CYCLOADDITION – FRAGMENTATION METHODOLOGY IN STEROIDAL HORMONE DESIGN

by

BONITA P. SMITH

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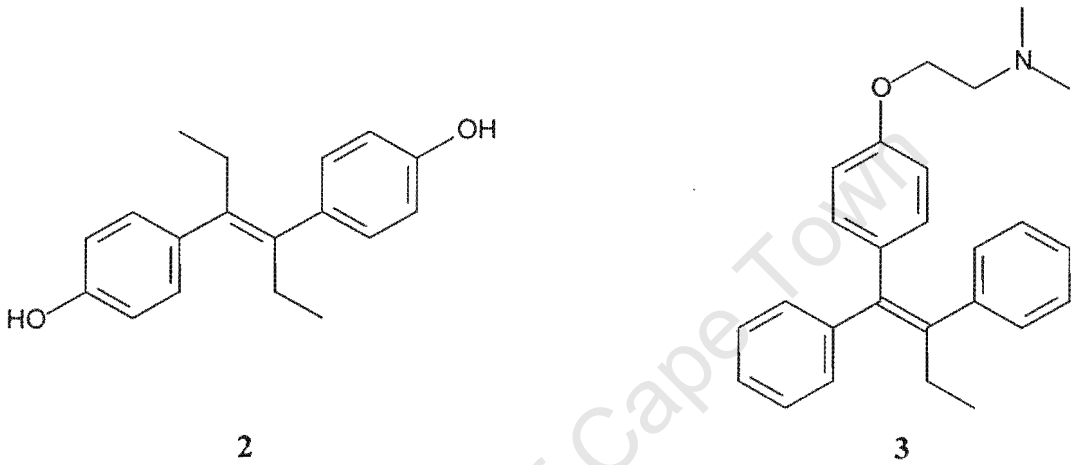
three-dimensional structure of the binding site itself is required.[5] This would enable identification of the exact structural details of estrogen analogues having a direct bearing upon receptor affinity and those which influence receptor activation. In this way the design and synthesis of ligands with the appropriate fit and reactivity to induce or block biological action would be possible.[5] However, until recently, full characterisation of the estrogen receptor protein by X-ray crystallography and NMR techniques had not been achieved, due to difficulties associated with isolation and purification of this labile protein.[2] As a consequence, two convergent structure prediction methods have been adopted in order to gain insight into the nature of the steroid binding site.[5] The one approach involves analyzing the amino acid sequence to predict secondary structure and identify possible binding sites using molecular modeling techniques. The other approach involves deducing a three-dimensional image of the hormone-binding site by analyzing binding and activity data of a large number of hormone analogues. This latter approach has led to the identification of important structure-activity relationships and, together with the molecular modeling, has furthered our understanding of the molecular basis of homone interaction. However further research is necessary before these approaches can provide a sufficiently stable basis for rational drug design.[5]

A general model for the estradiol-estrogen receptor complex has recently been reported based on the accumulated knowledge of binding of steroidal and non-steroidal estradiol analogues and affinity labeling studies.[6] What is understood from the correlation of receptor binding affinities and crystal structures is that the receptor binding is primarily the result of a tight association between the receptor and the phenolic A ring, while the interaction of the D ring 17β-hydroxy is responsible for inducing the biological response. Just prior to this reported model the crystal structure of the ligand binding domain of the estrogen receptor complexed with estradiol was published.[7] It demonstrated that the phenolic hydroxyl group of the A-ring and the 17β-hydroxyl group are involved in direct hydrogen bonds, while the remainder of the molecule participates in a number of hydrophobic contacts. This served to confirm the necessity for terminal hydrophilic functions for binding and activity. The estrogen receptor has also been found to accommodate a diverse array of aromatic structural types which do not contain the steroid nucleus, the most noteworthy of these being diethylstilbestrol **2**, which emerged as a potent, orally effective estrogen.[1] It has been suggested that it's high estrogenicity arises from the conformational similarity to estradiol and the presence of the two phenolic rings capable of imitating ring A of estradiol. The estrogenic potency displayed by

this, and many other nonsteroidal analogues, supports the fact that the steroid nucleus is not essential for estrogenic activity.[4] Estrogen antagonists, which compete for and bind to the receptor site, often have the essential phenolic ring for receptor binding, but either lack essential ring D elements associated with initiating activity or possess additional elements which prevent this initiation. The estrogen antagonist effect displayed by tamoxifen **3**, a nonsteroidal antiestrogen based on the triphenylethylene structure has been exploited clinically and is the basis of its widespread application in breast cancer treatment.[1]

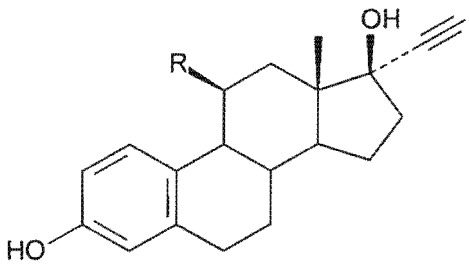


2 **3**

Figure 1.2

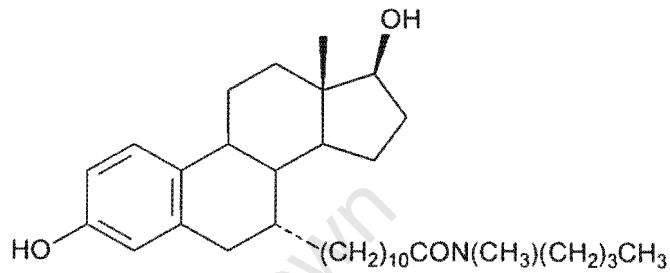
One of the earliest synthetic modifications of estradiol involved the introduction of a 17α-ethynyl moiety, which resulted in stabilisation of ring D to metabolic degradation such that it displayed an oral activity 20 times greater than estradiol.[1] This compound **4** forms the estrogenic ingredient widely used in oral contraceptives and hormone replacement therapy. Extensive research focussed on studying further variations in receptor binding and activity in response to substitution at various positions on the steroid nucleus identified C-7α and C-11β substitution as having the most significant influence on activity.[6] The region in the estrogen receptor corresponding to these sites is highly tolerant of large substitituents, as exemplified by the 11β-dialkylundecylamide **5** and the 7α-undecanamide **6** (ICI 164384). Both display strong receptor binding with negligible estrogenicity, making them amenable to use in treatment of breast cancer.[1] It is postulated that in these long chain analogues the end of the chain protrudes from the binding pocket into the surrounding medium.[6] In so doing, it gives them potential to interfere with the subsequent receptor interactions with other proteins

essential for activation of transcription. This interference of receptor activity forms the basis of the antagonist function of these, and other, analogues. A further interesting feature of both the 7α- and 11β- substituted analogues is the orthogonal relation of the substituents with respect to the relatively planar steroid skeleton. Evidently the high receptor affinity and antagonistic function requires the axial orientation of these substituents.[1]



4 R = H

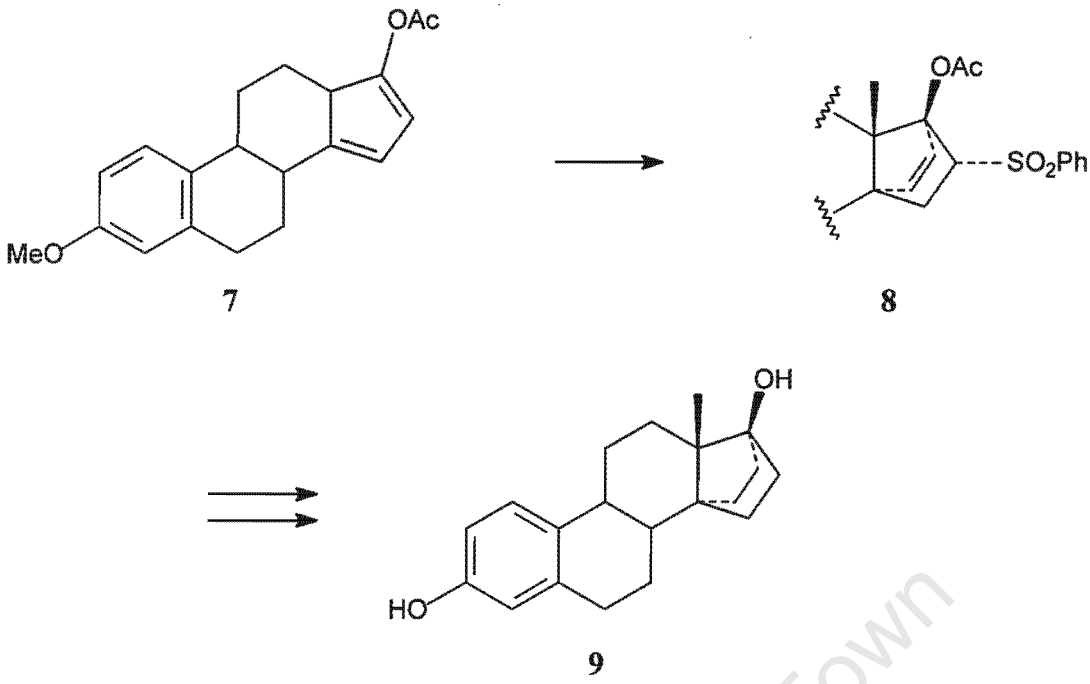
5 R = $(CH)_{10}CON(CH_3)CH(CH_3)_2$



6

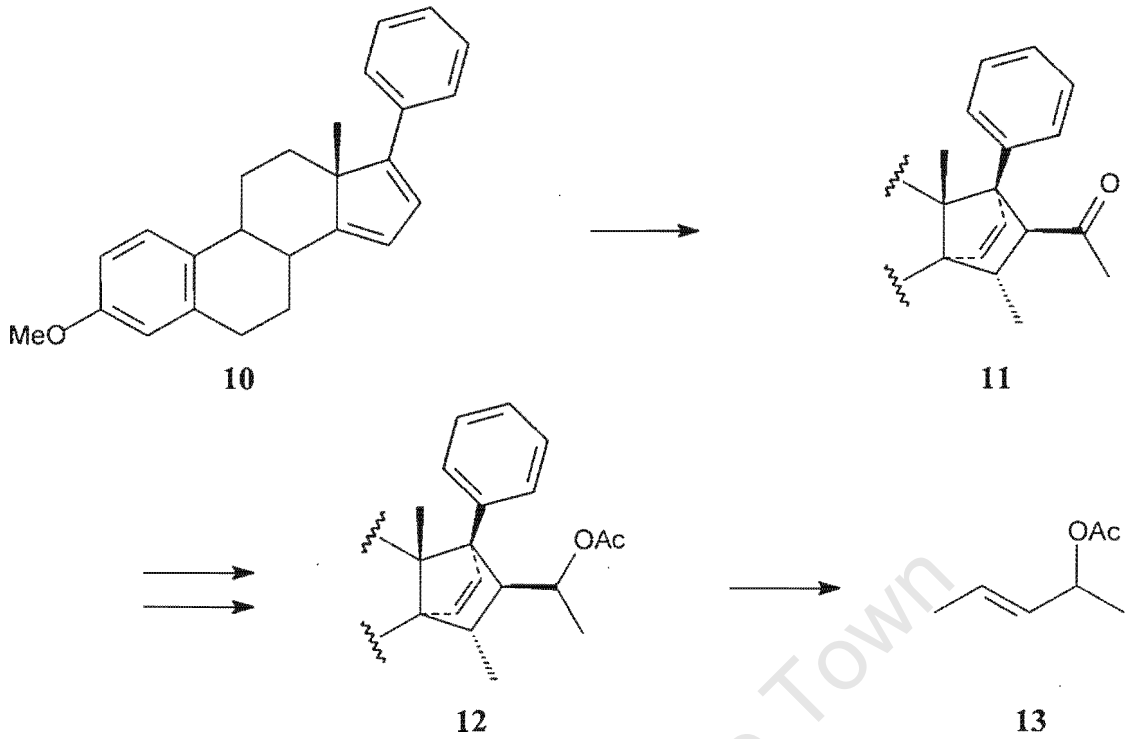
Figure 1.3

The finding that estradiol analoguess with a two-carbon bridge between the 14α- and 17α positions bind efficiently to the estrogen receptor and display oral estrogenicity comparable to 17α-ethynylestradiol,[8] prompted investigations into structure-activity relationships of ring D alkyl bridged compounds. The synthetic approach adopted towards ring D functionalised derivatives was based on the cycloaddition of an ethylene equivalent to the 14,16-steroid diene originally used by Solo et *al.*[9] in synthesizing 14,17α-ethano bridged progesterone analogues. Thus cycloaddition of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate **7** with phenyl vinyl sulphone, followed by reductive desulfonylation gave rise to 14,17α-ethano analogue **9** (Scheme 1.1).[8]



Scheme 1.1

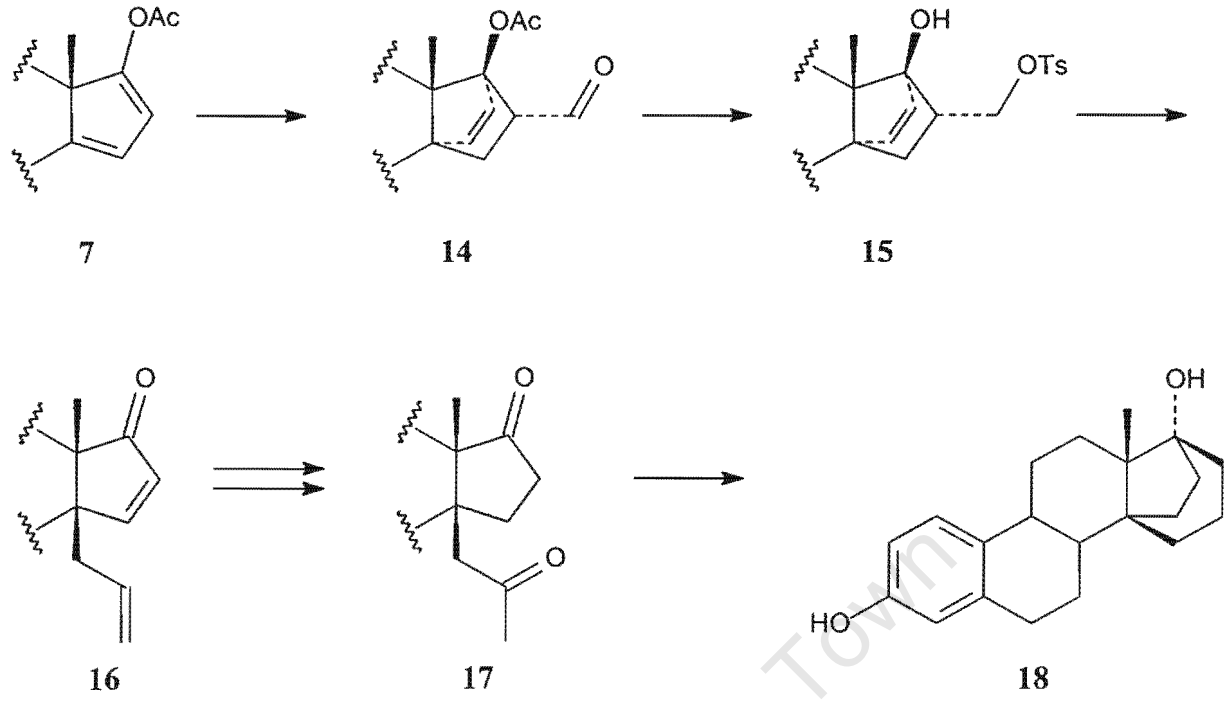
The particular synthetic utility of the foregoing methodology is due to the high stereo- and regiospecificity of the cycloaddition process. It is well established that cycloaddition to steroidal 14,16 dienes occurs almost exclusively at the less hindered β-face and gives rise to products from predominantly *endo* approach of the dienophile.[9] This high β-face and *endo* selectivity has been exploited by Winterfeldt *et al.*[10] in the synthesis of enantiopure building blocks, using 14,16 steroidal dienes as chiral templates. The general approach, exemplified in Scheme 1.2, involved cycloaddition of a nonsymmetrical dienophile to the steroidal diene, followed by a sequence of diastereoselective and regioselective steps, to yield pure enantiomers in the thermal retro process. This principle was further extended to the resolution of enantiomeric mixtures of dienophiles.



10 **11** **12** **13**

Scheme 1.2

Subsequent work by Bull and coworkers[11,12] involved the synthesis and biological testing of a number of bridged and bridge-functionalised estrogen analogues. Synthetic strategies incorporating an initial cycloaddition step were developed to target candidates of particular interest for testing the effect of ring size and orientation on estrogenicity. By making the appropriate choice of steroidal diene and dienophile, the derived cycloadducts were further manipulated using fragmentation, followed by homologation and intramolecular condensation methodologies to give the desired bridged analogues. This is exemplified in the reaction sequence for the synthesis of 14β,17β-propano analogue,[13a] which involved the initial cycloaddition of acrolein to the dienyl acetate **7** to give the carbaldehyde **14**. The derived 16α-tosyloxymethyl intermediate **15** was converted into the 14β-allyl derivative **16** by Wharton fragmentation. Hydrogenation and regioselective functionalisation of **16** gave the 14β-acetonyl-17-ketone **17**, which underwent intramolecular aldol condensation to give, after functional group modification, 14,17β-propanoestra-1,3,5(10)-triene-3,7α-diol **18** (Scheme 1.3).

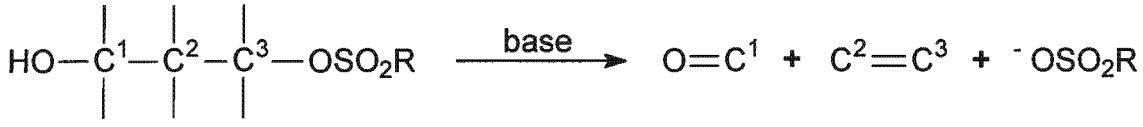


Scheme 1.3

Amongst others, the 14α,17α-propano[13b] and 14β,16β-propano[12] analogues of estradiol were successfully synthesised using elaborations of this approach and their biological activities tested. Results of competitive binding studies of the ring D propano-bridged analogues have shown that while the 14α,17α bridged analogue displays highly competitive binding, the β-series shows poor binding affinity for the estradiol receptor. This suggests that the ring D binding domain of the estrogen receptor, while able to accommodate steric bulk on the α-face, is sensitive to skeletal change on the β-face of the steroid.[13,14]

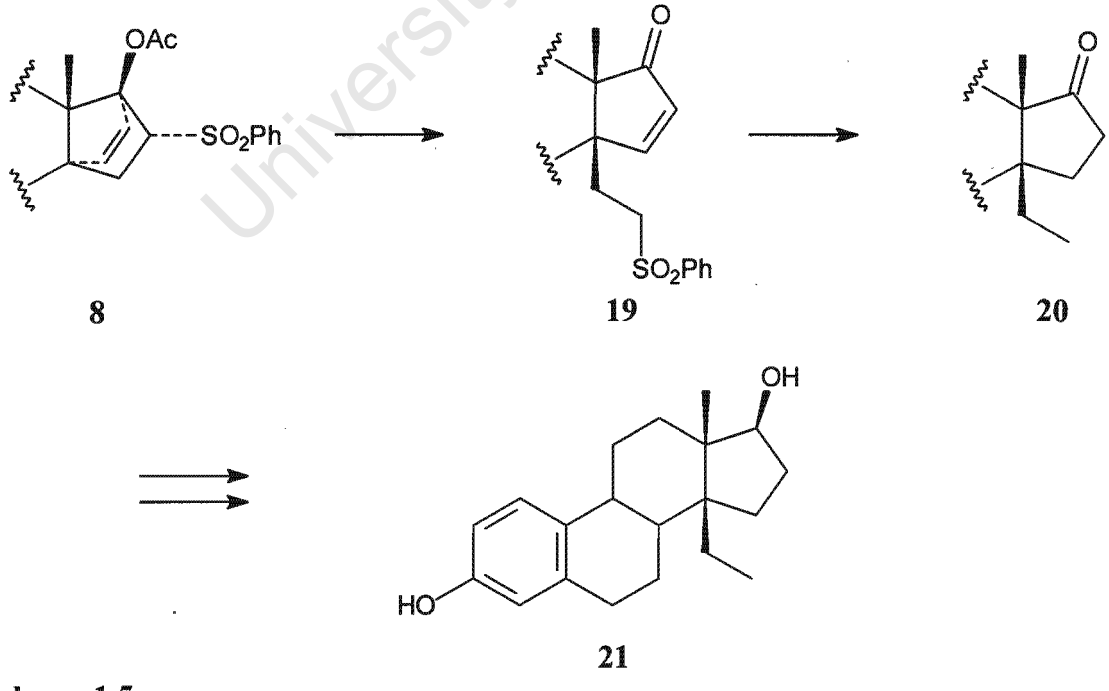
A key step in the reaction sequence for the 14β,17β-propano analogue involved the base fragmentation of the 16α-tosyloxymethyl intermediate **15**, which provides easy access to 14β-functionalised derivatives. The heterolytic fragmentation of 1,3-diol monosulfonate esters is known as the Wharton fragmentation,[15] and is a chemical consequence of through-bond orbital interaction. In this fragmentation, the compounds undergo olefin-forming fragmentation with the release of an electrofugal carbonyl fragment and loss of the nucleofugal sulfonate, as shown in the generalised Scheme 1.4. The process is a concerted one so long as an *anti*, but not necessarily antiperiplanar, relationship exists between the two

bonds undergoing cleavage. In this instance the base does not play its usual role in elimination reactions. Instead it serves to remove a proton from the hydroxyl group forming the alkoxide, which then induces ionization of the sulfonate ester bond by through-bond orbital interaction (TBI), enabling it to leave more readily.



Scheme 1.4

A variation of cycloaddition-fragmentation sequence was used in the synthesis of 14β-ethyl 17-ketone estrogen analogue **24**.[16] In this sequence the fragmentation step involved the retrograde cleavage of the phenyl vinyl sulfone cycloadduct **8**, which gave rise to the 14β-ethyl derivative **20** after reductive desulfonylation (Scheme 1.5). Further manipulation of **20** gave the 17β-estradiol analog **21** which was biologically tested and found to display moderate estrogenic activity.



8 **19** **20**

21

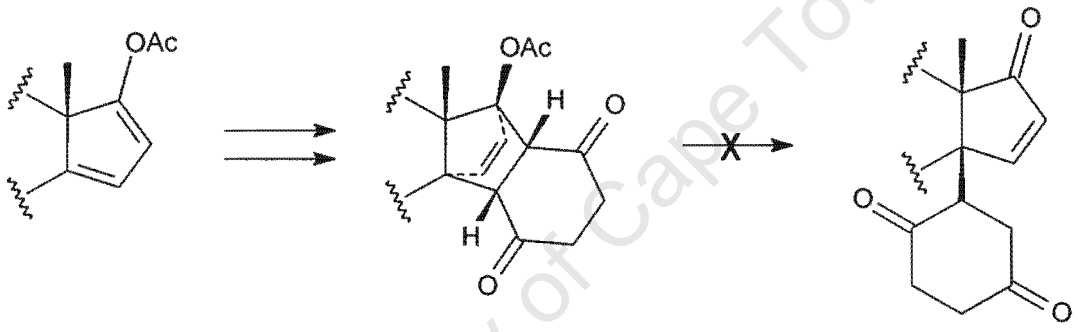
Scheme 1.5

There is much scope for exploiting this cycloaddition-fragmentation methodology further to form derivatives incorporating novel structural motifs at the 14β-position. It is apparent from examination of molecular models that substituents at this position extend nearly perpendicular to the plane of the ring C,D environment, reminiscent of the 7α- and 11β-substituents of numerous estrogen antagonists. As this orthogonality is suspected to form a structural basis for antagonistic effect, it was thought of interest to target 14β-aryl substituted analogues with the definitive aim of testing the influence of such a substituent on receptor binding. This contribution to the overall structure–activity programme will serve to further the understanding of the molecular basis of hormone action and the boundary conditions for receptor site access.

The work carried out in this project aims at extending cycloaddition-fragmentation methodology to cycloadducts formed from symmetrical cyclic dienophiles. The aim is to obtain intermediates in which functional group modification, preceding or following fragmentation, could lead to 14β-aryl estradiol analogues.

2. DISCUSSION

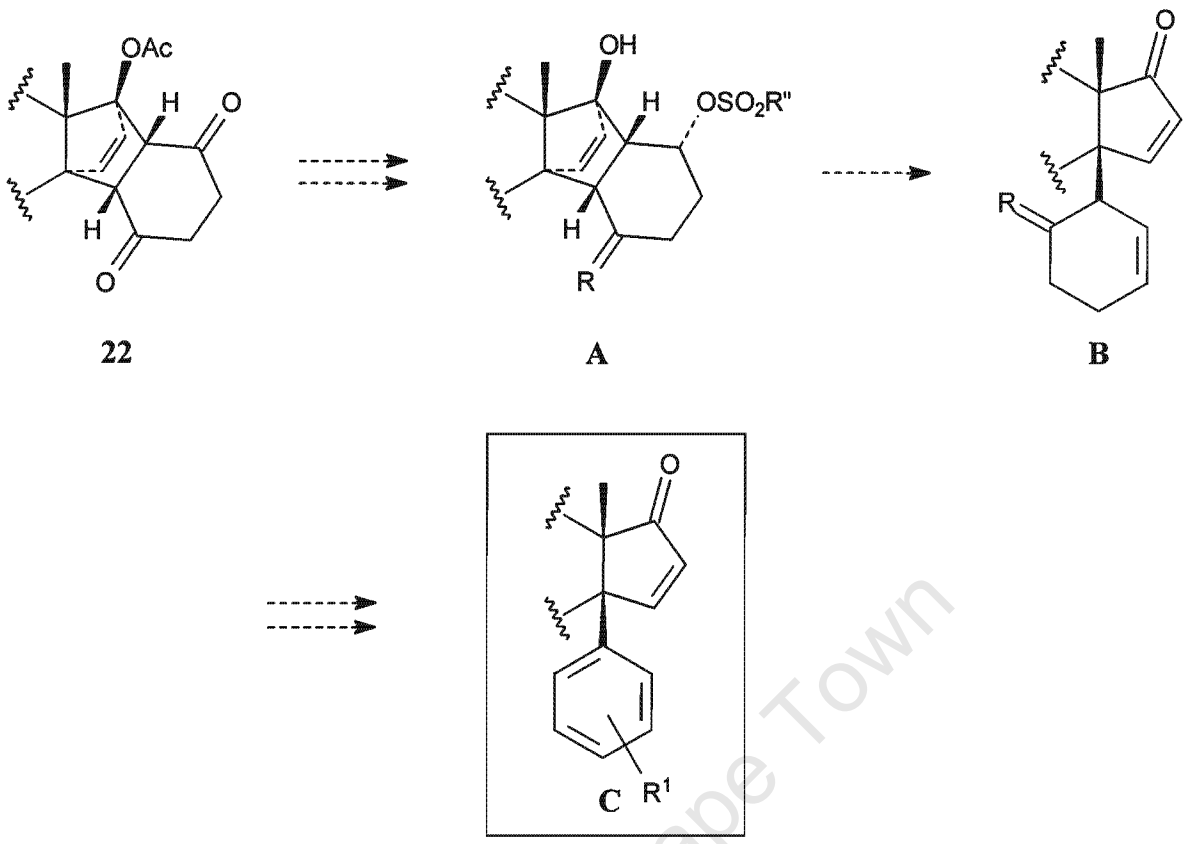
The dihydrocycloadduct **22** has been shown to be readily available *via* a two-step sequence involving the cycloaddition of dienyl acetate **7** and benzoquinone, followed by hydrogenation.[12] In addition, preliminary studies have shown that this intermediate fails to undergo a clean retroaldol cleavage to give the desired 14β-substituted intermediate **23** (Scheme 2.1). In this investigation we shall study the chemoselective reactivity of this dihydrocycloadduct **22**, with the intention of deriving a precursor suitable for Wharton fragmentation. The subsequent fragmentation process can, in this way, take place in a more controlled manner and ultimately provide access to 14β-aryl substituted analogues.



7 **22** **23**

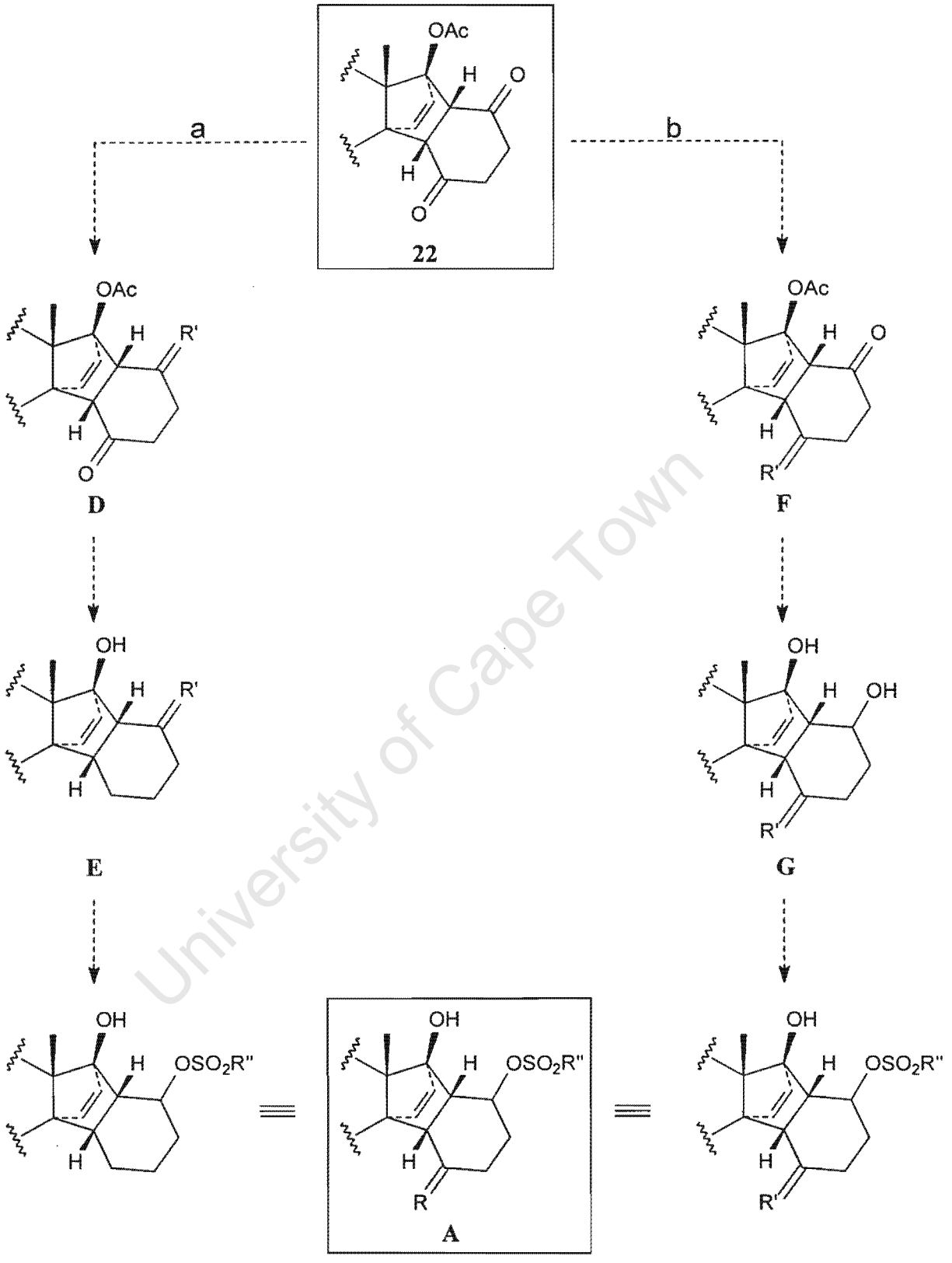
Scheme 2.1

The initial investigation was be directed towards chemoselectively manipulating the dihydrocycloadduct **22**, with the aim of securing an intermediate of the type **A**, having the 1,3 diol monosulfonate ester appropriate for Wharton fragmentation (Scheme 2.2). This should give rise to the 14β-cyclohexenoid intermediate **B**, which retains the differentiation and could be subsequently manipulated to give the 14β-aryl target **C**.



Scheme 2.2

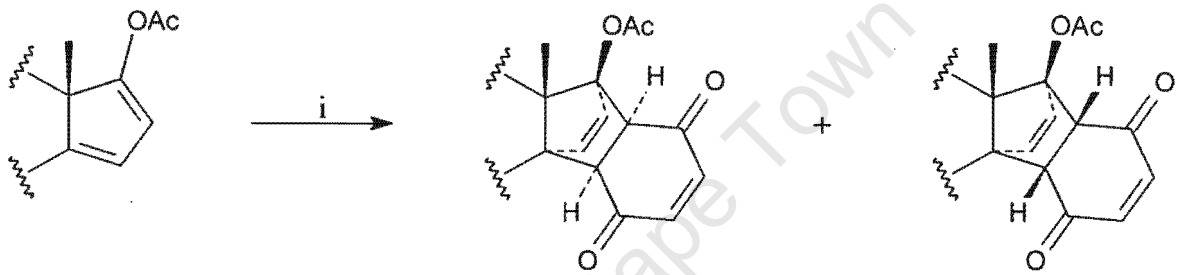
Depending on the chemoselective reactivity displayed by **22**, two possible routes towards **A** can be envisaged. These two pathways are represented in Scheme 2.3. Should the 3'-oxo group be selectively functionalised, for instance protected as a ketal, pathway **a** would be followed (Scheme 2.3). Reductive deoxygenation at C-6' gives the intermediate **E**, which upon sequential deprotection, reduction and sulfonylation, gives the desired target **A** ($R = H_2$). Pathway **b** on the other hand relies upon the 6'-oxo group being chemoselectively protected and provides a more direct route to the desired target. Reduction of **F**, followed by sulfonylation gives the target **A** (R = protected O). Once an intermediate of the type **A** is obtained, the feasibility of the fragmentation to give the 14β-cyclohexenoid substituted intermediate **B** would be tested.



Scheme 2.3

2.1 Synthesis of the benzoquinone dihydrocycloadduct 22

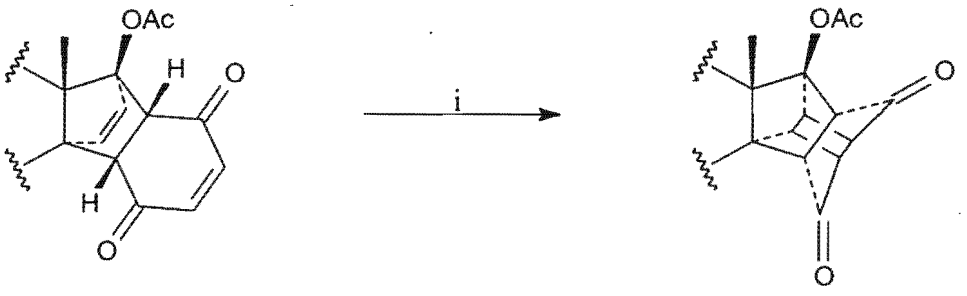
The cycloaddition of the dienyl acetate **7** with *p*-benzoquinone was carried in toluene at 0°C in the presence of boron trifluoride diethyl ether complex as reported,[12] giving rise to a two component mixture of products (TLC). Chromatography of the reaction mixture gave the β-*exo*- and β-*endo*-cycloadducts **24** and **25** in 6 and 72 % respectively (Scheme 2.4). The structural assignments were based on the well-precedented β-face selectivity in cycloadditions of analogous 14,16-dienes[9,10] and the favoured *endo*-approach of the dienophile according to frontier molecular orbital theory.[17]



7 **24** **25**

Scheme 2.4 *Reaction Conditions*: (i) *p*-benzoquinone, BF_3-OEt_2, toluene, 0°C

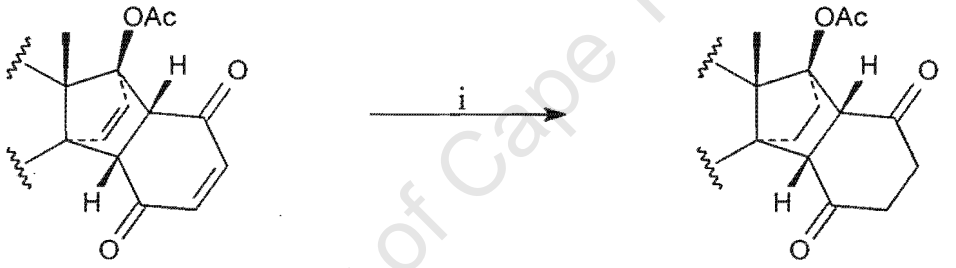
The major cycloadduct **25** was reported[12] to readily undergo an intramolecular [2+2] cycloaddition in the presence of light, giving the photocyclised dione **26** (Scheme 2.5). In order to avoid interference from this reaction, steps to ensure exclusion of light during the work-up procedure were taken.



