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Studies towards the synthesis of cheilanthane sesterterpenoids: superacidic cyclisation of methyl 13*Z*,17*Z*- and 13*Z*,17*E*-bicyclogeranylfarnesoates

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Abstract—Superacidic low temperature cyclisation of bicyclogeranylfarnesoic acid methyl esters (**1** and **2**) exhibiting the 13*Z*-configuration afforded cheilanthane and rearranged cheilanthane terpenoids as main products, along with scalarane compounds. In particular, 14-*epi*-cheilanthanic ester (**6**) was obtained together with 18-*epi*-scalaranic ester (**5**) by cyclisation of 13*Z*,17*Z*-bicyclogeranylfarnesoic acid methyl ester (**1**), whereas the rearranged 22(8→14)-abeo-cheilanthanic ester (**8**) was formed along with scalaranic ester (**7**) by cyclisation of 13*Z*,17*E*-bicyclogeranylfarnesoic acid methyl ester (**2**). The structure and stereochemistry of the new compounds **6** and **8** were established on the basis of their spectral data.

1. Introduction

Our systematic studies have proven that superacidic low temperature cyclisation of both aliphatic and partially cyclised terpenoids represents a general route to naturally occurring cyclic terpenoids. With very rare exceptions the superacidic cyclisation reactions are chemoselective, stereospecific and highly effective synthetic tools.[1–6]

As was reported previously,[3] the superacidic cyclisation of bicyclo-geranylfarnesoic acids and their esters with an internal 13*E*-bond proceeds selectively leading to tetracyclic scalarane compounds, that are a group of natural molecules, occurring in sponges and molluscs, with very promising pharmacological properties, the most important of which being the anti-inflammatory activity related to the inhibition of phospholipase A_2.[7]

Our work connected with the synthesis of bioactive sesterterpenoids with cheilanthane skeleton, led us to the necessity of deeper investigating the superacidic cyclisation involving substrates with *cis*-internal double bonds. Available data concerning the cyclisation reaction of substrates with internal *cis*-double bonds are relatively scarce and relate only to sesquiterpenes.[8] We present in this paper the results of superacidic cyclisation of 13*Z*-bicyclogeranylfarnesoic esters (**1**) and (**2**). Investigation of these substrates will prove if the regularities previously observed for cyclisation of sesquiterpenoic esters[8] are valid also for higher terpenoids. Besides, using these optically active substrates with a fixed stereochemistry of A and B rings would bring more light upon the mechanism and regularities of electrophilic cyclisation in general and of the superacid induced process in particular.

2. Results and discussion

The synthesis of isomeric 13*Z*-bicyclogeranylfarnesoic acid methyl esters (**1**) and (**2**) was accomplished starting from 13*Z*-bicyclogeranylgeranylacetone (**3**), prepared by a known method from manool (**4**)[9] (Scheme 1). The Wittig type reaction of ketone **3** with the trimethylphosphonoacetate under the conditions reported in the literature[10] leads to a mixture of 17*Z*- and 17*E*-isomeric esters **1** and **2** (82%, ratio ~1:3), which were separated by flash chromatography on a silica gel column impregnated with silver nitrate.

The cyclisation reaction of 13*Z*,17*Z*-ester **1** was conducted with 5 mol equiv. of FSO_3H at −78°C over a period of 15 min, quenching the reaction mixture with a solution of Et_3N in hexane (1:1). The crude reaction product, obtained after usual work-up, was analysed by ^1H NMR, revealing that two cyclisation products, esters **5** and **6**, were formed.

Keywords: cyclisation; superacid; terpenes and terpenoids; carbocations; cheilanthanes; scalaranes.

