DESIGN AND SYNTHESIS OF RING D MODIFIED STEROIDAL HORMONES

by

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I declare that 'Design and Synthesis of Ring D Modified Steroidal Hormones' is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references.

Signed by candidate

Claudia Grundler

To: Ruth, Sabine and Stephen

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SUMMARY

Cycloadditions of steroidal 14,16-dienes with ketene equivalents were investigated, as routes to estradiol and estriol analogues. The cycloadduct of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate and 2-chloroacrylonitrile underwent an unprecedented tandem rearrangement, on attempted alkaline hydrolysis to the corresponding ketone. This product, obtained in *ca.* 90% yield, was formulated as (16^1*R*)-3-methoxy-17-oxo-15ß,16^1-cyclo-14,16ß-ethano-14ß-estra-1,3,5(10)-triene-16^1-carbonitrile. The chemistry of the 16^1-carbonitrile was extensively studied and, in addition, the derived estradiol analogues were prepared and evaluated for receptor-binding affinity. The 16^1-carbonitrile, and its derivatives, could be transformed into 14,15-dihydrocyclobutano or 14ß,16ß-bridged compounds by cleavage of a cyclopropyl bond. Indeed, a 14,15-dihydrocyclobutano estradiol analogue was synthesised and submitted for biological evaluation.

The cycloadduct of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate and 2-acetoxyacrylonitrile afforded the corresponding 17-hydroxy 16-oxo compound on alkaline hydrolysis. The 17-hydroxy 16-oxo compound was efficiently converted to the 14α,17α-ethano 15,16-etheno compound by the Shapiro reaction. Reduction of the 17-hydroxy 16-oxo compound led to the formation of the corresponding 16,17-diols, which gave the derived 14ß-compounds on glycol cleavage. Furthermore, under acidic conditions the 16,17-diols were found to undergo high yield 16(17 → 17^1)*abeo* rearrangements, to afford 14,16-etheno compounds.

CONTENTS

1. INTRODUCTION

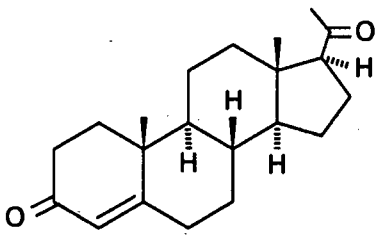
The binding of a hormone to the receptor is governed by two major constraints.[1] In the first instance steric accessibility is the deciding factor in recognition. The presence of a bulky group which does not fit into the three dimensional space presented by the receptor will prevent effective recognition. Secondly, if recognition is successful hydrogen bonding plays a major role in stabilising the hormone-receptor complex and in fixing the relative positions of the interacting moieties. Since hydrogen bonds are effective only over short distances, the positioning of the acceptor and donor atoms in the complex is critical for the summation of hydrogen-bond energies, that lead to the stabilisation of the complex.

The biological action[2] of the hormone originates from this hormone-receptor complex. The biological activity of the hormone (or hormone analogue) is determined by the concentration of the hormone-receptor complex at the site of action and by the intrinsic activity of the complex. In order to terminate the physiological effect and permit fresh stimulation, hormone receptor bonding must be reversible.

The natural steroidal hormones share the common structural feature of a perhydrocyclopenta[a]phenanthrene skeleton, which is itself devoid of biological properties. However, the presence of polar functional groups, most typically hydroxy and oxo groups at the extremities, unsaturation in ring A, together with angular methyl groups in an all *trans-transoid* array of the fused rings, constitutes the basis of the primary sex and adrenocortical hormones.

In steroidal hormones, small variations in these functional groups are sometimes responsible for totally different expressions of biological activity. For example, the introduction of a 21-hydroxy group into the primary gestagen, progesterone (**1**), affords deoxycorticosterone (**2**), one of the complex of adrenocortical hormones which displays mineralcorticoid activity. Accordingly, a great deal of research in this area has been devoted to studying the effect of variations in functional group patterns, rather than gross molecular modification of the parent skeleton, upon biological properties. The

purpose of much of this work has been to achieve enhanced or more selective hormonal activity. It is estimated[3] that some 100 000 steroid and steroid-like structures have been prepared by synthetic and semi-synthetic methods - this represents a small portion (probably no more than 10%) of possible variants.[4]



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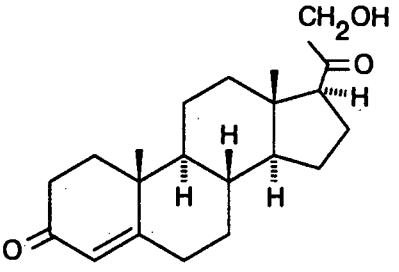

2 *

It is evident from the vast amount of knowledge which has accumulated[5] that structure-activity relationships are strongly influenced by the conformational properties of the steroidal hormones and many synthetic analogues. X-Ray crystallography, by which conformational trends can be determined, computer modelling of molecules and the experimentally determined biological activities of specific compounds have all aided in the mapping of steroid hormone receptors. Much remains to be done before the precise nature of the binding to the receptor, and the three-dimensional structure at the binding site itself, can be defined.

The ability of a receptor to recognise and bind a steroid is thought to be enhanced if the steroid molecule has sufficient conformational mobility to allow it to adapt easily to

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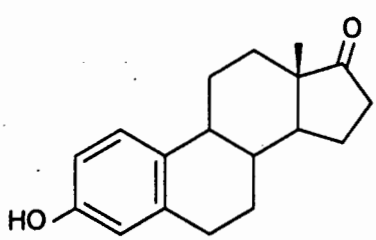
* All *trans-transoid* ring fusion as indicated; unless otherwise specified, configuration is assumed to be 8ß,9α,14α and is omitted in subsequent structural drawings for clarity

the requirements of the receptor.[6] Unsaturation in steroid rings lowers the free energy between conformers and may increase conformational mobility. The Δ^4-3-one A ring in many androgens, progestins and corticoids and ring B in estrogens exhibit greatest conformational flexibility.[5] Substitution can alter, limit or remove the flexibility of a steroid ring or side-chain and in this way limit the range of molecular interactions.

In view of the focus of this study upon the synthesis and properties of estrone-derived hormone analogues, the ensuing remarks are confined to some aspects of structure-activity relationships in the estrogens.

Structures with relatively high affinity for the estrogen receptor almost without exception contain a phenolic ring.[7] This feature facilitates interaction with the estrogen receptor (to the exclusion of other steroid hormone receptors) and thus determines estrogenic activity.[8]



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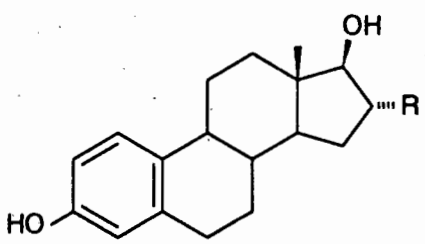
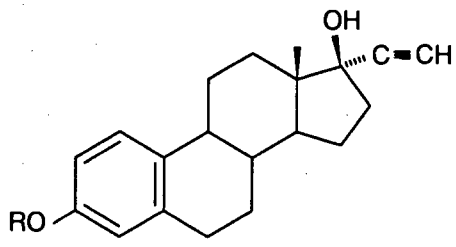


4 R=H

5 R=OH

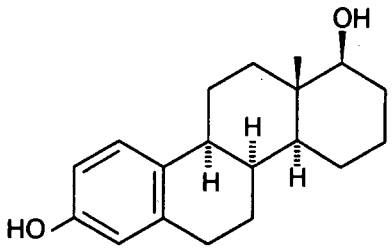
Estrone (**3**), estradiol (**4**) and estriol (**5**) are the most important naturally occurring estrogens and exhibit biological activities in the ratio 3:10:1 respectively.[3] These naturally occurring hormones, although physiologically active, cannot be utilized as oral estrogens. In 1938, Inhoffen *et al.*[9] discovered that addition of an ethynyl group at position 17 converted the orally almost-inactive estradiol into the potent and orally-active 17α-ethynylestradiol (**6**). This compound, and its 3-methyl ether, mestranol (**7**),[10] are used widely as drugs, especially in the fields of oral contraception and hormone supplementation therapy. This finding represented one of the important milestones in the development of structure-activity principles in steroidal hormones.



6 R=H

7 R=Me

Changes in the structure and configuration of the parent ring system are also responsible for modified hormonal properties. A number of 8α and 9ß derivatives have estrogenic activities comparable to that of estradiol,[5] although striking conformational differences exist between the steroids possessing the natural and unnatural configurations. For example, 17a-homo-8α-estra-1,3,5(10)-triene-3,17aß-diol (**8**) and 3-hydroxy-9ß-estra-1,3,5(10)-triene-11,17-dione (**9**) are more estrogenic than their respective natural isomers, which suggests that molecular planarity is not an essential criterion for activity.[7]



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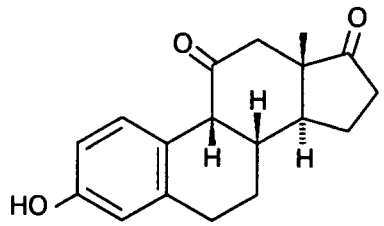
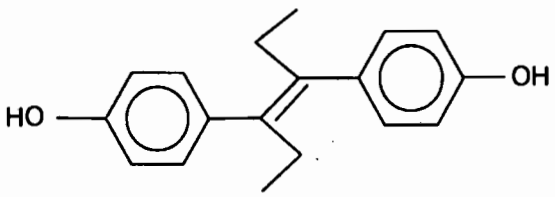


9

The affinity of diethylstilbesterol (**10**) for the estrogen receptor was proposed to be associated with a specific distance between the two hydroxyl groups.[11] X-Ray crystallographic studies have revealed that the distance between the terminal oxygen groups for diethylstilbestrol is significantly smaller than this distance in estradiol. This disparity suggests that a water molecule can play a significant role in acting as a link between estradiol and the receptor. Studies on non-steroidal systems[7] have shown that

tetrahydronaphthol (**11**) prevents binding of estradiol to the estrogen receptor and *p-sec*-amylphenol (**12**) will displace estradiol. This demonstrates that a large molecule with hydroxy groups at either end is not essential for binding and suggests that close association of the receptor occurs with the steroid A ring by relatively strong hydrogen bonds associated with the 3-hydroxy group.



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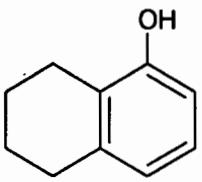

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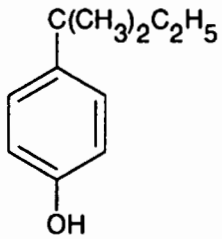
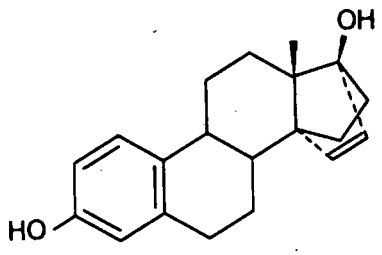


12

Removal of the 17-hydroxy group from estradiol significantly decreases binding and almost totally abolishes estrogenic activity.[7] On the other hand, the removal of the 3-hydroxy group almost eliminates receptor binding whilst retaining activity in proportion to the reduced amount of binding. This demonstrates that O(3) is more important to binding and O(17) more important to activity. O(17) probably plays a role in stabilising the hormone-receptor complex by hydrogen-bonding and its absence may alter the stability of the ring A binding interactions to the receptor.

The effect of substitution at C(17) has been reported[6] for both the 8ß- and 8α-estradiol series. 17α-Methyl, 17α-vinyl or 17α-ethynyl groups do not significantly interfere with binding, unlike the 17α-ethyl group. This group, in particular, inhibits hydrogen-bonding interactions between the steroid and its receptor by blocking approach to the lone pairs of electrons on oxygen, whereas 17α-ethynyl groups, at the other extreme, leave hydrogen bonding unimpaired and allow high biological activity. Reversal of the configuration of substitution at C(17) (to 17α-OH, 17ß-R) reduces the binding affinity of estradiol analogues; compounds of the 8α-series are always less effective than their natural 8ß-isomers.

Estradiol analogues (**13** and **14**) with a two-carbon bridge between the 14α and 17α positions also exhibit enhanced oral estrogenicity.[12] This finding arose from cycloaddition studies in 19-norsteroids, and has led to an expanding area of current research.



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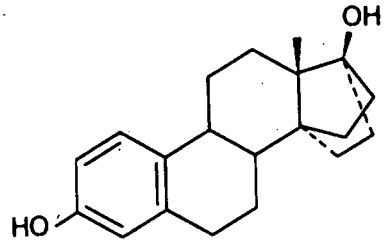

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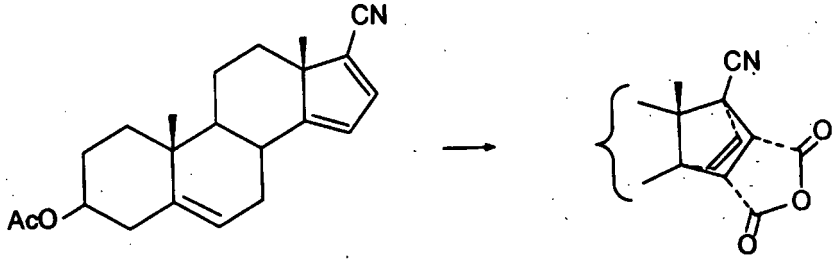
Cycloadditions of steroidal 14,16-diene systems are not new and in order to gain an understanding of these reactions and to appreciate the contribution which cycloaddition studies have made in the steroid field, a brief overview is given here.

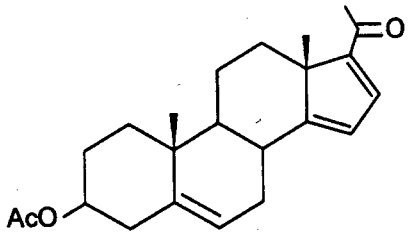
The first Diels-Alder cycloaddition of a steroidal 14,16-diene was reported in 1965.[13] The reaction between 3ß-acetoxyandrosta-5,10,16-triene-17-carbonitrile (**15**) and maleic anhydride, gave the cycloadduct (**16**).



15 **16**

Solo[13] assumed that the dienophile approaches the diene from the ß-face of the latter since a model suggested that this is less hindered. In addition, at the moderate reaction temperature used, the *endo*-orientation of the functional group was thought to

predominate and, by analogy to nonsteroidal systems, it was expected that the 'head-to-head' regioisomers would be obtained from monofunctionalised dienophiles.



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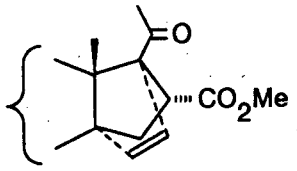

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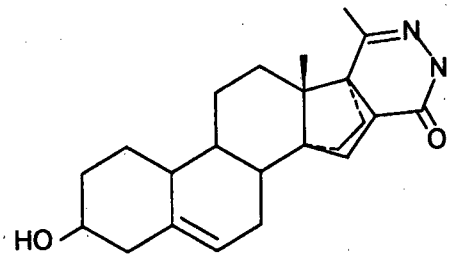

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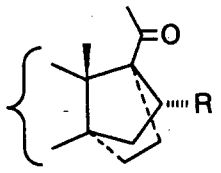
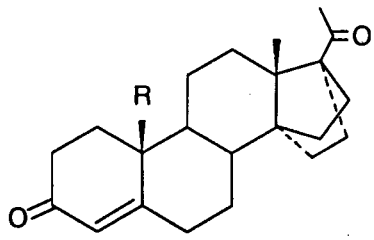


20 R=CO_2Me

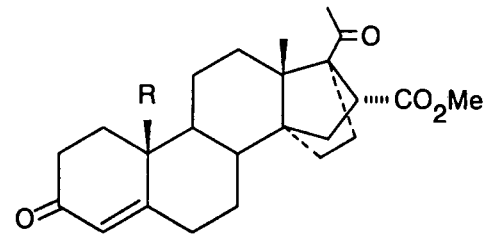
21 R=I

This expectation was realised when methyl acrylate underwent regioselective cycloaddition to 3-acetoxypregna-5,14,16-trien-20-one (**17**), to give the cycloadduct (**18**), which was treated with hydrazine to give the fused dihydropyridazone (**19**). Further structural evidence was obtained from NMR studies. Thus, the methyl signal for the carbomethoxy group of the 14α,17α-etheno compound (**18**) appeared at δ 3.58, but at δ 3.65 for the corresponding 14α,17α-ethano compound (**20**). The shielding of the methyl group by the olefinic bond in the etheno compound (**18**) was used as evidence in support of the *endo*-orientation of the 16-carbomethoxy group. It was further shown that no skeletal rearrangement had occurred during the conversion of the 14α,17α-etheno compound (**18**) into the 16α-iodo compound (**21**). An X-ray crystal structure of the 16α-iodo compound (**21**), confirmed the structure as drawn, and this demonstated that cycloaddition had occurred regio- and stereoselectively on the ß-face of the diene (**17**).



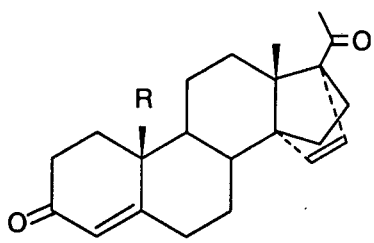
22 R=CH_3

23 R=H



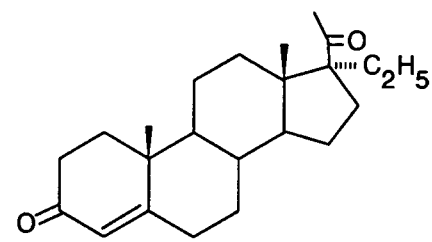
24 R=CH_3

25 R=H



26 R=H

27 R=CH_3



28

The gestagenic activities of several ring D bridged steroids have been studied. The activities, relative to progesterone, of the above progesterone analogues were determined by a Clauberg assay and were found to be:

(**22**)	1.3
(**23**)	17.6
(**24**)	0.16
(**25**)	4
(**26**)	0.6

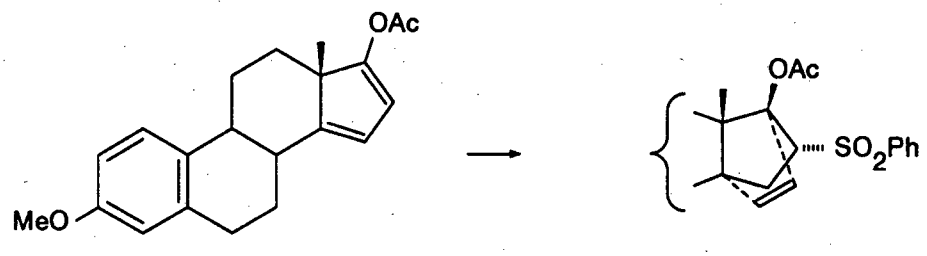
The Clauberg activity, found in the preliminary assays[17] of 14α,17α-ethenopregn-4-ene-3,20-dione (**27**) was high, but more extensive testing revealed[18] that it is low compared to that of 17α-ethylprogesterone (**28**). It is known that interaction of a gestagen with a Clauberg receptor does not involve the α face of the gestagen in the vicinity of ring D. Insertion of a two-carbon bridge between the 14α and 17α positions of progesterone requires a small deformation of ring D which results in the 17-acetyl group being

deflected toward the α side. Strong interaction of the 17-substituent with a Clauberg receptor together with ring D deformation serves to increase the apparent bulk of all ß substituents and the resultant steric hindrance leads to a decrease in the binding affinity between the hormone analogue and the Clauberg receptor. In support, it was shown[16] that 14α,17α-ethanopregn-4-ene-3,20-dione (**22**) exhibits an activity of 1.3 times that of progesterone whereas the activity of 19-nor-14α,17α-ethanopregn-4-ene-3,20-dione (**23**) is 17.6 times that of progesterone.

The role which functional groups can play in determining activity was also demonstrated by Solo.[15,16] Reductive removal of the 16α-carbomethoxy group from (**24**) and (**25**) to give (**22**) and (**23**) led to a significant increase in activity. This was partially negated in (**26**) where the 14,17α-etheno bridge was assumed to result in ring D deformation.

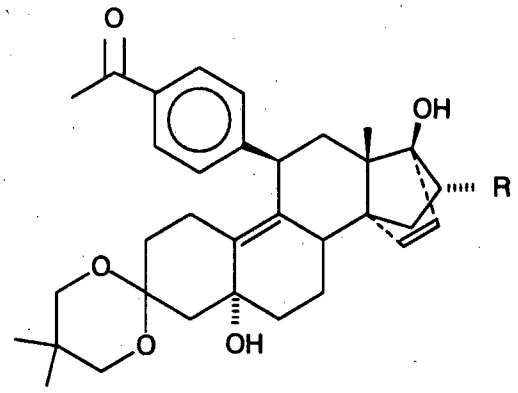
The work of Solo *et al.* demonstrated the feasibility of using cycloaddition methodology to synthesise ring D bridged steroidal hormone analogues, but the early work was limited by the unavailability of reactive 'ethylene equivalents' which could be used to obtain direct entry to unfunctionalised bridges. This necessitated the use of laborious multi-step reaction sequences to achieve this purpose.[14,19]

The development of phenyl vinyl sulphone (PVS) as an efficient ethylene equivalent[20] enabled the cycloaddition approach to be investigated in the 19-norsteroid series. Thus, cycloaddition of PVS to 3-methoxyestra-1,3,5(10),14,15-pentaen-17-yl acetate (**29**) gave a single cycloadduct (**30**), which underwent reductive desulphonylation to give the 14α,17α-etheno and derived 14,17α-ethanoestra-1,3,5(10)-triene-3,17ß-diols (**13**) and (**14**).[21] These compounds have been shown to display superior oral estrogenicity,[12] and the 14α,17α-etheno compound has been used as an intermediate in the synthesis of 14α-functionalised 19-norsteroids.



29 **30**

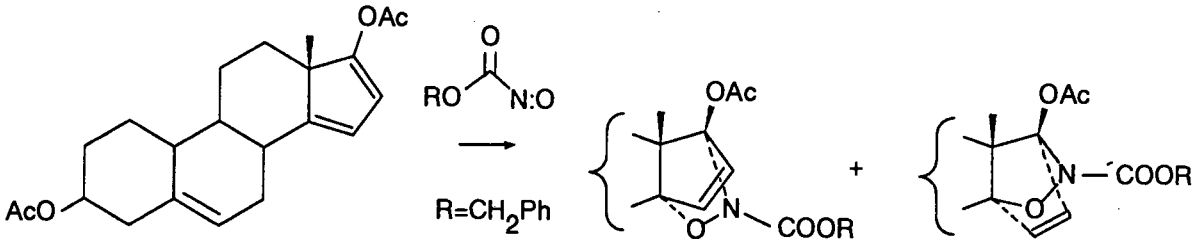
This approach has been used to synthesise 11ß-aryl 14α,17α-etheno 19-norsteroids[22] such as (**31**) and (**32**).



31 R=CO_2Et

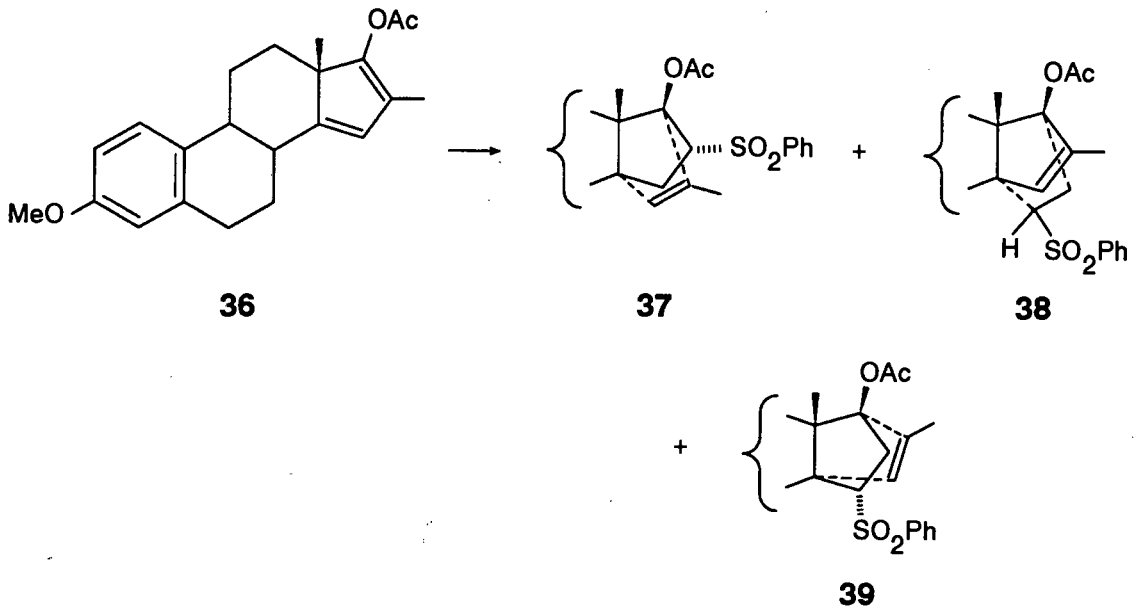
32 R=CN

This principle has also found application in the heterocycloaddition of benzyl nitrosoformate[23] to androsta-5,14,16-trien-3ß,17-diyl acetate (**33**) to prepare the cycloadducts (**34**) and (**35**) and hence, the derived 14α- and 14ß-hydroxy 17-ketones. The latter example illustrates a departure from the generality of the principle of preferred ß-face cycloaddition. In general, Diels-Alder cycloadducts of acyl nitroso compounds readily undergo retro [4 + 2] cycloaddition under mild thermal conditions.[24] Under such conditions, the thermodynamically more stable α-isomer (**34**) is expected to predominate, and it does in a 3.5:1 ratio.



33 **34** **35**

It has also been found that the presence of a 16-methyl group[25] has an adverse effect upon the regio- and stereoselectivity of cycloaddition of PVS to the 14,16-diene system. Thus, cycloaddition of PVS to 3-methoxy-16-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate (**36**) afforded a three component mixture of cycloadducts (**37**), (**38**) and (**39**). The 16-methyl group serves to depress the regio- and stereoselectivity in this Diels-Alder reaction and the *meta*-regioselectivity is attended by a significant loss of ß-face stereoselectivity.

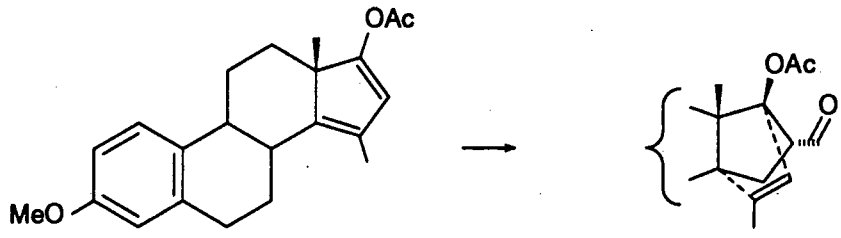


36 **37** **38**

39

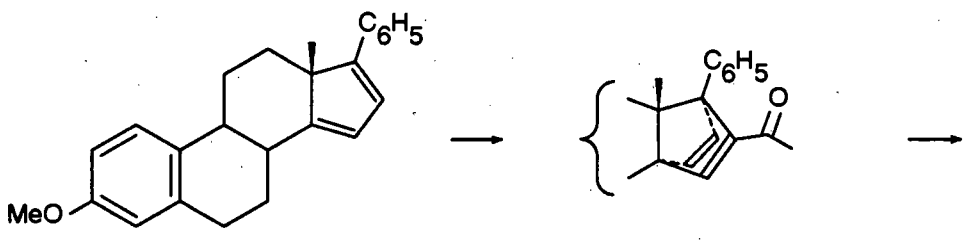
It has also been shown that the presence of a 15-methyl group appears to suppress the reactivity of PVS to the 14,16-diene (**40**). Loedolff,[26] failed to achieve cycloaddition of PVS to 3-methoxy-15-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate (**40**) under a variety of reaction conditions. It was concluded that the 15-methyl group deactivated the

diene by steric impedance which the PVS was not reactive enough to overcome. However, cycloaddition of the 14,16-diene (**40**) with acrolein gave a single cycloadduct, 17ß-acetoxy-3-methoxy-17^2-methyl-14,17α-ethenoestra-1,3,5(10)-triene-16α-carbaldehyde (**41**) (75%).

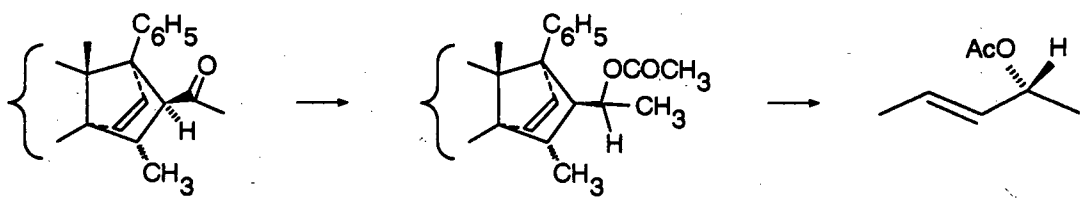


40 **41**

Cycloadditions of steroidal dienes have been used in order to obtain single enantiomers[27] by the retro-Diels Alder reaction of the modified cycloadducts. Thus the cycloaddition of 3-methoxy-17-phenylestra-1,3,5(10),14,16-pentaene (**42**) and butynone gave the cycloadduct (**43**) which was subjected to conjugate cuprate addition to give (**44**) and converted to (**45**). The thermal retro-Diels-Alder reaction of (**45**) afforded the optically pure (*R*)-acetate (**46**).



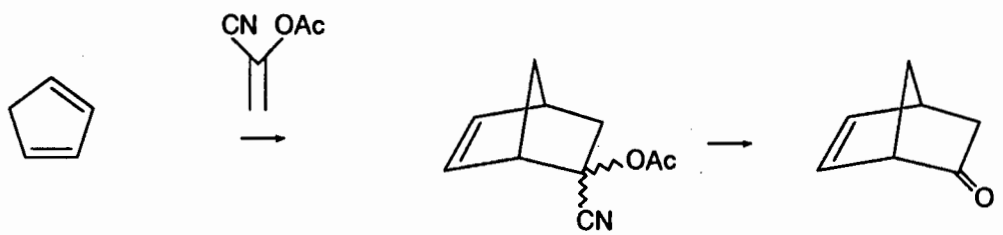
42 **43**



44 **45** **46**

Although not all the reported applications of steroidal Diels-Alder cycloadditions have been mentioned individually, it is clear from this survey that no studies have hitherto been undertaken upon the cycloaddition of 14,16-diene systems with ketene equivalents. Ketene does not undergo [4 + 2] cycloadditions, but rather [2 + 2] cycloaddition with olefins or dienes.[28] Indirect methods have been developed to achieve the formal Diels-Alder cycloaddition of ketene to 1,3-dienes. These involve cycloadditions with ketene equivalents, of which several have been developed. Such reagents most often contain an electron withdrawing substituent (eg. C=O, CN or NO_2) to ensure a reactive dienophile and, where necessary further terminal functionality to facilitate conversion of the functional groups in the resultant cycloadduct into an oxo group.

The interest in norbornenes led to the development of the first ketene equivalent, 2-acetoxyacrylonitrile. By cycloaddition of cyclopentadiene (**47**) with 2-chloroacrylonitrile Bartlett and Tate[29] obtained the cycloadduct (**48**) which, on saponification with sodium hydroxide at 100°C, gave bicyclo[2.2.1]hept-5-en-2-one (**49**) in 51% yield.

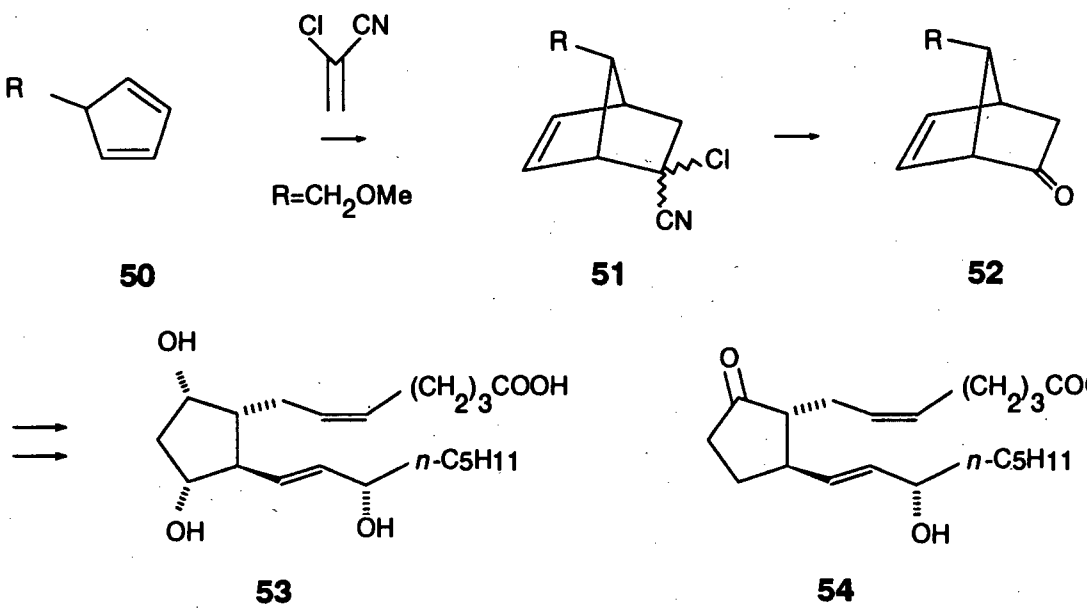


47 **48** **49**

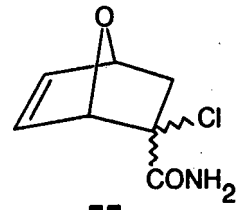
Since then, there have been numerous examples of the application of 2-acetoxyacrylonitrile as a ketene equivalent in cycloadditions. For example, cycloadditions with furan,[30] 6,6-dimethylfulvene[31] and heterodienes[32] [eg. N-(ethoxycarbonyl)dihydropyridine] gave rise to the cycloadducts which were converted first into the corresponding ketones and this into a wide variety of compounds. The use of catalysts such as ZnI_2[30] and a 5.0M solution of lithium perchlorate in diethyl ether[33]

have led to improvements in the cycloaddition reactions. Sodium methoxide in methanol[34] is now widely used to convert such cycloadducts into the corresponding ketones. Cycloadducts of furan are often converted to the cyanohydrins with NaOMe-MeOH but treatment with formalin[35] provides the desired ketone. Cycloadducts of 2-acetoxyacrylonitrile are readily converted to the ketone but its use is limited by high cost[36] and low reactivity.[37]

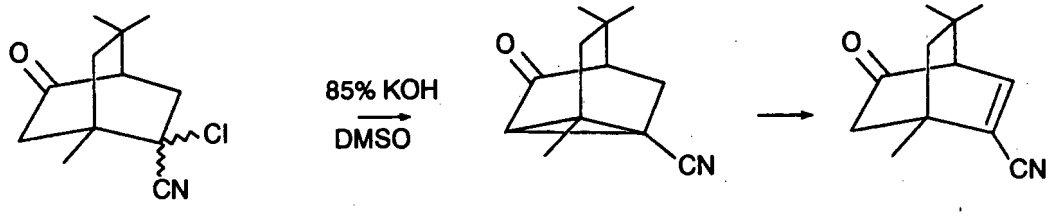
The limitations of 2-acetoxyacrylonitrile led to the development of 2-chloroacrylonitrile[38] as an alternative ketene equivalent. This reagent offers several advantages including higher regioselectivity,[39] greater reactivity[37] and lower cost.[36] This ketene equivalent led to a major breakthrough during the cycloaddition of 5-substituted cyclopentadienes[40] where 5-methoxymethyl-1,3-cyclopentadiene (**50**) was subjected to a Diels-Alder reaction with 2-chloroacrylonitrile to give the cycloadduct (**51**) which was hydrolysed into the corresponding ketone (**52**). Several steps were required to transform the ketone (**52**) into *rac*-prostaglandin $F_{2\alpha}$ (**53**) and *rac*-prostaglandin E_2 (**54**).



$Cu(BF_4)_2$ has been known since 1969[38] to catalyse cycloadditions with 2-chloroacrylonitrile. More recently, catalysis with the Cu(I)- and Cu(II)-salts $Cu(OAc)_2.H_2O$, CuCl and cupric tartrate[41] has been described. Numerous methods have been developed to transform the cycloadducts to the corresponding ketones. These include alkali in various media,[38,42,43] sodium sulphide in ethanol[39] and binary alkaline sulphide systems.[44] Several cases have been reported where none of these methods afforded the desired ketone.[45] In these cases the cycloadducts were either converted into the chloro amides[38] (e.g. **55**) or chloro acids,[41] underwent a facile rearrangement with concomitant reductive elimination of the chloride group[46] (e.g. **56** to **57**) or gave very poor or unreliable yields.[47]



55

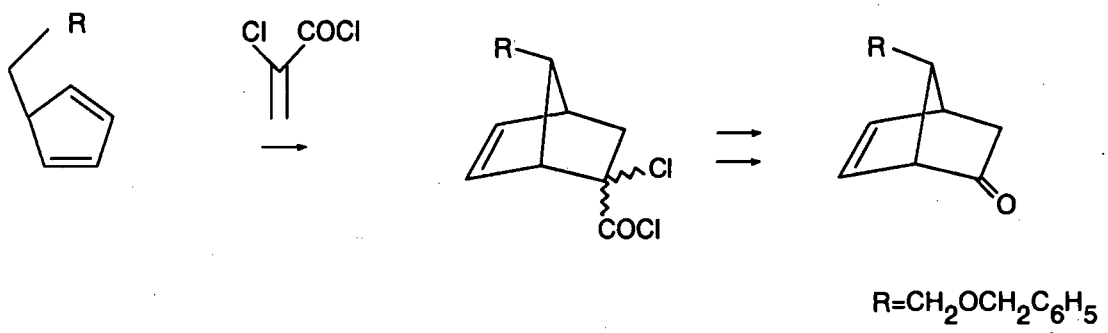


56 **57**

The chloro amides and chloro acids could be converted to the ketones by a route proceeding through the Curtius rearrangement of the α-chloroacryloyl azides.[48]

The use of 2-acetoxy- and 2-chloroacrylonitrile as dienophiles suffers from some disadvantages in cycloadditions with thermally sensitive and less reactive dienes.[37,49] For example, their application in prostaglandin synthesis using 5-substituted cyclopentadienes is complicated by the pronounced tendency of these systems to undergo thermally induced 1,5-sigmatropic rearrangements. In such instances, it has

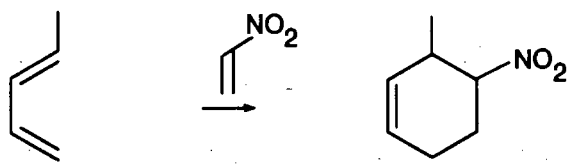
been found that 2-chloroacryloyl chloride[49] is sufficiently reactive to undergo cycloaddition at 0°C, without attendant isomerisation of the substrate. The cycloadducts are transformed to the ketones by a sequence involving the Curtius rearrangement.



$R=CH_2OCH_2C_6H_5$

The disadvantages of this procedure are the difficulties associated with the preparation[50] of 2-chloroacryloyl chloride and the need for a two-step rather than direct conversion to the ketone.

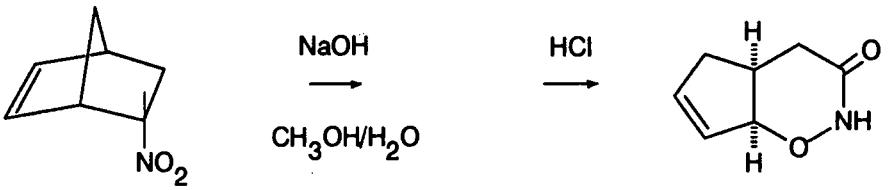
Nitroethylene is an excellent dienophile in Diels-Alder reactions and the nitro group serves as an effective regiochemical control element.[51] Cycloaddition of nitroethylene with (**58**) gave a single cycloadduct (**59**).



58 **59**

Cycloaddition to cyclopentadiene occurs at -100°C and to 5-substituted cyclopentadienes at -15 to 0°C.[52] The potential of nitroethylene lies in those cases where the substrates are sufficiently reactive to undergo reaction under mild conditions. Where more forcing conditions are required, the limited stability of the reagent complicates the reactions. Nitroethylene cycloadducts can be converted into the corresponding ketones by several methods. Classical Nef reaction conditions[53] are not effective in those cases

where the nitronic acid intermediates suffer the consequences of steric factors or if acid sensitive functional groups are present. In addition, isomerisation or molecular rearrangements may occur during the conversion.[54] For example, under acidic conditions the cycloadduct (**60**) gave rise to a product of rearrangement (**61**).



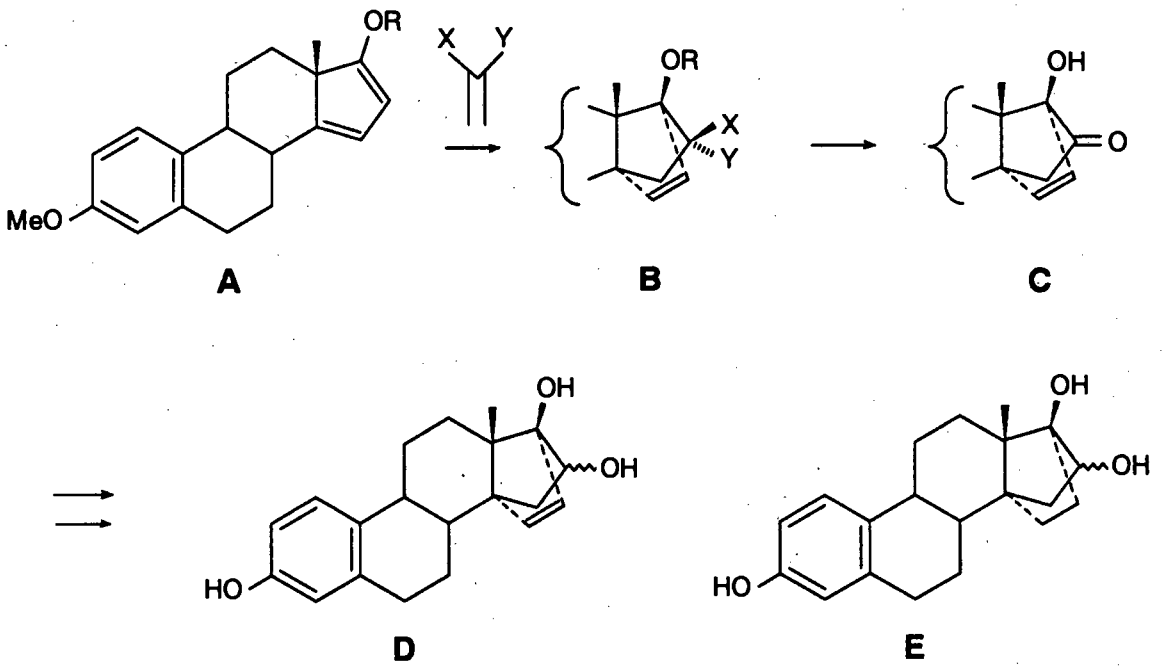
60 **61**

Other reagents used for the transformation are: potassium permanganate,[55] ammonium persulphate,[56] $TiCl_3$ (unbuffered),[57] $TiCl_3$ (NH_4-OAc buffered),[58] Et_3N-CS_2,[59] ozone,[60] alkaline sodium chlorite,[61] *t*-butyl hydroperoxide-$VO(acac)_2$,[62] basic silica gel,[63] ceric ammonim nitrate,[64] MoO_5.pyr.HMPA[65] and modifications of the Nef conditions.[66] The large number of methods developed for the conversion of nitroethylene cycloadducts to the ketone bears testimony to the difficulty associated with the transformation.

Several other ketene equivalents are known, but have attendant disadvantages. For example, acrylate[67] and acrylonitrile[42] derived cycloadducts require multistep procedures for conversion into the corresponding ketone. Others, such as vinylboronate esters[39] and vinyl acetate[42] suffer from low reactivity, whereas vinyl triphenylphosphonium bromide,[68] 'capto-dative' olefins[69] and methyl (alkylthio)propiolate[70] have hitherto found little favour in the recent literature.

2. OBJECTIVES

The main objective of this investigation was to extend previous findings of structure-activity relationships of 14,17-bridged 19-norsteroids,[12] by studying cycloadditions of selected ketene equivalents with 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl derivatives, and converting the cycloadducts into new hormone analogues.

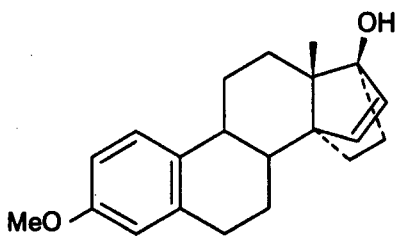


It was expected that the choice of appropriate ketene equivalents in the cycloaddition of 14,16-diene-17-yl derivatives (**A**; R=Ac, $SiMe_3$) would lead to intermediate (**B**). The first phase of the study required verification that the regioselectivity and stereoselectivity of cycloaddition conformed to that observed in analogous reactions. An essential feature of the overall strategy entailed conversion of the primary cycloadducts (**B**) into the 17ß-hydroxy-14α,17α-etheno-16-ketone (**C**), in order to obtain ready access to 14α,17α-etheno and 14α,17α-ethano analogues (**D** and **E** respectively) of estra-1,3,5(10)-triene-3,16α,17ß-triol (estriol) and the corresponding 16ß-epimers. The trends observed in the natural hormone series suggested that

biological evaluation of the estriol analogues (**D** and **E**) would make a meaningful contribution to the understanding of structure-activity principles in 14,17-bridged systems.

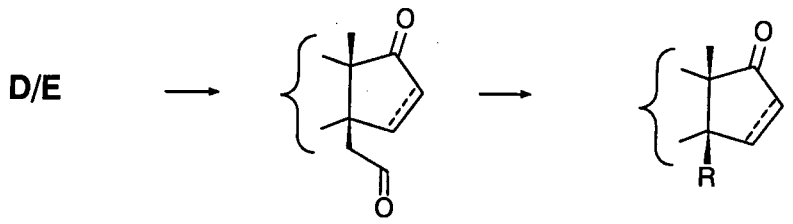
In practice, the cycloaddition studies were restricted to 2-chloroacrylonitrile and 2-acetoxyacrylonitrile, since an unprecedented rearrangement, accompanying the attempted conversion of (**B**) (X=Cl, Y=CN) into the corresponding ketone (**C**), led to a detailed study of a new series of skeletally modified 19-norsteroids. In addition, earlier work on 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17ß-ol suggested that other members of the bridged series, as exemplified by (**B**) - (**E**) would be susceptible to novel skeletal rearrangements.

Intermediates related to (**C**) - (**E**) could also be investigated as precursors of 3-methoxy-14,17α-ethanoestra-1,3,5(10),15-tetraen-17ß-ol (**F**) *via* elimination of 16-functionality. This objective was useful since the known route is extremely inefficient, and availability of the ß-bridged olefin would provide scope for examining a variety of new rearrangement options.



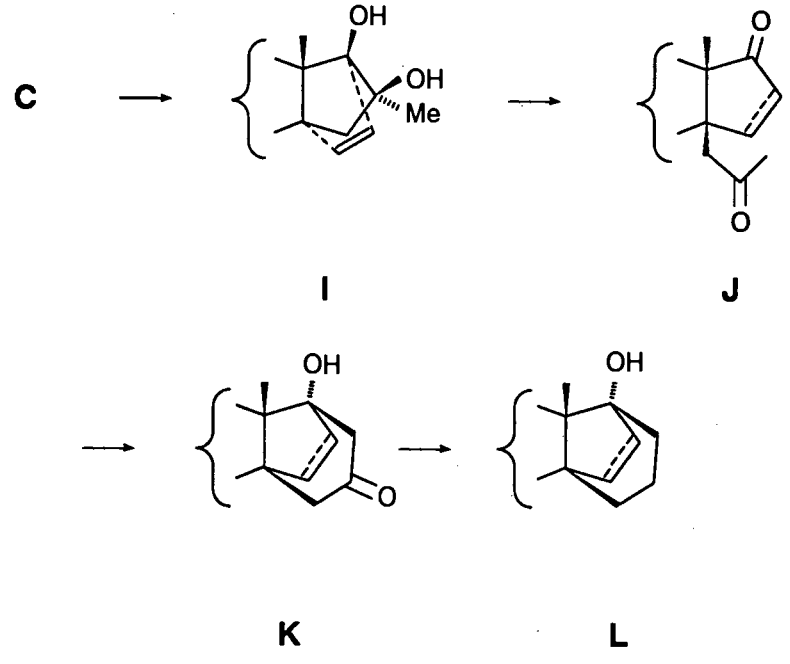
F

Complementary studies were planned, *via* oxidative cleavage of the precursors of the 16,17-diols (**D** and **E**), leading to 14ß-formylmethyl 19-norsteroids (**G**), upon which chemoselective homologation of the side-chain oxo-group would provide an entry to 14ß-chain extended 19-norsteroids (**H**).



G **H** (R= C_3-C_{10} chains)

Similarly, oxidative cleavage of methyl diols (**I**) derived from methylation of (**C**) would provide 14ß-acetonyl 19-norsteroids (**J**) as possible precursors of intramolecular aldol closure products (**K**) leading to 14ß,17ß-propano analogues (**L**) of estradiol.



I **J**

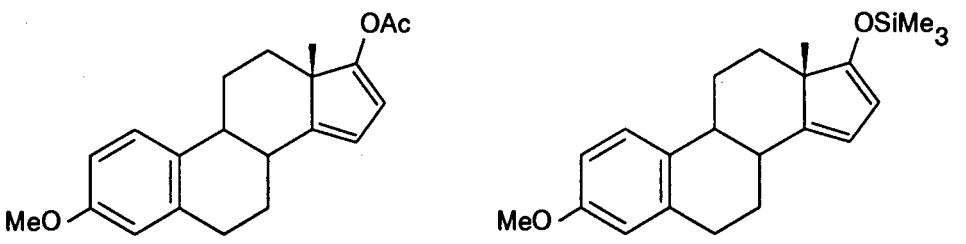
K **L**

3. DISCUSSION

3.1 Synthesis of the Steroidal 14,16-Dienes

3-Methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**29**) and 3-methoxy-17-trimethylsilyloxyestra-1,3,5(10),14,16-pentaene (**62**) (Scheme 3.1-1) were selected for this study.

SCHEME 3.1-1



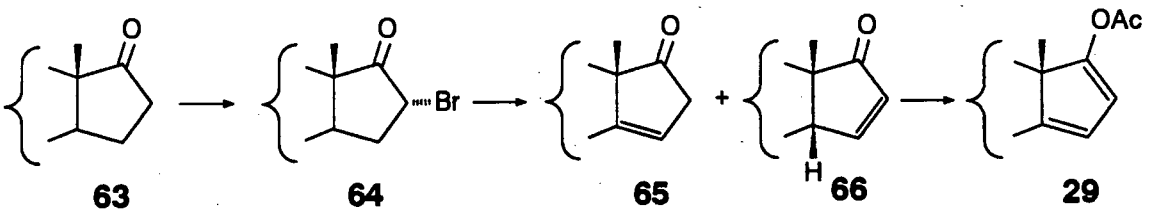
29 **62**

The dienyl acetate (**29**) has been used extensively for cycloaddition studies in this programme,[21] and it has been shown that the derived intermediates can readily be converted into 14,17-bridged estradiol analogues. In this work, the complementary investigation of cycloadditions upon the corresponding silyl dienyl ether (**62**) was considered desirable, since it was hoped that it might have some advantages in terms of cycloaddition reactivity and stabilisation of bridgehead functionality of the derived cycloadducts under certain reaction conditions. Cycloadditions upon related substrates have recently been reported.[22]

The steroidal 14,16-diene (**29**) was prepared by an adaptation of earlier literature methods, and involves a three-step reaction sequence without purification of the intermediates (Scheme 3.1-2). Estrone 3-methyl ether (**63**) was brominated selectively at C(16) in the presence of copper(II) bromide in refluxing benzene-methanol[71] to give the 16α-bromo derivative (**64**). Dehydrobromination of the 16-bromo compound (**64**) in

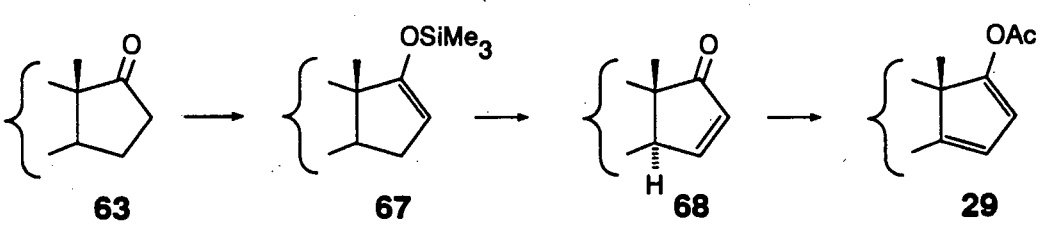
anhydrous deoxygenated *N,N*-dimethylformamide in the presence of lithium carbonate and lithium bromide gave the enones (**65**) and (**66**) which were acetylated[72] with acetic anhydride and isopropenyl acetate in the presence of toluene-*p*-sulphonic acid, to give the dienyl acetate (**29**). The pure dienyl acetate (**29**) was isolated in 63% yield from (**63**) after chromatography of the reaction product. The spectroscopic and analytical data were consistent with those of authentic material.

SCHEME 3.1-2



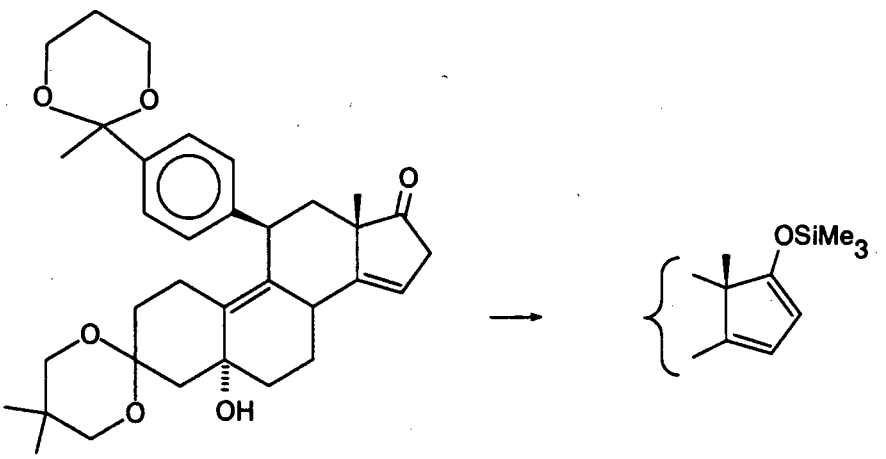
In an attempt to improve on the yield of this sequence an alternative route (Scheme 3.1-3) was investigated. This involved conversion of estrone 3-methyl ether (**63**) into the enol silyl ether (**67**),[73] subsequent formation of the conjugated enone (**68**)[74] and acetylation to afford the dienyl acetate (**29**). The poor overall yield of 25%, as well as the cost of the reagents involved, discouraged further investigation and optimisation of this route.

SCHEME 3.1-3



The method employed for the preparation of the silyl dienyl ether (**62**) entailed base-mediated deprotonation of the ß,γ-unsaturated enone (**65**) followed by trapping of the resultant 14,16-dienolate anion with trimethylchlorosilane. This procedure was similar to that employed by Scholz *et al.*[22] for the related conversion of the enone (**69**) into the corresponding silyl dienyl ether (**70**) (Scheme 3.1-4).

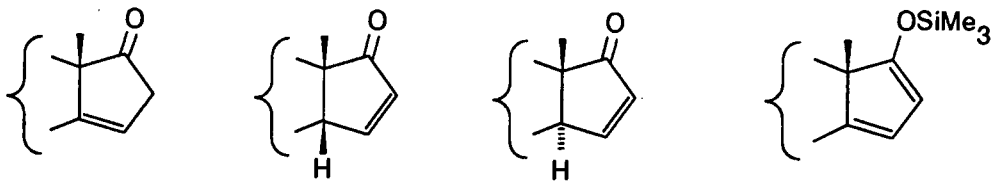
SCHEME 3.1-4



69 **70**

Treatment of the enone (**65**), obtained by separation of the mixture of enone intermediates (**65** + **66**) in the dienyl acetate (**29**) synthesis, with lithium diisopropylamide and trimethylchlorosilane in tetrahydrofuran at -78°C resulted in efficient conversion into the desired product (**62**). The NMR spectrum of (**62**) exhibited a diagnostic nine-proton singlet at δ 0.25 for the trimethylsilyl group, together with signals at δ 5.18 and 5.77 for the 16- and 15-protons respectively. The mass spectrum displayed a peak at *m/z* 354, consistent with the molecular formula of $C_{22}H_{30}O_2Si$. Purification of the dienyl silyl ether (**62**) was not attempted because it proved to be very labile on handling and on chromatography on silica gel.

