Reviews

Synthesis of sesquiterpenoids of the drimane group from labdane diterpenoids

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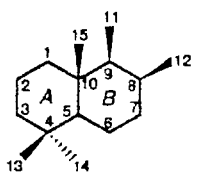
Data on the partial synthesis of enantiomerically pure sesquiterpenoids of the drimane group, including valuable biologically active natural compounds, from accessible labdane diterpenoids are surveyed.

Key words: drimane sesquiterpenoids, synthesis from labdane diterpenoids; sclareol, manool, neoabienols; zamoranic, labdanolic, and *trans*-communic acids; hispanolone, drimenol, polygodial, warburganal.

Introduction

The group of drimane sesquiterpenoids comprises compounds based on the carbon skeleton of drimane (**1**).[1] The name "drimane," proposed in 1959,[2] comes from the South American plant called *Drimys Winteri* Forst, from whose wood the parent compound of this group, drimenol (**2**), was isolated. These compounds proved to occur fairly frequently in nature. They have been found in higher plants, fungi, bacteria, mollusks, marine sponges, and other marine organisms.[3]



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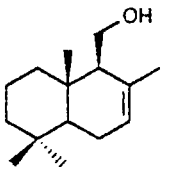

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Many drimane compounds are of certain practical interest, since they possess high biological activities. Among this group, there are substances exhibiting antimicrobial, antifungal, antifeedant, antiviral, immunomodulating (anticomplement), cytotoxic, phytotoxic, growth-controlling, *etc.*, activities.[3] The biological activity of drimane sesquiterpenoids has been considered in detail in a special review[3] and is not discussed here. The practically valuable properties of drimanes, on the one hand, and the fact that their contents in natural sources are relatively low, on the other hand, have stimulated studies on their synthesis.

Synthetic studies in the drimane series are of interest not only regarding the ultimate identification and the investigation of properties of natural biologically active compounds but also for the preparation of their analogs with simpler structures. In previous studies, mostly total syntheses of drimanes have been described;[4—6] they suffer from two drawbacks: first, most of them involve multistep procedures and, second, they yield racemic products. As a rule, only natural forms (single optical isomers) are biologically active; however, their proportions in the synthetic products cannot exceed 50%.

The structures of drimanes are similar to those of natural di-, sester- and triterpenoids; therefore, the lat-

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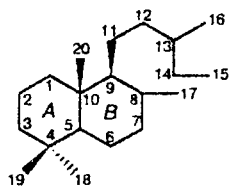
ter can be used for the synthesis of drimanes. An advantage of these partial syntheses (semisyntheses) is that in this case, drimanes are obtained in their natural optically active forms. Semi-syntheses of drimanes have been carried out mostly starting from tricyclic and bicyclic diterpenoids. However, bicyclic diterpenoids of the labdane group are still the most suitable starting compounds for the preparation of drimanes, because the carbon skeleton of labdane (**3**) is the closest in structure to that of drimane **1**, and, in addition, many of these compounds, for example, sclareol (**4**), manool (**5**), *cis*- and *trans*-neoabienols (**6a** and **6b**) and some others, are easily accessible.



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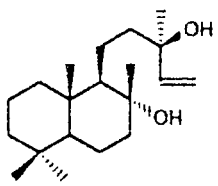

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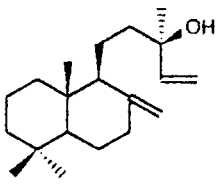

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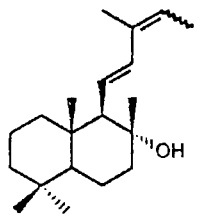


6a (13*Z*)
6b (13*E*)

Data on the raw material sources from which most of these labdanoids have been isolated, their accessibility, the contents of the target compounds in them, methods for their isolation, and industrial production of some labdane diterpenoids have been summarized in our monograph.[7] For those few labdanoids that were not covered by this publication,[7] similar data are given in the beginning of the corresponding sections.

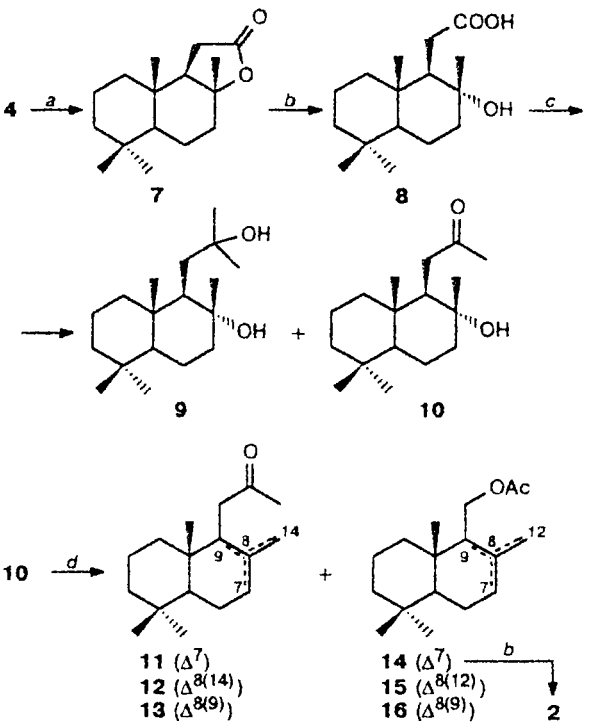
Despite the fact that some of the problems of the synthesis of drimanes from labdane diterpenoids have already been considered,[6] the published information was not exhaustive. In addition, the most interesting results in this field have been obtained over the last five years.

In this review, we survey the results of our studies and literature data (published before 1996). The partial syntheses of drimane derivatives are grouped according to the structures of the initial labdanoids.

Synthesis of drimanes from sclareol

The first synthesis of drimanes from labdane diterpenoids (Scheme 1)[8] was based on norambreinolide (**7**), a valuable product of oxidative cleavage of sclareol **4**. The development of methods for the synthesis of this compound attracts considerable attention.[7,9–13] The product of alkaline hydrolysis of norambreinolide **7**, hydroxy acid **8**, reacts with MeLi to give a mixture of diol **9** and hydroxy ketone **10** (their yields with allowance for the recovered initial compound (23%) were 18 and 80%, respectively).

Scheme 1



Reagents: *a*. CrO_3/AcOH; *b*. (1) NaOH—EtOH, (2) H^+; *c*. MeLi—Et_2O; *d*. $H_2O_2/BF_3 \cdot Et_2O$.

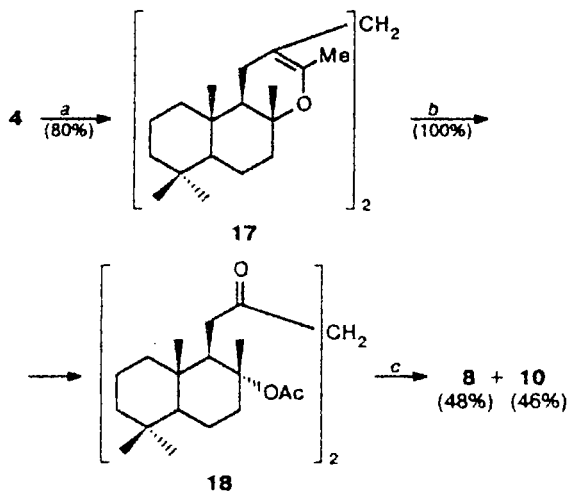
Oxidation of hydroxy ketone **10** with concentrated (93.6%) hydrogen peroxide in the presence of $BF_3 \cdot Et_2O$ gave a complex mixture of products, whose chromatography on silica gel impregnated with $AgNO_3$ afforded isomeric olefinic ketones **11**—**13**, drimenol acetate **14** (8.1%) and albicanyl acetate **15** (8.4%),* and their isomer **16** with a tetrasubstituted double bond (14.5%). The **14** : **15** : **16** ratio was 1.00 : 1.04 : 1.80. Natural drimenol **2** was obtained by alkaline hydrolysis of drimenyl acetate **14**.

Later,[10,11] a shorter pathway to hydroxy ketone **10** from sclareol **4** was developed. Ozonization of sclareol **4** in methanol and treatment of the ozonization product with ammonium chloride yielded compound **17**;[15] the latter is quantitatively converted into β-diketone **18** upon ozonization. Alkaline cleavage of compound **18**

* A biologically active substance, found later in marine organisms.[14]

gave a mixture of hydroxy acid **8** and hydroxy ketone **10** (Scheme 2).

Scheme 2

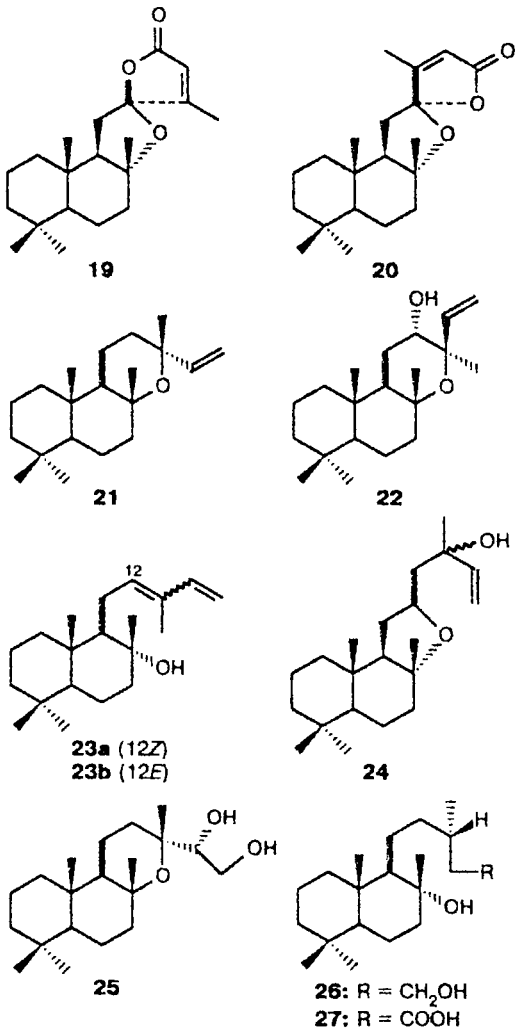


Reagents and conditions: *a*. (1) O_3—MeOH, (2) NH_4Cl; *b*. (1) O_3, (2) H_2O, Δ; *c*. KOH—EtOH.

It should be noted that norambreinolide **7** was prepared by the cleavage of not only sclareol **4** but also other labdane diterpenoids: α- and β-levantenolide (**19** and **20**, respectively),[16] manoyl oxide (**21**),[17—19] 12α-hydroxy-13-epimanoyl oxide (**22**),[20] *cis*-abienol (**23a**),[9,21—23] *trans*-abienol (**23b**),[9,24,25] stereoisomeric 8,12-epoxylabd-14-en-13-ols (**24**),[26] borjatriol (**25**),[27] labdane-8α,15-diol (**26**),[28,29] and labdanolic acid (**27**).[28,30] Thus, all syntheses of drimanes that include the step of preparation of norambreinolide **7** can be based on any of the above-listed labdanoids.

In a number of studies, norambreinolide **7** served as the starting compound for the synthesis of drimanes. For example, according to the published data,[31,32] by refluxing with concentrated H_2SO_4 in methanol, lactone **7** was converted into a mixture of unsaturated esters **28** and **29**;[33] oxidation of this mixture gave α,β-unsaturated keto ester **30**, which was decarboxylated during alkaline hydrolysis to yield drim-8(9)-en-7-one (**31**), a perfume[34] isolated from tobacco[35] (Scheme 3).