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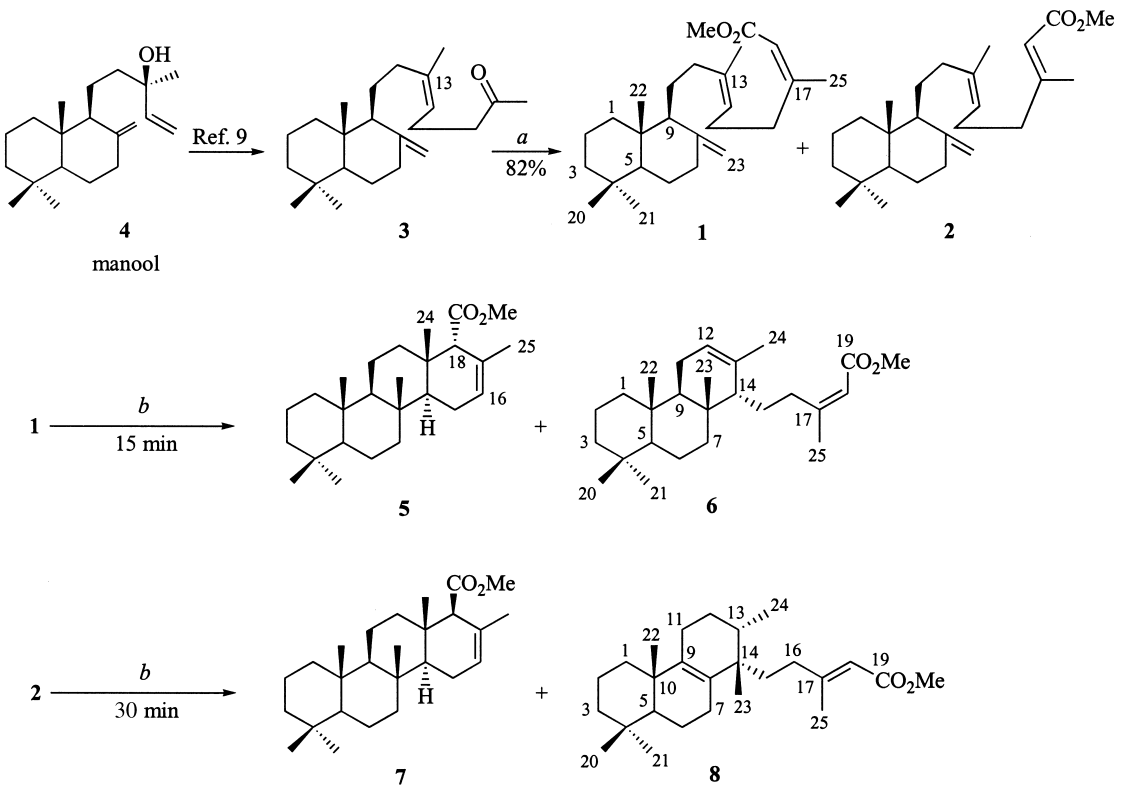


Scheme 1. *Reagents and conditions*: (a) $(MeO)_2P(O)CH_2CO_2Me$, MeONa, C_6H_6, reflux 2 h, 82% (**1**/**2**~1:3); (b) FSO_3H (5 equiv.), *i*-$PrNO_2$, −78°C, then Et_3N.

In order to separate the two components, that exhibited similar chromatographic behaviour, the mixture was subjected to hydrolysis with a 10% ethanolic solution of KOH at reflux (2 h). Under these conditions, only the ester **6** was hydrolysed, leaving **5** intact. After usual work-up, the reaction mixture was chromatographed on a silica-gel column to give, in order of increasing polarity, the known 18-*epi*-scalaranic ester (**5**) (26% isolated yield), identified by comparison of spectral data with those of an authentic sample,[3,11] and a fraction containing the acid corresponding to ester **6**. This fraction was treated with diazomethane to obtain **6**, which was finally purified by reversed phase HPLC (39% isolated yield). The molecular formula $C_{26}H_{42}O_2$ of **6**, deduced from HREIMS on the molecular ion at *m*/*z* 386, indicated six degrees of unsaturation. ^1H NMR spectrum showed singlets at δ 0.84, 0.88, 0.887 and 0.893 attributable to four tertiary methyls, a singlet at δ 3.67 due to $-CO_2Me$ group and two broad singlets at δ 1.71 and 1.91 attributable to two vinyl methyls (Table 1). The presence of two trisubstituted double bonds, one of which conjugated to the ester carboxyl group, was indicated by both ^1H NMR spectrum (two olefinic broad singlets at δ 5.23 and 5.63 coupled with methyls at δ 1.71 and 1.91, respectively) and ^{13}C NMR spectrum [signals at δ 119.6 (d), 136.5 (s), 115.6 (d) and 160.5 (s)]. All ^1H and ^{13}C NMR resonances (Table 1), assigned by analysis of 2D NMR spectra ($^1H-^1H$ COSY, HMQC and HMBC experiments), were consistent with the proposed tricyclic structure **6**, exhibiting a 14-*epi* cheilanthane skeleton. According to the *trans*-antiparallel addition principle, the prenyl chain at C-14 was axially oriented. This configuration was further supported by ^{13}C NMR data. In fact, the carbon spectrum of **6** showed down field shifted values for C-23 (δ 23.3) and C-9 (δ 47.2) and an up field shifted value for C-7 (δ 37.1), according to literature data for 8,14-*syn* isomer.[12]

The superacidic cyclisation of 13*Z*,17*E*-ester **2** with FSO_3H was conducted in the same conditions as above described for compound **1** (5 mol equiv. of FSO_3H, −78°C, 30 min) (Scheme 1). The reaction mixture was quenched with a solution of Et_3N in hexane (1:1), then the usual work-up afforded a crude reaction product, which was analysed by ^1H NMR, showing that also in this case two cyclisation products, esters **7** and **8**, were formed. The two reaction products were separated using the same procedure described above for esters **5** and **6**. The mixture was subjected to hydrolysis with a 10% ethanolic solution of KOH at reflux (2 h). Under these conditions, only ester **8** was hydrolysed, whereas **7** did not react. After usual work-up, the reaction mixture was chromatographed on a silica-gel column to give, in order of increasing polarity, the known scalaranic ester **7** (25% isolated yield), identified by comparison of spectral data with those of an authentic sample,[3,11] and a fraction containing the acid corresponding to ester **8**, which was methylated with diazomethane to give pure **8**. The molecular formula of **8**, $C_{26}H_{42}O_2$, the same as **6**, was derived from both EIMS and elemental analysis. Comparison of both ^1H and ^{13}C NMR spectra with those of **6** (Table 1) indicated the presence of a different carbon skeleton, exhibiting one secondary and four tertiary methyls, along with a vinyl methyl. In fact, ^1H NMR spectrum of **8** displayed 3H singlets at δ 0.83, 0.87, 0.96 and 1.04, a 3H doublet at δ 0.85 and a broad 3H singlet at δ 2.17, together with the singlet at δ 3.67 attributable to $-CO_2Me$ group. The presence of a tetrasubstituted double bond was indicated by two quaternary sp^2 carbons at δ 137.3 and

