SYNTHESIS OF 1α, 5α-CYCLOSTEROIDS

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YI REN

SYNTHESIS OF 1α,5α-CYCLOSTEROIDS

by

YI REN

A thesis submitted to the School of Graduate Studies in partial fulfilment of the requirements for the degree of Master of Science

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August 1992

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ISBN 0-315-78093-2

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Abstract

Epoxidation of 4,4-dimethylcholesta-1,5-dien-3-one with *m*-chloroperbenzoic acid gave a mixture of the epimeric 5α,6α-epoxy- and 5β,6β-epoxy-4,4-dimethylcholest-1-en-3-one. Unexpectedly, the major product was found to be the 5β,6β-epoxide, in contradiction to what had been reported by others. The unambiguous assignment of the structures of these epoxides was based upon ^{1}H NMR experiments and X-ray crystallographic analysis of the 5α,6α-epoxide. In this thesis, the chemistry of the 5β,6β-epoxide is described in the context of attempts at the synthesis of the corresponding 1α,5α-cyclosteroids.

The synthesis of a new 1α,5α-cyclosteroid, 4,4-dimethyl-1α,5α-cyclocholesta-3,7-dione, by lithium or ytterbium in liquid ammonia reduction of the *bis*-α,β-unsaturated ketone 4,4-dimethylcholesta-1,5-diene-3,7-dione, is described. The chemistry of the reductive cyclization is discussed. The ^{1}H-NMR spectra of the mono- and dihydroxy derivatives of the 1α,5α-cyclosteroid reveal an unusually high-field signal due to H-9. X-ray diffraction analysis of 7β-hydroxy-4,4-dimethyl-1α,5α-cyclocholestan-3-one indicates that ring B of the steroid nucleus possesses a boat conformation, and that H-9 partially eclipses the cyclopropyl ring. An anisotropic ring

current effect is postulated to account for the chemical shifts of H-9 in these cyclosteroids. The chemistry of these compounds are described.

Various other attempts at the synthesis of 1α,5α-cyclosteroids are also described.

Acknowledgements

I would like to extend my sincerest appreciation to my supervisor, Dr. P. E. Georghiou, for countless and very helpful instruction and discussions during the course of my research project. I also am greatly appreciative of the relationship that we have had.

I wish to express my sincerest appreciation to Dr. D. J. Burnell for many suggestions, for his superb graduate courses from which I benfitted so much, and for his ongoing encouragement. Dr. C. R. Jablonski and Ms. N. Brunet are greatly thanked for their generous contributions in the form of numerous high-quality high resolution NMR spectra. Dr. B. Gregory and Ms. M. Baggs are thanked for their mass spectral contributions. Dr. C. E. Loader is sincerely thanked for his help in the use of the PCs during the process of my thesis writing.

Special thanks are given to Dr. Yong-Jin Wu and Dr. Pei-Ying Liu for their support, encouragement and friendship.

I am deeply grateful to my fiancee Miss Sylvia Z. Zhao for her help in typing and for her love, support and

encouragement. These are always warm in my heart.

Financial support from Department of Chemistry and Memorial University, as well as from Dr. P. E. Georghiou is gratefully acknowledged.

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INTRODUCTION

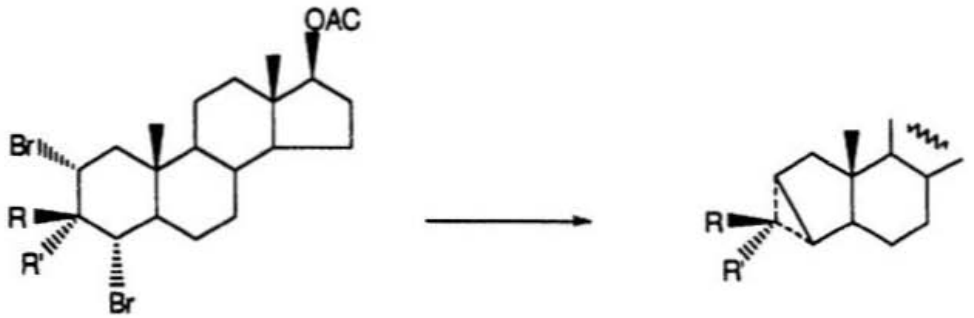
There are eight possible bicyclo [3.1.0] ring-A steroids. Of these only the 1α,5α-, 1β,5β-, 2β,4β-, 3α,5α- and 3β,5β-cyclosteroids have been reported. The following is a brief review of some representative examples.

(i) 2β,4β-Cyclosteroids.

Templeton and Wie[1a] reported the syntheses of 17β-acetoxy-2β,4β-cyclo-5α-androstan-3β-ol **(1a)** and 17β-acetoxy-2β,4β-cyclo-5α-androstan-3α-ol **(1b)**. They employed a zinc-copper couple to effect a 1,3-elimination of bromine from the corresponding 2α,4α-dibromides **(2a)** and **(2b)** respectively. Orr et al[1b] could effect the same transformation by using lithium in liquid ammonia (Scheme 1).

(ii) 3α,5α- and 3β,5β-Cyclosteroids.

The 3α,5α-cyclosteroids and 3β,5β-cyclosteroids are the best known of the bicyclo [3.1.0] ring-A steroids. They are prepared by either solvolytic[2,3] or photochemical[4] routes. The solvolysis of cholesteryl tosylate **(3)** gives 3α,5α-cyclocholesterol **(4, R=H)**, whereas, irradiation of cholesta-3,5-diene **(5)** yields 3β,5β-cyclocholesterol **(6, R=H)** (Scheme 2).



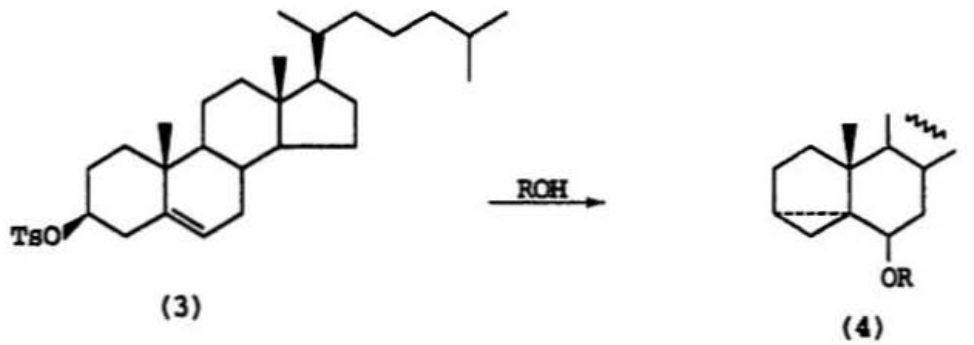
(2a): R=OH, R'=H

(2b): R=H, R'=OH

(1a): R=OH, R'=H

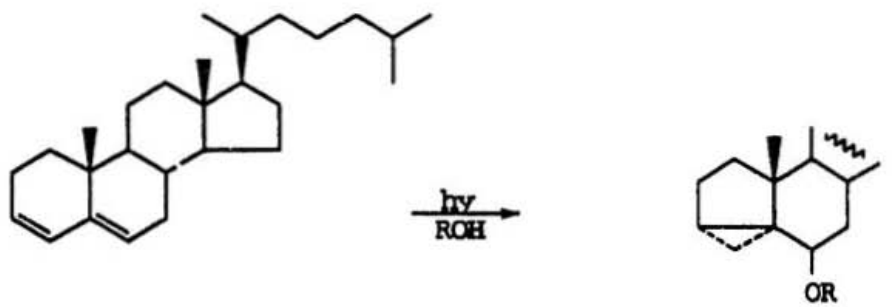
(1b): R=H, R'=OH

Scheme 1



(3)

(4)



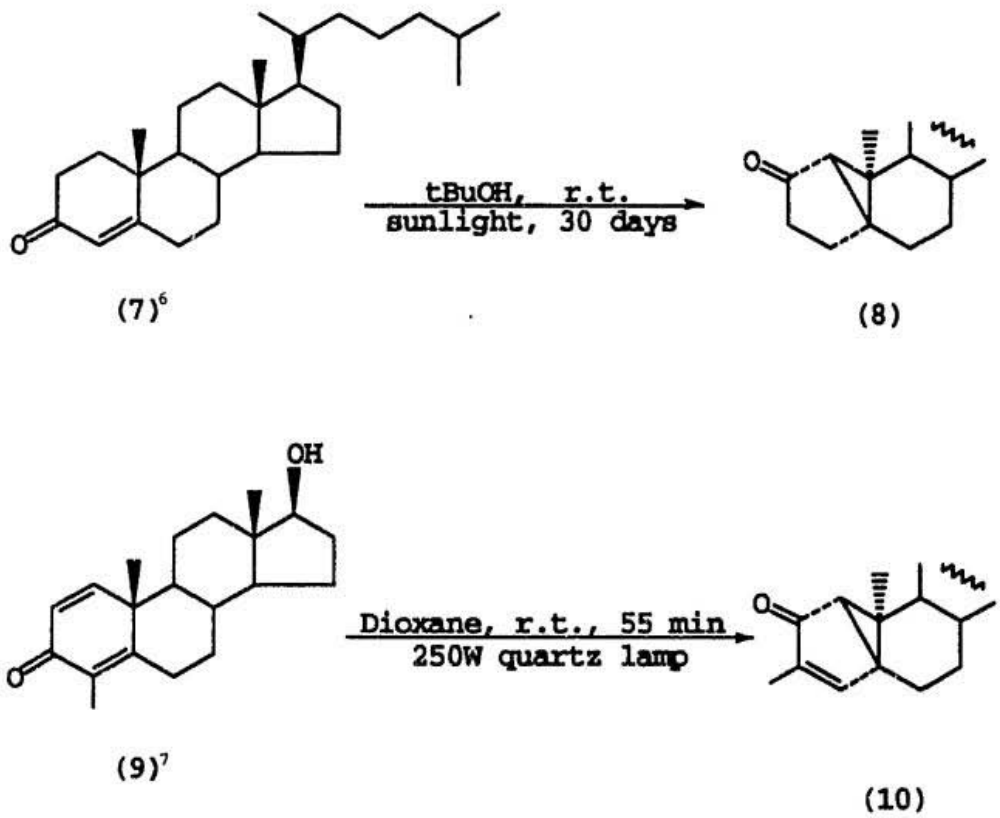
(5)

(6)

Scheme 2[5]

(iii) 1β,5β- and 1α,5α-Cyclosteroids.

1β,5β-Cyclosteroids can be prepared by photochemical methods via a $[\sigma^2+\pi^2]$ cycloaddition reaction. Scheme 3 shows two examples.



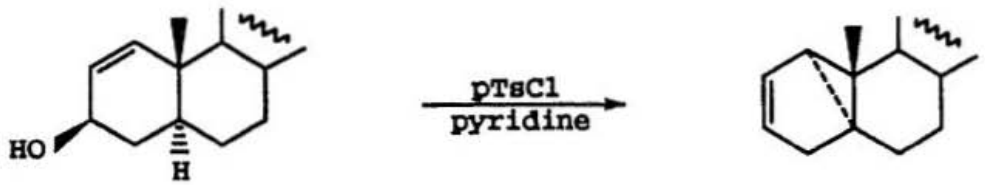
(7)[6] (8)

(9)[7] (10)

Scheme 3

By comparison with the 1β,5β-cyclosteroids, the 1α,5α-cyclocholesteroids are relatively rare. Laing and Sykes[8,9]

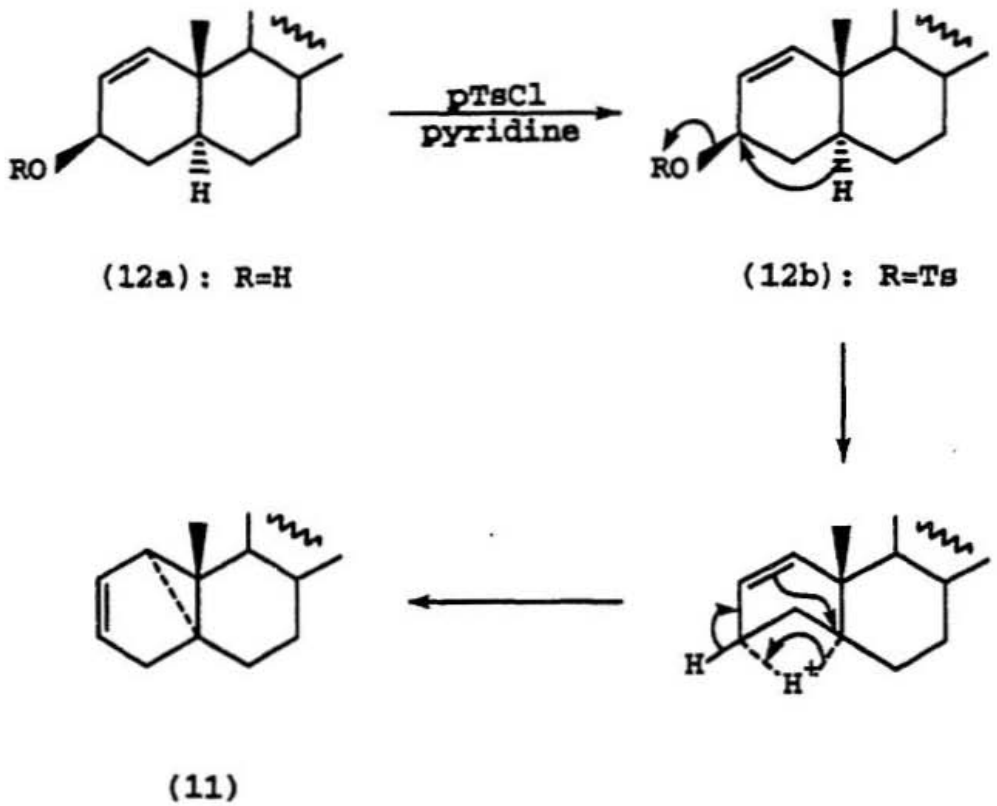
reported the synthesis of 1α,5α-cyclocholest-2-ene **(11)** directly from the *in-situ* formed *p*-toluenesulphonate of 5α-cholest-1-en-3β-ol **(12)** (Scheme 4).



(12) **(11)**

Scheme 4

To account for the formation of **(11)** from **(12a)**, Laing and Sykes proposed the mechanism shown in Scheme 5. The initial step involves a C-5α to C-3α transannular hydride displacement of the C-3 tosylate in **(12b)** resulting in the formation of a bridged non-classical ion. Proton elimination followed by π-bond rearrangement results in the formation of the 1α,5α-bridge (Scheme 5).



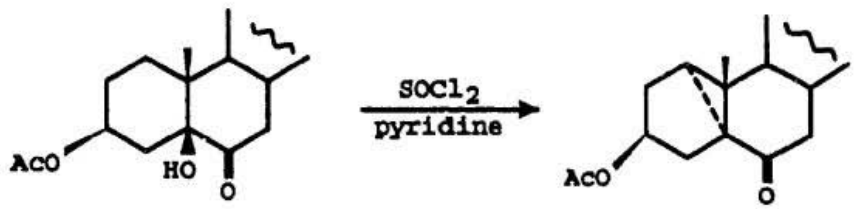
(12a): R=H

(12b): R=Ts

(11)

Scheme 5

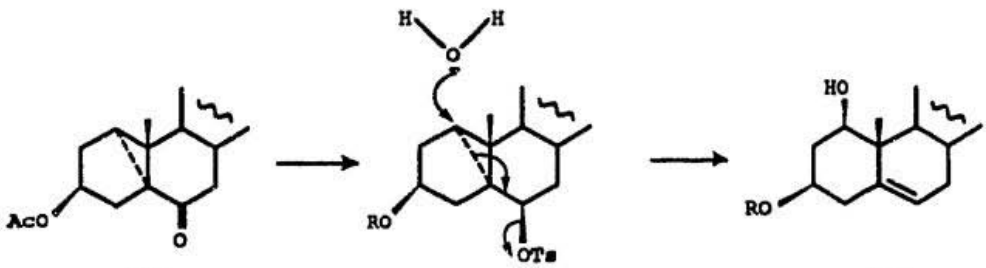
The same authors also reported[10] the synthesis of 3β-acetoxy-1α,5α-cyclocholestan-6-one **(13)** by treatment of 3β-acetoxy-5β-hydroxycholestan-6-one **(14)** with thionyl chloride in pyridine (Scheme 6).



(14) (13)

Scheme 6

Since compound **(13)** is functionalized at C-6 it could be used to study the potential for a cyclopropylcarbinol-homoallylic rearrangement with concomitant introduction of a functional group at C-1 via the reactions in Scheme 7.

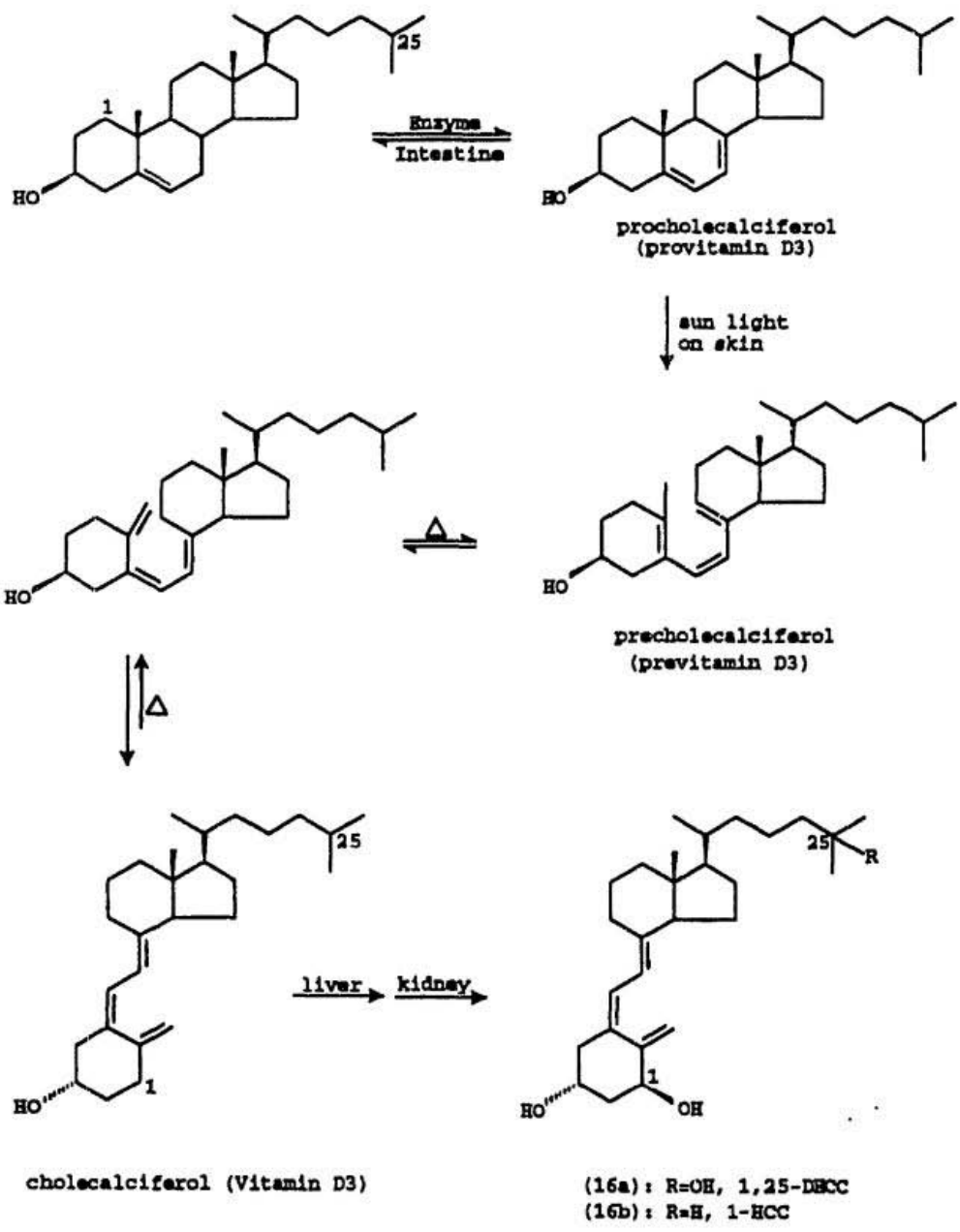


(13) (15)

Scheme 7

The resulting 1-substituted cholesterol **(15)** could be envisioned as a synthetic precursor for 1-substituted-(e.g. 1-hydroxy-) procholecalciferols ("provitamins D_3").[11,12] Scheme 8 shows the biosynthesis of 1(*S*),25-dihydroxycholecalciferol

(1,25-DHCC or "calcitriol") **(16a)** from cholesterol.



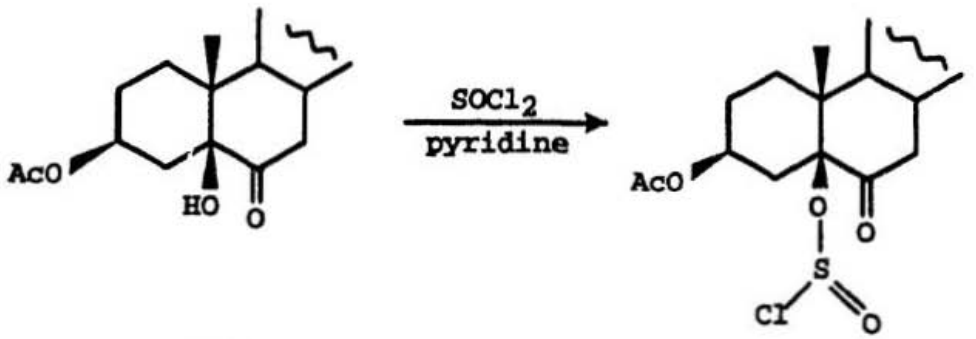
Scheme 8

DeLuca[13] and Barton *et al.*[12] reported that a synthetic analog of 1,25-DHCC **(16a)**, the mono-hydroxylated 1(*S*)-hydroxycholecalciferol (1-HCC) **(16b)** had biological activity comparable with that of **(16a)** itself. Hence, **(16b)** as well as its potential precursor **(15)** are themselves important synthetic targets.

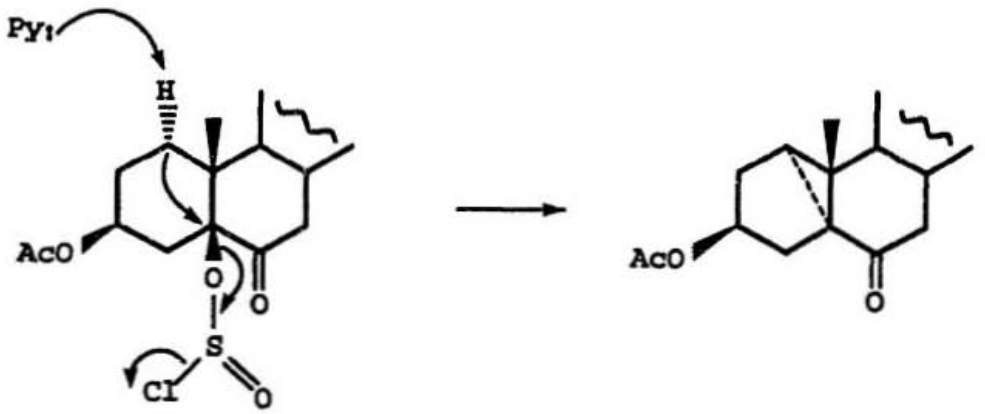
Georghiou and Just[14] reported obtaining different results when they used the procedure of Laing and Sykes[9] to synthesize **(13)**. Instead of obtaining **(13)** they obtained an isomeric compound **(17)** (see Scheme 10). Compound **(17)** had spectral and analytical data that were similar to those reported for **(13)**, except for a doublet at δ 4.98 ppm due to H-4 which was not noted by Laing and Sykes.

