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ADVANCES IN THE CHEMICAL SYNTHESIS OF WITHANOLIDES

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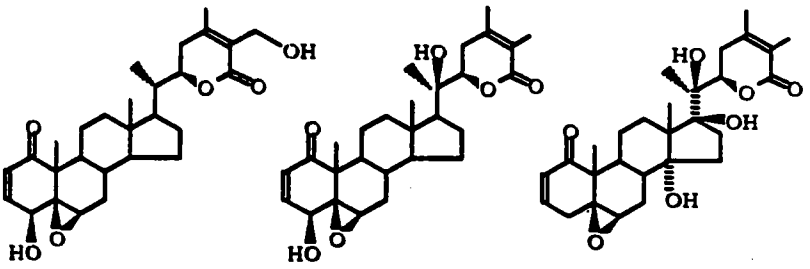
This review considers the current state of investigations into the chemical synthesis of phytosteroids of the withanolide group.

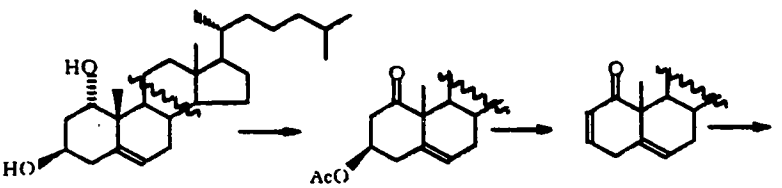
Withanolides form a broad group of polyhydroxysteroids of the ergostan series that have been isolated from plants of the Solanaceae family and are united by common features of their chemical structure [1-4]. Typical representatives of the withanolides include withaferin A (**1**), withanolide D (**2**), and withanolide E (**3**). It can be seen from the structural formulas given that the withanolides differ from other natural polyhydroxysteroids by the presence of a δ-lactone grouping in the side-chain and a number of characteristic substituents in rings *A* and *B*. Antimicrobial, antitumoral, immunotropic, antiinflammatory, hepatoprotective and cardiotonic properties have been detected in many representatives of this group of natural compounds [5-7]. In addition, the discovery in withanolides of antifeedant activity on insects [4, 8] is extremely important. Apparently it is just to this that the presence of these substances in plants is due. It may be assumed that plants prevent attack by phytophagous insects in this way [4].



1 **2** **3**

Possessing a broad spectrum of biological action, withanolides are extremely attractive objects for chemical synthesis from accessible steroidal raw material. It must be mentioned that both the lactone ring in the side-chain and the set of functional groups in rings *A* and *B* are characteristic only for withanolides and are not encountered in the structures of other natural compounds. Therefore, researchers faced with the task of synthesizing withanolides chemically have first tackled the problem of developing special methods of constructing these fragments of the structure on the basis of the available steroids to be used as the initial raw material. Only after these methods have been created does it become possible to realize any scheme of synthesis of the actual natural substances of the group under discussion. Therefore, in the first investigations devoted to the chemical synthesis of withanolides the task usually consisted in obtaining model compounds having at least some fragments of the structure either in the cyclic part of the molecule or in the side-chain.

Thus, Japanese researchers have performed the synthesis of the cholestane derivative (**9**), having just the same functions in rings *A* and *B* as in the withaferin A molecule [9, 10]. Acetylation of the more accessible 3β-hydroxy group in 1α-hydroxycholesterol (**4**) and Jones oxidation of the resulting monoacetate, formed in a yield of 60%, gave the acetoxyketone (**5**).



4 **5** **6**

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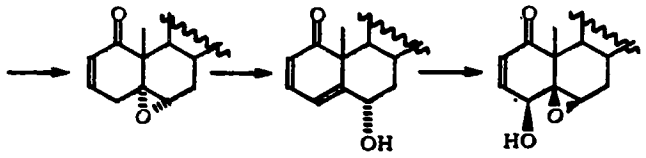
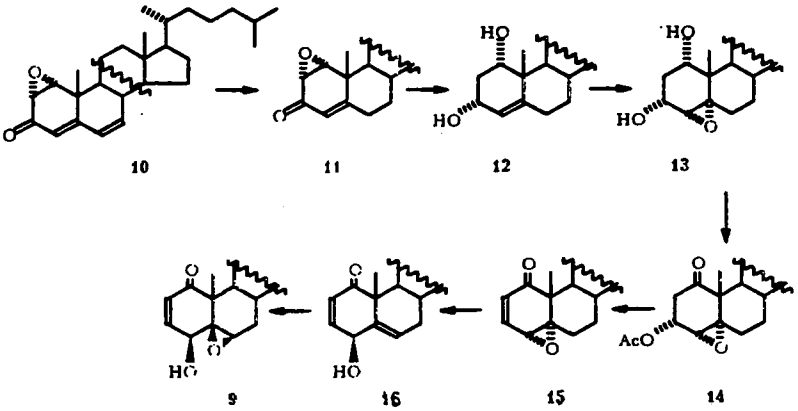


7 8 9

The interaction of the acetoxysteroid (**5**) with sodium hydroxide was accompanied by the formation of the dienone (**6**). Epoxidation of compound (**6**) with *m*-chloroperbenzoic acid formed a mixture (2:1) of 5,6-epoxides. The main product of this reaction – the 5α,6α-epoxide (**7**) – was isomerized under the action of sodium hydroxide to give a quantitative yield of the allyl alcohol (**8**). The action of methanesulfonyl chloride on the allyl alcohol (**8**) led to the mesylate, which was hydroxylated with osmium tetroxide, and the interaction of the resulting 4β,5β-diol with sodium hydroxide enabled the desired compound (**9**) to be obtained with an 85% yield.

An alternative synthesis of compound (**9**), which has the functional groups of withaferin A in rings *A* and *B*, has been given by Weissenberg et al. [11, 12]. Hydrogenation of 1α,2α-epoxycholesta-4,6-dien-6-one (**10**), obtained in two stages from cholesterol, formed the 1α,2α-epoxyenone (**11**). The lithium tetrahydroaluminate reduction of compound (**11**) led to the formation of the 1α,3α-diol (**12**) in high yield, and the epoxidation of (**12**) with perbenzoic acid gave the 4α,5α-epoxide (**13**).

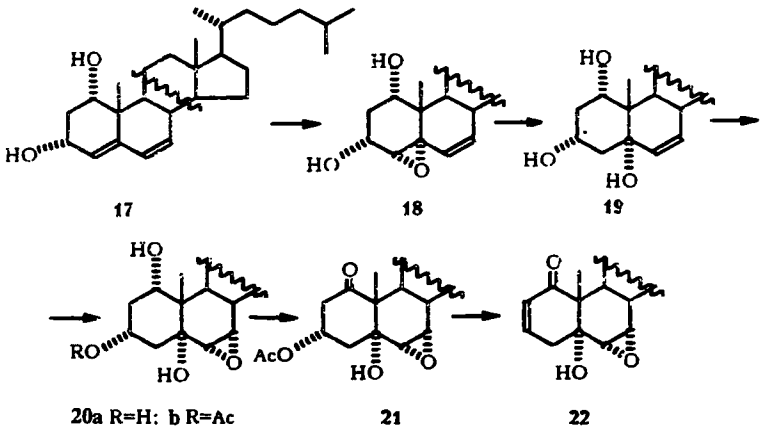
Selective acetylation of the 3α-hydroxy group in the dihydroxysteroid (**13**) and oxidation of the 1α-hydroxy group with chromium trioxide enabled the epoxyketone (**14**) to be synthesized, and elimination of the acetoxy group from this on alumina formed the epoxyenone (**15**). The hydrolytic opening of the epoxide ring in compound (**15**) in the presence of acid gave a 4β,5α-diol in which the 4β-hydroxy group was then acetylated and the 5α-hydroxy group was eliminated under the action of thionyl chloride, after which hydrolysis of the acetoxy group with barium methanolate gave the 4β-hydroxy-2,5-dien-1-one (**16**). Epoxidation of the electrophilic 5(6)-double bond in steroid (**16**) by perbenzoic acid led to the desired compound (**9**).