25 **26**

Scheme 2.5 *Reaction Conditions*: (i) hν, CH_2Cl_2

In order to obtain a stable derivative, the major cycloadduct **25** was hydrogenated in the presence of palladium on carbon as reported.[12] After 3 h the reaction was complete (TLC) and the tetrahydroproduct **27** was isolated in 95 % yield (Scheme 2.6).



25 **27**

Scheme 2.6 *Reaction Conditions*: (i) H_2, Pd on C, EtOAc

In contrast to previous reports,[12] these conditions resulted in reduction of the double bond of the etheno bridge, as well as that of the cyclohexenedione moiety.

The spectroscopic and analytical data were consistent with the assigned structure. The absence of the olefinic proton resonances in the 6.5-7.5 Hz region of the ^{1}H NMR spectrum confirmed that the etheno bridge had been reduced. A further distinguishing feature of the ^{1}H NMR spectrum was the multiplicity observed for the 15β-H and 16β-H signals. These were observed as doublets of doublets at δ 3.07 (*J* 12.6 and 2.4 Hz) and 4.12 (*J* 12.6 and 3.2 Hz) respectively. Their splitting pattern was consistent with a large vicinal *exo-exo* coupling[18] (12.6 Hz) and a smaller long-range W-coupling to an ethano bridge proton (see Figure 2.1). The presence of this long-range coupling serves to confirm the *endo*-orientation of the cyclohexanoid ring.

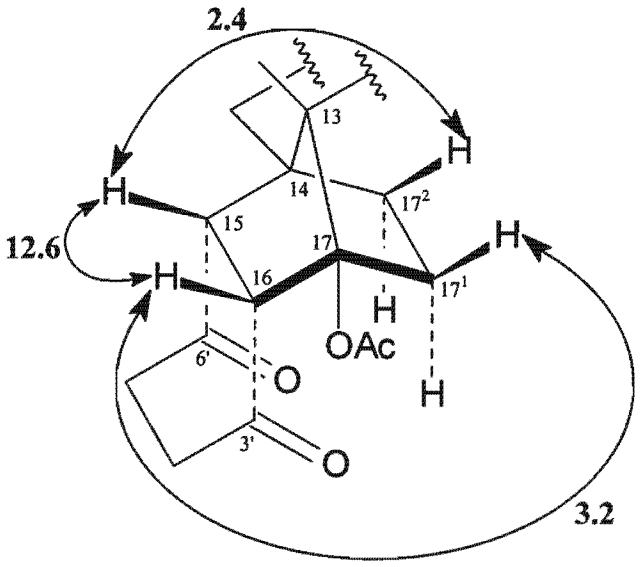


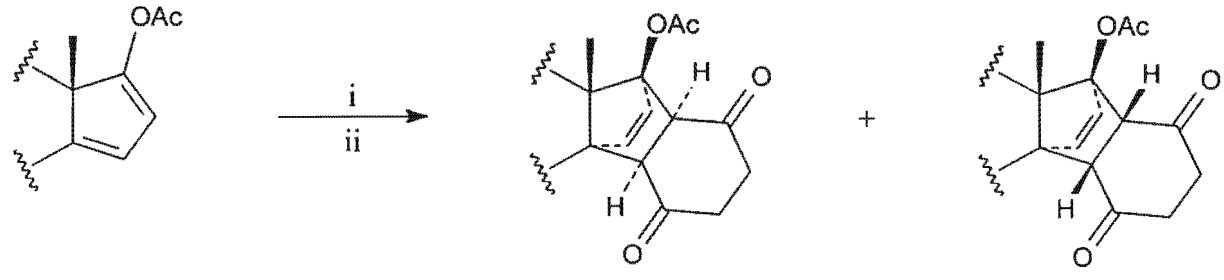
Figure 2.1

Selected ^{1}H NMR *J*-values (Hz) for the tetrahydro cycloadduct **27**

The ^{13}C NMR spectrum displayed singlet resonances at δ 170.4, 208.1 and 210.6 assigned to the 17β-acetoxy carbonyl, C-6' and C-3' respectively. The signals for the bridge carbons C-15 and C-16 resonated at δ 53.0 and 55.3, while the C-17 resonance was observed at δ 91.4.

In view of the lack of selectivity in the catalytic hydrogenation, an alternative method specific to enedione systems was sought. Selective hydrogenation of α,β-unsaturated γ-diketones has successfully been carried out with powdered zinc and acetic acid, and ultrasound has been demonstrated to effectively promote this reduction.[19] The advantages of this mild procedure are the ease with which the reaction is performed and worked up, the use of inexpensive reagents and the high selectivity for double bonds in enedione systems. Isolated double bonds remain unaffected by this reduction procedure.

In order to reduce handling of the cycloaddition reaction product and diminish the chance of photocyclisation of the major adduct, the crude cycloaddition mixture was immediately suspended in acetic acid and subjected to ultrasound in the presence of zinc powder. The reaction was complete after 3 h (TLC) and the minor and major dihydrocycloadducts **28** and **22** were isolated in 5 and 65 % respectively (yields from dienyl acetate) (Scheme 2.7).



7 **28** **22**

Scheme 2.7 *Reaction Conditions*: (i) *p*-benzoquinone, BF_3-OEt_2, toluene, 0°C; (ii) CH_3COOH, Zn, ultrasound

The *endo*-dihydrocycloadduct **22** displayed absorption peaks in the carbonyl region of the infrared spectrum at 1705 and 1738 cm^{-1} while those for the *exo*-dihydrocycloadduct **28** were observed at 1703 and 1742 cm^{-1}. The expected molecular ion of M^+ 434 was observed for both **28** and **22**.

Selected ^1H NMR data for **28** and **22** are summarised in Table 2.1. Both compounds displayed the characteristic etheno-bridge signals between δ 6.1 and 6.6, but lacked the enedione proton signals of the precursors.[12] A four-proton multiplet appeared between δ 2.4 and 2.7 for both **28** and **22** and was assigned to the 4'- and 5'- methylene protons.

The assignment of the 15β-H and 16β-H signals was based on the expected deshielding influence of the 17β-acetoxy group on the 16β-H. Analysis of the Heteronuclear Multiple Bond Correlation (HMBC) spectrum of the major cycloadduct **22** confirmed this assignment. The HMBC experiment is a two-dimensional ^1H-^{13}C correlation method which enables two and three bond connectivities to be determined.[20] A correlation from the C-17 signal at δ 95.6 was observed to the proton signal at δ 3.75 assigned to 16β-H, corresponding to a two-bond coupling. No correlation was observed from the C-17 signal to the more upfield signal at δ 3.32, assigned to 15β-H, as this corresponds to a smaller three-bond coupling. The opposite assignment of ring fusion signals would exclude this observation.

The ^1H NMR data alone does not allow for the unambiguous proof of the assigned stereochemistry. The assignment is based on the favoured β-*endo* approach of dienophile, as described earlier.

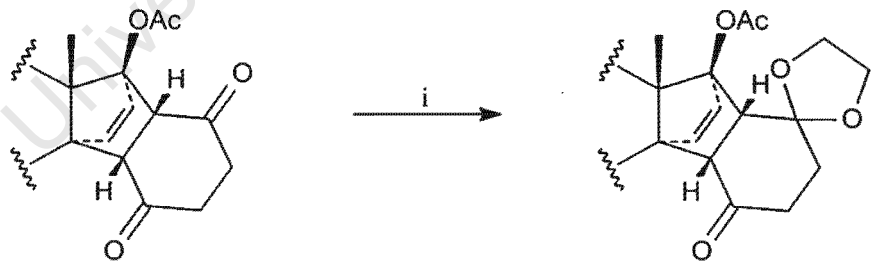
Table 2.1 Selected ^{1}H NMR data* for the *exo*-dihydrocycloadduct **28** and *endo*-dihydrocycloadduct **22**

Proton	28	22
4'-H_2 & 5'-H_2	2.45-2.60 (m)	2.57-2.68 (m)
15β-H	3.85 (d *J* 10.1)	3.32 (d *J* 9.6)
16β-H	4.50 (d *J* 10.1)	3.75 (d *J* 9.6)
17^1-H	6.34 (d *J* 6.0) †	6.59 (d *J* 6.2) †
17^2-H	6.18 (d *J* 6.0) †	6.25 (d *J* 6.2) †

* Data reported as chemical shift (in ppm), multiplicity and *J* values (in Hz)
† Interchangeable

2.2 Chemoselective ketalisation of the *endo*-dihydrocycloadduct 22

In line with the proposed reaction scheme, we first sought to carry out a chemoselective ketalisation of the dihydrocycloadduct **22.** The first attempt involved the treatment of **22** with ethylene glycol and *p*-toluenesulfonic acid in toluene, heated at reflux with constant removal of water. This however gave rise to an intractable mixture of products. An alternative approach using molecular sieves as drying agent proved successful, giving rise to a single product **29** in 78 % yield (Scheme 2.8).



22 **29**

Scheme 2.8 *Reaction Conditions*: (i) ethylene glycol, toluene, TsOH, 4Å molecular sieves, Δ

The spectroscopic and analytical data were consistent with monoketalisation. It was possible to fully assign the ^{1}H and ^{13}C NMR spectra of the monoketal **29** with the aid of COSY, HMQC (Heteronuclear Multiple Quantum Correlation) and HMBC spectra. The HMQC

experiment is a two-dimensional ^{1}H-^{13}C correlation method that allows for direct proton-carbon connectivities to be deduced.[20]

A distinguishing feature of the ^{1}H NMR spectrum was the four-proton multiplet centered at δ 3.96 assigned to the ketal methylene protons. The bridge proton signals appeared at δ 3.08 (d) and 3.34 (d). Comparison of these signals with those in the dihydrocycloadduct **22** (δ 3.32 and 3.75 for 15β- and 16β-H respectively) indicates that while one signal has remained essentially unchanged (15β-H), the other has moved significantly upfield. This is in accordance with the shift expected of the proton α to the newly formed ketal. On this basis the more upfield signal was tentatively assigned to 16β-H. However the appearance of a correlation in the HMBC spectrum between the C-8 signal and the upfield signal at δ 3.08, corresponding to a three-bond coupling, identified this signal as that due to 15β-H. In light of this the signal assignments were reversed. It is somewhat surprising that both bridge protons undergo a similar upfield shift as a result of monoketalisation.

The spectroscopic evidence confirming that chemoselective ketalisation of the 3'-oxo group had occurred was the appearance of a crosspeak between the ketal carbon signal at δ 108.7 and the 16β-H signal, corresponding to a two bond coupling. No correlation was observed to the 15β-H signal.

The coupling data for ring D and E protons are displayed in Figure 2.2. The 4'- and 5'-H signals appeared as complex multiplets in the upfield region of the ^{1}H NMR spectrum. The geminal protons at δ 2.25 (ddd, J 17.6, 9.7 and 6.6 Hz) and 2.41 (dddd, *J* 17.6, 9.6, 4.7 and 1.3 Hz) displayed a correlation in the HMQC spectrum to a methylene carbon signal at δ 36.7. In addition the latter carbon signal displayed a crosspeak in the HMBC spectrum to the 16β-H signal, which identifies it as C-4' and hence the proton signals as 4'-H's. The geminal proton signals at δ 1.89 (dddd, *J* 13.9, 9.6, 6.6 and 1.2 Hz) and 2.10 (obsc ddd) were assigned to the 5'-H's, and the C-5' was located to a signal at δ 30.8 by a correlation in the HMQC spectrum. The existence of long range W-coupling between one of the each of the methylene proton pairs to a bridge proton allowed for differentiation of the α- and the β-protons. Furthermore, its existence implies ring E adopts a boat conformation in which the carbonyl and ketal groups are oriented in the so-called "closed form",[21] as this is the only conformation which satisfies the W-geometry (see Figure 2.2). The long-range coupling was similarly reflected in the splitting patterns of the bridge protons.

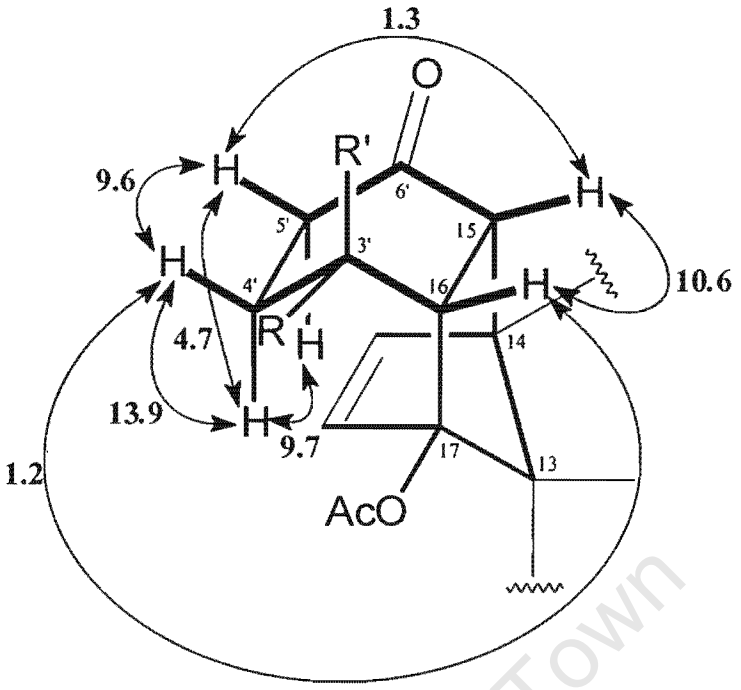


Figure 2.2

Selected *J* values (Hz) for 3'-monoketal **29** (RR'=$O(CH_2)_2O$)

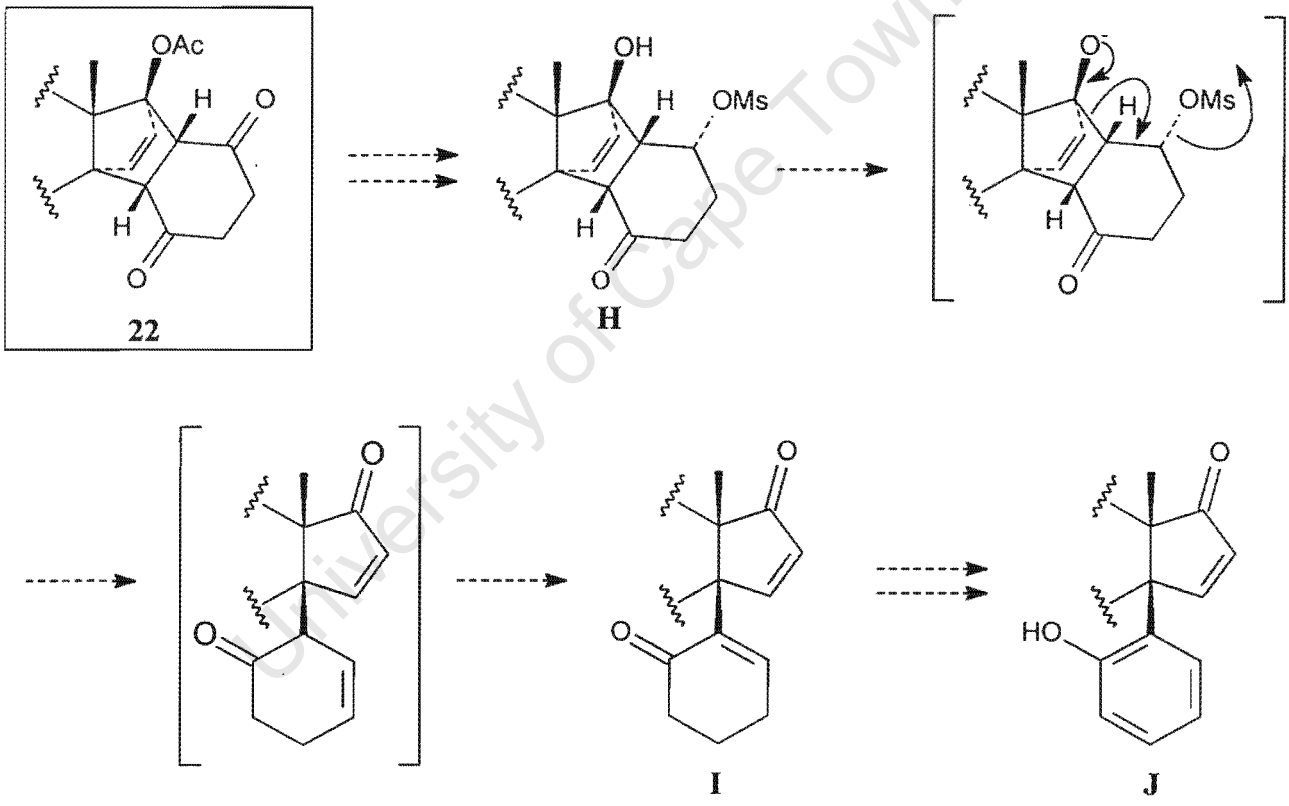
The ^{13}C NMR spectrum displayed doublet resonances at δ 51.2 and 56.2 which were assigned to C-16 and C-15 respectively on the basis of a crosspeak in the HMQC spectrum to the 16β-H and 15β-H signal respectively. The significant upfield shift of the C-16 resonance (~5ppm) compared to the dihydrocycloadduct **22** is consistent with the loss of a α-carbonyl group. The two triplet resonances at δ 64.0 and 65.4 were assigned to the ketal methylene carbons, while the acetoxy carbonyl and C-6' signals were observed at δ 169.8 and 211.8 respectively.

It would appear from models that approach of a nucleophile to the β-face of the cyclohexanedione moiety is not sterically impeded at either the 3'- or the 6'-oxo group. Therefore it is not possible to rationalise the observed chemoselectivity on steric grounds. It is possible that the hemiacetal formed in the first step of cyclic acetal formation is more stabilised at the 3' position than at the 6' position, possibly by interaction with the 17β-acetoxy group. This stabilization of the somewhat transient hemiacetal would enable the second nucleophilic addition to occur more readily, giving rise to the cyclic acetal exclusively at the 3'-position. This expression of chemoselectivity is gratifying and holds much promise for subsequent manipulations of the chemodifferentiated product. However, further work along

this line was postponed in favour of a more promising route based on the outcome of the previously reported Lithium tri-*sec*-butylborohydride (L-Selectride®) reduction of the dihydroadduct **22**.[12]

2.3 Chemoselective reduction of the *endo*-dihydrocycloadduct 22

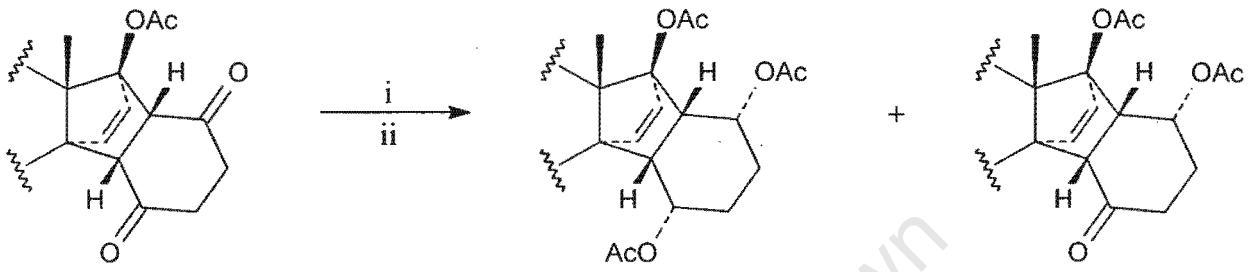
Preliminary work demonstrated that the dihydrocycloadduct **22** was chemoselectively reduced at the 3'-oxo group when treated with L-Selectride® at -78°C.[12] Based on this result, the following Scheme 2.9 was thought feasible.



Scheme 2.9

Sulfonylation of the L-Selectride reduced compound would give rise to a 1,3 diol monosulfonate ester **H**, which upon fragmentation produces, after double bond isomerisation, the 14β-cyclohexenoid intermediate **I**. Aromatisation would result to the desired target **J**.

In pursuance of this objective, we set out to first confirm the previously reported chemoselectivity for the L-Selectride reduction. The dihydrocycloadduct **22** was treated with L-Selectride in dry toluene at -78°C for 5 h and following an oxidative work-up procedure, was immediately acetylated using standard conditions. The 3'α,6'α,17β-triacetate **30** and 3'α,17β-diacetate **31** were isolated in 15 and 71 % yields respectively (Scheme 2.10).



22 **30** **31**

Scheme 2.10 *Reaction conditions*: (i) L-Selectride, toluene, -78°C; (ii) Ac_2O, py, DMAP

The analytical and spectral data confirmed the assigned structures of the triacetate **30** and diacetate **31**. Figure 2.3 presents selected ^1H NMR data for the diacetate **31**. The assignment of the ring-fusion proton signals was based once again on the expected deshielding influence of the proximal acetoxy group on the 16β-H. Thus the more upfield signal at δ 2.99 (d) was assigned to 15β-H and was split by a large vicinal coupling (11.3 Hz) to 16β-H. The signal at δ 3.29 (dd) was assigned to 16β-H and displayed a large vicinal coupling (11.3 Hz) as well as a smaller vicinal coupling (4.5 Hz) to 3'β-H. The latter coupling was matched in the signal for 3'β-H at δ 5.30 (td) which was further split by vicinal couplings of 4.5 and 1.7 Hz to the 4'-H's.

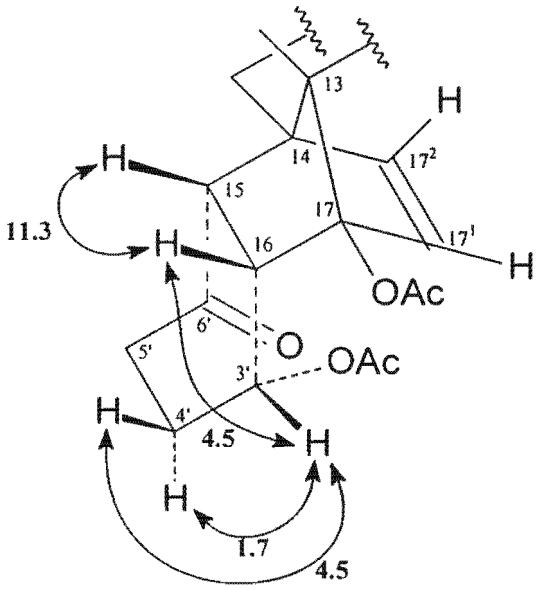


Figure 2.3

Selected ^{1}H *J* values (Hz) for the diacetate **31**

The configuration of C-3' was assigned on the basis of well precedented exclusive *exo*-face attack of hydride reagents to analogous bicyclic systems.[22,23] This *exo*-selectivity is the result of greater shielding of the *endo*-face by the etheno-bridge.

The ^{13}C NMR spectrum of the diacetate **31** revealed a doublet resonance at δ 67.1 corresponding to C-3', while the singlet carbonyl resonance at δ 209.4 was assigned to C-6'. The C-4' and C-5' signals were observed at δ 26.0 and 34.9 respectively, the former having shifted ~12ppm upfield from the corresponding signal in the dihydrocycloadduct **22**. This is in accordance with expectations for the transformation of the neighbouring oxo group to the corresponding acetyl. The signals at δ 50.1 and 55.1 were assigned to C-16 and C-15 respectively on the basis of correlations in the HSQC spectrum.

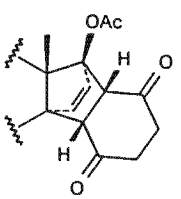
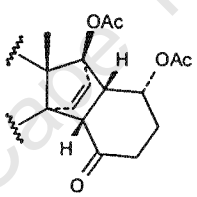
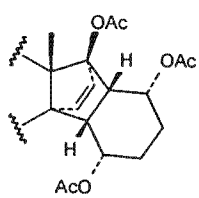
The ^{1}H NMR spectrum of the triacetate **30** displayed doublet of doublets at δ 2.55 (*J* 10.6 and 6.4) and 2.90 (*J* 10.6 and 6.4 Hz) assigned to 15β-H and 16β-H respectively. Their splitting pattern is consistent with a large vicinal 15β-16β coupling, and a smaller vicinal coupling to the adjacent carbinol proton. A two-proton multiplet at δ 5.35 was assigned to the 3'- and 6'-protons. In an attempt to achieve dispersion of this signal, the spectrum was recorded in deuteriobenzene. This resulted in the separation of the signal into two resonances at δ 5.12

(dt, *J* 6.7 and 2 x 3.4 Hz) and 5.39 (q, *J* 3 x 6.5 Hz). The stereochemistry was assigned as 3'β- and 6'β-H, based on the expected exclusive delivery of hydride to the β-face.

The ^{13}C NMR spectra displayed doublets at δ 67.3 and 68.8 assigned to C-3' and C-6'. The resonances for C-4' and C-5' were observed at δ 23.1 and 24.8, both shifted significantly upfield from the corresponding signals in the dihydrocycloadduct **22**. The signals for C-15 and C-16 similarly experienced an upfield shift of approximately 10 ppm to δ 46.7 and 45.0 respectively.

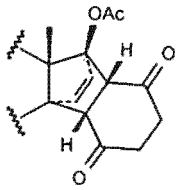
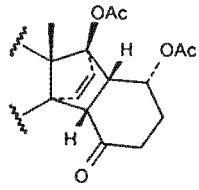
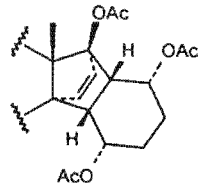
The diagnostic NMR data for the dihydrocycloadduct **22**, the diacetate **31** and the triacetate **30** are compared in Tables 2.2 and 2.3.

Table 2.2 Selected ^{1}H NMR data* for **22**, **30**, and **31**

Proton	**22** 	**31** 	**30** 
15β-H	3.32 (d, *J* 9.6)	2.99 (d, *J* 11.3)	2.55 (dd, *J* 10.6 & 6.4)
16β-H	3.75 (d, *J* 9.6)	3.29 (dd, *J* 11.3 & 4.5)	2.90 (dd, *J* 10.6 & 6.4)
3'β-H	-	5.30 (td, *J* 2 x 4.5 & 1.7)	5.35 (m)
6'β-H	-	-	
17^{1}-H & 17^{2}-H	6.25 & 6.59 (d, *J* 6.2)	6.20 (s, 2H)	6.01 & 6.33 (d, *J* 6.2)

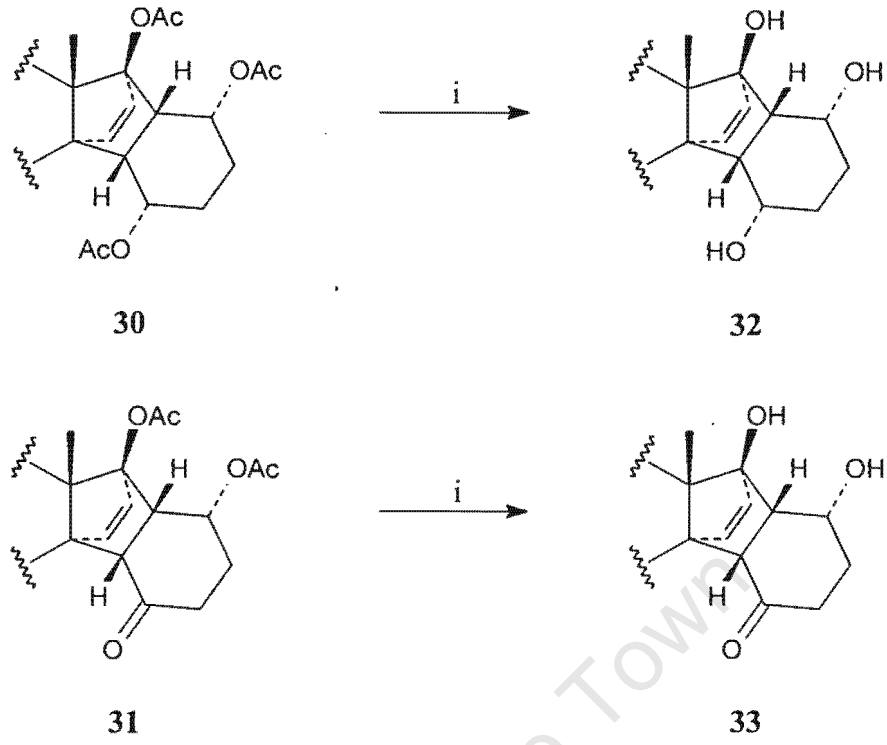
* quoted as chemical shift (in ppm), multiplicity and coupling constants (in Hz)

Table 2.3 Selected ^{13}C NMR data* of **22**, **30** and **31**

Carbon	**22** 	**31** 	**30** 
C-4'	38.1[1]	26.0	23.1†
C-5'	39.6[1]	34.9	24.8†
C-15	56.2[2]	55.1	46.7
C-16	56.5[2]	50.1	45.0
C-17[1]	131.6†	130.7†	130.1†
C-17[2]	134.9†	131.6†	130.4†
C-3'	206.8‡	67.1	67.3‡
C-6'	210.9‡	209.4	68.8‡

* reported as chemical shift (in ppm)
1,2,†,‡ interchangeable

In order to free the hydroxy groups for subsequent transformations, the triacetate **30** and diacetate **31** were each subjected to base treatment, giving rise to the 3'α,6'α,17β-triol **32** and 3'α,17β-diol **33** respectively (Scheme 2.11).

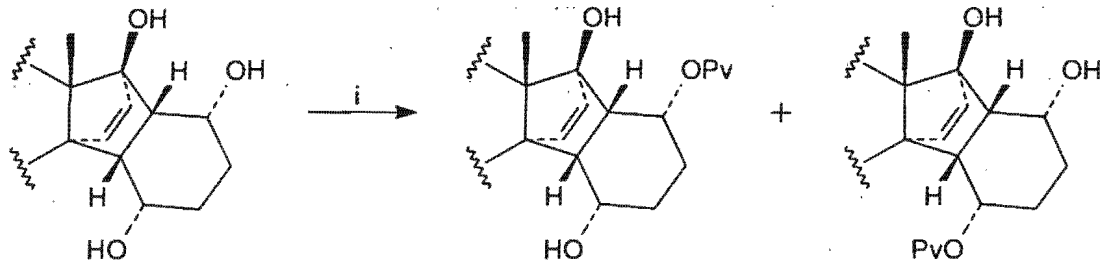


Scheme 2.11 *Reaction Conditions* (i) KOH, MeOH

This L-Selectride result has clearly demonstrated that the chemoselectivity previously reported and tentatively assigned by Sickle[12] is indeed high and provides an approach to implementation of the targeted fragmentation. The isolation of an over-reduced product under the conditions quoted here is likely the result of imperfect stoichiometric control, but the availability of the triol **32** provided scope for exploring the possibility of chemoselective differentiation of the 3'α- and 6'α- hydroxy groups.

A number of small-scale experiments, *inter alia* acetylation, mesylation and pivaloylation, were carried out on the triol **32**. Monitoring (TLC) of the acetylation and mesylation reactions indicated formation of complex mixtures with no clear major product, and so were not investigated further. Treatment of **32** with pivaloyl chloride in pyridine at room temperature proceeded slowly and incompletely, giving rise to a 1:1 mixture of less polar products **34** and **35**, accompanied by starting material (Scheme 2.12). Both products displayed a molecular ion of M^+ 480, corresponding to the monopivaloylated derivative. Analysis of the NMR data of the chromatographically-separated products confirmed this fact; however the data was insufficient to distinguish between the 3'α- and 6'α-pivaloates. The lack of chemoselectivity

observed in this reaction indicates that the 3'α-OH and 6'α-OH have comparable steric environments.



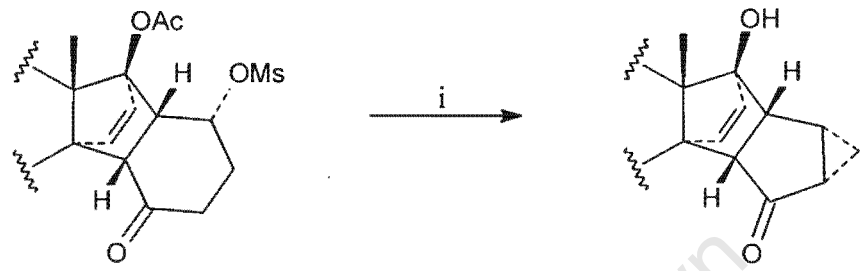
32 **34?** **35?**

Scheme 2.12 *Reaction Conditions:* (i) PvCl, py, RT

The next step towards the overall objective entailed selective sulfonylation of the secondary hydroxy group of the diol **33**. Initial experiments conducted with methanesulfonyl chloride in pyridine at low temperature (0°C) appeared to proceed as expected (TLC), but attempted work-up was complicated by difficulties in removing residual pyridine, resulting in the formation of a mixture of decomposition products. However a reaction carried out at -78°C using triethylamine and dichloromethane as solvent resulted in the formation of the 3'α-mesylate **36** in 63 % yield after 3 h (starting material was also recovered in 24 % yield). Although the lability of **36** prevented its full characterisation, a ^{1}H NMR spectrum of the chromatographically pure isolate revealed properties consistent with mesylation of the 3'α-hydroxy group. In particular the diagnostic sulfonate methyl signal was observed at δ 3.03 (3H, s). In addition the 3'β-H signal at δ 5.27 (td, *J* 2 x 4.5 and 1.5 Hz) was shifted 1 ppm downfield from the corresponding signal in the diol **33**. This downfield shift is in accordance with expectations for sulfonylation.[24]

Direct treatment of the crude 3'α-mesylate **36** with acetic anhydride and catalytic 4-(dimethylamino)pyridine gave the more stable 17β-acetoxy-3'α-mesylate **37** in 65 % yield (Scheme 2.13).

acetoxy and sulfonate methyl signals suggested they had been eliminated, yet there was no evidence of additional olefinic protons. A molecular ion of M^+ 376 was observed in the mass spectrum, corresponding to deacetylation and elimination of the elements of methanesulfonic acid. A complete analysis of the NMR data, with the aid of ^1H-^1H and ^1H-^{13}C correlated NMR studies, suggested that the structure was the ring-contracted derivative **38** (Scheme 2.14).



37 **38**

Scheme 2.14 *Reaction Conditions*: (i) KOH, MeOH, 1h

The infrared spectrum displayed absorption peaks at ν_{max} 3020 cm^{-1} and 1715 cm^{-1} corresponding to the hydroxy and carbonyl band respectively.

Figure 2.4 shows selected coupling data for the ring D and E protons. The signals at δ 3.07 (d) and 3.50 (dd) in the ^1H NMR spectrum were assigned to 17^6-H and 17^1-H respectively. The splitting pattern of the latter signal is consistent with a large vicinal coupling to 17^6-H (10.7 Hz) and a smaller synclinal coupling to 17^2-H (6.9 Hz). A highfield proton resonance at δ 0.80 (ddd, *J* 10.4, 8.1 and 5.2 Hz) displayed a correlation in the COSY spectrum to an obscured multiplet at δ 2.10. Both these signals displayed a correlation in the HMQC spectrum to a newly appeared methylene carbon signal at δ 9.2. Consequently these signals were assigned to the geminal partners 17^3α-H and 17^3β-H respectively. The two methine carbon signals at δ 19.7 and 32.1 were assigned to C-17^2 and C-17^4 respectively. A correlation in the HMQC spectrum from these signals to a two proton multiplet centered at δ 1.89 located the corresponding methine protons. This multiplet also displayed correlations in the COSY spectrum to the 17^3-H's, serving to confirm the assignment. The doublet resonances in the ^{13}C NMR spectrum at δ 47.0 and 62.6 were assigned to C-17^1 and C-17^6 respectively, on the basis of correlations in the HMQC spectrum. The C-17^5 resonance

appeared in the expected carbonyl region at δ 212.9. The NMR data for ring D and E are tabulated and compared to the acetoxy mesylate **37** in Tables 2.4 and 2.5.

