THE UNIVERSITY OF CALGARY

THE SYNTHESIS OF SAMANINE

BY

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ABSTRACT

This thesis describes the 10 step transformation of a commercially available and relatively cheap nitrogen-free steroid, testosterone acetate, into the rare alkaloid samanine. Testosterone acetate was first converted into 5β-androstane followed by the transposition of the oxygen functionality from C17 to C16 via an elimination-hydroboration-oxidation-inversion sequence, after which the nitrogen was introduced by a Schmidt reaction and the synthesis finally completed by a reduction.

This was the third synthesis of samanine and its overall yield (17%) and practicality compares favourably with the two previous ones, and paves the way for an even more efficient preparation of the alkaloid.

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I would like to express my sincerest gratitude to Professor Michael H. Benn for his guidance and for sharing his wealth of expertise in the art and discipline of science, throughout my program.

I would also like to thank Dr. R. Yamdagni for the numerous consultations we had and for his technical assistance, and Dr. Paul Brooks of I.S.P.G.C. for the mass spectra of samanine and its isomer.

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TABLE OF CONTENTS

LIST OF DIAGRAMS

LIST OF FIGURES

LIST OF SCHEMES

ABBREVIATIONS

The abbreviations used in this thesis are those commonly employed by the Journal of Organic Chemistry, and the Canadian Journal of Chemistry. In particular the following have been used.

9-BBN	9-borabicyclo[3.3.1]nonane
LAH	Lithium tetrahydridoaluminate
DEAD	Diethyl azodicarboxylate
TPP	Triphenylphosphium
Im	Imidazolyl
Py	Pyridine
THF	Tetrahydrofuran
HOAc	Acetic acid
BMS	Borane-dimethyl sulfide
PTLC	Preparative Thin Layer Chromatography
M^+	Molecular Ion
HPLC	High Pressure Liquid Chromatography
FT-IR	Fourier Transform Infrared Spectrometry
NMR	Nuclear Magnetic Resonance Spectroscopy
EIMS	Electron Impact Mass Spectrometry
GC	Gas Chromatography
FID	Flame Ionization Detector
TLC	Thin Layer Chromatography
MS	Mass Spectrometry
HRMS	High Resolution Mass Spectrometry
δ	Chemical Shifts (ppm)
R_f	The Motion of the Component Relative to the Solvent Front
br	Broad
s	Singlet
d	Doublet
t	Triplet
J	Coupling Constants (Hz)

COSY	Correlation Spectroscopy
XH CORR	Heteronuclear Correlation
DEPT	Distortionless Enhancement by Polarization Transfer

INTRODUCTION

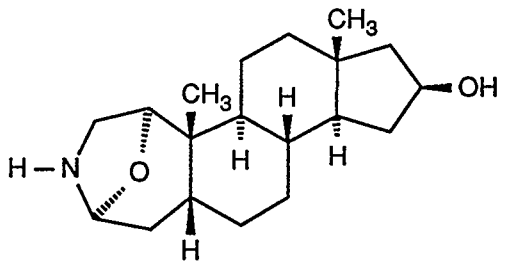
Alkaloids are generally understood to be basic nitrogenous organic natural products usually, but by no means exclusively, of plant origin. Many of them possess physiological activity and investigations of such properties have contributed much to the development of modern pharmacology. Thus, but to list a few examples: *d*-tubocurarine, an active ingredient of South American arrow poison, is a powerful skeletal muscle relaxant; emetine is an effective amoebicide; and quinine is a famous antimalarial. Alkaloids are classified as secondary metabolites, a reflection of our relatively poor understanding of their biological role. However, it can be speculated that alkaloids have an ecological role: serving to regulate the biology of other species which come in contact with their host organism and its immediate environment. Plant alkaloids are usually bitter constituents and it has been postulated that as a consequence they may protect against herbivores.[1]

As noted at the outset, alkaloids are not limited in nature solely to the plant kingdom. Apart from microbial sources, they have also been found in both invertebrates and vertebrates. In particular, amphibians have been shown to possess rare and unique alkaloids, usually present in only very small amounts. The potency of these amphibian alkaloids, as well as their unusual structures, have attracted considerable attention; as for example the role of alkaloids from Dendrobatid frogs in Colombian arrow poisons. For further details of this, as well as the general field of amphibian alkaloids, the reader is referred to a recent comprehensive review of these compounds by Daly and Spande.[2] Here the discussion will be confined to a brief survey of those isolated from salamanders.

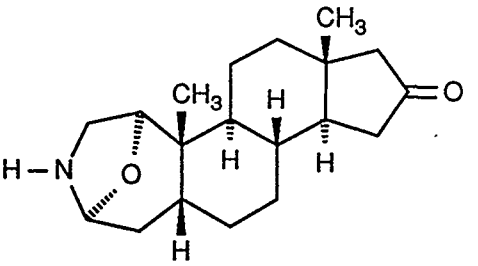
1.1 History of the Salamander Alkaloids

Since antiquity, the German fire salamander has been associated with the production of poisonous substances. A search for the active components resulted in the isolation of an alkaloidal substance called samandarine.[3] At the turn of the century, Faust[4,5] and Netolitzky,[6] both reported the finding of samanderine alkaloids in two subspecies of fire salamander *Salamandra maculosa taeniata* (Western Europe) and *S. maculosa maculosa* (Balkan states). In the late 1920's, Gessner *et al.*[7] first reported the pharmacological profile of the gummy poison obtained from the parotid and skin glands of the fire salamander. Several years later, Schöpf and colleagues purified and characterized a number of constituents from such a crude extract. Two major alkaloids were found: samandarine (**1**)[8-10] (60-70% total alkaloid content) and samandarone (**2**)[8-10] (10% total alkaloid content) together with two minor alkaloids samandaridine (**3**)[8,11,12] and cycloneosamandione (**4**)[8,9,11,13-18] (3% total alkaloid content). Subsequently other minor alkaloids were shown to be present. They include *O*-acetylsamandarine (**5**),[19] cycloneosamandaridine (or isocycloneosamandaridine) (**6**),[20-22] samandenone (**7**),[23,24] samandinine (**8**),[25] and samanine (**9**),[26] (see Diagram 1).

MAJOR ALKALOIDS

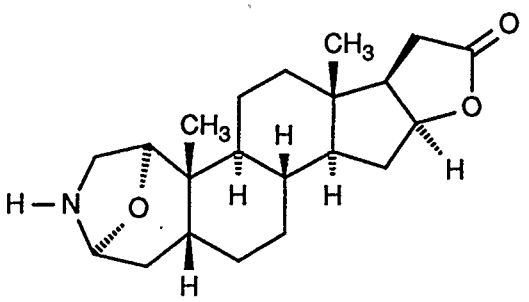


Samandarine (**1**)

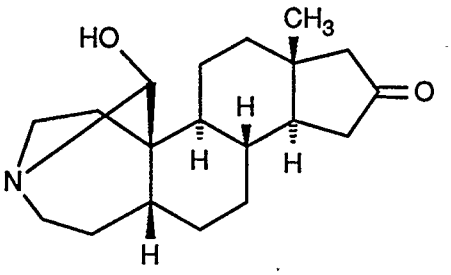


Samandarone (**2**)

MINOR ALKALOIDS



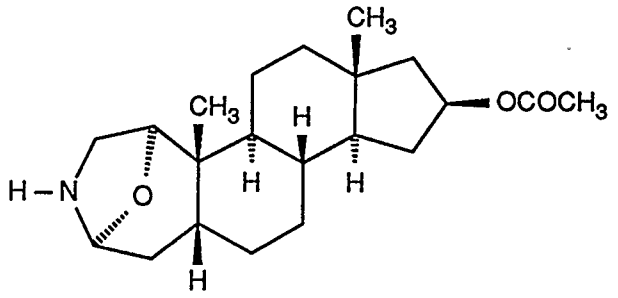
Samandaridine (**3**)



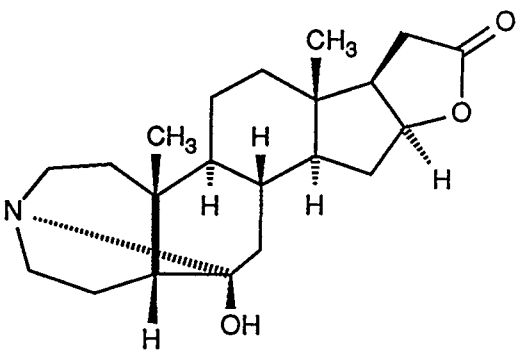
Cycloneosamandione (**4**)

Diagram 1. Structures of salamander alkaloids

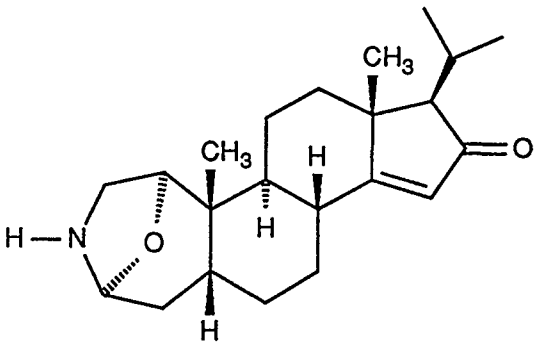
OTHER MINOR SALAMANDER ALKALOIDS



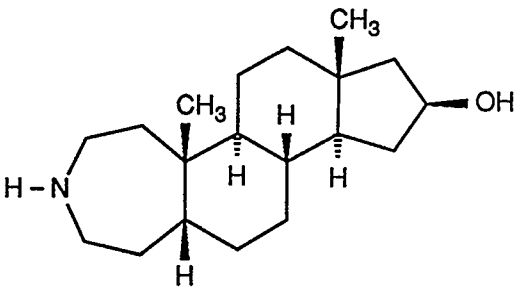
O-Acetylsamandarine (**5**)



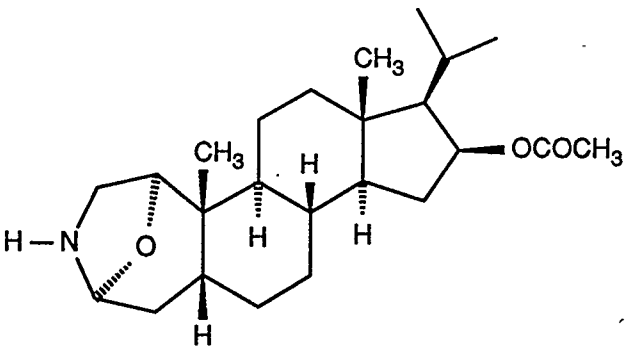
Isocycloneosamandaridine (**6**)



Samandenone (**7**)



Samanine (**9**)



Samandinine (**8**)

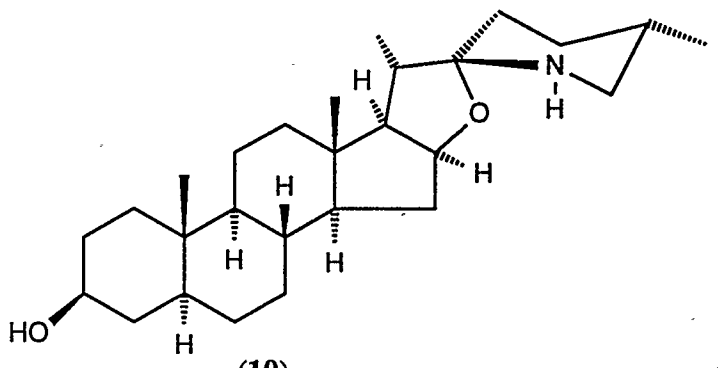
Diagram 1. (continued)

1.2 Structures of Salamander Alkaloids

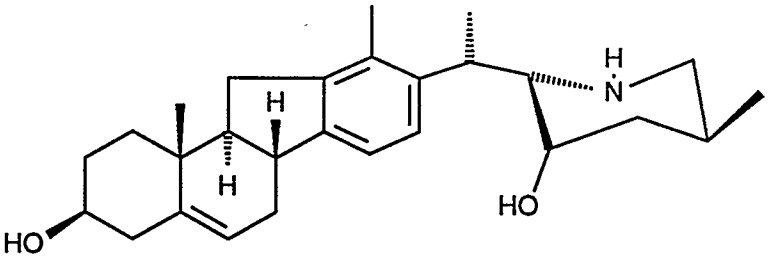
In 1961, Schöpf *et al.*[13-15] established the structures of samandarine (**1**) and samandarone (**2**) using both chemical and x-ray crystallographic methods. Later, the structures of samandaridine (**3**)[8,11,12] and cycloneosamandione (**4**)[9,16-18] were elucidated by x-ray crystallographic analysis and by partial synthesis. The structures of the other minor samandarine alkaloids were deduced using spectral properties[9,10,16,22,27] and ultimately by total synthesis[8,11,18-22,24,26,27,29-35] in addition to relating them to the more common samandarines previously characterized.

The common skeletal features of samandarine alkaloids is that they contain the 3-aza-A-homo-5β-androstane system. The individual alkaloids can be further subdivided into three categories: those with (1) a 1α,4α-oxygen bridged system, represented by samandarine (**1**); (2) carbinolamines, formed by the intramolecular cyclization of the 3-aza atom onto a carbonyl group (C19-aldehyde or C6-ketone), represented by cycloneosamandione(**4**), and isocycloneosamandaridine (**6**); and (3) an unmodified 3-aza-A-homo steroid system, as in samanine (**9**).

Other kinds of aza steroids are encountered in the plant kingdom, microorganisms, and amphibians. Their structural diversity can be illustrated by the following examples: tomatidine (**10**)[36] isolated from tomato (the 3-*O*-glycoside is fungitoxic); veratramine (**11**)[37] a C-nor-D-homosteroid from Veratum sp. (antifeedent); azasterol B (**12**)[38] a 15-aza-D-homosterol from the fungus *Geotrichum flavo-brunneum* (a fungicide); and batrachotoxin (**13**)[39,40] from poison-dart frog *Phyllobates aurotaenia* (Colombian arrow tip poison, cardiotonic agent and sodium channel activator), (see Diagram 2). As with the salamander alkaloids, details of their biosynthesis, in particular the ways in which the nitrogen atom is introduced into the steroid skeleton, are unknown.



(10)



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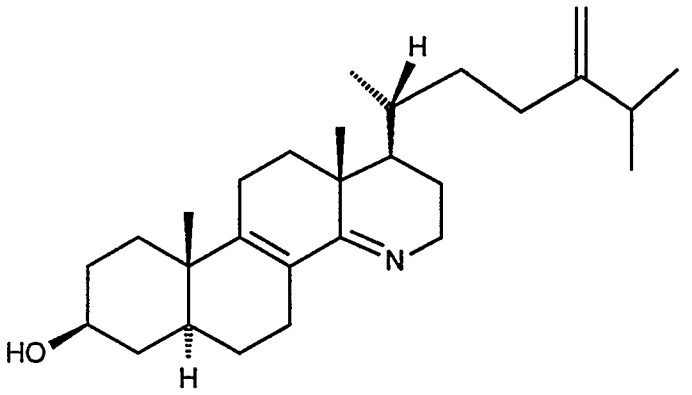

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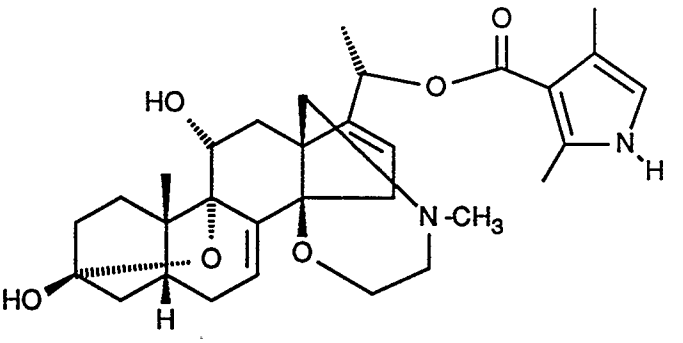


(13)

Diagram 2. Other naturally occuring aza steroids.

1.3 Pharmacological Properties of Salamander Alkaloids

The alkaloid mixture excreted from the skin glands of *S. maculosa* is very toxic to other animals[3] and salamanders themselves are not immune to the toxins. Initially, the toxicity begins with convulsions, weakening of respiration and reflexes. As well, cardiac arrhythmias begin to occur. This is followed by partial paralysis, and finally death. These physiological effects are thought to be mediated through the central nervous system;[3,41] however the precise mode of action of the samandarines has yet to be established. Another noteworthy pharmacological property of samandarine (**1**) is its potent local anesthetic activity. Recent evidence suggests that it acts at the level of the sodium channel[42,43] similar to the structurally different batrachotoxin (**13**).[44]

LITERATURE SURVEY OF THE SYNTHESES OF SALAMANDER ALKALOIDS

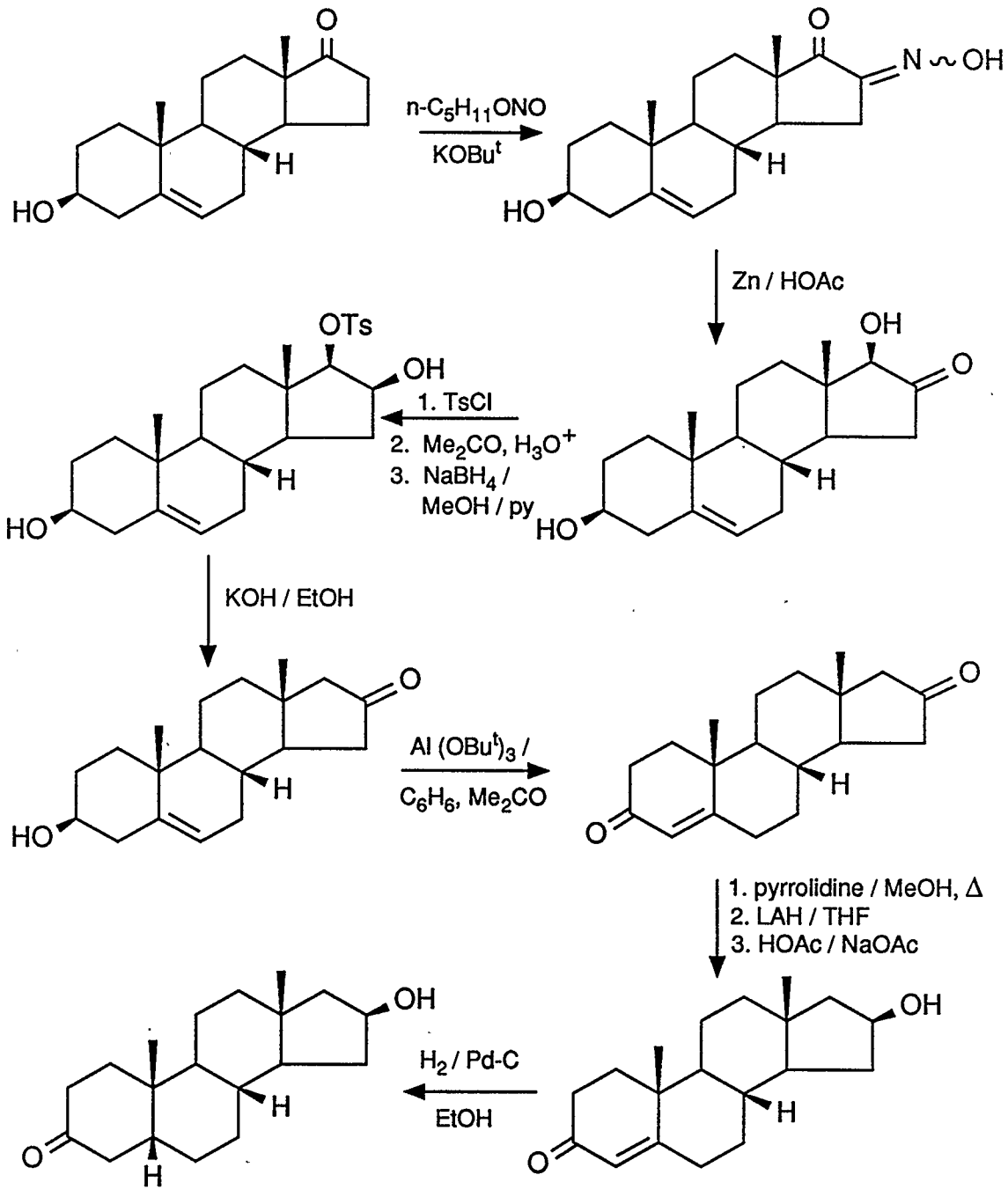
2.1 Syntheses of Salamander Alkaloids

A review of the syntheses of the oxazolidine (1α,4α-oxido bridged) and the carbinolamine salamander alkaloid systems can be found in the monograph by Daly and Spande.[2]