Table 1. NMR data for compounds **6** and **8**

Position	Compound **6**					Compound **8**				
	δ ^{1}H	m, *J* (Hz)	δ ^{13}C	m[a]	Long range connectivities[b]	δ ^{1}H	m, *J* (Hz)	δ ^{13}C	m[a]	Long range connectivities[b]
1	0.85	m	40.1	t	H-2a, H-9, H_3-22	1.01	ddd, 13, 12, 4	37.0	t	H_3-22
	1.61	m				1.75	m			
2	1.38	m	18.7	t	H-l a, H_2-3	1.45	m	19.2	t	H-3a
	1.60	m				1.55	m			
3	1.14	ddd, 14, 13, 4	42.0	t	H-2a. H_3-20, H_3-21	1.13	ddd, 13, 13, 4	41.6	t	H-1a, H_3-20,H_3-21
	1.38	m				1.38	m			
4	–		33.2	s	H_2-3, H-5, H_3-21	–		33.2	s	H-3a, H-5, H-6a, H_3-20, H_3-21
5	0.84	m	56.8d	d	H-3a, H_2-6, H_3-20, H_3-21	1.06	dd, 13, 4	51.5	d	H-la, H-5, H-6a, H_3-20, H_3-21
6	1.38	m	18.6	t	H-5, H_2-7	1.35	m	19.4	t	H-5, H_2-7
	1.60	m				1.65	m			
7	1.37 m m	m	37.1	t	H-5, H-9, H-14, H_3-23	2.02	m	27.2	t	H-5, H_2-6
	1.68	m								
8	–		37.2	s	H_2-6, H_2-15, H_3-23	–		130.8	s	H_2-7, H-11a, H-13, H_2-15, H_3-23
9	1.22	m	47.2	d	H_3-22, H_3-23	–		137.3	s	H_2-7, H_2-11, H_3-22
10	–		37.2	s	H-5, H_3-22	–		38.3	s	H_2-6,H_3-22
11	1.90	m	23.1	t	H_2-7, H-9	1.85	m	20.0	t	H_2-12
	1.80	m				1.95	m			
12	5.23	bs	119.6	d	H-11a, H_3-24	1.40	m	26.1	t	H_2-11, H_3,-24
						1.72	m			
13	–		136.5	s	H_3-24	1.60	m	34.7	d	H_3-23, H_3-24
14	1.21	m	54.7	d	H-7a, H-9, H-12, H_2-16. H_3-23	–		39.0	s	H-12a, H_2-15, H_3-23, H_3-24
15	1.30	m	30.4	t	H-14, H_2-16	1.40	m	34.1	t	H-13, H_2-16, H_3-23
	1.65	m				1.55	m			
16	2.53	ddd, l2, 12, 4	35.5	t	H-14, H-15a, H-18, H_3-25	2.08	m	35.5	t	H_2-15, H-18. H_3-25
	2.75	ddd, 12, 12, 6								
17	–		160.5	s	H-18, H_2-16, H_3-25	–		162.0	s	H_2-15, H_2-16, H-18, H_3-25
18	5.63	bs	115.6	d	H_2-16, H_3-25	5.68	d,1	114.6	d	H_2-16, H_3-25
19	–		166.4	s	H-18, OMe	–		167.3	s	H-18, H_3-25, OMe
20	0.84	s	21.9	q	H-3a, H_3-21	0.83	s	21.8	q	H-3a, H-5, H_3-21
21	0.887	s	33.5	q	H_2-3, H_3-20	0.87	s	33.2	q	H-3a, H-5, H_3-20
22	0.893	s	15.6	q	H-1a, H-5, H-9	0.96	s	19.8	q	H-1a, H-5, H-11a
23	0.88	s	23.3	q	H-9, H-14, H-7a	1.04	s	26.6	q	H-13, H_2-l5
24	1.71	d,1	23.5	q	H-12, H-14	0.85	d,7	14.7	q	H-12a, H-13
25	1.91	d,1	25.3	q	H_2-16, H-18	2.17	d,1	19.2	q	H_2-16
OMe	3.67	s	50.8	q	H-18	3.67	s	50.7	q	–

