Superacidic Cyclization of All-*trans*-ω-Acetoxyfarnesyl Benzyl Ether

Veaceslav Kulcițki,[a] Nicon Ungur,[a] Pavel F. Vlad,*[a] Margherita Gavagnin,[b] Francesco Castelluccio,[b] Guido Cimino[b]

[a] Institutul de Chimie al Academiei de Ştiinţe, str. Academiei 3, MD 2028 Chişinău, Republic of Moldova
Fax +3732-739775; E-mail: vlad@terp.ich.asm.md

[b] Istituto per la Chimica di Molecole di Interesse Biologico CNR,[1] Via Toiano 6, I- 80072, Arco Felice (Na), Italy

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Abstract: The superacidic cyclization of all-*trans*-ω-acetoxyfarnesyl benzyl ether **2** begins at the internal double bond giving a mixture of diastereomeric monocyclic compounds **5** and **6**, prenylated at *gem*-dimethyl groups.

Key words: cyclizations, superacids, terpenoids, carbocations

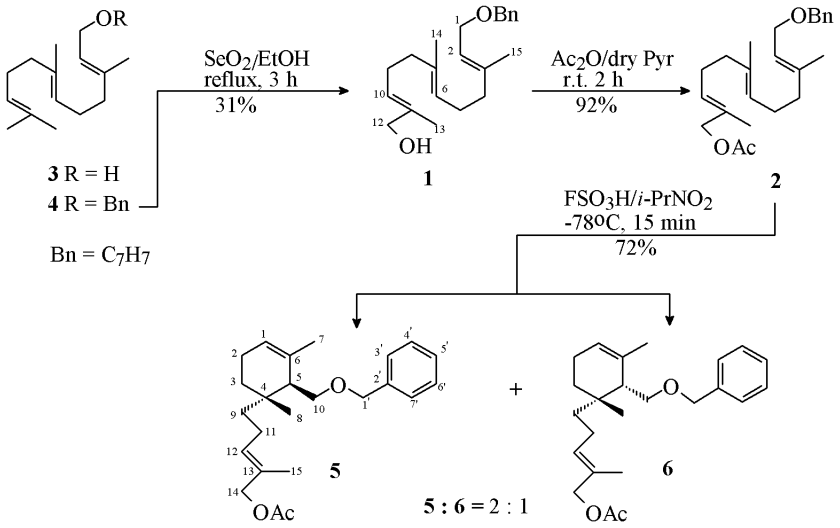
As reported recently,[2–6] superacidic low-temperature cyclization of aliphatic and partially cyclized terpenoids has been shown to constitute a general, one step, highly efficient, stereospecific structure- and chemoselective way to obtain fully cyclized terpenoids. Several types of compounds such as alcohols, hydroxy esters, acids, esters, oxides and lactones have been synthesized according to this method. However, superacidic cyclization turned out to be ineffective with epoxyterpenoids having terminal epoxy groups.[7,8] In fact, the terminal epoxy groups underwent isomerization under standard conditions of superacidic cyclization, giving rise to ketones in the case of β-terpenoids and, in the case of α-terpenoids, to (*E*)-allylic alcohols with a ω-hydroxy group, and partially to α-diols and their monofluorosulfonates, whereas carbocyclic compounds were not formed.

This fact led us to the idea that, on interaction of superacid with terpenoids containing ω-hydroxy groups and more than two isoprenic residues in their molecules, the cyclization process could be initiated from the internal double bond. In order to check this assumption, the benzyl ether of ω-hydroxyfarnesol **1** was synthesized and submitted to superacidic cyclization. Benzylic protection was selected due to its stability under reaction conditions and ensuring chemical uniformity of the cyclization process (unlike the acetate group for example). Under standard experimental conditions, cyclization of compound **1** afforded a complex mixture of products, whereas its acetate **2** smoothly reacted with 5 equivalents of fluorosulfonic acid. The results of this cyclization are reported here.

Compound **2** was prepared starting from farnesol **3** in three steps (Scheme 1), according to a literature procedure.[9] Compound **3** was protected as its benzyl ether **4**, which was oxidized to allylic alcohol **1** with selenium dioxide.[9] Treatment of **1** with acetic anhydride in pyridine afforded the target bifunctional compound **2**.