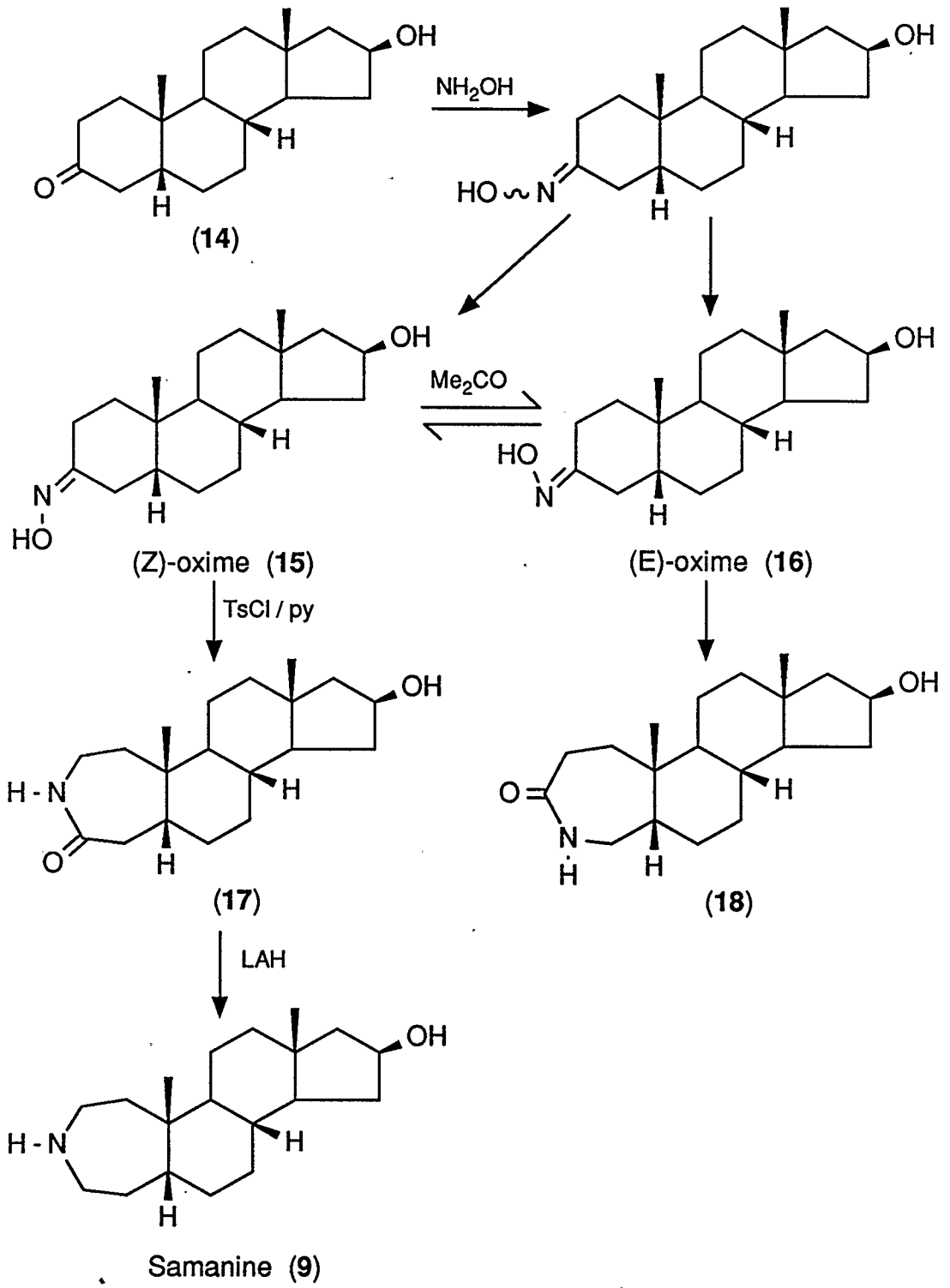
Although samanine (**9**) appears to be the simplest of the systems, only three syntheses have been reported. The first by Oka and Hara[30] in 1969 featured the Beckmann rearrangement of the oximes of the 3-keto-5β-steroid (**14**), (see Scheme 1). A mixture of the (Z)- and (E)- (*syn*- and *anti*-)oximes (3:2) (**15** and **16** respectively) was obtained. After the separation of the (Z)-isomer (**15**) its subsequent rearrangement gave the pure 3-aza lactam (**17**). The (E)-isomer (**16**) could be equilibrated to produce more of the (Z)-isomer (**15**). The final step in the synthesis of samanine (**9**) involved the LAH reduction of the 3-aza lactam (**17**).

A similar approach was used by Habermehl and Haaf,[26] except the oxime mixture was carried through to a lactam mixture (1:1), (**17** and **18** respectively) which was separated (refer to Scheme 1). Samanine (**9**) was then obtained from (**17**) as before.

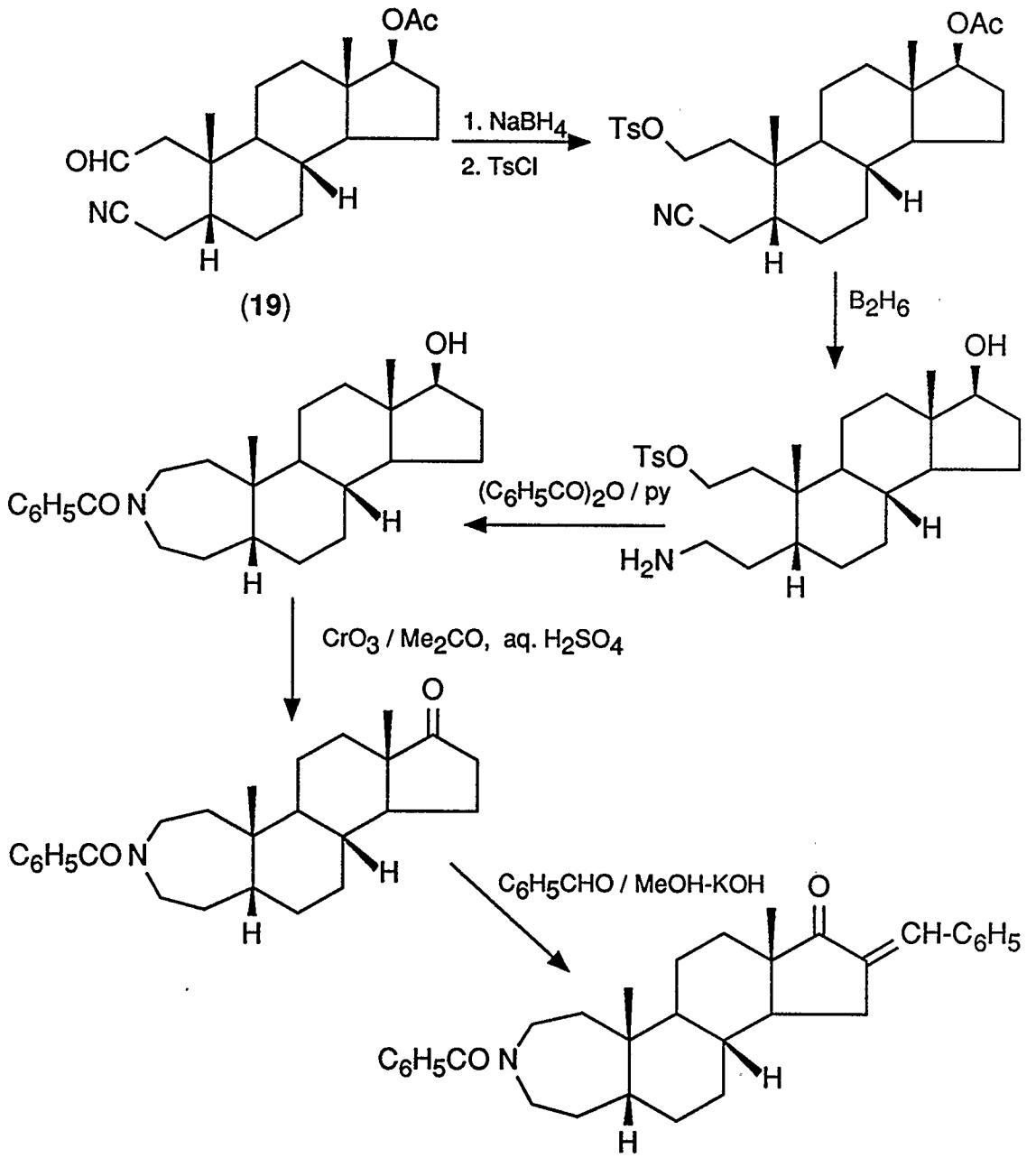
The third method employed in the synthesis of samanine (**9**) was reported by Rao and Weiler[35] in 1973. These authors utilized a 2,3-seco-5β-steroid (**19**) as their starting material (refer to Scheme 2) which allowed for the regiospecific synthesis of a 3-aza-A-homosamanine analogue (**20**). The authors have claimed that (**20**) is a useful intermediate for conversion to samanine (**9**) and its derivatives.



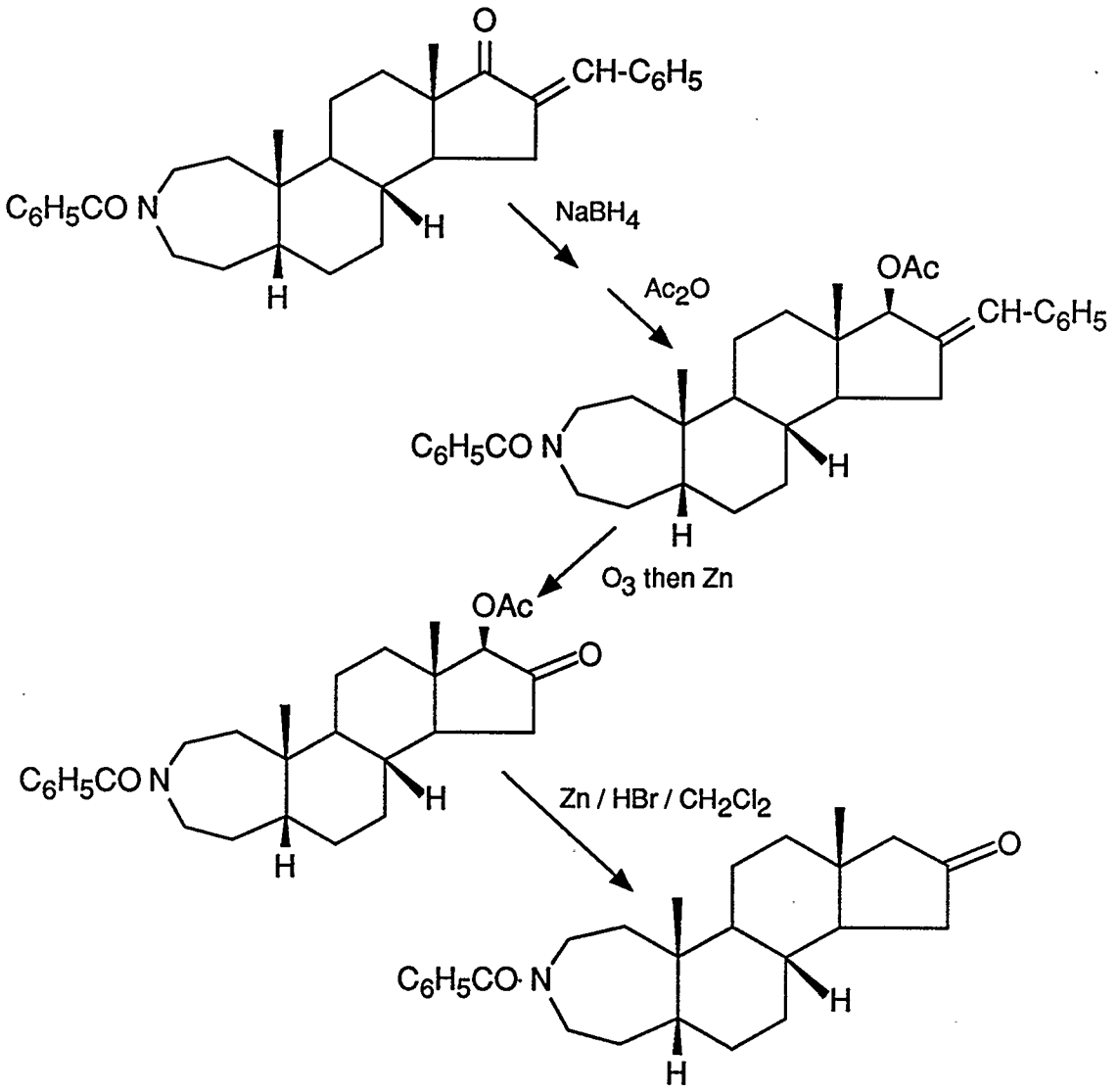
Scheme 1. The Oka and Hara / Habermehl and Haaf route in the synthesis of samanine (**9**) featuring the Beckmann rearrangement of the oximes isomers (**15** and **16**).[2]



Scheme 1. (continued).



Scheme 2. The Rao and Weiler 2,3-seco-5β-steroid (**19**) route to the 3-aza-A-homo ring system of samanine (**9**).[2]



N-Benzoyl-16-keto
Samanine analogue (**20**)

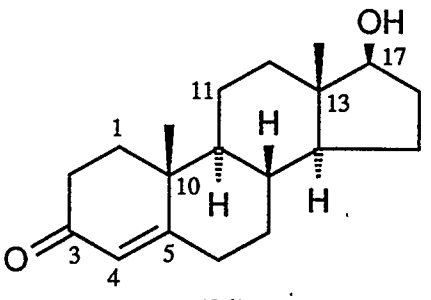
Scheme 2. (continued).

2.2 Objectives

Samandarine alkaloids are intriguing not only for their unusual structural features but also their toxicological and pharmacological properties which have not been fully characterized. All of these alkaloids have a 3-aza-A-homo system and a 5β-hydrogen. The objective of the work described in this thesis was to devise a practical synthesis of samanine (**9**) with the potential for producing analogues to be used in pharmacological testing. In the synthesis of samanine (**9**) from readily available steroids, two challenges had to be met: (1) the construction of 3-aza-A-homo-5β-androstane system; and (2) the 16β-hydroxylation of this skeleton.

2.3 Construction of the D-Ring System of Samanine

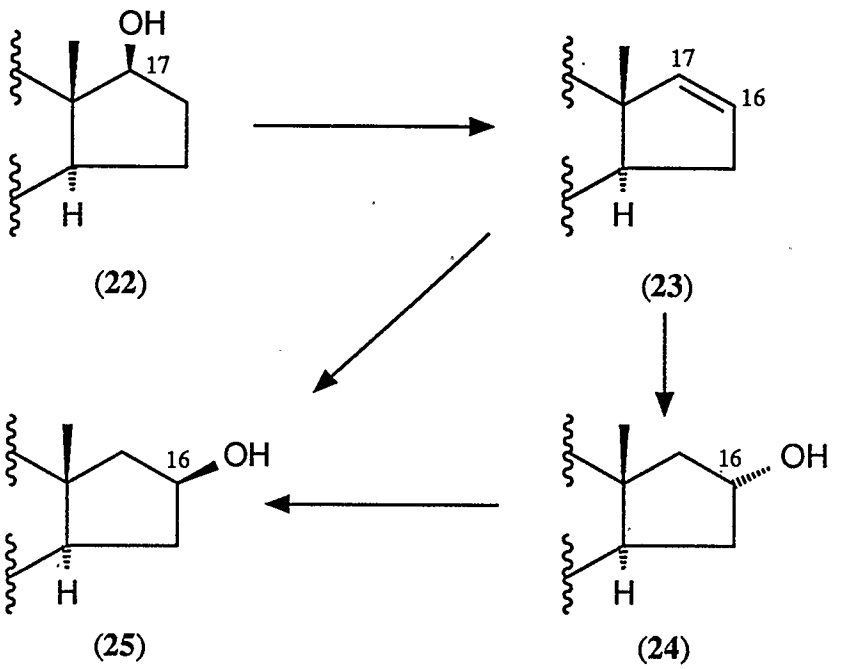
Our approach to the synthesis of samanine (**9**) involved a partial synthesis, i.e. the synthesis of (**9**) starting from commercially available and inexpensive steroids of natural origin. In practice these starting materials are either pregnane or androstane derivatives which have respectively either a two-carbon side-chain, or an oxygen function at C17. Shaw[45] explored the transformation of 16-pregnen-20-ones to androstan-16-ones via their conversion to 17(20)-en-16-ones followed by a Michael addition of water and a retroaldol cleavage of the side chain, but the overall yields were not satisfactory and we decided to rather work with androstanes as starting materials. This choice then requires the transposition of either a hydroxyl or carbonyl function from C17 to C16. Numerous methods have been described for 1,2-carbonyl transposition,[46,47] but after surveying them we decided to first attempt a 1,2-hydroxyl transposition on testosterone, (17β-hydroxy-4-androsten-3-one) (**21**), (Figure 1) this being the cheapest of the readily available androstane derivatives.



