ORGANOMERCURIALS IN THE SYNTHESIS OF TRIQUINANE-TYPE MOLECULES

by

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To my parents, for your help and support

and

to Ian, for all your encouragement

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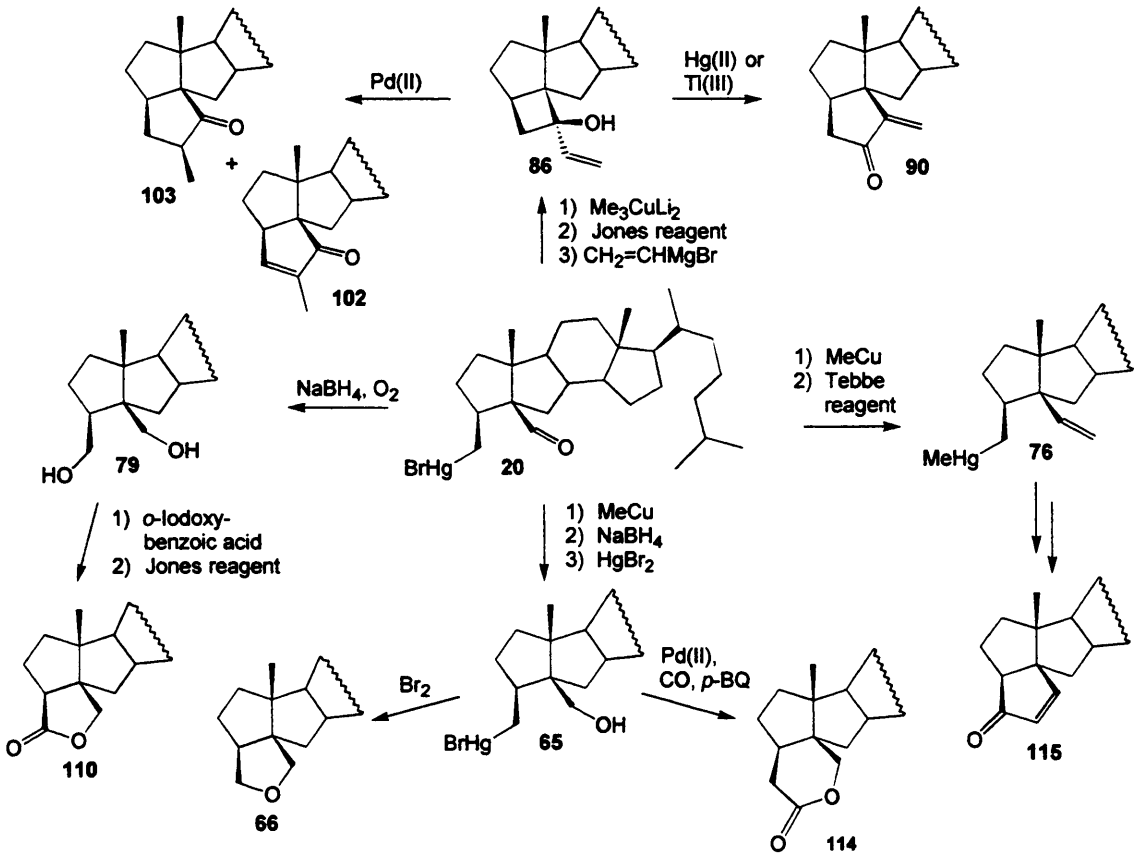
ABSTRACT

The synthesis and application of organomercurials as intermediates is discussed. Readily available organomercurial **20**[13] can be used as a versatile starting material for the construction of a variety of triquinane-type molecules. Thus cupration, followed by oxidation of the resulting alcohol gave the corresponding cylclobutanone,[42] whose treatment with vinylmagnesium bromide afforded **86**. The latter product can easily rearrange to afford **90**, **102** or **103**; the regioselectivity is controlled by the reagent/catalyst employed.

Reduction of **20** (using a novel protection-deprotection technique) furnished alcohol **65**, which was then converted into six-membered lactone **114**, via palladium(II) catalysed carbonylation.[112] Alcohol **65** was also used to afford tetrahydrofuran derivative **66**, upon treatment with bromine.

The synthetic utility of organomercurial **20** has been extended further by using a reductive demercuration process. This protocol has facilitated synthesis of diol **79**, which could then be selectively oxidised to subsequently afford lactone **110**. Treatment of bromomercurial **20** with methyl copper gave a methylmercurial derivative,[43] which could then be added to Tebbe reagent to furnish organomercurial **76**. Subsequent oxidation of **76** using the reductive demercuration technique, produced an alcohol that could be converted, over several steps, to provide a route to enone **115**.



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ABBREVIATIONS

Ac	-	acetyl
acac	-	acetylacetonate
approx	-	approximately
Bz	-	benzyl
calcd	-	calculated
CD_2Cl_2	-	deuterated dichloromethane
Ch	-	Chapter
CH_2Cl_2	-	dichloromethane
$CHCl_3$	-	chloroform
CO	-	carbon monoxide
DMAP	-	4-dimethylaminopyridine
DME	-	dimethoxyethane
DMF	-	N,N-dimethylformamide
DMSO	-	dimethylsulfoxide
E	-	Electrophile
Ed	-	Editor
equiv	-	equivalents
Et	-	ethyl
ether	-	diethyl ether
EtOH	-	ethanol
h	-	hour
HOMO	-	Highest Occupied Molecular Orbital
IR	-	Infra-Red
Jr	-	Junior
LUMO	-	Lowest Occupied Molecular Orbital
Me	-	methyl
MEK	-	methyl ethyl ketone
MeOH	-	methanol
Mes	-	mesyl
min	-	minutes
mp	-	melting point
Nu	-	nucleophile
NMR	-	Nuclear Magnetic Resonance
NOE	-	Nuclear Overhauser Enhancement
NOESY	-	Nuclear Overhauser Enhancement Spectroscopy
Nu	-	Nucleophile
p-BQ	-	para-benzoquinone
petroleum	-	petroleum ether
ppm	-	parts per million
rt	-	room temperature
sat	-	saturated
THF	-	tetrahydrofuran
TLC	-	Thin layer chromatography
TMS	-	tetramethylsilane
Vol	-	Volume

CHAPTER ONE

INTRODUCTION

An ultimate goal of synthetic organic chemistry is the discovery of novel and efficient routes to biologically significant molecules. The development of regio- and stereoselective reactions, particularly where reactivity is controlled by metals,[1-9] has allowed increased efficiency in synthetic steps, and achievement of goals not possible by traditional procedures.[10-12] Additional reaction paths can be generated via transmetallation,[6-12] a methodology that combines (often in one pot) the benefits of two or more metals in tandem reactions.

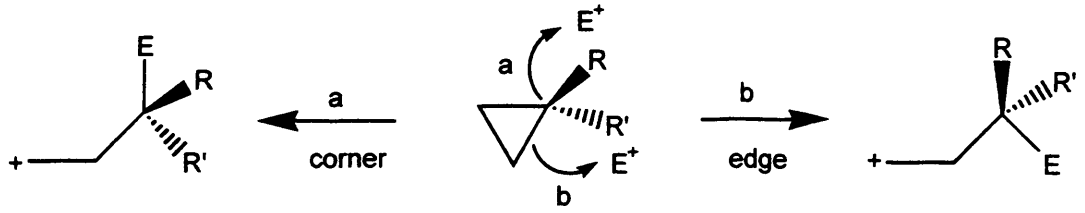
Stereoselective cleavage of a steroidal cyclopropane[13] provides an efficient synthesis of an organomercurial which can be used as a versatile starting material in the construction of a variety of triquinane-type molecules. This thesis is concerned with the development of synthetic routes using organic procedures and organometallic reagents to allow full utilisation of organomercurials in the formation of polycyclic structures. The methods of formation of organomercurials from cyclopropane derivatives are considered initially, followed by a discussion of the possible reaction pathways of these intermediates. Synthetic targets are then highlighted and experimental results are explained.

1.1 STEREOSELECTIVE CLEAVAGE OF CYCLOPROPANES

Stereo-controlled cyclopropanation,[14-24] catalysed by various metals,[25-40] followed by ring opening[14] is a strategy for construction of up to three contiguous chiral centres.[1] The benefits of this procedure can be further enhanced if the products are stable and hence can undergo additional transformations, such as transmetallation.[6-13,41-44] However, the mechanism for cleavage of the cyclopropane ring

was poorly understood until recently,[45,46] which hindered the synthetic uses of this reaction.

Two different mechanisms are known for the electrophilic cleavage of cyclopropanes, these being 'edge' or 'corner' attack by an electrophile resulting in retention or inversion respectively, at the centre to which the electrophile becomes linked. Synthetic interest in cyclopropane cleavage led to definitions relating to the mechanism and the reagent employed. Transition metals capable of backdonation (Pd,[47-50] Pt,[51-54] Rh[55] and Ir[56]) were found to prefer the 'edge' attack; halogens (Cl and Br)[57,58] react in the same way, (Scheme I).



Scheme I

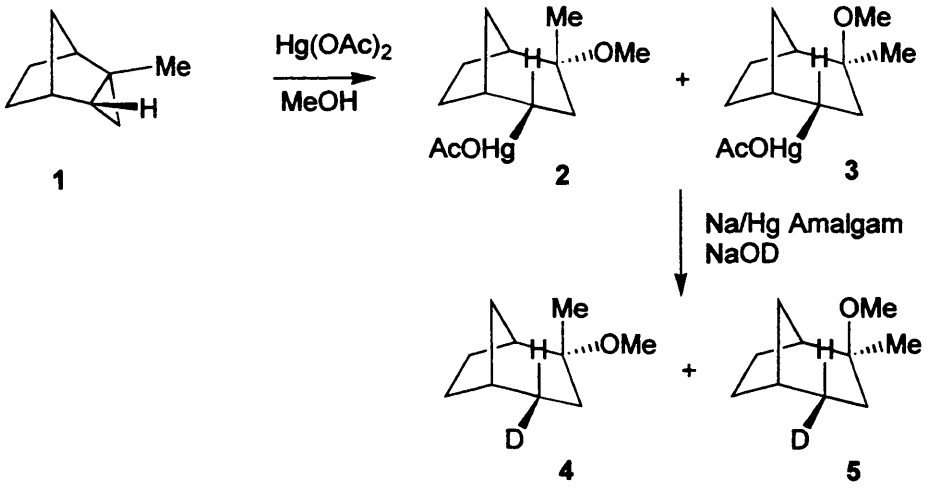
Lack of evidence for corner opening gave little support for this mechanism.[59-63] However, stereo-chemical arguments[64,65] and theoretical calculations[66] showed a role for corner protonated cyclopropane intermediates. Experiments in the late eighties and early nineties provided evidence that mercury(II),[13,67-69] thallium(III)[70] and deuteron,[67,68] all of which are poor back donors, are capable of stereospecific corner activation.

1.2 THE STEREOCHEMISTRY OF CYCLOPROPANE CLEAVAGE

Coxon *et al* have shown evidence for stereospecific formation and nucleophilic capture of unsymmetrical corner deuterated and mercurated cyclopropanes.[67,68] Incorporation of the cyclopropane into a polycyclic structure allowed simplification of

the stereochemical outcome of the reaction and also showed the importance of the carbon skeleton on the course of the reaction.

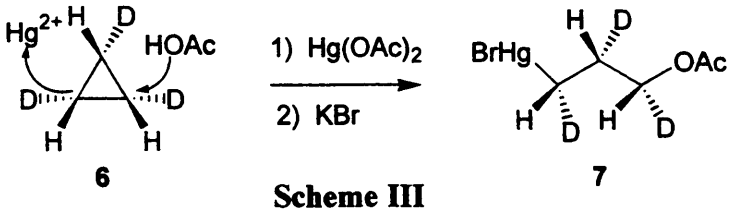
Reactions conducted on 2-methyl-endo-tricyclo[3.2.1.0]octane **1** with mercury acetate in methanol gave an 82% yield of **2** and **3**, (Scheme II). Whilst **2** was present in sufficient quantity to allow spectroscopic determination, it was necessary to synthesise an authentic sample of **3** for comparison. Identification of the way that the cyclopropane had opened, was confirmed, following stereospecific reduction of the organomercurial mixture. Sodium mercury amalgam in sodium deuteroxide was used to synthesise **4** and **5** as a (97 : 3) mixture. The observation of the C-4-*exo*-H in **4** and a C-4-endo deuterium in **5** allowed definition of the mercury acetate attack on **1** as occurring by a corner opening mechanism.



Scheme II

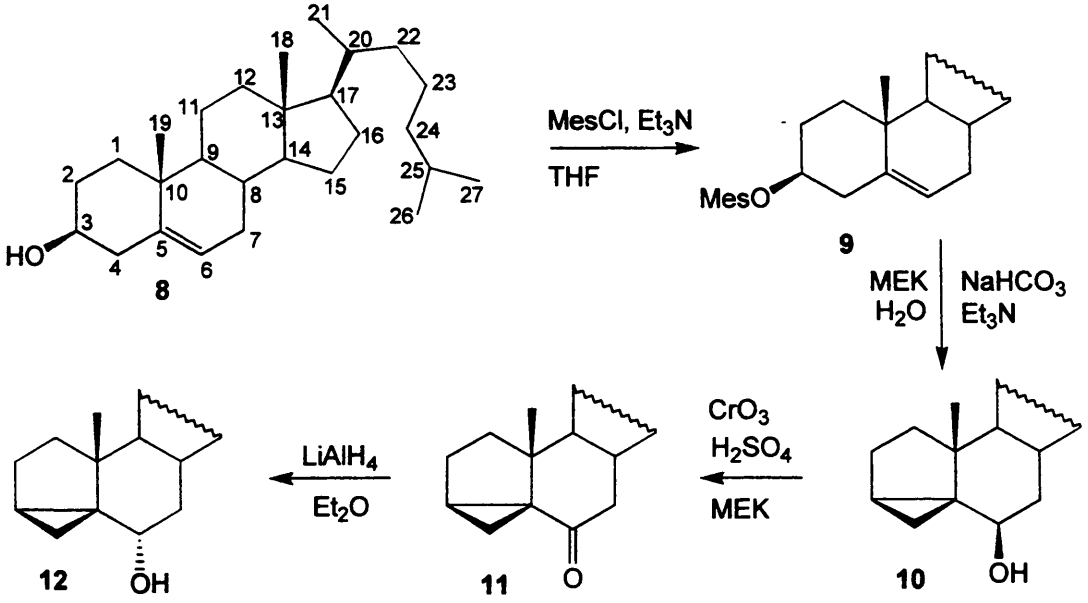
Using *cis*-tri-deuterated cyclopropane **6**, Lambert *et al* also showed that mercury opens cyclopropanes by a corner mechanism, (Scheme III).[69] This conclusion was based on the temperature dependence of the proton-proton vicinal coupling constants in 3-(bromomercurio)propyl acetate **7**. The double inversion pathway was interpreted in

terms of corner attack to form an unsymmetrical corner mercurated cyclopropane, which was opened by acetate with inversion of configuration.



6 7

Scheme III



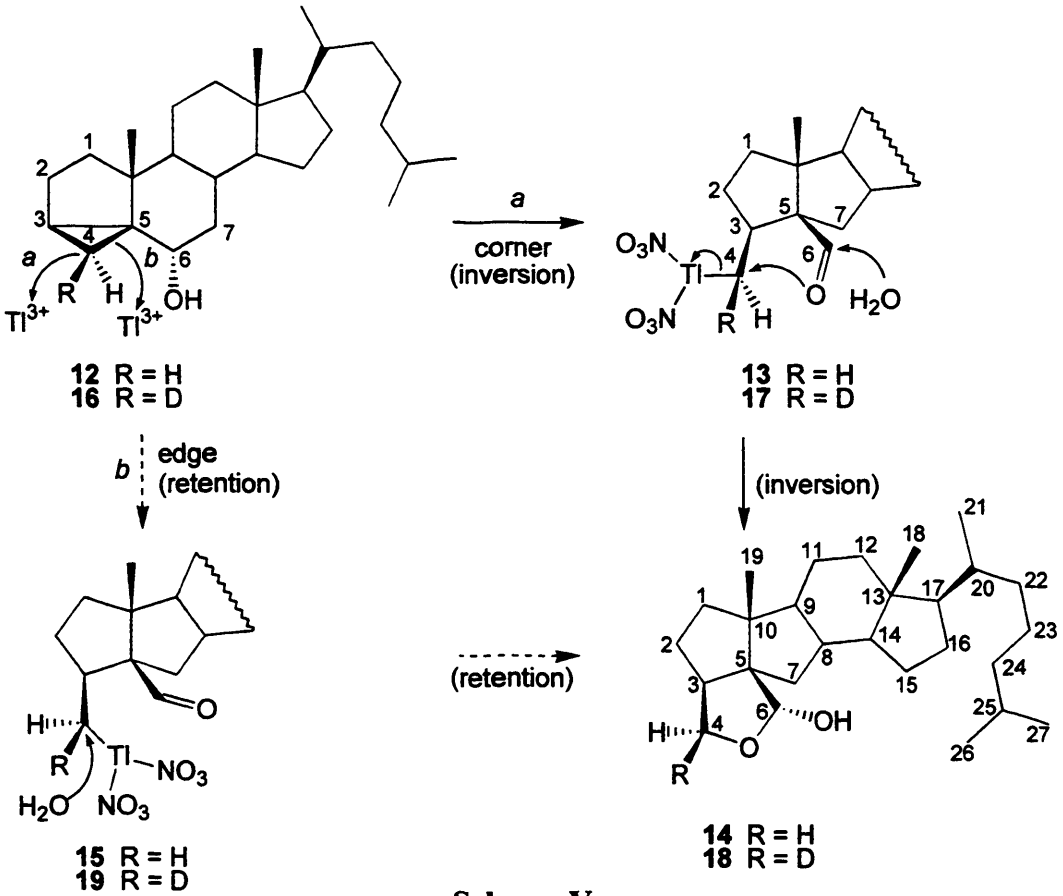
8 9 10 11 12

Scheme IV

At a similar time Kočovský and co-workers showed that thallium(III) was capable of stereospecific corner activation, initiating a unique skeletal rearrangement of 3α,5-cyclo-5α-cholestan-6α-ol.[70] This steroidal derivative is prepared in four steps from cholesterol, (Scheme IV).[71,72] The initial step involves formation and isolation of mesylate **9**. Refluxing a solution of this compound under buffered conditions facilitates synthesis of cyclopropyl derivative **10**. The configuration of the hydroxy group in this compound does not permit a molecular rearrangement, following treatment with thallium. Therefore, alcohol **10** was converted into its epimer **12**: oxidation of **10** with Jones reagent, followed by stereospecific reduction with lithium aluminium hydride,

afforded cyclopropyl derivative **12**, which can undergo a skeletal rearrangement with thallium(III).

Treatment of cyclopropyl alcohol **12** with thallium(III) nitrate and a trace of perchloric acid, in dioxane at room temperature, led to the isolation of lactol **14** (Scheme V). The reaction of the cyclopropyl alcohol can be summarised as follows: firstly, the C-4 - C-5 bond of the cyclopropane is broken. This occurs regioselectively between the most and the least substituted carbons.[73,74] Secondly, migration of the antiperiplanar C-6 - C-7 bond, and the reaction is completed by the S_N2 substitution of the thallium by oxygen during the closure of the lactol ring.



12 R = H
16 R = D

13 R = H
17 R = D

15 R = H
19 R = D

14 R = H
18 R = D

Scheme V

To determine the stereochemistry of the cyclopropane fission, the stereospecifically labelled compound **16** was synthesised.[75] On its reaction with

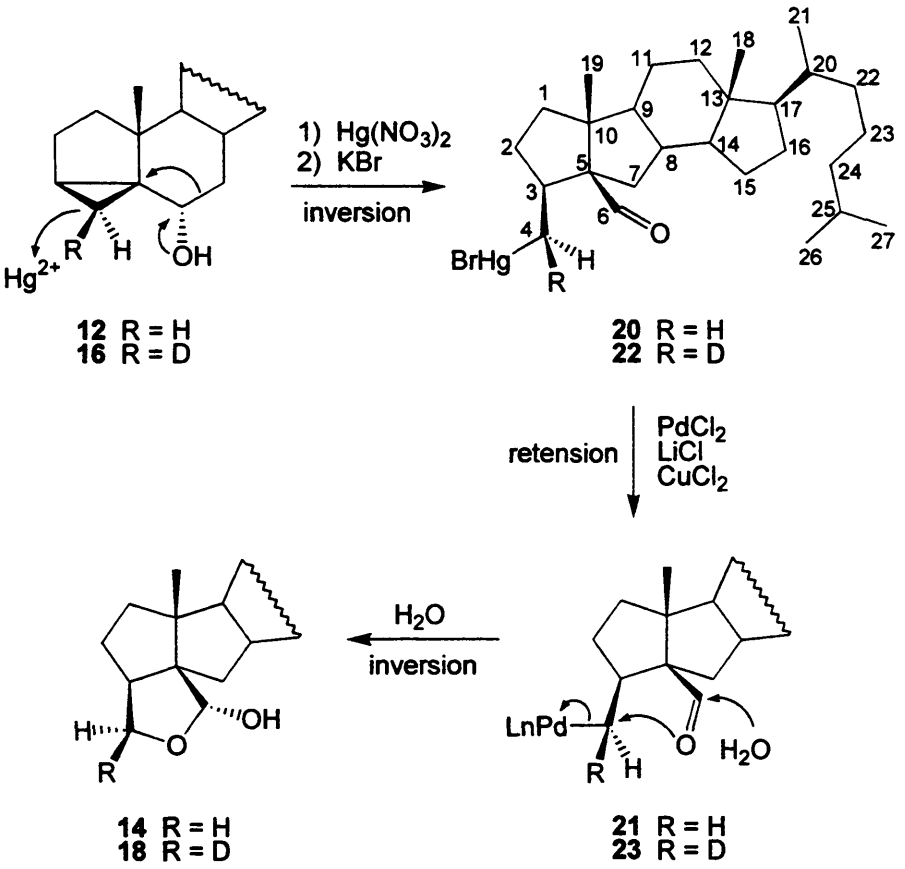
thallium(III), lactol **18** was produced. The ^{1}H NMR spectrum and NOE experiments proved that the deuterium was in position 4β. Formation of this product can be explained by initial corner attack by thallium with inversion, followed by nucleophilic substitution of thallium by oxygen.

It could be conjectured that the same product would arise from initial edge activation (**16** → **19**) followed by replacement of thallium for OH (from water) to give the corresponding alcohol, which would then spontaneously cyclise to lactol **18**. In order to rule out this possibility experiments were carried out using water enriched in ^{18}O. Reaction of **12** with thallium(III) produced lactol **14** with the label located only in the hydroxyl group. A complementary experiment was conducted by reacting ^{18}O-labelled alcohol **12** with thallium(III). The product obtained had the label located only in the ether oxygen, which supported the proposed corner opening mechanism and ruled out a double retention pathway.[70]

The same skeletal rearrangement was observed when cyclopropyl alcohol **12** was treated with mercury(II) nitrate, (Scheme VI).[13,41] It was found that, unlike the thallium example, (Scheme V), the organomercurial intermediate was a stable, isolable compound that did not instantaneously convert into the lactol. In order to prove that corner opening had also occurred in this case the configuration at C-4 had to be fixed. This was achieved by transmetallating with palladium(II), which is known to occur with retention of configuration,[77-81] and facilitated ring closure to form the known lactol **14**.

Stereospecifically labelled cyclopropyl alcohol **16** was treated with mercury(II) nitrate in the same way as the unlabelled analogue **12** and the reaction was quenched with potassium bromide solution. Catalytic reaction with Li_2PdCl_4 (generated from

palladium(II) chloride and lithium chloride) and copper(II) chloride, as the oxidant, furnished lactol **18**.[41] The deuterium was found to be in position 4β, therefore implying that mercury(II) also opened the cyclopropane via corner activation, initiating the unique skeletal rearrangement that has been shown to occur with thallium(III).



12 R = H
16 R = D

20 R = H
22 R = D

14 R = H
18 R = D

21 R = H
23 R = D

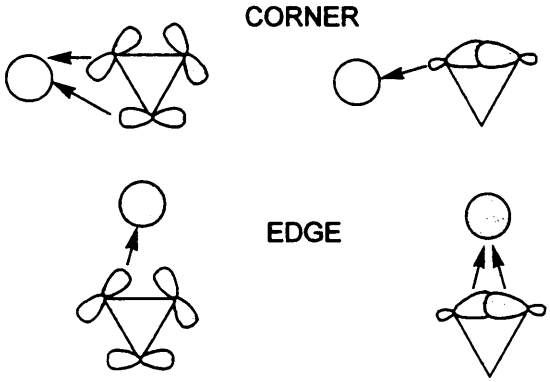
Scheme VI

1.3 THE MECHANISM OF CYCLOPROPANE CLEAVAGE

Coxon *et al* have given an explanation of why mercury(II) and thallium(III) promote corner opening of the cyclopropane.[67,68] The reasoning is based on the fact that neither mercury(II) nor thallium(III) are good back donors, and this is illustrated with orbital diagrams.[82,83] The attack by electrophiles at the corner of the cyclopropane reflects the favourable interaction of both the degenerate HOMO's of the cyclopropane

with the hydrogen 1s and d_σ LUMO of the electrophile, (Scheme VII). In edge attack the HOMO/LUMO interaction is favourable for the H 1s but not for the unsymmetrical orbital.

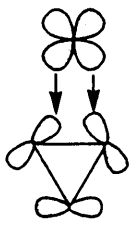
Interaction of the LUMO of the Electrophile with degenerate HOMO's of cyclopropane



Scheme VII

Back donation of the metals d_π electron density to the LUMO of the cyclopropane helps favour edge attack, (Scheme VIII). Transition metals capable of backdonation (Pd, Pt, Rh), provide a favourable interaction with the LUMO Walsh orbital of the cyclopropane, which allows oxidative addition at the edge of the cyclopropane. This interaction compensates for the more favoured σ-interaction at the corner of the cyclopropane. In the case of mercury(II) the donor ability[84] of the d_π orbitals is negligible, so the d_π HOMO / cyclopropane LUMO interaction has little or no effect.

Back donation of d_π-electrons to the LUMO of cyclopropane



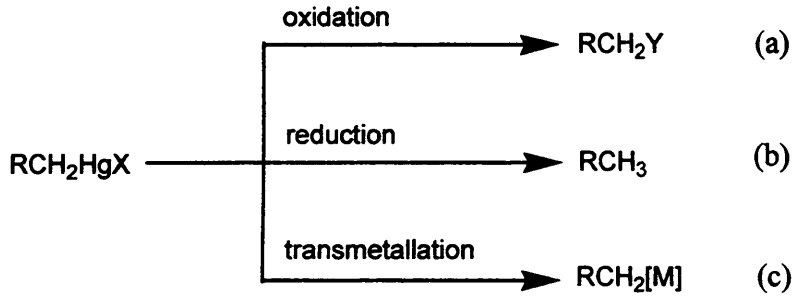
Scheme VIII

Mercury-mediated ring opening of cyclopropanes has been shown to occur with high levels of regioselectivity and stereoselectivity.[43,69,85] The regioselectivity can be explained due to cleavage of the bond between the most and the least substituted carbons. Factors such as the inductive effect of neighbouring functional groups, also need to be considered when explaining the regioselectivity of a particular reaction. The stereoselectivity of these reactions can be explained by a concerted mechanism, where the carbon-carbon bond breakage happens at almost the same time as formation of the new bonds. However, this is only the case for mono-cyclopropanes, as it has been shown that electrophilic opening of cyclopropane arrays occur through a stabilised free carbocation.[87]

1.4 APPLICATION OF ORGANOMERCURIALS

Organometallics can vary greatly in their reactivities; while alkyl lithiums, Grignard reagents and organocuprates are highly reactive, there are others such as organomercurials, organoboranes and organostannanes which are relatively stable. Organomercury compounds are one of the oldest groups of organometallics, which have been synthesised by many routes and have found various applications in organic chemistry.[88-92] Methods for preparation of these compounds include mercuration of organic halides, of cyclopropanes and arenes.[92] However, the most utilised and documented procedures are those collectively known as solvomercuration.[90] In these reactions an olefin or acetylene is treated with an electrophilic mercury salt, in the presence of the appropriate solvent or nucleophile, to afford products in which the mercury moiety and solvent, or nucleophile, have added across the unsaturated carbon-carbon bond.

The stability of organomercurials has enabled their reactivity to be explored. Numerous synthetic applications have been reported including halogenation, hetero-atom displacements, alkylation, alkene and alkyne addition and substitution processes, carbonylation and reduction.[89,92] These procedures generally allow utilisation and cleavage of the mercury within one reaction step and are often radical in nature. Pathways (a) and (b), (Scheme IX), show the two major routes, in which general syntheses from organomercurials have been documented.

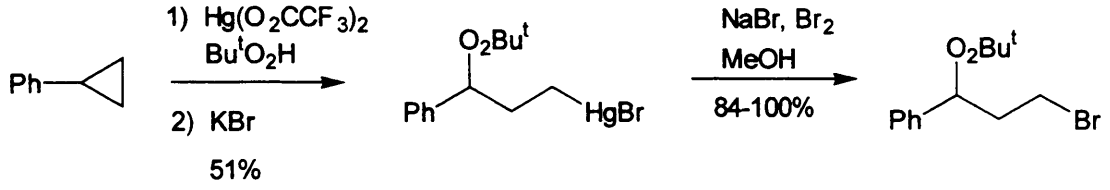


Scheme IX

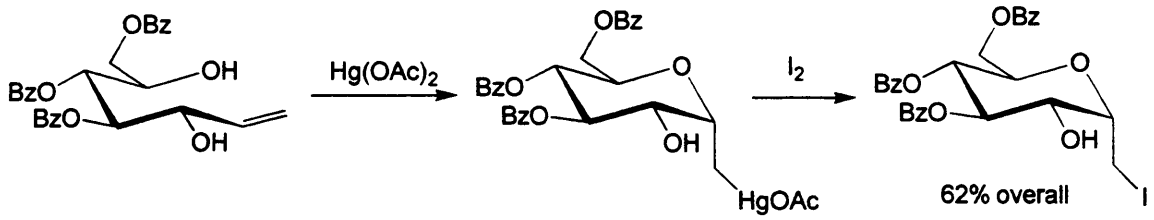
Oxidation of organomercurials can lead to useful hetero-atom substitutions allowing mercury to be replaced by halogen, oxygen, sulphur, nitrogen and phosphorous groups. The substitution of mercury by halogen has been used in synthesis for the preparation of radio-labelled compounds.[93] Halogenation is usually accomplished with bromine or iodine and can be used in the formation of alkyl, aryl, propargyl and vinyl halides.[92] The halogenation of organomercurials, prepared by solvomercuration, provides a convenient synthetic route for the addition of a nucleophile and a halogen across a cyclopropane[94] or a carbon-carbon double bond,[95] (Schemes X and XI).

The synthesis of compounds containing hetero-atoms, particularly oxygen, can be accomplished using organomercurials as intermediates. In the presence of oxygen, organomercurials can be reduced to form alcohols. This process has been used in

formation of hydroxytetrahydrofurans, carbohydrates, prostaglandins and nucleosides.[90,96] Ketones can also be produced in reasonable yields by reacting secondary alkylmercurials with ozone[97] or peracetic acid.[98]



Scheme X



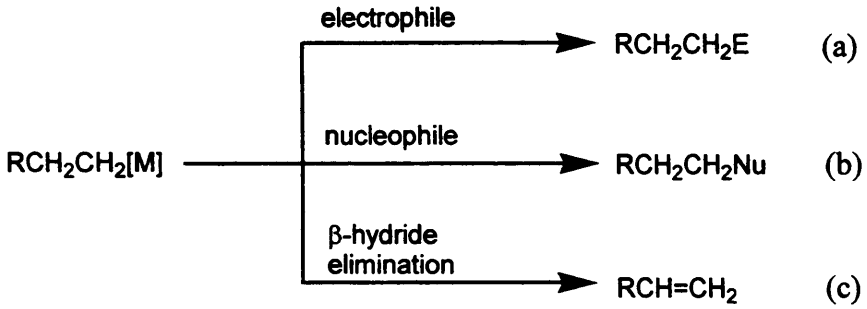
Scheme XI

Reduction of organomercurials is easily achieved by the use of the metal hydrides of boron, aluminium or tin. The most important use of reduction reactions is in the substitution of mercury for hydrogen in solvomercuration procedures, although this may sometimes be considered a waste of the functionality of mercury. Sodium borohydride is the most commonly used hydride, which, under alkaline conditions instantaneously reduces organomercuric salts to the corresponding hydrogen substitution product.[99] The mechanism of these reactions involves generation of an organomercury hydride, followed by decomposition via free radical intermediates, (Scheme XII).[100]

Scheme XII

The transmetallation of mercury, pathway (c) (Scheme IX), is not as well documented. It was thought that this procedure would be very useful synthetically as it

proceeds with retention of configuration (for palladium),[77-81] thus allowing further transformation of the intermediate. Three possible routes can be envisaged, (Scheme XIII); the reaction pathway which is followed depends on the nature of the organometallic reagent.



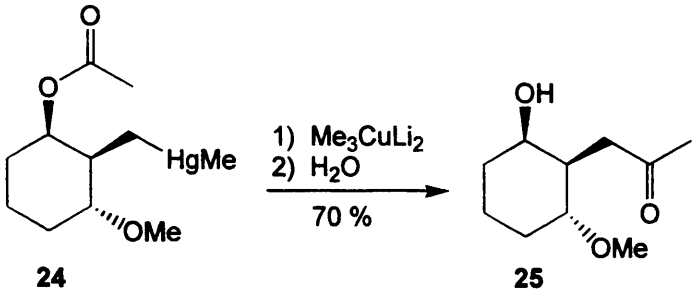
Scheme XIII

If the metal is hard[101] the attached carbon will become anionic and thus may attack electrophilic centres, as in pathway (a). In contrast if the metal is soft it will cause the carbon attached to it to become electrophilic in nature and thus susceptible to nucleophilic attack as in pathway (b). The third possibility, pathway (c), is β-hydride elimination via a *syn*-mechanism, producing a double bond.

Research within our group has involved exploring the applications of organomercurials, particularly with respect to transmetallation.[102,103] Several examples of pathways (a) - (c) are explained below.

The reaction of organomercurials with organocuprates provides examples of path (a). The addition of alkyl lithiums or Grignard reagents to carbonyl groups is widely used in synthesis[104] but an intramolecular version of this procedure had not been fully developed until recently.[105,106] The difficulty of generating the RMgHal or RLi (whilst in the presence of an unprotected carbonyl function) in order to carry out the

intramolecular reaction, can be overcome by using a less reactive organometallic species.[107] The schemes below show methods for this synthesis by activating the RHgX with organocuprates.[102,103]

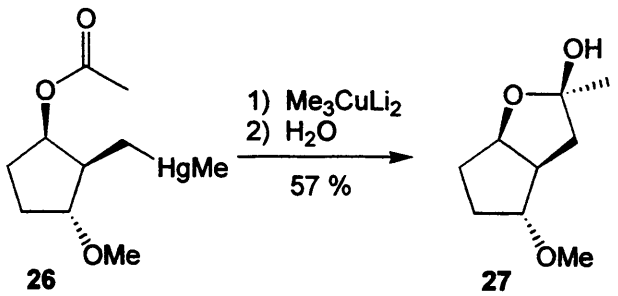


24 **25**

Scheme XIV

The six membered ring acetate **24**[103] was treated with Me_3CuLi_2 to afford the hydroxy ketone **25**, (Scheme XIV).[85] The organometallic species generated following reaction with the cuprate, reacts via attack on the neighbouring ester group. The cyclic intermediate produced, collapses on work up giving **25**.

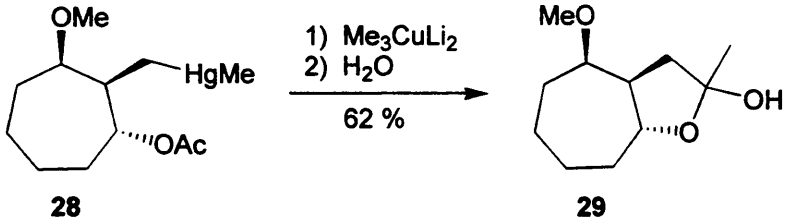
The five membered ring acetate **26** reacted upon treatment with the cuprate, yielding **27** as the only isolable product, (Scheme XV). In this case the cyclic intermediate was stable and did not collapse upon quenching.



26 **27**

Scheme XV

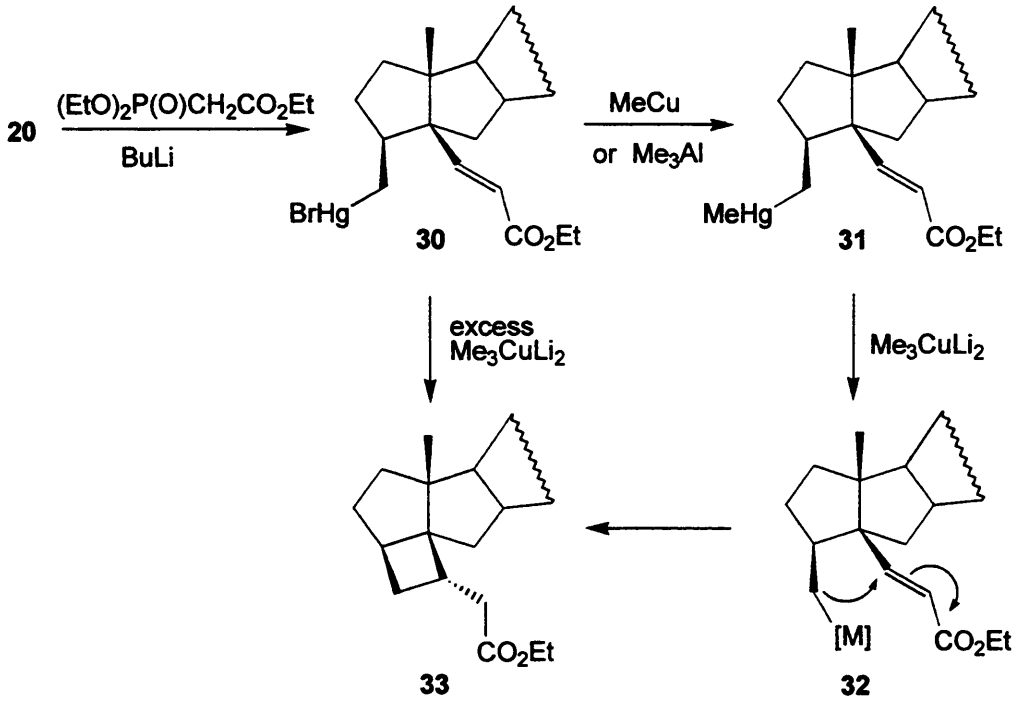
An isomeric, seven-membered analogue produced the expected hemiacetal **29**, as the only product upon its reaction with Me_3CuLi_2, (Scheme XVI). A mixture of two anomers (3.6 : 1) was obtained.



28 **29**

Scheme XVI

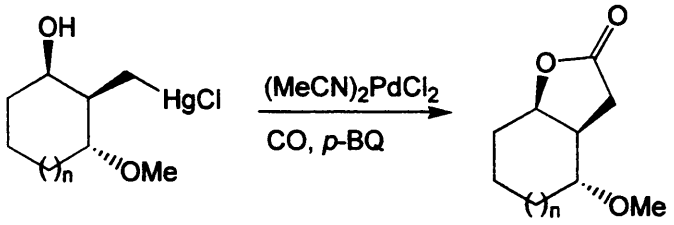
Intramolecular addition across an activated double bond has also been achieved, (Scheme XVII).[13] The α,β-unsaturated ester **30** was prepared from aldehyde **20** by a Horner-Emmons olefination. Organomercurial **30** was initially methylated with either methyl cuprate or trimethyl aluminium, then treated with Me_3CuLi_2. However, this furnished the desired cyclobutane derivative in low yield. A much better yield of **33** was obtained in one step, using an excess of Me_3CuLi_2. Formation of this product can be rationalised firstly by methylation on the mercury, followed by the reaction of the methyl mercurial group with the cuprate, then an intramolecular addition to the double bond.



Scheme XVII

Reaction of organomercurio aldehyde **20** with a palladium(II) catalyst generated in situ (Scheme VI), is an example of reaction type (b), (Scheme XIII). The transmetallation with palladium provides an electrophilic centre at C-4 which initiates the intramolecular attack from the nucleophilic oxygen of the aldehyde, producing lactol **14**.

Organomercurials can be transmetallated with palladium(II) to generate organopalladium species[41,108-110] which, in turn, are known to undergo carbonylation.[111] Transmetallation in chloromercurial **34,** (Scheme XVIII), followed by carbon monoxide insertion, promoted formation of an electrophilic carbon which could then undergo nucleophilic attack from the hydroxy group. This method is an example of pathway (b), (Scheme XIII), and it allows synthesis of a variety of *cis* and *trans* fused lactones via palladium(II) catalysed carbonylation.[44,86,112] Upon heating organomercurials **34, 36** and **38** with catalytic amounts of $(MeCN)_2PdCl_2$ and *p*-benzoquinone (2 equiv) in THF under an atmosphere of carbon monoxide for 4 days, lactones **35, 37** and **39** were produced with isolated yields of 60%, 59% and 52% respectively.



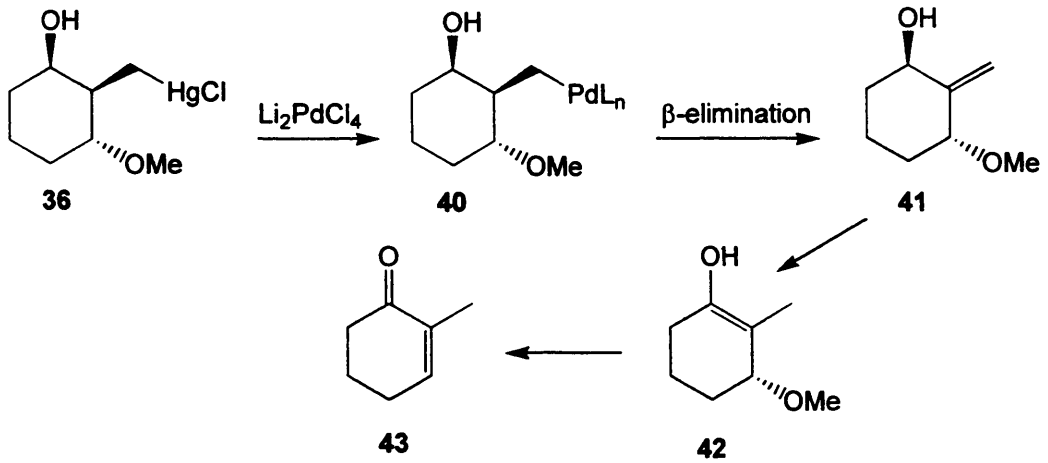
34 n = 0
36 n = 1
38 n = 2

35 n = 0
37 n = 1
39 n = 2

Scheme XVIII

The third possible reaction pathway which the intermediate transmetallated species could follow is β-hydride elimination, (Scheme XIII). This route was observed during the attempted synthesis of an oxetane ring.[103] Organomercurial **36** was treated with Li_2PdCl_4 and the reaction was worked up to afford methyl cyclohexenone **43**.

