Translated from *Uspekhi Khimii* 60 1283–1317 (1991) U.D.C. 547.92

The synthesis of brassinosteroids, a new class of plant hormones

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ABSTRACT. Data on methods of synthesis of brassinosteroids are correlated. In view of their extremely low reported content in nature, the role of chemical synthesis from other natural steroids as the main source of obtaining these hormones for detailed study and practical use is assessed.

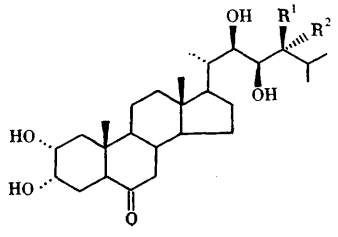
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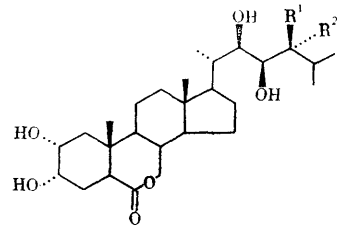
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I. Introduction

Hyopotheses have been expressed many times on the possible hormonal function of steroids in plants because of the numerous functions of steroidal compounds as hormones in man and the higher animals,[1,2] insects[3,4] and certain fungi,[5] and also of their wide distribution in the plant world.[1,3] The first real confirmation of the role of steroids as hormones in higher plants was obtained in 1979 when American scientists established the structure of brassinolide (VIII), a powerful growth stimulant, isolated from rape pollen.[6] Subsequently several compounds, structurally and functionally related to brassinolide, called the brassinosteroids (BS),[7–9] were isolated from various sources and identified, and heralded a new group of phytohormones. Some of these compounds, which today number close to 30, are given below.[10] The ecdysteroids are the closest in structure of the brassinosteroids.[3,4]



brassinone, $R^1=R^2=H$ (I)
castasterone, $R^1=Me$, $R^2=H$ (II)
epicastasterone, $R^1=H$, $R^2=Me$ (III)
homocastasterone, $R^1=Et$, $R^2=H$ (IV)
dolichosterone, $R^1R^2=CH_2$ (V)
homodolichosterone, $R^1R^2=CHMe$ (VI)



norbrassinolide, $R^1=R^2=H$ (VII)
brassinolide, $R^1=Me$, $R^2=H$ (VIII)
epibrassinolide, $R^1=H$, $R^2=Me$ (IX)
homobrassinolide, $R^1=Et$, $R^2=H$ (X)
dolicholide, $R^1R^2=CH_2$ (XI)
homodolicholide, $R^1R^2=CHMe$ (XII)

Features of the chemical structure of BS are the presence of 2α,3α- and (22*R*, 23*R*) diol groupings, a *trans* junction of rings A and B, and a 6-keto group [compounds (I)–(VI)] or a lactone function in ring B [compounds (VII)–(XII)]. Certain compounds do not contain some of the above groupings and are probably biosynthetic precursors of the corresponding BS with a complete set of functions. Compounds with an additional methyl group at C-25 have also been isolated.

In view of the extremely low BS content reported in plants (10^{-5}–10^{-12}%) and the short period in which they have been investigated, it must be assumed that the inventory of natural products of this type is far from complete. For the same reason it is difficult to judge at present the real distribution of BS in various plants. At the same time it follows quite unequivocally from the available data that the method of isolation from natural raw material cannot be considered as a practical route for providing the BS required for their study and possible use in plant culture. Individual attempts to make this approach of practical value have not changed the overall position.[11–13] This explains the wide range of investigations on BS synthesis begun in various countries directly after establishment of the brassinolide structure. Up to the present time several schemes have been developed for the partial synthesis of BS from other groups of natural steroids. Total synthesis is obviously only of theoretical interest since it requires the formation of the exceptionally complex stereochemistry of these considered compounds which contain 11–13 chiral centres in the molecule. It must be emphasised that even a partial synthesis is an extremely complex task particularly when forming the polyfunctional side chain.

Widespread investigations on the synthesis of BS have led to the publication of a large number of papers devoted to this problem, including several reviews.[7,8,14–28] In addition the rapid

accumulation of new information and the limited availability of the majority of foreign reviews, coupled with the lack of them in the domestic literature, has made preparation of the present review urgent.

II. General principles characteristic of syntheses of the natural brassinosteroids

Any scheme for the synthesis of BS may be divided provisionally into two parts, (a) the formation of the structural elements of the tetracyclic nucleus characteristic of BS and (b) construction of the side chain of the molecule. For the first time investigators have encountered the need to construct a polyfunctional side chain containing 4 asymmetric carbon atoms (a task only known in the case of the steroids, however that is simpler) and the traditional steroid chemistry methods developed during investigations on ecdysone synthesis may be used to functionalise the cyclic portion of the molecule.

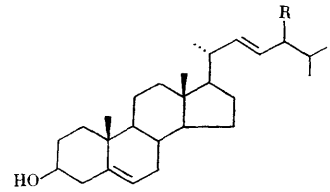
When solving problems of the strategy and tactics of BS synthesis, particularly for practical use, it is necessary to consider several circumstances, primarily the level of growth stimulating activity of a BS, its relative synthetic availability and sources of steroid raw material. The most acceptable starting materials are the available natural steroids containing a Δ^{22}-bond in the side chain, such as stigmasterol (XVI) and ergosterol (XVII). The available cholesterol (XVIII) and β-sitosterol (XIX), which do not contain such a bond, enable the preparation only of BS analogues with a non-functional side chain, possessing as a rule comparatively little activity. The use of 22-dehydrocampesterol (XIV) and brassicasterol (XV) is extremely attractive. These have recently become commercially available due to the development of efficient methods for their isolation.[29–33] Other possibilities are linked with the use as starting materials of cholic acid derivatives such as hyodeoxycholic acid (XX) and steroids of the pregnane series, particularly pregnenolone (XXI) which is used in the pharmaceutical industry for making drugs.

Depending on the starting materials used and the target products all the synthetic schemes may be divided into two large groups:

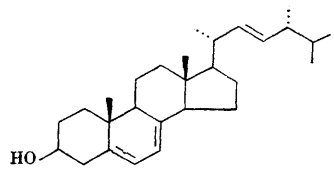
— syntheses retaining the native carbon skeleton of the starting material,

— syntheses forming new carbon–carbon bonds in the side chain.

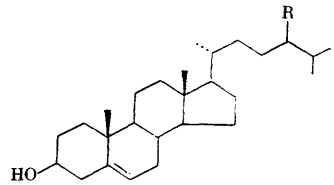
It is obvious that syntheses of the first group are simpler and more economical since no changes are required in the carbon skeleton. In addition the possibilities of using this approach are limited by the availability of sterols having the required carbon skeleton and functionality enabling construction of all the structural elements of the desired compound to be effected. For example the comparative availability of ergosterol and stigmasterol requires only direct functionalisation of the starting material, without breaking and forming new C–C bonds, in syntheses of epibrassinolide and homobrassinolide respectively. At the same time due to the limited availabity of 22-dehydrocampestrol (XIV), which possesses the appropriate carbon skeleton, the main method for the synthesis of brassinolide is still the conversion of stigmasterol into the 22-aldehyde [for example compounds (XXII) and (XXIII)] by fission of the $C_{22}-C_{23}$ bond and subsequent introduction of the $C_{23}-C_{28}$ fragment. Depending on the starting material, other variants of constructing the side chain of brassinolide include the introduction of $C_{22}-C_{28}$ or $C_{24}-C_{28}$ fragments (in the case of initial steroids of the pregnane series or the C_{23} series respectively)



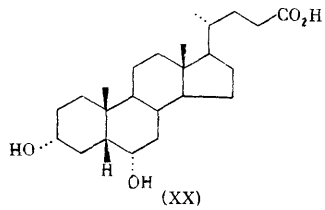
22-dehydrocholesterol, R = H (XIII)
22-dehydrocampesterol, R = α-Me (XIV)
brassicasterol, R = β-Me (XV)
stigmasterol, R = α-Et (XVI)



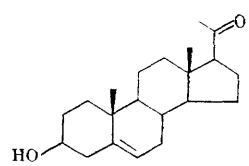
(XVII)



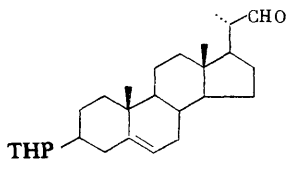
R = H (XVIII)
R = α-Et (XIX)



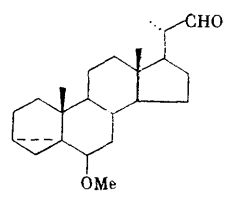
(XX)



(XXI)



(XXII)



(XXIII)

THP = tetrahydropyran-2-yl

An optimum choice of the sequence of transformations to be carried out in the cyclic portion and the side chain is absolutely essential for the provision of an efficient synthetic scheme, since in many cases the overall yield and number of stages is linked directly to it. Although the choice of variants for constructing structural fragments of the BS molecule is comparatively large, the sequence of using them in a synthetic scheme has paramount importance for the achievement of the maximum positive effect overall. A general illustration of the features and efficiency of the schemes developed for BS synthesis is given in Table 1.

Table 1. Syntheses of the most important natural BS.

