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SYNTHESIS OF *Achlya* POLYHYDROXYSTEROIDS

N. V. Kovganko and Zh. N. Kashkan

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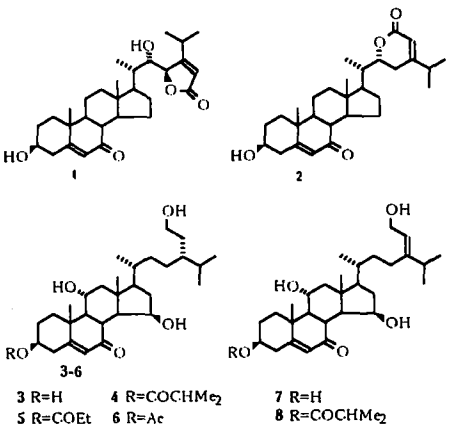
This review generalizes the results of investigations on the chemical synthesis of sex hormones of aquatic fungi of the Achlya *genus.*

Sex hormones, the chemical structure of which is that of C_{29}-polyhydroxysteroids, are extremely important for the normal vital activity of oomycetes of the genus *Achlya* [1, 2]. At the present time it is known that the processes of sexual development of these fungi are under the control of hormones: antheridiol (**1**), 23-deoxyantheridiol (**2**), oogoniols (**3-6**), and 24(28)-dehydrooogoniols (**7**, **8**). Possessing a very high biological activity in extremely low concentrations, these substances are not only of scientific but also of practical interest. In particular, antheridiol has been proposed as an agent for raising the productivity of agricultural plants [3]. Being extremely active substances, the sex hormones are produced by *Achlya* fungi in very low concentrations [4-6]. Consequently, the amounts of these substances required for scientific or practical purposes can be obtained only by means of chemical synthesis. For this reason investigations on the development of convenient methods of synthesis were begun immediately after the isolation of concrete substances and the determination of their structures.



Antheridiol (**1**) was the first of the *Achlya* sex hormones to be identified. The determination of its structure [7] enabled its chemical synthesis to be begun, and this was first achieved by American workers in 1969 [8]. In this synthesis, the interaction of the aldehyde (**9**) with the anion of ethyl 3,4-dimethylpent-*trans*-2-enoate led with a yield of 23% to the unsaturated lactone (**10**) the subsequent hydrolysis of which with sodium hydroxide, followed by treatment with hydrochloric acid, led to the formation of the unsaturated acid (**11**) with a yield of 86%.

Institute of Bioorganic Chemistry, Belarus Academy of Sciences, 5/2 Zhodinskaya ul., Minsk, Belarus 220141.
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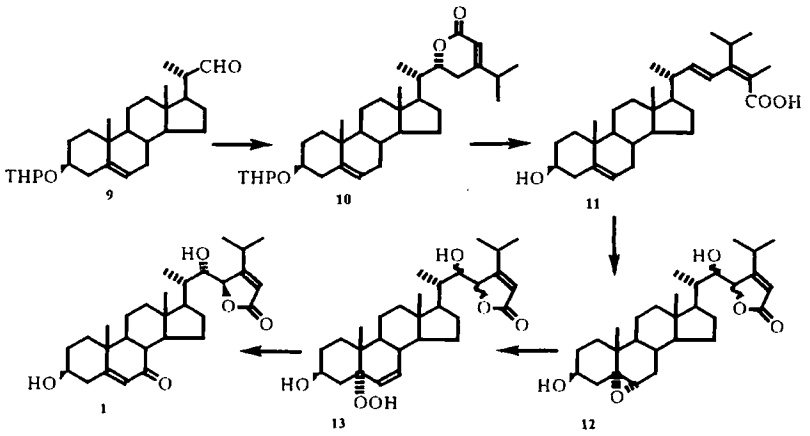
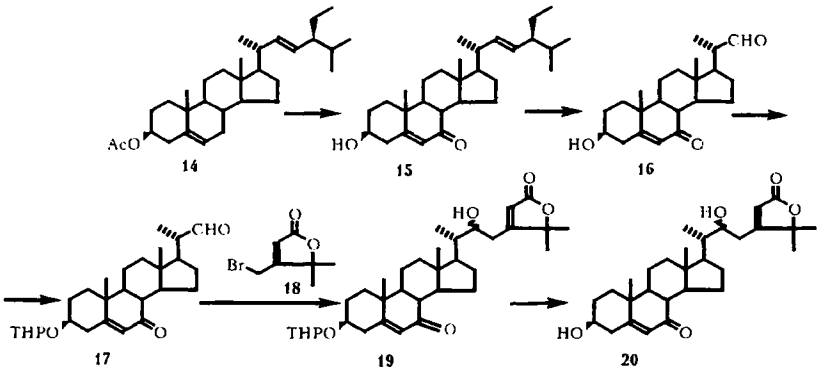
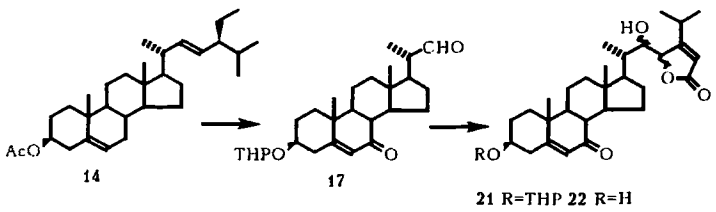


By the oxidation of steroid (**11**) with *m*-chloroperbenzoic acid and chromatographic separation of the mixture of products it was possible to obtain the γ-lactone (**12**) with a yield of 6%. The corresponding Δ^5-lactone was formed by the regeneration of the 5,6-double bond in compound (**12**) with zinc dust and sodium iodide in acetic acid, and the photooxidation of this lactone in the presence of the sensitizer hematoporphyrin gave the hydroperoxide (**13**). The oxidative rearrangement of (**13**) under the action of copper acetate led to the synthesis of 22,23-isoantheridiol and antheridiol (**1**) (the yields calculated on the epoxylactone (**12**) were 5 and 2.4%, respectively).



A synthesis of the antheridiol isomer (**20**) starting from stigmasterol acetate (**14**) has been described by McMorris [9]. Oxidation of stigmasterol acetate (**14**) with sodium chromate in a mixture of acetic acid and acetic anhydride, followed by hydrolysis of the 3β-acetoxy group with potassium carbonate gave the hydroxyketone (**15**). Ozonolysis of compound (**15**) followed by reduction with zinc in acetic acid led with 40% yield to the aldehyde (**16**). In steroid (**16**) the hydroxy group was protected by the formation of the tetrahydropyranyl ether (**17**). The Reformatskii reaction of aldehyde (**17**) with the bromolactone (**18**) gave a 15% yield of steroid (**19**), by hydrolysis of the protective group in which the dihydroxyketolactone (**20**) was obtained.

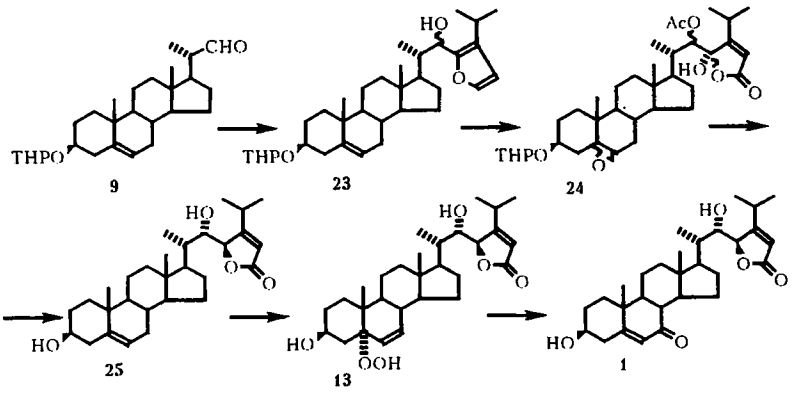


McMorris et al. [10, 11] first obtained the 22-aldehyde (**17**) from the readily available stigmasterol acetate (**14**) by the method developed previously [9]. Condensation of the 22-aldehyde (**17**) with γ-bromo-β-isopropylbutenolide gave product (**21**) in the form of a mixture of isomers possessing 1% of the biological activity of antheridiol. The authors were unable to isolate pure antheridiol from the mixture of reaction products.

