

**CYCLOADDITION STUDIES IN STEROIDAL
14,16-DIENES**

Submitted in accordance with the requirements
for the degree of

MASTER OF SCIENCE

in the subject

CHEMISTRY

by

MICHIEL C. LOEDOLFF

Supervisor: Professor J.R. Bull

Department of Chemistry

University of Cape Town

September 1991

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ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to everybody who played a contributing part in the production of this thesis, and in particular to the following:

My supervisor, Prof. J.R. Bull, for his excellent and devoted support.

Miss M.N. Nair, Mr N. Hendricks, and Mr G. Benincasa for their services in sample analysis.

My colleagues, Claudia Grundler, Anwar Jardine, Delene Kaiser, and Ed Sturrock, for all their helpfulness.

SUMMARY

Studies have been conducted in synthesising ring D-substituted steroidal 14,16-dienes. The aim was to explore the scope for carrying out cycloaddition reactions, and exploiting the built-in bridge substituents of derived 14,17-cycloadducts, for eventual conversion into bridge-functionalised 19-norsteroids.

Synthetic routes to three such dienyl systems were explored. In the first investigation, synthesis of 3-methoxy-15-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate was undertaken. The approach is based upon an overall 1,4-methylation of 3-methoxyestra-1,3,5(10),15-tetraen-17-one to give the corresponding 15 β -methyl 17-ketone, followed by formal dehydrogenation and enol acetylation to 3-methoxy-15-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate. Conjugate alkylation was performed on the Δ^{15} -17-ketone with lithium dimethylcuprate to obtain the 15 β -methyl 17-ketone with concomitant formation of a bisteroidal condensation product. The latter was shown to arise by a Michael-type condensation, involving reaction intermediates. Initial attempts to effect formal dehydrogenation of the 15 β -methyl 17-ketone were based upon a bromination-dehydrobromination sequence. This method proved inefficient and gave rise to a regioisomeric mixture of elimination products, as well as debrominated material. In an alternative conversion, the 15 β -methyl 17-ketone was converted into the corresponding 16-phenylselenide. Oxidation, followed by thermal selenoxide elimination gave the desired 15-methyl Δ^{15} -17-ketone (40 %), together with 3-methoxy-15-methyl-17a-oxa-17a-homoestra-1,3,5(10),15-tetraen-17-one (45 %), arising from Baeyer-Villiger oxidation. The most successful route to the 15-methyl Δ^{15} -17-ketone entailed Pd^{II}-mediated dehydrosilylation of the silyl enol ether derived from the 15 β -methyl 17-ketone. An overall conversion of 73 % was obtained.

It was further shown that the 15-methyl Δ^{15-17} -ketone could undergo further conjugate methylation to give the corresponding 15,15-dimethyl 17-ketone. This compound underwent highly stereoselective reduction with lithium aluminium hydride to give 3-methoxy-15,15-dimethylestra-1,3,5(10)-trien-17 β -ol.

Enol acetylation of the 15-methyl Δ^{15-17} -ketone yielded the derived 15-methyl 14,16-dien-17-yl acetate. Cycloaddition between this diene and acrolein, followed by decarbonylation of the product gave 3-methoxy-17²-methyl-14,17 α -ethenoestra-1,3,5(10)-trien-17 β -yl acetate.

In the second phase of the work, synthesis of 3-methoxyestra-1,3,5(10),14,16-pentaen-16,17-diol diacetate and 3-methoxyestra-1,3,5(10),14,16-pentaen-15,17-diol diacetate was investigated.

The planned strategy for synthesis of the 14,16-dienyl 16,17-diacetate entailed α -acetoxylation of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate, followed by enol acetylation. Exploratory enol acetylation experiments on a model compound, 3 β ,16 β -diacetoxyandrost-5(6),14-dien-17-one have, however, indicated an apparent inertness of this type of system, even under forcing conditions of enol acetylation.

The route to the 14,16-dienyl 15,17-diacetate entailed Michael addition of an hydroxy equivalent to 3-methoxyestra-1,3,5(10),15-tetraen-17-one, followed by sequential oxidation to the corresponding 15,17-diketone and enol acetylation. In a first approach, the Δ^{15-17} -ketone was treated with benzyl alcohol under strongly basic conditions, to give the 15 β -benzyloxy 17-ketone, hydrogenolysis of which gave the corresponding 15 β -alcohol. In an alternative approach, the Δ^{15-17} -ketone was converted into 3-methoxy-15 β ,16 β -epoxyestra-1,3,5(10)-trien-17-one, lithium dimethylcuprate-mediated reduction of which gave the 15 β -hydroxy 17-ketone.

Oxidation of the 15 β -hydroxy 17-ketone gave the corresponding 15,17-diketone, and forcing enol acetylation afforded the desired 14,16-dienyl 15,17-diacetate.

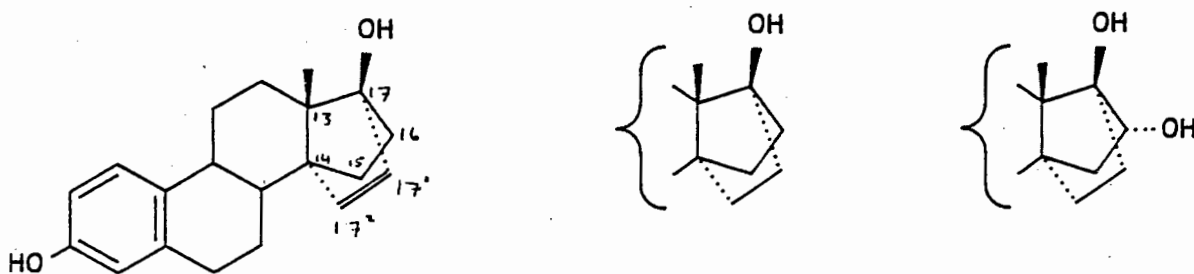
A preliminary cycloaddition experiment between this dienyl diacetate and phenyl vinyl sulphone failed to produce a cycloadduct. No definitive result has hitherto been obtained.

1. INTRODUCTION

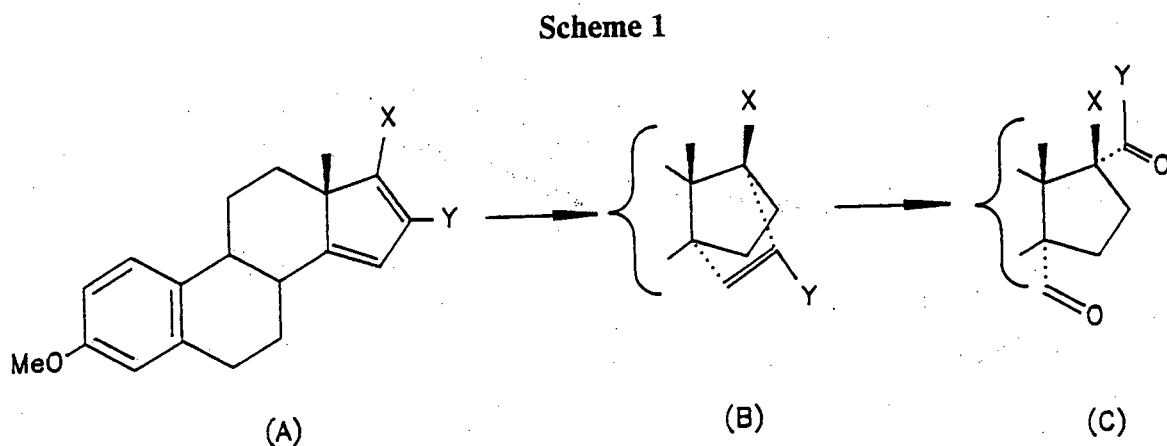
In most cases, the tetracyclic nucleus is a common feature in steroidal hormones of widely differing physiological activities. This ring system is thought to serve as a template for spatial positioning of attached polar functionalities in such a way that selective binding between the hormone and a defined receptor site is promoted. Changes in the substitution pattern are often attended by differences in binding characteristics.¹ This feature has become a useful experimental device, as it provides a basis for quantifying the influence of specific structural features upon binding sites.² In this way, 'mapping' of the spatial demands of a receptor site is facilitated. Notwithstanding numerous successes in empirical structure-activity studies of recent times,^{3,4} no general predictive principle of structure-activity has hitherto been established. Such an objective may be unattainable, but even the partial ability to quantify additive trends in functional group modification could have enormous value for designing specific hormones.⁵

Some years ago, it was established that the introduction of a 14,17 α -ethano bridge to progesterone resulted in a decrease in hormonal activity.⁶ This phenomenon was rationalised in terms of constraining the 17 β -acetyl substituent towards the α -side by the bridge, thereby inhibiting receptor binding ability. Subsequently, extensive work has been carried out on bridged and bridge-functionalised hormone analogues.⁷ It has been discovered that bridged analogues of estradiol and estriol of the type indicated in Figure 1 show enhanced hormonal activity.¹⁰

Figure 1



It has recently been shown that 14α -alkyl 19-norsteroids are conveniently attainable from a cycloaddition-oxidative cleavage route⁸ (Scheme 1). In this approach, an ethylene equivalent was reacted with a steroidal 14,16-diene (A), followed by oxidative cleavage of the residual olefinic bond in the resultant cycloadduct (B). In this way, ring D is restored with simultaneous functionalisation of C-14 and C-17 (C), depending on the X,Y substitution pattern in the original diene.

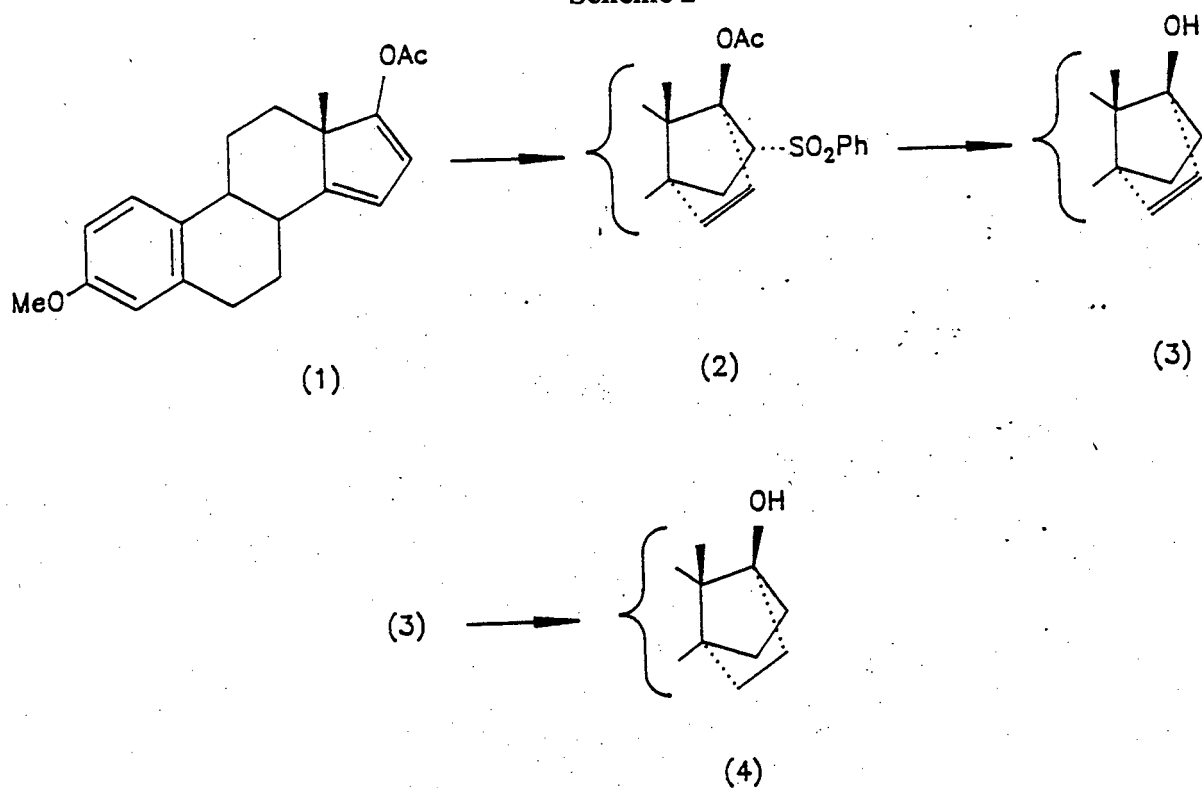


Two modes of X and Y substitution have hitherto been explored, both giving potential access to $14,17\alpha$ -bridged hormone analogues. In the first approach⁸ (Scheme 2), the 14,16-dien-17-yl acetate derivative of estrone 3-methyl ether (1) was treated with phenyl vinyl sulphone (PVS) under Diels-Alder conditions. A single cycloadduct (2), corresponding to β -face, 1,2-addition by the dienophile was isolated (Scheme 2).

Subsequent reduction of the bridged olefinic bond, followed by hydrolysis at C-17 gave access to an $14,17\alpha$ -ethano analogue (4) of estradiol.

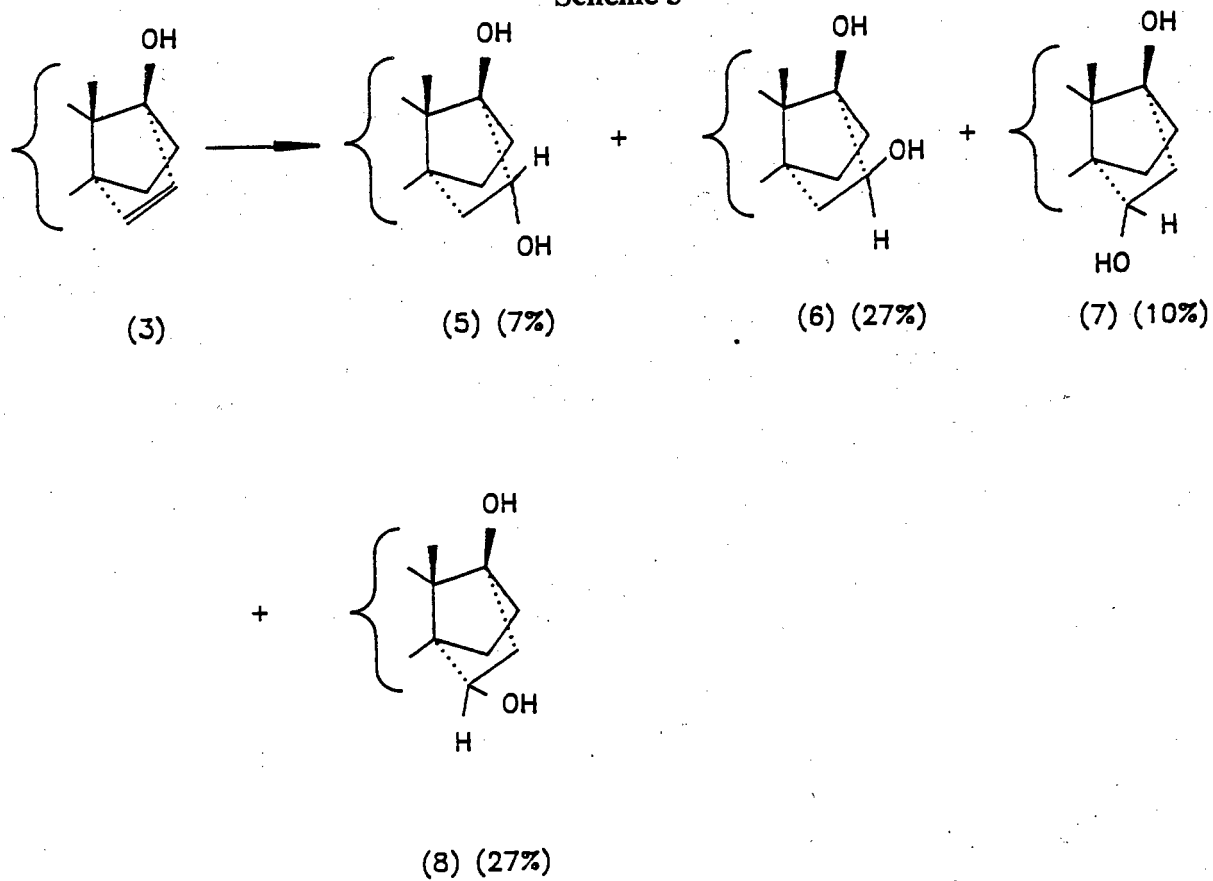
One approach to new estriol analogues bearing functionality on the α -bridge is to carry out regio- and stereoselective functionalisations of the bridged olefinic bond in the $14,17\alpha$ -etheno compound. However, the results of numerous attempts⁹ have indicated that selective functionalisation of (3) was unattainable. Additions to the

Scheme 2

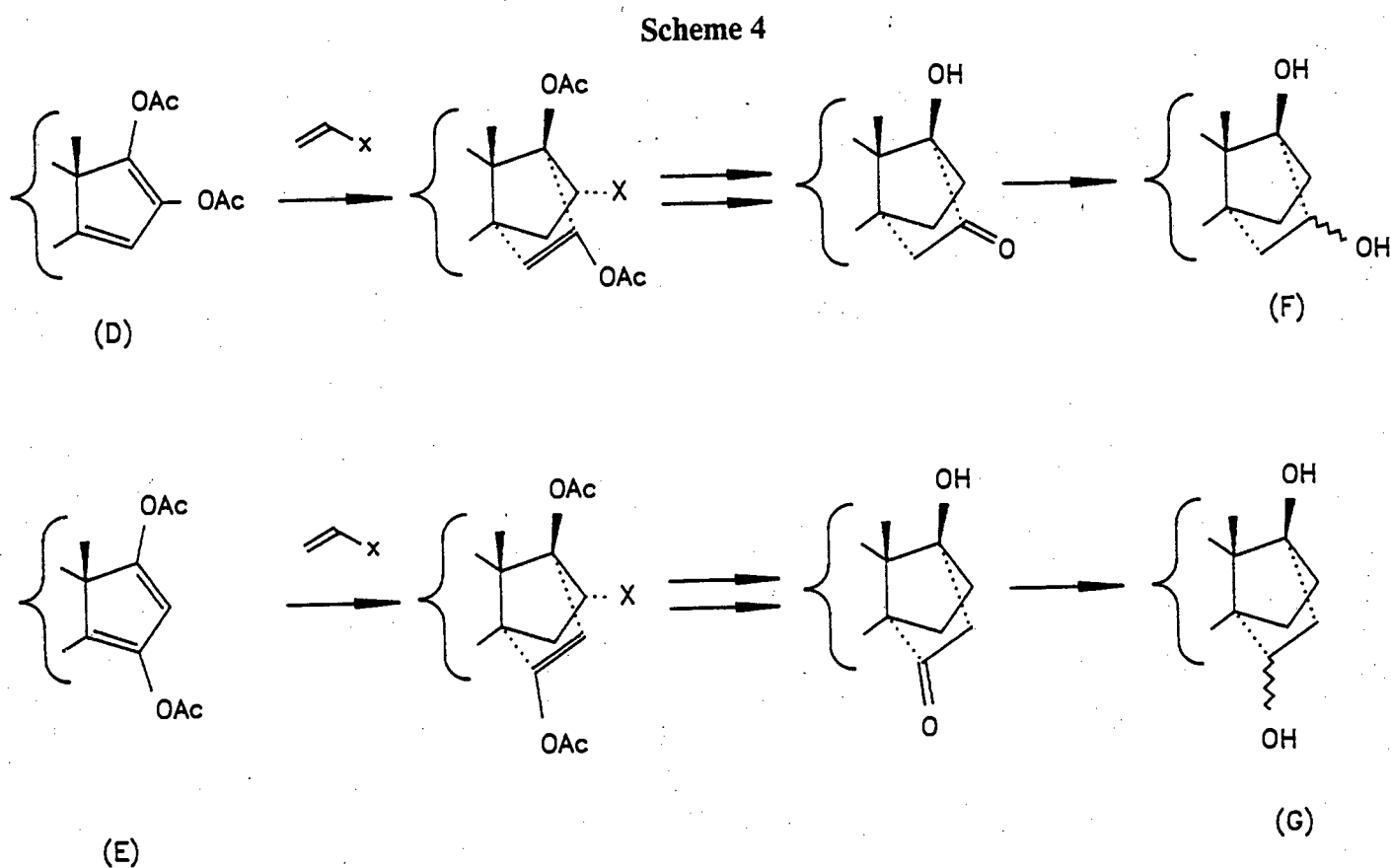


bridged olefinic bond suffered lack of differentiation; for example, hydroboration-oxidation of (3) led to formation of all four possible isomers (5, 6, 7, and 8) (1 : 3.9 : 1.4 : 3.9) (Scheme 3).

Scheme 3



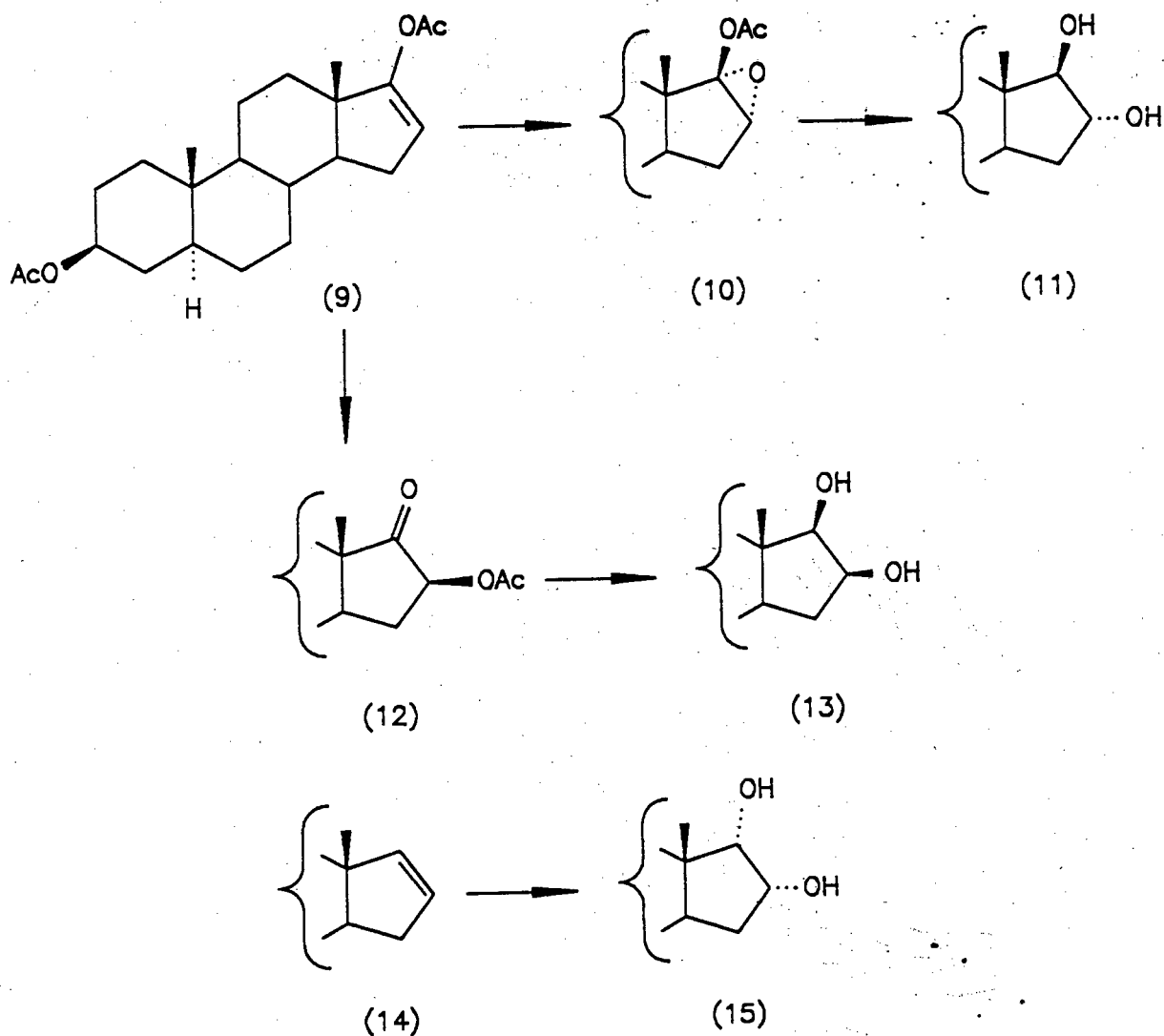
explore other approaches. For example, bridge-oxygenated intermediates can be envisaged by cycloaddition to C(16),C(17)- and C(15),C(17)-dioxygenated dienyl systems (D and E respectively). Reactions of this nature are expected to yield intermediates bearing built-in oxygen functionality as masked carbonyl groups. Deprotection of these groups, followed by reduction is expected to give access to the corresponding bridge-hydroxylated intermediates (F and G respectively) (Scheme 4). These intermediates are products obtained from the various hydroxylation reactions⁹ on (3).



