Steroids: Reactions and Partial Syntheses

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Reviewing the literature published during 1984

(Continuing the coverage of literature in *Natural Product Reports*, 1985, Vol. 2, p. 461)

Reviews have appeared on the following topics: radical chain reactions (with applications to steroids),[1] the synthesis of 11β-alkyl steroids,[2] biomimetic halogenation of steroids,[3] seco-steroids that contain a medium or large ring,[4] anti-glucocorticoid 11β-substituted 19-nor-steroids,[5] and the specific modification of steroid hormones.[6] Volume 2 of the 'Atlas of Steroid Structure' has appeared.[7]

1 Reactions

1.1 Alcohols, Carboxylic Acids and their Derivatives, Halides, and Epoxides

1.1.1 Oxidation, Substitution, and Reduction

The use of osmium tetroxide for oxidation of primary and secondary alcohols has been described.[8] While an 11β-ol, if it is unsubstituted at C-9, is oxidized by the Swern reagent (dimethyl sulphoxide–phosgene) to the 11-ketone in 58% yield, together with 13% of the 9(11)-ene, a 9α-fluoro-11β-ol is left largely unchanged.[9] A limited amount of a reagent consisting of ammonium molybdate $\{(NH_4)_6[Mo_7O_{24}]\}$, hydrogen peroxide, tetrabutylammonium chloride, and potassium carbonate oxidizes a 17-hydroxy-group to the 17-ketone, while leaving a 3β-hydroxy-5-ene or a 3β-hydroxy-5α-steroid unchanged; both hydroxyl groups are oxidized if more reagent is used and the reaction is allowed to take place for a longer time.[10]

t-Butoxysamarium di-iodide was the best of a number of transition-metal alkoxides that have been used to catalyse the Oppenauer oxidation; cholesterol was oxidized to cholest-4-en-3-one in 78% yield.[11] Steroid allylic alcohols are oxidized to the αβ-unsaturated ketones by pyridinium chlorochromate in the presence of pyrazole; saturated hydroxyl groups (even primary ones) are virtually unaffected. Six-membered heterocyclic amines, such as pyrazine, can be used in place of pyrazole.[12,13]

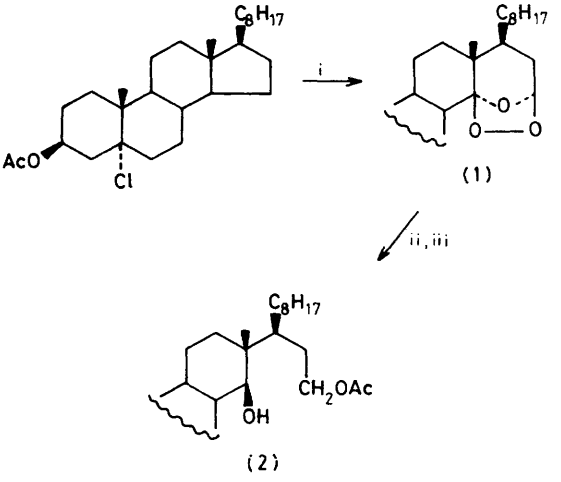
The first instance of the cleavage of a saturated steroid by the action of ozone on a solution of the substrate (as opposed to its action on the solid compound) is shown in Scheme 1. The ozonide (1), which is unexpectedly stable, was converted, by reduction with sodium borohydride followed by acetylation, into compound (2).[14]

5-Hydroperoxy-3β-hydroxy-5α-cholest-6-ene is converted into the 5α-hydroxy-6-ene by potassium superoxide in dimethyl sulphoxide that contains a crown ether, or by sodium hydroxide or potassium hydroxide in the presence of air; a 7α-hydroperoxy-5-ene behaves in a similar fashion. The reaction is of interest in connection with the idea that steroid hydroperoxides give hydroxy-radicals by the action of superoxide anion.[15,16]

5α-Cholestan-3β-yl acetate is reduced to 5α-cholestane by sodium in hexamethylphosphoramide and t-butyl alcohol.[17]

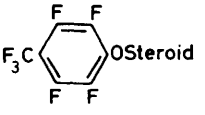
1.1.2 Ethers and Esters

Steroid phenols and, more slowly, steroid alcohols react with octafluorotoluene in the presence of sodium hydroxide and tetrabutylammonium hydrogen sulphate in dichloromethane to give the 2,3,4a,4a,4a,5,6-heptafluoro-*p*-tolyl ethers (3). The steroid is regenerated by treatment with sodium methoxide in



Reagents: i, O_3; ii, $NaBH_4$; iii, Ac_2O, NaOAc

Scheme 1



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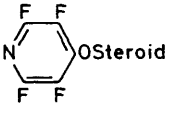


(4)

dimethylformamide; again, a phenolic ether is cleaved more rapidly than an alcoholic one, so that an alcoholic group can be protected in the presence of a phenolic group or *vice versa*. The protecting group is stable to a variety of standard reagents. In the same way, pentafluoropyridine yields the 2,3,5,6-tetrafluoropyridin-4-yl ethers (4).[18]

Methylthiomethyl ethers are susceptible to oxidation but they can be converted into alkoxymethyl ethers by treatment with mercuric chloride in the appropriate alcohol. The steroidal alcohols are recovered from the oxygen ethers by treatment with trityl tetrafluoroborate.[19]

Steroid hemisuccinates have been prepared by the reaction of the steroid alcohol or phenol with 2,2,2-trichloroethyl hydrogen succinate in the presence of *N,N'*-dicyclohexylcarbodi-imide and 4-(dimethylamino)pyridine, followed by unmasking of the trichloroethyl ester group with zinc; the method succeeds where more conventional ones fail[20] (*cf.* ref. 21). The γ-aminobutyrates of cholesterol and of dexamethasone have been synthesized by the action of t-butoxycarbonylaminobutyric anhydride on the steroid, followed by deprotection of the amino-group; both compounds were found to penetrate the brain to a much greater extent than does γ-aminobutyric acid itself.[22] Cholesterol, testosterone, and 17α-hydroxyprogesterone have been acylated by treatment with the 5-acyl-derivative of Meldrum's acid.[23] Ordinary methods of acylation either fail to yield retinoates of steroid alcohols or give very poor results, but the compounds can be prepared in yields of 70—90% by treatment of the steroid alcohol with retinylimidazolium tosylate; a number of 21-retinoates of glucocorticoids have been prepared in this way.[24] Some 3-cholesteryl derivatives of (4*Z*,9*Z*,15*Z*)- and (4*Z*,9*Z*,15*E*)-2,3-dihydrobilatriene have been synthesized.[25]

Catalytic rearrangement of the α-D-glucose 1,2-orthoacetates (5) of pregnenolone or 16,17-didehydropregnenolone with mercuric bromide in nitromethane gives the β-glycoside (6) in *ca* 56% yield, together with only 4% of the α-isomer.[26]

1.1.3 Opening of Epoxide Rings

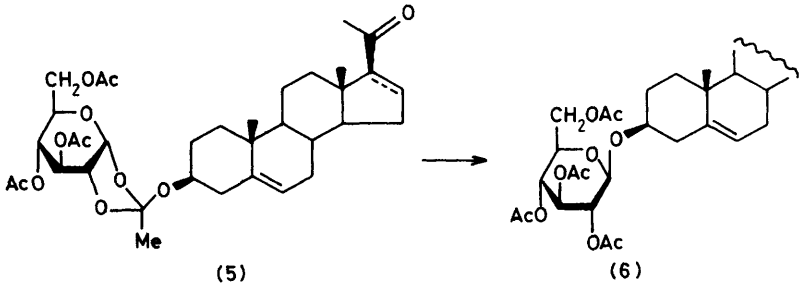
3β-Hydroxy-16α,17α-epoxypregn-5-en-20-one is converted into 3β,16α-diacetoxypregn-5-en-20-one by cathodic reduction (in a solution of tetramethylammonium bromide, with a catalytic quantity of hydrogen bromide) and subsequent acetylation.[27] 3β-Acetoxy-14β,15β-epoxy-5β-pregn-16-en-20-one, if treated with boron trifluoride, gives 3β-acetoxy-5β,14β-pregn-16-ene-15,20-dione, which can be reduced to 3β-acetoxy-5β,14β-pregnane-15,20-dione. Alternatively, the epoxide can be oxidized by chromic acid to give 3β-acetoxy-14α-hydroxy-5β-pregn-16-ene-15,20-dione, which is reduced by zinc to the same saturated dione.[28]

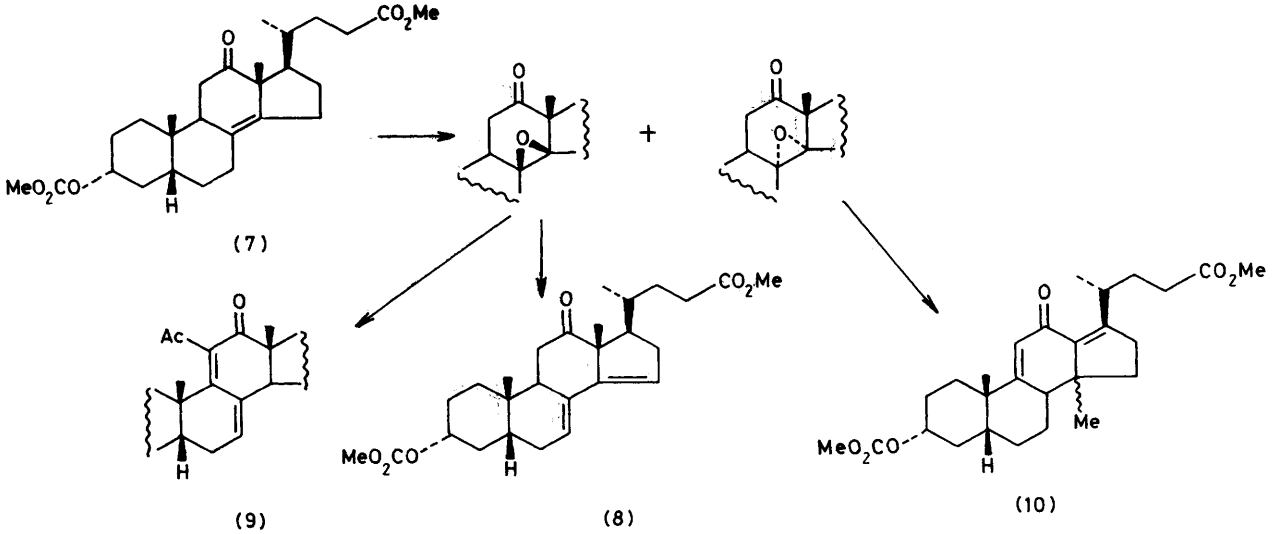
1α,3α-Dihydroxycholesta-4,6-diene is oxidized by *m*-chloroperoxybenzoic acid to 7α-(*m*-chlorobenzoyloxy)cholest-5-ene-1α,3α,4α-triol, probably *via* the 4α,5α-epoxide. 3β-Hydroxycholesta-4,6-diene, on the other hand, gives a mixture of 7β- and 7α-(*m*-chlorobenzoyloxy)cholest-5-ene-3β,4β-diol in a ratio of 5 : 1; in this instance, initial β-attack on the 4–5 double-bond was assumed to have taken place.[29]

The 12-oxo-8(14)-ene (7) is oxidized to a mixture of isomeric 14,15-epoxides by *m*-chloroperoxybenzoic acid. The β-epoxide is converted into the 12-oxo-7,14-diene (8) by boron trifluoride etherate or by perchloric acid in acetone; acetic anhydride, in the presence of boron trifluoride, gives the 11-acetyl-12-oxo-7,9(11)-diene (9). The α-epoxide, on the other hand, undergoes a partial backbone rearrangement if it is treated with boron trifluoride etherate, and yields compound (10).[30]

3α-Acetoxy-17β-benzoyloxy-5,6β-epoxy-4,4-dimethyl-A-homo-5β-androstane (11) is rearranged by potassium hydrogen carbonate in boiling methanol to give 17β-benzoyloxy-3α,5-epoxy-4,4-dimethyl-A-homo-5α-androstan-6β-ol (12).[31]

A number of steroid epoxides are reduced to the corresponding olefins by the action of triphenylphosphine and iodine in dichloromethane; it has been suggested that the role of the iodine is to enhance the electrophilicity of the phosphorus atom.[32]

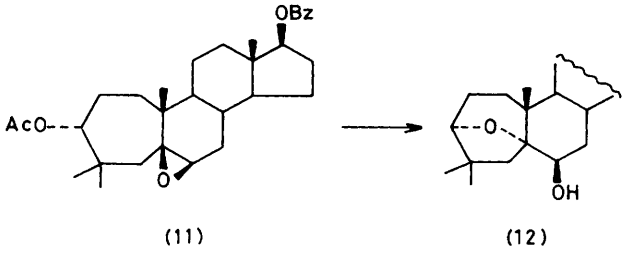




1.1.4 Other Reactions

2,3-Seco-5α-cholestane-2,3-diol (13) is converted, by its reaction with *o*-nitrophenyl selenocyanate, into a mixture of the 3-mono- (14) and 2,3-bis-(*o*-nitrophenylselenides) (15). Treatment of these compounds with hydrogen peroxide gives the 3-en-2-ol (16) and the 1,3-diene (17), respectively; the 4α-methyl derivative of compound (13) behaves similarly.[33]

The des-A-steroid (18), if treated with ethanolic hydrogen chloride, gives the 14β-hydroxy-compound (19) and the 14β-ethoxy-compound (20) and, possibly *via* compound (21), the 17-ethoxy-14β-16-en-15-one (22).[34]



(11) (12)

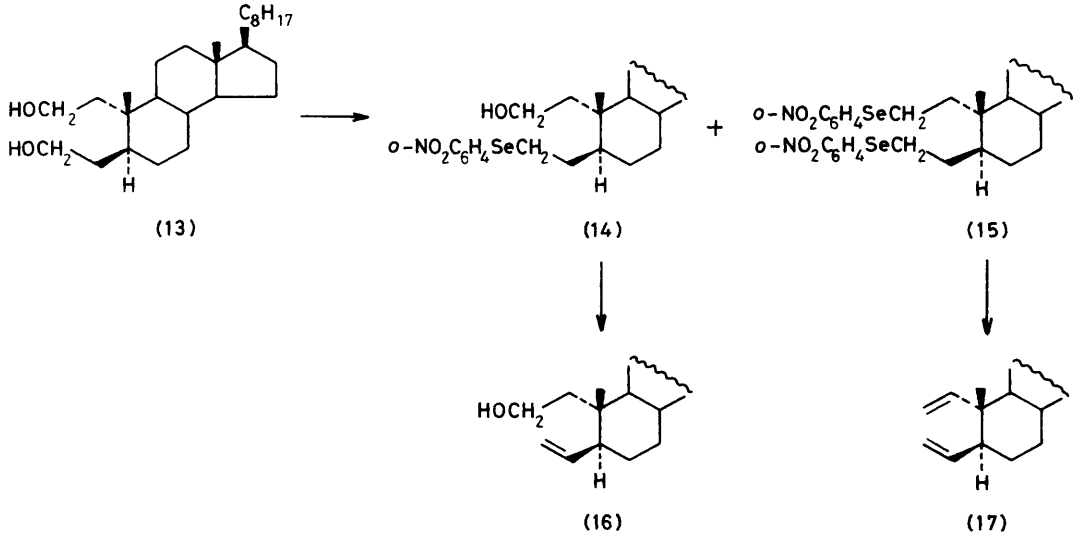
1.2 Unsaturated Compounds

1.2.1 Electrophilic Addition

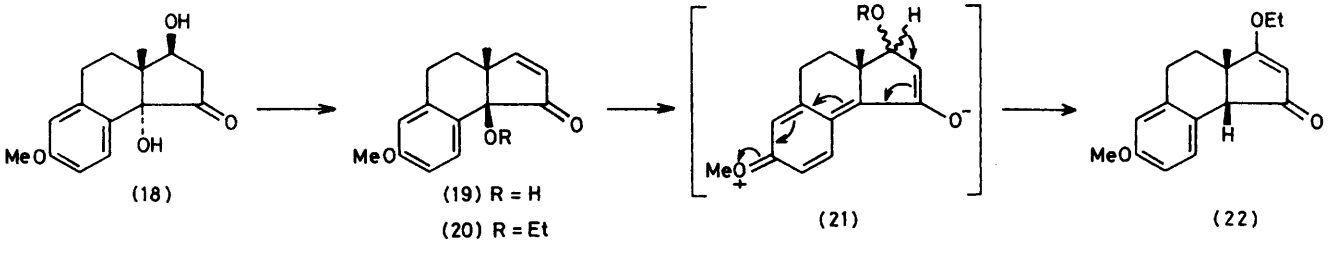
m-Chloroperoxybenzoic acid oxidizes (22*E*)-3α,5-cyclo-6β-methoxy-5α-cholest-22-ene (23) to the (22*R*,23*R*)-epoxide (24) and the (22*S*,23*S*)-epoxide (25) in a ratio of 2:1, while the corresponding (22*Z*)-olefin (26) gives the (22*R*,23*S*)-epoxide (27) and the (22*S*,23*R*)-epoxide (28) in a ratio of 5:1. Iodine and silver acetate, followed by sodium carbonate, give, largely or wholly, the (22*S*,23*S*)-epoxide (25) from the (22*E*)-ene and the (22*S*,23*R*)-epoxide (28) from the (22*Z*)-ene. The results have been compared with those of hydroboration and of oxidation with osmium tetroxide. The observed stereoselectivity can be explained by the preferred conformation of the transition state.[35]

1.2.2 Other Reactions of Olefinic Steroids

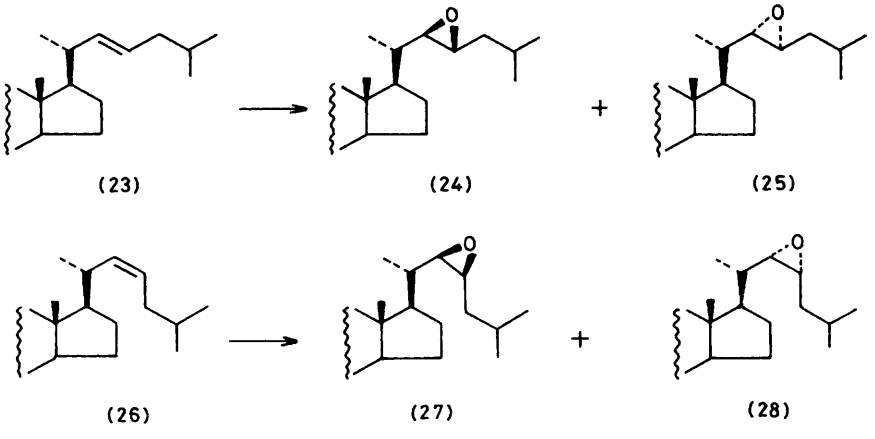
Cholest-1-en-3α- and -3β-ol and cholest-2-en-1α- and -1β-ol all undergo allylic rearrangement in the presence of 0.5 M-sulphuric acid in dioxan at 70 °C to give an equilibrium mixture that contains the isomers in a ratio of 20:25:52:3.[36] Dehydroepiandrosterone (29), if it is treated successively with



(13) (14) (15) (16) (17)



(18) (19) R = H (20) R = Et (21) (22)

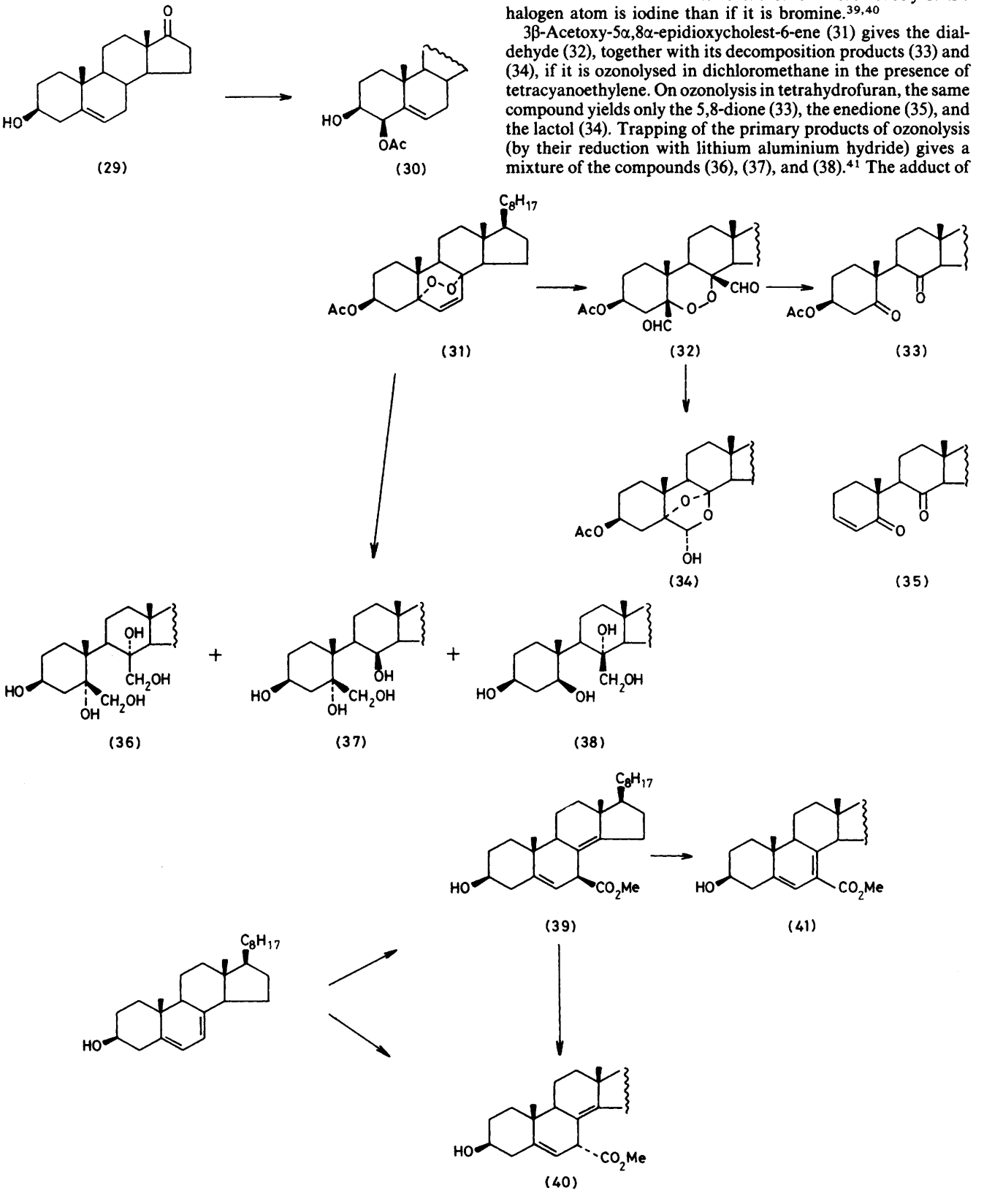


(23) (24) (25) (26) (27) (28)

bromine and silver acetate, gives predominantly 4β-acetoxy-3β-hydroxyandrost-5-en-17-one (30), probably *via* the 5α,6β-dibromide and the 6β-bromo-Δ⁴-compound. The 3-deoxy- and the 3α-chloro-analogues behave similarly, but the 3β-chloro- and 3β-bromo-analogues yield only the 5α,6β-dibromides.[37]

O. Nishikawa and his colleagues have studied the action of 1,3-dibromo-5,5-dimethylhydantoin, followed by 2,4,6-collidine, upon some cholesterol derivatives. The ratio of 5,7-diene to 4,6-diene varied from 1.7 to 5.5. With cholesterol itself, protecting groups at position 3 had little effect. In the case of 1α-hydroxycholesterol, however, carbamate groups at positions 1 and 3 had a considerable effect in increasing this ratio and also the yield of the 5,7-diene.[38] Steroids that contain double-bonds at C-2, C-4, or C-5 react with bromine and silver oxide to give the β-epoxide as the major product; this contrasts with the reaction with iodine and silver oxide, which gives (in most instances) a preponderance of the α-epoxide. The results have been rationalized in terms of the formation of a halonium ion intermediate which reverts to the olefin more readily if the halogen atom is iodine than if it is bromine.[39,40]

3β-Acetoxy-5α,8α-epidioxycholest-6-ene (31) gives the dialdehyde (32), together with its decomposition products (33) and (34), if it is ozonolysed in dichloromethane in the presence of tetracyanoethylene. On ozonolysis in tetrahydrofuran, the same compound yields only the 5,8-dione (33), the enedione (35), and the lactol (34). Trapping of the primary products of ozonolysis (by their reduction with lithium aluminium hydride) gives a mixture of the compounds (36), (37), and (38).[41] The adduct of



(29) (30) (31) (32) (33) (34) (35) (36) (37) (38) (39) (41) (40)

ergosterol with 1-phenyl-1,3,4-triazoline-2,5-dione gives the 6α,7α-diol or its cyclic osmate if it is oxidized with potassium permanganate or osmium tetroxide, respectively. However, it is attacked in the side-chain by iodine and silver acetate, by performic acid or peracetic acid, or by *m*-chloroperoxybenzoic acid to give 22,23-glycols (or their acetates) or 22,23-epoxides. It has been suggested that the oxidations that involve a three-membered ring in the product or in an intermediate favour attack on the side-chain, since a three-membered ring at positions 6 and 7 would involve too much steric strain.[42]

7,8-Didehydrocholesterol, on metallation with potassium trimethylsilylmethyl in tetrahydrofuran at a low temperature and subsequent carbonation and esterification, gives both isomers [(39) and (40)] of 7-methoxycarbonylcholesta-5,8(14)-dien-3β-ol; one of the isomers, believed to be the less hindered 7α-ester (40), is stable to sodium methoxide, but the other yields a mixture of the 5,7-diene (41) and the stable isomer (40) in a ratio of 1 : 5.[43]

Reduction of ergosterol and its derivatives with lithium in ethylamine gives mixtures of the Δ^5- and Δ^7-compounds. The proportion of the Δ^5-isomer is increased if the derivative is one that favours a negative charge at C-3 – as, for example, the lithio- or the benzoyl derivative. It is thought that this, in turn, favours the formation of a radical anion, with the radical centre at C-5.[44]

1.3 Carbonyl Compounds

1.3.1 Reduction and Dehydrogenation

A 7-oxo-(5α or 5β)-steroid is reduced by K-Selectride® (potassium tri-s-butylborohydride) at −45 °C to the 7α-hydroxy-compound; a 3,7-dioxo-5α-compound gives the 3α,7α-diol, but a 3,7-dioxo-5β-compound gives a mixture of products, of which the 3α,7α-diol is a minor constituent.[45] 3α,7α-Diacetoxy-12-oxo-5β-cholan-24-oic acid is reduced by sodium borohydride solely to the 12α-ol, but the corresponding methyl ester gives a mixture of 12-epimers.[46]

Steroid ketone tosylhydrazones are reduced by sodium borohydride in acetic acid to the corresponding methylene compounds; ester groups are unaffected by the reagent.[47]

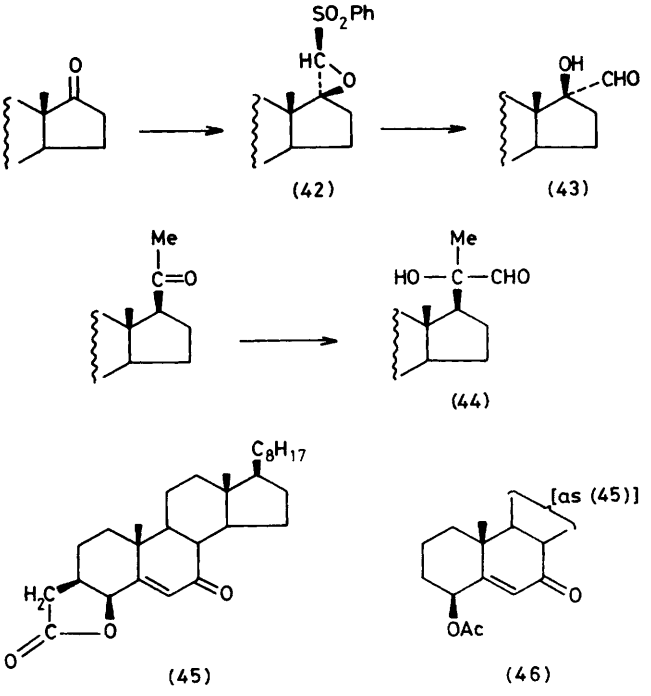
1.3.2 Other Reactions

A new method for the transposition of a carbonyl group from C-3 to C-2 involves 2,2-dichlorination of the 3-ketone, reduction with sodium borohydride to the 3β-ol, mesylation, and treatment with zinc to give the 2-chloro-Δ^2-compound. Finally, treatment with concentrated sulphuric acid affords the 2-ketone.[48]

A 3β-acetoxy-5α-hydroxy-6-ketone, if it is treated with boiling neat trichloroacetic acid under nitrogen, gives the 1,3,5(10)-trien-6-one. The use of tribromoacetic acid or the presence of oxygen encourages the formation of the corresponding 1-methyl-derivative. Since the starting material can be converted (by various acidic reagents) into the 2,4-dien-6-one, and this, in turn, gives the same compounds in which ring A is aromatic if it is treated with the trihaloacetic acids, the dienone appears to be an intermediate in the aromatization of the 3β-acetoxy-5α-hydroxy-6-one.[49]

Baeyer–Villiger oxidation of a 5α- or 5β-A-nor-2-one gives the 2-oxa-3-one and the 3-oxa-2-one in a ratio of *ca* 4 : 1. In the same way, a steroid 2-ketone gives the 2-oxa-A-homo-3-one and its 3-oxa-2-one isomer in a ratio of 3 : 1. These results have been explained as arising from relief of repulsive steric interactions in the transition state, in which migration of the carbon atom at position 1 is the more successful.[50]

