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Retro-aldol processes in steroid chemistry

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ABSTRACT. **This review is devoted to retro-aldol reactions in steroid chemistry. The mechanism of the two-centred inversion of the *C/D* ring junction is discussed, and its application to the synthesis of cardioaglycones [aglycones of cardioglycosides] outlined. Some stereochemical aspects of introducing a functionalised side chain at C_{17} is also examined.**

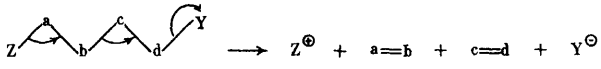
The bibliography contains 56 references.

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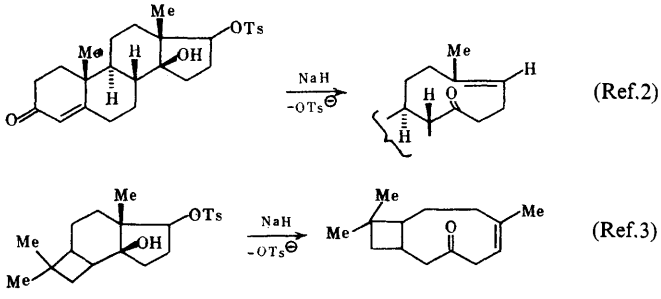
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I. Introduction

Hydroxyl and carbonyl groups on the steroid skeleton often determine biological activity as well as provide appropriate functionality for modifying steroidal structures in the search for compounds with physiological activity. Steroidal β-hydroxyketones are potentially interesting in this respect since there is the possibility of structural elaboration via retro-aldol cleavage. The latter cleavage is a fragmentation-type reaction which is initiated by bases or acids. Removal of a proton or anion proceeds more easily if the leaving group is in an anti-parallel configuration (by a Grob-type fragmentation):[1]



The decarboxylation of β-halogeno- and β-hydroxy-glycidic acids exemplifies this type of fragmentation, as also does, among others, the C-cleavage of 1,3-diol monosulphonates:



(Ref.2)

(Ref.3)

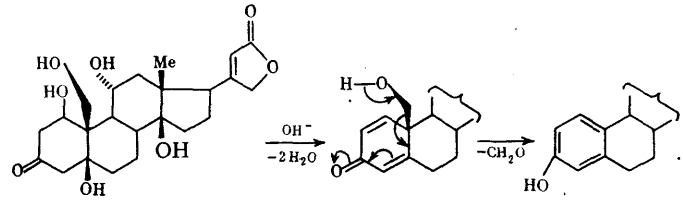
The shift of electron density on keto-enol tautomerism of aldols (−*E* effect in the $\rangle C=O$ group and +*E* effect in the $H-O-C\langle$ group) on treatment with appropriate reagents may be transmitted effectively along a conjugated chain, so that there is the possibility of conjugated retro-aldol processes of a 'remote' type (as is possible with retro-Michael reactions[1]).

Retro-aldol reactions have already been reviewed.[4–6] The present survey is devoted to retro-aldol processes in steroid chemistry and possible applications to the total synthesis of cardiotonic 14β-hydroxy derivatives of estratriene with natural configuration.

II. Retro-aldol reactions in steroid chemistry

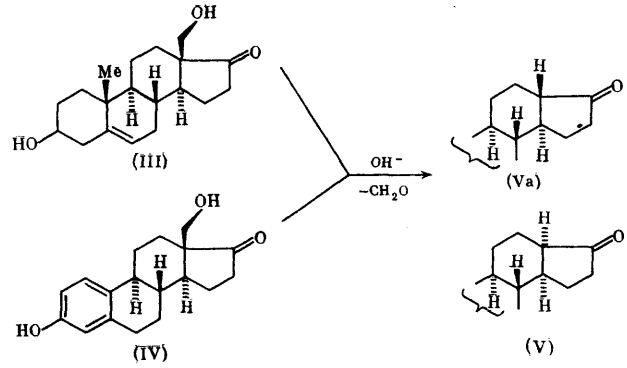
Many reactions of the retro-aldol type are known in steroids which have the basic tetracyclic skeleton (as illustrated in one of the earlier reviews[7]). These can be sub-divided into two categories: 1) retro-aldol cleavage of the side chain and 2) retro-aldol cleavage of the steroid skeleton.

Reactions in the first category have been applied in particular to the synthesis of 18-nor- and 19-nor-steroids, as well as to cleavage of the C_{17} side chain. Thus, the naturally occurring compound (I) is readily converted into the 19-norsteroid (II) via β-elimination of two molecules of water followed by retro-aldol cleavage of formaldehyde.[8] This is the only effective synthetic route to estrone derivatives.



(I) (II)

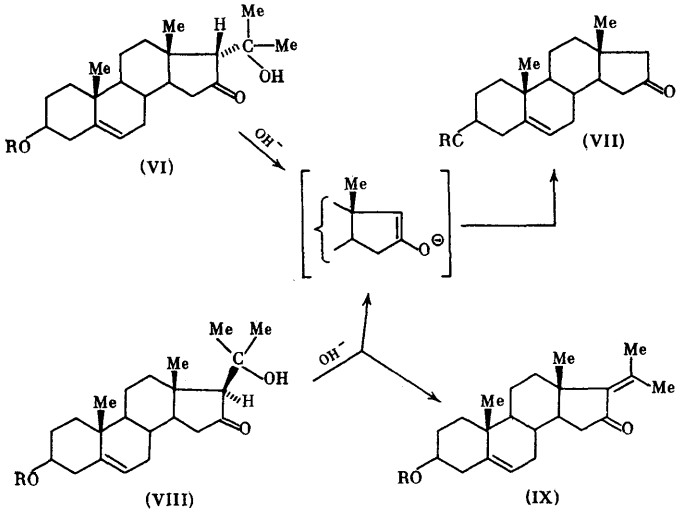
Treatment of 18-hydroxy-17-ketosteroids, (III) and (IV), with base, or pyrolysis of these compounds, also results in retro-aldol cleavage of formaldehyde with the formation of the corresponding 18-norsteroids:[9]



(III) (Va) (IV) (V)

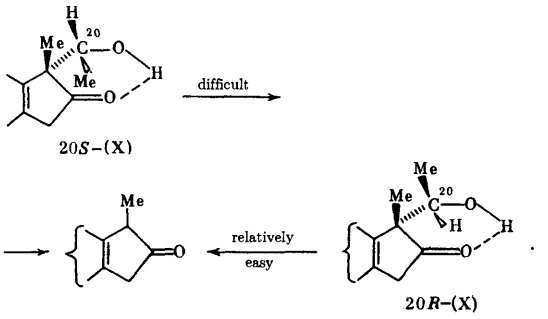
A product (V) with *cis*-fusion at the *C/D* ring junction is formed predominantly. It is possible that the corresponding *trans*-isomer (Va) is formed *in situ*, and then isomerises to the energetically more favourable *cis*-isomer (V) under acid catalysis. Such an isomerisation has, in fact, been observed with *trans*-hydrindan-1-one.[9]