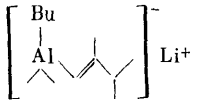
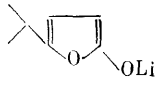
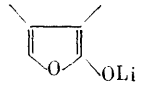
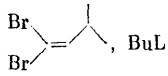
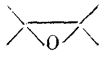
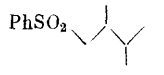
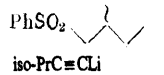
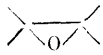
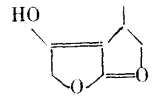
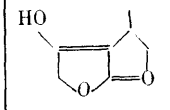
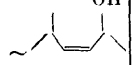
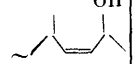
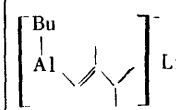
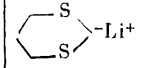
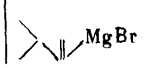
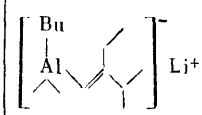
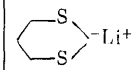
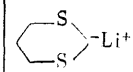
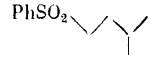
BS	Starting material	Type of synthesis	Method of forming side chain			No. of steps	Overall yield, %	Refs.
			carbon atoms introduced	substrate functional group	reagent			
(VIII)	(XXII)	S → B_k → A → B_l	1) C_{23}–C_{27}	–CHO	iso-PrC≡CLi	23	2.5	[34]
			2) C_{28}		$HCN-Et_3Al$		3.6	[35]
(VIII)	(XXIII)	»	C_{23}–C_{28}	–CHO		12	–	[36]
(VIII)	(XXIII)	»	C_{23}–C_{28}	–CHO		–	–	[37]
(VIII)	(XXIII)	»	C_{23}–C_{28}	–CHO		–	–	[37]
(VIII)	(XX)	»	C_{23}–C_{28}	–CHO	$Me_2CH_2COCHAsPh_3$	–	–	[38]
(VIII)	(XIV) + (XV)	B_k → A → S → B_l	–	–		10	0.9	[39]
(VIII)	(XVI)	»	1) C_{23}–C_{27}	–CHO	 , BuLi	15	7	[40]
			2) C_{28}		Me_3Al, BuLi	16	3	[41–45]
(VIII)	(XVI)	»	C_{23}–C_{26}	–CHO		19	1.3	[46–47]
(VIII)	(XVI)	B_k → S → A → B_l	C_{23}–C_{28}	–CHO		20	7.8	[48]
(VIII)	(XVI)	B_o → S → B_k → A → B_l	1) C_{23}–C_{27}	–CHO	iso-PrC≡CLi	15	8.5	[49–51]
			2) C_{28}		Me_3Al, BuLi			
(VIII)	(XXI)	»	C_{22}–C_{28}	=CO		25	7	[52, 53]
(VIII)	(XXI)	B_k → A → S → B_l	C_{22}–C_{28}	=CO		25	10.5	[54–56]
(VIII)	(XXIII)	S → B_k → A → B_l	1) C_{23}–C_{27}	–CHO	iso-PrC≡CMgBr	9	2.5	[57]
			2) C_{28}		$MeC(OEt)_3$			
(VIII)	(XXIII)	»	1) C_{23}–C_{24}	–CHO	HC≡CLi	24	5.3	[58–60]
			2) C_{28}	–C=CH	MeI, BuLi			
			3) C_{25}–C_{27}		$EtC(OEt)_3$			
(XI)	(XVI)	B_k → A → B_1 → S	C_{23}–C_{28}	–CHO		18	1.5	[42, 61–62]
(XI)	(XVI)	»	1) C_{23}	–CHO		20	7.6	[63, 64]
			2) C_{24}–C_{28}	–CHO				

Table 1 (continued).

BS	Starting material	Type of synthesis	Method of forming side chain			No. of steps	Overall yield, %	Refs.
			carbon atoms introduced	substrate functional group	reagent			
(IX)	(XVII)	$B_k \rightarrow A \rightarrow S \rightarrow B_l$	–	–	–	10	4.6	[65, 66]
(IX)	(XVII)	»	–	–	–	9	<2	[67]
(IX)	(XVII)	»	–	–	–	9	13	[68]
(IX)	(XVII)	»	–	–	–	9	4	[69]
(IX)	(XV)	»	–	–	–	5	20	[70]
(IX)	(XV)	»	–	–	–	7	–	[39]
(X)	(XVI)	»	–	–	–	8	–	[71, 72]
(X)	(XVI)	»	–	–	–	8	2.6	[73]
(X)	(XVI)	»	–	–	–	15	6.8	[74, 75]
(X)	(XVI)	»	–	–	–	11	<1	[76]
(X)	(XVI)	»	–	–	–	13	3.7	[76]
(X)	(XVI)	»	–	–	–	12	8.8	[77, 78]
(XII)	(XVI)	$B_k \rightarrow A \rightarrow B_l \rightarrow S$	–	–	–	12	1.4	[79]
(XII)	(XVI)	»	$C_{22}-C_{28}$	–CHO		18	2.6	[42, 80, 81]
(VII)	(XIII)	$S \rightarrow B_k \rightarrow A \rightarrow B_l$	–	–	–	9	4.3	[82–84]
(VII)	(XXII)	»	1) C_{23}	–CHO				
			2) $C_{24}-C_{27}$	–CHO	iso-BuMgBr	10	4.2	[82–84]
(VII)	(XXII)	»	$C_{23}-C_{27}$	–CHO	iso-PrC≡CLi	13	6.4	[35, 82]
(VII)	(XVI)	$B_k \rightarrow A \rightarrow B_l \rightarrow S$	1) C_{23}	–CHO				
			2) $C_{24}-C_{27}$	–CHO	iso-BuMgBr	20	9.8	[62]
(VII)	(XVI)	$B_k \rightarrow S \rightarrow A \rightarrow B_l$	$C_{23}-C_{27}$	–CHO		–	–	[85, 86]

Note. A denotes ring A with preformed functionality; B_o, B_k and B_l denote ring B with 6-hydroxy-, 6-keto- or with the 7-oxa-6-ketc functions respectively; S denotes preformed side chain.

Brassinosteroids belonging to the 6-keto steroid series with a saturated side chain are, in the majority of cases, direct synthetic precursors of the corresponding lactones since Baeyer-Villiger oxidation is particularly convenient after forming all the remaining structural fragments of the molecule. The only exceptions are the $\Delta^{24(28)}$-brassinosteroids in which lactonisation must be effected in one of the synthetic stages before construction of the unsaturated side chain. However, as in the first case, the preparation of steroids of this group, such as dolichosterone (V) [42,63] and homodolichosterone (VI),[42,87,88] differs from the synthesis of the corresponding 7-oxa derivatives (XI) and (XII) only in the absence of the lactonisation stage. The 24(28)-unsaturated BS containing an additional 25-methyl substituent, particularly 25-methyldolichosterone and 25-methyl-2,3,-diepidolichosterone have been obtained by a similar scheme.[89,90]

The synthesis of 6-desoxobrassinosteroids also includes the obligatory stage of obtaining the 6-keto derivatives, the carbonyl function being removed by hydrogenolysis in the concluding stage of the synthesis (in the case of saturated BS) or at the stage preceding the introduction of the unsaturated side chain [in the case of $\Delta^{24(28)}$-BS].[42,91] An example of the first approach in the synthesis of 6-deoxocastasterone[42] by the Huang-Minlon reduction of castasterone (II), and of the second is the preparation of 6-deoxo-dolichosterone via removal of the keto group of the intermediate 2α,3α-diacetoxy-20-methylpregnan-6-one by conversion into the ethylenedithioketal and desulphurisation of the latter with Raney nickel.[42]

The synthesis of the epimers and related 2-deoxy derivatives differs insignificantly from the preparation of 6-ketobrassinosteroids of the 2α,3α-dihydroxy series. In the case of typhasterol[35,49,58,59]

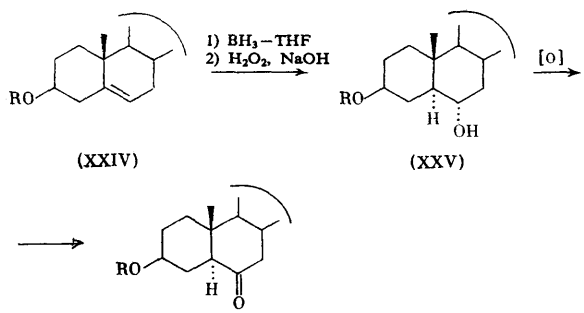
and teasterone[49,58,59,92] for example the 3-substituted 6-ketones are used directly.

III. Formation of functions characteristic of the cyclic portion of the brassinosteroid molecule

As already mentioned, the main starting materials used for BS synthesis are sterols and derivatives of pregnane and bile acids. In the majority of these compounds there is 3β-OH group and a Δ^5-bond or 5,7-diene system. The presence of the structural elements indicated limits the number of possible methods of forming BS functionality and determines the choice of corresponding transformations of the initial compound.

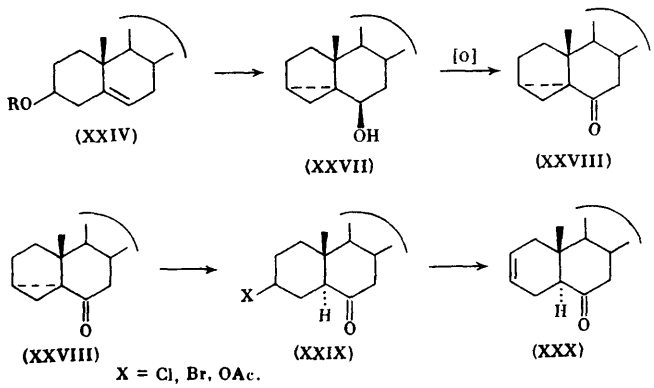
The methods usually used for creating 2α,3α-dihydroxy-6-keto functionality are known from classical steroid chemistry[1] and were later developed and improved during work on the synthesis of ecdysones.[3,4,93] They include as a rule the sequential introduction of the 6-keto group, a Δ^2-bond and its hydroxylation.