Formation of this product would have occurred following β-elimination yielding **41**. Isomerisation of the allylic alcohol, presumably by palladium,[113] affords enol **42** which would then have been converted into the conjugated ketone **43**.



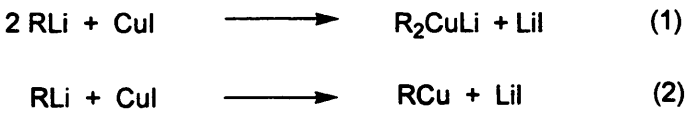
Scheme XIX

1.5 ORGANOCOPPER REAGENTS AND THEIR REACTION WITH ORGANOMERCURIALS

Organocuprates are one type of transition metal complex containing metal-carbon σ-bonds, that are used in transformations to form carbon-carbon and carbon-X bonds. The covalent nature of the copper-carbon σ-bond determines the reactivity of the bound organic group, restricting its reactions to those accessible to the transition metal, (e.g. oxidative addition, insertion, reductive elimination and β-hydrogen elimination). Organocuprates are among the most extensively used organometallic reagents; there is large variety of species which can be used in many different transformations.[123-126]

The most extensively used complexes are the lithium diorganocuprates, R_2CuLi. These soluble, thermally unstable complexes are generated in situ by the reaction of copper(I) iodide with two equivalents of an organolithium reagent, (Scheme XX, equation 1). The mono-alkyl copper complexes, RCu, (Scheme XX, equation 2) are

yellow, insoluble and are used less frequently in synthesis than lithium diorganocuprates.



Scheme XX

Despite the fact that dialkyl cuprates are very useful reagents, they suffer from a major limitation; only one of the two alkyl groups is transferred, which can lead to inefficiency when the R group is large or complex. Mixed alkyl heterocuprates are used to avoid this problem as the presence of one non-transferable group such as an alkoxide or cyanide stabilises the complex.[127] An example of this increased efficiency is in the conversion of acid chlorides to ketones.[9] Large excesses of lithium dialkyl cuprate are required to affect the reaction whereas only a stoichiometric amount of a mixed cuprate is required to provide high yields of ketones.

The boundaries of organocopper chemistry have been further expanded by development of thermally stable cuprates. Sterically hindered non-transferable ligands, such as diphenyl phosphide and dicyclohexylamide are used to prepare RCu(L)Li. These reagents are stable at 25 °C for over an hour and undergo typical organocuprate reactions.[127-130]

'Higher order' cuprates such as $R_2Cu(CN)Li_2$, formed by treatment of copper(I) cyanide with two equivalents of organolithium reagent, are more stable than R_2CuLi, and are effective in reactions with previously unreactive substrates.[131,132] The nature and existence of higher order cuprates is a subject of controversy, but the reagent mixtures do differ in reactivity from simple diorganocuprates.[133,134]

The popularity of organocopper complexes as reagents in organic synthesis has brought about numerous mechanistic investigations of both substitution and conjugate addition schemes.[126] Studies of the former have shown that no single interpretation can account for all the mechanistic and stereochemical results gathered previously.[135] The organocuprate itself may vary depending on solvent, method of preparation and presence of additives, therefore the likelihood of finding a common explanation is unlikely.

Organometallic reactions in Section 1.4 have shown the requirement for Me_3CuLi_2 for intramolecular additions to ester groups. This cuprate and others formed from non-integral ratios of organolithium to copper halide have been screened for their synthetic potential.[136-139] Certain advantages over Gilman reagents have been found,[140,141] however, the structure of these species has been debated.[135,137] Further explanation concerning the structure of Me_3CuLi_2 will clarify the different opinions on this matter, before discussion of the reactive species generated when organomercurials are added to cuprates.

Previous studies on the nature of Me_3CuLi_2 by Ashby[137] and Lipshutz[135] gave different conclusions based on NMR data. The experiments involved studying ^7Li and ^1H NMR spectra for various mixtures of methyl lithium and methyl cuprate. Ashby reported that Me_3CuLi_2 is a discrete species, but that it can exist in an equilibrium with Me_2CuLi and methyl lithium. Lipshutz argued that the trimethyl cuprate is in fact a mixture of Me_2CuLi and 'free' methyl lithium. This suggestion is based on similar results to that of Ashby, but in this case, the integration of the peaks in the NMR spectra had shown a ratio of 1 : 1, Me_2CuLi to methyl lithium. Lipshutz therefore concluded that ratios in excess of 1 : 2, methyl cuprate to methyl lithium, rather than forming

higher order cuprate derivatives, simply build up the concentration of free methyl lithium, regardless of the solvent present.

It is necessary to note that these experiments have been conducted in the absence of lithium iodide, which is not the case in many cuprate reactions. The evidence leading to these two opposing conclusions has been shown to be solvent dependent and the various species shown to exist by combined NMR experiments have not been readily detected by standard ^{1}H and ^{13}C NMR techniques, in samples containing lithium iodide. Experiments by Grech[103] with samples containing lithium iodide have conflicted with Lipshutz's hypothesis of a methyl lithium and Me_2CuLi mixture for the structure of Me_3CuLi_2. However, it has been suggested[135] that the presence of lithium iodide in NMR samples greatly effects the detection of various types of cuprate, having an effect on the structure and thus, on the reactivity of these species.

For a specific molecule, there is reason to believe that slightly more or less RLi to RCu might give considerably different results as compared to the better known ratios. There are literature cases where traditional cuprate ratios have been modified to improve results.[142] The extra RLi may serve many roles[143] including rapid conversion of the polymeric RCu formed during a reaction, into R_2CuLi.

The structure of the reactive species formed by treatment of organomercurials with cuprate has been considered.[103,144] Conclusions drawn from this work is based on various ^{1}H, ^{7}Li and ^{13}C NMR spectra recorded for methyl lithium, Me_2CuLi, Me_3CuLi_2 and mixtures of these reagents with model compounds. Over twenty years ago Whitesides proposed the cluster R-[Hg, Cu, Li]. $(C(CH_3)_3)_3$ as the species formed when an organomercurial was reacted with a cuprate.[144] This suggestion received additional

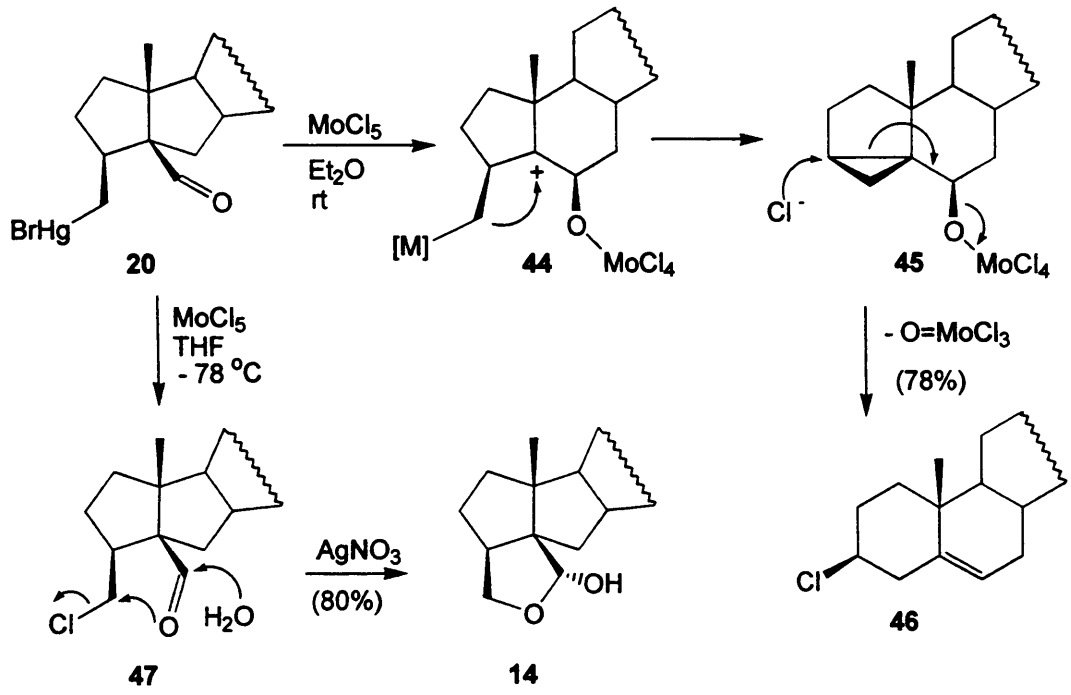
support when Grech ruled out other possibilities such as methylation of mercury or simple transmetallation, by experimentation with model compounds and the use of NMR spectroscopy.[103]

1.6 REARRANGEMENTS OF ORGANOMOLYBDENUM INTERMEDIATES

Transmetallation of organomercurial **20** with lithium, copper or palladium reagents has provided routes to a variety of compounds, (see Section 1.4). The reactivity of the intermediate organometallics has also been controlled by added ligands, which influence the course of the reaction.[41] Further products have also been synthesised from organomercurial **20**, by the use of molybdenum reagents.[42] Numerous molybdenum complexes had been documented previously,[145,146] however, their usage did not encompass transmetallation of organomercurials.

Two different forms of molybdenum were found to have potential to achieve rearrangement of organomercurial **20**.[102] Firstly, treatment with molybdenum(V) chloride afforded products, that were dependent on the solvent used in the reaction, (Scheme XXI).[42] If ether was used, the procedure afforded cholesteryl chloride **46**. Formation of this product has been explained following reactions using deuterated organomercurial **22**, and examination of the NMR spectra of the deuterated cholesteryl chloride obtained.[147] The mechanism has been shown to involve initial co-ordination to the aldehyde oxygen, which may trigger a Wagner-Meerwein migration generating carbocation **44**. Subsequent cyclopropane ring closure, would afford cyclopropyl intermediate **45**, which could then collapse via the '*iso*-steroid' rearrangement,[148] to furnish cholesteryl chloride **46**. An alternative pathway is observed when the reaction is

carried out in THF: chloro-aldehyde **47** is formed as the major product, rather than **46**.[147] Since **47** could not be completely purified and characterised,[103] its structure was determined by silver(I) mediated conversion to lactol **14**.

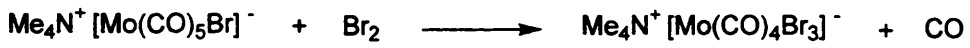


Scheme XXI

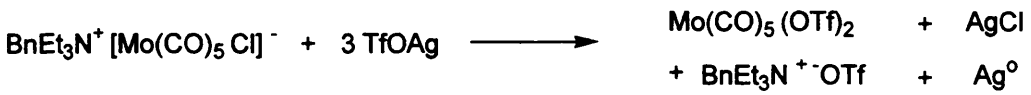
Molybdenum hexacarbonyl can be converted into several complexes following reaction with different quaternary ammonium halides, (Scheme XXII).[102,149] These reagents can be prepared in situ, or isolated and stored. Subsequent reactions can be carried out in situ, to synthesise additional reactive complexes including those formed upon reaction with bromine or silver triflate, (Schemes XXIII and XXIV).[102,149] The complex formed by reaction with bromine is the second molybdenum reagent which can be reacted with organomercurial **20**, to facilitate a molecular rearrangement.

$$Mo(CO)_6 + R_4N^+X^- \longrightarrow R_4N^+[Mo(CO)_5X]^- + CO$$

Scheme XXII

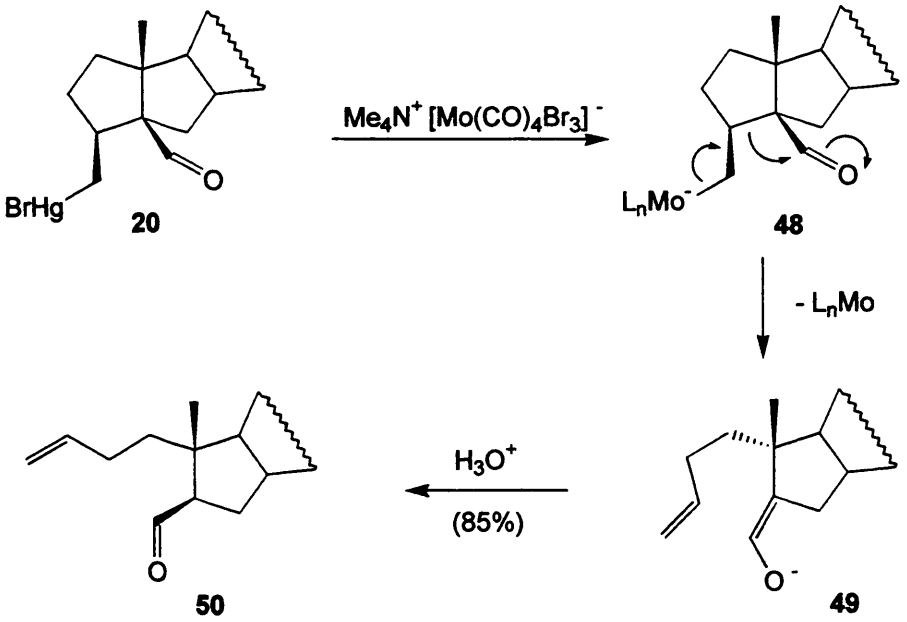


Scheme XXIII



Scheme XXIV

Transmetallation of **20** was accomplished using a molybdenum(II) reagent, (Scheme XXV). The intermediate organomolybdenum compound exhibited different behaviour to that observed with **44**, (Scheme XXI). Interaction of the aldehyde with the molybdenum is not a major factor in this reaction, since the negative charge on the transmetallated species **48**, prevents this occurring. The structure of this intermediate favours a novel reaction pathway, via a stereoelectronicaly controlled Grob-type fragmentation, which produces olefinic aldehyde **50**.[42]



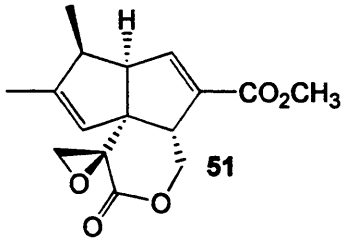
Scheme XXV

Transmetallation of organomercurials with molybdenum reagents has been achieved in the examples shown previously, (Schemes XXI and XXV). The type of complexes used in these reactions, or more specifically the oxidation state of molybdenum, determines how the organomolybdenum intermediates will react. Further

examples of the use of these and other molybdenum(II) reagents have been reported for the catalysis of allylic substitutuion,[149] and alkylation of electron-rich aromatics.[150]

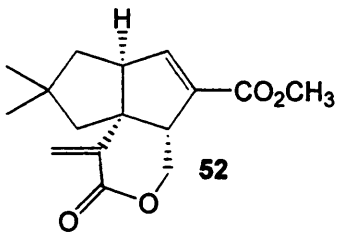
1.7 SYNTHESIS OF TRIQUINANES AND NATURAL PRODUCTS

Organomercurial intermediate **20** has been used in transformations with copper[43,46] and molybdenum reagents.[42,102] It was thought that this organomercurial would be a useful intermediate to further demonstrate the available synthetic methodology[151-163] and to provide an alternative route to angular triquinanes.[164-166] Although the experiments were confined to the steroid skeleton, the reactions were intended to be of a general nature so that they could be applied to other systems. Organomercurials could be used to devise new routes to enones, furans and lactones. Alternative procedures for synthesis of the basic structure of natural products such as pentalenolactones **51** and **52**, isolated from *Aspergillus* and *Streptomycis* strains,[167] (-)-silphiperfol-6-ene **53** isolated from the roots of *Silphium perfoliatum*,[168] or (-)-methyl cantabradienate **54** isolated from *Artemisia Cantabrica*,[169] could be envisaged.



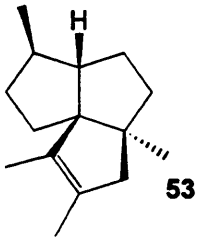
51

Pentalenolactone



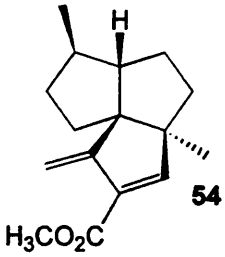
52

Pentalenolactone E



53

(-)-Silphiperfol-6-ene



54

(-)-Methyl Cantabradienate

CHAPTER TWO

SYNTHESIS AND USAGE OF ORGANOMERCURIALS

2.1 INTRODUCTION

Organomercurials are most often encountered as intermediates in synthesis, serving as a means of introducing a desired substituent into the structure of a molecule. The mercury is usually removed by reduction once it has played its role in the reaction. This situation is illustrated by oxymercuration of olefinic double bonds[91,92] and by cyclopropane cleavage.[60,86,91] These processes are not very economical since they generally require stoichiometric amounts of a toxic metal, which is used and cleaved within one procedure. A protocol to further utilise the presence of mercury within the molecule was therefore sought. If the organomercurial could be used in more than one productive step before cleavage, this would provide a more efficient utilisation of the mercurial component.

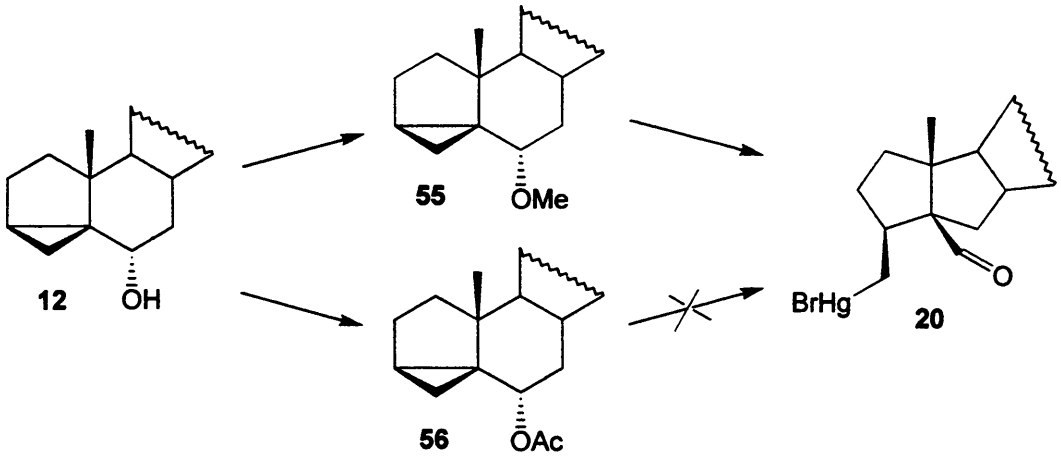
This chapter includes a discussion of the selectivity of the steroid rearrangement as shown in Schemes V and VI, in order to identify the scope of this procedure. The use of a cuprate and its reaction with a specific organomercurial is also considered, because formation an annulated cyclobutanol facilitated subsequent reactions, which showed synthetic potential. Additional work included developing a means of protecting the mercury component to allow functional group transformations: selective reduction of a carbonyl group, methylenation of an aldehyde and formation of oximes proved possible in the presence of the protected organomercurial.

2.2 CORNER OPENING IN STEROIDAL CYCLOPROPYL ALCOHOL DERIVATIVES

Treatment of cyclopropyl alcohol **12** with thallium(III) or mercury(II) gave the same, unique rearrangement by formation of two annulated five membered rings.[13,43,70]

The difference between these two reactions is the fate of the organometallics generated. Isolation of the organomercurial product was possible since organomercurials are generally more stable than their organothallium counterparts, which undergo nucleophilic displacement of thallium. The unique skeletal rearrangement is limited to mercury(II) and thallium(III), which are very soft Lewis acids.[101,104] Other isoelectronic cations (gold(I) and lead(IV)) and those of high redox potential, were found to be inert or to convert the compound to cholesterol or its esters.[102]

In order to maximise on the synthetic utility of this rearrangement, the reaction of several analogues with mercury(II) was considered. To analyse the selectivity of the reaction, the functionality at position C-6 in compound **12**, was altered, (Scheme XXVI).[170] Cyclopropyl alcohol **12** was treated with sodium hydride and methyl iodide to produce methoxy derivative **55**. Reaction of **12** with acetic anhydride and triethyl amine produced the acetate derivative **56**.

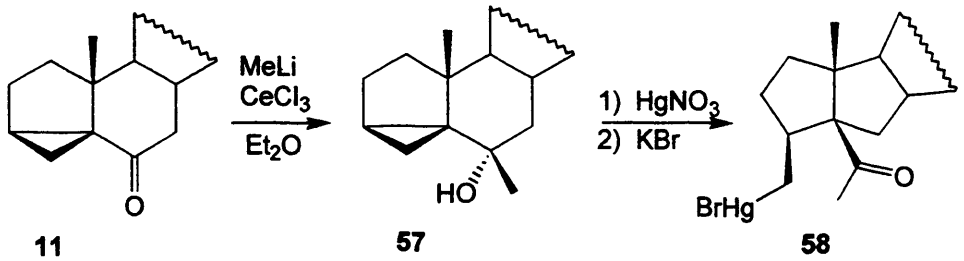


Scheme XXVI

The selectivity of the electrophilic cleavage of cyclopropane was tested with these analogues. Reaction of methoxy derivative **55** with mercuric nitrate in a mixture of DME and acetonitrile produced a considerably slower reaction than seen previously,

for the alcohol. After stirring overnight at room temperature organomercurial **20** was produced, (Scheme XXVI). However, when acetate **56** was subjected to the same conditions no reaction was observed.

To make additional use of the steroid rearrangement it would be helpful if organomercurials with different functional groups could be obtained. Further reactions could be envisaged for an organomercurial containing a ketone functionality, therefore synthesis of this compound was attempted. Cyclopropyl ketone **11** reacted with methyl lithium to give the required derivative **57** (Scheme XXVII), however, only a low yield of the required product was obtained, as a large amount of starting material was re-isolated. In order to increase the yield of the desired product an organocerium compound was formed by reacting anhydrous cerium(III) chloride with the methyl lithium. Upon addition of compound **11**, nucleophillic addition was achieved in reasonable yield (73%). The organocerium reagent is less basic than the corresponding alkyl lithium, hence the competitive deprotonation and subsequent enolization are disfavoured.[171] This reaction turned out to be stereoselective, affording only isomer **57**, the configuration of which was established by NOE experiments.



11 **57** **58**

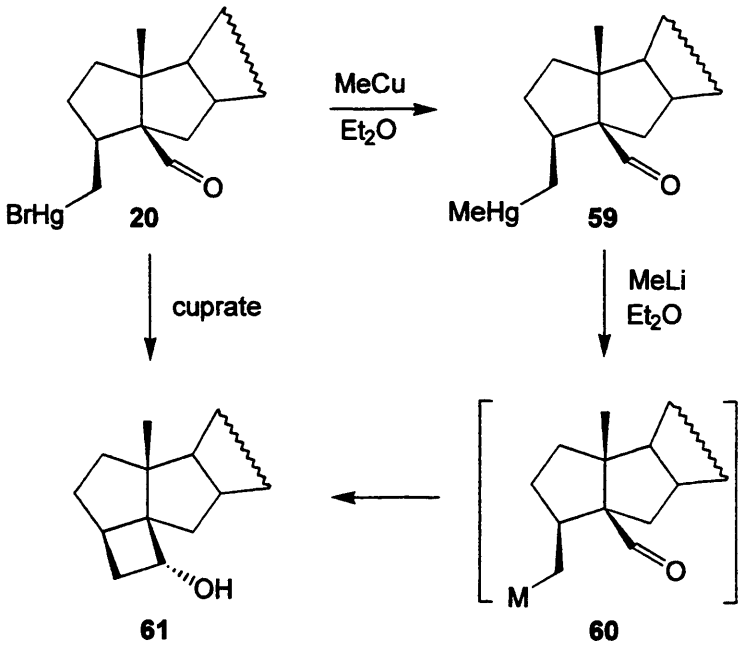
Scheme XXVII

Reaction of **57** with mercuric nitrate, as mentioned previously (in Section 1.2), did not give clean formation of the required organomercurial. A mixture of products was obtained, which were difficult to separate by chromatography. Approximately 50%

of a mixture containing an organomercurial could be isolated, which could only be confirmed as bromomercurio ketone **58** by comparison with a sample, prepared by a different route, (see Scheme XXIX).

2.3 ALTERNATIVE SYNTHESIS OF 58 USING 'Me_3CuLi_2'

The ability to activate organomercurials using copper reagents has been described previously.[43,102] However, to obtain yields consistent with published results, it was necessary to experiment with the conditions of generation and reaction of the cuprates. Documented procedures include the formation of cyclobutanol **61**,[13] (Scheme XXVIII). The reaction called for an excess of Me_2CuLi, but on repeating this experiment the reactions were found to be low yielding and side products were obtained. Due to the inconsistencies in this procedure (and with other organomercurials)[103] the conditions of this reaction were examined further.



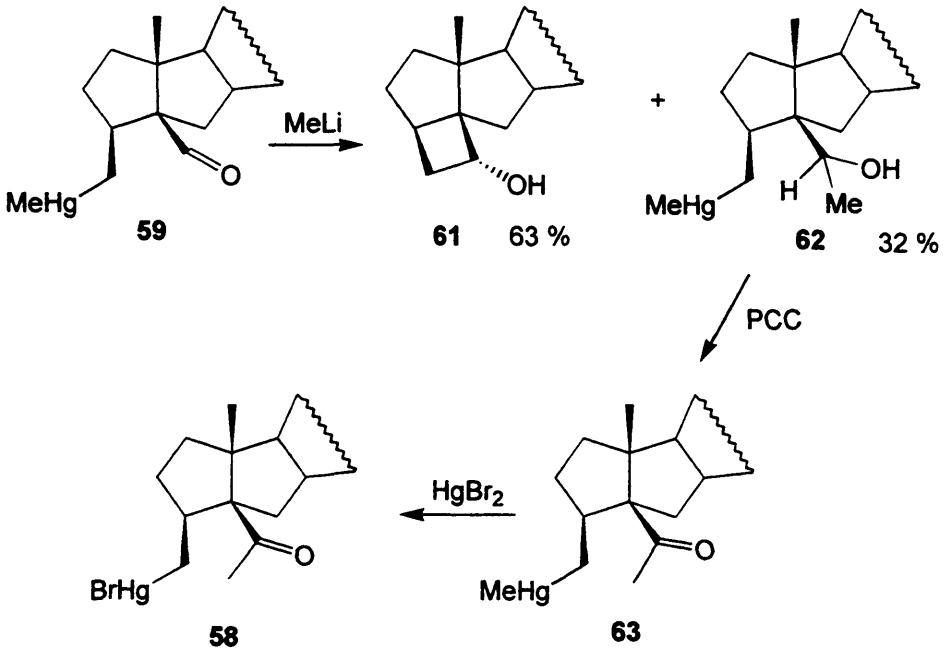
Scheme XXVIII

Freshly dried solvent was found to be required, either THF or ether depending on the reaction being carried out. Additional purification of the purchased copper(I) iodide did not affect the reactions but the quality of the methyl lithium was found to be important. Stock solutions of methyl lithium with a cloudy appearance were only found to be useful for reactions requiring an excess of methyl copper. Formation of methyl copper occurs when one equivalent of methyl lithium is added to one equivalent of copper iodide at low temperature, in an inert atmosphere. Addition of bromomercurio aldehyde **20**, either dissolved in THF or poured into the yellow methyl copper mixture, whilst cooled at -78 °C, allows immediate methylation on the mercury.

The ideal conditions for conversion of **20** into **61** were considered by examining reactions of methyl mercurio derivative **59**, with cuprate mixtures formed from two and three equivalents of methyl lithium to copper(I) iodide. To determine the amount of methyl lithium used in these reactions the solutions were titrated before use.[172] Initial formation of the cuprates was carried out at -35 °C. After stirring for five minutes a clear solution was obtained, then the mixture could be cooled to -78 °C and reacted with the organomercurial.

No reaction was observed when methyl mercurio aldehyde **59** was added to one equivalent of Me_2CuLi. However, use of 'Me_3CuLi_2' in a separate reaction did allow formation of cyclobutanol **61**. Bromomercurio aldehyde **20** was found to require two equivalents of 'Me_3CuLi_2' to achieve a 97% yield of the same product, (Scheme XXVIII). Methylation of the mercury is attained by addition of the first equivalent of cuprate and the second equivalent activates the mercurial functionality to allow an intramolecular addition to the carbonyl. Initial observation[13] of this novel route to an annulated cyclobutanol, using excess Me_2CuLi, can be attributed to the presence of

extra methyl lithium in the reaction mixture. Considering the previous assumption concerning the reactive copper species in this procedure, it is important to note that when investigating cuprate reactivity, titration of the alkyl lithium must be carried out.



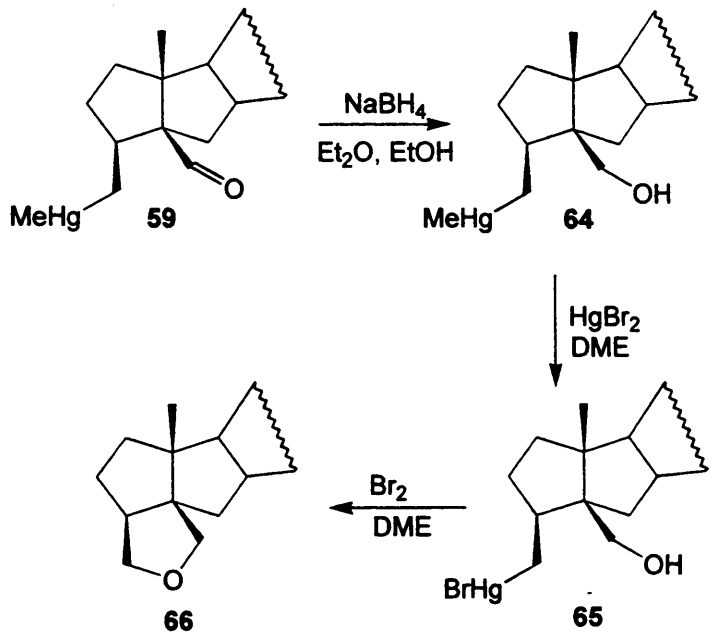
Scheme XXIX

During the studies with cuprates, isolation of a side product was achieved which initiated synthesis of bromomercurio ketone **58**, via an alternative route to that previously mentioned, (see Scheme XXVII). To attain the maximum amount of this side product, methyl mercurio aldehyde **59** was dissolved in THF and added slowly to a dilute solution containing 1.1 equivalents of methyl lithium, at - 78 °C. A 2 : 1 mixture of **61** and **62** was obtained, (Scheme XXIX). Oxidation of alcohol **62** using pyridinium chlorochromate yielded 93% of methyl mercurio ketone **63**, which was then treated with mercuric bromide to allow a functional group inter-conversion at mercury, (**63** → **58**). Formation of **58** by this method has provided an alternative, yet not high yielding route, for synthesis of a pure sample of this compound, rather than the mixture referred to previously (see Scheme XXVII).

2.4 PROTECTION - DEPROTECTION OF MERCURY

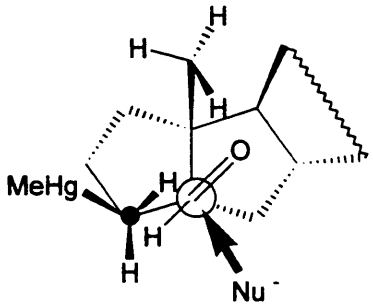
Since halomercurials are easily reduced even with mild reducing agents,[89,90] mercury must be protected if it is to be retained in the molecule, prior to reduction of neighbouring carbonyl groups. It has been shown earlier, that upon reaction with methyl copper, halomercurials (e.g. R-HgCl) undergo an instantaneous, high yielding methylation on mercury.[43,85] The resulting methyl mercurio derivatives (R-HgMe) have now been found to be stable to a number of hydride reagents, therefore reduction procedures and subsequent reactions can be carried out within the molecule, with retention of mercury. Cleavage of the mercury unit can be achieved, when required, following deprotection. Regeneration of the halomercurio functionality is sufficient to deprotect the mercury and make it susceptible to cleavage.

Methyl mercurio aldehyde **59** can be reduced with sodium borohydride to give alcohol **64** in 89% yield, (Scheme XXX). A brief screening showed that this reduction can also be carried out with $LiAlH(O^tBu)_3$, L-Selectride® or Super Hydride®, in high yields. In contrast, treatment with lithium aluminium hydride led to reduction of both functional groups. Treatment of the resulting alcohol **64**, with mercuric bromide furnished bromomercurio alcohol **65** (90%). The regenerated halomercurial functionality enables the carbon-mercury bond to be cleaved in subsequent reactions. In this example, bromomercurial alcohol **65** can easily be converted into the tetrahydrofuran derivative **66**, upon treatment with bromine. Initially a bromide derivative is formed but this is not stable and undergoes nucleophilic displacement by the hydroxy oxygen, affording tetrahydrofuran **66** in 89% yield.

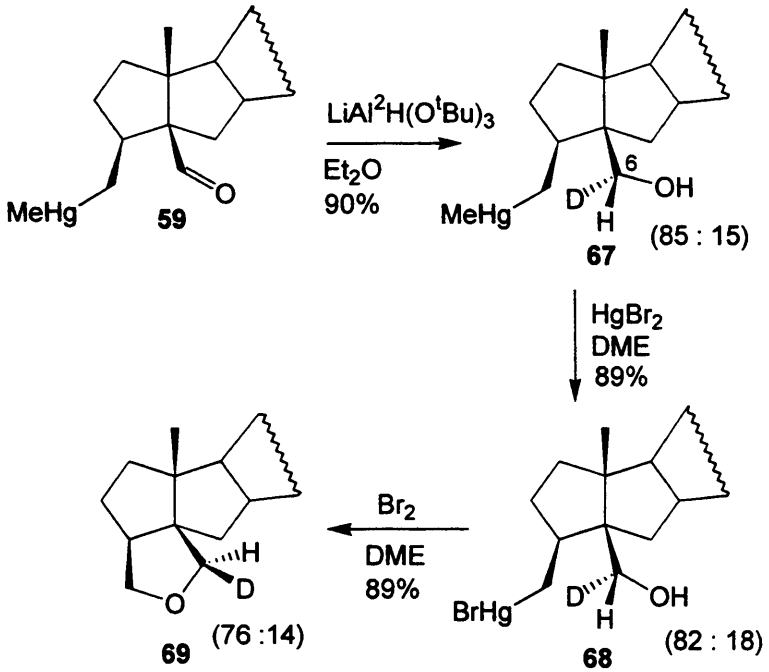


Scheme XXX

The reduction of steroidal aldehyde **59** turned out to be stereoselective. This became evident upon treatment of the aldehyde with $LiAl^2H(O^tBu)_3$, which yielded mainly alcohol **67**, (Scheme XXXI). The mixture contained 85% of **67** and 15% of its C-6 epimer. An almost identical stereoselectivity has been observed for Super Deuteride®, when an 87 : 13 ratio of isomers was obtained. The major product formed in this reaction can be explained by looking at a Newman projection of methyl mercurio aldehyde **59**, (see below). The reducing agent attacks on the least hindered side of the aldehyde conformation,[173] affording **67** as the major product. Nucleophilic attack at the aldehyde carbon in the most stable conformer affords the major product. The minor product arises from attack on the opposite side of the aldehyde to that shown, however, for this product to be formed the molecule is likely to be in a different conformation. Steric hindrance towards the approaching nucleophile and the conformers required to enable this approach, mean that the transition states are higher in energy and therefore this product is disfavoured.[176]



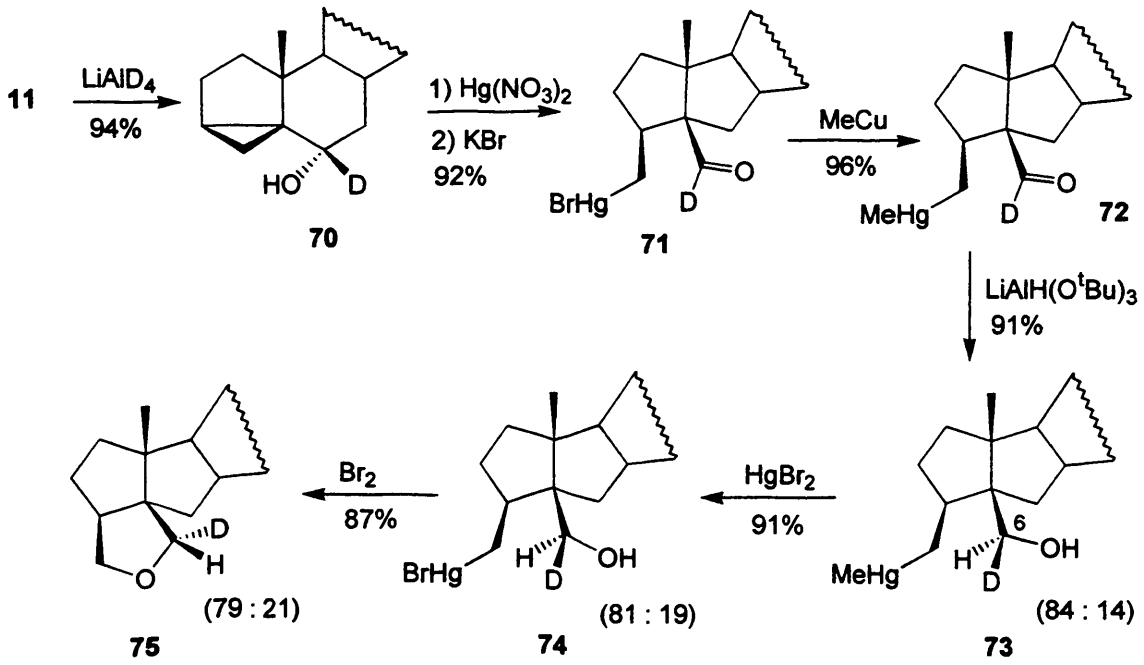
The configuration at the new centre has been established by converting the methyl mercurio alcohol compounds into rigid tetrahydrofuran derivatives (as shown in Schemes XXX - XXXII). Deuterated analogue **67** was treated with mercuric bromide to afford bromomercurial alcohol **68** (89%). Subsequent reaction of this product with bromine yielded tetrahydrofuran **69** (90%). Experimentation using the NOE technique on tetrahydrofuran **66** led to the assignment of the configuration at position C-6,[177] and retrospective determination of the major product diastereoisomers in the reduction procedures.



Scheme XXXI

In order to obtain the opposite stereochemistry in the deuterated alcohol at position C-6, a complementary experiment was conducted. Deuterated aldehyde **72**

(Scheme XXXII) was required to achieve this goal, which was synthesised in several steps from steroidal cyclopropyl derivative **11**. Reduction of the carbonyl with lithium aluminium deuteride furnished cyclopropyl alcohol **70**, which was then treated with mercuric nitrate as described previously (see Section 1.2). Methylation of the resulting bromomercurial aldehyde with methyl copper protected the mercury component allowing selective reduction of the aldehyde with $LiAlH(O^tBu)_3$. Alcohol **73** is present as the major isomer making up 84% of the mixture with the remaining 16% being isomer **67**. As explained earlier, determination of the configuration at position C-6, in the deuterated alcohols was achieved by the conversion of these compounds into derivatives in which position C-6 was fused within a ring. In this case methyl mercurio alcohol **73** was reacted with mercuric bromide to afford bromomercurial **74** (91%). Ring closure was achieved with bromine producing deuterated tetrahydrofuran **75** (87%).



Scheme XXXII

2.5 FUNCTIONAL GROUP TRANSFORMATIONS WITHIN MOLECULES CONTAINING MERCURY

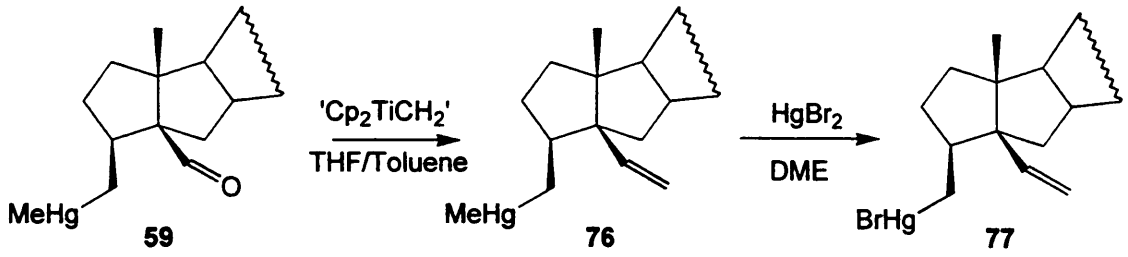
Protection of the mercurial component has allowed transformations to be carried out within the same molecule with retention of mercury. Procedures reported include stereoselective reduction of an aldehyde or ketone group,[112] and oxidation of secondary hydroxy groups using a mild oxidising agent such as pyridinium chlorochromate, as illustrated by Scheme XXIX. In developing protocols towards annulated cyclic structures it was necessary to synthesise organomercurials with functionality other than alcohols, aldehydes or ketones. Structures containing an alkene or oxime were required for experimental procedures, hence their synthesis was attempted with the aim of retaining the mercurial functionality within the molecules.

Methylenation of aldehyde **20** or **59** was considered initially. Due to steric effects influencing product yields,[178] the use of a Wittig reagent was eliminated. However, this synthetic transformation can often be achieved using geminal dimetallic derivatives[179] ($L_nM^1CH_2M^2L_m$) or with nucleophilic metallocarbenes ($L_nM{=}CH_2$), such as Tebbe reagent.[180] The latter reagent, $Cp_2TiCH_2AlClMe_2$, is very efficient in converting carbonyl groups into methylenes,[181] however, initial preparation of this reactive complex proved unsuccessful, therefore alternative procedures were considered.

Experimentation with the less hazardous titanocene methylene - zinc halide complex,[182] formed using titanocene dichloride with purified zinc powder and diiodomethane, gave insufficient reactivity. An alternative route in preparation of the titanocene methylidene complex, 'Cp_2TiCH_2' involves the synthesis of dimethyltitanocene. This is easily prepared by treatment of titanocene dichloride with

methyl lithium, providing a methylenating agent which is reasonably stable,[183] can be recrystalised and shows similar reactivity[184-186] to Tebbe's reagent.

