New approaches to stereo- and regiocontrolled transformation of linear isoprenoids

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New approaches suggested by the authors to the selective transformation of isoprene, 3-methylbut-3-en-1-ol, 6-methylhept-5-en-2-one and the series of monoisoprenoids into functionalized derivatives, which were used as the synthetic building blocks for the formation of naturally occurring terpenes, are reviewed.

Key words: linear C_5- and C_{10}-isoprenoids; 6-methylhept-5-en-2-one; benzenesulfinyl chloride; "activated" sulfoxides; ene and heterodiene reactions; allylic chlorination; cationic cyclization; pentaannelation; polyprenols; guaiane; iridoids; pimarane/rosane derivatives; stereospecific synthesis.

Introduction

An increasing interest in compounds of the terpene series, being the subject of fundamental biochemical studies and also potential effective preparations for medicine and agriculture, is related to their important role in the life of all living organisms, which has been revealed in recent years.

In particular, their representatives, *e.g.*, polyprenols and dolichols, ubiquinones, juvenile hormones, are natural regulators of important physiological processes, and isoprenoid pheromones and attractants provide interspecies and intraspecies communications of insects. However, isolation of individual terpenes from natural sources, in which they commonly exist in small concentrations as constituents of complex mixtures, as a rule, is difficult and expensive. Therefore, the chemical synthesis of terpenes is apparently the most practical source of these compounds, which are necessary to solve fundamental and applied problems.

A retrosynthetic analysis of any terpene structure reveals principally its biomimetic construction from synthetic blocks that are functionalized derivatives of isoprene or its nearest homologs. Moreover, this strategy is the most reasonable one in the most cases.

In the first part of this Review, some new approaches to selective functionalization of the simplest isoprenoids, *viz.*, isoprene, 3-methyl-3-butene-1-ol (isobutenylcarbinol), myrcene, geraniol, *etc.*, are considered. In the second part, the possibilities of an effective use of synthetic blocks (SB) prepared by these approaches to create natural terpenes of various classes and their analogs are demonstrated.

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1. New reactions in a series of simple acyclic isoprenoids

1.1. Synthesis of the functionalized C_5-isoprenoids

The C_5-isoprenoid SB bearing "activating" functional groups, which provide the construction of a regular oligoisoprene chain, are necessary for biomimetic syntheses of natural terpenes. Although E-C_5-homologization was principally studied long ago,[1] the stereospecific introduction of a trisubstituted Z-C_5-fragment into the linear chain was an unresolved problem until recently.

1.1.1. Synthesis of cis-1,4-bifunctionalized derivatives of isoprene by the reaction of isoprene with PhSOCl under high pressure. By the beginning of this study, the only example of stereospecific transformation of isoprene (**1**) to its *cis*-1,4-bifunctionalized derivative, useful for the introduction of the Z-unit into the oligoisoprene chain,[2] was a six-step synthesis of hydroxysulfonamide (**3**) (Scheme 1). On the basis of this compound, primarily the biomimetic, stepwise scheme of synthesis of polyprenols was realized.[3] Polyprenols are terpene alcohols that are widespread in Nature, and they are necessary participants in biosynthesis of carbohydrate-containing polymers of procaryotes and eucaryotes (see also Section 2.1).

The efficiency of the approach, which is based on fixation of the *cis*-configuration of the trisubstituted double bond in cyclic precursor **3**, *i.e.*, cycloadduct **2**, caused our interest in a search for alternative routes to compounds of the type of **3** on the basis of the heterodiene synthesis using **1** and the appropriate heterodienophile, *e.g.*, PhSOCl; the reaction of the latter with 1,3-dienes has not been studied previously.

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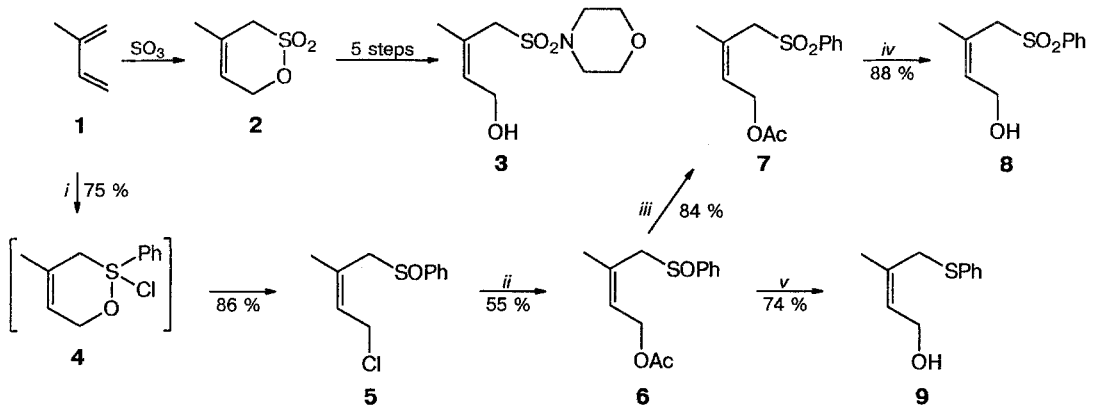
Scheme 1



Reagents and conditions: *i.* $PhSOCl/CH_2Cl_2$, 25 °C, 5 kbar; *ii.* KOAc(AgOAc)/AcOH, 25 °C; *iii.* $MCPBA/CH_2Cl_2$, −40 °C; *iv.* H_2SO_4(cat.)/MeOH, 25 °C; *v.* $LiAlH_4/Et_2O$, 10→25 °C.

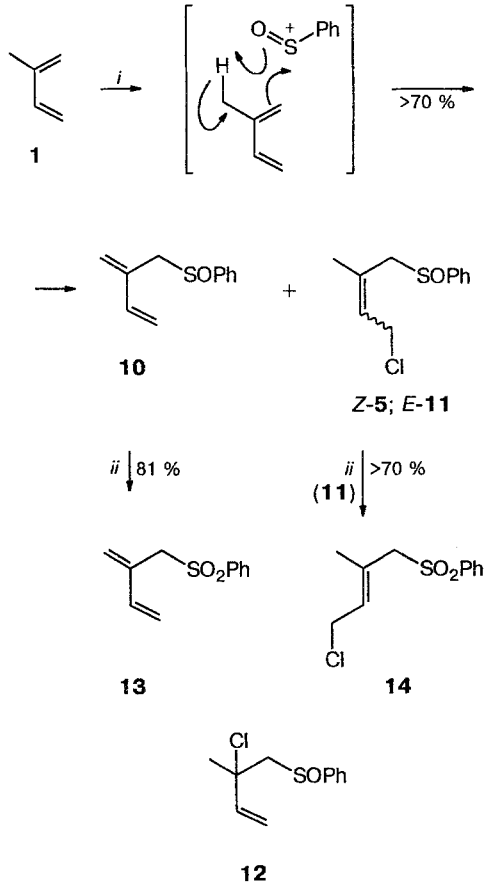
In the absence of a catalyst, the reaction of **1** with PhSOCl proceeds slowly and gives a complex mixture of compounds.[4] An attempt to accelerate this process by heating to 100 °C was also unsuccessful due to thermolability of both components.

Since the [4+2]-cycloaddition reactions are accelerated by high pressure,[5] this method was applied to the considered compounds. It appeared[4] that at 5 kbar, PhSOCl reacts smoothly with isoprene **1** even at 25 °C. Simultaneously, *Z*-chlorosulfoxide (**5**) is stereospecifically formed and isolated in *ca.* 75 % yield. Evidently, this is a result of primary cycloaddition of PhSOCl to **1**. The subsequent ionization of the S—Cl bond in hypothetical sulfurane intermediate **4** followed by the nucleophilic cleavage of the C—O bond in the corresponding sulfoxonium ion by the action of Cl^- affords sulfoxide **5** with the retention of the *cis*-configuration of the C=C bond.

Adduct **5** can be easily transformed into acetoxysulfoxide (**6**); oxidation of the latter by *m*-chloroperbenzoic acid (MCPBA) with subsequent deacetylation of the intermediate acetate **7** affords hydroxysulfone (**8**); the latter is applicable for the same purpose as sulfonamide **3** (see Section 2.1), but it is more accessible. Hydroxysulfide **9** was prepared through hydride reduction of acetate **6** by $LiAlH_4$.

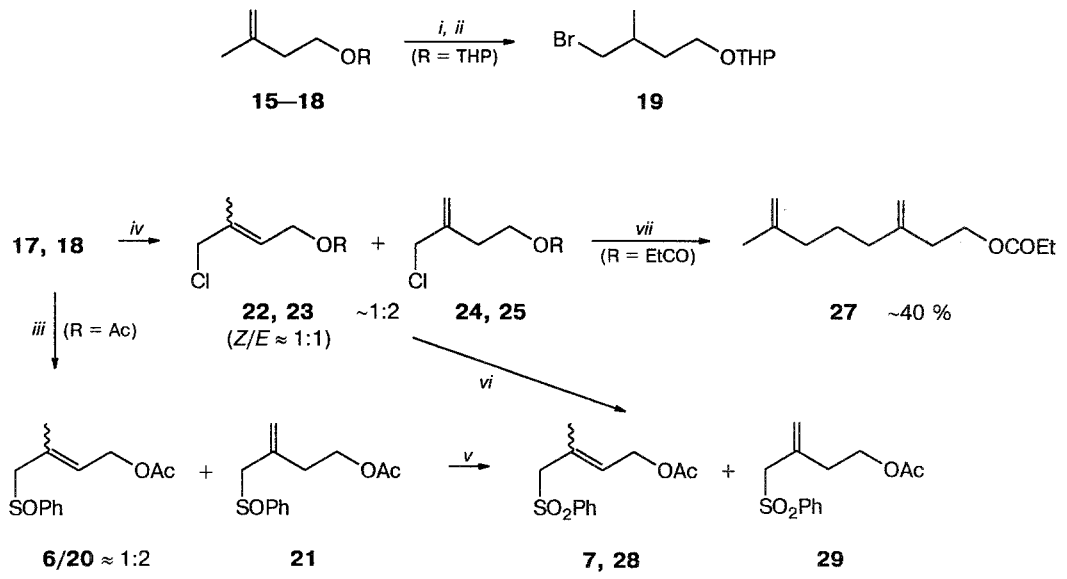
1.1.2. Lewis acid-catalyzed reaction of isoprene with PhSOCl. The literature data on Lewis acid-catalyzed sulfinylation of olefins by ArSOCl now include only a few examples[6] (see also Section 1.2.1). The possibility of involving 1,3-dienes in this reaction has not been studied previously. It turned out that in the presence of a Lewis acid, the reaction of isoprene **1** with PhSOCl proceeds rapidly even at a low temperature.[4] In $MeNO_2$ or Pr^nNO_2, in the presence of $AgBF_4$ or $ZnCl_2$, diene sulfoxide (**10**) is formed smoothly (Scheme 2).

Scheme 2



Reagents and conditions: *i.* $PhSOCl/AgBF_4/MeNO_2$, −25 °C ($ZnCl_2/Pr^nNO_2$, −70 °C); *ii.* $MCPBA/CH_2Cl_2$, −40 °C.

Scheme 3



R = H (**15**); THP (**16**); Ac (**17**, **22**, **24**); EtCO (**18**, **23**, **25**)

Reagents and conditions: *i.* BH_3/THF, 0 °C; *ii.* MeONa/Br_2/MeOH, −5→25 °C; *iii.* PhSOCl/$ZnCl_2$/Pr^iNO_2, −40→−10 °C; *iv.* SO_2Cl_2/Py/$LiClO_4$/CH_2Cl_2, −60 °C; *v.* MCPBA/CH_2Cl_2, −40 °C; *vi.* $PhSO_2Na$/DMF, 70 °C; *vii.* CH_2=C(Me)CH_2CH_2MgBr(**26**)/Li_2CuCl_4/THF, −70 °C.

An application of other Lewis acids ($Et_2O \cdot BF_3$, $SnCl_4$, $TiCl_4$, *etc.*) affords a series of side products, in particular, chlorosulfoxides *Z*-**5** and *E*-**11**.

The formation of diene sulfoxide **10** is considered as the result of ene reaction with the participation of phenylsulfoxonium ion, whereas chlorosulfoxides **5** and **11** are apparently produced by an allyl rearrangement of intermediate **12** similar to that observed previously[7] at the first stage of addition of PhSOCl to isoprene **1**. The structures of diene **10** and previously unknown *E*-sulfoxide **11** were confirmed by their transformation to known sulfones **13** and **14**[8] by MCPBA.

1.1.3. Synthesis of the functionalized C_5-isoprenoids from 3-methylbut-3-en-1-ol (15). There are no practically literature data on selective functionalization of carbinol **15**, which would make possible its use as SB for the synthesis of the "head to tail" regular oligoisoprene chain. In this connection, the simple procedure (Scheme 3) of transformation of **15** to bromoether **19** (the saturated C_5-isoprenoid SB)[9] is worthy of noting; **19** is required, in particular, for the transformation of plant polyprenols to hardly accessible dolichols of mammals (see Section 2.1). Hydroboration—bromination of tetrahydropyranyl (THP) ether **16** obtained from **15** in >50 % yield affords the desired bromide **19**; this transformation is an important modification of the known[10] four-step synthesis of the latter from the same precursor.

The direct phenylsulfinylation of 3-methylbut-3-en-1-ylacetate (**17**) by PhSOCl and $ZnCl_2$ under the conditions described above[11] appeared to be nonselective and gave a mixture of labile acetoxysulfoxides **6**, **20**, and **21** in a ratio of *ca.* 1:2:2, which is constant upon transformation of the latter to the related sulfones **7**, **28**, and **29** upon their oxidation by MCPBA. Allylic chlorination of acetate **17** or propionate **18** by SO_2Cl_2 in the presence of pyridine proceeds more selectively;[11] the overall efficiency of the chlorination in comparison to that previously achieved for the related olefins[12] was increased significantly by decreasing the temperature and using $LiClO_4$ as an additive to the reaction mixture.

A mixture of allyl chlorides **24**(**25**)/**22**(**23**) (*ca.* 2:1) having approximately equal ratios of *E*- and *Z*-stereoisomers in the pairs of trisubstituted olefins **22** and **23** was obtained in high yield. The reported regio- and stereoisomeric compositions were also found for a mixture of sulfones **7**, **28**, and **29**, which was prepared by treatment of chlorides **22** and **24** with $PhSO_2Na$ in dimethylformamide.

The mixtures of acetoxysulfones **7**, **28**, and **29** synthesized by two different routes could not be separated by chromatography, however, the major component, *i.e.*, homoallyl acetoxysulfone **29**, can be isolated in individual state after treatment of the initial mixture with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) and the subsequent chromatographic purification of **29** from the products of decomposition of acetoxysulfones **7** and **28**, which are labile in the presence of bases.

The lability of components **23** of the mixture of regio- and stereoisomeric chlorides **23/25**, which are structurally similar to **7**, **28**, made it possible to perform a facile synthesis of α-myrcenyl propionate (**27**), which is a component of sex pheromone of San Jose scale.[13] Compound **27** was obtained in *ca.* 40 % yield by treating a mixture of chlorides **23/25** with Grignard reagent **26** in the presence of Li_2CuCl_4; chromatography of the compounds formed did not reveal products of condensation related to transformation of trisubstituted olefins **23**.

1.2. Synthesis of functionalized linear C_{10}-isoprenoids

The variety of the general methods used in selective functionalization of linear monoisoprenoids now incorporates basically their transformations by the action of *N*-bromosuccinimide,[14] SeO_2,[15] and Bu^tOOH.[16] The possibilities of similar applications of sulfur-containing electrophilic reagents generated from PhSOCl, $SO(OMe)_2$, $SOCl_2$, and dimethyl sulfoxide (DMSO) are considered below.

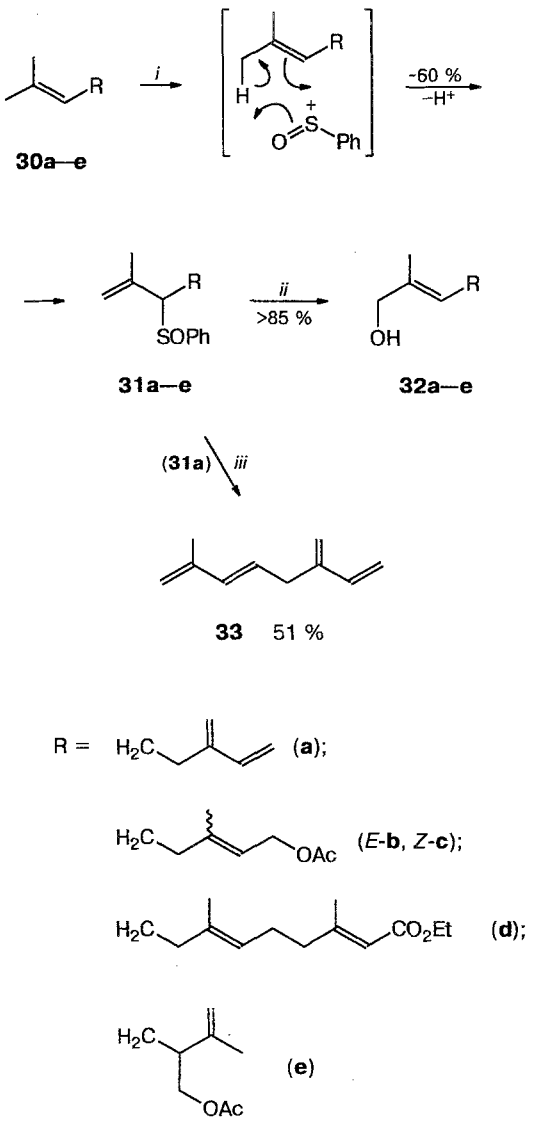
1.2.1. Regiospecific ene reactions of linear isoprenoids with PhSOCl, $SO(OMe)_2$, and $SOCl_2$. In light of our data on the Lewis acid-catalyzed ene reaction of PhSOCl with substrates **1** and **17**, it was interesting to investigate the possibility of involving oligoolefins of the monoterpene series in this reaction. It was established[17] that in the presence of $ZnCl_2$, myrcene (**30a**), geranyl acetate (**30b**), and neryl acetate (**30c**) react smoothly with PhSOCl (Pr^iNO_2, −50 to −20 °C), giving ω-terminal allyl sulfoxides **31a—c** (Scheme 4). The reaction proceeds chemo- and regiospecifically at the isopropylidene fragment of **30**, which is indicated by the absence of the corresponding regioisomers, which could be formed, if the other C=C bonds of the studied oligoolefins were involved in the reaction.

