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Steroids with a side chain containing a heterocyclic fragment: synthesis and transformations

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Abstract. The latest data on the methods for the formation of the side chains of steroids containing a heterocyclic fragment are surveyed and described systematically. Attention is concentrated on the methods for the transformation of heterocycles in order to achieve the stereoselective formation of chiral centres in the side chain characteristic of a series of natural polyhydroxysteroids — ecdysones, brassinosteroids, vitamin D metabolites, etc. The bibliography includes 133 references.

I. Introduction

A series of steroids, characterised by a high physiological activity, contain a heterocyclic fragment or a polyfunctionalised side chain as a structural element. Cardenolides, withanolides, ecdysones, etc. can be included among steroids of this kind.

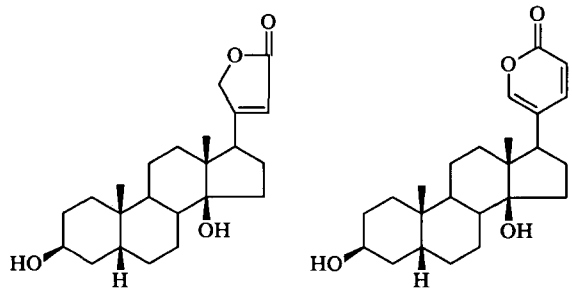
The present review is devoted to the formation and transformations of the steroid side chains containing a heterocyclic fragment and covers the literature for the last 15 years. Additional information on this problem can be found in other communications.[1-10]

The review includes problems concerning five-membered, six-membered, and the fairly rare four-membered heterocycles. The scope of the review precludes the consideration of steroid alkaloids and 17-spiroheterocycles. Dioxolans and acetonides, which actually constitute protective groups, are also excluded.

II. Synthesis of steroids containing a heterocycle in the C(17) position

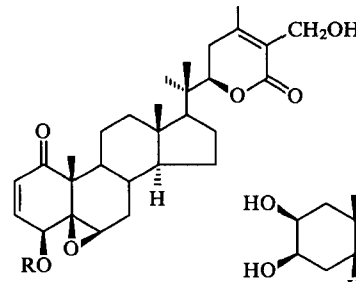
The synthesis of steroids having a heterocyclic substituent in the 17β-position involves mainly the development of convenient methods of construction of the side chain in cardenolides (five-membered lactones), bufadienolides (six-membered lactones), or their analogues, which are distinguished by a broad spectrum of biological activity.

The following most general approaches to their synthesis can be differentiated: (a) cyclisation of 21-derivatives of 20-ketosteroids involving a change in a functional group — primarily in the 21-position; (b) condensation of the reagent initially with the carbonyl group of the 21-derivatives of 20-ketosteroids followed by cyclisation; (c) addition of lithio-derivatives of heterocycles to the carbonyl group of 17-ketosteroids with subsequent transformation of the products.

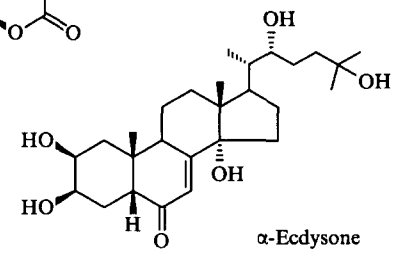


Digitoxigenin

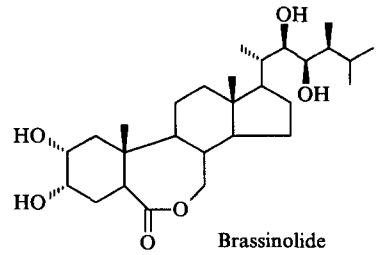
Bufalin



Withaferin A



α-Ecdysone



Brassinolide

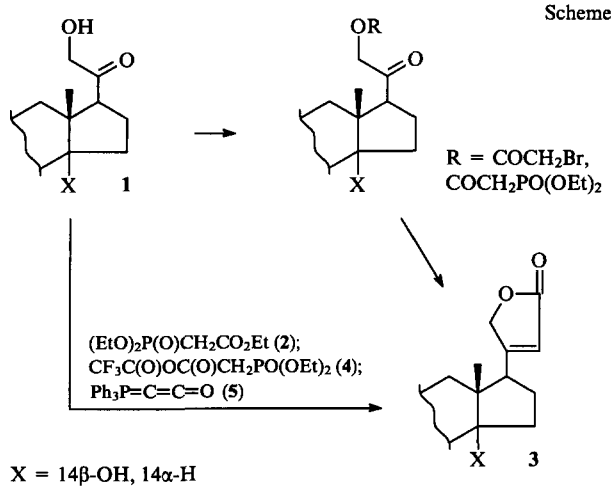
One of the main problems in the synthesis of cardiac aglycones is the formation of the butenolide side chain under mild conditions. The Horner–Emmons intermolecular condensation method is most attractive for this purpose. It includes either the esterification of the α-ketol **1** to the bromoacetate and the formation from the latter of a Wittig reagent and its cyclisation[3] or esterification[11-13] of the α-ketol with triethyl phosphonacetate **2** with simultaneous cyclisation to the lactone **3**. However, the

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large number of stages, which reduces the yield, in the first case and the poor reproducibility in the second hinder the use of this method. Attempts at improvement of the procedure by using new reagents have therefore not ceased. One of the versions involves the use of the mixed anhydride of trifluoroacetic and diethyl phosphonoacetic acids **4**.[14] Treatment of the ketol **1** with this reagent in the presence of potassium carbonate results in the formation of the lactone **3**. High yields of the lactone **3** have been obtained also using the ketene triphenylphosphoranylide **5**. Treatment of the ketol **1** with the latter results in the formation of the five-membered lactone **3** in one stage.[15] It is remarkable that this reaction does not involve the tertiary hydroxy-groups of the steroid (Scheme 1).

Scheme 1

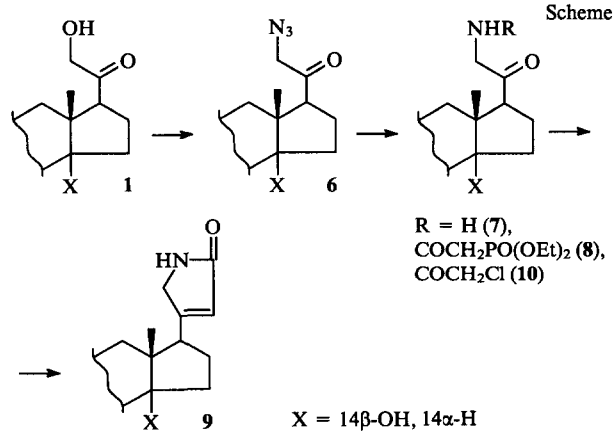


X = 14β-OH, 14α-H

The replacement of the hydroxy-group in the ketol **1** by the azide group or its conversion into the methanesulfonate or toluene-*p*-sulfonate, which undergo nucleophilic substitution, makes it possible to obtain a series of sulfur- and nitrogen-containing derivatives which afford heterocycles—analogues of digitoxigenin and bufalin—under mild conditions.

The reduction of the azide **6** to the amine **7** and acetylation of the latter with diethylphosphonacetic acid in the presence of dicyclohexylcarbodiimide lead[16] to the amide **8** and, after cyclisation, to the lactam **9**. This lactam is obtained by hydrogenating the azide **6** over $Pd/CaCO_3$ in the presence of chloroacetic anhydride.[17,18] The resulting chloroacetamide **10** is converted into a phosphonium salt and subjected to Wittig cyclisation (Scheme 2).

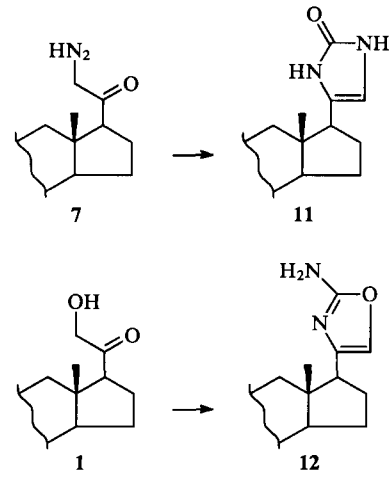
Scheme 2



X = 14β-OH, 14α-H

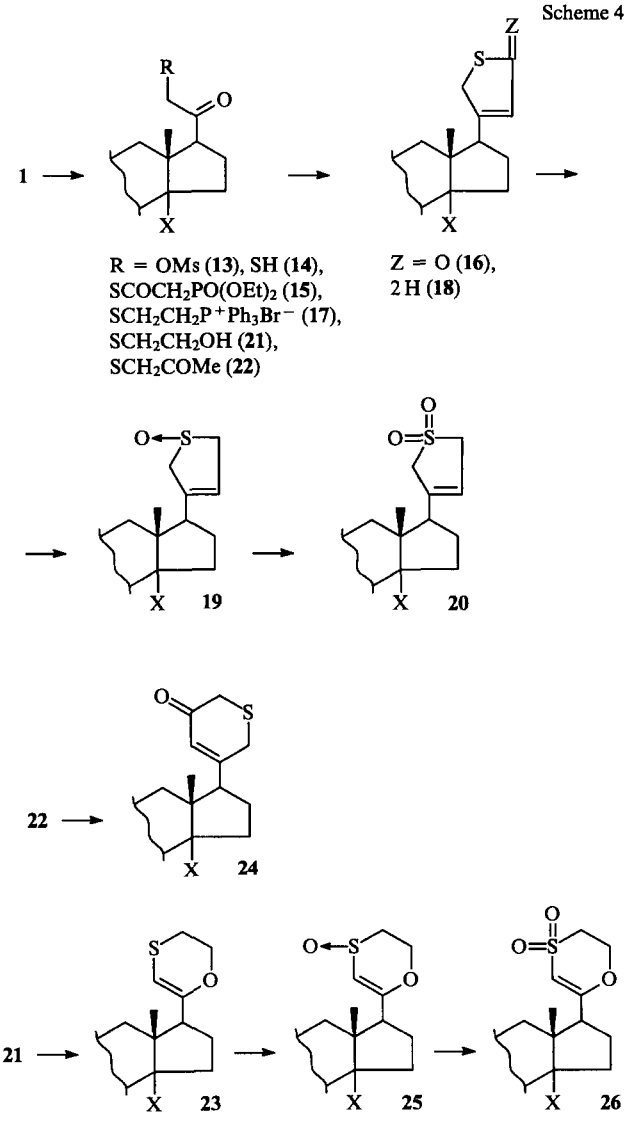
The imidazoline derivatives **11** were obtained from the amine **7** and were treated with carbamoyl chloride with subsequent cyclocondensation.[19] The aminooxazole **12** can be synthesised directly from the ketol **1** by treating the latter with cyanamide (Scheme 3).[20]

Scheme 3



The ease of the nucleophilic substitution of the methanesulfonate **13** makes it possible to form cyclic structures with the sulfur atom. The thiolactone **16** is formed via the phosphonate **15** from the thiol **14**, obtained by the reaction of the methanesulfonate **13** with sodium hydrogen sulfide. The 2,5-dihydrothiophene **18** is synthesised by substituting the methanesulfonate

Scheme 4

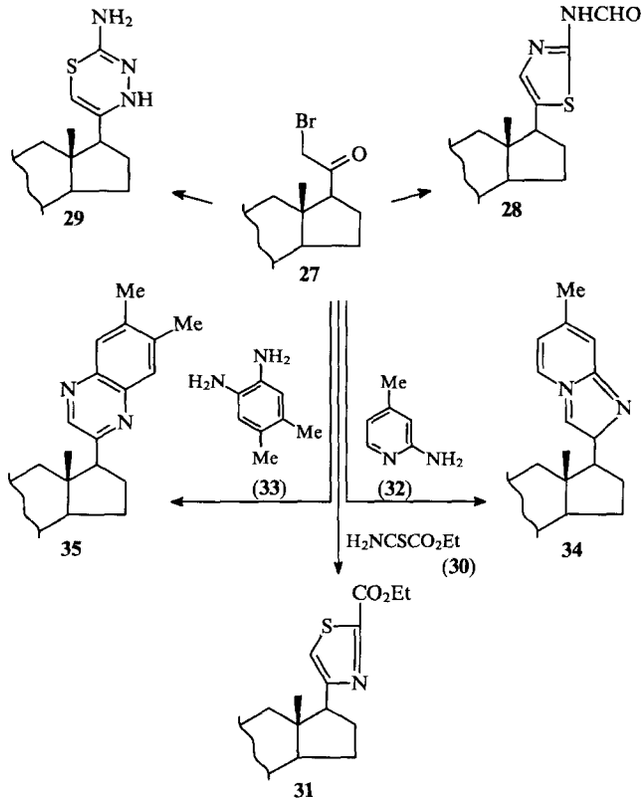


X = 14β-OH, 14α-H

group in compound **13** by the sodium salt of 2-mercaptoethyltriphenylphosphonium bromide and cyclisation of the intermediate **17**. The dihydrothiophene **18** is readily oxidised by sodium periodate to the sulfoxides **19** and the latter are oxidised in their turn to the sulfone **20** with *m*-chloroperbenzoic acid. Similar substitution of the methanesulfonate group in compound **13** by thiols can afford the derivatives **21** and **22**. The cyclisation of the former to the oxathiine **23** is achieved on treatment with acids, whilst cyclisation of the latter to the thiopyranone **24** is carried out in the presence of sodium methoxide. Similarly the oxathiine **23** can be oxidised[16,21] to the sulfoxides **25** and the sulfones **26** (Scheme 4).

The α-bromoketones **27** are used widely to synthesise steroids of different kinds with diaza- and thiaza-heterocycles in the side chain.[22-26] For example, their condensation with thiourea[22] in dimethylformamide (DMF) affords the thiazole **28**, the condensation with thiosemicarbazide[23] affords the thiadiazine **29**, the condensation with ethyl thioxamate[24] **30** gives rise to the thiazole **31**, while the condensation with aminopyridine[25] **32** or the diamine[26] **33** affords compounds **34** and **35** respectively (Scheme 5).

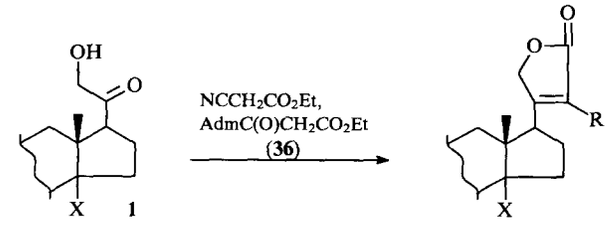
Scheme 5



In the cases considered, cyclisation to a heterocycle was preceded by reactions which did not involve the carbonyl group at C(20). Syntheses involving addition of various reagents to this centre and subsequent cyclisation are described below. They are mainly intended to produce the side chain in compounds related to digitoxigenin and its derivatives. Thus the condensation of the ketol **1** with cyanoacetic ester[27] or the acetoacetic ester derivative **36** affords the unsaturated cyanolactone **37** and the acyllactone **38** (Scheme 6).[28]

The lactone **3** ring was obtained from the ketosulfide **39** by reaction with bromoacetic ester in the presence of activated zinc.[29] The diastereoisomers **40** are converted, without separation, into the epoxyesters **41** via a methylsulfonium salt. The passage of the esters through a column with basic alumina led to cyclisation to the required lactone **3**. The Reformatskii reaction has been used successfully to synthesise the lactone **3** from the ketoacetate **42**.[30]

Scheme 6

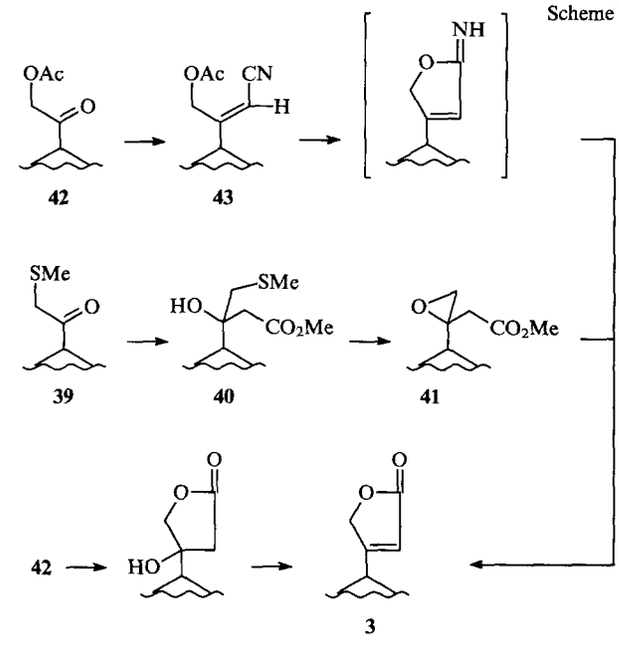


X = 14β-OH, 14α-H
Adm = Adamantine

R = CN (**37**),
C(O)Adm (**38**)

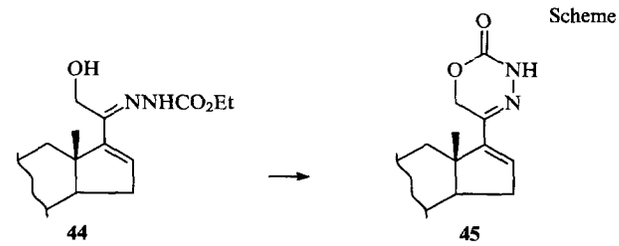
A more effective method, using the chemistry of phosphoranes, has been proposed.[31] The condensation of the ketoacetate **42** with diethyl cyanomethylphosphonate and subsequent treatment of the resulting nitrile **43** with toluene-*p*-sulfonic acid made it possible to isolate directly the lactone **3** (Scheme 7).

Scheme 7



An aza-analogue of cardiotonic steroids **45** of the type of bufalin has been obtained[32] by the alkaline treatment of the ethoxycarbonylhydrazone **44**. Evidently only the (*Z*)-isomers are capable of this kind of cyclisation (Scheme 8).

