Chemistry of Natural Compounds, Vol. 38, No. 2, 2002

PROGRESS IN THE CHEMICAL SYNTHESIS OF BRASSINOSTEROIDS

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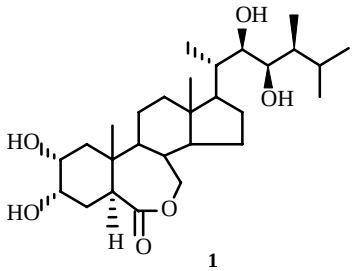
UDC 547.92

Studies on the chemical synthesis of brassinosteroid phytohormones that were published in 1995-2000 are reviewed.

Key words: brassinosteroids, synthesis.

Brassinosteroids include natural and synthetic polyhydroxysteroids with a common chemical structure and biological activity [1]. This group of compounds is named after the first representative brassinolide (**1**), which was isolated first from rape pollen. Two typical brassinosteroids are castasterone (**2**) and 24-epibrassinolide (**3**). Brassinosteroids in plants act as phytohormones and regulate various vital processes [2]. Certain brassinosteroids are exceedingly active plant-growth stimulators. Therefore, they are promising for increasing the harvest of agricultural crops [3]. 24-Epibrassinolide is still used in agriculture for this purpose [4].



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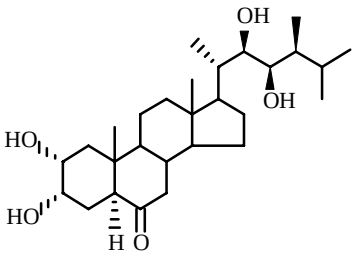

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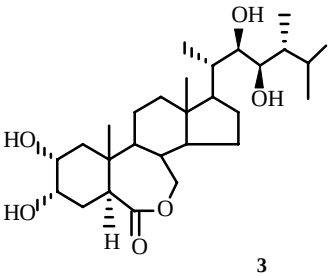

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Chemical synthesis is the only viable source of brassinosteroids for scientific and practical use because their content in plants is very low. Despite more than 20 years of research on brassinosteroids, progress on the chemical synthesis determines the further development of this field.

This review addresses the principal achievements on the chemical synthesis of brassinosteroids that were reported in 1995-2000. Earlier work in this area has been reviewed twice [5, 6]. It should also be noted that synthetic methods for brassinosteroids are reviewed to some extent in previous articles [7-10].

Many different methods were developed in early research on brassinosteroid synthesis to prepare brassinolide (**1**) and castasterone (**2**) [5, 6]. However, **1** and **2** are still the most attractive targets of synthetic chemists. Thus, yet another scheme for synthesizing brassinolide from stigmasterol (**4**) was recently proposed [11, 12]. According to it, **4** is first transformed into 22-aldehyde **5** according to a known method. Then, addition of the carbanion obtained from bis(phenylseleno)propane and *n*-butyllithium to the 22-aldehyde of **5** forms the Se derivative **6**, from which oxidation by H_2O_2 gives allyl alcohol **7** in 73% overall yield. Further epoxidation of the 23-double bond in **7** by cumene peroxide in the presence of L-(+)-diethyltartrate according to Sharpless gives *threo*-23,24-epoxide **8** and its erythro-isomer in yields of 49 and 21%, respectively. Opening of the epoxide ring in **8** by *iso*-propylmagnesium chloride in the presence of Cu(I) cyanide produces (22R,23R)-22,23-diol **9** in 82% yield. Subsequent lactonization of **9** by trifluoroperacetic acid in a Baeyer—Villiger reaction occurs with simultaneous hydrolysis of the protecting groups to give **1** in 53% yield (Scheme 1).

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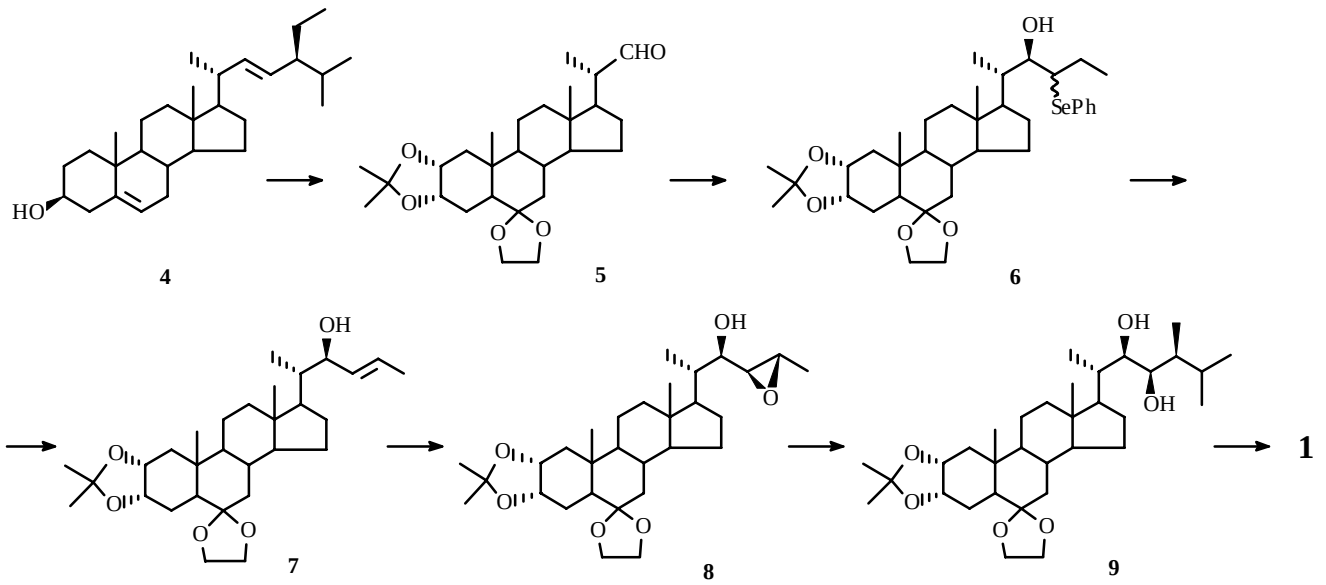
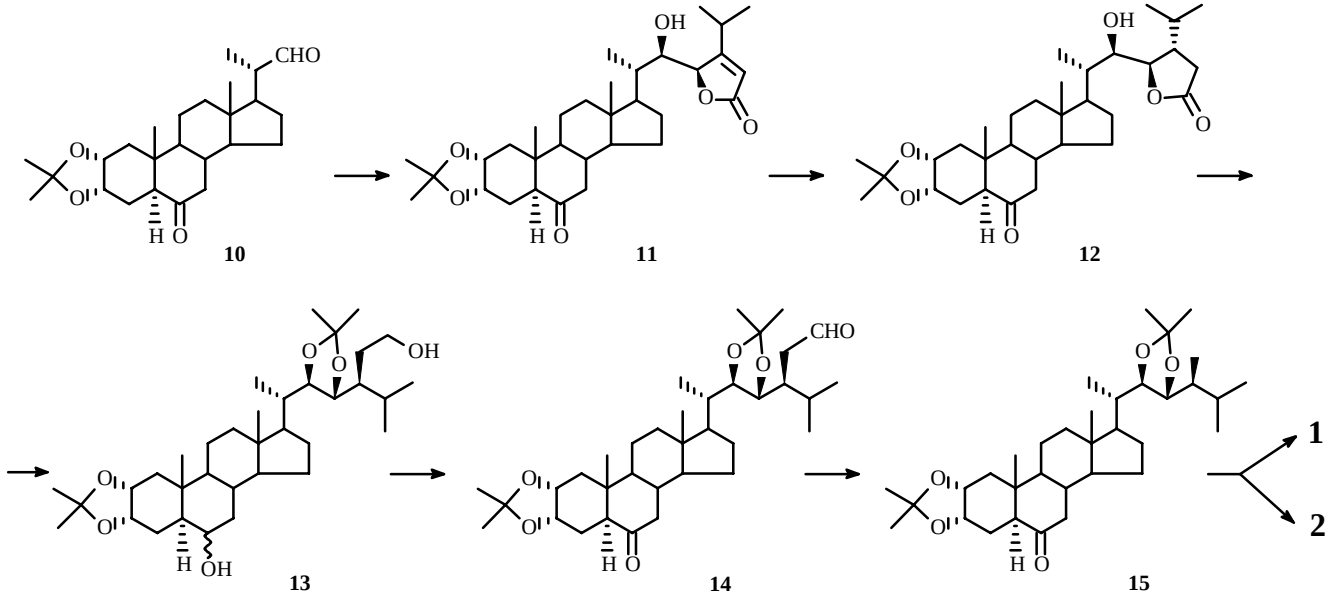


Scheme 1.

Replacing isopropylmagnesium chloride by other Grignard reagents in the step where the epoxide of **8** is opened enabled this scheme to be used to prepare brassinosteroid analogs containing various alkyl and cycloalkyl substituents in the side chain [11-14]. As it turned out, compounds containing cyclopropyl or cyclobutyl substituents in the side chain are 5-7 times more active as plant-growth stimulators than brassinolide [13, 14]. 25-Methoxy-, 25-fluoro-, and 25-azabrassinolide in addition to 25-fluorocastasterone are synthesized analogously from **8** [15]. The stereoselectivity of the epoxidation of several model 22-hydroxy-Δ^{22}-steroids by *m*-chloroperbenzoic acid and *t*-butylhydroperoxide in the presence of vanadyl acetylacetonate or molybdenum hexacarbonyl was also investigated for this scheme to increase the yield of the *threo*-22-hydroxy-23,24-epoxysteroids [16].

Allyl alcohol **7** was synthesized (73% overall yield) by an alternate method [17] by adding the arsenic ylide obtained from propenyltriphenylarsonium tetrafluoroborate to **5** with subsequent reduction of the resulting Δ^{24}-22,23-epoxysteroid by diisobutylaluminum hydride. Further transformations including Sharpless epoxidation, opening of the 23,24-epoxide ring, and hydrolysis of the protecting groups converted **7** to **2**.

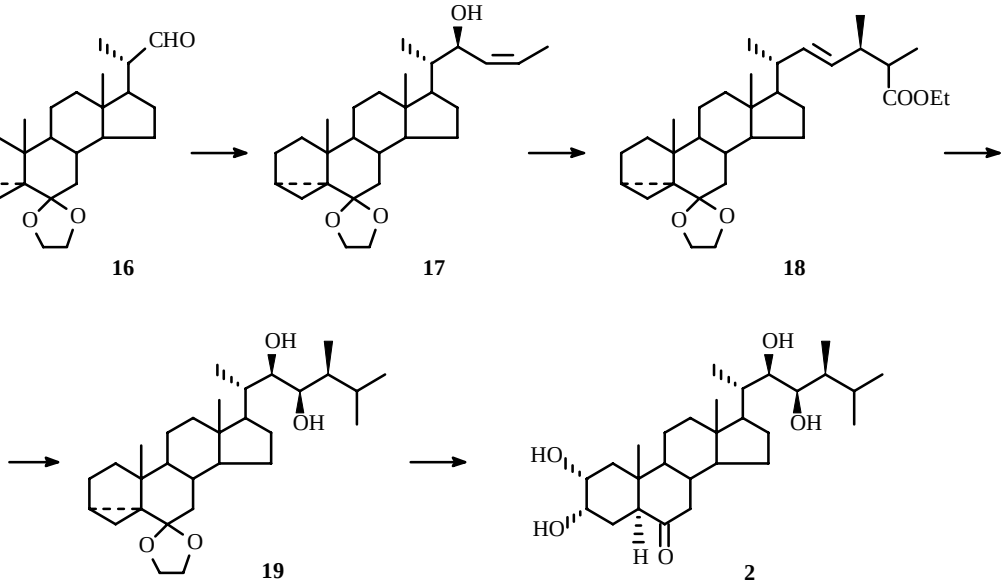


Scheme 2.

22-Aldehyde **10**, which is obtained by a multi-step synthesis from stigmasterol [18], is used as an intermediate in

brassinolide synthesis. Condensation of this steroid with 3-isopropylbut-2-enolide synthesizes the unsaturated lactone **11**. Catalytic hydrogenation of the double bond in **11** gives in high yield lactone **12** with the required (24S)-stereochemistry. Reduction of **12** by $LiAlH_4$ leads quantitatively to the corresponding 6,22,23,29-tetraol, in which the 22,23-diol is protected as the acetonide by reaction with acetone in the presence of camphorsulfonic acid. The remaining free hydroxyls in steroid **13** prepared this way are oxidized in the next step by pyridinium dichromate to form aldehyde **14** in 91% yield. Subsequent mild decarbonylation of **14** by *tris*(triphenylphosphine)rhodium(I) chloride gave the diacetonide of castasterone (**15**) in 72% yield. Baeyer—Villiger oxidation of this compound by trifluoroperacetic acid gave brassinolide **1** in 92% yield. Hydrolysis of the protecting groups in **15** by trifluoroacetic acid in methanol gives castasterone (**2**) in quantitative yield (Scheme 2).

