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ADVANCES IN THE CHEMICAL SYNTHESIS OF BRASSINOSTEROIDS

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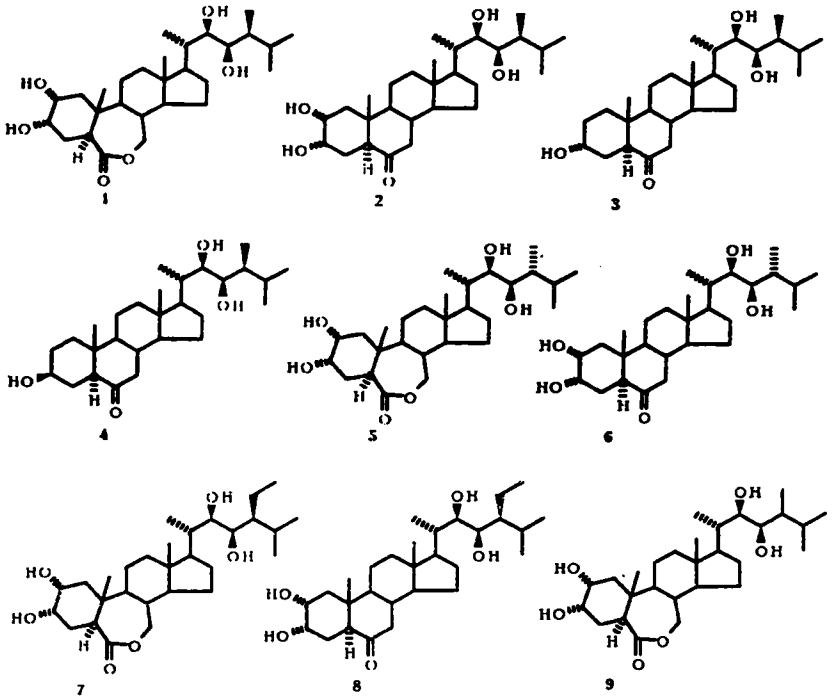
This review generalizes the latest advances in the chemical synthesis of the plant growth regulators brassinosteroids in 1990-1994.

The brassinosteroids comprise polyhydroxylated steroids isolated from plants or obtained synthetically and having similar chemical structures and a biological action consisting in the regulation of the growth of plants [1]. The name of this group of biologically active substances was derived from the first representative, brassinolide (**1**), isolated from rape pollen at the end of the 1980s. Exhibiting an extremely high biological activity, brassinosteroids are an object of intensive investigations in the field of the biochemistry and physiology of plants.

These bioregulators are present in plants in fairly low concentrations, which makes it practically impossible to obtain them from the natural raw material in amounts sufficient for scientific investigations and, all the more, for practical use. For this reason, progress in the study of the brassinosteroids depends wholly on their chemical synthesis from available steroid raw material.

In this review we consider investigations on the chemical synthesis of the brassinosteroids mainly in 1990-1994 appearing after the publication of a previous paper on this subject [2]. In addition, investigations are included that were published before this period but, for any reason, did not appear in the earlier review [2]. Of earlier reviews on the synthesis of brassinosteroids, we must mention [3]. In addition, literature reports up to 1990 on methods of synthesizing the substances under discussion are given in [4-10].



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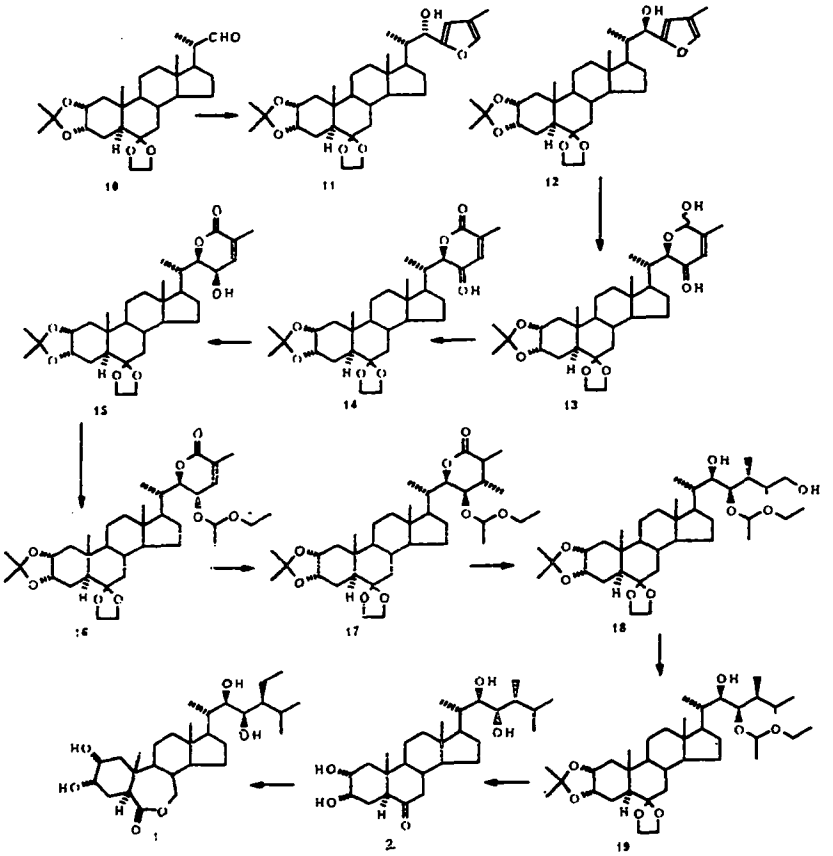
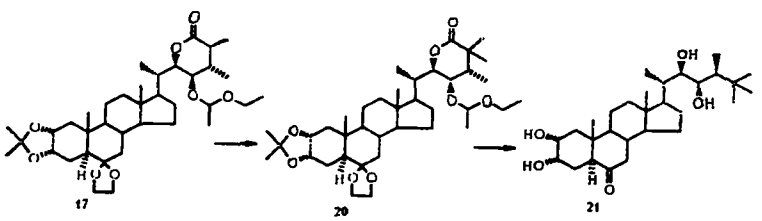
The most typical representatives of the brassinosteroids are brassinolide (**1**), castasterone (**2**), typhasterol (**3**), teasterone (**4**),. 24-epibrassinolide (**5**), 24-epicastasterone (**6**), 28-homobrassinolide (**7**), (24S)-24-ethylbrassinone (**8**), and 26,27-bisnorbrassinolide (**9**). The characteristic feature of a brassinosteroid molecule is the presence of a sterol skeleton hydroxylated at C-2, C-3, C-22, and C-23 with a strictly determined stereochemistry and a 6-keto group or a lactone grouping in ring *B*.



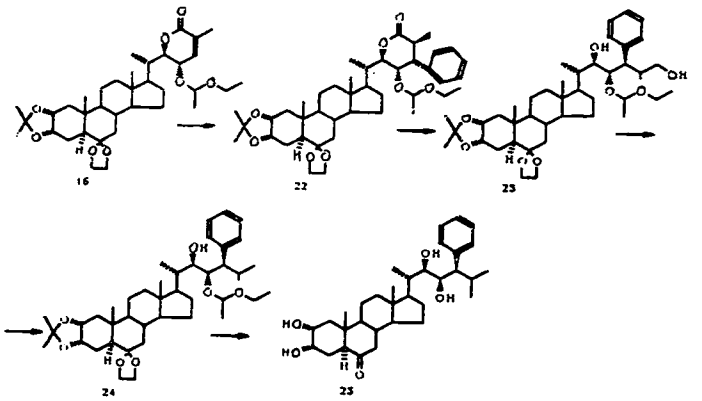
We must first discuss the results obtained in recent years in the chemical synthesis of brassinolide (**1**) and the brassinosteroids (**2**)-(**4**) having a side-chain with the same structure. As shown in [11, 12], the construction of the side-chain is based on the reaction of the 22-aldehyde (**10**) obtained from stigmasterol with 2-lithio-4-methylfuran to form the (22S)-22-alcohol (**11**) and the (22R)-22-alcohol (**12**) in yields of 20 and 58%, respectively. The oxidation of alcohol (**12**) with N-bromosuccinimide led with a yield of 92% to lactone (**13**), the further oxidation of which with pyridinium chlorochromate gave an 89% yield of the ketolactone (**14**). Reduction of the 23-keto group in compound (**14**) with sodium tetrahydroborate in the presence of cerium(III) chloride formed, with a yield of 97%, the (23R)-23-alcohol (**15**), which was then converted by reaction with ethyl vinyl ether into the 23-ethoxyethyl ether (**16**) with a yield of 94%.

The saturated lactone (**17**) was obtained with a yield of 85% by the 1,4-addition of lithium dimethylcuprate to the 24-double bond of the unsaturated lactone (**16**). The lactone grouping in compound (**17**) was reduced with lithium tetrahydroaluminate to give a 97% yield of the primary 26-alcohol (**18**). The 26-mesylate was obtained from alcohol (**18**) in the usual way and its reduction with lithium tetrahydroaluminate enabled compound (**19**) to be obtained with an overall yield of 79%. Hydrolysis of the protective groupings in steroid (**19**) by its interaction with a solution of 10% aqueous hydrochloric acid in tetrahydrofuran at the boil gave a 94% yield of catasterone (**2**), the synthesis of brassinolide (**1**) from which was possible by procedures developed previously.

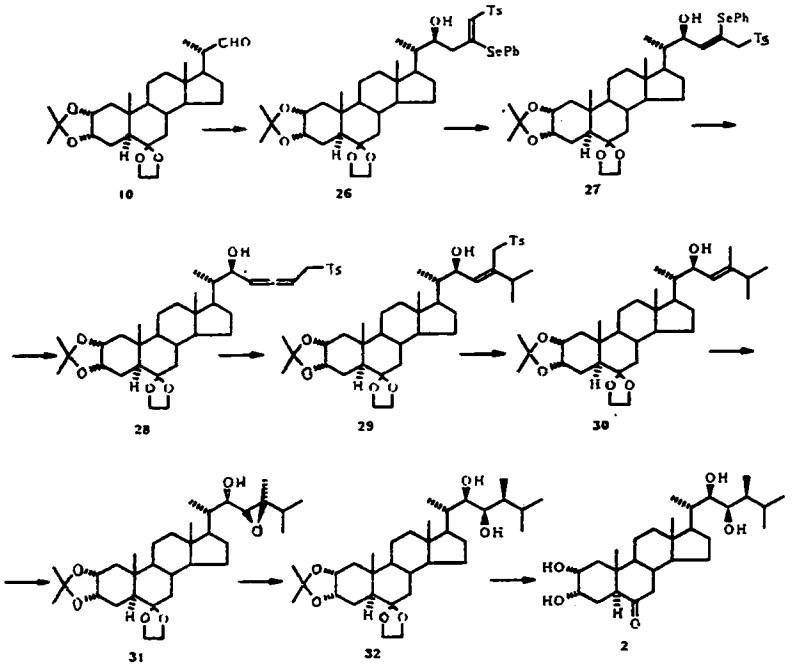


By its interaction with lithium diisopropylamide, Tsubuki et al. [12] obtained from compound (**17**) an anion the alkylation of which with methyl iodide formed a 13% yield of lactone (**20**). 25-Methylcastasterone (**21**) was synthesized from steroid (**20**) by methods basically analogous to those described above.

The synthesis of (24R)-24-phenylbrassinone (**25**) is also possible from the unsaturated lactone (**16**), as was described in the same paper [12]. The 1,4-addition of lithium diphenylcuprate to the 24-double bond of the unsaturated lactone (**16**) formed with a yield of 90% the (24R,25S)-24-phenyl derivative (**22**), which was converted by reduction with lithium tetrahydroaluminate into the 26-alcohol (**23**) with a yield of 71%. The unwanted 26-hydroxy group in compound (**23**) was eliminated via the mesylate with the formation of a 72% yield of steroid (**24**). Acid hydrolysis of the protective groupings in derivative (**24**) gave the required (24R)-24-phenylbrassinone (**25**).

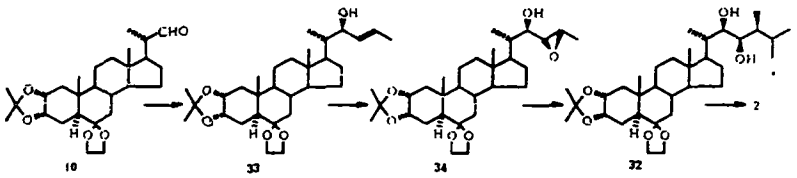


Back and Krishna [13] synthesized castasterone (**2**) with the use of an original scheme for constructing the side-chain. First, the 22-aldehyde (**10**) was obtained from stigmasterol. The addition of 3-lithio-1-(trimethylsilyl)propyne to aldehyde (**10**), followed by elimination of the silyl protective groups with tetrabutylammonium fluoride and selenosulfonation of the resulting acetylene with *Se*-phenyl tolueneselenosulfonate gave the 22-alcohol (**26**) and its (22S)-isomer in approximately equal proportions with an overall yield of 49%. Isomerization of compound (**26**) under the action of triethylamine led to the formation in 66% yield of the allyl sulfone (**27**), which, as a result of syn-elimination under the action of *tert*-butyl hydroxide was converted with 81% yield into the allene (**28**), existing in the form of a mixture of diastereomers. The necessary isopropyl group was introduced into allene (**28**) by the addition of lithium cyanoisopropyl(2-thienyl)cuprate. The steroid (**29**) so obtained with a yield of 31% was converted by reductive desulfonylation with magnesium in methanol into the allyl alcohol (**30**) in a yield of 51%.

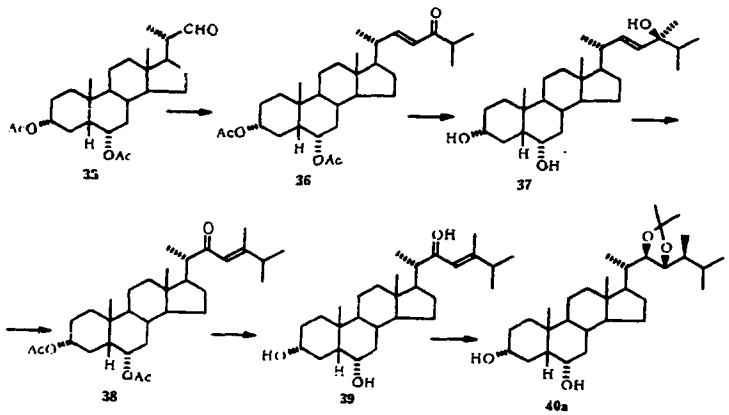


Epoxidation of the double bond in compound (**30**) with *m*-chloroperbenzoic acid enabled the epoxyalcohol (**31**) to be obtained with a yield of 91%. Reduction of the epoxide (**31**) with lithium tetrahydroborate in the presence of the complex of diborane with tetrahydrofuran gave a 73% yield of the (22R,23R)-22,23-diol (**32**). From steroid (**32**) by hydrolysis of the protective groupings with aqueous acetic acid an 82% yield of castasterone (**2**) was obtained.

Yet another synthesis of castasterone (**2**) and brassinolide (**1**) was achieved by Back et al. [14]. Stigmasterol was first converted into the 22-aldehyde (**10**). The addition of prop-1E-enyllithium to the aldehyde (**10**) led to the formation of the allyl alcohol (**33**). The Sharpless diastereoselective epoxidation of the 23-double bond in compound (**33**) formed the 22-hydroxy-23,24-epoxide (**34**). As a result of the opening of the epoxide ring with isopropylmagnesium chloride, compound (**34**) was converted into the (22R,23R)-22,23-diol (**32**) with the preformed brassinolide side-chain. Subsequent hydrolysis of the protective groupings in steroid (**32**) led to the formation of castasterone (**2**), the Baeyer-Villiger oxidation of which with trifluoroperacetic acid yielded brassinolide (**1**).