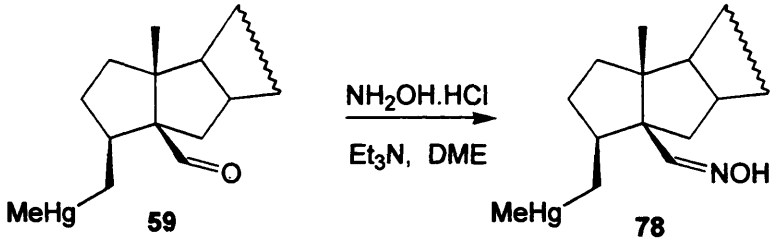
Addition of three equivalents of dimethyl titanocene in THF and one equivalent of pyridine, to a THF solution of methyl mercurio aldehyde **59**, followed by heating at 65 °C for 24 hours, produced 69% of the required methylenation product, **76** (Scheme XXXIII). To achieve a higher yielding reaction, Tebbe's reagent must be used, as the presence of an alkyl aluminium compound stabilises the intermediate complex and prevents decomposition.[187] Earlier methods of synthesising this complex rely on the use of Schlenk line techniques to recrystalise the air sensitive reagent, however, Tebbe's reagent can also be prepared *in situ* from trimethyl aluminium and titanocene dichloride, using only an inert gas manifold.[180]



Scheme XXXIII

Reaction of a THF solution of aldehyde **59** with two equivalents of Tebbe's reagent produces a quick and high yielding aldehyde methylenation. Within one hour at room temperature 98% of **76** is formed. This reagent could also be used in direct methylenations of halomercurials, however, in this case a mixture of **76**, **77** and a demercurated compound were obtained. If the synthesis requires keeping the halomercurial functionality this can be regenerated upon reaction with a mercuric halide. Formation of bromomercurial **77** was achieved in 96% yield by stirring with mercuric bromide at room temperature.

Introducing a nitrogen substituent into the structural framework of these molecules may provided an avenue to the formation of a lactam. A Synthesis was envisaged whereby an organomercurial could be activated with palladium, then undergo carbon monoxide insertion, followed by intramolecular coupling to an amine, providing a route to an annulated lactam. Conversion of the aldehyde in position C-6 into an oxime was to provide a starting point for this idea. The protected mercurial must be used to enable a high yield of the oxime product to be attained. Heating a mixture of methyl mercurio aldehyde **59** with hydroxlamine hydrochloride and triethylamine in DME for ten hours produces 93% of oxime derivative **78**, (Scheme XXXIV). Formation of the oxime provided another transformation that could be carried out in the presence of the mercury unit. Subsequent procedures required the oxime to be converted into an amine but unfortunately this could not be successfully achieved.



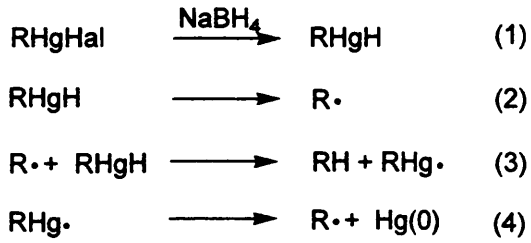
59 78

Scheme XXXIV

2.6 REDUCTIVE DEMERCURATION

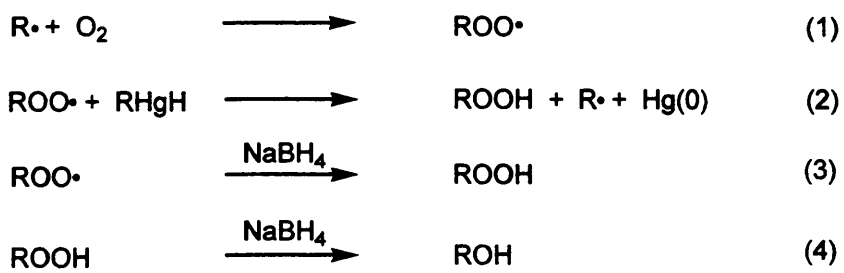
Organomercurials can be utilised in a number of ways to prepare a wide variety of hetero-atom containing compounds.[88-91] The thermal and solvolytic decomposition of intermediate organomercurials provides a convenient route to allyl esters, vinyl ethers, saturated ketones and many other functional groups. In order to maintain the ability to develop the steroidal structures further a synthesis was sought that did not rely solely on the reduction of the mercurial to an alkyl derivative.

The vast majority of organomercury compounds are inert to oxygen, this is one of the characteristics which make these compounds attractive synthetic intermediates. Secondary and tertiary alkyl mercurials are however slowly oxidised by air and can be cleaved under free radical conditions or at elevated temperatures. Organomercurial salts also react rapidly with sodium borohydride to generate free radicals which can be oxidised by air to the corresponding alcohols.[188] This process is called reductive demercuration and is a useful method for the oxidation of primary organomercurials, furnishing alcohol products.[92]



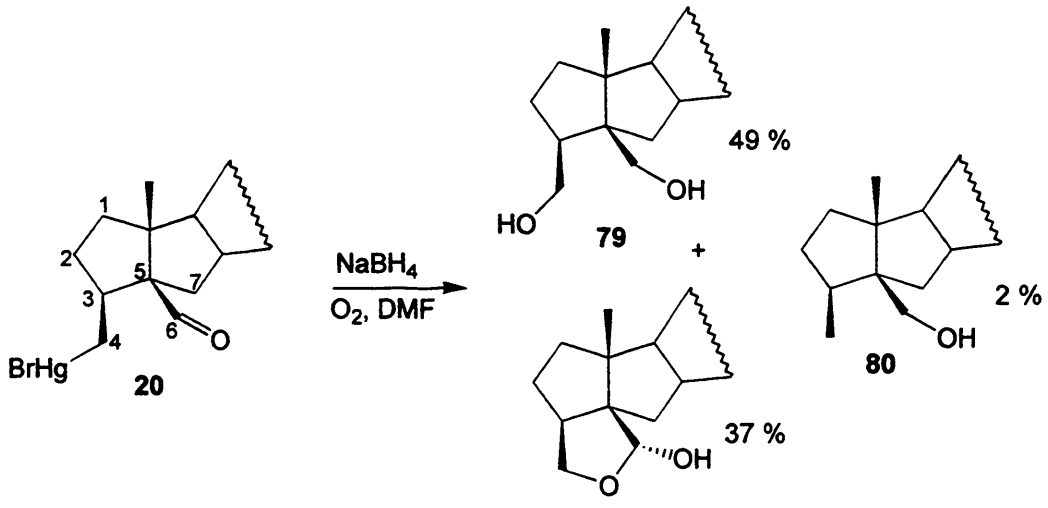
Scheme XXXV

Alkyl radicals are established intermediates in reductive demercuration of alkyl mercuric halides, by metal hydrides.[189-191] The mechanisms of these reactions have been carefully studied and have been explained for the reductive demercurations using sodium borohydride, (Scheme XXXV).[188,192,193] Molecular oxygen is an effective scavenger of the radicals generated from organomercurials, since it is highly reactive towards alkyl radicals but relatively unreactive towards primary organomercury compounds. Plausible intermediate steps in these experiments are listed in Scheme XXXVI.



Scheme XXXVI

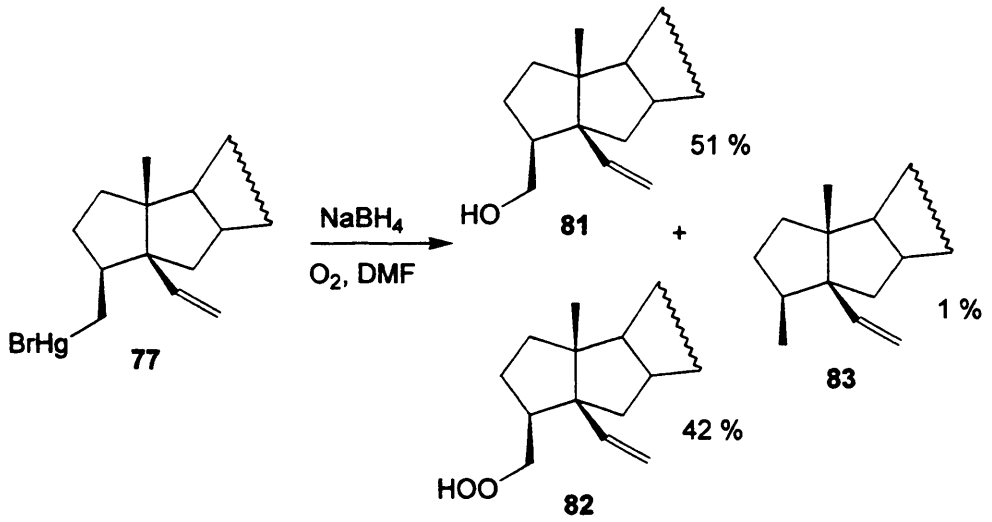
Reductive demercuration of bromomercurio aldehyde **20** did provide a quantity of the required diol **79** (49%), however, a substantial amount of lactol **14**, (37%), was also produced (Scheme XXXVII). The presence of this lactol can be rationalised by the formation of a radical at position C-4 and its capture, giving an alcohol which then initiates an intramolecular cyclisation by nucleophilic attack at the carbonyl group, affording lactol **14**. A small amount of an alkyl product **80** has also been isolated, due to the alkyl radical being reduced. Dropwise addition of the reducing agent and conducting reactions with high oxygen flow rates to ensure oxygen saturation, minimises this reaction pathway. Higher yields of diol **79** were achieved when bromomercurio alcohol **65** was subjected to the same reaction conditions as used previously, since intramolecular cyclisation is not a competitive pathway. Bromomercurio alcohol **65** was reduced in the presence of oxygen, affording an 84% yield of diol **79**, and 2% of alkyl derivative **80**.



Scheme XXXVII

Reductive demercuration of another intermediate was required for further synthetic procedures. In this case, bromomercurial **77** was to be converted into an alcohol derivative without reducing the C=C bond also present in the molecule.

Addition of a sodium borohydride solution to an oxygen saturated DMF solution of **77** furnished a mixture of products including the required alcohol **81**, (51% yield, Scheme XXXVIII). Surprisingly a large quantity of peroxide **82** was also produced, which turned out to be quite stable. Altering the reaction conditions did not facilitate a higher yield of the alcohol, since reduction of the alkene occurred when the reaction time was extended, or if excess sodium borohydride was used. To enable the required alcohol to be obtained in higher yield, a short reaction time was used and the mixture of products obtained was isolated. The peroxide was then reduced with sodium borohydride in the presence of cerium chloride, affording 82% overall conversion into alcohol **81**.



Scheme XXXVIII

2.7 CONCLUSIONS

A protocol for the protection - deprotection of organomercurials has been developed via methylation - demethylation. Since organomercurials are relatively stable and easy to handle, the documented functional group transformations help facilitate the more economic use of mercury compounds. A halomercurial can be expected to survive

a number of procedures in a multistep sequence before being activated and used, thus extending the scope of applications of organomercurials in synthesis.

Treatment of alkyl mercuric bromides with sodium borohydride is a mild and convenient way of producing alkyl radicals in solution. If the reaction medium is saturated with oxygen these radicals can be converted into alcohols, or they may be terminated via an intramolecular reaction as shown by formation of lactol **14** in Scheme XXXVI.

CHAPTER THREE

SYNTHESIS OF A TRIQUINANE-TYPE SKELETON

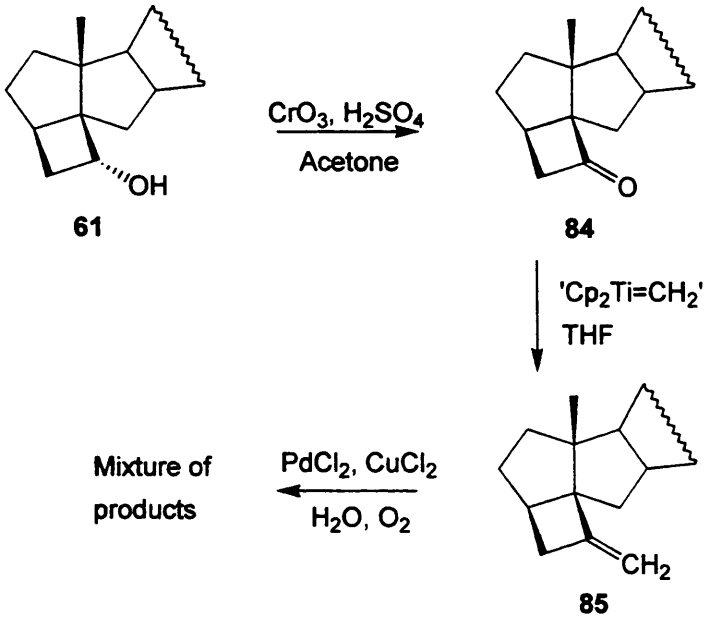
3.1 INTRODUCTION

Synthetic approaches towards naturally occurring triquinanes have been reported from various research groups.[163,194,195] The approaches include cascade rearrangements[196-203] carbene insertions,[204-207] cycloadditions,[208-215] cyclopropane rearrangements,[216,217] electrophilic cyclisations,[218,219] intramolecular radical additions,[220-225] the Pauson-Khand reaction,[226-231] and other methods.[232-245]

Initial consideration into the development of a triquinane group led to attempted synthesis of an annulated cyclopentanone. The key step in this route involved palladium(II) catalysed ring expansion of a methylene cyclobutane into a cyclopentanone. Formation of this product would require methylene cyclobutane **85** as the starting material, therefore, this compound was synthesised, in two steps from cyclobutanol **61**, (Scheme XXXIX). Oxidation of **61** with Jones reagent yielded 96% of cyclobutanone **84**. Subsequent treatment with Tebbe reagent, followed by heating at 65 °C for 2 hours, allowed formation of methylene cyclobutane **85** in 87% yield. The next step, involving ring expansion, required the conditions of the reaction to be investigated.

Substituted alkenes are oxidised to aldehydes and ketones using a method analogous to the Wacker process.[104] An intramolecular version of this transformation has also been reported,[246] and this led to an investigation into the potential ring expansion in methylene cyclobutane **85**. Treatment of a THF solution of **85** with palladium(II) chloride and copper(II) chloride, in the presence of water and oxygen, gave no reaction. Changing the solvent and bubbling oxygen through the mixture facilitated a slow reaction, although it gave an inseparable mixture of numerous

products. Since this procedure, which could have led to a triquinane structure was unsuccessful, further experimental routes were considered.



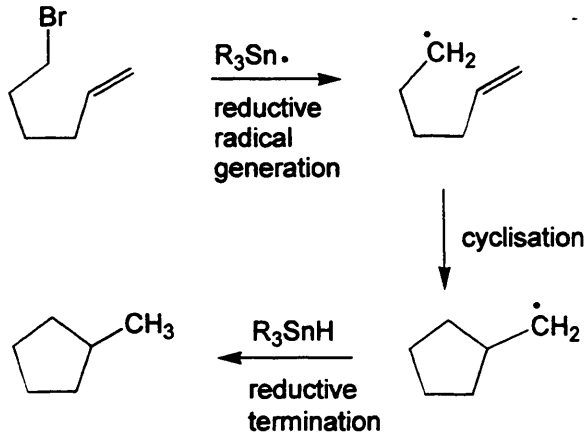
Scheme XXXIX

3.2 OXIDATIVE FRAGMENTATION-CYCLISATION REACTIONS

Snider's recent publication,[244] prompted another synthetic pathway towards development of an angular triquinane. The reported oxidative fragmentation-cyclisation sequences were key steps in the synthesis of natural products. It was hoped that this methodology could be adapted to facilitate transformations within the steroidal molecules. Initial consideration of the chemistry involved with oxidative fragmentation-cyclisation procedures enabled us to establish a starting compound for this approach.

Free radical cyclisation of alkenes has been widely used in synthesis of cyclic compounds.[247] The most utilised method is reduction of a halide or other functionality using a tin hydride. This approach can be limiting, as it results in formation of relatively unfunctionalised products, resulting from a net two electron reduction, (see example in Scheme XL). Oxidative free radical cyclisation, on the other hand, allows the potential

to develop functionalised products from simple precursors. The cyclic radicals generated in these procedures are oxidised to terminate the reaction. Synthesis using this protocol has been developed previously, with methods including halogen atom transfer[221,248,249] and with manganese(III)[250] and organocobalt[251] reagents.



Scheme XL

Cyclobutanes are regarded as an important source of a four carbon building block, via ring opening.[252,253] Relief of ring strain is the major factor in controlling fragmentation of these derivatives. Examples of oxidative fragmentation of cyclobutanols and cyclobutanones, have been documented. [254-258] Due to a recent publication concerning the use of manganese(III), in reactions with unsaturated cyclobutanols,[259] this metal was chosen for test procedures with a steroid derivative. The use of manganese(III) acetate in oxidative free radical cyclisation reactions has been derived from its known use in the oxidative addition of acetic acid to alkenes, forming gamma-lactones.[260]

Allylic cyclobutanols were treated with manganese(III) acetate in ethanol, to afford radicals which either rearranged or cyclised (in a 5-exo or 6-endo manner).[242,259] 2-Methylene cyclopentanones and cyclohexanones were the major products dependent

on substrate and reaction conditions. Due to the varied results in these procedures, it is important to discuss the effects that the reaction conditions have on the mechanism and products.

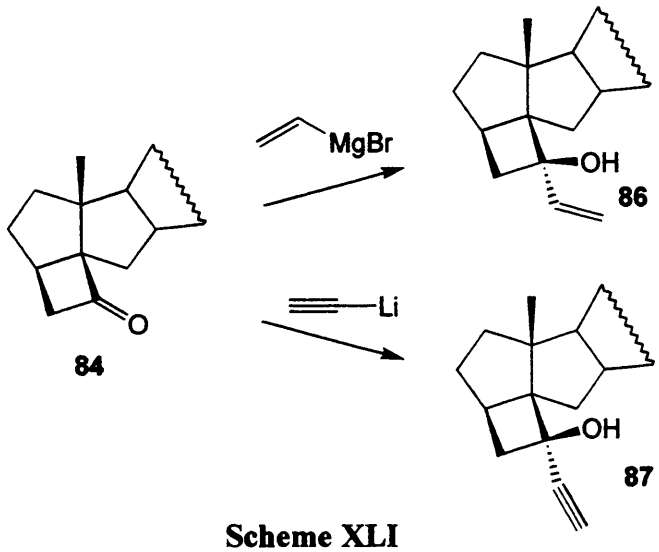
Oxidative termination of these radical reactions is usually accomplished with copper(II). Primary and secondary radicals react with copper(II) acetate to give organocopper intermediates, which undergo β-hydride elimination giving alkenes. Tertiary radicals are oxidised to carbocations. Kochi's studies of the mechanism of oxidation of alkyl radicals, by copper(II) acetate, established that an alkyl copper(II) intermediate is formed.[261,262] During the reaction copper(I) is produced, which is then reoxidised by manganese(III), hence two equivalents of manganese(III) acetate are required in these reactions. In principle only a catalytic amount of copper is needed.

Until recently it had been unclear whether manganese complexed radicals or free radicals are intermediates in these cyclisations. Curran showed that free radicals are produced in manganese(III) oxidations.[263] He concluded that if manganese complexed radicals are produced they must dissociate rapidly before cyclisation occurs.

Solvent effects on oxidative cyclisation have been considered.[264] Ethanol has been found to complement the typical solvent acetic acid. Advantages of this solvent include its ability to reduce primary radicals to alkanes. Acetylenes have also been used as substrates since the vinyl radicals formed can be reduced by ethanol to alkenes. A key difference in the choice of solvent is that primary cyclopentyl-methyl radicals are oxidised mainly to alkenes in ethanol, and mainly to alcohols or lactones in acetic acid. The ability of ethanol to act as a hydrogen atom donor in the reduction of primary and vinyl radicals can influence product yields. The route to cyclisation can also be

influenced by changing solvents. For instance, with unsaturated β-keto esters, a higher percentage of product due to a 5-exo cyclisation was found with ethanol as the solvent.[264]

Formation of cyclobutanone **84** provided the structural unit for development of a triquinane skeleton. It was reasoned that generation of an electron deficient centre at a substituent on the cyclobutane C-6 may trigger ring expansion of the four-membered ring. Ethynyl and vinyl cyclobutanols would be suitable for carrying out these transformations since these systems are known to undergo oxidative fragmentations.[244,259] Vinyl cyclobutanol **86** was prepared as a single product (97%), upon addition of cyclobutanone **84** to vinyl magnesium bromide, (Scheme XLI).[265] A suspension of lithium acetylide ethylenediamine complex was used to obtain **87**, in 62% yield, (14% of the starting material **84** was recovered).



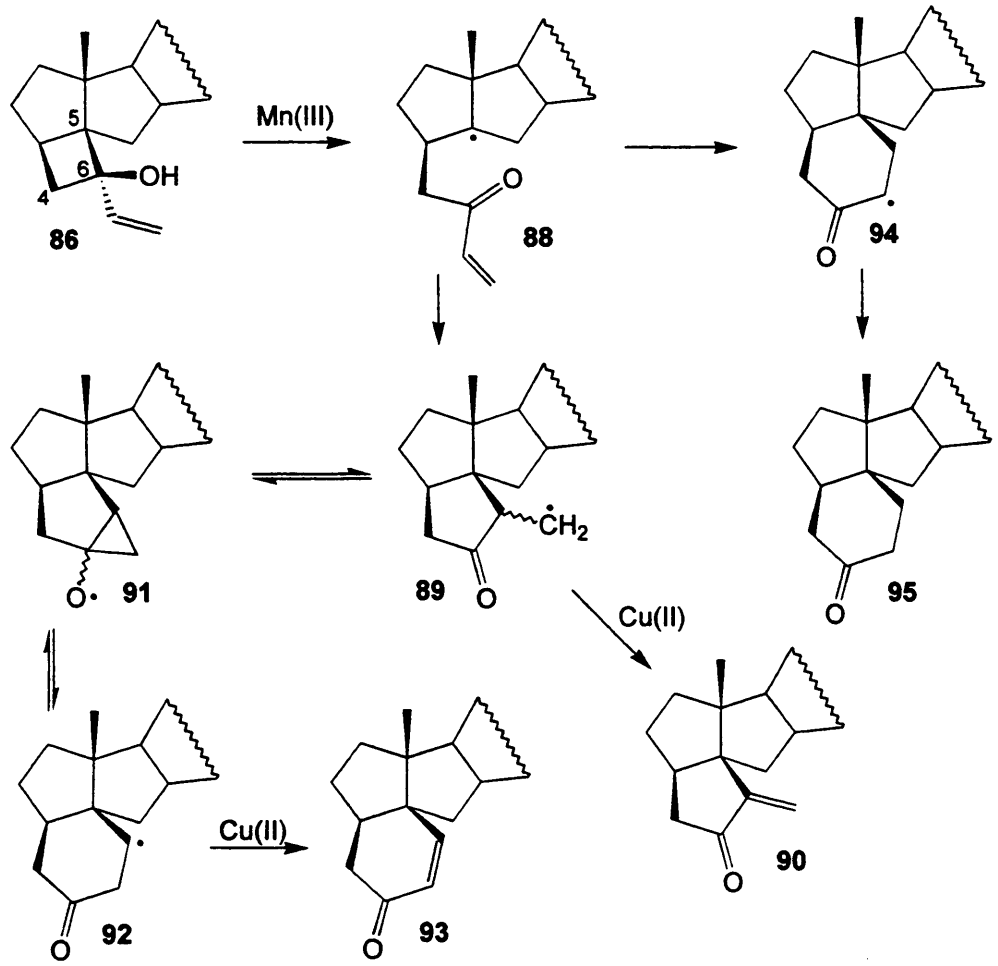
Scheme XLI

Reaction of vinyl cyclobutanol **86** with manganese(III) as described earlier presented a possible route to a methylene cyclopentanone. However, treatment of this compound with two equivalents of manganese(III) acetate and one equivalent of copper(II) acetate furnished an inseparable mixture of at least four products. The

different products are likely to have arisen due to fragmentation of the C-5 - C-6 cyclobutane bond, followed by various possible termination steps, (Scheme XLII).

Oxidation of vinyl cyclobutanol **86** would produce tertiary radical **88** which can undergo 5-exo cyclisation to β-keto-cyclopentyl-methyl radical **89**. Oxidation of this radical by copper(II) is likely to give α-methylene ketone **90**. Radical **89** could also rearrange to β-keto radical **92**, via cyclopropyloxy radical **91**. Oxidation of **92** with copper(II) would then afford cyclohexenone **93**. The alternative 6-endo cyclisation of the initial tertiary radical would provide a route to cyclohexanone **95**, since α-keto radicals are easily reduced and not easily oxidised.[259]

An alternative route to a 2-methylene cyclopentanone was developed by Snider, when reactions with a vinyl cyclobutanol gave complex mixtures of products.[244] Oxidative fragmentation of ethynyl cyclobutanols produces vinyl radicals which do not rearrange and are not oxidised but rather abstract a hydrogen atom to give the required product.[259] Manganese(III) picolinate, easily prepared from manganese(III) acetate and picolinic acid,[266] can be used as an alternative reagent in these reactions.[244,267] The use of copper(II) in the reaction mixture may not be required in addition to this reagent, since the picolinate species is capable of facilitating reduction of primary and secondary radicals.[268] Using this principle, ethylene cyclobutanol **87** was heated in a DMF solution of manganese(III) picolinate, which allowed isolation of 32% of α-methylene ketone **90**. Experimentation using **86** and manganese(III) picolinate, or **87** and manganese(III) acetate, under various conditions, did not facilitate higher yielding reactions in formation of α-methylene ketone **90**, or other products.



Scheme XLII

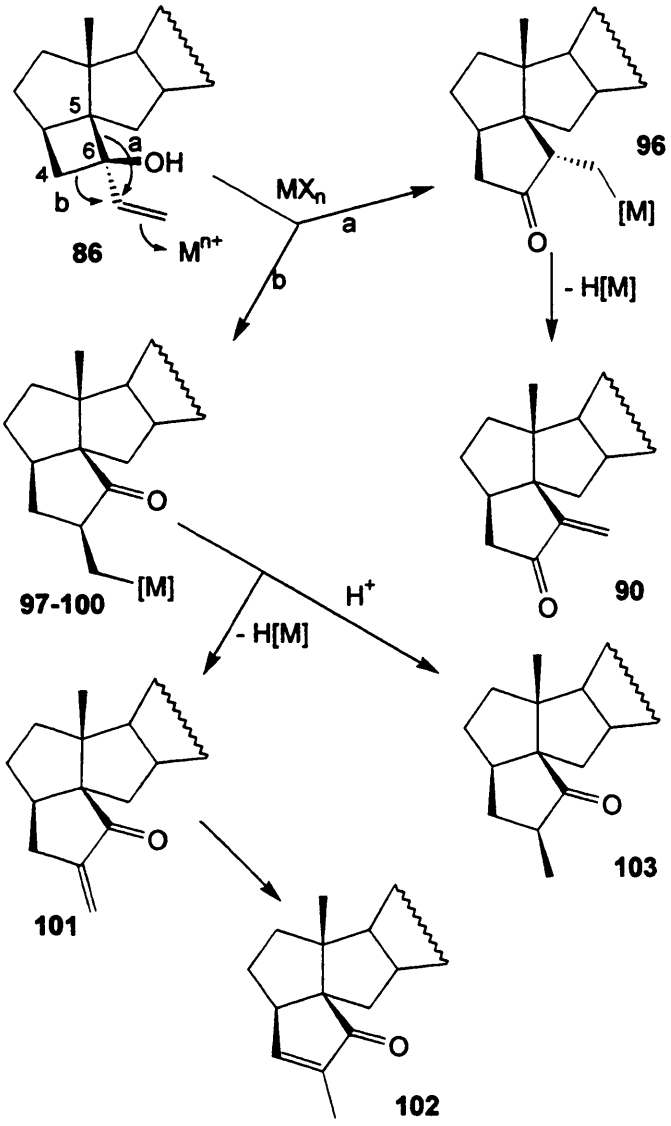
3.3 REAGENT CONTROLLED SKELETAL REARRANGEMENTS OF 86

Experimentation with oxidative fragmentation-cyclisation procedures allowed formation of α-methylene ketone **90** in a low yielding reaction. The route illustrated above, gave a non-conventional approach to a triquinane-type 5,5,5 skeleton since it also relied on stereoselective cleavage of a cyclopropane (Scheme VI) and an intramolecular organometallic addition to a carbonyl (Scheme XXVIII). As vinyl cyclobutanol **86** has been shown to be capable of oxidative fragmentation-cyclisation, it was reasoned that this compound would also be suitable to carry out ring expansions,[244,269-273] using

electrophilic reagents. The vinyl π-system should be susceptible to a Markovnikov controlled electrophilic attack,[274,275] thereby creating a partial positive charge at the desired position.

The reaction of vinyl cyclobutanol **86** with thallium(III) nitrate in THF afforded mainly the α-methylene ketone **90,** (Table, entry 1). This product is formed by the preferential migration of the quaternary carbon, (Scheme XLIII, path a). The isomeric α-methylene ketone **101**, (Scheme XLIII, path b), has been isolated as the minor product. The structural assignment for the isomers **90** and **101** was based on the signals of the methylene protons in the ^{1}H NMR spectra: compound **101** exhibits allylic coupling, whereas this is not seen for isomer **90**. This assignment was further corroborated by chemical experimentation (see below).

Reaction with the isoelectronic mercury(II) nitrate also furnished mainly **90**, (entry 2), accompanied by a small amount of **101**. An additional product has also been intercepted: organomercurial **99** was isolated following quenching of the reaction with sodium chloride solution. Its structure was confirmed by a single crystal X-ray analysis, (see Appendix I).[276] Formation of this product suggested that a stable organomercurial was created prior to formation of an α-methylene ketone. Further support for this pathway can be seen in the mass spectrum of **99**, because it lacks the molecular ion of the organomercurial and closely resembles the spectrum for **101**. This theory was corroborated by reaction of organomercurial **99** with palladium(II) nitrate, which facilitated synthesis of **102**.



97, M = $Tl(NO_3)_2$; **98**, M = $HgNO_3$; **99**, M = HgCl; **100**, M = PdL_nY

Scheme XLIII

Experimentation with other isoelectronic ions was less successful. Silver(I) triflate was inert, even after allowing for long reaction times, at elevated temperatures, whereas lead(IV) acetate[277] gave an intractable mixture of numerous products.

Similar reactivity to mercury(II) is often shown by palladium(II), which is an advantage in that palladium offers the capability to act as a catalyst, thus decreasing the hazards associated with using stoichiometric amounts of toxic metals in reaction procedures. However, the use of palladium(II) requires development of an efficient

catalytic cycle since palladium(0) is generated during the reaction. Mild oxidising agents such as copper(II),[111,279] *p*-benzoquinone[280-282] and oxygen[283-285] have been employed enabling palladium to be used in catalytic quantities.

Metal-Mediated or Catalysed Rearrangement of **86** in THF at Room Temperature

entry	reagent or catalyst	amount of reagent	Yields of products (%)				
			90	**101**	**102**	**103**	other (%)
1	$Tl(NO_3)_3$	1.1 equiv[a]	76	12	-	-	-
2	$Hg(NO_3)_2$	1.1 equiv[a]	52	13	-	-	**99** (23)
3	$Pd(NO_3)_2$	1.1 equiv[a]	36	2	54	2	-
4	$Pd(NO_3)_2$	5 mol %[b,c]	13	*	60	*	-
5	$Pd(NO_3)_2$	5 mol %[d,e,f]	-	-	30	-	-
6	$PdCl_2$	5 mol %[b,g]	11	3	33	28	-
7	$(PhCN)_2PdCl_2$	1.1 equiv[a]	27	1	14	53	-
8	$(PhCN)_2PdCl_2$	8 mol %[b,h]	12	2	11	72	-
9	$(MeCN)_2PdCl_2$	7 mol %[b,h]	18	2	17	56	-

* 3% of **101** and **103**, not separated. [a] 15 min. [b] 15h. [c] $Cu(NO_3)_2$ (2 equiv) used to reoxidize Pd(0) to Pd (II). [d] 10 days. [e] O_2 (~1.1 atm) used as oxidant. [f] In DMF. [g] $CuCl_2$ used as the oxidant. [h] *p*- Benzoquinone used as the oxidant.

In initial stoichiometric reactions, addition of palladium(II) nitrate to a THF solution of **86** furnished mainly a mixture of enone **102** and its isomer **90**, in approximately 3 : 2 ratio, (Table, entry 3). Suppression of the later product can be achieved in a catalytic experiment using copper(II) nitrate as the oxidant, (entry 4). A more selective reaction occurs by using oxygen as the oxidant: exclusive production of enone **102** was observed in DMF (entry 5), although only a low product yield was obtained. Synthesis utilising palladium(II) chloride was not very selective. In a

catalytic reaction, using copper(II) chloride as the oxidant, **102** and **103** were isolated as the major products, in approximately a 1 : 1 ratio (entry 6). Experimentation with palladium(II) acetate and trifluoroacetate did not give significant results when used catalytically, due either to decomposition or to low solubility of the catalyst.

Stoichiometric reaction of vinyl cyclobutanol **86** with bis-benzonitrile palladium(II) chloride furnished a combination of **90** and **103** in approximately a 1 : 2 relationship, (entry 7). The structure of α-methylene ketone **103** has been confirmed by experimentation. Thus, reduction of organomercurial **99** with lithium aluminium hydride, followed by oxidation with Jones reagent, afforded an α-methyl ketone, identical to **103**.[286] Higher yields of compound **103** have been achieved in catalytic versions of the above palladium reaction, using *p*-benzoquinone as the oxidising agent and either the same complex or its acetonitrile analogue (entries 8 and 9).

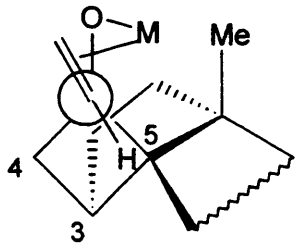
3.4 DISCUSSION

The observed reactivity exhibited by different electrophiles is noteworthy. Migration of the more substituted carbon is favoured with thallium(III) and mercury(II) (Scheme XLIII, path a). Reaction with these strong electrophiles, in this way, suggests that the electrophile co-ordinates to the C=C bond initially and that the subsequent rearrangement is electronically controlled. In contrast, the reactivity of palladium(II) is associated with the alternative ring expansion shown in path b.

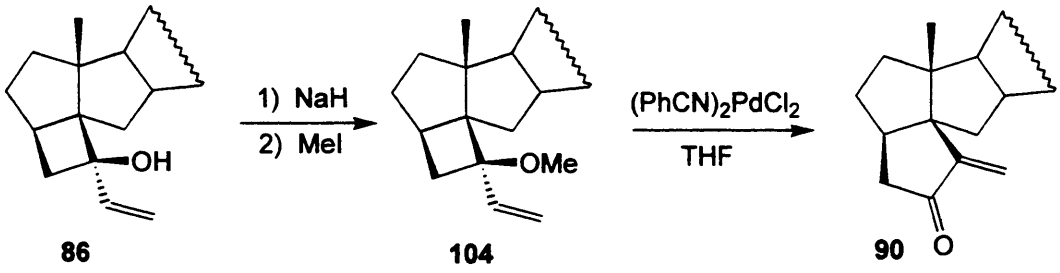
Catalytic palladium experiments have been shown to be more selective than their stoichiometric counterparts. This can be attributed to the modification in the transient species, for example in **100**, because of coordination[282] to the oxidant. The tendency of

the organopalladium intermediate to undergo β-hydride elimination (**100** → **101**), followed by isomerisation to **102**, is decreased by using palladium(II) nitrate. Protonolysis (**100** → **103**), is the favoured reaction course in this case. For a comparison see the table, entries 4 and 8. From these findings it can be seen that the fate of the palladium intermediate and the yield of products is dependent on the ligands co-ordinated to palladium.

Rationalisation of the path of reaction observed with the palladium reagents can be explained by the influence of the ligands in the reaction. The ability of the C-6 - vinyl bond to rotate allows the existence of various rotamers. A favourable rotamer will have allowed palladium to co-ordinate to the hydroxy group, (see diagram below).[287] Due to the close vicinity of the C-5 - C-6 bond and the palladium species, migration of the quaternary carbon is disfavoured, thereby allowing ring expansion as shown by path b (Scheme XLIII).



This hypothesis was tested by protection of the hydroxy group. Reaction of vinyl cyclobutanol **86** with sodium hydride and subsequent treatment with methyl iodide gave 87% of methoxy derivative **104** (Scheme XLIV). Catalytic experiments using bis-benzonitrile palladium(II) chloride proved most selective in ring expansion of **86**, therefore, this reagent was chosen to be reacted with methoxy derivative **104**. Following a catalytic reaction at room temperature, 75% of α-methylene ketone **90** was separated from smaller amounts of several products.



86 104 90

Scheme XLIV

Protection of the hydroxy group had the effect of altering the course of the reaction. Removal of the opportunity for the palladium species to co-ordinate to the hydroxy group, will alter the stability of the conformation of the vinyl and hydroxy groups, as shown in the diagram on the previous page. Since the methoxy group will cause increased steric hindrance above the plane of the molecule, it is likely that the electrophile will not approach from this direction. The most reactive conformation will allow the orientation of the vinyl group to be anti-periplanar to the C-5- C-6 bond, therefore allowing this bond to be cleaved, affording products as shown by path a, Scheme XLIII. It was expected that reaction of methoxy derivative **104**, with mercury(II), would furnish the same products as was formed with the unprotected substrate. This was found to be the case, (despite the reaction being slower), which further supports the theory that the reaction with mercury(II) is an electronically controlled process.

3.5 CONCLUSIONS

The chemical reactivity of a vinyl and ethynyl cyclobutanol in ring expansion has been discussed. While oxidative fragmentation-cyclisation offers the potential to develop functionalised cylcopentanes, the reactions were not sufficiently selective.

Experimentation with electrophiles however, gave the opportunity to control the regioselectivity of the cyclobutane ring expansion.

In summary, thallium(III) and mercury(II) favour migration of the most substituted carbon (Scheme XLIII, path a), whereas palladium(II) allows ring expansion by formation of a new bond between C-4 and C-6. The ability of the palladium complexes to co-ordinate to the hydroxy group and influence the regioselectivity of the reaction, has been demonstrated. Removing this capacity by protection of the hydroxy unit facilitates the expected migration of the quaternary carbon.

CHAPTER FOUR

FORMATION OF CARBO-CYCLES AND HETERO-CYCLES

4.1 INTRODUCTION

There have been many published results involving synthesis of higher terpenoids and steroids, several of which contain an α-methylene lactone moiety.[4] Various procedures have also been reported for the synthesis of enones, since this structural unit is found in many natural products.[288] Due to the abundance of molecules containing these structural features, synthetic routes were planned to construct structures containing an α-methylene lactone or enone mioety. The pentalenolactone family was of particular interest since these structures contain a *cis*-annulated carbo-cycle or hetero-cycle, joined to two five membered rings.[289] A pathway was envisaged in which the basic framework of pentalenolactone E **52** could be developed, through various steps from organomercurial **20**. Other procedures that were considered involved formation of annulated lactones and lactams.

4.2 SYNTHESIS OF THE PENTALENOLACTONE SKELETON

Interest surrounding biologically active natural products containing the α-methylene lactone moiety have led to numerous research groups developing synthetic routes to α-methylene-γ and δ-lactones.[290] Since organometallic reagents have been used to accomplish the skeletal transformations described thus far, a route was sought in which palladium could be used to accomplish a ring closure, affording an unsaturated lactone. The compound required for this procedure would need to contain both hydroxyl and alkene functional groups. Initial consideration for synthesis of a compound of this type was by conversion of lactol **14**.

In the synthesis of grandisol, the key steps involved cleavage of lactols to produce compounds containing hydroxyl and olefinic moieties.[291,292] These procedures rely on the fact that lactols can exist in an equilibrium mixture with the ring opened hydroxy aldehyde. The concentration of the hydroxy aldehyde is too low to be detected by NMR, but is sufficient to allow conversion of the aldehyde function by a Wittig reaction, into an alkene. In principle this methodology could be applied to other lactols, however, attempts to cleave lactol **14** in this manner were unsucessful.[293] The requirement for an intermediate as described above, led to an alternative synthesis using methylenation and reductive demercuration, (as described in Chapter Two), which facilitated compound **81**.

Total synthesis of the tricyclic structure of pentalenolactones has been approach from different angles,[216,294-300] however, the formation of the unsaturated lactone is the part of the synthesis which is important in this case. Various methods exist where the lactone is constructed initially, followed by an α-methylenation sequence. Procedures of this type include: alkylation of enol anions, α-methylene insertion via a Wittig reaction, reductive amination and reductive elimination of α-formyl lactones.[290] The organometallic syntheses used in the construction of unsaturated butyrolactones, include carbonylation of halovinylic or homopropargylic alcohols induced by nickel carbonyls or palladium catalysts.[304-306]

Palladium catalysed carbonylation of halides appears to be the best documented procedure.[307-310] Benzyl, allyl, aryl and vinyl halides containing primary, secondary or tertiary hydroxy groups are readily converted into a variety of lactones including butenolides.[309] Formation of these compounds has arisen from the knowledge that carboxylic esters can be synthesised by palladium-catalysed carbonylation of organic

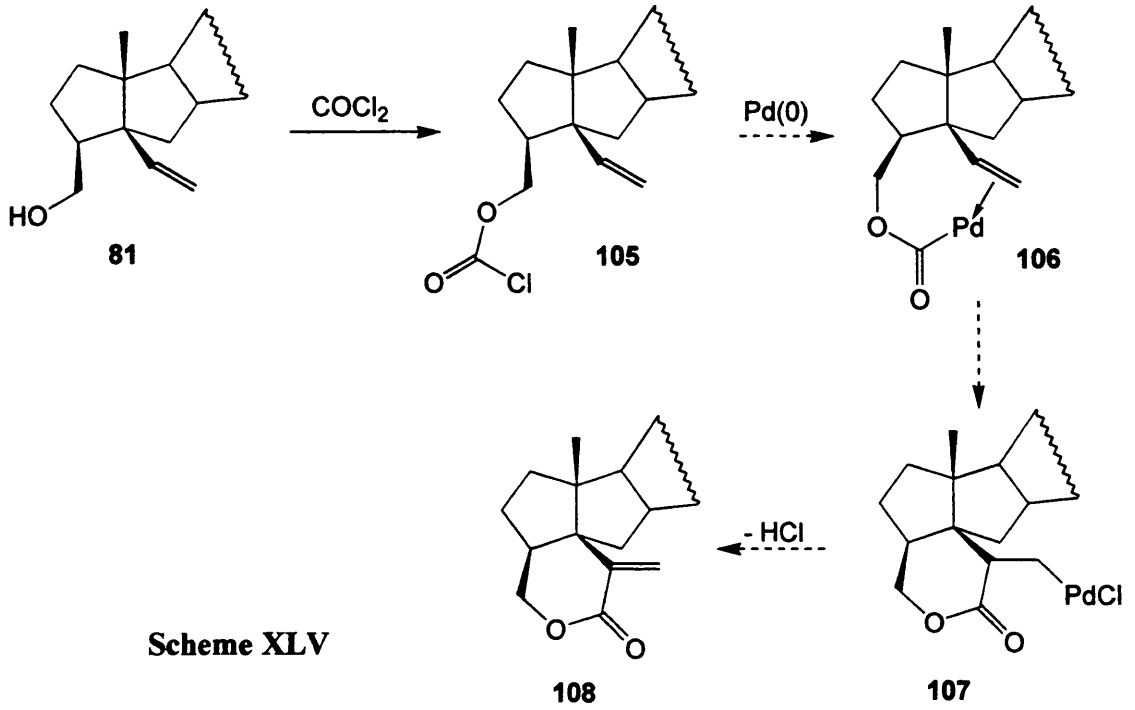
halides, in an alcohol solvent.[311] While the above procedures are generally carried out with catalytic amounts of palladium, reactions using stoichiometric amounts of nickel(IV) carbonyl have also been reported for reactions with alcoholic vinyl bromides or homo-propargylic alcohols.[312-314]

Organometallic procedures used in developing the α-methylene lactone skeleton generally use either stoichiometric quantities of metallic reagents or require several steps to obtain the starting materials for the reactions.[305-310,312,313] Therefore, a method was devised to allow intramolecular carboalkoxylation of homoallylic chloroformates affording unsaturated butyrolactones.[315] It was speculated that this method could also be applied in the development of a six-membered unsaturated lactone from compound **81**.