(**21**)

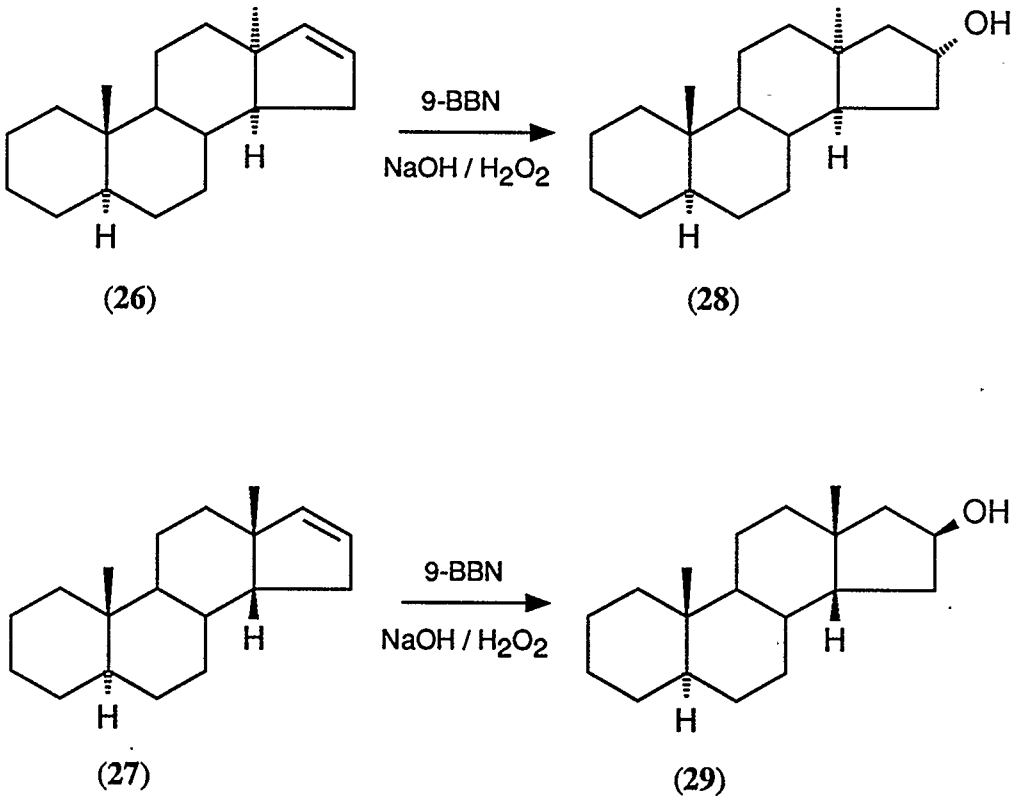
Figure 1. 17β-Hydroxy-4-androsten-3-one (Testosterone).

Our idea was that an elimination from a 17β-hydroxy-5β-androstane (**22**) to yield the 5β-androst-16-ene (**23**) might be followed by a regioselective rehydration, (see Scheme 3).



Scheme 3. Proposed route for the 1,2-transposition of a 17β-hydroxy (**22**) to a 16β-hydroxy steroid (**25**).

To achieve the latter we planned to use a bulky borane, with the expectation that it would add from the α-face, with the borane remote from the quaternary system at C13. In the literature we discovered some precedents supporting this approach in the report of Calinaud *et al.*[48] who hydroborated both 5α,13α,14α-androst-16-ene (**26**) and 5α,13β,14β-androst-16-ene (**27**) with 9-borabicyclo[3.3.1]nonane (9-BBN), and then oxidized the products and obtained the corresponding 16α- (**28**) and 16β-hydroxyl derivatives (**29**) respectively, as depicted in Scheme 4.



(26) (28)

(27) (29)

Scheme 4. Regioselective hydroboration of androst-16-ene derivatives to the corresponding alcohols.[48]

With this in mind we visualized the steric effects in androst-16-ene (**23**) as analogous to the 3,3-dimethylbutene system, which was known from the pioneering studies of Brown *et al.*[49,50] to undergo regioselective hydroboration in the desired manner (see Figure 2).

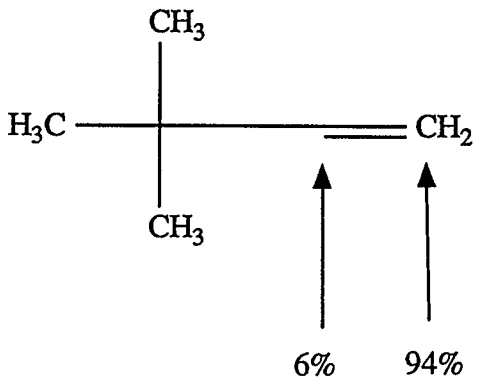
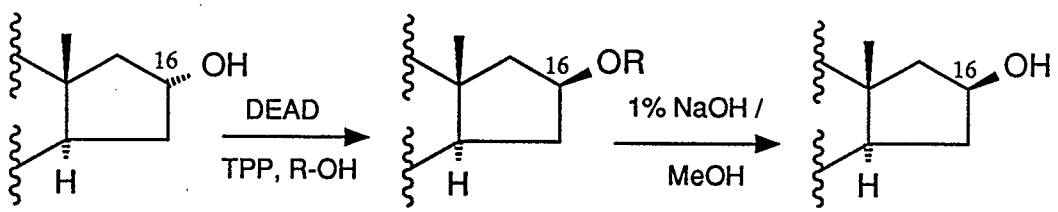


Figure 2. Hydroboration preferentially placing boron on the terminal position.

In our case this would then lead, after the oxidative workup, to either a 5β-androstan-16α-ol (**24**) or -16β-ol (**25**), but we anticipated that the former should predominate on account of the relative ease of approach of the borane to the less-hindered α-face of the alkene. In order to complete the D-ring of samanine (**9**) a final stereochemical inversion would then be needed to set up the required androstan-16β-ol (**25**), (see Scheme 3). Numerous methods exist for the inversion, either proceeding by way of nucleophilic substitution or an oxidation-reduction sequence.[51] Since the latter would have to be highly stereoselective to satisfy our needs we preferred to use the Mitsunobu reaction. This reaction is known to be work well for the conversion of secondary alcohols to esters with inverted stereochemistry.[52] The desired alcohol (**25**) can then be readily obtained by saponification of the ester (**30**), (see Scheme 5).



(24) (30) (25)

R= $COCH_3$, COC_6H_5

Scheme 5. Alcohol inversion at C16 using the Mitsunobu reaction.

RESULTS AND DISCUSSION

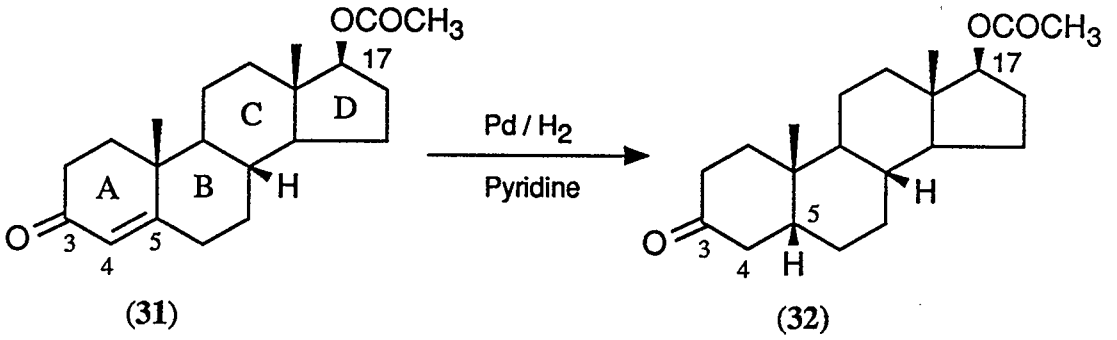
3.1 Catalytic Reduction of Steroid 4-en-3-one Systems

The A-ring of testosterone acetate (**31**) which consists of a 4-en-3-one system required some modification prior to our manipulation of its D-ring system. In particular the 4-en-3-one system has to be masked before the hydroboration step. We decided to reduce it, and convert the resulting ketone into a ketal. Reduction of the enone system could also be most useful in setting up the desired stereochemistry at the C5 ring junction by converting (**31**) to 5β-androstan-3-oxo-17β-yl acetate (**32**) as in Scheme 6.

In the literature we found numerous methods to reduce the olefin of enones selectively, with the product stereochemistry being a function of the catalysts and solvents employed for the hydrogenation.[53,54] For 4-en-3-one steroids hydrogenation in neutral solvents is said to produce varying mixtures of 5α- and 5β-isomers.[55,56] However, in acidic media the reduction was said to favour the 5β-product. Thus, the reduction of 4-en-3-one steroids in aqueous ethanolic hydrochloric acid, or aqueous hydrobromic acid in glacial acetic acid has been frequently used to prepare 5β-products, with the latter procedure recommended to give the highest yields of these products.[57-59]

However, we were unable to reduce testosterone acetate (**31**) under the conditions claimed by Nishimura *et al.*[57,58] to give optimal conversions to (**32**) (i.e. at atmospheric pressure and room temperature, using glacial acetic acid containing aqueous hydrogen bromide as solvent). We then used 95% ethanolic-hydrogen chloride as solvent under the same conditions: reduction occurred but the product was a mixture in which the β-isomer predominated over the α-isomer in unsatisfactory ratio (1.7:1). As the separation of the two isomers on column chromatography was laborious ($\Delta R_f = 0.08$, between the two isomers) we decided to abandon this procedure and turn our attention to reducing our 4-en-3-one steroid in basic media. Another method of Nishimura *et al.*[56] was used, in

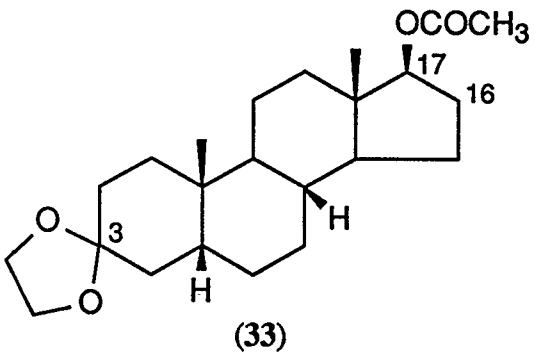
which testosterone acetate (**31**) was added to a prereduced palladium catalyst in pyridine. As before the hydrogenation was carried out at atmospheric pressure and room temperature. This method resulted in the formation of the desired 5β-isomer (**32**) in high yields (97%) and with great stereoselection (greater than 99% for the 5β-isomer), (see Scheme 6).



(**31**) (**32**)

Scheme 6. Catalytic hydrogenation of testosterone acetate (**31**).

The next step required the protection of the C3-keto functionality of (**32**) from borane reduction. For this purpose a ketal was formed, using ethylene glycol with *p*-toluenesulfonic acid as the catalyst. This reaction worked well and gave a high yield of (**33**), (see Figure 3). With the C3-keto group protected and the ring fusion at C5 fixed in a *cis*-configuration we could now leave the A-ring and concentrate on the manipulations required of the D-ring to effectively transpose the C17-hydroxyl to the C16 position.



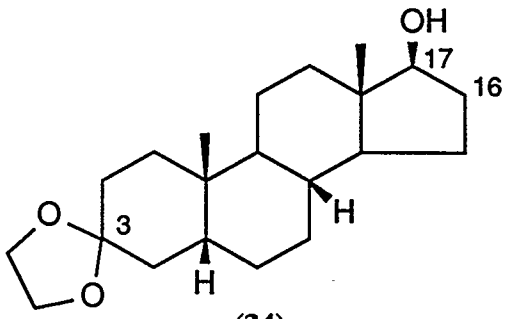
(**33**)

Figure 3. 3,3-Ethylenedioxy-5β-androstan-17β-yl Acetate (**33**).

3.2 Synthesising the 16-ene Steroid

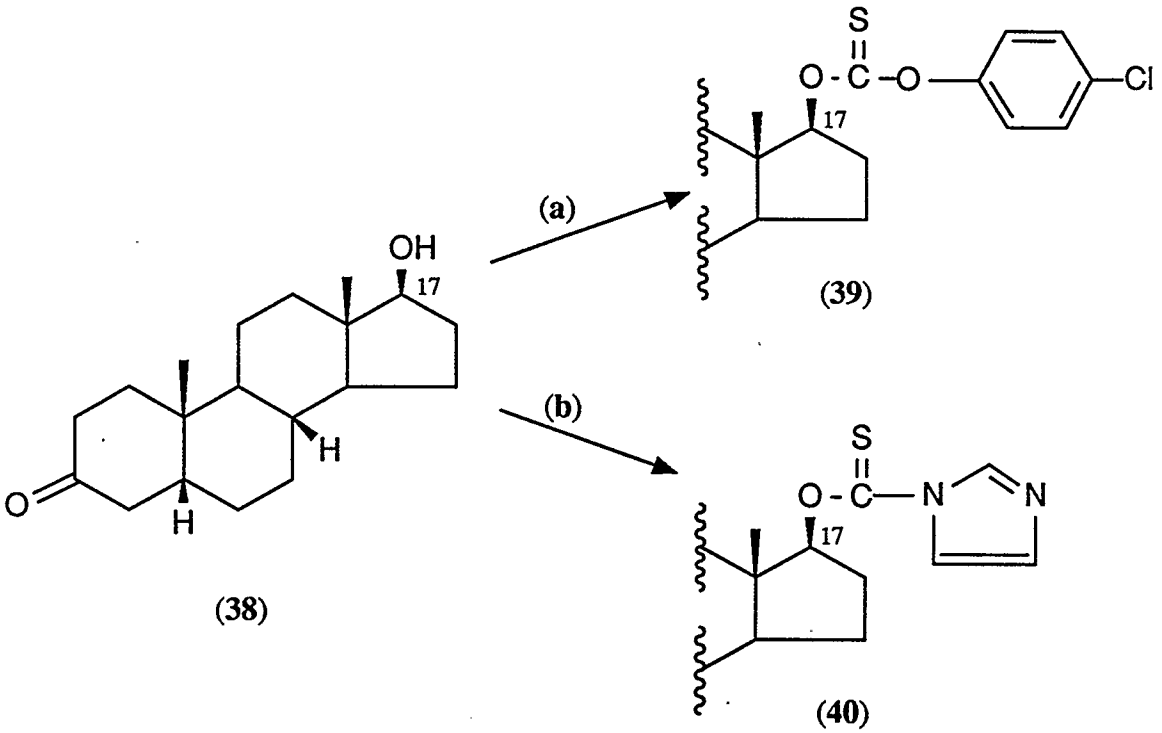
Following transesterification of (**33**) to (**34**) with methanolic sodium hydroxide, an alcohol function was unmasked at C17, (see Figure 4) and we then focused on its elimination. We contemplated using the standard methods of elimination, using either a tosylate or halide but our concerns were centred around the possiblity of competing S_N2 reactions which often plague E2 eliminations. With this in mind, we decided to proceed with the pyrolytic route. While pyrolytic elimination of esters is a commonly used method for compounds containing hydroxyl groups, the advent of organoselenium chemistry has provided an alternative method via the transformation of primary and secondary alcohols into aryl selenides[60] and conversion of these selenides to olefins via selenoxide eliminations; a process which occurs with great efficiency at relatively low temperature. Selenoxide elimination, like ester pyrolysis, proceeds through a *syn*-elimination and follows a concerted mechanism. This process is facile, stereospecific and high yielding in products. The only real limitation imposed in the use of selenium is that it is objectionable from an environmental point of view (ie. in terms of the disposal of selenium containing wastes). Nevertheless this problem induced us to first examine ester pyrolysis as a route to the 16-ene system.

Guided by the claims made in the literature for the pyrolysis of phenylthiono-carbonyl esters,[61-63] we first converted (**38**) [which itself was obtained from the acid hydrolysis of (**32**)], to the 4-chlorophenyl thionocarbonate derivative (**39**), (see Scheme 7).



(34)

Figure 4. 3,3-Ethylenedioxy-5β-androstan-17β-ol (**34**).



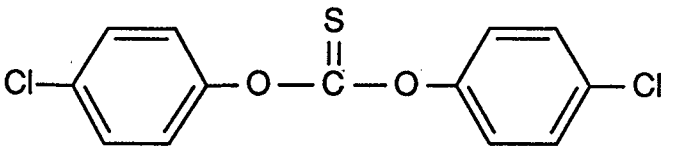
(38)

(40)

Scheme 7. Functionalization of the C17 hydroxyl of (**38**).
(**a**) *p*-Cl $C_6H_4OC(S)Cl$ / py;
(**b**) ImC(S)Im / THF , reflux.

However, we found that this was always accompanied by considerable amounts of the *bis*-(4-chlorophenyl) thionocarbonate (**41**), (see Figure 5) and chromatography was required to remove this by-product, whose formation is analogous to that observed by

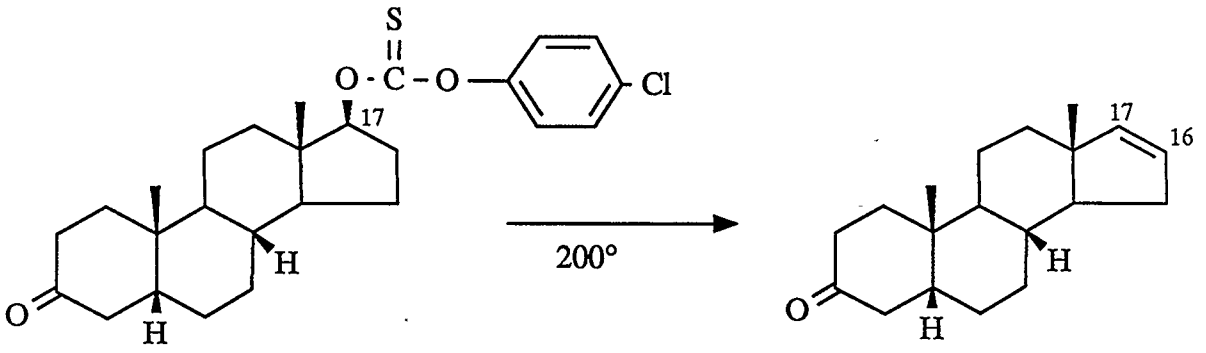
Gerlach and Müller[63] in esterifications with *O*-4-methylphenyl chlorothioformate.



(41)

Figure 5. *bis*-(4-Chlorophenyl) Thionocarbonate.

Although pyrolysis of (**39**) afforded the desired 16-ene (**42**), the overall yield from (**39**) was unsatisfactory (*ca.* 38%) (see Scheme 8).



