Superacidic cyclization of higher terpenoid acids and their esters

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The superacidic cyclization of aliphatic and partially cyclized C_{15}—C_{25} terpenoid acids and their esters proceeds structure-selectively and stereospecifically, affording α-isomers of completely cyclized epimeric β,γ-unsaturated acids or esters; the configuration of their carboxylic or ester groups is predetermined by the configuration of the double bond conjugated with the carboxyl or ester groups in the starting compounds.

Key words: terpenoids; acids; esters; superacidic cyclization, selectivity.

In the preceding paper,[1] we demonstrated that superacidic cyclization of terpenols and their acetates represents an efficient one-step chemo- and structurally selective, stereospecific synthetic route to cyclic C_{10}—C_{25} terpenols. Taking into account the lability of allylic hydroxyl and ester groups in an acidic medium, we considered it reasonable to carry out systematic comparative investigations on superacidic cyclization of terpenoid acids and their esters as well; the results of this study are presented in this article.

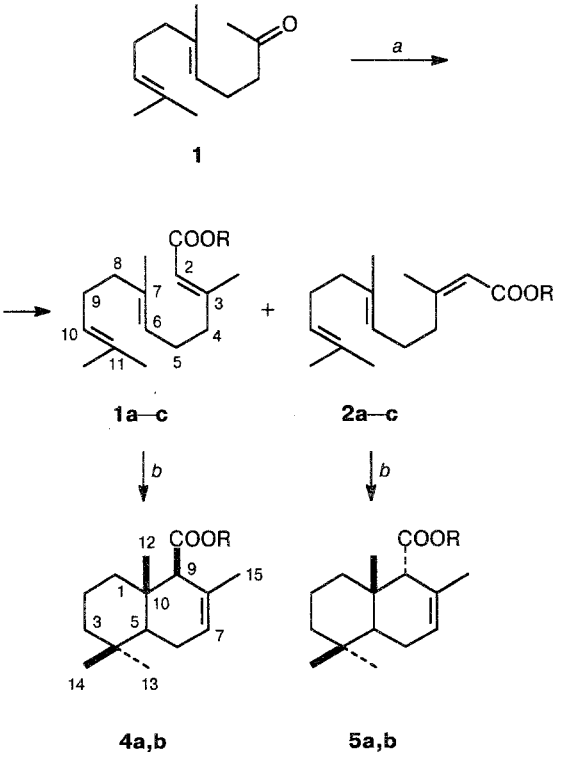
It should be noted that superacidic cyclization of monoterpenoic acids and their esters has clearly been successfully carried out previously.[2,3] The superacidic cyclization of stereoisomeric ethyl farnesoates has also been studied in detail.[4] Its structural and stereochemical features were elucidated, in particular, its stepwise mechanism; the yields of the reaction products were high.[4] Therefore, only superacidic cyclization of C_{15}—C_{25} terpenoid acids and their esters was studied in this work. The cyclization of methyl farnesoates (**1a** and **2a**) was performed by us in order to compare its results with the data on cyclization of the corresponding acids (**1b** and **2b**) and the data on the described[4] cyclization of ethyl farnesoates (**1c** and **2c**).

A mixture of esters **1a** and **2a** (3 : 1, GLC data) was obtained in 70 % yield from geranylacetone **3** using Wittig—Horner reaction (see Ref. 4), and it was separated by chromatography on a column with silica gel impregnated with $AgNO_3$ by the known procedure[5] ($AgNO_3/SiO_2$). Esters **1a** and **2a** were saponified with ethanolic alkali to the corresponding acids **1b** and **2b**.

Taking account of the previous data,[4] the cyclization of (*E,E*)-farnesoic acid **1b** was carried out at the substrate : cyclizing agent ratio of 1 : 5. In order to simplify the analyses, the crude reaction product was methylated with diazomethane, and methyl drim-7-en-11-oate (**4a**) was isolated in 91 % yield (Table 1). Along with target compound **4a**, a small amount of a polymeric product formed in the reaction (Scheme 1).

Superacidic cyclization of methyl (*E,E*)-farnesoate **1a** proceeds easier than that of acid **1b** itself, and the

Scheme 1



R = Me (**1a**, **2a**, **4a**, **5a**), H (**1b**, **2b**, **4b**, **5b**), Et (**1c**, **2c**)

Reagents and conditions:
a. $(MeO)_2P(O)CH_2CO_2Me$—NaH/DMSO;
b. FSO_3H—Pr^iNO_2.

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Table 1. Fluorosulfonic acid-catalyzed cyclization of terpenoid acids and their esters in 2-nitropropane