Thus, cycloaddition-hydrolysis methodology to oxygenated dienyl systems is hoped to provide more selective routes to bridge-oxygenated compounds, than stepwise transformation methods to the unsubstituted cycloadducts. This alternative method at least addresses the issue of regioselective hydroxylation of the cycloadduct. Routes to C(16),C(17)- and C(15),C(17)-dioxygenated systems are well documented. In the androstane series, treatment of 3 β ,17-diacetoxy-5 α -androst-16-

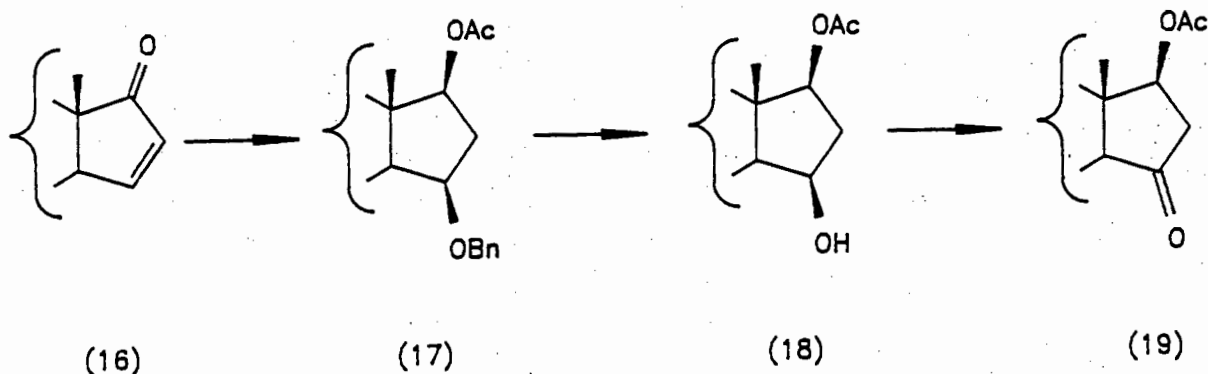
ene (9) with *m*-chloroperoxybenzoic acid gave the corresponding 16,17 α -epoxy 17 β -acetate (10). Upon reaction with lithium aluminium hydride, the epoxide was reductively opened, yielding the corresponding 16 α ,17 β -diol (11).¹¹ Still in the androstane series, it was noted by Johnson *et al.*¹² that the 16 β -acetoxy-17-ketone (12) was attainable by treating the Δ^{16-17} -enol acetate with lead tetraacetate. Hydrogenation of (12) gave the corresponding 16 β ,17 β -diol (13). A route to the related 16 α ,17 α -diol (15) was described by Altona.¹³ In this method, 3 β -acetoxy-5 α -androst-16-ene (14) was hydroxylated with osmium tetroxide, to afford the corresponding 16 α ,17 α -diol (15) (Scheme 5).

Scheme 5



Methods for obtaining 15,17-dioxygenated intermediates are based mainly upon conjugate benzyloxylation of the Δ^{15} -17-ketone, for both the androstane and estrone series. Reductive acetylation of the hence obtained 15 β -benzyloxy 17-ketone to the corresponding 15 β -benzyloxy 17 β -acetate (17), followed by hydrogenolysis gave the 15 β -hydroxy 17 β -acetate (18). Jones' oxidation of the latter yielded the 17 β -acetoxy 15-ketone (19)^{14,15} (Scheme 6).

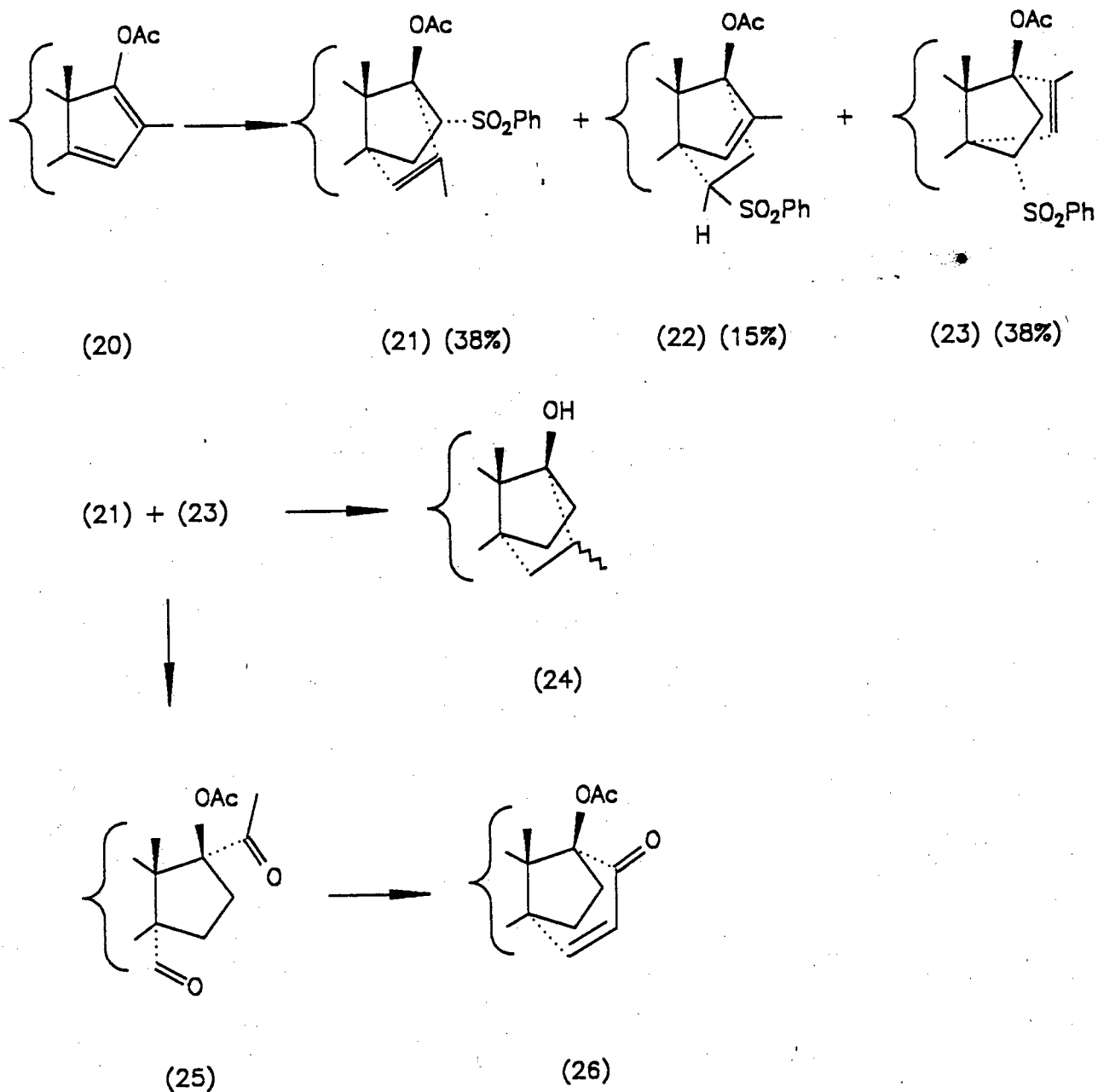
Scheme 6



(estrane or androstane)

A further aspect of the current research at the University of Cape Town entails an extension of the cycloaddition study to the 3-methoxy-16-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate (20).¹⁶ In accordance with the outcome in Scheme 1 (X=OAc, Y=Me), this would lead eventually to products (X=OAc; Y=Me), having the 19-norpregnane skeleton with 14 α -functionalised alkyl residues. In this case, a cycloaddition of PVS to (20) was accompanied by substantial loss of regio- and stereoselectivity, giving rise to a 3-component mixture of cycloadducts (21, 22 and 23) (2.5 : 1 : 2.5). Compounds (21 and 23) were utilised in convergent pathways. Reduction of the 17¹,17² bond, analogous to Scheme 4 gave a bridge-alkylated estradiol analogue (24). Oxidative cleavage of (21 and 23) gave access to 17 β -acetoxy-17 α -acetyl-14 α -carbaldehyde (25). The latter has also been transformed into an α,β -unsaturated 14,17 α -propeno-bridged intermediate (26) for the synthesis of 14,17 α -propano analogues of estradiol and estriol (Scheme 7).

Scheme 7

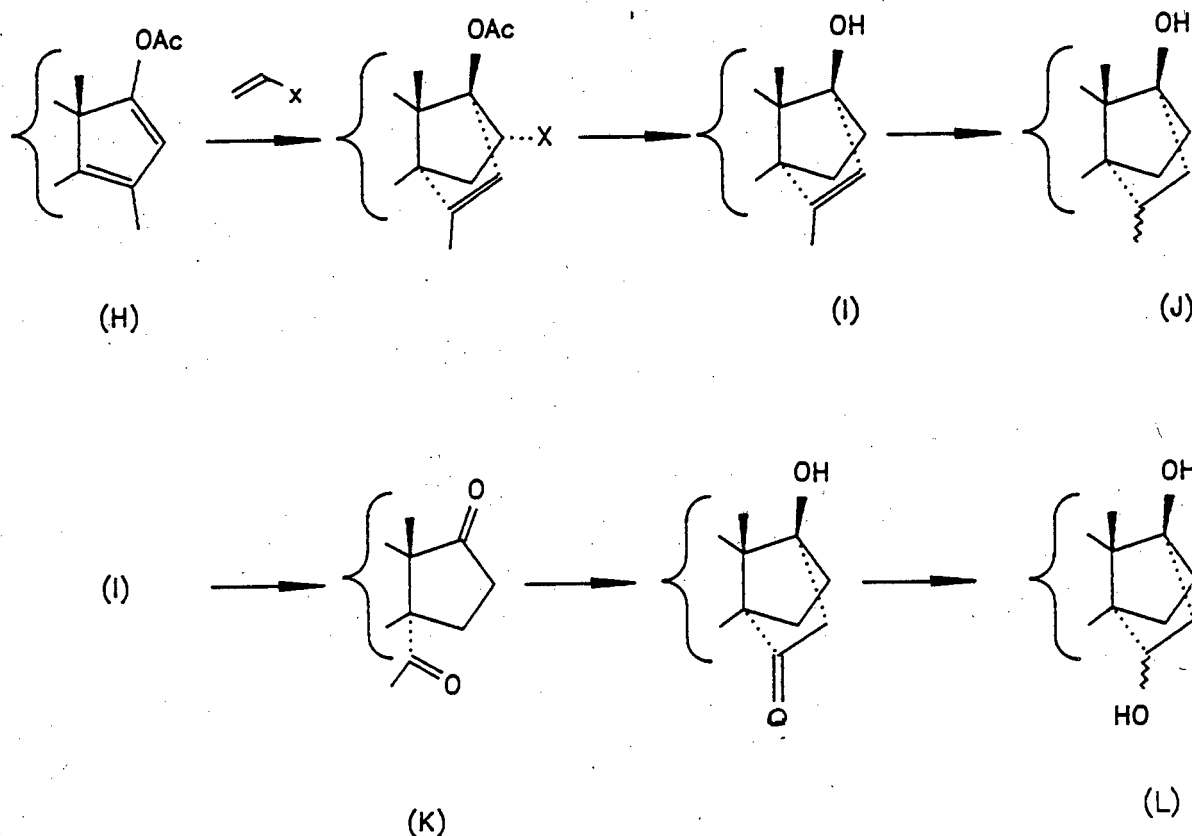


An extension of this work is based on cycloaddition studies to an isomeric 15-methyl dienyl acetate (**H**). The 15-methyl substituent is expected to reinforce the regio- and stereochemical outcome of cycloaddition, as compared to the 16-methyl case. It is further anticipated that the cycloadduct intermediates would provide access to novel 14,17 α -bridged estradiols (**I** and **J**) by conventional hydrogenation methods.

Applying oxidative cleavage methods to the cycloadduct (**I**) is envisaged to provide a route to new 14 α -acetyl intermediates (**K**). Upon ring closure of (**K**), access to a 17 α -hydrated compound (**L**) is obtained, *via* the 17 α -ketone (Scheme 8).

Complementarity between this method and that of cycloaddition to oxygenated dienes can be foreseen (see Scheme 4).

Scheme 8



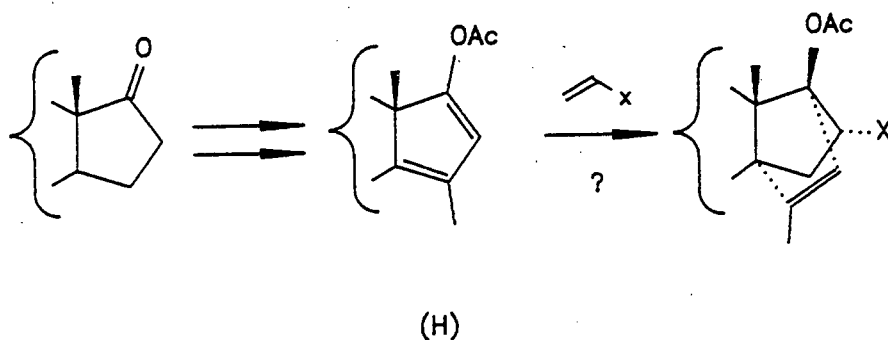
A literature survey has revealed limited exposure to 15-methyl 19-norsteroids. The Sandoz-Wander company hold a patent in which 3-methoxyestra-1,3,5(10),15-tetraen-17-one was treated with lithium dimethylcuprate to obtain exclusively the corresponding 15 β -methyl compound.¹⁷ Also, work carried out by Groen and Zeelen describes a route to the epimeric 15 α -methyl compound, based on total synthesis.¹⁸

2. OBJECTIVES AND APPROACH

The overall objective of this investigation was to develop synthetic approaches to ring D-modified 14,16-dien-17-yl acetates; in which additional functionality at C(15) or C(16) could be exploited to establish a cycloaddition-mediated strategy for generating systems having correspondingly functionalised α -bridges.

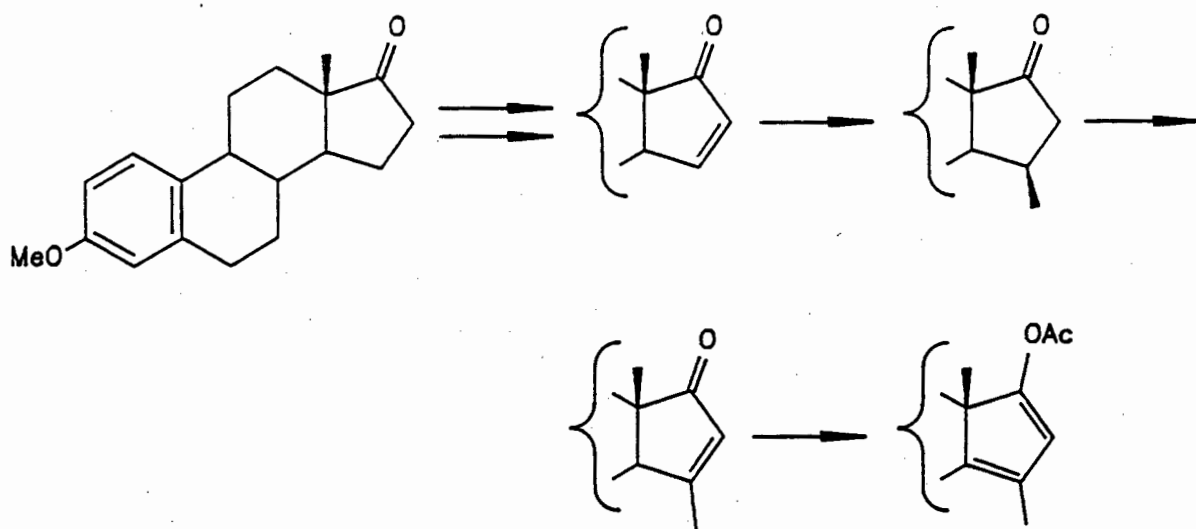
In the first phase of this investigation, it was planned to synthesise 3-methoxy-15-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate (**H**) for cycloaddition studies, to complement those carried out on the isomeric 16-methyl compound (Scheme 9).

Scheme 9



Accordingly, we set out to examine various approaches to the introduction of a 15-methyl group onto estrone 3-methyl ether, and to convert the intermediates into the cycloaddition substrate. The approach adopted for the work was to convert estrone 3-methyl ether into the corresponding Δ^{15-17} -ketone for conjugate alkylation, following established procedures.¹⁹ Formal dehydrogenation of the intermediate or a trapped enolate species was expected to furnish the desired 15-methyl Δ^{15-17} -ketone, which could then be converted into the derived dienyl acetate, using conventional methodology (Scheme 10).

Scheme 10



With this derived dienyl acetate in hand, it was planned to study the reactivity of the system towards various dienophiles. The presence of the 15-methyl group was expected to reinforce the regio- and stereoselectivity observed for the dienyl acetate lacking this group. However, it was not clear whether the reactivity of the diene would be influenced by the methyl group.

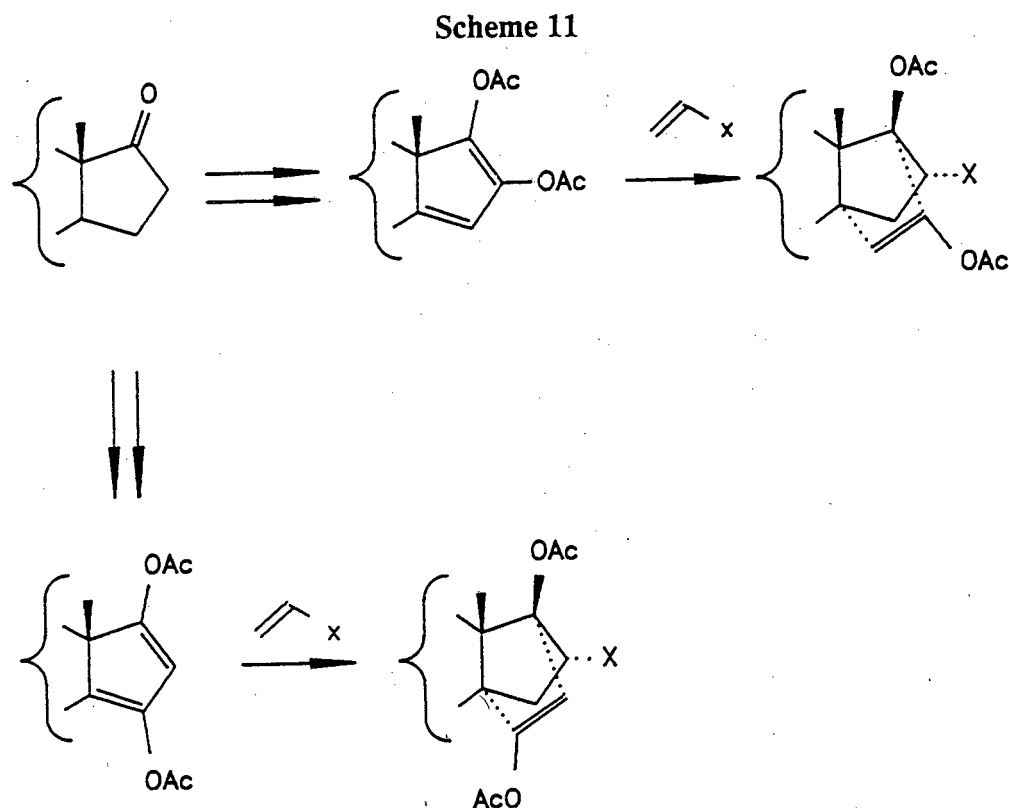
Cycloadducts derived from this reaction sequence were expected to provide useful intermediates to various transformations. Thus, conventional hydrogenation of a cycloadduct derived from a reaction with an ethylene equivalent would extend the work already carried out on 14,17 α -ethano analogues of estradiol. Furthermore, oxidative cleavage of the bridged olefinic bond, would lead to new intermediates for further transformations (see Scheme 8).

The second phase of the work was to investigate possible routes to 14,16-dienes bearing oxygen functionality at C(16) and C(17) or C(15) and C(17).

A route to the 14,16-dienyl-16,17-diol diacetate is envisaged through introduction of an α -oxygen functionality to a convenient substrate. Initial inclinations are

towards exploration of the Δ^{14-17} -ketone. In the case of diminished reactivity, reaction of a 14,16-dienyl system as a Δ^{16} -enol equivalent seems appropriate. This approach is analogous to that of Johnson ¹², as previously described. Enol acetylation of the resulting 16-acetoxy 17-ketone is expected to afford the desired diacetate (Scheme 11).

Access to the 14,16-dienyl-15,17-diol diacetate is anticipated by conjugate benzyloxylation to the Δ^{15-17} -ketone, followed by hydrogenolysis to obtain the corresponding 15β -alcohol. Oxidation to the 15,17-diketone, followed by enol acetylation is expected to furnish the desired 14,16-dienyl-15,17-diacetate (Scheme 11).



The intermediates derived from cycloaddition of these dienyl systems are expected to be converted into bridge-oxygenated analogues of estriol. Thus, deprotection of the bridge carbonyl groups, followed by reduction to the corresponding alcohols is expected to afford the desired systems. Furthermore, the 14,16-dienyl-16,17-

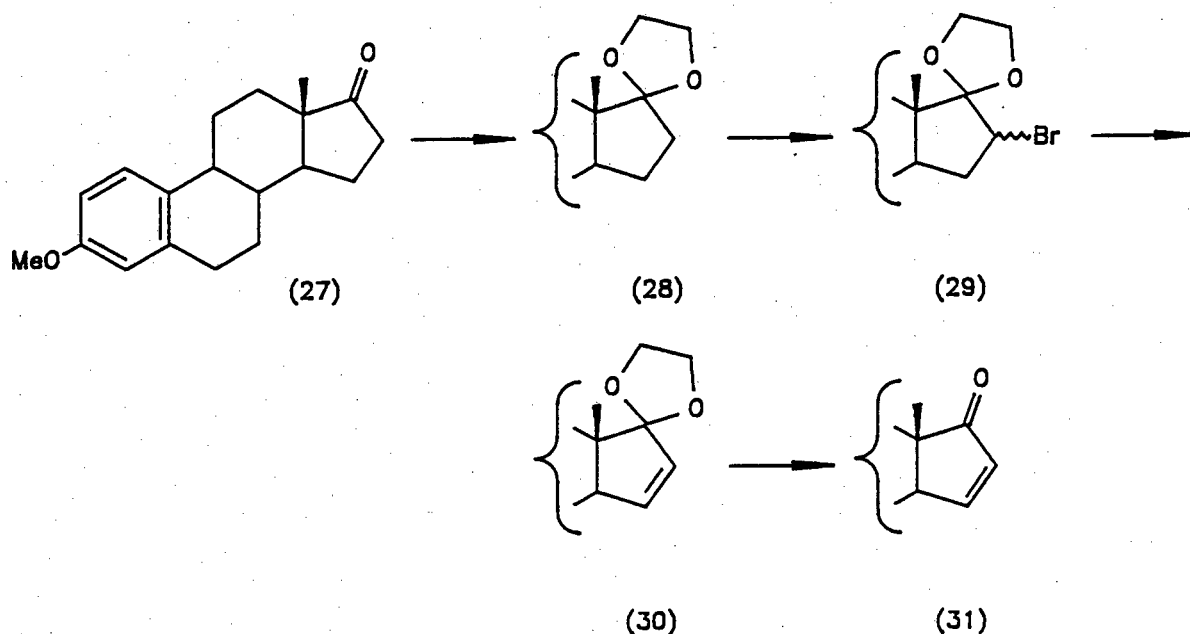
diacetate offers an alternative substrate for cycloaddition studies to 1,2-disubstituted dienes ¹⁶ (see Scheme 4). It would be interesting to compare the regio- and stereoselective outcome of an all-oxygen substituted dienyl system to that of a partly alkyl-substituted analogue.

