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SYNTHESIS OF ECDYSTEROIDS AND RELATED COMPOUNDS

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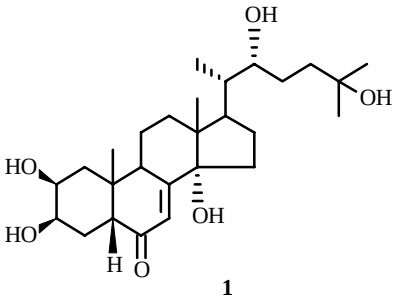
Literature data published in 1998-2002 on the chemical synthesis of ecdysteroids and their structural analogs were reviewed.

Key words: ecdysteroids, chemical synthesis.

Ecdysteroids are important steroidal hormones [1, 2] that form a large group of natural and synthetic compounds with chemical structures similar to that of the first representative, α-ecdysone (**1**), which was isolated from silkworm cocoons. A large number of these compounds has been observed in invertebrates, plants, and fungi [1-3]. They are divided into zoo-, phyto-, and mycoecdysteroids depending on the source from which they are isolated. The most characteristic features of the biological activity of ecdysteroids are hormonal control of molting and metamorphosis processes in insects at very low concentrations. Some ecdysteroids are toxic for insects if included in feed as a result of significant hormonal disruptions [1, 4-6]. Such specific hormonal functions of ecdysteroids make it possible to develop selective insecticides that are harmless for man and higher warm-blooded animals.



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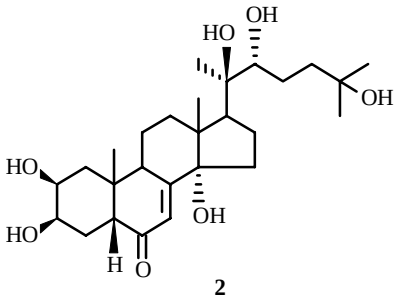

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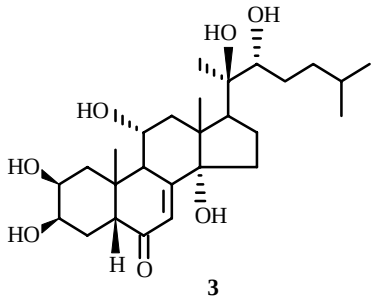

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The chemical structures of ecdysteroids consist of polyhydroxysteroids containing characteristic structural elements that join them into a single group. These elements include the 2,3-diol and 14α-hydroxy-Δ^7-6-ketone groups, *cis*-fusion of the A and B rings, and a steryl side chain with several hydroxyls. Characteristic representatives of ecdysteroids are α-ecdysone (**1**), 20-hydroxyecdysone (**2**), and ajugasterone C (**3**).

It is becoming more obvious that progress on the study of the biological activity of ecdysteroids and the prospects for their practical use depend on their availability. Their chemical synthesis from available starting materials is a critical problem because the natural sources of ecdysteroids are very limited. Considering the uniqueness of the ecdysteroid chemical structures, this problem can be solved successfully only with the invention of special synthetic methods that can introduce the necessary functional groups into the starting compounds. Special research on novel syntheses of ecdysteroides and their structural analogs is constantly conducted with this goal in mind.

Steroidal 5,6-epoxides are widely used in syntheses of ecdysteroids [1]. In particular, epoxidation of 3β-chloro-Δ^5-stigmastanes **5b-c** by *m*-chloroperbenzoic acid produced 5α,6α-epoxides **6b-c**, which then were used further to synthesize 5α-hydroxy derivatives of brassinosteroids [7]. Oxidation of **5a-c** by trifluoroperacetic acid was studied in a search for new synthetic routes to 5α,6α-epoxides of the **6a-c** type [8]. The starting 3β-chloro-Δ^5-steroids **5a-c** were prepared by previously developed methods using reactions of cholesterol **4a**, β-sitosterol **4b**, and stigmasterol **4c** with thionylchloride (Scheme 1).

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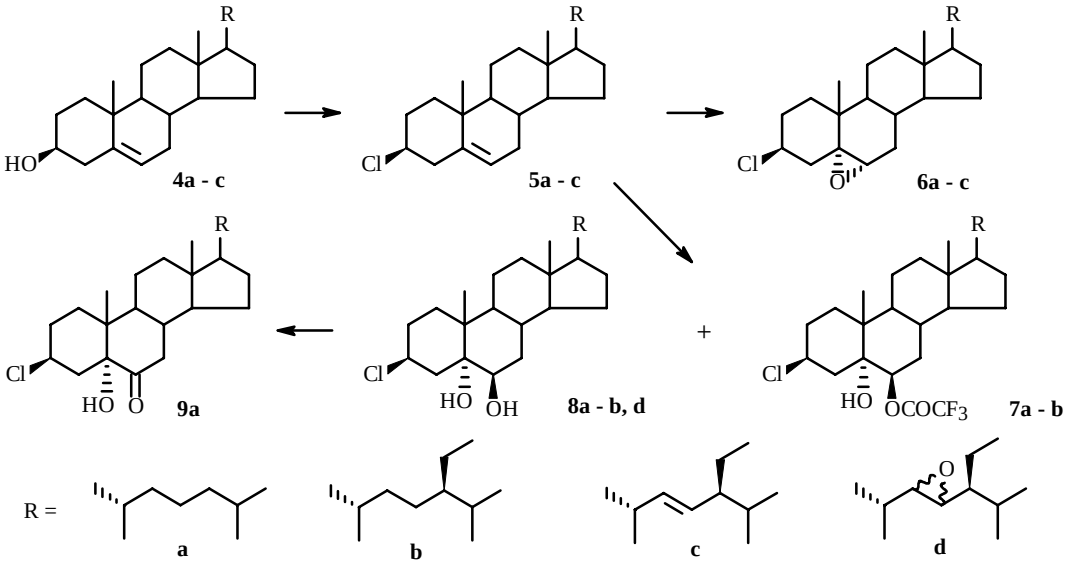
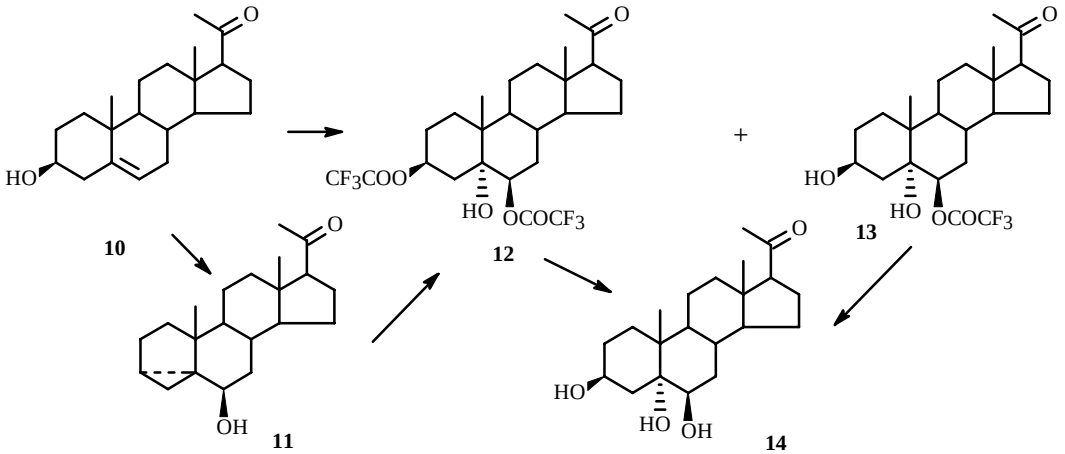


Scheme 1.

It was found that the reaction of 3β-chloro-Δ^5-steroids **5a-c** with trifluoroperacetic acid in $CHCl_3$ or CH_2Cl_2 is complicated and forms three products as a minimum. Thus, a mixture of 5α,6α-epoxide **6a**, the 6-trifluoroacetate of 5α,6α-diol **7a**, and pure 5α,6β-diol **8a** was isolated after oxidation of 3β-chlorocholest-5-ene **5a** with this reagent in $CHCl_3$ and subsequent chromatographic purification. The structure of compound **8a** was proven by Jones oxidation with chromic acid in acetone to the known 3β-chloro-5α-hydroxy-6-ketone **9a**. Hydrolysis of a mixture of **6a** and **7a** by aqueous NaOH in a mixture of ethanol and THF resulted in the isolation of unreacted 5α,6α-epoxide **6a** and 5α,6α-diol **8a**. Oxidation of 3β-chlorostigmastene **5b** by trifluoroperacetic acid occurs analogously. Chromatographic separation of the reaction-product mixture produced pure 5α,6α-epoxide **6b**, its mixture with the 6-trifluoroacetate **7b**, and 5α,6β-diol **8b**. Base hydrolysis of the mixture of **6b** and **7b** by aqueous NaOH in an ethanol—THF mixture isolated additional amounts of 5α,6α-epoxide **6b** and 5α,6β-diol **8b**. The total yields of these compounds were 15 and 53%, respectively.

Reaction products from oxidation of 3β-chlorostigmasta-5,22-diene **5c** by trifluoroperacetic acid were hydrolyzed by NaOH solution immediately without separation. 5α,6β-Dihydroxy-22,23-epoxysteroid **8d** was isolated in 65.4% yield as a mixture of the (22*R*,23*R*)- and (22*S*,23*S*)-epimers.

Next we studied oxidation by trifluoroperacetic acid of pregnane steroids **10** and **11** [9]. We found that the principal products from reaction of pregnenolone **10** with trifluoroperacetic acid are trifluoroacetates **12** and **13** in yields of 29 and 52%, respectively. Base hydrolysis of trifluoroacetates **9** and **10** forms 3β,5α,6β-triol **14**. We also determined whether pregnenolone **10** could be converted to triol **14** in high yield by oxidation with trifluoroperacetic acid and subsequent base hydrolysis of the resulting trifluoroacetates without separating and purifying them (Scheme 2).

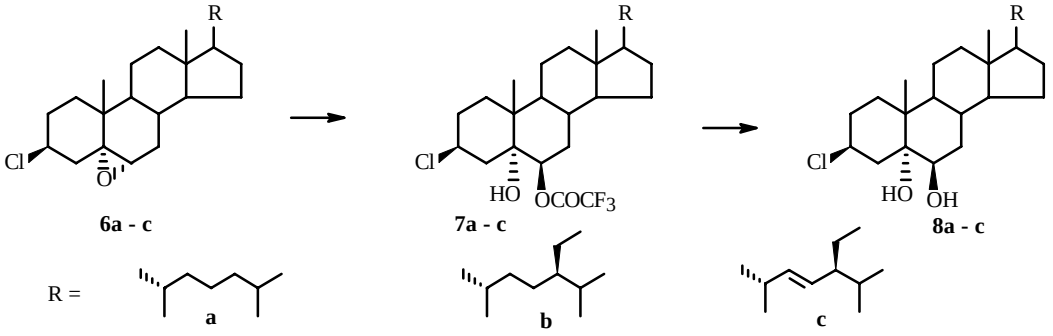


Scheme 2.

Trifluoroacetates **12** and **13** are produced by reaction of **11** with trifluoroperacetic acid. They are most probably formed by initial isomerization of **11** by trifluoroacetic acid into **10**, which is then oxidized by trifluoroperacetic acid.

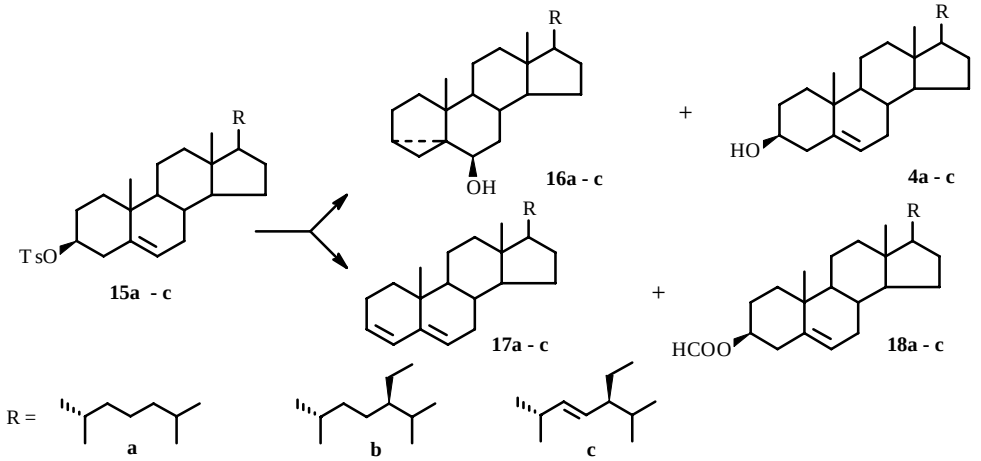
Thus, this reaction can be viewed as a synthetic method for introducing the 5α,6β-diol group into steroids. We note that 5α,6β-dihydroxysteroids have been isolated from various natural sources. They are also interesting independently as biologically active compounds. In particular, it has been demonstrated [10] that the 6-formate of 3β-chloro-5α,6β-diol **8a** exhibits high insecticidal activity for Colorado-beetle larvae.

One of the most probable paths to formation of trifluoroacetates **7a-b** may conclude with the opening of the 5α,6α-epoxide ring in **6a-b** by trifluoroacetic acid, which is present in the reaction mixture. A special investigation was performed to confirm this [11]. Starting 5α,6α-epoxides **6a-c** were prepared by reaction of sterols **4a-c** with thionylchloride and subsequent epoxidation of the resulting 3β-chloro-Δ^5-derivatives **5a-c** by *m*-chloroperbenzoic acid. As it turned out, the only products from reaction of **6a-c** with trifluoroacetic acid in $CHCl_3$ are the 6-trifluoroacetates of 5α,6β-diols **7a-c**. They are rather stable thermally and were isolated from the reaction mixture in high yield. The structures of **7a-c** were confirmed convincingly by hydrolysis with NaOH solution in an ethanol—THF mixture to 5α,6β-diols **8a-c** (Scheme 3).



Scheme 3.

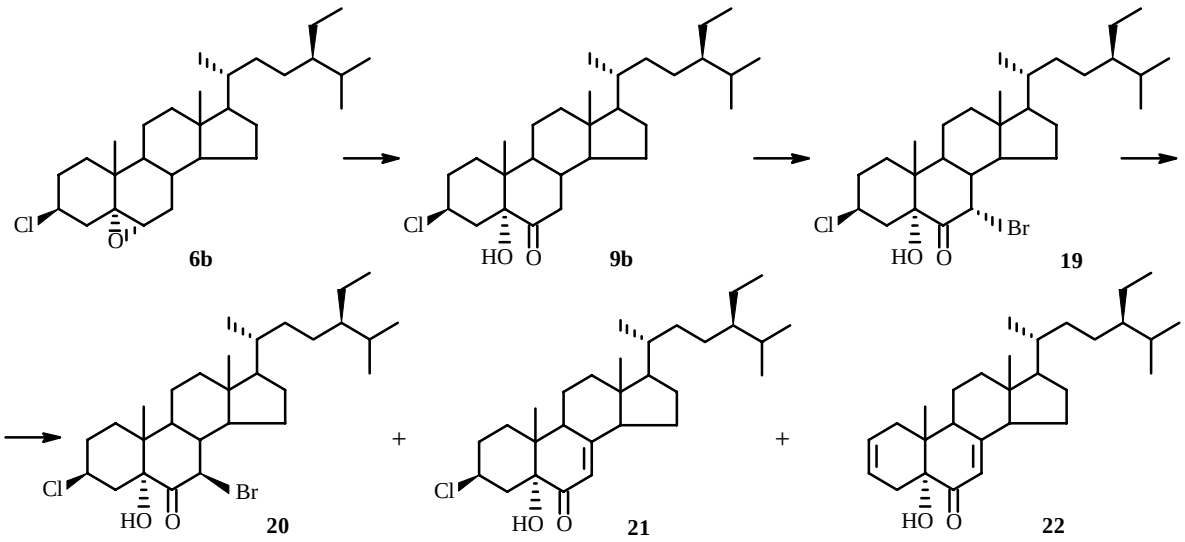
An important structural fragment that distinguishes ecdysteroids from other natural steroids is the 6-ketone. The most common method for introducing it is the rearrangement of tosylates (or mesylates) of 3β-hydroxy-Δ^5- or 3β-hydroxy-$\Delta^{5,7}$-sterols into 3α,5-cyclo-6β-hydroxysteroids and their subsequent oxidation to the 3α,5-cyclo-6-ketones [1]. However, the rearrangement in aqueous acetone in the presence of K (or Na) acetate that is usually used in experiments with sterols of the **4a-c** type has several drawbacks. Therefore, solvolysis of tosylates of sterols **15a-c** in aqueous DMF was studied in order to develop a new method for synthesizing 3α,5-cyclo-6β-hydroxysteroids [12]. Heating a solution of the tosylate of cholesterol **15a** in aqueous DMF in the presence of NaOAc formed four products. The main product was 3α,5-cyclo-6-alcohol **16a**, which was isolated in about 50% yield. The second compound was cholesterol **4a**, which was isolated in >10% yield. Besides these compounds, the formate of cholesterol **18a** was prepared in 25% yield from the reaction mixture. A minor product that was isolated from the reaction mixture in insignificant yield was 3,5-diene **17a**, which was formed by an elimination reaction (Scheme 4).