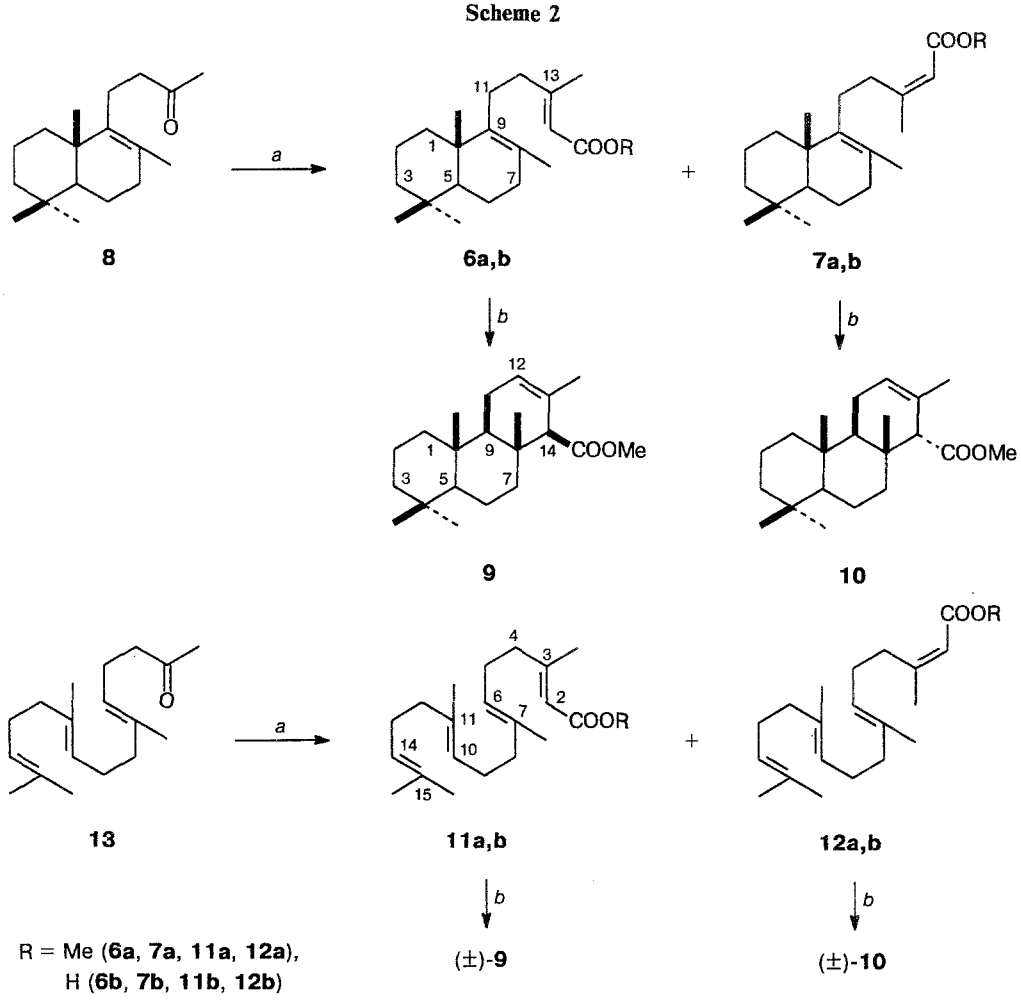
Entry	Substrate	Target product	FSO_3H,* *m*/mg	V_1**/mL	Substrate,* *m*/mg	V_2**/mL	*T*/°C	*t*/min	Composition of reaction products (%)	
									Target	Polymeric
1	**1b**	**4a**	105 (1.05)	0.6	50 (0.21)	1.0	−65±2	30	91.1	8.9
2	**1a**	**4a**	190 (1.90)	0.6	50 (0.20)	1.5	−75±2	10	92.2	7.8
3	**2b**	**5a**	90 (0.90)	0.5	40 (0.17)	1.0	−65±2	30	86.5	13.5
4	**2a**	**5a**	110 (1.10)	0.6	55 (0.22)	1.0	−75±2	30	90.4	9.6
5	**6a**	**9**	90 (0.90)	0.5	50 (0.16)	1.0	−80±2	15	92.2	7.8
6	**7a**	**10**	90 (0.90)	0.5	50 (0.16)	1.0	−70±2	15	91.4	8.6
7	**6b**	**9**	400 (4.00)	0.6	55 (0.16)	1.3	−50±2	30	92.5	7.5
8	**7b**	**10**	260 (2.60)	0.5	40 (0.13)	1.0	−50±2	45	86.5	13.5
9	**11a**	**9**	400 (4.00)	0.7	66 (0.21)	1.4	−60±2	25	92.4	7.6
10	**12a**	**10**	190 (1.90)	0.5	32 (0.10)	0.8	−60±2	40	85.3	14.7
11	**11b**	**9**	365 (3.65)	0.6	55 (0.18)	1.3	−50±2	40	86.2	13.8
12	**12b**	**10**	280 (2.80)	0.5	43 (0.14)	1.0	−50±2	60	81.2	18.8
13	**14b**	**17**	360 (3.60)	1.1	70 (0.18)	1.5	−55±2	30	82.3	17.7
14	**15b**	**18**	340 (3.40)	1.0	65 (0.17)	1.5	−45±2	40	77.8	22.2
15	**14a**	**17**	320 (3.20)	0.6	60 (0.16)	1.5	−45±2	30	79.9	20.1
16	**15a**	**18**	270 (2.70)	0.8	50 (0.13)	1.3	−45±2	50	74.2	25.8
17	**19b**	**17**	390 (3.90)	1.0	60 (0.15)	1.5	−45±2	50	72.5	27.5
18	**20b**	**18**	450 (4.50)	1.0	70 (0.18)	1.6	−40±2	60	69.7	30.3
19	**19a**	**17**	340 (3.40)	1.0	50 (0.13)	1.3	−40±2	50	70.2	29.8
20	**20a**	**18**	345 (3.45)	0.9	50 (0.13)	1.5	−40±2	90	67.5	32.5

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

cyclization can be realized under milder conditions (see Table 1, the yield of ester **4a** is 90 %). Under conditions of cyclization of acid **1b**, its (*Z*,*E*)-isomer **2b** gives the C_9-epimer of acid **4b** (**5b**, 86 % yield). The cyclization of (*Z*,*E*)-ester **2a** affords reaction product **5a** in higher yield (90 %) than that with the corresponding acid **2b**.

Thus, the superacidic cyclization of farnesoic acids and their esters is a highly efficient, structurally selective and stereospecific method of preparation of bicyclic sesquiterpene acids and drimanic esters. It should be noted that more drastic reaction conditions are needed for the acids than for the cyclization of the corresponding esters. In addition, *trans*-isomers of the

Scheme 2



Reagents and conditions: *a*. $(MeO)_2P(O)CH_2CO_2Me$—NaH/DMSO; *b*. FSO_3H—Pr^iNO_2.

substrates cyclize easier than the corresponding *cis*-isomers.

Electrophilic cyclization of diterpene acids and esters has been studied previously only for bicyclic substrates and only under action of ordinary acids.[5,6] In this reaction, relatively good yields of tricyclic isoagathane diterpenoids were obtained.[6] The cyclization of aliphatic diterpene acids and their esters is not yet practically studied.[6]

We studied the superacidic cyclization of both stereoisomeric bicyclic and aliphatic diterpene acids and their esters.