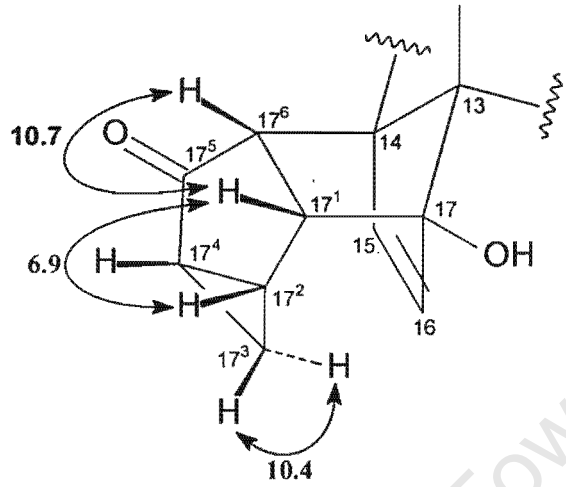


Figure 2.4

Selected ^{1}H NMR coupling data for **38** (*J* values in Hz)

Table 2.4 Selected ^{1}H NMR data* for 17β-acetoxy-3'α-mesylate **37** and ring-contracted **38**

Proton	37	Proton	38
15β-H	2.97 (d, J 11.6)	17^{6}-H	3.07 (d, J 10.7)
16β-H	3.35 (dd, J 11.6 & 4.5)	17^{1}-H	3.50 (d, J 10.7)
17^{1}-H	6.19 (d, J 6.2)†	16-H	6.03 (d, J 6.0)†
17^{2}-H	6.22(d, J 6.2)†	15-H	6.12 (d, J 6.0)†
3'β-H	5.27 (td, J 2 x 4.5 & 1.5)	17^{2}-H & 17^{4}-H	1.84-1.94 (m)
4'-H_2	2.41 (m)	17^{3}α-H	0.80 (ddd, J 10.4, 8.1 & 5.2)
5'-H_2		17^{3}β-H	2.10 (m)

* quoted as chemical shift (in ppm) multiplicity and coupling constants (in Hz)
† interchangeable

Table 2.5 Selected ^{13}C NMR data* for **37**and **38**

Carbon	37	Carbon	38
C-15	55.0	C-17^6	62.6
C-16	50.5	C-17^1	47.0
C-17	93.8	C-17	92.0
C-17^1	130.8†	C-15	133.0†
C-17^2	132.0†	C-16	138.9†
C-3'	74.3	C-17^2	19.7
C-4'	27.6	C-17^3	9.2
C-5'	34.6	C-17^4	32.1
C-6'	208.5	C-17^5	212.9

* quoted as chemical shift (in ppm)
† interchangeable

In view of the novelty of this reaction product, an X-ray crystallographic analysis was conducted on **38**, which verified the proposed structure. The compound crystallised in the P 2_1 space group, with two molecules per asymmetric unit. These molecules differed only slightly with respect to their torsional angles. The X-ray crystal structure is depicted in Figure 2.5.

Examination of the bond angles, torsional angles and bond lengths revealed no unexpected structural or conformational properties. The small torsional angles (in the range ±2 - 9°) for ring E indicated that this ring is almost planar. In addition the bond angles indicated in Table 2.6 are reconcilable with a cyclopropane ring. The stereochemistry of the cyclopropane ring was confirmed to be $17^2\alpha,17^4\alpha$ by the positive torsion angle O2-C17^5-C17^4-C17^3 (112.0°) and the negative torsion angle C17^3-C17^2-C17^4-C17^2 (-109.3).

Table 2.6 Selected bond angles (°) for **38**

C17^3-C17^2-C17^4	60.5
C17^3-C17^4-C17^2	58.94
C17^2-C17^3-C17^4	60.6

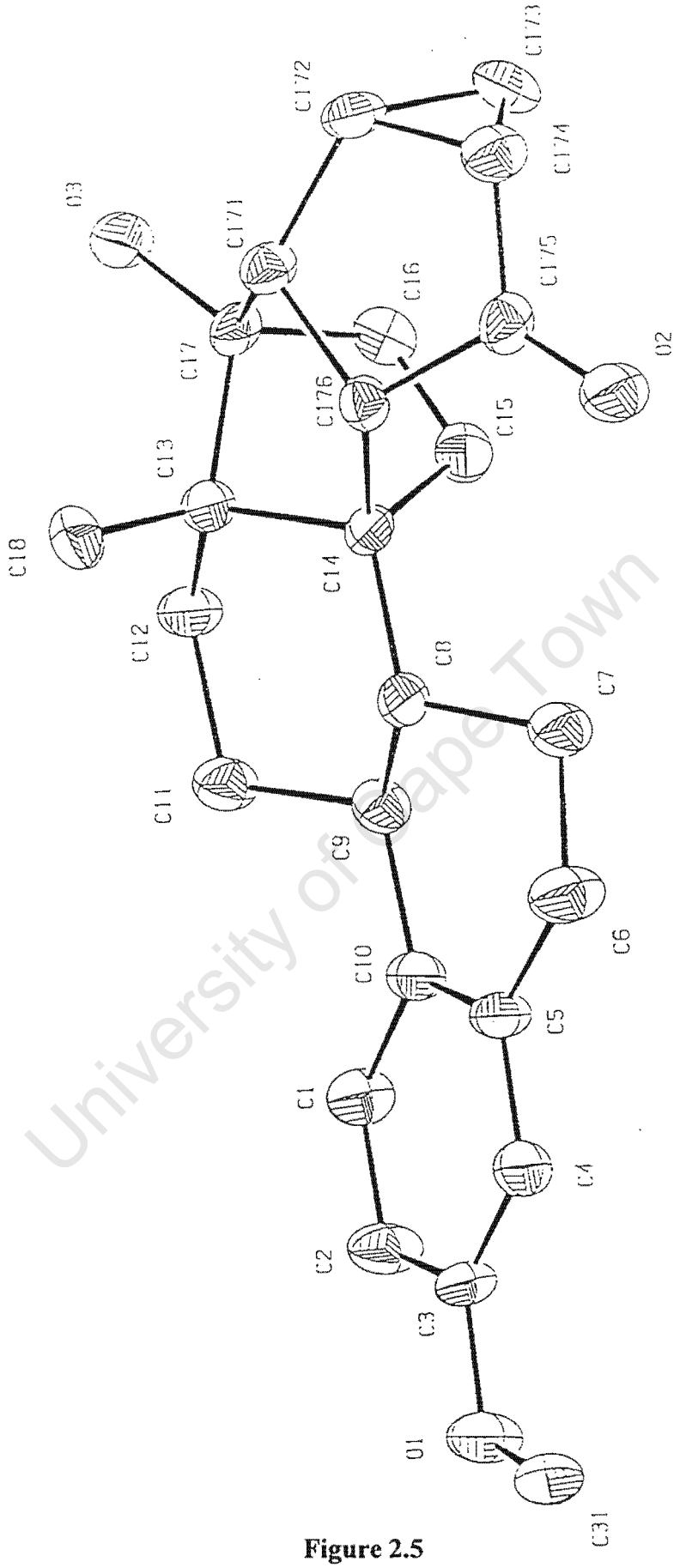
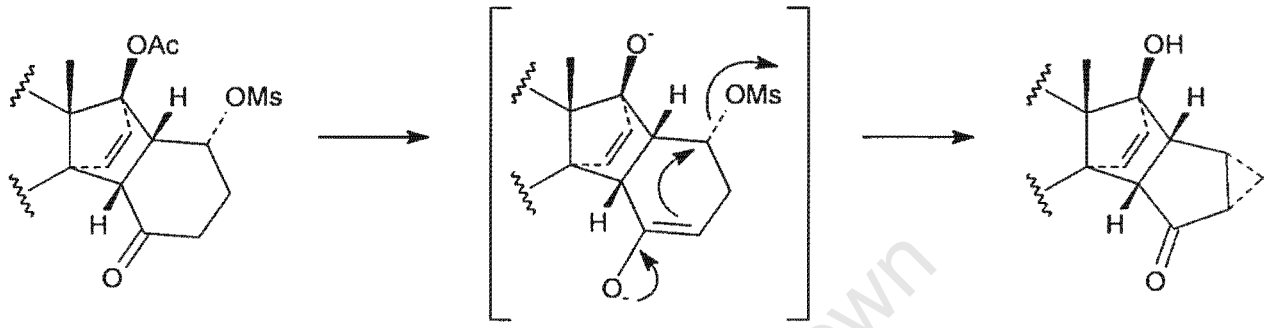


Figure 2.5
X-ray crystal Structure of the hexacyclic product **38**

It is evident that formation of the ring contracted product proceeds *via* a stereospecific transannular displacement, mediated by the enolate of the 6'-oxo group (Scheme 2.15). It is interesting to note that this reaction pathway competes successfully with the alternative Wharton fragmentation route, despite the presumed release of strain, which one might expect from the latter process.



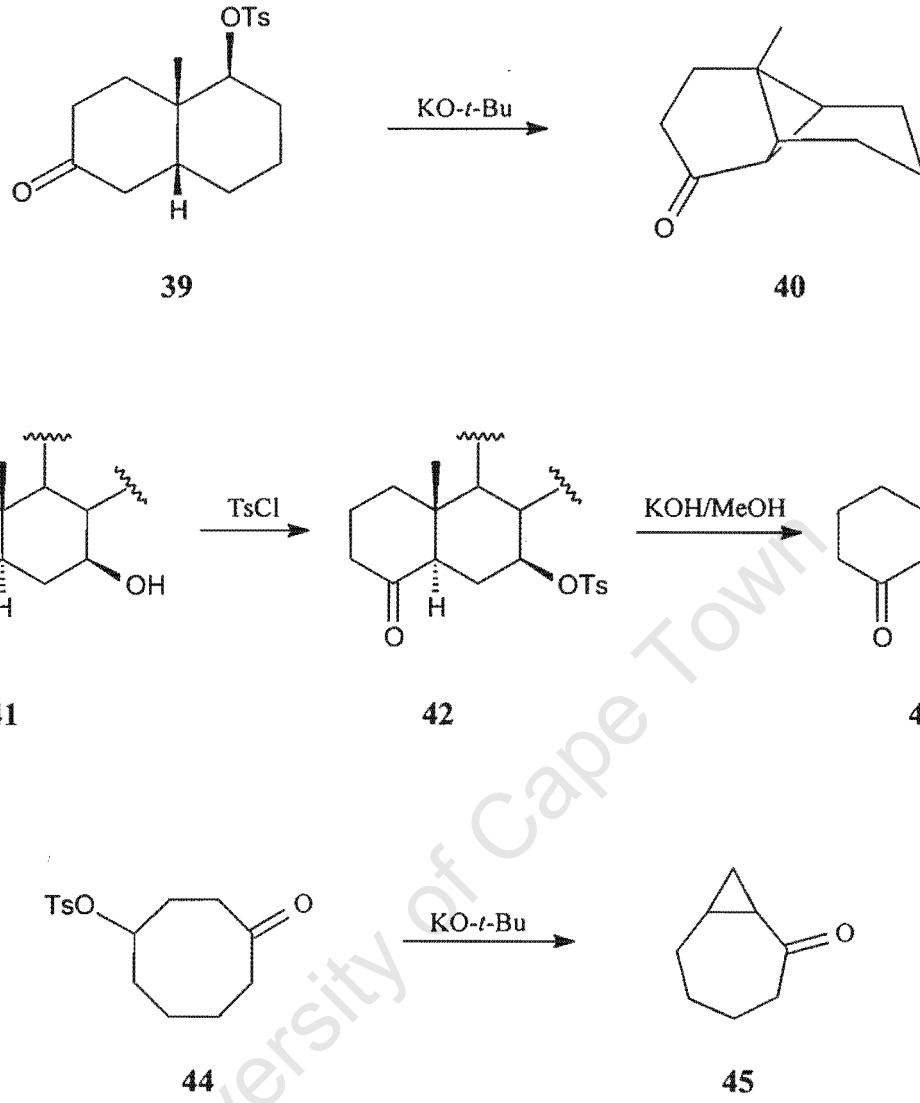
37 **38**

Scheme 2.15

The general principle of enolate-mediated transannular displacements, leading to bicylic products is well known and is exemplified in Scheme 2.16. Heathcock *et al.*[26] reported base catalysed cyclisation of oxo tosylates as a key reaction in the total synthesis of sesquiterpenoids. This led to the development of a general method for the construction of tricyclo[4.4.0.$0^{2,7}$]decanes. In a preliminary study, the synthesis of the desired tricyclic ketone **40** from the oxo tosylate **39** was reported by treatment with potassium *t*-butoxide in *t*-butyl alcohol.

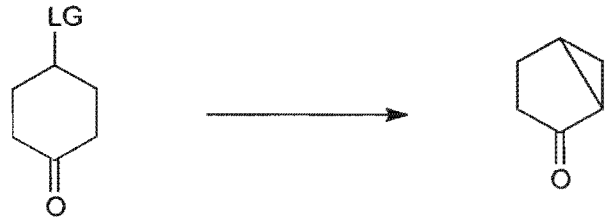
Davies *et al.*[27] reported a similar reaction in the synthesis of 5α,7α-cyclosteroids. The oxo-alcohol **41** was converted to the tosyl ester **42**, which on treatment with 5 % methanolic potassium hydroxide yielded 5α,7α-cyclocholestane **43.**

Crandall and coworkers[28] investigated the transannular cyclisation of 4-hydroxycyclooctanone derivatives such as the tosylate **44**. In this instance base treatment should promote proton removal at either side of the carbonyl group with equal facility. However cyclisation was found to proceed with a kinetic preference for cyclopropane formation, resulting in the formation of bicyclo[5.1.0]cyclooctan-2-one **45** exclusively.



Scheme 2.16

We are unable, however, to find precedent for the conversion of a 4-substituted cyclohexanone **K**, or an embedded variety of this substructure, to a derived bicyclo[3.1.0]hexanoid product **L** (Scheme 2.17). Thus, despite the failure of this approach to meeting our aim of achieving Wharton fragmentation, this investigation has uncovered an unexpected rearrangement pathway leading to a novel polycyclic steroid derivative.



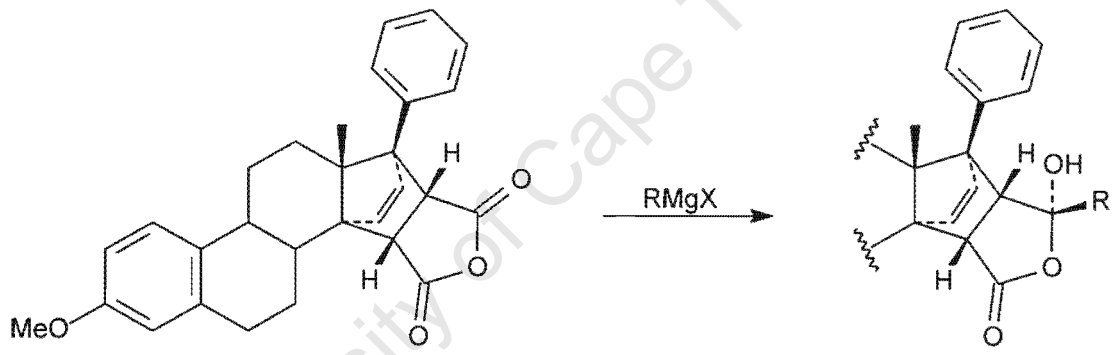
K **L**

Scheme 2.17

Although time did not permit full investigation of this reaction sequence, it is evident that an alternative approach to the desired target would necessitate blockage or modification of the 6'-oxo group in the 3'α-mesylate derivative. This would lead to an intermediate in which the Wharton fragmentation pathway should proceed, in the absence of the competing process.

2.4 Synthesis of 17β-acetoxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-15α,16α-dicarboxylic acid anhydride 48

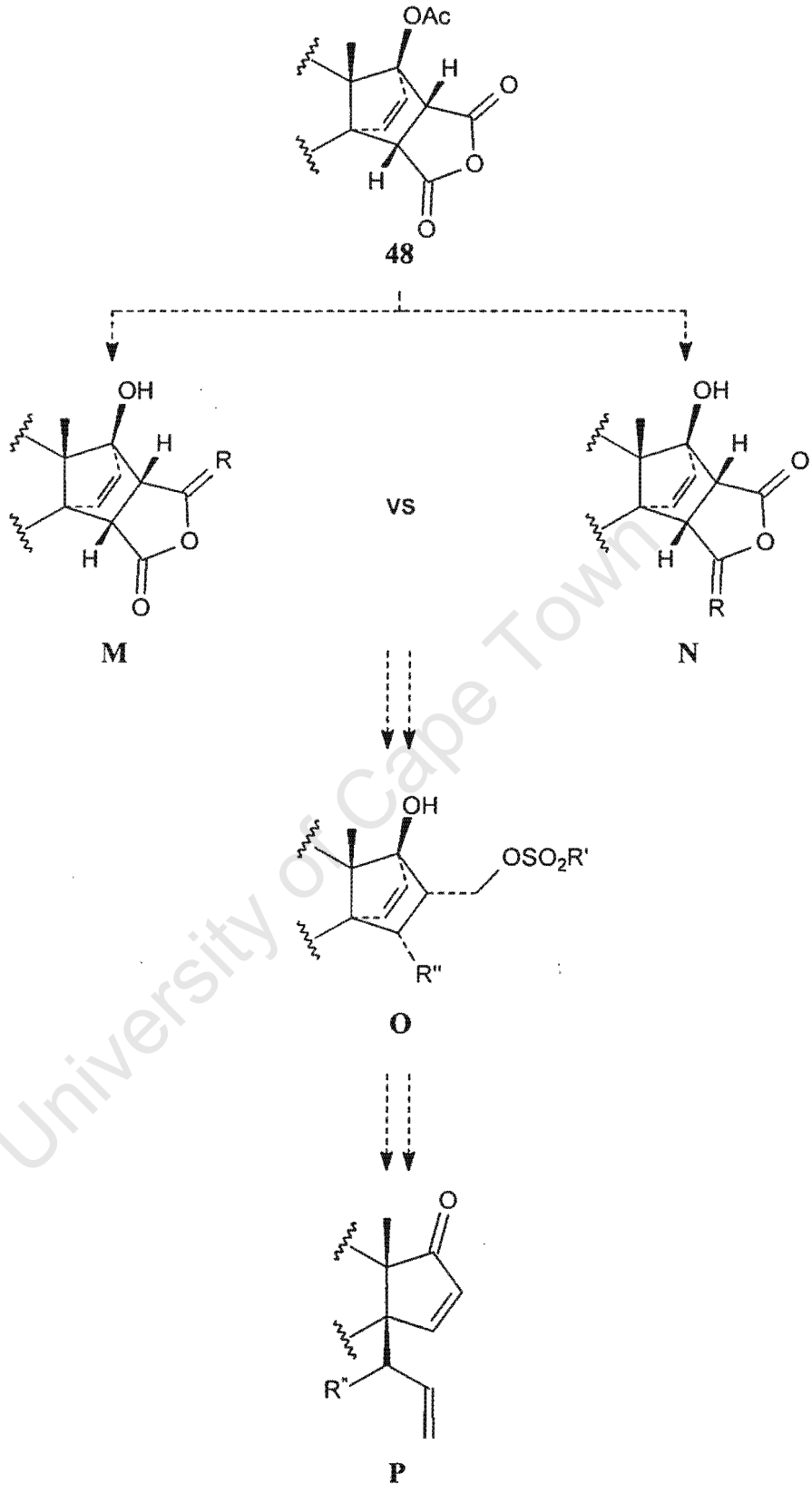
An alternative route towards the desired 14β-aryl target was explored, based on the maleic anhydride cycloadduct. The synthetic strategy was to chemoselectively manipulate the cycloadduct in such a way as to retain the oxygen functionality at the 2' position, in order to secure candidates suitable for Wharton fragmentation. Winterfeldt *et al.*[29] carried out selectivity studies on analogous steroid adducts from symmetrical dienophiles. These cycloadducts were reported to undergo nucleophilic attack at the carbonyl groups with high diastereoselectivity and remarkable chemoselectivity. For example, treatment of steroidal adduct **46** with various Grignard reagents gave rise to adducts of type **47** from preferential attack on the carbonyl group neighbouring the phenyl group (Scheme 2.18).



46 **47**

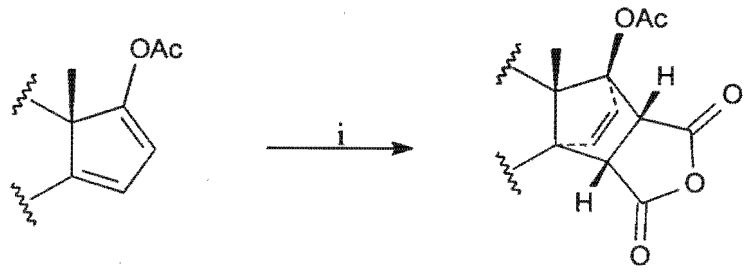
Scheme 2.18

Accordingly, it was decided to adopt a strategy based on hydride reduction of the maleic anhydride moiety. A possible approach could be to manipulate the chemoselectively-modified derivatives **M** or **N** to secure a suitable Wharton fragmentation precursor **O** (Scheme 2.19). Following fragmentation, ways to reconstruct the 14β-cyclohexanoid ring in the intermediate **P** would need to be investigated.



Scheme 2.19

The cycloaddition of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate **7** and maleic anhydride was performed in dry toluene in a sealed tube at 100°C for 16 h. A single, major cycloadduct **48** (91%) was obtained by direct crystallisation of the total reaction product (Scheme 2.20).



7 **48**

Scheme 2.20 *Reagents and Conditions*: (i) maleic anhydride, toluene, 100°C

The assignment was based once again upon the well-documented β-face selectivity in cycloadditions to steroidal 14,16-dienes[9,10] and the expectation of *endo*-orientation of the dienophile.[16] Although spectroscopic evidence failed to furnish unambiguous proof of the assigned stereochemistry, the spectroscopic and analytical data were consistent with the assigned structure. The infrared absorption peaks observed at 1862 and 1783 cm^{-1} are characteristic of cyclic anhydride carbonyl groups,[24] and a band at 1752 cm^{-1} is characteristic of an ester carbonyl group.

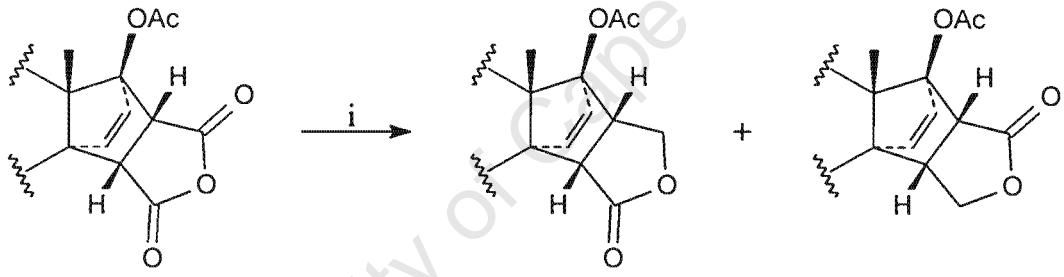
The ^1H NMR revealed two doublets at δ 3.47 (*J* 8.0 Hz) and 3.98 (*J* 8.0 Hz) assigned to 15β-H and 16β-H respectively. The assigments are based on the through-space deshielding influence the proximate 17β-acetoxy group is expected to have on the 16β-H., and were confirmed by the appearance of a correlation in the HMBC spectrum between the C-8 signal and the signal assigned to 15β-H. This corresponds to a three bond coupling, and the alternative assignment of bridge fusion protons would exclude this correlation.

The large coupling of 8.0 Hz displayed by the 15β- and 16β-protons is compatible with an *exo-exo* coupling.[17] Crosspeaks in the HMQC spectrum located the C-15 and C-16 signals at δ 50.5 and 51.4 respectively. The ^{13}C NMR spectrum displayed the expected carbonyl resonances at δ 169.6, 169.7 and 170.6.

2.5 Hydride reduction of the maleic anhydride cycloadduct 48

Having acquired the maleic anhydride cycloadduct in good yield, a preliminary investigation into the chemoselective reactivity of this substrate to hydride reduction was undertaken. There are many reports in the literature of reduction of cyclic anhydrides to lactones by metal hydrides.[30] Unsymmetrically substituted anhydrides can potentially yield two lactones, the distribution of which is determined by a number of factors such as the steric environment and electronic character of the two carbonyl groups as well as the hydride employed and reaction conditions.[31]

Treatment of the cycloadduct **48** with sodium borohydride in tetrahydrofuran at room temperature for 1 h gave a separable mixture of isomeric lactones **49** and **50** in 55 and 25 % yield respectively (Scheme 2.21).



44 **49** **50**

Scheme 2.21 *Reagents and conditions*: (i) $NaBH_4$, THF, 24°C

The infrared spectra of the products **49** (ν_{max} 1884 and 1741 cm^{-1}) and **50** (ν_{max} 1884 and 1762 cm^{-1}) supported the loss of a carbonyl functional group and hence confirmed reduction to γ-lactones had taken place. This was further confirmed in the ^{13}C-NMR spectrum of both products, by the loss of a carbonyl resonance and the appearance of a diagnostic triplet resonance at δ 69.0 associated with the methylene carbon of the lactone rings.

Differentiation of the isomers followed from close analysis of the ^{1}H and ^{13}C NMR spectra, with the aid of COSY, HSQC and HMBC spectra.

In the ^{13}C NMR spectrum of **50,** the singlets at δ 58.7 and 65.6 are characteristic of C-14 and C-13.[32] The former signal displayed crosspeaks in the HMBC spectrum to the methylene proton signals at δ 3.87 and 4.33, as well as to the signal assigned to 8β-H. Based on this

observation, the signal at δ 58.7 was assigned to C-14, and the lactone **50** assigned as that arising from reduction of the 5'-oxo group. The alternative assignment would exclude this correlation as the coupling of C-13 to methylene protons four bonds removed is not expected to be detected in this NMR experiment.

It was possible to differentiate the 5'α-H and 5'β-H by close analysis of the coupling behaviour of the ring D and E protons (refer to Figure 2.6). The methylene proton signals appeared at δ 3.87 (dd, *J* 9.5 and 3.9 Hz) and 4.33 (t, *J* 2 x 9.5 Hz). A crosspeak in the COSY spectrum from these protons located of signal for 15β-H at δ 3.03 (td). The signal displayed a large *exo-exo* coupling to 16β-H (*J* 9.5) and two vicinal couplings (*J* 9.5 and 3.9 Hz) to the 5'-H's. The smaller vicinal coupling constant of 3.9 Hz is indicative of an anticlinal relationship (ϕ ~ 120°) between 15β-H and 5'α-H. This coupling is reflected in the signal at δ 3.87. The larger vicinal coupling constant of 9.5 Hz is indicative of an eclipsed relationship, which is satisfied between 15β-H and 5'β-H (ϕ ~ 0°). This coupling was reflected in the signal at δ 4.33. The signal for 16β-H was located by the crosspeak in the COSY spectrum from the 15β-H signal to a doublet at δ 3.60 (*J* 9.5 Hz).

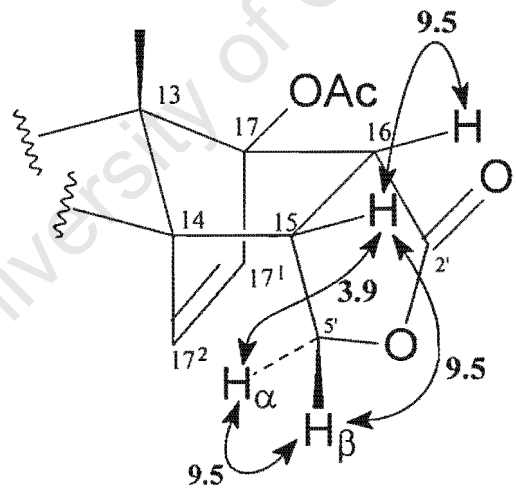


Figure 2.6

Selected *J* values (Hz) for ring D and E protons of **50**

A crosspeak in the HSQC spectrum located C-15 at δ 42.8 and C-16 at δ 51.5. The upfield shift of 7.5 Hz in the C-15 signal is to be expected due to the loss of the α-removed carbonyl group.[24] The signal for C-5' appeared at δ 69.0 (t), while that for C-2' appeared at δ 175.9 (s).

Having unambiguously assigned the structure of **50** as the 16α-carbolactone, it was confidently assumed that **49** was the 15α-carbolactone. In the ^{13}C-NMR spectrum of **49**, the singlets at δ 59.1 and 64.9 were assigned to C-14 and C-13 respectively. This was based on the appearance of a crosspeak in the HMBC spectrum between the signal at δ 59.1 and the signal assigned to 8β-H, which served to identify it as C-14. The fact that no correlations were observed between this signal, or the signal assigned to C-13, and the methylene proton signals further supports the assignment of lactone regiochemistry. A crosspeak from C-14 to a doublet at δ 3.25 (*J* 9.2 Hz) located 15β-H. Its geminal partner 16β-H was located by a crosspeak in the COSY to a triplet of doublets at δ 3.40 (*J* 2 x 9.2 and 4.4 Hz). The 2'-H protons resonated as doublet of doublets at δ 4.28 (*J* 10.7 and 9.2 Hz) and 4.52 (*J* 10.7 and 4.4 Hz). The former signal was assigned to 2'β-H based on its large vicinal coupling (9.2 Hz) to 16β-H, indicative of their eclipsed relationship. The signal at δ 4.52 due to the 2'α-H displayed a smaller coupling (4.4 Hz) consistent with an anticlinal relationship with 16β-H. Figure 2.7 displays the essential couplings of ring D and E protons.

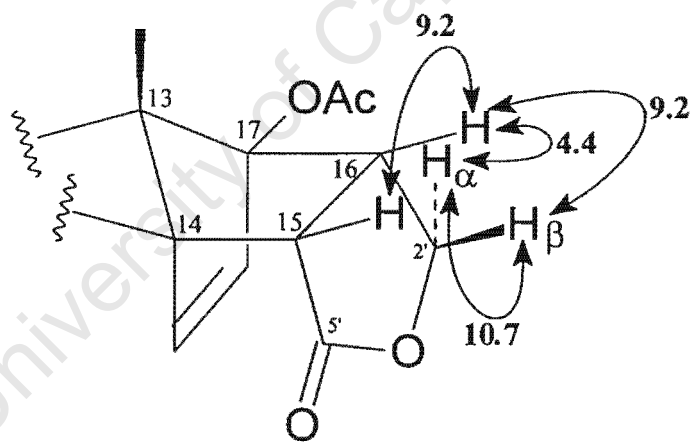
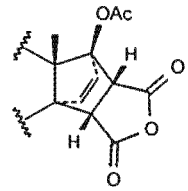
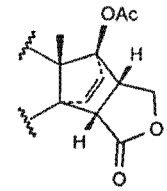
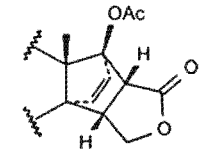


Figure 2.7

Selected *J* values (Hz) for ring D and E protons of **49**

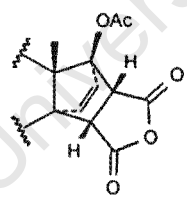
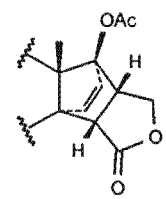
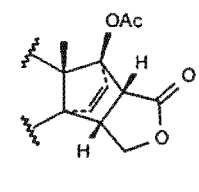
Crosspeaks in the HSQC spectrum located C-15 and C-16 at δ 52.8 and 46.2 respectively. The significant upfield shift in the C-16 resonance of 5 Hz is expected due to the loss of the α-carbonyl. A triplet signal at δ 69.0 was assigned to C-2' and a singlet at δ 176.8 was assigned to C-5'. The important NMR data are summarised in Table 2.7 and 2.8

Table 2.7 Ring D and E ^{13}C NMR Data* for the cycloadduct **48** and the lactones **49** and **50**

Carbon	48 	49 	50 
13	67.1	64.9	65.6
14	61.2	59.1	58.7
15	50.5	52.8	42.8
16	51.4	46.2	51.5
17	94.3	95.0	94.5
2'	169.6†	69.0	175.9
5'	169.7†	176.8	69.0
17^1	130.6‡	133.0	134.1
17^2	133.9‡	133.4	129.6

* quoted as chemical shift (in ppm)
†,‡ interchangeable

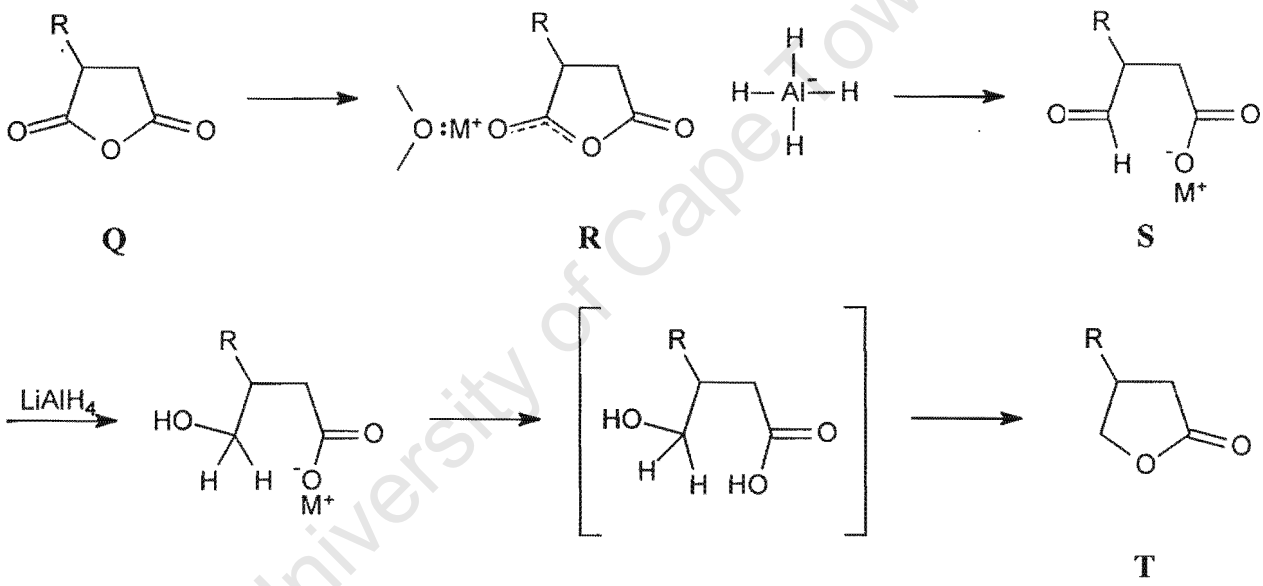
Table 2.8 ^1H NMR Data* for Ring E for the cycloadduct **48**, and the lactones **49** and **50**

Proton	48 		49 		50 	
	δ	*J*	δ	*J*	δ	*J*
15β	3.47	8.0	3.25	9.2	3.03	2 x 9.5 and 3.9
16β	3.98	8.0	3.40	2 x 9.2 and 4.4	3.60	9.5
Hα			4.52	10.7 and 4.4	3.87	9.5 and 3.9
Hβ			4.29	10.7 and 9.2	4.33	2 x 9.5

* chemical shift quoted in ppm and coupling constants in Hz

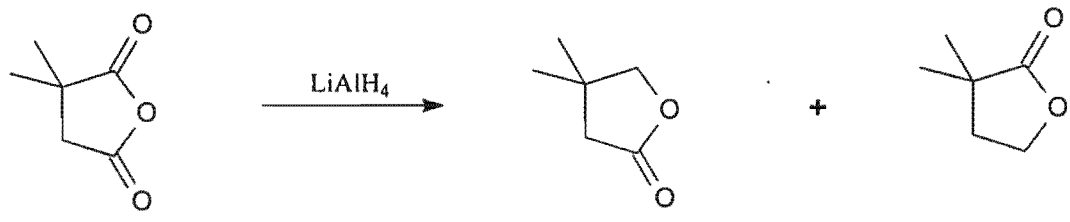
Having successfully assigned the lactones **49** and **50**, we sought to ascertain whether the chemoselectivity could be influenced by using a sterically more demanding hydride reagent. With this intention in mind, it was decided to carry out a reduction with L-Selectride. Treatment of the cycloadduct **48** with this reagent at - 78°C for 2 h, gave rise to **49** and **50** in the ratio 2.6:1, representing only a small improvement in the chemoselectivity observed for the sodium borohydride reduction.

