Chemistry of Natural Compounds and Bioorganic Chemistry

Superacidic low-temperature cyclization of terpenols and their acetates

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The superacidic low-temperature cyclization of terpenols and their acetates by fluorosulfonic acid represents a highly efficient chemo- and structurally selective and stereospecific process. Homoallylic alcohols (α-isomers of cycloterpenols) are the products of cyclization of terpenols; the configuration of the hydroxymethyl group in the products is predetermined by the configuration of the allylic double bond in aliphatic or partially cyclized precursors. The cyclization of terpenyl acetates yields monoacetates of fully cyclized diastereomeric primary-tertiary γ-diols. Their stereochemistry also depends on the configuration of the allylic double bond in the starting substrates.

Key words: terpenols; terpenyl acetates; cyclization, fluorosulfonic acid, drimanes, isoagathanes, scalaranes.

The majority of representatives of the broad class of natural terpenoids are cyclic, and, hence, their biogenesis includes electrophilic cyclization of polyolefinic aliphatic precursors as the most important step. To elucidate the mechanism of this biogenetic transition and to perform convenient, biomimetic syntheses of cyclic terpenoids, extensive investigations of electrophilic, acid-induced cyclization of terpenoids *in vitro* have been undertaken; ordinary Brönsted and Lewis acids have been used for this purpose.[1–5]

By the middle 1970s, the basic structural and spatial regularities of this reaction, its mechanism, and limitations were established by numerous extensive studies.[2,3,6] However, despite these achievements, the initiation of the cyclization of aliphatic terpenoids by ordinary Brönsted and Lewis acids did not result in high yields of regular cyclic terpenoids containing more than two carbocycles.

In 1973, A. V. Semenovskii, V. A. Smit, *et al.*[7,8] introduced fluorosulfonic acid for the cyclization of terpenoids; they demonstrated with several examples that fluorosulfonic acid as a cyclizing agent exceeds other acids, providing much higher structural selectivity in the reaction.

Later, in the study of cyclization of a series of labdane diterpenoids with fluorosulfonic acid, we have established that in this case the reaction characterizes by high structural selectivity as well.[9] Moreover, the reaction

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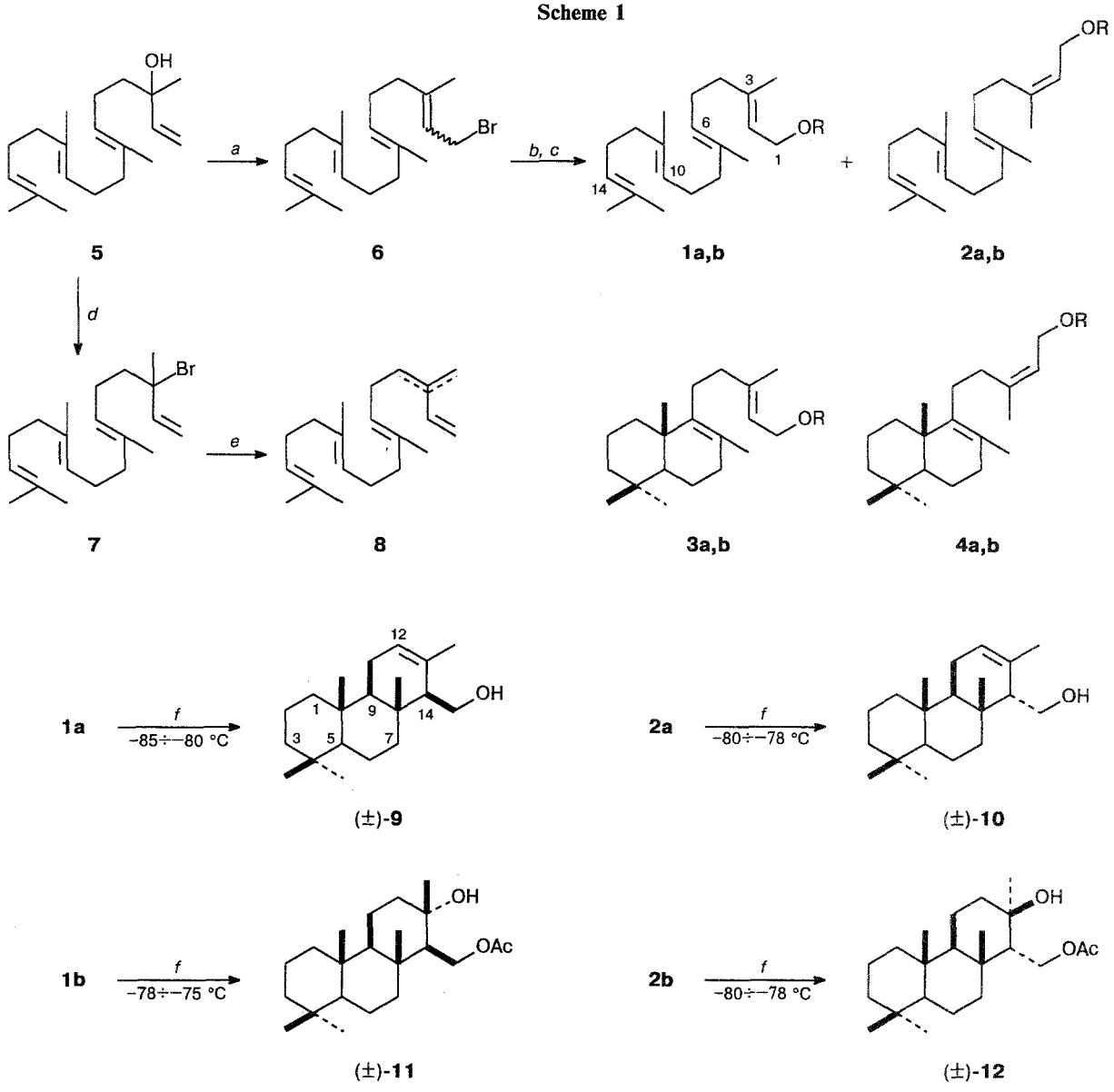
Scheme 1



R = H (**1a**, **2a**, **3a**, **4a**), Ac (**1b**, **2b**, **3b**, **4b**)

Reagents and conditions: *a*. PBr_3/Py—Et_2O, 0 °C; *b*. AcOK/DMF, 70 °C; *c*. KOH—EtOH; *d*. PBr_3/Py—Et_2O, −15÷−7 °C; *e*. Δ, 40—50 °C; *f*. FSO_3H—$PrNO_2$.

products, tricyclic isoagathane diterpenoids, appeared to differ from those obtained previously in the cyclization of the same compounds by ordinary acids (pimara- and rosadienes and giban-14α-ol),[10] thus indicating that the mechanism and the direction of the reaction have changed. A distinguishing feature of fluorosulfonic acid as a cyclizing agent as compared to ordinary acids has been revealed in these studies: the cyclization products of isomeric primary and tertiary allylic labdane alcohols were different.[11] It is known that the reaction of these isomeric alcohols with ordinary acids under the same conditions affords mixtures of the same products, which differ only in their proportion.[10]

The above results could be explained by the fact that fluorosulfonic acid as a superacid confers super-nonnucleophilic character to the reaction medium[12] that affects significantly the cyclization. This prompted us to carry out systematic studies on the cyclizations of various terpene compounds (alcohols, their acetates, acids, their esters, homo- and bishomoterpenoids) by

Table 1. Cyclization of terpenols and their acetates by fluorosulfonic acid in 1- or 2-nitropropane

Entry	Substrate	Target product	FSO_3H,* *m*/mg	V_1** /mL	Substrate,* *m*/mg	V_2** /mL	*T*/°C	*t*/min	Composition of the reaction mixture (%)		
									Target	Hydrocarbons	Polymers
1	**1a**	**9**	460 (4.60)	1.5	66 (0.23)	1.3	−85÷−80	4	87.2	8.1	4.7
2	**2a**	**10**	157 (1.57)	0.9	45 (0.16)	0.5	−80÷−78	40	61.1	8.9	29.9
3	**1b**	**11**	830 (8.30)	4.0	110 (0.33)	1.5	−78÷−75	20	72.2	20.8	7.0
4	**2b**	**12**	105 (1.05)	0.5	35 (0.11)	0.4	−80÷−78	80	64.7	9.3	26.0
5	**13a**	**18**	385 (3.85)	1.8	55 (0.15)	1.0	−85÷−80	90	57.6	6.0	36.4
6	**14a**	**19**	295 (2.95)	1.4	42 (0.12)	0.8	−85÷−80	90	55.2	9.0	35.8
7	**13b**	**20**	315 (3.15)	1.8	50 (0.12)	1.0	−85÷−80	60	60.5	7.0	32.5
8	**14b**	**21**	245 (2.45)	1.2	39 (0.10)	0.8	−85÷−80	90	56.0	7.0	37.0
9	**24a**	**18**	490 (4.90)	2.4	70 (0.20)	1.3	−85÷−80	120	56.3	9.0	34.7
10	**25a**	**19**	420 (4.20)	2.0	60 (0.17)	1.1	−85÷−80	120	54.3	10.2	35.5
11	**24b**	**20**	410 (4.10)	2.0	65 (0.16)	1.3	−85÷−80	90	58.4	9.0	32.6
12	**25b**	**21**	345 (3.45)	1.7	55 (0.14)	1.1	−85÷−80	90	55.2	11.7	33.1
13	**28a**	**30**	670 (6.70)	1.0	150 (0.67)	1.5	−85÷−80	7	57.9	12.5	29.6
14	**29a**	**31**	160 (1.60)	0.2	35 (0.16)	0.5	−82÷−80	55	63.2	12.4	24.4
15	**28b**	**32** **34**	320 (3.20)	1.0	80 (0.30)	1.0	−82÷−80	30	76.1 10.2	12.3	1.5
16	**29b**	**33**	220 (2.20)	0.5	60 (0.40)	0.4	−82÷−80	60	62.1	17.9	20.0
17	**35a**	**37**	715 (7.15)	3.5	110 (0.71)	3.0	−82÷−78	10	73.2	6.3	20.5
18	**36a**	**37**	350 (3.50)	1.7	54 (0.35)	1.8	−82÷−78	10	64.0	19.5	16.5
19	**35b**	**38a** **38b**	470 (4.70)	2.3	90 (0.46)	2.2	−85÷−80	60	65.0 7.0	5.2	22.8
20	**36b**	**38a** **38b**	425 (4.25)	2.0	85 (0.43)	2.1	−85÷−80	45	8.0 39.0	19.0	34.0

* Amounts (in mmol) are given in parentheses. ** V_1 and V_2 are the volumes of solvent for FSO_3H and substrate, respectively.

the superacid at low temperatures, which appeared optimal. The results of our studies have been partially published only as short communications.[13]

In the present paper, the complete data on the cyclization of β-terpenols and their acetates by fluorosulfonic acid are given. 1- and 2-nitropropanes were

found to be the most suitable solvents for the superacidic cyclization. The optimal temperature range to perform the reaction in these solvents is −85 to −60 °C. It should be noted that the successful realization of the reaction (with the acceptable duration), on going from mono- to sesqui-, di-, and sesterterpenoids, *i.e.*, with the increase in the molecular weight of the substrates, requires the increase in the cyclizing agent : substrate ratio. Analysis of this ratio allows to conclude that a part of fluorosulfonic acid is consumed for the solvation of the oxygen-containing functional groups and double bonds in the substrate.

