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SUPERACID CYCLIZATION OF (2*E*,6*E*,10*E*,14*E*)-8- PHENYLSULFONYLGERANYLFARNESOL TETRAHYDROPYRANYL ETHER

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*A mixture of (13*E*,17*E*)-12-phenylsulfonylbicyclogeranylfarnesol tetrahydropyranyl ether (**8**) and (13*E*,17*E*)-12-phenylsulfonylbicyclogeranylfarnesol (**9**) was formed by superacid low-temperature cyclization of exclusively trans-8-phenylsulfonylgeranylfarnesol tetrahydropyranyl ether (**1**). The structures of **8** and **9** were established using spectral data. The optically active form of **9** was also confirmed by retrosynthesis from (+)-sclareolide (**10**).*

Key words: superacid cyclization, sesquiterpenoids, terpenylphenylsulfones, synthesis.

Biomimetic superacid cyclization of terpenoids turned out to be an effective synthetic method for cyclic terpenoids [1-8]. We studied previously superacid cyclization of several α,ω-bifunctionalized mono- and sesquiterpenoids and showed that α,ω-geraniol derivatives gave cyclic products with the *n*-menthane structure [9] whereas α,ω-bifunctionalized sesquiterpenoids produced monocyclic derivatives of α-cyclogeraniol prenylated at the gem-dimethyl group, which were formed by initiation of the cyclization by protonation of the inner C-6—C-7 double bond [10]. Superacid cyclization of α,ω-bifunctionalized aliphatic (2*E*,6*E*,10*E*)-diterpenoids also begins with protonation of the inner C-10—C-11 double bond to form diterpenoids with the sacculatane carbon skeleton [11].

Herein we report the synthesis and superacid cyclization of the tetrahydropyranyl (THP) ether of the bifunctionalized derivative of exlusively *trans*-geranylfarnesol in which the second functional group, phenylsulfonyl, is located in the middle of the aliphatic carbon chain of the sesquiterpenoid on C-8. We selected the phenylsulfonyl group because it is easy to insert in the necessary position on the carbon chain, is stable toward superacid, and can be replaced by other functional groups.

The starting material for cyclization of the THP ether of exclusively *trans*-8-phenylsulfonylgeranylfarnesol (**1**) was prepared by etherification of exclusively *trans*-8-phenylsulfonylgeranylfarnesol (**2**) with dihydropyran (90% yield). Compound **2**, in turn, was synthesized in 91% yield by addition of commercially available (2*E*,6*E*)-farnesylchloride (**3**) to 8-phenylsulfonylgeraniol (**4**), which was prepared from the known ω-hydroxygeranylacetate (**5**) [12]. Bromination of the last by phosphorus tribromide produced 8-bromogeranylacetate (**6**) in 70% yield. This reacted smoothly with sodium phenylsulfonate to give 8-phenylsulfonylgeranylacetate (**7**). Saponification of **7** with alcoholic base gave 8-phenylsulfonylgeraniol (**4**) (Scheme 1).

Spectral and elemental analysis were used to find the structure of **2**. Its PMR spectrum contained signals for 6 methyls on double bonds, 5 vinyl protons, and >C=CHCH_2OH and >CHSO_2Ph groups. Its ^{13}C NMR spectrum exhibited signals for 6 methyls on fully substituted C atoms, 8 methylenes, and 11 methines, 6 fully substituted C atoms, and 16 sp^2-hybridized C atoms. Superacid cyclization of the THP ether of **1** by fluorosulfonic acid at -78°C in 2-nitropropane formed a mixture of compounds, from which column chromatography over silica gel isolated two pure compounds of different polarity. The PMR spectrum of the less polar minor cyclization product contained signals for 3 methyls on fully substituted C atoms, 3 methyls on C atoms of double bonds, 2 vinyl protons, and the THP and phenylsulfonyl groups. The ^{13}C NMR spectrum showed signals for 6 methyls, 13 methylenes, 10 methines, and 7 fully substituted C atoms. Based on the spectral data and elemental analysis, this compound was assigned the structure (8,13*E*,17*E*)-12-phenylsulfonylbicyclogeranylfarnesol THP ether (**8**).