One of the methods of obtaining 6-ketones widely used in BS synthesis consists of hydroboration of Δ^5-derivatives (XXIV) with the BH_3–THF complex, oxidation of the resulting trialkylborane with alkaline hydrogen peroxide and subsequent conversion of alcohol (XXV) into ketone (XXVI).[34–36,52–56,82,83]



(XXIV) (XXV) (XXVI)

Another more efficient and universal method, distinguished by its simplicity, consists of using the rearrangement, which is specific for Δ^5-steroids, of the 3-tosyloxy- or 3-mesyloxy derivatives (XXIV) into the cyclic alcohols (XXVII), which are then oxidised to the cycloketones (XXVIII).[39–47,49–51,57–62,65–81,84–87,90,94–95] The presence of a cyclopropane fragment in the latter molecule affords the possibility of conversion into the corresponding 3-substituted 6-ketones (XXIX), for example by fission of the propane ring by hydrochloric,[57,67,96] hydrobromic,[97–102] or by a mixture of acetic and sulphuric acids.[39,49,59,60]



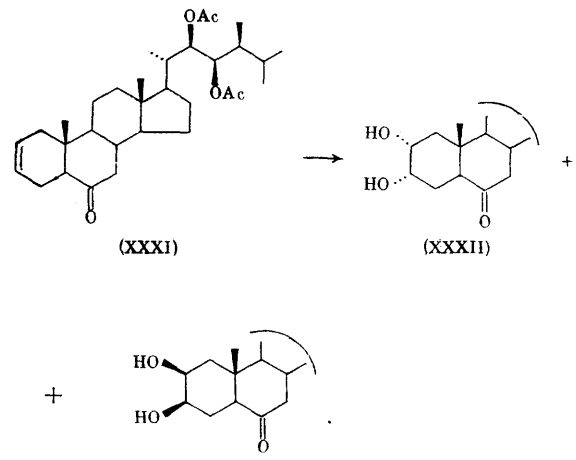
(XXIV) (XXVII) (XXVIII) (XXIX) (XXX)

Subsequent elimination of HX from the molecule of (XXIX, X = Cl, Br) gives the unsaturated ketones (XXX). A similar route comprising fission of the elements of TsOH or MsOH from (XXIX, X = OTs, OMs) may also be used.[39] However it is frequently used in syntheses including hydroboration of the Δ^5-bond.[34–36,52–56,82,83,103]

Recently the one-step transformation of the cycloketones (XXVIII) into Δ^2-steroids (XXX) has gained wide usage in syntheses of BS. The method is similar to that developed by Barton[104,105] and later used by other authors in BS synthesis[46,70,71] for the isomerisation of (XXVIII) by TsOH into the sulpholane. Examples are isomerisation by pyridinium hydrobromide,[106] and by sodium[50,107] or lithium[108,109] bromide in the presence of TsOH on boiling in DMF and also the recently proposed method[110] for thermal isomerisation by heating cycloketones in toluene with pyridinium tosylate. A possible mechanism for the reaction has been discussed.[111]

The introduction of 2α,3α-dihydroxy functionality into compound (XXX) is effected by hydroxylation of the Δ^2-bond by a catalytic or equimolar amount of osmium tetroxide[112–114] providing a high yield of α-diols (XXXII).[114]

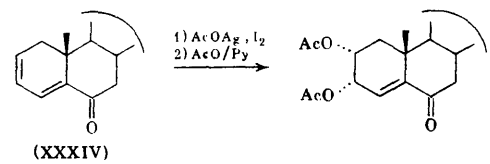
However, the formation of significant quantities of the isomeric dervatives (XXXIII) has been reported in certain cases. For example, diols (XXXII) and (XXXIII) were obtained in 77 and 14% yield respectively on hydroxylation of the enone (XXXI) with a catalytic amount of OsO_4.[49]



(XXXI) (XXXII)

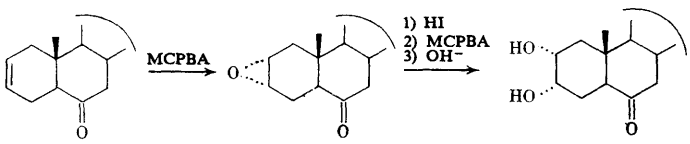
(XXXIII)

Methods of forming 2,3-dihydroxy functionality in ring *A* without using the expensive and toxic osmium tetroxide are of interest. One of them[115–125] is based on the Woodward hydroxylation of the $\Delta^{2,4}$-6-ketones (XXXIV). The formation of 2α,3α-dihydroxy derivatives, and not their 2β,3β-epimers,. occurs in contrast to the corresponding Δ^2-6-ketones.

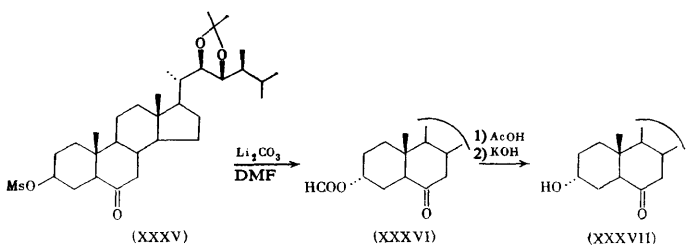


(XXXIV)

The second method consists of epoxidation of Δ^2-6-ketones with m-chloroperbenzoic acid (MCPBA) and subsequent transformation of the epoxide into the diol.

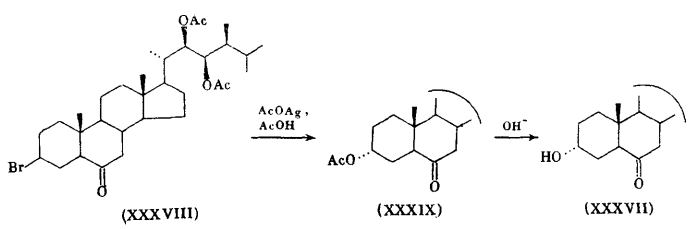


The usual method of obtaining BS of the 2-deoxy series consists of nucleophilic replacement of 3β-mesyloxy- or 3β-bromo-6-keto derivatives with the aim of reversing the configuration at C-3. Treatment of the sulphonate (XXXV) with lithium carbonate in DMF with subsequent boiling of the resulting 3α-formate (XXXVI) in aqueous acetic acid and hydrolysis with aqueous methanolic alkali leads to typhasterone (XXXVII) in 22% yield calculated on (XXXV).[35,59,60]



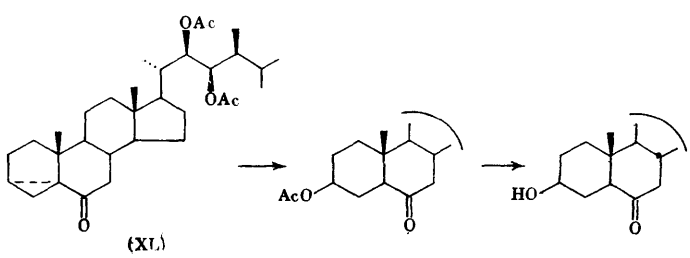
(XXXV) (XXXVI) (XXXVII)

A more effective method, using reaction of the bromide (XXXVIII) with silver acetate in acetic acid and subsequent hydrolysis of the triacetate (XXXIX), gave triol (XXXVII) in 46% overall yield.[49]



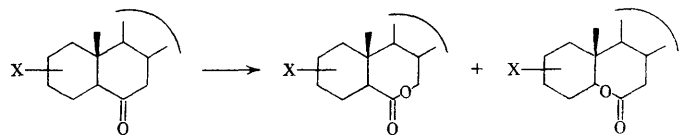
(XXXVIII) (XXXIX) (XXXVII)

The formation of 2β-6-keto functionality in the synthesis of teasterone was achieved by simple fission of the propane ring in compounds of type (XL) by a mixture of acetic and sulphuric acids[49,59,60] and subsequent alkaline hydrolysis of the acetate group.



(XL)

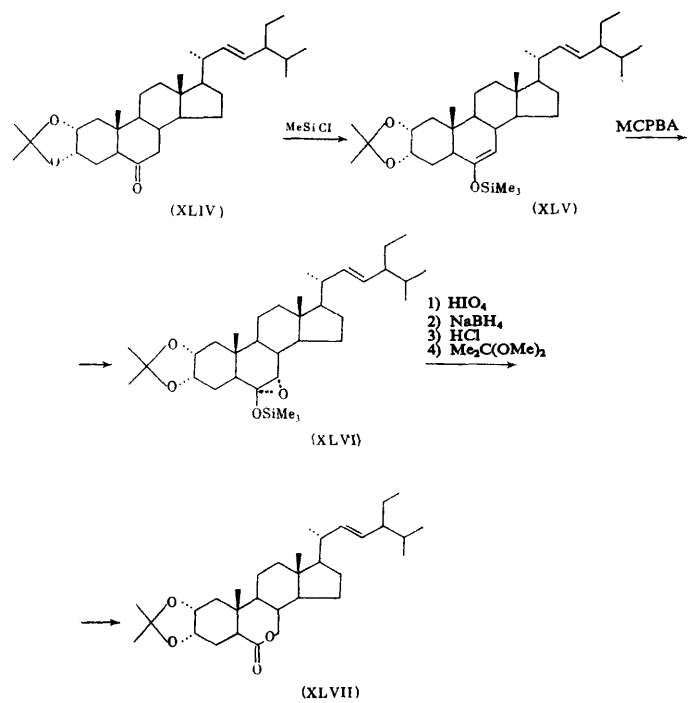
The standard method of introducing a lactone function into ring *B* is the Baeyer-Villiger oxidation of the 6-ketones (XLI) with trifluoroperacetic acid.[7,8,127–130] Since the ratio of the isomers (XLII) and (XLIII) formed depends appreciably on the nature and stereochemistry of the substituents in ring *A* [131] and is greatest in the case of 2α,3α-disubstituted derivatives, the oxidation is carried out, as a rule, as the final step of the synthesis being also linked with the relative lability of the lactone ring.



(XLI) (XLII) (XLIII)

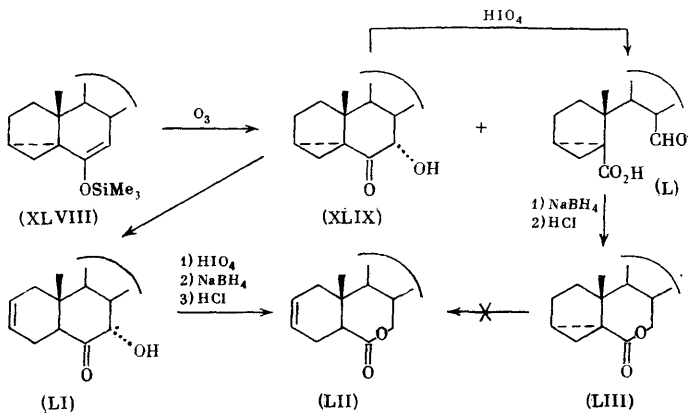
Although the fraction of the required lactones (XLII) is maximal for 2α,3α-diols, protected derivatives (acetates or acetonides) are usually used in the oxidation as a result of which a higher yield of products is achieved and separation of the regioisomers is facilitated. In addition, according to patent data,[132] good results may also be achieved on oxidation of unsubstituted 2α,3α(22*R*,23*R*)-tetraols with trifluoroperacetic acid in the presence of sodium trifluoroacetate. The application of MCPBA as a reagent for obtaining lactones according to Baeyer-Villiger has been reported.[72,79,133]

An alternative means of lactonising ring *B* through the silylated enol ether (XLV) obtained from the ketone (XLIV) was developed by Japanese workers in the synthesis of dolicholide.[42] Treatment of ether (XLV) with MCPBA gives epoxide (XLVI) (53%) together with a certain quantity of the 7α-hydroxy-6-ketone (17%). Oxidative fission of the epoxide (XLVI) with periodic acid, subsequent reduction and relactonisation with restoration of the protecting grouping in ring *A* led to lactone (XLVII).