Scheme 8

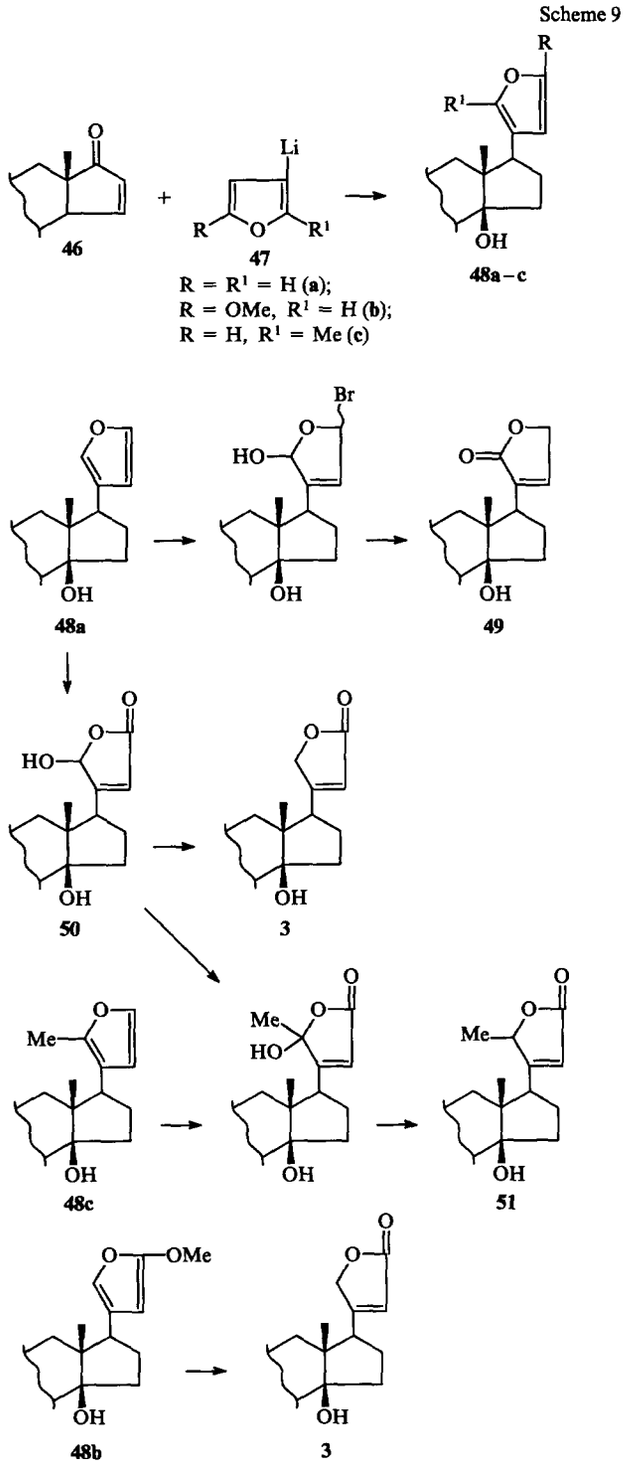


The chemistry of furan derivatives provides extensive possibilities for the synthesis of the lactone rings in cardenolides and bufadienolides. Thus the cardenolides **3**, the isocardenolide **49**, and the 21-hydroxy- and 21-methyl analogues **50** and **51** have been obtained by alkylating the 17-ketones with 3-lithiofurans and the transformation of the furylsteroids.[33-35]

These compounds were synthesised in the following way. As a result of the addition of 3-lithiofurans **47** to the ketone **46** and a series of transformations of the D ring of the steroid molecule, the

furyl steroids **48** were obtained. Oxidation of the furylsteroid **48a** with *m*-chloroperbenzoic acid and the reduction with $NaBH_4$ of the primary product—the hydroxylactone **50**—afforded the cardenolide **3**,[33] which can also be obtained as a result of the acid hydrolysis of the methoxy-group in the furyl steroid **48b**.[34] On the other hand, the oxidation of compound **48a** with *N*-bromosuccinimide leads to the lactone **49** which is isomeric with respect to compound **3** (Scheme 9).[33]

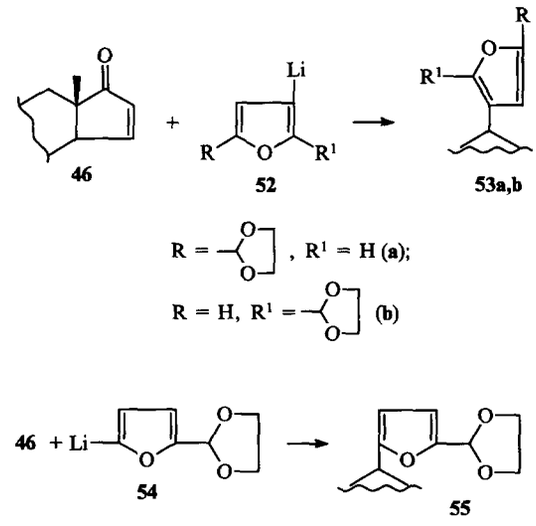
Scheme 9



Successive oxidation with *m*-chloroperbenzoic acid and reduction with $NaBH_4$ of the furylsteroid **48c** affords the 21-methyl derivative **51**. Another method of synthesis[35] of the cardenolide **51** involves the alkylation of the hydroxylactone **50** with methyllithium.

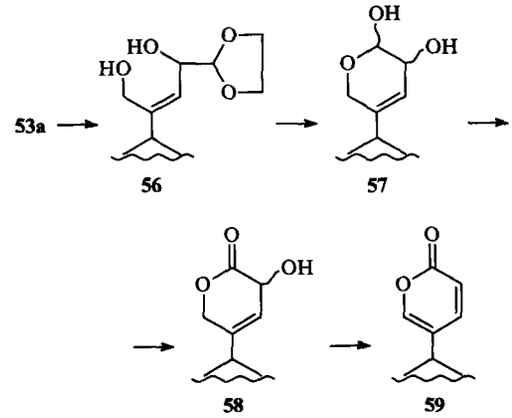
The method involving the alkylation of ketones by furans is suitable also for the synthesis of the lactone component of the bufalin and its α-, α′-, and β-isomers.[36–39] Thus alkylation of the ketone **46** by 3-lithiofurans **52a, b** or 2-lithiofuran **54** and subsequent transformations lead to the furylsteroids **53a, b** and **55** respectively (Scheme 10).

Scheme 10



The furylsteroid **53a** served as an intermediate in the synthesis of the pyrone fragment of bufalin[36,37] **59** and β-isobufalin[38,39] **63**. In the synthesis of bufalin, the furan **53a** was oxidised with oxygen in the presence of a sensitiser and the primary product—an endoperoxide—was cleaved with dimethyl sulfide to give an unstable ketoaldehyde. Without being isolated, the aldehyde was reduced with $NaBH_4$ to the hydroxyacetal **56**. Next the acetal was hydrolysed with hydrochloric acid, affording the six-membered lactol **57**, which was oxidised with silver carbonate on celite to the hydroxylactone **58**. The fragment **58** was converted into the lactone fragment of bufalin by refluxing its methanesulfonate with diazabicyclononene (Scheme 11).

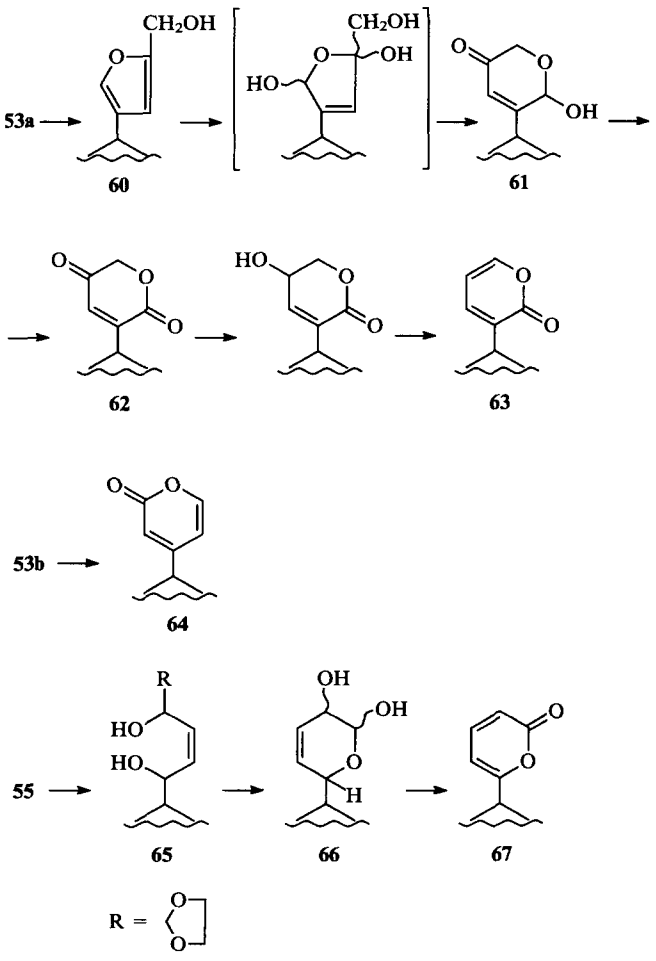
Scheme 11



In order to convert the furan ring of compound **53** into the lactone fragment of β-isobufalin, the acetal group was hydrolysed and the resulting aldehyde was reduced with $NaBH_4$ to the alcohol **60**. Oxidation of the alcohol **60** with *m*-chloroperbenzoic acid led to the ketolactol **61**, which was oxidised with chromic acid to the ketolactone **62** and the keto-group was then reduced selectively with zinc tetrahydroborate. The subsequent transformations into the pyrone ring of β-isobufalin were achieved via the methanesulfonate. A similar sequence of reactions in the case of the furan **53b** leads[38,39] to α-isobufalin **64**. In order to obtain α′-isobufalin

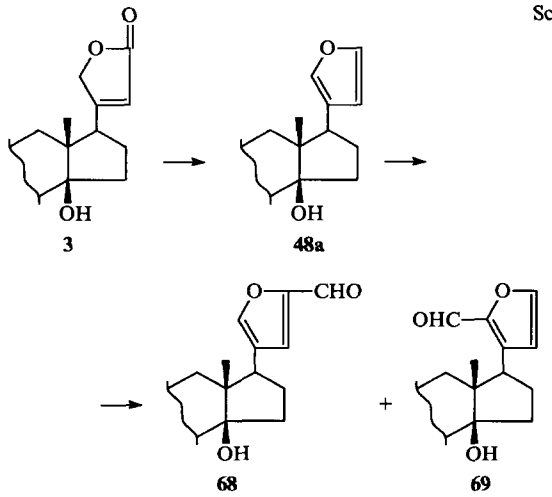
67, the furylsteroid **55** is oxidised with *N*-bromosuccinimide and the oxidation product is reduced with $NaBH_4$ to the diol **65**, the acetal group of which is hydrolysed to the lactol **66**, from which the lactone **67** is obtained in accordance with Scheme 12.

Scheme 12



Treatment of the lactone ring in compounds **3** with $LiAlH_4$ results in the formation[40] of the furan **48a**. This reaction has been used by Wiesner and coworkers[41,42] to synthesise bufalin and α- and β-isobufalins. Formylation of the furan **48a** gives rise to the aldehydes **68** and **69** (Scheme 13).

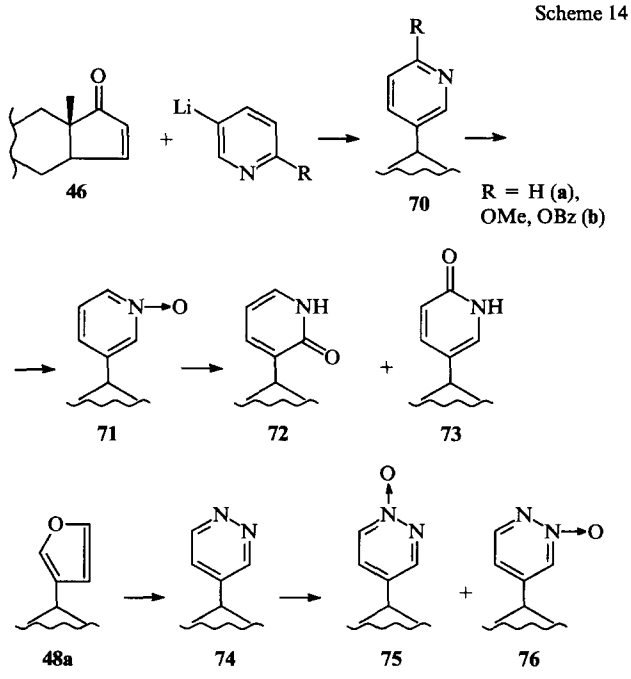
Scheme 13



The introduction of the acetal protective group into the aldehyde **68** leads to the furan **53a**, the subsequent transformations of which afford bufalin, while the reduction of the furans **68** and **69** with $NaBH_4$ affords the corresponding alcohols, from which α- and β-isobufalins were obtained.

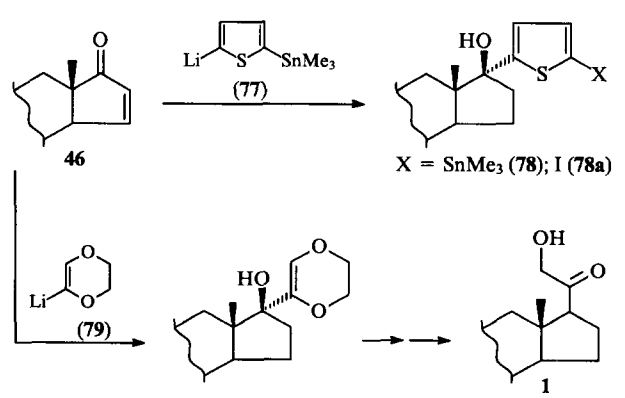
A series of aza-analogues of bufalin were obtained by alkylating the 17-ketosteroids **46** with 3-lithiopyridines. The transition from the pyridine to the pyridone ring was achieved by oxidising the pyridine **70a** with *m*-chloroperbenzoic acid to the *N*-oxide **71**, which afforded the pyridones **72** and **73** in equal proportions on refluxing in acetic anhydride and subsequent alkaline hydrolysis. In the case of compound **70b**, the pyridone **73** is formed as a result of the hydrogenolysis of the ether.[43-47] The reaction of the furan **48a** with *N*-bromosuccinimide and subsequent interaction of the oxidation product with hydrazine hydrate afford compound **74**, the treatment of which with *m*-chloroperbenzoic acid leads to a mixture of the *N*-oxides **75** and **76** in proportions of 3 : 2 (Scheme 14).[48,49]

Scheme 14



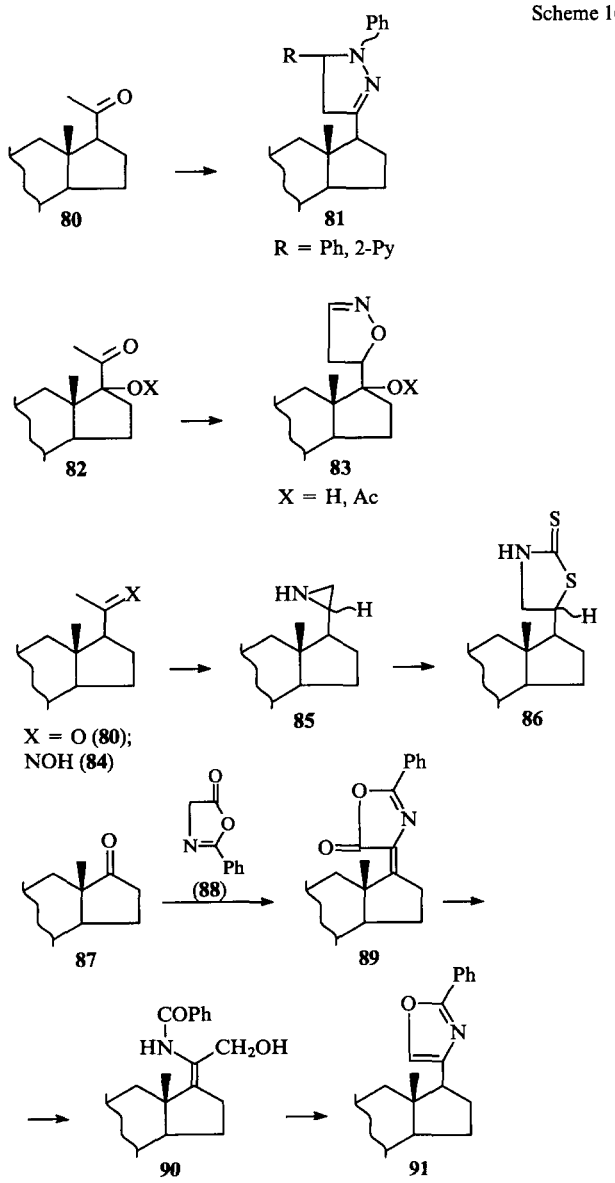
The alkylation of 17-ketosteroids by other heterocycles takes place just as readily. For example, the addition of the thiophene **77** gives rise to the product **78**, the ease of substitution of tin in which by iodine and other halogens makes it possible to obtain compounds with functional group substituents and to introduce radioactive isotopes.[50] Androstanes can be converted into pregnanes by reaction with the lithio-derivative **79** (Scheme 15)[51] (for a more detailed treatment, see Section V).