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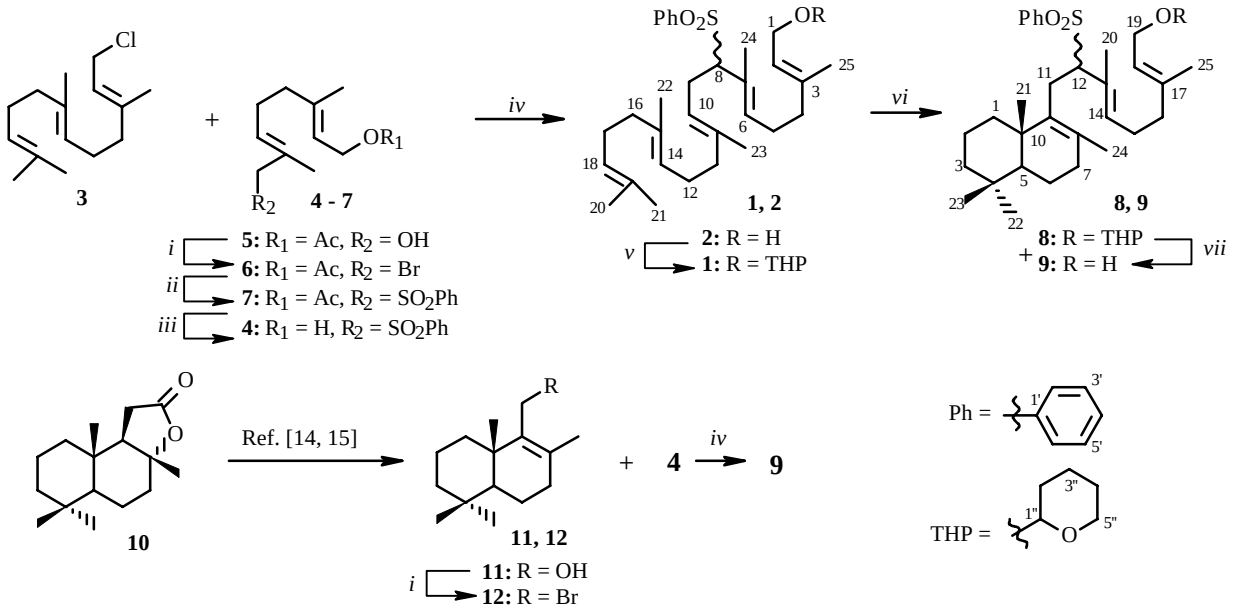
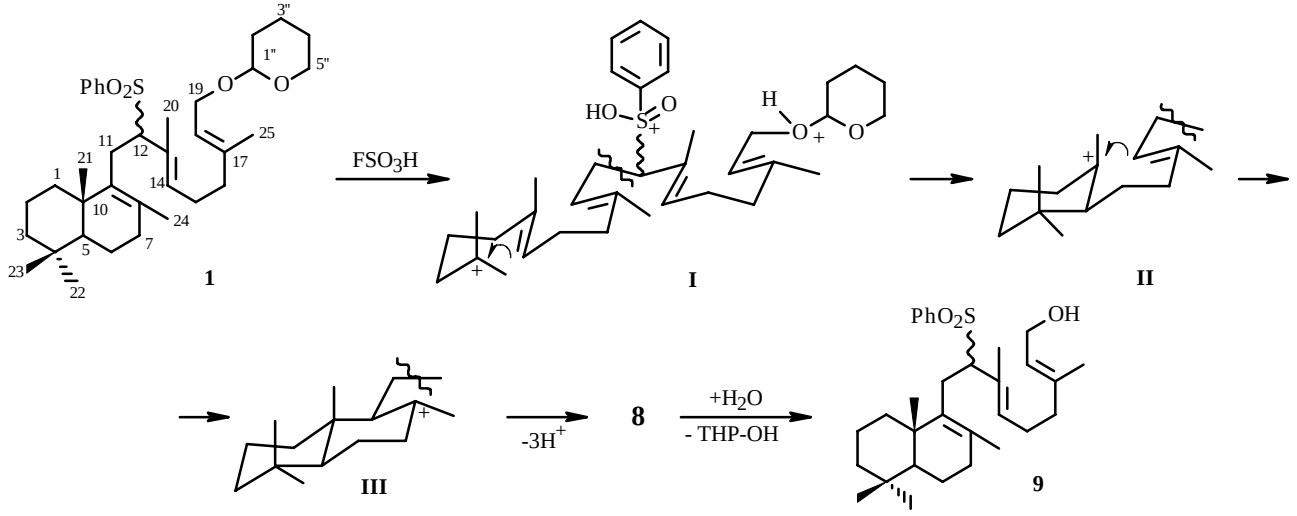


