Russian Chemical Reviews **64**(2) 187–200 (1995)
©1995 Russian Academy of Sciences and Turpion Ltd

UDC 542.91:547.379/547.544.548.737

Approaches to the total synthesis of sesquiterpenoids of the guaiane series

B T Zhuzbaev, S M Adekenov, V V Veselovskii

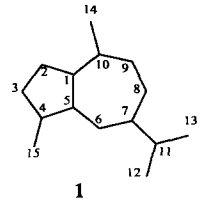
Contents

I. Introduction	187
II. Synthesis of guaiane sesquiterpenoids by the skeletal isomerisation of mono-, bi-, and tri-cyclic precursors	188
III. Pentacondensation of cycloheptane derivatives	194
IV. Heptacondensation of cyclopentane derivatives	197

Abstract. The approaches to the synthesis of guaiane sesquiterpenoids are considered. Attention is concentrated on the most general methods for the construction of their hydroazulene carbon skeleton. The bibliography includes 91 references.

I. Introduction

The guaiane series sesquiterpenoids **1**, which are widely distributed in nature,[1–4] are interesting objects to chemists engaged in synthesis. The development of research into their synthesis has also been stimulated by the discovery of many-sided biological activity in numerous representatives of compounds of this class.[4–6]



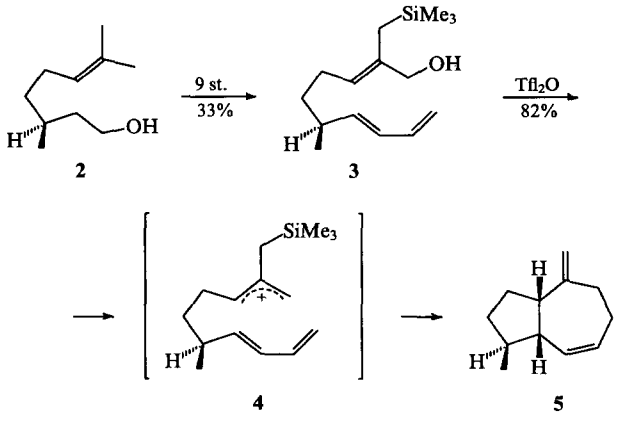
1

The present review includes data obtained on the synthesis of guaiane sesquiterpenoids (GS) mainly during the last 10–15 years as well as earlier studies which have not been adequately described in review articles[7–12] and a monograph.[13] Virtually all the known methods of synthesis of GS can be divided into three groups: (1) skeletal isomerisation of mono-, bi-, and tri-cyclic precursors; (2) pentacondensation of derivatives of cycloheptane; (3) the construction of the hydroazulene skeleton from suitably functionalised cyclopentanes. Two novel methods, based on the intramolecular cationoid [4 + 3]- and [3 + 2]-cycloadditions, remain outside the limits of this classification.

B T Zhuzbaev, S M Adekenov Laboratory of the Chemistry of Natural Products, Institute of Organic Synthesis and Coal Chemistry, National Academy of Sciences of the Republic of Kazakhstan, ul. 40 let Kazakhstana 1, 470061 Karaganda, Kazakhstan.
Tel. (7-321) 251 22 41.
V V Veselovskii Laboratory of Polyunsaturated Compounds, Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Leninskii prosp. 47, 117913 Moscow, Russian Federation.
Fax (7-095) 135 53 28. Tel. (7-095) 135 88 54.

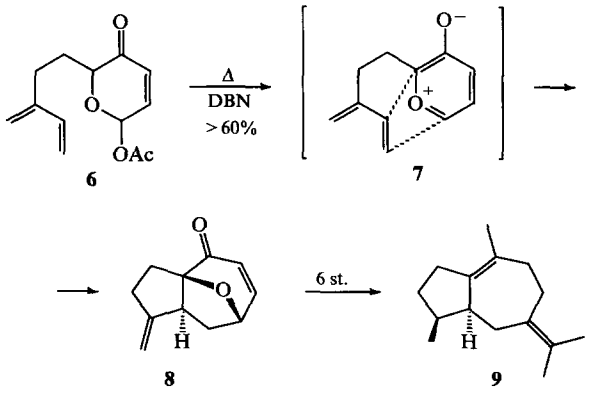
Received 31 October 1994
Uspekhi Khimii **64**(2) 198–212 (1995); translated by A K Grzybowski

According to the first of these,[14,15] the hydroazulene **5** is formed from the intermediate **4**, generated from the allyl alcohol **3**—a product of the nine-stage (9 st.) transformation of (*S*)-citronellol **2**. In view of the high stereoselectivity of the formation of the hydroazulene **5**, the use of this procedure may prove exceptionally effective for the construction of the molecules of *cis*-joined GS.[15]



Tfl = trifluoromethanesulfonyl.

In the second method, the key stage of the synthesis of (±)-β-bulnesene **9**[16,17] is the stereospecific conversion of the dihydropyranone **6** into the *trans*-joined hydroazulone **8**, probably via the pyrylium intermediate **7**.



DBN = 1,5-diazabicyclo[4.3.0]non-5-ene.

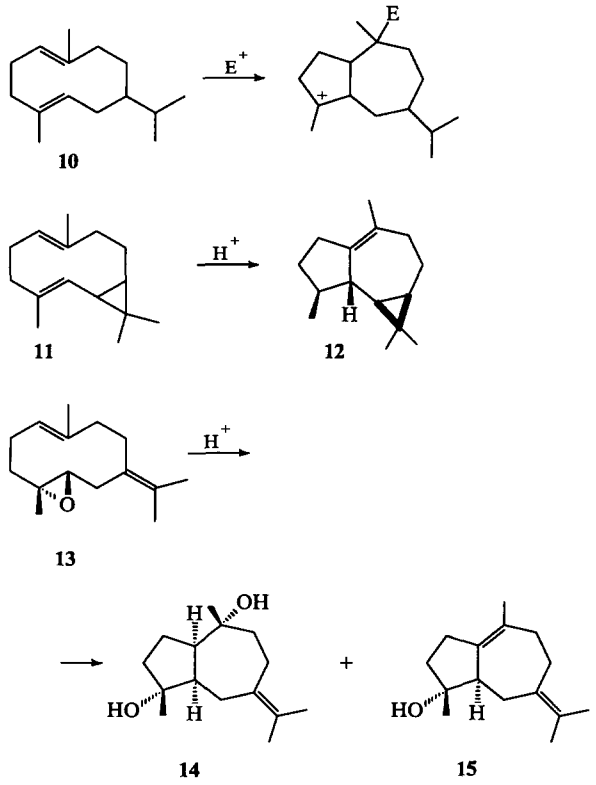
II. Synthesis of guaiane sesquiterpenoids by the skeletal isomerisation of mono-, bi-, and tri-cyclic precursors

This approach is used at present fairly widely. It proved particularly effective in the partial synthesis of guaianolides from germacrane and eudesmane sesquiterpene lactones.

1. Transformation of cyclodecane derivatives resembling biogenesis

According to Hendrickson,[18] the key stage in the biogenesis of GS is the anti-Markovnikov electrophilic cyclisation(EC) of their germacrane precursors of type **10** (Scheme 1).

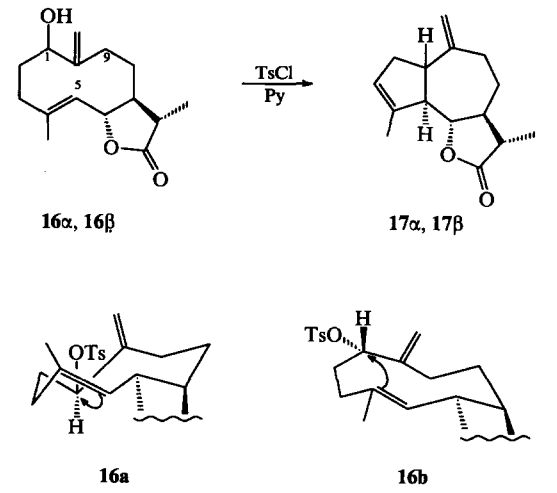
Scheme 1



This hypothesis stimulated a vigorous search for equivalent models. The result of such search has led to the development of a large number of biogenesis-like schemes for the synthesis of GS.[12,19] One of the early examples of the use of this approach is based on the acid-initiated conversion of bicyclogermacradiene **11** into a mixture of tricyclic products with a significant predominance of guaiane **12**.[20] Another example of the anti-Markovnikov electrocyclisation in the series of germacranes is the transformation of the epoxide **13** into a mixture of the diol **14** and the alcohol **15**.[21]

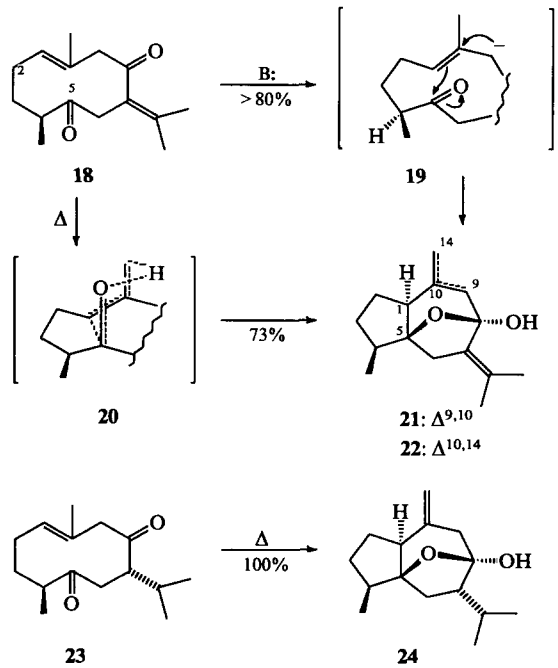
Analysis of the stereochemical results of such transformations permits the conclusion that the biomimetic reaction, proceeding via a concerted mechanism, is subject to conformational control.[12] This is confirmed, for example, by the results of the solvolytic electrocyclisation of gallicin **16β**[22] and of its C(1)-epimer **16α**,[23] which proceeds readily under the conditions of the tosylation of the secondary alcohols indicated (Scheme 2). The product of the cyclisation of gallicin **16β** is then the *cis*-joined guaianolide **17α**, the stereospecificity of the formation of which is evidently due to the preferred conformation **16a** of the initial allyl alcohol (and of its tosylate) with the equatorial orientation of the leaving group and with the disposition of the C(1), C(4), and C(5) centres in close proximity in space. The solvolysis of the epimer **16α**, leading to *trans*-**17β**, is treated taking into account the fact that the conformer **16b** is preferred.