The high selectivity of this reaction was also observed for sesquiterpenoid **30d** having the additional multiple bond in the middle of the chain[17] and in the case of irregular monoisoprenoid **30e** having two C=C bonds, but only the trisubstituted double bond is subjected to selective attack of the reagent.[18]

Sulfoxides **31a—e** are highly reactive. In the presence of phosphites, they undergo sulfoxide-sulfenate rearrangement (according to Evans[19]) into *E*-allyl alcohols **32a—e**. It should be noted that geranyl (**32b**) and neryl derivatives (**32c**) have been used previously as key compounds in the synthesis of a series of natural terpenes (*cf.*, see Ref. 20). This is also true for tetraene **33** readily formed in the $NaHCO_3$-catalyzed cleavage of sulfoxide **31a**.

In the Lewis acid-catalyzed ene type reaction of trisubstituted olefins of isoprenoid series **30**, dimethyl sulfite and thionyl chloride can also be involved.[21] It appeared that 2-methylpent-2-ene (**30f**) (taken as a model) and citronellyl acetate (**30g**) react with excess $SO(OMe)_2$ in the presence of $F_3B \cdot OEt_2$, affording allyl sulfinates **34f,g**, respectively (Scheme 5). When replacing $SO(OMe)_2$ by $SOCl_2$, the best results were obtained with Et_2AlCl as the catalyst. The yield of citronellyl derivative **34g** (after decomposition of the reaction mixture with MeOH in the presence of pyridine) was *ca.* 80 %. When diolefins **30b,h** were used as substrates terminal sulfinates **34b,h** were obtained, respectively. This observation revealed the chemoselectivity of this transformation.

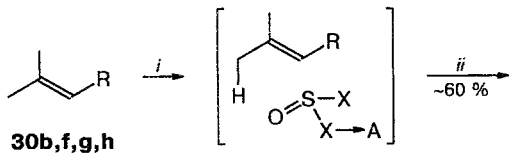
Scheme 4



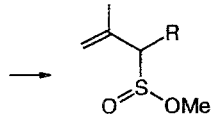
Reagents and conditions: *i.* $PhSOCl/ZnCl_2/Pr^iNO_2$, −50→ −20 °C; *ii.* $P(OMe)_3$/MeOH, Δ; *iii.* $NaHCO_3$/PhH, Δ.

1.2.2. Reaction of sulfoxide hydrochlorides and hydrobromides with trisubstituted olefins. New method of allylic halogenation of monoisoprenoids. The data now available[22] allow one to describe the interaction between sulfoxides and hydrogen halides (HCl, HBr, HI) as a

Scheme 5

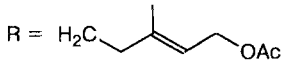


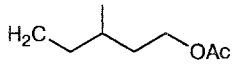
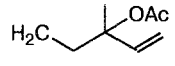
30b,f,g,h



34b,f,g,h

X = OMe, Cl; A = F_3B, Et_2AlCl

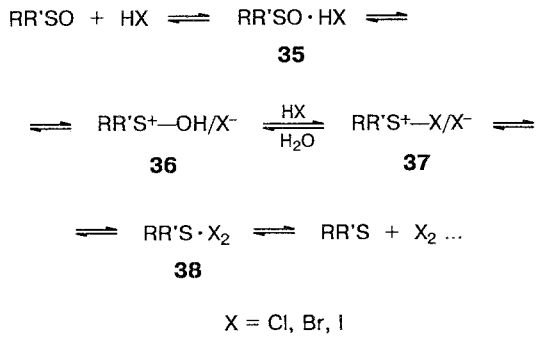
R =  **(b)**; Et **(f)**;

 **(g)**;  **(h)**

Reagents and conditions: *i.* $(MeO)_2SO/F_3B \cdot OEt_2$, −25 °C (for **30f,g**) or $SOCl_2/Et_2AlCl/CH_2Cl_2$, −40 °C (for **30b,g,h**); *ii.* MeOH/Py, 25 °C.

sequence of reversible reactions of intermediates **35**—**38** with increased thermodynamically controlled shift of the total equilibrium in the order: I>Br>Cl (Scheme 6).

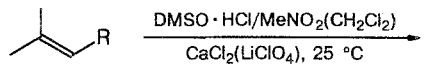
Scheme 6



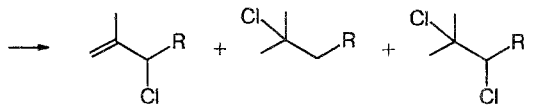
In this connection, it was interesting to study the possibility of using a rather stable salt DMSO · HCl (**35**, X = Cl)[23] as an equivalent of the labile complex $Me_2S \cdot Cl_2$ (**38**, X = Cl) or three-coordinated sulfonium cations **36**, **37** (X = Cl) in the reaction with the *C*-nucleophiles and, in particular, with olefins of the isoprenoid series.

It turned out[24] that 6-methylhept-5-en-2-ol (**30i**), citronellol (**30g**), and geraniol (**30b**) acetates react with 2—2.5 mol. eq. of DMSO · HCl in $MeNO_2$ in the presence of $CaCl_2$ (or molecular sieves) at 25 °C, affording a mixture of the corresponding chlorides **39** and **40** in 40—70 % yield in the ratio of *ca.* 3:2 (conversion of olefins is *ca.* 75 %) (Scheme 7). In all of the cases, monochlorides **39**, **40** are accompanied by *ca.* 10 % of the corresponding vicinal dichlorides **41**. The similar results are obtained for the complexes $(CH_2)_4SO \cdot HCl$ and $Ph_2SO \cdot HCl$.

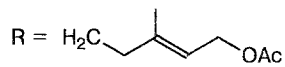
Scheme 7

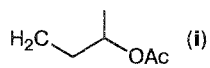


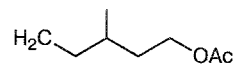
30b,g,i



39b,g,i **40b,g,i** **41b,g,i**

R =  **(b)**;

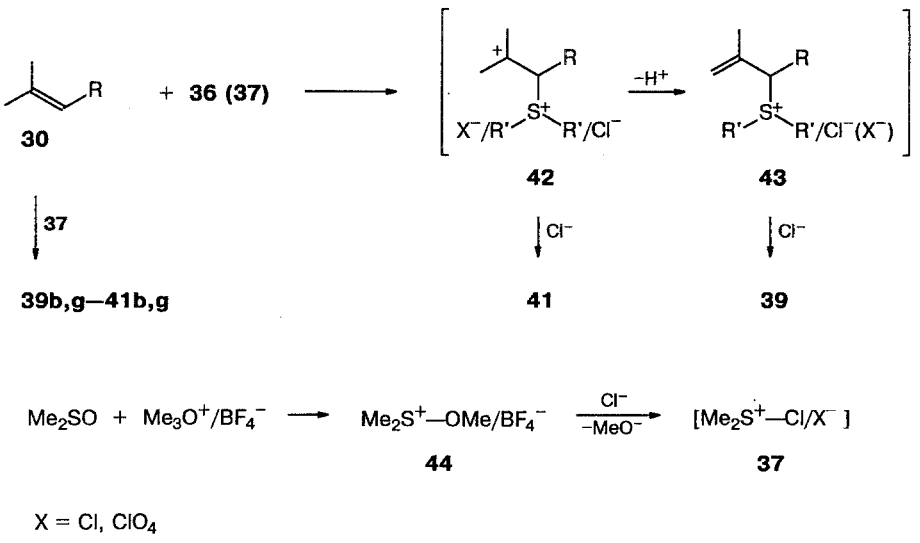
 **(i)**

 **(g)**;

Taking into account the nature of the components of the sequence of Scheme 6, one can describe the formation of compounds **39** and **41** by two competing processes. Since the oxidative potential of sulfoxide is evidently insufficient to transform Cl^- to Cl_2 (the difference between oxidation potential $Cl^- \rightarrow Cl^0$ and the reduction potential DMSO → Me_2S is *ca.* 2.5 V), the sequential redox process seems probable; this process involves nucleophilic attack on hydroxysulfonium (**36**, X = Cl) or chlorosulfonium (**37**, X = Cl) ions by olefin **30**, which initially gives intermediate **42** and, then, the adduct of the ene type **43** (Scheme 8). The nucleophilic cleavage of the C—S bond in such molecules and stabilization of carbenium ion **42** by the chloride ion completes the sequence of transformation accompanied by formation of the corresponding sulfide, which was in fact isolated.

An argument in favor of this mechanism is the formation of a mixture of chlorides **39b,g**—**41b,g** having practically the same ratio after subsequent treatment of olefins **30b,g** with dimethylmethoxysulfonium tetrafluoroborate (**44**) easily generated from DMSO and Meerwein salt, and then with $Et_3BnN^+Cl^-$ as a source of Cl^-. This indicates the important role of chlorosulfonium cation **37** in that process.

Scheme 8

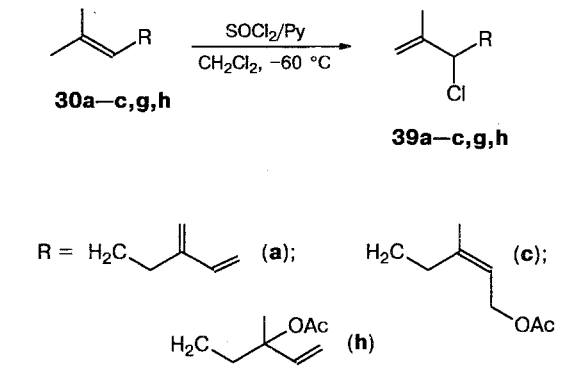


Considering the described transformations as reactions of Ad_E type of weak electrophiles **36** and **37** with trisubstituted olefins **30b,g,i**, one can expect their acceleration due to the "doping-effect" of $LiClO_4$ additives (*cf.* Ref. 25). In fact, treatment of acetates **30b,g** with a DMSO · HCl excess in the presence of *ca.* 1 mol. eq. of $LiClO_4$ affords[24] mixtures of chlorides **39b,g/40b,g** (*ca.* 4:1), containing <5 % of the corresponding dichlorides **41b,g**. The same effect of $LiClO_4$ additives was revealed in the reaction of olefins **30b,g** with chloride **37** generated from methoxysulfonium salt **44**.

Thus, addition of $LiClO_4$ significantly increases in chemoselectivity of the considered transformations with respect to allyl chlorides **39** which is probably related to stronger ionization of hypothetical sulfonium intermediates **36**, **37**, **42** and **43** than that in the absence of ClO_4^- (*cf.* Ref. 25).

As a whole, the $LiClO_4$-catalyzed reaction of isoprenoid oligoolefins **30** with DMSO · HCl can be considered as a convenient alternative to the methods of synthesis of terminal allyl chlorides of **39** type, of which the procedure of Masaki *et al.*[12] is the most preparative one, the latter involving the treatment of olefins similar to **30** with SO_2Cl_2 and pyridine in CCl_4 at 0 °C. However, the procedure does not provide complete conversion of starting substrates and it is accompanied by formation of *ca.* 10 % of dichlorides of **41** type. This method was substantially improved by carrying out the process in CH_2Cl_2 at significantly lower temperature.[26] Thus, upon the treatment of solutions of monoterpenol acetates **30a—c,g,h** in CH_2Cl_2, containing *ca.* 1.3 mol. eq. of pyridine at −60 °C with the same excess of SO_2Cl_2, the reaction practically completes for 10 min (Scheme 9). Moderately stable allyl chlorides **39b,c,g,h** and labile **39a** were isolated in >80 and *ca.* 40 % yields, respectively. The comparable results were obtained further by French chemists by using Na_2CO_3 addition for trapping HCl.[27]

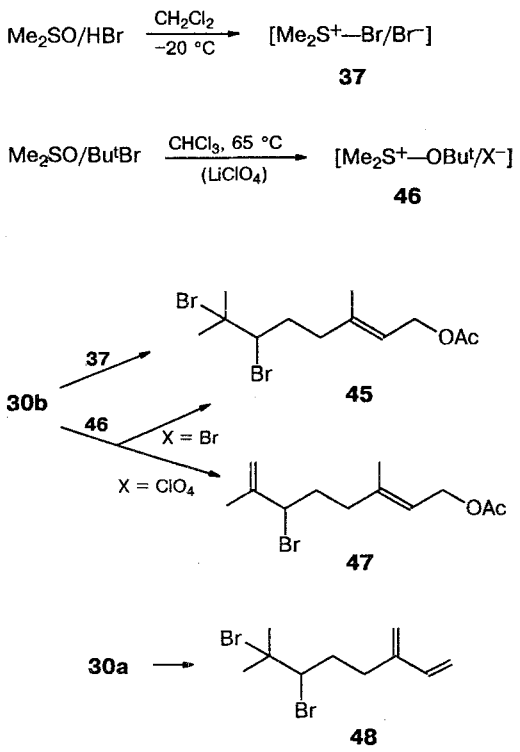
Scheme 9



According to Scheme 6, the reaction of sulfoxides with HBr is virtually a source of Br_2. In fact,[24] the DMSO · HBr complex in CH_2Cl_2 is rapidly consumed at −20 °C in the presence of 0.5 mol. eq. of geranyl acetate **30b**, affording bromide **45** in *ca.* 100 % yield. The latter was also obtained in *ca.* 70 % yield by treatment of a solution of **30b** in $CHCl_3$ with excesses of DMSO and Bu^{t}Br at 65 °C under conditions of a proposed[28] thermal decomposition of hypothetical alkoxysulfonium intermediate **46** (X = Br) leading to DMSO, HBr, and isobutene. Similarly, myrcene **30a** is smoothly transformed to dibromide **48** (Scheme 10).

In both cases, preferable bromination of the ω-terminal trisubstituted C=C bond of olefins **30** indicates the definite contribution of intermediates of **42** and **43** types, which result from interaction of **30** and bromosulfonium ion **37** (X = Br). When carrying out the reaction of **30b** with DMSO/Bu^{t}Br in the presence of equivalent amount of $LiClO_4$, a mixture of dibromide **45** and allyl bromide **47** (hardly available by other methods) in a ratio of *ca.* 1:3 (*ca.* 50 % yield) is formed, thus confirming that assumption.

Scheme 10



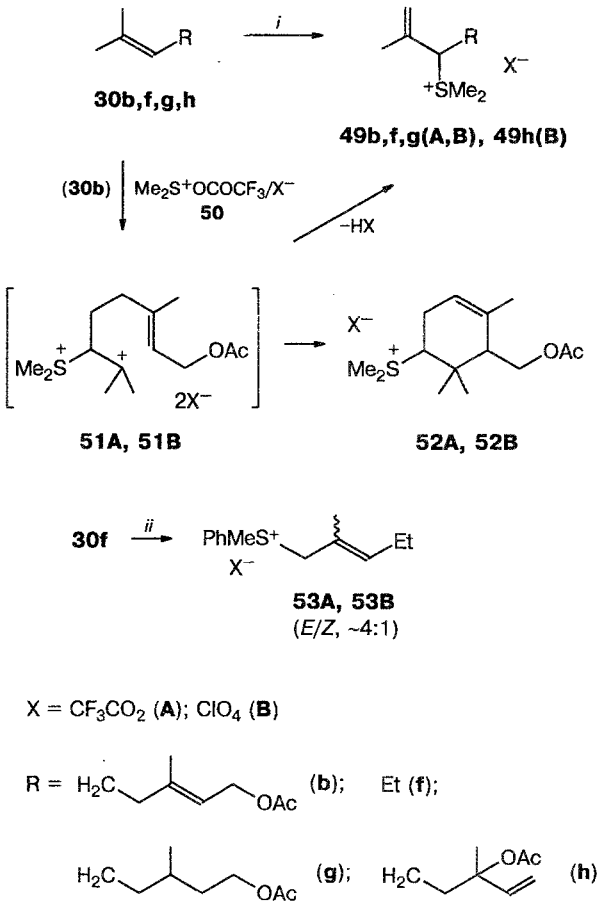
1.2.3. Reaction of the ene type between non-activated olefin and the "activated" sulfoxide and some properties of allylsulfonium salts formed. High selectivity of the reaction of hydroxy- and/or halosulfonium cations of the **36** and **37** types with the ω-terminal trisubstituted C=C bond of linear isoprenoids allowed one to assume the possibility of involving the related acyloxysulfonium salts, so-called "activated" sulfoxides, into similar reactions; "activated" sulfoxides are postulated as intermediates in the Pummerer reaction.[22,29]

In fact, it was established[30] that methylpentene **30f** (taken as a model compound) and monoterpenol acetates **30b,g** smoothly react with 3 mol. eq. of a mixture of DMSO—TFAA yielding the corresponding allylsulfonium trifluoroacetates **49A** practically quantitatively (Scheme 11). It should be stressed that involvement of nonactivated multiple bonds in such reaction was not observed previously.

Formation of salts **49A** may be considered as a result of attack on olefin **30** by acyloxysulfonium ion **50** (X = CF_3CO_2) generated under these conditions *via* dication of **51A** type, similar to intermediate **42**. This is confirmed indirectly by detection of *ca.* 10 % of cyclic salt **52A** in the reaction mixture in the case of geranyl acetate **30b**; **52A** arises, apparently, through cationic cyclization of **51A**.

Taking into account the above section, one can expect an existence of the "doping-effect" also in this Ad_E-reaction of cation **50** with olefins **30b,g**. In fact, treatment of the latter, as well as linalyl acetate **30h** with a small excess of reagent **50** and $LiClO_4$ at −10 to 0 °C

Scheme 11



Reagents and conditions: *i.* DMSO/TFAA($LiClO_4$)/CH_2Cl_2, −10→0 °C; *ii.* MeSOPh/TFAA($LiClO_4$)/CH_2Cl_2, −10→0 °C.

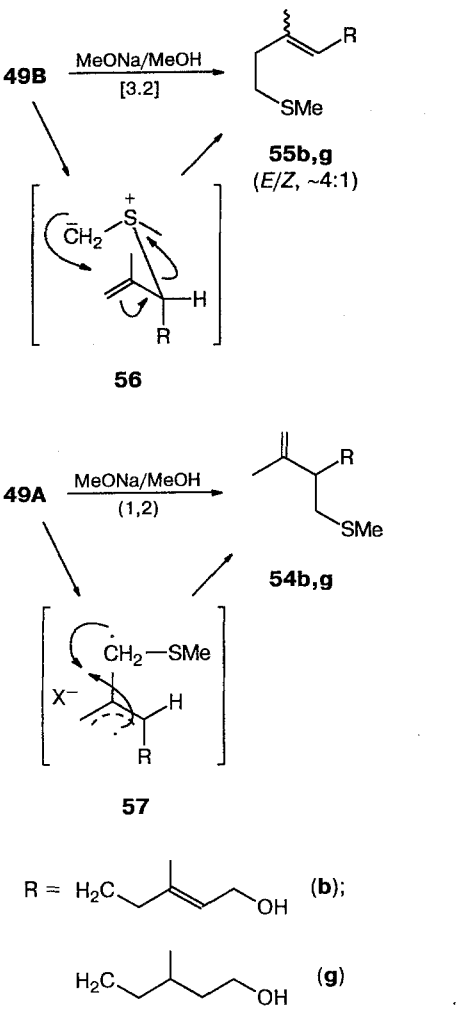
affords corresponding perchlorates **49B**, while in the case of geranyl acetate **30b**, they were obtained with an admixture of *ca.* 10 % of cyclic salt **52B**.