Superacidic cyclization of **2** was carried out by treatment with 5 equivalents of fluorosulfonic acid (−78 °C, 15 min) affording a 2:1 mixture of compounds **5** and **6** (72%). The reaction mixture was purified by reverse-phase HPLC giving compounds **5** and **6**.

^{1}H and ^{13}C NMR data (Table) of **5** and **6** were very similar, indicating that the two reaction products displayed the



Scheme 1

same carbon skeleton. In particular, both ^{1}H NMR spectra showed signals attributable to two methyl groups at carbon atoms carrying a double bond and two olefinic protons, suggesting that the molecules retained two of the three trisubstituted double bonds of the starting compound **2** and, consequently, should be monocyclic. Indeed, the presence of a singlet methyl signal (H_3-8), and of an ABX system, assignable to the methylene group (H_2-10) linked to the benzyloxy moiety, further coupled with an angular methine (H-5), strongly supported a monocyclic structure for both compounds, bearing a homoacetoxyprenyl chain and a methyl at C-4. Being epimers, the two molecules differed only in the stereochemistry at the chiral centre C-4. In order to establish the relative configuration for each compound, both a series of NOE difference experiments and conformational analysis were performed.

First of all, an energy minimization calculation on the two possible stereoisomers using DMM program,[10] revealed that for each molecule the energetically more favoured conformation exhibited the chain at C-5 in pseudoequatorial orientation. Therefore, based on this fixed chiral centre, the *trans*-isomer should display an equatorial homoprenyl chain at C-4, whereas in the *cis*-isomer the same homoprenyl moiety should be axially oriented. The irradiation of the proton H-5 resulted in a diagnostic enhancement of the methyl signal at C-4 in the isomer **6**, while a NOE interaction was observed between H-5 and H_2-9 in the isomer **5**. These results strongly supported a *trans* relative stereochemistry at C-4 and C-5 for compound **5**, whereas **6** was suggested to be the corresponding *cis*-isomer. According to this assignment, a 2:1 ratio of **5**/**6** was obtained with predomination of thermodynamically more favoured *trans*-isomer. All the proton and carbon resonances of **5** and **6** were easily assigned by 2D NMR experiments (^{1}H-^{1}H COSY, HETCOR and HMBC) and are reported in the Table.

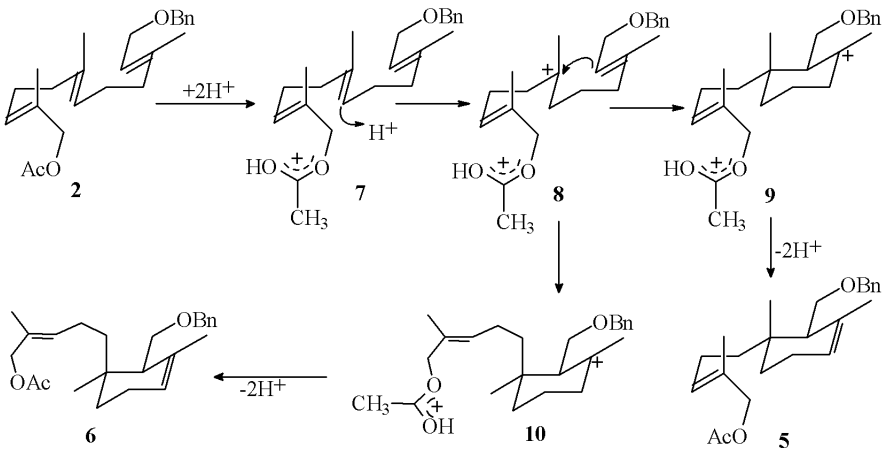
The formation of compounds **5** and **6** implies that the cyclization process occurred by protonation of the internal $\Delta^{6,7}$-double bond in the starting compound **2**. To the best of our knowledge, only two reports[11,12] describing such kind of cyclization have appeared in the literature. This unusual cyclization could be explained as follows.