Scheme 2



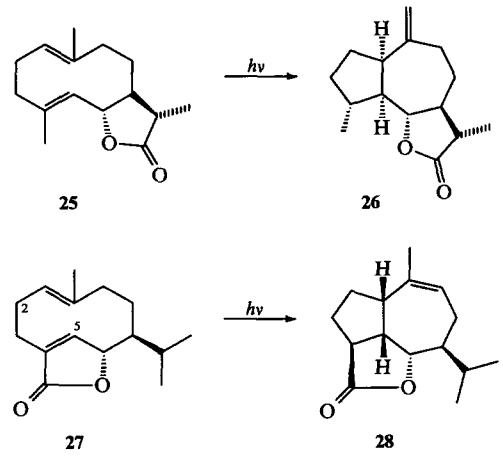
Rigid stereochemical control is also characteristic of the thermal or base-catalysed cyclisation of $\Delta^{1,10}$-5-ketogermacranes — the probable biogenetic precursors of the *trans*-joined 5-hydroxyguaianes.[12,24,25] Thus, on treatment with K_2CO_3 in methanol or with basic Al_2O_3 in benzene, the dehydrocurdione **18** is smoothly converted into the curcumenol **21**, evidently via a stage involving the formation of the allyl carbanion **19** (Scheme 3).[24] Its regioisomer **22** has been obtained in a high yield from the dehydrocurdione **18** under the conditions of the thermal reaction proceeding in accordance with a mechanism of the ene type via the probable transition state **20**. The thermolysis of the curdione **23** leads similarly to the curcumol **24** also without epimerisation of the centre adjoining the carbonyl group.[25]

Scheme 3

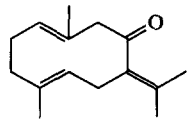


Individual examples of the stereospecific photocyclisation of compounds of the germacrane series to GS have been described. In particular, it has been shown that the sole product of the photolysis of dihydrocostunolide **25** is the *cis*-joined guaianolide **26**.[26] The irradiation of the germacranolide **27** leads similarly to the tricyclic lactone **28** (Scheme 4).[27]

Scheme 4



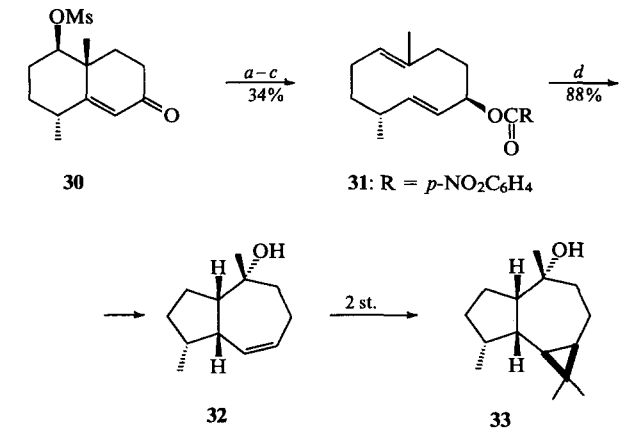
There are at present no reliable methods for the oxidative transformation of the functionalised germacrane skeleton into the guaiane skeleton. In a study recently undertaken for this purpose,[28] it has been shown that treatment of the germacratrienone **29**



with a solution of $Pb(OAc)_4$ in acetic acid results in the formation of a complex mixture of substances containing predominantly unsaturated *cis*-guaiane ketoacetates.

It is noteworthy that the syntheses of GS considered above, based on the transformation of germacranes which are difficult to obtain, are hardly of preparative value. The approach, developed by Marshall,[29] by virtue of which the type **31** cyclodecadienes, which are related to germacranes, become obtainable from decalin derivatives **30**, is of definite interest. For example, the Grob fragmentation of the methanesulfonate **30**, initiated by a strong base, readily affords the trisnorderivative of germacrane, the solvolysis of which in the form of the nitrobenzoate **31** leads stereospecifically to the hydroazulenol **32**, which is subsequently converted into (±)-globulol **33**.[30]

Scheme 5

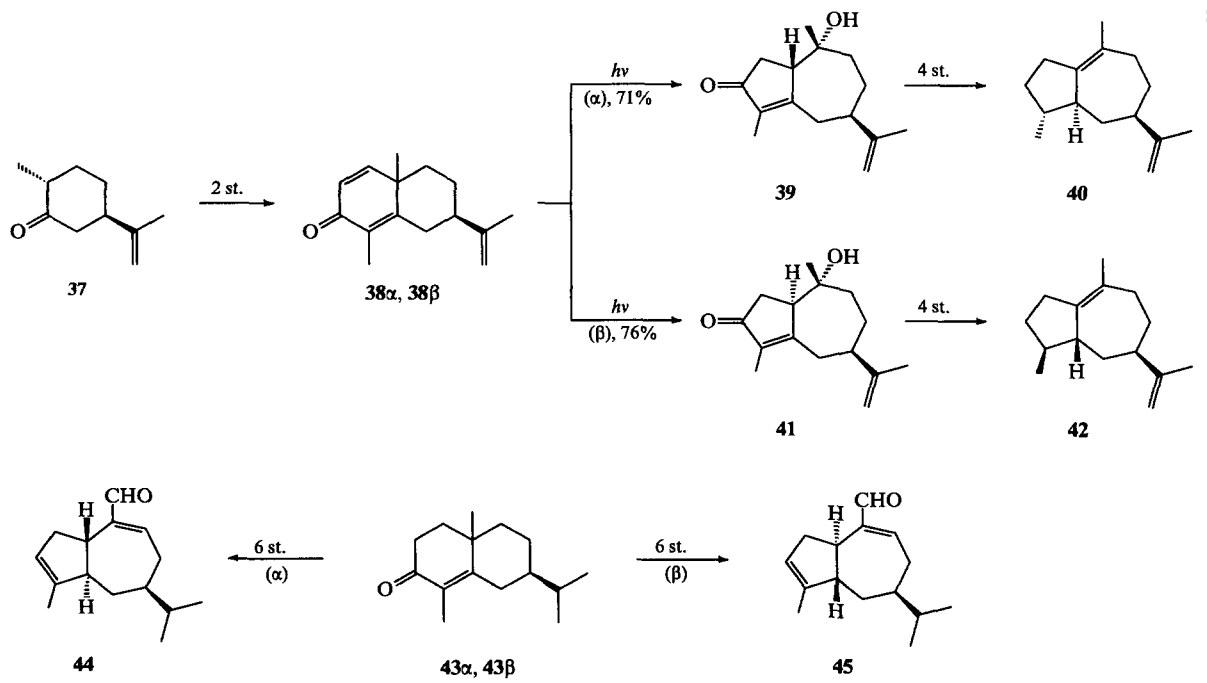


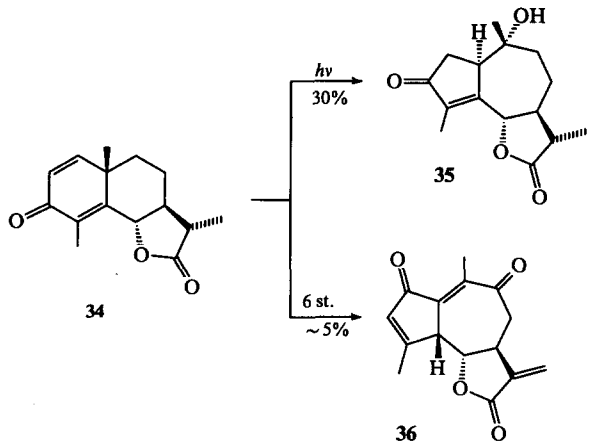
(*a*) BH_3; (*b*) NaOMe–MeOH; (*c*) *p*-$NO_2C_6H_4COCl$; (*d*) $NaHCO_3$, H_2O–$C_4H_8O_2$.

2. Skeletal rearrangements of derivatives of bicycloalkenes

The skeletal rearrangements of bicycloalkenes as a method for the construction of GS molecules has been studied mainly in relation to decalin derivatives, among which sesquiterpenes of the eudesmane series occupy an important place. One of the first examples of the application of this approach is the photoisomerisation of α-santonin **34** and some of its C(8)-derivatives to the corresponding type **35** guaianolides observed by Barton.[31,32] The latter are used subsequently in the partial synthesis of many natural products.[33] The stereospecific nature of the rearrangement, noted also for the photolysis of cross-conjugated tetrahydronaphthalenes related to compound **34**,[34–38] makes it possible to regard this procedure as a reliable means of obtaining the hydroazulene precursors of GS and some of their natural representatives. For example, the guaianolide **36** has been synthesised in this way from α-santonin **34**.[39] Data are available concerning the use of a series of derivatives of α-santonin **34** for the synthesis of (−)-estafiatin.[40]

Scheme 6

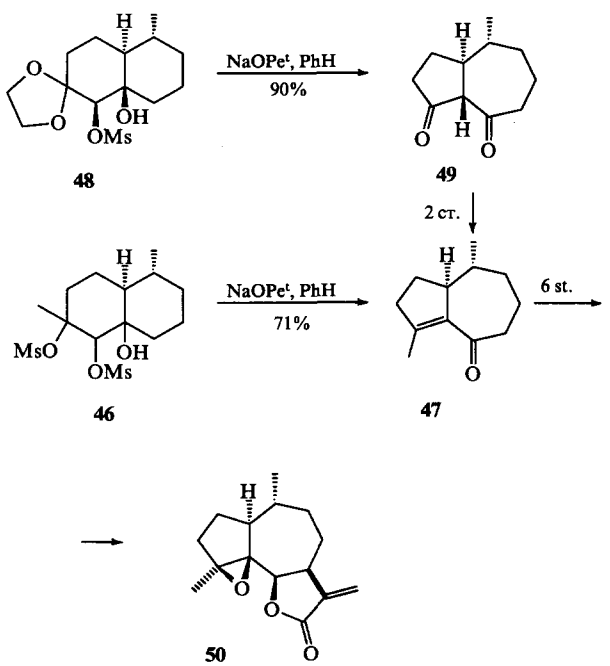




The methodology described above proved effective also in the syntheses of the bulnesenes **40** and **42** (Scheme 6), the key stage of which is the photolysis of the α- and β-dienones **38**, leading to the epimeric guaianes **39** and **41** respectively.[41,42] [The α- and β-dienones are obtained in their turn from (+)-dihydrocarvone **37** by Robinson's method.]

The dihydro-analogues of guaianes **39** and **41**, synthesised by the same procedure from the enones **43**, have been used in the synthesis of the corresponding stereoisomeric aldehydes **44** and **45** with the *trans*-joined hydroazulene skeleton.[43]

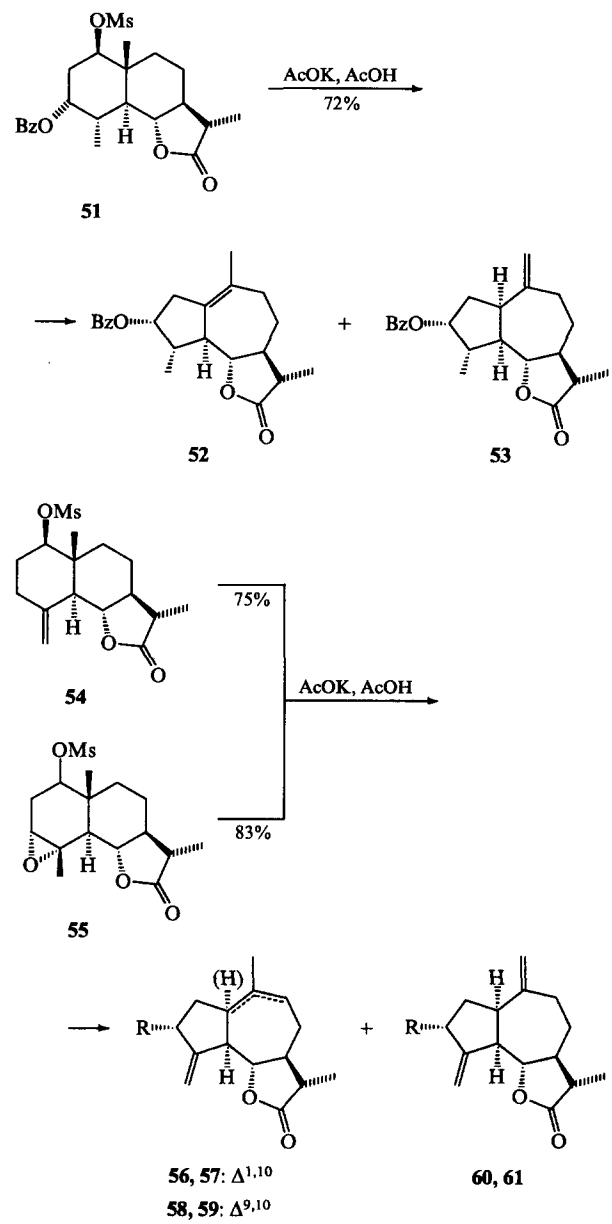
An alternative procedure, ensuring the stereospecific formation of the hydroazulene precursors of GS from perhydronaphthalenes, uses the solvolytic rearrangement of suitably functionalised derivatives. For example, a scheme for the total synthesis of the guaianolide **50** is based on a pinacol type rearrangement of the sum of the diastereoisomeric methanesulfonates **46**, leading to the hydroazulenone **47**. The latter can also be obtained from the diketone **49** — the product of the solvolysis of the methanesulfonate **48**.[44,45]



Pe^t = *tert*-pentyl (Translator).

The synthesis of diverse representatives of guaianolides from α-santonin **34** similarly involves the use of the skeletal isomerisation of the α-santonin derivatives **51**, **54**, and **55**.[46-50] It was found that the solvolysis of these methanesulfonates by potassium acetate in acetic acid leads to mixtures of the corresponding regioisomeric hydroazulenes *endo*-**52**, **56**–**59**, and *exo*-**53**, **60**, **61** in comparable proportions (Scheme 7).

