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THE CHEMICAL SYNTHESIS OF STEROLS: LATEST ADVANCES

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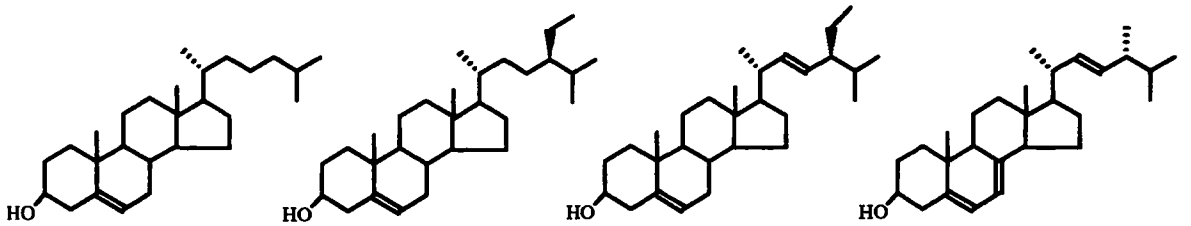
This review discusses the results of investigations on the chemical synthesis of sterols during 1981—1996.

Sterols are among the most important natural substances, fulfilling various biological functions in plants and animals [1, 2]. In terms of chemical structure, sterols are secondary alcohols with a carbon skeleton consisting of a tetracyclic steroid nucleus with three six-membered rings and one five-membered ring and a side-chain usually of 8—10 carbon atoms. The most typical sterols include cholesterol (**1**), β-sitosterol (**2**), stigmasterol (**3**), and ergosterol (**4**). These sterols are widely distributed in the animal and vegetable kingdoms and are used in the pharmaceutical chemical industry as raw materials for obtaining drugs by chemical and microbiological methods. Other sterols — and the number of representatives of this group of substances runs into hundreds — are frequently present in natural materials in very inconsiderable amounts. This circumstance makes it necessary to develop special methods for obtaining them, including, in the first place, chemical synthesis.

It must be mentioned that the chemical synthesis of sterols is widely used in steroid chemistry, and considerable advances are being made in this field. However, because of the limited volume of this paper we shall discuss only investigations published in the scientific literature during 1981—1996. The reviews [3—5] may prove useful to those wishing to become acquainted with earlier studies.



1 **2** **3** **4**

We shall first direct our attention to a discussion of syntheses of cholesterol (**1**), which are usually undertaken mainly with the aim of demonstrating the synthetic possibilities of some particular method of forming sterol side-chains.

Thus, Schmuff and Trost [6] have proposed several variants of the synthesis of cholesterol from androstenolone (**5**). Sterol (**5**) was first converted into the tosylate, the rearrangement of which in methanol in the presence of potassium acetate led with an overall yield of 81% to the β-methoxy derivative **6**. The Wittig—Horner reaction of steroid (**6**) with ethyltriphenylphosphonium bromide gave a 77% yield of the olefin (**7**) the allyl oxidation of which with selenium dioxide enabled the allyl alcohol (**8**) to be obtained with a yield of 80%. The further oxidation of the alcohol (**8**) with oxalyl chloride and dimethyl sulfoxide led quantitatively to the enone (**9**), the 1,4-addition to which of the appropriate lithium cuprate reagent formed, with a yield of 73%, the cholestane derivative (**10**) having the natural C-17 and C-20 stereochemistry. The Wolff-Kishner reduction of the 16-keto group in compound (**10**) using hydrazine hydrate enabled the 16-deoxy derivative (**11**) to be obtained, and hydrolysis of the protective groupings in rings *A* and *B* of compound (**11**) in aqueous dioxane in the presence of *p*-toluenesulfonic acid led in quantitative yield to cholesterol (**1**).

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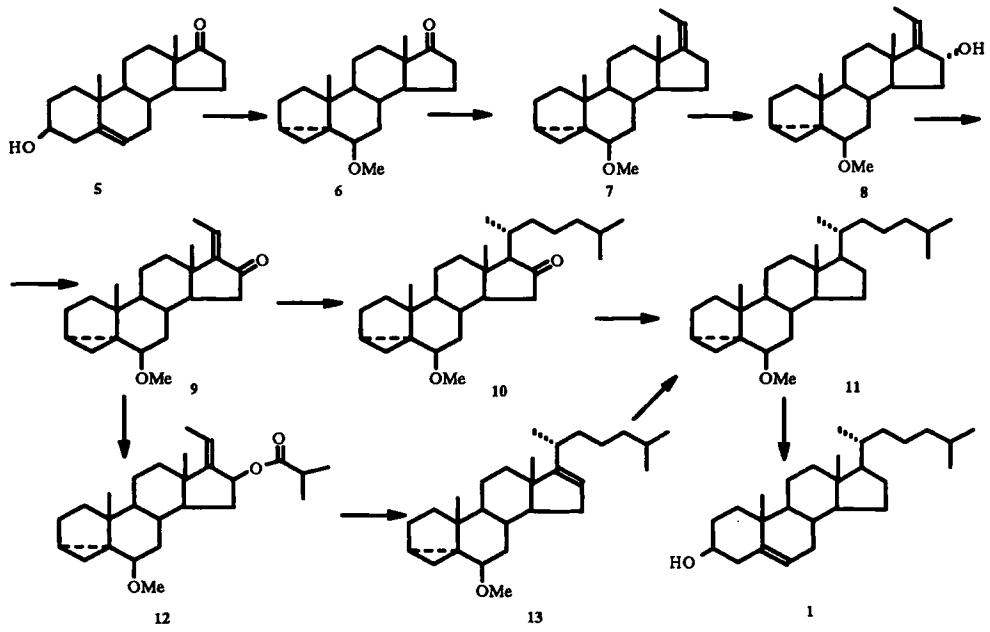
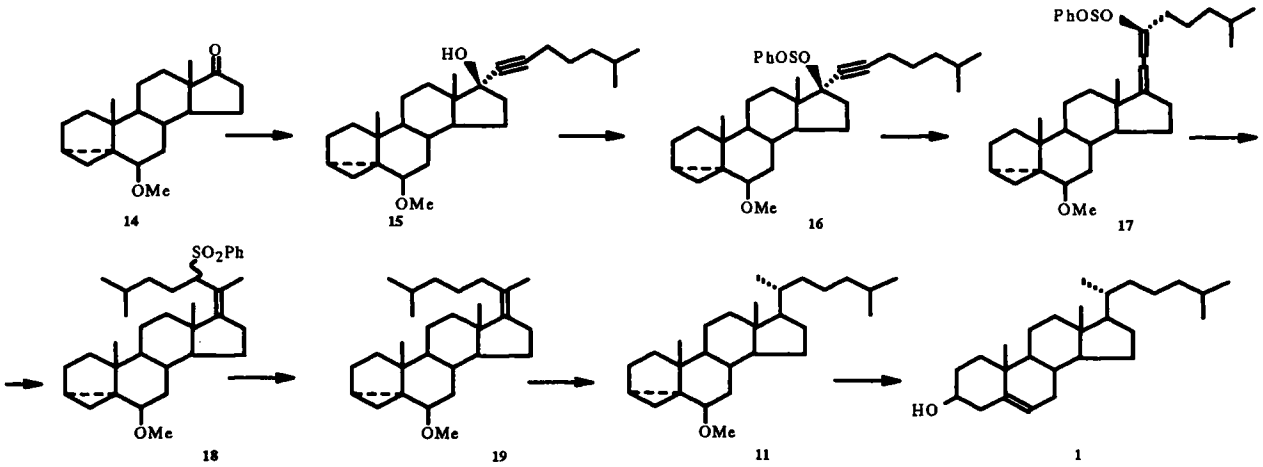
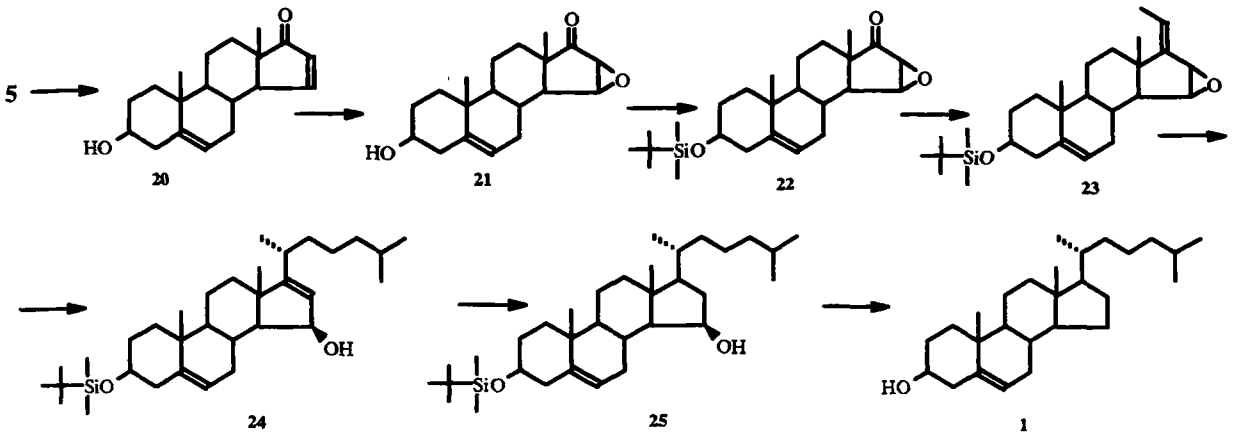


The second variant of the synthesis of cholesterol made use of the conversion of the enone (**9**) into the corresponding 16β-alcohol, the subsequent esterification of which with pivaloyl chloride in the presence of dimethylaminopyridine took place with the formation of the ester (**12**) with an overall yield of 63%. Interaction of compound (**12**) with the appropriate cyanocuprate reagent gave a 78% yield of cholestene (**13**), by the hydrogenation of the 16(17)-double bond in which with the aid of palladium on barium sulfate the cholestane derivative (**1**) was synthesized quantitatively. On the other hand, esterification of the 16α-alcohol (**8**) with phenyl isocyanate led to the corresponding 16-phenylcarbamate, from which the cholestene (**13**) was again obtained, with a yield of 36%, by condensation with a lithium cuprate reagent.

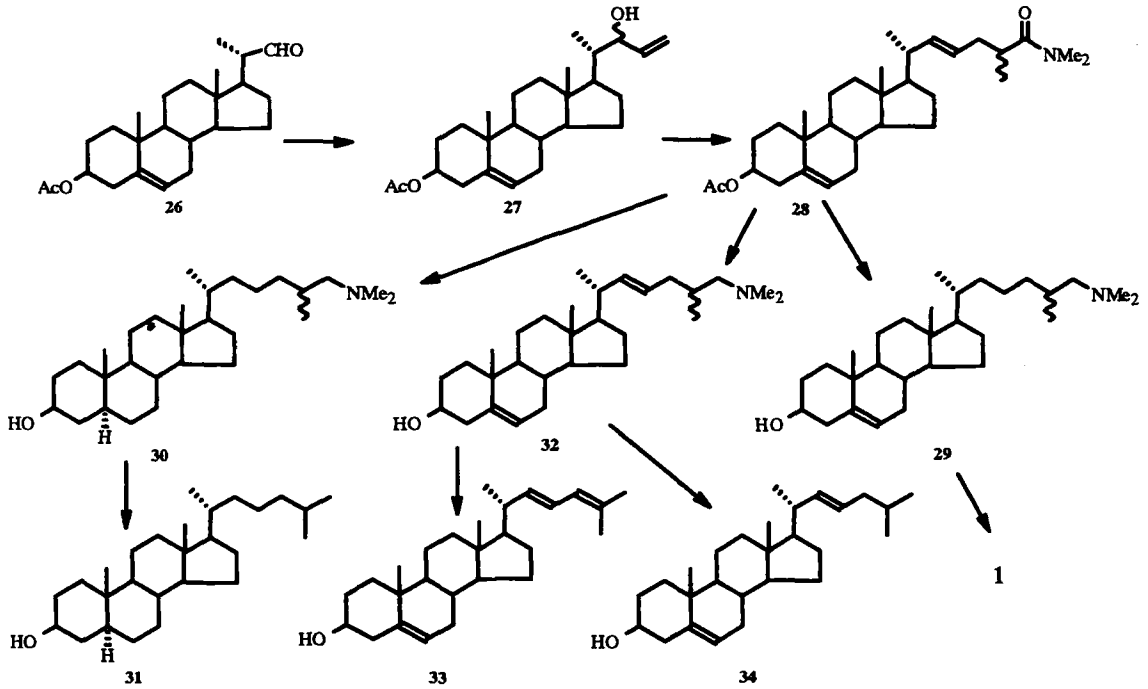
In [7], the synthesis of cholesterol started from the 17-ketone (**14**). The interaction of compound (**14**) with the lithium derivative of 6-methylhept-1-yne in the presence of lithium diisopropylamide in tetrahydrofuran gave a 75% yield of the propargyl alcohol (**15**). The reaction of the latter with benzenesulfinyl chloride in pyridine led with a yield of 85% to the sulfinate (**16**) which, as the result of a thermal 2,3-sigmatropic rearrangement in chlorobenzene in the presence of lithium carbonate, was converted quantitatively into the sulfonylallene (**17**). The further treatment of the allene (**17**) with lithium dimethylcuprate in tetrahydrofuran gave with a yield of 85% the (Z)-allyl sulfone (**18**) in the form of epimers at C-22. The reductive desulfonylation of steroid (**18**) with lithium in ethylamine led with a yield of 90% to the $\Delta^{17(20)}$-cholestene (**19**). The catalytic hydrogenation of compound (**19**) over palladium on carbon gave with a yield of 90% a methyl ether the isomerization of which in rings *A* and *B* in aqueous dioxane in the presence of *p*-toluenesulfonic acid formed cholesterol (**1**) quantitatively.



The construction of the side-chain of cholesterol (**1**) as the result of the 1,4-*trans*-addition of a cyanocuprate to alkylideneoxirans has been proposed [8]. The scheme of synthesis included the conversion of androstenolone (**5**) into steroid (**20**), followed by alkoxylation with the formation of the epoxyketone (**21**). By protecting the 3β-hydroxy group in compound (**21**) the silyl derivative (**22**) was obtained from (**5**) with an overall yield of 70%, and this was converted into compound (**23**) in a yield of 80% by the Wittig-Horner reaction. The addition of lithium isohexylcuprate led with a yield of 82% to the formation of the allyl alcohol (**24**) which then, as the result of hydrogenation of the 16-double bond over a platinum catalyst to the saturated steroid (**25**), conversion of the latter into the bis(dimethylamino)phosphoramidate, reduction with lithium in ethylamine to the corresponding 15-deoxy derivative, and, finally, elimination of the protective 3-silyl grouping, gave the end-product (**1**) with an overall yield of 72%.

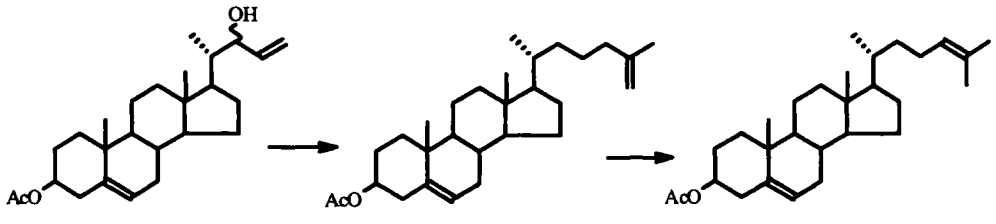


Kircher and Rosenstein [9] have proposed the synthesis of a number of sterols from the aldehyde (**26**). The interaction of compound (**26**) and vinylmagnesium bromide formed the allyl alcohol (**27**), the condensation of which with 1-(dimethylamino)-1-methoxyprop-1-ene in boiling benzene gave the amide (**28**) with a yield of 86%. The selective hydrogenation of the 22-double bond in steroid (**28**) over a platinum catalyst in ethyl acetate, with a yield of 95%, followed by the reduction of the amide function with a yield of 82% by the action of lithium tetrahydroaluminate in tetrahydrofuran led to the amine (**29**). By the oxidation of the amino group of the latter with hydrogen peroxide in methanol, elimination of the resulting N-oxide group with potassium hydroxide in pyridine to form the $\Delta^{25(26)}$-derivative with a yield of 67%, and hydrogenation of the latter in the presence of *tris*(triphenylphosphine)rhodium chloride led to cholesterol (**1**).



On the prolonged hydrogenation of compound (**28**) over palladium on carbon in a mixture of ethyl acetate and acetic acid, the saturated amine (**30**) was formed in a yield of 79%, and from this, by a method analogous to that described above, 5α-cholestan-3β-ol (**31**) was then obtained via 5α-cholest-25-en-3β-ol. In its turn, the direct reduction of the amide (**28**) with lithium tetrahydroaluminate gave an 81% yield of the unsaturated amine (**32**). Oxidation of the amine group in compound (**32**) with hydrogen peroxide in methanol followed by the elimination with barium hydroxide in pyridine of the N-oxide group so formed permitted the synthesis of cholesta-5,22,25-trien-3β-ol. Isomerization of the latter with potassium hydroxide in ethanol led to cholesta-5,22,24-trien-3β-ol (**33**) and partial hydrogenation of the 25(26)-double bond over a nickel catalyst in ethyl acetate to 22-dehydrocholesterol (**34**).

In [10], Kircher and Rosenstein proposed an improved procedure permitting the conversion of alcohol (**27**) into dehydrocholesterol acetate (**35**) with an overall yield of 69% without the isolation of the intermediate amide (**28**) and amine (**29**). It was also established that the isomerization of compound (**35**) with iodine in benzene formed desmosterol acetate (**36a**) with a yield of 83%.