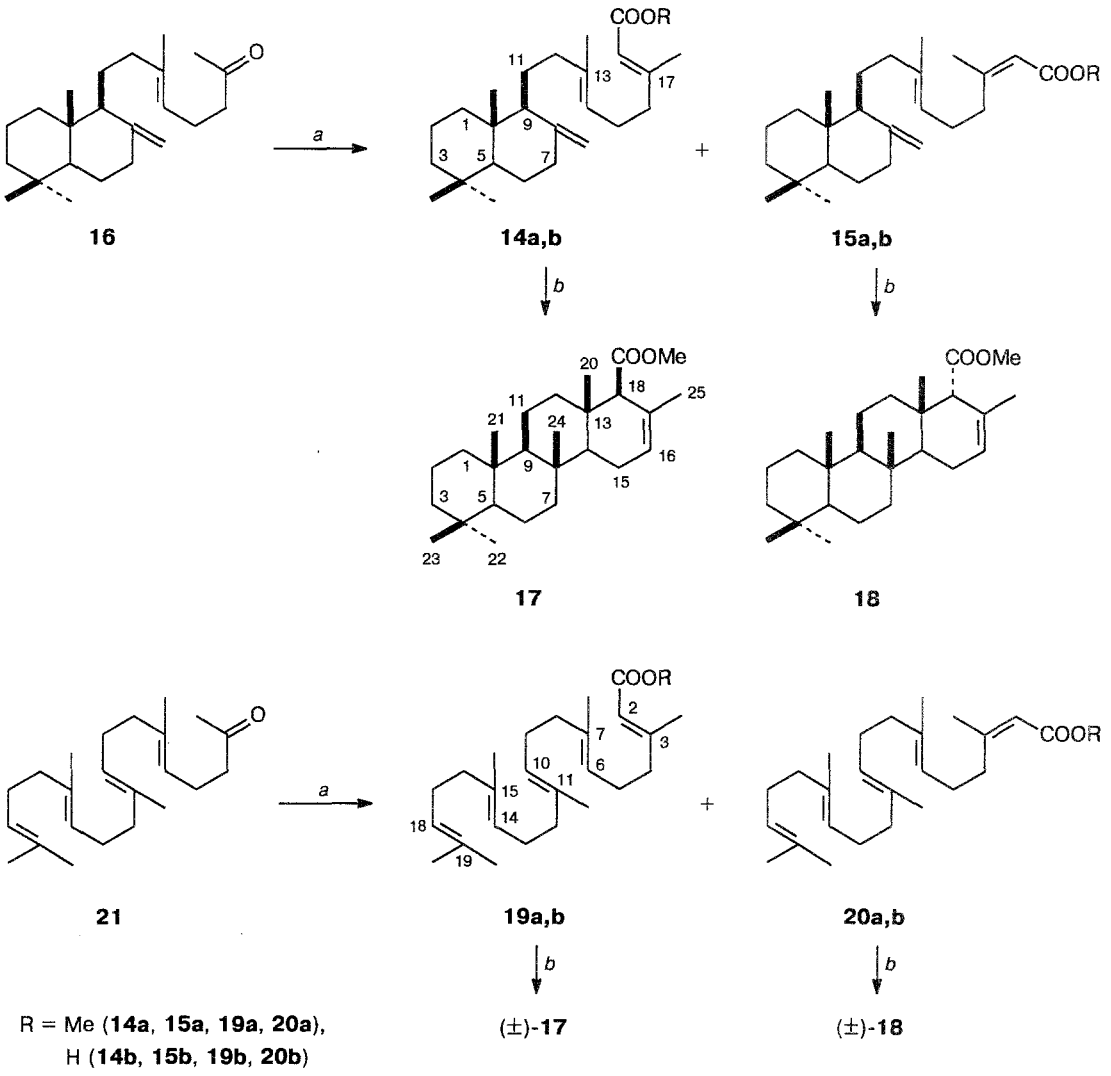
Optically active bicyclic esters (**6a** and **7a**) were synthesized from known unsaturated ketone (**8**)[7] and trimethyl phosphonoacetate using the Wittig—Horner reaction[8] (Scheme 2, 72 % yield, *Z*/*E*-isomeric ratio 1 : 3).

Superacidic cyclization of esters **6a** and **7a**[9] at −80 °C affords known C_{14}-epimeric isoagathane esters **9** and **10** in 91—95 % yield (see Scheme 2).[10] The cyclization of isomeric acids **6b** and **7b** followed by methylation of the reaction products with diazomethane gives esters **9** and **10** in 91 and 92 % yields, respectively.

It should be noted that in order to complete the reaction in the case of labdanoic acids **6b** and **7b** more drastic conditions are needed than for their esters **6a** and **7a**. As can be seen from the presented data, the superacidic cyclization of optically active bicyclic diterpene acid and their esters is a convenient, highly effective, structurally selective and stereospecific, method for the synthesis of optically active isoagathane diterpenoids.

Stereoisomeric (*E*,*E*,*E*)- and (*Z*,*E*,*E*)-geranylgeranoic acids (**11b** and **12b**) and their esters (**11a** and **12a**) were synthesized from (*E*,*E*)-farnesylacetone (**13**).[11] In the cyclization of (*E*,*E*,*E*)-geranylgeranoic acid **11b** under action of FSO_3H (substrate : cyclizing agent ratio 1 : 20, −50 °C, 40 min) with subsequent methylation of the reaction product with diazomethane, methyl (±)-14α*H*-isoagath-12-en-15-oate **9** was isolated in 86 % yield (see Scheme 2).[12] Under the similar conditions, (*Z*,*E*,*E*)-geranylgeranoic acid **12b** affords methyl

Scheme 3



Reagents and conditions: *a*. $(MeO)_2P(O)CH_2CO_2Me$—NaH/DMSO; *b*. FSO_3H—Pr^iNO_2.