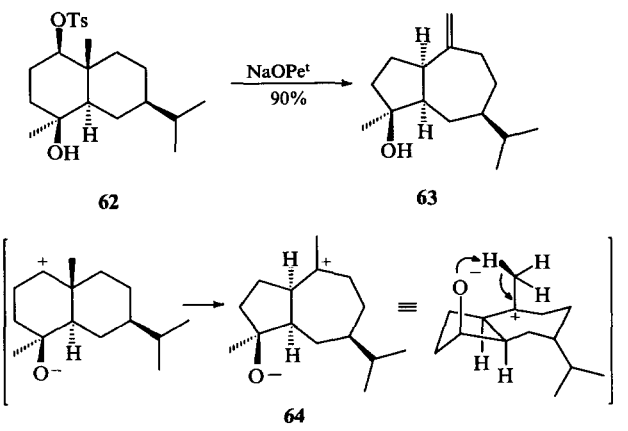
Scheme 7



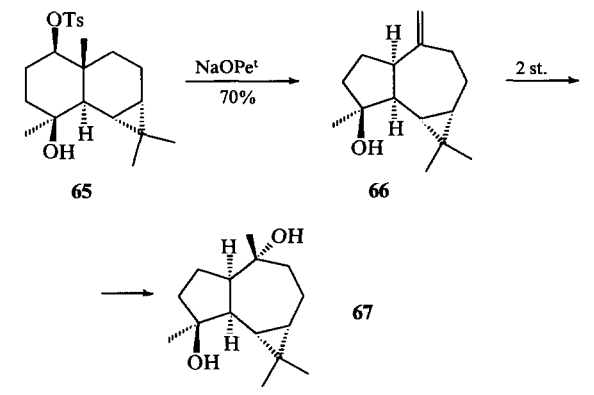
R = H (**56**, **58**, **60**), OAc (**57**, **59**, **61**).

The observation by de Groot and coworkers[51-53] that the *tert*-pentyloxide-initiated skeletal rearrangement of type **62** tosylates leads to a virtually quantitative yield of *exo*-methylene products, in particular to (±)-epi-nardol **63** (Scheme 8), is of special interest in this connection.

Scheme 8

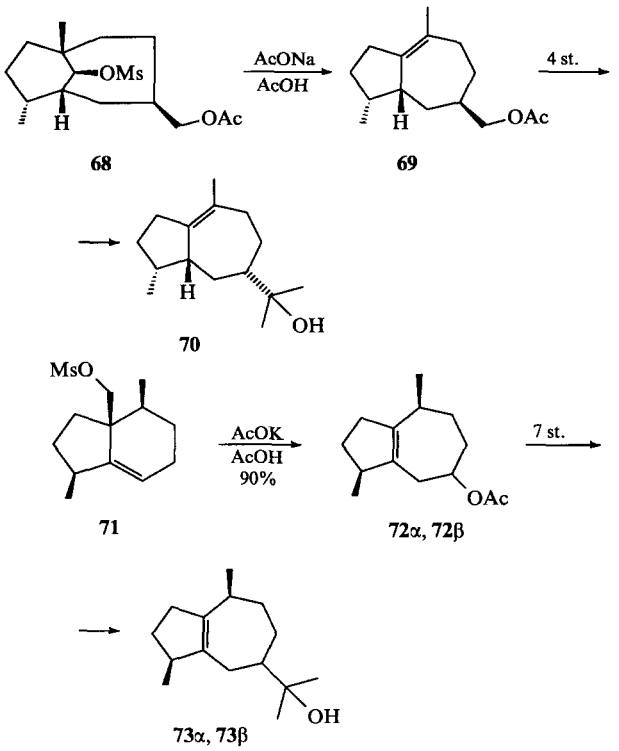


The significant increase in the regioselectivity of the reaction in this case can be accounted for by the presence in compound **62** of an axial hydroxy-group at the C(4) atom, its deprotonation and the involvement of the resulting alkoxide ion in the intramolecular elimination of a proton from the carbonium ion **64**, which leads to the alkene **63**.



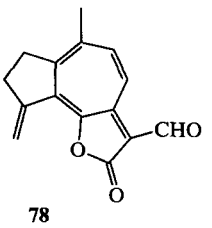
The isomerisation of the tricyclic tosylate **65** [53] leads similarly to the exclusive formation of the guaiane **66** — the key compound in the total synthesis of the natural diol **67**.

Thus the skeletal isomerisation of decalins is used fairly widely in the synthesis of hydroazulenoids. The use for this purpose of the skeletal rearrangement of other bicycloalkanes is so far restricted to only isolated examples (see also Heathcock and coworkers [8,9]). For example, the solvolysis of the bicyclic methanesulfonate **68** leads to smooth formation of the hydroazulenoid **69** from which (±)-bulnesol **70** was subsequently obtained. [54] In the scheme for the total synthesis of the guaiol **73β** and its epimer **73α**, the solvolytic isomerisation of the bicyclo[4.3.0]nonane derivative **71** to a mixture of the epimeric acetates **72** was employed as the key stage. [55]



Another novel method of synthesis of bulnesol **70** is based on the ability, observed by Sakai and coworkers, [56] of type **74** δ-diketones to undergo a rearrangement with ring expansion leading to cycloheptane derivatives under the conditions of the $F_3B.OEt_2$-initiated formation of an ethylene ketal. This reaction of the diketone **74** evidently includes the formation of the intermediate aldol **75** and the ethylene ketal of the β-hydroxyketone **76** and the cleavage of the latter to the hydroazulene **77** on treatment with a Lewis acid (Scheme 9).

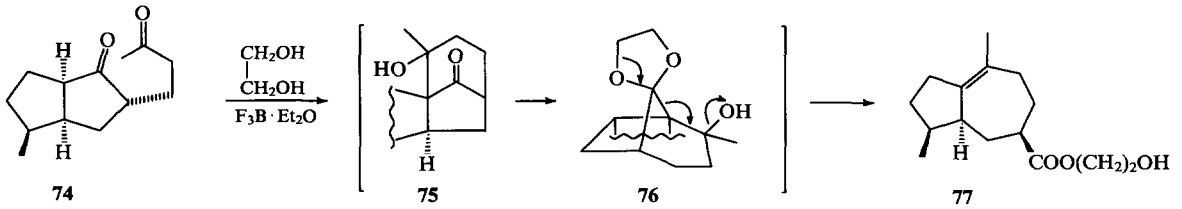
Mention must also be made of the recently developed scheme for the synthesis of the guaiane phytoalexin lettucenin A **78**, [57] in which use is made of the known ability of the type **79** dibromomethylcyclohexadienones to be converted into substituted tropones on treatment with $HSnBu_3$ (in the presence of a source of radicals).



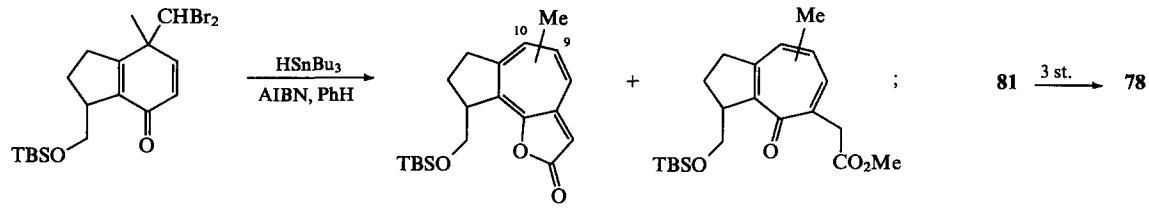
In the case of the hexadienones **79**, this reaction leads to a mixture of products **80–83** (Scheme 10) with compound **81** predominating. The latter was converted into the guaianolide **78** in three simple stages.

Thus the use of the skeletal isomerisation of bicycloalkanes is a fairly universal strategy applicable to the synthesis of a wide variety of representatives of GS.

Scheme 9



Scheme 10



79

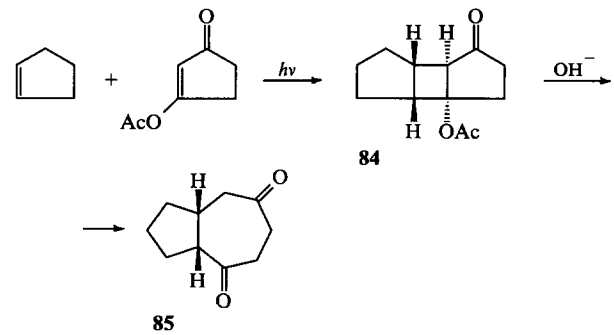
80: 9-Me
81: 10-Me

82: 9-Me
83: 10-Me

TBS = Bu^tMe_2Si.

3. Skeletal isomerisation of tricyclodecanes

The skeletal isomerisation of functionalised tricyclodecanes, involving the degradation of their cyclobutane fragment, serves as an effective method of synthesis of GS. The likely usefulness of this approach was first demonstrated by de Mayo and co-workers [58] in relation to the two-stage synthesis of the diketone **85** involving the retroaldo type of cleavage of the photoadduct of cyclopentene and cyclopentadione enol acetate.



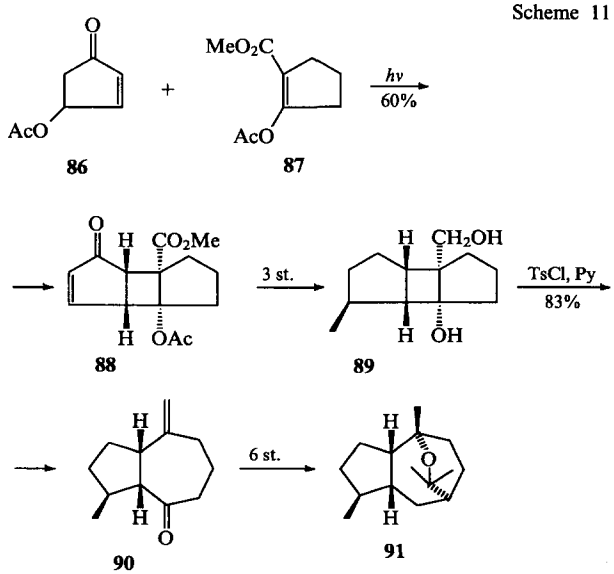
84

85

An evident advantage of this approach is the availability of compounds of type **84**, which have been synthesised by the [2 + 2]-cycloaddition of simple initial materials.

Thus the photochemical [2 + 2]-cycloaddition of substituted cyclopentenes **86** and **87**, leading predominantly to the cyclic adduct **88**, has been used in the total synthesis of (±)-5-epikessane **91** [59] in order to construct the carbon skeleton of the key tricyclodecane **89**. Next the enone **88** was converted in three stages, including the Michael methylation which proved stereospecific in this instance, into the diol **89**. The latter was smoothly cleaved under the conditions of the solvolysis into the hydroazulenone **90** — the precursor of (±)-5-epikessane **91** (Scheme 11).

Scheme 11



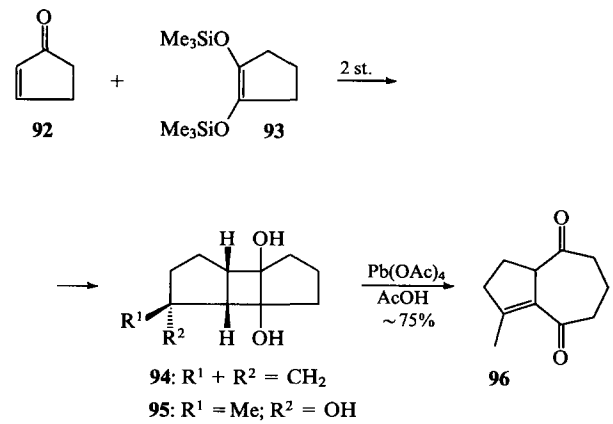
86 87

88 89

90 91

The tricyclic diol **94** and the triol **95** were obtained similarly from the cyclopentene derivatives **92** and **93**. The oxidative degradation of the diol and triol, accompanied in the case of the triol **95** by the degradation of the tertiary alcohol, affords smoothly the diketone **96** (Scheme 12).