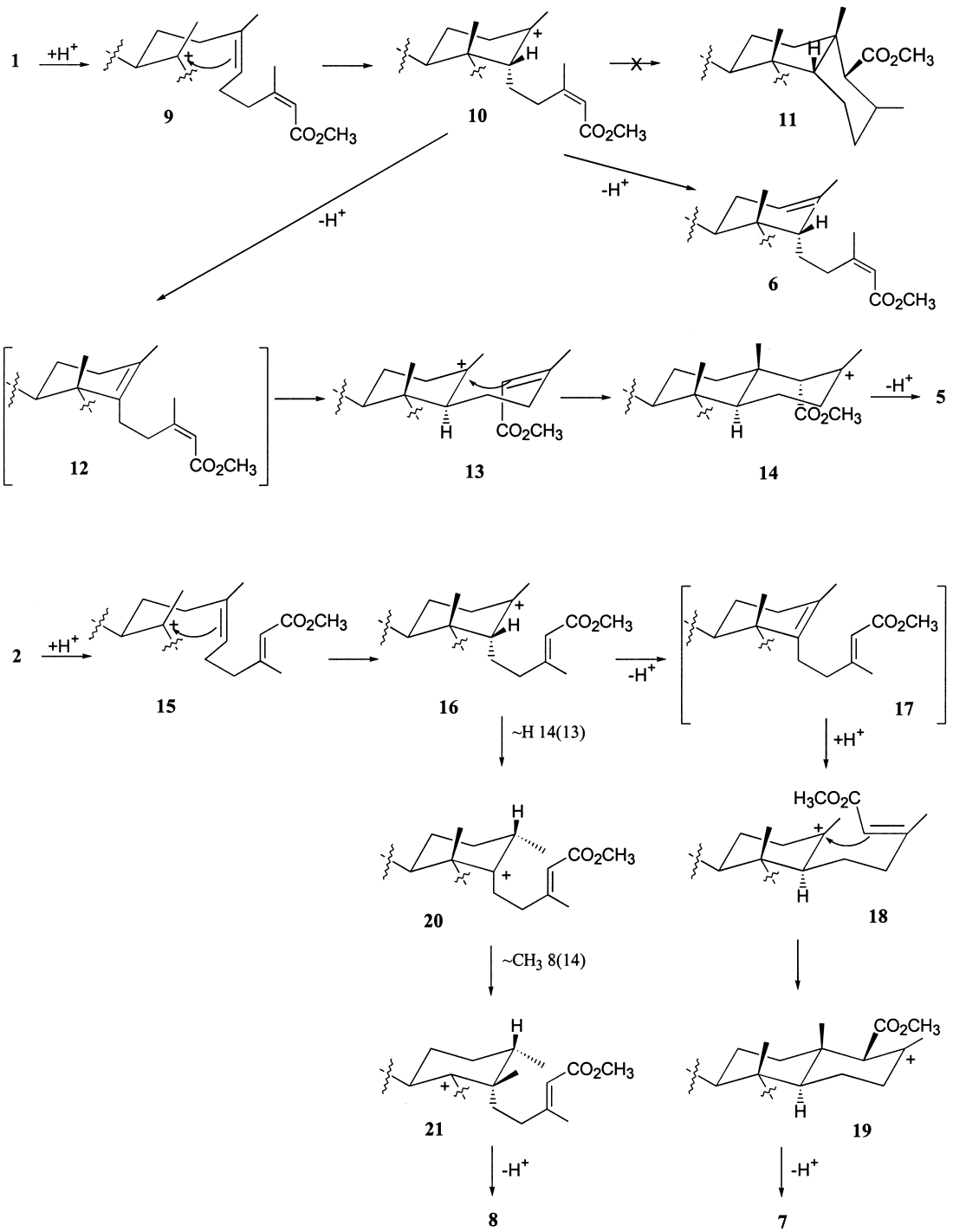
Bruker AA4 500 MHz and WM 400 MHz spectrometers, $CDCl_3$, chemical shifts (ppm) referred to $CHCl_3$, (δ 7.26) and to $CDC1_3$ (δ 77.0). Assignments made by ^{1}H–^{1}H COSY and HMQC experiments.
[a] By DEPT sequence.
[b] HMBC experiments (*J*=10 Hz).

130.8 in the ^{13}C NMR spectrum, which also displayed signals due to the *E*-trisubstituted double bond conjugated with the ester carboxyl group [δ 162.0 (s), 114.6 (d), 167.3 (s)]. These data suggested a tricyclic rearranged structure related to **6** [22(8⟶14)-abeo-cheilanthane skeleton], in which a double bond is located in the rings B and C junction position and consequently the angular methyl at C-8 is shifted to C-14, retaining the β-orientation. The relative *trans*-orientation of the two vicinal methyls at C-13 and C-14 was suggested by ^{13}C NMR values of C-24 (δ 14.7) and C-23 (δ 26.6), which were in accordance with literature data for natural bioactive terpenoids exhibiting the same partial structure.[13] The relative stereochemistry at chiral centres of ring C was further supported by diagnostic NOE effects between H_3-24 (δ 0.85) and H-11α (δ 1.95) and between H_3-22 (δ 0.96) and H-11β (δ 1.85). All ^{1}H and ^{13}C NMR resonances of **8** (Table 1) were assigned by analysis of 2D NMR spectra (^{1}H–^{1}H COSY, NOESY, HMQC and HMBC).

