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RECENT ADVANCES IN THE CHEMICAL SYNTHESIS OF ECDYSTEROIDS AND COMPOUNDS RELATED TO THEM

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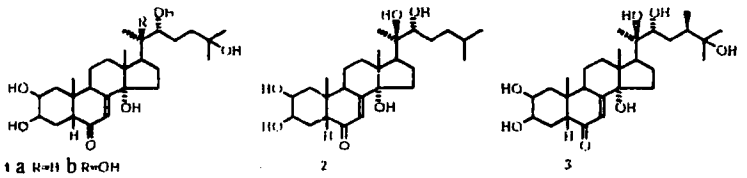
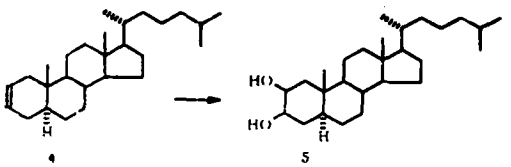
This review generalizes information on methods of synthesizing ecdysteroids and substances structurally close to them published in the literature during the last decade.

The ecdysteroids are a broad group of polyhydroxysteroids found in various species of invertebrate animals and plants and close in structure and biological action to their first representative, α-ecdysone [1, 2]. A fairly clear idea of the structure of ecdysteroids is given by the structural formulas of α-ecdysone (**1a**), 20-hydroxyecdysone (**1b**), ponasterone A (**2**), and makisterone (**3**). In insects and crustaceans ecdysteroids fulfil a number of different physiological functions, the best known of which consist in the hormonal control of processes of molting and metamorphosis. Ecdysteroids are also found in plants. They probably protect the plants from being eaten by phytophagous insects by causing a disturbance of the hormonal system of the latter on being ingested together with the food [3, 4].



Investigations of the chemical synthesis of ecdysteroids were begun in the mid-1960s, immediately after their detection in plant materials. Investigations reported in the press up to 1985 have been discussed in monographs previously [1, 5]. At the present time, this field of investigations is continuing to develop rapidly, and the object of this review is a generalization of results published after the appearance of the above-mentioned monographs.

Extremely important for the successful synthesis of ecdysteroids is the development of effective methods of introducing the functional groups characteristic for them into steroid molecules. Thus, to introduce a 2β,3β-diol grouping in the synthesis of ecdysteroids wide use is made of the *cis*-hydroxylation of the 2-double bond in *trans-A/B*-steroids by Woodward's method using silver acetate and iodine in aqueous acetic acid [1].



In a development of this method, Horiuchi and Satoh [6] have proposed to use copper(II) acetate in place of silver acetate. It was established that by the reaction of 5α-cholest-2-ene (**4**) with copper(II) acetate and iodine in acetic acid, followed by treatment of the products with a methanolic solution of potassium hydroxide, it is possible to obtain the 2β,3β-diol (**5**) with a yield of 91%.

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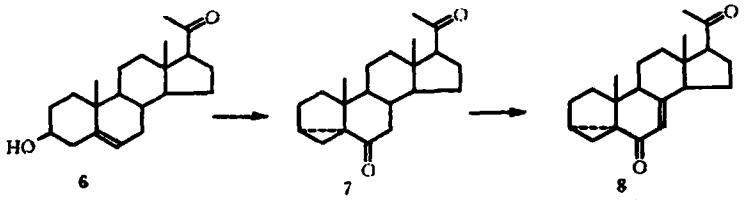
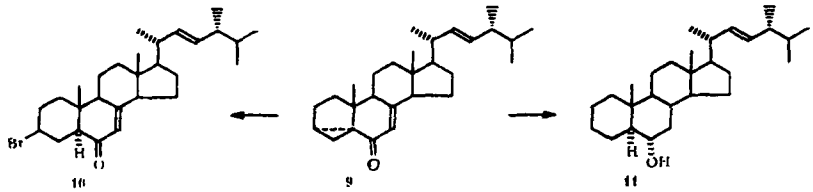
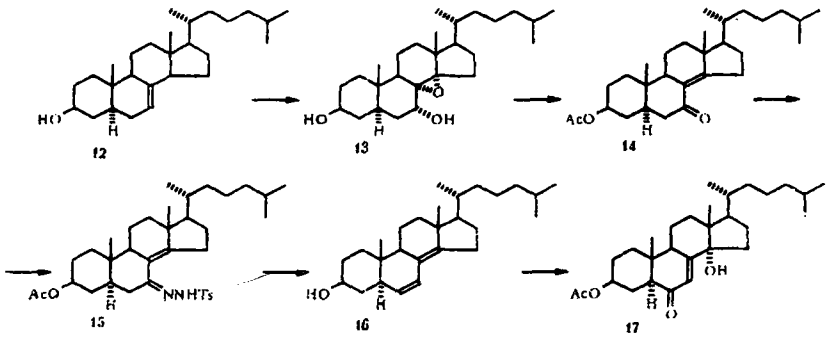


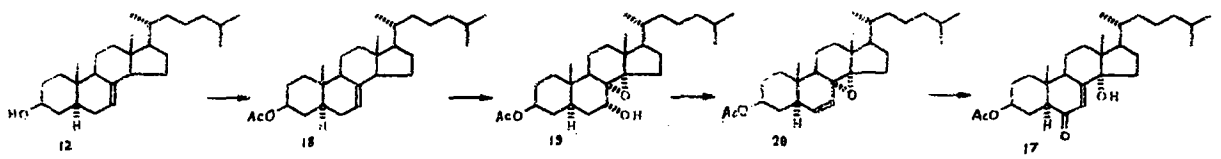
We have developed a method for obtaining the 3α,5-cyclo-Δ^7-6,20 diketone (**8**), which is of interest as an intermediate in the synthesis of ecdysteroids [7]. Pregnenolone (**6**) was first converted into its mesylate and the latter was then subjected to rearrangement under the action of potassium acetate in aqueous acetone, after which, without isolation from the reaction mixture, the resulting 3α,5-cyclo-6β-alcohol was subjected to Jones oxidation with the formation of the required 3α,5-cyclo-6,20-diketone (**7**). Selective oxidation of steroid (**7**) with trifluoroperacetic acid in methylene chloride formed the Δ^7-6-ketone (**8**) with a yield of 66%.



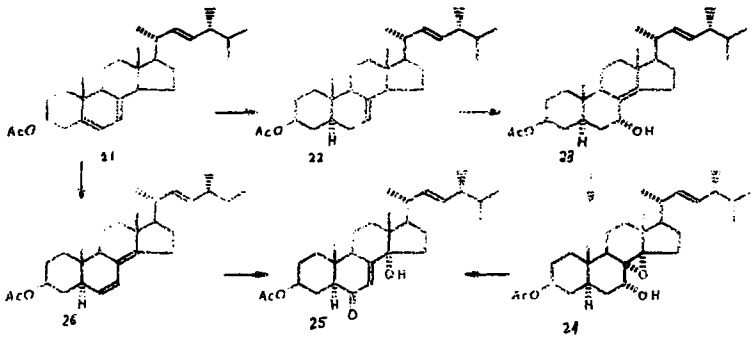
The interaction of the 3α,5-cyclo-6-ketosteroid (**9**) with hydrobromic acid gave a 51% yield of the 3β-bromo-6-ketone (**10**) [8]. This compound possesses a powerful insecticidal action on the larva of the Colorado beetle. The 6α-alcohol (**11**), formed with a yield of 71% by the Birch reduction of the 3α,5-cyclo-6-ketosteroid (**9**) with an excess of lithium [9], has proved to be an even more powerful insecticide.



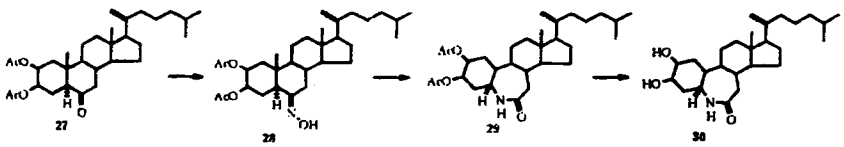
Recently, methods using Δ^7-steroids as the raw material have been proposed for the synthesis of ecdysteroids. The approaches developed amount in some way or other to converting the Δ^7-steroids into $\Delta^{6,8(14)}$-dienes, the transformation of which into 14α-hydroxy-Δ^7-6-ketones has been studied previously [1]. For example, in [10], with this aim, the oxidation of 5α-cholest-7-en-3β-ol (**12**) with two equivalents of *m*-chloroperbenzoic acid was used to give a 66% yield of the epoxydiol (**13**) the rearrangement of which under the action of hydrochloric acid and subsequent acetylation led to the acetoxyenone (**14**) with a yield of 75%. Then, by reaction with *p*-tolylsulfonylhydrazine, steroid (**14**) was converted into the tosylhydrazone (**15**) in quantitative yield. Under the action of methyllithium in the Shapiro reaction, compound (**15**) was converted mainly into the 6,8(14)-diene (**16**), from which it is possible to obtain the 14α-hydroxy-Δ^7-6-ketone (**17**).



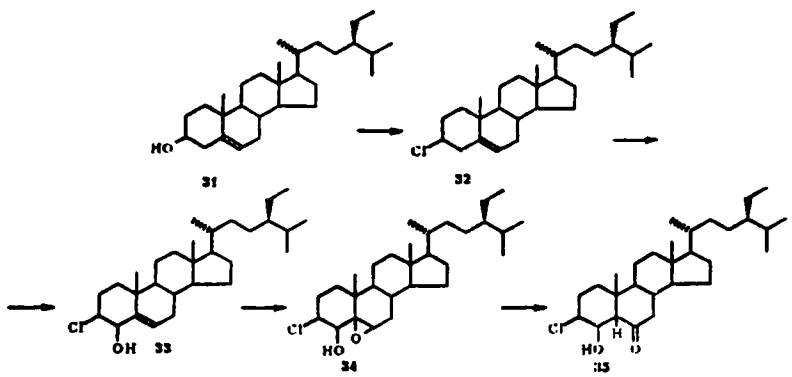
Another, more effective, approach to the synthesis of the 14α-hydroxy-Δ^7-6-ketone (**17**), also proposed in [10], likewise makes use of the epoxidation of the Δ^7-bond with two equivalents of *m*-chloroperbenzoic acid, although not in the steroid (**12**) itself but in its acetate (**18**), with the formation of the 7α-hydroxy-8α,14α-epoxide (**19**). Mesylation of the free 7α-hydroxy group in compound (**19**) led with a yield of 87% to the corresponding mesylate, the reaction of which with diazabicyclononane on heating gave the Δ^6-derivative (**20**). Oxidation of epoxide (**20**) with sodium dichromate in acetic acid formed the required hydroxyenone (**17**) with a yield of 83%. The overall yield of steroid (**17**) from sterol (**12**) by this scheme amounted to 40%.