Scheme 12

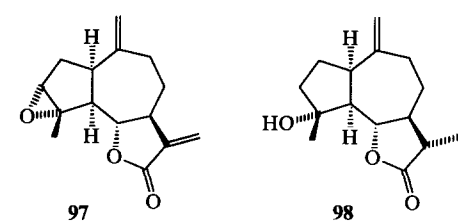


92 93

94: $R^1 + R^2 = CH_2$
95: R^1 = Me; R^2 = OH

96

The diketone was then used in the synthesis of (±)-estafiatin **97** and (±)-compressanolide **98**. [60–62]

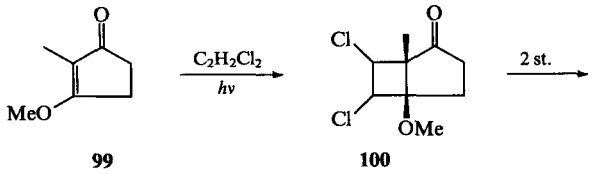


97 98

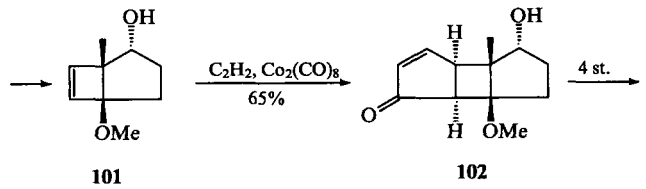
An alternative method of synthesis of the type **84** tricyclodecane compound has been used successfully in the synthesis of a GS precursor — the hydroazulenone **104**. [63] Thus the key stage in the synthesis of the hydroazulenone **104** is the formation of the tricyclic enone **102** under the conditions of the Pauson–Khand reaction of ethyne with the bicycloheptene **101**, which is formed in its turn from the photoadduct **100** of the methoxycyclopentenone **99** and *trans*-1,2-dichloroethene.

Yet another variation of this approach is the use of intramolecular [2 + 2]-cycloaddition in order to construct tricyclic precursors of hydroazulenoids. It was first demonstrated by Pattenden and coworkers [64] in relation to the photolysis of the enol acetate **105**.

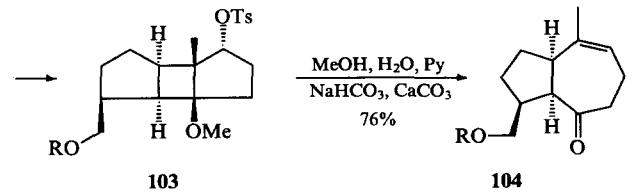
The effectiveness of this scheme in the synthesis of the hydroazulene **108** proved, however, to be low in view of the low regioselectivity of the photocyclisation of the enol acetate **105**, leading to a mixture of the isomeric tricycloalkanes **106** and **107** in proportions of approximately 3:2, and only the minor component **107** gives rise to the target diketone **108** on retroaldol cleavage.



99 100

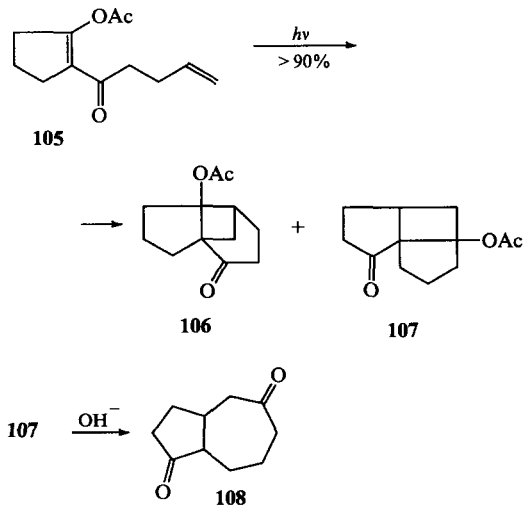


101 102



103 104

R = $SiPh_2Bu^t$.

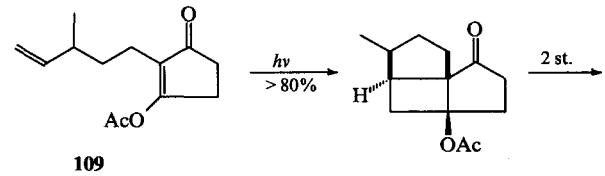


105 106 107 108

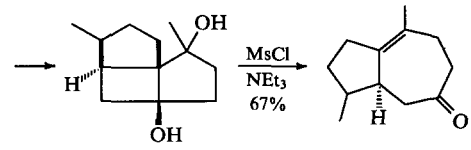
The photochemical [2 + 2]-cycloaddition of the enol acetate **109** takes place regiospecifically and leads to the sum of the epimeric tricyclodecanes **110** in a yield exceeding 80%.[65] The latter are then converted into the diols **111**, which are smoothly converted under the conditions of the solvolysis into a mixture of the epimeric hydroazulenones **112** in proportions of approximately 3:1. The conversion of the ketones **112** into the corresponding alkenes afforded the epimeric (±)-β-bulnesenes **9**.

An interesting development of this methodology arose in a recent study by Korean chemists,[66] who synthesised a series of hydroazulenones (compounds **116**, **120**, and **124**) from the readily available silyl vinyl ethers **113**, **117**, and **121**. The thermal [2 + 2]-cycloaddition of the latter to the dichloroketene generated in situ leads regio- and stereo-specifically to the tricyclic dichloro-derivatives **114**, **118**, and **122**. The reduction of the latter with Bu^n_3SnH in the presence of azobisisobutyronitrile (AIBN) leads to the tricyclodecanes **115**, **119**, and **123**, which are cleaved almost quantitatively under the conditions of mild desilylation by F^-, affording the diketones **116**, **120**, and **124** respectively.

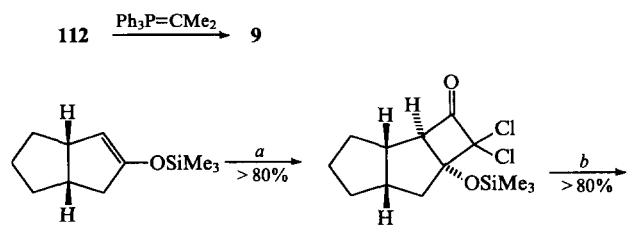
Thus an attractive feature of this approach is the possibility of its use from readily available starting materials, the choice of the key tricyclic structure ensuring the necessary functionalisation of the hydroazulene precursor of GS formed on its isomerisation.



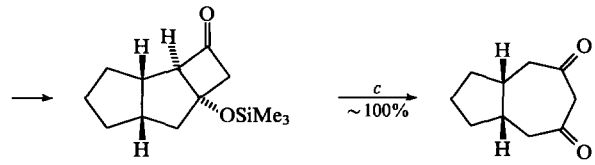
109 110α, 110β



111α, 111β 112α, 112β

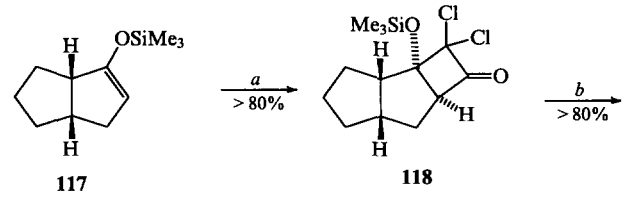


113 114

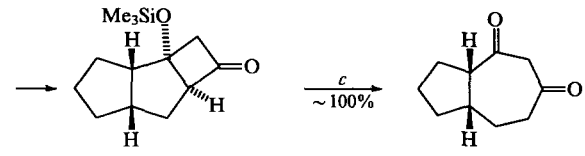


115 116

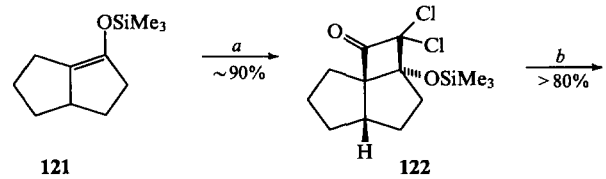
(*a*) Cl_3CCOCl, Zn; (*b*) Bu^n_3SnH, AIBN; (*c*) Bu^n_4NF.



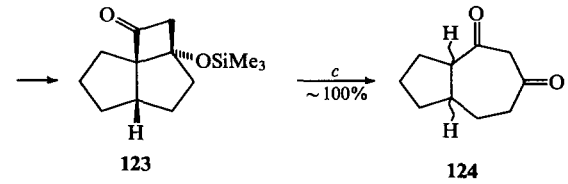
117 118



119 120



121 122



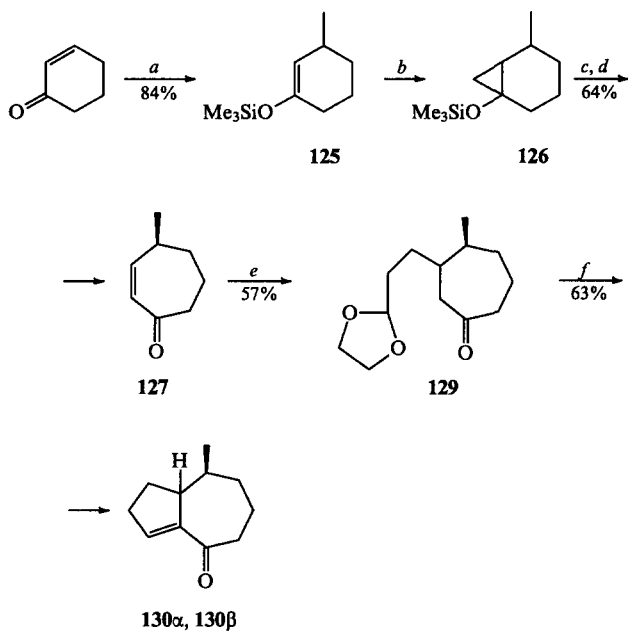
123 124

(*a*) Cl_3CCOCl, Zn; (*b*) Bu^n_3SnH, AIBN; (*c*) Bu^n_4NF.

III. Pentacondensation of cycloheptane derivatives

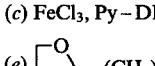
The strategy in the synthesis of GS based on the construction of their hydroazulene skeleton by the pentacondensation of cycloheptane derivatives was first employed as late as 1982.[67] Its subsequent development arose from effective methods being devised for the synthesis of suitably functionalised cycloheptane precursors. Thus Heathcock et al.[67] synthesised the cycloheptenone **127** from the cyclohexenone, which was converted, via the silyl vinyl ether **125** stage, into the bicyclic compound **126**. The latter underwent skeletal isomerisation to the cycloheptenone **127** (Scheme 13). The CuI-catalysed Michael coupling of the enone **127** and the Grignard reagent **128** takes place stereoselectively and leads to a mixture of the isomeric ethylene ketals **129** (*trans*:*cis* ≈ 4:1). Under the conditions of mild hydrolysis and as a result of the accompanying intramolecular crotonic condensation, the latter are smoothly converted into the epimeric hydroazulenes **130** in the same proportions.

Scheme 13



(*a*) Me_2CuLi, then Me_3SiCl, Et_3N; (*b*) CH_2I_2, Zn(Cu);

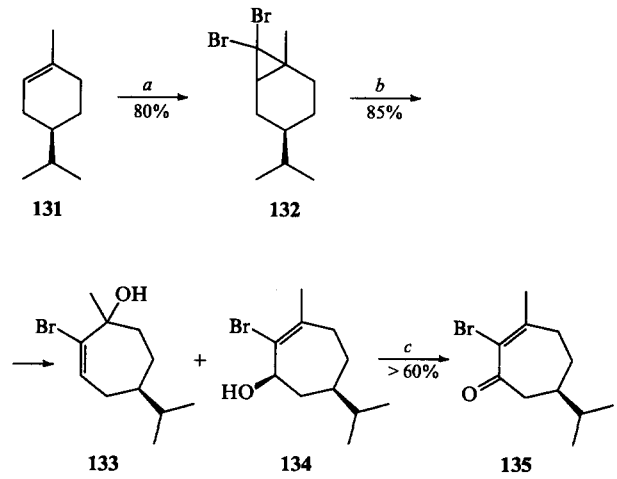
(*c*) $FeCl_3$, Py–DMF; (*d*) NaOAc, MeOH;

(*e*)  (**128**), CuI, THF; (*f*) 5% HCl, EtOH.