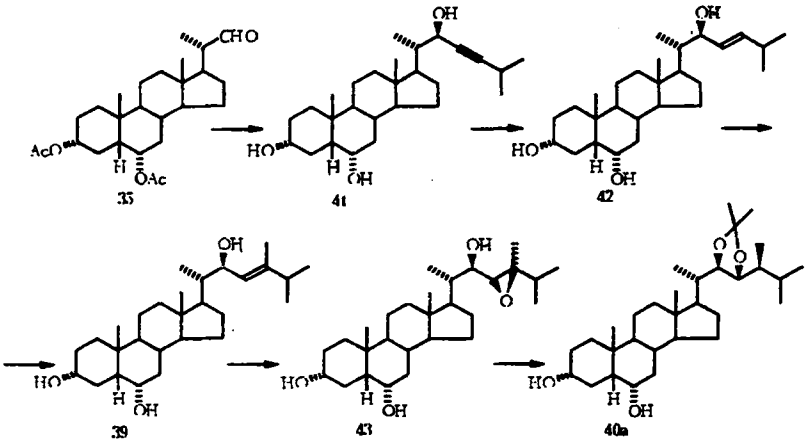


In the last stage of an improved synthesis of brassinolide (**1**), use was made of the direct trifluoroperacetic acid oxidation of compound (**32**) with protected 2α,3α-diol grouping and 6-keto group [15]. Under these conditions, hydrolysis of the protective groups and subsequent Baeyer-Villiger lactonization of the liberated 6-keto group took place. As a result, brassinolide (**1**) was formed with a yield of 63%. Analogously, 24-epibrassinolide (**5**) and its (22S,23S)- isomer, (22S,23S)-28-homobrassinolide, and 28-norbrassinolide have been synthesized from the corresponding 2α,3α-isopropylidenedioxy-22,23-dihydroxy-6,6-ethylenedioxysteroids.

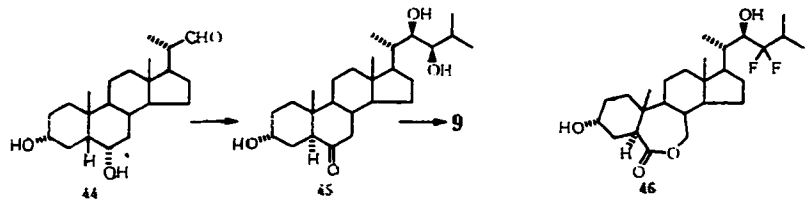


The synthesis of steroid (**40a**) — a known intermediate in the production of brassinolide — has been effected from the aldehyde (**35**) by a new scheme in six stages with an overall yield of 47% [16, 17]. First, the condensation of the aldehyde (**35**), obtained from hyodeoxycholic acid, with (3-methyl-2-oxobutyl)triphenylarsonium bromide led with a yield of 90% to the Δ^{22}-24-ketone (**36**), and from this the allyl alcohol (**37**) was obtained in quantitative yield by the addition of methyllithium to its keto group. After acetylation of the secondary hydroxy groups, compound (**37**) was converted by oxidation with pyridinium chlorochromate into the Δ^{23}-22-ketone (**38**) with a yield of 93%. Reduction of the 22-keto group in steroid (**38**) by diisobutylaluminum hydride gave a 95% yield of the allyl alcohol (**39**). Epoxidation of the 22-double bond in compound (**39**), reduction of the resulting epoxide with lithium tetrahydroborate, and subsequent formation of an acetonide by reaction with 2,2-dimethoxypropane enabled the target steroid (**40a**) to be obtained with an overall yield of 84%.

Recently [17, 18] yet another approach to the 22,23-monoacetonide (**40a**) has been developed. Alkylation of the aldehyde (**35**) with the anion obtained from 1,1-dibromo-3-methylbut-1-ene and *n*-butyllithium formed the (22R)-22-alcohol (**41**) and its (22S)-isomer with yields of 57 and 29%, respectively.



The partial hydrogenation of the propargyl alcohol (**41**) gave a 95% yield of the allyl alcohol (**42**). By the reaction of compound (**42**) with phenylselenyl chloride the corresponding sulfoxide was obtained, and this was then alkylated with methyl iodide and was converted by subsequent reduction with trimethyl phosphite into the allyl alcohol (**39**) with an overall yield of 47%. The reaction of steroid (**39**) with *m*-chloroperbenzoic acid formed the 22-hydroxy-23,24-epoxide (**43**) with a yield of 93%. The conversion of compound (**43**) into the required acetonide (**40a**) was achieved with an overall yield of 84% by reducing the epoxide ring with lithium tetrahydroborate in the presence of titanium tetraisopropanolate, followed by protection of the 22,23-diol so formed by reaction with 2,2-dimethoxypropane in acetone.



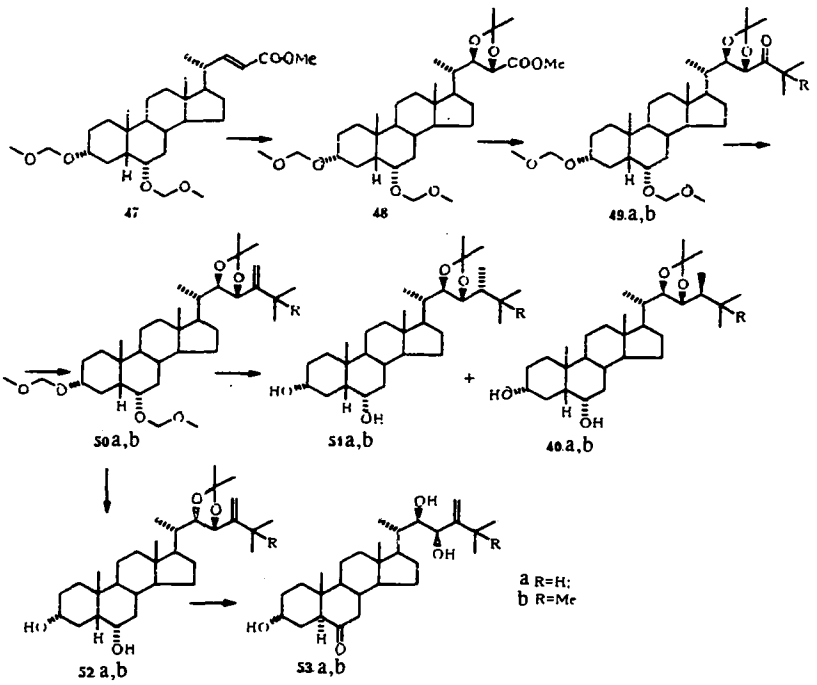
In [19], the synthesis of 26,27-bisnortyphasterol (**45**) and 26,27-bisnorbrassinolide started from the 22-aldehyde (**44**). The key stage in the formation of the side-chain in this investigation was the interaction of aldehyde (**44**) with 2-lithio-2-isopropyl-1,3-dithiane.

We may also note that the synthetic brassinosteroid (**46**), containing two fluorine atoms in the side-chain, has been obtained by the reaction of the 22-aldehyde (**35**) with the appropriate 2,2-difluoro enol silyl ether and subsequent transformation in rings *A* and *B* [20].

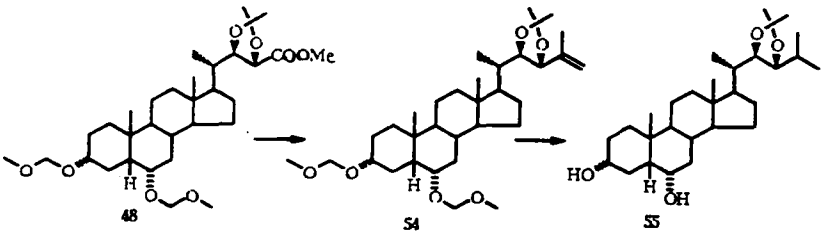
The *cis*-hydroxylation of the 22-double bond in the protected cholic acid derivative (**47**) under the action of osmium tetroxide in the presence of dihydroquinidine *p*-chlorobenzoate gave a 70% yield of a (22R,23S)-22,23-diol which was then converted by reaction with 2,2-dimethoxypropane into the acetonide (**48**) with a yield of 95% [21, 22].

As a result of the interaction of compound (**48**) with lithium tetrahydroborate and isopropylmagnesium chloride, the corresponding 24-alcohol was formed with a yield of 86%, and this was oxidized by pyridinium chlorochromate with an overall yield of more than 90% to the 24-ketone (**49a**). Then, the $\Delta^{24(28)}$-derivative (**50a**) was synthesized from ketone (**49a**) in a yield of 89% by means of the Wittig reaction. The catalytic hydrogenation of the double bond followed by removal of the protective groups under the action hydrochloric acid gave tetraols epimeric at C-24 which were then converted by reaction with 2,2-dimethoxypropane in the acetonides (**51a** and **40a**) with yields of 46 and 11%, respectively, from (**48**). As stated above, steroid (**40a**) is a known intermediate in the synthesis of brassinolide, and, thus, its preparation formally completes the synthesis.

Partial hydrolysis of the protective groupings in compound (**50a**) under the action of pyridinium tosylate gave, with a yield of 80%, the 3α,6α-diol (**52a**), the selective oxidation of the 6α-hydroxy group in which with pyridinium dichromate followed by hydrolysis of the acetonide grouping in the side-chain with simultaneous epimerization at C-5 led with an overall yield of 41% to 2-deoxydolichosterone (**53a**). The synthesis of 25-methylbrassinosteroids starting from compound (**48**) is also possible, as has been demonstrated by Zhow et al. [21, 22]. The interaction of steroid (**48**) with *tert*-butyllithium gave an 84%



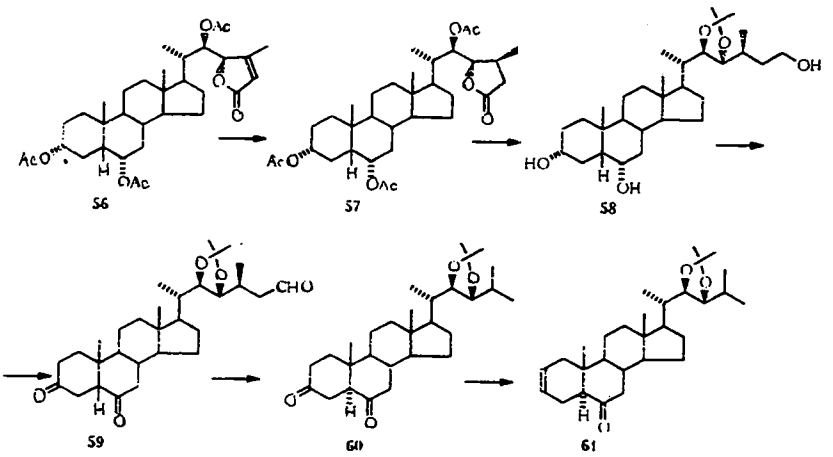
yield of the 25-methyl-24-ketone (**49b**), which was then converted with a yield of 87% by the Wittig reaction into the $\Delta^{24(28)}$-steroid (**50b**). Subsequent hydrogenation of the double bond in compound (**50b**), acid hydrolysis of the protective groupings, and, finally, the formation of a 22,23-acetonide enabled the 3α,6α-diols (**51b** and **40b**) to be obtained with yields of 34 and 23% from (**48**), respectively. As a result of partial hydrolysis of the protective groupings under the action of pyridinium tosylate, the 3α,6α-diol (**52b**) was obtained from steroid (**50b**) with a yield of 82.3%, and this was then converted in the usual way into the 3α-hydroxy-6-ketone (**53b**) with a yield of 38%.



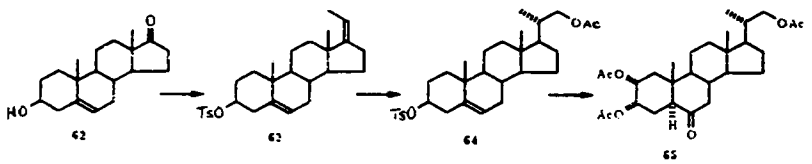
The possibility has also been considered of obtaining 26,27-bisnorbrassinolide (**9**) from compound (**48**) [21, 22]. The interaction of the ester (**48**) with methyllithium, followed by dehydration of the resulting alcohol via the mesylate, formed the unsaturated steroid (**54**) with a yield of 87%. Partial hydrolysis of the methoxymethyl groups under the action of pyridinium tosylate in *tert*-butanol with subsequent catalytic hydrogenation enabled compound (**54**) to be converted into the diol (**55**), the synthesis of 26,27-bisnorbrassinolide (**9**) from which has been published previously.

An improved synthesis of compound (**61**), from which 26,27-bisnorbrassinolide has also been obtained previously, has been described [23]. Here, hyodeoxycholic acid was first converted with a yield of 41% into the unsubstituted lactone (**56**). The catalytic hydrogenation of (**56**) gave a 95% yield of the saturated γ-lactone (**57**).

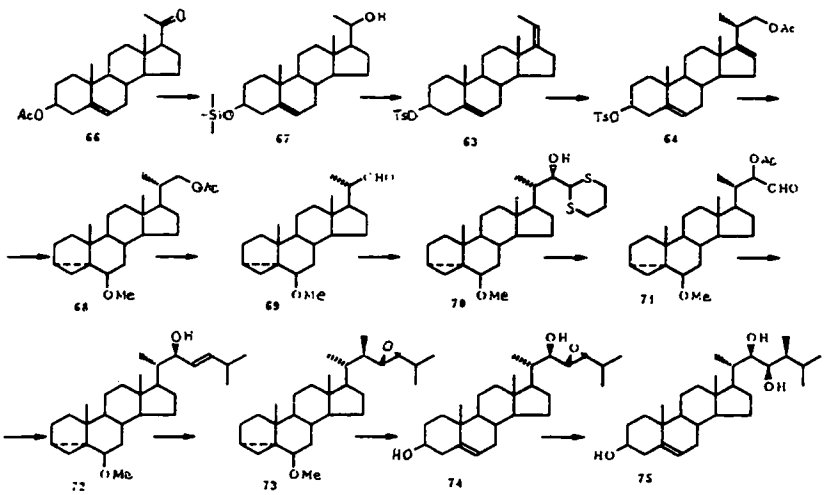
Reduction of the lactone (**57**) with lithium tetrahydroaluminate enabled the corresponding pentahydroxy derivative to be obtained with a yield of 92%, and this was then converted by reaction with 2,2-dimethoxypropane into the 22,23-acetonide (**58**) with a yield of 86%. When the remaining free hydroxy groups were oxidized with pyridinium dichromate, compound (**58**) gave a 79% yield of the 3,6-diketo-26-aldehyde (**59**). Decarbonylation of the aldehyde group in the latter under the action of tris(triphenylphosphine)rhodium chloride, followed by epimerization at C-5 in acetone in the presence of *p*-toluenesulfonic acid led to the formation of the 3,6-diketone (**60**) with an overall yield of 84%. The selective reductive elimination of the 3-keto group in compound (**60**) under the action of zinc amalgam and chlorotrimethylsilane enabled the required Δ^2-6-ketone (**61**) to be obtained with a yield of 57%.