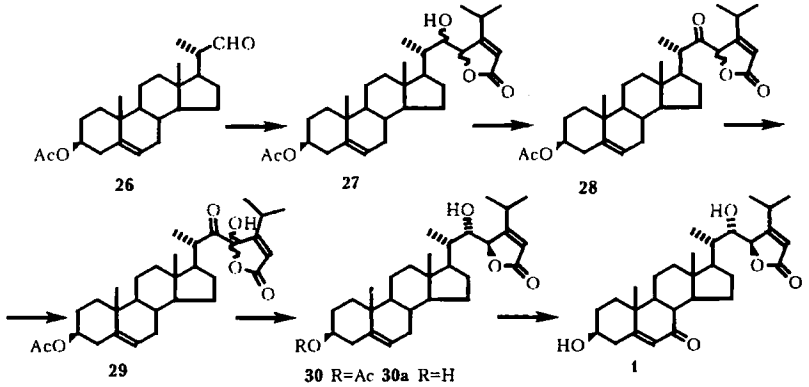
During further investigations, the same authors [10, 11] synthesized isopropylbutenolide and obtained its carbanion by reaction with trityllithium in tetrahydrofuran at −30°C. The carbanion reacted with aldehyde (**17**) at −70°C with the formation in a yield of 40% of product (**21**), the acid hydrolysis of which gave a mixture of the 22,23-epimers (**22**) quantitatively. Samples of both mixtures (**21**) and (**22**) showed only 10% of the biological activity of antheridiol. Again, it was impossible to isolate pure antheridiol by the chromatographic method and by repeated crystallization.

The (22S,23R)-configuration of the side-chain of antheridiol (**1**), synthesized by the stereoselective method developed starting from the aldehyde (**9**), was first established unambiguously by Edwards et al. [12]. Condensation of the 22-aldehyde (**9**) with the lithium derivative of isopropylfuran led to the formation of the alcohol (**23**) in a yield of 60%. Subsequent acetylation and reaction with *m*-chloroperbenzoic acid gave the lactone (**24**). The reduction of compound (**24**) with sodium tetrahydroborate to a mixture of epoxybutenolides, regeneration of the double bond in these under the action of zinc and sodium iodide in acetic acid, and acid hydrolysis of the Δ^5-acetoxy-γ-lactones formed gave a mixture of four isomeric dihydroxybutenolides. The required butenolide (**25**) was isolated from this mixture by thin-layer chromatography.

In completion of the synthesis, by the photooxidation of compound (**25**) in the presence of hematoporphyrin as sensitizer, followed by rearrangement of the resulting Δ^6-5α-peroxide (**13**) on treatment with copper(II) acetate, steroid (**1**) was obtained with a yield of 36%. All the physicochemical and biological characteristics of the antheridiol (**1**), synthesized with an overall yield of about 1%, calculated on the aldehyde (**9**), coincided completely with the properties of the natural hormone.



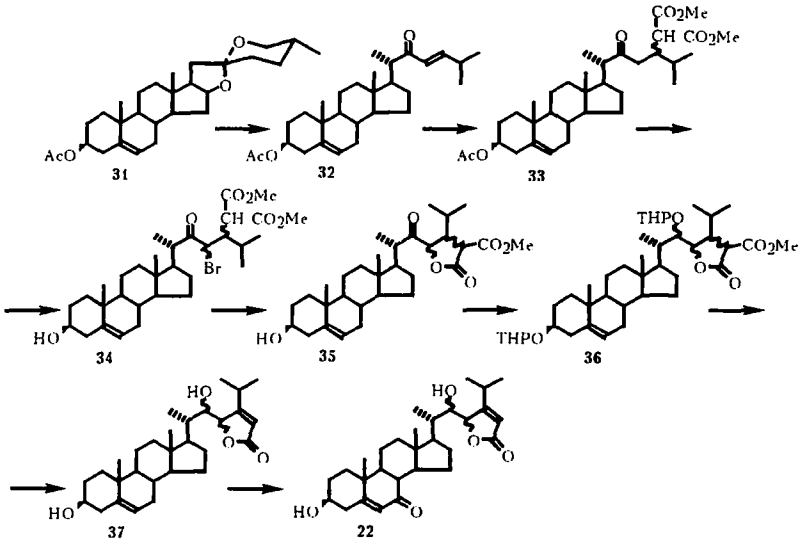
A rise in the yield of antheridiol (**1**) to 20% was achieved by a method proposed for changing the stereochemistry of the side-chains of its 22R,23S- and 22R,23R-isomers [11, 13]. Its essence consisted in the Jones oxidation of the mixture of antheridiol isomers (**27**), obtained with a yield of 70% from the 22-aldehyde (**26**) [10, 11], to a mixture of the corresponding ketones (**28**). By autooxidation in a mixture of tetrahydrofuran and methanol in the presence of silica gel at room temperature, the latter were converted quantitatively into the hydroxyketones (**29**).



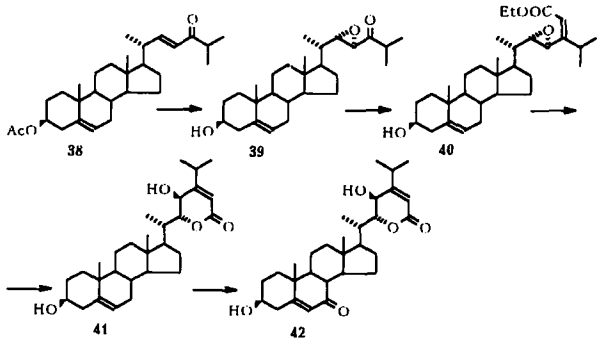
The reduction of compound (**29**) with sodium tetrahydroborate gave a mixture of products containing about 30% of steroid (**30**) with the natural (22S,23R)-configuration of the side-chain. After its separation, the remaining mixture of isomers was again subjected to the given sequence of reactions, and this was repeated until the maximum yield of the desired product had been achieved. In the final stage of the synthesis, after elimination of the acetate protection with dilute sulfuric acid, a 7-

keto group was introduced into the compound so obtained, (**30a**), by two methods. One of them consisted in photooxidation followed by rearrangement [8] and gave antheridiol (**1**) with a yield of 35%. A higher yield of (**1**) was obtained by converting the diol (**30**) into the tetrahydropyranyl ether, its oxidation with the Collins reagent, and the removal of protective groups. All the characteristics of the synthetic product and of natural antheridiol coincided completely.

Yet another attempt to synthesize antheridiol has been described in [14]. In this, the acetoxyenone (**32**) was obtained by a multistage synthesis from diosgenin acetate (**31**). The addition of dimethyl malonate to the double bond of steroid (**32**) enabled a mixture of two isomers (**33**) to be obtained. One of them, isolated by crystallization from methanol, was converted into the 23-bromo derivative (**34**) by hydrolysis to the monomethyl ester, its bromination, and the regeneration of the Δ^5-bond.