Stereoisomeric (*E,E,E*)- and (*Z,E,E*)-geranylgeraniols (**1a** and **2a**) and their acetates (**1b** and **2b**) were selected primarily for study of superacidic cyclization of alcohols and their acetates in order to compare the results with those obtained previously[9] in the cyclization of stereoisomeric bicyclic geranylgeraniols (**3a** and **4a**) and their acetates (**3b** and **4b**) (Scheme 1).

(*E,E,E*)- and (*Z,E,E*)-geranylgeraniol acetates **1b** and **2b** were synthesized by ordinary way from (*E,E*)-geranyllinalool (**5**). The latter was transformed by the known procedure[14] (using PBr_3) to a mixture of geranylgeranyl bromides (**6**) which afforded a mixture of acetates **1b** and **2b** (4 : 1) under the action of AcOK separated by chromatography on $AgNO_3$-impregnated SiO_2 ($AgNO_3/SiO_2$).[15] It should be noted that in the bromination of compound **5** at lower temperature (−10 °C), geranyllinalyl bromide (**7**) was apparently the major reaction product, since after the treatment of the reaction product with AcOK, only a mixture of hydrocarbons (**8**) was isolated. On alkaline saponification of acetates **1b** and **2b**, alcohols **1a** and **2a** were obtained, respectively (see Scheme 1).

The cyclization of (*E,E,E*)-geranylgeraniol **1a** by FSO_3H in Pr^nNO_2 (substrate—FSO_3H ratio is 1 : 20, 4 min) yields (±)-14α*H*-isoagath-12-en-15-ol (**9**) (87 %).[16] Under similar conditions, but for much longer reaction time (40 min), (*Z,E,E*)-geranylgeraniol **2a** affords (±)-14β*H*-isoagath-12-en-15-ol (**10**) (61 %).

Under similar conditions (Table 1), the cyclization of isomeric geranylgeranyl acetates **1b** and **2b** gave diastereomeric tricyclic hydroxyacetates: (±)-15-acetoxy-14α*H*-isoagathan-13α-ol (**11**) and (±)-15-acetoxy-14β*H*-isoagathan-13β-ol (**12**) (yields 72 and 65 %, respectively). Compounds **9**—**12** were identified by comparison with the corresponding optically active samples.[9] Small amounts of hydrocarbons and polymeric products were the only impurities in the superacidic cyclization of compounds **1a,b** and **2a,b**; they can be easily removed from the major reaction product by chromatography.

Thus, the superacidic cyclization of stereoisomeric geranylgeraniols **1a** and **2a** and their acetates **1b** and **2b** proved to be highly chemo- and regioselective and stereospecific, which allowed us to prepare stereoisomeric racemic isoagathane diterpenoids **9**—**12** in one step and in high yield. The structural and steric course of the cyclizations of aliphatic (**1a,b** and **2a,b**) and bicyclic (**3a,b** and **4a,b**) diterpenoids possessing the same configuration of the allylic double bond are identical. Moreover, the yields of the tricyclic compounds are also similar. Note that the cyclization of (*E,E,E*)-geranylgeranyl *p*-nitrobenzoate **1c** induced by a dimethylaniline—mercuric triflate complex was structurally nonselective and the yield of isoagathane compounds did not exceed 25 %.[17]

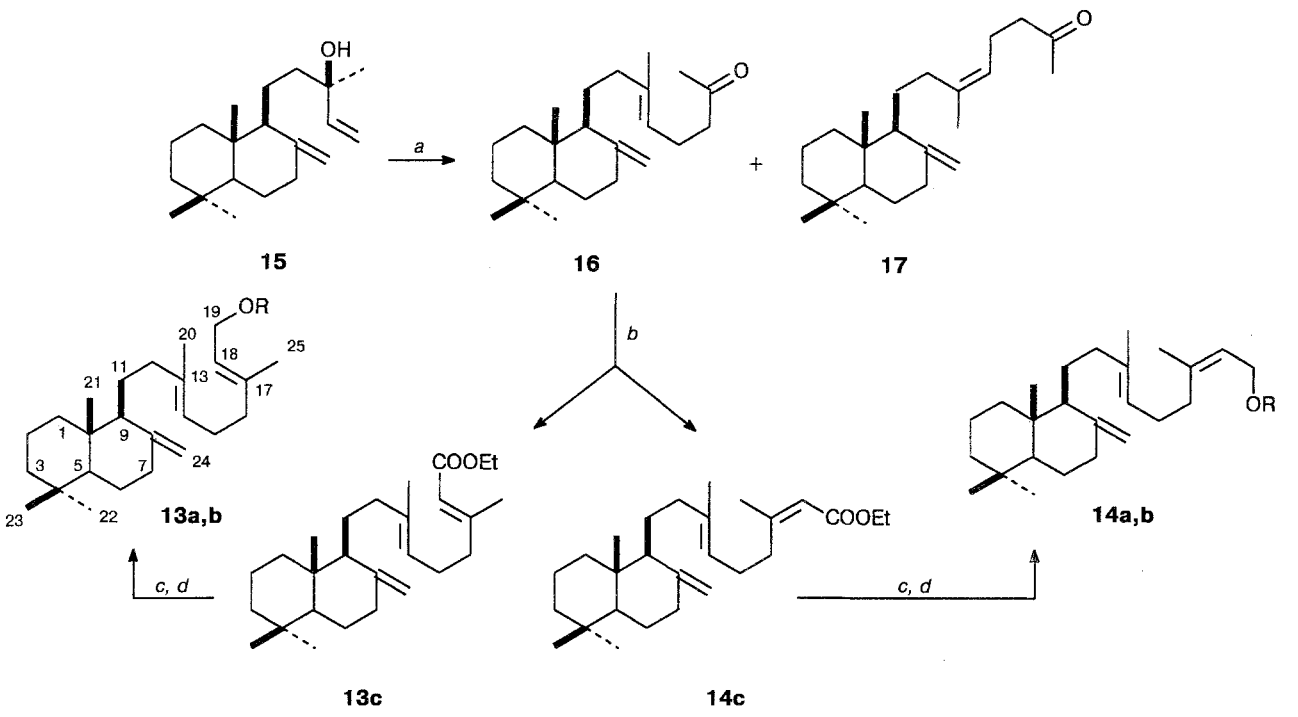
The excellent results on the cyclization of diterpenoids by FSO_3H shown above served as the basis for testing its efficiency as a cyclizing agent for more complex substrates of sesterterpenoid series.

Primarily, stereoisomeric bicyclogeranylfarnesols (**13a** and **14a**) and their acetates (**13b** and **14b**), synthesized from manool (**15**) as shown in Scheme 2, were taken as starting compounds. Using the described procedure,[18] **15** was transformed to a mixture of *trans*- and *cis*-bicyclogeranylacetones (**16** and **17**, 2 : 1)[19] by reaction with ethyl acetoacetate (EAA); the mixture was separated by chromatography on a column with $AgNO_3/SiO_2$. *trans*-Ketone **16** reacted with triethyl phosphonoacetate in the presence of NaH in DMSO[20] to give mixtures of (13*E*,17*E*)- and (13*E*,17*Z*)-bicyclogeranylfarnesoates (**13c** and **14c**, 3 : 1) (yield 78 %) also separated on a column with $AgNO_3/SiO_2$. Unsaturated esters **13c** and **14c** were reduced in a high yield to the corresponding allylic alcohols **13a** and **14a** by $LiAlH_3(OEt)$ in ether.[21] These alcohols were smoothly transformed to the corresponding acetates **13b** and **14b** by treatment with Ac_2O in pyridine.

The configuration of the allylic double bond in compounds **13a,b** and **14a,b** was established on the basis of the ^1H NMR spectra, since it is known[22] that the signal of the methyl group at this double bond is shifted upfield for the *trans*-isomers. On the contrary, in the ^1H NMR spectra of α,β-unsaturated esters **13c** and **14c**, the signal of this methyl group is shifted upfield for *cis*-isomer **14c**.[23]

Alcohols **13a** and **14a** react with FSO_3H in 2-nitropropane at the substrate—cyclizing reagent ratio equal to 1 : 25 yielding C(18)-epimeric tetracyclic scalarane sesterterpene alcohols (**18** and **19**, yields 58 and 55 %, respectively). Under the similar conditions (see Table 1), their acetates **13b** and **14b** transform to diastereomeric hydroxyacetates (**20** and **21**)[24] in yields 60 and 56 %, respectively. Thus, the reaction proceeds stereospecifically and structurally selectively. In addition to compounds **18**—**21**, small amounts of hydrocarbons (6—11 %) and polymeric product (20—30 %) were formed (Scheme 3). Known alcohols **18** and **19** were identified by comparison of their spectral data with those published previously.[19] According to the IR and ^1H NMR spectral data, the molecules of compounds **20** and **21** contain primary acetoxyl and tertiary hydroxyl groups, and the double bonds are absent. Consequently, they are tetracyclic compounds. The structure and the stereochemistry of these compounds followed from their chemical transformations. Dehydration of hydroxyacetate

Scheme 2



R = H (**13a**, **14a**), Ac (**13b**, **14b**)

Reagents and conditions: *a*. $MeCOCH_2CO_2Et$; *b*. $(EtO)_2P(O)CH_2CO_2Et$—NaH/DMSO; *c*. $LiAlH_3(OEt)$; *d*. Ac_2O—Py.