From a stereochemical point of view, it proved interesting to study the behaviour of the C_{17} epimers of 20-methylpregn-5-ene-3β,20-diol-16-one in basic and acidic media. Thus, it has been shown that, even at room temperature in aqueous methanolic K_2CO_3, the 17α-epimer (VI), having a quasi-axial orientation of the side chain, undergoes retro-aldol cleavage of the $C_{17}-C_{20}$ bond to give compound (VII); however, the 17β-epimer (VIII) reacts only on heating with strong base (KOH) to give a mixture of (VII) and the α,β-unsaturated ketone (IX).[10] Under acidic conditions, the reaction proceeds quite differently.† Thus, treatment of hydroxyketone (VIII) with perchloric acid in dioxane fails to undergo retro-aldol cleavage, affording, instead, the α,β-unsaturated ketone (IX) as the only product;[11] however, the 17α-epimer (VI) gives a mixture of (IX) and androst-5-en-3β-ol-16-one (VII).



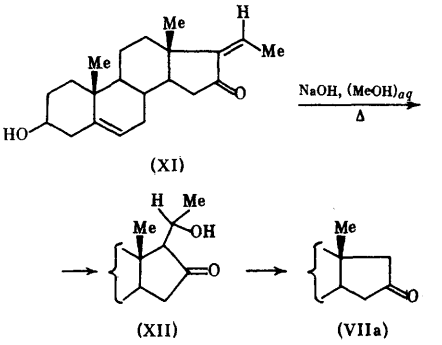
We believe that steric forces may be responsible for the different behaviour of epimers (VI) and (VIII) in basic media. In compound (VI), the approach of the base to the proton at C_{17} is sterically unfavourable as a result of the shielding effect of the angular 18-methyl group. Consequently, the base removes the hydroxylic proton with subsequent retro-aldol cleavage. Evidently, one must also consider the role of stereo-electronic factors. Thus, cleavage of the quasi-axial side-chain at C_{17} in (VI) should proceed more easily than cleavage of the equatorial side-chain in (VIII).[11] On the other hand, as a result of the increased availability of the proton at C_{17} in (VIII), the formation of intramolecular hydrogen bonding between the carbonyl group at C_{16} and the hydroxyl group at C_{20} is more favourable in (VIII) than in (VI), as confirmed by using Dreiding models. This further explains the reluctance of (VIII) to undergo retro-aldol cleavage.

Intramolecular hydrogen bonding may also explain why it is difficult to remove the 17α side-chain of 18-nor-17β-methylpregna-5,13(14)-dien-16-one (X) by retro-aldol cleavage, which only proceeds under forcing conditions (on heating with KOH in methanol):



It is interesting that the formation of a hydrogen-bonded conformer is more likely with the 20*S*-diastereoisomer of (X), having *anti*-oriented methyl groups on C_{17} and C_{20}, than with the 20*R*-diastereoisomer of (X) having the two methyl groups in the *syn*-orientation. Therefore one would anticipate that the 20*S*-diastereoisomer of (X) would be less disposed to undergo retro-aldol cleavage than the 20*R*-isomer. Unfortunately, Akhrem et al.[17] did not establish the absolute configuration at C_{20}. One should also note that the acidity of the OH group of the secondary alcohol (X) is less than that of the tertiary alcohol (VI)—an additional factor which explains the reluctance of (X) to undergo retro-aldol cleavage.[4]

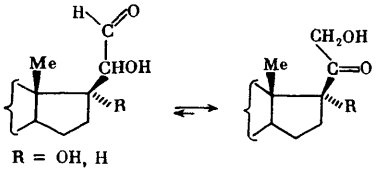
Prolonged heating of pregna-5,17(20)-dien-3β-ol-16-one (XI) in aqueous methanol containing NaOH also leads to 3β-hydroxy-androst-5-en-16-one (VIIa). In this instance, the β-hydroxyketone (XII) is formed initially by Michael addition, and then undergoes retro-aldol cleavage to give the final product (VIIa):[14]



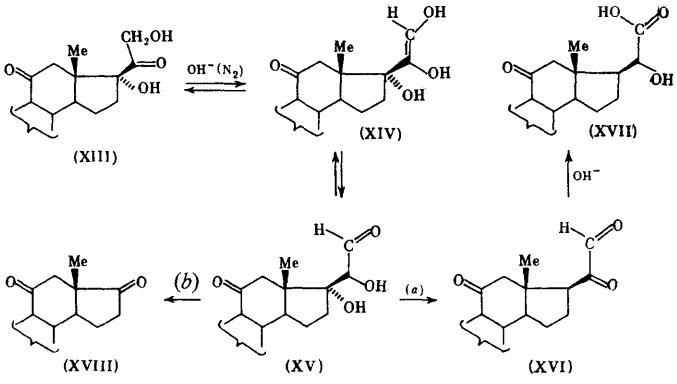
An interesting retro-aldol cleavage has been observed with a corticosteroidal β-hydroketone (XIII). This undergoes a tautomeric shift‡ on treatment with base (in the absence of oxygen) to give the dihydroxyaldehyde (XV), which subsequently cleaves in two ways: a) by initial dehydration to (XVI), followed by benzilic rearrangement to give the acid (XVII); and b) retro-aldol cleavage of the side

† The rate of dehydration of hydroxyketones increases on raising the temperature under acidic conditions.[12]

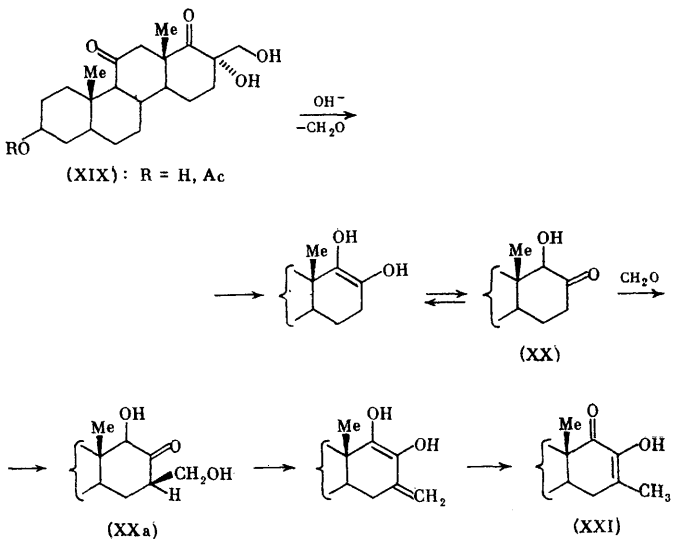
‡ The tautomeric conversion of aldols into the corresponding ketones has been applied to the synthesis of the corticoid side chain:[7]



chain to give the diketone (XVIII).[7,15] Compound (XIII) is also converted to (XVII) in acidic media.