In their paper,[9] Laing and Sykes did not present a mechanism to account for the putative formation of **(13)**. Georghiou[15] therefore proposed the following mechanism (Scheme 9). Treatment of hydroxy-ketone **(14)** with thionyl chloride in pyridine at low temperature should produce the chlorosulphite **(18)**. In order to form the cyclosteroid **(13)** it would be neccessary to have proton abstraction of the α-hydrogen at C-1 occur to form a carbanion at C-1. An intramolecular nucleophilic displacement of the chlorosulphite group **(19)** by the carbanion would result in the formation of the 1α,5α-

bridge.



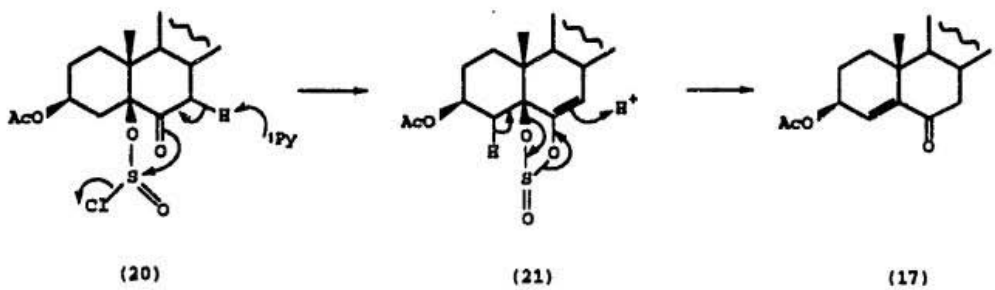
(14) (18)



(19) (13)

Scheme 9

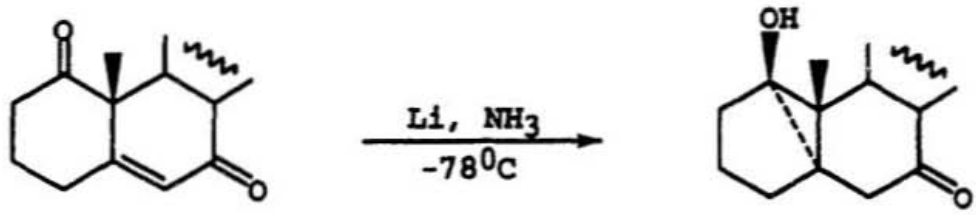
However, if instead, a proton is removed from the much more acidic C-7 position, an intramolecular displacement of chloride **(20)** from the cholrosulphite group could occur resulting in the formation of the cyclic enol-sulphite **(21)** (Scheme 10). In fact, Georghiou and Just[14] were able to isolate **(21)** as the exclusive product from the low temperature reaction of **(14)** with thionyl chloride in pyridine. This compound was very labile and decomposed on neutral alumina to afford among other products, compound **(17)**.



(20) (21) (17)

Scheme 10

The only other synthesis of a 1α,5α-cyclosteroid is that of Christensen and Reusch[16] who synthesized 1β-hydroxy-1α,5α-cyclocholestan-7-one **(22)** by lithium in liquid ammonia reduction of cholest-5-ene-1,7-dione **(23)** (Scheme 11).

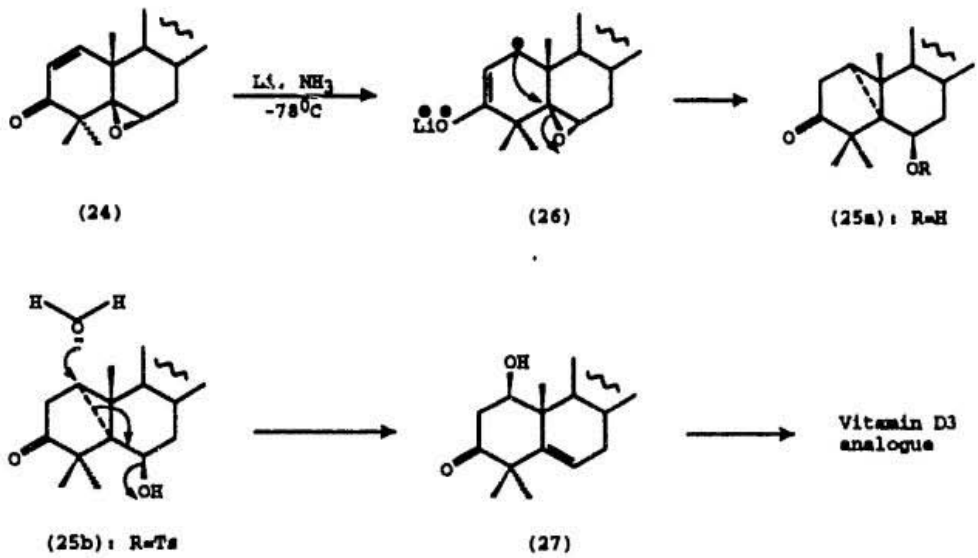


(23) **(22)**

Scheme 11

The 5β,6β-epoxide **(24)** can be envisioned as a potential precursor for the synthesis of the cyclosteroid **(25)**, an analog of **(13)**. As depicted in Scheme 12, **(25a)** could in principle be formed by an intramolecular ring opening of the epoxy group by the intermediate dianion **(26)**, which in turn might be generated by metal-liquid ammonia reduction.

A cyclopropylcarbinol-homoallylic rearrangement of the cyclosteroid **(25b)** could then transform it into, for example, 1β-hydroxy-4,4-dimethylcholest-5-en-3-one **(27)**. Compound **(27)** of course could be a precursor of a vitamin D_3 analog.



Scheme 12

The results of our efforts to form 1α,5α-cyclosteroids using 5β,6β-epoxide **(24)** and other potential precursors are the subject of this thesis.

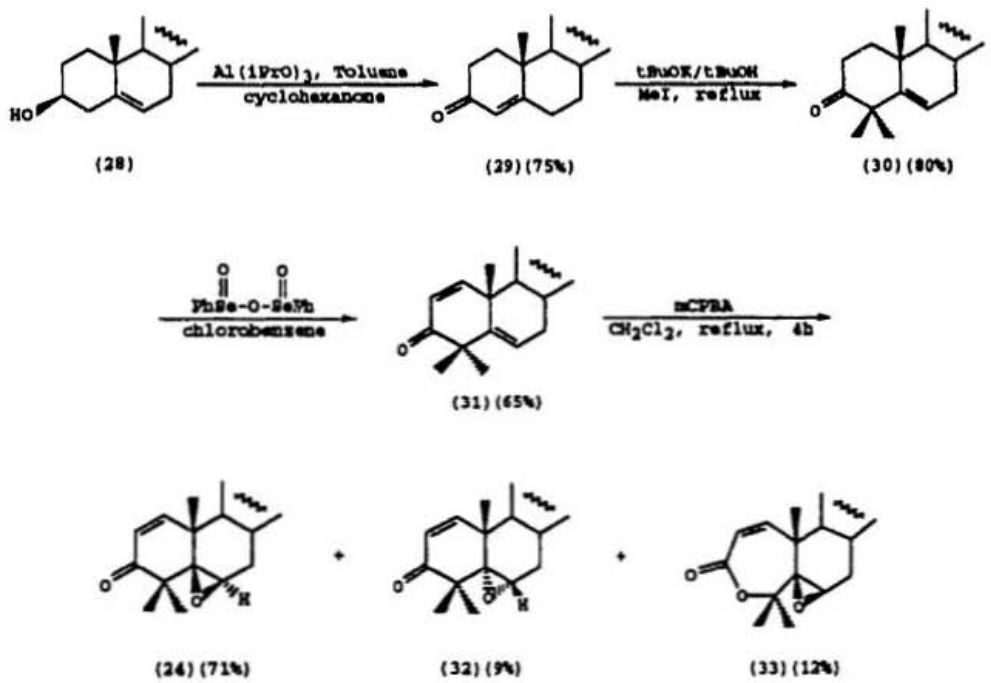
CHAPTER ONE

SYNTHESIS OF 5β,6β-EPOXY-4,4-DIMETHYLCHOLEST-1-EN-3-ONE AND UNEQUIVOCAL ASSIGNMENT OF ITS STRUCTURE

Cholesterol **(28)** was chosen as the starting compound for the synthesis of 5β,6β-epoxide **(24)**. Oppenauer oxidation[17] of **(28)** (Scheme 13) yielded cholest-4-en-3-one **(29)** in 75% yield. Treatment of **(29)** with potassium *t*-butoxide[18] in *t*-butanol and *in situ* trapping of the anion formed at C-4 with iodomethane gave 4,4-dimethylcholest-5-en-3-one **(30)** in 80% yield. Benzeneselenenic anhydride[19] oxidation of 4,4-dimethylcholest-5-en-3-one **(30)** afforded the 4,4-dimethylcholesta-1,5-dien-3-one **(31)** in good yield. Reaction of **(31)** with *m*-chloroperoxybenzoic acid (mCPBA) in refluxing dichloromethane solution for four hours gave a mixture of the 5β,6β- and 5α,6α-epoxides, **(24)** and **(32)** respectively. A small amount (12%) of the epoxy-lactone **(33)** was also formed.

Surprisingly, the major product was the 5β,6β-epoxide **(24)**, which comprised 71% of the mixture. The 5α,6α-epoxide **(32)** comprised only 9%. The assignment of structures to the epimeric epoxides were initially based on Cross' observations[20,21] of the H-6 chemical shift values of other 5β,6β- and 5α,6α-epoxides. The major product **(24)** had the

lower field chemical shift for the H-6 signal (δ 3.32 ppm), which was a broad singlet. The minor product **(32)** had the higher field chemical shift for the H-6 signal (δ 3.10 ppm) which was a sharp doublet (*J*= 3.6 Hz).



Scheme 13

Nuclear Overhauser effect difference (NOED) experiments on both epoxides suggested that these assignments were

correct. Separate, selective saturation of the signals due to the α- and β-C-4 methyl groups of the 5α,6α-epoxide **(32)** at δ 0.93 and 1.36 respectively, each enhanced the H-6 signal at δ 3.10 (16% and 3% respectively). By contrast, only when the signal for the α-C-4 methyl group of the 5β,6β-epoxide **(24)** at δ 0.94, was saturated was there any enhancement of the H-6 signal at δ 3.32 (20%). No corresponding enhancement was observed when the signal for the β-C-4 methyl group at δ 1.33 on **(24)** was irradiated.

Brynjolffssen *et al.*[22] reported obtaining a 60% yield of **(32)** when they treated **(31)** with mCPBA in refluxing dichloromethane. The melting point and ^{1}H-NMR data of what they presumed to be the 5α,6α-epoxide **(32)** were identical with our data for **(24)**. Since our NOED experiments were not necessarily unequivocal, direct proof by X-ray crystallographic analysis was obtained. Although both **(24)** and **(32)** were crystalline, only crystals of the latter compound were suitable for x-ray crystallography. The structure obtained (see Figure 1) confirmed our original assignment that **(32)** was indeed the 5α,6α-epoxide and that the assignment of Brynjolffssen *et al.* was incorrect. Using their conditions, we obtained **(32)** only as a minor product. The major product was different from the expected **(24)**. Elemental analysis, spectral and mass spectrometric data of this compound was consistent

with it being the epoxy-lactone **(33)**. This product was most likely formed by a Baeyer-Villager oxidation of **(24)** since the mCPBA was used in excess.

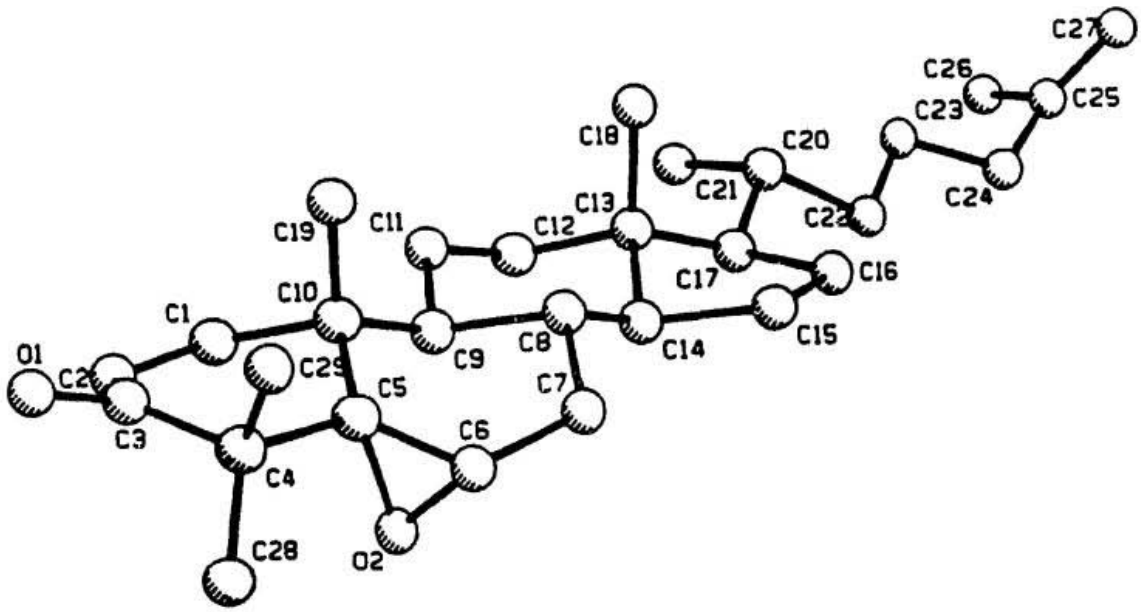


Figure 1. X-Ray crystal structure of **(32)**.

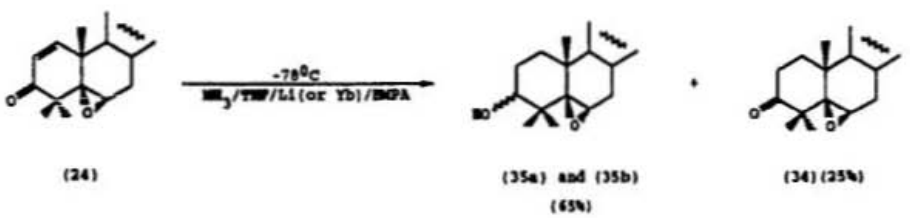
From the X-ray structure of 5α,6α-epoxide **(32)** depicted in Figure 1, H-6 is situated equidistantly from both the α- and the β-C-4 methyl group. As a result each methyl showed a positive NOE when the signal due for H-6 was saturated. The torsion angle of H6-C6-C7-H7α is -35°, while that of H6-C6-C7-H7β is 82°. These results are in accordance with the predictions from the Karplus curve for the observed coupling constants and splitting pattern for H-6.

In the case of the 5β,6β-epoxide **(24)**, since only the α-C-4 methyl had a positive NOE with H-6, it implied that the A-ring of 5β,6β-epoxide **(24)** could adopt a chair conformation while the B-ring was still a boat. The absence of an NOE between the β-C-4 methyl and H-6 does not necessarily mean that they are not in close proximity. Molecular models indicate that both the H6-C6-C7-H7α and the H6-C6-C7-H7β torsion angle are approximately 50°. The signal for H-6 is a broad singlet as would be expected from the Karplus curve, indicating a smaller coupling constant for H-6 than for the corresponding proton in the 5α,6α-epoxide **(32)**.

CHAPTER TWO

APPROACHES TO 1α,5α-CYCLOSTEROIDS FROM 5β,6β-EPOXY-4,4-DIMETHYLCHOLEST-1-EN-3-ONE

Epoxide **(24)** was treated with lithium in liquid ammonia under several different conditions. For example, higher temperatures (-35 °C), and the use of hexamethylphosphorous triamide (HMPA) were tried. The products which were obtained were mixtures which were separated by flash chromatography to afford 5β,6β-epoxy-4,4-dimethylcholestan-3-one **(34)**, and a mixture of the corresponding epimeric 3α- **(35a)** and 3β-alcohols **(35b)** (Scheme 14).

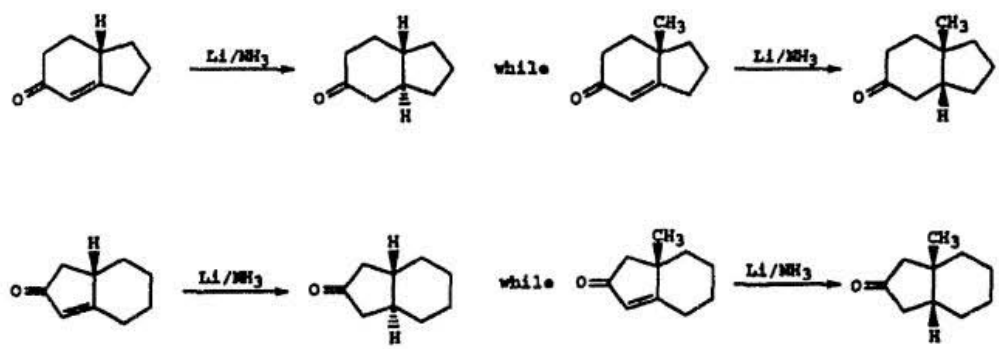


Scheme 14

The mixture of **(35a)** and **(35b)** was oxidized directly to **(34)** with pyridinium chlorochromate (PCC). The structure of epoxy-ketone **(34)** was confirmed by comparison with the product obtained by catalytic hydrogenation of **(24)**. Reaction of **(24)**

with ytterbium in liquid ammonia[23] gave the same result as with lithium in liquid ammonia. Thus, although the α,β-unsaturated carbonyl system could be reduced, presumably via the dicarbanion **(26)** (see Scheme 12), cyclization to **(25)** by intramolecular epoxide opening did not occur.

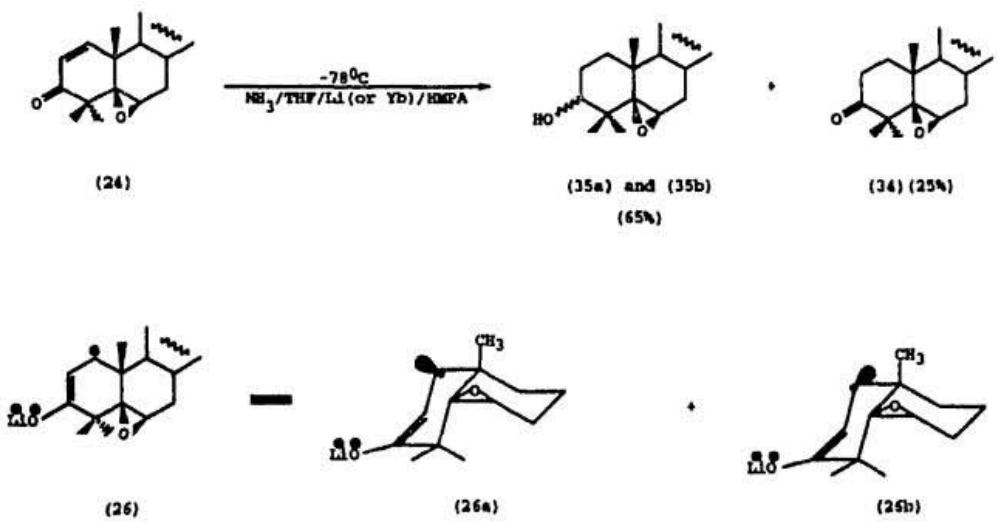
Pradhan[24] has reviewed the stereochemistry and mechanism of reduction of cyclic saturated and α,β-unsaturated ketones with alkali metals in protic solvents including liquid ammonia. Among the examples reviewed by Pradhan is the study shown in Scheme 15.



Scheme 15

The results were interpreted by consideration of the interactions involving the singly occupied molecular orbital (SOMO) initially formed when the electron was added to the π*

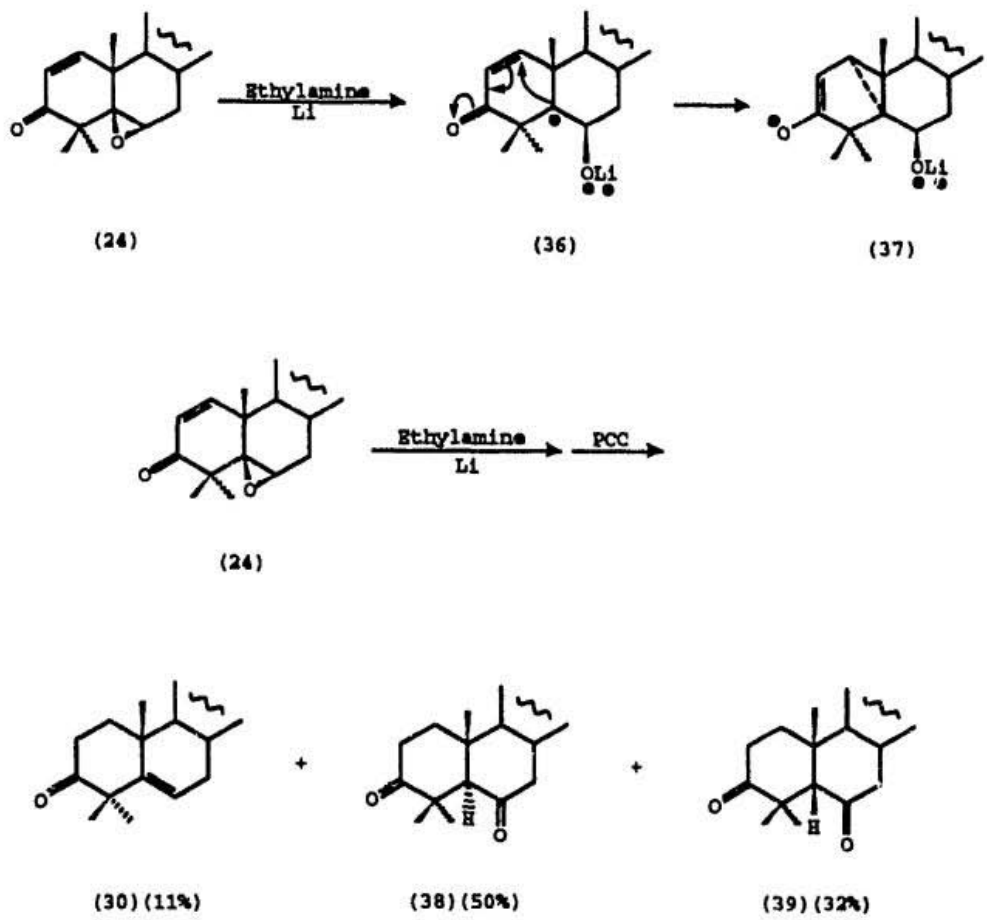
orbital of the α,β-unsaturated ketone. The direction of pyramidalization of the radical (and the ensuing carbanion) orbital was influenced by interactions with the σ-framework of the molecule. When the angular substituent is hydrogen, the carbanion which is formed will be mainly pyramidalized in the α-face resulting in the formation of *trans* product. With a methyl group at the angular position, the interaction of the radical orbital with the π*-orbital predominates since it is almost parallel to it. The resulting carbanion becomes pyramidalized in the β-face resulting in the formation of the *cis* product.



Scheme 16

It is possible that the desired transannular cyclization (Scheme 12) from the 5β,6β-epoxide **(24)** did not occur because the intermediate carbanion **(26)** was not pyramidalized favourably. That is, if it were preferentially pyramidalized at C-1 in the β-face **(26a)** as opposed to in the α-face **(26b)** it would not possess the correct stereochemistry for antiperiplanar attack on the epoxide. This would be the case as a result of the interactions with the σ-framework, especially with the C-19 methyl group. Proton abstraction from ammonia must therefore have occured faster than intramolecular cyclization.

It is known that reductions employing sodium or lithium in ethylamine can yield different results than when they are employed in liquid ammonia.[25,26] Hallsworth and Henbest[26] found that the course of reductive ring opening of 5β,6β-epoxycholestane could be altered when lithium was used with ethylamine. They proposed that a C-5 carbanion was formed directly by the reductive ring-opening of the epoxide under these conditions. Epoxide **(24)** was therefore treated with lithium in ethylamine at 0°C with the hope that a carbanion formed at C-5 in intermediate **(36)** would undergo an intramolecular Michael addition to form a 1α,5α-cyclosteroid **(37)** (Scheme 17).