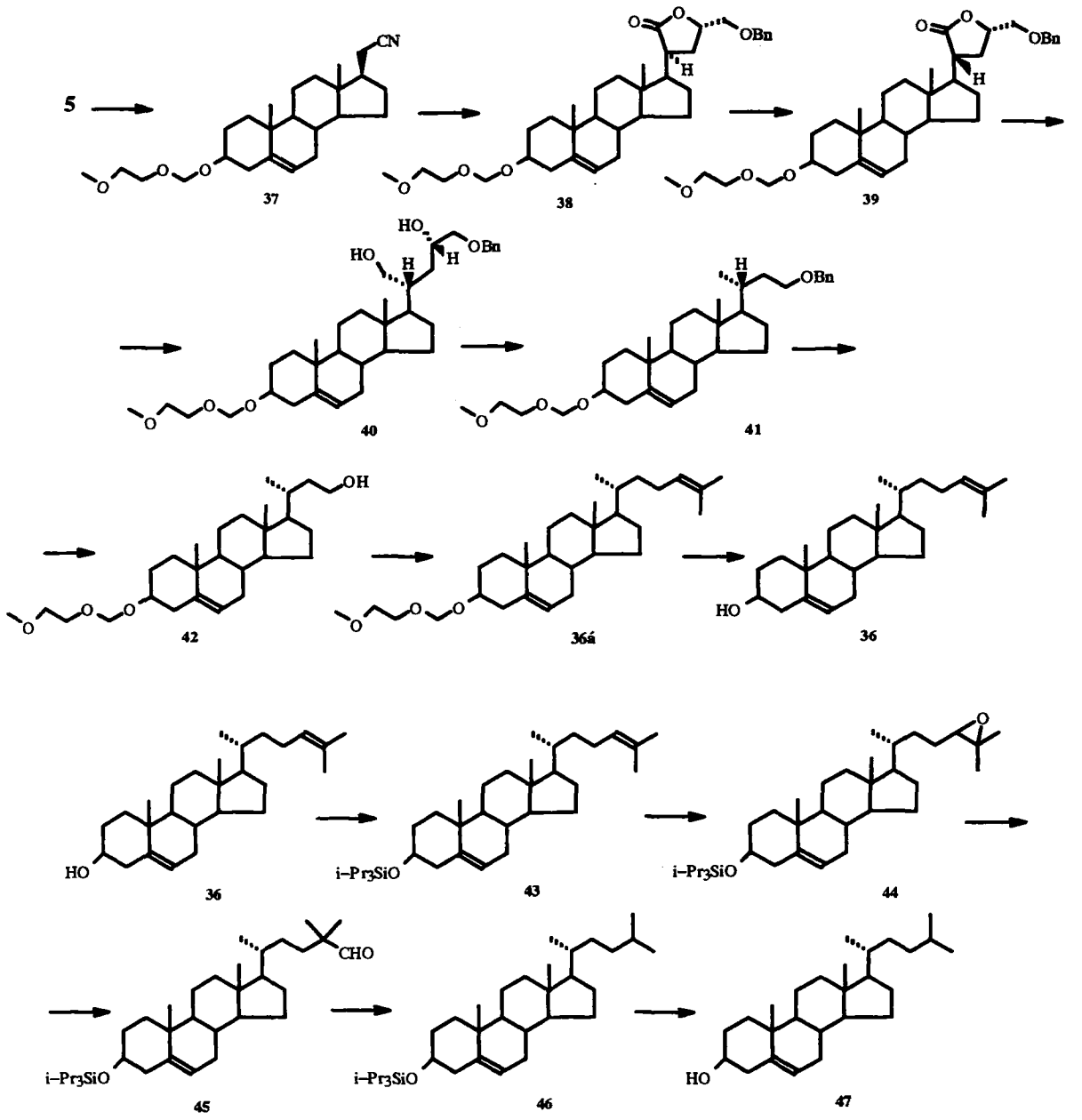


27 **35** **36a**

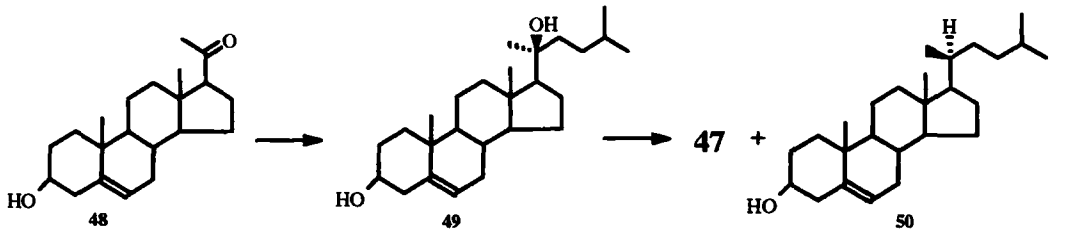
The synthesis of desmosterol (**36**) from androstenolone (**5**) has been achieved by the use of an original scheme for constructing the side-chain [11]. The first step was the condensation of androstenolone with diethylphosphonoacetonitrile in dimethoxyethane in the presence of sodium hydride to give an 83% yield of an α,β-unsaturated nitrile which was then subjected to quantitative reduction with magnesium in methanol, followed by the protection of the hydroxy group under the action of methoxyethoxymethyl chloride in the presence of N,N-diisopropylethylamine, with the formation of the (17R)- nitrile (**37**) in 85% yield. The condensation of compound (**37**) with (R)-benzyl 2,3-epoxypropyl ether in the presence of lithium hexamethyldisilylazide followed by hydrolysis in aqueous ethanol in the presence of potassium hydroxide of the cyanoalcohols so formed led with an overall yield of 72% to a mixture (4:1) of lactones (**38**) and (**39**). When this mixture was treated successively with lithium hexamethyldisilylazide and with an aqueous solution of sodium sulfate, the pure (20R)-lactone (**39**) was obtained with a yield of 75%.

The reduction of lactone (**39**) with lithium tetrahydroaluminate gave the diol (**40**) in quantitative yield. When the dimesylate of this compound was reduced with lithium triethylhydroborate the (20R)-steroid (**41**) was obtained with an overall yield of 45%. The Birch debenzylation of compound (**41**) with lithium in liquid ammonia took place with the formation of a 98% yield of the alcohol (**42**). This alcohol was then oxidized with oxalyl chloride and dimethyl sulfoxide by the Moffat-Swern reaction, and the resulting 23-aldehyde was converted by Wittig condensation with triphenylphosphonium isopropylide into the C-3-protected desmosterol derivative (**36b**). The synthesis of desmosterol was completed by the removal of the protective group in compound (**36b**) under the action of zinc bromide in methylene chloride.

In its turn, desmosterol (**36**) itself was used as the initial substance in the synthesis of halosterol (**47**) [12]. The interaction of sterol (**36**) with triisopropylsilyl triflate in methylene chloride in the presence of 2,6-lutidine gave a 96% yield of the silyl ether, which, under the action of *m*-chloroperbenzoic acid in a mixture of ether and methylene chloride, was converted with a yield of 43% into the 25,26-epoxide (**44**). Rearrangement of epoxide (**44**) under the action of methylaluminum *bis*(4-bromo-2,6-di-*tert*-butylphenoxide) in methylene chloride gave the aldehyde (**45**) with a yield of 68%. Its decarbonylation with *tris*(triphenylphosphine)rhodium chloride in benzonitrile enabled the silyl ether (**46**) to be obtained with a yield of 85%. Halosterol (**47**) was synthesized quantitatively by the desilylation of compound (**46**) with tetrabutylammonium fluoride in tetrahydrofuran.

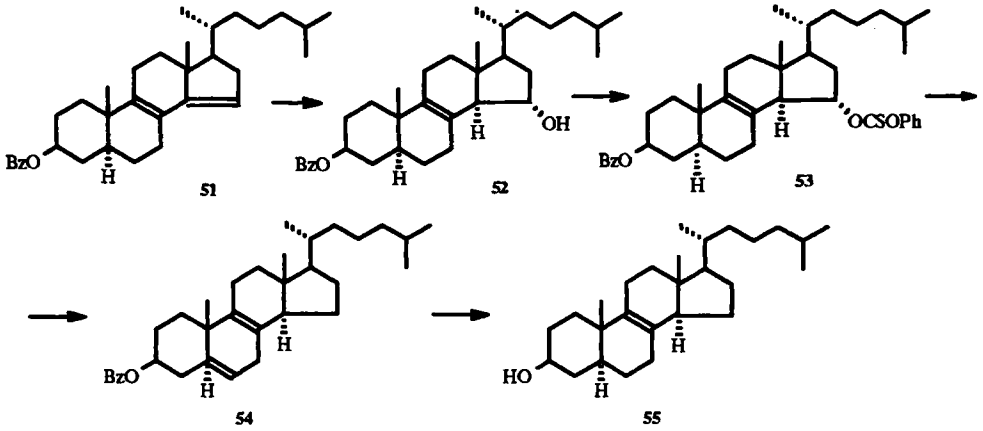


The synthesis of the (20R)- and (20S)- epimers of halosterol has also been achieved by Joseph and Nes [13]. The reaction of pregnenolone (**48**) with isoamylmagnesium bromide gave the diol (**49**) the subsequent transformation of which in rings *A* and *B* to the corresponding 3α,5-cyclosteroid, followed by dehydration, hydrogenation, and retrorearrangement, led to a mixture of the epimers (**47**) and (**50**) with an overall yield of 40% in a ratio of 59:41. It was established that the compound with the (20R)- configuration, (**47**), was identical with the natural product.



In the synthesis of 24,25-dihydrozymosterol (**55**) described in [14], the starting material was the 8,14-diene (**51**).

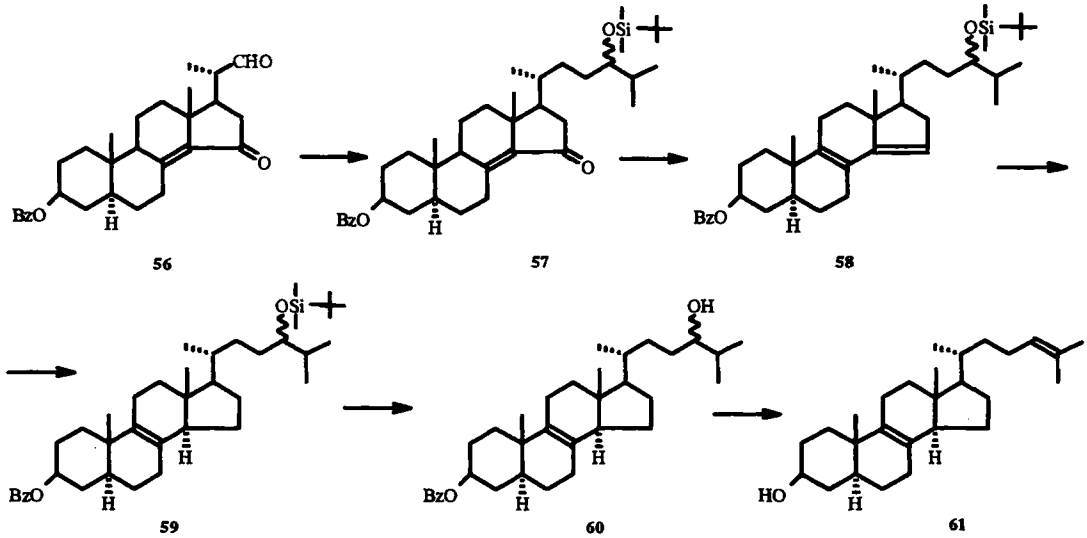
Hydroboration—oxidation of the more accessible 14-double bond in the molecule of this compound led to the formation of the alcohol (**52**) with a yield of 70%. The subsequent interaction of alcohol (**52**) with phenyl chlorothionoformate in pyridine permitted the formation in 95% yield of the thiocarbonate (**53**), the reduction of which with tributyltin hydride in the presence of azoisobutyronitrile in toluene gave a 90% yield of the benzoate (**54**). Hydrolyzing of the benzoate group in the latter under the action of sodium methanolate in a mixture of methanol and toluene gave the required sterol (**55**) with a yield of 95%.



51 52 53 54 55

To obtain zymosterol (**61**), Dolle et al. [14] used the 22-aldehyde (**56**) as the starting material. Its aldol-crotonic condensation with methyl isopropyl ketone in the presence of lithium diisopropylamide, followed by dehydration in a mixture of chloroform and toluene under the action of *p*-toluenesulfonic acid, selective hydrogenation of the 22-double bond over a Lindlar catalyst, reduction of the 24-keto group with the complex of diborane and *tert*-butylamine, and silylation, gave the silyl ether (**57**) with an overall yield of 85%. Then, by the reaction of trifluoromethanesulfonic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine, compound (**57**) was quantitatively converted into an enol trifluoromethanesulfonate, the reduction of which with formic acid in dimethylformamide in the presence of bis(acetato)bis(triphenylphosphine)palladium(II) and tributylamine gave the 8(9),14-didehydrosteroid (**58**) with a yield of 95%.

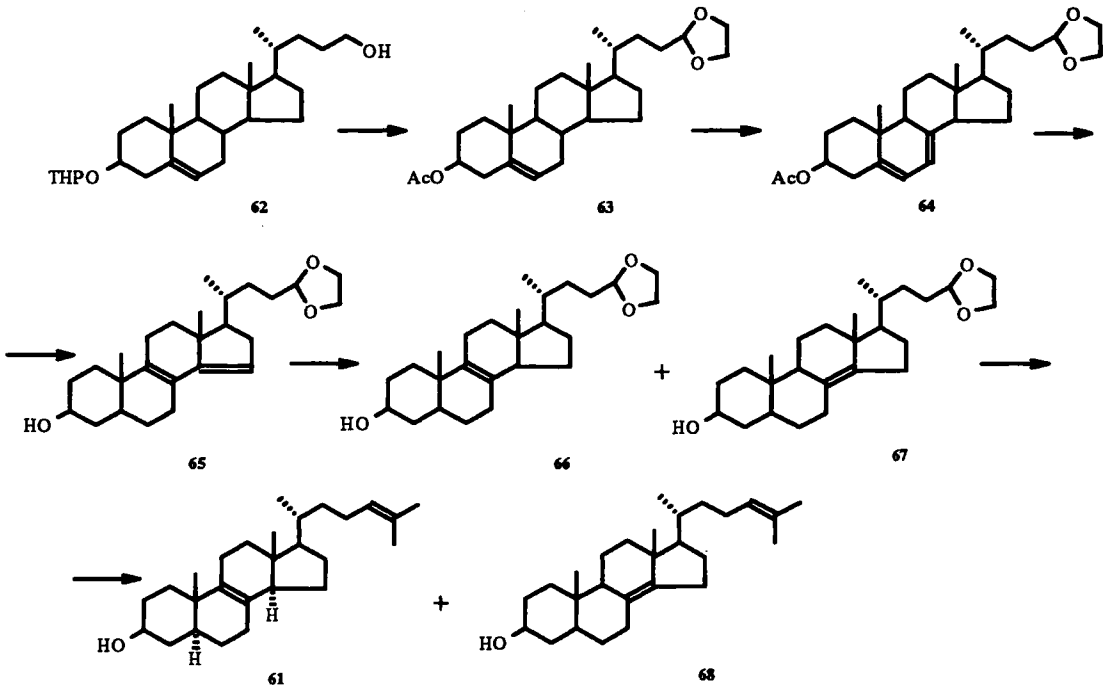
The hydroboration-oxidation of the sterically more accessible 14-double bond in the diene (**58**), the formation of the corresponding thiocarbonate from the resulting 5α-alcohol by reaction with phenyl chlorothionoformate in pyridine, and reduction of the thiocarbonate with tributyltin hydride in toluene in the presence of azoisobutyronitrile led with an overall yield of 70% to the 8(9)-dehydrosteroid (**59**). Removal of the silyl protection in (**59**) with tributylammonium fluoride in tetrahydrofuran enabled the 24-alcohol (**60**) to be obtained in quantitative yield, and dehydration of the latter by Martin sulfurane led with a yield of 90% to the corresponding Δ^{24}- derivative. Zymosterol (**61**) was synthesized by eliminating the protective group in this compound under the action of sodium methanolate in methanol.



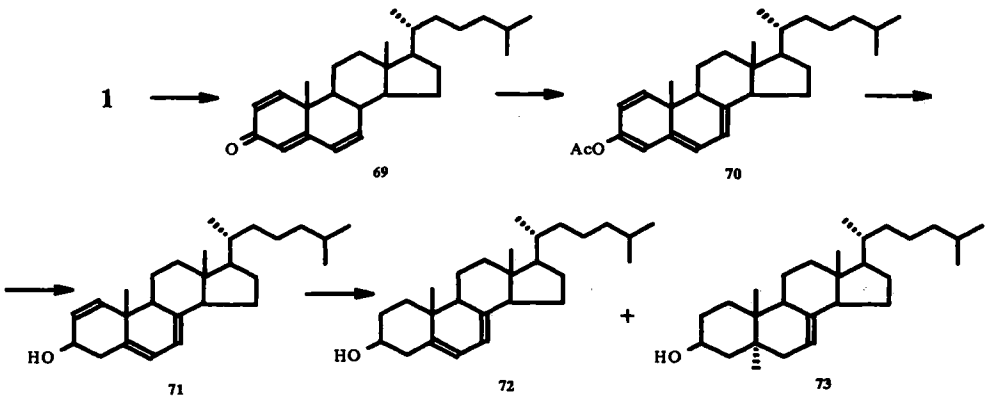
56 57 58 59 60 61

In yet another synthesis of zymosterol (**61**), published in [15], the initial substance was the 3,24-diol 3-tetrahydropyranyl ether(**62**). Its oxidation with pyridinium chlorochromate yielded the 24-aldehyde, the interaction of which with ethylene glycol in benzene in the presence of *p*-toluenesulfonic acid, followed by acetylation, led to the 24-(ethylene acetal) (**63**) with a yield of 75%. The allyl bromination of compound (**63**) with N-bromosuccinimide in carbon tetrachloride followed by dehydrobromination of the 7-bromide with tetrabutylammonium fluoride gave the diene (**64**) with an overall yield of 43%. Isomerization of the diene (**64**) by boiling it in benzene in the presence of *p*-toluenesulfonic acid and alkaline hydrolysis of the 3β-acetoxy group enabled the hydroxydiene (**65**) to be obtained with an overall yield of 55%.

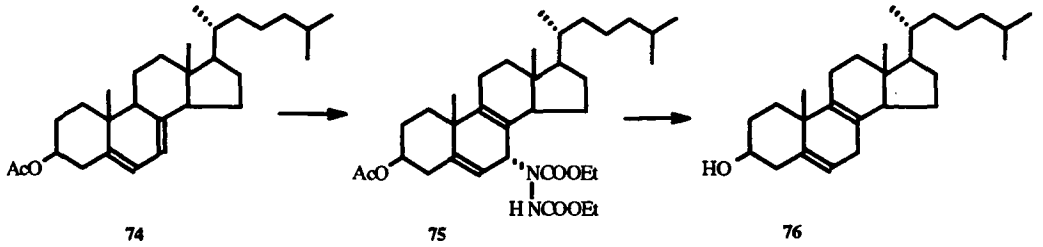
When the more accessible 14-double bond in compound (**65**) was hydrogenated over Raney nickel in ethanol, a mixture (1:1) of the $\Delta^{8(9)}$- and $\Delta^{8(14)}$- derivatives (**66**) and (**67**) was formed. By hydrolyzing this mixture with hydrochloric acid in acetone, followed by the Wittig condensation of the resulting 24-aldehydes with isopropylidenetriphenylphosphorane a mixture (1:1) of zymosterol (**61**) and cholesta-8(14),24-dien-3β-ol (**68**) was obtained in an overall yield of 40%. Pure zymosterol was isolated from this mixture by recrystallization from methanol.



Dolle et al. [16] have investigated several variants of the synthesis of 7-dehydrocholesterol (**72**) with the aim of obtaining a compound labeled with tritium in positions 1α and 2α. By the interaction of cholesterol (**1**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dioxane they obtained the $\Delta^{1,4,6}$-trien-3-one (**69**) in a yield of 55%, and this was then converted with a yield of 75% into the enol acetate (**70**) by reaction with isopropenyl acetate in the presence of *p*-toluenesulfonic acid. The reduction of compound (**70**) with calcium tetrahydroborate took place with the exclusive formation in 85% yield of the 3β-alcohol (**71**). Catalytic hydrogenation of the triene (**71**) in the presence of *tris*(triphenylphosphine)rhodium chloride formed a mixture of 7-dehydrocholesterol (**72**) and lathosterol (**73**) in a ratio of 4:1, and these were separated by chromatographic methods.