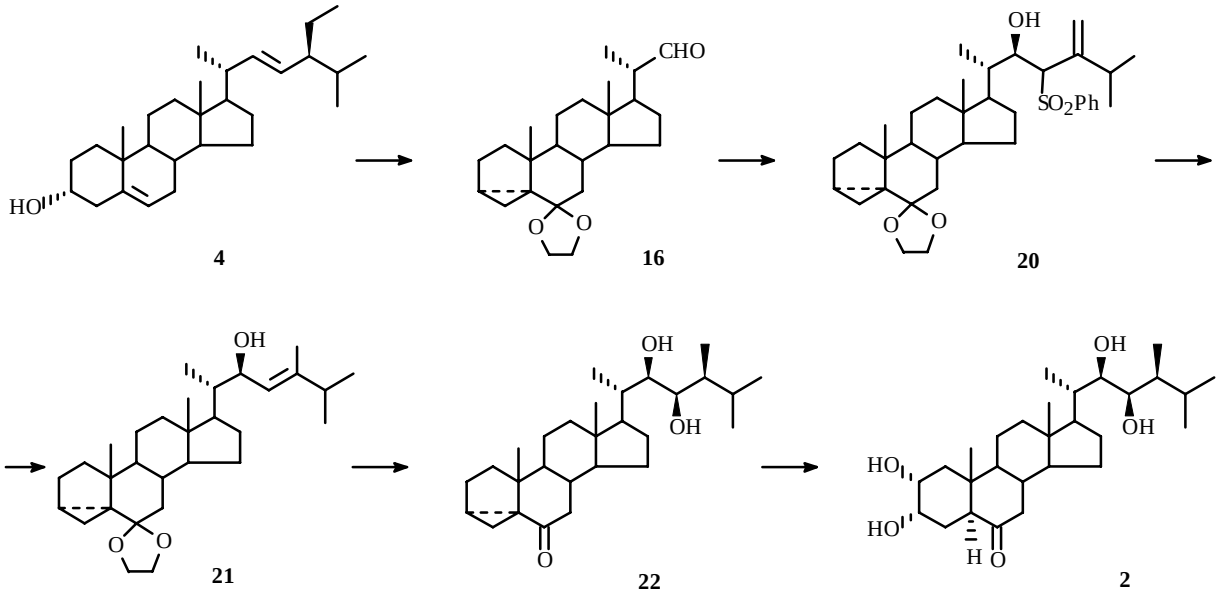
Castasterone (**2**) was synthesized from 22-aldegyde **16** in eight steps in 32% overall yield [19]. Addition to **16** of (Z)-prop-1-enylmagnesium bromide forms allyl alcohol **17**. Claisen rearrangement of **17** by triethylorthopropionate in the presence of propanoic acid produced ester **18**. The ester in **18** was reduced by $LiAlH_4$. The resulting alcohol reacts with methanesulfonyl chloride to give the mesylate, which is then reduced by $LiAlH_4$. *cis*-Hydroxylation of the 22-double bond in the reaction product by osmium tetroxide in the presence of the chiral ligand 1,4-*bis*(9-O-dihydroquinidyl)phthalazine led to 22,23-diol **19**, from which castasterone was obtained by previously developed methods. This same synthetic scheme was used to prepare 6-deoxoteasterone, 3-dehydro-6-deoxoteasterone, 6-deoxocastasterone, and 6-deoxotyphasterol (Scheme 3) [20].



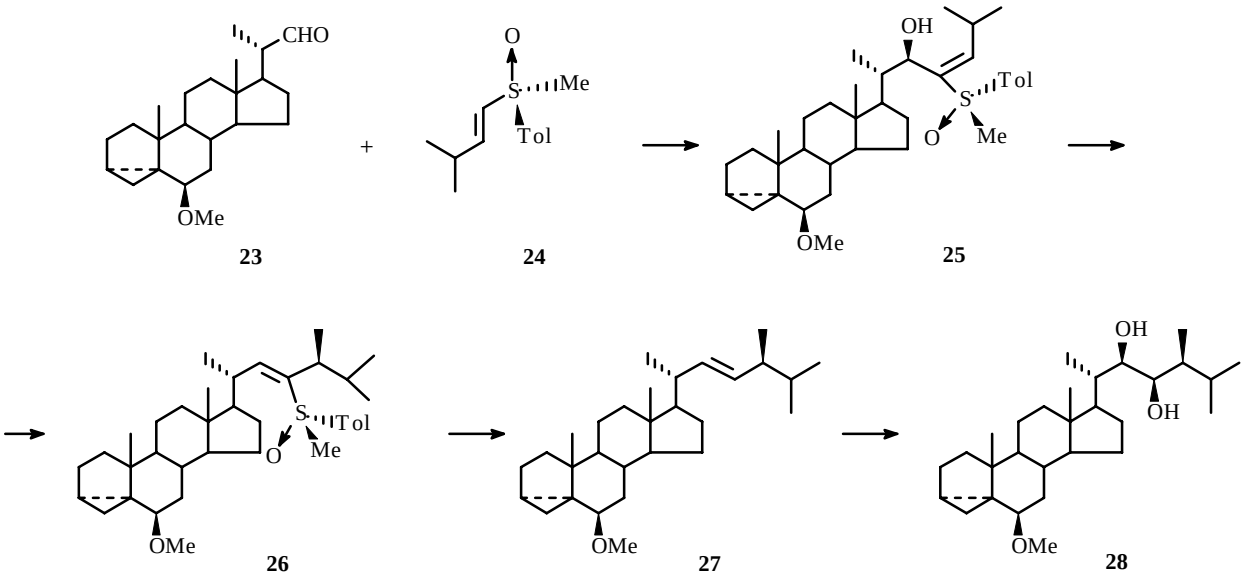
Scheme 3.

Compound **16** was used as an intermediate in an alternate synthesis of castasterone from stigmasterol [21, 22]. Alkylation of the aldehyde in **16** by the anion prepared from 2,3-dimethyl-3-acetoxy-4-benzosulfonylbutane and butyllithium gives sulfone **20**, desulfurization of which by litium in liquid ammonia produces allyl alcohol **21**. Epoxidation of the 23-double bond in **21** by *m*-chloroperbenzoic acid, reduction of the resulting 23,24-epoxide by diborane and $LiBH_4$, and acid hydrolysis of the protecting group in ring *B* gave 22,23-diol **22**. In the final synthetic steps, castasterone **2** is obtained by isomerization of the three-membered ring in steroid **22** by pyridinium hydrobromide and further *cis*-hydroxylation of the resulting Δ^2-bond by osmium tetroxide (Scheme 4).

Compounds for which the conversion into brassinolide or castasterone has already been studied were synthesized. Thus, addition to the 22-aldehyde **23** of chiral sulfone **24** to give allyl alcohol **25** provides a basis for a new synthesis of brassinolide [23]. Next, the 22-hydroxyl in steroid **25** is converted by reaction with methanesulfonic anhydride in pyridine into the mesylate, nucleophilic substitution of which by the appropriate methylcyanocuprate reagent, which occurs via an S_N2' mechanism, led to Δ^{22}-steroid **26**. Desulfurization of **26** by *t*-butyllithium gives **27**. Subsequent hydroxylation of the Δ^{22}-bond in **26** by potassium osmate and potassium ferricyanide in the presence of a chiral ligand gave the 22,23-diol **28**, which contains the already prepared side chain of brassinolide and castasterone (Scheme 5).



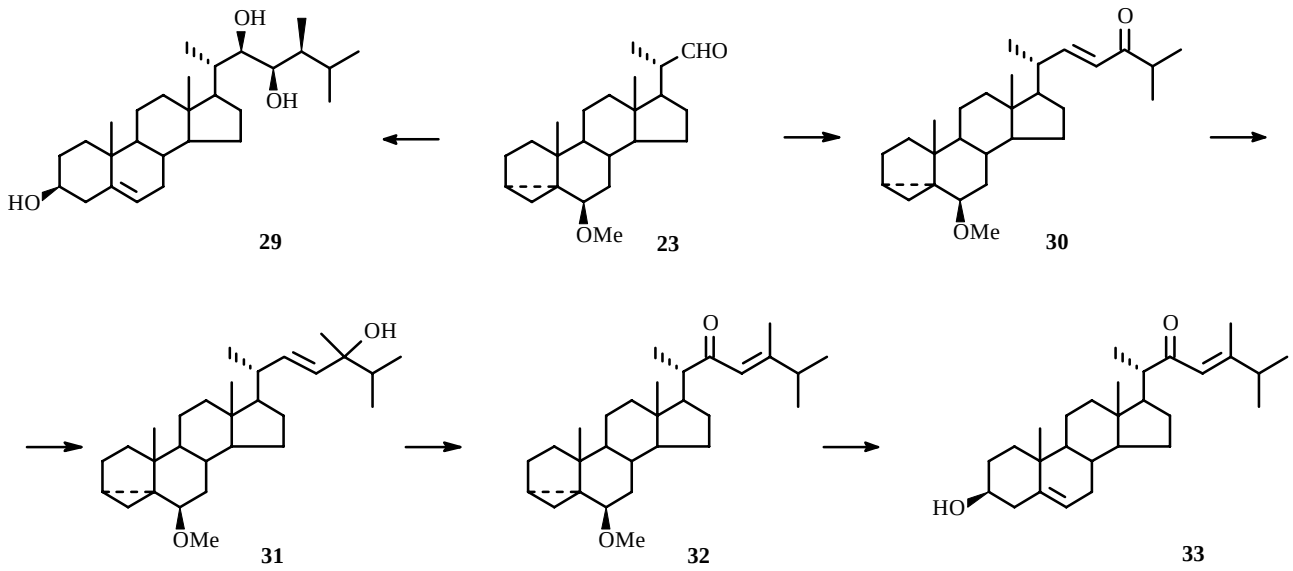
Scheme 4.



Scheme 5.

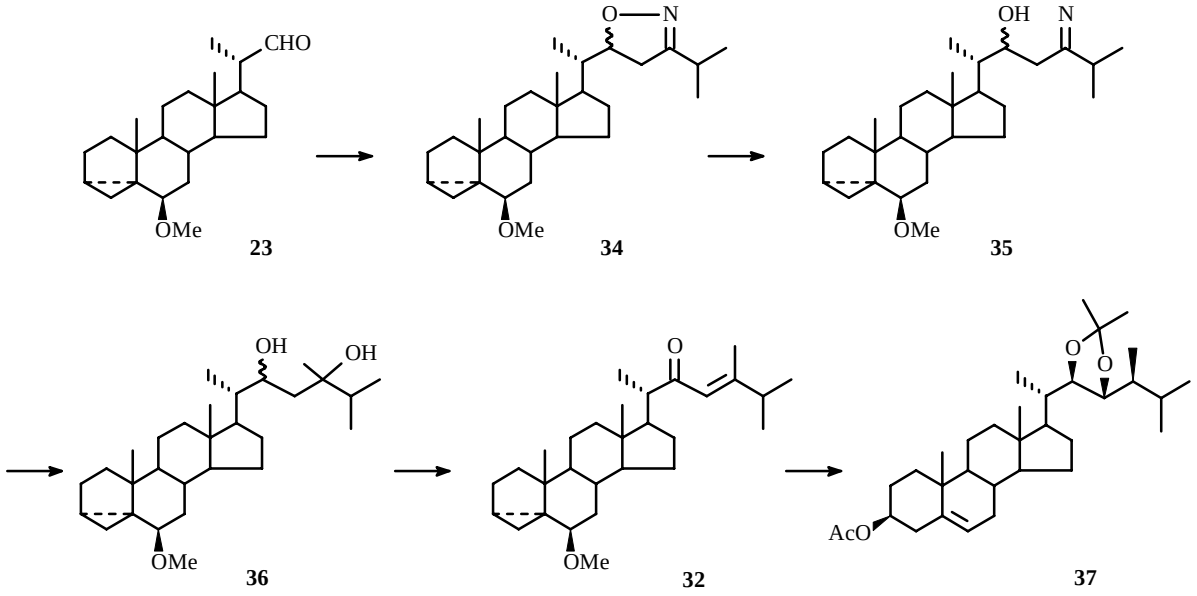
An alternate synthesis of steroid **28** from aldehyde **23** via isoxazole derivatives has been described [24, 25]. The synthesis of the analogous derivative **29** from the 22-aldehyde **23** using another scheme was reported [26].