10 11 12 13

9 16 15 14

The synthesis [13] of the cholestane derivative (**22**), having in rings *A* and *B* the same functional groups as in a number of withanolides started from the 1α,3α-diol (**17**). When compound (**17**) was oxidized with *tert*-butyl hydroperoxide in the presence of oxovanadium bisacetylacetonate, the 4α,5α-epoxide (**18**) was obtained. The lithium tetrahydroaluminate reduction of the epoxide ring in compound (**18**) led to the 1α,3α,5α-triol (**19**), which was converted by epoxidation with *m*-chloroperbenzoic acid into the trihydroxyepoxide (**20a**).



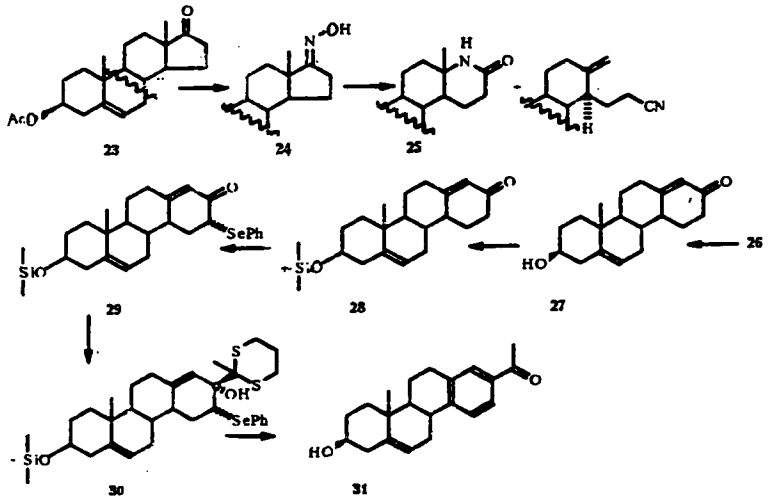
17 18 19

20a R=H; b R=Ac 21 22

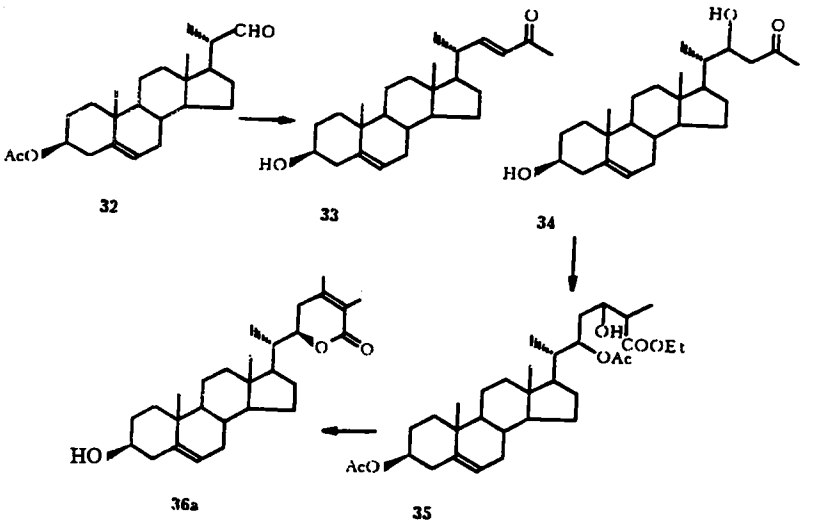
The more accessible 3α-hydroxy group in compound (**20a**) was acetylated with acetic anhydride in pyridine, to form the 3-monoacetate (**20b**). Jones oxidation of the 1α-hydroxy group in steroid (**20b**) led to the 1-ketone (**21**), and when this was kept with neutral alumina the desired steroid (**22**) was formed with an overall yield of 17% from the dienone (**17**).

In [14], a search for the most effective routes to the synthesis of rings *A* and *B* of the withanolides was the subject of a special investigation performed with the use of a bicyclic starting material derived from decalin and imitating the steroid molecule. Because the starting material and all the intermediates were not steroids, they will not be considered in detail here, in spite of the fact that the results obtained are of value for the subsequent synthesis of the withanolides themselves.

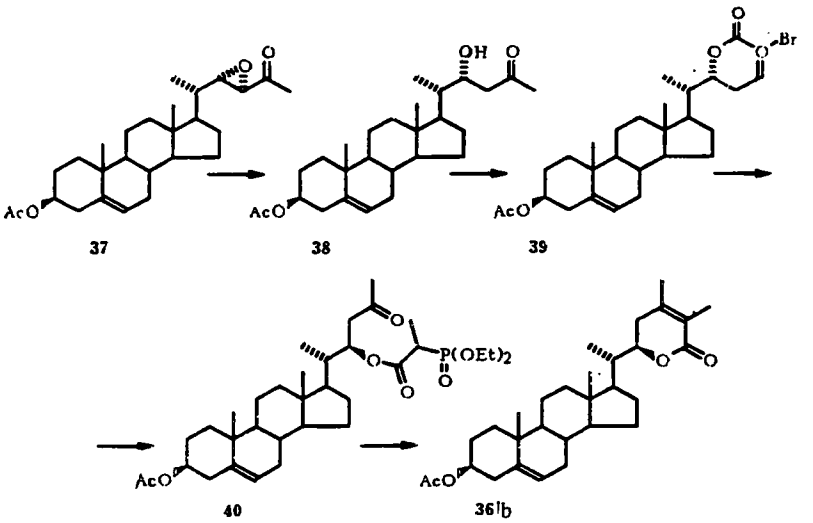
The synthesis of steroid (**31**), having the same aromatic ring and side-chain as the withasteroid Nic-10 isolated from *Nicandra physaloides*, started from the androstenolone acetate (**23**) [15, 16].