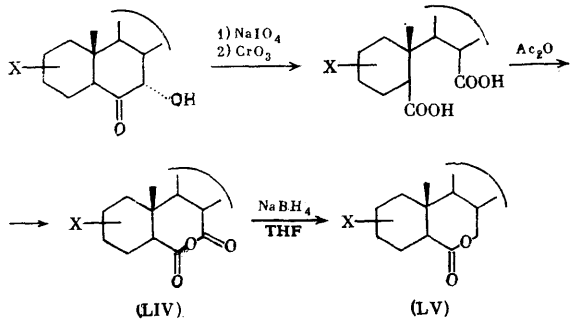


(XLIV) (XLV) (XLVI) (XLVII)

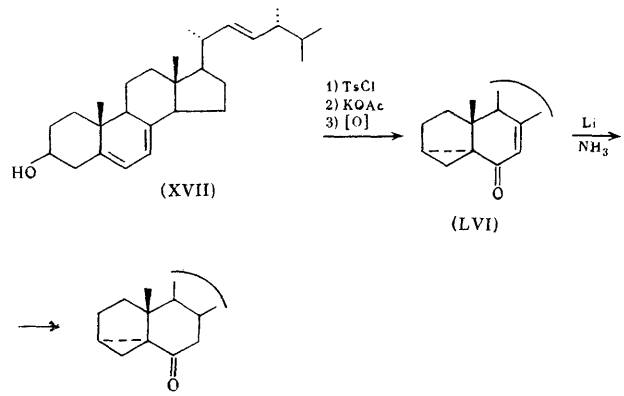
A modification of this approach is the recently proposed method[134] of forming the cyclic portion of brassinolide using ozonolysis of the silylated enol (XLVIII) which leads to a mixture of 7-hydroxy ketones (XLIX) and *B*-seco derivative (L) (depending on the reaction conditions the latter may not be formed). Fission of the hydroxyketones (XLIX) with periodic acid gives the aldehydoacid (L) in quantitative yield, which is then converted by borohydride reduction and acid treatment into the cyclic lactone (LIII). Since all attempts to transform (LIII) into the Δ^2-steroid (LII) proved to be unsuccessful, the latter was synthesised from the unsaturated ketol (LI) by a similar sequence of conversions in 79% yield calculated on ketol (XLIX).



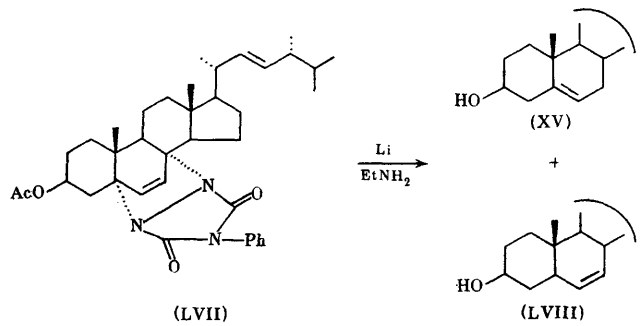
It must be noted that the principle of constructing the lactone fragment by the oxidative degradation of α-ketols of the (XLIX) type into *B*-seco derivatives and subsequent ring closure was proposed for the first time in a study[135] where a related sequence of conversions was carried out and the exceptionally high regioselectivity of the reduction of a carbonyl group in ring *B* of the anhydride (LIV) was shown to provide a high yield of the lactone (LV).



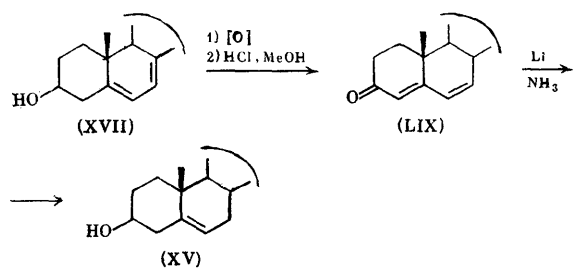
In conclusion it is necessary to mention the features of constructing the cyclic portion of the BS molecule when ergosterol (XVII) acts as starting material. The presence of an additional Δ^7-bond in its ring *B* requires an additional stage for its reduction with subsequent construction of the AB portion of the BS molecule by one of the means considered above. Thus reduction of the cyclic enone (LVI) was effected with lithium in liquid ammonia.[65]



According to another method[67] brassicasterol (XV) was obtained by the reduction of the adduct (LVII) with lithium in ethylamine. The adduct (LVII) was obtained from ergosterol acetate by Diels-Alder addition of 4-phenyl-1,2,4-triazolin-3,5-dione. The resulting mixture of 5,22- and 7,22-dienes (XV) and (LVIII) (3 : 2) was used for the following stage without separation. Different variants of the direct reduction of the ergosterol 5,7-diene system with dissolved metals (Li, Na, K) have been proposed,[69,105,136] and in the second of them attempts were undertaken to clarify the differences in the isomeric content of the products depending on the reaction conditions and the character of the substituent at position 3 of the ergosterol molecule from a mechanistic point of view. The formation of a mixture of Δ^5- and Δ^7-sterols is a drawback to the method described above for the reduction of ergosterol.



A sequence of reactions has been proposed[137] enabling brassicasterol to be obtained without admixture of its Δ^7-analogue. The Oppenauer oxidation of the hydroxydiene (XVII) and subsequent acidic isomerisation of the $\Delta^{4,7}$-3-ketone leads to the $\Delta^{4,6}$-3-ketone (LIX) which gives brassicasterol (XV) on reduction with Li in liquid ammonia.



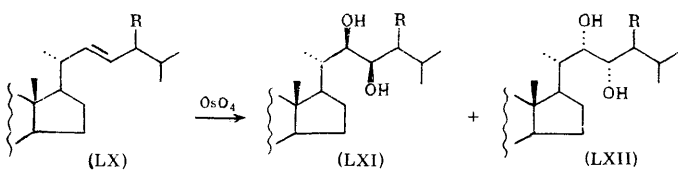
In spite of the fact that there is no information in the literature to data on the use of ergosterol in the synthesis of BS by alternative means, i.e. not by reduction but through the *trans*-formation of the Δ^7-bond, such an approach would seem to be extremely interesting.

IV. Construction of the side chains of brassinosteroids

The construction of the side chains of BS is a fairly complex problem for the solution of which it is necessary to develop original methods in addition to using known general principles.[3,4,93,138–140] Depending on the desired and the initial compounds the construction of the chain may be effected without changing or by changing the carbon skeleton of the initial molecule. In the latter case the key step of introducing the chain is usually a nucleophilic addition reaction of a suitable carbanion to a C-22, C-23 or C-24 carbonyl derivative of a steroid. The few examples to date of the use of other reactions to obtain a C–C bond may also be classified according to the number of the atom forming the new bond.

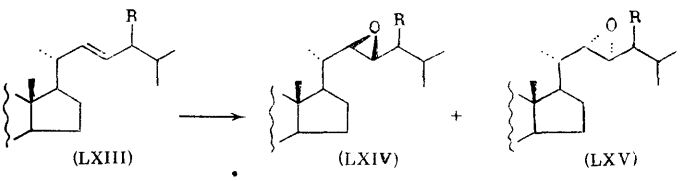
1. Syntheses retaining the carbon skeleton

When a side chain with a preformed carbon skeleton is present the problem of obtaining the BS reduces to the construction of the 22,23-diol grouping. The simplest method of introducing this is hydroxylation of a Δ^{22}-bond with osmium tetroxide.



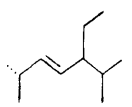
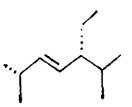
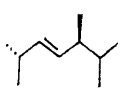
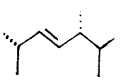
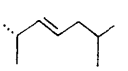
In all cases the reaction leads to the formation of both possible diols (LXI) and (LXII) the ratio of which depends on the size and configuration of the substituent R at C-24 (Table 2). Although the ratio of isomers, as a rule, proves to be unfavourable for the synthesis of the natural BS this route was used repeatedly for their preparation, particularly in the early period of investigations. In addition the method is used widely in the synthesis of the (22*S*,23*S*) analogues of the natural brassinosteroids[39,46,57,97–101,141–149] and is also used in the recently proposed process of isolating[150] 22,23-dihydroxycyclostigmastanones, intermediates for BS, from the mixture of phytosterols of sugar cane. Consideration of the mechanism of hydroxylation and the reasons for the preferential formation of isomers of type (LXII) has been undertaken.[77]

Other stereochemical results were observed in the oxidation of the Δ^{22}-bond with peracids leading to (22*R*,23*R*)-epoxide as the main reaction products.[138,143,151–153] For example on epoxidation of the dehydrocholesterol derivative (LXIII, R = H) the ratio of epoxides (LXIV) and (LXV) was 2:1,[143] and on oxidation of the related derivatives of campesterol (R = α-Me) and stigmasterol (R = α-Et) the ratios of the pairs of isomers (LXIV) and (LXV) were 1.5:1 [46] and 1.1:1 [76] respectively.