Replacing DMSO with PhSOMe in both variants of carrying out the reaction of methylpentene **30f** results in formation of primary sulfonium salts **53A** and **53B** in practically quantitative yield; the salts probably arise due to allylic isomerization of secondary salts of type **49**, which proceeds easily in this case.

Among the properties of previously unknown compounds **49**, the effect of counterion of the initial sulfonium salt on the direction of its rearrangement under the action of strong bases unprecedented in chemistry of the similar compounds is of greatest theoretical and synthetic interest.[30]

It was found that in the presence of MeONa (and $NaNH_2$ or Bu^nLi), perchlorates **49B** are smoothly transformed into the corresponding products of [3,2]-sigmatropic rearrangement (**55**), whereas under the same conditions, trifluoroacetates **49A** give sulfides **54** in good yield through 1,2-shift (Stevens rearrangement) (Scheme 12).

Scheme 12



The explanation of this phenomenon lies in the structure of parent sulfonium salts **49B** and **49A**, the first ones evidently are separated ion pairs giving classical ylides **56** under the action of base. In the case of trifluoroacetates **49A** (tight ion pair), a large compensation of positive charge by this counterion at the S atom results in sulfurane-like structure, in which homolysis of the C—S bond occurs accompanied by recombination of the pairs of stabilized radicals **57** to give the products of Stevens rearrangement (*cf.* Ref. 31).

1.2.4. Synthesis of α-functionalized derivatives of geraniol by the reaction of myrcene with PhSOCl under high pressure. Similar to isoprene, myrcene (**30a**) reacts smoothly with PhSOCl under 5 kbar pressure forming labile chlorosulfoxide **58**, the structure of which was confirmed by spectra and by its transformation to stable products[32] (Scheme 13). Thus, acetolysis of **58** affords acetate **60**, reduction of the latter by $LiAlH_4$ gives sulfide **62**, and hydrolysis of **58** gives hydroxysulfoxide **61**.

The transformation of sulfoxide **60** by the action of Me_3SiCl or AcCl to chlorosulfide **65** is worth noting; **65** probably results from the intramolecular attack of the trisubstituted double bond in generated hydroxysulfonium intermediate **63** (*cf.* Section 1.2.3) and the subsequent nucleophilic cleavage of cyclic sulfonium salt **64** by the chloride anion.[33]

Dehydrochlorination of **58** smoothly affords[33] diene sulfoxides **59** as a mixture of *E/Z*-isomers (*ca.* 4:1). An attempt at Michael addition of PhS^- to these activated dienes unexpectedly gave vicinal phenylthioalcohol **68** (Scheme 14). Evidently, the observed phenomenon may be explained as the initial formation of ambident ion **66** and, subsequently, the more thermodynamically preferable allyl sulfoxide **67**, which then undergoes sulfoxide-sulfenate rearrangement into alcohol **68**. It appears that the latter can be directly prepared from chloride **58** by the action of a PhSNa excess, which works initially as a dehydrochlorinating agent.

Thioalcohol **68** can be transformed to epoxymyrcene **69** (unaccessible through the direct epoxidation of myrcene **30a**) by subsequent treatment with the Meerwein reagent and alkali in accordance with the known procedure.[34]

Thus, the reaction of myrcene **30a** with PhSOCl under high pressure makes it possible to synthesize functionalized derivatives of **30a** and geraniol **30b**, which are of interest as multipurpose SB to prepare various terpenoid structures.

Thus, hydroxysulfoxide **61** can be transformed in one step (Scheme 15) to perillene (**72**), a component of communicative secretion of some insects.[13] The basis of this synthesis[33] is a possibility of Pummerer transformation (through the intermediate **70**) of the phenylsulfoxide moiety to the aldehyde group[29] in conjunction with the known tendency of aldehydoalcohols of type **71** to form furan ring.[35]

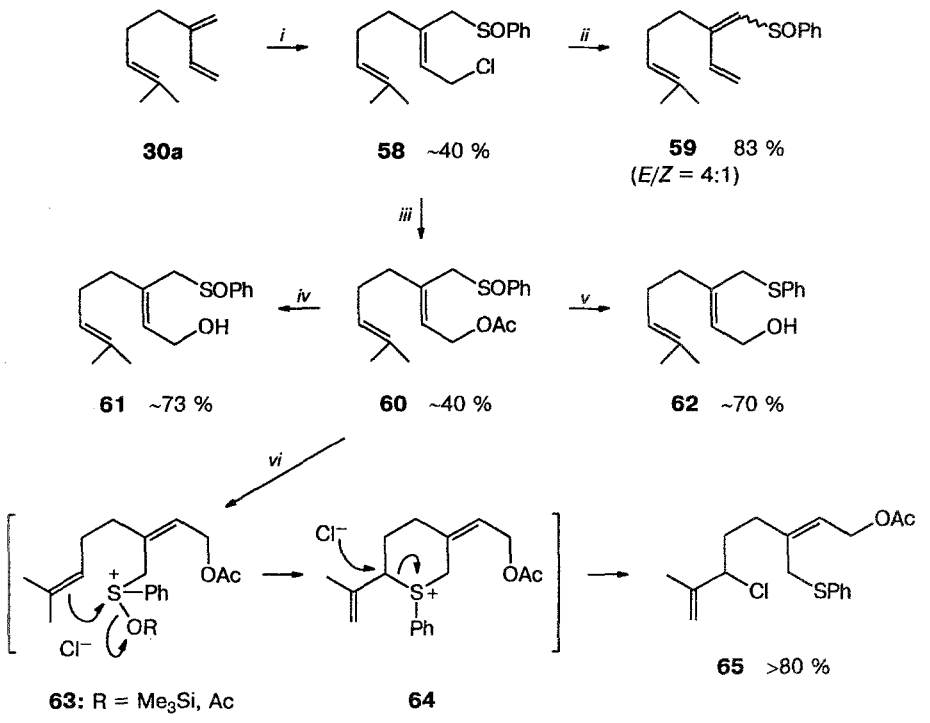
1.3. Stereocontrolled transformation of linear isoprenoids to functionalized cyclopentane and cyclohexane derivatives

Cyclopentane and cyclohexane moieties are the usual key fragments in a retrosynthetic analysis of molecules of numerous mono-, bi-, tri-, and polycyclic natural compounds of the terpene series. New approaches to the syntheses of cyclopentane and cyclohexane derivatives starting from the accessible linear precursors are discussed below.

1.3.1. Synthesis of 1,2,3-trisubstituted cyclopentanes by pentaannelation of linear isoprenoids. Syntheses of numerous natural compounds of the iridane and guaiane series are based on the use of specially functionalized 1,2,3-trisubstituted cyclopentanes as starting materials.[36,37]

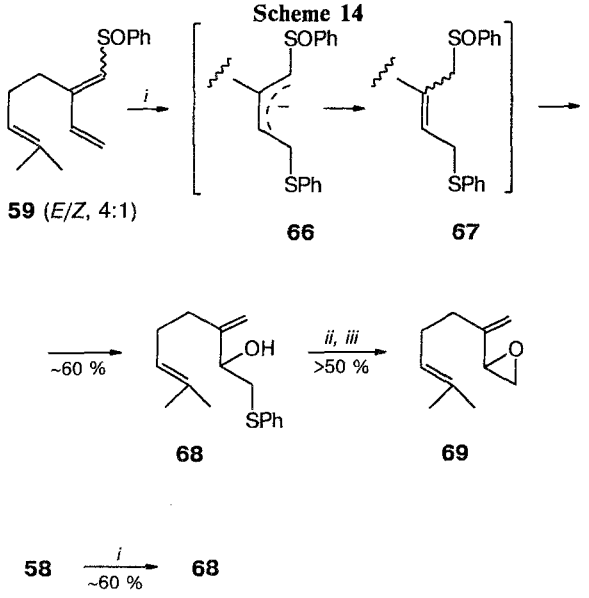
New methods of synthesis of these compounds are considered below; the first one is based on the stereo-

Scheme 13



Reagents and conditions: *i.* $PhSOCl/CH_2Cl_2$, 5 kbar, 25 °C; *ii.* $NaOH/Et_2O/MeOH/H_2O$, 25 °C; *iii.* AcOK/AcOH, 25 °C; *iv.* H_2SO_4(cat.)/MeOH, 25 °C; *v.* $LiAlH_4$/THF, 25 °C, *vi.* $Me_3SiCl(AcCl)/CH_2Cl_2$, −60→25 °C.

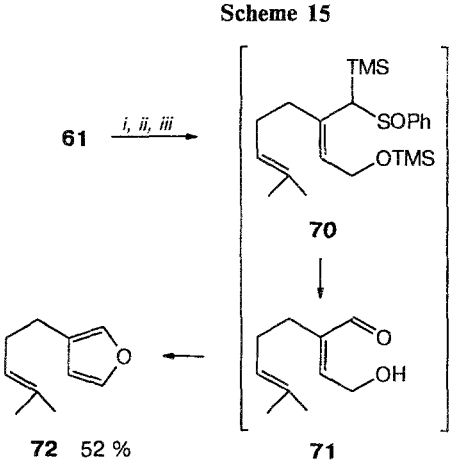
Scheme 14



Reagents and conditions: *i.* $PhSNa/MeOH$, Δ; *ii.* $Me_3O^+BF_4^-/CH_2Cl_2$, −10→25 °C; *iii.* NaOH, aq., 0→25 °C.

controlled transformation of commercially available 6-methylhept-5-en-2-one (methylheptenone, **73**).[38,39]

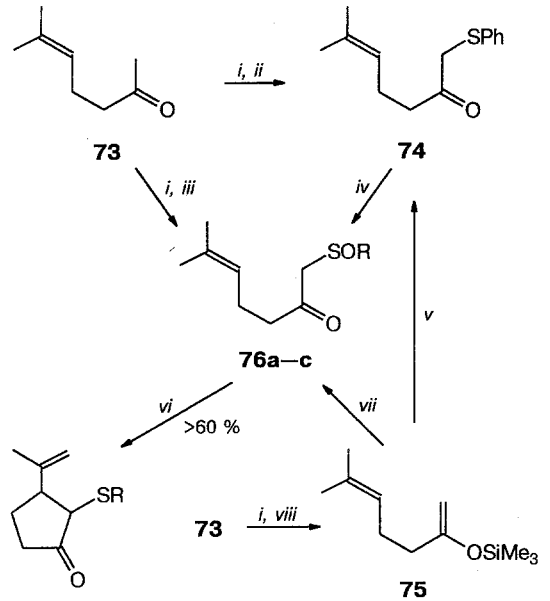
Scheme 15



Reagents and conditions: *i.* Bu^nLi/THF, −85 °C; *ii.* Me_3SiCl/THF, −85 °C; *iii.* H^+, 25 °C.

The latter was chosen as a starting compound taking into account the observation of Ishibasi *et al.*[40] on relatively easy transformation of ketosulfoxide **76a** by the action TFAA to a mixture of isomeric cyclopentanones **77a** and the evident possibility of preparation of sulfoxides related to **76a** by sulfinylation of ketone **73** (Scheme 16).

Scheme 16



R = Me (**a**); Bu^t (**b**); Ph (**c**)

Reagents and conditions: *i.* LDA/THF, −70 °C; *ii.* Ph_2S_2, −70→25 °C; *iii.* Bu^{t}SOCl, −70→25 °C; *iv.* H_2O_2/AcOH, 5→25 °C; *v.* PhSCl/CH_2Cl_2, −70→0 °C; *vi.* TFAA/CH_2Cl_2, 0→25 °C; *vii.* PhSOCl/CH_2Cl_2, −50→0 °C; *viii.* Me_3SiCl/THF, −70→0 °C.

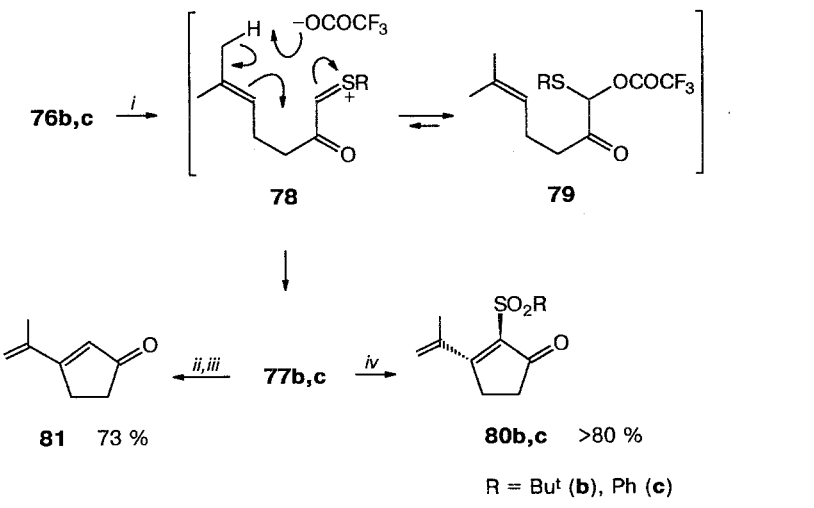
It turned out[38] that ketosulfoxide **76b** can be prepared in one step in ≥50 % yield by sulfinylation of Li enolate generated by deprotonation of ketone **73** with lithium diisopropylamide (LDA) under conditions of kinetic control using Bu^{t}SOCl. On the other hand, low-temperature sulfenylation of this enolate (or the known silyl ether **75** easily formed from above enolate) by the action Ph_2S_2 or PhSCl, respectively, smoothly affords ketosulfide **74**, subsequently oxidized selectively to phenylsulfoxide **76c**. However, the synthesis of the latter by sulfinylation of ether **75** by PhSOCl appears more effective.

It was found that like methylsulfoxide **76a**, previously unknown ketosulfoxides **76b,c** can be easily transformed to the related *trans*-disubstituted cyclopentanones **77b,c** by reaction with TFAA; in both cases, the amounts of *cis*-epimers in the reaction products do not exceed 15 %.[38]

This transformation is interpreted as the ene-type intramolecular reaction of the Pummerer intermediate **78** apparently existing in an equilibrium with *gem*-acyloxysulfide **79** (*cf.* Ref. 40) (Scheme 17). In fact, when the reaction of ketosulfide **76b** with TFAA was carried out in a probe of an NMR spectrometer, the proton signal of HCS (δ *ca.* 6 ppm) characteristic of structure **79** (R = Bu^t) was observed in the ^{1}H NMR spectrum of the reaction mixture even at −40 °C. Its relative integral intensity (RII) achieves maximum at −20 °C, and then at 25 °C decreases with a simultaneous increase in RII of the signals of final product **77b**. In the case of **76c**, its derivative **79** (R = Ph) appeared to be quite stable and it was isolated by chromatography on SiO_2. Refluxing of the latter in toluene (evidently, this treatment induces heterolysis of the C—O bond) affords cyclopentanone **77c** in ≥60 % yield.

The structures of newly prepared cyclopentanones **77b,c** were confirmed by their further transformations.

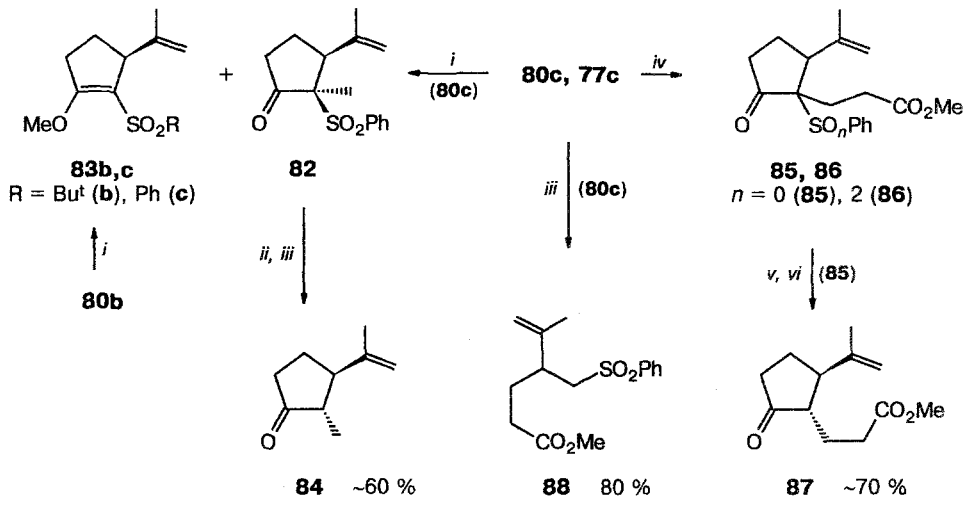
Scheme 17



R = Bu^t (**b**), Ph (**c**)

Reagents and conditions: *i.* TFAA/CH_2Cl_2, 0→25 °C; *ii.* MCPBA/CH_2Cl_2, −30 °C; *iii.* K_2CO_3/PhMe, Δ; *iv.* MCPBA/CH_2Cl_2, −20→25 °C.

Scheme 18



Reagents and conditions: *i.* NaH/DMF, 25 °C, then MeI; *ii.* Li/NH_3, −50 °C; *iii.* MeONa/MeOH, 25 °C; *iv.* CH_2=$CHCO_2Me$/THF, Bu^tOK for **77c**, DBU for **80c**, 25 °C; *v.* Al(Hg)/$EtOH/H_2O$, 25 °C; *vi.* Bu^tOK/THF, 25 °C.

Thus, oxidation of **77b,c** by 2 mol. eq. of MCPBA afforded the related *trans*-ketosulfones **80b,c** free of admixture of the corresponding *cis*-isomers.

In addition, phenylsulfide **77c** at low-temperature retardation of its oxidation by MCPBA at the stage of sulfoxide and mild thermolysis of the latter (without its isolation) smoothly transforms to known cyclopentenone **81** (see Ref. 38).