A synthesis of cholesta-5,8(9)-dien-3β-ol (**76**) was effected from 7-dehydrocholesterol acetate (**74**) [17]. Reaction of the diene (**74**) with diethyl azodicarboxylate in benzene gave a low yield of the adduct (**75**). Interaction of the latter with lithium in ethylamine led with good yield to the sterol (**76**).



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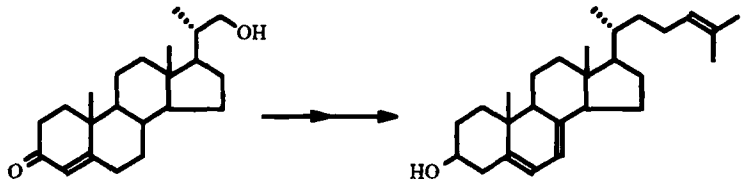
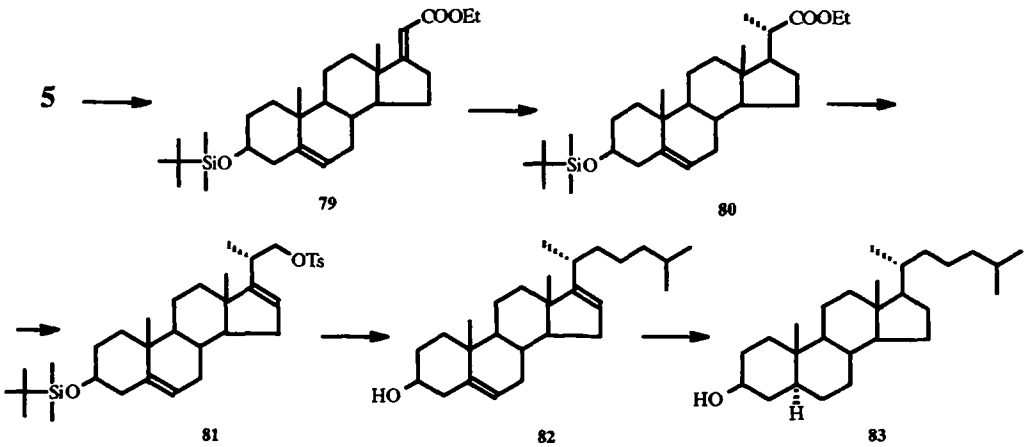
There is also a report [18] of the synthesis of 7-dehydrodesmosterol (**78**) in a six-stage synthesis from 22-hydroxy-23,24-bisnorcholen-3-one (**77**). However, it gives no details whatsoever of the synthesis.



77 78

A new synthesis of 5α-cholestan-3β-ol (**83**) has been published in [19, 20]. The interaction of 3β-hydroxyandrost-5-en-17-one (**5**) with *tert*-butyldimethylsilyl chloride and then with triethylphosphonoacetate and sodium ethanolate by the Wittig-Horner reaction gave a 97% yield of the ester (**79**), the metallization of which with lithium diisopropylamide in tetrahydrofuran followed by alkylation with methyl iodide led to the (20S)- ester (**80**) and its (20R)- isomer with yields of 88.6% and 5.4%, respectively.

When the ester function in compound (**80**) was reduced with lithium tetrahydroaluminate to the corresponding alcohol and this was then tosylated, the tosylate (**81**) was obtained with a yield of 93—98%, and the alkylation of the latter with the appropriate Grignard reagent and hydrolysis of the silyl protection gave the 5,16-dien-3β-ol (**82**) with a yield of 76%. Hydrogenation of the 5,16-dienic system over platinum in ethyl acetate led to the quantitative formation of 5α-cholestan-3β-ol (**83**).



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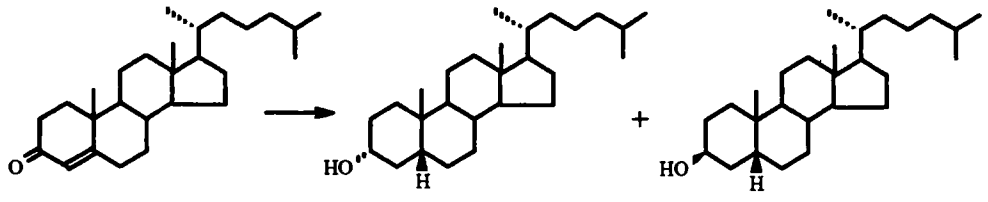
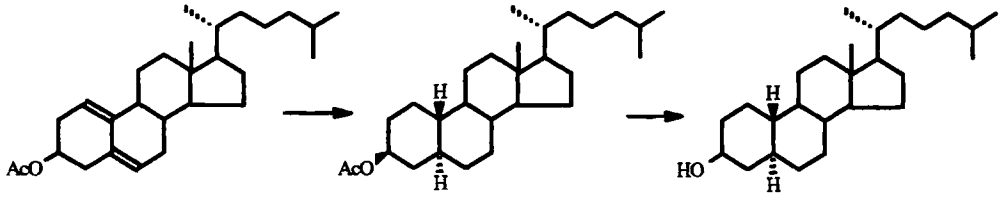
It has been established that the reduction of cholest-4-en-3-one (**84**) with Raney nickel in boiling isopropanol gives a mixture of the coprostanols (**85**) and (**86**) [21].



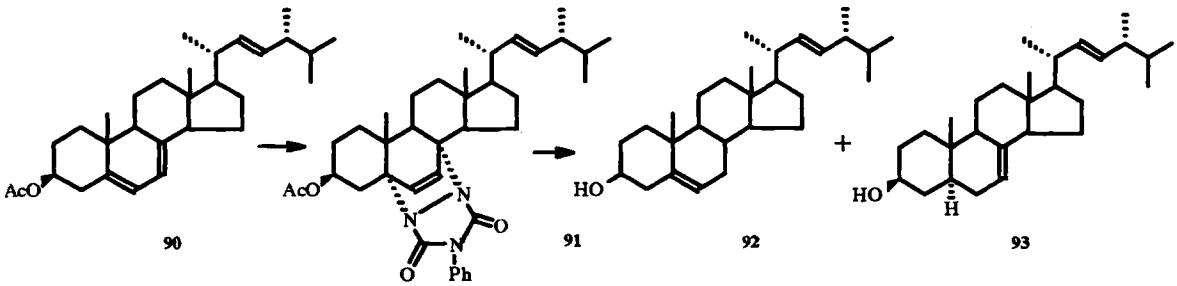
84 85 86

Characteristic for the marine sponge *Axinella polipoides* is the presence of 19-norsterols [1]. The synthesis of one of them — 19-nor-5α-cholestan-3β-ol (**89**) — was undertaken from the diene (**87**) [22]. Hydrogenation of the steroid (**87**) over a platinum catalyst in a mixture of ether and acetic acid formed the saturated compound (**88**) having the required stereochemistry at C-5 and C-10. Hydrolysis of the acetoxy group in this compound with potassium hydroxide in methanol led with an overall yield of 22% to the sterol (**89**).



87 88 89

As stated above, ergosterol (**4**) is one of the most widely distributed sterols. This circumstance permits its use as a raw material for the synthesis of various steroids, including sterols. Thus, the interaction of ergosterol acetate (**90**) with 4-phenyl-1,2,4-triazoline-3,5-dione has given the adduct (**91**) [23]. The Birch reduction of compound (**91**) with lithium in ethylamine took place with the formation of a mixture (3:2) of brassicasterol (**92**) and 5,6-dihydroergosterol (**93**). The authors concerned to [23] did not separate this mixture of sterols but used it subsequently in the synthesis of brassinosteroids .



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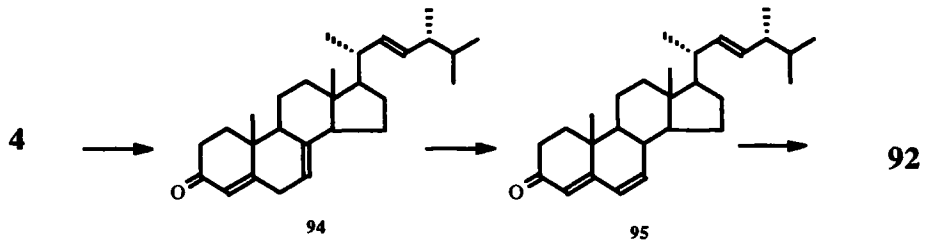
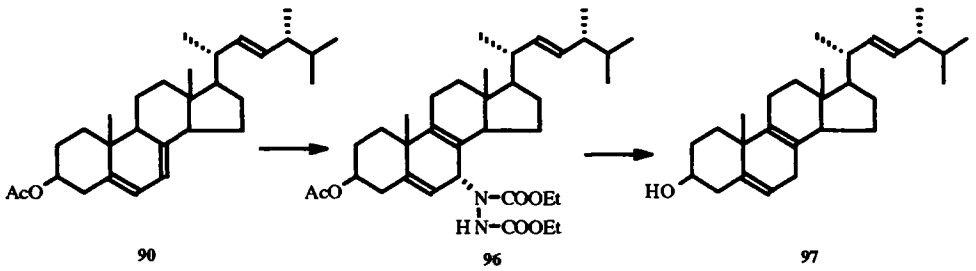
It was established later [24—26] that the direct reduction of ergosterol with lithium in ethylamine also leads to the formation of a mixture of the sterols (**92**) and (**93**). Another, independent, investigation of the Birch reduction of ergosterol under various conditions was undertaken by Barton et al. [27]. Its aim was to increase the yield of brassicasterol (**92**). These authors succeeded in finding the optimum conditions for obtaining the maximum amounts of sterol (**92**). For example, the reduction of ergosterol with lithium in a mixture of hexametapol and tetrahydrofuran, with the use 2,2,6,6-tetramethylpiperidine as the source of protons made it possible to obtain brassicasterol with a yield of more than 70%.

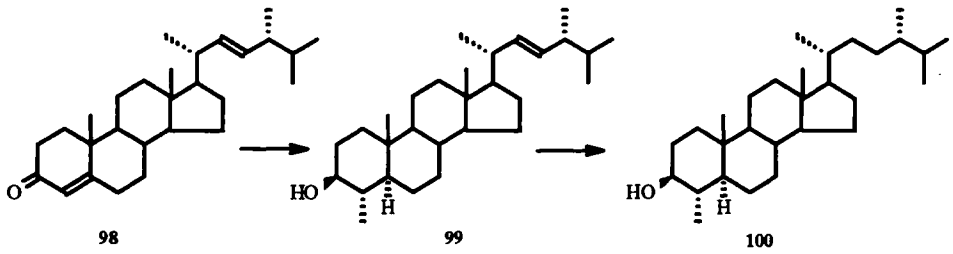
Khripach et al. [28] have also reported the results of a study of the reduction of ergosterol (**4**) with lithium under various conditions. As was to be expected, in the majority of cases the main reduction product was 5,6-dihydroergosterol (**93**). The best yield of brassicasterol was achieved in the reduction of ergosterol with lithium in a mixture of hexametapol and diethylamine (1:1). Under these conditions, sterols (**92**) and (**93**) were formed in equal amounts.



Yet another method of synthesizing brassicasterol (**92**) from ergosterol has been developed recently [29, 30]. Its Oppenauer oxidation gave a 90% yield of the $\Delta^{4,7}$-ketone (**94**), the isomerization of which under the action of hydrochloric acid in methanol took place with the formation of an 82% yield of the conjugated $\Delta^{4,6}$-3-ketone (**95**). The reduction of compound (**95**) with lithium in the presence of ammonium chloride in a mixture of liquid ammonia and tetrahydrofuran formed the required brassicasterol (**92**) with a yield of 74%. By this method, the overall yield of brassicasterol from ergosterol amounted to 50%.



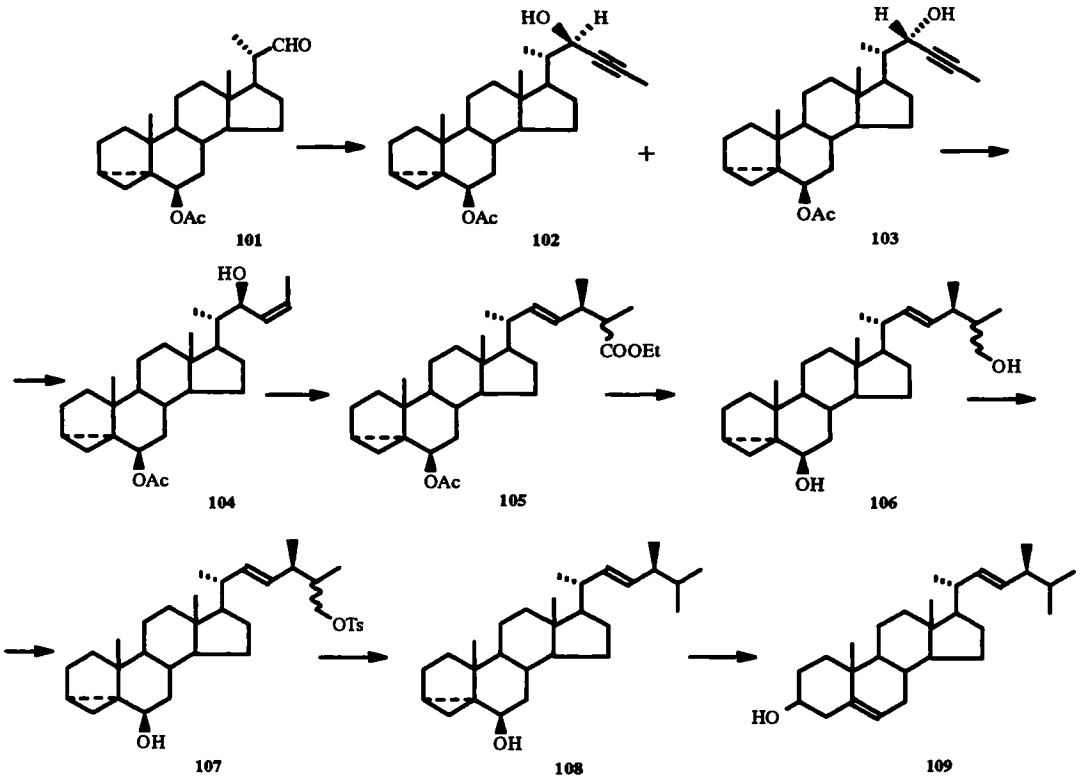
Anastasia et al. [31] synthesized lichesterol (**97**) from ergosterol acetate (**90**), which was first converted into the adduct (**96**) by reaction with diethyl azodicarboxylate. The reduction of this compound with lithium in ethylamine led to the desired sterol (**97**).



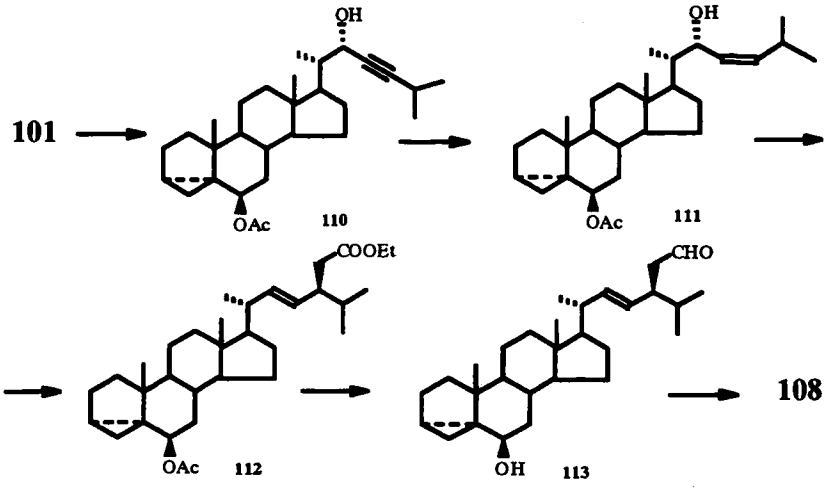
In order to confirm the C-24 configuration of a dinoflagellate sterol — 4α,24-dimethyl-5α-cholestan-3β-ol (**100**) — it was synthesized from the commercially available dienone (**98**) [32]. The 4α-methylsterol (**99**) was obtained by the methylation of the Δ^4-3-keto grouping in compound (**98**) with methyl iodide in *tert*-butanol in the presence of potassium *tert*-butanolate, followed by Birch reduction with lithium in liquid ammonia. Hydrogenation of the 22-double bond in the latter over a platinum catalyst led to the desired sterol (**100**). In [32], likewise, there is a report of the synthesis of the 24-epimer of sterol (**100**) from campesterol (in the form of a mixture with β-sitosterol) using Oppenauer oxidation followed by transformations of the resulting Δ^4-3-ketone analogous to those described above.

The synthesis of crinosterol (**109**), which is used as a starting material for obtaining brassinosteroids, has been achieved by Anastasia et al. [33]. The condensation with prop-1-ynylmagnesium bromide of the aldehyde (**101**) obtained from stigmasterol led to the formation of a mixture (1:1) of the alcohols (**102**) and (**103**) the chromatographic separation of which enabled the pure (22R)- epimer (**103**) to be obtained. By partial hydrogenation of the triple bond in compound (**103**) over a Lindlar catalyst the (Z)-allyl alcohol (**104**) was synthesized, and the allyl Claisen rearrangement of this under the action of triethyl orthopropionate formed the Δ^{22}- derivative (**105**). Reduction of the ethoxycarbonyl group in steroid (**105**) with diisobutylaluminum hydride, tosylation of the resulting 26-alcohol (**106**) to the tosylate (**107**), and reduction of the latter with lithium tetrahydroaluminate led to *i*-crinosterol (**108**).

Crinosterol (**109**) was obtained by the rearrangement of steroid (**108**) under the action of *p*-toluenesulfonic acid in aqueous dioxane. This synthesis of crinosterol was later repeated by Fujimoto et al. [34]. In addition, by using the same scheme of synthesis, they obtained β-sitosterol, campesterol, stigmasterol, poriferasterol, clionasterol, brassicasterol, and dihydrobrassicasterol.