Attempted synthesis of unsaturated lactones was carried out in two steps without isolation of the intermediates.[315] The documented reaction procedure was applied to compound **81**, as shown in Scheme XLV. The mechanism of the expected reaction would involve initial formation of chloroformate **105**, which could then be treated with Pd(0) in refluxing xylene, to allow insertion of palladium with concomitant co-ordination to the double bond as illustrated in **106**. Subsequent cyclisation and reductive elimination (**106** → **108**) would then afford the required product.

Treatment of **81** with phosgene (dissolved in ether) gave formation of chlorformate **105**. However, subsequent reactions of **105** with palladium(0) catalysts proved unsuccessful. Experimentation using freshly prepared $Pd(PPh_3)_4$, $Pd_2(dba)_3.CHCl_3$ or $Pd(dba)_2$ and alteration of the reaction conditions, by changing the

solvent and usage of base or triphenyl phosphine, did not give formation of the desired product.

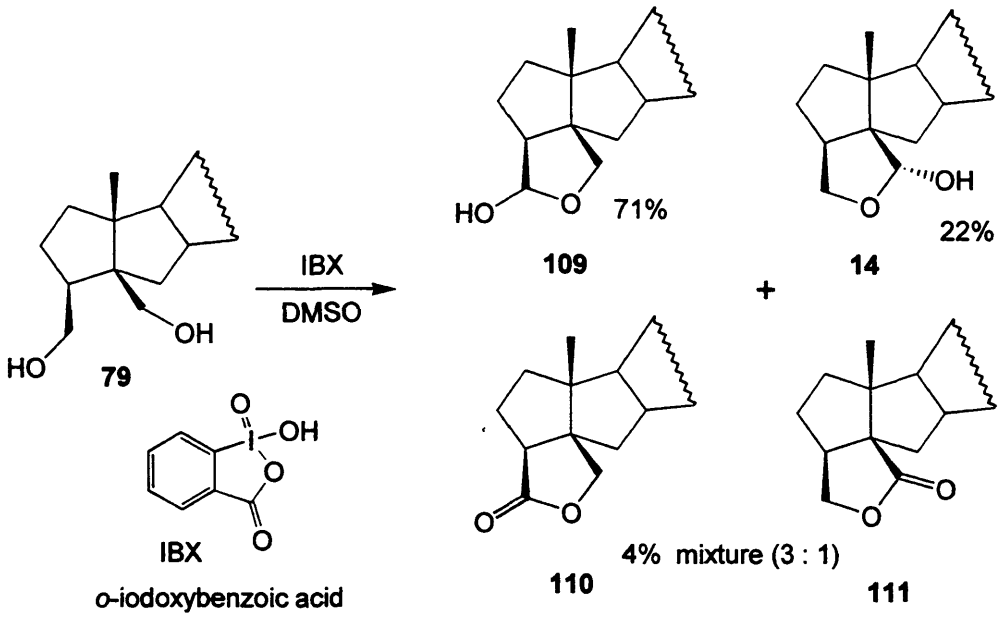


Scheme XLV

4.3 PREPARATION OF LACTONES

Lactones can be synthesised by a large number of routes including intramolecular cyclisations, condensations, oxidation, reduction and rearrangement procedures.[104,316] Synthesis of diol **79** by reductive demercuration, as described previously, (in Section 2.5), led us to develop a procedure that allowed formation of a five-membered lactone, analogous to one previously reported.[70] Documented procedures for oxidation of diols into lactones include the use of Fetizon reagent (silver oxide on celite),[317,318] $RuCl_2(PPh_3)_3$[319] or potassium permanganate with copper(II) sulphate.[320] These methods are used to oxidise primary alcohols in the presence of secondary alcohols, and give efficient conversion of primary-secondary, 1,4 and 1,5 diols, into five and six-membered ring lactones.

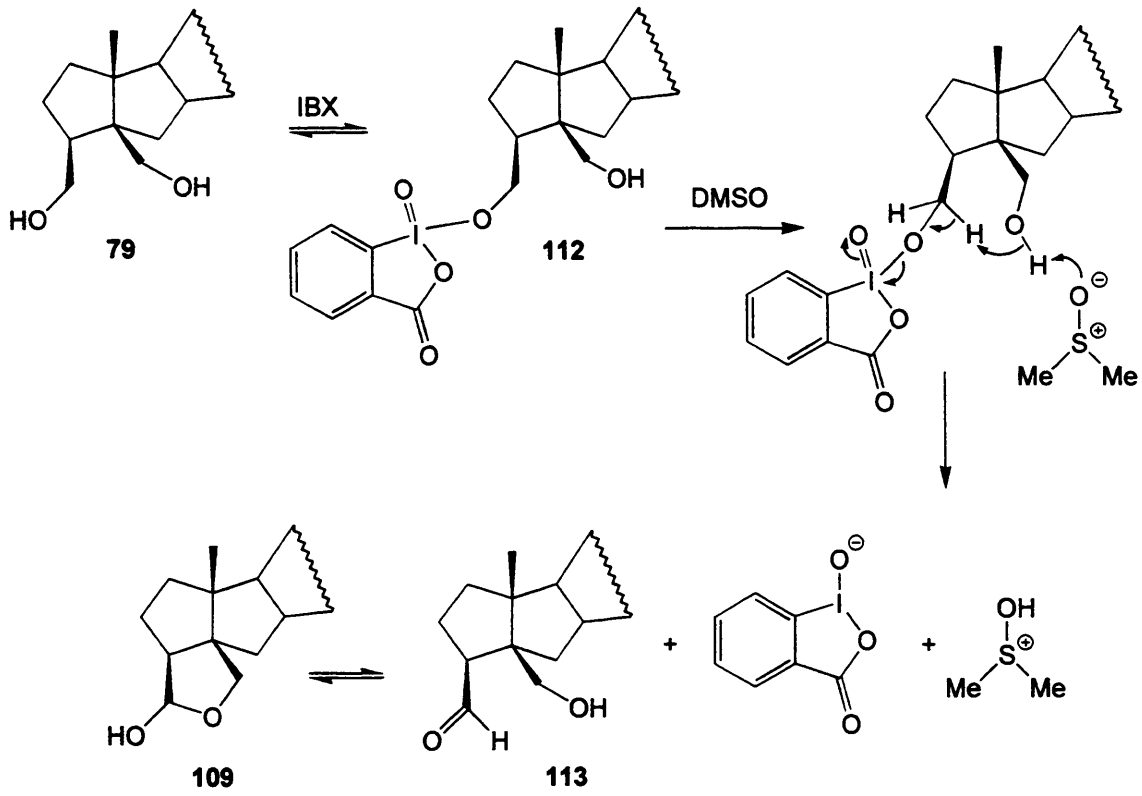
Corey has recently developed a method for selective oxidation of 1,4 diols,[321] using *o*-iodoxybenzoic acid (IBX), which prompted the idea to selectively oxidise diol **79** aiming on the synthesis of a new lactone structure. The procedure was developed from the use of IBX as an agent which efficiently oxidised primary and secondary alcohols to aldehydes and ketones.[322] IBX is prepared by oxidation of *o*-iodobenzoic acid with potassium bromate,[323] and is soluble in DMSO. Since DMSO has also been found to catalyse the formation of lactols from 1,4 diols,[321] this is usually the reagent of choice. However, experiments can also be conducted in acetone containing eight equivalents of DMSO.



Scheme XLVI

Reaction of diol **79** with IBX furnished a mixture of products, as shown in Scheme XLVI. The major product, lactol **109**, could be formed via the mechanism shown in Scheme XLVII. Formation of iodic ester **112** would occur initially, followed by the carbonyl-forming elimination reaction (**112** → **113**). Rate studies have shown that formation of the hydroxy-aldehyde compounds (such as **113**) is the rate limiting factor, in this procedure.[321] The suggested mechanism involves assistance by the second

hydroxyl group, which is influenced by the hydrogen bonded DMSO. Initial proton abstraction via a six-membered cyclic intermediate, followed by elimination, affords the hydroxy-aldehydes, which then cyclise to furnish lactols.



Scheme XLVII

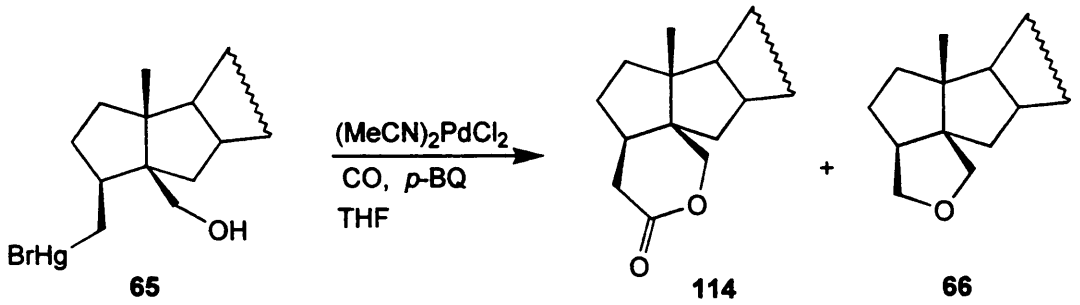
The steric hindrance associated with the formation of the iodic ester compounds, formed from diol **79**, is likely to be the prominent factor that influences formation of the lactols. In this particular reaction, lactol **14** is also isolated, but this product is obtained in much lower yield than **109**. A small amount of a mixture of lactones was also separated: a 3 : 1 ratio of **110** and known **111**[70] was determined by NMR.[324] Lack of substantial oxidation of the lactols can be explained due to the absence of the internal proton abstraction-elimination route, which influences reaction rates.[321] The lactols can easily be oxidised to give the corresponding lactones in good yield: treatment of **109** with Jones reagent yielded 98% of **110**. Likewise, lactone **111** was obtained from lactol **14**, in the same yield.

Various natural products contain a five-membered lactone annulated to another ring in a *cis* or *trans* manner.[325] Synthesis of the *cis*-lactones is often accomplished by halolactonisation and associated procedures.[284,326-327] The previous strategy, involving IBX has been used to form lactols, which are then subsequently oxidised to lactones. Whilst this procedure has been used in synthesis of a small range of *trans*-lactols, the reagent is generally most efficient at forming five-membered ring compounds because of the six-membered transition state.[321] The difficulty in obtaining *trans*-lactones[3] and apparent lack in literature procedures for obtaining four and six membered lactones *via* palladium(II) catalysed carbonylation,[328] led to the development of an alternative method for construction of both *cis* and *trans*-annulated lactones.[44]

Palladium(II) catalysed carbonylation has been used to synthesise α-methylene-γ-lactones from ethynyl alcohol or halogenated homoallylic precursors.[328] Whilst these procedures have provided routes to the formation of some natural products,[290] the presence of additional substituents in stereo-controlled positions may cause synthetic problems in some cases. An alternative strategy, involving transmetallation of mercury was developed to give an alternative synthetic pathway to those already documented, (see Scheme XVIII).[44] A variety of halomercurials containing a hydroxy group were treated with $(MeCN)_2PdCl_2$, in a carbon monoxide atmosphere, to furnished both *cis* and *trans*-fused five-membered lactones.[103] These reaction conditions were then tested to find out if a six-membered lactone could be formed.

Reaction of bromomercurio alcohol **65** with stoichiometric amounts of $(MeCN)_2PdCl_2$ and *p*-benzoquinone, under a carbon monoxide atmosphere, furnished six-membered lactone **114**, in 55% yield, after stirring for 17 hours at room temperature, (Scheme XLVIII). This product was also accompanied by the tetrahydrofuran

derivative **66** (11%), which is produced by intramolecular cyclisation. Reactions with catalytic amounts of palladium(II) turned out to be less effective; thus, upon heating **65** at 60 °C for 7 days, with 8 mol % of $(MeCN)_2PdCl_2$ and 2 equivalents of *p*-benzoquinone, lactone **114** (14%) and tetrahydrofuran **66** (44%) were isolated.



65 **114** **66**

Scheme XLVIII

The described palladium carbonylation reaction offers a method for construction of a six-membered lactone.[112] In this case, competitive 5-exo-tet cyclisation prevents the reaction from being high yielding, particularly in catalytic experiments. Previous reactions have shown that intramolecular cyclisation is not a reaction pathway followed during synthesis of five-membered lactones,[103] therefore, catalytic amounts of palladium(II) can be used in those reactions.

4.4 FORMATION OF ENONES AND LACTAMS

Since the routes described previously have allowed formation of a carbo-cycle and several oxo-cycles, largely by unconventional means, pathways were designed to use these products in further reactions in order to obtain additional annulated structures. In Section 1.2, synthesis of a nitrogen hetero-cycle was considered. Formation of a lactam was not possible using an organomercurial, therefore reactions involving cyclobutanone **84** were attempted. Ring expansions of cyclobutanones using the Beckman, Schmidt and other rearrangements have facilitated isolation of numerous

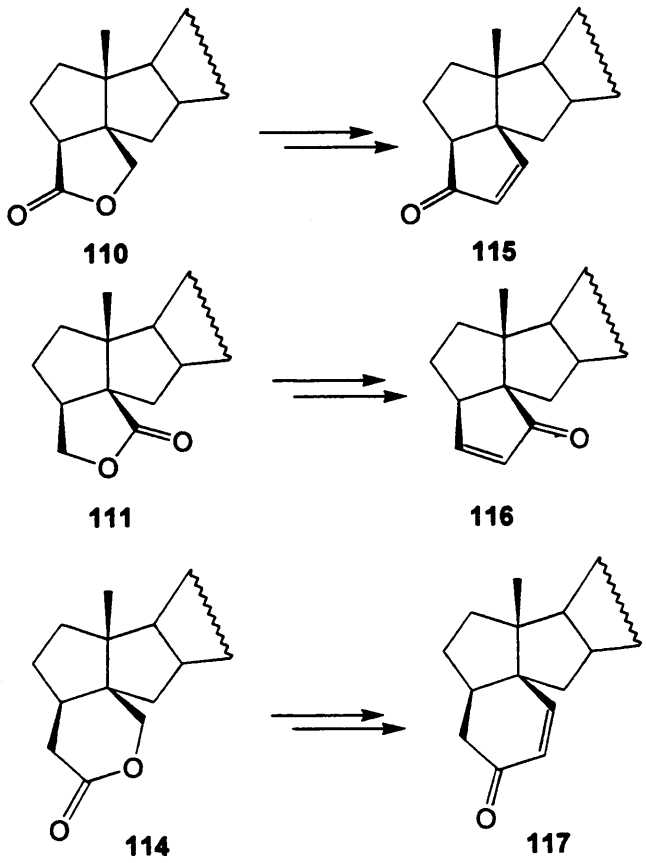
lactams.[316] The procedures which were considered in this case involved the Beckman rearrangement, in which oximes can be treated with one of numerous reagents to produce a substituted amide.[330]

Treatment of cyclobutanone **84** with hydroxylamine hydrochloride in pyridine at reflux, allowed formation of the corresponding oxime as an E/Z mixture. However, after subjecting the oxime compounds to either phosphorus(V) chloride, tosyl chloride, thionyl chloride or polyphosphoric acid, no reaction was observed, after prolonged reaction times. Since attempts at synthesising a nitrogen hetero-cycle were unsuccessful, experimentation was then directed towards formation of an enone moiety.

The rapid development of enone synthesis in the 1980s resulted from efforts to synthesise biologically important natural products, many of which contain an enone functionality.[288] Documented procedures for construction of the enone group include reactions involving condensation, oxidation, elimination, and insertion of carbon monoxide.[104] The most applicable route to formation of an annulated enone in a steroid derivative would be utilisation of an aldol condensation. To carry out this procedure, a compound containing two carbonyl functional groups is needed. This requirement then led to various precursors being considered, as illustrated by Schemes XLIX - LI.

Firstly the conversion of lactone **110**, **111** or **114** into enone **115**, **116** or **117** respectively, were considered. Functional group transformations of this type have been carried out previously.[330] Initially, it was hoped that using the literature procedure, which involved the use of methyl lithium, would result in opening of the lactone ring. However, experiments of this type afforded products in which the carbonyl had undergone nucleophilic attack, without cleavage of the heterocycle. Subsequent

attempts to induce ring opening gave complex mixtures of products, therefore an alternative reaction was considered.



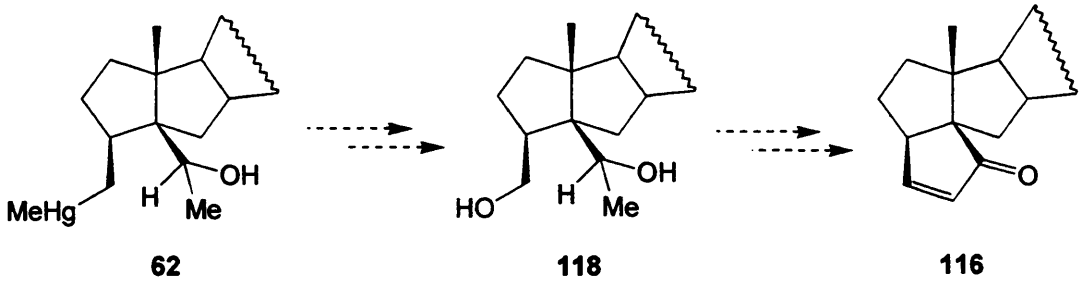
Scheme XLIX

Methylenation of aldehydes or ketones can be accomplished using Tebbe reagent, as illustrated in Chapter Two. Conversion of esters or lactones to vinyl ethers has also been demonstrated with this reagent.[181,331] Therefore, it was speculated that Tebbe reagent could be used to produce vinyl ethers, which could then be hydrolysed to afford compounds containing both hydroxy and ketone functional groups.

Formation of Tebbe reagent *in situ*, followed by addition of either lactone **110** or **111**, allowed formation of different compounds. However, attempts to isolate the major products from these reactions gave inconsistent results. Quenching the reactions with base, then removal of the precipitate and concentration of the supernatant, followed by

purification under neutral or basic conditions, did not afford the required vinyl ethers or hydrolsed products. Therefore alternative starting materials for synthesis of an enone were considered.

Since reductive demercuration had allowed high yielding conversions of bromomercurials into alcohol products, this method was considered to synthesise a compound that would be a suitable intermediate in formation of an enone group. Methylmercurial **62**, which had been isolated as a side product from a cuprate reaction (Scheme XXXIX), was then tested to determine whether it could be converted into products, that would undergo reductive demercuration.



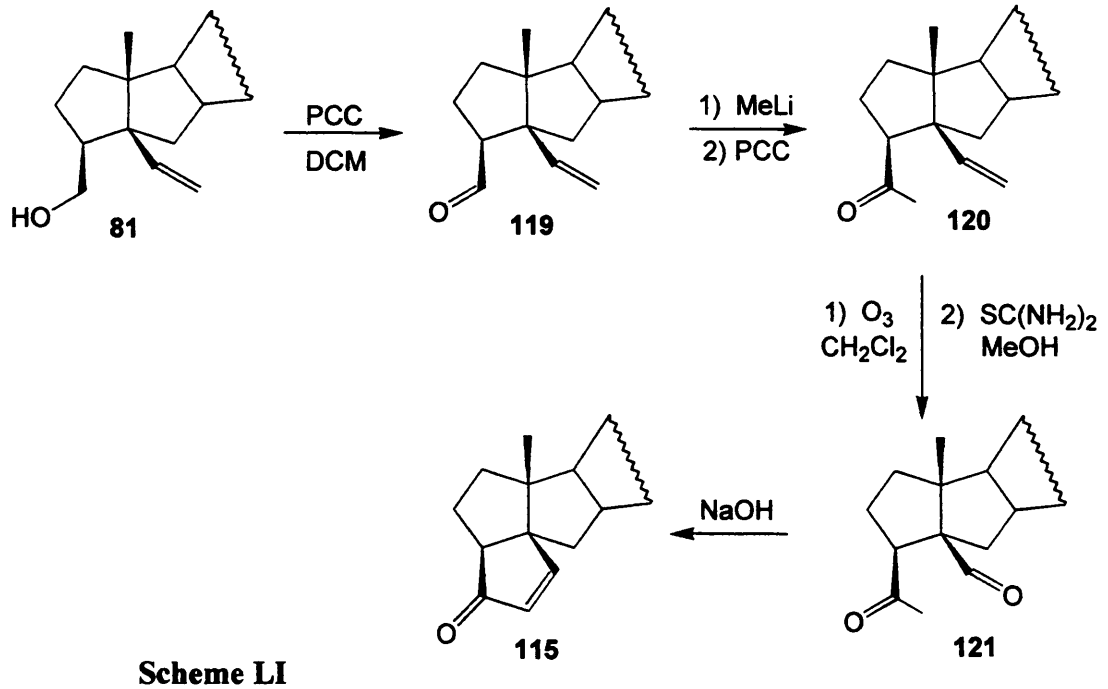
62 **118** **116**

Scheme L

Treatment of **62** with mercuric bromide did not give a high yielding conversion to a bromomercurial, unlike previously seen for other methyl mercurio derivatives. Therefore, the hydroxy group was oxidised prior to deprotection of the mercury, (see Scheme XXXIX). Reaction of **58** under the conditions for reductive demercuration gave a complex mixture of more than the expected three products, hence this pathway was not taken further, because the above procedures had been conducted following isolation of a low yield of **62**.

The final route was derived following successful oxidation of **77** using the reductive demercuration procedure, (Scheme XXXVIII). Alcohol **81** would need to

undergo reactions in which the hydroxy group was converted into a methyl ketone, and the olefin was converted into an aldehyde. The steps for this procedure were based on literature reactions which involved oxidation of the primary alcohol, treatment with methyl lithium and ozonolysis.[332] The oxidation in this published synthesis was accomplished using a large excess of pyridinium dichromate and stirring for 17 hours to afford a carboxylic acid. Oxidation of alcohol **81** was attempted using these conditions, however the reaction did not furnish the required carbonyl product, therefore, another procedure was required to convert the alcohol into a methyl ketone.



Scheme LI

The hydroxy group was transformed in three steps into methyl ketone **120**, (Scheme LI). Initial oxidation of alcohol **81** with pyridinium chlorochromate (PCC) furnished aldehyde **119** in 82% yield. Treatment of this compound with methyl lithium and subsequent reaction with PCC afforded 88% of methyl ketone **120**. Ozonolysis in dichloromethane and treatment of the product mixture with a methanolic solution of thiourea,[334] afforded 65% of the required compound **121**. Treatment of the latter

dicarbonyl compound with sodium hydroxide triggered an intramolecular aldol condensation, affording enone **115**.

4.5 CONCLUSIONS

Formation of alcohol **81** as an intermediate in synthesis of a pentalenolactone skeleton, did not help achieve this goal, but was instrumental in synthesis of enone **121**. Other reactions discussed in this chapter provided methods to synthesise new products, although different procedures would have to be considered to attain those target compounds that were not produced. For instance, development of an annulated cyclopentanone (via a ring expansion of cyclobutanone **84**) using reagents such as sulfonium methylide or bis(phenylthio)methyllithium,[335-338] may open up new possibilities in the formation of a conjugated enone.[339]

The above discussion shows experiments that could be considered if additional reactions were to be conducted. It should be noted, that amongst the successful procedures documented, a new route to the formation of lactones was attained. Organomercurials have been converted into lactones using palladium carbonylation. The strategy described offers a versatile stereo-controlled method for construction of annulated five and six-membered lactones.

SUMMARY

Stereo-electronically controlled cleavage of 3α,5-cyclo-5α-cholestan-6α-ol **12** has recently been described for mercury(II),[13] affording stable organomercurial **20** which was then investigated in terms of reactivity.[102] Transmetallation of **20** has been achieved with a palladium reagent,[41] furnishing lactol **14**, which could also be synthesised in two steps by initial treatment of **20** with molybdenum(V) chloride.[146] The reactivity of organomercurial **20** was explored further in experiments with a cuprate and a molybdenum reagent, which initiated an intramolecular addition to an aldehyde, and a fragmentation pathway.[42,43]

Reaction procedures discussed in this thesis have explained the use of organomercurials as intermediates in the formation of numerous products. A key feature in these syntheses was the development of a method for the protection-deprotection of organomercurials, which has been developed via methylation-demethylation. Methyl copper was the reagent used to methylate the organomercurials, affording methylmercurials which could then be subjected to a variety of reagents, to enable functional group transformations. This protocol facilitated selective reductions of an aldehyde or ketone group, present in the molecule, without cleavage of the mercury unit.[112] Methylenation and oxidation reactions have also been accomplished in the presence of a mercury group, both of which proved useful in synthesis of a precursor to enone **115**.

Halomercurials can be regenerated when required by treatment of the methyl derivatives with a mercuric halide. Transformation of the organomercurial in this way enables subsequent reactions to be conducted in which the mercury unit is cleaved.

Procedures of this type include the reaction of bromomercurio alcohol **65** with bromine, which furnishes tetrahydrofuran **66**. Organomercurial **65** can also undergo palladium(II) catalysed carbonylation, affording six-membered lactone **114**. The conditions of the latter experiment have been applied to a number of halomercurials, facilitating synthesis of *cis* and *trans*-five-membered lactones.[112]

An important procedure in this research involved the use of reductive demercuration, in which halomercurials can be converted into alcohols. Formation of diol **79** was accomplished using this methodology. Subsequent oxidation of **79** provided a selective approach to lactol **109**.

Preparation of cyclobutanol **61** by cuprate-mediated cyclisation of bromomercurial **20**,[13] provided the starting material to investigate ring expansion procedures. Development of vinyl cyclobutanol **86** enabled a protocol for the synthesis of a triquinane skeleton, to be established. It has been shown that the regioselectivity of the cyclobutane ring-expansion can be controlled, by the reagent/catalysed employed. Thallium(III) and mercury(II) favoured migration of the quaternary carbon affording mainly α-methylene ketone **90.** Reactions with palladium(II) reagents were found to favour an alternate route. The products that were isolated was dependent on which catalyst was used, since the ligands were found to influence the reaction pathway, affording functionalised cyclopentanes **101**, **102** and **103**.

It should be noted, that whilst these reactions were conducted on the steroid skeleton, it is believed that the reported findings are of a general nature. In view of the number of processes available for the preparation of organomercurials,[88-92] the documented methods can provide useful transformations for synthetic purposes.

EXPERIMENTAL

GENERAL METHODS

All reactions were carried out under N_2 unless otherwise indicated. Dry THF and toluene were obtained by distillation form sodium metal in the presence of benzoquinone. Dichloromethane and xylene were distilled from calcium hydride. Ether was distilled from $LiAlH_4$ or was sodium dried prior to use. Methanol and ethanol were dried by distillation from magnesium and iodine. Triethylamine and pyridine were dried over sodium hydroxide pellets. Routine drying of organic solutions was carried out using anhydrous magnesium sulphate. Standard workup of an ethereal solution means washing with 5% aqueous HCl solution, sat. aqueous $NaHCO_3$ solution and water, drying with $MgSO_4$, and removal of the solvent under vacuum. All products were dried under high vacuum before recording their yields. Petroleum refers to the petroleum ether fraction with bp 40 - 60 °C. The identity of samples prepared by different routes were checked by TLC, IR, MS and NMR. Yields are given for isolated products showing one spot on TLC with no impurities detectable in the NMR spectrum. All flash chromatography was carried out according to the method of Still,[339] using Kieselgel 60 (230 - 400 mesh) (Merck and Co), unless otherwise indicated. The amount of silica gel and the column size used for each separation was varied, with respect to the number of products, their relative polarities and the quantity of crude mixture being purified. Separation of products using a chromatotron were performed on model 7924T with Kieselgel 60 (PF 254) plates (Merck and Co). TLC was conducted on pre-coated aluminium sheets (60 - 254) with a 0.2 mm layer of thickness, manufactured by Merck and Co. Melting points were determined on a Kofler block and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 621 spectrometer. Optical rotations were measured on a Perkin-Elmer 141 or 341 polarimeter. Optical rotations and IR spectra were recorded in $CHCl_3$ unless otherwise indicated. The NMR spectra were recorded using $CDCl_3$ unless otherwise indicated. They were recorded at 25 °C on a Varian

Unity 400 (operating at 400 MHz for ^{1}H), or a Bruker AM-300 (operating at 300 MHz for ^{1}H and 75.47 MHz for ^{13}C), or a Bruker ARX-250 (operating at 250 MHz for ^{1}H and 62.90 MHz for ^{13}C). Chemical shifts were indirectly reference to TMS via the solvent signals ($CDCl_3$: 7.27 ppm for ^{1}H and 77.00 ppm for ^{13}C and CD_2Cl_2: 5.35 ppm for ^{1}H and 53.85 ppm for ^{13}C). The coupling constants were obtained by first-order analysis. The ^{1}H NMR peaks have been reported for the signals which are separated from the majority of peaks, which occur in a narrow band and are complex, due to the number of signals arising from the steroid compounds. The different types of carbon in the structures have been identified using DEPT techniques. Standard mass spectra and accurate mass measurements were recorded on a Kratos Concept 1H instrument using direct inlet and the lowest temperature enabling evaporation. Chemical ionisation was used in certain cases (with NH_3). The molecular ion and accurate mass values for compounds containing mercury have been reported for the ^{202}Hg isotope and for compounds containing bromine, the values have been reported for the ^{79}Br isotope. Elemental analysis was carried out by CHN Analysis, Wigston, Leicester or Butterworth Laboratories, Teddington, Middlesex. The X-ray data was obtained by Dr Vratislav Langer on a CCD detector-based SMART diffractometer (Siemens). The software package used for structure solution was SHELXS-86;[340] SHELXL-93 was used for structure refinement;[341] SHETXTL (Siemens 1994) was used for molecular graphics.

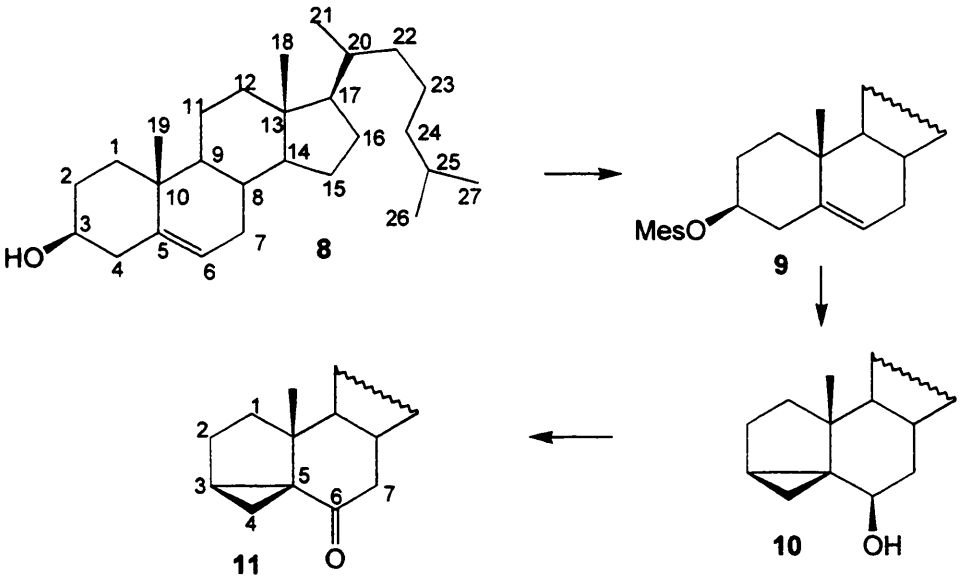
PHYSICAL DATA

In the NMR spectra, chemical shifts were expressed in ppm on the δ scale relative to the internal standard (TMS). The following abbreviations are used: s - singlet, d - doublet, t - triplet, m - multiplet, dd - doublet of doublets, dt - doublet of triplets, ddd - doublet of doublet of doublets, *J* - coupling constant (Hz). Mass spectra were determined in units of mass relative to charge (*m*/z).

EXPERIMENTAL

CHAPTER ONE

3α, 5-Cyclo-5α-cholestan-6-one (11)[72]

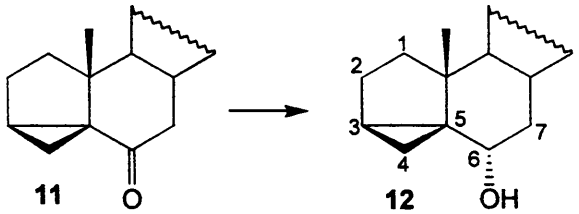


A solution of methanesulfonyl chloride (2.3 ml; 30 mmol) in dry THF (20 ml) was added slowly to a solution of cholesterol (7.693 g; 19.896 mmol) and triethylamine (5 ml) in dry THF (150 ml) at -10 °C. After stirring for 1 h, 15% aqueous NaCl solution (50 ml) was added, followed by ether (100 ml). The organic layer was separated and washed with 5% aqueous HCl solution (2 x 50 ml) and H_2O (2 x 50 ml). It was dried with $MgSO_4$ and the solvent evaporated.

The resulting 3β-mesyloxy-cholest-5-ene **9** was dissolved in butan-2-one (150 ml), triethylamine (7 ml), $NaHCO_3$ (3.4 g) and H_2O (40 ml) were added and the mixture was refluxed for 5 h. The organic layer was separated and washed with 15% aqueous NaCl solution (100 ml). Then the solution was cooled to 0 °C and Jones' reagent[343] (2.67 M CrO_3 in H_2SO_4; 5.5 ml) was added dropwise. The mixture was stirred at 0 °C for 3 h, and then quenched with 15% aqueous NaCl solution (50 ml). The organic layer was separated and washed with sat. aqueous $NaHCO_3$ solution (2 x 50 ml) and 15% aqueous NaCl solution (50 ml), then dried with $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography using a mixture of petroleum ether and ethyl acetate (20:1) as the eluant, which furnished **11** (5.385 g; 13.927 mmol;

70% yield from cholesterol), identical to an authentic sample:[102] mp 100 - 101.5 °C (acetone/MeOH), (literature mp 101 - 102 °C)[342]: $[\alpha]_D$ +44.9° (*c* 0.7); IR ν(C=O) 1675 cm^{-1}; ^1H NMR (300 MHz) δ 0.72 (s, 3 H, 18-H), 0.865 (d, *J* = 6.6Hz, 3 H, 26-H or 27-H), 0.869 (d, *J* = 6.6Hz, 3 H, 26-H or 27-H), 0.93 (d, *J* = 6.6 Hz, 3 H, 21-H), 0.94 (s, 3 H, 19-H), 2.06 (dt, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.6 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 3.3 Hz, 1 H, 7β-H), 2.43 (m, 1 H, 8β-H); ^{13}C NMR (75.47 MHz) δ 11.61 (C-4), 12.04 (C-18), 18.70 (C- 21), 19.68 (C-19), 22.57 (C-26 or C-27), 22.82 (C-26 or C-27), 22.88 (CH_2), 23.83 (CH_2), 24.05 (CH_2), 25.90 (CH_2), 28.00 (CH), 28.16 (CH_2), 33.46 (CH_2), 34.78 (CH), 35.29 (CH), 35.73 (CH), 36.11 (CH_2), 39.47 (CH_2), 39.73 (CH_2), 42.70 (C-13), 44.79 (CH_2), 46.07 (CH), 46.28 (C-5 or C-10), 46.73 (C-5 or C-10), 56.09 (CH), 56.98 (CH), 209.51 (C-6); MS EI *m*/z (%) 385 (30, M^+), 384 (100), 369 (12), 137 (10), 136 (29), 121 (15).

3α,5-Cyclo-5α-cholestan-6α-ol (12)[71]

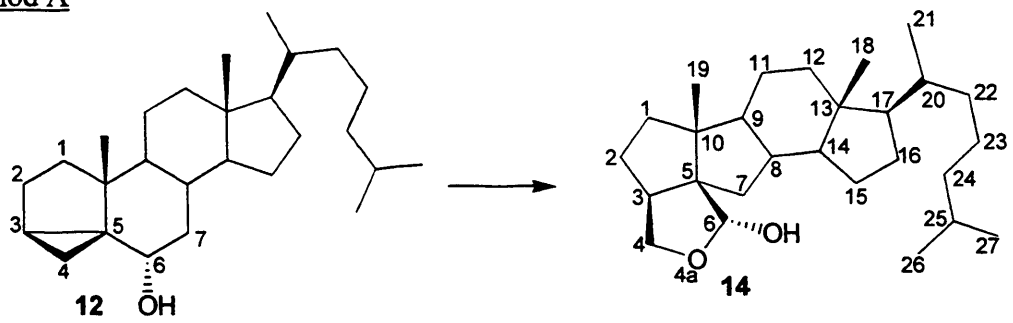


A solution of 3α,5-cyclo-5α-cholestan-6-one **11** (2.717 g; 7.064 mmol) in dry ether (50 ml)was added dropwise to a cooled (0 °C) solution of $LiAlH_4$ (260 mg; 6.851 mmol) in dry ether (50 ml) under nitrogen. The mixture was stirred for 1 h and then the excess reagent was decomposed by successive addition of H_2O (0.3 ml), 15% aqueous NaOH solution (0.3 ml), and H_2O (1 ml). The white precipitate was filtered off through a celite pad and washed with ether. The organic layer was washed with 5% aqueous HCl solution (20 ml), sat. aqueous $NaHCO_3$ solution (20 ml), and H_2O (2 x 20 ml). The solution was dried and the solvent removed, yielding amorphous **12** (2.490 g; 6.439 mmol; 94%), identical to an authentic sample:[102] IR ν_{max}(O–H) 3605 cm^{-1}; ^1H NMR

(300 MHz) δ 0.28 (t, J = 4.1 Hz, 1 H, 4β-H), 0.65 (dd, J = 8.1 Hz and 4.6 Hz, 1 H, 4α-H), 0.72 (s, 3 H, 18-H), 0.897 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.90 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.94 (d, J = 6.5 Hz, 3 H, 21-H), 0.95 (s, 3 H, 19-H), 3.93 (dd, $J_{6\beta\text{-H},7\alpha\text{-H}}$ = 11.3 Hz, $J_{6\beta\text{-H},7\beta\text{-H}}$ = 4.2 Hz, 1 H, 6β-H); ^{13}C NMR (75.47 MHz) δ 6.62 (C-4), 12.07 (C-18), 17.94 (C-19), 18.67 (C-3 and C-21), 22.56 (C-26 or C-27), 22.82 (C-26 or C-27), 23.17 (CH_2), 23.83 (CH_2), 24.24 (CH_2), 25.06 (CH_2), 28.00 (CH), 28.24 (CH_2), 32.76 (CH_2), 34.94 (CH), 35.78 (CH), 36.13 (CH_2), 39.50 (CH_2), 39.81 (C-13), 40.11 (CH_2), 40.23 (CH_2), 42.72 (C-5 or C-10), 44.93 (C-5 or C-10), 47.66 (CH), 56.21 (CH), 56.26 (CH), 67.16 (C-6); MS EI *m/z* (%) 387 (11, M^+), 386 (39), 372 (29), 371 (100), 369 (18), 368 (57), 353 (16), 332 (16), 331 (61), 231 (13).

4a-Oxa-A-bishomo-B-nor-3,5-cyclo-5α-cholestan-6α-ol (14)

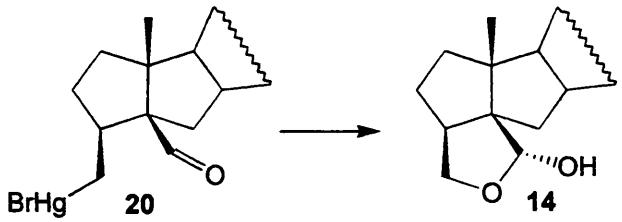
Method A[70]



Thallium(III) nitrate trihydrate (190 mg; 428 μmol) was added to a solution of cyclopropyl alcohol **12** (165 mg; 427 μmol) in dioxane (20 ml) containing 2 drops of 10% aqueous $HClO_4$ and the solution was stirred at rt for 5 h. A 10% aqueous $HClO_4$ solution (5 ml) was then added and the mixture was stirred for a further 5 h, then diluted with ether (20 ml) and worked up. The crude product was chromatographed by elution with a petroleum ether-ether mixture (9:1), to afford lactol **14** (103 mg; 256 μmol; 66%), identical to an authentic sample:[70] mp 156 - 158 °C (acetone); IR ν_{max}(O–H) 3620 and 3395 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.64 (s, 3 H, 18-H), 0.865 (d, J = 6.6 Hz, 3 H,

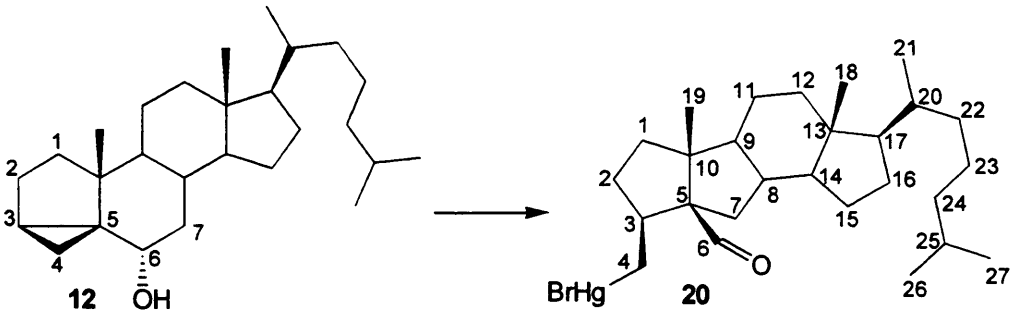
26-H or 27-H), 0.867 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.91 (s, 3 H, 19-H), 2.27 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.8 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.0 Hz, 1 H, 7β-H), 2.40 (m, 1 H, 3α-H), 2.76 (s, 1 H, 6α-OH), 3.41 (dd, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 8.7 Hz, $J_{3\alpha\text{-H},4\beta\text{-H}}$ = 4.7 Hz, 1 H, 4β-H), 4.18 (dd, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 8.7 Hz, $J_{3\alpha\text{-H},4\alpha\text{-H}}$ = 9.1 Hz, 1 H, 4α-H), 5.18 (s, 1 H, 6β-H); ^{13}C NMR (62.90 MHz) δ 12.22 (C-18), 18.53 (CH_3), 18.76 (CH_3), 22.19 (CH_2), 22.54 (C-26 or C-27), 22.80 (C-26 or C-27), 23.82 (CH_2), 24.48 (CH_2), 27.98 (CH), 28.45 (CH_2), 28.56 (CH_2), 35.65 (CH), 36.08 (CH_2), 36.21 (CH_2), 37.88 (CH_2), 39.47 (CH_2), 39.73 (CH_2), 40.92 (CH), 43.67 (C-13), 49.24 (CH), 53.03 (C-10), 55.08 (CH), 55.67 (CH), 56.56 (CH), 66.46 (C-5), 71.93 (C-4), 101.17 (C-6); MS EI *m/z* (%) 402 (18, M^+), 400 (32), 385(29), 384 (33), 358 (22), 357 (25) 356 (83).