Scheme 4.

Solvolysis of the tosylate of β-sitosterol **15b** produces mainly 3α,5-cyclo-6-alcohol **16b**. Minor reaction products are 3,5-diene **17b** and the 3-formate **18b**. It was found that solvolysis of the tosylate of stigmasterol **15c** under conditions analogous to those described above produced also 3α,5-cyclo-6-alcohol **16c**, stigmasterol **4c**, and the formate of stigmasterol **18c**, which were isolated from the reaction mixture in yields of 41.3, 19.4, and 32.6%, respectively.

Steroidal 3β-chloro-5α,6α-epoxides and 3β-chloro-5α-hydroxy-6-ketones were used further to prepare 5α-hydroxy-2,7-dien-6-ketosteroids, which are important intermediates in the synthesis of ecdysteroids [13]. Thus, reaction of **4b** with thionylchloride synthesized in 82% yield the corresponding 3β-chloro derivative **5b**. Further oxidation of **5b** by H_2O_2 in a mixture of formic acid and THF formed 5α,6α-epoxide **6b**, which then underwent Jones oxidation to 3β-chloro-5α-hydroxy-6-ketone **9b** in 62% yield. Bromination of **9b** in acetic acid in the presence of HBr with heating produced 3β-chloro-7α-bromo-6-ketone **19** in quantitative yield (Scheme 5).

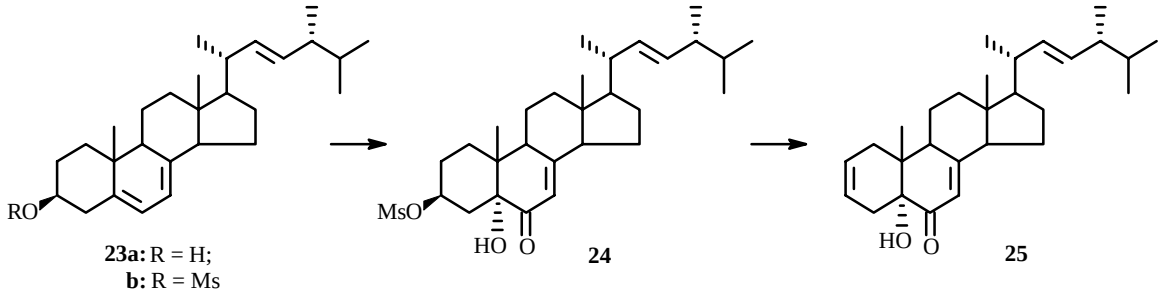


Scheme 5.

Dehydrohalogenation by lithium carbonate and bromide in DMF was used to introduce Δ^2- and Δ^7-bonds into **19**. Performing the elimination reaction with boiling produced a complicated product mixture. Isomerization to form 7β-bromo-6-ketone **20** in 65% yield was the main reaction at 100°C. The dehydrobromination product **21** was isolated in 13% yield and small quantities of the starting material were isolated in addition to the main product. It was then found that the yield of **20** increased to 71% by reaction of **19** in DMF with only Li_2CO_3. Significant quantities of the Δ^7-6-ketone were not observed. This can be explained by the fact that the absence of LiBr in the reaction mixture hindered markedly the dehydrobromination. As a result, the main reaction became the isomerization.

We studied the reaction of **19** with lithium carbonate and bromide in DMF at 130-135°C. Carrying out the reaction for 1.5 h produced 3β-chloro-5α-hydroxy-Δ^7-6-ketone **21** and 5α-hydroxy-$\Delta^{2,7}$-6-ketone **22** in yields of 42 and 33%, respectively. Extending the reaction time at 135°C to 6 h avoided the formation of **21** and formed **22** in 50% yield. It was also demonstrated that both **20** and **21** were dehydrohalogenated to **22** in yields of 47 and 38%, respectively, after reaction at 135°C for 6 h.

A second method for preparing 5α-hydroxy-2,7-dien-6-ketones is based on the use of sterols containing a 5,7-diene as the starting materials [14]. Therefore, ergosterol **23a** first reacted with methanesulfonyl chloride in pyridine to give mesylate **23b**, which was converted without purification by oxidation with chromic acid in a mixture of ether and CH_2Cl_2. Steroid **24** was isolated in 33% overall yield. The Δ^2-bond was introduced into **24** by elimination using Li_2CO_3 in DMF with boiling and a mixture of Li_2CO_3 and LiBr under analogous conditions. In both instances 5α-hydroxy-2,7,22-trien-6-one **25** was produced in approximately identical yields of 44-48% (Scheme 6).



23a: R = H;
b: R = Ms

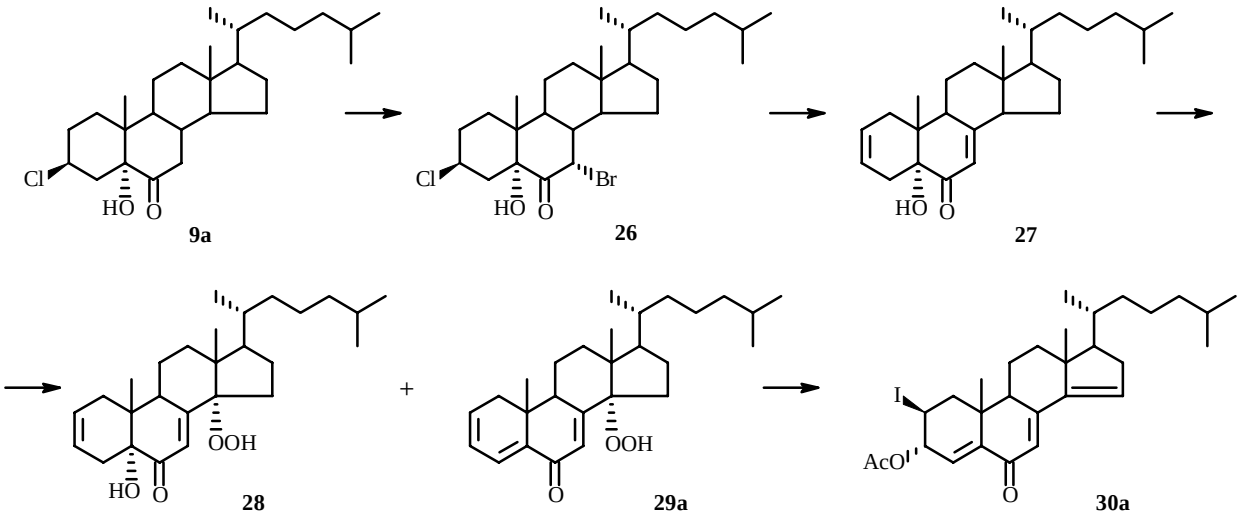
24 **25**

Scheme 6.

Dehydration of 5α-hydroxy-2,7-dien-6-ketosteroids was studied to prepare the corresponding 2,4,7-trien-6-ketosteroids, which we examined as intermediates in the synthesis of 4-dehydroecdysteroids [15]. We used a scheme that was developed earlier for the stigmastane series to synthesize 5α-hydroxy-2,7-dien-6-ketone **27**. The starting cholesterol **4a** first reacted with thionylchloride to give 3β-chloro derivative **5a** in quantitative yield. Then, treatment of **5a** with H_2O_2 in a formic acid—THF mixture followed by Jones oxidation with chromic acid formed the three products 3β-chloro-5α,6β-diol **8a**, its 6-monoformate, and 3β-chloro-5α-hydroxy-6-ketone **9a**, which were isolated in yields of 12, 15, and 30%, respectively [10]. Jones oxidation of a mixture of **8a** and its 6-formate gave additional quantities of **9a** in 77% yield. Repeated oxidation produced **9a** in 44% overall yield from **5a** [16].

Bromination of ketone **9a** with heating in acetic acid in the presence of HBr produced 3β-chloro-5α-hydroxy-7α-bromo-6-ketone **26** in 60% yield. Dehydrohalogenation of compound **26** by Li_2CO_3 and LiBr with heating in DMF under conditions used earlier for the stigmastane series gave the required 2,7-dien-5α-hydroxy-6-ketone **27** in 41% yield [16].

It was proposed to study the dehydration conditions of **27** for subsequent syntheses [15]. Several attempts to eliminate the 5α-hydroxyl in this compound by reaction with thionylchloride in pyridine were unsuccessful. Better results for dehydration of compound **27** were obtained with basic aluminum hydroxide in toluene with heating. Depending on the reaction conditions, 5-hydroxy-14α-hydroperoxy-5α-cholesta-2,7-dien-6-one **28** and 14α-hydroperoxycholesta-2,4,7-trien-6-one **29a** were isolated in yields of about 20 and 30%, respectively, in addition to unreacted starting material. We noted that the principal product of Woodward *cis*-hydroxyation of **29a** was 2β-iodo-3α-acetoxy-$\Delta^{4,7,14}$-6-ketosteroid **30a**, which was isolated after chromatographic purification in 36% yield [15] (Scheme 7).



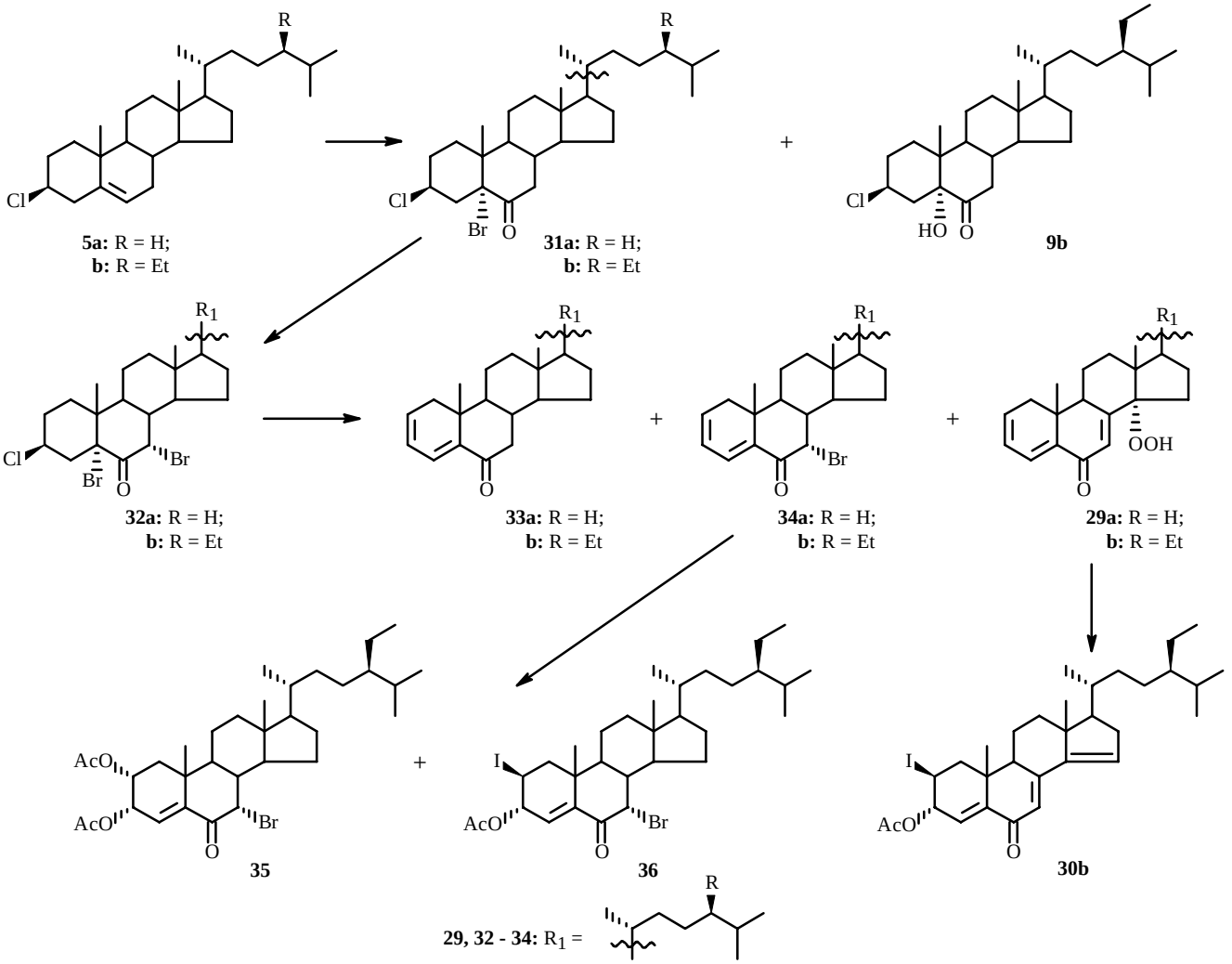
9a **26** **27**

28 **29a** **30a**

Scheme 7.

The comparatively low yield of compound **29a** by dehydration of **27** prompted us to develop alternative methods for synthesizing 14α-hydroperoxy-2,4,7-trien-6-ketosteroids [17]. Therefore, **4a** was first converted by reaction with thionylchloride in 96% yield to 3β-chloro derivative **5a**. Then, addition of HOBr to the 5(6)-double bond of **5a** and oxidation of the resulting

bromohydrin with chromic acid synthesized 3β-chloro-5α-bromo-6-ketosteroid **31a** in an overall yield of >70%. It should be noted that the preparation of **31a** from 3β-chloro-Δ^5-steroid **5a** without isolation of the intermediate bromohydrin has a certain advantage over the previously developed method [18] (Scheme 8).



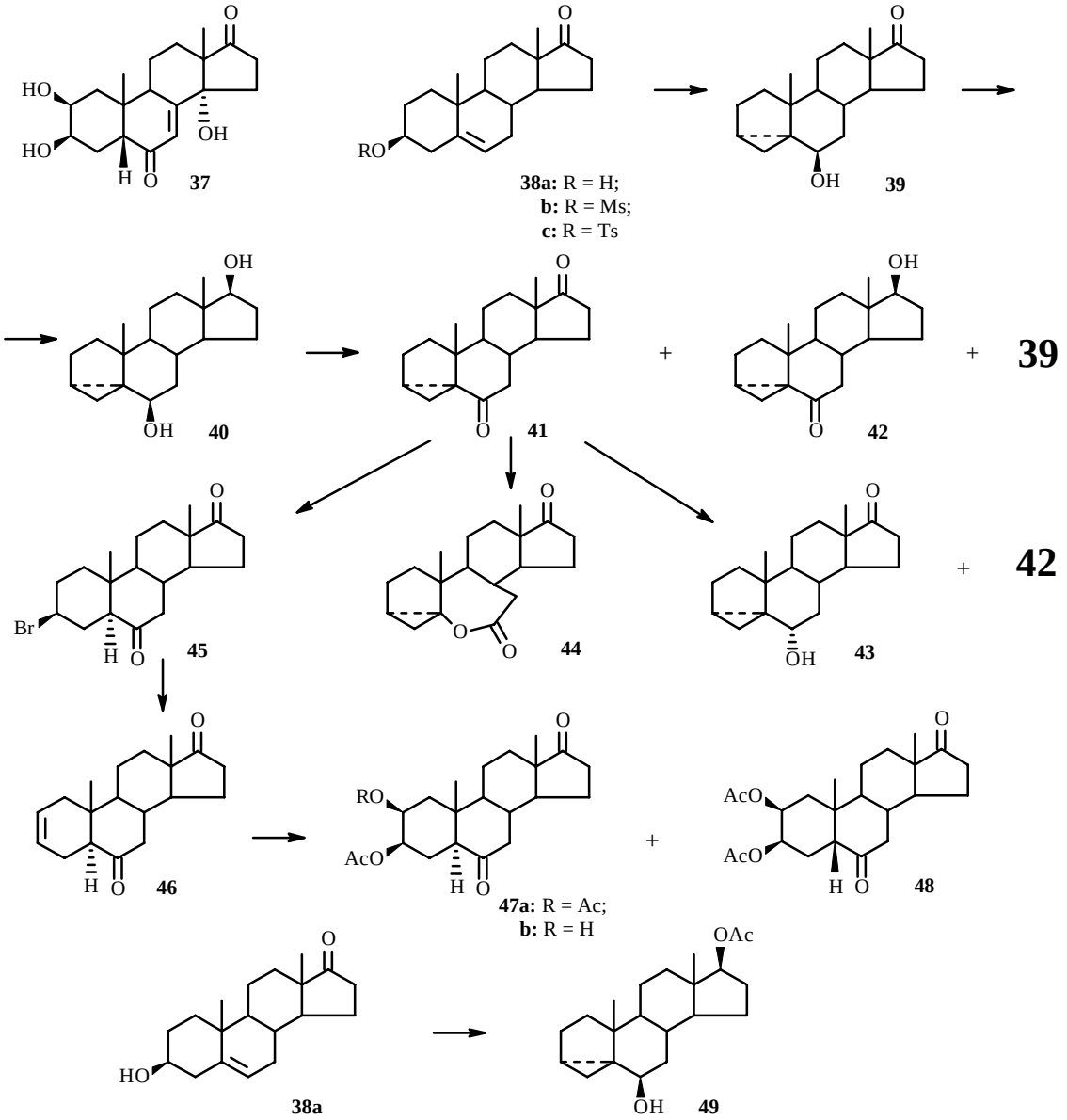
Scheme 8.