Scheme 15



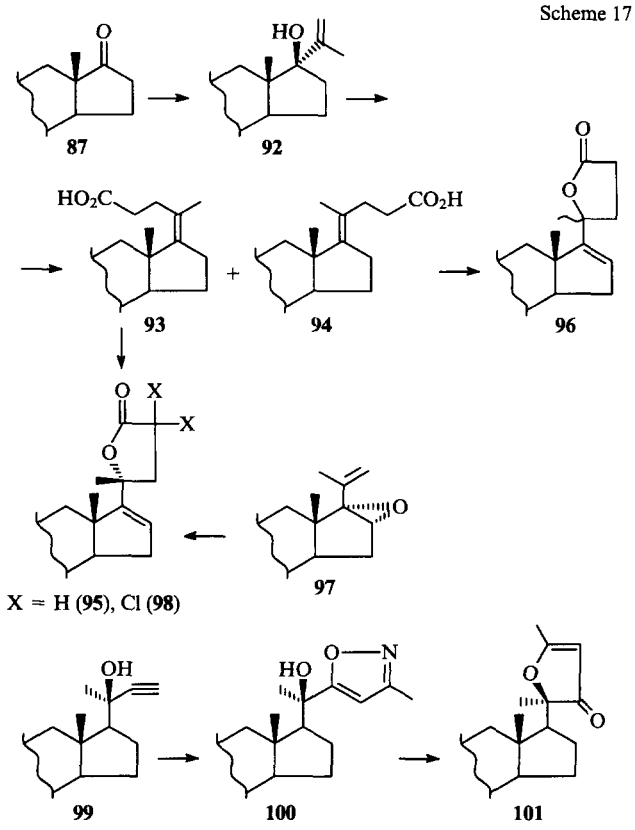
The synthetic possibilities of 20- and 17-ketosteroids for the construction of heterocycles containing nitrogen or sulfur are not limited to the examples described above. Thus the condensation of the ketosteroid **80** with benzaldehyde or 2-formylpyridine and subsequent treatment of the condensation product with phenylhydrazine afford the pyrazolines **81**.[52,53] When the ketol **82** or its acetate was refluxed in formamide in the presence of perchloric acid, the isoxazolines **83** were obtained.[54] The reduction of the oxime **84** with lithium tetrahydroaluminate afforded the aziridines **85**, the treatment of which with carbon disulfide leads to the thiazolidines **86**.[55] The condensation of the azalactone **88** with the ketone **87** affords the product **89** as a mixture of the (*Z*)- and (*E*)-isomers. The $TiCl_4$–pyridine system served as the catalyst in this reaction. Alkaline hydrolysis of compound **89** and subsequent reduction led to the synthesis of compound **90**, the hydrolysis of which with hydrochloric acid afforded the oxazole **91** (Scheme 16).[56]

Scheme 16



The application of a series of new reagents opens the way to the synthesis of rare compounds and compounds which are difficult to synthesise. Alkylation of the ketone **87** with isopropenyllithium gives rise to the allyl alcohol **92**, which, as a result of the Claisen rearrangement in the presence of ethyl orthoacetate, is converted into the acids **93** and **94** after separation and hydrolysis. Kosor and Bersz[57] carried out the lactonisation stage with chlorophenyl selenide in the presence of triethylamine, since the use of sulfuric acid led merely to the decomposition products of the steroid molecule. However, the lactone **95** was obtained from the acid **93** instead of the expected selenolactone (Scheme 17).

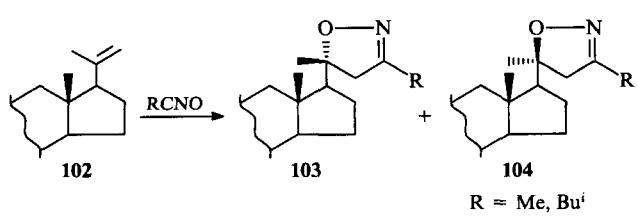
Scheme 17



A similar reaction occurs also with the acid **94**, which made it possible to obtain the isomeric lactone **96**. The dichloro-derivative **98** of the lactone **95** can be obtained stereoselectively[58] from the epoxyolefin **97** by the reaction of the latter with dichloroketene. The hydrogenation under acid conditions of the isoxazole **100**, obtained by the cycloaddition of the nitrile oxide to the acetylenic alcohol **99** led to high yields of the furanone **101**, which is otherwise difficult to obtain.[59]

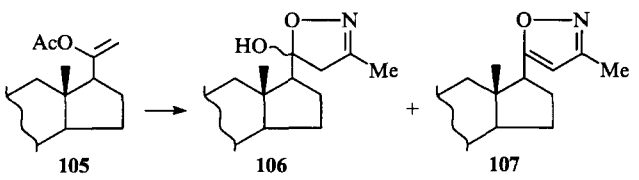
The previously unknown 17-isoxazolinylsteroids **103** and **104** have also been obtained[60] by the 1,3-dipolar cycloaddition of the corresponding nitrile oxides to the steroid 20(22)-olefins **102**. The addition of the nitrile oxides is regioselective and leads to the corresponding pairs of epimers at C(20) in proportions of 20*R*:20*S* = (2.5–3):1 (Scheme 18).

Scheme 18



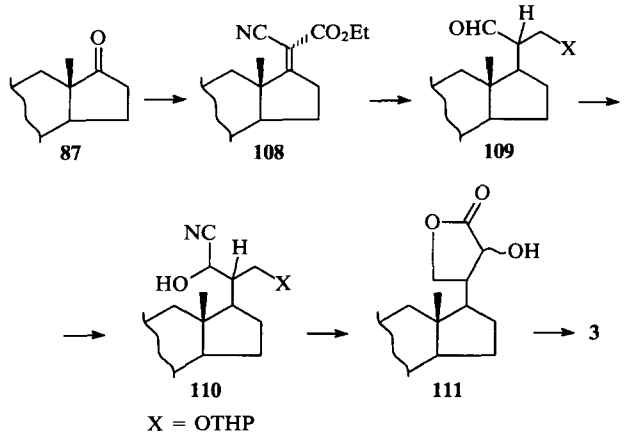
The use of the steroid enol ester **105** in the reaction with acetonitrile oxide leads to the formation of a mixture of a small amount of the isoxazoline **106** and its decomposition product—the isoxazole **107** (Scheme 19).[60]

Scheme 19



Other bifunctional compounds also serve, together with ketols, in the synthesis of cardiotonic steroids. Thus the product **108** of the condensation of the ketone **87** with cyanoacetic ester afforded the aldehyde **109** after the removal of the tetrahydropyranyl (THP) group (protecting the hydroxy-group) by treatment with $LiAlH_4$ in tetrahydrofuran (THF) and the reduction of the cyano-group with diisopropylaluminium hydride. This aldehyde is a common intermediate in the synthesis of the lactone ring in both cardenolides and bufadienolides. The γ-lactone was obtained from the cyanohydrin **110** by acid hydrolysis with simultaneous ring closure. The dehydration of the hydroxy-group in the resulting lactone **111** led to the required lactone **3** (Scheme 20).

Scheme 20

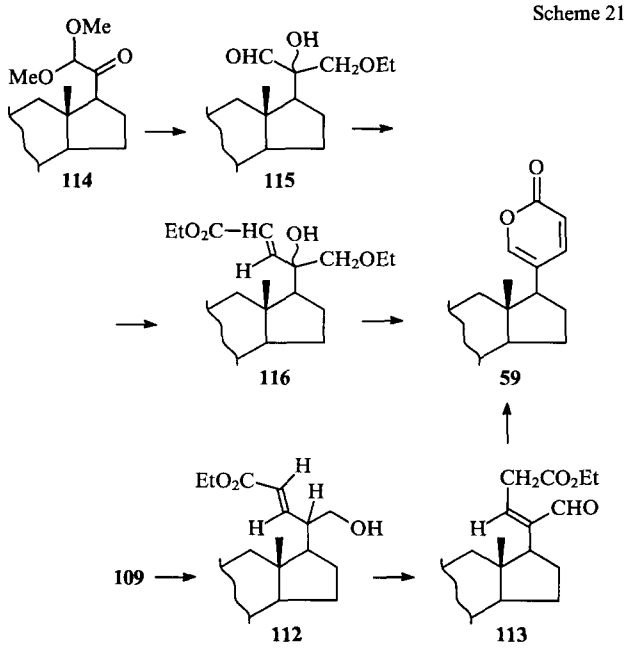


The δ-lactone **59** was formed by condensing the aldehyde **109** with the triethylphosphonoacetate ylide, the subsequent removal of the protective group, the oxidation of the alcohol **112** to the aldehyde **113** by pyridinium chlorochromate, and the cyclisation of the aldehyde to the lactone in the presence of toluene-*p*-sulfonic acid.[61,62] Engel and Dionne also used in an earlier study the aldehyde **113** in the synthesis of δ-pyrone **59**.[63]

The δ-lactone **59** can be obtained from the acetal of the ketoaldehyde **114**. The aldehyde **115** was synthesised by the reaction of the above acetal with the Grignard reagent, obtained from ethoxymagnesiochloromethane, and subsequent hydrolysis. The product **116** of its condensation with the triethylphosphonoacetate ylide afforded the required bufadienolide **59** after hydrolysis and lactonisation with iodine (Scheme 21).[64]

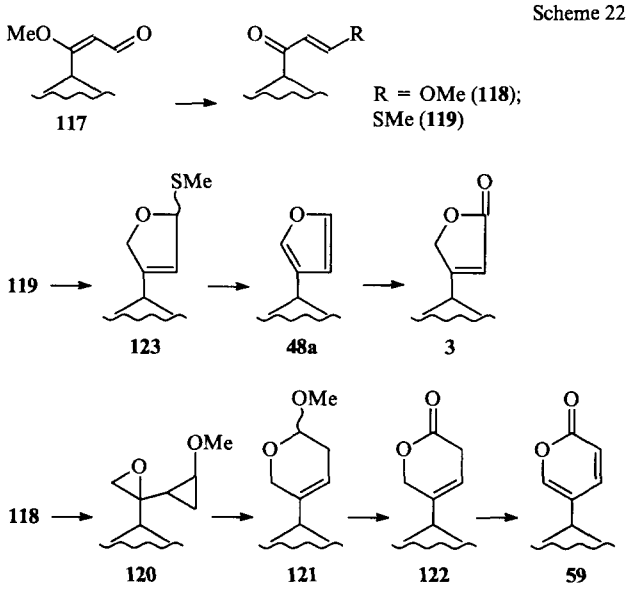
The enol ether **117** is a common intermediate (like compound **109**) in the synthesis of the γ- and δ-unsaturated lactones.[65,66] When it is heated in acidified methanol, compound **118** is obtained, while heating with methanethiol in benzene affords compound **119**. The reaction of the enol ether **118** with an excess of dimethylsulfonium methylide and subsequent treatment of the crude product with a methanol solution of HCl led to the dihydropyran **121**. After the hydrolysis of compound **121** and subsequent Jones oxidation, the lactone **122** was obtained. Its bromination and dehydrobromination by diazabicycloundecene led to the lactone **59**. The interaction of compound **119** with an equimolar amount of the methylide and subsequent desulfurisation led initially to the formation of the furan **48a** and then the lactone **3**. The formation of different compounds in the two fairly

Scheme 21



similar processes can be explained by the occurrence of different intermediates in these reactions. In the former case, the epoxide **120** is formed, its hydrolysis giving rise to the dihydropyran **121**, while in the latter case the intermediate is 2-methylthio-2,5-dihydrofuran **123** (Scheme 22).

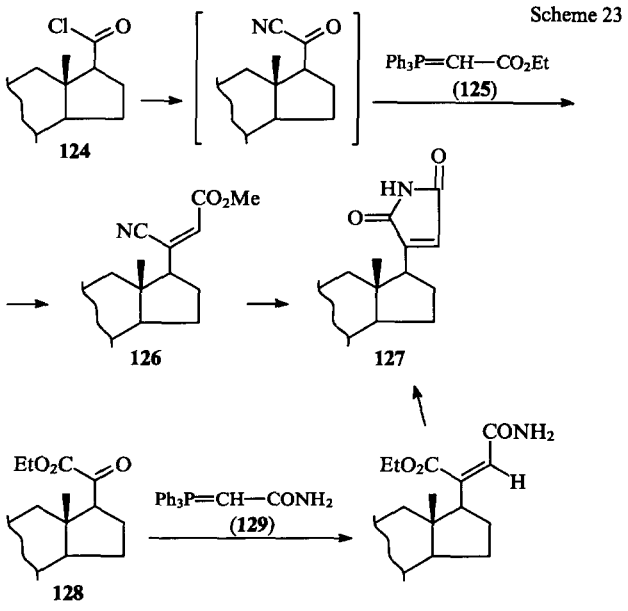
Scheme 22



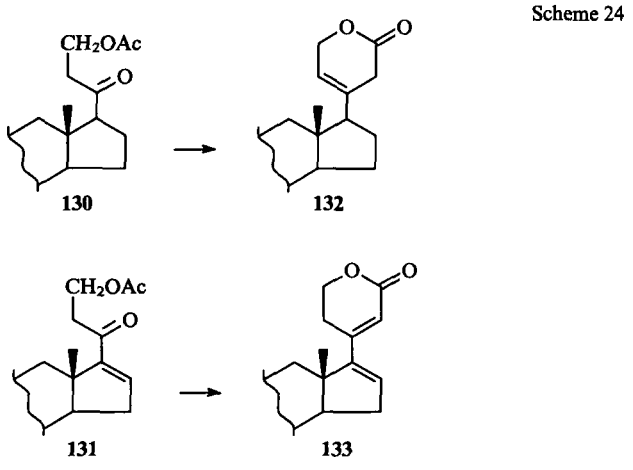
The cyanoacrylate **126**, obtained when the acid chloride **124** is treated with hydrogen cyanide in the presence of an excess of the ylide **125**, cyclises to the maleimide **127** on heating in a mixture of acetic acid, its anhydride, and sulfuric acid.[67] The maleimide **127** was synthesised in a higher yield from the ketoester **128** by condensing the latter with the ylide **129** and further cyclisation of the product (Scheme 23).[68]

An approach has been developed[69] to the synthesis of analogues of isobufadienolides from the ketoacetates **130** and **131**. Thus the lactone **132** has been obtained from the ketoacetate **130** under the conditions of the Reformatskii reaction with bromoacetic ester, while the ketoacetate **131** was converted under the same conditions into the conjugated lactone **133** (Scheme 24).

Scheme 23



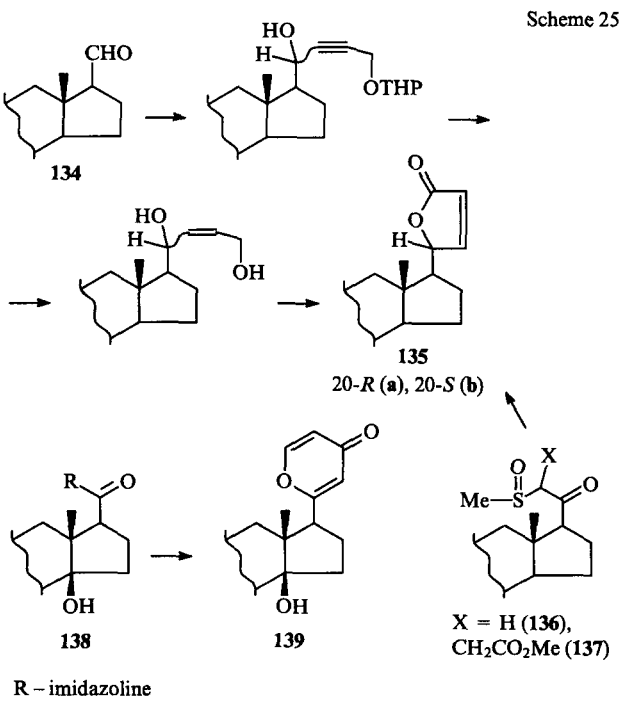
Scheme 24



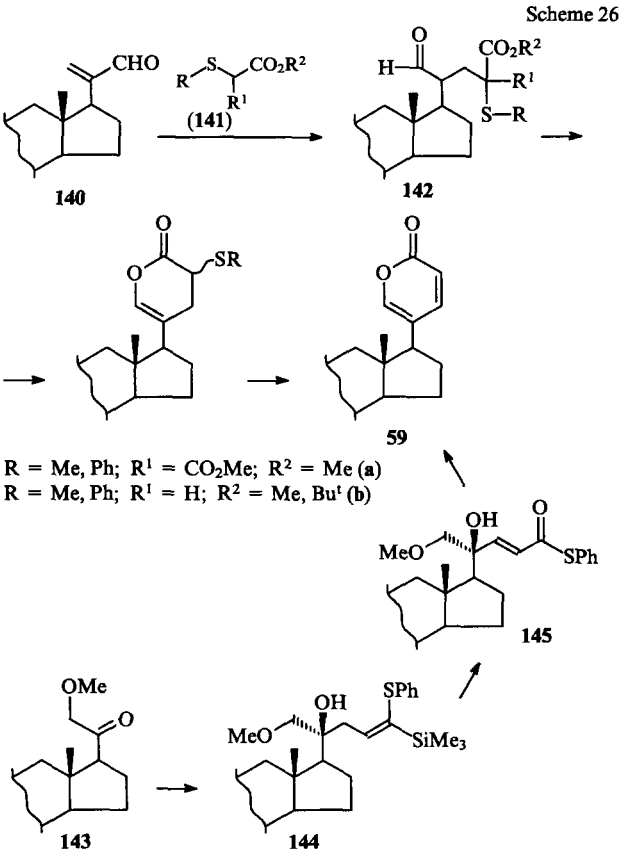
The isomeric lactones **135** have been obtained by alkylating the aldehyde **134** with acetylenes.[70] They had been synthesised previously[71] from bromoacetic ester and the ketosulfoxide **136** with subsequent reduction of compound **137** with $NaBH_4$. The addition of the potassium enolate derived from 4-methoxybut-3-en-2-one to the imidazoline derivative **138** led to the pyrone fragment of γ-isobufalin **139** (Scheme 25).[72]

The addition of sulfur-stabilised alkyl anions to carbonyl compounds proved to be effective for the synthesis of δ-unsaturated ketones.[73–76] Thus the Michael condensation of the aldehyde **140** with anions based on compounds **141** affords the 1,4-adducts **142**, the cyclisation and desulfurisation of which leads to the lactone fragment of bufalin **59**.[73–75] An interesting example of the formation of the δ-lactone from the ketoester **143** has been proposed.[76] The authors chose 1-phenylthio-1-trimethylsilyl-prop-2-ene as the equivalent of the homoenolate anion necessary for the introduction of three carbon atoms and capable of subsequent cyclisation to the pyrone ring. The addition of the propene to the ketoester **143** in the presence of butyllithium led to the formation of compound **144**. The oxidative desilylation reaction was achieved by treating the lithio-dianion of compound **144** with oxygen in solution in THF containing hexamethylphosphoramide. This resulted in the formation of the thioester **145** in 59% yield. Its cyclisation to the pyrone was achieved by treatment with hydrogen bromide in boiling acetonitrile (Scheme 26).[76]

Scheme 25



Scheme 26



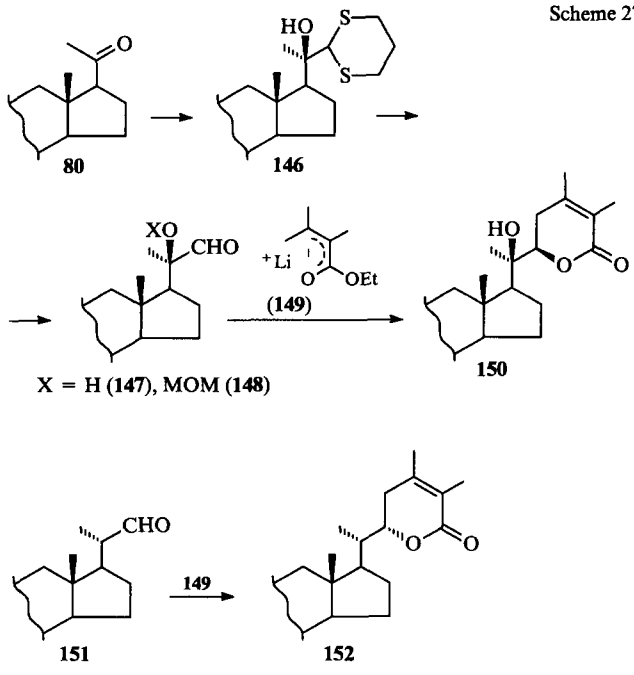
III. Synthesis of steroids containing a heterocycle in the C(20) position

This section is devoted to the methods of synthesis of the side chains of withanolides and jaborosalactones, which are homologues of cardenolides, i.e. compounds having a heterocycle in the C(20) position in the steroid molecule.