Olefination of **23** by the appropriate diethylalkylphosphonate via a Horner—Wadsworth—Emmons reaction was used to form the side chain of brassinolide [27]. This produced Δ^{22}-24-ketosteroid **30** in 73% yield. Addition to **30** of methyllithium gave 24-alcohol **31** as a mixture of (24S)- and (24R)-isomers (48 and 13% yields, respectively). Oxidation of the stereoisomers by pyridinium chlorochromate gave Δ^{23}-22-ketosteroid **32** in 95% yield. Isomerization of **32** by *p*-toluenesulfonic acid in dioxane gave steroid **33** in quantitative yield. Compound **33** is a known intermediate in the synthesis of brassinolide (Scheme 6).



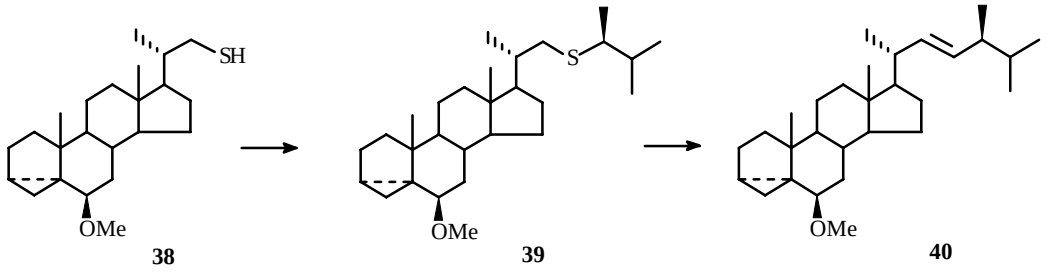
Scheme 6.

Still another method for forming the brassinolide side chain has been patented [28, 29]. Thus, 22-aldehyde **23** undergoes a Wittig reaction and a 1,3-dipolar cycloaddition to the resulting Δ^{22}-steroid of isobutyronitrile oxide to give isoxazolidine **34** in 90% overall yield. Reductive cleavage of the heterocycle in **34** by Raney nickel gives 22-hydroxy-24-ketosteroid **35** in 95% yield. Alkylation of **35** by methyllithium produces 22,24-diol **36**. Subsequent oxidation of the secondary hydroxyl in **36** by CrO_3 and dehydration by *p*-toluenesulfonic acid gave unsaturated ketosteroid **32** in 80% overall yield. Further transformations of **32**, including epoxidation of the 23-double bond by *m*-chloroperbenzoic acid and hydride reduction of the 23,24-epoxide ring, produce 22,23-diol **28** in 60% overall yield. In the final step, **28** undergoes isomerization in the *A* and *B* rings in acetic acid and protection of the 22,23-diol by reaction with acetone in the presence of *p*-toluenesulfonic acid to give steroid **37** in 90% overall yield (Scheme 7).



Scheme 7.

The brassinolide side chain can also be synthesized from steroidal mercaptan **38** [30]. Reaction of **38** with specially prepared (S)-2,3-dimethyliodobutane in DMF in the presence of NaH gives sulfide **39**, chlorination of which by *N*-chlorosuccinimide, subsequent oxidation by *m*-chloroperbenzoic acid, and reaction of the resulting chlorosulfone with potassium *t*-butoxide gives Δ^{22}-steroid **40** in 83% overall yield (Scheme 8). This compound was previously converted to brassinolide **1**.



38 **39** **40**

Scheme 8.

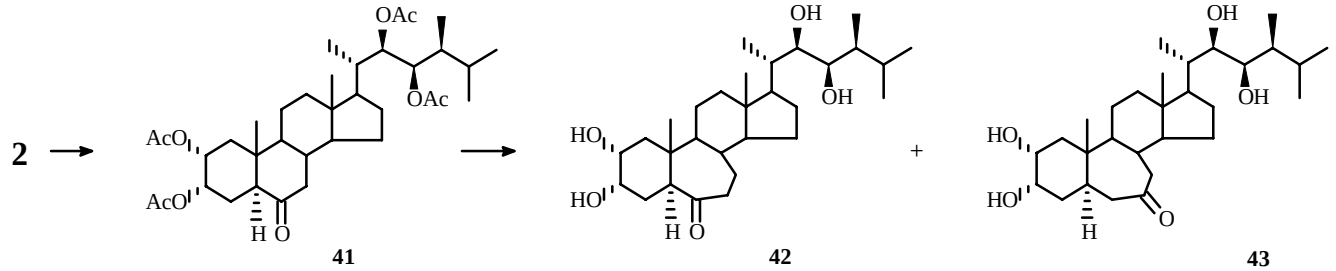
Extensive research on the chemical synthesis of brassinolide and castasterone resulted in these compounds becoming comparatively available. These brassinosteroids are more frequently being used as starting materials for preparing other biologically active compounds of this class. Thus, reaction of sodium methoxide and brassinolide causes its epimerization at C-5 to form 5-epibrassinolide. 2,3,5-Tri-epibrassinolide is prepared analogously from 2,3-di-epibrassinolide [32].

Dansyl derivatives of brassinosteroids were synthesized in order to use them in fluorescent analysis [33]. The 22,23-diol was reacted with dansylaminophenylboric acid to prepare the derivatives of the side chain. 6-Ketobrassinosteroids were modified on the cyclic part of the molecule by reaction with dansylhydrazine to give the corresponding hydrazones.

One method of deactivating brassinosteroids in plants is to glycosylate their free hydroxyls. In order to prevent this process, several methyl esters of brassinolide were prepared and studied [34]. It was found that the most active plant-growth stimulator was the 22,23-dimethylester of brassinolide. This compound is just as active as 24-epibrassinolide.

23-Dehydrobrassinolide was synthesized [35]. It turned out to be identical to the brassinosteroid cryptolide, which was identified in pollen and anthers of *Cryptomeria japonica*. Esters of teasterone with lauric and myristic acids were identified in lily pollen [36, 37]. Synthetic methods for preparing these were also proposed [37].

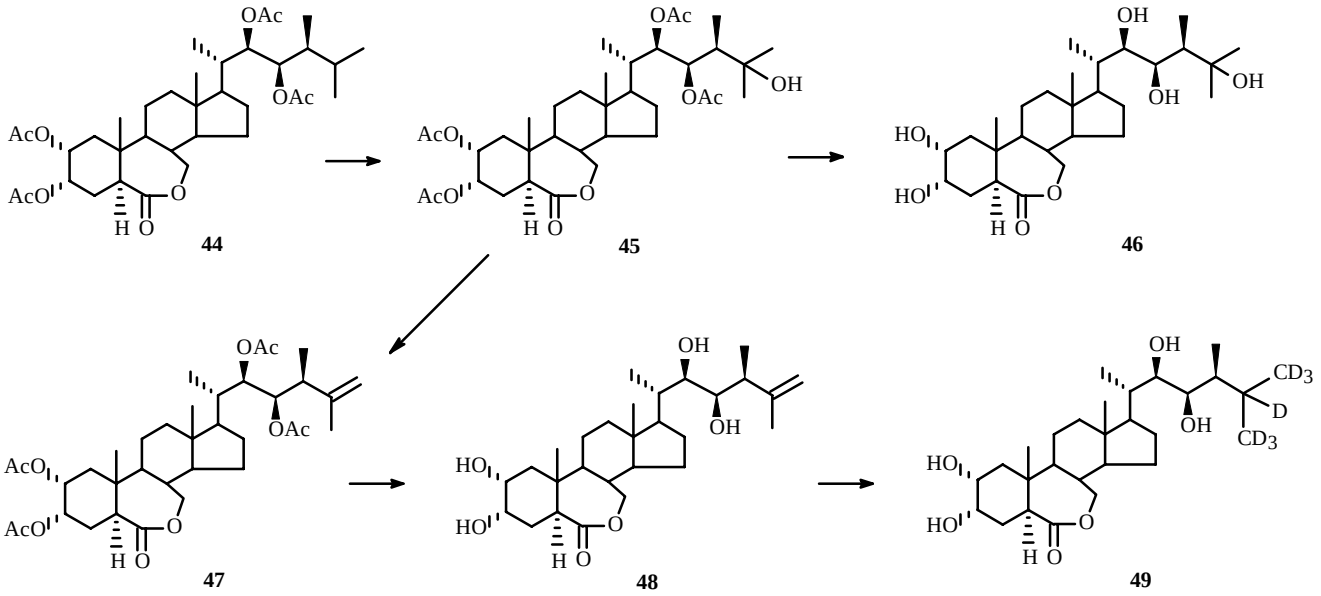
Various brassinolide analogs modified in ring *B* have been synthesized [38, 39]. For example, castasterone (**2**) is used as starting material to prepare carbocyclic analogs of brassinolide [39]. Acetylation of **2** by acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine gives tetraacetate **41** in quantitative yield. Reaction of **41** with trimethylsilyldiazomethane and BF_3 etherate and subsequent desilylation by HCl in the presence of silica gel incorporates a methylene into ring *B* in both possible α-positions to the 6-ketone. This forms the tetraacetates of the corresponding B-homo-6-keto- and B-homo-7-keto-derivatives in 80 and 7.5% yields. Hydrolysis of the acetoxyls in these compounds by KOH in aqueous methanol gives 6a-carbabrassinolide **42** and its regiomer **43** (Scheme 9).



41 **42** **43**

Scheme 9.

25-Hydroxybrassinosteroids were synthesized by direct introduction of an additional hydroxyl into their simplest derivatives [40, 41]. Thus, oxidation of brassinolide tetraacetate (**44**) by methyl(trifluoromethyl)dioxirane gave 25-hydroxysteroid **45** in 71% yield. Further hydrolysis of the acetoxyls in **45** by methanolic KOH and subsequent relactonization by HCl led to 25-hydroxybrassinolide (**46**) in 78% yield. 25-Hydroxyepicastasterone and 25-hydroxy-24-epibrassinolide were synthesized analogously from 24-epicastasterone 2,3-diacetate-22,23-acetonide [40, 41]. Then, products from oxidation of steroid **44** by methyl(trifluoromethyl)dioxirane were investigated in detail [42]. The 25-hydroxy derivative **45** was formed in 61% yield. The minor products from this reaction were the 14α-hydroxysteroid (6.5%), 14α,25-dihydroxysteroid (18%), and 25-hydroxy-15-ketosteroid (3.6%) (Scheme 10).

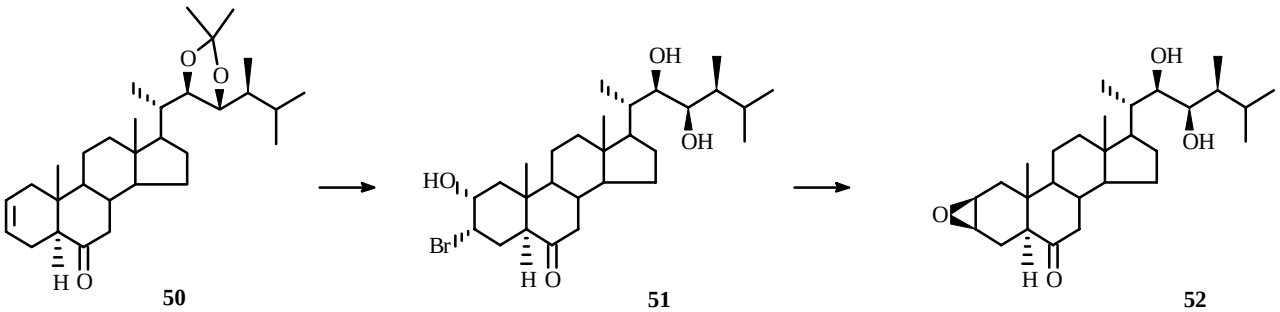


Scheme 10.

Brassinolide selectively labelled by deuterium in the side chain can be synthesized from 25-hydroxysteroid **45** [43]. Dehydration by thionylchloride in pyridine produces Δ^{25}-steroid **47** and its Δ^{24}(25)-isomer in a 65:35 ratio in 86% overall yield. In the next step, this inseparable mixture is hydrolyzed by KOH in aqueous methanol and relactonized on cation exchanger to form tetrahydroxylactone **48** in 51% yield. Catalytic deuteration of **48** over Pd on charcoal gives a mixture of deuterated products, 60% of which is [25,26,27-$^2H_7$]-brassinolide **49** (Scheme 10).