Analogously, reaction of **4b** with thionylchloride gave 3β-chloro derivative **5b**. Addition of HOBr to the 5(6)-double bond of **5b** in aqueous THF and subsequent oxidation with chromic acid without isolation of the resulting bromohydrin synthesized 3β-chloro-5α-bromo-6-ketosteroid **31b** in about 40% yield. It was also found that a side product in this synthesis is 3β-chloro-5α-hydroxy-6-ketone **9b** in 10% yield. In the next step, bromination of **31a** by heating in a mixture of HOAc—$CHCl_3$ in the presence of HBr gave 3β-chloro-5α,7α-dibromo-6-ketone **32a** in ~80% yield. Bromination under analogous conditions of **31b** gave 5α,7α-dibromo-6-ketone **32b** in >70% yield. Then steroid **32a** was dehydrohalogenated by Li_2CO_3 and LiBr in DMF with brief boiling to isolate 7α-bromo-2,4-dien-6-one **34a**, 14α-hydroperoxy-2,4,7-trien-6-one **29a**, and 2,4-dien-6-one **33a** in yields of 25, 21, and 23%, respectively. Analogous dehydrohalogenation of **32b** forms also 7α-bromo-2,4-dien-6-one **34b**, 14α-hydroperoxy-2,4,7-trien-6-one **29b**, and 2,4-dien-6-one **33b** in yields of 36, 30, and 17%, respectively.

It was found that Woodward hydroxylation of **34b** and subsequent acetylation forms mainly 2β-iodo-7α-bromo-3α-acetoxy-Δ^4-6-ketone **36** and 7α-bromo-2α,3α-diacetoxy-Δ^4-6-ketone **35** in yields of 22 and 30%, respectively. Woodward hydroxylation of **29b** and subsequent acetylation gives 2β-iodo-3α-acetoxy-$\Delta^{4,7,14}$-trien-6-one **30b**, which was isolated from the reaction products in 23% yield.

We also studied the comparative reactivity of the hydroxy- and ketone groups on C-6 and C-17 in 3α,5-cycloandrostane derivatives in an attempt to use rubrosterone **37** in the synthesis of the C_{19}-ecdysteroid [19]. The starting material in these syntheses is commercially available androstenolone **38a**, which was converted to mesylate **38b**. Rearrangement of **38b** by KOAc in aqueous acetone and subsequent oxidation of the resulting 3α,5-cyclo-6β-ol **39** with chromic acid produced 6,17-diketosteroid **41** in overall yield of 61%. Rearrangement of tosylate **38c** by K_2CO_3 in aqueous acetone and subsequent oxidation of the intermediate steroid **39** were used in a second approach. The required diketosteroid **41** was obtained from **38a** without isolation of the intermediates **38c** and **39** in overall yield of 74%.

One of the intermediates in previously developed synthetic schemes for **37** was 17β-hydroxy-6-ketone **42**. We hoped to synthesize alcohol **42** either by selective oxidation of 6β,17β-diol **40** or reduction of 6,17-diketone **41**. First, the usual rearrangement of androstenolone mesylate **38b** synthesized 6β-hydroxy-17-ketone **39** in 65% yield. Reduction of **39** with $NaBH_4$ gave **40** in 91% yield. Further oxidation of **40** with the calculated amount of chromic acid in acetone produced four compounds. The principal product was **41** in 62% yield. The required **42** was isolated as a mixture with **39** in overall yield of only 29%. The minor products were **39** and starting **40** in yields of 5 and 3%, respectively (Scheme 9).



Scheme 9.

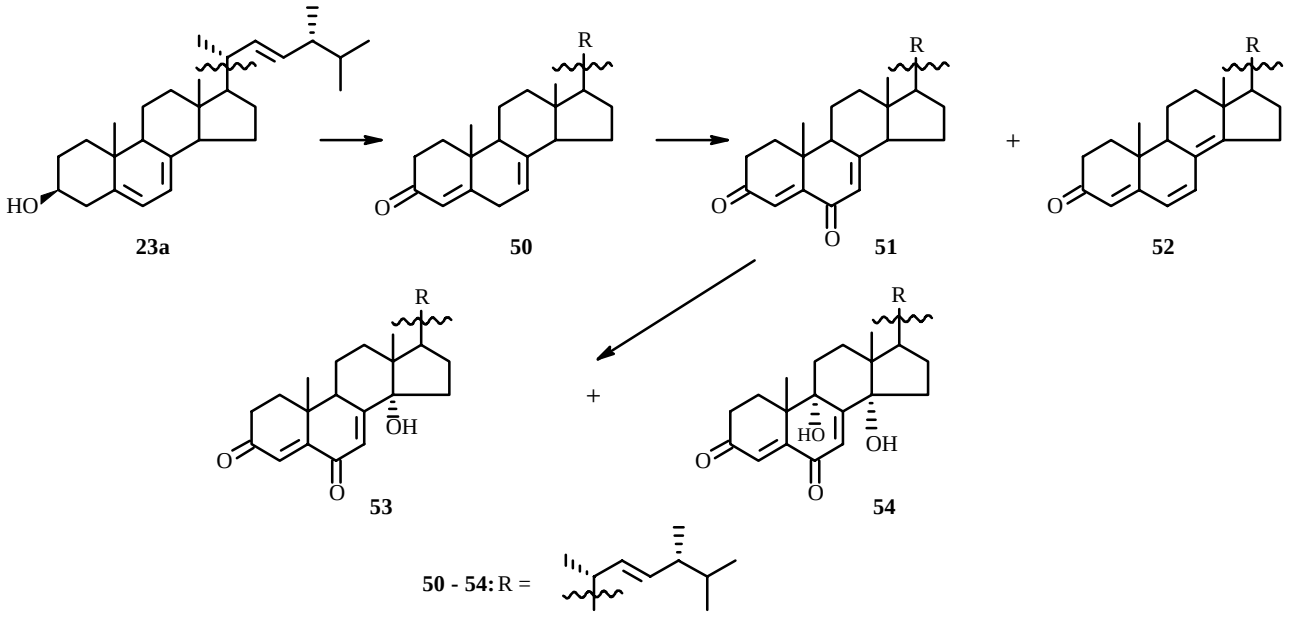
Next, reduction of **41** with $NaBH_4$ in CH_3OH forms a mixture of two compounds, the required 17β-hydroxy-6-ketone **42** and 6α-hydroxy-17-ketone **43** with the former predominating. However, the selectivity of this reaction is still insufficient to use it as a synthetic method for preparing rubrosterone. Oxidation of **41** with trifluoroacetic acid was also studied. The principal reaction product was lactone **44** in 32% yield.

Reaction of **41** with HBr in CH_3CO_2H produced 3β-bromo-6-ketone **45** in 91% yield. However, its dehydrobromination by Li_2CO_3 and LiBr in DMF with boiling was unsatisfactory. The desired Δ^2-steroid **46** could be isolated pure with a yield of only 23%. 3α-5-Cyclosteroid **41** was formed as a side product. Direct isomerization of **41** by reaction with *p*-toluenesulfonic acid in sulfolane with heating was a more convenient method for preparing **46** in 81% yield.

Then the reactivity of 2β,3β-diacetoxy-*trans*-A/B-6,17-diketosteroid **47a** was studied. This compound can be prepared through Woodward *cis*-hydroxylation of the Δ^2-bond in **46**. Therefore, **46** was first hydroxylated by AgOAc and I_2 in aqueous acetic acid. Then, the reaction product was isomerized with K_2CO_3 in aqueous methanol. Naturally, hydrolysis of the acetoxy group also occurred. Therefore, the resulting 2,3-diols were converted to acetates by acetylation with acetic anhydride in pyridine. A mixture of *trans*-A/B-6,17-diketosteroid **47a** and its *cis*-A/B-isomer **48** could be isolated in an overall yield of 25% as a result of these chemical transformations and subsequent chromatographic separation. In addition to these compounds, insignificant quantities of **7b** could also be isolated from the reaction mixture. Further acetylation of **47b** with acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine over 4 d produced practically pure **47a** in quantitative yield.

In the final step, mesylation of androstenolone **38a**, reduction of the 17-ketone in the resulting mesylate **38b**, and acetylation of the 17β-hydroxyl and isomerization in rings A and B with NaOAc in aqueous acetone produced 6β,17β-diol 17-monoacetate **49** in overall yield of about 30%. Compound **49** was previously used to synthesize structural analogs of rubrosterone [1]. The method developed by us for its synthesis without isolation of the intermediates has several advantages over the previously described method and is therefore interesting for preparing androstane ecdysteroids.

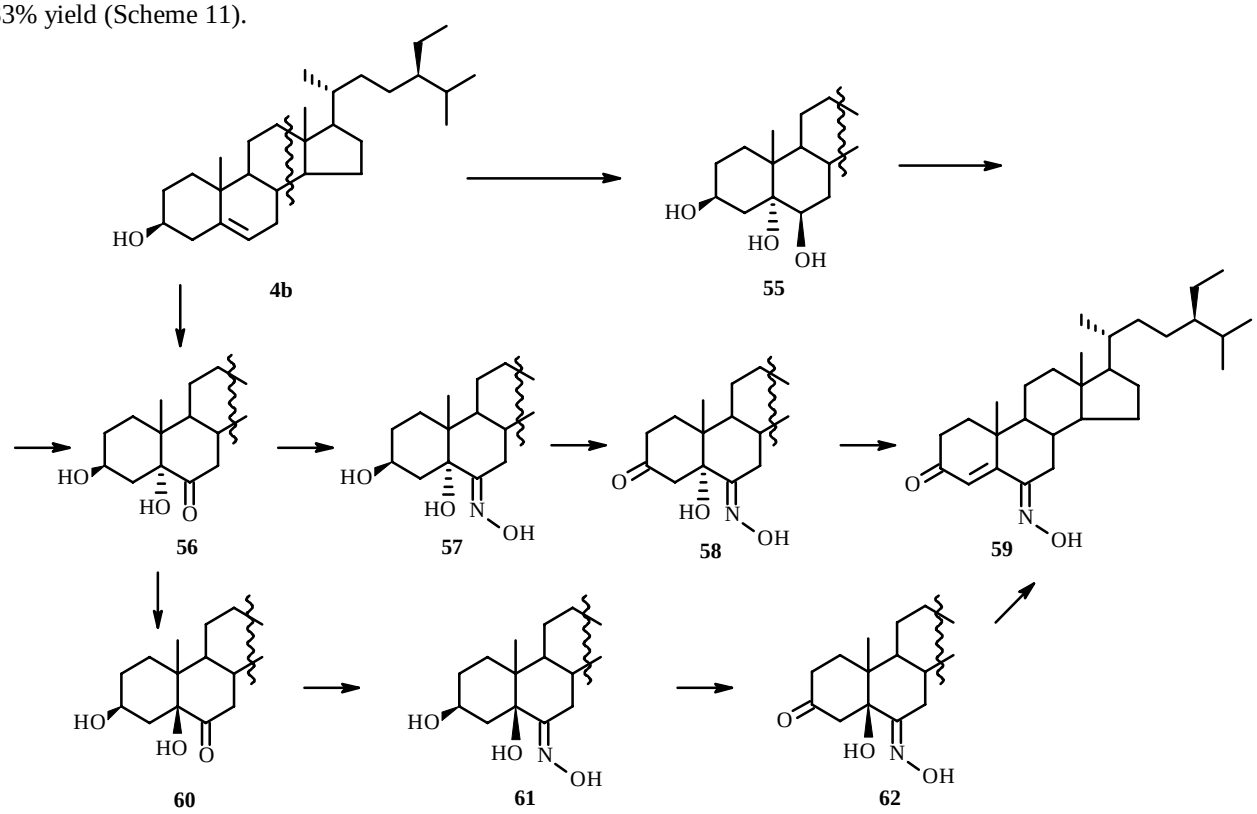
Various ergosterol derivatives with structures similar to ecdysteroids were isolated from various fungi [4]. The syntheses of (22*E*,24*R*)-ergosta-4,7,22-trien-3,6-dione **51** and its 9α,14α-dihydroxy derivative **54**, which is known as the previously identified calvasterol **B** [20, 21], have been reported [22, 23]. Interest in compounds of such structure has risen considerably. In particular, it was found [24, 25] that cholestane derivatives related to them participate in the biosynthesis of ecdysteroids in crustaceans (Scheme 10).



Scheme 10.

First ergosterol **23a** was oxidized according to Oppenauer. This produced $\Delta^{4,7,22}$-3-ketosteroid **50** in 74% yield. In the next step, **50** was oxidized with CrO_3 in a CH_2Cl_2—C_5H_5N mixture. The principal isolated reaction products were starting **50**, the desired $\Delta^{4,7,22}$-3,6-diketone **51**, and $\Delta^{4,6,8(14),22}$-3-ketone **52**. In the final step, **51** was oxidized with SeO_2 in dioxane. This formed 14α-hydroxy-$\Delta^{4,7,22}$-3,6-diketone **53** and 9α,14α-dihydroxy-$\Delta^{4,7,22}$-3,6-diketone **54**, which were isolated from the reaction mixture in yields of 24 and 23%, respectively [22, 23].

Sponges are a rich source of a large number of polyhydroxysteroids of various structure [26]. A report recently appeared on the isolation from *Cinachyrella alloclada* and *C. apion* of two steroid oximes [27]. One of these has the structure (24*R*,6*E*)-24-ethylcholest-6-hydroxyimino-4-en-3-one **59**. We developed a synthetic scheme that enables the preparation of the required oxime **59** by a short route in rather high overall yields [28]. Thus, starting **4b** was *trans*-hydroxylated in the first step with H_2O_2 in HCO_2H. This produced 3β,5α,6β-triol **55** in quantitative yield. Then, **55** was oxidized with N-bromosuccinimide in aqueous dioxane in 78% yield to 3β,5α-dihydroxy-6-ketone **56**. Reaction of **56** with hydroxylamine in ethanol in the presence of NaOAc produced oxime **57** in greater than 80% yield. Oxidation of **57** with chromic acid in THF synthesized 3-ketosteroid **58** in 55% yield. In the final step, **58** was dehydrated by basic Al_2O_3 with boiling in dioxane to **59** in 83% yield (Scheme 11).

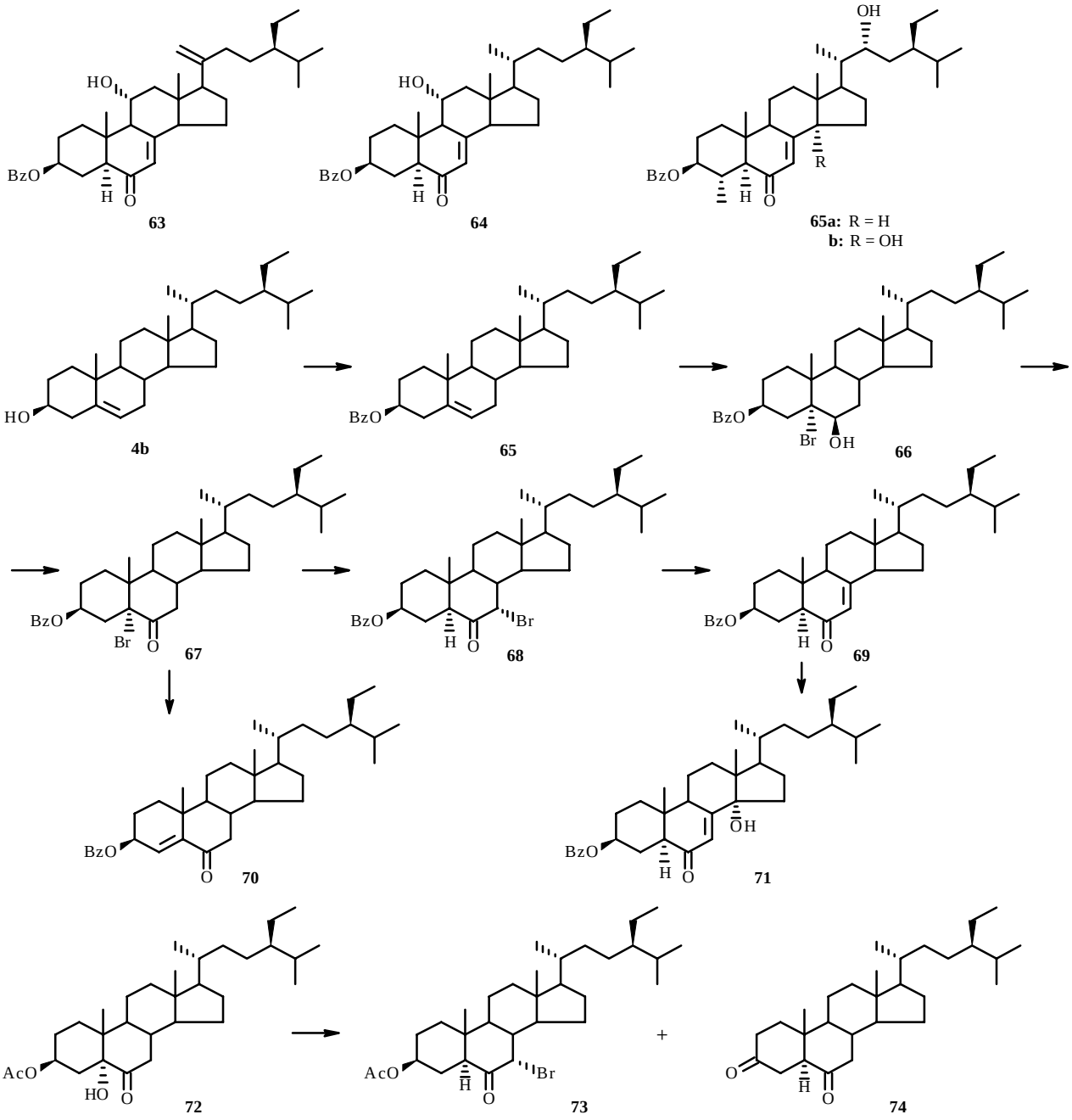


Scheme 11.