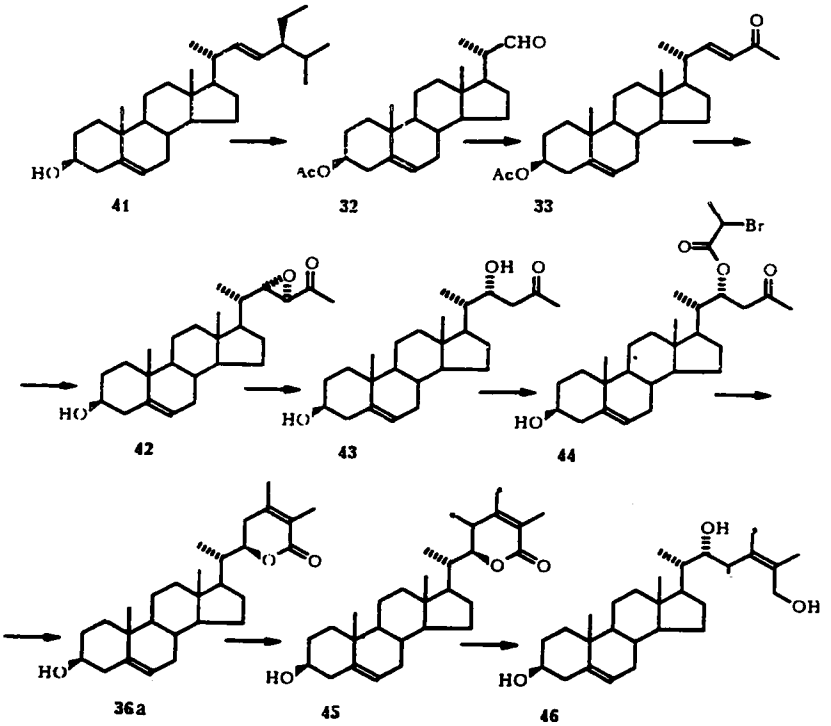
The initial ketone (**23**) was first converted into the (17E)-oxime (**24**) in the usual way. The interaction of oxime (**24**) with dimethyl sulfoxide, dicyclohexylcarbodiimide, and trifluoroacetic acid in benzene took place with the formation of the lactam (**25**) and the unsaturated nitrile (**26**), obtained with yields of 41 and 30%, respectively. It was then possible to synthesize the *D*-homosteroid (**27**) from the secosteroid (**26**) in an overall yield of about 60% by the initial hydrolysis of the 3β-acetoxy group and of the nitrile group under the action of sodium hydroxide, followed by cyclization of the resulting carboxylic acid with trifluoroacetic anhydride. In compound (**27**), the free 3β-hydroxy group was protected by the formation of the silyl ether (**28**) in 87% yield. The interaction of the enone (**28**) with lithium diisopropylamide gave the corresponding anion, which was converted by reaction with phenylselenyl chloride into the 16α-(phenyl selenide) in a yield of 66%. Condensation of compound (**29**) with 2-lithio-2-methyl-1,3-dithiane led with a yield of 54% to the dithioketal (**30**), the oxidation of which with hydrogen peroxide, followed by hydrolysis with aqueous hydrochloric acid and mercuric chloride, enabled the required steroid (**31**) to be synthesized with an overall yield of 70%.



The first investigation devoted to the synthesis of the δ-lactone grouping that is characteristic for the withanolides was that of Gonzalez et al. [17]. In it, the 22-aldehyde (**32**) was first subjected to aldol-crotonic condensation with acetone in the presence of sodium hydroxide, leading to the formation of the Δ^{22}-24-ketone (**33**) and the 22-hydroxy-24-ketone (**34**). As a result of protection of the hydroxy groups, followed by the Reformatskii reaction with ethyl α-bromopropionate, the ester (**35**) was obtained. Alkaline hydrolysis of the ester function in (**35**), followed by cyclization under the action of hydrochloric acid accompanied by dehydration of the tertiary 24-hydroxy group, permitted the synthesis of the δ-lactone (**36a**).

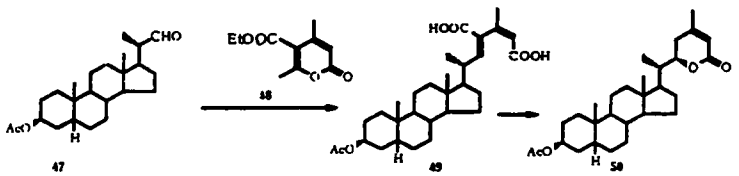


A more perfect method of constructing the withanolide side-chain has been proposed in [18]. According to this, the 22,23-epoxy-24-ketone (**37**) is reduced with sodium amalgam to form the 22-hydroxy-24-ketone (**38**). Acylation of the 22-hydroxy group in compound (**38**) with α-bromoacetyl bromide leads to the corresponding α-bromoacetate (**39**). The Arbuzov reaction with triethyl phosphite converts steroid (**39**) into the diethyl phosphonate (**40**). An intramolecular Wittig–Horner reaction of the yield obtained by the interaction of phosphonate (**40**) with sodium hydride leads to the desired unsaturated lactone (**36b**).



In [19], the synthesis of the triol (**46**) tritium-labeled at C-23 and C-28, which is of interest for studying the biosynthesis of withanolides in the plant *Nicandra physaloides*, was achieved via the lactone (**36a**). In this synthesis, the 22-aldehyde (**32**) was obtained from stigmasterol (**41**) by acetylation, protection of the 5(6)-double bond in the form of the dibromide, ozonolysis of the 22(23)-double bond, and regeneration of the double bond from the 5,6-dibromide.

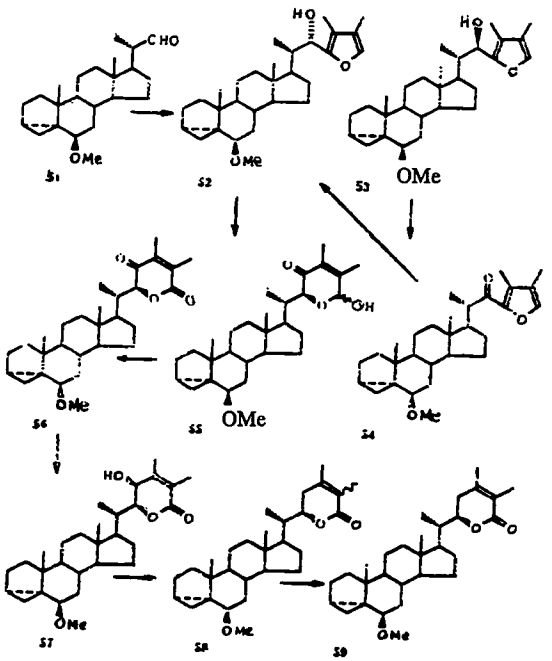
The Wittig reaction of aldehyde (**32**) with the appropriate phosphorus yield led to the Δ^{22}-24-ketone (**33**), the epoxidation of which with alkaline hydrogen peroxide gave the epoxyketone (**42**). Reduction of the epoxide ring in compound (**42**) by aluminum amalgam took place with the formation of the 22-hydroxy-24-ketone (**43**). Acylation of the 22-hydroxy group in steroid (**43**) with α-bromopropionyl bromide yielded the α-bromopropionate (**44**). The Arbuzov reaction of compound (**44**) with triethyl phosphite gave a diethyl phosphonate which was then, by an intramolecular Wittig–Hormer reaction, converted with an overall yield of 76% into the unsaturated lactone (**36a**). Boiling a solution of the lactone (**36a**) in tetrahydrofuran in the presence of tritiated water and diazabicyclononane led to the formation in high yield of lactone (**45**) tritium-labeled at C-24 and C-28. Reduction of the labeled lactone with lithium tetrahydroaluminate enabled the labeled triol (**46**) to be obtained from lactone (**36a**) with an overall yield of 89%.