(39) (42)

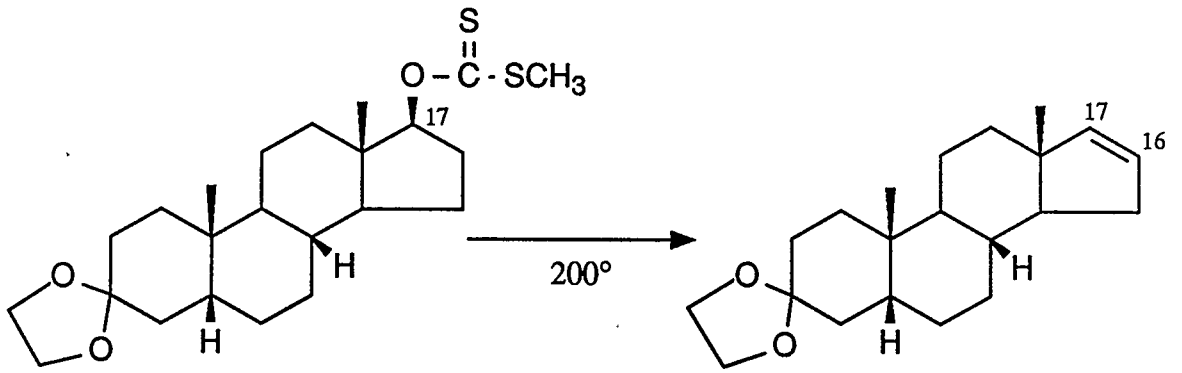
Scheme 8. Pyrolysis of (**39**) to the 16-ene steroid (**42**).

We therefore examined the thionocarbonylimidazolides (**36**) and (**40**), prepared by the reaction of (**34**) and (**38**) respectively with N,N'-thionocarbonyldiimidazolide as reported by Barton *et al.*[64,65] in the hope that yields for both (**36**) and (**40**) would improve, (see Schemes 7 and 9). Here too we encountered experimental difficulties in as much as the yield of (**36**) and (**40**) were modest (78% and 63% respectively), and extensive chromatographic purification was required in order to obtain pure material (see Schemes 7

and 9).

We therefore elected to examine other derivatives for ester pyrolysis. Possible candidates for such pyrolytic eliminations include xanthates (Chugaev reaction), carbonates, benzoates, acetates and N-oxides (Cope eliminations). The disadvantage with the pyrolysis of simple carboxylic acid ester is the requirement of high temperatures, in the order of 300 to 500°C, usually under reduced pressures.[66] These conditions preclude the presence of other thermally sensitive functionalities in the compound.

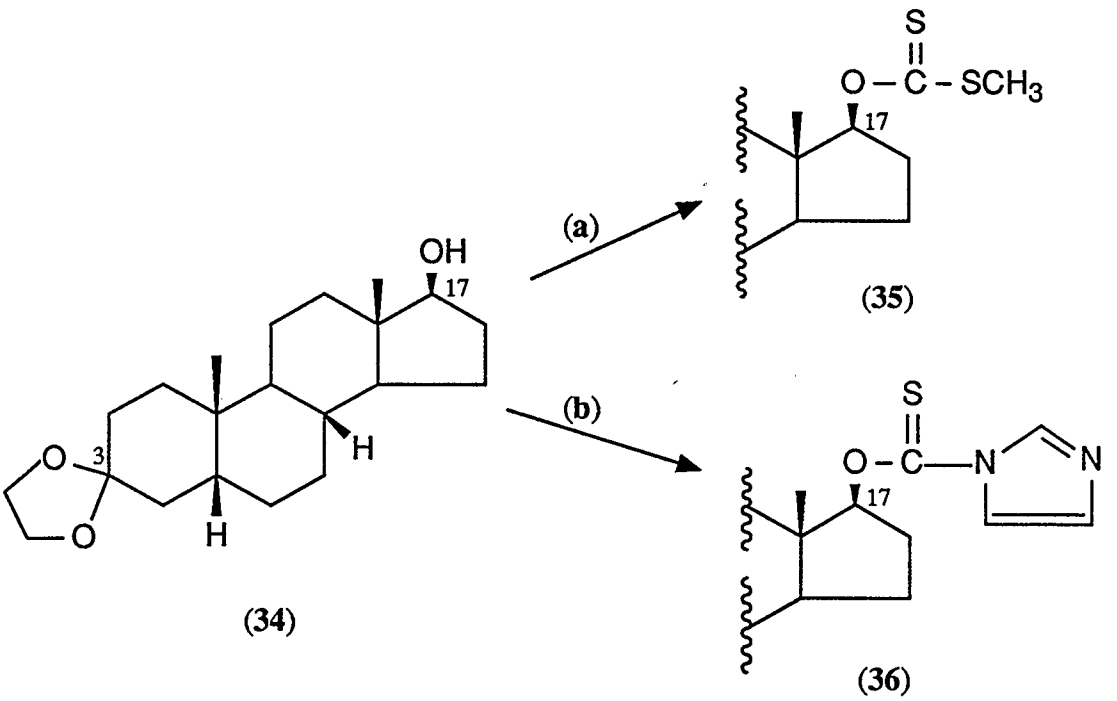
However the pyrolysis of xanthates occurs at a temperature considerably lower than carboxylic acid esters (100-200°C).[67] and as xanthates may be prepared directly from the alcohol in a relatively inexpensive and simple manner, they are practical intermediates. As with the other 17-derivatives, the elimination of 17β-xanthate (**35**) is necessarily regiospecific, away from the quaternary C13 site to form the 16-ene (**37**), (see Scheme 10).



(**35**) (**37**)

Scheme 10. Pyrolysis of the C17 xanthate (**35**) to the 16-ene steroid (**37**).

We therefore turned to the time-honoured Chugaev process. The xanthate (**35**) was readily produced in 91% yield by sequential treatment of (**34**) with methyl lithium, carbon disulfide and methyl iodide, and upon pyrolysis the 16-ene (**37**) was obtained in 87%



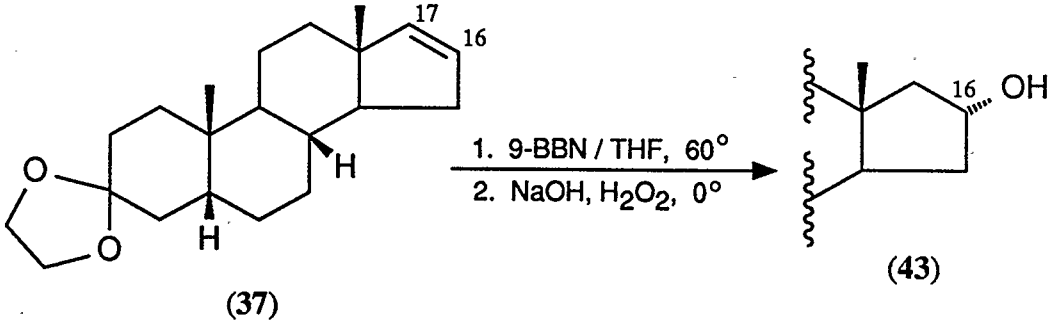
Scheme 9. Functionalization of the C17 hydroxyl of (**34**).
(**a**) MeLi / THF, -78°, then CS_2, followed by MeI;
(**b**) ImC(S)Im / THF , reflux.

overall yield. This therefore became our preferred route for the formation of the steroidal olefin (**37**), (see Scheme 10).

3.3 Functionalization of the 16-ene Steroid

We then proceeded to look at regioselectively functionalizing our 16-ene steroid (**37**). As previously noted, the decision to hydroborate (**37**) using a bulky, sterically hindered borane (i.e. 9-borabicyclo[3.3.1]nonane, 9-BBN) followed by an oxidative workup was guided by precedents reported in the literature.[48-50] The steroidal 16-ene system in (**37**) should be attacked preferentially at C16 by the borane. Steric interactions should also confer stereoselection on the hydroboration; attack by borane being from the least hindered α-face. In practice, hydroboration of (**37**) with 9-BBN followed by oxidation with alkaline hydrogen peroxide gave us a mixture shown by GC analysis to contain mainly 1,5-cyclooctanediol, and one other substance (**43**), together with a little recovered olefin (**37**), and an unidentified compound. Flash chromatography of the mixture resulted in the isolation of (**43**) (68%) and (**37**) (4%) (*cf.* Scheme 11). Similar results were obtained in subsequent experiments.

The 16α-hydroxyl stereochemistry of (**43**) was first deduced from a comparison of the chemicial shifts of the ^{13}C resonances attributed to C13, 14, 15, 16, and C17 with those from the same D-ring carbons in other 16- and 17-hydroxylated androstanes.[68] This identification of (**43**) was clinched by its subsequent transformation into the known compound (**14**) (see p. 29).



(37) (43)

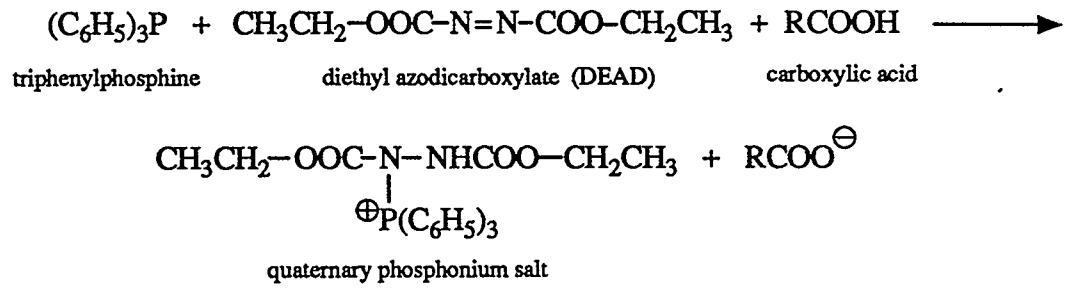
Scheme 11. The conversion of the 16-ene (**37**) to the 16α-hydroxy steroid (**43**).

The deprotection of the ketal at C3 was performed by the method of Grieco *et al.*[69] the protected steroid (**43**) was subjected to aqueous HCl (5%) in THF at room temperature overnight. By these means the regeneration of the C3 carbonyl group in compound (**44**) was achieved in high yield (90%).

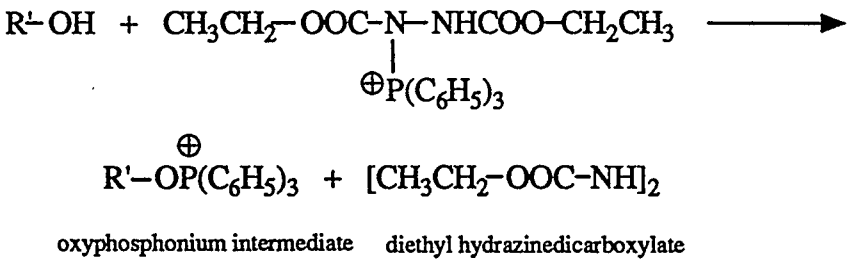
3.4 Inversion at the C16 Centre Using the Mitsunobu Reaction

The next procedure was to invert the C16 oxygen functionality from a 16α-ol steroid (**44**) to 16β-ester (**45** or **46**). This stereochemical inversion-esterification was achieved by a Mitsunobu reaction.[52] In a study of this process, Hughes *et al.*[70] pointed out that the potential for undesirable side reactions could be prevented if the carboxylic acid is initially present in the reaction. Initially the reaction involves the formation of a quaternary phosphonium salt. This is then followed by the alcohol activation step, which is faster than the S_N2 reaction, thus allowing for a buildup of the oxyphosphonium intermediate. The third step is the rate determining step (S_N2 reaction) which gives rise to ester formation with and an inversion of configeration at the carbon centre. It is this intermediate (oxyphosphonium species) that undergoes slow displacement by the carboxylate anion (Scheme 12).

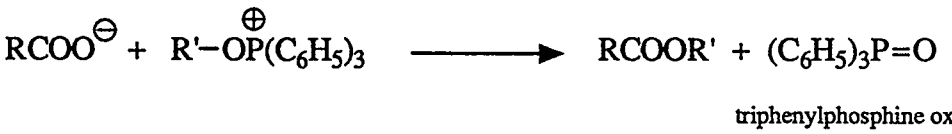
Step 1: Adduct Formation



Step 2: Alcohol Activation



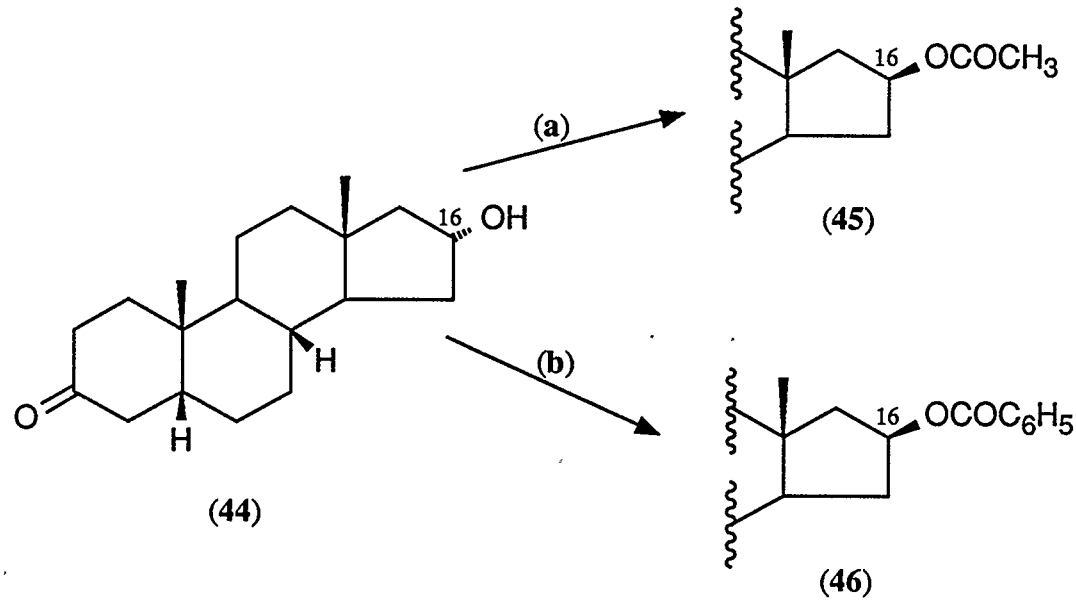
Step 3: S_N2 Reaction



Scheme 12. The three step mechanism in the Mitsunobu reaction.[70]

In our hands, the use of glacial acetic acid gave low yields (47%) of product (**45**) when the reaction was carried out for 36 hr in refluxing dry benzene, and similar results were obtained with that acid in other experiments. However, when benzoic acid was used a substantial improvement was observed. The yield of inverted product (**46**) was 75%, when the reaction was carried out under the same conditions as those used with acetic acid (Scheme 13).

The acetate ester (**45**) was then subjected to saponification using 1% NaOH in methanol following the procedure of Mashimo and Sato.[71] We did consider using aqueous HCl (5%) in THF as described previously in the hydrolysis of 5β-androstan-17β-yl acetate (**32**) but found experimentally that the yield of the known ketone[26] (**14**) was essentially quantitative (95%), and the reaction was complete in 2 hr, under basic conditions.

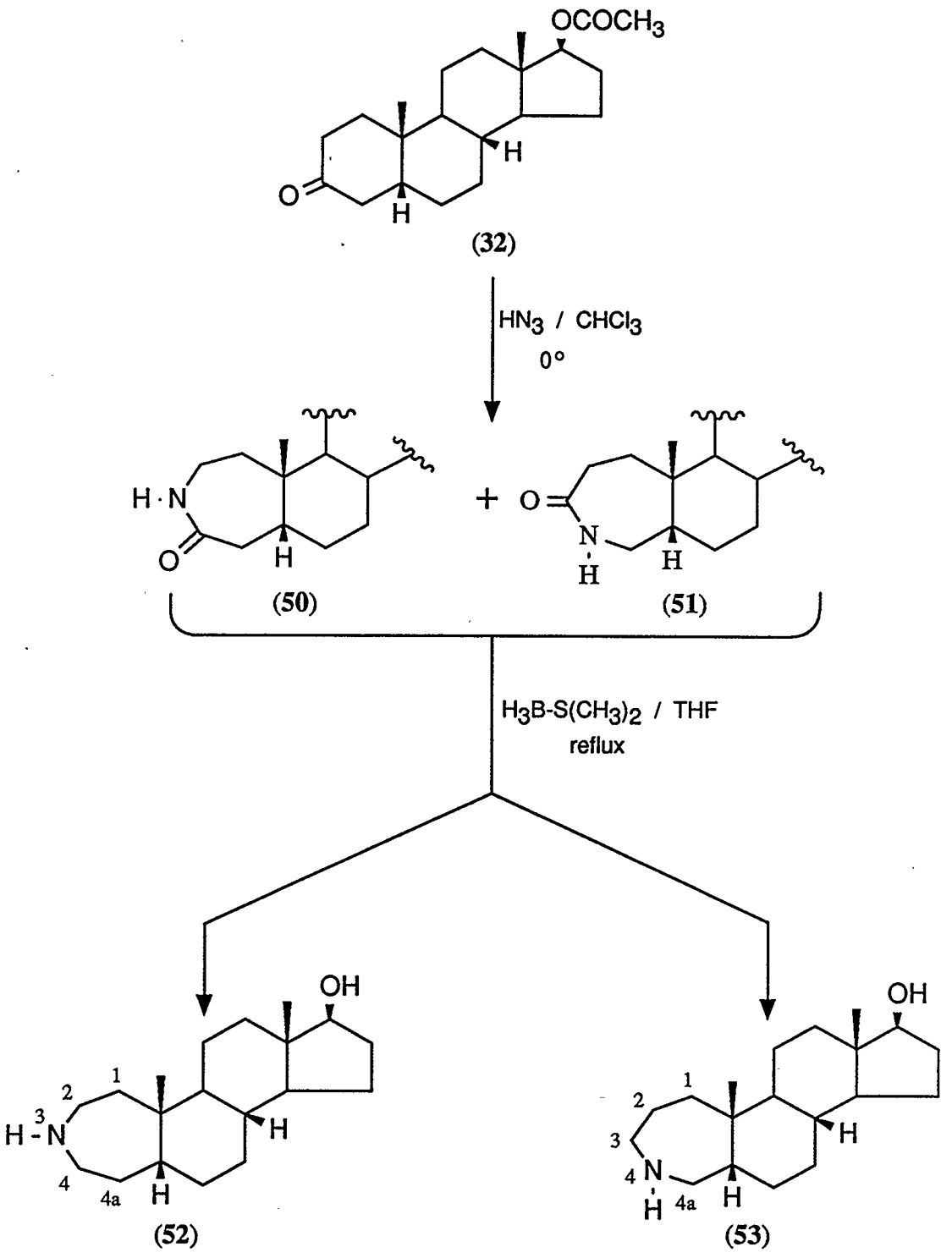


Scheme 13. The Mitsunobu reaction on the 16α-hydroxy steroid (**44**).
(**a**) DEAD, $(C_6H_5)_3P$, HOAc, C_6H_6;
(**b**) DEAD, $(C_6H_5)_3P$, C_6H_5COOH, C_6H_6.