It should be noted that steroidal oximes of analogous structures were synthesized specially and turned out to be exceedingly active inhibitors of aromatase [29]. Therefore, studies of the syntheses of steroidal oximes were continued [30] with β-sitosterol. As in the previous work [28], starting **4b** was *trans*-hydroxylated by H_2O_2 in HCO_2H in the first step and converted in quantitative yield to 3β,5α,6β-triol **55**. Oxidation of it with N-bromosuccinimide in aqueous dioxane produced 3β,5α-dihydroxy-6-ketone **56** in yields up to 80%. Isomerization with KOH in C_2H_5OH converted it in 70% yield to 3β,5β-dihydroxy-6-ketone **60**. Reaction of **60** with hydroxylamine in C_2H_5OH in the presence of NaOAc gave oxime **61** in quantitative yield. Then, **61** was oxidized with chromic acid in THF to form a mixture of 5β-hydroxy-3-ketosteroid **62** and unsaturated steroid **59**. Dehydration of the mixture of **62** and **59** with $Al(OH)_3$ in dioxane with boiling produced pure unsaturated oxime **59** (Scheme 11).

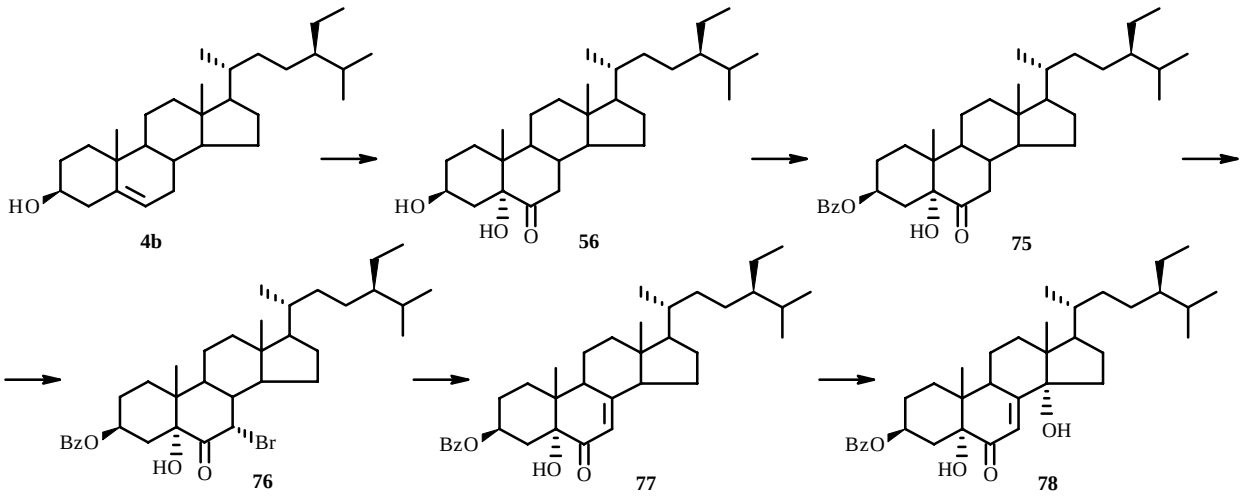
Phytosterols physanol A **63** and B **64** were isolated from fruit of *Physalis franchetti* [31]. Carpesterol **65a** and its 14α-hydroxy derivative **65b** from *Solanum xanthocarpum* have similar structures [32-35]. Structural analogs of these steroids have been prepared [36, 37]. Thus, **4b** was reacted with benzoylchloride in C_5H_5N to give benzoate **65** in 95% yield. Addition

of HOBr to the 5(6)-double bond of **65** produced bromohydrin **66** in 56% yield. Oxidation of the hydroxyl in **66** with chromic acid formed 5α-bromo-6-ketone **67** in quantitative yield. Reaction of **67** with HBr with heating in acetic acid gave the required 7α-bromo-6-ketone **68** in 16% yield. Dehydrobromination of **68** with Li_2CO_3 and LiBr in DMF with boiling produced Δ^7-6-ketone **69** in 62% yield. Analogous dehydrobromination of **67** formed Δ^4-6-ketone **70**. Allylic hydroxylation of **69** with SeO_2 in dioxane synthesized 14α-hydroxy derivative **71** in 37% yield. It was shown that reaction of 6-ketone **72** with HBr in acetic acid gives **73** and **74** in yields of 38 and 40%, respectively (Scheme 12).



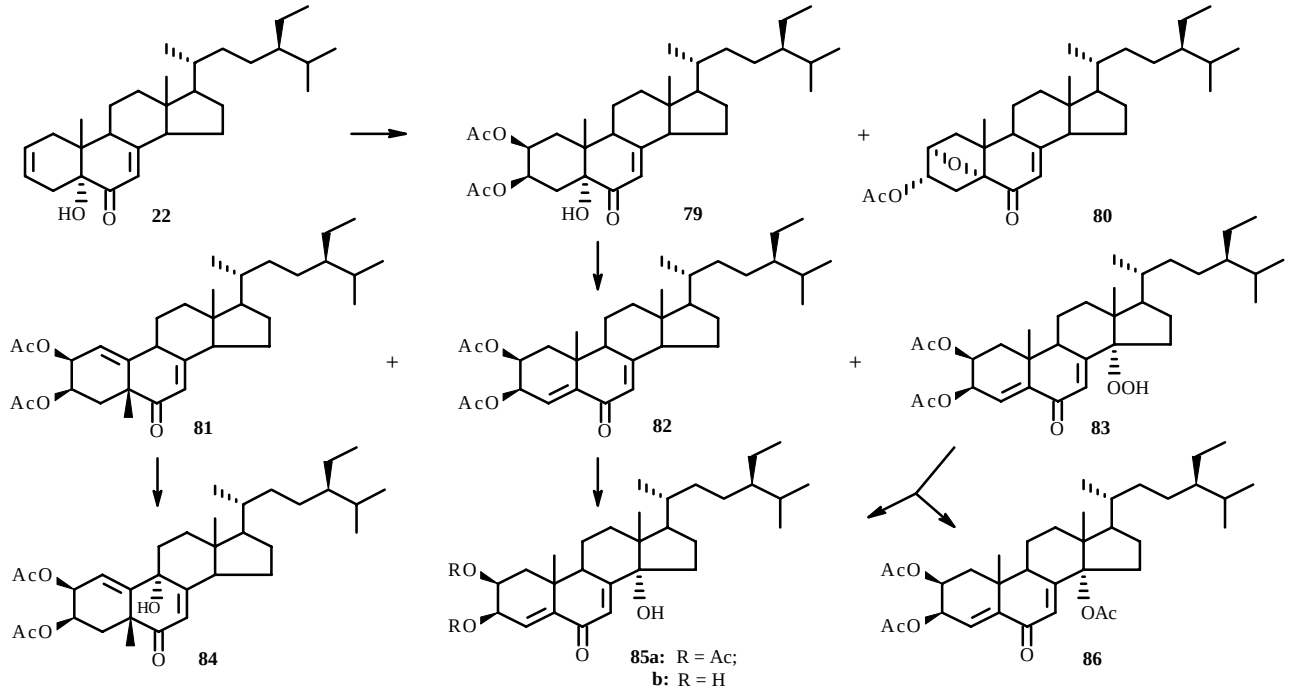
Scheme 12.

In addition to the above compounds, those related to physanols A and B that contain an additional 5α-hydroxyl were also synthesized [38]. First, starting β-sitosterol **4b** was *trans*-hydroxylated with H_2O_2 in HCO_2H. Further selective oxidation of the resulting 3β,5α,6β-triol converted it to 3β,5α-dihydroxy-6-ketosteroid **56**. In the next step, **56** was reacted with benzoylchloride in pyridine to give benzoate **75** in 81% yield. Further bromination of **75** in acetic acid produced 7α-bromoketone **76** in 92% yield. Dehydrobromination of **76** formed Δ^7-6-ketone **77**. Allylic oxidation by SeO_2 in dioxane was used to introduce the 14α-hydroxyl into **77**. This reaction produced the desired steroid **78** in 82% yield (Scheme 13).



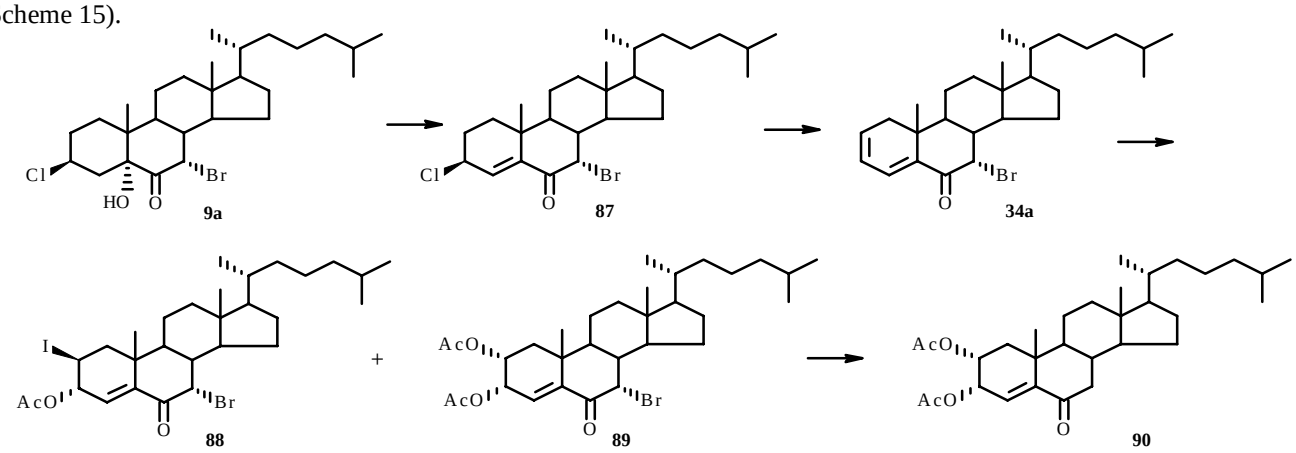
Scheme 13.

4-Dehydroecdysterone, a natural compound that contains 2β,3β,14α-trihydroxy-$\Delta^{4,7}$-6-ketone as a characteristic feature, was identified [39] as the 4-dehydroecdysterone. Thus, we developed a method for synthesizing 2β,3β,14α-trihydroxy-$\Delta^{4,7}$-6-ketosteroids [40]. First, 5α-hydroxy-2,7-dien-6-one (**22**) was synthesized from β-sitosterol **4b**. Further transformations of **22** included *cis*-hydroxylation of the 2(3)-double bond by AgOAc and I_2 in aqueous acetic acid and the Woodward reaction with subsequent acetylation to 2β,3β-diacetate **79** in 48% yield. The second product of this reaction is 3α-acetoxy-2α,5α-epoxysteroid **80** in 31% yield. Compound **79** was dehydrated by thionyl chloride in Py. This produced the required 4,7-dien-6-one **82** in 18% yield and 1(10),7-dien-6-one **81** and 14α-hydroperoxide **83** in yields of 7 and 51%, respectively. Dehydration of **79** with methanesulfonic acid and SO_2 in a Py—DMF mixture gave **82** and **81** in yields of 38 and 28%, respectively. Then, **82** underwent allylic hydroxylation with SeO_2 in dioxane to give 14α-hydroxy derivative **85a** in 51% yield. It was noted that **85a** can also be produced by reduction of **83** with NaI in acetic acid in 32% yield and subsequent acetylation by acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine. The second compound, 2β,3β,14α-triacetate **86**, was isolated in 25% yield. Next, reaction of **81** with SeO_2 in dioxane produced 9α-hydroxy derivative **84** in 44% yield. Hydrolysis of **85a** with K_2CO_3 in CH_3OH gave the desired 2β,3β,14α-trihydroxy-4,7-dien-6-one (**85b**) in 46% yield (Scheme 14).



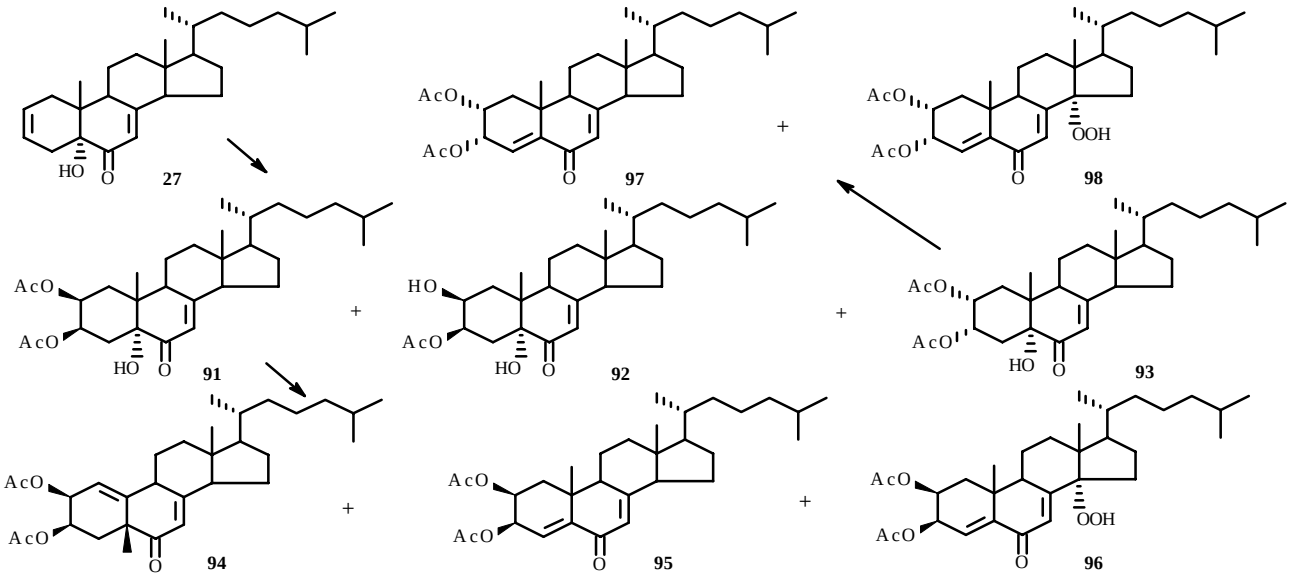
Scheme 14.

Natural ecdysteroids include 2α,3α-dihydroxy-$\Delta^{4,7}$-6-ketosteroids in addition to 2β,3β,14α-trihydroxy-$\Delta^{4,7}$-6-ketosteroids. Some of these are diaulusterols A and B, which were isolated from extracts of skin from *Diaulula sandiegensis* [41]. We also synthesized 2α,3α-dihydroxy-$\Delta^{4,7}$-6-ketosteroids [15], in particular, from 3β-chloro-7α-bromo-5α-hydroxy-6-ketosteroid **9a**. Dehydration of **9a** with thionylchloride in pyridine formed Δ^4-6-ketosteroid **87** in about 60% yield. Elimination of the sterically more accessible and reactive allyl Cl atom with Li_2CO_3 and LiBr in DMF with heating produced from **87** 7α-bromo-$\Delta^{2,4}$-6-ketosteroid **34a** in >20% yield. Dehydrochlorination of **87** with heating in 2,6-lutidine gave 2,4-dien-6-one **34a** in >40% yield. The principal products from Woodward *cis*-hydroxyation of **34a** and subsequent acetylation were 2β-iodo-3α-acetoxy-Δ^4-6-ketosteroid **88** and 2α,3α-diacetoxy-Δ^4-6-ketosteroid **89** in yields of 18 and 42%, respectively. In the next step, **89** was reacted with Li_2CO_3 and LiBr with heating in DMF. As it turned out, the principal product was Δ^4-6-ketone **90** (Scheme 15).