20 by phosphorous oxychloride in pyridine followed by saponification of the reaction product with ethanolic alkali afforded a mixture of isomeric unsaturated alcohols; according to spectral data, the isomer with the exocyclic double bond was predominant. An isomer of alcohols **22** possessing the trisubstituted Δ^{16}-double bond (**18**) was identified by comparison with an authentic sample. These data demonstrate the equatorial position of tertiary hydroxyl and acetoxymethyl groups in hydroxyacetate **20**. Dehydration of hydroxyacetate **21** by $POCl_3$ in Py followed by saponification of the reaction product with ethanolic alkali afforded a mixture of isomeric alcohols (**23**) with the major isomer having the trisubstituted double bond and identical to alcohol **19** (TLC and GLC data). Hence, both functional groups, hydroxyl and acetoxymethyl, are axial in hydroxyacetate **21**.

Thus, the superacidic cyclization of bicyclic sesterterpenoids **13a,b** and **14a,b** is a relatively short, efficient chemo- and structurally selective and stereospecific synthesis of tetracyclic scalarane sesterterpenoids in optically active form, whereas a few known methods of preparation of these compounds are multistep, and the yields of target products are low.[19, 25–28]

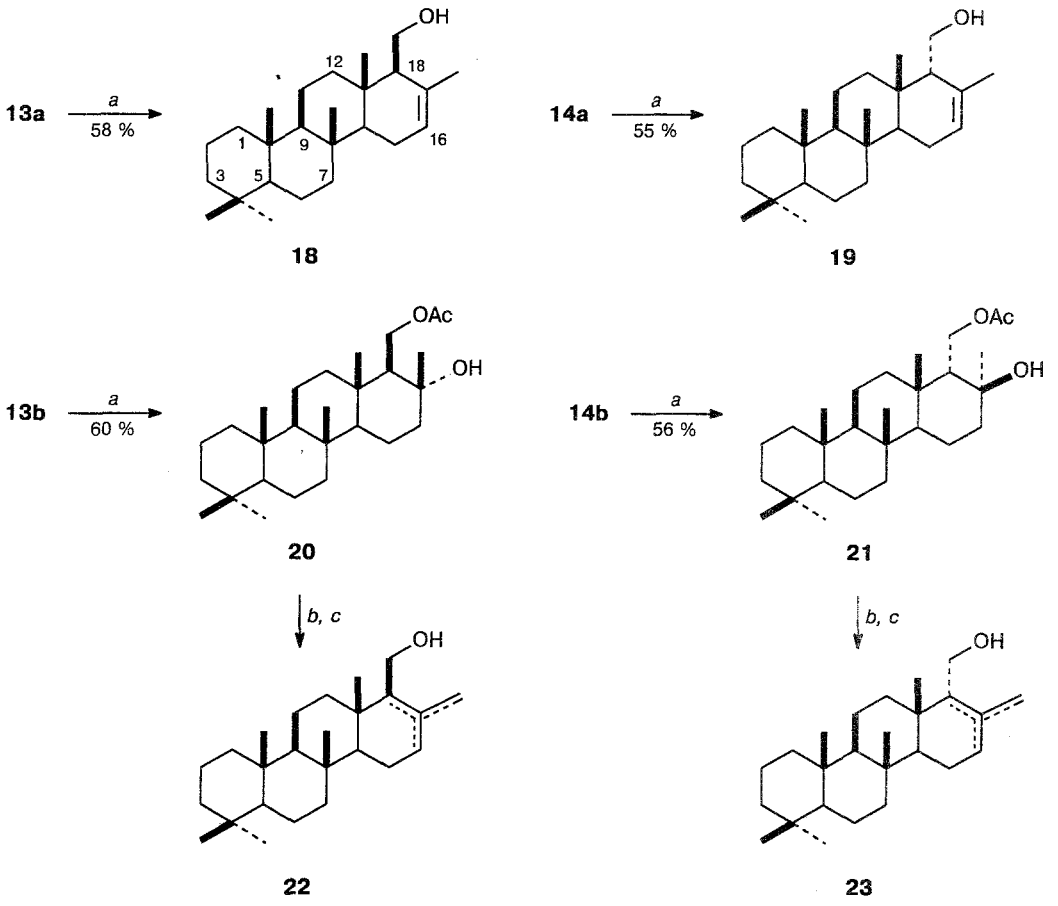
The aforementioned results on the cyclization of bicyclic sesterterpenoids prompted us to apply the superacidic cyclization in the biomimetic synthesis of scalarane tetracyclic sesterterpenoids directly from their aliphatic precursors.

There are only a few publications on the cyclization of aliphatic polyolefins (with irregular isoprene structure) into tetracyclic compounds induced by Lewis acids.[29–31] In all of the cases studied, the reaction was stereospecific, but structurally nonselective. The resulting reaction mixtures were complex, and the target compounds were difficult to isolate, this was achieved in low yield. Good yields of the tetracyclic products were achieved only when the isobutylidene group was introduced at the definite position of aliphatic compound in order to stabilize the intermediate bicyclic carbocation generated in the course of cyclization.[32] However, such approach makes much more difficult the synthesis of the starting compounds; in addition, isobutylidene group must be transformed to the methyl group, when isoprenoids of a regular structure are desired.

We have performed superacidic cyclization of (*E,E,E,E*)- and (*Z,E,E,E*)-geranylfarnesols (**24a** and **25a**) and their acetates (**24b** and **25b**). The starting compounds were synthesized from (*E,E*)-geranyllinalool (**5**) according to Scheme 4.

(*E,E*)-Geranyllinalool **5** was transformed using Carroll reaction to a mixture of (*E,E,E*)- and (*Z,E,E*)-geranylgeranylacetones (**26** and **27**, 3 : 1) in 77 % yield, which

Scheme 3



Reagents and conditions: *a*. FSO_3H—$PrNO_2$, −85÷−80 °C; *b*. $POCl_3$—Py; *c*. KOH—EtOH.

was separated by chromatography. The configuration of the Δ^5-double bond in these compounds was established on the basis of ^1H NMR spectra using literature data.[22] The *trans*-configuration was assigned to ketone **26**, the ^1H NMR signal of the C(6)—Me group of which was shifted upfield, and the *cis*-configuration of the double bond under consideration was assigned to its isomer **27**. *trans*-Ketone **26** was introduced into the reaction with triethyl phosphonoacetate[20] and a 9 : 1 mixture of *trans*- and *cis*-esters **24c** and **25c** was obtained; the mixture was separated by chromatography on a column with $AgNO_3/SiO_2$. The configuration of the Δ^2-double bond in esters **24c** and **25c** was established on the basis of the ^1H NMR spectra.[22] Esters **24c** and **25c** were reduced by $LiAlH_3(OEt)$[21] to corresponding alcohols **24a** and **25a**, which were transformed subsequently to acetates **24b** and **25b**.

The fluorosulfonic acid-induced cyclization of alcohols **24a**[33] and **25a** (for the conditions, see Table 1) gave racemic tetracyclic scalarenols **18** and **19** (yields 56 and 55 %, respectively), and the cyclization of acetates **24b**[33] and **25b** afforded hydroxyacetates **20** and **21** (yields 58 and 54 %) (Scheme 5).

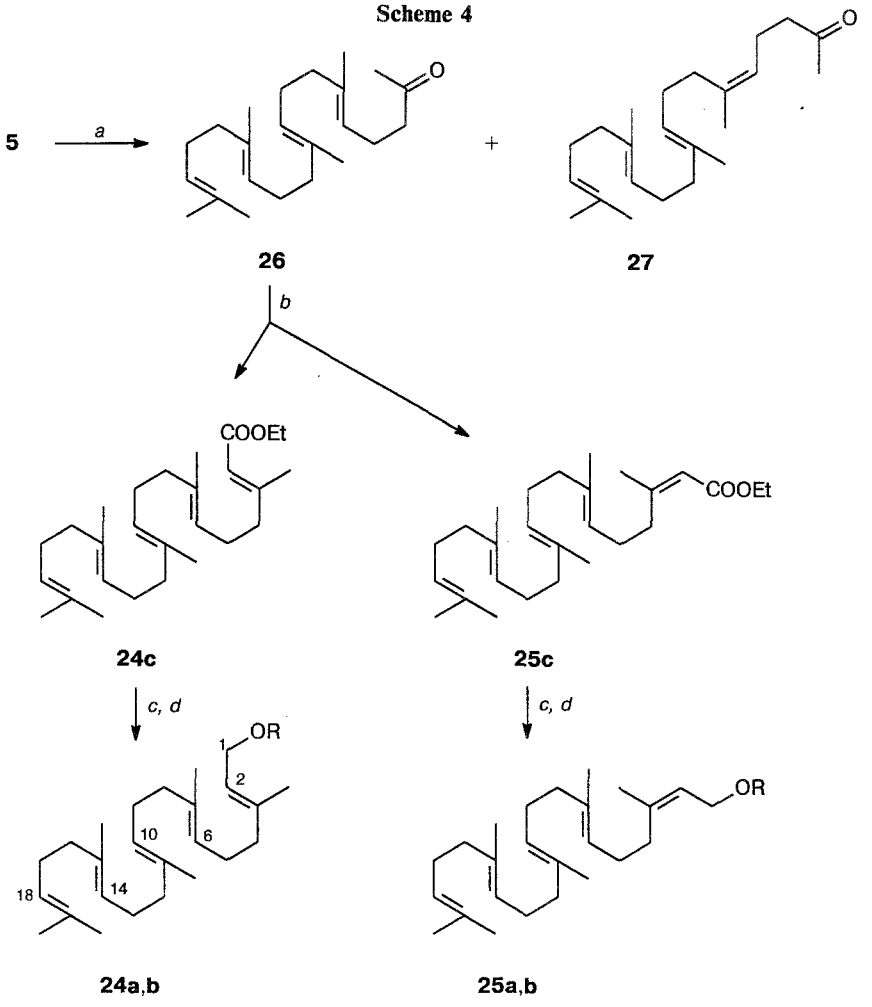
Like in the diterpenoid series (see above), the yields of compounds **18**—**21** formed in the superacidic cyclization of bicyclic and aliphatic sesterterpenoids are nearly the same. This fact confirms the hypothesis of Johnson *et al.*[32] that the efficiency of the cyclization of aliphatic compounds into tetracyclic ones depends on the stability of bicyclic carbocationic intermediates bearing a positive charge at C(8).

Thus, using the superacidic cyclization, we performed for the first time biomimetic, chemo- and structurally selective, stereospecific transformation of aliphatic sesterterpenoids into tetracyclic ones in good yields. For the first time, a configurationally pure tetracyclic product with 8 chiral carbon atoms was obtained stereospecifically in one step from an aliphatic compound.