A tentative explanation of the cyclisation reaction course is given in Scheme 2.

Protonation of the ester **1** generates the carbocation **9**, which is then attacked by the $\Delta^{13(14)}$-double bond from the α-side of the molecule (less sterically hindered), forming the tricyclic intermediate carbocation **10**. The hydrogen at C-14 has the β-orientation, due to the *cis*-configuration of the internal double bond in **1**. Although one can assume that carbocation **10** is stable at low temperatures in the superacidic media, nevertheless the closing of the D ring to give the C/D-*cis* fused scalarane **11** does not take place. Most likely, this is due to the steric hindrance created by the cyclic backbone to the lateral chain. This has been revealed on simulation molecular models using a MM2 method.[14] Minimisation of the steric energy for the carbocation **10** shows that the spatial arrangement of the lateral chain in **10**, so that the distance between C-13 and C-18 is lower then 3 Å, is accompanied by a high steric repulsion energy (Table 2).

The carbocation **10** leads by deprotonation to the cheilanthane trisubstituted isomer **6** and, most likely, also to the tetrasubstituted isomer **12**, which however was not detected. The subsequent protonation of **12** from the α-side gives rise to carbocation **13**, which due to the *cis*-configuration of the Δ^{17}-double bond, undergoes cyclisation from the α-side generating the carbocation **14**. Deprotonation



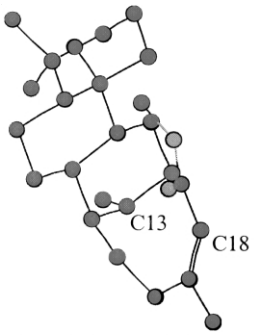
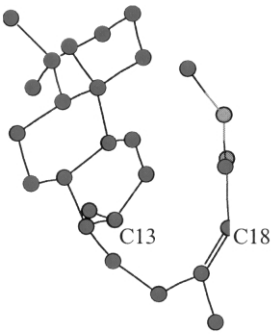
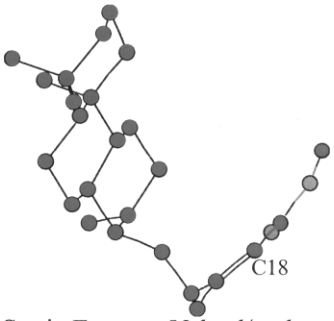
Scheme 2. Proposed mechanisms for cyclisation reaction of esters **1** and **2**.

of **14** leads to the ester **5**, having the α-oriented $-CO_2Me$ group (Scheme 2).

Protonation of the ester **2** generates the carbocation **15**, which cyclises from the α-side of the molecule (sterically less hindered) to form the intermediate carbocation **16**, where, analogously with carbocation **10**, the hydrogen at C-14 has the β-orientation. As in the case of transformation sequence of ester **1**, carbocation **16** undergoes deprotonation giving the cheilanthanic ester **17**, which can be further re-protonated. Protonation at C-14 from the α-side leads to carbocation **18**, which cyclises into the carbocation **19**. The orientation of the $-CO_2Me$ group in **19** should be β-, due to the *trans*-configuration of the Δ^{17}-double bond. Accordingly, the scalaranic ester **7**[3,11] is formed by deprotonation of **19**. At the same time, carbocation **16** by hydride shift leads to **20**, which can give the rearranged carbocation **21** by migration of the methyl group from the C-8 to C-14. The subsequent deprotonation of **21** leads to 22(8→14)-abeo-cheilanthane compound **8** (Scheme 2).

Based on the obtained results the following can be summarised.

Table 2. MM2 simulations of the steric energy for the intermediate **10** conformers

Iteration 0	Iteration 19	Iteration 417 (optimal)
		
Steric Energy *5354 kcal/mol*	Steric Energy *378 kcal/mol*	Steric Energy *52 kcal/mol*
Distance C_{13}-C_{18} *2.005 Å*	Distance C_{13}-C_{18} *2.795 Å*	Distance C_{13}-C_{18} *3.555 Å*

As in the case of sesquiterpenic esters with a *cis*-configuration of the internal double bond,[8] the cyclic scalaranic compounds **5** and **7** derived from superacidic cyclisation of the esters **1** and **2**, have *trans*-fused C/D rings. The same compounds were obtained by cyclisation of the esters **1** and **2** isomers with an internal 13-*trans*-double bond. This reaction pathway is due to the lowered nucleophilicity of the double bond, conjugated with the ester group.