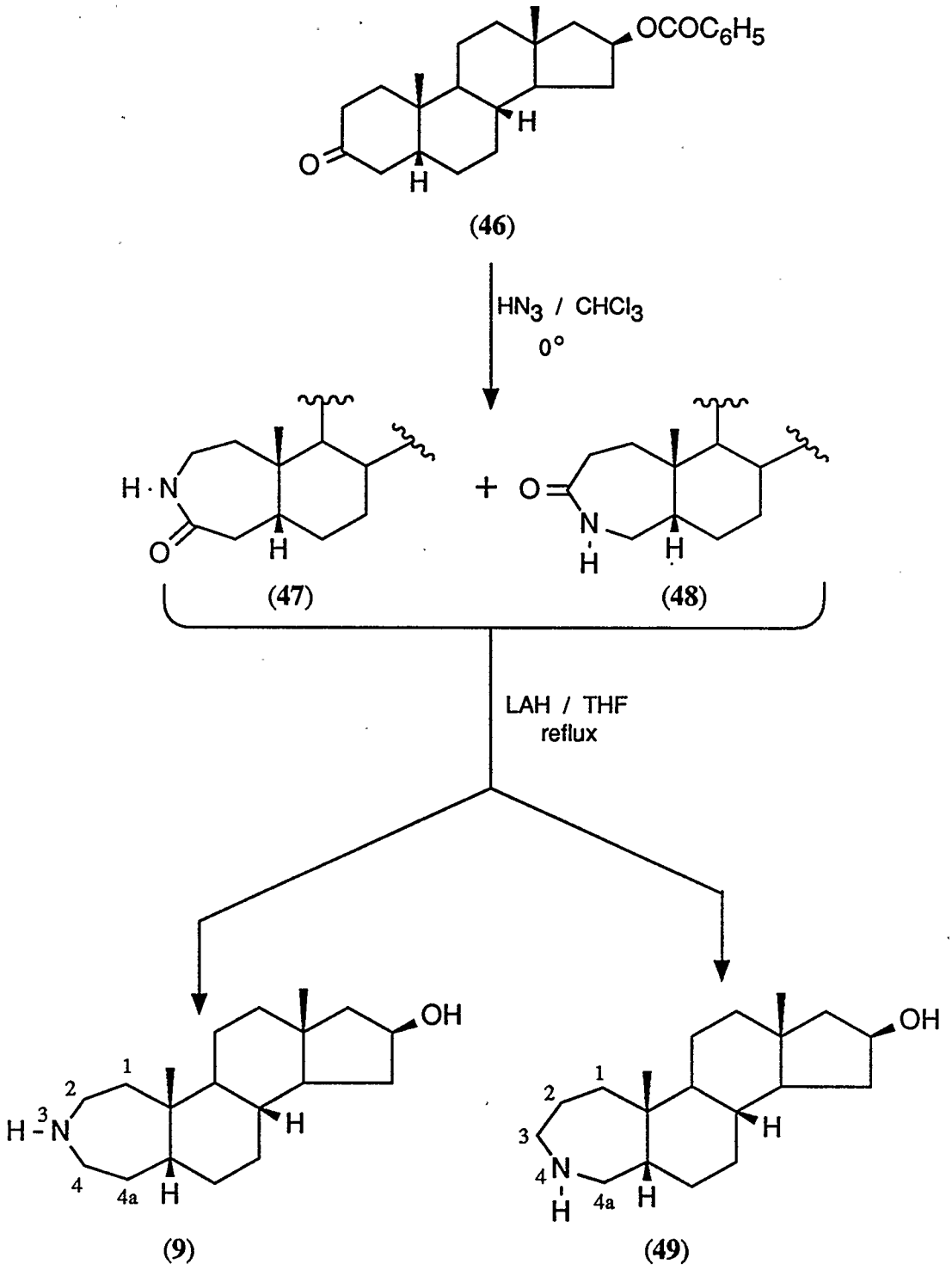
3.5 A-Ring Lactam Formation Using the Schmidt Reaction

Turning our attention once more to the A-ring, our next task was to incorporate nitrogen into this ring. In a sense, once having reached 16β-hydroxy-5β-androstan-3-one (**14**) a formal synthesis of samanine (**9**) is complete, since it is from this point that both Oka and Hara[30] and Habermehl and Haaf[26] prepared samanine (**9**). However we decided to explore the synthesis of samanine (**9**) using an alternative approach that appeared to be quicker than those used in the previous syntheses.

Our idea was to use the Schmidt reaction to generate the lactams directly from (**14**), bypassing the oxime formation used in previous syntheses. Our first application of this approach as described by Shaw[45] was on the model compound (**32**) which gave a lactam mixture (**50** and **51**) in 70% yield (see Scheme 14). Although the separation of the lactam mixture was possible, it required extensive chromatographic procedure. We therefore decided to reduce the lactam mixture first, and then to separate the two amine components by chromatography. When we performed the Schmidt reaction on (**45**), it too gave a (*ca.* 1:1) lactam mixture of (**47**) and (**48**) in 86% yield (see Scheme 15). Again, as with our model we elected to reduce the lactam isomers prior to separating the regioisomeric azasteroids.



Scheme 14. The Schmidt reaction on (**32**) followed by the borane-dimethyl sulfide (BMS) reduction of the lactams (**50** and **51**).



Scheme 15. The Schmidt reaction on (**45**) followed by LAH reduction of the lactams (**47**) and (**48**).

3.6 Reduction of the Lactams Using Borane-dimethyl Sulfide

In the literature, numerous examples of lactam reduction to cyclic amines were found using a variety of reagents.[72] However, while scrutinizing the individual methods we came to appreciate that in practice lactam reduction often gave low to modest yields of product.[73-78] However, we were encouraged by reports which indicated that borane-dimethyl sulfide (BMS) was the reagent of choice over any complex metal hydride[79] for reducing most amides to amines. We therefore first chose this reagent to reduce the lactam carbonyl of our model compounds (**50** and **51**) as depicted in Scheme 14. The reduction using BMS yielded 49% of a mixture of amines. The separation of the two components required PTLC, which gave the 4-aza- (**53**) in 21%, and the 3-aza-steroid (**53**) in 17% yield, based on the lactam mixture (**50** and **51**). We searched for the balance of the steroid, and detected some (by ^{1}H-NMR) remaining in the chloroform layer after this had been extracted with acid (ie. in the neutral/acid fraction from the reduction). We thought that this material might be borates, but we were unsuccessful in obtaining any more amine even after refluxing this neutral material for a prolonged time in methanolic HCl. Unimpressed by the performance of BMS, in the reduction of the lactam mixture (**48**) and (**49**), we decided to use the reliable metal hydride reagent LAH for the synthesis of samanine (**9**).

3.7 Reduction of the Lactams Using LAH

The reduction of the mixed lactams was performed in accordance with the procedure of Habermehl and Haaf,[26] but with a modification in the workup, where we followed the procedure of Mićović and Mihailovic.[80] The yield of the amine mixture (**9**) and (**49**) was 95% after repeated extraction of the precipitate as shown in Scheme 15. The separation of the two amine components on silica gel PTLC did not give clean distinct

bands of the two amine components. However we were able to remove the upper and lower portions of the bands leaving behind the central region. The amounts of recovered amine were (**9**) (0.042g; 52%) form the lower and (**49**) (0.032g; 40%) form the upper bands, based on the amount loaded onto the plates. This final separation was the least satisfactory step in our synthesis. Probably a better PTLC system could be developed, or a prep-HPLC separation. However, with samanine (**9**) attained we decided to terminate our investigation at this point.

CONCLUSION

Our unoptimised 10 step synthesis of samanine (**9**) in 17% yield from a relatively cheap, commercially available nitrogen-free steroid compares well with the two previous synthesis. Habermehl and Haaf reported a yield of 8% from the advanced intermediate 3β-hydroxy-5-androsten-16-one, while Oka and Hara achieved a 18% conversion of 3β-hydroxy-5α-androstan-3-one (epiandrostane). Probably the best procedure would be to combine the first steps of our synthesis with the final two of Oka and Hara i.e. preparation of 16β-hydroxy-5β-androstan-3-one (**14**) from testosterone acetate via hydroboration of the 16-ene, formation of the oximes, separation of these, isomerisation of the unwanted (E)- to (Z)-oxime, and then a Beckmann rearrangement of the (Z)-oxime to the 3-aza-lactam, and its reduction to samanine (**9**).

Thus we feel we have attained our objective of an improved preparation of samanine (**9**).

EXPERIMENTAL

1. Melting Points

Melting points were determined on a Leitz hot stage. All melting points are in degrees centigrade, and are uncorrected.

2. IR Spectra

A Nicolet DX system FT-IR spectrometer was used for the determination of IR spectra. All samples were prepared in KBr. The significant absorptions are reported as frequencies in wavenumber units (cm^{-1}).

3. ^{1}H-NMR and ^{13}C-NMR

The ^{1}H-NMR and ^{13}C-NMR spectra were determined with Bruker AC-200 or AM-400 spectrometers. All samples were dissolved and referenced using deuterochloroform (^{13}C δ 77.0), containing *ca.* 0.2% chloroform (^{1}H δ 7.27) or deuterobenzene (^{13}C δ 128.0), containing *ca.* 0.2% benzene (^{1}H δ 7.16). The chemical shifts of the other ^{1}H-NMR and ^{13}C-NMR signals are reported in ppm from these internal references. Where appropriate, ^{1}H-signal intensities are indicated in parentheses, as are any multiplicities, with the J-values in Hz. The numbers of H-atoms attached to carbon were determined using the Bruker Instrument Co. DEPT micro programs. In addition both COSY and XH-CORR micro programs were employed in some structural assignments. Only significant, characteristic ^{1}H-resonances are reported.

4. Mass Spectra

Low resolution EIMS were routinely obtained using a V.G. 7070F spectrometer by Mrs. Qiao Wu and the high resolution EIMS were obtained using a Kratos MS80RFA

GC/MS by Ms. Dorothy Fox both of the Department of Chemistry Instrument Facility. Both instruments were operated at 70 eV. All samples were introduced using a direct insertion probe. The reported figures given in parentheses after the mass indicate the percent relative intensity of the base peak. A value of 10% was arbitrarily chosen as a cut off, but we have also reported significant high-mass fragment ions, in addition to the molecular ion, when their abundance was lower than 10%.

5. Gas Chromatography

All GC retention times were recorded on a Hewlett-Packard 5890 Gas Chromatograph. The GC conditions were: initial oven temperature 200°; FID detector 250°C; initial oven time 1 min; rate 10°/min; final oven temperature 250°; helium carrier gas flow rate 25 mL/min; hydrogen flow 35 mL/min; air flow 500 mL/min; chart speed 5 cm/min; and a Megabore DB5 column (30 m x 0.53 mm I.D., film thickness 1.5 μm).

6. Flash Column Chromatography

The adsorbent used was silica gel 60 (E. Merck, 230-400 mesh). All columns were dry packed as recommended by Still *et al.*[81] The columns were eluted using positive air pressure. The solvent flow rate was 2 mL/min. Column loading was based on ΔR_f and column diameter.[81]

7. TLC

Silica gel 60 (E. Merck, F_{254}) plates (0.25 mm thick) 2.5 x 7.5 cm were used for analytical TLC, and phosphomolybdic acid was used to visualize the compounds on the developed plates. Solvent compositions are as stated in proportions by volume.

Phosphomolybdic acid spray reagent was prepared by dissolving ammonium molybdate (20 g) in a solution of sulphuric acid (25 ml) in water (400 ml). Plates sprayed with this reagent were briefly heated with a Heatgun®. The components appeared as dark blue spots on a white background.

8. Microanalysis

Elemental analyses for C, H, and N were performed on a Perkin Elmer CHN elemental analyzer 240B by Ms. Dorothy Fox of the Department of Chemistry Instrument Facility.

5.1 The Catalytic Hydrogenation of Testosterone Acetate; Preparation of (**32**)

a) The catalytic hydrogenation of testosterone acetate (**31**) (6.00 g; 18.2 mmol) was attempted according to the procedure of Nishimura *et al.*,[57,58] the solvent being glacial acetic acid (250 mL) containing aq. HBr (3N, 1.4 mL). The reduction was allowed to proceed for 24 hr prior to workup, but there was no indication of hydrogen uptake, and examination of the products by ^{1}H-NMR revealed only testosterone acetate (**31**).

b) An alternative procedure for catalytic hydrogenation of testosterone acetate (**31**) (5.00 g; 15.2 mmol), was carried out according to the procedure of Liston[59] using ethanol (95%, 250 mL). The desired product, 5β-androstan-3-oxo-17β-yl acetate, (**32**) and its 5α-isomer were isolated in 93% yield as a mixture (*ca.* 1:3 ratio of α:β-isomers). The two isomers could not be separated efficiently using flash column chromatography.

c) We also attempted to carry out the hydrogenation by a modified Liston[59] procedure in which conc. HCl (12N, 5 mL) was added to an ethanol solution (95%, 200 mL) containing testosterone (**21**) (5.11 g; 17.3 mmol). The reduction product was a *ca.* 1:1.7 ratio of α:β-isomers, which were separated by laborious column chromatographic procedures. This method was abandoned because it was time-consuming and inefficient.

d) Catalytic hydrogenation of testosterone acetate (**31**) (1.03 g; 3.03 mmol) in pyridine (100 mL) was carried out according to another procedure of Nishimura *et al.*[56] The catalyst palladium black was pre-reduced prior to the reduction of the substrate. The uptake of hydrogen was measured at a rate of 0.8-1 mL/min, and the hydrogenation time was 16 hr. The desired 5β-androstan-3-oxo-17β-yl acetate (**32**) was isolated in 97% yield. This procedure was repeated numerous times with reproducible results. The product was obtained as white plates, m.p. 142-145°, (lit.[82] m.p. 140-142°); IR (KBr) 2938, 1736, 1716, 1251 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.84 (s, 3H), 1.20 (s, 3H), 2.05 (s, 3H), 2.69 (br t, lH, J=13.5 Hz), 4.62 (dd, 1H, J=7.5 and 7.6 Hz); ^{13}C-NMR ($CDCl_3$) δ 37.2 (Cl), 37.1

(C2), 212.8 (C3), 42.3 (C4), 44.3 (C5), 25.4 (C6), 26.5 (C7), 35.4 (C8), 40.9 (C9), 35.0 (C10), 20.7 (C11), 37.1 (C12), 42.8 (C13), 50.8 (C14), 23.5 (C15), 27.6 (C16), 82.7 (C17), 12.1 (C18), 22.6 (C19), 21.1 (CH_3, acetate), 171.1 (C=O, acetate) (^{13}C-NMR values are within $\delta \pm 0.2$ as compared to those listed for 5β-androstan-3-oxo-17β-yl acetate (**32**) by Blunt and Strothers[68]); MS, m/z 332 (M^+) (6), 272 (32), 43 amu (100); Anal. calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.14, H, 9.70; HRMS, calcd for $C_{21}H_{32}O_3$ 332.2333, found 332.2353.

5.2 Preparation of 3,3-Ethylenedioxy-5β-androstan-17β-yl Acetate (**33**)

5β-Androstan-3-oxo-17β-yl acetate (**32**) (6.07 g; 18.24 mmol) was dissolved in benzene (75 mL). To this ρ-toluenesulfonic acid (12 mg) and ethylene glycol (10.2 mL; 183 mmol) were added and the mixture was then refluxed for 56 hr using a Dean-Stark trap to remove water. After allowing the reaction mixture to cool, crushed anhydrous K_2CO_3 (0.50 g; 0.36 mmol) was added and the suspension was stirred for 10 min. Distilled water (50 mL) was then added to the reaction flask. The pH of the aqueous solution was basic (pH 11). The benzene layer was separated from the aqueous phase and the aqueous layer was then extracted with chloroform (3 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous K_2CO_3, filtered, and the solvents removed under reduced pressure. The white colored foamy residue (**33**) amounted to (6.83 g; 99%); m.p. 97-99°; R_f 0.49 (hexanes-ethyl acetate, 4:1); IR (KBr) 2944, 1728, 1256, 1216, 1097 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.77 (s, 3H), 0.96 (s, 3H), 2.03 (s, 3H), 2.20 (m, lH), 3.94 (s, 4H, ethylenedioxy), 4.58 (dd, 1H, J=7.4 and 7.5 Hz); ^{13}C-NMR ($CDCl_3$) δ 37.2 (C1), 109.9 (C3), 39.9 (C5), 25.8 (C6), 27.6 (C7), 35.5 (C8), 40.9 (C9), 34.7 (C10), 20.6 (C11), 42.8 (C13), 50.9 (C14), 23.5 (C15), 27.6 (C16), 82.9 (C17), 12.1 (C18), 23.1 (C19), 64.2 and 64.1 (CH_2, ethylenedioxy resonances), 171.1 (C=O, acetate), 21.1 (CH_3, acetate), [30.1, 34.3, 35.7 (unassigned CH_2 resonances for C2, C4, C12)]; MS,

m/z 376 (M^+) (40), 333 (5), 316 (25), 125 (90), 99 (100), 55 (95), 43 amu (92); Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36, H, 9.64. Found: C, 73.03, H, 9.79.

5.3 The Transesterification Reaction on 3,3-Ethylenedioxy-5β-androstan-17β-yl Acetate; Preparation of (**34**)

Compound (**33**) (6.83g; 18.14 mmol) was dissolved in methanol (200 mL). To this solution was added sodium metal spheres (0.87 g, washed using pentane, then dried and cut into small pieces). The solution which resulted was allowed to stir for 12 hr at room temperature. The reaction was worked up by adding small lumps of dry ice (*ca.* 0.50g) and, when they had evaporated, this was followed by the addition of K_2CO_3 (0.50 g; 3.6 mmol). The resultant mixture was allowed to stir for 10 min at room temperature. The methanol was then removed under reduced pressure. The residue was then shaken with water (50 mL) and chloroform (4 x 50 mL). The combined chloroform extracts were washed with brine (100 mL) dried over anhydrous K_2CO_3, filtered, and evaporated to dryness under reduced pressure. A white colored amorphous material (**34**) was obtained (5.70 g; 94%), m.p. 158-159°; R_f 0.12 (hexanes-ethyl acetate, 4:1); IR (KBr) 3487, 2924, 1447, 1369, 1260, 1108, 1091 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.74 (s, 3H), 0.97 (s, 3H), 3.66 (ddd, 1H, J=7.5,8.0,and 10.6 Hz), 3.95 (s, 4H, ethylenedioxy) ; ^{13}C-NMR ($CDCl_3$) δ 36.9 (C1), 110.0 (C3), 40.1 (C5), 25.9 (C6), 26.6 (C7), 35.8 (C8), 40.9 (C9), 35.7 (C10), 20.7 (C11), 43.1 (C13), 51.2 (C14), 23.4 (C15), 30.6 (C16), 81.9 (C17), 11.1 (C18), 23.1 (C19), 64.2 and 64.1 (CH_2, ethylenedioxy resonances), [30.1, 34.3, 36.9 (unassigned CH_2 resonances for C2, C4, C12)]; MS, m/z 334 (M^+) (20), 125 (88), 99 (100), 55 (40), 41 (30), 32 amu (37); Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41, H, 10.25. Found: C, 75.33, H, 10.39; HRMS calcd for $C_{21}H_{34}O_3$ 334.2509, found 334.2501.