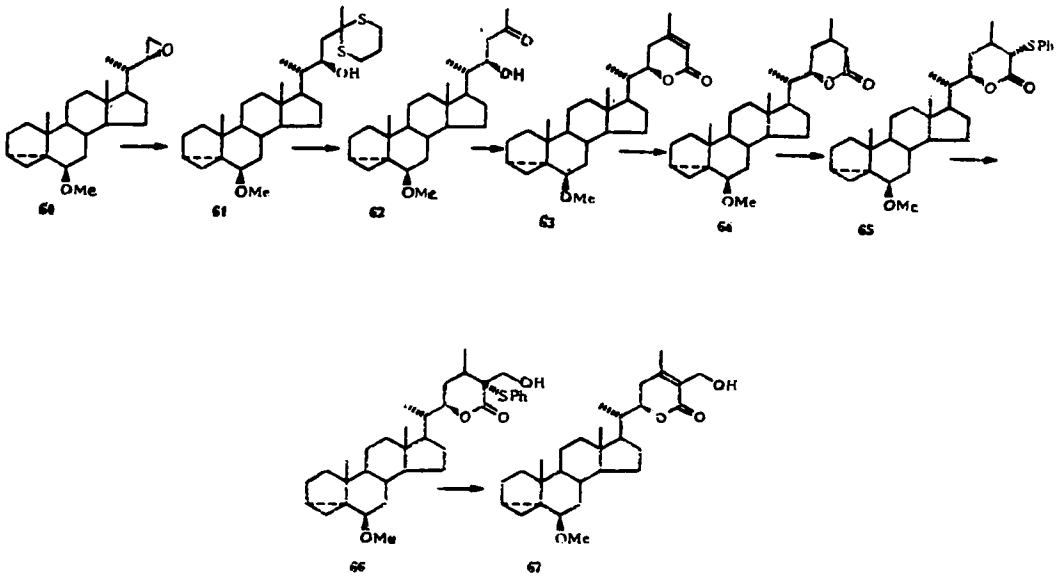


A new sequence of reactions has been proposed for the synthesis of lactone (**50**), the key stage of which is the condensation of aldehyde (**47**) with ethyl 4,6-dimethyl-2-oxo-2H-pyran-5-carboxylate (**48**) in methanol in the presence of caustic soda [20]. The choice of reaction conditions permitted the formation, after acetylation of the 3β-hydroxy group, of the diacid (**49**). Decarboxylation of the diacid (**49**) by heating in toluene in the presence of 2,4-dimethylpyridine took place with simultaneous cyclization and led to lactone (**50**) with a yield of 33%.

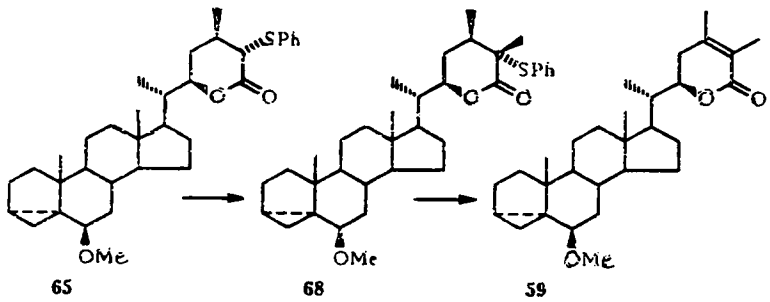
In [21], lactone (**59**) was synthesized from the 22-aldehyde (**51**). The condensation of aldehyde (**51**) with 2-lithio-3,4-dimethylfuran led to the formation, with an overall yield of 80%, of the alcohols (**52**) and (**53**) in a ratio of 1:3.8. It was possible to obtain an additional amount of the required steroid (**52**) from the alcohol (**53**) by oxidation with dichlorodicyanobenzoquinone in dioxane, giving a 61.4% yield of the 22-ketone (**54**), and reduction of the latter with lithium tetrahydroaluminate to form a mixture (16:1) of the alcohols (**52**) and (**53**). When compound (**52**) was oxidized with N-bromosuccinimide in aqueous tetrahydrofuran, the corresponding lactone was formed in a yield of 84.4%, and its further oxidation with pyridinium chlorochromate gave the δ-lactone (**56**). Without additional purification, this unstable lactone was reduced with sodium tetrahydroborate to the hydroxylactone (**57**) with an overall yield of 73.4% on the lactone (**55**).

In compound (**57**), the side-chain corresponds to the side-chain of withanolides of the R-type. Acetylation of the hydroxy group in steroid (**57**) gave an 85% yield of the acetate, and the reductive deacetoxylation of this by zinc amalgam in the presence of hydrogen chloride in ether led to the olefin (**58**) in a yield of 21%, together with the isolation of a considerable amount (77%) of unchanged starting material. Isomerization of the nonconjugated lactone (58) under the action of 1,8-diazabicyclo[5.4.0]undec-7-ene took place with the formation in a yield exceeding 90% of the conjugated lactone (**59**) having the side-chain of 27-deoxywithaferin A.



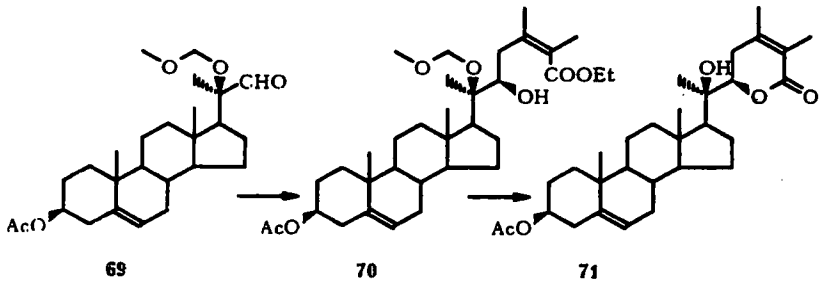


In [22] yet another scheme is proposed for the construction of the side-chains characteristic of the molecules of withaferin A and 27-deoxywithaferin A. The 22-hydroxydithioketal (**61**) was synthesized with a yield of 96% by the condensation of the (22S)-epoxide (**60**) with the anion obtained from 2-methyl-1,3-dithiane and butyllithium. The interaction of compound (**61**) with mercuric oxide and boron trifluoride etherate gave the 22-hydroxy-24-ketone (**62**) quantitatively. Acylation of the hydroxy group in steroid (**62**) with α-bromoacetyl bromide, a subsequent Arbuzov reaction with triethyl phosphite of the α-bromoacetate so formed to give a diethyl phosphonate, and an intramolecular Wittig–Horner reaction led to the lactone (**63**) with an overall yield of 70%. Hydrogenation of the double bond in compound (**63**) over palladium on carbon gave the saturated lactone (**64**) quantitatively. The reaction of compound (**64**) with lithium isopropylcyclohexylamide gave an anion the reaction of which with diphenyl disulfide in a mixture of tetrahydrofuran and hexametapol followed by the lithium isopropylcyclohexylamide isomerization of the phenyl sulfides formed led to the more stable (25R)-25-(phenyl sulfide) (**65**). Then an anion was obtained in the usual way from lactone (**65**), and its condensation with formaldehyde enabled the 25-hydroxymethyl derivative (**66**) to be obtained with a yield of 82%. When the sulfide group in steroid (**66**) was oxidized with *m*-chloroperbenzoic acid and the sulfoxide group formed was eliminated by heating to 100°C, the unsaturated lactone (**67**), having the same side-chain as withaferin A, was obtained with a yield of 70%.