The developed synthetic routes to the scalarane sesterterpenoids bearing functional groups in the cycle D make these compounds relatively accessible. They can serve as starting compounds for the synthesis of more complex, hardly available scalarane compounds and also substances possessing an interesting biological activity.

The results of the superacidic cyclization of stereoisomeric bicyclogeranylfarnesols **13a** and **14a**, their

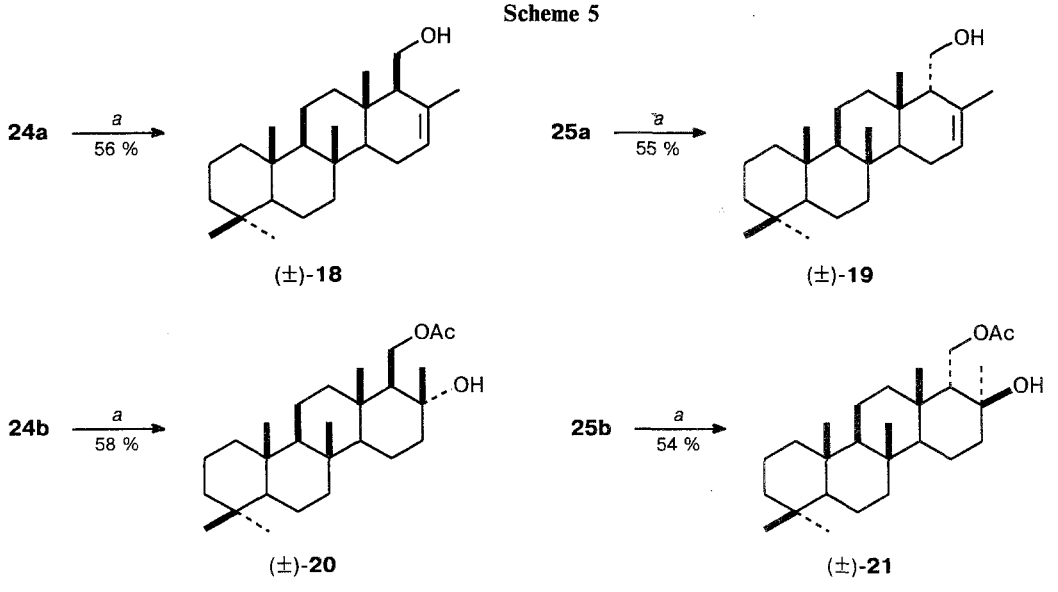
Scheme 4



R = H (**24a**, **25a**), Ac (**24b**, **25b**)

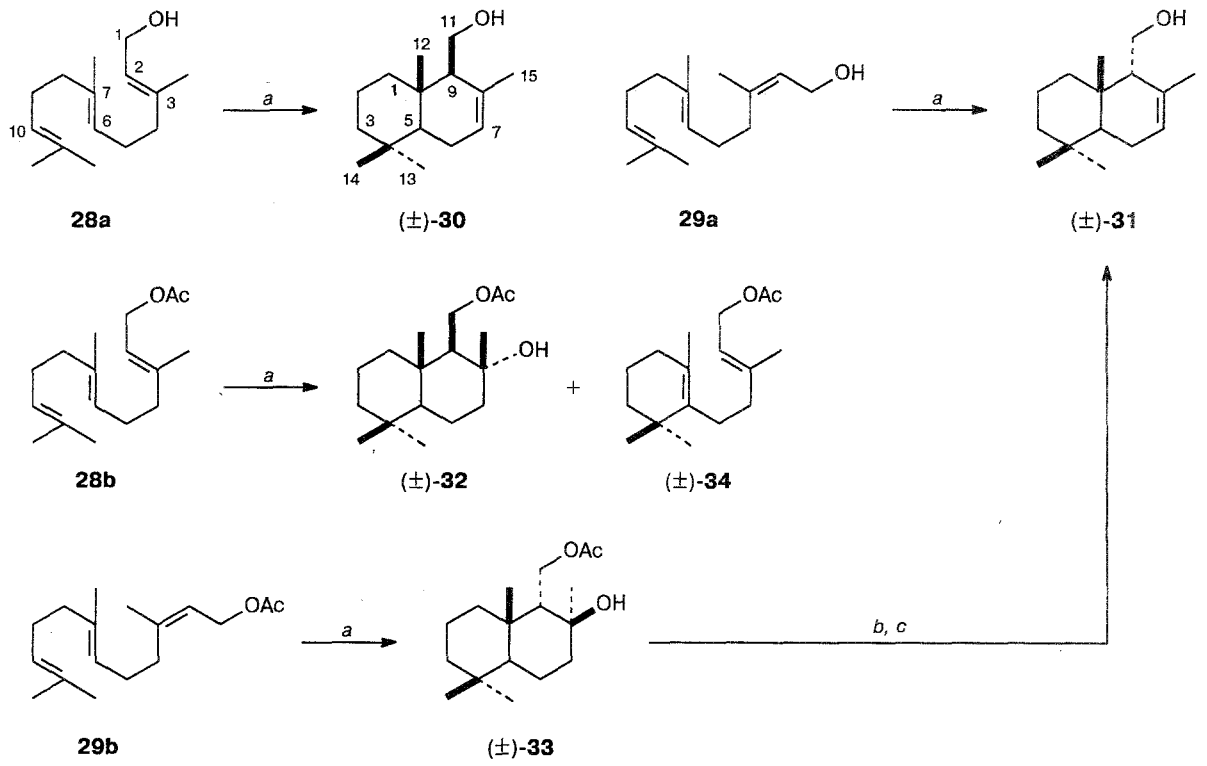
Reagents and conditions: *a*. $MeCOCH_2CO_2Et$, Δ; *b*. $(EtO)_2P(O)CH_2CO_2Et$—NaH/DMSO; *c*. $LiAlH_3(OEt)$; *d*. Ac_2O—Py.

Scheme 5



Reagents and conditions: *a*. FSO_3H—$PrNO_2$, −85÷−80 °C.

Scheme 6



Reagents and conditions: *a*. $FSO_3H—PrNO_2$, −85÷−80 °C; *b*. $POCl_3$—Py; *c*. KOH—EtOH.

acetates **13b** and **14b**, and aliphatic geranylfarnesols **24a** and **25a** and their acetates **24b** and **25b** indicate that the structural and stereochemical regularities in the superacidic low-temperature cyclization established for diterpene alcohols and their acetates are also valid in the case of sesterterpene compounds.

In order to examine the general character of these regularities, the superacidic cyclization of sesquiterpene and monoterpene compounds WAS also studied.

The cyclization of (*E,E*)-farnesol (**28a**) in a FSO_3H/Pr^nNO_2 system at the substrate—FSO_3H molar ratio equal to 1 : 1 afforded (±)-drimenol (**30**) in yield 71 % (Scheme 6) identified by comparison with an optically active sample. Under similar conditions, (*Z,E*)-farnesol (**29a**) gave (±)-9-epidrimenol (**31**) (yield 63 %) identified using the spectral data.[34—36]

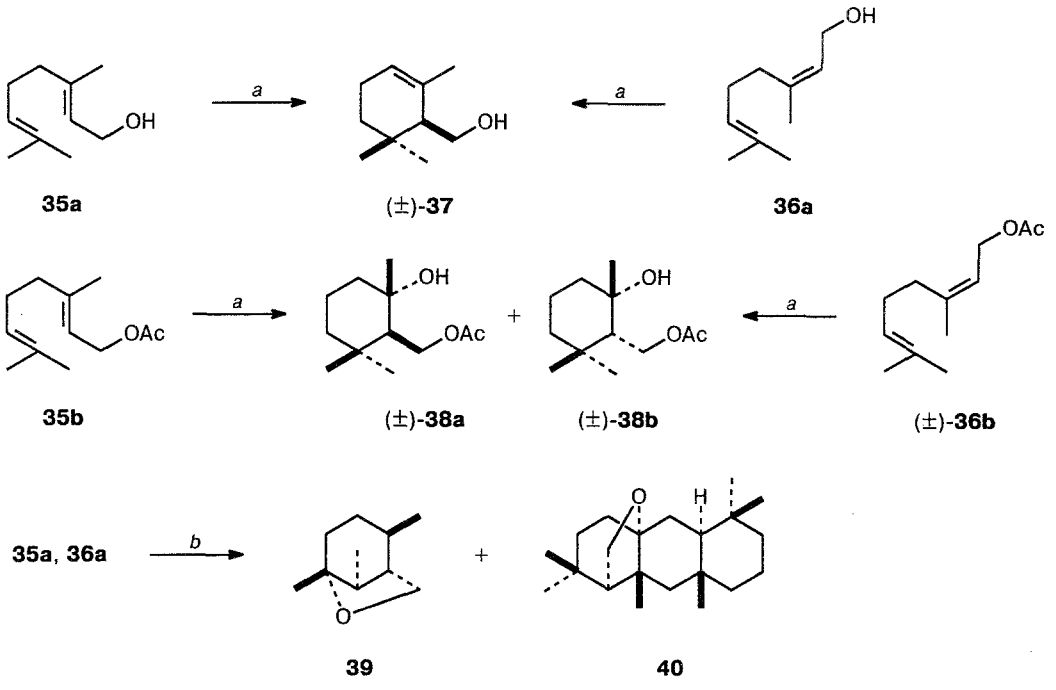
(±)-9α*H*-8α-Hydroxy-11-acetoxydrimane (**32**)[34] and (±)-9β*H*-8β-hydroxy-11-acetoxydrimane (**33**) were the major cyclization products of (*E,E*)- and (*Z,E*)-farnesyl acetates (**28b**) and (**29b**), respectively. Their yields were rather high (77 and 62 %, respectively). Hydroxyacetate **32** was identified by comparison with the analogous optically active sample, and the structure and stereochemistry of hydroxyacetate **33** were proved on the basis of the spectral data and the results of chemical transformations. Its dehydration in the $POCl_3$/Py system[37] followed by alkaline saponification of the reaction product yields a mixture of isomeric unsaturated alcohols, in which 9-epidrimenol **31** is the major component (spectral and chromatographic data). In the cyclization of sesquiterpenoids, small amounts of hydrocarbons and polymeric compounds are formed as side products. The cyclization of (*E,E*)-farnesyl acetate **28b** gives, along with these compounds, a small amount of β-monocyclofarnesyl acetate (**34**) (10 %), the yield of **34** achieves 70 %, if the reaction is interrupted after 1 min. This fact points to a the stepwise, rather than concerted mechanism of the superacidic cyclization of terpenols and their acetates including formation of intermediate carbocations.