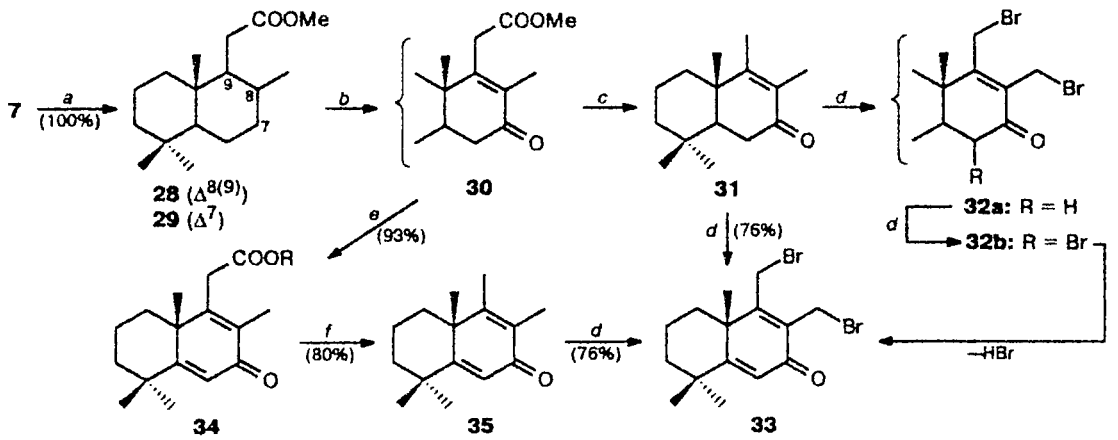
Due to the mutual arrangement of the functional groups and the C(6), C(11), and C(12) atoms activated by them in the molecule, ketone **31** is a valuable intermediate possessing its own "synthetic niche" on the way to important polyfunctional biologically active natural drimanes. However, the low yield of keto ester **30** (40—45%) in the oxidation remained the "bottle neck" of this synthesis, and numerous attempts to increase the yield by varying oxidants and reaction conditions failed. Electrooxidation of a mixture of esters **28** and **29** [36,37] was more successful. In this case, the yield of compound **30** was 60—65%. It was found that this yield depends on the proportion of isomer **28** in the initial mixture. The



mixture obtained by the method described previously[33] contained 66% compound **28**. Electrooxidation of individual compound **28** gives keto ester **30** in a yield of 80%. Due to the possibility of increasing the yield of compound **30** and the simplicity of its isolation, enone **31** has become a relatively easily accessible compound. Owing to this fact and to its valuable organoleptic properties, this compound is used as an important ingredient in compositions for aromatization of tobacco.[38]

Bromination of ketone **31** with *N*-bromosuccinimide (NBS) makes it possible to prepare, depending on the reaction conditions, dibromoketone **32a**, its mixture with tribromoketone **32b** and dibromodienone **33**, or dibromodienone **33** in good yields. Tribromoketone **32b** is unstable and readily eliminates HBr yielding dibromodienone **33**. The latter has also been obtained by a different method: keto ester **30** was dehydrogenated by SeO_2 to dienone keto ester **34**; the latter was converted into drima-5,8(9)-dien-7-one (**35**) by alkaline hydrolysis and decarboxylation. The yield of compound **35** based on the mixture of esters **28** and **29** amounted

Scheme 3



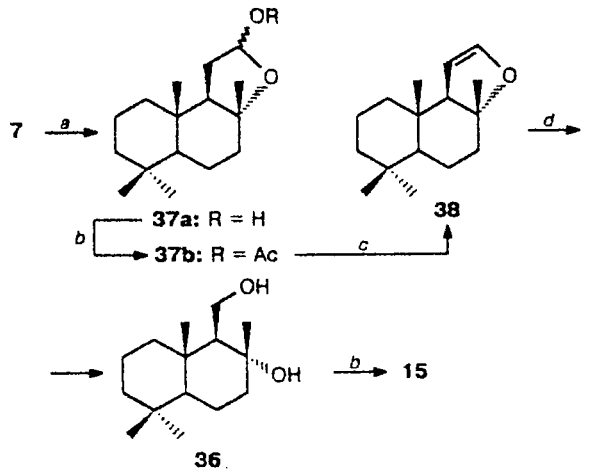
Reagents and conditions: *a*. MeOH/conc. H_2SO_4; *b*. $K_2Cr_2O_7$—AcOH; *c*. KOH—EtOH, Δ; *d*. NBS—CCl_4; *e*. SeO_2—dioxane; *f*. KOH—$(CH_2OH)_2$, Δ.

to 47%. The reaction of ketone **35** with NBS gave dibromodienone **33** (see Scheme 3).[37]

Compounds **31**, **32a**, **33**, and **35** can serve as the initial compounds in the syntheses of polyfunctional drimanes.

Based on norambreinolide **7**, Ohloff and Giersch[39] synthesized drimane-8α,11-diol (**36**) and albicanyl acetate **15** (Scheme 4). Norambreinolide **7** was reduced to semiacetal **37a**, which was converted into the corresponding acetate **37b** under standard conditions; the latter eliminates acetic acid on heating and thus yields cyclic vinyl ester **38**. The reductive ozonolysis of compound **38** gave diol **36**. Refluxing compound **36** with a Ac_2O + Py mixture led to albicanyl acetate **15**. The efficiency of this method is difficult to evaluate, because no description of the experiment is presented in the publication cited.[39]

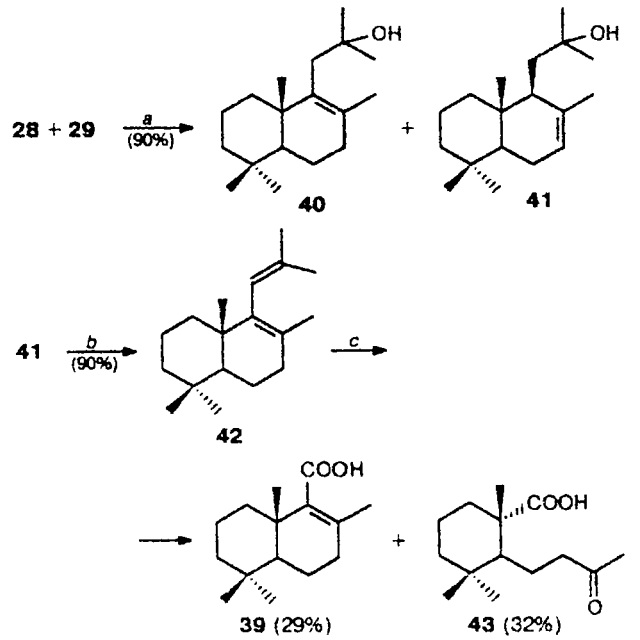
Scheme 4



Reagents and conditions: *a*. Bu^i_2AlH; *b*. Ac_2O/Py; *c*. 350 °C; *d*. (1) O_3—EtOH, (2) $NaBH_4$.

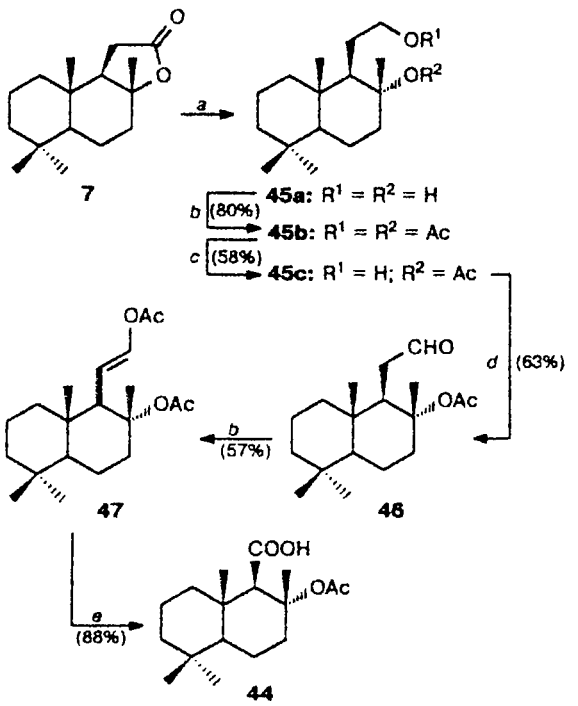
Norambreinolide **7** also served as the starting compound in the synthesis of drim-8(9)-en-11-oic acid (**39**) (Scheme 5).[40] The mixture of esters **28** and **29** obtained from it[33] was converted into a mixture of isomeric unsaturated alcohols **40** and **41** (1.0 : 2.3), which were separated by chromatography. Alcohol **40** reacted with *p*-toluenesulfonic acid to give a complex mixture of products, while its isomer **41** was converted under the same conditions into conjugated diene **42**. Ozonization of the latter gave a mixture of acids **39** and **43**. However,

Scheme 5



Reagents and conditions: *a*. MeLi—Et_2O; *b*. TsOH—C_6H_6, Δ; *c*. O_3—AcOEt/Py.

Scheme 6



Reagents: *a*. $LiAlH_4$—Et_2O; *b*. Ac_2O—DMAP—NEt_3; *c*. $NaHCO_3$—MeOH; *d*. $CrO_3 \cdot 2Py/CH_2Cl_2$; *e*. O_3—AcOEt/Py.

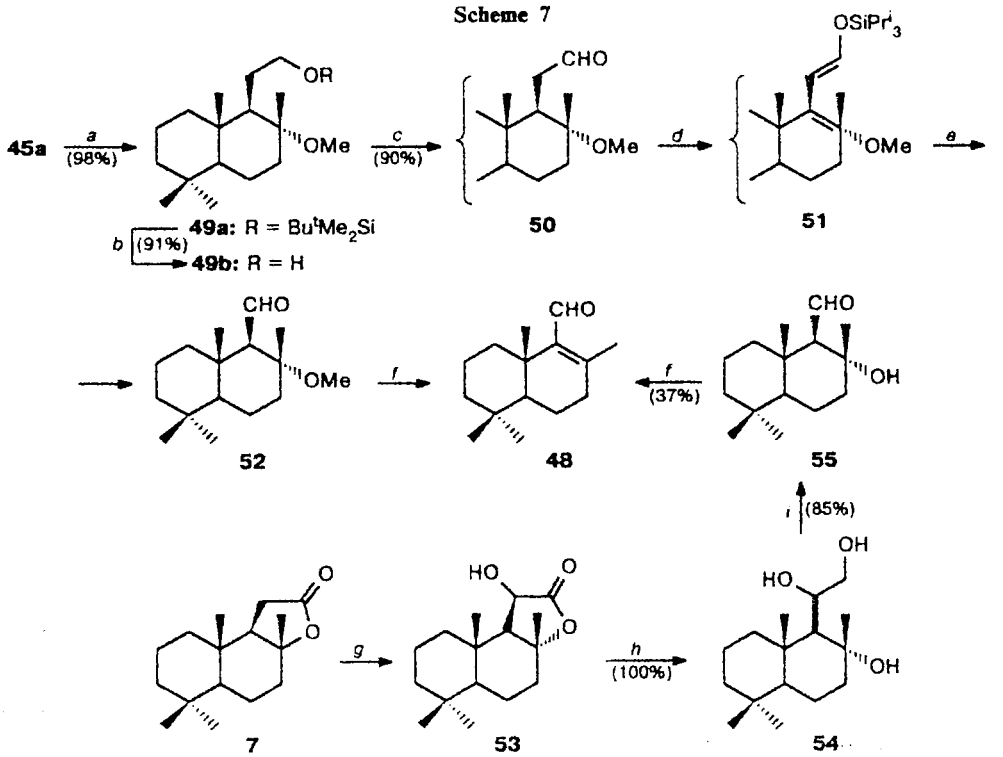
the selectivity of ozonization was low, and, therefore, the overall yield of the target acid **39** based on norambreinolide **7** amounted to 16%.