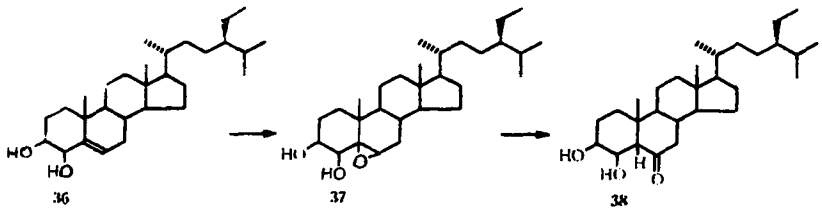
It has been shown that the method developed for synthesizing 14α-hydroxy-Δ^7-6-ketones from Δ^7-sterols is also applicable to the formation of compounds with a Δ^{22}-double bond in the side-chain [10]. Here the necessary dihydroergosterol acetate (**22**) was obtained by hydrogenating ergosterol over Wilkinson's catalyst, followed by acetylation. Oxidation of the $\Delta^{7,22}$-sterol (**22**) with selenium dioxide in aqueous dioxane gave a 55% yield of the allyl alcohol (**23**). The further oxidation of alcohol (**23**) with pyridinium dichromate led to the formation of the epoxyalcohol (**24**) (yield 41%), together with the corresponding $\Delta^{8(14)}$-7-ketone. Compound (**24**) was obtained with a yield of 47% by the direct oxidation of dihydroergosterol acetate (**22**) with *m*-chloroperbenzoic acid. The subsequent transformation of the epoxyalcohol (**24**) included its mesylation, elimination of the 7-mesyl group, and oxidation of the resulting 8α,14α-epoxy-Δ^6- derivative with sodium dichromate in acetic acid. It must also be mentioned that compound (**25**) can be obtained more simply: by isomerizing ergosterol acetate (**21**) to the 6,8(14)-diene (**26**), epoxidizing the latter with *m*-chloroperbenzoic acid at the 8(14)-double bond, and oxidizing the resulting Δ^6-8α,14α-epoxide with sodium dichromate [10]



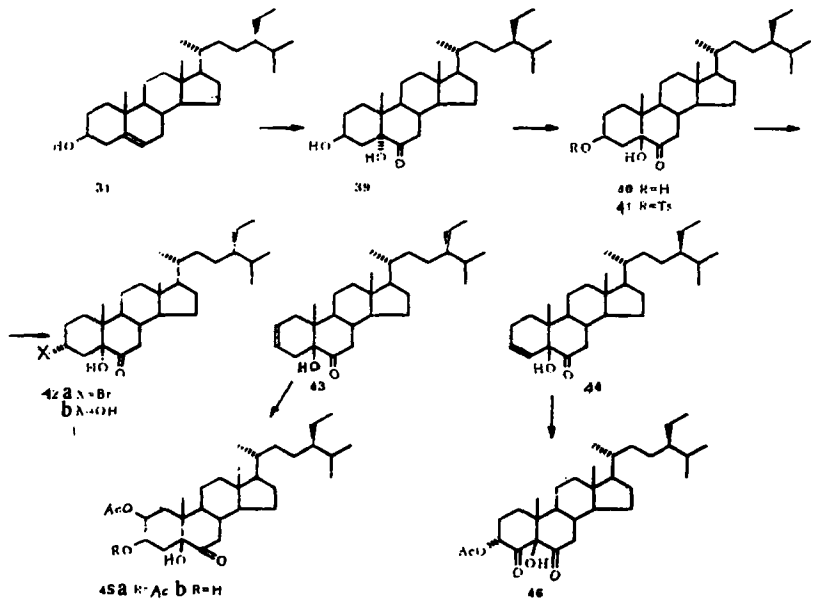
The synthesis of the ecdysteroid analog (**30**) containing an additional nitrogen atom in ring *B* was reported in [11]. The interaction of the diacetoxyketone (**27**) with hydroxylamine in pyridine formed the oxime (**28**) with a yield of 65%. The Beckmann rearrangement of the oxime (**28**) under the action of *p*-toluenesulfonyl chloride in pyridine, followed by decomposition of the tosylate with water, gave a 40% yield of the diacetoxylactam (**29**). Hydrolysis of the acetoxy function in steroid (**29**) with potassium carbonate in methanol enabled the dihydroxylactam (**30**) to be obtained with a yield of 91%.



The synthesis of the 4β-hydroxy-6-ketone (**35**), which exhibits a high activity as a plant growth stimulator, was undertaken from β-sitosterol (**31**) [12-14]. The reaction of the latter with thionyl chloride gave a high yield of the 3β-chloro derivative (**32**). By the allyl hydroxylation of compound (**32**) with selenium dioxide in dioxane it was possible to obtain the 4β-alcohol (**33**) with a yield of about 40%. The interaction of the 3,4-disubstituted Δ^5-steroid (**33**) with trifluoroperacetic acid in methylene chloride for half an hour led to the formation of the 5β,6β-epoxide (**34**) in a yield of more than 90%. Acid isomerization of the hydroxyepoxide (**34**) under the action of trifluoroacetic acid in methylene chloride enabled the 4β-hydroxy-6-ketone (**35**) to be obtained with a yield 67%. It was also established that performing the reaction of the Δ^5-steroid (**33**) with trifluoroperacetic acid for one and a half hours and more enabled the required steroid (**35**) to be obtained directly with a yield of 65%.



A synthesis of the 3β,4β-dihydroxy-6-ketone (**38**), having the same *cis-A/B* linkage as the ecdysteroids, started from β-sitosterol [15]. The allyl oxidation of β-sitosterol (**31**) with selenium dioxide in dioxane gave the 3β,4β-diol (**36**). Interaction of the Δ^5-steroid (**36**) with *m*-chloroperbenzoic acid led to the formation of the 5β,6β-epoxide (**37**) and its 5α,6α-isomer with yields of 44 and 28%, respectively. Rearrangement of the 5β,6β-epoxide (**37**) under the action of trifluoroacetic acid in chloroform enabled the required 3β,4β-dihydroxy-6-ketone (**38**) to be obtained with a yield of 74%.

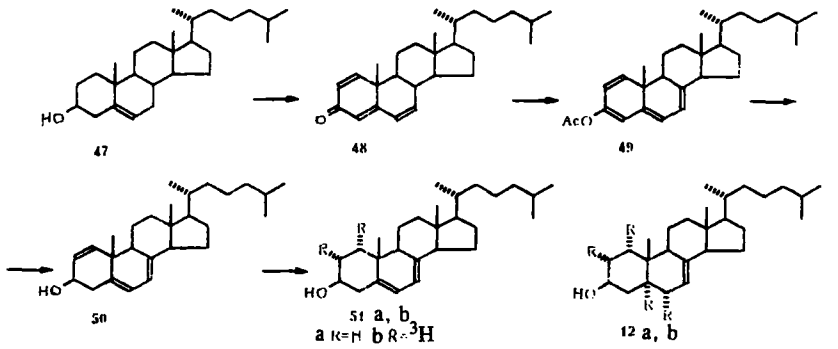


The possibility of introducing into steroids the 2β,3β,5β-trihydroxy-6-keto grouping characteristic for some phytoecdysteroids, such as polypodin B, has been studied by Kovganko and Kashkan [16]. The *trans*-hydroxylation of the initial β-sitosterol (**31**) with hydrogen peroxide in formic acid, followed by the selective Jones oxidation of the resulting 3β,5α,6β-triol, gave the 3β,5α-dihydroxy-6-ketone (**39**) in an overall yield of 55% [17]. Reversal of the configuration of the 5-hydroxy group in steroid (**39**) with the formation of the 3β,5β-dihydroxy-6-ketone (**40**) was achieved with a yield of 61% by reaction with potassium hydroxide in methanol [16]. Interaction of the diol (**40**) with *p*-toluenesulfonyl chloride in pyridine led to the quantitative formation of the 3-monotosylate (**41**).

It has been established that the reaction of compound (**41**) with lithium carbonate and bromide in dimethylformamide at the boil takes place in complex fashion. Together with the products of nucleophilic substitution, including the 3α-bromo-5β-hydroxy-6-ketone (**42a**) and the 3α,5β-dihydroxy-6-ketone (**42b**), elimination products — the Δ^2-5β-hydroxy-6-ketone (**43**) and

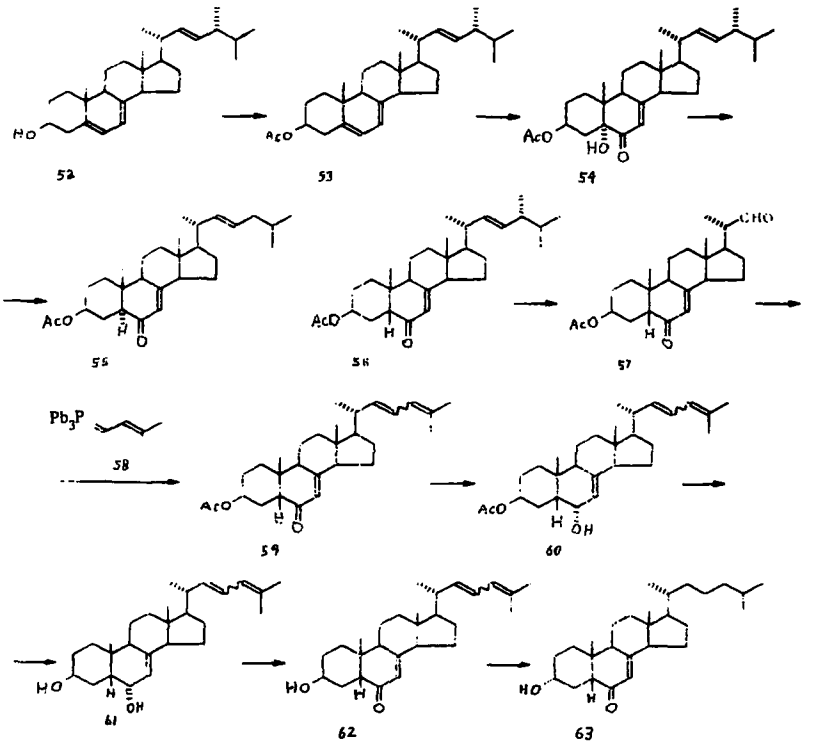
the Δ^3-5β-hydroxy-6-ketone (**44**) — were isolated. The hydroxylation of compounds (**43**) and (**44**) with a catalytic amount of osmium tetroxide and N-methylmorpholine N-oxide, followed by acetylation, produced the 2β,3β,5β-trihydroxy-6-ketone (in the form of the 2,3-diacetate (**45a**) and the 2-monoacetate (**45b**)) and the 3α-acetoxy-5β-hydroxy-6-ketone (**46**), respectively.

One of the important intermediates in the biosynthesis of ecdysteroids from cholesterol (**47**) in insects is 7-dehydrocholesterol (**51a**) [18]. Biochemical investigations require the tritium-labeled compound with a high specific activity.

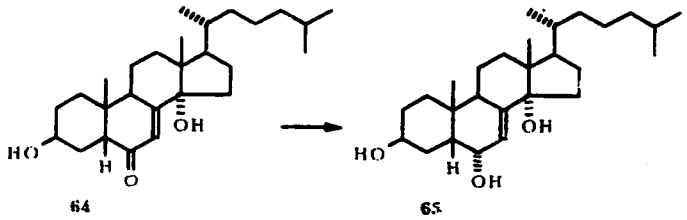


Dolle et al. [19] have investigated several variants of the synthesis of 7-dehydrocholesterol (**51**) labeled with tritium in positions 1α and 2α. The reaction of cholesterol (**47**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dioxane gave a 55% yield of the $\Delta^{1,4,6}$-trien-3-one (**48**), which was then converted by reaction with isopropenyl acetate in the presence of *p*-toluenesulfonic acid into the enol acetate (**49**) with a yield of 75%, Reduction of compound (**49**) with calcium tetrahydroborate took place with the exclusive formation of the 3β-alcohol (**50**) in 85% yield. Catalytic hydrogenation of triene (**50**) in the presence of chlorotriphenylphosphinerhodium formed a mixture (4:1) of 7-dehydrocholesterol (**51a**) and lathosterol (**12**), which were separated by chromatographic methods. Direct tritylation of the trienol (**50**) was used to obtain labeled 7-dehydrocholesterol (**51b**). The compound obtained in this way was fully suitable for biochemical investigations. In particular, it was established that the labeled 7-dehydrocholesterol was converted into α-ecdysone and 2-deoxyecdysone in the ovaries of females of the locust *Locusta migratoria*.