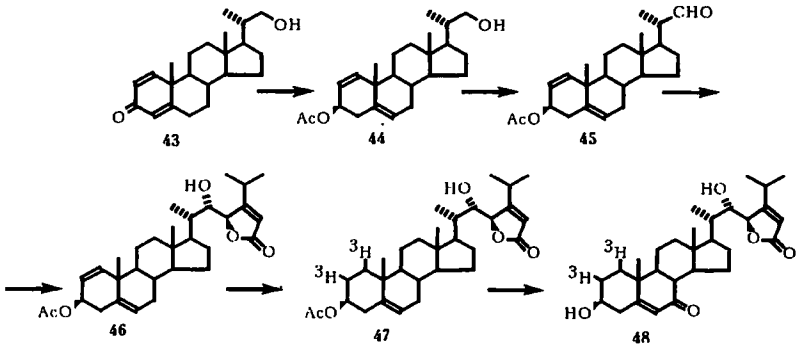
Treatment of the steroid (**34**) with sodium bicarbonate in methanol gave compound (**35**). Selective reduction of the 22-carbonyl group of its tetrahydropyranyl ether with lithium tetrahydroborate, the tetrahydropyranyl protection of the hydroxyls, and the subsequent boiling of steroid (**36**) with calcium carbonate, lithium iodide, and iodine took place with the formation of the α,β-unsaturated γ-lactone (**37**). To introduce a 7-keto group into the Δ^5-steroid (**37**), the authors used photooxidation in dimethylformamide in the presence of methylene blue as sensitizer, followed by rearrangement of the Δ^6-5α-peroxide under the action of copper(II) acetate, and obtained the desired product (**22**) with a yield of 28%. In a biological test, this substance showed about one tenth of the activity of antheridiol.



It structure was not accurately determined. It is assumed that it was either a pure epimer of the natural hormone or an epimer containing antheridiol as an impurity.

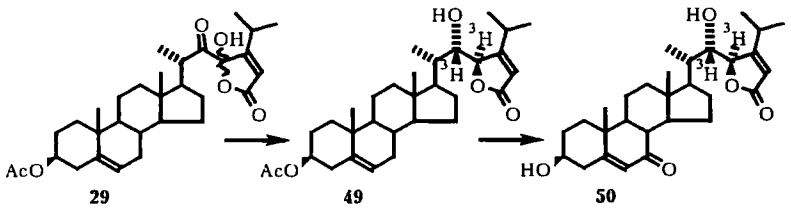
A successful synthesis of the 23-hydroxy-δ-lactone (**42**), which is an isomer of antheridiol, started from the α,β-unsaturated ketone (**38**) [15]. On the epoxidation of the 22(23)-double bond in compound (**38**) with hydrogen peroxide in methanol in the presence of alkali and subsequent hydrolysis of the acetoxy group, the 22S,23R-epoxy-24-ketone (**39**) was obtained with an overall yield of 70%. The ester (**40**), having the (E)-geometry of the 24(28)-double bond, was synthesized with a yield of 30% by condensing the steroid (**39**) with the ylide obtained from diethyl ethoxycarbonylmethylphosphonate.

By treating compound (**40**) with aqueous perchloric acid in methanol the hydroxylactone (**41**) was formed quantitatively. The photooxidation of steroid (**41**) in the presence of hematoporphyrin, followed by rearrangement of the resulting Δ^6-5α-hydroperoxide with copper acetate, enabled the final substance (**42**) to be obtained with a yield of 50%.



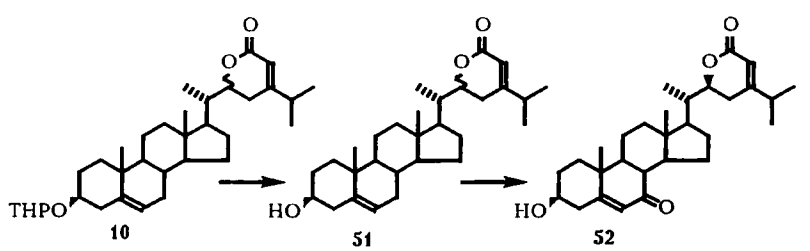
Tritium-labeled antheridiol (**48**) has been synthesized from the commercially available compound (**43**) with the aim of detecting the cytosolic receptors of aquatic fungi of the *Achlya* genus [16]. The tetrahydropyranyl protection of its hydroxy group, treatment with potassium *tert*-butanolate, reduction of the resulting 1,5-dien-3-one with potassium tetrahydroborate, acetate protection of the 3β-hydroxyl, and elimination of the tetrahydropyranyl protective group, performed successively, then gave the alcohol (**44**) in high yield.

By oxidizing the latter with pyridinium chlorochromate it was converted into the aldehyde (**45**), the condensation of which by a known method [11] with the enolate obtained by the interaction of the lithium derivative of triphenylmethane and 3-isopropyl-but-2-enolide led to the usual mixture of isomeric compounds. The yield of the required alcohol (**46**) was 3%. The ditritium derivative (**47**) was obtained in high yield by tritiating the more reactive disubstituted Δ^1-double bond of steroid (**46**) over tris(triphenylphosphine)rhodium chloride. Subsequent hydrolysis, silyl protection of the hydroxy group, oxidation by the complex of chromic anhydride with dimethylpyrazole, and acid hydrolysis gave, after chromatographic purification, the desired 1,2-[^{3}H]-antheridiol (**48**) with a yield of 54%.



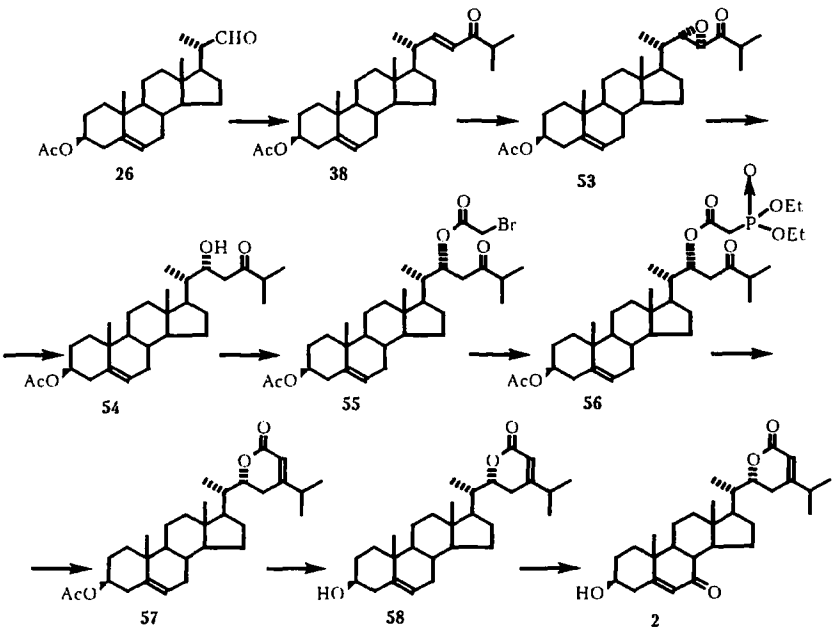
22,23-[^{3}H]-Antheridiol (**50**) has been synthesized for a study of metabolism [17]. Reduction of the γ-lactone (**29**) with tritiated sodium tetrahydroborate in a mixture of tetrahydrofuran and methanol gave the steroid (**49**). Hydrolysis of the latter with sulfuric acid in aqueous dioxane and photooxidation of the resulting 3β-alcohol in the presence of hematoporphyrin, followed by the copper(II)-chloride-catalyzed rearrangement of the Δ^6-5α-peroxide, led to the required tritium-labeled antheridiol (**50**).

Together with antheridiol (**1**), the related compound 22-deoxyantheridiol (**2**) has been isolated from *Achlya* aquatic fungi [18]. Reports [15, 18] describing the synthesis of 23-deoxyantheridiols epimeric at C_{22} are of great importance for establishing its structure.