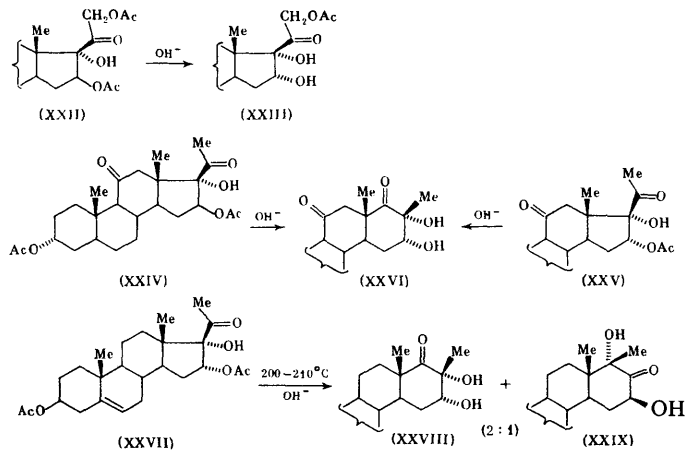


There are also examples of retro-aldol cleavage of formaldehyde from *D*-homosteroids (XIX), followed by its subsequent addition to the resulting ketone (XX). The hydromethyl derivative (XXa) is formed initially, and is then dehydrated to (XXI). This was confirmed by the independent conversion of (XX) into (XXI) on treatment with formaldehyde in basic media.[7]

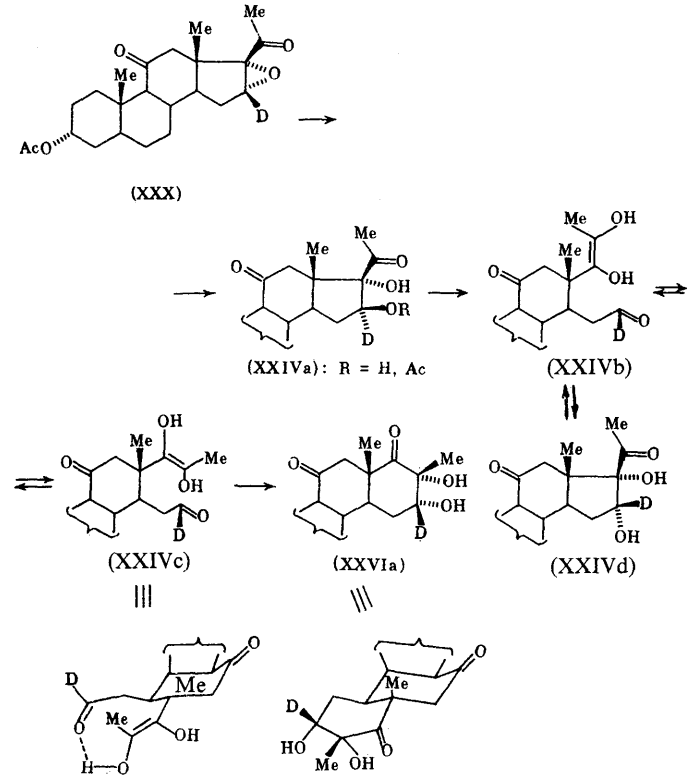


Based on stereochemical considerations, retro-aldol cleavage of the second type (i.e. of the steroid skeleton) may be further subdivided into 1) retro-aldol reactions not involving angular carbon atoms; and 2) retro-aldol reactions involving angular C-atoms (C_5, C_8, C_9, C_{10}, C_{13} and C_{14}).

Those examples in the first category are typified by elimination from C_{16} and C_{17}, but, in principle, retro-aldol cleavage is also possible at C_1, C_2, C_3, C_4, C_6, C_7, C_{11}, C_{12} and C_{15}. Such reactions can also lead to ring expansion or contraction of the skeleton (affording homo- and nor-steroids, respectively). The unusual inversion of configuration at C_{16} on hydrolysis of the 17α-hydroxy-corticosteroid (XXII) to (XXIII) in basic media can also be explained by a retro-aldol mechanism,[16] as also can the conversion of the epimeric 3α,16-diacetoxy-17α-hydroxypregna-11,20-diones, (XXIV) and (XXV), to the same 16α-hydroxy-*D*-homosteroid (XXVI); retro-aldol cleavage of the 11-deoxy-analogues, e.g. (XXVII), which gives a mixture of (XXVIII) and (XXIX), proceeds in a similar way.[17]

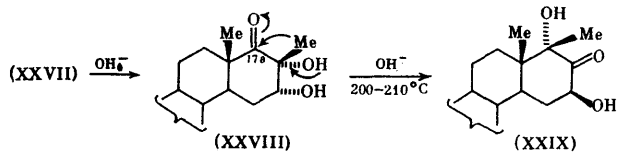


The mechanism of such reactions has been established by labelling experiments.[7]

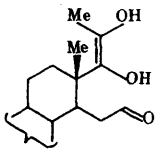


The formation of the *D*-homosteroid (XXVIa) and the epimerisation of (XXIVa) to (XXIVd) can be readily explained by the above scheme. Intramolecular hydrogen bonding in the intermediate 16,17-secosteroid (XXIVc) facilitates retro-aldol cleavage with subsequent formation of the *D*-homosteroid (XXVIa). The 16α-hydroxy and 17β-methyl groups in (XXVIa) are in a pseudoequatorial configuration relative to the *D*-ring (which is thereby stabilised in the boat conformation). The formation of the corresponding chair conformer would have required an unfavourable 1,3-diaxial interaction between the methyl groups at C_{17} and C_{13}.[7]

As has already been shown above, heating compound (XXVII) in basic media affords (XXVIII) as the main product together with (XXIX), in which the methyl group has migrated from C_{17} to C_{17a}.[17] We believe that this occurs as a result of rearrangement of (XXVIII) having a tertiary methyl group at C_{17}:

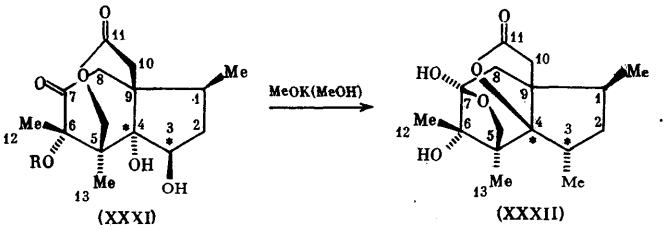


The driving force for this rearrangement is the release of strain energy associated with the 1,3-interaction of the methyl groups in the intermediate secosteroid:

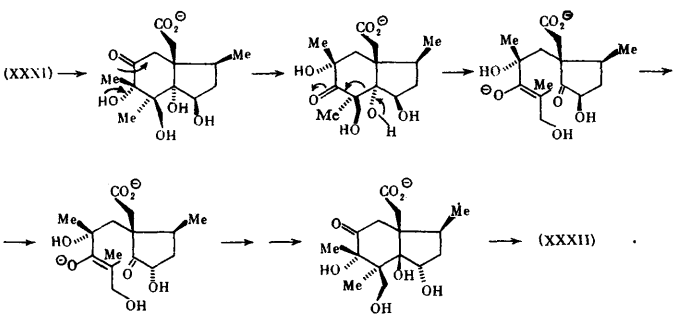


It is worth noting that the migration of the tertiary methyl group usually proceeds more easily under the action of acid. Under these conditions, migration is facilitated by the developing positive charge on the adjacent carbon atom, arising as a result of protonation of the carbonyl oxygen. Akhrem et al., in fact, found that under acidic conditions compound (XXVII) rearranges primarily to give (XXIX), and not (XXVIII).[17]

From X-ray structural analyses and chemical studies, Kouno et al. found that the naturally occurring pseudoanisatin (XXXI), having a complicated substituted hydrindane skeleton, rearranges in the presence of strong base.[18] The product had an unusual configuration at C_3 and C_4, and had been formed by an intramolecular translactonisation to give a stable *peri*-fused γ-lactone ring with simultaneous lactolide ring close involving C_7 and C_5:

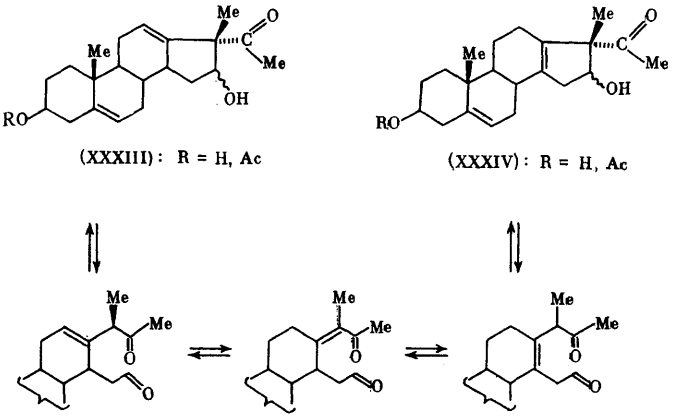


The inversion at C_4 is particularly interesting since, as a result of the reaction, the *trans*-hydrindane ring is converted into the *cis*-form. Barton has proposed a mechanism for this inversion, involving retro-aldol cleavage of the C_4-C_5 bond:[18]



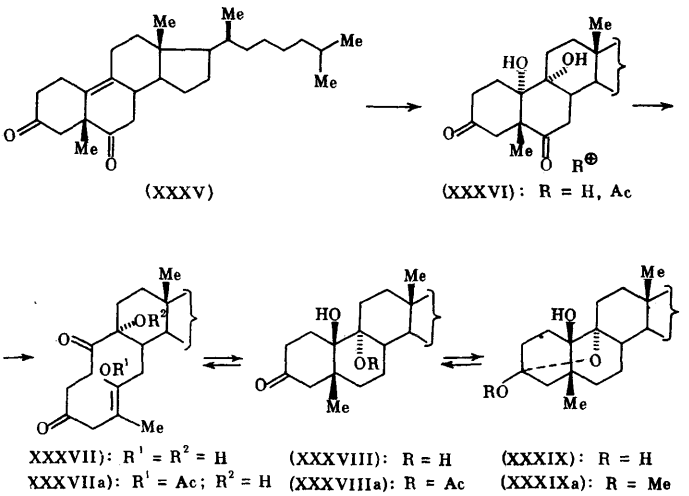
It is considered that the driving force for this rearrangement of pseudoanisatin is the release of strain energy associated with the octahydro-*trans*-indan ring.

In studying the saponification of steroids (XXXIII) and (XXXIV), Herzog et al. discovered that the two compounds were in equilibrium, the double bond shift, $\Delta^{12(13)} \rightleftarrows \Delta^{13(14)}$, being facilitated by a retro-aldol cleavage of the $C_{16}-C_{17}$ bond followed by re-aldolisation.[19]

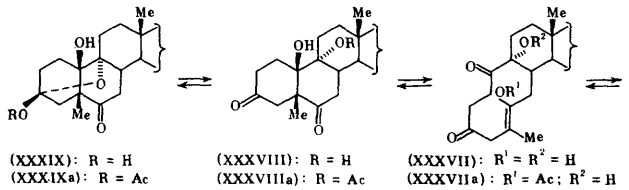


The second sub-category of retro-aldol cleavage, involving the angular carbon atoms, is especially interesting. These reactions lead to isomerisation and a variety of rearrangements.

A study of the dihydroxylation of compound (XXXV) to give (XXXVI) showed that the product subsequently rearranged via retro-aldol cleavage.[20] The *B*-ring of the *cis*-diol (XXVI) is forced into the boat conformation as a result of the steric requirements of the *trans-A/B* fusion. This facilitates retro-aldol isomerisation to give the energetically more favourable *cis-A/B* isomer (XXXVIII) having a chair conformation in ring *B*. This steroid was isolated as the transannular oxido tautomer (XXXIX).



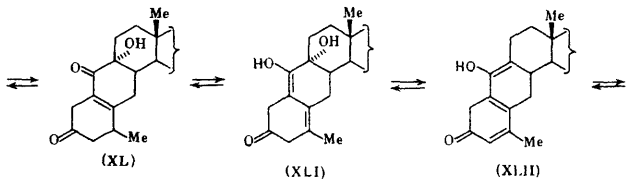
On treatment with base, the oxido compound (XXXIX) rearranges further to give (XL) [presumably via the same intermediate (XXXVII)].[20]



(XXXIX): R = H
(XXXIXa): R = Ac

(XXXVIII): R = H
(XXXVIIIa): R = Ac

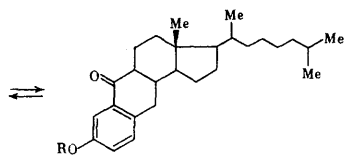
(XXXVII): $R^1 = R^2 = H$
(XXXVIIa): R^1 = Ac; R^2 = H



(XL)