The mechanism of hydride reduction of cyclic anhydrides is postulated to involve the initial activation of one carbonyl group by complexation with the metal cation (**R** in Scheme 2.22).[31a] Hydride delivery to the activated carbonyl group then follows, resulting in ring opening to give the formyl carboxylate **S**. A second equivalent of hydride then reduces the aldehyde function and lactonisation occurs on work-up to give **T**.



Scheme 2.22 Proposed mechanism of cyclic anhydride reduction by metal hydride

The observed trend in metal hydride reductions of unsymmetrically substituted cyclic anhydrides is often, but not always, preferential reduction at the carbonyl group adjacent to the more highly substituted carbon atom.[31-34] Thus the reduction of 2,2-dimethylsuccinnic anhydride **51** with lithium aluminium hydride gave rise to a 19:1 ratio of the 2 possible lactones **52** and **53** (Scheme 2.23).[31c]



49 **50** **51**

Scheme 2.23

Kayser *et al.*[31a] rationalised this trend in terms of the most favourable pathway for non-perpendicular attack by a nucleophile on the carbonyl function. At an approach distance of approximately 2Å, approach to the carbonyl function next to the more highly substituted carbon atom is effectively less hindered than the approach to the carbonyl group adjoining the unsubstituted carbon atom (Figure 2.8). This rationalisation however fails to explain the cases where steric factors are not applicable, such as planar cyclic anhydrides in which both carbonyl functions are equally accessible.[31b]

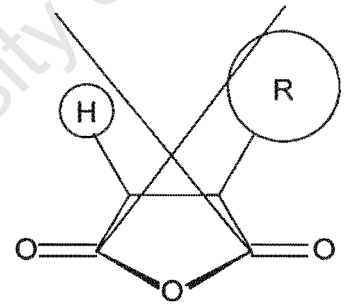
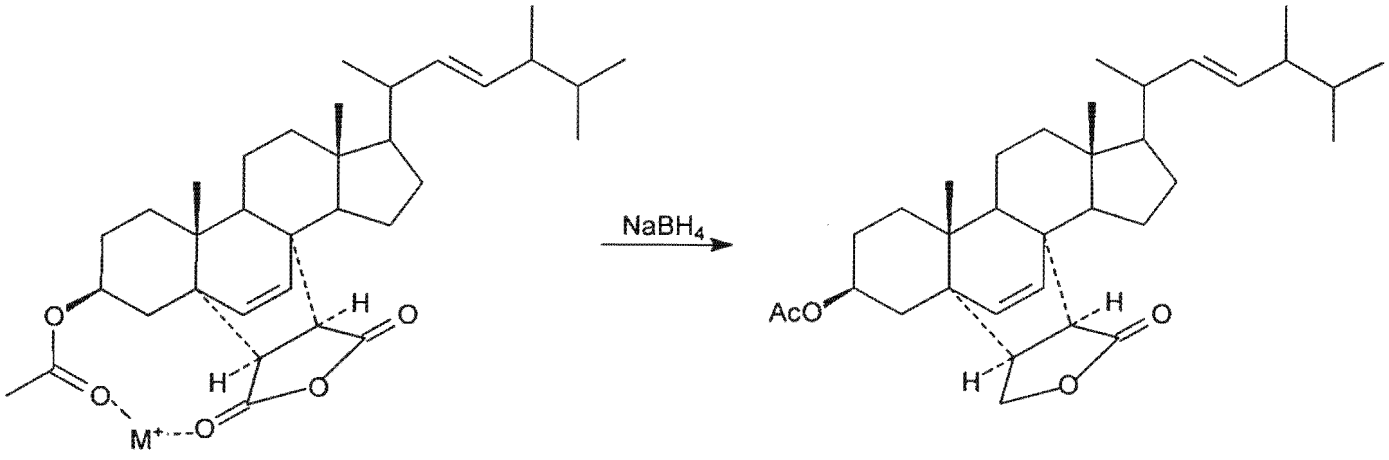


Figure 2.8

The observed pattern was then rationalised by evoking a different electronic character for the two carbonyl groups.[31c] Since electronic effects induce differences in electron availability on the two carbonyl groups, and the attack of the cation occurs preferentially on the oxygen having the most basic, non-bonding electrons, it is not surprising then that the greater reactivity is exhibited by the carbonyl group adjacent to a tertiary atom.

Further examination of the literature, however illustrates that in addition to the intrinsic reactivity of the carbonyl groups and steric congestion, other factors are implicated in the control of chemoselectivity of hydride reductions of cyclic anhydrides.[31] These include the possibility of antiperiplanar attack, nature of the cation and possibility of chelate formation. The observed selectivity is the net result of the interplay between these factors.[31]

It has been shown in bridged systems analogous to the maleic anhydride cycloadduct **48,** that the nucleophile adds only from the "convex" face of the molecule, as attack from the concave side is prevented by the π electrons of the double bond.[35] The anhydride ring of the cycloadduct **48** is rigidly planar due to its attachment to a bridged system and the carbonyl groups do not differ significantly from each other in steric accessiblity to the β-face. Therefore on the basis of steric hindrance, no chemoselectivity would be expected. The observed slight preponderance for lactone **49** over **50** in the hydride reduction could be interpreted in terms of the directing influence of the 17β-acetoxy group. It appears from examination of models that the 17β-acetate carbonyl group is able to participate readily with the 2'-oxo group and a reagent cation in an intramolecular chelated species. This chelate formation activates the implicated carbonyl group towards hydride transfer resulting in its preferential reduction. Indeed Le Quesne *et al.*[36] invoked a similar mechanism involving a solvated intramolecular species to explain the high degree of selectivity observed for metal hydride reduction of the Inhoffen adduct of ergosterol acetate and maleic anhydride **54** (Scheme 2.24). The importance of this chelation effect was confirmed by the diminished chemoselectivity displayed by the 3β-methoxy analogue in similar anhydride reductions. The methoxy substituent clearly has less of a directing influence than the acetoxy substituent.

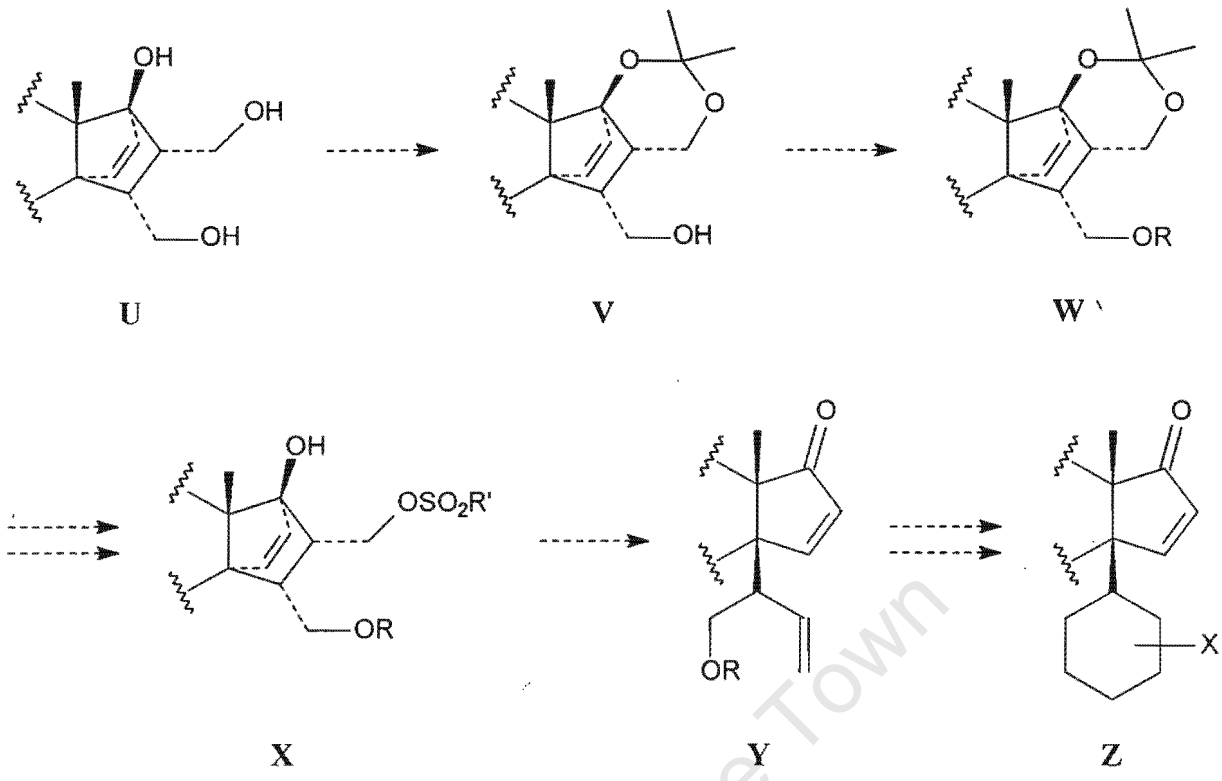


54 **55**

Scheme 2.24

The effect of the nature of counterion on this chelate formation was also recognised.[36] A lesser selectivity in the sodium aluminium hydride reduction of the Inhoffen adduct **54**, compared with the lithium aluminium reduction, was explained in terms of the lesser solvation of the sodium cation in the complex. The more mobile (higher solubility) and more available (solvent separated) lithium cation can form the activated complex more readily and assist in hydride transfer more effectively to the activated carbonyl group. The latter argument would explain the slight enhancement in chemoselectvity observed in the L-Selectride reduction of the maleic anhydride adduct **48**, when compared to the sodium borohydride process.

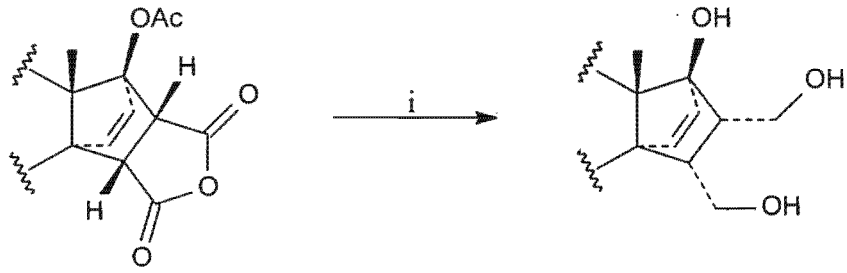
While this reduction reaction indicates access to differentiated derivatives, which could be appropriately manipulated to secure a candidate for Wharton fragmentation, this route was not pursued further. Instead the prospect of obtaining the triol **U** from exhaustive reduction of the cyclic anhydride encouraged the expectation that a synthetic route such as that outlined in Scheme 2.25 would provide facile access to a fragmentation precursor, ultimately leading to a desired 14β-cyclohexanoid substituted analogue.



Scheme 2.25

The scheme is based upon the assumption that formation of a six-membered 17β,16[1]-acetonide **V** should be favoured, allowing for differentiation of the primary alcohol groups. The free hydroxy group can then be selectively protected to give **W**, before deprotection of the acetonide. Sulfonylation of the free 16[1]-hydroxy gives the intermediate **X**, which is suitably set up for Wharton fragmentation. The expected fragmentation product **Y** can then be manipulated in such a way as to reconstruct a 14β-attached cyclohexanoid or benzenoid ring, giving the desired target **Z**.

Treatment of the maleic anhydride cycloadduct **48** with lithium aluminium hydride in tetrahydrofuran under reflux for 5 h, gave rise to a single, polar product. In order to avoid an aqueous work-up, the reaction was quenched with the minimum amount of water in triethylamine, followed by filtration through Celite, to remove all aluminum salts. Purification of the crude by chromatography gave rise to the 17β,15[1],16[1]-triol **56** in 72 % yield (Scheme 2.26). Spectroscopic and microanalytical data were consistent with the proposed structure. Due to the relative insolubility of **56** in most solvents, its NMR spectra were obtained by dissolution in deuteriopyridine.



46 **56**

Scheme 2.26 *Reaction conditions*: (i) $LiAlH_4$, THF, Δ

The essential coupling data of the ^{1}H NMR spectrum are displayed in Figure 2.9. The 15β- and 16β-proton signals appeared at δ 2.97 (ddd, *J* 10.3, 9.9 and 2.8 Hz) and 3.27 (ddd, *J* 10.3, 10.0 and 3.8 Hz) respectively. A crosspeak in the COSY spectrum from the 15β-H signal located the 15^1-methylene protons at 3.88 (t) and 4.31 (dd). Similarly, the 16^1-methylene protons were located at 4.18 (t) and 4.56 (dd).

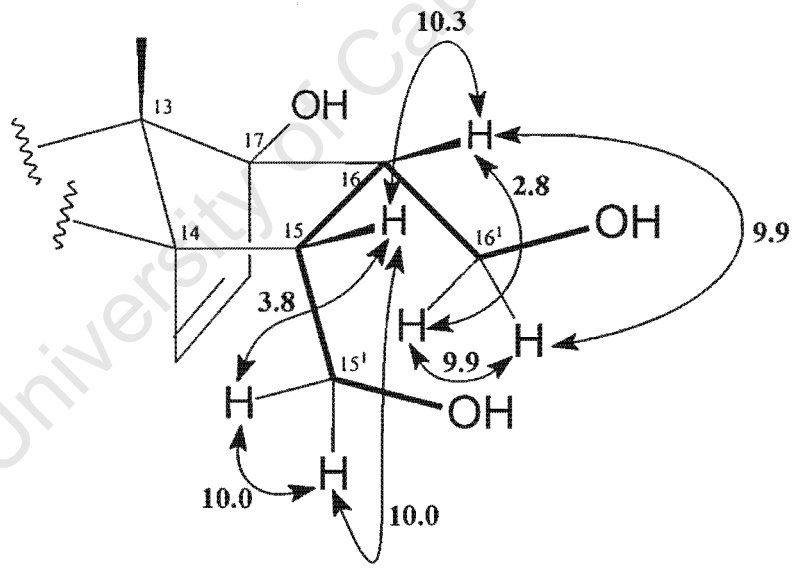


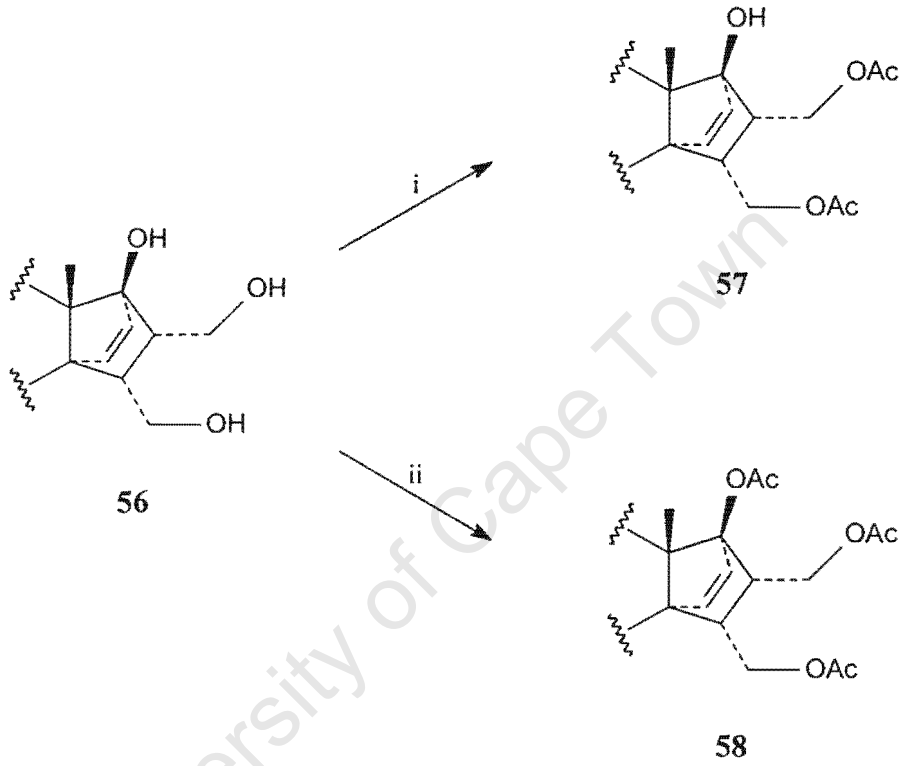
Figure 2.9

Selected ^{1}H NMR *J* values (Hz) for the triol **56**

The ^{13}C NMR spectrum displayed the expected methylene signals at δ 61.2 and 62.1, which were assigned to C-15^1 and C-16^1 respectively on the basis of crosspeaks in the HSQC spectrum to the respective methylene protons. The doublet resonances at δ 51.2 and 51.3 were similarly assigned to C-16 and C-15 respectively. The C-17 resonance appeared at δ 90.6,

shifted ~ 4 ppm upfield from the corresponding signal in the cycloadduct **48**. This is consistent with deacetylation

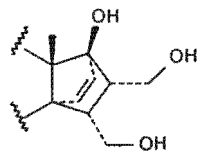
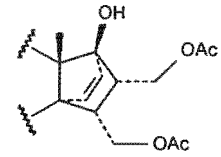
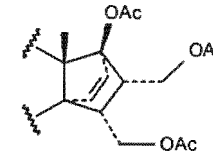
In order to be able to make meaningful comparisons of NMR data of the triol **56** with subsequent compounds, the $15^1,16^1$-diacetate **57** and $17\beta,15^1,16^1$-triacetate **58** were synthesised and their NMR spectra recorded in deuteriochloroform. (Scheme 2.27).



Scheme 2.27 *Reaction conditions*: (i) Ac_2O, py; (ii) Ac_2O, py, DMAP

The spectroscopic and analytical data were consistent with the assigned structures. The essential ^1H NMR data of the triol **56**, diacetate **57** and triacetate **58** are summarised in Table 2.9.

Table 2.9 Selected ^{1}H NMR data* for **56**, **57** and **58**

	56 (C_5D_5N) 	**57** 	**58** 
15β-H	2.97	2.65	2.57
	ddd, J 10.3, 9.9 and 2.8	td J 2 x 9.0 and 3.0 Hz	td J 2 x 8.5 and 3.4 Hz
16β-H	3.27	2.70	2.96
	ddd J 10.3, 10.0 and 3.8	obsc m	dt J 8.5 and 2 x 6.6
15^1-H_a	3.88	3.65	3.77
	t J 2 x 9.9	dd J 12.0 and 9.0	dd J 12.2 and 8.5
15^1-H_b	4.31	4.45	4.38
	dd J 9.9 and 2.8	dd J 12.0 and 3.0	dd J 12.2 and 3.4
16^1-H_a	4.18	4.17	4.06
	t J 2 x 10.0	dd J 11.3 and 7.4	dd J 11.5 and 6.6
16^1-H_b	4.56	4.27	4.19
	dd J 10.0 and 3.8	dd J 11.3 and 5.7	dd J 11.5 and 6.6
17^1-H	6.17	6.03 †	6.06 †
	d J 6.1	d J 6.2	d J 6.3
17^2-H	6.03	6.08 †	6.47 †
	d J 6.1	d J 6.2	d J 6.3
-OH	4.84, 6.37 and 6.48	1.61	-
OAc	-	2.05 and 2.08	2.04, 2.05 and 2.09

* quoted as chemical shift (in ppm), multiplicity and coupling constants (in Hz)
† interchangeable

As the triol **56** was a key intermediate in the proposed reaction sequence, a synthetically more efficient reduction was sought to afford improved yields. The experience with using LAH was that work-up complications resulted in unavoidable loss of material. Sodium-bis-(2-methoxyethoxy)aluminiumhydride, or Red-Al, was therefore considered as an alternative hydride reagent, as reports indicated this reagent displayed reducing abilities comparable to LAH.[37] In addition it has favourable qualities associated with it, such as its increased stability in air and solubility in aromatic hydrocarbons.[37] Treatment of the cycloadduct **48** with Red-Al

in refluxing tetrahydrofuran for 20 h resulted in conversion to the triol **56** in 90 % yield. Furthermore, the product was directly crystallised from the reaction mixture, thus circumventing chromatography, which was complicated due to the insolubility of the product in most organic solvents. This improvement in yield was encouraging and made this the reagent of choice.

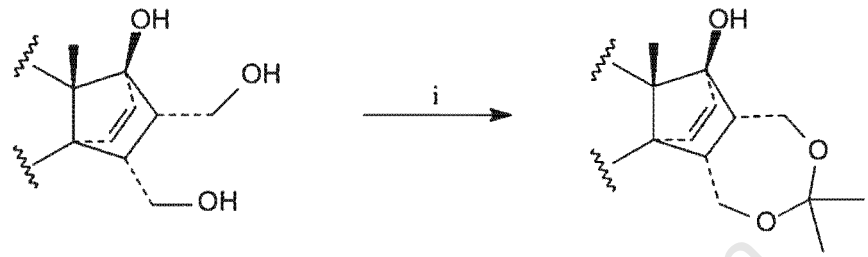
2.6 Chemoselective reactions of the 15^1,16^1,17β-triol 56

In order to implement the proposed scheme, selective protection of the 17β,16^1-diol in a cyclic acetal was attempted. The use of cyclic acetals for the specific protection of diol functions in polyhydric alcohols is prevalent.[38,39] In particular, the cyclic isopropylidene acetal, or acetonide, is the most commonly used protection for diol functions, particularly in carbohydrate chemistry.[39] In preparing acetonides of polyhydric alcohols where it is possible for 5-, 6- and 7-membered rings to form, a definite order of preference is usually observed. Barker *et al.*[40] studied the stereochemical factors which govern the preferential formation of a particular ring size when more than one is possible, and presented a set of empirical rules for predicting the product when preparing acetonides of polyhydric alcohols. In general 1,2-acetonides are formed in preference to 1,3-acetonides, but the extent to which the 1,2-derivative is favoured is dependent on structure. 1,4-acetonides have also been reported,[41] but they rank very low in the order of preference.

The 1,3-disposition of the 17β- and 16^1-hydroxyl groups of the triol **56** encouraged the expectation that the six-membered 17β,16^1-*O*-isopropylidene should form in preference to a seven-membered 1,3-dioxepan ring from the 1,4-disposed 15^1,16^1-hydroxy groups.

A commonly used procedure for preparation of isopropylidene derivatives of polyols is the acid catalysed exchange with 2,2-dimethoxypropane.[42] An advantage of this method is the small proportions of acid required to catalyse the reaction, allowing neutralisation to be affected simply. Furthermore, there is no need to displace the equilibrium by removing methanol from the mixture, although it is possible to do so. Our first attempt to effect acetonide formation utilised this methodology.

Treatment of the triol **56** with excess dimethoxypropane and catalytic *p*-toluenesulfonic acid in dry dichloromethane proceeded to give rise to a single product (TLC), however failed to go to completion. The use of 4Å molecular sieves to selectively absorb the methanol formed in the reaction resulted in complete conversion to a single product **59** in 75 % yield. (Scheme 2.28).



56 **59**

Scheme 2.28 *Reaction conditions*: (i) 2,2-dimethoxypropane, CH_2Cl_2, TsOH, 4Å molecular sieves

All spectroscopic and analytical data were consistent with a mono-isopropylidene derivative of the triol **56**. The mass spectrum displayed the expected molecular ion of M^+ 478 and the infrared spectrum revealed a broad absorption peak at 3449 cm^{-1} due to the hydroxy group. The ^1H NMR spectrum displayed a singlet at δ 1.37, integrating for six protons, distinctive of the acetonide methyl groups. Similarly the ^{13}C NMR spectrum revealed signals at δ 20.2(q) and 29.3(q) assigned to the acetonide methyl groups, and a singlet resonance at δ 101.3 assigned to the acetal carbon. Preliminary analysis of the spectroscopic data did not allow us to ascertain whether the 1,3- or 1,4-acetonide has formed. However closer scrutiny of these signals gave insights into ring size and configuration. Indeed Buchanan *et al.*[43-45] demonstrated that for a series of carbohydrate isopropylidene acetals of known structure, the ^{13}C chemical shifts of the acetal carbon and the methyl groups show a clear correlation with the acetal ring size and can even render further information on ring fusions and conformations. The results of this study are summarised in Table 2.10.

Table 2.10 Correlations of ^{13}C chemical shift for carbohydrate isopropylidene acetals

Ring size	Acetal carbon	Methyl carbons	Δδ (methyl carbons)
5	**108.1 – 111.4** (monocyclic or cis-fused to pyranoid or cyclohexane ring) **111.8 – 112.3** (trans-fused to pyranoid or cyclohexane ring) **111.3 - 115.7** (fused to furanoid ring)	**23.3 – 28.2**	**0.0 – 4.3**
6	**97.1 – 99.9** (chair form)	**18.2 – 19.3 and 28.6 – 29.2**	**9.8 – 10.9**
	100.6 – 101.1 (skew form)	**23.5 – 24.5**	**0.0 – 0.9**
7	**100.8 – 102.3**	**23.5 – 28.3**	**0.0 – 3.8**

The acetal carbon signal of **59** appeared at δ 101.3, which falls into the range for a six-membered 1,3-dioxane ring (skew form) as well as the range for a seven-membered 1,3-dioxepan ring. On this basis alone it is not possible to distinguish between the two. However, for the skew 1,3-dioxane ring, the methyl signals are almost equivalent, displaying a chemical shift separation of no more than 1 ppm. The methyl signal separation observed for **59** is 9.1 ppm, which then excludes the skew six-membered acetal ring. On this basis, the structure was tentatively assigned as the 15^1,16^1-*O*-isopropylidene derivative **59**, despite the fact that the methyl carbon signal separation was larger than is reported in Table 2.10. It is recognised that the results in the above table for seven-membered acetal rings were based on monocyclic 1,3-dioxepans. The greater constraint in bicyclic systems would be expected to result in a greater difference in chemical shift of these carbons.

The appearance of the C-17 resonance at δ 90.1, unshifted from its position in the triol **56** (δ 90.2) and the 15^1,16^1-diacetate **57** (δ 91.1) confirmed that the 17β-hydroxy group was still intact. The essential ^1H NMR coupling data of the acetonide ring protons are displayed in Figure 2.10.

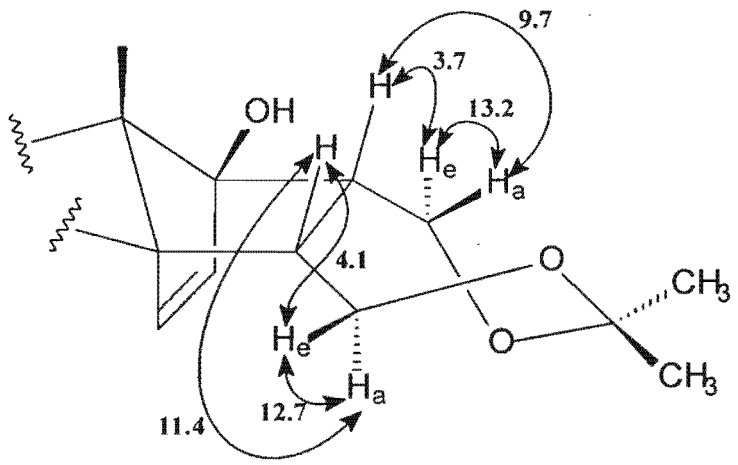


Figure 2.10

Selected ^{1}H NMR *J* values for 15^1,16^1-*O*-isopropylidene 17β-hydroxy **59**

The methylene proton resonances of the dioxepan ring were observed as doublet of doublets at δ 3.58, 3.71, 3.92 and 4.00. Their splitting patterns were consistent with a large geminal coupling and a vicinal coupling to its adjacent bridge proton. The non-equivalence of the vicinal coupling displayed by each of the geminal pairs to the bridge proton indicates that rather than being conformationally flexible, the seven-membered ring is fairly rigid in structure. A conformation which appears to be compatible with the coupling data is the twist-boat, as has been indicated in Figure 2.10. (Further support for this proposed conformation follows on page 54) The data were interpreted as follows:

The signal at δ 3.58 (*J* 12.7 and 11.4 Hz) and 4.00 (*J* 12.7 and 4.1 Hz) were assigned to the 15^1-H's by analogy to the diacetate **57** and triacetate **58**. The vicinal coupling of 11.4 Hz displayed by the former signal is characteristic of an antiperiplanar relationship with the 15β-H and was assigned to 15^1-H$_a$. The signal at δ 4.00 was assigned to 15^1-H$_e$, the vicinal coupling of 4.1 Hz indicative of a synclinal relationship to 15β-H.

The signals at δ 3.71 (dd, *J* 13.2 and 9.7 Hz) and 3.92 (dd, *J* 13.2 and 3.7 Hz) were assigned to the 16^1-H's. The vicinal coupling of the former signal is consistent with an eclipsed relationship to 16β-H, and was assigned to 16^1-H$_a$. The latter signal displayed a vicinal coupling consistent with a synclinal relationship to 16β-H and was assigned to 16^1-H$_e$.

Crosspeaks in the COSY spectrum from the methylene protons to a unresolved multiplet centered at δ 2.80 located the signals for 15β- and 16β-H. Full assignment of these signals was prohibited due to the superposition of the 6-H's.

The signals due to C-15^1 and C-16^1 were located by crosspeaks in the HSQC spectrum to δ 64.2 and 61.8 respectively. This downfield shift observed for these signals is consistent with their participation in the acetal linkages.

The first order character of the highfield resonances made it possible to unambiguously assign the ring B and C protons, with the additional aid of the COSY and HSQC spectra.

The essential features of the ^{1}H NMR are summarised in Table 2.11

Table 2.11 ^{1}H NMR data for the 15^1-16^1-*O*-isoproylidene **59**

δ/ppm	Integration	Mult.	*J*/Hz	Assignment
1.14	1H	ddd	13.1, 4.1 and 2.5	12β-H
1.36	1H	m	$W_{1/2}$ 43.3	11β-H
1.51	1H	td	2 x 11.7 and 2.8	8β-H
1.62	1H	dddd	2 x 11.7, 10.6 and 6.1	7α-H
1.96	1H	dddd	11.7, 5.7 and 2 x 2.8	7β-H
2.08	1H	td	2 x 13.1 and 4.3	12α-H
2.22	1H	dddd	13.4, 2 x 4.3 and 2.7	11α-H
2.44	1H	td	2 x 11.7 and 4.3	9α-H
2.71-2.89	4H	m	-	6α-,6β-,15β-,16β-H
3.58	1H	dd	12.7 and 11.4	15^1_n-H
3.71	1H	dd	13.3 and 9.7	16^1_n-H
3.92	1H	dd	13.0 and 3.7	16^1_x-H
4.00	1H	dd	12.7 and 4.1	15^1_x-H

The conformational properties of 1,3-dioxepan and its derivatives are expected to be rather similar to those of cycloheptane. Calculations have shown that there are four minimum-energy conformations of cycloheptane.[46] These are the twist-chair (TC), the chair (C), the twist-boat (TB) and the boat (B) (See Figure 2.11).

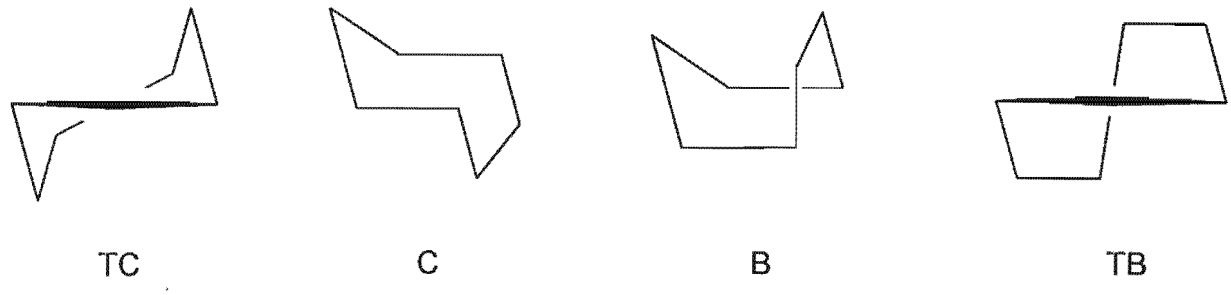
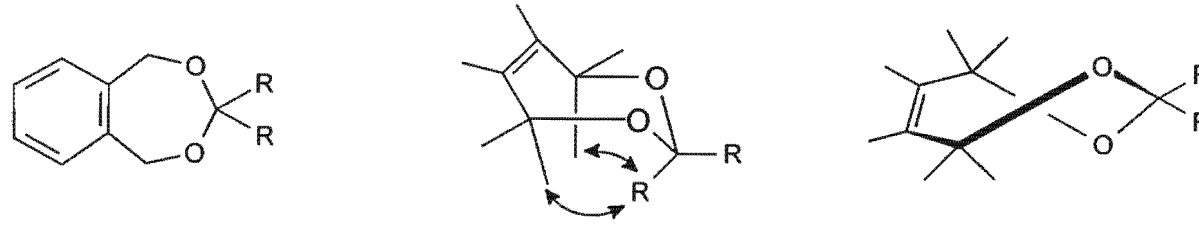


Figure 2.11

Various studies on the conformational behaviour of substituted seven-membered ring heterocycles using ^{1}H and ^{13}C dynamic NMR indicate that while most molecules exist as C forms, those containing the acetal function and the extremely crowded derivatives adopt predominantly the TB form.[47] The greater flexibility of the TB conformation allows for structural distortions in order to minimize strong nonbonding interactions, particularly the severe 4,7-diaxial interactions, otherwise present in the C conformation.

Work by St-Jacques and co-workers[48] in this area has shown that the introduction of an ortho-benzo group into the 1,3-dioxane ring, leading to the dioxepin family of heterocycles **60**, stabilizes the TB conformation significantly. Furthermore it was observed that the presence of two geminal substituents at the 2 position also stabilizes the TB form relative to the C form. In the TB form, these substituents occupy sterically less demanding isoclinal positions, in this way alleviating the destabilizing 1,3-diaxial CH_3-H interactions present in the chair form (see Figure 2.12).



60

R = H, OMe or CH_3

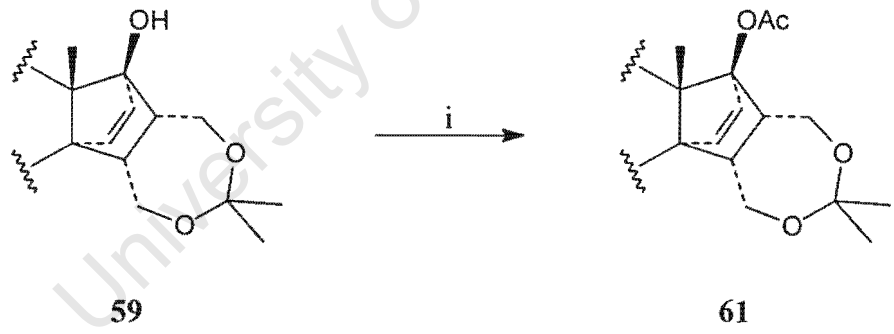
C

TB

Figure 2.12

In light of the foregoing statements and the similarity of the 2,2-dimethyl-1,3-dioxepin to the *cis*-fused dioxepan ring in **59**, it seems likely that that the TB conformation is the more stable one. This is in agreement with the foregoing analysis of the acetonide-ring coupling data, which appeared consistent with such a geometry. However, it is recognised that this may not be the only interpretation.

In order to establish unequivocally that **59** was indeed the $15^1,16^1$-*O*-, and not the 16^1,17β-*O*-isopropylidene derivative, it was subjected to mild acetylating conditions (Ac_2O, py), under which tertiary hydroxy groups are not usually acetylated. After 24 h at room temperature the mixture remained unchanged, and only after further stirring for 72 h did trace of a less polar product start emerging. This indicates that the free hydroxy group is probably tertiary and therefore that the 17β-OH is intact. The addition of catalytic 4-(dimethylamino)pyridine (DMAP) to acetylation reactions enhances the acetylation rate by a factor of 10^4 and makes the acetylation of tertiary hydroxyl groups possible in reduced reaction times.[38] Indeed, treatment of **59** with acetic anhydride, pyridine and DMAP at room temperature gave rise to the $15^1,16^1$-*O*-isopropylidene-17β-acetate **61** after 17 h in 91 % yield (Scheme 2.29).