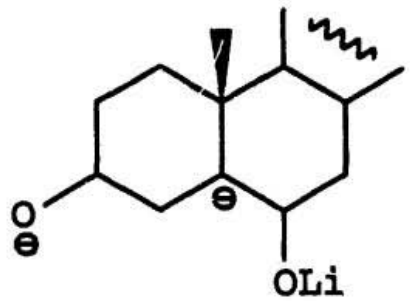
Scheme 17

A more complex mixture was obtained than those from the corresponding lithium-liquid ammonia reductions. The mixtures were simplified considerably by oxidation with PCC to afford only three compounds, none however being the desired cyclosteroid. The compounds were the C-5 epimeric 4,4-

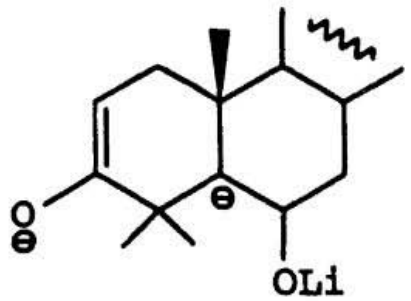
dimethylcholesta-3,6-diones **(38,39)** and 4,4-dimethyl- cholest-5-en-3-one **(30)**. The 5α-dione **(38)** was the major product (50%). The 5β-dione **(39)**, which was obtained in 32% yield, was epimerized to **(38)** by treatment with sodium methoxide. Thus, both the α,β-unsaturated carbonyl system and the epoxide were reduced under these conditions.

The initial complex mixture which was formed resulted from the fact that three asymmetric centres were produced during the reduction. PCC oxidation removed the two asymmetric centres at C-3 and C-6 by converting the epimeric diols into the corresponding ketones.

That compound **(30)** was obtained indicated that elimination of the epoxy oxygen had also occurred during the reaction with lithium in ethylamine. Hallsworth and Henbest[27] reported an analogous finding when they obtained approximately 11% of cholesterol when 5β,6β-epoxycholesterol was treated with lithium-ethylamine under similar conditions. The remainder of their reaction product was unreacted epoxycholesterol. They explained their result by suggesting that carbanion formation at C-5 was inhibited by the proximity to C-5 of the oxyanion at C-3 of the intermediate **(40)**. Thus, the only reaction they observed was the formation of a small amount of deoxygenation product (cholesterol).



(40)



(41)

In our case, reduction of the epoxide ring was found. Carbanion formation at C-5 would not be inhibited as was presumed to have been the case with 5β,6β-epoxycholesterol because the enolate oxyanion at C-3 of the intermediate **(41)** is sufficiently distant from C-5 due to the presence of the rigid double bond and the hindrance of the two methyls at C-4.

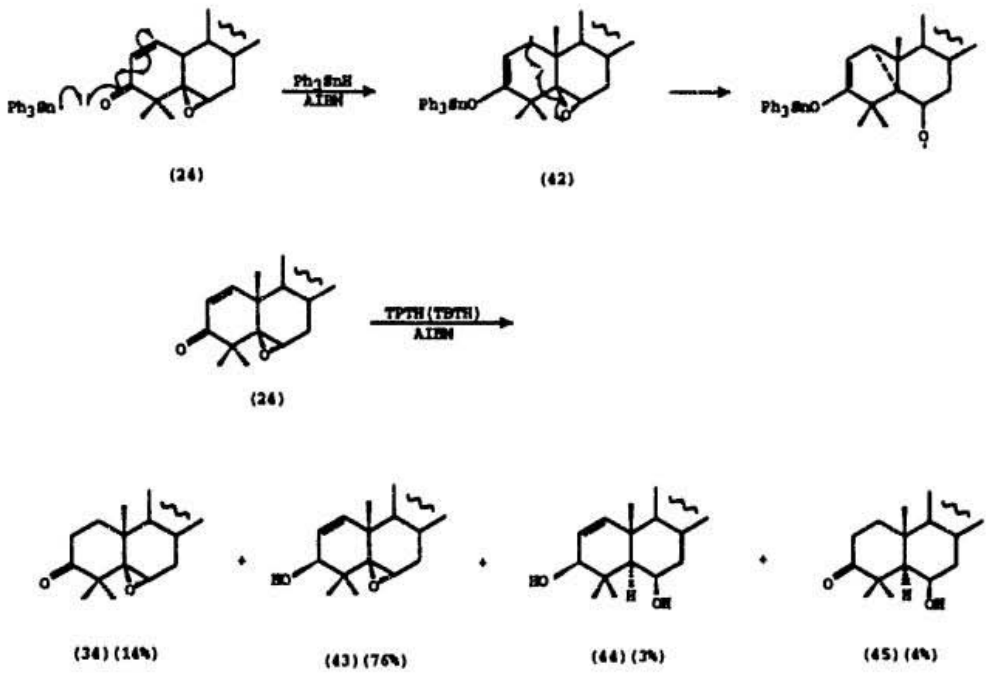
The absence of any cyclized product can be rationalized by the following argument. Formation of both **(38)** and **(39)** suggests that the carbanion at C-5 was pyramidalized in approximately equal amounts in the α- and β-faces. The carbanion that is pyramidalized in the β-face is not suitably oriented for transannular Michael addition and it undergoes

preferential proton abstraction from the ethylamine. When the angular substituent is hydrogen, the carbanion formed in the intermediate will mainly pyramidalize in the α-face, resulting in the formation of trans products. With a methyl group at the angular position the situation changes. The C-C σ-orbital dominates because the methyl is almost parallel to the concerned orbital so that the carbanion is now pyramidalized in the β-direction resulting in the production of the *cis* products.

On the other hand, if the C-5 carbanion was formed and pyramidalized in the α-face while the α,β-unsaturated ketone was still present, the transannular C-5 to C-1 cyclization would have been a 5-*endo*-*trig* type cyclization. According to Baldwin's rules, it is a disfavoured process. In our case, therefore, proton abstraction from ethylamine would be a much more favourable process than the cyclization.

Triphenyltin hydride (TPTH) and tributyltin hydride (TBTH) reduce α,β-unsaturated ketones by a radical mechanism.[28,29] It was therefore of interest to determine whether a radical-induced intramolecular cyclization[30] could be effected with our system with a tin enolate radical such as **(42)** (Scheme 18).

When a dilute solution of **(24)** was treated with TPTH and azo*bis*-isobutyronitrile (AIBN), a mixture of four compounds was obtained. The major product was the enol-epoxide **(43)** (76%), the keto-epoxide **(34)** (14%) and small amounts (3% and 4% respectively) of the corresponding epoxide ring-opened products, diol **(44)** and hydroxy-ketone **(45)**.



Scheme 18

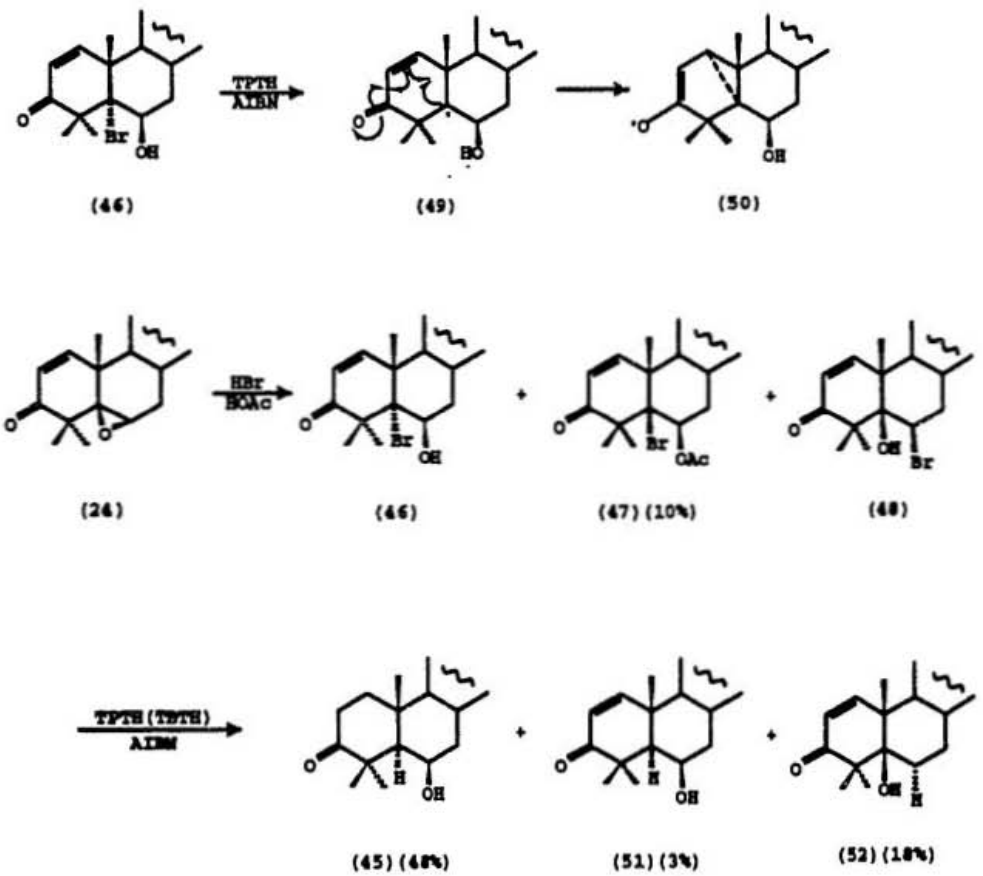
The fact that **(44)** and **(45)** were obtained albeit in small amounts, indicated that the epoxide ring could be opened by

TPTH/AIBN. Previous examples of epoxide ring opening which have been reported include an α,β-epoxyketone[31] and thionoimidazolides[30] prepared from α,β-epoxyalcohols. The structure of the hydroxy-ketone **(45)** was confirmed by its conversion to **(38)** by PCC oxidation (Scheme 17). The enol-epoxide **(43)** was identified by comparison with the product obtained by $NaBH_4$-reduction of **(24)**, and by PCC oxidation of **(43)** back to **(24)**.

These results can again be rationalized by considering that the radical formed at C-1 in intermediate **(42)** was mainly pyramidalized in the β-face. This of course, would not be suitable for the desired transannular cyclization (Scheme 18). Alternatively, whatever its direction of pyramidalization, the C-1 radical could, once formed, abstract hydrogen from TPTH faster than it could undergo cyclization.

Since we were unable to effect transannular cyclization using reductive methods on the α,β-unsaturated ketone-epoxide **(24)**, we explored the potential for a more typical radical cyclization route. Thus, as depicted in Scheme 19, if a bromide were present at C-5 **(46)**, TPTH could remove the halide and the resulting C-5 radical in the intermediate **(49)** might undergo transannular cyclization[32] to the double bond at C1-C2 to yield the corresponding 1α,5α-cyclosteroid **(50)**.

Reaction of **(24)** with HBr in acetic acid gave the bromohydrin **(46)**, its corresponding acetate **(47)** and the 6α-bromo-5β-hydroxy bromohydrin **(48)**. The bromohydrins could not be purified by chromatography, and during attempted separation both reverted back to starting material **(24)**. Only **(47)** could be isolated and characterized. Therefore, the crude



Scheme 19

bromohydrin mixture was treated with TBTH/AIBN in refluxing benzene. The resulting product mixture consisted of three compounds with spectral properties consistent with the structures **(45)**, **(51)** and **(52)** and an unstable fourth compound, which we were unable to characterise.

The major product (48%) was identical with **(45)**, which was obtained previously as in Scheme 18. This indicated that the bromine atom of the bromohydrin could indeed be removed by TPTH to form intermediate **(49)** with a radical at C-5, but that resulting radical did not undergo transannular addition to the α,β-unsaturated ketone to form the desired 1α,5α-cyclosteroid **(50)**.

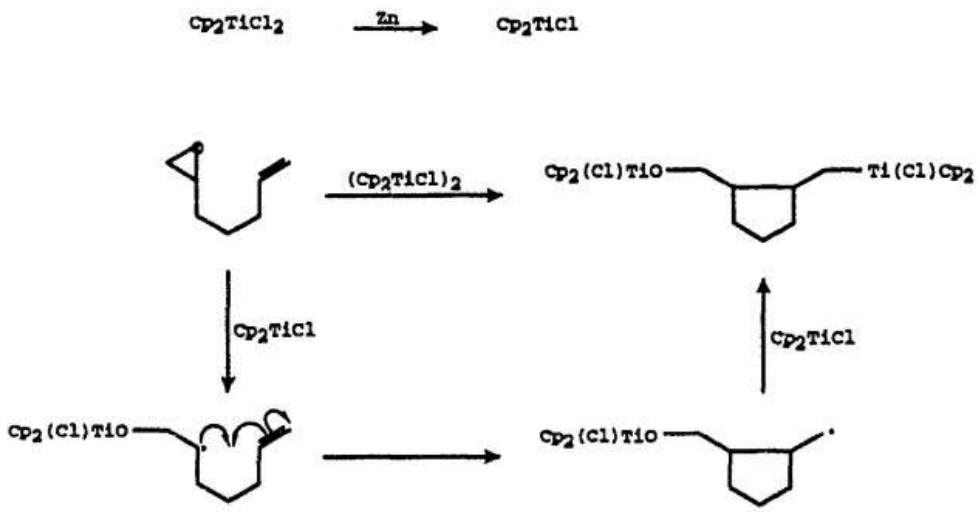
It is possible, of course, that the α,β-unsaturated ketone was reduced first so that no transannular Michael addition would occur. However, as **(51)** and **(52)** were also isolated, this result could imply that radical formation occurred at C-5 from bromohydrin **(46)** and at C-6 from bromohydrin **(48)**, while the α,β-unsaturated ketone was still present. Since compound **(51)** had a trans A/B ring junction, this result suggests that the radical formed at C-5 **(49)** was pyramidalized in the α-face which is required for the cyclization to occur, but that cyclization did not occur under these conditions. Here again the transannular C-5 to C-1

cyclization is a disfavoured 5-*endo-trig* type cyclization according to Baldwin's rules. Thus, hydrogen abstraction from TPTH by the C-5 radical was likely to have been faster than the cyclization.

Compound **(52)** was found to be inert to PCC oxidation, confirming the presence of a tertiary hydroxy group.

It is interesting to note that when the 5β,6β-epoxide group was present as in **(24)**, the major product of TPTH reduction was that in which the C-3 carbonyl group was reduced **(43)** (Scheme 18). Without the epoxide group present, however, normal reduction of the carbon-carbon double bond was preferred **(45)** (Scheme 19).

In 1988, Nugent and RajanBaBu[33] reported that *bis*(cyclopentadienyl)titanium(III) chloride promotes reductive cleavage of the C-O bond of an epoxide ring to generate a radical, which after cyclization could be efficiently scavenged by a second equivalent of titanium(III) to yield a cyclized product. Scheme 20[33] shows an example of this type of epoxyolefin cyclization. *Bis*(cyclopentadienyl)titanium(III) chloride is prepared by zinc reduction of commercially available *bis*(cyclopentadienyl)titanium(IV) dichloride.

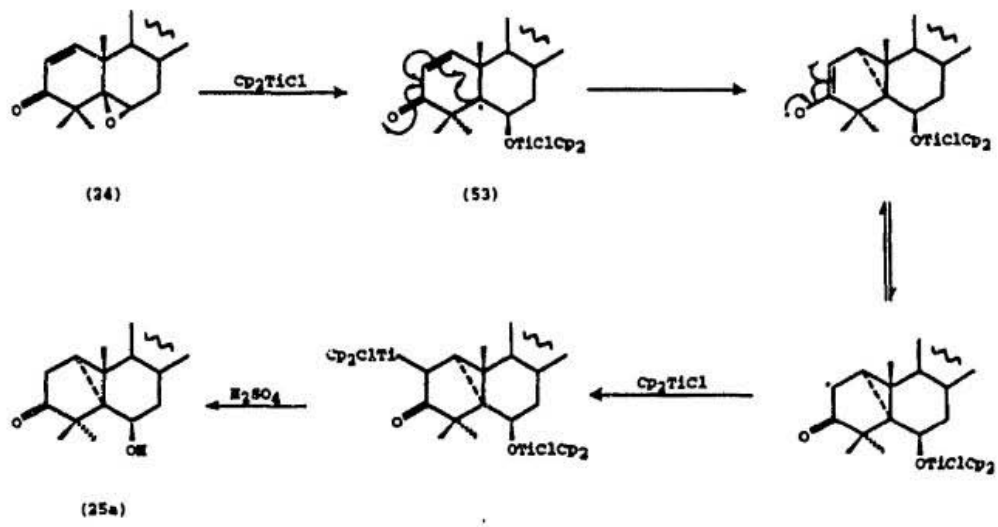


Scheme 20

It was then of interest to us if this process could occur with our system. As depicted in Scheme 21, it was hoped that, after reductive cleavage of the tertiary C-O bond, the radical formed at C-5 in intermediate **(53)** would be sufficiently long-lived to undergo a disfavoured 5-*endo-trig* type cyclization to give 1α,5α-cyclosteroid **(25a)**.

When epoxide **(24)** was treated with *bis*(cyclopentadienyl)titanium(III) chloride, the only product that was separated besides unreacted epoxide **(24)** was dienone **(31)**. Elimination of the epoxy oxygen obviously did occur, but

cyclization did not.

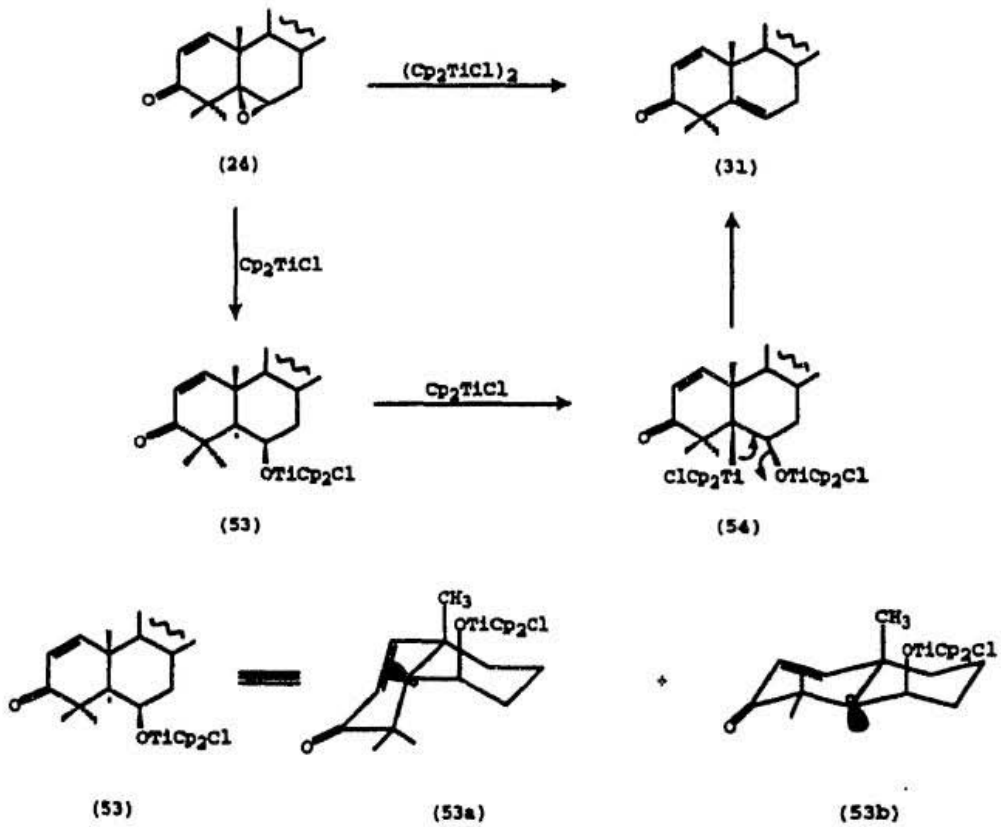


Scheme 21

The reactions shown in Scheme 22 can account for the observed product. In this scheme C-O bond cleavage indeed occurred with radical formation at C-5 **(53)**. Instead of cyclization, however, the radical was scavenged by a second equivalent of the titanium(III) reagent to form intermediate **(54)**. After *syn* elimination from **(54)** dienone **(31)** was formed as the final product.

Pyramidalization of the intermediate radical can again be invoked to rationalize the observation. The radical formed at C-5 would have been mainly pyramidalized in the β-face **(53a)**,

which would not be suitably oriented for the cyclization to occur. Alternatively, even if α-pyramidalization **(53b)** did occur, the 5-*endo-trig* type cyclization from C-5 to C-1 could be considered as too unfavoured and as a result the C-5 radical would react with a second equivalent of titanium(III) reagent to form **(54)**.



Scheme 22

CHAPTER THREE

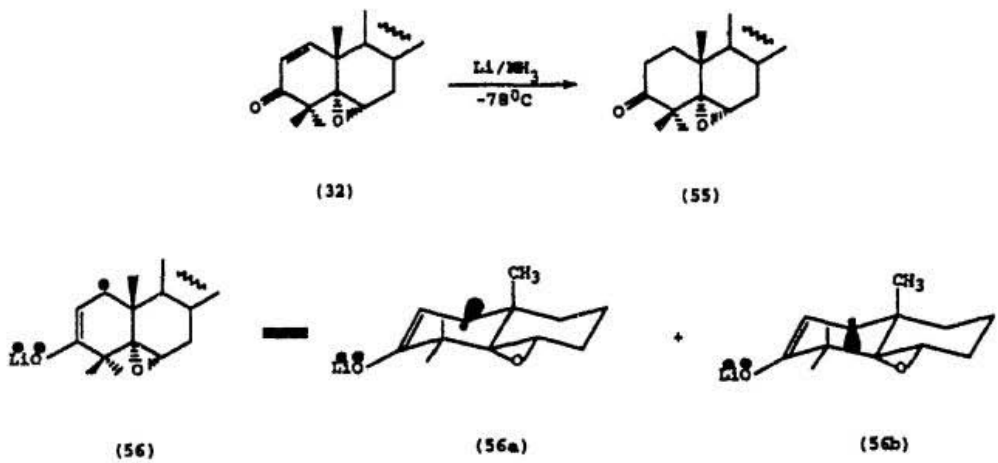
OTHER SYNTHETIC APPROACHES TOWARDS 1α,5α-CYCLOSTEROIDS

Since efforts using 5β,6β-epoxide **(24)** as a synthetic precursor for 1α,5α-cyclosteroids were unsuccessful, we evaluated 5α,6α-epoxide **(32)** as an alternative starting compound.

Epoxide **(32)** reacted with lithium in liquid ammonia at -78°C to yield 5α,6α-epoxy-4,4-dimethylcholestan-3-one **(55)** as the major product. Thus, although the α,β-unsaturated carbonyl system could be reduced, presumably via the dicarbanion **(56)**, cyclization via transannular attack of the epoxide did not occur (Scheme 23).

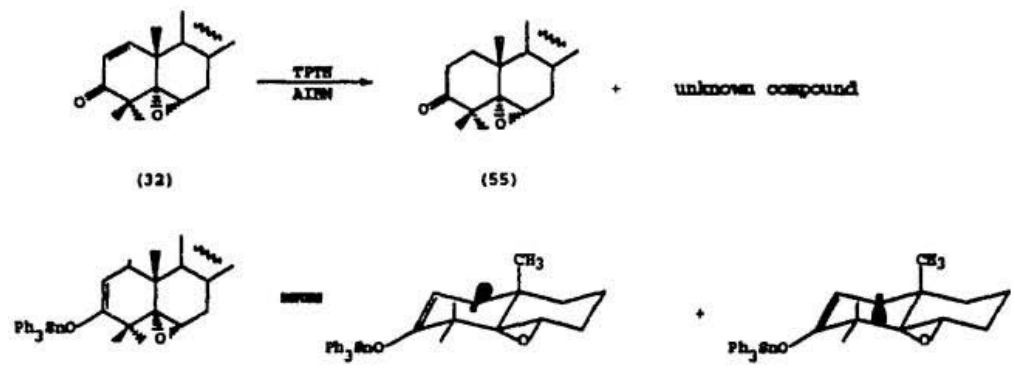
Here again the carbanion formed at C-1 will preferentially pyramidalize in the β-face **(56a)** as opposed to the α-face **(56b)** by the same argument used previously. However in this case the geometry was suitable for cyclization, and cyclization from C-1 to C-5 was a 3(or 5)-*exo-tet* type both favoured according to Baldwin's rules. However, cyclization still did not occur. It seems to us that the main reason for the failure of cyclization was that the carbanion at C-1 was sufficiently long-lived to undergo the desired cyclization

before being protonated by the ammonia.