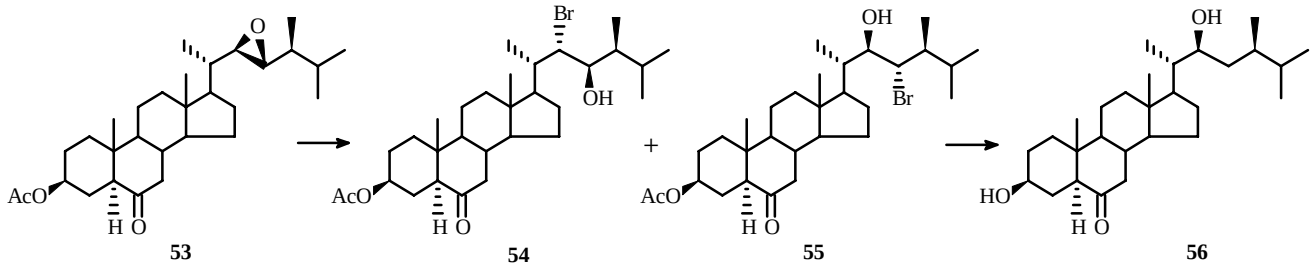
It should be pointed out that alternate synthetic methods that include gradual lengthening of the side chain of the corresponding starting steroids have been proposed for preparing 25-hydroxybrassinosteroids [44, 45].

Certain known intermediates in the syntheses of brassinolide and castasterone have been applied to the preparation of minor brassinosteroids that have been observed recently in plants. Δ^2-6-Ketosteroid **50** was used for just this purpose to synthesize the brassinosteroid secasterone (**52**) [46]. The key steps of this synthesis are addition to the 2-double bond of **50** of hypobromous acid and hydrolysis of the acetonide in the side chain to give bromohydrin **51**. Subsequent reaction with sodium methoxide produces secasterone (**52**) from **51** (Scheme 11). 24-Episecasterone was also synthesized analogously from the corresponding ergostane derivative.



Scheme 11.

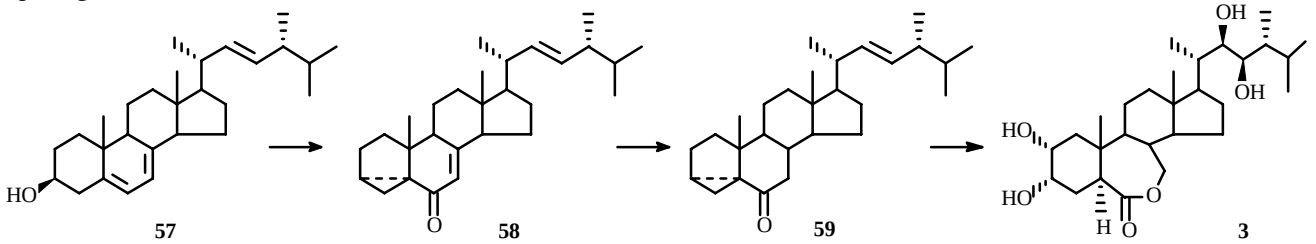
Cathasterone (**56**), which was first observed in cultivated cells of *Catharanthus roseus*, is one of the possible biosynthetic precursors of brassinolide [47]. The synthesis of this brassinosteroid from the known epoxyketosteroid **53** has been published [47, 48]. Opening of the epoxide ring in compound **53** by HBr forms regiomeric bromohydrins **54** and **55** with predominance of the former. Acetylation of the free 22-hydroxyl in **55** by acetic anhydride in the presence of 4-dimethylaminopyridine, reduction of the resulting diacetoxybromo-derivative by tri-*n*-butyltin hydride, and hydrolysis of the acetoxyls by methanolic KOH gave the required cathasterone (**56**) (Scheme 12). It should also be noted that 24-epicathasterone was prepared from the corresponding ergostane derivative through the 22,23-epoxide and the 22,23-bromohydrin [49, 50].



53 **54** **55** **56**

Scheme 12.

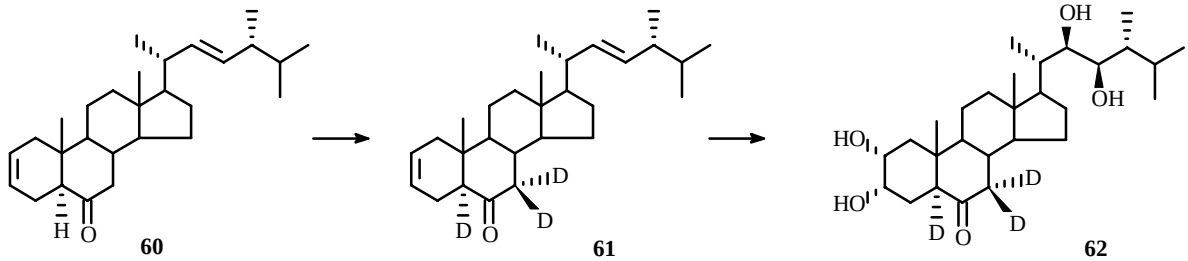
As mentioned above, the most important brassinosteroid from a practical viewpoint is 24-epibrassinolide (**3**), several approaches for the production of which from ergosterol **57** have been proposed [5, 6]. The most effective of the previously developed methods is shown in Scheme 13. It includes conversion of **57** into Δ^7-6-ketosteroid **58**, subsequent Birch reduction by lithium in liquid ammonia to 6-ketone **59**, and isomerization of the last into Δ^2-6-ketone **60**. Reduction of compound **58** by sodium dithionite in the presence of a phase-transfer catalyst was proposed in order to improve this synthetic scheme for preparing of steroid **59** [51, 52].



57 **58** **59** **3**

Scheme 13.

Δ^2-6-Ketosteroid **60** was used to synthesize deuterium-labelled brassinosteroid **62** [53]. Treatment of **60** with sodium deuteromethoxide in deuteromethanol produced deuterated **61** in quantitative yield. *cis*-Hydroxylation of **61** by osmium tetroxide and N-methylmorpholine-N-oxide formed [5,7,7^2-H_3]-24-epicastasterone (**62**) and its (22S,23S)-isomer in 19 and 46% yields, respectively (Scheme 14).

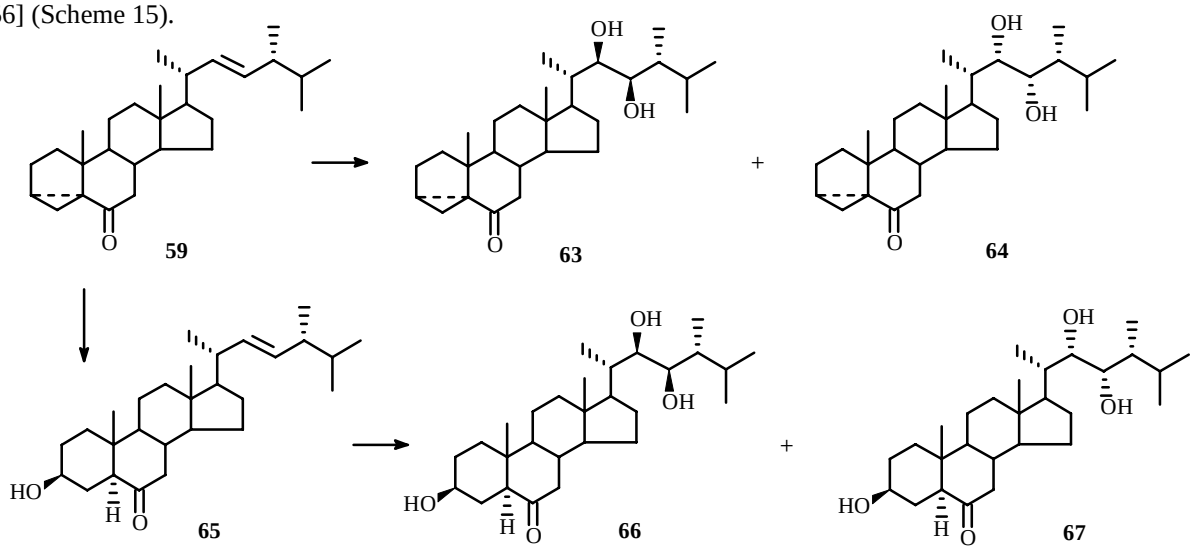


60 **61** **62**

Scheme 14.

An analogous approach to the synthesis of deuterium- and tritium-labelled brassinosteroids was proposed [54]. It also uses base-catalyzed exchange of H by D or T in the enolized positions of the cyclic part of known intermediates in the synthesis of (24R)-brassinosteroids of the ergostane series.

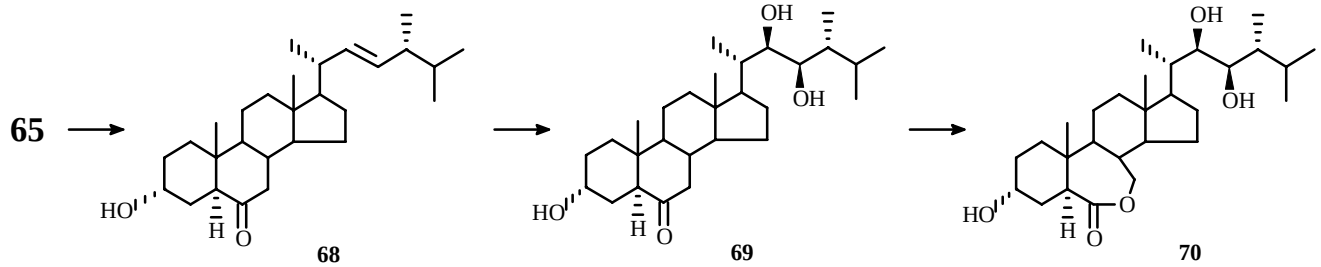
It should be noted that other natural brassinosteroids and their synthetic analogs were prepared from steroid **59** in addition to 24-epibrassinolide. Thus, it was demonstrated that 22,23-diols **63** and **64** are form in yields of 26 and 59%, respectively, upon *cis*-hydroxylation of the 22-double bond in steroid **59** by osmium tetroxide and N-methylmorpholine-N-oxide [55]. Steroid **59** was used [55, 56] to repeat the synthesis of 24-epiteasterone (**66**) that we developed [57]. Opening of the three-membered ring in compound **59** by acetic acid in the presence of sulfuric acid and subsequent hydrolysis of the resulting 3β-acetate by KOH produced 3β-hydroxy-6-ketosteroid **65** in 78% overall yield [55]. Subsequent *cis*-hydroxylation of the 22-double bond in **65** by osmium tetroxide and N-methylmorpholine-N-oxide effected the synthesis of 24-epiteasterone (**66**) and its (22S,23S)-isomer **67** in yields of 18 and 51%, respectively. Later it was observed that use of osmium tetroxide in the presence of potassium ferricyanide and a chiral ligand for *cis*-hydroxylation of compound **65** increases the yield of brassinosteroid **66** to 66% [56] (Scheme 15).



Scheme 15.

Inversion of the configuration of the 3β-hydroxyl in steroid **65** by diethylazodicarboxylate and triphenylphosphine in formic acid provides the basis for synthesizing 24-epityphasterol [56]. This produces the corresponding 3α-formoxy-6-ketone in 71% yield, hydrolysis of which by potassium carbonate in methanol led to 3α-hydroxy-6-ketone **68** in 79% yield.