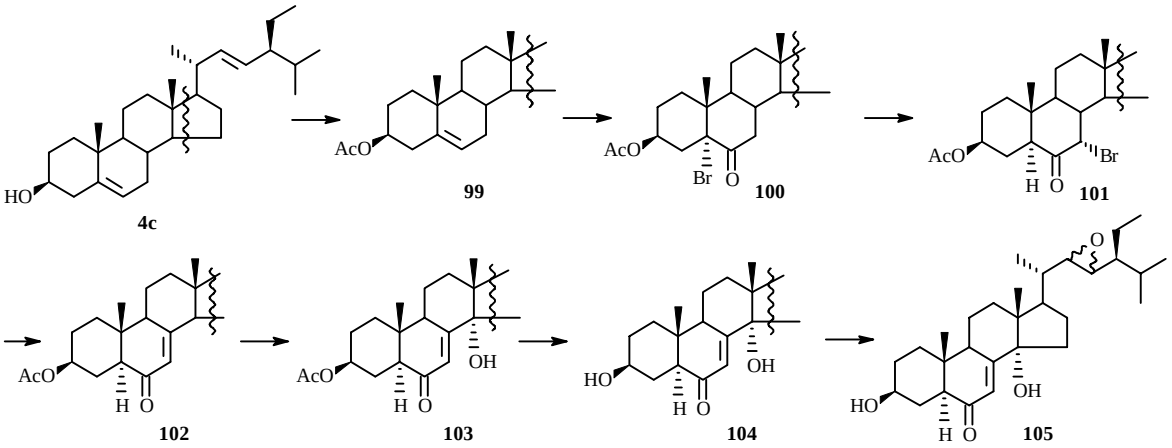
Scheme 15.

The approach studied above for synthesizing 2α,3α-dihydroxy-4,7-dien-6-ketosteroids did not give the expected results. Therefore, we used for this purpose *cis*-hydroxylation of the 2(3)-double bond in 5α-hydroxy-2,7-dien-6-ketosteroid **27** with OsO_4 via the Criegee reaction with subsequent elimination of the 5α-hydroxyl. It was found that reaction of **27** with OsO_4 and subsequent acetylation formed steroids **91**-**93**. The products of β-attack **91**-**92** were isolated in overall yield of about 30% whereas the yield of the product of α-attack **93** was only 15%. Steroid **91** was dehydrated with thionylchloride in pyridine. The principal product of this reaction was $\Delta^{4,7}$-6-ketone **95** in 21% yield. The formation of two more side products, **94** and **96**, was also noticed. Reaction of **93** with thionylchloride in pyridine produced steroid **97** in >70% yield. This is a synthetic analog of diaulusterol B. A minor product of this reaction was 14α-hydroperoxide **98** in 8% yield (Scheme 16).



Scheme 16.

We synthesized ecdysteroids and their analogs containing the necessary functional groups not only in the cyclic part of the molecule but also in the side chain. The starting material used to synthesize analogs of ecdysteroids with functional groups in the side chain was stigmasterol **4c** [42]. In the first step, it was converted with acetic anhydride into acetate **99** in >90% yield. Then, selective addition of HOBr to the sterically more available 5(6)-double bond and subsequent Jones oxidation of the bromhydrin with chromic acid synthesized 5α-bromo-6-ketone **100** in 51% overall yield. Reaction of **100** with aqueous HBr in acetic acid produced 7α-bromo-6-ketone **101** in 77% yield. The 22,23-double bond was retained in **101**. It can be assumed that conversion of **100** into **101** occurs through an S_N2 substitution mechanism (Scheme 17).

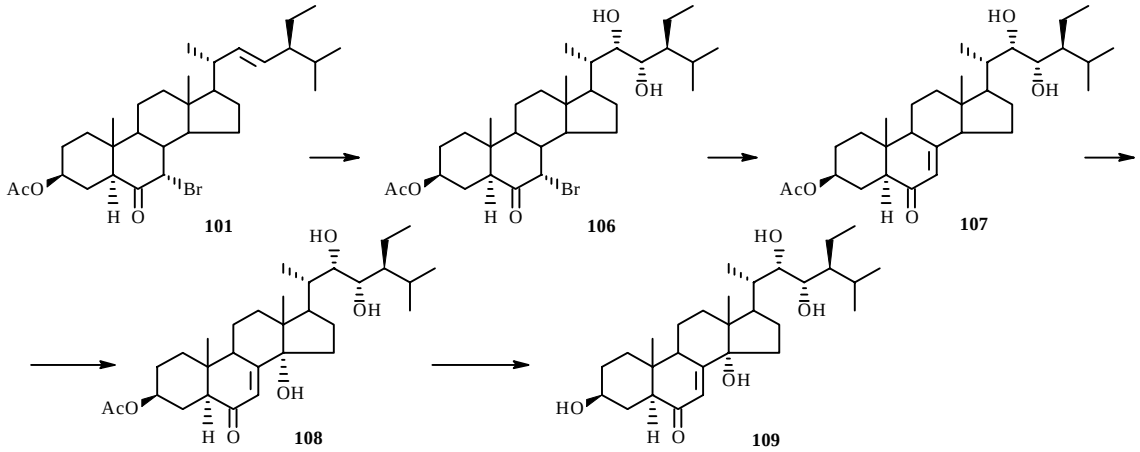


Scheme 17.

Dehydrobromination of **101** with Li_2CO_3 and LiBr in DMF with boiling produced 7,22-dien-6-one **102** in 60% yield. In the next step, dienone **102** underwent allylic oxidation with SeO_2 in dioxane to form 14α-hydroxy-7,22-dien-6-one **103** in 77% yield. Subsequent hydrolysis of the acetoxy in **103** with K_2CO_3 in CH_3OH produced alcohol **104** in quantitative yield. The presence in this compound of the Δ^{22}-bond makes it possible to introduce the required functional groups into the side chain. We demonstrated this by conversion of **104** into 22,23-epoxide **105**.

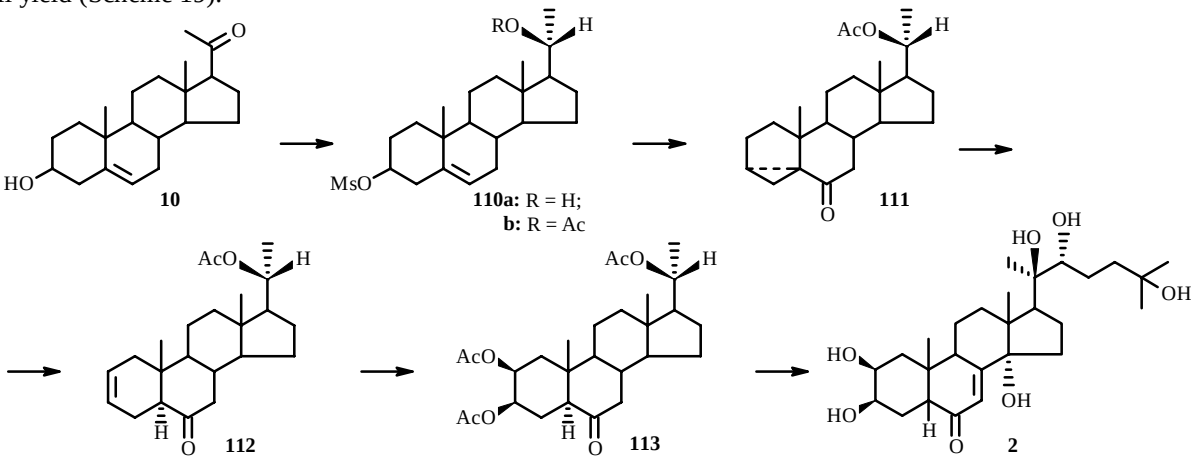
Reports of the isolation of ecdysteroids with a 22,23-epoxy in their structures have appeared. These include polyporusterones C and E [43], atrosterone B, and 25-hydroxyatrosterone B [44]. Reaction of **104** and *m*-chloroperbenzoic acid gave **105** in 85% yield.

Then, ecdysteroid analogs containing 22,23-diol groups were synthesized [45]. This structural fragment occurs in the ecdysteroids rapisterone [46], gerardiasterone [47], and 23-hydroxycyasterone [48]. First the double bond in **101** was Criegee *cis*-hydroxylated with OsO_4 to form **106** in about 80% yield. Dehydrobromination of **106** with Li_2CO_3 and LiBr in boiling DMF gave Δ^7-6-ketone **107** in 44% yield. Reaction of **107** with SeO_2 in dioxane synthesized 14α-alcohol **108** in about 60% yield. In the last step, the 3β-acetoxy in **108** was hydrolyzed by K_2CO_3 in aqueous CH_3OH to give the desired 3β,14α,22,23-tetrahydroxy-6-ketone **109** in 84% yield (Scheme 18).



Scheme 18.

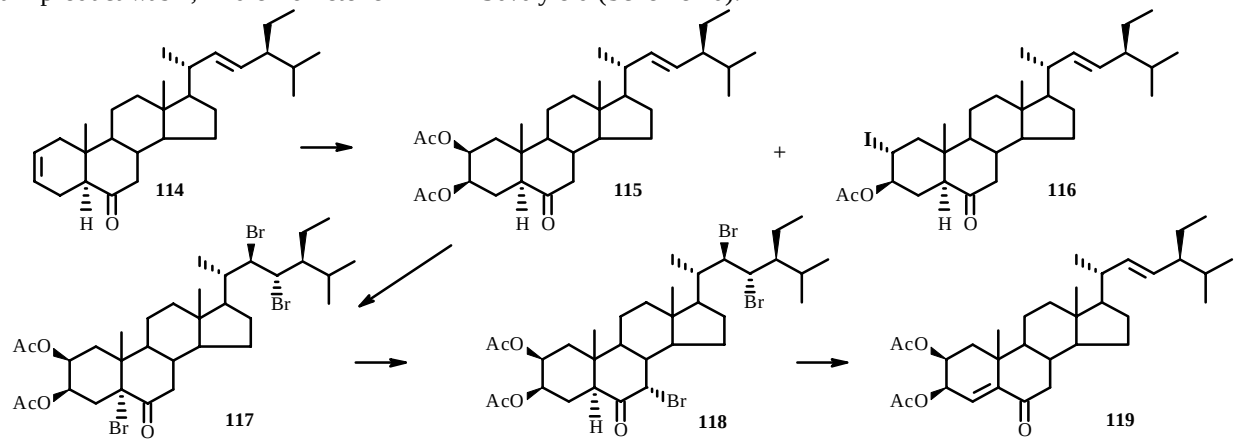
Pregnane derivative **113** [49], which was used previously to prepare 20-hydroxyecdysone **2**, has been synthesized [1]. In the first step, **10** was reacted with methanesulfonylchloride in pyridine to give the corresponding mesylate, which was then reduced with $NaBH_4$ to form alcohol **110a** in 66% overall yield. Reaction of **110a** with acetic anhydride in pyridine gave acetate **110b**, which was solvolyzed without purification with KOAc in aqueous acetone. The resulting 3α,5-cyclo-6β-alcohol was oxidized without isolation from the reaction mixture to 3α,5-cyclo-6-ketosteroid **111** in quantitative yield. Isomerization by *p*-toluenesulfonic acid and LiBr with heating in DMF was used to convert **111** into the Δ^2-6-ketosteroid **112** in 71% yield. In the final step, the Δ^2-bond in **112** was Woodward *cis*-hydroxylated with AgOAc and I_2 in aqueous acetic acid. The resulting 2β-acetoxy-3β-hydroxy-6-ketosteroid was acetylated by acetic anhydride to give 2β,3β,20β-triacetoxy-6-ketosteroid **113** in 46% overall yield (Scheme 19).



Scheme 19.

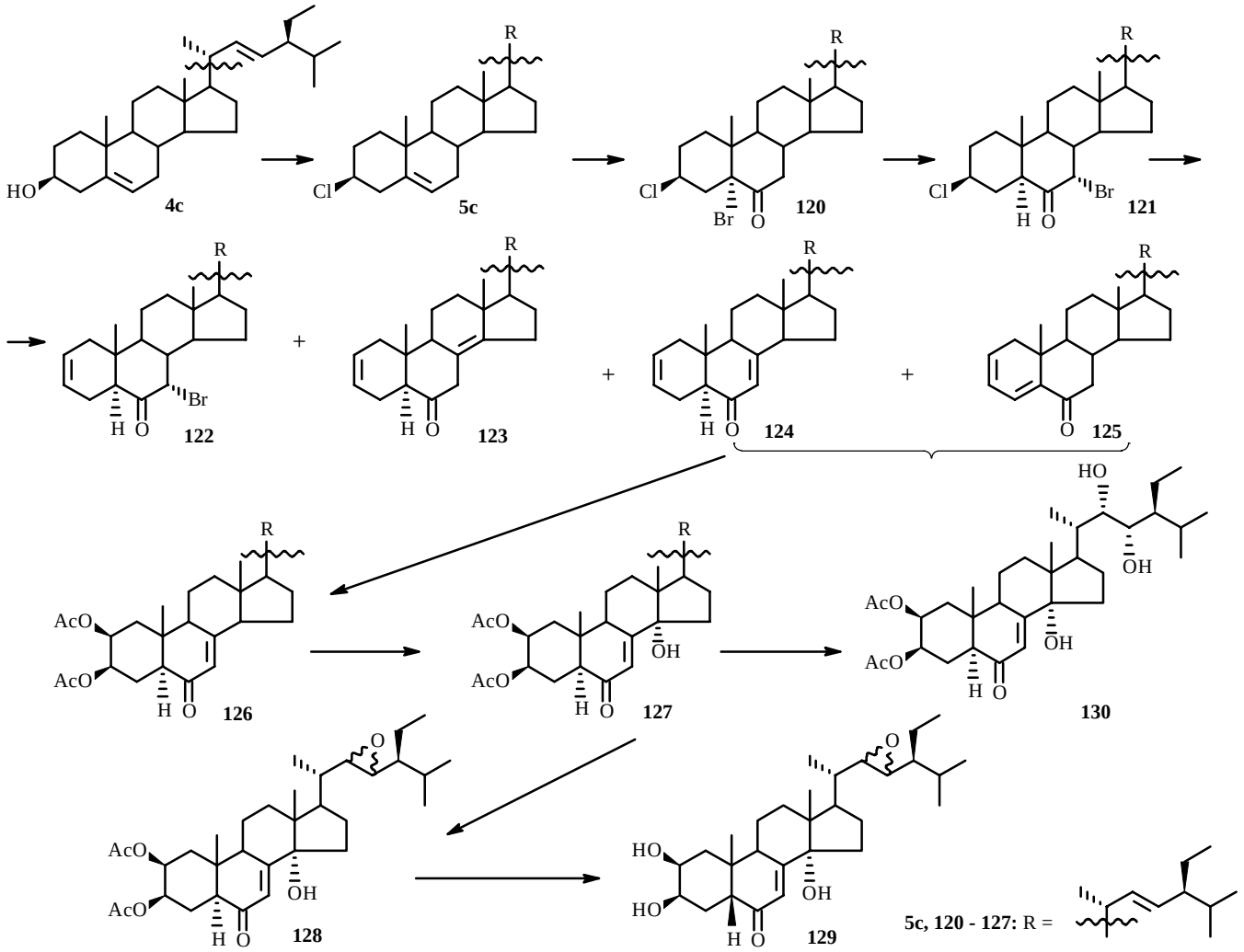
Then we synthesized compounds with structures similar to those of **105** and **109**, which contained additional 2β-hydroxyls [50]. Thus, reaction of **4c** with methanesulfonylchloride in pyridine gave the mesylate, which was solvolyzed without purification in aqueous acetone in the presence of KOAc. The resulting 3α,5-cycloalcohol underwent Jones oxidation directly in the reaction mixture. The resulting 3α,5-cyclo-6-ketosteroid was isomerized without purification with *p*-toluenesulfonic acid in sulfolane at 160°C. This approach could prepare 2,22-dien-6-one **114** in 68% overall yield based on starting **4c**. Woodward *cis*-hydroxylation with AgOAc and I_2 in aqueous acetic acid of the sterically more available Δ^2-double bond in **114** and subsequent acetylation produced 2β,3β-diacetoxy-6-ketosteroid **115** and 2α-iodo-3β-acetoxy-6-ketosteroid **116** in yields of 53 and 7%, respectively.

Bromination of **115** in a mixture of acetic acid and dichloroethane produced 5α,22,23-tribromo-6-ketosteroid **117** in 63% yield. Rearrangement of **117** into 7α-bromo-6-ketone **118** in 71% yield was effected using bromine and HBr in acetic acid. Dehydrobromination of **118** with Li_2CO_3 and LiBr in the presence of phenol in DMF with boiling was proposed. However, several attempts to use this method to prepare from **118** the corresponding $\Delta^{7,22}$-6-ketone were unsuccessful. It was found that the main product was 4,22-dien-6-ketone **119** in >50% yield (Scheme 20).