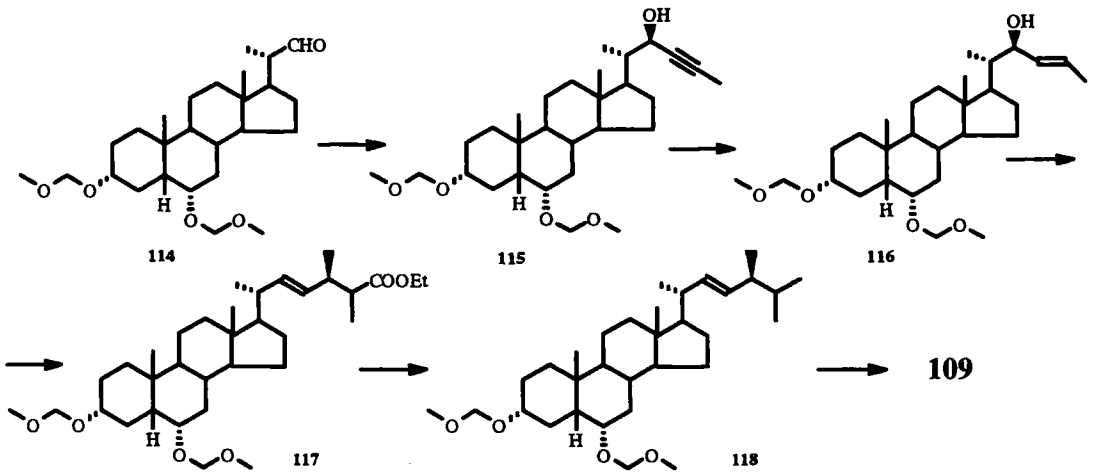


An alternative approach to the synthesis of compound (**108**) is described in [35]. The interaction of the aldehyde (**101**) and 3-methylbutynylmagnesium bromide formed a mixture (3:2) of the (22R)- and (22S)- alcohols from which the required (22S)- isomer was isolated by column chromatography. Partial hydrogenation of the triple bond in compound (**110**) over a Lindlar catalyst and Claisen rearrangement of the resulting (Z)-allyl alcohol (**111**) under the action of orthoformic ester led to the (22E,24S)-ester (**112**). *i*-Crinosterol (**108**) was synthesized by reduction of the ester grouping in compound (**112**) with diisobutylaluminum hydride and decarbonylation of the 29-aldehyde (**113**) so formed with tris(triphenylphosphine)rhodium chloride.



A synthesis of crinosterol in six stages from the aldehyde (**114**) obtained from hyodeoxycholic acid has been achieved by Chinese workers [36]. The main product of the interaction of the aldehyde (**114**) with the appropriate acetylenic Grignard reagent was the propargyl 22-alcohol (**115**). Partial reduction of the triple bond in steroid (**115**) with sodium bis(2-methoxyethoxy)aluminum hydride in toluene gave an 80% yield of the (22R,23E)-allyl alcohol (**116**). The interaction of compound (**116**) with propionic acid and orthoformic ester took place with the formation of the ester (**117**) with a yield of more than 90%. The subsequent reduction of compound (**117**) with diisobutylaluminum hydride and lithium tetrahydroaluminate enabled the protected (23E,24S)-24-methylcholestenol (**118**) to be obtained with a yield of 95%.

The further conversion of compound (**118**) into the required sterol (**109**) was consisted in the hydrolytic elimination of the protective groupings, tosylation of the 3- and 6-hydroxy groups, and solvolysis under the actions, first, of potassium acetate in dimethylformamide with heating and then of methanolic potassium hydroxide. The same authors [36] have also proposed a synthesis of brassicasterol, which is the epimer at C-24 of crinosterol (**109**). Its distinguishing feature consisted the partial hydrogenation of the propargyl alcohol (**115**) over a Lindlar catalyst with the formation of a (Z)-23(24)-olefin, a geometrical isomer of steroid (**116**). The subsequent transformation of compound (**116**) into brassicasterol was completely identical with that considered above in the synthesis of crinosterol (**109**).

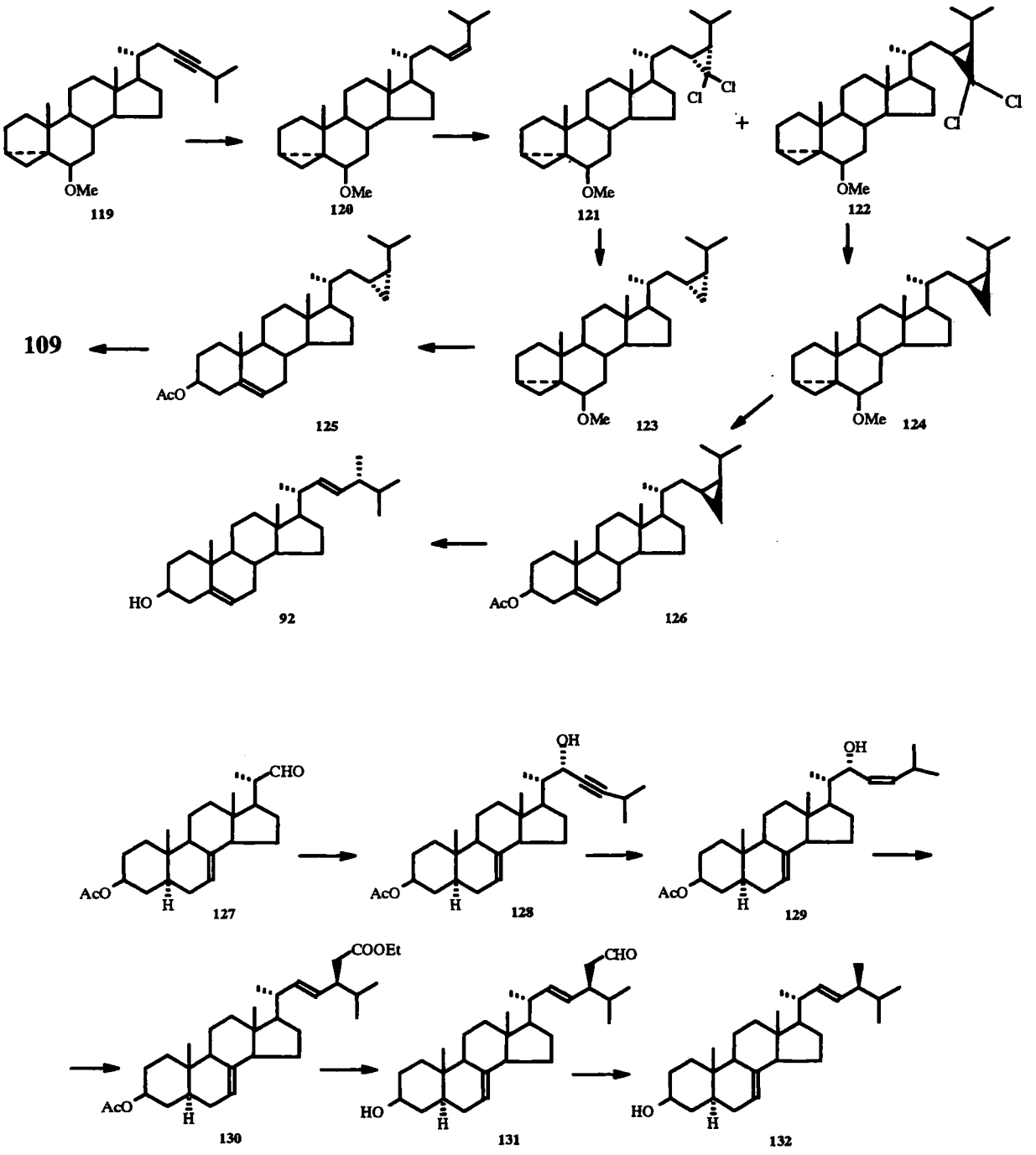


A scheme has been developed for the synthesis of crinosterol and brassicasterol from the acetylenic derivative (**119**) [37, 38]. Partial hydrogenation of the triple bond in steroid (**119**) over a Lindlar catalyst led to the (Z)-olefin (**120**) in 88% yield. Addition to the double bond in latter of dichlorocarbene, generated by the reaction of chloroform with caustic soda solution, led to the formation with a total yield of 78% of the dichlorocyclopropanes (**121**) and (**122**) in a ration of 3:2. The cyclopropanes (**123**) and (**124**) were obtained by the reduction of compounds (**121**) and (**122**), respectively, with lithium in liquid ammonia. The isomerization in rings *A* and *B* of the methyl ester (**123**) under the action of zinc acetate in acetic acid formed the acetate (**125**) with a yield of 90%. The acetate (**126**) was obtained analogously from the methyl ether (**124**) with a yield of 76%.

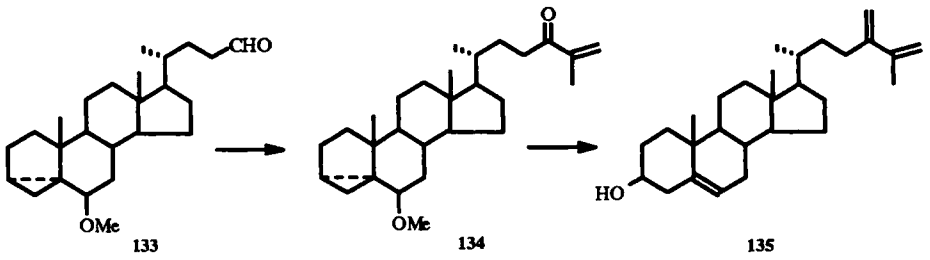
Isomerization of the three-membered ring in compound (**125**) with a solution of hydrogen chloride in acetic acid gave, with a yield of 41%, crinosterol acetate the reduction of which with lithium tetrahydroaluminate in ether led to crinosterol (**109**). In its turn, the isomerization of steroid (**126**) under analogous conditions enabled brassicasterol acetate to be obtained with a yield of 24%, and from this the free sterol (**92**) was synthesized by reaction with lithium tetrahydroaluminate.

The synthesis of stellasterol, which has the structure of (22E,24S)-5α-ergosta-7,22-dien-3β-ol (**132**) was undertaken with the aim of definitive proof of its C-24 stereochemistry [39]. The reaction of the initial 22-aldehyde (**127**) with (3-methylbutyl)magnesium bromide formed the (22S)-acetylenic alcohol (**128**) and its (22R)- isomer in a ratio of 3:2. Partial hydrogenation of the triple bond in compound (**128**) over a Lindlar catalyst led to the (Z)-allyl alcohol (**129**).

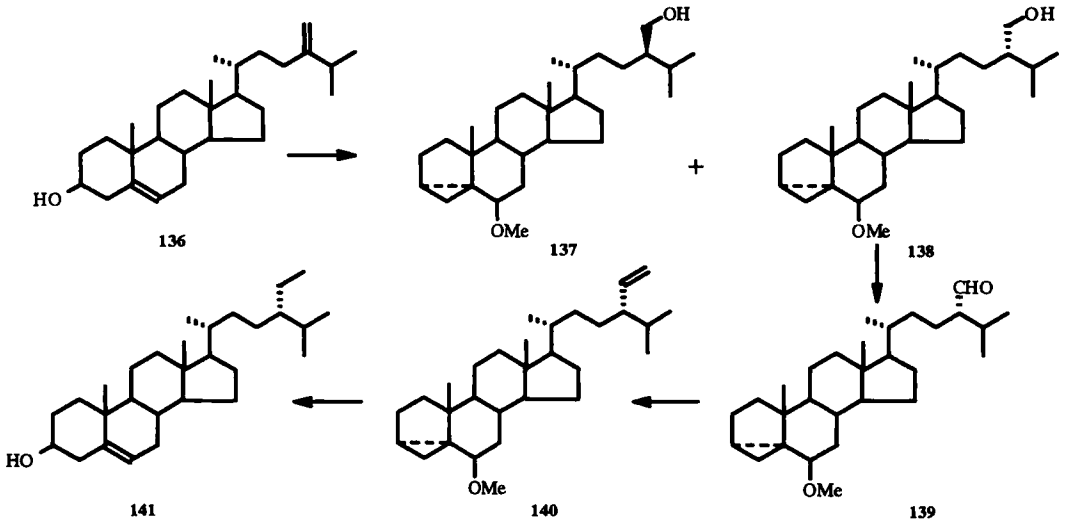
The ester (**130**) was formed as the result of a Claisen rearrangement taking place on the reaction of alcohol (**129**) with orthoacetic ester in xylene in the presence of propionic acid. The reduction of this ester with diisobutylaluminum hydride in toluene led to the aldehyde (**131**) the decarboxylation of which with tris(triphenylphosphine)rhodium chloride gave the desired stellasterol (**132**). 5,6-Dihydroergosterol (**93**) has been synthesized analogously from the isomeric steroid (**128**) [39].



The synthesis of ergosta-5,24(28)-trien-3β-ol (**135**), which had been isolated immediately before this from the soft coral *Sinularia gyrosa*, has been described [40] On the addition of isopropylmagnesium bromide to the 24-aldehyde (**133**), followed by oxidation of the resulting 24-alcohol with the Collins reagent, the enone (**134**) was obtained with an overall yield of 34%. The Wittig-Horner condensation of this enone with methyltriphenylphosphonium bromide in the presence of butyllithium followed by hydrolysis of the protective grouping in rings *A* and *B* under the action of *p*-toluenesulfonic acid in aqueous dioxane led to the desired sterol (**135**).



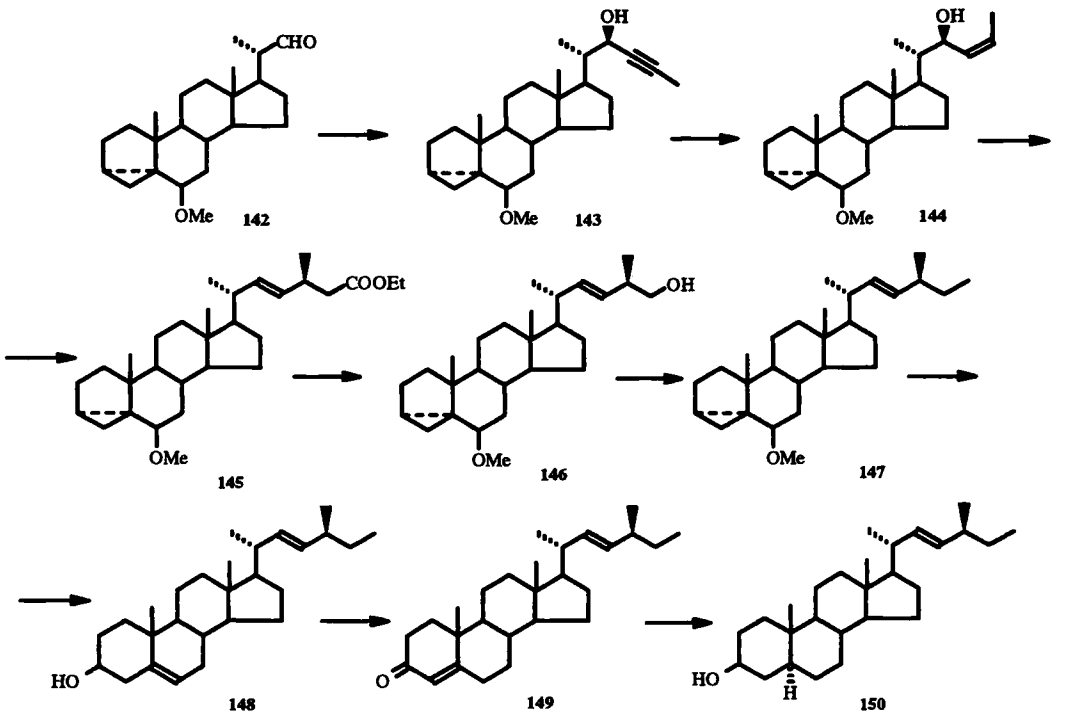
The conversion of 24-methylenecholesterol (**136**) into clinosterol (**141**) and β-sitosterol (**2**) has ben reported in [41]. The hydroboration—oxidation of the 24(28)-double bond after the conversion of the initial sterol (**136**) into the *i*-methyl ether with a yield of 83% led to formation of a mixture (1:1) of the 28-alcohols (**137**) and (**138**). Compounds (**137**) and (**138**) were separated by RF-HPLC and were then used in synthesis separately. When the alcohol (**138**) was oxidized with pyridinium chlorochromate the aldehyde (**139**) was obtained with a yield of about 80%.



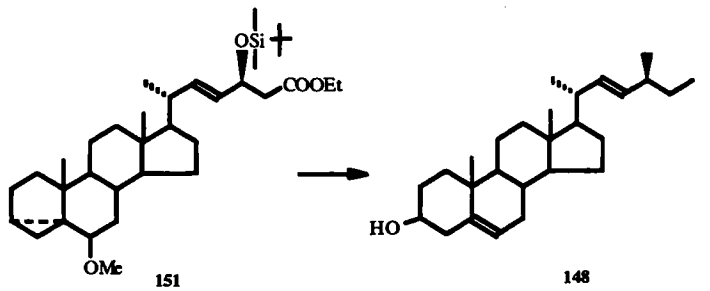
The condensation of aldehyde (**139**) with methyltriphenylphosphonium iodide in the presence of butyllithium gave the vinyl derivative (**140**) with a yield of 75—80%. Hydrogenation of the 28-double bond in steroid (**140**) over platinum in ethyl acetate, followed by hydrolysis to eliminate the protective grouping in rings *A* and *B*, led to clinosterol (**141**). β-Sitosterol was obtained analogously from the alcohol (**137**).

The synthesis of occelasterol (**148**) and patinosterol (**150**), which belong to the 27-norergostane series, from the 22-aldehyde (**142**) has been achieved [42]. On the interaction of the 22-aldehyde (**142**) with propynylmagnesium bromide in tetrahydrofuran the propargyl alcohol (**143**) and its (22S)- isomer were obtained in a ratio of 1:1 with a total yield of 79.2%. The partial hydrogenation of the triple bond in compound (**143**) over a Lindlar catalyst in the presence of quinoline led to the allyl alcohol (**144**). A Claisen rearrangement taking place on the reaction of the allyl alcohol (**144**) with orthoacetic ester in xylene in the presence of propionic acid gave the ester (**145**). By the reduction of the ester function in the latter with lithium tetrahydroaluminate in ether the alcohol (**146**) was obtained, and the tosylation of the latter with *p*-toluenesulfonic acid in pyridine, followed by reduction of the resulting tosylate with lithium tetrahydroaluminate in tetrahydrofuran, made it possible to synthesize the deoxy derivative (**147**).

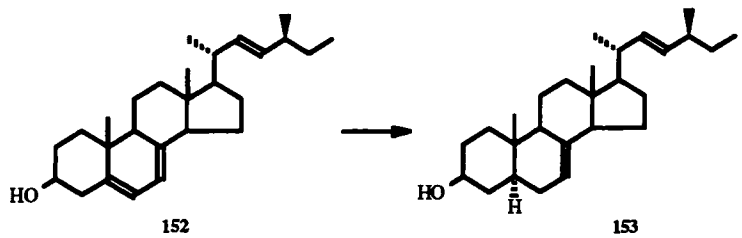
The hydrolytic elimination of the protective grouping in compound (**147**) with *p*-toluenesulfonic acid in aqueous dioxane gave occelasterol (**148**). 22,23-Dihydrooccelasterol was synthesized by the hydrogenation of steroid (**147**) over 5% palladium on carbon, followed by regeneration of the 3β-hydroxy-Δ^5-grouping. The Oppenauer oxidation of occelasterol (**148**) with acetone in benzene in the presence of aluminum isopropanolate gave the enol (**149**), the Birch reduction of which with lithium in liquid ammonia led to patinosterol (**150**).



We may also mention that occelasterol (**148**) has been obtained by Fujimoto et al. [43] from compound (**151**). The scheme of synthesis included the reduction of the latter with lithium tetrahydroaluminate, followed by mesylation of the resulting diol with methanesulfonyl chloride in triethylamine, reduction of the dimesylate with lithium tetrahydroaluminate, and, finally, acid isomerization of the *A/B* system.