On treatment with superacid, the ω-acetoxy group of **2** is protonated to give the carboxonium-ion **7** (Scheme 2), which does not allow the protonation of the terminal double bond because this would bring about the formation of an energetically unfavourable 1,3-dicationic system, whereas the protonation of $\Delta^{6,7}$-double bond occurs with the formation of the dication **8**, transformed into both dications **9** and **10**. Deprotonation of **9** and **10** led to the final compounds **5** and **6**, respectively. The dication **9** with two

Table ^{1}H and ^{13}C NMR Spectral Data ($CDCl_3$) of Compounds **5** and **6**[a]

Assignments[b]	**5**			**6**		
	^{1}H NMR δ, m,[c] *J* (Hz)	^{13}C NMR δ	m[c]	^{1}H NMR δ, m,[c] *J* (Hz)	^{13}C NMR δ	m[c]
1	5.42 *m*	122.4	d	5.40 *m*	122.1	*d*
2	1.94 *m*	22.7	t	1.97 *m*	22.8	*t*
3	1.52 *dt* (13, 8)	29.9	t	1.23 *m*	30.1	*t*
	1.30 *m*	–	–	1.49 *dt* (13, 8)	–	–
4	–	34.4	*s*	–	34.5	*s*
5	1.86 *m*	48.4	*d*	1.84 *m*	49.1	*d*
6	–	133.6	*s*	–	133.6	*s*
7	1.72 *d* (1.5)	23.2	*q*	1.74 *br s*	23.4	*q*
8	0.96 *s*	23.9	*q*	0.89 *s*	23.0	*q*
9	1.32 *m*	38.2	*t*	1.39 *ddd* (13, 11, 5)	39.1	*t*
	1.27 *m*	–	–	1.26 *m*	–	–
10	3.52 *dd* (10, 6)	70.6	*t*	3.51 *dd* (10, 5)	70.7	*t*
	3.43 *dd* (10, 3)	–	–	3.38 *dd* (10, 3)	–	–
11	1.98 *m*	22.2	*t*	2.05 *m*	22.0	*t*
12	5.43 *m*	130.6	*d*	5.40 *m*	131.0	*d*
13	–	129.3	*s*	–	129.3	*s*
14	4.44 *br s*	70.3	*t*	4.43 *br s*	70.5	*t*
15	1.64 *s*	13.8	*q*	1.63 *br s*	13.7	*q*
1'	4.48 *s*	73.0	*t*	4.46 *s*	73.1	*t*
2'	–	138.6	*s*	–	138.6	*s*
3', 7'	7.33 *m*	127.6	*d*	7.32 *m*	127.7	*d*
4', 6'	7.33 *m*	128.2	*d*	7.32 *m*	128.4	*d*
5'	7.27 *m*	127.4	*d*	7.27 *m*	127.4	*d*
$COCH_3$	2.07 *s*	21.0	*q*	2.07 *s*	21.0	*d*
$COCH_3$	–	171.0	*s*	–	171.1	*s*

[a] Assignments were made by 2D NMR experiments [^{1}H-^{1}H cosy, HETCOR, HMBC (*J* = 10 and 6 Hz)].
[b] Assignments refer to the numbering of the carbon atoms of the molecule.
[c] Denotes the multiplicity of the peak.



Scheme 2

equatorial chains is more stable and consequently compound **5** predominates over its diastereomer **6**.

In summary, the ω-allylic acetoxy group in the farnesol skeleton deactivates the terminal double bond. The cyclization process, starting from the internal double bond, gives rise to monocyclic terpenoids with prenylated *gem*-dimethyl groups in the ring. It should be mentioned that such cyclic compounds have been isolated from natural sources.[13,14] Some of them possess interesting biological activity, being at the same time hardly accessible by synthesis.

The IR spectra were taken on a Bio-Rad FTS 7 or a Specord 74 IR spectrophotometer. ^{1}H 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, referenced to $CHCl_3$ as internal standard (δ 7.26 for proton and δ 77.00 for carbon). Mass spectra were recorded on Kratos MSSO and TRIO 2000 instruments, coupled with an INTEL computer. Commercial Merck silica gel 60 (70−230 mesh ASTM) was used for column chromatography (CC), and Merck precoated Si gel plates were used for TLC. The chromatograms were sprayed with 0.1% $Ce(SO_4)_2$ in 2 N H_2SO_4 and heated at 80 °C for 5 min to detect the spots. HPLC purifications were conducted on a Waters liquid chromatograph equiped with a UV detector (254 n).