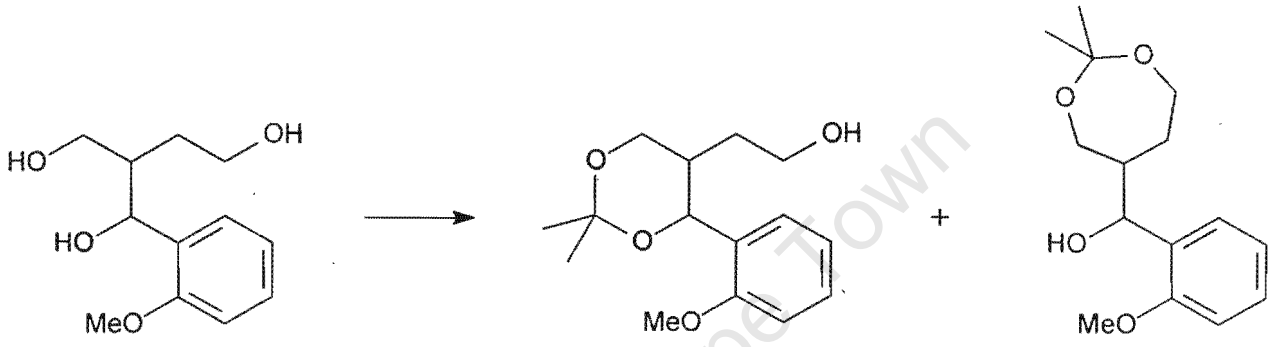


59 **61**

Scheme 2.29 *Reaction Conditions*: (i) Ac_2O, py, DMAP

The expected molecular ion was observed (M^+ 452), and the appearance of a peak at 1737 cm^{-1} in carbonyl region of the infrared spectrum confirmed the presence the acetoxy group. The ^1H and ^{13}C NMR spectra of the $15^1,16^1$-O-isporopylidene-17β-acetate **61** displayed similar characteristics to **59**. A noteworthy feature of the ^{13}C spectrum was the downfield shift observed in the C-17 resonance from δ 90.1 in **59** to δ 94.0 in **61**, characteristic of acetylation at this position.

The fact that the seven-membered 15^1,16^1-*O*-isopropylidene derivative is the only product from the acetonide reaction under these conditions is not remarkable. Brewster and Leach[41] reported the formation of the expected 1,3-dioxane **63** as well as an equal amount of the isomeric 1,3-dioxepane **64** when using dimethoxypropane and *p*-toluenesulfonic acid for ketalising the triol **62** (Scheme 2.30). Furthermore, numerous reports have demonstrated that the use of dimethoxypropane as acetalising agent can give rise to strained and otherwise inaccessible cyclic acetal derivatives.[49,50] The unique acetalising properties of this reagent are attributed to reaction under kinetic control.



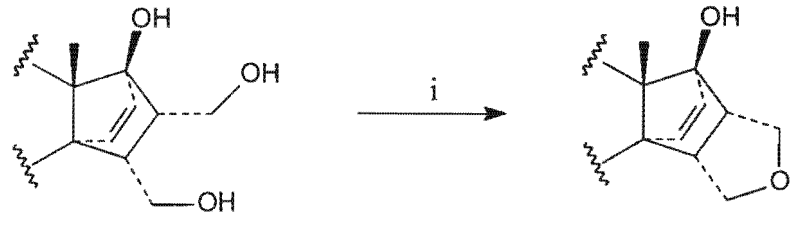
62 **63** **64**

Scheme 2.30

This outcome however does not allow for chemodifferentiation of the 15^1- and 16^1-hydroxy groups, which had been the original intent. In order to see whether the desired 17,16^1-*O*-isopropylidene derivative could be obtained under equilibrating conditions, the classic method of isopropylidenation using acetone and *p*-toluenesulfonic acid, in the presence of copper(II)sulfate was attempted.[50] The thermodynamic product is reported to prevail under these conditions.

Treatment of the triol **56** with acetone, *p*-toluenesulfonic acid and copper(II)sulfate at room temperature proceeded slowly, with the emergence of a single, less polar product (TLC). However prolonged reaction did not result in complete conversion of starting material. Attempts to drive the reaction to completion were made by increasing the reaction temperature, and after heating under gentle reflux for 19 h, the reaction was complete (TLC). A single crystalline compound was isolated in 65 % yield after column chromatography.

The expected molecular ion for a mono-isopropylidene derivative (M^+ 410) was not observed, but rather a peak at 352. Close examination of all spectroscopic and analytical data resulted in formulation of the product as that from dehydration of the triol, giving the tetrahydrofuran derivative **65** (Scheme 2.31).



56 **65**

Scheme 2.31 *Reaction conditions*: (i) acetone, TsOH, $CuSO_4$, Δ

In view of the fact that tetrahydrofuran derivatives are synthesised by acid catalysed dehydration of 1,4-dihydroxybutane and derivatives thereof,[51] this result is not surprising.

In the ^{1}H NMR spectrum the signal at δ 3.08 (td, *J* 2 x 8.3 and 3.2 Hz) was assigned to 16β-H. Its splitting pattern is compatible with a large geminal coupling to 15β-H, a large vicinal coupling to the eclipsed 2'β-H and a smaller vicinal coupling to the synclinal 2'α-H. The signal due to 15β-H was obscured by the 6-H_2 multiplet centered at δ 2.88 preventing additional coupling data from being elucidated. On the basis of the vicinal couplings displayed by the methylene protons, the signals at δ 3.67 (dd, *J* 9.4 and 7.5 Hz) and 3.69 (dd, *J* 9.2 and 8.1 Hz) were assigned to the β-orientated protons, while those at δ 3.54 (dd, *J* 9.2 and 3.6 Hz) and 3.67 (obsc dd) were assigned to the α-orientated protons.

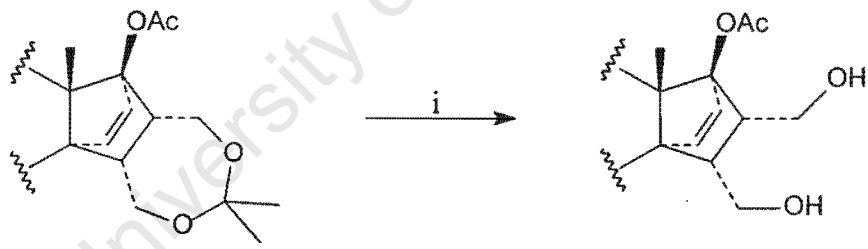
Of interest in the ^{1}H NMR spectrum is the significant upfield shift of the resonance assigned to 7β-H from δ 2.68 in the cycloadduct **46** to δ 1.69 in the tetrahydrofuran derivative **65**. This shift is to be expected on account of the absence of the 5'-carbonyl group, which has a through-space deshielding effect on 7β-H in cycloadduct **46**. Comparison of the ^{13}C spectrum of this compound with that of the triol **56** shows a substantial downfield shift of ~ 8Hz in the

methylene carbon signals to δ 68.0 and 69.7. This is characteristic of the change from hydroxy to ether functionality.

Given the lack of success in differentiating the primary hydroxy groups in the foregoing reactions, it was decided to abandon this line of approach. Rather an investigation into the scope for selectively protecting one of the primary hydroxy groups was undertaken. It was hoped that the use of bulky reagents, such as *p*-toluenesulfonyl chloride, would enhance the chemoselectivity of the process.

Cleavage of the acetonide of the acetoxy 16^1,17-*O*-isopropylidene **61** was first carried out. The reagent system, iodine and methanol, has been reported to achieve this deprotection highly efficiently and under conditions mild enough to be employed in the presence of other protecting groups, including acetoxy groups.[52] The work-up involves reducing the excess iodine with sodium thiosulfate.

A solution of **61** in 0.5 % iodine / methanol (w/v) was stirred for 3 h at room temperature, giving rise to the 15^1,16^1-diol-17β-acetate **66** in 76 % yield (Scheme 2.32).



61 **66**

Scheme 2.32 *Reaction conditions*: (i) 0.5% I_2/MeOH, RT

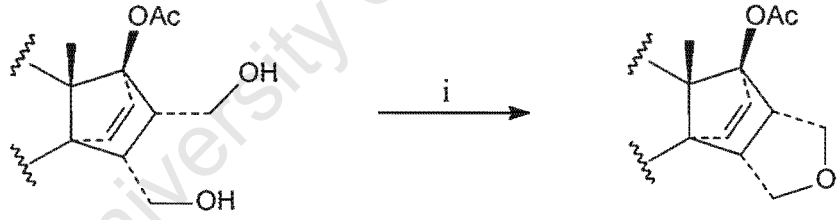
The appearance of the expected molecular ion M^+ 412 confirmed that cleavage of the acetonide had occurred. The infrared spectrum displayed a characteristic absorption band at 3438 cm^{-1} for the hydroxy groups, while the absorption band at 1736 cm^{-1} for the carbonyl group confirmed that the 17β-acetoxy group was intact.

In the ^{1}H NMR spectrum, the splitting patterns of the bridge protons and methylene protons were essentially the same as those in the ^{1}H NMR spectrum of the triacetate **58**.

Comparison of the ^{13}C chemical shift data of the triacetate **59** and acetoxy diol **66** indicates an upfield shift of ~ 2 ppm for the methylene carbons to δ 60.5 and 62.3, while the signal for C-17 resonated at a similar chemical shift of δ 94.6. This confirms the presence of the 17β-acetoxy group.

The acetoxy diol **66** was then treated with *p*-toluenesulfonyl chloride in pyridine at 0°C, and the reaction closely monitored by TLC. The formation of a major, less polar product as well as a minor product of intermediate R_f, became evident after 30 min. Stirring for a further 42 h at 0°C resulted in the accumulation of the major product and disappearance of the minor. However starting material was still evident. Stirring for a further 100 h at room temperature however did not result in depletion of the remaining starting material. The single product **67** was isolated in 41 % yield and starting material was recovered in 30 % yield.

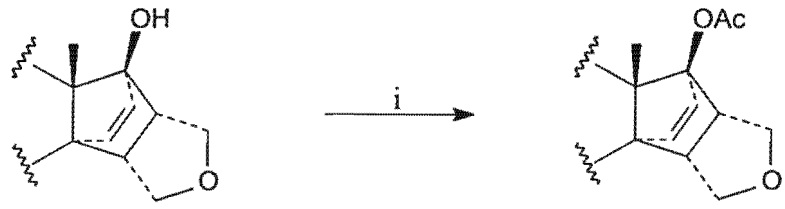
The presence of a molecular ion M^{+} 394 indicated that rather than tosylation having taking place, a loss of water to form the 15α,16α-tetrahydofuro-17β-acetate **67**, had occurred. (Scheme 2.33)



66 **67**

Scheme 2.33 *Reaction Conditions*: (i) TsCl, py

In order to confirm unequivocally that this was indeed the structure, the 15α,16α-tetrahydrofuro-17β-hydroxy derivative **65** was acetylated using standard conditions (Scheme 2.34), giving rise to a product in 79 % yield, whose spectroscopic and analytical data were identical to that of the 17β-acetoxy tetrahydrofuran derivative **67**.



65 **67**

Scheme 2.34 *Reaction Conditions*: (i) Ac_2O, py, DMAP

The ^1H NMR spectrum of **67** was similar to that of **65**. Full assignment of the methylene proton signals was restricted by their coincidental chemical shift equivalence. Greater dispersion of these signals was obtained when the ^1H spectrum was recorded in deuteriobenzene. The essential ^1H coupling data for ring D and E are displayed in Figure 2.13.

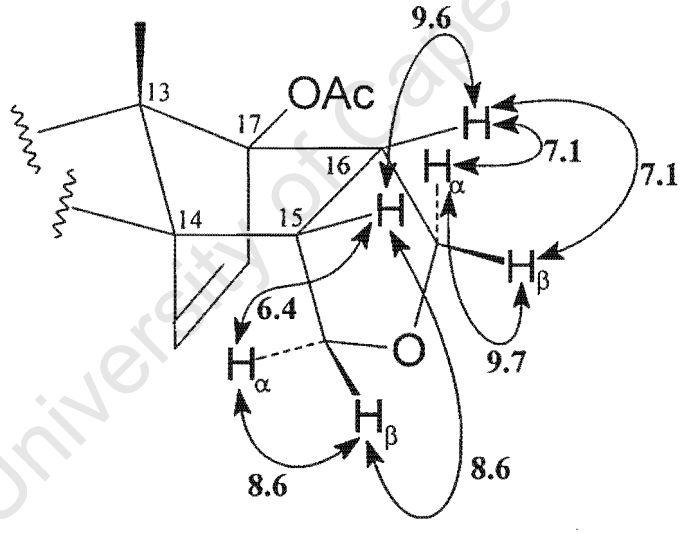
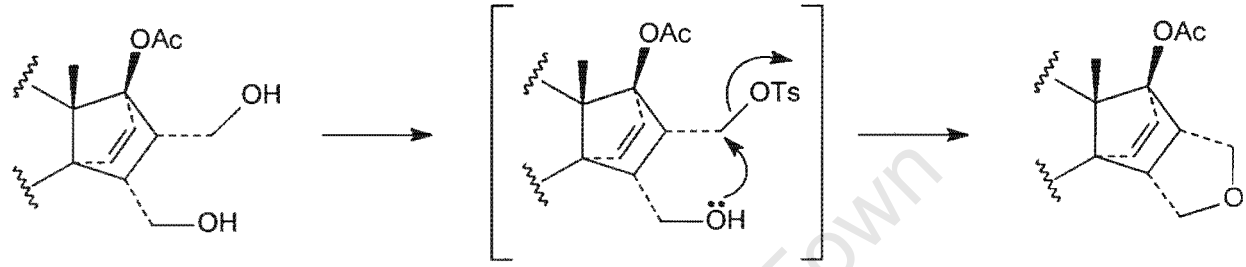


Figure 2.13

Selected ^1H NMR *J* values (Hz) for **67**

The signal for 16β-H was observed as a dt at δ 3.06 (*J* 9.6 and 2 x 7.1 Hz). The 15β-H signal was located by a crosspeak in the COSY spectrum to a multiplet at δ 2.62, which coincided with the 6-H's. This precluded full analysis of its coupling behaviour. Another crosspeak in the COSY spectrum from the 16β-H to dd at δ 4.03 and 4.18 (*J* 9.7 and 7.1 Hz) located the 2'-methylene protons. The 5'-methylene protons were located in a similar manner to the signals at δ 3.34 (dd, *J* 8.6 and 6.4 Hz) and 3.70 (t, *J* 2 x 8.6 Hz).

The formation of the anhydro ring under these conditions is not surprising. Indeed the intramolecular formation of inner cyclic ethers ("dehydration") when carrying out tosylation reactions on carbohydrates in the presence of pyridine is widely reported.[53] This occurs when the highly reactive sulfonyl ester is readily displaced upon formation by an intramolecular hydroxy group, giving rise to the anhydro ring. A possible mechanism for formation of the tetrahydrofuran derivative **67** is exemplified in Scheme 2.35.

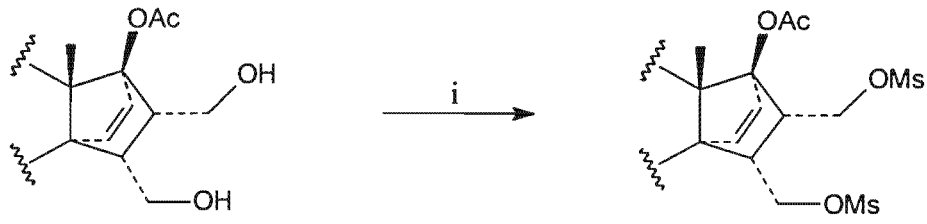


66 **67**

Scheme 2.35

Due to the unfavourable formation of the anhydro derivative, tosylation of the acetoxy diol **66** was not investigated further. Instead it was decided to carry out a protection using the less bulky methansulfonyl chloride. Methanesulfonate (mesyl) esters are about three times less reactive towards displacement than the corresponding tosylates[54] and so it was hoped that formation of the anhydro derivative would not interfere.

The procedure used by Crossland and co-workers[55] was employed, which deviates from the usual Tipson procedure[53] by the use of triethylamine as base and dichloromethane as solvent. These conditions are reported to be sufficiently mild that even very reactive systems, such as 1-methylcyclobutyl alcohol may be esterified, with little interference from side reactions. The reaction of the acetoxy diol **66** was conducted at –78 °C and was closely monitored by TLC. After 30 min, three distinct spots had emerged, which converged to the least polar spot after 3 h. The product was isolated in 83 % yield and was formulated as the 17β-acetoxy-15^1,16^1-dimethylsulphonate ester **68** (Scheme 2.36). No attempt was made to isolate the intermediates. It is suspected they correspond to the respective monomeyslates.

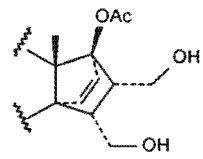
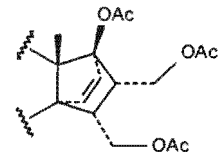
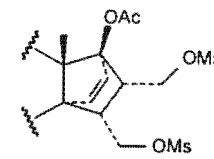


65 **68**

Scheme 2.36 *Reaction Conditions*: (i) MsCl, Et_3N, CH_2Cl_2, -78°C, 3h

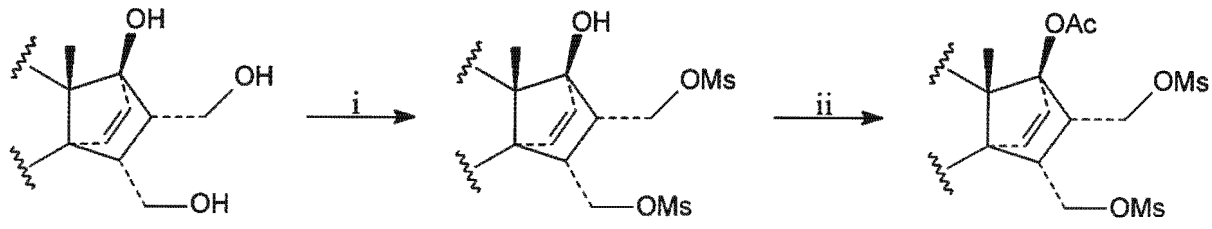
All spectroscopic and analytical properties were consistent with the assigned structure. The infrared spectrum displayed the characteristic acetoxy carbonyl absorption at 1743 cm^{-1} and the absorption peaks observed at 1362 and 1175 cm^{-1} were assigned to the sulfonyl groups. The 400 MHz ^1H NMR spectrum displayed two methyl singlets at δ 3.03 and 3.05 assigned to the methanesulfonyl methyl groups. The 17β-acetoxy methyl singlet appeared at δ 2.12. The 15β-, 16β- and methylene proton signals were unambiguously assigned with the aid of a COSY spectrum. Table 2.12 compares this ^1H NMR chemical shift data with that of the acetoxy diol **66** and the triacetate **58**. Inspection of this data shows that these signals for the acetoxy dimesylate **68** appear characteristically downfield compared to the acetoxy diol and triacetate, as a result of sulfonylation.

Table 2.12 Selected ^{1}H NMR data* for the acetoxy diol **66**, triacetate **58** and acetoxy dimesylate **68**

Proton	**66** 	**58** 	**68** 
15β-H	2.57 td, *J* 2 x 10.0 and 2.6	2.57 td, *J* 2 x 8.5 and 3.4	2.73 td, *J* 2 x 8.3 and 3.0
16β-H	2.89 td, *J* 2 x 10.0 and 3.1	2.96 dt, *J* 8.5 and 2 x 6.6	3.10 td, *J* 2 x 8.3 and 5.2
15^1-H	3.51 dd, *J* 11.5 and 10.0 4.05 dd, *J* 11.5 and 2.6	3.77 dd, *J* 12.2 and 8.5 4.38 dd, *J* 12.2 and 3.4	3.99 dd, *J* 10.7 and 8.3 4.57 dd, *J* 10.7 and 3.0
16^1-H	3.60 dd, *J* 11.3 and 10.0 3.81 dd, *J* 11.3 and 3.0	4.06 dd, *J* 11.5 and 6.6 4.19 dd, *J* 11.5 and 6.6	4.21 dd, *J* 10.3 and 8.3 4.42 dd, *J* 10.3 and 5.2
17^1-H & 17^2-H	5.95 and 6.28 d, *J* 6.0	6.06 and 6.47 d, *J* 6.3	6.10 and 6.51 d, *J* 6.3

* quoted as chemical shift (in ppm), multiplicity and coupling constants (in Hz)

The lack of chemoselectivity in the mesylation reaction is not surprising, considering that the reagent is relatively sterically undemanding. When the triol **56** was subjected to similar conditions, only at a temperature of –15 °C, a single product **69** was formed in 95 % yield after 6 h. This product, when subjected to standard acetylating conditions (Ac_2O, py, DMAP), gave rise to a product displaying identical spectroscopic and analytical data to **68** (Scheme 2.37).



56 **69** **68**

Scheme 2.37 *Reaction Conditions*: (i) MsCl, py, CH_2Cl_2, -15°C; (ii) Ac_2O, py, DMAP

Based on this outcome, **69** was confidently formulated as the 15^1,16^1-dimesylate-17β-alcohol. The ^1H and ^{13}C NMR spectra of **69** were similar to those of **68**. The only noteworthy difference in the ^1H NMR was the chemical shifts for 16β-H. Its signal appeared slightly downfield in the spectrum of the acetoxy dimesylate **68** compared with the dimesylate **69**, thus supporting the expected through space deshielding effect the 17β-acetoxy group has on this signal.

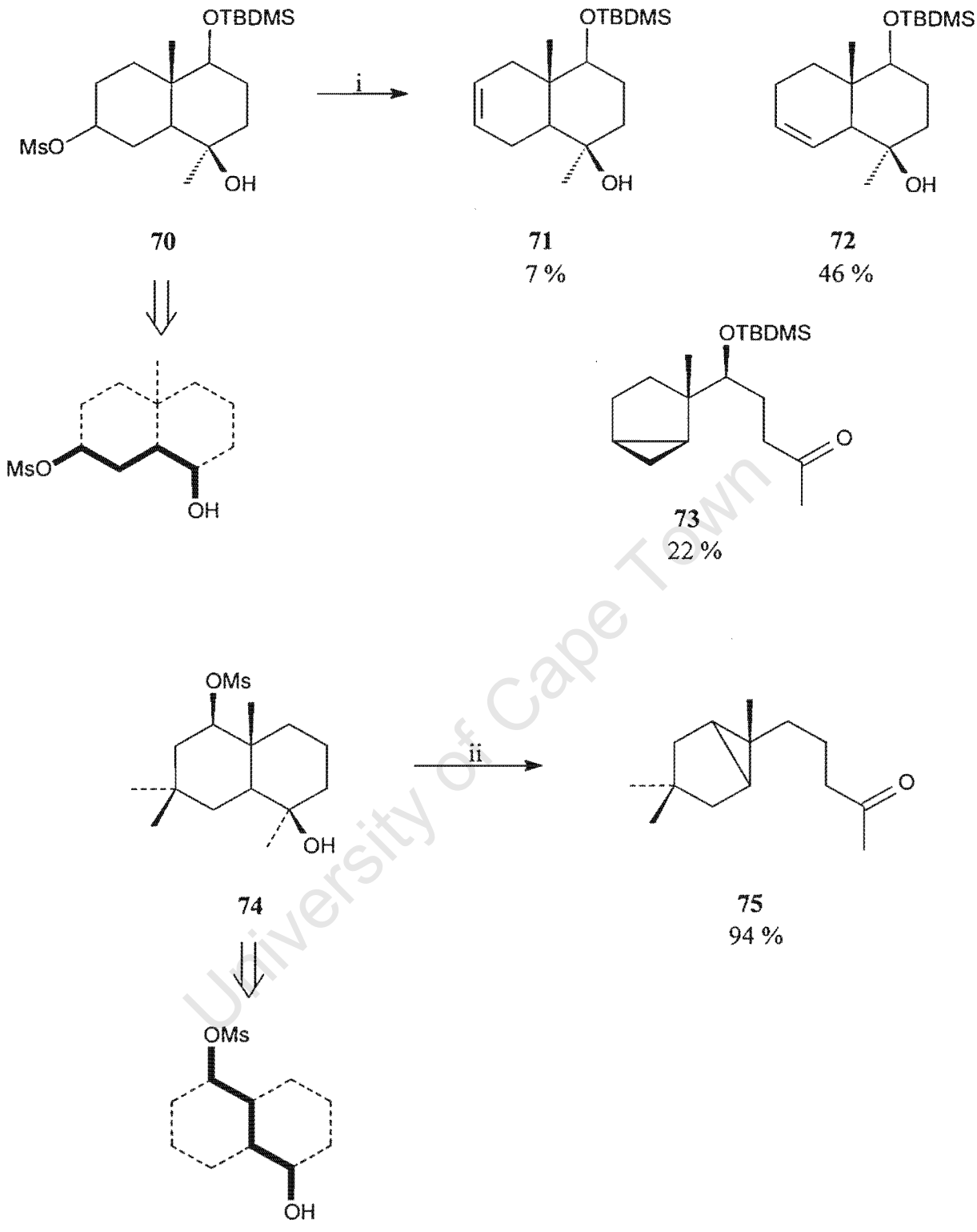
2.7 Base Treatment of 17β-acetoxy 15^1,16^1-dimesylate 68

In spite of not achieving the initial purpose of chemoselectively differentiating the primary hydroxy groups, this result has served the second purpose of forming an intermediate suitable for Wharton fragmentation. Indeed the 1,3-disposition of the bridgehead hydroxy (in **69**) or acetoxy (in **68**) and the 16α-mesyloxymethyl group encouraged the expectation that treatment with base should result in fragmentation to give a 14β-substituted product.

This type of heterolytic fragmentation is not limited to 1,3-diol monosulfonate esters. In previous work conducted by Wijnberg and co-workers[58] on the total synthesis of sesquiterpenes, it was found that perhydronaphthalene-1,4-diol monosulfonate esters react upon treatment with base to give rearrangement and/or elimination products. The formation of the alkoxide induces heterolysis of the sulfonate ester group *via* through bond interaction (TBI) as in the case with the Wharton fragmentation, only this time through three intervening C-C bonds rather than two. Studies conducted on the effect of the geometry of the relaying σ–bonds between the alcholate anion and the sulfonate ester bond on TBI and it's chemical

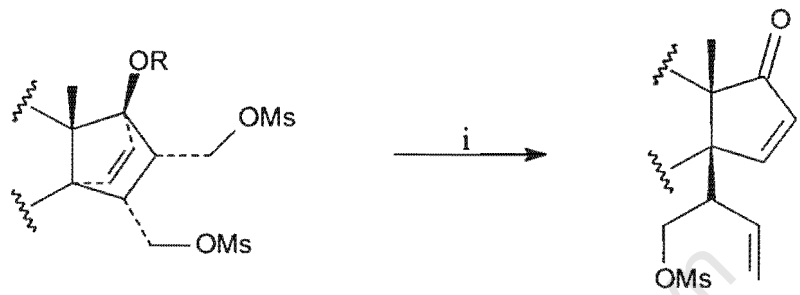
consequence on the heterolysis of sulfonate esters[59] demonstrated that a W arrangement of the σ-relay is the most favourable geometry for mediating TBI. Any deviation from the W arrangement makes transmission of TBI more difficult, thereby reducing the reactivity of such compounds. Furthermore those compounds possessing such a W arrangement were found to exhibit homofragmentation as the characteristic reaction pathway, as demonstrated for **74** in Scheme 2.38. This is because the fragmentation process can only occur if the back lobe of the polarised C-C-O bond can overlap with the p-orbital of the incipient cationic centre, and this is satisfied when the intervening bonds have the all-*trans* W arrangement. Without participation of this 1,3 bridged through space interaction, other products resulting from elimination and rearrangement are formed, as demonstrated for **70** in Scheme 2.38.

In view of the foregoing discussion, it is possible that treatment of dimesylate **68** or **69** with base, could give rise to two competing reaction pathways: Wharton fragmentation of the 1,3 diol monomesylate or heterolysis of the 1,4-diol monosulfonate ester. The outcome will be a product composition, which reflects the more or most favourable reaction pathway. This will be determined by the σ-relay having the geometry most favoured for the efficient transmission of TBI.



Scheme 2.38 *Reaction Conditions* (i) Na *tert*-amylate, Δ, 10 min; (ii) Na *tert*-amylate, Δ, 1 min

Treatment of the dimesylate **69** with M methanolic potassium hydroxide in tetrahydrofuran gave rise to single product after 45 min in 93 % yield. Similar treatment of the alkoxy dimesylate **68** gave rise to the identical product in 82 % yield after 90 min. The product was formulated as being the 14β-substituted derivative **76**, arising from Wharton fragmentation (Scheme 2.39).



68 R = Ac
69 R = OH

76

Scheme 2.39 *Reaction Conditions* (i) KOH, MeOH, THF

All spectroscopic and analytical properties were consistent with the assigned structure. The ^{1}H and ^{13}C NMR spectra of **76** displayed diagnostic signals for all elements of the 14β-allyl group and the ring D enone moiety. Some essential ^{1}H NMR data for **76** is displayed are Figure 2.14. The signals for the vinyl protons, 15- and 16-H, were observed as doublets at δ 7.42 and 6.34 (*J* 5.9 Hz) respectively, the coupling constant consistent with their *cis* arrangement. The doublet of triplets at δ 3.22 (*J* 9.8 and 2 x 5.9 Hz) was assigned to 2'-H, its splitting pattern consistent with couplings to three geminal protons. A correlation in the COSY spectrum to a doublet at δ 4.31 (*J* 5.9 Hz), integrating for two protons, located the 1'-H's. The third geminal partner, 3'-H, was located by another crosspeak to the signal at δ 6.03 (dt, *J* 16.8 and 2 x 9.8 Hz). The latter signal displays a large coupling to 4'-H_{trans} (16.8 Hz), its magnitude consistent with their trans relationship. The two slightly smaller couplings of 9.8 Hz correspond to couplings with 4'-H_{cis} and 2'-H. The 4'-H_{trans} signal appeared at δ 5.29 (*J* 16.8 Hz), while the 4'-H_{cis} appeared at δ 5.37 (dd, *J* 9.8 and 1.5 Hz). The smaller coupling (1.5 Hz) displayed by the latter proton signal corresponds to the geminal coupling to 4'-H_{trans}. This coupling is characteristically small due to the shielding effect of the double bond, as well as

the increase in bond angle (to ~120°) between the protons.[24] The 4'-H_{trans} signal did not however reflect this coupling (see Table 2.13).

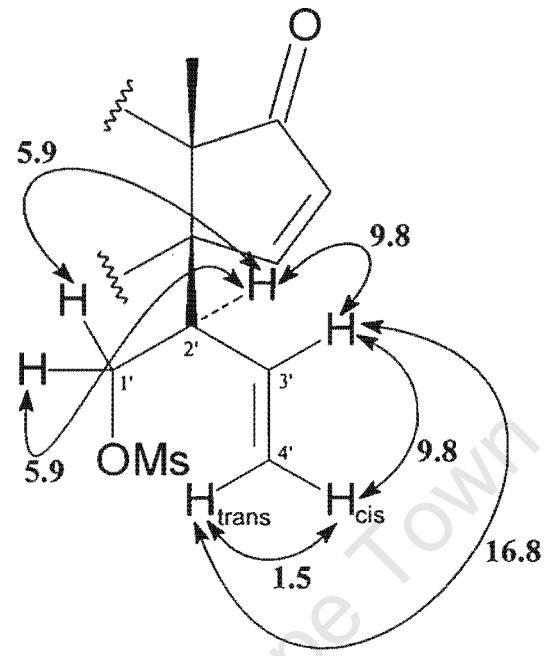


Figure 2.14

Selected ^{1}H NMR *J* values (Hz) for **76**

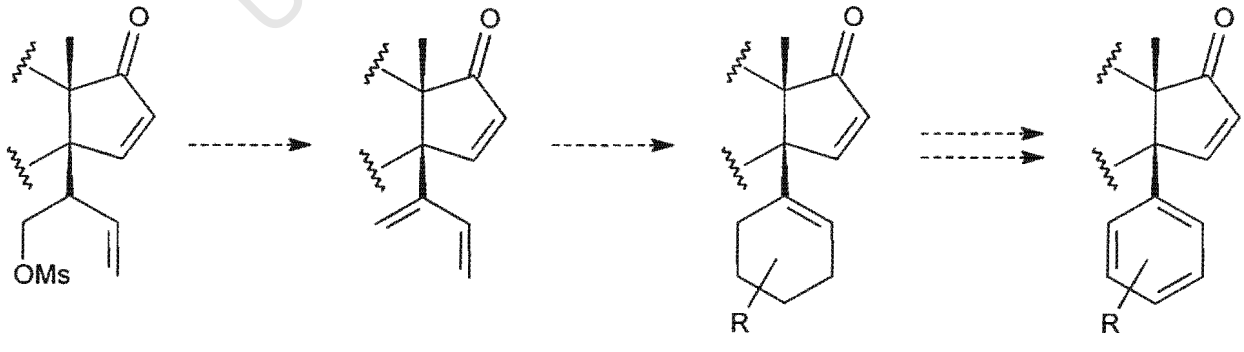
Full assignment of the ^{13}C NMR was made possible with the aid of HSQC and HMBC spectra. The C-17 signal appeared at δ 212.2, while the signals for C-15 and C-16 appeared at δ 132.3(d) and 163.5(d) in the characteristic olefinic carbon region. The signals for C-1', C-2', C-3' and C-4' were located by the relevant crosspeaks in the HSQC spectrum to resonances at δ 49.1 (d), 71.0 (t), 134.3 (d) and 121.6 (t) respectively. An noteworthy feature of the 13C NMR spectrum is the substantial downfield shift in the C-18 resonance of ~ 9 Hz to δ 24.3, as a result of the presence of the 17-carbonyl functionality.

The outcome of this reaction clearly indicates that Wharton fragmentation constitutes the most favoured pathway under these conditions, and confirms the feasibility of this fragmentation for furnishing 14β-functionalised intermediates.

Table 2.13 Selected ^{1}H NMR data for **76**

δ/ppm	Integration	Multiplicity	*J*/Hz	Assignment
3.22	1H	dt	9.8, 2 x 5.9	2'-H
4.31	2H	d	5.9	1'-H
5.29	1H	d	16.8	4'-H_{trans}
5.37	1H	dd	9.8, 1.5	3'-H
6.03	1H	dt	16.8, 2 x 9.8	4'-H
6.34	1H	d	5.9	16-H
7.42	1H	d	5.9	15-H

This foregoing synthetic strategy has demonstrated the successful chemoselective manipulation of cycloaddition derivatives to produce a suitable Wharton fragmentation precursor, which fragments cleanly and easily to produce the 14β-functionalised derivative **76**. Although time did not permit further investigation, it is anticipated that eliminatation of the mesylate of **76** would give the 14β-diene **77** (Scheme 2.40). Such an intermediate presents a perfect opportunity for exploiting cycloaddition methodology to achieve ring construction in a facile manner, thus providing access to the desired 14β-cyclohexenoid derivative **78**. Furthermore by making a suitable choice of dienophile, the appropriate functionality can be introduced into the ring which will then enable further manipulation of the 14β-cycloahexenoid derivative to give the desired 14β-aryl target **79**.



76 **77** **78** **79**

Scheme 2.40

3. EXPERIMENTAL

3.1 General

Melting points were determined on a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 Polarimeter using chloroform solutions unless otherwise stated, and are recorded in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer in chloroform solutions, unless otherwise stated. ^1H NMR spectra were recorded on a Varian Unity Spectrometer (400 MHz) at 400 MHz in deuteriochloroform solutions unless otherwise stated.^{13}C NMR spectra were recorded on a Varian Unity Spectrometer at 100 MHz. Elemental analyses were preformed using a Fisons EA 1108 CHNS-O instrument. Mass spectra were recorded on a VG micromass 16F mass spectrometer operating at 70eV with and accelerating voltage of 4 kV. Accurate masses were determined on a Kratos Limited MS9/50 spectrometer at the Cape Technikon.