5.4 The Preparation of 17β-Hydroxy-5β-androstan-3-one (**38**)

The ester (**32**) (2.72 g; 8.2 mmol) was dissolved in THF (75 mL) containing aq. HCl (6N, 10 mL) and the solution was allowed to stir overnight (12 hr) at room temperature. The solvent was removed under reduced pressure and the white solid which remained was then dissolved in distilled water (25 mL) and extracted using ether (4 x 25 mL). The ether extracts were combined, dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. Recrystallization from acetone-hexanes gave (**38**) as white flakes (2.20 g; 92%), m.p. 139.5-141°, (lit.[83] m.p. 139-140°, dil. acetone); R_f 0.39 (hexanes-ethyl acetate, 3:2); IR (KBr) 3467, 2951, 1701, 1052 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.76 (s,3H), 1.03 (s,3H), 2.67 (br t, 1H, J=13.4 Hz), 3.66 (br t, 1H, J=8.3 Hz); ^{13}C-NMR ($CDCl_3$) δ 31.1 (C1), 36.8 (C2), 212.9 (C3), 42.2 (C4), 44.2 (C5), 25.3 (C6) 26.4 (C7), 35.6 (C8), 40.9 (C9), 34.9 (C10), 20.7 (C11), 36.9 (C12), 43.1 (C13), 50.9 (C14), 23.3 (C15), 30.5 (C16), 81.7 (C17), 11.1 (C18), 22.6 (C19) [as lit.[68] for 17β-hydroxy-5β-androstan-3-one (**38**)]; MS, m/z 290 (M^+)(45), 272 (19), 257 (19), 247 (30), 220 (36), 161 (30), 121 (37), 107 (52), 95 (55), 81 (72), 67 (71), 55 (100), 41 amu (95); HRMS, calcd for $C_{19}H_{30}O_2$ 290.2247, found 290.2234.

5.5 Formation of 5β-Androstan-3-oxo-17β-yl (4-Chlorophenyl)thionocarbonate (**39**)

Following the procedure described by von Gerlach and Müller,[63] 17β-hydroxy-5β-androstan-3-one (**38**) (0.50 g; 1.70 mmol) was dissolved in dry pyridine (10 mL) under N_2 (g). To this, (4-chlorophenyl) chlorothionoformate (0.39 g; 0.19 mmol) dissolved in 1,4-dioxane (1 mL), was added dropwise. After the addition of the reagent, the solution turned amber yellow in color. The reaction was allowed to stir at room temperature for 36 hr. The solvent pyridine was then evaporated under vacuum and the residue was redissolved in chloroform (15 mL). The chloroform solution was washed with aq. HCl (0.5N, 2 x 20 mL), dried over anhydrous $MgSO_4$, filtered and evaporated to dryness under

vacuum. The brown colored residue (0.60 g) was flash chromatographed on silica gel (hexanes-ethyl acetate, 8:1) to yield two components with R_f 0.36 and 0.24. The major product was the *bis*-(4-chlorophenyl) thionocarbonate (**41**), a white solid (0.204 g), m.p. 150-154°; R_f 0.73 (hexanes-ethyl acetate, 8:1); IR (KBr) 3100, 2924, 1778, 1483, 1262, 1209, 1082, 1012, 829 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.17 (m, 2H), 7.43 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 194.1 (C=S, thiocarbonyl), (151.9, 129.8, 123.2, 122.2 aromatic ring resonances); MS, m/z 298 (M^+) (2), 270 (60), 171 (75), 143 (92), 111 (100), 99 (58), 75 (94), 40 amu (82); HRMS, calcd for $C_{13}H_8Cl_2O_2S$ 297.9623, found 297.9662.

The second component (**39**) was a fluffy white solid consisting of fine needles (0.20 g; 25%), m.p. 196.5-197°; IR (KBr) 2982, 2931, 2854, 1715, 1490, 1305, 1209, 1186, 833 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.91 (s, 3H), 1.05 (s, 3H), 2.68 (br t, 1H, J=14.2 Hz), 5.12 (dd, 1H, J=7.3 and 7.3 Hz), 7.07 (m, 2H, aromatic ring), 7.73 (m, 2H, aromatic ring); ^{13}C-NMR ($CDCl_3$) δ 37.1 (C1), 36.9 (C2), 212.6 (C3), 42.3 (C4), 44.2 (C5), 23.3 (C6), 26.4 (C7), 35.3 (C8), 40.9 (C9), 35.0 (C10), 20.6 (C11), 37.0 (C12), 43.4 (C13), 50.4 (C14), 23.5 (C15), 26.8 (C16), 95.6 (C17), 12.5 (C18), 22.6 (C19), 194.6 (C=S, thiocarbonyl), [151.8, 131.9, 129.5, 123.4 (aromatic ring resonances)].

Some remaining starting material (**38**), (0.30 g) was retained on the column during the chromatographic process.

5.6 The Pyrolysis of 5β-Androstan-3-oxo-17β-yl (4-Chlorophenyl)thiocarbonate) (**39**)

The pyrolysis of (**39**), (0.ll g; 0.23 mmol) was performed in a Kugelrohr apparatus. The pyrolysis oven-temperature was held at 200° for O.5 hr, while the contents of the flask were kept under a vacuum of 15 mm Hg provided by a water aspirator. The volatiles were collected using a dry ice-acetone cooling bath. The collected material was dissolved in 10 mL of chloroform and washed twice using NaOH (0.2N, 10 mL). The chloroform layer was then dried using anhydrous $MgSO_4$, filtered and evaporated to dryness under reduced pressure, to yield (**42**) (0.04 g); ^{1}H-NMR ($CDCl_3$) δ 0.79 (s, 3H), 1.07 (s, 3H), 2.73 (br t, 1H, J = 15.8 Hz), 5.72 (m, 1H, vinylic proton), 5.86 (m, 1H, vinylic proton), 7.16 (m, 2H, aromatic ring), 7.43 (m, 2H, aromatic ring) (see olefin product obtained from xanthate pyrolysis in section 4.10).

Despite repeated washing of this product with aq. NaOH, and column chromatography, we were unable to purify the 16-olefin (**42**). TLC (hexanes-ethyl acetate, 6:1) after column chromatography revealed three components: one major R_f 0.46 [16-ene (**42**)] and two minor components R_f 0.28 [starting material (**39**)] and 0.16 [not identified].

5.7 The Preparation of 5β-Androstan-3-oxo-17β-yl Imidazolylthiocarbonate (**40**)

The esterification of 17β-hydroxy-5β-androstan-3-one (**38**) (0.20 g; 0.69 mmol) with N,N'-thiocarbonyldiimidazole (0.75 g; 4.21 mmol) in refluxing dry THF (20 mL) was carried out according to the procedure of Barton *et al.*[64,65] After 12 hr of refluxing, the canary-yellow colored solution was evaporated to dryness under reduced pressure. The solid residue was then partitioned between aq. HCl (0.5N, 10 mL) and ether (4 x 10 mL). The combined ethereal extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude viscous, yellow colored residue (1.45 g) was purified by chromatography on silica gel. Hexanes-ethyl acetate (3:2) eluted material which was recrystallized from an acetone-hexanes mixture to

give fine colorless needles of (**40**), (0.18 g; 63%), m.p. 111-112.5°; IR (KBr) 3130, 3128, 2938, 1715, 1532, 1462, 1391, 1291, 1287, 1110, 1099 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.99 (s, 3H), 1.06 (s, 3H), 2.68 (br t, 1H, J = 14.7 Hz), 5.33 (dd, 1H, J = 7.2 and 7.3 Hz), 7.04 (t, 1H, J = 1.6 Hz), 7.67 (t, 1H, J = 1.4 Hz), 8.33 (t, 1H, J = 1.0 Hz); ^{13}C-NMR δ 37.2 (C1), 37.0 (C2), 212.5 (C3), 42.2 (C4), 44.1 (C5), 25.3 (C6), 26.4 (C7), 35.3 (C8), 40.9 (C9), 35.0 (C10), 20.6 (C11), 37.0 (C12), 43.8 (C13), 50.4 (C14), 23.6 (C15), 27.0 (C16), 91.7 (C17), 13.0 (C18), 22.6 (C19), 184.2 (C=S, thiocarbonyl), (136.6, 130.7, 117.8 imidazolide ring resonances); MS, m/z 400 (M^+) (4), 340 (6), 255 (75), 149 (100), 40 amu (82); Anal. Calcd. for $C_{23}H_{32}N_2O_2S$: C,68.96,H,8.05,N,7.00, Found: C,68.06,H,7.97,N,6.94; HRMS, cald. for $C_{23}H_{32}N_2O_2S$ 400.2187, found 400.2192.

5.8 The Preparation of the 17β-Xanthate Ester (**35**)

To flame dried glassware and under a nitrogen atmosphere was added a solution of (**34**) (1.02 g; 3.05 mmol in 20 mL of dry THF). After cooling the reaction flask in an acetone-dry ice bath, dry THF (20 mL) and a trace of 2,2'-biquinoline (*ca.* 5 mg) was added to the solution. To this solution methyl lithium in THF (0.5M, concentration determined by titrating against diphenylacetic acid, 6 mL; 3.0 mmol) was added. The solution turned light lime-green colour. This was quickly followed by the addition of carbon disulfide (0.75 mL; 3.36 mmol), which turned the color of the solution to a dark maroon. The reaction mixture was stirred for 15 min, and then methyl iodide (1 mL; 16 mmol) was added. Stirring was continued while the reaction was allowed to warm to room temperature gradually over 3 hr. The reaction mixture was poured into a beaker containing distilled water (200 mL) and the mixture was then transferred to a separating funnel and extracted with ether (4 x 50 mL). The combined ether extracts were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The brown colored crude product (1.45 g) on TLC (hexanes-ethyl acetate, 9:1)

was found to consist of three components with R_f 0.66. 0.53, and 0.37, the first two of which stained weakly with I_2, the latter intensely]. The entire sample was then subjected to flash column chromatography using silica gel and an isocratic solvent system (hexanes-ethyl acetate; 9:1). Combining those fractions which were homogeneous on TLC (R_f 0.37) and evaporation under reduced pressure gave the xanthate ester (5β-androstan-3-oxo-17β-yl S-methyldithiocarbonate) (**35**) (1.17 g; 91%). This result was reproduced in subsequent experiments. A small sample of product (**35**) was recrystallized from ether-hexanes to give flat translucent flakes, m.p. 117-117.5°; IR (KBr) 2917, 1448, 1230, 1070 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88 (s, 3H), 0.95 (s, 3H), 2.52 (s, 3H, S-CH_3), 3.92 (s, 4H, ethylenedioxy), 5.33 (dd, 1H, J = 7.2 and 7.2 Hz); ^{13}C-NMR ($CDCl_3$) δ 109.7 (C3), 39.9 (C5), 335.4 (C8), 40.8 (C9), 34.7 (C10), 20.5 (C11), 43.7 (C13), 50.5 (C14), 23.6 (C15), 91.9 (C17), 12.7 (C18), 23.9 (C19) 64.2 and 64.9 (CH_2, ethylenedioxy resonances), 18.7 (SCH_3), 215.5 (C=S), [37.3, 35.7, 34.2, 30.1, 27.1, 26.6, 25.7 (additional unassigned CH_2 resonances for C1, C2, C4, C6, C7, C12, C16)]; MS, m/z 424 (M^+) (1) 317 (50), 225 (35), 203 (18), 125 (50), 99 (100), 55 amu (40); Anal. Calcd. for $C_{23}H_{36}O_3S_2$: C, 65.05, H, 8.55. Found: C, 65.45, H, 8.40; HRMS, calcd. for $C_{23}H_{36}O_3S$ 424.2108, found 424.2113.

5.9 The Preparation of 3,3-Ethylenedioxy-5β-androstan-17β-yl Imidazolylthiocarbonate (**36**)

The esterification of 3,3-ethylenedioxy-5β-androstan-17β-ol (**34**) (1.04 g; 3.1 mmol) by N,N'-thiocarbonyldiimidazole (3.32 g; 18.9 mmol) in dry THF (60 mL) was carried out as described by Barton *et al.*[64,65] The solution was allowed to reflux for 16 hr. The workup involved pouring the yellow colored reaction mixture into distilled water (100 mL) and evaporating the resultant mixture to half-volume under reduced pressure, and then extracting the aqueous suspension with ether (4 x 50 mL). The combined ether extracts were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The crude product (2.01 g) was purified by flash column chromatography on silica gel using an isocratic solvent system (hexanes-ethyl acetate; 3:2). This gave the desired product (**36**) (1.07 g; 78%), m.p. 216-218°; R_f 0.48 (hexanes-ethyl acetate, 3:2); IR (KBr) 3135, 3114, 2931, 1475, 1330, 1282, 1230, 1101, 1001 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.95 (s, 3H), 0.98 (s, 3H), 3.95 (s, 4H, ethylenedioxy), δ 5.29 (dd, 1H, J = 7.2,7.2 Hz), 7.04 (t, 1H, J = 1.6 Hz), 7.62 (t, 1H, J = 1.5 Hz), 8.33 (t, 1H, J = 1.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 109.8 (C3), 39.8 (C5), 35.4 (C8), 40.8 (C9), 34.6 (C10), 20.5 (C11), 43.7 (C13), 50.4 (C14), 23.6 (C15), 91.9 (C17), 13.0 (C18), 23.0 (C19), 64.2 and 64.0 (CH_2, ethylenedioxy resonances), 184.1 (C=S, thiocarbonyl), (136.6, 130.7, and 117.8 imidazolide ring resonances), (additional unassigned CH_2 resonances for C1, C2, C4, C6, C7, C12, C16 are at 37.2, 35.6, 34.2, 30.1, 27.0, 26.5,and 25.7); MS, m/z 444 (M^+) (20), 316 (15), 125 (35), 99 (100), 81 (23), 69 (35), 55 (46), 41 amu (53). Anal. Calcd. for $C_{25}H_{36}N_2O_3S$: C, 67.53, H, 8.16, N, 6.30. Found: C, 67.70, H, 8.09, N, 6.40; HRMS, calcd for $C_{25}H_{36}N_2O_3S$ 444.2449, found 444.2456.

5.10 The Pyrolysis of the 17β-Xanthate Ester (**35**)

The pyrolysis of (**35**) (0.67 g; 1.58 mmol) was performed in a Kugelrohr apparatus. The pyrolysis oven temperature was held at 200°, for 4 hr, while the contents of the flask were kept under a vacuum of 12 mm Hg provided by a water aspirator. The volatiles were collected using dry ice-acetone cooling-bath. TLC (hexanes-ethyl acetate, 12:1) of the crude product revealed one major component R_f 0.33 [3,3-ethylenedioxy-5β-androst-16-ene (**37**)] and one minor component R_f 0.24 [17β-xanthate ester (**35**)]. Flash column chromatography using silica gel and the usual solvent system (hexanes-ethyl acetate, 12:1) of crude material (0.44 g) separated the 16-ene product (**37**) (0.33 g) from the 17β-xanthate ester (**35**) (0.035 g). The overall yield of (**37**) after chromatography was 87%. The product, 3,3-ethylenedioxy-5β-androst-16-ene (**37**) was obtained as an amorphous pale yellow solid , m.p. 69-70°; IR (KBr) 3031, 2924, 1448, 1096, 706 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.76 (s, 3H), 1.0 (s, 3H), 2.04 (br t, 1H, J = 13.5 Hz), 3.95 (s, 4H, ethylenedioxy), 5.70 (m, lH), 5.84 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 110.0 (C3), 40.7 (C5), 34.3 (C8), 40.0 (C9), 34.9 (C10), 20.9 (C11), 45.7 (C13), 56.2 (C14) 129.3 (C16), 143.9 (C17), 17.0 (C18), 23.1 (C19), 64.2 and 64.0 (CH_2, ethylenedioxy resonances), [35.1, 35.8, 34.2, 31.9, 30.1, 26.7, 26.4 (are unassigned CH_2 resonances for C1, C2, C4, C6, C7, C12, C15)]; MS, m/z 316 (M^+) (50), 187 (10), 125 (88), 99 (100), 79 (28), 55 (38), 41 amu (33); Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70, H, 10.19. Found: C, 79.57, H, 9.97; HRMS, calcd for $C_{21}H_{32}O_2$ 316.2404, found 316.2405.

5.11 The Preparation of 3,3-Ethylenedioxy-5β-androstan-16α-ol (**43**)

The hydroboration of the 16-ene steroid (**37**) (1.01 g; 3.2 mmol) using 9-borabicyclo[3.3.1]nonane (9-BBN)dissolved in THF (0.5M, 9.4 mL; 4.8 mmol) was carried out as described by Brown.[50] The reaction was allowed to stir at 60° for 16 hr under an atmosphere of N_2. The reaction was then subjected to an oxidative workup. The

reaction flask was first cooled using an ice-water bath, then aqueous NaOH (3N, 40 mL) was added, followed by the slow addition of H_2O_2 (30% aq., 40 mL), and finally potassium carbonate (0.50 g) after which the solution was stirred vigorously for 1 hr. The organic layer was then separated and the aqueous layer extracted using ether (4 x 50 mL). All organic layers were combined, washed with saturated potassium carbonate solution (150 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness under reduced pressure. TLC (hexanes-ethyl acetate, 3:2) revealed 3 minor components with R_f 0.84 (starting material), 0.55 (unidentified), 0.12 (unidentified material) and a major component R_f 0.43 [3,3-ethylenedioxy-5β-androstan-16-α-ol (**43**)]. Analysis by gas chromatography revealed components with retention times of 2.24, 10.37 and 10.86 min, corresponding to 1,5-cyclooctanediol; 3,3-ethylenedioxy-5β-androst-16-ene (**37**); and 3,3-ethylenedioxy-5β-androstan-16α-ol (**43**) respectively. Isolation of the major component was achieved by flash column chromatography on silica gel using hexane-ethyl acetate (3:2) to give (**43**), (0.72 g; 68%), m.p. 165-166.5°; IR (KBr) 3466, 2931, 1448, 1056 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.70 (s, 3H), 0.95 (s, 3H), 3.96 (s, 4H, ethylenedioxy), δ 4.46 (m, 1H, J = 6.5 Hz); ^{13}C-NMR ($CDCl_3$) δ 110.1 (C3), 40.1 (C5), 40.9 (C9), 34.8 (C10), 20.7 (C11), 38.9 (C12), 41.9 (C13), 52.2 (C14), 71.9 (C16), 52.2 (C17), 18.7 (C18), 23.1 (C19), 64.2 and 64.0 (CH_2, ethylenedioxy resonances), (as lit.[68] reference compounds 5α-androstan-16α- and 16β-ol); [37.3, 35.8, 35.6, 34.2, 30.2, 26.7, 26.6 (unassigned CH_2 resonances for C1, C2, C4, C6, C7, C8, C15)]; MS, m/z 334 (M^+) (18), 125 (92), 99 (100), 55 (32), 41 (27), 32 amu (60); Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40, H, 10.25. Found: C, 76.05, H, 10.16; HRMS, calcd for $C_{21}H_{34}O_2$ 334.2509, found 334.2506.