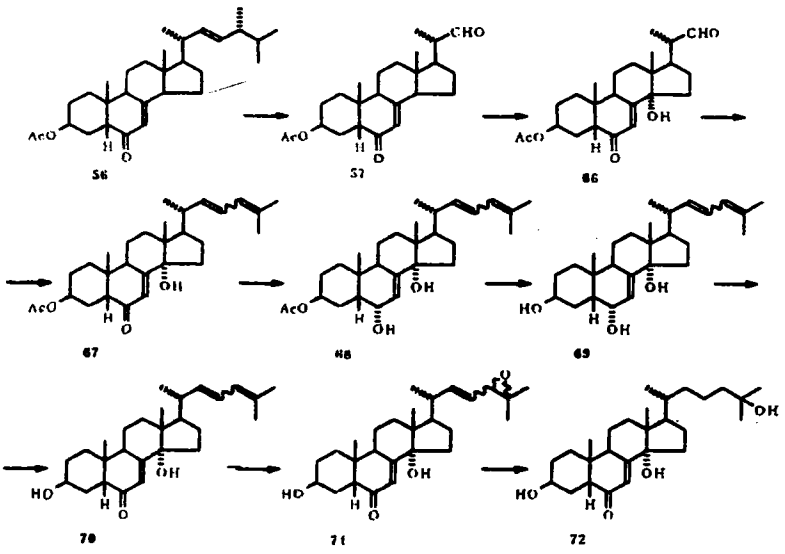
A synthesis of 2,14,22,25-tetradeoxyecdysone (**63**) labeled with four tritium atoms in the side-chain started from ergosterol [20]. In the scheme of synthesis developed, ergosterol (**52**) was converted into the 5α-hydroxy-6-ketone (**54**) by acetylation followed by oxidation of the resulting acetate (**53**) with chromium trioxide in aqueous acetic acid.



The reduction of the 5α-hydroxy group in compound (**54**) with zinc in hydrochloric acid took place with the formation in a yield of 70% of both possible isomers at C-5 with, naturally, a predominance of the *trans-A/B* isomer (**55**). Although the *cis-A/B*-steroid (**56**) was obtained with a yield of only 12%, it was nevertheless used subsequently because it had the required C-5 stereochemistry. In the case under consideration it is difficult to create this stereochemistry by other methods. The ozonolysis of the 22-double bond in steroid (**56**) gave the 22-aldehyde (**57**) in 75% yield. By the Wittig reaction between the 22-aldehyde (**57**) and the ylide (**58**) it was possible to synthesize the 22,24-diene (**59**) in the form of a mixture of the (22Z)- and (22E)- isomers in a ratio of 60:40 with a yield of 48%. In order to prevent epimerization at C-5, the keto group in compound (**59**) was reduced with sodium tetrahydroborate in the presence of cerium(III) chloride with the formation of the 6α-alcohol (**60**) in 60% yield. Hydrolysis of the acetoxy group in compound (**60**) with potassium carbonate in methanol gave an 83% yield of the 3β,6α-diol (**61**). The allyl 6α-hydroxy group in diol (**61**) was selectively oxidized with manganese dioxide to the Δ^7-6-ketone with a yield of 72%. Hydrogenation of the double bonds in the side-chain of compound (**62**) over 5% palladium on carbon made it possible to synthesize the 2,14,22,25-tetradeoxyecdysone (**63**) quantitatively. Tritylation of the 22,24-diene (**62**) under analogous conditions gave [$^3H_4$-22,23,24,25]-2,14,22,25-tetradeoxyecdysone with a specific activity of 115 Ci/mole



Earlier [21], for the preparation of the unlabeled 3β,6α,14α-trihydroxysteroid (**65**), which is of interest for biochemical investigations as a possible biosynthetic precursor of α-ecdysone, a method was proposed that consisted in the reduction of the 6-keto group in the dihydroxyketone (**64**) under the action of sodium tetrahydroborate in the presence of cerium(III) chloride. Later experiments showed that this method is unsuitable for the preparation of the tritium compound (**65**), possibly because of the very high dilution. It was found that the most successful method for the synthesis of the tritium-labeled triol (**65**) was one in which only sodium tetrahydroborate, without cerium(III) chloride, was used for the reduction of ketone (**64**), followed by tritiation and high-performance liquid chromatographic purification [22].



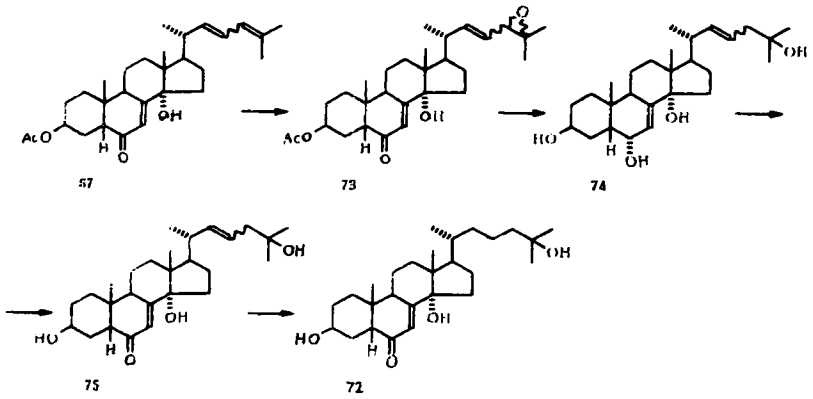
A synthesis of 2,22-dideoxyecdysone (**72**) made use of ergosterol as the starting material [23]. Ergosterol (**52**) was first converted via the acetate (**53**) and the 5α-hydroxy-6-ketone (**54**) into the $\Delta^{7,22}$-6-ketone (**56**). Then an attempt was made to introduce a 14α-group by the allyl oxidation of enol (**56**) with selenium dioxide in dioxane. However, compound (**56**) showed considerable inertness in this reaction, which can apparently be explained by steric hindrance to the approach of the reagent

to C-14 created both by the *cis-A/B* linkage and by the atoms of the side-chain. In the following stage of the reaction, therefore, steroid (**56**) was converted by mild ozonolysis into the 22-aldehyde (**57**), from which the 14α-hydroxy derivative was then obtained with a yield of 78% by reaction with selenium dioxide in dioxane. The Wittig reaction of steroid (**66**) with the ylide obtained from 4-bromo-2-methylbut-2-ene and triphenylphosphine led to the cholestane derivative (**67**) in the form of a mixture of the (22E)- and (22Z)- isomers in a ratio of 2:3. These isomers were separated by column chromatography and were then subjected to the necessary transformations separately. However, this is not shown in our scheme in order to save space.

To prevent isomerization at C-5 with the formation of the more stable *trans-A/B* isomer, the keto group in compound (**67**) was first reduced with sodium tetrahydroborate in the presence of cerium(III) chloride to the 6α-alcohol (**68**) the acetoxy group in which was converted into a 3β-hydroxy group by hydrolysis with potassium carbonate in aqueous methanol at the boil. In order to regenerate the 6-keto group, the triol (**69**) obtained in this way was oxidized selectively with manganese dioxide to the 3β,14α-dihydroxy-6-ketone (**70**). The later stages of the synthesis under discussion had the aim of introducing a 25-hydroxy group by the selective epoxidation of the diene grouping in compound (**70**) with *p*-nitroperbenzoic acid in the presence of sodium and potassium fluorides with the formation of the 24,25-epoxide (**71**) and its subsequent hydrogenation over a palladium catalyst with the formation of 2,22-dideoxyecdysone (**72**).

A deuterated version of the ecdysone derivative (**72**) was obtained similarly with the replacement of hydrogen in catalytic hydrogenation by deuterium. At the same time, attempts to use this scheme to obtain tritium-labeled 2,22-deoxyecdysone proved unsuccessful. A modified scheme was therefore developed later [24]. In this, the 24,25-monoepoxide (**73**) was obtained with a yield of 96% from the 22,24-diene (**67**) by regiospecific epoxidation with *m*-chloroperbenzoic acid in the presence of sodium and potassium fluorides [24]. The further reaction of compound (**73**) with lithium triethylhydroborate took place not only with the opening of the epoxide ring but also with the reduction of the 6-keto group and the elimination of the protective grouping from the 3β-hydroxy function

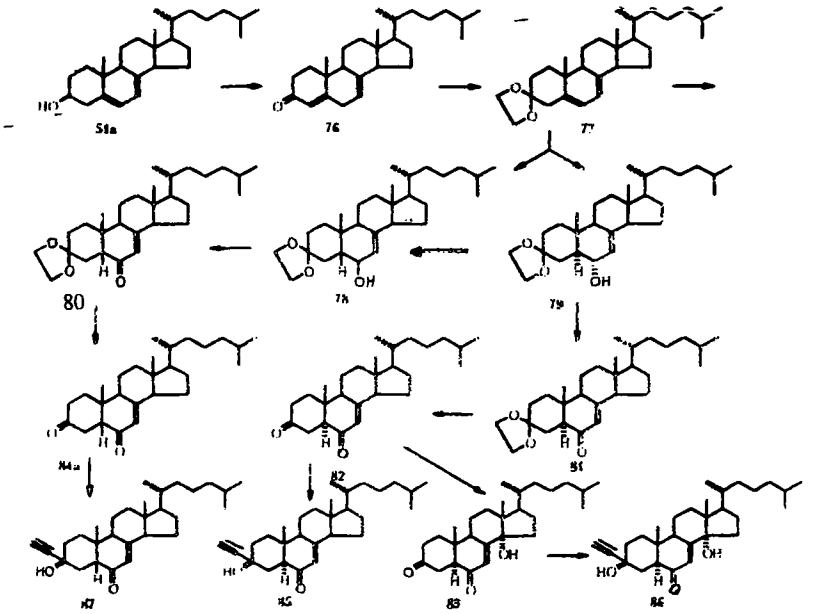
In the unstable 3β,6α,14α,25-tetraol (**74**) obtained in this way, the allyl 6α-hydroxy group was reoxidized to a 6-keto group by manganese dioxide with the formation of the trihydroxyenone (**75**) in a yield of 84%. The catalytic hydrogenation of the Δ^{22}-bond in compound (**75**) over 5% palladium on carbon completed the synthesis of 2,22-dideoxyecdysone (**72**). The use of tritium in place of hydrogen for hydrogenation enabled the corresponding tritium derivative to be obtained. It must also be mentioned that in the hydrogenation of compound (**75**) partial hydrogenolysis of the 25-hydroxy group was observed, with the formation of approximately 5% of 2,22,25-trideoxyecdysone, which was easily separated from the main reaction product by thin-layer chromatography.