(±)-14β*H*-isoagath-12-en-15-oate **10** in 81 % yield. Compared to acids **11b** and **12b**, their esters **11a** and **12a** cyclize more easily. For instance, the reaction of methyl (*E,E,E*)-geranylgeranoate **11a** with fluorosulfonic acid (−60 °C, 25 min) gives (±)-isoagathane ester **9** in 92 % yield. Under the same conditions, methyl (*Z,E,E*)-geranylgeranoate **12a** smoothly transforms to epimeric (±)-isoagathane ester **10** in 85 % yield.

Thus, using fluorosulfonic acid as a cyclizing agent, highly efficient, structurally selective and stereospecific biomimetic one-step transformations of aliphatic diterpene acids and their esters to tricyclic isoagathane compounds have been performed for the first time. It should also be noted that in this case, the cyclization of the acid proceeds more difficul than of the corresponding esters. It is noteworthy that for successful cyclization of diterpene acids and esters under appropriate reaction conditions, the ratio substrate : cyclizing agent should be higher than that for sesquiterpene compounds.

To the best of our knowledge, only one work on the cyclization of bicyclic esters of sesterterpene acids into scalarane tetracyclic compounds has been performed, $SnCl_4$ (Lewis acid) being used.[13] The structural selectivity of the reaction and, hence, the yields of target products in this cyclization were low. Therefore, study of superacidic cyclization of sesterterpene acids and their esters was of even greater interest. Primarily, stereoisomeric acids (**14b** and **15b**) and their methyl esters (**14a** and **15a**) were used as the starting compounds; **14a,b** and **15a,b** were synthesized by the known procedure[8] from (*E*)-bicyclogeranylgeranylacetone (**16**). The superacidic cyclization of (*E,E*)-acid methyl ester **14a** with fluorosulfonic acid[14] afforded the only product, *viz.*, the known tetracyclic ester (**17**) in 82 % yield (Scheme 3). In the cyclization of bicyclic (*Z,E*)-ester **15a** under the same conditions, epimeric ester (**18**) is formed in 78 % yield. Compounds **17** and **18** were identified by comparison of their physico-

chemical and spectral parameters with those published previously.[13]

As in the case of diterpene compounds, the cyclization of isomeric (17*E*)- and (17*Z*)-acids **14b** and **15b** occurs under more drastic conditions than in the case of their esters **14a** and **15a**, and the yields of product for the *cis*-isomers of acids and esters are less than those for the corresponding *trans*-isomers. It should also be noted that in the cyclization of bicyclic sesterterpene acids and their esters, the amount of polymeric product formed is 2 to 3 times higher than that in the cyclization of bicyclic diterpene acids and their esters.

In general, fluorosulfonic acid appears to be a highly efficient, structurally selective, and stereospecific cyclizing agent for the cyclization of stereoisomeric bicyclogeranylfarnesoic acids and their esters. Application of this reagent allowed to transform bicyclic sesterterpenoids to optically active tetracyclic scalarane sesterterpenoids in >70 % yields for the first time.

The above results on the cyclization of bicyclic sesterterpenoids to tetracyclic scalarane compounds prompted us to employ fluorosulfonic acid for biomimetic synthesis of the latter directly from their aliphatic precursors. Starting compounds (**19a,b**, **20a,b**) were synthesized using the known method[8] from (*E,E,E*)-geranylgeranylacetone (**21**).[1]

Racemic scalarane ester **17** was prepared by the reaction of (*E,E,E,E*)-geranylfarnesoic acid **19b** with FSO_3H (**19b** : cyclizing agent ratio 1 : 25, −40 °C, 50 min) followed by methylation of the reaction product with diazomethane (70 % yield)[14] (see Scheme 3). (*Z,E,E,E*)-Geranylfarnesoic acid **20b** affords epimeric racemic ester **18** in 67 % yield under the same conditions, but at the reaction time of 1.5 h. At the same substrate : cyclizing agent ratio (1 : 25), esters **19a** and **20a** reacts under milder conditions than the corresponding acids **19b** and **20b**: *E*-ester **19a** transforms into tetracyclic ester **17** in 50 min at −45 °C (72 %), and *Z*-ester **20a** transforms into racemic scalarané ester **18** over a period of 1 h at −40 °C in 70 % yield.

Thus, using fluorosulfonic superacid as cyclizing agent, we have performed in good yield one-step, biomimetic, chemo- and structurally selective, stereospecific cyclization of pentaene acyclic sesterterpenoids to tetracyclic scalarane compounds for the first time. Owing to this cyclization, some of the aforementioned compounds become relatively available and may serve as starting materials in synthetic studies in a series of scalarane sesterterpenoids.

The above results allow us to conclude that *superacidic cyclization of terpenoid acids and their esters is one of the most convenient and efficient routes for synthesizing cyclic terpenoids.* Polymeric compounds formed in small amounts are side products of the reaction, and, hence, isolation and purification of the target products are easy. In addition, the ester group can be easily reduced to oxygen-containing functional groups. The cyclization of the corresponding acids requires more drastic conditions, and the *trans*-compounds cyclize more easily than *cis*-substrates and give higher yields of the reaction products. In a series of C_{15}—C_{25} compounds, to complete the reaction under comparable conditions, the substrate : cyclizing agent ratio should be increased for substrates with a larger molecular mass.

Experimental

Melting points were measured with a Boetius heating stage. Specific optical rotations were measured with an SM polarimeter in $CHCl_3$. The IR spectra were recorded with a Specord IR-74 instrument in CCl_4, and the ^1H NMR spectra were registered with Tesla BS-476 (60 MHz) and Bruker AC-80 (80 MHz) spectrometers. GLC analyses were carried out with a Chrom-5 chromatograph (flame-ionization detector, 1500×3 mm glass column, stationary phases 5 % SE-30 or 5 % XE-60 on Chromaton N-AW-DMCS). Silica gels L 40/100 μm or L 100/250 μm or $AgNO_3$-impregnated silica gel[14] were used for column chromatography. 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 involved subsequent washing with water, saturated $NaHCO_3$, and water, drying over anhydrous Na_2SO_4, filtering, and removal of the solvent *in vacuo*.