SCHEME 3.1-5



65 **66** **68** **62**

Attempts were also made to achieve silylation of the conjugated enones (**66**) and (**68**), so that the method could be applied directly to the isomeric mixture obtained upon dehydrobromination of the bromo ketone (**64**). In this event, both isomers failed to form the desired product under similar reaction conditions, a result comparable to that reported by Scholz *et al.*.[22]

The lability of the trimethylsilyl derivative (**62**) prompted an attempt to synthesise the *tert*-butyldimethylsilyl ether since they are known to be more stable.[75] However, treatment of the Δ^{14}-17-ketone (**65**) with lithium diisopropylamide and *tert*-butyldimethylsilyl chloride, as before, failed to give the desired product.

3.2 Cycloadditions with Ketene Equivalents

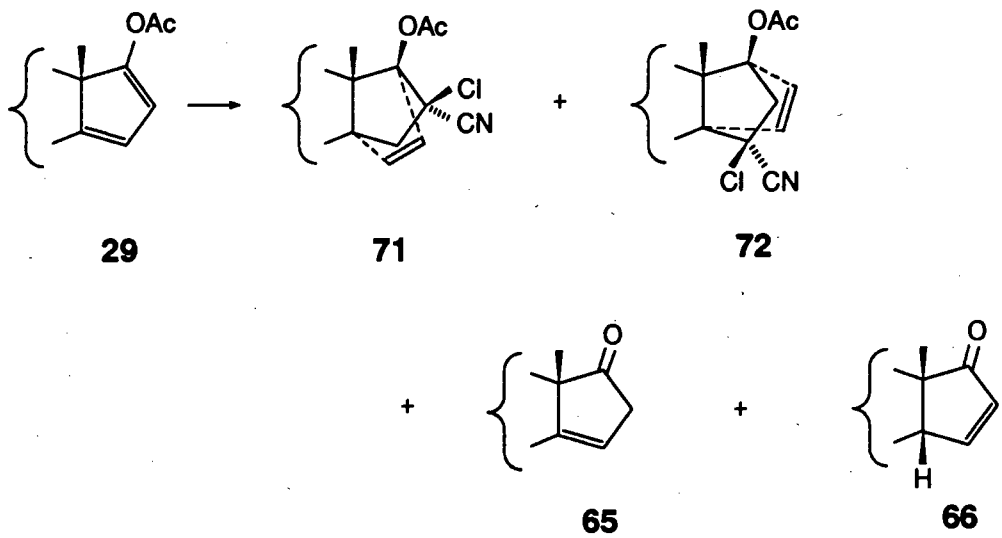
Initial experiments were carried out upon 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**29**). In all cases, the cycloadditions were performed in sealed tubes, which were flushed with nitrogen prior to commencement of the reaction.

Treatment of the dienyl acetate (**29**) with 2-chloroacrylonitrile (3 mol. equiv.; freshly distilled from hydroquinone) in dry benzene at 90°C proceeded slowly and, after *ca.* 68 and 92 h, required the addition of further aliquots of reagent (each 0.5 mol. equiv.) in order to proceed to completion. After a total period of 114 h at 90°C, the reaction was complete (TLC) and the products were isolated by crystallisation and repeated chromatography of mother-liquor residues, to give 17ß-acetoxy-16ß-chloro-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-16α-carbonitrile (**71**) (80.6%) and 17ß-acetoxy-15ß-chloro-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-15α-carbonitrile (**72**) (2%), accompanied by the enones (**65**) and (**66**) arising from hydrolysis of the starting material (Scheme 3.2-1). The enones (**65**) and (**66**) were identified by direct comparison with the enones isolated from the synthesis of the dienyl acetate (**29**). The spectroscopic and analytical data for these enones have been reported.[76] Separation of the minor cycloadduct (**72**) was difficult and required careful chromatography. However, subsequent experiments (see Section 3.3.1) revealed that the respective alkaline hydrolysis products of 17ß-acetoxy-16ß-chloro-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-16α-carbonitrile (**71**) and 17ß-acetoxy-15ß-chloro-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-15α-carbonitrile (**72**) could be separated with ease, and this method was employed in most of the ensuing work.

Formation of the enones (**65**) and (**66**) was ascribed to traces of acidic material arising from decomposition and probably polymerisation of 2-chloroacrylonitrile during the reaction. It is also possible that prior distillation of the reagent from hydroquinone was inadequate to prevent the exclusion of traces of acidic material in the reaction mixture from the outset. Accordingly a reaction was carried out, in which the dienophile was distilled over potassium hydroxide[34] prior to use. This modification was indeed

beneficial, since a reaction carried out upon the dienyl acetate (**29**) and 2-chloroacrylonitrile (3 mol. equiv.) in benzene at 100°C proceeded to completion in 120 h (TLC) without the formation of the enones (**65** and **66**). Furthermore, it proved unnecessary to add further reagent to the reaction mixture, and the overall yield of the cycloadducts (**71**) and (**72**) was increased to 92%.

SCHEME 3.2-1



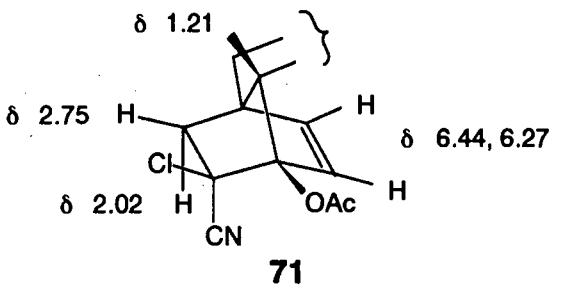
The structures of the cycloadducts (**71**) and (**72**) were assigned on the basis of analytical and spectroscopic data, and were supported by subsequent transformations. The relevant spectroscopic data are summarised here. The infrared spectra of (**71**) (ν_{max} 1749 and 2242 cm^{-1}) and (**72**) (ν_{max} 1742 and 2220 cm^{-1}) showed diagnostic absorption bands for the bridgehead acetoxy and nitrile groups respectively. The signals for the 15α- and 15ß-protons of (**71**) and the 16α- and 16ß-protons of (**72**) were well separated in the respective NMR spectra. These were assigned in accordance with the study by Davis and Van Auken,[77] who were able to make a complete analysis of the NMR spectra of three *endo-exo* pairs of 2-substituted norbornenes, two of which are illustrated in Scheme 3.2-2, by proton-proton decoupling. These results show that the 3*n*- and 3*x*-protons* are affected by the substituent and that the 3*x*-proton was always at lower field

---

* *n* endo; *x* exo

than the 3*n*-proton, regardless of the nature or position of the substituent. Thus, in the cycloadducts (**71**) and (**72**) the signal at higher field was assigned to the 15α- or 16α-proton and the signal at lower field to the 15ß- or 16ß-proton respectively. The shielding effect of the double bond on the *endo*-protons of the norbornene nucleus has been described before,[78] and is ascribed to the magnetic anisotropy of the 2,3-olefinic bond in this system.

SCHEME 3.2-2



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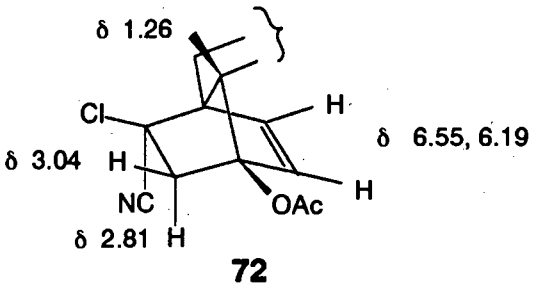

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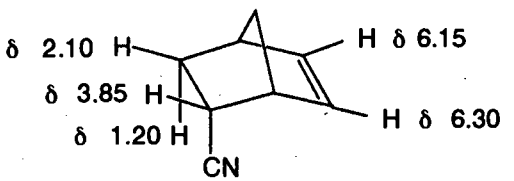

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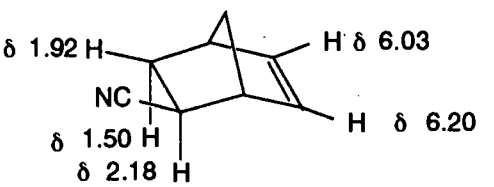

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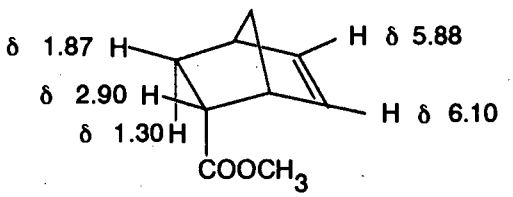

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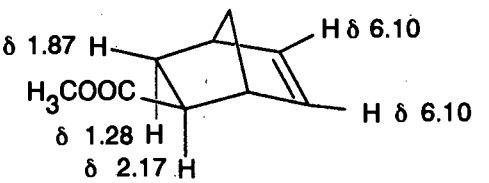


76

Some support for these assignments was obtained from the monosubstituted bridged compounds synthesised later in this work. In these compounds the coupling constants between the *exo-exo*, *endo-exo*, and *endo-endo* vicinal protons aid the assignments. We were tempted to assign the olefinic protons at C(17^1) and C(17^2) on the basis of the assignments made by Davis *et al.*,[77] however, the effect of the acetoxy bridgehead group

on the chemical shifts of the olefinic protons in such systems has not been defined. By comparing (**71**) and (**72**) it appears that the 17-acetoxy group has a greater deshielding effect on the 16ß-proton than on the 15ß-proton, if all other factors are ignored. Thus, we would expect the C(17^1) proton to be more deshielded by the bridgehead group than the C(17^2) proton and this would reinforce the deshielding effect of the substituents at C(16). However, without further supporting evidence it was felt that the olefinic protons at C(17^1) and C(17^2) could not be assigned with certainty.

Although the foregoing interpretation of the spectroscopic data provided no evidence for the 14,17-configuration of the cycloadducts, it was assumed that the analogy with the work of Solo *et al.*[13,12] provided a sound basis for the given assignments.

The regioselectivity of the cycloaddition was also based primarily upon analogy[13,14] and was confirmed by subsequent transformations of the cycloadducts (**71**) and (**72**). The regiochemical assignment for the major product (**71**) is consistent with the expectation based upon FMO interpretation[79] of the process. In the symmetry-allowed cycloadditions of unsymmetrically substituted dienes with unsymmetrically substituted dienophiles the regioselectivity of the cycloaddition is determined by the size of the atomic orbital coefficients. The FMO rules predict that the Diels-Alder reaction of any Z-substituted olefin with an $\ddot{X}$-substituted diene will give the 'ortho' cycloadduct in greater amount. In addition, Sauer[80] has made the general observation that the cycloaddition products obtained from 1-substituted butadienes and unsymmetrical dienophiles favoured the '*ortho*' (1,2)-adduct, irrespective of the electronic nature of the substituent. He further argued that the orientating forces for determining regiochemical outcome are relatively weak, and may be adversely affected by steric factors, giving rise to increased proportions of the '*meta*' (1,3)-cycloadduct, which approached the statistical value with greater steric demand.

A further consideration in these assignments was the configuration of the substituents at C(16) in (**71**) and at C(15) in (**72**). The given assignments were made in accordance with the *endo* addition rule.[81] According to this 'the maximum accumulation

of the double bonds' taking part in the reaction, as well as the π-bonds of the activating group(s) in the dienophile, are taken into account to predict the stereochemistry of the product(s). By this rule the nitrile group was expected to be in the *endo*-orientation, thus the chlorine group, by exclusion, would be *exo*-orientated.

In summary, the outcome of the reaction between 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**29**) and 2-chloroacrylonitrile is in accordance with expectations based upon mechanistic considerations and analogy with similar systems. The structural assignments are supported, if not proven, by spectroscopic data. This represents the first report of the detection and isolation, albeit in very low yield, of a 1,3-adduct (**72**) accompanying the major product (**71**) of cycloaddition on 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**29**).

In conclusion, further attention was given to optimisation of the reaction conditions for this cycloaddition, in view of the long reaction times required for the process. It was found that variation in the medium (xylene, toluene or tetrahydrofuran) did not influence the efficiency of the reaction, and accordingly, benzene was utilised in all the variation attempts.

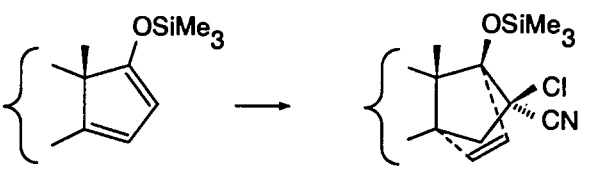
The efficiency of the cycloaddition appeared to be sensitive to temperature, since charring of the reaction mixture occurred at temperatures exceeding 100°C. At higher temperatures, the problem became serious, and darkening of the reaction mixture was accompanied by severely reduced yields of the cycloadducts (**71**) and (**72**), and attendant increases in the yields of the artefacts (**65**) and (**66**) arising from hydrolysis of the dienyl acetate(**29**). A method which has been used in order to limit polymerisation of the diene (eg. furan)[82] as well as the dienophile (eg. 2-chloroacrylonitrile)[43] during cycloaddition reactions, is the addition of hydroquinone. Hydroquinone, added to a cycloaddition reaction of 3-methoxyestra-1,3,5(10),14,16-pentaene-17-yl acetate (**29**) with 2-chloroacrylonitrile at 150°C, did not prevent charring from occurring and the presence of enones in the reaction mixture was evident (TLC). Attempts to catalyse the cycloaddition reaction between the dienyl acetate (**29**) and 2-chloroacrylonitrile at lower temperatures, by the addition of the Lewis acids titanium(IV) chloride, boron trifluoride

diethyl etherate or aluminium chloride caused complete reversion of the dienyl acetate (**29**) to the enones (**65**) and (**66**) and no further investigations were made.

One of the methods reported for the hydrolysis of a geminal chloro-cyano group to the corresponding oxo group requires the use of potassium hydroxide in the presence of dimethyl sulphoxide.[38] Since the cycloadduct (**71**) contains the alkali-labile 17ß-acetoxy group, it was expected that bridgehead hydrolysis would accompany any attempts to convert (**71**) into the corresponding 16-ketone. In the light of subsequent findings, the cycloaddition of 2-chloroacrylonitrile with 3-methoxy-17-trimethylsilyloxyestra-1,3,5(10),14,16-pentaene (**62**) was also investigated, in order to examine the influence of the resultant 17ß-trimethylsilyloxy group in the expected cycloadduct(s), upon hydrolysis of 16-functionality. Although, in their work dealing with the cycloaddition of 2-chloroacrylonitrile to 1,3-bis(trimethylsilyoxy)cyclohexa-1,3-dienes, Holmes *et al.*[83] 'expected that the silyl ether of these adducts would not be stable to the sodium sulphide-potassium hydroxide-95% ethanol, or the potassium hydroxide-dimethyl sulphoxide hydrolysis conditions' it was hoped that conditions could be found to preserve the bridgehead functionality in the further transformation of the cycloadduct.

Accordingly, the crude trimethylsilyl dienyl ether (**62**) was heated in benzene with 2-chloroacrylonitrile and hydroquinone in a sealed tube at 80°C for 94 h. Flash chromatography of the product gave the non-crystalline cycloadduct, 16ß-chloro-3-methoxy-17ß-trimethylsilyloxy-14,17α-ethenoestra-1,3,5(10)-triene-16α-carbonitrile (**77**) (51%) (Scheme 3.2-3).

SCHEME 3.2-3



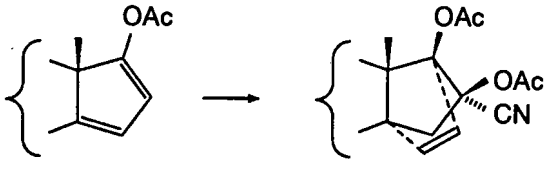
62 **77**

The properties of the product (**77**) were consistent with the proposed structure. In addition to a diagnostic IR absorption band at 2239 cm^{-1} for the nitrile group, the ^1H NMR spectrum exhibited the signals for the 15α- and 15ß-protons at δ 1.99 and 2.74 (each as a doublet, *J* 13.8 Hz), and for the 17^1- and 17^2-protons at δ 6.17 and 6.27 (each as a doublet, *J* 6.1 Hz). These signals were similar to those found in the corresponding 17ß-acetoxy compound (**71**). The mass spectrum of (**77**) displayed a peak at *m/z* 354 , consistent with a M^+ - $OSiMe_3$ fragment.

Although the cycloaddition of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**29**) with 2-chloroacrylonitrile proceeded efficiently, our subsequent attempts to convert the cycloadduct (**71**) into the corresponding 16-ketone failed (see later), and it was necessary to investigate the cycloaddition of alternative ketene equivalents with 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**29**).

A reaction of the dienyl acetate (**29**) with 2-acetoxyacrylonitrile in benzene, at 100°C for 240 h, gave the expected 16ß,17ß-diacetoxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-16α-carbonitrile (**78**) (69%) accompanied by starting material (21%) (Scheme 3.2-4). Although further amounts of the dienophile were added during the course of the reaction, it did not proceed to completion.

SCHEME 3.2-4



29 **78**

The product (**78**) displayed spectroscopic characteristics consistent with the assigned structure. The infrared spectrum exhibited a nitrile absorption band at 2240 cm^{-1} and a broad band at 1748 cm^{-1} for the acetoxy carbonyl groups. In addition, the ^1H

NMR spectrum exhibited signals for the 15α- and 15ß-protons at δ 1.85 and 2.69 (each as a doublet, *J* 14.2 Hz) and for the 17^1- and 17^2-protons at δ 6.23 and 6.38 (each as a doublet, *J* 6.2 Hz).

The lengthy reaction time, which was required as a result of the lower reactivity[37] of this dienophile compared to that of 2-chloroacrylonitrile, led to the investigation of modified reaction conditions. At elevated temperatures (*ca.* 140-150°C) the reaction mixture containing the dienyl acetate (**29**) and 2-acetoxyacrylonitrile in benzene became highly discoloured. Higher reaction temperatures could be employed without discolouration of the reaction medium, by the addition of hydroquinone. Where hydroquinone was added to a mixture of 2-acetoxyacrylonitrile and the dienyl acetate (**29**), at 150°C for 210 h, the cycloadduct (**78**) could be isolated in a yield of 81%. Recovered dienyl acetate (**29**) accounted for 16% of the total reaction product. The addition of hydroquinone was beneficial in this case, in contrast with the similar reaction with 2-chloroacrylonitrile.

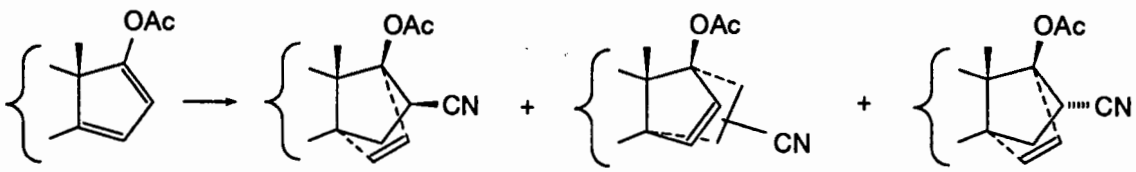
Commercially available 2-acetoxyacrylonitrile is stored over 4-*tert*-butylcatechol as a polymerisation inhibitor. Reaction of a benzene solution of the dienyl acetate (**29**) with 2-acetoxyacrylonitrile at 150°C over 261 h, in the presence of 4-*tert*-butylcatechol, gave the cycloadduct (**78**) (62%) and recovered starting material (**29**) (19%). In contrast to the 2-chloroacrylonitrile cycloadditions the enones, (**65**) and (**66**), were not observed in any of these reactions.

Grieco *et al.*[33] have reported that 5.0M lithium perchlorate in diethyl ether is a powerful medium for facilitating [4 + 2] cycloadditions. They obtained, amongst others, the cycloadduct of cyclopentadiene and 2-acetoxyacrylonitrile in a yield of 79% after 4 h at ambient temperature and pressure. When we applied these reaction conditions in the reaction between the dienyl acetate (**29**) and 2-acetoxyacrylonitrile no products were obtained at ambient temperature and increasing the temperature to 42°C led to the formation of the enones (**66**) and (**65**). It was concluded that the Lewis acidity of the lithium perchlorate is incompatible with the dienyl acetate (**29**) under these reaction conditions.

Acrylonitrile has been used as a ketene equivalent in cycloadditions,[42] but the further steps required to transform the cycloadduct into the target structure necessitate α-functionalisation, a redundant step if cycloaddition can be achieved with 1,1-difunctionalised dienophiles. The experiment described here was conducted in order to determine the regioselectivity and stereoselectivity of the reaction between the dienyl acetate (**29**) and acrylonitrile, and to use the product(s) for comparative spectroscopic purposes.

Treatment of the dienyl acetate (**29**) with acrylonitrile (3 mol. equiv.) in benzene at 125°C for 188 h afforded a chromatographically separable mixture of three cycloadducts 17ß-acetoxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-16ß-carbonitrile (**79**) (23%), an unidentified cycloadduct (**80**) (2%) and 17ß-acetoxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-16α-carbonitrile (**81**) (73%). The minor product (**80**) was not fully characterised, but a tentative structural assignment is suggested by exclusion, since later experiments (see Section 3.3.2) confirmed that it could not have arisen from ß-face cycloaddition to the dienyl acetate (**29**).

SCHEME 3.2-5



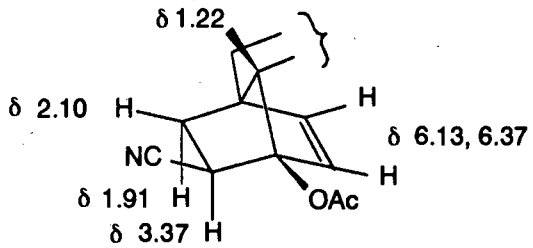
29 **79** **80** **81**

The structures of the major products (**79**) and (**81**) were assigned in accordance with the expectation that predominant ß-face and 1,2-regioselective cycloaddition had occurred, and that *endo*-stereoselectivity was operative. It has been recognised that acrylonitrile cycloadditions may display relatively poor *endo*-stereoselectivity,[84] and the result obtained here is comparable to that of the reaction between acrylonitrile and cyclopentadiene, where a *ca.* 3:2 ratio of *endo*- and *exo*-isomers is obtained.

Spectroscopic and analytical data confirmed that the products (**79**) and (**81**) were indeed 14,17-cycloadducts, but it was not possible to differentiate the isomers unambiguously by direct comparison of the spectroscopic data (Scheme 3.2-6). It is well established[85] that the magnitude of the coupling constant between two vicinal protons is dependent on the dihedral angle, substituents and on distortions from the normal tetrahedral angle. In norbornane and norbornene systems *cis*-vicinal coupling constants between pairs of *endo* protons are appreciably smaller than *cis*-vicinal coupling constants between pairs of *exo*-protons, even though the dihedral angle (0°) and the substituents are the same for both cases.[85] Relevant ^{1}H NMR data for the major cycloadducts (**79**) and (**81**) are illustrated in Scheme 3.2-6 together with the assignments of 3-*endo*- (**73**) and 3-*exo*-bicyclo[2.2.1]hept-2-ene (**74**) made by Davis *et al.*.[77]

In contrast to the bicyclo[2.2.1]hept-2-ene derivatives (**73**) and (**74**), the magnitudes of the *endo-endo* (9.4 Hz) and *exo-exo* (9.0 Hz) coupling constants for the cycloadducts (**79**) and (**81**) do not vary significantly and the stereochemistry at C(16) cannot be assigned on this basis. A comparison of the chemical shift and coupling constant values for the ring D signals of the cycloadducts (**79**) and (**81**) with those of the compounds (**73**) and (**74**) provide some support for the assignment of the structure of the 16ß- and 16α-carbonitriles (**79**) and (**81**). The *syn*-relationship of the 16ß-cyano and 13ß-methyl groups in (**79**) gave rise to deshielding of the latter signal by comparison with the 16α-cyano compound (**81**). The chemical shift difference between the 16-proton signals in the two isomers was too small to be diagnostic, and the ABX multiplets for the 15- and 16-protons were very similar. It was expected that inversion of configuration at C(16) would lead to a greater change in the chemical shift of the olefinic proton at C(17^1) than of the C(17^2) proton, owing to its closer proximity to C(16). However, it was found that the signals of both olefinic protons shifted by equal amounts and the C(17^1) and C(17^2) protons could not be assigned on this basis.

SCHEME 3.2-6

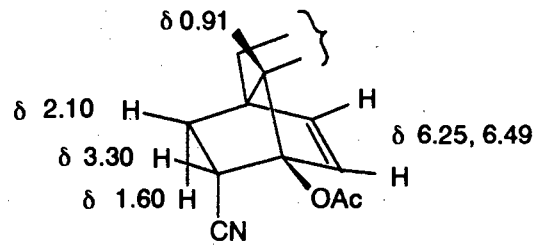


79

$J_{15\alpha,15\beta}$ 12.2 Hz

$J_{15\alpha,16\alpha}$ 9.4 Hz

$J_{15\beta,16\alpha}$ 4.9 Hz

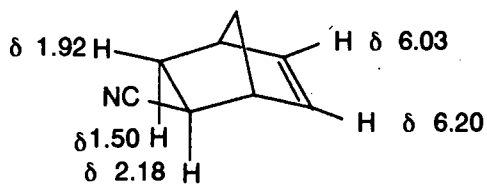


81

$J_{15\alpha,15\beta}$ 12.1 Hz

$J_{15\beta,16\beta}$ 9.0 Hz

$J_{15\alpha,16\beta}$ 3.9 Hz

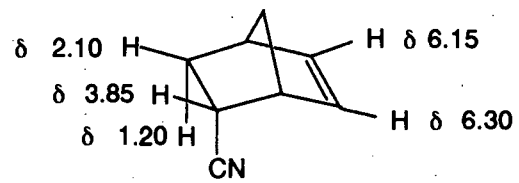


74

$J_{3n,3x}$ 12.5 Hz

$J_{2n,3n}$ 4.5 Hz

$J_{2n,3x}$ 4.2 Hz



73

$J_{3n,3x}$ 11.5 Hz

$J_{2x,3x}$ 9.1 Hz

$J_{2x,3n}$ 3.4 Hz

In addition, the NMR spectra of the compounds (**73**) and (**74**)[77] exhibited the signal for the proton *syn* to the cyano group at lower field than the corresponding proton in the isomeric compound. This effect was not observed for the cycloadducts (**79**) and (**81**) and it was concluded that the chemical shift of these protons is sensitive to the additional substituents.

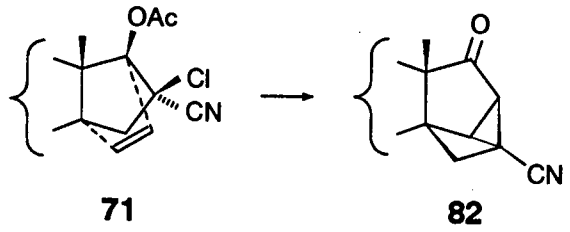
3.3 Reactions of the 14,17-Cycloadducts

3.3.1 Tandem Rearrangement of the 14,17-Cycloadducts (71) and (72)

The successful preparation of the cycloadducts (**71**) and (**72**), set the stage for exploiting the ketene equivalency of the dienophile, through hydrolysis of 16-functionality to the 16-ketone, and hence, synthesis of the derived hormone analogues. Initial attention was given to attempted conversion of the 16ß-chloro-16α-cyano compound (**71**) into the corresponding 16-ketone, owing to the greater efficency of the cycloaddition carried out with 2-chloroacrylonitrile.

Several methods have been reported for this step,[38,39,42,43] and we chose initially to conduct the reaction with potassium hydroxide in dimethyl sulphoxide, with a co-solvent in order to maintain a homogeneous reaction medium. It was expected that the bridgehead acetoxy group would undergo concomitant hydrolysis under these conditions. Treatment of the cycloadduct (**71**) with aqueous potassium hydroxide in dimethyl sulphoxide-tetrahydrofuran proceeded to completion in 5 h at 0°C, to give a single product in 90% yield.

SCHEME 3.3.1-1



71 **82**

It was evident that the desired reaction had not taken place since the product (**82**) displayed carbonyl (ν_{max} 1733 cm^{-1}) and nitrile (ν_{max} 2232 cm^{-1}) absorption in the infrared spectrum, but no hydroxy group absorption, and analytical data were consistent with a molecular formula $C_{22}H_{23}NO_2$.

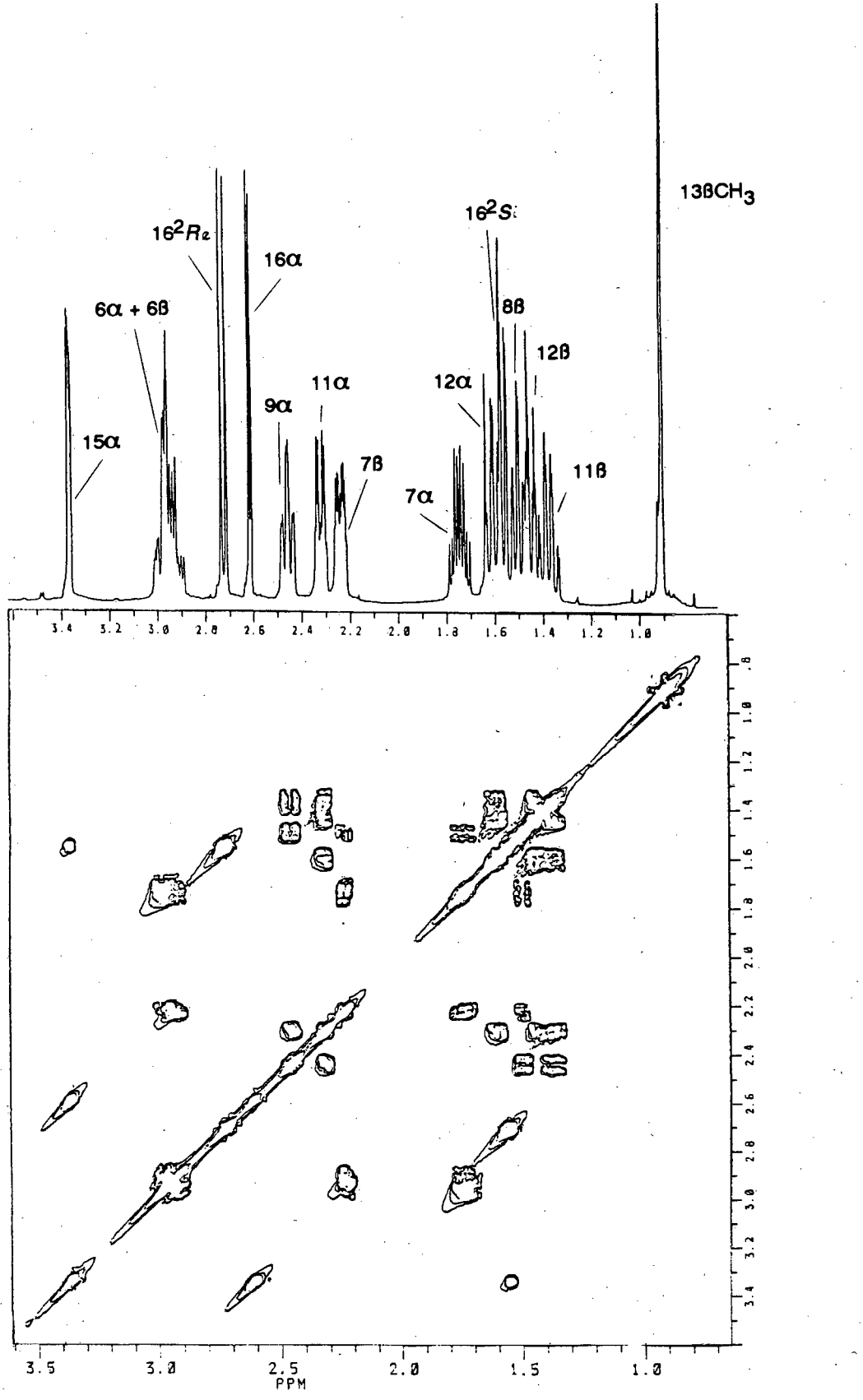


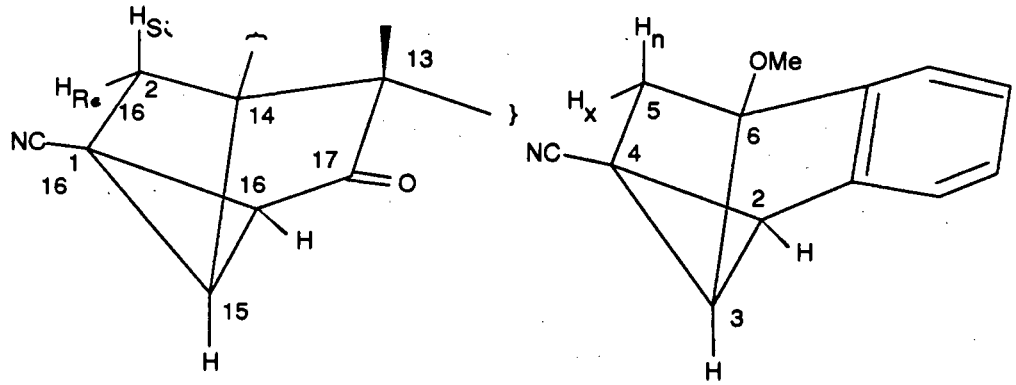
Figure 3.3.1-1: 500 MHz NMR spectrum (δ 3.6 - 0.6) and COSY plot of the cyano ketone (**82**)

Table 1: Assignments and couplings for the protons of the rearrangement product (**82**)

Assignment	δ(ppm)	Mult.	*J*/Hz			
1-H	7.17	d	8.6			
2-H	6.72	dd	8.6	2.6		
4-H	6.65	d	2.6			
6-H_2	2.93	m	-			
7α-H	1.73	qd	12.0	12.0	12.0	6.2
7ß-H	2.22	ddt	12.0	5.7	2.6	2.6
8ß-H	1.49	td	12.0	12.0	2.6	
9α-H	2.44	td	12.0	12.0	3.4	
11α-H	2.30	ddt	13.1	3.4	3.4	3.4
11ß-H	1.36	qd	13.1	13.1	12.0	3.4
12α-H	1.59	td	13.1	13.1	3.4	
12ß-H	1.43	dt	13.1	3.4	3.4	
15α-H	3.35	dd	4.5	2.4		
16α-H	2.60	d	4.5			
16^2-H_{re}	2.71	d	10.6			
16^2-H_{si}	1.55	dd	10.6	2.4		
13ß-Me	0.89	s	-			
3-OMe	3.77	s	-			

The product was formulated as (16^1R)-3-methoxy-17-oxo-15ß,16^1-cyclo-14,16ß-ethano-14ß-estra-1,3,5(10)-triene-16^1-carbonitrile (**82**) on the basis of a 500 MHz NMR spectrum. Figure 3.3.1-1 shows part (δ 0.6 - 3.6) of the 500 MHz NMR spectrum, together with the corresponding COSY plot, of the cyano ketone (**82**) recorded in deuteriochloroform. The signals for the aromatic and methoxy protons, which occurred in the lower field region (below δ 3.7), exhibited no coupling with any of the high field signals and have been excluded from the figure for clarity.

SCHEME 3.3.1-2



82 **83**

Table 2: Assignments and coupling constants for the protons of the rearrangement product (**82**) and the bridged system (**83**) (H*n endo*; H*x exo*)

Compound **82**				
Proton	δ(ppm)	mult.	Coupling	Hz
15α	3.35	dd	16α 16^2*Si*	4.5 2.4
16α	2.60	d	15α	4.5
16^2*Re*	2.71	d	16^2*Si*	10.6
16^2*Si*	1.55	dd	16^2*Re* 15α	10.6 2.4

Compound **83**				
Proton	δ(ppm)	mult.	Coupling	Hz
3	4.07	dd	2 5*n*	5.7 1.9
2	3.23	d	3	5.7
5*x*	2.98	d	5*n*	8.9
5*n*	1.47	dd	5*n* 3	8.9 1.9

It was possible to assign all the signals in the spectrum, with the aid of a COSY plot, and the chemical shifts and coupling constants are summarised in Table 1. These results demonstrated that the signals for protons in rings A, B and C were unaffected by comparison with those of estrone 3-methyl ether,[86] but an array of multiplets for the four-proton system in ring D provided a self-consistent set of assignments for a substituted tricyclo[3.2.0.$0^{2,7}$]heptanoid structure.

Analogy with the assignments reported by Paquette *et al.*[87] for compound (**83**) served to confirm these assignments (Table 2). The chemical shifts and coupling constants for the ring D protons of (**82**) are tabulated together with those of the analogous bridged system (**83**)[87] (Table 2; Page 39). Overall, there is remarkably good correspondence of coupling constants and in particular, the four-bond coupling between 16^2-H_{si} and 15-H (*J* 2.4 Hz) is very similar to the analogous coupling between 5-H*n* and 3-H (*J* 1.9 Hz) in (**83**).

In view of the surprising formation of the rearrangement product (**82**) an X-ray crystallographic structure determination was carried out to confirm the structure. Final fractional atomic coordinates and equivalent isotropic parameters for (**82**) are given in Table 4.3-2 (see Section 4). The atomic numbering and a perspective view of the molecule is shown in the Figure 3.3.1-2. The geometrical parameters for rings A, B and C are comparable to those calculated for 3-methoxy-14ß-estra-1,3,5(10)-trien-17-one.[88] Ring A does not deviate significantly from planarity. For this ring, the C-C distances and internal C-C-C angles are in the ranges 1.36(1) - 1.40(2)Å and 118.0(8) - 121.7(7)° respectively, in accordance with the unsaturation. For rings B and C the C-C and internal C-C-C angles (excluding the A-B linkage) are 1.50(1) - 1.58(2)Å and 107.3(8) - 115.(7)° respectively. Ring B adopts a predominantly half-chair conformation and ring C adopts a chair conformation. The bond lengths associated with the bridged ring D [1.49(1) - 1.59(1)Å] display no abnormalities. The internal bond angles in ring D [101.2(8) - 108.7(9)°] and in the cyclobutyl [87.6(7) - 94.2(8)°] and cyclopropyl [58.8(7) - 61.9(7)°]

rings conform to expectations for the strained tricyclic structure. A consequence of bridging is that ring D experiences some flattening, manifested in smaller than usual torsion angles at the C,D-ring junction. The C(17)-C(13)-C(14)-C(15) torsion angle is -34.8(1)° compared with a value of 36.2° calculated for 3-methoxy-14ß-estra-1,3,5(10)-trien-17-one.[88] The conformation of ring D has both envelope and half-chair characteristics.

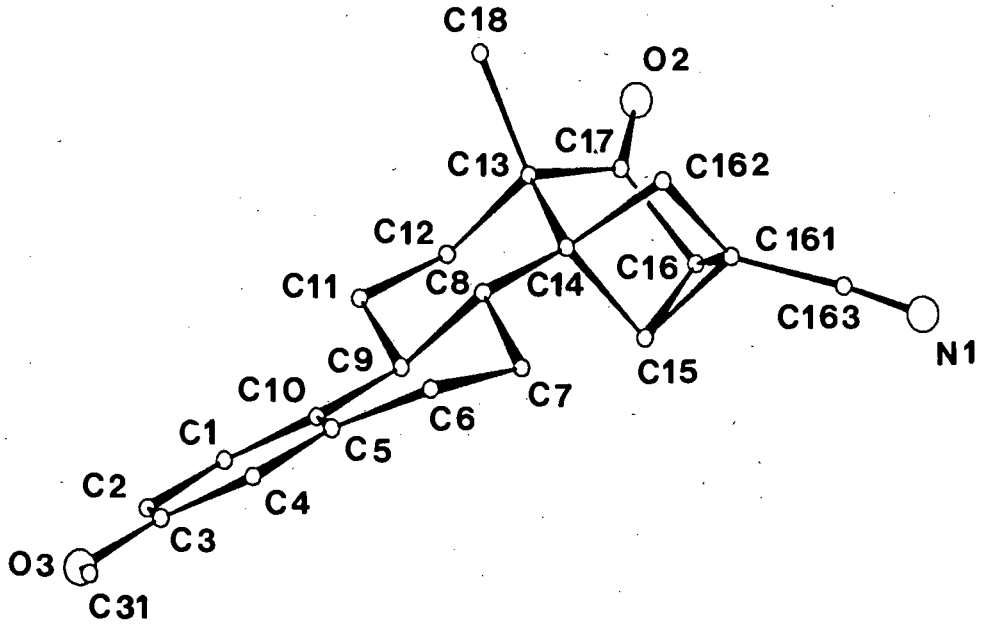
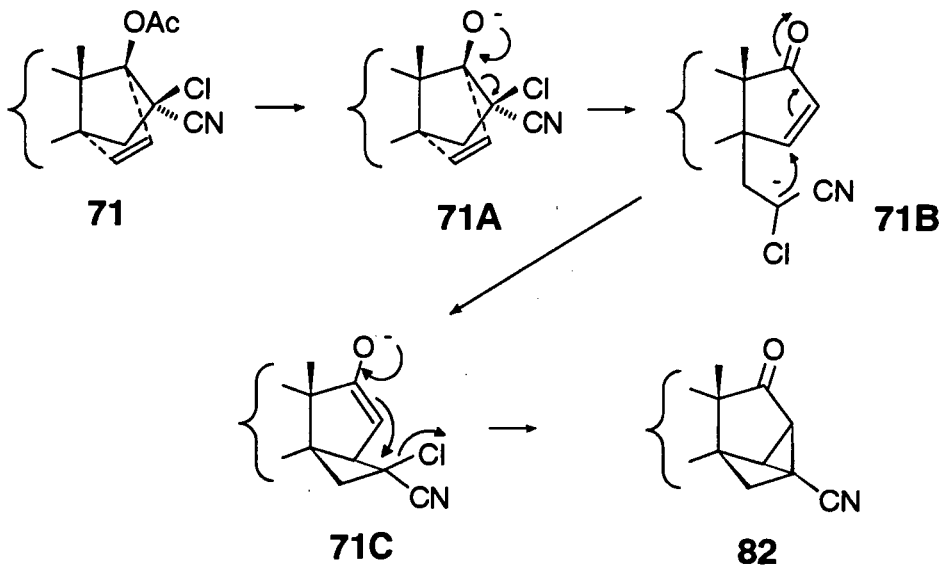


Figure 3.3.1-2: Perspective view of the cyano ketone (**82**) with its atomic labelling

Formation of the rearrangement product (**82**) is rationalised by the mechanism depicted in Scheme 3.3.1-3. It is proposed that the rearrangement is initiated by the hydrolysis of the bridgehead acetoxy group in the cycloadduct (**71**) to give the alkoxide intermediate (**71A**). Retrograde cleavage of the C(16)-C(17) bond to the 14ß-side chain enone (**71B**) is promoted by stabilisation of the negative charge by the terminal groups on the side chain. Intramolecular Michael addition of the side-chain anion, gives rise to

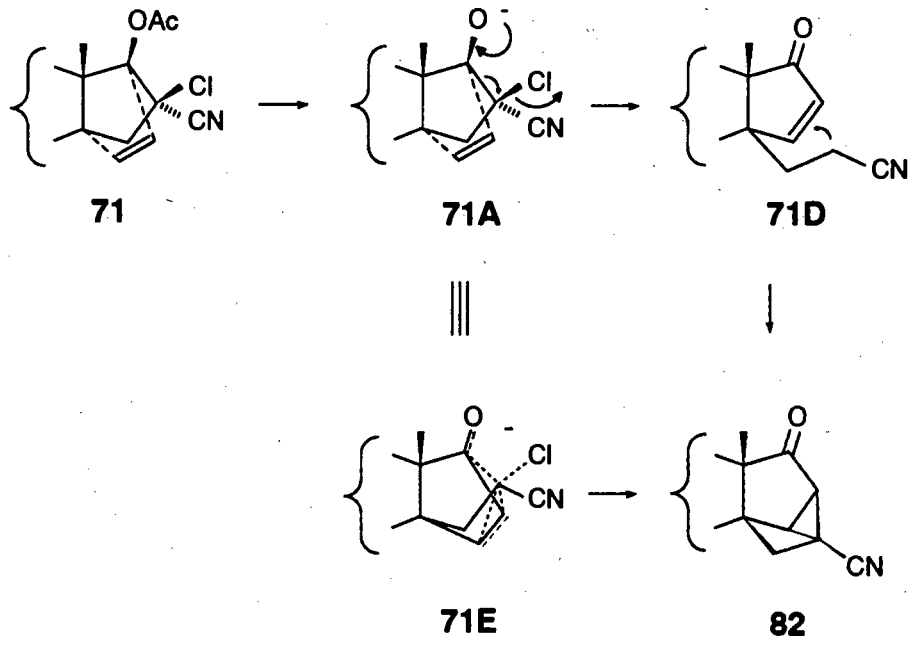
the enolate anion (**71C**), which undergoes intramolecular capture with expulsion of the chloro group.

SCHEME 3.3.1-3



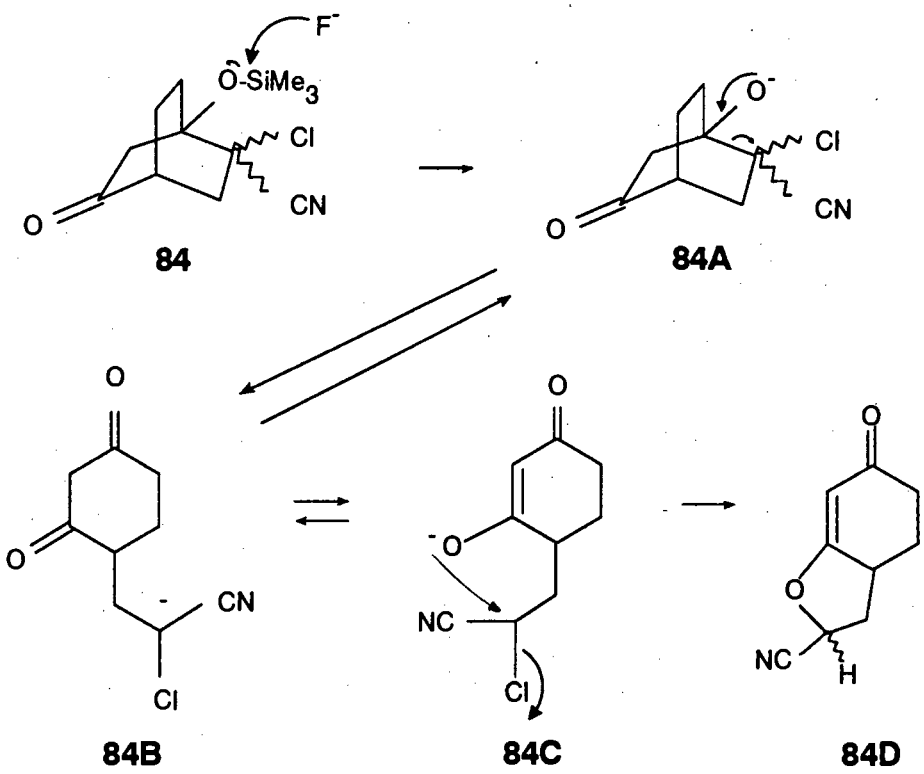
This tandem reaction sequence appears to be unprecedented, and the ease with which it proceeds together with our failure to detect or isolate discrete intermediates during the course of the reaction may suggest a concerted process following generation of the 17-alkoxy species (**71A**). Indeed it could be argued that a one-step generation of a carbenoid species (**71D**) followed by addition across the Δ^{15}-bond would account for the reaction course (Scheme 3.3.1-4). Perhaps the implied concertedness of the foregoing process could be depicted by the intermediate (**71E**). However, this proposal is conjectural in the absence of further supporting evidence. In the light of the energy requirements involved for the formation of four-membered rings,[89] this efficient rearrangement, by any mechanism, is indeed surprising.

SCHEME 3.3.1-4



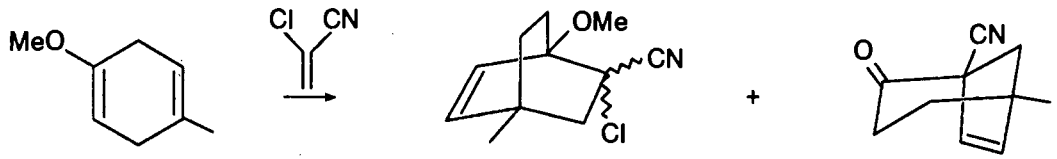
Furthermore, the initial steps in the proposed tandem mechanism (Scheme 3.3.1-3) bear a striking resemblance to those of an analogous class of rearrangements described by Holmes *et al.*.[83] In that work, the fluoride-mediated conversion of the cycloadduct (**84**) derived from the reaction of 1,3-bis(trimethylsilyloxy)cyclohexa-1,3-diene with 2-chloroacrylonitrile, into the cyano enol ether (**84D**), was rationalised by cleavage of the primary alkoxy species (**84A**) into a 2'-anion (**84B**) of a 4-(2-chloro-2-cyanoethyl)cyclohexane-1,3-dione intermediate. Intra- or intermolecular proton transfer could drive the 'possibly unfavourable equilibrium' to generate the enolate intermediate (**84C**), in which cyclisation of the oxygen terminus with displacement of the chloro group gave rise to the final product (**84D**).

SCHEME 3.3.1-5



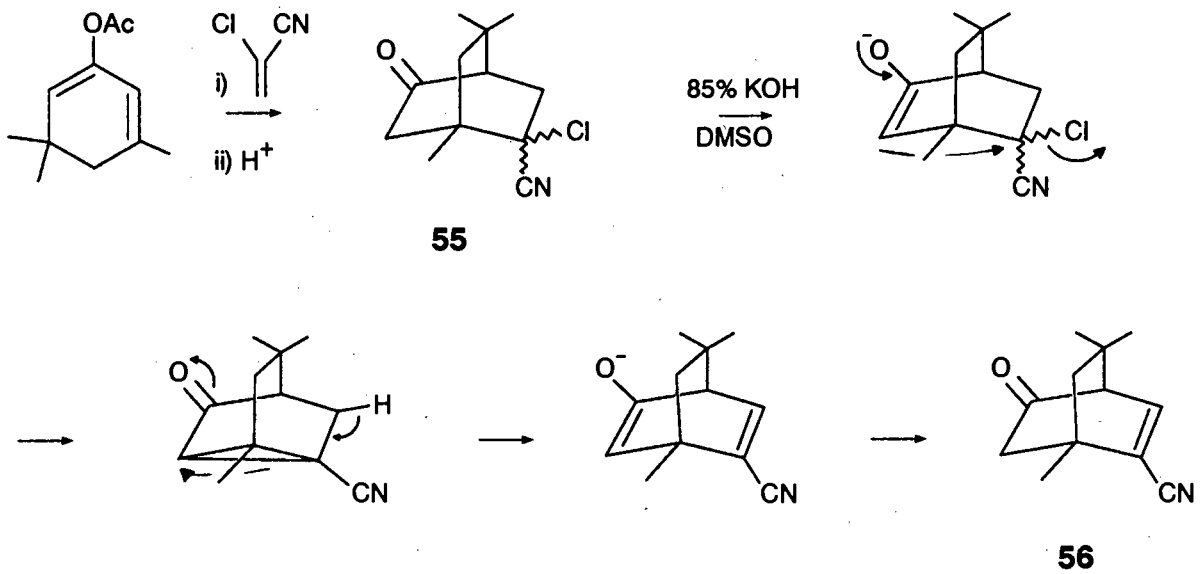
Rearrangements of several bridgehead oxygenated, 2-chloroacrylonitrile cycloadducts have been described. These occur either during the cycloaddition reaction, during attempted hydrolysis to the corresponding ketone or as a side reaction during another transformation. For example, cycloaddition of 1-methoxy-4-methylcyclohexa-1,4-diene with 2-chloroacrylonitrile leads to the expected cycloadduct but a considerable proportion of a rearrangement product is formed at elevated temperatures[90] (Scheme 3.3.1-6). The electron rich bridgehead group leads to a rearrangement which involves concomitant expulsion of the chloro group.

SCHEME 3.3.1-6



Cycloadducts of 2-chloroacrylonitrile which contain acidic protons or oxygenated functional groups in addition to the oxygenated bridgehead group, may undergo tandem rearrangements. On attempted alkaline hydrolysis of the cycloadduct (**55**) the product (**56**) was obtained.[46] The mechanism proposed for the formation of the product (**56**) is depicted in Scheme 3.3.1-7.

SCHEME 3.3.1-7

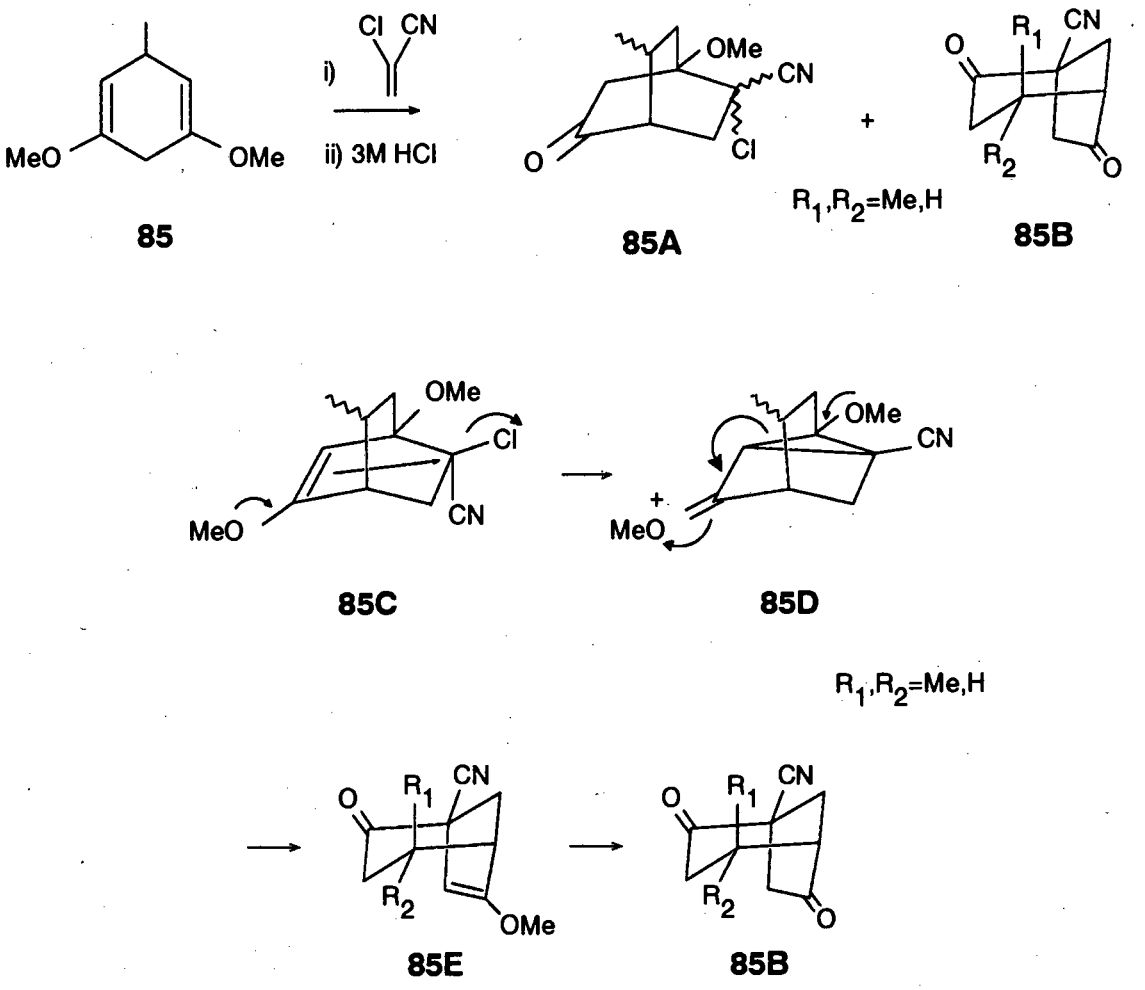


The reaction product obtained from the cycloaddition of the diene (**85**) with 2-chloroacrylonitrile was hydrolysed with 3M hydrochloric acid to give the cycloadducts (**85A**) in addition to the diketones (**85B**).[91] These compounds (**85B**) are proposed to form exclusively from the *endo* cycloadducts (**85C**) by a rearrangement which, with the

assistance of the enol ether oxygen lone pair, gives the tricyclic intermediates (**85D**), which collapse to the [3.2.1] systems (**85E**) and give rise to the diketones (**85B**) on acid hydrolysis (Scheme 3.3.1-8).