To study the synthetic utility of cyclopentanones **77b,c** and **80b,c**, a search of the conditions of their *C*(2)-alkylation of the cyclopentane ring and their selective functionalization of the isopropenyl fragment was performed.[39,41]

It turned out that methylation of ketosulfone **80c** by subsequent treatment with NaH and MeI in DMF proceeds chemo- and stereoselectively[41] (Scheme 18), giving *C*-alkyl derivative **82** in a high yield with a minor admixture (*ca.* 10 %) of **83c** easily separable by chromatography, which is a product of concurrent *O*-alkylation typical of such compounds (*cf.* Ref. 42).

Desulfonylation of **82** by Li/NH_3 followed by equilibrium *cis*—*trans*-isomerization of the obtained mixture of epimers by MeONa in MeOH afforded *trans*-disubstituted cyclopentanone **84**, which is the known intermediate in a synthesis of a pseudoguaianolide confertine.[43]

It is interesting to note that in alkylation[39] of ketosulfides **77b,c** and sulfone **80b** under the same conditions, *O*-alkyl derivatives are formed exclusively, *e.g.*, vinyl methyl ether **83b** in the case of ketosulfone **80b**.

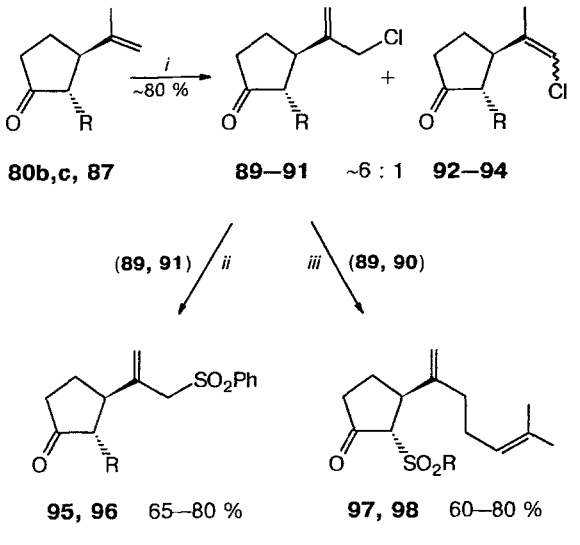
The obvious, facile introduction of the side carbon chain in molecules of cyclopentanones **77** or **80** is opened by the known capability of these compounds to react as CH-acid in Michael reactions. In fact, sulfide **77c** reacts with methyl acrylate in the presence of Bu^tOK affording a mixture of epimeric adducts **85** (*cis*-/*trans*-, *ca.* 2:3) in almost quantitative yield. Desulfurization of the latter by Al(Hg) gives a mixture of *cis*- and *trans*-ketoesters **87** (*ca.* 1:1); their equilibration by Bu^tOK gives thermodynamically preferable *trans*-**87** devoid of appreciable amounts of the *cis*-epimer.[44]

The condensation of ketosulfone **80c** with methyl acrylate failed in the presence of bases such as Bu^tOK or MeONa. In particular, using the latter in MeOH, the only product of the reactions was homoallyl sulfone **88**, evidently resulting from decyclization of **80c** which is similar to the "acidic" cleavage of β-dicarbonyl compounds. Preparation of the desired product of condensation of **80c** with methyl acrylate was effected by carrying out the reaction in the presence of DBU in THF; however, only *cis*-adduct **86** was obtained in a moderate yield.[44]

Selective functionalization of isopropenyl moiety of cyclopentanones **80b,c** and **87** appeared to be possible using the described above procedure (see Sections 1.1.3 and 1.2.2) of allylic chlorination of di- and trisubstituted olefins. Thus, treatment of compounds **80b,c** and **87** SO_2Cl_2 in the presence of pyridine affords corresponding allyl chlorides **89**—**91** and accompanying admixtures (*ca.* 15 %) of vinyl regioisomers **92**—**94** (Scheme 19).[41]

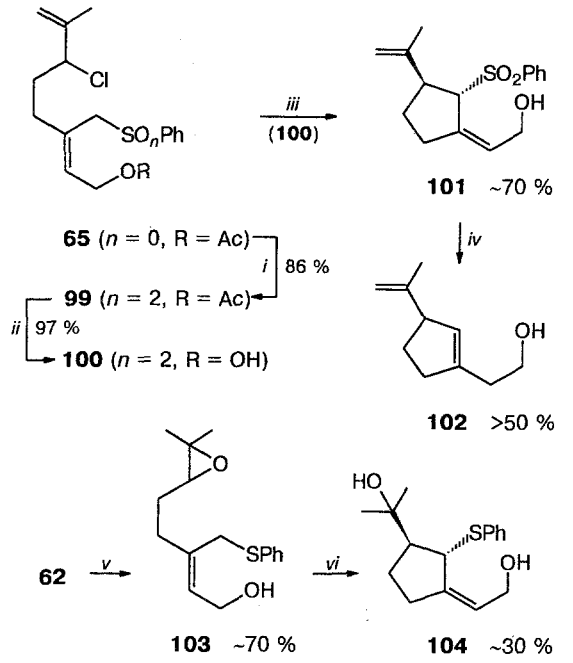
The presence of the latter does not preclude some selective transformations of allyl chlorides **89**—**91**. Thus, by the action of $PhSO_2Na$ **89** and **91** were transformed into the corresponding sulfones **95** and **96**, and the CuI-catalyzed condensation of **89** or **90** and prenylmagnesium chloride (PreMgCl) afforded smoothly the corresponding cross-coupling products (**97** or **98**). Simultaneously, in all of the cases considered, vinyl chlorides **92**—**94** appeared to be inert in the above conditions and they

Scheme 19



Reagents and conditions: *i.* SO_2Cl_2/Py/CH_2Cl_2, 0 °C; *ii.* $PhCO_2Na$/DMF, 50 °C; *iii.* PreMgCl/THF, −70 °C.

Scheme 20



Reagents and conditions: *i.* MCPBA/CH_2Cl_2, −40→25 °C; *ii.* H_2SO_4(cat.)/MeOH, 25 °C; *iii.* Bu^nLi/THF/HMPA, −85→25 °C; *iv.* Na/EtOH, −20→25 °C; *v.* NBS/THF/H_2O, 25 °C, then K_2CO_3/Et_2O/H_2O/$Bu_4N^+Br^-$, Δ; *vi.* Bu^nLi/THF/TMEDA, −78→25 °C.

were isolated from reaction mixtures by chromatography.[41]

Another approach to synthesis of 1,2,3-trisubstituted cyclopentanes (Scheme 20) uses geraniol derivatives **62** and **65** as linear precursors, which became accessible from the described above transformations of myrcene **30a** (see Section 1.2.4).

Thus, sulfide **65** was transformed through acetate **99** to hydroxysulfone **100**, deprotonation of the latter by a Bu^nLi excess afforded stereospecifically[33] the cyclization product, *i.e.*, cyclopentane **101**. A related product **104** of the 5-*exo*-cyclization of epoxysulfide **103** prepared by the selective van Tamelen epoxidation of olefin **62** was obtained in moderate yield by treatment of **103** with Bu^nLi in the presence of *N,N'*-tetramethylethylenediamine (TMEDA).[33]

The structures of newly synthesized compounds **99—104** were confirmed by their spectra and, in the case of **101**, by its desulfonylation accompanied by allyl shift of the C=C bond, smoothly resulting in homoallyl alcohol **102**.

Realization of yet another approach to the synthesis of 1,2,3-trisubstituted cyclopentanes is based on the use of the intramolecular variant of 1,3-dipolar [3+2]-cycloaddition of silyl nitronate **106** to the multiple bond of the same dipolarophile[45] (Scheme 21).

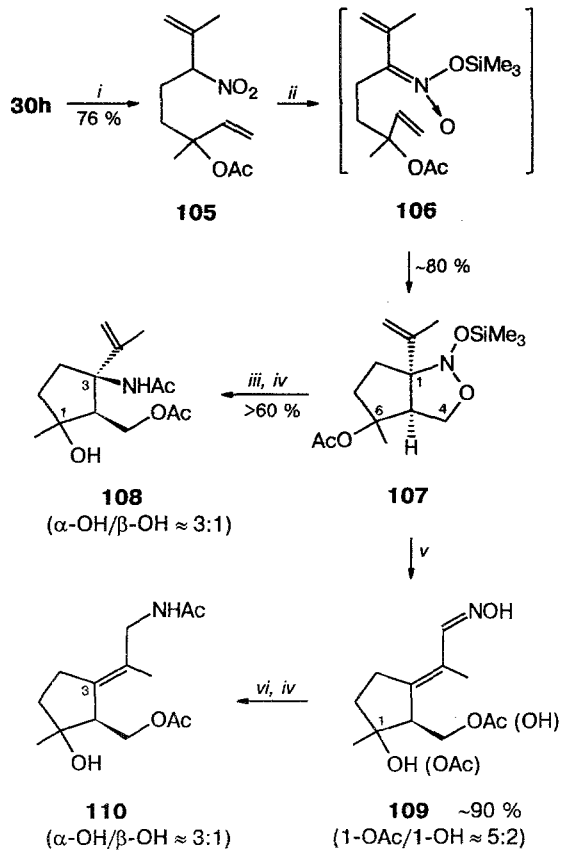
Thus, previously unknown nitroolefin **105** obtained from linalyl acetate **30h** under conditions of generation of silyl nitronate **106** by the action of *O,N*-bis-(trimethylsilyl)acetamide (BSA), is smoothly transformed to bicycloadduct **107**, which is a mixture of C(6)-epimers and N-invertomers. Cyclopentaneisoxazolidines **107** are evidently formed due to an intramolecular attack of the oxygen atom of dipole **106** on the less substituted C atom of the C=C bond of the latter.

It should be noted that such direction of cycloaddition is one of the first examples (*cf.* Ref. 46) of totally reversed regioselectivity usually observed for inter- and intramolecular reactions of silyl nitronates with monosubstituted olefins (see Ref. 47).

The reductive cleavage of the both N—O bonds in **107** by the action of Li in NH_3 gives[45] a mixture of C(1)-epimeric aminodiols characterized as *N,O*-diacetates **108**. The ratio of isomers (α-OH/β-OH ≈ 3:1) found for the latter, evidently correspond to that of parent **107**.

An unusual transformation of isoxazolidines **107** was observed[45] upon their desilylation by $KF \cdot 2H_2O$, affording unexpectedly a mixture of oximes **109** containing C(1)-epimers and OAc-regioisomers (Scheme 22). The treatment of this mixture of **109** with $LiAlH_4$ followed by acetylation of the intermediate aminodiols afforded a mixture of *N,O*-diacetates **110** in a practically the same C(1)-epimeric ratio as that in diacetates **108**. Formation of oximes **109** may be accounted for by allylic iso-

Scheme 21



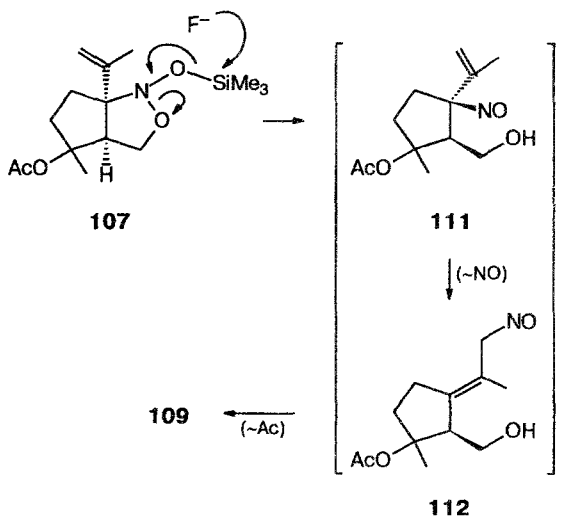
Reagents and conditions: *i.* $NaNO_2$/AcOH, 25 °C; *ii.* BSA/Et_3N/PhH, 80 °C; *iii.* Li/NH_3/THF, −60→−33 °C; *iv.* Ac_2O/Py, 25 °C; *v.* KF · $2H_2O$/THF/MeOH, 25 °C; *vi.* $LiAlH_4$/THF, 25 °C.

merization (unprecedented in the chemistry of nitroso compounds) of tertiary nitroso intermediates **111** initially formed from **107** by the action of F^- to primary **112** (see also Ref. 48). Subsequent stabilization of **112** to final products **109** also involves partial 1,3-O→O-migration of the tertiary acetyl residue (*cf.* Ref. 49).

1.3.2. Cationic cyclization (CC) of α-monoterpenols. In contrast to the thoroughly studied[50] biomimetic CC of terpenols of the β-series, *e.g.*, **113a—c**, affording compounds of the *p*-menthane (**A**) and ionane (**B**) groups, information on the similar transformation of α-monoterpenols **114a—c**, which are known to be easily prepared by hydride reduction of the corresponding allyl chlorides **39** (*e.g.*, see Ref. 51), was absent (Scheme 23).

It turned out that in the presence of some Brønstedt and Lewis acids (the best results were obtained for $F_3B \cdot OEt_2$), terpenols **114a—c** are transformed to mixtures of monocyclic (**115, 116**) and bicyclic (**117**) products.[52] The composition of these mixtures varies from **115/116/117** ≈ 12:7:1 in the case of α-geraniol **114a** to *ca.* 2:1:2 for α-nerol **114b** and lies in between for α-linalool **114c**.

Scheme 22



The formation of diolefins **115** and **116** evidently proceeds *via* intermediate carbenium ion **118**, whereas the most probable origin of fluoride **117** involves the intramolecular cationoid [3+2]-reaction in carbenium ion **119** followed by quenching of the reaction with F^-. This explanation is confirmed by the observed changes in ratio of the CC products in favor of monocyclic **115** and **116** in the case of α-geraniol **114a** and bicyclic **117** for α-nerol **114b**. This observation evidently results from the larger, kinetically determined contributions of transoid **118** and cisoid **119** carbenium ions, respectively.

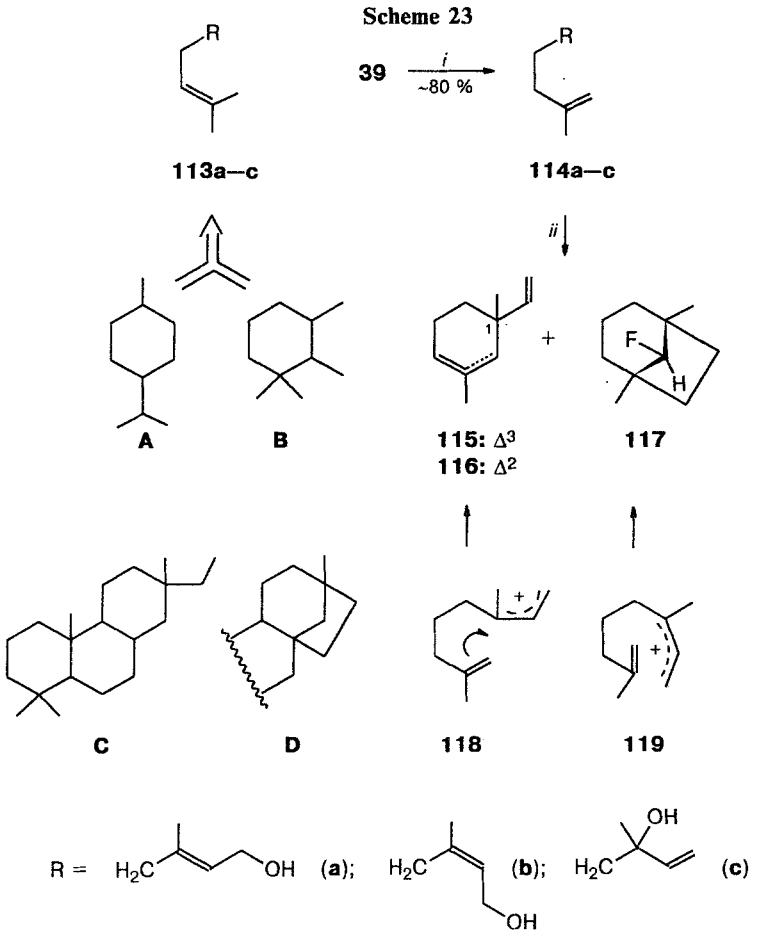
It should be noted that the above transformation of α-monoterpenols **114** is a simulation of the scheme previously proposed by Wenkert[53] for biosynthesis of tri- and tetracyclic diterpenes of pimarane (**C**) and gibane (stachane) (**D**) series, the structural fragments of which and monoisoprenoids **115—117** have the common carbon skeleton.

The discovered reaction of α-monoterpenols **114** is of general character. It appeared that the isoprenoids of α-series bearing additional substituents can be involved into this reaction. This makes possible to synthesize some hardly accessible derivatives of dimethylvinylcyclohexene[54] (Scheme 24).

Thus, sulfonyl derivative of α-geraniol **121** prepared from sulfoxide **31b** described in Section 1.2.1, by the action of $F_3B \cdot OEt_2$, affords a mixture of diastereomeric allylsulfones Δ^2-**123** (β-C(4)/α-C(4) ≈ 3:2) in a high total yield along with an admixture of Δ^1-regioisomer **123** (<5 %). Under the same conditions, CC of sulfone **122** prepared from homoallyl sulfide **54b** (see Section 1.2.3) affords cyclohexene Δ^1-**124** containing *ca.* 10 % of Δ^2-regioisomer **124**.

Analogously, allyl chloride **126** prepared from α-geranyl acetate **120** according to the above procedure (see Section 1.2.2) by the action of $F_3B \cdot OEt_2$ affords a mixture of isomers **127** in a ratio of *ca.* 4:1 in *ca.* 60 % yield.[54]

Scheme 23



Reagents and conditions: *i.* $LiAlH_4$/THF, Δ; *ii.* $F_3B \cdot OEt_2/CH_2Cl_2$, −30→10 °C.

CCs of chloride **39b** being a regioisomer of **126**, as well as described in Section 1.2.2 chloro derivatives of α-nerol **39c** and α-linalool **39h** are complicated due to the lability of the starting compounds and the reaction products and give in all of the cases in moderate yields vinyl chloride **125** containing an admixture of allylic regioisomer (<5 %).

Thus, CC of α-monoisoprenoids serves as a preparative method for hardly accessible derivatives of dimethylvinylcyclohexene; one of them, *viz.*, allylic chloride Δ^3-**127**, appears to be a convenient SB of carbon skeleton of tricyclic diterpenes (see below).