Method B[13]



Lithium chloride (23 mg; 542 μmol) was added to a solution of palladium(II) chloride (2.4 mg; 5 mol %) in DME (10 ml) and H_2O (2 drops) and the mixture was stirred at rt for 15 min. Copper(II) chloride (228 mg; 1.337 mmol) was then added and the mixture was stirred for an additional 15 min. Then a solution of bromomercurio aldehyde **20** (180 mg; 270 μmol) in DME (2 ml) was added and the mixture was stirred at rt for 12 h. The solution was diluted with ether (15 ml), washed with H_2O (5 x 10 ml) and sat. aqueous $NaHCO_3$ solution (10 ml), and dried with $MgSO_4$. The solvent was evaporated and the product chromatographed by elution with a petroleum ether-ether mixture (9:1) to produce lactol **14** (95 mg; 236 μmol; 87%) identical to the compound prepared by Method A.

3β-[(Bromomercurio)methyl]-A,B-bisnor-5β-cholestane-5-carbaldehyde (20)[13]

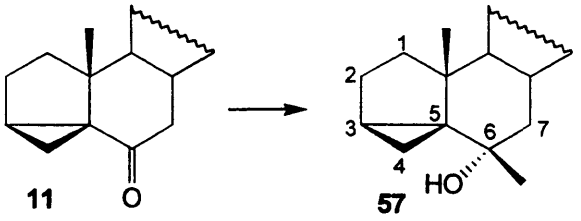


To a solution of cyclopropyl alcohol **12** (150 mg; 388 μmol) in DME (6 ml), was added acetonitrile (15 ml), whilst the solution was being stirred. Mercury(II) nitrate monohydrate (134 mg; 391 μmol) was then added and the mixture was stirred at room temperature for 1 h. Then the reaction was quenched with 10% aqueous KBr solution (5 ml) and the mixture was diluted with ether (25 ml). The organic layer was washed with sat. aqueous $NaHCO_3$ solution (2 x 10 ml) and H_2O (15 ml), then dried with $MgSO_4$, and the solvent was evaporated yielding **20** (253 mg; 380 μmol; 90%): mp 148 - 150 °C (CH_3Cl/EtOH), identical to an authentic sample,[13] which had mp 149 -151 °C:[102] IR (CH_2Cl_2) ν_{max}(C=O) 1704 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 0.61 (s, 3 H, 18-H), 0.863 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.865 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.95 (s, 3 H, 19-H), 2.48 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.2 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.8 Hz, 1 H, 7β-H), 9.73 (s, 1 H, 6-H); ^{13}C NMR (62.90 MHz, CD_2Cl_2) δ 12.32 (C-18), 18.92 (C-21), 19.80 (C-19), 21.46 (CH_2), 22.93 (C-26 or C-27), 22.69 (C-26 or C-27), 24.21 (CH_2), 24.76 (CH_2), 28.38 (C-25), 28.82 (C-11), 36.03 (C-4), 36.59 (CH_2), 37.10 (CH_2), 39.14 (CH_2), 39.70 (CH_2), 39.84 (2 x CH_2), 39.89 (CH_2), 44.06 (C-13), 44.67 (C-8), 53.36 (C-3), 56.09 (C-17), 57.13 (C-14), 58.47 (C-10), 59.53 (C-9), 71.00 (C-5), 206.53 (C-6); MS CI *m/z* (%) 684 (0.8, $[M + NH_4]^+$), 405 (26), 404 (83), 386 (19), 387 (19), 374 (21), 356 (29), 357 (41), 358 (56).

EXPERIMENTAL

CHAPTER TWO

3α,5-Cyclo-5α-cholestan-6β-methyl-6α-ol (57)

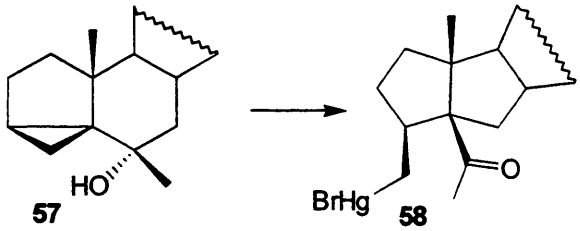


Cerium chloride heptahydrate (1.802 g; 4.837 mmol) was placed in a flask equipped with a stirring bead. The flask was gradually heated to 140 °C whilst stirring under vacuum. After 3 h the solid was cooled under nitrogen. THF (15 ml) was added with vigorous stirring and the resultant suspension was stirred overnight at rt. The flask was then immersed in an ice bath and methyl lithium (1.38 M in ether; 3.5 ml; 4.830 mmol) was added. After stirring for 1 h at 0 °C, a solution of compound **11** (1.236 g; 3.213 mmol) in THF (10 ml) was added. The mixture was stirred at 0 °C for 1 h, then quenched with 5% aqueous HCl solution (5 ml) and diluted with ether (60 ml). The organic layer was washed with 5% aqueous NaCl solution (30 ml), sat. aqueous $NaHCO_3$ solution (30 ml) and 5% aqueous NaCl (30 ml), dried, then evaporated. The crude product was purified by column chromatography using a petroleum ether-ether mixture (9:1) as the eluant, to afford unreacted **11** (148 mg; 385 μmol; 12%) as the least polar and amorphous **57** (940 mg; 2.346 mmol; 73%) as the most polar component. **57**: $[\alpha]_D$ +35.2° (*c* 1.9); IR ν_{max}(O–H) 3603 cm^{-1}; ^1H NMR (400 MHz) δ 0.29 (dd, *J* = 4.7 Hz, 1 H, 4β-H), 0.54 (dd, *J* = 8.2 Hz and 4.7 Hz, 1 H, 4α-H), 0.70 (s, 3 H, 18-H), 0.864 (d, *J* = 6.6 Hz, 3 H, 26-H or 27-H), 0.868 (d, *J* = 6.6 Hz, 3 H, 26-H or 27-H), 0.91 (d, *J* = 6.6 Hz, 3 H, 21-H), 0.92 (s, 3 H, 19-H), 0.98 (m, 1 H, 7α-H), 1.15 (m, 1 H, 12α-H), 1.27 (bd, 3 H, 6β-CH_3), 1.32 (m, 1 H, 3-H), 1.76 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.1 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 3.7 Hz, 1 H, 7β-H), 1.98 (ddd, *J* = 12.5, 6.9, 6.9 Hz, 1 H, 12β-H); NOE: 0.29 (4β-H) ↔ 0.92 (19-H), 0.54 (4α-H) ↔ 1.27 (6β-Me), 0.54 (4α-H) ↔ 1.32 (3-H), 1.27 (6β-Me) ↔

1.32 (3-H), 1.27 (6β-Me) ↔ 1.76 (7β-H); ^{13}C NMR (100.60 MHz) δ 6.81 (C-4), 12.17 (C-18), 18.69 (C-21), 20.10 (C-19), 22.37 (C-3), 22.57 (C-26 or C-27), 22.82 (C-26 or C-27), 23.06 (C-11), 23.19 (CH_2), 23.84 (CH_2) 24.31 (C-1), 27.30 (6β-CH_3), 28.02 (C-25), 28.27 (CH_2), 33.93 (C-2), 34.54 (C-14), 35.79 (C-20), 36.16 (CH_2), 39.51 (CH_2), 40.08 (C-12), 42.46 (C-5), 42.77 (C-13), 44.71 (C-10), 46.29 (C-7), 47.97 (C-9), 56.28 (C-17),56.29 (C-8), 69.90 (C-6); MS EI *m/z* (%) 400 (40, M^+), 386 (30), 385 (100), 383 (29), 382 (72), 367 (28), 357 (29), 345 (57), 247 (27). Anal. Calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.07. Found: C, 83.68; H, 11.98.

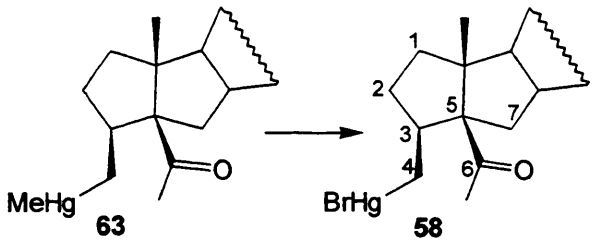
5-Acetyl-3β-[(bromomercurio)methyl]-A,B-bisnor-5β-cholestane (58)

Method A



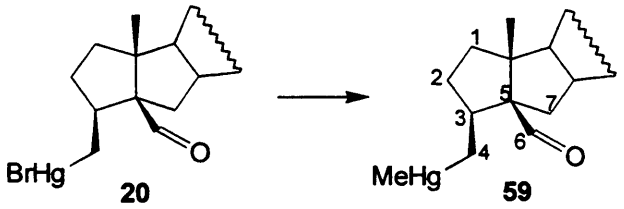
Mercury(II) nitrate monohydrate (130 mg; 379 μmol) was added to a stirred solution of **57** (150 mg; 374 μmol) in DME (6 ml) and acetonitrile (12 ml), then the mixture was stirred at rt. After 2 h aqueous 10% aqueous KBr solution (5 ml) was added, followed by ether (40 ml). The organic layer was washed with sat. aqueous $NaHCO_3$ solution (2 x 20 ml) and H_2O (20 ml), then dried and the solvent removed. Purification by column chromatography using a petroleum ether-ether mixture (24 : 1) as the eluant, furnished 120 mg of a single product by TLC. Mass spectra showed the presence of the required molecular ion, however ^{13}C NMR indicated the presence of additional species, which could not be separated, therefore an alternative route was used to obtain a pure sample of **58**.

Method B



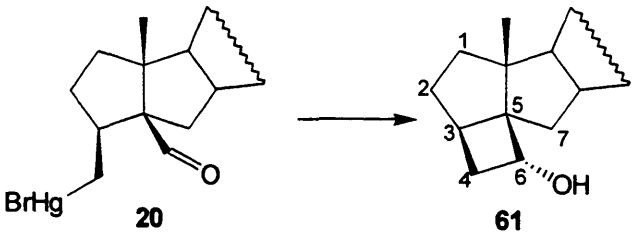
To a stirred solution of methyl mercurial **63** (165 mg; 268 μmol) in DME (10 ml) was added mercuric bromide (98 mg; 286 μmol) and the resulting mixture was stirred at rt for 2 h. Then the reaction was diluted with water (5 ml) and ether (40 ml). The organic layer was washed with sat. aqueous $NaHCO_3$ (20 ml) and H_2O (2 x 20 ml), then dried and the solvent evaporated. The crude product was chromatographed by elution with a petroleum ether-acetone mixture (97:3), which furnished amorphous **58** (149 mg; 220 μmol; 82%): $[\alpha]_D$ +45.6° (*c* 4.1); IR ν_{max}(C=O) 1684 cm^{-1}; ^1H NMR (250 MHz) δ 0.65 (s, 3 H, 18-H), 0.862 (d, *J* = 6.6 Hz, 3 H, 26-H or 27-H), 0.866 (d, *J* = 6.6 Hz, 3 H, 26-H or 27-H), 0.89 (s, 3 H, 19-H), 0.92 (d, *J* = 6.6 Hz, 3 H, 21-H), 2.13 (s, 3 H, $COCH_3$); ^{13}C NMR (62.90 MHz) δ 12.29 (C-18), 18.71 (C-21), 9.89 (C-19), 21.48 (CH_2), 22.51 (C-26 or C-27), 22.76 (C-26 or C-27), 23.83 (CH_2), 24.41 (CH_2), 27.94 (CH), 28.47 (CH_2), 31.99 ($COCH_3$), 35.04 (CH_2), 35.60 (CH), 36.17 (CH_2), 37.94 (CH_2), 38.16 (CH_2), 39.43 (CH_2), 39.55 (CH_2), 40.02 (CH_2), 43.91 (C-13), 43.37 (CH), 55.25 (CH), 55.64 (CH), 56.97 (CH), 57.68 (CH), 59.40 (C-10), 73.52 (C-5), 213.28 (C-6); MS CI *m/z* 700(4.0), 699 (3.0), 698 (5.6, $[M + NH_4]^+$), 697 (3.3), 696 (3.1), 401 (56), 400 (69), 399(100), 384 (44), 370 (64); HRMS EI *m/z* 680.25168 (calcd for $C_{28}H_{47}BrHgO$: 680.25166).

A,B-Bisnor-5β-cholestan-3β-[(methylmercurio)methyl]-5-carbaldehyde (59)[42]



Methyl lithium (1.4 M in ether; 1.3 ml; 1.820 mmol) was added to a suspension of copper(I) iodide (355 mg; 1.864 mmol) in dry ether (30 ml) at -35 °C. The resulting mixture was stirred at -35 °C for 10 min then cooled to -78 °C. A solution of organomercurial **20** (250 mg; 375 μmol) in THF (5 ml) was added and the mixture was stirred for an further 5 min. The excess reagent was decomposed by addition of 5% aqueous HCl solution (10 ml), then the mixture was diluted with ether (20 ml) and allowed to warm to rt. The organic layer was separated and washed with sat. aqueous $NaHCO_3$ solution (2 x 15 ml) and H_2O (2 x 15 ml), then dried and the solvent evaporated yielding oily methylmercurial **59** (221 mg; 368 μmol; 98%), which was identical to an authentic sample:[102] IR ν_{max}(C=O) 1710 cm^{-1}; ^1H NMR (250 MHz) δ 0.28 (s (83%) and d (17%), $J_{H,Hg}$ = 101.0 Hz, 3 H, $HgCH_3$), 0.59 (s, 3 H, 18-H), 0.86 (d, J = 6.9 Hz, 6 H, 26-H and 27-H), 0.91 (s, 3 H, 19-H), 2.36 (m, 1 H, 3α-H), 2.50 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.1 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.8 Hz, 1 H, 7β-H), 9.77 (s, 1 H, 6-H); ^{13}C NMR (62.90 MHz) δ 12.19 (C-18), 18.76 (C-21), 19.57 (C-19), 20.97 ($HgCH_3$), 21.08 (CH_2), 22.55 (C-26 or C-27), 22.80 (C-26 or C-27), 23.85 (CH_2), 24.37 (CH_2), 27.97 (C-25), 28.49 (C-11), 35.63 (CH), 36.21 (CH_2), 36.48 (CH_2), 39.45 (CH_2),39.59 (CH_2), 39.71 (CH_2), 39.89 (CH_2), 42.24 (CH_2), 43.67 (C-13), 44.04 (C-8), 54.37 (CH), 55.74 (CH), 56.88 (CH), 57.36 (C-10), 59.45 (C-14), 71.56 (C-5), 207.26 (C-6); MS EI *m/z* (%) 587 (1, M^+- CH_3), 559 (9), 547 (4), 386 (36), 385 (100); MS CI *m/z* (%) 621 (0.1, $[M + NH_4]^+$), 603 (1.3, MH^+), 585 (0.4), 576 (0.5), 559 (0.4), 547 (0.3), 385 (15), 358 (88), 203 (100).

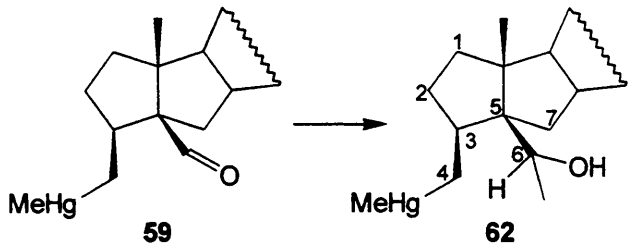
A-Homo-B-nor-3,5-cyclo-5α-cholestan-6α-ol (61)[43]



Methyl lithium (1.46 M in ether; 0.54 ml; 788 μmol) was added to a suspension of copper(I) iodide (50 mg; 262 μmol) in dry ether (10 ml) under nitrogen at -35 °C. The resulting mixture was stirred at -35 °C for 10 min and then it was cooled to -78 °C. A solution of organomercurial **20** (75 mg; 113 μmol) in THF (2 ml) was added and the mixture was stirred for an further 5 min. The excess reagent was decomposed by addition of 5% aqueous HCl solution (2 ml), then the mixture was diluted with ether (20 ml) and allowed to warm to rt. The organic layer was separated and washed with sat. aqueous $NaHCO_3$ solution (2 x 15 ml) and H_2O (2 x 15 ml), then dried and the solvent evaporated yielding **61** (42 mg; 109 μmol; 97%): mp 98 - 99.5 °C (acetone), identical to an authentic sample, which had mp 97-99 °C:[43] IR ν_{max}(O-H) 3600 and 3430 cm^{-1}; ^1H NMR (250 MHz) δ 0.63 (s, 3 H, 18-H), 0.87 (d, J = 6.6 Hz, 6 H, 26-H and 27-H), 0.90 (s, 3 H, 19-H), 2.23 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 13.4 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 7.8 Hz, 1 H, 7β-H), 2.40 (m, 1 H, 3α-H), 4.16 (dd, J = 5.4 Hz and 4.6 Hz, 1 H, 6β-H); ^{13}C NMR (62.90 MHz) δ 12.28 (C-18), 17.15 (C-19), 18.75 (C-21), 21.82 (CH_2), 22.54 (C-26 or C-27), 22.79 (C-26 or C-27), 23.80 (CH_2), 24.47 (CH_2), 27.98 (CH), 28.54 (CH_2), 28.93 (CH_2), 32.85 (CH_2), 34.93 (CH_2), 35.64 (CH), 36.22 (CH_2), 36.26 (CH_2), 39.48 (CH_2), 39.79 (CH_2), 40.93 (CH), 43.95 (C-13), 45.55 (CH), 53.46 (CH), 53.59 (C-10), 55.70 (CH), 57.05 (CH), 63.79 (C-5), 68.98 (C-6); MS EI *m/z* (%) 386 (14, M^+), 343 (28), 342 (100), 247 (22), 246 (11), 229 (13).

5-(Hydroxymethyl)-6-methyl-3β-[(methylmercurio)methyl]-

A,B-Bisnor-5β-cholestane (62)

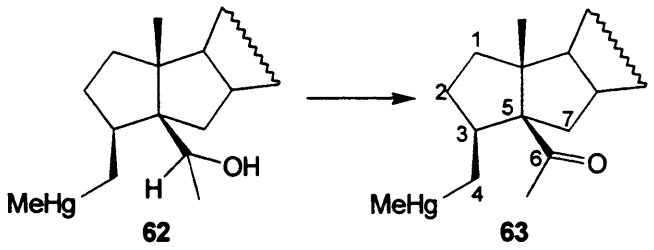


59 **62**

A solution of methylmercurio aldehyde **59** (1. 053 g; 1.751 mmol) in ether (50 ml) was added dropwise, over 10 min, to a solution of methyl lithium (1.4 M in ether; 1.4 ml; 1.960 mmol) in dry ether (100 ml) at -78 °C. After stirring for 1 min, the mixture was quenched with 5% aqueous HCl solution (10 ml) and allowed to warm to rt. The ethereal layer was washed with sat. aqueous $NaHCO_3$ solution (2 x 40 ml) and H_2O (2 x 40 ml), then dried and the solvent was removed under vacuum. The products were separated by column chromatography, using a petroleum ether-ether mixture (97:3) to furnish methyl mercurio derivative **62** (346 mg; 560 μmol; 32%), as a mixture of diastereoisomers, (which was oxidised to achieve full characterisation); cyclobutanol **61** (427 mg; 1.104 mmol; 63%) was isolated by eluting with a petroleum ether-ether mixture (17:3). **62**: IR ν_{max}(O-H) 3616 cm^{-1}; ^1H NMR (250 MHz) δ 0.28 (s, (83%) and d (17%), $J_{H,Hg}$ = 97.3 Hz, 3 H, $HgCH_3$), 0.64 (s, 3 H, 18-H), 0.88 (d, J = 6.6 Hz, 6 H, 26-H and 27-H), 0.89 (s, 3 H, 19-H), 0.93 (d, J = 6.6 Hz, 3 H, 21-H), 1.37 (d, J = 6.3 Hz, 3 H, CHOHCH_3), 4.04 (m, 1 H, 6-H); ^{13}C NMR (62.90 MHz) for the major isomer δ 12.47 (C-18), 18.78 (C-21), 20.04 (CH_3), 21.76 (CH_3), 22.02 (CH_3), 22.06 (CH_2), 22.57 (C-26 or C-27), 22.81 (C-26 or C-27), 23.85 (CH_2), 24.54 (CH_2), 27.99 (CH), 28.65 (CH_2), 35.68 (CH), 36.27 (CH_2), 38.97 (CH_2), 39.52 (CH_2), 39.91 (CH_2), 40.14 (CH_2), 40.41 (CH_2), 42.04 (CH), 43.79 (CH_2), 43.96 (C-13), 51.29 (CH), 53.44 (C-10), 55.78 (CH), 57.35 (CH), 58.43 (CH), 63.10 (C-5), 71.63 (C-6); MS EI *m/z* (%) 600 (2.9,

M^+-OH), 599 (4.2), 598 (2.4), 597 (1.7), 585 (0.03), 574 (0.07), 588 (2.4), 383 (45), 357 (34), 342 (13), 329 (10), 301 (27).

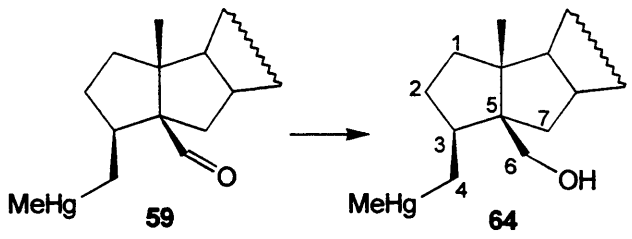
5-Acetyl-3β-[(methylmercurio)methyl]-A,B-bisnor-5β-cholestane (63)



62 **63**

Pyridinium chlorochromate (54 mg; 251 μmol) was added to a solution of methylmercurio derivative **62** (75 mg; 121 μmol) in dichloromethane (10 ml). The mixture was stirred at rt for 3 h, then filtered through a celite pad and the solvent was evaporated. The crude product was flushed through a short chromatography column using a petroleum ether-ether mixture (19:1), which yielded amorphous **63** (70 mg; 114 μmol; 93%): $[\alpha]_D$ +45.3° (*c* 2.5); IR ν_{max}(C=O) 1710 cm^{-1}; ^1H NMR (250 MHz) δ 0.26 (s (87%) and d (13%), $J_{Hg,H}$ = 100.5 Hz, 3 H, $HgCH_3$), 0.64 (s, 3 H, 18-H), 0.87 (d, *J* = 6.6 Hz, 3 H, 26-H and 27-H), 0.88 (s, 3 H, 19-H), 2.12 (s, 3 H, $COCH_3$), 2.42 (m, 1 H, 4-H); ^{13}C NMR (62.90 MHz) δ 12.30 (C-18), 14.14 ($HgCH_3$), 18.72 (C-21), 19.36 (C-19), 21.54 (CH_2), 22.52 (C-26 or C-27), 22.77 (C-26 or C-27), 23.84 (CH_2), 24.41 (CH_2), 27.96 (CH_2), 28.53 (CH_2), 32.00 ($COCH_3$), 34.25 (CH_2), 35.63 (CH_2), 36.22 (CH_2), 37.64 (CH_2), 38.89 (CH_2), 39.47 (CH_2), 39.76 (2 x CH_2), 43.16 (CH), 43.98 (C-13), 50.03 (CH), 55.71 (CH), 57.16 (CH), 57.56 (CH), 57.81 (C-10), 72.82 (C-5), 212.74 (C=O); MS EI *m/z* (%) 616 (0.3, M^+), 599 (0.4), 586 (0.16), 561 (2.1), 400 (30), 357 (39), 346 (56), 345 (100), 342 (33), 318 (45); HRMS EI *m/z* 616.35688 (calcd for $C_{29}H_{50}HgO$: 616.35680).

5-(Hydroxymethyl)-3β-[(methylmercurio)methyl]-A,B-bisnor-5β-cholestane (64)



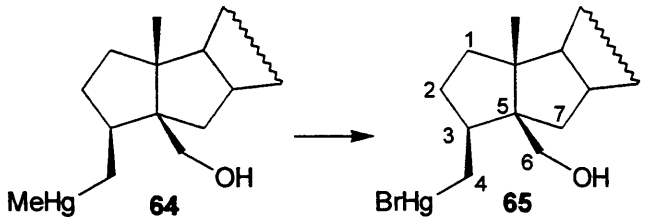
Method A[102]

Sodium borohydride (50 mg; 1.322 mmol) was added to a cooled (0 °C) stirred solution of aldehyde **59** (161 mg; 268 μmol) in ether (5 ml) and methanol (20 ml). The mixture was allowed to warm to rt and was stirred for 5 h. Then the excess reagent was decomposed with 10% aqueous HCl solution (5 ml) and the mixture was diluted with petroleum ether (40 ml). The organic layer was washed with sat. aqueous $NaHCO_3$ solution (2 x 20 ml) and H_2O (2 x 20 ml), then dried and the solvent removed under vacuum, to afford amorphous **64** (144 mg; 239 μmol; 89%): $[\alpha]_D$ +14.5° (*c* 2.5), identical to an authentic sample with $[\alpha]_D$ +14° (*c* 2.5):[102] IR ν_{max}(O–H) 3628 cm^{-1}; ^1H NMR (300 MHz) δ 0.25 (s (85%) and d (15%), $J_{H,Hg}$ = 96.8 Hz, 3 H, $HgCH_3$), 0.62 (s, 3 H, 18-H), 0.861 (d, *J* = 6.6 Hz, 3 H, 26-H or 27-H), 0.865 (d, *J* = 6.6 Hz, 3 H, 26-H or 27-H), 0.89 (s, 3 H, 19-H), 0.91 (d, *J* = 6.6 Hz, 3 H, 21-H), 3.52 and 3.73 (AB system, *J* = 10.9 Hz, 2 H, 6-H); ^{13}C NMR (75.47 MHz) δ 12.30 (C-18), 18.77 (C-21), 19.07 (C-19), 21.59 ($HgCH_3$), 21.83 (CH_2), 22.56 (C-26 or C-27), 22.81 (C-26 or C-27), 23.85 (CH_2), 24.53 (CH_2), 27.99 (CH), 28.58 (CH_2), 35.67 (CH), 35.81 (CH_2), 36.24 (CH_2), 38.71 (CH_2), 39.49 (CH_2), 39.90 (CH_2), 40.87 (CH_2), 41.28 (CH), 43.41 (CH_2), 43.79 (C-13), 49.58 (CH), 52.19 (C-10), 55.74 (CH), 56.66 (CH), 58.28 (CH), 59.96 (C-5), 64.96 (C-6); MS EI *m/z* 604 (1.1, M^+), 586 (3.2), 571 (4.3), 558 (1.4), 387 (83), 369 (100), 357 (64), 355 (80), 315 (51), 248 (41), 231 (56), 215 (71).

Method B

L-Selectride® (1 M in THF; 0.1 ml; 100 μmol) was added to a solution of aldehyde **59** (35 mg; 58 μmol) in ether (10 ml) at -78 °C. After stirring for 30 min the excess reagent was decomposed with H_2O. The mixture was treated with 30% aqueous H_2O_2 solution (0.25 ml) and 25% aqueous KOH solution (0.15 ml) and stirred for 2 h at 0 °C. Then ether (25 ml) and H_2O (5 ml) were added and the ethereal layer was separated. It was washed with 5% aqueous HCl solution (10 ml), sat. aqueous $NaHCO_3$ (10 ml) and H_2O (2 x 10 ml), and the solvent was evaporated to yield **64** (31 mg; 51 μmol; 89%), identical to a sample prepared by method A.

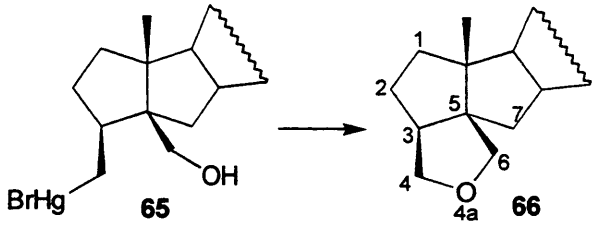
3β-[(Bromomercurio)methyl]-5-(hydroxymethyl)-A,B-bisnor-5β-cholestane (65)



Mercuric bromide (48 mg; 133 μmol) was added to a stirred solution of **64** (80 mg; 133 μmol) in DME (10 ml). The mixture was stirred for 2 h, then diluted with ether (40 ml) and quenched with H_2O (15 ml). The organic layer was washed with sat. aqueous $NaHCO_3$ solution (2 x 20 ml) and H_2O (20 ml), then dried and the solvent removed. The residue was chromatographed using a petroleum ether-ether mixture (19:1) as the eluant, which afforded **65** (80 mg; 120 μmol; 90%): mp 154 - 156 °C ($CHCl_3$/MeOH); $[\alpha]_D$ +24.6° (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2) ν(O–H) 3610 and 3480 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.63 (s, 3 H, 18-H), 0.857 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.860 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.90 (s, 3 H, 19-H), 3.54 and 3.71 (AB system, J = 10.7 Hz, 2 H, 6-H); ^{13}C NMR (62.90 MHz, CD_2Cl_2) δ 12.39 (C-18), 18.87

(C-21), 19.04 (C-19), 22.83 (CH_2), 22.67 (C-26 or C-27), 22.91 (C-26 or C-27), 23.98 (CH_2), 24.63 (CH_2), 28.09 (CH), 28.64 (CH_2), 35.77 (CH), 35.98 (CH_2), 36.33 (CH_2), 36.67 (CH_2), 38.53 (CH_2), 39.59 (CH_2), 39.88 (CH_2), 40.98 (CH_2), 41.29 (CH), 43.89 (C-13), 49.67 (CH), 52.73 (C-10), 55.84 (CH), 56.60 (CH), 58.31 (CH), 58 69 (C-5), 64.27 (C-6); MS CI *m/z* (%) 686 (0.4, $[M + NH_4]^+$), 656 (0.2), 404 (77), 388 (77), 371 (46), 358 (85), 341 (21), 247 (40), 231 (50), 203 (48). Anal. Calcd for $C_{27}H_{47}BrHgO$: C, 48.54; H, 7.09. Found: C, 48.37; H, 7.00.

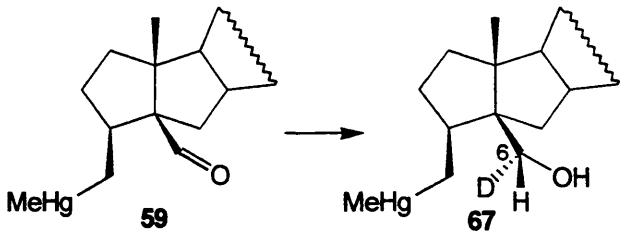
4a-Oxa-A-bishomo-B-nor-3,5-cyclo-5α-cholestane (66)



Bromine (0.5 M in chloroform; 0.3 ml; 150 μmol) was added to a solution of bromomercurio alcohol **65** (70 mg; 105 μmol) in DME (10 ml) at 0 °C. The mixture was allowed to warm to rt and was stirred for 5 h. After that time, the TLC analysis showed the reaction to be complete hence the excess reagent was decomposed by addition of sat. aqueous sodium thiosulphate solution (5 ml). Extraction of the product with ether (25 ml) followed by the workup and removal of the solvent gave tetrahydrofuran **66,** which was recrystalised from a mixture of chloroform and methanol to yield pure **66** (35 mg; 91 μmol; 86%): mp 106 - 108 °C ($CHCl_3$/MeOH); $[\alpha]_D$ +37.1° (*c* 10); ^1H NMR (400 MHz) δ 0.65 (s, 3 H, 18-H), 0.876 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.880 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.91 (s, 3 H, 19-H), 0.94 (d, J = 6.5 Hz, 3 H, 21-H), 1.06 (m, 1 H, 12β-H), 1.25 (m, 1 H, 7α-H), 1.71 (m, 1 H, 7β-H), 2.04 (m, 1 H, 12α-H), 2.26 (m, 1 H, 3α-H), 3.38 (d, J = 9.1 Hz, 1 H, 6α-H), 3.43 (dd, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 8.8 Hz, $J_{3\alpha\text{-H},4\beta\text{-H}}$ = 4.8 Hz, 1 H, 4β-H), 3.92 (t, J = 9.0 Hz, 1 H, 4α-H), 3.97 (d, J = 9.1 Hz, 1 H, 6β-H); NOE:

2.26 (3-H) ↔ 1.25 (7α-H), 3.38 (6α-H), 3.92 (4α-H), 2-H and 3.43 (4β-H), 3.38 (6α-H) ↔ 1.71 (7β-H), 1.25 (7α-H) and 0.91 (19-H), 3.43 (4β-H) ↔ 2-H, 2.26 (3-H), 3.92 (4α-H) ↔ 2.26 (3-H), 3.97 (6β-H) ↔ 2-H and 0.91 (19-H); ^{13}C NMR (100.60 MHz) δ 12.25 (C-18), 18.44 (C-19), 18.78 (C-21), 22.11 (C-11), 22.57 (C-26 or C-27), 22.82 (C-26 or C-27), 23.86 (CH_2), 24.53 (CH_2), 28.00 (C-25), 28.55 (2 x CH_2), 35.67 (C-20), 36.25 (CH_2), 37.01 (C-1), 39.50 (C-24), 39.78 (C-12), 41.04 (C-7), 41.19 (C-8), 43.75 (C-13), 52.56 (C-10), 53.26 (C-3), 54.94 (C-9), 55.71 (C-17), 56.67 (C-14), 62.75 (C-5), 74.59 (C-4), 76.43 (C-6); MS EI *m/z* (%) 387 (30), 386 (100, M^+), 246 (12), 237 (29), 231 (89); MS CI *m/z* 404 ($[M + NH_4]^+$). Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.46; H, 11.76.

(6*R*)-[6-^{2}H]-5-(Hydroxymethyl)-3β-[(methylmercurio)methyl]-A,B-bisnor-5β-cholestane - Major Isomer (67)



Method A

A solution of *t*-butanol (542 mg; 7.301 mmol) dissolved in ether (10 ml) was added dropwise to a stirred solution of lithium aluminium deuteride (99 mg; 2.357 mmol) in ether (15 ml), at -78 °C. The mixture was allowed to warm to rt and was stirred for 1 h. Then it was cooled to -78 °C and methyl mercurio aldehyde **59** (140 mg; 232.8 μmol) dissolved in ether (5 ml) was added and the reaction was stirred for 30 min at the same temperature. After this time, the excess reagent was quenched by addition of sat. aqueous NH_4Cl solution (5 ml). The white precipitate was filtered off and the

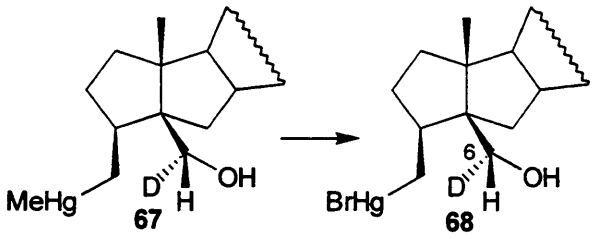
organic layer worked up to furnish amorphous **67** as the major isomer (85%), which was isolated with minor isomer **73** in a total yield of (126 mg; 209 μmol; 90%). **67** characterised in the presence of **73**: IR ν_{max}(O-H) 3620 and 3460 cm^{-1}; ^1H NMR (250 MHz) δ 0.25 (s (83%) and d (17%), $J_{H,Hg}$ = 97.5 Hz, 3 H, $HgCH_3$), 0.62 (s, 3 H, 18-H), 0.861 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.865 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.90 (s, 3 H, 19-H), 3.50 (s, 6-H); ^{13}C NMR (62.90 MHz) δ 12.26 (C-18), 18.75 (CH_3), 19.06 (CH_3), 21.58 ($HgCH_3$), 21.82 (CH_2), 22.56 (C-26 or C-27), 22.81 (C-26 or C-27), 23.84 (CH_2), 24.53 (CH_2), 27.98 (CH), 28.57 (CH_2), 35.67 (CH), 35.76 (CH_2), 36.23 (CH_2), 38.70 (CH_2), 39.48 (CH_2), 39.89 (CH_2), 40.83 (CH_2), 41.25 (CH), 43.42 (CH_2), 43.78 (C-13), 49.49 (CH), 52.15 (C-10), 55.73 (CH), 56.64 (CH), 58.26 (CH), 59.90 (C-5), 64.66 (t, C-6); MS EI m/z 605 (0.5, M^+), 587 (1.1), 572 (1.5), 558 (0.6), 389 (52), 370 (100), 357 (43), 316 (14), 217 (21).

Method B

Super Deuteride® (1 M in THF; 0.2 ml; 200 μmol) was added to a solution of methyl mercurio aldehyde **59** (80 mg; 133 μmol) in THF (20 ml) at -78 °C. The mixture was stirred for 10 min, then the excess reagent was decomposed by adding H_2O (0.5 ml). The reaction was completed by addition of 30% aqueous H_2O_2 solution (0.6 ml) and 25% aqueous KOH solution (0.4 ml), followed by stirring for 3 h. Then the mixture was diluted with ether (40 ml) and worked up to afford amorphous **67** as the major isomer (87%), which was isolated with minor isomer **73** in a total yield of (73 mg; 121 μmol; 91%). **67** characterised in the presence of **73**: ^1H NMR (250 MHz) δ 0.25 (s (82%), d (18%), $J_{H,Hg}$ = 97.8 Hz, 3 H, $HgCH_3$), 0.62 (s, 3 H, 18-H), 0.861 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.864 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.91 (s, 3 H, 19-H), 3.52 (s, 6-H).

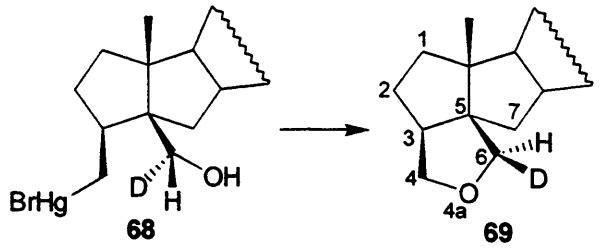
(6*R*)-[6-^{2}H]-3β-[(Bromomercurio)methyl]-5-(hydroxymethyl)-

A,B-bisnor-5β-cholestane - Major Isomer (68)



Mercuric bromide (415 mg; 1.151 mmol) was added to a stirred solution of **67** (679 mg; 1.124 mmol) in DME (25 ml). The mixture was stirred at rt for 2 h, then diluted with ether (60 ml) and H_2O (20 ml). The organic layer was washed with sat. aqueous $NaHCO_3$ solution (2 x 30 ml) and H_2O (30 ml) then the solution was dried and evaporated. The crude product was chromatographed using a petroleum ether-ether mixture (19:1) as the eluant, which afforded **68** as the major isomer (82%), isolated with minor isomer **74** in a total yield of (689 mg; 1.030 mmol; 89%). **68** characterised in the presence of **74**: mp 152 - 154 °C ($CHCl_3$/MeOH) (154 - 156 °C for the non-deuterated compound); IR (CH_2Cl_2) ν(O-H) 3600 and 3470 cm^{-1}; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 0.63 (s, 3 H, 18-H), 0.857 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.861 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.90 (s, 3 H, 19-H), 3.52 (s, 6-H); ^{13}C NMR (62.90 MHz, CD_2Cl_2) δ 12.39 (C-18), 18.94 (C-21), 19.08 (C-19), 22.13 (CH_2), 22.71 (C-26 or C-27) 22.96 (C-26 or C-27), 24.23 (CH_2), 24.87 (CH_2), 28.42 (CH), 28.93 (CH_2), 36.06 (CH_2), 36.10 (CH), 36.63 (2 x CH_2), 38.80 (CH_2), 39.88 (CH_2), 40.24 (CH_2), 41.22 (CH_2), 41.49 (CH_2), 41.49 (CH), 44.16 (C-13), 49.84 (CH), 52.88 (C-10), 56.14 (CH), 56.91 (CH), 58.57 (CH), 58.89 (C-5), 64.06 (t, C-6); MS CI *m/z* (%) 687 (3, $[M + NH_4]^+$), 405 (100), 387 (65), 372 (43), 358 (46), 357 (46), 272 (15), 247 (22), 232 (24), 203 (24).