The foregoing survey of related work on rearrangements of bridgehead oxygenated cycloadditions derived from 2-chloroacrylonitrile demonstrates that the tandem process described in this work is indeed unique, and that alkaline hydrolysis of the cycloadduct (**71**) is inappropriate for the preparation of the 14,17α-etheno 16-ketone.

SCHEME 3.3.1-8



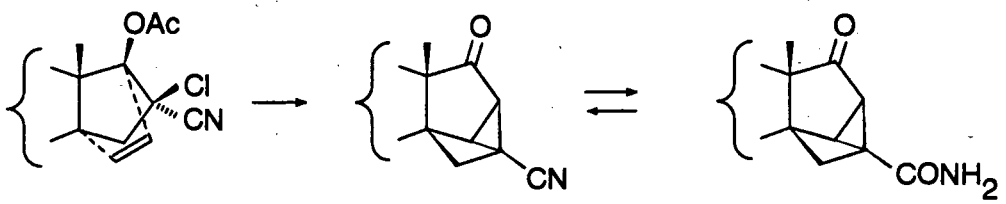
The rate of formation of the rearrangement product (**82**) from the cycloadduct (**71**) was investigated in reactions performed on a small scale at room temperature and

monitored by TLC. From these reactions it is clear that in the absence of dimethyl sulphoxide the rearrangement initiated by potassium hydroxide takes much longer (*ca.* 48 hours) to go to completion than a similar reaction in the presence of dimethyl sulphoxide (*ca.* 15 minutes). Large rate enhancements have been produced in base catalysed reactions by the use of dimethyl sulphoxide as solvent.[92] This is ascribed to the fact that in dipolar aprotic solvents, such as dimethyl sulphoxide, anions are much less solvated than in protic solvents. In particular, hydroxides are very soluble in dimethyl sulphoxide suggesting that the hydroxide ion is poorly solvated and thus very active in these solvents. By contrast, cations including alkali-metal cations, are strongly solvated and carry a large solvation sheath. This ensures good dissociation of ionic species and very reactive anions which accelerate these reactions. Small concentrations of protic molecules (eg. water) do not significantly lower the reaction rate since the solvent molecules compete effectively with the anions for protic molecules. The faster conversion of the cycloadduct (**71**) to the compound (**82**) was thus ascribed to the greater ability of dimethyl sulphoxide to enhance the nucleophilicity of anions, relative to reactions in protic solvents.

Failure to obtain the desired ketone with potassium hydroxide in dimethyl sulphoxide led to the investigation of different hydrolytic conditions. Treatment of the cycloadduct (**71**) with $Na_2S.9H_2O$ in ethanol[39] for 75 minutes at reflux gave a complex mixture of products. At room temperature the cycloadduct (**71**), stirred with $Na_2S.9H_2O$ in tetrahydrofuran-ethanol, gave several products, one of which corresponded to the rearrangement product (**82**) (TLC). No further consideration was given to these methods since too many products resulted. It was found that the addition of dimethyl sulphoxide to a reaction mixture containing the cycloadduct (**71**) and $Na_2S.9H_2O$ in tetrahydrofuran-ethanol at 18°C led to the smooth formation of the rearrangement product (**82**) in 85% yield. The method of Keirs *et al*,[93] which entailed stirring the cycloadduct (**71**) in tetrahydrofuran-water (3:1) with triethylamine, gave only unreacted (**71**) at 17°C and at 70°C after 44 h. No further attempts were made to obtain the desired 14,17-etheno 16-ketone from the 16-chloro-16-cyano cycloadduct (**71**).

It was found that prolonged treatment (23 h at 25°C) of the cycloadduct (**71**) with excess aqueous potassium hydroxide (6.3 mol. equiv.) in tetrahydrofuran-dimethyl sulphoxide led to the formation of (16^1*R*)-3-methoxy-17-oxo-15ß,16^1-cyclo-14,16ß-ethano-14ß-estra-1,3,5(10)-triene-16^1-carboxamide (**86**).

SCHEME 3.3.1-9



71 **82** **86**

Table 3: Assignments and coupling constants for the ring D protons of the 16^1-carboxamide (**86**)

Proton	δ(ppm)	Mult.	*J*/Hz	
15α	3.23	dd	4.3	2.3
16α	2.73	d	4.3	
16^2*Re*	2.57	d	10.0	
16^2*Si*	1.47	dd	10.0	2.3

The 500 MHz NMR spectrum of the 16^1-carboxamide (**86**) exhibited spectroscopic features similar to those observed for the 16^1-carbonitrile (**82**). Signal overlap occurred to a certain extent in the upfield region from δ 1.77-1.32. The most significant difference was in the presence of a broad, D_2O exchangeable doublet, centred at δ 5.88 which was

assigned to the amide protons. The chemical shifts and coupling constants for the ring D protons of the amide (**86**) are listed in Table 3.

Treatment of the carboxamide (**86**) with phosphorous pentoxide in refluxing toluene gave the carbonitrile (**82**).

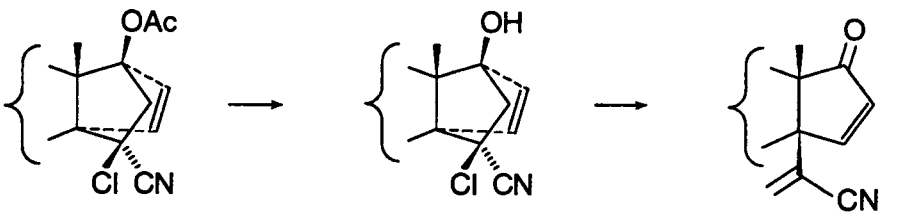
The mechanism proposed for the conversion of the cycloadduct (**71**) into the rearrangement product (**82**) implied that the absence of the 17^1,17^2-olefinic bond must lead to a different reaction course and indeed, in the absence of a Michael acceptor, it was possible that the desired hydrolysis to a 16-ketone might be achieved. Accordingly, catalytic hydrogenation of the 14,17-etheno compound (**71**) was attempted. The cycloadduct (**71**), in ethyl acetate, failed to undergo any reaction when stirred in the presence of palladium charcoal (10%) and hydrogen at 45 psi. As a consequence of the foregoing results, efforts to use compound (**71**) as an intermediate for preparation of 16-ketones in this series were abandoned.

However, it was of interest to ascertain whether the regioisomeric cycloadduct (**72**) could be induced to undergo conversion to a 15-ketone upon alkaline hydrolysis. Initial experiments, which were conducted upon the total cycloaddition product (**71** and **72**) revealed that in the presence of alkali, the major component (**71**) underwent the described rearrangement to give (**82**), whereas a minor product, which was readily separable from (**82**), was identified as 15ß-chloro-17ß-hydroxy-14,17α-ethenoestra-1,3,5(10)-triene-15α-carbonitrile (**87**). The structure of the 17-alcohol (**87**) followed from spectroscopic data. The infrared spectrum exhibited hydroxy absorption bands at 3595 and 3427 cm^{-1} and a nitrile absorption band at 2237 cm^{-1}. The NMR spectrum exhibited the 16α- and 16ß-protons, each as a doublet (J 13.4 Hz), at δ 2.17 and 3.08, respectively, and the 17^1- and 17^2-protons, each as a doublet (J 6.0 Hz), at δ 6.17 and 6.24 (Scheme 3.3.1-10).

It was therefore evident that the regioisomeric cycloadduct (**72**) is more resistant to functional group modification of the 15-substituents. Alkaline treatment of the 17-alcohol (**87**) with 2M-potassium hydroxide gave an incomplete reaction, whereas treatment with sodium sulphide in ethanol at 100°C gave complex mixtures. However,

treatment of the 17-alcohol (**87**) with sodium sulphide-potassium hydroxide in refluxing 95% ethanol furnished a 69% yield of a new product, the spectroscopic properties of which supported the structural assignment as 2-[3-methoxy-17-oxo-14ß-estra-1,3,5(10),15-tetraen-14-yl]acrylonitrile (**88**). The infrared spectrum exhibited a nitrile absorption band at 2222 cm^{-1} and a carbonyl absorption band at 1710 cm^{-1}. The NMR spectrum exhibited the 15'- and 16'-protons, each as a doublet (*J* 5.9 Hz), at δ 7.38 and 6.45, respectively. The protons at position 3 were exhibited, each as a singlet, at δ 6.75 and 6.22.

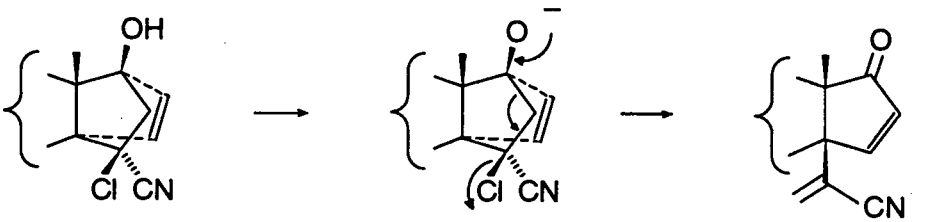
SCHEME 3.3.1-10



72 **87** **88**

Formation of the cleavage product (**88**) is ascribed to Grob-type fragmentation,[94] mediated by the bridgehead alkoxy group, and facilitated by the presence of the 15ß-chloro group as a 1,3-removed leaving group (Scheme 3.3.1-11)

SCHEME 3.3.1-11

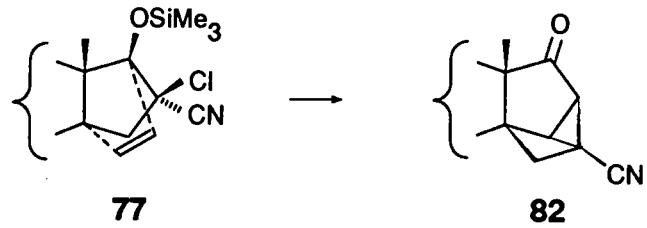


87 **87A** **88**

This reaction also finds no direct analogy in the literature, and suggests further scope for exploiting fragmentation methodology in bridgehead oxygenated cycloadducts derived from 2-chloroacrylonitrile.

From the reactions described it is clear that a bridgehead group, which is stable under the hydrolytic conditions required to convert the geminal chloro-cyano group to the corresponding ketone, is required. In pursuance of this objective the 17-silyl ether cycloadduct (**77**) has been synthesised. However, treatment of this cycloadduct (**77**) with 2M-potassium hydroxide in dimethyl sulphoxide-tetrahydrofuran, as before, gave the same product of rearrangement (**82**) obtained from the cycloadduct (**71**). No further attempts were made to obtain the 16-ketone from the silyl ether cycloadduct (**77**).

SCHEME 3.3.1-12



77 **82**

3.3.2 Reductive Dechlorination of the 14,17-Cycloadducts (71) and (72)

The failure of spectroscopic methods to confirm the structual assignments of the cycloadducts (**79**), (**80**) and (**81**), arising from the reaction between the dienyl acetate (**29**) and acrylonitrile, led to reliance upon literature precedent for this purpose. It was therefore of interest to correlate these products with others for which the structural assignments were more secure.

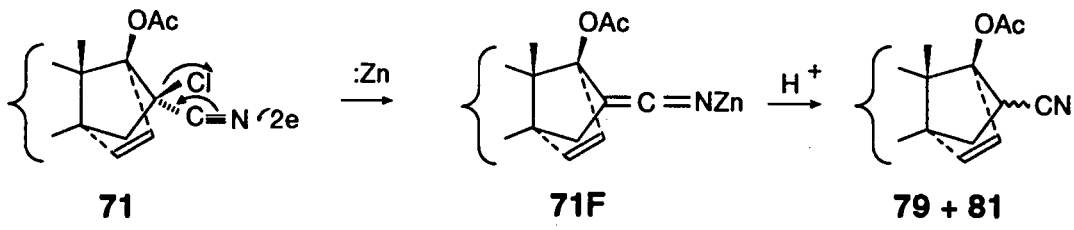
The foregoing rearrangement results on the cycloadducts (**71**) and (**72**) had the incidental effect of fixing the position of the geminal chloro-cyano substituents.

Accordingly, reductive dechlorination would be expected to lead to bridged cyano compounds of defined structure for comparison with those arising from the acrylonitrile cycloaddition.

Treatment of the 16ß-chloro-16α-cyano compound with freshly activated zinc powder in tetrahydrofuran and glacial acetic acid gave a readily separable mixture of the 16ß- and 16α-carbonitriles (**79**) and (**81**) in a ratio of 1.3:1, thereby confirming the assignments of the two major cycloadducts derived from the reaction of the dienyl acetate (**29**) with acrylonitrile.

The occurrence of both isomers during reductive dechlorination suggests that there is very little face selectivity in the protonation of the obligatory intermediate (**71F**)[95] arising from electron transfer to the substrate (**71**).

SCHEME 3.3.2-1

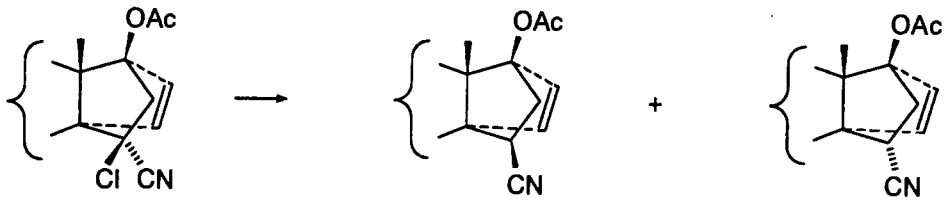


71 **71F** **79 + 81**

A similar reaction carried out upon the cycloadduct (**72**) gave 17ß-acetoxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-15ß-carbonitrile (**89**) and 17ß-acetoxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-15α-carbonitrile (**90**) in a ratio of 1.7:1 (Scheme 3.3.3-2).

The IR spectra of the products (**89**) (ν_{max} 2234 and 1734 cm^{-1}) and (**90**) (ν_{max} 2238 and 1736 cm^{-1}) showed diagnostic absorption bands for the bridgehead acetoxy and nitrile groups, respectively. The NMR spectra of the products (**89**) and (**90**), recorded in deuteriochloroform, were poorly resolved. However, a number of assignments could be made from the NMR spectra recorded in deuteriobenzene.

SCHEME 3.3.2-2



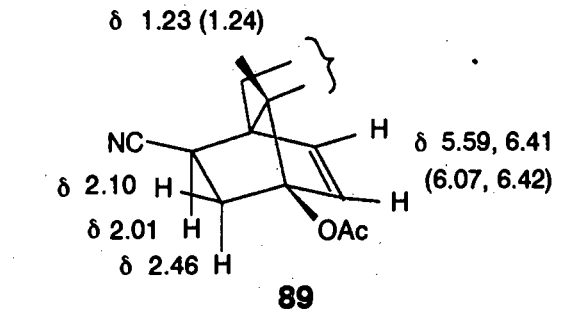
72 **89** **90**

Relevant ^1H NMR data for the compounds (**89**) and (**90**) are illustrated in Scheme 3.3.2-3, together with the NMR data for the compouds (**73**), (**74**), (**79**) and (**81**). The chemical shifts given in parentheses were obtained from the spectra recorded in deuteriochloroform. In the absence of conclusive evidence the configurational assignments of (**89**) and (**90**) are tentative. The vicinal *endo-endo* (9.4 Hz) and *exo-exo* (9.0 Hz) coupling constants are not definitive and cannot be utilised to determine the stereochemistry at C(15).

By comparison with the assignments made for the cycloadducts (**71**) and (**72**) (Scheme 3.2-2) it was expected that the 1,3-*syn* relationship of an *exo*-cyano group would result in greater deshielding of the 13ß-methyl protons. Thus, the compound (**89**) was assigned as the 15ß-carbonitrile and compound (**90**) as the 15α-carbonitrile. The signals for the 15α- (or 15ß-), 16α- and 16ß-protons were assigned on the basis of their respective coupling constants. This led to an anomaly since the signal for the proton geminal to cyano was not at lowest field. We believe that these NMR data warrant further attention in order to clarify the assignments.

The non-identity of the two 15-cyano compounds (**89**) and (**90**) with the very minor isomer (**80**), obtained in the acrylonitrile cycloaddition, proved by exclusion that the latter compound must have arisen from α-face attack of acrylonitrile upon the dienyl acetate (**29**).

SCHEME 3.3.2-3

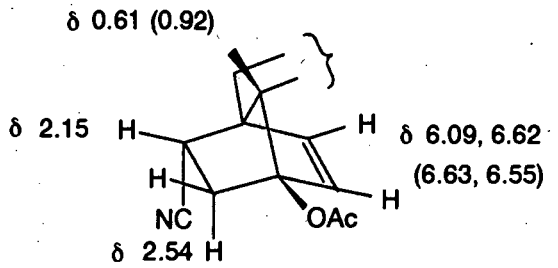


89

$^{J}_{16\alpha,16\beta}$ 11.8 Hz

$^{J}_{15\alpha,16\alpha}$ 9.4 Hz

$^{J}_{15\alpha,16\beta}$ 4.6 Hz

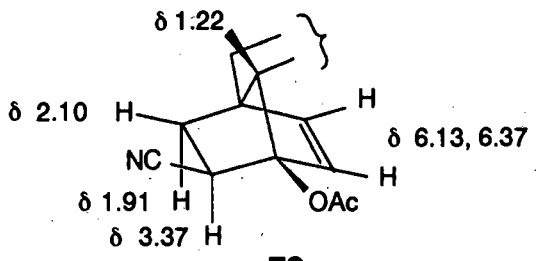


90

$^{J}_{16\alpha,16\beta}$ 11.4 Hz

$^{J}_{15\beta,16\beta}$ 9.0 Hz

$^{J}_{15\beta,16\alpha}$ 3.2 Hz

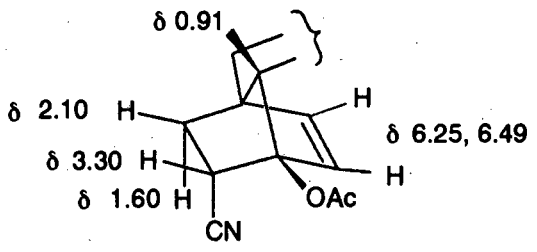


79

$^{J}_{15\alpha,15\beta}$ 12.2 Hz

$^{J}_{15\alpha,16\alpha}$ 9.4 Hz

$^{J}_{15\beta,16\alpha}$ 4.9 Hz

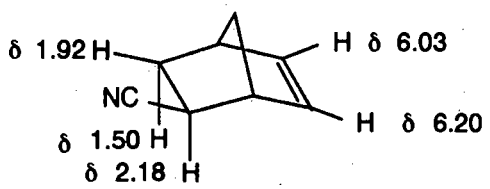


81

$^{J}_{15\alpha,15\beta}$ 12.1 Hz

$^{J}_{15\beta,16\beta}$ 9.0 Hz

$^{J}_{15\alpha,16\beta}$ 3.9 Hz

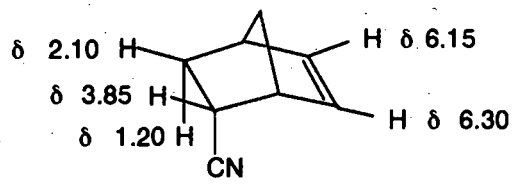


74

$^{J}_{3n,3x}$ 12.5 Hz

$^{J}_{2n,3n}$ 4.5 Hz

$^{J}_{2n,3x}$ 4.2 Hz



73

$^{J}_{3n,3x}$ 11.5 Hz

$^{J}_{2x,3x}$ 9.1 Hz

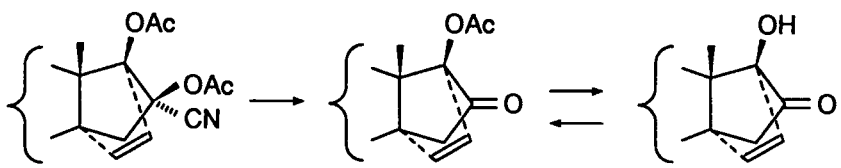
$^{J}_{2x,3n}$ 3.4 Hz

3.3.3 Synthesis and Reactions of 14,17-Bridged 16-Ketones

The failure of the attempted conversion of the 16-chloro-16-cyano cycloadduct (**71**) into the corresponding 16-ketone, necessitated the development of an alternative route to the key intermediate for the synthesis of estriol analogues. Accordingly attention was given to the conversion of the 2-acetoxyacrylonitrile cycloadduct (**78**) to the desired 16-ketone.

Treatment of the 16ß-acetoxy-16α-cyano cycloadduct (**78**) with aqueous 2M-potassium hydroxide in dimethyl sulphoxide-tetrahydrofuran (1:1) at 25°C for 25 h furnished 17ß-hydroxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-16-one (**91**) (82%) (Scheme 3.3.3-1).

SCHEME 3.3.3-1



78 **92** **91**

The infrared spectrum of the hydroxy ketone (**91**) displayed diagnostic absorption for the 17-hydroxy group (ν_{max} 3525 cm^{-1}) and the 16-oxo group (ν_{max} 1745 cm^{-1}). A 400 MHz NMR spectrum displayed signals at δ 2.00 and 2.20 for the 15ß- and 15α-protons, with a characteristically large geminal coupling (*J* 16.9 Hz) associated with carbonyl α-protons in a bridged ring system.[96] Interestingly, the 15ß-proton signal was further split (*J* 0.9 Hz) by a four-bond coupling to the 17^2-proton which, itself displayed the expected coupling (*J* 6.0 Hz) with its 17^1-neighbour and two small couplings (*J* 2 x 0.9 Hz). The source of this additional coupling of 0.9 Hz is not evident since it was not possible to detect a diagnostic cross-peak in a COSY plot. Four-bond couplings between

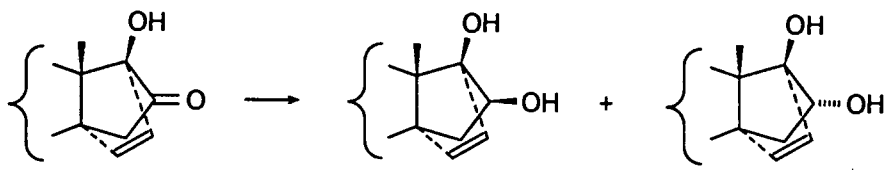
a vinyl proton and a transannular *exo*-neighbour, are rare, but its occurrence here is the probable consequence of the geometrical constraints imposed by C,D-ring fusion.

The conversion of the cycloadduct (**78**) into the 17-hydroxy-16-ketone (**91**) under the conditions described, proceeded via the intermediacy of the 17-acetoxy-16-ketone (**92**) which was detected by TLC during the course of the reaction. Although, the respective products (**91**) and (**92**) could be isolated and separated chromatographically, by interrupting the hydrolysis reaction before completion, this step was preparatively impractical. Furthermore, it was not possible to devise conditions for the exclusive formation of the intermediate (**92**). Accordingly, it was prepared by treatment of the hydroxy ketone (**91**) with acetic anhydride-pyridine in the presence of 4-(dimethylamino)pyridine. The 17-acetoxy-16-ketone (**92**) was not observed (by TLC) during the hydrolysis of the cycloadduct (**78**), to the 16-ketone (**91**), with methanolic potassium hydroxide or sodium methoxide in methanol.

The acetoxy ketone (**92**) displayed the expected carbonyl absorption at ν_{max} 1747 cm^{-1}, and the NMR signals for the bridged system were comparable to those of the hydroxy ketone (**91**). In this case however, the long-range coupling between 15ß-H and 17^2-H was manifested in the latter signal as unresolved broadening of the doublet (J 6.1 Hz) at δ 6.39.

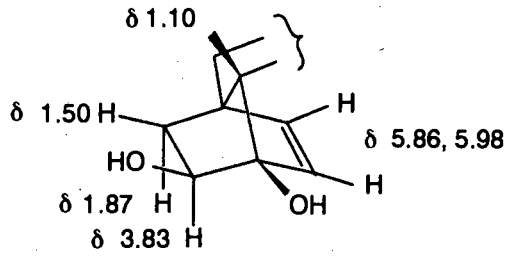
With the 16-ketones (**91**) and (**92**) in hand, attention was turned to the synthesis of 14α,17α-etheno- and 14α,17α-ethano-analogues of estriol. The reaction of the 16-ketone (**91**) with lithium aluminium hydride in tetrahydrofuran at 0°C for 2 h gave a separable mixture of the diols (**93**) (75%) and (**94**) (14%).

SCHEME 3.3.3-2



91 **93** **94**

SCHEME 3.3.3-3

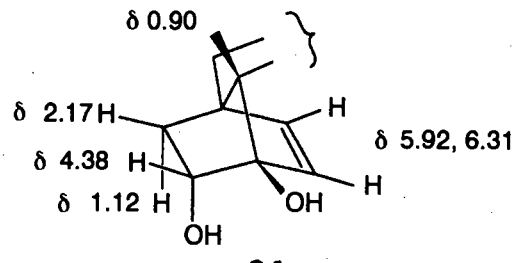


93

$J_{15\alpha,15\beta}$ 12.5 Hz

$J_{15\alpha,16\alpha}$ 7.6 Hz

$J_{15\beta,16\alpha}$ 2.9 Hz

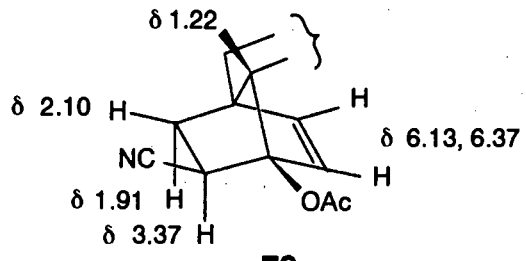


94

$J_{15\alpha,15\beta}$ 12.6 Hz

$J_{15\beta,16\beta}$ 7.7 Hz

$J_{15\alpha,16\beta}$ 2.4 Hz

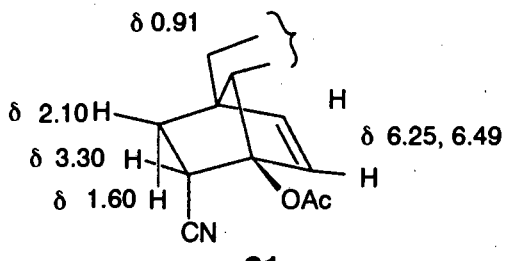


79

$J_{15\alpha,15\beta}$ 12.2 Hz

$J_{15\alpha,16\alpha}$ 9.4 Hz

$J_{15\beta,16\alpha}$ 4.9 Hz

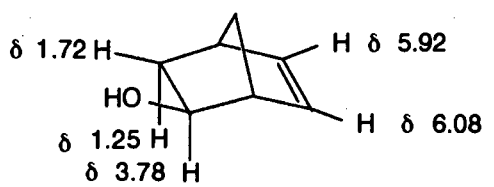


81

$J_{15\alpha,15\beta}$ 12.1 Hz

$J_{15\beta,16\beta}$ 9.0 Hz

$J_{15\alpha,16\beta}$ 3.9 Hz

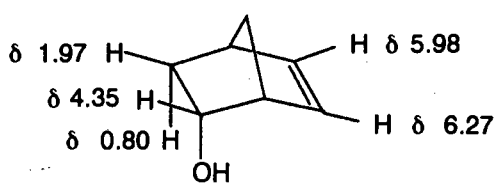


95

$J_{3n,3x}$ 12.0 Hz

$J_{2n,3n}$ 5.6 Hz

$J_{2n,3x}$ 3.1 Hz



96

$J_{3n,3x}$ 12.0 Hz

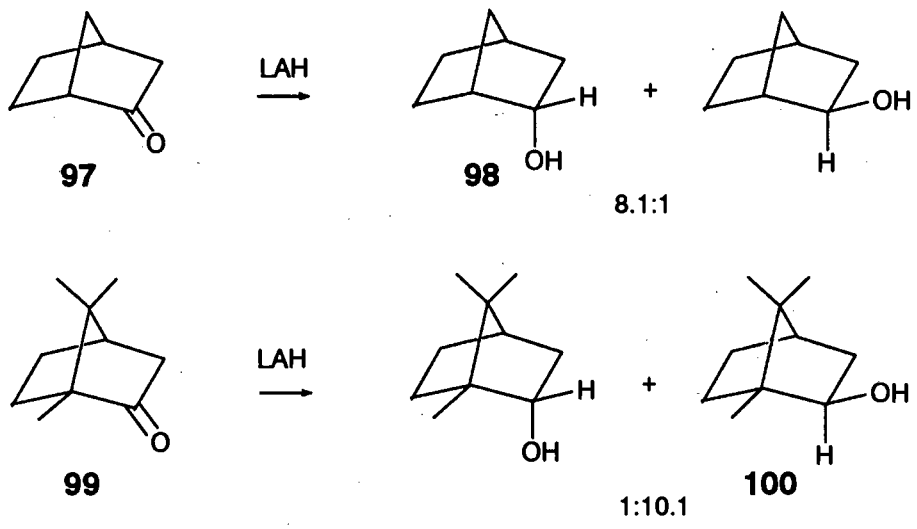
$J_{2x,3x}$ 8.0 Hz

$J_{2x,3n}$ 3.0 Hz

The NMR spectra of the isomers (Scheme 3.3.3-3) exhibited the expected array of signals associated with the bridged ring system, but it was not possible to distinguish between them on the basis of the coupling constants of the ABX multiplets for the 15α-, 15ß- and 16-protons, since these were remarkably similar. However, certain chemical shift differences were diagnostic. Thus, the relatively deshielded signal for the 13ß-methyl group in the 16ß-alcohol (**93**) was indicative of the 1,3-*syn* relationship with the *exo*-hydroxy group, whereas the downfield shift of the 17^1-proton signal in the 16α-alcohol (**94**) supported *endo*-orientation of the hydroxy group. The latter deshielding effect has been noted for the bicyclo[2.2.1]hept-5-en-2-ols (**95**) and (**96**), and leads to a greater difference between the chemical shifts of the olefinic protons in the *endo*- than in the *exo*-isomers.[77,97]

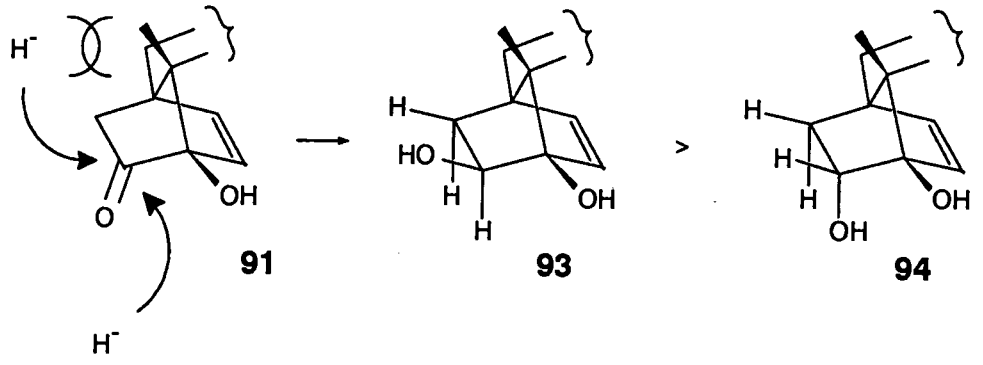
The stereoselectivity of the reduction of the hydroxy ketone (**91**) is consistent with the familiar pattern observed in comparable bridged bicyclic ketones.[98] Thus, whereas hydride attack upon norcamphor (**97**) (Scheme 3.3.3-4) occurs largely from the less hindered *exo*-face to give a *ca.* 8:1 mixture of isomers favouring the *endo*-alcohol (**98**), the presence of a *syn*-7-methyl group, as in camphor (**99**), results in reversal of the stereoselectivity to give mainly isoborneol (**100**), the *exo*-isomer.

SCHEME 3.3.3-4



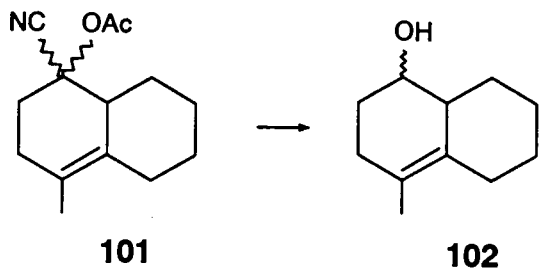
The steric environment of the carbonyl group in the hydroxy ketone (**91**) is very similar to that of camphor (**99**), since it has a 1,3-*syn* relationship with the 13ß-methyl group. Accordingly, *endo*-approach by hydride is favoured leading mainly to the 16ß-alcohol (**93**) (Scheme 3.3.3-5).

SCHEME 3.3.3-5



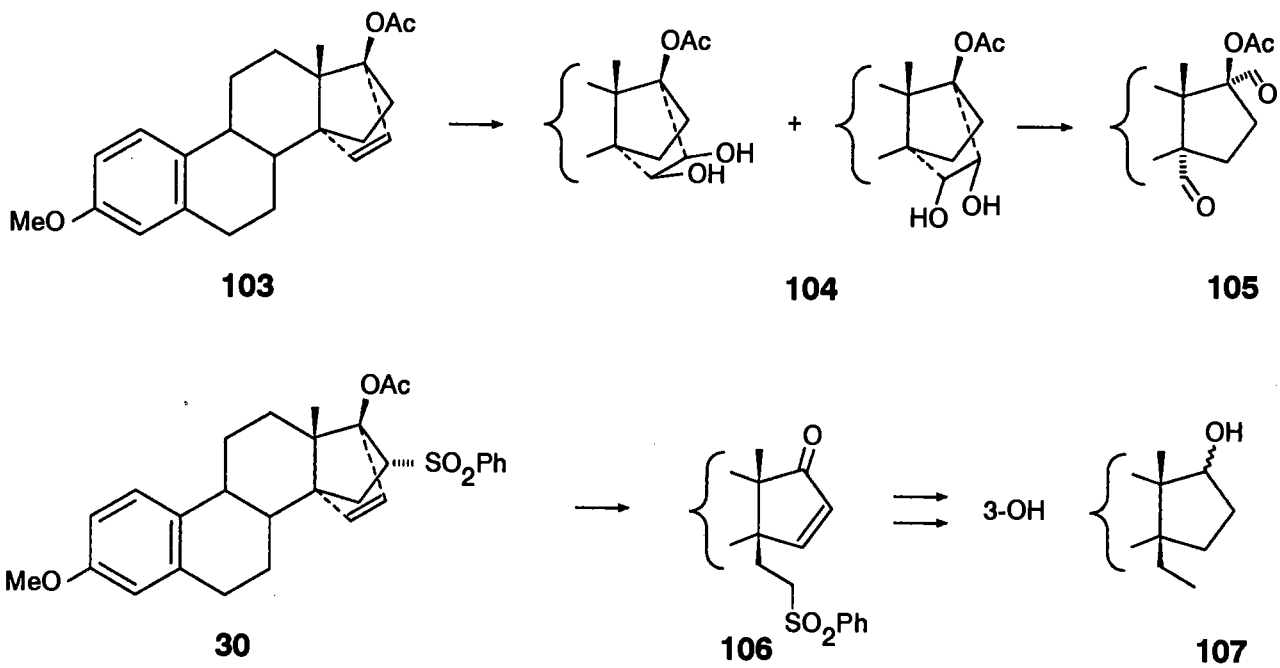
Wharton and Aw[99] have reported that treatment of the cycloadducts (**101**) with sodium borohydride results in direct conversion into the corresponding secondary alcohols (**102**). Accordingly, the cycloadduct (**78**) was treated with sodium borohydride in ethanol at 25°C for 23 h to give the 16ß-alcohol (**93**) (78%) accompanied by a small amount (4%) of the 16α-alcohol (**94**).

SCHEME 3.3.3-6



Whilst this work was in progress, the results of an independent study appeared in a patent application,[100] in which an unrelated route to 3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-16α,17ß-diol was described. It was further claimed that the derived 3,16α,17ß-triol displays potent oral estrogenicity. As a result of this report, further elaboration of the analogous estriol precursors (**93**) and (**94**) described in this work were terminated, and other aspects of the chemistry of these compounds were investigated.

SCHEME 3.3.3-7

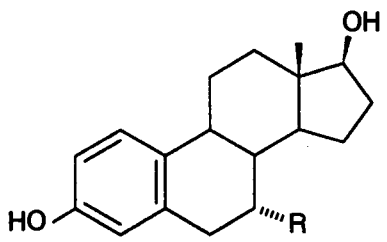


In the first place, the scope for employing the 16,17-diols as precursors of 14ß-functionalised alkyl 19-norsteroids was considered. Previous studies have established that oxidative cleavage of the 14α,17α-etheno bridge of (**103**) leads, *via* the vicinal diols (**104**), to the 14α-formyl compound (**105**),[21] whereas alkaline treatment of 3-methoxy-16α-phenylsulphonyl-14,17α-ethenoestra-1,3,5(10)-triene-17ß-yl acetate (**30**) resulted in retrograde cleavage of the 16,17-bond to give the 14ß-(14²-phenylsulphonyl)ethyl compound (**106**)[101] which could be converted into the 14ß-ethyl analogues of estradiol (**107**)[101] (Scheme 3.3.3-7). The 14ß-ethyl compounds have been shown to retain

estrogenic activity, and it was of interest to develop alternative routes in which extended 14ß-alkyl chains could be prepared.

The synthesis of chain extended 14ß-alkylamide derivatives was also of interest in the light of some recent findings (Scheme 3.3.3-8). Estradiol analogues, such as (**108**) and (**109**), bearing extended chains at the 7α-position show good to high affinity for the estrogen receptor.[102] The 7α-alkylamide derivative (**110**) is of particular interest since it possesses pure antiestrogenic activity.[102] 15α- and 15ß-Alkylamide derivatives of estradiol, for example (**111**) and (**112**), have also been synthesised and are undergoing investigation for biological activity.[103]

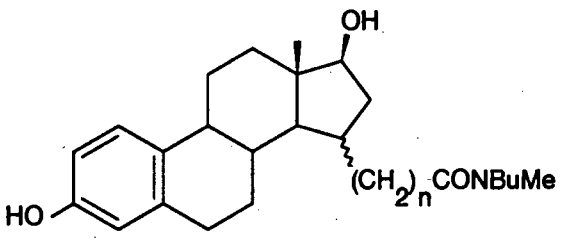
SCHEME 3.3.3.8



108 R=$(CH_2)_3CH_2OH$

109 R=$(CH_2)_{10}COO^-$

110 R=$(CH_2)_{10}CONBuMe$



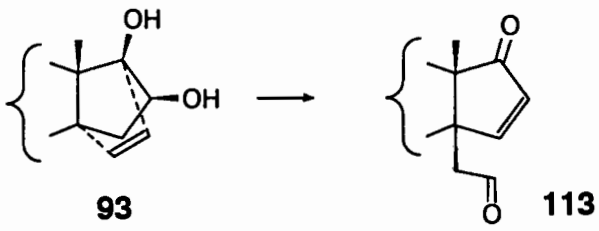
111 n=8

112 n=12

Treatment of the 16ß,17ß-diol (**93**) with sodium periodate in aqueous ethanol at 19°C resulted in quantitative conversion into a product, formulated as 14-formylmethyl-3-methoxy-14ß-estra-1,3,5(10),15-tetraen-17-one (**113**). Although the product survived flash chromatography, it proved to be too labile for further purification through recrystallisation and accordingly, could not be fully characterised. Nevertheless, an

NMR spectrum of the product obtained from flash chromatography displayed the expected signals for the formyl proton at δ 9.90 (as a broad singlet) together with those of the 15- and 16-protons at δ 7.40 and 6.29 (each 1H, d, *J* 5.9 Hz). In addition, the signals for the 14^1-protons were discerned at δ 2.74 (1H, d, *J* 17.0 and 1.5 Hz) and 2.93 (1H, d, *J* 17.0 and 2.7 Hz).

SCHEME 3.3.3-9

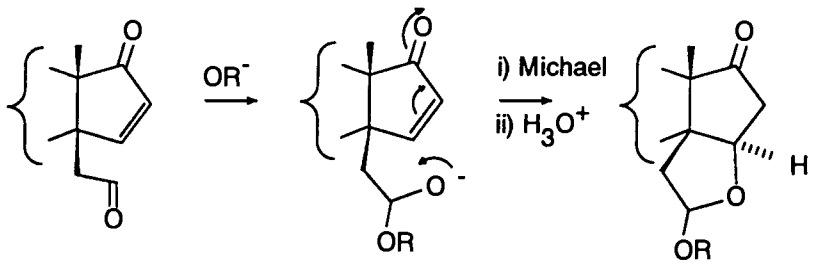


93 **113**

An experiment was conducted to compare the rates of periodate cleavage of the 16ß,17ß-diol (**93**) and the 16α,17ß-diol (**94**). TLC monitoring of reactions conducted under identical conditions revealed that cleavage of the 16ß,17ß-diol (**93**) occurred rapidly, whereas that of the 16α,17ß-diol proceeded exceptionally slowly. This is consistent with the relative reactivity of cyclic *cis*- versus *trans*-1,2-diols, in which formation of the obligatory cyclic periodate ester intermediate[104] in the former case proceeds with ease. It is reasonable in this case to liken the bridgehead-*exo* relationship of hydroxy groups in the 16ß,17ß-diol (**93**) to that of a cyclic *cis*-1,2-diol.

One of the factors responsible for the lability of the 14ß-formylmethyl compound (**113**) was demonstrated by brief treatment with methanolic potassium hydroxide in tetrahydrofuran at 20°C, which furnished a product formulated as 3,5'ξ-dimethoxy-dihydrofuro[3',2';14,15]-14ß-estra-1,3,5(10)-trien-17-one (**114**) (90%).

SCHEME 3.3.3-10



113 **113A** **114** R=Me

115 R=H

The structure of the compound (**114**) followed from a well resolved NMR spectrum (Table 4), which displayed a signal for the acetal-methyl group at δ 3.35, and a pair of ABX multiplets assigned to the protons on ring D and those of the fused heterocyclic moiety, respectively. However, the configuration at C(5') could not be determined from these data.

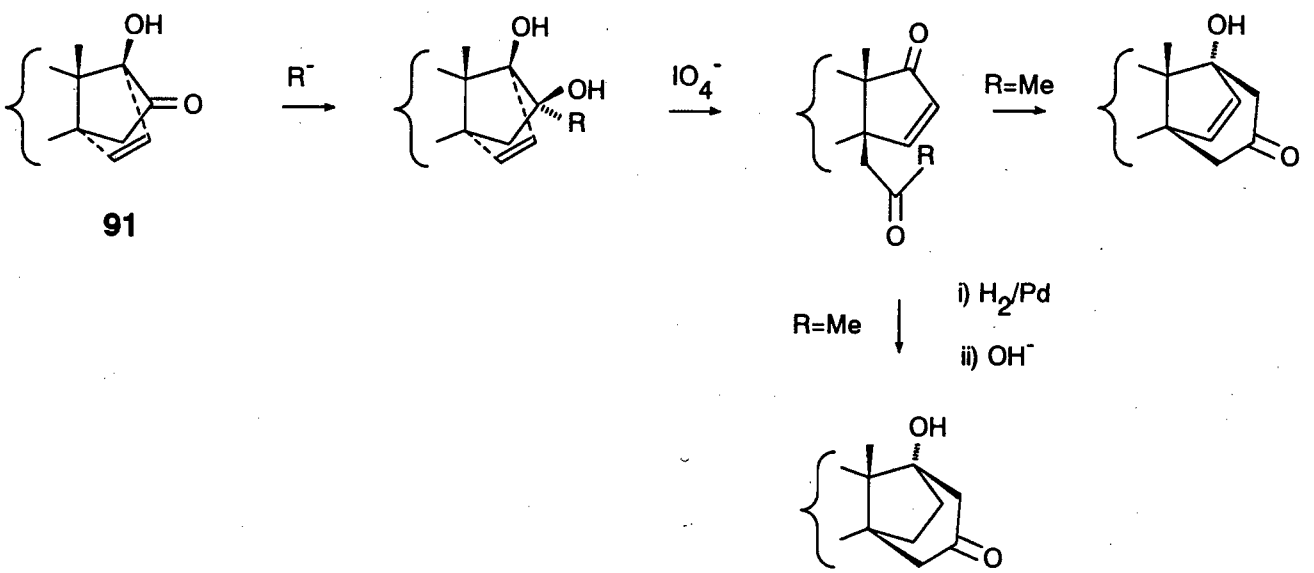
Table 4: The assignments and chemical shifts of the ring D protons of the compound (**114**)

Assign.	δ(ppm)	Mult.(*J*/Hz)	Coupling Assignments
15α-H	4.80	dd (9.2,4.5)	15α,16ß 4.5
16α-H	3.02	dd (20.1,9.2)	15α,16α 9.2
16ß-H	2.53	dd (20.1,4.5)	16α,16ß 20.1
4'ξ-H	1.77	dd (14.5,4.3)	4'α,4'ß 14.5
4'ξ-H	2.19	dd (14.5,6.2)	4'ξ,5'ξ 4.3
5'ξ-H	5.13	dd (6.2,4.3)	4'ξ,5'ξ 6.2
5'ξ-OMe	3.35	s -	
3-OMe	3.78	s -	

A plausible mechanism for the formation of compound (**114**) is depicted in Scheme 3.3.3-10. Hemiacetal formation (**113A**) resulting from attack of methanol on the formyl group is followed by intramolecular Michael addition to the Δ^{15}-17-one to give (**114**).

An analogous reaction carried out with aqueous potassium hydroxide gave several products, none of which were fully characterised. However, an NMR spectrum of the major product (**115**) (55%) exhibited the same pattern of signals observed in the NMR spectrum of (**114**). The presence of only one O-methyl group signal at δ 3.76 in the NMR spectrum and the presence of hydroxyl absorption bands at 3595 and 3447 cm^{-1} and a carbonyl absorption band at 1733 cm^{-1} in the infrared spectrum, suggested that this compound was 5'ξ-hydroxy-3-methoxy-dihydrofuro[3',2';14,15]-14ß-estra-1,3,5(10)-trien-17-one (**115**).

SCHEME 3.3.3-11

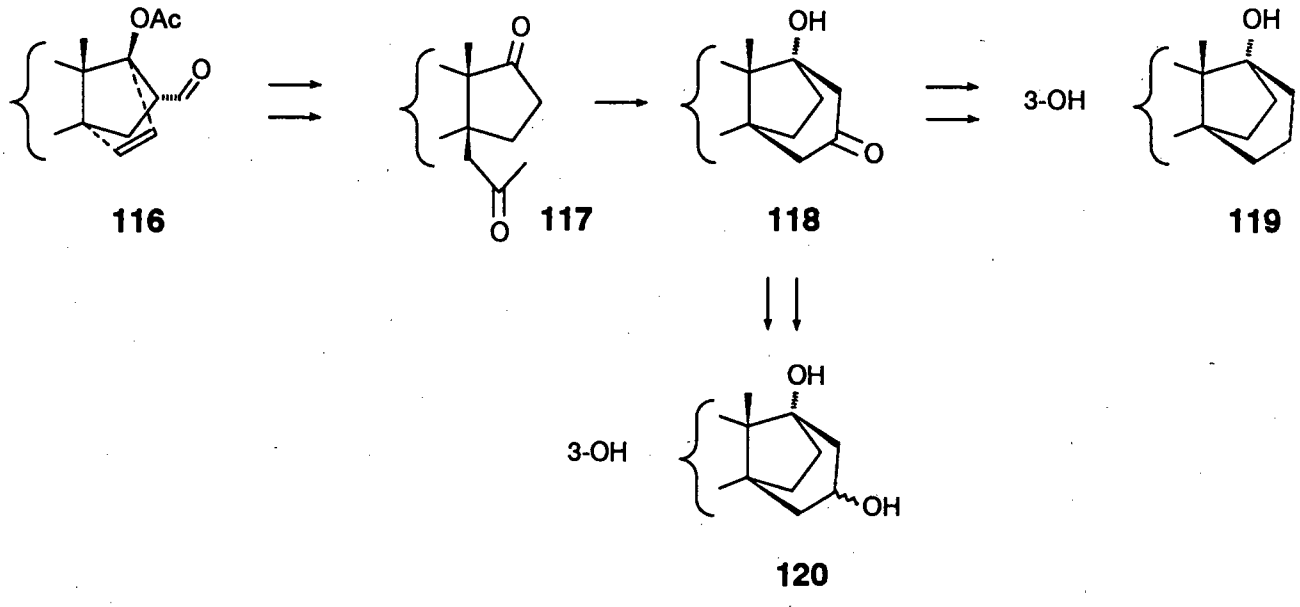


An indirect approach toward the synthesis of 19-norsteroids having extended 14ß-functionalised alkyl chains was also explored. Thus, it was considered that nucleophilic alkylation of the 16-ketone (**91**) followed by oxidative cleavage of the resultant 16-alkyl-16,17-diol would lead to 14ß-oxoalkyl enones (Scheme 3.3.3-11). The efficiency

of this approach would be influenced by the stereoselectivity of alkylation of the 16-ketone (**91**), since α-alkylation was clearly desirable in order to ensure ready oxidative cleavage of the intermediate. Aldol closure of 14ß-acetonyl derivatives, to ring D propano-bridged compounds, which can be further elaborated to afford the derived estradiol or estriol analogues, can also be envisaged by this route.

A method has been developed for the synthesis of 14α,17ß propano analogues of estradiol and estriol.[105] These compounds were prepared by cycloaddition of acrolein to the dienyl acetate (**29**), followed by conversion of the cycloadduct (**116**) into the acetonyl derivative (**117**) which underwent aldol closure in the presence of potassium hydroxide to afford the bridged compound (**118**). Subsequent transformations furnished either the estradiol analogue (**119**) or the estriol analogues (**120**). However, synthesis of the Δ^{15} analogues is precluded by this route.

SCHEME 3.3.3-12

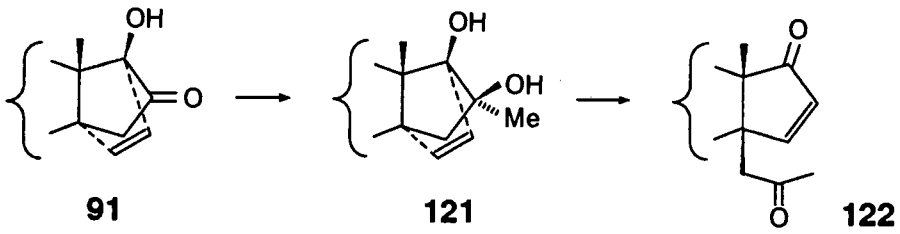


116 **117** **118** **119** **120**

Treatment of the ketone (**91**) with methyllithium in tetrahydrofuran-diethyl ether at 0-25°C proceeded very slowly to give a 16-methyl-16,17-diol (**121**) in 69% yield.

However, a Grignard reaction was more efficient, and gave an 89% yield of the product (**121**) after 2.5 h at room temperature.

SCHEME 3.3.3-13



91 **121** **122**

An NMR spectrum of the methylation product (**121**) supported the structural assignment. Thus, the chemical shift of the 13ß-methyl (δ 1.11) and 17^1- and 17^2-proton (δ 5.91 and 5.98) signals were similar to those of the 16ß,17ß-diol (**93**), and a similar argument could thus be used to exclude the epimeric assignment.

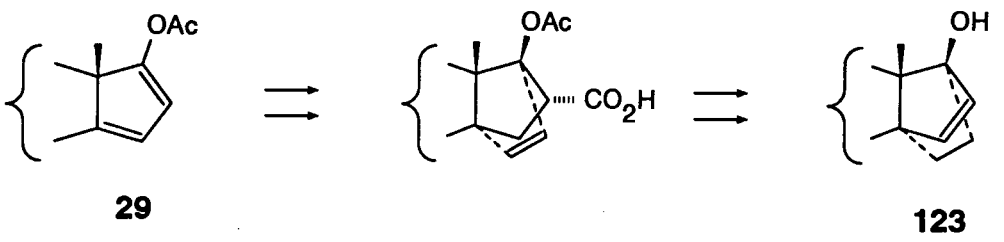
Furthermore, the analogous reaction on camphor[106] is reported to proceed *via endo*-face methylation to give 98% of the *exo*-alcohol and 2% of the *endo*-alcohol. The argument used in support of the stereoselectivity of hydride reduction also applies here.

Although the product was chromatographically and analytically homogeneous, the broad melting range suggested that it might be labile. Evidence for this was obtained by TLC of the material before and after a melting point determination, which revealed that some decomposition had occurred. The product of thermal decomposition could be isolated by prolonged heating of a solution of the 16-methyl-16,17-diol (**121**) in xylene at 140°C. However, purification of this compound was problematical and no structure could be assigned to this product. The NMR spectrum of this compound exhibited a three proton singlet at δ 2.21, signals at δ 2.76 and 3.05 (each 1H, d, *J* 18.3 Hz), in addition to signals at δ 6.23 and 7.41 (each 1H, d, *J* 6.0 Hz). The infrared spectrum exhibited a hydroxyl absorption band at 3601 cm^{-1} and a carbonyl absorption band at 1704 cm^{-1}. The mass spectrum exhibited a *m/z* peak at 338.

The 16α-methyl-16ß,17ß-diol (**121**) was subjected to the standard glycol cleavage conditions (sodium periodate in aqueous ethanol at 19°C). The reaction proceeded exceptionally slowly (78 h), in contrast to the comparable reaction of the 16ß,17ß-diol (**93**), probably as a consequence of additional steric hindrance associated with the presence of the 16α-methyl group. However, the product, isolated in 79% yield, showed the properties expected for 14-acetonyl-3-methoxy-14ß-estra-1,3,5(10),15-tetraen-17-one (**122**). Thus, infrared absorption at ν_{max} 1710 and 1699 cm^{-1} accounted for the 17- and 14²-oxo groups respectively, and the presence, in the NMR spectrum, of a three-proton singlet at δ 2.21 for an acetyl methyl group, together with the other expected resonances, was diagnostic. The foregoing reactions thus demonstrated the practicality of the alkylation-oxidative cleavage sequence to 14ß-oxoalkyl enones as envisaged.

The further utilization of the 16-ketone as an intermediate in the synthesis of bridged hormone analogues, entailed exploration of a new route to 14,17α-ethanoestra-1,3,5(10),15-tetraene-3,17ß-diol. This compound has been described in the patent literature,[107] but the method of preparation (Scheme 3.3.3-14) is based upon a reaction sequence in which cycloaddition of methyl acrylate to the dienyl acetate (**29**), is followed by conversion into an intermediate carboxylic acid derivative for oxidative decarboxylation to the olefin (**123**), a reaction which proceeds very inefficiently (*ca.* 40%).

SCHEME 3.3.3-14



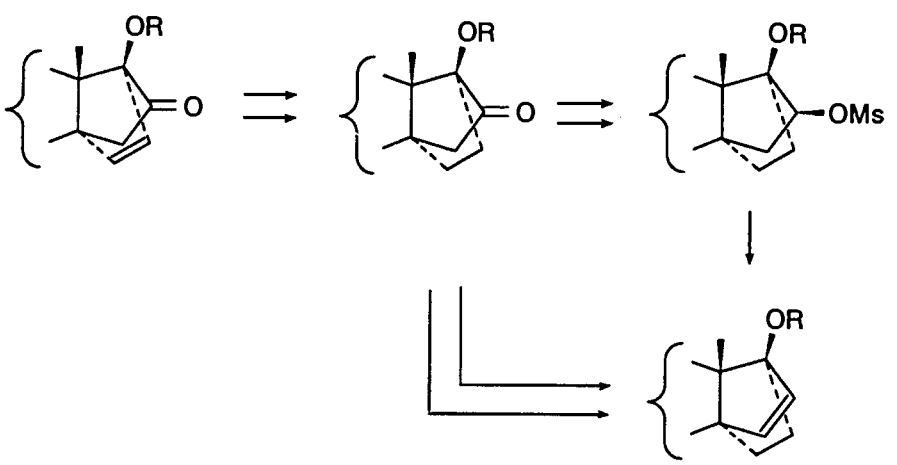
29 **123** (3-OH)

Although the synthesis of ß-bridged olefins can in principle be envisaged through cycloaddition of acetylene equivalents, followed by olefinic bond differentiation in the

cycloadduct, this pathway was expected to be beset by difficulties in dienophile reactivity, functional group modification of the cycloadducts, and uncertain chemoselectivity in the reduction of the 14α,17α-etheno bond. However, it was expected that availability of the 16-ketone (**91**) would provide synthetic pathways, in which the foregoing problems could be circumvented or overcome.