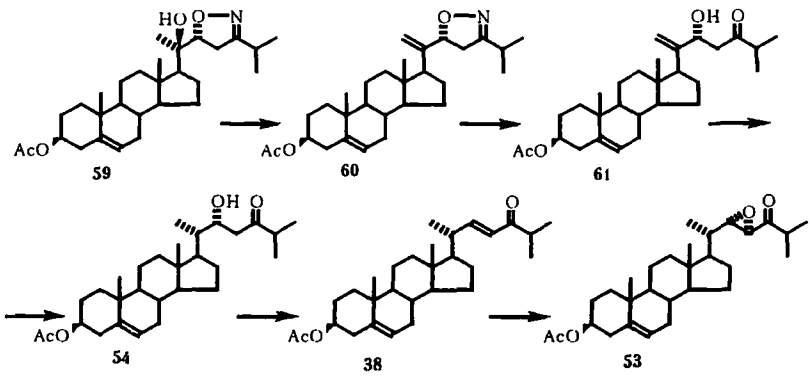


As noted above, the saturated lactone (**10**) was used in the synthesis of antheridiol [8]. Green et al. [18] started from this substance in their synthesis of the 22-epimer of 23-deoxyantheridiol (**52**). Hydrolysis of the steroid (**10**) in methanol in the presence of hydrochloric acid formed the alcohol (**51**). 22-Epi-23-deoxyantheridiol (**52**) was obtained in an overall yield of 50% by the photooxidation of compound (**51**) in pyridine, with the use of hematoporphyrin as sensitizer, and the subsequent oxidation of the resulting Δ^6-5α-hydroperoxide with copper(II) acetate.

The synthesis of 23-deoxyantheridiol (**2**) from the 22-aldehyde (**26**) was successfully achieved in 1978 [19]. The Wittig reaction of steroid (**26**) with the appropriate phosphorane gave the Δ^{22}-24-ketone (**38**) with a yield of 87%. The 22S,23R-epoxide (**53**) was synthesized quantitatively by epoxidizing the 22,23-double bond in compound (**38**) with 30% hydrogen peroxide in the presence of alkali, followed by acetylation. Reduction of the epoxide with aluminum amalgam to form the alcohol (**54**), acylation of the 22-hydroxy group, and heating the α-bromoacetate (**55**) with triethyl phosphite gave the phosphonate (**56**). An intramolecular Wittig–Horner reaction of steroid (**56**) on treatment with sodium hydride led to the saturated δ-lactone (**57**) the hydrolysis of which and the introduction of a 7-keto group into the resulting compound (**58**) enabled the desired product (**2**) to be obtained in an overall yield of 30% calculated on the aldehyde (**26**). It must be mentioned that in biological tests 23-deoxyantheridiol (**2**) showed negligible activity.

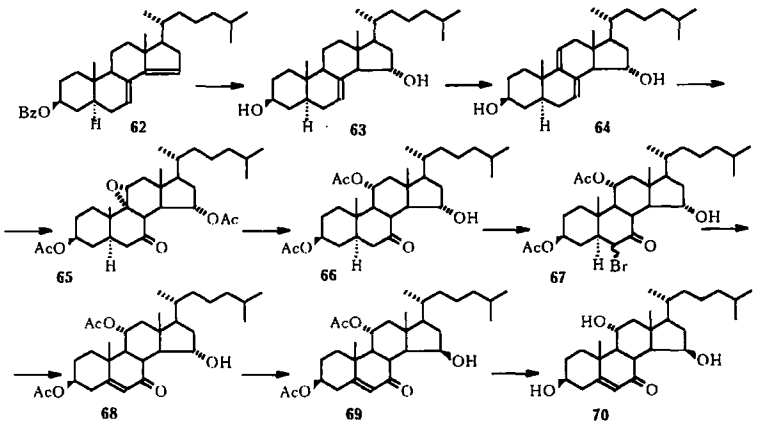


A fairly original route to the production of some intermediates in the synthesis of 23-deoxyantheridiol has been proposed by Khripach et al. [20]. The $\Delta^{20(21)}$-steroid (**60**) was synthesized in 74% yield by the dehydration with thionyl chloride of the hydroxyisoxazoline derivative (**59**), obtained by a somewhat complex method from pregnenolone acetate. Its hydrogenation over Raney nickel in the presence of boric acid led with a yield of 65% to the 22-hydroxy-24-ketone (**61**). Subsequent hydrogenation of the sterically more accessible 20(21)-double bond in compound (**61**) over platinum dioxide gave, with an overall yield of 59%, the steroid (**54**) and its 20-isomer in a ratio of 3:2.

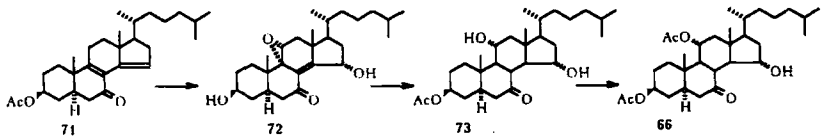


The Δ^{22}-24-ketone (**38**) was formed with a yield of 87% as a result of the dehydration of hydroxyketone (**54**) by boiling it in toluene in the presence of *p*-toluenesulfonic acid and calcium chloride. Epoxidation of the 22(23)-double bond in compound (**38**) with hydrogen peroxide in the presence of sodium hydroxide, followed by acetylation, gave in an overall yield of 84% the epoxyketone (**53**), the reduction of which with aluminum amalgam once more permitted the synthesis of the 22-hydroxy-24-ketone (**54**).

The year 1975 saw the isolation another group of steroid sex hormones, called oogoniols (**3-6**), from aquatic fungi of the *Achlya* genus [21]. However, the position of the primary hydroxy group of the side-chain in the molecules of these compounds was not established until 1978 [22].



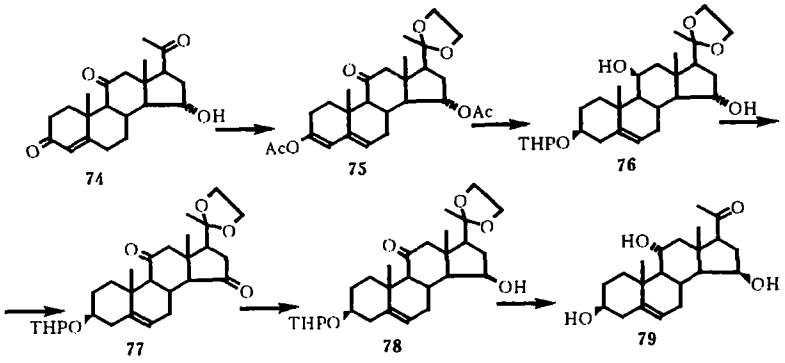
The first studies on the synthesis of the oogoniols were devoted to the introduction of the necessary functional groups into the cyclic part of the molecule. Thus, [23] describes the synthesis of the model compound (**70**) having in the cyclic part of its molecule the functional groups characteristic for the oogoniols. Saponification of the benzoate (**62**) gave a dienol, the hydroboration–oxidation of the 14,15-double bond in which led to the 15α-alcohol (**63**) with a yield of 78%. The dehydration product of (**63**) — (**64**) — was isolated in the form of the diacetate. Its epoxidation with performic acid took place with the formation of the epoxide (**65**). Subsequent alkaline treatment of compound (**65**), catalytic hydrogenation of the 8,9-double bond in the resulting 3β,11α,15α-triol, and boiling in alkaline methanolic solution with the aim of isomerization at C_8 and C_9 followed by selective acetate protection of the 3β- and 11α-hydroxy groups, gave the diacetate (**66**). Its bromination with pyridine hydrobromide perbromide and dehydrobromination of the resulting mixture of bromoketones epimeric at C_6 (**67**) led to the Δ^5-7-keto derivative (**68**).