i. PBr_3, Et_2O, Py, 0°C; *ii*. $NaSO_2Ph$, DMF, 70°C, 3 h; *iii*. 10% KOH/EtOH, reflux 2 h; *iv*. *n*-BuLi, THF, -78°C – > 0°C, 1.5 h, 91%; *v*. DHP, CH_2Cl_2, PyTs, 94%; *vi*. FSO_3H (5 eqv.), 2-nitropropane, -78°C, 15 min, then Et_3N; *vii*. *p*-TsOH, MeOH, 12 h.

Scheme 1.

The more polar major product was assigned structure **9** based on spectral data and elemental analysis (see Experimental), i.e., it was the hydrolysis product of **8**. This was confirmed by a separate experiment on hydrolysis of **8** by *p*-toluenesulfonic acid in methanol. The course of the cyclization of **1** is shown in Scheme 2. Apparently the superacid protonates not only the terminal bond but also the phenylsulfonyl group and the ether oxygen of the THP group. The cyclization occurs with closure of ring A (**I**) and then ring B (**II**) and produces a trication (**III**). Closely spaced positively charged centers in **III** on C-8 and in the phenylsulfonyl moiety prevent further closure of ring C. An analogous situation has been reported [13].



Scheme 2.

Finally the structure and stereochemistry of cyclization products **8** and **9** were confirmed by retrosynthesis of (13*E*,17*E*)-12-phenylsulfonylbicyclogeranylfarnesol (**9**) into the optically active form from commercially available (+)-norambreinolide (sclareolide) (**10**). Norambreinolide (**10**) was converted by the literature method [14,15] in six steps into *iso*-drimenol (**11**).

Reaction of **11** with phosphorus tribromide produced bromide **12**. Its addition to **4** gave a product with chromatographic and spectral properties that were identical to those of cyclization product **9**. The low yield of the addition product of **12** and **4** was apparently due to the lability of **12**.

Thus, we established that superacid cyclization of aliphatic bifunctional sesquiterpene **1**, in which one of the functional groups (phenylsulfonyl) is located in the middle of the molecule occurs selectively to give a bicyclic sesquiterpenoid that contains A and B rings. The reaction pathway can be explained by the fact that the phenylsulfonyl group is protonated. When the positive charge appears on C-8 during the cyclization, mutual repulsion of the positively charged atoms occurs. This deforms the cyclohexane-like conformation of the precursor and interrupts the cyclization with subsequent loss of the C-9 proton. However, it is also possible that protonation of the phenylsulfonyl group attracts to it electrons from the allyl double bond, which substantially reduces its nucleophilicity. The synergistic imposition of both these effects is also possible.

Such behavior during superacid cyclization of sesquiterpene substrates containing a phenylsulfonyl group at a certain location in the carbon skeleton can be used for directed synthesis, e.g., of bicyclic natural biologically active sesquiterpenoids [16-18].

EXPERIMENTAL

IR spectra were recorded on an FT-IR spectrometer; PMR and ^{13}C NMR spectra in $CDCl_3$, on Bruker AC 80 (80 and 20 MHz) and Bruker WM 300 (300 and 75.5 MHz) spectrometers. Chemical shifts are given in ppm. Signals were assigned relative to $CHCl_3$ as an internal standard (δ_H 7.26 and δ_C 77.0). Mass spectra were obtained in a VG Autospec, TRIO 1000 (Fisons), instrument by fast-atom bombardment (FAB) or chemical ionization (CI) at 70 eV. Column chromatography used Merck 60 silica gel (70-230 mesh, ASTM); TLC, Merck plates. Chromatograms were developed by $Ce(SO_4)_2$ solution (0.1%) in H_2SO_4 (2 N) followed by heating for 5 min at 80°C. Reaction mixtures in organic solvents were worked up by extracting with diethylether, washing the extract until the rinsings were neutral, drying over anhydrous Na_2SO_4, filtering, and removing solvent in vacuo.