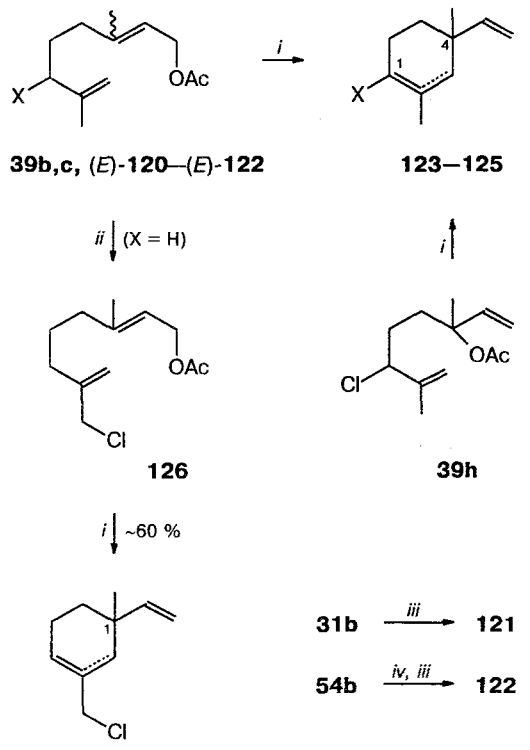
1.3.3. An effective procedure for Diels—Alder reactions using isoprene and myrcene under conditions of adsorption on a silica gel surface. It is known that running some intramolecular transformations, *e.g.*, the Khand—Poson reaction ([2+2+1]-cycloaddition) or the Carrol rearrangement ([3,3]-sigmatropic rearrangement), on the surface of chromatographic sorbents in the absence of solvents ("dry medium") allows the use of milder conditions and increasing efficiency of these processes.[55]

It was found[56] that similar experimental conditions also influence significantly the course of intermolecular [4+2]-cycloaddition reactions (Diels—Alder reactions). Thus, reactions of diene **1** and **30a** with acrolein **128a** and methyl vinyl ketone **128b** on the surface of SiO_2 (chromatographic grade) proceeds more regioselectively (the ratio of 1,4- and 1,3-regioisomers in a mixture of cycloadducts is *ca.* 19/1), in higher yield of products **129** and **130**, and at the temperature *ca.* 100 °C lower than that of the usual liquid-phase procedure; the latter gives[57] the mixtures of *para*- and *meta*-regioisomers in the ratio of *ca.* 2:1 for the same substrates (Scheme 25).

It was also established that the yields of cycloadducts **129—132** depend significantly on the reagent/sorbent weight ratio (R), while its optimum value varies for sorbents having different specific surface (S_{sp}). Thus, in model experiments, the yield of acetylcyclohexene in condensation of **128b** and butadiene on SiO_2 with S_{sp} *ca.* 400 $m^2\ g^{-1}$ at 20 °C for 30 min are 16, 78, 90, 79 % at R = 1/2, 1/10, 1/20, 1/40, respectively, but when SiO_2 with S_{sp} *ca.* 100 $m^2\ g^{-1}$ is used, they are 18, 30, 44, 57 % at R = 1/10, 1/20, 1/40, 1/100, respectively.

It is found that the activity of silica gel depends also on the presence of H_2O, which, as it is known, lowers its adsorption capacity. Thus, to obtain comparable results, the application of SiO_2 containing *ca.* 12 % of H_2O (the

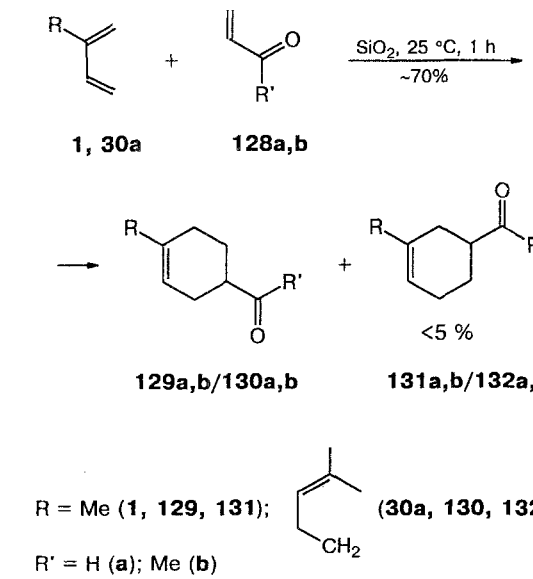
Scheme 24



X = H (**120**); SO_2Ph (**121, 123**); CH_2SO_2Me (**122, 124**); Cl (**39, 125**)

Reagents and conditions: *i.* $F_3B \cdot OEt_2/CH_2Cl_2$, −20→25 °C (for **121**, **122**, and **126**) or $H_2SO_4/MeNO_2$/pentane, −30 °C (for **39b,c,h**); *ii.* $SO_2Cl_2/Py/CH_2Cl_2$, −70 °C; *iii.* MCPBA/Et_2O, −30 °C; *iv.* Ac_2O/Py, 25 °C.

Scheme 25



equilibrium percentage of H_2O at 25 °C), requires 30—50 °C higher temperature than that of SiO_2 dried at 200 °C up to the constant weight. It was also noted that the presence of solvents (hexane, CH_2Cl_2) decreases the efficiency of diene condensation on SiO_2; this is evidently caused by partial desorption of the reagents from the surface of a sorbent.

The above data show (the similar results were also obtained for a representative series of dienes of non-isoprenoid nature[56]) that under conditions of a "dry medium", the Diels—Alder reactions proceed easier and more selectively than those in a liquid phase. In this respect, a similarity with the results obtained in catalysis of such processes by Lewis acids is observed. However, it is known that on the SiO_2 surface, Lewis centers are practically absent (*e.g.*, see Ref. 58). Apparently, the ability of the SiO_2 surface to supply polyfunctional character of the catalysis due to multicenter adsorption seems valuable. It is important that under conditions of monolayer adsorption (achieved for SiO_2 with S_{sp} *ca.* 400 $m^2\ g^{-1}$ at R *ca.* 1/10), the possibility to form prereaction complexes is simplified significantly due to weak van der Waals interactions of substrates devoid of shielding by solvation. Such drawing together of the reagents is probably a powerful factor to decrease an entropy barrier of cycloaddition and hence promote the reaction (*cf.* Ref. 59).

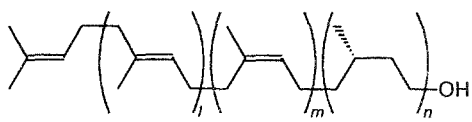
It should be noted that the found efficacious conditions of condensation of myrcene **30a** with dienophiles of **128** type are of definite practical interest, since cycloadducts **130** are intermediates in manufacturing of perfumes.

2. Synthesis of natural compounds starting from functionalized isoprene and monoisoprenoids derivatives

The above results allow one to prepare new C_5- and C_{10}-isoprenoid SB; the possibility of their application in synthesis of some natural terpenes (practically useful ones among them) is discussed in this Section.

2.1. Stereospecific synthesis of polyprenol analogs

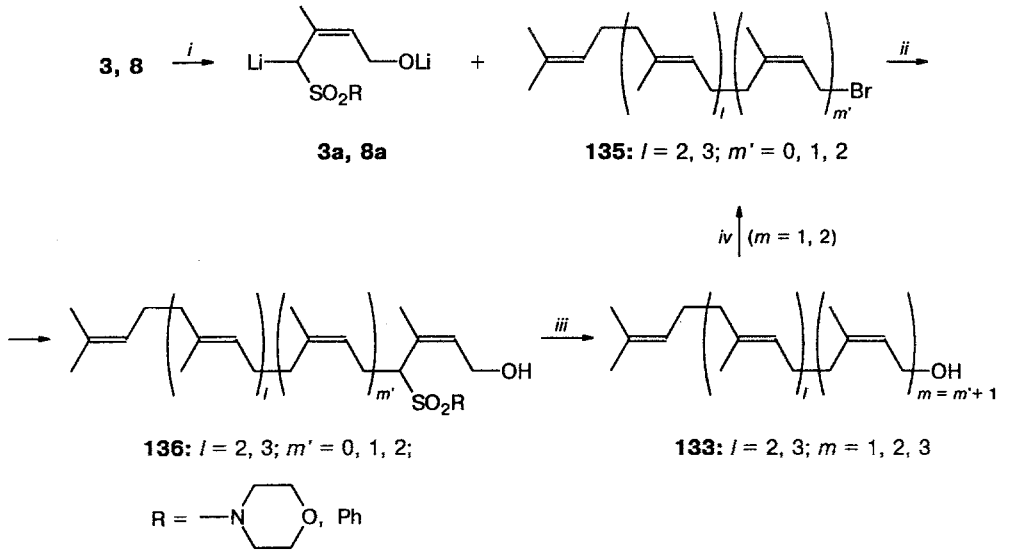
An interest in the synthesis of polyprenols **133** and dolichols **134** is stimulated by their role in biosynthesis of carbohydrate-containing biopolymers in cells of all organisms.[60] At the present time, they are considered as potential polyfunctional drugs.



133: l = 2, 3; $m \geq 3$, n = 0

134: l = 2, 3; $m >> 3$, n = 1

Scheme 26



Reagents and conditions: *i.* Bu^nLi/THF/HMPA, −70 °C; *ii.* THF, −70 °C; *iii.* Li/NH_3/*n*-C_6H_{14}/THF, −50 °C; *iv.* PBr_3/Py/THF, −20→25 °C.

For the first time, a stereospecific synthesis of the compound of this class, *viz.*, betuloprenol **133** (l = 2, m = 3, n = 0), was performed using the sequential scheme[3] based on stepwise homologization of prenyl halides of **135** type by *Z*-C_5-isoprenoid SB **3** (Scheme 26).

Further, this approach was used to synthesize a series of prenols **133** (l = 2, 3, m = 2, 3, n = 0) (see reviews[61] and references therein) (see Scheme 26). It turned out that the replacement of sulfonamide **3** by more available hydroxysulfone **8** does not effect the general efficiency of the synthetic scheme and gives comparable yields both at the stages of condensation of lithium derivatives **3a** and **8a** with allyl halides **135**, and at desulfonylation of the corresponding intermediate sulfonyl derivatives **136** affording target alcohols **133**. It should be noted that hexaprenol **133** (l = 3, m = 2, n = 0) and heptaprenol **133** (l = 3, m = 3, n = 0) previously isolated from fruits of the *Serenoa repens* palm tree possess the high activity in therapy of hypertrophy of prostate.[62]

On the basis of this methodology,[61] synthetic procedures for dolichols (**134**) and related compounds are worked out starting from saturated C_5-isoprenoid SB **19** and **137**, the latter of which, *viz.*, chiral hydroxysulfone **137** is found to be available from the known bromide **138**.[63]

Thus, desulfonylation of homoallylic sulfones **139**, which are products of the condensation of dilithium derivative (**137a**) of saturated sulfone **137** with bromides **135** (l = 2, 3, m = 2), smoothly afforded the corresponding terpenols **134** (l = 2, 3, m = 2), possessing the stereochemistry of natural alcohols of this series[63] (Scheme 27).

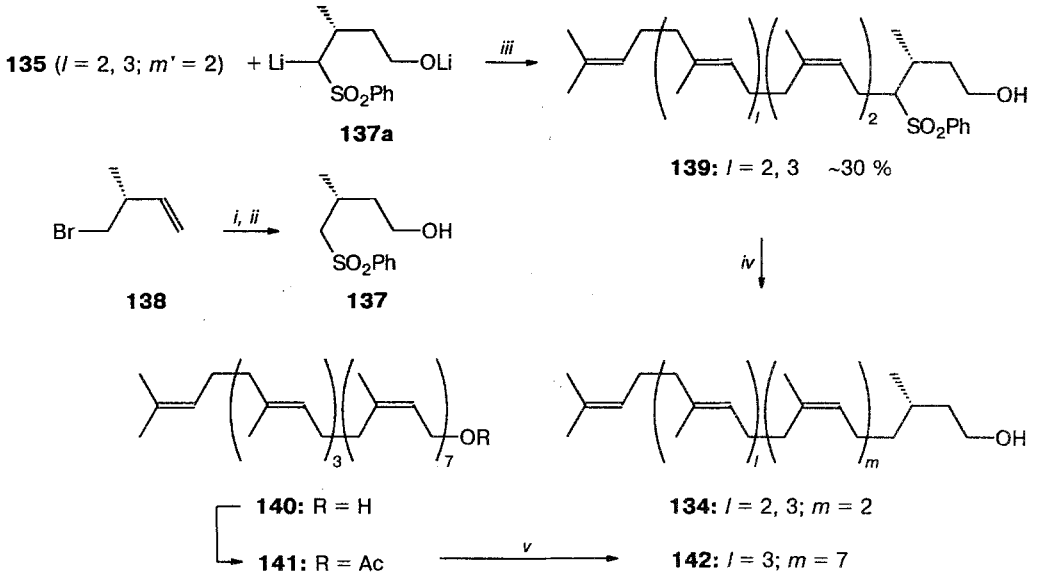
The similar procedure is used[9] for a synthesis of racemic dodecaprenol **142** (l = 3, m = 7) from available undecaprenol **140** using Suzuki coupling[64] of acetate **141** with Grignard reagent **143** prepared from (±)-bromoether **19** and then by the cleavage of the intermediate THP ether (without its isolation) by the action of TsOH · Py.

This methodology was found to be convenient for preparation of these prenols, which differ from the natural compounds of **133** series in stereochemistry of some chains of the regular oligoisoprene chain or in the nature of its ω-terminal fragment. For example, to elucidate the role of the terminal α-(*Z*)-isoprenoid units in polyprenols **133** responsible for biosynthesis of bacterial polysaccharides (see Ref. 65) the samples of compounds with alternating (*E*)- and (*Z*)-fragments were required. It should be noted that such terpenols are not found in the natural sources and, assuming the available data on biosynthesis of compounds of **133** series, their existence seems problematic.

Heptaprenol **148** required as one of possible objects for this study was synthesized in accordance with the stepwise scheme[66] starting from known[8a] *E*-hydroxysulfone **144** and sesterterpenyl bromide **135** (l = 3, m = 1) *via* sulfone **145**, triterpenol **146**, and hydroxysulfonamide **147** (Scheme 28).

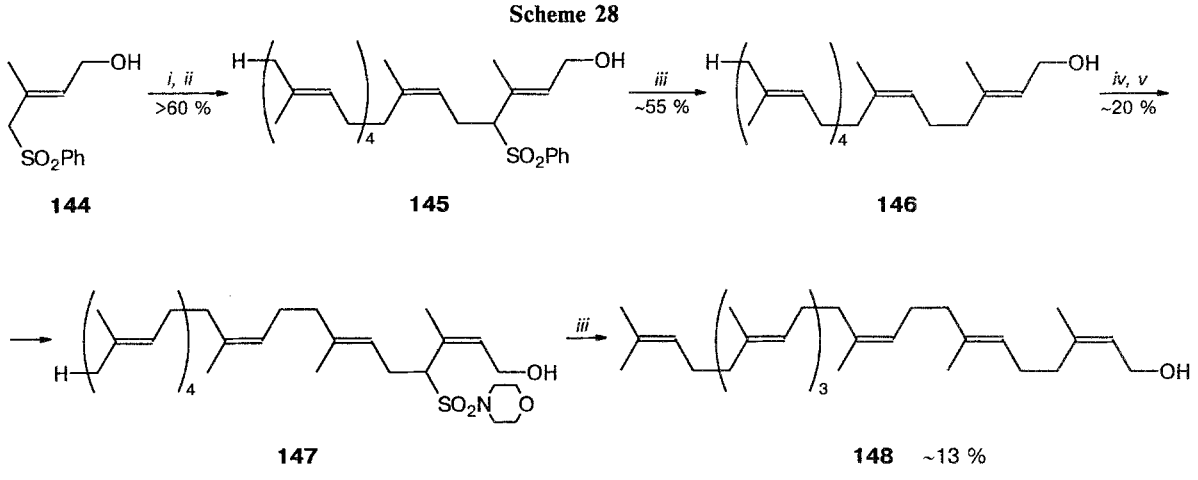
For this purpose, on the basis of the same stepwise approach, undecaprenol **140** and corresponding dolichol (±)-**142** were transformed into related artificial analogs **149** (see Ref. 66) and **150** (see Ref. 9), and solanesol

Scheme 27



Reagents and conditions: *i.* $PhSO_2Na$/DMF, 50 °C; *ii.* 9-BBN/THF, −25 °C, then H_2O_2/NaOAc, 0→25 °C; *iii.* THF/HMPA, −30 °C; *iv.* Li/NH_3/THF, −60 °C; *v.* $BrMgCH_2CH(Me)CH_2CH_2OTHP$ (**143**)/Li_2CuCl_4/THF, −20→25 °C, then TsOH · Py/THF, 25 °C.

Scheme 28



Reagents and conditions: *i.* Bu^nLi/*n*-C_6H_{14}/THF/HMPA, −60 °C; *ii.* **135** (*l* = 3, *m* = 1)/THF, −70 °C; *iii.* Na/NH_3/*n*-C_6H_{14}/Et_2O, −70 °C; *iv.* PBr_3/Py/THF, −20 °C; *v.* **3a**/THF/HMPA, −70 °C.

151 was converted to decaprenol **152** as well (see Ref. 66) (Scheme 29).

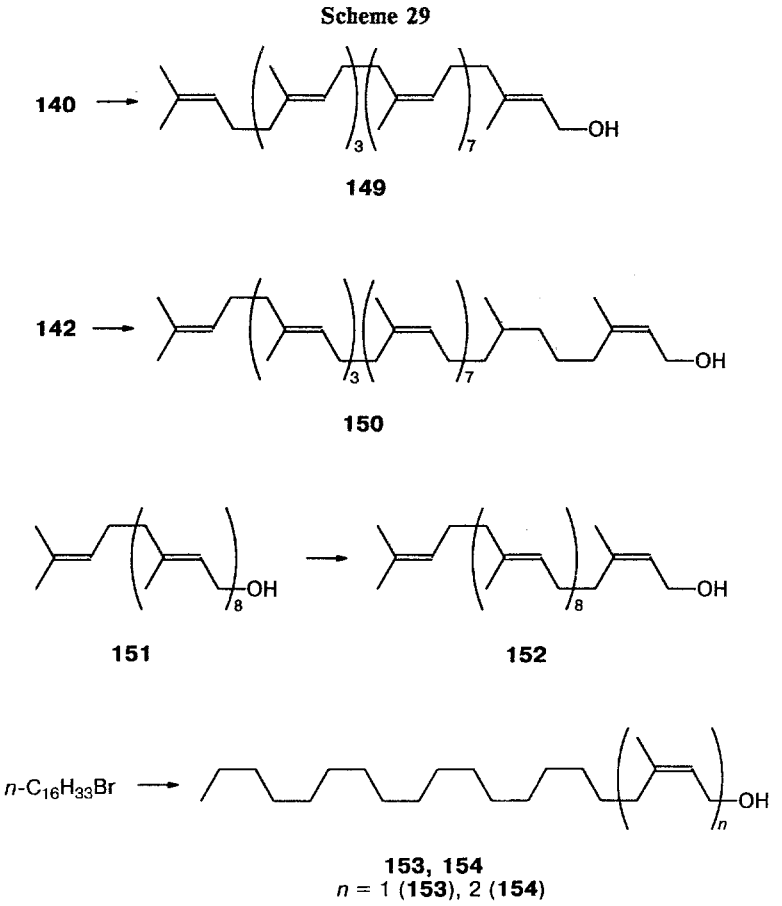
Finally, to study the dependence of biological activity of polyprenols on the nature of their ω-isoprenoid fragment, the synthesis of allylic alcohols **153** and **154** was performed, cetyl residue in their molecules simulates the demethylated and reduced fragment of the chain consisting of four isoprene units.[9]

2.2. Synthesis of irregular terpenols of the lavandulol series starting from 4-phenylthio-3-methylbut-2*Z*-en-1-ol

The above *cis*- and *trans*-C_5-homologizations of linear terpenols using *Z*-**3,8** and *E*-**144** SBs, respectively, are the method of stereospecific synthesis of regular oligoisoprene chains.