Hazra et al. [24] have described the transformation of androstenolone (**62**) into the 2α,3α,22-triacetoxy-6-ketone (**65**) in nine stages with an overall yield of 44%. Compound (**65**) is a known intermediate in the synthesis of 24-norbrassinolide, dolichosterone, and dolicholide. The key compound in the scheme developed for its synthesis was the pregnadiene (**63**), obtained from the 17-ketone (**62**) by the Wittig reaction, from which the unsaturated 22-acetate (**64**) was obtained by an ene reaction with paraformaldehyde. The conversion of the 3β-tosyloxy-Δ^5-grouping in compound (**64**) into the required 2α,3α-dihydroxy-6-keto grouping was effected by traditional methods.

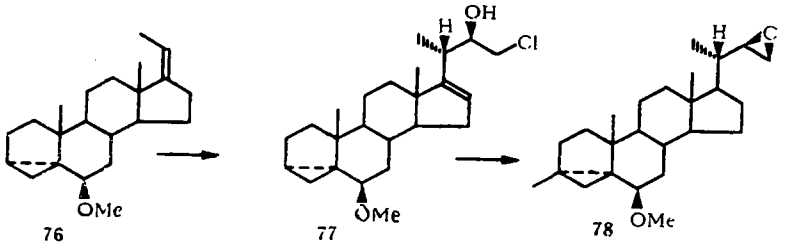


Subsequently [25, 26], the sequence of reactions developed for the formation of the C-17 and C-20 chiral centers with the configurations characteristic for the natural brassinosteroids was used in the synthesis of the (22R,23R)-3β,22,23-triol (**75**). In this case, compound (**75**), which is a known intermediate in the synthesis of brassinolide (**1**) was obtained from the starting material dehydropregnenolone acetate (**66**). It was then possible as a result of the catalytic hydrogenation of the 16-double bond in compound (**66**), alkaline hydrolysis of the 3β-acetoxy group, protection of the resulting 3β-hydroxy group in the form of the *tert*-butyldimethylsilyl ether, and reduction of the 20-keto group with lithium tetrahydroaluminate to synthesize in high yield the 20-hydroxy derivative (**67**) in the form of a mixture of the (20R)- and (20S)- isomers. Then the 3β-tosyloxypregnadiene (**63**) was obtained from the (20R)- isomer of steroid (**67**) by dehydration of the 20-hydroxy group with phosphorus oxychloride in pyridine, removal of the silyl protection with tetrabutylammonium chloride, and tosylation of the 3β-hydroxy group formed.



The ene reaction of steroid (**63**) with paraformaldehyde in the presence of acetic anhydride and chlorotriisopropoxytitanium with a yield of 82% formed the 16-unsaturated 22-acetate (**64**). Solvolysis of the tosylate (**64**) in methanol took place with the production of the corresponding 3α,5-cyclo-6β-methoxy derivative, the catalytic hydrogenation of the 16-double bond which enabled steroid (**68**) to be obtained. Alkaline hydrolysis of the 22-acetoxy group in compound (**68**) followed by oxidation of the 22-hydroxy group with pyridinium chlorochromate led to the 22-aldehdye (**69**). Condensation of the aldehyde (**69**) with the lithium derivative of 1,3-dithiane gave the thio-protected 22-hydroxy-23-aldehyde (**70**), which was then converted into the 22-acetate and, after elimination of the dithiolane protection, the 22-acetoxy-23-aldehyde (**71**) was obtained. The Wittig reaction of the aldehyde (**71**) with the appropriate ylide enabled the (22R,23S)-22-hydroxy-Δ^{23}-steroid (**72**) to be obtained with a yield of 77%.

The subsequent conversion of compound (**72**) into the required triol (**75**) included epoxidation of the 23-double bond, directed 22-hydroxylation with the formation of the epoxyalcohol (**73**) in a yield of 95%, transformation of the 3α,5-cyclo-6β-methoxy grouping under the action of *p*-toluenesulfonic acid in aqueous dioxane into the 3β-hydroxy-Δ^5-steroid (**74**), and, finally, the opening of the epoxide ring by trimethylaluminum in the presence of *n*-butyllithium with a yield of 91%.



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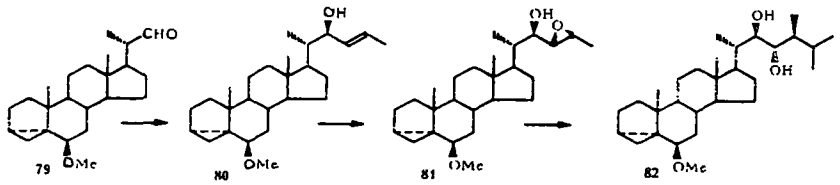
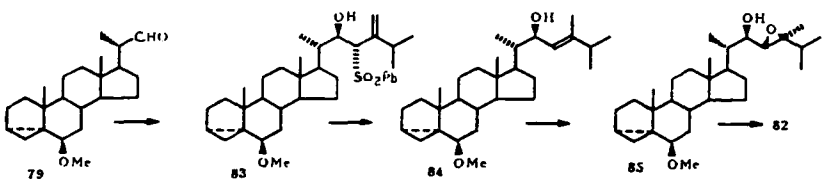
The 22,23-epoxide (**78**), the preparation of which from the unsaturated steroid (**76**) has been described in a patent [27], is of interest as an intermediate in the synthesis of brassinosteroids. The interaction of compound (**76**) with α-chloroacetaldehyde in the presence of dimethylaluminum chloride takes place with the formation of the 16-unsaturated chlorohydrin (**77**). The chlorohydrin (**77**) is then subjected to a reaction with sodium hydride to form the corresponding epoxide, the subsequent hydrogenation of the 16-double bond which leads to the saturated epoxide (**78**).



79 80 81 82

Yet another route to the formation of the brassinolide side-chain from the aldehyde (**79**) has been given in the literature [28]. The alkylation of aldehyde (**79**) with E-propenyllithium led with an overall yield of 75% to the formation of the allyl alcohol (**80**) and its 22-isomer in a ratio of 72:28. The subsequent Sharpless epoxidation of the 23-double bond in compound (**80**) with *tert*-butyl hydroperoxide in the presence of (+)-diethyl *L*-tartrate led with an overall yield of 95% to the epoxide (**81**) and its 23,24-isomer in a ratio of 7:3. As a result of the opening of the epoxide ring in compound (**81**) with a lithium cuprate reagent, the 22,23-diol (**82**) was obtained with a yield of 61%.



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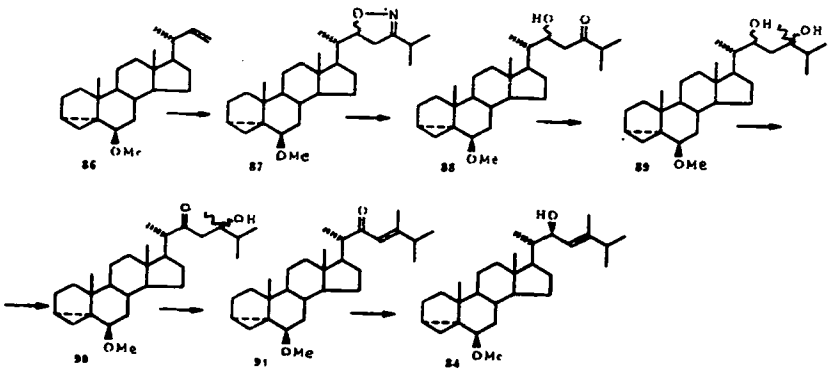
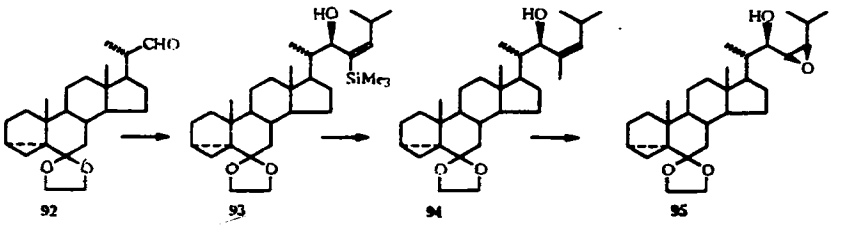
A synthesis of the brassinolide side-chain proposed by Khripach et al. [29] makes use of the alkylation of the 22-aldehyde (**79**) with the anion formed in the interaction of 3-acetoxy-4-phenylsulfonyl-2,3-dimethylbutane with lithium diisopropylamide. From the steroid (**83**) obtained in this way, the allyl alcohol (**84**) was synthesized by desulfuration with lithium in liquid ammonia. Epoxidation of the 23-double bond in compound (**84**) with *m*-chloroperbenzoic acid formed the epoxyalcohol (**85**). The opening of the epoxide ring with aluminum hydride gave the 22,23-diol (**82**).

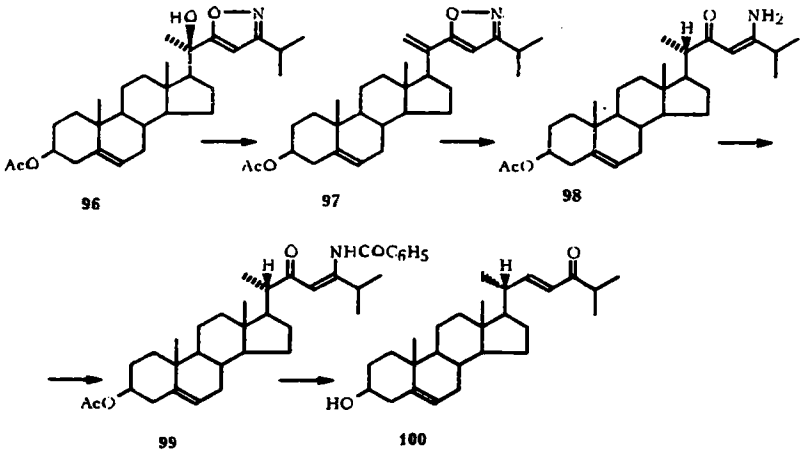
A method has been developed for obtaining the allyl alcohol (**84**) from the 22,23-unsaturated steroid (**86**) [30-32]. The cycloaddition of isobutyronitrile oxide to the double bond of compound (**86**) enabled the isoxazoline (**87**) to be synthesized with a yield of 95%. The reductive opening of the isoxazoline ring in steroid (**87**) under the action of Raney nickel in the presence of boric acid gave an 80% yield of the 22-hydroxy-24-ketone (**88**). By alkylation with methyllithium, this substance was converted with a yield of 80% into the 22,24-diol (**89**). Then Jones oxidation of the secondary 22-hydroxy group led with a yield of 60% to the 24-hydroxy-22-ketone (**90**), the dehydration of which with thionyl chloride in pyridine gave the Δ^{23}-22-ketone (**91**) with a yield of about 50%. By reduction of the 22-keto group in steroid (**91**) with diisobutylaluminum hydride, the required alcohol (**84**) was obtained.



The epoxyalcohol (**95**), from which, in principle, it is possible to synthesize brassinolide by known methods, has been obtained from the aldehyde (**92**) [33, 34]. Reaction of the latter with 1-lithio-3-methyl-1-(trimethylsilyl)but-1-ene formed the (22R)-22-alcohol (**93**) and its (22S)-isomer in a ratio of 10:1 with an overall yield of 97%. By the desilylation of compound (**93**) it was possible to obtain the allyl alcohol (**94**), and the epoxidation of this with *m*-chloroperbenzoic acid formed the 22-hydroxy-23,24-epoxide (**95**).



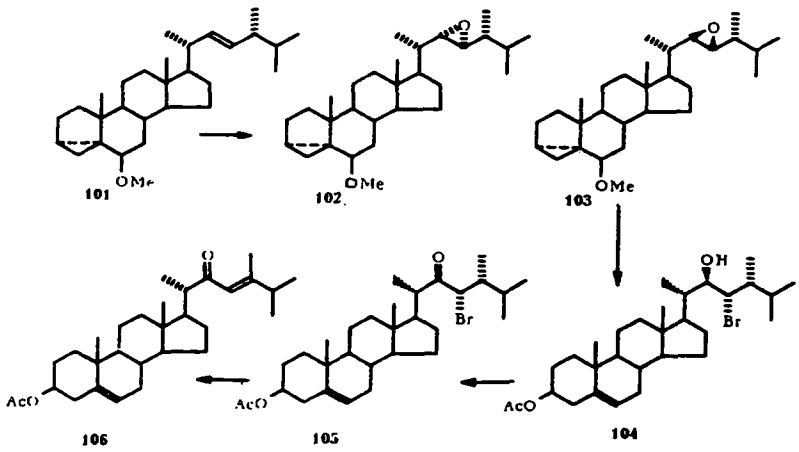
We may also note that the reaction of a 22-hydroxy-23-aldehyde steroid derivative with 2-methylthioallyl silyl ether has also been used for constructing the brassinolide side-chain [35].



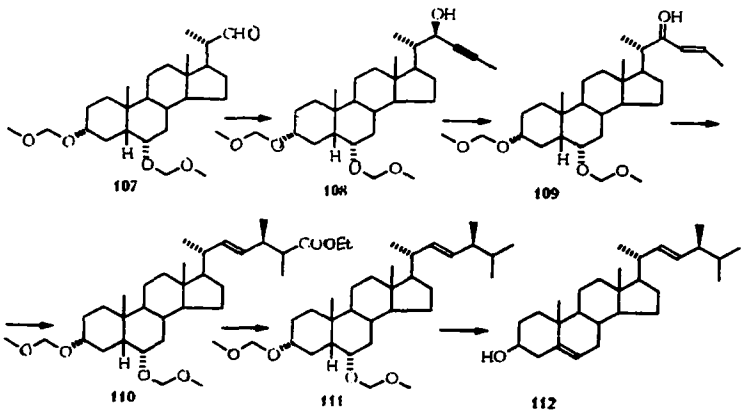
Khripach et al. [36] have described the transformation of the hydroxyisoxazole (**96**), obtained from pregnenolone, into the Δ^{22}-24-ketone (**100**), from which the synthesis of brassinosteroids is possible. The dehydration of compound (**96**) with sulfuric acid in dioxane gave the $\Delta^{20(21)}$-isoxazole (**97**), the hydrogenation of which over Raney nickel took place with the

formation of the (20S)-enaminoketone (**98**). The reaction of steroid (**98**) with benzoyl chloride gave a 95% yield of the N-benzoyl derivative (**99**), reduction of the 22-keto group in the molecule of which with sodium tetrahydroborate in ethanol, followed by hydrolysis of the protective groupings under the action of *p*-toluenesulfonic acid in dioxane, accompanied by the dehydration of the 22-hydroxy group, led to the unsaturated ketone (**100**) with a yield of 67%.

The conversion of the side-chain of ergosterol into the Δ^{23}-22-ketone (**106**), from which the synthesis of brassinolide is possible, has been described in [37]. When the Δ^{22}-steroid (**101**), synthesized from ergosterol, was epoxidized with *m*-chloroperbenzoic acid the (22S,23S)-22,23-epoxide (**102**) and the (22R,23R)-22,23-epoxide (**103**) were obtained with yields of about 30%. Isomerization of compound (**103**) in rings *A* and *B* by boiling in acetic acid and subsequent opening of the epoxide ring with hydrobromic acid led to the formation of bromohydrin (**104**) with an overall yield of 43%. The 23-bromo-22-ketone (**105**) was obtained with a yield of 90% by the Jones oxidation of steroid (**104**) with chromic acid. Dehydrobromination of the bromoketone (**105**) with lithium carbonate in dimethylformamide at the boil led to the enone (**106**) with a yield of 27%.