A new, and advantageous, procedure for the conversion of a 17-ketone into an α-hydroxy-aldehyde involves its reaction with chloromethyl phenyl sulphone in the presence of potassium t-butoxide, to give the epoxy-sulphone (42); the reaction of this compound with potassium t-butoxide, followed by a mineral acid, yields the 17β-hydroxy-17α-aldehyde (43). A



20-oxo-pregnane similarly gives the (20*R*)-20-hydroxy-23,24-dinorcholan-22-al (44).[51]

1.3.3 Reactions of αβ-Unsaturated Carbonyl Compounds and Enols or Enolic Derivatives

A 3-oxo-4-ene reacts with manganese(III) acetate in benzene to give a mixture of the 2α- and 2β-acetoxy-derivatives; a 20-oxo-14,16-diene is attacked at the α-methyl group and affords the 21-acetoxy-compound.[52] The same reagent, in acetic acid, oxidizes cholesta-3,5-dien-7-one to the lactone (45) of 4β-hydroxy-7-oxocholest-5-en-3β-ylacetic acid; the corresponding 5-en-7-one gives a mixture of the 4β-acetoxy-derivative (46) and the same lactone.[53]

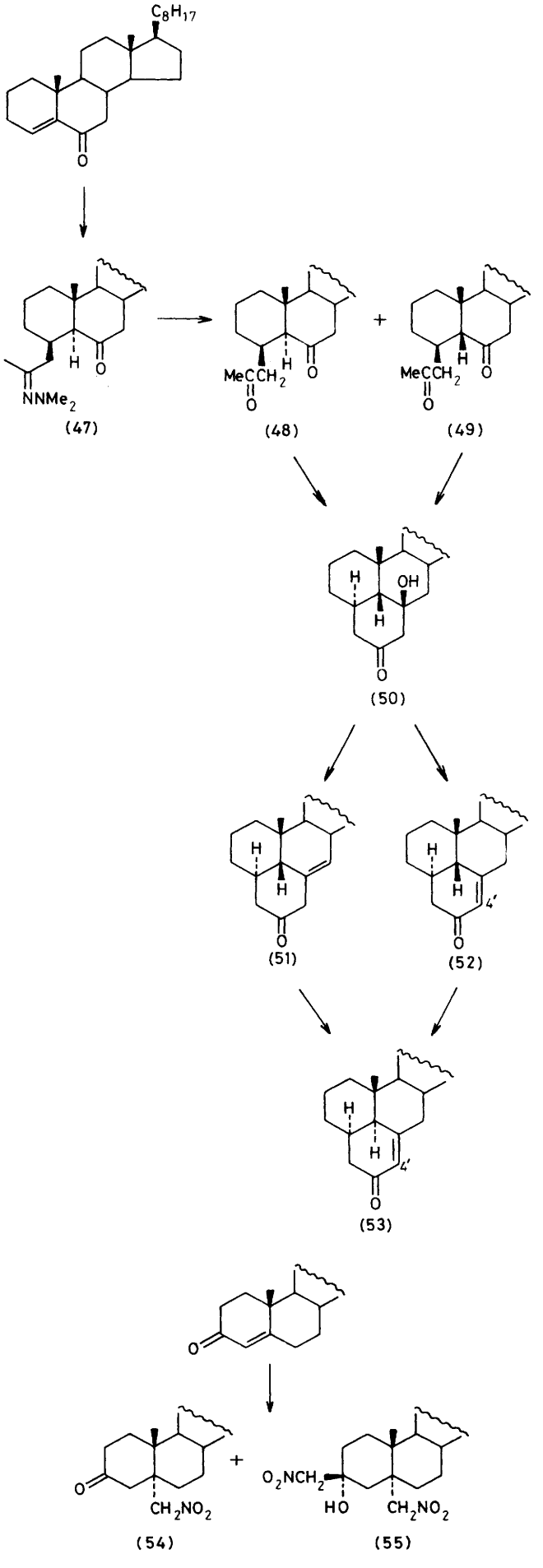
Cholest-4-en-6-one reacts with the reagent that is prepared from lithiated $Me_2C{=}NNMe_2$ and cuprous iodide in the presence of di-isopropyl sulphide to give the dimethylhydrazone (47); this is hydrolysed by acid to a mixture of the 5α- (48) and 5β-isomers (49) of the dione, either of which is cyclized by potassium hydroxide to compound (50). This last compound is dehydrated by thionyl chloride to the 6(7)-ene (51) (as the major product) and the 6(4′)-ene (52), but none of the 5(6)-ene was detected. The two isomers were each converted, under appropriate conditions, into the 5α-hydro-6(4′)-ene (53).[54]

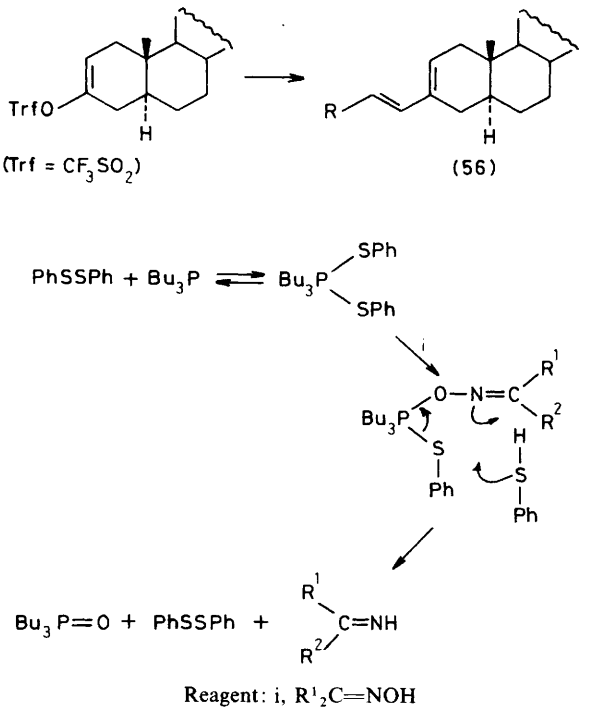
Michael addition of nitromethane to a 3-oxo-4-ene proceeds very slowly or not at all in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or tetrabutylammonium fluoride. However, at *ca* 9000 Bar, in the presence of either of these catalysts, fair yields of the 1 : 1 adduct (54) and the 2 : 1 adduct (55) are obtained; the formation of (55) could be controlled by varying the excess of nitromethane.[55]

The enol trifluoromethanesulphonate (triflate) of cholest-4-en-3-one is reduced by bis(triphenylphosphine)palladium acetate, in the presence of tributylammonium formate, to cholesta-3,5-diene; similarly, a 17-triflyloxy-16-ene gives the 16-unsubstituted 16-ene.[56] The reaction of a 3-triflyloxy-2-ene with a terminal olefin and the same palladium reagent yields the 3-[(*E*)-substituted vinyl]-2-ene (56), and 3-triflyloxy-3,5-dienes and 17-triflyloxy-16-enes react similarly.[57]

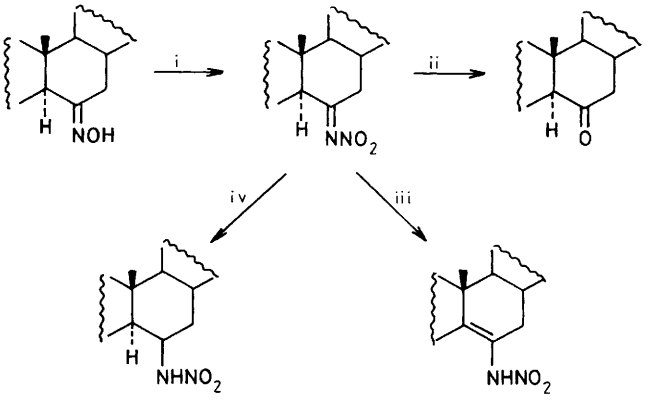
1.4 Compounds of Nitrogen, Sulphur, and Selenium

Cholest-5-ene and 3β-chlorocholest-5-ene react with nitrosyl chloride in carbon tetrachloride at 0 °C to give 5α-chloro-6β-





Scheme 2



Scheme 3

nitro-compounds.[58] 6-Nitro-5-enes are reduced with zinc–ammonia–methanol to the 6-oximino-5α-compounds.[59]

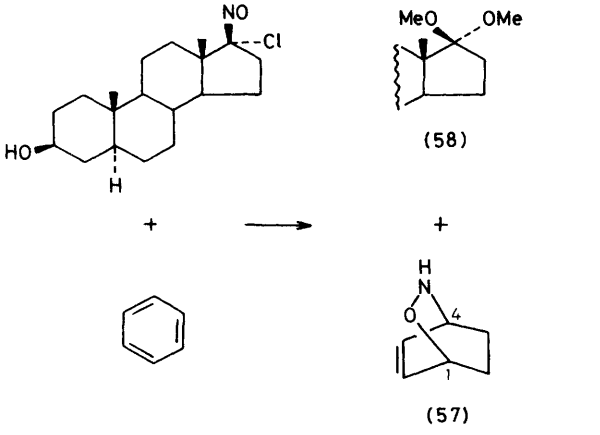
Oximes are reduced to imines by tributylphosphine in the presence of diphenyl disulphide, possibly by the mechanism shown in Scheme 2. By this means, 6-, 17-, and 20-ones may be regenerated from their oximes. Because the reaction mixture is self-drying, the imine is stable; therefore a 17-imino-steroid can be reduced *in situ* to the 17β-amino-steroid or allowed to react with hydrogen cyanide to give the 17α-cyano-17β-amino-compound.[60] A 6-oxime reacts with nitrous acid to yield the 6-nitro-imino-steroid, which undergoes the reactions shown in Scheme 3.[61]

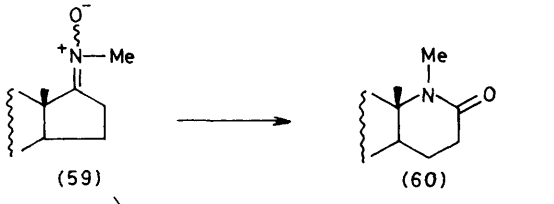
The asymmetry of a steroid is transferred to a non-steroid compound in the reaction of 17α-chloro-17β-nitroso-5α-androstan-3β-ol with benzene in methanol–chloroform to give the bridged 1,2-oxazine (57) [with the (1*R*,4*S*) configuration] and the dimethyl ketal (58) of the steroid 17-ketone.[62]

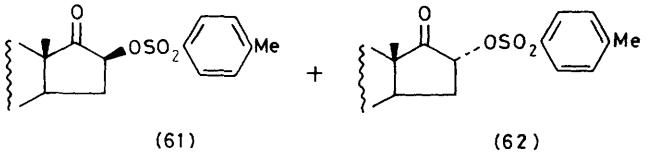
A 17-methylnitrone (59) reacts with toluene-*p*-sulphonyl chloride in aqueous pyridine to give the D-homo-lactam (60); under anhydrous conditions, the two reactants yield the isomeric 16-tosyloxy-17-ones (61) and (62). Benzoyl chloride

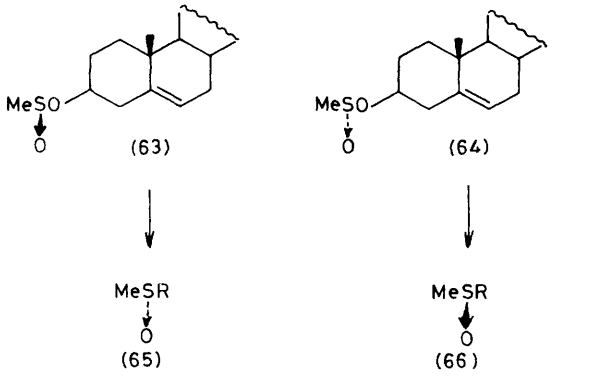
and acetic anhydride give the corresponding benzoate and acetate.[63]

3β-Acetoxy-21-(tetrahydropyran-2-yloxy)pregna-5,16-dien-20-one reacts with diphenylsulphimine in toluene at 80 °C for thirty hours to yield the 16α,17α-epimino-compound.[64] 6β-Acrylamido-5α-hydroxy-steroids are cyclized by potassium hydroxide or sodium hydroxide to give the *N*-lactyl-5β,6β-epimino-derivatives.[65]









Cholesterol, when it reacts with methanesulphinyl chloride in the presence of triethylamine, affords a mixture of the isomeric sulphinates (63) and (64), which can be separated (in low yield) by fractional crystallization; treatment of the isomers with Grignard reagents RMgBr gives methyl sulphoxides [(65) and (66)] of high optical purity.[66]

17β-(t-Butyldimethylsilyloxy)androst-4-en-3β-ol reacts with *N*-phenylselenylphthalimide and tributylphosphine to give the 3α- and 3β-phthalimido-steroids, rather than the expected 3-arylselenyl-derivatives; however, these compounds have been prepared from the steroid alcohol and *o*- or *p*-nitrophenyl selenocyanate.[67] A 20-hydrazono-steroid reacts with phenylselenyl bromide in the presence of *N*-t-butyl-*N'N'N''N''*-tetramethylguanidine to yield the 20-phenylselenyl-17-ene; 6- and 17-hydrazono-compounds are similarly converted into the unsaturated phenylselenyl-compounds.[68] A 3α-arylselenyl-4-ene is reduced by nickel boride to the unsubstituted Δ⁴-compound; similarly, a 2α-phenylselenyl-3-ketone is reduced to the 2-unsubstituted 3-ketone, along with some of the 3β-ol.[69]

1.5 Molecular Rearrangements

17β-Hydroxy-5α-androstan-3-one undergoes a Favorskii-type reaction when it is treated with iodosobenzene diacetate and potassium hydroxide, to give a mixture of the 2α- and 3α-carboxy-A-nor-compounds in which the former predominates.[70] R. M. Moriarty and his co-workers have suggested that the ring-contraction proceeds as shown in Scheme 4.[71]

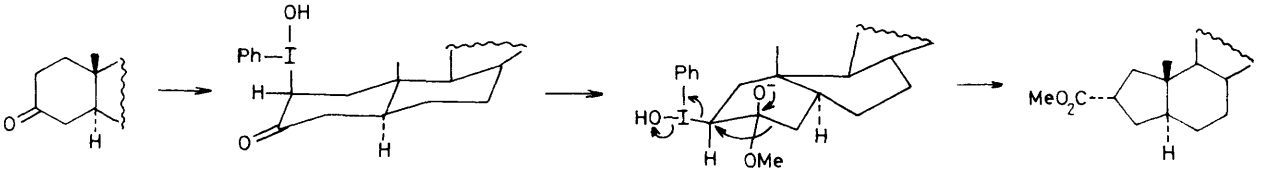
Methyl 3α-(t-butyldimethylsilyloxy)cholan-24-oate (67) undergoes loss of the silyloxy-group and backbone rearrangement if it is treated with trifluoroacetic anhydride and hexafluoroisopropyl alcohol in methylene chloride and yields the lactones (68) and (69), both as mixtures of 20-epimers; the six-membered lactone is the predominant product. If the reaction occurs in the absence of hexafluoroisopropyl alcohol, the main product is a mixture of the 20-isomers of compound (70), which is converted into the lactones (68) and (69) by treatment with antimony pentafluoride and hydrogen fluoride.[72]

A 6β,19-epoxide is cleanly formed from the 6β-hydroxy-compound when it reacts with iodosobenzene diacetate and iodine under irradiation with visible light. The same method can be applied to a (20*R*)- or (20*S*)-20-hydroxypregnane to give the 20-hydroxy-18-iodo-compound and to the furostan (71) to give the spirostan (72).[73]

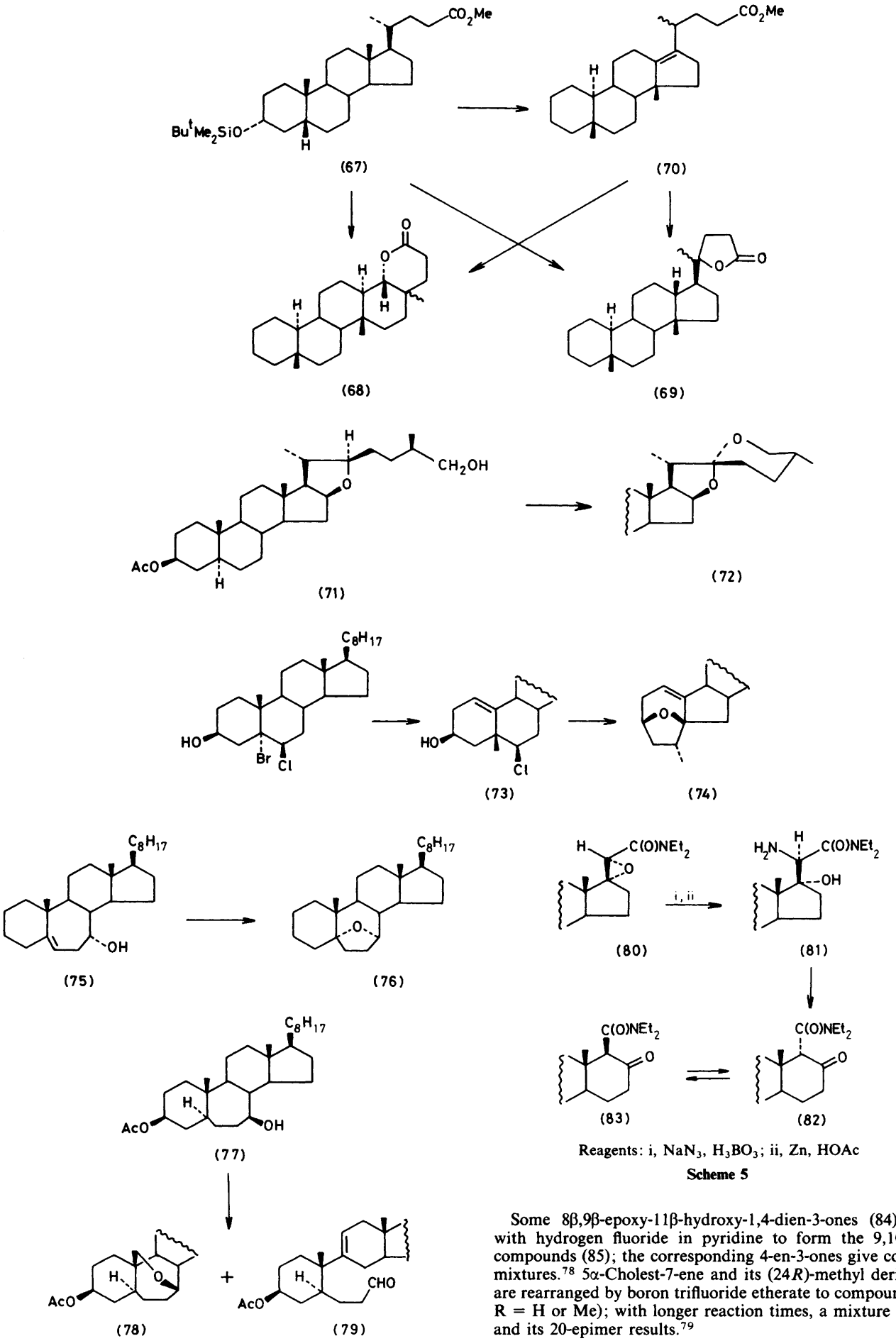
5-Bromo-6β-chloro-5α-cholestan-3β-ol is rearranged by silver-perchlorate-catalysed solvolysis to give, *inter alia*, 6β-chloro-5β-methyl-19-norcholest-1(10)-en-3β-ol (73); this is converted, under the reaction conditions, into the A-homo-B-nor-epoxide (74).[74]

B-Homocholest-5-en-7aα-ol (75) reacts with mercuric oxide and iodine under ultraviolet irradiation to give the 5α,7aα-epoxide (76) as the major product, accompanied by minor amounts of the 6-iodo-derivative; a similar reaction occurs with the 7aβ-ol.[75] 3β-Acetoxy-7aβ-hydroxy-B-homo-5α-cholestane (77), with lead tetra-acetate, yields only a few per cent of the 7aβ,19-epoxide (78) together with the aldehyde (79).[76]

A 17α,20-epoxy-21-carbodiethylamide (80) is converted, as shown in Scheme 5, into the (20*R*)-20-amino-17α-ol (81). Treatment of this compound with nitrous acid then causes D-homoannulation, to give the 17-oxo-17aα-carbodiethylamide (82), which is equilibrated (by alkali) to a 2 : 1 mixture with the 17aβ-isomer (83).[77]



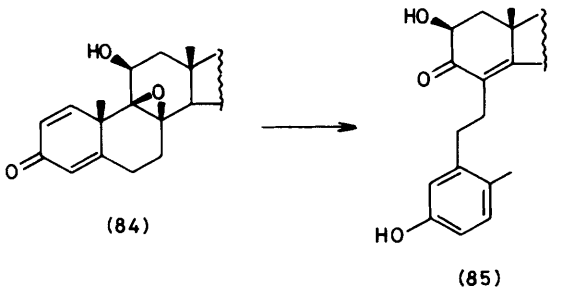
Scheme 4



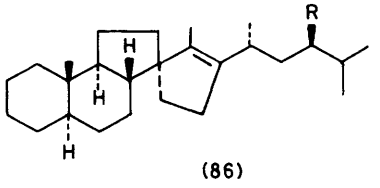
Reagents: i, NaN_3, H_3BO_3; ii, Zn, HOAc

Scheme 5

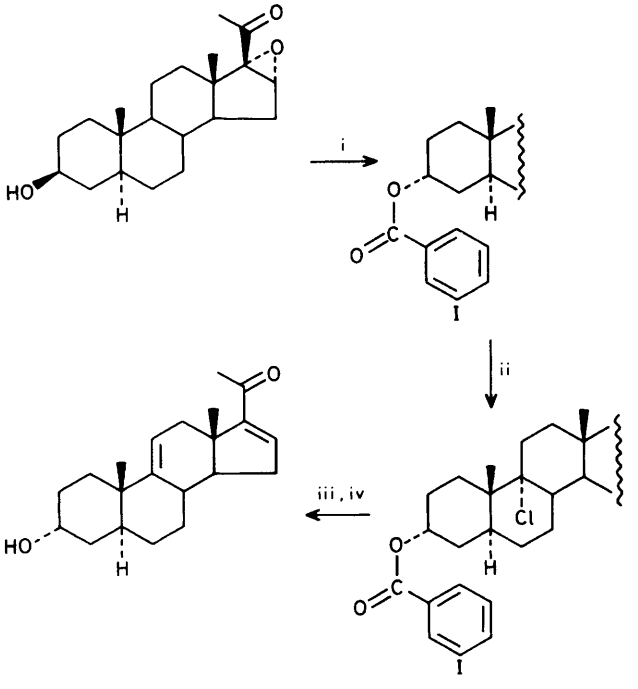
Some 8β,9β-epoxy-11β-hydroxy-1,4-dien-3-ones (84) react with hydrogen fluoride in pyridine to form the 9,10-seco-compounds (85); the corresponding 4-en-3-ones give complex mixtures.[78] 5α-Cholest-7-ene and its (24*R*)-methyl derivative are rearranged by boron trifluoride etherate to compound (86; R = H or Me); with longer reaction times, a mixture of (86) and its 20-epimer results.[79]



(84) (85)



(86)



Reagents: i, *m*-$IC_6H_4CO_2H$, Ph_3P, $EtO_2CN{=}NCO_2Et$; ii, $PhICl_2$, *hv*; iii, KOH; iv, $TiCl_3$, $LiAlH_4$

Scheme 6

1.6 Remote Functionalization Reactions

Breslow's method has been used in an improved method of preparation of 3α-hydroxy-5α-pregna-9(11),16-dien-20-one from 16α,17α-epoxy-3β-hydroxy-5α-pregnan-20-one; the route is shown in Scheme 6. A mixture of sulphuryl chloride and benzoyl peroxide may also be used in the chlorine-transfer reaction, with almost equally good results.[80]

17α-Chloro-3α-[3-(4-iodophenyl)benzoyloxy]-5α-cholestane (87) (itself the product of a remote functionalization reaction) is dehydrochlorinated by 50 equivalents of neat DBU to a 4:1 mixture of the 17(20)- olefin (mostly *E*) (88) and the 16(17)-olefin (89); the ratio is greatly reduced if even small amounts of solvent (or if even more DBU) are included in the reaction mixture. The only other base to equal DBU in the ratio of exocyclic to endocylic olefin that is produced is DBN (1,5-diazabicyclo[4.3.0]non-5-ene). A possible explanation is that the steroid molecules are packed, rather as other steroids form liquid crystals.[81]

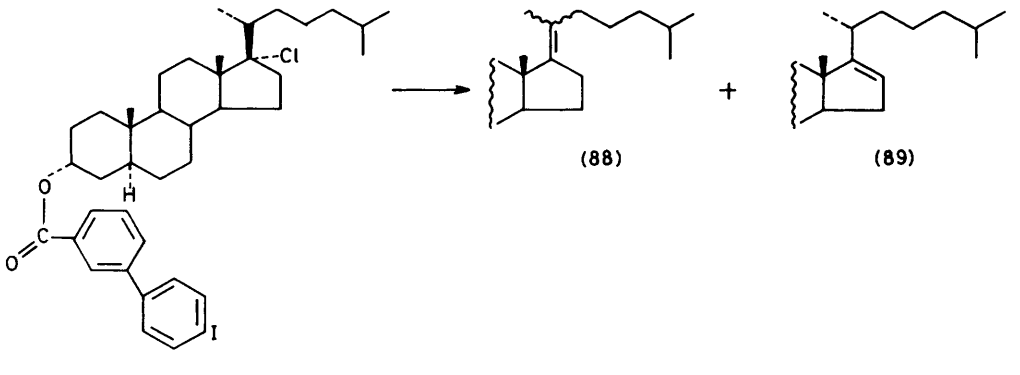
R. Breslow has studied remote functionalization from the β-face of the steroid molecule. 6β-[β-(Benzoylphenyl)propionyloxy]-3α,5-cyclo-5α-cholestane (90; $n = 2$), when it was irradiated in benzene and subsequently underwent the reactions that are shown in Scheme 7 gave 10% each of the 15-ketone (91), the 16-ketone (92), and the 18-carboxylic acid (93). There was no sign of attack on the nucleus if the higher homologue (90; $n = 3$) was subjected to the same reactions but if (90; $n = 4$) was used, attack occurred at C-16, C-18 (traces only), C-23 or C-24, and C-25.[82]

1.7 Photochemical Reactions

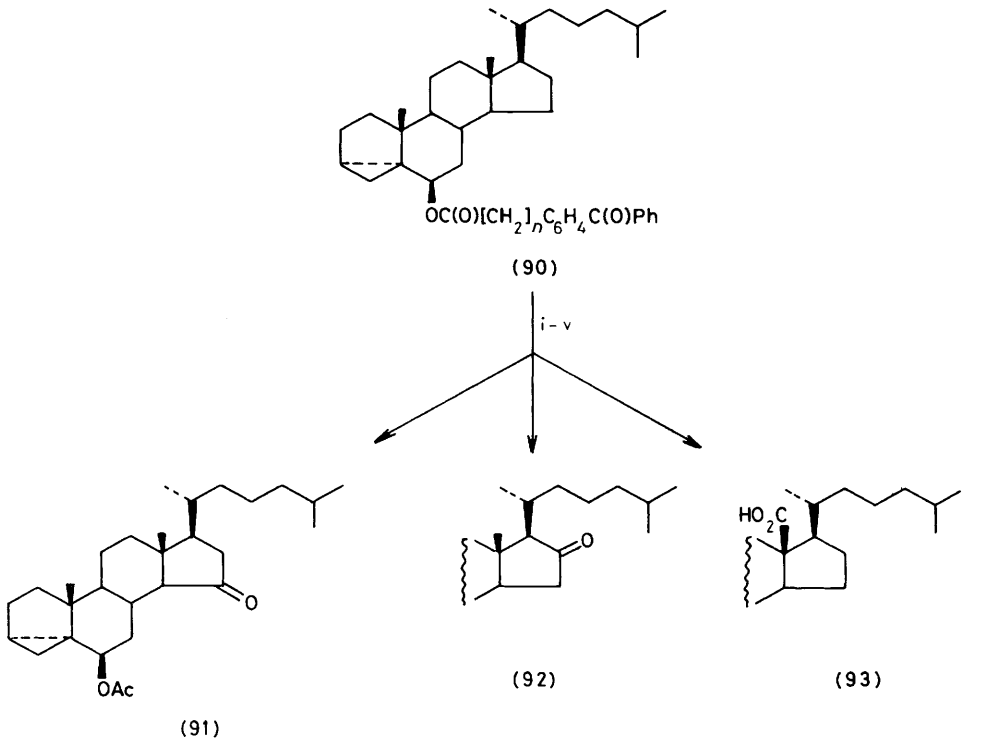
9,10-Dicyanoanthracene-sensitized photo-oxygenation of cholesterol gives, after reduction of the product with triphenylphosphine, 5α-cholest-6-ene-3β,5-diol and 7-hydroxycholesterol (both epimers) in a ratio of >9:1, identical with the result of oxidation by singlet oxygen and quite different from radical autoxidation processes.[83]

Photo-oxygenation of 9,11-didehydro-oestrone methyl ether, with Rose Bengal as a sensitizer, gives the 9,11-seco-compound (94).[84] Irradiation of a solution of the 5β-cholest-7-en-6-one (95) in oxygen-free isopropyl alcohol gave the isomeric 6-hydroxy-6-(1-hydroxy-1-methylethyl)-compounds (96) as major products; analogous compounds were obtained if other alcohols were used as solvent.[85]

Photocycloaddition of cyclopentene to 17β-acetoxy-5α-androst-1-en-3-one (97) gives the 1α,2α-compound (98) and the 1β,2α-compound (99); the *trans*-fused isomer isomerized to the 1β,2β-compound (100) if it was boiled with ethanolic sodium ethoxide for 3 days. The addition was quenched by penta-1,3-diene, indicating that an enone triplet state is involved. A similar sequence of reactions is shown by 2-methylpropene. Ketene bis-(2-methoxyethyl)acetal again reacts similarly, and the products [(101) and (102)] of cycloaddition are hydrolysed