Lactone **7** also gave rise to 8α-acetoxydriman-11-oic acid (**44**) (Scheme 6).[41] The product of the hydride reduction of lactone **7**, diol **45a**,[7] was converted into diacetate **45b**, which was selectively hydrolyzed to hydroxy acetate **45c** and then oxidized according to Collins to acetoxy aldehyde **46**. Enolacetylation of compound **46** followed by chromatography of the reaction product yielded *trans*-enol acetate **47**, which was cleaved by ozone in the presence of pyridine to give acetoxyacid **44**. The overall yield of acid **44** based on diol **45a** was 16%.

Drim-8(9)-en-11-al (**48**), an intermediate compound in the synthesis of substances inhibiting the *in vivo* transfer of cholesterol esters was synthesized from diol **45a** (Scheme 7).[42] Diol **45a** was converted into diether **49a**, which was subjected to selective hydrolysis followed by Swern oxidation to give methoxy aldehyde **50**. The latter was cleaved to give methoxy aldehyde **52** *via* silyl enol ether **51**; on treatment with *p*-toluenesulfonic acid, compound **52** eliminated methanol being thus converted into enal **48**. The overall yield of the target enal **48** based on the key intermediate **49b** was 53%.

The same authors[42] accomplished another version of the synthesis of enal **48** from norambreinolide **7** (see Scheme 7). The enolate of lactone **7** was treated successively with lithium diisopropylamide (LDA) and

Scheme 7



Reagents and conditions: *a*. (1) Bu^tMe_2SiCl, (2) MeI/NaH; *b*. Bu_4NF; *c*. $(COCl)_2$/DMSO; *d*. Pr^i_3OTf; *e*. O_3/Me_2S; *f*. TsOH—PhMe, Δ; *g*. (1) LDA, (2) 10-camphorsulfonyloxaziridine; *h*. $LiAlH_4$; *i*. $NaIO_4$.

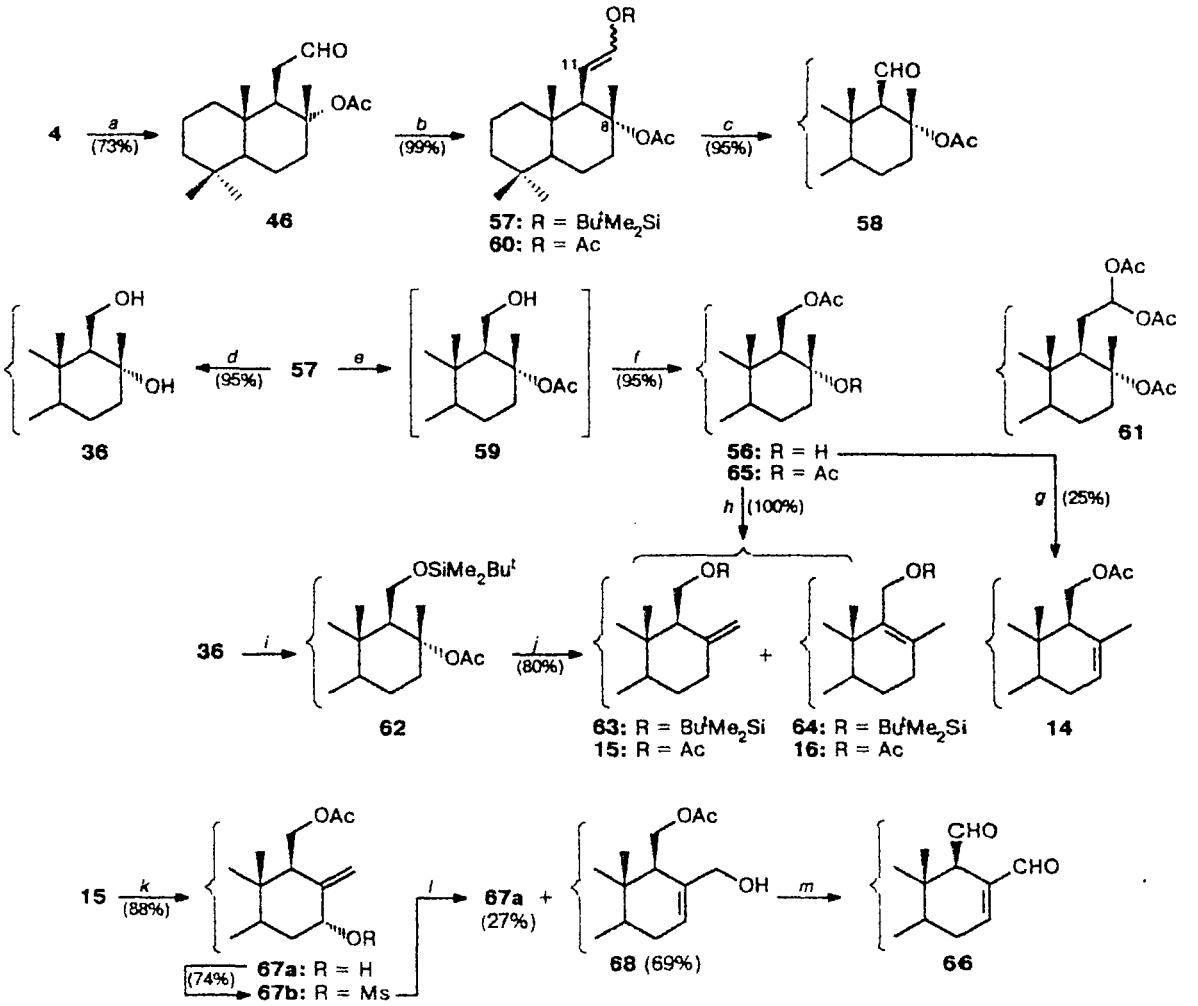
10-camphorsulfonyloxaziridine, which resulted in its hydroxylation at C(11) atom. The hydroxy lactone **53** thus formed was reduced to triol **54**, and the latter was converted in two steps into enal **48**. However, the final step was inefficient; therefore, although the latter pathway is shorter, the overall yield in the former version is higher (47 and 23.6%, respectively).

Barrero *et al.*[43,44] described a route for the transformation of sclareol **4** to drimanediol **36** and its 11-monoacetate **56** *via* acetoxy aldehyde **46**, resulting from the oxidation of sclareol **4** [45,46] (Scheme 8) carried out by the same researchers[47] by a modified procedure.

Shortening of the side chain in acetoxy aldehyde **46** was efficiently accomplished *via* a mixture of *E*- and *Z*-silyl ethers **57** (4 : 1), whose reductive ozonolysis afforded either acetoxy aldehyde **58** or diol **36**, depending on the reaction conditions (see Scheme 8). Reduction of the ozonization products with sodium borohydride gave the 11-monoacetate of drimanediol **56** in a high yield, *i.e.*, under these conditions, the process involves not only the reduction of peroxides to drimanediol 11-monoacetate (**59**) but also intramolecular transesterification of the latter with migration of the acetyl group from the O atom at C(8) to the primary hydroxy group at the C(11) atom.

An alternative route for the transformation of acetoxy aldehyde **46** into compounds **36**, **56**, and **58** *via* a mixture of *Z*/*E*-enol acetates **60** has also been studied.[43,44] However, the yield of isomers **60** (89%) was lower than the yield of silyl ethers **57**, due to the formation of acylal **61**. Besides, *Z*-enol acetate **60** is resistant to the action of ozone or the OsO_4—$NaIO_4$ system, and this also decreases the efficiency of the synthesis.

Scheme 8



Reagents and conditions: *a*. $OsO_4/NaIO_4$; *b*. Bu^tMe_2SiCl/NaH; *c*. O_3/Me_2S; *d*. $O_3/LiAlH_4$; *e*. $O_3/NaBH_4$; *f*. OH^-; *g*. $SnCl_4$—CH_2Cl_2; *h*. Δ; *i*. (1) Bu^tMe_2SiCl/DMAP, 2) Ac_2O—DMAP—NEt_3; *j*. collidine, Δ; *k*. SeO_2/Bu^tO_2H; *l*. AcONa—Me_2CO; *m*. (1) KOH—MeOH, (2) $(COCl)_2$/DMSO.

Hydroxy acetate **56** is dehydrated with $SnCl_4$ in CH_2Cl_2 to give drimenyl acetate **14**, which is the initial compound in the synthesis of biologically active natural drimanes.[43] It is noteworthy that dehydration under these conditions does not yield isomers of compound **14** differing in the position of the double bond.

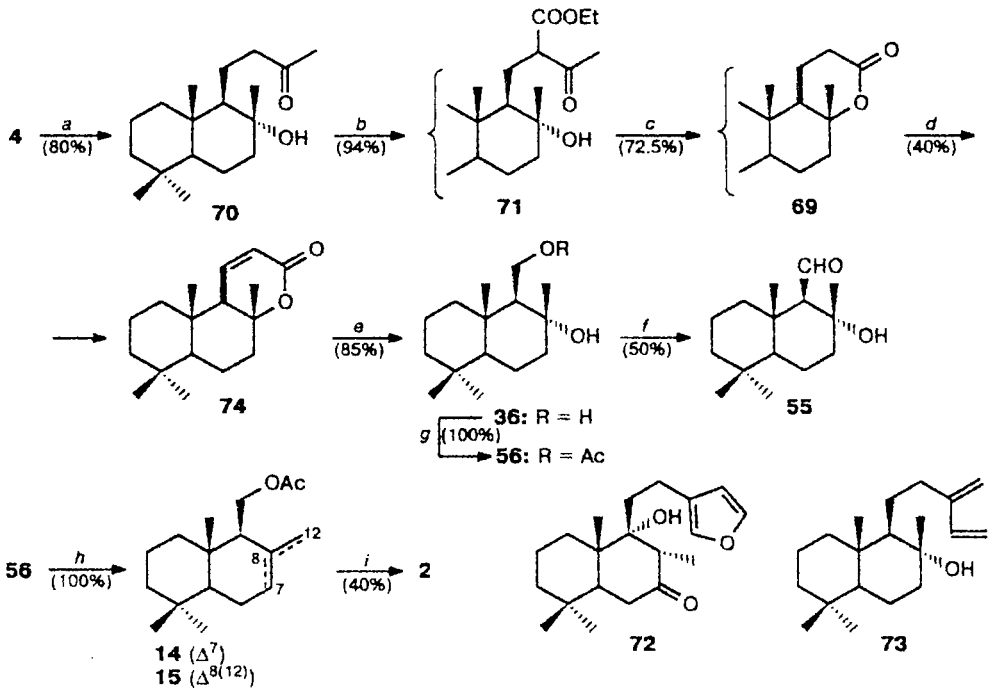
Drimanediol **36** was converted into albicanyl acetate **15**, which is an antifeedant for fishes.[14] For this purpose, the primary hydroxyl group in diol **36** was selectively silylated, and then the tertiary hydroxy group was acetylated to give etheroester **62**. Pyrolysis of the latter afforded a mixture of the silyl ether of albicanol **63** and its isomer **64** (2 : 1); they were converted into the corresponding acetates **15** and **16** by a standard procedure. Pyrolysis of diacetate **65** under the same conditions led to a mixture of acetates **15** and **16** in a ratio of 1 : 1, *i.e.*, in this case, the process was not selective.