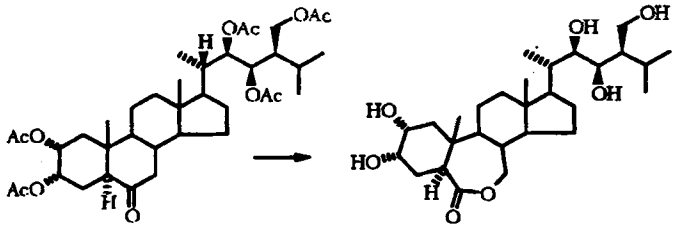
One of the possible starting materials in the preparation of brassinolide is crinosterol (**112**), which has the same carbon skeleton as this phytohormone and the necessary stereochemistry at C-24. The synthesis of crinosterol in six stages from the aldehyde (**107**) obtained from hyodeoxycholic acid has been achieved recently [38]. The interaction of aldehyde (**107**) with the appropriate acetylenic Grignard reagent, mainly propargyl, formed the 22-alcohol (**108**). As a result of partial hydrogenation of the triple bond in steroid (**108**) with sodium bis(2-methoxyethoxy)hydroaluminate, the (22R,23E)-allyl alcohol (**108**) was obtained with a yield of 80%. The interaction of compound (**109**) with propionic acid and orthoformic ester took place with the formation, in a yield of more than 90%, of the ester (**110**).



The subsequent reduction of compound (**110**) with diisopropylaluminum hydride and lithium tetrahydroaluminate enabled the (23E,24S)-24-methylcholestanol (**111**) to be obtained with a yield of 95%. The further transformation of compound (**111**) into the required sterol (**112**) consisted in the hydrolysis of the protective groupings, the tosylation of the 3- and 6-hy-

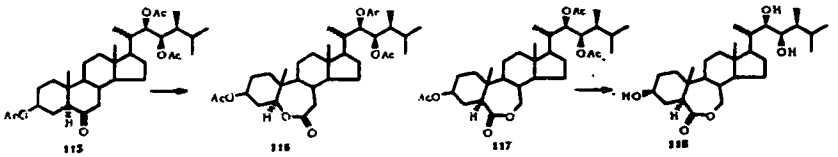
droxy groups, and a solvolysis reaction under the action, first, of potassium acetate in dimethylformamide with heating and then of methanolic potassium hydroxide. Of course, because of its complexity and multistage nature, the synthesis under discussion is mainly of scientific value. Zhow et al. [38] also proposed a synthesis of brassicasterol, which is an epimer at C-24 of crinosterol (**112**). Its distinguishing feature consists in the partial hydrogenation of the propargyl alcohol (**108**) over Lindlar catalyst with the formation of the 23(Z)-olefin, which is a geometric isomer of steroid (**109**). The further transformations of compound (**109**) into brassicasterol were completely identical with those discussed above in the synthesis of crinosterol (**112**).

28-Hydroxy derivatives of brassinosteroids, which possess plant-growth regulator activity, form the object of a patent [39]. For example, 28-hydroxybrassinolide (**114**) is obtained by the Baeyer-Villiger lactonization of the pentaacetoxyketone (**113**) followed by hydrolysis of the acetoxy groups with a methanolic solution of potassium hydroxide.

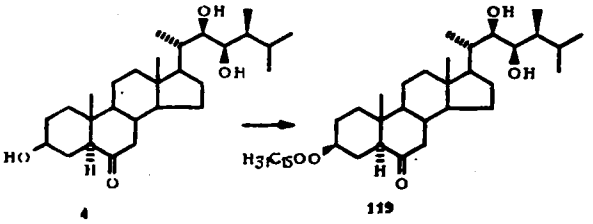


113 **114**

The synthesis of 2-deoxy-3-epibrassinolide (**118**) from teasterone triacetate (**115**) has been achieved [40]. The Baeyer-Villiger oxidation of the ketone (**115**) with trifluoroperacetic acid formed a 1:1 mixture of lactones (**116**) and (**117**). The required brassinosteroid (**118**) was obtained by hydrolyzing the protective acetoxy groups in the triacetoxylactone (**117**). It is reported that compound (**118**) is approximately ten times more active than typhasterol as a plant growth regulator.

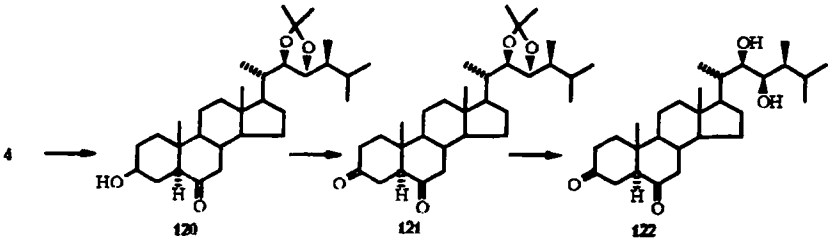


Esters of 2-deoxybrassinosteroids at the 3-hydroxy group are also the subject of a patent [41]. These substances are obtained by the partial acylation of the free brassinosteroids. For example, the interaction of teasterone (**4**) with palmitoyl chloride leads to the formation of teasterone 3-palmitate (**119**). Interest in the synthesis of substances with such a structure will undoubtedly increase, particularly now that it has become known that teasterone 3-myristate is present in plants [42].



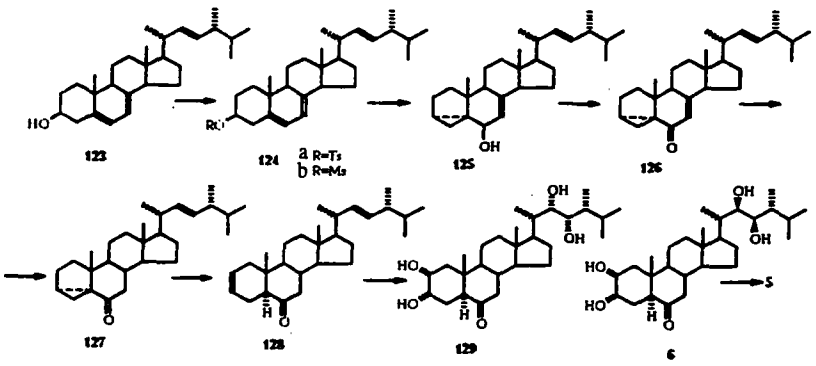
4 **119**

Recently [43], in an analysis of the brassinosteroids in wheat bran, a new compound of this group was isolated for which the structure of 3-dehydroteasterone (**122**) has been established. Brassinosteroid (**122**) has been synthesized from teasterone (**4**) [43]. First, teasterone (**4**) was converted by reaction with 2,2-dimethoxypropane into the acetonide (**120**), from which the 3,6-diketone (**121**) was then obtained by oxidation with pyridinium chlorochromate. 3-Deoxyteasterone (**122**) was formed as a result of the acid hydrolysis of the isopropylidenedioxy grouping in compound (**121**) under the action of aqueous acetic acid.



120 **121** **122**

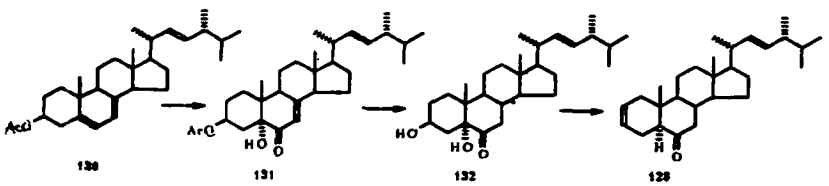
Traven' et al. [44] have performed an improved synthesis of 24-epibrassinolide (**5**) from ergosterol (**123**) by a known scheme in five stages with an overall yield of 25%. According to the scheme selected, ergosterol (**123**) was first converted into the tosylate (**124a**), which was then subjected successively to solvolysis, with the formation of the 3α,5-cyclo-6β-hydroxy derivative (**125**), and to oxidation with chromium trioxide in pyridine to the ketone (**126**).



In this investigation, ketone (**126**) was obtained from ergosterol in an overall yield of 56% without the isolation of the intermediates (**124a**) and (**125**). The reduction of compound (**126**) with lithium in liquid ammonia takes place in fairly complex fashion and, depending on the temperature and the ratio of the reactants, may lead to various products [45, 46]. However, when the unsaturated ketone (**126**) was reduced with lithium in a mixture of liquid ammonia and diethyl ether at −60 to −70°C for 5 min it was possible to obtain the saturated ketone (**127**) with a yield of more than 90%. The 2,22-dien-6-ol (**128**) was synthesized with a yield of 72% by the isomerization of the three-membered ring in steroid (**127**) with pyridinium hydrobromide in dimethylformamide. The *cis*-hydroxylation of dienone (**128**) with osmium tetroxide gave the tetrahydroxyketones (**129**) and (**6**) in a ratio of 3:1 with a total yield of 80%. The Baeyer-Villiger oxidation of the tetrahydroxyketone (**6**) with trifluoroperacetic acid completed the synthesis and enabled the required 24-epibrassinolide (**5**) to be obtained with a yield of 82%. (22S,23S,24R)-Brassinolide was synthesized by the analogous oxidation of the tetrahydroxyketone (**129**) with a yield of 80%.

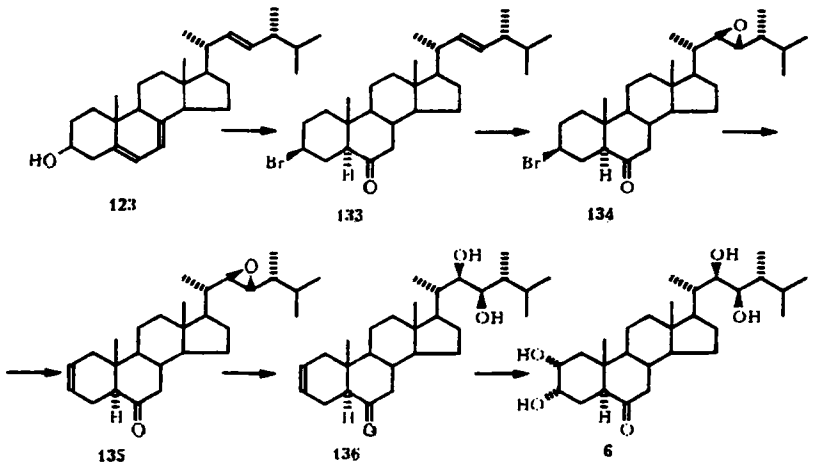
An improved method of synthesizing the 3α,5-cyclo-6β-ol (**125**) from ergosterol has been patented [47]. According to this, the initial ergosterol (**123**) is converted in quantitative yield by a rapid reaction with methanesulfonyl chloride in pyridine into the mesylate (**124b**), the solvolysis of which with the formation of the alcohol (**125**) is performed by boiling in aqueous acetone in the presence of potassium bicarbonate for 1-1.5 h. According to the patent [47], the yield of steroid (**125**) in the final stage amounts to 96.2%.

A synthesis of 24-epibrassinolide (**5**) from ergosterol (**123**) in which several stages have been improved has been performed by McMorris and Patil [48]. By mesylating ergosterol they obtained the mesylate (**124b**), the solvolysis of which, in aqueous acetone in the presence of potassium bicarbonate, and oxidation of the resulting 3α,5-cyclo-6β-alcohol (**125**) with chromium trioxide in pyridine led with an overall yield of 80% to the dienone (**126**). The dienone (**128**) was obtained with an overall yield of 80% by the Birch reduction of the 7-double bond in steroid (**126**) with lithium in a mixture of liquid ammonia and tetrahydrofuran, followed by isomerization of the three-membered ring under the action of lithium bromide in dimethylacetamide. From compound (**128**), on the *cis*-hydroxylation of the double bonds with osmium tetroxide in the presence of dihydroquinidine *p*-chlorobenzoate, methanesulfonamide, and potassium carbonate, 24-epicastasterone (**6**) and its (22S,23S)-isomer were obtained with yields of 80 and 8.5%, respectively. The direct lactonization of the tetrahydroxysteroid (**6**) with trifluoroacetic acid by the Baeyer-Villiger method enabled the required 24-epibrassinolide (**5**) to be synthesized with a yield of 80%. We may also mention that the similar oxidation of the tetrahydroxyketone (**6**) with trifluoroperacetic acid is a characteristic feature of the synthesis of 24-epibrassinolide (**5**) described in [49].



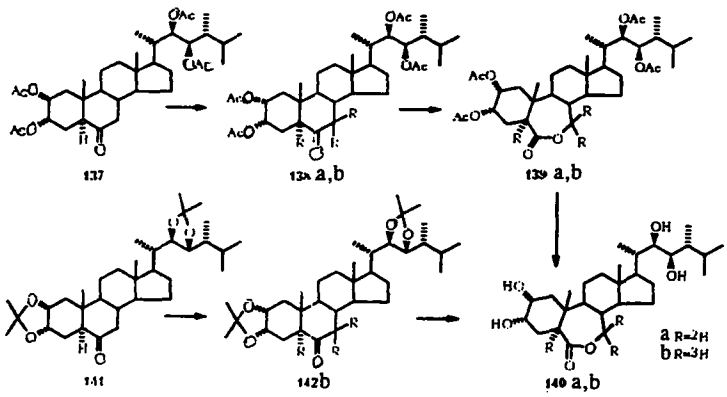
A new scheme has also been proposed for obtaining the 2,22-dien-6-one (**128**) [50]. The oxidation of ergosterol acetate (**130**) with chromium trioxide in ether gives the 5α-hydroxy-Δ^7-6-ketone (**131**). The interaction of this compound with lithium in a mixture of liquid ammonia and tetrahydrofuran by the Birch reaction takes place with reduction not only of the 7-double bond but also of the 5α-hydroxy group and with hydrolysis of the 3β-acetoxy group, giving the 3β-hydroxy-6-ketone (**132**) with a yield of 43%. The required ketone (**128**) is synthesized in a yield of 84% by the dehydration of compound (**132**) with copper sulfate on silica gel in tetrachloroethylene at the boil. According to [50], the overall yield of this substance from ergosterol is 36%.

In a synthesis of 24-epicastasterone (**6**) published in [51], ergosterol (**123**) was first converted in the usual way via the 3α,5-cyclo-6-ketone into the 3β-bromo-6-ketone (**133**). The reaction of compound (**133**) with *m*-chloroperbenzoic acid in chloroform gave a 58% yield of the (22R,23R)-3β-bromo-22,23-epoxide (**134**), which was dehydrobrominated with lithium carbonate in dimethylformamide to form the Δ^2-epoxyketone (**135**) in a yield of 78%. The (22R,23R)-dihydroxyenone (**136**) was obtained in an overall yield of 71%, without the isolation of the intermediate products, by the opening of the epoxide ring in steroid (**135**) with hydrobromic acid, acetylation of the resulting bromohydrins with acetyl chloride, nucleophilic replacement of the bromine atoms by acetoxy groups through the action of potassium acetate in aqueous acetic acid, and hydrolysis of the acetoxy groups with potassium hydroxide in methanol. Hydroxylation of the Δ^2-bond in compound (**136**) with osmium tetroxide led to 24-epicastasterone (**6**) with an overall yield of 55%, calculated on the bromoketone (**133**).