5.12 Deprotection of 3,3-Ethylenedioxy-5β-androstan-16α-ol; Preparation of (**44**)

Ketal deprotection of 3,3-ethylenedioxy-5β-androstan-16α-ol (**43**) was carried out by a procedure similar to that described by Grieco *et al.*[69] To a solution of the ketal (0.31 g; 0.98 mmol) in THF (20 mL) was added aq. HCl [5% (w/vol), 25 mL]. The reaction was allowed to stir at room temperature for 18 hr. The workup involved the extraction of the aqueous layer using ether (4 x 20 mL). The combined organic extracts were washed with brine (50 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The white residue 16α-hydroxy-5β-androstan-3-one (**44**) was dried under high vacuum to afford the product (0.25 g; 97%), m.p. 160-161° (acetone-hexanes); IR (KBr) 3416, 2945, 1701, 1047 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.70 (s, 3H), 1.00 (s, 3H), 2.67 (br t, 1H, J = 14 Hz), 4.44 (ddd, 1H, J = 2.1, 5.0, 7.7 Hz), ^{13}C-NMR ($CDCl_3$): δ 37.1 (C1), 36.9 (C2) 213.2 (C3), 42.3 (C4), 44.2 (C5), 25.9 (C6), 26.5 (C7), 33.3 (C8), 40.9 (C9), 34.9 (C10), 20.8 (C11), 37.1 (C12), 41.8 (C13), 52.0 (C14), 38.8 (C15), 71.6 (C16), 52.0 (C17), 18.6 (C18), 22.6 (C19) (reference compounds used 5α-androstan-16α-ol and 17β-hydroxy-5β-androstan-3-one, Blunt and Stothers[68]); MS, m/z 290 (M^+) (45), 272 (80), 201 (60), 95 (48), 81 (77), 69 (90), 55 (93), 41 amu (100); Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57, H, 10.41. Found: C, 78.54, H, 10.51; HRMS, calcd. for $C_{19}H_{30}O_2$ 290.2247, found 290.2238.

5.13 Mitsunobu Reaction on 16α-Hydroxy-5β-androstan-3-one (**44**)

Following the procedure of Mitsunobu,[52] the 16α-hydroxy steroid (**44**) (0.19 g; 0.7 mmol) was dissolved in dry benzene (15 mL). To this solution, triphenylphosphine (0.19 g; 0.72 mmol) and glacial acetic acid (0.041 mL; 0.72 mmol) were added and the mixture was allowed to stir for 5 min. Lastly, diethyl azodicarboxylate (0.12 mL; 0.72 mmol) in 5 mL of dry benzene was added and the solution was refluxed for 36 hr. After allowing the reaction flask to cool to room temperature, the solvent was evaporated to dryness under vacuum. The residue (0.78 g) was flash chromatographed on silica gel and eluted using an isocratic solvent mixture (hexanes-ethyl acetate, 3:1). The fractions were collected which corresponded to 5β-androstan-3-oxo-16β-yl acetate (**45**) (0.10 g; 47%), [R_f 0.39 (hexane-ethyl acetate, 3:1)]. The solid white crystalline material (**45**), had m.p. 143.5-144° (hexanes-acetone), [lit.[26] m.p. 143° (acetone)]; IR (KBr) 2931, 2861, 1724, 1709, 1251 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.92 (s, 3H), 1.05 (s, 3H), 2.03 (s, 3H), 2.69 (br t, 1H, J = 13 Hz). 5.14 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 37.1 (C1), 36.9 (C2), 212.9 (C3), 42.3 (C4), 44.2 (C5), 26.0 (C6), 26.5 (C7), 35.3 (C8), 40.8 (C9), 35.0 (C10), 20.8 (C11), 34.3 (C12), 40.1 (C13), 53.4 (C14), 38.8 (C15), 74.6 (C16), 48.0 (C17), 18.4 (C18), 22.6 (C19), 170.9 (C=O, acetate), 21.3 (CH_3, acetate); MS, m/z 332 (M^+) (3), 272 (100), 257 (63), 231 (32), 201 (70), 107 (55), 94 (68), 81 (62), 69 (55), 55 amu (84); Anal. calcd. for $C_{21}H_{32}O_3$: C, 75.86, H, 9.70. Found: C, 75.90, H, 9.75; HRMS, calcd for $C_{21}H_{32}O_3$ 332.2353, found 332.2348.

5.14 Saponification of 5β-Androstan-3-oxo-16β-yl Acetate; The Preparation of (**14**)

Following the procedure of Mashimo and Sato.,[71] the saponification of 5β-androstan-3-oxo-16β-yl acetate (**45**) (0.052 g; 0.16 mmol) using 1% NaOH/methanol (10 mL) was completed in 2 hr at room temperature. The workup procedure involved adjusting the pH to 5-6 using aq. HCl (6N). Methanol was then removed under reduced

pressure, and distilled water (10 mL) was added. The solution was then extracted using ether (5 x 10 mL), the ether extracts were combined and washed with brine (25 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The product, 16β-hydroxy-5β-androstan-3-one (**14**) was obtained as colorless needles, (0.043 g; 95%), m.p. 128.5-129° (hexanes-acetone), [lit.[26] m.p. 128° (methanol-water)]; IR (KBr) 3501, 2924, 2834, 1708, 1447, 1342, 1005 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.97 (s, 3H), 1.03 (s, 3H), 2.67 (br t, 1H, J = 13.3 Hz), 4.42 (m, 1H, J = 2.1, 5.5, 7.6 Hz) ^{13}C-NMR ($CDCl_3$) δ 37.1 (C1), 36.9 (C2), 213.3 (C3), 42.3 (C4), 44.2 (C5), 26.1 (C6), 26.5 (C7), 35.3 (C8), 26.1 (C9), 35.0 (C10), 20.8 (C11), 39.1 (C12), 40.3 (C13), 53.9 (C14), 37.1 (C15), 71.9 (C16), 51.3 (C17), 19.9 (C18), 22.6 (C19); HRMS, calcd for $C_{19}H_{30}O_2$ 290.2247, found 290.2239.

5.15 The Formation of 5β-Androstan-3-oxo-16β-yl Benzoate (**46**)

Following the procedure of Mitsunobu,[52] 16α-hydroxy-5β-androstan-3-one (**44**) (0.50 g; 1.70 mmol), triphenylphosphine (0.50 g; 1.90 mmol), and benzoic acid (0.24 g, 1.90 mmol) were dissolved in dry benzene (10 mL) and allowed to stir for 5 min. This was followed by the addition of diethyl azodicarboxylate (0.30 mL; 1.90 mmol dissolved in 1 mL of dry benzene) and the mixture was refluxed for 24 hr. The reaction was then allowed to cool to room temperature and the solvent was removed under reduced pressure. The crude material (1.55 g) was flash column chromatographed on silica gel and eluted using a mixture of hexanes-ethyl acetate (3:1) to give white crystalline material (**46**) (0.59 g; 87%), m.p. 167.5-168° (acetone-hexanes); R_f 0.41 (hexanes-ethyl acetate, 3:1); IR (KBr) 3052, 1715, 1708, 1448, 1292, 716 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.02 (s, 3H), 1.05 (s, 3H), 2.7 (br t, 1H, J = 14 Hz), 5.42 (m, 1H), 8.04 (m, 2H), 7.48 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ 37.2 (C1), 37.0 (C2), 212.8 (C3), 42.3 (C4), 44.3 (C5), 26.0 (C6), 25.6 (C7), 35.5 (C8), 41.1 (C9), 35.1 (C10), 20.9 (C11), 37.0 (C12), 40.3 (C13), 53.7 (C14), 38.8

(C15). 75.2 (C16), 48.3 (C17), 18.5 (C18), 22.7 (C19), 166.3 (C=O, benzoate ester), 132.7. 130.9, 129.5, 128.4, 128.3, 128.3 (aromatic ring resonances); MS, m/z 394 (M^+) (9), 378 (0.3), 272 (73), 257 (60), 231 (30), 202 (50), 147 (35), 105 (100), 77 (82), 55 (60), 41 amu (55); Anal. Calcd. for $C_{26}H_{34}O_3$: C, 79.15, H, 8.69. Found: C, 79.54, H, 8.34; HRMS, calcd for $C_{26}H_{34}O_3$ 394.2509, found 394.2513.

5.16 The Schmidt Reaction on 5β-Androstan-3-oxo-17β-yl Acetate (**32**)

A chloroform solution of hydrazoic acid was prepared as described by Shaw[45]. Sodium azide (15.5 g) was added to distilled water (10 mL) and the mixture was stirred. To this was added anhydrous chloroform (100 mL), and the mixture was stirred at room temperature for 30 min. After cooling the mixture in an ice-bath, conc. sulfuric acid (7.5 mL) was carefully added, dropwise, to the mixture. After completing the addition the suspension was stirred at 0° for a further 30 min. The supernatent was decanted from the solid, dried ($MgSO_4$) and filtered.

The standardization of this solution was performed as follows: one ml of the chlorform solution was added to 10 mL of distilled water and the mixture was stirred vigorously and then titrated against a standard solution of NaOH (0.0975M), with phenothalein used as indicator. The chloroform solution was found to be 1.42M in acid strength.

A solution of 5β-androstan-3-oxo-17β-yl acetate (**32**) (1.62 g; 4.9 mmol) in anhydrous chloroform (200 mL) was treated with the standardized solution of hydrazoic acid in chloroform (3.8 mL; 5.4 mmol) under anhydrous conditions. After cooling the mixture in an ice-water bath, concentrated sulfuric acid was added to it, dropwise, maintaining the temperature below 5°. The reaction was stirred for an additional 20 min at 0° after the addition of the concentrated sulfuric acid. The reaction mixture was then quenched with 200 mL of ice-water, with which it was stirred for 15 min. The reaction

mixture was then brought to a pH of *ca.* 7-8 using 5% NaOH, then the chloroform layer was separated from the aqueous layer. The aqueous layer was further extracted using chloroform (5 x 50 mL) and the organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. A white solid material was obtained which after recrystallization from hexanes/chloroform, gave the mixed lactams (**50** and **51**), (1.195 g; 70%); IR (film) 3374, 3206, 3093, 2931, 2847, 1736, 1680, 1631, 1244 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.73 (s, 3H), 0.95 (s, 3H), 1.98 (s, 3H), 4.55 (s, 1H, J = 7.7 Hz); ^{13}C-NMR ($CDCl_3$) δ [82.4, 50.3, 50.2, 45.2, 42.7, 42.0, 39.4, 35.3 (are unassigned CH resonances for C5, C8, C9, C14, C17)], [22.9, 20.8, 11.7 (are unassigned CH_3 resonances for C18, C19)]; [43.9, 40.1, 38.4, 36.8, 36.7, 36.6, 33.6, 29.3, 27.7, 27.2, 26.3, 25.3, 23.1, 20.5, 20.1 (are unassigned CH_2 resonances for C1, C2, C4, C4a, C6, C7, C11, C12, C15, C16)]; [42.2, 37.3, 37.1 (are quaternary carbons resonances for C10, C13)]; 170.9 (C=O, acetate); and 178.6, 177.9 (C=O, lactams).

5.17 The Reduction of the Lactam Mixture (**50** and **51**) Using Borane-Dimethyl Sulfide

In flame-dried glassware and under a positive N_2 atmosphere, the lactam mixture (**50** and **51**), (0.24 g; 0.70 mmol) was dissolved in THF (5 mL). The solution was then boiled under reflux for 10 min. This was followed by the addition of borane-dimethyl sulfide (BMS) (1:1 complex, 0.3 mL; 2.3 mmol) and the reaction mixture was refluxed 9 hr. This was followed by distillation under an atmosphere of N_2 to remove the dimethyl sulfide along with some of the THF (2 mL). Methanolic HCl (1N, 6 mL) was then added to the mixture, which was refluxed for a further 6 hr. After allowing the reaction mixture to cool, the solvent was removed under reduced pressure. The residue was redissolved in chloroform (10 mL) and extracted using aq. H_2SO_4 (1N, 7 x 2 mL) until a negative Mayer's test was obtained. The chloroform layer was then dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The weight of non-basic material was found to be 0.10

g. The combined acid extracts were basified with aqueous ammonia (sp. gr. 0.88) to pH 9, then extracted using chloroform (6 x 5 mL). The chloroform fractions were then combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and evaporated to dryness. TLC (hexanes-ethyl acetate-methanol-NH_4OH, 3:3:2:0.5) revealed two major spots, with R_f 0.38 and 0.27. The crude mixture (0.10 g) was separated on silica gel PTLC plates and developed twice using (hexanes-ethyl acetate-methanol-NH_4OH, 3:3:2:0.5). Bands corresponding to the two major products were located using iodine impregnated silica gel sprinkled on the sides of the plate, then scraped from the plates and the products eluted using ethyl acetate-methanol-NH_4OH (6:2:1) (20 mL) for each band. The eluates were then evaporated under reduced pressure and the residues were redissolved in chloroform (3 mL), dried ($MgSO_4$), filtered and recovered by removing the solvent under reduced pressure. The two individual components were then recrystallized from chloroform-hexane. The upper component (**53**), a white solid (0.041 g; 21%), m.p. 173-174.5°; IR (film) 3346, 2931, 2868, 1448, 1413, 1290, 1251, 1054 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0,75 (s, 3H), 0.97 (s, 3H), 2.06 (m, 1H), 2.62 (m, 2H), 2.90 (dd, 1H, J = 8.4 and 8.4 Hz), 3.07 (m, 1H) 3.64 (t, 1H, J = 8.5 Hz); ^{13}C-NMR ($CDCl_3$) δ 41.1 (C1), 29.1 (C2), 50.1 (C3), 50.8 (C4a), 50.75 (C5), 24.7 (C6), 27.2 (C7), 36.3 (C8), 48.6 (C9), 37.2 (C10), 20.9 (C11), 37.1 (C12), 42.9 (C13), 50.8 (C14), 23.4 (C15), 30.6 (C16), 82 (C17), 11.1 (C18), 22.4 (C19); MS, m/z 291 (M^+) (27), 289 (31), 276 (11), 260 (41), 110 (41), 70 (100), 43 (90); HRMS calcd for $C_{19}H_{33}NO$ 291.2562, found 291.2550.

The lower component (**52**), a slightly brown coloured solid (0.034 g; 17%), m.p. 198-199.5°; IR (film) 3381, 2931, 2868, 1416, 1272, 1054 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.75 (s, 3H), 0.95 (s, 3H), 2.05 (m, 1H), 2.70 (m, 2H), 2.89 (dd, 1H, J = 7.8 and 7.7 Hz), 3.13 (m, 1H), 3.64 (t, 1H, J = 8.5 Hz); ^{13}C-NMR ($CDCl_3$) δ 34.1 (C1), 50.8 (C2), 42.7 (C4) 46.0 (C4a), 49.4 (C5), 26.6 (C6), 30.9 (C7), 36.5 (C8), 45.4 (C9), 36.4 (C10), 20.91 (C11), 37.7 (C12), 42.9 (C13), 50.9 (C14), 23.4 (C15), 30.6 (C16), 81.9 (C17), 11.1 (C18), 22.4

(C19) (assignment based on separate COSY and XH-CORR experiments); MS, m/z 291 (M^+) (29), 289 (35), 276 (43), 122 (63), 56 (79), 43 (100); HRMS calcd for $C_{19}H_{33}NO$ 291.2562, found 291.2550.

5.18 The Schmidt Reaction on 5β-Androstan-3-oxo-16β-yl Benzoate (**46**)

A solution of 5β-androstan-3-oxo-16β-yl benzoate (**46**) (0.44 g, 1.10 mmol) in anhydrous chloroform (60 mL) was treated using freshly standardized HN_3 in chloroform (0.86 mL; 1.41 M), placed in an ice bath (0°) and allowed to stir for 5 min. This was followed by the slow addition of conc. H_2SO_4 (0.4 mL) and the reaction was allowed to stir for a further 20 min at 0°. Ice-water (25 mL, *ca.* ice 5 g) was added, and the mixture allowed to stir for 5 min.

The pH of the reaction mixture was then adjusted to 6-7 using a solution of aq. 5% NaOH, and the organic layer was then separated. The aqueous layer was further extracted with chloroform (7 x 30 mL). All the organic layers were then combined, washed with brine (100 mL), dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure to yield a white solid (0.53 g).

Flash column chromatography on silica gel [hexanes-ethyl acetate-methanol; (3:2:0.5)] of this product produced two components: a minor component R_f 0.6 (0.012 g) and a major component R_f 0.40 (0.44 g; 97%).

The spectroscopic properties of the minor component, which corresponds to a mixture of tetrazoles, were as follows: IR (film) 3346, 3065, 2931, 1715, 1448, 1229, 1110 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.03 (s, 3H), 1.15 (d, 3H, J = 2.3 Hz), 2.43 (m, 1H), 3.18 (m, 1H), 4.3 (m, 1H), 4.55 (m, 1H), 5.44 (m, 1H), 7.48 (m, 3H), 8.01 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 17.8, 18.4, 20.8, 21.1, 21.2, 25.3, 26.5, 27.2, 27.9, 29.2, 29.7, 34.5, 35.7, 35.8, 36.0, 37.5, 38.4, 38.7, 40.1, 40.9, 42.4, 43.1, 45.9, 46.3, 48.2, 49.5, 53.3, 75.0, 128.3, 129.4, 130.8, 132.7, 166.3; MS, m/z 434 (M^+) (1), 329 (50), 312 (75), 297 (55), 105 (100),

77 (75); HRMS, calcd for $C_{19}H_{29}N_4O$ 329.2344, found 329.2322; and for $C_{19}H_{28}N_4$ 312.2316, found 312.2289. The major component had the following spectroscopic properties: IR (film) 3304, 3227, 3065, 2931, 1715, 1666, 1448, 1279, 1117 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.99 (s, 3H), 2.45 (m, 2H), 3.04 (m, 1H), 5.39 (m, 1H), 6.95 (br s, 1H), 7.48 (m, 3H), 8.00 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 18.3, 20.6, 20.9, 23.0, 23.4, 26.2, 27.1, 28.0, 29.6, 29.9, 33.9, 34.3, 34.4, 35.6, 36.7, 37.2, 37.4, 38.7, 39.6, 40.1, 40.3, 42.3, 43.1, 44.1, 45.4, 48.1, 48.1, 53.3, 53.4, 75.0, 128.2, 128.5, 128.9, 129.3, 130.3, 130.7, 132.6, 166.1 (C=O, benzoate ester), 177.7 and 178.4 (C=O, lactam carbonyls).