Synthesis of methyl (*E,E*)- and (*Z,E*)-farnesoates (1a and 2a). A suspension of NaH (0.9 g) in DMSO (9 mL) was heated under Ar to 80 °C and stirred at this temperature for 40 min. Then the mixture was cooled to 0 °C and a solution of trimethyl phosphonoacetate (4.9 g) in DMSO (8 mL) was added with stirring. The temperature of the reaction mixture was increased to *ca.* 20 °C, the mixture was stirred for 10 min, and then a solution of (*E*)-geranylacetone **3** (2.7 g) in DMSO (6 mL) was added. The reaction mixture was stirred at 75 °C for 4 h, and then it was cooled and worked up. A mixture of methyl farnesoates **1a** and **2a** (3.7 g) (3 : 1, GLC data) was obtained and chromatographed on a column with $AgNO_3/SiO_2$ (85 g). A mixture of low-polar substances (0.037 g) was eluted with light petroleum and was not examined further. Then methyl (*Z,E*)-farnesoate **2a** (0.34 g) (a colorless viscous liquid) was eluted with a mixture of light petroleum : ethyl acetate (49 : 1). IR (CCl_4), ν/cm^{-1}: 1640 and 1705 (MeC=CHCOOMe). ^1H NMR (CCl_4), δ: 1.58 and 1.65 (both s, 9 H, 3 Me at C(7) and C(11)); 2.08 (s, 3 H, C(3)—Me); 3.63 (s, 3 H, CO_2Me); 5.03 (br.s, 2 H, C(6)—H and C(10)—H); and 5.55 (br.s, 1 H, C(2)—H). Then a mixture of esters **1a** and **2a** (0.83 g) was eluted from the column with a mixture of the same solvents, and finally methyl (*E,E*)-farnesoate **1a** (1.27 g) was eluted (a colorless viscous liquid). IR (CCl_4) ν/cm^{-1}: 1644 and 1710 (MeC=CHCOOMe). ^1H NMR (CCl_4), δ: 1.60 and 1.66 (both s, 9 H, 3 Me at C(7) and C(10)); 2.18 (s, 3 H, C(3)—Me); 3.63 (s, 3 H, CO_2Me); 5.04 (br.s, 2 H, C(6)—H and C(10)—H); and 5.58 (br.s, 1 H, C(2)—H).

(*E,E*)-Farnesoic acid (1b). A 10 % ethanolic solution of KOH (2.5 mL) was added to a solution of ester **1a** (0.22 g) in EtOH (1 mL), the mixture was heated under reflux for 2 h, and after the usual workup, a product (0.205 g) was obtained; it was chromatographed on a column with SiO_2 (4 g). Acid **1b** (0.176 g, 84.5 %, colorless viscous liquid) was eluted with a light petroleum : ethyl acetate mixture (4 : 1). Found (%): C, 76.54; H, 10.16. $C_{15}H_{24}O_2$. Calculated (%):

C, 76.23; H, 10.24. IR (CCl_4), ν/cm^{-1}: 1638 and 1690 (MeC=CHCOOH).

(*Z,E*)-Farnesoic acid (2b). A 10 % ethanolic solution of KOH (2 mL) was added to a solution of ester **2a** (0.160 g) in ethanol (1 mL), the mixture was heated under reflux for 2.5 h, and then worked up, the product (0.148 g) was obtained, and it was chromatographed on a column with SiO_2 (3 g). Acid **2b** (0.126 g, 84 %, a colorless viscous liquid) was eluted with a light petroleum : ethyl acetate mixture (4 : 1). Found (%): C, 76.39; H, 10.27. $C_{15}H_{24}O_2$. Calculated (%): C, 76.23; H, 10.24. IR (CCl_4), ν/cm^{-1}: 1640 and 1692 (MeC=CHCOOH).

Superacidic cyclization of terpenoid acids and their esters (general procedure). A solution of a definite amount of a substrate in a definite volume of 2-nitropropane chilled to a definite temperature was added with vigorous stirring to a solution of fluorosulfonic acid in a definite volume of 2-nitropropane chilled to the same temperature. The mixture was stirred at the selected temperature for a definite time, and a 50 % excess (with respect to the amount of cyclizing reagent used) of a mixture of Et_3N and light petroleum (1 : 1) was added; the mixture was worked up as usual. In the case of cyclization of an acid, the reaction product was methylated with excess of diazomethane in ether. After removal of the solvent, the residue was chromatographed on columns with SiO_2. The results obtained are listed in Table 1.

Methyl drim-7-en-11-oate (4a) (see Table 1, entries *1* and *2*): a colorless viscous liquid. Found (%): C, 76.34; H, 10.32. $C_{16}H_{26}O_2$. Calculated (%): C, 76.75; H, 10.47. IR (CCl_4), ν/cm^{-1}: 1730 (CO_2Me); 860, 1640 (C=CH); 1362, and 1380 (CMe_2). ^1H NMR (CCl_4), δ: 0.90 and 0.95 (both s, 9 H, 3 Me at C(4) and C(10)); 1.58 (s, C(8)—Me); 2.88 (br.s, 1 H, C(9)—H); 3.63 (s, 3 H, CO_2Me), and 5.46 (m, 1 H, C(7)—H).

Methyl 9-epidrim-7-en-11-oate (5a) (see Table 1, entries *3* and *4*): a colorless viscous liquid. Found (%): C, 76.98; H, 10.24. $C_{16}H_{26}O_2$. Calculated (%): C, 76.75; H, 10.47. IR (CCl_4), ν/cm^{-1}: 1727 (CO_2Me); 856, 1640 (C=CH); 1356, and 1380 (CMe_2). ^1H NMR (CCl_4), δ: 0.86 and 0.90 (both s, 9 H, 3 Me at C(4) and C(10)); 1.55 (s, C(8)—Me); 2.40 (br.s, 1 H, C(9)—H); 3.59 (s, 3 H, CO_2Me), and 5.43 (m, 1 H, C(7)—H).