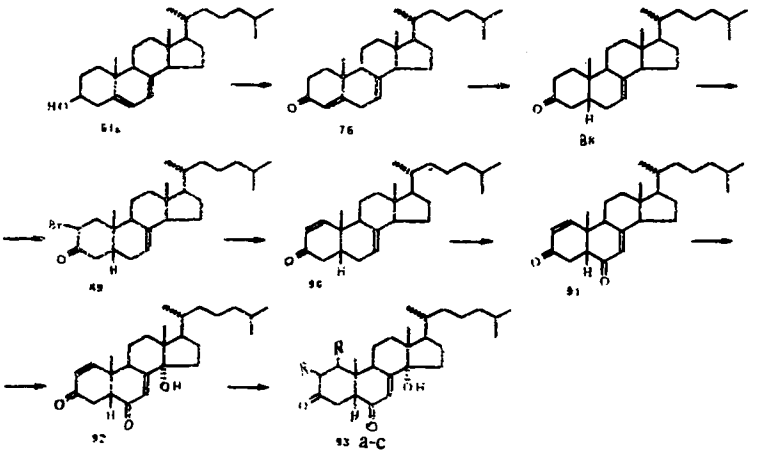
A new approach to the synthesis of 3-dehydroecdysteroids given in the literature [25, 26] makes use of the hydroboration-oxidation of 5,7-dienes. The Oppenauer oxidation of 7-dehydrocholesterol (**51a**) gave an 85% yield of the 4,7-dien-3-one (**76**). Protection of the keto group in compound (**76**) in the form of the ethyl ketal by reaction with ethylene glycol in the presence of *p*-toluenesulfonic acid was accompanied by migration of the 4-double bond in ring *B* and led to the formation of diene (**77**) in 68% yield. It is known that on the hydroboration–oxidation of 7-dehydrocholesterol (**51a**) the corresponding 6α-alcohol, in which there is *trans-A/B* linkage, is obtained [1]. Here the stereochemistry of the product is determined by the approach of the reagent to the less hindered α-side of the steroid molecule. At the same time, in compound (**77**) the α-side is somewhat hindered by the oxygen atom of the ethylene ketal grouping at C-3. This led to the situation that on the hydroboration–oxidation of the 5,7-diene (**77**) the *cis-A/B*-6β-alcohol (**78**) and the *trans-A/B*-6α-alcohol (**79**) were formed, these being isolated with yields of 36 and 29%, respectively [26]. The oxidation of both alcohols (**78**) and (**79**) with manganese

dioxide gave high yields of the corresponding 6-ketosteroids (**80**) and (**81**) retaining the C-5 sterochemistries of the initial substances. Hydrolysis of the ethylene ketal function in steroid (**81**) under the action of an aqueous alcoholic solution of hydrochloric acid permitted its quantitative conversion into the 3,6-diketone (**82**).

The allyl oxidation of compound (**82**) gave a 54% yield of the 14α-hydroxy derivative (**83**). In its turn, hydrolysis of the ethylene ketal grouping of the *cis-A/B*-steroid (**80**) was effected under the action of 15% aqueous sulfuric acid adsorbed on silica gel. Under these conditions, no epimerization at C-5 was observed, and the *cis-A/B*-3,6-diketone (**84a**) was isolated from the reaction mixture with a yield of 93%. From compounds (**82**), (**83**) and (**84a**) have been synthesized the corresponding 3β-ethynyl-3α-hydroxy derivatives (**85-87**), which are of interest as inhibitors of ecdysteroid biosynthesis. A two-stage ethynylation procedure was used. In the first stage, on the reaction of the 3-keto groups in steroids (**82**), (**83**) and (**84a**) with lithium trimethylsilylacetylide, obtained from trimethylsilylacetylene and butyllithium, the corresponding trimethylsilylacetylene derivatives were formed with yields of 40-70%. Then the trimethylsilyl groupings in these compounds were eliminated quantitatively by the action of tetrabutylammonium fluoride.



To elucidate individual stages of the biosynthesis of ecdysteroids in insects, Dolle et al. [27] developed a scheme for the synthesis of the 14α-hydroxy-Δ^7-3,6-diketone (**93a**) (R = H) which also permitted the preparation of its labeled derivatives (**93b**) (R = ^{2}H) and (**93c**) (R = ^{3}H).



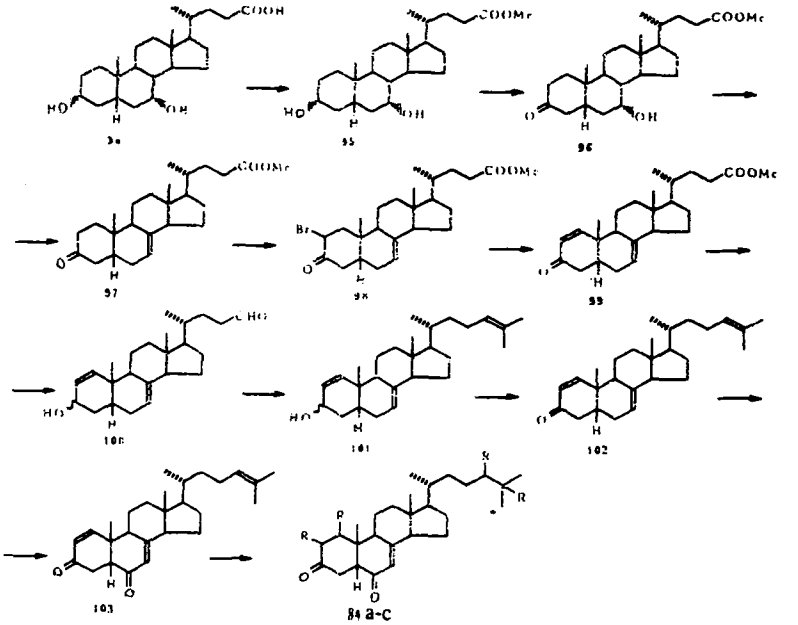
The Oppenauer oxidation of the initial 7-dehydrocholesterol (**51a**) gave an 85% yield of the $\Delta^{4,7}$-3-ketone (**76**). Selective hydrogenation of the less sterically hindered 4-double bond in compound (**76**) over palladium on carbon took place

with the formation of an 85% yield of the *cis-A/B*-steroid (**88**), which was then subjected to bromination in the α-position to the 3-keto group with tri-N-methylanilinium perbromide. The 2β-bromo-3-ketone (**89**) obtained in this way with a yield of 80% was converted into the $\Delta^{1,7}$-3-ketone (**90**) by dehydrobromination under the action of lithium bromide and lithium bicarbonate in dimethylformamide at the boil. The allyl oxidation at C-6 of steroid (**90**) with pyridinium dichromate in methylene chloride took place with the formation in low yield (30%) of the 3,6-diketone (**91**), the molecule of which retained the desired *cis-A/B*-linkage. The allyl hydroxylation of the dienediketone (**91**) with selenium dioxide in boiling dioxane led to a 75% yield of the required 14α-hydroxy derivative (**92**), which, in the concluding stage of the synthesis, was subjected to hydrogenation over palladium on carbon. Depending on the hydrogen isotopes used for hydrogenation, this gave 14α-hydroxy-Δ^7-3,6-diketone (**93a**) (R = ^{1}H) or its derivative (**93b**) (R = ^{2}H) or (**93c**) (R = ^{3}H).

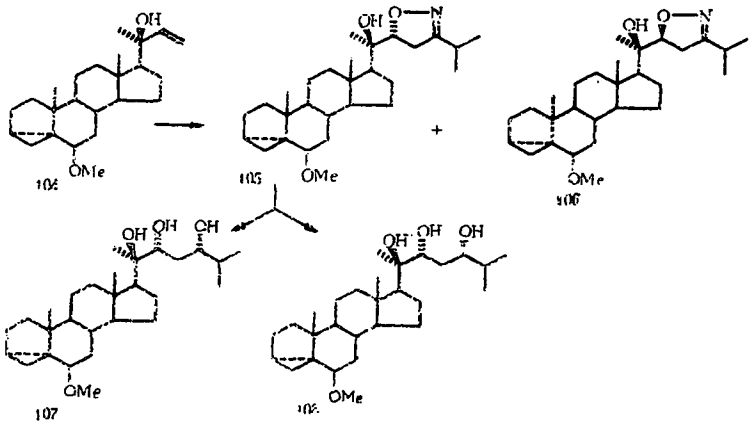
In [28] the synthesis of the 5β-diketone (**84**) labeled simultaneously in the cyclic part of the molecule and in the side-chain started from deoxychenocholic acid (**94**), which, in the first stage, was converted by reaction with methanol in the presence of hydrochloric acid into the methyl ester (**95**). The regioselective oxidation of one of the hydroxy groups under the action of oxygen in the presence of platinum, compound (**95**), gave the 7-hydroxy-3-ketone (**96**), the dehydration of which with phosphorus oxychloride in pyridine took place with the formation of the Δ^7-3-ketone (**97**) as the main product. On the bromination of steroid (**97**) in the α-position to the 3-keto group with tri-N-methylanilinium perbromide the 2β-bromo-3-ketone (**98**) was obtained in quantitative yield, and by the dehydrobromination of this with lithium carbonate and lithium bromide in dimethylformamide at the boil the $\Delta^{1,7}$-3-ketosteroid (**99**) was successfully synthesized. On the reaction of the latter with diisobutylaluminum hydride the ester function and the 3-keto group were reduced simultaneously.

The same authors succeeded in selecting conditions (and, for this, cooling to -75°C was necessary) such that the reduction of the ester function stopped at the stage of formation of an aldehyde. Compound (**100**) was obtained with a yield of 92% in the form of a mixture (7:1) of the 3α-hydroxy and 3β-hydroxy isomers. Using the Wittig reaction, the action on the aldehyde (**100**) of the ylide obtained from triphenylisopropylphosphonium bromide and sodium amide gave the cholestane derivative (**101**), and the oxidation of the 3-hydroxy group in this with manganese dioxide led to the $\Delta^{1,7,24}$-3-ketone (**102**).

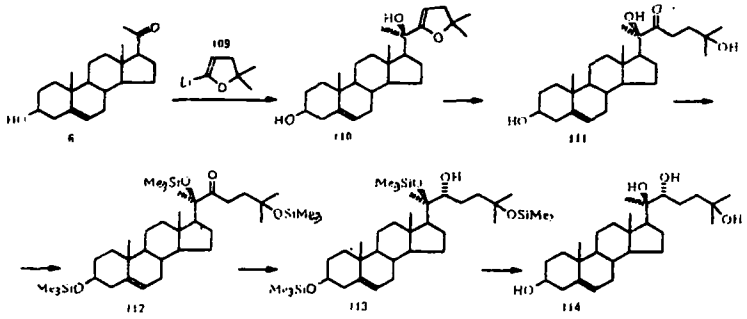
The allyl oxidation of compound (**102**) at C-6 with pyridinium dichromate enabled a 6-keto group to be introduced into the steroid molecule. The required 3,6-diketone (**103**) obtained in this way with a yield of 14%, in which, as before, the *cis-A/B*-linkage was retained, was converted by hydrogenation, deuteration, or tritiation over a palladium catalyst into the product required for ecdysteroid synthesis (**84**) (a: R = ^{1}H; b: R = ^{2}H; c: R = ^{3}H). It is interesting to note that the ^{3}H NMR spectrum showed that in compound (**84c**) more than 40% of the radioactive label was present in the 26- and 27-methyl groups.