Scheme 20.

The unsuccessful transformation of **118** made it necessary to seek alternative methods for synthesizing 7,22-dien-6-ketosteroids from stigmasterol. Therefore, we first prepared from the reaction of **4c** and thionylchloride 3β-chloro derivative **5c** in quantitative yield. Selective addition to the sterically more accessible 5(6)-double bond of HOBr followed by oxidation with chromic acid without isolation of the resulting bromohydrin converted **5c** to 3β-chloro-5α-bromo-6-ketosteroid **120** in 50% overall yield. Reaction of **120** and HBr in acetic acid gave **121** in 86% yield (Scheme 21).

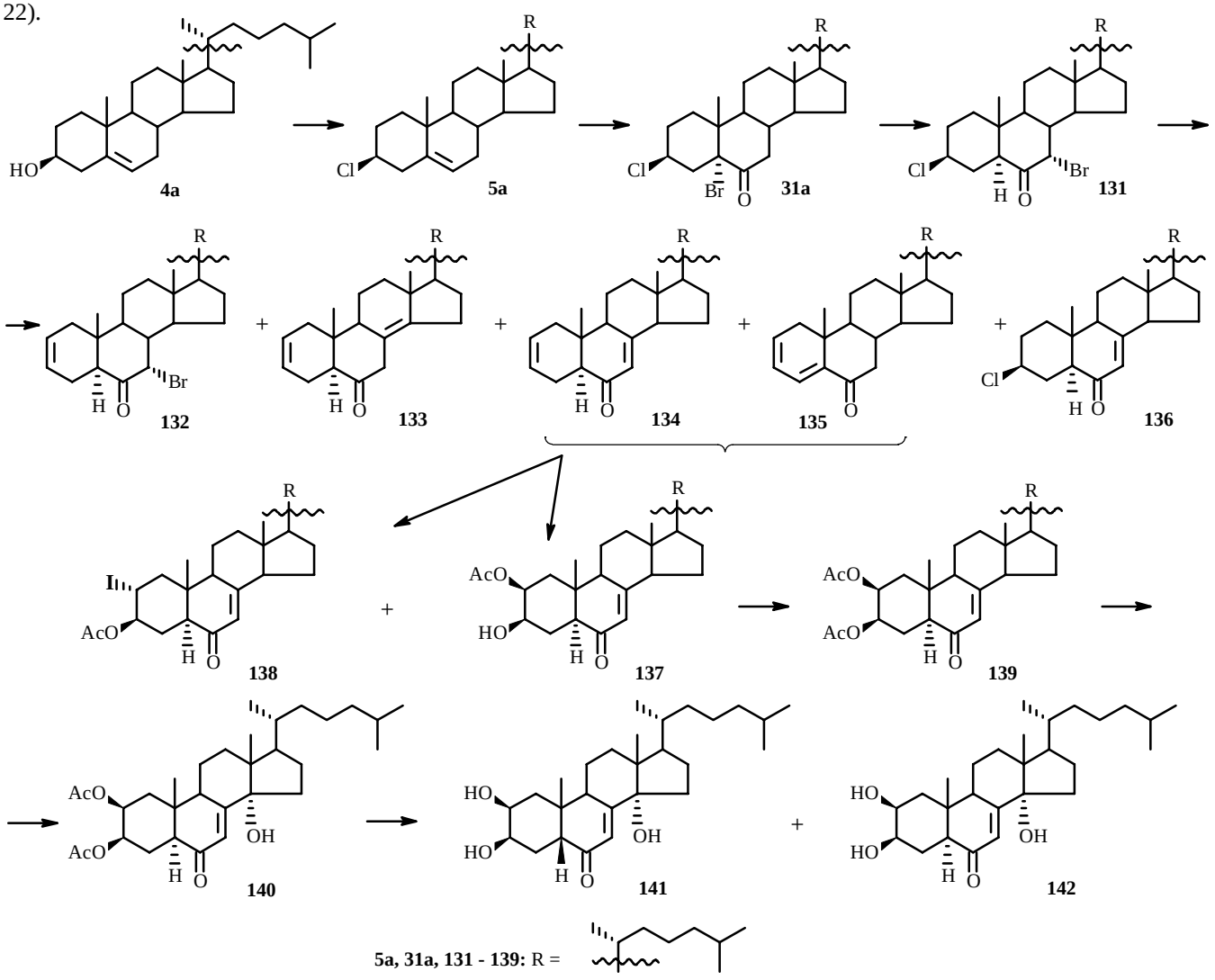


Scheme 21.

Dehydrohalogenation of **121** with Li_2CO_3 and LiBr in DMF was complicated and produced 7α-bromo-$\Delta^{2,22}$-6-ketone **122**, $\Delta^{2,8(14),22}$-6-ketone **123**, $\Delta^{2,7,22}$-6-ketone **124**, and $\Delta^{2,4,22}$-6-ketone **125** in yields of 11, 28, 32, and 10%, respectively. The last two compounds formed a mixture that could not be separated despite several attempts. Therefore, we were forced to use the mixture of **124** and **125** in the next reaction without separating them. Woodward *cis*-hydroxylation and subsequent acetylation of the mixture with acetic anhydride in pyridine isolated the desired 2β,3β-diacetoxy-$\Delta^{7,22}$-6-ketone **126** in >40% yield. Then, **126** underwent allylic hydroxylation with SeO_2 in dioxane to form **127** in 64% yield. Epoxidation of the 22(23)-double bond in **127** with *m*-chloroperbenzoic acid produced in 96% overall yield 22,23-epoxide **128** as a mixture of the (22*R*,23*R*)- and (22*S*,23*S*)-isomers with predominance of the former. The acetates in **128** were hydrolyzed with K_2CO_3 in aqueous CH_3OH. This also isomerized C-5 to give the more stable *cis*-A/B-steroid **129**, which we isolated in 38% yield. Hydroxylation of the 22(23)-double bond in **127** with OsO_4 in pyridine led to 22*S*,23*S*-diol **130** in about 70% yield (Scheme 21).

An analogous scheme was used to synthesize 22,25-dideoxyecdysone **141** and its 5α-isomer **142** [51]. In the first step, starting cholesterol **4a** was reacted with thionylchloride to give 3β-chloro derivative **5a** in 96% yield. Then, addition to the 5(6)-double bond of **5a** of HOBr and oxidation of the resulting bromohydrin with chromic acid synthesized 3β-chloro-5α-bromo-

6-ketosteroid **31a** in >70% overall yield. Reaction of **31a** with HBr in acetic acid produced 3β-chloro-7α-bromo-6-ketone **131** in 82% yield. In the next step, **131** underwent dehydrohalogenation upon boiling with Li_2CO_3 and LiBr in DMF. Chromatographic separation of the products isolated 7α-bromo-Δ^2-6-ketone **132**, $\Delta^{2,8(14)}$-6-ketone **133**, a mixture of $\Delta^{2,7}$-6-ketone **134** and $\Delta^{2,4}$-6-ketone **135**, and 3β-chloro-Δ^7-6-ketone **136**. Compounds **132** and **136** were obtained in insignificant yields of 9 and 10%, respectively. The desired 2,7-dien-6-one **134** was isolated as a mixture with **135** in a 3.3:1 ratio (Scheme 22).



Scheme 22.

The mixture of **134** and **135** underwent Woodward *cis*-hydroxylation to give 2β-acetoxy-3β-hydroxy-Δ^7-6-ketone **137** as the predominant product. Acetylation of the mixture with acetic anhydride in pyridine produced 2α-iodo-3β-acetoxy-Δ^7-6-ketone **138** and 2β,3β-diacetoxy-Δ^7-6-ketone **139** in yields of 3 and 55%, respectively, calculated based on **134**. Reaction of **139** with SeO_2 in dioxane gave 14α-hydroxy-Δ^7-6-ketone **140** in about 90% yield. In the final step, the acetoxyl in **140** was hydrolyzed by K_2CO_3 in aqueous CH_3OH. This also partially epimerized C-5 to form the corresponding *cis*-A/B-isomer. The reaction produced the desired 22,25-dideoxyecdysone **141** and its 5α-isomer **142** in yields of 40 and 36%, respectively.

The structures of the synthesized compounds were proved using various spectra, the application of which usually did not cause any particular difficulties. Nevertheless, special investigations were required in several instances to establish the relationships between the structures and IR [52] and ^{13}C NMR spectra [53-58].

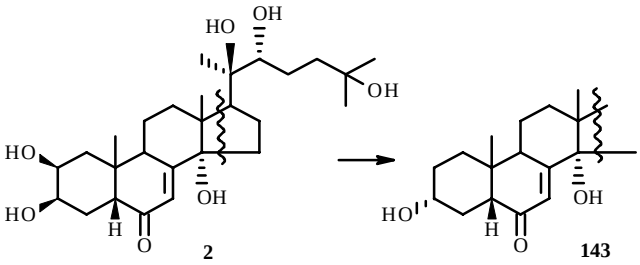
Most of the prepared ecdysteroids and synthetic intermediates were checked for insecticidal activity relative to the Colorado beetle *Leptinotarsa decemlineata* [10, 59-65]. Among these, compounds exhibiting a significant toxic effect on the

pest were found. In particular, according to biological tests, it was found that the most active compounds are **9a-b**, **31a**, **32b**, **51**, **56**, **82**, **85b**, **101-103**, **117**, **121-122**, **137**, and **140**. This gives hope that active and selective insect growth and development regulators will be found among this group of compounds.

The early stages of the research on the synthesis of ecdysteroids was typified by a large number of scientific studies on the introduction of ecdysteroid side chains into the corresponding starting pregnane and androstane steroids. Such studies have become less significant at this time. As an example, the study [66] in which a new method for constructing the characteristic 20,22,25-trihydroxycholestane side chain of ecdysteroids can be mentioned. It was based on radical addition of THF to the 20-ketone of the starting pregnane in the presence of samarium iodide.

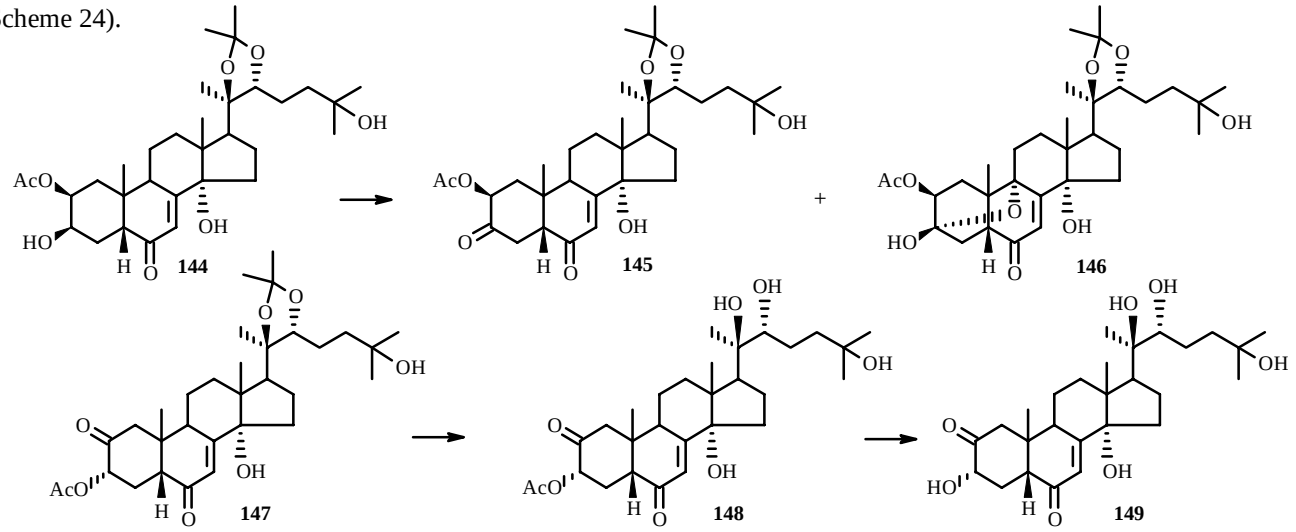
Significant effort has been applied in recent years to the development of new methods for chemical transformation of the most common phytoecdysteroids, in particular, 20-hydroxyecdysone **2**. The advantage of such an approach to the synthesis of ecdysteroids is that a large number of functional groups are present in the starting materials and do not have to be introduced. This significantly decreases the total number of synthetic steps. However, only specific organic reactions can be used because the ecdysteroids contain several hydroxyls that must usually be protected and labile 14α-hydroxy-Δ^7-6-ketones. The different reactivity of the hydroxyls of ecdysteroids that are due to their different positions and conformations can be used in minor chemical transformations [1]. The 2β-hydroxyl, at which reactions can be carried out selectively, are the most reactive in ecdysteroids. For example, selective conversion of 20-hydroxyecdysone into 2-dansyloxy-20-hydroxyecdysone has been reported [67].

Difficultly accessible phytoecdysteroid 2-deoxy-3-epi-20-hydroxyecdysone **143** was synthesized from 20-hydroxy-ecdysone **2** [68]. The desired ecdysteroid and its 5α-analog and 3-dehydro-20-hydroxyecdysone and its 5α-epimer were obtained (Scheme 23).



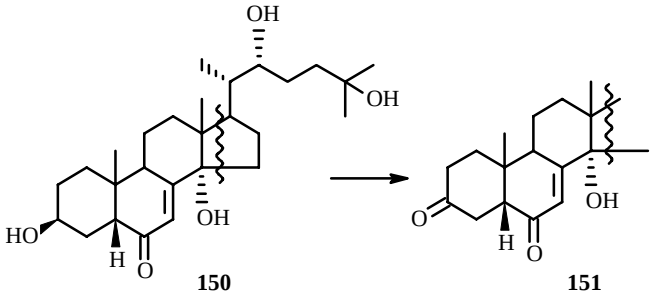
Scheme 23.

Phytoecdysteroid 2-dehydro-3-epi-20-hydroxyecdysone **149** was recently isolated from *Froelichia floridana* [69] and was synthesized from **2** [70]. For this, the 20-hydroxyecdysone was converted by a known method into **144**, oxidation of which by CrO_3 in pyridine gave 3-ketosteroid **145** and 3α,9α-epoxysteroid **146**, which were isolated in yields of 43 and 23%, respectively. Isomerization of **145** on silica gel produced 3α-acetoxy-2-ketone **147** in 61% yield. Removal of the acetonide in it with 70% acetic acid and further hydrolysis of the acetoxy in **148** with guanidinium acetate gave phytoecdysteroid **149** (Scheme 24).



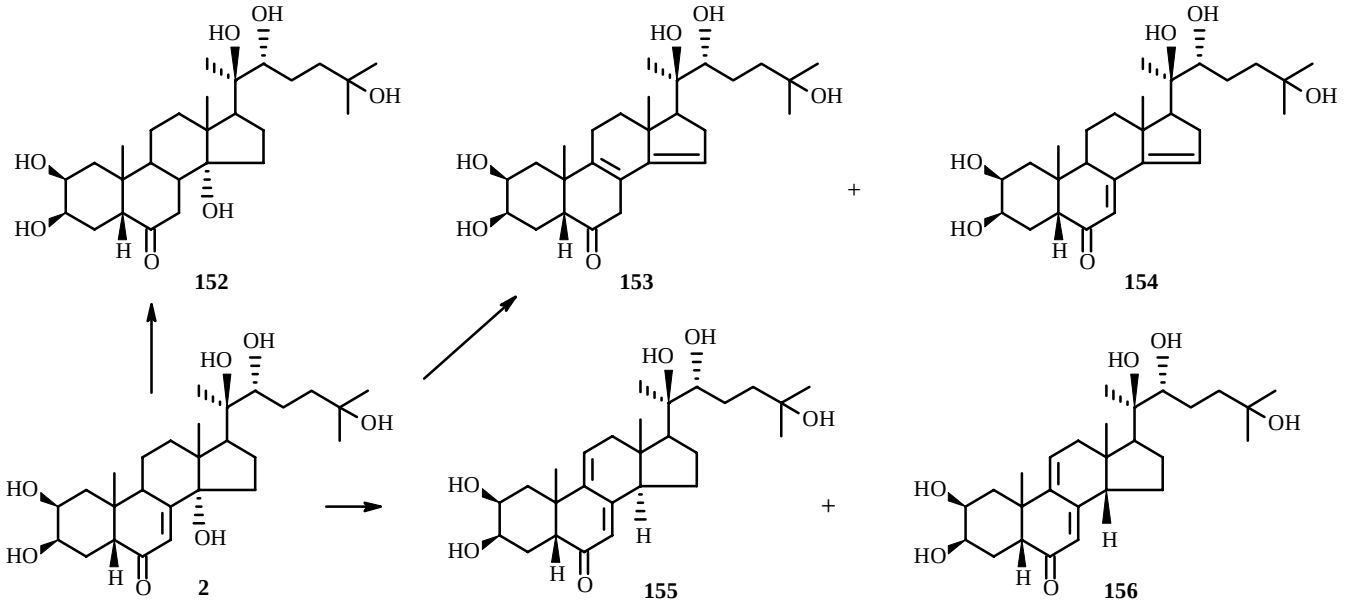
Scheme 24.