Synthesis of 8-Phenylsulfonylgeranylacetate (7). A solution of phosphorus tribromide (9.12 g, 33.69 mmol) in dry ether (12 mL) was added dropwise to a stirred solution of 8-hydroxygeranylacetate (**5**, 5.20 g, 24.50 mmol) [12] in dry ether (43 mL) with cooling on an ice bath. The mixture was stirred for 2 h at room temperature and treated with saturated $NaHCO_3$ solution. The ether layer was separated, washed with NaCl solution, dried, and concentrated in vacuo. The resulting bromide **6** (4.73 g, 70%) was added to a solution of the sodium salt of benzenesulfonic acid (3.40 g, 20.60 mmol) in dry DMF (24 mL). The mixture was stirred at room temperature under Ar in the dark for 3 h, treated with NaCl solution, and extracted with ether. The extract was worked up as usual to afford a liquid product that was chromatographed over a SiO_2 (150 g) column with gradient elution by petroleum ether:AcOEt to elute 8-phenylsulfonylgeranylacetate (**7**, 4.27 g, 74%) as a colorless oil, $C_{18}H_{24}SO_4$.

IR spectrum (liquid film, ν, cm^{-1}): 1725, 1307, 1210, 1130.

PMR spectrum (80 MHz, δ_H, ppm, J/Hz): 1.66 (6H, s, H_3-9 and H_3-10), 1.96 (3H, s, $OCOCH_3$), 3.63 (2H, s, H_2-8), 4.46 (2H, d, J = 7.0, H_2-1), 5.00-5.30 (2H, m, H-2 and H-6), 7.45-7.85 (5H, m, Ar–H).

Synthesis of 8-Phenylsulfonylgeraniol (4). A solution of **7** (4.77 g, 14.88 mmol) in EtOH (5.0 mL) was treated with KOH in alcohol (10%, 40 mL) and refluxed for 2 h. After the usual work up, the crude product (4.05 g) was chromatographed over a SiO_2 (120 g) column with elution by petroleum ether:AcOEt (9:1) to afford 8-phenylsulfonylgeraniol (**4**, 3.90 g, 93%) as a colorless oil, $C_{16}H_{22}SO_3$.

IR spectrum (liquid film, ν, cm^{-1}): 3640, 3550, 1300, 1135, 990.

PMR spectrum (80 MHz, δ_H, ppm, J/Hz): 1.67 (6H, s, H_3-9 and H_3-10), 3.64 (2H, s, H_2-8), 4.05 (2H, d, J = 6.7, H_2-1), 5.05-5.35 (2H, m, H-2 and H-6), 7.50-7.75 (5H, m, Ar–H).

Synthesis of 8-Phenylsulfonylgeranylfarnesol (2). A stirred solution of **4** (403 mg, 1.37 mmol) in dry THF (4 mL) and hexamethylphosphortriamide (HMPA, 0.4 mL) was treated at -78°C under Ar with *n*-BuLi (2.74 mmol) in hexane. The temperature of the mixture was gradually increased to 0°C over 1 h and then again reduced to -78°C. The mixture was treated dropwise with a solution of (*E*,*E*)-farnesyl chloride (**3**, 330 mg, 1.37 mmol) in dry THF (4 mL) and HMPA (0.4 mL). The temperature of the mixture was gradually increased to room temperature, at which it was stirred overnight and worked up as

usual. The product (642 mg) was chromatographed over a SiO_2 (24 g) column with gradient elution by petroleum ether:AcOEt to afford 8-phenylsulfonylgeranylfarnesol (**2**, 344 mg, 50%) as a colorless oil, $C_{31}H_{46}SO_3$.

IR spectrum (liquid film, ν, cm $^{-1}$): 3458, 2922, 1446, 1304, 1145, 1084, 990.

PMR spectrum (300 MHz, δ_H, ppm, J/Hz): 1.54 (3H, s, H_3-23), 1.55 (3H, s, H_3-22), 1.58 (3H, s, H_3-21), 1.61 (3H, s, H_3-20), 1.65 (3H, s, H_3-25), 1.68 (3H, s, H_3-24), 3.46 (1H, dd, J_1 = 4.0, J_2 = 11.7, H-8), 4.11 (2H, d, J = 6.7, H_2-1), 4.86 (1H, t, J = 6.5, H-18), 5.04 (1H, t, J = 6.7, H-14), 5.14 (1H, t, J = 6.9, H-10), 5.23 (1H, t, J = 6.7, H-2), 5.35 (1H, t, J = 7.5, H-6), 7.50-7.88 (5H, m, Ar–H).