Albicanyl acetate **15**, in its turn, was converted into polygodial **66**, one of the most important biologically active natural drimanes. Acetate **15** was oxidized into 11-acetoxy-7-hydroxydrim-8(12)-ene (**67a**); solvolysis of its mesylate (**67b**) was largely accompanied by allylic rearrangement and gave a mixture of hydroxy acetates **67a** and **68** (see Scheme 8). Alkaline hydrolysis of compound **68** and subsequent Swern oxidation led to polygodial **66**. The overall yield of compound **66** based on albicanyl acetate **15** was 40%.

A route for the transformation of sclareol **4** to drimane involving an intermediate formation of ambreinolide **69** has also been reported. This δ-lactone was synthesized for the first time by oxidative cleavage of the triterpene ambrein, which is present in ambergris.[7] Owing to the high value of this compound for the syntheses of perfumes with the amber odor, the development of methods for its preparation has received much attention.[7] The first synthesis of compound **69** was accomplished based on sclareol **4** (Scheme 9).[48] Oxidation of sclareol by $KMnO_4$ gave rise to ketol **70**, which reacted with diethyl carbonate to give compound **71**. Acid cleavage of keto ester **71** afforded ambreinolide **69**.[49] Later, ketol **70** was obtained in a high yield from manoyl oxide **21**,[7,19] while ambreinolide was also prepared from other easily accessible labdanoids, *viz.*, manool **5**,[50] hispanolone (**72**),[51] and isoabienol (**73**).[25,52,53] Some new versions of the synthesis of ambreinolide from sclareol **4** have also been reported.[9,54]

The reaction of ambreinolide **69** with dicyanodichloroquinone (DDQ) afforded 11(12)-dehydroambreinolide (**74**) (yield 40%). When $Pb(OAc)_4$ was used as the oxidizing agent, the outcome of the reaction was inferior. The reductive ozonolysis of dehydroambreinolide **74** resulted in the formation of drimanediol **36**, and the latter was converted into 8α-hydroxydriman-11-al **55** and drimenol **2**, as shown in Scheme 9.[55]

Scheme 9

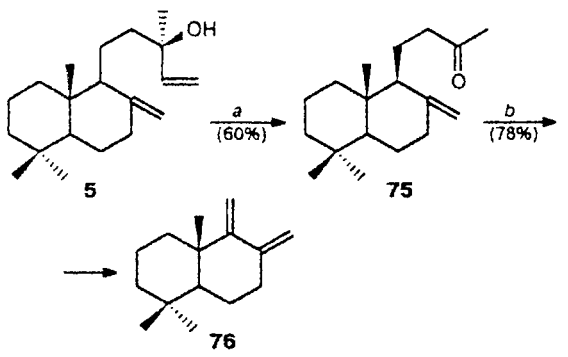


Reagents and conditions: *a*. $KMnO_4$; *b*. $(EtO)_2CO/NaH$; *c*. KOH—EtOH; *d*. DDQ—dioxane, Δ; *e*. (1) O_3—CH_2Cl_2, (2) a 70% solution of $NaAl(CH_2CH_2OMe)_2H_2$ in C_6H_6; *f*. CrO_3/Py; *g*. Ac_2O/Py; *h*. $POCl_3$/Py; *i*. KOH—MeOH.

Synthesis of drimanes from manool

It has been noted above that ambreinolide **69**, a precursor in the synthesis of drimanes, can also be obtained from manool **5**. In addition, the transformation of manool into diol **45a**, which has also been used as the initial compound in the synthesis of drimanes, has been reported.[56,57] Besides, drimanes have been obtained from manool *via* 14,15-bisnorlabd-8(17)-en-13-one (**75**), one of the most typical and important products of its oxidative cleavage (Scheme 10).[7] Notice also that fairly effective procedures for the synthesis of this compound from sclareol **4** have been developed.[9,58,59] Manool **5** itself was also prepared from sclareol **4**.[60,61] Ohloff *et al.*[62] found that on UV-irradiation, ketone **75** in pentane undergoes type II Norrish fermentation to give a mixture of no less than twelve products, drima-8(12),9(11)-diene (**76**) being one of the major products (yield 22.5%). However, notice that Jeger *et al.*[63] obtained an enantiomer of diene **76** in a quantitative yield by irradiation of an enantiomer of ketone **75** at −72 °C. Later, it was found[64] that diene **76** can be isolated in a relatively high yield (50%, or 78% based on the converted ketone **75**) if the photolysis is carried out at 5 °C and a more powerful source of radiation is used.

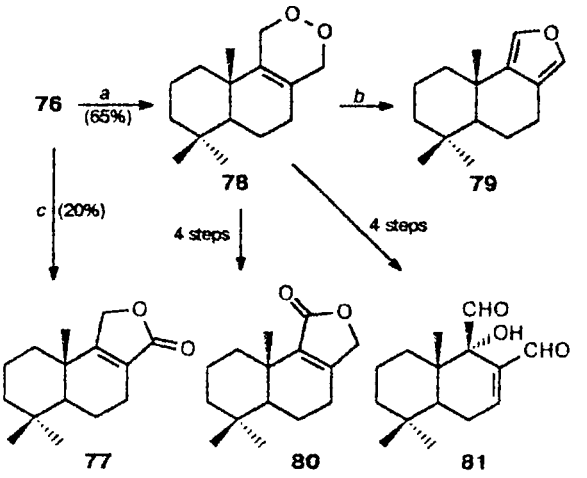
Scheme 10



Reagents and conditions: *a.* $KMnO_4/MgSO_4$; *b.* *hv*.

Diene **76** proved to be a convenient multipurpose synthon for the syntheses of a series of valuable biologically active natural drimanes. For example, its photosensitized oxidation in the presence of a dye (Bengal Rose) led to confertifolin (**77**), and its irradiation in the presence of *meso*-tetraphenylporphyrin afforded endoperoxide **78**, which underwent isomerization and dehydration under the action of Al_2O_3 or $FeSO_4$ to give eurifuran (**79**) (Scheme 11).[64] Endoperoxide **78** was converted in four steps into isodrimenine (**80**)[65] or warburganal (**81**).[66] Alternative pathways from diene **76** to eurifuran **79** and warburganal **81** in which diene is oxidized at the first step by thallium triacetate have also been reported;[5,67] however, these transformations are less efficient than those mentioned above.

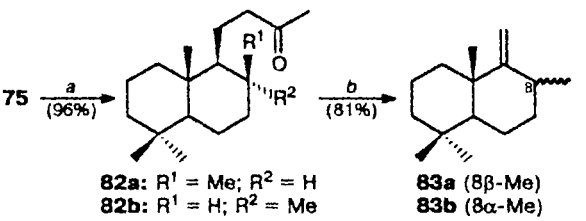
Scheme 11



Reagents and conditions: *a.* *hv*/O_2/*meso*-tetraphenylporphyrin; *b.* Al_2O_3 or $Fe(SO)_4$; *c.* *hv*/O_2/Bengal Rose.

The product of hydrogenation of ketone **75**, a mixture of saturated ketones **82a** and **82b** (4 : 1), was also subjected to photolysis. When this mixture is exposed to UV light in a hexane solution, a mixture of drim-9(11)-enes **83a** and **83b** (1 : 1) epimeric at the C(8) atom is formed, *i.e.*, during the photolysis, ketone **82a** undergoes epimerization at the C(8) atom (Scheme 12).[68]

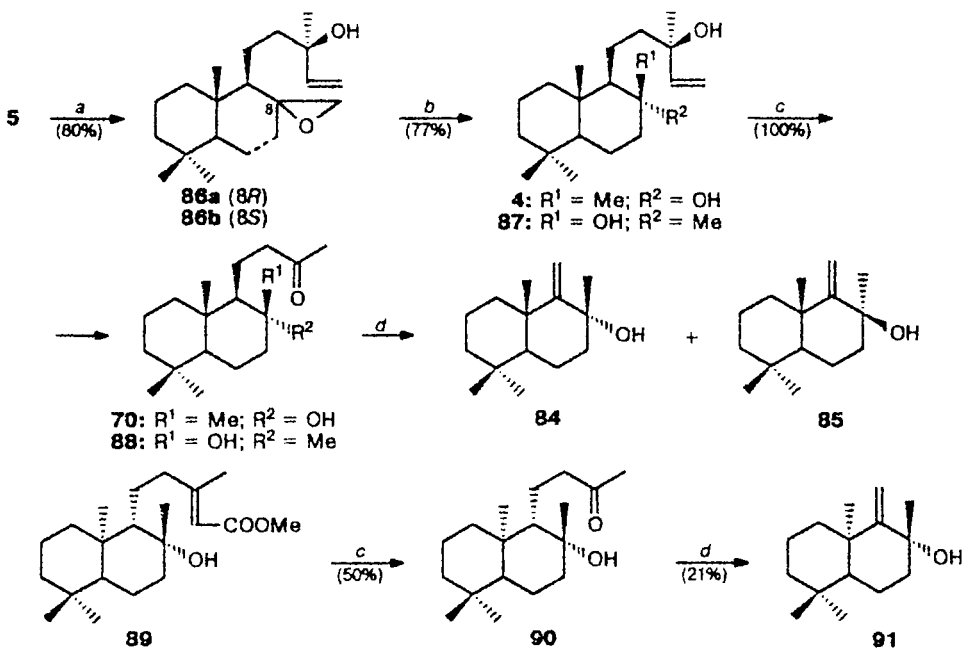
Scheme 12



Reagents and conditions: *a.* H_2/Pd/C—AcOEt; *b.* *hv*.