There are two main approaches to the synthesis of the lactone fragment of withanolides and jaborosalactones — via the addition of stabilised lithio-enolates or lithiodithianes and via the addition of lithiofurans and transformation of the latter.

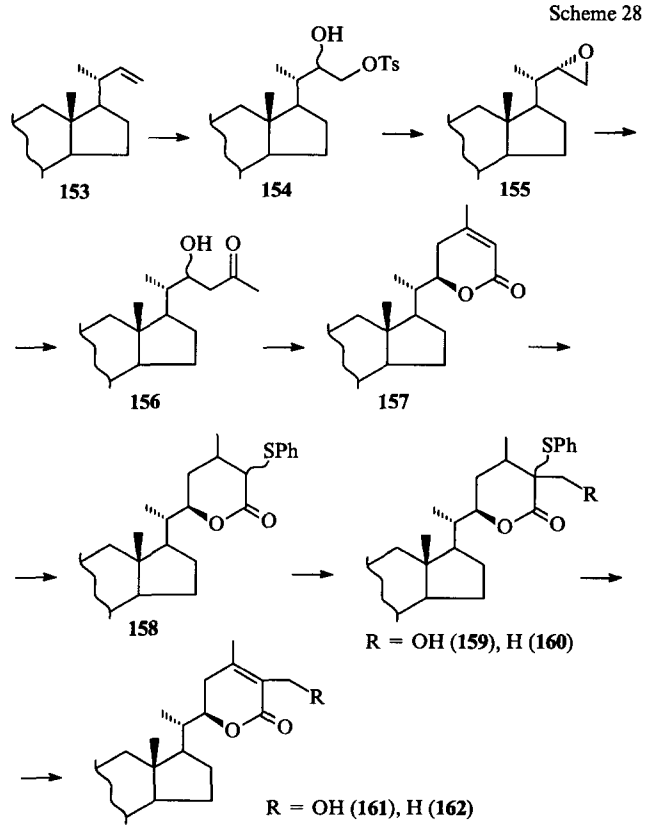
The aldehyde **147**, which is the starting material of the synthesis of the lactone fragment of the withanolide D, was synthesised by adding the anion of 1,3-dithiane to the ketone **80** with subsequent hydrolysis of the hydroxythioacetal **146**. After the protection of the hydroxy-group in the form of the methoxymethyl ester (MOM) **148** and the addition of the lithio-enolate **149**, formed from α,β-dimethylcrotonate and lithium diisopropylamide, the required lactone **150** was obtained.[77,78] It is of interest that the addition of the enolate **149** to the aldehyde **151** afforded the lactone **152** with the stereochemical configuration at C(22) opposite to that in 27-deoxywithaferin A, the attempts to invert the configuration proving unsuccessful (Scheme 27).[78]

Scheme 27



Since the addition of the enolate **149** to the aldehyde **151** does not ensure the required stereochemical configuration of the C(22) centre, another sequence of reactions, permitting the introduction of the hydroxy-group with the required configuration, was selected for the construction of the side chain in withaferin A, 27-deoxywithaferin A, and jaborosalactones. For this purpose, the olefin **153** was treated with OsO_4 and the reaction product was toluene-*p*-sulfonated, which led to a mixture of the isomeric toluene-*p*-sulfonates **154** in proportions of 5 : 1. The main isomer was converted quantitatively into the chiral epoxide **155**. The regiospecific alkylation of the epoxide with the 2-methyl-1,3 dithiane anion followed by the elimination of the thioketal ensured the necessary (22*R*)-configuration in the ketol **156**. Cyclisation to the lactone **157** was achieved by the McMorris method.[79] After the reduction of the double bond and treatment with diphenyldisulfide, the sulfide was obtained as a mixture of isomers with respect to C(24) (3 : 2). In order to obtain the side chain of jaborosalactone and withaferin A, the lithio-anion of the sulfide was treated[80,81] with monomeric formaldehyde, which afforded compound **159**, while for the synthesis of the side chain of 27-deoxywithaferin A the lithio-anion was treated with methyl iodide,[80–82] which afforded the methyl derivative **160**. Next, the sulfides were oxidised to the sulfoxides in both cases and after desulfurisation the required lactones **161** and **162** were obtained (Scheme 28).

Scheme 28



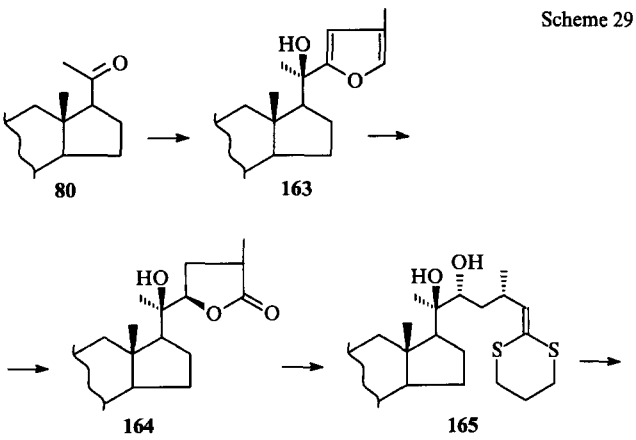
The synthesis of the side chain in withanolides by the addition of 2-lithio-4-methylfuran to the ketone **80** with formation of the furylsteroid **163** has been described.[83] After two-stage oxidation (with *m*-chloroperbenzoic acid and pyridinium chlorochromate) and hydrogenation over platinum dioxide, the lactone **164** was obtained. Its reduction with diisobutylaluminium hydride afforded a lactol, the treatment of which with 2-lithio-2-trimethylsilyldithiane resulted in the formation of the thioacetal **165**. The lactone **166**, obtained from the thioacetal after cyclisation in the presence of camphorsulfonic acid, was alkylated with methyl iodide in the presence of lithium isopropylcyclohexylamide. The lactone **167** was successfully converted into the sulfide, oxidised to the sulfoxide, and desulfurised. However, together with the required lactone **150**, the *exo*-product **168** was obtained in proportions of 1 : 4.2. The isomerisation of the *exo*-product to the *endo*-product was achieved on heating the lactone **168** in a sealed tube with rhodium trichloride in dry ethanol at 100 °C (Scheme 29).

The stereoselective epoxidation of the unsaturated ketones **169** with alkaline hydrogen peroxide proved to be an extremely useful reaction for the synthesis of 22,26-lactones.[79] Thus the ketol **171** was obtained by reducing the epoxide **170** with aluminium amalgam and was used as an intermediate in the synthesis of 23-deoxyantheridiol. The ketol **171** was converted into the bromoacetic ester **172** and the latter afforded the phosphonate **173** on heating with triethyl phosphite as a result of the Arbuzov reaction. The intermolecular Horner–Emmons condensation led to the required δ-lactone **174** (Scheme 30).

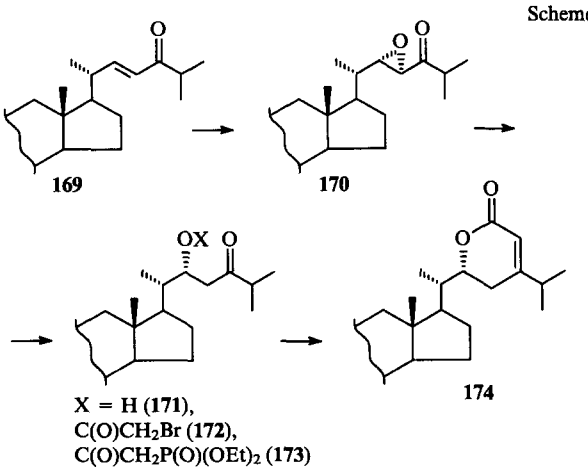
A compound with the side chain of withanolides was obtained from the ketone **175** by employing the sequence of reactions described above (Scheme 31).[84]

The isoxazoline **176** can serve as an intermediate in the formation of the side chain of 23-deoxyantheridiol.[85] Thus the 22-acetoxy-24-ketone **178**, formed after the acetylation of the β-ketol **177** (the product of the cleavage of the isoxazoline **176**) is converted by the Reformatskii reaction, followed by refluxing in acetic anhydride, into the δ-lactone **174** (Scheme 32).

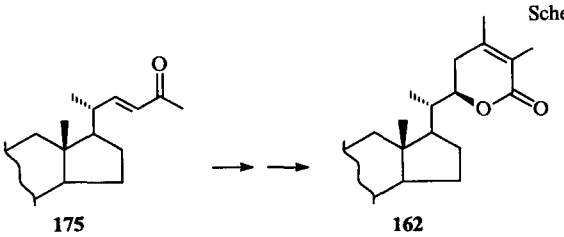
Scheme 29



Scheme 30

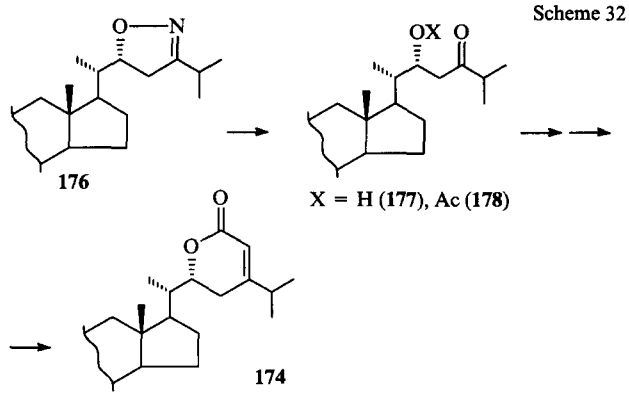


Scheme 31



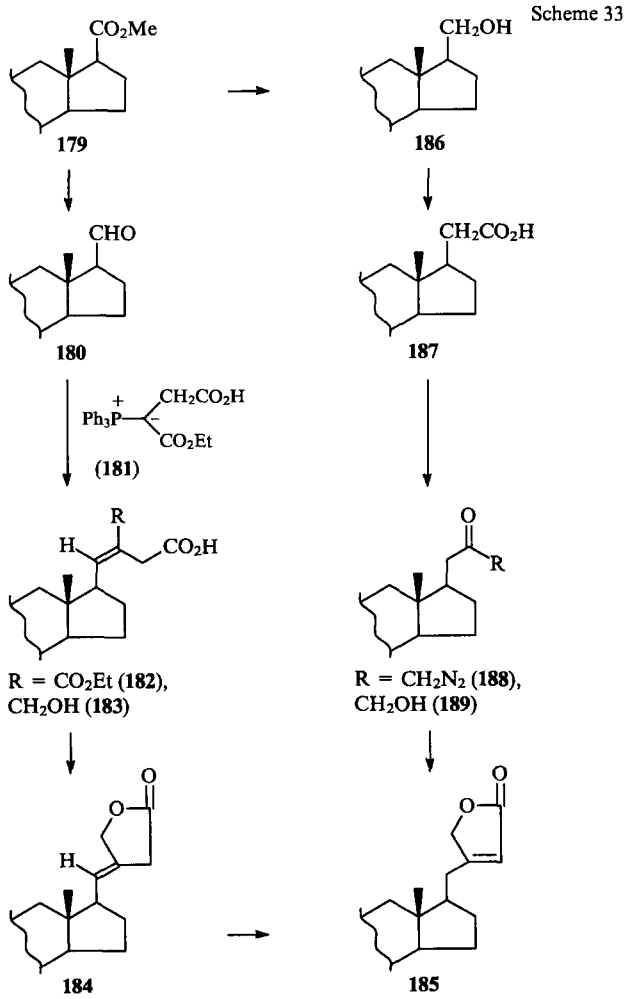
The synthesis of homologues of cardiotonic steroids was based on the approaches described in the previous section. The key feature of their synthesis is the stage in which the chain is lengthened by a CH_2 group. Thus the aldehyde **180**, obtained by reducing the ester **179**, was used[86] to synthesise the cardenolide homologue **185**. The lactone fragment was introduced by means

Scheme 32



of the Witting reagent **181** obtained from triphenylphosphine and maleic anhydride. The product of the addition of this reagent to the aldehyde **180** — the half-ester **182** — was reduced with sodium diethylaluminium hydride to the alcohol **183**, which cyclised to the lactone **184** on heating in acetic anhydride. The shift of the double bond was achieved by treating the lactone **184** with alkali-activated alumina (Scheme 33).

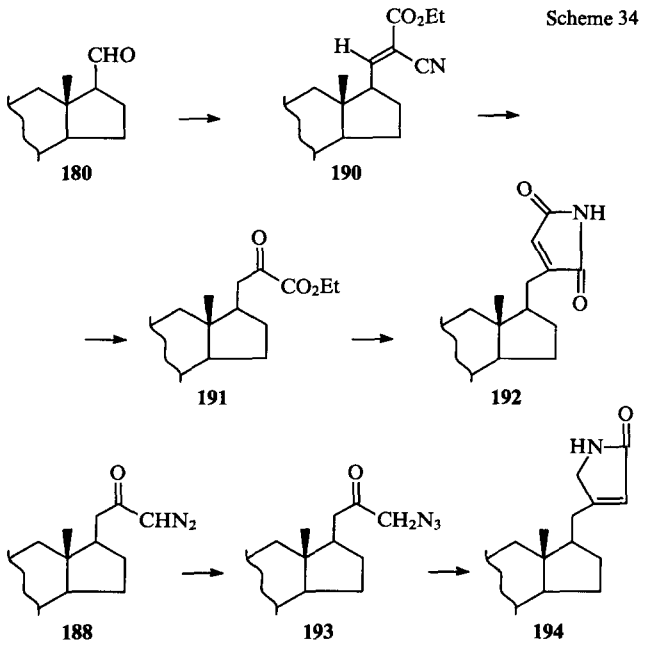
Scheme 33



The unsaturated lactone **185** had been synthesised previously from the alcohol **186**, which was converted[87] via the toluene-*p*-sulfonate into a nitrile and, after hydrolysis, into the acid **187**. Treatment of the acid by the Arndt–Eistert method afforded the diazoketone **188**, which was converted into the hydroxyketone **189** and further into the lactone **185** using the method described by Fritsch et al.[11]

The approaches described have been applied in the synthesis of homologues of steroid compounds containing various heterocycles (maleimide, lactams, and thiazoles) in the side chain. Thus the ketoester **191** was obtained from the aldehyde **180** via the product of its condensation with the cyanoacetic ester **190**.[68] Compound **191** was transformed into the maleimide **192**. The lactam **194** was synthesised[88] from the diazoketone **188** by treatment with toluene-*p*-sulfonic acid, substitution of the toluene-*p*-sulfonate group by the azide group, and further transformation of the azide **193** (Scheme 34).[17,18]

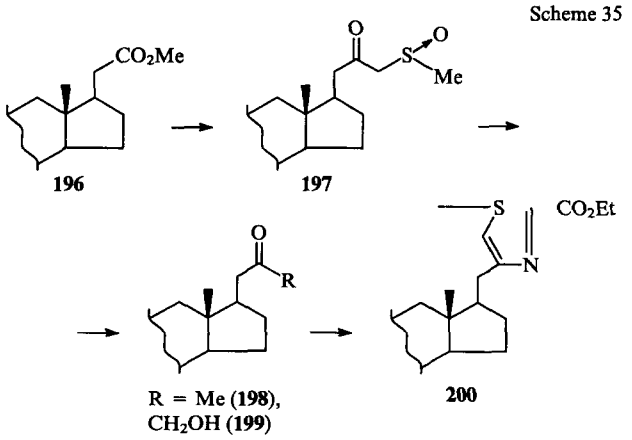
Scheme 34



180 **190** **191** **192** **188** **193** **194**

The methyl ester **196** served as the starting compound in the synthesis[89] of the thiazole **200**. It was converted into the ketone **198** by reducing with aluminium amalgam the ketosulfoxide **197** obtained from the ester **196** by treating the latter with dimsylsodium. Next the ketone **198** was oxidised via the silyl ether of the enol to the ketol **199**, which was converted in the usual way into an α-bromoketone. The addition of thioxamate to the latter by the Hantzch method afforded the thiazole **200** (Scheme 35).