^{13}C NMR spectrum (75.5 MHz, δ_C, ppm): 16.4 (q, C-24), 16.5 (q, C-25), 16.6 (q, C-23), 16.7 (q, C-22), 18.1 (q, C-21), 24.8 (q, C-20), 26.6 (t, C-5), 26.1 (t, C-9), 26.9 (t, C-17), 27.1 (t, C-13), 39.1 (t, C-16), 40.0 (t, C-12), 40.1 (t, C-4), 59.6 (t, C-1), 74.3 (t, C-8), 118.7 (d, C-10), 124.1 (d, C-14), 124.2 (d, C-2), 124.5 (d, C-18), 124.7 (d, C-6), 129.2 (d, C-3′), 129.3 (d, C-2′), 131.7 (s, C-19), 133.9 (s, C-4′), 135.6 (s, C-15), 135.7 (s, C-11), 138.8 (s, C-3), 138.9 (s, C-7), 139.2 (s, C-1′).

Mass spectrum (*m*/*z*, *I*, %): 499 (3) $[M + H]^+$, 480 (5), 408 (4), 367 (5), 355 (7), 339 (56), 310 (7), 271 (23), 189 (22), 135 (72), 109 (100).

Synthesis of 8-Phenylsulfonylgeranylfarnesol Tetrahydropyranyl Ether (1). A solution of **2** (190 mg, 0.38 mmol) in CH_2Cl_2 (0.8 mL) was treated with dihydropyran (51 mg, 45.65 mmol) and pyridinium *p*-toluenesulfonate (PyTs 45 mg, 0.18 mmol) and stirred for 12 h at room temperature. The usual work up afforded crude product (236 mg) that was chromatographed over a SiO_2 (4 g) column with gradient elution by petroleum ether:AcOEt to afford geranylfarnesol THP ether (**1**, 200 mg, 90%) as a colorless liquid, $C_{36}H_{54}SO_4$.

IR spectrum (liquid film, ν, cm $^{-1}$): 2924, 1446, 1383, 1305, 1146, 1083, 1023, 905, 813.

PMR spectrum (300 MHz, δ_H, ppm, J/Hz): 1.52 (3H, s, H_3-23), 1.55 (3H, s, H_3-22), 1.57 (3H, s, H_3-21), 1.59 (3H, s, H_3-20), 1.60 (3H, s, H_3-25), 1.66 (3H, s, H_3-24), 3.48 (1H, dd, J_1 = 8.4, J_2 = 11.8, H-8), 3.96 (2H, dd, J_1 = 7.6, J_2 = 11.2, H_2-1), 4.16-4.23 (2H, m, H_2-5″), 4.59 (1H, s, H-1″), 4.87 (1H, t, J = 6.8, H-18), 5.06 (1H, t, J = 6.8, H-14), 5.19 (1H, t, J = 6.8, H-10), 5.25 (1H, t, J = 6.8, H-2), 5.37 (1H, t, J = 6.5, H-6), 7.47-7.87 (5H, m, Ar–H).

^{13}C NMR spectrum (75.5 MHz, δ_C, ppm): 16.4 (q, C-22 and C-23), 16.7 (q, C-25), 18.1 (q, C-21), 20.0 (t, C-9), 23.7 (t, C-4″), 24.3 (q, C-24), 25.9 (q, C-20), 26.1 (t, C-3″), 26.8 (t, C-13), 26.9 (t, C-17), 27.1 (t, C-5), 31.1 (t, C-12), 31.2 (t, C-2″), 40.0 (t, C-4), 40.1 (t, C-16), 62.7 (d, C-8), 62.8 (t, C-1), 64.1 (t, C-5″), 98.4 (d, C-1″), 118.8 (d, C-10), 121.3 (d, C-2), 121.5 (d, C-14), 124.2 (d, C-18), 124.7 (d, C-6), 126.7 (s, C-19), 129.1 (s, C-7), 129.3 (d, C-2′), 131.7 (d, C-3′), 133.9 (s, C-2), 135.6 (s, C-4′), 135.8 (s, C-11), 138.8 (s, C-15), 139.2 (s, C-1′).