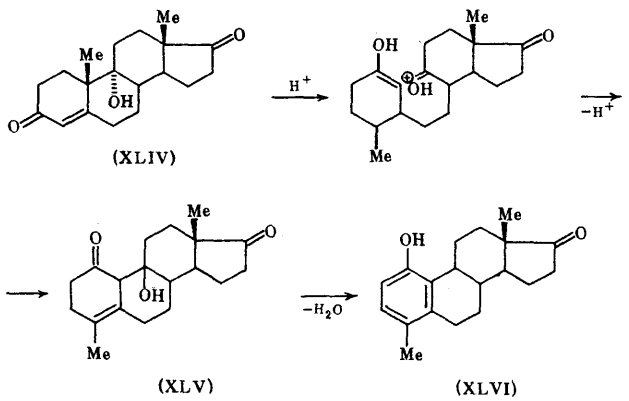
(XLI)

(XLII)



(XLIII): R = H
(XLIIIa): R = Ac

References have also been made to 'remote' retro-aldol reactions, facilitated by conjugation between the keto and hydroxyl group.[21,22] This is exemplified below.

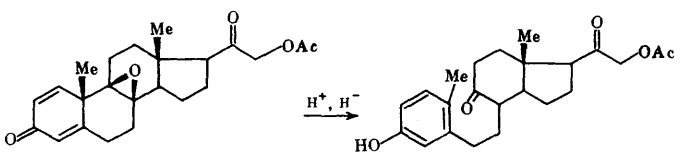


(XLIV)

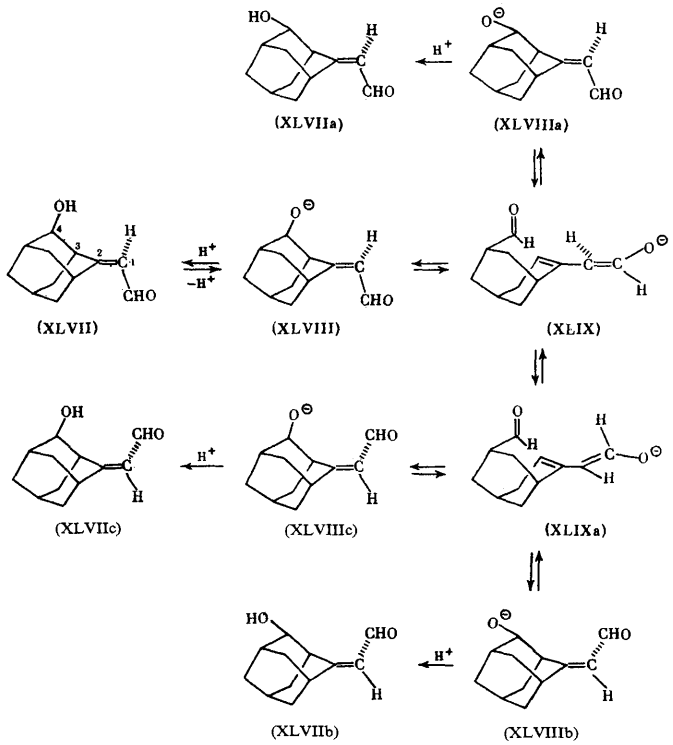
(XLV)

(XLVI)

In such instances, the vinylogous aldol fragment is well disposed to retro-aldol cleavage in acidic media. This is further facilitated by the lack of a labile proton between the functional groups, so that dehydration of the substrate is precluded. However, this is not so in the product (XLV), dehydration of which proceeds readily to give the phenolic ketone (XLVI). Conjugated epoxyketones also undergo such 'remote' retro-aldol cleavage, as illustrated below:[23]



An interesting example of a 'remote' retro-aldol cleavage has been reported in adamantane chemistry. Thus, treatment of (*E*)-(1*R*)-4(a)-hydroxy-2-adamantylideneacetaldehyde (XLVII) with NaH affords anion (XLVIII), which undergoes retro-aldol ring opening to give the isomeric anion (XLIX). The enolate group of the latter is conformationally flexible, so that an equilibrium is established with the stereoisomer (XLIXa). The anions (XLVIIIa–c) are formed by subsequent re-aldolisation, and protonation of the reaction mixture leads to a mixture of all four epimeric hydroxyaldehydes (XLVII, XLVIIa–c) in 33:8:27:32 proportion.[24]



(XLVIIa)

(XLVIIIa)

(XLVII)

(XLVIII)

(XLIX)

(XLVIIc)

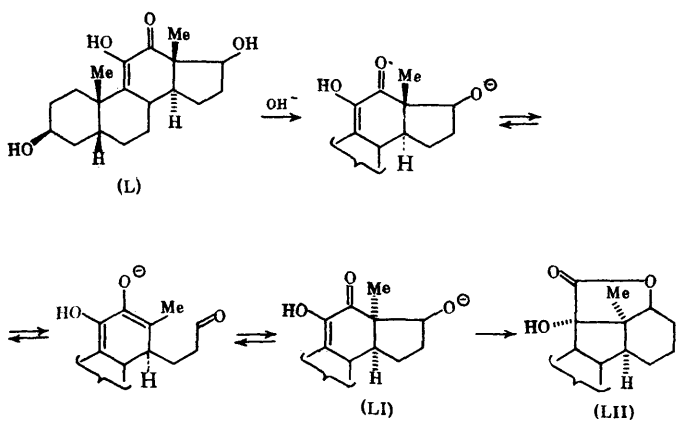
(XLVIIIc)

(XLIXa)

(XLVIIb)

(XLVIIIb)

Retro-aldol reactions may compete with other processes. Thus, the diketone (L), in which benzilic rearrangement is sterically inhibited, undergoes an initial retro-aldol cleavage on treatment with base (NaOH in propanol) to give anion (LI), having the thermodynamically more stable *cis*-*C*/*D* ring fusion.