Synthesis of methyl (13*E*)- and (13*Z*)-bicyclogeranylgeranoates (6a and 7a). A mixture of esters **6a** and **7a** (3.1 g, 3 : 1) was obtained from NaH (0.57 g), trimethyl phosphonoacetate (4.8 g), and bicyclofarnesylacetone **8**[7] (3 g) as described above; the mixture was chromatographed on a column with $AgNO_3/SiO_2$ (120 g). A mixture of low-polar substances (0.065 g) was eluted with light petroleum and was not examined further; ester **7a** (0.384 g, a colorless viscous liquid) was eluted with a light petroleum : ethyl acetate mixture (19 : 1). **7a**. $[\alpha]^{22}_D$ +42.3° (*c* 1.1). IR (CCl_4), ν/cm^{-1}: 1640, 1712 (MeC=CHCOOMe); 1347, 1369 (CMe_2). ^1H NMR (CCl_4), δ: 0.85, 0.92, and 0.97 (all s, 9 H, 3 Me at C(4) and C(10)); 1.65 (s, 3 H, C(8)—Me); 1.92 (s, 3 H, C(13)—Me); 3.63 (s, 3 H, CO_2Me); and 5.53 (br.s, 1 H, C(14)—H). Ref. 10: $[\alpha]_D$ +55.5°. A mixture of esters **6a** and **7a** (0.723 g) was subsequently eluted with the same solvent mixture.

Ester **6a** (1.29 g, a colorless viscous liquid) was eluted with the same solvent mixture (93 : 7). **6a**: $[\alpha]^{22}_D$ +62.4 (*c* 1.7). IR (CCl_4), ν/cm^{-1}: 1650, 1710 (MeC=CHCOOMe); 1357, and 1368 (CMe_2). ^1H NMR (CCl_4), δ: 0.86, 0.92 and 0.96 (all s, 9 H, 3 Me at C(4) and C(10)); 1.58 (s, 3 H, C(8)—Me); 2.15 (s, 3 H, C(13)—Me); 3.62 (s, 3 H, CO_2Me); and 5.58 (br.s, 1 H, C(14)—H). Ref. 10: $[\alpha]_D$ +50.8°.

(13*Z*)-Bicyclogeranylgeranoic acid (7b). A 10 % ethanolic solution of KOH (5 mL) was added to a solution of ester **7a** (0.15 g) in EtOH (2 mL), and the mixture was heated under reflux for 3.5 h; after the usual workup, the product (0.14 g) was obtained; it was chromatographed on a column with SiO_2 (3 g). (13*Z*)-Acid **7b** (0.116 g, 80.8 %, a colorless viscous liquid) was eluted with a light petroleum : ethyl acetate mixture (4 : 1). **7b**: Found (%): C, 78.67; H, 10.44. $C_{20}H_{32}O_2$. Calculated (%): C, 78.90; H, 10.59. IR (CCl_4), ν/cm^{-1}: 1640 and 1692 (MeC=CHCOOH).

(13*E*)-Bicyclogeranylgeranoic acid (6b). A 10 % ethanolic solution of KOH (15 mL) was added to a solution of ester **6a** (0.460 g) in EtOH (3 mL), the mixture was heated under reflux for 4 h; after usual workup, the product (0.410 g) was obtained; it was chromatographed on a column with SiO_2 (8 g). (13*E*)-Acid **6b** (0.39 g, 88.7 %, a colorless viscous liquid) was eluted with a light petroleum : ethyl acetate mixture (4 : 1). **6b**: Found (%): C, 78.72; H, 10.78. $C_{20}H_{32}O_2$. Calculated (%): C, 78.90; H, 10.59. IR (CCl_4), ν/cm^{-1}: 1645 and 1700 (MeC=CHCOOH).

Methyl 14α*H*-isoagath-12-en-15-oate (9) (see Table 1, entries *5* and *7*): m.p. 102—103.5 °C (from MeOH); $[\alpha]^{22}_D$ −62° (*c* 1.1). IR (CCl_4), ν/cm^{-1}: 1725 (CO_2Me); 853, 1636 (C=CH); 1332, and 1367 (CMe_2). ^1H NMR (CCl_4), δ: 0.83, 0.87, and 0.92 (all s, 12 H, 4 Me at C(4), C(8) and C(10)); 1.55 (s, 3 H, C(13)—Me); 2.78 (br.s, 1 H, C(14)—H); 3.60 (s, 3 H, CO_2Me); and 5.37 (m, 1 H, C(12)—H). Ref. 16: m.p. 104—105 °C; $[\alpha]_D$ −58°.

Methyl 14β*H*-isoagath-12-en-15-oate (10) (see Table 1, entries *6* and *8*): m.p. 80.5—81.5 °C (from MeOH); $[\alpha]^{22}_D$ +188° (*c* 1.3). IR (CCl_4), ν/cm^{-1}: 1724 (CO_2Me); 835, 1630 (C=CH); 1340, and 1376 (CMe_2). ^1H NMR (CCl_4), δ: 0.82 and 0.88 (both s, 12 H, 4 Me at C(4), C(8) and C(10)); 1.55 (s, 3 H, C(13)—Me); 2.33 (br.s, 1 H, C(14)—H); 3.62 (s, 3 H, CO_2Me); and 5.47 (m, 1 H, C(12)—H). Ref. 16: m.p. 79 °C; $[\alpha]_D$ +197°.

Synthesis of methyl (*E,E,E*)- and (*Z,E,E*)-geranylgeranoates (11a and 12a). A mixture of esters **11a** and **12a** (3.06 g, 3 : 1) was obtained from NaH (0.37 g), trimethyl phosphonoacetate (3.3 g), and (*E,E*)-farnesylacetone **13** (2.8 g) as described above; the mixture was chromatographed on a column with $AgNO_3/SiO_2$ (78 g). A mixture of low-polar substances (0.068 g) was eluted with light petroleum and was not examined further; ester **12a** (0.32 g, a colorless viscous liquid) was eluted with a light petroleum : ethyl acetate mixture (19 : 1). IR (CCl_4), ν/cm^{-1}: 1645 and 1718 (MeC=CHCOOMe). ^1H NMR (CCl_4), δ: 1.62 and 1.71 (both s, 12 H, 4 Me at C(7), C(11), and C(15)); 1.92 (s, 3 H, C(3)—Me); 3.62 (s, 3 H, CO_2Me); 5.03 (br.s, 3 H, C(6)—H, C(10)—H, and C(14)—H); and 5.45 (br.s, 1 H, C(2)—H).