3. DISCUSSION

3.1 Synthesis of 3-Methoxy-15-methylestra-1,3,5(10),14,16-pentaen-17-yl Acetate (45)

The starting material for this study, 3-methoxyestra-1,3,5(10),15-tetraen-17-one (31) was prepared from estrone by standard methods¹⁹ (Scheme 12). Estrone 3-methyl ether (27) was treated with ethylene glycol and toluene-*p*-sulphonic acid in refluxing benzene in a Dean-Stark trap for 18 h. The resultant ketal (28) was brominated with phenyltrimethylammonium tribromide in dry tetrahydrofuran (THF) to give the 16-bromo-17-ketal (29). This compound was subjected to dehydrohalogenation with potassium *t*-butoxide in refluxing xylene. Deprotection of the product (30) with toluene-*p*-sulphonic acid in aqueous acetone gave 3-methoxyestra-1,3,5(10),15-tetraen-17-one (31). The overall yield for the conversion of estrone 3-methyl ether (27) into the Δ^{15} -compound (31) was *ca* 73 %. The procedure was amenable to large-scale preparation of the enone, since the intermediates and product were formed cleanly, and chromatography was not required.

Scheme 12



3.1.1 Conjugate Alkylation The primary step in our synthetic strategy entailed conjugate methylation of the Δ^{15-17} -ketone (31). This reaction has been reported for (31) in the patent literature,¹⁷ but few details are available. We chose to examine the reaction in detail, with the aim to explore the scope for obtaining a reliable and selective conversion to the desired product, and further to study the scope for trapping the intermediate enolate species in preparation for the following step of introducing the Δ^{15} bond.

Organocuprate methodology has developed into a powerful and selective class of C-C bond-forming reactions, which has found wide use in synthesis. Mechanistic studies continue to cast new light upon the salient features of the reaction.

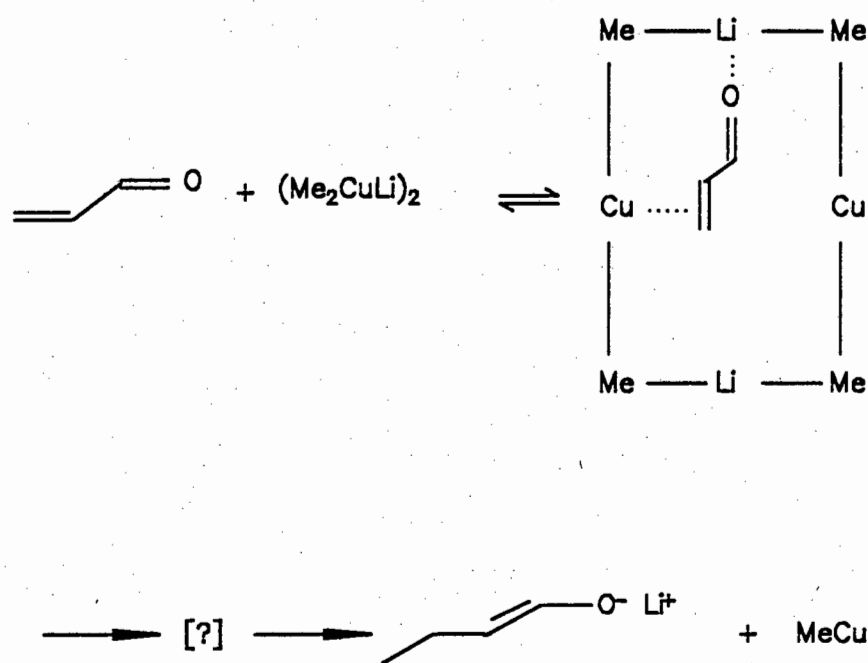
Initial concepts were based upon complexation of the substrate carbonyl oxygen to the copper complex.²⁰ Conjugate addition was seen to commence by a single electron transfer from the cuprate to the substrate. This is followed by Cu-C bond formation to give a Cu^{III} intermediate. After C-C bond formation, the lithium enolate is formed as an observed product.

An alternative route to the Cu^{III} complex has been proposed via electron transfer within a charge transfer complex.²¹

Earlier studies by Ullenius *et al.*²² presented ^1H and ^{13}C nmr evidence for a cuprate-enone d,π^* complex formed upon addition of lithium dimethylcuprate to an α,β -unsaturated carbonyl compound. The d-orbitals of the metal interact as a d-base with the α,β -carbonyl carbons (π_3^*) of the enone, which, in turn, acts as a π -acid. At -40°C , this d,π^* complex was shown to exist in equilibrium with the reactants. As the temperature was increased, the conjugate addition product was formed, in concert with disappearance of the d,π^* complex (Scheme 13). Support for these findings was given by Corey and Boaz.²³ In their work, a yellow precipitate was isolated from an

incomplete reaction at -78°C between an α,β -unsaturated enone and lithium dimethylcuprate. After suspension of this solid in diethyl ether or THF in the presence of chlorotrimethylsilane, the conjugate addition product was obtained. Their conclusion was that this precipitate had to be the d,π^* complex. Subsequent work by Ullenius *et al.*²⁴ provided definite proof of this type of complexation. In an ^{13}C nmr study, a C2-labelled methyl cinnamate was treated with lithium dimethylcuprate at -78°C . An immediate downfield shift of the signal originating from this labelled carbon was noted. Upon increasing the temperature, this signal has shifted again, corresponding to formation of the reaction product.

Scheme 13

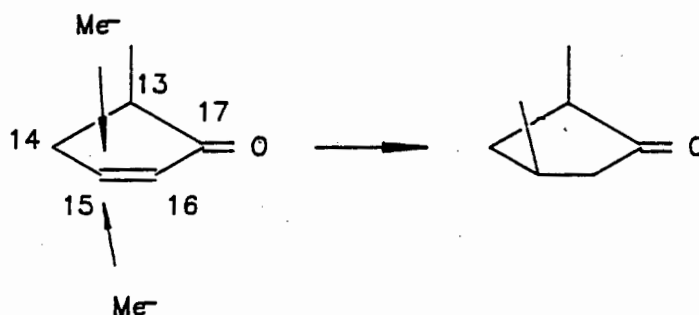


From these results, it was concluded that initial cuprate-enone complexation has to be an initial step in the reaction mechanism. The subsequent sequence of events ultimately leading to C-C bond formation are rather tentative at this stage, in that no generally accepted mechanistic details are available.

In the present study, a question of some interest was to interpret the stereochemical outcome of conjugate methylation to the Δ^{15-17} -ketone (31). Steric arguments are in

favour of 15α -substitution in the product, thereby minimising eclipsing interactions. However, stereoelectronic factors favour a different outcome. Molecular modelling studies have suggested that ring D of the enone (31) has an envelope conformation, the plane being defined by C14, C15, C16, and C17.²⁵ The p-orbitals on the Δ^{15} -double bond are twisted with their upper lobes slightly upwards, towards the C13 methyl group. Thus, reagent approach onto the β -face acquires optimal overlap of the orbitals involved. This condition is impeded on the α -face. A kinetic product of orbital control hence arises, giving the 15β -epimer, as indicated in Figure 2.

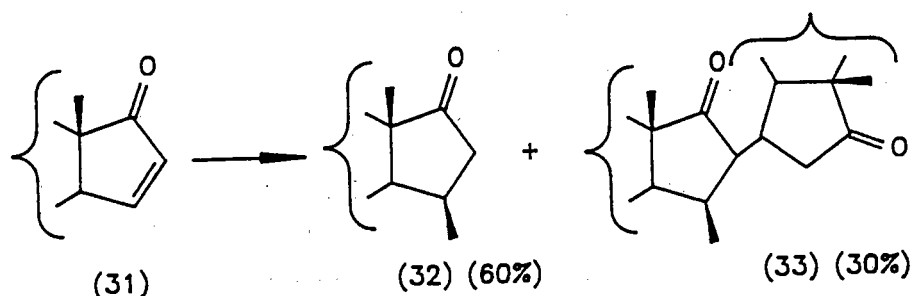
Figure 2



In an initial experiment, the Δ^{15} -17-ketone (31) in THF at 0°C was treated with lithium dimethylcuprate [generated conventionally by the addition of methyllithium (2 mol) to copper(I) iodide (1 mol) suspended in diethyl ether at 0°C]. After 15 min at 0°C , the reaction was complete (t.l.c. monitoring). Chromatography gave 3-methoxy- 15β -methylestra-1,3,5(10)-tetraen-17-one (32) (60%), accompanied by a non-crystalline by-product (33) (30%) (Scheme 14). The spectroscopic properties of the 15β -methyl 17-ketone (32) were compatible with the assigned structure, in that a 3-proton doublet (J 7.4 Hz) appeared at δ 1.16 in the 200 MHz nmr spectrum. However, it was not possible to discern any nmr signals which gave an indication of the assigned configuration at C(15). Accordingly, we assume that the stereoelectronically favoured reaction course was followed. Support for this claim was obtained from spectroscopic evidence of a derived product (see later). The by-product (33) displayed nmr and mass spectral properties consistent with a bisteroid structure. Thus, a molecular ion at m/e 580 suggested a methyl bisteroidal

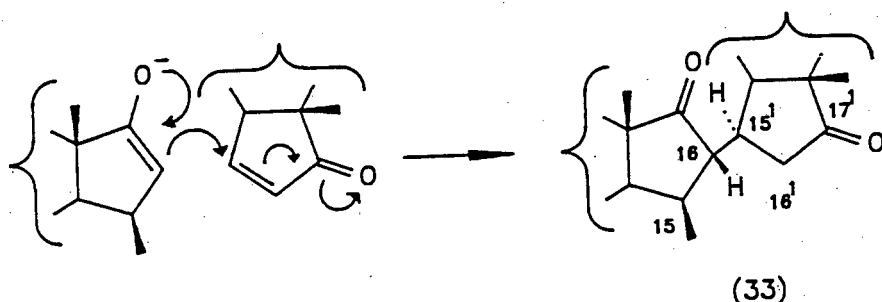
diketone. Furthermore, ^{13}C signals originating from ring D carbons appeared in duplicate, whereas the remainder of the signals overlapped, giving peaks of double intensity. On the basis of this evidence, we propose a structure based upon C(16)-C(15 1) bond formation (Scheme 14).

Scheme 14



This by-product is thought to arise by a competitive Michael-type condensation, involving the lithium enolate of (32) and unreacted (31) (Scheme 15). To test this proposal, the methyl ketone (32) was treated with lithium diisopropylamide in THF at 0°C , and the resultant enolate species was treated in turn with the enone (31). In this way, apart from the presence of cuprate reagents, the conditions under which the bisteroid would be expected to be formed during conjugate methylation, were simulated. After a lengthy and incomplete reaction (3 h at 0°C), a bisteroid, identical in analytical data to (33) was indeed isolated in a 50 % yield, together with starting materials.

Scheme 15

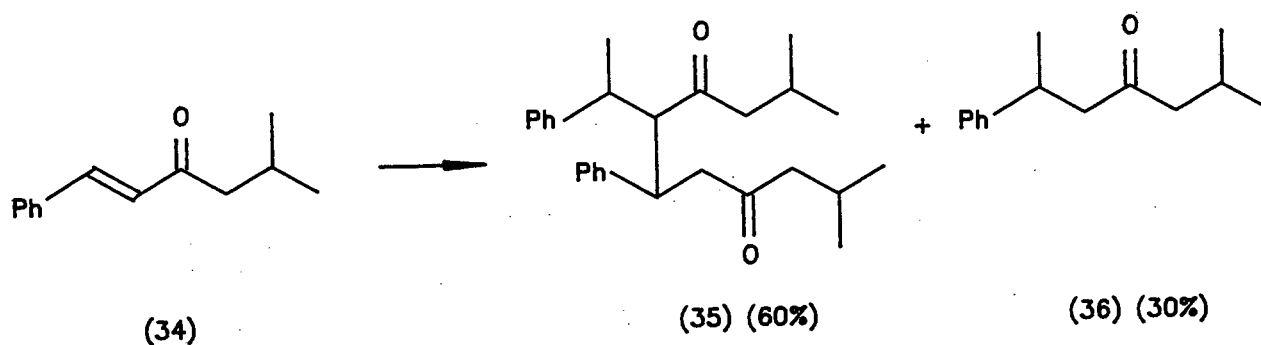


No irrefutable proof of the stereochemical assignment of the C(16)-C(15 1) bond can be offered. However, it is reasonable to assume that conjugate addition of the steroidal enolate of (32) to the $\Delta^{15,17}$ -ketone (31) would form a 15β -bond with the

latter compound, and at the same time, be obliged to react from the sterically less impeded α -face at C(16). Unfortunately, the bisteroid failed to crystallise despite numerous attempts. Therefore, it was not possible to obtain X-ray crystallographic evidence for the proposed structure.

A literature search revealed that only one analogous side-reaction has been reported. From the lithium dimethylcuprate mediated conjugate alkylation of styryl isobutyl ketone (34), Blanch and co-workers²⁶ have reported the isolation and characterisation of a secondary reaction product (Scheme 16). The structure of their by-product was elucidated as 2,10-dimethyl-6-phenyl-5-(1-phenyl)ethylundecane-4,8-dione (35) (60 %).

Scheme 16



Clearly, starting material acted as a Michael-acceptor to the alkylated enolate (36), in total analogy to the present case presented here. The authors noted, however, that formation of the desired alkylation product (36) could be optimised to 71 % at the expense of the condensation product (35) by avoiding the accumulation of an excess of the starting material during the course of the reaction.

In this work, attempts were made to improve the overall conversion of the Δ^{15-17} -ketone (31) to the derived 15β -methyl ketone (32) and to suppress formation of the by-product, The following experiments were conducted.

(a) It was initially argued that the competing reaction might be inhibited by avoiding an excess of unreacted enone (31) in the reaction medium. In an experiment, the enone (31) was added very slowly over a period of 1 h to the reagent at 0°C. However, no significant change in the product distribution (32):(33) was noted.

(b) Another variation was based upon high dilution of the reaction medium. It was thought that this condition would limit the statistical probability of an enolate-enone interaction. No improvement was made.

(c) The reagent was prepared as before at 0°C, and then cooled to and maintained at -78°C for the duration of the reaction. It was reasoned that lower temperatures might control the side reaction more efficiently. The outcome remained unchanged.

(d) A slow addition of substrate was repeated at -78°C, without success.

The next two attempts were both successful, and are based on various literature reports.

Thus, it has been recognised for some time that conjugate alkylation reactions can be enhanced by the addition of Lewis acids, prior to introduction of the substrate.²⁷ The presumed effect of the Lewis acid is that of substrate activation via complexation with a lone pair of electrons on oxygen of the α,β -unsaturated carbonyl system. This generates a more reactive electrophile, leading to decreased reaction times and improved yields.

However, it recently came to light that the above assumption may represent only a partial truth. In a study on the effects of boron trifluoride-diethyl ether complex ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) on lower order organocuprates (R_2LiCu), Lipshutz and co-workers²⁸

have reported on a twofold role of the Lewis acid. In addition to substrate activation,²⁷ the BF₃ served to modify the structure of the cuprate itself, affording a more reactive, different cuprate-Lewis acid combination. Upon ¹H nmr examination of Me₂CuLi, containing two equivalents of BF₃.Et₂O at -80°C, the immediate appearance of three new signals, in addition to the expected singlet at δ -1.5²⁹ was observed. These new peaks were rationalised in terms of sequestration of MeLi by BF₃.Et₂O from the dimeric Me₂CuLi (i.e. Me₄Cu₂Li₂),³⁰ i.e.:



Thus, apart from MeLi.BF₃ at δ 0.16, the aggregate Me₃Cu₂Li²⁹ was produced in equal amounts. The ratio of the singlet at δ -0.35 to that at δ -1.31 was 1:2, as expected for Me₃Cu₂Li, which contains magnetically nonequivalent methyl groups. Over a period of 1.5 h, further build-up of Me₃Cu₂Li and MeLi.BF₃ occurred at the expense of Me₂CuLi, to a total of ca 80 % of the total mixture. All of these changes occurred before substrate introduction, and these findings proved that beyond any reasonable doubt, modification of the original cuprate by the Lewis acid had taken place.

In the presence of BF₃.Et₂O, the major contributor towards product formation, for the case of lower order organocuprates, therefore has to be Me₃Cu₂Li. Support for this assumption was found in kinetic runs.²⁸

(e) Thus, BF₃.Et₂O was added to a solution of lithium dimethylcuprate at -78°C, prior to substrate addition. The rate of conjugate addition was greatly increased and the methyl ketone (32) was exclusively obtained. This result is in accordance to the above findings. Conjugate alkylation did indeed occur much faster (5 min, compared to 20 min, uncatalysed). The fact that no bisteroid was isolated is ascribed to the much faster consumption of starting enone by the cuprate reagent.

reagent. Thus, any accumulation of enone, which could lead to the side-reaction was avoided.

An alternative approach to optimisation of the conjugate alkylation pathway is based upon the work of Alexakis³¹ and Johnson.³² A method was proposed, in which addition of the substrate to the cuprate was preceded by an addition of trimethylchlorosilane (TMSCl). Trapping of the enolate from the conjugate alkylation therefore occurs as it is generated, and not during the work-up, as is more conventional.³³ The former idea was founded upon evidence that reaction between an organocuprate and TMSCl is very slow at low temperatures.²³ ¹H nmr studies at -50°C have indicated very little change in the position of the cuprate methyl signal upon addition of TMSCl. At 0°C, however, conversion of TMSCl into tetramethylsilane by the organocuprate was more rapid.

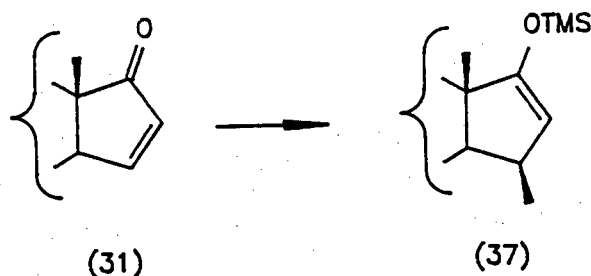
The transitional d,π^* -cuprate-enone complex is thought to be trapped by TMSCl, thereby making this initial step essentially irreversible and forcing conversion to a β -carbon adduct. A faster reaction rate with concomitant *O*-silylation trapping of the enolate is thus achieved.

Interestingly enough, in his paper, Alexakis has expressed comment on the absence of 'unidentified, high molecular weight by-products' that had often formed during the conventional (ie without TMSCl) organocuprate alkylation of α,β -unsaturated esters.³¹ It is tempting to speculate on analogy between these 'unknown' side-products and the bisteroid of the present case.

(f) Thus, TMSCl was added to the cuprate at -78°C, followed by the substrate (31). Again, the reaction rate was enhanced and upon work-up, the derived silyl enol ether (37) was obtained as an only product (Scheme 17). The derived enol silyl ether is unable to participate in any side reactions. This product was never

characterised, but a small scale hydrolysis experiment with hydrochloric acid gave the 15 β -methyl 17-ketone (32).

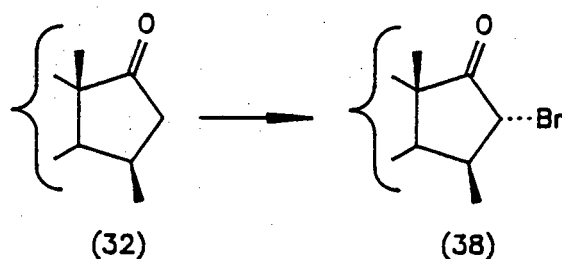
Scheme 17



3.1.2 Trapping-Dehydrogenation Various methods are possible for the conversion of the 15 β -methyl 17-ketone (32) into the corresponding 15-methyl- Δ^{15} -17-ketone (39). We chose initially to examine the conventional stepwise method based upon sequential bromination-dehydrobromination.

Thus, the ketone (32) and copper(II) bromide were refluxed in methanolic benzene, to give a single product (38) in acceptable yield (82 %) (Scheme 18).

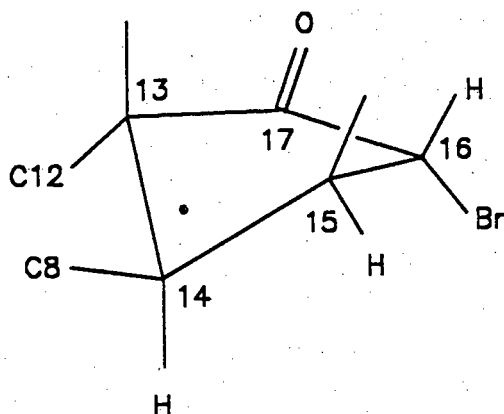
Scheme 18



This bromoketone proved useful in assigning the overall ring D stereochemistry. In the ^1H nmr spectrum, a one-proton doublet (δ 4.37, J 1.8 Hz) was assigned to 16-H, coupling to 15-H. The latter, in turn, resonated at δ 2.75 as a quintet of doublets (J 4 x 7.8 and 1.8 Hz). Equivalent coupling (J 7.8 Hz) of 15-H to both 15-Me and 14 α -H was evident, whereas 15-H couples weakly (J 1.8 Hz) to 16-H. All of these assignments were confirmed by a COSY spectrum. Applying

this coupling information to the Karplus equation afforded a unique configurational assignment. The protons on C-14 and C-15 must be *syn*, implying a 15β -Me stereochemistry for the methyl group. Further, 15-H and 16-H possess a *trans* relationship, pointing to a 16α -bromo configuration. Inversion of the stereochemistry at either or both of C-15 and C-16 would lead to significant differences in the observed coupling. In the light of these findings, earlier assumptions about β -face conjugate alkylation of (31) to give (32) are clearly valid. A perspective view of ring D of (38) is shown in Figure 3.

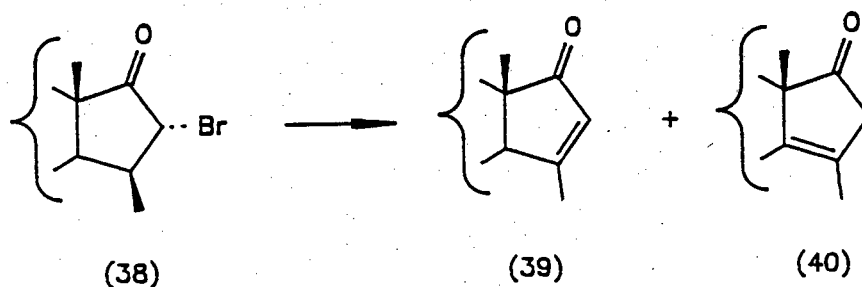
Figure 3



(38)

Treatment of the bromoketone (38) with lithium carbonate and lithium bromide in refluxing dimethylformamide was expected to effect dehydrobromination. A very slow reaction (22 h) gave a three-component mixture (Scheme 19). Two of these constituents were assumed to be the enones (39) (13 %) and (40) (41.5 %), analogous to those described by Johnson.¹⁹

Scheme 19



Tentative structural assignments were based upon the respective carbonyl stretching frequencies. The conjugate enone (39) had an absorption ν_{CO} 1688 cm^{-1} , whereas (40) had ν_{CO} 1741 cm^{-1} .