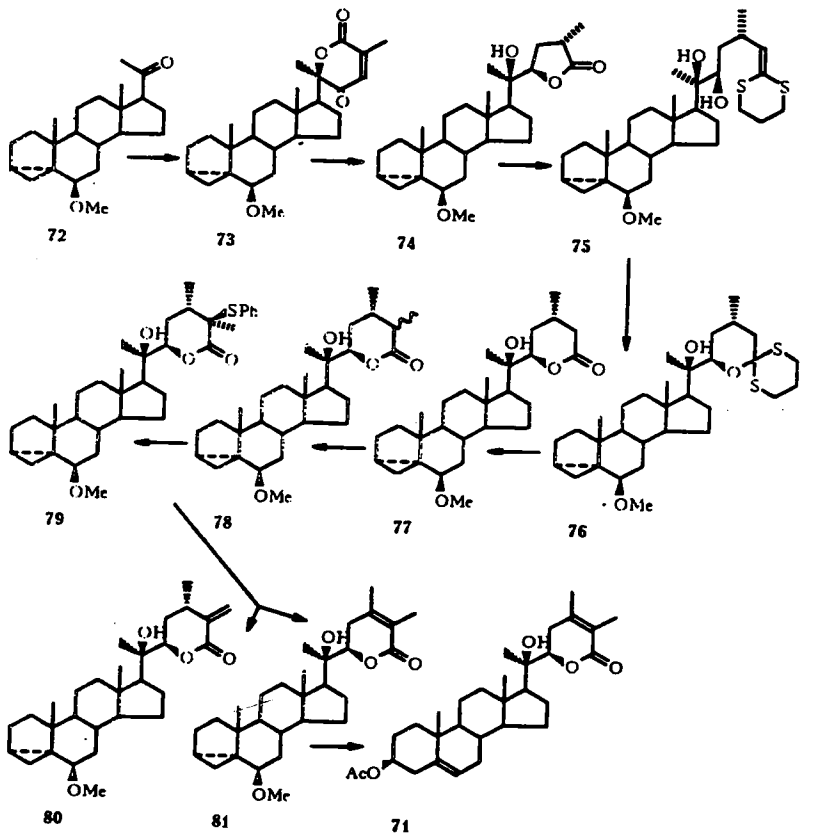


It has been shown in [22] that it is also possible to synthesize steroid (**59**) with the side-chain of 27-deoxywithaferin A from the phenyl sulfide (**65**). On the interaction of methyl iodide with the anion obtained by the reaction of sulfide (**65**) with lithium isopropylcyclohexylamide, the methyl derivative (**68**) was formed with a yield of 86%. Oxidation of the sulfide group in compound (**68**) with *m*-chloroperbenzoic acid to a sulfoxide group and its subsequent thermal elimination enabled the required unsaturated lactone (**59**) to be synthesized with a yield of 83%.

The synthesis of lactone (**71**), having the side-chain of withanolide D, started from the protected 20-hydroxy-22-aldehyde (**69**) [23].



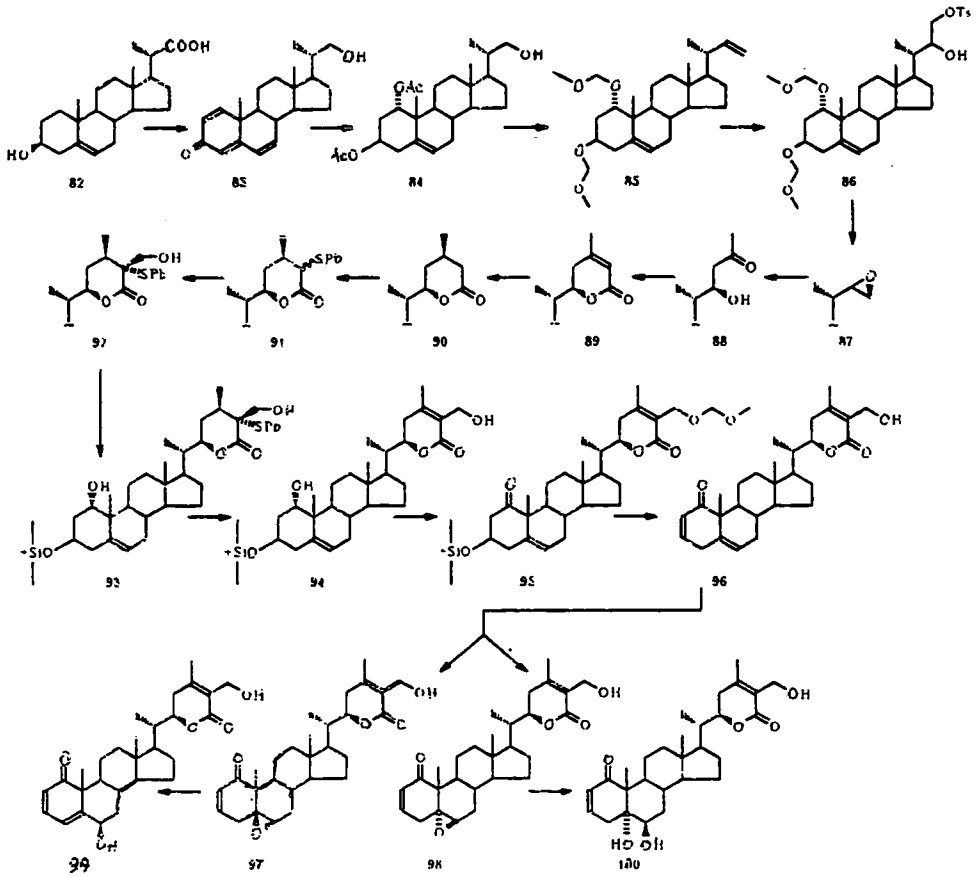
Alkylation of the aldehyde (**69**) with the lithium derivative of ethyl 2,3-dimethylbutenoate formed in 44% yield the steroid (**70**) having a similar stereochemistry of the 22-hydroxy group. The reaction of compound (**70**) with iodine in tetrahydrofuran proceeded with the formation of a high yield of the required hydroxylactone (**71**).



The addition of 2-lithio-4-methylfuran to the pregnane derivative (**72**) lies at the basis of another of the syntheses of the withanolide lactone grouping [24]. By the *m*-perbenzoic acid oxidation of the furyl alcohol so formed, followed by oxidation of the resulting lactone with pyridinium chlorochromate, the δ-lactone (**73**) was synthesized with a yield of 80%. Hydrogenation of the δ-lactone (**73**) over platinum dioxide formed the γ-lactone (**74**). Reduction of lactone (**74**) with diisobutylaluminum hydride and interaction of the lactone so formed with 2-lithio-2-trimethylsilyl-1,3-dithiane enabled the ketene dithioacetal (**75**) to be obtained. Cyclization of compound (**75**) under the action of camphorsulfonic acid led to the quantitative formation of the thio derivative (**76**) the hydrolysis of which in the presence of periodic acid gave the δ-lactone (**77**) in 94% yield.