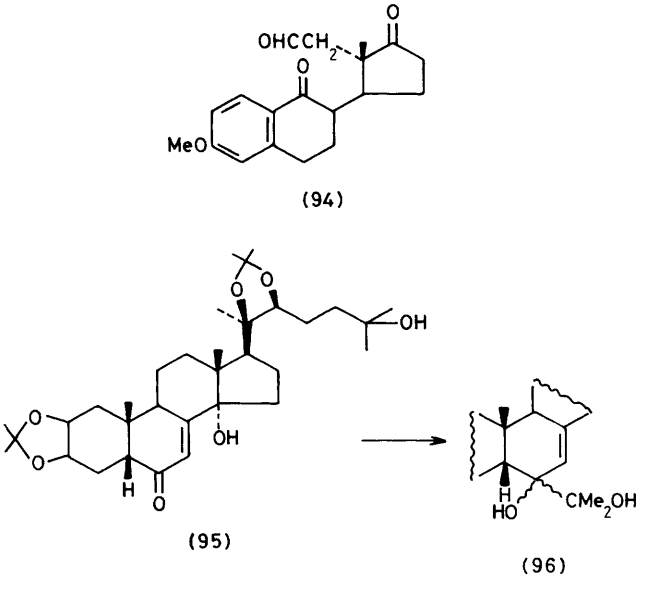


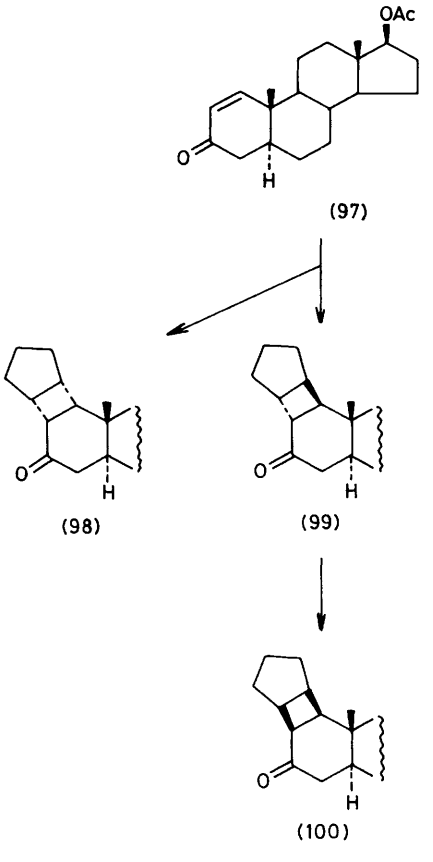
(87) (88) (89)



Reagents: i, *hν*; ii, $LiAlH_4$; iii, Ac_2O, pyridine; iv; $SOCl_2$, pyridine; v, RuO_4

Scheme 7



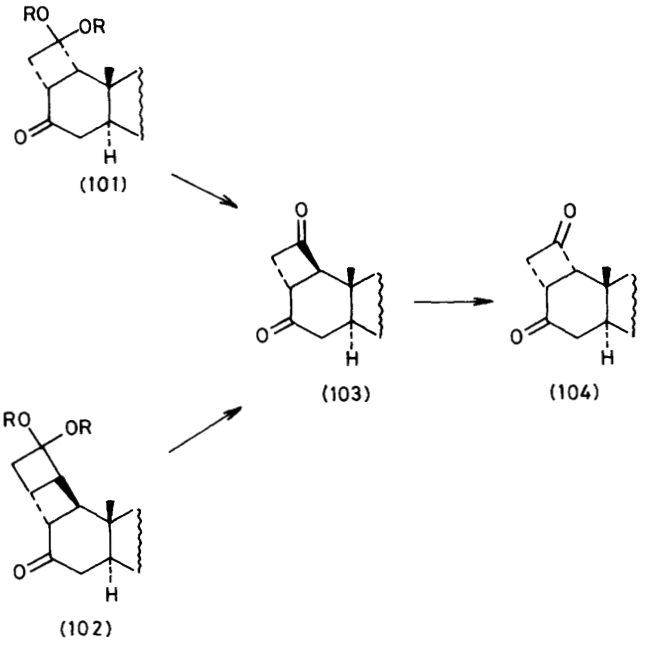


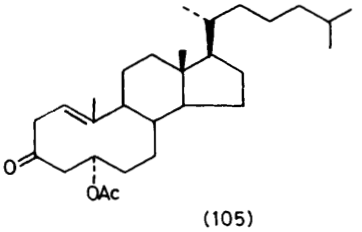
by toluene-*p*-sulphonic acid to give, *inter alia*, the *trans*-fused cyclobutanone (103); this isomerizes to the 1α,2α-compound (104) in boiling pyridine. The unusual stability of the *trans*-fused compounds has been attributed to the inaccessibility of the 2β-hydrogen atom.[86]

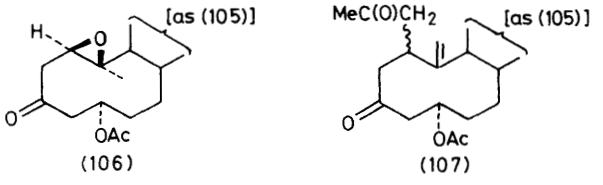
Irradiation of the (*E*)- and (*Z*)-isomers of the 5,10-seco-steroid (105) in dioxan or isopropyl alcohol merely causes equilibration of the two compounds. However, with acetone as solvent, in the presence of air, compounds (106) and (107) are also formed.[87]

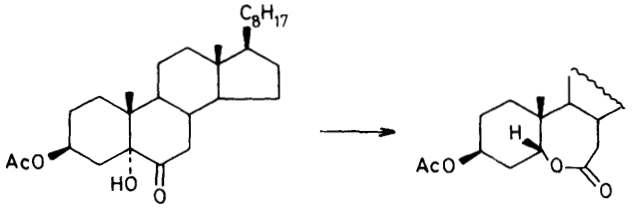
The stereospecificity of the photochemical conversion of 3β-acetoxy-6-oxo-5α-cholestan-5-ol (108) into 3β-acetoxy-6-oxa-7-oxo-B-homo-5β-cholestane (109) has been confirmed, as has the stereospecificity of the conversion of the 5β-hydroxy-epimer of (108) into the 5-epimer of (109). Labelling experiments have shown that the hydrogen atom at C-5 of (109) originates from the 7α-position and that the hydrogen of the 5-hydroxyl group of (108) appears at C-7a of (109).[88]

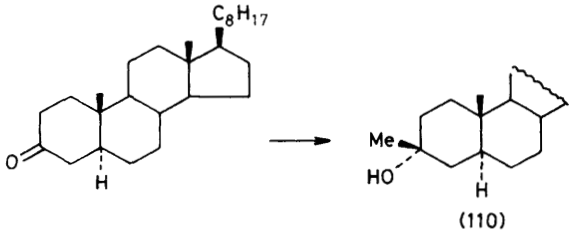
Details have been published of the conversion of 5α-cholestan-17β-ol into 17-oxa-5α-cholestane and its 13α-isomer, and of the preparation of 3-oxa-5α-cholestane (dimethylated at

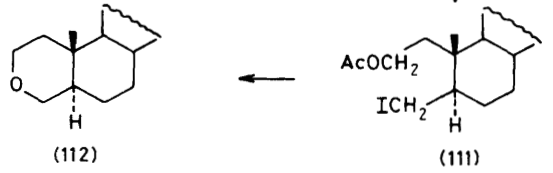












C-2 or C-4) from the 3β-ol. 3-Oxa-5α-cholestane (112) itself can be prepared from 5α-cholestan-3-one by conversion into the 3β-methyl-3α-ol (110), then by reaction with mercuric oxide and iodine; a minor product is compound (111), which can be hydrolysed and cyclized to the 3-oxa-compound (112). Tracer experiments have shown that the oxygen atom in these products derives from the hydroxyl group of the starting material, rather than from mercuric oxide.[89]

Compound (113) and its 11α-epimer are both converted into the 13α-isomers [as (114)] by irradiation with ultraviolet light; the ease of the reactions and the high yields are worthy of note.[90]

The nitronate that can be derived from a 17β-nitro-compound and sodium ethoxide is converted (by irradiation with ultraviolet light) into a mixture of the hydroxamic acid (115) (as the major product), the 13α- and 13β-17-ketones (116), and the 17β,18-cyclo-compound (117); 3β-acetoxy-17β-nitro-13α-androstane yields the 17-ketone as the major product, as well as the 13α-isomer of the hydroxamic acid, but no cyclo-compound can be detected. Irradiation of the oxaziridine (118) gives the lactam (119) as the predominant product.[91]

2 Partial Synthesis

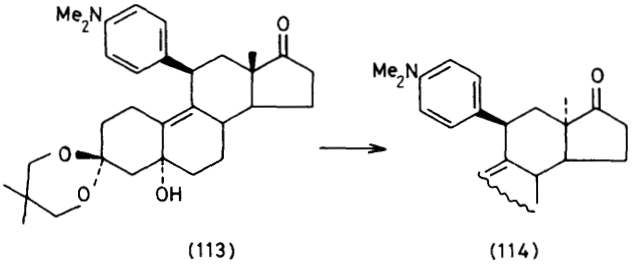
2.1 Derivatives and Analogues of Cholestane

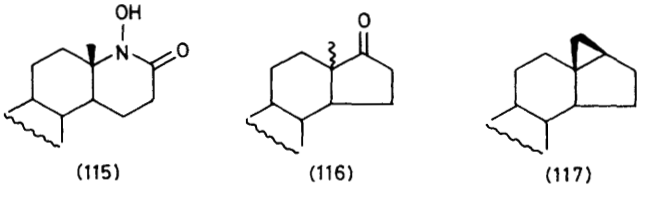
Reviews have been published on the synthesis of brassinolide[92] and on the biosynthesis of ergosterol.[93]

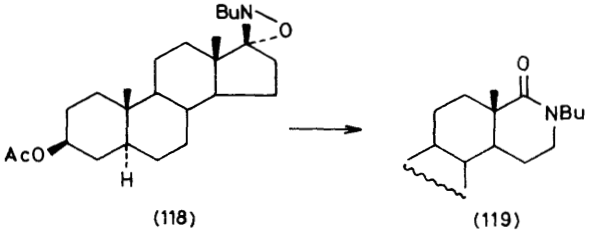
15β-Hydroxycholesterol (120) and its 20-epimer (121) have been synthesized from dehydroepiandrosterone as summarized in Scheme 8; the additions of the palladium complex are completely regio- and stereo-specific.[94]

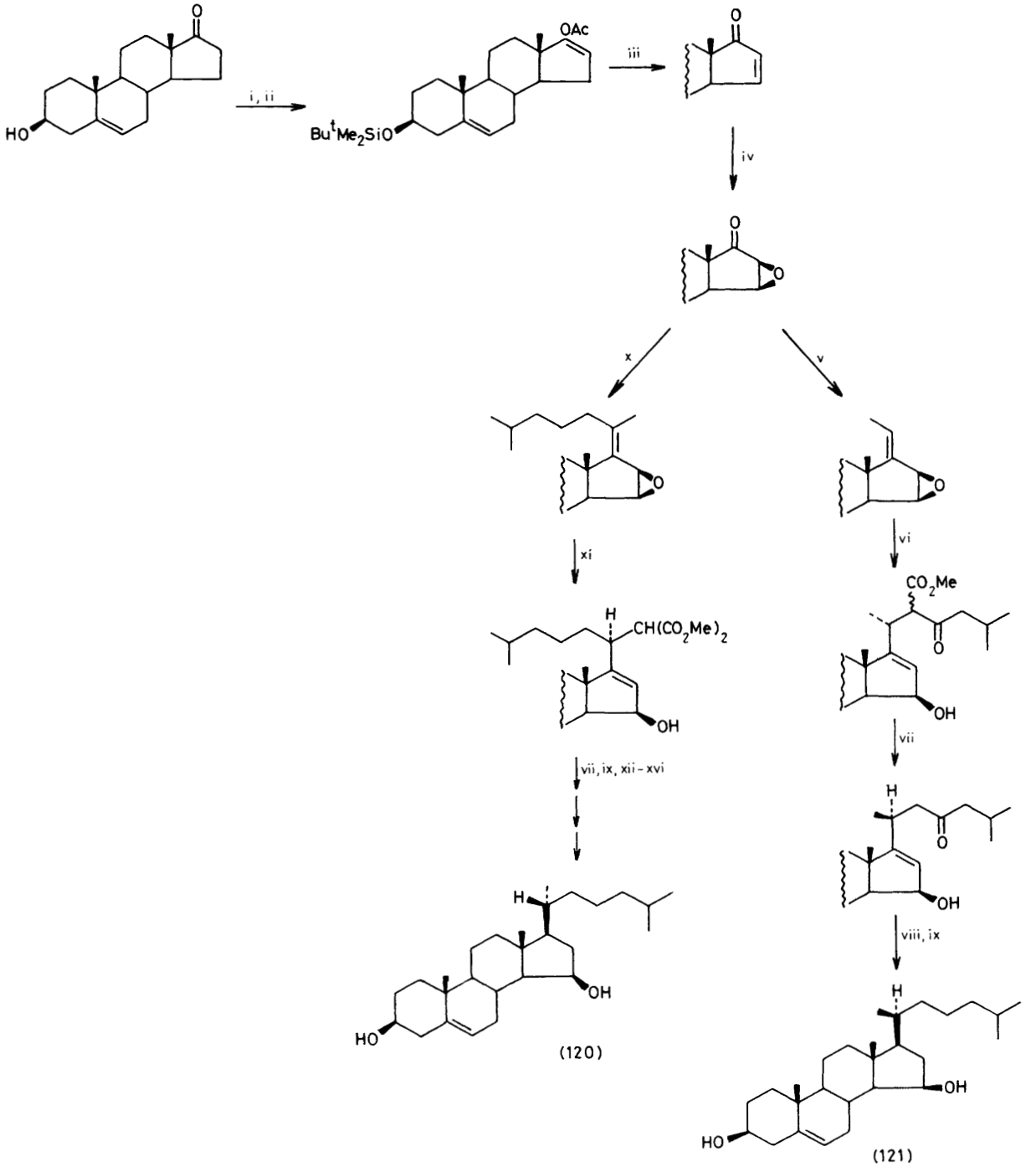
7,8,9,11-Tetradehydrocholesteryl acetate, which can be prepared by dehydrogenation of the 7,8-didehydro-derivative with mercuric acetate in acetic acid, can be purified by reverse-phase high-performance liquid chromatography on silica; the purified material keeps much better than the simply crystallized material.[95]

Syntheses of 2α- and 2β-tritiocholesterol[96] and of the 3α-tritio-derivatives of cholesterol and β-sitosterol[97] have been published.









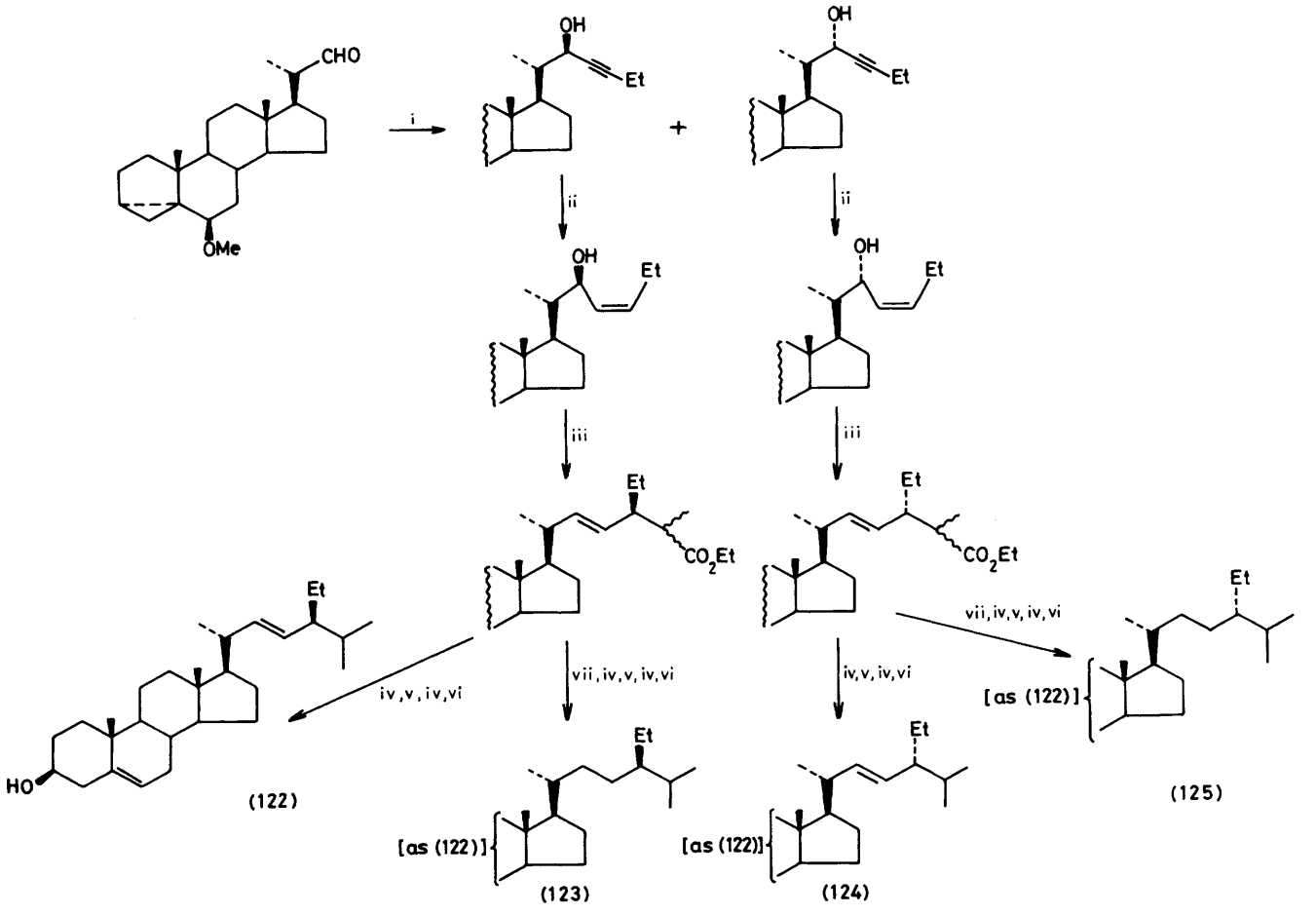
Reagents: i, Bu^{t}Me$_2$SiCl, imidazole; ii, H$_2$C=C(Me)OAc; iii, H$_2$C=CHCH$_2$OCO$_2$Me, Pd(OAc)$_2$, Bu$_3$SnOMe; iv, H$_2$O$_2$, OH$^-$; v, MeCH=PPh$_3$; vi, Me$_2$CHCH$_2$C(O)CH$_2$CO$_2$Me, Pd$_3$(TBAA)$_3$, P(OCH$_2$CH$_2$)$_3$CEt; vii, NaI, HMPA; viii, NH$_2$OH, OH$^-$; ix, H$_2$, Pt; x, Me$_2$CHCH$_2$CH$_2$CH=PPh$_3$; xi, CH$_2$(CO$_2$Me)$_2$, Pd$_3$(TBAA)$_3$, P(OCH$_2$CH$_2$)$_3$CEt; xii, EtOCH=CH$_2$; xiii, Bu$^i_2$AlH; xiv, CrO$_3$; xv, Rh(PPh$_3$)$_3$Cl; xvi, TsOH

Scheme 8

A biosynthetic pathway for the formation of 24-methylsterols from acetate has been proposed, on the basis of labelling patterns.[98] Syntheses of stigmasterol (122), β-sitosterol (123), poriferasterol (124), and clionasterol (125) from 3α,5-cyclo-6β-methoxy-23,24-dinor-5α-cholan-22-al are shown in Scheme 9; the corresponding 24-methyl analogues are produced similarly. All of these compounds are used by larvae of the silkworm (*Bombyx mori*), and all are converted by them into cholesterol.[99]

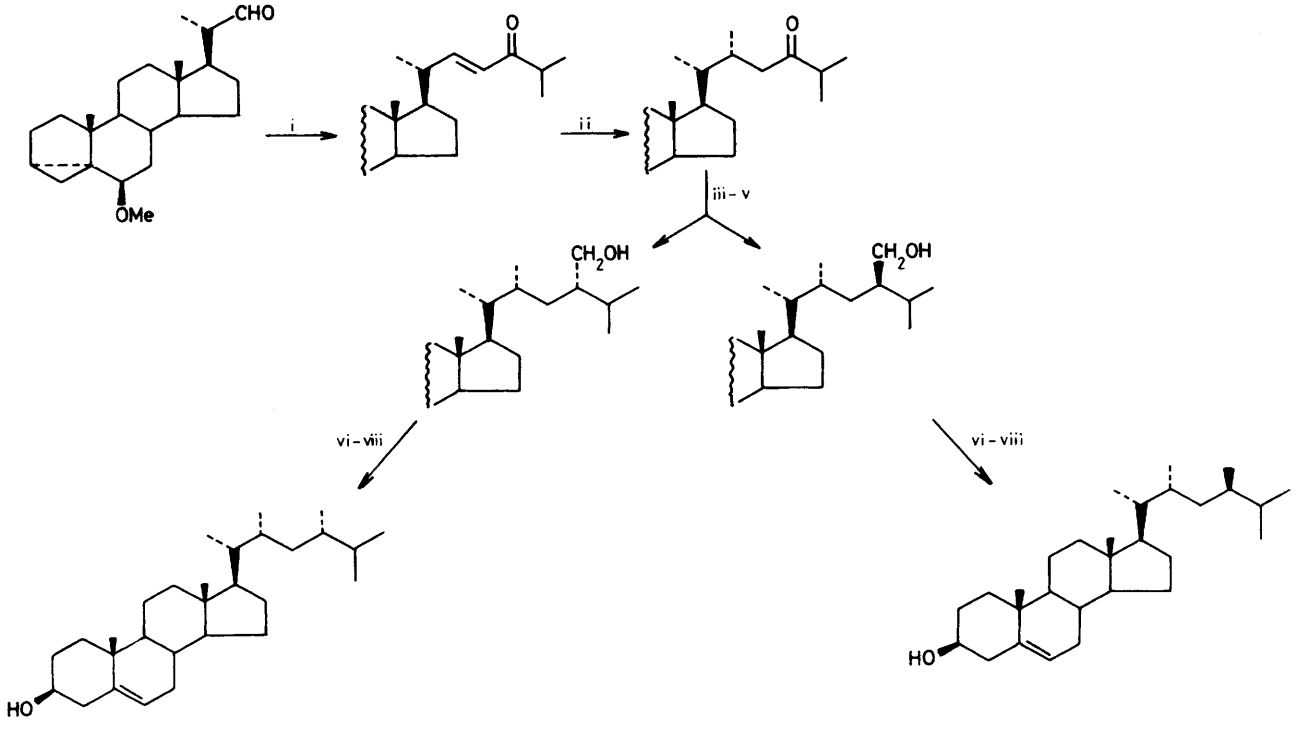
The isomers of 22,24-dimethylcholesterol have not been found in Nature, but, in order to expedite the search for them, they have been synthesized. The two (22*R*)-compounds were prepared as shown in Scheme 10, and all four isomers were produced as shown in Scheme 11. The final assignment of configuration came from a synthesis of the two (24*S*)-isomers from brassicasterol *i*-methyl ether (Scheme 12).[100]

Glaucasterol, which has been isolated from the soft coral *Sarcophyton glaucum*, is known to be one of the isomers of (22*E*)-24,26-cyclocholesta-5,22-dien-3β-ol (126), but the configurations at C-24 and C-25 were unknown; both the (24*S*,25*S*)-isomer (127) and the (24*R*,25*R*)-isomer (128) have been synthesized, as shown in Scheme 13. Glaucasterol has



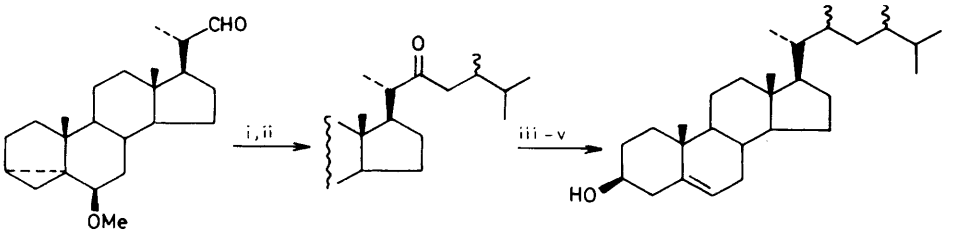
Reagents: i, EtC≡CMgBr; ii, H_2, Lindlar catalyst; iii, $EtC(OEt)_3$, $EtCO_2H$; iv, $LiAlH_4$; v, $MeSO_2Cl$; vi, TsOH; vii, H_2, Pd

Scheme 9



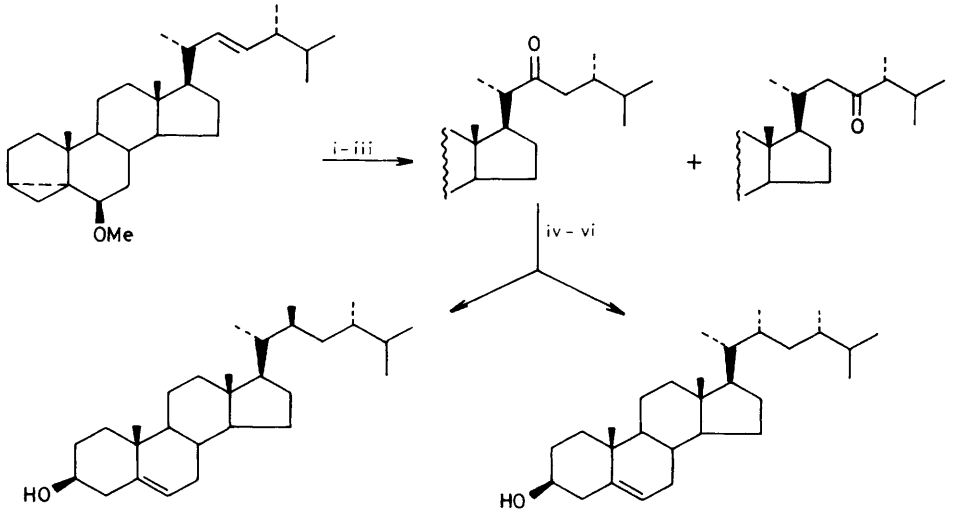
Reagents: i, $Ph_3P{=}CHC(O)CHMe_2$; ii, $LiCuMe_2$; iii, $H_2C{=}PPh_3$; iv, BH_3; v, H_2O_2; vi, $MeSO_2Cl$; vii, $LiAlH_4$; viii, H^+

Scheme 10



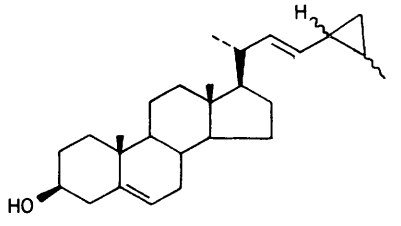
Reagents: i, $Me_2CHCHMeCH_2MgBr$; ii, CrO_3; iii, $H_2C{=}PPh_3$; iv, H_2, Pt; v, H^+

Scheme 11



Reagents: i, *m*-$ClC_6H_4CO_3H$; ii, $LiAlH_4$; iii, CrO_3; iv, $H_2C{=}PPh_3$; v, H_2, Pt; vi, H^+

Scheme 12



(126)