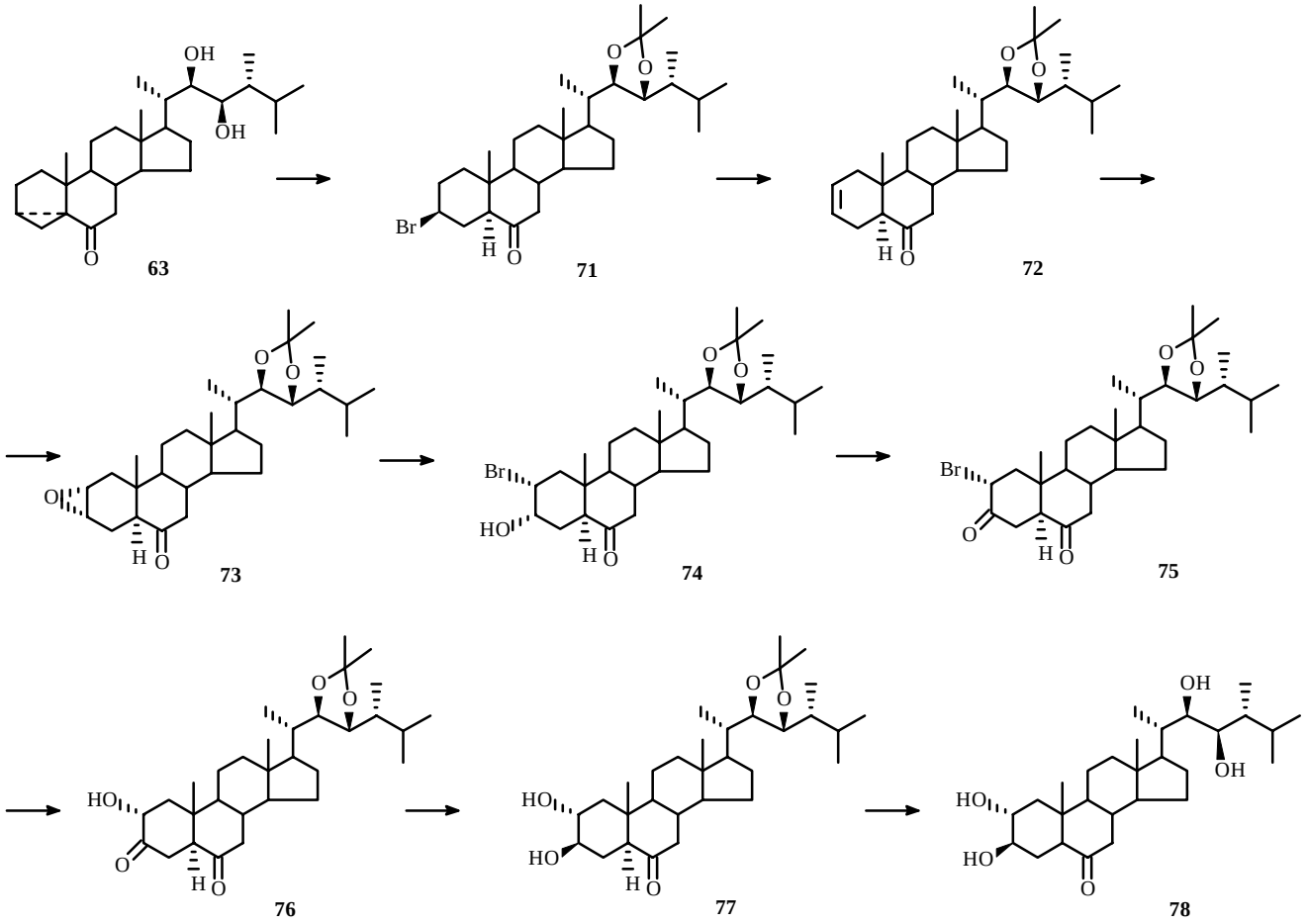
Subsequent *cis*-hydroxylation of the Δ^{22}-bond in **68** by osmium tetroxide and potassium ferricyanide in the presence of a chiral ligand gave 24-epityphasterol (**69**) in 73% yield. Baeyer—Villiger oxidation of **69** enabled the synthesis of 2-desoxy-24-epibrassinolide **70**. It should be noted that we previously developed a synthesis of 24-epityphasterol (**69**) [58] (Scheme 16).



Scheme 16.

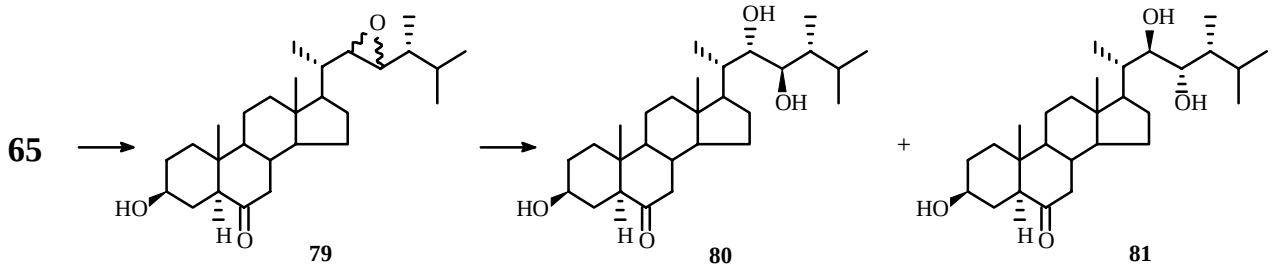
3,24-Diepicastasterone was synthesized in 13 steps in 3% overall yield [59]. 22,23-Dihydroxy-3α,5-cyclo-6-ketosteroid **63** was prepared by the usual method from ergosterol and used as an intermediate. Reaction of **63** with HBr in acetone opens the three-membered ring and protects the 22,23-diol. 3β-Bromo-6-ketosteroid **71** is formed in quantitative yield. Further dehydrobromination of steroid **71** by lithium carbonate in DMF produced Δ^2-6-ketone **72** in 57% yield. Epoxidation of the Δ^2-bond in **72** by *m*-chloroperbenzoic acid gives 2α,3α-epoxide **73** in 77% yield. Then, **73** is opened by HBr in acetone to form quantitatively *trans*-diaxial 2β-bromo-3α-hydroxy-6-ketone **74**. Oxidation of the free 3α-hydroxyl in **74** by chromic acid in

acetone to the 3-ketone occurs simultaneously with epimerization at C-2 to form 2α-bromo-3,6-diketosteroid **75** in 67% yield. In the next step, the Br in steroid **75** is displaced in aqueous acetone in the presence of potassium carbonate to give 2α-hydroxy-3,6-diketone **76** in 87% yield. Selective reduction of the 3-ketone by $NaBH_4$ with extensive cooling in ethanol produced 2α,3β-dihydroxy-6-ketosteroid **77** in 50% yield. Removal of the protecting group in the side chain in aqueous dioxane in the presence of sulfuric acid gave the desired 3,24-diepicastasterone (**78**) in 90% yield (Scheme 17).



Scheme 17.

Epoxidation of the Δ^{22}-bond in **65** produces a mixture of the corresponding (22S,23S)- and (22R,23R)-epoxides **79**. Hydrolysis of them gives 22,24-diepicastasterone (**80**) and 23,24-diepicastasterone (**81**) [60] (Scheme 18).

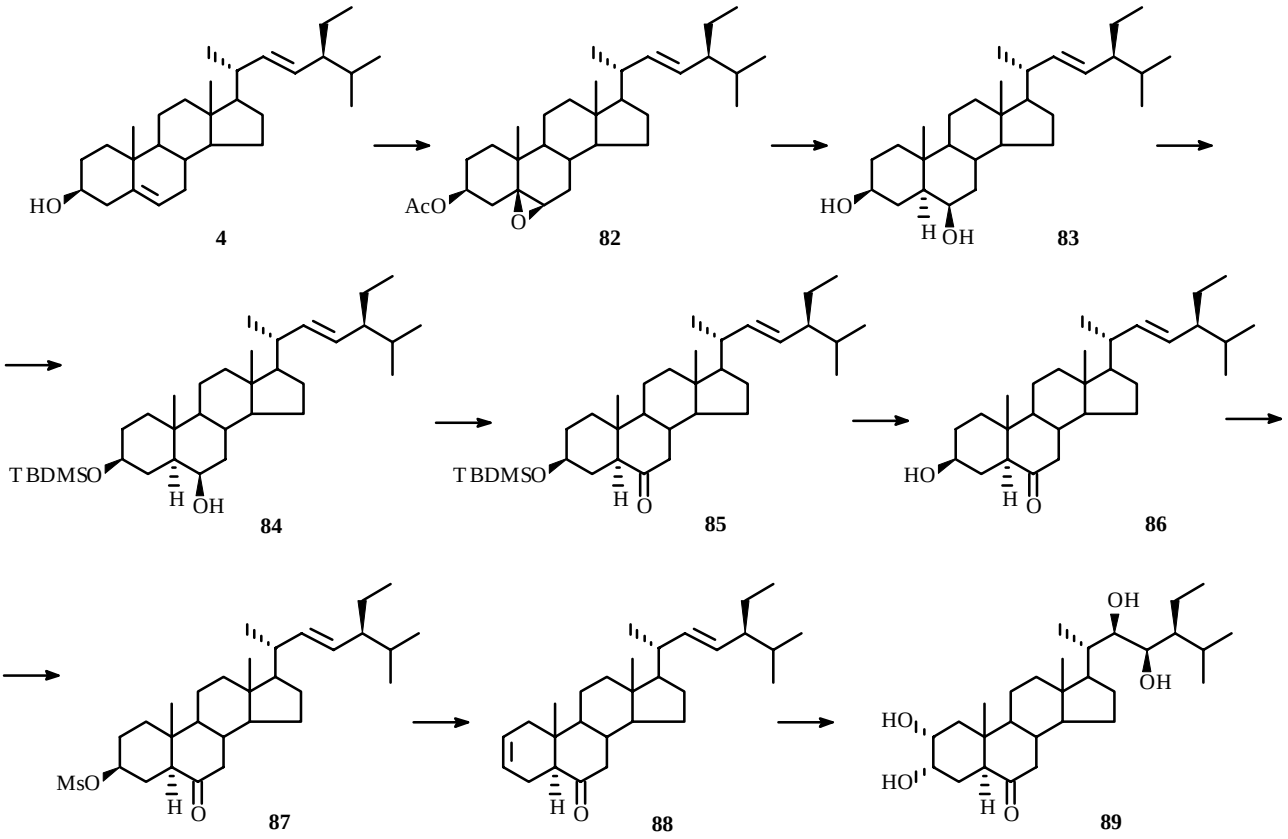


Scheme 18.

The synthesis of brassinosteroid analogs deserves attention. The adduct of ergosterol and maleic anhydride was used as an intermediate [61, 62].

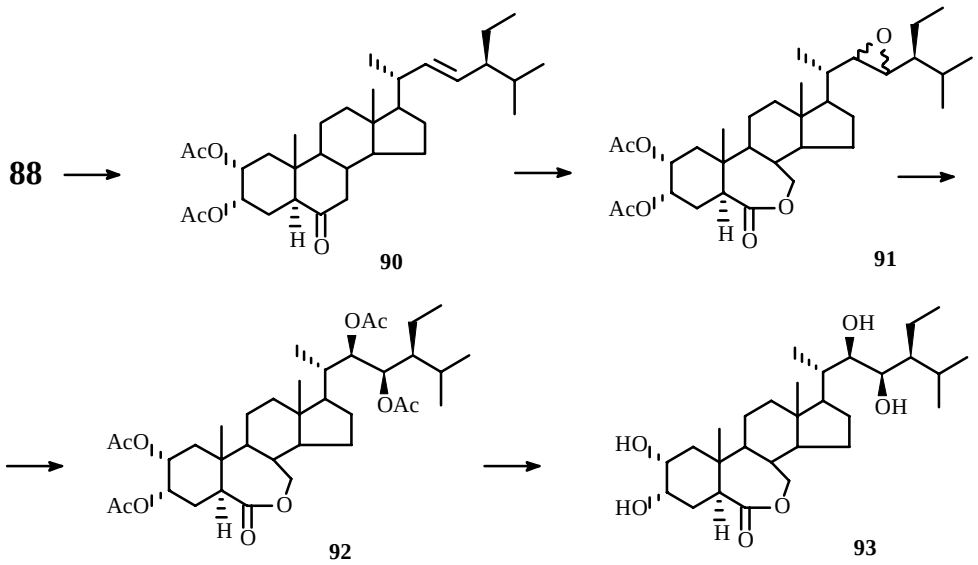
Stigmasterol (**4**), like ergosterol, remains an important starting material for the preparation of brassinosteroids. In the

examined examples, the synthesis of brassinosteroids from stigmasterol included cleavage of the side chain at C-22 and subsequent attachment of the new side chains, for example, of brassinolide and castasterone. However, transformations of stigmasterol with retention of the side chain and conversion of its Δ^{22}-bond into 22,23-diols is still important. For example, a new transformation of stigmasterol (**4**) into (24S)-24-ethylbrassinone (**89**), which is a natural brassinosteroid, has been described [63, 64]. First 5β,6β-epoxide **82** is prepared from stigmasterol. Then, **82** is reduced by $LiAlH_4$ in 44% yield to 3β,6β-diol **83**. The sterically more available 3β-hydroxyl in **83** is protected by forming *t*-butyldimethylsilyl ether **84** in quantitative yield. Oxidation of **84** by pyridinium chlorochromate in methylenechloride gives 6-ketone **85** in 95% yield. Hydrolysis of the silyl protecting group by tetra-*n*-butylammonium fluoride gave 3β-hydroxy-6-ketosteroid **86** in quantitative yield. Then, **86** was reacted with methanesulfonyl chloride in pyridine to give mesylate **87** in quantitative yield. Elimination by LiBr in DMF with boiling formed from **87** $\Delta^{2,22}$-6-ketone **88** in 72% yield. *cis*-Hydroxylation of the double bonds in **88** by potassium osmate and potassium ferricyanide in the presence of a chiral ligand led to brassinosteroid **89** in 34% yield (Scheme 19).