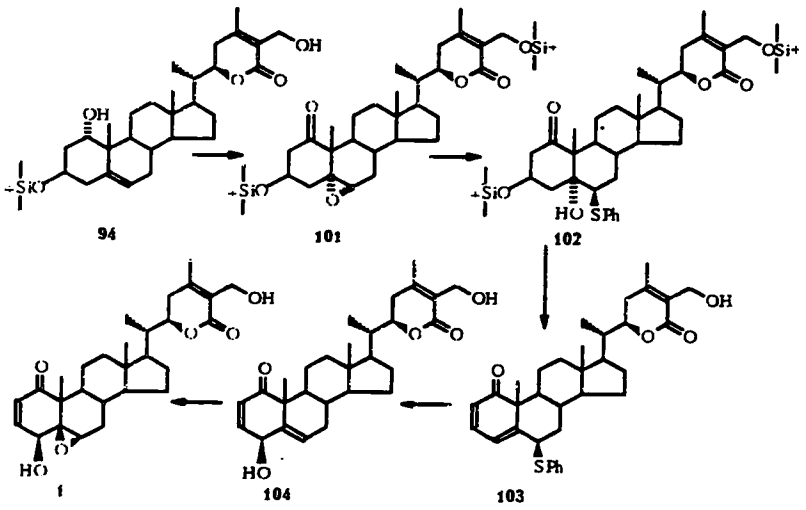
The methyl derivative (**78**) has been synthesized by the alkylation with methyl iodide of the anion obtained from lactone (77). Treatment of compound (**78**) with lithium isopropylcyclohexylamide and diphenyl disulfide led to the sulfide (**79**) with an overall yield of 80%, calculated on the lactone (**77**). Oxidation of sulfide (**79**) with *m*-chloroperbenzoic acid and elimination of the sulfoxide group so formed gave a mixture (4.2:1) of the unsaturated lactones (**80**) and (**81**). From steroid (**81**), by isomerizing rings *A* and *B* through heating in acetic acid, it was possible to obtain the acetoxylactone (**71**), from the *exo*-olefin (**80**), by an analogous reaction, followed by isomerization of the double bond in the lactone ring under the action of rhodium chloride and acetylation, the acetoxylactone (**71**) was again formed.

The successful development of methods of constructing withanolide side-chains and introducing functional groups into rings *A* and *B* has made it possible to pass from models to the synthesis of the natural compounds themselves.



Synthesis of the withanolides jaborosalactones A, B, and D has been performed, starting from the acid (**82**) [25, 26]. The lithium tetrahydroaluminate reduction of acid (**82**), followed by dichlorodicyanobenzoquinone oxidation, gave the trienone (**83**) with an overall yield of 53%, and this was then converted in four stages into the 1α,3β-diacetate (**84**). The olefin (**85**) was synthesized in an overall yield of 81% by oxidation of the 22-hydroxy group with pyridinium dichromate, the Wittig reaction of the aldehyde formed, the alkaline hydrolysis of the acetoxy group, and protection of the hydroxy groups in the form of methoxymethyl ethers. Hydroxylation of the double bond of steroid (**85**) with osmium tetroxide and N-methylmorpholine N-oxide, followed by selective tosylation of the primary 22-hydroxy group, enabled the tosylate (**86**) to be synthesized with an overall yield of 62%, and this was converted into the epoxide in quantitative yield by reaction with potassium carbonate in methanol. The regiospecific alkylation of epoxide (**87**) with the anion of 2-methyl-1,3-dithiane, followed by deketalization under the action of mercuric oxide and boron trifluoride etherate, led with a yield of 78% to the hydroxyketone (**88**). The successive interaction of compound (**88**) with α-bromoacetyl bromide, triethyl phosphite, and sodium hydride took place with the quantitative formation of the unsaturated lactone (**89**). Hydrogenation of the double bond in compound (**89**) in the presence of a palladium catalyst gave a quantitative yield of the saturated lactone (**90**). The sulfenylation of lactone (**90**) with diphenyl disulfide led to the production in 75% yield of the sulfide (**91**) in the form of a mixture (3:2) of the (25S)- and (25R)-isomers. Under the action of lithium isopropylcyclohexylamide, the sulfide (**91**) formed an anion the interaction of which with monomeric formaldehyde led with a yield of 76% to derivative (**92**). The acid hydrolysis of compound (**92**) with the aim of eliminating the methoxymethyl protective groupings and the selective silylation of the 3β-hydroxy group formed steroid (**93**) in 63% yield. Oxidation of sulfide (**93**) with *m*-chloroperbenzoic acid to the sulfoxide and subsequent thermal desulfuration led to the unsaturated lactone (**94**) the primary hydroxy group in which was protected while the secondary one was oxidized with pyridinium dichromate to the 1-ketone (**95**). Hydrolysis of the protective groups in compound (**95**) and elimination of the 3-hydroxy group gave an 81% yield of the dienone (**96**), epoxidation of the 5(6)-double bond in which led to a mixture (1:2.5) of jaborosalactone A (**97**) and the 5α,6α-epoxide (**98**) with an overall yield of 71%. After the separation of the mixture,

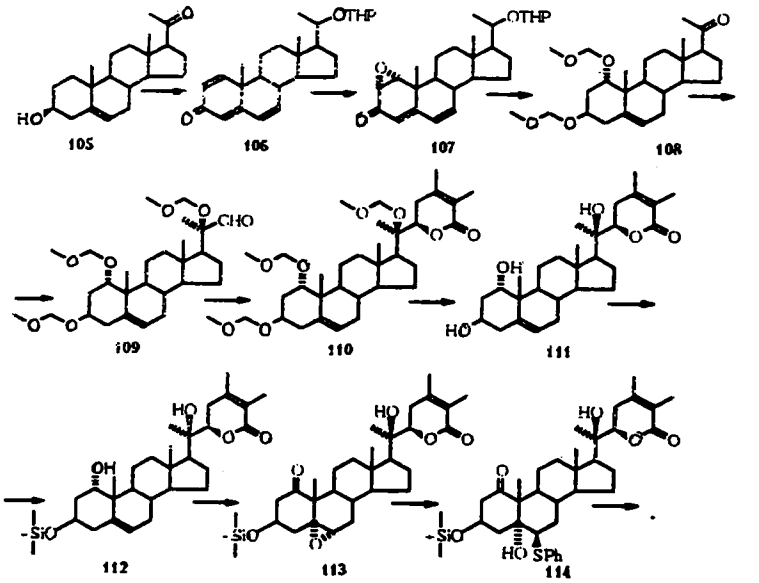
jaborosalactone B (**99**) was synthesized from jaborosalactone A (**97**) by isomerization under the action of caustic potash. Acid hydrolysis of the 5α,6α-epoxy group in steroid (**98**) with aqueous perchloric acid gave jaborosalactone D (**100**).