This methodology may acquire special interest in connection with the recent studies by Brocksom et al.,[68] who used the industrially available (+)-menthene **131** in order to synthesise the bicycloheptane **132**. The oxidation of the regioisomeric alcohols **133** and **134**, formed on skeletal rearrangement of compound **132** catalysed by Ag^+ ions, affords smoothly the chiral cycloheptenone **135** as the sole product.

In a recently published study,[69] the cycloheptenones **142** and **143**, related to the ethylene ketals **129**, were obtained by isomerisation under solvolytic conditions of the bicyclo[3.2.0]-heptane derivatives **140** and **141** respectively (Scheme 14).

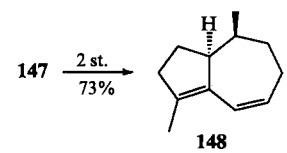
The latter proved to be obtainable by means of the thermal [2 + 2]-cycloaddition of dichloroketene to the silyl vinyl ether **136**.[70] The dehalogenation of the resulting bicycloheptanone **137** by Bu^n_3SnH in the presence of AIBN and the coupling of the resulting ketone **138** with the corresponding organomagnesium reagents **128** and **139** leads to compound **140** and **141**. The hydrogenation of the alkenes **142** and **143** over a rhodium catalyst, accompanied by the partial reduction of the ketones **129**



(*a*) $CHBr_3$, $C_{16}H_{34}Me_3N^+Br^-$; (*b*) $AgNO_3$, Me_2CO-H_2O (9:1);

(*c*) $C_5H_5N^+HClCrO_3^-$, CH_2Cl_2.

and **146** to the alcohols **144** and **145**, and then cyclisation of the latter led ultimately to the hydroazulenone **130α** described above and the azulenone **147** — the key compound in the synthesis of (±)-clavukerin A **148**.

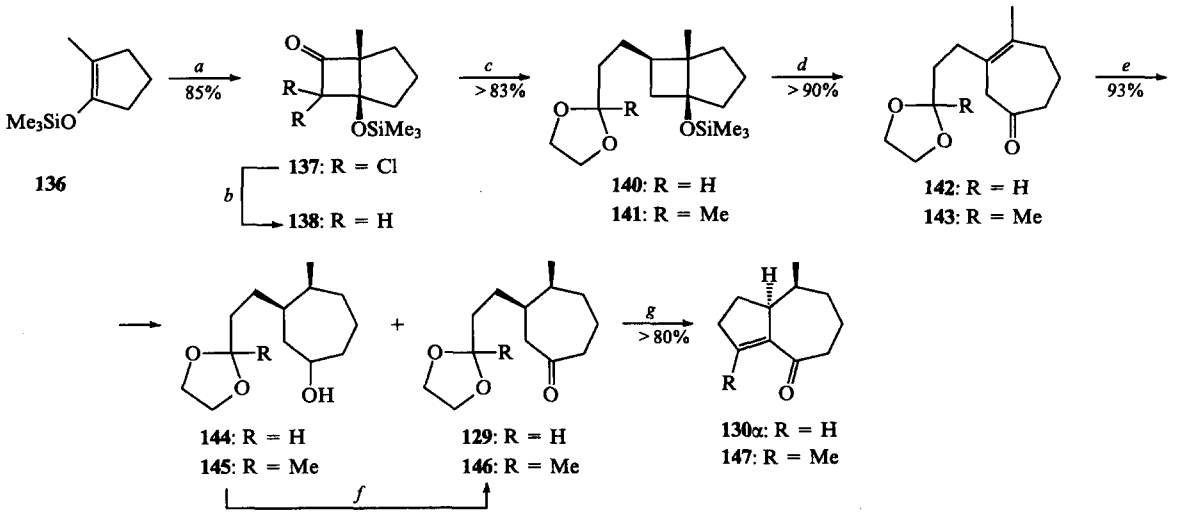


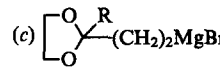
Mori and coworkers[71] developed a novel scheme for the total synthesis of the guaiane **159**. Compound **152**, a cycloheptene precursor of compound **149**, was obtained in 14% yield from alkylglutaric acid **149** via the intermediate bisdiazodiketone **151**, which cyclises to the enedione **152** in the presence of copper acetylacetonate (Scheme 15). The product of the hydrogenation of compound **152** — the cycloheptanedione **153** — was then converted into the monoketal **154**, the regio- and stereo-selective alkylation of which by the bromo-derivative **155** and subsequent ozonolysis of the resulting alkene **156** led ultimately to the diketone **157**. On treatment with a base, the latter cyclises smoothly to the hydroazulenone **158**, the eight-stage transformation of which afforded the target product (±)-**159**.

The γ-diketone **167**, structurally related to the diketone **157** and employed recently[72] in the total synthesis of (±)-gnididione **168**, was synthesised from methylglutaric acid anhydride **160** (Scheme 16). The ketodiester **162** was obtained by coupling compound **160** with the dilithium derivative **161**. It was subsequently converted into the hydrazone **163**, which underwent smoothly the Dieckmann condensation with formation of the bicyclic compound **164**. The alkylation by the bromo-derivative **166** of the ketone **165**, obtained from compound **164**, required the use of a double excess of the deprotonating agent and afforded the required diketone **167** as the sole product, which exists in the enolic form.

Yet another aspect of the approach under consideration, the development of which appears especially attractive, involves the use of the industrially available 2,4,6-cycloheptatrienone (tropone) as the starting material for the synthesis of GS. This methodology was first applied by Rigby and coworkers[73–75] in the total syntheses of (±)-estafiatin **97**, (±)-dehydrocostus-lactone **169**, and (±)-grosshemin **170**, which are discussed in detail in two reviews.[11,13]

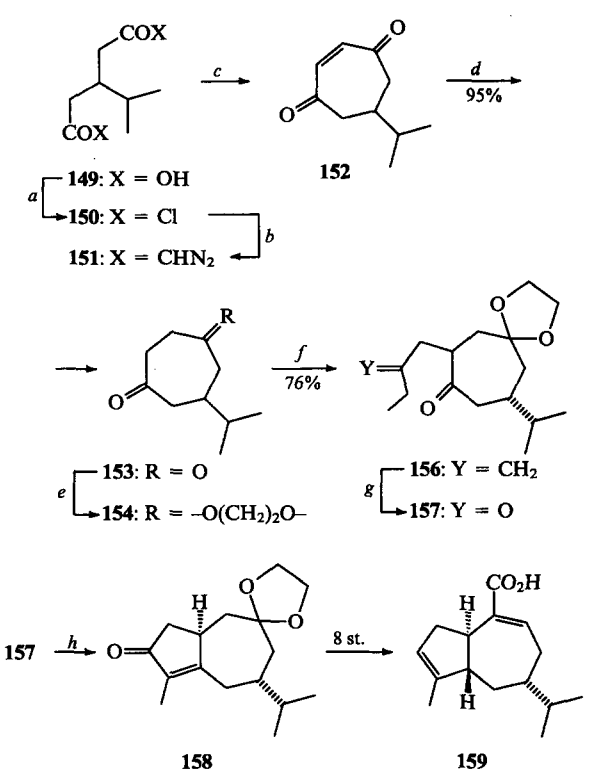
Scheme 14



(*a*) Cl_3CCOCl, Zn; (*b*) Bu^n_3SnH, AIBN; (*c*)  (**128**: R = H, **139**: R = Me), THF

(*d*) MsCl, Et_3N, CH_2Cl_2; (*e*) H_2, Rh/Al_2O_3, EtOAc; (*f*) $(C_5H_5NH)_2Cr_2O_7$, CH_2Cl_2; (*g*) 5% HCl, EtOH.

Scheme 15

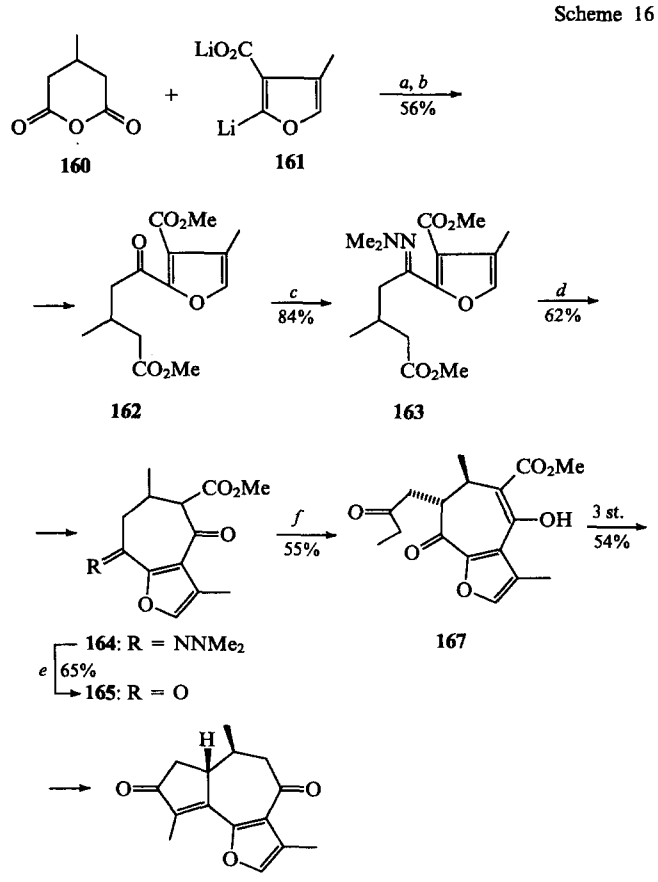


(*a*) PCl_5; (*b*) $CH_2N_2-Et_2O$; (*c*) $Cu(acac)_2$, PhH; (*d*) H_2, Pd/C, EtOH;

(*e*) TsOH, , PhH; (*f*) $LiNPr^i_2$, THF, $EtCCH_2Br$ (**155**), CH_2

(*g*) O_3, MeOH, Me_2S; (*h*) NaOH, $H_2O-EtOH$.

Scheme 16



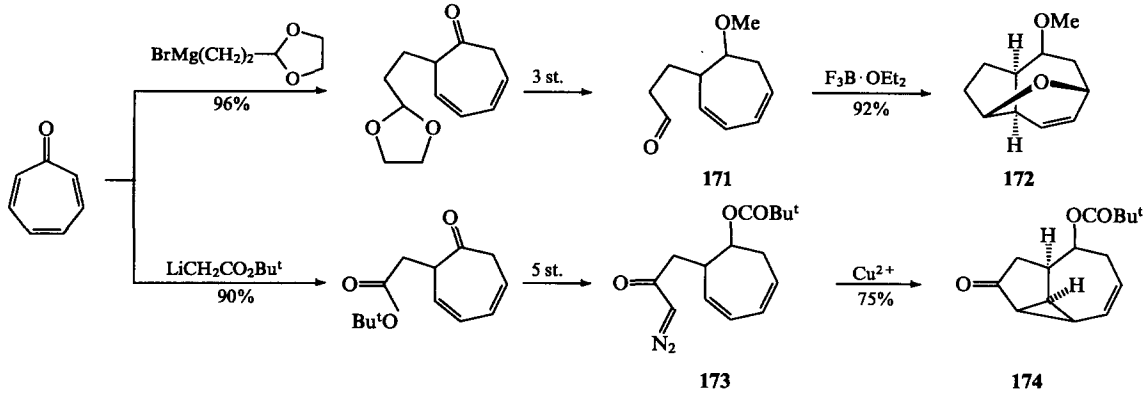
(*a*) THF; (*b*) AcCl, MeOH; (*c*) Me_2NNH_2, AcOH–EtOH;

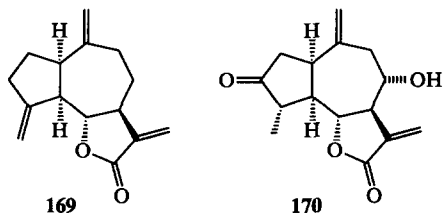
(*d*) $NaN(SiMe_3)_2$, Et_2O; (*e*) MeI, EtOH;

(*f*) $LiN(Pr^i_2)$, $EtCOCH_2Br$ (**166**), THF.