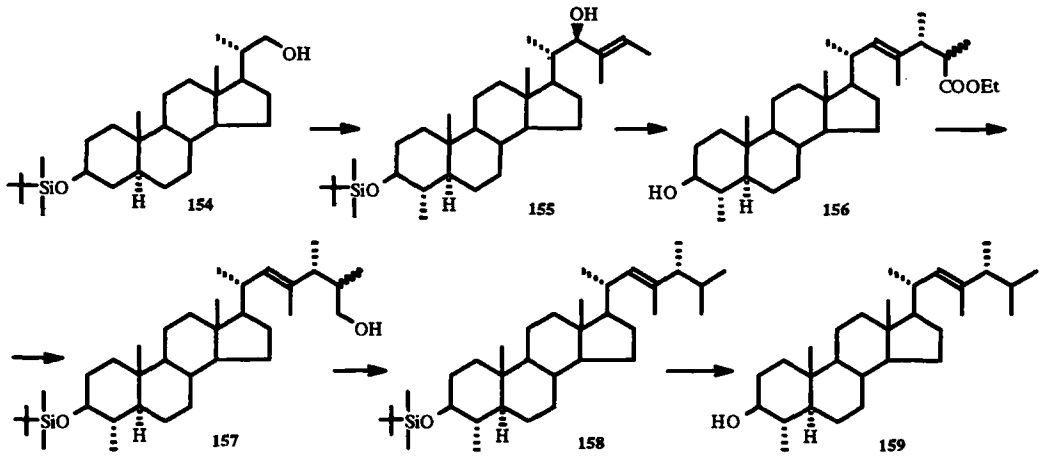


In its turn, the natural sterol amuresterol (**153**) was obtained with a yield of 30% by the hydrogenation of sterol (**152**) in benzene in the presence of *tris*(triphenylphosphine)rhodium chloride [44].



The main steroids of dinoflagellates include dinosterol (**159**). Its synthesis from the 22-alcohol (**154**) was undertaken by Shu and Djerassi [45]. By the oxidation of the alcohol (**154**) with pyridinium chlorochromate in methylene chloride followed by the condensation of the resulting 22-aldehyde with 2-lithiobut-2-ene they obtained the allyl alcohol (**155**) and its isomer.

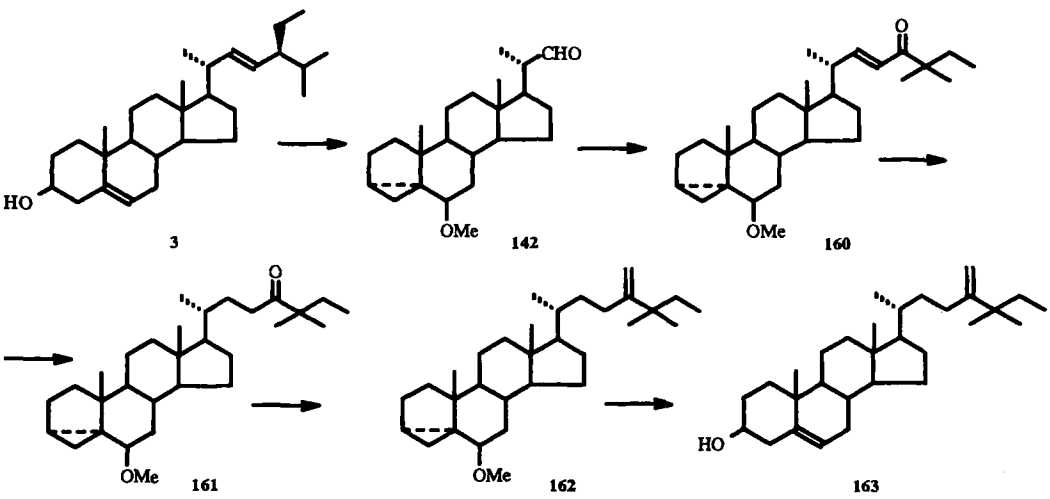
The ester (**156**) was synthesized in a yield of 44% as the result of a Claisen orthoester rearrangement taking place on the reaction of alcohol (**155**) with ethyl orthopropionate in the presence of propionic acid, followed by removal of the silyl protection with lithium tetrafluoroborate in a mixture of methylene chloride and acetonitrile.



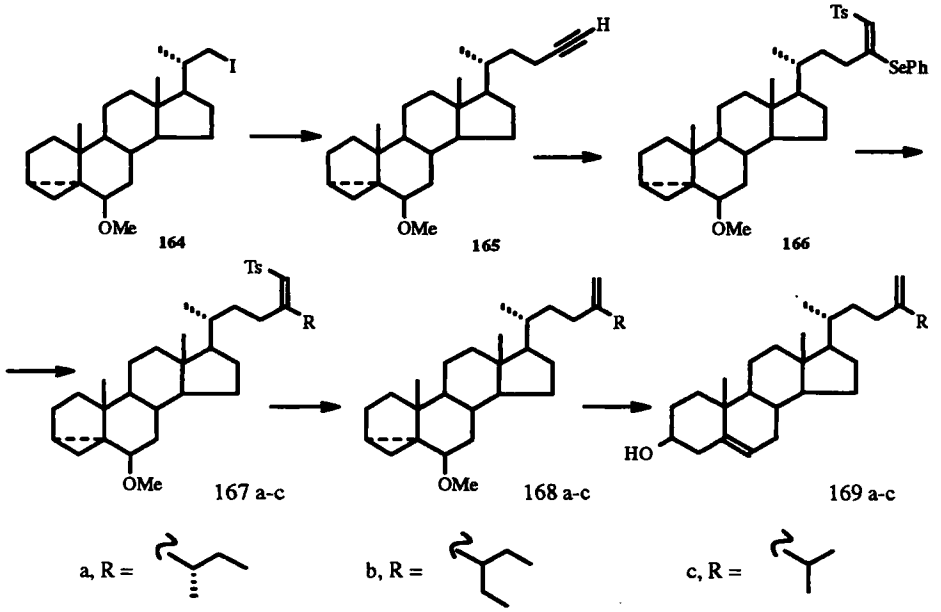
Subsequently, the 3β-hydroxy group in compound (**156**) was silylated and the ester group was reduced by lithium tetrahydroaluminate with the formation of the alcohol (**157**) in an overall yield of 76.5%. Mesylation of the free 27-hydroxy group in steroid (**157**) with methanesulfonyl chloride in methylene chloride in the presence of triethylamine followed by reduction of the mesylate with lithium tetrahydroaluminate in ether gave the deoxy derivative (**158**) with an overall yield of 93%. Elimination of the silyl protection in compound (**158**) with lithium tetrafluoroborate in a mixture of methylene chloride and acetonitrile permitted the synthesis of dinosterol (**159**) with a yield of 94%. It must also be mentioned that the same authors [45] obtained the 24-epimer of dinosterol, and also 23,24-dimethyl-22-dehydrocholesterol and its 24-epimer by analogous schemes of synthesis.

A new sterol, mutasterol (**163**), having the structure of 25-ethyl-24-methylenecholesterol, has been isolated from the Caribbean sponge *Xestospongia* [46]. In this investigation, in order to prove its structure, it was also obtained by partial synthesis. For this, the starting material was stigmasterol, which was converted by a known method into the aldehyde (**142**). The crotonic condensation of compound (**142**) with 3,3-dimethylpentan-2-one in the presence of lithium diisopropylamide gave the enone (**160**) in low yield. Hydrogenation of the double bond in compound (**160**) over palladium on carbon gave the 24-ketone (**161**) in quantitative yield.

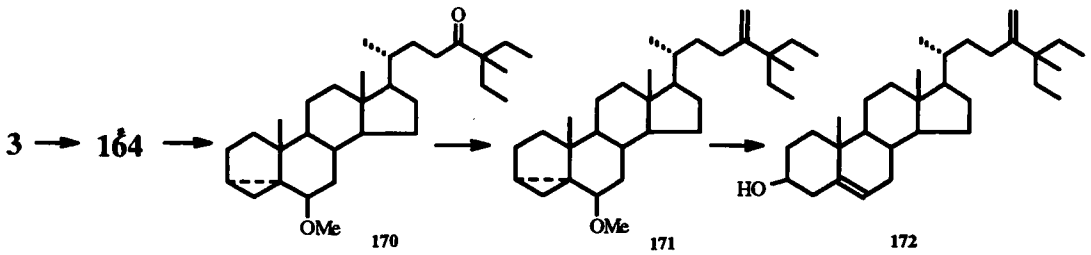
The Wittig-Horner reaction of the ketone (**161**) with methyltriphenylphosphonium bromide gave the 24(28)-dihydro derivative (**162**) with a yield of 61%. The isomerization of compound (**162**) in rings *A* and *B* under the action of *p*-toluenesulfonic acid in aqueous dioxane enabled the synthesis to be completed with the formation of mutasterol (**163**) in a yield of 74%.



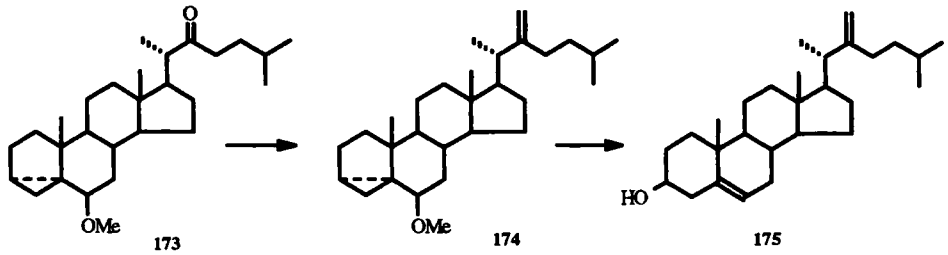
The synthesis of a number of marine sterols having a 24(28)-double bond in their side-chain has been effected [47] with the use of a scheme including a stage of the selenosulfonation of acetylenes. As a result of the interaction of the 22-iodide (**164**) with 3-lithio-1-trimethylsilylprop-1-yne followed by elimination of the silyl protection with tetrabutylammonium fluoride in tetrahydrofuran, the acetylene (**165**) was obtained with a yield of 73%. The reaction of compound (**165**) with *p*-tolyl phenylselenosulfate in benzene in the presence of azoisobutyronitrile gave an 80% yield of the 1,2-adduct (**166**). The alkylation of steroid (**166**) with a cuprate reagent obtained from the appropriate alkyllithium and phenylselenylcopper led with a yield of 39—56% to the substitution products (**167a—c**). The desulfonylation of the sulfones (**167a—c**) with sodium amalgam took place with the formation of the 24(28)-dehydro derivatives (**168a—c**). Hydrolysis of the protective grouping in rings *A* and *B* of compounds (**168a—c**) in aqueous dioxane in the presence of *p*-toluenesulfonic acid produced 24(28)-dehydroaplysterol (**169a**), the ketosterol (**169b**), and ostreasterol (24-methylenecholesterol) (**169c**), respectively.



A synthesis of the 25-methylketosterol (**172**), found in the marine sponge *Xestospongia*, started from stigmasterol (**3**) [48]. First, stigmasterol was converted in six stages by a method developed previously into the 22-iodide (**164**). The interaction of the 22-iodide (**164**) with the enolate of 3-ethyl-3-methylpentanone led to the formation of ketone (**170**) with a yield of 31%. The Wittig-Horner condensation of ketone (**170**) with methyltriphenylphosphonium bromide gave compound (**171**), the acid hydrolysis of the protective grouping in rings *A* and *B* of which permitted the synthesis of the required sterol (**172**) in two stages with an overall yield of 34%.

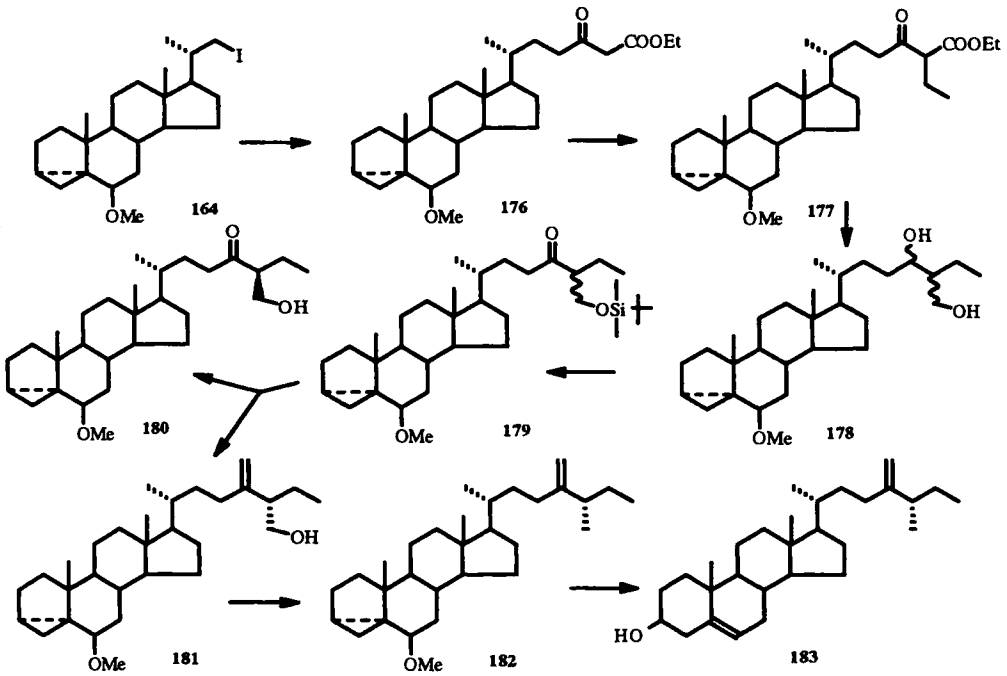


In 1981, 22-methylenecholesterol (**175**) was isolated from the Black Sea sponge *Halichondria panicca* [49]. For a complete proof of its structure, it was synthesized by the authors concerned. By a Wittig condensation, the ketone (**173**) gave the methyl ether (**174**) having a 22-methylene group with a yield of 80%. Subsequent hydrolysis of compound (**174**) with aqueous dioxane in the presence of *p*-toluenesulfonic acid led with yield of 70% to the required sterol (**175**).

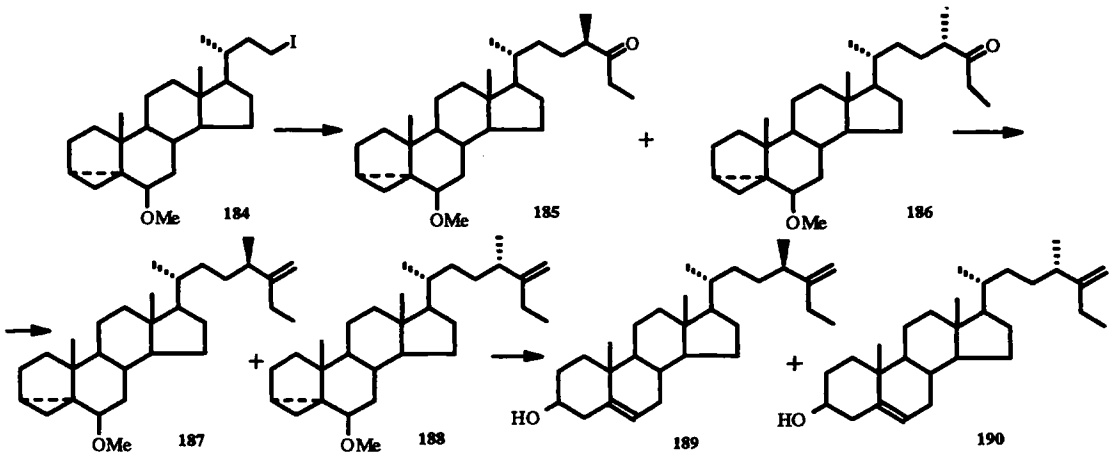


24(28)-Dehydroaplysterol (**183**) was also synthesized from the 22-iodide (**164**) [50]. Interaction of the iodide (**164**) with the dianion of acetoacetic ester in tetrahydrofuran gave an 87% yield of the product of γ-alkylation (**176**), which was then alkylated with ethyl iodide in the presence of potassium tert-butanolate to form the α-ethyl-β-ketoester (**177**) in 94% yield. The reduction of steroid (**177**) with lithium tetrahydroaluminate in ether gave the diol (**178**) quantitatively in the form of a mixture of isomers. Protection of the primary hydroxy group in steroid (**178**) by reaction with tert-butyldimethylsilyl chloride in dimethylformamide in the presence of imidazole, followed by oxidation of the secondary hydroxy group with pyridinium chlorochromate led with an overall yield of 87% to the 24-ketone (**179**).

Equal amounts of the 26-alcohols (**180**) and (**181**) were obtained in a combined yield of 64% by condensing ketone (**179**) with methyltriphenylphosphonium iodide in the presence of *n*-butyllithium and subsequent removal of the protective silyl group with tetrabutylammonium fluoride. Compound (**181**) was converted into the methyl ether (**182**) by interaction with *p*-toluenesulfonyl chloride in pyridine followed by replacement of the tolyloxy group on an iodine atom by reaction with sodium iodide in acetone and reduction of the resulting iodide with sodium tetrahydroborate in dimethyl sulfoxide. Removal of the protective grouping in rings *A* and *B* of compound (**182**) with aqueous dioxane in the presence of *p*-toluenesulfonic acid enabled 24(28)-dehydroaplysterol (**183**) to be obtained. The alcohol (**180**) was converted into the (24R)- isomer of 24(28)-dehydroaplysterol analogously.

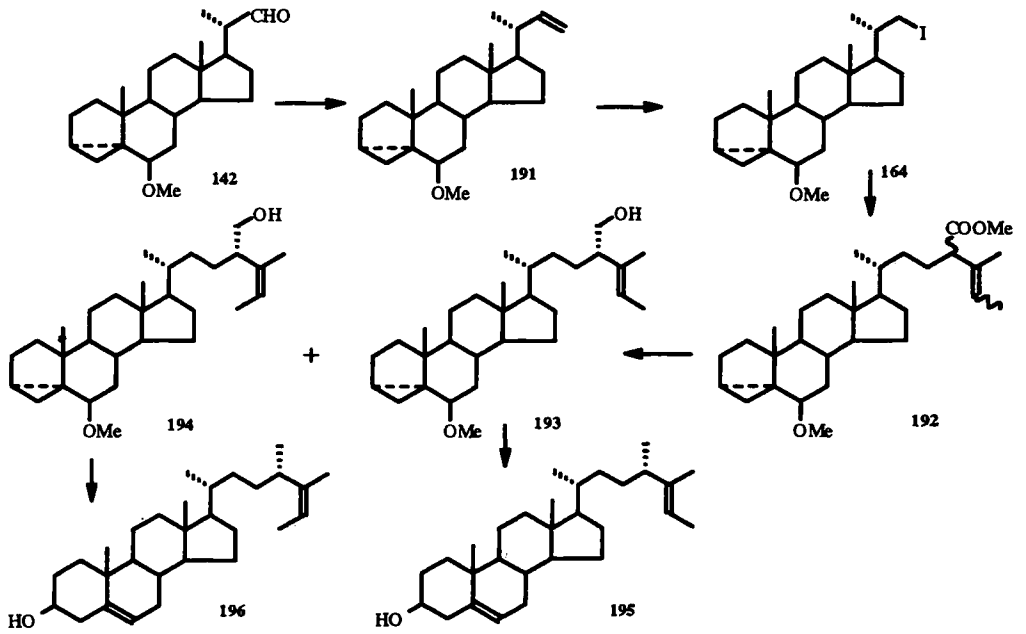


25-Dehydroaplysterol (**189**) and its isomer (**190**) have been synthesized from the 23-iodide (**184**) [51]. The alkylation of compound (**184**) with the anion obtained from pentan-3-one led with a total yield of 73% to the 25-ketones (**185**) and (**186**). The subsequent interaction of compounds (**185**) and (**186**) with methyltriphenylphosphonium iodide in dimethyl sulfoxide in the presence of potassium hydride gave the olefins (**187**) and (**188**) with a yield of 40%. When compounds (**187**) and (**188**) were boiled in aqueous dioxane in the presence of *p*-toluenesulfonic acid, regeneration of the 3β-hydroxy-Δ^5- grouping took place with the formation of sterols (**189**) and (**190**) in a yield of 86%.