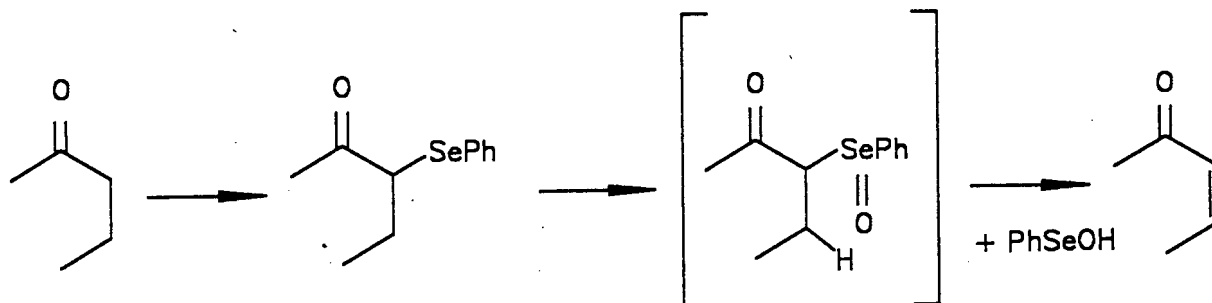
The third component from the dehydrobromination reaction was the parent 15 β -methyl-17-ketone (32) (23 %). The bromoketone (38) was thought to undergo debromination during the prolonged reaction, and work-up related protonation of the enolate completed the reversion to (32). In a similar study on a related 17 α -bromo-16-ketone, formation of the saturated 16-ketone was noticed.³⁴ In this case, the absence of a vicinal C-H bond for elimination of HBr appeared to give rise to effective debromination.

Dehydrobromination is generally accepted to be favoured by an antiperiplanar arrangement of eliminating elements. These elements in (38) (ie 15 α -H and 16 α -Br) were shown to be *syn* to each other. It is hence tempting to speculate that (38) must first undergo epimerisation C-16, in order to generate the desired configuration for HBr elimination. However, during the reaction progress, no such an intermediate was detectable (t.l.c. monitoring). The only elimination option is hence that of *syn* dehydrobromination. Although uncommon and inefficient, cases of the latter are known.^{35,36} In a study on *trans*-1,2-dibromocyclohexanes,³⁶ it was reported that *syn* elimination of HBr was indeed possible when the bromo group occupied an equatorial orientation. Analogy to (38) is thus indicated, because the 16 α -Br substituent occupies a pseudo-equatorial position on the five-membered ring D. The combined overall yield of the mixture of enones (39 and 40) based on (31) was a rather dismal 40 %. Further work on this approach, and complete characterisation of the products was abandoned in favour of alternative methods.

A second approach to the enone (39) was based upon selenium methodology. Numerous cases are known, in which α -phenylselenenyl ketones are converted into their corresponding α,β -unsaturated carbonyl compounds.³⁷ This involves oxidation

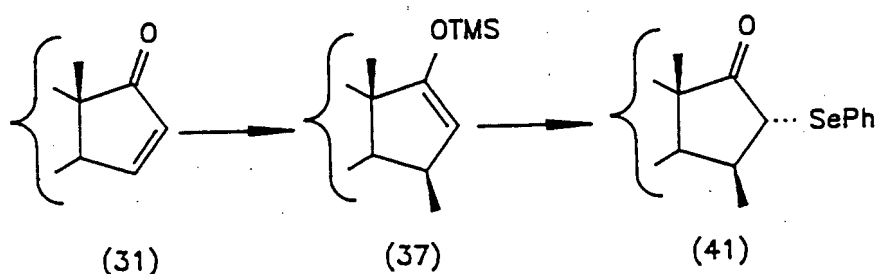
of the selenium substituent to the selenoxide level, followed by elimination of phenylselenenic acid (Scheme 20). The sigmatropic [2,3]-thermolysis of the selenoxide occurs entirely in the *syn* mode.

Scheme 20



On the basis of the bromination-dehydrobromination results, considerable advantages were thus perceived in exploring a selenium-mediated route to the enone (39). The most efficient α -selenenylation procedure of (32) was obtained by treating the derived enol silyl ether (37) with phenylselenenyl chloride in the presence of a Lewis acid. This method gave a much cleaner reaction and better yields of (41) (i.e. 80 %) than direct selenenylation of the lithium enolate, obtained from the organocopper alkylation of (31) (Scheme 21).

Scheme 21



Despite various attempts, (41) failed to crystallise. A full characterisation was thus not performed and the total crude product was committed to subsequent conversions.

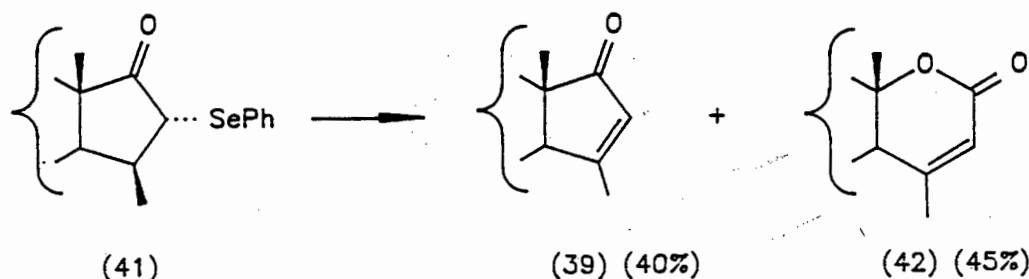
Having established an efficient selenenylation pathway, the next step was to find a suitable oxidising agent. Of the various oxidants available for oxidising selenides up

to the selenoxide level, *m*-chloroperoxybenzoic acid (MCPBA) and hydrogen peroxide solutions are most frequently used.³⁷ A further virtue of MCPBA is that exact amounts of reagent can easily be measured. Sodium periodate is an alternative option, but the necessity of using aqueous media limits the usefulness of this oxidant for this work.

In a related study, employing sulphoxide chemistry, Trost and co-workers³⁸ have established a reaction sequence in which the α -phenylsulphide of estrone 3-methyl ether was oxidised up to the corresponding α -sulphoxide by MCPBA. This oxidation, based on a stoichiometric amount of oxidant, was complete within 5 min at 0°C, with no overoxidation. Subsequent thermolysis of the sulphoxide afforded the corresponding Δ^{15-17} -ketone, in excellent overall yield.

Encouraged by these findings, we attempted the analogous reaction on the α -phenylselenide (41). Prolonged reaction at 0°C failed to convert the substrate into the corresponding selenoxide. Upon raising the temperature, starting material decomposition was noted (t.l.c.). The reaction was repeated with 30 % hydrogen peroxide. Over the temperature range 0-25°C, oxidation occurred within 1.5 h, with concomitant thermolysis to give a mixture of two products (Scheme 22). The primary product was identified as a D-homo lactone (42) (45 %), followed by the desired enone (39) (40 %). The ¹H nmr spectrum of (39) showed 15-Me at δ 2.25 (s) and 16-H at δ 5.77br (s), supporting the assigned structure. From the presence of (42), it appears that the expected enone (39) had undergone competing Baeyer-Villiger oxidation to produce the lactone.

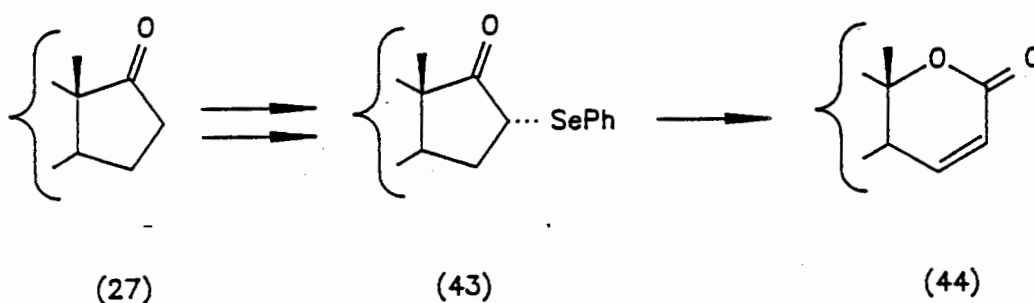
Scheme 22



Literature precedent for this type of Baeyer-Villiger reaction is documented. In an analogous study on estrone 3-methyl ether by Williams³⁹, the enol lactone (44) was isolated as an only product (Scheme 23). Upon selective hydrogenation of the Δ^{15} -bond of their compound, the saturated lactone was obtained. The latter compound was identical to the material obtained from direct Baeyer-Villiger oxidation of estrone by trifluoroperoxyacetic acid.⁴⁰

Structural confirmation of (42) was obtained by comparing the spectroscopic data with those of (44). The latter compound was prepared in three steps from the silyl enol ether of estrone 3-methyl ether (Scheme 23), following the same procedure as Williams (*cf* ref. 39).

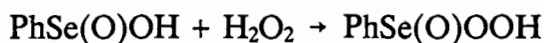
Scheme 23



The ^1H nmr of (44) showed 15-H at δ 7.18 (d, J 8.5 Hz) and 16-H at δ 6.08 (d, J 8.5 Hz), suggesting a conjugated lactone. For compound (42), the vinylic proton 16-H resonated at δ 5.88 (q, J 1.5 Hz). The 15-Me group resonated at δ 2.10 (t, J 1.5 Hz). Coupling between 15-Me and 16-H, and between 15-Me and 14α -H was thus indicated, although no structural conclusions could be drawn from these data alone. However, upon comparing ultraviolet and infrared data of the two compounds, the situation changed. Compound (44) showed λ_{max} 243 nm ($\log \epsilon$ 4.33) and ν_{max} 1710 cm^{-1} . The substituted lactone (42) had λ_{max} 245 nm ($\log \epsilon$ 4.31) and ν_{max} 1705 cm^{-1} . Therefore, based upon the high degree of compatibility of UV and IR data, and further knowing that (44) is conjugated, it was concluded that both lactones possess similar overall structures.

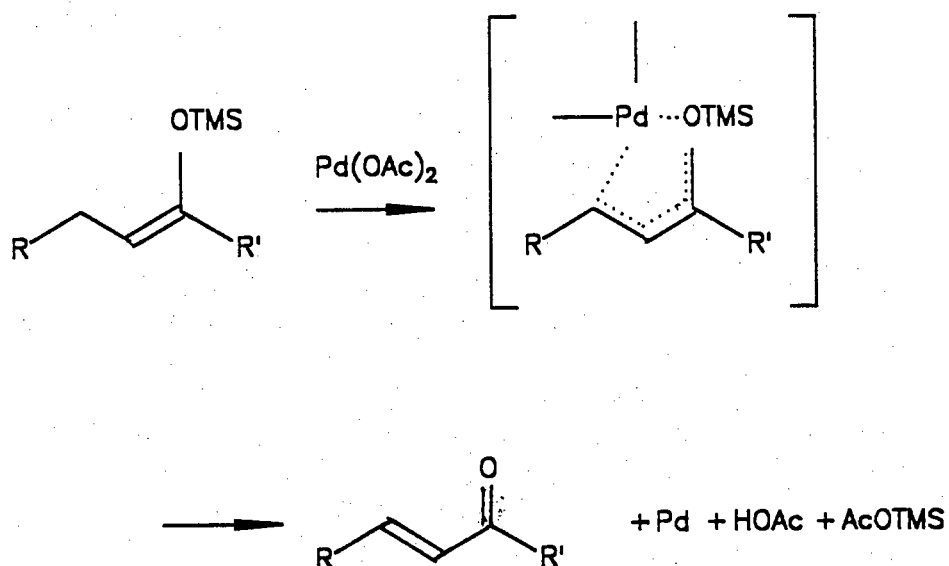
At this stage, a question of considerable interest seems to be why the Baeyer-Villiger oxidation occurred, and why the 15-methyl- Δ^{15-17} -ketone (**39**) was isolated, compared with the unsubstituted case, in which only the unsaturated lactone (**44**) was obtained.

In the original paper on this topic,³⁹ attempts to convert either the saturated ketone or the derived enone into the lactone by hydrogen peroxide failed. The authors concluded that the phenylselenenyl group had to play a participating role as a Baeyer-Villiger oxidant. Subsequent work by Grieco⁴¹ has established that phenylperoxyseleninic acid (PhSeO_3H) is a powerful Baeyer-Villiger oxidant for conversion of ketones into their corresponding lactones. This reagent can readily be generated *in situ* from phenylseleninic acid:



It was noted⁴¹ that this reagent is more potent than 40 % peroxyacetic acid or MCPBA as a Baeyer-Villiger oxidant. Furthermore, estrone 3-methyl ether was converted into the corresponding lactone by this reagent,⁴¹ hereby giving additional support to the findings of Williams. Similar work done by Syper⁴² has indicated that PhSeO_3H , in the presence of excess H_2O_2 , is capable of catalytically performing Baeyer-Villiger oxidations on aldehydes and ketones. Hydrogen peroxide was required to reconvert PhSeO_2H to the active PhSeO_3H . With these facts in hand, the identity of the Baeyer-Villiger oxidant during the reaction of the present case became clearer. The by-product of the selenoxide thermolysis, i.e. phenylselenenic acid (PhSeOH), is susceptible to further oxidation, to give PhSeO_2H and PhSeO_3H . Thus, after the selenoxide elimination, excess oxidant can generate selenium species capable of initiating Baeyer-Villiger oxidations. The observation that the expected 15-methyl- Δ^{15-17} -ketone (**39**) was obtained from the 15-methyl intermediate (**41**) may be ascribed to some remote substituent effect by the methyl

Scheme 25



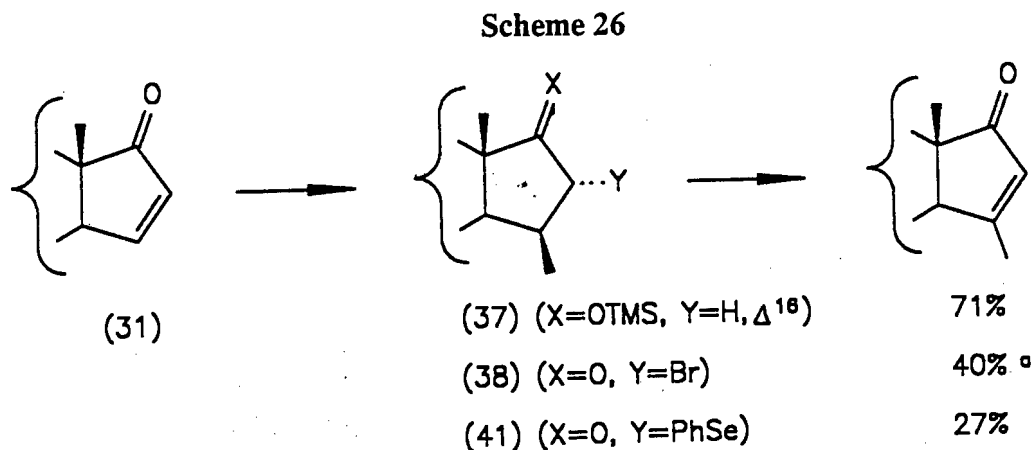
introduced catalytic dehydrosilylation procedures with oxygen over silica-supported palladium. The catalyst was prepared by ion exchange of silica gel (SiO_2) with $[\text{Pd}(\text{NH}_3)_4]\text{Cl}_2$, followed by heat fusion and reduction of Pd^{II} to give between 3.9 and 4.2 wt % Pd^0/SiO_2 . Reaction of this catalyst (0.1 mol. equiv.) with a silyl enol ether in a suitable solvent in the presence of oxygen at 35°C , afforded good yields of the corresponding α,β -unsaturated carbonyl compounds.

For present purposes, only the $\text{Pd}(\text{OAc})_2$ reaction was explored. Thus, treatment of the silyl enol ether (37) with 1 mol. equiv. $\text{Pd}(\text{OAc})_2$ in acetonitrile at 60°C gave the 15-methyl- Δ^{15-17} -ketone (39) in a 70 % yield, followed by some saturated ketone (32) (20 %).⁴³

This reaction sequence required a minimum handling of sensitive intermediates. The silyl enol ether (37) was directly available from the conjugate alkylation-trapping of (31) and the total crude product upon work-up could be committed to dehydrosilylation. For this two-step formal β -alkylation of (31), the best overall yield obtained was 71 %. This is greatly superior to any of the other methods attempted in this work. The reaction sequence is also far more convenient to perform and requires much milder conditions.

The results obtained from the foregoing experiments are compared in Scheme 26.

Yields given are based upon (31).



^a Mixture of enones

3.1.3 Enol Acetylation and Cycloaddition Studies Two approaches to enol acetylation of the 15-methyl- Δ^{15} -17-ketone (39) were explored. In an earlier stage of the work, the total crude product from dehydrobromination of (38) was treated under the standard conditions of enol acetylation. This mixture of enones gave a mere 42 % of dienyl acetate (45), clearly as a result of impurities present in the mixture (Scheme 27). In the second approach, the pure 15-methyl- Δ^{15} -17-ketone (39), as obtained from pathways discussed in the foregoing section, was converted into 3-methoxy-15-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate (45). A much better yield of 78 % was hereby obtained. From the ^1H nmr spectrum of (45), ring D could be uniquely characterised by four distinctive signals. (Table 1).

Initial cycloaddition experiments were carried out with phenyl vinyl sulphone, since our strategic plan required the preparation of cycloadducts from ethylene equivalents. It was hoped that, by analogy with the related work, a single isomer derived from β -face 1,2-addition to (45) would be obtained. The extra methyl group on this 15-methyl dienyl acetate (45) was expected to reinforce the unexceptional

regiochemical outcome. Dienes bearing terminal electron releasing groups favour 1,2-additions. Such disubstituted systems often show enhanced regioselective properties.⁴⁷

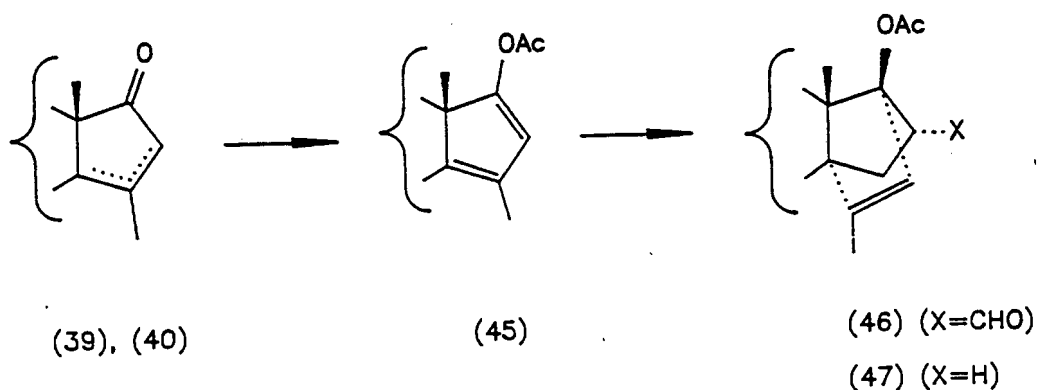
Table 1

δ_H	Assignment
1.06 (3H, s)	13 β -Me
2.03 (3H, s)	15-Me
2.21 (3H, s)	17-OAc
5.95 (1H, s)	16-H

The reaction between PVS and the 15-methyl dienyl acetate (**45**) was carried out under a variety of temperature and solvent conditions, but failed to give any cycloadducts. On each occasion, starting material was recovered. From this it was concluded that the 15-methyl group deactivates the diene by steric impedance and that phenyl vinyl sulphone was not reactive enough to overcome this steric barrier.

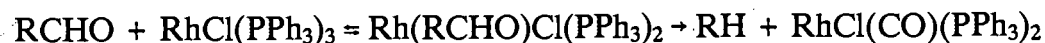
Consequently, a more reactive dienophile was considered. Treatment of (**45**) with acrolein, in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, gave rise to a single cycloadduct (**46**) (75 %) under very mild conditions (16 h at 20°C) (Scheme 27). No irrefutable evidence for the regio- and stereochemical outcome of cycloaddition was obtainable from a 200 MHz ^1H nmr spectrum and the structure was assigned by analogy.⁸

Scheme 27



Nmr signals consistent with the proposed reaction product were fully assigned and are listed in Table 2. The aldehydic proton (16^1-H) at δ 9.46 appeared as a doublet (J 4.34 Hz), coupling to $16\beta\text{-H}$. Owing to its complexity, the fine structure of the $16\beta\text{-H}$ signal could not be assigned. It is further interesting to note that 17^1-H and 17^2-Me displayed coupling to another. The methyl signal appeared as a doublet (J 1.5 Hz), and 17^1-H only showed peak broadening. This type of coupling was also observed for both the 15-methyl- Δ^{15-17} -ketone (**39**) and the corresponding 15-methyl lactone (**47**).

Decarbonylation of this cycloadduct was achieved with Wilkinson's catalyst, $\text{RhCl}(\text{PPh}_3)_3$, to obtain (**47**). The reaction was non-catalytic and required a stoichiometric amount of reagent. Mechanistically, this reaction involves oxidative addition of the aldehyde to the Rh-complex, followed by reductive elimination of the product, i.e.:



Catalytic decarbonylation of aldehydes with Rh-based reagents is, however, possible.⁴⁸ The difficulty in obtaining catalytic activity with $\text{RhCl}(\text{PPh}_3)_3$ lies in the prohibitive temperatures required to expel CO from $\text{RhCl}(\text{CO})(\text{PPh}_3)_2$, in order to regenerate the active species of $\text{RhCl}(\text{PPh}_3)_3$.

The most distinctive differences in the spectra of (**46**) and (**47**) is the disappearance of the aldehydic signal. Further, the signal from $16\beta\text{-H}$ of (**47**) could no longer be detected. Comparative signals are listed in Table 2.

The foregoing experiments demonstrate that the reactivity of the 15-methyl dienyl acetate (**45**) is depressed relative to that of unsubstituted dienyl acetate (**1**).

Table 2

	46	47
13 β -Me	0.96 (s)	0.88 (s)
17 ² -Me	1.89 (d, <i>J</i> 1.5 Hz)	1.80 (d, <i>J</i> 1.3 Hz)
17 β -OAc	2.11 (s)	2.08 (s)
16 β -H	3.09 (m)	obsc.
17 ¹ -H	6.04br (s)	5.94br (s)
16 ¹ -H	9.46 (d, <i>J</i> 4.3 Hz)	-

However, the successful cycloaddition of acrolein, followed by decarbonylation resulted in achievement of the desired objective, to generate a cycloadduct from an 'ethylene equivalent'. The practicality of developing this sequence further is likely to be limited by the cost-ineffective decarbonylation step. Further work on the cycloaddition options to this new ring D dienyl acetate can be envisaged, but were not further explored in this investigation.

3.2 Related Aspects of Ring D Chemistry

Some reactions were carried out on the 15-methyl- Δ^{15} -17-ketone (39) and derived products in order to explore the scope for developing synthetic routes to new hormone analogues.

Treatment of the 15-methyl- Δ^{15} -17-ketone (39) with lithium dimethylcuprate in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in THF at -78°C gave 3-methoxy-15,15-dimethylestra-1,3,5(10)-trien-17-one (48) in 70 % yield (Scheme 28). The structure of the product was confirmed by spectroscopic data. With the aid of a COSY plot, the ring D proton signals were clearly discerned. The distinctive AB-multiplet (J 16.4 Hz) for the 16- CH_2 group was diagnostic for the assigned structure. Treatment of this compound with lithium aluminium hydride (LAH) effected the stereoselective reduction to the 17 β -alcohol (49). The stereochemistry at C-17 was assigned by means of the coupling pattern of 17-H. This signal was observed at δ 3.71 as a double doublet (J 10.7 and 7.9 Hz). Coupling constants of this magnitude are characteristic for 17 β -alcohols. In a comparative study, the 15 β -methyl-17-ketone (32) was also reduced with LAH. Again, a single product, assigned as the corresponding 17 β -alcohol (50) was obtained. Ring D signals were slightly more complex, and only a few could be rigorously identified. These assignments are shown in Table 3.