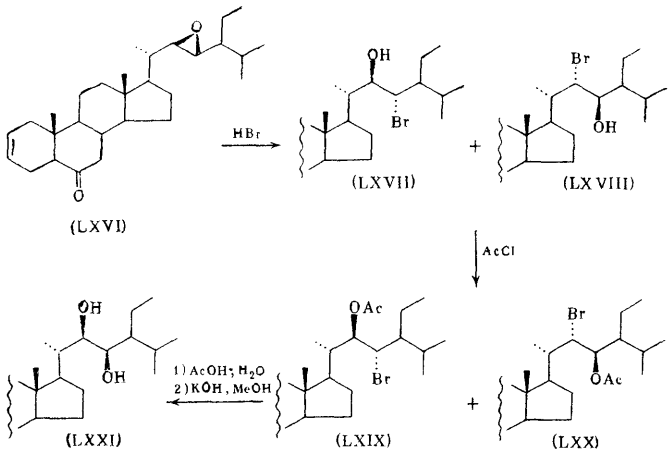
The resulting epoxides differ in chromatographic mobility, the (22*R*,23*R*) derivatives being usually less polar. It was shown[154] that ^{13}C NMR spectroscopy may serve as a convenient method for assigning configuration at the C-22 and C-23 centres.

Table 2. Ratio of isomeric diols on hydroxylation of Δ^{22}-steroids with osmium tetroxide.

Side chain structure	Ratio (LXI):(LXII)	Refs.
	1:6.7	[133]
	1:2.0	[134]
	1:4.6	[133]
	1:6.5	[57]
	1:1.0	[67, 133]
	1:2.7	[69]
	1:2.4	[112]
	1:2.3	[133]
	1:2.5	[135]
	1:2.3	[133]

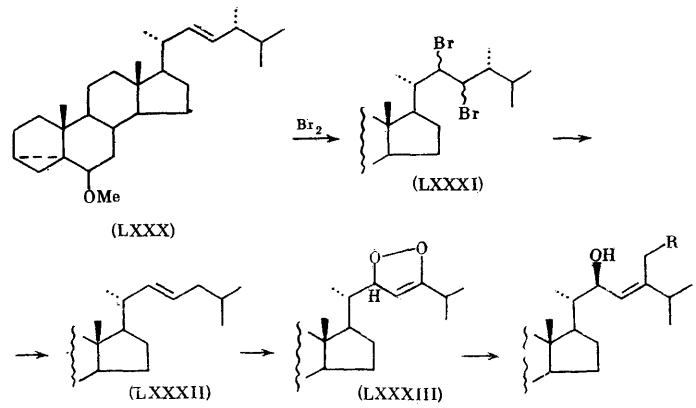
The predominant formation of (22*R*,23*R*)-epoxides on reacting Δ^{22}-steroids with peracids enabled a route to be proposed for the synthesis of (22*R*,23*R*)-diols which is more efficient than hydroxylation with OsO_4 and is based on a transformation of the epoxide ring.[46,47,74–78,155] Thus, in order to form the homobrassinolide (X) side chain, the epoxide (LXVI) was treated with HBr giving a mixture of the bromohydrins (LXVII) and (LXVIII). Treatment with acetic anhydride in pyridine led to the acetates (LXIX) and (LXX) the hydrolysis of which with 80% acetic acid at

90–100 °C proceeds with the inversion of the configuration of the carbon atom linked to bromine. The diol (LXXI) was obtained by subsequent deacylation of the hydroxy-acetates.[74,75] The application of this approach provides a fairly efficient route to brassinosteroids of the natural type.

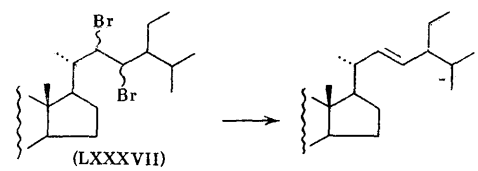


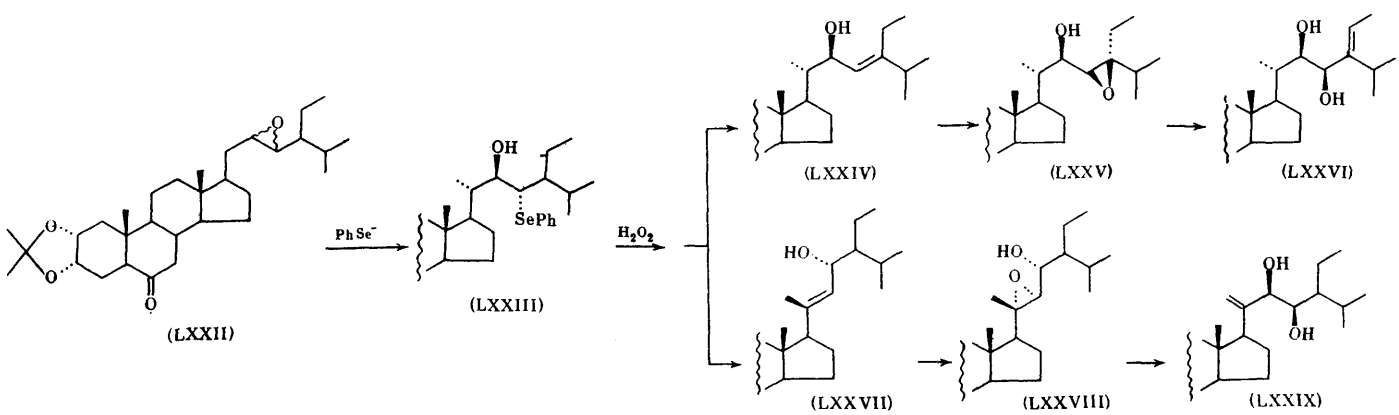
The formation of the C-24 centre with retention of the carbon skeleton of the initial steroid has been described with few examples. This route is used particularly to obtain homodolicholide (XII) and homodolichosterone (VI) from stigmasterol (XVI) through 22,23-epoxides of the (LXXII) type.[79,87] Fission of the epoxide ring of (LXXII) by the phenylselenyl anion, obtained from diphenyl diselenide and sodium borohydride, led to the alcohol (LXXIII) mixed with its regioisomer. Treatment of the mixture with hydrogen peroxide gave an inseparable mixture of the allylic alcohols (LXXIV) and (LXXVII) the epoxidation of which with subsequent treatment of the epoxides (LXXV) and (LXXVIII) with aluminium isopropoxide gave a mixture of the diols (LXXVI) and (LXXIX). After separation of the mixture the diol (LXXVI) was converted into homodolicholide (XII). A similar means of constructing the side chain was used in the synthesis of dolicholide (XI).[156]

A method of converting the side chain of ergosterol into the 23-ene-22α-hydroxy derivative (LXXXVI), a key intermediate in the synthesis of brassinolide (VIII),[36] has been proposed.[136] It comprises the bromination of the methyl ether (LXXX), subsequent conversion of the dibromide (LXXXI) into diene (LXXXII), treatment of a solution of the diene in pyridine with molecular oxygen and fission of the epoxide (LXXXIII) by hydrogenation over Lindlar catalyst. Removal of the OH group at C-28 in the alcohol (LXXXIV) was effected by conversion of it into the mesylate with subsequent reduction of (LXXXV) with lithium aluminium hydride.



It is interesting that the dibromide (LXXXVII) of the stigmasterol series undergoes debromination under dehydrobromination conditions[157] and this may be used for the protection of the Δ^{22}-bond.[98]

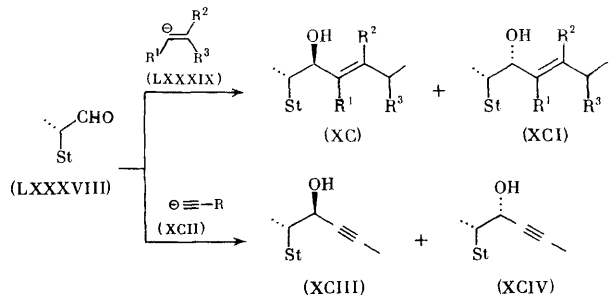




2. Construction of the side chain with the formation of new carbon–carbon bonds

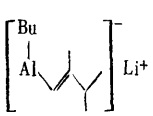
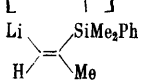
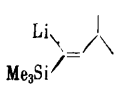
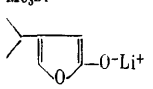
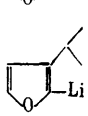
a) Syntheses with the participation of the C-22 centre

The presence of a Δ^{22}-bond in the stigmasterol molecule enables reconstruction of the carbon skeleton to be carried out in the following way. The missing portion of the chain containing the centres C-24, C-25 and C-23 in final form or accessible to the final form is added to a C_{22} fragment (22-aldehyde) obtained for example by ozonolysis of a sterol derivative with a protected Δ^5-bond. In the majority of cases vinyl (LXXXIX) [36,42,61,62,80,81,158–159] or ethynyl (XCII) [34,35,40–45,49–51,57–60,82,160–163] carbanions, obtained from the corresponding organometallic compounds, were used as nucleophiles for addition to the aldehyde (LXXXVIII). In all cases a mixture of the 22α-OH-(XC), (XCIII) and 22β-OH-(XCI), (XCIV) isomers was formed by the reaction



St = steroidal skeleton

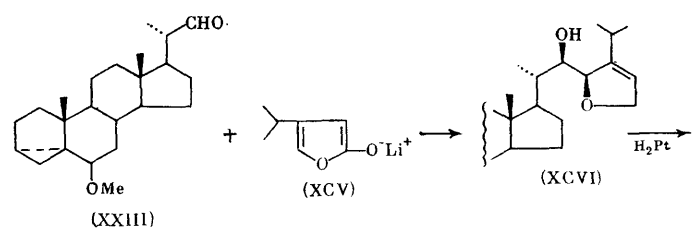
Table 3. Comparative efficiency of reagents in the nucleophilic addition to the 22-aldehyde.