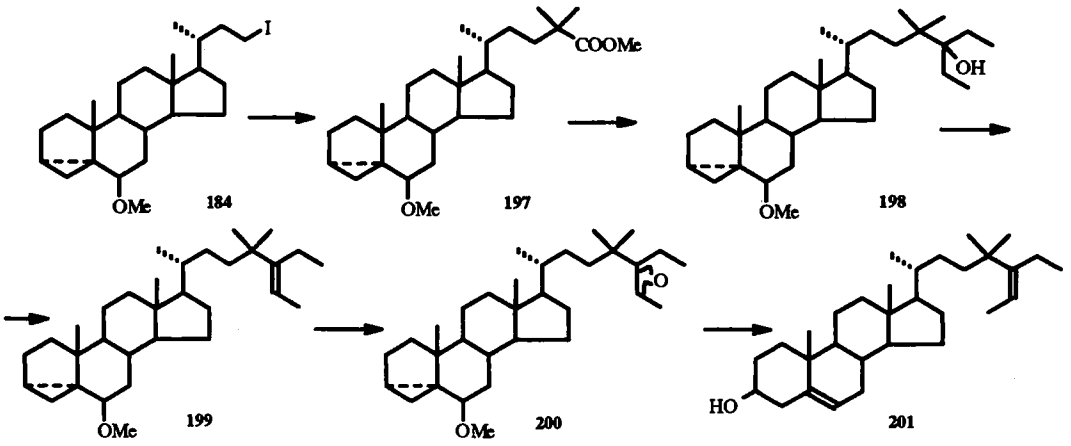


Two new sterols — jaspisterol (**195**) and isojaspisterol (**196**) — have been isolated from the sponge *Jaspis stellifera* [52]. Their synthesis was undertaken by the authors concerned [52] with the aim of confirming their structures. When the 22-aldehyde (**142**) was condensed with methyltriphenylphosphonium iodide and *n*-butyllithium in the Wittig-Horner reaction, the olefin (**191**) was obtained with a yield of 93%. The hydroboration—oxidation of the double bond in compound (**191**) led with a yield of 80% to the 23-alcohol, the interaction of which with *p*-toluenesulfonyl chloride in pyridine followed by the reaction of the resulting 23-tosylate with sodium iodide in acetone permitted the synthesis of the 23-iodide (**164**) with an overall yield of 72%.

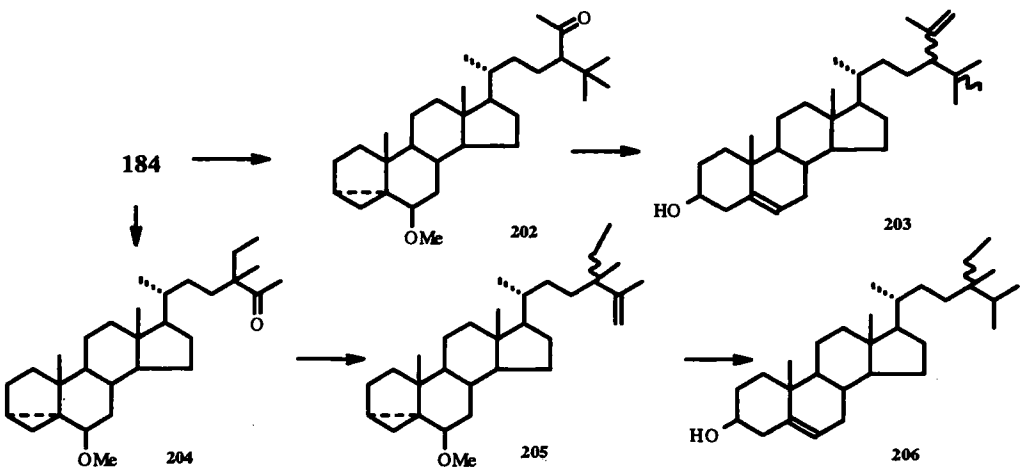
With lithium diisopropylamide, methyl *trans*-3-methylpent-3-enoate gave an anion the treatment of which with the iodide (**164**) led quantitatively to the ester (**192**) in the form of four isomers. The ester function of steroid (**192**) was reduced by lithium tetrahydroaluminate to form four isomeric alcohols in a total yield of 94%. The separation of this mixture gave the four pure alcohols, which were then used in synthesis separately. Thus, the *i*-methyl ether of jaspisterol was obtained by the tosylation of one of these alcohols (**193**) followed by the replacement of the tosylate group by iodine under the action of sodium iodide in acetone and reduction of the resulting derivative with sodium tetrahydroborate. The hydrolysis of this compound in the presence of *p*-toluenesulfonic acid enabled jaspisterol to be obtained with an overall yield of 62% from the alcohol (**193**). Steroid (**194**) was converted into isojaspisterol (**196**) analogously.



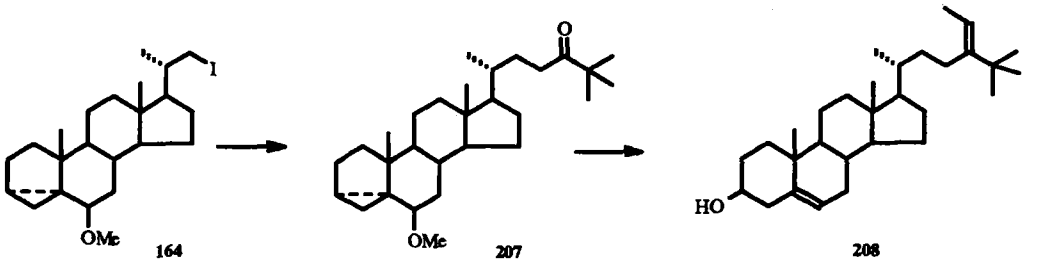
Two sponge sterols, xestospongesterol (**201**) and isoxestospongesterol, have been synthesized from the 23-iodide (**184**) [53]. The interaction of compound (**184**) with methyl isobutyrate in the presence of lithium diisopropylamide gave the ester (**197**), the condensation of which with ethylmagnesium bromide led to the alcohol (**198**). This alcohol was converted into the olefin (**199**) by dehydration with thionyl chloride in pyridine. The side-chain in compound (**199**) corresponds to that of isoxestospongesterol, and this was in fact obtained by regenerating the 3β-hydroxy-Δ^5- grouping with aqueous dioxane in the presence of *p*-toluenesulfonic acid. To obtain xestospongesterol (**201**), the olefin (**199**) was converted by reaction with *m*-chloroperbenzoic acid in methylene chloride into the epoxide (**200**). The subsequent reaction of epoxide (**200**) with potassium methanolate and hexamethyldisilane in hexametapol and isomerization in rings *A* and *B* in aqueous dioxane in the presence of *p*-toluenesulfonic acid completed the synthesis of the desired sterol (**201**).



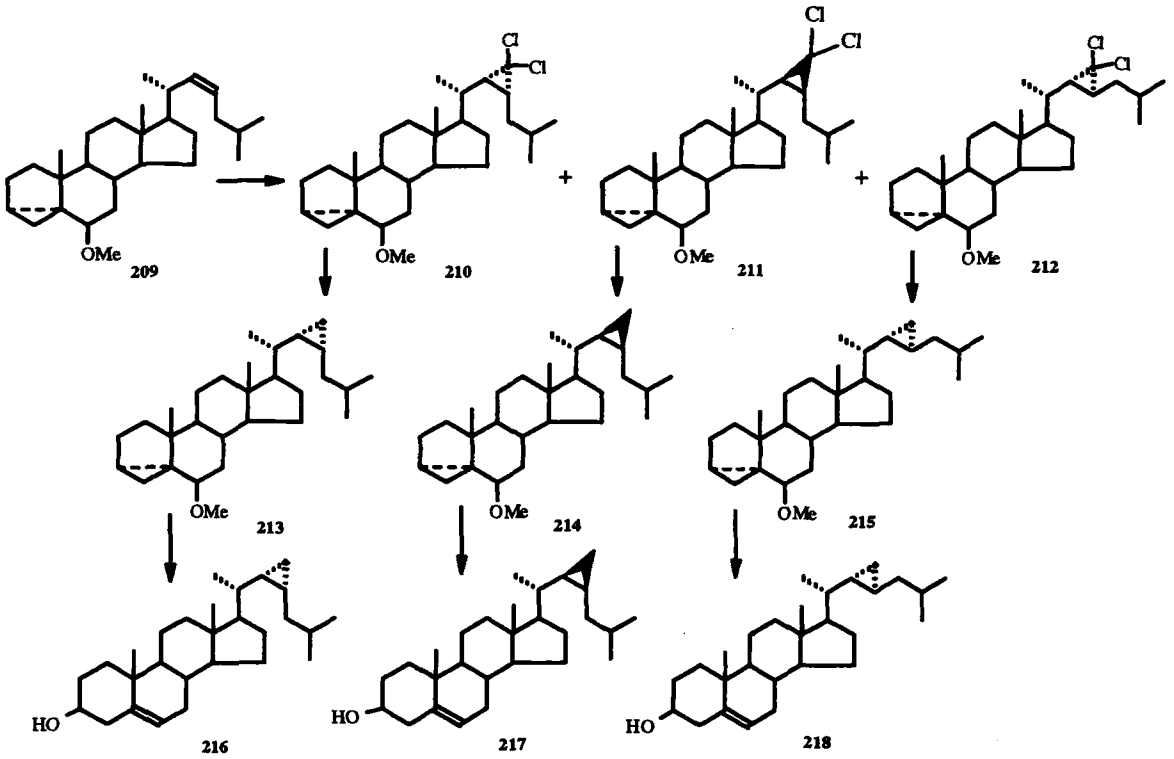
In syntheses of axinyssasterol (**203**) and 24-ethyl-24-methylcholesterol (**206**) undertaken to prove the structures of these natural sterols isolated from a sponge *Pseudoaxinyssa sp.*, the 23-iodide (**184**) was again used as the starting point [54]. When the iodide (**184**) was condensed with methyl neopentyl ketone in tetrahydrofuran in the presence of lithium diisopropylamide, the ketone (**202**) was formed, and the subsequent Wittig-Horner reaction of this with methyltriphenylphosphonium iodide and acid hydrolysis in rings *A* and *B* led to axinyssasterol (**203**). In its turn, condensation of the iodide (**184**) with methyl *sec*-butyl ketone in tetrahydrofuran in the presence of lithium diisopropylamide gave the ketone (**204**), and from this, by a Wittig condensation, the olefin (**205**) was obtained. Hydrogenation of the double bond in (**205**) over platinum in ethyl acetate and hydrolysis of the protective grouping in rings *A* and *B* completed the synthesis of 24-ethyl-24-methylcholesterol (**206**).



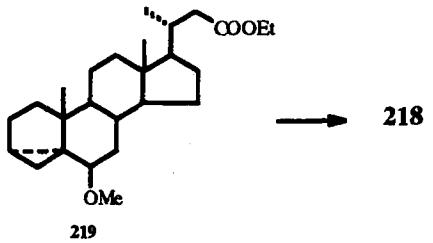
The interaction of the 22-iodide (**164**) with methyl tert-butyl ketone in the presence of lithium diisopropylamide led to the formation of ketone (**207**) [54]. By the Wittig-Horner condensation of this ketone (**207**) with ethyltriphenylphosphonium bromide and subsequent hydrolysis of the protective grouping in rings *A* and *B*, 25-methylfucosterol (**208**) was obtained.



Natural steroids having a three-membered ring in the side-chain include (22R,23R)-22,23-methylenecholesterol (**218**). This substance and its isomers (**216**) and (**217**) have been synthesized from the olefin (**209**) [55]. As a result of the addition of dichlorocarbene, generated by the reaction of chloroform with a 50% aqueous solution of caustic soda in the presence of triethylammonium chloride, to the double bond of steroid (**209**) the dichlorocyclopropanes (**210**—**212**) were obtained in a ratio of 65:20:15. The reduction of compounds (**210**—**212**) with lithium in liquid ammonia led to the cyclopropanes (**213**—**215**), respectively, and the acid hydrolysis of the protective grouping in rings *A* and *B* of these gave the sterols (**216**—**218**).

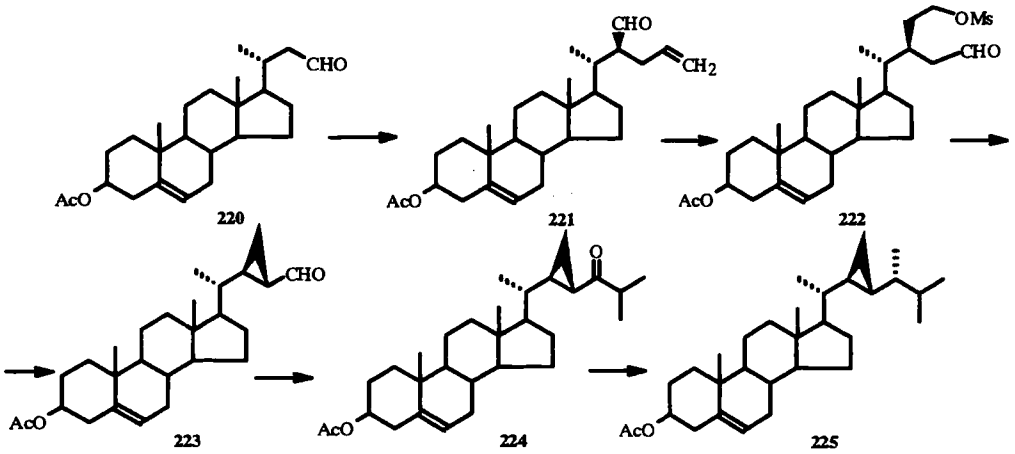


We may also mention that the synthesis of (22R,23R)-22,23-methylenecholesterol (**218**) from the readily available ester (**219**) has been described by Kim [56].



A stereoselective synthesis of demethylgorgosterol (**225**) and three of its stereoisomers has been undertaken by Sato et al. [57]. First, the 23-aldehyde (**220**) was converted into a piperidine enamine the alkylation at C-22 of which as the result of a Claisen rearrangement led to the unsaturated aldehyde (**221**).

The unsaturated aldehyde (**221**) was then converted into the mesylate (**222**) the treatment of which with potassium *tert*-butanolate led to cyclization with the formation of the cyclopropane (**223**). Grignard alkylation of the aldehyde function in steroid (**223**) followed by the oxidation of the 24-hydroxy group in the addition product gave the 24-ketone (**224**). By means of a Wittig reaction, compound (**224**) was converted into a 24-methylene derivative the hydroboration—oxidation of the 24(28) double bond in which, mesylation of the resulting 28-alcohol, and, finally, reduction of the 28-mesylate with lithium tetrahydroaluminate completed the synthesis of demethylgorgosterol (**225**).

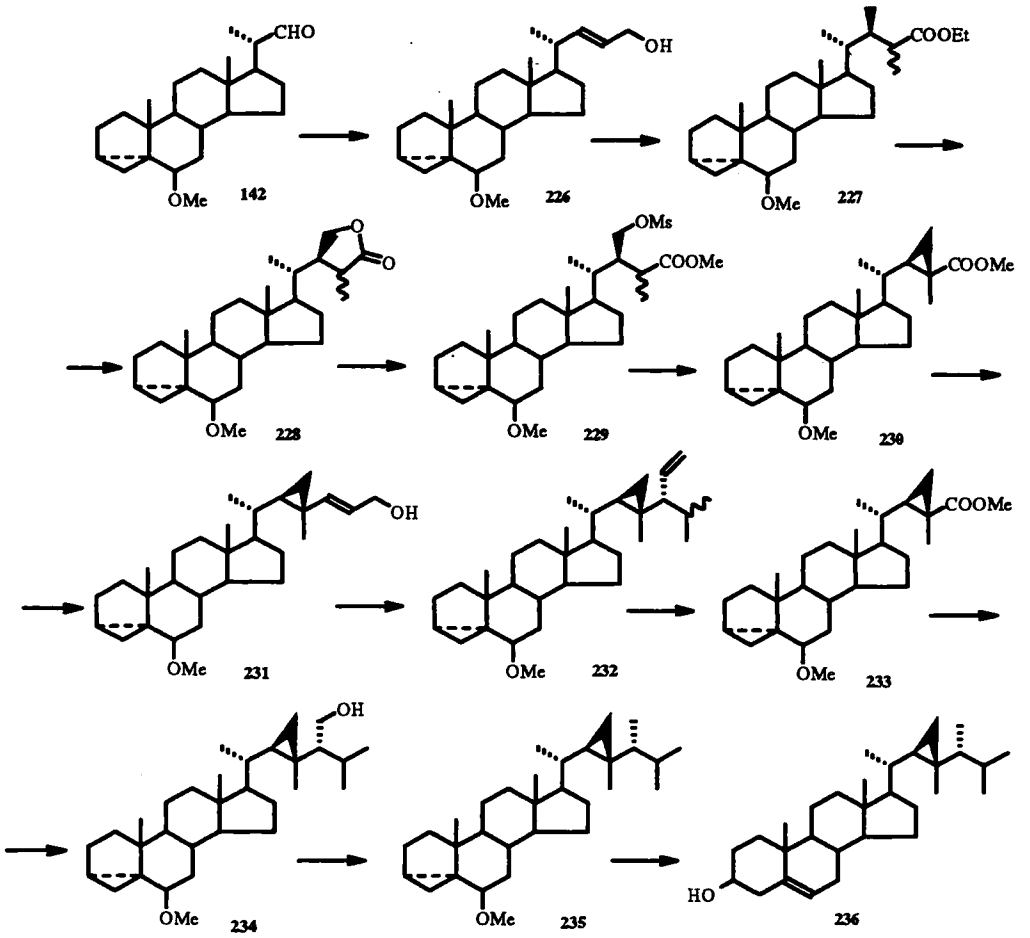


Gorgosterol (**236**), which has been detected in marine invertebrates [1], is a sterol containing a cyclopropane ring in the side-chain. Its synthesis has been achieved by Terasawa et al. [58]. The aldehyde (**142**), obtained in three stages from stigmasterol, was converted by the Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane, followed by reduction with diisobutylaluminum hydride, into the (22E)-24-alcohol (**226**) with an overall yield of 85%. The subsequent Claisen rearrangement of compound (**226**) under the action of triethyl orthopropionate in the presence of propionic acid led with a yield of 56% to the formation of the ester (**227**). The lactone (**228**) was synthesized with a yield of 44% by the ozonolysis of the double bond in steroid (**227**) followed by reduction with sodium tetrahydroborate. Hydrolysis of the lactone (**228**) with potassium hydroxide followed by methylation of the carboxy group with diazomethane and mesylation enabled the mesylate (**229**) to be synthesized with a yield of 90%.