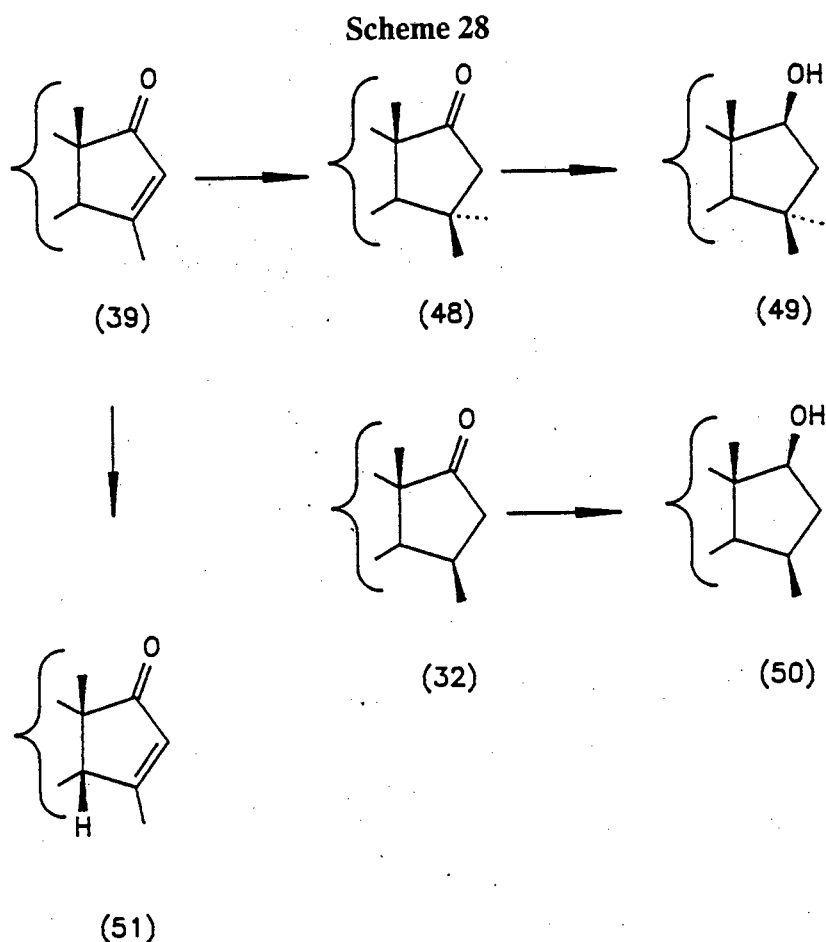
Table 3

	(49)	(50)
13 β -Me	0.92 (s)	0.91 (s)
14 α -H	1.06 (d, <i>J</i> 11.2 Hz)	obsc.
15 α -Me	1.11 * (s)	-
15 β -Me	1.14 * (s)	1.02 (d, <i>J</i> 7.4 Hz)
16 α -H	1.90 (d, <i>J</i> 13.0 and 7.9 Hz)	obsc.
16 β -H	1.61 (dd, <i>J</i> 13.0 and 10.2 Hz)	obsc.
17 α -H	3.71 (dd, <i>J</i> 10.2 and 7.9 Hz)	3.68 (dd, <i>J</i> 9.8 and 8.0 Hz)

* Interchangeable

As part of an investigation into new routes to 14-substituted 19-norsteroids, the potential of base- and acid-mediated rearrangements of 14,15-methylene 17-ketones for generating possible intermediates to the former family of compounds was explored.⁴⁹ In the event, acid treatment of 3-methoxy-14,15 α -methylene-estra-1,3,5(10)-trien-17-one gave rise to a complex mixture containing ring D-homologated products of skeletal rearrangement, as well as the 14 β -epimer of estrone 3-methyl ether (51). High field nmr studies, as well as molecular mechanics calculations have indicated that ring C of (51) is conformationally deformed to a twist-boat. Ring D is largely deflected towards the α -side of the molecule. ⁴⁹

In this study, an alternative route to (51) was obtained upon acid treatment of (39) (Scheme 28). From the original work by Johnson,¹⁹ exposure of the unsubstituted enone (31) to toluene-*p*-sulphonic acid afforded a mixture (1 : 2.5) of the corresponding 14 β -compound, as well as the β,γ -enone.



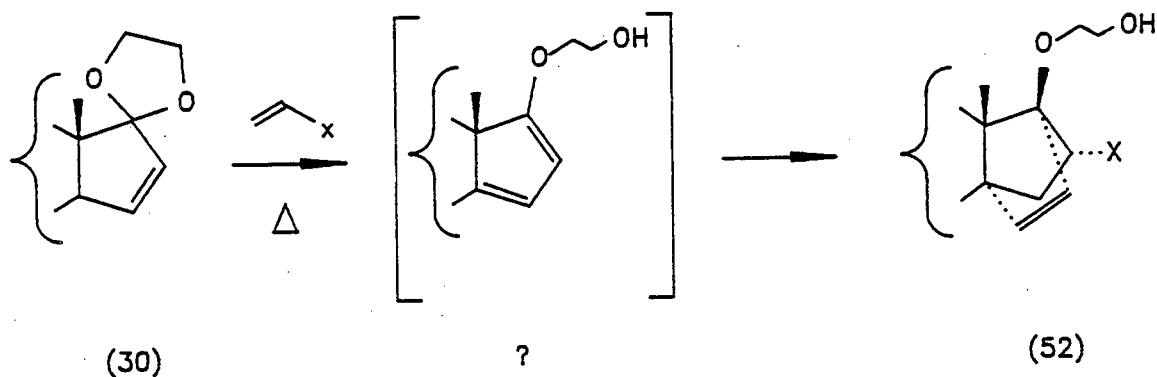
An outstanding feature of the ^1H nmr spectrum of (51) is the signal obtained from 14 β -H. An isolated doublet at δ 2.75 (J 5.1 Hz) is observed, obtained from coupling to 8 β -H.

Arising out of the results hitherto presented in this investigation, some tangential issues of interest to the broader programme on structure-activity relationships on ring D bridged compounds were also addressed. In a recent communication, Tsuji *et al.*⁵⁰ have established that the ethylene acetal of cyclopent-2-en-1-one is capable

of acting as a diene, *via* its ring-opened form. Good yields were obtained from cycloadditions to a variety of dienophiles.

We were intrigued by the possibility of extending this principle to the vinylogous case represented by the Δ^{15-17} -ketal (30). Thus, if it is possible to envisage 14α -proton abstraction comparable to α^1 -deprotonation represented by the cyclopentane model, it might be possible to circumvent the need to prepare the 14,16-dien-17-yl acetate for cycloadditive purposes. (Scheme 29)

Scheme 29



In the event, treatment of (30) with PVS failed to give any trace of the desired cycloaddition product (52). However, we were astonished to note that the recovered starting material (95 %) showed migration of the olefinic bond to give the Δ^{14-17} -ketal (53).

This result led to speculation that isomerisation may have been mediated by traces of acid at elevated temperature and could indeed represent thermodynamic equilibration reminiscent of that which occurs in isomerisation of Δ^4 - to Δ^5 -octalones.⁵¹

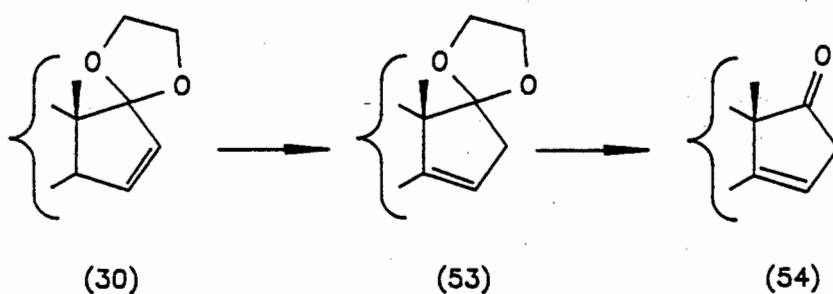
Thus, treatment of the Δ^{15-17} -ketal (30) with a catalytic amount of toluene-*p*-sulphonic acid in benzene at refluxing temperature, achieved migration of the

double bond to give (53) (Scheme 30). Some amount of the conjugated enone (31) (*ca* 5 %), originating from ketal hydrolysis, was also obtained. In an attempt to control this side reaction, the isomerisation was repeated at 20°C. This resulted in slower conversion of (30)→(53), with increased amounts of (31) being isolated.

This sequence for converting an α,β -unsaturated ketone equivalent into the corresponding β,γ -unsaturated ketone as applied to (30) can be seen complementary to a deconjugation route described by Babler *et al.*⁵². In their work, an α,β -unsaturated ketone was acetalised to the corresponding β,γ -unsaturated ketal, which upon careful hydrolysis furnished the corresponding β,γ -unsaturated ketone.

The acetal function of (53) could easily be hydrolysed at 0°C with trifluoroacetic acid. It was essential to maintain a low temperature, in order to prevent isomerisation of the cleaved product (54) to the thermodynamically favoured α,β -unsaturated ketone (31).⁵³

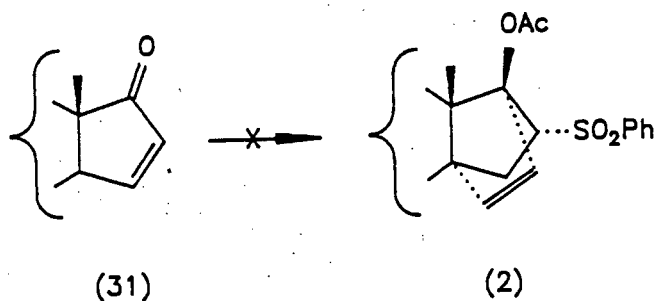
Scheme 30



In a second attempted variation on the cycloaddition theme, the Δ^{15-17} -ketone (31) was treated under conditions of enol acetylation, in the presence of a dienophile. This compound is a precursor to the dienyl acetate (1) and the feasibility of a 'one-pot' enol acetylation-cycloaddition reaction seemed interesting. A three day exposure of the material to the conditions of enol acetylation did not, however, afford a cycloadduct. Instead, only the dienyl acetate (1) was recovered (Scheme 31). Upon prolonged treatment under conditions of elevated temperature,

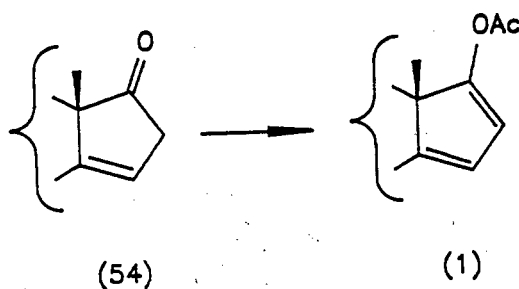
an intractable mixture was obtained, showing total decomposition of all organic material with extensive charring. It was concluded that cycloaddition was solvent dependent and that the dienyl acetate was sensitive to prolonged exposure to heat and organic acids. No further modifications of these reaction conditions were attempted.

Scheme 31



Finally, having established a route to the Δ^{14} -17-ketone (54), the conditions for conversion of this enone into dienyl acetate (1) were explored. It was reasoned that much milder conditions would be required, since the Δ^{14} -double bond was already in position. The transformation would only entail abstraction of a relatively acidic α -proton in (54), compared to abstraction of an allylic proton in (31). Thus, treatment of the Δ^{14} -17-ketone with acetic anhydride and a catalytic amount of toluene-*p*-sulphonic acid at 20°C, furnished the dienyl acetate (1) in an 80 % yield (Scheme 32).

Scheme 32

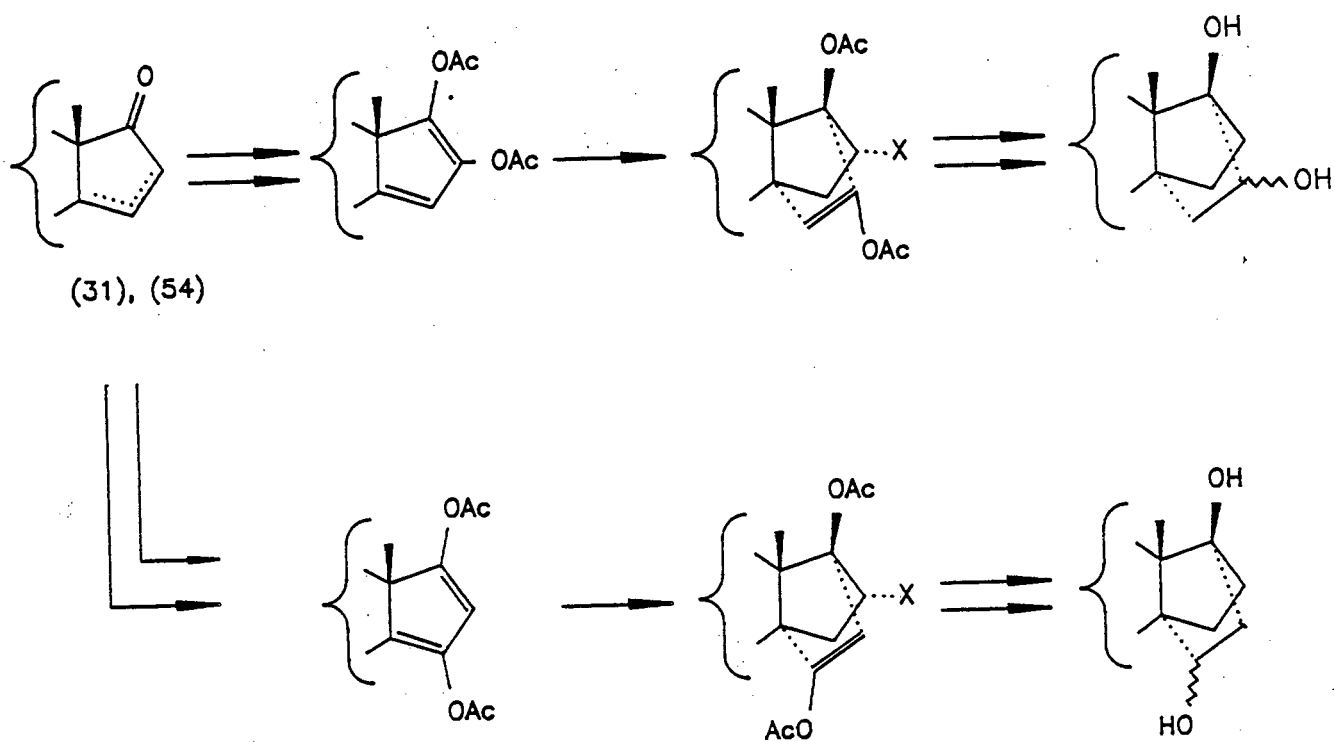


This methodology offers a six-step alternative to the existing 3-step route.⁸ An advantage is that clean, crystalline material is obtainable from every step. Further, the conversion of enone into dienyl acetate occurs far more readily and with improved yield.

3.3 Attempted Synthesis of 16,17- and 15,17-Diacetoxy 14,16-Dienes

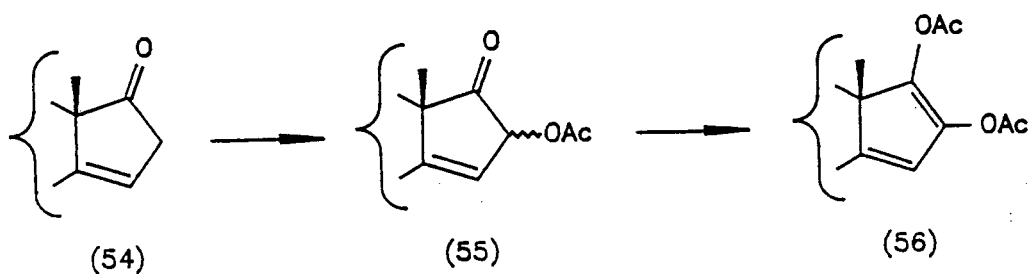
As part of the overall objective of this project, synthetic routes to 16,17-diacetoxy- and 15,17-diacetoxy-14,16-dienes were sought in order to examine the scope for developing a cycloaddition-mediated route to the correspondingly functionalised α -bridged compounds, and hence, regiospecifically the corresponding estriol analogues (Scheme 33)

Scheme 33



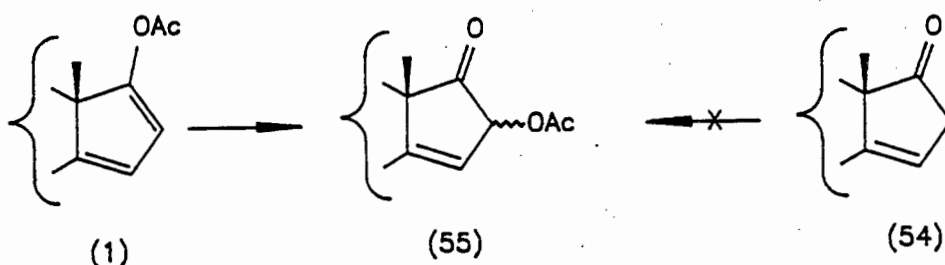
Our foregoing results have provided an efficient route to the Δ^{14} -17-ketone (54). It was reasoned that the compound should readily undergo α -acetoxylation, and that the derived 16-acetoxy- Δ^{14} -17-ketone (55) could be induced to undergo enol acetylation to the first target diene (56) (Scheme 34).

Scheme 34



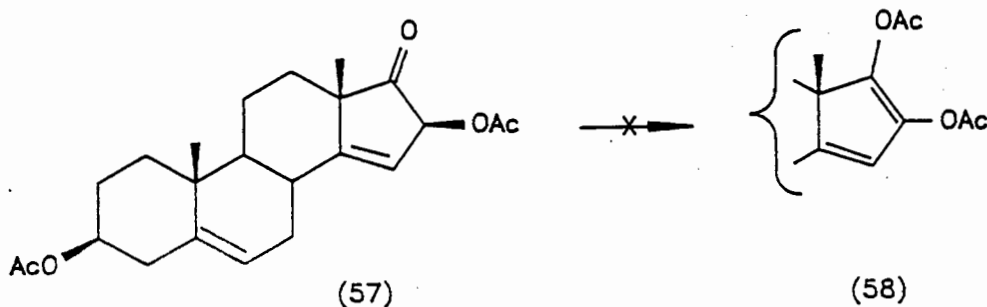
Lead tetraacetate has been known to effect α -acetoxylation of carbonyl compounds.⁵³ Conditions of either refluxing benzene, or lower temperature treatment in the presence of a Lewis acid were reported to give efficient conversions. Nevertheless, numerous attempts to convert (54) into (55) were utterly unsuccessful. As an alternative, the dienyl acetate (1) was treated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to react as an enol equivalent with $\text{Pb}(\text{OAc})_4$. The latter was separated from residual acetic acid by azeotropic benzene distillation immediately prior to use. This method proved successful, affording the 16-acetoxy- Δ^{14} -17-ketone (55) (Scheme 35). An AB-multiplet (J 2.2 Hz) for both 15-H (δ 5.80) and 16-H (δ 5.50) supported the 16-acetoxy 17-ketone assignment of (55), compared to its possible regioisomeric 17-acetoxy 16-ketone isomer. The stereochemistry at C(16) remains, however, unassignable from present data.

Scheme 35



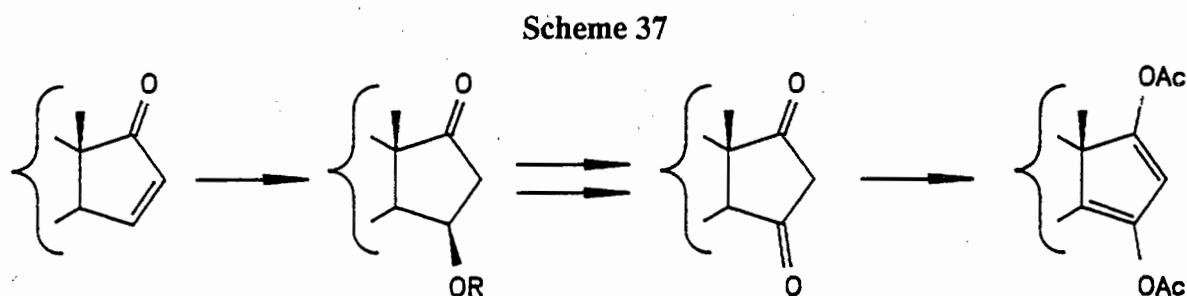
Enol acetylation studies were carried out on a model compound, 3 β ,16 β -diacetoxyandrosta-5(6),14-dien-17-one (57)⁵⁵. Forcing conditions of enol acetylation failed to effect any change. Base treatment, followed by excess acetyl chloride yielded an unexpected, more polar product (t.l.c.), which decomposed upon exposure to silica gel for chromatography (Scheme 36). In the light of these findings, no further enol acetylation attempts were carried out on (55).

Scheme 36



Attention was turned to a study of the second target system, the 15,17-diacetoxy-14,16-diene (**63**). In this instance, it was reasoned that Michael addition of a masked hydroxy group, followed by functional group manipulation would lead to a 15,17-diketone, which was expected to undergo enol acetylation to the desired compound (**63**).

A convenient way to introduce an oxygen function at C-15 is *via* conjugate benzyloxylation. Hydrogenolysis, followed by mild oxidation, was expected to produce the corresponding 15,17-diketone. The standard conditions of enol acetylation were subsequently expected to afford the 14,16-dienyl-15,17-diacetate. The desired reaction outcome is shown in Scheme 37.

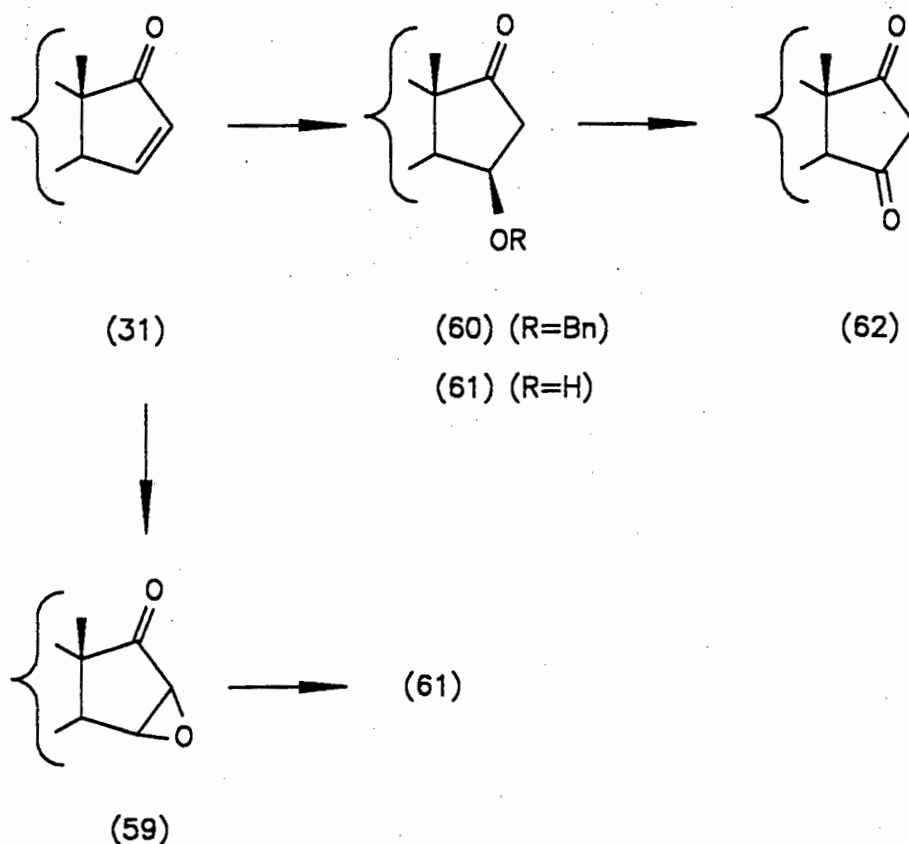


Thus, treatment of the enone (**31**) with benzyl alcohol under strongly basic conditions¹⁴ achieved conjugate addition to yield the 15 β -benzyloxy-17-ketone (**60**). This compound readily underwent hydrogenolysis upon treatment with palladium on carbon in the presence of hydrogen, to give the 15 β -alcohol (**61**) (Scheme 38). The benzyloxylation procedure suffers from the inconvenience of having to remove residual benzyl alcohol after the reaction work-up, a procedure demanding prolonged high temperature and vacuum treatment. Consequently, the scope for an alternative approach for achieving the conversion (**31**) \rightarrow (**61**) was explored. Oxygen functionality was introduced by an epoxidation-cleavage route.