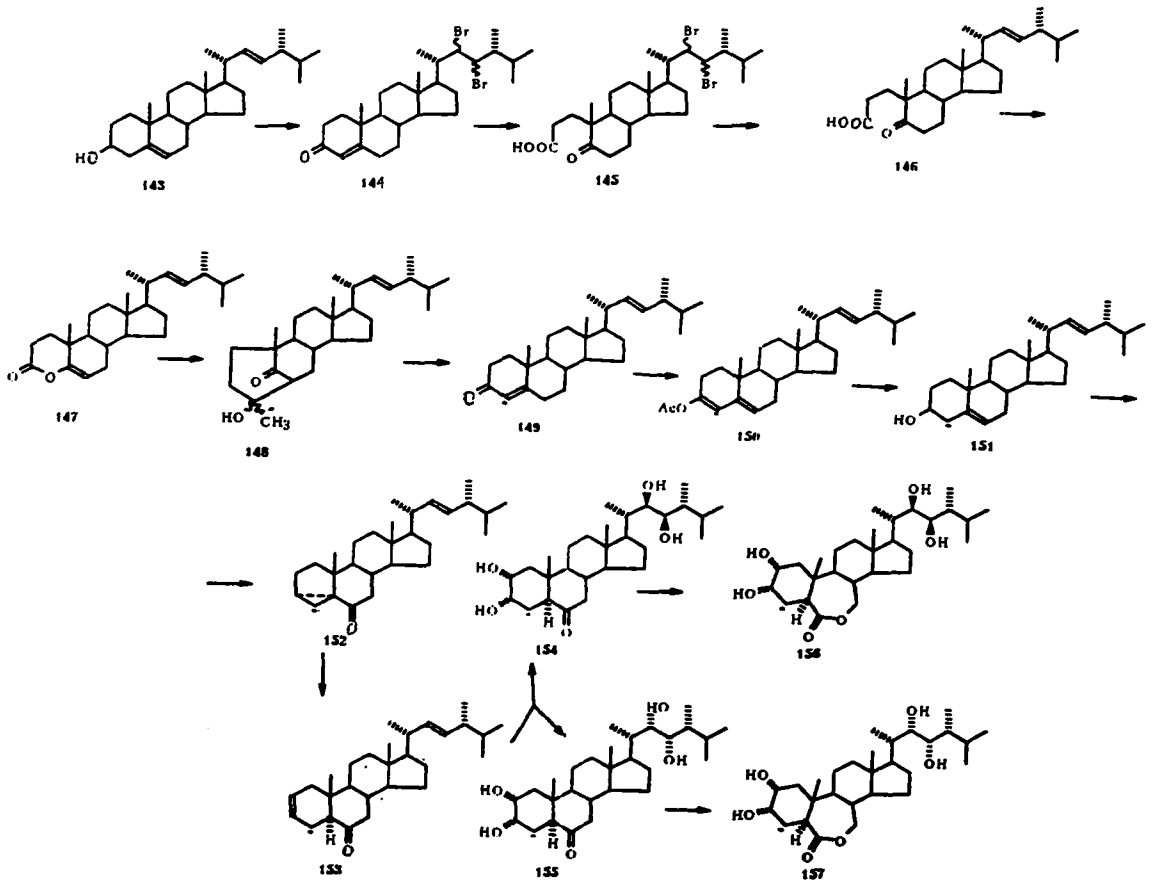
Two methods have been proposed for the synthesis of 24-epibrassinolide labeled with deuterium or tritium in positions 5 and 7 [52]. The first consists in the use of 24-epicastasterone tetraacetate (**137**) for these purposes. From this substance the deuterium derivative (**138b**) was obtained with a yield of about 95% by replacing hydrogen atoms with deuterium from heavy water ^2H_2O in dimethylformamide and triethylamine. As a result of Baeyer-Villiger oxidation with trifluoroperacetic acid, ketone (**138a**) was then converted with a yield of 84% into lactone (**139a**), the hydrolysis of the acetoxy groups in which with potassium carbonate in aqueous methanol gave the possibility of obtaining [5,7,7-$^2H_3$]-24-epibrassinolide (**140a**) with a yield of 94%. The tritium derivative (**138a**) was synthesized from the tetrahydroxyketone (**137**) analogously, and its lactonization with the formation of lactone (**139b**) and hydrolysis of the acetoxy groups enabled [5,7,7-$^3H_3$]-24-epibrassinolide (**140b**) to be obtained. In an alternative method of synthesizing labeled 24-epibrassinolide (**140b**), the replacement of hydrogen by tritium in 24-epicastasterone 2,3,22,23-diacetonide (**141**) was used. Subsequent Baeyer-Villiger lactonization of the [5,7,7-$^3H_3$]-6-ketone (**142b**) obtained in this way took place with the simultaneous hydrolysis of the protective isopropylidenedioxy groupings and led to the labeled 24-epibrassinolide (**140b**).

The synthesis of a number of brassinosteroids labeled with the isotope ^{14}C have started from brassicasterol [53]. The first stages of the synthesis had the aim of introducing a radioactive label into the brassicasterol molecule (**143**) with the formation of [4-^{14}C]-brassicasterol (**151**). The Oppenauer oxidation of brassicasterol (**143**) gave an 89% yield of the $\Delta^{4,22}$-3-ketone in which the 22-double bond was protected in the form of the dibromide with the formation of steroid (**144**) in a yield of 67%. Ozonolysis of the 4-double bond in compound (**144**) followed by oxidative cleavage of the resulting ozonide with hydrogen peroxide led to the seco-ketoacid (**145**), elimination of the dibromide grouping in which with the aid of zinc dust in acetic acid enabled the seco-acid (**146**) to be obtained with an overall yield from (**144**) of 49%. The interaction of the seco-acid (**146**) with acetic anhydride in the presence of sodium acetate gave the enol lactone (**147**) with a yield of more than 80%. The

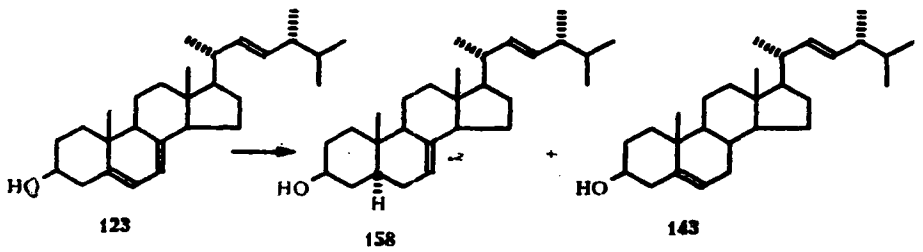


Grignard reaction of lactone (**147**) with the Grignard reagent obtained from labeled [^{14}C]-methyl iodide and magnesium formed the abeo-steroid (**148**) with a radiochemical yield of 76.1%. The treatment of compound (**148**) with sodium hydroxide provided the possibility of obtaining [4-^{14}C]-brassicasterone (**149**) with a yield of about 90%.

By reaction with isopropenyl acetate in the presence of *p*-toluenesulfonic acid, the enone (**149**) was converted into the enol acetate (**150**) the reduction of which with sodium tetrahydroborate led to [4-^{14}C]-brassicasterol (**151**). Then the labeled sterol (**151**) was subjected to mesylation, rearrangement of the mesylate into the 3α,5-cyclo-6β-alcohol and oxidation of the latter to the 3α,5-cyclo-6-ketone (**152**). Rearrangement of the 3α,5-cyclo-6-ketone (**152**) under the action of lithium bromide and camphorsulfonic acid in dimethylacetamide led to the formation of the labeled 2,22-dien-6-one (**153**) with a yield of 81%. The labeled [4-^{14}C]-24-epicastasterone (**154**) and its (22S,23S)-isomer (**155**) were synthesized with yields of 26.9 and 35.2%, respectively, by the hydroxylation of compound (**153**) with osmium tetroxide. Baeyer-Villiger lactonization of ketone (**154**) with trifluoroperacetic acid gave the required [4-^{14}C]-24-epibrassinolide (**156**). The labeled lactone (**157**) was synthesized from ketone (**155**) analogously. It must be mentioned that, for final purification, compounds (**156**) and (**157**) were converted into tetraacetates and these were subjected to the chromatographic elimination of impurities and were then hydrolyzed.

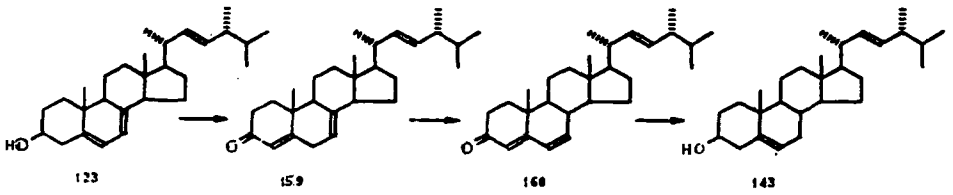


With the aim of developing a convenient method of obtaining brassicasterol (**143**), Kripach et al. [54] studied the reduction of ergosterol (**123**) with lithium under various conditions. As was to be expected, in the majority of cases the main reduction product was 5,6-dihydroergosterol (**158**). The best yield of brassicasterol was achieved in the reduction of ergosterol with lithium in a 1:1 mixture of hexametapol and diethylamine. Under these conditions, sterols (**158**) and (**143**) were formed in equal amounts.



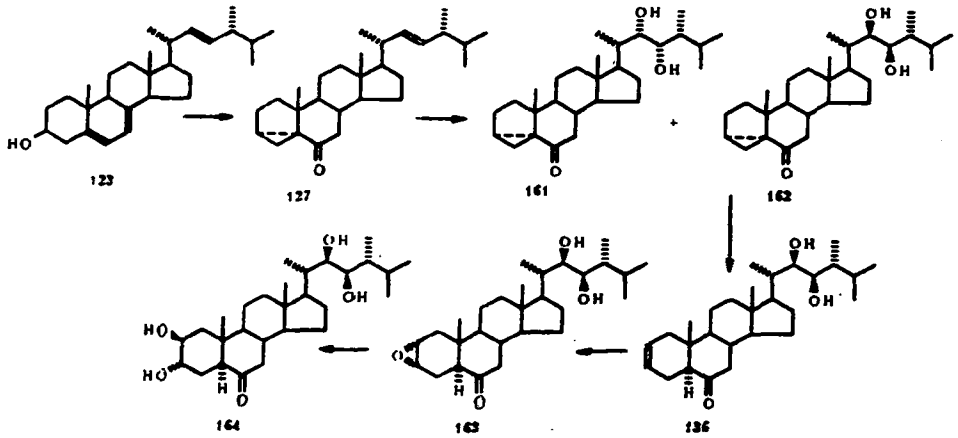
123 **158** **143**

Yet another method of synthesizing brassicasterol (**143**) from ergosterol (**123**) has recently been developed [55, 56]. The Oppenauer oxidation of ergosterol gave a 90% yield of the $\Delta^{4,7}$-3-ketone (**159**), the isomerization of which under the action of hydrochloric acid in methanol took place with the formation in 82% yield of the conjugated $\Delta^{4,6}$-3-ketone (**160**). Reduction of compound (**160**) with lithium in the presence of ammonium chloride in a mixture of liquid ammonia and tetrahydrofuran formed the required brassicasterol (**143**) with a yield of 74%. The overall yield of brassicasterol from ergosterol by this method amounted to 55%.



123 **159** **160** **143**

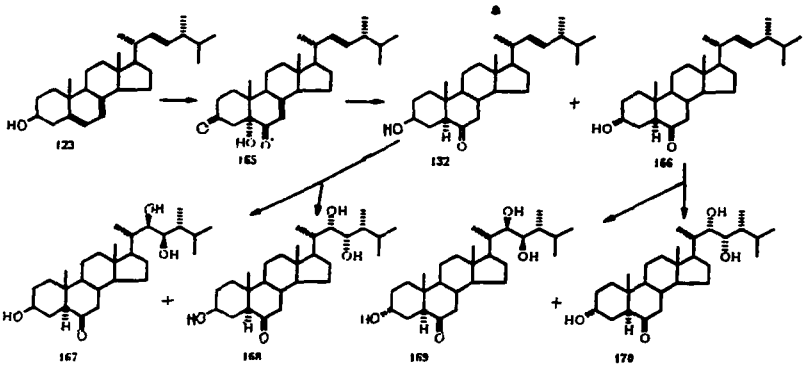
In a patent [57] it is proposed to use for the preparation of brassinosteroids not pure sterols but a mixture of them isolated from rapeseed or soybean oil. The scheme of synthesis here includes the main stages of converting 3β-hydroxy-Δ^5-sterols into 3α,5-cyclo-6-ketones, their subsequent conversion into Δ^2-6-ketones, hydroxylation, and Baeyer-Villiger lactonization. In particular, the (22S,23S)- isomer of 24-epibrassinolide has been obtained from soybean sterols by this method.



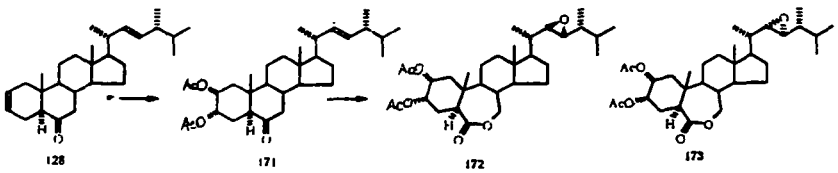
123 **127** **161** **162** **164** **163** **126**

2,24-Diepicastasterone (**164**) has been synthesized in eight stages with an overall yield of 9% from ergosterol (**123**) [58]. As a result of tosylation, solvolysis of the tosylate with the formation of a 3α,5-cyclo-6β-alcohol, oxidation of the 6β-hydroxy group, and Birch reduction of the 7-double bond, ergosterol was converted into the 6-ketone (**127**) with an overall

yield of 56%. Hydroxylation of the Δ^{22}-bond in compound (**127**) with N-methylmorpholine N-oxide and a catalytic amount of osmium tetroxide gave the (22S,23S)-22,23-diol (**161**) and the (22R,23R)-22,23-diol (**162**). Isomerization of the three-membered ring in steroid (**162**) formed the Δ^{2}-6-ketone (**136**) the epoxidation of which with trifluoroperacetic acid took place with the formation of the 2α,3α-epoxide (**163**). Acid hydrolysis of the epoxide ring in compound (**163**) enabled the required brassinosteroid (**164**) to be obtained. Analogously, the same authors succeeded in converting the (22S,23S)-22,23-dihydroxy-6-ketone (**161**) into the (22S,23S)- isomer of 2,24-diepicastasterone with an overall yield of 12%, calculated on the ergosterol.

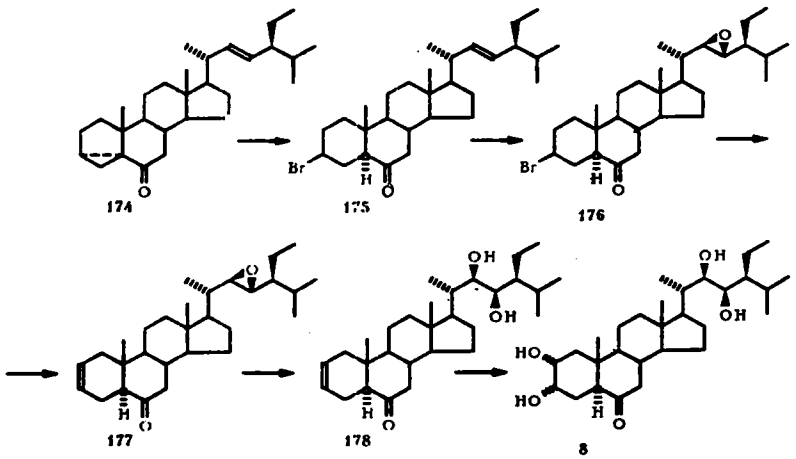


We have developed a synthesis of brassinosteroids from ergosterol (**123**) via the hydroxyketone (**165**) formed by its Jones oxidation [59]. With the aim of saturating the 7-double bond and hydrogenolizing the 5α-hydroxy group, the hydroxydiketone (**165**) was first subjected to Birch reduction with lithium in a mixture of liquid ammonia and hexametapol. The main products of this reaction were the 3β-hydroxy-6-ketone (**132**) and the 3α-hydroxy-6-ketone (**166**), isolated with yields of 23 and 12%, respectively. By the Criegee *cis*-hydroxylation of the Δ^{22}-steroid (**132**) under the action of an equimolar amount of osmium tetroxide in pyridine, 24-epiteasterone (**167**) and its (22S,23S)- isomer (**168**) were obtained with yields of 26 and 65% [59]. The analogous transformation of the Δ^{22}-steroid (**166**) led to the formation of 24-epityphasterol (**169**) and (22S,23S,24R)-typhasterol (**170**) with yields of 29 and 49%, respectively [60].