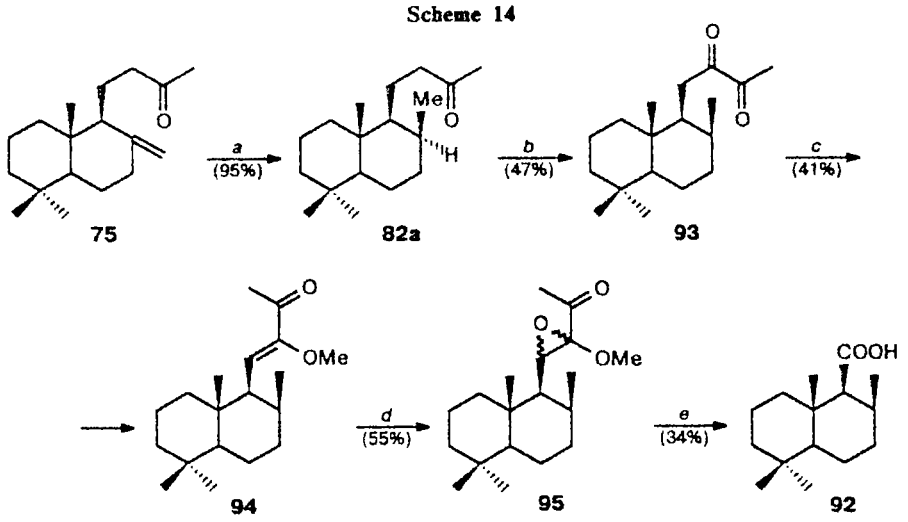
Manool **5** served as the initial compound in the synthesis of drim-9(11)-en-8-ols epimeric at the C(8) atom (**84** and **85**), which are sporogeneous substances of the mold fungus *Aspergillus oryzae*[69] used in Japan for bread baking and in the production of some drinks (sake and the like).[70] Epoxidation of compound **5** in the presence of $NaHCO_3$ gave enantiomeric epoxides **86a,b**, which were reduced into a mixture of sclareol **4** and 8-episclareol (**87**). This mixture was oxidized to give a mixture of ketones **70** and **88**, whose photolysis in hexane afforded a mixture of drim-9(11)-en-8α-ol **84** and drim-9(11)-en-8β-ol **85** (Scheme 13).[70] Based on this, it was concluded[70] that the natural derivatives are antipodes of compounds **84** and **85**. Moreover, to con-

Scheme 13



Reagents and conditions: *a*. *m*-CPBA/$NaHCO_3$; *b*. $LiAlH_4$; *c*. $KMnO_4/MgSO_4$; *d*. *hv*.

Scheme 14



Reagents: *a*. H_2/Pt; *b*. O_2/Bu^tOK; *c*. MeI/NaH—THF; *d*. *m*-CPBA; *e*. $BF_3 \cdot Et_2O$.

firm this conclusion, the researchers cited[70] synthesized *ent*-drim-9(11)-en-8-ol (**91**), which was identical, in their opinion, to one of the natural compounds, from methyl *ent*-8α-hydroxylabd-13-en-15-oic acid (**89**) *via* ketol **90** (see Scheme 13). However, later it was shown[71] that natural drimanes from *Aspergillus oryzae* belong nevertheless to the normal stereochemical series, and their absolute configuration is represented by the formulas **84** and **85**. Apparently, the authors of the paper under consideration[70] determined incorrectly the sign of the optical rotation for compounds **84**, **85**, and **91**.

Grant *et al.*[72] synthesized (8*S*)-driman-11-oic acid (**92**) based on ketone **75** (Scheme 14). It should be noted that, in contrast to the data reported earlier,[68] hydrogenation of ketone **75** over platinum afforded[72] only (8*S*)-epimer **82a**; the side chain in this compound was cleaved as shown in Scheme 14. However, most of the steps of this synthesis gave products in relatively low

yields, and the acid **92** obtained in this way contained no functional groups other than the carboxyl group.

Synthesis of drimanes from neoabienols

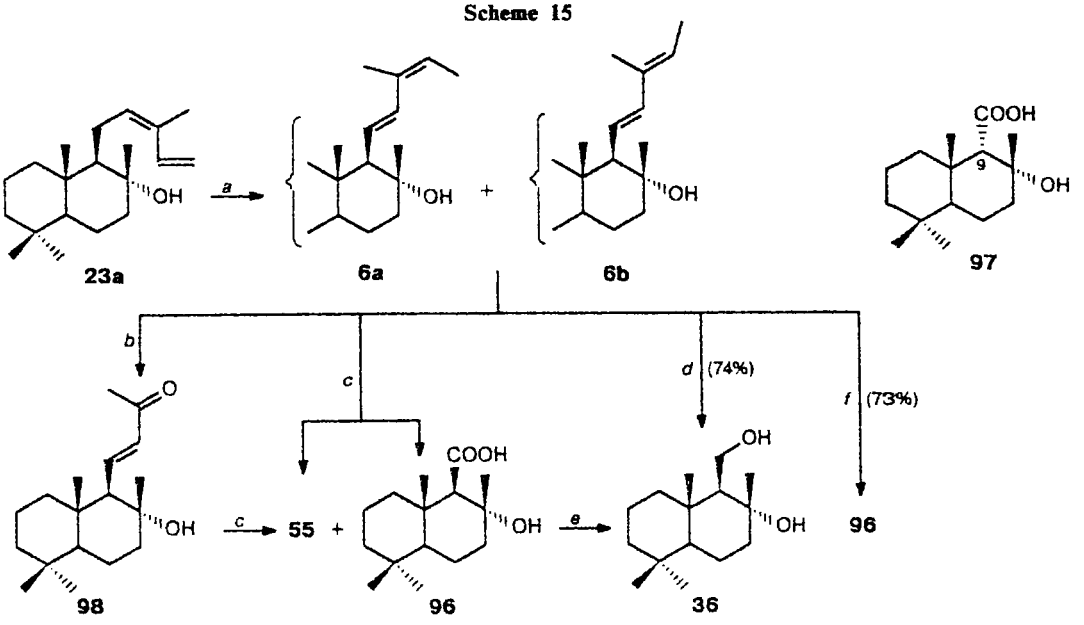
cis-, *trans*-Neoabienols **6a** and **6b** [73] with a double bond at the C(11) atom are extremely convenient labdanoids for use in the synthesis of drimanes. Oxidative cleavage of their molecules at this double bond leads directly to drimanes. In addition, neoabienols **6a,b** are readily accessible. They do not occur in nature themselves but result from a sigmatropic rearrangement of *cis*-abienol **23a** [73,74] that occurs during vacuum rectification of some conifer oleoresins containing it[75—77] (Scheme 15). Ozonization of *cis*-neoabienol **6a** followed by thermolysis of the resulting ozonide in water or oxidation of the neutral ozonolysis products by $KMnO_4$ afforded[75] a C_{15}-hydroxy acid, to which structure **96** was ascribed. However, physicochemical characteristics of this compound differed from those reported by other researchers.[78] In reality, the authors of the earlier study[75] probably obtained the epimer of hydroxy acid **96** at the C(9) atom (**97**).

A detailed study of the ozonization of neoabienols **6a,b** showed[79] that their oxidation by one equivalent of ozone yields only 8α-hydroxy-14,15-bisnorlabd-11-en-13-one (**98**), irrespective of the solvent and of the procedure used for the workup of the products. In this case, the double bond at C(13) atom is oxidized selectively. This bond is also the first to be cleaved when excess ozone is used in the reaction. Ozonization of a mixture of compounds **6a** and **6b** in hexane and subsequent decomposition of their ozonides by heating with water gave a mixture of extremely unstable 8α-hydroxydriman-11-al **55** (60%) and 8α-hydroxydriman-11-oic acid **96** (25%). When the ozonides were subjected to oxidative cleavage by hydrogen peroxide, acid **96** (its physicochemical characteristics were in good agreement with those reported previously[78]) became the major reaction product (yield 73%). The structure and stereochemistry of acid **96** are also confirmed by the fact that its reduction affords drimane-8α,11-diol **36**. The major product (formed in 74% yield) of the exhaustive ozonization of a mixture of neoabienols in MeOH followed by the reduction of ozonization products by sodium borohydride is drimanediol, a significant intermediate on the way to natural drimane derivatives. Ozonization of hydroxy ketone **98**, which has been found in some natural sources, was also studied.[7,80—83] It was shown that when neoabienols **6a,b** and hydroxy ketone **98** are ozonized under identical conditions, the character and the yields of reaction products are completely parallel to each other. Thus, ozonolysis of neoabienols **6a,b** opens an efficient route to drimane sesquiterpenoids.

Synthesis of drimanes from 13-oxo-14,15-bisnorlabd-7-en-17-oic and zamoranic acids

Spanish chemists carried out targeted and systematic studies on the synthesis of drimane sesquiterpenoids from two accessible labdanoids, *viz.*, 13-oxo-14,15-bisnorlabd-7-en-17-oic (**99a**) and zamoranic (**100**) acids, extractive substances isolated from *Halimium viscosum*[84,85] and *Halimium verticilatum*[85] plants. The contents of compounds **99a** and **100** in *Halimium viscosum* amounts to ~0.2 and 2.2% of the dry substance

Scheme 15



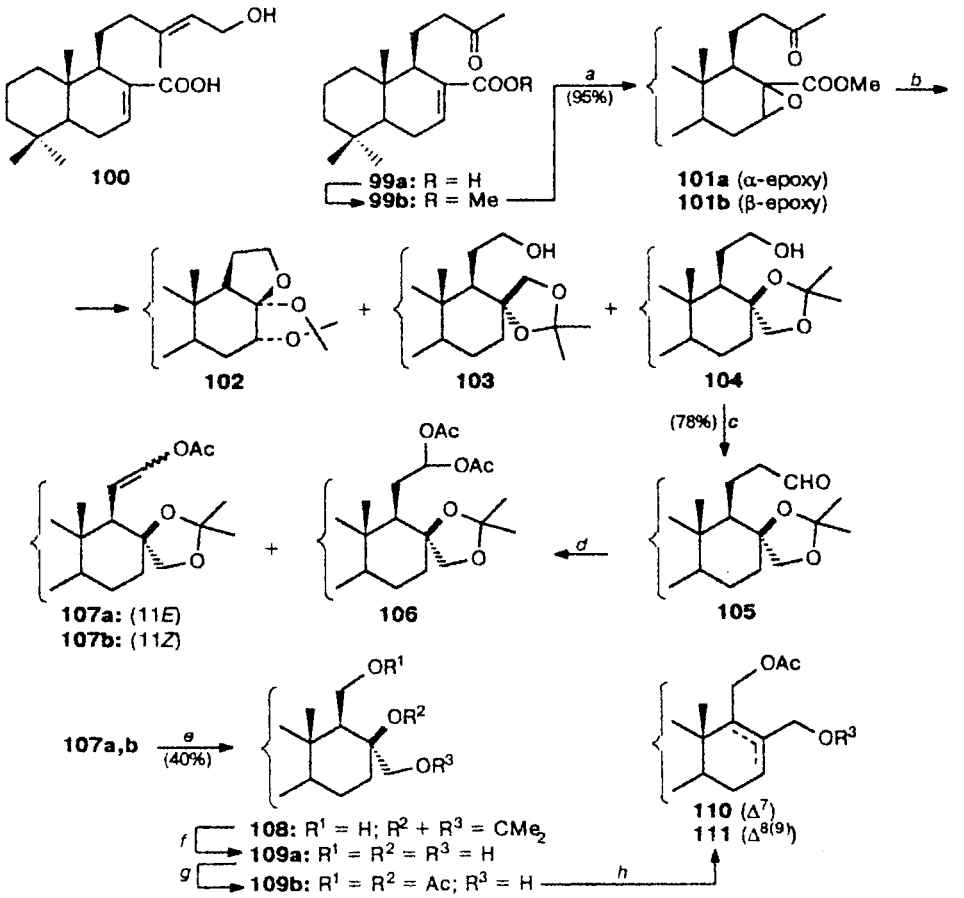
Reagents and conditions: *a*. Δ; *b*. O_3 (1 equiv.); *c*. O_3—C_6H_{14}, H_2O/Δ; *d*. O_3—MeOH, $NaBH_4$; *e*. $LiAlH_4$; *f*. O_3—C_6H_{14}, H_2O_2.

of plant,* respectively. Acid **99a** was converted into drimane derivatives according to Scheme 16.[86] Its methyl ester **99b** was subjected to Baeyer—Villiger oxidation to give a mixture of α- and β-epoxy esters **101a** and **101b** (1 : 1). This reaction occurs very slowly and is completed over a period of 15 days. A mixture of compounds **102—104** (the yield of the latter was 60%) was obtained by hydride reduction of a mixture of esters **101a** and **101b** and the subsequent protection of the diol group in the reaction products by 2,2-dimethoxypropane. Product **104** was oxidized into aldehydoketal **105**; enolacetylation of the latter yielded a mixture of compounds **106** (20%), **107a**, and **107b** (the overall yield of the two latter compounds was 69%). Reductive ozonolysis of a mixture of enol acetates **107a** and **107b** afforded product **108**. However, *trans*-enol acetate **107a** did not undergo ozonization (37% w/w of the mixture of the initial compounds remained unchanged). Taking into account the recovered initial compound, the yield of product **108** was only 40%. Hydrolysis of compound **108** led to drimane-8α,11,12-triol (**109a**). Acetylation of the latter under standard conditions gave rise to hydroxy acetate **109b**, which was dehydrated to yield a mixture of isomeric diacetates **110** and **111**. Both of these compounds have been used previously in the synthesis of biologically active drimanes polygodial **66** and warburganal **81**.[6] Generally, it should be noted that the above-described synthesis of drimanes from keto acid **99a** is a multistep and cumbersome procedure that requires hard-to-get and expensive reagents; in addition, it is relatively inefficient, since many of its steps afford mixtures of products, and the yields of the target products are relatively low. Other known routes for passing from oxoacid **99a** to drimanes[86] proved to be even less efficient.