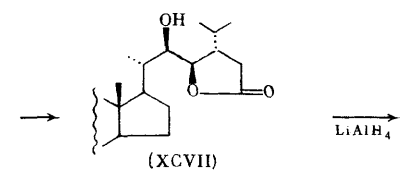
Reagent	Overall Yield, %	Ratio of isomers 22α-OH:22β-OH	Refs.
Li–C≡CPr-iso	76	1:1	[34]
	76	3:2	[35]
	68	1.1:1	[42]
	54	8.5:1.5	[36]
	64	3:1	[158]
	97	10:1	[159]
	90	8:1	[37]
	96	4.5:1	[164]
	99	7:3	[165]
$Me_2CHC{\equiv}CSnBu_3$	78	9:1	[163]

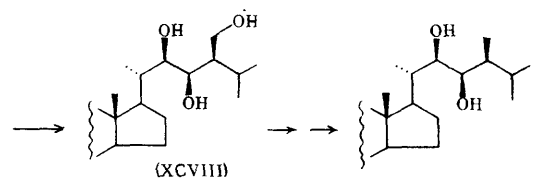
The ratios, yield and the route of further transformations into the desired products is determined by the structure of the nucleophile. Attempts have been undertaken in the course of investigations on the synthesis of BS to optimise the key stage (aldol reaction) by choice of reagent. The comparative efficiency of some of these is given in Table 3.

Among the reagents studied the heterocyclic derivatives provide a high yield and good stereoselectivity for the process and seem extremely promising. In addition the adducts formed in these cases enabled, as a rule, ready transformation into the desired compound through the minimum number of stages. Thus the use of the anion of 3-isopropylbut-2-enolide (XCV) in the reaction with the aldehyde (XXIII) enabled the formation of centres C-22 and C-23 simultaneously with a high stereoselectivity.[37]

Subsequent reduction of the butenolide intermediate (XCVI) also occurred selectively leading to the (24*S*)-isomer in 78% yield. The reductive fission of lactone (XCVII), protection of the dihydroxy grouping in the trihydroxy derivative (XCVIII), oxidation of the hydroxyl at C-29 into the ketone and decarbonylation completed the formation of the side chain of brassinolide with an overall yield of 32% calculated on aldehyde (XXIII).

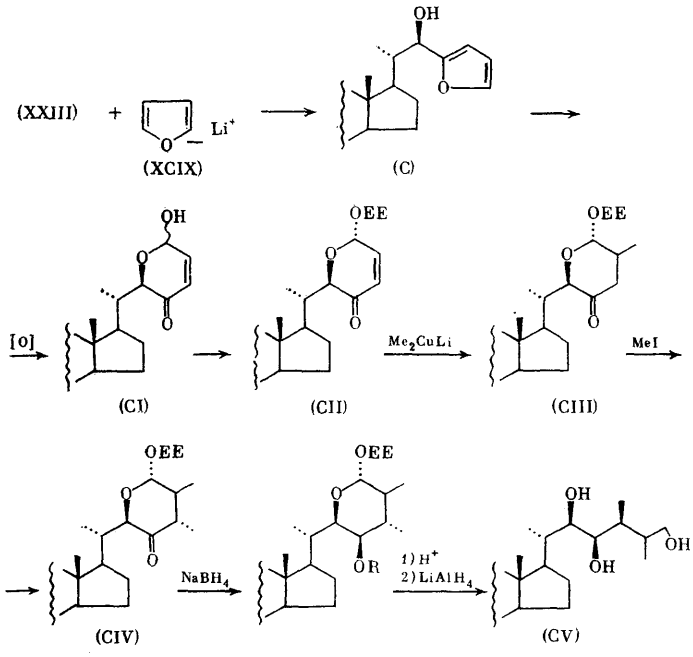






A related method of constructing the brassinolide side chain through the lactone (XCVII) obtained by the transformation of adducts of aldehyde (XXIII) with 3-isopropyl-2-lithiofuran has been used.[164] It is characterised by high yield and good selectivity at the addition stage, however it requires a large number of stages for the subsequent transformation into the desired product.

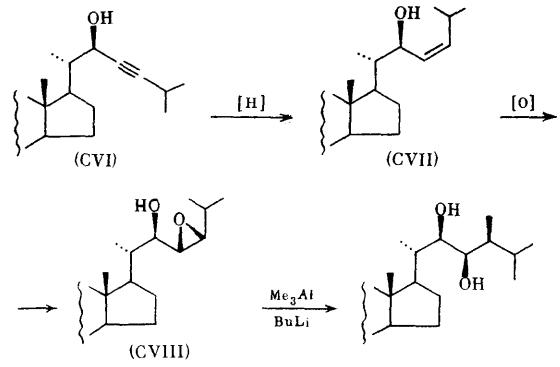
The route based on the use of the 2-lithiofuran (XCIX) is similar to those considered.[165]



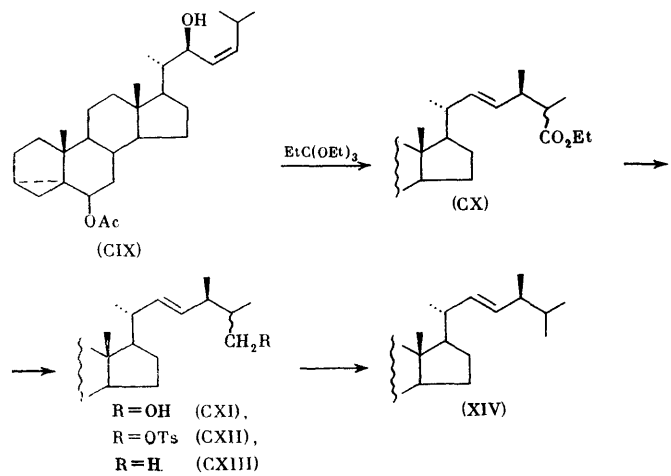
The adduct (C) formed in this case was oxidised with *N*-bromosuccinimide to the lactone (CI) as an unseparable mixture of anomers which was converted into a mixture of the corresponding ethoxyethyl ethers with (CII) predominating. The sequence of stages of conjugated addition of lithiummethylcuprate to the enone (CII), α-methylation of ketone (CIII), sodium borohydride reduction of the carbonyl group in the dimethyllactone (CIV) and ring opening gave the triol (CV). Protection of the *vic*-diol grouping and removal of the 27-hydroxy function by hydride reduction of the corresponding mesylate led to the formed side chain of brassinolide in an overall yield of more than 40% calculated on (XXIII).

In the syntheses based on the use of the acetylenic alcohols (CVI) the comparatively low stereoselectivity of the stage of adding the acetylides may be partially compensated by converting the by-product 22β-alcohol into the 22α-alcohol by the sequence of stages of oxidation to the ketone and hydride reduction,[35,42] leading to inversion of the configuration at C-22. The usual route of the subsequent conversions includes hydrogenation of the acetylenic alcohols (CVI) over Lindlar catalyst[34,35,57,160] or Raney nickel in the presence of ethylenediamine[42,44] to the *cis*-olefin (CVII), epoxidation of the latter with t-butyl hydroperoxide in the presence of vanadyl acetylacetonate[34–36] or by the action of MCPBA [40–42] and ring opening of the epoxide (CVIII) with trimethylaluminium in the presence of n-butyllithium.[40–45,49–51]

The accomplishment of the last stage is, however, linked with distinct practical difficulties[35] since introduction of the methyl group at position C-24 is sometimes carried out by a complex multistage synthesis[25–34] comprising hydrocyanation of the epoxide (CVIII) and subsequent transformation of the CN group on C-24 into methyl.



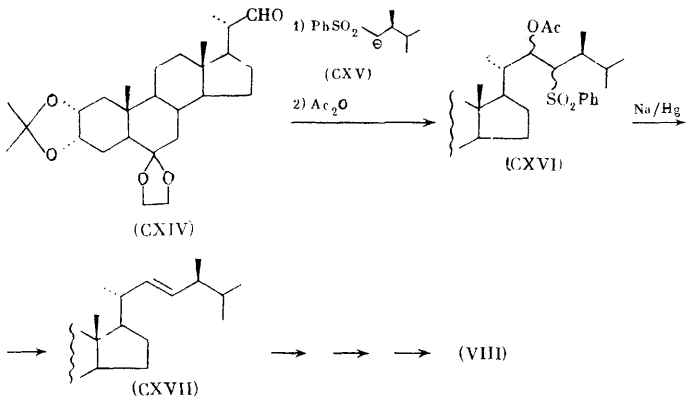
Another route for transforming the allylic alcohols (CVII) to the brassinolide side chain is the application of the Claisen rearrangement.[57,58,160] Thus rearrangement of the alcohol (CIX) using triethyl orthopropionate gave a mixture of epimers at C-25 of the ester (CX), the reduction of which led to the corresponding alcohol (CXI). Subsequent tosylation of (CXI) and reduction of the tosylate (CXII) with lithium aluminium hydride gave the cyclic alcohol (CXIII) which was then isomerised into 22-dehydrocampesterol (XIV).[160]



A drawback of this approach to BS synthesis is the need to apply to compound (XIV) the methods considered above for the functionalisation of a side chain with a preformed carbon skeleton which leads to a comparatively low yield of final product with a significant total number of steps (more than 20).

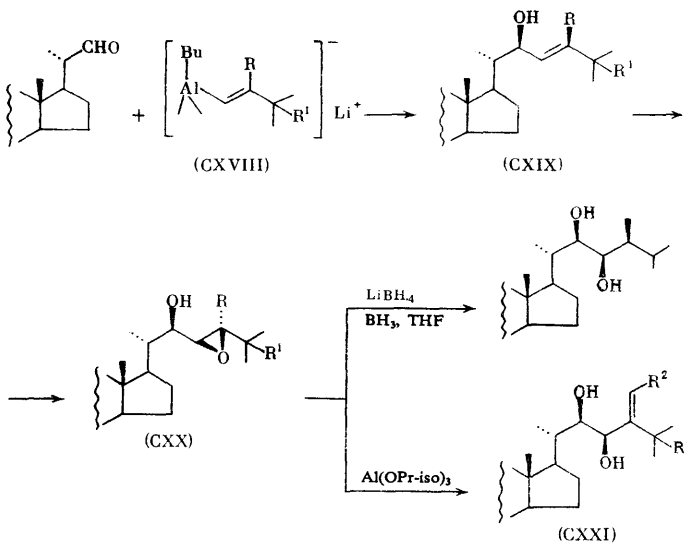
The formation of only one centre at C-24 at the first stage of making the Δ^{22}-derivatives has been used[46–48] and is based on the reaction of anion (CXV), generated from the corresponding sulphone, with aldehyde (CXIV). Acetylation of the product and reduction of the acetoxysulphone (CXVI) with sodium amalgam leads to compound (CXVII), which has the side chain of

22-dehydrocampesterol, and was converted into brassinolide (VIII) through the 22,23-epoxide.