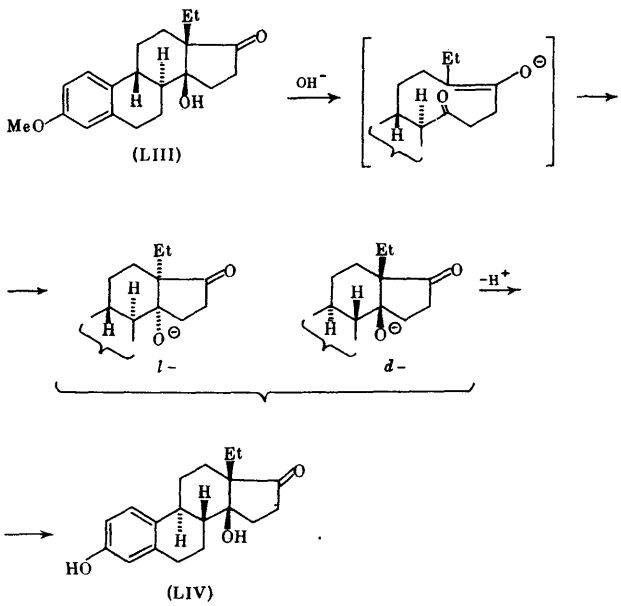
(L)

(LI)

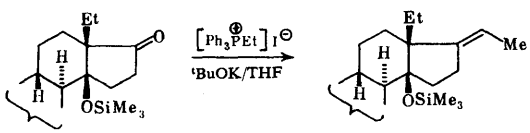
(LII)

The anion (LI) is known to undergo benzilic rearrangement[25] and, on subsequent acidification, affords the 13-*iso*-11;17-lactone (LII). The structure of the latter has been reliably established by X-ray crystallographic analysis.[26]

We have also discovered a novel rearrangement involving the *C/D* ring junction of a 14-hydroxy-17-ketosteroid. Thus, attempted Wittig olefination of the *trans-anti-cis*-hydroxyketone (LIII), obtained by reductive cyclisation,[27] resulted in isomerisation to the abnormal *trans-syn-cis*-isomer (LIV) rather than the expected side-chain formation at C_{17}. The rearrangement involves retro-aldol cleavage of the *C/D* ring junction, as shown below:[28]



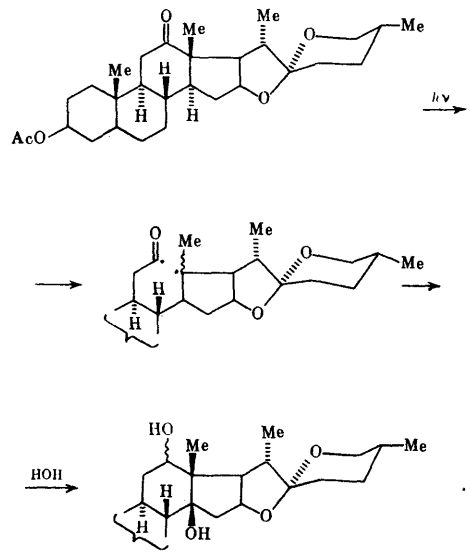
Wittig reaction does take place, however, if the 14-hydroxyl group is protected as the trimethylsilyl derivative:[27]



Strong nucleophiles (not associated with Wittig reagents) also induce the above *C/D* ring inversion[28] to give the same product (LIV) in high yield (>80%).[27] This methodology has proved attractive in the total synthesis of cardioaglycones having the natural *cis-C/D* ring fusion.

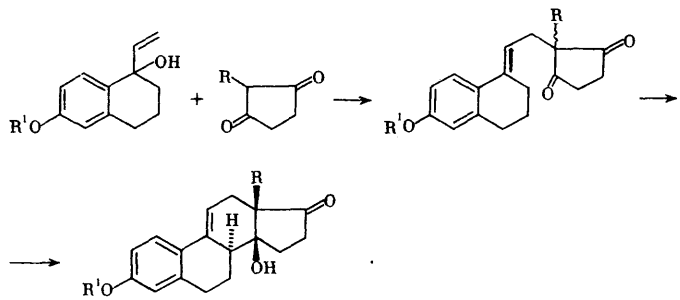
III. The two-centred inversion of the *C/D* ring junction and approaches towards the total synthesis of cardiotonic steroids

By virtue of their positive ionotropic effect on cardiac insufficiency, cardioglycosides have been broadly used medicinally. Their aglycones are steroidal, being characterised by a 14β-hydroxy group (or, in rare instances, by a 14β,15β-oxido group), as well as an unsaturated lactone residue appended at the 17β-position (a butenolide residue in cardenolides, and an α-pyrone residue in butadienolides).[29] The syntheses of such cardioaglycones have been carried out in several laboratories (for examples see Schonfeld et al.[30]). In the construction of the butenolide residue, C_{21}, steroids have been primarily used as starting material,[31] although references have also been given to syntheses based on 17-ketoandrostanes.[31,32] In all of these syntheses, the 14β-hydroxy group has been introduced via the corresponding Δ^{14}-steroid. Welzel and Stein devised a partial synthesis of digoxigenin via photochemical rearrangement of hecogenin, which is readily available from natural (plant) sources.[33] Irradiation initially affords an aldehyde, which then undergoes a Prins cyclisation:



Although it is customary to use cardioglycosides in experimental therapy, the aglycones themselves are also biologically active,[29,30] and the transformations of such aglycones have been studied from both the theoretical and practical viewpoint. Thus, it has been shown that 14β-hydroxy derivatives of estratriene possess inhibitory activity of Na^+,K^+-ATPase and may also have potential cardiotonic activity.[34]

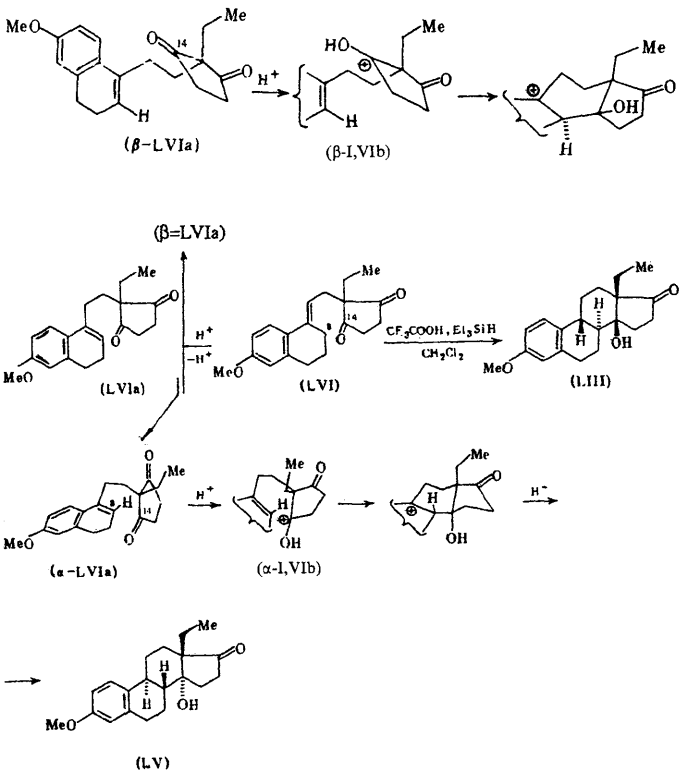
The incorporation of the 14β-hydroxy group in the estrane skeleton can be readily achieved by ring closure of the readily available 8,14-seco-$\Delta^{1,3,5(10),9(11)}$-estratetraene-14,17-dione (Torgov reaction):[35]