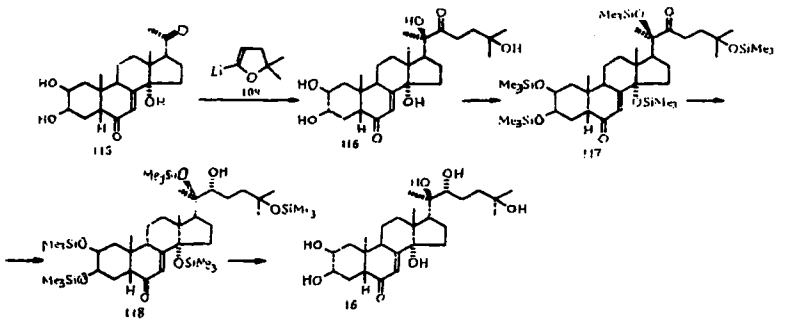
For the synthesis of ecdysteroids having a 20,22,24-trihydroxy grouping in the side-chain, a method for its formation from the allyl alcohol (**104**) proposed by Hedtmann et al. [29] may be of interest. The cycloaddition of isobutyronitrile oxide to the double bond of compound (**104**) formed the isoxazolines (**105**) and (**106**). Opening the heterocycle in steroid (**105**) under the action of Raney nickel in the presence of boric acid led to the 20,22,24-triols (**107**) and (**108**). It must be mentioned that in compound (**107**) the side-chain has the same structure as in the phytoecdysteroids ponasterone C and pterosterone.



A new method of constructing the side-chain of 20,22,25-trihydroxyecdysteroids from 20-ketosteroids has been proposed in [30, 31]

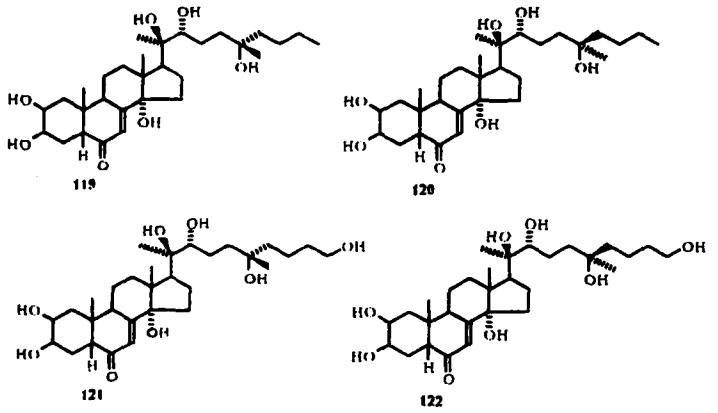


The approach developed is based on the interaction of the 20-ketone (**6**) with the lithium derivative of dihydrofuran (**109**) to form the 20-hydroxysteroid (**110**), which, without isolation from the reaction mixture, was converted under the action of hydrochloric acid into the 20,25-dihydroxy-22-ketone (**111**) in an overall yield of 70%. The authors established that direct reduction of the 22-keto group in compound (**111**) with sodium tetrahydroborate led to the required (20R,22S)-20,22,25-triol with a yield of only 20%. The main product of this reaction, isolated with a yield of about 60% was its isomer, the (20R,22S)-20,22,25-triol. In order to increase the yield of the required steroid (**114**), the hydroxy groups in compound (**111**) were silylated by reaction with trimethylsilyl triflate, which gave an 86% yield of the 3,20,25-tris(trimethylsilyl) ether (**112**). Reduction of the 22-keto group in steroid (**112**) with diisobutylaluminum hydride gave a 72% yield of the 22-alcohol (**113**) having the required C-22 stereochemistry. Hydrolysis of the protective silyl groups in compound (**113**) with tetrabutylammonium fluoride led to the required tetraol (**114**) with a yield of 78%.

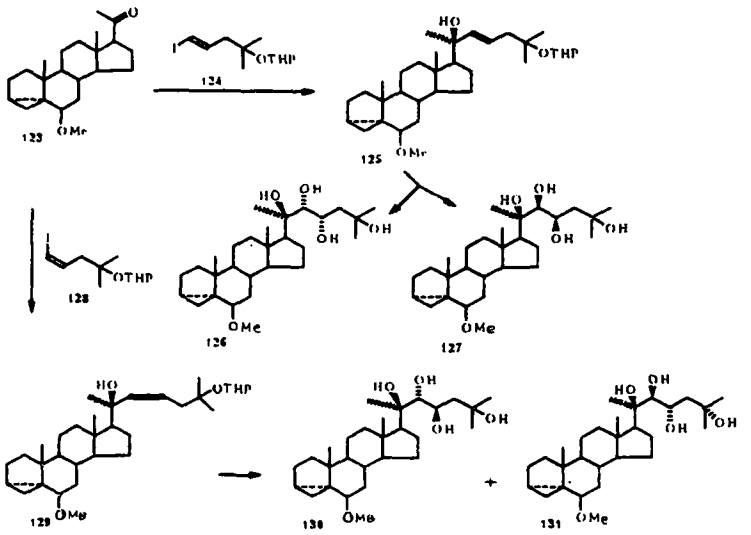


The conversion of poststerone (**115**) into 20-hydroxyecdysone (**1b**) has been achieved with the aid of the scheme developed by Hedtmann et al. [30, 31]. By alkylation of the 20-keto group in the molecule of poststerone with the lithium derivative of dihydrofuran (**109**), followed by reaction of the resulting addition product with hydrochloric acid in tetrahydrofuran, the pentahydroxy-6,22-diketone (**116**) was obtained with an overall yield of 79%.

Silylation of the hydroxy groups in compound (**116**) with trimethylsilyl triflate in the presence of 2,6-lutidine led to the formation in 74% yield of the fully silylated derivative (**117**). The reaction of steroid (**117**) with diisobutylaluminum hydride took place with the reduction of both keto groups. However, the subsequent oxidation with activated manganese dioxide of the allyl 6-hydroxy group formed in the reduction product permitted the synthesis with an overall yield of 83% of the (22R)-22-alcohol (**118**) containing only trace amounts of the (22S)-isomer. Hydrolysis of the trimethylsilyl groups in steroid (**118**) with tetrabutylammonium fluoride led to 20-hydroxyecdysone (**1b**) with a yield of 80%.



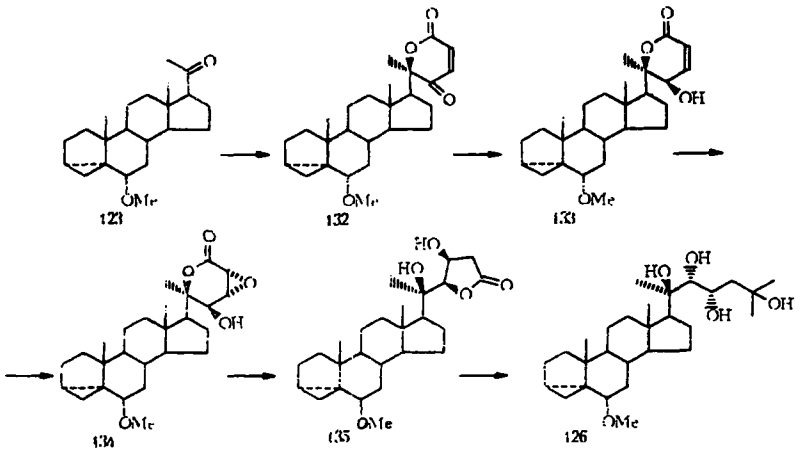
Later, by the scheme developed, ecdysteroids (**119-122**) were synthesized as a result of the use for alkylating poststerone (**115**) of the corresponding 5-lithium derivatives of 3,3-disubstituted 2,3-dihydrofurans and subsequent transformations analogous to those described above in the synthesis of 20-hydroxyecdysone [30, 31].



For an accurate determination of the stereochemistry of the side-chain of the phytoecdysteroid gerardiasterone, the model compounds (**126-131**) were synthesized [32]. Thus, the addition to the 20-ketone (**123**) of the lithium derivative obtained from the (E)-olefin (**124**) and *tert*-butyllithium led to the formation with a yield of 70% of the (22R,22E)-allyl alcohol (**125**). On the *cis*-hydroxylation of the Δ^{22}-steroid (**125**) with the stoichiometric amount of osmium tetroxide in pyridine, followed by hydrolysis of the tetrahydropyranyl protective groupings in the presence of camphorsulfonic acid, the alcohols (**126**) and (**127**) were obtained with a total yield of 85% in a ratio of 76:24. It was established that when dihydroquinine *p*-chlorobenzoate was added as a chiral ligand during hydroxylation the ratio of compounds (**126**) and (**127**) became 91:9. At the same time, another chiral ligand, dihydroquinidine *p*-chlorobenzoate, changed it to 13:87. In its turn, in the condensation of the 20-ketosteroid (**123**) with the lithium derivative obtained from the (Z)-olefin (**128**) and *tert*-butyllithium, the (20R,22Z)-allyl alcohol (**129**) was formed in a yield of 84%.

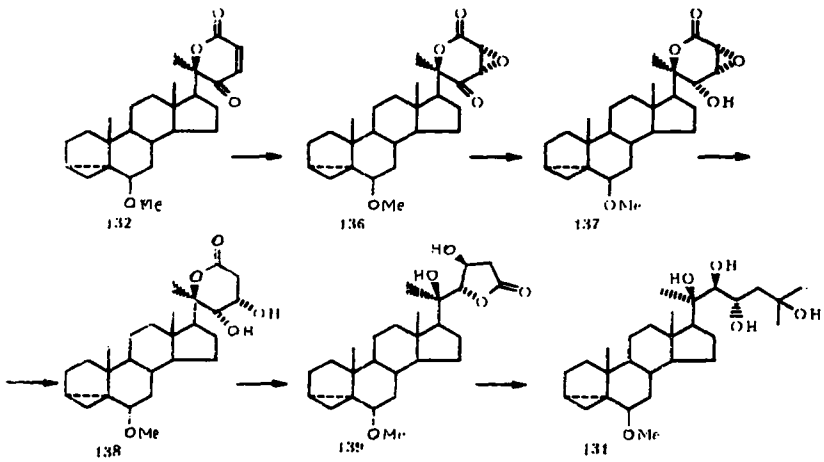
The hydroxylation of the double bond in steroid (**129**) with osmium tetroxide in pyridine followed by elimination of the tetrahydropyranyl grouping by hydrolysis in the presence of camphorsulfonic acid led with a total yield of 93% to the al-

cohols (**130**) and (**131**) in a ratio of 54:46. Performing the hydroxylation reaction with the use of dihydroquinine *p*-chlorobenzoate as chiral ligand made this ratio 71:29. With dihydroquinidine *p*-chlorobenzoate, compounds (**130**) and (**131**) were obtained from the Δ^{22}-steroid (**129**) in a ratio of 35:65.



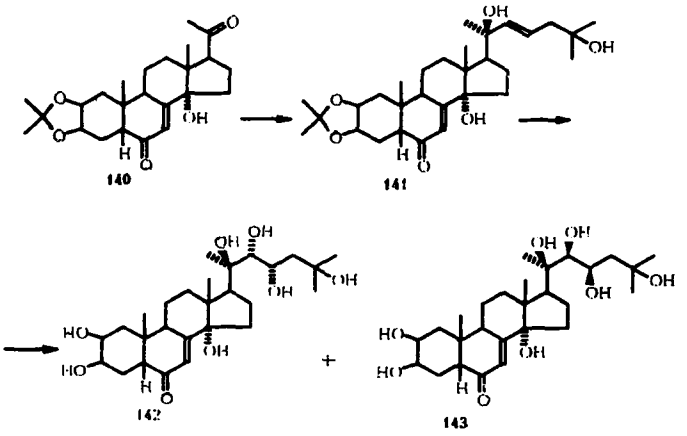
However, the authors were unable to determine accurately the configurations of the C-22 and C-23 centers in steroids (**126-131**) on the basis of the results of an analysis of ^{1}H NMR spectra. For this reason, two of them were subsequently obtained by alternative methods.