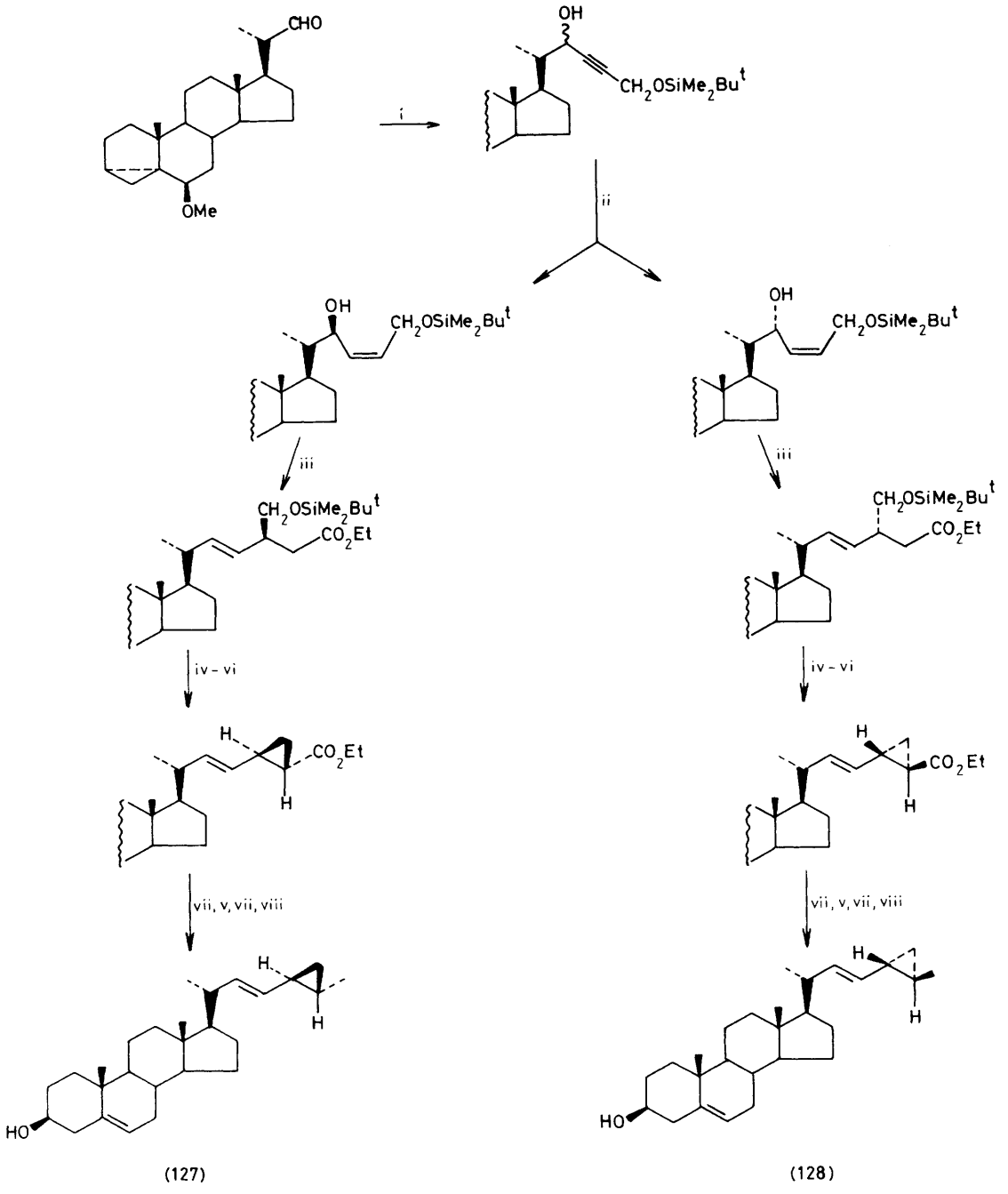
been shown to be identical with the former isomer.[101] All four isomers of 24-hydroxymethyl-6β-methoxy-26-methyl-3α,5-cyclo-26,27-cyclo-5α-cholestane, with the *trans* configuration around the cyclopropane ring in the side-chain, have been synthesized as shown in Scheme 14, and converted into the corresponding isomers of 24,26-dimethyl-26,27-cyclocholesterol, all of which have been assigned configurations; petrosterol has the (24*R*,25*R*,26*R*) configuration (129).[102] The four isomers of 22,23-methylenecholesteryl acetate have been synthesized. On treatment with trifluoroacetic acid, the *trans*-disubstituted cyclopropanes (130) and (132) gave, *inter alia*, backbone-rearranged products (131) and (133), respectively, as mixtures of epimers at C-20, while the *cis*-substituted compounds gave complex mixtures of rearranged side-chain isomers. A conformational explanation has been offered.[103]

24-Methylenecholesteryl benzoate reacts with osmium tetroxide to give the two 24-isomers of 24,28-dihydroxy-24-methylcholesteryl benzoate (134). These are separated [as their 28-esters with (2*R*)-2-methoxy-2-trifluoromethylphenylacetic acid] by preparative-scale t.l.c. The two isomers are converted into the 24,28-epoxides (135) by hydrolysis, mesylation, and treatment with a base. From tracer experiments with the [23,23,25-$^3H_3$]-epoxides, which were fed to the larvae of *Tenebrio molitor*, it appears that only the (24*R*)-epoxide is utilized.[104]

The reaction of 3β-hydroxy-23,24-dinorchol-5-en-22-al with a lithium acetylide gives the two ethynylcarbinols with very little stereoselectivity. However, if the mixture is oxidized to the acetylenic ketone (136), the reduction of this compound with (*R*)-*B*-3-pinanyl-9-borabicyclo[3.3.1]nonane ['Alpine-borane'; derived from (+)-α-pinene] gives the (22*R*)-ethynylcarbinol (137) and the (22*S*)-isomer (138) in a ratio of *ca* 125 : 1; if the enantiomeric reagent was used it gave a mixture in which the ratio of (22*S*)-isomer to (22*R*)-isomer was 2.7 : 1. The results have been explained as being due to the reinforcement or opposition of two asymmetric inductive effects. Reduction of the acetylenic ketone with lithium tri(s-butyl)borohydride gives the (22*S*)-product (138) with acceptable selectivity (*ca* 11 : 1) if the alkyl group of the acetylene is large, but 1,4-reduction begins to compete as the alkyl group becomes smaller.[105]

A new synthesis of 25-hydroxycholesterol (139) from 3β-(tetrahydropyran-2-yloxy)pregn-5-en-20-one is shown in Scheme 15.[106]

The (25*R*)- and (25*S*)-isomers of 5β-cholestane-3α,7α,12α,26-tetraol are intermediates in the biosynthetic pathway from cholesterol to cholic acid. Earlier methods of synthesis are inconvenient or unsatisfactory, but the method of synthesis of the mixed isomers that is shown in Scheme 16 is an improvement.[107] Again, the 24-isomers of 24-methyl-5β-cholestane-3α,7α,12α,25-tetraols, which were required for an investigation into the pathway of degradation of β-sitosterol to bile acids, have been prepared (Scheme 17).[108]



Reagents: i, LiC≡CCH$_2$OSiMe$_2$Bu^t; ii, H$_2$, Lindlar catalyst; iii, MeC(OEt)$_3$, MeCO$_2$H; iv, PhCO$_2$H, Bu$_4$N$^+$F$^-$; v, MsCl; vi, KOBu^t; vii, LiAlH$_4$; viii, TsOH

Scheme 13

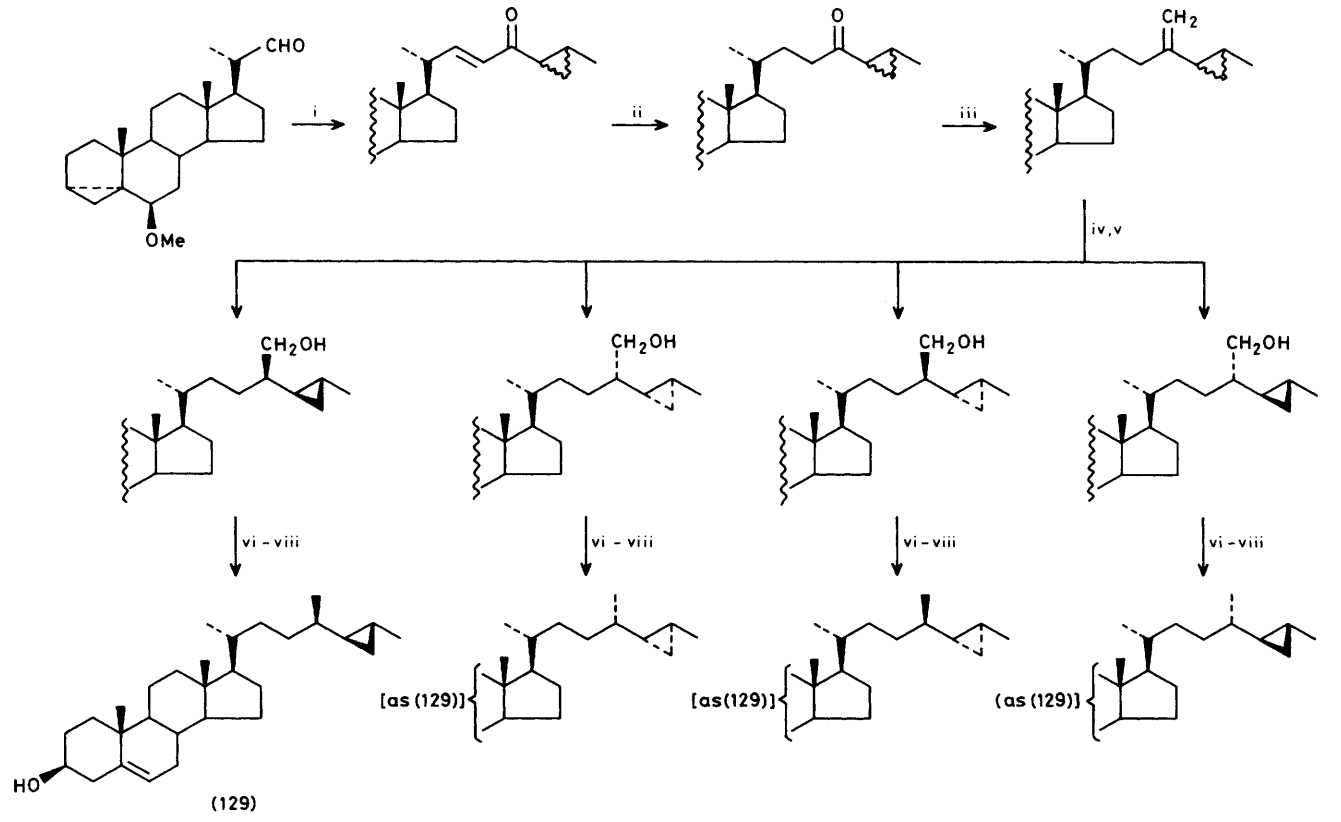
Reviews have been published on the isolation, synthesis, and biological activity of brassinolide and its synthetic analogues[109] and on the bioassay, isolation, purification, and structure elucidation of the brassinosteroids and their classification and occurrence in higher plants.[110]

A new method of synthesis of brassinolide (140) is illustrated in Scheme 18; the first condensation is quite stereoselective as long as the temperature is kept low. The method is higher-yielding than those that have previously been described.[111] The conversion of ergosterol into compound (141), which is an intermediate for the synthesis of brassinolide, is illustrated in Scheme 19.[112]

24-*epi*-Brassinolide (142) and the corresponding (22*S*,23*S*)-isomer (143) have been prepared by the short route from brassicasterol mesylate that is shown in Scheme 20.[113] All of the known naturally occurring brassinosteroids have been synthesized by the methods shown in Schemes 21–25.[114–116]

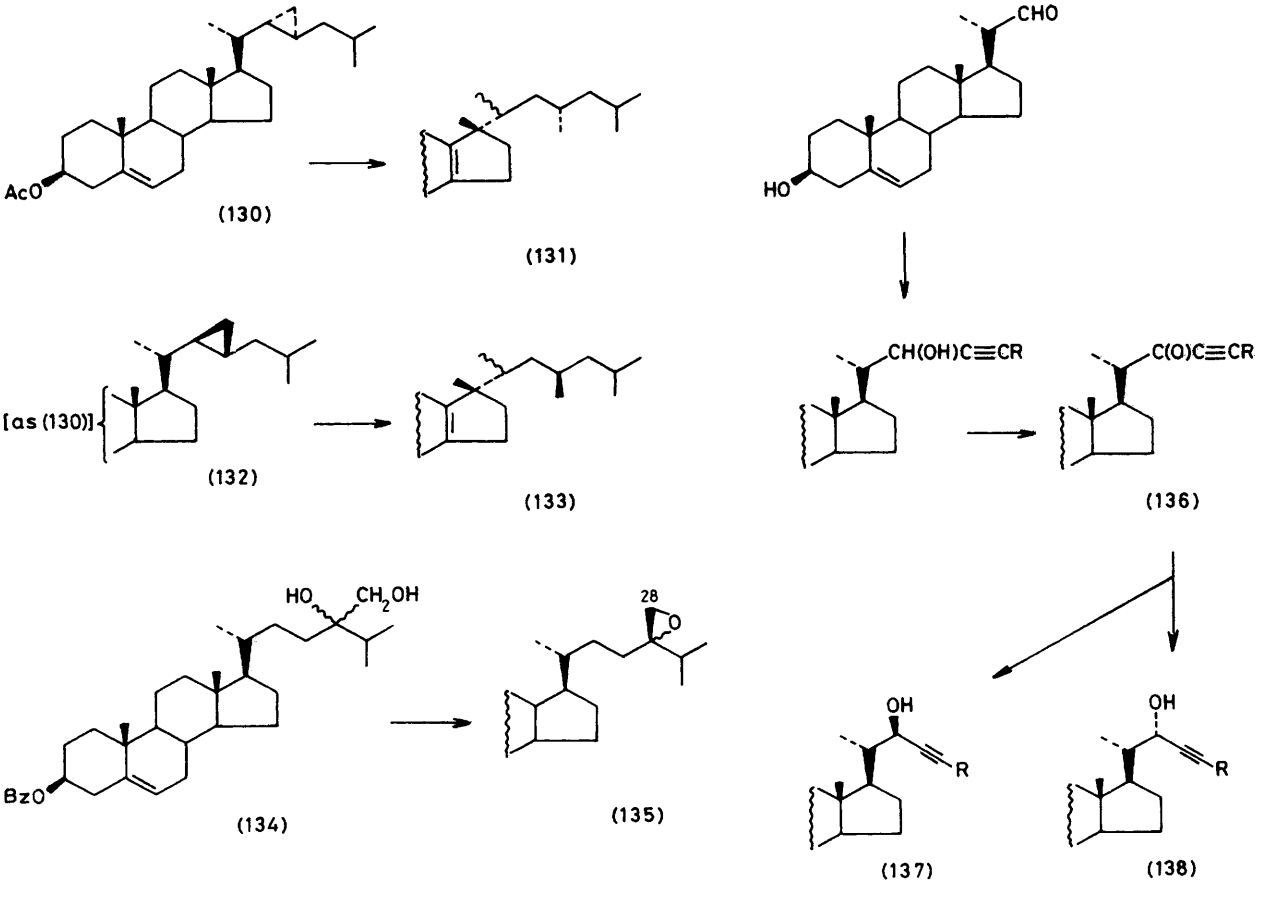
Some 28-homobrassinosteroids in which there are modifications in rings A and B have been synthesized and their plant-growth-promoting activities have been tested; some structure–activity relations have been proposed.[117] Syntheses of some analogues of brassinolide from stigmasterol and β-sitosterol have been published.[118]

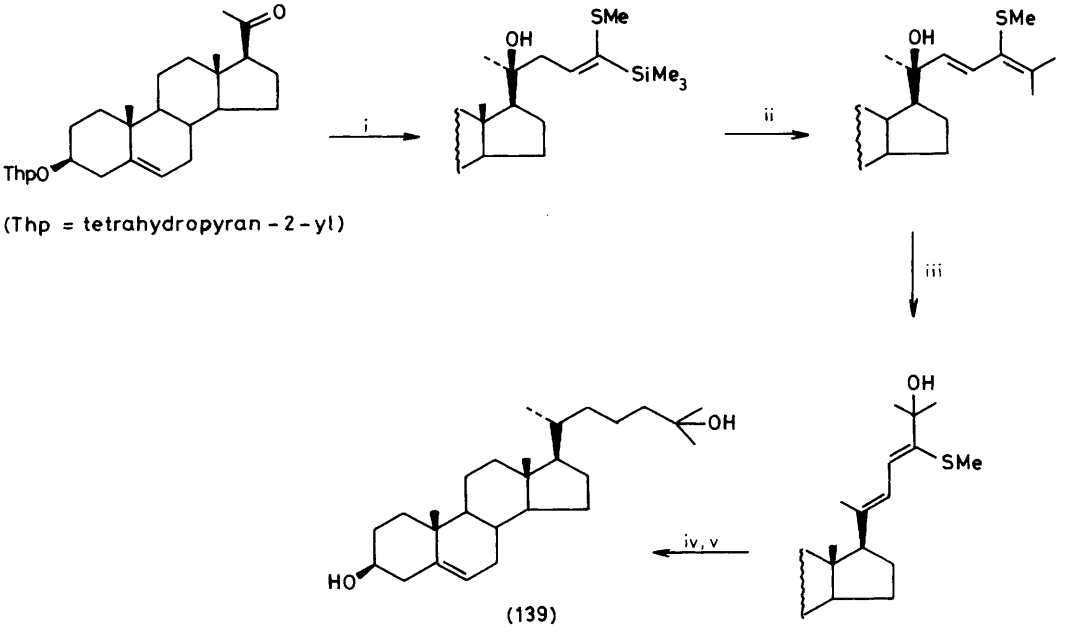
A new, stereocontrolled synthesis of the side-chain of ecdysone is shown in Scheme 26; this is one of the simplest methods, so far, for this purpose.[119]



Reagents: i, $Ph_3P{=}CHC(=O)$–cyclopropyl; ii, $NaBH_4$; iii, $Ph_3P{=}CH_2$; iv, BH_3; v, H_2O_2; vi, MsCl; vii, $LiAlH_4$; viii, H^+

Scheme 14

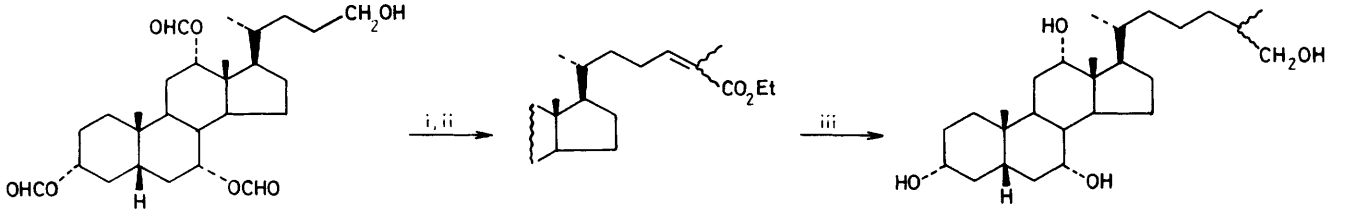




(Thp = tetrahydropyran-2-yl)

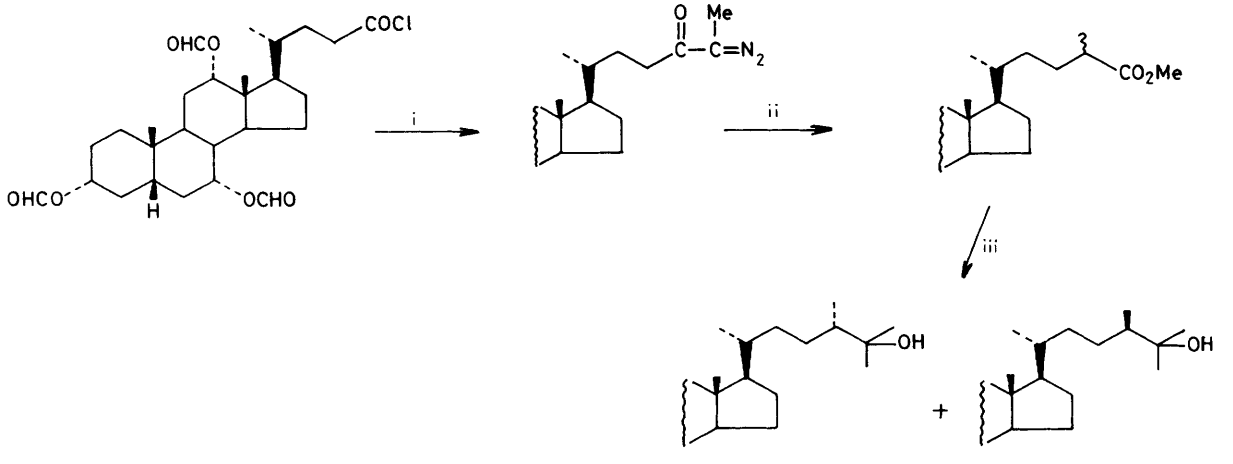
Reagents: i, $MeSCH(SiMe_3)CH{=}CH_2$, Bu^sLi; ii, Me_2CO, Bu^sLi; iii, $NiCl_2$; iv, Ni; v, H^+

Scheme 15



Reagents: i, pyridinium chlorochromate; ii, $MeC(CO_2Et){=}PPh_3$; iii, $LiAlH_4$

Scheme 16

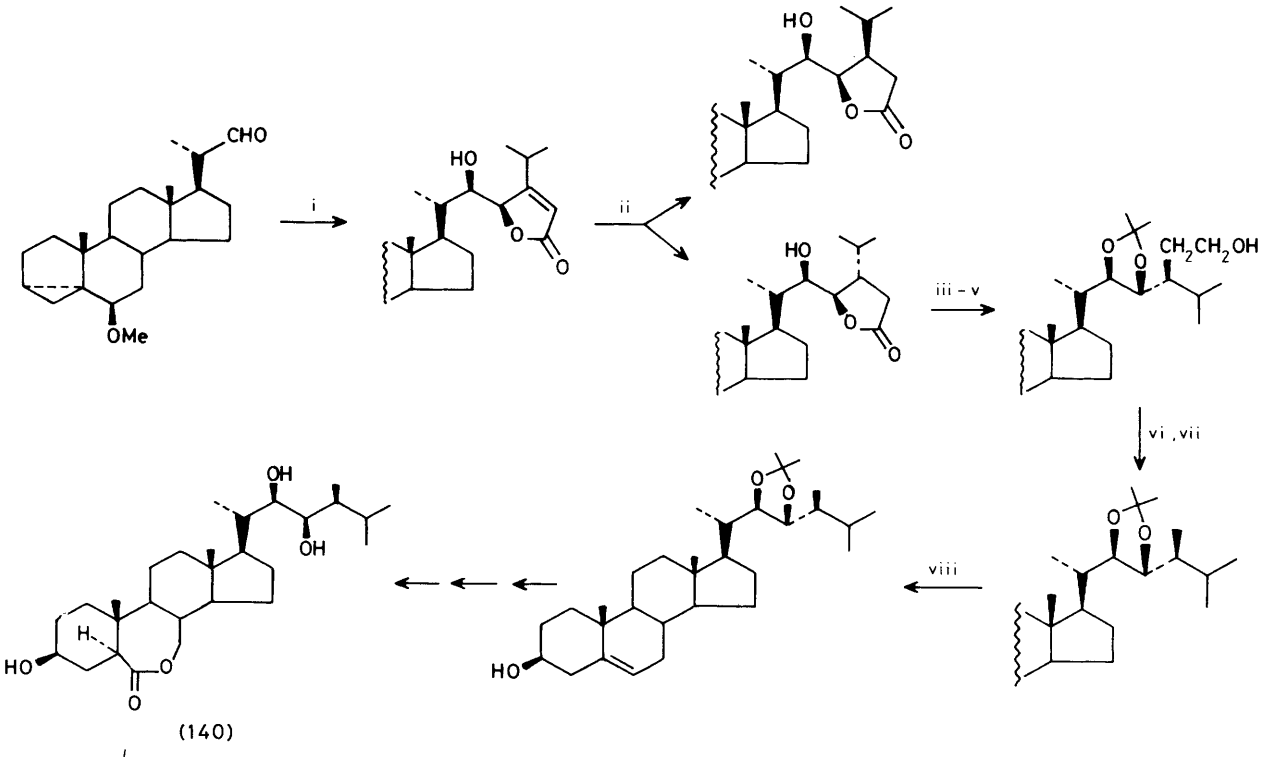


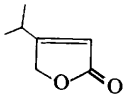
Reagents: i, $MeCH{=}N_2$; ii, $PhCO_2Ag$, MeOH; iii, MeMgI

Scheme 17

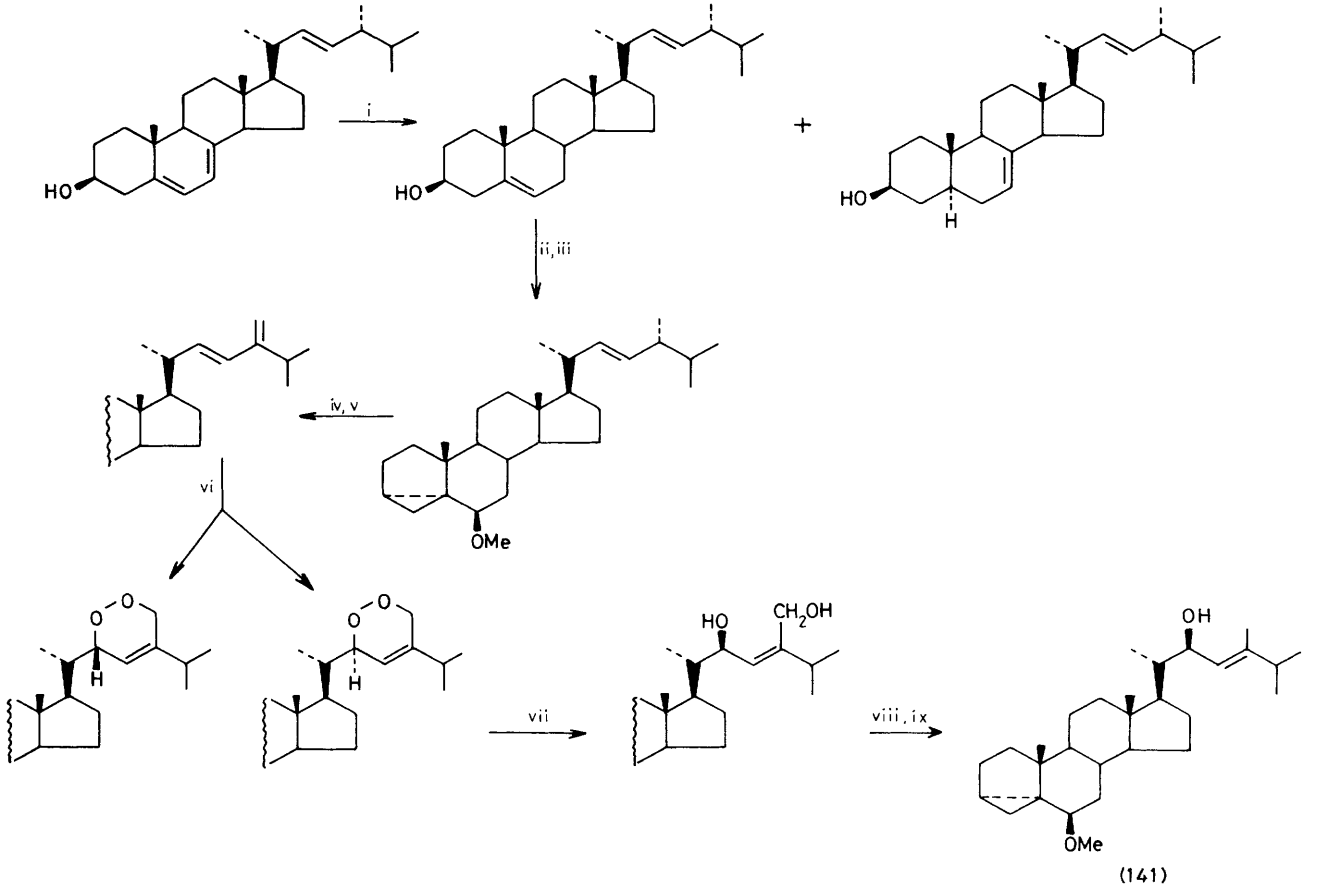
In an investigation into the chemistry of the colour reaction between furost-20-enes and Ehrlich's reagent (*p*-dimethylaminobenzaldehyde), 3β,26-dimethoxyfurosta-5,20-diene (144) was treated with the reagent, to give (after chromatography) colourless needles of the 23-(4-dimethylaminobenzylidene)-derivative (145); it has been suggested that the red colour arises from the formation, under the influence of the acid, of the quinonoid form (146).[120]

Chenodesoxycholic acid (147) has been synthesized from 3α,7α-dihydroxyandrostan-17-one by the method that is indicated in Scheme 27.[121] The isomers of 3α,7-dihydroxy-7-methyl-5β-cholan-24-oic acid and of 7-methyl-lithocholic acid



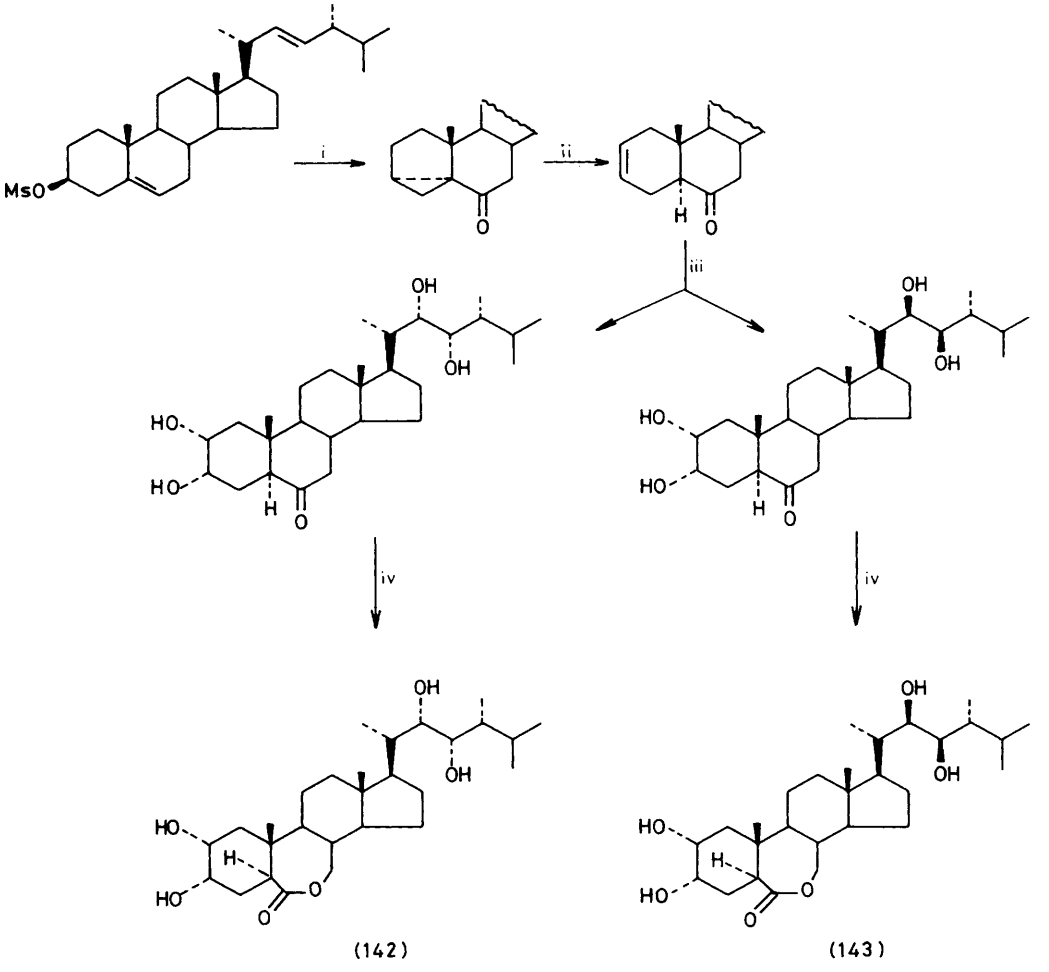
Reagents: i,  , $LiNPr^i_2$; ii, H_2, Pt; iii, $LiAlH_4$; iv, $Me_2C(OMe)_2$, pyridinium tosylate; v, MeOH; vi, pyridinium chlorochromate; vii, $(Ph_3P)_3RhCl$; viii, H^+