Similar principles may be used to obtain the 28-nor analogues of BS containing no chiral centre at C-24.[48,85]

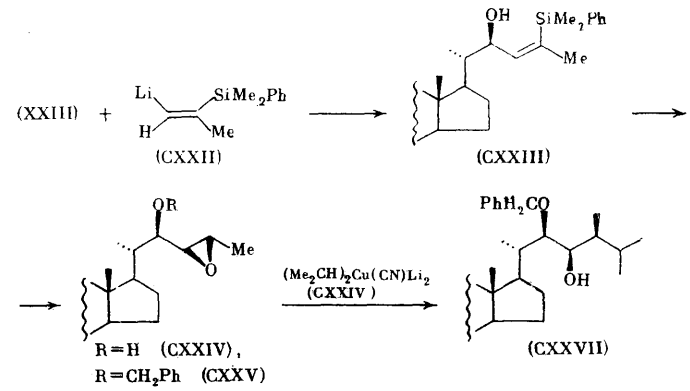
Among the methods using vinyl carbanions the most used are reactions with the lithium alkylaluminium derivatives (CXVIII)[36,42,61,62,80,81] leading to the formation of the Δ^{23}-derivatives (CXIX) as in the case of the allylic alcohols (CVII) considered above.



R=Me, Et; R^1=H, Me; R^2=H, Me

Further transformation is effected by conversion into the 22,23-epoxide and subsequent reductive fission of the oxide ring of (CXX) contrary to the Markownikoff rule leading to the brassinolide side chain.[36] Isomerisation of the epoxides (CXX) on boiling in toluene with aluminium isopropoxide is a convenient method of obtaining the diols (CXXI),[42,61,62,80,81] which are intermediates for 24(28)-unsaturated brassinosteroids.

The vinylsilanes (CXXII) have been shown to be useful in the reaction with the aldehyde (XXIII).[158] Epoxidation of the adduct (CXXIII) with subsequent removal of the dimethylphenylsilyl grouping gives the epoxide (CXXIV). Interaction of the benzyl ether (CXXV) with the mixed cuprate (CXXVI) and subsequent fission of the ether (CXXVII) with lithium in liquid ammonia leads to a diol with a complete brassinolide side chain.

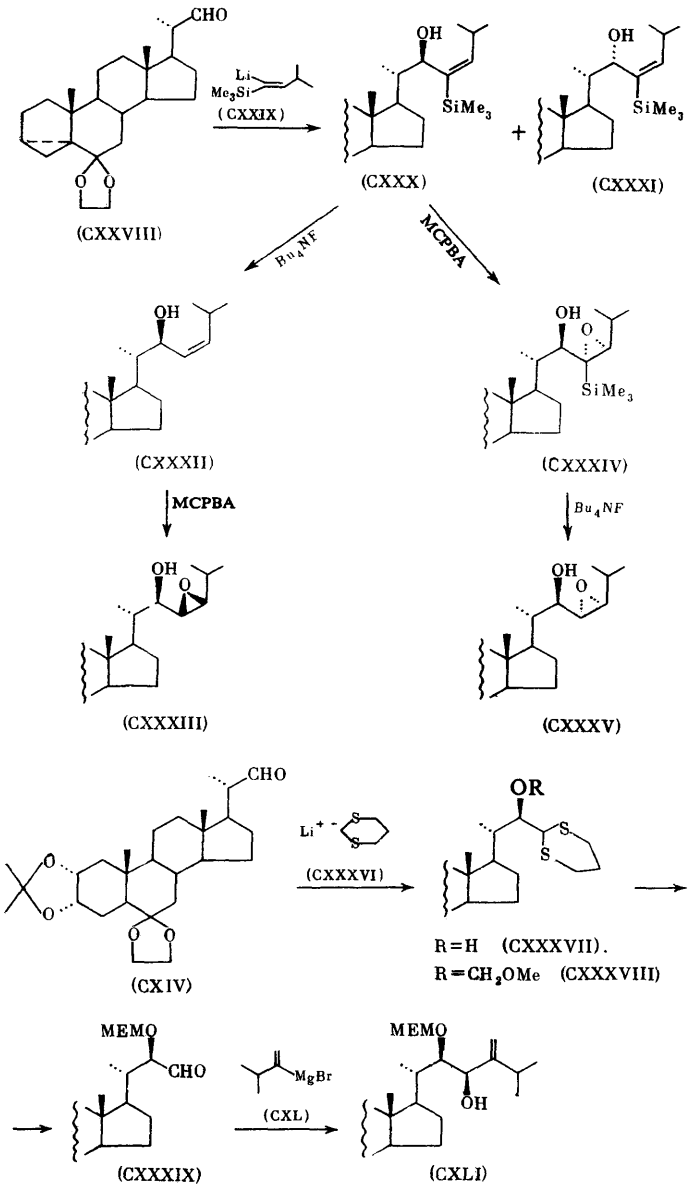


A method of forming the brassinolide side chain using vinylsilanes of type (CXXIX) has been proposed.[159] The presence of a bulky substituent stabilising the carbanion and bonded directly to the anionic centre of the nucleophile enabled a significant increase in the stereoselectivity of the reaction and in the yield of adduct. Thus addition of the anion (CXXIX) to the aldehyde (CXXVIII) proceeds with the formation of the alcohols (CXXX) and (CXXXI) in a ratio of 10:1 in 97% overall yield.

Desilylation of (CXXX) and subsequent epoxidation of (CXXXII) led to the epoxide (CXXXIII) from which the brassinolide side chain may be constructed by the methods described above.[40–45,49–51] A change in the reaction sequence [epoxidation of (CXXX) and then desilylation of (CXXXIV)] led to the isomeric epoxide (CXXXV).

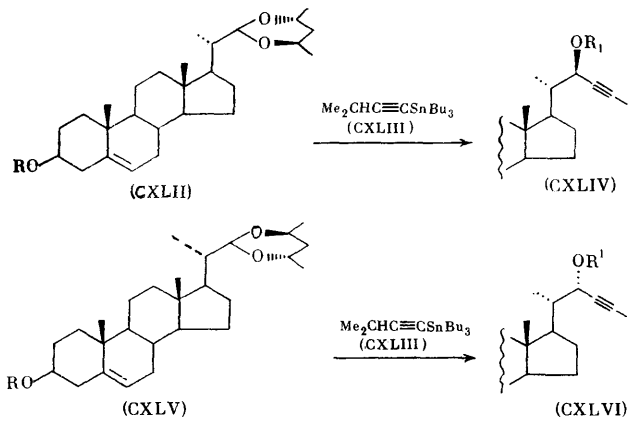
Treatment of the aldehyde (CXIV) with the lithium salt of the dithiane (CXXXVI) in tetrahydrofuran at −20 °C and subsequent protection of the hydroxy group in the adduct (CXXXVII) with chloromethyl methyl ether led to the dithiane (CXXXVIII) in 85% yield. Its dethioacetalation proceeds quantitatively without epimerisation at C-22 and gives the aldehyde (CXXXIX) which was then used for the stereoselective formation of the C-23 centre in the synthesis of dolicholide (XI) and dolichosterone (V)[63,64] by reaction with the Grignard reagent (CXL) obtained from 2-bromo-3-methyl-1-butene. Conversion of the alcohol (CXLI), formed selectively in 73% yield, into the corresponding diol was achieved by the sequential stages of protecting the 23-hydroxy group as the acetate,

hydrolysis with dilute hydrochloric acid, acetylation and saponification of the diacetate with potassium hydroxide solution.



28-Norbrassinolide was synthesised by a similar route using isobutylmagnesium bromide.[63,82,84] The selective addition of vinylstannanes to the 23-aldehyde has been described.[166]

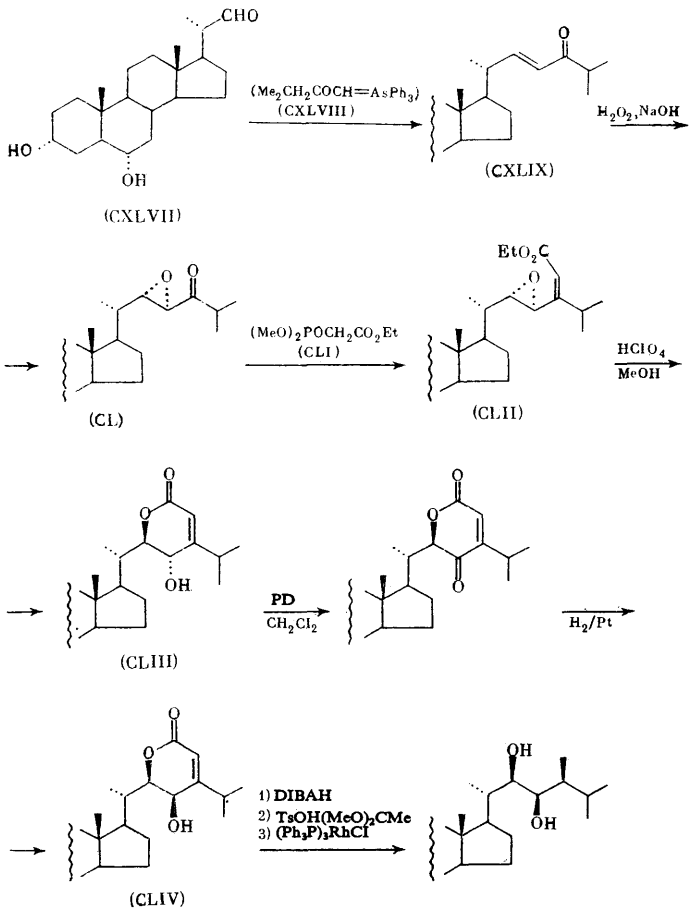
According to patent literature[167,168] an efficient means of influencing the stereochemistry of 22-hydroxy derivatives consists of the use in the addition reaction of the stereoisomeric acetals (CXLII) and (CXLV), which correspond to the aldehyde with added 2-methylpentane-2,4-diol. Their reaction with the acetylide (CXLIII) occurs with high stereoselectivity, leading to an epimeric mixture of the acetylenic derivatives (CXLIV) and (CXLVI) in a ratio of 95:5 and 11:89 for (CXLII) and (CXLV) respectively.