Epoxidation of the enone (**31**) was carried out according to a literature method, using alkaline hydrogen peroxide.⁵⁶ This α -epoxyketone (**59**) displayed some interesting spectroscopic features. The expected doublet coupling was observed at

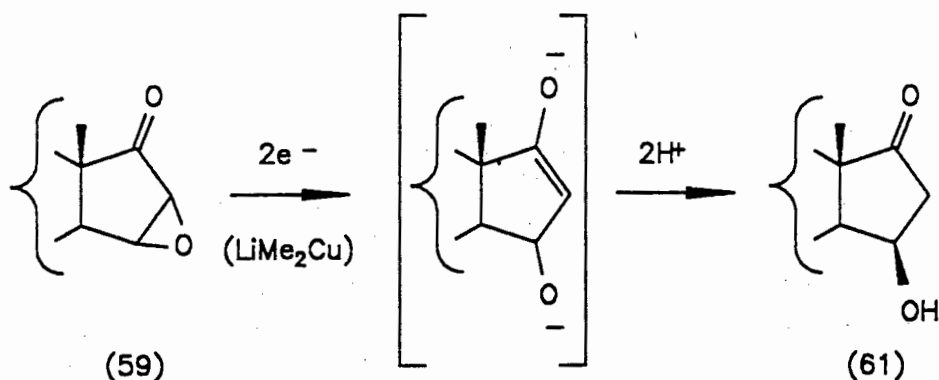
δ 3.93 for $15\alpha\text{-H}$ (d, J 2.9 Hz) and $16\alpha\text{-H}$ (δ 3.33, d, J 2.9 Hz). However, $15\alpha\text{-H}$ does not appear to couple to $14\alpha\text{-H}$. This seems to suggest that $15\alpha\text{-H}$ and $14\alpha\text{-H}$ are on a orthogonal torsion angle, thereby eliminating scalar coupling.

Scheme 38



It has been reported that ring A steroidal α -epoxyketones⁵⁷ readily undergo reaction with lithium dimethylcuprate to give the derived β -hydroxy ketones. As by-products, varying amounts of the corresponding enones, derived from β -elimination of the primary product, as well as the subsequently 1,4-alkylated ketones were obtained. These products were thought to form during the work-up. A proposed mechanism for this type of epoxide reduction is based upon the postulated single electron donating capabilities of organocopper compounds. A single electron is transferred onto the carbonyl oxygen, resulting in formation of a radical anion, followed by another transfer to give the dianion. Work-up related protonation affords the β -hydroxy ketone (Scheme 39).

Scheme 39

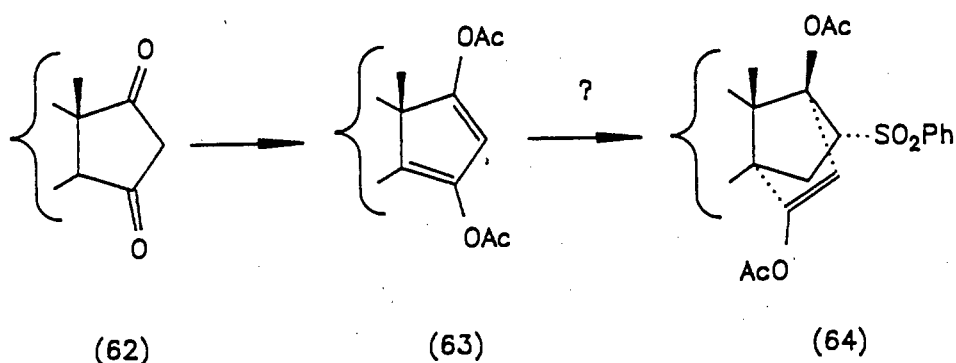


Thus, in this work, treatment of the epoxy ketone (59) with lithium dimethylcuprate in THF at $0^\circ C$ afforded exclusively the 15β -alcohol (61) (Scheme 39). The reaction was quenched at low temperature, thereby minimising the risk of β -elimination and related side reactions. This method gave an overall yield of 62 % and is comparable to that obtained from benzylation-hydrogenolysis. The advantage of the cuprate-mediated reaction sequence is a greater experimental ease of handling the labile product.

Oxidation of the 15β -hydroxy-17-ketone (61) to the corresponding 15,17-diketone (62) seemed challenging. In a related reaction sequence,⁵⁸ an oxidation with pyridinium chlorochromate was carried out. Prolonged reaction conditions were required, giving capricious yields. As an alternative oxidant for compound (61), Jones' reagent was explored. Oxidation was carried out at $0^\circ C$ and after a period of 20 min, a single product, corresponding to the 15,17-diketone (62) was isolated. No side products, derived from oxidation of the benzylic positions C-6 and C-9 were obtained (Scheme 38).

Conversion of the diketone (62) into the 14,16-dienyl-15,17-diacetate (63) was achieved under forcing conditions of enol acetylation (Scheme 40). Prolonged high temperature treatment with acetic anhydride, followed by very careful work-up was required to prevent hydrolysis of the acetoxy groups.

Scheme 40



The ^1H nmr of (63) displayed the expected features. No differentiation could be made between the acetoxy groups (δ 2.18 and 2.21, both s, 3H), and 16-H appeared at δ 6.15 (s).

In a preliminary experiment, it was reported⁵⁹ that this dienyl diacetate (63) underwent cycloaddition with phenyl vinyl sulphone, to give a product which was not rigorously purified, but characterisation by nmr and mass spectral data supported the argument of the cycloadduct structure (64).

However, in this work no success was achieved in reproducing this result. Several variations of reaction conditions were attempted, but to no avail. Not even acrolein as dienophile managed to effect a cycloaddition. We tentatively concluded that, as in the case of the 15-methyl dienyl acetate (45), the steric demands of (63) are deactivating reactivity towards cycloaddition. However, further work is necessary in order to exhaust all the possible experimental variations, in view of the preliminary report above.

In conclusion, the proposed approach (Scheme 33) to functionalised bridged compounds through 16,17- and 15,17-diacetoxy 14,16-dienes does not yet appear to hold much promise, both in the preparation of the substrate in one case, and in the

reaction of the diene in the other. Some options for future consideration include the attempted cycloaddition of such systems with more reactive dienophiles, or the substitution of acetoxy groups by other protected functionality, to achieve the same overall objective

4. EXPERIMENTAL

General

Spectra were recorded as follows: infrared, Perkin-Elmer 983, chloroform solutions; ultraviolet, Phillips PU 870 UV/VIS spectrophotometer, chloroform solutions; ^1H and ^{13}C n.m.r., Varian VXR-200 (tetramethylsilane as internal standard) (200.1 and 50.3 MHz respectively), deuteriochloroform solutions; mass (electron impact) VG micromass 16F (recorded at 70 eV, with ion source temperature of 180-200°C). Optical rotations were determined in chloroform solutions at 20°C with a Perkin-Elmer 141 polarimeter. Microanalysis for C, H, and N were carried out using a Heraeus CHN-rapid combustion analyser.

Melting points were determined on a Reichert-Jung hot-stage microscope and are uncorrected.

Thin layer chromatography was performed on aluminium-backed silica gel 60 F₂₅₄ plates in various solvent systems, applying the ascending technique. Upon development, the plates were sprayed with a solution of ammonium ceric sulphate in 5M sulphuric acid and heated to 200°C for 5 min. Silica gel for column chromatography refers to Merck Kieselgel 60: 70-230 mesh for gravity columns, and 230-400 mesh for flash chromatography.

Commonly used solvents were purified as described below.

Tetrahydrofuran and Diethyl ether: Dried over sodium wire and distilled prior to use from sodium wire, using benzophenone as indicator.

Benzene, Toluene, and Xylene: Dried, distilled from, and stored over sodium wire.

Acetic anhydride and Isopropenyl acetate: Fractionally distilled and stored over Molecular Sieve (Type 4A)

Ethyl acetate: Washed with saturated aqueous sodium carbonate and brine, dried over sodium sulphate and distilled.

The phrase 'the residue upon work-up', or 'the standard work-up' refers to extraction of the reaction mixture with the solvent in parentheses (x3), washing of the combined organic phase with brine (x2), followed by drying through a cone of magnesium sulphate and removal of the solvent under reduced pressure.

Unless otherwise specified, all reactions were carried out in oven-dried glassware and under an atmosphere of dry nitrogen.

3-Methoxyestra-1,3,5(10),15-tetraen-17-one (31)

To a stirred solution of estrone (20 g, 73.9 mmol) in dry acetone (2000 ml) was added dimethyl sulphate (60 ml) and pulverised potassium carbonate (200 g). After 20 h at 20°C, aqueous ammonia (75 ml; 25 %) was added. The mixture was filtered, and water (200 ml) was added to the concentrated filtrate. The combined chloroform extracts (x3) were evaporated to a small volume and the product was precipitated with ethyl acetate to yield estrone 3-methyl ether (**27**) (20.1 g; 95.5 %), m.p. 115-117°C (lit.,⁶⁰ m.p. 115-116°C).

This product (15.0 g; 52.8 mmol) was dissolved in benzene (300 ml). Ethanediol (15 ml; 296 mmol) and toluene-*p*-sulphonic acid monohydrate (600 mg) were added, and the solution was refluxed (Dean-Stark). After 18 h, the mixture was poured into saturated aqueous sodium hydrogen carbonate (200 ml). The standard work-up (benzene) gave the 17-ketal (**28**) as a colourless crystalline residue (16.7 g; 96 %). A deoxygenated solution of this product and phenyltrimethylammonium tribromide (19.4 g) in dry tetrahydrofuran (150 ml) was stirred at 20°C for 30 min. Saturated aqueous sodium hydrogen carbonate (150 ml) was added, and the precipitate was filtered off and washed with water. The material was dried *in vacuo* to give the 16 α -bromo-17-ketal (**29**) (19.6 g; 95 %) as colourless crystals, m.p. 198-200°C (lit.,¹⁹ m.p. 198-200°C).

This bromoketal, (**29**) together with potassium *t*-butoxide (12.0 g) (freshly sublimed) was dissolved in dry xylene (550 ml) and refluxed for 16 h. Ice water (350 ml) was added. The residue upon work-up (ethyl acetate) was recrystallised from ethyl acetate-methanol to give the Δ^{15} -17-ketal (**30**) (13.9 g; 88 %), m.p. 125-127°C (lit.,¹⁹ m.p. 125-126°C).

A solution of this ketal (**30**) (2.5 g; 7.8 mmol) and toluene-*p*-sulphonic acid monohydrate (360 mg; 1.89 mmol) in acetone-water (6:1; 175 ml) was stirred at 20°C for 4 h. Standard work-up (ethyl acetate) gave the Δ^{15} -17-ketone (**31**) (2.11 g; 91 %), m.p. 179-180°C (from ethyl acetate-methanol) (lit.,¹⁹ m.p. 180-181°C); $[\alpha]_D^{25}$ -41° (c 1.0); ν_{\max} 1609 cm⁻¹ (CO); δ_H 1.11 (3H, s, 13 β -Me), 2.94 (2H, m, 6-H₂), 3.79

(3H, s, 3-OMe), 6.08 (1H, dd, J 6.0 and 3.2 Hz, 16-H), 6.67 (1H, d, J 2.6 Hz, 4-H), 6.74 (1H, dd, J 8.6 and 2.6 Hz, 2-H), 7.21 (1H, d, J 8.6 Hz, 1-H), and 7.63 (1H, dd, J 6.0 and 1.3 Hz, 15-H); δ_C 20.9 (C-18), 25.5 (C-11), 26.7 (C-7), 29.4 (C-8), 35.6 (C-12), 45.1 (C-6), 51.5 (C-13), 55.2 (3-OMe), 56.1 (C-14), 111.6 (C-2), 113.9 (C-4), 126.0 (C-1), 131.9 (C-16), 137.5 (C-5), 157.7 (C-3), 158.1 (C-15), and 212.9 (C-17) (Found: C, 81.2^s; H, 7.9 %; M^+ , 282. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.8^s %; M , 282).

3-Methoxy-15 β -methylestra-1,3,5(10)-trien-17-one (32)

(a) Methyllithium (26 ml; 1.4 M) was added to a stirred slurry of copper(I) iodide (3.43 g; 18.0 mmol) in dry diethyl ether (20 ml) at 0°C. To the resultant clear solution of lithium dimethylcuprate was added the Δ^{15} -17-ketone (31) (4.24 g; 15.0 mmol) in dry tetrahydrofuran (100 ml). The mixture was stirred at 0°C. After 15 min, saturated aqueous ammonium chloride was added. The residue upon work-up (ethyl acetate) (4.38 g) comprised two components (t.l.c.). Chromatography on silica gel (200 g) with ethyl acetate-hexane (1:4) as eluent gave the 15 β -methyl-17-ketone (32) (2.70 g; 60 %), m.p. 127-129°C (from acetone-methanol) (lit.,¹⁷ m.p. 122-124°C); $[\alpha]_D +74^\circ$ (c 1.0); ν_{max} 1725 cm^{-1} (CO); δ_H 1.07 (3H, s, 13 β -Me); 1.16 (3H, d, J 7.4 Hz, 15 β -Me), 2.91 (2H, m, 6-H₂), 3.79 (3H, s, 3-OMe), 6.69 (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); δ_C 17.0 (15-Me), 17.9 (C-18), 25.6 (C-15), 26.8 (C-11), 27.7 (C-7), 29.5 (C-8), 34.1 (C-16), 35.9 (C-12), 44.5 (C-6), 44.8 (C-9), 47.5 (C-13), 55.2 (3-OMe), 111.4 (C-2), 113.9 (C-4), 126.0 (C-1), 132.5 (C-10), 137.8 (C-5), 157.7 (C-3), and 221.3 (C-17) (Found: C, 80.7; H, 8.6 %; M^+ , 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8 %; M , 298), followed by the bisteroid, 3-methoxy-16 α -[3-methoxy-17-oxo-estra-1,3,5(10)-trien-15 β -yl]-15 β -methylestra-1,3,5(10)-trien-17-one (33) (1.36 g; 31 %) as an oil, $[\alpha]_D +131^\circ$ (c 1.0); ν_{max} 1727 cm^{-1} (CO); δ_H 1.05 and 1.11 (each 3H, s, 13 β - and 13¹ β -Me), 1.18 (3H, d, J 7.4 Hz, 15 β -Me), 2.91 (4H, m, 6- and 6¹-H), 3.81 (6H, s, 3- and 3¹-OMe), 6.69 (2H, d, J 2.7 Hz, 4- and 4¹-H), 6.73 (2H, dd, J 8.6 and 2.7 Hz, 2- and 2¹-H), and 7.21 (2H, d, J 8.6 Hz, 1- and 1¹-H); δ_C 17.2 (C-18 and -18¹), 25.2 and 25.5 (C-15 and

-15¹), 26.7 and 26.8 (C-11 and -11¹), 26.9 and 28.4 (C-7 and -7¹), 29.2 and 29.4 (C-8 and -8¹), 33.9 and 34.2 (C-12 and -12¹), 35.5 and 35.8 (C-16 and -16¹), 44.4 and 44.9 (C-6 and -6¹), 46.6 and 47.5 (C-13 and -13¹), 50.6 and 51.9 (C-14 and -14¹), 54.45 (C-15¹), 55.2 (3- and 3¹-OMe), 111.4 and 111.5 (C-2 and -2¹), 113.9 (C-4 and -4¹), 125.9 (C-1 and -1¹), 132.2 and 132.3 (C-10 and -10¹), 137.6 and 138.0 (C-5 and -5¹), 157.7 (C-3 and -3¹), 221.2, and 221.6 (C-17 and -17¹) (Found: C, 80.2; H, 8.4 %; M^+ , 580. $C_{39}H_{48}O_4$ requires C, 80.65; H, 8.3 %; M , 580)

(b) A solution of lithium dimethylcuprate (1.05 mmol) in dry diethyl ether (2 ml) was prepared as in (a). The Δ^{15} -17-ketone (31) (239 mg; 0.85 mmol) in dry tetrahydrofuran (10 ml) was slowly added over a period of 1 h. Stirring was continued for a further 10 min. The reaction was worked up as before.

Chromatography of the residue (220 mg) on silica gel (12 g) with ethyl acetate-hexane (1:4) as eluent gave the 15 β -methyl-17-ketone (32) (147 mg; 58 %), followed by the bisteroid (33) (58.0 mg; 24 %).

(c) Lithium dimethylcuprate (1.5 mmol) in dry diethyl ether (2 ml) was prepared as detailed in a foregoing experiment. This solution was diluted by adding dry tetrahydrofuran (40 ml). The Δ^{15} -17-ketone (31) (200 mg; 0.71 mmol) was added in further dry tetrahydrofuran (10 ml). After stirring at 0°C for 20 min, the reaction was worked up and the residue (206 mg) was chromatographed as before (15 g silica gel) to give the 15 β -methyl-17-ketone (32) (127 mg; 60 %), followed by the bisteroid (33) (70 mg; 34 %).

(d) Lithium dimethylcuprate (1.5 mmol in 2 ml diethyl ether) was prepared as before. The solution was cooled to -78°C, and the Δ^{15} -17-ketone (31) (200 mg; 0.71 mmol) in dry tetrahydrofuran (10 ml) was added. After 20 min, the reaction was worked up and chromatographed as before (278 mg crude onto 27 g silica gel) to obtain the 15 β -methyl-17-ketone (32) (204 mg; 72 %), followed by the bisteroid (33) (36 mg; 13 %).

(e) Following the usual way for lithium dimethylcuprate preparation (0.88 mmol in 1 ml dry diethyl ether) and cooling the solution to -78°C, the Δ^{15} -17-ketone (31)

(123 mg; 0.43 mmol) was added in dry tetrahydrofuran (5 ml) over a period of 1 h. After stirring for a further 5 min, the reaction was worked up (128 mg crude) and chromatographed (12 g silica gel) as previously to give the 15 β -methyl-17-ketone (32) (105 mg; 82 %), followed by the bisteroid (33) (36 mg; 13 %).

(f) Boron trifluoride-diethyl ether complex (0.1 ml; 0.8 mmol) was added to a solution of lithium dimethylcuprate (0.78 mmol) in dry diethyl ether (1 ml) at -78°C. After stirring for 5 min, the Δ^{15} -17-ketone (31) (101 mg; 0.36 mmol) in dry tetrahydrofuran (4 ml) was added. Low temperature stirring was maintained for 5 min. The residue upon work-up was chromatographed as previously to give only the 15 β -methyl-17-ketone (32) (97 mg; 90 %).

(g) Lithium dimethylcuprate (0.63 mmol) in dry diethyl ether (1 ml) was prepared as detailed previously. The reagent was cooled to -78°C, triethylamine (0.1 ml; 0.8 mmol) and trimethylchlorosilane (0.1 ml; 0.78 mmol) were added, followed by the Δ^{15} -17-ketone (31) (84 mg; 0.30 mmol) in dry tetrahydrofuran (4 ml). After 5 min, saturated aqueous ammonium chloride was added. The residue upon work-up (ethyl acetate) comprised a colourless oil (87 mg). A solution of this product in dry tetrahydrofuran (2 ml) was treated with 5M hydrochloric acid (0.5 ml) at 20°C for 1 h. Saturated aqueous sodium hydrogen carbonate (2 ml) was added, and the standard work-up (ethyl acetate) gave the 15 β -methyl 17-ketone (32) (65 mg; 92 %).

3-Methoxy-16 α -[3-methoxy-17-oxo-estra-1,3,5(10)-trien-15 β -yl]-15 β -methylestra-1,3,5(10)-trien-17-one (33)

n-Butyl lithium (1.0 ml; 1.6M) was added to a solution of diisopropylamine (0.5 ml; 3.3 mmol) in dry tetrahydrofuran (1 ml) at 0°C. The mixture was stirred for 5 min, before it was cooled to -78°C. To the resulting clear solution of lithium diisopropylamide was slowly added the 15 β -methyl-17-ketone (32) (100 mg; 0.33 mmol) in dry tetrahydrofuran (5 ml). Low temperature stirring was maintained for 1 h. The Δ^{15} -17-ketone (31) (116 mg; 0.41 mmol) in tetrahydrofuran (7 ml) was

added, and the mixture was warmed to 0°C. After a further hour of stirring, saturated aqueous ammonium chloride was added and the residue upon work-up (210 mg) was chromatographed on silica gel (20 g), eluting with ethyl acetate-hexane (1:9). The fractions in order of elution comprised unreacted Δ^{15} -17-ketone (31) (37 mg) and 15 β -methyl-17-ketone (32) (49 mg), followed by the bisteroid (33) (97 mg; 51 %).

