. Narang, B.G. Balaram Gupta, R. Malhotra, J.Org.Chem., 1979, 44, 1247.

99. H.C. Beyerman, G.J. Heiszwolf, J.Chem.Soc., 1963, 755.

100. D.L. Boger, M.D. Mullican, J.Org.Chem., 1980, 45, 5002.

101. B.M. Trost, T.N. Salzman, K.J. Hiroi, J.Amer.Chem.Soc., 1976, 98, 4887.

102. R.B. Turner, J.A. Meschino, J.Amer.Chem.Soc., 1958, 80, 4862.

103. D. Bondon, Y. Pietrasantra, B. Pucci, Tetrahedron Lett., 1977, 10, 821.

104. E.M. Kosower, G.S. Wu, J.Org.Chem., 1963, 28, 633.

105. L.C. King, G.K. Ostrum, J.Org.Chem., 1964, 29, 3459.

106. S.S. Yuan, Steroids, 1982, 79, 279.

107. J.W. Cornforth, Sir R. Robinson, J.Chem.Soc., 1949, 1855.

108. L. Nedelec, J.C. Gasc, R. Bucourt, Tetrahedron, 1974, 30, 3263.

109. H. Sakurai, K. Miyoshi, Y. Nakadaira, Tetrahedron Lett., 1977, 2671.

110. C.H. Heathcock, J.E. Ellis, Tetrahedron Lett., 1971, 52, 4995.

111. J.A. Marshall, W.I. Fanta, J.Org.Chem., 1964, 29, 2501.

112. Y. Yamoto, H. Kaneko, Tetrahedron, 1965, 21, 2501.

113. N.S. Bhacca, D.H. Williams, Tetrahedron Lett., 1964, 3127.

114. B.J. Hunt, W. Rigby, Chem. & Ind., 1967, 1868.

115. W.C. Still, M. Kahn, A. Mitra, J.Org.Chem., 1978, 43, 2923.

116. Z.G. Hajos, D.R. Parrish, E.P. Oliveto, Tetrahedron, 1968, 24, 2039.

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As part of the research programme, the author has attended the following lecture courses at Sheffield City Polytechnic and Sheffield University:

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The author has attended symposia on:

Natural Product Chemistry (London 1980)

Stereochemistry (Sheffield 1978, 1979, 1980 and 1981)

The author has also undertaken a three months training period at the collaborating body's laboratory during which time he presented monthly progress reports.