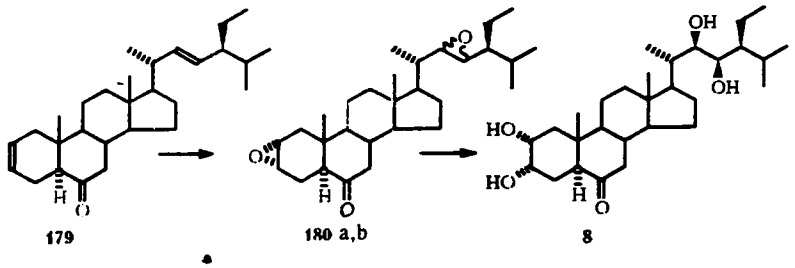
Judging from patent information [61, 62], analogs of the brassinosteroids containing, in addition to the lactone ring *B*, also a 2α,3α-diacetoxy or a 2α,3α-isopropylidenedioxy group and a 22,23-epoxide ring are active plant growth regulators. 2,22-Diene-6-ketosteroids are used as the starting materials for the synthesis of such substances. In particular, on the selective *cis*-hydroxylation of the sterically more accessible 2-double bond by N-methylmorpholine N-oxide and a catalytic amount of osmium tetroxide, the 2,22-diene-6-ketone (**128**) gave the corresponding 2α,3α-diol, which was then converted into the 2α,3α-diacetate (**171**). Interaction of the enone (**171**) with *m*-chloroperbenzoic acid took place with the simultaneous epoxidation of the 22-double bond and the lactonization of ring *B*. As a result of this reaction the epoxylactones (**172**) and (**173**) were obtained.

We have performed the synthesis of (24S)-24-ethylbrassinone (**8**) from stigmasterol [63-65]. Stigmasterol was first converted with a yield of 80% into the 3α,5-cyclo-6-ketone (**174**). Opening the three-membered ring in compound (**174**) with hydrobromic acid enabled the 3β-bromo-6-ketone (**175**) to be obtained with a yield of more than 90%. Epoxidation of the Δ^{22}-steroid (**175**) with *m*-chloroperbenzoic acid formed the (22R,23R)-22,23-epoxide (**176**) and its (22S,23S)- isomer with yields of 51 and 34%, respectively. The epoxyenone (**177**) was obtained with a yield of 70% by the dehydrobromination of the bromoepoxyketone (**176**) with lithium carbonate in dimethylformamide. The (22R,23R)-22,23-diol (**178**) was synthesized from epoxide (**177**) in an overall yield of 65%, without isolation of the intermediate products, by the opening of the epoxide ring with hydrobromic acid, acetylation of the resulting bromohydrins with acetyl chloride, nucleophilic replacement of the bromine atoms by acetoxy groups under the action of potassium acetate, and, finally, hydrolysis of the acetoxy groups with potassium hydroxide in methanol. Hydroxylation of the Δ^{2}-bond in steroid (**178**) with osmium tetroxide in pyridine led in quantitative yield to (24S)-24-ethylbrassinone (**8**).

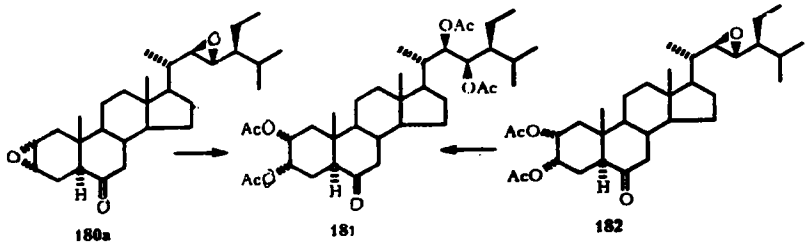


Methods have recently been developed for converting the 2,22-dien-6-one (**179**) obtained from stigmasterol into (24S)-24-ethylbrassinone (**8**) without the use of expensive osmium tetroxide [66, 67]. Thus, epoxidation of the dienone (**179**) with *m*-chloroperbenzoic acid yielded the (22R,23R)-2α,3α,22,23-diepoxide (**180a**) and its (22S,23S)-isomer (**180b**) in a ratio of 1.6:1 [66].

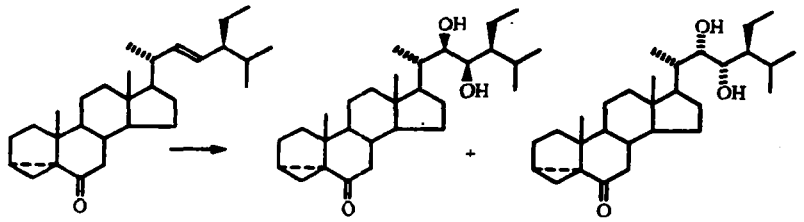
Without separation, compounds (**180a** and **b**) were then subjected to an epoxide-ring-opening reaction under the action of 48% hydrobromic acid in a mixture of acetic acid and chloroform. The resulting bromohydrins were acetylated with acetyl chloride and then the bromine atoms were replaced by acetoxy groups with potassium acetate in aqueous acetic acid, and the tetraacetates formed were hydrolyzed with a methanolic solution of potassium hydroxide. As a result of these transformations, (24S)-24-ethylbrassinone (**8**) was obtained with an overall yield of 14% [66].



There is also a report on the conversion of the (22R,23R)-2α,3α,22,23-diepoxide (**180a**), obtained by the epoxidation of dienone (**179**) with perbenzoic acid [67]. Interaction of the diepoxide (**180a**) with hydrobromic acid in acetic acid followed by replacement of the bromine atoms under the action of aqueous acetic acid gave (24S)-24-ethylbrassinone tetraacetate (**181**). The analogous transformation of the (22R,23R)-22,23-epoxide (**182**) also led to (**181**).



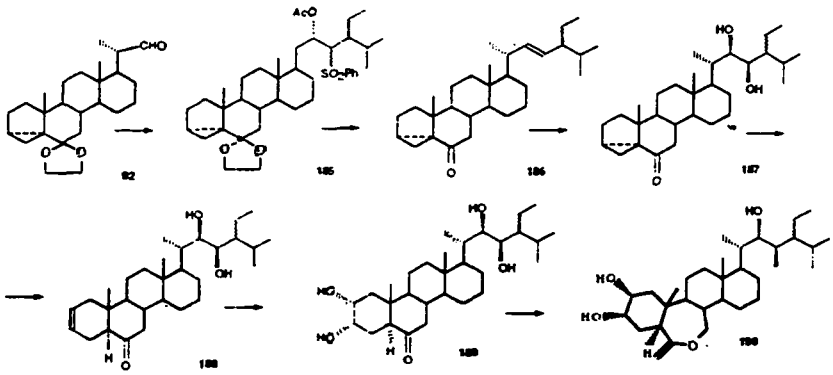
It is known [1, 3] that the hydroxylation of Δ^{22}-stigmastenes with osmium tetroxide takes place mainly with the formation of (22S,23S)-22,23-diols. At the same time, natural brassinosteroids are (22R,23R)-22,23-diols. Consequently, although 2α,3α-diols are also readily obtained by the hydroxylation of a Δ^{2}-bond with osmium tetroxide, this method is unsuitable for obtaining (22R,23R)-2α,3α,22,23-tetraols from $\Delta^{2,22}$-stigmastadienes. In this connection, the predominant formation of (22R,23R)-22,23-diols on the hydroxylation of Δ^{22}-stigmastenes with osmium tetroxide in the presence of dihydroquinidin-9-yl- phenanthren-9-yl ether discovered by Brosa et al. [68] is of interest. Under the conditions given, (24S)-24-ethylbrassinone (**8**) was obtained in good yield from the 2,22-dien-6-one (**179**).



174 183 184

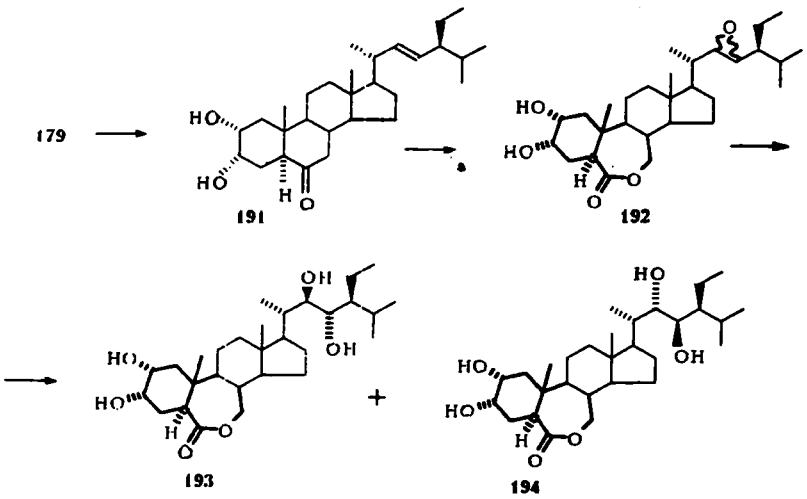
Later [69, 70], a special investigation was made of the stereochemistry of the *cis*-hydroxylation of the 22-double bond in steroids (**127**) and (**174**) by osmium tetroxide in the presence of chiral ligands. It was established that the hydroxylation of the ergostane derivative (**127**), which has a (24R)-24-methyl group, with osmium tetroxide in the presence of dihydroquinidine *p*-chlorobenzoate leads to the formation in a total yield of 94% of the (22R,23R)-22,23-diol (**162**) and the (22S,23S)-22,23-diol (**161**) in a ratio of 8:1. At the same time, the analogous reaction of the stigmastenone (**174**), which has a (24S)-24-ethyl group, permits the formation of the (22R,23)-22,23-diol (**183**) and the (22S,23S)-22,23-diol (**184**) in a total yield of 93% at a (**183**):(**184**) ratio of only 1.5:1. Far better results are obtained in the *cis*-hydroxylation of the stigmastenone (**174**) in the presence of dihydroquinidin-9-yl phenanthren-9-yl ether. In this case, the diols (**183**) and (**184**) are formed in a ratio of 8:1, which, in principle, confirms the analogous results obtained by Brosa et al [68].

Some improvements in the synthesis of 28-homobrassinolide (7) from stigmasterol are also given in [71]. These have enabled the overall yield of 28-homobrassinolide to be brought up to 21%.

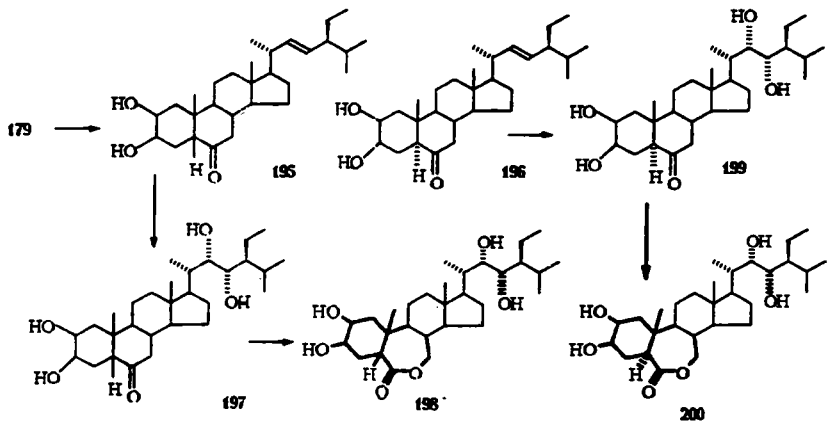


In the synthesis of (24R)-28-homobrassinolide (**190**), a traditional scheme of constructing the side-chain via sulfones was used [72]. Alkylation of the aldehyde (**92**), obtained in five stages from stigmasterol, with the anion of 2-ethyl-3-methylbutyl phenyl sulfone followed by acetylation of the 22-alcohol formed with acetic anhydride enabled the acetoxysulfone (**185**) to be obtained in the form of a mixture of all the possible isomers at C-22, C-23, and C-24. Reduction of compound (**185**) with sodium amalgam and hydrolysis of the protective grouping in ring *B* with aqueous acetic acid led to the Δ^{22}-6-ketosteroid (**186**) with an overall yield of about 70%. The (22R,23R)-22,23-dihydroxy-6-ketone (**187**) was synthesized from (**186**) by the Criegee *cis*-hydroxylation of the Δ^{22}-double bond with osmium tetroxide, followed by separation of the isomers. Isomerization of the three-membered ring in steroid (**187**) with pyridinium hydrobromide took place with the formation in an 80% yield of the Δ^{2}-6-ketone (**188**) the hydroxylation of which with osmium tetroxide gave a quantitative yield of (24R)-24-ethylbrassinone (**189**). Before lactonization, the hydroxy groups in compound (**189**) were acetylated. The subsequent oxidation with trifluoroperacetic acid of the tetraacetoxyketone so formed and hydrolysis under the action of potassium hydroxide of the acetoxy groups in the lactone obtained led to the desired (24R)-28-homobrassinolide (**190**) with an overall yield of 42.5%, calculated on the ketone (**189**).

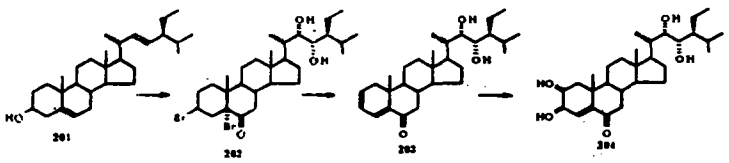
A special investigation [73] has been devoted to the synthesis of isomers of 28-homobrassinolide containing *trans*-22,23-diol groupings in the side-chain. The *cis*-hydroxylation of the Δ^{2}-bond in dienone (**179**) with osmium tetroxide and N-methylmorpholine N-oxide gave the 2α,3α-dihydroxy-6-ketone (**191**) with a yield of 77%. The interaction of compound (**191**) with *m*-chloroperbenzoic acid for six days led with a yield of 70% to the epoxylactone (**192**) in the form of a mixture of (22R,23R)- and (22S,23S)-isomers. Hydrolysis of the epoxide rings in steroid (**192**) with a solution of perchloric acid in tetrahydrofuran for two days led to the formation of the necessary tetrahydroxylactones (**193**) and (**194**) with yields of 40%.