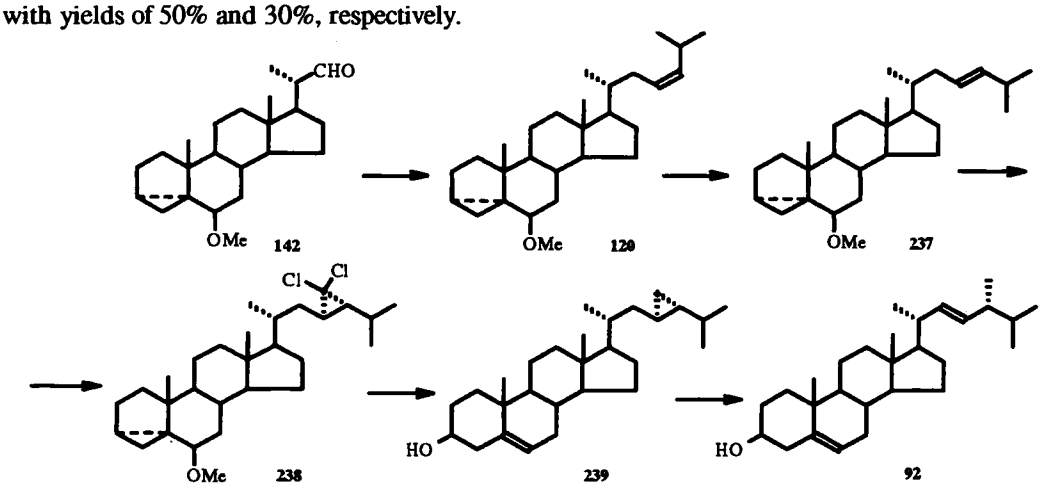
By cyclizing compound (**229**) under the action of potassium *tert*-butanolate in a mixture of tetrahydrofuran and benzene it was possible to obtain the cyclopropane derivative (**230**) with a yield of 80%. The subsequent reduction of the ester function in compound (**230**) with lithium tetrahydroaluminate, oxidation of the alcohol formed with pyridinium chlorochromate, Wittig condensation of the resulting aldehyde with (ethoxycarbonylmethyl)triphenylphosphorane, and reduction with diisobutylaluminum hydride led with an overall yield of 72% to the allyl alcohol (**231**).

The Claisen rearrangement of alcohol (**231**) with triethyl orthopropionate took place with the formation in a yield of 45% of a mixture (8:1) of the ester (**232**) and its epimer at C-24. Then the ester (**232**) was converted with an overall yield of 83% into the olefin (**233**) as a result of the successive reactions of reduction with lithium tetrahydroaluminate, mesylation of the alcohol obtained, and reduction of the mesylate with lithium tetrahydroaluminate. Ozonization of the double bond in steroid (**233**) followed by treatment with sodium tetrahydroborate gave the alcohol (**234**) with an overall yield of 55%.

Elimination of the hydroxy group in it was achieved with an overall yield of 83% by conversion into the mesylate followed by reduction of the latter. In the steroid (**235**) so synthesized the 3β-hydroxy-Δ^5- grouping was regenerated by hydrolysis with aqueous dioxane in the presence of *p*-toluenesulfonic acid, forming gorgosterol (**236**) with a yield of 92%.



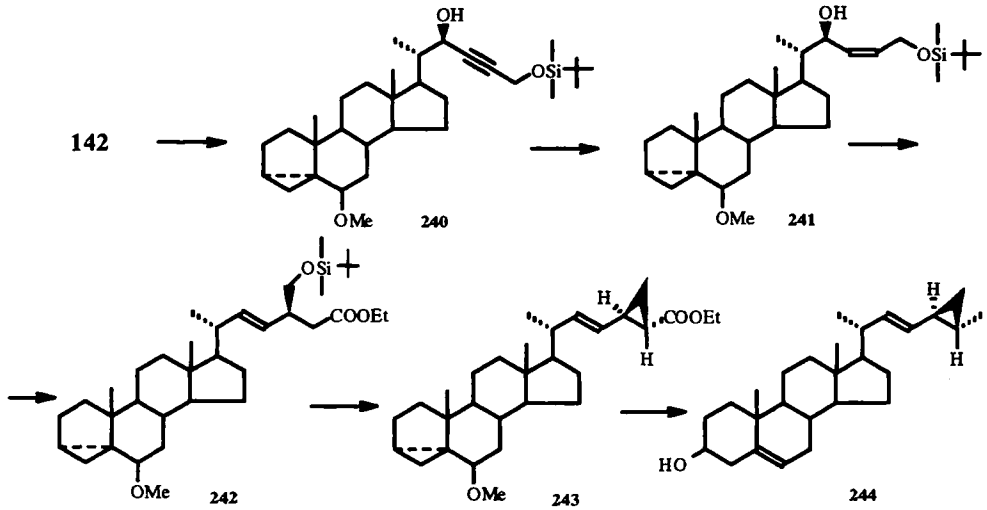
In order to prove the structure of the natural (23R,24R)-methylenecholesterol (**239**), it was synthesized from the 22-aldehyde (**142**) [59]. By the Wittig reaction, aldehyde (**142**) yielded the *cis*-steroid (**120**), which was then isomerized with an overall yield of 79% into the *trans*- isomer (**237**) by the successive action of *m*-chloroperbenzoic acid in methylene chloride and then of lithium diphenylphosphide and methyl iodide in tetrahydrofuran. The addition of dichlorocarbene, generated by the reaction of chloroform with 50% caustic soda solution in the presence of benzyltriethylammonium chloride, to the double bond of compound (**237**) took place with the formation of the dichlorocyclopropane (**238**) and its isomers at C-23 and C-24, which were isolated with yields of 50% and 30%, respectively.



When the dichlorocyclopropane (**238**) was reduced with lithium in liquid ammonia followed by hydrolysis of the protective grouping in rings *A* and *B* with aqueous dioxane in the presence of *p*-toluenesulfonic acid, (23R,24R)-methylenecholesterol (**239**), which proved to be identical with the natural sterol, was obtained with an overall yield of 70%.

It must also be mentioned that the isomerization of a natural specimen of (**239**) under the action of an acid formed brassicasterol (**92**) with a yield of 40% [59].

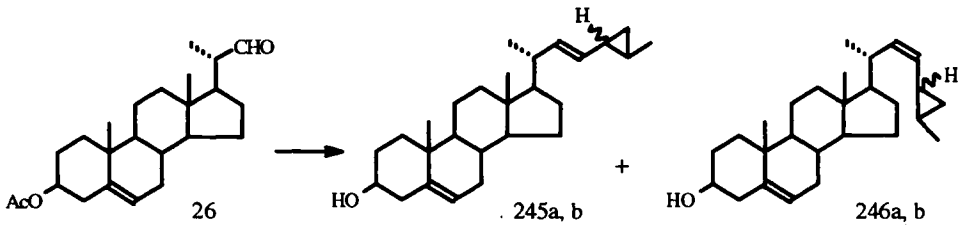
The synthesis of glaucasterol (**244**) was carried out from the 22-aldehyde (**142**) with the aim of proving the (24S,25S)-stereochemistry of the natural substance isolated previously from the soft coral *Sarcophyton glaucum* [60]. Alkylation of the 22-aldehyde with the lithium derivative of 3-(*tert*-butyldimethylsilyloxy)prop-1-yne formed a mixture (3:2) of the (22R)- alcohol (**240**) and its (22S)- isomer. Partial hydrogenation of the triple bond in compound (**240**) over a Lindlar catalyst in the presence of quinoline led with a yield of 90% to the allyl alcohol (**241**) having the (Z)-geometry of the 23-double bond. As a result of the Claisen orthoester rearrangement in the reaction of alcohol (**241**) with orthoacetic ester in the presence of propionic acid in toluene, the (24S)-steroid (**242**) was obtained with a yield of 65%. Hydrolysis of the silyl grouping in compound (**242**) under the action of tetrabutylammonium fluoride in the presence of benzoic acid with the formation of the corresponding 28-alcohol in a yield of 70%, the formation of its mesylate by reaction with methanesulfonyl chloride in pyridine, and the subsequent closure of the three-membered ring with a yield of 76% on the interaction of the mesylate with potassium *t*-butanolate in a mixture of tetrahydrofuran and benzene permitted the synthesis of the ester (**243**).



Reduction of the ester function in the latter with lithium tetrahydroaluminate followed by mesylation of the resulting alcohol with methanesulfonyl chloride in triethylamine, reduction of the mesylate with lithium tetrahydroaluminate, and isomerization in rings *A* and *B* under the action of *p*-toluenesulfonic acid in aqueous dioxane gave glaucasterol (**244**) with an overall yield of 50%.

It must be mentioned that there is a report [61] of another synthesis of glaucasterol. Unfortunately it includes no details whatever of this synthesis.

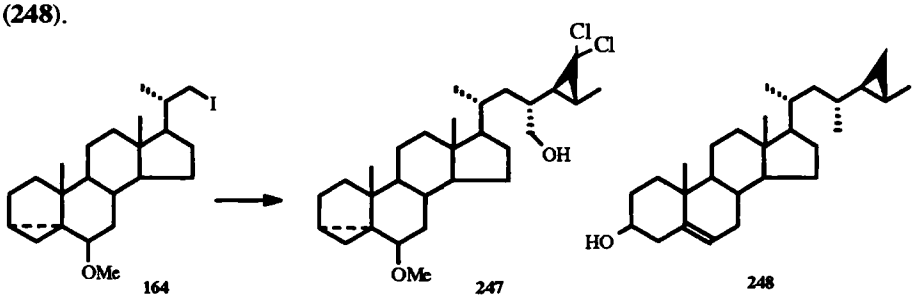
On the Wittig-Horner reaction of the 22-aldehyde (**26**) with *trans*-2-methylcyclopropylmethyltriphenylphosphonium bromide the sterols (**245a, b**), and (**246a, b**) were formed [62]. It was established that the mixture of compounds (**245a** and **b**) was identical with papakusterol, isolated from gorgonians. It has also been reported [62, 63] that natural papakusterol is a mixture of both possible isomers with a predominance of the (24S,25S)- diastereomer.



A new sterol — 29-norhebesterol (**248**) — has been isolated as a metabolite of labeled (24S)-methylcholesterol from the sponge *Petrosia ficiformis* [64]. The structure of this substance has been confirmed by chemical synthesis from the 22-iodide (**164**). A mixture of four isomeric dichlorocyclopropanes was obtained by the interaction of iodide (**164**) with the anion obtained from ethyl pent-*trans*-3-enoate, the lithium tetrahydroaluminate reduction in ether of the ester so formed with a yield

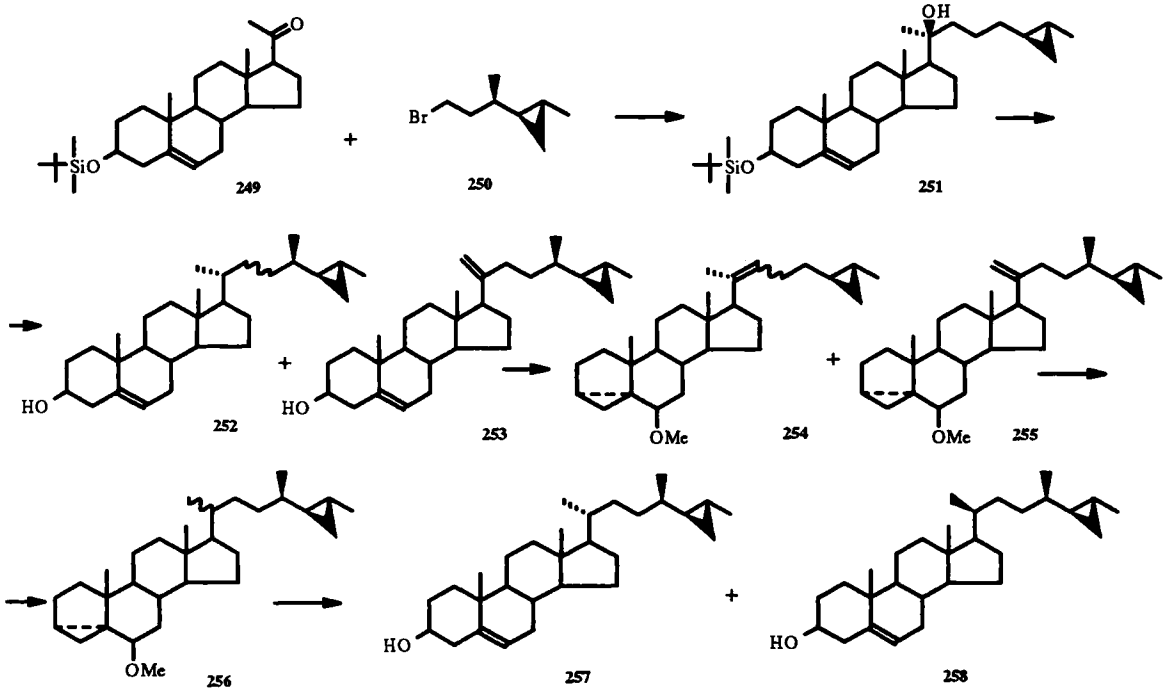
of 90%, acetylation with acetic anhydride in pyridine, addition of the dichlorocarbene generated by the reaction of chloroform with a solution of caustic soda in the presence of triethylammonium chloride, and reduction of the acetoxy group with lithium tetrahydroaluminate. This mixture was then separated by preparative thin-layer chromatography, which enabled the pure cyclopropane (**247**) to be isolated.

Compound (**247**) was then tosylated with *p*-toluenesulfonyl chloride in pyridine, the resulting tosylate was reduced with sodium tetrahydroborat in dimethyl sulfoxide, chlorine atoms were reduced with lithium in liquid ammonia, and the protective grouping in rings *A* and *B* was hydrolyzed with aqueous dioxane in the presence of *p*-toluenesulfonic acid with the formation of the desired sterol (**248**).



The synthesis of petrosterol (**257**), which has a three-membered ring in the side-chain, started from the C-3-protected pregnenolone (**249**) [65]. As a result of the addition to the keto group of compound (**249**) of the bromo derivative (**250**), specially obtained from (-)-carvone, in a mixture of tetrahydrofuran and hexametapol in the presence of samarium(II) iodide the 20-hydroxysteroid (**251**) was obtained with a yield of 90%. Subsequent dehydration of the alcohol (**251**) with a methanolic solution of hydrochloric acid led to the quantitative formation of a mixture (15:1) of the $\Delta^{20(22)}$ - and $\Delta^{20(21)}$ - derivatives (**252**) and (**253**), respectively. Without separation, this mixture was treated with *p*-toluenesulfonyl chloride in pyridine and the subsiquent rearrangement of tosylate by the heating in methanol in the presence of pyridine and was converted with an overall yield of 87% into a mixture of the methyl ethers (**254**) and (**255**).

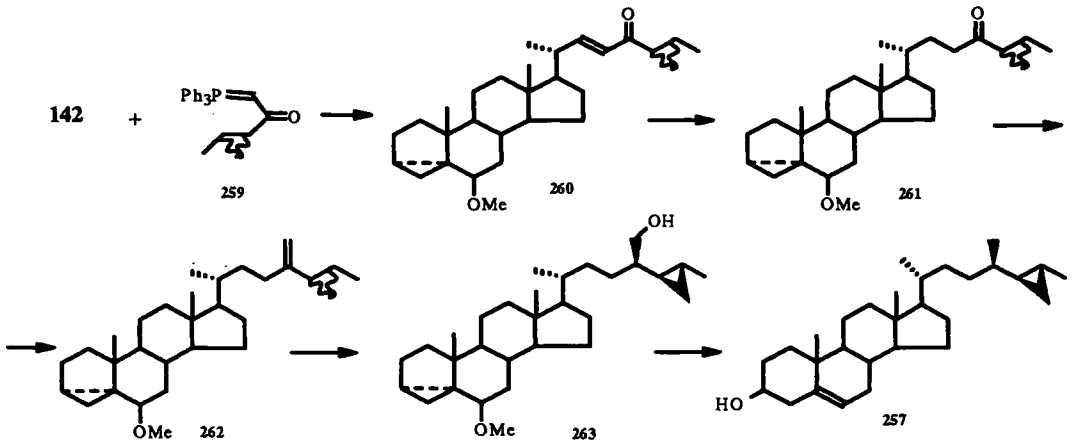
The hydrogenation of the mixture of compounds (**254**) and (**255**) over palladium on carbon gave an 89% yield of the saturated derivative (**256**)in the form of a mixture of epimers at C-20. The isomerization of compound (**256**) in rings *A* and *B* under the action of *p*-toluenesulfonic acid in aqueous dioxane led to the formation of petrosterol (**257**) and its 20-epimer (**258**), which were isolated with yields of 55 and 36%, respectively.