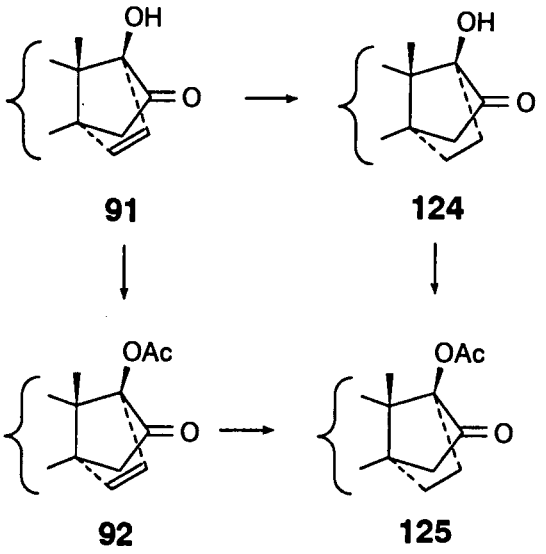
The approaches envisaged for this purpose (Scheme 3.3.3-15) entailed catalytic hydrogenation of the 14α,17ß-etheno bridge in the 16-ketone (**91**), followed by direct or indirect reductive elimination of the 16-oxo group. Alternatively, the 14,17-ethano intermediate could be converted, *via* hydride reduction, into the corresponding 16-alcohol(s) for derivatisation (e.g. as mesylates) and elimination. It was expected that protection of the bridgehead 17-hydroxy group might be required in certain steps, in order to prevent participation or rearrangement reactions.

SCHEME 3.3.3-15



In the first instance, attention was given to pathways *via* 16-mesylates. Catalytic hydrogenation of the 14α,17α-etheno-16-ketone (**91**) proceeded smoothly in the presence of 10% palladium on carbon in ethyl acetate at 20°C and hydrogen at atmospheric pressure, to give the dihydro compound (**124**) (91%), the spectroscopic and analytical properties of which were in accordance with expectations.

SCHEME 3.3.3-16

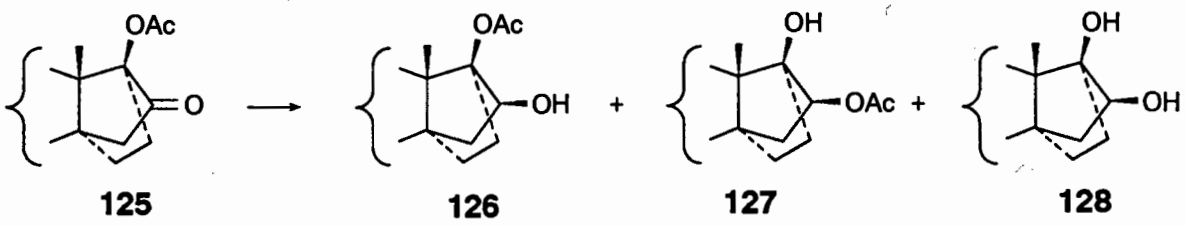


Re-introduction of the bridgehead 17-acetoxy group was considered necessary prior to reduction of the 16-oxo group. Acetylation of the 17-alcohol (**124**) in the presence of acetic anhydride and DMAP in pyridine at 20°C was incomplete after 111 h and gave 17ß-acetoxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-16-one (**125**) (46%) and unreacted (**124**) (52%). A similar reaction carried out in triethylamine also failed to proceed to completion. At a slightly elevated temperature (50°C), a reaction in pyridine was complete after 19 h, but the reaction mixture was highly discoloured and the yield of the acetate (**125**) was only 74%. These results contrast with the ready acetylation of the 14α,17α-etheno-17-alcohol (**91**), to give the corresponding 14α,17α-etheno-17-acetate (**92**). Accordingly, the reversed sequence of reactions was adopted with success. The 14α,17α-etheno acetate (**92**) underwent ready catalytic hydrogenation under standard conditions to give the 14α,17α-ethano-17-acetate (**125**) (99%). The spectroscopic and analytical data were in accordance with expectations.

For the selective reduction of the 16-oxo group in (**125**), with preservation of the 17ß-acetoxy group, sodium borohydride was considered appropriate.[108] A reaction of (**125**) with sodium borohydride in ethyl acetate-ethanol at 0°C proceeded slowly, and was incomplete after 30 h. In addition to starting material (**125**) (35%), the 17ß-acetoxy-

16ß-alcohol (**126**) (47%), the 16ß-acetoxy-17ß-alcohol (**127**) (16%) and the 16ß,17ß-diol (**128**) (2%) were isolated (Scheme 3.3.3-17). A melting point of 169-171°C recorded for the 16ß,17ß-diol (**128**) compares favourably with the melting point (170-172°C) reported[100] for this compound.

SCHEME 3.3.3-17



125 **126** **127** **128**

Table 5: Assignments and couplings for the alcohols (**126**), (**127**) and (**128**)

Compd.	**126**	**127**	**128**
Assign.	δ (*J*/Hz)	δ (*J*/Hz)	δ (*J*/Hz)
13ß-Me	1.09	0.98	1.00
15α-H	2.10 (12.4, 8.3)	2.19 (12.9, 8.1)	2.06 (12.8, 7.9)
15ß-H	?	?	?
16α-H	4.54 (8.3, 4.4)	4.75 (8.1, 4.0)	3.80 (7.9, 4.0)

The infrared spectra of the alcohols (**126**) (ν_{max} 3601 and 1722 cm^{-1}), (**127**) (ν_{max} 3585 and 1738 cm^{-1}) and (**128**) (ν_{max} 3606 cm^{-1}) were in accordance with expectations. The stereochemistry at position C(16) for the alcohols (**126**), (**127**) and (**128**) could not be assigned unambiguously from the NMR spectra. The argument used in support of the stereoselectivity of the hydride reductions of the 14α,17α-etheno-16-ketone (**91**) also applies here. The NMR data for the alcohols (**126**) (**127**) and (**128**) are summarised in Table 5. Although four-bond couplings, diagnostic for *endo*-isomers of

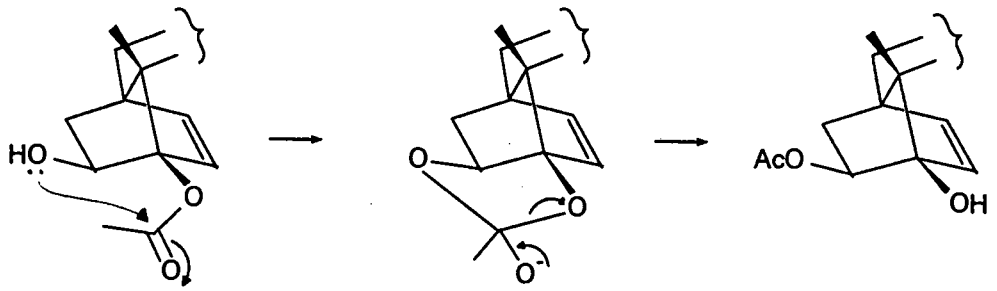
bicyclo[2.2.1]heptane systems, are not always observed, the absence of such couplings in the NMR spectra of the compounds (**126**), (**127**) and (**128**) gave some support for our assignment of 16ß-stereochemistry.

No direct proof was obtained for the structure of the alcohol (**127**), as the product arising from transacetylation. However, subsequent findings supported this assignment. The reduction of the 16-ketone (**125**) with $NaBH_4$ was repeated in the presence of cerium(III) chloride heptahydrate ($CeCl_3.7H_2O$). It is well established[109] that the reducing properties of $NaBH_4$ are modified in the presence of metal salts. This is especially true for the lanthanide metals where coordination of the metal to the carbonyl group enhances the rate of reduction. By the addition of $CeCl_3.7H_2O$ we wished to increase the rate of carbonyl reduction and thereby limit the amount of the product (**127**) arising from transacetylation. Reduction of the 16-ketone (**125**) in tetrahydrofuran-ethanol in the presence of $CeCl_3.7H_2O$ and excess $NaBH_4$ at 0°C led to rapid (65 min) and exclusive formation of the 16ß-alcohol (**126**) (90%). However, under the same conditions addition of small aliquots of $NaBH_4$, at intervals of 1 h, over 7 h gave (**126**) (83%), (**127**) (9%) and (**128**) (4%). In the absence of excess $NaBH_4$ the reduction of the 16-ketone (**125**) was necessarily slow and led to the formation of greater amounts of the transacetylated product (**127**) at the expense of the 17ß-acetoxy-16ß-hydroxy (**126**). The 17ß-acetoxy-16ß-alcohol (**126**) in tetrahydrofuran was converted to the 16ß-acetoxy-17ß-alcohol (**127**) by treatment with $NaBH_4$ at room temperature.

The acetoxy groups of the compounds (**126**) and (**127**) were hydrolysed in individual experiments with lithium aluminium hydride in tetrahydrofuran at room temperature for 10 min. Both (**126**) and (**127**) furnished the 16ß,17ß-diol (**128**). Hydrogenation of the 14α,17α-etheno-16ß,17ß-diol (**93**) in the presence of 10% palladium on carbon and hydrogen at atmospheric pressure in ethyl acetate at 20°C over 1.5 h gave the same product, namely the 14α,17α-ethano-16ß,17ß-diol (**128**). In contrast, hydrogenation of the 14α,17α-etheno-16α,17ß-diol (**94**) was incomplete after 20 h under standard hydrogenation conditions and furnished a product of distinctly different polarity to that of the 14α,17α-ethano-16ß,17ß-diol (**128**).

The mechanism by which the transesterification of (**126**) to give (**127**) is rationalised is depicted in Scheme 3.3.3-18.

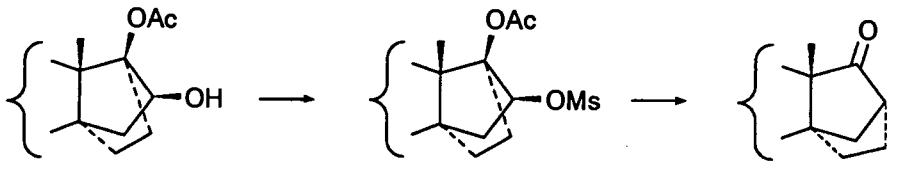
SCHEME 3.3.3-18



126 **127**

Consideration was given to $NaBH_3CN$[110] as the reductant. Reduction of the 16-ketone (**125**) in tetrahydrofuran-glacial acetic acid with $NaBH_3CN$ at 140°C was incomplete after 12 days. In addition to starting material the only product which could be isolated was the product arising from transacetylation, namely (**127**).

SCHEME 3.3.3-19



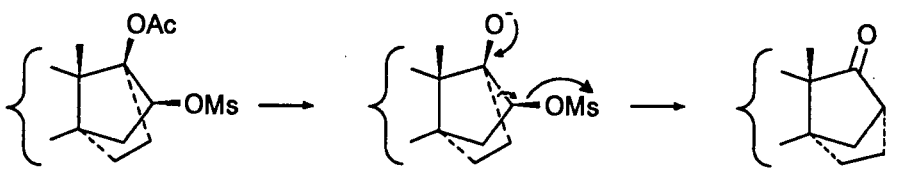
126 **129** **130**

The further investigation of a possible route to the 14ß,17ß-etheno compound was carried out with the 17ß-acetoxy-16ß-alcohol (**126**) (Scheme 3.3.3-19). Thus, treatment of (**126**) with methanesulphonyl chloride in pyridine at 4°C for 45 h furnished the corresponding 16ß-mesylate (**129**) (96%) which displayed the expected infrared absorption at ν_{max} 1356 and 1177 cm^{-1} for the sulphonate group. In addition to the

expected signals the NMR spectrum of the mesylate (**129**) exhibited a signal for the methyl protons of the methanesulphonyloxy group as a singlet at δ 2.94.

Attempts to achieve the desired elimination of the methanesulphonyloxy group in (**129**) were unsuccessful. For example prolonged contact with neutral alumina in toluene at 20°C or treatment with 1,8-diazabicylo[5.4.0]undec-7-ene in refluxing toluene resulted in recovery of starting material. However, when the mesyloxy compound (**129**) was exposed to basic alumina in toluene at 22 °C for 3 h, a single product (**130**) was formed in 80% yield. Infrared absorption at 1729 cm^{-1} indicated the presence of a carbonyl group and the absence of downfield NMR signals for the methine protons attached to an oxygen bearing carbon or for olefinic protons supported formulation as 3-methoxy-14,16α-ethanoestra-1,3,5(10)-trien-17-one (**130**). An obscured broad doublet ($J \cong 4.2$ Hz) at δ 2.66 was compatible with assignment to the bridgehead 16-proton. It is apparent that this product (**130**) was formed through hydrolysis of the 17-ester in (**129**), followed by a 17[1](17 → 16)*abeo* rearrangement with expulsion of the mesyloxy group.

SCHEME 3.3.3-20



129 **129A** **130**

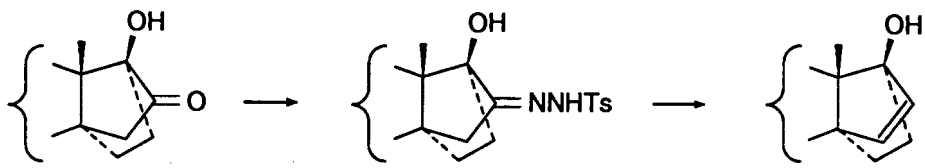
As a result of this finding, attention reverted to carrying out direct or indirect methods of elimination upon the 16-ketone (**125**). A direct method[111] which has found limited application in the past involves reaction of a ketone with zinc in the presence of trimethylchlorosilane. However, the 16-ketone (**125**) was recovered unchanged after treatment with this reagent in tetrahydrofuran at 50°C for 24 h.

Among the numerous methods for reductive elimination of a ketone *via* an intermediate derivative, the Shapiro reaction and its variants have found particular

favour.[112] The reaction sequence entails conversion of the ketone into the corresponding arenesulphonylhydrazone, followed by treatment with an alkyllithium to achieve conversion into the corresponding vinyllithium intermediate, which is protonated during the work-up procedure.

Various conditions were investigated to achieve efficient conversion of the 17ß-hydroxy-16-ketone (**124**) into the corresponding tosylhydrazone (**131**). The 17-hydroxy-16-ketone (**124**) was selected in preference to the corresponding 17-acetoxy-16-ketone (**125**) since the bridgehead functionality would be superfluous during the subsequent eliminations. The most efficient conversion of the 16-ketone (**124**) to the 16-tosylhydrazone (**131**) was obtained when a solution of the 16-ketone (**124**) in tetrahydrofuran was treated with toluene-*p*-sulphonylhydrazide in the presence of a catalytic amount of trifluoroacetic acid at 20 °C. After 52 h, 17ß-hydroxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-16-tosylhydrazone (**131**) (92%) was isolated in addition to unreacted starting material (**124**) (7%) (Scheme 3.3.3-21).

SCHEME 3.3.3-21



124 **131** **132**

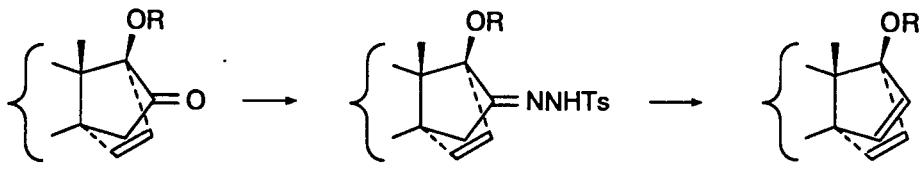
Efficient conversion of the 16-ketone (**124**) to the tosylhydrazone (**131**) could also be obtained with concentrated hydrochloric acid as the catalyst but traces of side products made this method less desirable. Attempts to speed up the reaction by increasing the temperature were abandoned owing to the poor yields of the tosylhydrazone (**131**) obtained as a result of the increased formation of side products. The infrared spectrum exhibited a C=N absorption band at 1675 cm^{-1} and SO absorption bands at 1347 and 1164 cm^{-1}. The NMR spectrum of the tosylhydrazone (**131**) exhibited the signal for the

aromatic methyl protons at δ 2.41 and the signals for the *o*- and *m*-protons of the tosylhydrazone group at δ 7.31 and 7.82 (each 2H, d, *J* 8.4 Hz).

The tosylhydrazone (**131**) in tetrahydrofuran was treated with four equivalents of *n*-butyllithium at 65°C for 50 min to give the olefin (**132**) (78%). The overall yield of 3-methoxy-14,17α-ethanoestra-1,3,5(10),15-tetraen-17ß-ol (**132**) from the starting dienyl acetate (**29**) is estimated at *ca.* 39%, a considerable improvement upon the method described in the patent literature,[107] for the preparation of the corresponding 3,17-diol (**123**).

The infrared spectrum exhibited a hydroxyl absorption band at 3600 cm^{-1} and a C=C absorption band at 1676 cm^{-1}. The NMR spectrum of the olefin (**132**) exhibited the 15- and 16-protons at δ 5.89 and 6.04 (each 1H, d, *J* 6.0 Hz).

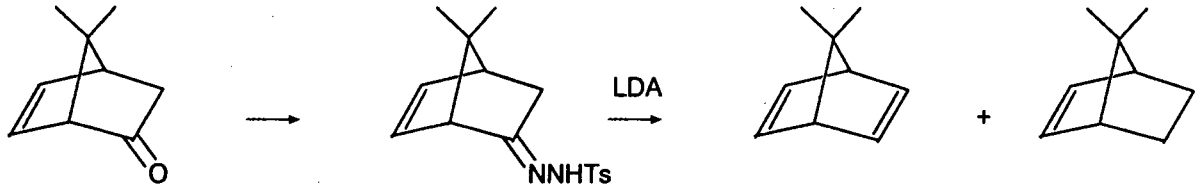
SCHEME 3.3.3-22



The success of the Shapiro reaction in the foregoing case, suggested that a similar reaction could be applied to the 14α,17α-etheno-16-ketone (**91**) leading to formation of bridged diene systems (Scheme 3.3.3-22), since the derived estradiol analogues could be used to extend the structure-activity studies in this series. Furthermore, dienes of this type would provide scope for studying the chemoselectivity of addition reactions to the respective etheno bridges. Jefford *et al.*[113] achieved some measure of success with this approach. They were able to convert 7,7-dimethylnorbornene (**133**) to the tosylhydrazone (**134**) (84%) by refluxing with toluene-*p*-sulphonylhydrazide in ethanol for 10 h (Scheme 3.3.3-23). This was followed by treatment with lithium

diisopropylamide in tetrahydrofuran to give 7,7-dimethylnorbornadiene (**135**) (43%) in addition to 7,7-dimethylnorbornene (**136**) in a 7:3 ratio.

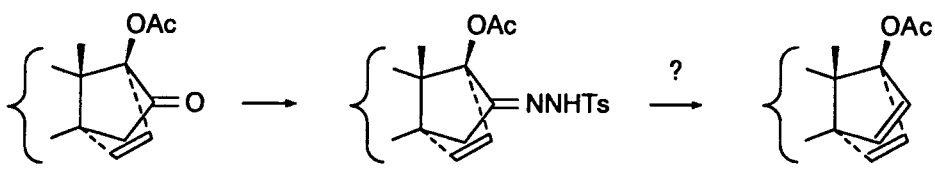
SCHEME 3.3.3-23



133 **134** **135** **136**

However, treatment of the 17-hydroxy-16-ketone (**91**) with *p*-toluenesulphonylhydrazide at 22°C gave rise to an intractable mixture of products. It is suspected that the presence of the etheno bridge and an unprotected bridgehead hydroxy group under acid catalysis may have induced skeletal rearrangements of the type associated with these structural features in related systems.[114] Furthermore, attempted formation of the tosylhydrazone of the 17-acetoxy-16-ketone (**92**) (Scheme 3.3.3-24) proceeded very sluggishly, and only 6% yield of the desired product (**137**) was obtained after 12 days at 20°C together with unreacted 16-ketone. Attempts to improve the conversion of the acetoxy ketone (**92**) to the tosylhydrazone (**137**), at an elevated temperature (70°C), were abandoned due to the formation of numerous side products.

SCHEME 3.3.3-24



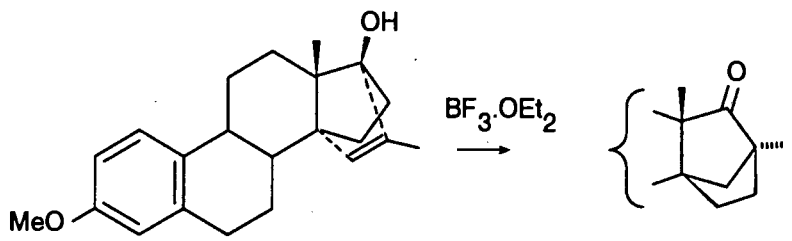
92 **137** **138**

The spectroscopic data were in accordance with expectations. Purification of the tosylhydrazone (**137**) proved problematical and analytical data could not be obtained for this compound. As a result of the poor overall conversion to the tosylhydrazone (**137**) no attempts were made to obtain the diene (**138**).

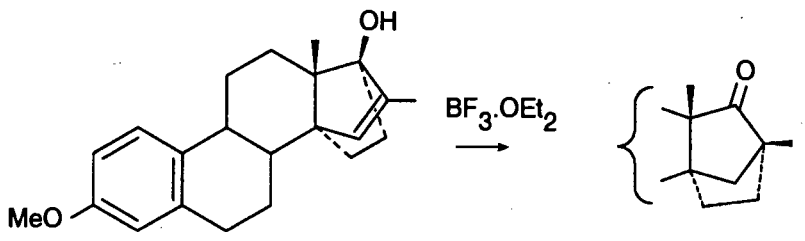
3.3.4 Skeletal Rearrangements of 16,17-Functionalised 14α,17α-Etheno Compounds

The incidental observation in the foregoing section, of a skeletal rearrangement during attempted elimination of the 16ß-mesyloxy group, in (**129**) suggested that the bridgehead hydroxy compounds in this series might be susceptible to such rearrangements.

SCHEME 3.3.4-1



139 **141**



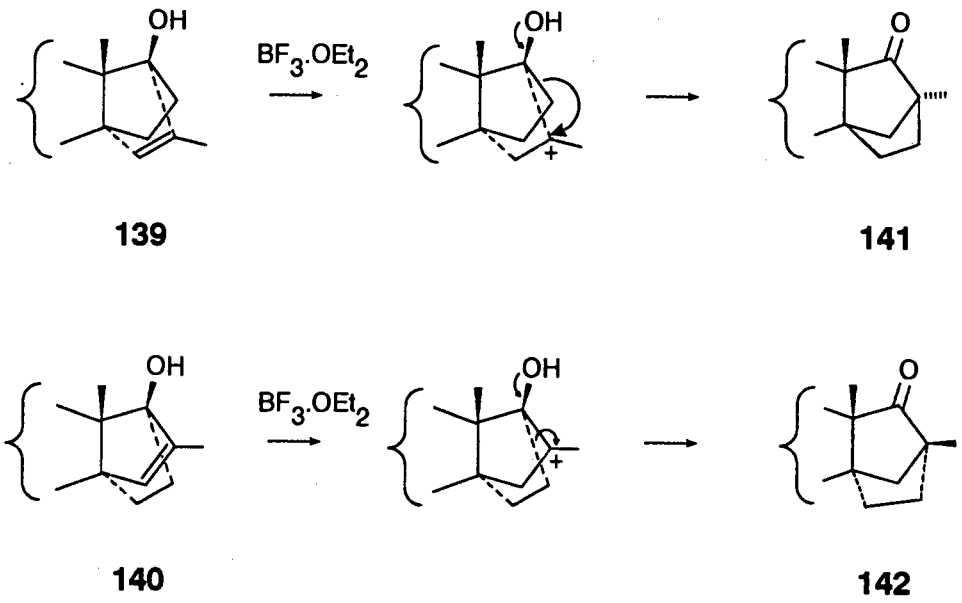
140 **142**

It has been demonstrated[114] that under acidic conditions, 14,17-bridged estradiol analogues may provide practical synthetic routes to representative 14,16-ethano-17-

ketones, which can be further elaborated into 19-norsteroid hormone analogues. For example, the 14,17-bridged compounds (**139**) and (**140**) were converted into the 14,16-ethano compounds (**141**) and (**142**), respectively with boron trifluoride diethyl etherate at 25°C (Scheme 3.3.4-1).

The mechanism is proposed to involve initial protonation of the etheno bridge of (**139**) and (**140**) followed by a 16(17 → 17[1])*abeo* rearrangement to give (**141**) and (**142**) respectively (Scheme 3.3.4-2). The products (**141**) and (**142**) arise from ß- and α-bridge migration respectively.

SCHEME 3.3.4-2

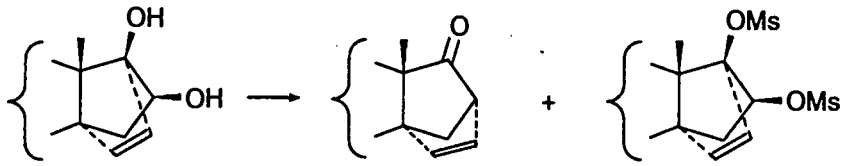


In the first instance it was of interest to ascertain whether the 14α,17α-etheno compound (**93**) could be induced to undergo an analogous 17[1](17 → 16)*abeo* rearrangement. Accordingly, the 14α,17α-etheno-16ß,17ß-diol (**93**) was treated with methanesulphonyl chloride in pyridine at 20°C to give the rearranged product 3-methoxy-14,16α-ethenoestra-1,3,5(10)-trien-17-one (**143**) (69%) accompanied by a smaller amount (24%) of the 16ß,17ß-dimesylate (**144**) (Scheme 3.3.4-3). The structure of the product (**143**) followed from spectroscopic data. The infrared spectrum exhibited

a carbonyl absorption band at 1726 cm^{-1}. The 400 MHz NMR spectrum was well resolved in terms of the chemical shifts of the signals but the fine structure of many of these signals was too complex for comprehensive analysis. Thus, the signals for the 15ξ-, 16ß- and 16^1-protons were displayed as multiplets at δ 2.03 (br d, *J ca.* 9 Hz), 3.17 ($W_{\frac{1}{2}}$ 6.3 Hz), and 6.13 ($W_{\frac{1}{2}}$ 10.9) respectively. The signal for a second 15ξ-proton was exhibited at δ 2.14 (d, *J* 9.1 Hz) and that of the 16^2-proton at δ 6.59 (d, *J* 5.8 Hz).

The infrared spectrum of the dimesylate (**144**) exhibited SO absorption bands at 1350 and 1330 cm^{-1} and the NMR spectrum displayed signals in accordance with expectations. The signals for the methyl protons of the 16ß- and 17ß-methanesulphonyloxy groups were displayed at δ 3.10 and 3.16.

SCHEME 3.3.4-3

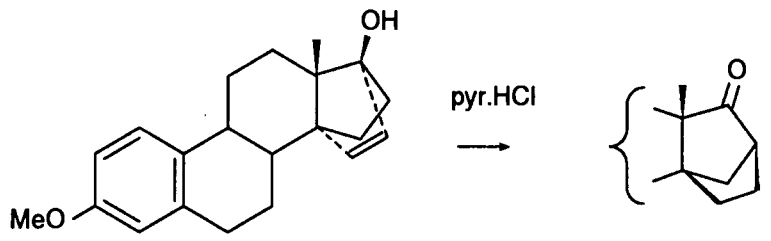


93 **143** **144**

The 14α,16α-etheno-17-ketone (**143**) could be obtained in 86% yield by treatment of the 16ß,17ß-diol (**93**) in benzene with toluene-*p*-sulphonic acid absorbed onto silica gel at 70°C for 25 h. This compound (**143**) is the unsaturated analogue of the 14α,16α-ethano-16-ketone (**130**) obtained from basic alumina treatment of the mesylate (**129**). In order to verify these assignments the 14α,16α-etheno-17-ketone (**143**) was hydrogenated in the presence of 10% palladium on carbon and hydrogen at atmospheric pressure in ethyl acetate to give the 14α,16α-ethano-17-ketone (**130**) (99%). This compound was found to be identical to an authentic sample of (**130**) prepared earlier. The 14α,16α-ethano-17-ketone (**130**) could be obtained directly by treatment of the 14α,17α-ethano-16ß,17ß-diol (**128**) in benzene with toluene-*p*-sulphonic acid adsorbed onto silica gel at reflux for 3 h. The epimeric 14ß,16ß-ethano bridged compound has

been described.[114] Thus, treatment of the hydroxy olefin (**145**) with anhydrous pyridinium hydrochloride gave the 14ß,16ß-ethano-17-ketone (**146**)[114] (Scheme 3.3.4-4).

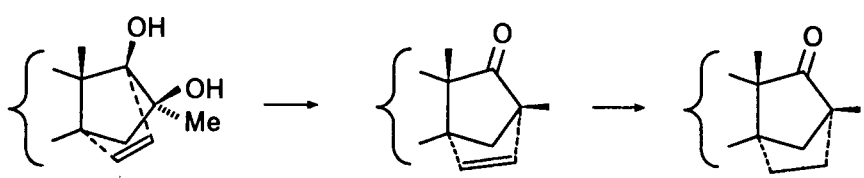
SCHEME 3.3.4-4



145 **146**

The efficient conversion of the 14,17-bridged compounds (**139**) and (**140**) to the 14,16-ethano compounds (**141**) and (**142**)[114] with the use of boron trifluoride diethyl etherate prompted the use of this Lewis acid for the transformation shown in Scheme 3.3.4-5. Treatment of the 16α-methyl-16ß,17ß-diol (**121**) in benzene with boron trifluoride diethyl etherate at 21°C for 50 min gave the 14α,16α-etheno-16ß-methyl-17-ketone (**147**) (92%). The infrared spectrum of the compound (**147**) exhibited a carbonyl absorption band at 1723 cm^{-1}. The NMR spectrum exhibited the signals for the 16^1- and 16^2-protons at δ 5.80 and 6.58 (each 1H, d, *J* 5.5. Hz) and the signals for the 15α- and 15ß-protons at δ 1.92 and 2.15 (each 1H, d, *J* 9.0 Hz).

SCHEME 3.3.4-5

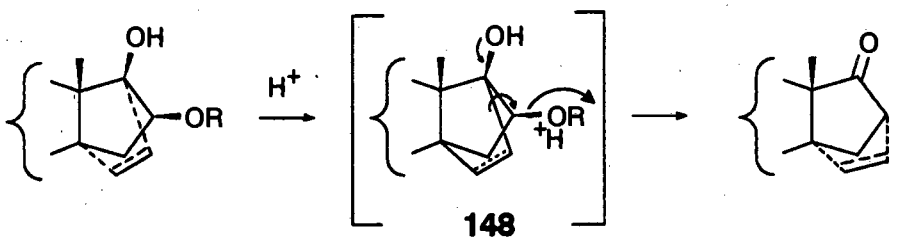


121 **147** **142**

The 14α,17α-etheno-16ß-methyl compound (**147**) was hydrogenated under standard conditions to give the 14α,16α-ethano-16ß-methyl compound (**142**). The mass spectrum exhibited a *m/z* peak at 324 which is consistent with the required molecular formula of $C_{22}H_{28}O_2$. A melting point of 105-108°C recorded for the methyl ketone (**142**) compares favourably with the melting point (107-109°C) reported[114] for this compound. A crystal structure determination of the 14α,16α-ethano-16ß-methyl (**142**) has been reported.[114]

From these rearrangements it is clear that protonation of the hydroxy group at C(16) (**148**) takes precedence over protonation of the olefinic bond (Scheme 3.3.4-6). Consequently, migration of the C(17[1])-C(17) bond to C(16), is the only reaction pathway observed.

SCHEME 3.3.4-6



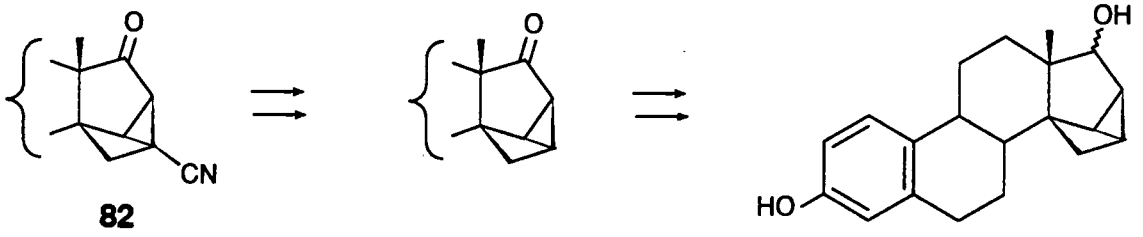
148

3.4 Reactions of the Ring D Tricyclic Cyano Ketone (82)

3.4.1 Reductive Decyanation of the Cyano Ketone (82)

The unique structure of the bridged cyano ketone (**82**) provided an inviting target for the synthesis of estradiol analogues for biological evaluation. The planned approach was to carry out reductive decyanation, directly if possible, followed by reduction of the 17-oxo-group and deprotection at C(3) (Scheme 3.4.1-1). The synthesis of both 17-isomers was considered desirable, since the steric influence of the bridged structure upon the receptor binding characteristics associated with ring D could not be predicted from a comparison of either isomer with estradiol.

SCHEME 3.4.1-1

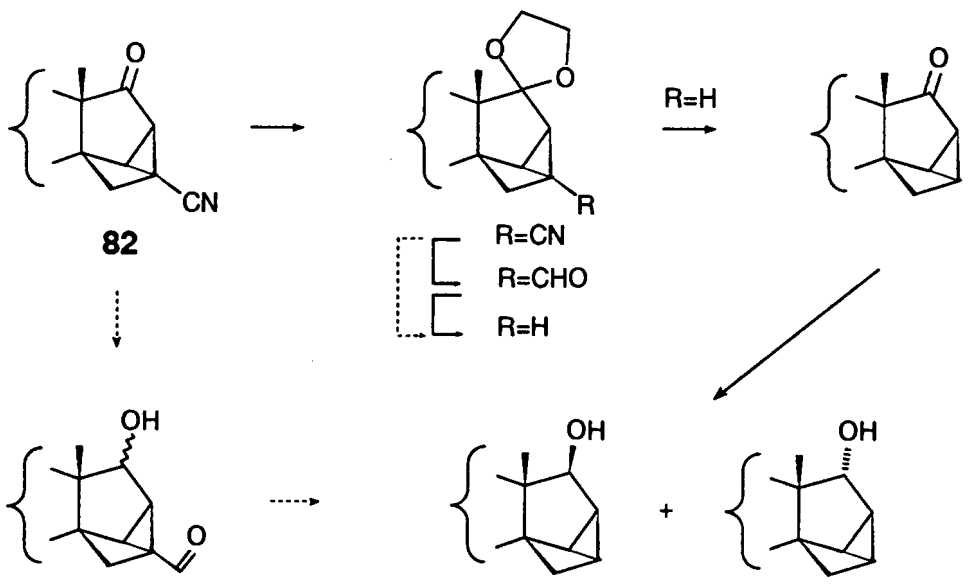


82

Several methods have been reported to effect the reductive decyanation of alkyl nitriles. The use of alkali metal-ammonia reduction in the presence of a proton source[115] was excluded, since concomitant Birch reduction of ring A would result. Accordingly, other methods were attempted including treatment of the cyano ketone (**82**) with potassium in the presence of dicyclohexano-18-crown-6,[116] or with sodium and iron(III) acetylacetonate.[117] However, neither of these reactions proceeded cleanly, and later comparison of the multi-component reaction mixtures revealed that the desired product was not present.

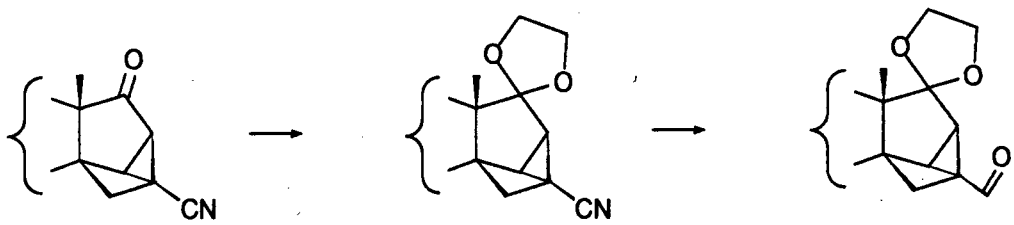
The impracticality of direct reductive decyanation necessitated the development of a stepwise route to the target compounds. This approach (Scheme 3.4.1-2) was based upon sequential protection at C(17), controlled reduction of the 16[1]-cyano group to the corresponding 16[1]-formyl group, and decarbonylation. Deprotection at C(17) would then set the stage for examining the stereoselectivity of reduction of the 17-oxo group, and deprotection at C(3), to give the estradiol analogues. Success in this approach would then enable a more expeditious synthesis, based upon simultaneous reduction of the 16-cyano and 17-oxo groups, to be investigated.

SCHEME 3.4.1-2



Treatment of the cyano ketone (**82**) with ethylene glycol and catalytic toluene-*p*-sulphonic acid in refluxing toluene for 24.5 h, with removal of water, furnished the 17-ketal (**149**) (98%), the spectroscopic and analytical data of which were consistent with the assigned structure.

SCHEME 3.4.1-3



82 **149** **150**

The selective reduction of nitriles to aldehydes by metal hydrides has been reviewed.[118] The reaction proceeds *via* nucleophilic attack of hydride upon the nitrile, with subsequent hydrolysis of the intermediate aldimine species.[119] Although lithium aluminium hydride and sodium borohydride have been used for this conversion, over-reduction is a common problem. Among the substituted hydrides, diisobutylaluminium hydride[120] has proven to be particularly effective in achieving selective reduction. Reactions are typically conducted in toluene or other aprotic solvents at low temperature, followed by hydrolysis of the aldiminoaluminium intermediate.

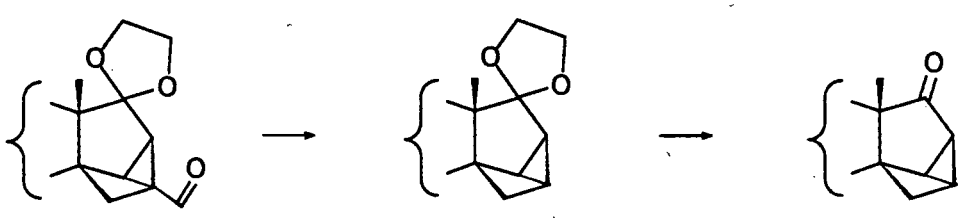
The cyano ketal (**149**) in toluene under nitrogen was treated with diisobutylaluminium hydride for 160 min at -78°C to give, (16^1*R*)-17,17-ethylenedioxy-3-methoxy-15ß,16^1-cyclo-14,16ß-ethano-14ß-estra-1,3,5(10)-triene-16^1-carbaldehyde (**150**) in 83% yield. The structure of the product (**150**) was evident from infrared absorption at ν_{max} 1686 cm^{-1}, and the one-proton NMR signal at δ 8.86, for the formyl group. In addition, the characteristic NMR signals for key ring D protons confirmed that the bridged structure was intact.

Aldehydes can be decarbonylated[121] with chlorotris(triphenylphosphine)-rhodium(I) [$RhCl(PPh_3)_3$] (Wilkinson's catalyst) or other catalysts eg. palladium or nickel complexes. Decarbonylation of aldehydes with stoichiometric amounts of $RhCl(PPh_3)_3$ occurs under mild conditions[122] since this catalyst readily abstracts carbon monoxide from a wide variey of species to form the very stable *trans*-carbonylchlorobis(triphenylphosphine)rhodium(I) [*trans*-$RhCl(CO)(PPh_3)_2$], which is

catalytically inactive. Catalytic decarbonylation[122] of aldehydes requires elevated temperatures (often >200°C). At these temperatures *trans*-$RhCl(CO)(PPh_3)_2$ is the true catalyst.[122] $RhCl(PPh_3)_3$ is readily synthesised from $RhCl_3.3H_2O$[123] with triphenylphosphine in ethanol.

Reductive decarbonylation was achieved by refluxing the formyl ketone (**150**) in deoxygenated toluene with 1.1 mol. equiv. of $RhCl(PPh_3)_3$ for 20 h, to give (16^1*S*)-17,17-ethylenedioxy-3-methoxy-15ß,16^1-cyclo-14,16ß-ethano-14ß-estra-1,3,5(10)-triene (**151**) (92%). The progress of the reaction could be followed by means of the colour change from dark red to yellow. Where catalytic amounts of $RhCl(PPh_3)_3$ were used the reaction mixture turned yellow before complete conversion of the formyl ketone (**150**) to the decarbonylated product (**151**) had occurred. Since low yields often result from pyrolysis of aldehydes at the elevated temperatures required for catalytic decarbonylation, catalytic decarbonylation was not attempted at higher temperatures.

SCHEME 3.4.1-4



150 **151** **152**

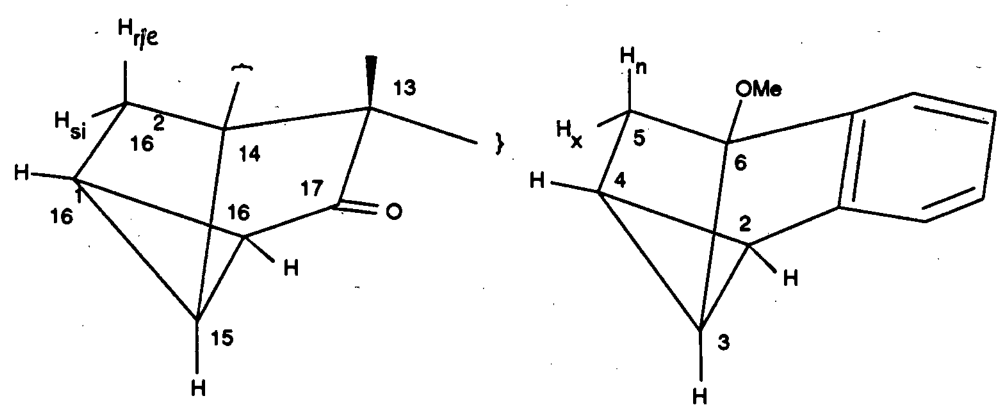
The analytical and spectroscopic properties of the ketal (**151**) were consistent with the expected structure. Although the NMR spectrum of (**151**) was rather uninformative owing to poor resolution in the high-field region, the absence of a signal for the formyl proton was diagnostic.

Deprotection of the ketal (**151**) with aqueous 6M-hydrochloric acid in tetrahydrofuran at 0°C for 6 min furnished (16^1*S*)-3-methoxy-15ß,16^1-cyclo-14,16ß-ethano-14ß-estra-1,3,5(10)-trien-17-one (**152**) (92%). The overall conversion of the

cyano ketone (**82**) into the corresponding ketone (**152**) was thus achieved in *ca.*75% yield over three steps.

The ketone (**152**) was of particular interest, since it is the structural analogue of estrone 3-methyl ether, and accordingly, a detailed NMR investigation was carried out. A 400 MHz NMR spectrum of (**152**) in deuteriochloroform was reasonably well-resolved, although some of the ring B and ring C proton signals were partly obscured. The signals for the ring D protons were readily identified, and a COSY plot and selective irradiation were employed to confirm the assignments. Figure 3.4.1-1 (Page 87) shows part (δ 3.1 - 0.7) of the 400 MHz NMR spectrum of the ketone (**152**), together with the corresponding COSY plot.

SCHEME 3.4.1-5



152 **153**

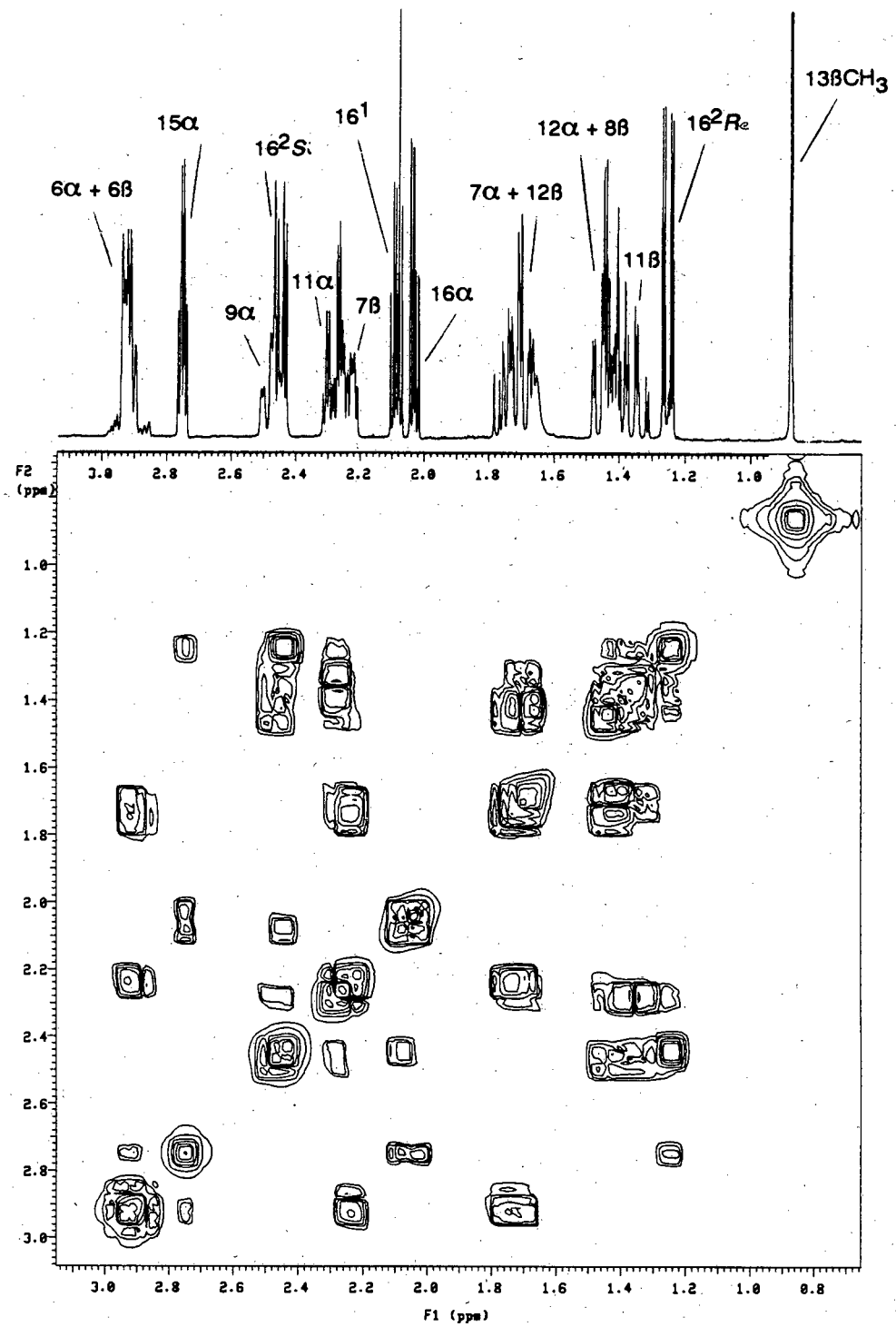


Figure 3.4.1-1: 400 MHz NMR spectrum (δ 3.1 - 0.7) and COSY plot of the tricyclic ketone (**152**)

Table 6: Assignments and couplings of the ketone (**152**) and the compound (**153**)

Compound **152**				
δ(ppm)	Proton	Mult.(*J*/Hz)	Coupling Assignments	
2.76	15α	ddd (4.1, 3.7, 2.9)	15ß,16α	4.1
2.04	16α	dd (6.5, 4.1)	15ß,16^1	3.7
2.10	16^1	ddd (6.5, 3.9, 3.7)	15α,16^2*Re*	2.9
1.26	16^2*Re*	dd (10.5, 2.9)	16α,16^1	6.5
2.45	16^2*Si*	dd (10.5, 3.9)	16^1,16^2*Si*	3.9
			16^1,16^2*Re*	0
			16^2*Re*,16^2*Si*	10.5

Compound **153**				
δ(ppm)	Proton	Mult.(*J*/Hz)	Coupling Assignments	
3.06	3	ddd (5.4, 4.4, 2.8)	2,3	5.4
2.50	2	dd (5.4, 5.4)	3,4	4.4
1.95	4	ddd (5.4, 4.4, 3.4)	3,5*n*	2.8
0.90	5*n*	dd (8.8, 2.8)	2,4	5.4
2.39	5*x*	dd (8.8, 3.4)	4,5*x*	3.4
			4,5*n*	0
			5*n*,5*x*	8.8

The chemical shifts and coupling constants for the signals of the ring D protons of the tricyclic ketone (**152**) are given in Table 6, along with comparative data reported by Paquette[87] for compound (**153**) (Scheme 3.4.1-5). [In the case of compound (**153**) the structure is represented as the enantiomer for ease of comparison].

A comparison of the data for compounds (**152**) and (**153**) reveals good correspondence of coupling constants, given the slight conformational differences imposed by substitution of the respective tricyclo[3.2.0.0^{2,7}]heptanoid systems. As in the case of the 16^{1}-cyano 17-ketone (**82**), the presence of a four-bond coupling between 15-H and 16^{2}-H_{re} is a distinctive characteristic of this structure. It is also notable that the absence of coupling between the vicinal 16^{1}- and 16^{2}*Re* protons reflects a near-orthogonal relationship between these neighbours.

An X-ray crystal structure of the ketone (**152**) confirmed the structure, and demonstrated the expected close correspondence in conformational properties with those of the cyano ketone (**82**). The atomic numbering and a perspective view of the molecule is shown in Figure 3.4.1-2.

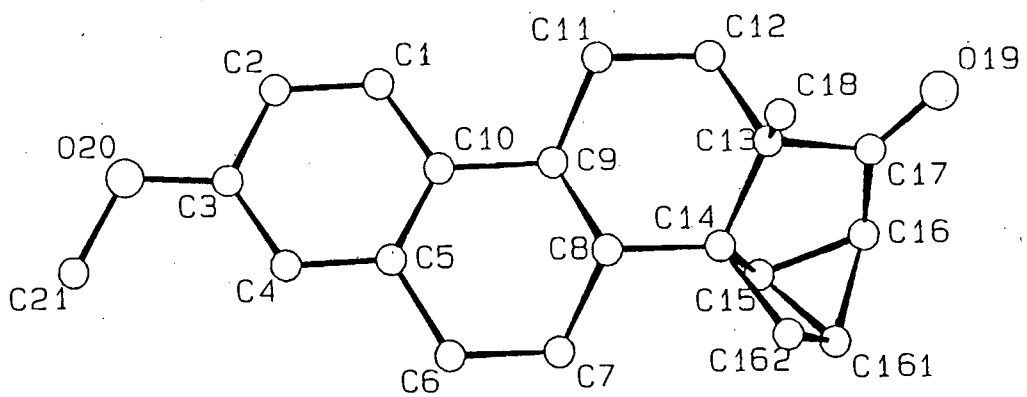


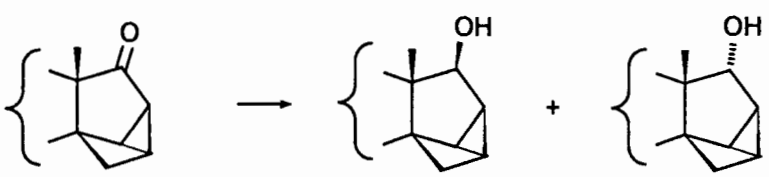
Figure 3.4.1-2: Perspective view of the ketone (**152**) with its atomic labelling

Final fractional atomic coordinates and equivalent isotropic parameters for the ketone (**152**) are given in Table 4.3-3 (see Section 4). The geometrical parameters for rings A,B and C are comparable to those determined for the cyano ketone (**82**). Ring A does not differ significantly from planarity. For this ring, the C-C distances and internal C-C-C angles are in the ranges 1.37(6) - 1.40(6)Å and 117.4(4) -122.(4)° respectively.

For rings B and C the C-C distances and internal C-C-C angles (excluding the A-B linkage) are 1.51(6) - 1.54(6)Å and 108.9(3) - 114.7(4)° respectively. Ring B adopts a half-chair conformation whereas ring C adopts a chair conformation. The bond lengths associated with the bridged ring D [1.47(7) - 1.58(6)Å] display no abnormalities. The internal bond angles in ring D [100.5(3) - 110.1(4)°] and in the cyclobutyl [87.4(3) - 93.1(4)°] and cyclopropyl [58.7(3) - 61.6(3)°] rings are similar to those determined for (**82**). The C(17)-C(13)-C(14)-C(15) torsion angle is -33.3(4)° which, when compared to 3-methoxy-14ß-estra-1,3,5(10)-trien-17-one, suggests that ring D experiences some flattening as a consequence of bridging. The conformation of ring D is between a half-chair and an envelope.

Completion of the synthetic sequence required reduction of the 17-ketone (**152**) to the 17ß- and/or 17α-alcohols. Treatment of (**152**) with lithium aluminium hydride in tetrahydrofuran at reflux over 8 h afforded a separable mixture of the 17ß-alcohol (**154**) (40%) and the 17α-alcohol (**155**) (58%) in the ratio 1:1.5.

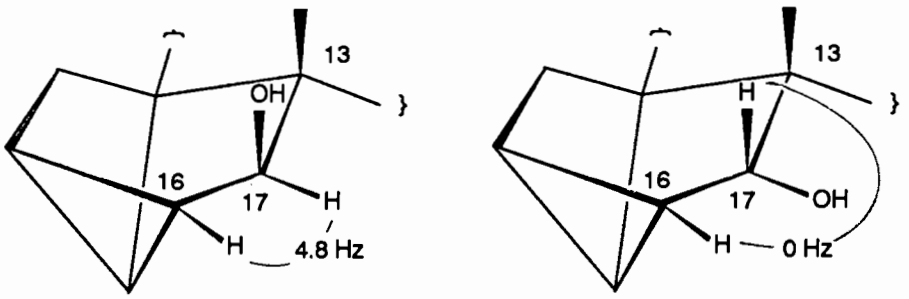
SCHEME 3.4.1-6



152 **154** **155**

The isomers were readily distinguished by a comparison of the signals for the 17-protons. Thus, the 17ß-alcohol (**154**) displayed 17α-H as a one-proton doublet (*J* 4.8 Hz) at δ 3.94, whereas the 17α-alcohol (**155**) displayed 17ß-H as a one-proton singlet at δ 4.18. An inspection of models (Figure 3.4.1-3) revealed that the torsion angle between 17α-H and 16α-H in (**154**) is ≅ 20°whereas that between 17ß-H and 16α-H is (**155**) is ≅ 90°.

Figure 3.4.1-3



154 **155**

The lack of stereoselectivity with hydride reduction of (**152**) was not unexpected since the 17-oxo group is sterically hindered, and skeletal elements on the α- and ß-faces make it difficult to compare this case with those of other steroidal 14α- or 14ß-ketones. Although the foregoing result served our purpose very well, in providing ready access to both isomers, it was of interest to compare other reducing agents.

Reduction of the ketone (**152**) with sodium borohydride in tetrahydrofuran-ethanol at 0°C for 40 h, gave the 17ß- (**154**) (21%) and 17α-alcohols (**155**) (67%) in a *ca.* 1:3.2 ratio. Reduction of the ketone (**152**) with $NaBH_4$ thus shows slightly greater stereoselectivity than lithium aluminium hydride. This suggests that the ß-face of (**152**) is somewhat less hindered, and the greater steric demand of borohydride therefore results in more stereoselective production of the 17α-isomer (**155**).

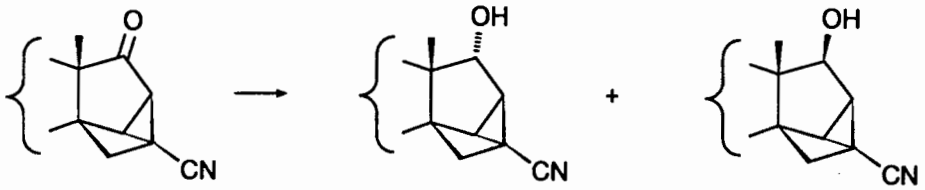
The use of dissolving metal reduction methodology was also considered since it was hoped that this might give an indication of which of the 17-alcohols represents the thermodynamically favoured isomer. The unique characteristics of the skeleton made a prediction of this relationship difficult. In general, reductions of hindered ketones with alkali metals in the presence of a proton donor are expected to furnish the thermodynamically favoured isomer, whereas reductions of sterically hindered ketones may give rise to inconclusive results or even predominant formation of the thermodynamically disfavoured isomer.[124]

Treatment of the 17-ketone (**152**) with sodium in isopropanol at 20°C was unsuccessful, but prolonged (19 h) treatment at 75°C afforded a mixture comprising starting material (**152**) (20%) and a *ca.* 1:1 mixture (54%) of the 17ß- and 17α-alcohols (**154**) and (**155**). From this experiment, it was concluded that the hindered environment of C(17) may be responsible for a very small difference in thermodynamic stability of the 17ß- and 17α-alcohols.