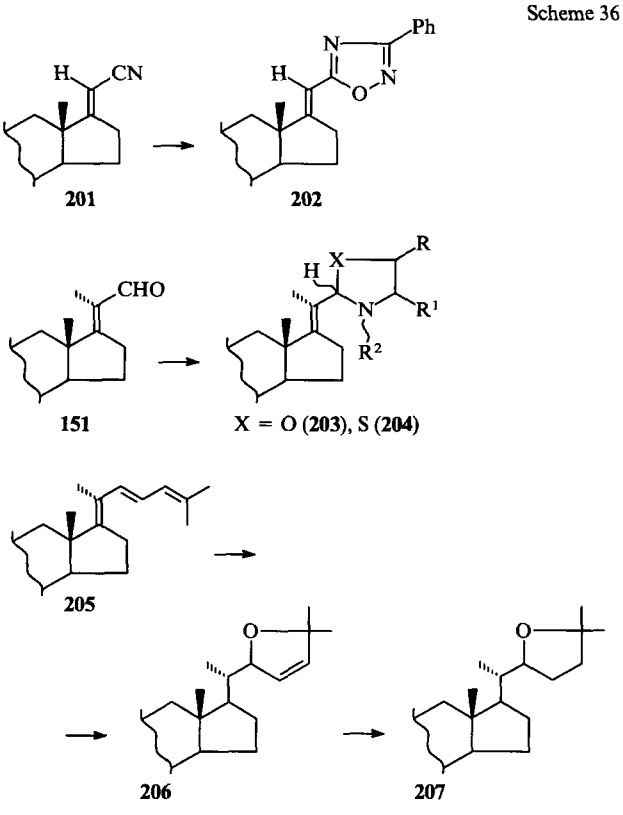
Scheme 35



196 **197** R = Me (**198**), CH_2OH (**199**) **200**

Apart from the approaches described above, steroids with a heterocycle in the C(20) position can be obtained by the dipolar cycloaddition of nitrile oxides, by the condensation of amino-alcohols, and by the hydroxymercuration of dienes. Thus the addition of benzonitrile oxide to the nitrile **201** led[90] to the formation of the oxadiazole **202**, while the condensation of amino-alcohols or aminothiols with the aldehyde **151** led to the formation of the oxazolidines **203** or the thiazolidines **204** respectively.[91] When an attempt was made to obtain the 22,25-dihydroxy-derivative from the diene **205** under hydroxymercuration conditions, the product **206** was isolated. Its reduction over $Pd/BaSO_4$ led to the formation[92] of the tetrahydrofuryl derivative **207** (Scheme 36).

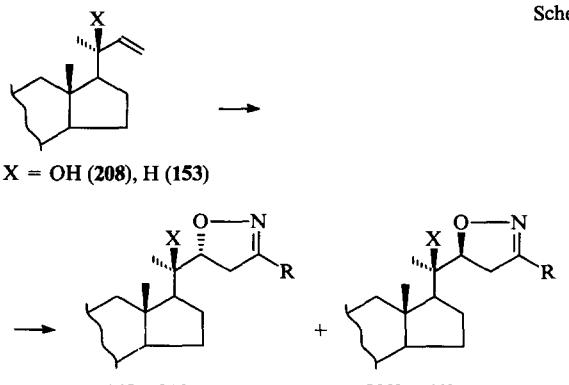
Scheme 36



201 **202** **151** X = O (**203**), S (**204**) **205** **206** **207**

The synthesis of the new heterocyclic steroids **209** and **210** was achieved by the 1,3-dipolar cycloaddition of a series of nitrile oxides to the Δ^{22}-steroids **208** and **153** respectively.[85,93-97] The cycloaddition takes place stereoselectively[93] and in the case of allyl alcohols the epimer ratio 22*S*:22*R* reaches 6:1. The yield of the adducts depends on the nature of the substituents R in the nitrile oxide, diminishing when nitrile oxides with functional group substituents are used (Scheme 37).

Scheme 37



X = OH (**208**), H (**153**)

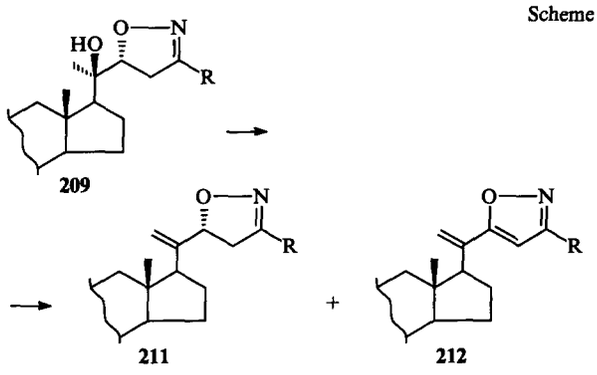
209a, 210a **209b, 210b**

X = OH; R = Me, Pr^i, CO_2Et (**209**); X = H; R = Pr^i (**210**)

The observation[98] of the dehydrogenation of the steroid isoxazolines **209**, which makes it possible to achieve their transition to the corresponding isoxazoles **212**, is interesting. In the study of the dehydration reaction on treatment with thionyl chloride in chloroform, the formation of the isoxazole **212** as a side product together with the main product—the olefin **211**—was

established. The replacement of chloroform by pyridine or DMF led to the preferential formation of compounds **212** (Scheme 38).

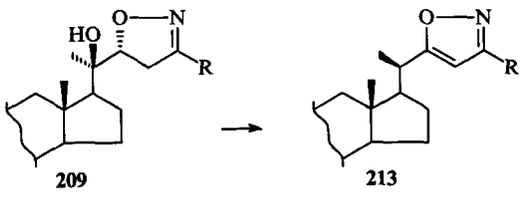
Scheme 38



R = Me, Pr^i, CO_2Et

A novel synthesis of 20-isosteroid isoxazoles has been proposed.[96] It consists in the transformation of the isoxazoline **209** into the isoxazole **213** with the simultaneous formation of a chiral centre at C(20). It was found that treatment of the isoxazoline **209** with trifluoroacetic acid in boiling nitromethane in the presence of lithium perchlorate affords only one C(20) isomer of compound **213** in a high yield (Scheme 39).

Scheme 39



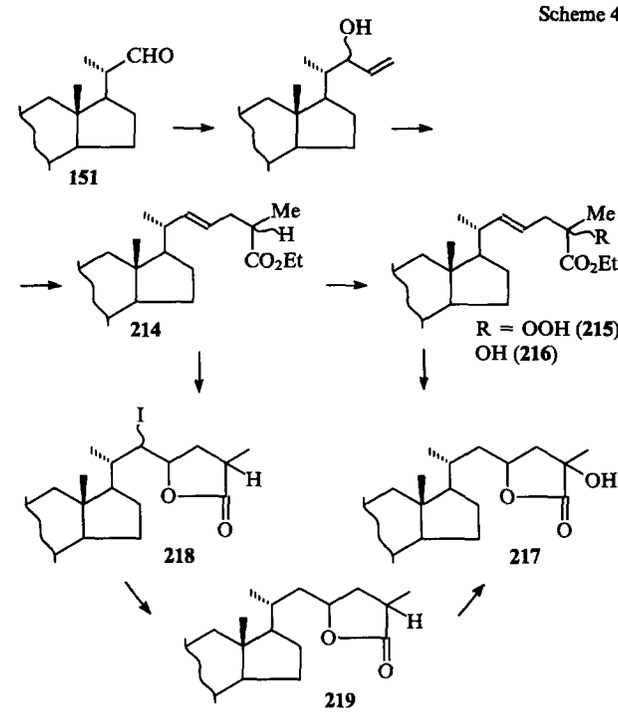
R = Me, Pr^i, CO_2Et

IV. Synthesis of steroids containing a heterocycle in the C(22) position

The approaches to the synthesis of the 25-hydroxycholecalciferol-26,23-lactone — the only known metabolite of vitamin D_3 having a lactone ring in the side chain — and several other compounds with the heterocycle in the C(22) position are considered in this section.

A new metabolite of vitamin D, having a 26,23-lactone ring, was isolated in 1979, but the stereochemical configuration of the C(23) and C(25) centres was not established. Synthetic chemists are therefore faced with the problem of not only obtaining this compound by chemical means but also of establishing the stereochemical configuration of the C(25) and C(23) centres. For this purpose, all four diastereoisomers were synthesised. One of the first syntheses of the side chain was achieved as follows. The aldehyde **151** was alkylated with vinylmagnesium bromide and the resulting mixture of isomers was used in the Claisen reaction with an excess of triethyl orthopropionate. This resulted in the formation of the ester **214**, which was converted into the enolate and oxidised at −78 °C with molecular oxygen. The hydroperoxide **215** formed in this reaction was reduced with triethyl phosphite, which afforded the α-hydroxyester **216**. After hydrolysis, the mixture of diastereoisomers was treated with iodine and potassium iodide under basic conditions, which led to the formation of a mixture of iodolactones. After their reduction with tributyltin hydride and separation, four diastereoisomers of compound **217** were obtained. However, the authors attributed[99] to the natural lactone the erroneous (23*R*,25*S*)-configuration (Scheme 40).

Scheme 40



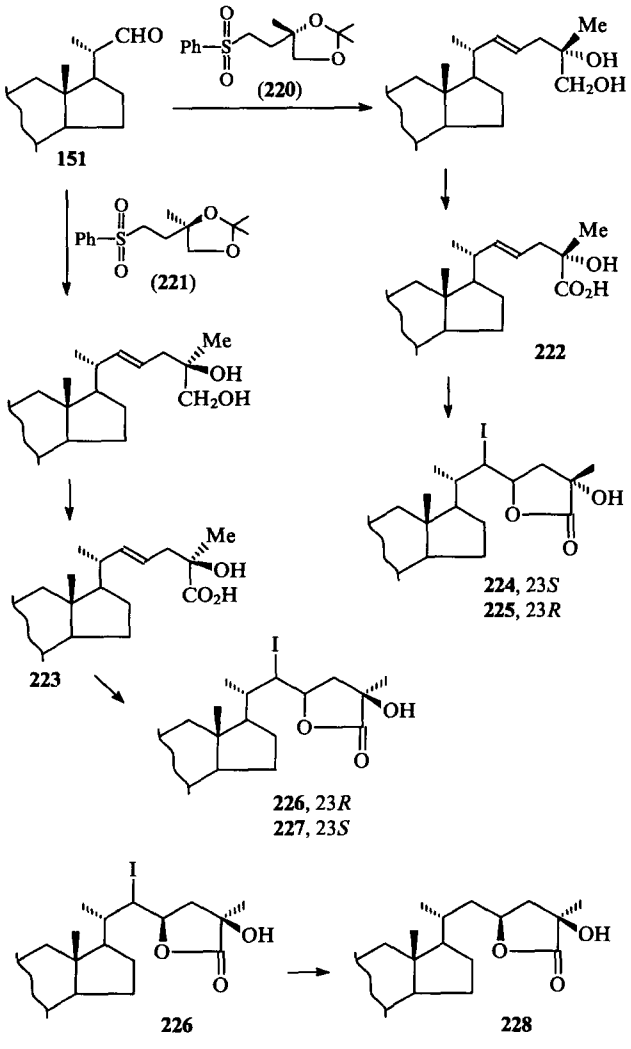
This procedure largely repeats the earlier synthesis,[100] in which the 25-hydroxy-group was introduced, in contrast to the method described above, in the last stage (after the reduction of the iodolactone **218** and the oxidation of the lactone enolate **219** by the MoO_3–pyridine–hexamethylphosphoramide complex). The authors determined the configuration of only the C(23) centre as 23*R*.

Several studies have been devoted to the determination of the structure of the above compound.[101–103] In order to avoid difficulties in the separation of the four diastereoisomers and to investigate in detail the iodolactonisation process, the stereoselective synthesis of the α-hydroxyacids **222** and **223** was carried out. The sulfones **220** and **221**, obtained respectively from (*S*)-(+)-citromalic acid (2-methylmalic acid)[101] and (*R*)-(−)-citromalic acid were used as the reagent with the required chirality.[102] The addition of these sulfones to the aldehyde **151** with subsequent desulfurisation, hydrolysis, and two-stage oxidation of the alcohol to the acid under mild conditions led to the hydroxyacids **222** and **223**. The iodolactonisation (iodine, MeCN) and reduction of the iodolactones led to the formation of two diastereoisomers of compounds **224**–**227** in each case (Scheme 41).

In their study of the iodolactonisation process[103] under various conditions, the authors observed that the selectivity of this reaction depends on stereochemical configurations at C(25) and the reaction conditions. The product **226** obtained by iodolactonisation under basic conditions afforded the lactone **228** in 56% yield relative to the acid **223** after reduction with tributyltin hydride. After the appropriate transformations of the cyclic component of this compound, its parameters proved to be identical with those of the natural metabolite. Thus the configuration of the C(23) and C(25) centres of the vitamin D metabolite was determined as 23*S*, 25*R*.

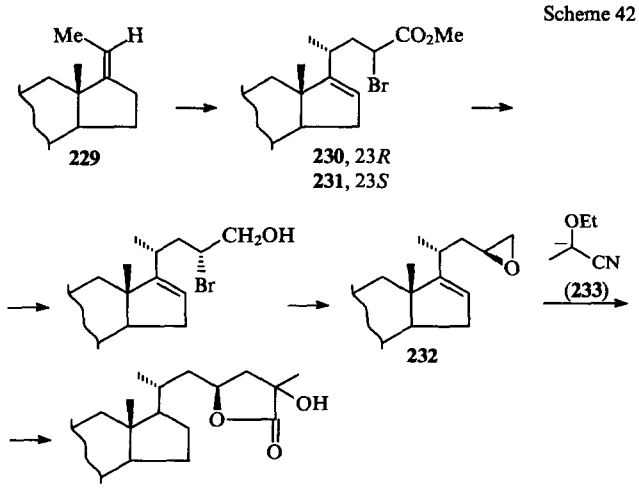
Yet another example of the synthesis of the side chain of the calciferol lactone, based on the introduction of chirality initially in the C(23) position, has been proposed.[104] Addition of α-bromoacrylate to the olefin **229** in the presence of ethylaluminium dichloride afforded a mixture of bromo-derivatives in the proportions **230**:**231** = 13:87. The required diastereoisomer **230** was isolated from the mixture produced by reaction with lithium bromide in acetone. After four repetitions of this procedure, the bromo-derivative **230** was obtained from the

Scheme 41



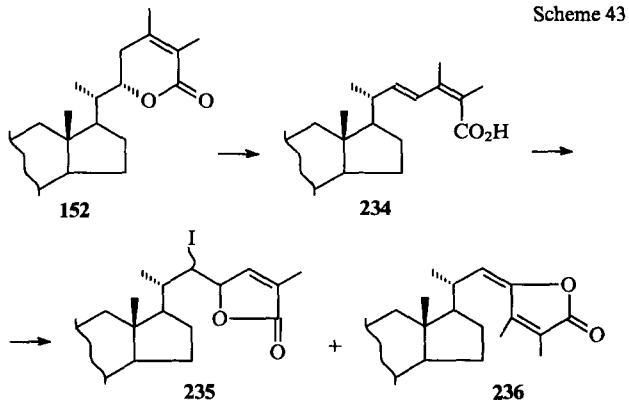
olefin in 63% yield. The ethoxycarbonyl group in compound **230** was reduced to the alcoholic group. The resulting bromohydrin afforded the epoxide **232** after treatment with a base. The missing three carbon atoms were introduced into the molecule by the addition of the anion **233** obtained from acetaldehyde cyanohydrin. After the hydrolysis of the intermediate, a 1 : 1 mixture of the lactones was isolated (Scheme 42).

Scheme 42



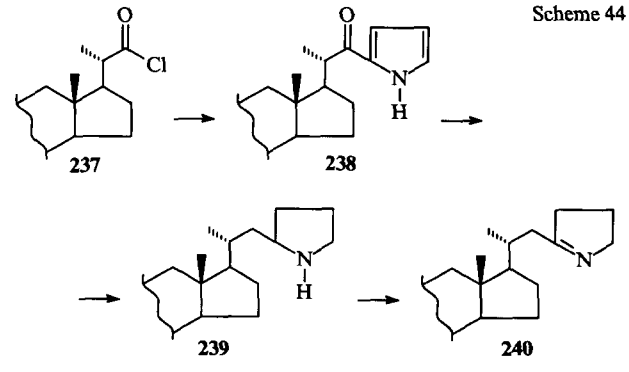
Steroids having a heterocyclic substituent in the C(22) position have not so far attracted much attention from organic chemists and syntheses of compounds of this kind are fairly rare. Thus the lactones **235** and **236**, which are structurally similar to calciferol lactone, have been isolated[78] after treating with iodine and selenium compounds the acid **234** obtained by hydrolysing compound **152** (Scheme 43).

Scheme 43



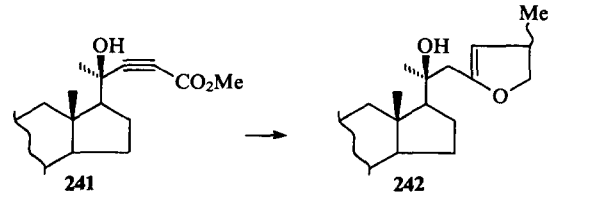
Compound **240**, which is related to steroid alkaloids, was synthesised in accordance with Scheme 44.[105] The acid chloride **237** was treated with pyrrolylmagnesium bromide and the adduct **238** was hydrogenated over Raney nickel, which led to the reduction of the pyrrole ring and the removal of the carbonyl group. The resulting stereoisomeric mixture of the pyrrolidines **239** was converted by reaction with *N*-bromosuccinimide into *N*-chloroamines, which afforded the pyrroline **240** after alkaline treatment.