The condensation of the 20-ketosteroid (**123**) with 2-lithiofuran, oxidation of the resulting furan derivative with N-bromosuccinimide in aqueous tetrahydrofuran, and oxidation of the lactone so formed with pyridinium chlorochromate led with an overall yield of 83% to the unsaturated ketolactone (**132**). Reduction of the keto group in compound (**132**) with sodium tetrahydroborate in the presence of cerium(III) chloride gave a 97% yield of the allyl alcohol (**133**), which was epoxidized with sodium hypochlorite to form the epoxide (**134**) as the sole product with a yield of 62%. The interaction of the epoxyalcohol (**134**) with sodium phenylseleno(triisopropoxy)borate (obtained from diphenyl diselenide and sodium tetrahydroborate in isopropanol) took place with the regioselective opening of the epoxide ring and subsequent cyclization with the formation of the dihydroxy-γ-lactone (**135**) in a yield of 63%. In the concluding stage of the synthesis, the tetraol (**126**) was obtained with a yield of 25% from compound (**135**) by reaction with methylmagnesium bromide.

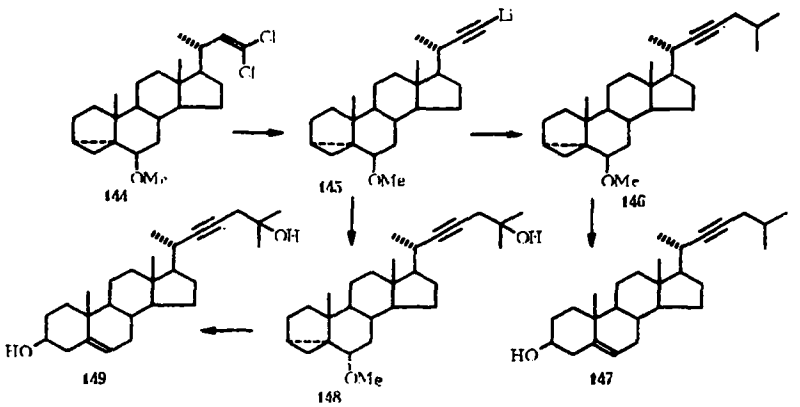


For the synthesis of the tetrahydroxysteroid (**131**) from the 20-ketosteroid (**123**), the sequence of stages was somewhat varied. First, as in the preceding synthesis, the initial compound (**123**) was converted into the unsaturated ketolactone (**132**). Epoxidation of the latter with alkaline hydrogen peroxide led with a yield of 80% to epoxide (**136**), the reduction of which with sodium tetrahydroborate in tetrahydrofuran at −70°C formed the epoxide (**137**) in a yield of 87%. Lactones (**138**) and (**139**) were obtained in equal amounts with a total yield of 53% by the reductive cleavage of epoxide (**137**) under the action of diphenyl diselenide and sodium tetrahydroborate in isopropanol. Tetraol (**131**) was synthesized in a yield of 22% from lactones (**138**) and (**139**) by the Grignard reaction with methylmagnesium bromide. Analysis of ^{1}H NMR spectra showed that the side-chain of gerardiasterone and of the tetraol (**126**) were identical. This made it possible to synthesize gerardiasterone (**142**) itself from poststerone (**115**) [32].

The alkylation of poststerone acetonide (**140**) with the anion obtained from the tetrahydropyranyl ether of (E)-4-iodo-2-methylpent-4-en-2-one and *tert*-butyllithium led to the formation of the allyl alcohol (**141**) with a yield of 70%. On the *cis*-hydroxylation of the Δ^{22}-bond in compound (**141**) with osmium tetroxide in pyridine, followed by hydrolysis of the protective groupings in the presence of camphorsulfonic acid, gerardiasterone (**142**) and its (22S,23R)-isomer (**143**) were formed in a ratio of 79:21. The use in the osmium tetroxide hydroxylation reaction of dihydroquinine *p*-chlorobenzoate as a chiral ligand permitted the ecdysteroids (**142**) and (**143**) to be obtained in a ratio of 95:5. At the same time, the presence of another chiral ligand — dihydroquinidine *p*-chlorobenzoate — in the reaction mixture led to the formation of compounds (**142**) and (**143**) in a ratio of 21:79.

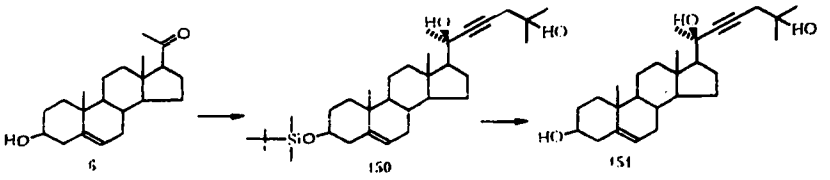


There is also a report in the literature [33] that, in addition to gerardiasterone, the same authors have synthesized the phytoecdysteroid abutasterone [33].



To study the biosynthesis of ecdysteroids in insects and other arthropods there is a need for substances selectively inhibiting various stages of this process. Enzymes participating in the biosynthesis of ecdysteroids — or, at least, its later stages — belong to the cytochrome P-450-dependent monoxygenases [18]. The activity of such enzymes can be irreversibly suppressed by acetylenic compounds. As such, great interest is presented by substances that are structural analogs of ecdysteroids and contain triple bonds in various positions of the molecule. Thus, Burger et al. [34] have synthesized cholesterol derivatives containing 22(23)-triple bonds. Interaction with butyllithium of the dichlorovinylsteroid (**144**) obtained from stigmasterol formed the acetylide (**145**), which, without isolation, was then subjected to hydrolysis or to alkylation with various alkyl halides. In this way, the corresponding acetylenic steroids with side-chains of different lengths were obtained. In particular, the alkylation of the lithium acetylide (**145**) with isobutyl bromide led to the formation of compound (**146**), and acid hydrolysis of the protective 3α,5-cyclo-6β-methoxy grouping in the latter permitted the synthesis of the acetylenic cholesterol derivative (**147**).

By the alkylation of compound (**145**) with methyl iodide, the formation of the corresponding lithium derivative from the reaction product and its subsequent interaction with acetone, it was possible to obtain the acetylenic 25-hydroxysteroid (**148**). The acetylenic 25-hydroxycholesterol (**149**) was then synthesized by hydrolysis of the protective groupings in rings *A* and *B*.

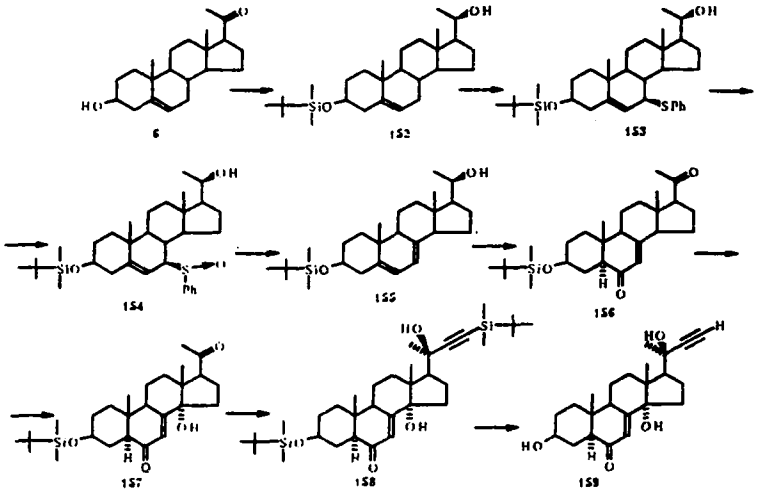


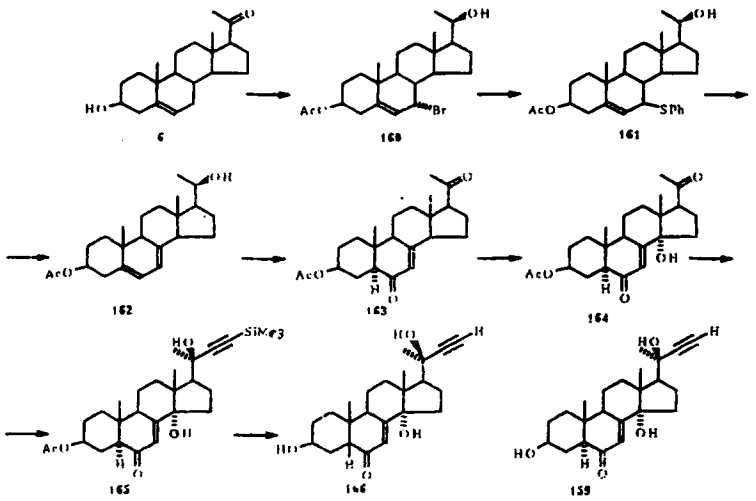
To obtain 22(23)-acetylenic derivatives of cholesterol with hydroxy groups at C-20 and C-25, Burger et al. [34] developed a scheme of synthesis starting from pregnenolone (**6**). The 3β-hydroxy grouping in the pregnenolone molecule was first protected in the form of the *tert*-butyldimethylsilyl ether. Subsequent alkylation of the 20-keto group with the appropriate lithium acetylide enabled derivative (**150**) with the required side-chain to be obtained. Removal of the protective silyl grouping under the action of tetrabutylammonium fluoride formed the desired compound (**151**). Experiments with isolated prothoracic glands of the locust *Locusta migratoria* showed that among the compounds studied (**151**) was the most active irreversible selective inhibitor of the C-22 hydroxylase system.

One of the enzymes taking part in the biosynthesis of ecdysteroids is C-22 hydroxylase, under the action of which a 22-hydroxy group is introduced into the steroid molecule [18]. With the aim of finding compounds selectively inhibiting this enzyme, structural analogs of ecdysteroids having a triple bond in the side-chain have been synthesized [35, 36].

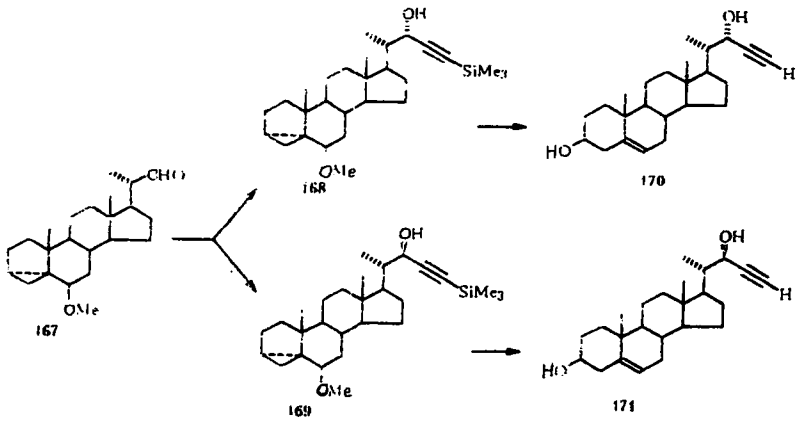
Mauvais et al. [35] have synthesized compound (**159**), which has, in the cyclic part, the functional groups characteristic for ecdysteroids and, in the side-chain, together with a 20-hydroxy group, a 22(23)-triple bond, this compound being of interest as a C-22 hydroxylase inhibitor.