In order to investigate the effect of the C(16^1)-nitrile group on the face selectivity of hydride reductions of the C(17)-oxo group, the following reductions were carried out on the cyano ketone (**82**).

A suspension of the cyano ketone (**82**) in ethanol was treated with $NaBH_4$ at room temperature for 2 h, to give (16^1*R*)-17α-hydroxy-3-methoxy-15ß,16^1-cyclo-14,16ß-ethano-14ß-estra-1,3,5(10)-triene-16^1-carbonitrile (**156**) (59%) and the 17ß-hydroxy-16^1-carbonitrile (**157**) (27%) in a 2.2:1 ratio. As in the reduction of the 17-ketone (**152**), reduction of the cyano ketone (**82**) with $NaBH_4$ favoured the formation of the α-isomer. The 17-hydroxy-16^1-carbonitriles (**156**) and (**157**) were assigned on the basis of their respective NMR spectra. The 17α-isomer (**156**) displayed 17ß-H as a one-proton singlet at δ 4.26, whereas the 17ß-isomer (**157**) displayed 17α-H as a one-proton doublet (*J* 4.6 Hz) at δ 4.07.

SCHEME 3.4.1-7

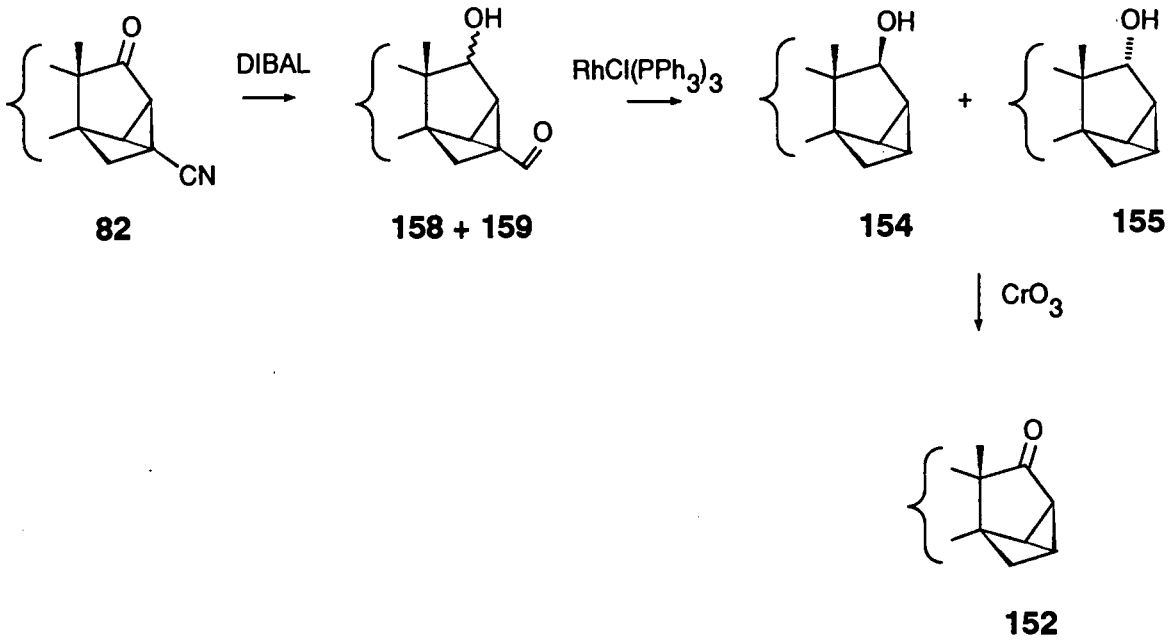


82 **156** **157**

In addition, reduction of the cyano ketone (**82**) in tetrahydrofuran under nitrogen with lithium tri(*s*-butyl)borohydride (L-Selectride) at 0°C for 1 h, gave only the 17ß-alcohol (**157**) (73%). It is known that this reagent is extremely sensitive to the steric

environment of cyclic ketones, and that reduction of unhindered ketones with L-Selectride can give rise to reversal of the stereoselectivity which obtains with simple hydrides.[125] This result suggests that the relative steric shielding of the ß-face of the 17-oxo group on (**82**) towards L-Selectride is greater than that of the α-face.

SCHEME 3.4.1-8

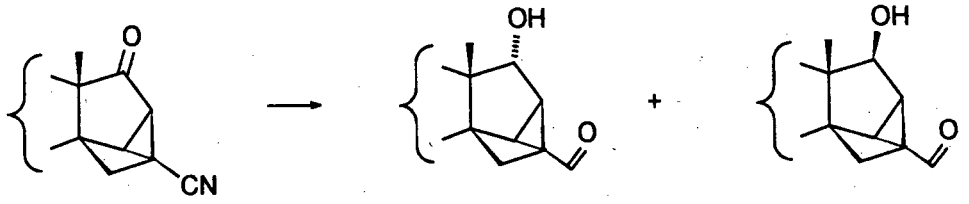


82 **158 + 159** **154** **155** **152**

The success of the foregoing route in providing equal access to the immediate precursors of both target estradiol analogous prompted an investigation of the shorter reaction sequence. Thus the cyano ketone (**82**) in toluene was treated with diisobutylaluminium hydride at -78°C to give a mixture of 17α- and 17ß-hydroxy 16[1]-carbaldehydes (**158** and **159**) (*ca.* 80%) (Scheme 3.4.1-8), which was not separated or characterised, but subjected to direct decarbonylation with $RhCl(PPh_3)_3$ in toluene at reflux for 19 h to give the 17ß-alcohol (**154**) (34%) and the 17α-alcohol (**155**) (43%). The overall yield of 79% from the cyano ketone (**82**) represents an improvement of *ca.* 20% in the stepwise route. It is evident that the brevity and efficiency of this sequence

makes it the route of choice in preparing the respective 17-alcohols (**154**) and (**155**). In addition, the mixture of alcohols could be efficiently converted into the corresponding 17-ketone by treatment with Jones' reagent in acetone at 0°C; thus this pathway was also the preferred one for preparation of (**152**) for further studies (see later).

SCHEME 3.4.1-9

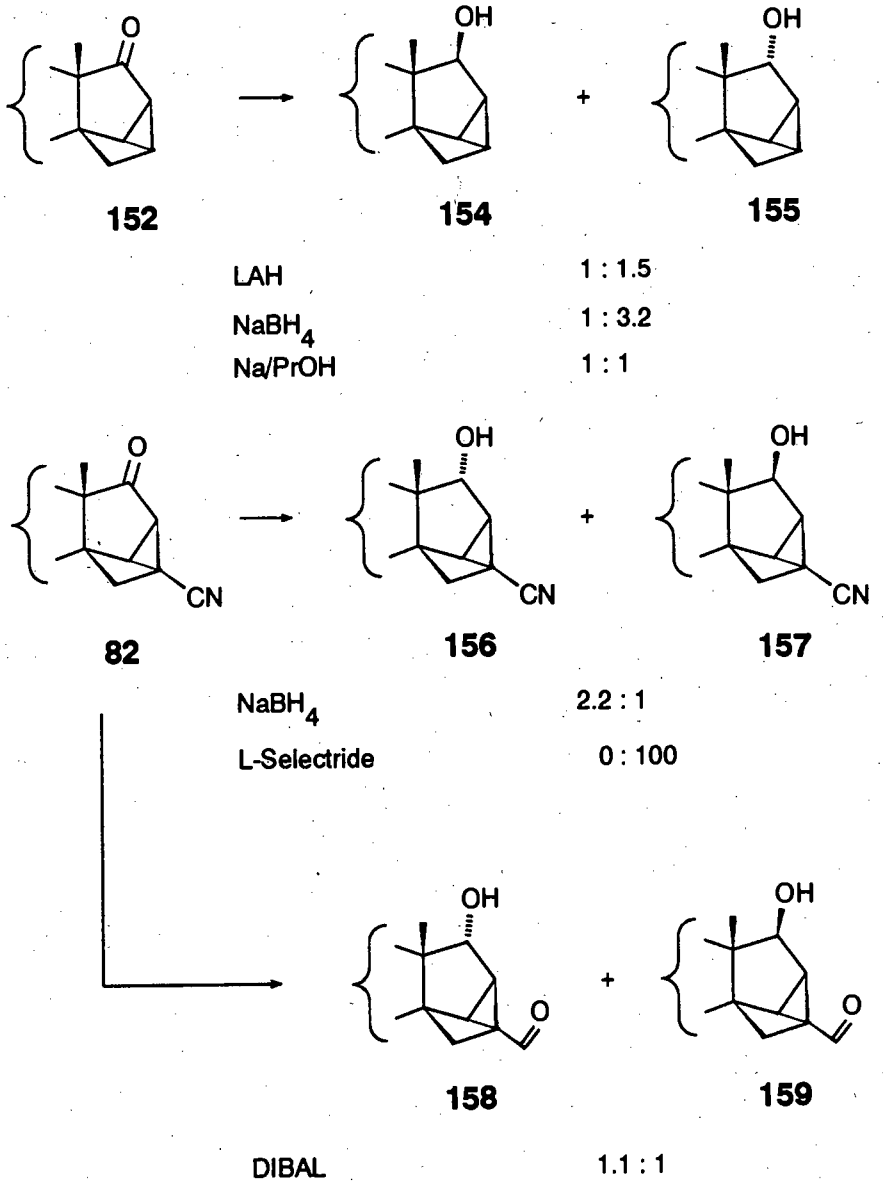


82 **158** **159**

In the light of the hydride reductions of the 17-oxo groups of (**82**) and (**152**) it was of interest to compare the results obtained by diisobutylaluminium hydride reduction of the cyano ketone (**82**) and, in addition, to characterise the formyl alcohols (**158** and **159**). A solution of the cyano ketone (**82**) in toluene under nitrogen was treated with diisobutylaluminium hydride at -78°C for 1 h to give, (16^1*R*)-17α-hydroxy-3-methoxy-15ß,16^1-cyclo-14,16ß-ethano-14ß-estra-1,3,5(10)-triene-16^1-carbaldehyde (**158**) (43%) and the 17ß-hydroxy-16^1-carbaldehyde (**159**) (38%), in the ratio 1.1:1. The 17-alcohols (**158**) and (**159**), were readily assigned on the basis of their respective NMR spectra. The 17α-alcohol (**158**) displayed 17ß-H as a one-proton singlet at δ 4.20, whereas the 17ß-alcohol (**159**) displayed 17α-H as a one-proton doublet (*J* 4.7 Hz) at δ 4.12.

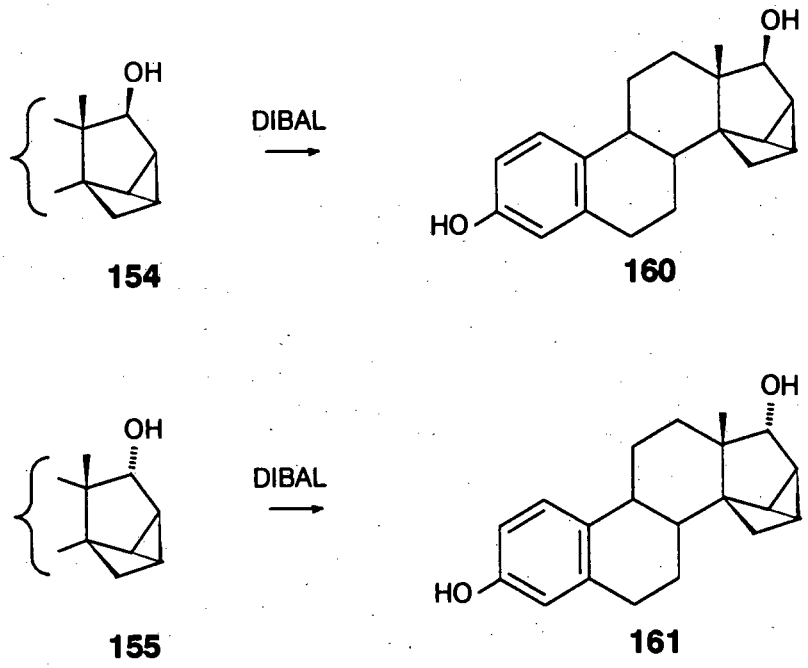
In summary, the results obtained from the hydride reductions of the cyano ketone (**82**) as well as the ketone (**152**) are illustrated in Scheme 3.4.1-10. Formation of the α-alcohol is favoured by the hydrides lithium aluminium hydride, sodium borohydride and diisobutylaluminium hydride (DIBAL). However, complete reversal of stereoselectivity is obtained with L-Selectride.

SCHEME 3.4.1-10



With the alcohols (**154**) and (**155**) in hand, the preparation of the corresponding estradiols entailed demethylation at C(3). Several methods exist for cleavage of aryl alkyl ethers,[126] but the success achieved with DIBAL in steroidal systems[118] made this our first choice. The individual alcohols (**154**) and (**155**), in toluene were refluxed with 10 mol. equiv. of DIBAL for 23.5 h, to give (16^1*S*)-15ß,16^1-cyclo-14,16ß-ethano-14ß-estra-1,3,5(10)-triene-3,17ß-diol (**160**) (79%) and the 3,17α-diol (**161**) (95%), respectively.

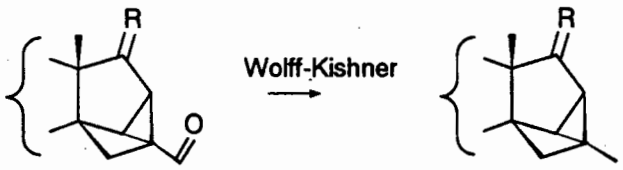
SCHEME 3.4.1-11



The respective products (**160**) and (**161**) were characterised by appropriate analytical and spectroscopic data, and have been subjected to biological evaluation, the results of which are discussed later (see Section 3.5).

Further modification of this novel tricyclic structure was envisaged as involving synthesis of estradiol analogues with functionality at position C(16^1), notably a methyl group. Although several attempts were made to obtain this compound, these reactions were characterised by poor yields and inexplicable losses of material. In addition, the products obtained were non-crystalline and could not be fully characterised. These reactions are briefly described here.

SCHEME 3.4.1-12



158 R = α-OH, β-H
150 R = OCH_2CH_2O

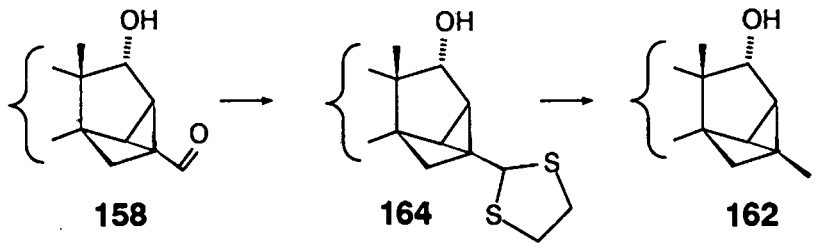
162 R = α-OH, β-H
163 R = OCH_2CH_2O

In the first instance the Huang-Minlon modification[127] of the Wolff-Kishner reduction was employed in order to effect the conversion of the alcohol (**158**) to the desired compound. Thus the alcohol (**158**) in ethylene glycol was heated with hydrazine hydrate to 140°C for 80 min after which time the reaction mixture was cooled and potassium hydroxide pellets were added. The open reaction mixture was heated to drive off excess hydrazine and water, then refluxed at 220°C for 7 h to give, after methylation of the crude reaction product, the compound (**162**) (30%) which exhibited the expected spectroscopic features. The NMR spectrum exhibited two singlets (each 3H) at δ 0.88 and 1.16 which were assigned to the 13ß-Me and 16^1-Me protons, respectively. The infrared spectrum exhibited hydroxyl absorption bands at 3605 and 3454 cm^{-1} and the mass spectrum exhibited a *m/z* peak at 324, consistent with the required molecular formula of $C_{22}H_{28}O_2$.

Similarly, use of the same procedure with the ketal (**150**) gave, after remethylation of the reaction product, what appeared to be the (16^1)-methyl ketal (**163**) (20%). The NMR spectrum exhibited two singlets (each 3H) at δ 0.75 and 1.18 which were assigned to the 13ß-Me and 16^1-Me protons respectively, in addition to the signal for the ketal protons at δ 3.83-4.08. The mass spectrum exhibited a *m/z* peak at 366, consistent with the required molecular formula of $C_{24}H_{30}O_3$.

The reason for these poor yields is not clear, but it is possible that the tricyclic ring D skeleton is sensitive to the strongly alkaline reaction conditions required for the elimination of the hydrazone intermediate.

SCHEME 3.4.1-13



158 **164** **162**

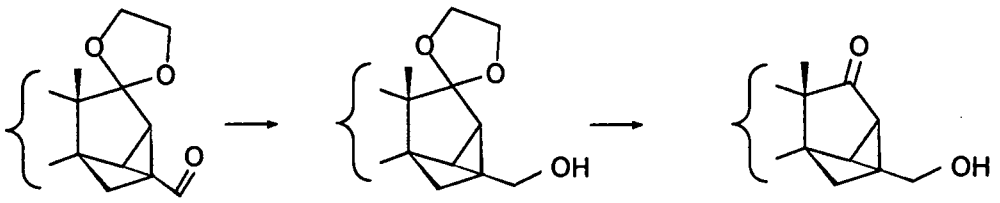
Our next consideration was the use of a two step method which involves formation of the thioacetal from the formyl alcohol (**158**), followed by Raney nickel reductive desulphurisation to afford the C(16^1)-methyl compound. The alcohol (**158**) in tetrahydrofuran was treated with ethanedithiol and catalytic boron trifluoride diethyl etherate at 0°C for 20 min to give the non-crystalline thioacetal (**164**) (97%). An NMR spectrum of the chromatographically pure material exhibited a four-proton multiplet for the thioacetal protons at δ 3.22 and a singlet for 16^1-C*H*$S_2C_2H_4$ at δ 4.52. The infrared spectrum confirmed the absence of a carbonyl group but a hydroxyl absorption band was present at 3606 cm^{-1}. The mass spectrum exhibited a *m/z* peak at 414, consistent with the required molecular formula of $C_{24}H_{30}O_2S_2$.

The thioacetal (**164**) in acetone (or ethanol) was treated with Raney nickel at room temperature to give the desired compound (**162**) in poor yield (*ca.* 20%). Deactivation of the Raney nickel, by refluxing in acetone prior to addition of the thioacetal (**164**), did not serve to increase the yield of the C(16^1)-methyl compound (**162**) obtained.

The poor results obtained during the synthesis of the C(16^1)-methyl compounds (**162**) and (**163**) discouraged further investigations along this line. Instead, conversion of the formyl ketone (**150**) into novel estriol analogues was considered. Thus, reduction of the formyl ketone (**150**) with lithium aluminium hydride in tetrahydrofuran at 19°C for 30 min gave, (16^1*R*)-17,17-ethylenedioxy-16^1-hydroxymethyl-3-methoxy-15ß,16^1-cyclo-14,16ß-ethano-14ß-estra-1,3,5(10)-triene (**165**) (83%). The infrared spectrum

exhibited a hydroxyl absorption band at 3604 cm^{-1} and the NMR spectrum exhibited the 16^1-CH_2OH protons at δ 3.57

SCHEME 3.4.1-14



150 **165** **166**

The ketal (**165**) was deprotected with aqueous 6M-hydrochloric acid in tetrahydrofuran at 0°C for 1 h to give (16^1R)-hydroxymethyl-3-methoxy-15ß,16^1-cyclo-14,16ß-ethano-14ß-estra-1,3,5(10)-trien-17-one (**166**) (80%). The infrared spectrum exhibited hydroxyl absorption bands at 3609 and 3416 cm^{-1} and a carbonyl absorption band at 1710 cm^{-1}. The NMR signals for the ring D protons of the ketone (**166**) exhibited the spectral pattern common to these systems.

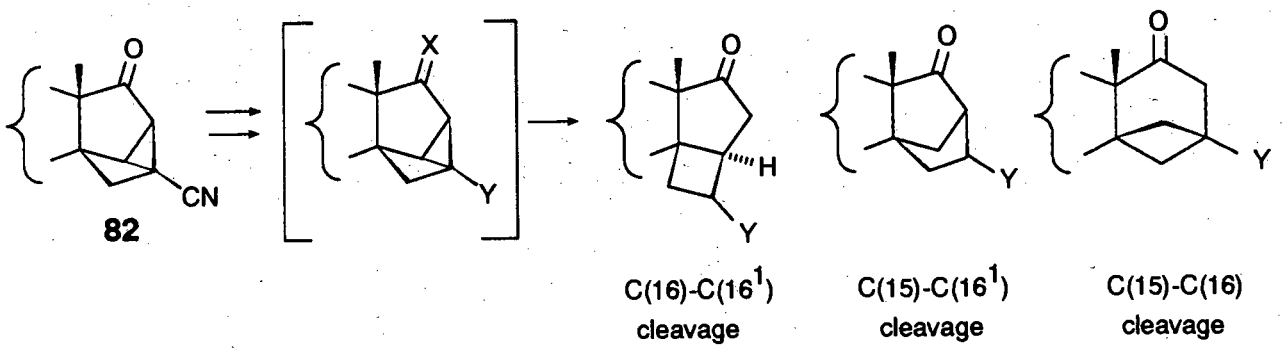
Although access to the hydroxy ketone (**166**) thus established the feasibility of preparing new estriol analogues based upon 17-alcohols having 16^1-hydroxymethyl groups, the scarcity of material precluded further investigations.

3.4.2 Selective Bond Cleavages of the Cyano Ketone (**82**) *and its Derivatives*

The cyano ketone (**82**) and its functionally modified derivatives, provide models for a study of selective C-C bond cleavages in ring D. The presence of 1,3-removed functionality separated through a cyclopropyl ring bond suggests that (**82**), and those derivatives in which the 17-oxo group or the 16^1-cyano group are either modified or protected, could be induced to undergo reductive cleavages of one of the bonds on the

cyclopropyl ring. In principle three such transformations are possible, leading to 14,15-ethano (i.e. 14,15-cyclobutano-), 14,16-ethano- or 14,16-methano-D-homo ring systems (Scheme 3.4.2-1).

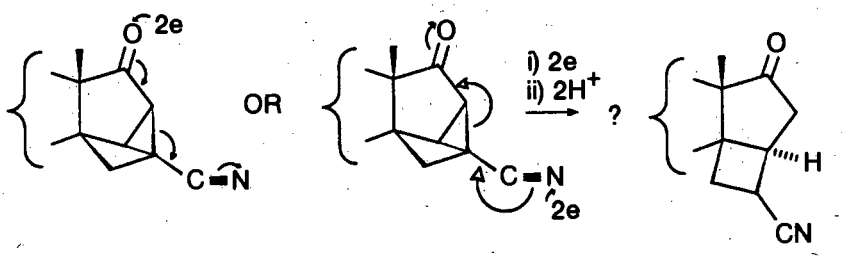
SCHEME 3.4.2-1



Apart from the intrinsic interest in examining the scope for controlling these processes, it was recognised that the novel products could be converted into estradiol analogues for further structure-activity studies in this series.

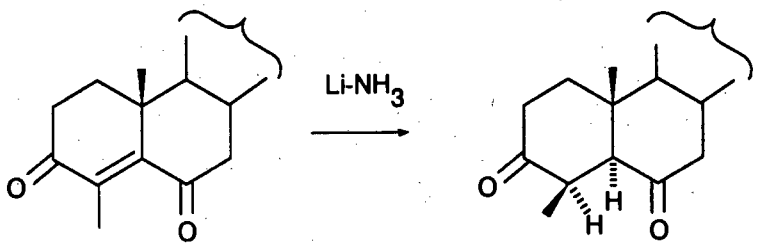
In the first phase of this study, consideration was given to dissolving metal reductions of the cyano ketone (**82**), in the expectation that regiospecific cleavage of the C(16)-C(16¹) cyclopropyl bond could thus be achieved.

SCHEME 3.4.2-2



This expectation was based upon the structural and electronic analogy with enediones, and related 1,4-dicarbonyl systems, in which the addition of electrons at the terminus results in reduction of the conjugated olefinic bond (e.g. **167** → **168**)[128] (Scheme 3.4.2-3), and the recognition that a conjugated cyclopropyl ring can mimic an olefinic bond under certain reaction conditions.[129] As a result of ring strain the bonds of the cyclopropyl ring display more *p* character than normal sp^3 hybridised bonds.

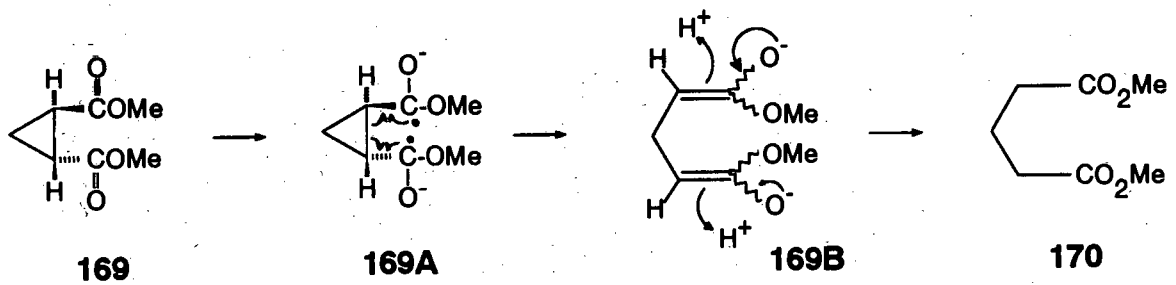
SCHEME 3.4.2-3



167 **168**

The extension of this argument, to regiospecific reductive cleavages of an intervening cyclopropyl C-C bond would be expected to lead to a 1,5-dicarbonyl systems. An

SCHEME 3.4.2-4



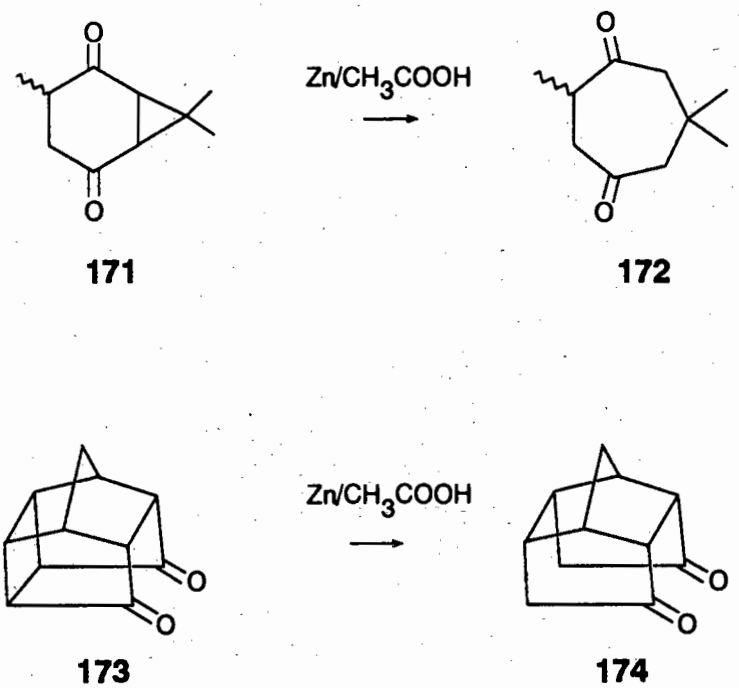
169 **169A** **169B** **170**

example of such a reduction can be found in the conversion of the cyclopropyl compound (**169**) to the diester (**170**).[130] The reaction proceeds *via* a two-electron

addition to give the dianion diradical (**169A**), which is cleaved to yield a bis(ester enolate) (**169B**), protonation of which leads to the final product (**170**).

In certain systems, the reduction potential of the zinc-acetic acid system is sufficient to result in C-C bond cleavage. For example, treatment of the cyclopropyl compound (**171**) with zinc-acetic acid affords the dione (**172**)[131] and the strained 1,4-dicarbonyl system (**173**) gives rise to compound (**174**)[132] (Scheme 3.4.2-5).

SCHEME 3.4.2-5



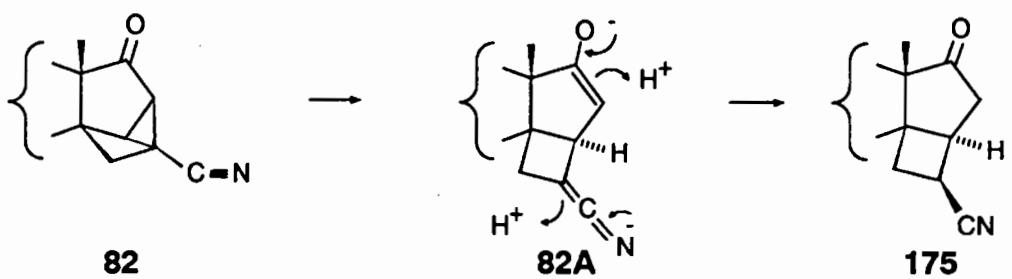
Initial attempts were made to carry out reductive cleavage of the cyano ketone (**82**) with freshly activated zinc dust in glacial acetic acid-tetrahydrofuran, since it is known that enediones undergo ready reduction in this medium.[133] In this event, the cyano ketone (**82**) failed to react under these conditions at 20°C. However, treatment of the cyano ketone (**82**) under these conditions at 85°C led to an intractable mixture, and this approach was abandoned.

Consideration was thus given to reduction with a dissolving metal in liquid ammonia. Various experiments were carried out, and it was found that calcium in liquid

ammonia resulted in a clean and efficient reduction. The choice of calcium was based upon its relatively low reduction potential by comparison with the alkali metals, which was expected to provide for more controlled reduction. Calcium-ammonia has found particular favour as a reagent for selective deacetoxylation of α-acetoxy ketones,[134] without over-reduction which occurred with the use of lithium-ammonia.

Addition of the cyano ketone (**82**) in tetrahydrofuran to a solution of calcium in liquid ammonia-tetrahydrofuran at -78°C, followed after 3 min by destruction of the excess calcium with bromobenzene, and protonation with ammonium chloride, resulted in efficient conversion into 3-methoxy-17-oxo-dihydrocyclobuta[14,15]-14ß-estra-1,3,5(10)-triene-3'ß-carbonitrile (**175**) (71%) (Scheme 3.4.2-6).

SCHEME 3.4.2-6



82 **82A** **175**

The structure of the product was based upon the interpretation of the spectroscopic data. The presence of the functional groups at C(17) and C(3') was evident from IR absorption at 1735 and 2237 cm^{-1} respectively. A 400 MHz NMR spectrum of (**175**) displayed first-order mulitplets for all the ring D and the cyclobutane ring system protons, with the exception of 15α-H (Figure 3.4.2-1). In addition, it was possible to discern the 11- and 12-proton multiplets, which demonstrated that the chair conformation is preserved in ring C. The assignments and couplings for the ring D protons of compound (**175**) appear in Table 7.

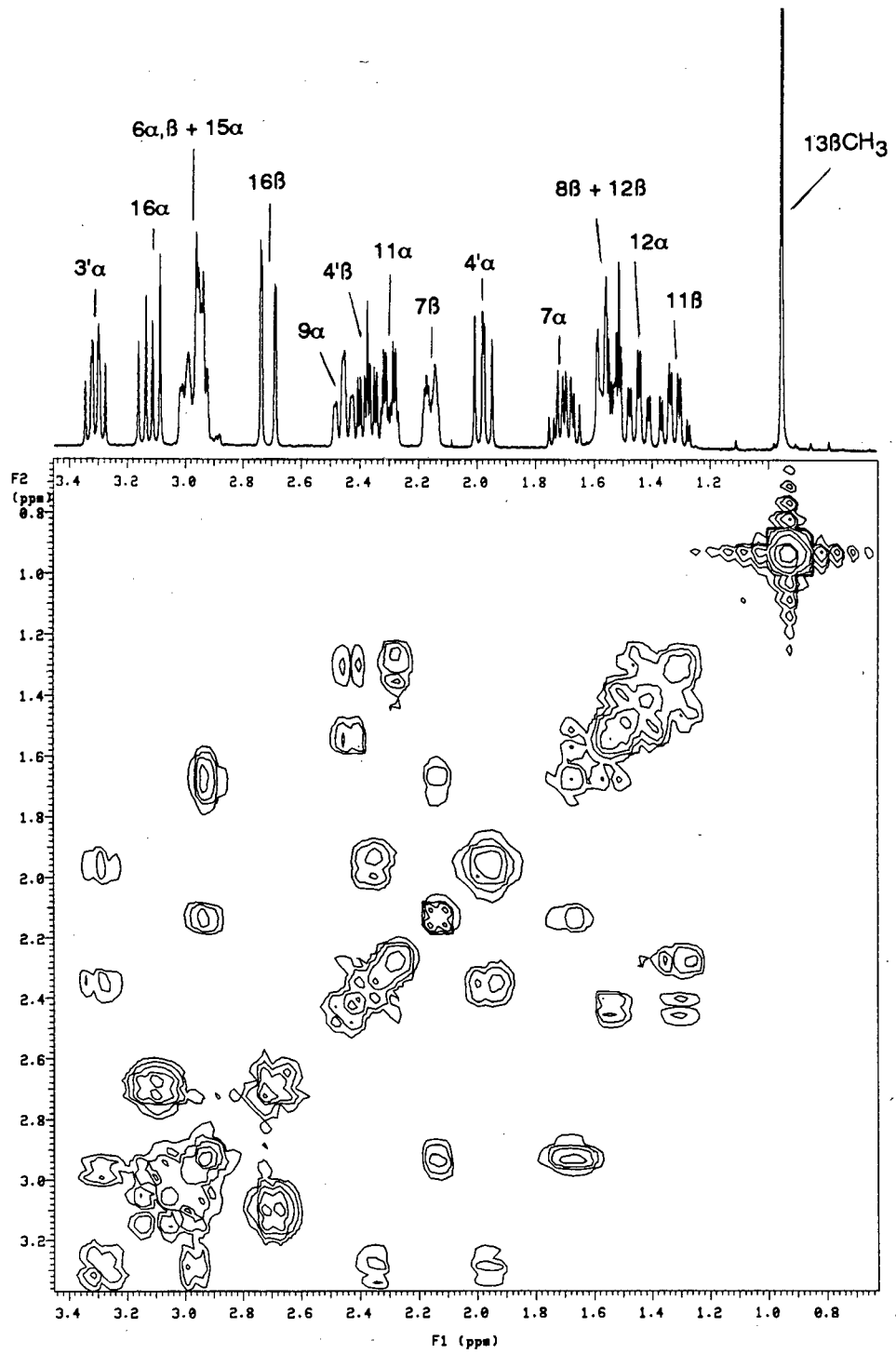


Figure 3.4.2-1: 400 MHz NMR spectrum (δ 3.4 - 0.7) and COSY plot of the 3'ß- carbonitrile (**175**)

Table 7: Couplings and assignments of the ring D and cyclobutano protons of the 3'ß-carbonitrile (**175**)

Proton	δ(ppm)	Mult.	*J*/Hz		
15α	2.98	m	-		
16α	3.13	dd	19.3	10.4	
16ß	2.72	dd	19.3	1.5	
3'α	3.31	ddd	9.5	9.5	7.9
4'α	1.98	dd	12.9	9.5	
4'ß	2.38	ddd	12.9	9.5	3.9

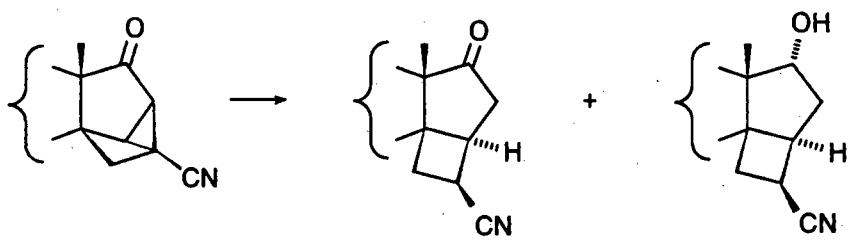
The key signals which supported the structural assignment were as follows: the 16α-and 16ß-H signals occur at δ 3.13 and 2.72 respectively and display the typically large coupling (*J* 19.3 Hz) for the geminal pair α to carbonyl group. Their respective assignments are evident from coupling with 15α-H. Inspection of a model reveals that 16α-H is practically eclipsed with 15α-H giving rise to a large vicinal coupling (*J* 10.4 Hz), whereas the torsion angle between 15α-H and 16ß-H is ≅ 90°, giving rise to a small vicinal coupling (*J* 1.5 Hz). Although the 15α-H signal was obscured by the signal for the 6α- and 6ß-protons, that at C(3') was downfield as expected for attachment to the CN-bearing carbon atom, and showed the expected couplings with the 4'-protons, and a large coupling (*J* 7.9 Hz) with 15α-H. This can more readily be accommodated by assignment as a 3'ß-cyano derivative, since the 3'α and 15α-protons are nearly eclipsed in this arrangement.

The origin of a long range coupling present in the 4'ß-proton multiplet was not evident from the model, and the assignment of configuration at C(3') must be regarded as tentative in the absence of the epimeric carbonitrile for comparison. However, it is noteworthy that other 3'-substituted compounds related to (**175**), but derived from a stereocontrolled opening of the C(16)-C(16^1) bond, displayed a different pattern of multiplets for the C(3')-H signal (see later).

It is reasonable to conclude that the reduction proceeded as planned, and that kinetically controlled protonation of the intermediate nitrile carbanion proceeded from the less hindered *exo* (i.e.α-) face to give the 3'ß-carbonitrile (**175**).

Attempts were made to reproduce the foregoing reduction of the cyano ketone (**82**) with lithium in liquid ammonia but this resulted in poor yields of the primary cleavage product (**175**) accompanied by larger amount of a product resulting from over-reduction. An experiment in which rapid addition of the cyano ketone (**82**) to a solution of lithium in liquid ammonia-tetrahydrofuran resulted in the temporary loss of the blue colour, gave rise to the compound (**175**) (4%) accompanied by a 51% yield of a product assigned as 17α-hydroxy-3-methoxy-dihydrocyclobuta[14,15]-14ß-estra-1,3,5(10)-triene-3'ß-carbonitrile (**176**), together with unidentified polar products.

SCHEME 3.4.2-7



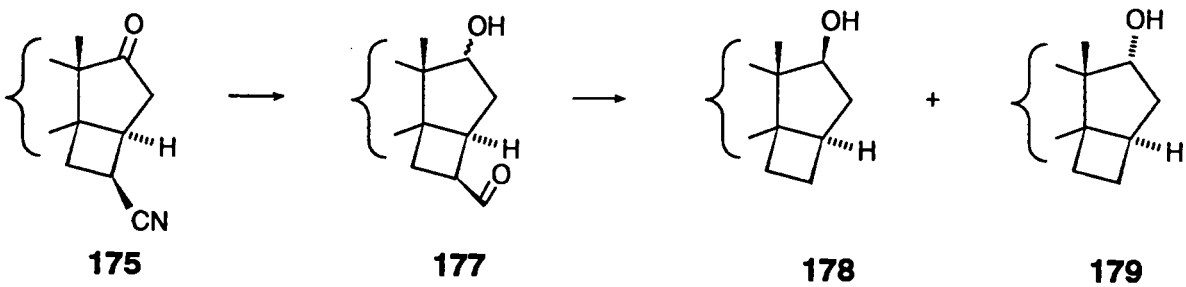
82 **175** **176**

The assignment at C(17) in the alcohol (**176**) was based upon an NMR signal at δ 4.40 (dd, *J* 10.5 and 7.2 Hz). A comparison with steroidal 14ß-methyl 17-alcohols[135] revealed that there is a distinctive difference between the 17-H signal of the 17α- and 17ß-alcohols. Although extrapolation to 14,15-cyclobutano systems is arguable, it provided a self-consistent basis for this assignment, which was further supported by subsequent reactions (see later).

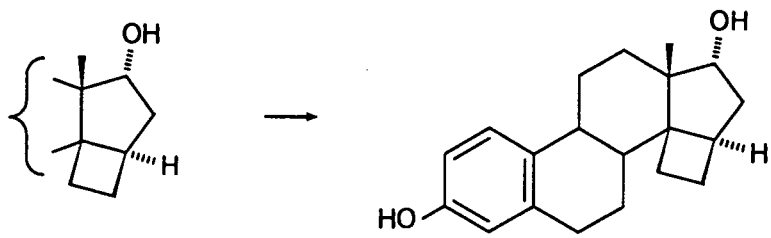
The successful regiospecific reduction of the C(16)-C(16[1]) bond provided the basis for a synthesis of 14,15-cyclobutano analogues of estradiol. Thus, treatment of the cyano ketone (**175**) in toluene with diisobutylaluminium hydride at -78°C gave rise to the

product mixture (**177**) (98%) derived from concomitant reduction at C(3') and C(17). This mixture of 17ξ–hydroxy 3'-carbaldehydes (**177**) in toluene was subjected to decarbonylation with $RhCl(PPh_3)_3$ at reflux for 7.5 h to give 3-methoxy-dihydrocyclobuta[14,15]-14ß-estra-1,3,5(10)-trien-17ß-ol (**178**) (8%) and the 17α-alcohol (**179**) (51%) (Scheme 3.4.2-8).

SCHEME 3.4.2-8



175 **177** **178** **179**



179 **180**

A comparison of the NMR spectra of the products revealed that the signal for 17α-H in the 17ß-alcohol (**178**) appeared as a one-proton doublet (*J* 5.8 Hz) at δ 3.81, whereas that of 17ß-H, in the 17α-alcohol (**179**), appeared as a one-proton triplet (*J* 2 x 8.8 Hz) at δ 4.28. These data were compared with those of 14ß-methyl 17-alcohols,[135] and the compatibility of the trends was taken as evidence in support of the assignments. Models of the respective alcohols (**178**) and (**179**) suggest that the favoured ring D conformation will result in torsion angles of ±20° and ±165° between 17ß-H and the 16-

protons in the 17α-alcohol (**179**), whereas the corresponding torsion angles between 17α-H and the 16-protons in the 17ß-alcohol (**178**) will be ±30° and ±90°.

Only the 17α-alcohol (**179**) was available in sufficient quantity for synthesis of the estradiol analogue (**180**). This was carried out by treatment of (**179**) in toluene with DIBAL at reflux for 66 h to give a 93% yield of dihydrocyclobuta[14,15]-14ß-estra-1,3,5(10)-triene-3,17α-diol (**180**), the analytical and spectroscopic properties of which were satisfactory. The product (**180**) was submitted for biological evaluation (see later).

Other approaches to selective cleavage of the cyclopropyl bonds in the cyano ketone (**82**) were also investigated. It is known that cyclopropyl rings can undergo metal catalysed hydrogenolysis.[136] However, attempted hydrogenolysis of (**82**) in ethyl acetate in the presence of palladium on carbon and hydrogen at 2.4 atm was unsuccessful.

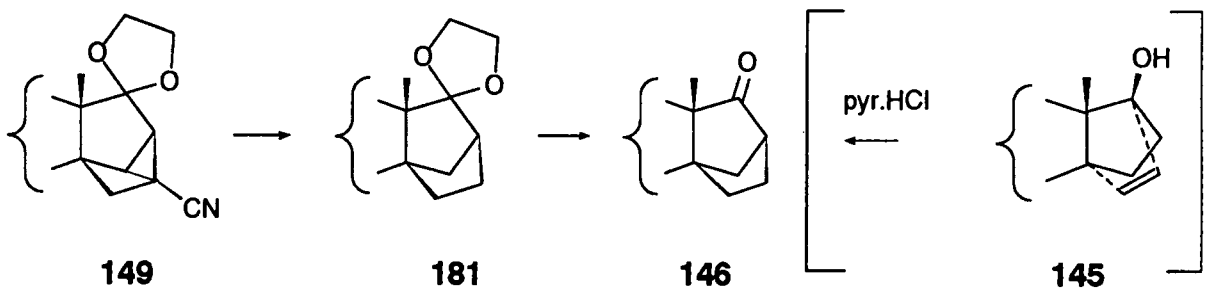
Similarly, attempts to induce acid-mediated rearrangements of the cyano ketone (**82**), through protonation at either or both of the functional groups failed. The starting material (**82**) was recovered unchanged after treatment with hydrogen chloride at 70°C, concentrated hydrochloric acid at 23°C, toluene-*p*-sulphonic acid at 100°C, $AlCl_3$ at room temperature and hydrogen bromide (48% in acetic acid) at 80°C.

An alternative approach to selective bond cleavage was undertaken *via* prior protection of the 17-oxo group. Thus, it was reasoned that dissolving metal reduction of the cyano ketal (**149**) might give rise to an alternative mode of α-bond cleavage, since the reaction would then entail addition of electrons to an α-cyclopropyl carbonitrile.

In the event, treatment of the ketal (**149**) with calcium in liquid ammonia gave an intractable, polar mixture. Although a similar reaction with lithium in liquid ammonia at -78°C for 4 min was also complex, it proved possible to isolate a less polar product in 25% yield. This product, 17,17-ethylenedioxy-3-methoxy-14,16ß-ethano-14ß-estra-1,3,5(10)-triene (**181**), showed the absence of a cyano group, and a molecular structure $C_{23}H_{30}O_3$, consistent with reductive cleavage of a C-C bond. Although spectroscopic examination failed to shed light on the structure, deprotection at C(17) afforded 3-methoxy-14,16ß-ethano-14ß-estra-1,3,5(10)-trien-17-one (**146**) (99%) which was

identified by comparison with authentic material prepared by acid-catalysed rearrangement of the 14α,17α-etheno 17-alcohol (**145**)[114] (Scheme 3.4.2-9).

SCHEME 3.4.2-9



149 **181** **146** **145**

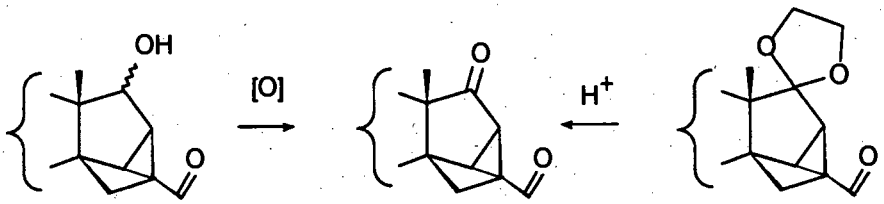
Formation of the product (**181**) suggests that, in the absence of potentiating functionality at C(17), the addition of electrons to the bridged cyano group proceeds with reductive cleavage of the cyclopropyl bond which is best aligned for orbital overlap with the cyano group. Models suggest that this is the C(15)-C(16^1) bond. It is evident however, that the primary product of bond cleavage must undergo reprotonation in order to achieve subsequent reductive decyanation. In the absence of an added proton donor under the reaction conditions used here, this is difficult to explain. Although ammonia is sufficiently acidic to protonate a simple carbanion, the basicity of the carbanion α to a nitrile is insufficient for this purpose. However, it is possible that the adventitious presence of a proton source may have accounted for the rather inefficient overall reaction to the observed product. Although the examination of reductants other than dissolving metals might be warranted in this case, further work was not carried out.

The availability of the 16^1-carbaldehydes (**150**), (**158**) and (**159**), obtained as intermediates in the preceding reactions, provided the opportunity to ascertain whether selective C(16)-C(16^1) bond cleavage would also be obtained for dissolving metal reduction of the derived 17-oxo 16^1-carbaldehyde (**182**).

Accordingly, the mixture of 17ξ-hydroxy 16^1-carbaldehydes (**158** and **159**), obtained from diisobutylaluminium hydride reduction of the cyano ketone (**82**), was

oxidised with pyridinium dichromate in dichloromethane to give (16^{1}R)-3-methoxy-17-oxo-15ß,16^1-cyclo-14,16ß-ethano-14ß-estra-1,3,5(10)-triene-16^1-carbaldehyde (**182**) in a 60% yield. A more efficient preparation of the 17-oxo 16^1-carbaldehyde (**182**) was *via* acid-mediated deprotection of the 17-ketal (**150**), which gave the desired product in 87% yield, accompanied by a small amount of an unidentified product.

SCHEME 3.4.2-10



158 + 159 **182** **150**

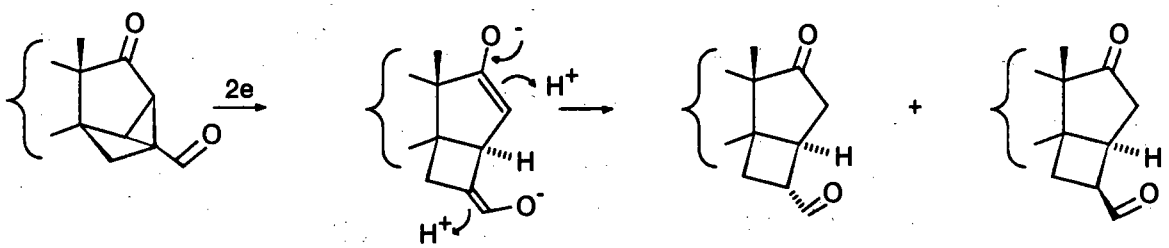
A 400 MHz NMR spectrum of the formyl ketone (**182**) displayed the features associated with the tricyclic ring D and shows close correspondence with the data for the corresponding cyano ketone (**82**). The assignments and couplings for the ring D protons of the formyl ketone (**182**) appear in Table 8.

Table 8: Assignments and couplings of the ring D protons of the formyl ketone (**182**)

δ(ppm)	Proton	Mult.	*J*/Hz	
3.39	15α	dd	15α,16α	4.5
2.89	16α	d	15α,16^2*Si*	2.4
2.79	16^2*Re*	d	16^2*Re*,16^2*Si*	11.0
1.37	16^2*Si*	dd		
8.97	16^1-CHO	s	-	

Treatment of the formyl ketone (**182**) with calcium in liquid ammonia, as described previously, gave a mixture of isomers, which was partially separable by chromatography. The minor isomer (*ca.* 7%) was assigned as 3-methoxy-17-oxo-dihydrocyclobuta[14,15]-14ß-estra-1,3,5(10)-triene-3'α-carbaldehyde (**183**) and the major isomer (*ca.* 42%) as the corresponding 3'ß-carbaldehyde (Scheme 3.4.2-11). The yields are estimates based upon the incomplete separation of (**183**) and (**184**) during chromatography, and the minor isomer could only be partially characterised owing to scarcity of material. However, the broad carbonyl absorption at ν_{max} 1725 cm^{-1} together with the NMR data were consistent with the proposed structure.

SCHEME 3.4.2-11



182 **182A** **183** **184**

The major isomer (**184**) exhibited infrared absorption at 1731 and 1710 cm^{-1} for the carbonyl groups, and a 400 MHz NMR spectrum provided compelling evidence for the structure. The assignments for the ring D protons of (**184**) are given in Table 9 and the ring D couplings of (**184**) are compared with those of the analogous 3'ß-carbonitrile (**185**) in Table 10. The NMR spectrum (δ 3.5 - 0.8) is shown in Figure 3.4.2-2 together with the COSY plot of this region.

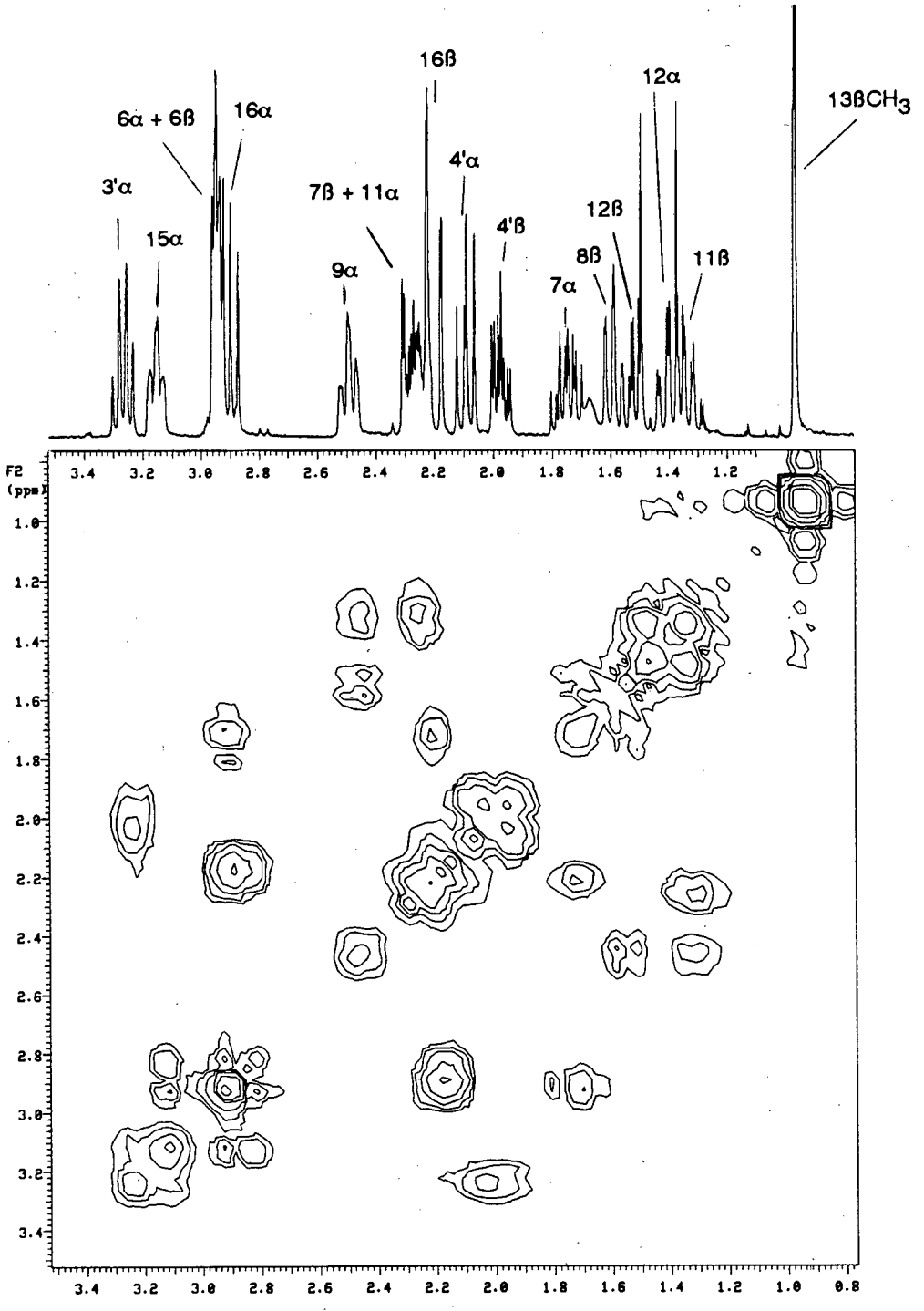


Figure 3.4.2-2: 400 MHz NMR spectrum (δ 3.5 - 0.8) and COSY plot of the 3'ß-carbaldehyde (**184**)

Table 9: Assignments and couplings for the ring D protons of the formyl ketone (**184**)

δ(ppm)	Proton	Mult.	*J*/Hz		
3.15	15α	br t	-		
2.91	16α	dd	19.4	10.3	
2.20	16ß	dd	19.4	1.7	
3.21	3'α	ddd	10.0	8.6	8.6
2.09	4'α	dd	13.0	10.0	
1.97	4'ß	ddd	13.0	8.6	3.8
9.67	3'α-CHO	d	0.8		

Table 10: Comparative couplings of the ring D protons of (**175**) and (**184**)

175		**184**	
16α,16ß	19.3	16α,16ß	19.4
15α,16α	10.4	15α,16α	10.3
15α,16ß	1.5	15α,16ß	1.7
3'α,4'α	9.5	3'α,4'α	10.0
3'α,4'ß	9.5	3'α,4'ß	8.6
3'α,15α	7.9	3'α,15α	8.6
4'α,4'ß	12.9	4'α,4'ß	13.0
4'ß,15α	3.9	4'ß,15α	3.8

Most notably, the multiplets assigned to the ring D fused cyclobutane ring protons showed close correspondence with those of the structurally similar 3'ß-cyano 17-ketone (**175**). The 15α-H signal can be identified as a broad triplet (*J ca.* 2 x 10.3 Hz, *W* 7.3 Hz) at δ 3.15, but the origin of the smaller coupling (*J* 3.8 Hz) exhibited by 4'ß-H is not clear from the COSY plot of (**184**).