Scheme 44



The dihydrofuran derivative **242**, the structure of the side chain of which is similar (according to the authors) to that in shidasterone, was obtained by the reaction of methyl acetylenecarboxylate **241** with methylmagnesium iodide (Scheme 45).[106]

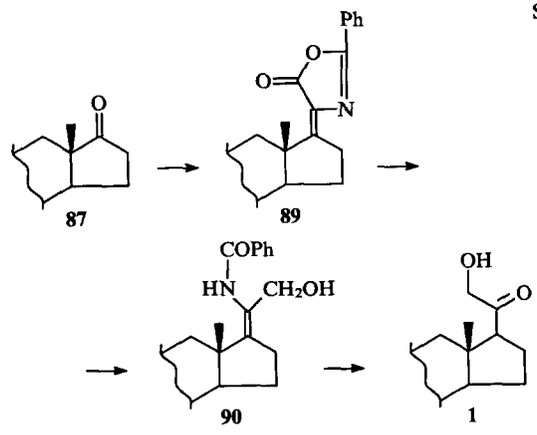
Scheme 45



V. Syntheses of the side chains of steroids including the transformation of heterocyclic structures

The synthetic possibilities of heterocycles for the construction of the side chains of steroids have not so far been employed in due measure. The only heterocycles which have found fairly extensive applications in the synthesis are probably furan derivatives. Nevertheless heterocyclic structures are attractive because of their fairly ready transformation into an open chain, which has stimulated interest in these compounds. This section deals with the syntheses of compounds with the side chains of the natural corticoids, ecdysones, brassinosteroids, vitamin D metabolites, etc. with participation of heterocyclic intermediates. The role of these intermediates is associated with the utilisation of the latent functionality of the heterocycle, which makes it possible to introduce the necessary substituents into definite positions, and also with the possibility of the stereocontrol of the products by virtue of the different accessibility of different sides of the heterocycle to the reagent. For example, the transformation of the heterocyclic derivatives **89** and **243**, obtained from the ketone **87**, makes it possible to form the side chain of corticosteroids.[51,56] Thus treatment of the product of alkaline hydrolysis with acetic acid and subsequent reduction of the heterocycle **89** via compound **90** lead to the formation of 21-hydroxyprogesterone **1** (Scheme 46).[56]

Scheme 46

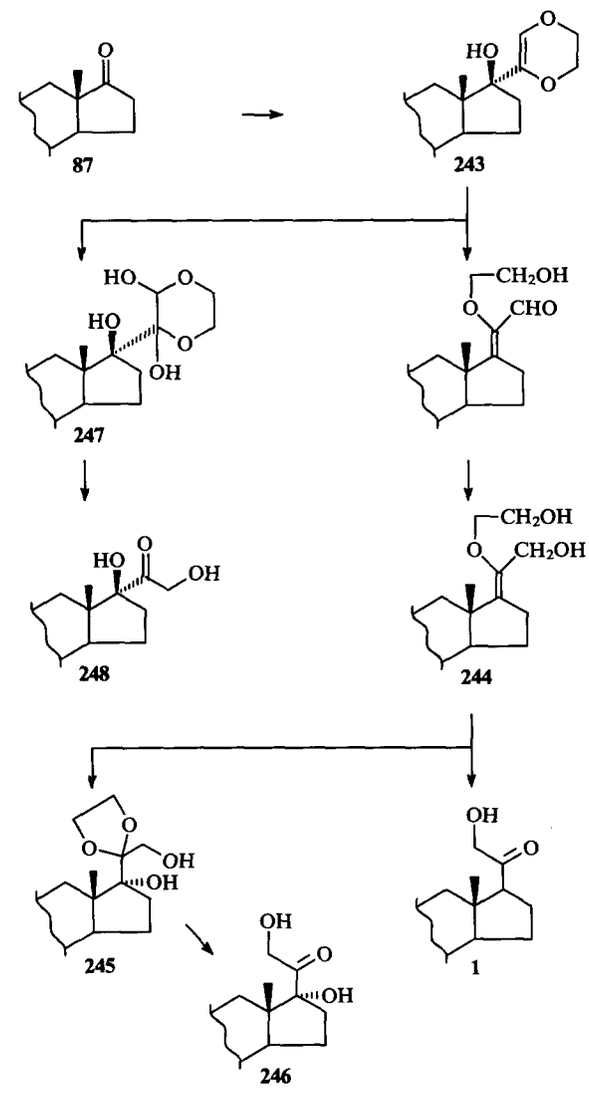


The cleavage of the heterocycle in compound **243** by various methods makes it possible to achieve the transition to a whole series of derivatives.[51] The acid-catalysed allyl rearrangement of compound **243** under very mild conditions (SiO_2, 5% oxalic acid) leads to the enol ether of an α-ketoaldehyde. Its reduction with $LiAlH_4$ and the subsequent hydrolysis of the ethyl ether afford the ketone **1**. Oxidation with *m*-chloroperbenzoic acid of the reduction product **244** led to the formation of the ketal **245** (via intramolecular cyclisation which followed the opening of the oxiran ring), the acid hydrolysis of which led to the ketodiol **246** with the natural orientation of the side chain. The authors also obtained the isomer of this compound with the 17α-configuration from the dioxene **243** (Scheme 47).

For this purpose, compound **243** was oxidised with *m*-chloroperbenzoic acid in methanol. The oxidation reaction occurred regioselectively at the electron-unsaturated C=C bond and led to the hemiacetals **247** in the form of a mixture of isomers with respect to C(20) and C(21). After their reduction with $NaBH_4$ and hydrolysis, the ketodiol **246** was obtained.

Barton and coworkers[107] developed a convenient and effective method for the conversion of cholic acids into pregnanes via oxazolines. The authors chose boric acid as the catalyst. Boric acid can react with cholic acid and the aminoalcohol, affording an intermediate of type **249** with an activated carbonyl group. Its subsequent reactions can lead to oxazolines. Using this method, the oxazoline **251** was obtained from the acid **250** in 95% yield.

Scheme 47

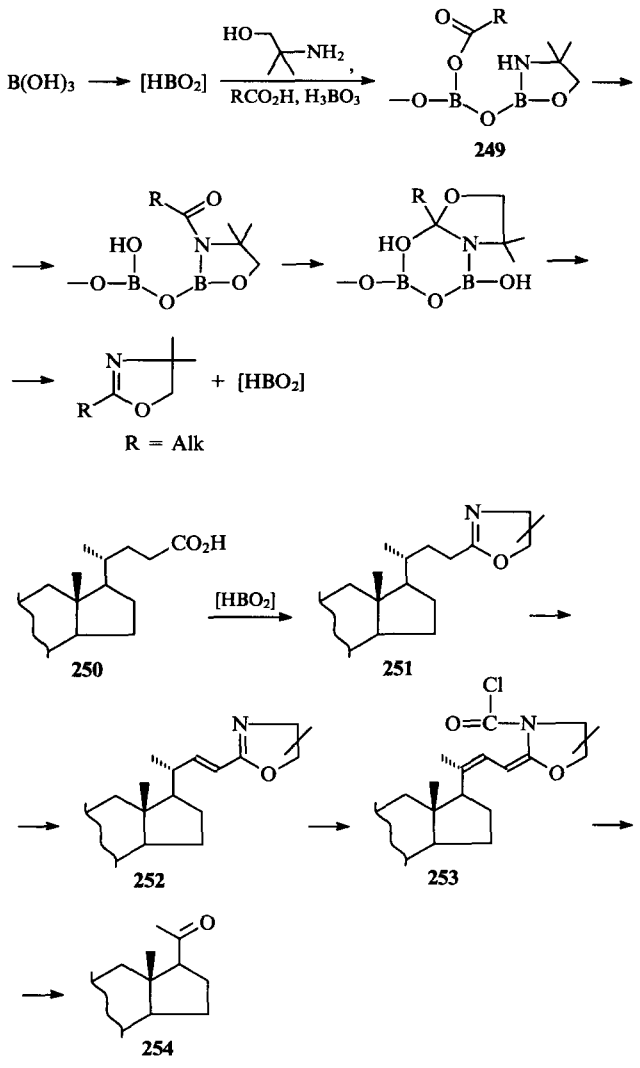


When it was heated with benzeneselenic acid in pyridine, the dehydrogenated compound **252** was obtained in a quantitative yield. In order to obtain the $\Delta^{20(22)}$-bond, the oxazoline **252** was acylated with phosgene at the nitrogen atom and the product **253** was ozonised, which led to the ketone **254** (Scheme 48).

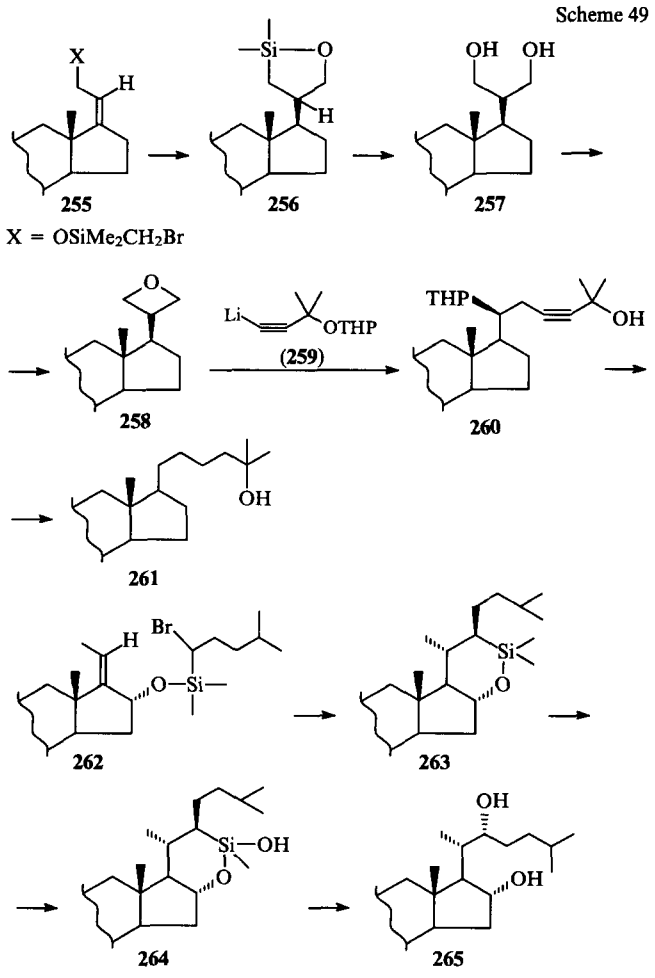
It has been observed recently[108,109] that the intramolecular cyclisation of α-silylsteroid groups to siloxanes proceeds with a high degree of selectivity, which makes it possible to employ the resulting siloxanes in the synthesis of the side chains. Thus the siloxanes **256** have been obtained[108] from the silyl ethers **255** by treatment with tributyltin hydride, while the siloxane **263** was obtained from the ether **262**.[109] Oxidation of the siloxanes **256** with hydrogen peroxide afforded the diol **257**. The latter was cyclised to the oxetan **258**, which was alkylated with lithium acetylide **259** in the presence of boron trifluoride etherate. This led to the isolation of the alcohol **260**. After removal of the 21-hydroxy-group via the methanesulfonate, hydrogenation of the triple bond, and hydrolysis, the tertiary alcohol **261** was obtained with the isosteroid (20*S*) side chain. The siloxane **263** proved to be resistant to the action of various oxidising agents, including concentrated (90%) hydrogen peroxide in DMF. Therefore, in order to open the heterocycle, the siloxane **263** was treated with KOH in dimethyl sulfoxide (DMSO), which led to a mixture of silanols **264**. The latter were readily oxidised with hydrogen peroxide to the diol **265** (Scheme 49).

Steroid γ-lactones have found applications as intermediates in the synthesis of the side chains of desmosterol[110] and (20*S*)-cholic acids.[111] The use of intermediates of this kind made it possible to

Scheme 48



Scheme 49



form stereoselectively the 20*R* or 20*S* centre in the steroid molecule via the controlled protonation of the lactone enolate. The nitrile **266** was obtained in two stages from the ketone **87**. Its condensation with (*S*)-benzyl 2,3-epoxypropyl ether **267** in the presence of lithium hexamethyldisilazide afforded a mixture of the corresponding cyanoalcohols **268**, which could not be separated. After the hydrolysis of the cyanoalcohols (KOH, EtOH), a mixture of the lactone **269** and its C(20) epimer was obtained. The mixture was treated with lithium hexamethyldisilazide in THF at −78 °C and then with a saturated solution of Na_2SO_4 at the same temperature, which led to the selective protonation of the enolate intermediate **270** at C(20) from the less hindered side (opposite to the benzyl group) and to the exclusive formation of the (20*S*)-lactone **269**. The latter was reduced with $LiAlH_4$ to the diol **271**, which was converted into the dimethanesulfonate and reduced selectively with lithium triethylboron hydride to the methanesulfonate **272**. Dehydration, reductive debenzylation, oxidation, and hydrogenation led to the formation[111] of compounds **273** and **274**, which had been isolated previously from marine organisms (Scheme 50).

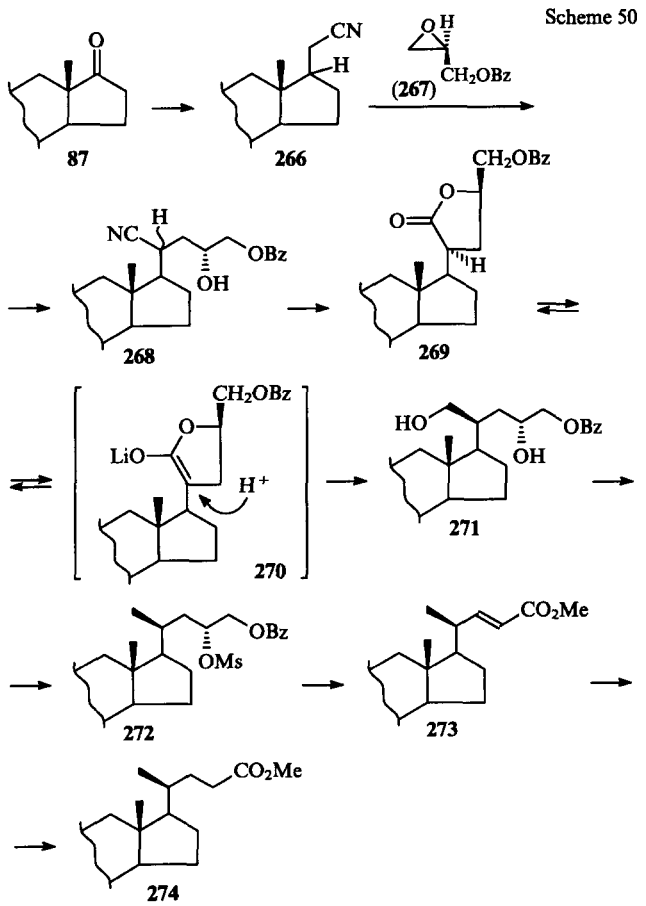
In the synthesis of desmosterol, the addition of the (*R*)-benzyl 2,3-epoxy propyl ether **275** to the nitrile **266** led, after cyclisation, to a 4 : 1 mixture of the lactone **276** and its C(20) epimer **277**. The protonation of this mixture under the conditions described above afforded exclusively the (20*R*)-lactone **277** (i.e. the minor component of the initial mixture). Like the lactone **269**, the lactone **277** was reduced and converted into the methanesulfonate **278** and the latter afforded the alcohol **279** as a result of reduction and debenzylation. The alcohol was oxidised to the aldehyde **280**, from which the product **282**, having the desmosterol side chain, was obtained on condensation with the ylide **281** (Scheme 51).[110]

The chemistry of furan derivatives has found an application also in the synthesis of side chains of ecdysones and brassinosteroids. The side chains of these compounds have from two (α-ecdysone) to four (brassinolide) chiral centres and several hydroxy-groups in different positions, which greatly complicates the synthesis of compounds of this kind. The use of heterocyclic intermediates in the synthesis in many respect helps in the solution of the problems of regio- and stereo-selectivity arising in this connection.

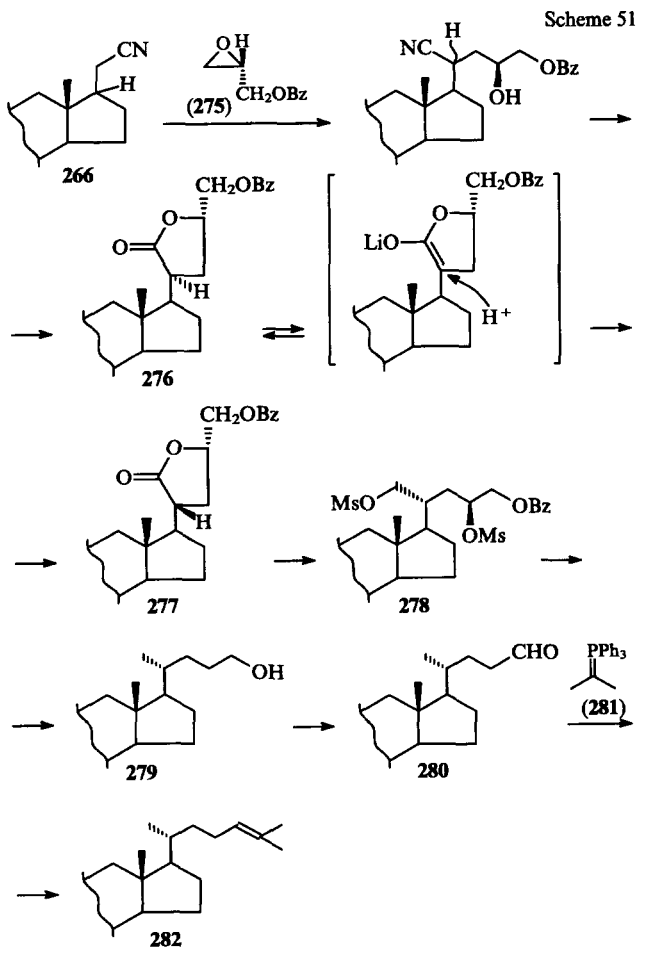
The dihydrofuran **283** was used to synthesise the side chain of 20-hydroxyecdysone.[112] The addition of its lithio-derivative to the ketone **80** led to a mixture of compounds **284** and **285** in 85% yield without any admixture of the (20*S*)-isomers. The dihydrofuran **284** was converted into compounds **285** by brief treatment with 0.1% HCl in THF. The reduction of the ketodiol **285** with Li selectride afforded, as expected, the (22*S*)-alcohol **286** (the ratio of the alcohol **286** to the isomer **287** was 16 : 1). Nevertheless, this product ratio as altered by protecting the hydroxygroup in the ketodiol **285** by forming the trimethylsilyl ether. The subsequent reduction with Li selectride at −78 °C and hydrolysis of the silyl ether led to the formation of the triol **287** in 58% yield (Scheme 52).