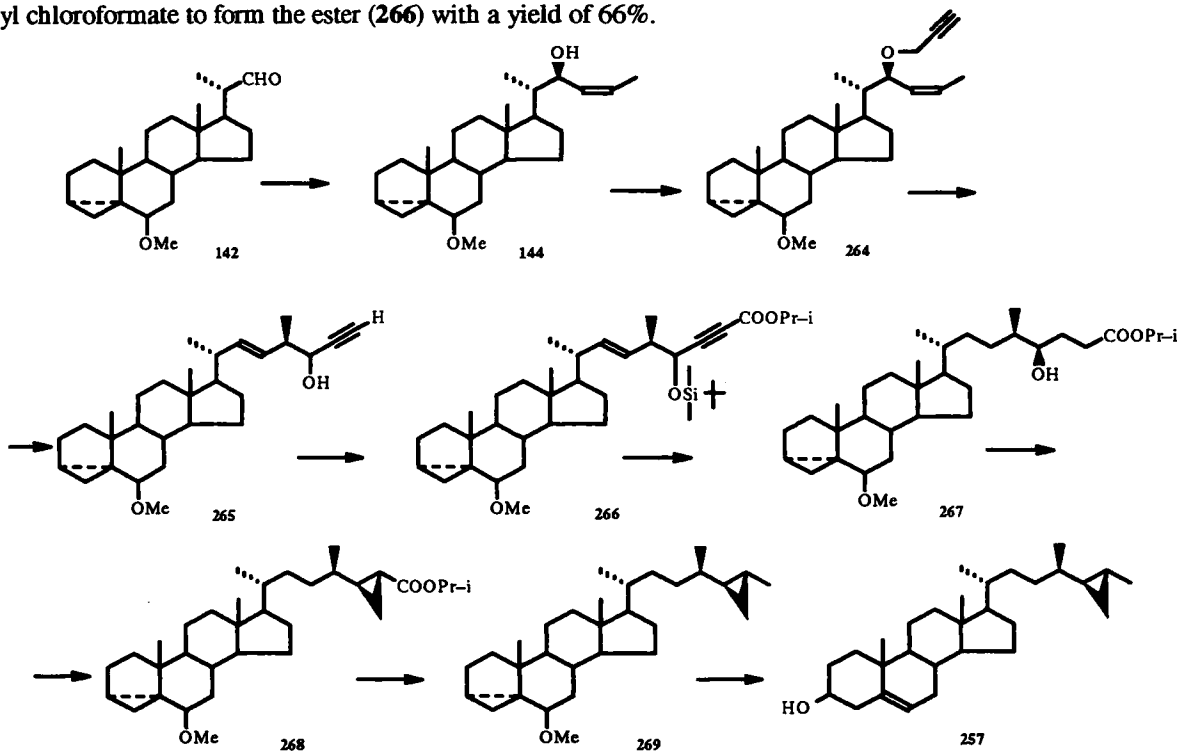
An earlier synthesis of petrosterol (**257**) and three of its isomers started from the aldehyde (**142**) [66]. Its condensation with the ylide (**259**) in benzene gave a 74% yield of the enone (**260**) in the form of a mixture of isomers. When the steroid

(**260**) was reduced with sodium tetrahydroborate in pyridine, the saturated ketone (**261**) was formed with a yield of 80%, and the condensation of this with methyltriphenylphosphorane gave the olefin (**262**) with a yield of 90%. The hydroboration —oxidation of the double bond in the latter led to the formation with a 90% overall yield of a mixture of four isomeric alcohols, from which the required cyclopropyl alcohol (**263**) was isolated by high-performance liquid chromatography.

By reaction with *p*-toluenesulfonyl chloride in pyridine, compound (**263**) was converted into its tosylate, which was then reduced with lithium tetrahydroaluminate in ether, and in the product of this reaction the 3β-hydroxy-Δ^5- grouping was regenerated with the formation of petrosterol (**257**) in an overall yield of 65—80%. Another three isomers of petrosterol were obtained analogously from the corresponding isomers of the alcohol (**263**).



Yet another synthesis of petrosterol (**257**), described in [67], also started from the 22-aldehyde (**142**). First, the aldehyde (**142**) was converted in two stages, as described in [42], into the (22S,23Z)-allyl alcohol (**144**). The reaction of this alcohol (**144**) with propargyl bromide in a mixture of 50% caustic soda and tetrahydrofuran in the presence of tetrabutylammonium phosphate led with a yield of 35% to the propargyl ether (**264**). In a [2,3]-sigmatropic Wittig rearrangement taking place in the action of butyllithium on compound (**264**) the (24R,25S)-propargyl alcohol (**265**) was obtained with a yield of 50%. The hydroxy group in compound (**265**) was protected by reaction with *tert*-butylmethylchlorosilane in the presence of imidazole, after which the silyl ether so obtained in quantitative yield was subjected to reactions first with butyllithium and then with isopropyl chloroformate to form the ester (**266**) with a yield of 66%.



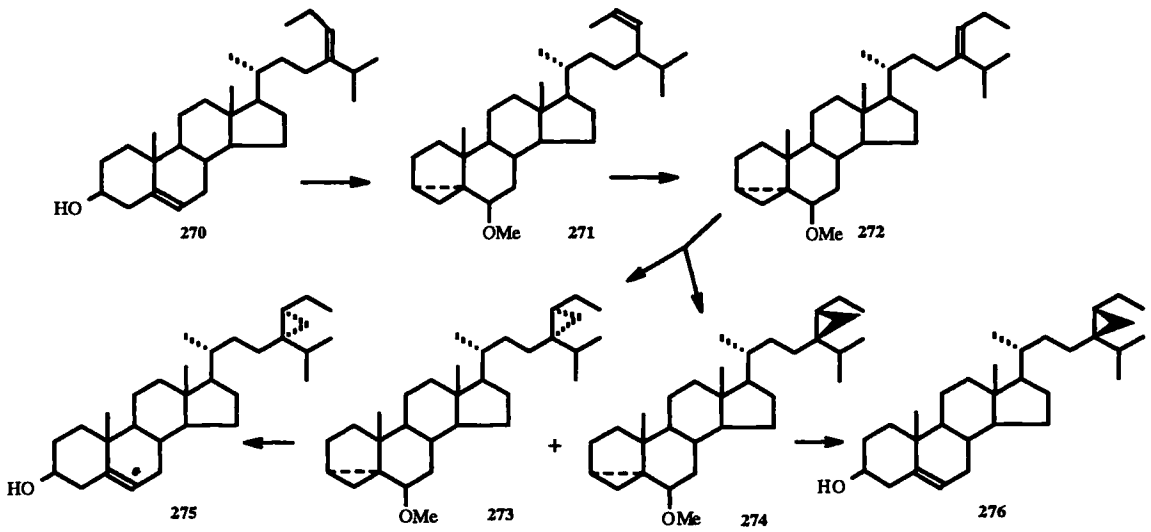
Elimination of the silyl protection in sterol (**266**) with a yield of 84% under the action of tetrabutylammonium fluoride followed by hydrogenation over palladium on carbon in ethyl acetate led with a yield of 74% to the hydroxyester (**267**). The hydroxy group in compound (**267**) was mesylated with methanesulfonyl chloride in methylene chloride in the presence of triethylamine. Subsequent cyclization under the action of potassium tert-butanolate in a mixture of tetrahydrofuran and benzene of the mesylate obtained enabled the trans-cyclopropane (**268**) to be obtained with a yield of 69%. Reduction of the ester grouping in compound (**268**) with lithium tetrahydroaluminate, mesylation of the alcohol formed with methanesulfonyl chloride in the presence of triethylamine, and, finally, reduction of the mesylate with lithium tetrahydroaluminate gave the cyclopropane (**269**).

By regenerating the 3β-hydroxy-Δ^5-grouping in the latter with *p*-toluenesulfonic acid in aqueous dioxane, petrosterol (**257**) was synthesized with an overall yield of 49% from compound (**267**).

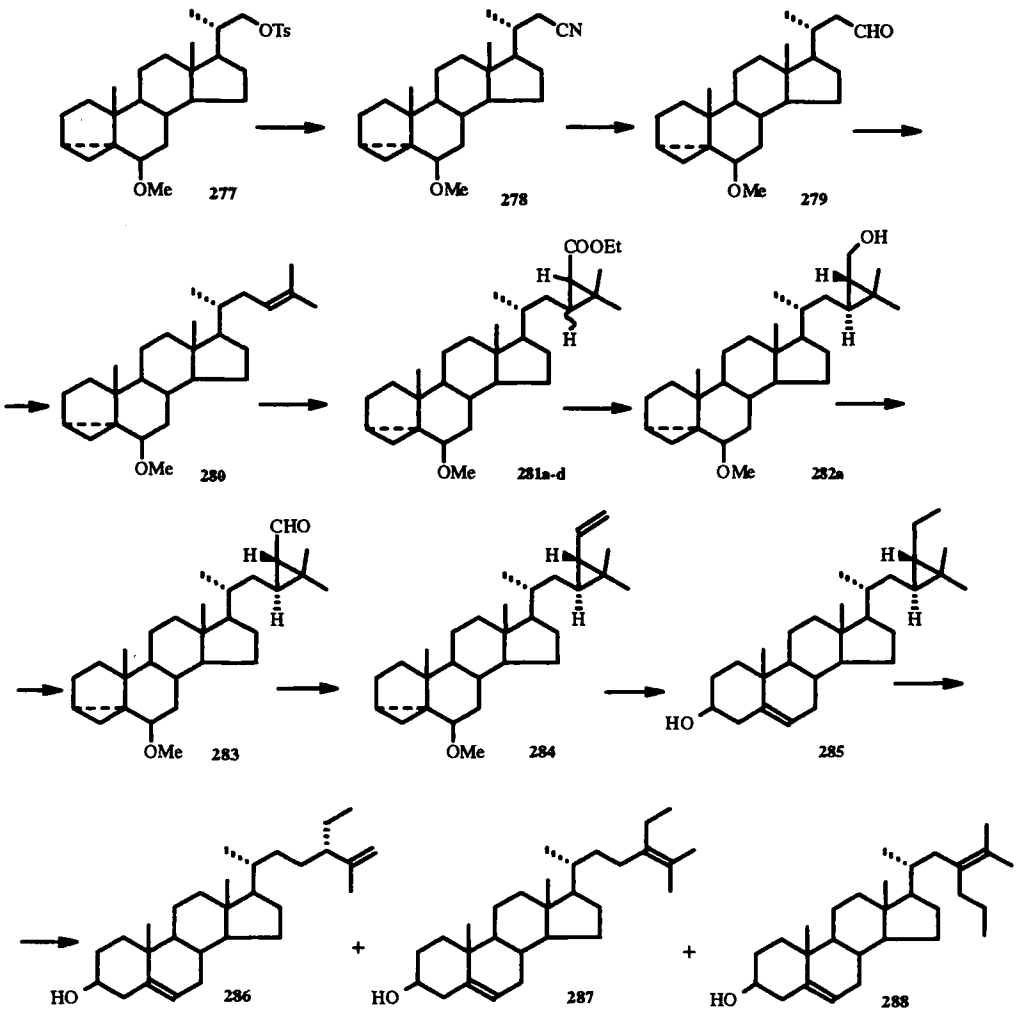
One of the minor steroids identified in a marine sponge belonging to the genus *Pseudoaxinyssa* was 24-propyl-24,28-methylenecholesterol [68]. In order to prove the structure of this sterol, the authors concerned [68] synthesized four of its possible isomers from (E)-24-propylidenecholesterol (**270**). Thus, the interaction of compound (**270**) with *p*-toluenesulfonyl chloride in pyridine with the subsequent solvolysis of the resulting tosylate in methanol in the presence of potassium acetate gave the methyl ether (**271**). A reaction with *m*-chloroperbenzoic acid in methylene chloride and then with lithium diphenylphosphide and methyl iodide in tetrahydrofuran enabled substance (**271**) to be converted into its (Z)- isomer (**272**).

Cyclopropanes (**273**) and (**274**) were synthesized by the addition to the double bond of olefin (**272**) of dichlorocarbene, generated by the reaction of chloroform with 50% caustic soda in the presence of triethylbenzylammonium chloride, followed by reduction of the dichlorocyclopropanes so formed with lithium in liquid ammonia. Hydrolysis of the protective grouping in rings *A* and *B* of compound (**273**) with aqueous dioxane in the presence of *p*-toluenesulfonic acid gave the sterol (**275**). The methyl ether (**274**) yielded the sterol (**276**) analogously. In its turn, the (E)-steroid (**271**) was used analogously for the synthesis of another two isomeric sterols.

A comparison of the ^{1}H NMR spectra of the synthetic substances with the spectrum of a natural specimen showed that the structure of the latter can be expressed by one of the formulas (**275**) and (**276**). The authors of [68] were unable to determine the structure of the 24-propyl-24,28-methylenecholesterol more accurately.



The synthesis of nicasterol (**285**), isolated from the fungus *Calyx nicaensis*, was effected from the 20-tosylate (**277**) [69]. A reaction of the tosylate with potassium cyanide in dimethyl sulfoxide gave the nitrile (**278**) in quantitative yield, and the reduction of this with diisobutylaluminum hydride in toluene took place with the formation of the aldehyde (**279**) in a yield of 80%. Condensation of the latter with isopropyltriphenylphosphonium iodide in tetrahydrofuran in the presence of butyllithium led to the olefin (**280**) with a yield of 62%.



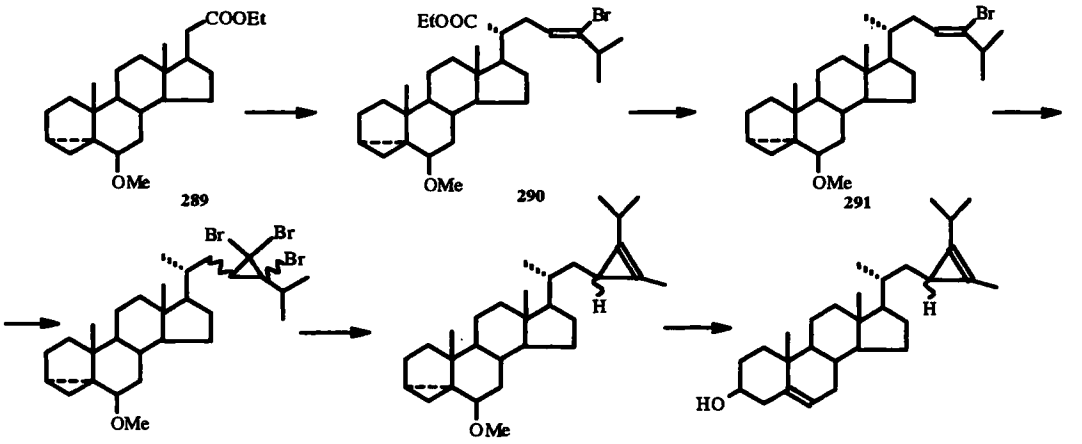
Addition to the double bond of compound (**280**) of the carbene generated from ethyl diazoacetate took place with the formation of the cyclopropanes (**281a—d**) in the form of a mixture of two *trans*- and two *cis*- isomers. It was possible to separate this mixture partially by high-performance liquid chromatography and to isolate a mixture of the required *trans*-(23S,24S)- isomer (**281a**) with one of the *cis*- isomers (**281c**) with a yield of 33%. When this mixture was reduced with lithium tetrahydroaluminate in ether, a mixture of the corresponding alcohols (**282**) was obtained, and by the chromatographic separation of this the pure (23S,24S)- isomer (**282a**) was successfully isolated.

Oxidation of the alcohol (**282a**) with pyridinium chlorochromate in methylene chloride led to the aldehyde (**283**) the Wittig addition to which of methyltriphenylphosphorane gave the terminal olefin (**284**). Hydrogenation of the double bond in compound (**284**) over rhodium on carbon in methanol followed by hydrolysis of the protective grouping in rings *A* and *B* by the action of *p*-toluenesulfonic acid in a mixture of dioxane and water permitted the synthesis of nicasterol (**285**) with an overall yield of 66%.

Simultaneously, the same authors [69] obtained the (23R,24R)- isomer of nicasterol analogously from the other (23R,24R)-*trans*- isomer of the ester (**281b**). It has also been reported that the action of trifluoroacetic acid in benzene on nicasterol (**285**) formed clerosterol (**286**), stigma-5,24(25)-dien-3β-ol (**287**)and 24-methyl-23-propyl-26,27-dinor-23(24)-dien-3β-ol (**288**) with yields of about 20%.

A synthesis the 23S-23*H*- and 23R-23*H*-isocalisterols, (**294a**) and (**294b**), respectively, isolated previously from the sponges *Calyx nicaensis* and *C. podarypa* has been described in [70]. The (20R)- derivative (**290**) was synthesized in a yield of 80% by the alkylation of the anion obtained from ester (**289**) with (Z)-1,3-dibromo-4-methylpent-2-ene. Reduction of the ester grouping in compound (**290**) with diisobutylaluminum hydride in a mixture of hexane and methylene chloride, followed by tosylation of the resulting 21-alcohol with *p*-toluenesulfonyl chloride in a mixture of pyridine and methylene chloride and reduction of the 21-tosylate with lithium triethylhydroborate enabled the bromovinyl derivative (**291**) to be obtained with an

overall yield of 80%.



(23, 24S) **292a**
(23, 24S) **292b**

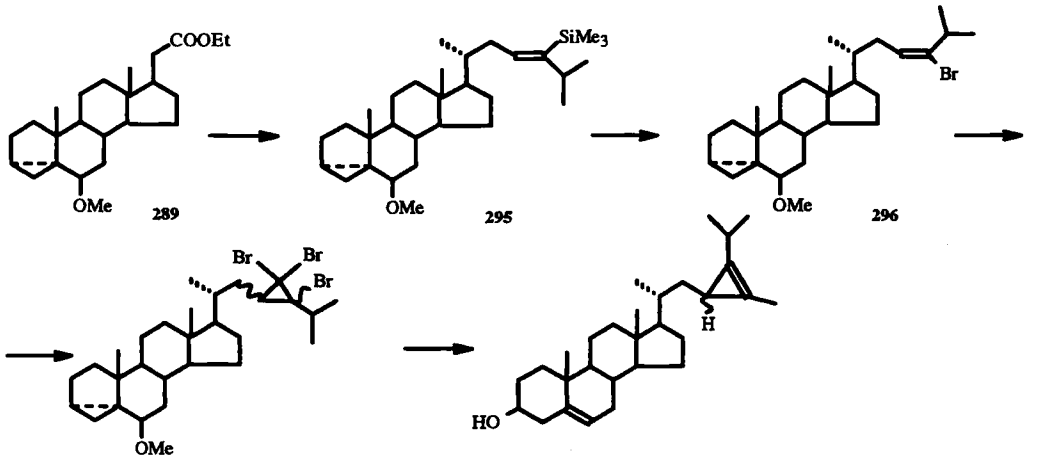
(23S) **293a**
(23S) **293b**

(23S) **294a**
(23S) **294b**

The addition to the double bond of steroid (**291**) of dibromocarbene, generated by the reaction of bromoform with 50% caustic soda in the presence of cetrimide as phase-transfer catalyst led with an overall yield of 50% to the (23R,24S)- and (23S,24R)- diastereomers (**292a** and **b**), respectively, in a ratio of 1:1. The (23S)-cyclopropene (**293b**) was synthesized with a yield of 60% by the successive reactions of the (23R,24S)-tribromocyclopropane (**292a**) with methyllithium in ether and with methyl iodide.

The (23R)-cyclopropane (**293a**) was obtained analogously from the (23S,24R)-tribromocyclopropane (**292b**). The regeneration of the 3β-hydroxy-Δ^5-groupings in compounds (**293a** and **b**) with *p*-toluenesulfonic acid in aqueous dioxane enabled the required sterols (**294a**) and (**294b**), respectively, to be obtained.

Yet another approach to the synthesis of compounds (**294a** and **b**), described in [70], involved the conversion of the ester (**289**) into the silyl derivative (**295**). The bromination of steroid (**295**) with bromine in carbon tetrachloride, followed by desilylation with tetrabutylammonium fluoride gave the (23E)-24-bromide (**296**) with an overall yield of 80%. By the addition to the double bond of the latter of dibromocarbene, generated by the reaction of bromoform with 50% caustic soda in the presence of triethylbenzylammonium chloride, the (23R,24R)-tribromocyclopropane (**292c**) and its (23S,24S)- isomer (**292d**) were obtained with a yield of 50%, and these were then converted into the sterols (**294a and b**) by successive interactions with methyllithium and with methyl iodide and hydrolysis under the action of *p*-toluenesulfonic acid in aqueous dioxane.



(23R, 24R) **292c**
(23S, 24S) **292d**

294a, b

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