16 α -Bromo-3-methoxy-15 β -methylestra-1,3,5(10)-trien-17-one (38)

The 15 β -methyl-17-ketone (32) (190 mg; 0.64 mmol) and copper(II) bromide (360 mg; 1.61 mmol) were dissolved in refluxing methanol-benzene (1:1; 20 ml). After 50 min, the warm reaction solution was filtered (celite pad) and the methanol was removed *in vacuo*. Water (20 ml) was added to the concentrated filtrate, and the standard work-up (chloroform) gave a yellow-brown crystalline product (222 mg). The crude material was chromatographed on silica gel (10 g) with toluene as eluent, to yield the 16 α -bromo-15 β -methyl-17-ketone (38) (198.3 mg; 82 %), m.p. 162-165°C (from chloroform-methanol); $[\alpha]_D + 71^\circ$ (c 1.0), ν_{\max} 1755 cm⁻¹ (CO); δ_H 1.11 (3H, s, 13 β -Me), 1.28 (3H, d, *J* 7.7 Hz, 15 β -Me), 2.75 (1H, d quint, *J* 4 x 7.7 and 1.8 Hz, 15 α -H), 2.95 (2H, m, 6-H₂), 3.79 (3H, s, 3-OMe), 4.37 (1H, d, *J* 1.8 Hz, 16 β -H), 6.67 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), and 7.20 (1H, d, *J* 8.5 Hz, 1-H); δ_C 16.0 (15-Me), 18.1 (C-18), 25.4 (C-11), 26.7 (C-7), 29.3 (C-8), 34.85 (C-12), 35.4 (C-16), 41.1 (C-6), 44.25 (C-9), 47.9 (C-13), 49.1 (C-14), 54.0 (C-15), 55.3 (3-OMe), 111.5 (C-2), 113.9 (C-4), 125.9 (C-1), 132.1 (C-10), 137.6 (C-5), 157.7 (C-3), and 221.3 (C-17) (Found: C, 63.3; H, 6.6 %; *M*⁺, 375/377 (1:1). C₂₀H₂₅BrO₂ requires C, 63.65; H, 6.7 %; *M*, 377)

3-Methoxy-15-methylestra-1,3,5(10),15-tetraen-17-one (39)

(a) Lithium diisopropylamide (1.06 mmol) in dry tetrahydrofuran (4 ml) was prepared as previously described. The solution was cooled to -78°C and the 15 β -methyl-17-ketone (32) (315 mg; 1.05 mmol) in dry tetrahydrofuran (5 ml) was

slowly added. Low temperature stirring was maintained for 45 min. Trimethylchlorosilane (1.4 ml; 11.0 mmol) was added and the mixture was allowed to warm to 20°C. After 30 min, t.l.c. indicated the absence of starting material. The flask was cooled to 0°C and saturated aqueous ammonium chloride was added. The residue upon work-up (ethyl acetate) (385 mg) was dissolved in acetonitrile (5 ml) and added to a deoxygenated solution of palladium(II) acetate (233 mg; 1.04 mmol) in further acetonitrile (4 ml). Stirring was maintained for 2 h at 60°C. The hot reaction mixture was filtered and concentrated to give a dark crystalline product (484 mg). Chromatography on silica gel (24 g), with ethyl acetate-toluene (1:4) as eluent gave 15 β -methyl-17-ketone (**32**) (62 mg; 20 %), followed by 3-methoxy-15-methylestra-1,3,5(10),15-tetraen-17-one (**39**) (216 mg; 70 %), m.p. 156-158°C (from ethyl acetate-methanol); $[\alpha]_D -17^\circ$ (c 1.0); ν_{\max} 1688 cm⁻¹ (CO); δ_H 1.11 (3H, s, 13 β -Me), 2.25 (3H, s, 15-Me), 2.94 (2H, m, 6-H₂), 3.79 (3H, s, 3-OMe), 5.77br (1H, s, 16-H), 6.66 (1H, d, *J* 2.5 Hz, 4-H), 6.75 (1H, dd, *J* 8.6 and 2.5 Hz, 2-H), and 7.23 (1H, d, *J* 8.6 Hz, 1-H); δ_C 20.9 (C-18), 21.5 (15-Me), 25.6 (C-11), 27.7 (C-7), 29.2 (C-9), 29.3 (C-8), 36.8 (C-12), 45.2 (C-6), 52.6 (C-13), 55.2 (3-OMe), 57.3 (C-14), 111.5 (C-2), 113.6 (C-4), 126.1 (C-1), 128.7 (C-16), 132.0 (C-10), 137.3 (C-5), 157.7 (C-3), 175.2 (C-15), and 212.1 (C-17) (Found: C, 81.3; H, 8.1^s %; *M*⁺, 296. C₂₀H₂₄O₂ requires C, 81.0, H, 8.2 %; *M*, 296).

(b) Lithium dimethylcuprate (0.79 mmol) in dry diethyl ether (1 ml) was prepared as described previously. The reagent was cooled to -78°C, triethylamine (0.1 ml; 0.8 mmol) and trimethylchlorosilane (0.1 ml; 0.78 mmol) were added, followed by the Δ^{15} -17-ketone (**31**) (106 mg; 0.37 mmol) in dry tetrahydrofuran (4 ml). After 5 min, saturated aqueous ammonium chloride was added. The residue upon work-up (ethyl acetate) comprised a colourless oil (109 mg). This product was treated under similar conditions of dehydrosilylation as detailed above [66 mg palladium(II) acetate in 5 ml acetonitrile], to yield the 15-methyl Δ^{15} -17-ketone (**39**) (80 mg; 73 %).

(c) Lithium dimethylcuprate (1.09 mmol) in dry diethyl ether (2 ml) was prepared as before and cooled to -78°C . To this solution was added trimethylchlorosilane (0.12 ml; 0.99 mmol) and triethylamine (0.14 ml; 1.0 mmol). After stirring for 5 min, the Δ^{15} -17-ketone (**31**) (114 mg; 0.51 mmol) in dry tetrahydrofuran (2 ml) was added. Stirring was continued at -78°C for 5 min. Residual reagent was quenched with saturated aqueous ammonium chloride. The standard work-up (ethyl acetate) gave a clear oily residue (150 mg). The latter was dissolved in dry tetrahydrofuran (2 ml). After cooling to -78°C , boron trifluoride-diethyl ether complex (0.1 ml; 0.79 mmol) was added, followed by phenylselenenyl chloride (191 mg; 1.0 mmol) in dry tetrahydrofuran (1 ml). Stirring was continued, with slow warming to 0°C . The mixture was poured into ice water (5 ml) and the residue upon work-up (chloroform) (181 mg) was chromatographed on silica gel (18 g), eluting with ethyl acetate-toluene (1:9) to give the assumed 15β -methyl- 16α -phenylselenenyl-17-ketone (**41**) as a clear oil (145 mg; 80 %) (Found: M^+ , 453. $\text{C}_{26}\text{H}_{30}\text{O}_2\text{Se}$ requires M , 453.5), followed by some 15β -methyl-17-ketone (**32**) (12 mg; 10 %).

The selenide (**41**) (145 mg; 0.32 mmol) was dissolved in dichloromethane (3 ml). Pyridine (1 ml) was added, and the solution was cooled to 0°C . Hydrogen peroxide (30 %; 0.5 ml) was slowly added. The solution was stirred for 1.5 h, with slow warming to 20°C . Saturated aqueous sodium hydrogen carbonate was added, and the residue upon work-up (chloroform) (87 mg) was chromatographed on silica gel (8 g), eluting with ethyl acetate-toluene (1:9). The first product to elute was the expected 15-methyl- Δ^{15} -17-ketone (**39**) (38 mg; 40 %), followed by 3-methoxy-15-methyl-17 α -oxa-17 α -homoestra-1,3,5(10),15-tetraen-17-one (**42**) (45 mg; 45 %), m.p. $185\text{--}187^{\circ}\text{C}$ (from ethyl acetate-methanol); $[\alpha]_{\text{D}} -14^{\circ}$ (c 1.0); ν_{max} 1705 cm^{-1} (CO); λ_{max} 245 nm (log ϵ 4.45); δ_{H} 1.31 (3H, s, 13β -Me), 2.10 (3H, t, J 1.5 Hz, 15-Me), 2.87 (2H, m, 6- H_2), 3.79 (3H, s, 3-OMe), 5.88 (1H, q, J 1.5 Hz, 16-H), 6.68 (1H, d, J 2.7 Hz, 4-H), 6.75 (1H, dd, J 8.4 and 2.7 Hz, 2-H), and 7.17 (1H, d, J 8.4 Hz, 1-H); δ_{C} 18.8 (C-18), 23.0 (15-Me), 25.4 (C-11), 29.2 (C-7), 30.3 (C-8), 38.3 (C-12), 38.5 (C-6), 42.9 (C-9), 50.3 (C-13), 55.2 (3-OMe), 111.4 (C-2), 113.4 (C-4), 119.4 (C-15),

125.2 (C-1), 132.2 (C-10), 137.9 (C-5), 158.0 (C-3), 158.8 (C-16), and 164.1 (C-17) (Found: C, 76.7; H, 7.5 %; M^+ , 312. $C_{20}H_{24}O_3$ requires C, 76.9; H, 7.7 %; M , 312).

3-Methoxy-17 α -oxa-17 α -homoestra-1,3,5(10),15-tetraen-17-one (44)

Lithium diisopropylamide (5.8 mmol) in dry tetrahydrofuran (2 ml) was prepared as detailed previously. To this solution at -78°C was added estrone-3-methyl ether (**27**) (166 mg; 0.58 mmol) in further dry tetrahydrofuran (3 ml). Low temperature stirring was maintained for 45 min, before trimethylchlorosilane (0.4 ml; 3.2 mmol) was added. The solution was allowed to warm to 0°C . After 30 min, saturated aqueous ammonium chloride was added. The residue upon work-up (ethyl acetate) comprised a clear oil (201 mg; 97 %).

To a solution of this product (201 mg; 0.56 mmol) in dry tetrahydrofuran (2 ml) at -78°C were sequentially added boron trifluoride-diethyl ether complex (0.1 ml; 0.8 mmol) and phenylselenenyl chloride (181 mg; 0.9 mmol) in dry tetrahydrofuran (1 ml). The mixture was allowed to warm to 25°C . After 20 min, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate (10 ml) at 0°C . The residue upon work-up (ethyl acetate) (246 mg) was filtered through silica gel (2.5 g), eluting with hexane followed by ethyl acetate, to obtain the 16-phenylselenenyl-17-ketone (**43**) as a clear glass (197 mg; 80 %).

This selenide (**43**) (197 mg; 0.45 mmol) was dissolved in methanol-dichloromethane (1:5) (40 ml) and cooled to 0°C . Hydrogen peroxide (30 %; 0.1 ml) was slowly added. The mixture was allowed to warm to 25°C and stirred for 2 h. Saturated aqueous sodium hydrogencarbonate was added. Work-up (ethyl acetate) gave the lactone (**44**) as an only product (110 mg; 82 %), m.p. $199-201^\circ\text{C}$ (from acetone-methanol) (lit.,³⁹ m.p. $199-201^\circ\text{C}$); $[\alpha]_D -10^\circ$ (c 0.9); ν_{\max} 1710 cm^{-1} (CO); λ_{\max} 243 nm (log ϵ 4.33); δ_H 1.37 (3H, s, $13\beta\text{-Me}$), 2.91 (2H, m, 6- H_2), 3.77 (3H, s, 3-OMe), 6.08 (1H, dd, J 9.8 and 2.3 Hz, 16-H), 6.65 (1H, d, J 2.7 Hz, 4-H), 6.73 (1H, dd, J 8.5 and 2.7 Hz, 2-H), 6.93 (1H, dd, J 9.8 and 2.1 Hz, 15-H), and 7.18 (1H, d, J 8.5 Hz, 1-H); δ_C 18.5 (C-18), 26.1 (C-11), 27.0 (C-7), 29.5 (C-8), 38.1 (C-12), 38.6

(C-6), 43.3 (C-9), 47.3 (C-13), 55.2 (3-OMe), 83.4 (C-14), 111.8 (C-2), 113.7 (C-4), 121.9 (C-15), 126.1 (C-1), 130.9 (C-10), 137.3 (C-5), 145.0 (C-16), 157.9 (C-3), and 163.8 (C-17) (Found: C, 76.6; H, 7.5 %; M^+ , 298. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4 %; M , 298).

3-Methoxy-15-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate (45)

(a) A deoxygenated solution of the 16α -bromo- 15β -methyl-17-ketone (**38**) (490 mg; 1.30 mmol), lithium bromide (800 mg; 9.22 mmol), and lithium carbonate (690 mg; 9.35 mmol) in dry *N,N*-dimethylformamide (15 ml) was refluxed for 22 h. The warm solution was poured into a mixture of water-glacial acetic acid (1:1; 14 ml). The residue upon work-up (ethyl acetate) (370 mg) was chromatographed on silica gel (35 g), using ethyl acetate-toluene (1:9) as eluent, to give the 15β -methyl-17-ketone (**32**) (90 mg; 23 %), 15 -methyl- Δ^{15} -17-ketone (**39**) (50 mg; 13 %), ν_{\max} 1688 cm^{-1} (CO), and 15 -methyl- Δ^{14} -17-ketone (**40**) (160 mg; 41.5 %), ν_{\max} 1741 cm^{-1} (CO). The combined enones (**39**) and (**40**) (210 mg; 0.71 mmol), together with toluene-*p*-sulphonic acid monohydrate (63 mg; 0.33 mmol), were refluxed in isopropenyl acetate (15 ml) and acetic anhydride (5 ml) for 5 h. The cooled solution was poured into ice water (20 ml) and the liberated acetic acid was neutralised by additions of solid sodium hydrogen carbonate. The residue upon work-up (ethyl acetate) (220 mg) was chromatographed on silica gel (20 g) with ethyl acetate-hexane (1:9) as eluent to give *3-methoxy-15-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate (45)* (101 mg; 42 %), m.p. 128-130.5°C (from acetone-methanol); $[\alpha]_D +243^\circ$ (c 0.9); ν_{\max} 1729 (CO) and 1368 cm^{-1} (OAc); δ_H 1.06 (3H, s, 13β -Me), 2.03 (3H, s, 15-Me), 2.21 (3H, s, 17-OAc), 2.91 (2H, m, 6-H₂), 3.79 (3H, s, 3-OMe), 5.95 (1H, s, 16-H), 6.65 (1H, d, J 2.7 Hz, 4-H), 6.73 (1H, d, J 8.7 and 2.7 Hz, 2-H), and 7.20 (1H, d, J 8.7 Hz, 1-H); δ_C 14.5 (17-OCOCH₃), 17.9 (C-18), 21.2 (15-Me), 27.2 (C-11), 27.9 (C-7), 30.9 (C-8), 35.3 (C-12), 40.8 (C-6), 46.8 (C-9), 52.0 (C-13), 55.2 (3-OMe), 111.9 (C-2), 113.6 (C-4), 116.5 (C-15), 126.1 (C-14), 127.7 (C-1), 131.9 (C-10), 137.7

(C-5), 139.9 (C-16), 157.7 (C-3), 161.4 (C-17), and 168.1 (17-OCOCH₃) (Found: C, 77.8; H, 7.5%; *M*⁺, 338. C₂₂H₂₆O₃ requires C, 78.1; H, 7.8%; *M*, 338.5).

(b) To a deoxygenated solution of the 15-methyl- Δ^{15} -17-ketone (**39**) (112 mg; 0.38 mmol) in isopropenyl acetate (2.5 ml) and acetic anhydride (1 ml) was added toluene-*p*-sulphonic acid monohydrate (31 mg, 0.16 mmol). The mixture was refluxed for 2 h. The work-up described above yielded 130 mg of crude product, comprising one constituent only. Chromatography on silica gel (13 g), eluting with ethyl acetate-toluene (1:4) gave the 15-methyl dienyl acetate (**45**) (100 mg; 78 %).

Attempted cycloaddition between the 15-methyl dienyl acetate (45) and phenyl vinyl sulphone

(a) The 15-methyl dienyl acetate (**45**) (115 mg; 0.39 mmol) and phenyl vinyl sulphone (72 mg; 0.43 mmol) were dissolved in dry xylene (2 ml) in a pressure tube. The latter was purged with dry nitrogen and heated to 145°C for 96 h. No reaction was observed.

(b) The above reaction was repeated in toluene, also without success.

(c) Repeating the above reaction in benzene, at both 120°C and at 60°C, still failed to produce any cycloaddition.

17 β -Acetoxy-3-methoxy-17²-methyl-14,17 α -ethenoestra-1,3,5(10)-triene-16 α -carbaldehyde (46)

The 15-methyl dienyl acetate (**45**) (150 mg; 0.44 mmol) was dissolved in dry toluene (3 ml). To this solution was added acrolein (0.1 ml; 1.5 mmol). The mixture was cooled to 0°C and boron trifluoride-diethyl ether complex (0.1 ml; 0.8 mmol) was added. Stirring was commenced for 16 h, with slow warming to 20°C. The solution was poured into ice water (5 ml) and the residue upon work-up (ethyl acetate) (150 mg) was chromatographed on silica gel (15 g), eluting with ethyl acetate-hexane (1:4), to give the *cycloadduct* (**46**) (130 mg; 75 %), m.p. 170-173°C (from ethyl acetate-methanol); [α]_D +125° (c 1.0); ν_{\max} 1369 (OAc), 1709 (CO aldehyde), and 1729 cm⁻¹ (CO acetate); δ_{H} 0.96 (3H, s, 13 β -Me), 1.89 (3H, d, *J* 1.5 Hz, 17²-Me),

2.11 (3H, s, 17-OAc), 2.82 (2H, m, 6-H₂), 3.09 (1H, m, 16 β -H), 3.78 (3H, s, 3-OMe), 6.04 (1H, s, 17¹-H), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.74 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H), 7.22 (1H, d, *J* 8.5 Hz, 1-H), and 9.46 (1H, d, *J* 4.3 Hz, 16¹-H); δ_C 14.2 (17-OCOCH₃), 16.7 (C-18), 21.3 (17²-Me), 24.1 (C-11), 27.9 (C-7), 31.2 (C-8), 32.6 (C-12), 39.6 (C-16), 40.9 (C-6), 46.8 (C-9), 55.2 (3-OMe), 56.2 (C-13), 57.3 (C-15), 60.2 (C-17¹), 93.9 (C-17²), 112.0 (C-2), 113.7 (C-4), 126.4 (C-14), 127.6 (C-1), 132.6 (C-10), 138.1 (C-5), 145.5 (C-17), 157.5 (C-3), 171.1 (17-COCH₃), and 202.1 (16-CHO) (Found: C, 75.8; H, 7.7 %; *M*⁺, 394. C₂₅H₃₀O₄ requires C, 76.1; H, 7.7 %; *M*, 394.5).

3-Methoxy-17²-methyl-14,17 α -ethenoestra-1,3,5(10)-trien-17 β -yl acetate (47)

The cycloadduct (46) (50 mg; 0.13 mmol) and *tris*(triphenylphosphine)rhodium(I) chloride (130 mg; 0.14 mmol) were dissolved in refluxing toluene (2 ml). After 60 h at 112°C, the solution was filtered and evaporated. The residue (162 mg) was chromatographed on silica gel (20 g), eluting with ethyl acetate-toluene (1:19) to give *3-methoxy-17²-methyl-14,17 α -ethenoestra-1,3,5(10)-trien-17 β -yl-acetate (47)* (40 mg; 84 %), m.p. 117-121°C (from ethyl acetate-methanol); $[\alpha]_D +92^\circ$ (c 1.0); ν_{\max} 1368 (OAc), 1729 cm⁻¹ (CO acetate); δ_H 0.88 (3H, s, 13 β -Me), 1.80 (3H, d, *J* 1.3 Hz, 17²-Me), 2.08 (3H, s, 17-OAc), 3.77 (3H, s, 3-OMe), 5.94br (1H, s, 17¹-H), 6.63 (1H, d, *J* 2.9 Hz, 4-H), 6.73 (1H, dd, *J* 8.3 and 2.9 Hz, 2-H), and 7.23 (1H, d, *J* 8.3 Hz, 1-H); δ_C 15.9 (17-OCOCH₃), 16.5 (C-18), 21.4 (17²-Me), 23.7 (C-16), 26.3 (C-11), 28.6 (C-7), 29.5 (C-12), 30.2 (C-6), 40.4 (C-8), 46.7 (C-9), 55.2 (3-OMe), 57.2 (C-15), 58.4 (C-13), 62.1 (C-14), 96.2 (C-17), 111.9 (C-2), 113.7 (C-16), 126.5 (C-17¹), 127.3 (C-1), 132.1 (C-10), 138.0 (C-5), 145.7 (C-17²), 156.2 (C-3), and 170.7 (17-OCOCH₃) (Found: C, 78.3; H, 8.3 %; *M*⁺, 366. C₂₄H₃₀O₃ requires C, 78.6^s; H, 8.2^s %; *M*, 366.5).

3-Methoxy-15,15-dimethylestra-1,3,5(10)-trien-17-one (48)

To a solution of lithium dimethylcuprate (1.1 mmol) in dry diethyl ether (2 ml) (prepared as previously described) at -78°C was added boron trifluoride-diethyl

ether complex (0.1 ml; 0.80 mmol), followed by the 15-methyl- Δ^{15} -17-ketone (**39**) (163 mg; 0.55 mmol) in dry tetrahydrofuran (2 ml). After 30 min, saturated aqueous ammonium chloride was added. The standard work-up (ethyl acetate) gave a crystalline residue, which upon chromatography on silica gel (5 g), eluting with ethyl acetate-toluene (1:19) gave the 15,15-dimethylketone (**48**) (146 mg; 70 %), m.p. 145-148°C (from ethyl acetate-methanol); $[\alpha]_D + 75^\circ$ (*c* 1.0); ν_{\max} 1727 cm^{-1} (CO); δ_H 1.10 (3H, s, 13 β -Me), 1.28 and 1.29 (each 3H, s, 15 α - and 15 β -Me), 1.84 (1H, d, *J* 10.9 Hz, 14 α -H), 2.09 and 2.61 (each 1H, d, *J* 19.4 Hz, 16 α - and 16 β -H), 2.93 (2H, m, 6-H₂), 3.78 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C 17.8 (C-18), 24.5 (15-Me), 26.0 (C-11), 28.2 (C-7), 29.8 (C-6), 34.2 (C-12), 34.6 (15-Me), 35.5 (C-15), 37.5 (C-8), 44.9 (C-9), 50.2 (C-13), 53.6 (C-16), 55.2 (3-OMe), 58.4 (C-14), 111.6 (C-2), 113.6 (C-4), 126.4 (C-1), 132.2 (C-10), 137.4 (C-5), 157.6 (C-3), and 221.4 (C-17) (Found: C, 80.5; H, 8.8 %; *M*⁺, 312. C₂₁H₂₈O₂ requires C, 80.7; H, 9.0 %; *M*, 312).

3-Methoxy-15,15-dimethylestra-1,3,5(10)-trien-17 β -ol (**49**)

Lithium aluminium hydride (30 mg; 0.79 mmol) was added to a solution of the dimethyl ketone (**48**) (50 mg; 0.16 mmol) in dry tetrahydrofuran (2 ml) at 0°C. The mixture was stirred at 25°C for 20 min. Residual reagent was destroyed with ethyl acetate at 0°C. Upon work-up (chloroform), the residue was recrystallised to give the 15,15-dimethyl 17 β -alcohol (**49**) (43 mg; 85 %), m.p. 87-91°C (from chloroform-hexane), $[\alpha]_D + 75^\circ$ (*c* 1.1), ν_{\max} 3606 cm^{-1} (OH); δ_H 0.92 (3H, s, 13 β -Me), 1.06 (1H, d, *J* 11.2 Hz, 14 α -H), 1.11 and 1.14 (each 3H, s, 15 α - and 15 β -Me), 1.61 (1H, dd, *J* 13.0 and 10.2 Hz, 16 β -H), 1.90 (1H, dd, *J* 13.0 and 7.9 Hz, 16 α -H), 2.86 (2H, m, 6-H₂), 3.71 (1H, dd, *J* 10.2 and 7.9 Hz, 17 α -H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C 13.5 (C-18), 25.6 (15-Me), 26.1 (C-11), 28.5 (C-7), 29.9 (C-6), 35.0 (C-12), 36.2 (C-15), 37.1 (C-8), 38.8 (15-Me), 44.9 (C-9), 45.6 (C-13), 50.1 (C-16), 55.2 (3-OMe), 58.1 (C-14), 79.8 (C-17), 111.4 (C-2), 113.6 (C-4), 126.3 (C-1), 132.9 (C-10),

137.7 (C-5), and 157.5 (C-3) (Found: C, 80.0; H, 9.5 %; M^+ , 314. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6 %; M , 314).

3-Methoxy-15 β -methylestra-1,3,5(10)-trien-17 β -ol (50)

To a solution of the 15 β -methyl 17-ketone (32) (52 mg; 0.17 mmol) in dry tetrahydrofuran (2 ml) at 0°C was added lithium aluminium hydride (67 mg; 1.7 mmol). Stirring was maintained at 25°C for 20 min. Residual hydride was destroyed with ethyl acetate at 0°C. The residue upon work-up (chloroform) was recrystallised to give the 15 β -methyl-17 β -alcohol (50) (45 mg; 88%), m.p. 111-113°C (from ethyl acetate-hexane); $[\alpha]_D +5^\circ$ (c 1.0); ν_{max} 3607 cm^{-1} (OH); δ_H 0.91 (3H, s, 13 β -Me), 1.02 (3H, d, J 7.4 Hz, 15 β -Me), 2.88 (2H, m, 6-H₂), 3.68 (1H, dd, J 9.8 and 8.0 Hz, 17 α -H), 3.77 (3H, s, 3-OMe), 6.64 (1H, d, J 2.7 Hz, 4-H), 6.71 (1H, dd, J 8.4 and 2.7 Hz, 2-H), and 7.20 (1H, d, J 8.4 Hz, 1-H); δ_C 14.4 (15-Me), 18.2 (C-18), 25.7 (C-11), 27.7 (C-7), 29.1 (C-12), 29.6 (C-15), 35.9 (C-8), 38.8 (C-14), 40.8 (C-6), 43.3 (C-13), 44.5 (C-9), 51.6 (C-16), 55.2 (3-OMe), 81.9 (C-17), 111.3 (C-2), 113.8 (C-4), 125.9 (C-1), 133.2 (C-10), 138.1 (C-5), and 157.5 (C-3) (Found: C, 79.9; H, 9.3%; M^+ 300. $C_{20}H_{28}O_2$ requires C, 80.0; H, 9.4%; M 300).