A more selective method was proposed by Kametani and coworkers.[113-115] After treatment of the furan **288** with *m*-chloroperbenzoic acid in sodium acetate and chloroform, the hemiacetal **289** was obtained and the oxidation of the latter with pyridinium chlorochromate afforded the lactone **290**. The stereoselective hydrogenation of the lactone **290** over PtO_2 proved to be the key stage. Hydrogen added from the less hindered side (opposite the bulky steroid skeleton) of the lactone afforded a mixture of the lactone **291** and its isomerisation

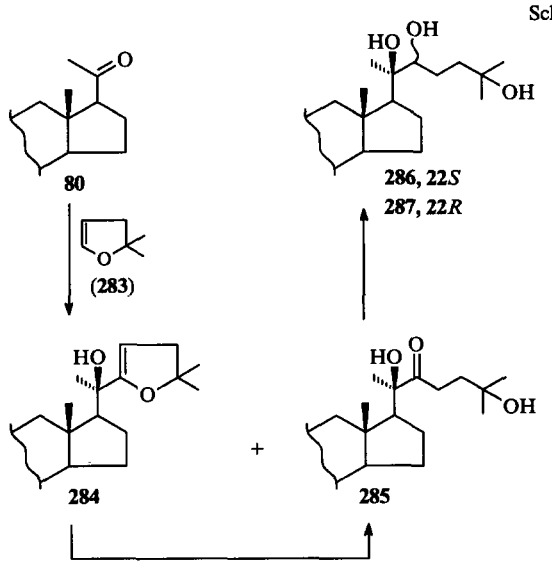
Scheme 50



Scheme 51

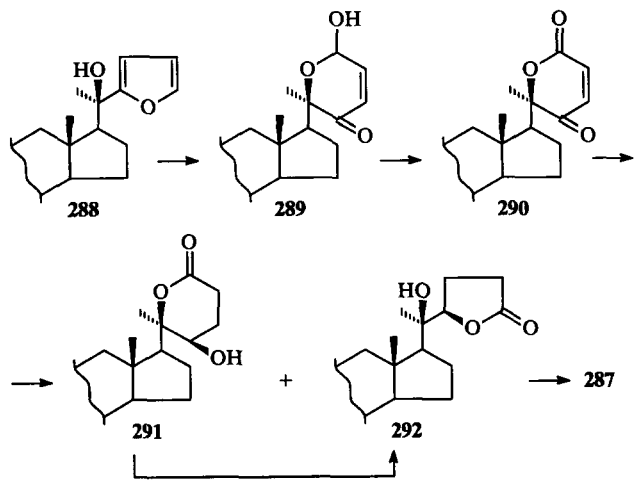


Scheme 52



product **292** (3 : 2) in an almost quantitative yield. The lactone **291** was converted by treatment with aqueous alkali into the thermodynamically more stable lactone **292**, which was alkylated with methyl magnesium bromide. Ultimately the (20*R*, 22*R*)-diol **287** was obtained in 88% yield. The stereoselective formation of the C(22) centre of ecdysones constitutes an appreciable advantage of the above investigation, because the reduction of 22-ketones by hydrides affords mainly the (22*S*)-hydroxy derivative (Scheme 53).[2]

Scheme 53

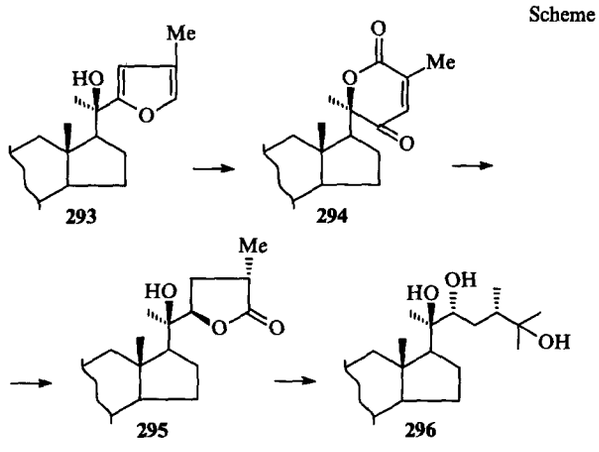


This approach was also applied to the synthesis of the side chain of makisterone A (three chiral centres in the side chain) and its 24-isomer.[115] The lactone **294** was obtained from the furan **293** and its stereoselective hydrogenation and recyclisation afforded the lactone **295** in a quantitative yield. The epimakisterone **296** was obtained by alkylating the latter with methylmagnesium bromide (Scheme 54).

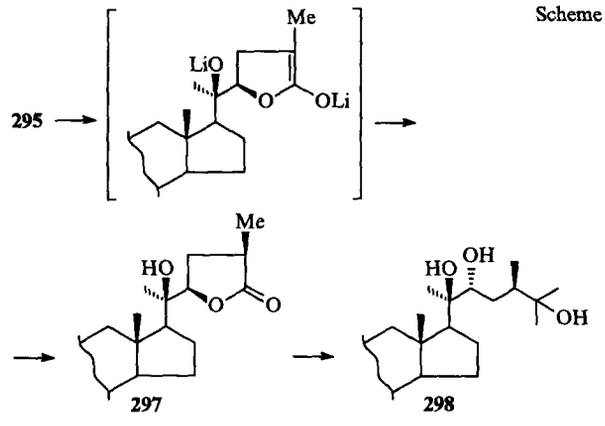
The side chain of makisterone was formed by inverting the C(24) centre in the lactone **295**, which is achieved by the kinetic protonation of γ-butyrolactone. For this purpose, the lactone **295** was enolised by treatment with lithium diisopropylamide and the enolate was treated at −78 °C with a Na_2SO_4 solution, which afforded the lactones **297** and **295** in proportions of 87 : 13 (Scheme 55).

Synthesis using furans has been applied also to the formation of the side chain of α-ecdysone.[116–118] After the dehydration on silica gel of the product of the addition of compound **299** to the ketone **80**, namely 2-lithio-5-methylfuran, the furan derivative **300**

Scheme 54



Scheme 55

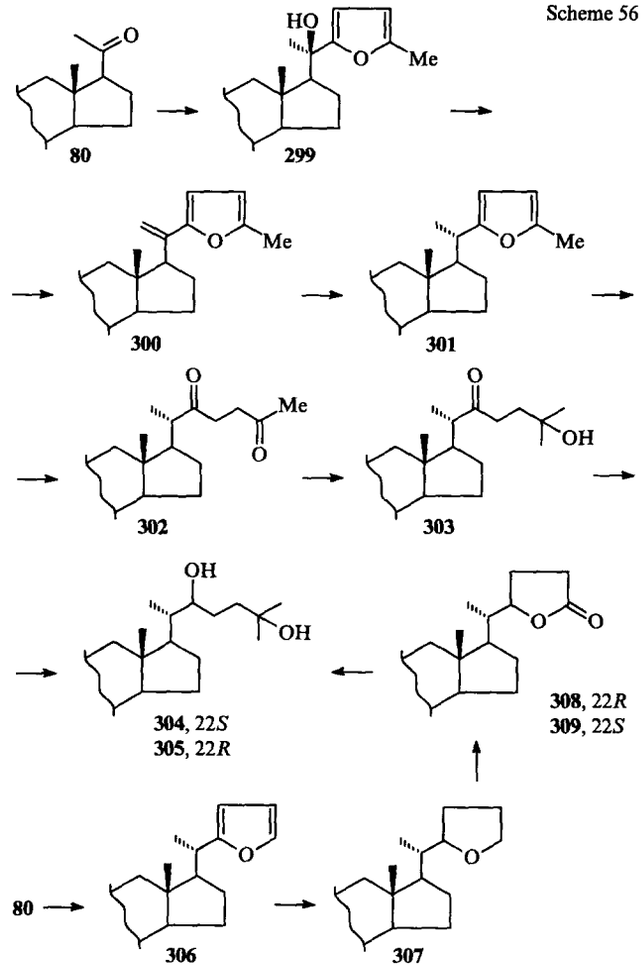


was obtained. The hydrogenation of its $\Delta^{20(21)}$-bond on Pd/C took place stereoselectively and afforded the product **301** without an admixture of the isomer. The furan ring in compound **301** was opened under acid conditions and the resulting diketone **302** was alkylated with methyllithium. The only product of this reaction was the ketol **303**, which was subjected to hydride reduction. As already pointed out, this process takes place with the preferential formation of the (22*S*)-isomer, which is uncharacteristic of the side chain of ecdysones. The best result was achieved using zinc tetrahydroborate in ether as the reductant.[116,117] The ratio of the (22*S*)- and (22*R*)-isomers was 2 : 1 (Scheme 56).

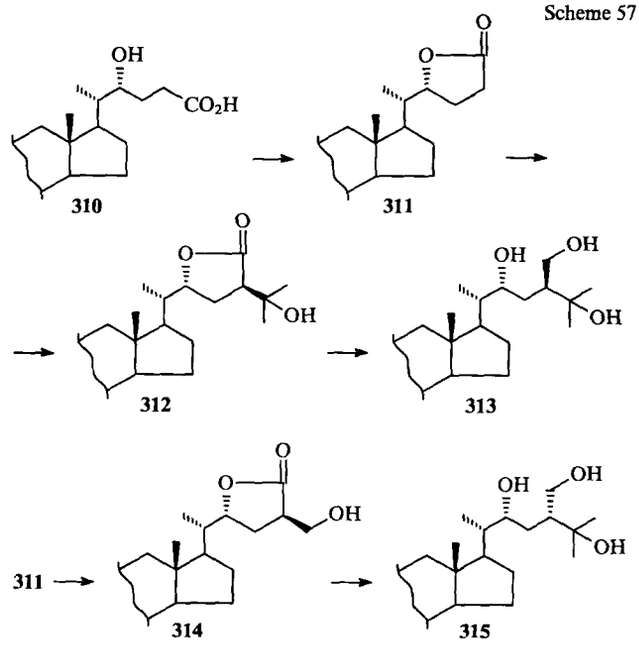
An increase in the yield of the (22*R*)-isomer was achieved by altering the strategy for establishing the chirality of C(22).[118] The furan **306**, obtained by the same mechanism as compounds **301**, was reduced over a rhodium-aluminium catalyst and the reduction product **307** was oxidised with ruthenium oxide. This resulted in the formation of a 1 : 1 mixture of the butenolides **308** and **309**. Grignard reaction with methylmagnesium bromide afforded the diols **304** and **305**.

An elegant method for the monitoring of the stereochemistry of the products formed via the steroid γ-lactones has been proposed[119] in order to establish the stereochemistry of depresosterol. The lactone **311**, obtained from the acid **310**, was enolised by treatment with lithium diisopropylamide and acetone was added, which led to the hydroxylactone **312**. This was converted, after reduction with $LiAlH_4$, into compound **313**, the latter proving to be the 24-stereoisomer of the natural steroid. Since the inversion of the C(24)-centre in the hydroxylactone **312** is impossible, the substituents were introduced at C(28) starting from the lactone **311**. The lactone enolate was treated with gaseous formaldehyde, which led to the hydroxylactone **314**, and the alkylation of the latter with methyllithium afforded the alcohol **315**, isomeric with respect to C(24), which is identical with the natural alcohol (Scheme 57).

Scheme 56



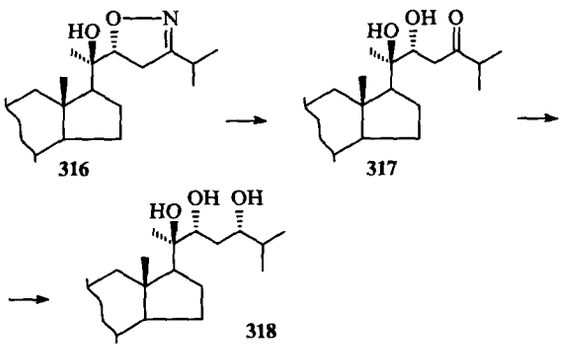
Scheme 57



A procedure using the synthetic possibilities of isoxazolines has been proposed recently for the construction of the side chain in ecdysteroids. Thus the reductive cleavage of the isoxazoline **316** on Raney nickel in the presence of an inorganic acid results in the formation of the β-ketol **317**. The reduction of its carbonyl group with sodium tetrahydroborate in alcohol led to the formation of two alcohols isomeric with respect to C(24). The side chain of the

(24*S*)-epimer **318** corresponds to that of the side chain of the phytoecdysones ponasterone C and pterosterone (Scheme 58).[120,121]

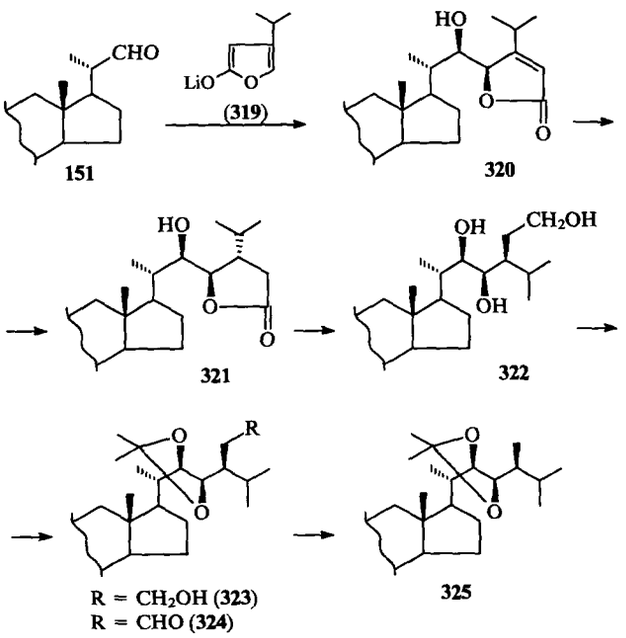
Scheme 58



The isolation in 1979 of brassinolide—the first phytohormone having a steroid structure—initiated a multiplicity of studies devoted to its partial chemical synthesis. Heterocyclic intermediates have been used[95,122–127] for the selective formation of the side chain in this compound. As in the case of ecdysones, syntheses involving furan derivatives have come to be most widely used.

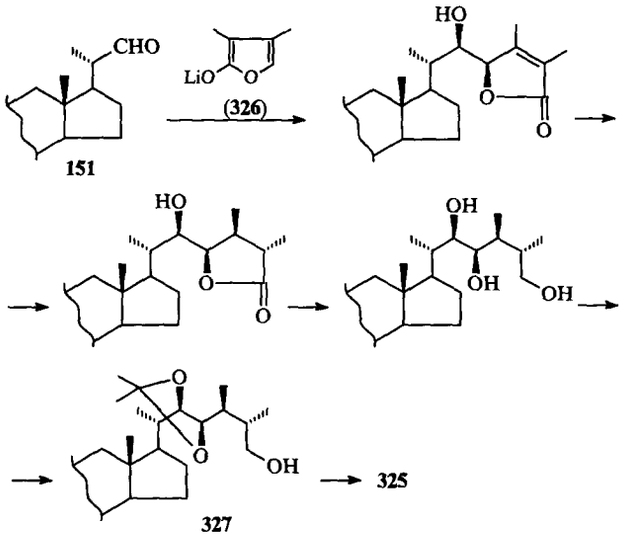
Having selected the aldehyde **151** as the starting material for the synthesis of side chains, it is necessary to form three chiral centres at C(22), C(23), and C(24). The use of furan derivatives[122–125] makes it possible to introduce the required functional groups in these positions, maintaining a high stereoselectivity. Thus the addition of the lithium enolate **319** at −78 °C to the aldehyde and treatment of the reaction mixture at this temperature (kinetic conditions) with dilute hydrochloric acid led to the formation of the butenolide **320** with the (22*R*, 23*R*)-configuration in 65% yield.[122] When the reaction mixture was treated at 0 °C, the main product was the (22*R*, 22*S*)-isomer, i.e. the thermodynamically more stable product is formed at a higher temperature (Scheme 59).

Scheme 59



Hydrogenation of the lactone **320** on platinum afforded a mixture of isomers with respect to C(24) in proportions of 78 : 22 in a quantitative yield. Since the constant for the spin–spin coupling of the protons of C(23) and C(24) in the main isomer **321** was smaller, the (24*S*)-configuration was attributed to the latter. After the reduction of the lactone **321** with $LiAlH_4$, the triol **322** was obtained and its refluxing with 2,2-dimethoxypropane in the presence of pyridinium toluene-*p*-sulfonate led to the formation of the acetonide **323** and the mixed acetal at C(29). The crude product was then refluxed in methanol, which afforded only the acetal **323** in 92% yield. The latter was oxidised with pyridinium chlorochromate and the resulting aldehyde **324** was decarbonylated with tris(triphenylphosphine)rhodium chloride. As a result of these transformations, the (24*S*)-methyl derivative **325** was obtained from the aldehyde **151** in an overall yield of 32%. A shorter synthesis of the side chain of brassinolide is possible when the lithium derivative **326** is used: a similar chain of transformations afforded the acetonide **327**, the treatment of which with methanesulfonyl chloride in pyridine and subsequent reduction of the methanesulfonate with $LiAlH_4$ lead to compound **325** (Scheme 60).[122]