All-*trans*-ω-Hydroxyfarnesyl Benzyl Ether 1

To a solution of **4**[9] (2.18 g, 6.99 mmol) in EtOH (4 mL) was added SeO_2 (410 mg, 3.68 mmol) and the solution was refluxed for 2 h. After removal of the precipitated Se, the solution was concentrated. Chromatography of the crude product (2.47 g) on silica gel afforded the starting ether **4** (645 mg, 30%) and the all-*trans*-ω-hydroxyfarnesyl benzyl ether **1** (710 mg, 31%):

IR ($CHCl_3$): ν = 3400, 2930, 1670, 1450, 1068, 770 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (s, 9 H, CH_3-13, CH_3-14 and CH_3-15), 3.83 (m, 2 H, H_2-12), 3.90 (d, 7 Hz, 2 H, H_2-1), 4.30 (s, 2 H, CH_2Ph), 5.10 (m, 2 H, H-2 and H-6), 5.35 (m, 1 H, H-10), 7.20−7.30 (m, 5 H, Ar-1H).

The spectral data (IR, ^{1}H NMR) were identical to those described in the literature.[9]

All-*trans*-ω-Acetoxyfarnesyl Benzyl Ether 2

A solution of **1** (650 mg, 1.98 mmol) in anhyd pyridine (5 mL) was treated with Ac_2O (1 mL) and the mixture was kept at r.t. for 2 h. H_2O (10 mL) was added carefully to the mixture and the product was extracted with Et_2O (3 × 10 mL). The extract was washed with 10% H_2SO_4 (2 × 5 mL), H_2O (2 × 10 mL), dried (Na_2SO_4) and concentrated. The crude reaction product (727 mg) was chromatographed on a silica gel column (petroleum ether/Et_2O, 97:3) to give 675 mg (92%) of **2.**

IR ($CHCl_3$): ν = 1735, 1455, 1380, 1235, 1065, 1020 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, 3 H, CH_3-13), 1.60 (s, 3 H, CH_3-14), 1.65 (s, 3 H, CH_3-15), 2.07 (s, 3 H, $OcOCH_3$), 4.03 (m, 2 H, H_2-1), 4.44 (br s, 2 H, H_2-12), 4.50 (s, 2 H, CH_2Ph), 5.12 (m, 2 H, H-2 and H-6), 5.40 (m, 1 H, H-10), 7.20−7.35 (m, 5 H, Ar-H).

Anal. calc. for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.76; H, 9.22.

Superacidic Cyclization of All-*trans*-ω-acetoxyfarnesyl Benzyl Ether 2

To a solution of **2** (70 mg, 0.19 mmol) in 2-nitropropane (1.5 mL) cooled to −78 °C, was added a solution of FSO_3H (95 mg, 0.95 mmol) in the same solvent (1 mL) with vigorous stirring. After 15 min of stirring at the same temperature, the mixture was quenched by adding a 50% excess of Et_3N in hexane (1:1, 0.35 mL). H_2O (5 mL) was added carefully to the mixture and the product was extracted with Et_2O (3 × 5 mL). The extract was washed with 10% H_2SO_4 (2 × 5 mL), H_2O (2 × 10 mL), dried (Na_2SO_4) and filtered. The solvent was evaporated in vacuo and the crude product (69 mg) was purified on a silica gel column (1.0 g) (petroleum ether/Et_2O, 97:3) to give 50.2 mg (72%) of a 2:1 mixture of **5** and **6**. The mixture of **5** and **6** was separated by HPLC [semipreparative Nova-Pack C-18 column, MeOH/H_2O (95:5), flow rate 1.5 mL/min], affording pure **5** (19.5 mg) and **6** (9.2 mg).

Compound 5

IR ($CHCl_3$): ν = 1741, 1453, 1378, 1232, 1101, 756 cm^{-1}.

MS: *m*/*z* (%) = 370 (M^+, 2), 310 (M^+−AcOH, 9), 262 (4), 219 (42), 202 (100), 189 (98), 175 (28), 161 (79), 119 (97), 91(99).

Anal. calc. for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.77; H, 9.21.

Compound 6

IR ($CHCl_3$): ν = 1741, 1452, 1375, 1233, 1096, 741 cm^{-1}.

MS: *m*/*z* (%) = 370 (M^+, 1), 310 (4), 262 (13), 219 (60), 202 (100), 189 (78), 175 (32), 161 (74), 119 (99), 91 (98).

Anal. calc. for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.83; H, 9.20.

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