We have found that reductive ring closure of the secodiketone (LVI) (by a modified Torgov reaction)[27] leads stereoselectivity to the saturated *trans-anti-cis*-estrane (LIII).[36] The formation of the *trans-syn-cis*- (LIV) [37] and *trans-anti-trans*-isomer (LV) [38] was

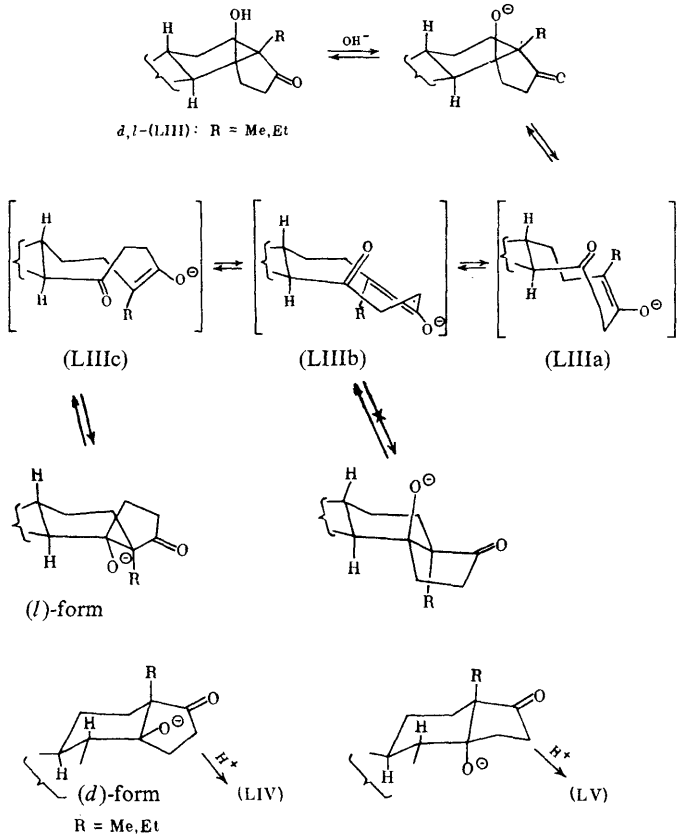
energetically unfavourable (see Scheme 1). Further details of this transformation are available.[39–41]

Scheme 1



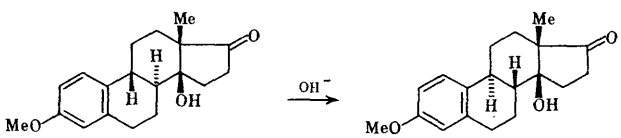
It has also been found that the product of reductive ring closure (LIII) [36] isomerises in the presence of a strong nucleophile (for example, under the conditions of the Wittig olefination) to give the thermodynamically more favourable (by 0.8 kcal/mole) natural isomer (LIV).[33] This isomerisation proceeds via an intermediate 13,14-secosteroid,§ formed as a result of retro-aldol cleavage of the $C_{13}-C_{14}$ bond (Scheme 2).[28] Further details are also available.[39,42]

Scheme 2



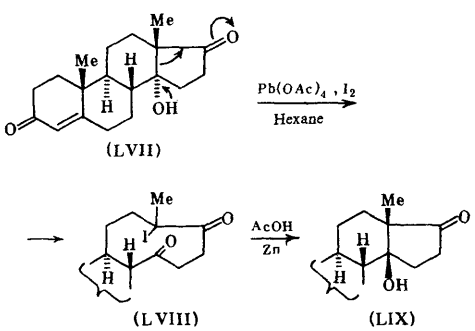
Thus, the (*l*)-diastereomer is obtainable from the *d*-diastereomer, and the (*d*)-isomer from the (*l*)-isomer.[28]

The C_{18}-unsubstituted analogue—(*d,l*)-3-methoxy-14β-hydroxyestra-1,3,5(10)-trien-17-one—under the same conditions also affords the natural isomer¶ as a result of retro-aldol cleavage and re-aldolisation:[44,45]

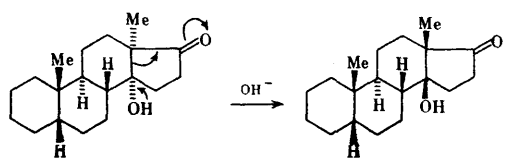


It should be pointed out (with reference to the mechanism depicted in Scheme 2) that although the formation of the 14α-hydroxy isomer (LV) is possible, in principle, its strain energy (31.9 kcal/mole) is significantly greater than that (29.1 kcal/mole) of the 14β-hydroxy isomer (LIV) and that (29.9 kcal/mole) of isomer (LIII).[39] Hence the formation of (LV), although possible on theoretical grounds,[42] is unlikely.

§The anionic form of the 13,14-seco-13(17)-en-17-one should be primarily in the conformation (LIIIc) since molecular models have shown that conformers (LIIIa), and especially (LIIIb), are severely hindered sterically. In actual fact, the 13,14-secosteroid (LVIII), obtained from (LVII), reacts with Zn dust in acidic media to give the natural isomer (LIX) as the sole product:[43]



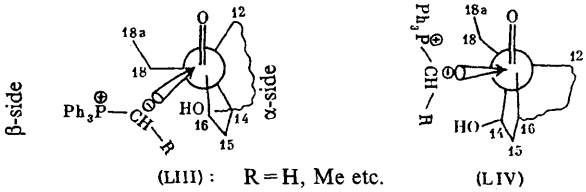
¶We also believe that the 18-retro-14α-hydroxysteroid[46] would isomerise to the natural form under the same conditions:[28]



The synthesis of the 14β-hydroxyestratriene (LIV), having the same configuration as natural cardioaglycones, can thus be achieved in two high-yielding stages — by reductive cyclisation of Torgov's readily available secodiketone, followed by isomerisation of the resulting (LIII). In the development of this method as a route to analogous estratriene and 19-norandrostane aglycones (the latter being obtainable by reduction of the former) with low toxicity, an important consideration was the choice of side-chain functionality at C_{17}. Here, we focussed our attention on stereochemical aspects of incorporating the C_{17} side chain by applying Wittig olefination with 17-oxosteroids (in competition with retro-aldol cleavage) and Grignard addition to the same substrates.