Thus, the structural and stereochemical regularities of the cyclization of sesquiterpenols and their acetates proved to be similar to those for di- and sesterterpenoids.

It should be noted, that in the cyclization of (*E,E*)-farnesol **28a** by ordinary Brönsted acids, drimane sesquiterpenoids are not formed.[38]

Monoterpenoids, geraniol (**35a**), nerol (**36a**), and their acetates (**35b** and **36b**), are cyclized rather smoothly by fluorosulfonic acid.[39] Geraniol and nerol give the same product, *i.e.*, α-cyclogeraniol (**37**) in yields of 73 and 63 %, respectively (Scheme 7). Mixtures of the same diastereomeric hydroxyacetates (**38a,b**) are formed in the cyclization of geranyl and neryl acetates **35b** and **36b**; only the proportion of hydroxyacetates **38a** : **38b** changes: it is 9 : 1 for the cyclization of geranyl acetate **35b**, and 1 : 5 for the cyclization of neryl acetate **36b**.

Scheme 7



Reagents and conditions: *a*. $FSO_3H—PrNO_2$, −85÷−80 °C; *b*. $FSO_3H—SbF_5—SO_2FCl$.

It should be noted that in superacidic cyclization of geraniol **35a** and nerol **36a** by the action of stronger acid ($FSO_3H—SbF_5$ mixtures), the carbocations formed undergo further transformations affording γ-oxides (**39** and **40**).[40]

The presented data indicate that the superacidic cyclization of monoterpenyl acetates is just stereoselective, but not stereospecific reaction. This distinction in behavior of monoterpenoids and higher terpenoids in the superacidic cyclization can be apparently explained by conformational mobility of monocyclic carbocation intermediates.

Generalizing the above data on superacidic low-temperature (−85 to −60 °C) cyclization of aliphatic and partially cyclized $C_{10}—C_{25}$ terpenols and their acetates by fluorosulfonic acid, one can note the following general regularities of the reaction:

1. The reaction is chemo- and structurally selective and stereospecific.

2. In the cyclization of terpenols, totally cyclized homoallylic alcohols with a trisubstituted double bond (α-isomers) are formed. The configuration of the hydroxymethyl group in these alcohols is predetermined by the stereochemistry of the starting terpenols; *viz.*, terpenols with *trans*-configuration of the allylic double bond (**41**) transform into cyclic alcohols (**42**) with an equatorial hydroxymethyl group, and *cis*-terpenols (**43**) transform into products (**44**) having the axial hydroxymethyl group (Scheme 8).

3. The cyclization of terpenyl acetates affords monoacetates of totally cyclized diols. *trans*-Terpenyl acetates (**45**) give cyclic compounds (**46**), the tertiary hydroxyl and acetoxymethyl groups in which have an equatorial configuration, and *cis*-terpenyl acetates (**47**) transform into cyclic compound (**48**), in which these functional groups are axial.

The above regularities are partially violated for monoterpenoids, apparently, for conformational reasons. In the cyclization of monoterpenyl acetates, the reaction is no longer stereospecific, but it remains stereoselective.

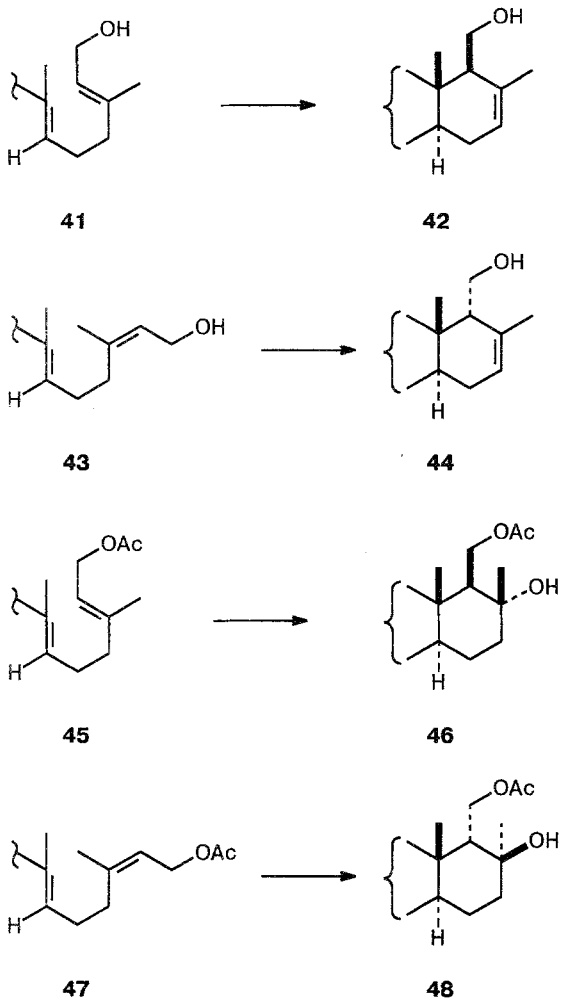
Along with the major reaction products, only small amounts of hydrocarbons and polymeric compounds are formed. Therefore, chromatographic isolation of the reaction products is not difficult. It should be also noted that there is no need to protect the hydroxyl groups in the superacidic cyclization of terpenols.

The above regularities are also valid in the superacidic cyclization of α-terpenols and their acetates[41]; the higher structural efficiency is the only distinction of this reaction.

Experimental

Melting points were determined with a Boetius heating stage. Optical rotations were measured in $CHCl_3$ with a SM polarimeter. The IR spectra were recorded with a Specord IR-74 instrument in CCl_4, and the ^1H NMR spectra were measured with Tesla BS-476 (60 MHz) and Bruker AC-80 (80 MHz) spectrometers. GLC analyses were carried out with a Chrom-5 chromatograph equipped with a flame-ionization detector (1500×3 mm glass column, 5 % SE-30 or 5 % XE-60 stationary phases on Chromaton N-AW-DMCS). Column chromatography

Scheme 8



was performed on L 40/100 μm and L 100/250 μm silica gel and silica gel impregnated with $AgNO_3$.[15] Silica gel LS 5/40 μm was used for TLC.

The workup of the reaction mixtures in organic solvents involved exhaustive extraction with diethyl ether and washing with water up to neutral reaction, and in the case of acidic solutions the workup included subsequent washing with water, saturated $NaHCO_3$, and water, drying over anhydrous Na_2SO_4, filtration, and removal of the solvent *in vacuo*.

Synthesis of a mixture of isomeric geranylgeranyl acetates 1b and 2b. A solution of PBr_3 (0.8 mL, 8.423 mmol) in anhydrous ether (2 mL) was added with stirring to a solution of (*E,E*)-geranyllinalool **5** (2 g, 6.896 mmol) in anhydrous ether (20 mL) and dry pyridine (0.8 mL) chilled to 0 °C. The mixture was stirred for 3 h and then treated as described above; the reaction product (2.33 g) was dissolved in DMF (10 mL) and freshly fused AcOK (2.2 g) was added with stirring. The mixture was stirred at *ca.* 20 °C for 3 h and at 60—65 °C for 5 h. After the workup of the mixture, the reaction product (1.93 g) was obtained; it was chromatographed on a column with $AgNO_3/SiO_2$ (35 g). A mixture of low-polar compounds (0.105 g) was eluted with light petroleum that was not examined further. Then compound **2b** (0.23 g) was eluted with a light petroleum : ethyl acetate mixture (49 : 1) as a colorless viscous liquid. Found (%): C, 79.32; H, 10.96. $C_{22}H_{36}O_2$. Calculated (%): C, 79.46; H, 10.91. IR, ν/cm^{-1}: 1227, 1735 (OAc); 830, and 1664 (C=CH). ^1H NMR (CCl_4), δ: 1.56 (s, 6 H, C(15)—Me_2); 1.58 (s, 3 H, C(11)—Me); 1.65 (s, 3 H, C(7)—Me); 1.75 (s, 3 H, C(3)—Me); 1.93 (s, 3 H, OAc); 4.46 (d, 2 H, CH_2O, J = 7 Hz); 5.05 (m, 3 H, C(6)—H, C(10)—H and C(14)—H); and 5.30 (t, 1 H, C(2)—H, J = 7 Hz).

A mixture of acetates **1b** and **2b** (0.574 g) was eluted with a mixture of the same solvents (19 : 1); then pure compound **1b** (0.884 g) was obtained as a viscous colorless liquid. IR, ν/cm^{-1}: 1231, 1740 (OAc); 840, and 1660 (C=CH). ^1H NMR (CCl_4), δ: 1.58 (s, 9 H, C(11)—Me and C(15)Me_2); 1.66 (s, 3 H, C(7)—Me); 1.68 (s, 3 H, C(3)—Me); 1.95 (s, 3 H, OAc); 4.47 (d, 2 H, CH_2O, J = 7 Hz); 5.05 (m, 3 H, C(6)—H, C(10)—H and C(14)—H); and 5.26 (t, 1 H, C(2)—H, J = 7 Hz).

***(E,E,E)*-Geranylgeraniol (1a).** A 10 % ethanolic solution of KOH (5 mL) was added to a solution of (*E,E,E*)-geranylgeranyl acetate **1b** (0.43 g, 1.295 mmol) in EtOH (2 mL) and the mixture was heated under reflux for 2.5 h. After the workup, compound **1a** was obtained (0.356 g, yield 95 %, a viscous colorless liquid). IR, ν/cm^{-1}: 3467, 3610 (OH); 830, and 1657 (C=CH). ^1H NMR (CCl_4), δ: 1.55 (s, 9 H, C(11)—Me and C(15)Me_2); 1.61 (s, 3 H, C(7)—Me); 1.68 (s, 3 H, C(3)—Me); 2.36 (br.s, 1 H, OH); 3.95 (d, 2 H, CH_2O, J = 7 Hz); 5.03 (m, 3 H, C(6)—H, C(10)—H and C(14)—H); and 5.30 (t, 1 H, C(2)—H, J = 7 Hz).

***(Z,E,E)*-Geranylgeraniol (2a).** A 10 % ethanolic solution of KOH (3 mL) was added to a solution of (*Z,E,E*)-geranylgeranyl acetate **2b** (0.12 g, 0.361 mmol) in EtOH (1 mL) and the mixture was heated under reflux for 3 h. After the workup, compound **2a** was obtained (0.098 g, 93 %, a viscous colorless liquid). Found (%): C, 82.77; H, 11.67. $C_{20}H_{34}O$. Calculated (%): C, 82.69; H, 11.80. IR, ν/cm^{-1}: 3455, 3615 (OH); 832, and 1660 (C=CH). ^1H NMR ($CDCl_3$), δ: 1.60 (s, 9 H, C(11)—Me and C(15)Me_2); 1.68 (s, 3 H, C(7)—Me); 1.76 (s, 3 H, C(3)—Me); 2.42 (br.s, 1 H, OH); 4.10 (d, 2 H, CH_2O, J = 7 Hz); 5.09 (m, 3 H, C(6)—H, C(10)—H and C(14)—H); and 5.42 (t, 1 H, C(2)—H, J = 7 Hz).