The similar approach to the irregular natural struc-

Scheme 29



tures of lavandulol type **155a** was worked out[67] on the basis of accessible (see Section 1.1.1) hydroxysulfide **9** using ambident properties characteristic of allylsulfide carbanions,[68] which are also exhibited in the case of dianion **156** generated from **9** (Scheme 30).

It was revealed that the treatment of the latter with prenyl chloride **157a** affords a mixture of regioisomers **158a/159a** (*ca.* 1:2) resulting from the electrophilic attack of allyl anion **156** on γ- and α-carbon atoms, respectively. When geranyl chloride **157b** was used, the ratio of **158b/159b** *ca.* 3:2 was observed, which appeared to be more favorable (**158c/159c** ≈ 2:1) in the case of sesterterpenyl bromide **157c**.

The above mixtures (except monoterpene derivatives **158a/159a**) were subject to chromatographic separation to isolate sesquiterpene (**158b**) and triterpene components (**158c**) required for the final stage, their desulfurization (Ca/NH_3) afforded racemic forms of the natural alcohols of plant origin, *viz.*, sesquilavandulol **155b** (see Ref. 69) and ulmoprenol **155c** (see Ref. 70).

The alternative synthesis of (±)-sesquilavandulol **155b** involves condensation of allylic sulfoxide **160c** (prepared from (±)-lavandulol **155a** (see Section 1.2.1)) and prenylmagnesium chloride (PreMgCl) catalyzed by the Kochi reagent. However, (±)-**155b** resulting from S_N2'-reaction contained an admixture of Z-Δ^4-stereoisomer (*ca.* 20 %).[18]

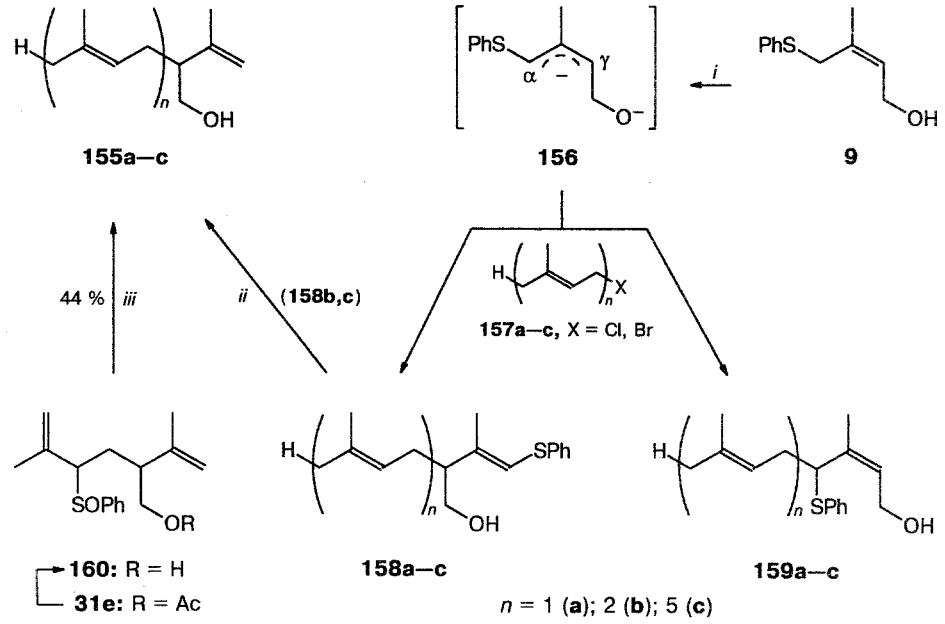
2.3. Synthesis of some oxygen-containing monoisoprenoids starting from 2-phenylsulfinylmethyl-1,3-butadiene

Extrapolation of the Diels—Alder reaction to the synthesis of carbo- and heterocyclic structures, including natural ones, implies the use of functionalized 1,3-dienes, in particular those that allow transformation of the intermediate cycloadducts by simple operations to the compounds, inaccessible by direct diene synthesis (*e.g.*, see Ref. 71).

From this point of view, it seems promising to use isoprene sulfoxide **10** (see Section 1.1.2); this possibility is illustrated by the syntheses of some oxygen-containing monoterpenes of *p*-menthane and carane series[72] (Scheme 31).

Determination of the composition of condensation products of **10** and methyl vinyl ketone **128b** allowed us to estimate the regioselectivity of the cycloaddition reaction of this diene and unsymmetric dienophile, in this case, it affords a mixture of diastereomeric *para*- and *meta*-cycloadducts **161/162** in the ratio of *ca.* 3:1. The major regioisomer is easily separated by crystallization; the subsequent sulfoxide-sulfenate rearrangement gives a mixture of previously unknown ketols **163** with significant predominance of *trans*-**163** isomer. The latter was separated by chromatography on SiO_2 and transformed

Scheme 30



Reagents and conditions: *i.* Bu^nLi/THF/HMPA, −70 °C; *ii.* Ca/NH_3/THF, −70 °C; *iii.* PreMgCl/Li_2CuCl_4/THF, −20→25 °C.

to (±)-$\Delta^{1(7)}$-menthane-2,8-diol **164** by treatment with MeMgI in practically quantitative yield.[72]

The reaction of diene **10** with a moderately active dienophile, *i.e.*, dimethylcyclopropene, requires a high-pressure technique[72] giving a mixture of diastereomeric sulfoxides **165** (*ca.* 1:1) in a high yield. By the action of $P(OMe)_3$, sulfoxides **165** rearrange into carenols **166** with the same predominance of *trans*-**166** like in the case of **163**. Finally, oxidation of allylic alcohols **166** with bis(trimethylsilyl)chromate, which usually proceeds for such compounds with complete allylic isomerization, smoothly afforded carenal **167** subsequently transformed to (±)-form of natural chaminic acid **168** (see Ref. 73).

Thus, the three-step synthesis of **168** from [4+2]-cycloadducts **165** is an equivalent of Diels—Alder cycloaddition of exclusively labile 1,3-butadien-2-carboxylic acid to dimethylcyclopropene.

2.4. Synthesis of the AI component of the sex pheromone of the red San Jose scale (*Aonidiella aurantii*)

Although the natural attractant of this pest, which damages citrus plants, *i.e.*, acetate **174**, possesses (3*S*,6*R*)-configuration, confirmed by numerous syntheses of its optically active forms,[74] its biological activity is not inhibited by the presence enantiomers. Therefore, effective methods of preparation of the (±)-form of acetate **174** are of practical interest. We worked out[75] a simple method of synthesis of (±)-**174** starting from available sulfide **54g**, which can be prepared from (±)-citronellyl acetate **30g** (see Section 1.2.3).

Acetate of **54g** (**169**) was initially oxidized with MCPBA to acetoxysulfone **170**, deacetylation of **170** afforded hydroxysulfone **171** being a key compound in the synthesis of **174** (Scheme 32).

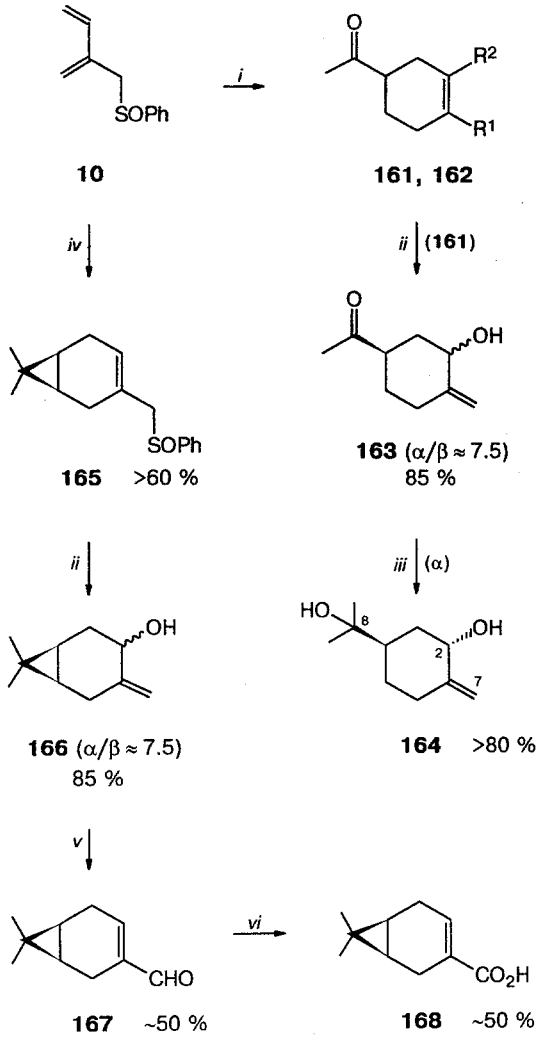
It turns out that treatment of **171** with *ca.* 5 mol. eq. of Bu^nLi followed by treatment with *ca.* 5 mol. eq. of allyl bromide (AllBr) in THF yields tris-allyl (All) derivative **172** (>60 %), the latter is formed by deprotonation of methylene and methyl groups neighboring to sulfonyl group. Reductive desulfonylation of **172** smoothly affords alcohol **173**, acetylation of the latter gives the desired product (±)-**174** in an overall yield of *ca.* 15 % with respect to starting (±)-citronellyl acetate **30g**.

2.5. Synthesis of cyclopentanoids of the iridane series

Cyclopentanoids are widespread in Nature, compounds of the iridane series **175** are among them.[36] In recent years, an interest in such terpenoids manifests itself in elaborating preparative methods starting from linear precursors (*e.g.*, see Ref. 76). This methodology can be illustrated by biomimetic synthesis of bicyclic iridoids **177** obtained in >40 % yield by treatment of epoxide **69** (accessible from myrcene **30a**, see Section 1.2.4) with $F_3B \cdot OEt_2$ (see Ref. 33), apparently, *via* the intermediate **176** (Scheme 33).

The prepared product is a mixture of stereoisomers

Scheme 31

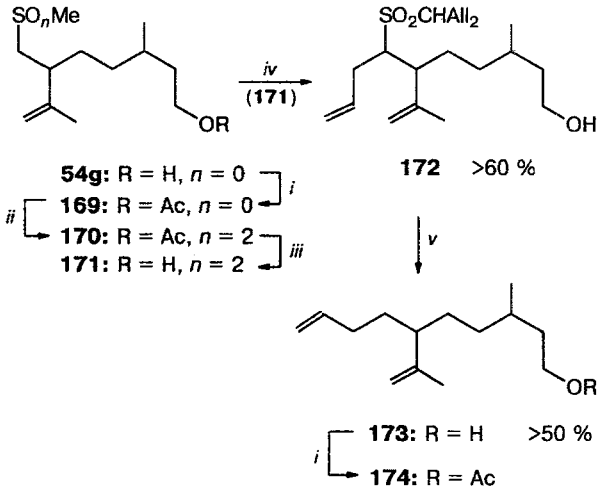


161: $R^1 = CH_2SOPh$, $R^2 = H$

162: $R^1 = H$, $R^2 = CH_2SOPh$

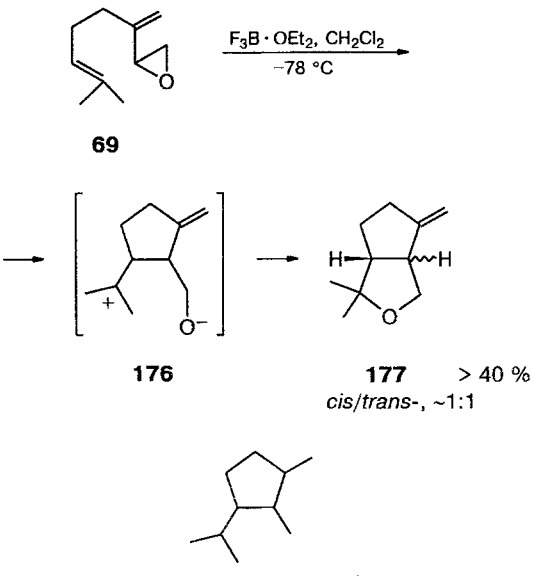
Reagents and conditions: *i.* **128b**/PhH, Δ; *ii.* $P(OMe_3)$ MeOH, Δ; *iii.* MeMgI/THF, 25 °C; *iv.* 2,2-Dimethylcyclopropene/CH_2Cl_2, 5 kbar, 80 °C; *v.* CrO_3/$(Me_3Si)_2O/CH_2Cl_2$, 25 °C; *vi.* Ag_2O/MeOH/H_2O, 25 °C.

Scheme 32



Reagents and conditions: *i.* Ac_2O/Py, 25 °C; *ii.* MCPBA/Et_2O, −40→25 °C; *iii.* $LiAlH_4$/THF, −20 °C; *iv.* Bu^nLi/n-C_6H_{14}/THF, −60 °C, then AllBr/THF/HMPA, −60→10 °C; *v.* Na/NH_3/THF, −70→−40 °C.

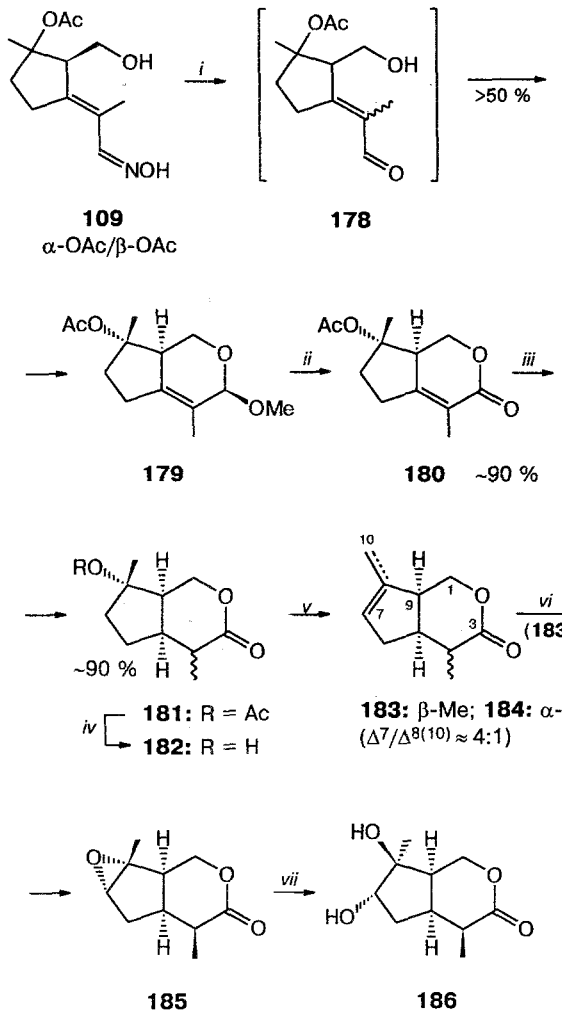
Scheme 33



(*cis-/trans-*, *ca.* 1:1), while *cis*-**177** isolated by chromatography on SiO_2 in individual state is a racemic form of hop ether (a component of hop essential oil) synthesized previously using much more complicated procedures.[36]

The variants of stereocontrolled transformation of isoprenoids to 1,2,3-trisubstituted cyclopentanes (Section 1.3.1) open new possibilities of rather simple transfer from linear precursors to compounds of **175** series. An example is the synthesis of iridolactone **186** from oximes **109** (available from linalyl acetate **30h**, Section 1.3.1) (Scheme 34).[77] Thus, after mild hydrolysis of oximes **109** in the presence of $Tl(NO_3)_3$, bicyclic acetal **179** was isolated from a reaction mixture by chromatography on SiO_2 in >50 % yield, this acetal was related to the major component of the mixture of **109** (α-OAc-epimer). The formation of **179** evidently proceeds *via* acroleins **178**; the acid present in the reaction mixture favors their *E/Z*-isomerization.

Scheme 34



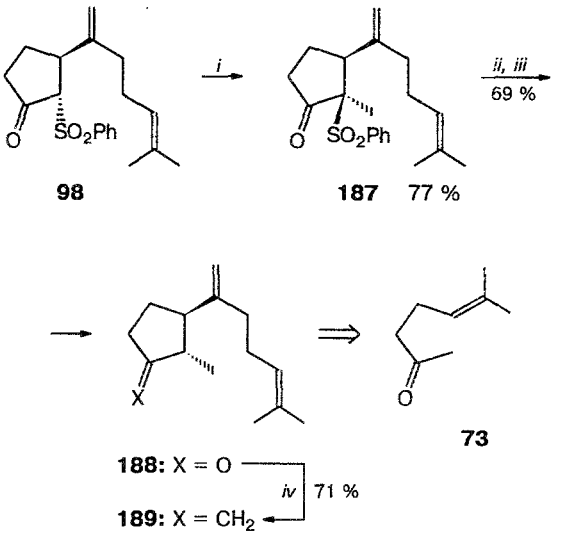
Reagents and conditions: *i.* $Tl(NO_3)_3/HClO_4/MeOH$, 25 °C; *ii.* CrO_3/aq. H_2SO_4, 25 °C; *iii.* $NiCl_2 \cdot 6H_2O/NaBH_4$, 0→25 °C; *iv.* $HClO_4$(aq.)/MeOH, 25 °C; *v.* DMSO, Δ; *vi.* MCPBA/Et_2O, 25 °C; *vii.* KOH/DMSO(aq.), Δ, then $NaHSO_4$ to pH ≈ 3.

Acetal **179** was oxidized to lactone **180** by Jones reagent, hydride reduction of **180** by nickel boride, which appeared to be nonstereoselective in this case, afforded a C(4)-epimeric mixture (*ca.* 1:1) of saturated acetoxylactones **181** in a high yield. On the next step, **181** were transformed to carbinols **182**; their dehydration afforded a mixture of corresponding olefins **183** and **184** in ratios of *ca.* 4:1 in both cases related to $\Delta^7/\Delta^{8,10}$-regioisomers.