In such a way, the superacidic low temperature cyclisation of bicyclogeranylfarnesoic acids esters with 13-*cis* configuration leads to the formation of mixtures of tetracyclic scalaranic and tricyclic compounds, with the latter predominating. Consequently, the configuration of internal Δ^{13}-double bond does not influence the mode of C/D rings junction in the tetracyclic scalarane sesterterpenes: the 13-*cis* isomers give the same C/D *trans*-fusion as in the case of 13-*trans* isomers cyclisation. This is possible when the precursors of tetracyclic scalaranic esters **5** and **7** are tricyclic cheilanthane compounds **12** and **17**, displaying a tetrasubstituted Δ^{13}-double bond. These hypothetical intermediates are easily further cyclised to tetracyclic compounds under the reaction conditions. The configuration of Δ^{17}-double bond in esters **1** and **2** determinates the steric orientation of the $-CO_2Me$ group in the scalarane compounds: cyclisation of 17*E*-ester **1** leads to scalarane compounds with a pseudoequatorial $-CO_2Me$ group, whereas cyclisation of 17*Z*-ester **2** leads to scalarane compounds with a pseudoaxial $-CO_2Me$ group. The formation of cheilanthane tricyclic ester **6** by cyclisation of 13*Z*,17*Z*-bicyclic ester (**1**) also confirms that the ring closure takes place from the less hindered α-side of the molecule: the configuration at C-14 in **6** is *R* (14-*epi*-cheilanthane series).

The obtained results show that the behaviour of esters **1** and **2** on the superacidic treatment is quite different. The carbocation **10**, which is formed during the cyclisation of ester **1**, is stabilised by elimination of proton either from C-12 or C-14 positions with formation of compounds **6** and **12**, respectively. On the contrary, the carbocation **16**, which is derived from the ester **2**, eliminates the proton only from the C-14 position, most likely for steric reasons, to give the intermediate **17** which is further cyclised to scalaranic ester (**7**) by protonation at C-14 from the sterically less crowded α-side. In the same time the carbocation **16** suffers a C-14–C-13 hydride shift with subsequent migration of the methyl group from C-8 to C-14 leading to carbocation **21** which eliminates the proton from C-9 giving the final rearranged compound **8**.

3. Experimental

3.1. General procedures

Melting points were measured on a Kofler apparatus and are uncorrected. The IR spectra were taken on a Bio-Rad FTS 7 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker WM 500, Bruker AM 400 and Bruker WM 300 spectrometers; chemical shifts are reported in ppm and are referred to $CHCl_3$ as internal standard (δ 7.26 for proton and δ 77.0 for carbon). Optical rotations were measured in $CHCl_3$ on a Jasco DIP 370 polarimeter, using a 10-cm cell. EIMS spectra were recorded on a Carlo Erba TRIO 2000 spectrometer, coupled with an INTEL computer. Semipreparative HPLC purifications were carried out on Waters liquid chromatographic system. Commercial Merck Si gel 60 (70–230 mesh ASTM) was used for column chromatography, and Merck precoated Si gel plates were used for TLC. The chromatograms were sprayed with 0.1% $Ce(SO_4)_2$ in 2N H_2SO_4 and heated at 80°C for 5 min to detect the spots. The work-up of the reaction mixtures in organic solvents included exhaustive extraction with diethyl ether and washing with water up to neutral reaction, drying over anhydrous Na_2SO_4, filtration, and removal of the solvent in vacuo.

3.1.1. Synthesis of methyl 13*Z*,17*Z*- and 13*Z*,17*E*-bicyclogeranylfarnesoates (1) and (2). A solution of sodium methoxide in methanol [105.0 mg (4.56 equiv.) of sodium metal in 2.7 ml of methanol] was slowly added to a stirred solution of 13*Z*-bicyclogeranylgeranylacetone **3** (500.0 mg, 1.52 mmol) and trimethylphosphonoacetate (830.1 mg, 4.56 mmol) in benzene (35 ml). After refluxing for 2 h, the mixture was cooled, treated with ice-water (30 ml) and extracted with Et_2O (3×15 ml). After usual

work-up the solvent was removed in vacuo and the residue (521.1 mg) was chromatographed on SiO_2·$AgNO_3$ (18 g) column by elution with light petroleum ether/Et_2O gradient giving, in order of increasing polarity 78.5 mg (12%) of 13*Z*,17*Z*-ester **1**, 124.3 mg (19%) of mixture of esters **1** and **2** (~1:2) and 315.1 mg (51%) of 13*Z*,17*E*-ester **2**.