5.19 The Reduction of the Lactam Mixture (**47** and **48**) Using LAH

The LAH reduction of the lactam mixture (**47** and **48**) was performed following the procedure of Habermehl and Haaf.[26] The lactam mixture (**47** and **48**), (0.20 g; 0.5 mmol) was dissolved in dry THF (25 mL) and added to a flame-dried flask, and kept under a N_2 atmosphere. The flask was cooled in an ice-water bath and the solution was stirred while a suspension of LAH (0.44 g; 10.2 mmol) in dry THF (20 mL) was added via a syringe. After the addition of the LAH was completed the syringe was rinsed into the reaction vessel with a little THF (5 mL). The reaction mixture was then refluxed for 20 hr.

The reaction mixture was cooled in an ice-water bath, and then worked up by the method of Mićović and Mihailoviv.[80] The stirred reaction mixture was first cautiously treated, dropwise, with distilled water (0.44 mL), then, after the reaction had subsided, with 15% aq. NaOH solution (0.44 mL), and then finally with more distilled water (1.3 mL). This produced a fine granular grey precipitate which was easily filtered on a Celite pad. The filter cake was washed with ether (3 x 15 mL), and the combined filtrate and washings evaporated to dryness under reduced pressure. The filter cake was then stirred in ether overnight and then the ether extract evaporated to yield a little more solid. TLC (hexanes-ethyl acetate-methanol-NH_4OH, 2:3:2:0.5) of the combined residues (0.14 g)

revealed two major components with R_f 0.66 and 0.61. A portion of the crude mixture (0.08 g) was separated on silica gel PTLC plates and developed twice using (hexanes-ethyl acetate-methanol-NH_4OH, 2:3:2:0.5). Bands corresponding to the two major products were located using iodine impregnated silica gel sprinkled on the sides of the plate, then scraped from the plates and the products eluted using ethyl acetate-methanol-NH_4OH (6:2:1) (25 mL). The solvent was then removed under reduced pressure and the residues redissolved in benzene (*ca.* 5 mL); dried over anhydrous K_2CO_3, filtered and recovered by removing the solvent under reduced pressure. The component with R_f 0.66 (**49**), was a white solid (0.032 g; 40%), m.p. 166.5-168° (ethanol-water), [lit.[26] m.p. 166-168° (ethanol-water)]; IR (KBr) 3381, 3283, 3220, 2924, 2847, 1560, 1448, 1413, 1377, 1342, 1293, 1251, 1181, 1159, 1131, 1082, 1047, 1040, 1012, 955, 927, 899, 871, 836, 815, 794, 674, 618, 541 cm^{-1}; ^{1}H-NMR (C_6D_6) δ 0.88 (s, 3H), 1.04 (s, 3H), 2.03 (m, 1H), 2.52 (m, 2H), 2.79 (dd, 1H, J = 8.3 and 8.3 Hz), 2.91 (m, 1H), 4.16 (m, 1H); ^{13}C-NMR (C_6D_6) δ 41.1 (C1), 29.4 (C2), 50.8 (C3), 51.9 (C4a), 50.1 (C5), 24.9 (C6), 28.2 (C7), 36.2 (C8), 48.6 (C9), 37.3 (C10), 21.3 (C11), 39.7 (C12), 40.3 (C13), 53.9 (C14), 37.6 (C15), 71.6 (C16), 51.2 (C17), 19.2 (C18), 22.6 (C19); MS, m/z 291 (M^+) (24), 289 (7), 276 (45), 274 (10), 260 (12), 217 (7), 201 (8), 124 (9), 121 (9), 110 (30), 109 (11), 107 (15), 105 (15), 97 (14), 96 (16), 95 (24), 93 (23), 91 (20), 84 (20), 83 (16), 82 (19), 81 (29), 79 (23), 77 (14), 72 (19), 71 (49), 70 (100), 69 (41), 68 (25), 67 (29), 57 (48), 56 (52), 55 (46), 53 (14), 44 (88), 43 (71), 42 (24), 41 (59); HRMS calcd for $C_{19}H_{33}NO$ 291.2564, found 291.2565.

The component with R_f 0.61 (**9**) was obtained as translucent white crystals (0.042 g; 52%), m.p. 194-195° (ethanol-water), [lit.[26] m.p. 193-195° (ethanol-water)]; IR (KBr) 3395, 3290, 3135, 2924, 1448, 1377, 1342, 1300, 1270, 1244, 1221, 1204, 1185, 1174, 1159, 1141, 1131, 1114, 1091, 1079, 1062, 1043, 1010, 979, 957, 958, 920, 877, 836, 821, 809, 796 cm^{-1}; ^{1}H-NMR (C_6D_6) δ 0.78 (m, 2H), 0.90 (s, 3H), 1.08 (s, 3H), 2.07 (dt, 1H, J

= 7.2 and 7.4 Hz), 2.60 (m, 2H), 2.73 (m, 1H, J = 7.6 and 7.8 Hz), 3.06 (m, 1H), 4.10 (m, 1H); ^{1}H-NMR ($CDCl_3$) δ 0.91 (m, 1H), 0.96 (s, 6H), 1.05 (m, 2H), 2.19 (m, 1H), 2.67 (m, 2H), 2.89 (dd, 1H, J = 7.9 and 14.0 Hz), 3.12 (m, 1H), 4.39 (m, 1H); ^{13}C-NMR (C_6D_6) δ 31.4 (C1), 51.9 (C2), 43.0 (C4), 46.6 (C4a), 49.6 (C5), 27.6 (C6), 30.2 (C7), 36.4 (C8), 45.4 (C9), 34.6 (C10), 21.3 (C11), 39.8 (C12), 37.3 (C13), 54.0 (C14), 37.6 (C15), 71.7 (C16), 51.4 (C17), 19.2 (C18), 22.4 (C19); MS, m/z 291 (M^+) (44), 290 (15), 289 (24), 276 (71), 274 (24), 258 (9), 219 (10), 217 (9), 124 (17), 123 (16), 122 (59), 121 (14), 119 (12), 111 (11), 110 (27), 109 (25), 108 (18), 107 (23), 105 (20), 97 (20), 96 (62), 95 (27), 93 (33), 91 (25), 84 (16), 83 (29), 82 (46), 81 (42), 80 (12), 79 (3), 77 (17), 71 (25), 70 (58), 69 (36), 68 (18), 67 (36), 58 (54), 57 (79), 56 (91), 55 (56), 53 (16), 45 (12), 44 (100), 43 (84), 42 (32), 41 (66); HRMS calcd for $C_{19}H_{33}NO$ 291.2564, found 291.2558.

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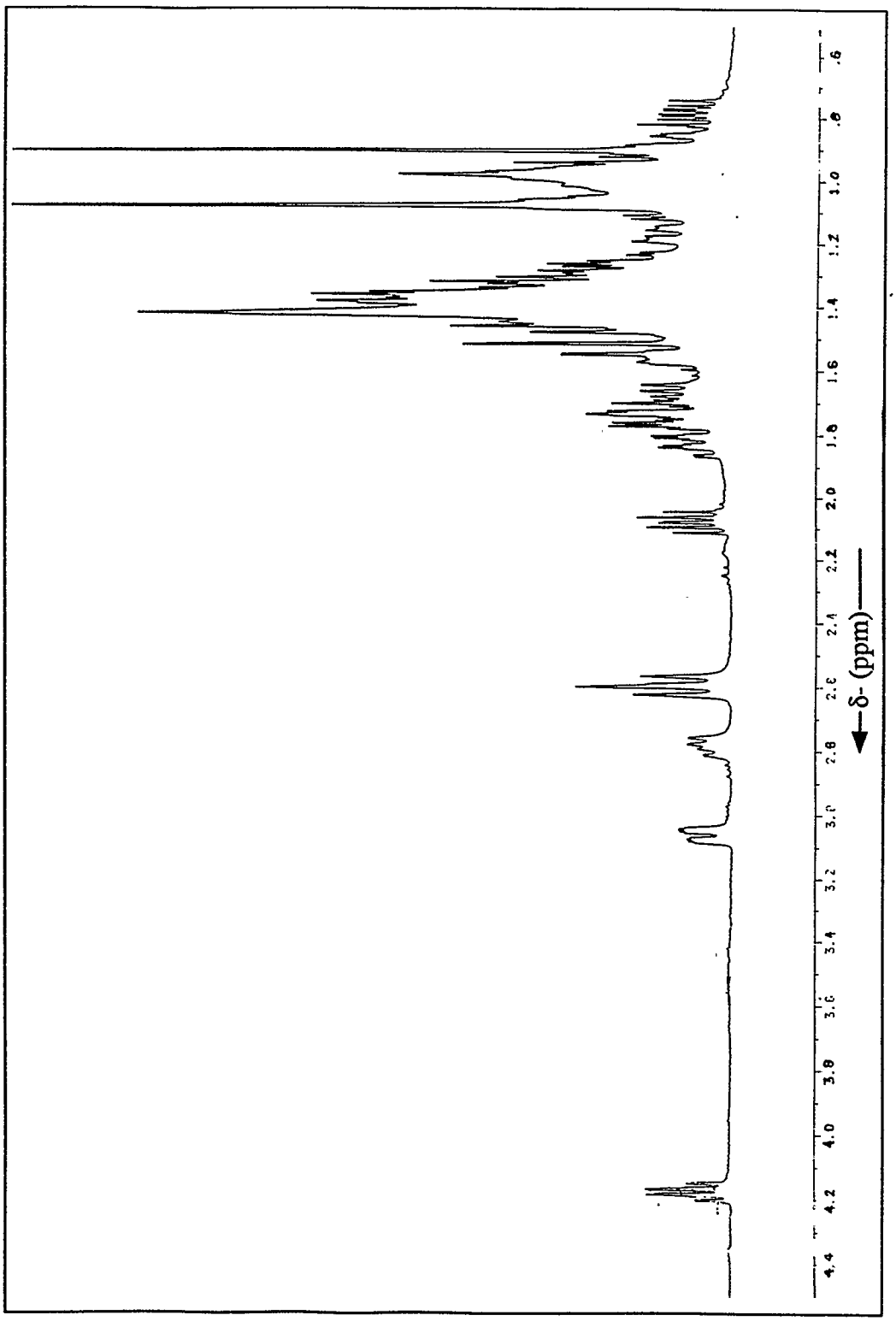
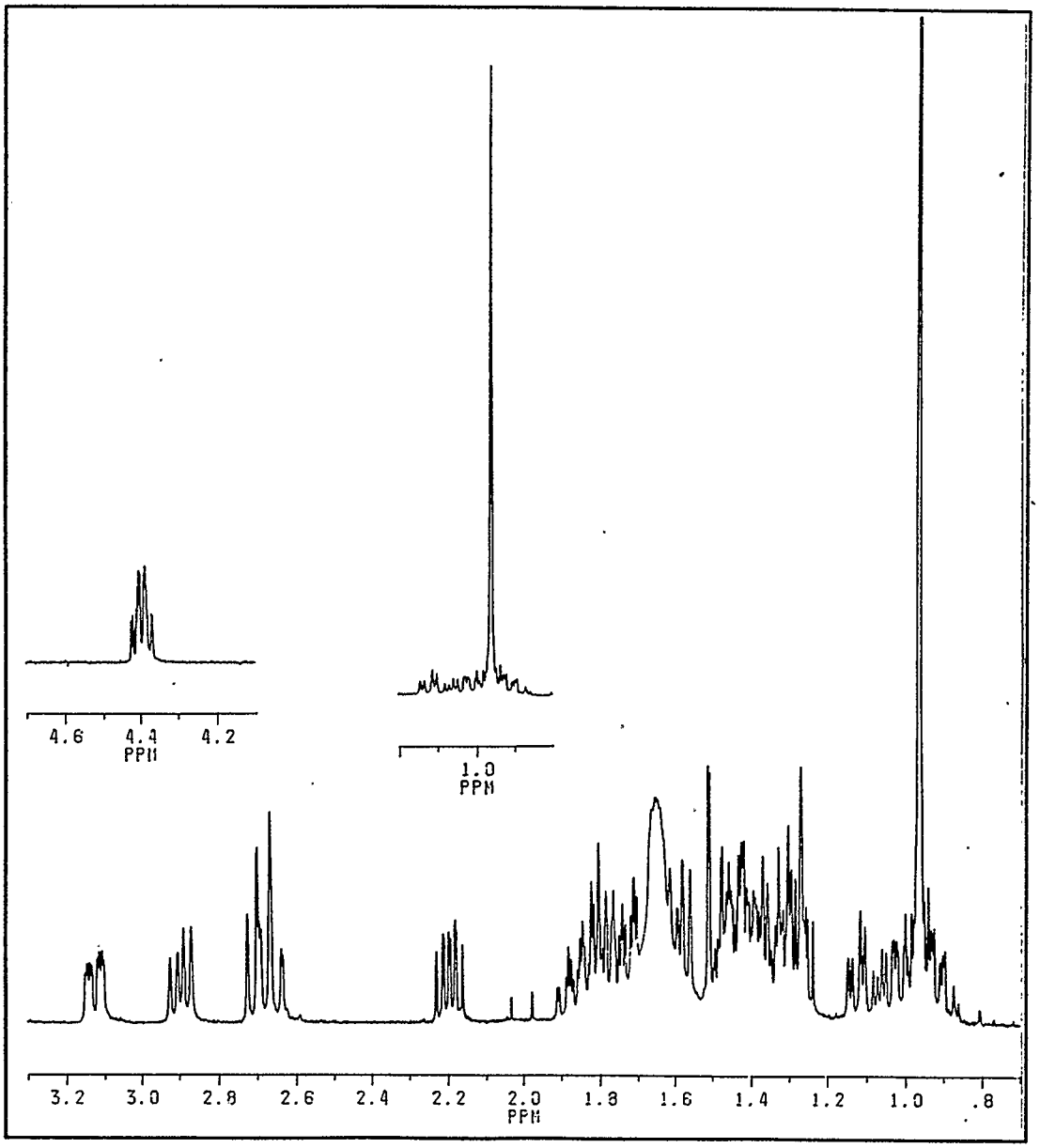
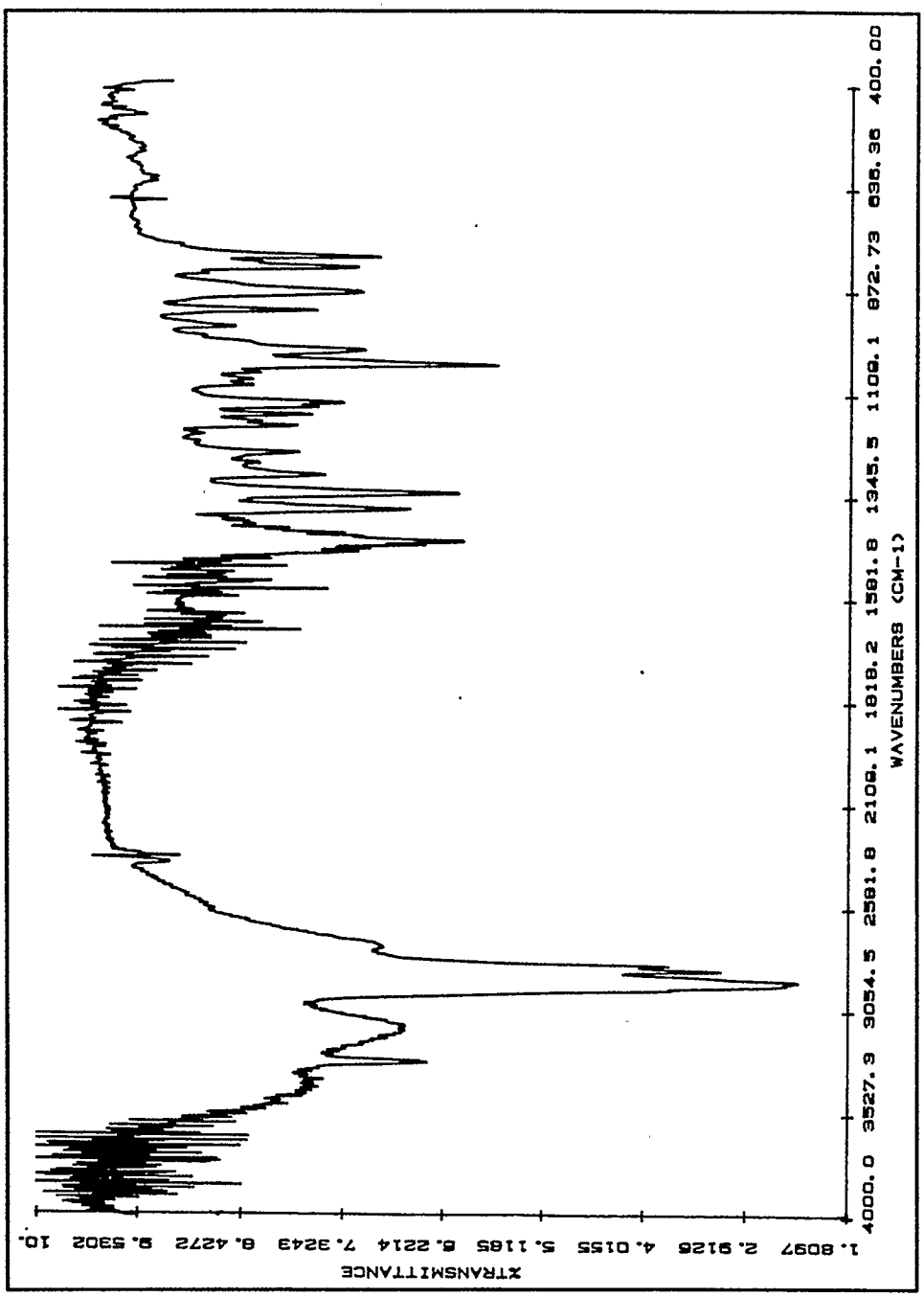
SPECTRA



Spectra 7.1 400 MHz ^{1}H-NMR (C_6H_6) Spectrum of Samanine (**9**).



Spectra 7.2 400 MHz ^{1}H-NMR ($CDCl_3$) Spectrum of Samanine (9).



Spectra 7.3 IR(KBr) Spectrum of Samanine (**9**).