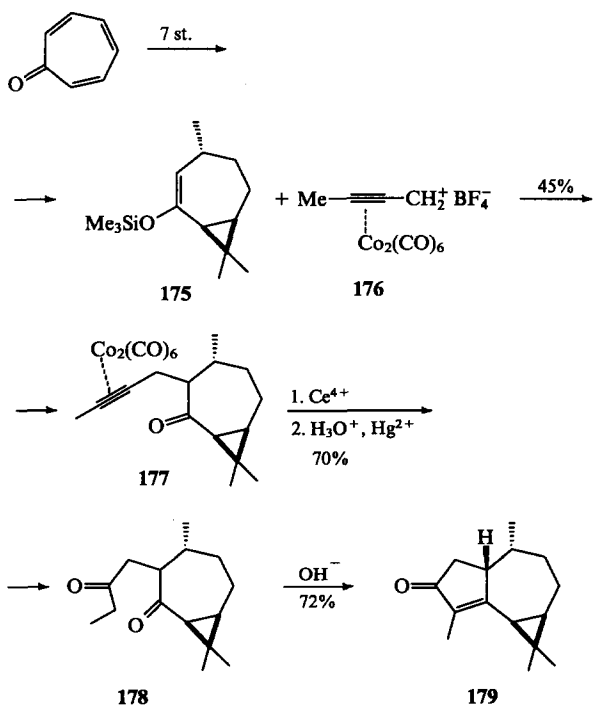
The principal stages of the syntheses of these compounds are presented in Scheme 17. Thus the hydroazulene precursor of the guaianolides **97** and **169** — the epoxide **172** — was obtained as a result of the $F_3B.OEt_2$-catalysed cyclisation of the aldehyde **171**.[73] The known ability of tropone to interact with organometallic reagents via the 1,8-addition mechanism is used in its turn to synthesise the aldehyde **171**. The tricyclic compound **174**, which is of key importance in the synthesis of grosshemin **170**, was obtained similarly. It is a product of the $Cu/CuSO_4$-catalysed cyclisation of the diazoketone **173**.[74]

Scheme 17





Yet another synthetic scheme, based on the 11-stage transformation of tropone into (±)-cyclocolorenone **179**,[76] involves the condensation of the silyl ether **175** with the cationoid complex **176**. The resulting diastereoisomeric adducts **177** were converted into a mixture of epimeric γ-diketones **178** (*cis*: *trans* ≈ 8:1) by successive demetallation and hydration in the presence of Hg^{2+}. The dominant component, compound *cis*-**178**, was isolated chromatographically and was smoothly cyclised to the target product **179** by treatment with a base.

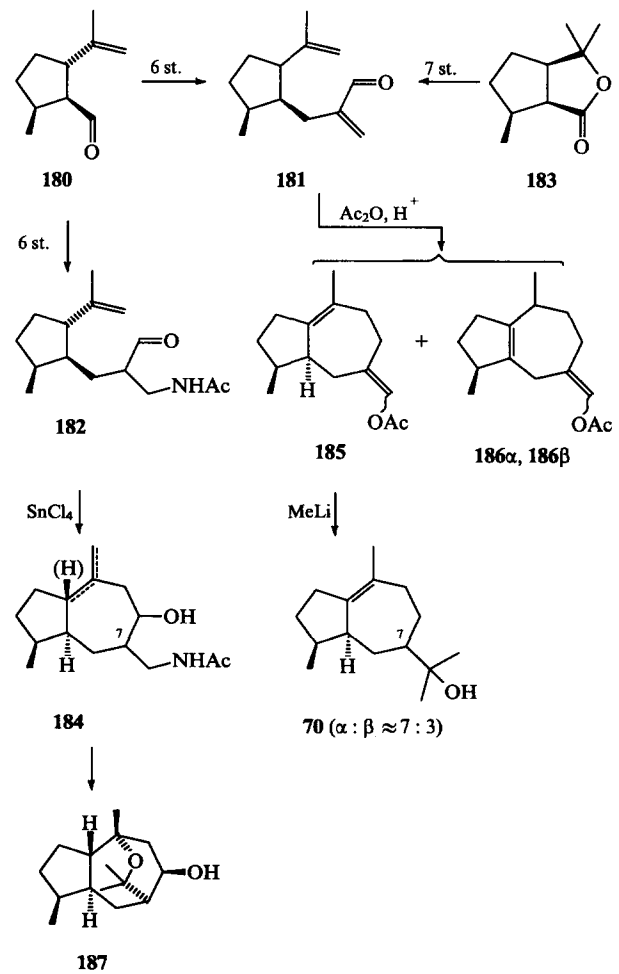


Thus examples of the application of this strategy in the synthesis of GS considered in this section demonstrate the possibility of its successful use to obtain diverse natural products from readily available starting materials.

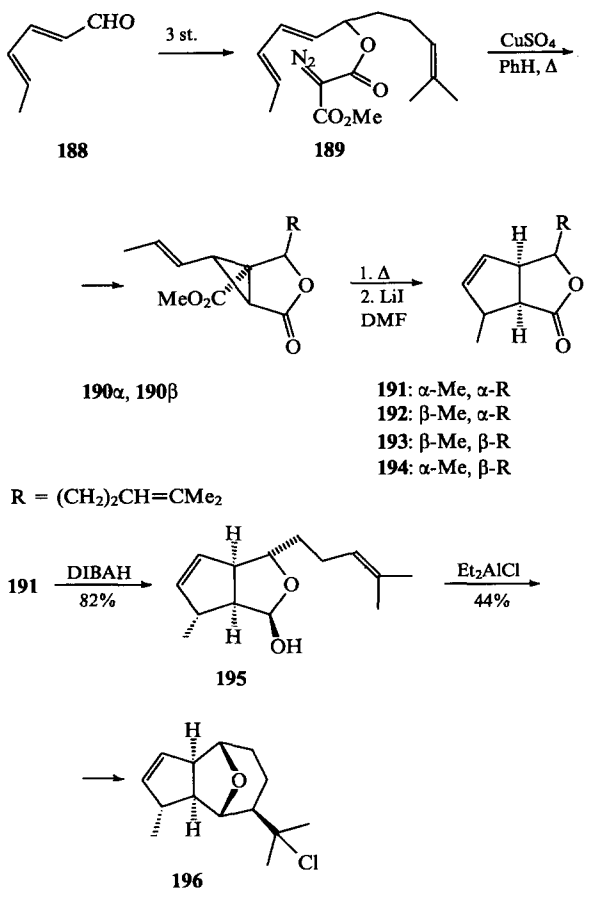
IV. Heptacondensation of cyclopentane derivatives

In contrast to the approach described in the previous section, the present one involves the construction of the hydroazulene skeleton of the GS by the closure to a seven-membered ring of the side chains of suitably functionalised cyclopentane precursors. For example, Andersen and coworkers, who were the first to apply this strategy in the total synthesis of certain natural guaianes,[77–79] used the unsaturated aldehydes **182** and *trans*- and *cis*-**181** as the cyclopentane precursors. The aldehydes **182** and *trans*-**181** were synthesised from the product **180** of the photocyclisation of citral, while compound *cis*-**181** was obtained from the lactone **183**. The principal results of these investigations, which have been analysed in a review,[9] are illustrated by Scheme 18.

Scheme 18



Scheme 19



In particular, the regioselectivity of the electrocyclisation of the unsaturated aldehyde *trans*-**181** proved to be low, which significantly reduced the overall effectiveness of the synthesis of (±)-bulnesols **70**. The latter were obtained as a result of the further transformation of the hydroazulene precursor **185**, which predominates in the **185**:**186α** ≈ 2:1 mixture.[77] The unsaturated aldehyde *cis*-**181** is cyclised similarly, affording the sum of the regioisomers **185** and **186β** (~3:1).[78] The intramolecular version of the Prins reaction also leads to a mixture of the regio- and stereo-isomeric hydroazulenoids **184** in the case of the aldehyde **182**. *exo*-Methylene 7α-epimers, employed subsequently in the synthesis of (±)-kessanol **187**, were isolated chromatographically and their overall yield was ~40%.[79]

In order to develop further this methodology, Hudlicky et al.[80] investigated the possibility of obtaining the guaiane structures from the bicyclic hemiacetal **195** synthesised from a suitably substituted diazoketone **189** (Scheme 19). The diazoketone **189**, prepared from sorbaldehyde **188**, cyclises smoothly in the presence of Cu^{2+} ions with formation of the epimeric cyclopropanolides **190** (α:β ≈ 2:1), which can be readily separated chromatographically. Each of them undergoes subsequent thermolysis and demethoxycarbonylation, which results in the formation of **191**:**192** ≈ 2:1 and **193**:**194** ≈ 3:1 mixtures of the stereoisomeric cyclopentanolides. The possibility of using lactones of this type as the precursors of GS has been demonstrated in relation to the lactone **191**, which was isolated chromatographically in a pure state. It was reduced by diisobutylaluminium hydride (DIBAH) to the hemiacetal **195**, which cyclises stereospecifically to the hydroazulenoid **195** on treatment with Et_2AlCl.

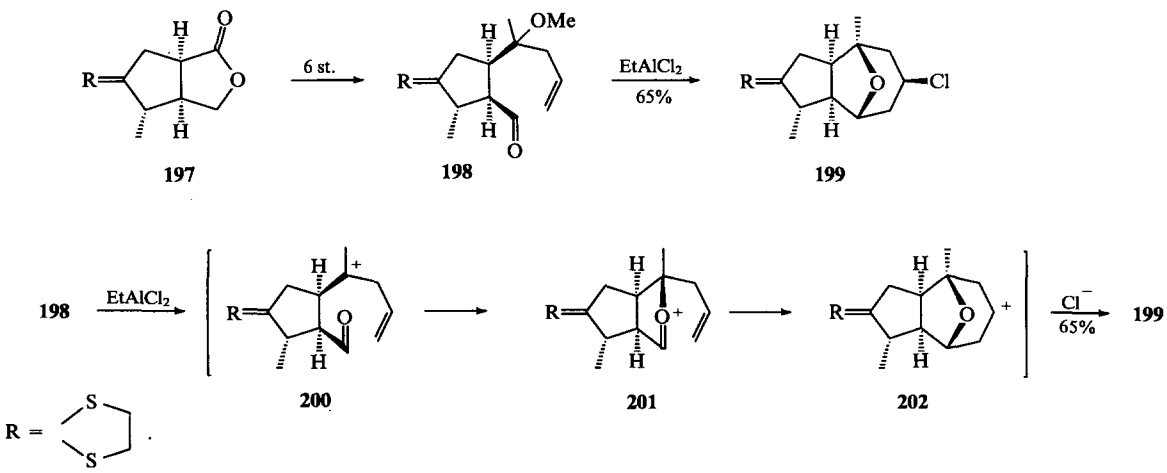
The intramolecular Prins reaction of the unsaturated aldehyde **198**, obtained from the chiral cyclopentanolide **197**,[81] was recently used similarly[82] in the enantioselective synthesis of the hydroazulenoid **199**, homochiral with respect to grosshemin **170** (Scheme 20). The formation of the enantiomerically pure hydroazulenoid **199** as the only product of the cyclisation of the mixture of the diastereoisomers of compound **198** can be explained by their initial cleavage on treatment with $EtAlCl_2$ and by the stabilisation of the cation **200**, arising as a result of such cleavage, in the form of the oxonium ion **201**. The electrophilic attack by the latter on the multiple bond in the side chain of the same molecule and the interaction of the resulting carbonium ion **202** with the excess $EtAlCl_2$ lead ultimately to the chloro-derivative **199** in ~65% yield.