Mass spectrum (*m*/*z*, *I*, %): 498 (3) $[M - C_5H_8O]^+$, 480 (21), 422 (6), 355 (5), 339 (100), 271 (21), 203 (20), 161 (24), 147 (43).

Superacid Cyclization of 1. A cooled (-78°C) solution of **1** (85 mg, 0.146 mmol) in 2-nitropropane (1.4 mL) was stirred and treated with a solution cooled to the same temperature of fluorosulfonic acid (37 mg, 0.37 mmol) in 2-nitropropane (0.1 mL). The reaction mixture was stirred at -78°C for 15 min and treated with Et_3N:hexane (1:1, 1.0 mL). After the usual work up, the crude product (100 mg) was chromatographed over a SiO_2 (4 g) column with gradient elution by petroleum ether:AcOEt to afford (13*E*,17*E*)-12-phenylsulfonylbicyclogeranylfarnesol THP ether (**8**, 9 mg, 8%) and (13*E*,17*E*)-12-phenylsulfonylbicyclogeranylfarnesol (**9**, 21 mg, 25%).

Compound 8, colorless liquid, $C_{36}H_{54}SO_4$.

IR spectrum (liquid film, ν, cm $^{-1}$): 2927, 2854, 1446, 1378, 1304, 1146, 1086.

PMR spectrum (300 MHz, δ_H, ppm, J/Hz): 0.80 (3H, s, H_3-21), 0.87 (3H, s, H_3-23), 1.05 (3H, s, H_3-22), 1.52 (3H, s, H_3-24), 1.57 (3H, s, H_3-20), 1.63 (3H, s, H_3-25), 3.15-3.30 (2H, m, H_2-5″), 3.38 (1H, dd, J_1 = 6.9, J_2 = 11.2, H_A-19), 3.44 (1H, dd, J_1 = 3.8, J_2 = 11.2, H_B-19), 3.60-3.67 (1H, m, H-12), 4.80-4.86 (1H, m, H-1″), 5.21 (1H, t, J = 5.6, H-14), 5.32 (1H, m, H-18), 7.54-7.88 (5H, m, Ar–H).

^{13}C NMR spectrum (75.5 MHz, δ_C, ppm): 15.5 (q, C-25), 16.7 (t, C-2), 19.6 (t, C-4″), 19.7 (t, C-6), 20.1 (q, C-21), 20.4 (q, C-24), 21.1 (q, C-23), 24.4 (t, C-11), 26.7 (q, C-20), 24.5 (t, C-3″), 26.8 (t, C-15), 29.5 (t, C-2″), 33.0 (q, C-22), 33.1 (t, C-7), 33.2 (s, C-4), 34.9 (t, C-1), 38.8 (s, C-10), 45.5 (t, C-16), 46.3 (t, C-3), 50.8 (d, C-5), 52.3 (d, C-12), 59.7 (t, C-19), 63.3 (t, C-5″), 97.1 (d, C-1″), 120.4 (d, C-18), 127.7 (d, C-14), 128.5 (s, C-8), 129.1 (d, C-2′ and C-6′), 129.3 (d, C-3′ and C-5′), 133.8 (s, C-9), 134.6 (s, C-13), 135.3 (s, C-17), 135.6 (d, C-4′), 139.8 (s, C-1′).

Compound 9, colorless liquid, $C_{31}H_{46}SO_3$.

IR spectrum (liquid film, ν, cm $^{-1}$): 3449, 2931, 2856, 1447, 1380, 1304, 1145, 1085, 895.

PMR spectrum (300 MHz, δ_H, ppm, J/Hz): 0.84 (3H, s, H_3-21), 0.88 (3H, s, H_3-23), 1.08 (3H, s, H_3-22), 1.52 (3H, s, H_3-24), 1.57 (3H, s, H_3-20), 1.64 (3H, s, H_3-25), 3.33-3.49 (2H, m, H_2-19), 3.98 (1H, d, J = 9.8, H-12), 5.19-5.24 (1H, m, H-14), 5.27-5.35 (1H, m, H-18), 7.53-7.89 (5H, m, Ar–H).