Reactions were monitored by thin layer chromatography using aluminium-backed silica gel F_{254} plates. Once developed, the plates were visualised by spraying with a cerium(IV) ammonium sulfate solution in sulphuric acid and heated in an oven at 200°C. Column chromatography was carried out using Merck Kieselgel 60: 70-23- mesh for gravity columns and 230-400 mesh for flash chromatography.

Commonly used solvents were purified as follows:

Tetrahydrofuran – dried over sodium and then distilled from sodium and benzophenone under argon atmosphere prior to use.

Toluene – distilled from sodium and stored over sodium wire

Acetic anhydride – fractionally distilled

Pyridine – distilled from potassium hydroxide and stored over potassium hydroxide pellets

Dichloromethane – dried over phosphorus pentoxide and distilled prior to use

Triethylamine – distilled from potassium hydroxide and stored over potassium hydroxide pellets.

3.2 Experimental

Cycloaddition of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate 7 with *p*-benzoquinone

Boron trifluoride-diethyl ether (0.05 cm^3, 0.4 mmol) was added to the dienyl acetate 7 (973 mg, 3.0 mmol) and *p*-benzoquinone (486 mg, 4.5 mmol) in dry toluene (25 cm^3) at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 2 h, then ice-water added and the mixture extracted with ethyl acetate. The combined organic phase was washed successively with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the crude material (1.23 g) on silica gel (90 g) using ethyl acetate-toluene (3:7) as eluent gave 3-methoxy-3',6'-dioxo-15α*H*,16α*H*-benzo[15,16]-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate **24** (65 mg, 5 %), m.p. 175-178°C (from acetone-methanol) (lit.,[12] m.p. 177-179°C) followed by 3-methoxy-3',6'-dioxo-15β*H*,16β*H*-benzo[15,16]-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate **25** (933 mg, 72 %), m.p. 144-146°C (lit.,[12] m.p. 145-148°C).

Hydrogenation of benzoquinone cycloadducts 24 and 25

a) The major cycloadduct **25** (732 mg, 1.7 mmol) in ethyl acetate (50 cm^3) at 24°C was hydrogenated at atmospheric pressure in the presence of palladium on carbon (10 %, 143 mg). After 3 h the mixture was filtered through Celite, and the filtrate evaporated under reduced pressure to give the crude residue (720 mg). Direct crystallisation of the reaction product gave 3-*methoxy*-3'(4'H),6'(5'H)-*dioxo*-15βH,16βH-*benzo*[15,16]-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl acetate* **27** (690 mg, 95 %), m.p. 215-217°C (from chloroform-methanol); $[\alpha]_D$ +49° (*c* 1.0); ν_{max}/cm^{-1} 1737 and 1708 (CO); δ_H (400 MHz) 1.05 (3H, s, 13β-Me), 1.46 (1H, ddd, *J* 12.8, 4.3 and 2.3 Hz, 12β-H), 1.69 (1H, td, *J* 2 x 11.4 and 2.7 Hz, 8β-H), 2.09 (3H, s, 17-OAc), 2.30 (1H, dddd, *J* 13.2, 6.0 and 2 x 3.0 Hz, 7α-H), 2.33-2.45 (2H, m, 6α- and 6β-H), 2.68 (1H, *J* 2 x 11.4 and 4.8 Hz, 9α-H), 2.72-2.87 (4H, m, 4'- and 5'-H), 3.07 (1H, d, *J* 12.6 and 2.4 Hz, 15β-H), 3.77 (3H, s, 3-OMe), 4.12 (1H, d, *J* 12.6 and 3.2 Hz, 16β-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, d, *J* 8.7 and 2.8 Hz, 2-H), 7.19 (1H, d, *J* 8.7 Hz, 1-H);

δ_C(100 MHz) 15.3 (q, C-18), 21.8 (q, 17-OCO*C*H$_3$), 22.2 and 25.5 (each t, C-17^1 and C-17^2), 24.7 (t, C-7), 26.8 (t, C-11), 27.2 (t, C-12), 30.1 (t, C-6), 38.1 and 39.8 (each t, C-4' and C-5'), 40.3 and 40.7 (each d, C-8 and C-9),), 50.6 and 51.6 (each s, C-13 and C-14), 53.0 and 55.3 (each d, C-15 and C-16), 55.2 (q, 3-Me), 91.4 (s, C-17), 111.6 (d, C-2), 113.4 (d, C-4), 126.4 (d, C-1), 132.7 (s, C-10), 137.9 (s, C-5), 157.6 (s, C-3), 170.4 (s, 17-O*C*OCH$_3$), 208.1 and 210.6 (each s, C-3' and C-6') (Found: C, 74.0; H, 7.7 %; M$^+$, 436. $C_{27}H_{32}O_5$ requires C, 74.3; H 7.4 %; *M*, 436).

b) Boron trifluoride-diethyl ether (0.18 cm^3, 1.39 mmol) was added to the dienyl acetate 7 (3.00 g, 9.26 mmol) and *p*-benzoquinone (1.50 g, 13.88 mmol) in dry toluene (60 cm^3) at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 3 h, then ice-water added and the mixture extracted with ethyl acetate. The combined organic phase was washed successively with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give the crude material (4.31 g). A suspension of this crude in acetic acid (45 cm^3) was treated with zinc dust (1.5 g, 22.9 mmol) under ultrasound conditions for 3 h. The zinc was then filtered off, and the solution diluted with water. After extraction with dichloromethane, the combined organic phases were washed with aqueous sodium hydrogen carbonate (3x) and brine, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the crude residue (3.91 g) on silica gel (200 g) using ethyl acetate-toluene (1:9) as eluent gave 3-*methoxy*-3'(4'H),6'(5'H)-*dioxo*-15α*H*,16α*H*-*benzo*[15,16]-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl acetate* **28** (208 mg, 5 %), m.p. 142-143°C (from ethyl acetate-hexane); $[\alpha]_D$ +56° (*c* 1.0); ν_{max}/cm^{-1} 1705 and 1738 (CO); δ_H (400 MHz) 0.96 (3H, s, 13β-Me), 1.43 (1H, qd, *J* 3 x 13.7 and 4.5 Hz, 11β-H), 1.62 (1H, ddd, *J* 14.1, 4.5 and 2.5 Hz, 12β-H), 2.37 (1H, dddd, *J* 13.7, 2 x 4.8 and 2.5 Hz, 11α-H), 2.17 (3H, s, 17-OAc), 2.48-2.70 (4H, m, 4'- and 5'-H), 3.79 (3H, s, 3-OMe), 3.85 and 4.50 (each 1H, d, *J* 10.1 Hz, 15α- and 16α-H), 6.18 and 6.34 (each 1H, d, *J* 6.0 Hz, 17^1- and 17^2-H), 6.63 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, d, *J* 8.4 and 2.8 Hz, 2-H), 7.21 (1H, d, *J* 8.4 Hz, 1-H); δ_C(100 MHz) 15.0 (q, C-18), 21.7 (q, 17-OCO*C*H$_3$), 26.0 (t, C-7), 27.2 (t, C-11), 30.6 (t, C-12), 31.3 (t, C-6), 37.5 (d, C-8), 38.4 (d, C-9), 38.4 and 38.7 (each t, C-4' and C-5'), 48.9 (d, C-16), 53.2 (d, C-15), 55.2 (q, 3-OMe), 59.7 and 62.6 (each s, C-13 and C-14), 95.9 (s, C-17), 112.0 (d, C-2), 113.7 (d, C-4), 127.2 (d, C-1), 132.0 (s, C-10), 135.1 and 136.1 (each d, C-17^1 and C-17^2), 138.2 (s, C-5), 157.6 (s, C-3), 170.6 (s, 17-O*C*OCH$_3$), 207.9 and 208.4 (each s, C-3' and C-6') (Found: C, 74.1; H, 6.9 %; M$^+$, 434. $C_{27}H_{30}O_5$ requires C, 74.6; H 6.9 %; *M*, 434) followed by 3-

methoxy-3'(4'*H*),6'(5'*H*)-dioxo-15β*H*,16β*H*-benzo[15,16]-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate **22** (2.60 g, 65 %), m.p. 162°C (from acetone-methanol); $[\alpha]_D$ +85° (*c* 1.0); ν_{max}/cm^{-1} 1703 and 1742 (CO); δ_H (400 MHz) 1.02 (3H, s, 13β-Me), 1.52 (1H, qd, *J* 3 x 11.5 and 6.1 Hz, 7α-H), 1.70 (1H, td, *J* 2 x 11.3 and 2.6 Hz, 8β-H), 2.16 (3H, s, 17-OAc), 2.57-2.68 (4H, m, 4'- and 5'-H), 2.75-2.92 (2H, m, 6α- and 6β-H), 3.32 (1H, d, *J* 9.6 Hz, 15β-H), 3.75 (1H, d, *J* 9.6 Hz, 16β-H), 3.77 (3H, s, 3-OMe), 6.25 and 6.59 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, d, *J* 8.4 and 2.8 Hz, 2-H), 7.17 (1H, d, *J* 8.4 Hz, 1-H); δ_C (100 MHz) 16.0 (q, C-18), 21.6 (q, 17-OCO*C*H$_3$), 24.3 (t, C-7), 26.7 (t, C-11), 28.6 (t, C-12), 30.1 (t, C-6), 38.1 and 39.6 (each t, C-4' and C-5'), 40.0 and 40.9 (each d, C-8 and C-9), 55.2 (q, 3-OMe), 56.2 and 56.5 (each d, C-15 and C-16), 60.7 and 62.9 (each s, C-13 and C-14), 95.6 (s, C-17), 111.9 (d, C-2), 113.4 (d, C-4), 127.0 (d, C-1), 131.8 (s, C-10), 131.6 and 134.9 (each d, C-17^1 and C-17^2), 137.9 (s, C-5), 157.6 (s, C-3), 170.2 (s, 17-O*C*OCH$_3$), 206.8 and 210.9 (each s, C-3' and C-6') (Found: C, 74.5; H, 6.7 %; M^+, 434. $C_{27}H_{30}O_5$ requires C, 74.6; H 6.9 %; *M*, 434).

3',3'(4'*H*)-Ethylenedioxy-3-methoxy-6'(5'*H*)-oxo-15β*H*,16β*H*-benzo[15,16]-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate 29

To a stirred solution of the cycloadduct **22** (100 mg, 0.23 mmol) in dry toluene (25 cm^3) was added ethane diol (2 cm^3, 36 mmol) and *p*-toluenesulfonic acid (20 mg, 0.11 mmol). The solution was heated under reflux for 3.5 h using molecular sieves as drying agent. The solution was allowed to cool and aqueous sodium hydrogen carbonate added. The reaction mixture was extracted with ethyl acetate and the combined organic phase washed with water, brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the crude (138 mg). Flash chromatography of the crude on silica gel (20 g) using ethyl acetate-hexane (3:7) as eluent gave the ketal **29** (86 mg, 78 %), m.p. 146-148°C; $[\alpha]_D$ +61° (*c* 1.0); ν_{max}/cm^{-1} 1694 and 1740 (CO); δ_H (400 MHz) 1.02 (3H, s, 13β-Me), 1.10 (1H, ddd, *J* 13.5, 4.1 and 2.7 Hz, 12β-H), 1.28 (1H, dddd, *J* 2 x 13.5, 12.0 and 4.1 Hz, 11β-H), 1.56 (1H, td, *J* 2 x 12.0 and 2.0 Hz, 8β-H), 1.61 (1H, qd, *J* 2 x 12.0, 10.5 and 6.4 Hz, 7α-H), 1.89 (1H, dddd, *J* 13.9, 9.6, 6.6 and 1.2 Hz, 4'β-H), 2.10 (3H, s, 17-OAc), 2.25 (1H, ddd, *J* 17.6, 9.7 and 6.6 Hz, 5'α-H), 2.37 (1H, td, *J* 2 x 13.5 and 4.7 Hz, 12α-H), 2.41 (1H, dddd, *J* 17.6, 9.6, 4.7 and 1.3 Hz, 5'β-

H), 2.56 (1H, td, *J* 2 x 12.0 and 4.0 Hz, 9α-H), 2.74-2.86 (2H, m, 6α- and 6β-H), 3.08 (1H, dd, *J* 10.6 and 1.3 Hz, 15β-H), 3.34 (1H, dd, *J* 10.6 and 1.2 Hz, 16β-H), 3.76 (3H, s, 3-OMe), 3.89-4.04 (4H, m, $O(CH_2)_2O$), 6.16 and 6.64 (each 1H, d, *J* 6.1 Hz, 17^1- and 17^2-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, d, *J* 8.4 and 2.8 Hz, 2-H), 7.19 (1H, d, *J* 8.4 Hz, 1-H); δ_C (100 MHz) 15.6 (q, C-18), 21.8 (q, 17-OCO*C*H_3), 24.8 (t, C-7), 27.3 (t, C-11), 28.7 (t, C-12), 30.4 (t, C-6), 30.8 and 36.7 (each t, C-4' and C-5'), 40.3 and 40.4 (each d, C-8 and C-9), 51.2 (d, C-16), 55.2 (q, 3-OMe), 56.2 (d, C-15), 58.7 and 63.6 (each s, C-13 and C-14), 64.0 and 65.4 (each t, $O(CH_2)_2O$), 94.4 (s, C-17), 108.7 (s, C-3'), 111.9 (d, C-2), 113.4 (d, C-4), 127.2 (d, C-1), 129.3 and 132.9 (each d, $C\text{-}17^1$ and $C\text{-}17^2$), 132.1 (s, C-10), 138.0 (s, C-5), 157.5 (s, C-3), 169.8 (s, 17-O*C*OCH$_3$), 211.8 (s, C-6') (Found: C, 72.6; H, 7.3 %; M^+, 478. $C_{29}H_{34}O_6$ requires C, 72.8; H 7.2 %; *M*, 478).

L-Selectride® reduction of the dihydrocycloadduct 22

The dihydrocycloadduct **22** (500 mg, 1.16 mmol) was dissolved in dry toluene (50 cm^3), then the solution cooled to -78°C and L-Selectride (1.6 cm^3 of a 1.0 M solution in tetrahydrofuran, 1.6 mmol) added. The mixture was stirred at -78°C for 5 h, then saturated aqueous ammonium chloride added and the mixture allowed to warm to room temperature. Aqueous sodium hydroxide (5 %, 25 cm^3) was added slowly followed by hydrogen peroxide (30 %, 25 cm^3), the mixture stirred for 0.5 h and then extracted with dichloromethane. The combined organic phases were washed successively with saturated sodium hydrogen carbonate, water and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude material (559 mg) was dissolved in pyridine (7 cm^3) and acetic anhydride (1.25 cm^3, 13.25 mmol) and 4-(dimethylamino)pyridine (28 mg, 0.23 mmol) added. The mixture was stirred for 16 h, then water added and stirring continued for 30 min. After extraction with ethyl acetate, the combined organic phases were washed with aqueous sodium hydrogen carbonate, water and brine, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the crude material (575 mg) on silica gel (50 g) using ethyl acetate-hexane (3:7) as eluent gave 3-*methoxy-hexahydro*-15β,16β-*benzo*[15,16]-14,17α-*ethenoestra*-1,3,5(10)-*triene*-17β,3'α,6'α-*triyl triacetate* **30** (91 mg, 15 %), m.p. 186-188°C (from ethyl acetate-hexane); $[\alpha]_D$ +115° (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 1727 (CO); δ_H (400 MHz) 1.00 (3H, s, 13β-Me), 1.08 (1H, ddd, *J* 13.2, 4.0 and 2.8 Hz, 12β-H), 1.26 (1H, dddd, *J* 3 x 13.7 and 4.0 Hz, 11α-H), 2.01, 2.02 and

2.07 (each 3H, s, 3'-, 6'- and 17-OAc), 2.40 (1H, td, *J* 2 x 13.7 and 3.6 Hz, 12α-H), 2.55 (1H, dd, *J* 10.6 and 6.4 Hz, 15β-H), 2.78-2.86 (2H, m, 6α- and 6β-H), 2.90 (1H, dd, *J* 10.6 and 6.4 Hz, 16β-H), 3.77 (3H, s, 3-OMe), 5.35 (2H, m, 3'- and 6'-H), 6.01 and 6.33 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, d, *J* 8.6 and 2.8 Hz, 2-H), 7.20 (1H, d, *J* 8.6 Hz, 1-H); δ_H (400 MHz, C_6D_6) 0.76 (3H, s, 13β-Me), 1.60, 1.72 and 1.77 (each 3H, s, -OAc), 2.11 (1H, dddd, *J* 13.4, 2 x 4.4 and 2.2 Hz, 11α-H), 2.48 (1H, td, *J* 2 x 11.5 and 3.9 Hz, 9α-H), 3.38 (3H, s, 3-OMe), 5.12 (1H, dt, *J* 6.7 and 2 x 3.4 Hz, -C*H*(OH)), 5.39 (1H, q, *J* 3 x 6.5 Hz, -C*H*(OH)), 5.82 and 6.49 (each 1H, d, *J* 6 Hz, 17^1- and 17^2-H), 6.63 (1H, d, *J* 2.4 Hz, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), 7.13 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 15.8 (q, C-18), 21.5, 21.6 and 21.7 (each q, 17-, 3'- and 6'-$OCOCH_3$), 23.1 and 24.8 (each t, C-4' and C-5'), 25.2 (t, C-7), 27.4 (t, C-11), 29.0 (t, C-12), 30.5 (t, C-6), 40.4 and 40.6 (each d, C-8 and C-9), 45.0 (d, C-16), 46.7 (d, C-15), 55.2 (q, 3-O*C*H_3), 58.5 and 63.1 (each s, C-13 and C-14), 67.3 and 68.8 (each d, C-3' and C-4'), 95.0 (s, C-17), 112.0 (d, C-2), 113.4 (d, C-4), 127.3 (d, C-1), 130.1 and 130.4 (each d, C-17^1 and C-17^2), 132.2 (s, C-10), 137.5 (s, C-5), 157.5 (s, C-3), 169.9, 170.0 and 170.2 (each s, 3'-, 6'- and 17-O*C*OCH$_3$) (Found: C, 70.8; H, 7.6 %; M^+, 522. $C_{31}H_{38}O_7$ requires C, 71.2; H 7.3 %; *M*, 522) followed by 3-methoxy-6'(5'*H*)-oxo-tetrahydro-15β,16β-benzo[15,16]-14,17α-ethenoestra-1,3,5(10)-triene-17β,3'α-diyl diacetate **31** (393 mg, 71 %), m.p. 187-191°C (from ethyl acetate-hexane); $[\alpha]_D$ +95° (*c* 1.0); ν_{max}/cm^{-1} 1736 (CO); δ_H (400 MHz) 1.03 (3H, s, 13β-Me), 1.12 (1H, ddd, *J* 13.4, 4.3 and 2.4 Hz, 12β-H), 1.30 (1H, qd, *J* 3 x 12.0 and 4.3 Hz, 11β-H), 1.47 (1H, td, *J* 2 x 12.0 and 2.8 Hz, 8β-H), 1.99 and 2.09 (each 3H, s, 3'α- and 17β-OCOC*H*$_3$), 2.63 (1H, td, *J* 2 x 12.0 and 3.7 Hz, 9α-H), 2.73-2.88 (2H, m, 6α- and 6β-H), 2.99 (1H, d, *J* 11.3 Hz, 15β-H), 3.29 (1H, dd, *J* 11.3 and 4.5 Hz, 16β-H), 3.78 (3H, s, 3-OMe), 5.30 (1H, td, *J* 2 x 4.5 and 1.7 Hz, 3'-H), 6.20 (2H, s, 17^1- and 17^2-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, d, *J* 8.6 and 2.8 Hz, 2-H), 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C(100 MHz) 15.4 (q, C-18), 21.3 and 21.5 (each q, 3'- and 17-OCO*C*H_3), 26.0 (t, C-4'), 26.4 (t, C-7), 27.9 (t, C-11), 28.1 (t, C-12), 30.8 (t, C-6), 34.9 (t, C-5'), 40.2 and 40.3 (each d, C-8 and C-9), 50.1 and 55.1 (each d, C-15 and C-16), 55.2 (q, 3-O*C*H_3), 57.5 and 62.2 (each s, C-13 and C-14), 67.1 (d, C-3'), 93.8 (s, C-17), 112.0 (d, C-2), 113.4 (d, C-4), 127.5 (d, C-1), 130.7 and 131.6 (each d, C-17^1 and C-17^2), 132.2 (s, C-10), 138.0 (s, C-5), 157.4 (s, C-3), 170.0 and 170.1 (each s, 3'- and 17-O*C*OCH$_3$), 209.4 (s, C-6'); (Found: C, 72.3; H, 7.4 %; M^+, 478. $C_{29}H_{34}O_6$ requires C, 72.8; H 7.2 %; *M*, 478).

3-Methoxy-hexahydro-15β,16β-benzo[15,16]-14,17α-ethenoestra-1,3,5(10)-triene-17β,3'α,6'α-triol 32

Methanolic potassium hydroxide (0.3 cm^3, 1 M) was added to a solution of the triacetate **30** (50 mg, 0.1 mmol) in tetrahydrofuran (2 cm^3) and the mixture stirred at 24°C for 1 h. Aqueous ammonium chloride was added and the mixture extracted with chloroform. The combined organic phases were washed with water and brine, dried ($MgSO_4$), and evaporated under reduced pressure. Crystallisation of the residue (45 mg) from acetone-methanol gave the triol **32**(30 mg, 80 %), m.p. 223-226°C; $[\alpha]_D$ +70° (*c* 1.0 in C_5H_5N); ν_{max}/cm^{-1} 3370br (OH); δ_H (400 MHz, C_5D_5N) 1.19 (3H, s, 13β-Me), 1.28 (1H, s, -OH), 1.56 (1H, td, *J* 2 x 11.0 and 3.5 Hz, 8β-H), 1.66-1.71 (2H, m, 4'-H and 5'-H), 1.98-2.08 (3H, m, 4'-H, 5'-H and 7α-H), 2.28 (1H, dddd, *J* 13.4, 6.6 and 2 x 3.5 Hz, 7β-H), 2.37 (1H, dd, *J* 10.7 and 4.3 Hz, 15β-H), 2.67 (1H, dd, *J* 10.7 and 3.8 Hz, 16β-H), 2.79–2.90 (2H, m, 6β- and 6α-H), 3.68 (3H, s, 3-OMe), 4.40 (1H, dt, *J* 8.6 and 2 x 4.2 Hz, 6'-H), 4.72 (1H, dt, *J* 7.0 and 2 x 3.6 Hz, 3'-H), 4.79 (1H, s, -OH), 6.29 and 6.45 (each 1H, d, *J* 5.9 Hz, 17^1- and 17^2-H), 6.78 (1H, d, *J* 2.7 Hz, 4-H), 6.88 (1H, d, *J* 8.6 and 2.7 Hz, 2-H), 7.29 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 14.0 (q, C-18), 25.9 (t, C-4'), 27.4 (t, C-7), 27.8 (t, C-11), 27.9 (t, C-12), 28.6 (t, C-6), 30.6 (t, C-5'), 41.2 (2C, d, C-8 an d C-9), 50.6 (d, C-15), 51.0 (d, C-16), 55.2 (q, 3-OMe), 59.5 and 62.4 (each s, C-13 and C-14), 64.3 (d, C-3'), 67.0 (d, C-6'), 91.0 (s, C-17), 112.1 (d, C-2), 113.9 (d, C-4), 127.2 (d, C-1), 130.7 and 134.0 (each d, $C\text{-}17^1$ and $C\text{-}17^2$), 138.8 (2C, s, C-5 and C-10), 158.1 (s, C-3) (Found: C, 75.1; H, 8.3 %; M^+, 396. $C_{25}H_{32}O_4$ requires C, 75.7; H 8.1 %; *M*, 396).

3-Methoxy-6'(5'*H*)-oxo-tetrahydro-15β,16β-benzo[15,16]-14,17α-ethenoestra-1,3,5(10)-triene-17β,3'α-diol 33

Methanolic potassium hydroxide (1.5 cm^3, 1 M) was added to a solution of the diacetate **31** (230 mg, 0.48 mmol) in tetrahydrofuran (12 cm^3) and the mixture stirred at 24°C for 3 h. Aqueous ammonium chloride was added and the mixture extracted with chloroform. The combined organic phases were washed with water and brine, dried ($MgSO_4$), and evaporated under reduced pressure. Filtration of the residue (174 mg) through silica gel (16 g) using ethyl acetate-hexane (4:1) as eluent, gave the diol **33** (158 mg, 83 %), m.p. 179-180°C (from

acetone); $[\alpha]_D$ +112° (*c* 0.9); ν_{max}/cm^{-1} 3513br (OH) and 1710 (CO); δ_H (400 MHz) 1.00 (3H, s, 13β-Me), 2.55 (1H, td, *J* 2 x 11.6 and 3.9 Hz, 9α-H), 2.67 (1H, s, -OH), 2.79-2.82 (2H, m, 6α- and 6β-H), 3.01 (1H, d, *J* 10.5 Hz, 15β-H), 3.06 (1H, dd, *J* 10.5 and 4.1 Hz, 16β-H), 3.77 (3H, s, 3-OMe), 4.38 (1H, dt, *J* 8.2 and 2 x 4.1 Hz, 3'-H), 6.12 and 6.25 (each 1H, d, *J* 6.0 Hz, 17^1- and 17^2-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, d, *J* 8.6 and 2.8 Hz, 2-H), 7.19 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 15.0 (q, C-18), 25.2 (t, C-4'), 26.5 (t, C-7), 27.3 (t, C-11), 29.2 (t, C-12), 30.5 (t, C-6), 35.9 (t, C-5'), 40.6 and 40.7 (each d, C-8 and C-9), 51.3 and 56.8 (each d, C-15 and C-16), 55.2 (q, 3-OMe), 60.2 and 62.7 (each s, C-13 and C-14), 67.0 (d, C-3'), 91.0 (s, C-17), 111.9 (d, C-2), 113.4 (d, C-4), 127.3 (d, C-1), 132.2 (s, C-10), 133.3 and 135.2 (each d, C-17^1 and C-17^2), 138.1 (s, C-5), 157.5 (s, C-3), 212.9 (s, C-6') (Found: C, 76.1; H, 7.7 %; M^+, 394. $C_{25}H_{30}O_4$ requires C, 76.1; H 7.7 %; *M*, 394).

Pivaloylation of the triol 32

Pivaloyl chloride (0.1 cm^3, 0.85 mmol) was added to a stirred solution of the triol 32 (67 mg, 0.17 mmol) in dry pyridine (3 cm^3) at 0°C. The solution was allowed to warm to room temperature and stirring continued for 48 h. Water was added and the reaction mixture extracted with ethyl acetate. The combined organic phase was washed successively with water and brine, dried (MgSO4) and the solvent evaporated under reduced pressure. Flash chromatography of the crude residue (73 mg) using ethyl acetate-hexane (1:1) as eluent gave 3'α-pivaloyloxy 6'α,17β-diol **34?** (13 mg, 16 %), δ_H (400 MHz) 1.02 (3H, s, 13β-CH_3), 1.20 (9H, m, 3'α-OPv), 2.39 (1H, dd, *J* 11.1 and 4.6 Hz), 2.47 (1H, m, 9α-H), 2.59 (1H, dd, *J* 11.1 and 4.6 Hz), 2.74 (1H, d, *J* 12.5 Hz), 2.82-2.89 (2H, m, 6α- and 6β-H), 3.78 (3H, s, 3-OMe), 4.28 (1H, m), 5.44 (1H, td, *J* 2 x 4.4 and 2.4 Hz), 5.60 and 6.22 (each 1H, d, *J* 6.0 Hz, 17^1- and 17^2-H), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 15.3 (q, C-18), 25.3, 26.5, 26.6, 27.0, 27.1, 29.7, 30.1 (t, C-6), 39.1 [s, -OCO*C*$(CH_3)_3$], 40.2 and 40.5 (each d, C-8 and C-9), 49.0 and 49.7 (each d, C-15 and C-16), 55.2 (q, 3-OMe), 59.6 and 62.8 (each s, C-13 and C-14), 67.0 and 68.9 (each d, C-3' and C-6'), 89.8 (s, C-17), 111.6 (d, C-2), 113.4 (d, C-4), 126.6 (d, C-1), 133.0 (s, C-10), 133.1 and 134.2 (each d, C-17^1 and C-17^2), 138.2 (s, C-5), 157.5 (s, C-3), 178.9 (s, 3'α-O*C*OCMe_3); m/z 480 (M^+) followed by 6'α-pivaloyloxy-3'α,17β-diol **35?** (14 mg, 17 %), δ_H (400 MHz) 1.02 (3H, s, 13β-CH_3), 1.20 (9H, m, 6'α-OPv), 3.77 (3H, s, 3-OMe), 4.28 (1H, m), 5.54 (1H,

m), 5.98 and 6.10 (each 1H, d, *J* 6.1 Hz, 17^1- and 17^2-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.70 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H), 7.21 (1H, d, *J* 8.7 Hz, 1-H); δ_C (100 MHz) 15.3 (q, C-18), 24.3, 25.2, 26.4, 26.7, 26.9, 27.2, 29.7, 30.3 (t, C-6), 39.0 [s, -OCO*C*$(CH_3)_3$], 40.3 and 40.8 (each d, C-8 and C-9), 47.9 and 48.6 (each d, C-15 and C-16), 55.2 (q, 3-OMe), 59.2 and 62.6 (each s, C-13 and C-14), 64.8 and 70.5 (each d, C-3' and C-6'), 90.8 (s, C-17), 111.9 (d, C-2), 113.4 (d, C-4), 127.0 (d, C-1), 132.4 (s, C-10), 131.3 and 135.3 (each d, C-17^1 and C-17^2), 137.7 (s, C-5), 157.6 (s, C-3), 176.9 (s, 6'α-O*C*OCMe$_3$), m/z 480 (M^+) followed by starting material (44 mg, 65 %).

3-Methoxy-6'(5'*H*)-oxo-tetrahydro-15β,16β-benzo[15,16]-14,17α-ethenoestra-1,3,5(10)-triene-17β,3'α-diol 3'-methanesulfonate 36

To a solution of the diol **33** (100 mg, 0,25 mmol) in methylene chloride (5 cm^3) containing triethylamine (0.6 cm^3) stirred at –78°C was added methanesulfonyl chloride (130 mg, 1,14 mmol). The mixture was stirred at –78°C for 3 h and then water added. The mixture was extracted with methylene chloride; an ice-cold work-up of the combined organic phase was carried out with HCl (2M), saturated sodium hydrogen carbonate solution, and brine. The solvent was then dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give the crude (118 mg). Flash chromatography on silica gel (12 g) using ethyl acetate-hexane (1:1) as eluent gave the 3'α-mesylate **36** (75 mg, 63 %), δ_H (400 MHz) 0.99 (3H, s, 13β-Me), 1.47 (1H, td, *J* 2 x 11.4 and 2.9 Hz, 8β-H), 1.92 (1H, dddd, *J* 13.4, 6.0 and 2 x 2.9 Hz, 7β-H), 2.59 (1H, td, J 2 x 11.4 and 3.7 Hz, 9α-H), 2.72-2.87 (2H, m, 6α- and 6β-H), 3.01 (1H, d, *J* 11.2 Hz, 15β-H), 3.03 (3H, s, 3'-OSO_2CH_3), 3.18 (1H, dd, *J* 11.2 and 4.8 Hz, 16β-H), 3.77 (3H, s, 3-OMe), 5.33 (1H, td, *J* 2 x 4.8 and 2.0 Hz, 3'-H), 5.86 and 6.20 (each 1H, d, *J* 6.0 Hz, 17^1- and 17^2-H), 6.61 (1H, d, *J* 2.6 Hz, 4-H), 6.71 (1H, d, *J* 8.4 and 2.6 Hz, 2-H), 7.21 (1H, d, *J* 8.4 Hz, 1-H) followed by starting material (24 mg, 24%).

17β-acetoxy-3-methoxy-6'(5'*H*)-oxo-tetrahydro-15β,16β-benzo[15,16]-14,17α-ethenoestra-1,3,5(10)-triene-17β,3'α-diol 3'α-methanesulfonate 37

The alcohol **36** (75 mg, 0.16 mmol) was dissolved in dry pyridine (3 cm^3) and acetic anhydride (0.3 cm^3, 3.18 mmol) and 4-(dimethylamino)pyridine (20 mg, 0.16 mmol) were added. The mixture was stirred at room temperature for 24 h, then water added and stirring continued for a further 30 min. The reaction mixture was extracted with ethyl acetate and the combined organic phases were washed with aqueous sodium hydrogen carbonate, water and brine, and then dried ($MgSO_4$). Evaporated of the solvent under reduced pressure gave the crude (88 mg). Flash chromatography on silica gel (10 g) using ethyl acetate-hexane (1:1) as eluent gave the 17β-acetoxy 3'α-mesylate **37** (53 mg, 65 %), m.p. 150°C (from ethyl acetate-hexane); $[\alpha]_D$ +82° (*c* 1.0); ν_{max}/cm^{-1} 1750 (CO) and 1344 (SO); δ_H (400 MHz) 1.01 (3H, s, 13β-Me), 1.12 (1H, ddd, *J* 13.4, 4.3 and 2.5 Hz, 12β-H), 1.28 (1H, dddd, *J* 2 x 13.6, 11.7 and 4.3 Hz, 11β-H), 1.45 (1H, td, *J* 2 x 11.7 and 2.9 Hz, 8β-H), 1.83 (1H, dddd, *J* 2 x 13.6, 11,7 and 5.9 Hz, 7α-H), 2.11 (3H, s, 17-OAc), 2.25 (1H, dddd, *J* 13.6, 2 x 4.2 and 2.5 Hz, 11α-H), 2.62 (1H, td, *J* 2 x 11.7 and 4.2 Hz, 9α-H), 2.72-2.86 (2H, m, 6α- and 6β-H), 2.97 (1H, d, *J* 11.6 Hz, 15β-H), 3.00 (3H, s, 3'-OSO_2CH_3), 3.35 (1H, dd, *J* 11.6 and 4.5 Hz, 16β-H), 3.76 (3H, s, 3-OMe), 4.38 (1H, dt, *J* 2 x 4.5 and 1.5 Hz, 3'-H), 6.19 and 6.22 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.60 (1H, d, *J* 2.7 Hz, 4-H), 6.70 (1H, d, *J* 8.7 and 2.7 Hz, 2-H), 7.19 (1H, d, *J* 8.7 Hz, 1-H); δ_C (100 MHz) 15.7 (q, C-18), 21.7 (q, 17-OCO*C*H_3), 26.6 (t, C-7), 27.6 (t, C-4'), 28.2 and 28.4 (each t, C-11 and C-12), 30.9 (t, C-6), 34.6 (t, C-5'), 39.1 (q, 3'-OSO_2*C*H_3), 40.4 and 40.5 (each d, C-8 and C-9), 50.5 (d, C-16), 55.0 (d, C-15), 55.4 (q, 3-O*C*H_3), 58.1 and 62.6 (each s, C-13 and C-14), 74.3 (d, C-3'), 93.8 (s, C-17), 112.2 (d, C-2), 113.6 (d, C-4), 127.7 (d, C-1), 130.8 and 132.0 (each d, C-17^1 and C-17^2), 132.2 (s, C-10), 138.2 (s, C-5), 157.6 (s, C-3), 170.2 (s, 17-O*C*OCH$_3$), 208.5 (s, C-6') (Found: C, 65.2; H, 6.8; S, 5.9 %; M^+, 514. $C_{28}H_{34}O_7S$ requires C, 65.3; H, 6.7; S, 6.2 %; *M*, 514).