It is thus evident that reduction of the carbaldehyde (**182**) proceeds similarly to that of the corresponding cyano ketone (**82**), although the protonation step of the intermediate bis enolate (**182A**) appears to be less stereoselective than that of the corresponding intermediate in the reduction of (**82**).

The rather disappointing yield obtained with calcium-ammonia reduction of the formyl ketone (**182**) prompted an examination of alternative approaches. However, lithium-ammonia reduction was much less efficient, giving rise to only 22% of the oxo carbaldehydes (**183**) and (**184**) together with products of over-reduction which were not characterised. Similarly, attempted zinc-acetic acid reduction of (**182**) was inefficient since no reaction occurred at 20°C, but an intractable mixture resulted at reflux temperature.

In order to complete the study of all the possible functional group variants, and their influence upon selective bond cleavage of the 15ß,16^1-cyclo 14ß,16ß-ethano ring system, it remained to study the reactions of the ring D tricyclic 17-ketone (**152**). In this instance, the absence of the 16^1-cyano group would give an indication of which of the cyclopropyl bonds α to the 17-oxo group, i.e. C(16)-C(16^1) or C(15)-C(16), was susceptible to cleavage under conditions of dissolving metal reduction.

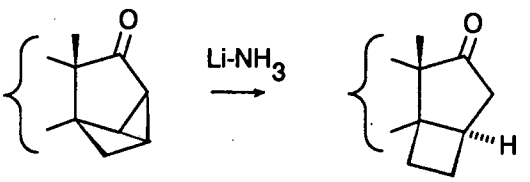
In the case of the ketone (**152**), it was possible to draw analogy with previous work carried out on the dissolving metal reductions of α-cyclopropyl ketones.[137] In general, it has been concluded that the overall reaction involves the addition of two electrons by the metal with concomitant opening of one of the two cyclopropyl bonds conjugated with an adjacent π-centre. This is then followed by protonation of the resultant $^{\gamma}$-removed carbanion (probably by ammonia), and ketonisation upon addition of a proton source.

Reductive ring cleavage is promoted by ring strain and product stability. Where the two cyclopropyl bonds are non-equivalent, preferential cleavage of one of the two conjugated cyclopropyl bonds occurs. Norin,[138] has suggested that the regioselectivity obtained in these reactions results from cleavage of the cyclopropane bond which possesses maximum overlap with the π-orbital of the carbonyl group. Additional factors,[139] such as steric and electronic effects of substituent groups, substitution of the

cyclopropyl bonds adjacent to the carbonyl group, stabilisation of the transition state by delocalisation of charge, (in)stability of the activated complex, etc. have been proposed to play a role in the determination of the product.

Treatment of the ketone (**152**) with lithium-ammonia-tetrahydrofuran at -78°C proceeded smoothly to give the 14,15-cyclobutano 17-ketone (**185**) in 84% yield. The structure of (**185**) was evident from infrared absorption at ν_{max} 1725 cm^{-1}, and the appearance in the NMR spectrum of signals at δ 2.13 (dd, *J* 19.0 and 1.8 Hz) and 3.10 (dd, *J* 19.0 and 10.2 Hz) for the 16ß- and 16α-protons respectively. Thus both signals corresponded closely to those of the 16-protons in related systems. The ketone was also correlated with the 14,15-cyclobutano 17-alcohols (**178**) and (**179**) obtained by an independent route. Thus, a small scale reduction of (**185**) furnished the corresponding 17-alcohols. An analogous reaction on (**152**), carried out with calcium-ammonia, gave the 14,15-cyclobutano 17-ketone (**185**) in 74% yield.

SCHEME 3.4.2-12



152 **185**

Since the ketone (**152**) represents a skeletally novel analogue of estrone 3-methyl ether, it was considered important to obtain detailed structural information for the purpose of suppporting structure-activity studies in this series. Accordingly, an X-ray crystal structure determination was carried out on (**185**). The atomic numbering and a perspective view of the molecule is shown in Figure 3.4.2-3.

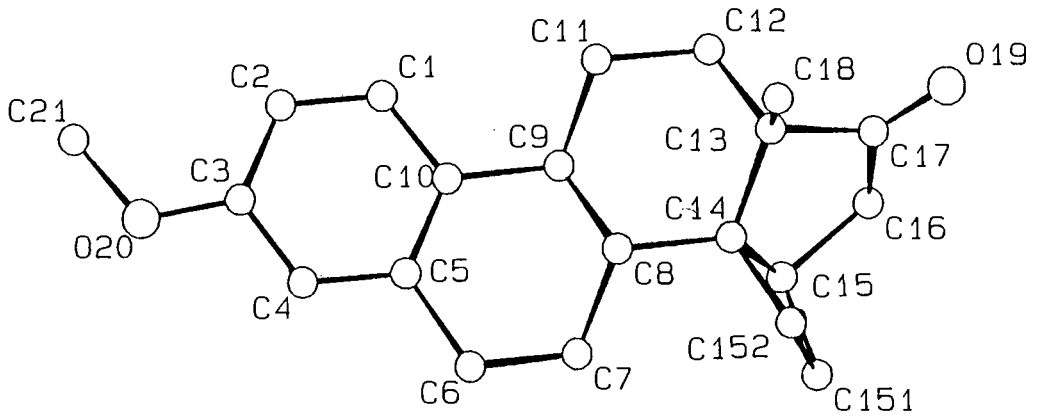


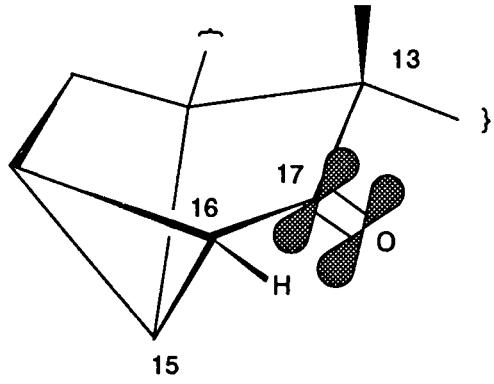
Figure 3.4.2-3: Perspective view of the dihydrocyclobuta[14,15] 17-ketone (**185**) with its atomic labelling

The final fractional atomic coordinates and equivalent isotropic parameters are given in Table 4.3-4 (see Section 4). The geometrical parameters for rings A, B and C are comparable to those determined for (**82**). Ring A does not deviate significantly from planarity. For this ring, the C-C distances and internal C-C-C angles are in the ranges 1.37(7) - 1.40(7)Å and 119.3(4) - 122.5 (4)° respectively. For rings B and C the C-C distances and internal C-C-C angles (excluding the A-B linkage) are 1.51(7) - 1.54(7)Å and 108.4(3) - 114.8(3)° respectively. Ring B adopts a half-chair conformation whereas ring C adopts a chair conformation. The bond lengths associated with the bridged ring D [1.51(5) - 1.58(5)Å] display no abnormalities. The internal bond angles in ring D

[102.6(3) - 108.7(3)°] and in the cyclobutyl [87.2(3) - 90.1(3)°] ring are similar to those determined for (**82**) and (**152**). The C(17)-C(13)-C(14)-C(15) torsion angle of -27.1(4)° suggests that ring D of (**185**) experiences more flattening than those of (**82**) and (**152**), as a consequence of the cleavage of the cyclopropyl bond. Ring D adopts a conformation between that of an envelope and a half-chair.

Thus, the structure determination confirmed all the expected conformational properties of the system. The regiospecificity of the dissolving metal reduction is in accordance with expectations based on the work of Norin.[138] From a model it is clear that the C(16)-C(16^1) bond of the cyclopropyl ring is closer to colinearity, and therefore shows better orbital overlap, with the π-orbitals of the 17-carbonyl group than the C(15)-C(16) bond (Figure 3.4.2-4).

Figure 3.4.2-4



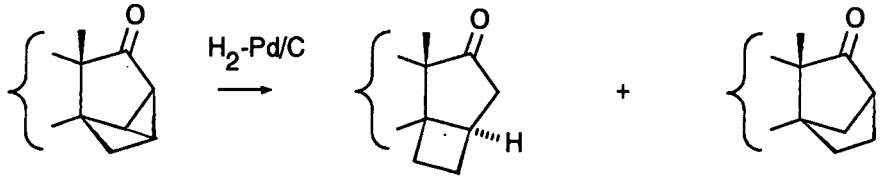
152

Although the foregoing experiment demonstrated that the C(16)-C(16^1) bond in the ketone (**152**) is the stereoelectronically favoured one for reductive cleavage by dissolving metals, it is less evident which of C(15)-C(16), C(16)-C(16^1) or C(15)-C(16^1) would be sterically more accessible to catalytic hydrogenation. In general, hydrogenolysis of cyclopropane derivatives occurs by preferential cleavage of the bond between the two least substituted carbon atoms.[136] If, however, the geometry of the

reactant is such that one bond of the ring is more strained than the other two, hydrogenolysis tends to occur in that bond regardless of alkyl substituents.[129]

Catalytic hydrogenation of the ketone (**152**) in ethyl acetate, in the presence of palladium on carbon and hydrogen at atmospheric pressure at 23°C over 75 h gave, 3-methoxy-dihydrocyclobuta[14,15]-14ß-estra-1,3,5(10)-trien-17-one (**185**) (25%) and the 14ß,16ß-ethano 17-ketone (**146**) (39%). The products were identified by comparison with authentic samples.

SCHEME 3.4.2-13



152 **185** **146**

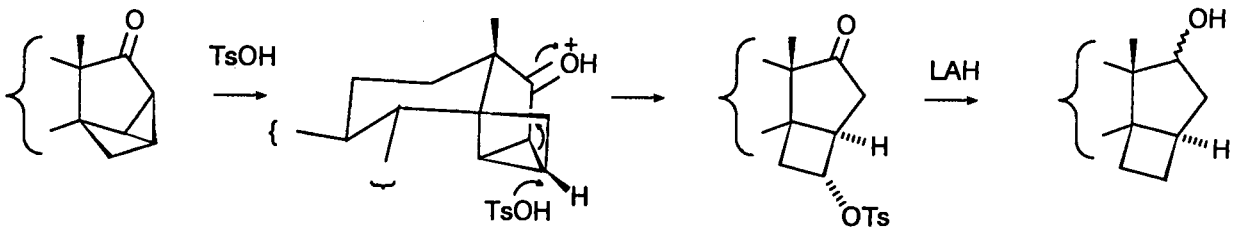
Although the difference in regioselectivity manifested in this reaction is relatively small, it is possible to infer that the slight preponderance of the 14ß,16ß-ethano product (**146**) is associated with greater relief of steric strain in breaking the C(15)-C(16^1) bond than the C(16)-C(16^1) bond. Alternatively, approach of the convex *exo*-face of the tricyclic system in (**152**) to the catalyst surface may be sterically slightly more favoured. The absence of a product arising from C(15)-C(16) bond cleavage suggests that ring C hinders access to this bond.

The reactivity of the ring D tricyclic ketone (**152**) toward acid reagents was also investigated since it was reasoned that protonation of the carbonyl group might initiate α-bond migration leading to rearrangement products.

Initial experiments in which the ketone (**152**) was treated with Lewis acids ($BF_3.OEt_2$ and $AlCl_3$) failed to give any reaction. However, when the ketone (**152**) was refluxed in benzene with toluene-*p*-sulphonic acid for prolonged periods a single product (69%) was isolated. That this reaction was not catalytic was demonstated when

spectroscopic examination revealed that the elements of toluene-*p*-sulphonic acid had been added to (**152**), and the product was formulated as 3-methoxy-3'α-toluene-*p*-sulphonyloxy-dihydrocyclobuta[14,15]-14ß-estra-1,3,5(10)-trien-17-one (**186**).

SCHEME 3.4.2-14

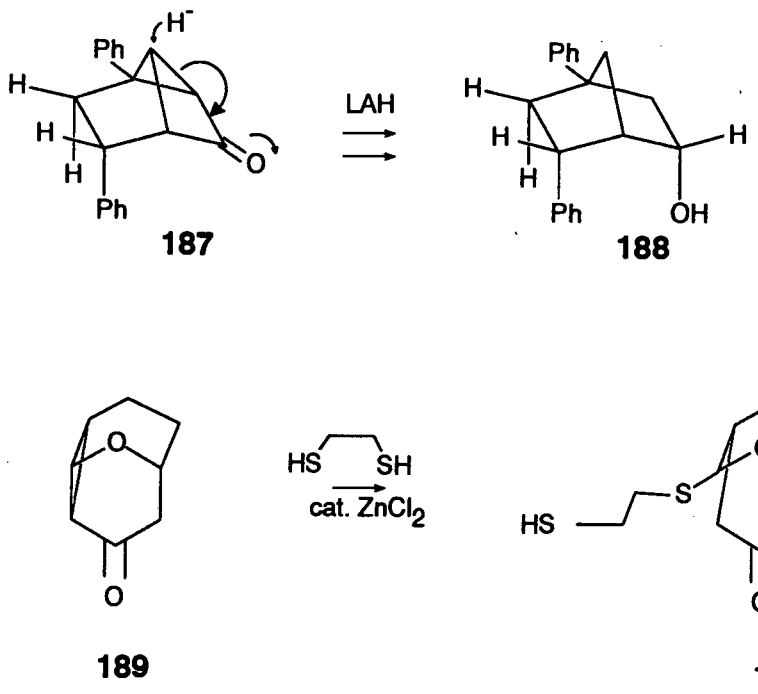


152 **152A** **186** **178 + 179**

In addition to the typical signals for the tosyl group, the NMR spectrum exhibited few identifiable signals. The signal for 3'ß-H appeared downfield at δ 4.22 (br ddd, *J ca.* 7.5, 2.6 and 1.3 Hz) as expected for attachment to a tosyloxy-bearing carbon atom. The signals for 16α- and 16ß-H resembled those observed in related compounds. Thus, 16α-H appeared as a double doublet at δ 3.07 (*J* 18.1 and 10.9 Hz) and 16ß-H as a doublet at δ 2.03 (*J* 18.1 Hz). On the basis of the couplings of 3'ß-H we concluded that the configuration at C(3') differed from that of the 3'ß-carbonitrile (**175**) obtained from calcium-ammonia reduction of the ring D tricyclic precursor (**82**). Further support for the configurational assignment of a 3'α-tosyloxy group was obtained from a compound (**191**) synthesised later. On the basis of the foregoing evidence it was concluded that addition of the tosyloxy group occurred stereoselectively at C(16^1) of the protonated tricyclic ketone (**152A**) (Scheme 3.4.2-14). The formal reaction outcome is thus a 1,5-addition product (**186**). It was confirmed that addition had occurred at C(16^1), leading to C(16^1)-C(16) cleavage, and not at C(15), resulting in C(15)-C(16) cleavage, by treatment of the 3'α-tosyloxy 17-ketone (**186**) with lithium aluminium hydride in benzene at *ca.* 80°C, which resulted in the formation of the desulphonylated 17-alcohols

Since cyclopropane rings resemble double bonds they may undergo analogous addition reactions.[140] In addition, the torsional strain in a cyclopropyl ring imparts a high degree of reactivity, which can lead to fragmentation.[141] Monoactivated cyclopropanes found in ring systems which render them particularly strained can be opened by nucleophilic attack (even in the absence of potentiating protic or Lewis acids).[142] Treatment of the tricyclic compound (**187**) in tetrahydrofuran with lithium aluminium hydride at reflux affords the product (**188**)[143] where the cyclopropyl ring is cleaved and the carbonyl group is reduced. In the presence of an acid catalyst and 1,2-ethanedithiol (**189**) affords the ketone (**190**)[141] (Scheme 3.4.2-15).

SCHEME 3.4.2-15



187 **188**

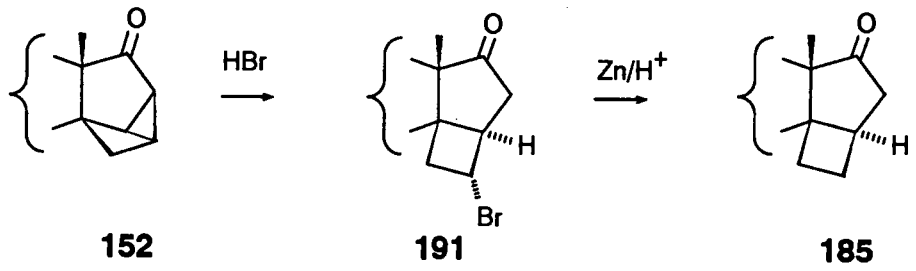
189 **190**

The cyclopropyl bond which is cleaved is the one best situated for overlap with the carbonyl group.[142] If this position is hindered to nucleophilic attack, the other cyclopropyl bond which is in conjugation will be cleaved.[144] Our results are thus in accord with expectations. From the metal-ammonia reductions of the ketone (**152**) we know that C(16[1])-C(16) is the cyclopropyl bond most favourably situated for

conjugation with the 17-carbonyl group. In addition, C(16[1]) is more accessible to nucleophilic attack than C(15) which further promotes attack at this position.

The ketone (**152**) in benzene underwent a similar reaction in the presence of hydrogen bromide in acetic acid, at reflux to give the corresponding 3'α-bromo 17-ketone (**191**) (66 %) (Scheme 3.4.2-16). Although the reaction proceeded slowly but uneventfully up to about 65% conversion, it proved impossible to force it to a conclusion despite prolonged treatment with excess reagent.

SCHEME 3.4.2-16



152 **191** **185**

The structure of the 3'α-bromo 17-ketone (**191**) followed from NMR data which showed satisfactory correspondence with that of the corresponding 3'α-tosyloxy 17-ketone (**186**), thereby establishing the configuration at C(3') and also providing evidence for a similar mechanism of formation. Although the spectral resolution was good, numerous signals were non first-order and could not be assigned with certainty. However, the 3'ß-H signal was well resolved and appeared downfield at δ 2.93 (ddd, *J* 9.0, 4.5 and 2.4 Hz). The couplings of the 3'-protons support the configurational assignments at this position for the compounds (**175**) (**184**), (**186**) and (**191**) (Table 11). Thus, the 3'α-H signal of the compounds (**175**) and (**184**), arising from calcium-ammonia reduction of the corresponding tricyclic compounds, exhibits three large couplings whereas 3'ß-H of the compounds (**186**) and (**191**), arising from nucleophilic addition to the ketone (**152**), exhibits three coupling of varying magnitude.

Table 11: NMR Data for the 3'-protons of the compounds (**175**), (**184**), (**186**) and (**191**)

Compd.	Assignment	δ(ppm)	Couplings (*J*/Hz)		
175	3'α-H	3.31	9.9	9.5	7.9
184	3'α-H	3.21	10.0	8.6	8.6
186	3'ß-H	4.22	7.5	2.6	1.3
191	3'ß-H	3.93	9.0	4.5	2.4

Reductive debromination of (**191**) with zinc in acetic acid proceeded slowly but cleanly to give the parent 17-ketone (**185**), identified by comparison with an authentic sample of (**185**).

3.5 Binding Studies

This work has led to the synthesis of novel ring D bridged steroids. In addition, three estradiol analogues were synthesised and pathways to further estradiol and estriol analogues were established. The estradiol analogues (**160**), (**161**) and (**180**) (Scheme 3.4.2-17) were submitted for receptor-binding assay. Receptor binding assay plays an important role in studies on structure-activity relations of hormones.[2] The principle goal of such work is the development of active compounds superior to the native hormone. This may be manifested by higher activity or greater differentiation of activities, as well as oral activities.

The affinities the estradiol analogues (**160**), (**161**), and (**180**) were determined by the method of competitive binding. The affinity of the hormone analogue for the receptor is measured in terms of the 'competition factor' (CF) which is defined as the ratio of the concentration of the test sample (c_{test}) and that of the reference substance (c_{ref}) required for 50% competition.[2]

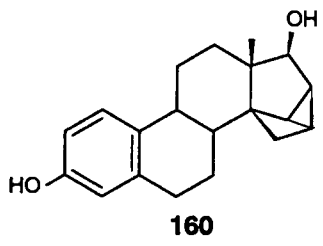
$$CF = \frac{c_{test} \text{ at } 50\% \text{ competition}}{c_{ref} \text{ at } 50\% \text{ competition}}$$

Estradiol is taken as the reference substance and therefore has a CF value of unity. Hormone analogues with competition factors in the region of unity are regarded as highly competitive whereas analogues with competition factors of less than unity are potentially more active than estradiol. The competition factors of the estradiol analogues (**160**), (**161**) and (**180**) are given in Table 12. The analogues (**160**) and (**180**) exhibit high affinity for the hormone receptor whereas the affinity of the analogue (**161**) for the hormone receptor is rather poor.

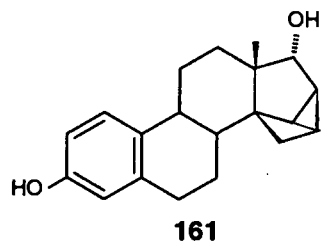
Table 12: Competition Factors of the Estradiol Analogues (**160**), (**161**) and (**180**)

Compound no.	Competition Factor
160	2.5
161	6.5
180	2.0

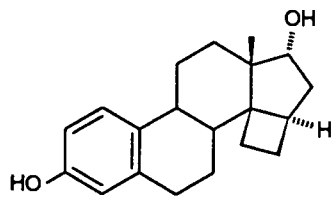
SCHEME 3.5-1



160



161



180

4. EXPERIMENTAL

4.1 General

All melting points were determined on a Reichert hot-stage apparatus and are uncorrected.

Specific rotations ($[\alpha]_D$) were determined in chloroform, unless otherwise specified, using a Perkin-Elmer 141 polarimeter and are recorded in units of 10^{-1} deg cm^2 g^{-1}.

Infrared spectra were recorded in chloroform using a Perkin-Elmer 983 spectrophotometer. The following abbreviations were used: br, broad band.

Proton nuclear magnetic resonance (^1H nmr) spectra were recorded on a Varian VXR-200 (4.7 T), Varian Unity (9.4 T) and Bruker WM 500 (11.7 T), for solutions in deuteriochloroform, unless otherwise specified. Tetramethylsilane (TMS) was used as internal standard. The chemical shifts (δ) are given in ppm relative to TMS (δ 0.00).

Carbon-13 nuclear magnetic resonance spectra were recorded on a Varian VXR-200, 50 MHz spectrometer, a Varian Unity, 100 MHz spectrometer or a Bruker WM 500, 125 MHz spectrometer for solutions in deuteriochloroform. The chemical shifts (δ) are given in ppm relative to the TMS signal which is centred at δ 0.00.

The following abbreviations have been used in the ^1H and ^{13}C nmr spectra: s, singlet; d, doublet; dd, double doublet; ddd, doublet of doublet of doublets; t, triplet; q, quartet; m, multiplet; qd, quartet of doublets; dt, doublet of triplets; td, triplet of doublets; ddt, doublet of doublet of triplets; br, broad; obsc., obscured; exch., exchange, $W_{\frac{1}{2}}$, peak width at half height and J, coupling constant.

Elemental analyses were performed using a Heraues CHN-rapid combustion analyser.

Mass spectra were recorded on a VG micromass 16F mass spectrometer (operating at 70 eV with an accelerating voltage of 4 kV).

All reactions were monitored by thin-layer chromatography (tlc) using Merck F_{254} precoated silica gel plates. Detection was done using an ultra-violet lamp (wavelength 254 nm) and by heating the plate at 200°C after spraying with a 1% solution of cerium sulphate in 3M sulphuric acid.

Column chromatography was carried out on silica gel (Kieselgel 60, Merck). The amount of silica gel and the eluent mixture used are specified in each experiment.

Commonly used solvents were purified as described below.

Tetrahydrofuran: Dried over sodium wire and then distilled from sodium and benzophenone under an argon atmosphere immediately before use.

Benzene, toluene and xylene: Distilled from sodium wire and stored over sodium wire.

Triethylamine and pyridine: Distilled from potassium hydroxide and stored over potassium hydroxide pellets.

Ether: Distilled from sodium wire immediately prior to use.

Concentration of the organic phase under reduced pressure refers to removal of the solvent under reduced pressure on a Büchi Rotary Evaporator.

3-*Methoxyestra*-1,3,5(10),14,16-*pentaen*-17-*yl Acetate* (**29**)

(a) Copper(II) bromide (40 g; 179 mmol) was added to a warm solution of estrone 3-methyl ether (**63**) (20 g; 70.3 mmol) in benzene (160 ml) and methanol (160 ml) and the mixture was heated under reflux for 1 h. The mixture was filtered hot and the filtrate was poured into a mixture of chloroform (1000 ml) and water (1000 ml). The mixture was shaken vigorously and refiltered through a Celite pad. The organic layer was washed with water (2 x 570 ml) and brine (570 ml), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude bromide (**64**) (26.4 g) as a crystalline residue.

A deoxygenated solution of the crude bromide (**64**) (26.4 g), lithium bromide (45 g) and lithium carbonate (40 g) in dry *N,N*-dimethylformamide (250 ml) was heated under reflux under nitrogen for 4 h. The solution was cooled, poured into a mixture of acetic acid (250 ml) and water (1200 ml), and the product was extracted with ether (4 x 450 ml). The extract was washed with sodium hydrogen carbonate solution (4 x 450 ml) and brine (450 ml), dried over $MgSO_4$ and evaporated under reduced pressure to give the crude product (20.2 g), comprising a mixture of the Δ^{14}-17-ketone (**65**) and the 14ß-H-Δ^{15}-17-ketone (**66**), as a dark red gum.

A solution of the crude enones (**65** + **66**) (20.2 g) and toluene-*p*-sulphonic acid monohydrate (8.2 g) in acetic anhydride (210 ml) and isopropenyl acetate (210 ml) was heated under reflux for 4 h. The cooled solution was poured into ice and water and stirred for 2 h while liberated acetic acid was neutralised with solid sodium hydrogen carbonate. Water was added and the aqueous phase was extracted with ether (4 x 450 ml). The extract was dried ($MgSO_4$) and evaporated to give a dark red oil (21 g). Chromatography of the product (21 g) on silica gel (520 g), with toluene as eluent, gave the dienyl acetate (**29**) (14.1 g; 61%), m.p. 123-125°C (lit.,[72] m.p. 123-125°C) identical to an authentic sample.

(b) A solution of estrone 3-methyl ether (**63**) (200 mg; 0.71 mmol) in tetrahydrofuran (7.5 ml) was added slowly to lithium diisopropylamide [generated *in situ* from diisopropylamine (0.3 ml; 2.1 mmol) and *n*-butyllithium (15% in benzene, 0.6

ml; 1.0 mmol) in tetrahydrofuran (3 ml)] under nitrogen at 0°C. After 10 min at 0°C trichloromethylsilane (0.45 ml; 3.5 mmol) was added and after an additional 1 h the mixture was evaporated under reduced pressure. The residue (210 mg) was adsorbed onto coarse silica gel (1g). Flash chromatography of this mixture on silica gel (10 g), with ethyl acetate-hexane (1:3) as eluent, gave the enol silyl ether (**67**) (193 mg; 77%).

A solution of the enol silyl ether (**67**) (193 mg; 0.54 mmol) in acetonitrile (1 ml) was added to a solution of palladium(II) acetate (60 mg; 0.27 mmol) and *p*-benzoquinone (30 mg; 0.27 mmol) in acetonitrile (10 ml) at 18°C under nitrogen. After 1 h, the reaction mixture was warmed to 50°C and, after a further 3 h water, was added and the reaction mixture was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The product (182 mg) was chromatographed on silica gel (18 g), with ethyl acetate-toluene (1:9) as eluent, to give an unidentified product (46 mg) followed by the Δ^{15}-17-ketone (**68**) (83 mg; 55%) identical to an authentic sample of (**68**), m.p. 179-180°C (lit.,[76] 180-181°C).
The Δ^{15}-17-ketone (**68**) (83 mg; 0.29 mmol) in isopropenyl acetate (1.5 ml) was treated with acetic anhydride (1.5 ml) and catalytic toluene-*p*-sulphonic acid and heated under reflux. After 5 h at reflux aqueous sodium hydrogen carbonate was added and the reaction mixture was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The product (97 mg) was chromatographed on silica gel (9 g), with toluene as eluent, to give the dienyl acetate (**29**) (56 mg; 60%), identical to material obtained in the foregoing experiment.

Cycloaddition of 3-*Methoxyestra*-1,3,5(10),14,16-*pentaen*-17-*yl Acetate* (**29**) with 2-*Chloroacrylonitrile*

(a) A solution of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**29**) (10 g; 30.9 mmol) and 2-chloroacrylonitrile (7.5 ml; 93.9 mmol) in anhydrous benzene (40 ml) was maintained at 90°C in a sealed tube. Two further aliquots of 2-chloroacrylonitrile (each 0.5 ml; 6.3 mmol) were added after 68 and 92 h. After 114 h the reaction mixture

was filtered through Celite and evaporated under reduced pressure. Crystallisation of the residue (12 g), from chloroform-methanol, gave 17ß-*acetoxy*-16ß-*chloro*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16α-*carbonitrile* (**71**) (8.17 g; 64%), m.p. 182-185°C; $[\alpha]_D$ +130° (*c* 0.6); ν_{max} 2242 (CN), 1749 (CO), and 716 (CCl) cm^{-1}; δ_H (200 MHz) 1.21 (3H, s, 13ß-Me), 2.02 (1H, d, *J* 13.7 Hz, 15α-H), 2.24 (3H, s, 17ß-OAc), 2.55 (1H, m, 9α-H), 2.75 (1H, d, *J* 13.7 Hz, 15ß-H), 2.88 (2H, m, 6α- and 6ß-H), 3.77 (3H, s, 3-OMe), 6.27 and 6.44 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.19 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 169.2 (17-O*C*OCH$_3$), 157.6 (C-3), 137.3 (C-5), 133.6 and 132.8 (C-17^1 and C-17^2), 131.3 (C-10), 127.0 (C-1), 118.4 (16-CN), 113.7 (C-4), 112.0 (C-2), 98.2 (C-17), 62.3, 62.0 and 56.7 (C-13, C-14 and C-16), 55.2 (3-OMe), 46.5 (C-15), 39.4 (C-9), 38.6 (C-8), 31.0, 26.7 and 23.8 (C-7, C-11 and C-12), 29.8 (C-6), 21.3 (17-OCO*C*H$_3$), and 15.7 (C-18)(Found: C, 70.1; H, 6.6; N, 3.4%; M^+, 412. $C_{24}H_{26}ClNO_3$ requires C, 70.0; H, 6.4; N, 3.4%; *M*, 411).

Chromatography of the mother liquor residue (4 g) on silica gel (200 g), with toluene as eluent, gave the dienyl acetate (**29**) (0.25 g; 2.5%), a mixed fraction of the cycloadducts (**71** and **72**) (2.45 g; 19%), 3-methoxyestra-1,3,5(10),14-tetraen-17-one (**65**) (0.08 g; 1%), m.p. 98-103°C (from chloroform-methanol)(lit.,[76] 103-104°C) followed by 3-methoxy-14ß-estra-1,3,5(10),15-tetraen-17-one (**66**) (0.8 g; 9%), m.p. 92-97°C (from chloroform-hexane)(lit.,[76] 101-102°C).

Recrystallisation of the mixed fraction gave further cycloadduct (**71**) (1.9 g; 15%). Chromatography of the mother liquor residue (0.5 g) on silica gel (100 g), with toluene as eluent, gave 17ß-*acetoxy*-15ß-*chloro*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-15α-*carbonitrile* (**72**) (0.27 g; 2%), m.p. 162-164°C (from chloroform-methanol); $[\alpha]_D$ +73° (*c* 1.0); ν_{max} 2220 (CN) and 1742 (CO) cm^{-1}; δ (200 MHz) 1.26 (3H, s, 13ß-Me), 1.72 (1H, m, 7α-H), 2.12 (3H, s, 17ß-OAc), 2.60 (1H, m, 9α-H), 2.81 (1H, d, *J* 13.7 Hz, 16α-H), 2.92 (2H, m, 6α- and 6ß-H), 3.04 (1H, d, *J* 13.7 Hz, 16ß-H), 3.78 (3H, s, 3-OMe), 6.19 and 6.55 (each 1H, d, *J* 6.1 Hz, 17^1- and 17^2-H), 6.65 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.20 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz)

170.5 (17-$OCOCH_3$), 157.8 (C-3), 137.6 (C-5), 136.1 and 132.5 (C-17^1 and C-17^2), 131.0 (C-10), 127.5 (C-1), 118.3 (15-CN), 113.8 (C-4), 112.0 (C-2), 91.3 (C-17), 63.5, 62.0 and 60.2 (C-13, C-14 and C-15), 55.3 (3-OMe), 49.2 (C-16), 40.0 (C-9), 38.0 (C-8), 31.1, 27.1 and 24.0 (C-7, C-11 and C-12), 30.0 (C-6), 21.2 (17-$OCOCH_3$), and 16.3 (C-18)(Found: C, 69.6; H, 6.2; N, 3.3%; M^+, 412. $C_{24}H_{26}ClNO_3$ requires C, 70.0; H, 6.4; N, 3.4; *M*, 411) followed by further cycloadduct (**71**) (0.20 g; 1.6%).

(b) A solution of the dienyl acetate (**29**) (0.5 g; 1.5 mmol) and 2-chloroacrylonitrile (0.37 ml; 4.6 mmol) (freshly distilled from potassium hydroxide) in benzene was heated at 100°C in a sealed tube under a nitrogen atmosphere. After 120 h the reaction mixture was evaporated under reduced pressure.

Chromatography of the product (660 mg) on silica gel (50 g), with toluene as eluent, gave a mixture of the cycloadducts (**71** and **72**) (584 mg; 92%).

Synthesis and Cycloaddition of 3-*Methoxy-17-trimethylsilyloxyestra*-1,3,5(10),14,16-*pentaene* (**62**)

A solution of 3-methoxyestra-1,3,5(10),14-tetraen-17-one (**65**) (100 mg; 0.36 mmol) in tetrahydrofuran (3 ml) was added, over 8 min, to lithium diisopropylamide [generated *in situ* from *n*-butyllithium (1.6M solution in hexanes; 1.1 ml; 1.76 mmol) and diisopropylamine (0.52 ml; 3.6 mmol) in tetrahydrofuran (10 ml) at 0°C] at -78°C. Two aliquots of trimethylchlorosilane (each 0.2 ml; 1.58 mmol) were added after 30 and 60 min at -78°C. After 100 min at -78°C, aqueous ammonium chloride was added. The reaction mixture was extracted with chloroform, and the extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give 3-methoxy-17-trimethylsilyloxyestra-1,3,5(10),14,16-pentaene (**62**) (100 mg; 80%) as an oil; δ (200 MHz) 0.25 (9H, s, 17-$OSiMe_3$), 1.04 (3H, s, 13ß-Me), 2.93 (2H, m, 6α- and 6ß-H), 3.78 (3H, s, 3-OMe), 5.18 (1H, d, *J* 2.3 Hz, 16-H), 5.77 (1H, m, *W* 4.4 Hz, 15-H), 6.67 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H), and 7.23 (1H, d, *J* 8.5 Hz, 1-

H)(Found: M^+, 354. $C_{22}H_{30}O_2Si$ requires M, 354). The reaction product was used directly in the next experiment.

The reaction product (**62**) (100 mg), 2-chloroacrylonitrile (0.086 ml; 1.08 mmol) and hydroquinone (20 mg) in anhydrous benzene (1.5 ml) were heated in a sealed tube under a nitrogen atmosphere at 80°C. After 94 h the reaction mixture was filtered through Celite and evaporated under reduced pressure.

Flash chromatography of the product (130 mg) on silica gel (10 g), with toluene as eluent, gave 16ß-chloro-3-methoxy-17ß-trimethylsilyloxy-14,17α-ethenoestra-1,3,5(10)-triene-16α-carbonitrile (**77**) (80 mg; 51%) as an oil; $[\alpha]_D$ +118° (*c* 5.7); ν_{max} 2240 (CN) cm^{-1}; δ (200 MHz) 0.26 (9H, s, 17ß-$OSiMe_3$), 1.16 (3H, d, *J* 0.7 Hz, 13ß-Me), 1.99 (1H, d, *J* 13.8 Hz, 15α-H), 2.23 (1H, m, 11α-H), 2.50 (1H, m, 9α-H), 2.74 (1H, d, 13.8 Hz, 15ß-H), 2.86 (2H, m, 6α- and 6ß-H), 3.78 (3H, s, 3-OMe), 6.17 and 6.27 (each 1H, d, *J* 6.1 Hz, 17^1- and 17^2-H), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.19 (1H, d, *J* 8.6 Hz, 1-H)(Found: M^+-$OSiMe_3$, 354. $C_{25}H_{32}ClNO_2Si$ requires *M*, 442).

Cycloaddition of 3-*Methoxyestra*-1,3,5(10),14,16-*pentaen*-17-*yl acetate* (**29**) *with* 2-*Acetoxyacrylonitrile*

(a) A solution of the dienyl acetate (**29**) (2 g; 6.2 mmol) and 2-acetoxyacrylonitrile (0.5 ml; 4.7 mmol) in anhydrous benzene (6 ml) was heated in a sealed tube under a nitrogen atmosphere at 100°C. Further aliquots of 2-acetoxyacrylonitrile were added after 23 h (0.5 ml; 4.7 mmol), 71 and 144 h (each 0.1 ml; 0.9 mmol), and 168 h (0.8 ml; 7.2 mmol). After 240 h the cooled reaction mixture was filtered through Celite and evaporated under reduced pressure.

Chromatography of the residue (2.2 g) on silica gel (150 g), with toluene as eluent, gave the dienyl acetate (**29**) (421 mg; 21%) followed by 16ß,17ß-*diacetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16α-*carbonitrile* (**78**) (1.85g; 69%), m.p. 140-145°C (from dichloromethane-methanol); $[\alpha]_D$ +161° (*c* 1.0); ν_{max} 2240 (CN), 1748

(CO), and 729 (CCl) cm^{-1}; δ_H (200 MHz) 1.23 (3H, s, 13ß-Me), 1.85 (1H, d, *J* 14.2, 15α-H), 2.07 (3H, s, 16ß-OAc), 2.21 (3H, s, 17ß-OAc), 2.51 (1H, m, 9α-H), 2.69 (1H, d, *J* 14.2 Hz, 15ß-H), 2.84 (2H, m, 6α- and 6ß-H), 3.76 (3H, s, 3-OMe), 6.23 and 6.38 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.18 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 169.2 and 169.0 (16- and 17-O*C*OCH$_3$), 157.6 (C-3), 137.4 (C-5), 134.7, and 131.2 (C-17^1, and C-17^2), 131.4 (C-10), 126.9 (C-1), 117.0 (16-CN), 113.7 (C-4), 111.9 (C-2), 97.4 (C-17), 79.4 (C-16), 61.1, and 55:7 (C-13 and C-14), 55.2 (3-OMe), 44.1 (C-15), 39.6 (C-9), 38.4 (C-8), 29.8 (C-6), 29.8, 26.4 and 23.7 (C-7, C-11 and C-12), 21.3 and 20.9 (16- and 17-OCO*C*H$_3$), and 15.6 (C-18)(Found: C, 71.8; H, 6.6; N, 3.2%; M^+, 435. $C_{26}H_{29}NO_5$ requires C, 71.7; H, 6.7; N, 3.2%; *M*, 435).

b) The dienyl acetate (**29**) (2 g; 6.2 mmol), 2-acetoxyacrylonitrile (0.7 ml; 6.6 mmol) and hydroquinone (50 mg) in anhydrous benzene (6 ml) were heated in a sealed tube under a nitrogen atmosphere at 150°C. Further aliquots of 2-acetoxyacrylonitrile (each 0.1 ml; 0.9 mmol) were added after 42, 90, 114, and 162 h. After 210 h the reaction was worked-up and chromatographed, as described above, to give the dienyl acetate (**29**) (320 mg; 16%) followed by the cycloadduct (**78**) (2.18 g; 81%).

c) The dienyl acetate (**29**) (2 g; 6.2 mmol), 2-acetoxyacrylonitrile (0.7 ml; 6.6 mmol) and 4-*tert*-butylcatechol (50 mg) in anhydrous benzene (6 ml) were heated in a sealed tube under a nitrogen atmosphere at 150°C. Further aliquots of 2-acetoxyacrylonitrile (each 0.1 ml; 0.9 mmol) were added after 45, 96, 140, and 213 h. After 261 h the reaction was worked-up and chromatographed, as described above, to give the dienyl acetate (**29**) (373 mg; 19%) followed by the cycloadduct (**78**) (1.67g; 62%).

Cycloaddition of 3-*Methoxyestra*-1,3,5(10),14,16-*pentaen*-17-*yl acetate* (**29**) with *Acrylonitrile*

A solution of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**29**) (0.5 g; 1.54 mmol) and acrylonitrile (0.3 ml; 4.56 mmol) in anhydrous benzene (4 ml) was heated in a sealed tube under a nitrogen atmosphere at 125°C. After 188 h the reaction mixture was evaporated to dryness.

Chromatography of the crystalline product (666 mg) on silica gel (50 mg), with ethyl acetate-benzene (1:99) as eluent, gave 17ß-*acetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16ß-*carbonitrile* (**79**) (135 mg; 23%), m.p. 184-189°C (from chloroform-methanol); $[\alpha]_D$ +155° (*c* 1.0); ν_{max} 2238 (CN) and 1738 (CO) cm^{-1}; δ (200 MHz) 1.22 (3H, s, 13ß-Me), 1.91 (1H, dd, *J* 12.2 and 9.4 Hz, 15α-H), 2.10 (1H, dd, *J* 12.2 and 4.9 Hz, 15ß-H), 2.23 (3H, s, 17ß-OAc), 2.48 (1H, m, 9α-H), 2.88 (2H, m, 6α- and 6ß-H), 3.37 (1H, dd, *J* 9.4 and 4.9 Hz, 16α-H), 3.79 (3H, s, 3-OMe), 6.13 and 6.37 (each 1H, d, *J* 6.1 Hz, 17^2- and 17^1-H), 6.65 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.5 Hz, 1-H)(Found: C, 76.6; H, 7.3, N, 3.8%; M^+, 377. $C_{24}H_{27}NO_3$ requires C, 76.4, H, 7.2; N, 3.7% *M*, 377), an unidentified cycloadduct (**80**) as an oil (10 mg, 2%); $[\alpha]_D$ +25° (*c* 0.4); ν_{max} 2235 (CN) and 1736 (CO) cm^{-1}; δ (200 MHz) 1.24 (3H, s, 13ß-Me), 2.13 (3H, s, 17ß-OAc), 2.54 (1H, dd, *J* 12.2 and 9.5 Hz), 2.86-3.05 (2H, m, 6α- and 6ß-H), 3.78 (3H, s, 3-OMe), 6.07 and 6.43 (each 1H, d, *J* 6.0 Hz, 15- and 16-H), 6.66 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H)(Found: M^+, 377. $C_{24}H_{27}NO_3$ requires *M*, 377) followed by 17ß-*acetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16α-*carbonitrile* (**81**) (427 mg; 73%), m.p. 224-227°C (from chloroform-methanol); $[\alpha]_D$ +110° (*c* 1.0); ν_{max} 2242 (CN) and 1749 (CO) cm^{-1}; δ (200 MHz) 0.91 (3H, s, 13ß-Me), 1.60 (1H, dd, *J* 12.1 and 3.9 Hz, 15α-H), 2.10 (1H, dd, *J* 12.1 and 9.0 Hz, 15ß-H), 2.15 (3H, s, 17ß-OAc), 2.50 (1H, m, 9α-H), 2.88 (2H, m, 6α- and 6ß-H), 3.30 (1H, dd, *J* 9.0 and 3.9 Hz, 16ß-H), 3.78 (3H, s, 3-OMe), 6.25 and 6.49 (each 1H, d, *J* 6.2 Hz, 17^2- and 17^1-H), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.19 (1H,

d, *J* 8.6 Hz, 1-H)(Found: C, 76.6; H, 7.4; N, 3.7%; M^+, 377. $C_{24}H_{27}NO_3$ requires C, 76.4; H, 7.2; N, 3.7%; *M*, 377).

Alkaline Treatment of 17ß-*Acetoxy*-16ß-*chloro*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16α-*carbonitrile* (**71**)

(a) A solution of the cycloadduct (**71**) (1.7 g; 4.1 mmol) in tetrahydrofuran (25 ml) and dimethyl sulphoxide (25 ml) at 0°C under nitrogen was treated with aqueous 2M-potassium hydroxide (5.2 ml; 10.4 mmol). After 5 h at 0°C saturated aqueous ammonium chloride was added and the tetrahydrofuran was removed under reduced pressure. Water was added and the residue was extracted with chloroform. The extract was washed with brine and water, dried ($MgSO_4$), and concentrated under reduced pressure.

Chromatography of the product (1.8 g) on silica gel (130 g), with ethyl acetate-toluene (1:9) as eluent, gave (16^{1}R)-3-*methoxy*-17-*oxo*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16^1-*carbonitrile* (**82**) (1.24 g; 90%), m.p. 158-161°C (from chloroform-methanol); $[\alpha]_D$ +164° (*c* 1.0); ν_{max} 2232 (CN) and 1733 (CO) cm^{-1}; δ_H (500 MHz) 0.89 (3H, s, 13ß-Me), 1.36 (1H, qd, *J* 2 x 13.1, 12.0 and 3.4 Hz, 11ß-H), 1.43 (1H, dt, *J* 13.1 and 2 x 3.4 Hz, 12ß-H), 1.49 (1H, td, *J* 2 x 12.0 and 2.6 Hz, 8ß-H), 1.55 (1H, dd, *J* 10.6 and 2.4 Hz, 16^2*S*-H), 1.59 (1H, td, *J* 2 x 13.1 and 3.4 Hz, 12α-H), 1.73 (1H, qd, *J* 3 x 12.0 and 6.2 Hz, 7α-H), 2.22 (1H, ddt, *J* 12.0, 5.7 and 2 x 2.6 Hz, 7ß-H), 2.30 (1H, ddt, *J* 13.1 and 3 x 3.4 Hz, 11α-H), 2.44 (1H, td, *J* 2 x 12.0 and 3.4 Hz, 9α-H), 2.60 (1H, d, *J* 4.5 Hz, 16α-H), 2.71 (1H, d, *J* 10.6 Hz, 16^2*R*-H), 2.87-2.98 (2H, m, 6α- and 6ß-H), 3.35 (1H, dd, *J* 4.5 and 2.4 Hz, 15α-H), 3.77 (3H, s, 3-OMe), 6.65 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.17 (1H, d, *J* 8.6 Hz, 1-H); δ_C (125 MHz) 212.5 (s, C-17), 157.9 (s, C-3), 137.3 (s, C-5), 130.6 (s, C-10), 126.4 (d, C-1), 117.6 (s, 16^1-CN), 113.6 (d, C-4), 112.0 (d, C-2), 55.2 (q, 3-OMe), 53.2 and 52.9 (each s, C-13 and C-14), 39.0 (d, C-9), 37.5 (d, C-16), 37.2 (d, C-8), 36.5 (d, C-15), 30.0 (t, C-12), 29.7 (t, C-6), 27.7 (t, C-16^2), 25.0 (t, C-11), 24.5 (t, C-7), 12.4 (s, C-16^1), and

11.8 (C-18)(Found: C, 79.2; H, 7.0; N, 4.1%; M^+, 333. $C_{22}H_{23}NO_2$ requires C, 79.3; H, 7.0; N, 4.2%; *M*, 333).

(b) A solution of the cycloadduct (**71**) (1 g; 2.4 mmol) in tetrahydrofuran (13 ml) and dimethyl sulphoxide (30 ml) at 25°C under nitrogen was stirred with aqueous 1.5M-potassium hydroxide (10 ml; 15.0 mmol) at 25°C. After 23 h, saturated aqueous ammonium chloride was added, and the mixture was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure.

Crystallisation of the product (0.8 g), from ethanol, gave (16^{1}R)-3-*methoxy*-17-*oxo*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16^1-*carboxamide* (**86**) (684 mg; 80%), m.p. 252-255°C; $[\alpha]_D$ +96° (*c* 0.8); ν_{max} 3407 (NH), 1725 (17-CO), and 1675 ($CONH_2$) cm^{-1}; δ_H (500 MHz) 0.96 (3H, s, 13ß-Me), 1.37obsc. (1H, qd, *J* 2 x 13.2, 12.4 and 3.2 Hz, 11ß-H), 1.44obsc. (1H, dt, *J* 13.4 and 2 x 3.2 Hz, 12ß-H), 1.45-1.51obsc. (1H, m, 8ß-H), 1.47obsc. (1H, dd, *J* 10.0 and 2.3 Hz, 16^2*S*-H), 1.63-1.76 (2H, m, 7α- and 12α-H), 2.16 (1H, ddt, *J* 12.8, 5.5 and 2 x 2.6 Hz, 7ß-H), 2.30 (1H, ddt, *J* 13.2 and 3 x 3.2 Hz, 11α-H), 2.46 (1H, td, *J* 2 x 12.4 and 3.2 Hz, 9α-H), 2.57 (1H, d, *J* 10.0 Hz, 16^2*R*-H), 2.73 (1H, d, *J* 4.3 Hz, 16α-H), 2.85-2.93 (2H, m, 6α- and 6ß-H), 3.23 (1H, dd, *J* 4.3 and 2.3 Hz, 15α-H), 3.76 (3H, s, 3-OMe), 5.88 (2H, br d, exch. by D_2O, 16^1-$CONH_2$), 6.63 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.18 (1H, d, *J* 8.6 Hz, 1-H); δ_C (125 MHz) 216.0 (s, C-17), 171.2 (s, 16^1-$CONH_2$), 157.8 (s, C-3), 137.5 (s, C-5), 131.2 (s, C-10), 126.5 (d, C-1), 113.7 (d, C-4), 111.9 (d, C-2), 55.2 (q, 3-OMe), 52.7 and 51.3 (each s, C-13 and C-14), 39.0 (d, C-9), 38.9 (d, C-16), 37.6 (d, C-8), 37.5 (d, C-15), 30.5 (t, C-12), 29.8 (t, C-6), 29.5 (s, C-16^1), 26.2 (t, C-16^2), 25.3 (t, C-11), 24.7 (t, C-7), and 12.2 (q, C-18)(Found: C, 75.3; H, 6.9; N, 3.8%; M^+, 351. $C_{22}H_{25}NO_3$ requires C, 75.2; H, 7.2; N, 4.0%; *M*, 351).

Alkaline Treatment of 17ß-*Acetoxy*-15ß-*chloro*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-15α-*carbonitrile* (**72**)

(a) A solution of the cycloadduct (**72**) (53 mg; 0.14 mmol) in tetrahydrofuran (1.2 ml) and dimethyl sulphoxide (1.2 ml) was treated with aqueous 2M-potassium hydroxide (0.18 ml; 0.36 mmol) at 0°C. After 75 min at 0°C saturated aqueous ammonium chloride was added, and the mixture was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure.

Flash chromatography of the product (59 mg) on silica gel (5 g), with ethyl acetate-toluene (1:9) as eluent, gave 15ß-*chloro*-17ß-*hydroxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-15α-*carbonitrile* (**87**) (43 mg; 90%), m.p. 149-151°C (from chloroform-hexane); $[\alpha]_D$ +96° (*c* 1.0); ν_{max} 3595 and 3427 (OH), 2237 (CN), and 717 (CCl) cm^{-1}; δ (200 MHz) 1.23 (3H, s, 13ß-Me), 1.72 (1H, m, 7α-H), 2.17 (1H, d, *J* 13.4 Hz, 16α-H), 2.56 (1H, m, 9α-H), 2.91 (2H, m, 6α- and 6ß-H), 3.08 (1H, d, *J* 13.4 Hz, 16ß-H), 3.78 (3H, s, 3-OMe), 6.17 and 6.24 (each 1H, d, *J* 6.0 Hz, 17^1- and 17^2-H), 6.65 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), and 7.20 (1H, d, *J* 8.5 Hz, 1-H)(Found: C, 71.0; H, 6.2; N, 3.9%; M^+, 369. $C_{22}H_{24}ClNO_2$ requires C, 71.4; H, 6.5; N, 3.8%; *M*, 369).

(b) A solution of compound (**87**) (50 mg; 0.14 mmol) in 95% ethanol (25 ml) was treated with sodium sulphide nonahydrate (33 mg; 0.14 mmol) and 1M-potassium hydroxide (95% solution in ethanol; 0.3 ml; 0.3 mmol) at reflux. After 7.5 h aqueous ammonium chloride was added and the solvent was evaporated under reduced pressure. The aqueous phase was extracted with ethyl acetate, and the extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure.

The product (55 mg) was chromatographed on silica gel (5 g), with ethyl acetate-toluene (1:9) as eluent, to give 2-[3-*methoxy*-17-*oxo*-14ß-*estra*-1,3,5(10),15-*tetraen*-14-*yl*]*acrylonitrile* (**88**) (31 mg; 69%), m.p. 125-128°C (from chloroform-methanol); $[\alpha]_D$ +337° (*c* 0.5); ν_{max} 2222 (CN) and 1710 (CO) cm^{-1}; δ (200 MHz) 1.03 (3H, s, 13'ß-Me), 2.89-2.78 (2H, m, 6'α- and 6'ß-H), 3.75 (3H, s, 3'-OMe), 5.75 and 6.22 (each 1H, s, 3-

H_2), 6.45 (1H, d, *J* 5.9 Hz, 16'-H), 6.56 (1H, d, *J* 2.6 Hz, 4'-H), 6.70 (1H, dd, *J* 8.6 and 2.6 Hz, 2'-H), 7.01 (1H, d, *J* 8.6 Hz, 1'-H), and 7.38 (1H, d, *J* 5.9 Hz, 15'-H)(Found: C, 79.1; H, 7.3; N, 4.0%; M^+, 333. $C_{22}H_{23}NO_2$ requires C, 79.3; H, 7.0; N, 4.2%; *M*, 333).

Reductive Dechlorination of the Cycloadducts (**71**) *and* (**72**)

(a) A solution of the cycloadduct (**71**) (200 mg; 0.49 mmol) in tetrahydrofuran (2.4 ml) and glacial acetic acid (2.4 ml) was stirred with freshly activated zinc dust (160 mg) at 21°C. After 3.25 h aqueous sodium hydrogen carbonate was added and the reaction mixture was extracted with chloroform. The extract was washed with sodium hydrogen carbonate and water, dried ($MgSO_4$), and concentrated under reduced pressure.

The product (180 mg) was chromatographed on silica gel (18 g), with ethyl acetate-benzene (1:99) as eluent, to give 17ß-acetoxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-16ß-carbonitrile (**79**) (70 mg; 38%) followed by 17ß-acetoxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-16α-carbonitrile (**81**) (91 mg; 50%). Both compounds were identical to authentic samples of (**79**) and (**81**) prepared in a previous experiment.

(b) Treatment of the cycloadduct (**72**) (218 mg; 0.53 mmol) in tetrahydrofuran-glacial acetic acid with zinc dust, as described in the foregoing experiment, followed by chromatography of the product (221 mg) on silica gel (21 g), with ethyl acetate-toluene (1:49) as eluent, gave 17ß-acetoxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-15ß-carbonitrile (**89**) as a colourless glass (92 mg; 46%); $[\alpha]_D$ +4° (*c* 3.0); ν_{max} 2234 (CN) and 1734 (CO) cm^{-1}; δ (200 MHz in C_6D_6) 1.23 (3H, s, 13ß-Me), 1.75 (3H, s, 17ß-OAc), 2.01 (1H, dd, *J* 9.4 and 4.6 Hz, 15α-H), 2.10 (1H, dd, *J* 11.8 and 4.6 Hz, 16ß-H), 2.23 (1H, m, 9α-H), 2.46 (1H, dd, *J* 11.8 and 9.4 Hz, 16α-H), 3.53 (3H, s, 3-OMe), 5.59 and 6.41 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.75 (1H, d, *J* 2.7 Hz, 4-H), 6.92 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), and 7.18 (1H, d, *J* 8.5 Hz, 1-H)(Found: M^+, 377. $C_{24}H_{27}NO_3$ requires *M*, 377) followed by 17ß-*acetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-15α-*carbonitrile* (**90**) (54 mg; 27%), m.p. 203-207°C (from chloroform-

methanol); $[\alpha]_D$ +144° (*c* 1.0); ν_{max} 2238 (CN) and 1736 (CO) cm^{-1}; δ (200 MHz in C_6D_6) 0.61 (3H, s, 13ß-Me), 1.74 (3H, s, 17ß-OAc), 2.15 (1H, dd, *J* 9.0 and 3.2 Hz, 15ß-H), 2.33 (1H, m, 9α-H), 2.54 (1H, dd, *J* 11.4 and 3.2 Hz, 16α-H), 2.82 (2H, m, 6α- and 6ß-H), 3.52 (3H, s, 3-OMe), 6.09 and 6.62 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.77 (1H, d, *J* 2.6 Hz, 4-H), 6.90 (1H, dd, *J* 8.7 and 2.6 Hz, 2-H), and 7.15 (1H, d, *J* 8.7 Hz, 1-H)(Found: C, 76.5; H, 6.9; N, 3.8%; M^+, 377. $C_{24}H_{27}NO_3$ requires C, 76.4; H, 7.2; N, 3.7%; *M*, 377).