A mixture of esters **11a** and **12a** (0.62 g) and then ester **11a** (0.75 g, a colorless viscous liquid) were eluted with a mixture of the same solvents. **11a**. IR (CCl_4), ν/cm^{-1}: 1642 and 1712 (MeC=CHCOOMe). ^1H NMR (CCl_4), δ: 1.58 and 1.67 (both s, 12 H, 4 Me at C(7), C(11) and C(15)); 2.14 (s, 3 H, C(3)—Me); 3.60 (s, 3 H, CO_2Me); 5.02 (br.s, 3 H, C(6)—H, C(10)—H, and C(14)—H); and 5.53 (br.s, 1 H, C(2)—H).

(*Z,E,E*)-Geranylgeranoic acid (12b). Ester **12a** (0.18 g) was saponified with a 10 % ethanolic solution of KOH (3 mL) as described above; acid **12b** (0.16 g, 92 %) was obtained as a colorless viscous liquid. IR (CCl_4), ν/cm^{-1}: 1638 and 1692 (MeC=CHCOOH).

(*E,E,E*)-Geranylgeranoic acid (11b). Ester **11a** (0.25 g) was saponified with a 10 % ethanolic solution of KOH (3 mL)

as described above; acid **11b** (0.22 g, 93 %) was obtained as a colorless viscous liquid. IR (CCl_4), ν/cm^{-1}: 1635 and 1685 (MeC=CHCOOH). The product was identical with an authentic sample.

Synthesis of methyl (13*E*,17*E*)- and (13*E*,17*Z*)-bicyclogeranylfarnesoates (14a and 15a). A mixture of esters **14a** and **15a** (5.2 g, 3 : 1) was obtained from NaH (1.4 g), trimethyl phosphonoacetate (3.9 g), and (13*E*)-bicyclogeranylgeranylacetone **16** (5 g) as described above. The mixture of esters was chromatographed on a column with $AgNO_3/SiO_2$ (140 g). A mixture of low-polar substances (0.08 g) was eluted with light petroleum, and ester **15a** (0.467 g) was eluted with a light petroleum : ethyl acetate mixture (19 : 1). **15a** is a colorless viscous liquid; $[\alpha]^{22}_D$ +9.2° (*c* 1.4). IR (CCl_4), ν/cm^{-1}: 1730 (CO_2Me); 890, 1635 (C=CH_2); and 840 (C=CH). ^1H NMR (CCl_4), δ: 0.67 (s, 3 H, C(10)—Me); 0.75 and 0.85 (both s, 6 H, C(4)—Me_2); 1.57 (s, 3 H, C(13)—Me); 2.01 (s, 3 H, C(17)—Me); 3.57 (s, 3 H, CO_2Me); 4.45 and 4.73 (both m, 2 H, C=CH_2); 4.81 (br.s, 1 H, C(14)—H); 5.03 (m, 1 H, C(18)—H). A mixture of esters **14a** and **15a** (1.21 g) was eluted with a light petroleum : ethyl acetate mixture (19 : 1), and ester **14a** (1.76 g) was eluted from the column with a mixture of the same solvents (93 : 7). **14a** is a colorless viscous liquid; $[\alpha]^{23}_D$ +17.7 (*c* 2.1). IR (CCl_4), ν/cm^{-1}: 1720 (CO_2Me); 889, 1640 (C=CH_2); and 853 (C=CH). ^1H NMR (CCl_4), δ: 0.65 (s, 3 H, C(10)—Me); 0.77 and 0.86 (both s, 6 H, C(4)—Me); 1.53 (s, 3 H, C(13)—Me); 2.14 (s, 3 H, C(17)—Me); 3.57 (s, 3 H, CO_2Me); 4.42 and 4.73 (both m, 2 H, C=CH_2); 4.98 (m, 1 H, C(14)—H); and 5.53 (br.s, 1 H, C(18)—H).

Starting (13*E*)-bicyclogeranylgeranylacetone **16** (0.9 g) was eluted with a light petroleum : ethyl acetate mixture (9 : 1).

(13*E*,17*Z*)-Bicyclogeranylfarnesoic acid (15b). A 10 % ethanolic solution of KOH (3 mL) was added to a solution of ester **15a** (0.30 g) in EtOH (1 mL); the mixture was heated under reflux for 2 h, and after the usual workup, the product (0.276 g) was chromatographed on a column with SiO_2 (2 g). Elution with a light petroleum : ethyl acetate mixture (3 : 1) afforded (13*E*,17*Z*)-acid **15b** (0.24 g, 83 %) as a colorless viscous liquid; $[\alpha]^{23}_D$ +7.3° (*c* 1.1). Found (%): C, 80.18; H, 11.07. $C_{25}H_{40}O_2$. Calculated (%): C, 80.59; H, 10.82. IR (CCl_4), ν/cm^{-1}: 1695 and 1640 (MeC=CHCOOH).

(13*E*,17*E*)-Bicyclogeranylfarnesoic acid (14b). A 10 % ethanolic solution of KOH (10 mL) was added to a solution of ester **14a** (0.75 g) in EtOH (2 mL); the mixture was heated under reflux for 3 h, and after the usual workup, the product (0.71 g) was chromatographed on a column with SiO_2 (7 g). Elution with a light petroleum : ethyl acetate mixture (3 : 1) afforded acid **14b** (0.62 g, 86 %) as a colorless viscous liquid; $[\alpha]^{23}_D$ +21.2° (*c* 1.7). Found (%): C, 80.84; H, 10.69. $C_{25}H_{40}O_2$. Calculated (%): C, 80.59; H, 10.82. IR (CCl_4), ν/cm^{-1}: 1693 and 1638 (MeC=CHCOOH).