(17^1*R*,17^2*S*,17^4*S*,17^6*S*)-3-Methoxy-17^5-oxo-17^1,17^6;17^2,17^4-bicyclo-14,17β-hexano-14β-estra-1,3,5(10) 15-tetraen-17α-ol 38

The mesylate **37** (74 mg, 0.14 mmol) was dissolved in dry tetrahydrofuran (6 cm^3) and methanolic potassium hydroxide (M, 1 cm^3) was added. The mixture was stirred at 25°C for 1 h, then the solution acidified with aqueous HCl (M). The reaction mixture was extracted with ethyl acetate and the combined organis phase washed with aqueous sodium hydrogen carbonate (x2), brine and dried ($MgSO_4$). The solvent was evaporated to dryness under reduced pressure to give the crude residue (62 mg). Flash chroamtaography of the crude on silica gel (9 g) using ethyl acetate-hexane (1:1) as eluent gave the product **38** (40 mg, 74 %), m.p. 212-215°C (from ethyl acetate); $[\alpha]_D$ +127° (*c* 1.1); ν_{max}/cm^{-1} 3020 (OH) and 1715 (CO); δ_H (400 MHz) 0.80 (1H, ddd, *J* 10.4, 8.1 and 5.2 Hz, 17^{3}α-H), 1.02 (3H, s, 13β-Me), 1.09 (1H, ddd, *J* 12.8, 4.3 and 2.6 Hz, 12β-H), 1.30 (1H, dddd, *J* 2 x 13.4, 11.4 and 4.3 Hz, 11β-H), 1.43 (1H, td, *J* 2 x 11.4 and 2.6 Hz, 8β-H), 1.55 (1H, dddd, *J* 2 x 12.9, 11.4 and 7.0 Hz, 7α-H), 1.61 (1H, s, 17-OH), 1.84-1.94 (2H, m, 17^2- and 17^4-H), 2.10 (1H, m, 17^3-H), 2.21 (1H, dddd, *J* 13.4, 2 x 4.0 and 2.6 Hz, 11α-H), 2.42 (1H, td, *J* 2 x 11.4 and 4.0 Hz, 9α-H), 2.75 (1H, dddd, *J* 12.9, 5.3 and 2 x 2.6 Hz, 7β-H), 2.88 (2H, m, 6α- and 6β-H), 3.07 (1H, d, *J* 10.7 Hz, 17^{6}β-H), 3.50 (1H, dd, *J* 10.7 and 6.9 Hz, 17^{1}β-H), 3.79 (3H, s, 3-OMe), 6.03 and 6.12 (each 1H, d, *J* 6.0 Hz, 15- and 16-H), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, d, *J* 8.8 and 2.8 Hz, 2-H), 7.19 (1H, d, *J* 8.8 Hz, 1-H); δ_H (400 MHz, C_6D_6) 0.27 (1H, ddd, *J* 10.4, 7.9 and 5.0 Hz, 17^{3}α-H), 0.68 (3H, s, 13β-Me), 0.84 (1H, ddd, *J* 13.2, 4.3 and 2.7 Hz, 12β-H), 1.11 (1H, dddd, *J* 2 x 13.2, 11.8 and 4.3 Hz, 11β-H), 1.25 (1H, td, *J* 2 x 11.8 and 2.8 Hz, 8β-H), 1.50 (1H, dddd, *J* 2 x 13.3, 11.8 and 6.1 Hz, 7α-H), 1.79 (1H, m, 17^{3}β-H), 1.83 (1H, td, *J* 2 x 13.2 and 4.0 Hz, 12α-H), 1.98 (1H, dddd, *J* 13.2, 2 x 4.0 and 2.7 Hz, 11α-H), 2.24 (1H, td, *J* 2 x 11.8 and 4.0 Hz, 9α-H), 2.57 (1H, d, *J* 10.7 Hz, 17^{6}β-H), 2.73-2.87 (2H, m, 6α- and 6β-H), 2.98 (1H, dd, *J* 10.7 and 7.1 Hz, 17^{1}β-H), 3.37 (3H, s, 3-OMe), 5.67 (2H, s, 15- and 16-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, d, *J* 8.8 and 2.8 Hz, 2-H), 7.07 (1H, d, *J* 8.8 Hz, 1-H); δ_C (400 MHz) 9.2 (t, C-17^3), 15.0 (q, C-18), 19.7 (d. C-17^2), 25.0 (t, C-7), 26.8 and 26.9 (each t, C-11 and C-12), 30.4 (t, C-6), 32.1 (t, C-17^4), 40.0 (d, C-8), 40.5 (d, C-9), 47.0 (d, C-17^1), 55.2 (q, 3-O*C*H$_3$), 59.8 and 67.2 (each s, C-13 and C-14), 62.6 (d, C-17^6), 92.0 (s, C-17), 111.8 (d, C-2), 113.5 (d, C-4), 127.1 (d, C-1), 132.2 (s, C-10), 133.0 and 138.9 (each d, C-15

and C-16), 138.4 (s, C-5), 157.5 (s, C-3), 212.9 (s, C-17[5]) (Found: C, 79.5; H, 7.9 %; M^+, 376. $C_{25}H_{28}O_3$ requires C, 79.9; H, 7.5 %; *M*, 376).

Cycloaddition of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate 7 with maleic anhydride

A solution of dienyl acetate **7** (751 mg, 2.32 mmol) and maleic anhydride (337 mg, 3.4 mmol) in anhydrous toluene (7 cm^3) was heated in a sealed tube under nitrogen at 100°C. After 16 h, the mixture was allowed to cool and the solvent was evaporated under reduced pressure. The solid residue (1.04 g) was recrystallised from acetone to give 17β-*acetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-15α,16α-*dicarboxylic acid anhydride* **48** (891 mg, 91 %), m.p. 230°C; $[\alpha]_D$ +141° (*c* 1.0); ν_{max}/cm^{-1} 1862, 1783 and 1752 (CO); δ_H (400MHz) 1.03 (3H, s, 13β-Me), 1.21-1.34 (2H, m, 12β- and 11β-H), 1.63-1.75 (2H, m, 7α- and 8β-H), 2.18 (3H, s, 17-OAc), 2.28 (1H, m, 11α-H), 2.34 obsc (1H, td, *J* 2 x 13.1 and 4.9 Hz, 12α-H), 2.55 (1H, td, *J* 2 x 11.1 and 3.6 Hz, 9α-H), 2.68 (1H, m, 7β-H), 2.91 (2H, m, 6α- and 6β-H), 3.47 (1H, d, *J* 8.0 Hz, 15β-H), 3.78 (3H, s, 3-OMe), 3.98 (1H, d, *J* 8.0 Hz, 16β-H), 6.24 (1H, d, *J* 6.2 Hz, 17^2-H), 6.55 (1H, d, *J* 6.2 Hz, 17^1-H), 6.65 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H), 7.18 (1H, d, *J* 8.7 Hz, 1-H); δ_C (100 MHz) 15.5 (q, C-18), 21.6 (q, 17-OCO*C*H_3), 24.5 (t, C-7), 27.1 (t, C-11), 29.9 (t, C-12), 30.3 (t, C-6), 40.3 and 40.5 (each d, C-8 and C-9), 50.5 (d, C-15), 51.4 (d, C-16), 55.4 (q, 3-OMe), 61.2 (s, C-14), 67.1 (s, C-13), 94.3 (s, C-17), 112.3 (d, C-2), 113.8 (d, C-4), 127.5 (d, C-1), 130.6 (d, $C-17^2$), 133.9 (d, $C-17^1$), 131.2 (s, C-10), 137.9 (s, C-5), 157.9 (s, C-3), 169.6 and 169.7 (each s, C-2' and C-5'), 170.6 (s, 17-O*C*OCH$_3$) (Found: C, 70.7; H, 6.5 %; M^+, 422. $C_{25}H_{26}O_6$ requires C, 71.1; H, 6.2 %; *M*, 422).

Reduction of the cycloadduct 48

a) A solution of cycloadduct **48** (200 mg, 0.47 mmol) in anhydrous tetrahydrofuran (10 cm^3) was added slowly to a stirred, ice-cold suspension of sodium borohydride (22 mg, 0.6 mmol) in anhydrous tetrahydrofuran (3 cm^3). The reaction mixture was allowed to warm to room temperature and stirring was continued under nitrogen for 60 min. The reaction was quenched

with aqueous ammonium chloride, and the mixture was extracted with dichloromethane. The combined organic phase was washed successively with water and brine, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. Flash chromatography of the residue (174 mg) on silica gel (20 g) using ethyl acetate-hexane (3:7) as eluent gave 3-*methoxy*-5'(4'H)-*oxo*-14,17α-*etheno*-2',3'-*dihydro*-15β,16β-*furo*[4',3':15,16]*estra*-1,3,5(10)-*trien*-17β-*yl acetate* **49** (106 mg, 55 %), m.p. 191-193°C (from ethyl acetate-hexane); $[\alpha]_D$ +125° (*c* 1.0); ν_{max}/cm^{-1} 1884 and 1741 (CO); δ_H (400MHz) 1.04 (3H, s, 13β-Me), 1.26-1.38 (2H, m, 11β- and 12β-H), 1.58-1.69 (2H, m, 7α- and 8β-H), 2.12 (3H, s, 17β-OAc), 2.14 obsc (1H, td, *J* 2 x 13.8 and 4.7 Hz, 12α-H), 2.25 (1H, m, 11α-H), 2.52 (1H, td, *J* 2 x 11.2 and 4.4 Hz, 9α-H), 2.88-2.92 (3H, m, 6α-, 6β- and 7β-H), 3.27 (1H, d, *J* 9.2 Hz, 15β-H), 3.40 (1H, td, *J* 2 x 9.2 and 4.4 Hz, 16β-H), 3.78 (3H, s, 3-OMe), 4.29 (1H, dd, *J* 10.6 and 9.2 Hz, 2'β-H), 4.51 (1H, dd, *J* 10.6 and 4.4 Hz, 2'α-H), 6.27 (1H, d, J 6.2 Hz, 17^2-H), 6.50 (1H, d, *J* 6.2 Hz, 17^1-H), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.20 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100MHz) 15.0 (q, C-18), 21.3 (q, 17-OCO*C*H_3), 24.6 (t, C-7), 26.9 (t, C-11), 28.7 (t, C-12), 30.3 (t, C-6), 40.3 (d, C-8), 40.7 (d, C-9), 46.1 (d, C-16), 52.8 (d, C-15), 55.2 (q, 3-OMe), 59.1 (s, C-14), 64.9 (s, C-13), 69.0 (t, C-2'), 95.0 (s, C-17), 112.0 (d, C-2), 113.4 (d, C-4), 127.2 (d, C-1), 131.6 (s, C-10), 133.0 (d, C-17^1), 133.4 (d, C-17^2), 138.2 (s, C-5), 157.5 (s, C-3), 171.1 (s, 17-O*C*OCH$_3$), 176.8 (s, C-5') (Found: C, 73.5; H, 7.1 %; M^+, 408. $C_{25}H_{28}O_5$ requires C, 73.5; H, 6.9 %; *M*, 408) followed by 3-*methoxy*-2'(3'H)-*oxo*-14,17α-*etheno*-4',5'-*dihydro*-15β,16β-*furo*[4',3':15,16]*estra*-1,3,5(10)-*trien*-17β-*yl acetate* **50** (48 mg, 25 %), m.p. 217-218°C (from acetone-methanol); $[\alpha]_D$ +181° (*c* 0.9); ν_{max}/cm^{-1} 1884 and 1762 (CO); δ_H (400MHz) 1.02 (3H, s, 13β-H), 1.52 (1H, td, *J* 2 x 11.0 and 2.7 Hz, 8β-H), 1.60 (1H, m, 7β-H), 1.75 (1H, dddd, *J* 2 x 12.4, 11.0 and 7.4 Hz, 7α-H), 2.16 (3H, s, 17β-OAc), 2.25 (1H, m, 11α-H), 2.39 (1H, td, *J* 2 x 13.7 and 4.2 Hz, 12α-H), 2.55 (1H, td, *J* 2 x 11.0 and 3.7 Hz, 9α-H), 2.87-2.90 (2H, m, 6α- and 6β-H), 3.03 (1H, td, *J* 2 x 9.5 and 3.9 Hz, 15β-H), 3.60 (1H, d, *J* 9.5 Hz, 16β-H), 3.77 (3H, s, 3-OMe), 3.87 (1H, dd, *J* 9.5 and 3.9 Hz, 5'α-H), 4.33 (1H, t, *J* 2 x 9.5 Hz, 5'β-H), 6.21 (1H, d, *J* 6.2 Hz, 17^2-H), 6.52 (1H, d, *J* 6.2 Hz, 17^1-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.74 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), 7.2 (1H, d, *J* 8.5 Hz, 1-H); δ_C (100 MHz) 14.9 (q, C-18), 21.5 (q, 17-OCO*C*H_3), 24.7 (t, C-7), 27.2 (t, C-11), 29.9 (t, C-6), 30.3 (t, C-12), 39.4 and 39.9 (each d, C-8 and C-9), 42.8 (d, C-15), 51.5 (d, C-16), 55.2 (q, 3-OMe), 58.7 (s, C-14), 65.6 (s, C-13), 69.0 (t, C-5'), 94.5 (s, C-17), 112.1 (d, C-2), 113.7 (d, C-4), 127.3 (d, C-1), 129.6 (d, C-17^2), 134.1 (d, C-17^1), 131.2 (s, C-10), 137.0 (s, C-5), 157.6 (s, C-

3), 169.8 (s, 17-O*C*OCH$_3$), 175.9 (s, C-2') (Found: C, 73.4; H, 7.0 %; M$^+$, 408. $C_{25}H_{28}O_5$ requires C, 73.5; H, 6.9 %; *M*, 408).

b) To a stirred solution of the cycloadduct **48** (50 mg, 0.12 mmol) in dry tetrahydrofuran (2.5 cm^3) at –78°C was added L-Selectride (0.26 cm^3, 0.26 mmol). The reaction mixture was stirred for 2h at –78°C and then aqueous ammonium chloride solution was added and the cooling removed. Aqueous sodium hydroxide (5 cm^3, 5 %) was added slowly followed by hydrogen peroxide (5 cm^3, 30 %), the mixture stirred for 0.5 h and then extracted with ethyl acetate. The combined organic phases were washed successively with saturated sodium hydrogen carbonate, water and brine, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the crude (48 mg) on silica gel (5 g) using ethyl acetate-hexane (3:7) as eluent gave **49** (23 mg, 48 %) followed by **50** (9 mg, 19 %).

c) A solution of the cycloadduct **48** (95 mg, 0.22 mmol) in anhydrous tetrahydrofuran (10 cm^3) was added to a suspension of LAH (80 mg, 2.1 mmol) in anhydrous tetrahydrofuran (5 cm^3) at 0°C with stirring. The mixture was refluxed for 5 h under nitrogen. The reaction was quenched with water-triethylamine, added at 0°C, and stirring continued for 30min. The reaction mixture was filtered through Celite, washing with ethyl acetate-triethylamine (1:1) followed by methanol-ethyl acetate (1:9). The filtrate was evaporated under reduced pressure to give the crude residue (98 mg). Flash chromatography on silica gel (15g) using methanol-chloroform (1:19) as eluent gave 3-*methoxy*-15α,16α-*bis(hydroxymethyl)*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*ol* **56** (60 mg, 72 %), m.p. 218-222°C (from methanol-chloroform); $[\alpha]_D$ +117° (*c* 0.8, pyridine); ν_{max}/cm^{-1} 3515 br (OH); δ_H (400MHz, C_5D_5N) 1.17 (3H, s, 13β-Me), 1.31-1.42 (2H, m, 12β-H and 11β-H), 1.58 obsc (1H, qd, *J* 3 x 11.9 and 5.7 Hz, 7α-H), 2.26-2.35 (2H, m, 7β- and 11α-H), 2.30 obsc (1H, td, *J* 2 x 13.8 and 5.0 Hz, 12α-H), 2.48 (1H, td, *J* 2 x 11.0 and 3.8 Hz, 9α-H), 2.70-2.86 (2H, m, 6α-H and 6β-H), 2.98 (1H, ddd, *J* 10.3, 9.9 and 2.8 Hz, 15β-H), 3.28 (1H, ddd, *J* 10.3, 10.0 and 3.8 Hz, 16β-H), 3.74 (3H, s, 3-OMe), 3.88 (1H, t, *J* 2 x 9.9 Hz, 15^1-H), 4.19 (1H, t, *J* 2 x 10.0 Hz, 16^1-H), 4.32 (1H, dd, *J* 9.9 and 2.8 Hz, 15^1-H), 4.58 (1H, dd, *J* 10.0 and 3.8 Hz, 16^1-H), 4.84 (1H, s, -OH), 6.02 (1H, d, *J* 6.1 Hz, 17^2-H), 6.17 (1H, d, *J* 6.1 Hz, 17^1-H), 6.37 and 6.48 (each 1H, s, -OH), 6.78 (1H, d, *J* 2.7 Hz, 4-H), 6.91 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), 7.29 (1H, d, *J* 8.5 Hz, 1-H); δ_C (100 MHz) 14.5 (q, C-18), 26.0 (t, C-7), 27.5 (2C, t, C-11 and C-12), 30.1 (t, C-6), 40.6 (2C, d, C-8 and C-9), 50.9 (d, C-16), 51.0 (d, C-15), 54.8 (q, 3-OMe), 59.0 (s, C-14), 60.9 (s, C-

14), 60.8 (t, C-16^1), 61.8 (t, C-15^1), 90.2 (s, C-17), 112.0 (d, C-2), 113.2 (d, C-4), 127.4 (d, C-1), 131.9 (d, C-17^2), 132.8 (s, C-10), 136.4 (d, C-17^1), 137.8 (s, C-5), 157.7 (s, C-3) (Found: C, 74.2; H, 8.1 %; M^+, 370. $C_{23}H_{30}O_4$ requires C, 74.6; H, 8.2 %; *M*, 370).

d) To a stirred solution of the cycloadduct **48** (300 mg, 0.71 mmol) in anhydrous tetrahydofuran (10 cm^3) at 0°C was added sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) (1.7 cm^3, 8.7 mmol) dropwise. The reaction mixture was heated under reflux for 21 h. The mixture was allowed to cool before adding water-triethylamine (1:3, 4 cm^3) and stirring was continued for a further 30 min. The reaction mixture was then filtered through Celite, washing with ethyl acetate-triethylamine (1:1, 50 cm^3) followed by methanol-ethyl acetate (1:9, 30 cm^3). The filtrate was evaporated to dryness under reduced pressure to give a solid residue. Recrystalisation from methanol- chloroform gave the triol **56** (261 mg, 90 %).

Acetylation of the triol 56

a) The triol **56** (50 mg, 0.14 mmol) was dissolved in dry pyridine (2 cm^3), and acetic anhydride (0.1 cm^3, 1.1 mmol) was added. The mixture was stirred under nitrogen at room temperature for 20 h. Water was added and stirring continued for 30 min. The aqueous phase was extracted with ethyl acetate and the combined organic phase washed with aqueous sodium bicarbonate, water, brine and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the crude product (70 mg). Flash chromatography of the residue on silica (10 g) using ethyl acetate-hexane (3:7) as eluent gave 3-*methoxy*-15α,16α-*bis(acetoxymethyl)*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*ol* **57** (51 mg, 83 %), m.p. 169-171°C (from ethyl acetate); $[\alpha]_D$ +144° (*c* 1.0); ν_{max}/cm^{-1} 1735(CO) and 3490 (OH); δ_H (400MHz) 1.00 (3H, s, 13β-Me), 1.23 (1H, ddd, *J* 13.0, 4.0 and 2.5 Hz, 12β-H), 1.61 (1H, s, -OH), 1.67 (1H, dddd, *J* 2 x 11.9, 10.5 and 6.0 Hz, 7α-H), 2.05 and 2.08 (each 3H, s, OAc), 2.23 (1H, ddd, *J* 13.6, 2 x 4.0 and 2.6 Hz, 11α-H), 2.48 (1H, td, *J* 2 x 11.4 and 4.0 Hz, 9α-H), 2.65 (1H, td, *J* 2 x 9.0 and 3.0 Hz, 15β-H), 2.70 (1H, m, 16β-H), 2.79-2.89 (2H, m, 6α- and 6β-H), 3.65 (1H, dd, *J* 12.0 and 9.0 Hz, 15^1-H), 3.78 (3H, s, 3-OMe), 4.17 (1H, dd *J* 11.3 and 7.4 Hz, 16^1-H), 4.27 (1H, dd, *J* 11.3 and 5.7 Hz, 16^1-H), 4.45 (1H, dd, *J* 12.0 and 3.0 Hz, 15^1-H), 6.03 and 6.08 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, dd, *J* 8.4 and 2.8 Hz, 2-H), 7.20 (1H, d, *J* 8.4 Hz, 1-H); δ_C (100 MHz) 14.5 (q, C-18),

21.0 and 21.1 (each q, OCO*C*H$_3$), 25.5 (t, C-7), 27.2 (t, C-11), 27.3 (t, C-12), 30.1 (t, C-6), 40.0 and 40.4 (d, C-8 and C-9), 45.7 and 46.8 (each d, C-15 and C-16), 55.2 (q, 3-OMe), 59.2 and 61.1 (each s, C-13 and C-14), 63.9 and 64.0 (each t, C-15^1 and C-16^1), 91.1 (s, C-17), 111.9 (d, C-2), 113.3 (d, C-4), 127.2 (d, C-1), 132.2 (s, C-10), 132.8 and 136.1 (each d, C-17^1 and C-17^2), 137.6 (s, C-5), 157.5 (s, C-3), 170.7 and 170.8 (each s, O*C*OCH$_3$) (Found: C, 71.4; H, 7.8 %; M$^+$, 454. $C_{27}H_{34}O_6$ requires C, 71.3; H, 7.5 %; *M*, 454).

b) The triol **56** (149 mg, 0.40 mmol) was dissolved in dry pyridine (3 cm^3), and acetic anhydride (0.5 cm^3, 5.3 mmol) and 4-(dimethylamino)pyridine (13 mg, 0.1 mmol) were added. The mixture was stirred under nitrogen at room temperature for 20 h. Water was added and stirring continued for 30min. The reaction mixture was extracted with ethyl acetate. The combined organic phase was washed with 3M HCl, aqueous sodium bicarbonate, brine and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the product 3-*methoxy*-15α,16α-*bis(acetoxymethyl)*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl acetate* **58** (170 mg, 85 %), m.p. 150-152°C (from ethyl acetate); $[\alpha]_D$ +99° (*c* 1.0); ν_{max}/cm^{-1} 1884, 1735 and 1653 (CO); δ_H (400MHz) 1.01 (3H, s, 13β-Me), 1.11 (1H, ddd, *J* 13.5, 3.8 and 3.3 Hz, 12β-H), 1.31 (1H, dddd, *J* 2 x 13.5, 12.0 and 3.3 Hz, 11β-H), 1.58 (1H, td, *J* 2 x 12.0 and 2.4 Hz, 8β-H), 1.69 (1H, dddd, *J* 2 x 12.0, 10.5 and 6.0 Hz, 7α-H), 2.04, 2.05 and 2.09 (each 3H, s, OAc), 2.16-2.23 (2H, m, 7β-H and 11α-H), 2.30 (1H, td, *J* 2 x 13.5 and 4.5 Hz, 12α-H), 2.50 (1H, td, *J* 2 x 12.0 and 3.6 Hz, 9α-H), 2.57 (1H, td, *J* 2 x 8.5 and 3.4 Hz, 15β-H), 2.79-2.89 (2H, m, 6α- and 6β-H), 2.96 (1H, dt, *J* 8.5 and 2 x 6.6 Hz, 16β-H), 3.77 (1H,dd, *J* 12.2 and 8.5 Hz, 15^1-H), 3.78 (3H, s, 3-OMe), 4.06 (1H, dd, *J* 11.5 and 6.6 Hz, 16^1-H), 4.19 (1H, dd, *J* 11.5 and 6.6 Hz, 16^1-H), 4.38 (1H, dd, *J* 12.2 and 3.4 Hz, 15^1-H), 6.06 and 6.47 (each 1H, d, *J* 6.3 Hz, 17^1- and 17^2-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.18 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 15.0 (q, C-18), 20.9, 21.0 and 21.6 (each q, OCO*C*H$_3$), 25.2 (t, C-7), 27.3 (t, C-11), 29.1 (t, C-12), 30.1 (t, C-6), 39.9 and 40.2 (d, C-8 and C-9), 45.1 and 45.3 (each d, C-15 and C-16), 55.2 (q, 3-OMe), 58.1 and 62.2 (each s, C-13 and C-14), 62.7 and 63.7 (each t, C-15^1 and C-16^1), 94.8 (s, C-17), 111.9 (d, C-2), 113.2 (d, C-4), 127.2 (d, C-1), 130.2 and 132.6 (each d, C-17^1 and C-17^2), 132.18 (s, C-10), 137.5 (s, C-5), 157.5 (s, C-3), 170.0, 170.8 and 170.9 (each s, -O*C*OCH$_3$) (Found: C, 69.9; H, 7.3 %; M$^+$, 496. $C_{29}H_{36}O_7$ requires C, 70.2; H, 7.3 %; *M*, 496).

3-Methoxy-15α,16α-bis(hydroxymethyl)-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol 15^1,16^1-acetonide 59

The triol **56** (400 mg, 1.1 mmol) was suspended in freshly distilled dichloromethane (10 cm^3) to which was added dry dimethoxypropane (1.3 cm^3), toluene-*p*-sulfonic acid (41 mg, 0.2 mmol) and 4Å molecular sieves. The reaction mixture was stirred at room temperature under nitrogen for 5 h and was then quenched by filtering the solution onto aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic phase washed with water, brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a crude residue (410 mg). Flash chromatography on silica (35 g) using ethyl acetate-hexane (3:7) as the eluent gave the acetonide **59** (332 mg, 75 %), m.p. 183-186°C (from acetone); $[\alpha]_D$ +104° (*c* 1.1); ν_{max}/cm^{-1} 3449br (OH); δ_H (400MHz) 1.00 (3H, s, 13β-Me), 1.14 (1H, ddd, *J* 13.1, 4.1 and 2.5 Hz, 12β-H), 1.37 [6H, s, C(C*H*$_3$)$_2$], 1.51 (1H, td, *J* 2 x 11.7 and 2.8 Hz, 8β-H), 1.62 (1H, dddd, *J* 2 x 11.7, 10.6 and 6.1 Hz, 7α-H), 1.70 (1H, s, -OH), 1.96 (1H, dddd, *J* 11.7, 5.7 and 2 x 2.8 Hz, 7β-H), 2.08 (1H, td, *J* 2 x 13.1 and 4.3 Hz, 12α-H), 2.22 (1H, dddd, *J* 13.4, 2 x 4.3 and 2.7 Hz, 11α-H), 2.44 (1H, td, *J* 2 x 11.7 and 4.3 Hz, 9α-H), 2.71-2.89 (4H, m, 6α-, 6β-, 15β- and 16β-H), 3.58 (1H, dd, *J* 12.7 and 11.4 Hz, 15^1-H), 3.71 (1H, dd, *J* 13.2 and 9.7 Hz, 16^1-H), 3.77 (3H, s, 3-OMe), 3.92 (1H, dd *J* 13.2 and 3.7 Hz, 16^1-H), 3.99 (1H, dd, *J* 12.7 and 4.1 Hz, 15^1-H), 5.98 and 6.05 (each 1H, d, *J* 6.0 Hz, 17^1- and 17^2-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, dd, *J* 8.4 and 2.8 Hz, 2-H), 7.18 (1H, d, *J* 8.4 Hz, 1-H); δ_C (100 MHz) 14.2 (q, C-18), 20.2 [q, C(*C*H$_3$)], 26.2 (t, C-7), 26.9 and 27.0 (each t, C-11 and C-12), 29.3 [q, C(*C*H$_3$)], 30.0 (t, C-6), 39.9 (d, C-8), 40.3 (d, C-9), 49.9 and 50.2 (each d, C-15 and C-16), 55.1 (q, 3-OMe), 58.7 (s, C-14), 62.1 (s, C-13), 61.8 (t, C-16^1), 64.2 (t, C-15^1), 90.1 (s, C-17), 101.3 (s, *C*(CH$_3$)$_2$), 111.7 (d, C-2), 113.2 (d, C-4), 127.0 (d, C-1), 132.4 (s, C-10), 132.4 and 135.3 (each d, C-17^1 and C-17^2), 137.6 (s, C-5), 157.4 (s, C-3) (Found: C, 75.7; H, 8.3 %; M$^+$, 410. $C_{26}H_{34}O_4$ requires C, 76.1; H, 8.4 %; *M*, 410).

17β-Acetoxy-3-methoxy-15α,16α-bis(hydroxymethyl)-14,17α-ethenoestra-1,3,5(10)-triene 15^1,16^1-acetonide 61

The acetonide **59** (300 mg, 0.7 mmol) was dissolved in pyridine (5 cm^3) and acetic anhydride (0.7 cm^3, 7.4 mmol) and 4-(dimethylamino)pyridine (22 mg, 0.2 mmol) added. The mixture

was stirred at room temperature for 17 h, then water added and stirring continued for 30 min. The reaction mixture was extracted into ethyl acetate and the combined organic phase washed with aqueous sodium bicarbonate, water, brine and then dried ($MgSO_4$). The solvent was evaporated to dryness to give the crude material (323 mg) which was chromatographed on silica (30 g) using ethyl acetate-hexane (1:4) as eluent to give the 17β-acetate **61** (303 mg, 91 %), m.p. 113-116°C (acetone-methanol); $[\alpha]_D$ 81° (*c* 1.0); ν_{max}/cm^{-1} 1736 (CO); δ_H(400MHz) 1.03 (3H, s, 13β-Me), 1.10 (1H, ddd, *J* 12.9, 3.8 and 2.6 Hz, 12β-H), 1.36 [6H, s, $-C(CH_3)_2$], 1.52 (1H, td, *J* 2 x 11.5 and 3.0 Hz, 8β-H), 1.98 (1H, dddd, *J* 12.4, 6.2 and 2 x 3.0 Hz, 7β-H), 2.07 (3H, s, 17-OAc), 2.18 (1H, dddd, *J* 13.3, 2 x 3.7 and 2.6 Hz, 7α-H), 2.27 (1H, td, *J* 2 x 12.9 and 3.7 Hz, 12α-H), 2.46 (1H, td, *J* 2 x 11.5 and 3.7 Hz, 9α-H), 2.72 (1H, ddd, *J* 11.7, 9.6 and 4.5 Hz, 15β-H), 2.78-2.90 (2H, m, 6α- and 6β-H), 2.97 (1H, td, *J* 2 x 9.6 and 4.3 Hz, 16β-H), 3.60 (1H, dd, *J* 12.8 and 11.7 Hz, 15^1-H), 3.68 (1H, dd, *J* 13.3 and 9.6 Hz, 16^1-H), 3.77 (3H, s, 3-OMe), 3.84 (1H, dd, *J* 13.3 and 4.3 Hz, 16^1-H), 4.02 (1H, dd, *J* 12.8 and 4.5 Hz, 15^1-H), 6.04 and 6.46 (each 1H, d, *J* 6.3 Hz, 17^1- and 17^2-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), 7.18 (1H, d, *J* 8.5 Hz, 1-H); δ_C (100MHz) 14.7 (q, C-18), 20.1 [q, $-C(CH_3)_2$], 21.6 (q, $COCH_3$), 26.2 (t, C-7), 27.2 (t, C-11), 29.1 (t, C-12), 29.5 [q, $-C(CH_3)_2$], 30.0 (t, C-6), 39.8 and 40.1 (each d, C-8 and C-9), 48.8 and 48.9 (each d, C-15 and C-16), 55.2 (q, 3-OMe), 57.5 and 63.3 (each s, C-13 and C-14), 62.1 and 64.3 (each t, $C-15^1$ and $C-16^1$), 94.0 (s, C-17), 101.2 [s, $-C(CH_3)_2$], 111.8 (s, C-2), 113.2 (s, C-4), 127.1 (d, C-1), 130.3 and 132.4 (each d, $C-17^1$ and $C-17^2$), 132.3 (s, C-10), 137.6 (s, C-5), 157.4 (s, C-3), 170.4 (s, $-COCH_3$) (Found: C, 74.8; H, 8.0 %; M^+, 452. $C_{28}H_{36}O_5$ requires C, 74.3; H, 8.0 %; *M*, 452).

3-Methoxy-14,17α-etheno-tetrahydro-15β,16β-furo[4',3':15,16]estra-1,3,5(10)-trien-17β-ol 65

The triol **56** (85 mg, 0.3 mmol) was dissolved in dry acetone (10 cm^3) to which was added anhydrous copper sulfate (50 mg, 0.3 mmol) and tosic acid (a few crystals). The reaction mixture was heated under reflux under nitrogen for 19 h, after which solid potassium carbonate was added. Stirring was continued for a further 60 min, the reaction mixture then filtered and the solvent evaporated under reduced pressure. Flash chromatography of the crude residue (110 mg) on silica gel (12 g) using methanol-chloroform (1:19) as eluent gave

the tetrahydrofuran derivative **65** (53 mg, 65 %), m.p. 200-204°C (from ethyl acetate); $[\alpha]_D$ +179° (*c* 1.1); ν_{max}/cm^{-1} 3600br (OH); δ_H (400MHz) 1.06 (3H, s, 13β-Me), 1.14 (1H, ddd, *J* 13.2, 4.3 and 2.6 Hz, 12β-H), 1.33 (1H, dddd, *J* 2 x 13.2, 11.6 and 4.3 Hz, 11β-H), 1.46 (1H, td, *J* 2 x 11.6 and 3.1 Hz, 8β-H), 1.61-1.76 (2H, m, 7α-H and 7β-H), 1.94 (1H, bs, -OH), 2.13 (1H, td, *J* 2 x 13.2 and 4.2 Hz, 12α-H), 2.23 (1H, dddd, *J* 13.2, 2 x 4.2 and 2.6 Hz, 11α-H), 2.50 (1H, td, *J* 2 x 11.6 and 4.2 Hz, 9α-H), 2.85-2.90 (3H, m, 6α-, 6β- and 15β-H), 3.08 (1H, td, *J* 2 x 8.3 and 3.2 Hz, 16β-H), 3.54 (1H, dd, *J* 9.2 and 3.6 Hz, 2'- or 5'-H), 3.67 (1H, dd, *J* 9.4 and 7.5 Hz, 2'- or 5'-H), 3.69 (1H, dd, *J* 9.2 and 8.1 Hz, 2'- or 5'-H), 3.76 (1H, obsc dd, 2'- or 5'-H), 3.77 (3H, s, 3-OMe), 6.03 and 6.14 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), 7.21 (1H, d, *J* 8.5 Hz, 1-H); δ_C (100 MHz) 14.3 (q, C-18), 24.6 (t, C-7), 27.1 (t, C-11), 27.8 (t, C-12), 30.1 (t, C-6), 39.9 and 40.1 (d, C-8 and C-9), 52.3 and 54.0 (each d, C-15 and C-16), 55.2 (q, 3-OMe), 59.0 and 64.1 (each s, C-13 and C-14), 68.0 and 69.7 (each t, C-2' and C-5'), 91.4 (s, C-17), 111.8 (d, C-2), 113.6 (d, C-4), 127.2 (d, C-1), 132.0 (s, C-10), 133.0 and 135.1 (each d, $C\text{-}17^1$ and $C\text{-}17^2$), 137.5 (s, C-5), 157.4 (s, C-3) (Found: C, 78.4; H, 8.0 %; M^+, 352. $C_{23}H_{28}O_3$ requires C, 78.4; H, 8.0 %; *M*, 352).