Organoarsenic compounds have been used to form the brassinolide side chain.[169] The aldehyde (CXLVII) obtained from hyodeoxycholic acid (XX) was treated with the ylid (CXLVIII) with the formation of α,β-unsaturated ketone (CXLIX).

Epoxidation of (CXLIX) with alkaline hydrogen peroxide gave the epoxyketone (CL) which, by Wittig-Horner reaction with compound (CLI), was converted into the epoxyester (CLII). The lactone (CLIII) was obtained by acid treatment of (CLII). The natural stereochemistry of the substituent at C-22 was thus formed. Inversion of the configuration at C-23 was achieved by sequential oxidation and reduction of the 23-hydroxyl group. Reduction of (CLIV) with diisobutylaluminium hydride (DIBAH), treatment of the resulting hemiacetal with 2,2-dimethoxypropane and

decarbonylation completed construction of the brassinolide side chain.

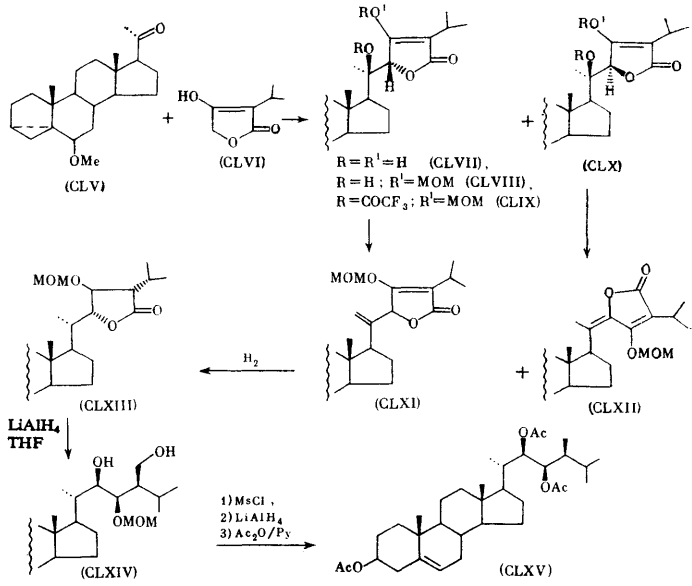


PD = pyridinium dichromate

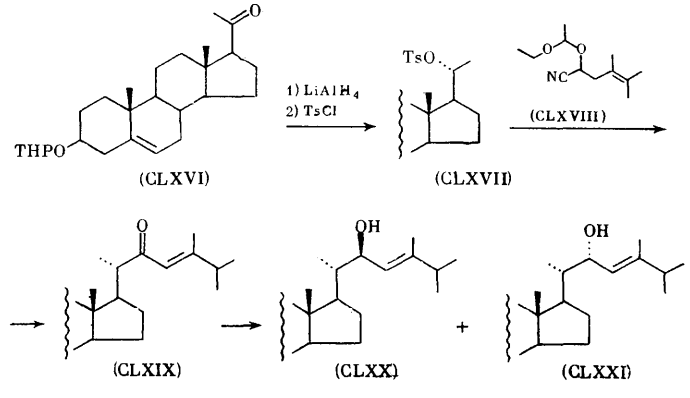
b) Syntheses with the participation of the C-20 centre

The main part of this section consists of syntheses the key stage of which is the nucleophilic addition reaction of the 3-isopropyltetronic acid anion (CLVI) to a C-20-ketone of the pregnane series (CLV).[52–55] It is interesting to note that the addition succeeds only for the derivatives (CLVII) with an unprotected hydroxyl group and the reaction does not take place in the case of the corresponding methoxymethyl ether. The diol (CLVII), obtained together with a little epimer (CLX) in a ratio of 91:9 in 84% overall yield, is used for further conversions. Protection of the secondary hydroxy group in compound (CLVII) as the methoxymethyl ether and subsequent treatment of (CLVIII) with trifluoroacetic anhydride in the presence of triethylamine and 4-pyrrolidinopyridine led to the acetate (CLIX), which on boiling in benzene with 1,8-diazabicyclo[5,4,0]undec-7-ene gave a mixture of the 5-ylidenetetronates (CLXI) and (CLXII) in a ratio of 82:18 in 73% overall yield. The saturated lactone (CLXIII) was obtained as the main product by catalytic hydrogenation of the main isomer (CLXI). Reductive fission of the ring in compound (CLXIV), removal of the 28-hydroxy group by conversion of the alcohol (CLXIV) into the 28-mesyloxy derivative with subsequent reduction with lithium aluminium hydride and acetylation led to the triacetate (CLXV) in 29% yield [based on (CLV)] which has the brassinolide side chain with protected hydroxyl groups.[52–56] A similar sequence of reactions for the tetronate (CLXII) enabled preparation of a side chain with a 22(*S*),23(*S*),24(*R*) configuration of substituents.

Another route using the 20-ketopregnanes to construct the brassinosteroid side chain, which has been suggested[170] includes conversion of the 20-keto group of pregnenolone (CLXVI) into a (20*R*)-tosyl (CLXVII) and subsequent alkylation of the tosylate (CLXVII) with the protected cyanohydrin (CLXVIII). Reduction of the resulting enone (CLXIX) with diisobutylaluminium hydride leads to the formation of a mixture of the allylic alcohols (CLXX) and (CLXXI) in a ratio of 97:3. Further construction of the brassinolide side chain from allylic alcohol (CLXX) was carried out similarly to that described previously.[136]

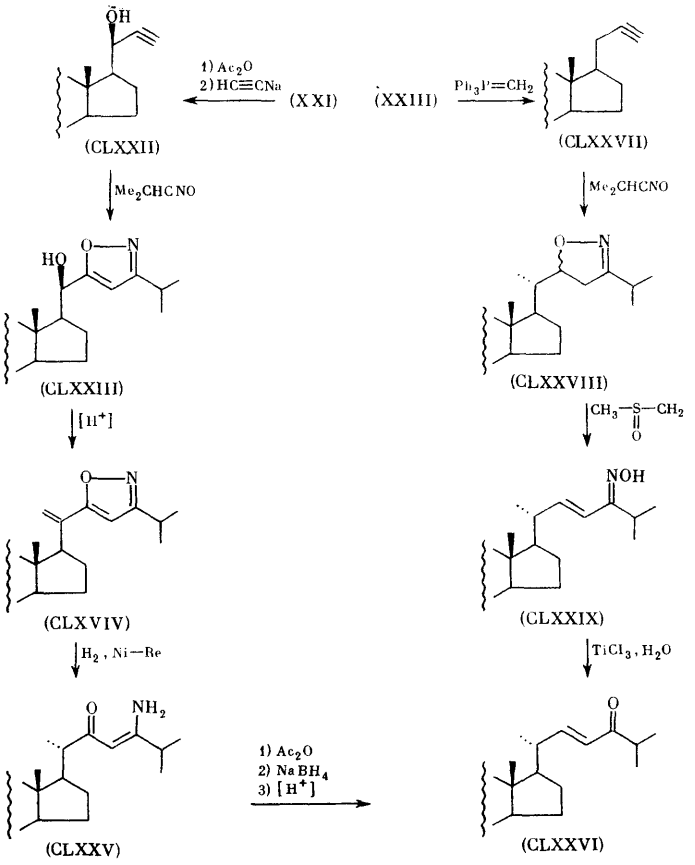


MOM – methoxymethyl



The method of constructing steroidal side chains using the nitrile oxide approach[171–181] possesses great potential and may be used successfully in the synthesis of brassinosteroids. Two means of obtaining the Δ^{22}-24-ketone (CLXXVI) from pregnenolone (XXI)

are shown below. The first method comprises the addition of isobutyronitrile oxide to the acetylenic alcohol (CLXXII), dehydration of the alcohol (CLXXIII), hydrogenation of (CLXXIV) and conversion of the enaminoketone (CLXXV) into the Δ^{22}-24-ketone (CLXXVI) by sequential acetylation, borohydride reduction and acid hydrolysis. The route to (CLXXVI) through the isoxazoline (CLXXVIII), obtained from the olefin (CLXXVII) and isobutyronitrile oxide by a 1,3-dipole cycloaddition reaction, is more convenient. Isomerisation of the isoxazoline (CLXXVIII) by base leads to the α,β-unsaturated oxime (CLXXIX), treatment of which titanium trichloride gives (CLXXVI). The use of Δ^{22}-24-ketones in the synthesis of brassinosteroids has been demonstrated[169,182,183]



In addition to the approaches discussed it is also necessary to mention the recently proposed improved methods of obtaining starting and intermediate compounds for the synthesis of BS, including the 20-formyl-[184–186] and 20-carboxypregnanes,[181,187,188] the 22,23-diols and their derivatives[150,189] and a new method of forming the side chain through 17(20)-pregnenes.[190,191]

Simultaneously with the development of investigations on the synthesis of the natural brassinosteroids attempts have been undertaken to obtain biologically active analogues of them differing in the structure of the side chain or of the cyclic portion of the molecule. In some cases as, for example, in the synthesis of epibrassinolide (IX), preparation by the synthetic route[39,69–70] preceded detection of the hormone in nature. The same methods are generally used to make modified BS as for the natural compounds. Up to the present the synthesis of a large number of derivatives has been effected, including compounds with a transformed side chain,[39,46,57,61,97–101,133–140] a modified cyclic fragment[145,192,217–222] or containing modification in both portions of the molecule.[192,207,209–215,223,224] As might be expected compounds are found among the analogues synthesised which are comparable in activity with the natural hormones. This shows the prospect of further search in this direction.

The methods discussed for forming the cyclic portion and the side chains of BS encompass data published up to the present in the scientific and patent literature. In addition investigations in this region continue to develop vigorously which affords the promise in the very short term of original approaches and of a wider application of methods and reactions known and used in other classes of natural products to the synthesis of BS.

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