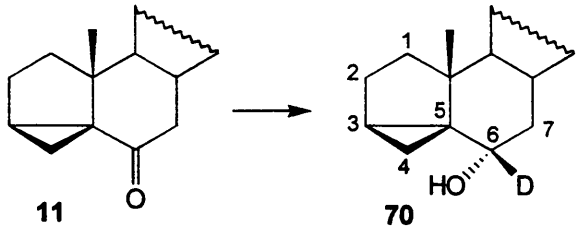
[6β-^{2}H]-4a-Oxa-A-bishomo-B-nor-3,5-cyclo-5α-cholestane - Major isomer (69)



68 **69**

Bromine (0.5 M in chloroform; 0.4 ml; 200 μmol) was added to a solution of bromomercurio alcohol **68** (110 mg; 164 μmol) in DME (10 ml), at 0 °C and the mixture was warmed to rt, then stirred for 5 h. The excess reagent was decomposed by addition of sat. aqueous sodium thiosulphate solution (5 ml), the product was extracted with ether (30 ml) and the organic layer was worked up. The crude product was purified by column chromatography, eluting with a petroleum ether-ether mixture (19:1), which furnished deuterated tetrahydrofuran **69** as the major product (76%), isolated in the presence of minor epimer **75**, in a total yield of (57 mg; 147 μmol; 90%). **69** measured in the presence of **75**: mp 104 - 107 °C ($CHCl_3$/MeOH) (106 - 108 °C for the non-deuterated compound); ^{1}H NMR (250 MHz) δ 0.63 (s, 3 H, 18-H), 0.86 (d, J = 6.5 Hz, 6 H, 26-H and 27-H), 0.89 (s, 3 H, 19-H), 0.92 (d, J = 6.6 Hz, 3 H, 21-H), 2.02 (m, 1 H, 12α-H), 2.27 (m, 1 H, 3α-H), 3.43 (dd, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 8.8 Hz, $J_{3\alpha\text{-H},4\beta\text{-H}}$ = 4.8 Hz, 1 H, 4β-H), 3.91 (t, J = 9.0 Hz, 1 H, 4α-H), 3.36 (s, 6α-H); ^{13}C NMR (62.90 MHz) δ 12.20 (C-18), 18.39 (C-19), 18.73 (C-21), 22.07 (CH_2), 22.53 (C-26 or C-27), 22.78 (C-26 or C-27), 23.84 (CH_2), 24.49 (CH_2), 27.97 (CH), 28.50 (CH_2), 28.53 (CH_2), 35.66 (CH), 36.23 (CH_2), 36.97 (CH_2), 39.48 (CH_2), 39.76 (CH_2), 40.94 (CH_2), 41.16 (CH), 43.71 (C-13), 52.46 (C-10), 53.20 (CH), 54.91 (CH), 55.70 (CH), 56.65 (CH), 62.61 (C-5), 74.54 (C-4), 75.98 (t, C-6); MS EI *m/z* (%) 388 (30), 387 (100, M^+), 247 (13), 233 (30), 232 (90); MS > 97 % ^{2}H (d_1).

[6β-^{2}H]-3α-5-Cyclo-5α-cholestan-6α-ol (70)

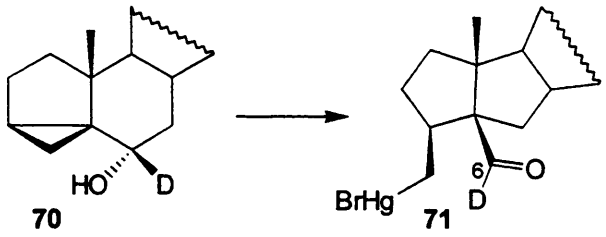


11 **70**

A solution of ketone **11** (2.8 g; 7.279 mmol) in dry ether (50 ml) was added dropwise to lithium aluminium deuteride (305 mg; 7.264 mmol) in dry ether (50 ml) at 0 °C. The mixture was stirred for 1.5 h at 0 °C, then the excess reagent was then decomposed by successive addition of H_2O (0.3 ml), 15% aqueous NaOH solution (0.3 ml), and H_2O (1 ml). The solid residue was filtered off and the organic layer washed with 5% aqueous HCl solution (20 ml), sat. aqueous $NaHCO_3$ solution (20 ml), and H_2O (2 x 20 ml). The solution was dried and evaporated yielding amorphous **70** (2.65 g; 6.836 mmol; 94%): IR ν_{max}(O–H) 3610 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.24 (t, J = 4.1 Hz, 1 H, 4β-H), 0.60 (dd, J = 8.1 Hz and 4.6 Hz, 1 H, 4α-H), 0.68 (s, 3 H, 18-H), 0.863 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.866 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.92 (s, 3 H, 19-H); ^{13}C NMR (62.90 MHz) δ 6.58 (C-4), 12.05 (C-18), 17.94 (C-19), 18.64 (C-21), 18.67 (C-3), 22.57 (C-26 or C-27), 22.82 (C-26 or C-27), 23.17 (CH_2), 23.83 (CH_2), 24.24 (CH_2), 25.07 (CH_2), 28.01 (CH), 28.24 (CH_2), 32.75 (CH_2), 34.94 (CH), 35.78 (CH), 36.13 (CH_2), 39.14 (CH_2), 39.50 (C-13), 39.72 (CH_2), 40.12 (CH_2), 42.72 (C-5 or C-10), 44.94 (C-5 or C-10), 47.65 (CH), 56.23 (CH), 56.26 (CH), 66.93 (t, C-6); MS CI (%) 405 (100, $[M + NH_4]^+$) 387 (40), 357 (59), 342 (21), 301 (40); MS > 98% ^{2}H (d_1).

[6-^{2}H]-3β-[(Bromomercurio)methyl]-A,B-bisnor-

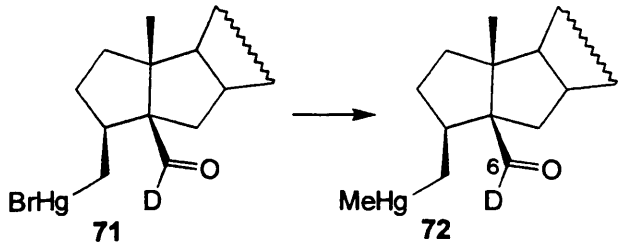
5β-cholestane-5-carbaldehyde (71)



Mercury(II) nitrate monohydrate (2.2 g; 6.421 mmol) was added to a stirred solution of deuterated cyclopropyl alcohol **70** (2.48 g; 6.397 mmol) in DME (30 ml) and acetonitrile (75 ml), then the mixture was stirred for 1.5 h and worked up by adding 10% aqueous KBr solution (20 ml) and ether (70 ml). The organic layer was washed with sat. aqueous $NaHCO_3$ solution (2 x 50 ml) and H_2O (50 ml), then it was dried and the solvent evaporated. The crude product was recrystalised from a mixture of $CHCl_3$ and EtOH (3:2), which yielded pure **71** (3.92 g; 5.876 mmol; 92%): mp 148 - 150 °C (148 - 149.5 °C for the non-deuterated compound); IR (CH_2Cl_2) ν(C=O) 1700 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 0.62 (s, 3 H, 18-H), 0.858 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.862 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.92 (d, J = 6.5 Hz, 3 H, 21-H), 0.94 (s, 3 H, 19-H), 2.44 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.1 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.8 Hz, 1 H, 7β-H); ^{13}C NMR (75.47 MHz, CD_2Cl_2) δ 12.33 (C-18), 18.92 (C-21), 19.79 (C-19), 21.47 (CH_2), 22.69 (C-26 or C-27), 22.93 (C-26 or C-27), 24.22 (CH_2), 24.73 (CH_2), 28.38 (C-25), 28.83 (C-11), 35.09 (C-4), 36.03 (C-20), 36.59 (C-22), 37.03 (C-7), 39.15 (C-2), 39.71 (C-1), 39.83 (C-12 or C-24), 39.90 (C-12 or C-24), 44. 05 (C-13), 44.67 (C-8), 53.34 (C-3), 56.08 (C-17), 57.12 (C-14), 58.41 (C-10), 59.52 (C-9), 70.84 (C-5), 206.07 (t, C-6); MS CI (%) 685 (1, $[M + NH_4]^+$), 405 (100), 388 (26), 357 (24), 262 (26), 207 (22), 126 (41), 74 (58).

[6-^{2}H]-3β-[(Methylmercurio)methyl]-A,B-bisnor-

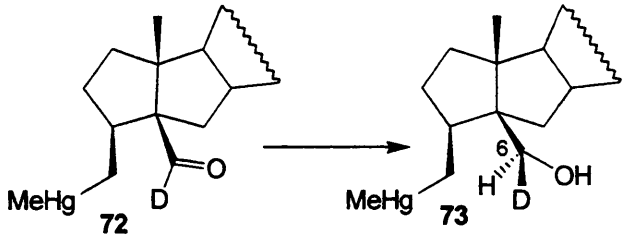
5β-cholestane-5-carbaldehyde (72)



Methyl lithium (1.4 M in ether; 1.7 ml; 2.365 mmol) was added to a suspension of copper(I) iodide (450 mg; 2.365 mmol) in dry ether (30 ml) at -35 °C. The resulting mixture was stirred at -35 °C for 10 min and then it was cooled to -78 °C. A solution of organomercurial **71** (312 mg; 468 μmol) in THF (5 ml) was added and the mixture was stirred for an further 5 min. The excess reagent was decomposed by addition of 5% aqueous HCl solution (5 ml), then the mixture was diluted with ether (20 ml) and allowed to warm to rt. The organic layer was separated and washed with sat. aqueous $NaHCO_3$ solution (2 x 15 ml) and H_2O (2 x 15 ml), then dried and the solvent evaporated yielding oily methylmercurial **72** (270 mg; 449 μmol; 96%): IR ν_{max}(C=O) 1707 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.28 (s (83 %) and d (17 %), $J_{H,Hg}$ = 101.0 Hz, 3 H, $HgCH_3$), 0.59 (s, 3 H, 18-H), 0.855 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.857 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.89 (s, 3 H, 19-H), 2.35 (m, 1 H, 3α-H), 2.45 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.1 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.8 Hz, 1 H, 7β-H); ^{13}C NMR (62.90 MHz) δ 12.18 (C-18), 18.74 (C-21), 19.55 (C-19), 20.97 ($HgCH_3$), 21.06 (CH_2), 22.54 (C-26 or C-27), 22.79 (C-26 or C-27), 23.83 (CH_2), 24.36 (CH_2), 27.96 (C-25), 28.47 (C-11), 35.61 (CH), 36.19 (CH_2), 36.39 (CH_2), 39.43 (CH_2), 39.56 (CH_2), 39.71 (CH_2), 39.89 (CH_2), 42.24 (CH_2), 43.65 (C-13), 44.00 (C-8), 54.33 (CH), 55.72 (CH), 56.85 (CH), 57.31 (C-10), 59.44 (C-14), 71.38 (C-5), 206.91 (t, C-6); MS EI *m/z* (%) 602 (0.2, M^+), 559 (8), 548 (4), 386

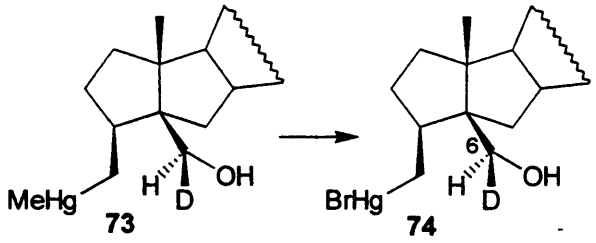
(100), 368 (11); MS CI *m/z* (%) 621 (4, $[M + NH_4]^+$), 605 (8), 586 (3), 559 (5), 548 (3), 405 (40), 386 (100), 357 (10), 234 (50).

(6*S*)-[6-^{2}H]-5-(Hydroxymethyl)-3β-[(methylmercurio)methyl]-A,B-bisnor-5β-cholestane - Major Isomer (73)



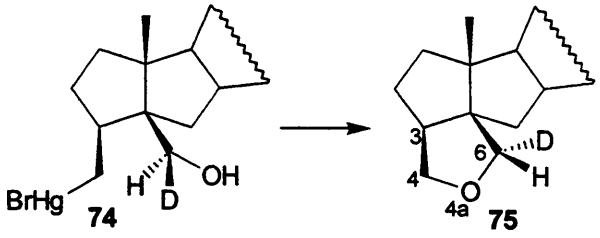
A solution of *t*-butanol (185 mg; 2.491 mmol) dissolved in ether (20 ml) was added dropwise to a stirred solution of lithium aluminium hydride (31.5 mg; 830 μmol) in ether (15 ml), at -78 °C. The mixture was allowed to warm to rt and was stirred for 1 h. Then it was cooled to -78 °C and methyl mercurio aldehyde **72** (57 mg; 95 μmol) dissolved in ether (5 ml) was added and the reaction was stirred for 30 min at the same temperature. After this time, the excess reagent was quenched by addition of sat. aqueous NH_4Cl solution (5 ml). The white precipitate was filtered off and the organic layer worked up to furnish amorphous **73** as the major isomer (84%), which was isolated with minor isomer **67** in a total yield of (52 mg; 86 μmol; 91%). **73** was characterised in the presence of **67**: ^{1}H NMR (250 MHz) δ 0.25 (s (83%) and d (17%), $J_{H,Hg}$ = 97.5 Hz, 3 H, $HgCH_3$), 0.61 (s, 3 H, 18-H), 0.861 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.865 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.90 (s, 3 H, 19-H), 3.71 (s, 6-H).

(6*S*)-[6-^{2}H]-3β-[(Bromomercurio)methyl]-5-(hydroxymethyl)-A,B-bisnor-5β-cholestane - Major Isomer (74)



Mercuric bromide (51 mg; 142 μmol) was added to a stirred solution of **73** (82 mg; 136 μmol) in DME (10 ml). The reaction was stirred at rt for 2 h, then diluted with ether (40 ml) and H_2O (15 ml). The organic layer was washed with sat. aqueous $NaHCO_3$ solution (2 x 20 ml) and H_2O (20 ml), then the solution was dried and evaporated, to furnish **74** as the major isomer (81%), isolated with minor isomer **68**, in a total yield of (82.4 mg; 123 μmol; 91%): mp 153 - 155 °C ($CHCl_3$/MeOH) (154 - 156 °C for the non-deuterated compound); ^{1}H NMR (250 MHz, CD_2Cl_2) δ 0.63 (s, 3 H, 18-H), 0.856 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.860 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.90 (s, 3 H, 19-H), 3.69 (s, 6-H).

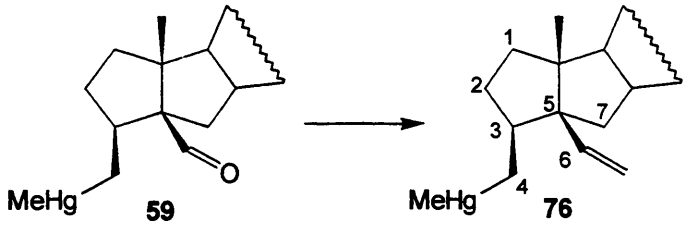
[6α-^{2}H]-4a-Oxa-A-bishomo-B-nor-3,5-cyclo-5α-cholestane - Major isomer (75)



Bromine (0.5 M in chloroform; 0.45 ml; 225 μmol) was added to a solution of bromomercurio alcohol **74** (142 mg; 212 μmol) in DME (10 ml) at 0 °C. The mixture was warmed to rt and stirred for 5 h, then the excess reagent was decomposed by addition of sat. aqueous sodium thiosulphate solution (5 ml). The product was extracted with ether (30 ml) and the organic layer worked up. Purification by column

chromatography, using a petroleum ether-ether mixture (19:1) as the eluant, furnished **75** as the major product (79%), isolated in the presence of minor isomer **69**, in a total yield of (71 mg; 184 μmol; 87%). **75**: mp 104 - 106 °C ($CHCl_3$/MeOH) (106 - 108 °C for the non-deuterated compound); ^1H NMR for **75** measured in the presence of **69**, (250 MHz) δ 0.64 (s, 3 H, 18-H), 0.86 (d, J = 6.6 Hz, 6 H, 26-H and 27-H), 0.89 (s, 3 H, 19-H), 0.92 (d, J = 6.6 Hz, 3 H, 21-H), 2.03 (m, 1 H, 12α-H), 2.26 (m, 1 H, 3α-H), 3.43 (dd, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 8.8 Hz, $J_{3\alpha\text{-H},4\beta\text{-H}}$ = 4.7 Hz, 1 H, 4β-H), 3.91 (t, J = 8.8 Hz, 1 H, 4α-H), 3.94 (s, 6β-H). MS > 97% ^2H (d_1).

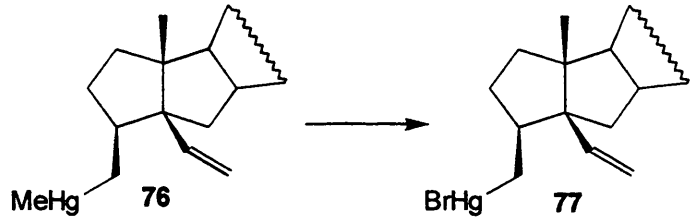
3β-[(Methylmercurio)methyl]-5-(vinyl)-A,B-bisnor-5β-cholestane (76)



Titanocene dichloride (243 mg; 976 μmol) was placed in a dry two neck flask with a condenser and a septum attached. Freshly dried toluene (2 ml) was added, and the flask was cooled to -78 °C. Trimethyl aluminium (2 M in toluene; 1 ml; 2 mmol) was added and the mixture was warmed slowly to 65 °C, then heated at this temperature for 18 h. After cooling to 0 °C, a solution of methyl mercurio aldehyde **59** (197 mg; 327 μmol) in THF (10 ml) was added to the flask. The solution was allowed to warm to rt and was stirred for 30 min. The mixture was then poured into cooled ether (40 ml) and worked up with 15% aqueous NaOH solution (5 ml). After leaving to stand for 10 min, to allow precipitation of the titanium salts, the ethereal solution was dried and the residue was purified by column chromatography, using hexane as the eluant, affording **76** (192 mg; 32 μmol; 98%) as a colourless oil: $[\alpha]_D$ +25.7° (*c* 2.0); IR ν_{max}(C=C)

1632 cm^{-1}, ν_{max}(CH=CH_2) 906 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.19 (s (81%) and d (19%), $J_{H,Hg}$ = 101.1 Hz, 3 H, $HgCH_3$, 0.61 (s, 3 H, 18-H), 0.74 (s, 3 H, 19-H), 0.862 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.866 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 2.10 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.3 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.9 Hz, 1 H, 7β-H), 2.30 (m, 1 H, 4-H), 5.03 (m, 2 H, CHCH_2), 5.84 (dd, J_{trans} = 17.3 Hz, J_{cis} = 11.0 Hz, 1 H, C-6); ^{13}C NMR (62.90 MHz) δ 12.31 (C-18), 18.80 (C-21), 20.96 (CH_3), 21.49 (CH_3), 21.72 (CH_2), 22.59 (C-26 or C-27), 22.84 (C-26 or C-27), 23.91 (CH_2), 24.58 (CH_2), 28.02 (CH), 28.61 (CH_2), 35.73 (CH), 36.30 (CH_2), 38.40 (CH_2), 38.86 (CH_2), 38.90 (CH_2), 39.54 (CH_2), 39.95 (CH_2), 41.96 (CH_2), 43.39 (CH), 43.82 (C-13), 54.87 (C-10), 55.08 (CH), 55.83 (CH), 57.10 (CH), 59.02 (CH), 63.01 (C-5), 111.28 (CH=CH_2), 142.44 (C-6); MS EI *m/z* (%) 599 (4, M^+), 384 (35, M^+- $HgCH_3$), 383 (100), 341 (28), 257 (14), 229 (11), 215 (14), 189 (13), 175 (15), 161 (14); HRMS EI *m/z* 599.35406 (calcd for $C_{29}H_{50}Hg$: 599.35406).

3β-[(Bromomercurio)methyl]-5-(vinyl)-A,B-bisnor-5β-cholestane (77)



Mercuric bromide (18 mg; 50 μmol) was added to a solution of methyl mercurial **76** (30 mg; 49 μmol) in DME (10 ml) and the mixture stirred at rt for 2 h. Ether (40 ml) and H_2O (10 ml) were added and the ethereal layer was washed with sat. aqueous $NaHCO_3$ solution (20 ml) and H_2O (2 x 20 ml), and the solution was dried and evaporated. Purification by column chromatography using petroleum ether as the eluant furnished 77 (31 mg; 47 μmol; 96%): mp 97 - 98 °C (petroleum ether/MeOH); $[\alpha]_D$ +28.0° (*c* 1.5); IR ν_{max}(C=C) 1632 cm^{-1}, ν_{max}(CH=CH_2) 907 cm^{-1}; ^{1}H NMR (250 MHz)

δ 0.62 (s, 3 H, 18-H), 0.78 (s, 3 H, 19-H), 0.872 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.875 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 2.15 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.3 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.9 Hz, 1 H, 7β-H), 2.32 (m, 1 H, 4-H), 5.18 (m, 2 H, CH=CH_2), 5.82 (dd, J_{trans} = 17.6 Hz, J_{cis} = 11.0 Hz, 1 H, 6-H); ^{13}C NMR (62.90 MHz) δ 12.23 (C-18), 18.72 (C-21), 20.61 (C-19), 21.51 (CH_2), 22.52 (C-26 or C-27), 22.78 (C-26 or C-27), 23.80 (CH_2), 24.47 (CH_2), 27.91 (CH), 28.47 (CH_2), 35.59 (CH), 35.67 (CH_2), 36.17 (CH_2), 36.92 (CH_2), 38.01 (CH_2), 38.29 (CH_2), 39.42 (CH_2), 39.71 (CH_2), 43.27 (CH), 43.72 (C-13), 53.39 (CH), 55.24 (C-10), 55.67 (CH), 56.84 (CH), 58.77 (CH), 62.36 (C-5), 113.78 (C=*C*H_2), 140.76 (C-6); MS EI *m/z* (%) 665 (2), 650 (4), 552 (2), 384 (100), 342 (32), 257 (17), 215 (16); MS CI *m/z* (%) 683 (0.1, $[M + NH_4]^+$); HRMS EI *m/z* 665.26457 (calcd for $C_{28}H_{47}BrHg$: 665.26457). Anal. Calcd for $C_{28}H_{47}BrHg$: C, 50.64; H, 7.13. Found: C, 50.69; H, 7.00.

Reductive Demercuration of Bromomercurio Aldehyde 20

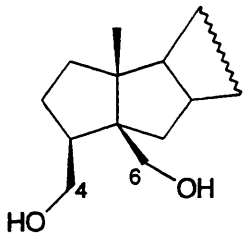
Organomercurial **20** (1.494 g; 2.243 mmol) was placed in a Dreschler bottle and dissolved in DMF (45 ml). A septum was fixed to the bottle and one large bore needle was used as a vent. Three syringe needles were extended to the base of the container and were used to pass oxygen through the mixture for 10 min, maintaining a pressure of 8 lb/in^2. A mixture of sodium borohydride (270 mg; 7.137 mmol) and DMF (31 ml) was then added dropwise, over a period of 10 min. Oxygen was bubbled through the mixture during this time and for an additional 5 min after the addition of the sodium borohydride mixture. The oxygen supply was then turned off and the reaction quenched with H_2O (5 ml). Allowing the mixture to stand facilitated precipitation of elemental mercury, which was then separated from the solution by decantation. (If the mercury did not drop out of

solution, the mixture was centrifuged.) Ether (60 ml) and 15% aqueous NaCl solution (30 ml) were added to the supernatant and the organic layer was separated. The ethereal layer was washed with sat. aqueous $NaHCO_3$ (30 ml) and 15% aqueous NaCl solution (2 x 30 ml), then the solution was dried and the crude product chromatographed. Elution with a petroleum ether-ether mixture (23:2) yielded alcohol **80** (17 mg; 44 μmol; 2%) as the least polar component; lactol **14** (334 mg; 829 μmol; 37%) was eluted with (4:1) mixture and diol **79** (445 mg; 1.100 mmol; 49%) was obtained as the most polar component using a petroleum ether-ether-acetone mixture (8:1:1).

Reductive Demercuration of Bromomercurio Alcohol 65

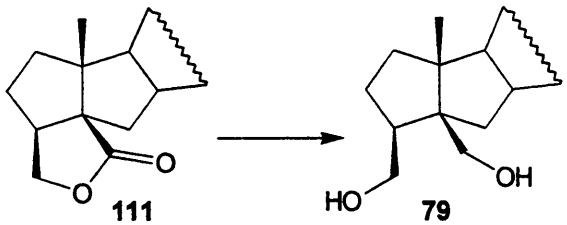
The reaction procedure used for this experiment was the same as explained above. Bromomercurio alcohol **65** (712 mg; 1.066 mmol) was dissolved in DMF (21 ml) and the solution was saturated with oxygen. A mixture of sodium borohydride (56 mg: 1.480 mmol) and DMF (7 ml) was added dropwise, over a period of 10 min, then the reaction was worked up. The crude mixture was purified by chromatography using a petroleum ether-ether mixture (4 : 1) to elute alcohol **80** (8 mg; 21 μmol; 2%), as the least polar component; diol **79** (362 mg; 895 μmol; 84%) was obtained using a mixture of petroleum ether, ether and acetone (8:1:1).

3β-(Hyroxymethyl)-5-(hydroxymethyl)-A,B-bisnor-5β-cholestane (79)



Reductive demercuration of bromomercurial **65** afforded diol **79** in 84% yield: mp 145 - 146.5 °C (acetone); $[\alpha]_D$ +16.8° (*c* 1.5); IR ν_{max}(O–H) 3610 and 3420, ν_{max}(C–O) 1040 cm^{-1}; ^1H NMR (250 MHz) δ 0.63 (s, 3 H, 18-H), 0.83 (s, 3 H, 19-H), 0.86 (d, J = 6.6 Hz, 6 H, 26-H and 27-H), 0.89 (d, J = 6.6 Hz, 3 H, 21-H), 3.05 (br s, 2 H, OH), 3.38 and 3.83 (AB system, $J_{6\alpha\text{-H},6\beta\text{-H}}$ = 11.0 Hz, 2 H, 6-H), 3.62 and 3.79 (ABX system, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 11.2 Hz, $J_{3\alpha\text{-H},4\text{-H}}$ = 3.6 Hz, 2 H, 4-H); ^{13}C NMR (62.90 MHz) δ 12.22 (C-18), 18.61 (C-19), 18.74 (C-21), 21.94 (CH_2), 22.53 (C-26 or C-27), 22.79 (C-26 or C-27), 23.83 (CH_2), 24.51 (CH_2), 27.54 (CH_2), 27.98 (CH), 28.56 (CH_2), 35.65 (CH), 36.20 (CH_2), 39.45 (CH_2), 39.46 (CH_2), 39.79 (CH_2), 40.39 (CH), 42.06 (CH_2), 43.69 (C-13), 51.73 (CH), 52.13 (C-10), 55.79 (CH), 56.32 (CH), 57.83 (CH), 57.86 (C-5), 64.14 (C-4 or C-6), 64.97 (C-4 or C-6); MS EI *m/z* (%) 404 (2, M^+), 387 (30), 386 (100), 374 (14), 373 (13), 371 (15), 358 (13), 357 (25), 356 (73), 355(24), 327 (11), 247 (12), 246 (19), 233 (17), 232 (55), 231 (49), 219 (15), 215 (24), 213 (19), 201 (18), 177 (11), 173 (13), 161 (12), 159 (16); HRMS EI *m/z* 404.36546 (calcd for $C_{27}H_{48}O_2$: 404.36543).

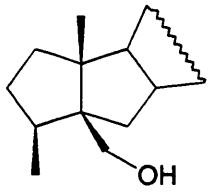
Method B



111 **79**

A solution of lactone **111** (60 mg; 150 μmol) in ether (10 ml) was added to lithium aluminium hydride (11 mg; 295 μmol) in ether (15 ml) at 0 °C. The mixture was stirred at rt for 45 min and then worked up. The solvent was removed yielding diol **79** (54 mg; 134 μmol; 89 %), which was identical to a sample prepared by reductive demercuration.

5-(Hydroxymethyl)-3β-Methyl-A,B-bisnor-5β-cholestane (80)



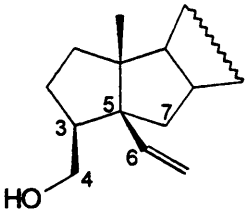
Reductive demercuration of bromomercurial **20** furnished alcohol **80** in 2% yield: IR ν_{max}(O–H) 3615 cm^{-1}; ^1H NMR (250 MHz) δ 0.63 (s, 3 H, 18-H), 0.85 (s, 3 H, 19-H), 0.86 (d, J = 6.9 Hz, 6 H, 26-H and 27-H), 0.99 (d, J = 6.9 Hz, 3 H, 4-H), 3.42 and 3.66 (AB system, J = 10.7 Hz, 2 H, 6-H); ^{13}C NMR (62.90 MHz) δ 12.66 (C-18), 16.39 (C-4), 19.17 (CH_3), 19.33 (CH_3), 22.49 (CH_2), 22.98 (C-26 or C-27), 23.23 (C-26 or C-27), 24.27 (CH_2), 24.97 (CH_2), 28.41 (CH), 29.01 (CH_2), 31.42 (CH_2), 36.10 (CH), 36.65 (CH_2), 38.97 (CH_2), 39.91 (CH_2), 40.32 (CH_2), 40.77 (CH), 41.57 (CH_2), 43.20 (CH), 44.16 (C-13), 52.05 (C-10), 56.16 (CH), 56.76 (CH), 58.11 (C-5), 58.14 (CH), 65.12 (C-6); MS EI *m/z* (%) 389 (30), 388 (100), 370 (21), 357 (27), 248 (18), 234 (29), 233 (54), 217 (16), 205 (25), 203 (19).

Reductive Demercuration of Bromomercurial 77

This reaction was carried out using the same apparatus and procedure as described for bromomercurial **20**. A mixture of sodium borohydride (450 mg; 11.895 mmol) and DMF (50 ml) was added dropwise, to an oxygen saturated solution of bromomercurial **77** (5.303 g; 7.984 mmol) in DMF (135 ml). The reaction was worked up and the crude mixture was chromatographed using petroleum ether-ether mixtures to obtain the products. Compound **83** (46 mg; 120 μmol; 1%) was eluted first using a (97:3) mixture of the solvents. Alcohol **81** (2.431 g; 6.067 mmol; 51%) was separated

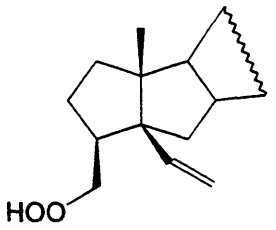
with a (19:1) mixture, and peroxide **82** (2.082 g; 4.997 mmol; 42%) was obtained using a (9:1) mixture.

3β-(Hydroxymethyl)-5-(vinyl)-A,B-bisnor-5β-cholestane (81)



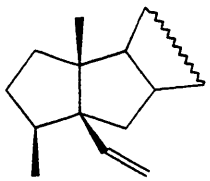
Reductive demercuration of bromomercurial **77** furnished alcohol **81** in 51 % yield: $[\alpha]_D$ +45.4° (*c* 1.9); IR ν_{max}(O–H) 3628 cm^{-1}, ν(C=C) 1632 cm^{-1}, ν(C–O) 1080 cm^{-1} and ν(CH=CH_2) 906 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.62 (s, 3 H, 18-H), 0.77 (s, 3 H, 19-H), 0.875 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.879 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.92 (d, J = 6.6 Hz, 3 H, 21-H), 2.23 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.6 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.6 Hz, 1 H, 7β-H), 3.53 (ABX system, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 11.1 Hz, $J_{3\alpha\text{-H},4\text{-H}}$ = 7.2 Hz, 2 H, 4-H), 5.07 (dd, J_{cis} = 10.9 Hz, J_{gem} = 1.6 Hz, 1 H, CH=CH_2), 5.11 (dd, J_{trans} = 17.5 Hz, J_{gem} = 1.6 Hz, 1 H, CH=CH_2), 5.88 (dd, J_{trans} = 17.5 Hz, J_{cis} = 10.9 Hz, 1 H, 6-H); ^{13}C NMR (62.90 MHz) δ 12.25 (C-18), 18.76 (C-21), 20.42 (C-19), 21.85 (CH_2), 22.55 (C-26 or C-27), 22.80 (C-26 or C-27), 23.87 (CH_2), 24.50 (CH_2), 27.99 (CH), 28.57 (CH_2), 28.79 (CH_2), 35.68 (CH), 36.25 (CH_2), 38.46 (CH_2), 39.50 (CH_2), 39.60 (CH_2), 39.83 (CH_2), 42.48 (CH), 43.77 (C-13), 55.22 (C-10), 55.74 (CH), 56.24 (CH), 56.80 (CH), 58.36 (CH), 59.89 (C-5), 64.09 (C-4), 111.44 (CH=CH_2), 140.44 (C-6); MS EI *m/z* (%) 400 (21, M^+), 386 (16), 385 (55), 370 (30), 369 (100), 245 (13), 161 (11); HRMS EI *m/z* 400.37051 (calcd for $C_{28}H_{48}O$: 400.37052). Anal. Calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.07. Found: C, 84.27; H, 11.89.

3β-(Peroxymethyl)-5-(vinyl)-A,B-bisnor-5β-cholestane (82)



Reductive demercuration of bromomercurial **77** furnished peroxide **82** in 42 % yield: $[\alpha]_D$ + 62.3° (*c* 3.0); IR ν_{max}(O-H) 3533 and 3425 cm^{-1}, ν_{max}(C=C) 1632 cm^{-1}, ν_{max}(CH=CH_2) 906 cm^{-1}, ν_{max}(O-O) 855 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.62 (s, 3 H, 18-H), 0.77 (s, 3 H, 19-H), 0.87 (d, *J* = 6.6 Hz, 3 H, 26-H and 27-H), 0.90 (d, *J* = 6.6 Hz, 3 H, 21-H), 2.19 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.7 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.8 Hz, 7β-H), 3.81 (t, *J* = 9.1 Hz, 1 H, 4-H), 3.98 (dd, *J* = 5.4 and 9.8 Hz, 1 H, 4-H), 5.05 (m, 2 H, CH=CH_2), 5.77 (dd, J_{trans} = 17.8 Hz, J_{cis} = 11.0 Hz, 1 H, 6-H); ^{13}C NMR (62.90 MHz) δ 12.23 (C-18), 18.74 (C-21), 20.37 (C-19), 21.77 (CH_2), 22.53 (C-26 or C-27), 22.78 (C-26 or C-27), 23.86 (CH_2), 24.48 (CH_2), 27.97 (CH), 28.55 (CH_2), 29.52 (CH_2), 35.66 (CH), 36.24 (CH_2), 38.29 (CH_2), 38.86 (CH_2), 39.49 (CH_2), 39.82 (CH_2), 42.46 (CH), 43.76 (C-13), 51.26 (CH), 54.75 (C-10), 55.74 (CH), 56.82 (CH), 58.32 (CH), 60.25 (C-5), 78.52 (C-4), 111.66 (CH=CH_2), 139.60 (C-6); MS EI *m/z* (%) 416 (3, M^+), 401 (13), 400 (19), 399 (29), 398 (46), 386 (33), 385 (100), 383 (15), 370 (30), 369 (78), 355 (19), 340 (19), 327 (13), 245 (12), 243 (13), 173 (12), 161 (14), 159 (12); HRMS EI *m/z* 416.36544 (calcd for $C_{28}H_{48}O_2$: 416.36543).

3β-(Methyl)-5-(vinyl)-A,B-bisnor-5β-cholestane (83)

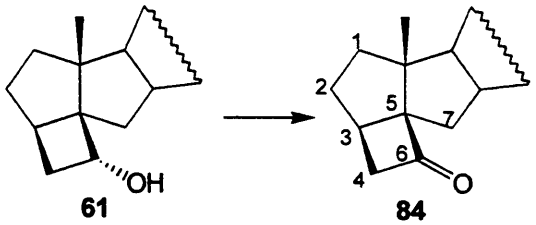


Reductive demercuration of bromomercurial **77** furnished compound **81** in 1 % yield: $[\alpha]_D$ +39.1° (*c* 3.2); IR ν_{max}(C=C) 1632 cm^{-1}, ν_{max}(CH=CH_2) 906 cm^{-1}; ^1H NMR (250 MHz) δ 0.62 (s, 3 H, 18-H), 0.76 (s, 3 H, 19-H), 0.80 (d, J = 6.9 Hz, 3 H, 4-H), 0.872 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.875 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.92 (d, J = 6.6 Hz, 3 H, 21-H), 2.12 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.6 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.6 Hz, 1 H, 7β-H) 5.00 (m, 2 H, CH=CH_2), 5.80 (dd, J_{trans} = 16.7 Hz, J_{cis} = 11.6 Hz, 1 H, 6-H); ^{13}C NMR (62.90 MHz) δ 12.28 (C-18), 15.28 (C-4), 18.77 (C-21), 20.96 (C-19), 21.87 (CH_2), 22.56 (C-26 or C-27), 22.81 (C-26 or C-27), 23.88 (CH_2), 24.55 (CH_2), 28.00 (CH), 28.61 (CH_2), 33.48 (CH_2), 35.71 (CH), 36.28 (CH_2), 38.45 (CH_2), 38.81 (CH_2), 39.52 (CH_2), 39.95 (CH_2), 42.42 (CH), 43.80 (C-13), 47.86 (CH), 54.53 (C-10), 55.79 (CH), 56.96 (CH), 58.52 (CH), 61.09 (C-5), 110.71 (CH=CH_2), 141.30 (C-6); MS EI *m/z* (%) 385 (20), 384 (66, M^+), 370 (30), 369 (100), 327 (12), 288 (12), 271 (19), 230 (16), 229 (54), 174 (15), 173 (13), 161 (19), 159 (14); HRMS EI *m/z* 384.37559 (calcd for $C_{28}H_{48}$: 84.37560).

EXPERIMENTAL

CHAPTER THREE

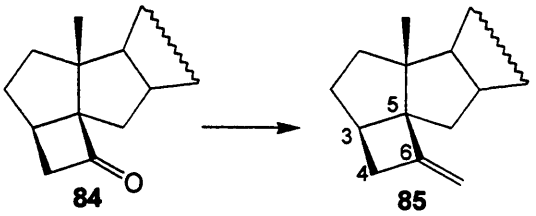
A-Homo-B-nor-3,5-cyclo-5α-cholestane-6-one (84)[42]



61 **84**

Jones' reagent (2.67 M; 1.2 ml) was added to a solution of cyclobutanol **61** (900 mg; 2.327 mmol) in acetone (20 ml) at 0 °C and the mixture was stirred for 10 min. The excess reagent was decomposed with methanol (5 ml) and the mixture was diluted with ether (30 ml) and H_2O (10 ml). The chromium salts were filtered off and the organic layer was washed with sat. aqueous $NaHCO_3$ solution (15 ml) and H_2O (2 x 15 ml). Column chromatography was used to purify the residue, using a petroleum ether-ether mixture (19 : 1) as the eluant, which afforded **84** (850 mg; 2.210 mmol; 95%): mp 117 - 119 °C (acetone), identical with an authentic sample (mp 112 - 115 °C);[43] IR ν_{max}(C=O) 1755 cm^{-1}; ^1H NMR (250 MHz) δ 0.63 (s, 3 H, 18-H), 0.87 (d, J = 6.6 Hz, 6 H, 26-H and 27-H), 0.93 (s, 3 H, 19-H), 2.26 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 13.5 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 7.6 Hz, 1 H, 7β-H), 2.30 (m, 1 H, 3α-H), 2.58 (dd, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 17.6 Hz, $J_{3\alpha\text{-H},4\beta\text{-H}}$ = 6.6 Hz, 1 H, 4β-H), 2.87 (dd, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 17.6 Hz, $J_{3\alpha\text{-H},4\alpha\text{-H}}$ = 8.5 Hz, 1 H, 4α-H); ^{13}C NMR (62.90 MHz) δ 12.21 (C-18), 18.74 (C-21), 19.65 (C-19), 21.83 (CH_2), 22.54 (C-26 or C-27), 22.79 (C-26 or C-27), 23.82 (CH_2), 24.26 (CH_2), 27.97 (CH), 28.50 (CH_2), 30.37 (CH_2), 35.05 (CH_2), 35.60 (CH), 35.74 (CH_2), 36.19 (CH_2), 39.46 (CH_2), 39.48 (CH_2), 39.86 (CH), 41.86 (CH), 44.01 (C-13), 47.21 (CH_2), 53.35 (CH), 55.66 (CH), 56.71 (CH), 58.64 (C-10), 83.91 (C-5), 212.98 (C-6); MS CI *m/z* (%) 402 (100, $[M + NH_4]^+$), 385 (29, MH^+).

6-Methylene-A-Homo-B-nor-3,5-cyclo-5α-cholestane (85)

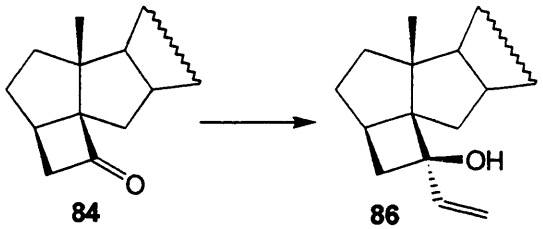


84 85

Titanocene dichloride (184 mg; 739 μmol) was placed in a dry two-neck flask fitted with a condenser and a septum. Freshly dried toluene (3 ml) was added and the mixture cooled to -78 °C. Trimethyl aluminium (2 M in toluene; 0.8 ml; 1.6 mmol) was added to the flask, then the mixture was allowed to warm slowly and was heated at 65 °C for 18 h. Then the reaction was then cooled to 0 °C and a solution of cyclobutanone **84** (80 mg; 208 μmol) in THF (10 ml) was added. The mixture was heated at 65 °C for 2 h, it was allowed to cool, then was poured into ice-cold ether (40 ml) and worked up with 15% aqueous NaOH solution (5 ml). After leaving to stand for 10 min to allow precipitation of the titanium salts, the ethereal solution was dried and the solvent was removed. The residue was adsorbed onto silica gel, and the mixture was placed on the top of a chromatography column. The product was flushed through the column using petroleum ether as the eluant, and the solvent was evaporated, to furnish **85** (69 mg; 180 μmol; 87%) as a colourless oil: $[\alpha]_D$ +15.1° (*c* 3.6); IR ν_{max}(C=C) 1666 cm^{-1}, ν_{max}(C=CH_2) 872 cm^{-1}; ^1H NMR (250 MHz) δ 0.65 (s, 3 H, 18-H), 0.86 (s, 3 H, 19-H), 0.872 (d, *J* = 6.6 Hz, 3 H, 26-H or 27-H), 0.875 (d, *J* = 6.6 Hz, 3 H, 26-H or 27-H), 0.93 (d, *J* = 6.6 Hz, 3 H, 21-H), 2.30 (m, 1 H, 4-H), 2.57 (dddd, *J* = 15.5, 8.4 2.0 and 1.9 Hz, 1 H, 4-H), 4.70 (dd, *J* = 2.7 and 2.7 Hz, 1 H, C=CH*H*), 4.74 (dd, *J* = 2.0 and 2.0 Hz, 1 H C=C*H*H); ^{13}C NMR (62.90 MHz) δ 12.34 (C-18), 18.78 (C-21), 19.18 (C-19), 22.23 (CH_2), 22.56 (C-26 or C-27), 22.81 (C-26 or C-27), 23.87 (CH_2), 24.50 (CH_2), 28.01 (CH), 28.58 (CH_2), 29.38 (CH_2), 31.99 (CH_2), 35.61 (CH_2), 35.69 (CH), 36.27 (CH_2),

39.52 (CH_2), 39.87 (CH_2), 41.53 (CH), 41.91 (CH_2), 44.00 (C-13), 46.39 (CH), 53.41 (CH), 54.72 (C-10), 55.76 (CH), 57.03 (CH), 68.04 (C-5), 103.96 (C=CH_2), 154.29 (C-6); MS EI *m/z* (%) 383 (31), 382 (100, M^+), 368 (23), 367 (78), 354 (13), 269 (27), 247 (22), 227 (11), 175 (15), 174 (16), 173 (25), 163 (11), 161 (32), 160 (16), 159 (33), 157 (11); HRMS EI *m/z* 382.35995 (calcd for $C_{28}H_{46}$: 382.35995).