Scheme 18



Reagents: i, Li, $EtNH_2$; ii, TsCl; iii, MeOH, pyridine; iv, Br_2; v, $(Me_2N)_2C{=}NH$; vi, O_2, *hv*, haematoporphyrin; vii, H_2, Lindlar catalyst; viii, MsCl; ix, $LiAlH_4$

Scheme 19



Reagents: i, KOAc or NaOAc, Me_2SO; ii, TsOH, sulpholan; iii, *N*-methylmorpholine *N*-oxide, OsO_4 (catalytic); iv, CF_3CO_3H

Scheme 20

were prepared as possible gallstone-dispersing agents which would not be metabolized to the toxic lithocholic acid.[122] Very pure 3α,7α-dihydroxy-12-oxo-5β-cholan-24-oic acid has been prepared from 3,7,12-tris(dehydro)cholic acid by using 3α-hydroxysteroid dehydrogenase and 7α-hydroxysteroid dehydrogenase in the presence of NADH; it was needed as an intermediate to chenodeoxycholic acid without the generation of the toxic lithocholic acid.[123]

If methyl lithocholate acetate or methyl hyodesoxycholate diacetate reacts with elementary fluorine, they are each converted into the 14α- and 17α-fluoro-derivatives, with the former predominating; the absence of fluorination at C-9 has been attributed to the steric hindrance that is exerted by ring A. Methyl deoxycholate diacetate yields, in addition to these derivatives, the 5β-fluoro-compound, while the cholic acid derivative gives only the 17α-fluoro-compound, and methyl 3α-acetoxy-12-oxo-5β-cholan-24-oate yields only the 5β-fluoro-compound.[124]

Methods have been published for the deuteriation of bile acids in ring A or ring B[125] and in rings A, B, and C or in rings A and B and the side-chain, or in ring C and the side-chain.[126] By using the synthesis that is illustrated in Scheme 28, it is possible to label the side-chain of a bile acid with ^{13}C at positions 23 and 24, or with deuterium at C-22 and C-23.[127,128] Various bile acids have been labelled with ^{18}O in the 3α-hydroxy-group by oxidizing the 3-hydroxy-group to a ketone (by silver carbonate on Celite), converting it into an ethylene ketal, and regenerating the carbonyl group with acid in dioxan that contains $H_2{}^{18}O$; finally, the ketone group is reduced with sodium borohydride. Under the best conditions, an enrichment of 16—20% results.[129]

2.2 Vitamins D, their Derivatives, and their Metabolites

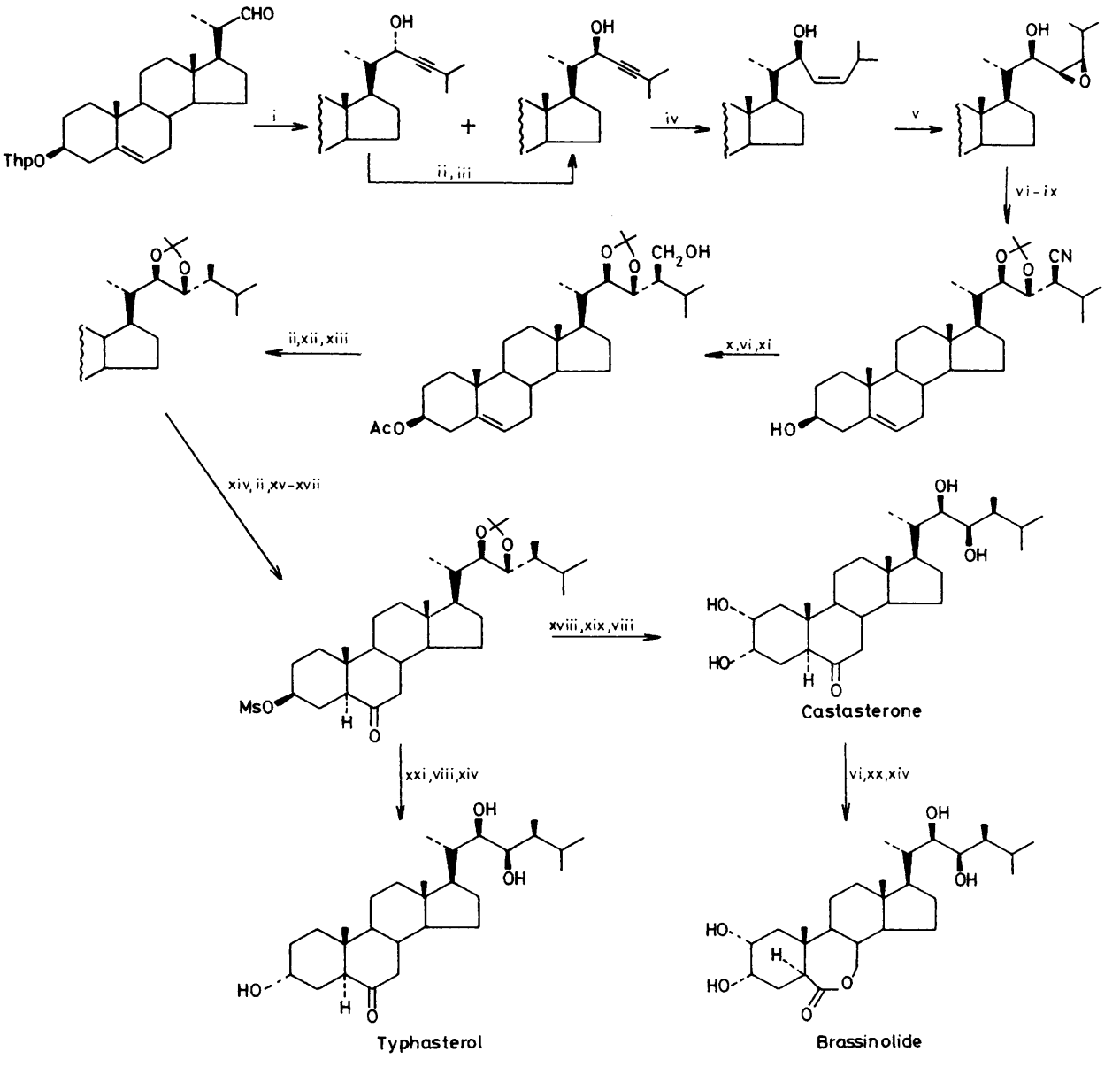
A review has appeared on commercial applications of laser chemistry, including the selective-wavelength synthesis of the vitamins D.[130] Approaches to the synthesis of seco-steroids that are related to vitamins D have also been reviewed.[131]

Calciol* (vitamin D) has been synthesized from Grundemann's ketone (148) as shown in Scheme 29; the correct (+)-isomer of 1-hydroxymethyl-2-methylenebicyclo[3.1.0]hexane (149) is obtained from the racemic material by esterification with (+)-(*S*)-*O*-methylmandelic acid and separation of the diastereoisomers by preparative-scale h.p.l.c. Condensation of the corresponding aldehyde with the bromomethylene-compound (150), followed by rearrangement (catalysed by toluene-*p*-sulphonic acid), gives calciol (151) and its (5*E*)-isomer (12).[132]

A simple and stereoselective synthesis of ercalcidiol (25-hydroxyergocalciferol) (153) is shown in Scheme 30.[133] Ercalcidiol (154) and its 24-epimer (155) have been synthesized by the method shown in Scheme 31; the two compounds were obtained in similar amount and were separated by h.p.l.c.[134]

The (24*R*)-epimer (156) and the (24*S*)-epimer (157) of (22*E*)-1α,24-dihydroxy-22,23-didehydrocalciol have been synthe-

* The nomenclature for the vitamins D and their analogues is based on the IUPAC—IUB recommendations (*Eur. J. Biochem.*, 1982, **124**, 223).



(Thp = tetrahydropyran-2-yl)

Reagents: i, $Pr^iC{\equiv}CLi$; ii, MsCl; iii, KO_2, 18-crown-6; iv, H_2, Lindlar catalyst; v, Bu^tO_2H, $V(O)[MeC(O)CHC(O)Me]_2$; vi, Ac_2O, pyridine; vii, HCN, $AlEt_3$; viii, H^+; ix, Me_2CO; x, Pr^i_2AlH; xi, $NaBH_4$; xii, NaI; xiii, Bu_3SnH; xiv, OH^-; xv, BH_3; xvi, H_2O_2; xvii, pyridinium chlorochromate; xviii, LiBr, dimethylformamide; xix, *N*-methylmorpholine *N*-oxide, OsO_4; xx, CF_3CO_3H; xxi, Li_2CO_3, dimethylformamide

Scheme 21

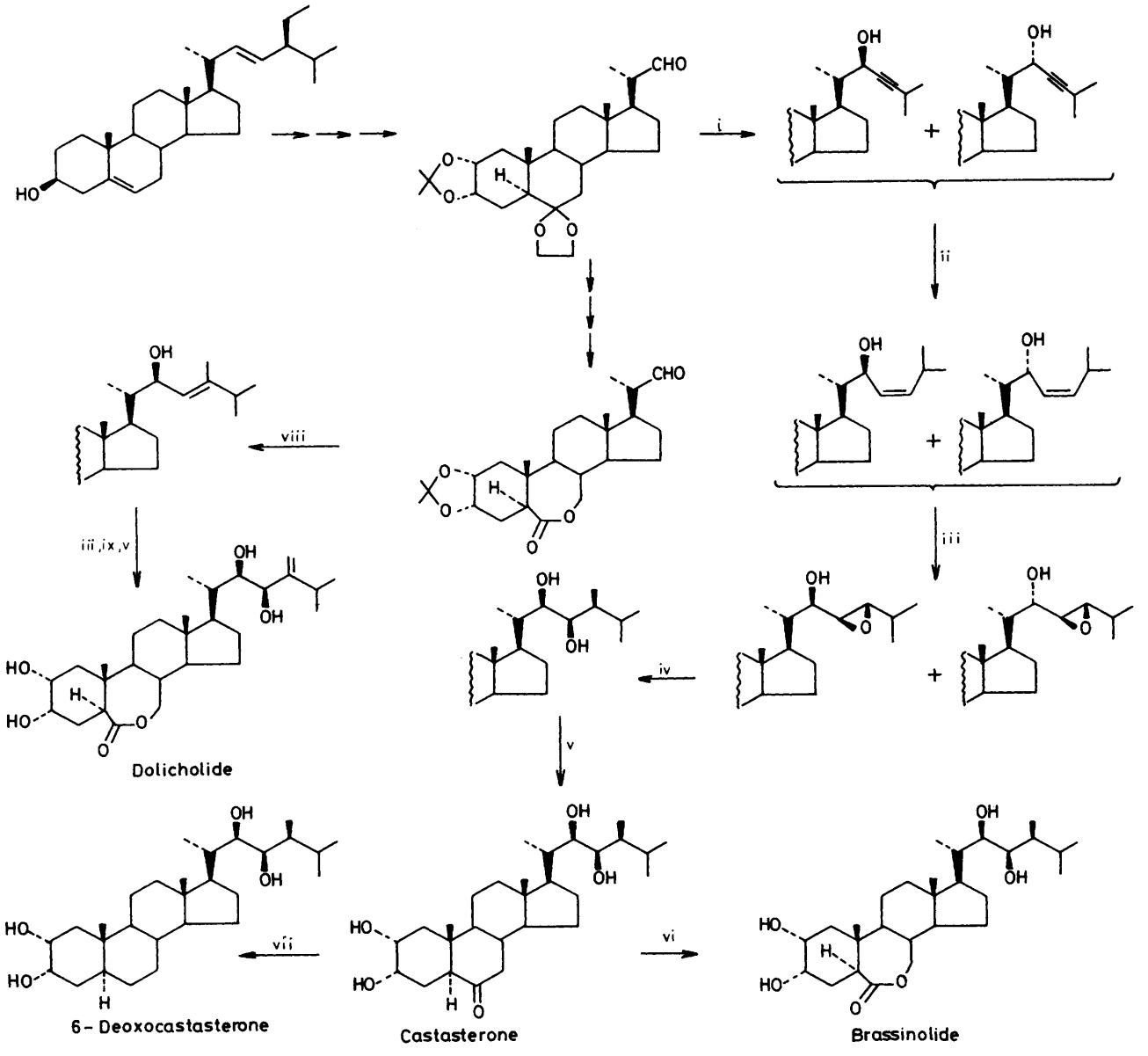
sized; the (24*R*)-compound has less activity than its epimer, but neither equals that of 1α,25-dihydroxycalciol.[135]

Irradiation of 26,26-dideuterio-25-hydroxy-7,8-didehydrocholesterol with light of wavelength 254 nm for 70 seconds gives a mixture of 2.8% of starting material, 72% of 26,26-dideuteriotacalcidiol (26,26-dideuterio-25-hydroxytachysterol$_3$), and 25.2% of (6*Z*)-26,26-dideuteriotacalcidiol (26,26-dideuterio-25-hydroxyprevitamin D_3). Further irradiation (at 337 nm) with light from a nitrogen laser for 110 seconds changes the proportions of these compounds to 4.5%, 7.6%, and 83%, respectively, and also leads to the formation of 26,26-dideuterio-25-hydroxylumisterol$_3$; if this mixture is heated in benzene at 60 °C it gives 26,26-dideuteriocalcidiol in 60% yield.[136]

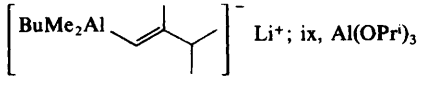
(24*R*)-24,25-Dihydroxyergosterol and its 24-epimer have been synthesized, separated, and converted into 24-hydroxyercalcidiol (24,25-dihydroxyergocalciferol) (158) and its 24-epimer (159).[137] (25*R*)-26-Hydroxy-23-oxocalcidiol (160) has been synthesized and then converted by a kidney homogenate from vitamin-D-deficient chicks into the 1α-hydroxy-derivative (161); this compound differed from the major metabolite of calcitriol (1α,25-dihydroxycholecalciferol) to which this structure has been assigned.[138]

A synthesis of (1*S*,6*Z*)-1-hydroxytacalciol (1α-hydroxyprevitamin D_3) (164) uses (6*Z*)-tacalciol (previtamin D_3) (162) as starting material; the 6,8-diene system is protected by a Diels–Alder reaction with 1-phenyl-1,3,4-triazoline-2,5-dione, and the product is converted (by successive oxidation and reduction) into compound (163). Removal of the diene-protecting group with alkali in the presence of oxygen gives the desired product (164).[139]

Calciol is oxidized by *m*-chloroperoxybenzoic acid to the



Reagents: i, $LiC{\equiv}CPr^i$; ii, H_2, Ni; iii, *m*-$ClC_6H_4CO_3H$; iv, Me_3Al, BuLi; v, AcOH; vi, CF_3CO_3H; vii, N_2H_4, OH^-; viii,



; ix, $Al(OPr^i)_3$

Scheme 22

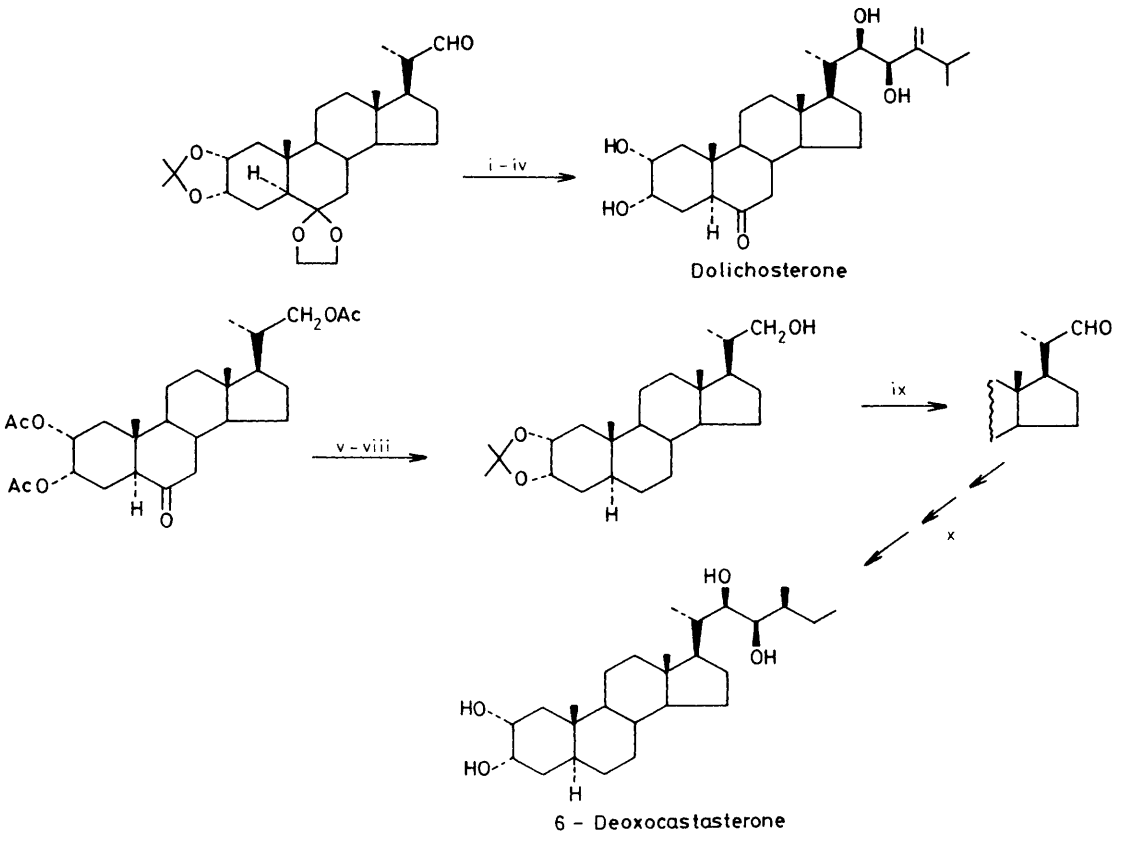
(7*R*)-7,8-epoxide (165), for which the structure was ascertained by *X*-ray analysis; this corrects a structure that had previously been assigned to the product.[140,141] Epoxidation with t-butyl hydroperoxide, catalysed by $V(O)[MeC(O)CHC(O)Me]_2$, gives only the (5*S*)-5,6-epoxide (166).[141]

7,8-Didehydro-11α-hydroxycholesterol (168) has been synthesized as shown in Scheme 32; note the abnormal ring-opening product of compound (167). Compound (168) was converted into 11α-hydroxycalciol (169) in the usual way.[142]

(1*S*)-1-Fluorocalcidiol (170) has been prepared; part of the synthesis is shown in Scheme 33. The object was to block (1*S*)-hydroxylation, so that the activity that is conferred by 24- and 25-hydroxy-groups could be examined independently of the activity that arises from the (1*S*)-hydroxy-group. Although the fluoro-compound was strongly bound by the chick intestinal receptor for (1*S*)-1-hydroxycalcidiol, it did not stimulate intestinal transport of calcium or the mobilization of calcium in bone.[143] (1*S*)-1-Fluorocalciol has been prepared by a similar method, leaving no doubt as to the configuration at position 1; it proved to be different from a compound that was known to be a 1-fluoro-calciol but for which the configuration at C-1 was uncertain.[144] 23,23-Difluorocalcidiol (171) has been prepared in order to test the significance of 23-hydroxylation of calciol.[145]

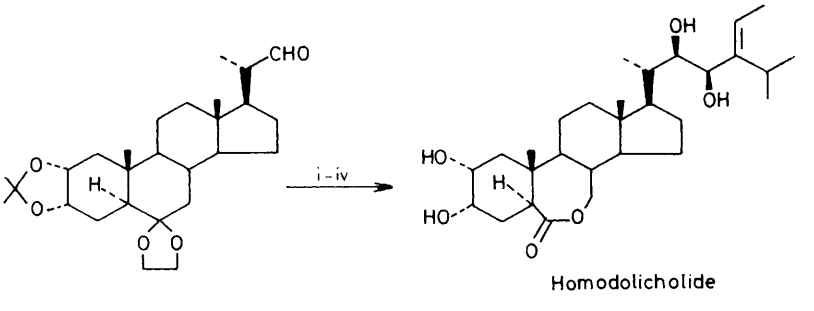
Analogues of calciol (*a*) with a spirostan side-chain, (*b*) with a nitrogen atom replacing C-20, and (*c*) with an NH group replacing C-22 have been prepared by conventional methods.[146]

The analogue (172) of previtamin D_3 and its 1-epimer have been synthesized; they did not yield more than a few per cent of



Reagents: i, $\left[BuMe_2Al\right]^-$ Li^+; ii, *m*-$ClC_6H_4CO_3H$; iii, $Al(OPr^i)_3$; iv, H^+; v, $(CH_2SH)_2$, BF_3; vi, Raney nickel; vii, OH^-; viii, $Me_2C(OMe)_2$; ix, pyridinium chlorochromate; x, see Scheme 22, reagents i—iv

Scheme 23



Reagents: i, $\left[BuMe_2Al\right]^-$ Li^+; ii, *m*-$ClC_6H_4CO_3H$; iii, $Al(OPr^i)_3$; iv, H^+

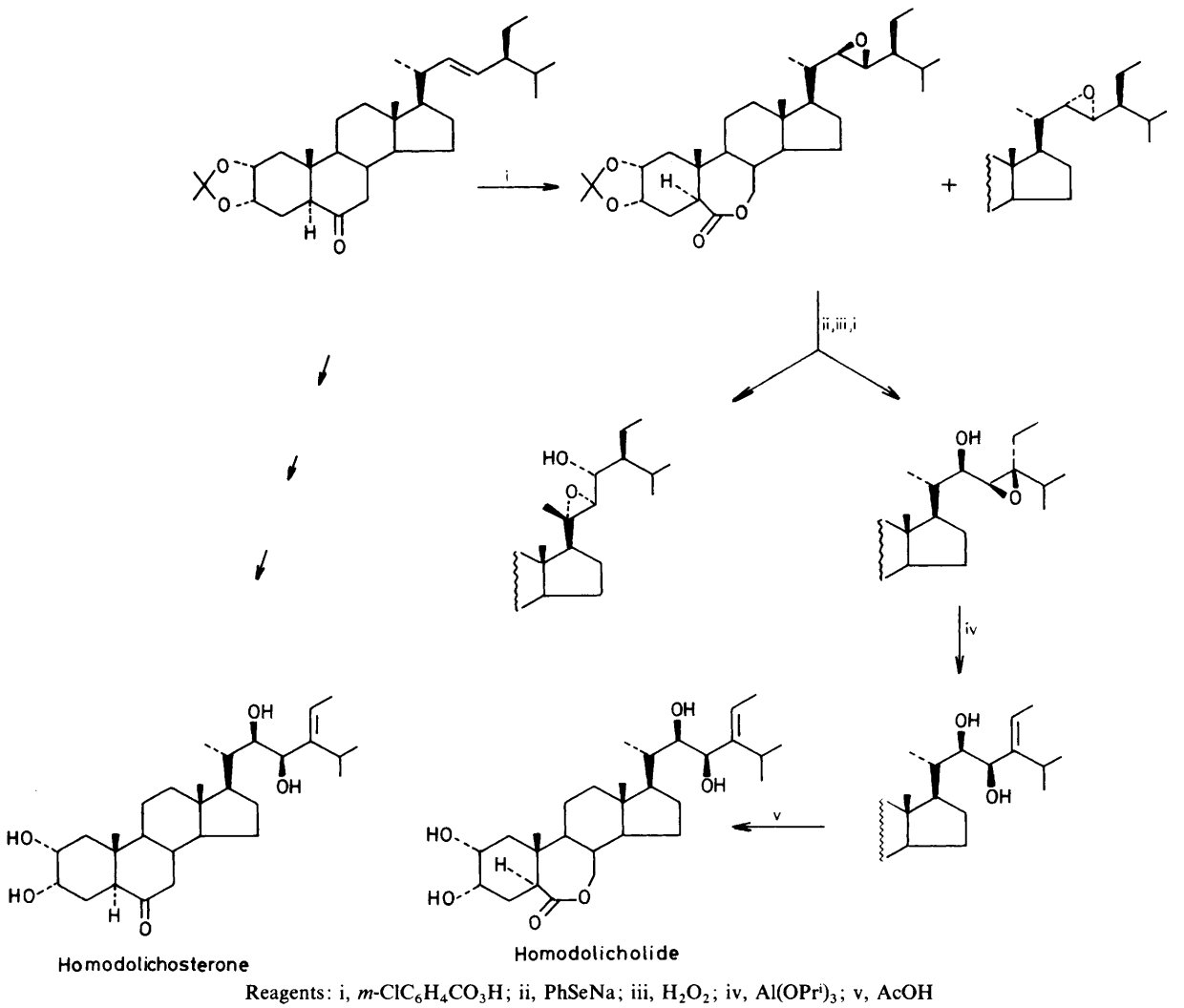
Scheme 24

the vitamin D analogue when they were allowed to equilibrate and did not elicit intestinal absorption of calcium or the mobilization of calcium in bone.[147]

For the synthesis of (24*R*)-24-hydroxy-[26,26,26,27,27,27-$^3H_6$]calcidiol, methyl 3β-hydroxychol-5-en-24-oate (173) was converted (as shown in Scheme 34) into the calciol analogue (174), which was treated with [$^3H_3$]methylmagnesium bromide to give the 24-isomers [(175) and (176)] of 24,25-dihydroxy-[26,26,26,27,27,27-$^3H_6$]calciol. These were separated [as their tris(trimethylsilyl)-derivatives] by preparative h.p.l.c. and finally desilylated.[148]

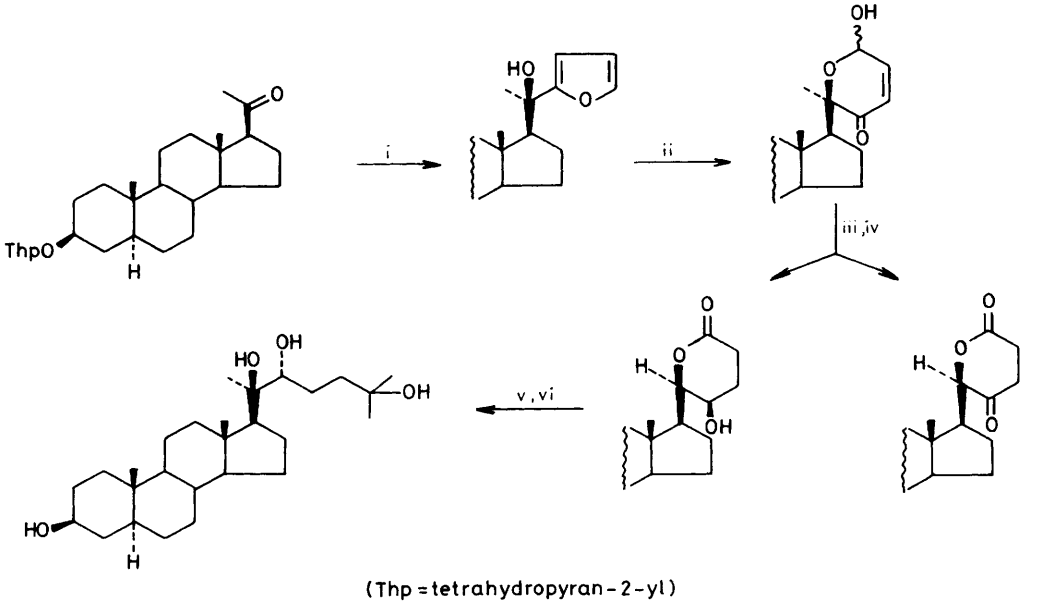
2.3 Pregnanes

17α-Ethynyl-17β-methanesulphonyloxy-3-methoxyoestra-1,3,5(10)-triene reacts with lithium copper halides ($LiCuX_2$) to form the vinylacetylene (177) and the halogeno-allene (178). The configuration of the bromo-compound was established by



Reagents: i, *m*-$ClC_6H_4CO_3H$; ii, PhSeNa; iii, H_2O_2; iv, $Al(OPr^i)_3$; v, AcOH