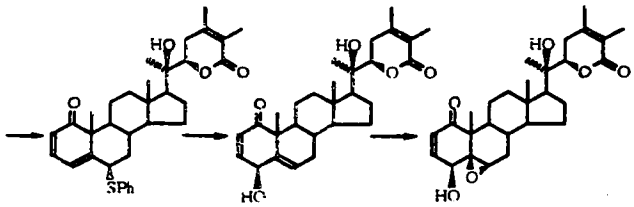


The synthesis of withaferin A was effected from the 3-protected trihydroxylactone (**94**) using a method developed previously for introducing functional groups into rings *A* and *B* [26, 27]. As a result of the epoxidation of the 5(6)-double bond in steroid (**94**) with *m*-chloroperbenzoic acid, protection of the primary 27-hydroxy group in the form of the methoxymethyl ether, and oxidation of the 1α-hydroxy group with pyridinium dichromate, the 1-keto-5,6-epoxysteroid (**101**) was synthesized with a yield of 49%. Opening of the epoxide ring in steroid (**101**) under the action of thiophenol in the presence of alumina led to the formation with a yield of 37% of the 6β-phenylthio derivative (**102**). Hydrolysis of the methoxymethyl grouping of compound (**102**) in the presence of *p*-toluenesulfonic acid was accompanied by the elimination of the 5α-hydroxy group, leading in this way to the quantitative formation of the 6β-phenylthiodienone (**103**). By oxidizing the sulfide group in derivative (**103**) with *m*-chloroperbenzoic acid to the corresponding sulfoxide and subsequent sulfoxide—sulfenate rearrangement under the action of triethyl phosphite, the 4β-hydroxydienone (**104**) was obtained with a yield of 52%. Epoxidation of the 5(6)-double bond in steroid (**104**), the stereochemistry of which is determined by the configuration of the 4β-hydroxy group, gave withaferin A (**1**).

Subsequently, 27-deoxywithaferin A was synthesized from the lactone (**91**) [26, 27]. Alkylation of lactone (**91**) with methyl iodide formed the corresponding 27-deoxy analog of the phenylthiolactone (**92**), from which 27-deoxywithaferin A, was obtained by methods analogous to those in the synthesis of withaferin A (**1**).

Methods for the synthesis of 20-hydroxywithanolides such as withanolide D (**2**) from pregnane derivatives have been developed [26, 27]. In such a scheme, the tetrahydropyranyl ether (**106**) was obtained by the reduction of pregnenolone (**105**) with sodium tetrahydroborate, oxidation with dichlorodicyanobenzoquinone, and protection of the 20-hydroxy group. The interaction of compound (**106**) with alkaline hydrogen peroxide led to the formation of the 1α,2α-epoxide (**107**).





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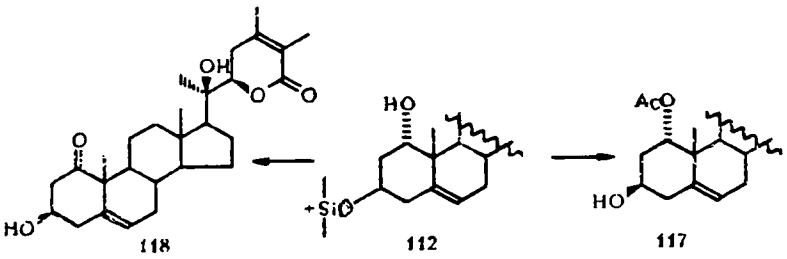
Reduction of the epoxyketone (**107**) by lithium in liquid ammonia gave a 1α,3β-diol, the hydroxy groups in which were protected by the formation of the methoxymethyl ether, and then the 20-tetrahydropyranyl ether was hydrolyzed and the 20-hydroxy group was oxidized with pyridinium chlorochromate. From the 20-ketone (**108**) obtained in this way the 22-aldehyde was synthesized by alkylation with the lithium salt of 1,3-dithiane, hydrolysis of the resulting dithioacetal with mercuric oxide and boron trifluoride etherate, and protection of the 20-hydroxy group. Alkylation of the aldehyde (**109**) with the enolate anion obtained from ethyl α,β-dimethylcrotonic acid and lithium diisopropylamide gave lactone (**110**) with a yield of 86%. Hydrolysis of the protective methoxymethyl groups in compound (**110**) with hydrochloric acid in tetrahydrofuran led with a yield of 82% to the trihydroxylactone (**111**), identical with the natural withanolide deacetylphysalolactone B. Selective silylation of the sterically more accessible 3β-hydroxy group in compound (**111**) enabled the silyl ether (**112**) to be obtained with a yield of 90%. Epoxidation of compound (**112**) with *m*-chloroperbenzoic acid and oxidation of the 1α-hydroxy group with pyridinium dichromate led to the 5α,6α-epoxy-1-ketosteroid (**113**). By the opening of the epoxide ring in compound (**113**) with thiophenol, a 75% yield of the 6β-thio derivative (**114**) was obtained, and the interaction of this with *p*-toluenesulfonic acid hydrate in boiling benzene formed the 6β-phenylthio-2,4-dien-1-one (**115**) with a yield of 84%. Oxidation of the sulfide with *m*-chloroperbenzoic acid and rearrangement of the resulting sulfoxide under the action of trimethyl phosphite enabled the 4β-hydroxy-2,5-dien-1-one (**116**) to be obtained with a yield of 55%. Withanolide D (**2**) was synthesized from steroid (**16**) with a yield of 72% by the epoxidation of the 5(6)-double bond.

The acetylation of compound (**112**) followed by acid hydrolysis of the 3-silyloxy group gave a 68% yield of the withanolide physalolactone B (**117**).



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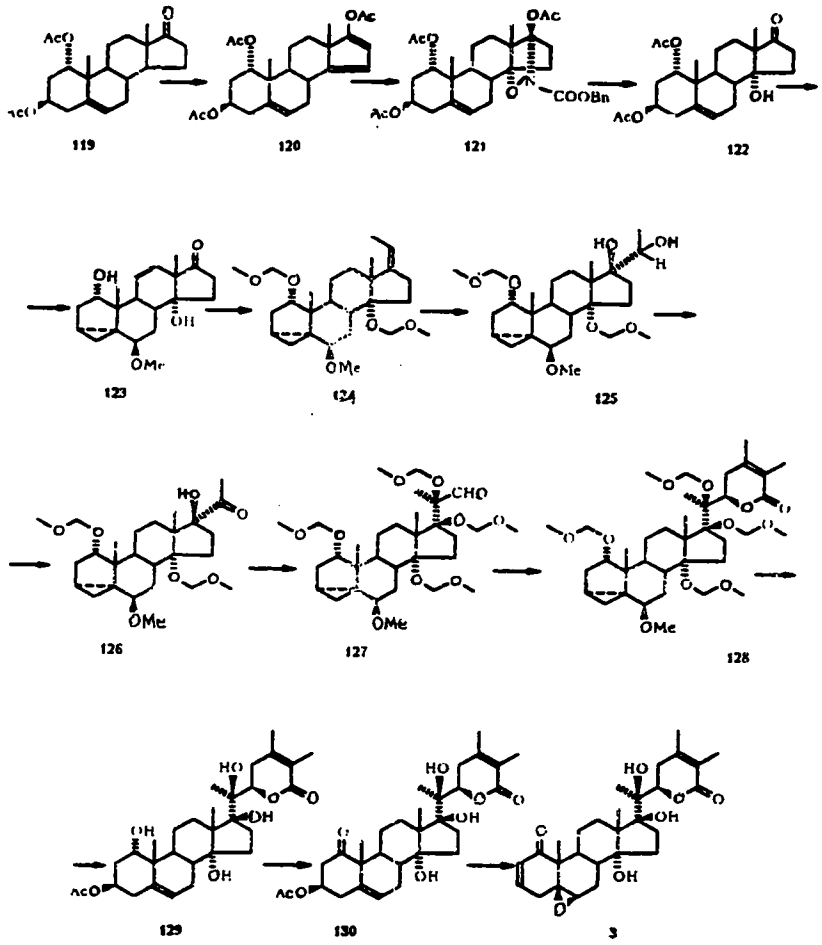
In its turn, oxidation of the hydroxylactone (**112**) with pyridinium dichromate, followed by acid hydrolysis enabled yet another withanolide – 3β,20R-dihydroxy-1-oxowitha-5,24-dienolide (**118**) – to be obtained with a yield of 61%.