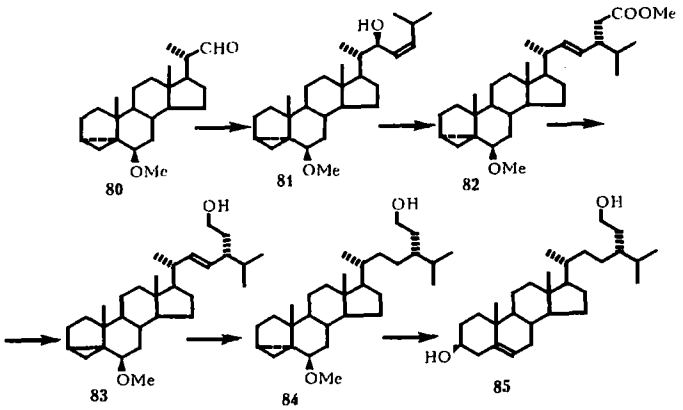
The conversion of the latter into the desired compound (**70**) consisted in the oxidation of steroid (**68**) to the 7,11-diketone, followed by the hydride reduction of its two keto groups, oxidation of the allyl hydroxyl with the formation of the 15β-hydroxy derivative (**69**), and the hydrolysis of its 3β,11α-acetate groups. The polyhydroxysteroid (**70**) obtained in this way was contaminated with the 15α-isomer. In biological tests, compound (**70**) did not reveal the activity characteristic for the oogoniol (**3**).

Another route to steroid (**66**) has been proposed by Anastasia et al. [24, 25]. The first stage consists in the oxidation of the dienone (**71**) with *m*-chloroperbenzoic acid in dichloromethane to the allyl epoxide (**72**) with a yield of 65%. Catalytic hydrogenation of the 8,14-double bond in compound (**72**) over a palladium catalyst gives ketone (**73**) with the unnatural orientation of the hydrogen atoms at C_8 and C_9. Then, as in the method of [23], steroid (66) is obtained in high yield by treatment with potassium hydroxide in methanol and selective acetylation.

A method of constructing a steroid nucleus possessing the 11α- and 15β-hydroxy groups characteristic for the oogoniols has been proposed by Weihe and McMorris [26].



According to the scheme of synthesis, the progesterone derivative (**74**) was converted by treatment with acetyl chloride in acetic anhydride and protection of the 20-keto group of the enol acetate, obtained quantitatively, into the ketal (**75**). Its interaction with sodium tetrahydroborate, the tetrahydropyranyl protection of the 3β-hydroxy group of the Δ^5-derivative formed, and reaction with lithium tetrahydroaluminate gave the diol (**76**). The oxidation of compound (**76**) with the complex of chromium trioxide and pyridine to the diketone (**77**) and its reduction with sodium tetrahydroborate took place with the formation of a readily separable mixture of the 15β- and 15α-hydroxy derivatives in a ratio of 5.8:1.

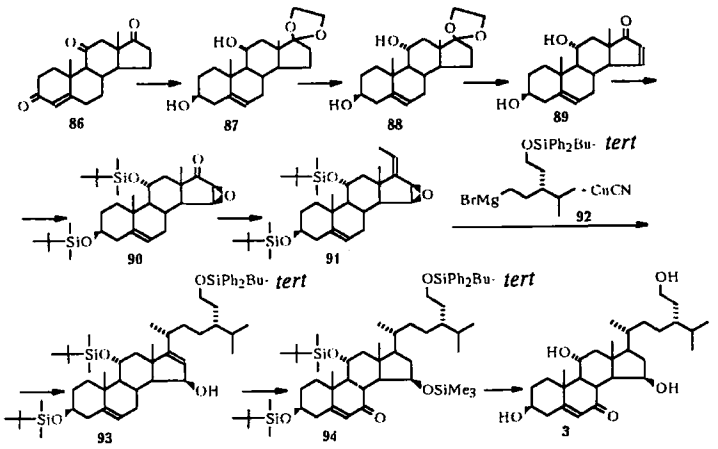


Reduction of the 15β-alcohol (**78**) with lithium in liquid ammonia and elimination of the protective groups with *p*-toluenesulfonic acid gave the required trihydroxyketone (**79**). The overall yield of compound (**79**) from the initial steroid (**74**) amounted to 16%. It must be mentioned that the 20-keto group of the triol synthesized (**79**) may be useful for attaching a side-chain.

Simultaneously with the development of methods for introducing functional groups into the cyclic part of the molecule, investigations were being carried out on the construction of the side-chain of the oogoniols with an accurately established stereochemistry at C_{24}, which could not be determined on the basis of an analysis of spectral characteristics.

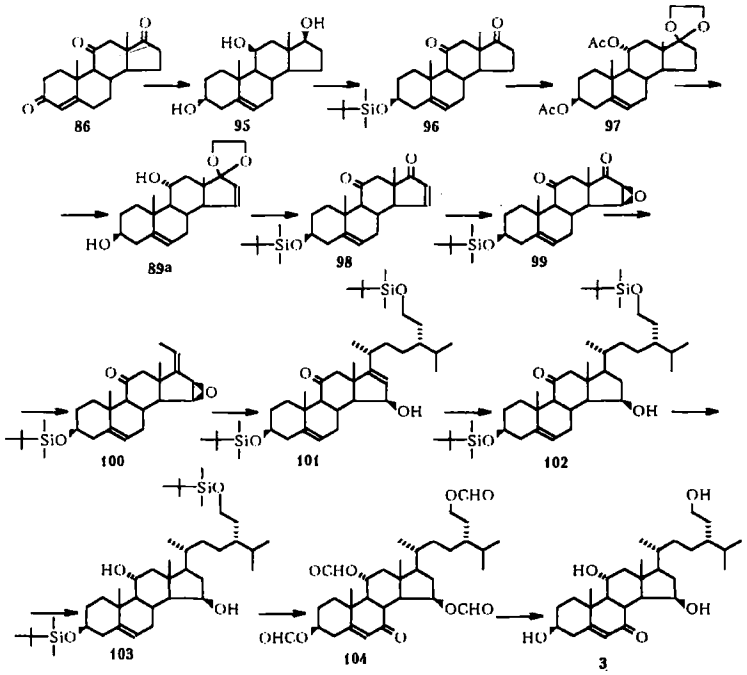
For example, Wiersig et al. [27], having synthesized the model compound (**85**) and its (24S)-isomer confirmed the revised structure of oogoniol (**3**) [22]. As the initial steroid in this scheme they selected the aldehyde (**80**), readily obtainable from stigmasterol. The interaction of this aldehyde with 2-isopropylvinyllithium took place with the formation of the 22S-allyl alcohol (**81**) in a yield of 48%. The alcohol (**83**) was synthesized by a Claisen rearrangement of compound (**81**) on its being boiled with trimethyl orthoacetate in xylene, followed by the lithium tetrahydroaluminate reduction of the resulting methyl ether/ester (**82**). The construction of the oogoniol side-chain was completed by the hydrogenation of the Δ^{22}-bond in compound (**83**) and isomerization of the steroid (**84**) so formed to the 3β-hydroxy-Δ^5-derivative (**85**).

The synthesis of the oogoniol (**3**) from adrenosterone (**86**) is described in [28]. According to this scheme, by reaction with acetic anhydride and acetyl chloride the 3-keto group of steroid (**86**) was converted into an enol acetate group, the 17-keto group was protected in the form of the ethylene ketal, and the 3β,11β-dihydroxy derivative (**87**) was obtained by reducing the residual free 11-keto group with sodium tetrahydroborate. Then the 3β,11α-dihydroxy derivative (**88**) was synthesized by selective acetylation of the 3β-hydroxy group, oxidation of the 11β-hydroxy group with pyridinium chlorochromate, and reduction of the resulting 11-ketone with lithium in a mixture of liquid ammonia and dioxane.