At the beginning of the synthesis, the 3β-hydroxy group in the molecule of the initial pregnenolone (**6**) was protected in the form of a silyl ether, and the 20-keto group was then reduced, with the formation of the (20R)-20-alcohol (**152**) in an overall yield of 85%. The allyl bromination of compound (**152**) with 2,3-dibromo-5,5-dimethylhydantoin, followed by isomerization of the resulting mixture of 7α- and 7β-bromides under the action of lithium bromide, led to a product consisting of the 7α-bromide alone, and the interaction of this with thiophenol gave the sulfide (**153**). Oxidation of the sulfide (**153**) with *m*-chloroperbenzoic acid formed the sulfoxide (**154**), an elimination reaction of which with triethylamine enabled the 5,7-diene (**155**) uncontaminated with the 4,6-diene to be obtained with an overall yield of 56% from steroid (**152**). The hydroboration–oxidation of diene (**155**) formed an 86% yield of the 6α-alcohol (**156**), and oxidation of the latter with pyridinium chlorochromate gave the 6,20-diketone in 81% yield. The allyl oxidation of compound (**156**) with selenium dioxide in dioxane formed the 14α-hydroxy-Δ^7-6,20-diketone (**157**) with a yield of 82%. Trimethylsilylacetylenylmagnesium bromide was added to the 20-keto group of steroid (**157**) with the formation of an 83% yield of the propargyl alcohol (**158**), the silyl protective groups of which were hydrolyzed with a complex of hydrogen fluoride and pyridine in the concluding stage of the synthesis, giving the required steroid (**159**) quantitatively.

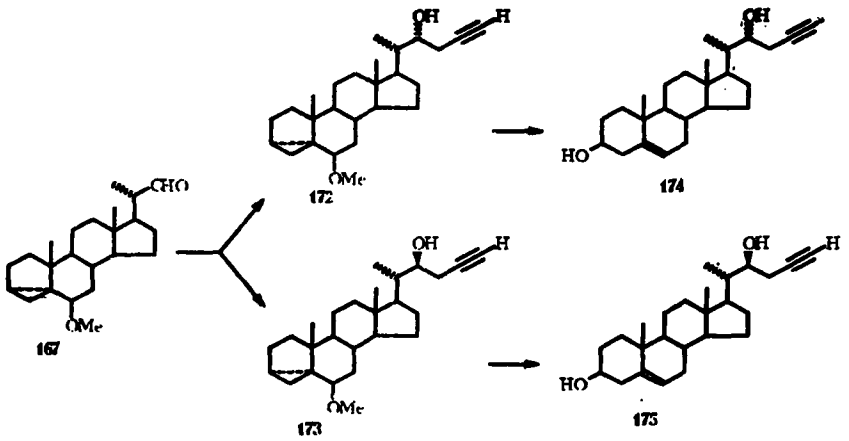




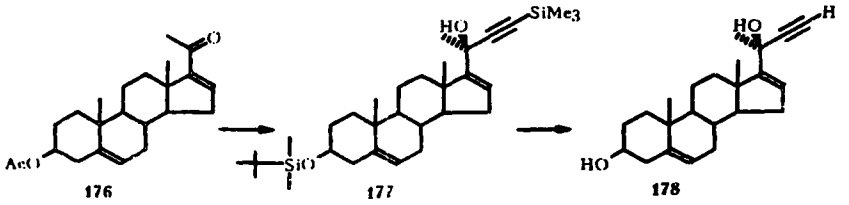
Later, because of the poor reproducibility of some of its stages, the synthesis discussed above was improved [36]. The 7α-bromo derivative (**160**) was obtained from pregnenolone (**6**) as a result of acetylation of the 3β-hydroxy group, reduction of the 20-keto group with L-selectride, allyl bromination at C-7 under the action of 2,3-dibromo-5,5-dimethylhydantoin with the formation of a mixture of 7α- and 7β-bromides, and the subsequent isomerization of this mixture with tetrabutylammonium fluoride. Replacement of the bromine atom in compound (**160**) by thiophenol permitted the synthesis of the 7β-thiosteroid (**161**). Oxidation of the sulfur atom in sulfide (**161**) with *m*-chloroperbenzoic acid to the corresponding sulfoxide and then *cis*-elimination of the 7β-sulfoxide group by heating in toluene led with an overall yield of 53% from the initial pregnenolone (**6**) to the 5,7-diene (**162**). The hydroboration–oxidation of the 5-double bond in diene (**162**) followed by the oxidation of the 6α- and 20-hydroxy groups in the reaction products with pyridinium chlorochromate enabled the 6,20 diketone (**163**) to be obtained, and the allyl oxidation of this with selenium dioxide in dioxane formed the 14α-hydroxy-6,20-diketone (**164**). Selective ethynylation of the 20-keto group in compound (**164**) under the action of lithium trimethylsilylacetylide took place with the formation of the propargyl alcohol (**165**) in 88% yield. When steroid (**165**) was treated with potassium carbonate in a mixture of methanol, tetrahydrofuran, and water, hydrolysis of the protective groupings took place with the simultaneous formation of a mixture of isomers at C-5. In this way the desired compounds (**166**) and (**159**) were synthesized. We may also note that in the same investigation [36], the 14-deoxy analogs of steroids (**166**) and (**159**) were also obtained from the 6,20-diketone (**163**) by the use of the above-described sequence of reactions.



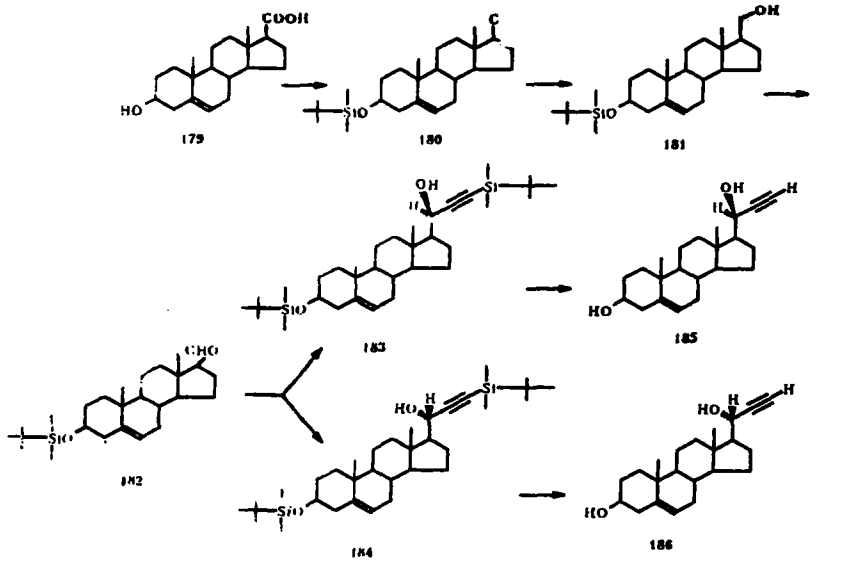
The synthesis of the propargyl alcohols (**170**) and (**171**), which are of interest as inhibitors of ecdysone C-25 hydroxylase, has been achieved, starting from the ergosterol aldehyde (**167**) [37]. The interaction of aldehyde (**167**) with lithium trimethylsilylacetylide formed the 22-alcohols (**168**) and (**169**) with a total yield of 85%. Diol (**170**) was obtained in moderate yield from compound (**168**) by isomerization under the action of *p*-toluenesulfonic acid in aqueous dioxane. Steroid (**169**) was converted into the diol (**171**) analogously.



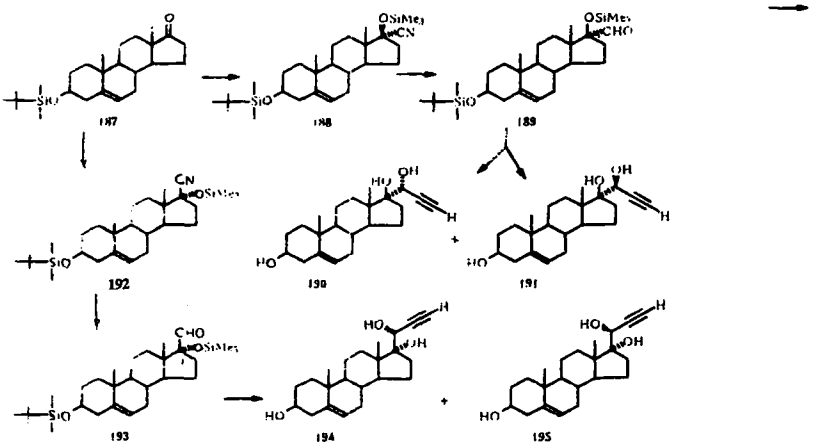
In its turn, condensation of the aldehyde (**167**) with propargylmagnesium bromide led to the 22-alcohols (**172**) and (**173**) with a total yield of 80%. Diols (**174**) and (**175**) were obtained from steroids (**172**) and (**173**), respectively, by isomerization in rings *A* and *B* under the action of *p*-toluenesulfonic acid in aqueous dioxane. It has been reported [37] that, in concentrations of 10^{-5} M, compounds (**170**), (**171**), and (**174**) exhibit an appreciable inhibitory action on the biosynthesis of ecdysone in the prothoracic glands of the larvae of the locust *Locusta migratoria*. At the same time, compound (**175**) possessed no such inhibitory action whatever.



Dehydropregnenolone (**176**) has been used as the starting material for the synthesis of the propargyl alcohol (**178**), which is of interest as an inhibitor of the biosynthesis of ecdysteroids [38]. The hydroxy group in the molecule of the initial steroid was first protected quantitatively by reaction with *tert*-butyldimethylchlorosilane in the presence of diisopropylethylamine, and then the propargyl alcohol (**177**) was obtained with a yield of 82% by condensing the reaction product with lithium trimethylsilylacetylide. Elimination of the silyl protective groups in compound (**177**) with tetrabutylammonium fluoride in tetrahydrofuran enabled the desired steroid (**178**) to be obtained quantitatively.

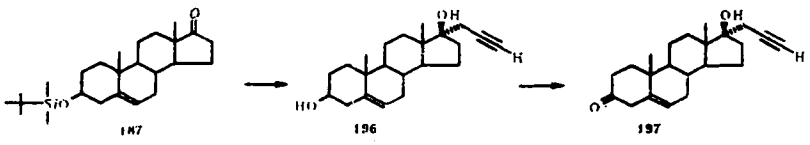


Compounds with a triple bond in the side-chain that are potential inhibitors of the biosynthesis of ecdysteroids have also been obtained from the ethenic acid (**179**) [38]. The carboxy group in the molecule of the ethenic acid (**179**) was first methylated with diazomethane to form the corresponding methyl ester, and the silylation of the 3β-hydroxy group in this then led to compound (**180**) in an overall yield of 93%. When the ester function in steroid (**180**) was reduced with lithium tetrahydroaluminate the primary alcohol (**181**) was formed quantitatively, and the oxidation of the latter with dimethyl sulfoxide and oxalyl chloride enabled the aldehyde (**182**) to be obtained with a yield of 91%. Condensation of the aldehyde (**182**) with lithium trimethylsilylacetylide took place with the quantitative formation of a mixture of the propargyl alcohols (**183**) and (**184**), elimination of the silyl protections from which with tetrabutylammonium fluoride gave quantitative yields of diols (**185**) and (**186**), respectively.