Methyl 18α*H*-scalar-16-en-19-oate (17) (see Table 1, entries *13* and *15*): m.p. 167—169 °C (from light petroleum); $[\alpha]^{22}_D$ +65.7° (*c* 3.6). Found (%): C, 80.96; H, 10.84. $C_{26}H_{42}O_2$. Calculated (%): C, 80.77; H, 10.95. IR (CCl_4), ν/cm^{-1}: 1722 (CO_2Me); 840 and 1653 (C=CH). ^1H NMR (CCl_4), δ: 0.86, 0.90, and 0.92 (all s, 15 H, 5 Me at C(4), C(8), C(10), and C(13)); 1.58 (s, C(17)—Me); 2.76 (br.s, 1 H, C(18)—H); 3.58 (s, 3 H, CO_2Me); and 5.41 (m, 1 H, C(16)—H). Ref. 13: m.p. 165—169 °C.

Methyl 18β*H*-scalar-16-en-19-oate (18) (see Table 1, entries *14* and *16*): a colorless viscous liquid; $[\alpha]^{25}_D$ −26.5° (*c* 2.3). Found (%): C, 81.04; H, 10.82. $C_{26}H_{42}O_2$. Calculated (%): C, 80.77; H, 10.95. IR (CCl_4), ν/cm^{-1}: 1715 (CO_2Me); 847, and 1635 (C=CH). ^1H NMR (CCl_4), δ: 0.83, 0.86, and 0.95 (all s, 15 H, 5 Me at C(4), C(8), C(10), and C(13)); 1.60 (s, 3 H, C(17)—Me); 2.20 (br.s, 1 H, C(18)—H); 3.63 (s, 3 H, CO_2Me); and 5.58 (m, 1 H, C(16)—H).

Synthesis of methyl (*E*,*E*,*E*,*E*)- and (*Z*,*E*,*E*,*E*)-geranylfarnesoates (19a and 20a). A mixture of esters **19a** and **20a** (3.16 g, 4 : 1) was obtained from NaH (0.7 g), trimethyl phosphonoacetate (2.3 g), and (*E*,*E*,*E*)-geranylgeranylacetone **21** (3 g) as described above. The mixture was chromatographed on a column with $AgNO_3/SiO_2$ (95 g). A mixture of low-polar substances (0.08 g) was eluted with light petroleum and was not examined further; ester **20a** (0.42 g, a colorless viscous liquid) was eluted with a light petroleum : ethyl acetate mixture (49 : 1). Found (%): C, 81.12; H, 10.89. $C_{26}H_{42}O_2$. Calculated (%): C, 80.77; H, 10.95. IR (CCl_4), ν/cm^{-1}: 1715 (CO_2Me); 850, and 1640 (C=CH). ^1H NMR ($CDCl_3$), δ: 1.61 (s, 12 H, 4 Me at C(11), C(15), and C(19)); 1.67 (s, 3 H, C(7)—Me); 2.01 (s, C(3)—Me); 3.62 (s, 3 H, CO_2Me); 5.07 (m, 4 H, H at C(6), C(10), C(14), and C(18)); and 5.60 (br.s, 1 H, C(2)—H). The mixture of esters **19a** and **20a** (1.14 g) was eluted with the same solvent. Subsequent elution afforded ester **19a** (0.624 g, a colorless viscous liquid). Found (%): C, 80.54; H, 10.83. $C_{26}H_{42}O_2$. Calculated (%): C, 80.77; H, 10.95. IR (CCl_4), ν/cm^{-1}: 1720 (CO_2Me); 853, and 1643 (C=CH). ^1H NMR ($CDCl_3$), δ: 1.60 (s, 12 H, 4 Me at C(11), C(15), and C(19)); 1.70 (s, 3 H, C(7)—Me); 2.15 (s, 3 H, C(3)—Me); 3.63 (s, 3 H, CO_2Me); 5.09 (m, 4 H, H at C(6), C(10), C(14), and C(18)); and 5.62 (br.s, 1 H, C(2)—H). Starting (*E*,*E*,*E*)-geranylgeranylacetone **21** (0.65 g) was eluted with a light petroleum : ethyl acetate mixture (9 : 1).

(*E*,*E*,*E*,*E*)-Geranylfarnesoic acid (19b). A 10 % ethanolic solution of KOH (5 mL) was added to a solution of ester **19a** (0.45 g) in EtOH (2 mL); the mixture was heated under reflux for 3 h, and after the usual workup, the product (0.43 g) was chromatographed on a column with SiO_2 (6 g). (*E*,*E*,*E*,*E*)-Acid **19b** (0.388 g, 89 %, a colorless viscous liquid) was eluted with a light petroleum : ethyl acetate mixture (4 : 1). Found (%): C, 80.23; H, 10.88. $C_{25}H_{40}O_2$. Calculated (%): C, 80.59; H, 10.82. IR (CCl_4), ν/cm^{-1}: 1690 and 1644 (MeC=CHCOOH).

(*Z*,*E*,*E*,*E*)-Geranylfarnesoic acid (20b). A 10 % ethanolic solution of KOH (4 mL) was added to a solution of ester **20a** (0.38 g) in EtOH (1 mL), the mixture was heated under reflux for 2 h, and after the usual workup, the product obtained (0.36 g) was chromatographed on a column with SiO_2 (4 g). (*Z*,*E*,*E*,*E*)-Acid **20b** (0.30 g, 82 %, a colorless viscous liquid) was eluted with a light petroleum—ethyl acetate (4 : 1) mixture. Found (%): C, 80.14; H, 10.96. $C_{25}H_{40}O_2$. Calculated (%): C, 80.59; H, 10.82. IR (CCl_4), ν/cm^{-1}: 1695 and 1653 (MeC=CHCOOH).

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