Scheme 23

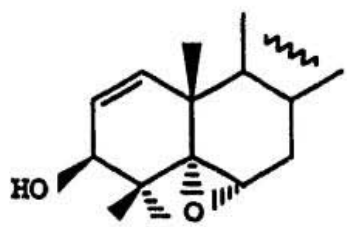
The reactions of **(32)** with TPTH and TBTH were also investigated (see Scheme 24).



Scheme 24

Again, as in the corresponding reaction with **(24)** (see Scheme 18), the radical formed at C-1 was not sufficiently long-lived to effect cyclization and instead abstracted hydrogen from the TPTH or TBTH more rapidly.

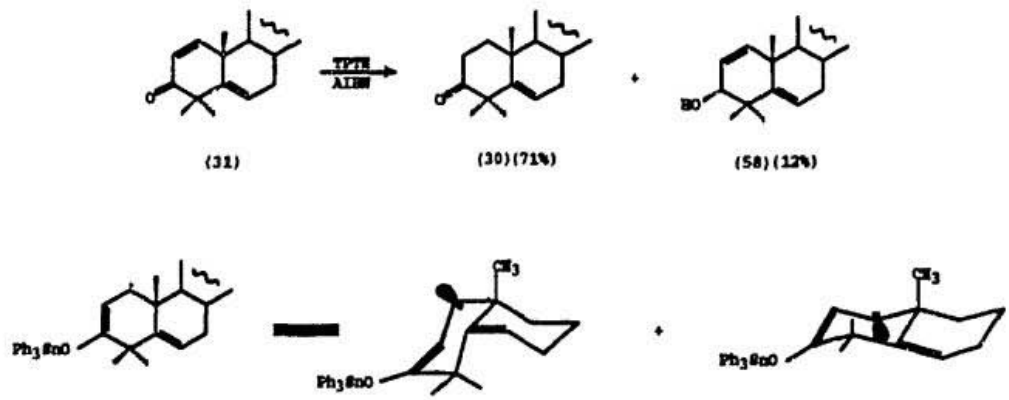
A likely product from the TPTH reduction of 5α,6α-epoxide **(32)** would be **(57)**. An attempt to synthesize **(57)** by direct $NaBH_4$ reduction of **(32)** gave at least four products by tlc. Insufficient quantities were obtained to characterize fully these products. The epoxide **(57)** was labile and decomposed either during the reaction or upon work-up.



(57)

In order to ascertain whether radical-induced cyclization would be effected with a different substrate, compound **(31)** was reacted with TPTH (or TBTH). As depicted in Scheme 25, 4,4-dimethylcholest-5-en-3-one **(30)** and 4,4-dimethylcholesta-1,5-dien-3β-ol **(58)** were obtained in 71% and 12% yields,

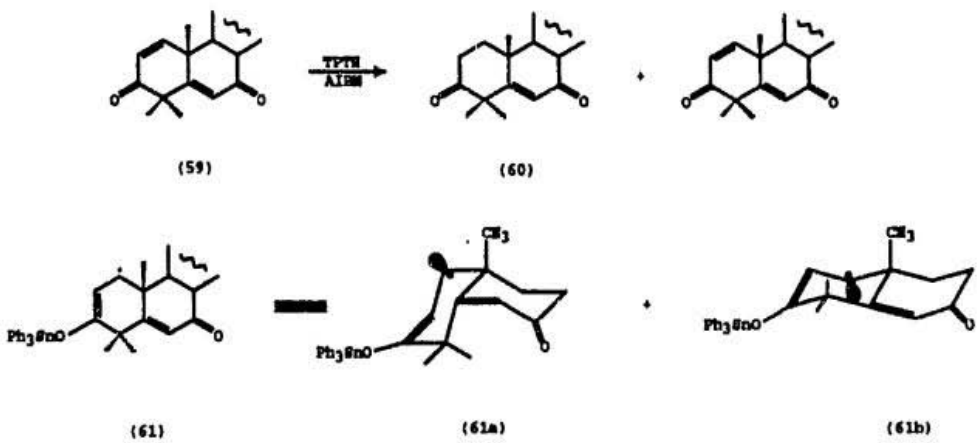
respectively. The structure of **(58)** was confirmed by comparison with the product obtained from $NaBH_4$ reduction of **(31)**. Thus, as seen previously, the α,β-unsaturated ketone could be reduced without any cyclization occurring.



Scheme 25

4,4-Dimethylcholesta-1,5-diene-3,7-dione **(59)** was also reacted with TPTH and TBTH (Scheme 26). The only product obtained besides unreacted starting material was 4,4-dimethylcholest-5-ene-3,7-dione **(60)**. This suggested that the tin enolate **(61)** could have been formed but as seen in the previous examples, hydrogen abstraction could have occurred faster than any Michael-type intramolecular addition to the C-5 - C-7 α,β-unsaturated ketone. This would be especially

likely if the radical at C-1 were preferentially pyramidalized in the β-face (**61a**), and thus could not undergo the intramolecular cyclization. Our results also imply that the reduction of the A-ring α,β-unsaturated ketone is faster than that of the B-ring α,β-unsaturated ketone.



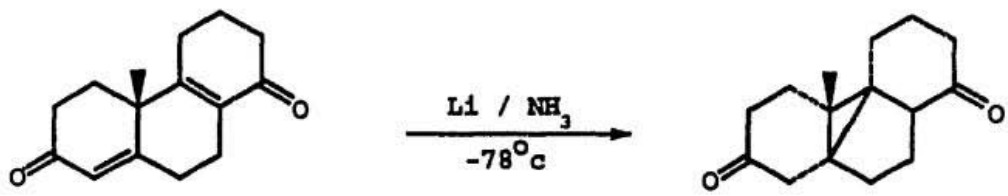
Scheme 26

CHAPTER FOUR

SYNTHESIS AND CHEMISTRY OF

4,4-DIMETHYL-1α,5α-CYCLOCHOLESTA-3,7-DIONE (62)

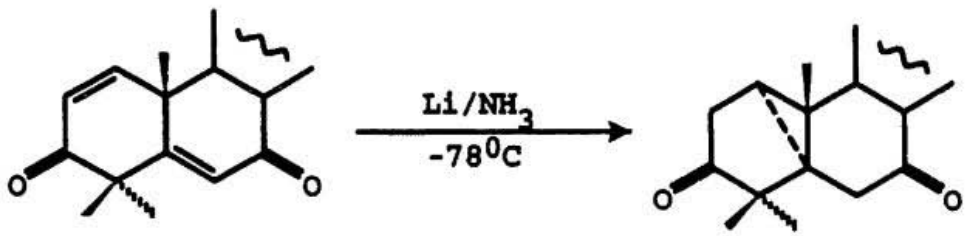
In 1989 Wenkert and Moeller[34] reported an intramolecular reductive coupling of the *bis*-α,β-unsaturated ketone **(63)** to give **(64)** in 97% yield (Scheme 27).



(63) **(64)**

Scheme 27

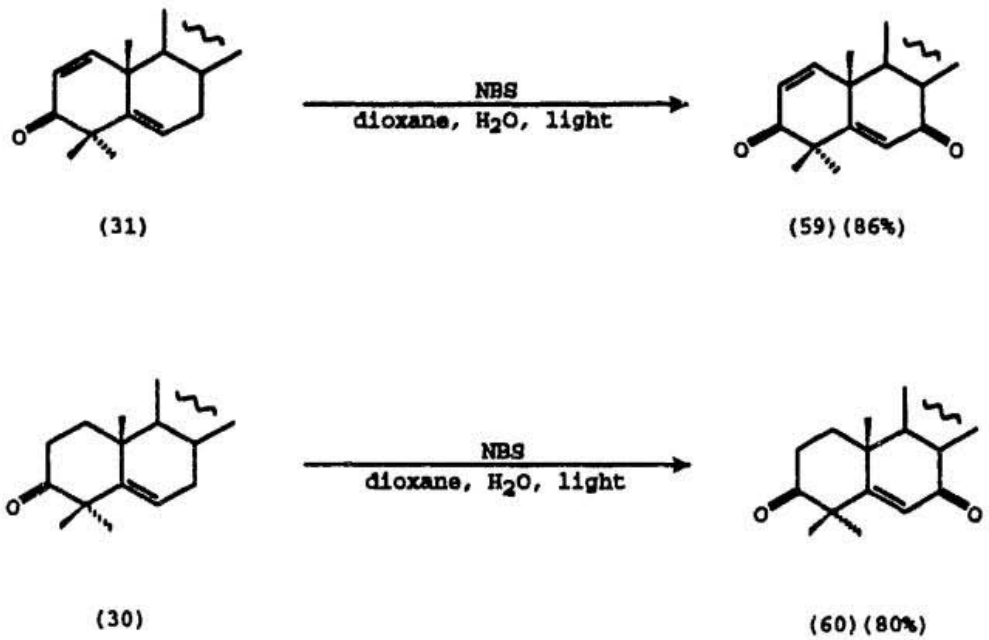
It was described earlier (Scheme 26) that the *bis*-α,β-unsaturated ketone **(59)** was used to evaluate the potential for a radical-induced cyclization with TPTH (or TBTH). It was of interest to determine whether **(59)** by analogy with Wenkert and Moeller's system, could undergo a similar intramolecular reductive coupling to give **(62)** (Scheme 28).



(59) **(62)**

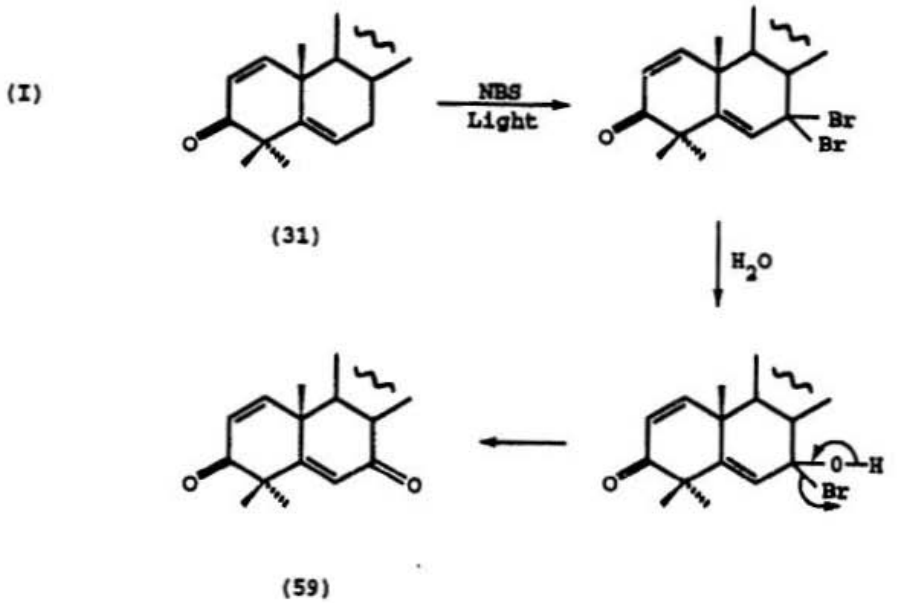
Scheme 28

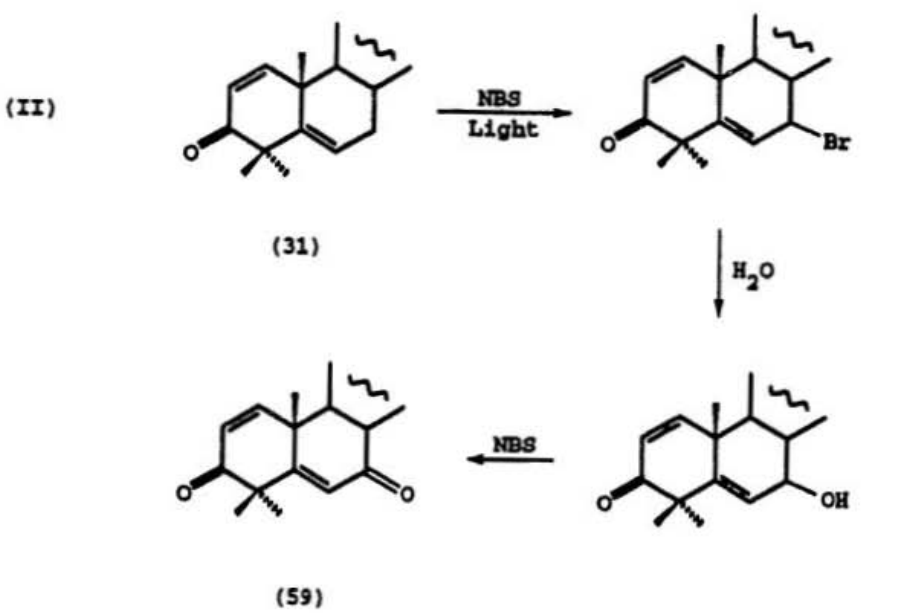
Dienedione **(59)** was prepared by photo-oxidation[35] of the dienone **(31)** in dioxane with N-bromosuccinimide (NBS). A similar allylic oxidation occurred when 4,4-dimethylcholest-5-en-3-one **(30)** was treated under the same conditions to yield 4,4-dimethylcholest-5-ene-3,7-dione **(60)** (Scheme 29).



Scheme 29

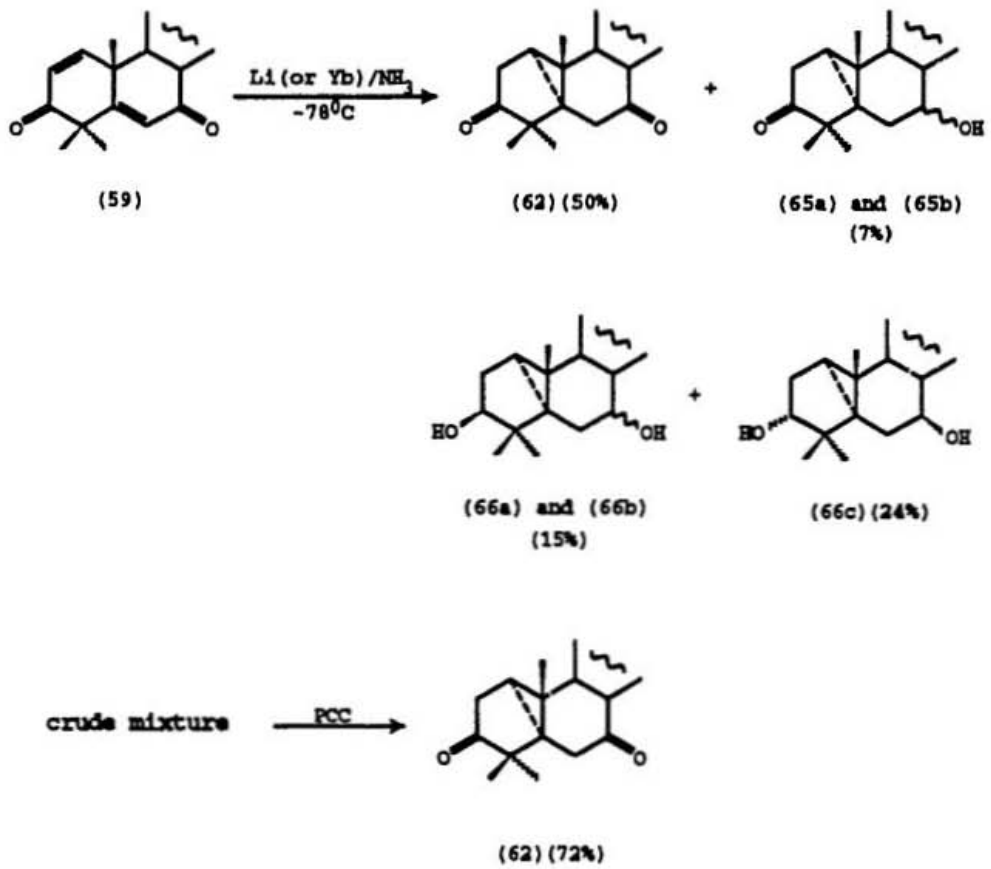
The mechanism of the reaction is believed to involve a bromination followed by hydrolysis, as depicted in pathway I or II in Scheme 30.





Scheme 30

When **(59)** was reacted with lithium in liquid ammonia, a mixture of several products was obtained. The mixture was simplified considerably by oxidation using PCC to afford a single product in 72% yield.



Scheme 31

This product showed two carbonyl absorptions in its IR spectrum, at 1,742 cm^{-1} and 1,713 cm^{-1}, which are consistent

with a cyclopentanone and a cyclohexanone, respectively. These data, and the mass spectrum are in agreement with the 1α,5α-cyclosteroid structure **(62)**. However, there was no cyclopropyl C-H infrared absorption discernable in the 3,040 cm^{-1} region. Furthermore, the ^{1}H-NMR spectrum was not unambiguous. An anticipated high field signal corresponding to the cyclopropyl proton[36] on C-1 (H-1) was not evident (Figure 2).

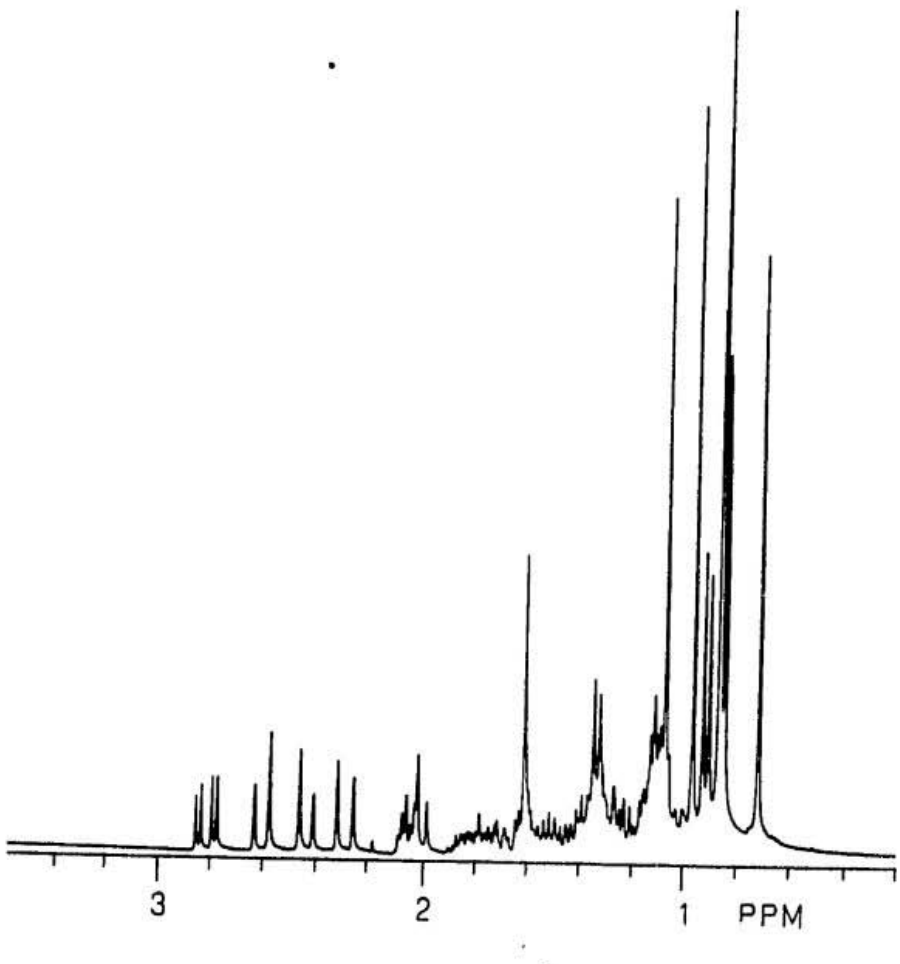
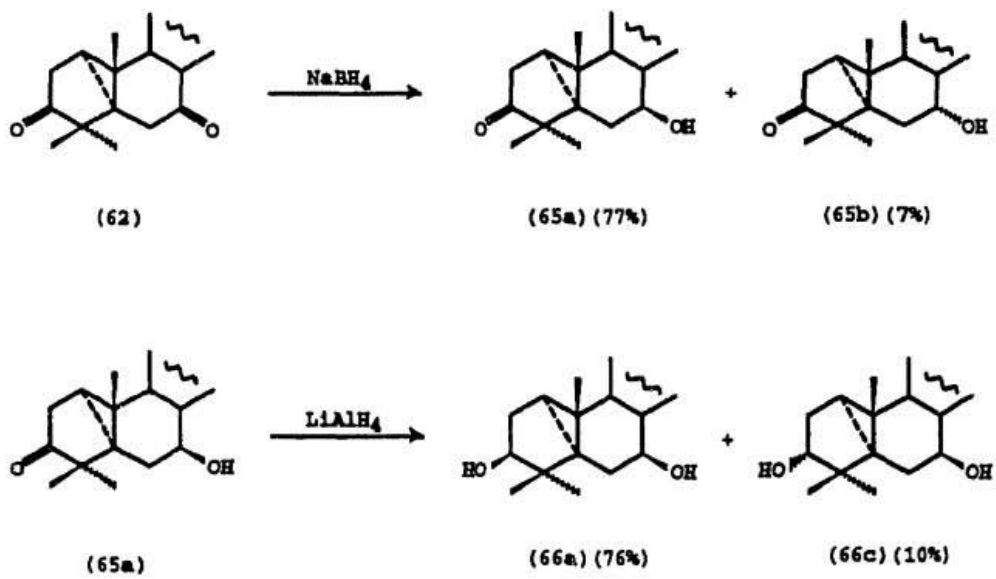


Figure 2. 300 MHz ^{1}H-NMR spectrum of **(62)**.

Although **(62)** was crystalline and a data set was collected by X-ray diffraction, there were insufficient data points to solve a structure since two crystallographically distinct steroid molecules were found to be present in the unit cell. Therefore in order to obtain more suitable crystals for X-ray diffraction, derivatives of **(62)** were prepared. Selective reduction of **(62)** using $NaBH_4$ reduced the sterically less hindered C-7 ketone to give the 7β-hydroxy compound **(65a)** as the major product, and the 7α-epimer **(65b)** as the minor product.



Scheme 32

The IR spectrum of **(65a)** showed only a single carbonyl absorption at 1,739 cm^{-1} and a sharp absorption at 3,620 cm^{-1} corresponding to the hydroxyl group. The ^{1}H-NMR spectrum (Figue 3) revealed an unexpected double triplet centred at δ 0.52 ppm, with the C-18 methyl signal being at δ 0.71 ppm. COSY indicated that this signal unexpectedly belonged to H-9 and confirmed that it was not due to the cyclopropyl proton H-1. In fact, H-1 was located as a doublet at δ 0.93 ppm.