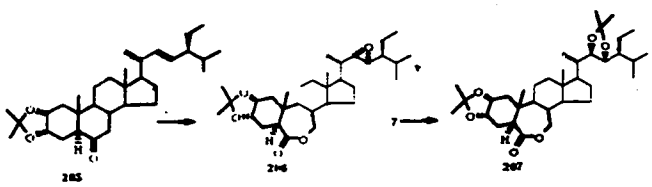
The synthesis of structural analogs of 28-homobrassinolide that are of interest as antiecdysteroids has been achieved, starting from stigmasterol [74]. According to the scheme of synthesis developed, stigmasterol was converted in the usual way via 3α,5-cyclosteroids into the 2,22-dien-6-one (**179**). Hydroxylation of the sterically more accessible 2-double bond in compound (**179**) with silver acetate and iodine in aqueous acetic acid by the Woodward reaction, followed by hydrolysis of the acetoxy group in the hydroxylation product, accompanied by partial epimerization at C-5, led to the 2β,3β-diols (**195**) and (**196**) with yields of 34 and 11%, respectively. Hydroxylation of the Δ^{22}-bond in steroid (**195**) with osmium tetroxide and N-methylmorpholine N-oxide gave a 65% yield of the (22S,23S)-tetrahydroxyketone (**197**), which was then oxidized with trifluoroperacetic acid to the tetrahydroxylactone (**198**) with a yield of 63%. Analogously, by the Criegee reaction, compound (**196**) was converted with a yield of 63% into the tetrahydroxyketone (**199**), the Baeyer-Villiger lactonization of which under the same conditions as for steroid (**197**) gave the tetrahydroxylactone (**200**) with a yield of 66%.



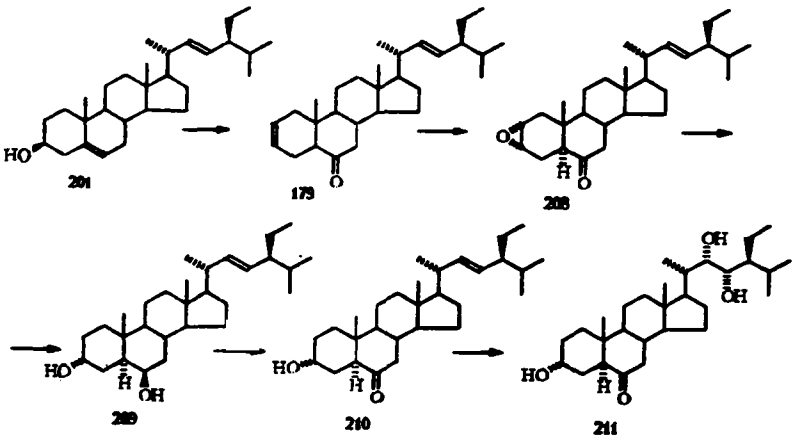
The tetrahydroxyketone (**204**), which possesses a high phytostimulating action, has been synthesized from stigmasterol (**201**) [75]. Stigmasterol was first converted in the usual way into the 3α,5-cyclo-6-ketone (**174**) the hydroxylation of which with osmium tetroxide in pyridine enabled the (22S,23S)-22,23-diol (**184**) to be obtained with a yield of 91%. The bromination of compound (**184**) gave an 87% yield of the 3β,5α-dibromo-6-ketone (**202**), and the dehydrobromination of the latter with lithium carbonate in dimethylformamide gave the 2,4-dien-6-one (**203**) with a yield of 73%. On the *cis*-hydroxylation of the diene grouping in compound (**203**) by the Woodward reaction with silver acetate and iodine in aqueous acetic acid, the corresponding 2α,3α-diol 3-acetate was formed with a yield of 55%, and the hydrolysis of the acetoxy group in this with potassium hydroxide in methanol gave an 80% yield of the required brassinosteroid (**204**). It is interesting to note that the 22,23-dihydroxy-6-ketone (**184**) also possesses considerable activity as a plant growth stimulator [76].



The brassinosteroid 2,3-acetonides (**206**) and (**207**), which possess a prolonged action as plant growth regulators, have been patented [77]. The epoxylactone (**206**) is obtained by the interaction of the enol (**205**) with *m*-chloroperbenzoic acid for two weeks at room temperature. In its turn, the diacetonide (**207**) is formed in the reaction of 28-homobrassinolide (**7**) with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid.

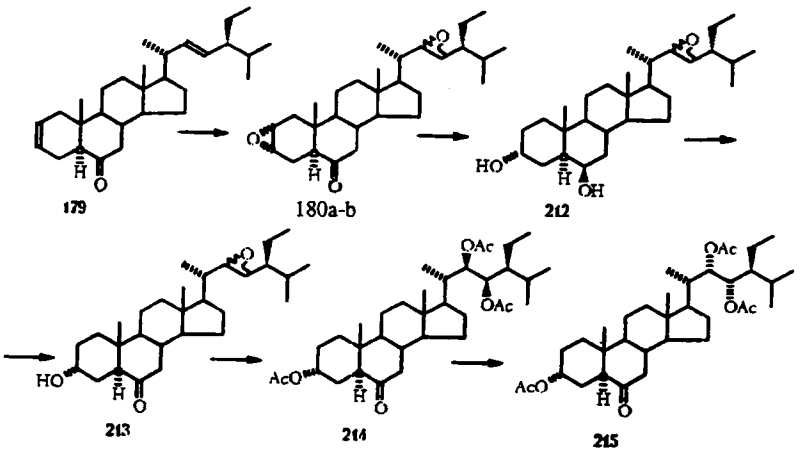


We have developed a new scheme for the synthesis of 3α-hydroxy-6-ketobrassinosteroids from 3β-hydroxy-Δ^5-steroids and, in particular, from stigmasterol [60]. Thus, the 3α,5-cyclo-6-ketosteroid (**174**) has been obtained by the solvolysis of stigmasterol tosylate (**201**) and the Jones oxidation of the resulting 3α,5-cyclo-6β-hydroxysteroid. The opening of the three-membered ring in compound (**174**) with hydrobromic acid formed the 3β-bromo-6-ketone (**175**) the dehydrobromination of which with lithium carbonate and bromide in dimethylformamide led to the corresponding Δ^2-6-ketone (**179**). Monoepoxidation of the 2,22-dien-6-one (**179**) with the calculated amount of *m*-chloroperbenzoic acid gave a 54% yield of the 2α,3α-epoxide (**208**). The selective epoxidation of the Δ^2-bond in this case is explained by its greater steric accessibility. In the interaction of the 2α,3α-epoxy-6-ketosteroid (**208**) with lithium tetrahydroaluminate, reduction took place both of the 2α,3α-epoxide ring and of the 6-keto group, the main reaction product, isolated with a yield of 59%, being the 3,6-diol (**209**). The selective Jones oxidation of the 6β-hydroxy group in steroid (**209**) gave a 52% yield of the 3α-hydroxy-6-ketone (**210**), and (22S,23S)-28-homotyphasterone (**211**) was synthesized with a yield of 97% by the *cis*-hydroxylation of the Δ^{22}-steroid (**210**).



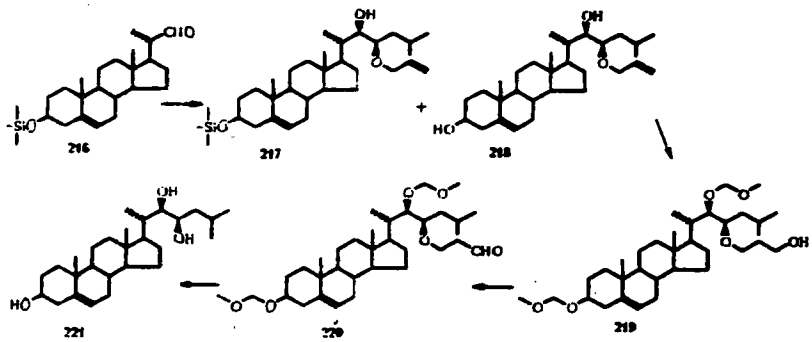
Later [78], we synthesized the triacetates of 28-homotyphasterol (**214**) and of its (22S,23S)-isomer (**215**) by the same scheme. Epoxidation of the dienone (**179**) with an excess of *m*-chloroperbenzoic acid gave a yield of about 70% of the 2α,3α,22,23-diepoxide (**180a,b**) in the form of a mixture of the (22R,23R)- and (22S,23S)-isomers. The main product of the lithium tetrahydroaluminate reduction of the diepoxide (**180a,b**) was the 3α,6β-dihydroxy-22,23-epoxysteroid (**212**), isolated with a yield of 32%. The 6-ketone (**213**) was obtained from compound (**212**) with a yield of 32% by the selective Jones oxidation of the 6β-hydroxy group. To synthesize *cis*-22,23-diols from 22,23-epoxides we have used a procedure including their opening with hydrogen bromide, acetylation of the resulting *trans*-bromohydrins, and nucleophilic replacement of the bromine atoms by acetoxy groups, taking place with reversal of the configuration. The application of this sequence to the 22,23-epoxy-

steroid (**213**) enabled us to obtain the (22R,23R)-3α,22,23-triacetoxy-6-ketone (**214**) and its (22S,23S)-isomer (**215**) with yields of 26 and 23%, respectively.

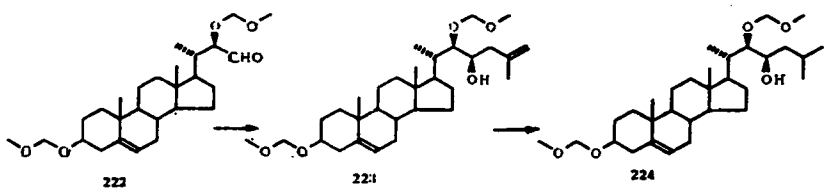


Furuta and Yamamoto [79] have described the synthesis of the 3β,22,23-triol (**221**) — an important intermediate in the production of brassinone and 28-norbrassinone. Alkylation of the 22-aldehyde (**216**) with (1-allyloxy-3-methylbutyl)tributyllead in the presence of titanium tetrachloride formed the steroids (**217**) and (**218**), which were isolated with yields of 25 and 11%, respectively. The free hydroxy groups in compound (**218**) were protected in the form of methoxymethyl ethers.

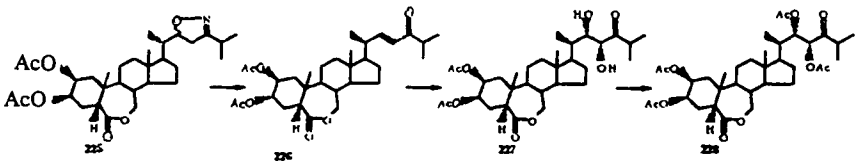
The product of this reaction was then subjected to hydroboronation with thexylborane and to oxidation by alkaline hydrogen peroxide. As the result of these reactions, protected triol (**219**) was obtained, and its oxidation with pyridinium chlorochromate formed the aldehdye (**220**). The triol (**221**) was synthesized from compound (**220**) by the elimination of the protective groups through the successive action first of a solution of potassium carbonate and then of a methanolic solution of hydrogen chloride.



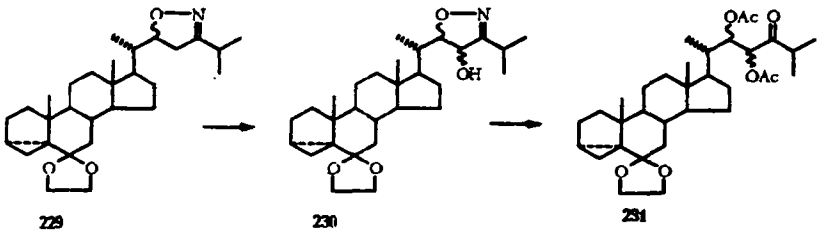
A method has been developed for forming a cholestane side-chain containing a (22R,23R)-diol function [80]. The unsaturated (22R,23R)-22,23-diol (**223**) was obtained as the main product of the alkylation of the protected 22-hydroxy-23-aldehyde (**222**) with isobutene in the presence of tin tetrachloride. The catalytic hydrogenation of the 25(26)-double bond in compound (**223**) then led to the protected (22R,23R)-22,23-dihydroxycholesterol (**224**).



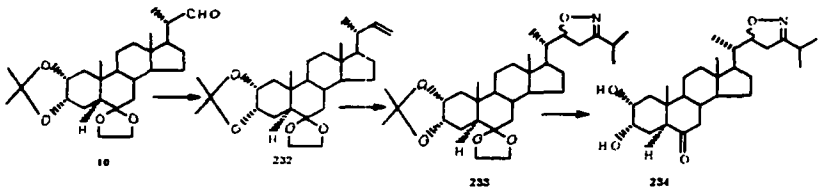
The reductive cleavage of the isoxazoline (**225**) followed by dehydration of the 22-hydroxy-24-ketone formed gave an 81% yield of the Δ^{22}-24-ketone (**226**) [81]. Hydroxylation of the 22-double bond in (**226**) with osmium tetroxide led in 66% yield to the 22,23-dihydroxyketone (**227**), which was then converted into the tetraacetate (**228**) in the usual way. The authors report that the 22,23-dihydroxy-24-ketosteroid (**227**) is unstable and changes in the course of 4-5 h into a 22-aldehyde as a result of the cleavage of the 22(23) bond.



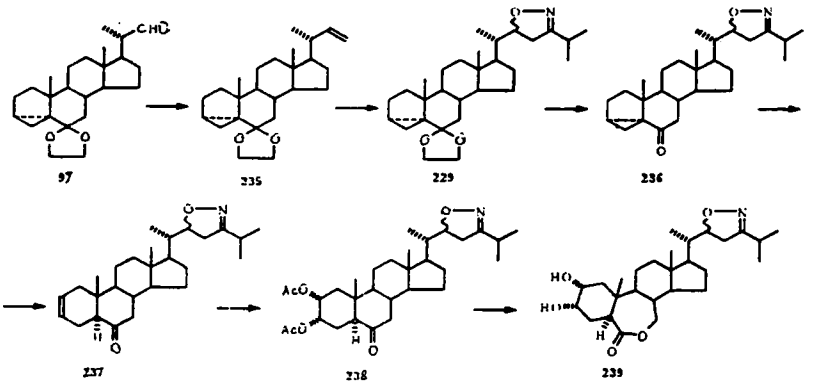
The possibility of obtaining derivatives of 22,23-dihydroxy-24-ketosteroids from the isoxazoline (**229**) has been demonstrated [82]. In this work, an anion was obtained from steroid (**229**), taken in the form of a mixture of the (22R)- and (23S)-isomers, by its reaction with lithium diisopropylamide, and the interaction of the anion with trimethyl borate followed by the oxidation of the resulting 23-borate with *tert*-butyl hydroperoxide led to the 23-hydroxy derivative (**230**) with an overall yield of 80%. Reductive cleavage of the isoxazoline ring in compound (**230**) with Raney nickel in an acid medium, followed by acetylation, gave the 22,23-diacetoxy-24-ketone (**231**) in the form of a mixture of *trans*-22,23-isomers.



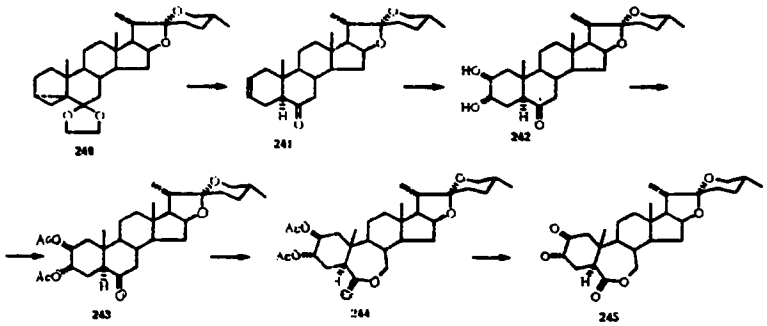
The synthesis of structural analogs of brassinosteroids containing an isoxazoline ring in the side-chain has been described in [83]. Here, by the Wittig reaction, the 22-aldehyde (**10**) was converted with a yield of 80% into the Δ^{22}-steroid (**232**). Reaction of the latter with isobutyronitrile oxide led with a yield of 80% to the isoxazoline (**233**) in the form of a mixture of (22R)- and (22S)-isomers in a ratio of 3:2. Hydrolysis of the protective groupings in compound (**233**) with dilute acetic acid enabled the 2α,3α-dihydroxy-6-ketone (**234**) to be synthesized in quantitative yield.