Alkaline Treatment of 16ß,17ß-*Diacetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16α-*carbonitrile* (**78**)

A solution of the cycloadduct (**78**) (2.92 g; 6.70 mmol) in dimethyl sulphoxide (50 ml) and tetrahydrofuran (50 ml) under nitrogen was treated with aqueous 2M-potassium hydroxide (11.8 ml; 23.6 mmol) at 0°C and warmed to room temperature after 30 min. After a total reaction time of 25 h aqueous ammonium chloride was added and the reaction mixture was extracted with chloroform and the extract washed with water, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the product on silica gel (150 g), with ethyl acetate-toluene (1:9) as eluent, gave 17ß-*hydroxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-16-*one* (**91**) (1.79 g; 82%), m.p. 154-158°C (from chloroform-methanol); $[\alpha]_D$ +432° (*c* 1.0); ν_{max} 3525 (OH) and 1745 (CO) cm^{-1}; δ_H (400 MHz) 0.94 (3H, d, *J* 0.6 Hz, 13ß-Me), 2.00 (1H, dd, *J* 16.9 and 0.9 Hz, 15ß-H), 2.20 (1H, d, *J* 16.9 Hz, 15α-H), 2.59 (1H, m, 9α-H), 2.89 (2H, m, 6α- and 6ß-H), 3.77 (3H, s, 3-OMe), 5.82 (1H, dt, *J* 6.0 and 2 x 0.9 Hz, 17^2-H), 6.43 (1H, d, *J* 6.0 Hz, 17^1-H), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.24 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 215.3 (C-16), 157.6 (C-3), 140.8 ($C-17^1$), 131.2 ($C-17^2$), 137.6 (C-5), 131.7 (C-10), 126.9 (C-1), 113.8 (C-4), 111.9 (C-2), 95.4 (C-17), 62.7 and 53.8 (C-13 and C-14), 55.2 (3-OMe), 40.1 (C-9), 38.2 (C-8), 37.6, 26.7, 26.3 and 24.4 (C-7, C-11, C-12 and C-15), 30.0 (C-6), and 14.3 (C-18)(Found: C, 77.3; H, 7.7%; M^+, 324. $C_{21}H_{24}O_3$ requires C, 77.8; H, 7.5%; *M*, 324).

17ß-*Acetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-16-*one* (**92**)

A solution of the 16-ketone (**91**) (220 mg; 0.68 mmol) and 4-(dimethylamino)pyridine (10 mg) in pyridine (5 ml) and acetic anhydride (0.5 ml) was stirred at 17°C for 20 h. Aqueous sodium hydrogen carbonate and water were added and the reaction mixture was extracted with chloroform. the extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the product (267 mg) on silica gel (27 g), with ethyl acetate-toluene (1:9) as eluent, gave 17ß-*acetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-16-*one* (**92**) (230 mg; 92%), m.p. 222-225°C (from chloroform-methanol); $[\alpha]_D$ +360° (*c* 1.0); ν_{max} 1747 br (CO) cm^{-1}; δ (200 MHz) 1.04 (3H, d, *J* 0.6 Hz, 13ß-Me), 1.97 (1H, dd, J 16.7 and 0.8 Hz, 15ß-H), 2.18 (3H, s, 17ß-OAc), 2.20 (1H, d, *J* 16.7 Hz, 15α-H), 2.59 (1H, m, 9α-H), 2.89 (2H, m, 6α- and 6ß-H), 3.78 (3H, s, 3-OMe), 6.39 and 6.47 (each 1H, d, *J* 6.1 Hz, 17^1- and 17^2-H), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.74 (1H, dd, *J* 8.3 and 2.7 Hz, 2-H), and 7.23 (1H, d, *J* 8.3 Hz, 1-H)(Found: C, 75.1; H, 7.5%, M^+, 366. $C_{23}H_{26}O_4$ requires C, 75.4; H, 7.2%; *M*, 366).

Hydride Reductions of 17ß-*Hydroxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-16-*one* (**91**)

(a) A solution of the 16-ketone (**91**) (400 mg; 1.23 mmol) at 0°C in tetrahydrofuran (10 ml) under nitrogen was treated with lithium aluminium hydride (150 mg; 4.0 mmol). After 2 h at 0°C, aqueous sodium hydrogen carbonate was added followed by water and the reaction mixture was extracted with dichloromethane. The organic phase was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure.

The product (430 mg) was chromatographed on silica gel (40 g), with ethyl acetate-toluene (3:7) → (1:1) as eluent, to give 3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-16ß,17ß-diol (**93**) (300 mg; 75%), m.p. 158-162°C (from chloroform-methanol) (lit.,[100] 162°C); $[\alpha]_D$ +146° (*c* 1.0); ν_{max} 3605 and 3430 (OH) cm^{-1}; δ_H (200 MHz) 1.10 (3H, d, *J* 0.8 Hz, 13ß-Me), 1.50 (1H, dd, *J* 12.5 and 2.9 Hz, 15ß-H), 1.87 (1H, dd, *J* 12.5 and 7.6

Hz, 15α-H), 2.31 (1H, d, *J* 2.9 Hz, exch. by D_2O, 16ß-OH), 2.42 (1H, m, 9α-H), 2.83 (2H, m, 6α- and 6ß-H), 3.75 (3H, s, 3-OMe), 3.83 (1H, dt, *J* 7.6 and 2 x 2.9 Hz → dd, *J* 7.6 and 2.9 Hz on D_2O exch., 16α-H), 5.86 and 5.98 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.69 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.20 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 157.4 (C-3), 137.9 (C-5), 136.2 and 135.3 (C-17^1 and C-17^2), 132.5 (C-10), 127.1 (C-1), 113.7 (C-4), 111.7 (C-2), 90.3 (C-17), 75.9 (C-16), 58.8 and 55.1 (C-13 and C-14), 55.2 (3-OMe), 39.8 (C-9), 39.0 (C-8), 35.2, 28.9, 26.7 and 24.0 (C-7, C-11, C-12 and C-15), 30.2 (C-6), and 14.5 (C-18)(Found: C, 77.1; H, 8.1%; M^+, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; *M*, 326) followed by 3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-16α,17ß-diol (**94**) (58 mg; 14%), m.p. 187-192°C (from methanol-toluene) (lit.,[100] 195°C); $[\alpha]_D$ +169° (*c* 1.0); ν_{max} 3593 and 3420 (OH) cm^{-1}; δ (200 MHz) 0.90 (3H, s, 13ß-Me), 1.12 (1H, dd, *J* 12.6 and 2.4 Hz, 15α-H), 2.17 (1H, dd, *J* 12.6 and 7.7 Hz, 15ß-H), 2.36 (1H, br s, exch. by D_2O, 16α-OH), 2.83 (2H, m, 6α- and 6ß-H), 3.75 (3H, s, 3-OMe), 4.38 (1H, br s → br dd, *J* 7.7 and 2.4 Hz on D_2O exch., 16ß-H), 5.92 and 6.31 (each 1H, d, *J* 6.0 Hz, 17^1- and 17^2-H), 6.60 (1H, d, *J* 2.6 Hz, 4-H), 6.69 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H), and 7.18 (1H, d, *J* 8.5 Hz, 1-H)(Found: 326. $C_{21}H_{26}O_3$ requires *M*, 326).

(b) A suspension of cycloadduct (**78**) (1.56 g; 3.6 mmol) in anhydrous ethanol (25 ml) under nitrogen was treated with sodium borohydride (647 mg; 17.1 mmol) at 22°C. After 23 h the reaction was quenched with water and extracted with ethyl acetate. The extract was washed with aqueous ammonium chloride, dried ($MgSO_4$), and evaporated under recuded pressure.

Chromatography of the product (1.33 g) on silica gel (133 g), with ethyl acetate-toluene (3:7) as eluent, gave the 16ß,17ß-diol (**93**) (907 mg; 78%) followed by the 16α,17ß-diol (**94**) (48 mg; 4%). These compounds were identical to authetic samples of (**93**) and (**94**) isolated in (a) above.

14-*Formylmethyl-3-methoxy*-14ß-*estra*-1,3,5(10),15-*tetraen*-17-*one* (**113**)

A solution of the 16ß,17ß-diol (**93**) (100 mg; 0.27 mmol) in ethanol (12 ml) was treated with sodium periodate (6% aqueous solution; 5.0 ml; 1.4 mmol) at 20°C. After 1 h at 20°C ethylene glycol and water were added. The reaction mixture was extracted with chloroform and the organic phase was dried ($MgSO_4$), and evaporated to dryness.

Flash chromatography of the product (138 mg) on silica gel (10 g), with ethyl acetate-toluene (1:9) as eluent, gave 14-formylmethyl-3-methoxy-14ß-estra-1,3,5(10),15-tetraen-17-one (**113**) (95 mg; 99%), m.p. 80-87°C (from ethyl acetate-hexane); ν_{max} 1706 br (CO) cm^{-1}; δ (200 MHz) 1.04 (3H, s, 13ß-Me), 2.74 (1H, dd, *J* 17.0 and 1.5 Hz, 14^1ξ-H), 2.75obsc. (2H, m, 6α- and 6ß-H), 2.93 (1H, dd, *J* 17.0 and 2.7 Hz, 14^1ξ-H), 3.74 (3H, s, 3-OMe), 6.29 (1H, d, *J* 5.9 Hz, 16-H), 6.54 (1H, d, *J* 2.5 Hz, 4-H), 6.69 (1H, dd, *J* 8.6 and 2.5 Hz, 2-H), 7.03 (1H, d, *J* 8.6 Hz, 1-H), 7.40 (1H, d, *J* 5.9 Hz, 15-H), and 9.90 (1H, br s, 14^1-CHO)(Found: M^+, 324. $C_{21}H_{24}O_3$ requires *M*, 324). The compound (**113**) was too labile for further purification.

Alkaline Treatment of 14-*Formylmethyl*-3-*methoxy*-14ß-*estra*-1,3,5(10),15-*tetraen*-17-*one* (**113**)

(a) A solution of compound (**113**) (50 mg; 0.15 mmol) in tetrahydrofuran (2 ml) was treated with 2M-methanolic potassium hydroxide (0.03 ml; 0.06 mmol) at 22°C. After 30 min at 22°C aqueous ammonium chloride was added and the reaction mixture was extracted with chloroform. The extract was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure.

The product (88 mg) was adsorbed onto coarse silica gel (2 g) and chromatographed on silica gel (5 g), with ethyl acetate-hexane (1:4) as eluent, to give 3,5'ξ-*dimethoxy-dihydrofuro*[3',2';14,15]-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**114**) (61 mg; 90%), m.p. 125-130°C (chloroform-methanol); $[\alpha]_D$ +52° (*c* 0.6); ν_{max} 1731 (CO) cm^{-1}; δ (200 MHz) 1.12 (3H, s, 13ß-Me), 1.77 (1H, dd, *J* 14.5 and 4.3 Hz, 4'ξ-H), 2.19 (1H, dd, *J* 14.5 and 6.2 Hz, 4'ξ-H), 2.53 (1H, dd, *J* 20.1 and 4.5 Hz, 16ß-H), 2.89 (2H, m, 6α-

and 6ß-H), 3.02 (1H, dd, *J* 20.1 and 9.2 Hz, 16α-H), 3.35 (3H, s, 5'ξ-OMe), 3.78 (3H, s, 3-OMe), 4.80 (1H, dd, *J* 9.2 and 4.5 Hz, 15α-H), 5.13 (1H, dd, *J* 6.2 and 4.3 Hz, 5'ξ-H), 6.64 (1H, d, *J* 2.6 Hz, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.22 (1H, d, *J* 8.6 Hz, 1-H)(Found: C, 73.9; H, 8.0%; M^+, 356. $C_{22}H_{28}O_4$ requires C, 74.1; H, 7.9%; *M*, 356).

(b) A solution of coumpoud (**133**) (58 mg; 0.18 mmol) in tetrahydrofuran (2 ml) was treated with aqueous 2M-potassium hydroxide (0.03 ml; 0.06 mmol) at 22°C for 30 min after which time the reaction was worked up as described in (a) above. Chromatography of the product (65 mg) on silica gel (7 g), with ethyl acetate-toluene (1:9) as eluent, gave an unidentified product (17 mg; 28%), m.p. 171-176°C (from chloroform-methanol); ν_{max} 1751 (CO) cm^{-1}; δ (200 MHz) 1.24 (3H, s, 13ß-Me), 2.01 (1H, dd, *J* 13.3 and 2.5 Hz), 3.80 (3H, s, 3-OMe), 3.90 (1H, d, *J* 3.6 Hz), 5.24 (1H, d, *J* 3.6 Hz), 5.73 (1H, d, *J* 2.3 Hz), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.76 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H), and 7.23 (1H, d, *J* 8.7 Hz, 1-H)(Found: M^+, 340), a mixture of products (17 mg) followed by 5'ξ-hydroxy-3-methoxy-dihydrofuro[3',2';14,15]-14ß-estra-1,3,5(10)-trien-17-one (**115**) (34 mg; 55%) as an oil; ν_{max} 3595 (OH) and 1733 (CO) cm^{-1}; δ (200 MHz) 1.12 (3H, s, 13ß-Me), 1.75 (1H, dd, *J* 14.9 and 4.5 Hz, 4'ξ-H), 2.21 (1H, dd, *J* 14.9 and 6.1 Hz, 4'ξ-H), 2.65 (1H, dd, *J* 20.1 and 4.5 Hz, 16ß-H), 2.86 (2H, m, 6α- and 6ß-H), 3.05 (1H, dd, *J* 20.1 and 9.2 Hz, 16α-H), 3.76 (3H, s, 3-OMe), 4.79 (1H, dd, *J* 9.2 and 4.5 Hz, 15α-H), 5.66 (1H, dd, *J* 6.1 and 4.5 Hz, 5'ξ-H), 6.62 (1H, d, *J* 2.7 Hz, 2-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.20 (1H, d, *J* 8.6 Hz, 1-H)(Found: M^+, 342. $C_{21}H_{26}O_4$ requires *M*, 342).

3-Methoxy-16α-methyl-14,17α-ethenoestra-1,3,5(10)-triene-16ß,17ß-diol (**121**)

(a) A solution of the 16-ketone (**91**) (100 mg; 0.31 mmol) in tetrahydrofuran (0.25 ml) and diethyl ether (1.25 ml) at 0°C under nitrogen was treated with methyllithium (5% solution in ether; 1.9 ml; 3.2 mmol). After 2.75 h at 0°C more methyllithium (0.6 ml; 1.0 mmol) was added at 0°C and the mixture was then allowed to come up to room temperature. After 21 h at room temperature the reaction was quenched with water, and the reaction mixture was extracted with chloroform. The extract was dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the product (101 mg) on silica gel (10 g), with ethyl acetate-toluene (1:4) as eluent, gave *3-methoxy-16α-methyl-14,17α-ethenoestra-1,3,5(10)-triene-16ß,17ß-diol* (**121**) (72 mg; 69%), m.p. 170-185°C (from chloroform-methanol); $[\alpha]_D$ +170° (*c* 1.0); ν_{max} 3607 and 3555 (OH) cm^{-1}; δ (200 MHz) 1.11 (3H, d, *J* 0.8 Hz, 13ß-Me), 1.23 (3H, s, 16α-Me), 1.52 (1H, d, *J* 12.2 Hz, 15α-H), 1.89 (1H, d, *J* 12.2 Hz, 15ß-H), 2.46obsc. (1H, m, 9α-H), 2.83 (2H, m, 6α- and 6ß-H), 3.75 (3H, s, 3-OMe), 5.91 and 5.96 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.69 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.20 (1H, d, *J* 8.5 Hz, 1-H)(Found: C, 77.2; H, 8.1%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340).

(b) The 16-ketone (**91**) (60 mg; 0.19 mmol) in tetrahydrofuran was added to methylmagnesium iodide [prepared from methyl iodide (0.10 ml; 1.6 mmol) and magnesium (60 mg; 2.5 g atom) in ether (4 ml)] at 21°C. After 2.5 h at 21°C water was added and the reaction mixture was extracted with chloroform, and the extract was dried ($MgSO_4$), and evaporated under reduced pressure.

Flash chromatography of the product (60 mg) on silica gel (16 g), with ethyl acetate-toluene (1:9) as eluent, gave 3-methoxy-16α-methyl-14,17α-etheno-14ß-estra-1,3,5(10)-triene-16ß,17ß-diol (**121**) (56 mg; 89%) identical to an authentic sample of (**121**) obtained in (a) above.

Thermal Decomposition of 3-*Methoxy*-16α-*methyl*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16ß,17ß-*diol* (**121**)

A solution of the 16-methyl 16ß,17ß-diol (50 mg; 0.15 mmol) in toluene (5 ml) was heated in a sealed tube at 140°C. After 82 h at 140 °C the reaction mixture was evaporated under reduced pressure.

Chromatography of the product (70 mg) on silica gel (15 g), with ethyl acetate-toluene (3:7) as eluent, gave an unidentified compound (19 mg) as an oil; ν_{max} 1704 (CO) cm^{-1}; δ (200 MHz) 0.95 (3H, s, 13ß-Me), 2.21 (3H, s), 2.74 (2H, m, 6α- and 6ß-H), 2.76 and 3.05 (each 1H, d, *J* 18.3 Hz), 3.73 (3H, s, 3-OMe), 6.23 and 7.41 (each 1H, d, *J* 5.9 Hz), 6.53 (1H, d, *J* 2.7 Hz, 4-H), 6.68 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), and 7.02 (1H, d, *J* 8.5 Hz, 1-H)(Found: M^+, 338) followed by unreacted starting material (**121**) (20 mg; 40%).

14-*Acetonyl*-3-*methoxy*-14ß-*estra*-1,3,5(10),15-*tetraen*-17-*one* (**122**)

A solution of the 16ß-hydroxy-16α-methyl compound (**121**) (58 mg; 0.17 mmol) in ethanol (5 ml) at 19°C was treated with sodium periodate (6% aqueous solution; 3 ml; 0.84 mmol) at 19°C. After 78 h at 19°C, ethylene glycol was added and the reaction mixture was extracted with chloroform and the extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the product (62 mg) on silica gel (8 g), with ethyl acetate-toluene (1:4) as eluent, gave 14-*acetonyl*-3-*methoxy*-14ß-*estra*-1,3,5(10),15-*tetraen*-17-*one* (**122**) (46 mg; 79%), m.p. 98-102°C (from ethanol); $[\alpha]_D$ +235° (*c* 1.1); ν_{max} 1710 and 1699 (CO) cm^{-1}; δ (200 MHz) 0.95 (3H, s, 13ß-Me), 2.21 (3H, s, 14^3-H_3), 2.75obsc. (2H, m, 6α- and 6ß-H), 2.76 and 3.05 (each 1H, d, *J* 18.2 Hz, 14^1-H_2), 3.73 (3H, s, 3-OMe), 6.23 (1H, d, *J* 6.0 Hz, 16-H), 6.52 (1H, d, *J* 2.7 Hz, 4-H), 6.68 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H), 7.01 (1H, d, *J* 8.7 Hz, 1-H), and 7.40 (1H, d, *J* 6.0 Hz, 15-H)(Found: C, 77.8; H, 7.5%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; *M*, 338).

17ß-*Hydroxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-16-*one* (**124**)

A solution of the 16-ketone (**91**) (946 mg; 2.90 mmol) in ethyl acetate (15 ml) at 23°C was stirred in the presence of palladium on carbon (10% ,280 mg) and hydrogen at atmospheric pressure, until hydrogen uptake ceased (*ca.* 3 h). The reaction mixture was filtered through Celite and the catalyst was thoroughly washed with ethyl acetate.

The filtrate was evaporated, and the residue was crystallised from chloroform-methanol, to give 17ß-*hydroxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-16-*one* (**124**) (624 mg; 66%), m.p. 169-171°C; $[\alpha]_D$ -62° (*c* 1.0); ν_{max} 3526 (OH) and 1746 (CO) cm^{-1}; δ (200 MHz) 0.82 (3H, s, 13ß-Me), 2.89 (2H, m, 6α- and 6ß-H), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.74 (1H, dd, *J* 8.8 and 2.4 Hz, 2-H), and 7.23 (1H, d, *J* 8.8 Hz, 1-H)(Found: C, 77.1; H, 7.7%; M^+, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; *M*, 326).

Chromatography of the mother liquor (250 mg) on silica gel (25 g), with ethyl acetate-toluene (1:4) as eluent, gave further (**124**) (240 mg; 25%).

17ß-*Acetoxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-16-*one* (**125**)

(a) A solution of the 17-hydroxy-16-ketone (**124**) (868 mg; 2.66 mmol) and 4-(dimethylamino)pyridine (10 mg) in pyridine (20 ml) at 20°C was treated with acetic anhydride (0.5 ml; 5.3 mmol). After 111 h at 20°C, aqueous sodium hydrogen carbonate was added. The reaction mixture was extracted with chloroform, and the extract was washed with aqueous sodium carbonate and water, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the product (950 mg) on silica gel (82 g), with ethyl acetate-toluene (1:9) as eluent, gave 17ß-*acetoxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-16-*one* (**125**) (450 mg; 46%), m.p. 215-216°C (from chloroform-methanol); $[\alpha]_D$ -30° (*c* 0.9); ν_{max} 1762 (CO) and 1741 (CO) cm^{-1}; δ (200 MHz) 0.93 (3H, s, 13ß-Me), 2.13 (3H, s, 17ß-OAc), 2.76 (1H, m, 9α-H), 2.88 (2H, m, 6α- and 6ß-H), 3.77 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.21 (1H,

d, *J* 8.6 Hz, 1-H)(Found: C, 74.6; H, 7.6%; M^+, 368. $C_{23}H_{28}O_4$ requires C, 75.0; H, 7.7%; *M*, 368) followed by unreacted 17ß-hydroxy-16-ketone (**124**) (454 mg; 52%).

(b) A solution of the 14α,17α-etheno-16-ketone (**92**) in ethyl acetate (14 ml) was stirred in the presence of palladium on carbon (10%, 80 mg) and hydrogen at atmospheric pressure at room temperature until hydrogen uptake ceased (*ca.* 1.25 h). The reaction mixture was filtered and the catalyst thoroughly washed with ethyl acetate and chloroform to give, after evaporation of the solvent, the 17-acetoxy-16-ketone (**125**) (228 mg; 99%) identical to an authentic sample of (**125**) obtained in (a).

Hydride Reductions of 17ß-*Acetoxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-16-*one* (**125**)

(a) The 17ß-acetoxy-16-ketone (**125**) (100 mg; 0.27 mmol) in ethyl acetate (10 ml) and ethanol (10 ml) at 0°C was treated with sodium borohydride (24 mg; 0.63 mmol). After 30 h at 0°C water and aqueous sodium hydrogen carbonate were added and the reaction mixture was extracted with chloroform, and the extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the product (102 mg) on silica gel (13 g), with ethyl acetate-toluene (3:17) as eluent, gave 17ß-acetoxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-16-one (**125**) (35 mg; 35%), 17ß-*acetoxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-16ß-*ol* (**126**) (47 mg; 47%), m.p. 149-154°C (from chloroform-methanol); $[\alpha]_D$ +58° (*c* 0.9); ν_{max} 3601 (OH) and 1722 (CO) cm $^{-1}$; δ (200 MHz) 1.09 (3H, s, 13ß-Me), 1.82 (1H, s, exch. by D_2O, 16ß-OH), 2.10 (1H, dd, *J* 12.4 and 8.3 Hz, 15α-H), 2.11 (3H, s, 17ß-OAc), 2.63 (1H, m, 9α-H), 2.87 (2H, m, 6α- and 6ß-H), 3.77 (3H, s, 3-OMe), 4.54 (1H, dd, *J* 8.3 and 4.4 Hz, 16α-H), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.7 Hz, 2-H), and 7.22 (1H, d, *J* 8.4 Hz, 1-H)(Found: C, 74.4; H, 8.0%; M^+, 370. $C_{23}H_{30}O_4$ requires C, 74.5; H, 8.2%; *M*, 370), 16ß-*acetoxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17ß-*ol* (**127**) (16 mg; 16%), m.p. 165-170°C (from

chloroform-methanol); $[\alpha]_D$ +76° (*c* 0.9); ν_{max} 3584 (OH) and 1738 (CO) cm^{-1}; δ (200 MHz) 0.98 (3H, s, 13ß-Me), 1.84obsc. (1H, br s, exch. by D_2O, 17ß-OH), 2.08 (3H, s, 16ß-OAc), 2.19 (1H, dd, *J* 12.9 and 8.1 Hz, 15α-H), 2.63 (1H, m, 9α-H), 2.85 (2H, m, 6α- and 6ß-H), 3.77 (3H, s, 3-OMe), 4.75 (1H, dd, *J* 8.1 and 4.0 Hz, 16α-H), 6.63 (1H, d, *J* 2.4 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.4 Hz, 2-H), and 7.22 (1H, d, *J* 8.5 Hz, 1-H)(Found: C, 74.4; H, 8.2%; M^+, 370. $C_{23}O_{30}O_4$ requires C, 74.5; H, 8.2%; *M*, 370) followed by 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-16ß,17ß-diol (**128**) (2 mg; 2%), m.p. 169-171°C (from dichloromethane-*n*-pentane) (lit.,[100] 171-172°C); $[\alpha]_D$ +44° (*c* 0.9); ν_{max} 3606 (OH) cm^{-1}; δ (200 MHz) 1.00 (3H, s, 13ß-Me), 2.06 (1H, dd, *J* 12.8 and 7.9 Hz, 15α-H), 2.61 (1H, m, 9α-H), 2.85 (2H, m, 6α- and 6ß-H), 3.77 (3H, s, 3-OMe), 3.80obsc. (1H, dd, *J* 7.9 and 4.0 Hz, 16α-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.22 (1H, d, *J* 8.6 Hz, 1-H)(Found: M^+, 328. $C_{21}H_{28}O_3$ requires *M*, 328).

(b) A solution of the 17-acetoxy-16-ketone (**125**) (100 mg; 0.27 mmol) and cerium(III) chloride heptahydrate (103 mg; 0.28 mmol) in ethanol (2 ml) and tetrahydrofuran (5 ml) at 0°C was treated with sodium borohydride (15 mg; 0.40 mmol). After 45 min a further aliquot of sodium borohydride (5 mg; 0.13 mmol) was added. After a total reaction time of 65 min at 0°C, water was added followed by sodium hydrogen carbonate. The reaction mixture was extracted with chloroform, and the extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the product (103 mg) on silica gel (10 g), with ethyl acetate-toluene (3:17) as eluent, gave the 17ß-acetoxy-16ß-alcohol (**126**) (90mg; 90%) identical to an authentic sample of (**126**) obtained in (a) above.

(c) A solution of the 17ß-acetoxy-16-ketone (**125**) (100 mg; 0.27 mmol) and cerium(III) chloride heptahydrate (100 mg; 0.27 mmol) in tetrahydrofuran (15 ml) at 0°C under nitrogen was treated with excess sodium borohydride, added in small portions at intervals of 1 h. After 7 h at 0°C, water was added and the aqueous phase was

extracted with chloroform, and the extract was dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the product (106 mg) on silica gel (10 g), with ethyl acetate-toluene (3:17) as eluent, gave the 17ß-acetoxy-16ß-alcohol (**126**) (84 mg; 83%), the 16ß-acetoxy-16ß-alcohol (**127**) (9 mg; 9%) followed by the 16ß,17ß-diol (**128**) (5 mg; 4%). These compounds were identical to authentic samples of (**126**), (**127**) and (**128**) obtained in (a) above.

3-*Methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16ß,17ß-*diol* (**128**)

A solution of the 16ß,17ß-diol (**93**) (50 mg; 0.15 mmol) in ethyl acetate (5 ml) at 23°C was hydrogenated in the presence of palladium on carbon (10%, 20 mg) and hydrogen at atmospheric pressure until hydrogen uptake ceased (*ca.* 1.5 h). The reaction mixture was filtered and the catalyst was thoroughly washed with dichloromethane and the filtrate evaporated under reduced pressure.

Chromatography of the product (51 mg) on silica gel (5 g), with ethyl acetate-toluene (3:7) as eluent, gave the 14α,17α-ethano-16ß,17ß-diol (**128**) (50 mg; 100%) identical to an authentic sample of (**128**) obtained above.

17ß-*Acetoxy*-16ß-*methanesulphonyloxy*-3-*methoxy*-14,17α-*ethano-estra*-1,3,5(10)-*triene* (**129**)

A solution of the 16ß-alcohol (**126**) (90 mg; 0.24 mmol) in pyridine (6 ml) at 0°C under nitrogen was treated with methanesulphonyl chloride (0.09 ml; 0.53 mmol). After 48 h at 0°C, aqueous sodium hydrogen carbonate was added and the aqueous phase was extracted with chloroform, and the extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure.

The product (137 mg) was chromatographed on silica gel (9 g), with ethyl acetate-toluene (3:17) as eluent, to give 17ß-*acetoxy*-16ß-*methanesulphonyloxy*-3-*methoxy*-

14,17α-*ethanoestra*-1,3,5(10)-*triene* (**129**) (105 mg; 96%), m.p. 152-154°C (from ethyl acetate); $[\alpha]_D$ +97° (*c* 1.0); ν_{max} 1727 (CO), 1356 and 1177 (SO) cm^{-1}; δ (200 MHz) 1.07 (3H, s, 13ß-H), 2.09 (3H, s, 17ß-OAc), 2.34 (1H, dd, *J* 14.1 and 7.6 Hz, 15α-H), 2.84 (2H, m, 6α- and 6ß-H), 2.94 (3H, s, 16ß-OSO_2Me), 3.76 (3H, s, 3-OMe), 5.17 (1H, dd, *J* 7.6 and 3.8 Hz, 16α-H), 6.62 (1H, d, *J* 2.4 Hz, 4-H), 6.71 (1H, dd, *J* 8.3 and 2.4 Hz, 2-H), and 7.20 (1H, d, *J* 8.3 Hz, 1-H)(Found: C, 64.1; H, 7.4; M^+, 448. $C_{24}H_{32}O_6S$ requires C, 64.3; H, 7.2; *M*, 448).

3-Methoxy-14,16α-*ethanoestra-1,3,5(10)-trien-17-one* (**130**)

The mesyloxy compound (**129**) (69 mg; 0.15 mmol) in toluene (3 ml) at 22°C, was stirred over basic alumina. After 3 h at 22°C the reaction mixture was filtered and the filtrate was evaporated to dryness.

Chromatography of the product (46 mg) on silica gel (8 g), with ethyl acetate-toluene (1:19) as eluent, gave *3-methoxy*-14,16α-*ethanoestra-1,3,5(10)-trien-17-one* (**130**) (38 mg; 80%), m.p. 179-181°C (from chloroform-methanol); $[\alpha]_D$ +112° (*c* 1.1); ν_{max} 1729 (CO) cm^{-1}; δ (200 MHz) 1.02 (3H, s, 13ß-Me), 2.59obsc. (1H, m, 9α-H), 2.66obsc. (1H, br d, *J* 4.2 Hz, 16ß-H), 2.88 (2H, m, 6α- and 6ß-H), 3.77 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), and 7.20 (1H, d, *J* 8.6 Hz, 1-H)(Found: C, 81.3; H; 8.0%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310) followed by starting material (**129**) (10 mg; 14%).

17ß-*Hydroxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16-*tosylhydrazone* (**131**)

A solution of the 16-ketone (**124**) (100 mg; 0.31 mmol) in tetrahydrofuran (2 ml) was treated with toluene-*p*-sulphonylhydrazide (80 mg; 0.43 mmol) and a catalytic amount of trifluoroacetic acid and stirred at 20°C. After 52 h, aqueous sodium hydrogen carbonate was added and the reaction mixture was extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure.

Crystallisation of the product (170 mg) from chloroform-methanol gave 17ß-*hydroxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16-*tosylhydrazone* (**131**) (115 mg; 76%), m.p. 148-151°C (from chloroform-toluene); $[\alpha]_D$ -33° (*c* 0.6); ν_{max} 3544 (OH), 1675 (C=N), 1347 and 1164 (SO) cm^{-1}; δ (200 MHz) 0.53 (3H, s, 13ß-Me), 1.97 and 2.09 (each 1H, d, *J* 16.0 Hz, 15α- and 15ß-H), 2.41 (3H, s, Ar-Me), 2.65 (1H, m, 9α-H), 2.84 (2H, m, 6α- and 6ß-H), 3.76 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.70 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), 7.18 (1H, d, *J* 8.5 Hz, 1-H), 7.31 and 7.82 (each 2H, d, *J* 8.4 Hz, Ar-H)(Found: C, 67.6; H, 7.0; N, 5.4%; M^+-$NNHSO_2C_6H_4CH_3$, 310. $C_{28}H_{34}N_2O_4S$ requires C, 70.0; H, 6.9; N, 5.7%; *M*, 494). Chromatography of the mother liquor (63 mg) on silica gel (6 g), with ethyl acetate-toluene (1:4) as eluent, gave unreacted 16-ketone (**124**) (7 mg; 7%) followed by further 16-tosylhydrazone (**131**) (25 mg; 16%).

3-Methoxy-14,17α-*ethanoestra*-1,3,5(10),15-*tetraen*-17ß-*ol* (**132**)

A solution of the 16-tosylhydrazone (**131**) (80 mg; 0.16 mmol) in tetrahydrofuran (6 ml) at 65°C under nitrogen was treated with *n*-butyllithium (1.6M solution in hexanes; 0.4 ml; 0.64 mmol). After 50 min at 65°C aqueous sodium hydrogen carbonate and water were added and the reaction mixture was extracted with dichloromethane. The organic phase was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure.

The product (58 mg) was chromatographed on silica gel (8 g), with ethyl acetate-toluene (1:4) as eluent, to give 3-methoxy-14,17α-ethanoestra-1,3,5(10),15-tetraen-17ß-ol (**132**) (39 mg; 78%), m.p. 103-108°C (from chloroform-methanol); $[\alpha]_D$ -20° (*c* 0.5); ν_{max} 3600 (OH) and 1676 (C=C) cm^{-1}; δ (200 MHz) 0.90 (3H, s, 13ß-Me), 2.75 (1H, m, 9α-H), 2.92 (2H, m, 6α- and 6ß-H), 3.78 (3H, s, 3-OMe), 5.89 and 6.04 (each 1H, d, *J* 6.0 Hz, 15- and 16-H), 6.64 (1H, d, *J* 2.5 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.5 Hz, 2-H), and 7.22 (1H, d, *J* 8.4 Hz, 1-H)(Found: M^+, 310.192. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310.193).

Mesylation-Rearrangement of 3-*Methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16ß,17ß-*diol* (**93**)

A solution of the 16ß,17ß-diol (**93**) (100 mg; 0.31 mmol) in anhydrous pyridine (1 ml) was treated with methanesulphonyl chloride (0.07 ml; 0.9 mmol) and stirred at room temperature under nitrogen. After 2 h water was added and the reaction mixture was extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the product (152 mg) on silica gel (10 g), with ethyl acetate-toluene (1:19) as eluent, gave 3-*methoxy*-14,16α-*ethenoestra*-1,3,5(10)-*trien*-17-*one* (**143**) (66 mg; 69%), m.p. 199-203°C (from chloroform-methanol); $[\alpha]_D$ -392° (*c* 1.0); ν_{max} 1726 (CO) cm^{-1}; δ_H (400 MHz) 1.10 (3H, s, 13ß-Me), 1.38 (1H, td, *J* 2 x 13.3 and 3.9 Hz, 12α-H), 1.54-1.68 (2H, m, 7ξ- and 11ß-H), 1.84 (1H, td, *J* 2 x 11.5 and 2.3 Hz, 8ß-H), 1.89-1.98 (2H, m, 7ξ– and 12ß-H), 2.03 (1H, br d, *J ca.* 9.1 Hz,15ξ-H), 2.14 (1H, d, *J* 9.1 Hz, 15ξ-H), 2.33 (1H, ddt, *J* 13.6 and 3 x 4.2 Hz, 11α-H), 2.74 (1H, td, *J* 2 x 11.8 and 4.2 Hz, 9α-H), 2.93 (2H, m, 6α- and 6ß-H), 3.17 (1H, m, $W_{½}$16ß-H), 3.78 (3H, s, 3-OMe), 6.13 (1H, m, $W_{½}$ 10.9 Hz, 16^1-H), 6.59 (1H, d, *J* 5.8 Hz, 16^2-H), 6.66 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.5 Hz, 1-H); δ_C 217.4 (C-17), 157.6 (C-3), 144.9 and 132.3 (C-16^1 and C-16^2), 137.7 (C-5), 130.4 (C-10), 126.4 (C-1), 113.9 (C-4), 111.6 (C-2), 58.1 and 46.2 (C-13 and C-14), 56.6, 39.3 and 36.7 (C-8, C-9 and C-16), 55.2 (3-OMe), 48.8, 35.3, 29.8, 26.0 and 24.6 (C-6, C-7, C-11, C-12 and C-15), and 18.2 (C-18)(Found: C, 81.7; H, 7.7%; M^+, 308. $C_{21}H_{24}O_2$ requires C, 81.8; H, 7.8%; *M*, 308) followed by 16ß,17ß-bis(methanesulphonyloxy)-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene* (**144**) (35 mg; 24%), m.p. 128-131°C (from chloroform-methanol); $[\alpha]_D$ +129° (*c* 0.7); ν_{max} 1350, and 1330 (SO) cm^{-1}; δ (200 MHz) 1.21 (3H, s, 13ß-Me), 1.98 (1H, dd, *J* 12.9 and 2.9 Hz, 15ß-H), 2.18 (1H, dd, *J* 12.9 and 7.5 Hz, 15α-H), 2.86 (2H, m, 6α-and 6ß-H), 3.10 and 3.16 (each 3H, s, 16ß- and 17ß-OSO_2Me), 3.77 (3H, s, 3-OMe), 4.87 (1H, dd, *J* 7.5 and 2.9 Hz, 16α-H), 6.28 and 6.41 (each 1H, d, *J* 6.4 Hz, 17^1- and 17^2-H), 6.63 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H,

dd, *J* 8.5 and 2.6 Hz, 2-H), and 7.20 (1H, d, *J* 8.5 Hz, 1-H)(Found: C, 57.4; H 6.0%; M^+, 483. $C_{23}H_{30}O_7S_2$ requires C, 57.2; H, 6.3%; *M*, 483).

Acid Mediated Rearrangement of the 16ß,17ß-*Diol* (**93**)

The 16ß,17ß-diol (**93**) (250 mg; 0.77 mmol) in anhydrous benzene (25 ml) at 70°C was treated with toluene-*p*-sulphonic acid monohydrate (3% adsorbed onto silica gel; 1 g; 0.16 mmol). After 2.5 h at 70°C, the reaction mixture was filtered and the filtrate evaporated under reduced pressure.

Chromatography of the product (250 mg) on silica gel (13 g), with ethyl acetate-toluene (1:19) as eluent, gave 14,16α-etheno-3-methoxyestra-1,3,5(10),trien-17-one (**143**) (204 mg; 86%) identical to an authentic sample of (**143**) obtained above.

Hydrogenation of the 14α,16α-*Etheno Compound* (**143**)

(a) A solution of the 14α,16α-etheno compound (**143**) (70 mg; 0.23 mmol) was hydrogenated in the presence of palladium on carbon (10%, 20 mg) and hydrogen at atmospheric pressure in ethyl acetate (8 ml) at 24°C until hydrogen uptake ceased (*ca.* 1 h). The catalyst was removed by filtration and thoroughly washed with ethyl acetate. The filtrate concentrated under reduced pressure.

Chromatography of the product (71 mg) on silica gel (7 g), with ethyl acetate-toluene (1:19) as eluent, gave 3-methoxy-14,16α-ethanoestra-1,3,5(10)-trien-17-one (**130**) (70 mg; 99%) identical to an authentic sample of (**130**) obtained above.

Acid Mediated Rearrangement of the 16ß,17ß-Diol (**128**)

A suspension of the 16ß,17ß-diol (**128**) (15 mg; 0.05 mmol) in anhydrous benzene (2 ml) was refluxed with toluene-*p*-sulphonic acid (3% adsorbed onto silica gel; 0.8 g; 0.13 mmol). After 3 h the reaction mixture was filtered and the filtrate evaporated under

reduced pressure to give the crystalline product 3-methoxy-14,16α-ethano-estra-1,3,5(10)-trien-17-one (**130**) (14 mg; 93%) identical to an authentic sample of (**130**) obtained above.

Acid Mediated Rearrangement of 3-*Methoxy*-16α-*methyl*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16ß,17ß-*diol* (**121**)

A solution of the 16ß-hydroxy-16α-methyl compound (**121**) (40 mg; 0.12 mmol) in anhydrous benzene (1 ml) at 21°C was treated with boron trifluoride etherate (0.06 ml; 0.49 mmol). After 50 min at 21°C, aqueous sodium hydrogen carbonate was added and the aqueous phase was extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the product (37 mg) on silica gel (4 g), with ethyl acetate-toluene (1:49) as eluent, gave 3-*methoxy*-16ß-*methyl*-14,16α-*ethenoestra*-1,3,5(10)-*trien*-17-*one* (**147**) (36 mg; 92%), m.p. 148-149°C (from chloroform-methanol); $[\alpha]_D$ -340° (*c* 1.0); ν_{max} 1723 (CO) cm^{-1}; δ (200 MHz) 1.10 (3H, s, 13ß-Me), 1.33 (3H, s, 16ß-Me), 1.92 and 2.15 (each 1H, d, *J* 9.0 Hz, 15α- and 15ß-H), 2.35 (1H, ddt, *J* 13.4, 2 x 4.6 and 3.9 Hz, 11α-H), 2.75 (1H, dt, *J* 11.0 and 2 x 4.4 Hz, 9α-H), 2.95 (2H, m, 6α- and 6ß-H), 3.80 (3H, s, 3-OMe), 5.80 and 6.58 (each 1H, d, *J* 5.5 Hz, 16^1- and 16^2-H), 6.68 (1H, d, *J* 2.7 Hz, 4-H), 6.75 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H), and 7.24 (1H, d, *J* 8.7 Hz, 1-H)(Found: C, 81.9; H, 8.2%; M^+, 322. $C_{22}H_{26}O_2$ requires C, 82.0; H, 8.1%, *M*, 322).

Hydrogenation of 16ß-*Methyl*-14,16α-*etheno*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (**148**)

The 14,16α-etheno compound (**147**) (10 mg; 0.03 mmol) in ethyl acetate (2 ml) at 20°C, was hydrogenated in the presence of palladium on carbon (10%, 3 mg) and hydrogen at atmospheric pressure until hydrogen uptake ceased (*ca.* 1 h). The catalyst was filtered off and thoroughly washed with ethyl acetate and chloroform and the filtrate was concentrated under reduced pressure. Passage of the product (12 mg), through a silica gel filtration column with ethyl acetate-toluene (1:49) as eluent, gave 16ß-methyl-14,16α-ethano-3-methoxyestra-1,3,5(10)-trien-17-one (**148**) (9 mg; 90%), m.p. 105-108°C (from ethyl acetate-hexane) (lit.,[114] 107-109°C).

(16^{1}R)-17,17-*Ethylenedioxy*-3-*methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16^1-*carbonitrile* (**149**)

The carbonitrile (**82**) (540 mg; 1.6 mmol) and toluene-*p*-sulphonic acid monohydrate (50 mg; 0.29 mmol) in ethylene glycol (2.0 ml) and toluene (54 ml) were distilled slowly in a Dean and Stark apparatus. After 7.5 h the volume was reduced to *ca.* 30 ml and the mixture was refluxed with return of the condensate through molecular sieves (4 Å) for a further 17 h. Aqueous sodium hydrogen carbonate was added to the cooled reaction mixture and the product was extracted with toluene. The extract was washed with water and aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated under reduced pressure to give a crystalline residue (632 mg).

Recrystallisation from chloroform-methanol gave (16^{1}R)-17,17-*ethylenedioxy*-3-*methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16^1-*carbonitrile* (**149**) (565 mg; 92 %), m.p. 232-237°C; $[\alpha]_D$ +133° (*c* 1.1); ν_{max} 2226 (CN) cm^{-1}; δ (200 MHz) 0.72 (3H, s, 13ß-Me), 1.84 (1H, dd, *J* 9.7 and 2.2 Hz, 16^2*S*-H), 2.17 (1H, d, *J* 5.2 Hz, 16α-H), 2.41 (1H, d, *J* 9.7 Hz, 16^2*R*-H), 2.89 (2H, m, 6α- and 6ß-H), 2.99 (1H, dd, *J* 5.2 and 2.2 Hz, 15α-H), 3.75 (3H, s, 3-OMe), 3.84-4.11 (4H, m, 17-OCH_2CH_2O), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.70 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), and 7.18 (1H, d, *J* 8.5 Hz,

1-H)(Found: C, 76.1; H, 7.3; N, 3.7%; M^+, 377. $C_{24}H_{27}NO_3$ requires C, 76.4; H, 7.2; N, 3.7,%; *M*, 377).

Flash chromatography of the mother liquor on silica gel (7 g), with ethyl acetate-toluene (1:19) as eluent, gave further 17-ketal (**149**) (39 mg; 6%).

(16^{1}R)-17,17-*Ethylenedioxy*-3-*methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16^1-*carbaldehyde* (**150**)

A solution of the ketal (**149**) (400 mg; 1.06 mmol) in anhydrous toluene (80 ml) at -78°C under nitrogen was treated with diisobutylaluminium hydride (20% solution in hexane; 3.6 ml; 3.6 mmol). After 160 min, aqueous ammonium chloride was added at -78°C. The reaction mixture was acidified with dilute sulphuric acid and extracted with ethyl acetate, and the extract was washed with sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure.

Flash chromatography of the residue (378 mg) on silica gel (40 g), with ethyl acetate-toluene (1:9) as eluent, gave (16^{1}R)-17,17-*ethylenedioxy*-3-*methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16^1-*carbaldehyde* (**150**) (335 mg; 83%), m.p. 190-194°C (from chloroform-hexane); $[\alpha]_D$ +165° (*c* 0.8); ν_{max} 1685 (CO) cm^{-1}; δ (200 MHz) 0.77 (3H, s, 13ß-Me), 1.62 (1H, dd, *J* 10.3 and 1.9 Hz, 16^2*S*-H), 2.45obsc. (1H, d, *J ca.* 5 Hz, 16α-H), 2.49obsc. (1H, d, *J ca.* 10 Hz, 16^2*R*-H), 2.84 (2H, m, 6α- and 6ß-H), 3.05 (1H, dd, *J* 5.3 and 1.9 Hz, 15α-H), 3.74 (3H, s, 3-OMe), 3.83-4.05 (4 H, m, 17-OCH_2CH_2O), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.69 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H), 7.19 (1H, d, *J* 8.7 Hz, 1-H), and 8.86 (1H, s, CHO)(Found: C, 75.7; H, 7.2%; M^+, 380. $C_{24}H_{28}O_4$ requires C, 75.8; H, 7.4%; *M*, 380).

(16^{1}S)-17,17-*Ethylenedioxy*-3-*methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene* (**151**)

The 16^1-carbaldehyde (**150**) (340 mg; 0.89 mmol) and $RhCl(PPh_3)_3$ (912 mg; 0.99 mmol) in deoxygenated toluene (25 ml) were refluxed under nitrogen. After 20 h ethanol was added to the cooled reaction mixture and most of the $RhCl(CO)(PPh_3)_2$ was removed by filtration. The filtrate was evaporated to dryness under reduced pressure.

Chromatography of the product (805 mg) on silica gel (34 g), with ethyl acetate-toluene (1:99) as eluent, gave (16^{1}S)-17,17-*ethylenedioxy*-3-*methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene* (**151**) (291 mg; 92%), m.p. 159-163°C (from chloroform-methanol); $[\alpha]_D$ +117° (*c* 1.0); δ (200 MHz) 0.73 (3H, s, 13ß-Me), 2.40 (1H, dt, *J* 2 x 11.6 and 3.8 Hz, 9α-H), 2.85 (2H, m, 6α- and 6ß-H), 3.75 (3H, s, 3-OMe), 3.84-4.09 (4 H, m, 17-OCH_2CH_2O), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.69 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), and 7.20 (1H, d, *J* 8.5 Hz, 1-H)(Found: C, 78.4; H, 8.2%; M^+, 352. $C_{23}H_{28}O_3$ requires C, 78.4; H, 8.0%; *M*, 352).

(16^{1}S)-3-*Methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**152**)

A solution of the 17-ketal (**151**) (150 mg; 0.43 mmol) in tetrahydrofuran (6 ml) and methanol (18 ml) at 0°C was treated with 6M-hydrochloric acid (1.2 ml; 7.2 mmol). After 6 min at 0°C, solid sodium hydrogen carbonate was added and the mixture was diluted with water and extracted with chloroform. The extract was washed with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated under reduced pressure.

Crystallisation of the residue (154 mg), from chloroform-methanol, gave (16^{1}S)-3-*methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**152**) (110 mg; 84%), m.p. 179-184°C; $[\alpha]_D$ +171° (*c* 1.0); ν_{max} 1711 (CO) cm^{-1}; δ (400 MHz) 0.87 (3H, s, 13ß-Me), 1.26 (1H, dd, *J* 10.5 and 2.9 Hz, 16^2*R*-H), 1.37 (1H, qd, *J* 2 x 13.4, 12.0 and 3.2 Hz, 11ß-H), 1.41-1.49 (2H, m, 12α- and 8ß-H), 1.67-1.76 (2H, m, 7α- and 12ß-H), 2.04 (1H, dd, *J* 6.5 and 4.1 Hz, 16α-H), 2.10 (1H, ddd, *J* 6.5, 3.9 and 3.7 Hz,

16^{1}α-H), 2.22-2.26 (1H, m, 7ß-H), 2.29 (1H, ddt, *J* 13.2 and 3 x 3.7 Hz, 11α-H), 2.45 (1H, dd, *J* 10.5 and 3.9 Hz, 16^2*S*-H), 2.48 (1H, td, *J* 2 x 11.5 and 3.2 Hz, 9α-H), 2.76 (1H, ddd, *J* 4.1, 3.7 and 2.9 Hz, 15α-H), 2.92 (2H, m, 6α- and 6ß-H), 3.78 (3H, s, 3-OMe), 6.66 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.5 Hz, 1-H); δ_C (100 MHz) 218.8 (C-17), 157.6 (C-3), 137.7 (C-5), 131.7 (C-10), 126.5 (C-1), 113.6 (C-4), 111.8 (C-2), 55.2 (3-OMe), 53.9 and 52.9 (C-13 and C-14), 39.2 (C-9), 37.9 (C-8), 32.9 and 20.4 (C-16 and C-16^1), 30.8 (C-15), 30.6 (C-12), 30.0 (C-6), 26.0 (C-16^2), 25.4 and 24.7 (C-7 and C-11), and 12.1 (C-18)(Found: C, 81.7; H, 7.7%; M^+, 308. $C_{21}H_{24}O_2$ requires C, 81.8; H, 7.8%; *M*, 308).

Chromatography of the mother liquor on silica gel (1.6 g), with ethyl acetate-toluene (1:19) as eluent, gave further 17-ketone (**152**) (10 mg; 8 %).

Reductions of (16^{1}S)-3-*Methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**152**)

(a) The 17-ketone (**152**) (398 mg; 1.3 mmol) in tetrahydrofuran (24 ml) under nitrogen was treated with excess lithium aluminium hydride at reflux. After 8 h, the reaction mixture was cooled and the excess reagent was destroyed by the addition of aqueous ammonium chloride. The mixture was extracted with ethyl acetate, and the extract was washed with aqueous ammonium chloride and water, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the residue (411 mg) on silica gel (40 g), with ethyl acetate-chloroform (1:99) as eluent, gave the (16^{1}S)-3-*methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*trien*-17ß-*ol* (**154**) (159 mg; 40%), m.p. 141-145°C (from methanol-water); $[\alpha]_D$ +133° (*c* 0.55); ν_{max} 3606 (OH) cm^{-1}; δ (200 MHz) 0.82 (3H, s, 13ß-Me), 1.39obsc. (1H, dd. *J* 9.6 and 2.5 Hz, 16^2*R*-H), 2.21obsc. (1H, dd, *J* 9.6 and 4.1 Hz, 16^2*S*-H), 2.85 (2H, m, 6α- and 6ß-H), 3.75 (3H, s, 3-OMe), 3.94 (1H, d, *J* 4.8 Hz, 17α-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.69 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.19 (1H, d, *J* 8.5 Hz, 1-H)(Found: C, 81.0; H, 8.5%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*,

310) followed by (16^{1}S)-3-*methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*trien*-17α-*ol* (**155**) (232 mg; 58%), m.p. 129-132°C (from ethyl acetate-hexane); $[\alpha]_D$ +75° (*c* 0.52); ν_{max} 3606 (OH) cm^{-1}; δ (200 MHz) 0.90 (3H, s, 13ß-Me), 1.27 (1H, dd, *J* 10.2 and 2.5 Hz, 16^2*R*-H), 2.13 (1H, dd, *J* 10.2 and 4.1 Hz, 16^2*S*-H), 2.43 (1H, m, 9α-H), 2.89 (2H, m, 6α- and 6ß-H), 3.78 (3H, s, 3-OMe), 4.18 (1H, s, 17ß-H), 6.65 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.24 (1H, d, *J* 8.5 Hz, 1-H)(Found: C, 81.3; H, 8.3%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310).

(b) A solution of the 17-ketone (**152**) (48 mg; 0.16 mmol) in tetrahydrofuran (5 ml) and ethanol (20 ml) at 20°C under nitrogen was treated with excess sodium borohydride. After 40 h at 20°C water was added and the reaction mixture was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the product (48 mg) on silica gel (6 g), with ethyl acetate-chloroform (1:99) as eluent, gave 17ß-alcohol (**154**) (10 mg; 21%) followed by 17α-alcohol (**155**) (32 mg; 67%) identical to authentic sample of (**154**) and (**155**) obtained in (a) above.

(c) A solution of the 17-ketone (**152**) (50 mg; 0.16 mmol) in 2-propanol (8 ml) was stirred in the presence of sodium metal at 75°C under nitrogen. After 19 h at 75°C methanol was added to the cooled reaction mixture and the product was extracted with chloroform, and the extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the product (87 mg) on silica gel (5 g), with ethyl acetate-toluene (1:19) as eluent, gave unreacted 17-ketone (**152**) (10 mg; 20%) followed by a mixed fraction of the 17-alcohols (**154** and **155**) (27 mg; 54%).

Rechromatography of the mixed fraction on silica gel (5.5 g), with ethyl acetate-chloroform (1:99) as eluent, gave the 17ß-alcohol (**154**) (12 mg; 24%), a mixed fraction

of the 17-alcohols (2 mg; 4%) followed by the 17α-alcohol (**155**) (12 mg; 24%) identical to authentic samples of (**154**) and (**155**) obtained in (a) above.

Reductions of (16¹*R*)-3-*Methoxy*-17-*oxo*-15ß,16¹-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16¹-*carbonitrile* (**82**)

(a) A vigorously stirred suspension of the carbonitrile (**82**) (100 mg; 0.30 mmol) in ethanol (10 ml) at 20°C was treated with sodium borohydride (55 mg; 1.5 mmol). After 2 h at 20°C, water was added and the product was extracted with ethyl acetate. The organic phase was washed with aqueous ammonium chloride and water, dried ($MgSO_4$) and evaporated under reduced pressure.