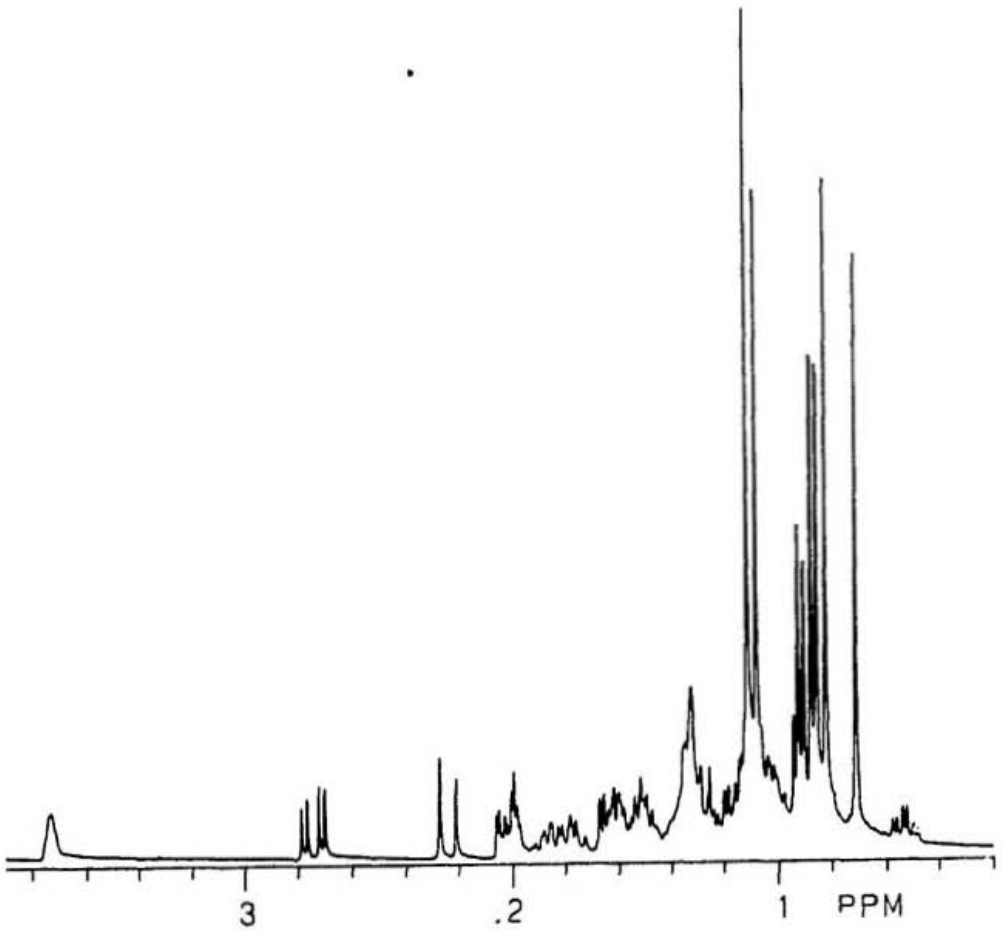


Figure 3. 300 MHz ^{1}H-NMR spectrum of **(65a)**.

HETCOR, APT and NOED experiments (Figure 4, also see Table I in Appendix for detail) were in agreement with the assignments given to the ^{1}H-NMR spectrum of **(65a)**. For example, saturation of the signals due to H-2α at δ 2.74 ppm, and also of the H-9 signals enhanced the H-1 doublet. The double triplet due to H-9 is not as clearly evident in the ^{1}H-NMR spectrum of **(65b)** but is shifted downfield into the envelope region, and could not be clearly discerned in the 300 MHz spectrum. Saturation of the signal due to H-1 enhanced the H-2α and H-9 signals.

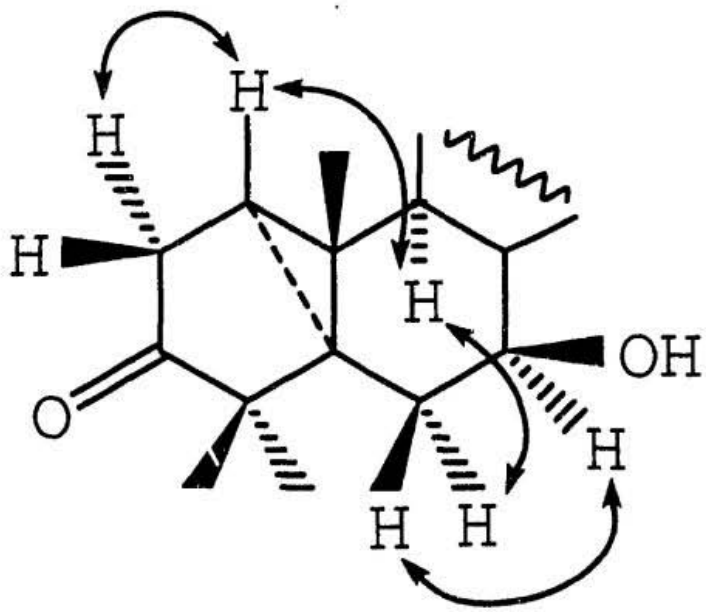


Figure 4. Selected NOE correlations for **(65a)**.

The X-ray diffraction analysis of **(65a)** confirmed the 1α,5α-cyclosteroidal structure (Figure 5). Ring B is in a clearly defined boat conformation, which is consistent with the NOED data.

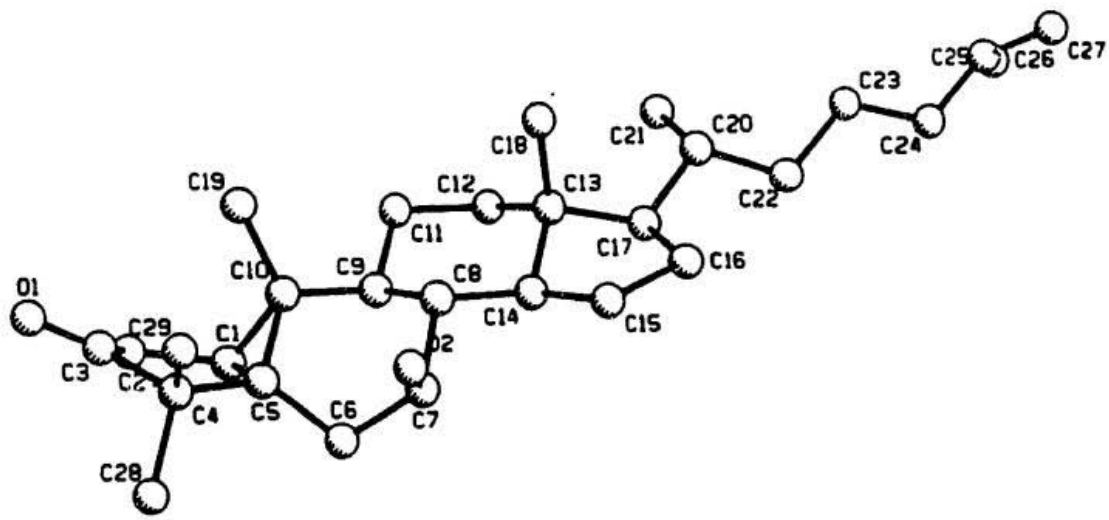


Figure 5. X-Ray crystal structure of **(65a)**.

Lithium aluminium hydride was needed to reduce the C-3 carbonyl of **(65a)** to produce diol **(66a)** (Scheme 32). A small amount of the C-3 epimeric diol **(66c)** was also obtained. The ^{1}H-NMR spectrum of **(66a)** showed the double triplet, although it was shifted further upfield to δ 0.37 ppm. COSY confirmed that this signal was due to H-9. The H-1 doublet was located at δ 0.72 ppm. HETCOR, APT and NOED spectra (Figure 6, also see Table I in Appendix for detail) of **(66a)** were also in agreement with this structural assignment. For instance, saturation of the signals due to H-2α at δ 2.48 ppm, and also of the H-9 signal, enhanced the H-1 doublet. Correspondingly, saturation of signal due to H-1 enhanced the H-9 signal (Figure 6).

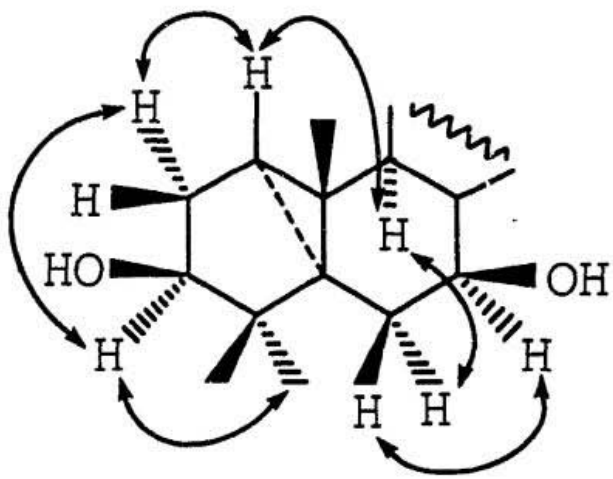
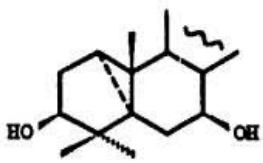
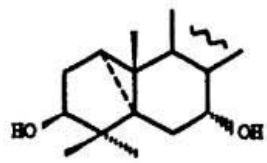


Figure 6. Selected NOE correlations for **(66a)**.

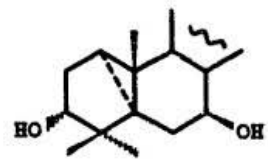
When compound **(62)** itself was reduced with lithium aluminium hydride, a 2:1 mixture of **(66a)** and its C-7 α-epimer **(66b)** was obtained. The chemical shifts of H-9 in **(66a)** and **(66c)** were shifted further upfield by 0.15 ppm and 0.21 ppm relative to that of H-9 in **(65a)**.



(66a)



(66b)



(66c)

The high-field ^{1}H-NMR signals which were observed for H-9 at δ 0.52 ppm for **(65a)** and at δ 0.37 ppm for **(66a)**, respectively, are unprecedented for such a methine proton in a steroid molecule. Molecular models of **(65a)** indicate that the cyclopropyl ring partially eclipses H-9. This is especially so when ring B is in the boat conformation that is observed in the crystal structure of **(65a)** and that is suggested by the NOED experiments on these compounds.

Since X-ray crystallographic data for the other 1α,5α-cyclosteroids that were synthesized were not available, we conducted molecular modelling calculations.[37] The calculated

torsion angles of **(62)**, **(65a)**, **(65b)** and **(66a)** indicate that the cyclopropyl ring partially eclipses H-9 in all cases, but within a very narrow range. The H_9-C_9-C_{10}-C_1 and corresponding $H_{6\alpha}$-C_6-C_5-C_1 torsion angles obtained directly from the crystal structure of **(65a)** are -12° and -7° (Figure 7), respectively, and from the modelling calculations these were -7.1° and -7.0°, respectively. The two torsion angles of relevance are tabulated in Table II (see Appendix).

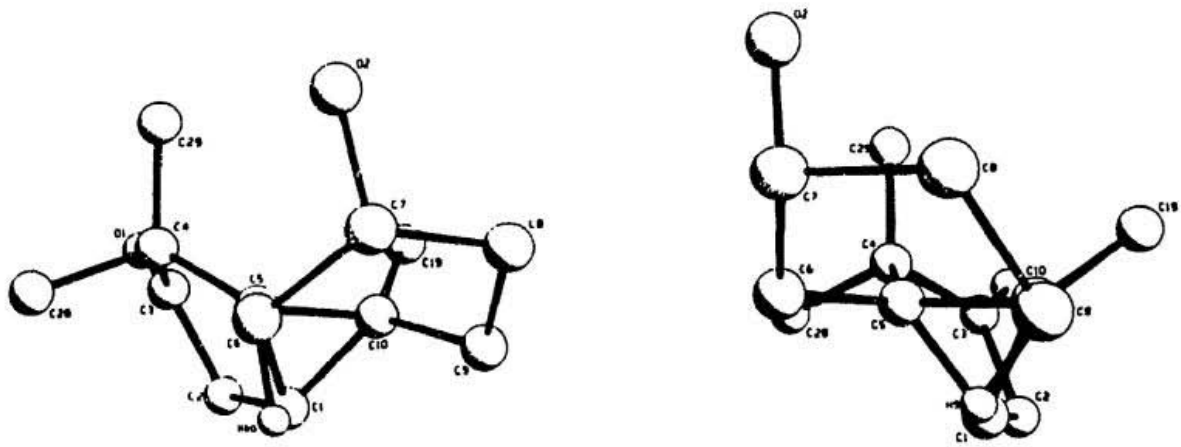


Figure 7. Pluto drawings showing the torsion angles $H_{6\alpha}$-C_6-C_5-C_1 (left) and H_9-C_9-C_{10}-C_1 (right) in **(65a)**.

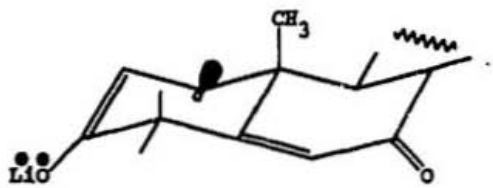
It is possible that the unusual signals observed for H-9 are influenced by an anisotropic cyclopropyl ring current effect. This effect is in turn obviously strongly influenced by the nature of the functional groups at C-3 and C-6.

With samples of compounds **(62)**, **(65a-b)** and **(66a-c)** isolated and characterized, the lithium-liquid ammonia reduction of **(59)** was re-investigated and the crude mixture obtained directly from the reaction was chromatographed. The products obtained consisted of **(62)**, the epimeric mono-alcohols **(65a-b)**, and the epimeric diols **(66a-c)** (Scheme 31). The combined yield of these products amounted to an overall yield of 90% of the 1α,5α-cyclosteroid. PCC oxidation of the mixture to **(62)** resulted in a decrease in the yield. Reduction of **(59)** using ytterbium[23] in liquid ammonia, followed by PCC oxidation of the crude reduction mixture gave the same overall yield of the diketone **(62)**.

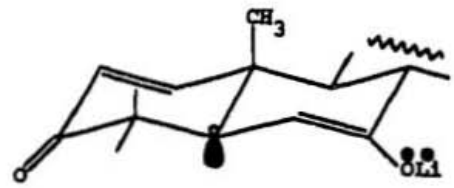
There are several mechanistic alternatives that can account for this Michael addition of one metal-enolate carbanion to the other α,β-unsaturated ketone.

If the enolate carbanion was formed at C-1 the transannular cyclization is a favoured 3-*exo-trig* and/or a 5-*exo-trig* ring closure according to Baldwin's rules. On the

other hand, if the C-1 carbanion was preferentially pyramidalized in the β-face of the molecule **(67)** it would not possess the correct stereochemistry for intramolecular Michael addition to the α,β-unsaturated ketone at C-5 - C-7. When dienedione **(59)** underwent reaction with TPTH or TBTH (Scheme 26), the C-1-C-2 double bond was preferentially reduced with no corresponding reduction of the C-5-C-6 double bond, which suggests that carbanion formation at C-1 is more favoured.



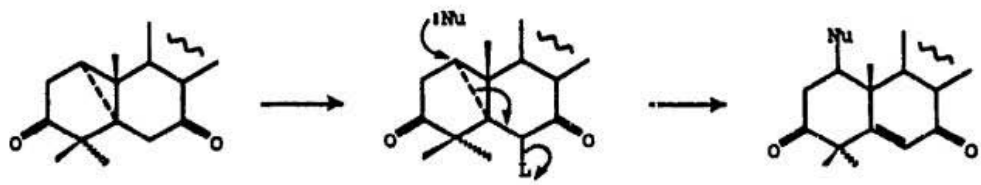
(67)



(68)

Alternatively, if the carbanion was generated more rapidly at C-5, analysis of the σ-framework[24] suggests that it is more likely to be pyramidalized predominantly in the α-face **(68)** of the molecule. This would favour the intramolecular Michael cyclization from this direction even though this mode would involve a 3-*exo-trig* and/or a 5-*endo-trig* (disfavoured) mode of cyclization.

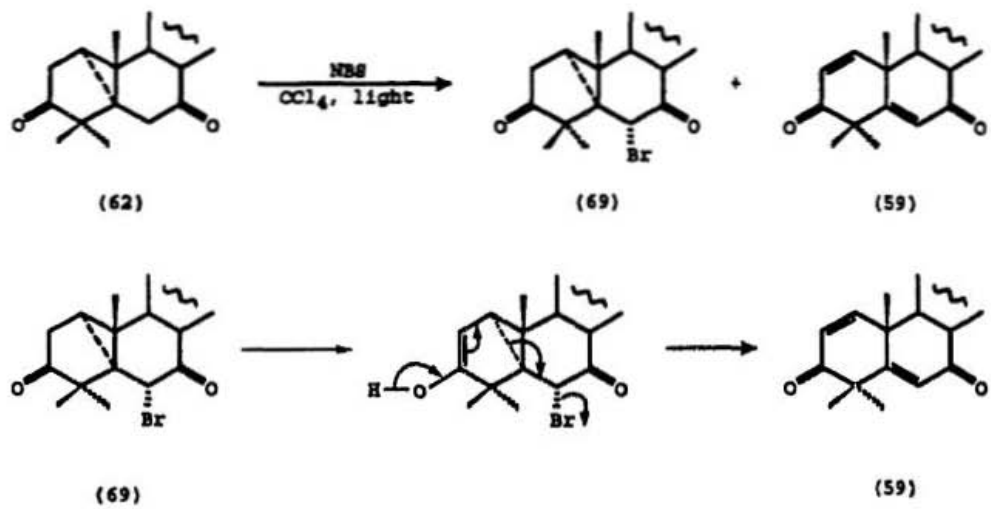
The introduction of a suitable leaving functional group (L) at the C-6 position would produce a system that might undergo a cyclopropylcarbinol-homoallylic rearrangement with a suitable nucleophile to give a C-1-substituted steroid as shown in Scheme 33.



(62)

Scheme 33

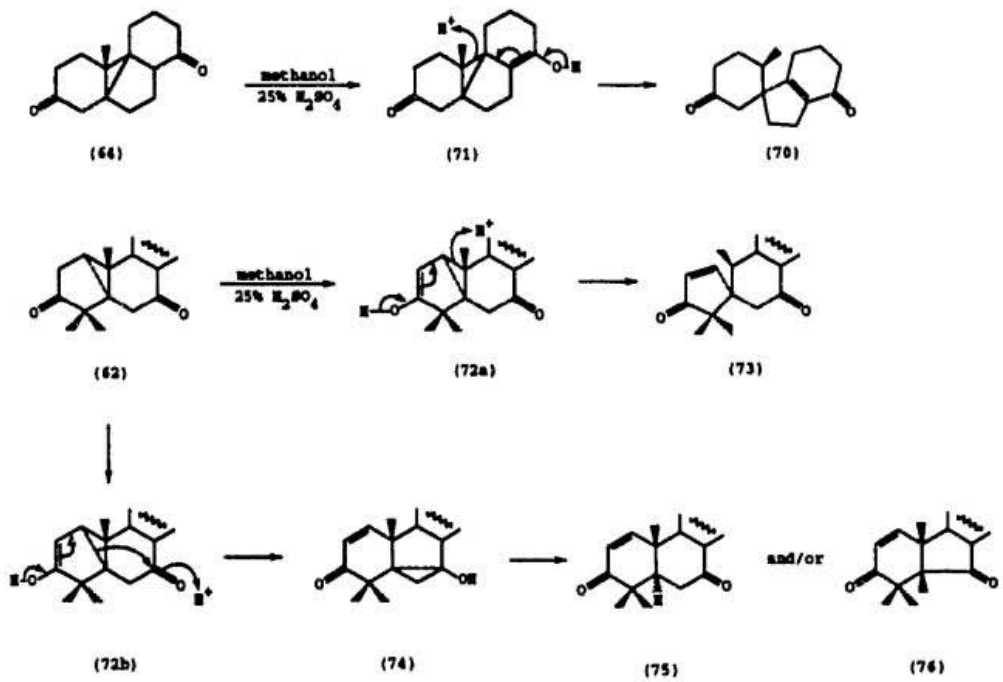
Introduction of a bromine atom at C-6 was accomplished by photocatalysed NBS reaction of **(62)** to afford the 6α-bromide **(69)**. This product was not stable enough to be purified. When the crude reaction mixture was flash chromatographed, **(69)** was isolated in only 8% overall yield. The major product was **(59)**, which could result from enolization of **(69)** and subsequent transannular elimination of hydrogen bromide (Scheme 34). This approach was not investigated any further due to time constraints.



Scheme 34

Wenkert and Moeller[34] had noted that exposure of their tetracyclic product **(64)** to methanol in 25% sulphuric acid resulted in a rearrangement to afford a spirodiketone **(70)** via the enol **(71)** (Scheme 35). We were therefore interested in examining the reactivity of our cyclosteroid **(62)** using similar reaction conditions. It was anticipated that if the C-1 - C-10 bond were to cleave as shown in **(72a)**, that a spiro compound **(73)** would be expected. If however, the C-1 - C-5 bond were to break as shown in **(72b)**, a cyclopropanol **(74)** could be formed but it would not be expected to survive the acidic conditions, and would rearrange to form **(75)** and/or

(76). Of course, the former would be produced if the C-5 -C-7 bond cleaves, and the latter would be produced if the C-6 - C-7 bond cleaves. When **(62)** was subjected to Wenkert and Moeller's reaction conditions however, no change was observed, even when the mixture was refluxed for several hours.



(64) (71) (70)

(62) (72a) (73)

(72b) (74) (75) (76)

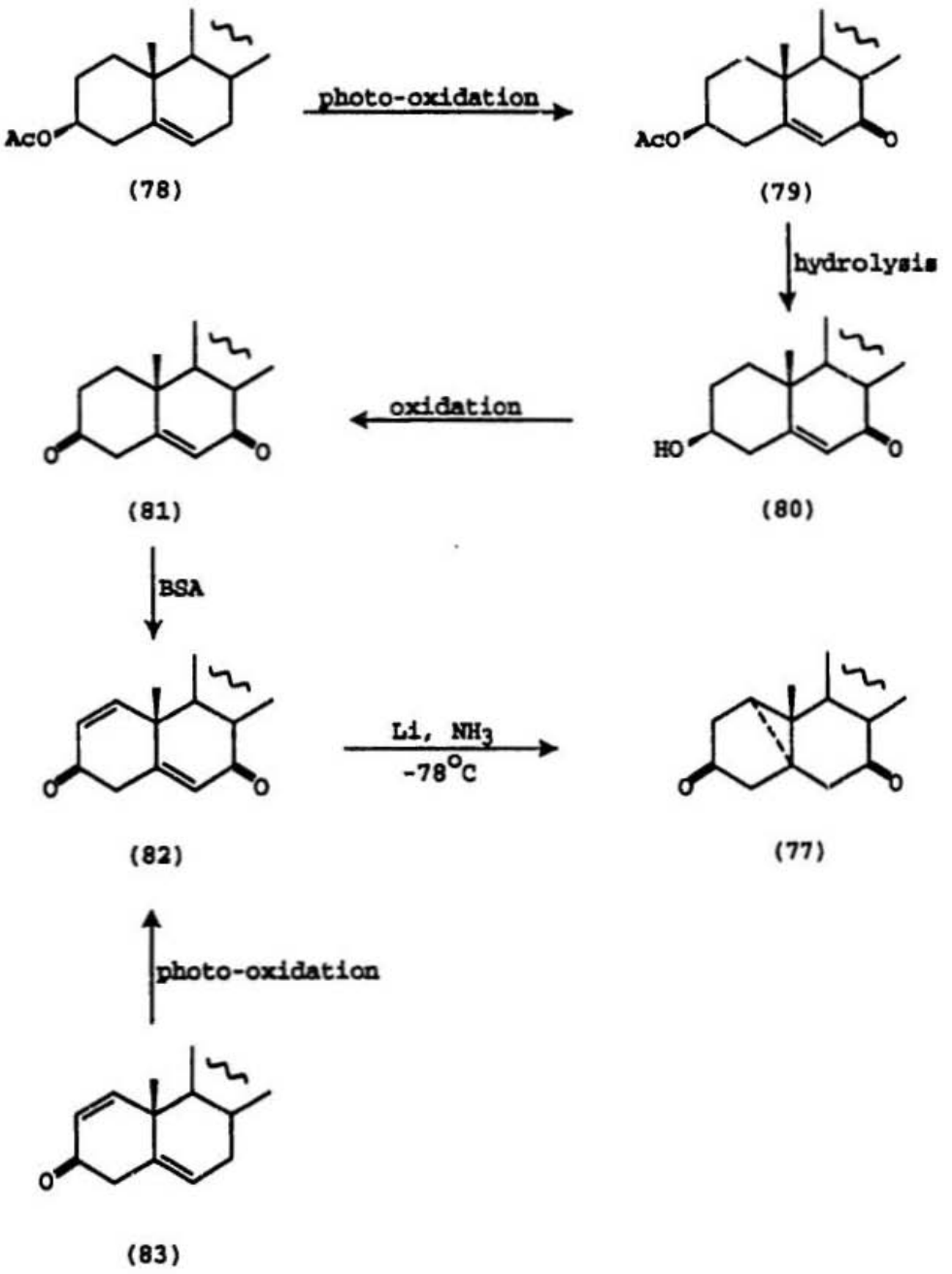
Scheme 35

CHAPTER FIVE

OTHER SYNTHETIC INVESTIGATIONS

The approaches which we had investigated up to this point all used cholesterol derivatives that had geminal methyl groups at the C-4 position. Cholecalciferols, of course, do not contain these methyl groups at C-4. However since this position is very labile, the methyl groups in this study should be considered to have been readily accessible "blocking groups" for C-4. The methyl groups are not to be considered as being typical "protecting group" since once introduced, these methyl groups cannot easily be removed. A dithiane would have served as possibly a better protecting group for C-4 as it would more easily be removed after completion of the desired transformation. However, besides being easier to synthesize, 4,4-dimethyl steroids had another advantage in that there are many that have been reported in the literature, potentially making characterization of our products easier.