As mentioned above, *trans-anti-cis*-14-hydroxysteroids (LIII) undergo retro-aldol cleavage under the conditions of the Wittig olefination to give, ultimately, the natural isomers (LIV), which may then participate in the Wittig reaction. This interesting result can be explained as follows. As is evident from the Newman projection, based on X-ray crystallographic data,[36,37] the *cis*-orientation of the π-orbitals of the C—O bond (relative to the angular group) in the unnatural isomers (LIII) would necessarily direct *syn*-planar attack of the Wittig reagent,[47] approach of which would be sterically hindered (Scheme 3).[49,50] Replacement of the methyl group at C_{13}, or in the Wittig reagent, by ethyl or by a larger hydrophobic group adds significantly to this steric hindrance, and the Wittig reaction becomes even less likely.

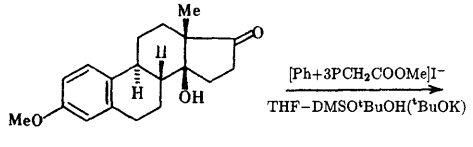
Scheme 3

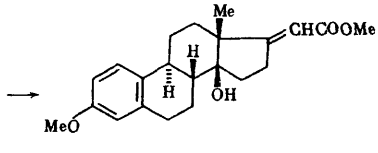


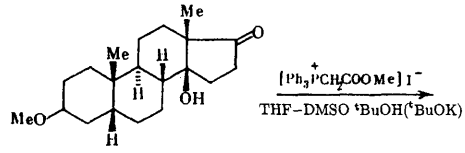
(LIII): R = H, Me etc. (LIV)

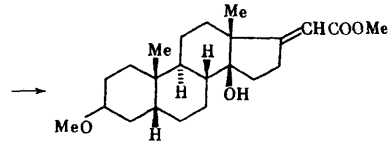
In the natural isomers (LIV), approach of the Wittig reagent from the β-side (*syn*-attack) proceeds considerably more easily to give the intermediate phosphonio-betaine complex (although, even here, large substituents in the vicinity of the reaction centre may still inhibit side chain formation).

Wittig olefination of natural 17-ketosteroids is exemplified below:[51—53]



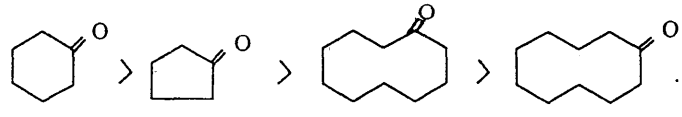






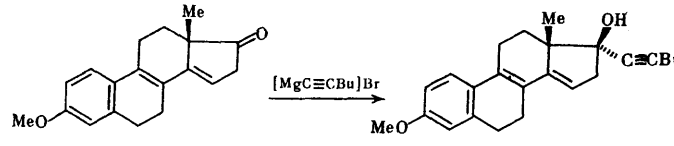
In these reactions, it is important that a hydrophilic group is present in the Wittig reagent, which facilitates olefination via intermolecular hydrogen-bonding with the 14-hydroxy group. The formation of 17-alkylidenesteroids is also favoured because in such instances there would be no repulsion (*syn*) between the substituent at C_{13} and the newly formed side chain at C_{17}.

Suppression of the Wittig reaction with the unnatural isomers (LIII) is apparently due to preferential deprotonation of the axial 14-hydroxy group by the nucleophilic reagent. This induces retro-aldol cleavage to give the corresponding 13,14-secosteroid, which then undergoes conformational isomerisation and re-aldolisation with the formation of the energetically more favourable natural isomers (LIV). The equatorial 14β-hydroxy group in the latter is inert to the incoming nucleophile as a consequence of either shielding by the neighbouring C_{13} axial substituent or the energetically unfavourable reversal of the isomerisation to give (LIII). Furthermore, the formation of the intermediate Wittig betaine complex depends on the size and nature of the cyclic ketone. Thus, it has been established[1] that the reactivity of the keto group decreases in the following order:

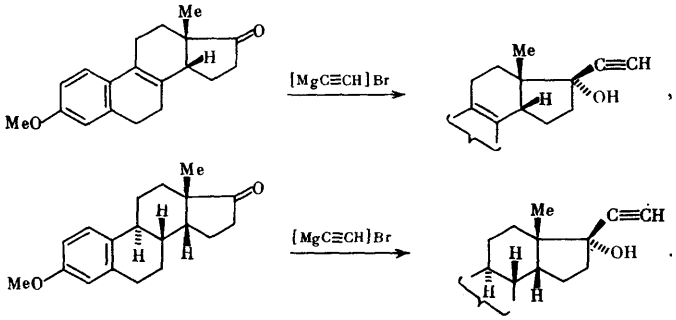


This explains why the keto group of the intermediate anions (LIIIa, b, c) (Scheme 2), which arise during the isomerisation of (LIII) to (LIV), is inert to Wittig reagents.

It is worth noting that, in *cis-C/D*-steroids, the angle ($\theta^{cis} \approx 110-120°$) between the plane of the *D*-ring and the remainder of the steroid skeleton is such that attack of nucleophiles from the α-side (Scheme 3) would be unfavourable.[54] However, in the corresponding *trans-C/D*-steroids and/or those containing endocyclic double bonds, the angle between the planes ($\theta^{trans} = 170-180°$) [55] is such that attack from the α-side is favourable on steric grounds so that the keto group at C_{17} is available for Wittig olefination or nucleophilic addition of Grignard reagents (to give 17β-alkyl derivatives):[50]



It should be further noted that Grignard addition does take place with 17-keto-*cis*-*C*/*D*-steroids having *trans-syn-cis* skeletal fusion or where there is a 8(9)-double bond, i.e. where a 13β-axial alkyl group and an equatorial 14β-hydroxy group or 14β-hydrogen are present:[56]



At the same time, 14β-hydroxyestratrienes of unnatural configuration and/or $\Delta^{9(11)}$-derivatives, where there is a 13β-equatorial and 14β-axial group, are sterically crowded in the vicinity of C_{17} so that the $sp^2 \rightarrow sp^3$ transformation at this atom (on formation of the intermediate Wittig betaine or on addition of Grignard reagents) is inhibited.

***

Steroids having a β-hydroxyketo residue undergo retro-aldol cleavage in basic media. Conformational isomerisation of the products, followed by re-aldolisation, may then take place. This is notably exemplified by the *C*/*D* ring inversion of 14-hydroxy-17-ketosteroids, of which the natural *trans-anti-cis*-isomers readily undergo retro-aldol cleavage in basic media (or under the conditions of the Wittig reaction) to give the corresponding 13,14-secosteroids. Conformational isomerisation of the latter, followed by re-aldolisation, leads to the energetically more favourable isomers having the *trans*-s*yn-cis*-fusion characteristic of natural cardio-active steroids. This isomerisation may be applied in the synthesis of 14β-hydroxyestratrienes and (after reduction of the *A*-ring) analogues of cardioaglycones. 17-Ketosteroids with the natural configuration may be functionalised at C_{17}, e.g. by Wittig olefination or Grignard addition.

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