Superacidic cyclization of terpenols and their acetates (general procedure). A solution of definite amount of a substrate in definite volume of 1- or 2-nitropropane chilled to the required temperature was added to a solution of fluorosulfonic acid in definite amount of the same solvent chilled to the same temperature with vigorous stirring. The mixture was stirred at the required temperature for specified time, then a 50 % excess (with respect to the amount of FSO_3H used) of a Et_3N solution in equal volume of light petroleum was added. The temperature of the reaction mixture was raised to ambient, and then it was extracted with ether three times. The ethereal extract was washed with a 10 % solution of H_2SO_4, water, a saturated solution of $NaHCO_3$, and water, dried, and filtered, and the solvent was removed *in vacuo*. The residue was chromatographed on a column with SiO_2, using light petroleum and its gradient mixtures with ethyl acetate (up to 20 % of EtOAc). The results obtained are listed in Table 1.

Reaction of manool 15 with ethyl acetoacetate. Manool **15** (5 g, 17.241 mmol) was dissolved in freshly distilled ethyl acetoacetate (7.5 mL, 58.84 mmol), and the solution was heated at 150—170 °C for 2 h in a Favorsky flask until distillation of ethanol ceased and then additionally for 1 h at 210—220 °C. The mixture was cooled, diluted with ether (80 mL), and worked up as usual, and a mixture of ketones **16** and **17** (5.3 g, 3 : 1, GLC data) was obtained. The mixture

was chromatographed on a column with $AgNO_3/SiO_2$ (90 g). A mixture low-polar compounds (0.18 g) was eluted with light petroleum that was not examined further. (13*Z*)-Bicyclogeranylgeranylacetone (**17**) (0.64 g) was eluted with a light petroleum : ethyl acetate mixture (19 : 1); the product was identical with an authentic sample.[18] A mixture of ketones **16** and **17** (2.80 g) and then ketone **16** (1.39 g) were eluted from the column with the same solvent mixture. The total yield of ketones **16** and **17** was 85 %.

Reaction of (13*E*)-bicyclogeranylgeranylacetone (16) with triethyl phosphonoacetate. A suspension of NaH (0.095 g, 3.96 mmol) in DMSO (2 mL) was heated to 80 °C under Ar, and the mixture was stirred at 80 °C for 45 min. Then the mixture was chilled to 0 °C, and triethyl phosphonoacetate (0.8 g, 3.57 mmol) in DMSO (4 mL) was added with stirring. The temperature of the reaction mixture was raised to ambient, the mixture was stirred for 10 min, and then a solution of ketone **16** (0.7 g, 2.12 mmol) in DMSO (5 mL) was added. The mixture was stirred at 80 °C for 6 h and then chilled and worked up as usual. A mixture of esters **13c** and **14c** (0.74 g, 3 : 1, 79 %) was obtained and chromatographed on a column with $AgNO_3/SiO_2$ (18 g). A mixture of low-polar compounds (0.026 g) was eluted with light petroleum that was not examined further. (17*Z*)-Ester **14c** (0.085 g) was eluted with a light petroleum : ethyl acetate mixture (19 : 1) as a colorless viscous liquid, $[\alpha]^{20}_D$ +3.8° (*c* 2.1). Found (%): C, 81.05; H, 11.09. $C_{27}H_{44}O_2$. Calculated (%): C, 80.94; H, 11.07. IR, ν/cm^{-1}: 1710 (CO_2Et); 890, 1640 ($C=CH_2$); 857, and 1645 (C=CH). ^1H NMR (CCl_4), δ: 0.67 (s, 3 H, C(10)—Me); 0.80 and 0.88 (both s, 6 H, C(4)Me_2); 1.25 (t, 3 H, $OCH_2\underline{Me}$, *J* = 7 Hz); 1.64 (s, 3 H, C(13)—Me); 2.05 (s, 3 H, C(17)—Me); 4.05 (q, 2 H, $OC\underline{H}_2Me$, *J* = 7 Hz); 4.50 and 4.78 (both br.s, 2 H, $C=CH_2$); 5.07 (m, 1 H, C(14)—H); 5.55 (br.s, 1 H, C(18)—H).

A mixture of esters **13c** and **14c** (0.252 g) was eluted from the column with the same eluent, and then (17*E*)-ester **13c** (0.33 g) was eluted as a colorless viscous liquid, $[\alpha]^{20}_D$ +23.4° (*c* 1.7). Found (%): C, 80.86; H, 11.16. $C_{27}H_{44}O_2$. Calculated (%): C, 80.94; H, 11.07. IR, ν/cm^{-1}: 1140, 1710 (CO_2Et); 886, 1638 ($C=CH_2$); 853, and 1668 (C=CH). ^1H NMR (CCl_4), δ: 0.67 (s, 3 H, C(10)—Me); 0.80 and 0.88 (both s, 6 H, C(4)Me_2); 1.23 (t, 3 H, $OCH_2\underline{Me}$, *J* = 7 Hz); 1.60 (s, 3 H, C(13)—Me); 2.14 (s, 3 H, C(17)—Me); 4.02 (q, 2 H, $OC\underline{H}_2Me$, *J* = 7 Hz); 4.45 and 4.75 (both br.s, 2 H, $C=C\underline{H}_2$); 5.02 (m, 1 H, C(14)—H); 5.55 (br.s, 1 H, C(18)—H).

(13*E*,17*E*)-Bicyclogeranylfarnesol (13a). An ethereal solution (1.0 mL) of $LiAlH_3(OEt)$ (0.017 g, 0.20 mmol) (prepared as described in Ref. 21) was added to a solution of ethyl (13*E*,17*E*)-bicyclogeranylfarnesoate (**13c**) (0.17 g, 0.425 mmol) in anhydrous ether (1.5 mL), and the mixture was kept at ambient temperature for 2 h. The mixture was worked up as usual and compound **13a** (0.14 g, 91 %) was obtained as a colorless viscous liquid, $[\alpha]^{20}_D$ +24° (*c* 2.7). Found (%): C, 83.87; H, 11.78. $C_{25}H_{42}O$. Calculated (%): C, 83.73; H, 11.81. IR, ν/cm^{-1}: 3410, 3615 (OH); 883, 1637 ($C=CH_2$); 850, and 1662 (C=CH). ^1H NMR (CCl_4), δ: 0.67 (s, 3 H, C(10)—Me); 0.80 and 0.86 (both s, 6 H, C(4)Me_2); 1.25 (s, 3 H, C(13)—Me); 1.51 (s, 3 H, C(17)—Me); 3.97 (d, 2 H, CH_2O, *J* = 7 Hz); 4.47 and 4.77 (both br.s, 2 H, $C=CH_2$); and 4.83—5.52 (m, 2 H, C(14)—H and C(18)—H).

(13*E*,17*Z*)-Bicyclogeranylfarnesol (14a). An ethereal solution (0.6 mL) of $LiAlH_3(OEt)$ (0.01 g, 0.12 mmol) was added to a solution of ethyl (13*E*,17*Z*)-bicyclogeranylfarnesoate (**14c**) (0.1 g, 0.25 mmol) in anhydrous ether (0.8 mL), and the mixture was kept at *ca.* 20 °C for 2.5 h. After ordinary workup, compound **14a** (0.0784 g, 87.6 %) was obtained as a colorless viscous liquid; $[\alpha]^{20}_D$ +8.1° (*c* 2.9). Found (%): C, 83.94; H, 11.77. $C_{25}H_{42}O$. Calculated (%): C, 83.73; H, 11.81. IR, ν/cm^{-1}: 3453, 3608 (OH); 890, 1640 ($C=CH_2$); 840, and 1663 (C=CH). ^1H NMR (CCl_4), δ: 0.60 (s, 3 H, C(10)—Me); 0.75 and 0.80 (both s, 6 H, C(4)Me_2); 1.18 (s, 3 H, C(13)—Me); 1.58 (s, 3 H, C(17)—Me); 2.40 (br.s, 1 H, OH); 3.96 (d, 2 H, CH_2O, *J* = 6 Hz); 4.50 and 4.71 (both br.s, 2 H, $C=CH_2$); and 4.87—5.50 (m, 2 H, C(14)—H and C(18)—H).

(13*E*,17*E*)-Bicyclogeranylfarnesyl acetate (13b). Ac_2O (0.2 mL, 2.12 mmol) was added to a solution of (13*E*,17*E*)-bicyclogeranylfarnesol (**13a**) (0.124 g, 0.346 mmol) in dry pyridine (1.8 mL), and the mixture was kept at *ca.* 20 °C for 3.5 h and worked up as usual. The reaction product (0.136 g) obtained was chromatographed on a column with SiO_2 (1.6 g). Compound **13b** (0.127 g, 92 %) was eluted with a light petroleum : ethyl acetate mixture (9 : 1) as a colorless viscous liquid; $[\alpha]^{20}_D$ +19.6° (*c* 2.9). Found (%): C, 81.12; H, 11.09. $C_{27}H_{44}O_2$. Calculated (%): C, 80.94; H, 11.07. IR, ν/cm^{-1}: 1230, 1736 (OAc); 882, 1640 ($C=CH_2$); 855, and 1667 (C=CH). ^1H NMR (CCl_4), δ: 0.67 (s, 3 H, C(10)—Me); 0.80 and 0.87 (both s, 6 H, C(4)Me_2); 1.25 (s, 3 H, C(13)—Me); 1.58 (s, 3 H, C(17)—Me); 1.97 (s, 3 H, OAc); 4.45 (d, 2 H, CH_2O, *J* = 7 Hz); 4.58 and 4.75 (both br.s, 2 H, $C=CH_2$); and 5.20 (m, 2 H, C(14)—H and C(18)—H).