Since we had succeeded in forming the 4,4-dimethyl-1α,5-cyclosteroid **(62)** we were interested in determining whether the synthesis the corresponding 1α,5α-cyclosteroid **(77)** which does not contain the geminal dimethyl group. Scheme 36 outlines the reaction sequence examined.


AcO
photo-oxidation
AcO
(78)
(79)
hydrolysis
oxidation
HO
(81)
(80)
BSA
Li, NH3
-78°C
(82)
(77)
photo-oxidation
(83)

Scheme 36

Direct photooxidation of cholesta-1,5-dien-3-one **(83)** or cholesteryl acetate **(78)** using Finucane's method[35] (Scheme 29) produced complex mixtures whose components could not be separated. However, 3β-acetoxycholest-5-en-7-one **(79)** could be obtained in 58% yield by $HgBr_2$-catalyzed[38] uv-irradiation of **(78)**. Hydrolysis with potassium carbonate converted **(79)** to its corresponding alcohol **(80)**. Attempted oxidation of **(80)** using several different reagents failed to give useful quantities of the desired product, cholest-5-ene-3,7-dione **(81)**.

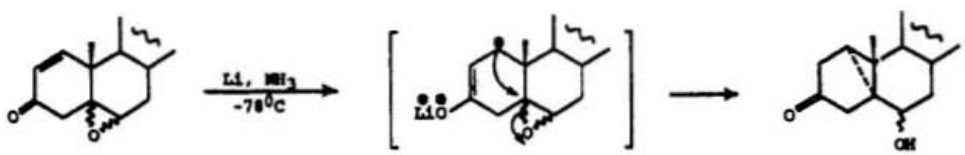
PCC and pyridinum dichromate (PDC) oxidation of compound **(80)** all produced complex mixtures whose components could not be separated and identified. Oxidation using Swern[39] conditions was then evaluated by conducting model experiments on cholesterol **(28)**. Cholest-4-en-3-one **(29)** was easily obtained as a major product. However, when oxidation of **(80)** using the same conditions was attempted, the reaction failed to go to completion. In fact only 10% of **(80)** was oxidized to the desired cholest-5-ene-3,7-dione **(81)**, with most of the starting material **(80)** remaining unchanged.

Various modifications to the conditions were undertaken to enhance the yield to acceptable levels. At temperatures below -78°C no reaction occurred. The most suitable

temperature was -60°C. When the reaction was carried out above 0°C more undesired side products were produced. When two equivalents of activated DMSO were used, the yield did not increase. If a large excess of DMSO were used however, the reaction produced a complex mixture, which could not be separated and characterized.

Since **(81)** could not be obtained in a reasonable yield, this approached was abandoned.

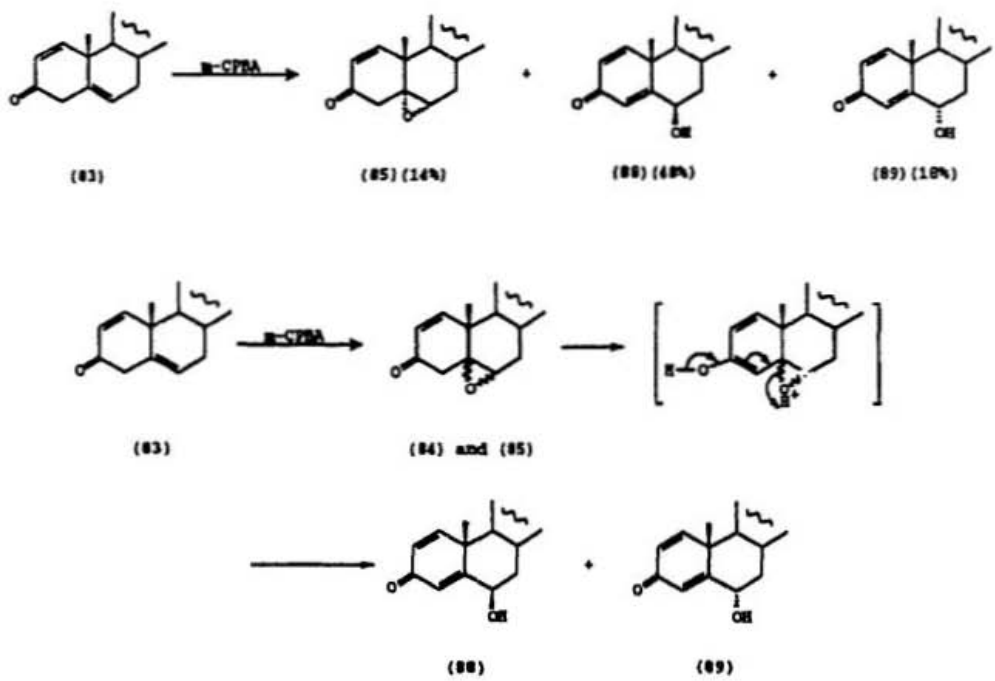
We also conducted a preliminary investigation of the reaction sequence shown in Scheme 37. It was hoped that with the absence of the geminal methyl groups at C-4, that steric hindrance would be reduced towards the intramolecular nucleophilic epoxide opening of the 5β,6β-epoxide **(84)** or 5α,6α-epoxide **(85)**, as shown in **(86)** (Scheme 37).



(84) and (85) **(86)** **(87)**

Scheme 37

Epoxidation of cholesta-1,5-dien-3-one **(83)** with mCPBA in refluxing dichloromethane solution for four hours gave a mixture of the 5α,6α-epoxycholest-5-en-3-one **(85)**, 6β-hydroxycholesta-1,4-dien-3-one **(88)** and 6α-hydroxycholesta-1,4-dien-3-one **(89)**. The yield of 5α,6α-epoxide **(85)** was only 14%, with none of the 5β,6β-epoxide **(84)** being obtained. As expected it appeared that these epoxides were more labile than their corresponding dimethyl analogs **(24)** and **(32)**. The epoxide ring opening sequence shown in Scheme 38 accounts for the formation of **(88)** and **(89)** from **(84)** and **(85)**, respectively.



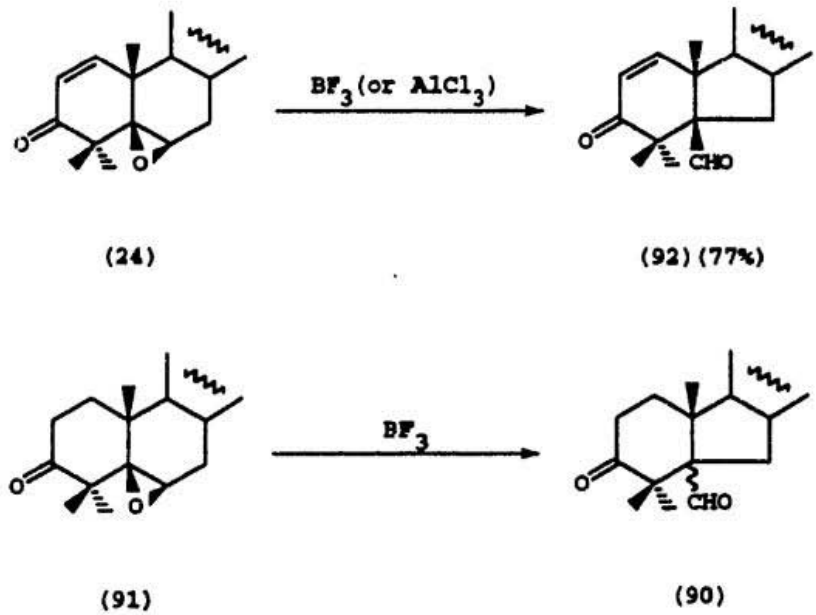
Scheme 38

Since we only had 14 mg of **(85)** and due to time constraints its reaction with lithium in liquid ammonia was not examined.

Halsall *et al.*[21] have reported obtaining a *B*-nor-keto-aldehyde **(90)** when 5β,6β-epoxy-4,4-dimethylcholestan-3-one **(91)** was reacted with BF_3-etherate. They were unable to assign the stereochemistry to the aldehyde at C-5 in **(90)**. Since we had the analogous 5β,6β-epoxide **(24)** on hand, we examined its reaction with BF_3-etherate. The reaction produced a mixture of several products, the major one (77%) being **(92)** (Scheme 39). This compound and the analogous **(90)** obtained by Halsall *et al.* can be formed via a pinacol-type rearrangement. Mechanistically, the C-5 aldehyde group in both products could be expected to be "β", or *cis* to the C-19 methyl group.

NOED experiments on **(92)** were undertaken. The ^{1}H-NMR signals due to the α- and β- C-4 methyl groups and the C-19 methyl groups were located at δ 1.17, 1.04 and 1.04 ppm, respectively. Saturation of the signal due to the aldehyde proton at δ 9.57 ppm enhanced the signals due to both the C-19 methyl and the β-C-4 methyl groups by 1%. This evidence ruled out the possibility of an α-configuration for the aldehyde group since in this case only the 4α-methyl could be expected to be positively enhanced. However, these results were not

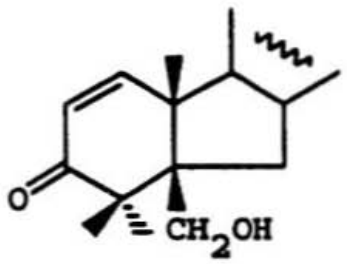
neccessarily unequivocal since the C-19 and β-C-4 methyl signals overlapped and only a relatively small NOED was observed. Suitable crystals of **(92)** for X-ray crystallography could not be obtained, therefore **(92)** was selectively reduced with $NaBH_4$ to the corresponding keto-carbinol **(93)**.



(24) **(92)(77%)**

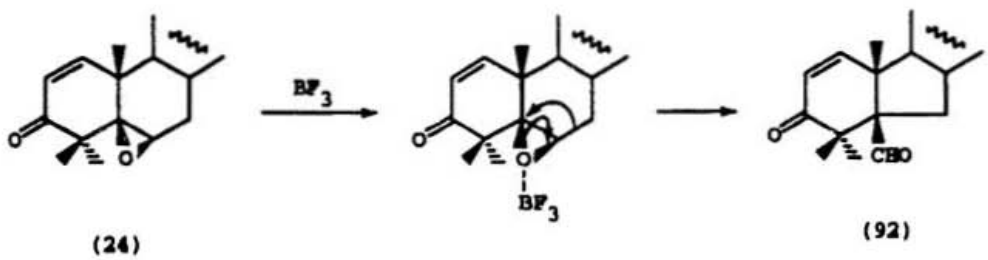
(91) **(90)**

Scheme 39



(93)

NOED experiments on **(93)** confirmed the structure. Irradiation of the signal due to the methylene protons of the carbinol group at δ 3.71 ppm enhanced the signals due to the C-19 methyl group at δ 1.21 ppm and the β-C-4 methyl group at δ 1.09 ppm by 1.7% and 2.3%, respectively. The likely mechanism for the formation of **(92)** is most likely as shown in Scheme 40. Reaction of **(24)** with $AlCl_3$ gave essentially the same results.



(24) **(92)**

Scheme 40

By extension of these arguments therefore, the product of Halsall *et al.*, **(90)**, most likely also had the aldehyde group at C-5 in the β-postion, *cis* to the C-19 methyl group.

EXPERIMENTAL

Melting points (mp) were determined on a Fisher-Johns apparatus and are uncorrected. Infrared (ir) spectra were recorded on a Mattson Polaris FT instrument. Mass spectral (ms) data were from a V.G. Micromass 7070HS instrument. ^{1}H-NMR spectra were recorded with a GE GN-300NB Spectrometer at 300 MHz. ^{13}C-NMR spectra were recorded with the same instrument at 75.47 MHz. The solvents used are noted in the experimental details. Proton nuclear Overhauser effect difference (NOED) spectra were obtained from zero-filled 32K data tables to which a 1-2 Hz exponential line-broadening function had been applied. A set of four "dummy" scans was employed to equilibrate the spins prior to data acquisition. No relaxation delay was applied between successive scans of a given frequency. Ultraviolet (uv) spectra were determined on a Unicam SP.800 Ultraviolet spectrophotometer. Microanalyses were performed by Canadian Microanalytical Service Ltd., Delta, B.C.

Preparation of 5β,6β-Epoxy-4,4-dimethylcholest-1-en-3-one ***(24)*** *and 5α,6α-epoxy-4,4-dimethylcholest-1-en-3-one* ***(32)*****.**

A solution of dienone **(31)**[19] (1050 mg, 2.55 mmol) in 20 ml CH_2Cl_2 was refluxed under argon. *m*-Chloroperoxybenzoic acid

(50-60%, 865 mg, 2.76 mmol) in 20 ml CH_2Cl_2 was added dropwise over 0.5 h. The mixture was stirred at reflux for 4 h. The solution was extracted with ether (x4) and the combined organic layers were washed with 10% $NaHCO_3$ (x3) and saturated NaCl (x4), dried ($MgSO_4$) and concentrated. Chromatography (10% benzene in hexane over aluminium oxide (Grade III) yielded the lactone **(33)** (142 mg, 12%), 5β,6β-epoxide **(24)** (776 mg, 71%) and 5α,6α-epoxide **(32)** (99 mg, 9%). For **(24)**, m.p. 101-102 °C (Found: C, 81.79; H, 10.44%. $C_{29}H_{46}O_2$ requires C, 81.63; H, 10.87; O, 7.50%); $\nu_{max}(CCl_4)/cm^{-1}$ 1687 (α, β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 0.67 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.6Hz, 27-Me), 0.90 (3H, d, J=6.5Hz, 21-Me), 1.77 -1.90 (1H, mm), 0.94 (3H, s, 4α-Me), 1.27 (3H, s, 19-Me), 1.33 (3H, s, 4β-Me), 2.01 (1H, dt, J=3.4, 12.7Hz), 2.14 (1H, ddd, J=2.2, 4.3, 14.9Hz, 7-H), 3.32 (1H, s, 6-H), 5.93 (1H, d, J=10.5Hz, 2-H), 6.90 (1H, d, J= 10.5Hz, 1-H); m/z(%): 426(65, M^+), 398(25), 383(15), 356(10), 339(4), 295(5), 247(17), 161(19), 136(82), 107(58), 81(61), 43(100). For **(32)**, m.p. 132.0-135.0 °C (Found: C, 81.69; H, 10.79%. $C_{29}H_{46}O_2$ requires C, 81.63; H, 10.87; O, 7.50%); $\nu_{max}(CCl_4)/cm^{-1}$ 1681 (α, β-unsaturated ketone); δ_H(300 MHz; $CDCl_3$) 0.65 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.6Hz, 27-Me), 0.90 (3H, d, J=6.6Hz, 21-Me), 0.93 (3H, s, 4α-Me), 1.31 (3H, s, 19-Me), 1.36 (3H, s, 4β-Me), 3.10 (1H, d, J=3.6Hz, 6-H), 5.99 (1H, d, J=10.3Hz, 2-H), 7.11 (1H, d,

J=10.3Hz, 1-H); m/z(%): 426(21, M⁺), 411(9), 383(13), 365(4), 343(3), 300(3), 275(10), 247(15), 43(100).

X-ray structure determination of ***(32)***.

Data collection was on a Rigaku AFC6S diffractometer with graphite monochromated CuKα radiation (λ = 1.54178 Å) and a 2KW sealed tube generator. Crystallographic data are summarized in Table III. Cell dimensions were determined by least-squares refinement using the setting angles of 18 carefully centred reflections in the range $48.34 < 2\theta < 49.61°$. Data were collected at a temperature of 25 ± 1 °C using the ω2θ scan technique to a maximum of 2θ value of 120.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.35° with a take-off angle of 6.0°. Scans of $(1.84 + 0.3 \tan \theta)°$ were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 2 rescans) and the counts were accumulted to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal-to-detector distance was 400.0 mm. Reference reflections measured during data collection showed no decrease in intensity. An empirical absorption correction was applied using the DIFABS[40] program,

and resulted in transmission factors ranging from 0.74 to 1.18. Corrections were applied for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 0.76059 E-06). The structure was solved by direct methods[41,42] Non-H atoms were refined either anisotropically or isotropically. Full-matrix least-squares refinements on *F* converged to *R*=0.100, R_w= 0.073, G.o.F=2.80. Weights were based on counting statistics and included a factor (p=0.01) to downweight the intense reflections. The largest peaks in the final difference Fourier map were +0.31 and -0.32 e/Å^3 respectively. Neutral atom scattering factors were taken from Cromer and Waber[43]. Anomalous dispersion effects were included in Fcalc[44]. Values for $\Delta f'$ and $\Delta f''$ were taken from Cromer[45]. All calculations were made with the TEXSAN[46] crystallographic software. Figure 1 was prepared from the output of PLUTO[47].

Formation of 5β,6β-epoxy-4,4-dimethyl-4-oxa-A-homocholest-1-en-3-one lactone ***(33)***.

A solution of dienone **(31)** (51 mg, 0.12 mmol) in 10 ml CH_2Cl_2 was refluxed under Ar. *m*-Chloroperoxybenzoic acid (50-60%, 300 mg, 0.96 mmol) in 10 ml CH_2Cl_2 was added dropwise over 0.5 h. The mixture was stirred at reflux for 12 h. The solution was extracted with ether (x4) and the combined organic layers were washed with 10% $NaHCO_3$(X3) and saturated

NaCl (X4), dried ($MgSO_4$) and concentrated. Chromatography (10% benzene in hexane over aluminum oxide) yielded the lactone **(33)** (27 mg, 48%), and a mixture containing 5α,6α-epoxide **(32)** (6 mg, 12%). For lactone **(33)**, m.p. 177.5-178.5 °C (Found: C, 78.24; H, 10.09%. $C_{29}H_{46}O_3$ requires C, 78.68; H, 10.47; O, 10.84%); $\nu_{max}(CCl_4)/cm^{-1}$ 1754 (ε-lactone); δ_H(300MHz; $CDCl_3$) 0.64 (3H, S, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.6Hz, 27-Me), 0.89 (3H, d, J=6.6Hz, 21-Me), 1.19 (3H, s, Me), 1.31 (3H, s, Me), 1.39 (3H, s, Me), 1.77 -1.90 (1H, mm), 1.98 (1H, dt, J=3.4, 12.6Hz), 2.13 (1H, dt, J=3.2, 14.0Hz, 7-H), 3.20 (1H, br d, J=1.9Hz, 6-H), 5.19 (1H, d, J=7.3Hz, 2-H), 6.26 (1H, d, J=7.3Hz, 1-H); m/z(%): 442(1, M⁺), 427(3), 399(13), 371(10), 353(2), 329(3), 287(3), 262(7), 175(6), 153(25), 123(40), 43(100).

Preparation of 5β,6β-epoxy-4,4-dimethylcholestan-3-one (34).

Freshly condensed ammonia (30 ml, dried over sodium at -78 °C) was allowed to distil into a stirring suspension of lithium (20 mg, 2.9 mmol) in anhydrous THF (5 ml) at -78 °C and the stirring continued until the metal had dissolved. A solution of 5β,6β-epoxide **(24)** (190 mg, 0.45 mmol) in anhydrous THF (5 ml) was added dropwise over 1 h and the solution stirred at -78°C for another 1 h. Enough NH_4Cl was added to discharge the blue colour and the ammonia was allowed to evaporate. Upon the addition of 30 ml of ether and 20 ml of

water the aqueous layer was extracted with ether. The combined ether solutions were washed, dried and evaporated as usual. Chromatography of the residue and gradient elution with hexane-ethyl acetate yielded 5β,6β-epoxy-4,4-dimethylcholestan-3-one **(34)** (124 mg, 65%) and a mixture of the corresponding epimeric 3α- and 3β- alcohols **(35a, 35b)** (48 mg, 25%). For compound **(34)**, m.p. 197.0-198.0 °C (needles from hexane-methanol; lit[21]: 197-200 °C); $\nu_{max}(CCl_4)/cm^{-1}$ 1716 (saturated ketone); δ_H(300 MHz; $CDCl_3$) 0.64 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.6Hz, 27-Me), 0.87 (3H, s, Me), 0.89 (3H, s, Me), 0.90 (3H, d, J=6.4Hz, 21-Me), 1.21 (3H, s, Me), 1.78 -1.90 (1H, mm), 1.98 (1H, dt, J=3.4, 12.5Hz), 2.01 -2.06 (2H, mm), 2.15 (1H, dt, J= 3.2, 14.2Hz, 7-H), 2.40 -2.58 (2H, mm), 3.07 (1H, s, 6-H); m/z(%): 428(32, M⁺), 400(15), 385(10), 343(14), 330(9), 301(2), 273(4), 247(9), 137(100), 107(47), 81(50), 55(94).

*PCC oxidation of mixture of **(35a, 35b)**.*

The mixture of the epimeric 3α- and 3β- alcohols **(35a)**, **(35b)** (40 mg, 0.09 mmol) was suspended in anhydrous CH_2Cl_2 (10 ml) and pyridinium chlorochromate (PCC) (41 mg, 0.19 mmol) was added in one portion to the magnetically stirred solution. After 2 h the reaction solution was put on the top of a short silica gel column and was washed by sufficient ether. Evaporation of the ether yielded 5β,6β-epoxy-4,4-

dimethylcholestan-3-one **(34)** (34 mg, 84%).

*Hydrogenation of β-epoxide **(24)**.*

To a solution of 5β,6β-epoxide **(24)** (51 mg, 0.12 mmol) in ethyl acetate (100 ml) was added Pd-C (5%, 15 mg) and the mixture stirred under H_2 atmosphere (1 atm) for 2 h. The reaction solution was applied onto a silica gel column and eluted with sufficient ether. Evaporation of the ether gave 5β,6β-epoxy-4,4-dimethylcholestan-3-one **(34)** in quantitative yield.