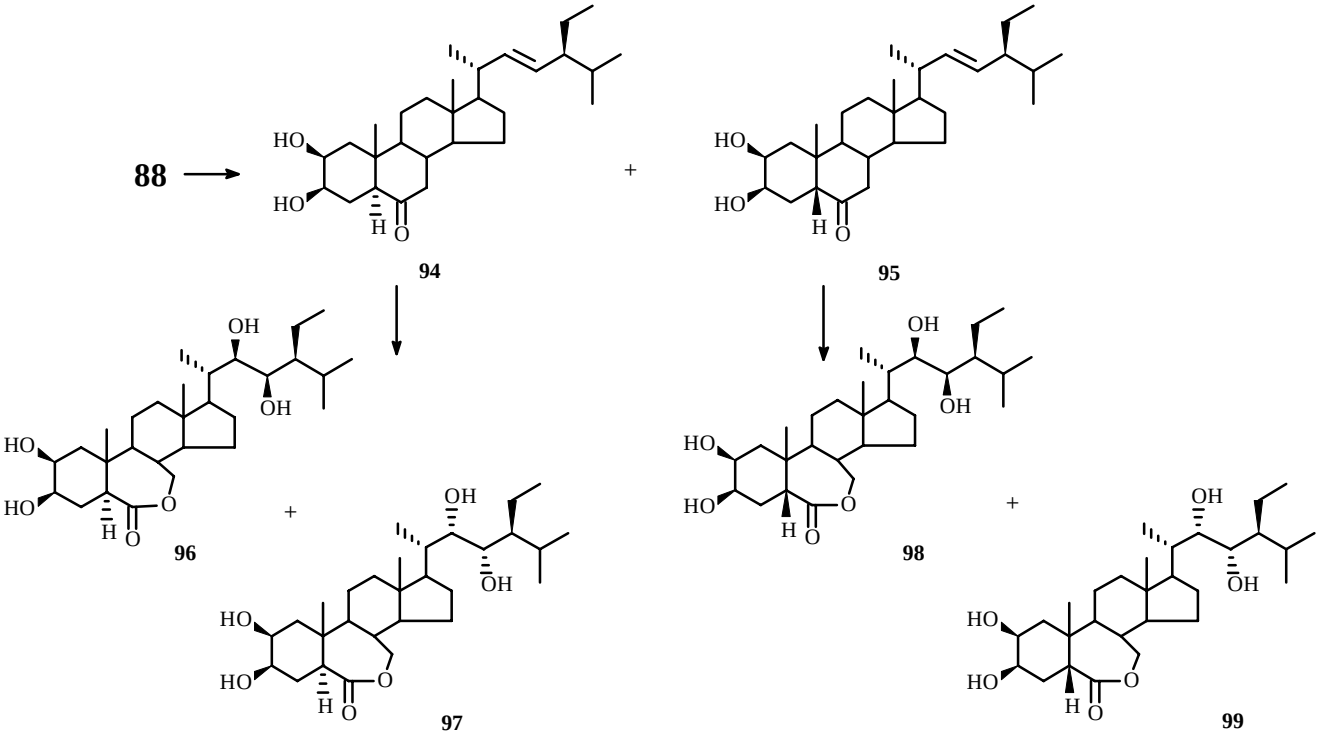
Scheme 19.

Compound **88** was also used to synthesize 28-homobrassinolide **93** from stigmasterol [65]. *cis*-Hydroxylation of the sterically more available 2-double bond in steroid **88** by trimethyltetradecylammonium permanganate gave the corresponding 2α,3α-diol as the principal product in 82% yield. This was transformed into diacetate **90** by the usual method. Oxidation of **90** by trifluoroperacetic acid produced epoxylactone **91** as a mixture of (22R,23R)- and (22S,23S)-isomers in 63% yield. Opening of the 22,23-epoxide ring by LiBr in acetonitrile, acetylation of the resulting bromohydrins, substitution of the Br in the resulting bromohydrin acetates by hydroxyls upon heating in acetic acid, and, finally, acetylation with acetic anhydride in the presence of 4-dimethylaminopyridine gave tetraacetoxylactone **92** and its (22S,23S)-isomer (53 and 32% yields, respectively). Hydrolysis of the acetoxyls in **92** by potassium carbonate in methanol upon boiling gave 28-homobrassinolide **93**. The overall yield of **93** according to the 12-step scheme is 15.6% (Scheme 20).



Scheme 20.

The isomers of 28-homobrassinolide at C-2, C-3, and C-5 were synthesized using Woodward hydroxylation of $\Delta^{2,22}$-6-ketosteroid **88** by silver acetate and iodine in aqueous acetic acid [66]. This reaction and subsequent hydrolysis by KOH in methanol produced from **88** 2β,3β-diols **94** and **95**. Further hydroxylation of the Δ^{22}-bond in compound **94** by osmium tetroxide and subsequent Baeyer—Villiger lactonization of its products led to tetrahydroxylactones **96** and **97**. Compounds **98** and **99** were synthesized analogously from dihydroxyketone **95** (Scheme 21).

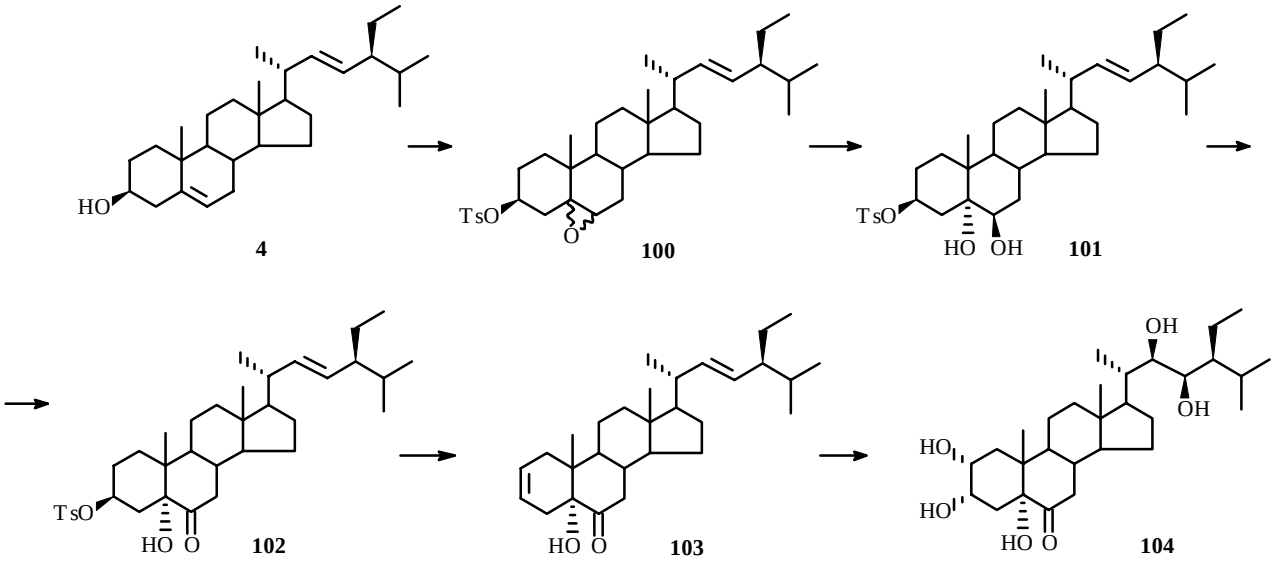


Scheme 21.

The C-2 and C-3 isomers of 28-homobrassinolide and brassinolide were synthesized later [67].

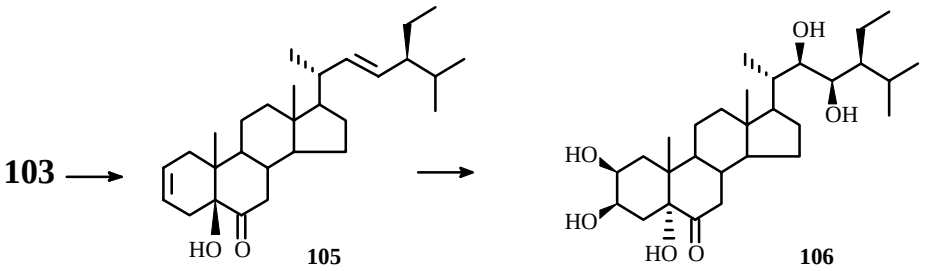
Direct oxidation of $\Delta^{2,22}$-6-ketosteroid **88** by molecular oxygen in the presence of the aldehyde was also studied [68]. This procedure enabled several brassinosteroid analogs with lactone ring *B* and 2,3- and 22,23-epoxys in their structures to be prepared immediately in one step.

We proposed a synthetic method for brassinosteroids [69] with additional 5α-hydroxyls and developed it further [64, 70]. According to the developed scheme [70], first stigmasterol (**4**) is reacted with *p*-toluenesulfonyl chloride in pyridine to give the tosylate, epoxidation of which by *m*-chloroperbenzoic acid in methylene chloride gave 5,6-monoepoxide **100** as a mixture of α- and β-isomers. Oxidation by chromic acid in acetone of **100** passed through 5α,6β-diol **101** into 5α-hydroxy-6-ketone **102**. Elimination by LiBr in DMF gave Δ^2-5α-hydroxy-6-ketone **103**, prepared from stigmasterol in 33% overall yield. *cis*-Hydroxylation of the $\Delta^{2,22}$-bond in compound **103** by osmium tetroxide and N-methylmorpholine-N-oxide in the presence of dihydroquinidine 9-O-(9′-phenanthryl)tin ester as a chiral ligand forms pentahydroxyketone **104** in 31% yield (Scheme 22). The minor products of this reaction are 2β,3β- and (22S,23S)-isomers of compound **104** in 16 and 15% yields, respectively. The published scheme [64] for synthesizing brassinosteroid **104** differs from that discussed above only in the details.



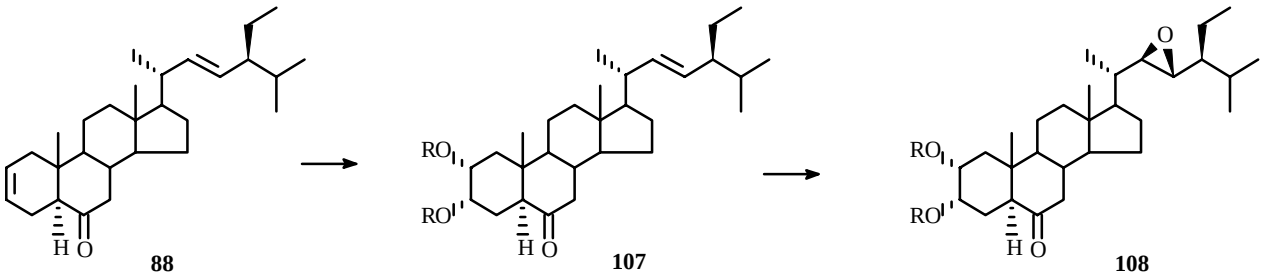
Scheme 22.

Isomerization of **103** by methanolic KOH gave 5β-hydroxy-6-ketosteroid **105** in 28% yield [70]. *cis*-Hydroxylation of **105** forms pentahydroxyketone **106** and its (22S,23S)-isomer in 27 and 17% yields, respectively (Scheme 23).