However, later a successful one-step transition from keto ester **99b** to drimane sesquiterpenoids was accomplished.[87] Photolysis of ester **99b** gave diene drimane ester **112** (with allowance for the recovered initial compound (39%), the yield was 86.4%). In order to synthe-

* Zamoranic acid occurs in the plant in both free and acetylated forms. Acetylzamoranic acid accounts for ~25% of its total content.

Scheme 16



Reagents and conditions: *a*. *m*-CPBA; *b*. (1) $LiAlH_4$—THF, Δ, (2) $Me_2C(OMe)_2$/TsOH; *c*. CrO_3/Py; *d*. Ac_2O/DMAP/NEt_3; *e*. O_3—CCl_4, $LiAlH_4$—THF; *f*. TsOH—MeOH; *g*. Ac_2O/Py; *h*. $POCl_3$/Py.

size natural polyfunctional drimanes from ester **112**, its oxidation under the action of OsO_4 was studied. However, this reaction occurs ambiguously and leads to a complex mixture of products. The attempts to oxidize ester **112** at the C(6) position using various oxidizing agents containing hexavalent chromium were also unsuccessful. This synthesis was accomplished according to Scheme 17. Ester **112** was oxidized by *m*-CPBA to give a mixture of epoxy esters **113** and **114** (3 : 7) in a quantitative yield. The isomer **114** was treated with chlorosulfenyl isocyanate to yield a mixture of products **115** and **116**. Compound **116** was converted into α,β-unsaturated ketone **117** by oxidation under mild conditions; the latter compound was reduced into a mixture of epimeric alcohols **118** and **119**. The major product, **119**, was subjected to alkaline hydrolysis to afford natural sesquiterpenoid pereniporin B (**120**),[88] possessing antimicrobial and cytotoxic activities (see Scheme 17). The overall yield of compound **120** based on the diene ester **112** was 12%.

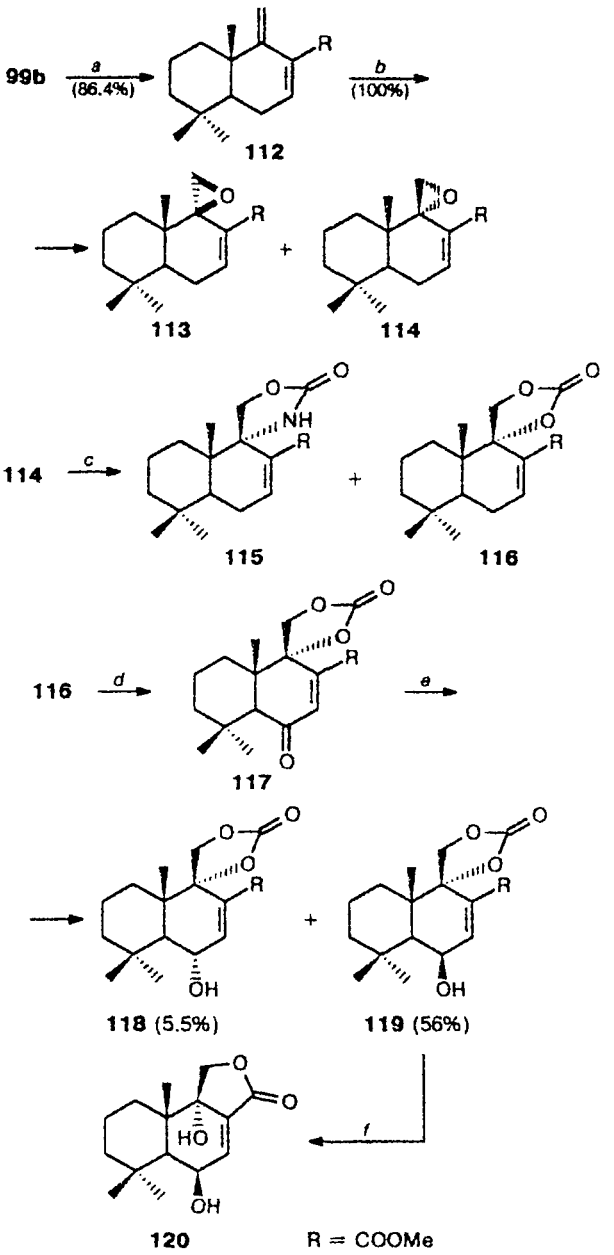
Epoxyester **114** also served as the initial compound in the synthesis of both polygodial **66** and warburganal **81**. On treatment with $BF_3 \cdot Et_2O$, it isomerized into a mixture of aldehydoesters **121** and **122** (1 : 19). Hydride reduction of the latter gave known diol **123** [89,90] (Scheme 18), whose oxidation according to Swern afforded polygodial **66**.[89] Diol **123** was smoothly acetylated under standard conditions yielding diacetate **110**; the latter was further oxidized with selenium dioxide to hydroxy diacetate **124**. Hydrolysis of this compound resulted in the formation of triol **125**, whose oxidation according to Swern gave warburganal **81**. The yields of compounds **66** and **81** based on keto ester **99b** amounted to 44.6 and 31.5%, respectively.

Transformation of zamoranic acid **100** into bisnorlabdane oxoester **99b** was also accomplished (Scheme 19).[87] Epoxidation of its methyl ester **100a** gave a mixture of stereoisomeric epoxyesters **126** in a quantitative yield; this mixture was converted into a mixture of oxoester **99b** and orthoesters **127** and **128** by treatment with orthoperiodic acid. When ester **100a** was directly oxidized by oxidizing agents such as O_3, $KMnO_4$, or CrO_3 in AcOH, the yield of oxoester **99b** was lower.

In order to elucidate the effect of the nature of the functional group at the C(7) atom on the yield of drimane derivatives, 12-acetoxydrima-7,9(11)-diene (**129**) was synthesized in two ways[91,92] from the zamoranic acid **100**, and then polygodial **66** and warburganal **81** were prepared from acetoxydiene **129**. The first version of the synthesis of compound **129** is shown in Scheme 20. The hydroxyl group in the molecule of methyl zamoranate **100a** was protected by converting it into the corresponding THP derivative. The reaction product **130a** was reduced into hydroxy ester **130b**, which was acetylated to give diester **130c**. The protective THP group was removed by hydrolysis, and hydroxy acetate **131** was thus obtained. The overall yield of compound **131** based on **130a** was 94%. Hydroxy acetate **131** was selectively epoxydized at the double bond in the side chain to give a mixture of epoxy alcohols **132**, which was then cleaved with orthoperiodic acid to acetoxy ketone **133**; photolysis of the latter gave acetoxy diene **129**.

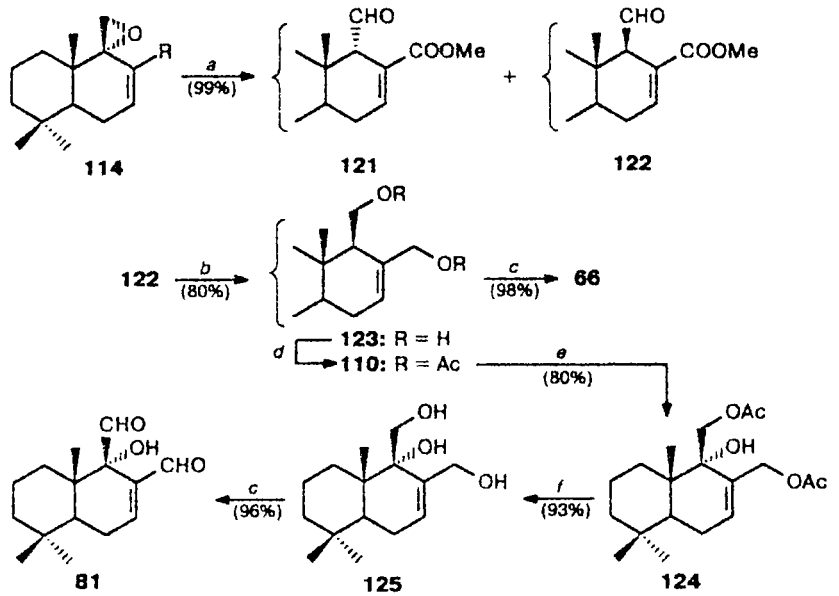
The second version of the synthesis of acetoxy diene **129** is presented in Scheme 21. Zamoranic acid **100** was reduced to diol **134a**, which was converted into diacetate

Scheme 17



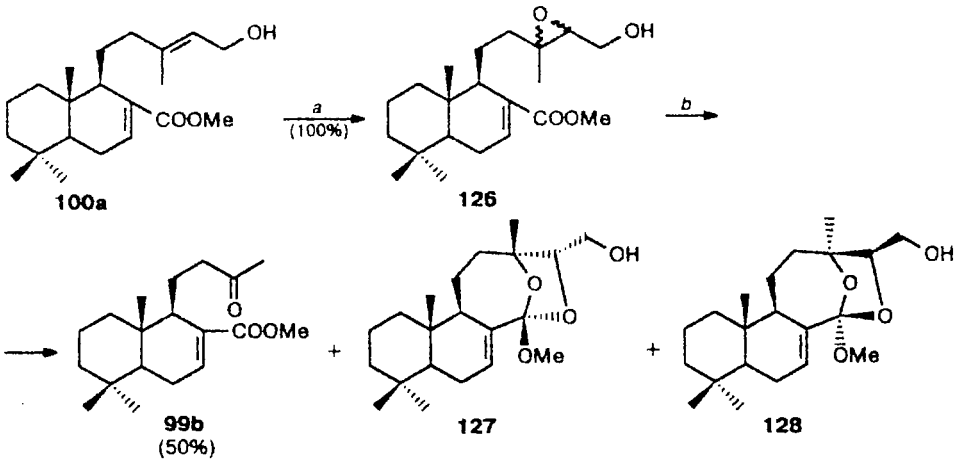
Reagents and conditions: *a.* $h\nu/C_6H_{14}$; *b.* *m*-CPBA; *c.* ClSNCO; *d.* CrO_3—AcOH; *e.* $NaBH_4/CeCl_3$; *f.* NaOH.