(13*E*,17*Z*)-Bicyclogeranylfarnesyl acetate (14b). Ac_2O (0.1 mL, 1.06 mmol) was added to a solution of 13*E*,17*Z*-bicyclogeranylfarnesol (**14a**) (0.072 g, 0.20 mmol) in dry pyridine (1.2 mL); the mixture was kept at *ca.* 20 °C for 4 h and worked up as usual. Compound **14b** (0.075 g) was obtained as a colorless viscous liquid, $[\alpha]^{20}_D$ +7.8° (*c* 2.6). Found (%): C, 81.06; H, 10.94. $C_{27}H_{44}O_2$. Calculated (%): C, 80.94; H, 11.07. IR, ν/cm^{-1}: 1230, 1735 (OAc); 890, 1642 ($C=CH_2$); 853, and 1664 (C=CH). ^1H NMR (CCl_4), δ: 0.67 (s, 3 H, C(10)—Me); 0.80 and 0.87 (both s, 6 H, C(4)Me_2); 1.23 (s, 3 H, C(13)—Me); 1.65 (s, 3 H, C(17)—Me); 1.92 (s, 3 H, OAc); 4.46 (d, 2 H, CH_2O, *J* = 7 Hz); 4.52 and 4.78 (both br.s, 2 H, $C=CH_2$); and 5.17 (m, 2 H, C(14)—H and C(18)—H).

18α*H*-Scalar-16-en-19-ol (18) (see Table 1, entry *5*): m.p. 165—166.5 °C (from light petroleum); $[\alpha]^{23}_D$ +31.7° (*c* 2.3). Found (%): C, 83.62; H, 11.78. $C_{25}H_{42}O$. Calculated (%): C, 83.73; H, 11.81. IR, ν/cm^{-1}: 1040, 3435, and 3600 (OH). ^1H NMR (CCl_4), δ: 0.80 (s, 3 H, C(10)—Me); 0.83 (s, 6 H, C(4)Me_2); 0.93 (s, 6 H, C(8)—Me and C(13)—Me); 1.58 (s, 3 H, C(17)—Me); 3.50 (m, 2 H, CH_2O); and 5.41 (m, 1 H, C(16)—H).

18β*H*-Scalar-16-en-19-ol (19) (see Table 1, entry *6*): viscous liquid, $[\alpha]^{20}_D$ −8.5° (*c* 1.0). Found (%): C, 83.56; H, 11.79. $C_{25}H_{42}O$. Calculated (%): C, 83.73; H, 11.81. IR, ν/cm^{-1}: 1055, 3445, 3624 (OH); 848, and 1670 (C=CH). ^1H NMR (CCl_4), δ: 0.83 and 0.90 (both s, 9 H, C(4)Me_2 and C(10)—Me); 0.98 (s, 6 H, C(8)—Me and C(13)—Me); 1.55 (s, 3 H, C(17)—Me); 3.61 (m, 2 H, CH_2O); and 5.53 (m, 1 H, C(18)—H).

18α*H*-Scalarane-17α,19-diol 19-monoacetate (20) (see Table 1, entry *7*): m.p. 203.5—205 °C (from light petroleum); $[\alpha]^{20}_D$ −1.6° (*c* 2.9). Found (%): C, 77.38; H, 11.10. $C_{27}H_{46}O_3$. Calculated (%): C, 77.46; H, 11.07. IR ($CHCl_3$), ν/cm^{-1}: 1217, 1720 (OAc); 3448, and 3583 (OH). ^1H NMR ($CDCl_3$), δ: 0.80 (s, 9 H, C(8)—Me, C(10)—Me and C(13)—Me); 0.83 (s, 6 H, C(4)Me_2); 1.25 (s, 3 H, C(17)—Me); 2.03 (s, 3 H, OAc); 2.33 (m, 1 H, OH); and 4.26 (d, 2 H, CH_2O, *J* = 5 Hz).

18β*H*-Scalarane-17β,19-diol 19-monoacetate (21) (see Table 1, entry *8*): amorphous compound, $[\alpha]^{20}_D$ −32.4° (*c* 2.9). Found (%): C, 77.29; H, 11.16. $C_{27}H_{46}O_3$. Calculated (%): C, 77.46; H, 11.07. IR ($CHCl_3$), ν/cm^{-1}: 1230, 1725 (OAc); 3420, and 3580 (OH). ^{1}H NMR ($CDCl_3$), δ: 0.78 (s, 3 H, C(10)—Me); 0.81 (s, 6 H, C(4)Me$_2$); 0.95 (s, 6 H, C(8)—Me and C(13)—Me); 1.23 (s, 3 H, C(17)—Me); 2.03 (s, 3 H, OAc); 2.30 (m, 1 H, OH); and 4.27 (d, 2 H, CH_2O, J = 6 Hz).

Mixture of scalarane alcohols 23. $POCl_3$ (0.05 mL) was added to a chilled to −10 °C solution of hydroxyacetate **21** (38 mg) in pyridine (1.5 mL); the mixture was stirred at −10 °C for 30 min. Then the mixture was heated to *ca.* 20 °C and stored for 2.5 h, ice was added, and the mixture was worked up as usual. The reaction product (29 mg) obtained was saponified by refluxing in 10 % ethanolic solution of KOH (1.5 mL) for 1 h. After ordinary workup, a mixture of isomeric alcohols **23** (21 mg) was obtained. Scalarane alcohol possessing trisubstituted double bond **19** was a major component (65 %, GLC conditions: T_{col} 230 °C, T_{inj} 250 °C, He was used as a carrier gas, 45 mL min^{-1}).

Mixture of scalarane alcohols 22. $POCl_3$ (0.07 mL) was added to a chilled to −10 °C solution of hydroxyacetate **20** (43 mg) in pyridine (1.8 mL); the mixture was stirred at −10 °C for 1 h. Then the mixture was heated to *ca.* 20 °C and left for 5 h. After the workup, the reaction product (32 mg) was obtained and then saponified by refluxing in 10 % ethanolic solution of KOH (2 mL) for 2.5 h. After ordinary workup, a mixture of isomeric alcohols **22** (23 mg) was obtained. Strong bands at 890 and 1640 cm^{-1} were observed in the IR spectrum of the product. The content of the isomer possessing exocyclic double bond was *ca.* 60 % (GLC data, the conditions see above).

Reaction of (*E,E*)-geranyllinalool (5) with ethyl acetoacetate. Freshly distilled ethyl acetoacetate (1.3 mL, 10.20 mmol) was added to geranyllinalool **5** (0.89 g, 3.07 mmol); the solution was heated in a Favorsky flask at 150—170 °C for 2 h until distillation of ethanol ceased and additionally for 1 h at 210—220 °C. The reaction product was worked up as usual, and a mixture of ketones **26** and **27** (0.92 g, 3 : 1) was obtained (GLC conditions: T_{col} 200 °C, T_{inj} 250 °C, 5 % SE-30 on Chromaton N-AW-DMCS, He was used as carrier gas, 45 mL min^{-1}). The mixture was chromatographed on a column with $AgNO_3/SiO_2$ (25 g). A mixture of low-polar compounds (0.02 g) was eluted with light petroleum and was not examined further. (*Z,E,E*)-Geranylgeranylacetone **27** (0.12 g, a colorless viscous liquid) was eluted with a light petroleum : ethyl acetate mixture (97 : 3). Found (%): C, 83.72; H, 11.44. $C_{23}H_{38}O$. Calculated (%): C, 83.57; H, 11.59. IR, ν/cm^{-1}: 1720 (COMe); 853, and 1662 (C=CH). ^{1}H NMR (CCl_4), δ: 1.51 (s, 12 H, Me groups at double bonds); 1.61 (s, 3 H, C(6)—Me); 1.99 (s, 3 H, COMe); and 5.01 (m, 4 H, vinylic protons). Then a mixture of ketones **26** and **27** (0.212 g) and finally (*E,E,E*)-geranylgeranylacetone **26** (0.453 g) were eluted from the column with the same solvent mixture. **26:** a colorless viscous liquid. Found (%): C, 83.64; H, 11.62. $C_{23}H_{38}O$. Calculated (%): C, 83.57; H, 11.59. IR, ν/cm^{-1}: 1723 (COMe); 850, and 1660 (C=CH). ^{1}H NMR (CCl_4), δ: 1.51 (s, 12 H, Me groups at double bonds); 1.57 (s, 3 H, C(6)—Me); 1.96 (s, 3 H, COMe); 4.98 (m, 4 H, vinylic protons). Starting geranyllinalool **5** (0.084 g) was eluted with a mixture of the same solvents (9 : 1). The total yield of ketones **26** and **27** was 85 % (with respect to conversion of the starting compound).

Reaction of (*E,E,E*)-geranylgeranylacetone (26) with triethyl phosphonoacetate. A suspension of NaH (0.32 g, 13.3 mmol) in 10 mL DMSO was heated under Ar to 75 °C and the mixture was stirred at 75 °C for 45 min. Then the mixture was cooled to 0 °C and a solution of triethyl phosphonoacetate (2.8 g) in DMSO (15 mL) was added with stirring. The reaction mixture was heated to *ca.* 20 °C and stirred for 10 min; then a solution of compound **26** (2.4 g) in DMSO (12 mL) was added. The mixture was stirred at 80 °C for 7 h, cooled, and worked up as usual. The reaction product (2.57 g) was obtained and chromatographed on a column with $AgNO_3/SiO_2$ (95 g). A mixture of low-polar compounds (0.057 g) was eluted with light petroleum and was not examined further; a mixture of esters **24c** and **25c** (0.265 g), then pure ethyl (*E,E,E,E*)-geranylfarnesoate (**24c**) (1.67 g) were eluted with a light petroleum : ethyl acetate mixture (19 : 1), **24c:** a colorless viscous liquid. Found (%): C, 80.80; H, 11.09. $C_{27}H_{44}O_2$. Calculated (%): C, 80.94; H, 11.07. IR, ν/cm^{-1}: 1715 (O—C=O); 853, and 1643 (C=CH). ^{1}H NMR (CCl_4), δ: 1.25 (t, 3 H, $OCH_2\underline{Me}$, J = 7 Hz); 1.56 (s, 15 H, 5 Me groups at double bonds); 2.12 (s, 3 H, C(3)—Me); 4.07 (q, 2 H, $OC\underline{H}_2Me$, J = 7 Hz); 5.07 (m, 4 H, vinylic protons); and 5.58 (br.s, 1 H, C(2)—H).

The subsequent elution with a mixture of the same solvents (4 : 1) recovered ketone **26** (0.24 g).