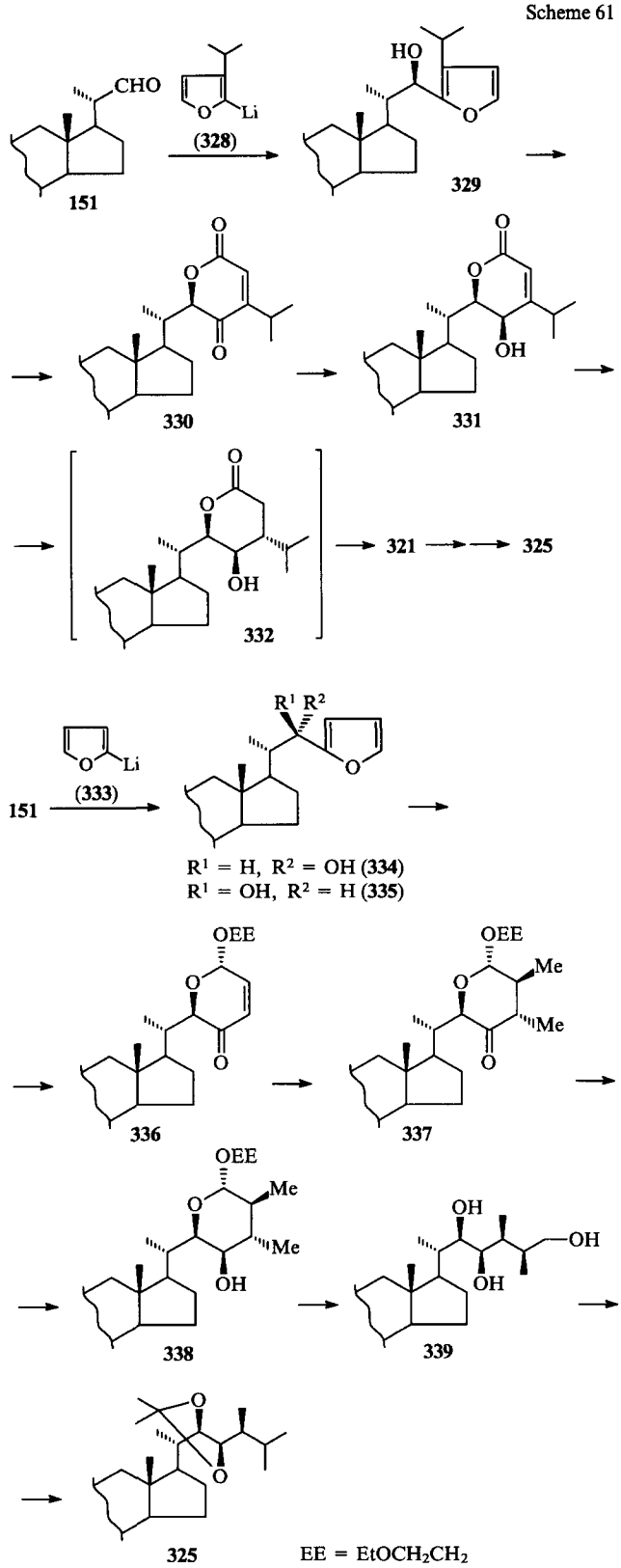
Scheme 60



The side chain of brassinolide was also formed by alkylating the aldehyde **151** with the lithiofurans **328** and **333**.[123,124] In the former cases, alkylation afforded 81% of the furylsteroid **329**, the successive oxidation of which the *m*-chloroperbenzoic acid and pyridinium chlorochromate led to the ketolactone **330**. The ketone functional group in compound **330** was reduced with sodium tetrahydroborate, which afforded exclusively the hydroxylactone **331**. Finally, its hydrogenation on PtO_2 and isomerisation (0.5 M NaOH) of the primary product **332** to the thermodynamically more stable γ-lactone led to the formation of 72% of the lactone **321** and 25% of its (24*R*)-isomer.[123] The addition of the furan **333** was less selective (**334** : **335** = 3 : 7), but the isomer **334** was converted into compound **335** by oxidising it with pyridinium chlorochromate and subsequently reducing the 22-ketone. As in the previous cases, the oxidation of the α-hydroxyfuran with *N*-bromosuccinimide led to a mixture of lactols, which were converted into ethoxyethyl ethers and separated. The ratio of the main product **336** to its 26-isomer was 3 : 1. Subsequently the ether **336** was subjected to coupled alkylation with lithium dimethylcuprate and methyl iodide. These reactions proceeded smoothly and it was assumed that the addition occurred on the opposite side of the plane of the ring in relation to the neighbouring group. The reduction of the carbonyl group of the dimethyl derivative **337** leads to the exclusive formation of the alcohol **338**. Hydrolysis of the ether group (10% HCl) and treatment with $LiAlH_4$ afforded the triol **339**, the subsequent transformations of which into compound **325** were described above (Scheme 61).[124]

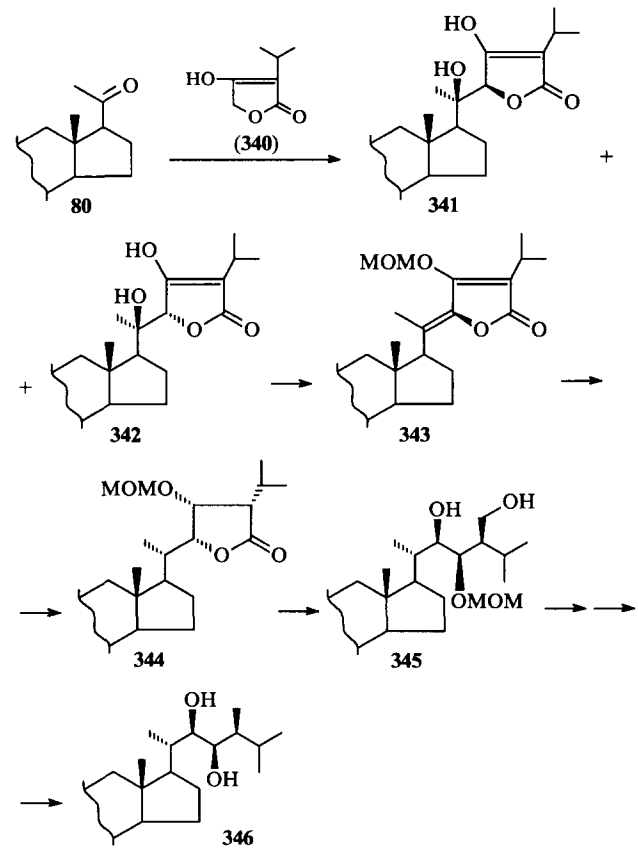
Kametani's group[125] were able to achieve the stereocontrolled formation of four chiral centres at once in the side chain of brassinolide. Alkylation of the ketone **80** with a fourfold excess

Scheme 61



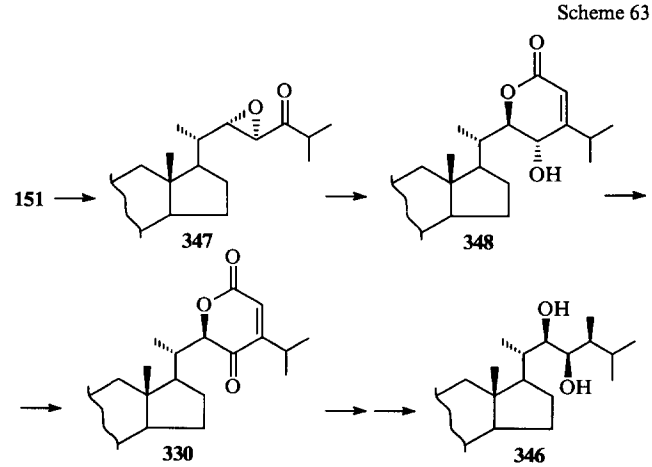
of the butenolide dianion **340** afforded a 9:91 mixture of the diastereoisomers **341** and **342** (84%), the enolic hydroxy-groups of which were protected by forming methoxymethyl ethers. The removal of the tertiary hydroxy-group of the MOM ether of the isomer **342** (via the formation of the trifluoroacetate) and hydrogenation over a rhodium catalyst of the (*Z*)-isomer **343** formed preferentially afforded the sole product **344** with the required stereochemical configuration of all four chiral centres in the side chain. After the reduction of the lactone **344** with $LiAlH_4$ to the alcohol **345**, the primary hydroxy-group of the latter was converted into the methanesulfonate and reduced, which led to the side chain of the brassinolide **346** (Scheme 62).

Scheme 62



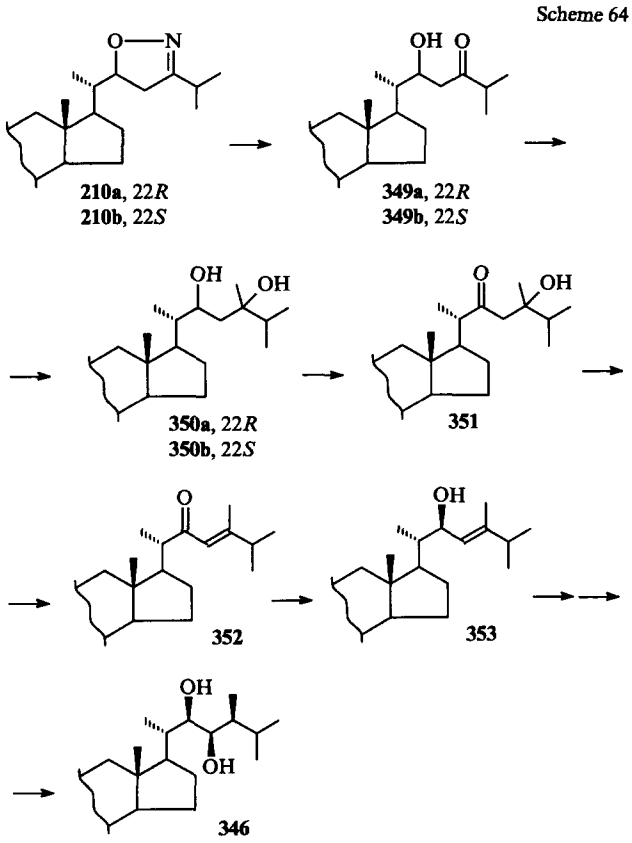
A somewhat different approach to increasing the length of the side chain of brassinolide, leading to common heterocyclic intermediates, has been developed by Chinese workers.[126] The aldehyde **151** was converted into the epoxyketone **347** by the method proposed in the synthesis of deoxyantheridiol.[79] The Wittig–Horner reaction of the epoxyketone with methoxycarbonylmethylphosphonate and subsequent lactonisation of the (*Z*)-isomer under acid conditions [occurring with inversion of the configuration at C(22)] ensured the formation of the hydroxylactone **348**. The oxidation of the hydroxy-group of this compound with pyridinium chlorochromate afforded the known intermediate **330**, the subsequent transformations of which lead to the side chain of brassinolide (Scheme 63).

Scheme 63



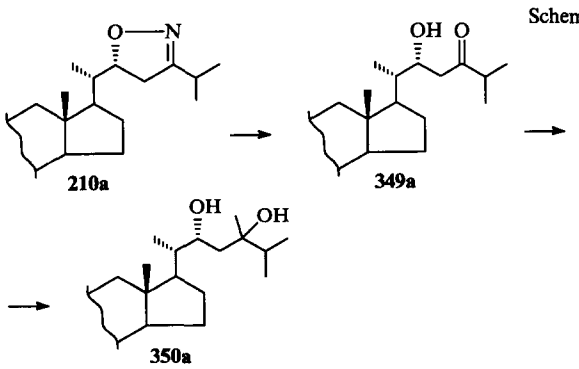
The growth of the side chain of brassinolide was achieved also by using isoxazoline intermediates.[95] Thus cleavage of the isoxazolines **210a, b** in the presence of acid on Raney nickel, the subsequent alkylation of the β-ketols **349** with methyllithium, oxidation of the resulting diols **350** by the Jones reagent, and finally dehydration of the tertiary alcohols **351** by thionyl chloride in pyridine led to the formation of the steroid 23-en-22-one **352**. Reduction of the eneketone **352** with diisobutylaluminium hydride leads[95] to the allyl alcohol **353** with a high stereoselectivity. The subsequent formation of the side chain of brassinolide can be readily achieved by Siddall's method (Scheme 64).[127]

Scheme 64



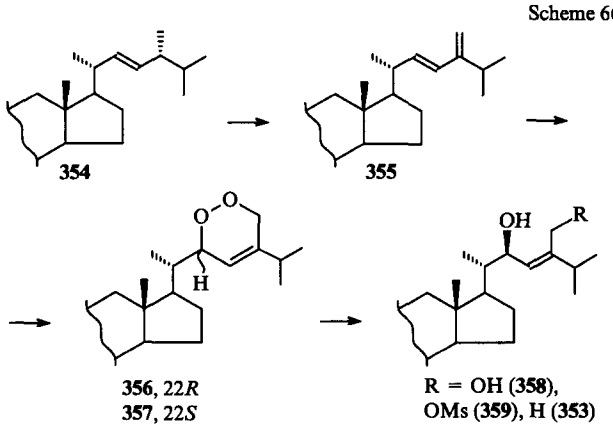
It is noteworthy that,using the (22*R*)-isoxazoline **210a**, it is possible to achieve, by means of a similar scheme, the formation of the side chain of the sapogenin isolated from the soft coral *Asterospicularia randalli* (Scheme 65).[128]

Scheme 65



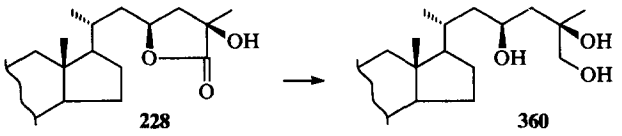
The use of heterocyclic derivatives[129] made it possible for the first time to transform the side chain ergosterol into the alcohol **353** (the intermediate in many syntheses of brassinolide and dolicholide[127]) without its cleavage. Thus the olefin **354** was converted via a bromination–dehydrobromination reaction into the diene **355**, the oxidation of which with molecular oxygen in pyridine under intense illumination in the presence of a sensitiser led to the chromatographically separatable mixture of the epidioxides **356** and **357** (in proportions of 7 : 3). The (22*R*)-isomer was reduced on the Lindlar catalyst to the diol **358**, the primary hydroxy-group of which was removed by reducing its methanesulfonate **359** with $LiAlH_4$. Analogous transformations of the epidioxide **357** led to the (22*S*)-isomer of the alcohol **353** (Scheme 66).

Scheme 66



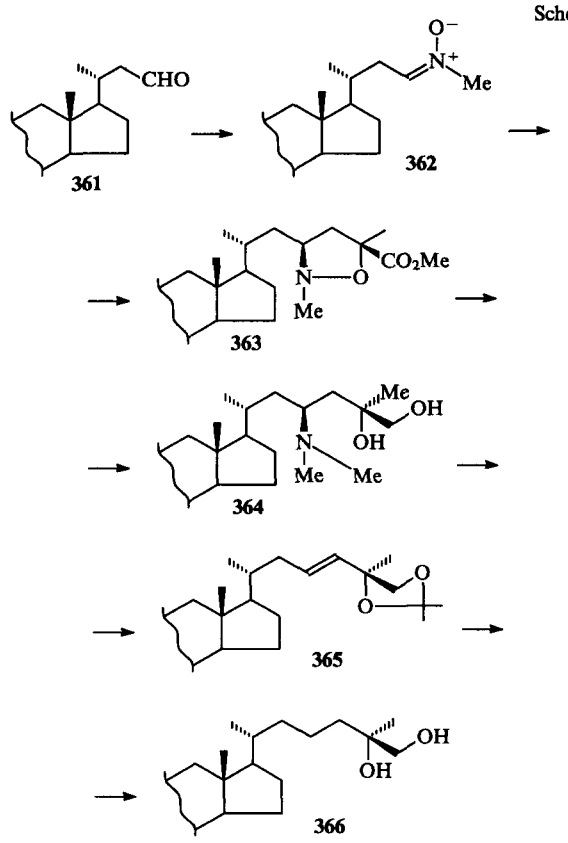
Heterocyclic intermediates have been used in a number of studies[103,130] of the vitamin D_3 metabolites, undertaken to achieve stereocontrol in the formation of the side chain. In particular, in the synthesis 23,25,26-trihydroxy-vitamin D_3 **360**, the intermediate of this kind was the lactone **228** (calciferol-lactone), the reduction of which with $LiAlH_4$ afforded the required product (Scheme 67).

Scheme 67



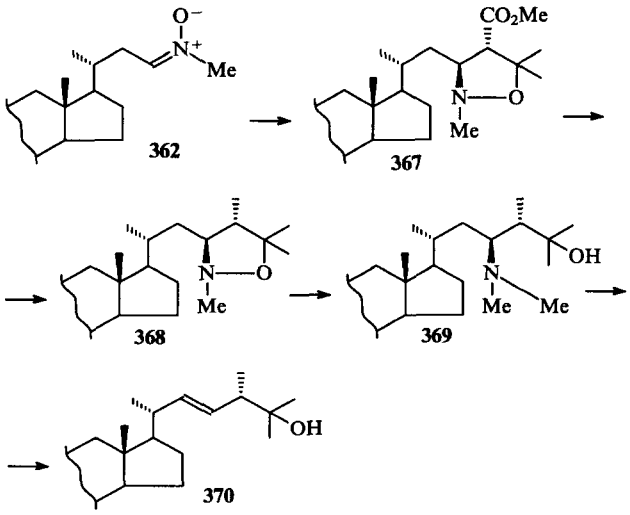
Uskokovic and coworkers[131–133] developed a fairly effective stereoselective method of synthesis of vitamin D_3[131] and D_2[132,133] metabolites via the cycloaddition of steroid nitrones to olefins. The synthesis of the side chain of 1α-(25*S*),26-trihydroxycholecalciferol **362**, a new vitamin D_3 metabolite isolated in 1981, has been described.[131] The nitrone **366** was obtained from the aldehyde **361** and *N*-methylhydroxylamine in the form of one (*Z*)-isomer, the structure of which was determined by X-ray diffraction. The cycloaddition of methylacrylate to this compound afforded a mixture of four isoxazolidines diastereoisomeric with respect to C(23) and C(25). The existence of thermal equilibrium between them makes it possible to monitor the stereochemical configuration of the product. For this purpose, after the separation of the required (*S,S*)-isomer, the other three were heated at 140 °C in xylene in the presence of an excess of methyl methacrylate. This again led to four isomers. By several repetitions of the process, the required isomer **363** was obtained from compound **362** in 71% yield. The isoxazolidine **363** was then treated with methyl iodide and the product was reduced with $LiAlH_4$, which afforded 86% of the aminodiol **364**. The aminodiol was converted into the acetonide and the amino-group was eliminated by the Hofmann method. This resulted in the formation of the olefin **365**, the hydrogenation of which over palladium on charcoal and hydrolysis led to the diol **366** (Scheme 68).

Scheme 68



The same approach has been used[132, 133] for the synthesis of a vitamin D_2 metabolite — 1α,25-dihydroxyergocalciferol **370**. The addition of 3,3-dimethylacrylate to the nitrone **362** in boiling xylene led to the formation (in contrast to the previous case) of only two of the four possible diastereoisomers (*RR* and *SS*) in proportions of 1 : 1. The enrichment in the required (*SS*)-isomer **367** was carried out by a procedure similar to that described above. Next the carboxymethyl group in compound **367** was reduced to the hydroxy-group and the latter was removed via the toluene-*p*-sulfonate, affording the isoxazolidine **368**. Its alkylation at the nitrogen atom and subsequent cleavage of the ring led to the aminoalcohol **369**. Its deamination ensured the formation of the *trans*-Δ^{22}-steroid **370** (Scheme 69).

Scheme 69



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