The residue (115 mg) was chromatographed on silica gel (17 g), with ethyl acetate-chloroform (1:9) as eluent, to give (16¹R)-17α-*hydroxy*-3-*methoxy*-15ß,16¹-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16¹-*carbonitrile* (**156**) (44 mg; 44%), m.p. 150-154°C (from ethyl acetate-hexane); $[\alpha]_D$ +114° (*c* 1.0); ν_{max} 3600 and 3422 (OH), and 2225 (CN) cm^{-1}; δ (200 MHz) 0.92 (3H, s, 13ß-Me), 1.73 (1H, d, *J* 6.8 Hz, exch. by D_2O, 17α-OH), 2.07 (1H, d, *J* 5.2 Hz, 16α-H), 2.42 (1H, d, *J* 10.8 Hz, 16²*R*-H), 2.92 (2H, m, 6α- and 6ß-H), 3.05 (1H, br dd, *J ca.* 5 and 2 Hz, 15α-H), 3.78 (3H, s, 3-OMe), 4.26 (1H, d, *J* 6.8 Hz → s on D_2O exch., 17ß-H), 6.66 (1H, d, *J* 2.3 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.3 Hz, 2-H), and 7.22 (1H, d, *J* 8.5 Hz, 1-H)(Found: C, 78.7; H, 7.6; N, 4.2%; *M*+, 335. $C_{22}H_{25}NO_2$ requires C, 78.8; H, 7.6; N, 4.2%; *M*, 335), a mixed fraction of (**156**) and (**157**) (51 mg) followed by (16¹R)-17ß-*hydroxy*-3-*methoxy*-15ß,16¹-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16¹-*carbonitrile* (**157**) (1 mg; 1%), m.p. 137-141°C (from ethyl acetate-hexane); $[\alpha]_D$ +129° (*c* 1.0); ν_{max} 3607 and 3440 (OH), and 2225 (CN) cm^{-1}; δ (200 MHz) 0.86 (3H, s, 13ß-Me), 1.83obsc. (1H, d, *J* 4.8 Hz, exch. by D_2O, 17ß-OH), 1.88 (1H, dd, *J* 9.7 and 2.0 Hz, 16²*S*-H), 2.42obsc. (1H, t, *J* 2 x 4.8 Hz, 16α-H), 2.47obsc. (1H, d, *J* 9.7 Hz, 16²*R*-H), 2.92 (2H, m, 6α- and 6ß-H), 3.02 (1H, dd, *J* 4.8 and 2.0 Hz, 15α-H), 3.78 (3H, s, 3-OMe), 4.07 (1H, t, *J* 2 x 4.8 Hz → d, *J* 4.8 on D_2O exch., 17α-H), 6.65 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H),

and 7.19 (1H, d, *J* 8.6 Hz, 1-H)(Found: C, 78.7; H, 7.7; N, 4.1%; M^+, 335. $C_{22}H_{25}NO_2$ requires C, 78.8; H, 7.5; N, 4.2%; *M*, 335).

The mixed fraction (51 mg) was rechromatographed on silica gel (5 g), with ethyl acetate-chloroform (1:9) as eluent, to give further (**156**) (15 mg; 15%), a mixed fraction of (**156**) and (**157**) (2 mg) followed by further (**157**) (26 mg; 26%).

(b) A solution of the carbonitrile (**82**) (100 mg; 0.30 mmol) in tetrahydrofuran (5 ml) at 0°C under nitrogen was treated with lithium tri(*s*-butyl)borohydride (M in tetrahydrofuran; 0.38 ml; 0.33 mmol). After 1 h aqueous sodium hydrogen carbonate was added and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure.

Chromatography of the product (159 mg) on silica gel (15 g), with ethyl acetate-toluene (1:4) as eluent, gave 17ß-alcohol (**157**) (73 mg; 73%) identical to an authentic sample of (**157**) isolated in (a) above.

(c) A solution of the cyano ketone (**82**) (290 mg; 0.87 mmol) in toluene (50 ml) at -78°C under nitrogen was treated with diisobutylaluminium hydride (20% solution in hexane; 2.7 ml; 2.7 mmol). After 60 min at -78°C, the reaction was quenched with water. Aqueous sodium hydrogen carbonate was added and the mixture was extracted into ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a product which was used directly in the next experiment.

The mixture of 17ξ-hydroxy-16^1-carbaldehydes (**158** and **159**) (306 mg) in deoxygenated toluene (42 ml) under nitrogen was refluxed with $RhCl(PPh_3)_3$ (700 mg; 0.76 mmol). After 19 h at reflux, ethanol was added to the cooled reaction mixture which was filtered through Celite and the filtrate was evaporated under reduced pressure.

The residue (400 mg) was chromatographed on silica gel (62 g), with ethyl acetate-chloroform (1:99) as eluent, to give the 17ß-alcohol (**154**) (97 mg; 36%), the 17α-

alcohol (**155**) (116 mg; 43%), identical to authentic samples of (**154**) and (**155**) isolated above, followed by starting material (**82**) (20 mg; 7%).

(d) A solution of the carbonitrile (**82**) (0.8 g; 2.4 mmol) in anhydrous toluene (32 ml) at -78°C under nitrogen was treated with diisobutylaluminium hydride (1.5M solution in toluene; 5.0 ml; 7.5 mmol). After 60 min at -78°C the reaction was quenched with water. A similar work up to that described in (a) above gave a crystalline product (1.13 g).

Chromatography on silica gel (80 g), with ethyl acetate-chloroform (1:4) as eluent, gave (16^{1}R)-17α-*hydroxy*-3-*methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16^1-*carbaldehyde* (**158**) (346 mg; 43%), m.p. 134-137°C (from ethyl acetate-hexane); $[\alpha]_D$ +115° (*c* 1.0); ν_{max} 3608 and 3436 (OH), and 1684 (CO) cm^{-1}; δ (200 MHz) 0.96 (3H, s, 13ß-Me), 1.75 (1H, d, *J* 6.4 Hz, exch. by D_2O, 17α-OH), 2.32obsc. (1H, d, *J* 5.1 Hz, 16α-H), 2.48 (1H, d, *J* 11.0 Hz, 16^2*R*-H), 2.87 (2H, m, 6α- and 6ß-H), 3.12 (1H, br dd, *J ca.* 5 and 2 Hz, 15α-H), 3.78 (3H, s, 3-OMe), 4.28 (1H, d, *J* 6.4 Hz → s on D_2O exch., 17ß-H), 6.64 (1H, d, *J* 2.5 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.5 Hz, 2-H), 7.22 (1H, d, *J* 8.5 Hz, 1-H), and 8.81 (1H, s, CHO)(Found: C, 77.7; H, 7.7%; *M*$^+$, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; *M*, 338) followed by (16^{1}R)-17ß-*hydroxy*-3-*methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16^1-*carbaldehyde* (**159**) (310 mg; 38%), m.p. 178-183°C (from ethyl acetate-hexane); $[\alpha]_D$ +134° (*c* 1.0); ν_{max} 3608 and 3440 (OH), and 1688 (CO) cm^{-1}; δ_H (200 MHz) 0.91 (3H, s, 13ß-Me), 1.60 (1H, dd, *J* 10.5 and 1.9 Hz, 16^2*S*-H), 1.73 (1H, d, *J* 4.7 Hz, exch. by D_2O, 17ß-OH), 2.58 (1H, d, *J* 10.5 Hz, 16^2*R*-H), 2.76 (1H, t, *J* 2 x 4.7 Hz, 16α-H), 2.88 (2H, m, 6α- and 6ß-H), 3.09 (1H, dd, *J* 4.7 and 1.9 Hz, 15α-H), 3.78 (3H, s, 3-OMe), 4.12 (1H, t, *J* 2 x 4.7 Hz → d, *J* 4.7 Hz on D_2O exch., 17α-H), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.8 and 2.8 Hz, 2-H), 7.20 (1H, d, *J* 8.8 Hz, 1-H), and 8.91 (1H, s, CHO); δ_C (50 MHz) 197.3 (16^1-CHO), 157.7 (C-3), 137.8 (C-5), 131.9 (C-10), 126.5 (C-1), 113.6 (C-4), 111.9 (C-2), 81.6 (C-17), 55.2 (3-OMe), 54.1, 48.2 and 34.8 (C-13, C-14 and C-16^1), 40.6 (C-15), 39.0 (C-9), 38.2 (C-8 and C-16), 34.0, 26.4, 24.7 and 21.8 (C-7, C-11, C-12

and C-16[2]), 30.1 (C-6), and 12.6 (C-18)(Found: C, 78.1; H, 7.8%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; *M*, 338).

Oxidation of a Mixture of the 17α- and 17ß-*Alcohols* (**154**) and (**155**)

A solution of the alcohols (**154** and **155**) (539 mg; 1.74 mmol) in acetone (10 ml) 0°C was oxidised with Jones' reagent for 30 min, then water was added and the product was extracted with chloroform, the extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure.

Flash chromatography of the product (520 mg) on silica gel (52 g) with ethyl acetate-toluene (1:49) as eluent, gave the 17-ketone (**152**) (483 mg; 90%) identical to an authentic sample of (**152**) obtained above.

(16[1]S)-15ß,16[1]-*Cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-3,17ß-*diol* (**160**)

A solution of the 3-methyl ether (**154**) (150 mg; 0.47 mmol) in toluene (27 ml) under nitrogen was treated with diisobutylaluminium hydride (20% solution in hexane; 3.9 ml; 3.9 mmol) at reflux for 23.5 h. Aqueous ammonium chloride and water were added to the cooled reaction mixture. The mixture was acidified with hydrochloric acid and extracted into ethyl acetate. The extract was washed with aqueous ammonium chloride and water, dried ($MgSO_4$), and evaporated under reduced pressure.

Flash chromatography of the product (150 mg) on silica gel (15 g), with methanol-chloroform (1:19) as eluent, gave (16[1]S)-15ß,16[1]-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-3,17ß-*diol* (**160**) (113 mg, 79%), m.p. 247-249°C (from chloroform-methanol); $[\alpha]_D$ +118° (*c* 0.41); ν_{max} 3567 (OH) cm^{-1} (Found: C, 81.0; H, 7.8%; M^+, 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%; *M*, 296).

(16¹S)-15ß,16¹-*Cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-3,17α-*diol* (**161**)

Treatment of the 3-methyl ether (**155**) (109 mg; 0.35 mmol) with diisobutylaluminium hydride (3.5 ml; 3.5 mmol) for 23.5 h, as described in the foregoing experiment, followed by the similar work-up, and chromatography of the product (120 mg) on silica gel (12 g), with ethyl acetate-chloroform (1:1) as eluent, gave (16¹S)-15ß,16¹-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-3,17α-*diol* (**161**) (100 mg; 95%), m.p. 205-210°C (from acetone-hexane); $[\alpha]_D$ +79° (*c* 0.46 in tetrahydrofuran); ν_{max} 3574 (OH) cm^{-1} (Found: C, 80.9; H, 7.9%; M^+, 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%; *M*, 296).

(16¹R)-17,17-*Ethylenedioxy*-16¹-*hydroxymethyl*-3-*methoxy*-15ß,16¹-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene* (**165**)

A solution of the formyl ketal (**150**) (200 mg; 0.53 mmol) in tetrahydrofuran (20 ml) was added over 15 min to a vigorously stirred suspension of lithium aluminium hydride (100 mg; 2.6 mmol) in tetrahydrofuran (20 ml) at room temperature under nitrogen. After an additional 15 min, aqueous sodium hydrogen carbonate was added to the reaction mixture. The organic phase was extracted with chloroform and the combined organic phase was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure.

Chromatography of the product (219 mg) on silica gel (20 g), with ethyl acetate-toluene (3:7) as eluent, gave (16¹R)-17,17-*ethylenedioxy*-16¹-*hydroxymethyl*-3-*methoxy*-15ß,16¹-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene* (**165**) (166 mg; 83%), m.p. 98-101°C (from chloroform-methanol); $[\alpha]_D$ +106° (*c* 1.0); ν_{max} 3604 (OH) cm^{-1}; δ (200 MHz) 0.77 (3H, s, 13ß-Me), 1.61 (1H, dd, *J* 9.5 and 2.6 Hz, 16²*R*-H), 2.17 (1H, d, *J* 9.5 Hz, 16²*S*-H), 2.87 (2H, m, 6α- and 6ß-H), 3.54 and 3.61 (each 1H, d, *J* 11.8 Hz → s on D_2O exch., 16¹-CH_2OH), 3.77 (3H, s, 3-OMe), 3.82-4.07 (4H, m, 17-OCH_2CH_2O), 6.63

(1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.5 Hz, 1-H)(Found: C, 75.1; H, 8.2%; M^+, 382. $C_{24}H_{30}O_4$ requires C, 75.4; H, 7.9%; *M*, 382).

16^1-*Hydroxymethyl*-3-*methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**166**)

A solution of the hydroxymethyl ketal (**165**) (170 mg; 0.45 mmol) in tetrahydrofuran (5 ml) at 0°C was treated with aqueous 6M-hydrochloric acid (0.22 ml; 1.32 mmol). After 1 h, aqueous sodium hydrogen carbonate was added and the organic phase was extracted with chloroform. The combined organic phase was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure.

Chromatography of the product (124 mg) on silica gel (130 mg) with ethyl acetate-toluene (3:1) as eluent, gave 16^1-*hydroxymethyl*-3-*methoxy*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**166**) (121 mg; 80%), m.p. 192-196°C (from ethyl acetate); $[\alpha]_D$ +145° (*c* 1.0); ν_{max} 3609 and 3416 (OH), and 1710 (CO) cm^{-1}; δ (200 MHz) 0.90 (3H, s, 13ß-Me), 1.34 (1H, dd, *J* 10.4 and 2.9 Hz, 16^2*R*-H), 2.08 (1H, d, *J* 4.3 Hz, 16α-H), 2.47 (1H, d, *J* 10.4 Hz, 16^2*S*-H), 2.83 (1H, dd, *J* 4.3 and 2.9 Hz, 15α-H), 2.92 (2H, m, 6α- and 6ß-H), 3.64 and 3.76 (each 1H, d, *J* 12.2 Hz, 16^1-C*H*$_2$OH), 3.78 (3H, s, 3-OMe), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.8 and 2.7 Hz, 2-H), and 7.21 (1H, d, *J* 8.8 Hz, 1-H)(Found: C, 78.1; H, 7.9; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7; *M*, 338).

Calcium-Ammonia Reduction of (16^{1}R)-3-*Methoxy*-17-*oxo*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16^1-*carbonitrile* (**82**)

(a) A solution of the carbonitrile (**82**) (250 mg; 0.75 mmol) in tetrahydrofuran (15 ml) was added dropwise over 15 min to a stirred mixture of calcium metal (300 mg; 7.5 g atom) in anhydrous liquid ammonia (25 ml) (freshly distilled from sodium) and anhydrous tetrahydrofuran (10 ml) at -78°C under nitrogen. After 3 min bromobenzene (1 ml; 9.5 mmol) was added. After the reaction mixture had turned colourless solid ammonium chloride was added, followed by water. The ammonia was allowed to

evaporate and the residue was extracted with ethyl acetate, and the extract was washed with aqueous ammonium chloride and water, dried ($MgSO_4$), and concentrated under reduced pressure.

The residue (348 mg) was chromatographed on silica gel (25 g), with ethyl acetate-toluene (1:19) as eluent, to give 3-*methoxy*-17-*oxo*-15αH-*dihydrocyclobuta*[14,15]-14ß-*estra*-1,3,5(10)-*triene*-3'ß-*carbonitrile* (**175**) (178 mg; 71%), m.p. 158-161°C (from chloroform-methanol); $[\alpha]_D$ +170° (*c* 1.0); ν_{max} 2237 (CN) and 1735 (CO) cm^{-1}; δ_H (400 MHz) 0.93 (3H, s, 13ß-Me), 1.33 (1H, qd, *J* 3 x 12.8 and 3.5 Hz, 11ß-H), 1.45 (1H, td, *J* 2 x 12.8 and 3.5 Hz, 12α-H), 1.51-1.60 (2H, m, 8ß- and 12ß-H), 1.71 (1H, qd, *J* 3 x 12.1 and 6.8 Hz, 7α-H), 1.98 (1H, dd, *J* 12.9 and 9.5 Hz, 4'α-H), 2.17 (1H, m, $W_{\frac{1}{2}}$ 10.1 Hz, 7ß-H), 2.30 (1H, ddt, *J* 12.8, 3 x 3.5 Hz, 11α-H), 2.38 (1H, ddd, *J* 12.9, 9.5 and 3.9 Hz, 4'ß-H), 2.46 (1H, br t, *J ca.* 2 x 11 Hz, $W_{\frac{1}{2}}$ 3.7 Hz, 9α-H), 2.72 (1H, dd, *J* 19.3 and 1.5 Hz, 16ß-H), 2.93-3.02 (3H, m, 6α-, 6ß- and 15α-H), 3.13 (1H, dd, *J* 19.3 and 10.4 Hz, 16α-H), 3.31 (1H, ddd, *J* 2 x 9.5 and 7.9 Hz, 3'α-H), 3.75 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.18 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 218.2 (C-17), 157.7 (C-3), 137.0 (C-5), 130.4 (C-10), 127.4 (C-1), 119.3 (3'-CN), 113.5 (C-4), 112.3 (C-2), 55.2 (3-OMe), 53.3 and 51.5 (C-13 and C-14), 40.7 and 38.7 (C-8 and C-9), 37.8 (C-16), 33.2 (C-15), 32.9, 26.9 and 23.7 (C-7, C-11 and C-12), 31.5 (C-4'), 30.5 (C-6), 23.8 (C-3'), and 12.4 (C-18)(Found: C, 78.7; H, 7.5; N, 4.3%; M^+ 335. $C_{22}H_{25}NO_2$ requires C, 78.8; H, 7.5; N, 4.2%; *M*, 335).

(b) A solution of the carbonitrile (**82**) (243 mg; 0.73 mmol) in tetrahydrofuran (6 ml) was added rapidly to a stirred mixture of lithium metal (61 mg; 8.8 g atom) in anhydrous liquid ammonia (30 ml) (freshly distilled from sodium) and tetrahydrofuran (24 ml) at -78°C under nitrogen. The solution became colourless but regained its blue colour after several min and, after an additional 1 min, solid ammonium chloride was added. Water was added and after the ammonia had evaporated, the residue was extracted with ethyl acetate. The extract was washed with brine and water, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the residue (253 mg) on silica gel (24 g), with ethyl acetate-toluene (1:19) as eluent, gave the 16,16[1]-seco compound (**175**) (4 mg; 2%) followed by 17α-*hydroxy*-3-*methoxy*-*dihydrocyclobuta*[14,15]-14ß-*estra*-1,3,5(10)-*triene*-3'ß-*carbonitrile* (**176**) (125 mg; 51%), m.p. 185-188°C (from chloroform-hexane); $[\alpha]_D$ +70° (*c* 1.0); ν_{max} 3006 (OH) and 2235 (CN) cm^{-1}; δ (200 MHz) 0.93 (3H, s, 13ß-Me), 2.35 (1H, dd, *J* 14.3 and 7.2 Hz, 16ß-H), 2.68 (1H, br t, *J ca.* 9.0 and *W* 4 Hz, 15ß-H), 2.91 (2H, m, 6α- and 6ß-H), 3.13 (1H, ddd, *J* 2 x 9.6 Hz and 9.0 Hz, 3'α-H), 3.78 (1H, s, 3-OMe), 4.40 (1H, dd, *J* 10.5 and 7.2 Hz, 17ß-H), 6.63 (1H, d, *J* 2.8 Hz, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.25 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 157.6 (C-3), 137.3 (C-5), 131.5 (C-10), 127.4 (C-1), 120.0 (3'-CN), 113.4 (C-4), 112.1 (C-2), 79.8 (C-17), 55.2 (3-OMe), 52.9 and 44.6 (C-13 and C-14), 41.4 (C-8), 39.1 (C-9), 35.1 (C-15), 34.0 (C-16), 30.7 (C-6), 29.3, 28.8, 26.6 and 23.8 (C-7, C-11, C-12 and C-4'), 22.4 (C-3'), and 15.7 (C-18)(Found: C, 78.3; H, 8.2; N, 4.1%; M^+, 337. $C_{22}H_{27}NO_2$ requires C, 78.3; H, 8.1; N, 4.2%; *M*, 337).

Diisobutylaluminium Hydride Reduction-Decarbonylation of 3-*Methoxy*-17-*oxo*-*dihydrocyclobuta*[14,15]-14ß-*estra*-1,3,5(10)-*triene*-3'ß-*carbonitrile* (**175**)

A solution of compound (**175**) (358 mg; 1.1 mmol) in toluene (52 ml) at -78°C under nitrogen was treated with diisobutylaluminium hydride (20% solution in hexane; 3.2 ml; 3.2 mmol). After 3 h at -78°C, aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the extract was washed with aqueous ammonium chloride and water, dried ($MgSO_4$), and evaporated under reduced pressure to give a product (350 mg) which was used directly in the following experiment.

The mixture of 17ξ-hydroxy-3'-carbaldehydes (**178** and **179**) (350 mg) in deoxygenated toluene (30 ml) under nitrogen was refluxed with $RhCl(PPh_3)_3$ (1.31 g; 1.4 mmol). After 7.5 h ethanol was added to the cooled reaction mixture and most of the catalyst was removed by filtration. The filtrate was evaporated to dryness.

Flash chromatography of the product (1.3 g) on silica gel (43 g), with ethyl acetate-

toluene (1:49) as eluent, gave 3-*methoxy-dihydrocyclobuta*[14,15]-14ß-*estra*-1,3,5(10)-*trien*-17ß-*ol* (**178**) (32 mg; 8%), m.p. 68-69°C (from chloroform-methanol); $[\alpha]_D$ +85° (*c* 1.0); ν_{max} 3612 (OH) cm^{-1}; δ (200 MHz) 0.91 (3H, s, 13ß-Me), 2.82 (2H, m, 6α- and 6ß-H), 3.71 (3H, s, 3-OMe), 3.81 (1H, d, *J* 5.8 Hz, 17α-H), 6.57 (1H, d, *J* 2.7 Hz, 4-H), 6.65 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), and 7.15 (1H, d, *J* 8.5 Hz, 1-H)(Found: C, 80.3; H, 9.0%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.4; H, 9.0; *M*, 312) followed by 3-*methoxy-dihydrocyclobuta*[14,15]-14ß-*estra*-1,3,5(10)-*trien*-17α-*ol* (**179**) (203 mg; 51%), m.p. 49-51°C (from dichloromethane-methanol); $[\alpha]_D$ +80° (*c* 0.96); ν_{max} 3608 (OH) cm^{-1}; δ (200 MHz) 0.90 (3H, s, 13ß-Me), 2.89 (2H, m, 6α- and 6ß-H), 3.77 (3H, s, 3-OMe), 4.38 (1H, t, *J* 2 x 8.8 Hz, 17ß-H), 6.63 (1H, d, *J* 2.5 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.5 Hz, 2-H), and 7.24 (1H, d, *J* 8.5 Hz, 1-H)(Found: C, 80.6; H, 8.9%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.4; H, 9.0%; *M*, 312).

Dihydrocyclobuta[14,15]-14ß-*estra*-1,3,5(10)-*triene*-3,17α-*diol* (**180**)

A solution of the 3-methyl ether (**179**) (144 mg; 0.46 mmol) in anhydrous toluene (29 ml) under nitrogen was treated with diisobutylaluminium hydride (20% solution in hexane; 4.9 ml; 4.9 mmol) under reflux. After 66 h, the reaction mixture was cooled to room temperature, and quenched by the addition of aqueous ammonium chloride. Water was added and the aqueous phase was extracted with ethyl acetate after acidification with dilute acetic acid. The organic phase was washed with saturated aqueous ammonium chloride and water, dried ($MgSO_4$), and evaporated to dryness.

Flash chromatography of the product (149 mg) on silica gel (16 g), with ethyl acetate-toluene (1:4) as eluent, gave *dihydrocyclobuta*[14,15]-14ß-*estra*-1,3,5(10)-*triene*-3,17α-*diol* (**180**) (129 mg; 93%), m.p. 205-207°C (from diisopropyl ether); $[\alpha]_D$ +93° (*c* 0.68 in tetrahydrofuran); ν_{max} 3459 (OH) cm^{-1} (Found: C, 80.3; H, 8.8%; M^+, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%; *M*, 298).

Lithium-Ammonia Reduction of (16[1]R)-17,17-*Ethylenedioxy*-3-*methoxy*-15ß,16[1]-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16[1]-*carbonitrile* (**149**)

Lithium metal (63 mg; 9.1 g atom) was added to a stirred mixture of anhydrous liquid ammonia (30 ml) (freshly distilled from sodium) and anhydrous tetrahydrofuran (22 ml) to give a blue solution. A solution of the ketal (**149**) (275 mg; 0.73 mmol) in tetrahydrofuran (70 ml) was added to this mixture at -78°C. After 4 min solid ammonium chloride was added in portions, and the reaction mixture stirred at -78°C until it became colourless. Water was added and the ammonia was allowed to evaporate and the residue was extracted with ethyl acetate, and the extract was washed with brine and water, dried ($MgSO_4$), and concentrated under reduced pressure.

The product (277 mg) was chromatographed on silica gel (28 g), with ethyl acetate-hexane (1:4) as eluent, to give 17,17-*ethylenedioxy*-3-*methoxy*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene* (**181**) (65 mg; 25%), m.p. 133-137°C (from chloroform-methanol); $[\alpha]_D$ +52° (*c* 1.0); δ (200 MHz) 0.95 (3H, s, 13ß-Me), 2.24 (1H, m, 11α-H), 2.42 (1H, m, 9α-H), 2.82 (2H, m, 6α- and 6ß-H), 3.75 (3H, s, 3-OMe), 3.80-3.84 (4H, m, 17-OCH_2CH_2O), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.68 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.5 Hz, 1-H)(Found: C, 77.8; H, 8.5%; M^+, 354. $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354).

3-*Methoxy*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**146**)

The 17-ketal (**181**) (15 mg; 0.04 mmol) in tetrahydrofuran (3 ml) and methanol (4 ml) at 0°C was treated with 6M-hydrochloric acid (0.2 ml; 1.2 mmol). After 4 h at 0°C, aqueous sodium hydrogen carbonate was added and the product was extracted with chloroform, and the extract was washed with sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated under reduced pressure.

Flash chromatography of the product (15 mg) on silica gel (3 g), with ethyl acetate-toluene (1:49) as eluent, gave 3-methoxy-14,16ß-ethano-14ß-estra-1,3,5(10)-trien-17-one (**146**) (13 mg; 99%), m.p. 167-172°C (from chloroform-methanol)(lit.,[114] 168-

170°C); $[\alpha]_D$ +174° (*c* 0.5); ν_{max} 1731 (CO) cm^{-1}; δ_H (200 MHz) 1.06 (3H, s, 13ß-Me), 2.32 (1H, ddt, *J* 12.7 and 3 x 3.5 Hz, 11α-H), 2.53 (1H, m, 9α-H), 2.65 (1H, d, *J* 3.9 Hz, 16α-H), 2.88 (2H, m, 6α- and 6ß-H), 3.77 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 222.3 (C-17), 157.6 (C-3), 137.9 (C-5), 132.4 (C-10), 126.6 (C-1), 113.6 (C-4), 111.7 (C-2), 55.2 (3-OMe), 52.7 and 48.7 (C-13 and C-14), 50.4 (C-16), 40.2 (C-9), 38.7 (C-8), 30.5 (C-6), 33.8, 30.5, 26.1, 25.7, 25.1 and 23.8 (C-7, C-11, C-12, C-15, C-16^1 and C-16^2), and 16.9 (C-18)(Found: C, 81.1; H, 8.3%; *M*+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310).

(16^{1}R)-3-*Methoxy*-17-*oxo*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16^1-*carbaldehyde* (**182**)

(a) A mixture of the 17ξ-hydroxy-16^1-carbaldehydes (**158** and **159**) (50 mg; 0.15 mmol) in dichloromethane (3 ml) at 0°C was treated with pyridinium dichromate (84 mg; 0.22 mmol) and after 2 h at 0°C, the reaction mixture was kept at 20°C for 22 h, then water was added and the product was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure.

Chromatography of the product (52 mg) on silica gel (5 g), with ethyl acetate-toluene (3:17) as eluent, gave (16^{1}R)-3-*methoxy*-17-*oxo*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16^1-*carbaldehyde* (**182**) (30 mg; 60%), m.p. 182-187°C (from ethyl acetate); $[\alpha]_D$ +200° (*c* 0.8); ν_{max} 1731 (CO) and 1697 (CO) cm^{-1}; δ_H (400 MHz) 0.94 (3H, d, *J* 0.6 Hz, 13ß-Me), 1.37 (1H, dd, *J* 11.0 and 2.4 Hz, 16^2*S*-H), 2.19 (1H, m, 7ξ-H), 2.33 (1H, ddt, *J* 13.4 and 3 x 3.7 Hz, 11α-H), 2.48 (1H, td, *J* 2 x 11.8 and 3.7 Hz, 9α-H), 2.79 (1H, d, *J* 11.0 Hz, 16^2*R*-H), 2.89 (1H, d, *J* 4.5 Hz, 16α-H), 2.92 (2H, m, 6α- and 6ß-H), 3.39 (1H, dd, *J* 4.5 and 2.4 Hz, 15α-H), 3.78 (3H, s, 3-OMe), 6.66 (1H, d, *J* 2.8 Hz, 4-H), 6.74 (1H, dd, *J* 8.4 and 2.8 Hz, 2-H), 7.21 (1H, d, *J* 8.4 Hz, 1-H), and 8.97 (1H, s, 16^1-CHO); δ_C (100 MHz) 214.0 (C-17), 194.0 (16^1-CHO), 157.8 (C-3), 137.5 (C-5), 130.9 (C-10), 126.5 (C-1), 113.6 (C-4), 112.0 (C-2), 55.2 (3-OMe), 53.7 and 51.8

(C-13 and C-14), 39.1 (C-9), 38.8 (C-16), 38.5 (C-15), 37.5 (C-8), 37.4 (C-16^1), 30.6, 25.3, 24.5 and 23.6 (C-7, C-11, C-12 and C-16^2), 29.8 (C-6), and 12.2 (C-18)(Found: C, 78.7; H, 7.1%; M^+, 336 . $C_{22}H_{24}O_3$ requires C, 78.5; H, 7.2%; *M*, 336).

(b) A solution of the 17,17-ethylenedioxy-16^1-carbaldehyde (**150**) (300 mg; 0.79 mmol) in tetrahydrofuran (8 ml) at 0°C was treated with 6M-hydrochloric acid (0.3 ml; 1.8 mmol) and after 90 min at 0°C the reaction was allowed to come up to room temperature. After a total reaction time of 230 min aqueous sodium hydrogen carbonate was added and the reaction mixture was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), and evaporated to dryness.

Chromatography of the product (320 mg) on silica gel (30 g), with ethyl acetate-toluene (1:9) as eluent, gave the formyl ketone (**182**) (230 mg; 87%) identical to an authentic sample of (**182**) isolated in (a) above followed by an unidentified compound (32 mg).

Calcium-Ammonia Reduction of (16^{1}R)-3-*Methoxy*-17-*oxo*-15ß,16^1-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*triene*-16^1-*carbaldehyde* (**182**)

A solution of the formyl ketone (**182**) (100 mg; 0.30 mmol) in tetrahydrofuran (4 ml) was added dropwise over 6 min to a stirred mixture of calcium metal (130 mg; 3.2 g atom) in anhydrous liquid ammonia (55 ml) (freshly distilled from sodium) and tetrahydrofuran (4 ml) at -78°C under nitrogen. After an additional 10 min, bromobenzene (0.5 ml; 4.8 mmol) was added and after the reaction mixture had become colourless, solid ammonium chloride was added, followed by water. The ammonia was allowed to evaporate and the aqueous phase was extracted with chloroform, and the extract was washed with aqueous ammonium chloride and water, dried ($MgSO_4$) and concentrated under reduced pressure.

The residue (136 mg) was passed through a filtration column of silica gel with ethyl acetate-toluene (1:9) as eluent. Recrystallisation of this product (90 mg) from ethyl

acetate gave 3-methoxy-17-oxo-dihydrocyclobuta[14,15]-14ß-estra-1,3,5(10)-triene-3'ß-carbaldehyde (**184**) (19 mg; 19%), m.p. 162-168°C; $[\alpha]_D$ +185° (*c* 1.0); ν_{max} 1731 (17-CO) and 1704 (CHO) cm^{-1}; δ (400 MHz) 0.97 (3H, s, 13ß-Me), 1.33 (1H, qd, *J* 3 x 13.3 and 3.0 Hz, 11ß-H), 1.40 (1H, td, *J* 2 x 13.3 and 3.1 Hz, 12α-H), 1.51 (1H, dt, *J* 13.3 and 2 x 3.0 Hz, 12ß-H), 1.59 (1H, td, *J* 2 x 12.5 and 1.8 Hz, 8ß-H), 1.70-1.80 (1H, m, 7α-H), 1.97 (1H, ddd, *J* 13.0, 8.6 and 3.8 Hz, 4'ß-H), 2.09 (1H, dd, *J* 13.0 and 10.0 Hz, 4'α-H), 2.20 (1H, dd, *J* 19.4 and 1.7 Hz, 16ß-H), 2.24-2.31 (2H, m, 7ß- and 11α-H), 2.50 (1H, br t, *J ca.* 2 x 11.2 and $W_{\frac{1}{2}}$ 7.1 Hz, 9α-H), 2.91 (1H, dd, *J* 19.4 and 10.3 Hz, 16α-H), 2.96 (2H, m, 6α- and 6ß-H), 3.15 (1H, br t, *J ca.* 10.3 and $W_{\frac{1}{2}}$ 7.4 Hz, 15α-H), 3.21 (1H, ddd, *J* 10.0 and 2 x 8.6 Hz, 3'α-H), 3.78 (3H, s, 3-OMe), 6.65 (1H, d, *J* 2.8 Hz, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.22 (1H, d, *J* 8.6 Hz, 1-H), and 9.67 (1H, d, *J* 0.8 Hz, 3'α-CHO); δ_C (100 MHz) 219.4 (C-17), 202.0 (3'-CHO), 157.6 (C-3), 137.4 (C-5), 130.9 (C-10), 127.4 (C-1), 113.5 (C-4), 112.2 (C-2), 55.2 (3-OMe), 51.7 and 49.7 (C-13 and C-14), 44.2 (C-3'), 41.2 (C-8), 38.9 (C-9), 36.0, 33.4, 27.1, 26.5 and 23.8 (C-7, C-11, C-12, C-16 and C-4'), 33.5 (C-15), 30.8 (C-6), and 12.6 (C-18)(Found: M^+, 338.187. $C_{22}H_{26}O_3$ requires *M*, 338.188).

Flash chromatography of the mother liquor material (48 mg) on silica gel (9.6 g), with ethyl acetate-toluene (1:9) as eluent, gave 3-methoxy-17-oxo-dihydrocyclobuta[14,15]-14ß-estra-1,3,5(10)-triene-3'α-carbaldehyde (**183**) (7 mg) as an oil; ν_{max} 1725 (CO) cm^{-1}; δ (200 MHz) 1.01 (3H, s, 13ß-Me), 2.85 (2H, m, 6α- and 6ß-H), 3.24 (1H, dd, *J* 17.4 and 9.9 Hz, 16α-H), 3.76 (3H, s, 3-OMe), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.19 (1H, d, *J* 8.6 Hz, 1-H), and 9.80 (1H, s, 3'ß-CHO), a mixed fraction of (**183** and **184**) (5 mg) followed by further (**184**) (23 mg; 23%).

Metal-Ammonia Reduction of (16[1]R)-3-*Methoxy*-15ß,16[1]-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**152**)

(a) A solution of the 17-ketone (**152**) (50 mg; 0.16 mmol) in tetrahydrofuran (2 ml) was added dropwise over 5 min to a stirred mixture of lithium metal (12 mg; 1.7 g atom) in anhydrous liquid ammonia (10 ml) (freshly distilled from sodium) and tetrahydrofuran (1 ml) at -78°C under nitrogen. After an additional 5 min solid ammonium chloride was added and the reaction was worked up as described previously.

Flash chromatography of the product (47 mg) on silica gel (5 g), with ethyl acetate-toluene (1:19) as eluent, gave 3-methoxy-dihydrocyclobuta[14,15]-14ß-estra-1,3,5(10)-trien-17-one (**185**) (42 mg; 84%), m.p. 115-116°C (from ethyl acetate-hexane); $[\alpha]_D$ +213° (*c* 0.4); ν_{max} 1725 (CO) cm^{-1}; δ_H (400 MHz) 0.93 (3H, s, 13ß-Me), 2.13 (1H, dd, *J* 19.0 and 1.8 Hz, 16ß-H), 2.46 (1H, t, *J* 11.3 and 2.4 Hz, 9α-H), 2.65 (1H, br t, 15α-H), 2.93 (2H, m, 6α- and 6ß-H), 3.10 (1H, dd, *J* 19.0 and 10.2 Hz, 16α-H), 3.78 (3H, s, 3-OMe), 6.65 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 221.9 (C-17), 157.5 (C-3), 137.8 (C-5), 131.6 (C-10), 127.3 (C-1), 113.5 (C-4), 112.0 (C-2), 55.2 (3-OMe), 53.5 and 52.4 (C-13 and C-14), 43.1 (C-16), 41.2 (C-9), 38.7 (C-8), 33.0, 26.9, 26.3, 25.7 and 23.9 (C-7, C-11, C-12, C-3' and C-4'), 30.9 (C-6), 30.3 (C-15), and 12.5 (C-18)(Found: C, 81.3, H, 8.4%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310) followed by 14,16ß-ethano-3-methoxy-14ß-estra-1,3,5(10)-trien-17-one (**146**) (39 mg; 39%) identical with an authentic sample of (**146**) obtained above.

(b) Similar treatment of the 17-ketone (**152**) (50 mg; 0.16 mmol) with calcium metal (65 mg; 1.6 g atom) in liquid ammonia-tetrahydrofuran, gave 3-methoxy-dihydrocyclobuta[14,15]-14ß-estra-1,3,5(10)-trien-17-one (**185**) (34 mg; 74%) identical with an authentic sample of (**185**) isolated above.

Hydrogenation of (16[1]R)-3-*Methoxy*-15ß,16[1]-*cyclo*-14,16ß-*ethano*-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**152**)

A solution of the 17-ketone (**152**) (100 mg; 0.32 mmol) in ethyl acetate (5 ml) at ambient temperature was stirred in the presence of palladium on carbon (10%, 100 mg) and hydrogen at atmospheric pressure. After 75 h, the catalyst was filtered off, thoroughly washed with ethyl acetate and the filtrate was evaporated under reduced pressure.

The product (94 mg) was adsorbed onto coarse silica gel (0.4 g) and chromatographed on silica gel (9 g), with ethyl acetate-hexane (1:9) as eluent, to give 3-*methoxy-dihydrocyclobuta*[14,15]-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**185**) (35 mg; 25%) identical with an authentic sample of (**185**) isolated above.

3-*Methoxy*-3'α-*toluene*-p-*sulphonyloxy-dihydrocyclobuta*[14,15]-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**186**)

The 17-ketone (**152**) (50 mg; 0.16 mmol) in benzene (5 ml) under nitrogen was refluxed with toluene-*p*-sulphonic acid monohydrate (93 mg; 0.49 mmol). After 6.6 h aqueous sodium hydrogen carbonate was added slowly to the cooled reaction mixture and the product was extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure.

The residue (84 mg), was adsorbed onto coarse silica gel (0.3 g), and chromatographed on silica gel (5 g), with ethyl acetate-hexane (1:4) as eluent, to give 3-methoxy-3'α-toluene-*p*-sulphonyloxy-dihydrocyclobuta[14,15]-14ß-estra-1,3,5(10)-trien-17-one (**186**) (54 mg; 69%), m.p. 104-109°C (from chloroform-hexane); $[\alpha]_D$ +122° (*c* 0.7); ν_{max} 1731 (CO), and 1174 (SO) cm^{-1}; δ_H (200 MHz) 0.94 (3H, s, 13ß-Me), 1.67 (1H, ddd, *J* 3 x 12.0 and 6.6 Hz, 7α-H), 2.03 (1H, d, *J* 18.1 Hz, 16ß-H), 2.45 (3H, s, 3'-$OSO_2C_6H_4$*Me*), 2.83-2.92 (2H, m, 6α- and 6ß-H), 3.07 (1H, dd, *J* 18.1 and 10.9 Hz, 16α-H), 3.79 (3H, s, 3-OMe), 4.22 (1H, br ddd, *J ca.* 7.5, 2.6 and 1.3 Hz, 3'ß-H), 6.65 (1H, d, *J* 2.6 Hz, 4-H), 6.73 (1H, dd, 8.6 and 2.6 Hz, 2-H), 7.18 (1H, d, *J* 8.6

Hz, 1-H), 7.35 and 7.76 (each 2H, d, *J* 8.0 Hz, 3'-$OSO_2C_6H_4Me$); δ_C (50 MHz) 218.7 (C-17), 157.6 (C-3), 145.0 (C-1 of 3'-$OSO_2C_6H_4Me$), 137.9 (C-5), 133.5 (C-4 of 3'-$SO_2C_6H_4Me$), 131.1 (C-10), 129.9 (*m*-C's of 3'-$OSO_2C_6H_4Me$), 127.8 (*o*-C's of 3'-$OSO_2C_6H_4Me$), 127.3 (C-1), 113.4 (C-4), 112.2 (C-2), 79.1 (C-15[1]), 55.2 (3-OMe), 37.8 (C-6), and 13.8 (C-18)(Found: M^+, 480.200. $C_{28}H_{32}O_5S$ requires *M*, 480.197).

3'α-*Bromo*-3-*methoxy-dihydrocyclobuta*[14,15]-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**191**)

A solution of the 17-ketone (**152**) (140 mg; 0.45 mmol) in anhydrous benzene (2.8 ml) was heated with hydrogen bromide (48% in acetic acid, 0.14 ml; 1.24 mmol) in a sealed tube at 70°C. After 22 h, sodium hydrogen carbonate was added to the cooled reaction mixture. The product was extracted with chloroform, and the extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure.

Chromatography of the product (180 mg) on silica gel (14 g), with ethyl acetate-toluene (1:49) as eluent, gave 3'α-*bromo*-3-*methoxy-dihydrocyclobuta*[14,15]-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**191**) (116 mg; 66%), m.p. 148-151°C (from chloroform-methanol); $[\alpha]_D$ +164° (*c* 0.7); ν_{max} 1731 (CO), and 697 (CBr) cm^{-1}; δ_H (400 MHz) 1.00 (3H, s, 13ß-Me), 1.32 (1H, dq, *J* 3 x 12.8 and 3.9 Hz, 11ß-H), 1.51 (1H, td, *J* 2 x 12.8 and 3.7 Hz, 12α-H), 1.83 (1H, ddd, *J* 3 x 12.4 and 5.1 Hz, 7α-H), 2.28 (1H, ddt, *J* 12.8 and 3 x 3.7 Hz, 11α-H), 2.40 (1H, br t, *J ca.* 11.2 and $W_{\frac{1}{2}}$ 6.8 Hz, 9α-H), 3.79 (3H, s, 3-OMe), 3.93 (1H, ddd, *J* 9.0, 4.5 and 2.4 Hz, 3'ß-H), 6.67 (1H, d, *J* 2.8 Hz, 4-H), 6.74 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.20 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 218.8 (C-17), 157.6 (C-3), 137.9 (C-5), 131.2 (C-10), 127.3 (C-1), 113.4 (C-4), 112.1 (C-2), 55.2 (3-OMe), 51.9 and 50.3 (C-13 and C-14), 45.3 (C-3'), 42.3, 41.5 and 39.1 (C-8, C-9 and C-15), 42.1 (C-16), 36.3, 35.2, 27.0 and 25.9 (C-7, C-11, C-12 and C-4'), 30.9 (C-6), and 14.2 (C-18)(Found: C, 64.8; H, 6.9%; M^+, 388. $C_{21}H_{25}BrO_2$ requires C, 64.8; H, 6.9%; *M*, 388) followed by starting material (**152**) (45 mg; 32%).

Reductive Debromination of 3'α-*Bromo*-3-*methoxy-dihydrocyclobuta*[14,15]-14ß-*estra*-1,3,5(10)-*trien*-17-*one* (**191**)

A solution of the bromo compound (**191**) (50 mg; 0.13 mmol) in tetrahydrofuran (1 ml) and glacial acetic acid (1 ml) at 20°C was treated with excess freshly activated zinc dust. After 42 h at 20°C, aqueous sodium hydrogen carbonate was added and the reaction mixture was filtered through Celite. Water was added to the filtrate and it was extraced with chloroform. The organic phase was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure.

Flash chromatography of the product (40 mg) on silica gel (5 g), with ethyl acetate-toluene (1:19) as eluent, gave 3-methoxy-dihydrocyclobuta[14,15]-14ß-estra-1,3,5(10)-trien-17-one (**185**) (34 mg; 83%) identical to an authentic sample of (**185**) obtained above.

4.3 Crystal Structure Data

The structures of the compounds (**82**), (**152**) and (**185**) were solved by direct methods (SHELXS-86[145]) and refined using SHELX-76.[146] The non-hydrogen atoms were modelled anisotropically and the hydrogen atoms were placed in calculated positions. Some of the data obtained from the crystal structure determinations are listed in the tables below.

Table 4.3-1: Crystallographic data acquisition and refinement details for compounds (**82**), (**185**) and (**152**).

Compound no.	**82**	**185**	**152**
Empirical formula	$C_{22}H_{23}O_2N$	$C_{21}H_{26}O_2$	$C_{21}H_{24}O_2$
Molecular weight	333.43	310.44	308.42
Crystal dimension, mm	0.25 x 0.38 x 0.50	0.28 x 0.28 x 0.44	0.31 x 0.31 x 0.31
Space group (no.)	$P2_1$	$P2_1$	$P2_12_12_1$
Cell dimensions a,Å	9.305(1)	10.334(1)	6.213(1)
b,Å	5.9134(3)	8.1762(8)	11.621(1)
c,Å	16.806(2)	10.755(1)	22.628(2)
ß,°	102.17(1)	111.466(9)	90
Z	2	2	4
Volume,Å^3	904.0(2)	845.6(3)	1633.7(3)
D(calc),g.cm^{-3}	1.23	1.219	1.254
λ,cm^{-1}	0.73	0.71	0.74
Radiation (λ,Å)	MoK_α 0.7107	MoK_α 0.7107	MoK_α 0.7107

T,°C	20	20	20
F(000)	356	336	664
Scan type	ω-2θ	ω-2θ	ω-2θ
Scan Range,θ°	1<θ>25	1<θ>25	1<θ>25
Zone collected: h	±11	±12	7
k	7	9	13
l	20	12	26
Maximum scan time, sec.	40	40	40
Scan angle (ω + domb tanθ)°	0.85, 0.35	0.85, 0.35	0.85, 0.35
Aperture size, mm	1.20 + 1.05tanθ	1.20 + 1.05tanθ	1.20 + 1.05tanθ
Reflections collected	1638	1685	1715
Decay, %	3.0	1.5	0.8
Unique reflections used(F>)	1460	1320	1251
Parameters refined	245	214	215
Max. positional shift/esd	<0.1	0.016	0.019
Residual electron density, Maximum	0.27	0.13	0.18
Minimum	-0.35	-0.19	-0.23
R	0.0855	0.038	0.047
R_w	0.0855	0.036	0.044
W	1	0	0

TABLE 4.3-2: Fractional atomic coordinates (x 10^4) and Thermal Parameters (x 10^3 Å^2) with e.s.d. s in parentheses for Compound (**82**).

Atom	x/a	y/b	z/c	Uiso/Uequiv(*)
C(1)	1541(10)	0(0)	396(5)	47(3) *
C(2)	1932(11)	-403(27)	-331(6)	53(4) *
C(3)	2876(9)	-2177(25)	-414(6)	45(3) *
C(4)	3383(10)	-3540(24)	251(6)	48(3) *
C(5)	3653(12)	-4659(25)	1706(6)	63(4) *
C(7)	3489(10)	-3716(25)	2534(5)	51(4) *
C(8)	1903(10)	-2915(23)	2477(5)	41(3) *
C(9)	1624(9)	-863(24)	1878(5)	39(3) *
C(10)	2033(10)	-1364(24)	1073(6)	43(4) *
C(11)	66(10)	54(25)	1795(6)	49(3) *
C(12)	-280(10)	626(24)	2611(5)	48(4) *
C(13)	-58(10)	-1449(25)	3219(6)	44(3) *
C(14)	1520(9)	-2342(24)	3274(5)	39(3) *
C(15)	2507(11)	-595(24)	3845(6)	49(4) *
C(16)	1571(11)	-89(25)	4443(6)	48(4) *
C(17)	-11(12)	-484(25)	4041(7)	62(4) *
C(18)	-1319(11)	-3148(27)	2958(7)	61(4) *
O(3)	3195(7)	-2426(23)	-1164(4)	59(3) *
O(2)	-1037(9)	-58(26)	4347(5)	89(4) *
C(31)	4102(13)	-4301(28)	-1277(7)	69(5) *
C(161)	2548(10)	-2215(26)	4536(5)	45(3) *
C(162)	1892(11)	-4111(24)	4001(6)	46(4) *
C(163)	3673(12)	-2397(28)	5317(7)	62(4) *
N(1)	4546(11)	-2477(29)	5853(6)	83(5) *

TABLE 4.3-3: Fractional atomic coordinates (x 10^4) and Thermal Parameters (A^2 x 10^3) with e.s.d. s in parentheses for Compound (**152**)

Atom	x/a	y/b	z/c	Uiso/Uequiv(*)
C(1)	-2413(8)	10225(3)	91(2)	46(1) *
C(2)	-1837(8)	9483(3)	534(2)	54(2) *
C(3)	50(8)	8863(3)	494(2)	47(2) *
C(4)	1341(7)	8981(3)	0(2)	46(1) *
C(5)	743(6)	9732(3)	-454(2)	41(1) *
C(6)	2181(7)	9801(4)	-988(2)	56(2) *
C(7)	1098(7)	10342(3)	-1522(2)	49(2) *
C(8)	-89(6)	11439(3)	-1351(2)	37(1) *
C(9)	-1928(7)	11130(3)	-920(2)	37(1) *
C(10)	-1156(6)1	0369(3)	-414(2)	37(1) *
C(11)	-3132(7)	12216(3)	-726(2)	49(2) *
C(12)	-4043(7)	12847(3)	-1260(2)	52(2) *
C(13)	-2295(7)	13187(3)	-1705(2)	41(1) *
C(14)	-983(6)	12117(3)	-1874(2)	36(1) *
C(15)	-2398(7)	11459(4)	-2336(2)	49(2) *
C(161)	-1129(8)	11977(4)	-2816(2)	56(2) *
C(162)	593(7)	12427(4)	-2396(2)	51(2) *
C(16)	-3342(8)	12443(4)	-2667(2)	56(2) *
C(17)	-3463(7)	13471(4)	-2282(2)	52(2) *
C(18)	-1010(9)	14212(4)	-1476(2)	68(2) *
O(19)	-4434(6)	14352(3)	-2376(1)	80(1) *
O(20)	473(6)	8137(3)	960(1)6	5(1) *
C(21)	2285(9)	7393(4)	910(2)	63(2) *

TABLE 4.3-4: Fractional atomic coordinates (x 10^4) and Thermal Parameters (A^2 x 10^3) with e.s.d. s in parentheses for Compound (**185**)

Atom	x/a	y/b	z/c	Uiso/Uequiv(*)
C(1)	-2781(4)	-3559(6)	-610(4)	48(2) *
C(2)	-3202(4)	-4240(6)	346(4)	52(2) *
C(3)	-3392(4)	-3251(6)	1306(4)	47(2) *
C(4)	-3180(4)	-1587(7)	1270(4)	44(1) *
C(5)	-2755(3)	-894(6)	304(3)	38(1) *
C(6)	-2581(4)	938(6)	298(3)	48(2) *
C(7)	-1841(4)	1524(6)	-605(3)	42(1) *
C(8)	-2397(3)	644(6)	-1951(3)	34(1) *
C(9)	-2033(3)	-1175(6)	-1716(3)	39(2) *
C(10)	-2539(4)	-1886(6)	-661(3)	37(2) *
C(11)	-2556(4)	-2114(6)	-3027(4)	52(2) *
C(12)	-1969(4)	-1412(6)	-4023(4)	49(2) *
C(13)	-2354(4)	407(6)	-4323(3)	41(1) *
C(14)	-1936(3)	1388(5)	-3023(3)	35(1) *
C(15)	-361(4)	1875(6)	-2627(4)	48(2) *
C(16)	-11(4)	1540(7)	-3871(4)	62(2) *
C(17)	-1361(4)	1061(6)	-4964(4)	49(2) *
C(18)	-3882(4)	581(7)	-5244(4	)57(2) *
O(19)	-1611(3)	1202(6)	-6143(3)	68(1) *
O(20)	-3768(3)	-3796(0)	2329(3)	63(1) *
C(21)	-3767(5)	-5526(7)	2535(5)	68(2) *
C(151)	-736(4)	3679(6)	-2521(4)	62(2) *
C(152)	-2285(4)	3258(6)	-3248(4)	46(2) *

5. APPENDIX

5.1 Nomenclature

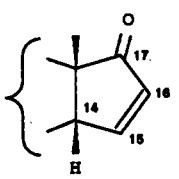
The compounds synthesised in this investigation were named according to the IUPAC steroid rules.[147] The name of the parent steroid is determined by the recommendation (3S-6.3) which states that 'a name should be derived by the fewest number of modifications of the fundamental parent system'. The use of a steroid name implies that atoms, or groups, attached at the bridgehead positions 8,9,10,13 and 14 are orientated as follows: 8ß, 9α, 10ß, 13ß and 14α, and a side chain at position 17 is assumed to be ß-orientated (3S-1.5). An example of this is 3-methoxy-14ß-estra-1,3,5(10),15-tetraen-17-one (**66**). If the steroid contains chiral centres not defined by the parent name the absolute stereochemistry at the positions is defined by α, ß, R or S (or ξ when the configuration is unknown) prefixed by the appropriate locant (3S-1.3).

When additional rings are formed within, or on, the steroid nucleus, it is often desirable to retain the steroid stem name, since it implies the stereochemistry of most of the chiral centres (3S-9.4). Steroids with non-adjacent ring positions linked by a bridge eg. -O-O- or $-(CH_2)_n-$ are named by the appropriate name and locants to indicate its attachment and α or ß to indicate stereochemistry where necessary. With linear bridges the atoms may be labelled for identification by the superscripts number starting from the higher numbered attachment position. This is illustrated in the figure of 17ß-acetoxy-16ß-chloro-3-methoxy-14,17α-etheno-estra-1,3,5(10)-triene-16α-carbonitrile (**71**)

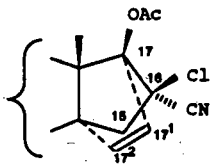
When an additional ring is formed by means of a direct link between any two atoms of the steroid ring system or the attached side chain, the name of the steroid is prefixed by cyclo; this prefix is preceded by the numbers of the positions joined by the new bond and Greek letter (α, ß, ξ) denoting the configuration associated with the new bond, unless that designation is already implicit in the name eg. (16^1*R*)-3-methoxy-17-oxo-15ß,16^1-cyclo-14,16ß-ethano-14ß-estra-1,3,5(10)-triene-16^1-carbonitrile (**82**). In this work several derivatives bearing a tricyclic ring D were synthesised. The plane of the

cyclobutyl ring is orthogonal to the plane defined by ring A, B and C and the protons at C(16^2) are thus designated as either 16^2*Re*-H or 16^2*Si*-H.

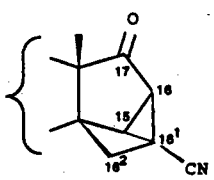
Fusion of a carbocyclic or heterocyclic ring component with the maximum number of non-cumulative double bonds to a steroid may be indicated by a modification of fusion nomenclature (3S-10.2). The preferred component is always the steroid. The name of the carbocyclic or heterocyclic attached component is modified to give its prefix form and is cited in front of the steroid name with the nature of the fusion indicated between square brackets. The numbering of the steroid moiety is retained; the atoms of the attached component are identified by primed locants. Those involved in fusion are cited in the order corresponding to those of the steroid eg. 3,5'ξ-dimethoxy-dihydrofuro[3',2';14,15]-14ß-estra-1,3,5(10)-trien-17-one (**114**).



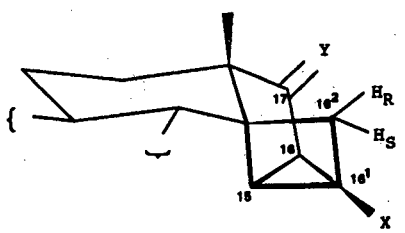
66

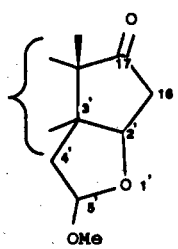


71



82





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