^{13}C NMR spectrum (75.5 MHz, δ_C, ppm): 14.1 (q, C-25), 16.4 (t, C-2), 18.7 (t, C-6), 19.8 (q, C-21), 20.0 (q, C-24), 21.6 (q, C-23), 24.9 (t, C-11), 25.2 (q, C-20), 27.7 (t, C-15), 32.3 (q, C-22), 32.4 (t, C-7), 33.3 (s, C-4), 34.4 (t, C-1), 38.8 (s, C-10), 44.3 (s, C-16), 46.0 (t, C-3), 51.3 (d, C-5), 52.2 (d, C-12), 59.4 (t, C-19), 118.4 (d, C-18), 122.6 (d, C-14), 126.9 (s, C-8), 129.3 (d, C-2′ and C-6′), 129.5 (d, C-3′ and C-5′), 131.4 (s, C-9), 132.3 (s, C-13), 133.3 (s, C-17), 137.2 (d, C-4′), 140.0 (s, C-1′).

Hydrolysis of 8. A solution of **8** (21 mg, 0.036 mmol) in methanol (1.5 mL) was treated at room temperature under Ar with *p*-toluenesulfonic acid (1.0 mg, 0.006 mmol). The mixture was stirred for 12 h and worked up as usual. The product (18 mg) was chromatographed over a SiO_2 (0.3 g) column with gradient elution by petroleum ether:AcOEt to afford **9** (15.1 mg, 85%). Its spectral properties (IR, PMR, ^{13}C NMR) were identical to those of **9** prepared by superacid cyclization.

Synthesis of 9. A solution of phosphorus tribromide (653 mg, 1.78 mmol) in dry ether (0.5 mL) was added dropwise to a stirred solution of bicyclic alcohol **11** (395 mg, 1.78 mmol) [15] in dry ether (3.1 mL) and pyridine (0.2 mL) with cooling on an ice bath and then stirred for 2 h at room temperature. The usual work up afforded crude bromide **12** (486.8 mg, 96%), which was used in the following step without further purification. A stirred solution of **4** (401 mg, 1.36 mmol) in dry THF (5.8 mL) and HMPA (0.65 mL) was treated at -78°C under Ar with *n*-BuLi in hexane (2.73 mmol). The temperature of the mixture was gradually increased to 0°C over 1 h. The mixture was cooled again to -78°C and treated dropwise with **12** (389 mg, 1.36 mmol) in dry THF (5.8 mL) and HMPA (0.65 mL). The temperature of the mixture was gradually increased to room temperature, at which it was stirred overnight and worked up as usual. The product was chromatographed over a SiO_2 (32 g) column with gradient elution by petroleum ether:AcOEt to afford **9** (180 mg, 26%) as a colorless oil.

IR spectrum (liquid film, ν, cm $^{-1}$): 3452, 2930, 2860, 1445, 1380, 1307, 1140, 1085, 893.

PMR spectrum (300 MHz, δ_H, ppm, J/Hz): 0.83 (3H, s), 0.89 (3H, s), 1.07 (3H, s), 1.52 (3H, s), 1.58 (3H, s), 1.65 (3H, s), 3.30-3.50 (2H, m), 3.98 (1H, d, J = 9.5), 5.20-5.25 (1H, m), 5.27-5.36 (1H, m), 7.52-7.90 (5H, m).

^{13}C NMR spectrum (75.5 MHz, δ_C, ppm): 14.7 (q, CH_3), 16.4 (t, CH_2), 18.5 (t, CH_2), 19.8 (q, CH_3), 20.1 (q, CH_3), 21.5 (q, CH_3), 24.8 (t, CH_2), 25.2 (q, CH_3), 27.5 (t, CH_2), 32.1 (q, CH_3), 32.4 (t, CH_2), 33.1 (s, C), 34.3 (t, CH_2), 38.6 (s, C), 44.2 (t, CH_2), 45.7 (t, CH_2), 51.4 (d, CH), 53.2 (d, CH), 60.1 (t, CH_2), 118.7 (d, CH), 122.4 (d, CH), 126.7 (s, C), 129.1 (d, 2CH), 129.3 (d, 2CH), 131.0 (s, C), 132.1 (s, C), 133.4 (s, C), 137.1 (d, CH), 139.8 (s, C).

The spectral properties (IR, PMR, ^{13}C NMR) of the product were identical to those for racemic **9** formed by cyclization of aliphatic ether **1**.

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