6α-Vinyl-A-homo-B-nor-3,5-cyclo-5α-cholestane-6β-ol (86)

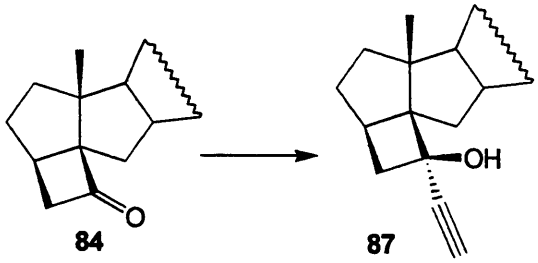


84 **86**

Magnesium (340 mg; 14 mmol) was placed into a three-necked flask, fitted with a pressure-equalised dropping funnel, an acetone-dry ice condenser (equipped with a nitrogen bubbler) and a septum, then covered with dry THF (10 ml). A crystal of iodine was added to activate the magnesium and initiate the formation of the Grignard reagent. Vinyl bromide (0.6 ml; 910 mg; 8.508 mmol) was condensed from a cylinder into a sealed measuring tube at -35 °C. The cylinder was removed, then a cannula was fitted to the tube and placed under the surface of the THF, in the reaction flask. The tube was gently heated so that vinyl bromide could slowly bubble into the THF over a period of approx 5 min. After the fizzing had ceased, the mixture was stirred at rt for and additional 15 min. A solution of cyclobutanone **84** (1.095 g; 2.847 mmol) in THF (20 ml) was then added dropwise and the mixture stirred at 40 °C for 1 h. The reaction was then cooled by an ice bath and quenched with sat. aqueous NH_4Cl solution (5 ml). The product was taken up into ether and the organic layer worked up. Column chromatography using petroleum ether and ether (49 : 1), as the eluant, furnished amorphous **86** (1.139 g; 97%): $[\alpha]_D$ +44.2° (*c* 1.6); IR ν_{max}(O–H) 3595 cm^{-1}, ν_{max}(C=C)

1640 cm^{-1}, ν_{max}($CH=CH_2$) 912 cm^{-1}; ^1H NMR (250 MHz) δ 0.63 (s, 3 H, 18-H), 0.93 (s, 3 H, 19-H), 5.04 (dd, J_{cis} = 10.7 Hz, J_{gem} = 1.2 Hz, 1 H, CH=C*H*H), 5.12 (dd, J_{trans} = 17.3 Hz, J_{gem} = 1.2 Hz, 1 H, CH=C*H*H), 6.11 (dd, J_{trans} = 17.3 Hz, J_{cis} = 10.7 Hz, 1 H, C*H*=CH_2); ^{13}C NMR (62.90 MHz) δ 12.26 (C-18), 18.76 (C-21), 18.87 (C-19), 21.36 (CH_2), 22.55 (C-26 or C-27), 22.80 (C-26 or C-27), 23.81 (CH_2), 24.43 (CH_2), 27.97 (CH), 28.59 (CH_2), 28.77 (CH_2), 35.64 (CH), 36.22 (CH_2), 36.48 (CH_2), 36.94 (CH_2), 39.48 (CH_2), 39.75 (CH_2), 39.89 (CH_2), 40.41 (CH), 42.13 (CH), 43.86 (C-13), 54.06 (CH), 55.65 (CH), 56.62 (C-10), 57.19 (CH), 65.63 (C-5), 77.42 (C-6), 108.59 (CH_2), 145.79 (CH); MS EI *m/z* (%) 413 (17), 412 (54, M^+), 357 (15), 343 (29), 342 (100), 341 (28), 327 (27), 257 (26), 247 (61), 246 (16), 229 (38), 187 (24), 170 (17); HRMS EI *m/z* 412.37051 (calcd for $C_{29}H_{44}O$: 412.37051); Anal. Calcd for $C_{29}H_{46}O.1/3H_2O$: C, 83.19; H, 11.72. Found: C, 83.46; H, 11.94.

6α-Ethynyl-A-homo-B-nor-3,5-cyclo-5α-cholestane-6β-ol (87)

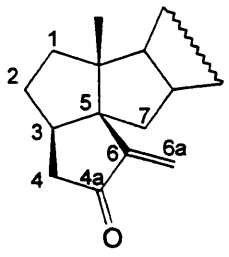


84 **87**

A solution of cyclobutanone **84** (147 mg; 382 μmol) in THF (4 ml) was added dropwise to a stirred suspension of lithium acetylide-ethylenediamine complex (336 mg; 1.887 mmol) in THF (4 ml) at rt. After stirring for 5 min, the reaction mixture was cooled to 0 °C and quenched with sat. aqueous NH_4Cl solution (5 ml). The resulting mixture was diluted with ether (30 ml) and the organic layer was washed with H_2O (10 ml) and 15% aqueous NaCl solution (2 x 10 ml). The ethereal solution was dried and evaporated and the crude product was resubjected to the reaction with the lithium

acetylide suspension. Column chromatography using a petroleum ether-ether mixture (24 : 1) afforded unreacted ketone **84** (21 mg; 55 μmol; 14%) as the least polar and alcohol **87** (97 mg; 236μmol; 62%) as the most polar component: mp 99.5 - 101 °C (MeOH); IR ν_{max}(O-H) 3595 cm^{-1}, ν_{max}(C≡CH) 3303 cm^{-1}; ^1H NMR (250 MHz) δ 0.65 (s, 3 H, 18-H), 0.87 (d, J = 6.6 Hz, 6 H, 26-H and 27-H), 0.92 (d, J = 6.6 Hz, 3 H, 21-H), 1.23 (s, 3H, 19-H), 2.41 (m, 1H, 4-H), 2.49 (m, 1 H, 4-H), 2.64 (s, 1 H, C≡CH); ^{13}C NMR (62.90 MHz) δ 12.27 (C-18), 18.75 (C-19 or C-21), 18.77 (C-19 or C-21), 21.40 (CH_2), 22.56 (C-26 or C-27), 22.80 (C-26 or C-27), 23.82 (CH_2), 24.47 (CH_2), 27.98 (CH), 28.59 (2 x CH_2), 35.65 (CH), 36.23 (CH_2), 36.94 (CH_2), 37.89 (CH_2), 39.49 (CH_2), 39.71 (CH_2), 40.39 (CH), 41.46 (CH_2), 42.16 (CH), 43.86 (C-13), 54.85 (CH), 55.65 (CH), 56.49 (C-10), 57.11 (CH), 65.60 (C-5), 72.25 (C-6 or *C*≡CH), 72.87 (C-6 or *C*≡CH), 88.91 (C≡*C*H); MS EI *m/z* (%) 411 (7), 410 (20, M^+), 343 (27), 342 (100), 327 (16), 247 (39), 246 (15), 229 (28), 187 (12); HRMS EI *m/z* 410.35488 (calcd for $C_{29}H_{46}O$: 410.35487).

6–Methylene-A-bishomo-B-nor-3,5-cyclo-5α-cholestan-4a-one (90)



Manganese(III) picolinate (172 mg; 461 μmol) and **87** (76 mg; 186 μmol) were dissolved in degassed DMF (5 ml) and the mixture was heated at 100 °C for 3 h. Then the reaction was quenched with H_2O (5 ml) and diluted with ether (40 ml). The ethereal layer was washed with 15% aqueous NaCl solution (2 x 15 ml) and H_2O (15 ml), then dried and the solvent removed under vacuum. Purification by column chromatography using a petroleum ether-ether mixture (19 : 1) furnished **90** (24 mg; 58 μmol; 32%): mp

85.5 - 87 °C (MeOH/$CHCl_3$); $[\alpha]_D$ -21.5° (*c* 1); IR ν_{max}(C=CH_2) 3000 cm^{-1}, ν(C=O) 1712 cm^{-1}, ν(C=C) 1630 cm^{-1}; ^1H NMR (400 MHz) δ 0.67 (s, 3 H, 19-H), 0.68 (s, 3 H, 18-H), 1.10 (m, 1 H, 12α-H), 1.27 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.2 Hz, $J_{7\alpha\text{-H},8\beta\text{-H}}$ = 12.2 Hz, 1 H, 7α-H), 1.60 (dd, $J_{2\alpha\text{-H},2\beta\text{-H}}$ = 12.9 Hz, $J_{1\beta\text{-H},2\beta\text{-H}}$ = 5.9 Hz, 1 H, 2β-H), 1.95 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.2 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 5.4 Hz, 1 H, 7β-H), 1.96 (dddd, $J_{2\alpha\text{-H},2\beta\text{-H}}$ = 12.9 Hz. $J_{2\alpha\text{-H},1\beta\text{-H}}$ = 12.9 Hz, $J_{2\alpha\text{-H},1\alpha\text{-H}}$ = 6.5 Hz, $J_{2\alpha\text{-H},3\alpha\text{-H}}$ = 5.9 Hz, 1 H, 2α-H), 2.03 (dd, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 19.2 Hz, $J_{3\alpha\text{-H},4\beta\text{-H}}$ = 9.4 Hz, 1 H, 4β-H), 2.06 (ddd, $J_{12\alpha\text{-H},12\beta\text{-H}}$ = 12.8 Hz, $J_{11\alpha\text{-H}.12\beta\text{-H}}$ = 3.4 Hz, $J_{11\beta\text{-H},12\beta\text{-H}}$ = 3.4 Hz, 1 H, 12β-H), 2.33 (ddd, $J_{3\alpha\text{-H},3\beta\text{-H}}$ = 19.2 Hz, $J_{3\alpha\text{-H},4\alpha\text{-H}}$ = 9.4 Hz, $J_{3\alpha\text{-H},4\beta\text{-H}}$ = 9.4 Hz, $J_{2\alpha\text{-H},3\alpha\text{-H}}$ = 5.9 Hz, 1 H, 3α-H), 2.50 (dd, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 19.2 Hz, $J_{3\alpha\text{-H},4\alpha\text{-H}}$ = 9.4 Hz, 1 H, 4α-H), 5.22 (d, *J* = 1 Hz, 1 H, (*E*)-C=C*H*H), 6.04 (d, *J* = 1 Hz, 1 H, (*Z*)-C=C*H*H); ^{13}C NMR (62.90 MHz) δ 12.21 (C-18), 18.70 (C-21), 22.29 (CH_2), 22.51 (C-26 or C-27), 22.59 (C-26 or C-27), 22.76 (C-19), 23.80 (CH_2), 24.56 (CH_2), 27.71 (CH_2), 27.74 (CH), 28.52 (CH_2), 35.61 (CH), 36.17 (CH_2), 36.54 (CH_2), 39.44 (CH_2), 39.63 (CH_2), 42.07 (CH_2), 42.45 (CH), 43.64 (C-13), 46.14 (CH), 48.04 (CH_2), 54.86 (C-10), 55.62 (CH), 55.97 (CH), 56.39 (CH), 64.19 (C-5), 116.54 (C-6a), 154.17 (C-6), 208.44 (C-4a); MS EI *m/z* (%) 411 (32), 410 (100, M^+), 326 (17), 297 (15), 257 (23), 256 (22), 255 (57), 155 (15); CI *m/z* 411 (MH^+), 428 ($[M + NH_4]^+$); HRMS (EI) *m/z* 410.35486 (calcd for $C_{29}H_{46}O$: 410.35487); Anal. Calcd for $C_{29}H_{46}O$: C, 84.81; H, 11.29. Found: C, 84.98; H, 11.15.

Reaction of 86 with Thallium(III) Nitrate

Thallium(III) nitrate trihydrate (229 mg; 514 μmol) was added to a solution of **86** (204 mg; 495 μmol) in THF (15 ml). The mixture was stirred at rt for 15 min then diluted with 15% aqueous NaCl solution (2ml) and ether (35 ml), and the organic layer

was worked up. The crude mixture was chromatographed, by elution with a petroleum ether-ether mixture (49 : 1), to afford **101** (24 mg; 12%) as the less polar compound and **90** (154 mg; 76%) as the more polar component.

Reaction of 86 with Mercury(II) Nitrate

Mercury(II) nitrate monohydrate (160 mg; 466 μmol) was added to a solution of **86** (192 mg; 495 μmol) in THF (15 ml). The mixture was stirred at rt for 15 min then treated with 15% aqueous NaCl solution (15 ml) and stirred for a further 5 min. The crude product was taken up into ether and the ethereal solution worked up. Separation of the mixture was achieved by chromatography: elution with a petroleum ether-ether mixture (49:1) afforded **101** (25 mg; 13%) as the less polar and **90** (100 mg; 52%) as the more polar component. Further elution with a petroleum ether-ether mixture (9:1) furnished **99** (69 mg; 23%).

Stoichiometric Reaction of 86 with Palladium(II) Nitrate

Palladium(II) nitrate (35 mg; 152 μmol) was added to a solution of **86** (56 mg; 135 μmol) in THF (5 ml) and the resulting solution was stirred at rt for 15 min. The mixture was then treated with 15% aqueous NaCl solution (5 ml) and diluted with ether. The organic layer was washed with H_2O (2 x 10 ml), then dried and the solvent was evaporated. Separation of the products was carried out by column chromatography: elution with a petroleum ether- ether mixture (49:1) gave products in the following order: **103** (1.3 mg; 2%), **101** (1.3 mg; 2%), **102** (30 mg; 54%), and **90** (20 mg; 36%).

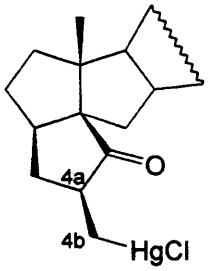
Catalytic Reaction of 86 with Palladium(II) Nitrate

Palladium(II) nitrate (13 mg; 5 mol %) and copper(II) nitrate (725 mg; 3 mmol) were added to a solution of **86** (438 mg; 1.061 mmol) in THF (10 ml) and the resulting solution was stirred at rt for 15 h. The mixture was then treated with 15% aqueous NaCl solution (5 ml) and diluted with ether. The organic layer was washed with H_2O (2 x 20 ml), then dried and the solvent was evaporated. Separation of the products was carried out by column chromatography: elution with a petroleum ether-ether mixture (49:1) gave products in the following order: **101** and **103** (14 mg; 3%; not separated), **102** (263 mg; 60%) and **90** (58 mg; 13%).

Catalytic Reaction of 86 with Bis(benzonitrile)-Palladium(II) Chloride

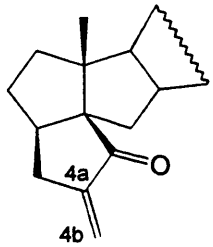
$(PhCN)_2PdCl_2$ (3.6 mg; 8 mol %) and *p*-benzoquinone (26 mg; 242 μmol) were added to a solution of **86** (50 mg; 121 μmol) in THF (5 ml) and the resulting solution was stirred at rt for 15 h. The mixture was then diluted with ether (25 ml) and the ethereal solution was washed with 10% aqueous sodium dithionite solution (2 x 10 ml) and water (2 x 10 ml). The solution was dried and the solvent evaporated, then chromatography was used to separate the mixture of products. Elution with petroleum ether and ether (49 : 1) gave products in the following order: **103** (36 mg; 72%), **101** (0.9 mg; 2%), **102** (5.5 mg; 11%), **90** (5.8 mg; 12%).

4a-[(Chloromercurio)methyl]-A-bishomo-B-nor-3,5-cyclo-5α-cholestan-6-one (99)



Treatment of **86** with mercury(II) nitrate and 15% aqueous NaCl solution, as described previously, afforded chloromercurial **99** in 23% yield: mp 158 - 159.5 °C ($MeOH/CHCl_3$); $[\alpha]_D$ -48.6° (*c* 3.0); IR ν_{max}(C=O) 1712 cm^{-1}; ^1H NMR (250 MHz) δ 0.66 (s, 3 H, 18-H), 0.74 (s, 3 H, 19-H), 0.86 (d, *J* = 6.6 Hz, 26-H and 27-H), 0.91 (d, *J* = 6.6 Hz, 3 H, 21-H); ^{13}C NMR (62.90 MHz) δ 12.29 (C-18), 18.73 (C-21), 22.06 (CH_2), 22.53 (C-26 or C-27), 22.79 (C-26 or C-27), 23.02 (C-19), 23.82 (CH_2), 24.32 (CH_2), 26.59 (CH_2), 27.96 (CH), 28.02 (CH_2), 28.54 (CH_2), 35.58 (CH), 36.18 (CH_2), 36.85 (CH_2), 39.44 (CH_2), 39.57 (CH_2), 42.24 (CH), 43.44 (CH_2), 43.76 (C-13), 47.83 (CH), 50.55 (CH), 55.65 (CH), 55.78 (CH), 56.48 (CH), 58.04 (C-10), 68.81 (C-5), 226.84 (C-6); MS EI *m/z* (%) 411 (32, M^+- HgCl), 410 (100, M^+- HHgCl), 297 (11), 202 (13), 174 (21), 172 (21), 163 (11); MS CI *m/z* 412 (MH^+- HgCl); Anal. Calcd for $C_{29}H_{47}ClHgO$: C, 53.78; H, 7.31. Found: C, 53.55; H, 7.54.

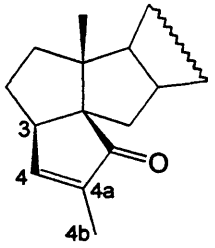
4a-Methylene-A-bishomo-B-nor-3,5-cyclo-5α-cholestan-6-one (101)



Treatment of **86** with thallium(III) nitrate, as described previously, afforded **101** in 12% yield: mp 92 - 94 °C ($CHCl_3$/MeOH); $[\alpha]_D$ +22.6° (*c* 1.5); IR ν_{max}(C=O) 1710 cm^{-1}, ν_{max}(C=C) 1635 cm^{-1}; ^1H NMR (400 MHz) δ 0.67 (s, 3 H, 18-H), 0.77 (s, 3 H,

19-H), 0.84 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 11.8 Hz, $J_{7\alpha\text{-H},8\beta\text{-H}}$ = 11.8 Hz, 1 H, 7α-H), 1.44 (m, 1 H, 1β-H), 1.65 (m, 2 H, 1α-H and 2β-H), 1.71 (m, 1 H, 8β-H), 1.92 (m, 1 H, 2α-H), 2.05 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 11.8 Hz. $J_{7\beta\text{-H},8\beta\text{-H}}$ = 5.8 Hz, 1 H, 7β-H), 2.28 (m, 1 H, 3α-H), 2.72 (m, 1 H, 4α-H), 5.19 (narrow m, 1 H, (*E*)-C=C*H*H), 5.92 (narrow m, 1 H, (*Z*)-C=C*H*H); NOESY cross-peaks have been identified for (*E*)-4b-H ↔ 4α-H and 4β-H, 7α-H ↔ 3α-H, 2α-H ↔ 3α-H, 4β-H ↔ 2β-H, 4β-H ↔ 1β-H; ^{13}C NMR (62.90 MHz) δ 12.30 (C-18), 18.76 (C-21), 20.82 (C-19), 22.15 (CH_2), 22.54 (C-26 or C-27), 22.80 (C-26 or C-27), 23.85 (CH_2), 24.36 (CH_2), 27.98 (CH), 28.58 (CH_2), 29.71 (C-4), 32.02 (CH_2), 35.63 (CH), 36.22 (CH_2), 36.78 (CH_2), 39.47 (CH_2), 39.69 (CH_2), 42.18 (CH), 42.46 (CH_2), 43.79 (C-13), 46.91 (C-3), 55.72 (CH), 55.89 (CH), 56.70 (CH), 58.30 (C-10), 69.43 (C-5), 116.06 (C-4b), 146.86 (C-4a), 212.01 (C-6); MS EI *m/z* (%) 411 (32), 410 (100, M^+), 297 (10), 174 (10); HRMS EI *m/z* 410.35487 (calcd for $C_{29}H_{46}O$: 410.35487); Anal. Calcd for $C_{29}H_{46}O$: C, 84.81; H, 11.29. Found: C, 84.73; H, 11.60.

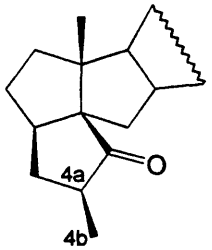
4a-Methyl-A-bishomo-B-nor-3,5-cyclo-5α-cholest-4-en-6-one (102)



Treatment of **86** with a catalytic amount of palladium(II) nitrate, as described previously, afforded **102** in 60% yield: mp 113.5 - 115.5 °C (MeOH); $[\alpha]_D$ -54.6° (*c* 1.2); IR ν_{max}(C=CH_2) 3005 cm^{-1}, ν_{max}(C=O) 1690cm^{-1}, ν_{max}(C=C) 1640 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.66 (s, 3 H, 18-H), 0.73 (s, 3 H, 19-H), 0.86 (d, *J* = 6.6 Hz, 6 H, 26-H and 27-H), 0.89 (d, *J* = 6.6 Hz, 3 H, 21-H), 1.73 (t, ^4J = 1.7 Hz, 3 H, 4b-H), 2.12 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.3 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.6 Hz, 1 H, 7β-H), 2.71 (d, $J_{2\alpha\text{-H},3\alpha\text{-H}}$ = 6.9 Hz, 1 H,

3α-H), 6.96 (br s, 1 H, 4-H); ^{13}C NMR (75.5 MHz) δ 10.17 (C-4b), 12.36 (C-18), 18.79 (C-21), 20.93 (C-19), 22.07 (CH_2), 22.56 (C-26 or C-27), 22.82 (C-26 or C-27), 23.88 (CH_2), 24.40 (CH_2), 27.43 (CH_2), 28.01 (CH), 28.59 (CH_2), 35.21 (CH_2), 35.66 (CH), 36.26 (CH_2), 38.48 (CH_2), 39.50 (CH_2), 39.69 (CH_2), 41.81 (CH), 43.95 (C-13), 53.35 (CH), 55.41 (CH), 55.77 (CH), 56.19 (C-10), 57.02 (CH), 67.20 (C-5), 141.50 (C-4a), 158.30 (C-4), 213.19 (C-6); MS EI *m/z* (%) 411(32), 410 (100, M^+), 297 (39), 270 (23), 256 (11), 255 (33); CI 411 (MH^+); HRMS EI *m/z* 410.35484 (calcd for $C_{29}H_{46}O_2$: 410.35487); Anal. Calcd for $C_{29}H_{46}O.1/3H_2O$: C, 83.59; H, 11.29. Found: C, 83.48; H, 11.29.

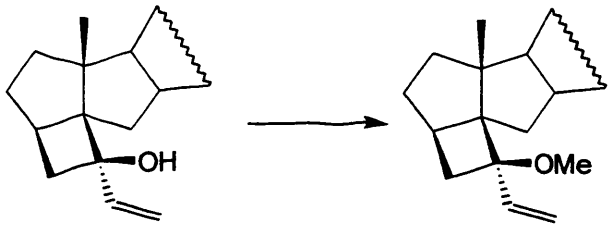
4a-Methyl-A-bishomo-B-nor-3,5-cyclo-5α-cholestan-6-one (103)



Treatment of **86** with a catalytic amount of $(PhCN)_2PdCl_2$, as described previously, afforded **103** in 72% yield: mp 87.5 - 89 °C (MeOH /$CHCl_3$); $[\alpha]_D$ +34.4° (*c* 0.7); IR ν_{max}(C=O) 1718 cm^{-1}; ^1H NMR (400 MHz) δ 0.66 (s, 3 H, 18-H), 0.77 (s, 3 H, 19-H), 0.81 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 11.9 Hz, $J_{7\alpha\text{-H},8\beta\text{-H}}$ = 11.5 Hz, 1 H, 7α-H), 1.04 (d, ^3J = 6.8 Hz, 3 H, 4b-H), 1.05 (m, 1 H, 12α-H), 1.14 (m, 1 H, 4β-H), 1.45 (ddd, $J_{1\alpha\text{-H},1\beta\text{-H}}$ = 12.8 Hz, $J_{1\beta\text{-H},2\alpha\text{-H}}$ = 12.8 Hz, $J_{1\beta\text{-H},2\beta\text{-H}}$ = 6.5 Hz, 1 H, 1β-H), 1.62 (m, 1 H, 2-H), 1.62 (dd, $J_{1\alpha\text{-H},1\beta\text{-H}}$ = 12.8 Hz, $J_{1\alpha\text{-H},2\alpha\text{-H}}$ = 7.1 Hz, $J_{1\alpha\text{-H},2\beta\text{-H}} \cong$ 0 Hz, 1 H, 1α-H), 1.71 (dddd, *J* = 11.5, 11.5, 11.2 and 5.7 Hz, 1 H, 8β-H), 1.88 (m, 1 H, 2α-H), 1.89 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 11.9 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 5.7 Hz, 1 H, 7β-H), 2.02 (ddd, *J* = 12.7, 3.3 and 3.3 Hz, 1 H, 12β-H), 2.09 (m, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 12.3 Hz, $J_{3\alpha\text{-H},4\alpha\text{-H}}$ = 7.9 Hz, $J_{4\alpha\text{-H},4a\alpha\text{-H}}$ = 7.9 Hz, 1 H, 4α-H), 2.17

(m, 1 H, 4aα-H), 2.20 (m, 1 H, 3α-H); NOESY cross peaks have been identified for 4b-H ↔ 19-H, 4aα-H ↔ 7β-H, 3α-H ↔ 4α-H, 7β-H ↔ 8β-H, and 3α-H ↔ 7α-H; ^{13}C NMR (62.90 MHz) δ 12.24 (C-18), 13.57 (C-4b), 18.72 (C-21), 22.09 (C-11), 22.42 (C-26 or C-27), 22.49 (C-19), 22.77 (C-26 or C-27), 23.82 (CH_2), 24.32 (CH_2), 27.95 (C-25), 28.06 (C-2), 28.55 (CH_2), 33.72 (C-4), 35.60 (C-20), 36.20 (CH_2), 36.88 (C-1), 39.45 (CH_2), 39.67 (C-12), 42.53 (C-8), 43.43 (C-7), 43.73 (C-13), 44.87 (C-4a), 48.69 (C-3), 55.68 (C-17), 55.77 (C-8), 56.57 (C-14), 57.23 (C-10), 68.41 (C-5), 225.87 (C-6); MS EI *m/z* (%) 413 (32), 412 (100, M^+), 272 (31), 262 (11), 258 (22), 257 (62), 151 (36); CI 413 (MH^+), 430 ($[M + NH_4]^+$), 397 (M^+- CH_3); HRMS EI *m/z* 412.37054 (calcd for $C_{29}H_{48}O$: 412.37052); Anal. Calcd for $C_{29}H_{48}O.¼H_2O$: C, 83.49; H, 11.72. Found: C, 83.69; H, 11.81.

6β-Methoxy-6α-vinyl-A-homo-B-nor-3,5-cyclo-5α-cholestane (104)



86 **104**

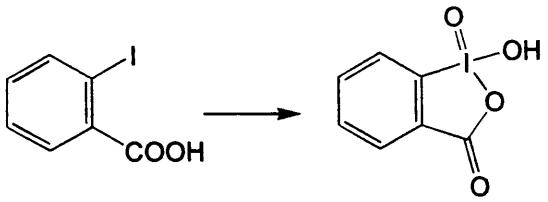
Sodium hydride, (20 mg; 833 μmol; obtained from a 60% oil suspension by washing with petroleum ether) was placed in a flask and covered with THF (5 ml), then cooled to 0 °C. A solution of vinyl cyclobutanol **86** (69 mg; 167 μmol) dissolved in THF (5 ml) was added and the mixture was stirred for 30 min. Then methyl iodide (0.1 ml; 288 mmol) was added and the reaction stirred at 45 °C for a further 1 h. The mixture was diluted with ether (15 ml), quenched with water (1 ml), then worked up. The product was chromatographed using a petroleum ether-ether mixture (99 : 1), which afforded methoxy derivative **104** (60 mg; 145 μmol; 87%) as a colourless oil: $[\alpha]_D$

+32.8° (*c* 3.5); IR ν_{max}(C=C) 1638 cm^{-1}; ^1H NMR (250 MHz) δ 0.63 (s, 3 H, 18-H), 0.869 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.871 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 1.21 (s, 3 H, 19-H), 3.05 (s, 3 H, OCH_3), 5.17 (m, 2 H, CH=CH_2), 5.87 (m, J_{trans} = 14.1 Hz, J_{cis} = 6.7 Hz, 1 H, CH=CH_2); ^{13}C NMR (62.90 MHz) δ 12.26 (C-18), 18.78 (C-21), 19.09 (C-19), 21.48 (CH_2), 22.55 (C-26 or C-27), 22.79 (C-26 or C-27), 23.84 (CH_2), 24.46 (CH_2), 27.99 (CH), 28.54 (CH_2), 28.61 (CH_2), 30.05 (CH_2), 35.66 (CH), 36.27 (CH_2), 37.21 (CH_2), 39.42 (CH_2), 39.52 (CH_2), 39.86 (CH_2), 40.37 (CH), 42.49 (CH), 43.89 (OCH_3), 50.18 (C-13), 54.33 (CH), 55.73 (CH), 56.70 (C-10), 57.19 (CH), 64.76 (C-5), 81.99 (C-6), 112.30 (CH=CH_2), 142.49 (CH=CH_2); MS EI *m/z* (%) 427 (33), 426 (100, M^+), 411 (34), 397 (12), 394 (21), 379 (12), 353 (16), 342 (32), 341 (25), 327 (16), 313 (15), 247 (43), 246 (12), 229 (28), 187 (19), 165 (17), 164 (22), 163 (28), 161 (12); HRMS EI *m/z* 426.38616 (calcd for $C_{30}H_{50}O$: 426.38617).

EXPERIMENTAL

CHAPTER FOUR

Synthesis of *o*-Iodoxybenzoic Acid[323]

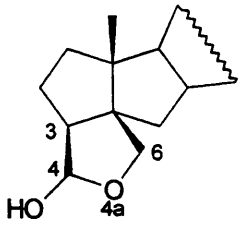


Dilute sulphuric acid (45 ml; 0.73 M) and 2-iodobenzoic acid (5.210 g; 21.008 mmol) were placed in a flask, which was then fitted with a reflux condenser and a water trap. The mixture was heated to 55 °C and $KBrO_3$ (4.630 g; 27.723 mmol) was added in small portions over 30 min, whilst the mixture was being vigorously stirred. After 4 h the mixture was cooled in ice. The solid was filtered off, then washed with H_2O (30 ml) and EtOH (30 ml) yielding *o*-iodoxybenzoic acid (5.259 g; 18.781 mmol; 89%): mp 231 - 233 °C (lit[323] gives 233 °C).

Selective Oxidation of Diol 79

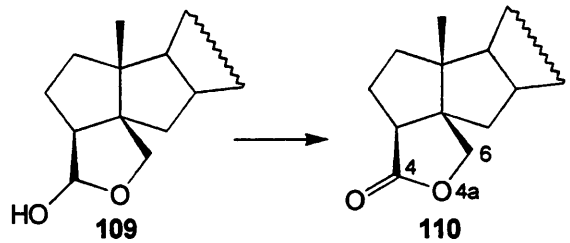
o-Iodoxybenzoic (435 mg; 1.553 mmol) was added to a solution of diol **79** (420 mg; 1.038 mmol) in DMSO (20 ml) and the mixture was stirred at rt for 45 min. The reaction mixture was then diluted with ether (60 ml) and quenched with H_2O (10 ml). The white precipitate was filtered off through a celite pad and the organic layer was washed with 5% aqueous NaCl solution (3 x 30 ml) and H_2O (30 ml). The solvent was dried and removed, then the crude mixture was flushed through a short column using a petroleum ether-acetone mixture (3:1). The products were separated using a chromatotron by elution with a petroleum ether-acetone mixture (19:1), which furnished **110** and **111** (17 mg; 4%; not separated), **14** (92 mg; 228 μmol; 22%) and **109** (296 mg; 735 μmol; 71%).

4a-Oxa-A-bishomo-B-nor-3,5-cyclo-5α-cholestan-4-ol (109)



Lactol **109** was obtained from diol **70** in 71% yield: mp 122.5 - 124 °C (acetone); $[\alpha]_D$ +61.4° (*c* 2.4); IR ν_{max}(O–H) 3602 cm^{-1}; ^1H NMR (250 MHz) δ 0.63 (s, 3 H, 18-H), 0.87 (d, *J* = 6.6 Hz, 6 H, 26-H and 27-H), 0.90 (s, 3 H, 19-H), 2.73 (broad s, 1 H, 4-OH), 3.90 and 4.00 (AB system, *J* = 9.1 Hz, 2 H, 6-H), 5.09 (d, *J* = 1.9 Hz, 1 H, 4-H); ^{13}C NMR (62.90 MHz) δ 12.21 (C-18), 18.74 (C-21), 19.11 (C-19), 22.08 (CH_2), 22.54 (C-26 or C-27), 22.79 (C-26 or C-27), 23.83 (CH_2), 24.47 (CH_2), 26.67 (CH_2), 27.98 (CH), 28.52 (CH_2), 35.64 (CH), 36.21 (CH_2), 37.48 (CH_2), 39.47 (CH_2), 39.68 (CH_2), 39.90 (CH_2), 41.04 (CH), 43.70 (C-13), 52.40 (C-10), 54.83 (CH), 55.66 (CH), 56.52 (CH), 61.23 (CH), 62.63 (C-5), 74.00 (C-6), 105.08 (C-4); MS EI *m/z* (%) 402 (4, M^+), 401 (21), 400 (68), 385 (12), 384 (30), 287 (12), 279 (17), 247 (13), 246 (39), 245 (100), 174 (18), 173 (17), 160 (15); HRMS EI *m/z* 402.34974 (calcd for $C_{27}H_{46}O_2$: 402.34978).

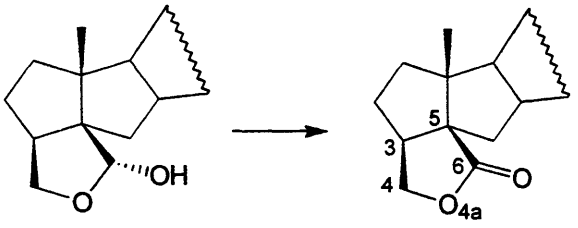
4a-Oxa-A-bishomo-B-nor-3,5-cylco-5α-cholestan-4-one (110)



Jones' reagent[343] (0.15 ml; 2.67 M) was added to a solution of lactol **109** (71 mg; 176 μmol) in acetone (10 ml) and the mixture was stirred for 15 min at rt. Methanol (5 ml) and ether (50 ml) were added, then the mixture was stirred for 5 min and the ethereal layer was washed with sat. aqueous $NaHCO_3$ solution (2 x 20 ml) and H_2O (2 x

20 ml). The solvent was dried and evaporated yielding lactone **110** (69 mg; 172 μmol; 98 %): mp 111 - 112.5 °C (MeOH); $[\alpha]_D$ +72.4° (c 1.46); IR ν_{max}(C=O) 1762 cm^{-1}; ^1H NMR (250 MHz) δ 0.64 (s, 3 H, 18-H), 0.87 (d, *J* = 6.6 Hz, 26-H and 27-H), 0.92 (d, 3 H, *J* = 6.6 Hz, 21-H), 0.95 (s, 3 H, 19-H), 2.61 (d, *J* = 6.6 Hz, 1 H, 3-H), 4.06 and 4.43 (AB system, *J* = 9.4 Hz, 2 H, 6-H); ^{13}C NMR (62.90 MHz) δ 12.19 (C-18), 18.73 (C-21), 20.03 (C-19), 20.05 (CH_2), 22.53 (C-26 or C-27), 22.77 (C-26 or C-27), 23.83 (CH_2), 24.41 (CH_2), 26.23 (CH_2), 27.97 (CH), 28.47 (CH_2), 35.60 (CH), 36.19 (CH_2), 37.42 (CH_2), 39.47 (2 x CH_2), 40.55 (CH), 41.96 (CH_2), 43.72 (C-13), 52.66 (CH), 53.21 (C-10), 55.39 (CH), 55.63 (CH), 56.18 (CH), 58.04 (C-5), 74.44 (C-6), 180.33 (C-4); MS EI *m/z* (%) 401 (22), 400 (73, M^+), 260 (9), 246 (38), 245 (100), 160 (11); HRMS EI *m/z* 400.33411 (calcd for $C_{27}H_{44}O_2$: 400.33413).

4a-Oxa-A-bishomo-B-nor-3,5-cyclo-5α-cholestan-6-one (111)[70]

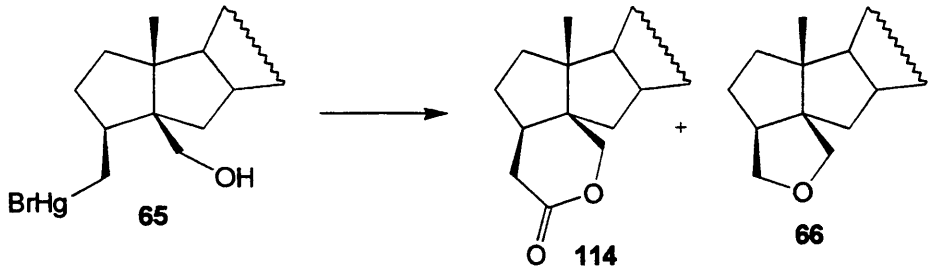


14 **111**

Jones' reagent[343] (0.25 ml; 2.67 M) was added to a solution of lactol **14** (146 mg; 363 μmol) in acetone (15 ml) and the mixture was stirred for 15 min at rt. Methanol (5 ml) and ether (50 ml) were then added, the mixture was stirred for 5 min and the ethereal layer was washed with sat. aqueous $NaHCO_3$ solution (2 x 20 ml) and H_2O (2 x 20 ml). The solvent was dried and evaporated yielding lactone **111** (143 mg; 357 μmol; 98 %): mp 137 - 139 °C (authentic sample[70] had mp 139-141 °C); IR ν_{max}(C=O) 1758 cm^{-1}; ^1H NMR (250 MHz) δ 0.66 (18-H), 0.862 (d, *J* = 6.6 Hz, 3 H, 26-H or 27-H), 0.866 (d, *J* = 6.6 Hz, 3 H, 26-H or 27-H), 0.92 (d, *J* = 6.6 Hz, 3 H, 21-H), 0.98 (s, 3 H,

19-H), 2.26 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.3 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.0 Hz, 1 H, 7β-H), 2.73 (m, 1 H, 3α-H), 3.76 (t, J = 9.1 Hz, 1 H, 4-H) 4.31 (t, J = 9.6 Hz, 1 H, 4-H); ^{13}C NMR (62.90 MHz) δ 12.28 (C-18), 18.77 (C-19), 20.83 (C-21), 22.12 (CH_2), 22.57 (C-26 or C-27), 22.82 (C-26 or C-27), 23.86 (CH_2), 24.32 (CH_2), 27.53 (CH_2), 28.00 (CH), 28.54 (CH_2), 35.62 (CH), 36.22 (CH_2), 36.38 (CH_2), 39.48 (CH_2), 39.52 (CH_2), 41.73 (CH_2), 41.90 (CH), 43.81 (C-13), 49.12 (CH), 54.96 (CH), 55.70 (CH), 56.53 (CH), 58.04 (C-10), 62.16 (C-5), 69.29 (C-4), 182.15 (C-6); MS EI *m/z* (%) 400 (2, M^+), 385 (9), 356 (15), 256 (13), 167 (13), 149 (64), 129 (16); HRMS EI *m/z* 400.33409 (calcd for $C_{27}H_{44}O_2$: 400.33409).

Stoichiometric Palladium(II)-Mediated Carbonylation of 65

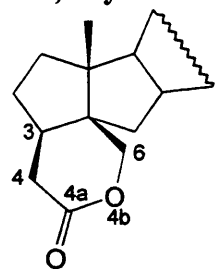


p-Benzoquinone (32 mg; 296 μmol) and **65** (89 mg; 133 μmol) were added to a mixture of $(MeCN)_2PdCl_2$ (38 mg; 145 μmol) and THF (10 ml), then the flask was fitted with a CO balloon, the air was evacuated from the flask and the CO was let in. The mixture was stirred at rt for 17 h, then quenched with H_2O (5 ml), and diluted with ether (50 ml). The ethereal layer was washed with 10% aqueous sodium dithionite solution (2 x 25 ml) and H_2O (20 ml). The solution was dried and the solvent evaporated, then the residue was absorbed onto silica gel. Column chromatography was used to purify the mixture using petroleum ether and ether (4:1) as the eluant, which furnished the tetrahydrofuran derivative **66** (5.4 mg; 14 μmol; 11 %) as the least polar and lactone **114** (30 mg; 73 μmol; 55 %) as the more polar component.

Palladium(II)- Catalysed Carbonylation of 65

p-Benzoquinone (51 mg; 472 mmol) and bromomercurio alcohol **65** (134 mg; 200 μmol) were added to a mixture of $(MeCN)_2PdCl_2$ (4 mg; 15 μmol; 8 mol %) and THF (10 ml), then the flask was fitted with a CO balloon, the air was evacuated from the flask and the CO was let in. The ethereal layer was washed with 10% aqueous sodium dithionite solution (2 x 25 ml) and H_2O (20 ml), then the solution was dried and the solvent evaporated. The crude mixture was chromatographed using a petroleum ether-ether mixture: tetrahydrofuran **66** (35 mg; 89 μmol; 44 %) was obtained with a (49:1) mixture and lactone **114** (12 mg; 29 μmol; 14 %) was obtained with a (4:1) mixture.