Compound **1**. Colourless viscous liquid; $[\alpha]_D^{25}$=+5.2 (*c* 0.21, $CHCl_3$); IR ν_{max} (liquid film) 840, 890, 1150, 1224, 1380, 1438, 1635, 1730 cm^{-1}; ^1H NMR (300 MHz) δ_H: 0.67 (3H, s, H_3-22), 0.80 (3H, s, H_3-20), 0.87 (3H, s, H_3-21), 1.68 (3H, bs, H_3-24), 1.87 (3H, bs, H_3-25), 2.70–0.70 (20H, m), 3.67 (3H, s, OMe), 4.57 (1H, bs, H-23a), 4.83 (1H, bs, H-23b), 5.10–5.20 (1H, m, H-14), 5.65 (1H, bs, H-18); ^{13}C NMR (75.5 MHz) δ_C: 166.7 (C-19), 160.5 (C-17), 148.8 (C-8), 136.4 (C-13), 124.5 (C-14), 115.7 (C-18), 106.2 (C-23), 56.2 (C-9), 55.1 (C-5), 50.7 (–OMe), 42.2 (C-3), 39.6 (C-10), 39.0 (C-1), 38.4 (C-7), 33.7 (C-16), 33.6 (2C, C-21 and C-4), 30.6 (C-12), 26.6 (C-15), 25.3 (C-25), 24.5 (C-6), 23.3 (C-24), 21.7 (C-20), 21.6 (C-11), 19.4 (C-2), 14.5 (C-22). EIMS *m*/*z* (%) 386 (M^+, 8), 371 (50), 339 (6), 245 (40), 205 (52), 149 (65), 137 (60), 121 (80), 81 (100). Anal. calcd for $C_{26}H_{42}O_2$: C 80.77, H 10.94; Found: C 80.56, H 10.78.

Compound **2**. Colourless viscous liquid; $[\alpha]_D^{25}$=+14.7 (*c* 0.31, $CHCl_3$); IR ν_{max} (liquid film) 889, 1150, 1224, 1382, 1440, 1648, 1724 cm^{-1}; ^1H NMR (300 MHz) δ_H: 0.67 (3H, s, H_3-22), 0.80 (3H, s, H_3-20), 0.87 (3H, s, H_3-21), 1.67 (3H, bs, H_3-24), 2.40–0.70 (20H, m), 2.15 (3H, bs, H_3-25), 3.68 (3H, s, OMe), 4.56 (1H, bs, H-23a), 4.85 (1H, bs, H-23b), 5.04–5.10 (1H, m, H-14), 5.66 (1H, bs, H-18); ^{13}C NMR (75.5 MHz) δ_C: (C-17 and C-18 not detected) 148.8 (C-8), 137.1 (C-13), 123.7 (C-14), 115.2 (C-18), 106.2 (C-23), 56.1 (C-9), 55.1 (C-5), 50.8 (–OMe), 42.2 (C-3), 41.3 (C-16), 39.7 (C-10), 39.0 (C-1), 38.4 (C-7), 33.6 (2C, C-21 and C-4), 30.5 (C-12), 25.9 (C-15), 24.5 (C-6), 23.3 (C-24), 21.7 (C-20), 21.6 (C-11), 19.4 (C-2), 18.8 (C-25), 14.5 (C-22). EIMS *m*/*z* (%) 386 (M^+, 7), 371 (25), 339 (7), 245 (17), 191 (24), 177 (34), 137 (75), 114 (70), 81 (100). Anal. calcd for $C_{26}H_{42}O_2$: C 80.77, H 10.94; Found: C 80.63, H 10.79.

3.1.2. Superacidic cyclisation of methyl 13*Z*,17*Z*-bicyclogeranylfarnesoate (1). A solution of methyl 13*Z*,17*Z*-bicyclogeranylfarnesoate (**1**) (40.0 mg, 0.103 mmol) in *i*-$PrNO_2$ (0.7 ml), cooled at −78°C, was treated with FSO_3H (52.0 mg, 0.52 mmol) in *i*-$PrNO_2$ (0.3 ml), under stirring. After 15 min, the reaction was stopped by adding a solution of Et_3N (1.0 ml) in light petroleum ether (1.0 ml). The usual work up gave 39.4 mg of a crude residue, which was used in the next step without any purification. The residue (39.4 mg) was dissolved in EtOH (0.8 ml) and 10% KOH/EtOH solution (2.5 ml) was added. The reaction mixture was refluxed for 2 h. The usual work-up yielded 38.7 mg of crude reaction product, which was chromatographed on a SiO_2 (1.0 g) column. Elution with a light petroleum ether/Et_2O gradient gave, in order of increasing polarity, 10.4 mg (26%) of ester (**5**), which showed spectral data (MS, IR, ^1H and ^{13}C NMR) identical with those reported in literature[3,11] and 25.2 mg (63%) of acid-containing fraction.