Scheme 18



Reagents: *a*. $BF_3 \cdot Et_2O$; *b*. $LiAlH_4$; *c*. $(COCl)_2$/DMSO; *d*. Ac_2O/Py; *e*. SeO_2; *f*. K_2CO_3—MeOH.

Scheme 19



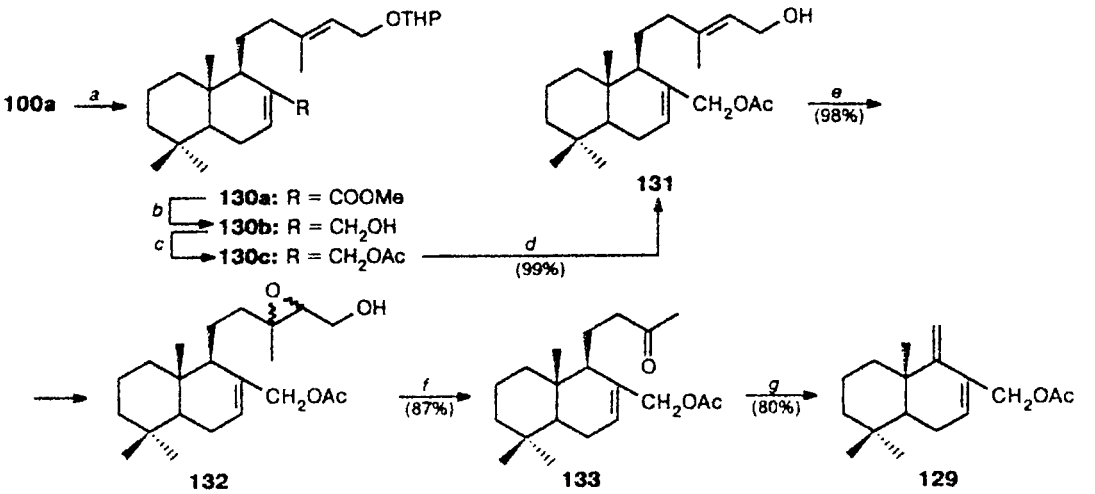
Reagents: *a*. *m*-CPBA; *b*. H_5IO_6.

134b under standard conditions. The latter was selectively hydrolyzed to give hydroxy acetate **131**, whose subsequent transformations are shown in Scheme 20.

The yield of acetoxy diene **129** based on zamoranic acid **100** was markedly higher (64%) than the yield of diene ester **112** (43%). This is due to the fact that cleavage of epoxy acetates **132** with orthoperiodic acid is more efficient.

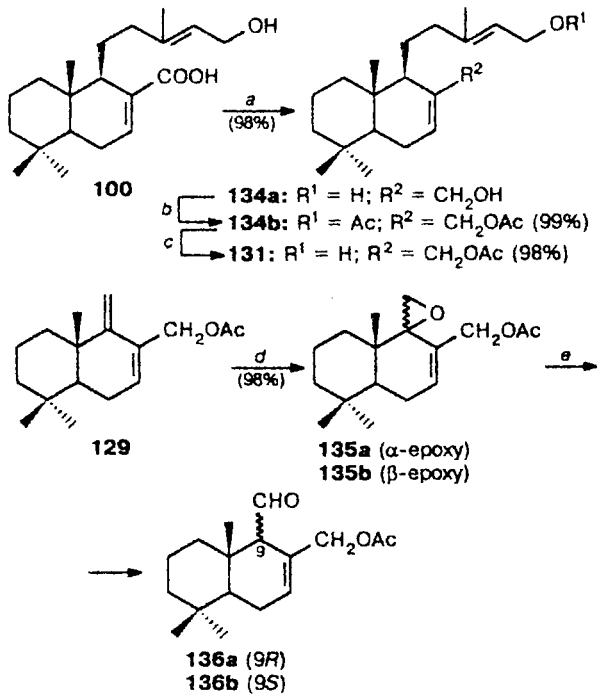
Further synthesis of diol **123** from acetoxy diene **129** was carried out similarly to its preparation from diene ester **112**. The **135a**/**135b** ratio was equal to 4 : 1; in addition, isomerization of epoxy acetate **135a** with boron trifluoride etherate was not a concerted reaction but occurred *via* the carbocation at the C(9) atom. Thus, there is no need to separate preliminarily the mixture of epoxy acetates, and, besides, the mixture of aldehydo acetates **136a** and **136b** (1 : 19) should also be reduced without separation, because during its chromatography on SiO_2, acetoxy aldehyde **136b** isomerizes into the undesired epimer **136a**. The precursor of warburganal **81**, triol **125**, was synthesized from acetoxy diene **129** in two ways. The first route involving the intermediate synthesis of epoxy acetate **135a** is similar to the synthesis of compound **81** from epoxy ester **114**. Epoxy acetate **135a** reacted with chlorosulfenyl isocyanate to give a mixture of compounds **136b**, **137**, and **138** (Scheme 22).

Scheme 20



Reagents and conditions: *a*. THP/TsOH; *b*. $LiAlH_4$; *c*. Ac_2O/Py; *d*. TsOH—MeOH; *e*. *m*-CPBA; *f*. H_5IO_6; *g*. *hv*.

Scheme 21

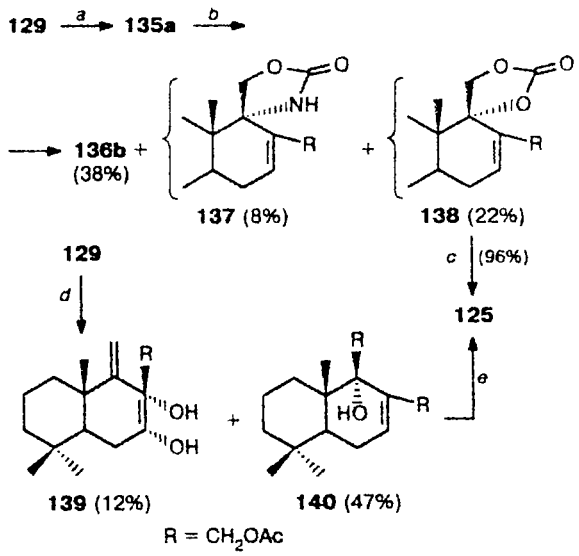


Reagents: *a*. $LiAlH_4$; *b*. Ac_2O/Py; *c*. K_2CO_3—MeOH; *d*. *m*-CPBA; *e*. $BF_3 \cdot Et_2O$.

Hydrolysis of carbonate **138** afforded the target triol **125**; however, the yield of carbonate **138** in the previous step was relatively low (22%).

The second route,[92] whose first step involves hydroxylation of acetoxy diene **129** with osmic acid, proved

Scheme 22



Reagents: *a*. *m*-CPBA; *b*. $ClSO_2NCO$; *c*. NaOH—dioxane; *d*. (1) OsO_4/NMO, (2) Ac_2O/Py; *e*. $LiAlH_4$.

to be more efficient. To make the isolation more convenient, the product of oxidation was acetylated under standard conditions and then chromatographed. The version in which a catalytic amount of OsO_4 is used in the presence of a co-oxidant, *N*-methylmorpholine *N*-oxide (NMO), seems to be the optimal. This procedure ensures regioselectivity of the process and the maximum yield of the desired product and leads to a mixture of compounds **139** and **140**. However, in this case, too, the reaction occurs very slowly, and even after

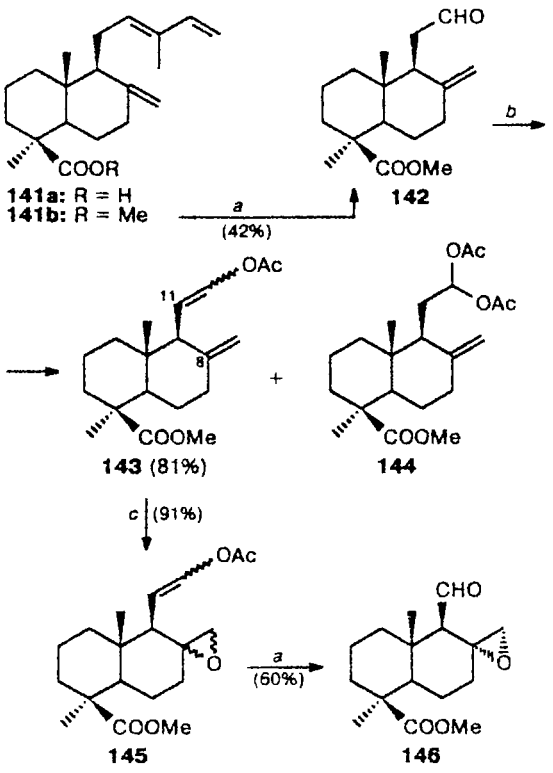
6 days (the optimal duration), 14% of the initial compound is recovered unchanged. Reduction of hydroxy diacetate **140** yields triol **125**.

Synthesis of drimanes from trans-communic acid

trans-Communic acid (**141a**) is also an accessible labdanoid,[7] which can be used in the synthesis of drimanes. This acid occurs as the major component in the extracts from cypress plants.[93] It can be isolated by crystallization from the acidic part of some of them after methylation as the corresponding methyl ester (**141b**).[94] The selective cleavage of the double bond at the C(12) atom in ester **141b** is the key step on the pathway to drimanes. This step was found to be best accomplished by controlled ozonolysis of triene **141b** at −78 °C in CH_2Cl_2 followed by reduction of the ozonide by Me_2S; the yield of aldehydoester **142** thus obtained reached 42%, while 40% of the initial *trans*-communate recovered unchanged (Scheme 23).[95] Enolacetylation of compound **142** gave a mixture of *Z*/*E*-enol esters **143** in a good yield and a small amount of acylal **144**. Epoxidation of isomers **143** occurred selectively at the semicyclic double bond to give a mixture of esters **145**. Its ozonolysis afforded polyfunctional drimane derivative **146**. The researchers were not able to accomplish the selective cleavage of the double bond at the C(11) atom in enol acetate **143**, because oxidation involved both double bonds.

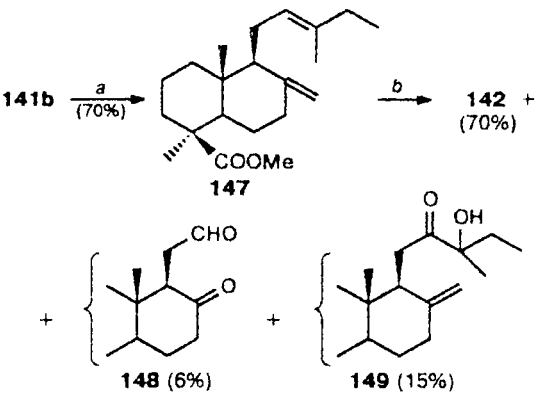
An alternative procedure for the preparation of aldehydoester **142** from *trans*-communate **141** has also been reported;[94] the method involves selective reduction of the double bond at the C(14) atom in ester **141b** by diimide, and the dihydro ester **147** thus obtained is oxidized by catalytic amounts of OsO_4 and $NaIO_4$ in aqueous *tert*-butanol (Scheme 24). This yields a mixture of products **142**, **148**, and **149**.