*Reaction of 5β,6β-epoxide **(24)** with lithium-ethylamine.*

A solution of β-epoxide **(24)** (200 mg, 0.47 mmol) in ethylamine (anhydrous, 99%, 15 ml) was stirred at 0 °C while lithium (108 mg, 15.5 mmol) was added. The mixture was stirred at 0 °C for 1.5 h before ether was added to discharge the blue colour. After the addition of 30 ml of ether and 20 ml of water the aqueous layer was extracted with ether. The combined ether solutions were washed, dried and evaporated as usual. Tlc showed the residue to be a complex mixtures which was difficult to separate. The crude residue in was suspended in CH_2Cl_2 (10 ml) and PCC (700 mg, 3.25 mmol) and CH_3COONa (200 mg, 2.44 mmol) were added together in one portion to the magnetically stirred solution. After 2 h the reaction mixture was directly placed onto a short silica gel column and was

washed with sufficient ether. Evaporation of the ether yielded a mixture of three major products. Silica gel chromatography using a gradient solvent system of hexane-ethyl acetate gave 4,4-dimethylcholest-5-en-3-one **(30)** (21 mg, 11%), 4,4-dimethyl-5α-cholesta-3,6-dione **(38)** (100 mg, 50%) and 5β-4,4-dimethylcholesta-3,6-dione **(39)** (65 mg, 32%). For compound **(38)**, m.p. 139.5-140.5 °C (plates from acetone-methanol; lit.[21]: 141-142 °C); $\nu_{max}(CCl_4)/cm^{-1}$ 1714 (saturated ketones); δ_H(300 MHz; $CDCl_3$) 0.68 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.87 (3H, d, J=6.6Hz, 27-Me), 0.91 (3H, d, J=6.5 Hz, 21-Me), 1.12 (3H, s, Me), 1.13 (3H, s, Me), 1.50 (3H, s, Me), 1.95 (1H, t, J=12.5Hz, 7α-H), 2.22 (1H, ddd, J=2.8, 4.2, 14.4Hz, 2α-H), 2.31 (1H, dd, J=4.2, 12.5Hz, 7β-H), 2.39 (1H, s, 5-H), 2.81 (1H, dt, J=5.9, 14.6Hz, 2β-H); m/z(%): 428 (37, M^+), 413(9), 400(3), 371(35), 315(9), 273(11), 262(4), 231(9), 165(40), 137(67), 43(100). For compound **(39)**, m.p. 118-119 °C (lit.[21]: 112-114 °C); $\nu_{max}(CCl_4)/cm^{-1}$ 1707 (saturated ketones); δ_H(300MHz; $CDCl_3$) 0.67 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.87 (3H, d, J=6.6Hz, 27-Me), 0.91 (3H, d, J=6.5Hz, 21-ME), 0.96 (3h, s, Me), 1.15 (3H, s, Me), 1.17 (3H, s, Me), 1.93 -2.09 (3H, mm), 2.38 (1H, d, J=1.5Hz, 5-H), 2.44 (1H, t, J=4.2Hz), 2.50 (1H, dd, J=1.7, 4.2Hz). m/z(%): 428(17, M^+), 400(5), 373(2), 331(100), 302(3), 273(10), 247(8), 191(15), 83(62), 43(74).

*Epimerization of **(39)** to **(38)**.*

To a solution of 4,4-dimethyl-5β-cholesta-3,6-dione **(39)** (20 mg) in dry methanol (50 ml) was added sodium and and the mixture was stirred at room temperature for 3 h. Water (10 ml) was added in to quench the reaction. The solution was extracted with ether and the combined ether layers were washed, dried and evaporated to gave 4,4-dimethyl-5α-cholesta-3,6-dione **(38)** in quantitative yield.

*Reaction of 5β,6β-epoxide **(24)** with triphenyltin hydride.*

A solution of β-epoxide **(24)** (113 mg, 0.26 mmol) in dry benzene (50 ml) was refluxed under argon while triphenyltin hydride (TPTH) (435 mg, 1.24 mmol) and a trace amount of azobisisobutyronitrile (AIBN) (7 mg, 0.04 mmol) in dry benzene (30 ml) was added dropwise over 20 h. The mixture was stirred at reflux for 50 h before a small amount of water was added to quench the reaction. The residue obtained after evaporating the solvent was placed directly onto a silica gel column. Elution first with pure benzene removed the TPTH derivatives completely. Subsequent elution using a hexane-ethyl acetate gradient solvent system gave in the following order of elution: 5β,6β-epoxy-4,4-dimethylcholestan-3-one **(34)** (15 mg, 14%); 6β-hydroxy-4,4-dimethylcholestan-3-one **(45)** (5 mg, 4%); 5β,6β-epoxy-4,4-dimethylcholest-1-en-3β-ol **(43)** (87 mg, 76%) and 4,4-dimethylcholest-1-ene-3β,6β-diol **(44)** (3 mg, 3%). For

compound **(43)**, m.p. 158.0-159.0 °C (Found: C, 81.37; H, 11.18%. $C_{29}H_{48}O_2$ requires C, 81.25; H, 11.29; O, 7.46%); $\nu_{max}(CCl_4)/cm^{-1}$ 3632, 3611 (O-H); δ_H(300MHz; $CDCl_3$) 0.63 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.8Hz, 27-Me), 0.88 (3H, s, Me), 1.02 (3H, s, Me), 1.08 (3H, s, Me), 1.76 -1.88 (1H, mm), 1.96 (1H, dt, J=3.4, 12.6Hz), 2.14 (1H, ddd, J=2.1, 4.4, 14.8Hz, 7-H), 3.28 (1H, s, 6-H), 4.08 (1H, s, 3-H), 5.50 (1H, dd, J=1.4, 10.4Hz, 2-H), 5.87 (1H, dd, J=2.5, 10.4Hz); m/z(%): 428(9, M^+), 410(8), 395(4), 360(7), 331(3), 273(2), 227(3), 175(7), 121(43), 95(52), 43(100). For compound **(44)**, $\nu_{max}(CCl_4)/cm^{-1}$ 3624 (two free O-H); δ_H(300MHz; $CDCl_3$) 0.70 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.6Hz, 27-Me), 0.91 (3H, d, J=6.5Hz, 21-Me), 1.09 (3H, s, Me), 1.14 (3H, s, Me), 1.28 (3H, s, Me), 1.76 (1H, s, 5α-H), 1.78 -1.83 (2H, mm), 2.01 (1H, dt, J=3.4, 12.6Hz), 3.81 (1H, d, J=8.2Hz, 3-H), 4.41 (1H, s, 6-H), 5.36 (1H, dd, J=1.6, 10.4Hz, 1-H), 5.74 (1H, dd, J=2.3, 10.4Hz, 2-H). For compound **(45)**, m.p. 152.5-153.5 °C (Found: C, 81.00; H, 11.54%. $C_{29}H_{50}O_2$ requires C, 80.87; H, 11.70; O, 7.43%); $\nu_{max}(CCl_4)/cm^{-1}$ 3621 (Free O-H), 1707 (saturated ketone). δ_H(300MHz, $CDCl_3$) 0.71 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.87 (3H, d, J=6.6Hz, 27-Me), 0.91 (3H, d, J=6.5Hz, 21-Me), 1.15 (3H, s, Me), 1.38 (3H, s, Me), 1.43 (3H, s, Me), 1.68 (1H, s), 1.75 - 1.86 (3H, mm), 1.95 (1H, ddd, J=3.0, 6.0, 13.1Hz), 2.01 (1H, dt, J=3.3, 12.8Hz), 2.26 (1H, ddd, J=3.0, 4.6, 14.9Hz, 2-H),

2.76 (1H, dt, J=6.0, 14.6, 14.6Hz, 2-H), 4.34 (1H, s, 6-H). m/z(%): 430(4, M^+), 412(18), 397(4), 357(4), 327(3), 257(12), 187(17), 145(15), 107(27), 81(36), 43(100).

Sodium borohydride reduction of 5β,6β-epoxide ***(24)***.

To a solution of 5β,6β-epoxide **(24)** (100 mg, 0.24 mmol) in methanol (30 ml) was added $NaBH_4$ (53 mg, 1.4 mmol) and $CeCl_3.7H_2O$ (100 mg, 0.27 mmol). The mixture was stirred at room temperature for 45 min before a small amount of water was added to quench the reaction. The mixture was extracted with ether and the combined ether layers were washed, dried and evaporated as usual. Silica gel chromatography of the residue and elution with a hexane-ethyl acetate gradient solvent system yielded 5β,6β-epoxy-4,4-dimethylcholest-1-en-3β-ol **(43)** (89 mg, 87%).

PCC oxidation of hydroxy-ketone ***(45)***.

To a solution of 6β-hydroxy-4,4-dimethylcholestan-3-one **(45)** (10 mg, 0.024 mmol) in anhydrous CH_2Cl_2 (10 ml) was added pyridinium chlorochromate (PCC) (10 mg, 0.049 mmol) in one portion and the mixture was stirred at room temperature for 2 h. The reaction solution was placed onto a silica gel column and was eluted with a sufficient amount of ether. Evaporation of the ether yielded 4,4-dimethyl-5α-cholesta-3,6-dione **(38)** (9 mg, 92%).

Preparation of bromohydrin acetate ***(47)***.

To a solution of 5β,6β-epoxide **(24)** (100 mg, 0.24 mmol) in dry glacial acetic acid (10 ml) with stirring at 10 °C was added a solution of hydrogen bromide (3.7%) in acetic acid (9 ml, 0.41 mmol) by syringe over 30 min. After stirring at 10 °C for 8 h, the reaction mixture was poured onto ice-water and extracted with ether. The combined ether layers were washed, dried and evaporated as usual. Silica gel chromatography of the residue and elution with a hexane-ethyl acetate gradient solvent system afforded 5β,6β-epoxide **(24)** (89 mg, 85%), bromohydrin acetate **(47)** (13 mg, 10%) and a compound (5 mg) whose structure was not determined. For compound **(47)**, m.p. 180-182 °C (needles from acetone-water). $\nu_{max}(CCl_4)/cm^{-1}$ 1747 (ester carbonyl), 1692 (α,β-unsaturated ketone); δ_H(300MHz, $CDCl_3$) 0.73 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.87 (3H, d, J=6.6Hz, 27-Me), 0.92 (3H, d, J=6.5Hz, 21-Me), 1.45 (3H, s, Me), 1.515(3H, s, Me), 1.69 (3H, s, Me), 2.09 (1H, dt, J=3.3, 12.8Hz), 2.14 (3H, s, acetate methyl), 2.20 -2.34 (2H, mm), 5.59 (1H, br s, 6-H), 5.94 (1H, d, J=10.3Hz, 2-H), 6.83 (1H, d, J=10.5Hz, 1-H). m/z(%): 426(2, M$^+$-Br,CH_3CO), 410(7), 408(8), 395(3), 393 (6), 367(3), 365(5), 339(5), 337(2), 149(11), 147(8), 81(38), 79(24), 43(100).

In-situ reaction of bromohydrin (46) with triphenyltin hydride.

To a solution of 5β,6β-epoxide **(24)** (100 mg, 0.24 mmol) in dry glacial acetic acid (10 ml) with stirring at 10 °C was added a solution of hydrogen bromide (3.7%) in glacial acetic acid (0.8 ml, 0.37 mmol) by syringe over 30 min. After stirring at 10 °C for 90 min, the reaction mixture was poured onto ice-water. The precipitate was filtered and washed with ice-water to remove all traces of acetic acid. The colourless residue was vacuum-dried and then was dissolved in dry benzene (50 ml) and refluxed. Tributyltin hydride (TBTH) (97%, 0.06 ml, 0.22 mmol) in dry benzene (10 ml), and a catalytic amount of AIBN were then added dropwise over 1 h. The mixture was stirred at reflux for 2 h. A small amount of water was added to the reaction solution to quench the reaction. The residue after evaporation of the solvent was placed directly onto a silica gel column. Elution first with pure benzene removed the TBTH derivatives. Subsequent elution with the hexane-ethyl acetate gradient solvent system gave 6β-hydroxy-4,4-dimethylcholestan-3-one **(45)** (49 mg, 48%), 6β-hydroxy-4,4-dimethyl-5α-cholest-1-en-3-one **(51)** (3 mg, 3%), 5β-hydroxy-4,4-dimethylcholest-1-en-3-one **(52)** (18 mg, 18%) and an unstable compound (17 mg, 17%). For compound **(51)**, $\nu_{max}(CCl_4)/cm^{-1}$ 3622 (Free O-H), 1676 (α,β-unsaturated ketone). δ_H(300MHz, $CDCl_3$) 0.74 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz,

26-Me), 0.87 (3H, d, J=6.6Hz, 27-Me), 0.92 (3H, d, J=6.5Hz, 21-Me), 1.22 (3H, s, Me), 1.39 (3H, s, Me), 1.41 (3H, s, Me), 1.64 (1H, d, J=1.4Hz, 5-H), 1.77 -1.90 (2H, mm), 2.06 (1H, dt, J=3.3, 3.3, 12.9Hz, 8-H), 4.40 (1H, s, 6-H), 5.82 (1H, d, J=10.3Hz, 2-H), 6.97 (1H, d, J=10.3Hz, 1-H). For compound **(52)**, $\nu_{max}(CCl_4)/cm^{-1}$ 3626 (Free O-H), 1686 (α, β-unsaturated ketone). δ_H(300MHz, $CDCl_3$) 0.704(3H, s, 18-Me), 0.861(3H, d, J=6.6Hz, 26-Me), 0.865(3H, d, J=6.6Hz, 27-Me), 0.91 (3H, d, J=6.5Hz, 21-Me), 1.22 (3H, s, Me), 1.30 (3H, s, Me), 1.37 (3H, s, Me), 2.03 (1H, dt, J=3.3, 12.9Hz), 2.14 (1H, ddd, J=2.1, 4.5, 14.1Hz), 5.88 (1H, d, J=10.5Hz, 2-H), 6.56 (1H, d, J=10.4Hz, 1-H).

Bis(cyclopentadienyl)titanium(III) chloride reduction of ***(24)***.

Cp_2TiCl_2 (185 mg, 0.74 mmol) was mixed with sufficient granular zinc in a flame-dried flask, under N_2. Dry THF (20 ml) was added to the flask via a syringe. The mixture was stirred vigorously for 1.5 h, during which time the solution changed to a dark blue color which indicated that $(CpTiCl)_2$ had formed. This solution was transferred using a syringe to a flame-dried flask containing **(24)** (100 mg, 0.23 mmol) in dry THF (10 ml), under N_2. The mixture was refluxed for 5 h before 5% H_2SO_4 was added in to quench the reaction. The reaction mixture was extracted with ether and the combined ether extracts were washed, dried and evaporated as usual. Silica

gel chromatography of the residue and elution with 2% ethyl acetate in hexane gave 4,4-dimethylcholesta-1,5-dien-3-one **(31)** (48 mg, 51%) and unreacted **(24)** (44 mg).

Li/NH_3 reduction of 5α,6α-epoxy-4,4-dimethylcholest-1-en-3-one ***(32)***.

Freshly condensed ammonia (10 ml, dried over sodium at -78 °C) was allowed to distil into a stirring suspension of lithium (10 mg, 1.4 mmol) in anhydrous THF (1 ml) at -78 °C. Stirring was continued until the metal had dissolved. A solution of 5α,6α-epoxide **(32)** (55 mg, 0.13 mmol) in anhydrous THF (1 ml) was added dropwise by syringe, over 1 h and the solution stirred at -78 °C for an additional 1 h. Sufficient NH_4Cl was added to discharge the blue colour and the ammonia was allowed to evaporate. Diethyl ether (30 ml) and water (20 ml) was added to the residue. The aqueous layer was extracted with two additional portions of ether (30 ml portions) and the combined ether extracts were washed, dried and evaporated as usual. Chromatography of the residue and gradient elution with hexane-ethyl acetate yielded 5α,6α-epoxy-4,4-dimethyl-cholestan-3-one **(55)** (40 mg, 72%). For compound **(55)**, $\nu_{max}(CCl_4)/cm^{-1}$ 1713 (saturated ketone); δ_H (300 MHz; $CDCl_3$) 0.61 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.6Hz, 27-Me), 0.87 (3H, s, Me), 0.89 (3H, J=6.7Hz, 21-Me), 0.99 (3H, s, Me), 1.231(3H, s, Me), 2.34-2.45(1H, mm, 2-H),

2.70-2.80(1H, mm, 2-H), 3.04 (1H, d, J=4.5Hz, 6-H).

*Reaction of 5α,6α-epoxide **(32)** with triphenyltin hydride.*

A solution of **(32)** (50 mg, 0.12 mmol) in dry benzene (50 ml) was refluxed under argon while triphenyltin hydride (TPTH) (493 mg, 1.40 mmol) and a trace amount of azo*bis*isobutyronitrile (AIBN) in dry benzene (30 ml) was added dropwise over 5 h. The mixture was stirred at reflux for 24 h before a small amount of water was added to quench the reaction. The residue obtained after evaporating the solvent was placed directly onto a silica gel column. Elution first with pure benzene removed the TPTH derivatives completely. Subsequent elution using a hexane-ethyl acetate gradient solvent system gave 5α,6α-epoxy-4,4-dimethylcholestan-3-one **(55)** (24 mg, 47%) and another compound (20 mg) whose structure could not be identified.

*Triphenyltin hydride reduction of **(31)**.*

To a solution of **(31)** (110 mg, 0.27 mmol) refluxing in dry benzene (50 ml) under argon, was added a solution of triphenyltin hydride (TPTH) (513 mg, 1.46 mmol) and a trace amount of AIBN in dry benzene (30 ml) dropwise over 5 h. The reaction was refluxed for 20 h before it was quenched by the addition of a small amount of water. The residue after evaporating the solvent was chromatographed directly. Elution

first with pure benzene removed the TPTH derivatives; on the same column, chromatography using a hexane-ethyl acetate gradient system yielded 4,4-dimethylcholest-5-en-3-one **(30)** (79 mg, 71%) and 4,4-dimethylcholest-1,5-dien-3β-ol **(58)** (13 mg, 12%). Compound **(30)**, had m.p. 174-175 °C (lit[48]: 176-177 °C). Compound **(58)**, m.p. 130-132 °C was identical with a sample prepared by sodium borohydride reduction of **(31)**. Its spectral properties were: Ir (CCl_4) 3650 cm^{-1}; NMR ($CDCl_3$) δ 0.69 (3H, s, 18-Me), 0.86 (6H, d, J=6.5Hz, 26-Me, 27-Me), 0.91 (3H, d, J=6.5Hz, 21-Me), 1.037 (3H, s, Me), 1.14 (3H, s, Me), 1.14 (3H, s, Me), 3.83 (1H, d, J=6.5Hz, 3-H), 5.43 (1H, d, J=10.3Hz, 1-H), 5.49 (1H, t, J=3.2Hz, 6-H), 5.73 (1H, dd, J=2.3, 10.3Hz, 2-H). Anal. Calcd for $C_{29}H_{48}O.\ (CH_3OH)_{0.25}$: C, 82.79; H, 11.50. Found: C, 82.87; H, 11.47.

*Tributyltin hydride reduction of **(59)**.*

To a solution of **(59)** (121 mg, 0.28 mmol) refluxing in dry benzene (50 ml) under argon, was added a solution of tri-*n*-butyltin hydride (TBTH) (0.15 ml, 0.56 mmol) and a trace amount of AIBN in dry benzene (30 ml) dropwise over 5 h. The mixture was refluxed for 24 h and then the reaction was quenched by the addition of a small amount of water. The residue obtained after evaporating the solvent was chromatographed by flash chromatography. Elution first with benzene eluted the TPTH derivatives; further elution with 5%

ethyl acetate-hexane gave 4,4-dimethylcholest-5-ene-3,7-dione **(60)** (46 mg, 38%) and unreacted **(59)** (64 mg, 53%). For compound **(60)**, m.p. 164-165 °C (lit[18]: 163-165 °C); Ir (CCl_4) 1716 and 1676 cm^{-1}; NMR ($CDCl_3$) δ 0.70 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.87 (3H, d, J=6.6Hz, 27-Me), 0.93 (3H, d, J=6.6Hz, 21-Me), 1.07 (3H, s, Me), 1.32 (3H, s, Me), 1.32 (3H, s, Me), 1.48 -1.56 (2H, mm), 1.60 -1.66 (2H, mm), 1.79 -1.93 (2H, mm), 2.04 -2.18 (2H, mm), 2.30 (1H, t, J=11.04Hz, 8-H), 2.38 -2.41 (1H, m), 2.60 (1H, dd, J=6.6, 11.5Hz, 2-H), 2.63 (1H, d, J=10.6Hz, 2-H), 5.90 (1H, s, 6-H).

*4,4-Dimethylcholesta-1,5-diene-3,7-dione **(59)**.*

A suspension of calcium carbonate (505 mg, 5.05 mmol) in a solution of 4,4-dimethylcholesta-1,5-dien-3-one[19] **(31)** (1072 mg, 2.61 mmol) in dioxane (200 ml) containing water (20 ml) was irradiated at room temperature and N-bromosuccinimide (NBS) (1062 mg, 5.97 mmol) was added in a single batch. After 1 h, the reaction mixture was filtered into water, extracted with ether and the combined ether layers were washed, dried and evaporated as usual. Flash chromatography of the residue using hexane-ethyl acetate gave 4,4-dimethylcholest-1,5-diene-3,7-dione **(59)** (952 mg, 86%), m.p. 93-94 °C. Ir (CCl_4) 1692 and 1672 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.75 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.87 (3H, d, J=6.6Hz, 27-Me), 0.93 (3H, d,

J=6.5Hz, 21-Me), 1.69 (1H, dd, J=3.7, 12.8Hz), 1.75 -1.81 (2H, mm), 1.84 -1.95 (1H, m), 2.11 (1H, dt, J=3.2, 13.0Hz, C-12β), 2.20 -2.32 (1H, m), 2.41 (1H, t, J=11.0Hz, H-8), 5.97 (1H, s, H-6), 6.04 (1H, d, J=10.4Hz, H-2), 6.92 (1H, d, J=10.4Hz, H-1); MS *m/e* (relative intensity): 424(13, M⁺), 409(10), 381(2), 275(55), 247(8), 216(10), 149(30), 43(100); molecular ion mass 424.3363, calcd for $C_{29}H_{44}O_2$ 424.3339. Anal. Calcd for $C_{29}H_{44}O_2$: C, 82.02; H, 10.44. Found: C, 82.05; H, 10.34.

4,4-Dimethylcholest-5-ene-3,7-dione ***(60)***.

A suspension of calcium carbonate (100 mg, 1.00 mmol) in a solution of 4,4-dimethylcholest-5-en-3-one **(30)** (204 mg, 0.49 mmol) in dioxane (40 ml) containing water (4 ml) was irradiated at room temperature and NBS (237 mg, 1.33 mmol) was added in a single batch. After 1 h, the reaction mixture was filtered into water, extracted with ether and the combined ether layers were washed, dried and evaporated as usual. Chromatography of the residue and elution with hexane-ethyl acetate gradient solvent system gave 4,4-dimethylcholest-5-ene-3,7-dione **(60)** (164 mg, 80%).

4,4-Dimethyl-1α,5α-cyclocholesta-3,7-dione ***(62)***.

Freshly condensed ammonia (15 ml, dried over sodium at -78 °C) was allowed to distil into a stirred suspension of

lithium (40 mg, 5.6 mmol) in anhydrous tetrahydrofuran (THF) (2.5 ml) at -78 °C. The stirring was continued until the metal had dissolved. A solution of diendione **(59)** (463 mg, 1.1 mmol) in anhydrous THF (5 ml) was added over 3 h using a syringe pump. The solution was stirred at -78 °C for a further 1 h. Ammonium acetate was added to discharge the blue colour and the ammonia was allowed to evaporate. The residue was extracted with ether and water. The aqueous layer was extracted with ether, the combined ether solutions washed, dried over magnesium sulphate and evaporated to dryness. The crude residue (457 mg) was suspended in anhydrous CH_2Cl_2 (100 ml) and PCC (550 mg, 2.19 mmol) was added in one portion to the stirred solution. After 2 h the reaction mixture was transferred onto a short silica gel column which was eluted with ether. Evaporation of the solvent yielded a residue (368 mg). Flash chromatography of the residue using hexane-ethyl acetate yielded 4,4-dimethyl-1α,5α-cyclocholesta-3,7-dione **(62)** (335 mg, 72%), m.p. 107.0-108.0 °C. Ir (CCl_4) 1713 and 1742 cm_{-1}; ^{1}H-NMR ($CDCl_3$) 0.72 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.6Hz, 27-Me), 0.87 (3H, s, 19-Me), 0.92 (3H, d, J=6.6Hz, 21-Me), 0.96 (3H, s, 4β-Me), 1.07 (3H, s, 4α-Me), 1.34 (1H, d, J=6.0Hz, 1α-H), 2.03 (1H, t, J=11.8Hz, 8-H), 2.28 (1H, d, J=19.0Hz, 2β-H), 2.44 (1H, d, J=16.0Hz, 6α-H), 2.60 (1H, d, J=16.0Hz, 6β-H), 2.81 (1H, dd, J=6.1, 19.0Hz, 2α-H); MS *m/e* (relative intensity):

426(100, M$^+$), 411(12), 383(8), 355(12), 328(14), 275(40), 247(17), 163(32), 135(78), 95(76), 55(100); molecular ion mass 426.3461, calcd for $C_{29}H_{46}O_2$ 426.3495. Anal. Calcd for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.77; H,10.73.