The presented composition of the mixture was determined by preparative chromatographic isolation of regioisomeric pairs **183** and **184**. The first was subjected to mild epoxidation with MCPBA thus yielding epoxide **185** (*ca.* 60 %) isolated from the reaction mixture; its opening in alkaline conditions gave the target *trans*-diol **186**, a racemic form of an isomer of villosol, iridolactone recently isolated from stems of the plant *Patrinia villosa* used in medicine.[78]

A further example of realization of the accepted methodology[41] is a synthesis of sesquiterpene cyclopentanoid **189** based on ketosulfone **98** (for preparation of **98** see Section 1.3.1) (Scheme 35).

Scheme 35



Reagents and conditions: *i.* NaH/DMF, then MeI, 25 °C; *ii.* Li/NH_3, −50 °C; *iii.* MeONa/MeOH, 25 °C; *iv.* $CH_2{=}PPh_3$/THF, 25 °C.

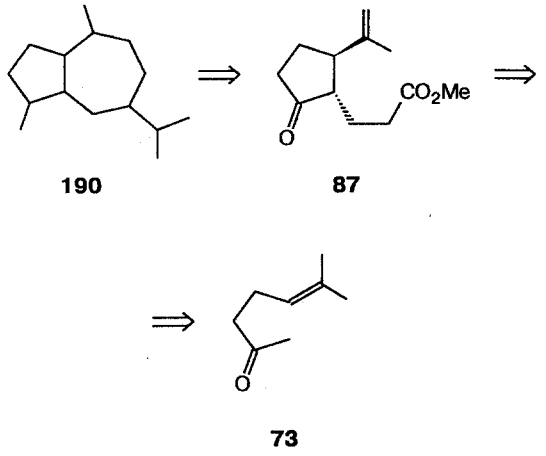
Starting from **98**, the crystalline product of its C-methylation (**187**) was initially prepared, then transformed smoothly to *trans*-disubstituted cyclopentanone **188**. Wittig methylenation of ketone **188** afforded target C_{15}-hydrocarbon **189** in >70 % yield and stereochemical purity of *ca.* 95 %. **189** possesses the backbone typical of metabolites of some fungi (*e.g.*, see Ref. 79).

2.6. Synthesis of compounds of guaiane series

Sesquiterpenoids of guaiane series **190** are products of metabolism of numerous plants. The high pharmacological and pesticidal activities recently revealed for compounds of this class[80] makes extensive elaboration of their syntheses on the basis of accessible starting materials important. Two novel variants of the synthesis of carbon skeleton **190** based on methylheptenone **73** as the starting compound are discussed below (Scheme 36). Stereocontrolled transformation of **73** to cyclopentane SB **87**, common to both schemes, was considered in Section 1.3.1.

According to the first one, ketone **87** was primarily transformed to ethylene ketal **191**, reduction of the

Scheme 36



latter with DIBAH smoothly afforded aldehyde **192** (see Ref. 81) (Scheme 37). An attempt to involve **192** in the desired 7-*exo*-cyclization under conditions of Lewis acidcatalyzed Prince reaction unexpectedly yielded transketalization product **193**. The similar approach based on the ability of unsaturated acetals to undergo intramolecular reaction of ene type under the same conditions also failed in the case of **193**; for example, treatment of **193** with $SnCl_4$ resulted in resinification products.

The negative result of CC for **193** is evidently related to the presence of carbonyl group in its molecule, for this reason it was transformed to methylcarbinol group. Grignard reaction appeared highly stereoselective in the case of ketone **193**, and thus prepared tertiary alcohol **194** was used later in a form of silyl ether **195**. The latter easily undergoes the desired cyclization in the presence of $SnCl_4$ to form C(6)-epimeric bicyclic products **196** ($\alpha/\beta \approx 2:1$) subsequently transformed by routine procedures to hydroazulenone **197**. Evidently, functionalization of the latter allows its transformation to compounds of **190** series.

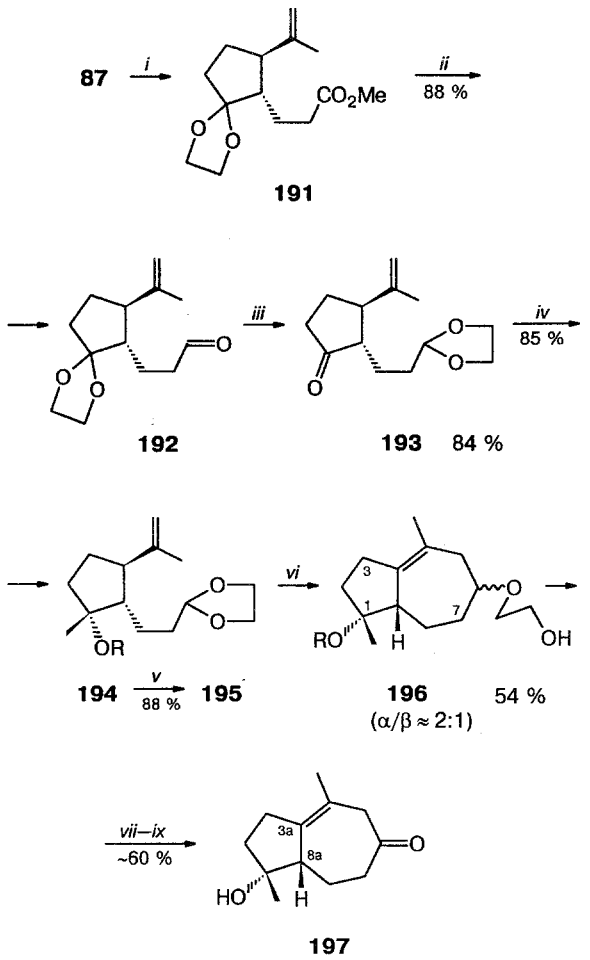
The shorter route from ketoester **87** to bicyclic precursors of **190**[82] appeared to be possible through the stage of its selective transformations to allyl sulfone **96**, which was easily methylenated to diolefin **198** (Scheme 38).

The latter easily undergoes Dieckmann-type cyclization by treatment with $NaN(SiMe_3)_2$ stereospecifically affording bicyclic sulfone **199**. Its desulfonylation proceeds practically without allylic shift of the C=C bond giving hydroazulenone **200**.

The further use of the latter to obtain target structures of **190** series required selective introduction of the C_3-fragment to the C(7) center of this molecule, that was achieved by means of one of modern variants of aldol condensation.

Thus, stepwise treatment of ketone **200** with LDA, $ZnCl_2$, and an acetone excess affords regio- and stereospecifically hydroxyketone **201** (75 % yield at *ca.* 40 % conversion of **200**). This is apparently a result

Scheme 37



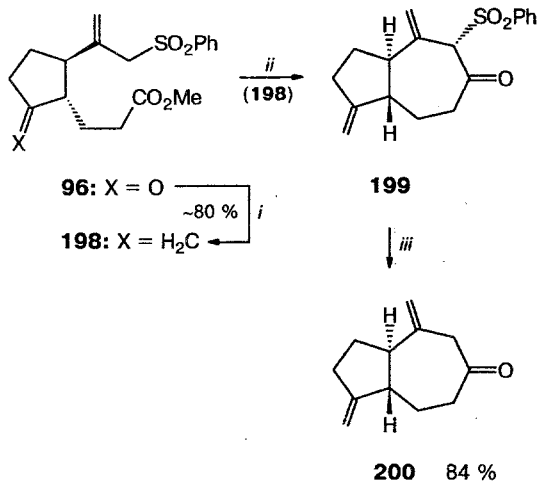
R = H (**194**); Bu^tMe_2Si (**195, 196**)

Reagents and conditions: *i.* $(CH_2OH)_2$/TsOH/PhH, Δ; *ii.* DIBAH/PhMe, −78→0 °C; *iii.* $ZnCl_2/CH_2Cl_2$, 25 °C; *iv.* MeMgI/Et_2O, −20→25 °C; *v.* $Bu^tMe_2SiSO_3CF_3$/2,6-lutidine/CH_2Cl_2, 0→25 °C; *vi.* $SnCl_4$/PhMe, −20 °C; *vii.* Bu^nLi/THF, −78 °C, then *p*-TsCl, then NaI/Zn/THF, Δ; *viii.* $(COCl)_2$/DMSO/CH_2Cl_2, −60 °C, then Et_3N; *ix.* HF(aq.)/MeOH/THF, 25 °C.

of electrophilic attack of a kinetically controlled $\Delta^{4(10),6}$-enolate of the **202** type, rather than a thermodynamically preferable dienolate of the **203** type, which appears inactive under the reaction conditions. The latter gives parent ketone **200** upon hydrolytic decomposition of the reaction mixture (Scheme 39).

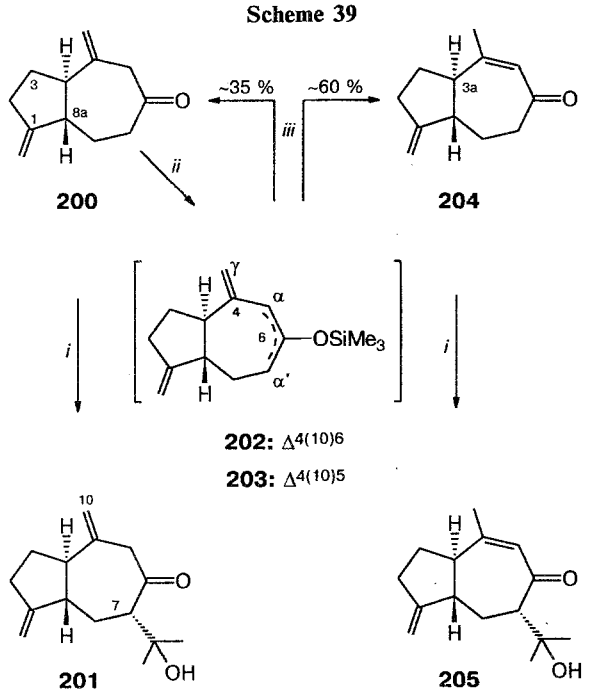
The above information is not in conflict with the data on silylation of ketone **200**. Thus, its treatment with LDA and then Me_3SiCl affords a mixture vinylsilyl ethers **202** and **203** (*ca.* 2:3). During mild hydrolysis of the mixture, a mixture of ketone β,γ-**200** and α,β-unsaturated **204** (readily separable by chromatography) is formed in a high yield; the ratio **200/204** is similar to

Scheme 38



Reagents and conditions: *i.* $CH_2Br_2/Zn/TiCl_4/CH_2Cl_2$, 25 °C; *ii.* $NaN(SiMe_3)_2/PhH$, 25 °C; *iii.* Al/Hg/EtOH, 25 °C.

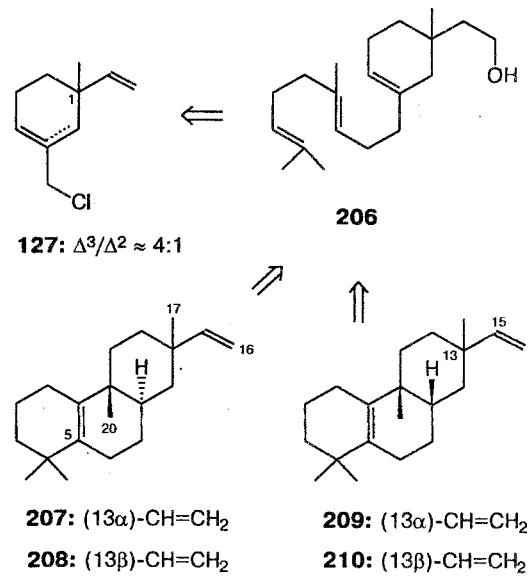
Scheme 39



Reagents and conditions: *i.* LDA/THF, −78 °C, then $ZnCl_2$, then Me_2CO, −45 °C; *ii.* LDA/THF, −10 °C, then Me_3SiCl/Et_3N/THF, −10 °C; *iii.* H_2SO_4(aq.)/THF, 25 °C.

that found for silyl ethers. The major product **204** evidently arises due to the characteristic of 1-silyloxy-1,3-dienes[83] preferable electrophilic attack of their γ-position that is related to the primary protonation of the C(10) center in ether **203**. The aldol condensation of ketone **204** with acetone under the above conditions also appears stereospecific thus yielding ketol **205** (*ca.* 70 %) with complete conversion of the starting material.

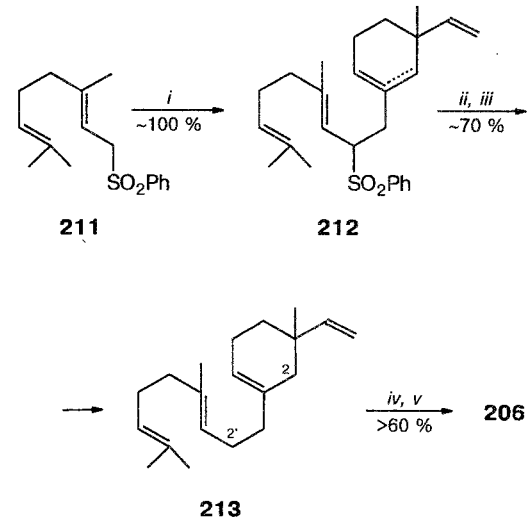
Scheme 40



2.7. Synthesis of diterpenes of rosane series

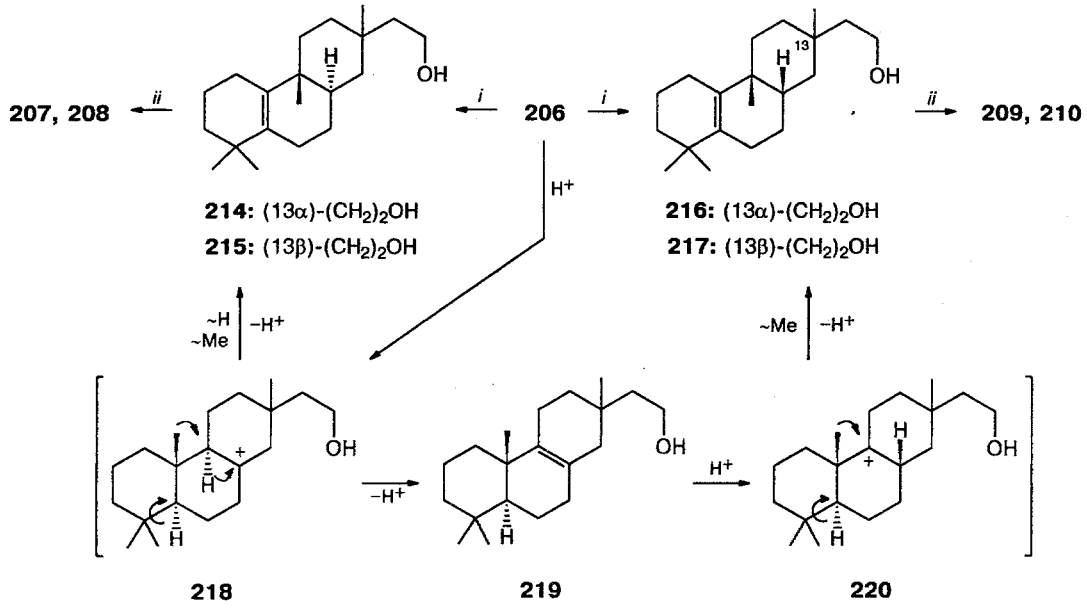
It was noted in Section 1.3.2 that dimethylvinylcyclohexenes formed in CC of α-monoterpenols are structurally similar to the fragments of tricyclic diterpenes of the pimarane/rosane group; hence it is possible to use them in total synthesis of the latter (Scheme 40).

Scheme 41



Reagents and conditions: *i.* $Bu^nLi/n\text{-}C_6H_{14}$/THF/HMPA, −78 °C, then **127**/THF; *ii.* Li/NH_3/THF, −78 °C; *iii.* SiO_2/10 % $AgNO_3$; *iv.* 9-BBN/THF, 0→25 °C; *v.* H_2O_2/15 % aq. NaOH, 0→25 °C.

Scheme 42



Reagents and conditions: *i.* HSO_3F/Pr^iNO_2, −80 °C; *ii.* NaH/THF, 60 °C, then CS_2, 0→60 °C, then NaI, then PhMe, Δ (in a sealed tube).

According to one of the variants, building of the carbon skeleton of racemic *trans*-**B/C-207, 208** and *cis*-**B/C**-rosadiene **209, 210** was performed through CC of their **A/B**-seco-precursor **206**.

The latter was prepared from allyl chloride Δ^3-**127** (available as a mixture with *ca.* 20 % of its Δ^2-regioisomer, see Section 1.3.2) in three steps including condensation of **127** with geranyl sulfone **211**[84] (Scheme 41). Reductive desulfonylation of intermediate sulfone **212** afforded diterpenoid **213**. After careful purification from the admixture of $\Delta^{2'}$-isomer, **213** was smoothly transformed to target alcohol **206** by selective anti-Markovnikov hydroxylation.

The optimum conditions for CC of the latter are use of *ca.* 10 mol. eq. of fluorosulfonic acid at −80 °C. The CC yields a mixture of tetracyclic alcohols **214/215/216/217** (*ca.* 90 %) in the ratio of *ca.* 3:1:4:3 (Scheme 42).[85]

One can explain the formation of *trans*-**B/C-C**(13)-epimers **214** and **215** assuming carbenium ion intermediate **218**. Predominant *cis*-**B/C**-rosenols **216** and **217** probably arise due to kinetically controlled protonation of pimarenol **219** (however, we failed to observe it among the reaction products) affording ion **220** and the further *syn*-1,2-methyl shift in the latter. Individual components of the reaction mixture **214—217** were isolated by preparative chromatography on SiO_2 and subsequently transformed to corresponding target tricyclic hydrocarbons **207—210** by dehydration.