Transformation of 2-deoxyecdysone **150** into phytoecdysteroid silenosterone **151** has been reported [71]. The key steps of the synthetic scheme are acetylation of **150** with acetic acid in pyridine to the 3,22-diacetate, partial alkaline hydrolysis of the 3-acetoxy with KOH in CH_3OH to a 3-hydroxy, its Jones oxidation with chromic acid in acetone to a 3-ketone, and alkaline hydrolysis of the 22-acetoxy with KOH in CH_3OH to give the desired **151**. The use of KOH for partial hydrolysis of the 3-acetoxy in the intermediate 2-deoxyecdysone 3,22-diacetate causes, according to PMR spectra, epimerization at C-5 to give the more stable *trans*-A/B isomer and not the *cis*-A/B isomer as reported [71]. Based on the literature data [71], **151** is still produced. Therefore, we think that its formation can be explained by another epimerization at C-5 in the last step of alkaline hydrolysis of the 22-acetoxy into 5α-silenosterone 22-acetate (Scheme 25).



Scheme 25.

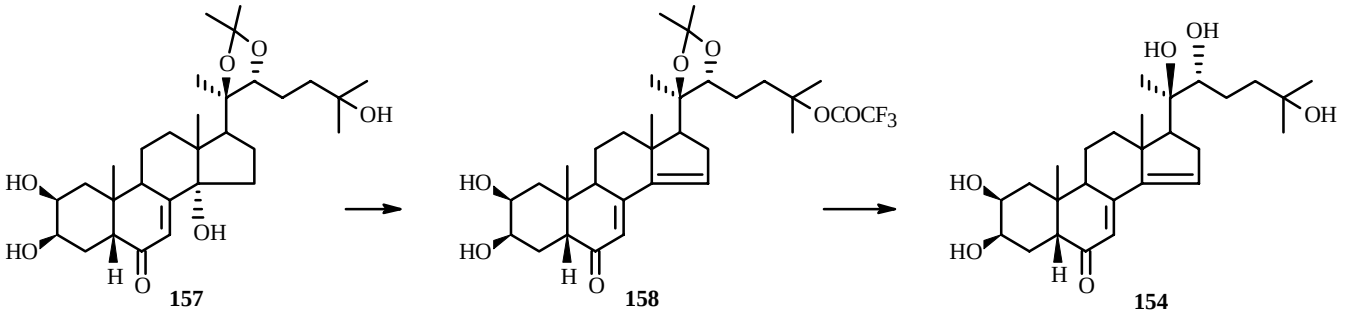
The 7(8)-double bond in steroids is known to be highly sterically hindered. Therefore, it is not hydrogenated catalytically. However, it was demonstrated [72] that hydrogenation of **2** over Pd on C (10%) in the presence of $NaNO_2$ gives 7(8)-dehydro-20-hydroxyecdysone **152** in quantitative yield. Hydrogenation of other ecdysteroids occurs analogously to produce the corresponding 7(8)-dihydroecdysteroids (Scheme 26).



Scheme 26.

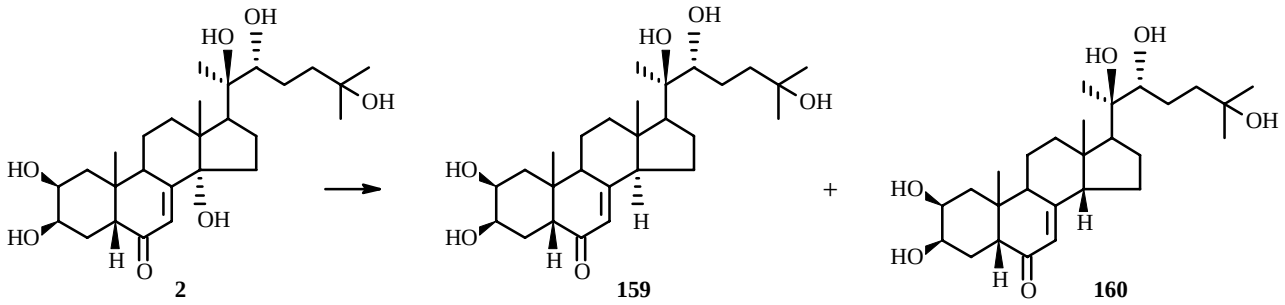
Dehydration of **2** with HCl in C_2H_5OH forms phytoecdysteroids podecdysone B **153**, stachysterone B **154**, and 14-deoxy-$\Delta^{7,9(11)}$-6-ketosteroids **155** and **156** [73]. Thermal dehydration of the 20-hydroxyecdysone adsorbed on Al_2O_3 is more selective. This produced **153** in 50% yield [73] (Scheme 26).

Phytoecdysteroid stachysterone B was also synthesized from mono- and diacetonides of 20-hydroxyecdysone [74]. Thus, reaction of the 20,22-monoacetonide of **157** with trifluoroacetic anhydride in a mixture of pyridine and $CHCl_3$ produced 7,14(15)-dien-6-one **158** in 83% yield. Successive hydrolysis with first $NaHCO_3$ in CH_3OH and then 70% acetic acid converted **158** to **154** (Scheme 27).



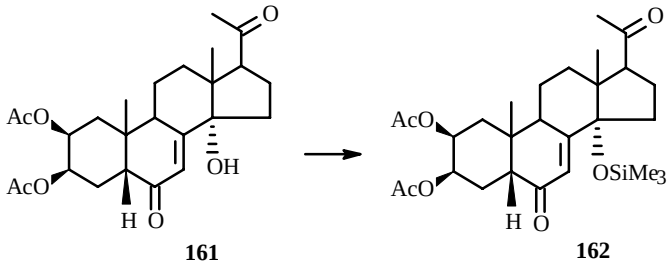
Scheme 27.

Reduction of **2** with Zn dust in acetic acid has been studied [75]. It was found that the principal products are 14-deoxy derivatives **159** and **160** in yields of 57 and 24%, respectively. A minor product was 7(8)-dehydro-20-hydroxyecdysone **152** in 5% yield (Scheme 28).



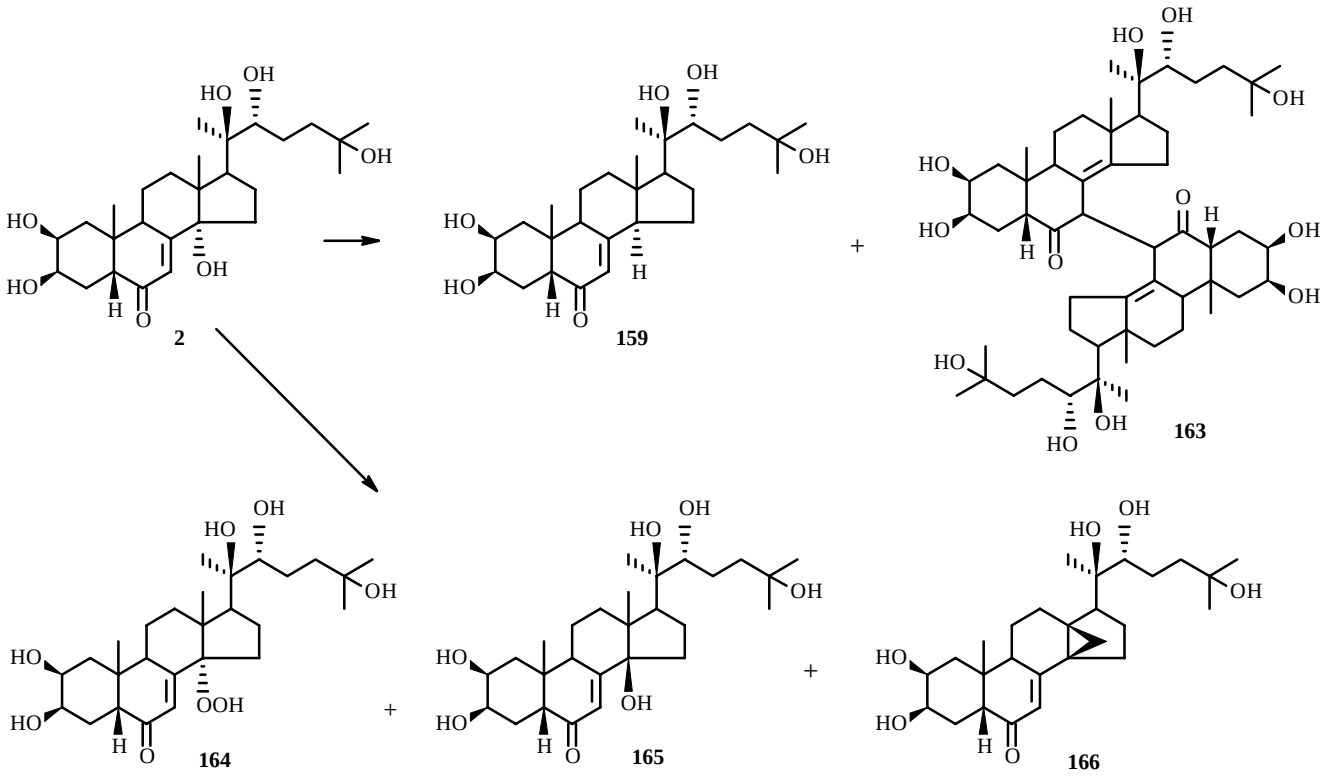
Scheme 28.

It has been noted [76, 77] that trimethylsilyl ethers of ecdysteroids at the difficultly accessible 14α-hydroxyl can be produced through reaction with (trifluoromethyl) trimethylsilane in THF at 0°C in the presence of catalytic amounts of tetrabutylammonium fluoride. Thus, the 2,3-diacetate of poststerone **161** gave under these conditions silyl ether **162** in 83% yield. It was also found that reaction of this reagent with free ecdysteroids formed the corresponding fully silylated derivatives [78] (Scheme 29).



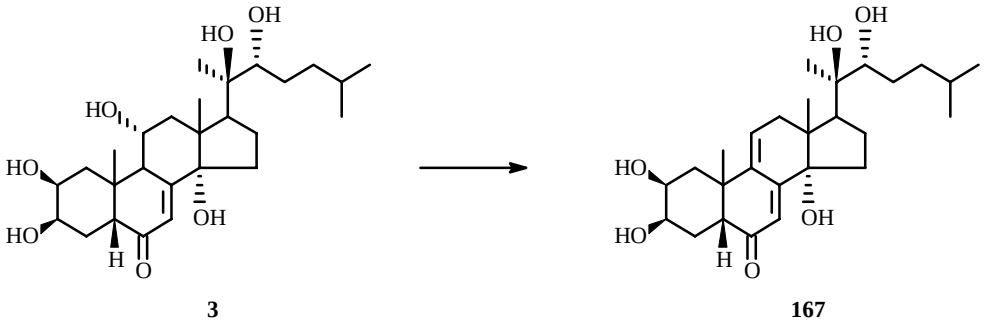
Scheme 29.

The photolysis of **2** in aqueous solution has been described [79-82]. It was found that these transformations are exceedingly complicated. The principal products are **159** and **163-166** (Scheme 30).



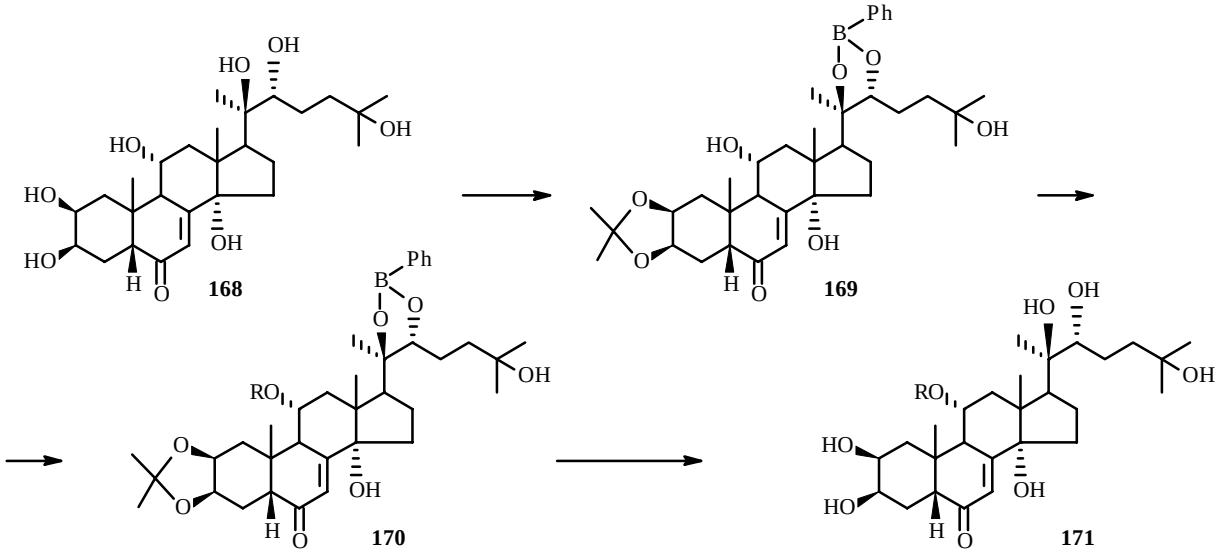
Scheme 30.

Dehydration of ajugasterone C **3** [73] with methanolic NaOH (5%) produced the phytoecdysteroid dacryhainansterone **167**. The corresponding kaladasterone and 25-hydroxydacryhainansterone were synthesized analogously from muristerone A and turkesterone (Scheme 31).



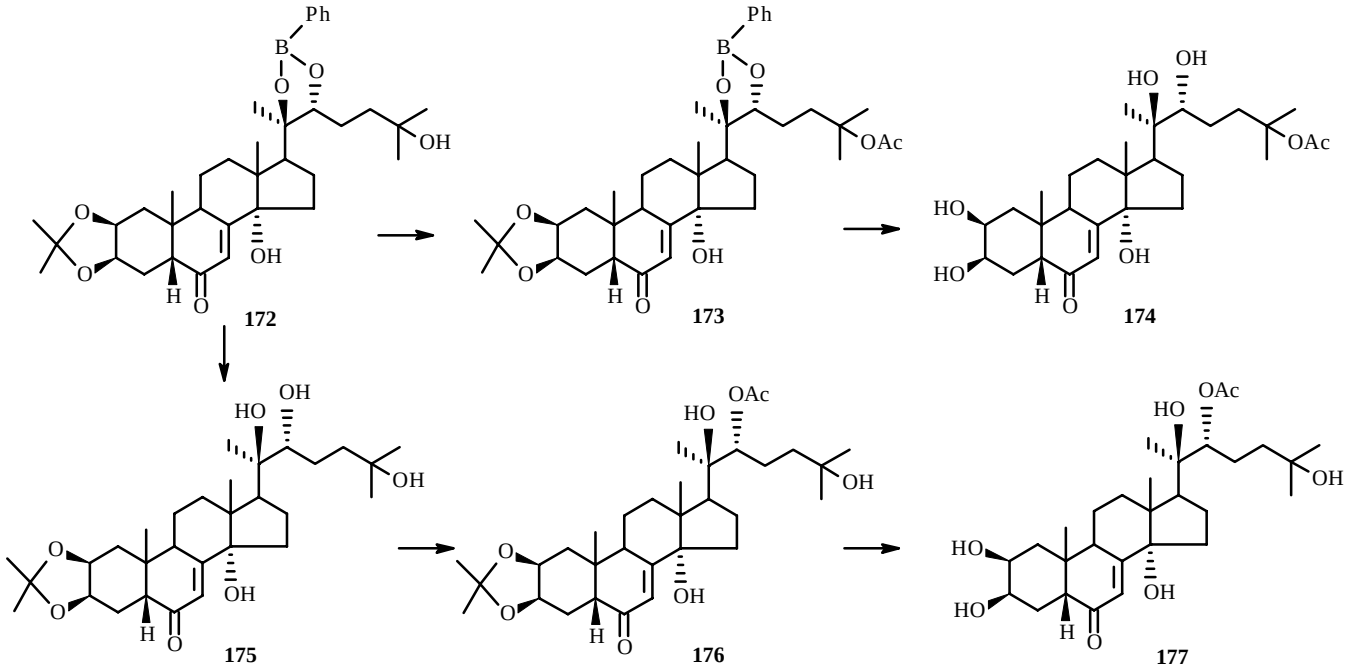
Scheme 31.

Monoacyl derivatives of the 11α-hydroxyl of the phytoecdysteroid turkesterone **168** have been synthesized [83]. For this, **168** was reacted successively with phenylboronic acid and acetone to give 2,3-acetonido-20,22-phenylboronate **169**. Compound **169** was esterified with anhydrides of the appropriate carboxylic acids to give esters **170**. In the final step, hydrolysis of the protecting groups in **170** with HCl in dioxane gave the target monoethers of turkesterone **171** (Scheme 32).