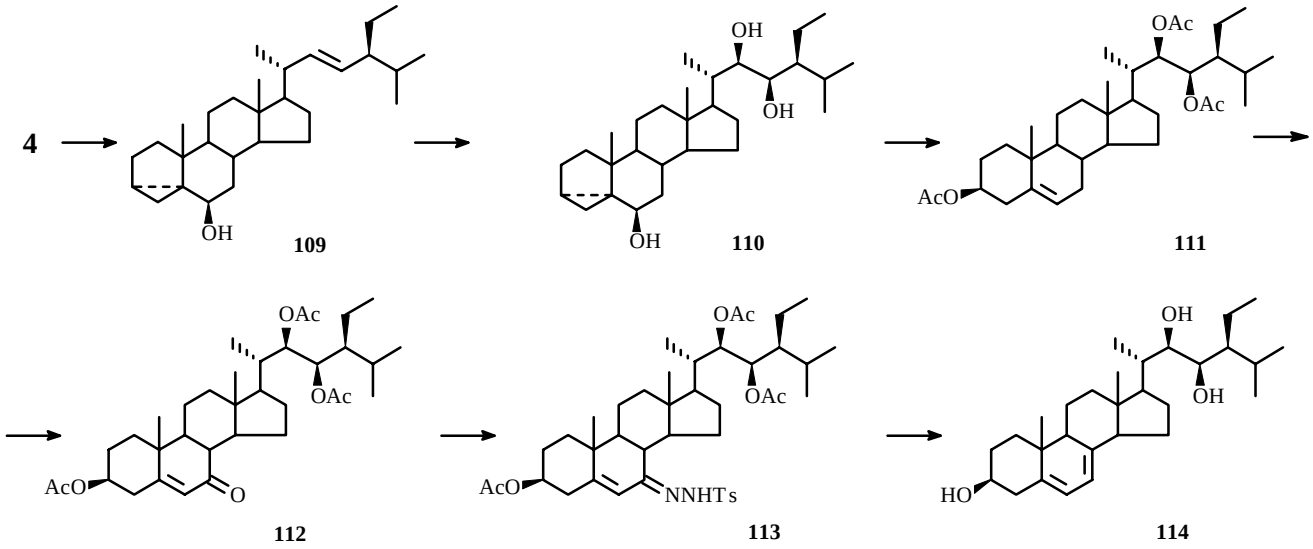
Scheme 23.

According to the patent literature [71], brassinosteroid esters **108** (R = Et or Pr) are rather active plant-growth stimulators. They were synthesized by selective *cis*-hydroxylation of dienone **88** at the sterically more accessible Δ^2-bond by osmium tetroxide and N-methylmorpholine-N-oxide to give the corresponding 2α,3α-diol, esterification of which by propionic or butyric anhydride produced the corresponding dipropionates or dibutyrates **107** (R = Et or Pr). In the final step the Δ^{22}-bond in compounds **107** is converted by *m*-chloroperbenzoic acid into a 22,23-epoxy to give the desired steroids **108** (Scheme 24).



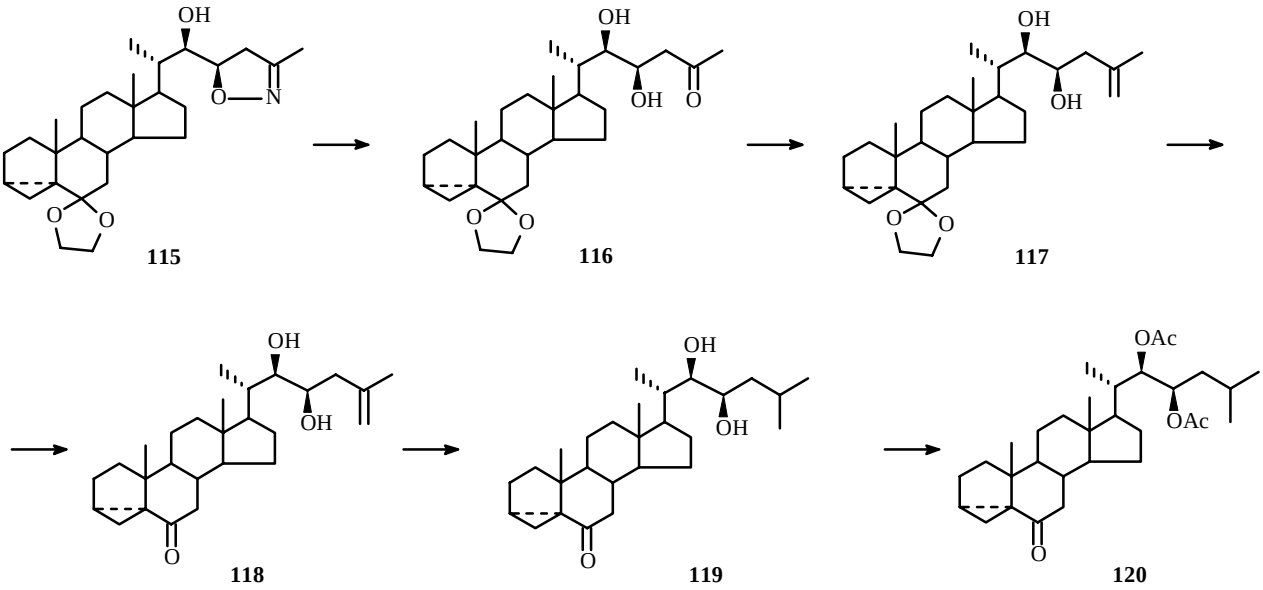
Scheme 24.

Brassinosteroid analogs with modified rings *B* were synthesized from stigmasterol [72]. First stigmasterol (**4**) was transformed as usual to the 3α,5-cyclo-6β-hydroxy derivative **109**, the Δ^{22}-bond of which was hydroxylated by osmium tetroxide and potassium ferricyanide in the presence of a chiral ligand to give 22,23-diol **110** and its (22S,23S)-isomer in yields of 40 and 17%, respectively. Isomerization of **110** by sulfuric acid in aqueous THF forms the corresponding 3,22,23-triol in 79% yield. Acetylation of this by acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine afforded triacetate **111** in 82% yield. Allylic oxidation of steroid **111** by pyridinium dichromate synthesized Δ^5-7-ketone **112** in 59% yield. Reaction with tosylhydrazine transformed **112** quantitatively into hydrazone **113**. Reaction of **113** with lithium hydride in toluene formed the corresponding 5,7-diene in 60% yield. Hydrolysis of the acetoxyls by methanolic KOH led to 3β,22,23-trihydroxysteroid **114** in 74% yield. Another brassinosteroid with the Δ^5-7-ketone in its structure is formed by analogous hydrolysis of the acetoxyls in compound **112** in 72% yield. Then, reduction of the 7-ketone in steroid **112** by $NaBH_4$ or L-selelectride produced the corresponding 7β- and 7α-alcohols in 92 and 70% yields. Subsequent hydrolysis of the acetoxyls in these compounds gave the corresponding 3,7,22,23-tetrahydroxy derivatives (Scheme 25).

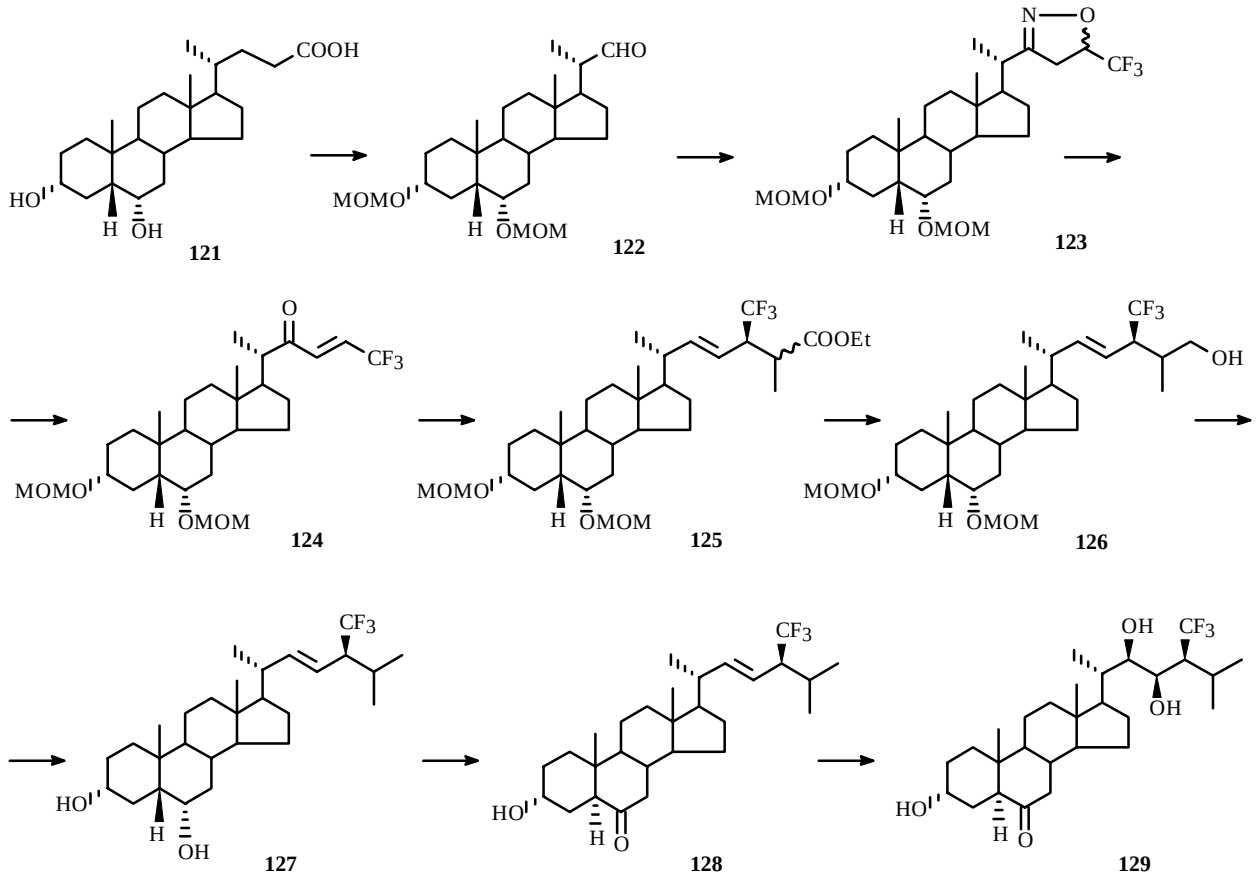


Scheme 25.

A new method for constructing the side chain of brassinolide and 28-norbrassinolide using isoxazolidine derivative **115** was developed [73]. Reductive cleavage of the heterocycle of compound **115** forms 22,23-dihydroxy-25-ketosteroid **116**. This compound is reacted in the next step with methyltriphenylphosphonium iodide and butyllithium to give Δ^{25}-steroid **117** in 85% yield. Removal of the protecting group in **117** synthesized 6-ketosteroid **118**. Hydrogenation of the Δ^{25}-bond in compound **118** over Pd on $BaSO_4$ gave saturated 22,23-dihydroxy-6-ketosteroid **119**, which was then converted as usual to diacetate **120** (Scheme 26).



Scheme 26.



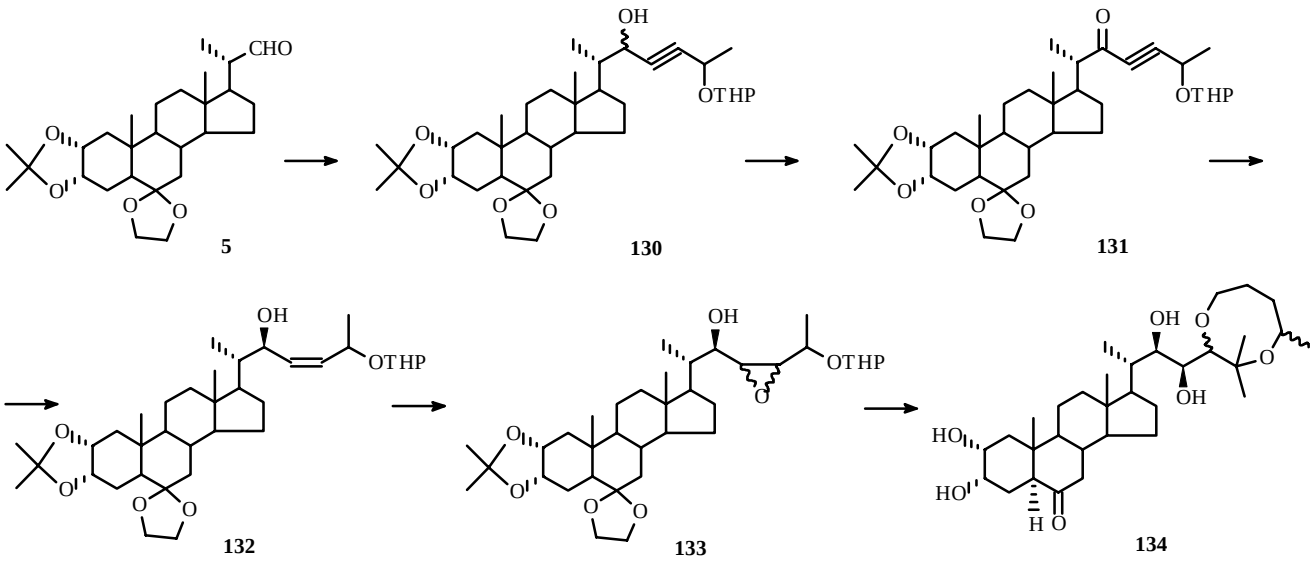
Scheme 27.