Ethyl (*Z,E,E,E*)-geranylfarnesoate (25c). A fraction containing a mixture of esters **24c** and **25c** (0.265 g) was rechromatographed on a column with $AgNO_3/SiO_2$ (6.5 g). Ester **25c** (0.11 g) was eluted with a light petroleum : ethyl acetate mixture (19 : 1) as a colorless viscous liquid. Found (%): C, 80.72; H, 10.94. $C_{27}H_{44}O_2$. Calculated (%): C, 80.94; H, 11.07. IR, ν/cm^{-1}: 1710 (O—C=O); 850, and 1644 (C=CH). ^{1}H NMR (CCl_4), δ: 1.18 (t, 3 H, $OCH_2\underline{Me}$, J = 7 Hz); 1.50 (s, 15 H, 5 Me groups at double bonds); 2.05 (s, 3 H, C(3)—Me); 4.02 (q, 2 H, $OC\underline{H}_2Me$, J = 7 Hz); 4.98 (m, 4 H, vinylic protons); and 5.51 (br.s, 1 H, C(2)—H). A mixture of esters **24c** and **25c** (0.08 g) and then *trans*-ether **24c** (0.06 g) were eluted from the column with a mixture of the same solvents (9 : 1).

(*E,E,E,E*)-Geranylfarnesol (24a). An ethereal solution (3.8 mL) containing $LiAlH_3(OEt)$ (0.063 g, 0.77 mmol) was added to a solution of compound **24c** (0.63 g, 1.575 mmol) in anhydrous ether (6 mL). After storage at *ca.* 20 °C (3 h) and ordinary workup, the reaction product (0.55 g) was obtained; it was chromatographed on a column with SiO_2 (10 g). Starting ester **24c** (0.062 g) was eluted with a light petroleum : ethyl acetate mixture (9 : 1), and then compound **24a** was eluted with a mixture of the same solvents (4 : 1). **24a** (0.475 g, 84 %): a colorless viscous liquid. Found (%): C, 83.86; H, 11.79. $C_{25}H_{42}O$. Calculated (%): C, 83.73; H, 11.81. IR, ν/cm^{-1}: 1048, 3410, 3615 (OH). ^{1}H NMR (CCl_4), δ: 1.61 (s, 15 H, 5 Me groups at double bonds); 1.67 (s, 3 H, C(3)—Me); 2.28 (br.s, 1 H, OH); 4.03 (d, 2 H, CH_2O, J = 6 Hz); 5.10 (m, 4 H, vinylic protons); and 5.38 (m, 1 H, C(2)—H).

(*Z,E,E,E*)-Geranylfarnesol (25a). An ethereal solution (1.1 mL) containing $LiAlH_3(OEt)$ (0.02 g, 0.243 mmol) was added to a solution of compound **25c** (0.18 g, 0.45 mmol) in anhydrous ether (1.8 mL). The mixture was kept at *ca.* 20 °C for 3.5 h, and after ordinary workup, the reaction product (0.15 g) was obtained; it was chromatographed on a column with SiO_2 (2.5 g). Starting ether **25c** (11 mg) was eluted with a light petroleum : ethyl acetate mixture (9 : 1), and then compound **25a** was eluted with a mixture of the same solvents (4 : 1). **25a** (0.13 g, 81 %): a colorless viscous liquid. Found (%): C, 83.67; H, 11.88. $C_{25}H_{42}O$. Calculated (%): C, 83.73; H, 11.81. IR, ν/cm^{-1}: 1050, 3400, and 3618 (OH). ^{1}H NMR (CCl_4), δ: 1.62 (s, 15 H, 5 Me groups at double bonds); 1.70

(s, 3 H, C(3)—Me); 4.15 (d, 2 H, CH_2O, J = 6 Hz); 5.13 (m, 4 H, vinylic protons); and 5.42 (m, 1 H, C(2)—H).

(*E,E,E,E*)-Geranylfarnesyl acetate (24b). Ac_2O (0.2 mL, 2.12 mmol) was added to a solution of compound **24a** (0.126 g, 0.352 mmol) in dry pyridine (2 mL); the mixture was kept at *ca.* 20 °C for 5 h and after ordinary workup, compound **24b** (0.130 g) was obtained as a colorless viscous liquid. Found (%): C, 80.78; H, 11.12. $C_{27}H_{44}O_2$. Calculated (%): C, 80.94; H, 11.07. IR, ν/cm^{-1}: 1225, 1734 (OAc); 847, and 1653 (C=CH). ^{1}H NMR (CCl_4), δ: 1.60 (s, 15 H, 5 Me groups at double bonds); 1.68 (s, 3 H, C(3)—Me); 1.95 (s, 3 H, OAc); 4.47 (d, 2 H, CH_2O, J = 6 Hz); 5.07 (m, 4 H, vinylic protons); and 5.30 (m, 1 H, C(2)—H).

(*Z,E,E,E*)-Geranylfarnesyl acetate (25b). Ac_2O (0.2 mL, 2.12 mmol) was added to a solution of compound **25a** (0.11 g, 0.307 mmol) in dry pyridine (2 mL); the mixture was kept at *ca.* 20 °C for 6.5 h, and after ordinary workup, compound **25b** (0.114 g) was obtained as a colorless viscous liquid. Found (%): C, 80.81; H, 10.89. $C_{27}H_{44}O_2$. Calculated (%): C, 80.94; H, 11.07. IR, ν/cm^{-1}: 1220, 1730 (OAc); 848, and 1650 (C=CH). ^{1}H NMR (CCl_4), δ: 1.61 (s, 15 H, 5 Me groups at double bonds); 1.73 (s, 3 H, C(3)—Me); 1.98 (s, 3 H, OAc); 4.46 (d, 2 H, CH_2O, J = 6 Hz); 5.09 (m, 4 H, vinylic protons); and 5.35 (m, 1 H, C(2)—H).

Drimenol (30) (see Table 1, entry *13*): a colorless viscous liquid. IR, ν/cm^{-1}: 1030, 3450, 3627 (OH); 834, 1664 (C=CH). ^{1}H NMR (CCl_4), δ: 0.80 (s, 3 H, C(10)—Me); 0.86 (s, 6 H, C(4)Me_2); 1.76 (s, 3 H, C(8)—Me); 2.20 (br.s, 1 H, OH); 3.67 (m, 2 H, CH_2O); and 5.38 (m, 1 H, C(7)—H).

9-Epidrimenol (31). *A* (see Table 1, entry *14*): a colorless viscous liquid. IR, ν/cm^{-1}: 1028, 3500, 3610 (OH); 840, and 1668 (C=CH). ^{1}H NMR (CCl_4), δ: 0.88 (s, 6 H, C(4)—Me and C(10)—Me); 0.96 (s, 3 H, C(4)—Me); 1.70 (s, 3 H, C(8)—Me); 2.28 (br.s, 1 H, OH); 3.62 (m, 2 H, CH_2O); and 5.48 (m, 1 H, C(7)—H).

B. $POCl_3$ (0.06 mL) was added to a chilled solution of hydroxyacetate **33** (0.04 g) in pyridine (1.7 mL), and the mixture was stirred for 40 min. Then it was heated to *ca.* 20 °C and kept for 3.5 h. Ice was added, and after ordinary workup, the reaction product (0.032 g) was obtained; it was saponified by refluxing in 10 % ethanolic solution of KOH (1.7 mL) for 1 h. After ordinary workup, a mixture of isomeric drimane alcohols (0.023 g) was obtained, in which alcohol **31** was a major component (60 %) (GLC conditions: T_{col} 210 °C, T_{inj} 230 °C, He was used as carrier gas, 45 mL min^{-1}).

(±)-Drimane-8α,11-diol 11-monoacetate (32) (see Table 1, entry *15*): a viscous oil. IR, ν/cm^{-1}: 1236, 1732 (OAc); 1373, 1384 (C(4)Me_2); 1030, 3510, and 3600 (OH). ^{1}H NMR (CCl_4), δ: 0.78 (s, 3 H, C(10)—Me); 0.83 and 0.85 (both s, 6 H, C(4)Me_2); 1.17 (s, 3 H, C(8)—Me); 2.02 (s, 3 H, OAc); and 3.44 (m, 2 H, CH_2O).

β-Monocyclofarnesyl acetate (34) (see Table 1, entry *15*): a viscous oil. IR, ν/cm^{-1}: 1225, 1720 (OAc). ^{1}H NMR (CCl_4), δ: 0.80 and 0.88 (both s, 6 H, C(4)Me_2); 1.20 (s, 3 H, C(6)—Me); 1.25 (s, 3 H, C(9)—Me); 1.97 (s, 3 H, OAc); 3.93 (m, 2 H, CH_2O); and 5.41 (m, 1 H, C(10)—H).

(±)-Drimane-8β,11-diol 11-monoacetate (33) (see Table 1, entry *16*): a viscous oil. IR, ν/cm^{-1}: 1230, 1732 (OAc); 1360, 1377 (C(4)Me_2); 1025, 3495, and 3600 (OH). ^{1}H NMR (CCl_4), δ: 0.86 (s, 3 H, C(10)—Me); 0.97 and 1.08 (both s, 6 H, C(4)Me_2); 1.25 (s, 3 H, C(8)—Me); 1.95 (s, 3 H, OAc); and 3.61 (m, 2 H, CH_2O).

α-Cyclogeraniol (37) (see Table 1, entries *17* and *18*): a colorless viscous liquid. IR, ν/cm^{-1}: 1020, 3448, 3637 (OH); 846, and 1656 (C=CH). ^{1}H NMR (CCl_4), δ: 0.88 and 0.98 (both s, 6 H, C(4)Me_2); 1.73 (s, 3 H, C(6)—Me); 2.30 (br.s, 1 H, OH); 3.62 (d, 2 H, CH_2O, J = 5 Hz); and 5.45 (m, 1 H, C=CH).

Hydroxyacetate (38a) (see Table 1, entries *19* and *20*): a viscous oil. IR, ν/cm^{-1}: 1030, 3473, 3590 (OH); 1230, and 1725 (OAc). ^{1}H NMR (CCl_4), δ: 0.87 and 0.98 (both s, 3 H, C(4)Me_2); 1.12 (s, 3 H, C(6)—Me); 1.97 (s, 3 H, OAc); 2.52 (br.s, 1 H, OH); and 4.23 (d, 2 H, CH_2O, J = 4 Hz).

Hydroxyacetate (38b) (see Table 1, entries *19* and *20*): a viscous oil. IR, ν/cm^{-1}: 1040, 3460, 3600 (OH); 1230, and 1730 (OAc). ^{1}H NMR (CCl_4), δ: 0.97 (s, 6 H, C(4)Me_2); 1.20 (s, 3 H, C(6)—Me); 1.97 (s, 3 H, OAc); and 4.27 (d, 2 H, CH_2O, J = 4 Hz).

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