Another approach to the synthesis of brassinosteroid analogs with an isoxazoline ring, described in [83], consists in the initial construction of the side-chain, starting from the 22-aldehyde (**92**), followed by the introduction of the necessary functional groups into rings *A* and *B*. First, the aldehyde (**92**) was converted by the Wittig reaction into the Δ^{22}-steroid (**235**). In the following stage the isoxazoline (**229**) in the form of a 4:1 mixture of (22R)- and (22S)-isomers was synthesized with a yield of 75% by the cycloaddition of isobutyronitrile oxide to the Δ^{22}-steroid (**235**). After elimination of the protective grouping from the 6-keto group in compound (**229**), the 3α,5-cyclo-6-ketone (**236**) was obtained, and this was then subjected to isomerization under the action of pyridinium hydrobromide in dimethylformamide to give the Δ^{2}-6-ketone (**237**) with a yield of 80%. On the *cis*-hydroxylation of the Δ^{2}-bond in steroid (**237**) with a catalytic amount of osmium tetroxide and N-methylmorpholine N-oxide by the Criegee reaction, the 2α,3α-dihydroxy-6-ketone (**234**) was obtained, and this was then converted in the usual way into the diacetate (**238**) with a yield of 96%. The Baeyer-Villiger oxidation of compound (**238**) with trifluoroperacetic acid led with the high yield of 85% to the corresponding diacetoxylactone, hydrolysis of the acetoxy group in which with potassium hydroxide in methanol enabled the 2α,3α-dihydroxylactone (**239**) to be obtained with a yield of 90%.

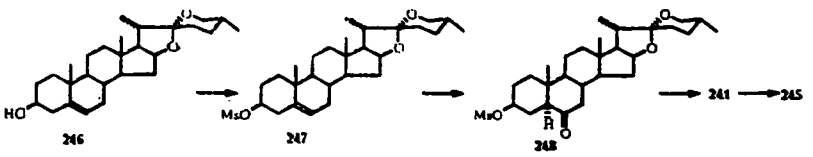


A number of investigations have been devoted to obtaining structural analogs of the brassinosteroids from steroid sapogenins. Thus, in the synthesis described in [84], diosgenin (**246**) was converted in the usual way into the 3α,5-cyclo-6-ketone (**240**), the three-membered ring in which was isomerized under the action of pyridinium hydrobromide with the formation of the Δ^2-6-ketone (**241**) in a yield of 75%. Hydroxylation of the Δ^2-bond in compound (**241**) with N-methylmorpholine N-oxide and a catalytic amount of osmium tetroxide permitted the 2α,3α-diol (**242**) to be obtained with a yield of about 70%, and this was then acetylated with acetic anhydride in pyridine, giving the 2α,3α-diacetoxy-6-ketone (**243**) with a yield of 91%. The 2α,3α-diacetoxylactone (**244**) was synthesized with a yield of 75% by the Baeyer-Villiger lactonization of compound (**243**), and the hydrolysis of its acetoxy groups led with a yield of 80% to the desired compound (**245**).

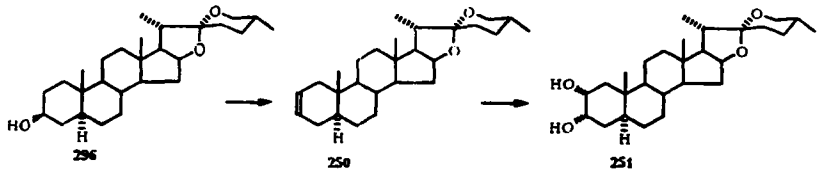


Roughly the same synthesis of brassinosteroid analogs from diosgenin, although with somewhat differing initial stages, has been described by Tian [85]. According to the selected scheme of synthesis from diosgenin (**246**), the mesylate (**247**) was obtained with a yield of 90% by reaction with methanesulfonyl chloride in pyridine. The hydroboration–oxidation of the 5(6)-double bond under the action of a complex of diborane with dimethyl sulfide and then of alkaline hydrogen peroxide followed by oxidation of the resulting 6α-alcohol with pyridinium dichromate gave the 3β-mesyloxy-6-ketone (**248**) with an overall yield of 84%.

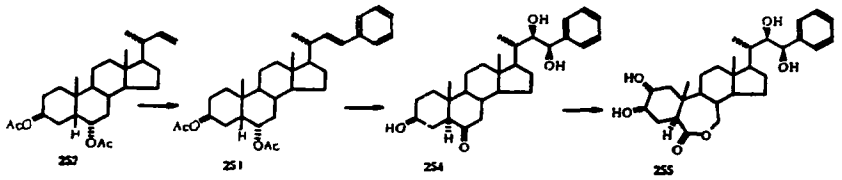
The Δ^2-6-ketone (**241**) was synthesized in a yield of 72% by an elimination reaction in which steroid (**248**) was boiled in dimethylformamide in the presence of lithium bromide. In this reaction the formation of the corresponding 3α,5-cyclo-6-ketone as a by-product was observed. The further transformations of the Δ^2-6-ketone (**241**) into the final product (**245**) were, in principle, analogous to those described previously by other workers [84]. They included hydroxylation of the 2-double bond by a catalytic amount of osmium tetroxide and N-methylmorpholine N-oxide, leading with a yield of 96% to the 2α,3α-diol (**242**), acetylation of the latter to the 2α,3α-diacetate (**243**), lactonization with trifluoroperacetic acid to form the lactone (**244**) and its regiomer, and, finally, hydrolysis of the acetoxy groups with caustic soda in methanol to the final dihydroxylactone (**245**).



The synthesis of a structural analog of the brassinosteroids from tigogenin (**249**) has been carried out by Coll et al. [86]. In this, tigogenin was converted into the corresponding tosylate, which then, by an elimination reaction, gave the Δ^2-steroid (**250**). Hydroxylation of the 2-double bond in compound (**250**) with osmium tetroxide led to the formation of the required 2α,3α-dihydroxyspirostan (**251**).

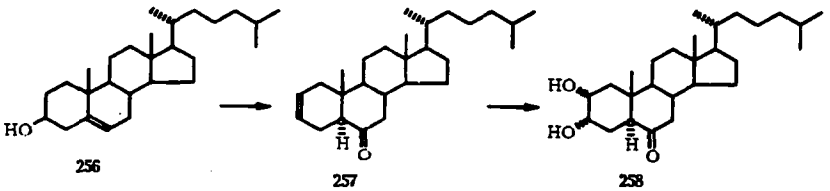


As well as steroid saponins, the steroid alkaloid solanidine has found use as the starting compound for the synthesis of structural analogs of the brassinosteroids. This enabled Quyen et al. [87] to obtain a number of compounds, in addition to rings *E* and *F* corresponding to solanidine, the functional groups in rings *A* and *B* characteristic for brassinosteroids.

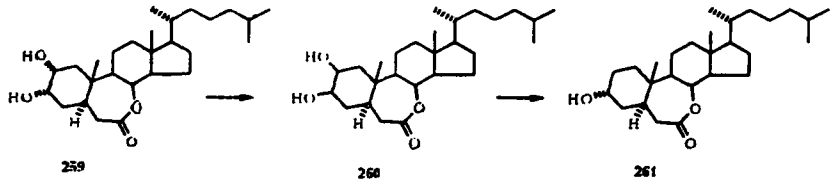


A synthesis of 23-phenylbrassinosteroids of types (**254**) and (**255**) from the Δ^{22}-steroid (252), obtained from hyodeoxycholic acid, has been achieved [88]. Compound (**253**) was obtained with a yield of 71% by the Heck reaction of the olefin (**252**) with iodobenzene in the presence of palladium(II) acetate and triphenylphosphine. Subsequent transformations in rings *A* and *B* and hydroxylation of the 22-double bond with osmium tetroxide in the presence of dihydroquinidine *p*-chlorobenzoate permitted the synthesis of the (22R,23R)-3α,22,23-trihydroxy-6-ketone (**254**), which was then converted by the usual method into the 2α,3α,22,23-tetrahydroxylactone (**255**) with an overall yield of 10% from (**252**).

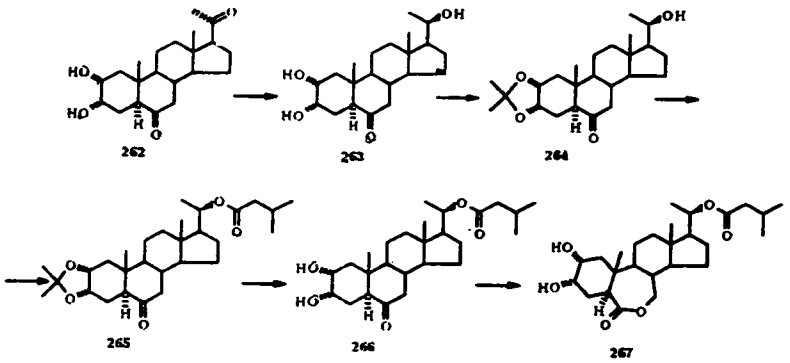
Syntheses of the 2α,3α-dihydroxy-6-ketosteroid (**258**), which may be regarded as a structural analog of brassinone, from cholesterol (**256**) via the Δ^2-ketone (**257**) have been described [89, 90]. It must be mentioned that compound (**258**) as a model aroused the interest of various groups of researchers even in the early stages of the study of the brassinosteroids. Therefore, the results obtained in [89, 90] were, in general, a repetition of those already known. At the same time, some improvements can also be seen in these syntheses. In particular, in [90] a promising, in our view, method for the introduction of a 2α,3α-diol group was developed which does not involve the use of the expensive and toxic osmium tetroxide. Thus, it was reported that the 2α,3α-dihydroxy-6-ketosteroid (**258**) can be obtained in a yield of 89% by the reaction of the Δ^2-6-ketone (**257**) with the calculated amount of potassium permanganate in acetone in the presence of polyethyleneglycol-800.



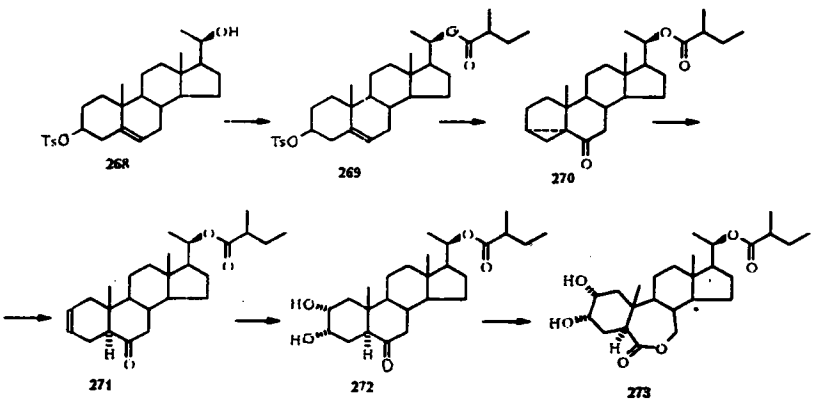
Kohout [91] has described the synthesis of a number of brassinosteroid analogs with a 7-oxo-7α-oxa grouping in ring *B* and a cholestane side-chain without functional groups. It was found that compounds (**259**) and (**260**) possess a low activity as plant growth stimulators. Among the compounds synthesized, the most active phytostimulator is the 3α,4α-dihydroxylactone (**261**).



The synthesis of brassinosteroid analogs that are esters of (20R)-20-hydroxypregnane has been described in [92]. Selective reduction with tris-*tert*-butoxyaluminum hydride of the 6,20-diketone (**262**) gave a 61% yield of the (20R)-2α,3α,20-trihydroxy-6-ketone (**263**), in which the 2α,3α-diol grouping was then protected as an acetonide with the formation of derivative (**264**). Acylation of the 20-hydroxy group of steroid (**264**) with 3-methylbutanoyl chloride in pyridine enabled the ester (**265**) to be obtained with a yield of 50%, and hydrolysis of the 2α,3α-isopropylidenedioxy grouping then led to the dihydroxylactone (**266**) with a yield of 75%. The Baeyer-Villiger oxidation of ketosteroid (**266**) with trifluoroperacetic acid gave a 34% yield of the dihydroxylactone (**267**). Acylation of the 20-alcohol (**264**) with 2-methylbutanoyl chloride gave a 16% yield of the corresponding ester, acid hydrolysis of the acetonide grouping in which enabled the dihydroxylactone (**272**) to be obtained with a yield of 75%, and this was then converted with a yield of 41% into the lactone (**273**).

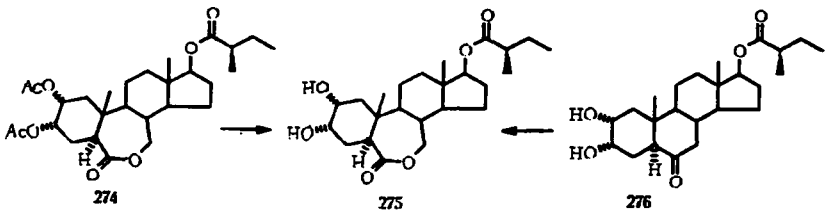


Furthermore, in [92] yet another method of synthesizing the 2α,3α-dihydroxyketone (**272**) is described, from (20R)-pregn-5-ene-3,20-diol 3-tosylate (**268**). The ester (**269**) was obtained by acylating the 20-hydroxy group in (**268**) with 2-methylbutanoyl chloride, and the solvolysis of the 3β-tosyloxy group in this under the action of potassium carbonate in aqueous acetone led to the formation with a yield of 96% of the corresponding 3α,5-cyclo-6β-alcohol, which was then subjected to Jones oxidation to give a 90% yield of the 3α,5-cyclo-6-ketone (**270**). Isomerization of compound (**270**) under the action of pyridinium tosylate in dimethylacetamide took place with the formation of a 73% yield of the Δ^2-6-ketone (**271**), hydroxylation of the double bond in which with osmium tetroxide gave the required brassinosteroid (**272**) practically quantitatively.



The dihydroxylactone (**276**) has been patented as plant growth stimulator [93]. The scheme proposed for its synthesis includes in the final stage hydrolysis of the protective groupings (2α,3α-diacetoxy or 2,3-acetonide) in an alkaline or acid medium, respectively. For example, when the diacetoxylactone (**274**) was treated with potassium carbonate in aqueous methanol the required steroid (**275**) was obtained with a yield of less than 50%. In addition, it has been reported [49] that lactone (**275**) can be obtained by the direct Baeyer-Villiger oxidation with trifluoroperacetic acid of the 2α,3α-dihydroxy-6-lactone (**276**).

Takatsuto and Shimazaki [94] have studied the production from 3β-hydroxy-6-ketosteroids of the corresponding Δ^2-6-ketones, which are important intermediates in the synthesis of the brassinosteroids. They established that the best results can be obtained by performing the elimination reaction of the initial 3β-tosylates under the action of lithium bromide in dimethylformamide in the presence of pyridine or sodium acetate.



274 275 276

There is no doubt that attention is merited by recently published attempts to develop methods for the total synthesis of the brassinosteroids [95-97]. However, since they have not yet led to the creation of any interesting structures whatever, we shall not consider them in detail here.

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