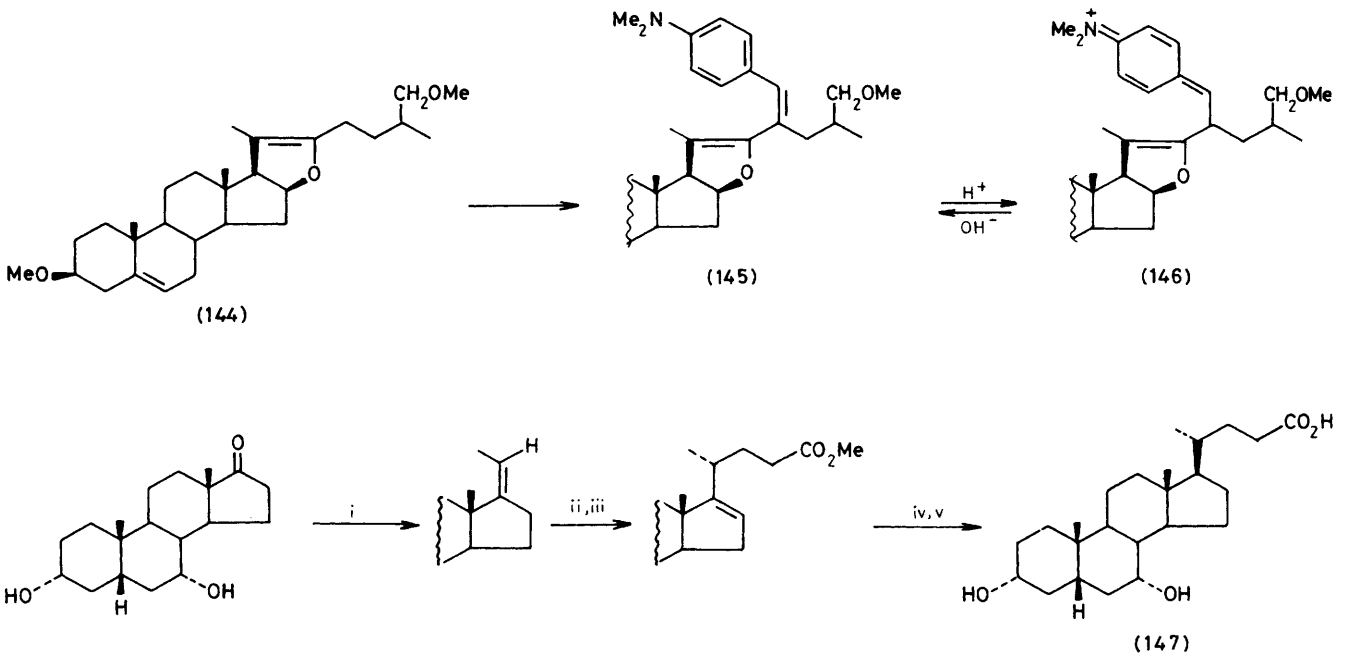
Scheme 25



(Thp = tetrahydropyran-2-yl)

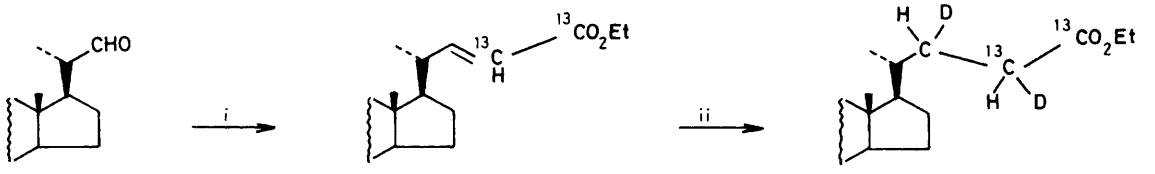
Reagents: i, 2-Furyl-lithium; ii, *m*-$ClC_6H_4CO_3H$; iii, pyridinium chlorochromate; iv, H_2, Pt; v, pyridinium tosylate; vi, MeMgBr

Scheme 26



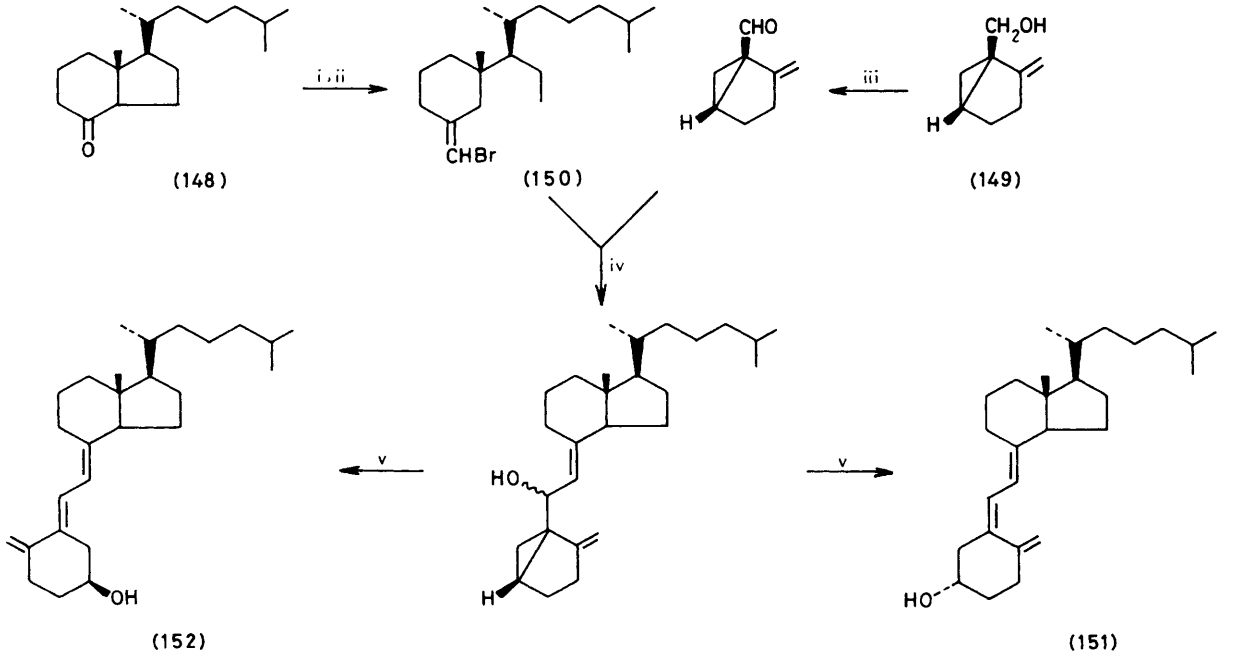
Reagents: i, $Ph_3P{=}CHMe$; ii, Ac_2O, pyridine; iii, $H_2C{=}CHCO_2Me$, $EtAlCl_2$; iv, H_2, Pd; v, OH^-

Scheme 27



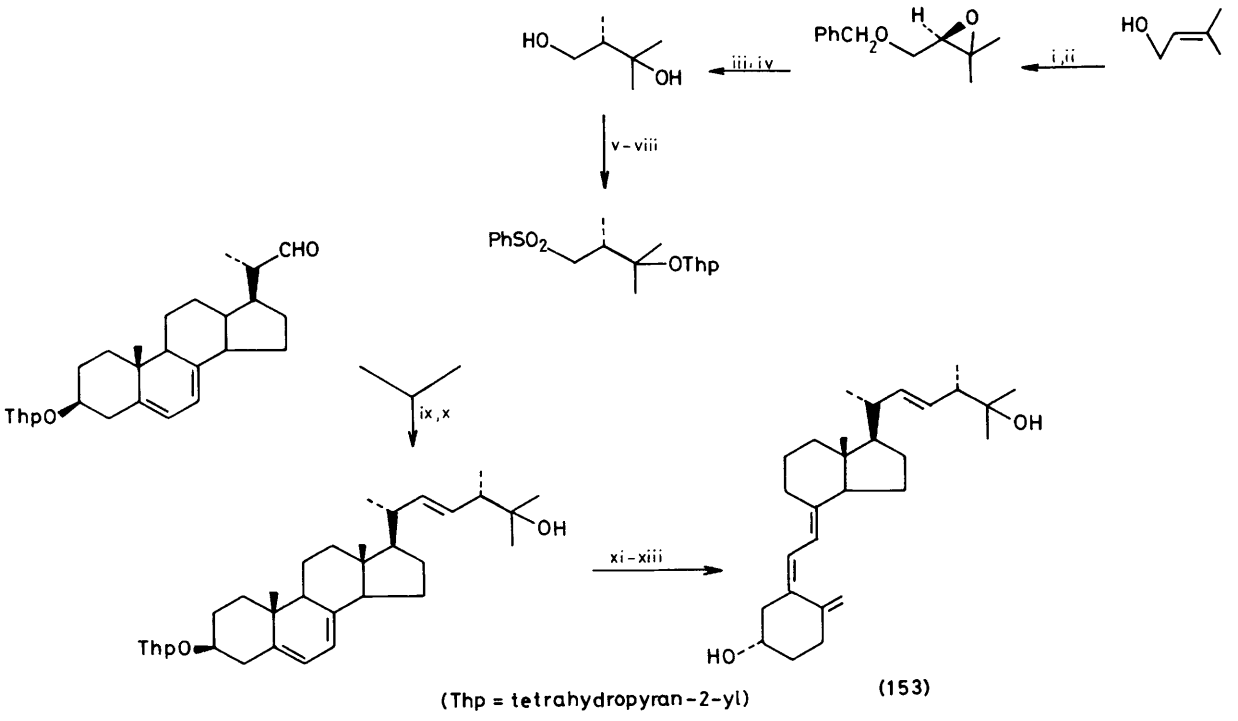
Reagents: i, $Ph_3P{=}{}^{13}CH^{13}CO_2Et$; ii, D_2, Pt

Scheme 28



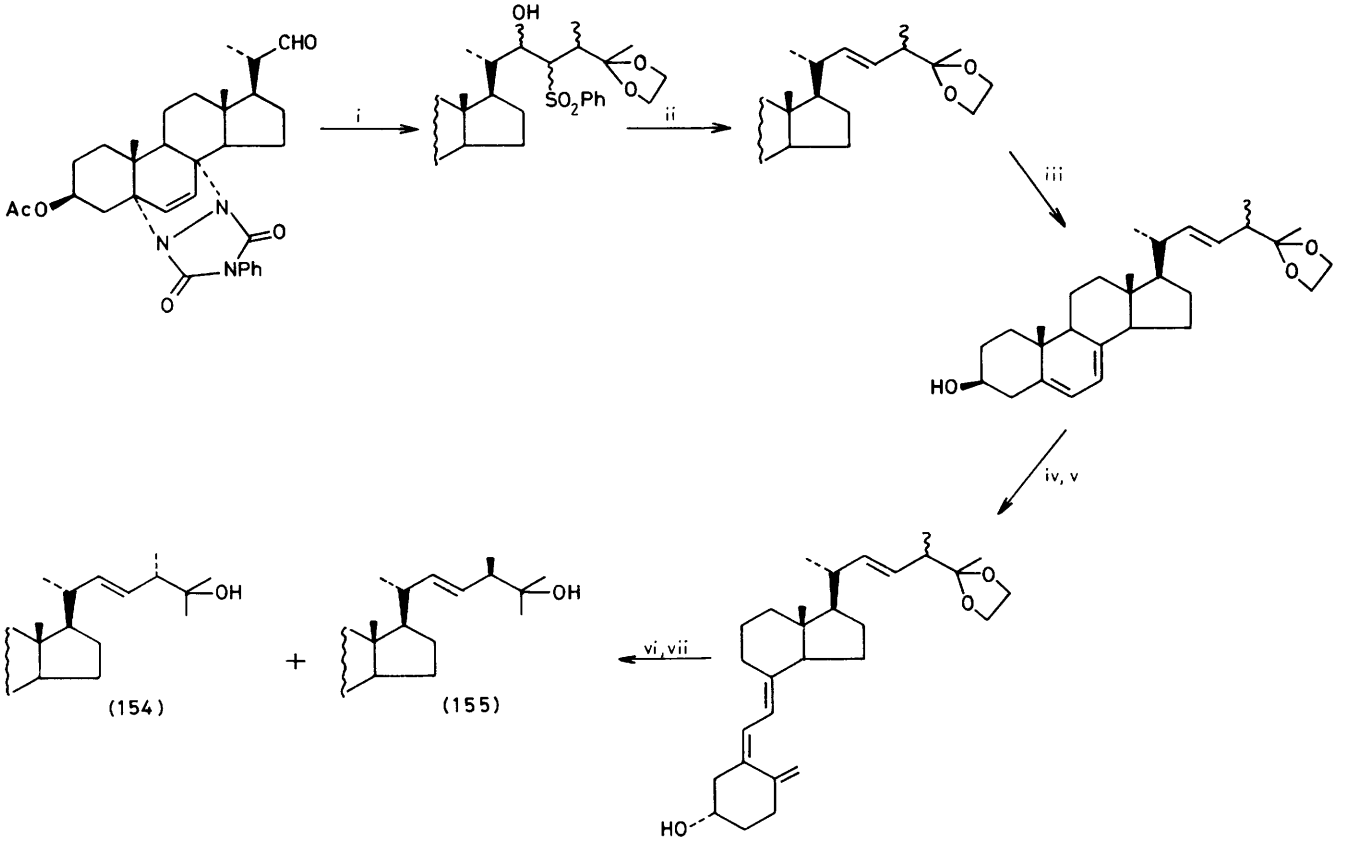
Reagents: i, CH_2Br_2, $(C_6H_{11})_2NLi$; ii, Zn, AcOH; iii, pyridinium chlorochromate; iv, $LiBu^t$; v, TsOH

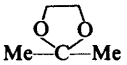
Scheme 29



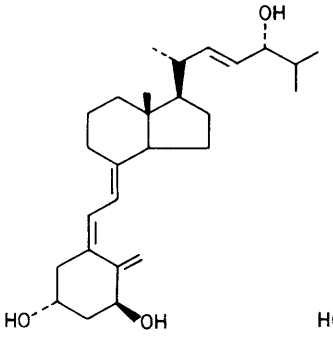
Reagents: i, Bu^tO_2H, $Ti(OPr^i)_4$, (−)-dibutyl D-tartrate; ii, $PhCH_2Cl$; iii, $LiCuMe_2$; iv, H_2, Pd; v, TsCl; vi, PhSH; vii, H_2O_2, Na_2WO_4; viii, dihydropyran; ix, Pr^i_2NLi; x, sodium amalgam; xi, H^+; xii, *hν*; xiii, heat

Scheme 30

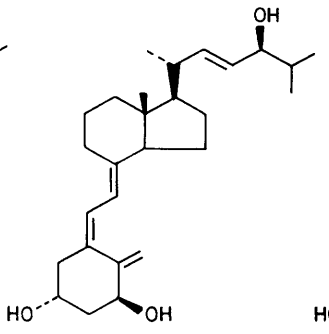


Reagents: i, $PhSO_2CH_2CH$  , EtMgBr; ii, sodium amalgam; iii, $LiAlH_4$; iv, *hν*; v, heat; vi, TsOH; vii, MeMgI

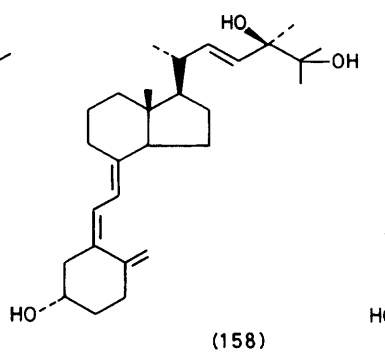
Scheme 31



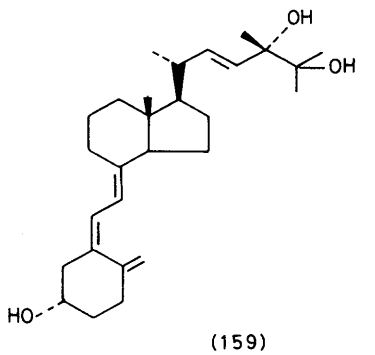
(156)



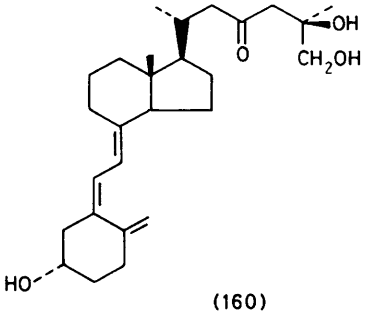
(157)



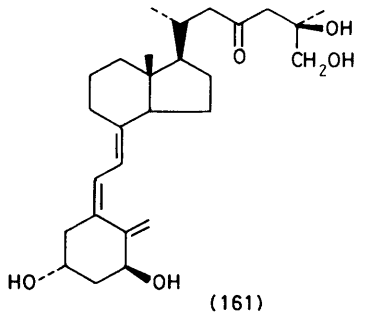
(158)



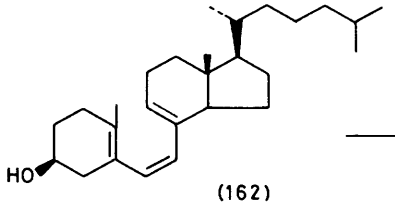
(159)



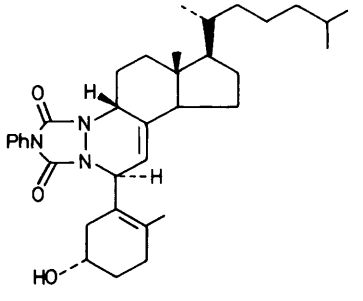
(160)

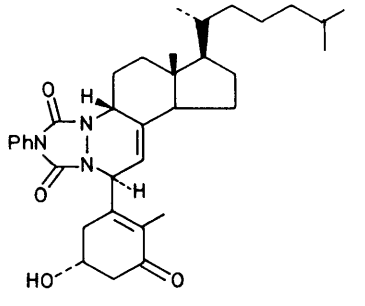


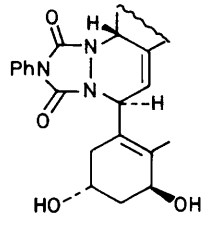
(161)



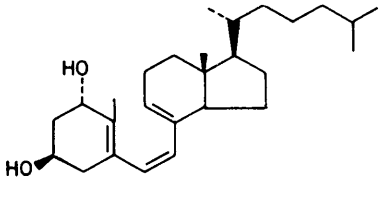
(162)



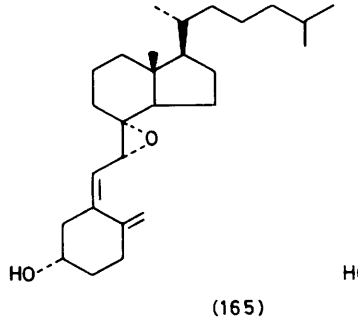




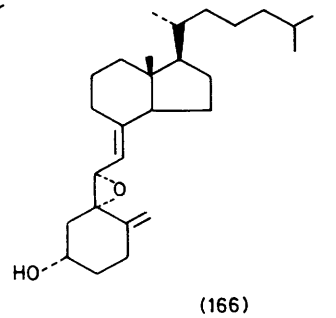
(163)



(164)



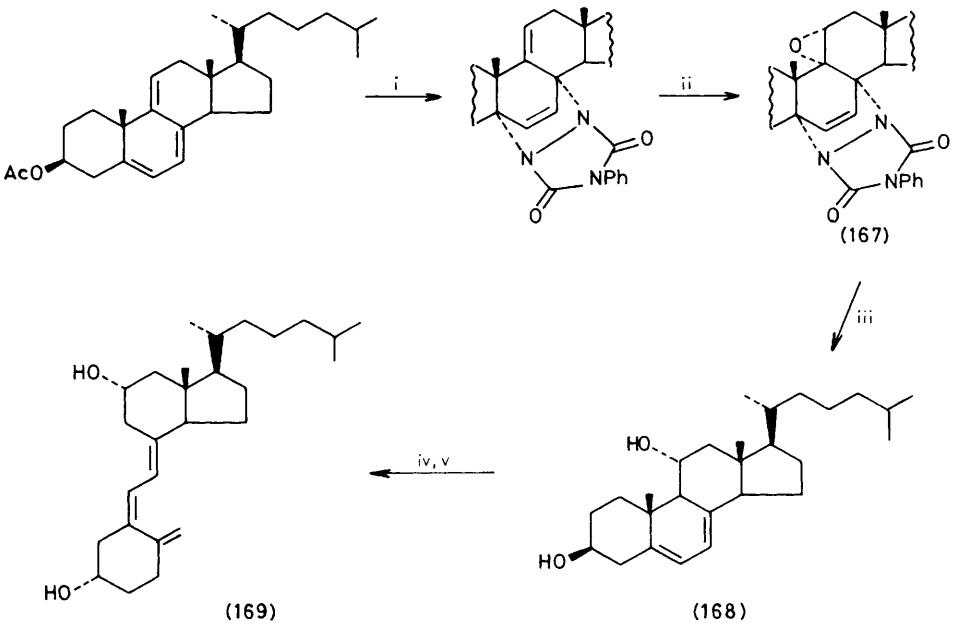
(165)

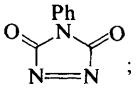


(166)

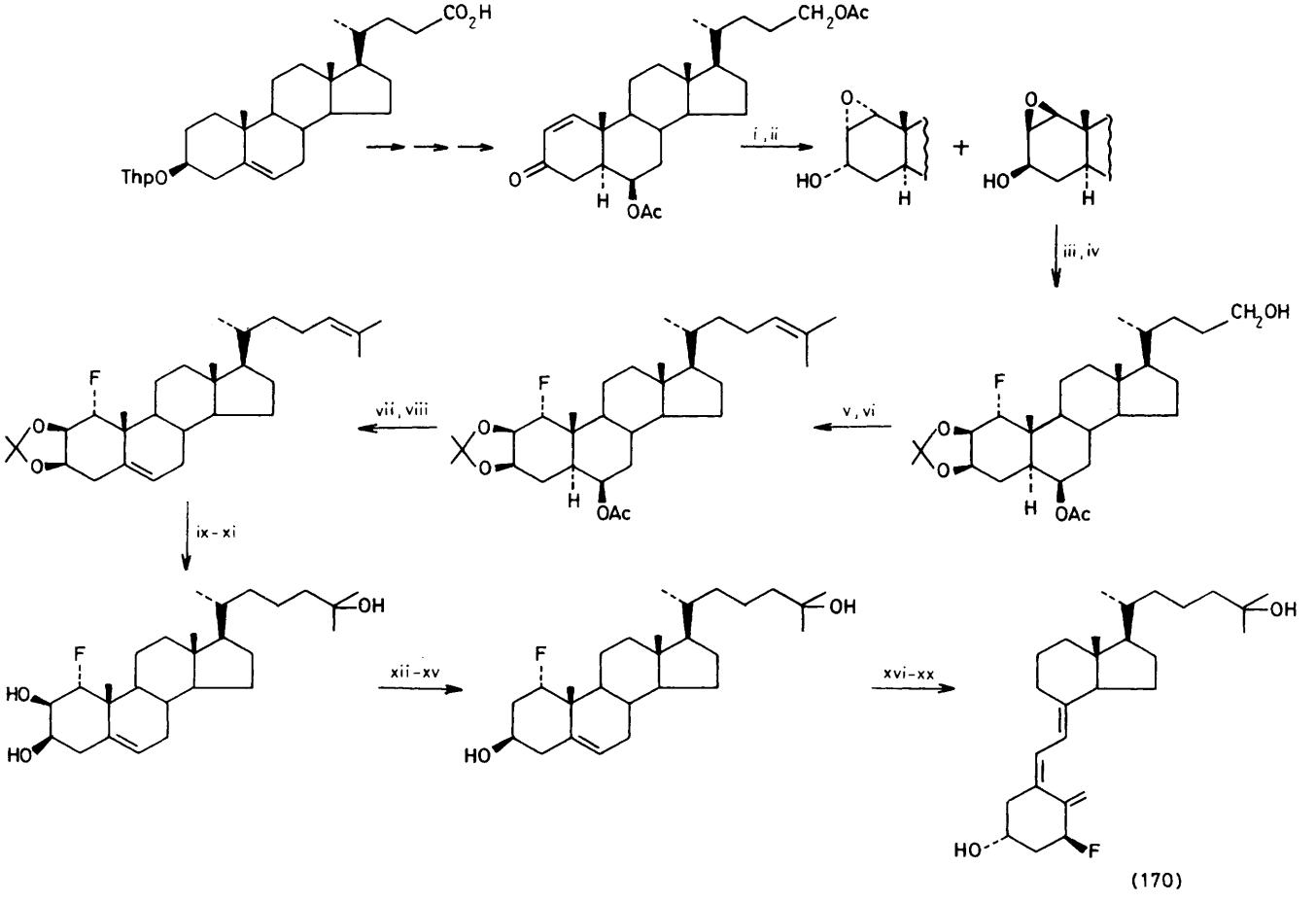
X-ray analysis. The 21-isomers were prepared from the isomeric ethynylcarbinol; this could not be mesylated, even in the presence of n-butyl-lithium, but it was methanesulphinylated in the presence of triethylamine, and the methanesulphinate (complexed with boron trifluoride) was allowed to react with lithium copper halides to give the halogeno-allenes, of opposite configuration to those described earlier.[149]

Silylation of the cyanohydrin from dehydroepiandrosterone acetate, followed by drastic treatment with methylmagnesium bromide (at 60 °C for 10 hours, in anisole) and subsequent deprotection, gave 17α-hydroxypregnenolone.[150] A novel method for the conversion of 17-ketones into 21-hydroxy-20-



Reagents: i,  ; ii, *m*-$ClC_6H_4CO_3H$; iii, $LiAlH_4$; iv, *hν*; v, heat

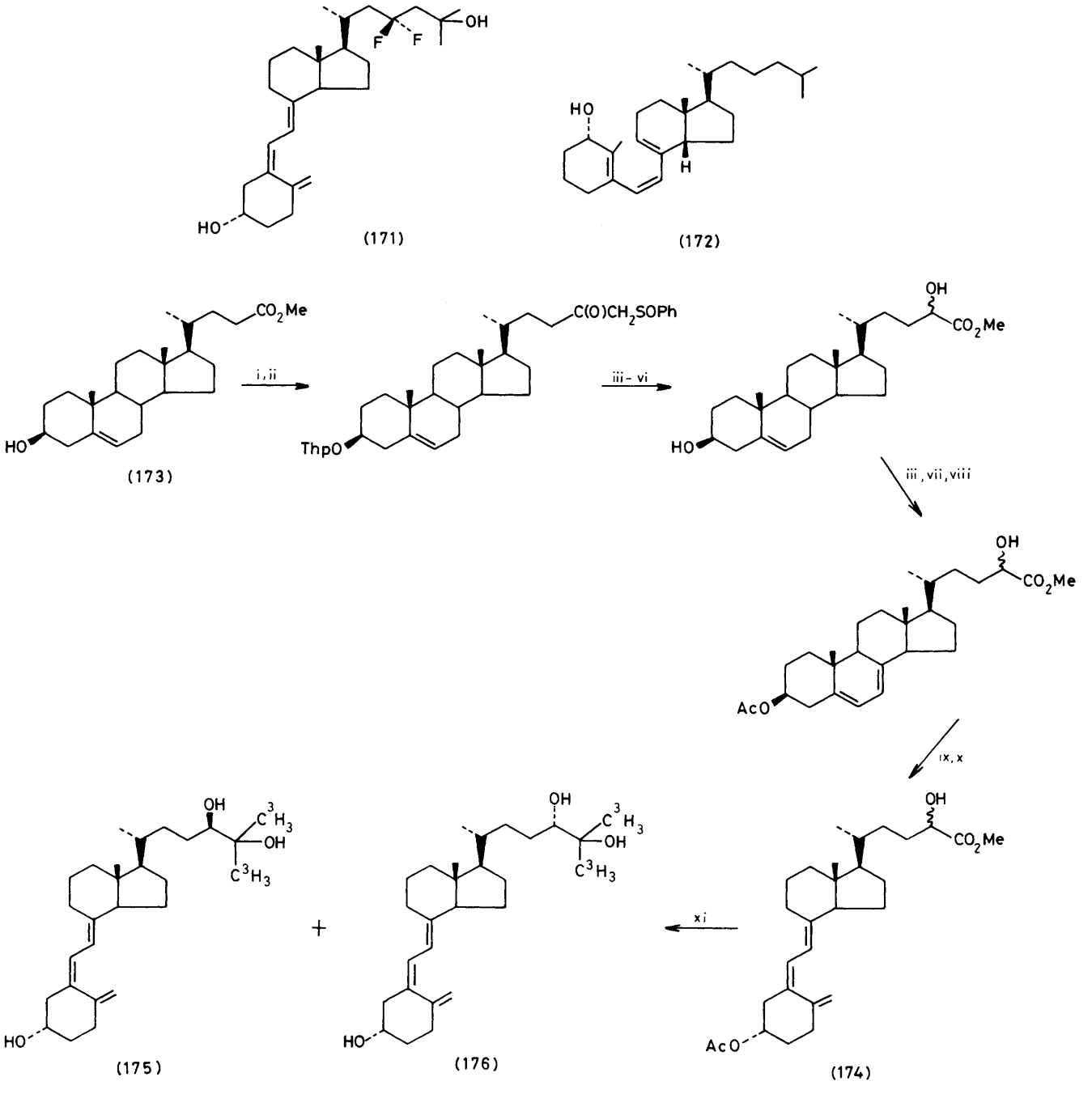
Scheme 32



(Thp = tetrahydropyran-2-yl)

Reagents: i, $CeCl_3$, $NaBH_4$; ii, *m*-$ClC_6H_4CO_3H$; iii, KHF_2, $HOCH_2CH_2OH$; iv, Me_2CO, TsOH; v, $(COCl)_2$, Me_2SO; vi, $Me_2C{=}PPh_3$; vii, KOH; viii, $POCl_3$, pyridine; ix, $Hg(OAc)_2$; x, $NaBH_4$; xi, TsOH; xii, Bu^tMe_2SiCl, imidazole; xiii, NaH, CS_2, MeI; xiv, Bu_3SnH; xv, Bu_4NF; xvi, Ac_2O, pyridine; xvii, *N*-bromosuccinimide; xviii, *hν*; xix, heat; xx, KOH