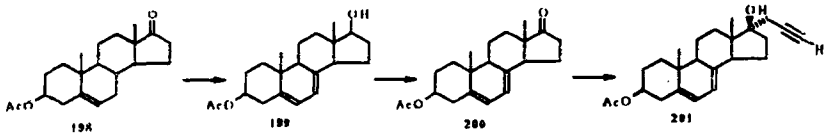
The synthesis of potential inhibitors of the biosynthesis of ecdysteroids from androstenolone protected at the 3-hydroxy group (**187**) has been described in [39]. Condensation of the 17-ketone (**187**) with trimethylsilyl cyanide led quantitatively to the protected cyanohydrin (**188**) the reduction of which with diisobutylaluminum hydride gave the aldehyde (**189**) in practically quantitative yield. The reaction of aldehyde (**189**) with lithium trimethylsilylacetylide, followed by elimination of the silyl protective groups with tetrabutylammonium fluoride, formed the triols (**190**) and (**191**) in a ratio of 97:3 with a total yield of 86%. The analogous condensation of aldehyde (**189**) with trimethylsilyacetylenylmagnesium bromide at −78°C, followed by hydrolysis of the silyl groups, led to the triols (**190**) and (**191**) in a ratio of 13:87 with a total yield of 89%.

The cyanohydrin (**192**) was synthesized in a yield of 90% by the reaction of the 17-ketone (**187**) with potassium cyanide followed by silylation, and its reduction with diisobutylaluminum hydride enabled the aldehyde (**193**) to be obtained with a yield of 95%. Interaction of the aldehyde (**193**) with lithium trimethylsilylacetylide, followed by hydrolysis of the silyl groups with tetrabutylammonium fluoride, led to the formation of triols (**194**) and (**195**) in a ratio of 96:4 with a total yield of 84%. At the same time, condensation of the aldehyde (**193**) with trimethylsilyacetylenylmagnesium bromide at −78°C gave, after hydrolysis of the protective groups, triols (**194**) and (**195**) in a ratio of 28:72 with a total yield of 90%. It has been reported [39] that, in concentrations of 10^{-5} M, the acetylenic alcohols (**190**), (**191**), (**194**), and (**195**) inhibit the biosynthesis of α-ecdysone in the prothoracic glands of the locust *Locusta migratoria* by 50-60%.

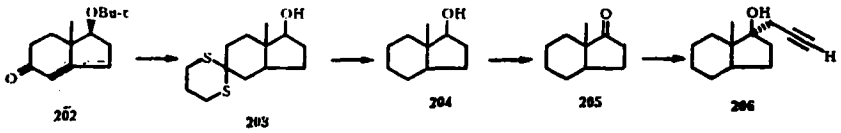


When the androstenolone protected at the 3β-hydroxy group (**187**) was condensed with propargylmagnesium bromide and the silyl protection was then eliminated, the propargyl alcohol (**196**) was obtained with an overall yield of 87% [38]. By oxidation of the 3β-hydroxy group in compound (**196**) with pyridinium chlorochromate adsorbed on neutral alumina (in order to prevent migration of the double bond), the ketoalcohol (**197**) was synthesized with a yield of 81%.

In order to obtain a structural analog of diol (**196**) containing an additional 7-double bond and having the structure of the diene (**201**), a scheme of synthesis from androstenolone (**198**) has been developed [38].

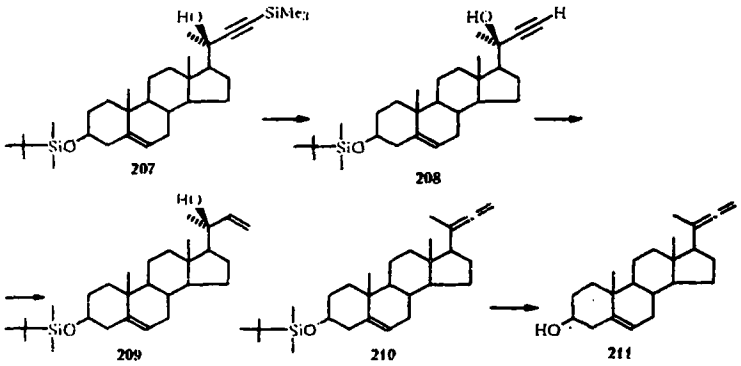


The 17-keto group in compound (**198**) was first reduced by L-selectride with the quantitative formation of the 17β-alcohol. The reduction product was subjected to allyl bromination with 2,3-dibromo-5,5-dimethylhydantoin, the resulting 7-bromide was converted by reaction with thiophenol into a sulfide which was then oxidized with *m*-chloroperbenzoic acid to the sulfoxide, and this, by an elimination reaction under the action of triethylamine, formed the 5,7-diene (**199**) with an overall yield from (**198**) of 51%. The oxidation of steroid (**199**) with pyridinium chlorochromate gave an 82% yield of the 17-ketone (**200**), and the condensation of this with propargylmagnesium bromide enable the required acetylenic derivative (**201**) to be obtained with a yield of 77%.



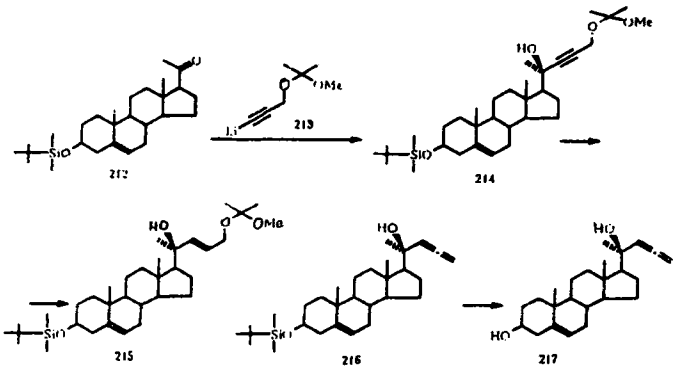
In order to determine the smallest structure necessary for the presence of an inhibiting action on the biosynthesis of ecdysteroids, the bicyclic derivative (**206**) has been synthesized [38]. The dithioketal (**203**) was obtained from the protected hydroxyindanone (**202**) in a yield of 95% by reaction with propanedithiol in the presence of camphorsulfonic acid (when hydrolysis of the *tert*-butoxy group also takes place). Compound (**203**) was desulfurized with a yield of 40% with Raney nickel to the indanol (**204**) which was then oxidized with pyridinium chlorochromate on alumina to form the ketone (**205**) with a yield of 76%. The required acetylenic alcohol (**206**) was obtained in 71% yield by the reaction of ketone (**205**) with propargylmagnesium bromide.

It is known from the biochemical literature that, as well as acetylenes, allenes are inhibitors of cytochrome P-450 oxidase. Such reports have served as grounds for the synthesis of a number of steroids having an allene group in the side-chain in order to find among them selective inhibitors of the biosynthesis of ecdysteroids [40, 41].

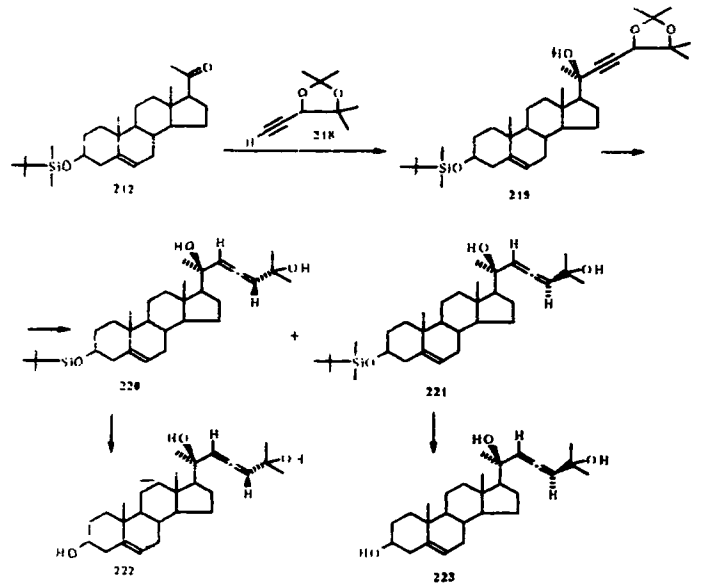


Thus, on the interaction of compound (**207**) with potassium carbonate in a mixture of tetrahydrofuran, ethanol, and water, selective hydrolysis of the trimethylsilyl group took place with the formation of 90% of the propargyl alcohol (**208**) [40]. Reduction of the triple bond in steroid (**208**) with a mixture of lithium tetrahydroaluminate and aluminum chloride led to the allyl alcohol (**209**) and the allene (**210**) with yields of 35 and 56%, respectively. The required allene (**211**) was synthesized quantitatively from compound (**210**) by elimination of the silyl protection.

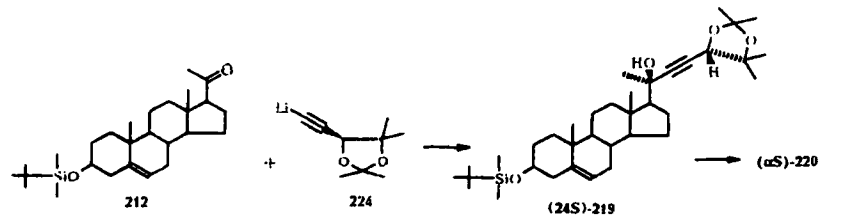
Continuing this investigation, Burger et al. [40] achieved the synthesis of the allenic steroid (**217**) containing the 20-hydroxy group that is characteristic for ecdysteroids. Thus, the interaction of the 20-ketone (**212**) with the specially synthesized lithium acetylide (**213**) led with quantitative yield to the (20R)-propargyl alcohol (**214**). Reduction of the triple bond in compound (**214**) with lithium tetrahydroaluminate gave the allyl alcohol (**215**) and the allene (**216**) with yields of 19 and 77%, respectively. Hydrolysis of the silyl protection of the hydroxy group in compound (**216**) with tetrabutylammonium fluoride gave the dihydroxyallene (**217**) with a yield of 96%.



The synthesis of steroids containing in the side chain, in addition to an allene grouping, the hydroxy groups at C-20 and C-25 that are characteristic for ecdysteroids has also been undertaken [40]. The key stage of this synthesis was the condensation of pregnenolone protected at the 3-hydroxy group (**212**) with the lithium acetylide obtained from the substituted acetylene (**218**) and methyllithium.



This formed the propargyl alcohol (**219**) with a yield of 93%. Reduction of compound (**219**) with lithium tetrahydroaluminate led to the formation with approximately equal yields (42%) of the chiral allenes (**220**) and (**221**). Removal of the silyl protective groups from steroids (**220**) and (**221**) with tetrabutylammonium fluoride gave the allenic triols (**222**) and (**223**), respectively, in practically quantitative yields.



Later, the scheme for synthesizing allenes (**222**) and (**223**) was improved by the use of specially synthesized chiral lithium derivatives for condensation with ketone (**212**) [41]. Thus, the interaction of the 20-ketone (**212**) with the acetylide (**224**), having the (S)-configuration of the chiral center, formed the (24S)-isomer of the propargyl alcohol (**219**). Reduction of this compound with lithium tetrahydroaluminate led with a yield of 88% to the pure (αS)-isomer (**220**). The allene (**221**), can be obtained analogously.

It has been reported [40] that, in concentrations of 10^{-4} M, all the allenes synthesized — (**211**), (**217**), (**222**) and (**223**) — possess an inhibiting action on the biosynthesis of ecdysteroids in the prothoracic glands of the larvae of *Locusta migratoria in vitro*.

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