3-Methoxy-15α,16α-bis(hydroxymethyl)-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate 66

The acetoxy acetonide **61** (215 mg, 0.5 mmol) was dissolved in iodine/methanol (0.5 %, $5cm^3$) and stirred for 3 h. The excess iodine was reduced by adding thiosulphate solution (0.1 M, 3 cm^3), and stirring was continued for a further 30 min. The reaction mixture was extracted into chloroform and the combined organic phase washed with water, brine and then dried ($MgSO_4$). The organic phase was then evaporated to dryness to give the crude material (210 mg) which was chromatographed on silica (20 g) using ethyl acetate-hexane (1:1) as eluent to give the diol **66** (149 mg, 76 %), m.p. 172-173°C (from ethyl acetate-hexane); $[\alpha]_D$ +94° (*c* 1.0); ν_{max}/cm^{-1} 1736 (CO) and 3438br (OH); δ_H (400MHz) 0.99 (3H, s, 13β-Me), 1.06 (1H, ddd, *J* 13.4, 3.8 and 2.6 Hz, 12β-H), 1.56 (1H, td, *J* 2 x 11.8 and 2.7 Hz, 8β-H), 1.65 (1H, m, 7α-H), 1.70 (1H, s, -OH), 2.08 (3H, s, 17-OAc), 2.08-2.19 (2H, m, 7β-H and 11α-H), 2.25 (1H, td, *J* 2 x 13.4 and 3.9 Hz, 12α-H), 2.44 (1H, td, *J* 2 x 11.8 and 3.3 Hz, 9α-H), 2.57

(1H, td, *J* 2 x 10.0 and 2.6 Hz, 15β-H), 2.76-2.85 (2H, m, 6α- and 6β-H), 2.89 (1H, td, *J* 2 x 10.0 and 3.1 Hz, 16β-H), 3.44 (1H, s, -OH), 3.51 (1H, dd, *J* 11.5 and 10.0 Hz, 15^1-H), 3.60 (1H, dd, *J* 11.3 and 10.0 Hz, 16^1-H), 3.74 (3H, s, 3-OMe), 3.81 (1H, dd, *J* 11.3 and 3.1 Hz, 16^1-H), 4.05 (1H, dd, *J* 11.5 and 2.6 Hz, 15^1-H), 5.95 and 6.28 (each 1H, d, *J* 6.0 Hz, 17^1- and 17^2-H), 6.59 (1H, d, *J* 2.7 Hz, 4-H), 6.69 (1H, dd, *J* 8.4 and 2.7 Hz, 2-H), 7.15 (1H, d, *J* 8.4 Hz, 1-H); δ_C (100MHz) 14.8 (q, C-18), 21.6 (q, $COCH_3$), 25.9 (t, C-7), 27.4 (t, C-11), 28.6 (t, C-12), 30.1 (t, C-6), 40.0 and 40.1 (each d, C-8 and C-9), 49.0 and 49.3 (each d, C-15 and C-16), 55.2 (q, 3-OMe), 57.9 and 62.1 (each s, C-13 and C-14), 60.5 and 62.3 (each t, C-15^1 and C-16^1), 94.6 (s, C-17), 111.9 (s, C-2), 113.2 (s, C-4), 127.2 (d, C-1), 130.4 and 131.6 (each d, C-17^1 and C-17^2), 132.3 (s, C-10), 137.5 (s, C-5), 157.4 (s, C-3), 170.6 (s, -$COCH_3$) (Found: C, 72.4; H, 7.8 %; M+, 412. $C_{25}H_{32}O_5$ requires C, 72.8; H, 7.8 %; *M*, 412).

3-Methoxy-14,17α-etheno-tetrahydrofuro[4',3':15,16]estra-1,3,5(10)-trien-17β-yl acetate 67

a) The acetoxy glycol **66** (146 mg, 0.4 mmol) was dissolved in pyridine (6 cm^3) and p-toluenesulfonyl chloride (133 mg, 0.7 mmol) added at 0°C. The reaction mixture was stirred for 48 h at 0°C followed by 100 h at room temperature. Water was added and stirring continued for a further 30 min. The reaction mixture was extracted into ethyl acetate and the combined organic phase washed with 10 % HCl (3x), aqueous sodium hydrogen carbonate, brine and then dried ($MgSO_4$). The organic phase was evaporated to dryness to give the crude material (170 mg) which was chromatographed on silica (18 g) using ethyl acetate-hexane (2:3) as eluent to give starting material **66** (43 mg, 30 %) and the ether **67** (81 mg, 41 %), m.p. 165-167°C (from acetone); $[\alpha]_D$ +135° (*c* 1.0); ν_{max}/cm^{-1} 1734 (CO); δ_H(400MHz) 1.11 (3H, s, 13β-Me), 2.09 (3H, s, 17-OAc), 2.50 (1H, td, *J* 2 x 11.4 and 3.8 Hz, 9α-H), 2.80-2.90 (2H, m, 6α- and 6β-H), 2.99 (1H, ddd, *J* 9.6, 8.6 and 6.3 Hz, 15β-H), 3.22 (1H, dt, *J* 9.7 and 2 x 6.7 Hz, 16β-H), 3.38 (1H, dd, *J* 8.6 and 6.3 Hz, 5'-H), 3.78 (3H, s, 3-OMe), 3.79 (1H, m, 2'- or 5'-H), 3.80 (1H, m, 2'- or 5'-H), 3.84 (1H, dd, *J* 9.9 and 6.4 Hz, 2'- or 5'-H), 6.12 and 6.37 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H), 7.21 (1H, d, *J* 8.7 Hz, 1-H); δ_H(400MHz, C_6D_6) 0.95 (3H, s, 13β-Me), 1.66 (3H, s, 17-OAc), 2.55-2.69 (3H, m, 6α-, 6β- and 15β-H), 3.06 (1H, dt, *J* 9.6 and 2 x 7.1 Hz, 16β-

H), 3.34 (1H, dd, *J* 8.6 and 6.4 Hz, 5'-H), 3.42 (3H, s, 3-OMe), 3.70 (1H, t, *J* 2 x 8.6 Hz, 5'-H), 4.03 (1H, dd, *J* 9.7 and 7.1 Hz, 2'-H), 4.18 (1H, dd, *J* 9.7 and 7.1 Hz, 2'-H), 5.80 and 6.44 (each 1H, d, *J* 6.3 Hz, 17^1- and 17^2-H), 6.69 (1H, d, *J* 2.7 Hz, 4-H), 6.79 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), 7.12 (1H, d, *J* 8.5 Hz, 1-H); δ_C(100MHz) 14.7 (q, C-18), 21.4 (q, $COCH_3$), 24.8 (t, C-7), 27.2 (t, C-11), 29.5 (t, C-12), 30.1 (t, C-6), 39.7 (2C, d, C-8 and C-9), 53.1 and 53.7 (each d, C-15 and C-16), 55.2 (q, 3-OMe), 56.9 (s, C-14), 66.1 (s, C-13), 69.3 and 69.7 (each t, C-15^1 and C-16^1), 94.7 (s, C-17), 111.9 (s, C-2), 113.6 (s, C-4), 127.2 (d, C-1), 132.0 (s, C-10), 133.3 and 133.4 (each d, C-17^1 and C-17^2), 137.6 (s, C-5), 157.5 (s, C-3), 171.0 (s, 17-*C*OCH_3) (Found: C, 76.0; H, 7.6 %; M+, 394. $C_{25}H_{30}O_4$ requires C, 76.1; H, 7.7 %; *M*, 394).

b) Acetic anhydride (0.2 cm^3, 2.1 mmol) and 4-(Dimethylamino)pyridine (5 mg, 0.04 mmol) were added to a stirred solution of the tetrahydrofuran **65** (58 mg, 0.16 mmol) in pyridine (3 cm^3). The mixture was stirred at room temperature for 18 h, then water added and stirring continued for 30 min. The reaction mixture was extracted into ethyl acetate and the combined organic phase washed with aqueous sodium bicarbonate, water, brine and then dried ($MgSO_4$). The solvent was evaporated to dryness to give the crude material (60 mg) which was chromatographed on silica gel (10 g) using ethyl acetate-hexane (1:5) as eluent to give the acetoxy ether **67** (50 mg, 79 %), m.p. 165-167°C (from acetone).

3-Methoxy-15α,16α-bis(methanesulfonyloxymethyl)-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate 68

a) The acetoxy diol **66** (80 mg, 0.2 mmol) was dissolved in dry dichloromethane (5 cm^3) and triethylamine (0.5 cm^3) was added. The solution was cooled to –78°C and methanesulfonyl chloride (75 mg, 0.7 mmol) was added dropwise over a period of 5 min. Stirring was continued at –78°C for 3 h until the reaction was complete (TLC). The cooling was removed and water added. The reaction mixture was then extracted with dichloromethane. The combined organic phase was washed with hydrochloric acid (10%), saturated sodium hydrogen carbonate solution, brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the crude (101 mg). Flash chromatography of the residue on silica (11 g) using ethyl acetate-hexane (1:1) as eluent gave the 17β-acetoxy dimesylate **68** (92 mg, 83

%), m.p. 182-183°C (from ethyl acetate-hexane); $[\alpha]_D$ +91° (*c* 1.0); ν_{max}/cm^{-1} 1743 (CO), 1362 and 1175 (SO); δ_H (400MHz) 1.03 (3H, s, 13β-Me), 1.62 (1H, td, *J* 2 x 11.4 and 3.0 Hz, 8β-H), 1.71 (1H, dddd, *J* 2 x 11.7, 10.0 and 6.3 Hz, 7α-H), 2.12 (3H, s, 17-OAc), 2.50 (1H, td, *J* 2 x 11.4 and 3.4 Hz, 9α-H), 2.73 (1H, td, *J* 2 x 8.3 and 3.0 Hz, 15β-H), 2.85-2.92 (2H, m, 6α- and 6β-H), 3.03 and 3.05 (each 3H, s, $-SO_2CH_3$), 3.10 (1H, td, *J* 2 x 8.3 and 5.2 Hz, 16β-H), 3.77 (3H, s, 3-OMe), 3.99 (1H,dd, *J* 10.7 and 8.3 Hz, 15^1-H), 4.21 (1H, dd *J* 10.3 and 8.3 Hz, 16^1-H), 4.42 (1H, dd, *J* 10.3 and 5.2 Hz, 16^1-H), 4.57 (1H, dd, *J* 10.7 and 3.0 Hz, 15^1-H), 6.10 and 6.51 (each 1H, d, *J* 6.3 Hz, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.6 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H), 7.18 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 15.0 (q, C-18), 21.6 (q, $OCOCH_3$), 25.4 (t, C-7), 27.3 (t, C-11), 28.7 (t, C-12), 30.0 (t, C-6), 37.3 and 37.6 (each q, $-SO_2CH_3$), 39.7 and 40.1 (d, C-8 and C-9), 45.9 and 46.4 (each d, C-15 and C-16), 55.2 (q, 3-OMe), 58.5 and 62.6 (each s, C-13 and C-14), 67.6 and 68.0 (each t, $C-15^1$ and $C-16^1$), 94.3 (s, C-17), 112.1 (d, C-2), 113.3 (d, C-4), 127.2 (d, C-1), 130.8 and 132.7 (each d, $C-17^1$ and $C-17^2$), 131.7 (s, C-10), 137.3 (s, C-5), 157.6 (s, C-3), 170.2 (s, $-OCOCH_3$) (Found: C, 56.3; H, 6.3; S, 11.2 %; M^+, 568. $C_{27}H_{36}O_9S_2$ requires C, 57.1; H, 6.4; S, 11.3 %; *M*, 568).

b) i) The triol **56** (250 mg, 0.68 mmol) was dissolved in dry dichloromethane (2 cm^3) and dry pyridine (4.5 cm^3). The solution was cooled to –15°C and methanesulfonyl chloride (200 mg, 1.76 mmol) was added dropwise over a period of 10 min. Stirring was continued at –15°C for 6 h until the reaction was complete (TLC). The cooling was removed and water added. The reaction mixture was then extracted with dichloromethane. The combined organic phase was washed with hydrochloric acid (10%), saturated sodium hydrogen carbonate solution, brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the product *3-methoxy-15α,16α-bis(methanesulfonyloxymethyl)-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol* **69** (340 mg, 95 %), m.p. 147-148°C (from ethyl acetate-hexane); $[\alpha]_D$ +130° (*c* 0.9); ν_{max}/cm^{-1} 3522br (OH), 1360 and 1174 (SO); δ_H (400MHz) 1.01 (3H, s, 13β-Me), 1.22 (1H, ddd, *J* 12.8, 4.4 and 2.6 Hz, 12β-H), 1.37 (1H, qd, *J* 3 x 12.4 Hz, 11β-H), 2.24 (1H, dddd, *J* 12.4, 2 x 4.2 and 2.6 Hz, 11α-H), 2.48 (1H, td, *J* 2 x 12.4 and 4.2 Hz, 9α-H), 2.79 (1H, td, *J* 2 x 8.6 and 3.0 Hz, 15β-H), 2.83-2.92 (3H, m, 6α-, 6β- and 16βH), 3.05 and 3.06 (each 3H, s, $-SO_2CH_3$), 3.78 (3H, s, 3-OMe), 3.94 (1H,dd, *J* 10.6 and 8.6 Hz, 15^1-H), 4.30 (1H, dd *J* 10.3 and 7.1 Hz, 16^1-H), 4.48 (1H, dd, *J* 10.3 and 5.1 Hz, 16^1-H), 4.59 (1H, dd, *J* 10.6 and 3.0 Hz,

15^1-H), 6.03 and 6.10 (each 1H, d, *J* 6.0 Hz, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), 7.19 (1H, d, *J* 8.5 Hz, 1-H); δ_C (100 MHz) 14.4 (q, C-18), 25.5 (t, C-7), 26.9 (t, C-12), 27.1 (t, C-11), 30.1 (t, C-6), 37.3 and 37.6 (each q, $-SO_2CH_3$), 39.8 and 40.3 (d, C-8 and C-9), 46.9 and 47.1 (each d, C-15 and C-16), 55.2 (q, 3-OMe), 59.7 and 61.4 (each s, C-13 and C-14), 68.1 and 68.5 (each t, $C-15^1$ and $C-16^1$), 90.6 (s, C-17), 112.0 (d, C-2), 113.2 (d, C-4), 127.1 (d, C-1), 131.7 (s, C-10), 133.0 and 135.7 (each d, $C-17^1$ and $C-17^2$), 137.3 (s, C-5), 157.6 (s, C-3) (Found: C, 57.1; H, 6.4; S, 11.8 %; M^+, 526. $C_{25}H_{34}O_8S_2$ requires C, 57.1; H, 6.5; S, 12.2 %; *M*, 526).

ii) To a stirred solution of the dimesylate **69** (135 mg, 0.26 mmol) in dry pyridine (3 cm^3), was added acetic anhydride (0.25 cm^3, 2.65 mmol) and 4-(dimethylamino)pyridine (13 mg, 0.1 mmol). The mixture was stirred under nitrogen at room temperature for 15 h. Water was added and stirring continued for 30 min. The reaction mixture was extracted with dichloromethane. The combined organic phase was washed with HCl (3M), aqueous sodium hydrogen carbonate, brine and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give 17β-acetoxy dimesylate **68** (121 mg, 82 %), m.p. 182-183°C (from ethyl acetate-hexane).

(2'*R*)-14-(1'-Methanesulfonyloxybut-3-en-2-yl)-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one 76

(a) The 17β-acetoxy 15^1,16^1-dimesylate **68** (100 mg, 0.18 mmol) was dissolved in freshly distilled methylene chloride and methanolic potassium hydroxide (M, 1 cm^3) was added. After 90 min at 20°C the reaction was complete (TLC). Water was added and the mixture acidified with aqueous hydrochloric acid (1M), and extracted with dichloromethane. The combined organic phase was washed with aqueous sodium bicarbonate solution, water, brine and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the crude residue (82 mg). Flash chromatography of the crude on silica gel (10 g) using ethyl acetate-hexane (1:1) as eluent gave the product **76** (62 mg, 82 %), m.p 150-151°C (from ethyl acetate-hexane); $[\alpha]_D$ +139° (*c* 1.0); ν_{max}/cm^{-1} 1705 (CO); δ_H (400MHz) 1.06 (3H, s, 13β-Me), 1.23 (1H, dddd, *J* 2 x 12.2, 10.2 and 6.9 Hz, 11β-H), 1.33 (1H, m, 12β-H), 2.04 (1H, td, *J* 2 x 12.1 and 1.8 Hz, 8β-H), 2.70-2.77 (2H, m, 6α- and 6β-H), 2.99 (3H, s, $-SO_2CH_3$), 3.22 (1H, dt, *J* 9.8 and 2 x 5.9 Hz, 2'-H), 3.72 (3H, s, 3-OMe), 4.31 (2H, d, *J* 5.9 Hz, 1'-H_2), 5.29

(1H, d, *J* 16.8 Hz, 4'-H), 5.37 (1H, dd, *J* 9.8 and 1.5 Hz, 4'-H), 6.03 (1H, dt, *J* 16.8 and 2 x 9.8 Hz, 3'-H), 6.34 (1H, d, *J* 5.9 Hz, 16-H), 6.52 (1H, d, *J* 2.7 Hz, 4-H), 6.68 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H), 7.00 (1H, d, *J* 8.7 Hz, 1-H), 7.42 (1H, d, *J* 5.9 Hz, 15-H); δ_C (100 MHz) 24.3 (q, C-18), 24.8 (t, C-7), 27.8 (t, C-12), 29.0 (t, C-11), 30.7 (t, C-6), 32.7 (d, C-9), 37.8 (q, -SO_2CH_3), 42.1 (d, C-8), 49.1 (d, C-2'), 52.6 (s, C-13), 55.2 (q, 3-OMe), 57.1 (s, C-14), 71.0 (t, C-1'), 112.6 (d, C-2), 112.8 (d, C-4), 121.6 (t, C-4'), 128.4 (d, C-1), 132.3 (d, C-15), 132.7 (s, C-10), 134.3 (d, C-3'), 136.8 (s, C-5), 157.3 (s, C-3), 163.5 (d, C-16), 212.2 (s, C-17) (Found: C, 67.0; H, 7.0; S, 7.1 %; M^+, 430. $C_{24}H_{30}O_5S$ requires C, 67.0; H, 7.1; S, 7.5 %; *M*, 430).

b) Similar alkaline treatment of the 17β-hydroxy 15^1,16^1-dimesylate **69** (100 mg, 0.19 mmol) was complete after 45 min. Isolation and chromatography gave the product **76** (76 mg, 93 %).

3.3 Crystal Structure Determination

A single crystal was glued on a glass fibre. X-ray intensity data were collected at 173 K using a Nonius Kappa CCD with 1.5 kW graphite monochromated Mo radiation. The strategy for the data collection was evaluated using the *Collect* Software.[60] The detector to crystal distance was 40 mm. Data were collected by a phi scan and several omega scans. The data were scaled and reduced using *Denzo-SMN.*[61] Unit cell dimensions were refined on all data.

The structure was solved and refined using *SHELX97.*[62] There is no disorder, and the thermal ellipsoids for all atoms are reasonable. Hydrogen atoms were placed in calculated positions and included in the model during later stages of the refinement. Plots of the molecular structure were obtained with *ORTEP* [63] and *PLATON.* [64]

The ring-contracted **38** crystallised in the monoclinic crystal system, in the space group P 2_1. There are two molecules with the formula $C_{25}H_{28}O_3$ in the asymmetric unit which differ slightly with respect to their torsion angles. The molecular structures of the two molecules have been designated **38(A)** and **38(B)**.

Details of the data collection and refinement are given in Table 3.1.
Atomic coordinates are given in Tables 3.2 and 3.3.

Table 3.1 Crystal data and structure refinement for (17^1R,17^2S,17^4S,17^6S)-3-methoxy-17^5-oxo—17^1,17^6;17^2,17^4-bicyclo-14,17β-hexano-14β-estra-1,3,5(10) 15-tetraen-17α-ol 38

Empirical formula	$C_{25}H_{28}O_3$	
Formula weight	376.47	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2_1	
Unit cell dimensions	a = 8.067(1) Å	□= 90°.
	b = 17.259(3) Å	□= 101.63(1)°.
	c = 14.148(2) Å	□ = 90°.
Volume	1929.4(3) $Å^3$	
Z	4	
Density (calculated)	1.296 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	808	
Theta range for data collection	2.58 to 25.35°.	
Index ranges	-9<=h<=8, -19<=k<=20, -17<=l<=15	
Reflections collected	8621	
Independent reflections	6141 [R(int) = 0.0331]	
Completeness to theta = 25.35°	99.2 %	
Max. and min. transmission	0.9698 and 0.9555	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6141 / 1 / 512	
Goodness-of-fit on F^2	0.970	
Final R indices [I>2sigma(I)]	R1 = 0.0467, wR2 = 0.0816	
R indices (all data)	R1 = 0.0890, wR2 = 0.0942	
Absolute structure parameter	0.9(11)	
Extinction coefficient	0.0134(11)	
Largest diff. peak and hole	0.186 and -0.198 $e.Å^{-3}$	

Table 3.2 Fractional Atomic Coordinates and Thermal Parameter (Å) for 38(A)

	x	y	z	U(eq)
C1A	7845(3)	3197(2)	8160(2)	31(1)
C2A	8590(4)	3360(2)	9109(2)	35(1)
C3A	10178(3)	3694(2)	9320(2)	29(1)
C4A	11010(3)	3848(2)	8581(2)	28(1)
C5A	10272(3)	3670(2)	7625(2)	26(1)
C6A	11277(3)	3865(2)	6868(2)	42(1)
C7A	10522(3)	3537(2)	5875(2)	35(1)
C8A	8615(3)	3684(2)	5649(2)	24(1)
C9A	7781(3)	3211(2)	6345(2)	27(1)
C10A	8656(3)	3354(2)	7397(2)	26(1)
C11A	5854(3)	3338(2)	6169(2)	34(1)
C12A	4982(3)	3207(2)	5111(2)	32(1)
C13A	5794(3)	3695(2)	4416(2)	25(1)
C14A	7745(3)	3534(2)	4608(2)	22(1)
C15A	7742(3)	2717(2)	4230(2)	27(1)
C16A	6432(3)	2631(2)	3504(2)	26(1)
C17A	5514(3)	3395(2)	3361(2)	24(1)
C18A	5284(3)	4544(2)	4501(2)	34(1)
C171A	6682(3)	3963(2)	2935(2)	25(1)
C172A	7342(3)	3763(2)	2019(2)	30(1)
C173A	8298(3)	3033(2)	1938(2)	34(1)
C174A	9262(3)	3768(2)	2282(2)	31(1)
C175A	9765(3)	3854(2)	3329(2)	27(1)
C176A	8245(3)	4042(2)	3775(2)	23(1)
C31A	12359(4)	4280(2)	10512(2)	37(1)
O1A	10828(2)	3840(1)	10283(1)	37(1)
O2A	11238(2)	3833(2)	3775(1)	42(1)
O3A	3849(2)	3371(1)	2791(1)	37(1)

Table 3.3 Fractional Atomic Coordinates and Thermal Parameter (Å) for 38(B)

	x	y	z	U(eq)
C1B	12232(4)	1195(2)	6220(2)	30(1)
C2B	11380(3)	1129(2)	5267(2)	29(1)
C3B	9669(3)	966(2)	5074(2)	25(1)
C4B	8808(3)	928(2)	5819(2)	27(1)
C5B	9652(3)	1011(2)	6775(2)	24(1)
C6B	8624(3)	1017(2)	7552(2)	30(1)
C7B	9635(3)	892(2)	8557(2)	29(1)
C8B	11297(3)	1334(2)	8762(2)	23(1)
C9B	12378(3)	1066(2)	8037(2)	26(1)
C10B	11415(3)	1115(2)	6995(2)	24(1)
C11B	14119(3)	1455(2)	8220(2)	35(1)
C12B	15118(3)	1311(2)	9250(2)	32(1)
C13B	14104(3)	1585(2)	9999(2)	24(1)
C14B	12294(3)	1211(2)	9786(2)	21(1)
C15B	12754(3)	381(2)	10087(2)	26(1)
C16B	14094(3)	385(2)	10804(2)	27(1)
C17B	14582(3)	1219(2)	11028(2)	25(1)
C18B	14161(3)	2475(2)	10011(2)	34(1)
C171B	13201(3)	1598(2)	11504(2)	25(1)
C172B	12706(3)	1265(2)	12404(2)	31(1)
C173B	12142(3)	449(2)	12451(2)	39(1)
C174B	10823(3)	1070(2)	12161(2)	34(1)
C175B	10246(3)	1174(2)	11115(2)	29(1)
C176B	11608(3)	1562(2)	10670(2)	24(1)
C31B	7173(4)	654(2)	3899(2)	39(1)
O1B	8924(2)	874(1)	4116(1)	34(1)
O2B	8797(2)	1039(2)	10669(2)	42(1)
O3B	16200(2)	1366(1)	11598(1)	33(1)

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LOCANT	δC (ppm)			
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	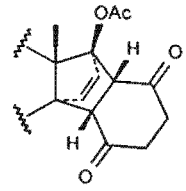	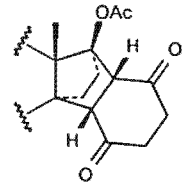	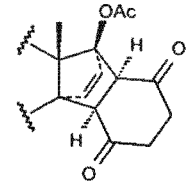	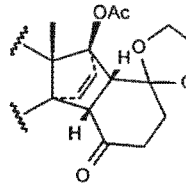
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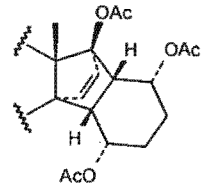
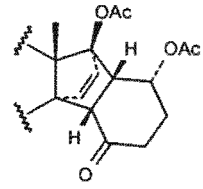
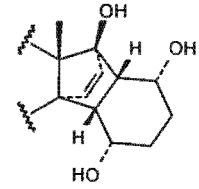
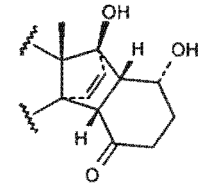
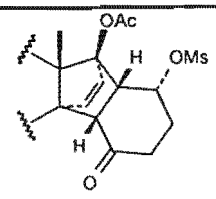
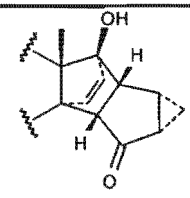
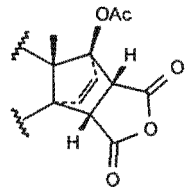
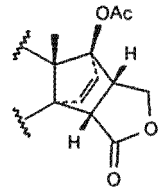
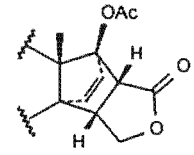
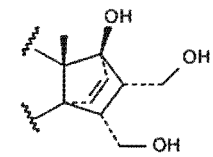
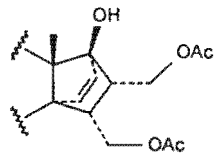
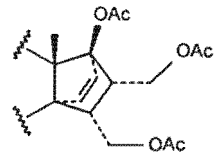
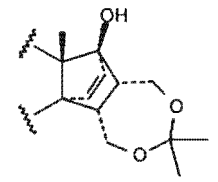
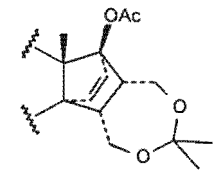
C2	111.9	111.6	112.0	111.9
C3	157.6	157.6	157.6	157.5
C4	113.4	113.4	113.7	113.4
C5	137.9	137.9	138.2	138.0
C6	30.1	30.1	31.3	30.4
C7	24.3	24.7	26.0	24.8
C8	40.0	40.3†	37.5	40.3†
C9	40.9	40.7†	38.4	40.4†
C10	131.8	132.7	132.0	132.1
C11	26.7	26.8	27.2	27.3
C12	28.6	27.2	30.6	28.7
C13	60.7†	50.6†	59.7†	63.6
C14	62.9†	51.6†	62.6†	58.7
C15	56.2‡	53.0‡	53.2	56.2
C16	56.5‡	55.3‡	48.9	51.2
C17	95.6	91.4	95.9	94.4
C18	16.0	15.3	15.0	15.6
$C17^1$	131.6†	22.2†	135.2†	129.3
$C17^2$	134.9†	24.7†	136.1†	132.9
3-OMe	55.2	55.2	55.2	55.2
C-4'	38.1†	38.1†	38.6†	30.8
C-5'	39.6†	39.8†	38.7†	36.7
C-3'	206.8‡	210.6	207.9‡	108.7
C-6'	210.9‡	208.1	208.4‡	211.8
OAc (CH_3)	21.6	21.8	21.7	21.8
OAc (C=O)	170.2	170.4	170.6	169.8

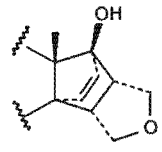
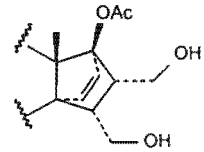
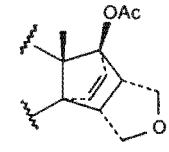
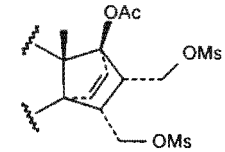
† interchangeable
‡ interchangeable

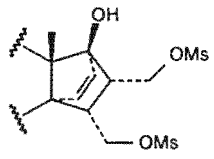
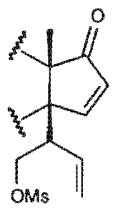
LOCANT	δC (ppm)			
	30	**31**	**32**	**33**
				
C1	127.3	127.5	127.2	127.3
C2	112.0	112.0	112.1	111.9
C3	157.5	157.4	158.1	157.5
C4	113.4	113.4	113.9	113.4
C5	137.5	138.0	138.8	138.1
C6	30.5	30.8	30.6	30.5
C7	25.2	26.4	25.9	26.5
C8	40.4†	40.2†	41.2	40.6†
C9	40.6†	40.3†	41.2	40.7†
C10	132.2	132.2	130.7	132.2
C11	27.4	27.9	27.4	27.3
C12	29.0	28.1	27.8	29.2
C13	63.1	62.2	59.4†	60.2†
C14	58.5	57.5	62.4†	62.7†
C15	46.7	55.1	50.6	51.3‡
C16	45.0	50.1	51.0	56.8‡
C17	95.0	93.8	91.0	91.0
C18	15.8	15.4	14.0	15.0
C17[1]	130.1†	130.7†	130.7†	133.3†
C17[2]	130.4†	131.6†	134.0†	135.2†
3-OMe	55.2	55.2	55.2	55.2
C-4'	23.1†	26.0	27.9†	25.2
C-5'	24.8†	34.9	28.6†	35.9
C-3'	67.3‡	67.1	64.3	67.0
C-6'	68.8‡	209.4	67.0	212.9
OAc (CH_3)	21.5, 21.6 & 21.7	21.3 & 21.5	-	-
OAc (C=O)	169.9, 170.0 & 170.2	169.9 & 170.1	-	-

LOCANT	δC (ppm)	LOCANT	δC (ppm)
	37		38
			
C1	127.7	C1	127.1
C2	112.2	C2	111.8
C3	157.6	C3	157.5
C4	113.6	C4	113.5
C5	138.2	C5	138.4
C6	30.9	C6	30.4
C7	26.6	C7	25.0
C8	40.4†	C8	40.0
C9	40.5†	C9	40.5
C10	132.2	C10	132.2
C11	28.2†	C11	26.8
C12	28.4†	C12	26.9
C13	58.1‡	C13	67.2
C14	62.6‡	C14	59.8
C15	55.0	C15	133.0†
C16	50.5	C16	138.9†
C17	93.8	C17	92.0
C18	15.7	C18	15.0
$C17^1$	130.8†	$C17^1$	47.0
$C17^2$	132.0†	$C17^2$	19.7
3-OMe	55.4	$C17^3$	9.2
C-4'	27.6	$C17^4$	32.1
C-5'	34.6	$C17^5$	212.9
C-3'	74.3	$C17^6$	62.6
C-6'	208.5	3-OMe	55.2
OAc (CH_3)	21.7		
OAc (C=O)	170.2		

LOCANT	δC (ppm)			
	48	49	50	56
				
C1	127.2	127.2	127.3	127.4
C2	112.1	112.0	112.1	112.0
C3	157.7	157.5	157.6	157.7
C4	113.6	113.4	113.7	113.2
C5	137.7	138.2	137.0	137.8
C6	30.3	30.3	30.3	30.1
C7	24.5	24.6	24.7	26.0
C8	40.3†	40.3	39.4†	40.6
C9	40.5†	40.7	39.9†	40.6
C10	130.9	131.6	131.2	132.8
C11	27.1	26.9	27.2	27.5
C12	29.9	28.7	29.9	27.5
C13	67.1	64.9	65.6	60.9
C14	61.2	59.1	58.7	59.0
C15	50.5	52.8	42.8	50.9†
C16	51.4	46.2	51.5	51.0†
C17	94.3	95.0	94.5	90.2
C18	15.5	15.0	14.9	14.5
$C15^1$	169.4†	176.8	69.0	61.8
$C16^1$	169.7†	69.0	175.9	60.8
$C17^1$	133.9	133.0	134.1	136.4
$C17^2$	130.6	133.4	129.6	131.9
3-OMe	55.4	55.2	55.2	54.8
OAc (CH_3)	21.6	21.3	21.5	-
OAc (C=O)	170.6	171.1	169.8	-

LOCANT	δC (ppm)			
	57	58	59	61
				
C1	127.2	127.2	127.0	127.1
C2	111.9	111.9	111.7	111.8
C3	157.5	157.5	157.4	157.4
C4	113.3	113.2	113.2	113.2
C5	137.6	137.5	137.6	137.6
C6	30.1	30.1	30.0	30.0
C7	25.5	25.2	26.2	26.2
C8	40.0†	39.9	39.9	39.8†
C9	40.4†	40.2†	40.3	40.1†
C10	132.2	132.1	132.4	132.3
C11	27.2	27.3	26.9	27.2
C12	27.3	29.1	27.0	29.1
C13	61.1	62.2	62.1	63.3
C14	59.2	58.1	58.7	57.5
C15	46.8	45.1†	49.9†	48.8†
C16	45.7	45.3†	48.9†	48.9†
C17	91.1	94.8	90.1	94.0
C18	14.5	15.0	14.2	14.7
$C15^1$	63.9†	62.7†	64.2	62.1†
$C16^1$	64.0†	63.7†	61.8	64.3†
$C17^1$	132.8‡	130.2‡	132.4	130.3‡
$C17^2$	136.0‡	132.6‡	135.3	132.4‡
3-OMe	55.2	55.2	55.1	55.2
OAc (CH_3)	21.0 & 21.1	21.0, 21.1 & 21.6	-	21.6
OAc (C=O)	170.7 & 170.8	170.0, 170.7 & 170.8	-	170.4
-C($\underline{C}H_3$)$_2$	-	-	20.2 & 29.3	20.1 & 29.5
-$\underline{C}$(CH_3)$_2$	-	-	101.3	101.2

LOCANT	δC (ppm)			
	65	66	67	68
				
C1	127.2	127.2	127.2	127.2
C2	111.8	111.9	111.9	112.1
C3	157.4	157.4	157.5	157.6
C4	113.6	113.2	113.7	113.3
C5	137.5	137.5	137.6	137.3
C6	30.1	30.1	30.1	30.0
C7	24.6	25.9	24.8	25.4
C8	39.9†	40.1†	39.7	39.7†
C9	40.1†	40.2†	39.7	40.1†
C10	132.0	132.3	132.0	131.7
C11	27.1	27.4	27.2	27.3
C12	27.8	28.6	29.5	28.7
C13	64.1	62.1	66.1	62.6
C14	59.0	57.9	56.9	58.5
C15	52.3†	49.0†	53.1†	45.9†
C16	54.0†	49.3†	53.7†	46.4†
C17	91.4	94.6	94.7	94.3
C18	14.3	14.8	14.7	15.0
$C15^1$	68.0†	60.5†	69.3†	67.6†
$C16^1$	69.7†	62.3†	69.7†	68.0†
$C17^1$	133.0‡	130.4‡	133.4‡	130.8‡
$C17^2$	135.1‡	131.6‡	133.5‡	132.7‡
3-OMe	55.2	55.2	55.2	55.2
OAc (CH_3)	-	21.6	21.4	21.6
OAc (C=O)	-	170.6	171.0	170.2
$SO_2\underline{C}H_3$	-	-	-	37.3 & 37.6

LOCANT	δC (ppm)	
	69	76
		
C1	127.1	128.4
C2	112.0	112.6
C3	157.6	157.3
C4	113.2	112.8
C5	137.3	136.8
C6	30.1	30.7
C7	25.5	29.0
C8	39.8	32.7†
C9	40.3	42.1†
C10	131.7	132.7
C11	27.1	24.8
C12	26.9	27.8
C13	61.4	52.6
C14	59.7	57.1
C15	46.9†	132.3
C16	47.1†	163.5
C17	90.6	212.2
C18	14.4	24.3
$C15^1$	68.1†	C-1' 71.0
$C16^1$	68.5†	C-2' 49.1
$C17^1$	133.0†	C-3' 134.3
$C17^2$	135.7†	C-4' 121.6
3-OMe	55.2	55.2
SO_2CH_3	37.3 & 37.6	37.8