Two variants of the heptacondensation of substituted cyclopentanes have been achieved using the *trans*-ketoester **203**, obtainable from methylheptenone, as the monocyclic precursor of the GS.[83] Thus the cyclopentanone **203** was initially converted into the ethylene ketal, the reduction of which by DIBAH affords smoothly the aldehyde **204** (Scheme 21).[84]

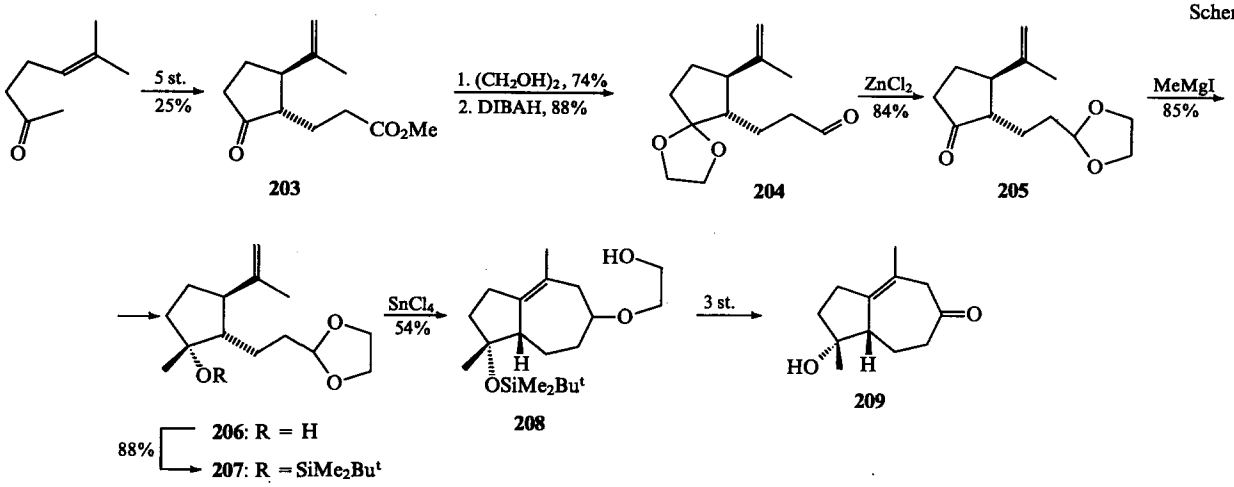
The attempt to cyclise the latter under the conditions of the Lewis acid-catalysed Prins reaction unexpectedly led to the product of intramolecular transketalisation — the ketone **205**, which was subsequently converted into the silyl ether **207** in two stages, including the reaction with MeMgI, which proved to be highly stereoselective. Treatment of the silyl ether with $SnCl_4$ leads to the bicyclic product **208**, the conversion of which into the hydroazulenone **209** is carried out in three stages.

A shorter route to the formation of guaiane structures from the ketoester **203** proved possible[85,86] via the Dieckmann intramolecular cyclisation of the sulfonecarboxylate **212** (Scheme 22). The latter was obtained from the ketoester **203** in three stages via the chloroderivative **210** and the sulfone **212**. Treatment of the sulfonecarboxylate **212** with sodium *N*,*N*'-bistrimethylsilylamide in benzene leads stereospecifically to the hydroazulenone

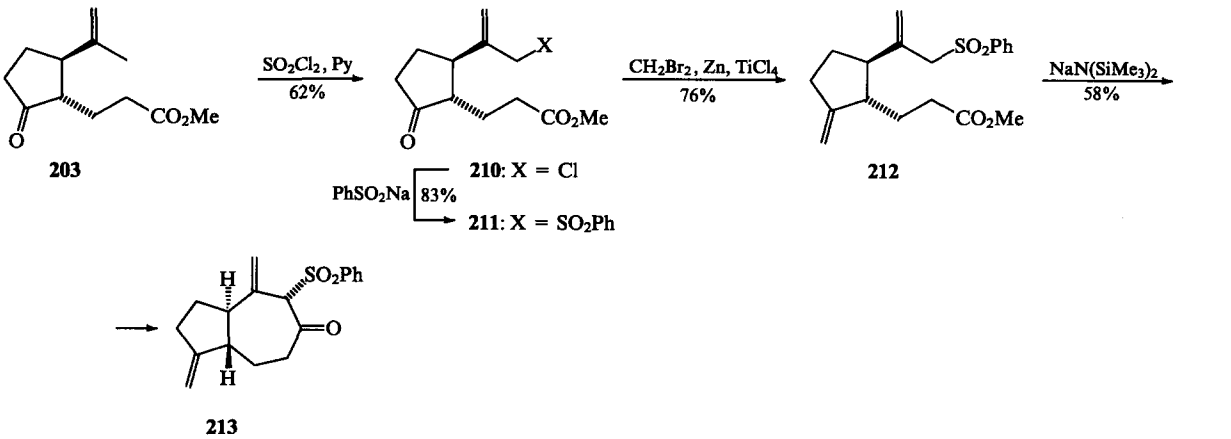
Scheme 20



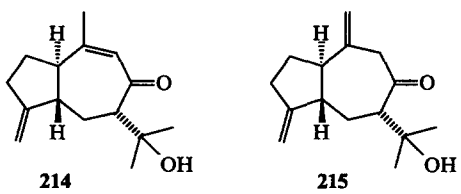
Scheme 21



Scheme 22



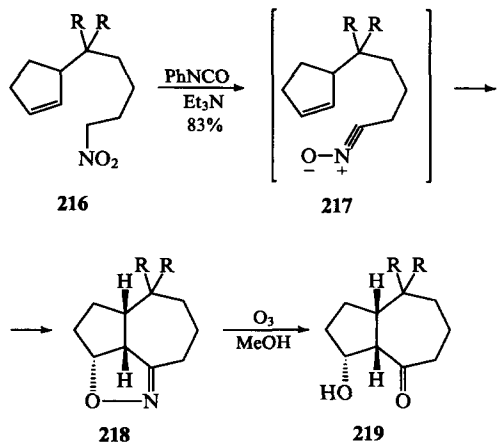
213, which was used further in the synthesis of the ketoalcohols **214** and **215** having the guaiane skeleton.



Among other known methods for the heptacondensation of substituted cyclopentanes, a novel procedure, employed in the synthesis of the hydroazulenone **219** and involving the intramolecular [3 + 2]-cycloaddition of the nitrile oxide **217** generated in situ from the nitroalkene **216**, may be of definite interest for the synthesis of the hydroazulene precursors of GS.[87]

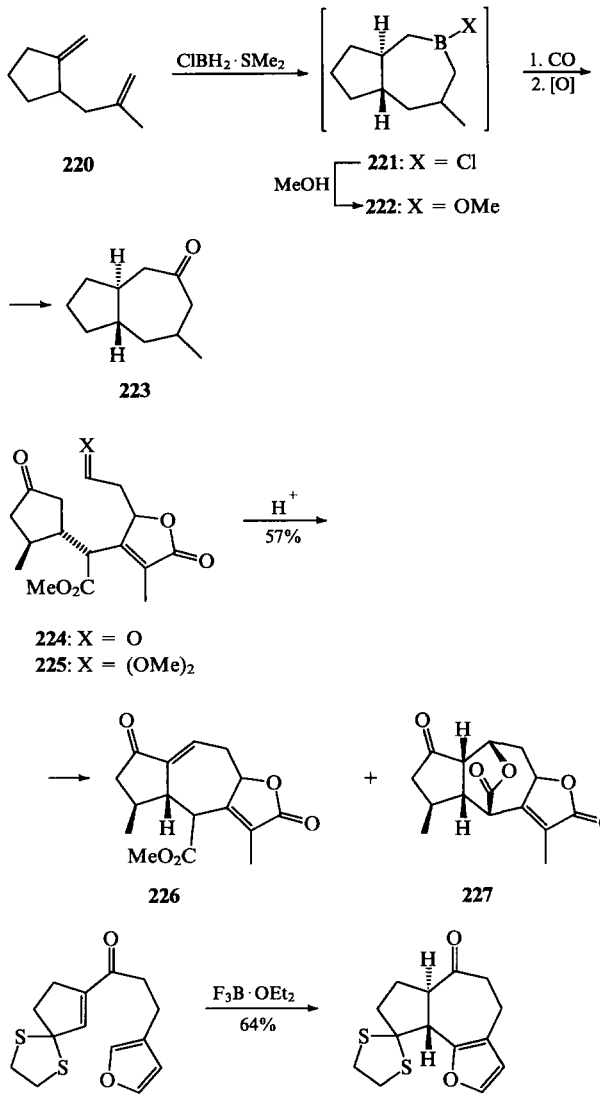
Yet another variant of a nontraditional attainment of the same aim has been recently demonstrated by Stevenson and Bryson.[88] The hydroboration of the diene **220** by $ClBH_2.SMe_2$ leads to the smooth formation of the boracyclane **221**, the conversion of which into the hydroazulenone **223** has been achieved by means of standard carbonylation.

The scheme for the total synthesis of guaianolides proposed by Winterfeldt and coworkers,[89] in which the stage involving the cleavage of the acetal **225** to the aldehyde **224** by CF_3COOH is accompanied by the formation of the diastereoisomeric enones **226** and an insignificant amount of the transesterification product **227**, is based on the intramolecular crotonic type condensation of the ketoaldehyde **224**.



R = CO_2Me

It is noteworthy that the heptacondensation of substituted cyclopentanones, carrying in the side chain a lactone ring already formed or its synthetic equivalent, is regarded nowadays[89–91] as a promising approach to the construction of the tricyclic skeleton of guaianolides and related furanoterpenoids. One of the variants of the application of this strategy consists, for example, in the electrocyclisation of the cyclopentane derivative **228**, terminated by a furan substituent, which affords the furanohydroazulenone **229** as the only product.[90]

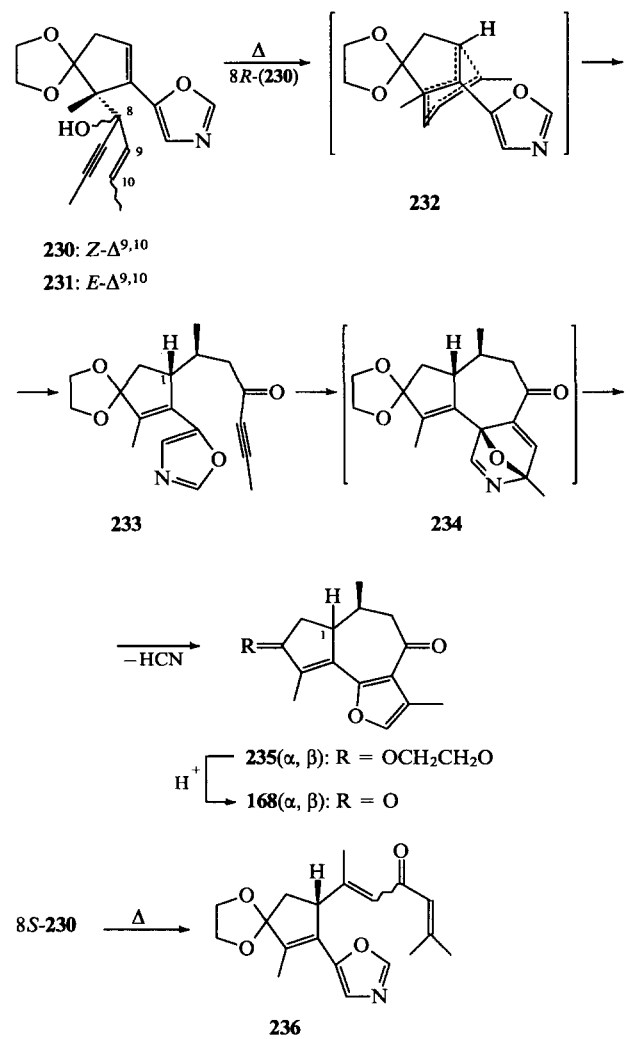


220 223 226 227 228 229

The recently published study[91] on the total synthesis of (±)-gnididione **168**, the key stage of which is the intramolecular [4 + 2]-cycloaddition of the oxazole **233** — the product of the oxy-Cope rearrangement of the tertiary alcohol **230**, is of interest in this connection (Scheme 23). It was found that the formation of the chair-shaped transition state **232**, leading to the secohydroazulenoid **233**, is favoured by the (*R*)-configuration of the C(8) centre of the carbinol **230**. In the case of the thermolysis of the (*S*)-carbinol **230**, the preferential formation of the dienone **236** is observed. The dienone arises as a result of the involvement of the ethyne fragment of the molecule of compound **230** in the rearrangement. Under more severe conditions, the transformation of the carbinol **230** is not limited to the formation of the oxazole **233**, which is converted as a result of the thermal [4 + 2]-cycloaddition into the unstable cyclic adduct **234**, cleaved subsequently to give the target furanoterpenoid in the form of its ethylene ketal **235β**. It is noteworthy that the relative configuration of the substituents at the C(1) atom of the ketal **235** is controlled by the (*Z*)-geometry of the butenyl residue of the initial alcohol **230**. It was found that, when the carbinol **231** with a transoid $\Delta^{9,10}$ bond is used, the above sequence of reactions makes it possible to obtain the C(1)-epimer of gnididione **168β** — the hydroazulenoid **168α**.