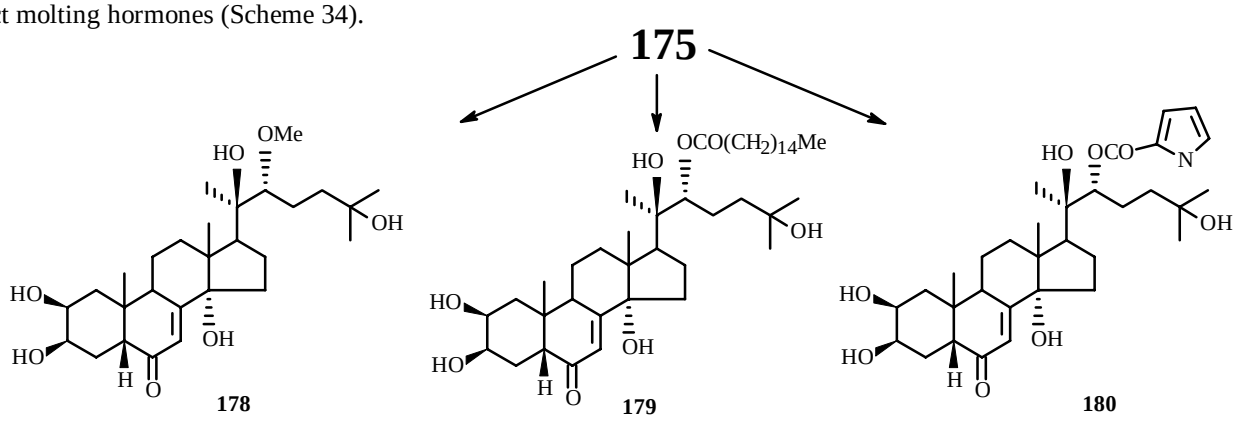
Scheme 32.

Several improved methods for synthesizing acetates and palmitates of 20-hydroxyecdysone have been proposed [84-87]. For example, reaction of **2** with phenylboronic acid and then of the resulting 20,22-phenylboronate with 2,2-dimethoxypropane in acetone in the presence of *p*-toluenesulfonic acid gave 2,3-acetonido-20,22-phenylboronate **172** in high yield. Reaction of **172** with a large excess of acetic anhydride in pyridine gave 25-acetate **173** in 90% yield. The protecting group in the side chain of **173** was removed with H_2O_2 in aqueous THF to give the corresponding 20,22-diol in 50% yield. The acetonide in it was hydrolyzed using KU-2 cation exchanger in the H-form to form acetate **174** in 60% yield. Hydrolysis of **172** with H_2O_2 in aqueous THF gave the 2,3-monoacetonide of **175** in 58% yield. Acetylation of the secondary 22-hydroxyl in **175** with acetic anhydride in pyridine gave 22-acetate **176** in 58% yield. Hydrolysis of the acetonide in **176** in the presence of KU-2 in the H-form synthesized 22-acetate of 20-hydroxyecdysone **177** in 73% yield (Scheme 33).



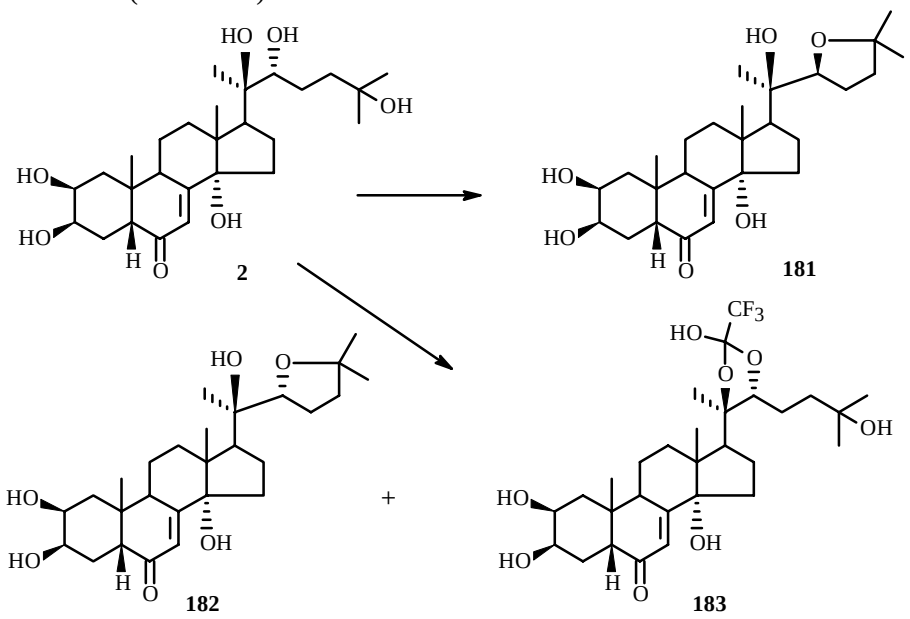
Scheme 33.

Several derivatives of the 22-hydroxyl of 20-hydroxyecdysone were synthesized [88]. Thus, reaction of **175** with methyliodide in the presence of silver oxide in DMF and subsequent removal of the protecting group in ring A with acetic acid (70%) gave 22-methyl ether **178**. The 22-ethyl ether of 20-hydroxyecdysone was synthesized analogously. Esterification of **175** with palmitic chloride in a mixture of pyridine and benzene and further hydrolysis of the acetonide gave 22-palmitate **179**. Reaction of **175** with the anhydride of pyrrole-2-carboxylic acid in a mixture of triethylamine and dioxane in the presence of dimethylaminopyridine and subsequent acid hydrolysis of the 2,3-acetonide isolated ester **180**. The 22-O-(furan-2-carboxylate)-, 2-O-(thiophene-2-carboxylate)-, and other esters of 20-hydroxyecdysone were synthesized by the same method [88]. Experiments in vivo with larvae of the house fly *Musca domestica* found that the synthesized compounds are highly active as insect molting hormones (Scheme 34).



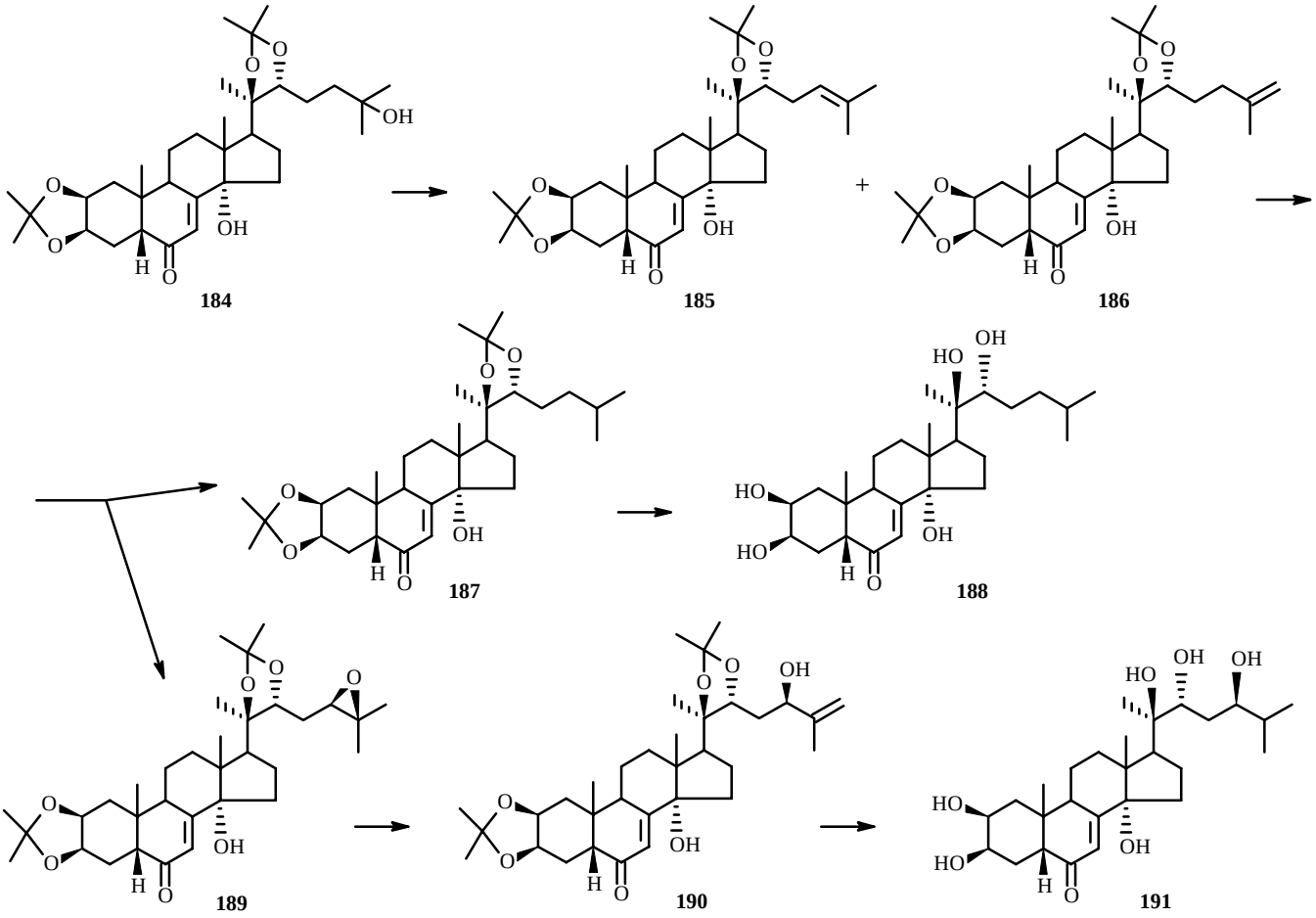
Scheme 34.

It was demonstrated [89-91] that reaction of **2** with a two-fold excess of trifluoroacetic anhydride in $CHCl_3$ for 15 min formed (22*S*)-shidasterone **181** in 37.5% yield. Then it was found [92, 93] that the analogous reaction of **2** with a three-fold excess of trifluoroacetic anhydride in $CHCl_3$ for 1.5 h gave the rare phytoecdysteroid shidasterone **182**. A second product of this reaction was orthoester **183** (Scheme 35).



Scheme 35.

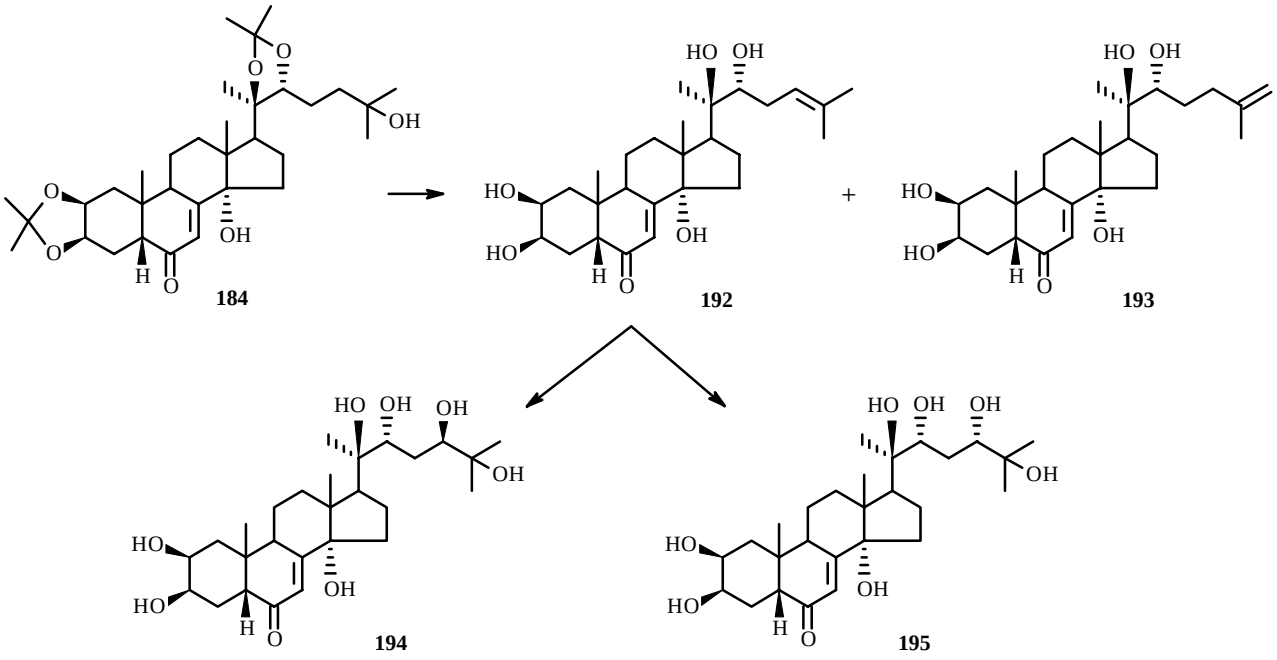
Ponasterone A was synthesized from **2** [94-96]. Thus, reaction of the diacetonide of 20-hydroxyecdysone **184** with methanesulfonylchloride in pyridine in the presence of dimethylaminopyridine gave a mixture (3:1) of alkenes **185** and **186** in overall yield of 87%. Hydrogenation of this mixture over Raney nickel produced quantitatively the diacetonide of ponasterone A **187**, hydrolysis of which with aqueous acetic acid (70%) gave the 20,22-monoacetonide of ponasterone A in quantitative yield. Further hydrolysis with acetic acid (70%) in the presence of $ZnCl_2$ gave ponasterone A **188** in 24% yield in addition to the unreacted 20,22-monoacetonide in 43% yield (Scheme 36).



Scheme 36.

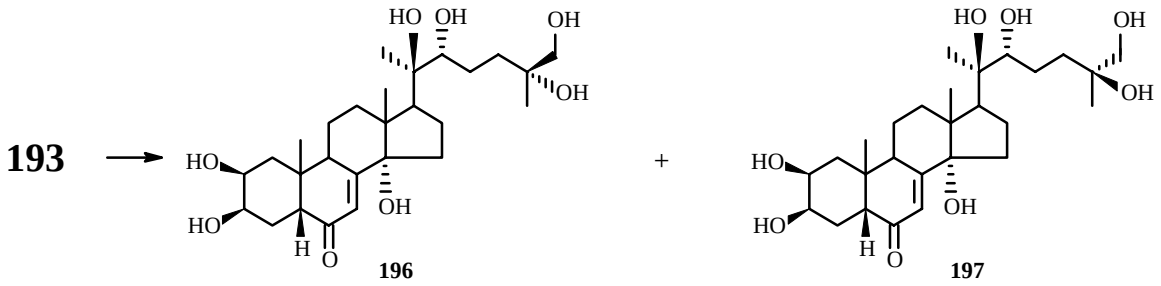
24-Epipterosterone **191** was synthesized from **2** in an analogous manner [97]. First, 20-hydroxyecdysone gave 2,3,20,22-diaceonide **184**, reaction of which with methanesulfonylchloride in pyridine formed a mixture of steroids **185** and **186**. Epoxidation of this mixture with *m*-chloroperbenzoic acid formed a mixture of all possible epoxides, chromatographic separation of which produced pure 24,25-epoxysteroid **189** in 34% yield. Isomerization of **189** with LiBr in acetonitrile synthesized allyl alcohol **190** in 50% yield. Catalytic hydrogenation of the 25(26)-double bond in **190** over Pd on C (5%) proceeded quantitatively. Protecting groups were removed from the resulting product by acid hydrolysis with acetic acid (70%) to form the desired 24-epipterosterone **191** in 74% yield (Scheme 36).

Several rare phytoecdysteroids were synthesized from **2** [98]. First, 20-hydroxyecdysone was converted as usual into 2,3,20,22-diacetonide **184**. Then, reaction of **184** with methanesulfonylchloride in pyridine in the presence of DMF with cooling followed by reaction of the resulting 25-mesylate with heating to room temperature formed a mixture of diacetonides of stachysterone C **185** and 25,26-didehydroponasterone A **186** in 87% overall yield. Removal of the protecting groups with acetic acid (70%) produced stachysterone C **192** and 25,26-didehydroponasterone A **193**. Criegee *cis*-hydroxylation of **192** with OsO_4 synthesized phytoecdysteroids 24-epiabutasterone **194** and abutosterone **195** in a 2:1 ratio in 88% overall yield. Use of various chiral ligands in the hydroxylation of **192** increased the content in the mixture of **194** (Scheme 37).



Scheme 37.

It was found [99] that *cis*-hydroxylation of **193** with OsO_4 formed 20,26-dihydroxyecdysone as a mixture of two diastereomers **196** and **197** in about equal quantities (Scheme 38).



Scheme 38.

Thus, chemical synthesis of ecdysteroids at present is a dynamically developing area in the chemistry of natural compounds. In our opinion, the results are very important not only to the chemistry and biochemistry of ecdysteroids but also to the chemistry of steroids in general.

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