Scheme 33

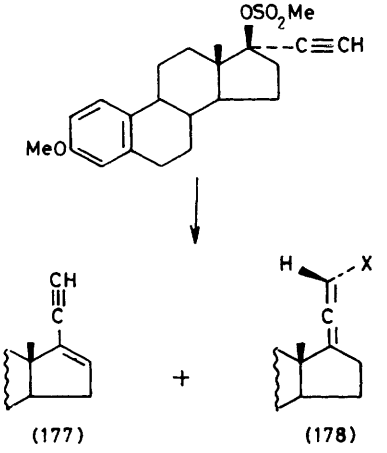


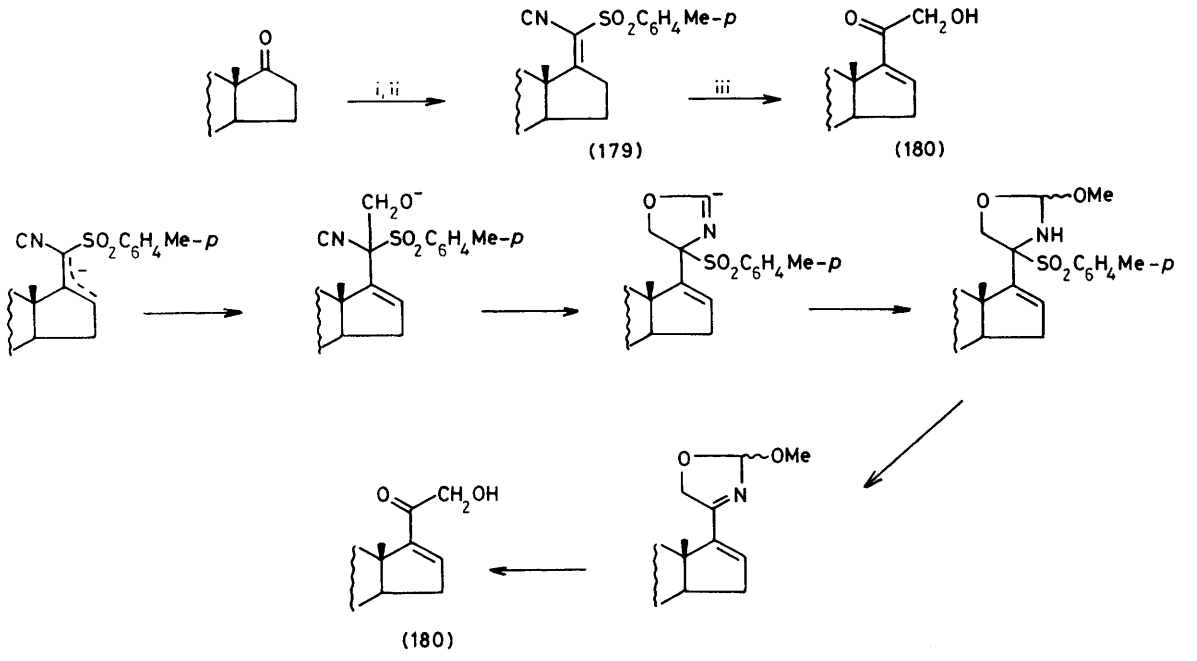
Reagents: i, Dihydropyran; ii, PhSOMe, $LiNPr^i_2$; iii, Ac_2O, pyridine; iv, OH^-; v, CH_2N_2; vi, H^+; vii, dibromodimethylhydantoin; viii, 2,4,6-collidine; ix, *hν*; x, heat; xi, C^3H_3MgBr

Scheme 34

oxo-pregnanes is shown in Scheme 35. It involves their treatment with toluene-*p*-sulphonylmethyl isocyanide in the presence of potassium t-butoxide, then with phosphorus oxychloride; the product is the olefin (179), which, if it is allowed to react first with formaldehyde and sodium hydroxide (in the presence of a phase-transfer catalyst) and then with sulphuric acid, yields the 21-hydroxy-16-en-20-one (180). In the course of these reactions, 4-en-3-ones can be protected as their enol ethers, but 1,4-dien-3-ones, 11-ketones, and 11β-hydroxy-groups require no protection. The second stage of the reaction is thought to proceed *via* the intermediates that are shown in Scheme 35.[151] Another route to 21-hydroxy- and 17α,21-dihydroxy-20-ketones is shown in Scheme 36.[152]

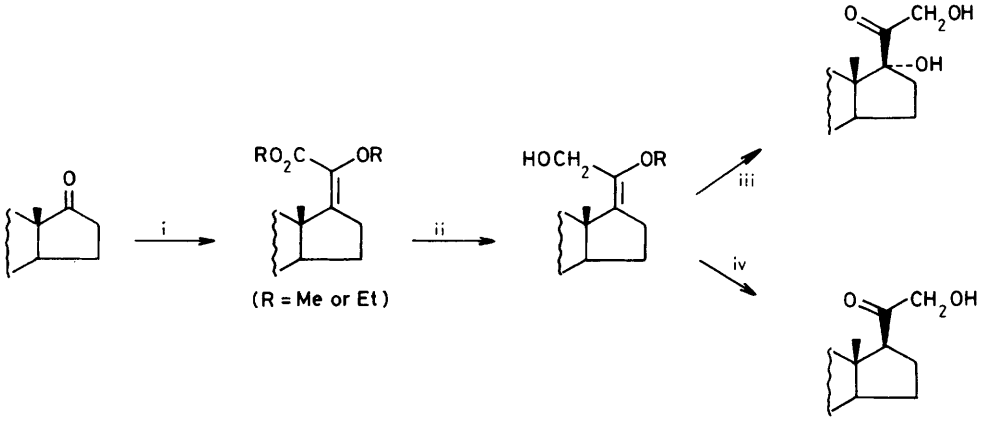
The side-chain of a bile acid can be degraded to acetyl by reaction with *NN*-carbonyldi-imidazole [to give the imidazolide (181)] and then photolysis [to yield the 20,22-olefin (182)]; ozonolysis, followed by treatment with zinc, produces the





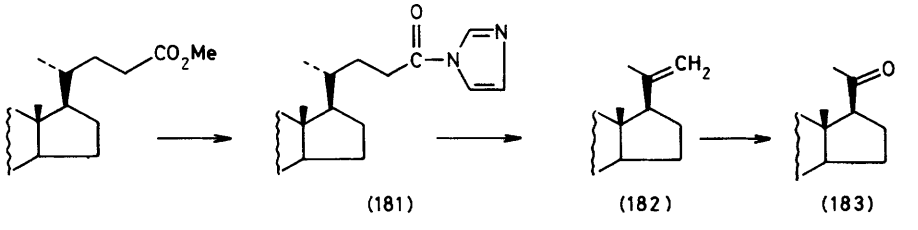
Reagents: i, $TsCH_2NC$; ii, $POCl_3$; iii, HCHO

Scheme 35



Reagents: i, $ROCCl_2CO_2R$, Zn, Et_2AlCl; ii, Bu^i_2AlH; iii, *m*-$ClC_6H_4CO_3H$; iv, H^+

Scheme 36

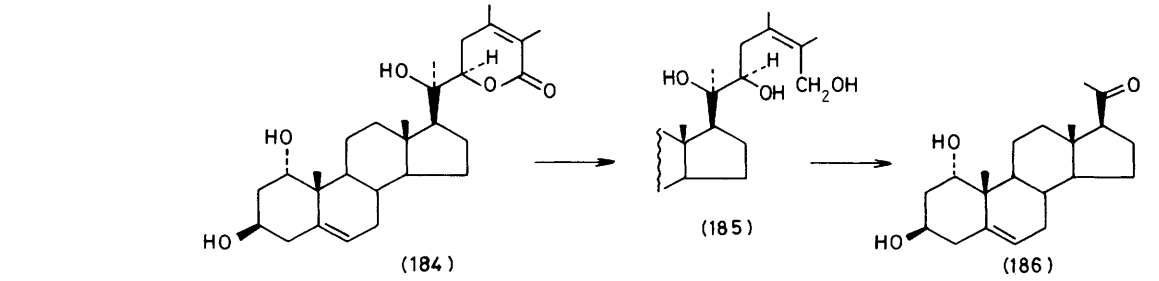


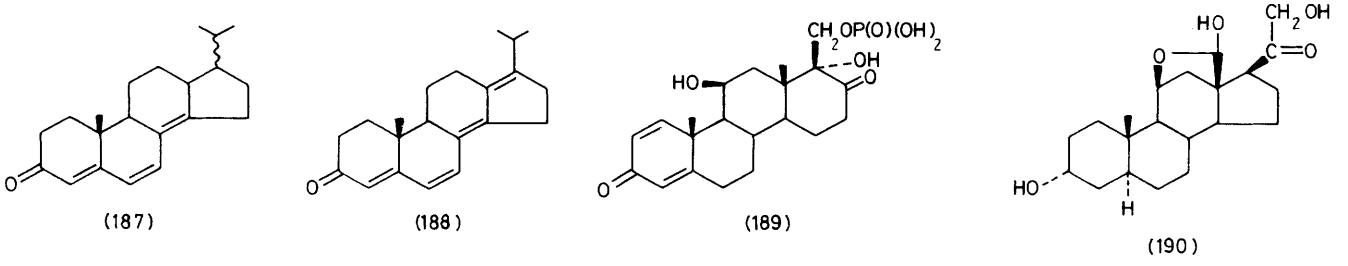
pregnanone (183).[153] Yet another route from bile acids to pregnan-20-enes, *via* Δ^{22} olefins and 22-aldehydes, has been described by R. Mickova.[154]

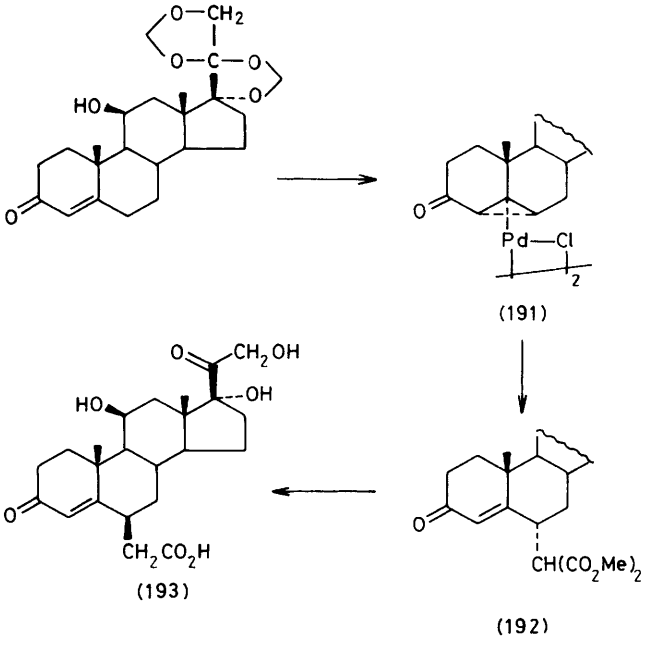
1α,3β-Dihydroxypregn-5-en-20-one (186) has been obtained from (20*R*,22*R*)-1α,3β,20-trihydroxywitha-5,24-dienolide (184) by treatment with lithium aluminium hydride (in order to open the lactone ring) followed by oxidation of the product (185) with metaperiodic acid.[155]

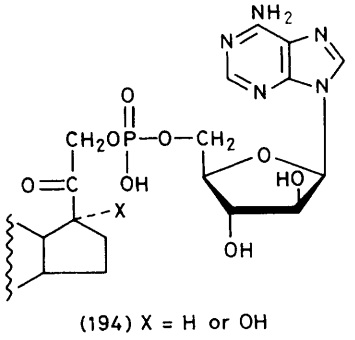
In a spectroscopic and chemical study of the colour reaction of progesterone in sulphuric acid, the tetraene (188) and the triene (187) were isolated.[156] A synthesis of B-norprogesterone from dehydroepiandrosterone has been described.[157] Anaerobic decomposition of prednisolone phosphate in aqueous phosphate or borax at 120 °C gave the D-homo-compound (189).[158]

17-Monoesters of 17α,21-dihydroxy-20-ones have been prepared from a 17,21-orthoester by the action of aluminium silicate in aqueous methanol; migration of the acyl group to the 21-position was largely avoided.[159] During a study of the reduction of a 17α,21-dihydroxy-20-ketone by sodium boro-









(194) X = H or OH

hydride in a two-phase system, in the presence of calcium chloride, it was found that the proportion of the 20α-alcohol increased as the concentration of calcium chloride was increased to 0.7 grams per cubic centimetre of water, and that as the temperature was reduced to −27 °C the proportion of 20α-isomer was as high as 92% in the case of prednisolone, although it was somewhat less in the case of the 11-deoxy-derivative. The method of reduction is much less satisfactory if the steroid does not contain a 17α-hydroxy-group. The effect of the calcium chloride is to complex the side-chain in an orientation that is favourable to attack by the reagent from the β-side.[160] A 17α,21-dihydroxy-20-ketone was found to be reduced by trimethylsilyl iodide in acetonitrile to the 17-deoxy-compound, with the 17,21-dideoxy compound as a very minor product; the yield of the latter compound was greater if chloroform was used as the solvent. 17α-Hydroxy-20-ketones that lack a hydroxyl group at C-21 are stable to these conditions.[161]

An improved method of synthesis of the tetrahydroaldosterone (190), which is a human urinary metabolite of aldosterone, has been described.[162] If the 17α,20 : 20,21-bismethylenedioxy-derivative of hydrocortisone is mixed with sodium palladium chloride (Na_2PdCl_4) it gives the steroid–palladium complex (191), which reacts with malonic ester to give the derivative (192), from which 6β-carboxymethylhydrocortisone (193) can be prepared by successive reaction with lithium iodide, an alkali, and aqueous formic acid.[163]

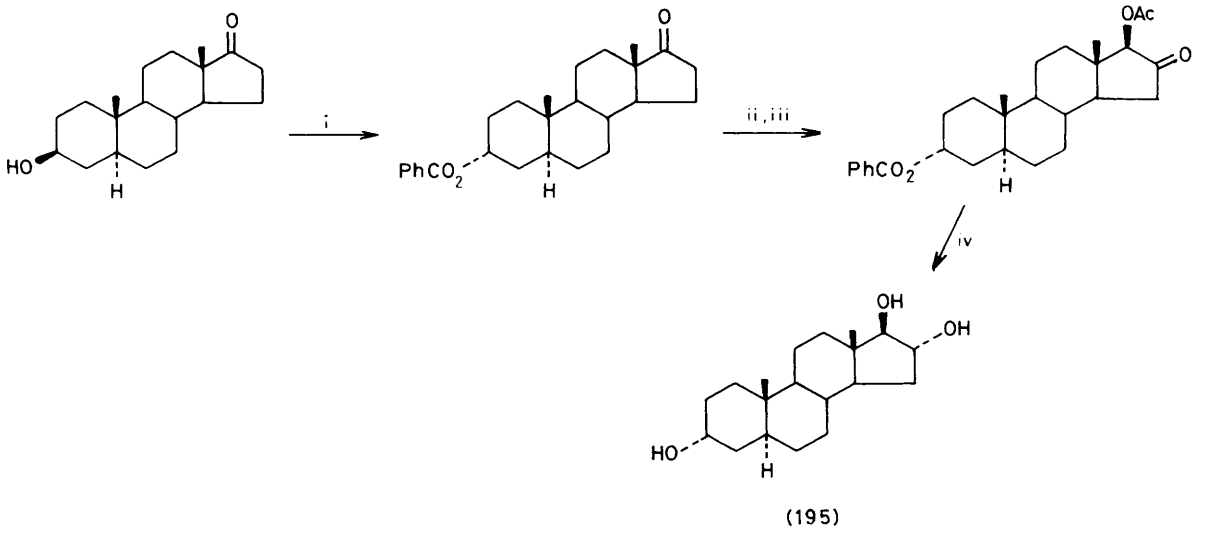
The 9-(β-D-arabinofuranosyl)adenine 5′-monophosphate esters (194) of a number of corticosteroids have been prepared; several were discovered to be active in inhibiting the growth of L-1210 lymphoid leukaemia cells *in vitro*.[164] Some 3-glucuronides of 21-carboxylic acids that are derived from corticoids have been synthesized as possible metabolites of the corticoids.[165]

Progesterone has been labelled with ^{131}I at C-19[166] and with ^{18}F at C-21.[167]

2.4 Androstanes and Oestranes

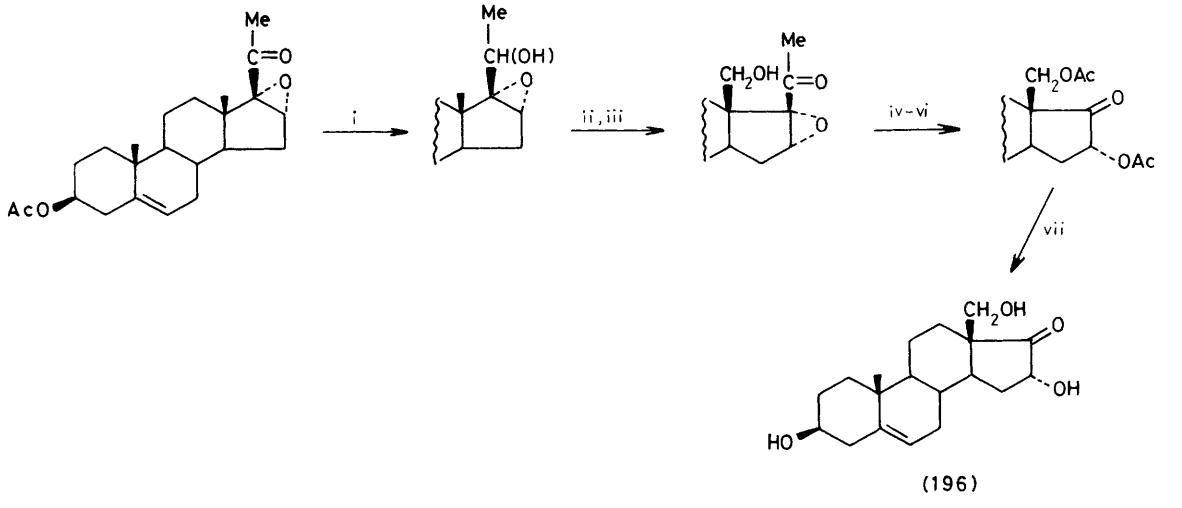
A new route to A-nortestosterone has been reported.[168] 17α-Hydroxy-19-norandrosta-4,14-dien-3-one was oxidized by *m*-chloroperoxybenzoic acid to the 14α,15α-epoxide as the principal product, whereas the 17β-hydroxy-compound yielded a preponderance of the 14β,15β-epoxide.[169] The four isomeric 3β-acetoxy-16-methylandrost-5-en-17-ols have been synthesized by an unambiguous route; hitherto there has been doubt about their stereochemistry.[170]

5α-Androstane-3α,16α,17β-triol (195) has been synthesized as shown in Scheme 37; it was considered to be a possible rat testicular steroid.[171] A neonatal urinary metabolite has been assigned the structure 3β,16α,18-trihydroxyandrost-5-en-17-one, but there is some doubt about the configuration at C-16; the compound (196) has now been prepared by an unambiguous route (Scheme 38) and the 16α-configuration of the metabolite has been confirmed. The 16β-isomer was obtained only as its triacetate, which underwent rearrangement (even on enzymic hydrolysis) to form the 17β-hydroxy-16-ketone.[172]



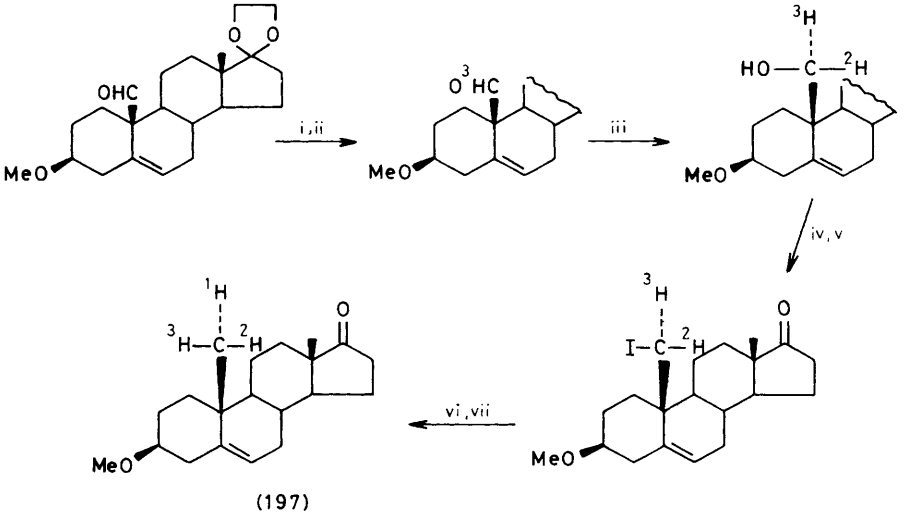
Reagents: i, $PhCO_2H$, Ph_3P, $EtO_2CN{=}NCO_2Et$; ii, $H_2C{=}C(Me)OAc$, TsOH; iii, *m*-$ClC_6H_4CO_3H$; iv, $LiAlH_4$

Scheme 37



Reagents: i, $NaBH_4$; ii, $Pb(OAc)_4$, I_2, *hν*; iii, CrO_3; iv, Ac_2O, pyridine; v, NH_2OH; vi, $POCl_3$, pyridine; vii, MeOH–HCl or enzyme from *Helix pomatia*

Scheme 38



Reagents: i, NaB^3H_4; ii, CrO_3, pyridine; iii, $LiAl(OCHBu^t_2)_3{}^2H$; iv, H^+; v, $(PhO)_3\overset{+}{P}Me\ I^-$; vi, $LiBEt_3H$; vii, CrO_3

Scheme 39

5α-Androst-16-en-3-one has been prepared that is labelled with tritium at positions 5 and 6.[173] 3β-Methoxyandrost-5-en-17-one that is labelled at C-19 with protium, deuterium, and tritium has been synthesized in (19*R*)- and (19*S*)-forms. A method of synthesis of the (19*R*)-isomer (197) is shown in Scheme 39; the (19*S*)-form is produced in a similar manner.[174]

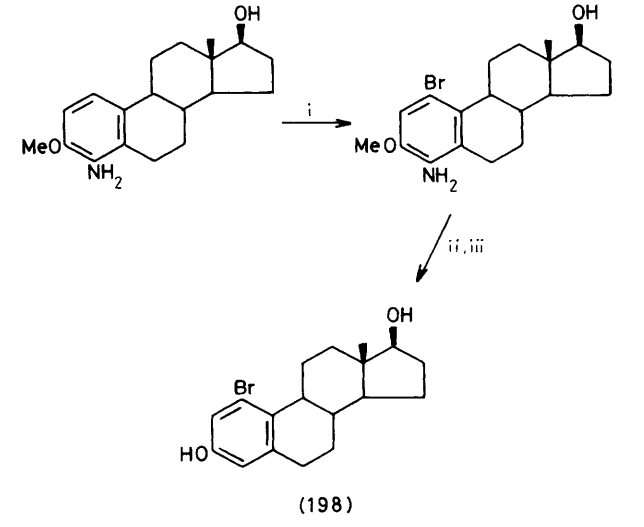
Various approaches to the production of oestrone have been reviewed.[175]

Both 2- and 4-bromo-17β-oestradiol are much less protein-bound than oestradiol and, furthermore, they are not concentrated in tissues that contain receptors for oestrogens; this might be a consequence of a bromine atom that is close to the phenolic hydroxyl group. Therefore, 1-bromo-17β-oestradiol (198) has been synthesized as shown in Scheme 40.[176] Oestrone acetate, when it was treated with hydrogen peroxide in hydrogen fluoride that contained antimony pentafluoride, gave a mixture that contained 10-hydroxyoestra-1,4-diene-3,17-dione (199), 1-hydroxyoestrone (200; R = H) and its 3-acetate (200; R = Ac), and 2,4-dihydroxyoestra-1,3,5(10)-trien-17-one (201; R = H) and its 2-acetate (201; R = Ac). These last compounds are thought to arise *via* a spiro-intermediate (202).[177] 4-Hydroxyoestrone is oxidized by manganese dioxide in chloroform to the 3,4-quinone; the 2,3-quinone is formed similarly, but it is too unstable to be isolated.[178]

A 3-silylated oestradiol reacts with chromium hexacarbonyl to form α- and β-isomers of the complex. These can be separated on a silica column (see Scheme 41) and then used to produce the 6α- and 6β-alkyloestradiols as indicated in the Scheme.[179]

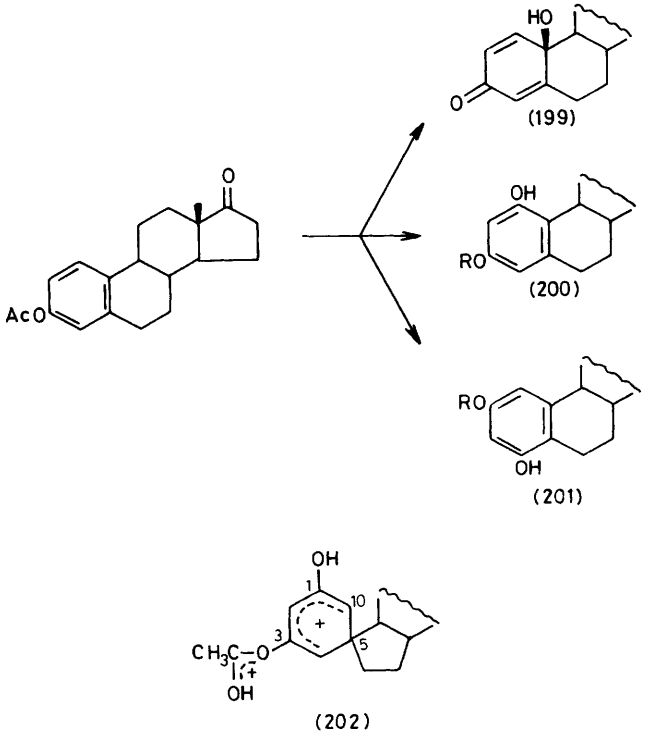
16β-Fluoro-oestrone has been synthesized from the 3-triflate of 16α-triflyloxyoestrone and tetrabutylammonium fluoride; the 16α-epimer was obtained similarly from the 16β-triflate. The displacements with fluoride ion occur under unusually mild conditions.[180] 3-Methoxyoestra-1,3,5(10)-trien-16-one was prepared from the 17β-hydroxy-16-ketone by formation of the toluene-*p*-sulphonate, reduction of the 16-keto-group with lithium aluminium hydride, and hydrolysis of the product.[181]

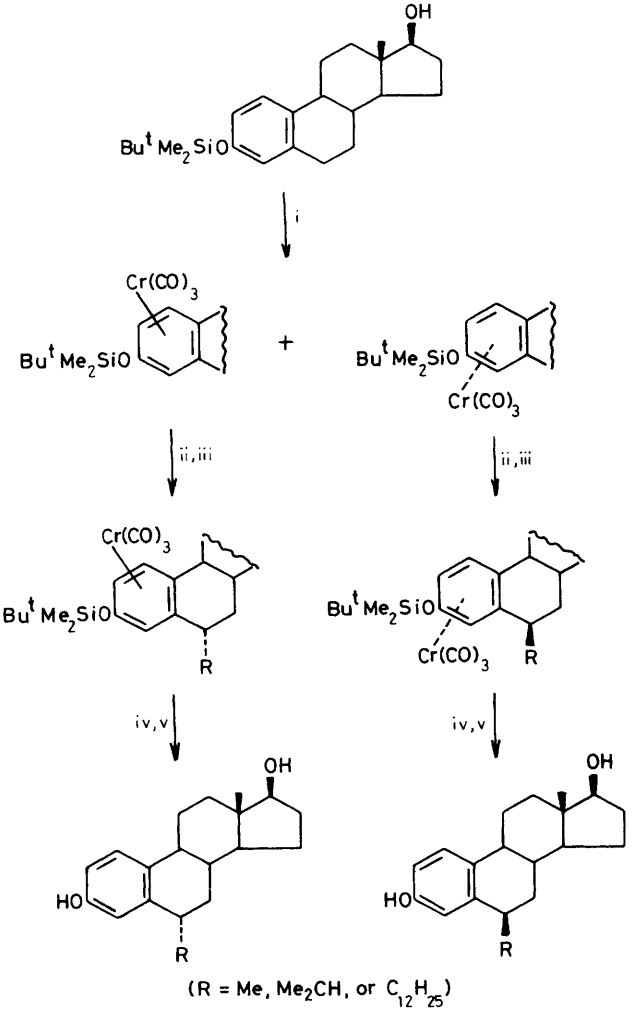
17α-Ethynyl-17β-ols have been converted into the bromo- and iodo-ethynyl compounds by their reaction with *N*-bromo- and *N*-iodo-succinimide, with silver nitrate as catalyst.[182] Two methods are shown in Scheme 42 for the synthesis of (20*E*)-17α-iodovinyl-17β-oestradiol, which is suitable for labelling.[183,184] Oestriol that is labelled with deuterium at positions 2, 4, and 16β has been prepared from the reaction of 2,4,16α-tribromo-



Reagents: i, BrCl; ii, HNO_2, H_2O_2; iii, BBr_3

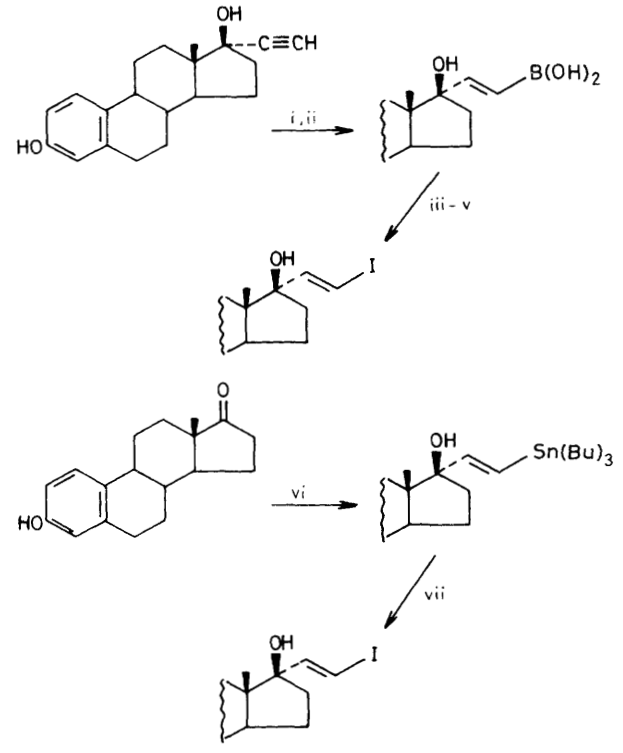
Scheme 40

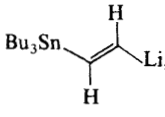




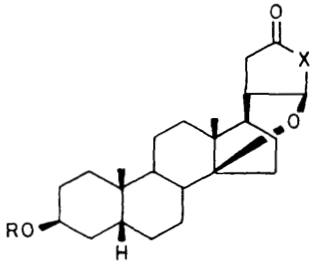
Reagents: i, $Cr(CO)_6$; ii, Bu^tMe_2SiCl; iii, RI, $(Me_3Si)_2NNa$; iv, *hv*, air; v, $Bu_4N^+ F^-$