Compound **5**. Colourless viscous liquid; $[\alpha]_D^{25}$=−22.6 (*c* 0.20, $CHCl_3$) [lit.[3] $[\alpha]_D$=−26.5 (*c* 2.3, $CHCl_3$)]; ^1H NMR (300 MHz, selected values) δ_H: 0.79 (3H, s, H_3-20), 0.83 (6H, s, H_3-21 and H_3-22), 0.89 (3H, s, H_3-23), 0.91 (3H, s, H_3-24), 1.60 (3H, s, H_3-25), 2.47 (1H, bs, H-18), 3.69 (3H, s, OMe), 5.58 (1H, bs, H-16); ^{13}C NMR (75.5 MHz) δ_C: 174.8, 128.5, 124.6, 61.9, 60.8, 56.1, 51.4, 46.7, 42.1, 41.6, 39.7, 39.2, 37.5, 37.4, 36.4, 33.4, 33.3, 22.9, 22.6, 22.4, 21.3, 18.6, 18.2, 17.4, 17.0, 16.5. The acid fraction (25.2 mg), was treated with a saturated solution of CH_2N_2 in Et_2O (2.0 ml). After 20 min, the solvent was removed in vacuo and residue was purified on a column with SiO_2 (0.5 g) (light petroleum ether as eluent) to give 24.5 mg of mixture containing the ester **6**, which was further submitted to HPLC purification [semipreparative Nova-Pack C-18 column, MeOH/H_2O (95:5), flow rate 1.5 ml/min, affording pure ester **6** (15.6 mg, 39%).

Compound **6**. Colourless viscous liquid; $[\alpha]_D^{25}$=+54.1 (*c* 0.2, $CHCl_3$); IR ν_{max} (liquid film) 857, 1155, 1236, 1382, 1443, 1660, 1724 cm^{-1}; ^1H and ^{13}C NMR data (Table 1); EIMS *m*/*z* (%) 386 (M^+, 5), 371 (5), 273 (8), 259 (15), 220 (98), 205 (100), 177 (58), 145 (72), 105 (88), 73 (91). HREIMS: 386.3195, calcd for $C_{26}H_{42}O_2$ 386.3185.

3.1.3. Superacidic cyclisation of methyl 13*Z*,17*E*-bicyclogeranylfarnesoate (2). Using the above described procedure, methyl 13*Z*,17*E*-bicyclogeranylfarnesoate (**2**) (60.0 mg, 0.155 mmol) in *i*-$PrNO_2$ (1.0 ml) was cooled at −78°C and treated with FSO_3H (80.2 mg, 0.80 mmol) in *i*-$PrNO_2$ (0.4 ml), under stirring. After 30 min, the reaction was stopped by adding a solution of Et_3N (1.5 ml) in petroleum ether (1.5 ml). The usual work up gave 58.3 mg of a crude residue, which was used in the next step without any purification. The residue (58.3 mg) was dissolved in EtOH (1.0 ml) and 10% KOH/EtOH solution (3.0 ml) was added. The reaction mixture was refluxed for 2 h. The usual work-up yielded 56.4 mg of crude reaction product, which was chromatographed on SiO_2 (1.2 g) column by elution with light petroleum ether/Et_2O gradient giving, in order of increasing polarity, 14.8 mg (25%) of ester **7**, which showed spectral data (MS, IR, ^1H and ^{13}C NMR) identical with those described in literature[3,11] and 37.8 mg (63%) of an acid-containing fraction. Compound **7**: colourless crystals, mp 170–171.5°C (from light petroleum ether), [lit.[3] mp 167–169°C (from light petroleum ether), lit.[11] mp 165–169°C (from light petroleum ether)]; $[\alpha]_D^{25}$=+62.4 (*c* 0.43, $CHCl_3$) [lit.[3] $[\alpha]_D$=+65.7 (*c* 3.6, $CHCl_3$)]; ^1H NMR (400 MHz, selected values) δ_H: 0.80 (3H, s, H_3-20), 0.83 (6H, s, H_3-21 and H_3-22), 0.91 (3H, s, H_3-23), 0.92 (3H, s, H_3-24), 1.59 (3H, bs, H_3-25), 2.89 (1H, bs, H-18), 3.66 (3H, s, OMe), 5.51 (1H, bs, H-16); ^{13}C NMR (100 MHz) δ_C: 173.4, 128.9, 124.0, 62.6, 61.2, 56.5, 54.8, 51.0, 42.2, 41.9, 41.8, 39.9, 37.7, 37.4, 36.3, 33.3 (2C), 22.6, 21.4, 21.2, 18.6, 18.2, 17.5, 16.9, 16.4, 15.4. To an aliquot of the above acid-containing fraction (20.0 mg, 0.054 mmol) in Et_2O (0.5 ml) was added a saturated solution of CH_2N_2 in Et_2O (1.0 ml). After 20 min, the solvent was removed in vacuo to give 20.4 mg of residue, which was purified on a SiO_2 column (0.5 g), (light petroleum ether as eluent) to give 18.9 mg (91%) of methyl ester **8**.

Compound **8**. Colourless crystals, mp 110–111°C (from

light petroleum ether); $[\alpha]_D^{25}=+22.3$ (*c* 0.31, $CHCl_3$); IR ν_{max} (liquid film) 865, 1151, 1225, 1379, 1436, 1648, 1722 cm^{-1}; ^1H and ^{13}C NMR data (Table 1). EIMS *m/z* (%) 386 (M^+, 4), 371 (8), 312 (17), 259 (100), 245 (13), 163 (34), 149 (30). Anal. calcd for $C_{26}H_{42}O_2$: C 80.77, H 10.94; found: C 80.81, H 10.84.

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