*7β-Hydroxy-4,4-dimethyl-1α,5α-cyclocholestan-3-one(**65a**) and 7α-hydroxy-4,4-dimethyl-1α,5α-cyclocholestan-3-one (**65b**).*

A solution of **(62)** (105 mg, 0.25 mmol) in methanol (30 ml), $NaBH_4$ (85 mg, 2.25 mmol), and $CeCl_3.7H_2O$ (111 mg, 0.30 mmol) was stirred at room temperature for 48 h. A small amount of water was added to quench the reaction. The resulting solution was extracted with ether and the combined ether layers were washed, dried and evaporated as usual. Flash chromatography using hexane-ethyl acetate yielded 7β-hydroxy-4,4-dimethyl-1α,5α-cyclocholestan-3-one **(65a)** (81 mg, 77%), m.p. 207.5-208.5 °C, and 7α-hydroxy-4,4-dimethyl-1α,5α-cyclocholestan-3-one **(65b)** (8 mg, 7%). Compound **(65a)** had the following properties: Ir (CCl_4) 3620 and 1739 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.52 (1H, dt, J=5.0, 12.0Hz, C-9), 0.71 (3H, s, 18-Me), 0.82 (3H, s, 19-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.6Hz, 27-Me), 0.91 (3H, d, J=6.4Hz, 21-Me), 0.93 (1H, d, J=6.5Hz, 1-H), 1.08 (3H, s, 4α-Me), 1.11 (3H, s, 4β-Me), 1.20 (1H, dt, J=4.7, 11.0Hz, 8-H), 1.65 (1H, dd, J=5.2, 15.8Hz, 6α-H), 2.00 (1H, dd, J=3.2, 15.8Hz, 6β-H), 2.24 (1H, d, J=18.9Hz, 2β-H), 2.74 (1H, dd, J=6.2, 19.0Hz, 2α-H),

3.73 (1H, br s, H-7); MS *m/e* (relative intensity): 428(7, M+), 410(22), 395(9), 325(4), 297(15), 187(14), 152(100), 95(43), 43(64); molecular ion mass 428.3618, calcd for $C_{29}H_{48}O_2$ 428.3652. Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.14; H, 11.16. Compound **(65b)** had the following spectral properties: IR (CCl_4) 3629 and 1736 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.70 (3H, s, C-18), 0.85 (3H, s), 0.86 (3H, d, J=6.6Hz, C-26), 0.86 (3H, d, J=6.6Hz, C-27), 0.91 (3H, d, J=6.5Hz, C-21), 1.03 (3H, s), 1.04 (3H, s), 2.27 (1H, d, J=19.1Hz, C-2α), 2.72 (1H, dd, J=6.0, 19.1Hz, C-2β), 3.96 (1H, br s, C-7).

X-ray structure determination of ***(65a)***.

Data collection was on a Rigaku AFC6S diffractometer with graphite monochromated CuKα radiation (λ = 1.54178 Å) and a 2KW sealed tube generator. Crystallographic data are summarized in Table IV. Cell dimensions were determined by least-squares refinement using the setting angles of 23 carefully centred reflections in the range 45.95 < 2θ <48.76°. Data were collected at a temperature of 25 ± 1 °C using the ω2θ scan technique to a maximum of 2θ value of 120.2°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.33° with a take-off angle of 6.0°. Scans of (1.68 + 0.3 tan θ)° were made at a speed of 8.0°/min (in omega). The weak reflections (I < 10.0σ(I)) were rescanned (maximum of 2 rescans) and the

counts were accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal-to-detector distance was 400.0 mm. Reference reflections measured during data collection showed no decrease in intensity. An empirical absorption correction was applied using the DIFABS[40] program, and resulted in transmission factors ranging from 0.83 to 1.21. Corrections were applied for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 0.35143 E-06). The structure was solved by direct methods[41,42] Non-H atoms were refined either anisotropically or isotropically. Full-matrix least-squares refinements on F converged to R=0.057, R_w= 0.045, G.o.F=1.68. Weights were based on counting statistics and included a factor (p=0.01) to downweight the intense reflections. The largest peaks in the final difference Fourier map were +0.19 and -0.16 e/Å^3 respectively. Neutral atom scattering factors were taken from Cromer and Waber[43]. Anomalous dispersion effects were included in Fcalc[44]. Values for $\Delta f'$ and $\Delta f''$ were taken from Cromer[45]. All calculations were made with the TEXSAN[46] crystallographic software. Figure 5 was prepared from the output of PLUTO[47].

4,4-Dimethyl-1α,5α-cyclocholesta-3β,7β-diol ***(66a)*** *and 4,4-dimethyl-1α,5α-cyclocholesta-3α,7β-diol* ***(66c)***.

To a solution of 7β-hydroxy-4,4-dimethyl-1α,5α-cyclocholestan-3-one **(65a)** (51 mg, 0.12 mmol) in dry ether (10 ml) was injected a solution of $LiAlH_4$ (30 mg, 0.79 mmol) in dry ether (20 ml) over 30 min. The mixture was stirred at room temperature for 4 h before a small amount of water was added to quench the reaction. The solution was extracted with ethyl acetate and the combined organic layers were washed, dried and evaporated as usual. Chromatography of the residue and elution with 10% ethyl acetate in hexane yielded 4,4-dimethyl-1α,5α-cyclocholesta-3β,7β-diol **(66a)** (39 mg, 76%) and 4,4-dimethyl-1α,5α-cyclocholesta-3α,7β-diol **(66c)** (5 mg, 10%). Compound **(66a)** m.p. 148-150 °C had the following spectral properties: Ir (CCl_4) 3630 cm^{-1}; NMR ($CDCl_3$) δ 0.37 (1H, dt, J=4.7, 12.1Hz, 9-H), 0.71 (3H, s, 18-Me), 0.72 (1H, d, J=5.0Hz, H-1), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.6Hz, 27-Me), 0.91 (3H, d, J=6.6Hz, 21-Me), 1.04 (3H, s, 4β-H), 1.10 (3H, s, 4α-H), 1.18 (1H, dt, J=3.5, 10.8Hz, 8-H), 1.30 (3H, s, 19-H), 1.51 (1H, dd, J=3.8, 14.9Hz, 6α-H), 1.60 (1H, dd, J=2.1, 14.2Hz, 2β-H), 1.98 (1H, dd, J=3.1, 14.9Hz, 6β-H), 2.48 (1H, ddd, J=6.6, 9.7, 15.0Hz, 2α-H), 3.63 (1H, br s, 7-H), 4.06 (1H, dd, J=2.4, 9.7Hz, 3-H). Anal. Calcd for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.61; H, 11.61. The minor product, compound **(66c)** had the following spectral properties: Ir

(CCl_4) 3621 cm-1; NMR ($CDCl_3$) δ 0.31 (1H, dt, J=4.7, 12.1Hz, 9-H), 0.70 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.6Hz, 27-Me), 0.90 (3H, d, J=6.5Hz, 21-Me), 0.98 (3H, s, Me), 1.05 (3H s, Me), 1.06 (3H, s, Me), 3.69 (1H, br s, 7-H), 3.90 (1H, t, J=8.4Hz, 3-H).

Lithium aluminium hydride reduction of ***(62)***.

A solution of $LiAlH_4$ (30 mg, 0.79 mmol) in dry ether (20 ml) was added over 30 min to a solution of **(62)** (50 mg, 0.12 mmol) in dry ether (10 ml). After the addition was completed, the mixture was refluxed for 6 h before a small amount of water was added in to quench the reaction. The solution was extracted with ethyl acetate and the combined organic layers were washed, dried and evaporated as usual. TLC showed a single spot, but proton nmr showed it to be a 2:1 mixture of 4,4-dimethyl-1α,5-cyclocholesta-3β,7β-diol **(66a)** and its epimer 4,4-dimethyl-1α,5α-cyclocholesta-3β,7α-diol **(66b)** which could not be separated by column chromatography. For compound **(66b)**, δH (300MHz; CDCl3) 0.70 (3H, s, 18-Me), 0.95 (3H, s, Me), 1.03 (3H, s, Me), 1.31 (3H, s, Me), 2.52 (1H, ddd, J=6.6, 9.9, 15.0Hz, 2α-H), 3.86 (1H, br s, 7-H), 4.01 (1H, dd, J=2.6, 10.0Hz, 3-H).

*Bromination of **(62)**.*

A solution of **(62)** (30 mg, 0.07 mmol) in dry carbon tetrachloride (5 ml) was irradiated under visible light at room temperature while NBS (15 mg, 0.08 mmol) in dry carbon tetrachloride (10 ml) was added by syringe over 30 min, followed by a trace amount of AIBN. The mixture was stirred under irradiation for 24 h before the reaction was terminated by evaporation of the solvent. Column chromatography of the residue yielded **(69)** (3 mg, 8%) and 4,4-dimethyl-cholest-1,5-diene-3,7-dione **(59)** (22mg, 74%). Compound **(69)** had the following spectral properties: Ir (CCl_4) 1713 and 1746 cm^{-1}; NMR ($CDCl_3$) δ 0.72 (3H, s, 18-Me), 0.86 (3H, s, Me), 0.86 (3H, d, J=6.5Hz, 26-Me), 0.86 (3H, d, J=6.5Hz, 27-Me), 0.92 (3H, d, J=6.5Hz, 21-Me), 0.97 (3H, s, Me), 1.19 (3H, s, Me), 1.81 (1H, d, J=6.3Hz, 1-H), 2.36 (1H, d, J=18.9Hz, 2β-H), 2.92 (1H, dd, J=6.3, 18.9Hz, 2α-H), 4.59 (1H, s, 6β-H).

*Acidic treatment of **(62)**.*

To a solution of **(62)** (38 mg, 0.089 mmol) in methanol (3 ml) at 70 °C, H_2SO_4 (3M, 5 ml) was added dropwise, over 30 min. The mixture was stirred at the same temperature for 24 h but no change was evident by tlc. The mixture was then refluxed for a further 5 h with still no change evident. After work-up **(62)** was recovered unchanged.

Preparation of 3β-acetoxycholest-5-en-7-one (79).

Cholesteryl acetate **(78)** (1.25 g, 2.92 mmol) was dissolved in *t*-butanol (250 ml) in a 500-ml beaker and was vigorously stirred under uv-irradiation while $HgBr_2$ (3.3 g, 9.16 mmol) was added in portions over 4 h. After stirring for an additional hour, the reaction was quenched by evaporating the *t*-butanol under vacuum on a rotary evaporator. Water (100 ml) and ether (150 ml) was added to the residue. The ether layer was separated and the aqueous layer was extracted with two additional portions of ether. The combined ether extracts were washed, dried and evaporated as usual. Silica gel chromatography of the residue and elution with 10% ethyl acetate in hexane gave 3β-acetoxycholest-5-en-7-one **(79)** (748 mg, 58%).

Hydrolysis of (79).

To a solution of **(79)** (680 mg, 1.54 mmol) in methanol (300 ml) was added K_2CO_3 (4 g) in a single portion and the solution was stirred at room temperature for 2 h. The reaction was quenched by evaporating the methanol on a rotary evaporator and the residue was extracted with water and ether. The combined ether extracts were washed, dried and evaporated as usual. Silica gel chromatography of the residue and elution with 10% ethyl acetate in hexane gave 3β-hydroxycholest-5-en-7-one **(80)** (460 mg, 75%).

*Swern oxidation of **(80)**.*

To a solution of oxalyl chloride (100 ul, 1.15 mmol) in dry CH_2Cl_2 (5 ml) was added DMSO (100 ul, 1.41 mmol) at -60 °C. The mixture was stirred at -60 °C for 30 min before a solution of **(80)** (234 mg, 0.58 mmol) in dry CH_2Cl_2 (5 ml) was injected via a syringe over 20 min. The mixture was stirred at -60 °C for 30 min and triethylamine (0.5 ml, 3.59 mmol) was added via a syringe and the mixture was stirred at the same temperature for another 30 min. The cooling bath was removed and water was added to quench the reaction. The reaction mixture was extracted with ether. The combined ether extracts were washed, dried and evaporated as usual. Silica gel chromatography of the residue and elution with 5% ethyl acetate in hexane gave cholest-5-ene-3,7-dione **(81)** (24 mg, 10%) and unreacted **(80)** (195 mg). For compound **(81)**, $\nu_{max}(CCl_4)/cm^{-1}$ 1692 (α,β-unsaturated ketone), 1704 (saturated ketone); δ_H (300 MHz; $CDCl_3$) 0.77 (3H, s, 18-Me), 0.87 (3H, d, J=6.6Hz, 26-Me), 0.87 (3H, d, J=6.6Hz, 27-Me), 0.93 (3H, d, J=6.4Hz, 21-Me), 1.18 (3H, s, 19-Me), 2.68-2.98(5H, mm), 4.73 (1H, s, 6-H).

*Epoxidation of cholesta-1,5-dien-3-one **(83)**.*

A solution of dienone **(83)** (95 mg, 0.25 mmol) in 10 ml CH_2Cl_2 was refluxed under argon. *m*-Chloroperoxybenzoic acid (102 mg, 50-60%, 0.32 mmol) in 5 ml CH_2Cl_2 was added dropwise over 0.5 h. The mixture was stirred at reflux for 4 h. The

solution was extracted with ether (x4) and the combined organic layers were washed with 10% $NaHCO_3$ (x3) and saturated NaCl (x4), dried ($MgSO_4$) and concentrated to dryness. Chromatography on silica gel using 5% ethyl acetate gave 5α,6α-epoxycholest-5-en-3-one **(85)** (14 mg, 14%), 6β-hydroxycholesta-1,4-dien-3-one **(88)** (48 mg, 48%) and 6α-hydroxycholesta-1,4-dien-3-one **(89)** (18 mg, 18%). For compound **(85)**, $\nu_{max}(CCl_4)/cm^{-1}$ 1689 (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 0.66 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.87 (3H, d, J=6.6Hz, 27-Me), 0.91 (3H, d, J=6.5Hz, 21-Me), 1.31 (3H, s, 19-Me), 2.04 (1H, d, J=17.7Hz, 4-H), 3.08 (1H, d, J=4.2Hz, 6-H), 3.20 (1H, d, J=17.7Hz, 4-H), 6.01 (1H, dd, J=0.7, 10.3Hz, 2-H), 7.14 (1H, d, J=10.3Hz, 1-H). For compound **(88)**, $\nu_{max}(CCl_4)/cm^{-1}$ 1666 (C-3 carbonyl); δ_H (300 MHz; $CDCl_3$) 0.77 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.6Hz, 27-Me), 0.91 (3H, d, J=6.5Hz, 21-Me), 4.53 (1H, br s, 6-H), 6.14 (1H, d, J=1.8Hz, 4-H), 6.20 (1H, dd, J=1.8, 10.1Hz, 2-H), 7.06 (1H, d, J=10.1Hz, 1-H). For compound **(89)**, $\nu_{max}(CCl_4)/cm^{-1}$ 1666 (C-3 carbonyl); δ_H (300 MHz; $CDCl_3$) 0.73 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.6Hz, 27-Me), 0.90 (3H, d, J=6.5Hz, 21-Me), 1.21 (3H, s, 19-Me), 4.44-4.50(1H, m, 6-H), 6.25 (1H, dd, J=1.9, 10.1Hz, 2-H), 6.48 (1H, t, J=1.8Hz, 4-H), 7.03 (1H, d, J=10.1Hz, 1-H).

Formation of 4,4-dimethyl-5β-carboxaldehyde-B-norcholest-1-en-3-one ***(92)*** *.*

To a solution of β-epoxide **(24)** (110 mg, 0.26 mmol) in dry benzene (5 ml) with stirring at room temperature was added boron trifluoride etherate (0.1 ml, 0.8 mmol) by syringe. After stirring at room temperature for 30 min, the reaction mixture was quenched by pouring into $NaHCO_3$ solution (3%) and extracted with ether. The combined ether extracts were washed, dried and evaporated as usual. Silica gel chromatography using the hexane-ethyl acetate gradient solvent system yielded the B-nor aldehyde **(92)** (86 mg, 77%), and two other products which could not be characterised due to their instability. For compound **(92)**, m.p. 103.5-104.5 °C (plates from ethanol-water). (Found: C, 81.51; H, 10.78%. $C_{29}H_{46}O_2$ requires C, 81.63; H, 10.87; O, 7.50%); $\nu_{max}(CCl_4)/cm^{-1}$ 1729 (aldehyde), 1688 (α,β-unsaturated ketone); δ_H(300MHz, $CDCl_3$) 0.64 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.86 (3H, d, J=6.6Hz, 27-Me), 0.91 (3H, d, J=6.5Hz, 21-Me), 1.04 (3H, s, 4β-Me), 1.04 (3H, s, 19-Me), 1.11 (1H, dd, J=11.2, 13.0Hz, 7-H), 1.17 (3H, s, 4α-Me), 1.83 -1.90 (1H, mm), 2.04 (1H, dt, J=2.8, 12.9Hz), 2.41 (1H, dd, J=7.0, 13.0Hz, 7-H), 5.94 (1H, d, J=10.23Hz, 2-H), 6.63 (1H, d, J=10.23Hz, 1-H), 9.57 (1H, s, 6-H); HRMS for $C_{29}H_{46}O_2$, calcd 426.3495, found 426.3495. m/z(%): 426(7, M+), 397(7), 356(5), 313(3), 261(9), 243(3), 149(35), 43(100).

Sodium borohydride reduction of ***(92)*****.**

To a solution of the B-nor-aldehyde **(92)** (51 mg, 0.12 mmol) and $CeCl_3.7H_2O$ (56 mg, 0.15 mmol) was added $NaBH_4$ in small portions over 4 h until the starting material almost disappeared according to tlc. The reaction mixture was stirred at room temperature for an additional hour before a small amount of water was added to quench the reaction. The reaction mixture was extracted with ether and the combined ether layers were washed, dried and evaporated as usual. Chromatography of the residue and elution with the hexane-ethyl acetate gradient solvent system gave 4,4-dimethyl-5β-hydroxymethyl-B-norcholest-1-en-3-one **(93)** (45 mg, 88%). For compound **(93)**, m.p. 150-151 °C (Found: C, 81.05; H, 11.17%. $C_{29}H_{48}O_2$ requires C, 81.25; H, 11.29; O, 7.46%); $\nu_{max}(CCl_4)/cm^{-1}$ 3630 (Free O-H), 3493 (intermolecular and weakly bonded O-H), 1685 (α,β-unsaturated ketone); δ_H(300MHz, $CDCl_3$) 0.66 (3H, s, 18-Me), 0.86 (3H, d, J=6.6Hz, 26-Me), 0.87 (3H, d, J=6.6Hz, 27-Me), 0.92 (3H, d, J=6.5Hz, 21-Me), 1.09 (3H, s, 4β-Me), 1.12 -1.16 (1H, m, 7α-H), 1.21 (3H, s, 19-Me), 1.22 (3H, s, 4α-Me), 1.35 (1H, br s, 7β-H), 1.65 -1.74 (1H, m), 1.81 -1.93 (1H, m), 2.04 (1H, dt, J=3.2, 12.8Hz, 12β-H), 3.71 (2H, br s, 6-methylene), 5.82 (1H, d, J=10.2Hz, 2-H), 6.54 (1H, d, J=10.2Hz, 1-H); m/z(%): 428(23.6, M^+), 413(8), 410(7), 398(14), 397(34), 385(7), 358(22), 261(12), 166(14), 149(43), 121(66), 43(100).

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Table I. NOED data for (62), (65a) and (66a): Asterisks (*) denote signals which were saturated.

NOED data for **(62)**:

Proton:	H1	H2a	H2b	H3	H4a	H4b	H5	H6a	H6b	H7	H8	H9	H10	H11a,b	H18	H19
δ (ppm):	1.34	2.81	2.27	-	1.07	0.96	-	2.44	2.60	-	2.03	1.18	?	?	0.72	0.87
NOED	*	6.6%						2.0%				17.6%				
NOED	2.2%	*	8.1%													
NOED		9.4%	*													
NOED	10.2%	5.1%			*				14.7%							
NOED	0.6%							*	17.2%							
NOED					1.5%			17.3%	*							
NOED	10.2%											*				
NOED											13.6%				*	
NOED			7.5%								6.1%					*

NOED data for **(65a)**:

Proton:	H1	H2a	H2b	H3	H4a	H4b	H5	H6a	H6b	H7	H8	H9	H10	H11a,b	H18	H19
δ (ppm):	0.93	2.72	2.42	-	1.08	1.11		?	1.98	3.73	1.15-1.20	0.52			0.71	0.82
NOED	*	5.7%										10.0%				
NOED		*	4.6%													
NOED		3.7%	*													
NOED					*	sat'd			10.5%							
NOED					sat'd	*										1.5%
NOED								*	3.8%							
NOED								5.5%	*	3.0%						
NOED										*						
NOED										3.0%	*				2.4%	
NOED	13.5%							3.4%				*				
NOED											5.9%				*	
NOED			5.8%													*

NOED data for **(66a)**:

Proton:	H1	H2a	H2b	H3	H4a	H4b	H5	H6a	H6b	H7	H8	H9	H10	H11a,b	H18	H19
δ (ppm):	0.73	2.50	1.67	4.07	1.10	1.04	-	1.51	2.00	3.63	1.20	0.37	-	1.5	0.71	1.95
NOED	*	3.7%										12.4%				
NOED	6.0%	*	6.6%	6.0%												
NOED		5.6%		*	1.1%											
NOED				6.9%	*	2.0%				4.0%					1.0%	
NOED					sat'd	*										1.5%
NOED					0.7%			4.7%	*	2.0%						
NOED								3.0%	1.0%	*						
NOED	13.2%							3.9%				*				
NOED											10.0%				*	0.5%
NOED						3.7%									2.0%	*

TABLE II. Calculated torsion angles

Compound	H_9-C_9-C_{10}-C_1	H_{6a}-C_6-C_5-C_1
(62)	-6.9°	-5.9°
(65a)	-7.1°	-7.0°
(65b)	-7.8°	-6.4°
(66a)	-5.9°	-5.0°

Note: The corresponding torsion angles calculated from the single crystal structure of **(65a)** were -12° and -7.0°, respectively.

TABLE III. Crystal Data for (32)

Molecular formula	$C_{29}H_{46}O_2$
Formula mass	426.70
Crystal system	Monoclinic
Space group	$P2_1$ (No. 4)
Cell dimensions *a* (Å)	6.454 (4) (Å)
b (Å)	11.284 (4) (Å)
c (Å)	18.024 (6) (Å)
β(deg)	98.57 (5)°
Cell volume (Å)	1298 (1)
Z	2
d_{calc}(g cm^{-3})	1.097
F(000)	476
μ(cm^{-1})	4.71
Crystal dimensions (mm)	0.300 X 0.200 X 0.150
T (K)	298
$2\theta_{max}$ (deg)	120.1
Independent reflections	1831
Acceptance ($I_{net}/\sigma I_{net} \geq$)	1.5
Observed reflections	837

TABLE IV. Crystal Data for (65a)

Molecular formula	$C_{29}H_{48}O_2$
Formula mass	428.70
Crystal system	Monoclinic
Space group	$P2_1$ (No. 4)
Cell dimensions *a* (Å)	6.748 (2) (Å)
b (Å)	10.872 (2) (Å)
c (Å)	17.789 (2) (Å)
β (deg)	97.10 (2)°
Cell volume (Å^3)	1295.1 (5)
Z	2
d_{calc} (g cm^{-3})	1.099
F(000)	476
μ (cm^{-1})	4.72
Crystal dimensions (mm)	0.400 X 0.200 X 0.120
T (K)	298
$2\theta_{max}$ (deg)	120.1
Independent reflections	2064
Acceptance ($I_{net}/\sigma I_{net} \geq$)	2.5