The hydroxy groups in steroid (**88**) were protected in the form of acetates. Bromination of the compound obtained with pyridinium bromide perbromide, followed by dehydrobromination of the 16α-bromoketal with potassium *tert*-butanolate, and acid hydrolysis of the ketal group led to the formation of the 5,15-dien-17-one (**89**). The epoxyketone (**90**) was synthesized by silyl protection of the hydroxy group and selective epoxidation with hydrogen peroxide in the presence of sodium hydroxide, and the Wittig–Horner reaction of this with ethyltriphenylphosphonium bromide and lithium diisopropylamide led to the formation of the epoxypregnene (**91**) with a yield of 90%. The cuprate reagent (**92**) was obtained from (R)-(+)-limonene by a multistage synthesis, and its addition to the epoxysteroid (**91**) took place with the formation of the allyl alcohol (**93**) in a yield of 93%. Selective hydrogenation of the 16(17)-double bond in compound (**93**) over platinum dioxide, silyl protection of the 15β-hydroxy group, and allyl oxidation with a complex of chromium trioxide and 3,5-dimethylpyrazole led to the protected oogoniol derivative (**94**). The oogoniol (**3**) was obtained by hydrolyzing the protective groups in steroid (**94**) with aqueous hydrofluoric acid. The overall yield of the polyhydroxysteroid (**3**) by this scheme was 7%.

A synthesis of the oogoniol (**3**) from androstenone (**86**) extremely similar to that discussed above was performed in [29]. According to the scheme of synthesis developed, androstenone was first converted into the 3-enol acetate, the reduction of which with sodium tetrahydroborate led to the formation of triol (**95**) with a yield of 84%. Then the most sterically accessible 3β-hydroxy group in triol (**95**) was protected selectively in the form of a silyl ether, and the residual free hydroxy groups were oxidized quantitatively with pyridinium dichromate to the 11,17-diketone (**96**).



The corresponding 3β-hydroxy-17-(ethylene ketal) was synthesized in an overall yield of 96% by the hydrolysis of the silyl protective grouping in compound (**96**) under the action of *p*-toluenesulfonic acid in a mixture of water, acetone, and methanol, followed by the ketalization of the 17-keto group under the action of ethylene glycol. The reduction of the 11-keto group in the latter compound with sodium in propanol gave a 93% yield of the 3β,11α-diol, which was converted by acetylation with a yield of 97% into the 3,11-diacetate (**97**). Bromination of the ethylene ketal (**97**) with pyridinium bromide perbromide led with a yield of 94% to the 16α-bromide, by the hydrolysis of the acetoxy group in which with a solution of potassium hydroxide in aqueous dimethyl sulfoxide, followed by dehydrobromination with potassium *tert*-butanolate in dimethyl sulfoxide, the dihydroxyketal (**89a**) was obtained in an overall yield of 84%.

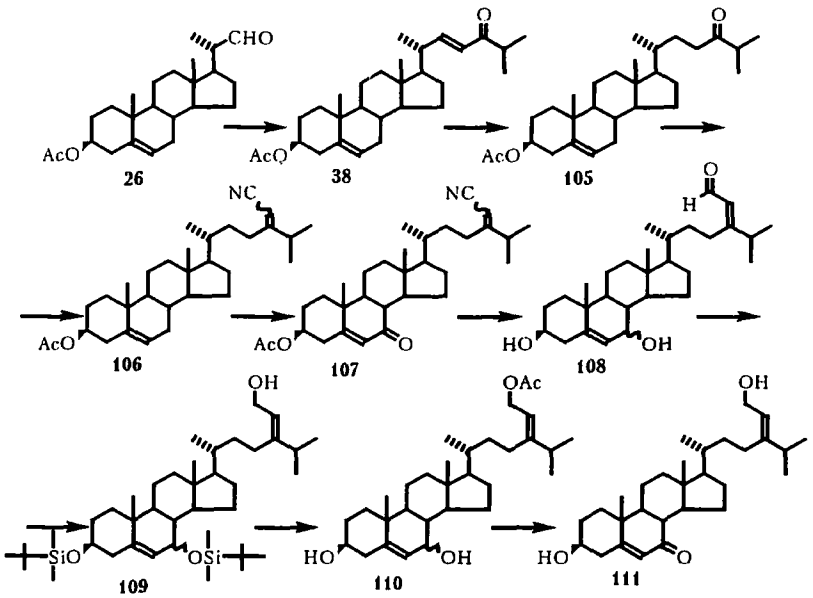
The 5,15-diene-11,17-dione (**98**) was synthesized in an overall yield of 80% from compound (**89a**) by removing the protective grouping from the 17-keto group, silylating the 3β-hydroxy group, and oxidizing the 11α-hydroxy group with pyridinium dichromate. The 15β,16β-epoxide (**99**) was obtained with a yield of 87% by the selective epoxidation of the 15-double bond in compound (**98**) with sodium hypochlorite in a mixture of alcohol and pyridine. The Wittig–Horner condensation of compound (**99**) with the ylide obtained from ethyltriphenylphosphonium bromide and lithium diisopropylamide led to the formation of the (E)-epoxypregnene (**100**).

As a result of the 1,4-addition to compound (**100**) of the appropriate lithium cuprate reagent, obtained from (R)-(+)-limonene, the 15β-hydroxystigmastane derivative (**101**) was synthesized in an overall yield of 61% from steroid (**99**). The selective hydrogenation of the 16-double bond in compound (**101**) over platinum on carbon enabled product (**102**) with the natural configuration of the C_{17} center to be obtained in a yield of 90%, and the reduction of the 11-keto group in this with sodium in propanol led to the protected tetraol (**103**).

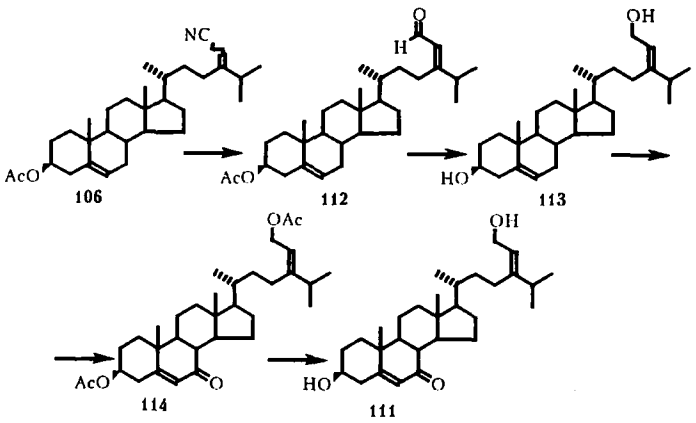
The oogoniol tetraformate (**104**) was obtained with a yield of 68% by the hydrolysis of the protective groups in steroid (**103**) under the action of an aqueous solution of *p*-toluenesulfonic acid, protection of the hydroxy groups in the form of formates, and allyl oxidation at C_7 with a complex of chromium trioxide and 3,5-dimethylpyrazole. Hydrolysis of the formate groups in (**104**) with potassium carbonate in methanol led to the formation of the oogoniol (**3**) with a yield of 46%.

In 1979, steroids close to the oogoniols — 24(28)-dehydrooogoniol (**7**) and 24(28)-dehydrooogoniol-1 (**8**) — were detected in aquatic fungi of the *Achlya* genus [30].