Scheme 41



Reagents: i, catecholborane; ii, H_2O; iii, Ac_2O, pyridine; iv, ICl; v, NaOAc, Na_2CO_3; vi,  Li, BuLi; vii, NaI, H_2O_2

Scheme 42



(203)

oestrone and sodium deuteroxide in deuterium oxide followed by reduction of the product with sodium borodeuteride.[185]

The syntheses of the 11-mono-hemisuccinate and the 11-(β-D-glucopyranosiduronate) of 11α-hydroxy-17β-oestradiol have been described; they were required for use in radioimmunoassay.[186]

2.5 Cardenolides and Bufadienolides

Reviews have been published on the partial synthesis of analogues of cardiotonics,[187] on interconversions, partial synthesis, and structure–activity relationships of cardenolides and bufadienolides,[188] and on the Koenigs–Knorr glycosidation of hydroxy-cardenolides.[189]

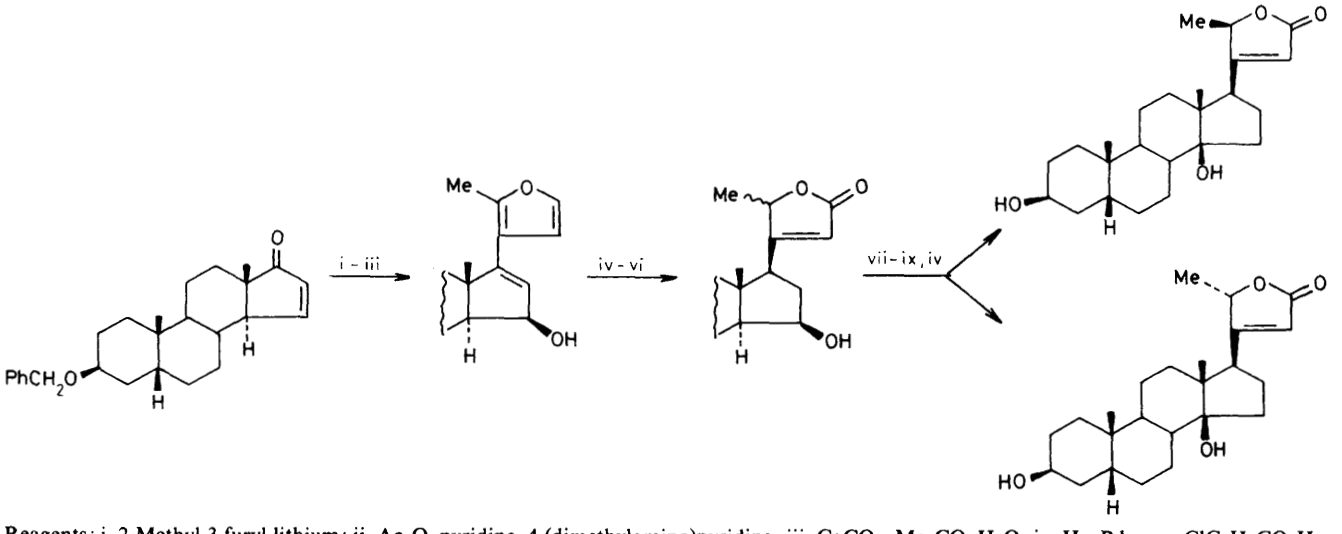
Saponification of acylcardenolide glycosides with ammonia gives the 14β,21-epoxycardenolides (203; X = O) and the corresponding lactams (203; X = NH).[190] A 14α-15-oxa-D-homo-analogue of the cardiac aglycons and the corresponding isocardenolide have been synthesized.[191]

If there are distinct receptors for the inotropic effect and for the cardiac toxic effect of cardenolides, one of the isomers of a 21-alkylcardenolide should be inotropic and non-toxic while the reverse effects should be shown by the other isomer. Both isomers of 21-methyldigitoxigenin have been synthesized (Scheme 43). The epimers were separated by t.l.c. and their structures were determined by *X*-ray analysis. The glucoside of the (21*R*)-isomer was almost as potent as digitoxin, but very much less toxic; however, the (21*S*)-isomer also had low toxicity, but it was relatively weakly active.[192] A synthesis of (21*R*)-21-methyldigitoxin from digitoxin has been described.[193]

In model experiments, the δ-lactam (204), which is related to bufadienolides, has been prepared.[194]

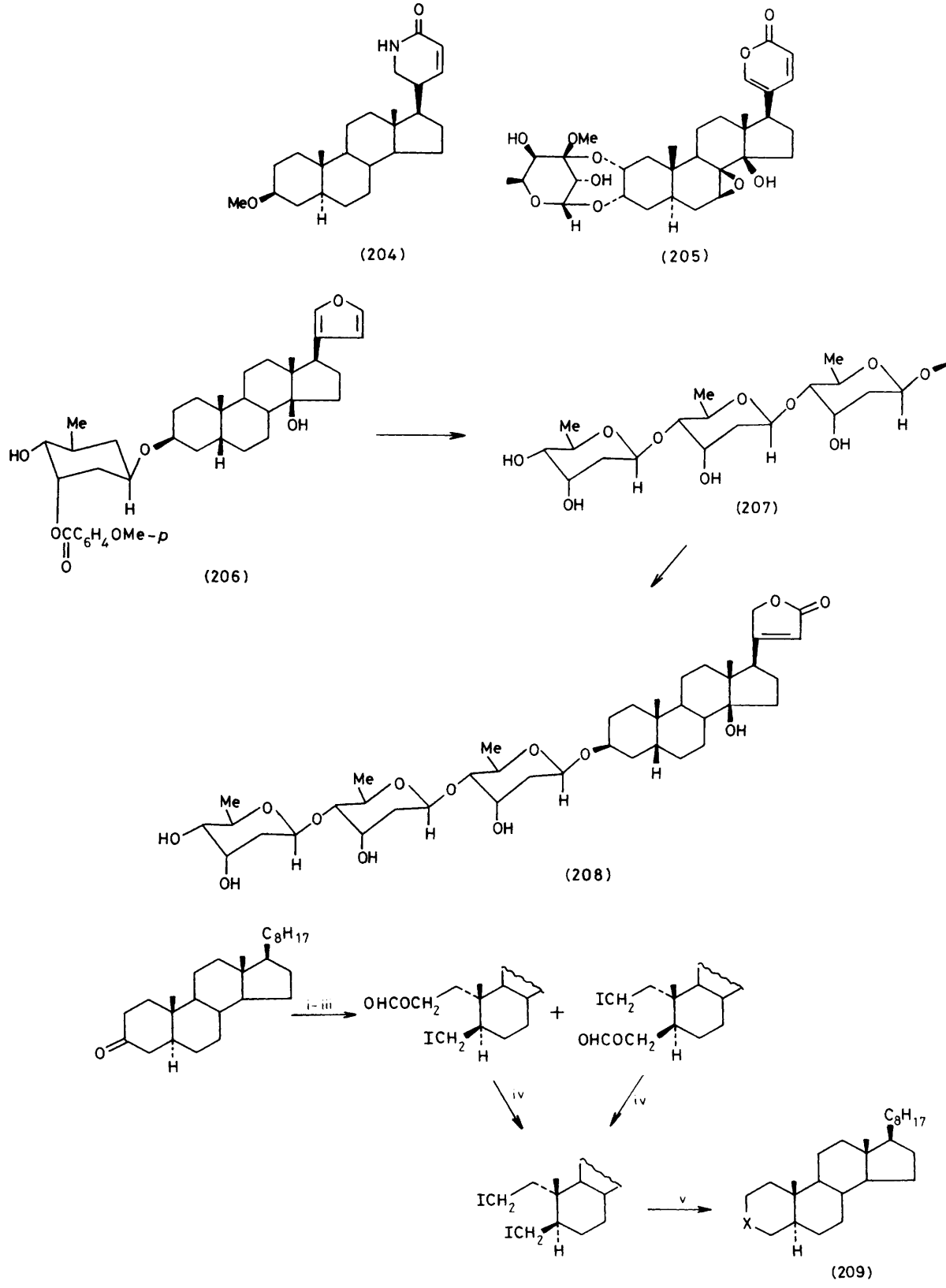
The structure of cotyledoside has been corrected to (205) on the basis of n.m.r. measurements.[195] A stereoselective synthesis of digitoxin (208) from compound (206) *via* the tridigitoxoside (207) has been published.[196] Some side-chain analogues of digitoxigenin β-D-digitoxoside have been synthesized from the cardiac glycoside. The digitoxosides were about ten times as active as the free genins as inhibitors of Na^+/K^+-transporting ATPase; their acetonides were only twice as active.[197]

Chemical methods for the formation of glycosides are unsuitable in the case of, for example, steroids that contain a lactone ring or an aldehyde, because of their tendency to decompose during deacetylation; also, tertiary hydroxyl groups will undergo dehydration during the formation of a glycoside. Therefore, 3-*O*-β-glucosides and 3-*O*-β-galactosides of a number of cardiac aglycons have been synthesized by treatment of



Reagents: i, 2-Methyl-3-furyl-lithium; ii, Ac_2O, pyridine, 4-(dimethylamino)pyridine; iii, $CaCO_3$, Me_2CO, H_2O; iv, H_2, Pd; v, *m*-$ClC_6H_4CO_3H$; vi, $NaBH_4$; vii, $SOCl_2$; viii, *N*-bromoacetamide; ix, Ni

Scheme 43



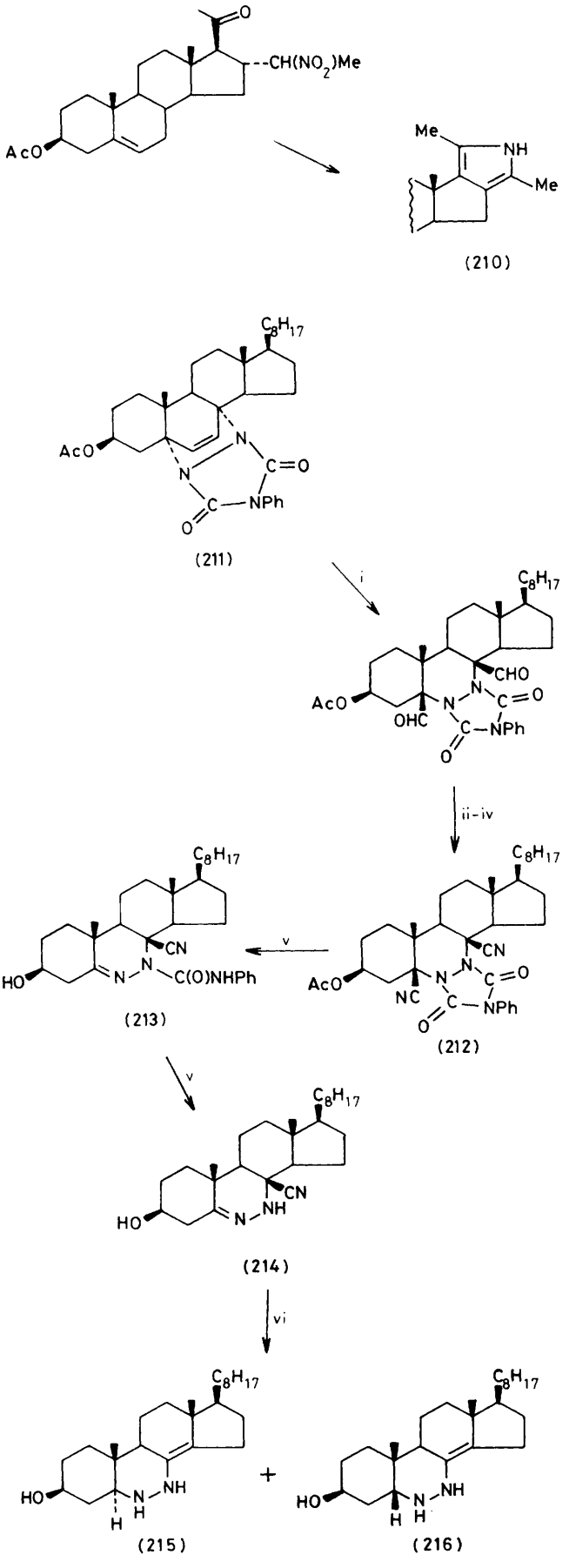
Reagents: i, *m*-$ClC_6H_4CO_3H$; ii, Bu^i_2AlH; iii, HgO, I_2, *hν*; iv, Me_3SiI; v, Na_2S or RNH_2

Scheme 44

the aglycon with the appropriate phenyl-β-glycoside in the presence of β-galactosidase in aqueous acetonitrile.[198] Cleavage of cardiac glycosides that contain doubly linked sugars may be achieved with pyridine, alumina, or phenylhydrazine; the genin is obtained in reasonable yield.[199]

2.6 Heterocyclic Compounds

5α-Cholestan-3-one has been converted, *via* the 2,3-di-iodo-A-nor-2,3-seco-5α-cholestane, into 3-(substituted aza)- and 3-thia-5α-cholestane [(209; R = R′N) or (209; R = S)] (Scheme 44); in the same way, a 16-ketone was converted into the 16-aza-



Reagents: i, O_3; ii, NH_2OH; iii, acetylation; iv, heat; v, KOH; vi, $LiAlH_4$

Scheme 45

and 16-thia-compounds. A 5α-6-ketone was converted, by a modification of the method, into the 5β-6-thia-compound;[200] 3-, 4-, 6-, and 16-oxa-steroids can be prepared in an analogous manner.[201]

3β-Acetoxy-16α-(1-nitroethyl)pregn-5-en-20-one is reduced by tributylphosphine and diphenyl disulphide to the pyrrole compound (210); a nitromethyl group at C-17 is simply reduced to the nitrile. The mechanism of the reaction is thought to involve reduction of the nitro-group, first to an oxime, then to an imine, by the quinquevalent phosphorus species $Bu_3P(SPh)_2$.[202]

The adduct of 7,8-didehydrocholesteryl acetate and 1-phenyl-1,3,4-triazoline-2,5-dione (211) (Scheme 45) was ozonized to the 5β,8β-dialdehyde, which was then converted, *via* the dioxime, into the 5β,8β-dicyano-compound (212). Treatment of this compound with an alkali yielded 7-anilinocarbonyl-8β-cyano-6,7-diazacholest-5-ene-3β-ol (213); further hydrolysis removed the anilinocarbonyl group and gave compound (214). The remaining cyano-group could not be removed with a base, but lithium aluminium hydride eliminated the cyano-group as well as reducing the 5–6 double-bond, and gave 6,7-diaza-5α-cholest-8(14)-en-3β-ol (215) as the major product and its 5-epimer (216) in much smaller yield (Scheme 45).[203]

Iodination of pseudodiosgenin (217) gives a mixture of the 23-epimers of the tetrahydrofuran (218) and the 20-epimers of diosgenin (219).[204]

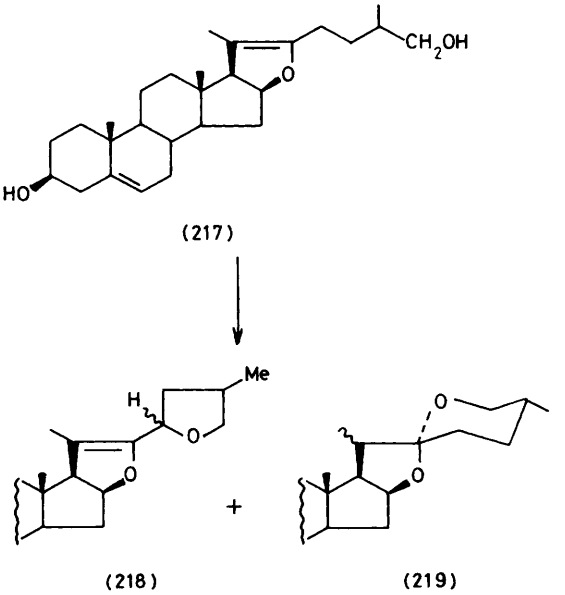
In order to study the effect of making ring A of a steroid rigid on its ability to bind to progesterone receptors, some 1a,11α-epoxy-1α-methyl-steroids have been prepared as shown in Scheme 46.[205]

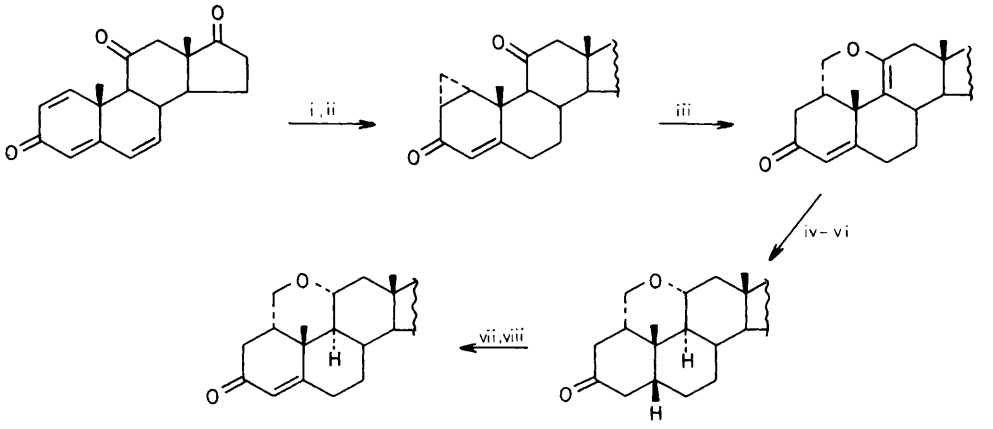
5α-Cholestan-3-one 3,3-ethylenedithioketal (220) reacts with benzeneselenyl chloride in methylene chloride to give the dihydrodithiin (221); in the same way, a 17-ketone gave the 16,17-dihydrodithiin, and trimethylene dithioketals gave the seven-membered-ring compounds. The reaction probably proceeds as shown in Scheme 47.[206]

A 21-(thiazol-4-yl)-compound (222) has been prepared from the corresponding 21-carboxylic ester.[207] A steroid (223) in which a thiazole ring is fused to carbon atoms 1 and 2 has been prepared from 2-amino-oestrone methyl ether.[208]

The ethoxycarbonylhydrazone of 17β-acetoxy-5α-androstan-3-one reacts with thionyl chloride to give the 1-sulphinyl-[2,3-*d*]thiadiazole (224). The tosyl- and formyl-hydrazones give only the 1-unsubstituted compound, while the acetylhydrazone gives a mixture of the two.[209]

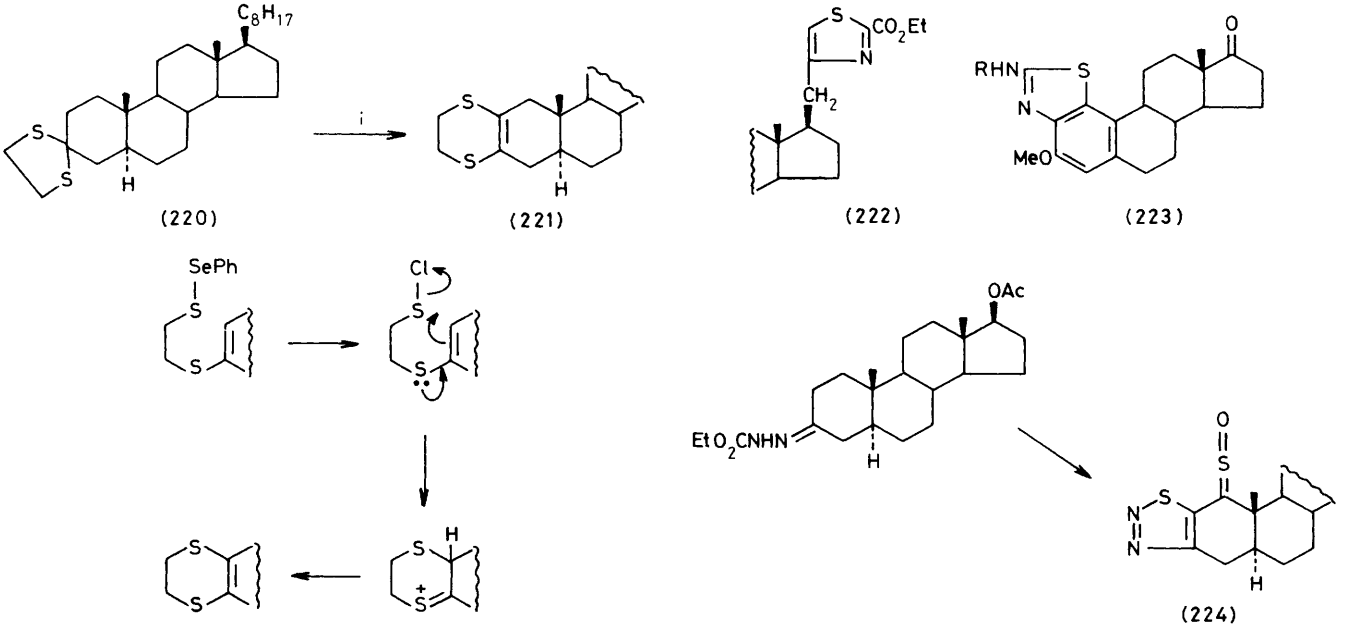
In the search for antagonists for aldosterone, the phosphorus-containing heterocycles (225; X = O) and (225; X = NMe)





Reagents: i, $Me_2S(O)=CH_2$; ii, H_2, Pd; iii, HBr; iv, $Me_3SiSCH_2CH_2SSiMe_3$, $ZnBr_2$; v, Et_3SiH, CF_3CO_2H; vi, H_5IO_6; vii, $H_2C=C(Me)OAc$, TsOH; viii, *N*-bromoacetamide, CCl_4

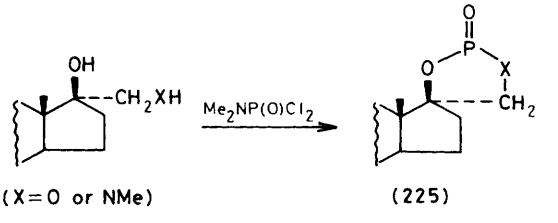
Scheme 46



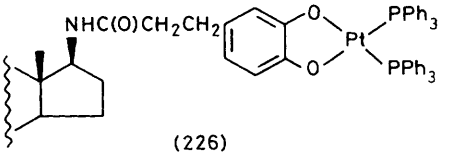
Reagents: i, PhSeCl

Scheme 47

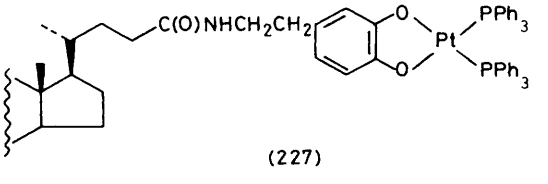
were prepared as indicated.[210] Platinum complexes of the types (226) and (227) have been synthesized; they are about as active as *cis*-dichlorodiaminoplatinum(II) as anti-tumour agents.[211]



(X=O or NMe)



(226)



(227)

2.7 Cyclopropano-steroids

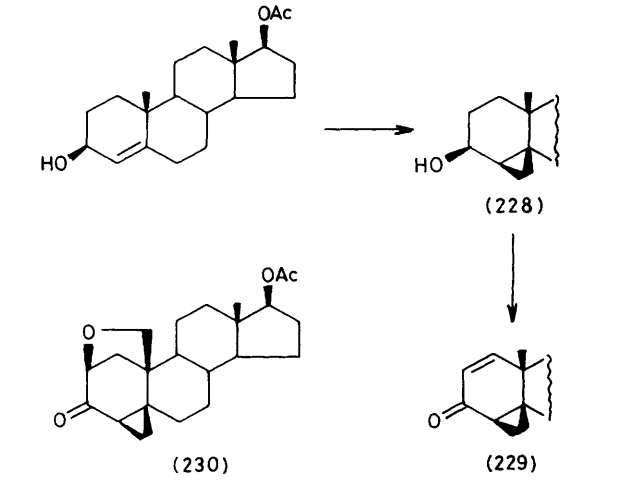
17β-Acetoxyandrost-4-en-3β-ol has been converted, by treatment with methylene iodide and a zinc–copper couple, into the 4β,5-methylene-5β-compound (228), from which 17β-acetoxy-4β,5-methylene-5β-androst-1-en-3-one (229) was prepared. In the same way, 17β,19-diacetoxy-4β,5-methylene-5β-androstan-3-one gave the 2β-bromo-derivative, which was converted (by treatment with potassium methoxide) into 17β-acetoxy-2β,19-epoxy-4β,5-methylene-5β-androstan-3-one (230).[212]

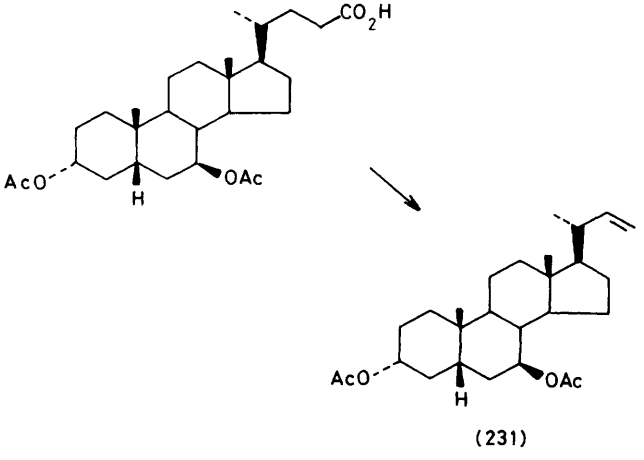
3α,7β-Diacetoxy-24-nor-5β-chol-22-ene (231), which was prepared from the corresponding cholan-24-oic acid by oxidative decarboxylation, reacted with ethyl diazoacetate in the presence of dirhodium(II) tetra-acetate [$Rh_2(OAc)_4$] to give, after hydrolysis, 3α,7β-dihydroxy-22,23-methylene-5β-cholan-24-oic acid (232) as a mixture of all four stereoisomers at positions 22 and 23.[213]

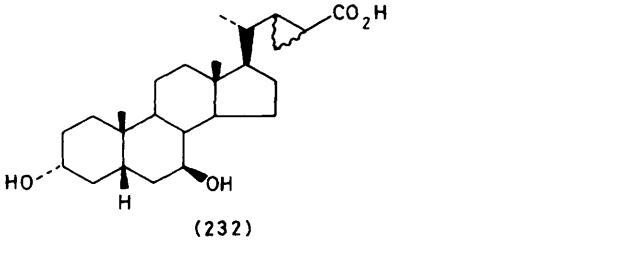
2.8 Microbiological Transformations

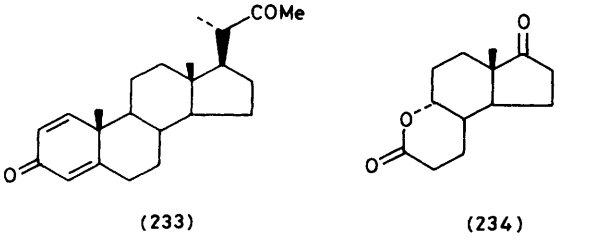
Reviews have appeared dealing with the microbiological conversions of steroids,[214,215] with the use of immobilized cells for this purpose,[216] and with the use of plant cell cultures for the production of various compounds, including steroids.[217]

A number of papers have been published on the use of *Arthrobacter simplex*, immobilized in various ways, for the 1,2-didehydrogenation of Δ^4-3-ketones[218–221] and on the use of *Rhizopus nigricans*, also immobilized, for 11α-hydroxylation.[222]









Spores of *Aspergillus ochraceus*, immobilized in diatomaceous earth or in a polyacrylamide gel, were as effective as the free spores in effecting 11α-hydroxylation, and could be used repeatedly.[223,224]

Heat-dried cells of *Arthrobacter simplex* can be used, with advantage in yield and simplicity, to achieve 1,2-didehydrogenation. The highest rates of 1,2-didehydrogenation of androsta-4,9(11)-diene-3,17-dione were obtained for cells that had been dried at 40—60 °C.[225]

Cholic acid has been converted into 3α,7α-dihydroxy-12-oxo-5β-cholan-24-oic acid by a 12α-hydroxysteroid dehydrogenase in the presence of $NADP^+$; the nicotinamide cofactor can be regenerated.[226]

Cholesterol, stigmasterol, β-sitosterol, and the sterol fractions of 'tall oils' have been converted into 22-hydroxy-23,24-dinorchola-1,4-dien-3-one by fermentation with *Mycobacterium* CCM 3528 and into the corresponding 17-ketone by *Mycobacterium* CCM 3529; yields are good in both types of conversion.[227] A closer study of the conversion of cholesterol with the first of these organisms showed that minor products included 24-norchola-1,4-diene-3,22-dione (233) and the corresponding Δ^4-compound.[228] Some derivatives of bile acids are degraded by *Alcaligenes faecalis* to the Δ^4- or $\Delta^{1,4}$-3-oxo-bisnorcholanal.[229,230]

Cholesteryl methyl ether, potassium cholesteryl sulphate, and 3-chlorocholest-5-ene are all degraded by *Moraxella* species (which may, advantageously, be immobilized) to the corresponding 17-ones, without undergoing modification of ring A.[231]

Cholesterol, stigmasterol, and β-sitosterol are degraded by fermentation with a mutant strain of *Rhodococcus australis* CSIR-236.457 to give good yields of compound (234).[232]

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