Scheme 23



Reagents: *a*. (1) O_3—CH_2Cl_2, (2) Me_2S; *b*. Ac_2O/DMAP/Et_3N; *c*. *m*-CPBA.

Scheme 24



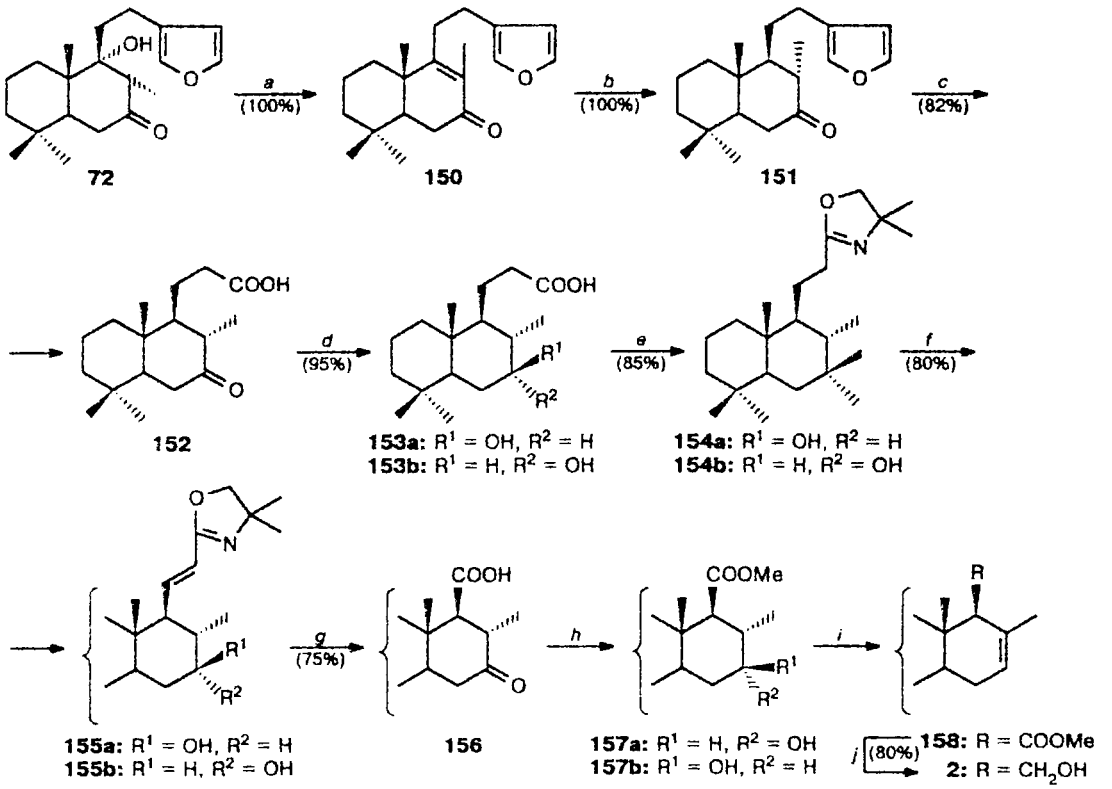
Reagents: *a*. N_2H_2; *b*. OsO_4/$NaIO_4$.

Synthesis of drimanes from hispanolone

Drimanes have also been synthesized from a readily accessible labdanoid, hispanolone **72** isolated from *Ballota hispanica* and *Galeopsis angustifolia*.[96,97] Its content in the dry plant is 2.3%. Hispanolone **72** was dehydrated in a quantitative yield to give α,β-unsaturated ketone **150**, which was reduced by sodium dithionate in the presence of a phase transfer catalyst (PTC) to afford keto furan derivative **151**. Exhaustive ozonolysis of compound **151** with the subsequent oxidative decomposition of the ozonization product resulted in the formation of oxoacid **152**. The latter was reduced into a mixture of epimeric hydroxy acids **153a** and **153b**, which reacted with 2-amino-2-methylpropanol in the presence of boric acid to afford a mixture of oxazolines **154a** and **154b**. Its dehydration led to a mixture of compounds **155a** and **155b**, whose ozonization followed by oxidative cleavage of the ozonization products by the Jones reagent yielded 7-oxodriman-11-oic acid (**156**) (Scheme 25).

Keto acid **156** was converted into a mixture of hydroxy esters **157a** and **157b**, which was dehydrated by heating in hexamethapol to give methyl drim-7-en-

Scheme 25



Reagents and conditions: *a*. $SOCl_2$/Py; *b*. $Na_2S_2O_4$/PTC; *c*. (1) O_3—CH_2Cl_2/MeOH, (2) H_2O_2/NaOH; *d*. $NaBH_4$; *e*. $Me_2C(NH_2)CH_2OH/H_3BO_3$; *f*. $PhSeOH/H_2O_2$; *g*. (1) O_3—CH_2Cl_2/MeOH, (2) CrO_3/H_2SO_4; *h*. (1) $NaBH_4$, (2)CH_2N_2; *i*. HMPA/Δ; *j*. $LiAlH_4$.

11-oate (**158**) (yield 25% based on oxoacid **156**). Hydride reduction of ester **158** led to drimenol **2**;[98] however, its yield based on hispanolone **72** (over 13 steps) was as low as 8%.

Synthesis of drimanes from labdanolic acid

The parent of the group of labdane diterpenoids, labdanolic acid **27**, is also a readily accessible compound.[7,99] Based on acid **27**, 8α-acetoxydriman-11-oic acid (**44**)* and drima-7,9(11)-diene (**159**), intermediates suitable for the preparation of biologically active natural drimanes, were synthesized (Scheme 26).[100]

Labdanolic acid **27** was converted into acetoxylabdanolic acid **27a**, which was decarboxylated to give unsaturated acetate **160**. Cleavage of the double bond in the molecule of **160** was accomplished *via* a mixture of epoxy acetates **161**. Photolysis of acetoxy ketone **162** thus obtained gave diene **159**, *i.e.*, not only acetone but also acetic acid was eliminated under the conditions of photolysis.[100] The overall yield of diene **159** based on labdanolic acid **27** was 22.6% over the four steps of the synthesis.

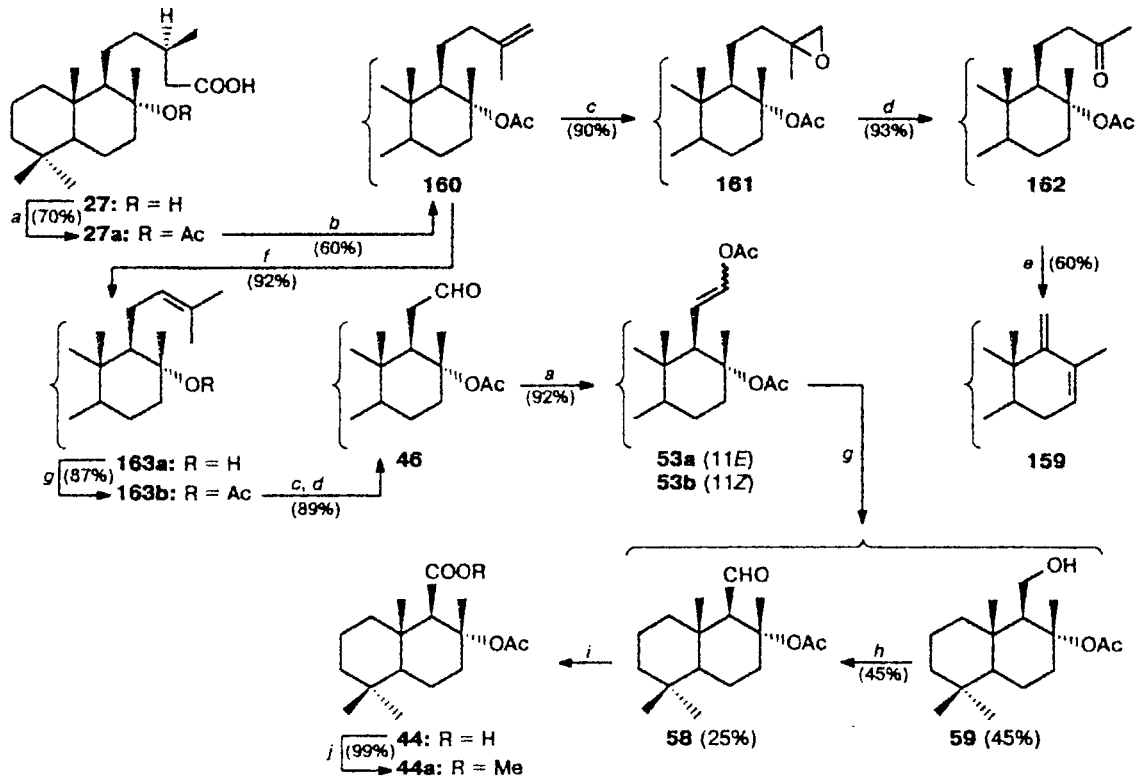
On treatment with lithium in ethylene diamine, unsaturated acetate **160** was transformed into unsaturated alcohol **163a** (this was accompanied by hydrolysis of the acetate group). Cleavage of the double bond in the corresponding acetate **163b** gave acetoxy aldehyde **46**,[41] which was subsequently converted into a mixture of *E*- and *Z*-enol acetates **53a,b** in a high yield. Ozonization of this mixture and hydride reduction of the ozonization products resulted in the formation of a mixture of hydroxy acetate **59** and acetoxy aldehyde **58**. Compound **58** was oxidized into acetoxy acid **44**; the latter was methylated by CH_2N_2 to yield the corresponding ester **44a** (see Scheme 26). Hydroxy acetate **59** can be oxidized to acetoxy aldehyde **58** by the Swern method.

* * *

Thus, drimane compounds were obtained in the enaniomerically pure optically active forms by partial syntheses from many accessible labdanoids, most of which can be isolated from natural plant sources by relatively simple procedures in relatively large amounts or even on an industrial scale. At present, the labdanoids mentioned above are not equally suitable as initial compounds for the synthesis of drimanes. In fact, whereas some labdanoids such as sclareol **4**, manool **5**, neoabienols

* Previously[41] acid **44** was synthesized from sclareol **4**.

Scheme 26



Reagents and conditions: *a.* Ac_2O/Et_3N/DMAP; *b.* $Pb(OAc)_4/Cu(OAc)_2$; *c.* *m*-CPBA; *d.* HIO_4; *e.* *hν*; *f.* $Li(CH_2NH_2)_2$; *g.* $O_3/NaBH_4$; *h.* $(COCl)_2$/DMSO; *i.* $NaClO_2$; *j.* CH_2N_2.

6a,b, and manoyl oxide **21** can be converted into drimane compounds in two to four steps using accessible and cheap reagents, the preparation of drimanes from labdanolic (**27**), zamoranic (**100**), and communic (**141a**) acids and hispanolone **72** requires multistep procedures associated with the use of expensive reagents or reagents difficult to access; therefore, the practical value of these methods still remains problematic. Hence, the development of simpler and more convenient methods for the synthesis of drimane compounds from these and some other labdanoids is still an urgent and promising task.

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