* * *

Scheme 23



232 233 234 236

In conclusion one should note that the search for the specific syntheses of sesquiisoprenoids of the guaiane series makes a significant contribution to the development of the fundamental and methodological aspects of modern organic chemistry. In addition, further studies in this field are of current interest, because they make it possible to discover reliable sources of these terpenoids, which are difficult to obtain from natural raw materials, as well as their analogues, including compounds which are of definite interest for medicine and agriculture.

References

1. P de Mayo *The Chemistry of Natural Products* Vol. 2,3 (New York: Interscience, 1959) (Translated into Russian; Moscow: Izd. Inostr. Lit., 1963)
2. K S Rybalko *Prirodnye Seskviterpenovye Laktony* (Natural Sesquiterpene Lactones) (Moscow: Meditsina, 1978)
3. N H Fischer, E T Olivier, H D Fischer *Fortschr. Chem. Org. Naturst.* **38** 47 (1979)
4. A D Kagarlitskii, S M Adekenov, A N Kupriyanov *Seskviterpenovye Laktony Rastenii Tsentral'nogo Kazakhstana* (Sesquiterpene Lactones of Plants of Central Kazakhstan) (Alma-Ata: Nauka, 1987)
5. E Rodrigues, G H N Towers, J C Mitchel *Phytochemistry* **15** 1573 (1976)
6. A K Picman *Biochem. Syst. Ecol.* **14** 225 (1986)
7. J A Marshall *Synthesis* 517 (1972)
8. C H Heathcock, in *Total Synthesis of Natural Products* Vol. 2 (Ed. I Apsimon) (New York: Wiley, 1973) p. 395

9. C H Heathcock, S L Graham, M C Pirrung, F Plavac, C T White, in *Total Synthesis of Natural Products* Vol. 5 (Ed. I Apsimon) (New York: Wiley, 1973) p. 333
10. M Vandewalle, P DeClercq *Tetrahedron* **41** 1767 (1985)
11. J H Rigby, in *Studies in Natural Products Chemistry* Vol. 1 *(Stereoselective Synthesis)* (Ed. A Rahman) (Amsterdam: Elsevier, 1988) Part A, p. 547
12. A G Gonzalez, A Galindo, H Mansilla *Heterocycles* **28** 529 (1989)
13. S M Adekenov, A D Kagarlitskii *Khimiya Seskviterpenovykh Laktonov* (The Chemistry of Sesquiterpene Lactones) (Alma-Ata: Gylym, 1990)
14. R J Giguere, S M Duncan, J M Bean, L Purvis *Tetrahedron Lett.* **29** 6071 (1988)
15. R J Giguere, S M Tassely, M I Rose, V V Krishnamurthy *Tetrahedron Lett.* **31** 4577 (1990)
16. P G Sammes, L J Street *J. Chem. Soc., Chem. Commun.* 666 (1983)
17. S M Bromidge, P G Sammes, L J Street *J. Chem. Soc., Perkin Trans. 1* 1725 (1985)
18. J B Hendrickson *Tetrahedron* **7** 82 (1959)
19. W Parker, J S Roberts, R Ramage *Quart. Rev.* **21** 331 (1967)
20. K Nishimura, N Shinoda, Y Hirose *Tetrahedron Lett.* **10** 3097 (1969)
21. E D Brown, J K Sutherland, T W Sam *J. Chem. Soc., Perkin Trans. 1* 2332 (1975)
22. A G Gonzalez, A Galindo, H Mansilla *Tetrahedron* **36** 2015 (1980)
23. A G Gonzalez, A Galindo, H Mansilla, J A Palenzuela *Tetrahedron Lett.* **24** 969 (1983)
24. Y Shiobara, T Iwata, M Kodama, Y Asakawa, T Takemoto, Y Fukazava *Tetrahedron Lett.* **26** 913 (1985)
25. X Li, L Wu, Z Ji, Y Harigaya, Y Konda, M Iguchi *J. Heterocycl. Chem.* **25** 1403 (1988)
26. R E K Winter, R F Lindauer *Tetrahedron* **32** 955 (1976)
27. G L Lange, M Lee *J. Org. Chem.* **52** 325 (1987)
28. E Tsankova, V Enev *Tetrahedron* **43** 4425 (1987)
29. J A Marshall, W F Huffman, J A Ruth *J. Am. Chem. Soc.* **94** 4691 (1972)
30. J A Marshall, J A Ruth *J. Org. Chem.* **39** 1971 (1974)
31. D H R Barton, P de Mayo, M Shafiq *J. Chem. Soc.* 929 (1957)
32. D H R Barton, J E D Levisalles, J T Pinhey *J. Chem. Soc.* 3472 (1962)
33. D H R Barton, J T Pinhey, R J Wells *J. Chem. Soc.* 2518 (1964)
34. D Caine, J B Dawson *J. Org. Chem.* **29** 3108 (1964)
35. P J Kropp *J. Org. Chem.* **29** 3110 (1964)
36. D Caine, J F DeBardeleben Jr *Tetrahedron Lett.* **6** 4585 (1965)
37. D Caine, J F DeBardeleben Jr, J B Dawson *Tetrahedron Lett.* **7** 3627 (1966)
38. K Schaffner, in *Advances in Photochemistry* Vol. 4 (New York: Interscience, 1966) p. 81
39. A E Greene, M T Edgar *J. Org. Chem.* **54** 1468 (1989)
40. M T Edgar, A E Greene, P Crabbe *J. Org. Chem.* **44** 159 (1979)
41. E Piers, K F Cheng *Can. J. Chem.* **45** 1591 (1967)
42. E Piers, K F Cheng *Can. J. Chem.* **48** 2234 (1970)
43. T Kumonaka, Y Kanai, M Yanagiya, T Matsumoto *Chem. Lett.* 1715 (1982)
44. G H Posner, G L Loomis, R D Mittal, W J Frasee, D M Schmit, K A Babiak *Tetrahedron Lett.* **19** 4213 (1978)
45. G H Posner, K A Babiak, G L Loomis, W J Frasee, R D Mittal, I L Karle *J. Am. Chem. Soc.* **102** 7498 (1980)
46. M Ando, A Akahane, K Takase *Chem. Lett.* 727 (1978)
47. M Ando, H Yamaoka, K Takase *Chem. Lett.* 501 (1982)
48. M Ando, A Akahane, H Yamaoka, K Takase *J. Org. Chem.* **47** 3909 (1982)
49. M Ando, A Ono, K Takase *Chem. Lett.* 493 (1984)
50. M Ando, H Kusaka, H Ohara, K Takase, H Yamaoka, Y Yanagi *J. Org. Chem.* **54** 1952 (1989)
51. J B P A Wijnberg, Ae de Groot *Tetrahedron Lett.* **28** 3007 (1987)
52. J B P A Wijnberg, L H D Jenniskens, G A Brunekreef, Ae de Groot *J. Org. Chem.* **55** 941 (1990)
53. L H D Jenniskens, J B P A Wijnberg, Ae de Groot *J. Org. Chem.* **56** 6585 (1991)
54. J A Marshall, J J Partridge *J. Am. Chem. Soc.* **90** 1090 (1968)
55. J A Marshall, A E Greene *J. Org. Chem.* **37** 982 (1972)
56. M Tanaka, H Suemune, K Sakai *Tetrahedron Lett.* **29** 1733 (1988)
57. K Monde, M Takasugi, N Katsui, T Masamune *Chem. Lett.* 1283 (1990)
58. H Hikino, P de Mayo *J. Am. Chem. Soc.* **86** 3582 (1964)
59. H-J Liu, S P Lee *Tetrahedron Lett.* **8** 3699 (1977)
60. D Termont, P DeClercq, D DeKeukeleire, M Vandewalle *Synthesis* 46 (1977)
61. A A Devreese, M Demuynck, P J DeClercq, M Vandewalle *Tetrahedron* **39** 3039 (1983)
62. A A Devreese, M Demuynck, P J DeClercq, M Vandewalle *Tetrahedron* **39** 3049 (1983)
63. V Sampath, E C Lund, M J Knudsen, M M Olmstead, N E Schore *J. Org. Chem.* **52** 3595 (1987)
64. M J Begley, M Mellor, G Pattenden *J. Chem. Soc., Chem. Commun.* 235 (1979)
65. W Oppolzer, R D Wylie *Helv. Chim. Acta* **63** 1198 (1980)
66. C S Pak, S K Kim, H K Lee *Tetrahedron Lett.* **32** 6011 (1991)
67. C H Heathcock, C M Tice, T C Germroth *J. Am. Chem. Soc.* **104** 6081 (1982)
68. T J Brocksom, E T C Pesquero, F T Lopes *Synth. Commun.* **20** 1181 (1990)
69. S K Kim, C S Pak *J. Org. Chem.* **56** 6829 (1991)
70. C S Pak, S K Kim *J. Org. Chem.* **55** 1954 (1990)
71. K Okada, K Koseki, T Katahara, K Mori *Agric. Biol. Chem.* **49** 487 (1985)
72. C D Buttery, A G Cameron, C P Dell, D W Knight *J. Chem. Soc. Perkin Trans. 1* 1601 (1990)
73. J H Rigby, J Z Wilson *J. Am. Chem. Soc.* **106** 8217 (1984)
74. J H Rigby, C Senanayake *J. Am. Chem. Soc.* **109** 3147 (1987)
75. J H Rigby, J Z Wilson *J. Org. Chem.* **52** 34 (1987)
76. M Saha, B Bagby, K M Nicholas *Tetrahedron Lett.* **27** 915 (1986)
77. N H Andersen, H Uh *Synth. Commun.* **3** 115 (1973)
78. N H Andersen, H Uh *Tetrahedron Lett.* **14** 2079 (1973)
79. N H Andersen, F A Golec *Tetrahedron Lett.* **18** 3783 (1977)
80. T Hudlicky, S V Govindan, J O Frazier *J. Org. Chem.* **50** 4166 (1985)
81. H-J Schifer, K-H Baringhaus *Liebigs Ann. Chem.* 351 (1990)
82. H-J Schifer, K-H Baringhaus *Liebigs Ann. Chem.* 355 (1990)
83. V V Veselovskii, B T Zhuzbaev, K M Turdybekov, S M Adekenov, Yu T Struchkov, A M Moiseenkov *Izv. Akad. Nauk., Ser. Khim.* 118 (1993)
84. B T Zhuzbaev, V V Veselovskii, A V Buevich, A M Moiseenkov *Izv. Akad. Nauk., Ser. Khim.* 122 (1993)
85. V V Veselovsky, B T Zhuzbaev, A M Moiseenkov *Mendeleev Commun.* 167 (1992)
86. A M Moiseenkov, B T Zhuzbaev, V V Veselovskii, K M Turdybekov, A V Buevich, S M Adekenov, Yu T Struchkov *Izv. Akad. Nauk., Ser. Khim.* 126 (1993)
87. A P Kozikowski, B B Mugrage, B C Wang, Z Xu *Tetrahedron Lett.* **24** 3705 (1983)
88. J W S Stevenson, T A Bryson *Chem. Lett.* 5 (1984)
89. W Kübler, O Petrov, E Winterfeldt, L Ernst, D Schomburg *Tetrahedron* **44** 4371 (1988)
90. S P Tanis, G M Johnson, M C McMills *Tetrahedron Lett.* **29** 4521 (1988)
91. P A Jacobi, H G Selnick *J. Org. Chem.* **55** 202 (1990)