The synthesis of (+)-withanolide E (**3**) from the 1α,3β-diacetoxy-17-ketone (**119**) is described in [29]. The first stages of the synthesis had the aim of introducing a 14α-hydroxy group. The 17-ketone (**119**) was first converted by reaction with trimethyliodosilane into the corresponding enolic silyl ether, from which steroid (**120**) was synthesized with an overall yield of 86% by its reaction with palladium(II) acetate in the presence of potassium carbonate in acetonitrile and conversion of the resulting product into the enol acetate by interaction with isopropenyl acetate. As the result of the 1,4-cycloaddition of benzyl nitrosoformate, obtained by the oxidation of benzyl N-hydroxycarbamate with tetrabutylammonium periodate, to the diene grouping of compound (**120**), followed by isomerization of the minor adduct by boiling in toluene, it was possible to obtain the 14α-hydroxy-17-ketone (**122**) in an overall yield of 85%. Hydrogenation of steroid (**121**) over 5% palladium on barium carbonate and subsequent reaction with copper(II) chloride in aqueous tetrahydrofuran led to the 14α-hydroxy-17-ketone (**122**) with an overall yield of 79%.

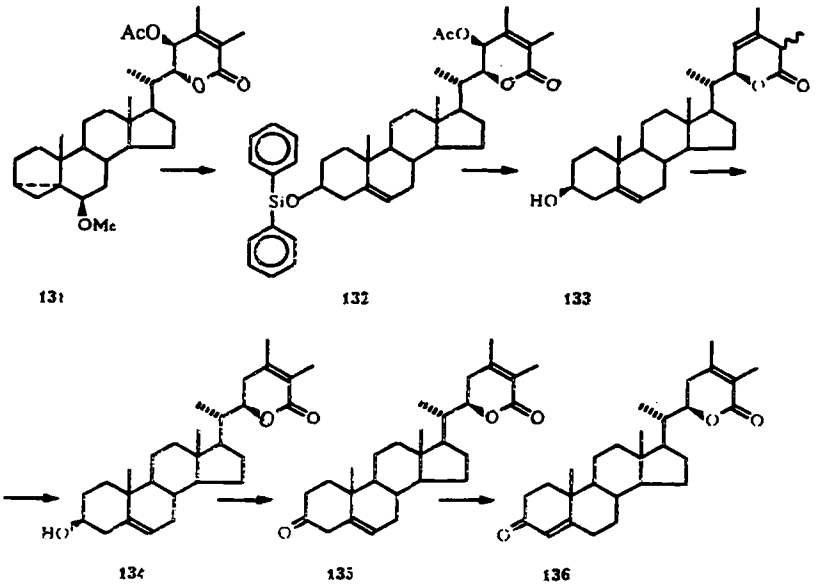
Before the introduction of the necessary side-chain into steroid (**122**), in order to protect the hydroxy group already present a transformation was made in the cyclic part of the molecule.



For this, hydrolysis of the diacetate (**122**) with potassium hydroxide gave a quantitative yield of the 1α,3β-diol, from which, by selective reaction with *p*-toluenesulfonyl chloride in pyridine, the 3-monotosylate was synthesized; the remaining free secondary 1α-hydroxy group was converted into a trimethylsilyl ether by reaction with trimethylsilyl triflate. The tosylate was subjected to solvolysis in methanol in the presence of potassium acetate, and, finally, the 1-trimethylsilyl ether was hydrolyzed by tetrabutylammonium fluoride, to form the 3α,5-cyclosteroid (**123**) with an overall yield of 50%. The free hydroxy groups in compound (**123**) were converted into methoxymethyl ethers, and a subsequent Wittig reaction of the 17-ketone with ethylidenetriphenylphosphorane led to the (17Z)-ethylidene derivative (**124**) in an overall yield of 85%.

On the hydroxylation of the 17(20)-double bond in compound (**124**) with osmium tetroxide, separation of the resulting mixture (1.4:1) of diols, and the Swern oxidation of the main diol (**125**) with dimethyl sulfoxide and trifluoroacetic anhydride, the 17β-hydroxy-20-ketone (**126**) was obtained with an overall yield of 89%. The addition of vinyllithium to the 20-keto group of steroid (**126**) took place with the quantitative formation of the corresponding allyl alcohol, protection of the 14- and 20-hy droxy groups in which in the form of methoxymethyl ethers and subsequent ozonolysis gave the 22-aldehyde (**127**) with an overall yield of 70%. Alkylation of the 22-aldehyde (**127**) with the anion obtained from ethyl α,β-dimethylcrotonate and lithium diisopropylamide took place with the formation of the δ-lactone (**128**) having the required stereochemistry of the C-14, C-17, C-20, and C-22 atoms.

Hydrolysis of the protective groups in compound (**128**) with aqueous sulfuric acid in dioxane led to the corresponding pentaol, the selective acetylation of the 3β-hydroxy group in which led in 72% yield to the 3-monoacetate (**129**). The Swern oxidation of the 1α-hydroxy group in steroid (**129**) gave a 78% yield of the 1-ketone (**130**), from which, by interaction with 1,5-bicyclo[4,3,0]non-5-enone and epoxidation with *m*-chloroperbenzoic acid, (+)-withanolide E (**3**) was synthesized with an overall yield of 71%.



In [21], starting from the acetoxylactone (**131**), obtained by acetylation of the hydroxylactone (**57**), an attempt was made to synthesize minabeolide-3 (**136**), isolated previously from the soft coral *Minabea sp.* [30]. On isomerization in rings *A* and *B* under the action of *p*-toluenesulfonic acid in aqueous dioxane, steroid (**131**) gave the corresponding Δ^5-3β-alcohol the hydroxy group of which was protected quantitatively by reaction with *tert*-butylchlorodiphenylsilane to form the silyl ether (**132**). The reductive deacetoxylation of compound (**132**) by zinc amalgam in ether in the presence of hydrogen chloride led with a yield of 80% to the corresponding nonconjugated unsaturated lactone, the silyl protective group in which was subjected to hydrolysis with hydrofluoric acid in acetonitrile to form the hydroxylactone (**133**) in 93.3% yield. The double bond in compound (**133**) was isomerized by 1,8-diazabicyclo[5.4.0]undec-7-ene with the quantitative formation of the conjugated lactone (**134**). The Swern oxidation of the 3β-hydroxy group in the latter gave an 88.4% yield of the Δ^5-3-ketone (**135**), the isomerization of which with oxalic acid in ethanol led in quantitative yield to compound (**136**), identical with natural minabeolide-3.

Thus, on the basis of the examples discussed above it may be concluded that chemical syntheses of such complex structures as the withanolides may be fully included among the achievements of modern organic synthesis. At the same time, because of their complexity, at present they are inferior in efficiency to the traditional phytochemical methods of isolating withanolides from plants. However, it may be hoped that in future the chemical synthesis of withanolides and compounds related to them will become an important supplement to the phytochemical and biotechnological methods of obtaining these biologically active substances.

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