The synthesis of the model compound (**111**), which is a structural analog of 24(28)-dehydrooogoniol, was undertaken from the 22-aldehyde (**26**), which is readily obtainable from stigmasterol [31]. First, by Wittig–Horner condensation with the appropriate phosphonate, the 22-aldehyde (**26**) was converted with a yield of 84% into the Δ^{22}-24-ketone (**38**). The hydrogenation of compound (**38**) over palladium on barium sulfate gave a 93% yield of 24-ketocholesterol acetate (**105**). The condensation of steroid (**105**) with the anion obtained from diethyl cyanomethylphosphonate led with a yield of 86% to the unsaturated nitrile (**106**) in the form of a mixture (3:1) of the E- and Z-isomers. The photooxidation of compound (**106**) in the presence of hematoporphyrin, followed by rearrangement of the resulting 5α-hydroperoxide under the action of copper acetate, led to the 7-ketone (**107**) with an overall yield of about 50%.

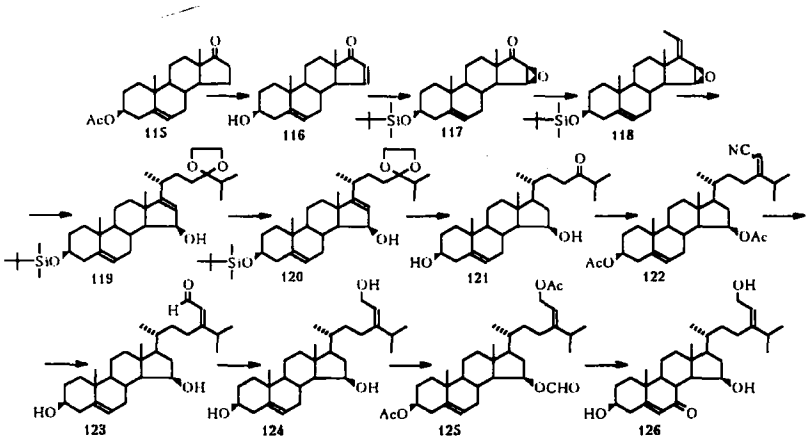


Reduction of steroid (**107**) with diisobutylaluminum hydride gave the dihydroxyaldehyde (**108**). As a result of the protection of the hydroxy groups in compound (**108**) in the form of *tert*-butyldimethylsilyl ethers and subsequent reduction of the aldehyde group with diisobutylaluminum hydride it was possible to obtain the protected 3,7,29-triol with a yield of more than 70%. Acetylation of the free 29-hydroxy group in compound (**109**) and elimination of the protective silyl groups under the action of tetrabutylammonium fluoride in tetrahydrofuran permitted the synthesis of the 29-monoacetate of the 3β,7,29-triol (**110**). The final product of this synthesis, the dihydroxyketone (**111**), was formed with a yield of about 80% on the selective oxidation of the allyl 7-hydroxy group in steroid (**110**) under the action of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, followed by hydrolysis of the 29-acetoxy group with potassium carbonate in aqueous methanol.



A different sequence of reactions was used in a second, more effective method, of synthesizing the dihydroxyketone (**111**), also published in [31]. Here, the unsaturated nitrile (**106**) was first subjected to reduction by diisobutylaluminum hydride and was then acetylated with the formation of the aldehyde (**112**) in high yield. The subsequent reduction of steroid (**112**) with diisobutylaluminum hydride permitted the synthesis in a yield of 75% of 29-hydroxyfucosterol (**113**). The acetylation of compound (**113**) led to the 3,29-diacetate, the allyl oxidation of which with the complex of chromium trioxide and 3,5-dimethylpyrazine gave the 7-ketone (**114**) in 50% yield. Hydrolysis of the acetoxy group in steroid (**114**) under the action of potassium carbonate in aqueous methanol formed the required dihydroxyketone (**111**). The overall yield of this substance from the aldehyde (**112**) by the scheme of synthesis that has been described amounted to 7%.

The synthesis described in [32] of 15β,29-dihydroxy-7-oxofucosterol (**126**), which is the 11-deoxy derivative of 24(28)-dehydrooogoniol, started from androstenolone acetate (**115**).

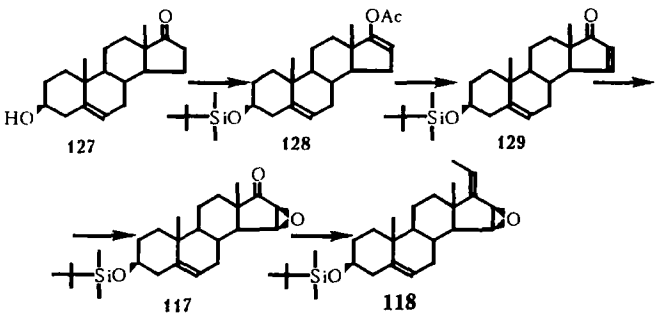


First, the 17-(ethylene ketal) was obtained by the reaction of steroid (**115**) with ethylene glycol in the presence of *p*-toluenesulfonic acid. The bromination of this compound with pyridinium bromide perbromide led to the formation in 90% yield of the corresponding 16(α)-bromo derivative, the interaction of which with aqueous potassium hydroxide at the boil in a mixture of benzene and methanol led to the hydrolysis of the 3β-acetoxy group in a yield of 92%. Subsequent dehydrobromination under the action of potassium *tert*-butanolate in dimethyl sulfoxide with a yield of 86% and hydrolysis of the ethylene ketal grouping

with a yield of 92% in aqueous acetone in the presence of *p*-toluenesulfonic acid led to the hydroxydienone (**116**). Then the hydroxy group in compound (**116**) was protected in the form of the *tert*-butyldimethylsilyl ether with a yield of 76% after which the nucleophilic 15-double bond was epoxidized under the action of sodium hypochlorite with the formation of an 85% yield of the 15β,16β-epoxy-17-ketosteroid (**117**).

In the following stage, the (E)-5,17(20)-diene (**118**) was synthesized with a yield of 80% by the Wittig reaction from the 17-ketone (**117**) and the ylide obtained from ethyltriphenylphosphonium bromide. As a result of the 1,4-addition, catalyzed by copper(I) cyanide, of the Grignard reagent obtained from 2-(2-bromoethyl)-2-isopropyl-1,3-dioxolane, the $\Delta^{17(20)}$-16,17-epoxide (**118**) was converted with a yield of 80% into the 5,16(17)-diene (**119**). On catalytic hydrogenation of the 16-double bond in compound (**119**) over platinum on carbon, the steroid (**120**) was obtained in quantitative yield.

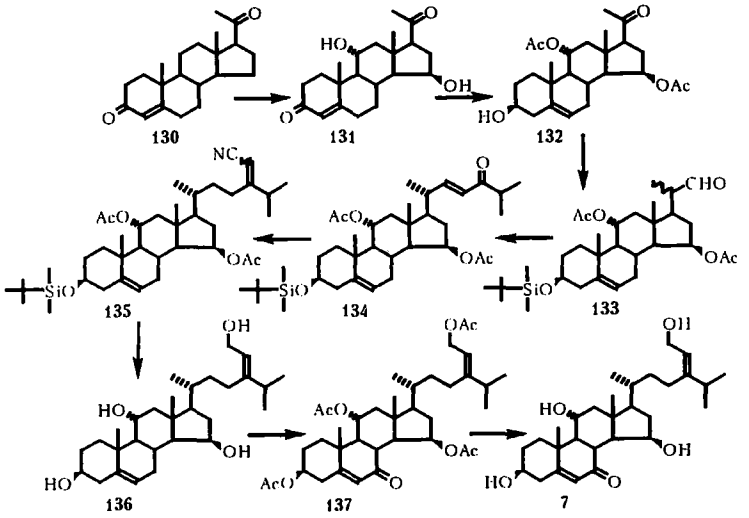
The hydrolysis of the protective groupings in compound (**120**) in aqueous tetrahydrofuran in the presence of *p*-toluenesulfonic acid gave a 95% yield of the 3β,15β-dihydroxy-24-ketone (**121**) which was then converted quantitatively in the usual way into the diacetate. The Horner–Emmons reaction of the latter with diethyl cyanomethylphosphonate enabled the unsaturated nitrile (**122**) to be obtained with a yield of 80% in the form of a 4:1 mixture of the E- and Z-isomers. Reduction of the nitrile (**122**) with diisobutyl aluminum hydride led with a yield of 95% to the dihydroxyaldehyde (**123**). Compound (**123**) was acetylated quantitatively to the diacetate, the reduction of which with diisobutylaluminum hydride gave an 80% yield of the triol (**124**). Reaction of the triol (**124**) with acetic anhydride in pyridine at room temperature for an hour led in almost quantitative yield to the 3,29-diacetate, the subsequent esterification of which with formic acetic anhydride in pyridine gave the 3,29-diacetoxy-15-formate (**125**) in practically quantitative yield. The allyl oxidation of steroid (**125**) with the complex of chromium trioxide and 3,5-dimethylpyrazole proceeded with the formation in 64% yield of the corresponding 7-keto derivative, hydrolysis of the protective groups in which with potassium carbonate in aqueous methanol completed the synthesis by giving a 95% yield of the required 3,15,29-trihydroxy-7-ketone (**126**).