3-Methoxy-15-methyl-14 β -estra-1,3,5(10),15-tetraen-17-one (51)

The Δ^{15} -17-ketone (39) (178 mg; 0.6 mmol) and toluene-*p*-sulphonic monohydrate (126 mg; 0.6 mmol) were refluxed in dry benzene (12 ml) for 30 min. Water (10 ml) was added and the residue upon workup (ethyl acetate) comprised 3-methoxy-15-methyl-14 β -estra-1,3,5(10),15-tetraen-17-one (51)⁴⁹ (170 mg; 96 %), as an oil, $[\alpha]_D +24^\circ$ (c 1.0); ν_{max} 1690 cm^{-1} (CO); δ_H 1.12 (3H, s, 13 β -Me), 2.17 (3H, s, 15-Me), 2.72 (1H, d, J 5.1 Hz, 14 β -H), 2.81 (2H, m, 6-H₂), 3.71 (3H, s, 3-OMe), 5.98 (1H, s, 16-H), 6.58 (1H, d, J 2.6 Hz, 4-H), 6.72 (1H, dd, J 8.6 and 2.6 Hz, 2-H), and 7.05 (1H, d, J 8.6 Hz, 1-H); δ_C 20.9 (C-18), 23.9 (15-Me), 28.4 (C-11), 28.8 (C-7), 30.5 (C-9), 31.6 (C-8), 33.8 (C-12), 38.9 (C-6), 50.3 (C-13), 55.2 (3-OMe), 57.9 (C-14), 112.4 (C-2), 113.2 (C-4), 128.6 (C-1), 131.1 (C-16), 133.4 (C-10), 137.3 (C-5), 157.3 (C-3),

177.1 (C-15), and 213.7 (C-17) (Found: C, 80.9; H, 8.0 %; M^+ , 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2 %; M , 296).

Attempted synthesis of 17 β -(2'-hydroxyethoxy)-16 α -phenylsulphonyl-14,17 α -ethenoestra-1,3,5(10)-triene (52)

A mixture of the Δ^{15} -17-ketal (**30**) (103 mg; 0.32 mmol) and phenyl vinyl sulphone (60 mg; 0.36 mmol) was heated in acetonitrile (1.5 ml) to 60°C for 96 h. The residue obtained upon evaporation of the solvent (160 mg) was chromatographed on silica gel (15 g) with ethyl acetate-hexane (1:9) as eluent, to obtain a product identified as 17,17-ethylenedioxy-3-methoxyestra-1,3,5(10),14-tetraene (**53**) (98 mg; 95 %), m.p. 115-118°C (from ethyl acetate-methanol) (lit.,⁶¹ m.p. 121-122°C); $[\alpha]_D +89^\circ$ (c 1.0); δ_H 1.10 (3H, s, 13 β -Me), 1.90 (2H, m, 6-H₂), 3.33 (3H, s, 3-OMe), 3.95 (4H, m, 17-ketal), 5.32br (1H, s, 15-H), 6.64 (1H, d, J 2.8 Hz, 4-H), 6.73 (1H, dd, J 8.4 and 2.8 Hz, 2-H), and 7.25 (1H, d, J 8.4 Hz, 1-H); δ_C 19.4 (C-18), 24.9 (C-11), 27.2 (C-7), 29.6 (C-8), 29.8 (C-9), 30.7 (C-12), 39.0 (C-6), 41.3 (C-16), 43.1 (C-13), 55.1 (3-OMe), 64.3 and 64.9 (17-ketal), 111.7 (C-2), 113.7 (C-4), 114.4 (C-17), 126.8 (C-1), 132.1 (C-15), 132.6 (C-10), 136.1 (C-14), 137.9 (C-5), and 151.4 (C-3) (Found: C, 77.5; H, 7.9%; M^+ , 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; M , 326)

17,17-Ethylenedioxy-3-methoxyestra-1,3,5(10),14-tetraene (53)

The Δ^{15} -17-ketal (**30**) (576 mg; 1.77 mmol) and toluene-*p*-sulphonic acid monohydrate (27 mg; 0.14 mmol) were dissolved in dry benzene (30 ml). After heating to reflux for 20 min, the solution was cooled and poured into water (20 ml). The residue upon work-up (ethyl acetate) (570 mg) was chromatographed on silica gel (57 g), eluting with ethyl acetate-toluene (1:9) to give the Δ^{14} -17-ketal (**53**) (510 mg; 88 %), followed by some enone (**31**) (25 mg; 5%).

3-Methoxyestra-1,3,5(10),14-tetraen-17-one (54)

The Δ^{14} -17-ketal (**53**) (450 mg; 1.38 mmol) was dissolved in dry tetrahydrofuran (22 ml). After cooling to 0°C, trifluoroacetic acid (1 ml) was slowly added. Low temperature stirring was maintained for 30 min, after which the solution was poured into cold saturated aqueous sodium hydrogencarbonate (5 ml). The residue upon work-up (chloroform) (170 mg) was chromatographed on silica gel (17g), eluting with ethyl acetate-toluene (1:24) to yield the Δ^{14} -17-ketone (**54**) (350 mg; 89%), m.p. 100-102°C (ethyl acetate-methanol) (lit.,¹⁹ m.p. 103-104°C); $[\alpha]_D +271^\circ$ (c 1.05); ν_{\max} 1735 cm^{-1} (CO); δ_H 1.15 (3H, s, 13 β -Me), 2.93 (2H, m, 6-H₂), 3.77 (3H, s, 3-OMe), 5.59br (1H, s, 15-H), 6.65 (1H, d, *J* 2.7 Hz, 4-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); δ_C 20.0 (C-18), 24.8 (C-11), 26.5 (C-7), 29.6 (C-8), 33.2 (C-12), 38.9 (C-6), 41.5 (C-9), 44.6 (C-13), 51.0 (C-16), 55.1 (3-OMe), 111.7 (C-2), 113.1 (C-4), 113.9 (C-14), 126.5 (C-1), 131.4 (C-15), 137.6 (C-5), 152.4 (C-3), 157.7 (C-10), and 212.5 (C-17) (Found C, 80.5; H, 7.9 %; *M*⁺, 282. C₁₉H₂₂O₂ requires C, 80.8; H, 7.8^s %; *M*, 282).

Attempted 'one-pot' cycloaddition to 3-methoxy-16 α -phenylsulphonyl-14,17 α -ethnoestra-1,3,5(10)-trien-17 β -yl acetate (2)

A solution of the Δ^{15} -17-ketone (**31**) (62 mg; 0.22 mmol), phenyl vinyl sulphone (78 mg; 0.46 mmol), and toluene-*p*-sulphonic acid monohydrate (16 mg; 0.08 mmol) in acetic anhydride-isopropenyl acetate (1:1; 2 ml) was heated to 100°C for 96 h in a sealed tube. The cooled mixture was poured into ice water and the liberated acetic acid was neutralised by addition of solid sodium hydrogen carbonate. The residue upon work-up (ethyl acetate) (60 mg) was chromatographed on silica gel (6 g) with ethyl acetate-hexane (1:9) as eluent to give the 14,16-dienyl 17-acetate (**1**) (55 mg; 77 %); m.p. 123-125°C (lit.,⁶² m.p. 123-125°C); δ_H 1.09 (3H, s, 13 β -Me), 2.25 (3H, s, 17-OAc), 2.91 (2H, m, 6-H₂), 3.79 (3H, s, 3-OMe), 5.89 and 6.17 (each 1H, d, *J* 2.5 Hz, 15- and 16-H), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.75 (1H, dd, *J* 8.8 and 2.7 Hz, 2-H), and 7.24 (1H, d, *J* 8.8 Hz, 1-H).

Synthesis of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (1) under mild conditions

A solution of the Δ^{14} -17-ketone (**54**) (107 mg; 0.38 mmol) and toluene-*p*-sulphonic acid monohydrate (20 mg; 0.11 mmol) in acetic anhydride-isopropenyl acetate (1:1; 4 ml) was stirred at 20°C for 1 h. Saturated aqueous sodium hydrogen carbonate (5 ml) was added, and the liberated acetic acid was neutralised by addition of solid sodium hydrogen carbonate. The residue upon work-up (ethyl acetate) (107 mg) was chromatographed on silica gel (10 g) with ethyl acetate-hexane (1:9) as eluent, to give the 14,16-dienyl-17-acetate (**1**) (99 mg; 80 %).

16 ξ -Acetoxy-3-methoxyestra-1,3,5(10),14-tetraen-17-one (55)

A solution of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**1**) (56 mg; 0.17 mmol) in dry toluene (1 ml) was added to lead tetraacetate (85 %) (1.0 g; 1.92 mmol) (dried from acetic acid by azeotropic distillation with benzene) in toluene (6 ml). The mixture was cooled to 0°C and boron trifluoride-diethyl ether complex (0.05 ml; 0.4 mmol) was added. After stirring for 1 h with slow warming to 20°C, saturated aqueous sodium hydrogen carbonate (10 ml) was added and the precipitated lead oxide was filtered. The residue upon work-up (ethyl acetate) (80 mg) was chromatographed on silica gel (8 g), with ethyl acetate-toluene (1:19) as eluent to give the 16 ξ -acetoxy 17-ketone (**55**) (51 mg; 88 %), m.p. 112-114°C (from ethyl acetate-methanol); $[\alpha]_D^{25} +30^\circ$ (*c* 0.7); ν_{\max} 1738, 1758 cm^{-1} (CO); δ_H 1.26 (3H, s, 13 β -Me), 2.11 (3H, s, 16-OAc), 2.96 (2H, m, 6H₂), 3.78 (3H, s, 3-OMe), 5.50 (1H, d, *J* 2.2 Hz, 16 ξ -H), 5.80 (1H, d, *J* 2.2 Hz, 15-H), 6.66 (1H, d, *J* 2.6 Hz, 4-H), 6.74 (1H, dd, *J* 8.7 and 2.6 Hz, 2-H), and 7.19 (1H, d, *J* 8.7 Hz, 1-H); δ_C 20.2 (16-OCOCH₃), 20.8 (C-18), 24.6 (C-11), 26.3 (C-7), 29.5 (C-8), 34.2 (C-12), 39.0 (C-6), 44.9 (C-16), 49.5 (C-13), 55.2 (3-OMe), 111.9 (C-2), 113.9 (C-4), 114.2 (C-14), 115.3 (C-9), 126.5 (C-1), 130.9 (C-15), 137.4 (C-5), 157.8 (C-3), 159.4 (C-10), 170.5 (17-OCOCH₃), and 213.7 (C-17) (Found: C, 74.3; H, 7.0 %; *M*⁺, 340. C₂₁H₂₄O₄ requires C, 74.1; H, 7.1 %; *M*, 340).

Attempted synthesis of 3 β -acetoxyandrosta-5(6),14,16-triene-16,17-diol diacetate (58)

A solution of 3 β ,16 β -diacetoxyandrosta-5(6),14-dien-17-one (57)⁵⁵ (50 mg; 0.13 mmol) and toluene-*p*-sulphonic acid monohydrate (15 mg; 0.08 mmol) in acetic anhydride-isopropenyl acetate (1:1; 2 ml) was heated to 110°C for 4 h. No product formation was detected (t.l.c.).

15 β -Benzyloxy-3-methoxyestra-1,3,5(10)-trien-17-one (60)

Sodium hydride (400 mg; 16.7 mmol) (50%) was added to benzyl alcohol (8 ml; 77.3 mmol) in small portions at 20°C. The resulting alcoholate was slowly added to a solution of the Δ^{15} -17-ketone (31) (1.0 g; 3.54 mmol) in benzyl alcohol (25 ml) at -10°C. The mixture was stirred for 16 h, with slow warming. Ice water (20 ml) was added and the residue upon work-up (ethyl acetate) was distilled under high vacuum (60°C; 2 mm Hg) to remove residual benzyl alcohol. The crystalline product hence obtained (1.2 g) was chromatographed on silica gel (120 g), eluting with ethyl acetate-toluene (1:49), to give mainly the 15 β -benzyl ether (60) (995 mg; 72 %), m.p. 91-94°C (from ethyl acetate-methanol) (lit.,¹⁴ m.p. 94-98°C); $[\alpha]_D +71^\circ$ (c 1.0); ν_{\max} 1732 cm⁻¹ (CO); δ_H 1.22 (3H, s, 13 β -Me), 2.91 (2H, m, 6-H₂), 3.74 (3H, s, 3-OMe), 4.29br (1H, q, *J* 5.1 Hz, 15 α -H), 4.39 and 4.64 (each 1H, d, *J* 4.6 Hz, 15 β -OCH₂Ph), 6.66 (1H, d, *J* 2.4 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), 7.21 (1H, d, *J* 8.6 Hz, 1-H), and 7.23 (5H, s, 15 β -OCH₂Ph); δ_C 17.6 (C-18), 25.7 (C-7), 26.3 (C-11), 29.5 (C-12), 32.7 (C-8), 34.9 (C-16), 43.2 (C-6), 44.2 (C-9), 47.3 (C-13), 54.6 (C-14), 55.2 (3-OMe), 71.4 (C-15), 74.3 (15-OCH₂Ph), 111.5 (C-2), 113.9 (C-4), 126.1 (C-1), 127.2 (C-2 and C-6 of 15-OCH₂Ph), 127.5 (C-4 of 15-OCH₂Ph), 128.3 (C-3 and C-5 of 15-OCH₂Ph), 132.2 (C-10), 137.8 (C-5), 138.4 (C-1 of OCH₂Ph), 157.6 (C-3), and 219.6 (C-17) (Found: C, 79.6; H, 7.6 %; *M*⁺, 390. C₂₆H₃₀O₃ requires C, 79.9^s; H, 7.7^s %; *M*, 390.5).

3-Methoxy-15 β ,16 β -epoxyestra-1,3,5(10)-trien-17-one (59)

To a solution of the Δ^{15} -17-ketone (**31**) (56 mg; 0.20 mmol) in dry tetrahydrofuran-*t*-butyl alcohol (2:1) (1.5 ml) at 0°C was added aqueous 10M-sodium hydroxide (0.025 ml) and hydrogen peroxide (30 %; 0.25 ml). The solution was stirred for 2 h with slow warming to 25°C. Residual oxidant was neutralised with aqueous sodium sulphite. The residue upon work-up (ethyl acetate) was recrystallised to give the epoxy ketone (**59**) (40 mg; 70 %), m.p. 189-191°C (from ethyl acetate-hexane) (lit.,⁵⁶ m.p. 189-190°C); $[\alpha]_D -12^\circ$ (*c* 0.9); ν_{\max} 1742 cm⁻¹ (CO); δ_H 1.19 (3H, s, 13 β -Me), 2.99 (2H, m, 6-H₂), 3.33 (1H, d, *J* 2.9 Hz, 16 α -H), 3.78 (3H, s, 3-OMe), 3.93 (1H, d, *J* 2.9 Hz, 15 α -H), 6.66 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.3 and 2.6 Hz, 2-H), and 7.16 (1H, d, *J* 8.3 Hz, 1-H); δ_C 19.4 (C-18), 25.4 (C-11), 26.4 (C-7), 29.2 (C-9), 32.8 (C-12), 35.3 (C-8), 42.3 (C-13), 45.0 (C-6), 52.1 (C-14), 53.4 (C-15), 55.2 (3-OMe), 55.4 (C-16), 111.6 (C-2), 113.9 (C-4), 125.9 (C-1), 131.7 (C-10), 137.4 (C-5), 157.7 (C-3), and 213.0 (C-17) (Found: C, 76.2; H, 7.3 %; *M*⁺, 298. C₁₉H₂₂O₃ requires C, 76.5; H, 7.4 %; *M*, 298).

15 β -Hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (61)

(a) To a solution of the benzyl ether (**60**) (592 mg; 1.52 mmol) in dry ethyl acetate (20 ml) was added palladium on carbon (474 mg; 10 %). The mixture was stirred under hydrogen (1 atmosphere) for 2 h at 20°C. Removal of the catalyst (filtration) and the solvent (*in vacuo*) afforded the 15 β -hydroxy-17-ketone (**61**) (400 mg; 88 %), m.p. 186-189°C (from ethyl acetate-hexane) (lit.,¹⁴ m.p. 186-188°C); $[\alpha]_D +92^\circ$ (*c* 0.9); ν_{\max} 1730 cm⁻¹ (CO); δ_H 1.23 (3H, s, 13 β -Me), 2.92 (2H, m, 6-H₂), 3.78 (3H, s, 3-OMe), 4.68br (1H, s, 15-H), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.74 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), and 7.21 (1H, d, *J* 8.5 Hz, 1-H); δ_C 17.8 (C-18), 25.7 (C-7), 26.4 (C-11), 29.4 (C-6), 32.9 (C-12), 34.7 (C-16), 44.4 (C-9), 46.9 (C-8), 47.1 (C-13), 54.6 (3-OMe), 55.2 (C-14), 67.2 (C-15), 111.6 (C-2), 113.9 (C-4), 126.2 (C-1), 132.0 (C-10), 137.6 (C-5), 157.7 (C-3), and 219.6 (C-17) (Found: C, 75.6^s; H, 8.1 %; *M*⁺, 300. C₁₉H₂₄O₃ requires C, 76.0; H, 8.0^s %; *M*, 300).

(b) Lithium dimethylcuprate (0.2 mmol) in dry diethyl ether (0.5 ml) was prepared at 0°C as previously described. A solution of the epoxy ketone (**59**) (30 mg; 0.1 mmol) in dry tetrahydrofuran (1 ml) was slowly added. Stirring was maintained at 0°C for 10 min. Saturated aqueous ammonium chloride was added and the residue upon work-up (ethyl acetate) comprised the 15 β -hydroxy-17-ketone (**61**) (27 mg; 89 %).

3-Methoxyestra-1,3,5(10)-triene-15,17-dione (**62**)

The 15 β -hydroxy-17-ketone (**61**) (263 mg; 0.88 mmol) was dissolved in dry acetone (5 ml). This solution was cooled to 0°C and 8M-aqueous chromic acid (0.5 ml) was slowly added. After 20 min at 20°C, saturated aqueous sodium disulphite was added. The acetone was removed (*in vacuo*), and the residue upon work-up (ethyl acetate) was crystallised from ethyl acetate to obtain the 15,17-diketone (**62**) (224 mg; 85 %), m.p. 165-167°C (from ethyl acetate-hexane); $[\alpha]_D +70^\circ$ (c 1.0); ν_{\max} 1728 cm⁻¹ (CO); δ_H 1.08 (3H, s, 13 β -Me), 2.44 (2H, m, 6-H₂), 2.97 (2H, m, 2 x 15-H), 3.78 (3H, s, 3-OMe), 6.65 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.2 and 2.7 Hz, 2-H), and 7.19 (1H, d, *J* 8.2 Hz, 1-H); δ_C 16.8 (C-18), 25.3 (C-11), 26.5 (C-7), 29.3 (C-12), 30.4 (C-6), 35.0 (C-16), 43.4 (C-9), 46.3 (C-8), 52.7 (C-13), 55.2 (3-OMe), 61.9 (C-14), 111.7 (C-2), 113.8 (C-4), 126.2 (C-1), 130.8 (C-10), 137.8 (C-5), 157.8 (C-3), 207.0 (C-15), and 210.6 (C-17) (Found: C, 76.3; H, 7.4 %; *M*⁺, 298. C₁₉H₂₂O₃ requires C, 76.5; H, 7.4 %; *M*, 298).

3-Methoxyestra-1,3,5(10),14,16-pentaen-15,17-diol diacetate (**63**)

The 15,17-diketone (**62**) (224 mg; 0.75 mmol) and toluene-*p*-sulphonic acid monohydrate (80 mg; 0.4 mmol) were refluxed in acetic anhydride-isopropenyl acetate (1:1) (4 ml) for 5 h. After cooling to 25°C, the solution was poured into ice water (5 ml) and solid sodium hydrogencarbonate was added until no further effervescence was detected. The residue upon work-up (dichloromethane) (260 mg) was chromatographed on silica gel (26 g), eluting with ethyl acetate-hexane (1:3), to

obtain the 14,16-dienyl-15,17-diacetate (**63**) (228 mg; 84 %), m.p. 78-81°C (from dichloromethane-hexane); $[\alpha]_D +211^\circ$ (c 1.0); ν_{\max} 1311, 1344 (OAc), 1705br cm^{-1} (CO); δ_H 1.15 (3H, s, 13 β -Me), 2.18 and 2.21 (each 3H, s, 15- and 17-OAc), 2.92 (2H, m, 6-H₂), 3.78 (3H, s, 3-OMe), 6.15 (1H, s, 16-H), 6.64 (1H, d, J 2.6 Hz, 4-H), 6.72 (1H, dd, J 8.4 and 2.6 Hz, 2-H), and 7.21 (1H, d, J 8.4 Hz, 1-H); δ_C 17.8 (C-18), 20.8 and 21.1 (15- and 17-COCH₃), 25.7 (C-11), 27.0 (C-7), 30.4 (C-8), 34.9 (C-12), 35.8 (C-6), 46.2 (C-9), 49.3 (C-13), 55.2 (3-OMe), 109.4 (C-16), 111.8 (C-2), 113.8 (C-4), 127.3 (C-1), 128.3 (C-14), 131.3 (C-10), 137.5 (C-5), 138.5 (C-15), 157.6 (C-3), 160.4 (C-17), and 167.4 and 169.1 (15- and 17-COCH₃) (Found: C, 71.9; H, 6.7 %; M^+ , 382. C₂₃H₂₆O₅ requires C, 72.2; H, 6.8^s %; M 382).

*17²-Acetoxy-3-methoxy-16 α -phenylsulphonyl-14,17 α -ethenoestra-1,3,5(10)-trien-17 β -yl acetate (**64**)⁵⁹*

The 14,16-dienyl-15,17-diacetate (**63**) (251 mg; 0.66 mmol) and phenyl vinyl sulphone (133 mg; 0.78 mmol) were heated in xylene to 120°C for 60 h in a pressure tube. The residue obtained upon solvent evaporation (288 mg) was chromatographed on silica gel (30 g), eluting with ethyl acetate-hexane (1:4) to give the cycloadduct (**64**) (55 mg; 15 %); δ_H 0.87 (3H, s, 13 β -Me), 1.56 and 2.11 (each 3H, s, 17 β - and 17²-OAc), 3.71 (2H, m, 6-H₂), 3.74 (3H, s, 3-OMe), 4.28 (1H, dd, J 9.0 and 4.6 Hz, 16 β -H), 6.01 (1H, d, J 6.1 Hz, 17¹-H), 6.60 (1H, d, J 2.8 Hz, 4-H), 6.69 (1H, dd, J 8.6 and 2.8 Hz, 2-H), 7.15 (1H, d, J 8.6 Hz, 1-H), 7.55 (2H, m, m -H x2 of PhSO₂), 7.62 (1H, m, p -H of PhSO₂), and 7.88 (2H, m, o -H x2 of PhSO₂) (Found: M^+ , 550. C₃₁H₃₄O₇S requires M , 550), followed by various uncharacterised fractions (200 mg).

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