References

1. (a) H. O. Huisman, *Pure and Appl. Chem.*, 1977, **49**, 1307; (b) G. Cainelli and G. Cardillo, *Accounts Chem. Res.*, 1981, **14**, 89.
2. A. M. Moiseenkov, E. V. Polunin, and A. V. Semenovsky, *Tetrahedron Lett.*, 1979, 4759; E. V. Polunin, A. M. Moiseenkov, and A. V. Semenovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1981, 1354 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1981, **30**, No. 6 (Part 2) (Engl. Transl.)].
3. A. M. Moiseenkov, E. V. Polunin, and A. V. Semenovsky, *Tetrahedron Lett.*, 1981, 3309; A. M. Moiseenkov, M. A. Novikova, E. V. Polunin, and S. I. Torgova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1983, 1557 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1983, **32**, 1407 (Engl. Transl.)].
4. A. M. Moiseenkov, V. V. Veselovsky, Z. G. Makarova, V. M. Zhulin, and W. A. Smit, *Tetrahedron Lett.*, 1984, **25**, 5929; V. V. Veselovsky, Z. G. Makarova, A. I. Lutsenko, W. A. Smit, A. M. Moiseenkov, and V. M. Zhulin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 811 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 738 (Engl. Transl.)].
5. V. M. Zhulin and S. I. Volchek, *Khim. Geterotsikl. Soedin.*, 1979, 1443 [*Chem. Heterocycl. Compd.*, 1979 (Engl. Transl.)].
6. G. Glaros and S. Sullivan, *Synthetic Commun.*, 1976, **6**, 495; B. B. Snider, *J. Org. Chem.*, 1981, **46**, 3155; N. A. Meanwell and C. R. Johnson, *Synthesis*, 1982, 283.
7. G. Kresze and W. Koshban, *Liebigs Annalen Chem.*, 1970, **731**, 67.
8. (a) W. E. Truce, C. T. Goralski, L. W. Christensen, and R. H. Bavry, *J. Org. Chem.*, 1970, **35**, 4217; (b) P. J. R. Nederlof, M. J. Moolenaar, E. R. de Waard, and H. O. Huisman, *Tetrahedron*, 1978, **34**, 447.

9. V. V. Veselovsky, V. A. Koptenkova, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 2296 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 2110 (Engl. Transl.)].
10. M. Ladlow and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1107.
11. V. V. Veselovsky, S. P. Skorobogatov, M. A. Novikova, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 591 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 513 (Engl. Transl.)].
12. Y. Masaki, K. Sakuma, and K. Kaji, *Chem. Pharm. Bull.*, 1985, **33**, 1930.
13. A. M. Moiseenkov, K. V. Lebedeva, and B. A. Czeskis, *Usp. Khim.*, 1984, **53**, 1709 [*Russ. Chem. Rev.*, 1984, **53**, 989 (Engl. Transl.)].
14. E. E. van Tamelen, *Accounts Chem. Res.*, 1968, **1**, 111.
15. N. Rabjohn, in *Organic Reactions*, Ed. W. G. Dauben, John Wiley, New York, 1976, **24**, 261.
16. K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, 1973, **95**, 6136; A. Pfenningen, *Synthesis*, 1986, 89.
17. A. M. Moiseenkov, V. A. Dragan, V. A. Koptenkova, and V. V. Veselovsky, *Synthesis*, 1987, 814; V. V. Veselovsky, V. A. Dragan, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 2787 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 2583 (Engl. Transl.)].
18. V. V. Veselovsky, V. A. Dragan, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 1906 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 1734 (Engl. Transl.)].
19. D. A. Evans and G. C. Andrews, *Accounts Chem. Res.*, 1974, **7**, 147.
20. G. Büchi and H. Wüest, *Helv. Chim. Acta*, 1967, **50**, 2440; R. Chen and D. A. Rowand, *J. Am. Chem. Soc.*, 1980, **102**, 6609; K. Mori, M. Waku, and M. Sakakibara, *Tetrahedron*, 1985, **41**, 2825.
21. V. A. Dragan and A. M. Moiseenkov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 105 [*Russ. Chem. Bull.*, 1993, **42**, 95 (Engl. Transl.)].
22. W. O. Ranky and D. G. Nelson, in *Organic Sulfur Compounds*, Ed. N. Kharasch, Pergamon Press, New York, 1961, Ch. 17; K. Mislow, T. Simmons, J. T. Melillo, and A. L. Terney, Jr., *J. Am. Chem. Soc.*, 1964, **86**, 1452; D. Landini, F. Montanary, H. Hogeveen, and G. Maccagnani, *Tetrahedron Lett.*, 1964, 2691; J. P. Marino, in *Topics in Sulfur Chemistry*, Ed. A. Senning, G. Thieme Publ., Stuttgart, 1976, **1**; A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.
23. A. Queen, A. E. Lemire, A. F. Janzen, and M. N. Paddon-Row, *Canad. J. Chem.*, 1978, **56**, 2884.
24. A. M. Moiseenkov, V. A. Dragan, A. V. Lozanova, and V. V. Veselovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 1797 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1988, **37**, 1603 (Engl. Transl.)].
25. W. A. Smit, N. S. Zefirov, I. V. Bodrikov, and M. Z. Krimer, *Accounts Chem. Res.*, 1979, **12**, 282.
26. V. V. Veselovsky, V. A. Dragan, N. M. Gafurov, S. M. Adekenov, A. D. Kagarlitskii, B. I. Maximov, O. S. Chizhov, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 2423 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1988, **37**, 2185 (Engl. Transl.)].
27. M. Bulliard, G. Balme, and J. Gore, *Tetrahedron Lett.*, 1989, **30**, 5767.
28. A. Dossena, R. Marchelli, and G. Casnati, *Gazz. Chim. Ital.*, 1985, **115**, 29.
29. A. M. Moiseenkov, V. A. Dragan, and V. V. Veselovsky, *Usp. Khim.*, 1991, **60**, 1255 [*Russ. Chem. Rev.*, 1991, **60**, 643 (Engl. Transl.)].
30. V. V. Veselovsky, V. A. Dragan, and A. M. Moiseenkov, *Tetrahedron Lett.*, 1988, **29**, 6637; A. M. Moiseenkov, V. A. Dragan, and V. V. Veselovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 365 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 314 (Engl. Transl.)].
31. (a) A. C. Knipe, in *The Chemistry of the Sulphonium Group*, Eds. C. J. M. Stirling and S. Patai, John Wiley and Sons, New York, 1981, Part 1, 313; (b) A. Fava, in *Studies in Organic Chemistry*, **19**. *Organic Sulfur Chemistry: Theoretical and Experimental Advances*, Eds. F. Bernardy, I. G. Csizmadia, and A. Mangini, Elsevier, Amsterdam, 1985, 299.
32. A. M. Moiseenkov, V. V. Veselovsky, Z. G. Makarova, and V. M. Zhulin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 1143 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 1057 (Engl. Transl.)].
33. V. V. Veselovsky and A. M. Moiseenkov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 113 [*Russ. Chem. Bull.*, 1993, **42**, 102 (Engl. Transl.)].
34. D. G. Farum, T. Veysoglu, A. M. Carde, B. Duhl-Emswiler, T. A. Pancoast, and T. J. Reitz, *Tetrahedron Lett.*, 1977, 4009.
35. T. Nishio and Y. Omote, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1703; H. Nishiyama and M. Sasaki, *Chem. Lett.*, 1981, 1363.
36. F. Erman, in *Studies in Organic Chemistry*, Ed. P. G. Gassman, Marcel Dekker Inc., New York, 1985, **11A**, 725.
37. B. T. Zhuzbaev, S. M. Adekenov, and V. V. Veselovsky, *Usp. Khim.*, 1995, **64**, 198 [*Russ. Chem. Rev.*, 1995, **64** (Engl. Transl.)].
38. B. T. Zhuzbaev, V. V. Veselovsky, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 1569 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 1386 (Engl. Transl.)].
39. B. T. Zhuzbaev, V. V. Veselovsky, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 2578 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 2252 (Engl. Transl.)].
40. H. Ishibashi, S. Harada, M. Okada, and M. Ikeda, *Synthesis*, 1986, 847.
41. V. V. Veselovsky, B. T. Zhuzbaev, S. M. Adekenov, A. S. Shashkov, and A. M. Moiseenkov, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 658 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 517 (Engl. Transl.)].
42. F. Cooke and P. Magnus, *J. Chem. Soc., Chem. Commun.*, 1976, 519; B. M. Trost and J. E. Vincent, *J. Am. Chem. Soc.*, 1980, **102**, 5680.
43. G. Quinkert, H.-G. Schmalz, E. Walzer, S. Gross, T. Kowalczyk-Przewloka, C. Schierloh, G. Dürner, I. W. Bats, and H. Kessler, *Liebigs Annalen Chem.*, 1988, 283.
44. V. V. Veselovsky, B. T. Zhuzbaev, K. M. Turdybekov, S. M. Adekenov, Yu. T. Struchkov, and A. M. Moiseenkov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 118 [*Russ. Chem. Bull.*, 1993, **42**, 106 (Engl. Transl.)].
45. V. V. Veselovsky, A. V. Belyankin, B. I. Maximov, Yu. A. Strelenko, and A. M. Moiseenkov, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 377 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 292 (Engl. Transl.)].
46. W. Dehaen and A. Hassner, *Tetrahedron Lett.*, 1990, **31**, 743.
47. V. A. Tartakovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 165 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 147 (Engl. Transl.)].
48. A. M. Moiseenkov, A. V. Belyankin, A. V. Buevich, and V. V. Veselovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 461 [*Russ. Chem. Bull.*, 1994, **43**, 420 (Engl. Transl.)].
49. A. A. Akhrem, A. M. Moiseenkov, and Yu. D. Kaznacheev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1967, 2336 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1967 (Engl. Transl.)].
50. E. E. van Tamelen, *Accounts Chem. Res.*, 1975, **8**, 152; W. S. Johnson, *Angew. Chem. Int. Ed. Engl.*, 1976, **15**, 9; F. Erman, in *Studies in Organic Chemistry*, Ed. P. G. Gassman, Marcel Dekker Inc., New York, 1985, **11A**, 329.

51. L. Novak, L. Poppe, Cs. Szantay, and E. Szabo, *Synthesis,* 1985, 939.
52. V. V. Veselovsky, V. A. Dragan, and A. M. Moiseenkov, *Tetrahedron Lett.,* 1990, **31**, 1187; A. M. Moiseenkov, V. V. Veselovsky, V. A. Dragan, A. V. Ignatenko, and Yu. A. Strelenko, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1990, 1368 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.,* 1990, **39**, 1233 (Engl. Transl.)].
53. E. Wenkert, *Chem. Industry* (London), 1955, 282.
54. A. M. Moiseenkov, V. A. Dragan, V. V. Veselovsky, B. A. Czeskis, N. A. Shpiro, and A. S. Shashkov, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1990, 1361 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.,* 1990, **39**, 1226 (Engl. Transl.)].
55. S. O. Simonian, W. A. Smit, A. S. Gybin, A. S. Shashkov, G. S. Mikaelian, V. A. Tarasov, I. I. Ibragimov, R. Caple, and D. E. Froen, *Tetrahedron Lett.,* 1986, **27**, 1245; W. A. Smit, S. I. Pogrebnoi, Yu. B. Kalyan, and M. Z. Krimer, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1987, 959 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.,* 1987, **36**, 888 (Engl. Transl.)].
56. V. V. Veselovsky, A. S. Gybin, A. V. Lozanova, A. M. Moiseenkov, W. A. Smit, and R. Caple, *Tetrahedron Lett.,* 1988, **29**, 175; V. V. Veselovsky, A. S. Gybin, A. V. Lozanova, A. M. Moiseenkov, and W. A. Smit, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1990, 107 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.,* 1990, **39**, 94 (Engl. Transl.)].
57. A. S. Onishchenko, *Diene Synthesis,* Davey, New York, 1964; H. Wollveber, *Diels—Alder Reaction,* Thieme, Stuttgart, 1972.
58. L. H. Little, *Infrared Spectra of Adsorbed Species,* Academic Press, New York, 1966.
59. F. M. Menger, *Accounts Chem. Res.,* 1985, **18**, 128.
60. F. W. Hemming, *Biosci. Rep.,* 1982, **2**, 203; F. W. Hemming, *New. Comp. Biochem.,* 1985, **10**, 261; J. W. Rip, C. A. Rupar, K. Ravi, and K. K. Carrol, *Progr. Lipid Res.,* 1985, **24**, 269; V. N. Shibaev, *Adv. Carbohydr. Chem. Biochem.,* 1987, **44**, 277.
61. N. Ya. Grigorieva, V. V. Veselovsky, and A. M. Moiseenkov, *Khim.-Farm. Zhurn.,* 1987, 845; V. V. Veselovsky, N. Ya. Grigorieva, and A. M. Moiseenkov, *Chem. Phys. Lipids,* 1989, **51**, 147; A. M. Moiseenkov, N. Ya. Grigorieva, and V. V. Veselovsky, *Zh. Vsesoyuz. Khim. obshch. im. D. I. Mendeleeva,* 1991, 435 [*Mendeleev Chem. J.,* 1991 (Engl. Transl.)]; N. Ya. Grigorieva and O. A. Pinsker, *Usp. Khim.,* 1994, **63**, 177 [*Russ. Chem. Rev.,* 1994, **63**, 169 (Engl. Transl.)].
62. G. Jommi, L. Verotta, P. Gariboldi, and P. Gabetta, *Gazz. Chim. Ital.,* 1988, **118**, 823.
63. V. V. Veselovsky, V. A. Koptenkova, M. A. Novikova, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1989, 2052 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.,* 1989, **38**, 1887 (Engl. Transl.)].
64. S. Suzuki, F. Mori, T. Takigawa, K. Ibata, J. Ninagawa, T. Nishida, M. Mizuno, and Y. Tanaka, *Tetrahedron Lett.,* 1983, **24**, 5103.
65. L. L. Danilov, T. N. Druzhinina, N. A. Kalinchuk, S. D. Mal'tsev, and V. N. Shibaev, *Chem. Phys. Lipids,* 1989, **51**, 191.
66. M. A. Novikova, A. V. Lozanova, V. V. Veselovsky, V. A. Dragan, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1987, 356 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.,* 1987, **36**, 315 (Engl. Transl.)].
67. A. M. Moiseenkov, V. A. Koptenkova, and V. V. Veselovsky, *Dokl. Akad. Nauk SSSR,* 1988, **299**, 1402; V. V. Veselovsky, V. A. Koptenkova, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1989, 372 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.,* 1989, **38**, 321 (Engl. Transl.)].
68. J.-F. Biellmann and J.-B. Ducep, in *Organic Reactions,* Ed. W. G. Dauben, John Wiley, New York, 1982, **27**, 1.
69. K. H. Kubeczka, G. Schmaus, and V. Formacek, in *Progress Essential Oil Res., Proc. XVI Intern. Symp. Essential Oils,* 1986, 271, *Chem. Abstrs.,* 1986, **105**, 120461j.
70. Z. Horii, Y. Ozaki, K. Nagao, and S.-W. Kim, *Tetrahedron Lett.,* 1978, 5015.
71. T. Mandai, K. Osaka, M. Kawagishi, M. Kawada, and J. Otera, *J. Org. Chem.,* 1984, **49**, 3595; M. Petrzilka and J. I. Grayson, *Synthesis,* 1981, 753; P. J. Proteau and P. B. Hopkins, *J. Org. Chem.,* 1985, **50**, 141; R. R. Schmidt, *Acc. Chem. Res.,* 1986, **19**, 250.
72. V. V. Veselovsky, Z. G. Makarova, A. I. Lutsenko, N. A. Shpiro, V. M. Zhulin, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1988, 810 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.,* 1988, **37**, 692 (Engl. Transl.)].
73. K. Gollnick and G. Schade, *Tetrahedron,* 1966, **22**, 133.
74. K. Mori, in *The Total Synthesis of Natural Products,* Ed. J. ApSimon, John Wiley & Sons Inc., New York, 1992, **9**, 320.
75. V. A. Dragan, V. V. Veselovsky, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1989, 1143 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.,* 1989, **38**, 1038 (Engl. Transl.)].
76. W. Oppolzer and E. J. Jacobsen, *Tetrahedron Lett.,* 1986, **27**, 1141; B. M. Trost and K. Matsuda, *J. Am. Chem. Soc.,* 1988, **110**, 5233; B. Hanquet, B. Tabyaoui, J.-C. Caille, M. Farnier, and R. Guilard, *Canad. J. Chem.,* 1990, **68**, 620; G. Agnel, Z. Owczarczyk, and E. Negishi, *Tetrahedron Lett.,* 1992, **33**, 1543; Y. Yokoyama and K. Tsuchikura, *Tetrahedron Lett.,* 1992, **33**, 2823.
77. A. M. Moiseenkov, A. V. Belyankin, A. V. Buevich, and V. V. Veselovsky, *Izv. Akad. Nauk, Ser. Khim.,* 1995, 1581 [*Russ. Chem. Bull.,* 1995, **44**, 1520 (Engl. Transl.)].
78. C.-J. Xu, X.-Y. Zeng, and D.-Q. Yu, *Yaoxue Xuebao* (*Acta Pharm. Sinica*), 1985, **20**, 652, *Chem. Abstrs.,* 1986, **104**, 65906k.
79. S. Nazoe, M. Goi, and N. Morisaki, *Tetrahedron Lett.,* 1970, 1293; J. R. Hanson, P. B. Hitchcock, and R. Nyfeler, *J. Chem. Soc., Perkin Trans. I,* 1975, 1586.
80. E. Rodrigues, G. H. N. Towers, and J. C. Mitchel, *Phytochemistry,* 1976, **15**, 1573; A. K. Picman, *Biochem. Syst. Ecol.,* 1986, **14**, 225; A. D. Kagarlitskii, S. M. Adekenov, and A. N. Kupriyanov, *Seskviterpenovye laktony rastenii Tsentral'nogo Kazakhstana* [*Sesquiterpene Lactones from Plants of Central Kazakhstan*], Nauka Kaz. SSR, Alma-Ata, 1987 (in Russian).
81. B. T. Zhuzbaev, V. V. Veselovsky, A. V. Buevich, and A. M. Moiseenkov, *Izv. Akad. Nauk, Ser. Khim.,* 1993, 122 [*Russ. Chem. Bull.,* 1993, **42**, 110 (Engl. Transl.)].
82. A. M. Moiseenkov, B. T. Zhuzbaev, V. V. Veselovsky, K. M. Turdybekov, A. V. Buevich, S. M. Adekenov, and Yu. T. Struchkov, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1993, 126 [*Russ. Chem. Bull.,* 1993, **42**, 113 (Engl. Transl.)].
83. I. Fleming, J. Goldhill, and I. Paterson, *Tetrahedron Lett.,* 1979, 3205.
84. V. A. Dragan, V. V. Veselovsky, E. D. Daeva, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1991, 857 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.,* 1991, **40**, 757 (Engl. Transl.)].
85. V. A. Dragan, V. V. Veselovsky, and A. M. Moiseenkov, *Mendeleev Commun.,* 1991, 36; A. M. Moiseenkov, V. A. Dragan, V. V. Veselovsky, and A. S. Shashkov, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1991, 1896 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.,* 1991, **40**, 1682 (Engl. Transl.)].

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