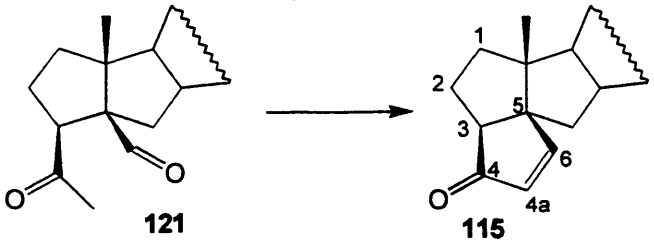
4b-Oxa-A-trishomo-B-nor-3,5-cyclo-5α-cholestane-4a-one (114)



Palladium(II)-mediated carbonylation of **65**, as described above, furnished lactone **114** in 55% yield: mp 142 -144 °C (MeOH); $[\alpha]_D$ +25.6° (*c* 1.7); IR ν_{max}(C=O) 1740 cm^{-1}; ^1H NMR (250 MHz) δ 0.65 (s, 3 H, 18-H), 0.87 (d, *J* = 6.6 Hz, 6 H, 26-H and 27-H) 0.92 (d, *J* = 6.3 Hz, 21-H), 0.98 (s, 3 H, 19-H), 2.56 (m, 1 H, 4-H), 4.02 and 4.16 (AB system, *J* = 11.6 Hz, 2 H, 6-H); ^{13}C NMR (62.90 MHz) δ 12.21 (C-18), 17.97 (C-19), 18.72 (C-21), 21.68 (CH_2), 22.53 (C-26 or C-27), 22.77 (C-26 or C-27), 23.80 (CH_2), 24.41 (CH_2), 27.97 (CH), 28.46 (CH_2), 30.63 (CH_2), 35.32 (CH_2), 35.61 (CH), 36.18 (CH_2), 36.77 (CH_2), 39.45 (CH_2), 39.50 (CH_2), 40.76 (CH), 43.73 (C-13), 44.99 (CH_2), 46.86 (CH), 53.78 (C-10), 54.54 (CH), 54.67 (C-5), 55.61 (CH), 56.50 (CH),

72.55 (C-6), 174.27 (C-4a); MS EI *m/z* (%) 415 (26), 414 (83, M^+), 261 (12), 260 (47), 259 (100), 231 (15); HRMS EI *m/z* 414.34981 (calcd for $C_{28}H_{46}O_2$: 414.34978).

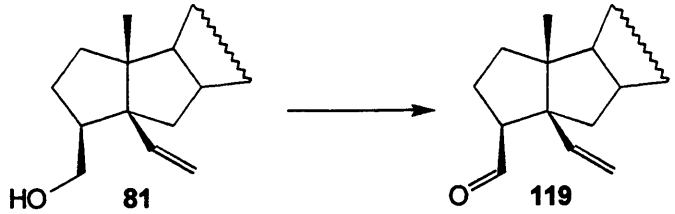
A-Bishomo-B-nor-3,5-cyclo-cholest-4a-en-4-one (115)



121 **115**

10% aqueous NaOH solution (3 ml) was added to a solution of **121** (40 mg; 96 μmol) in THF (3 ml) and the resultant mixture was stirred at rt for 45 min. Then the mixture was diluted with ether (35 ml) and the ethereal layer was extracted and worked up. The crude mixture was purified by column chromatography using a petroleum ether-ether mixture as the eluant which allowed separation of enone **115** (13 mg; 33 μmol; 34 %): mp 104 - 105 °C (MeOH); IR ν_{max}(C=O) 1692 cm^{-1}, ν_{max}(C=C) 1635 cm^{-1}; ^1H NMR (250 MHz) δ 0.69 (s, 3 H, 18-H), 0.84 (s, 3H, 19-H), 0.871 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.874 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.94 (d, J = 6.6 Hz, 21-H), 6.03 (d, J = 5.7 Hz, 1 H, (6-H), 7.44 (d, J = 5.3 Hz, 1 H, 4a-H); MS EI *m/z* (%) 397 (26), 396 (83, M^+), 256 (12), 242 (32), 241 (100), 133 (9); HRMS EI *m/z* 396.33918 (calcd for $C_{28}H_{44}O$: 396.33922).

A,B-Bisnor-5β-cholestan-5-vinyl-3β-carbaldehyde (119)

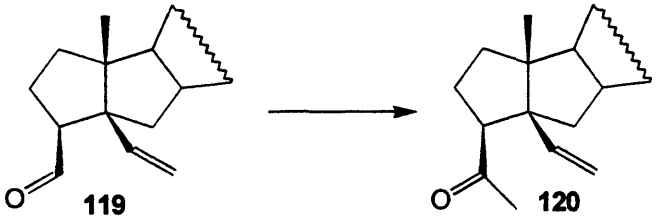


81 **119**

PCC (1.262 g; 5.855 mmol) was added to a stirred solution of **81** (1.272 g; 3.175 mmol) in dichloromethane (30 ml) and the mixture was stirred at rt for 2.5 h. Then the solution was filtered through a celite pad, the solvent was removed and the residue was

absorbed onto silica gel. The silica mixture was then placed on the top of a column and purified by chromatography using a petroleum ether-ether mixture (49 : 1) as the eluant, which afforded oily **119** (1.044 g; 2.619 mmol; 82%): $[\alpha]_D$ +76.4° (*c* 3.7); IR ν_{max}(CHO) 2733 cm^{-1}, ν_{max}(C=O) 1712 cm^{-1}, ν_{max}(C=C) 1634 cm^{-1}, ν_{max}(CH=CH_2) 909 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.63 (s, 3 H, 18-H), 0.82 (s, 3 H, 19-H), 0.87 (d, J = 6.6 Hz, 6 H, 26-H and 27-H), 0.92 (d, J = 6.6 Hz, 3 H, 21-H), 2.31 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.7 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.6 Hz, 1 H, 7β-H), 2.67 (dt, J = 7.2 Hz and 2.2 Hz, 1 H, 3α-H), 5.09 (m, 2 H, CH=CH_2), 5.83 (m, J_{trans} = 17.6 Hz, J_{cis} = 10.7 Hz, 1 H, 6-H), 9.64 (d, J = 2.5 Hz, 1 H, 4-H); ^{13}C NMR (62.90 MHz) δ 12.25 (C-18), 18.75 (C-21), 20.02 (C-19), 21.96 (CH_2), 22.54 (C-26 or C-27), 22.78 (C-26 or C-27), 23.86 (CH_2), 24.47 (CH_2), 25.49 (CH_2), 27.98 (CH), 28.53 (CH_2), 35.66 (CH), 36.23 (CH_2), 38.21 (CH_2), 39.49 (CH_2), 39.75 (CH_2), 40.89 (CH_2), 42.03 (CH), 43.81 (C-13), 55.34 (C-10), 55.73 (CH), 56.66 (CH), 57.89 (CH), 60.83 (C-5), 65.41 (CH), 112.95 (CH=CH_2), 139.83 (C-6), 204.60 (C-4); MS EI *m/z* (%) 399 (20), 398 (66, M^+), 383 (26), 380 (13), 370 (30), 369 (71), 355 (22), 340 (29), 327 (35), 243 (24), 215 (18), 187 (17), 173 (27), 161 (22); HRMS EI *m/z* 398.35480 (calcd for $C_{28}H_{46}O$: 398.35487).

3β-Acetyl-5-vinyl-A,B-bisnor-5β-cholestane (120)

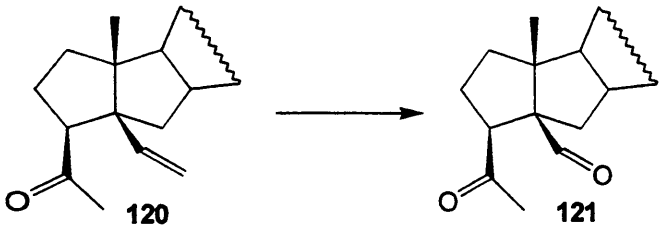


119 **120**

Methyl lithium (1.9 ml; 1.35 M, 2.565 mmol) was added to a cooled (-78 °C), stirred solution of **119** (986 mg; 2.473 mmol) in ether (30 ml) and the mixture was stirred at -78 °C for 15 min. The excess reagent was quenched with H_2O (1 ml), then the mixture was diluted with ether (30 ml) and the ethereal layer was separated and worked

up. The solvent was dried and evaporated, then the residue was redissolved in dichloromethane (30 ml). PCC (990 mg; 4.593 mmol) was added to flask and the mixture was stirred for rt for 2 h. Then the solution was filtered through a celite pad, the solvent was removed and the residue was absorbed onto silica gel. The silica mixture was then placed on the top of a column and purified by chromatography using a petroleum ether-ether mixture (49 : 1) as the eluant, which afforded **120** (898 mg; 2.176; 88%): mp 84 - 85 °C (MeOH); $[\alpha]_D$ +102.0° (*c* 4.5); IR ν_{max}(C=O) 1698 cm^{-1}, ν_{max}(C=C) 1636 cm^{-1}, ν_{max}(CH=CH_2) 914 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.63 (s, 3 H, 18-H), 0.77 (s, 3 H, 19-H), 0.871 (d, *J* = 6.6 Hz, 3 H, 26-H or 27-H), 0.874 (d, *J* = 6.6 Hz, 3 H, 26-H or 27-H), 0.93 (d, *J* = 6.6 Hz, 3 H, 21-H), 2.02 (s, 3 H, $COCH_3$), 2.37 (dd, *J* = 12.4 Hz, 5.8 Hz, 1 H, 7β-H), 2.82 (dd, *J* = 10.1 Hz and 6.3 Hz, 1 H, 3α-H), 4.99 (m, J_{cis} = 10.9 Hz, 1 H, CH=C*H*H), 5.03 (m, J_{trans} = 17.5 Hz, 1 H, CH=C*H*H), 5.68 (dd, J_{trans} = 17.5 Hz, J_{cis} = 10.9 Hz, 1 H, 6-H); ^{13}C NMR (62.90 MHz) δ 12.22 (C-18), 18.75 (C-21), 20.72 (C-19), 21.89 (CH_2), 22.54 (C-26 or C-27), 22.78 (C-26 or C-27), 23.85 (CH_2), 24.51 (CH_2), 27.77 (CH_2), 27.98 (CH), 28.54 (CH_2), 30.56 ($COCH_3$), 35.66 (CH), 36.25 (CH_2), 38.91 (CH_2), 39.49 (CH_2), 39.74 (CH_2), 41.94 (CH_2), 43.16 (CH), 43.70 (C-13), 55.75 (CH), 56.16 (C), 56.69 (CH), 59.15 (CH), 60.57 (C), 67.26 (CH), 111.48 (CH=CH_2), 140.09 (*C*H=CH_2), 209.74 (C-4); MS EI *m/z* (%) 413 (25), 412 (80, M^+), 398 (12), 397 (39), 394 (25), 379 (15), 370 (27), 369 (89), 354 (23), 341 (15), 328 (34), 327 (100), 257 (16), 187 (23), 173 (23), 161 (21); HRMS EI *m/z* 412.37050 (calcd for $C_{29}H_{48}O$: 412.37052).

3β-Acetyl-A,B-bisnor-5β-cholestan-5-carbaldehyde (121)



121 (238 mg; 577 μmol) was dissolved in dichloromethane (10 ml) and placed into a three necked flask that was fitted with a septum, a bubbling device and an gas outlet. The apparatus was flushed with nitrogen and the solution was cooled to -35 °C, then ozone was bubbled into the solution until TLC showed that all the starting material had reacted (approx 1 h). The apparatus was flushed with nitrogen then thiourea (45 mg; 591 μmol) dissolved in MeOH (5 ml) was added. The reaction mixture was stirred at -35 °C for 1 h, 0 °C for 30 min and rt for 1 h, then the solution was diluted with dichloromethane (25 ml) and filtered. The filtrate was absorbed onto silica gel and the solvent was evaporated. The mixture was then placed on the top of a column and was purified by chromatography, eluting with various petroleum ether-ether mixtures. The polarity of the solvent mixture was gradually increased from (97 : 3) to (88 :12), which facilitated removal of the impurities followed by elution of the most polar constituent that was the required product. Removal of the solvent afforded **121** (155 mg; 374 μmol; 65%): m.p. 127 - 129 °C ($CHCl_3$/MeOH); $[\alpha]_D$ +24.9° (*c* 3.8); IR ν_{max}(C=O) 1700 and 1713 cm^{-1}; ^1H NMR (250 MHz) δ 0.64 (s, 3 H, 18-H), 0.863 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 0.866 (d, J = 6.6 Hz, 3 H, 26-H or 27-H), 1.01 (s, 3 H, 19-H), 2.14 (s, 3 H, $COCH_3$), 2.38 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.9 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.3 Hz, 1 H, 7β-H), 2.87 (t, J = 7.9 Hz, 1 H, 3α-H), 9.57 (s, 1 H, 6-H); ^{13}C NMR (62.90 MHz) δ 12.19 (C-18), 18.73 (C-21), 19.67 (C-19), 21.64 (CH_2), 22.52 (C-26 or C-27), 22.76 (C-26 or C-27), 23.83 (CH_2), 24.32 (CH_2), 27.97 (CH), 28.45 (CH_2), 29.46 (CH_2), 29.53 ($COCH_3$), 35.59

(CH), 36.19 (CH_2), 39.36 (CH_2), 39.45 (CH_2), 39.47 (CH_2), 40.69 (CH_2), 43.67 (C-13), 43.73 (CH), 55.67 (CH), 56.50 (CH), 56.78 (C-10), 58.67 (CH), 64.03 (CH), 68.35 (C-5), 204.68 (C-6), 209.29 (C-4); MS EI *m/z* (%) 415 (31), 414 (100, M^+), 400 (22), 399 (67), 386 (20), 371 (27), 358 (31), 353 (28), 343 (19), 167 (17); HRMS EI *m/z* 414.34975 (calcd for $C_{28}H_{46}O_2$: 414.34978).

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APPENDIX

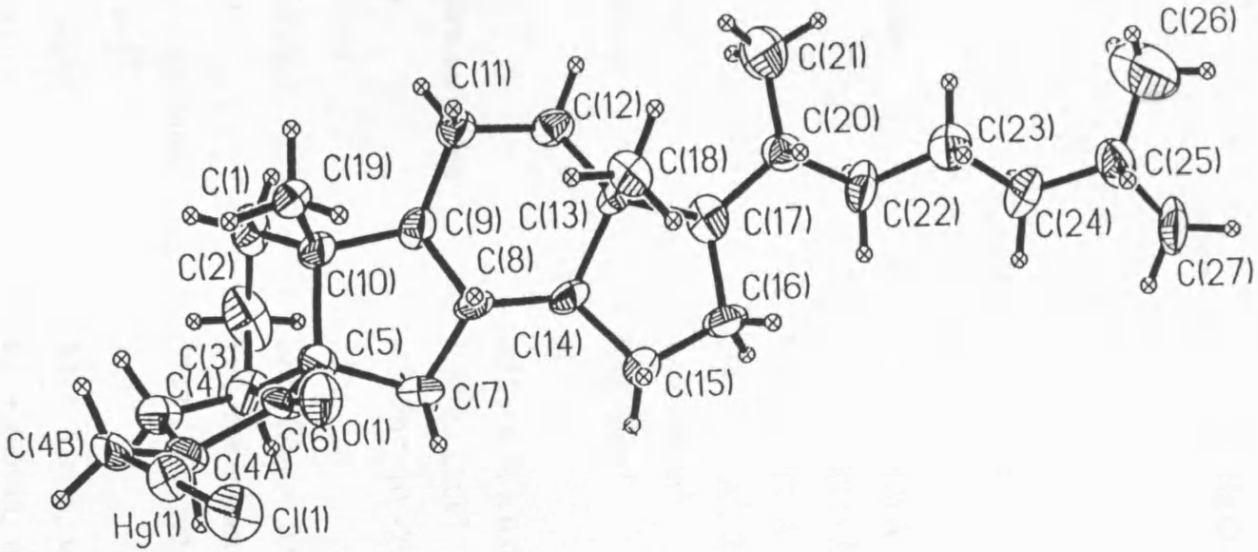
ORTEP DIAGRAM OF ORGANOMERCURIAL 99

X-RAY CRYSTAL DATA FOR 99

PUBLICATION

Selective Reduction of the Carbonyl Group in Organomercurials. A Facile Method for the Protection - Deprotection of the Mercurio Group and a New Route to Annulated Lactones

P. Kočovský, V. Dunn, J. M. Grech, J. Šrogl and W. L. Mitchell, Tetrahedron Lett., **1996**, *37*, 5585.



ORTEP DIAGRAM OF ORGANOMERCURIAL 99

CRYSTAL DATA AND STRUCTURE REFINEMENT FOR 99

Identification code	8a
Empirical formula	$C_{29} H_{47} Cl Hg O$
Formula weight	647.71
Temperature	295(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 10.319(2) Å $\alpha = 90°$
	b = 7.0740(11) Å $\beta = 90.875(13)°$
	c = 19.837(2) Å $\gamma = 90°$
Volume, Z	1447.9(4) $Å^3$, 2
Density (calculated)	1.486 mg/m^3
Absorption coefficient	5.425 mm^{-1}
F(000)	652
Crystal size	0.15 × 0.10 × 0.02 mm
Theta range for data collection	1.97^0 to 24.00°
Limiting indices	-11<=h<=10, -7<=k<=7, -19<=l<=22
Reflections collected	5573
Independent reflections	3847 [R_{int} = 0.0810]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3847 / 1 / 297
Goodness-of-fit on F^2	1.217
Final R indices [$I>2\sigma_I$]	R1 = 0.0596, wR2 = 0.1063
R indices (all data)	R1 = 0.0940, wR2 = 0.1269
Absolute structure parameter	-0.03(2)
Largest diff. peak and hole	0.436 and -0.889 $e.A^{-3}$

ATOMIC COORDINATES ($\times 10^4$) AND EQUIVALENT ISOTROPIC DISPLACEMENT PARAMETERS ($A^2 \times 10^3$) FOR 99. U(eq) IS DEFINED AS ONE THIRD OF THE TRACE OF THE ORTHOGONALIZED Uij TENSOR

	x	y	z	U(eq)
Hg(1)	4110(1)	5359(2)	4957(1)	89(1)
Cl(1)	6358(4)	5400(23)	4936(2)	112(1)
O(1)	3170(9)	5518(41)	3634(5)	95(4)
C(1)	-745(20)	7762(35)	3189(11)	113(7)
C(2)	-1351(19)	5772(69)	3247(12)	150(15)
C(3)	-240(20)	4657(26)	3548(11)	104(7)
C(4)	24(15)	4892(30)	4302(10)	97(8)
C(4A)	1445(17)	4519(24)	4388(9)	86(5)
C(4B)	2151(15)	5354(56)	5007(7)	106(6)
C(5)	1001(12)	5355(54)	3197(7)	77(4)
C(6)	2040(15)	5197(46)	3710(7)	74(5)
C(7)	1387(21)	4269(24)	2536(11)	90(6)
C(8)	1800(16)	5833(19)	2073(9)	74(6)
C(9)	750(17)	7312(26)	2187(9)	78(5)
C(10)	627(17)	7445(24)	2963(8)	78(5)
C(11)	942(20)	9094(23)	1776(8)	95(6)
C(12)	1088(17)	8605(23)	1036(9)	84(5)
C(13)	2194(19)	7232(27)	889(10)	67(6)
C(14)	1900(13)	5419(47)	1330(7)	76(4)
C(15)	2866(28)	3945(31)	1076(11)	107(9)
C(16)	2895(23)	4329(28)	336(11)	95(7)
C(17)	2192(21)	6223(32)	155(10)	86(7)
C(18)	3497(17)	8078(27)	1066(9)	87(6)
C(19)	1592(20)	8895(22)	3256(8)	93(6)
C(20)	2752(20)	7300(25)	-403(9)	89(5)
C(21)	2133(29)	9200(36)	-552(11)	181(13)
C(22)	2716(17)	6085(25)	-1047(9)	103(7)
C(23)	3592(20)	6671(29)	-1598(11)	109(7)
C(24)	3588(15)	5253(58)	-2200(8)	105(6)
C(25)	4582(19)	5691(60)	-2725(11)	120(11)
C(26)	4536(51)	7371(59)	-3117(22)	230(24)
C(27)	4492(39)	3971(52)	-3208(16)	166(17)

BOND LENGTHS [Å] FOR 99

Hg(1)-C(4B)	2.03(2)
Hg(1)-Cl(1)	2.321(4)
O(1)-C(6)	1.20(2)
C(1)-C(10)	1.51(2)
C(1)-C(2)	1.55(5)
C(2)-C(3)	1.51(3)
C(3)-C(4)	1.53(2)
C(3)-C(5)	1.55(2)
C(4)-C(4A)	1.50(2)
C(4A)-C(4B)	1.54(3)
C(4A)-C(6)	1.56(2)
C(5)-C(6)	1.47(2)
C(5)-C(10)	1.59(4)
C(5)-C(7)	1.57(3)
C(7)-C(8)	1.50(2)
C(8)-C(9)	1.53(2)
C(8)-C(14)	1.51(2)
C(9)-C(10)	1.55(2)
C(9)-C(11)	1.52(2)
C(10)-C(19)	1.54(2)
C(11)-C(12)	1.52(2)
C(12)-C(13)	1.53(2)
C(13)-C(18)	1.51(3)
C(13)-C(14)	1.59(3)
C(13)-C(17)	1.62(3)
C(14)-C(15)	1.53(3)
C(15)-C(16)	1.49(3)
C(16)-C(17)	1.56(2)
C(17)-C(20)	1.47(3)
C(20)-C(22)	1.54(2)
C(20)-C(21)	1.52(3)
C(22)-C(23)	1.49(2)
C(23)-C(24)	1.56(3)
C(24)-C(25)	1.50(3)
C(25)-C(26)	1.42(5)
C(25)-C(27)	1.55(4)

ANGLES [degrees] FOR 99

C(4B)-Hg(1)-Cl(1)	178.1(7)
C(10)-C(1)-C(2)	106(2)
C(3)-C(2)-C(1)	102(2)
C(2)-C(3)-C(4)	117(2)
C(2)-C(3)-C(5)	107(2)
C(4)-C(3)-C(5)	106(2)
C(4A)-C(4)-C(3)	104.6(14)
C(4B)-C(4A)-C(4)	118(2)
C(4B)-C(4A)-C(6)	112(2)
C(4)-C(4A)-C(6)	104.2(14)
C(4A)-C(4B)-Hg(1)	115.0(12)
C(6)-C(5)-C(10)	116(3)
C(6)-(C5)-C(3)	105(2)
C(10)-C(5)-C(3)	103(2)
C(6)-C(5)-C(7)	110(2)
C(10)-C(5)-C(7)	105.9(13)
C(3)-C(5)-C(7)	116(2)
O(1)-C(6)-C(5)	127(2)
O(1)-C(6)-C(4A)	124(2)
C(5)-C(6)-C(4A)	109.1(13)
C(8)-C(7)-C(5)	103(2)
C(7)-C(8)-C(9)	101.8(13)
C(7)-C(8)-C(14)	119(2)
C(9)-C(8)-C(14)	110(2)
C(10)-C(9)-C(8)	104.9(14)
C(10)-C(9)-C(11)	120(2)
C(8)-C(9)-C(11)	113.0(14)
C(9)-C(10)-C(1)	113(2)
C(9)-C(10)-C(5)	102.1(14)
C(1)-C(10)-C(5)	106(2)
C(9)-C(10)-C(19)	111(2)
C(1)-C(10)-C(19)	113(2)
C(5)-C(10)-C(19)	110.9(14)
C(12)-C(11)-C(9)	110.3(14)
C(11)-C(12)-C(13)	114.5(14)

C(18)-C(13)-C(12)	112(2)
C(18)-C(13)-C(14)	112(2)
C(12)-C(13)-C(14)	105(2)
C(18)-C(13)-C(17)	112(2)
C(12)-C(13)-C(17)	117(2)
C(14)-C(13)-C(17)	98(2)
C(8)-C(14)-C(15)	121(2)
C(8)-C(14)-C(13)	114(2)
C(15)-C(14)-C(13)	103.7(13)
C(14)-C(15)-C(16)	103(2)
C(15)-C(16)-C(17)	111(2)
C(20)-C(17)-C(16)	116(2)
C(20)-C(17)-C(13)	117(2)
C(16)-C(17)-C(13)	100(2)
C(17)-C(20)-C(22)	109(2)
C(17)-C(20)-C(21)	116(2)
C(22)-C(20)-C(21)	109(2)
C(20)-C(22)-C(23)	117(2)
C(24)-C(23)-C(22)	113(2)
C(23)-C(24)-C(25)	114(3)
C(26)-C(25)-C(24)	122(3)
C(26)-C(25)-C(27)	109(2)
C(24)-C(25)-C(27)	103(3)

Symmetry transformation used to generate equivalent atoms.

ANISOTROPIC DISPLACEMENT PARAMETERS ($Å^2$ x 10^3) FOR 99. THE ANISOTROPIC DISPLACEMENT FACTOR EXPONENT TAKES THE FORM $-2\pi^2$ [$h^2 a^{*2}$ U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Hg(1)	100(1)	87(1)	81(1)	4(1)	11(1)	2(1)
Cl(1)	85(3)	123(3)	129(3)	6(9)	-5(2)	-3(9)
O(1)	68(6)	123(11)	93(7)	-8(14)	11(5)	-9(15)
C(1)	78(16)	157(21)	105(16)	18(15)	32(12)	48(15)
C(2)	60(12)	265(48)	124(16)	42(29)	3(11)	-7(27)
C(3)	94(16)	93(18)	126(17)	-11(11)	12(13)	-34(11)
C(4)	65(11)	87(22)	139(16)	31(13)	46(10)	6(10)
C(4A)	85(13)	81(12)	92(13)	31(9)	15(10)	11(9)
C(4B)	136(16)	106(12)	75(10)	35(22)	10(10)	52(25)
C(5)	62(9)	81(9)	86(10)	23(22)	15(7)	12(21)
C(6)	68(9)	59(11)	96(10)	32(15)	15(8)	0(15)
C(7)	103(16)	49(10)	117(17)	14(11)	-13(14)	9(11)
C(8)	86(11)	46(16)	89(12)	-1(8)	0(9)	20(9)
C(9)	66(12)	92(13)	77(12)	-4(10)	-7(9)	29(10)
C(10)	84(14)	73(12)	76(12)	0(9)	1(10)	29(10)
C(11)	135(17)	80(12)	70(12)	-3(10)	-9(11)	29(12)
C(12)	82(13)	77(12)	92(13)	0(10)	-19(10)	23(10)
C(13)	75(14)	55(11)	71(12)	-13(9)	-10(10)	22(10)
C(14)	62(9)	63(9)	103(10)	-4(22)	4(7)	26(19)
C(15)	164(28)	69(15)	87(17)	-6(12)	32(17)	15(16)
C(16)	132(22)	54(10)	100(17)	-6(11)	-7(15)	23(14)
C(17)	88(16)	103(15)	66(11)	-19(9)	-28(11)	-24(12)
C(18)	83(15)	94(14)	83(12)	8(11)	-15(10)	-22(11)
C(19)	141(18)	64(11)	74(12)	-6(9)	6(11)	19(12)
C(20)	116(16)	72(12)	78(12)	-1(10)	-7(11)	-6(11)
C(21)	288(38)	172(26)	84(16)	19(15)	10(19)	55(24)
C(22)	108(14)	114(18)	87(12)	-42(10)	32(11)	-15(11)
C(23)	108(16)	111(15)	109(16)	-10(12)	5(13)	-10(12)
C(24)	100(12)	116(15)	99(12)	-35(23)	3(10)	28(25)
C(25)	107(14)	159(32)	94(14)	43(21)	17(11)	31(22)
C(26)	310(66)	180(38)	198(45)	47(36)	-24(41)	-35(38)
C(27)	203(37)	213(35)	84(19)	19(21)	78(22)	72(27)

HYDROGEN CO-ORDINATES (x 10^4) AND ISOTROPIC DISPLACEMENT PARAMETERS (A^2 x 10^3) FOR 99.

	x	y	z	U(eq)
H(1A)	-1222(20)	8520(35)	2861(11)	125(15)
H(1B)	-753(20)	8405(35)	3621(11)	125(15)
H(2A)	-2093(19)	5776(69)	3541(12)	125(15)
H(2B)	-1611(19)	5281(69)	2809(12)	125(15)
H(3)	-367(20)	3313(26)	3447(11)	88(19)
H(4A)	-190(15)	6162(30)	4448(10)	125(15)
H(4B)	-480(15)	3994(30)	4559(10)	125(15)
H(4A1)	1556(17)	3145(24)	4409(9)	88(19)
H(4B1)	1902(15)	4642(56)	5402(7)	125(15)
H(4B2)	1858(15)	6645(56)	5068(7)	125(15)
H(7A)	2092(21)	3393(24)	2624(11)	125(15)
H(7B)	654(21)	3580(24)	2348(11)	125(15)
H(8)	2631(16)	6338(19)	2237(9)	88(19)
H(9)	-62(17)	6748(26)	2022(9)	88(19)
H(11A)	205(20)	9927(23)	1830(8)	125(15)
H(11B)	1711(20)	9753(23)	1936(8)	125(15)
H(12A)	1229(17)	9763(23)	786(9)	125(15)
H(12B)	282(17)	8055(23)	872(9)	125(15)
H(14)	1041(13)	4976(47)	1185(7)	88(19)
H(15A)	2568(28)	2671(31)	1166(11)	125(15)
H(15B)	3715(28)	4121(31)	1283(11)	125(15)
H(16A)	2477(23)	3296(28)	95(11)	125(15)
H(16B)	3788(23)	4395(28)	192(11)	125(15)
H(17)	1291(21)	5923(32)	33(10)	88(19)
H(18A)	3618(53)	9219(96)	813(47)	141(21)
H(18B)	4168(18)	7193(73)	960(58)	141(21)
H(18C)	3534(46)	8361(162)	1540(14)	141(21)
H(19A)	1587(84)	8832(112)	3740(9)	141(21)
H(19B)	1345(62)	10141(27)	3113(46)	141(21)
H(19C)	2447(24)	8616(96)	3099(46)	141(21)
H(20)	3665(20)	7531(25)	-288(9)	88(19)
H(21A)	2404(94)	9637(83)	-986(28)	141(21)
H(21B)	2397(88)	10093(54)	-213(35)	141(21)
H(21C)	1207(29)	9073(48)	-552(56)	141(21)
H(22A)	1835(17)	6083(25)	-1224(9)	125(15)
H(22B)	2928(17)	4794(25)	-923(9)	125(15)
H(23A)	3328(20)	7906(29)	-1762(11)	125(15)
H(23B)	4468(20)	6782(29)	-1418(11)	125(15)
H(24A)	2735(15)	5257(58)	-2413(8)	125(15)
H(24B)	3746(15)	3990(58)	-2027(8)	125(15)
H(25)	5435(19)	5644(60)	-2502(11)	88(19)
H(26A)	4942(121)	7150(82)	-3542(36)	141(21)
H(26B)	4986(129)	8363(80)	-2881(39)	141(21)
H(26C)	3650(51)	7734(119)	-3193(61)	141(21)
H(27A)	3761(88)	4126(107)	-3508(47)	141(21)
H(27B)	4388(142)	2835(56)	-2950(16)	141(21)
H(27C)	5271(68)	3888(129)	-3465(54)	141(21)

Pergamon

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Selective Reduction of the Carbonyl Group in Organomercurials. A Facile Method for the Protection-Deprotection of the Mercurio Group and a New Route to Annulated Lactones

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Abstract: Reduction of the carbonyl group in organomercurials can be carried out with retention of the mercury, provided it is protected by methylation. Thus, the bromomercurio aldehyde **6** is first methylated by MeCu to give **11**, whose reduction with $NaBH_4$, $LiAlH(t\text{-}BuO)_3$, L-Selectride®, or superhydride® affords the alcohol **12**. Mercury is then deprotected by treatment with $HgBr_2$ (**12** → **13**). The resulting alcohol **13** undergoes the palladium(II)-catalyzed carbonylation to produce the corresponding lactone **15**. Five- and six-membered lactones are readily accessible via this methodology.

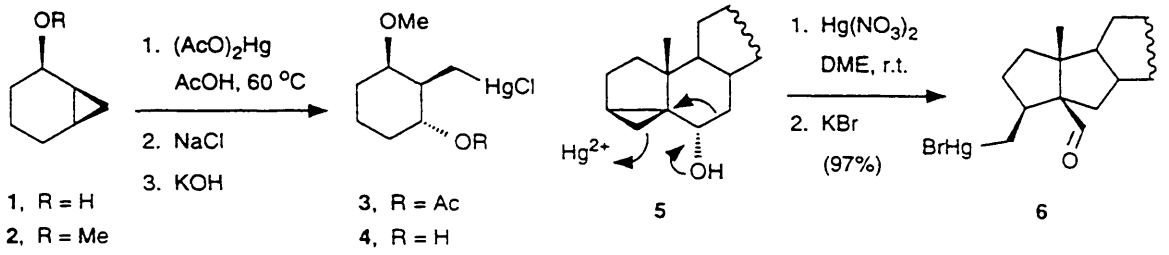
Organomercurials are frequently encountered intermediates in organic synthesis.[1] The usual role of mercury is to serve as a vehicle introducing a desired substituent. In most cases, after having served its purpose, mercury is removed by reduction.[1,2] This scenario is exemplified by the well known oxymercuration of olefinic double bonds[1] and by cyclopropane cleavage.[3-5] However, this is not the most economic strategy because, in general, stoichiometric processes, employing either expensive or toxic metals, should capitalize on the presence of the metal in the molecule by engaging it in more than one productive step.

As part of a program aimed at the more atom-economic utilization of organomercurials, we have recently shown that the C-HgX group can serve as a store of the carbon-metal bond. The mercurio group would be activated later in the synthetic scheme, eventually effecting, e.g., an intramolecular addition across a C=O or an activated C=C bond.[4-6]

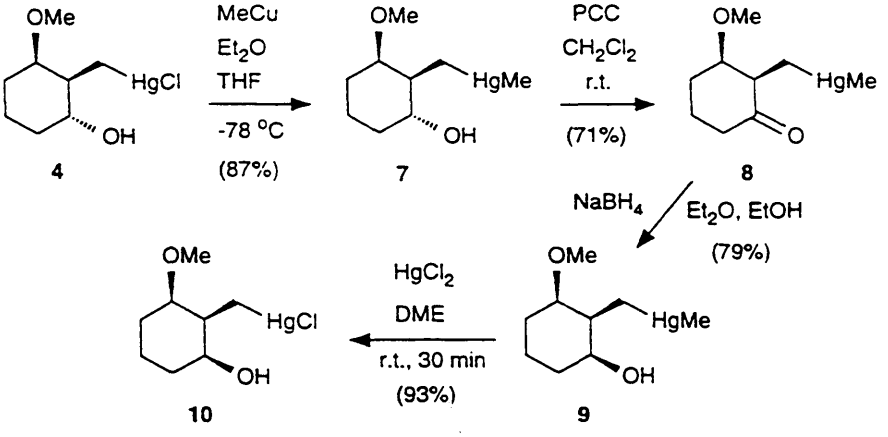
Organomercurials are relatively stable and easy-to-handle,[1] so that the R-HgX group (X = halogen) can be expected to survive a number of operations in a multiple-step sequence, before actually being activated and used. However, these compounds can easily be reduced even with relatively mild reducing agents,[1] which considerably limits the scope of this methodology. In order to avoid the latter flaw, we have developed a protocol that involves protection of the mercurio group from reduction and its subsequent deprotection.

We have shown earlier that, on reaction with MeCu, halomercurials (e.g., R-HgCl) undergo an instantaneous, high yielding methylation on mercury.[4,5] We now wish to report that the resulting methylmercurio derivatives R-HgMe are stable to a number of hydride reagents and that the halomercurio functionality can then be regenerated by treatment with HgX_2.

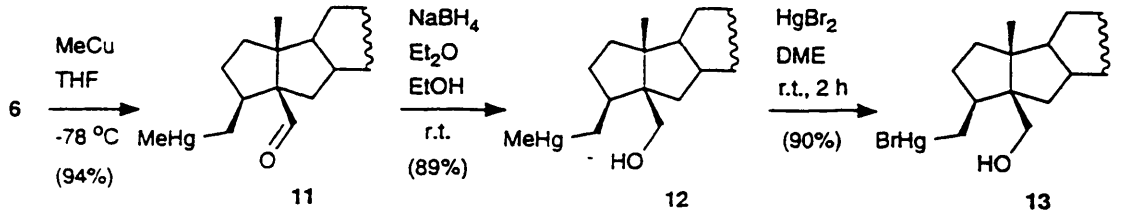
To develop this method, we have utilized two model compounds: the chloromercurio alcohol **4** and the steroidal aldehyde **6**. The former compound was prepared from the cyclopropyl alcohol **1**,[8] via a sequence involving protection of the OH group by MeI/NaH methylation (**1** → **2**; 69%), cyclopropane ring opening[3,5] with $(AcO)_2Hg$ (**2** → **3**; 74%), and saponification (**3** → **4**; 98%).[9] The aldehyde **6** has been readily obtained from the cyclopropyl derivative **5** (which, in turn, was prepared in four steps from cholesterol[10]) via the mercury(II)-mediated rearrangement.[4]



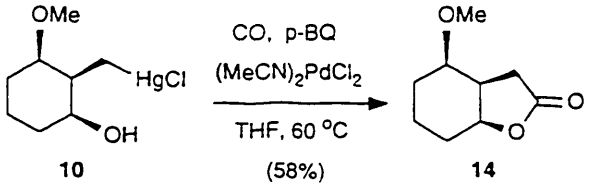
The chloromercurio alcohol **4** was first methylated with MeCu (generated in situ from equimolar amounts of MeLi and CuI) to afford the methylmercurio derivative **7**.[11] The latter compound was then oxidized with pyridinium chlorochromate (PCC) and the resulting ketone **8** stereoselectively reduced with $NaBH_4$ to give the inverted alcohol **9** as the major product (16:1). Finally, the chloromercurio grouping was regenerated by treatment with $HgCl_2$ (**9** → **10**).

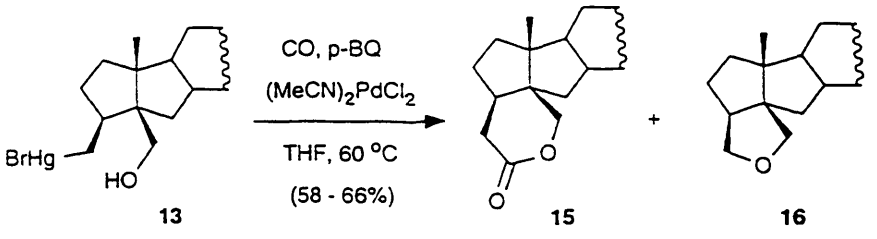


Similarly, methylation of the steroidal aldehyde with MeCu (**6** → **11**),[4] followed by the $NaBH_4$ reduction, gave the alcohol **12**. Treatment of the latter product with $HgBr_2$ furnished the bromomercurio alcohol **13**. A brief screening showed that the reduction (**11** → **12**) can also be carried with $LiAlH(t\text{-}BuO)_3$, L-Selectride®, or superhydride® in high yields.[12] By contrast, treatment with $LiAlH_4$ led to the reduction of both functional groups.



On heating at 60 °C with $(MeCN)_2PdCl_2$ (10 mol%) and 2 equivs of *p*-benzoquinone (*p*-BQ) in THF under an atmosphere of CO for 4 days,[13] the chloromercurio alcohol **10** has been almost quantitatively consumed, giving almost exclusively the five-membered lactone **14**, which was isolated as a pure compound in 58% yield.[14] On the other hand, the organomercurial **13** exhibited high conversion to the corresponding lactone only when the reaction was carried out with a stoichiometric amount of Pd^{2+} (still in the presence of *p*-BQ which, apparently, serves as a ligand[15]). The six-membered lactone **15** (55%)[16] thus formed, was accompanied by the tetrahydrofuran derivative **16** (11%).[17] The catalytic version (8 mol% of Pd^{2+}, 60 °C, 7 days) gave rise to a mixture of **15** (14%) and **16** (44%), with the latter product dominating. These results indicate that the lactonization will be less successful if a competing pathway, such as a 5(O)^n-*exo*-tet cyclization,[18] is available. By contrast, synthesis of 5-membered lactones does not seem to suffer from that kind of competition, for the only available 4-(O)^n-*exo*-tet cyclization is much less likely.





In conclusion: We have developed a protocol for the protection/deprotection of the organomercurials, namely via the methylation-demethylation. The protected organomercurials are stable to a number or hydride reagents, enabling a selective reduction of an aldehyde or ketone group, present in the molecule. The resulting halomercurio alcohols readily afford either 5- or 6-membered lactones on the Pd(II)-catalyzed carbonylation. This protocol represents a novel approach to the synthesis of lactones and supplements those in existence.[19]

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7. Kočovský, P.; Šrogl, J.; Gogoll, A.; Hanuš, V.; Polášek, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1086.
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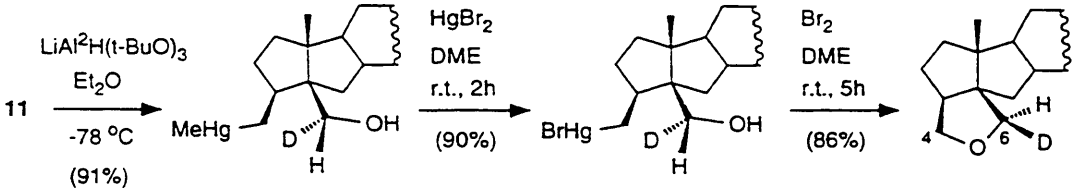
11. The diagnostic feature for the MeHg group is a singlet (83%) and a doublet (17%) of the methyl group in the ^{1}H NMR spectrum, which appear at 0.22 ppm; the doublet (J = 102 Hz) corresponds to the coupling with the less abundant ^{199}Hg isotope.
12. The reduction turned out to be stereoselective, as revealed by using $LiAl^2H(t\text{-}BuO)_3$, which gave mainly the alcohol **i**. The configuration at the new center of chirality (i.e. C-6) has been established via converting the latter alcohol into the rigid tetrahydrofuran derivative **iii**; the NOE technique has been used to unequivocally assign the signals to the respective protons of the CH_2-O-CH_2 group in the unlabeled analogue **16** [δ 3.41 (d, J = 9.1 Hz, 6α-H), 3.47 (dd, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 8.8 Hz, $J_{3\alpha\text{-H},4\beta\text{-H}}$ = 4.8 Hz, 4β-H), 3.95 (t, J = 9.0 Hz, 4α-H), 4.00 (d, J = 9.1 Hz, 6β-H) ppm]. An almost identical stereoselectivity has been observed for super deuteride® (87:13). Reduction of the deuterated aldehyde with $LiAlH(t\text{-}BuO)_3$ gave a complementary result.



i (85 : 15) ii iii

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14. **14:** IR ν(C=O) 1770 cm^{-1}; ^{13}C NMR δ 177.3 ppm.
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18. For notation, see: Kočovský, P.; Stieborová, I. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1969.
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