Hydroxycholic acid (**121**) was the starting material for the preparation of the new brassinolide **129** [74]. First, 22-aldehyde **122** was prepared by previously developed methods from **121**. Then, **122** was transformed as usual into the oxime in 75% yield, reaction of which with N-chlorosuccinimide gave the chlorooxime. Reaction of this with 3,3,3-trifluoroprop-1-ene in the presence of triethylamine formed trifluoromethylisoxazolidine **123**. Reductive cleavage of steroid **123** over Raney nickel

in the presence of boric acid and subsequent dehydration of the resulting 24-hydroxy-22-ketone that was formed in quantitative yield by methanesulfonyl chloride and triethylamine in methylenechloride gave Δ^{23}-22-ketone **124**. Reduction of the ketone in **124** by diisobutylaluminum hydride produced the 22-alcohol in 69% yield, Claisen rearrangement of which with triethylorthopropionate in the presence of propionic acid produced ester **125** in 95% yield. Reduction of the ester in compound **125** by $LiAlH_4$ formed alcohol **126** in 96% yield. Conversion of this alcohol to the mesylate, reduction of the mesylate by $LiAlH_4$, and hydrolysis of the protecting groups in rings *A* and *B* by pyridinium *p*-toluenesulfonate gave dihydroxysteroid **127**. Selective oxidation of the 6β-hydroxyl in **127** by pyridinium dichromate and isomerization at C-5 by HCl gave 3α-hydroxy-6-ketone **128** in 60% overall yield. Hydroxylation of the Δ^{22}-bond in **128** by osmium tetroxide and potassium ferricyanide in the presence of a chiral ligand formed the trifluoromethyl derivative of typhasterol **129** in 88% yield (Scheme 27).

It should be noted that bile acids saw limited application during the studied period for the synthesis of brassinosteroids. The synthesis of very simple analogs of brassinosteroids from chenodeoxycholic acid is also of some interest [75, 76]. The situation is analogous for the use of steroid sapogenins to synthesize brassinosteroids. In this respect, only a few studies can be mentioned [77, 78], in which tigogenin was used as starting material for this purpose.

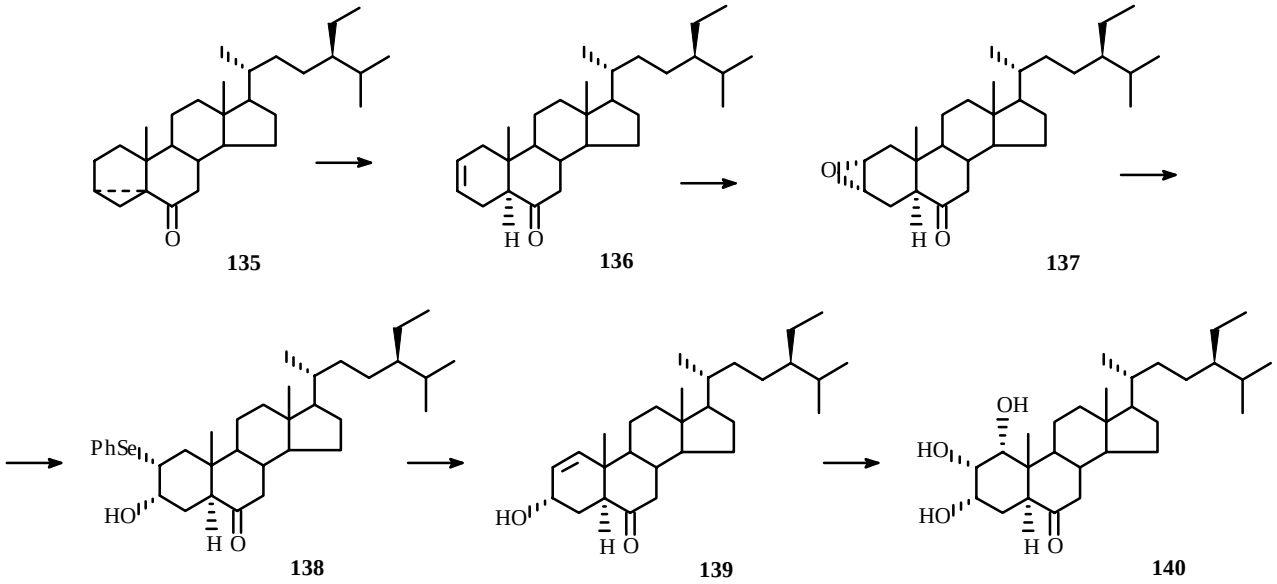
The brassinosteroid analog **134**, which represents a new structural type, was synthesized [79]. Reaction of 22-aldehyde **5** with the appropriate lithium derivative gave propargyl alcohol **130** as a 1:1 mixture of the (22R)- and (22S)-isomers. Oxidation of the hydroxyl in compound **130** by pyridinium chlorochromate in methylenechloride formed 22-ketosteroid **131** in 81% yield. Reduction of **131** by (R)-alpine-borane and subsequent catalytic hydrogenation produced (22R,23Z)-allyl alcohol **132**. Epoxidation of the double bond in **132** by *m*-chloroperbenzoic acid gave epimeric 23,24-epoxides **133**. Reaction of **133** with triethylaluminum in the presence of *n*-butyllithium and subsequent acid hydrolysis of the protecting groups gave the final brassinosteroid **134** (Scheme 28).



Scheme 28.

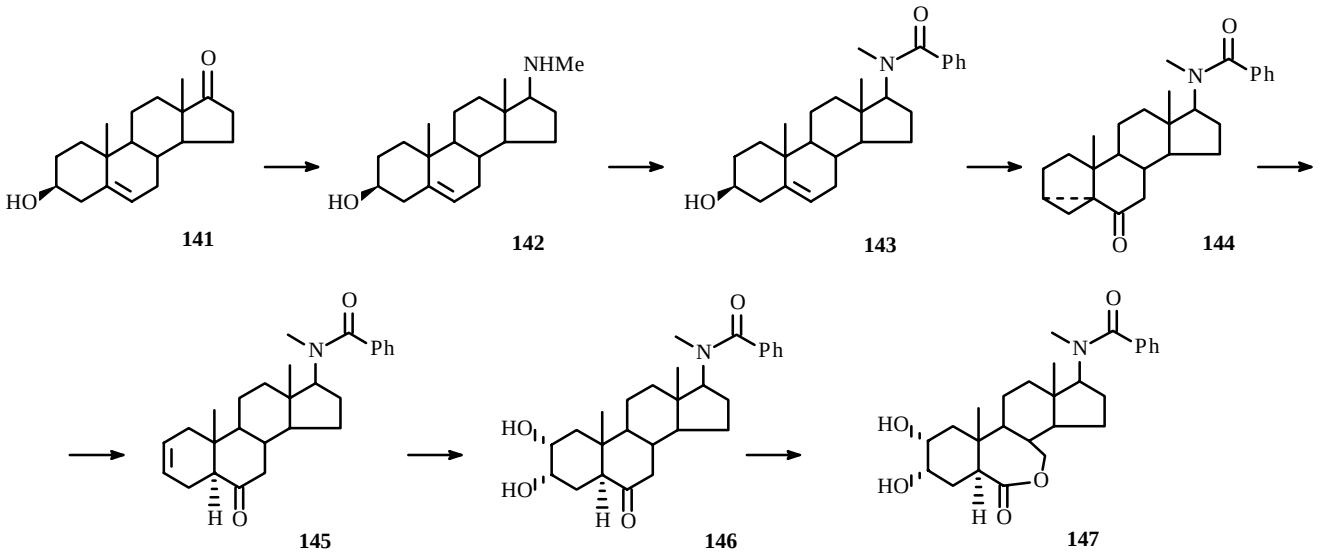
Another original brassinosteroid analog with an azide in the side chain was synthesized in 12 steps from stigmasterol [80]. The presence of the azide in the molecule makes it possible in principle to use this compound as a photo-active marker of the brassinosteroid receptor.

The synthesis of brassinosteroid analog **140**, with an additional 1α-hydroxyl in its structure, has been reported [81]. First, β-sitosterol was transformed by the usual methods into 3α,5-cyclo-6-ketosteroid **135**, isomerization of which by pyridinium hydrobromide in DMF gave Δ^2-6-ketone **136** in 52% yield. Oxidation of the Δ^2-bond in compound **136** by *m*-chloroperbenzoic acid to 2α,3α-epoxide **137**, opening of which by phenylselenylanion, and subsequent oxidation of the resulting hydroxyselenide **138** by hydrogen peroxide gave allylic alcohol **139**. In the final step, the double bond in compound **139** was *cis*-hydroxylated by osmium tetroxide in pyridine to form 1α,2α,3α-trihydroxy-6-ketosteroid **140** (Scheme 29).



Scheme 29.

Significant attention was paid during the studied period to the synthesis of various structural analogs of pregnane [82, 83] and androstane [84-88] brassinosteroids. An example of these studies is the synthesis of brassinosteroid analog **140** with a benzamide in the side chain [84]. Starting androstenolon **141** was transformed into the N-methylamine derivative **142**, from which benzamide **143** was then synthesized. Further transformation of **143** included formation of 3α,5-cyclo-6-ketone **144** and its isomerization to Δ^2-6-ketone **145**. Hydroxylation of the Δ^2-bond in steroid **145** formed 2α,3α-dihydroxy-6-ketone **146**, Baeyer—Villiger lactonization of which gave the desired lactone **147** (Scheme 30).

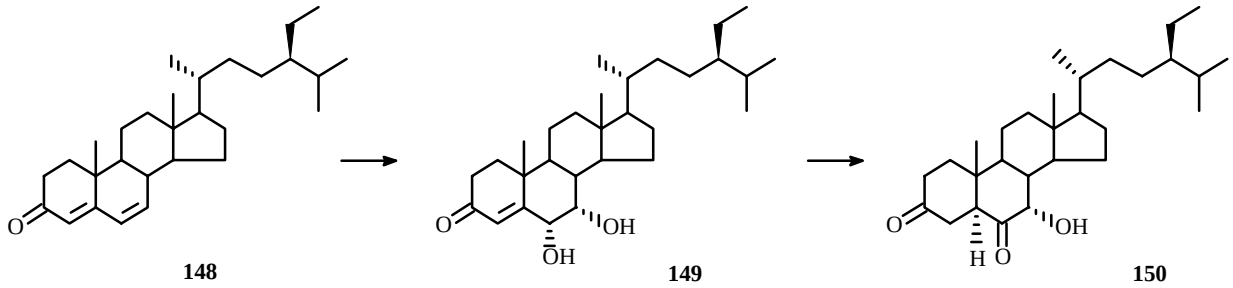


Scheme 30.

The synthesis of brassinosteroids has been investigated for more than two decades. Therefore, the development of new synthetic methods is apparently no longer the most urgent problem in this area. Several special studies of this problem have recently appeared [89-91]. Thus, a patent [89] describes a new method of catalytic asymmetric dihydroxylation of olefins in the presence of chiral ligands. One of the features of this method is the use of polymeric dihydroquinidine and dihydroquinine derivatives as the chiral ligands. The effect of added methanesulfonamide on the rate and product distribution from *cis*-

hydroxylation of Δ^{22}-steroids by osmium tetroxide in the presence of chiral ligands was studied in order to increase the yield of the corresponding (22R,23R)-22,23-diols [90].

A new attempt was made to form lactone ring *B* that is characteristic of brassinosteroids in 3 β-hydroxy-$\Delta^{5,7}$-steroids, for example, ergosterol [91]. Thus, the model 4,6-dien-3-ketone **148** was prepared from β-sitosterol and hydroxylated by osmium tetroxide and N-methylmorpholine-N-oxide to give 6α,7α-diol **149** in 63% yield. Reaction of compound **149** with potassium carbonate in methanol causes rearrangement to 7α-hydroxy-6-ketone **150** in 39% yield. Transformation of this class of compounds in several steps to the required lactones was noted earlier (Scheme 31).



148 **149** **150**

Scheme 31.

Considering the exceedingly complex problems that arise constantly in forming numerous chiral centers, research on the total synthesis of brassinosteroids at present is languishing. Only studies of the possibility of using intramolecular Diels—Alder cyclization in the initial steps of the total synthesis of castasterone are notable [92, 93].

In conclusion, it should be noted that research in general on the chemical synthesis of brassinosteroids is, as before, one of the most rapidly developing areas of steroid chemistry.

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