An alternative method of synthesizing the epoxypregnadiene (**118**) from androstenolone (**127**) has been described by Japanese workers [33]. The reaction of the 3β-hydroxy group in the androstenolone molecule with *tert*-butyldimethylchlorosilane led to the corresponding silyl ether with a yield of 98%, and the reaction of the latter with isopropenyl acetate in the presence of *p*-toluenesulfonic acid gave the enol acetate (**128**) in a yield of 79%. By the reaction of compound (**128**) with allyl methyl carbonate, catalyzed by palladium(II) acetate and tributyltin butoxide, it was possible to obtain the $\Delta^{5,15}$-17-ketone (**129**) with a yield of 89%. Epoxidation of the 15-double bond in steroid (**129**) with *tert*-butyl hydroperoxide in aqueous Triton B led to the formation of the β-epoxide (**117**) in a yield of 77%. The unsaturated epoxide (**118**) was synthesized in a yield of 77% from ketone (**117**) by the Wittig–Horner reaction with the ylide obtained from ethyltriphenylphosphonium bromide and *n*-butyllithium.

In 1983, by the application of an approach developed on model compounds to the construction of the side-chain, American workers achieved the synthesis of 24(28)-dehydrooogoniol (**7**) [34], details of which were published later [35].

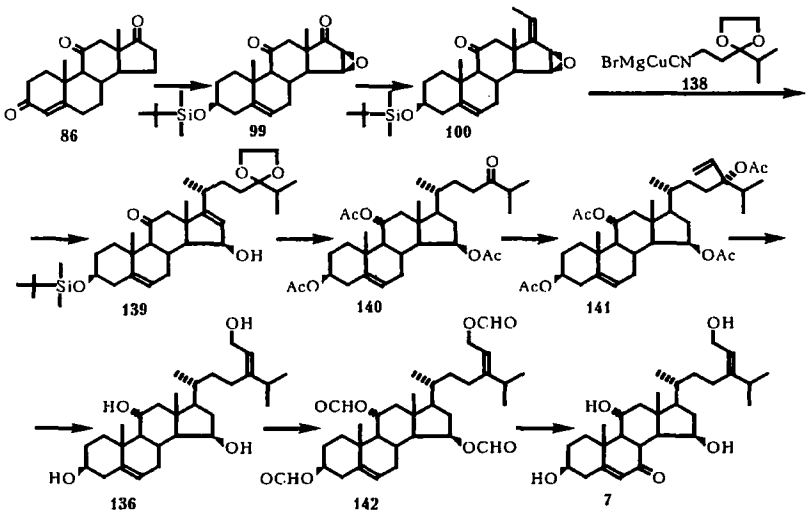
The initial compound in this synthesis was progesterone (**130**) which was converted by microbiological oxidation into 11α,15β-dihydroxyprogesterone (**131**) with a yield of 40%. We may note that by chemical synthesis it is possible to obtain compound (**79**), which is related to the diol (**131**), from 15α-hydroperoxypregn-4-ene-3,11,20-triol (**74**) with a yield of only 16% [26]. Boiling steroid (**131**) with acetic anhydride and acetyl chloride formed the 11,15-diacetoxy-3-enol acetate, protection of the 20-keto group in which in the form of the acetonide, reduction of the 3-keto group with sodium tetrahydroborate, and elimination of the protection from the 20-keto group led to the 11,15-diacetate of the 3β,11α,15β-trihydroxy-20-ketone (**132**). The 3β-hydroxy group remaining free in compound (**132**) was protected in the form of a silyl ether, and condensation at the 20-keto group with methoxymethyltriphenylphosphorane and cleavage of the resulting enol ether with trimethylsilyl iodide yielded the 22-aldehyde (**133**) (mixture of isomers at C_{20} with a predominance of the substance with the natural configuration).



Condensation of the aldehyde (**133**) with the anion of diethyl (3-methyl-2-oxobutyl)phosphonate gave an 80% yield of the $\Delta^{5,22}$-24-ketone (**134**). Selective hydrogenation of the Δ^{22}-bond in compound (**134**) over a palladium catalyst took place quantitatively. Subsequent condensation at the 24-keto group with the anion of diethyl cyanomethylphosphonate led to the synthesis of a mixture of the E- and Z-isomeric nitriles (**135**) in a ratio of 4:1. Reduction of the nitriles (**135**) with diisobutylaluminum hydride, followed by hydrolysis of the resulting imine with dilute acetic acid, led to the formation of a mixture of unsaturated 29-aldehydes, from which, after reacetylation of the hydroxy group, the pure E-isomer (50%) was isolated by chromatography on silica gel.

On subsequent reduction with diisobutylaluminum hydride it was converted into the tetraol (**136**). As a result of acetylation and allyl oxidation with the complex of chromium trioxide and 3,5-dimethylpyrazole the ketosteroid (**137**) was obtained with a yield of 50%. Alkaline hydrolysis of the protective groups in compound (**137**) gave 24(28)-dehydrooogoniol (**7**) with a low yield (35%), which it is possible to raise by using, in place of acetate, the readily eliminated formate protection of the 15β-hydroxy group in the alcohol (**136**), as shown, for example in [32].

Yet another synthesis of 24(28)-dehydrooogoniol (**7**) has been proposed in [36]. In this method, the 11α- and 15β-hydroxy groups are introduced into adrenosterone (**86**) as a result of chemical transformations. The key intermediate (**100**) is first obtained by a known method [29]. Its interaction with the cuprate reagent (**138**), prepared as described in [32], gives the 1,4-adduct (**139**). The following selective hydrogenation of the Δ^{16}-bond in compound (**139**), reduction of the 11-keto group with sodium in *n*-propanol, elimination of the acetal protection in the side-chain, and acetylation enable the ketone (**140**) to be synthesized almost quantitatively.



The natural hormone (7) has been obtained from compound (**140**) by two methods, one of which is described in papers already mentioned here [31, 32, 34, 35] and gives 24(28)-dehydrooogoniol (7) contaminated with 25% of the readily eliminated Z-isomer. According to the second method, ketone (**140**) is converted in high yield exclusively into the E-isomer (**136**) by reaction with vinylmagnesium bromide followed by a [bis(acetonitrile)palladium chloride]-catalyzed rearrangement of the tetraacetate (**141**) formed after protection of the hydroxy groups, and hydrolysis. After formate protection of its hydroxy groups, a 7-keto group was introduced into the tetraformate (**142**) by oxidation with the complex of chromium trioxide and 3,5-dimethylpyrazole. Subsequent hydrolysis of the 7-keto derivative so obtained gave 24(28)-dehydrooogoniol (7) with an overall yield of 6%, calculated on adrenosterone (**86**).

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