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SYNTHESIS FROM GERANIOL OF (2*E*,6*E*,10*E*,14*E*)-16- HYDROXYGERANYLGERANIOL AND SOME OF ITS DERIVATIVES

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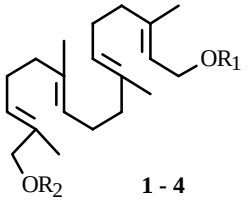
Several α,ω-bifunctional derivatives of E,E,E-*geranylgeraniol were prepared via convergent synthesis starting with geraniol (**8**), which was converted in three steps into the tetrahydropyranyl ether of 8-chlorogeraniol (**9**) and 8-hydroxygeranylphenylsulfone (**10**). Combination of synthons **9** and **10** with subsequent reductive removal of the phenylsulfonyl group produced the tetrahydropyranyl ether of ω-hydroxygeranylgeraniol (**5**), hydrolysis of which gave exclusively trans-ω-hydroxygeranylgeraniol (**1**). Derivatives **5**-**7** of geranylgeraniol were synthesized using standard methods.*

Key words: aliphatic diterpenoids, natural compounds, synthesis, combination reaction, alcohols.

Diterpenoids have been isolated from plants, fungi, and marine organisms [1]. Natural aliphatic diterpenoids are usually monofunctional compounds although certain *α,ω*-bifunctional representatives are also known. For example, the biologically active *α,ω*-bifunctional diterpenoids **1**-**4** were isolated from the fungus *Boletinus cavipes* [2]. These compounds turned out to be inhibitors of peroxide formation in macrophagous cells and can be used to prevent illnesses caused by such compounds.



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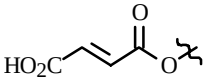

fumaryloxy group

1: $R_1 = R_2 = H$
2: $R_1 = R_2$ = fumaryloxy
3: $R_1 = H$, R_2 = fumaryloxy
4: R_1 = fumaryloxy, $R_2 = H$

Herein we report the synthesis of exclusively *trans*-16-hydroxygeranylgeraniol (**1**) and its *α,ω*-bifunctional analogs **5**-**7** (Scheme 1) starting from the commercially available monoterpenol geraniol (**8**). The synthetic approach to the *α,ω*-bifunctional aliphatic diterpenoids **1** and **5**-**7** consisted of combination of synthons **9** and **10**, which were prepared from the single precursor **8** (Scheme 1). Compound **9** was synthesized in three steps. Protection of the hydroxyl in **8** with dihydropyran gave tetrahydropyranyl ether **11**. The terminal methyl in **11** was selectively oxidized by selenium dioxide to give hydroxyether **12**. Replacement of the hydroxyl in **12** by Cl gave bifunctional derivative **9**.

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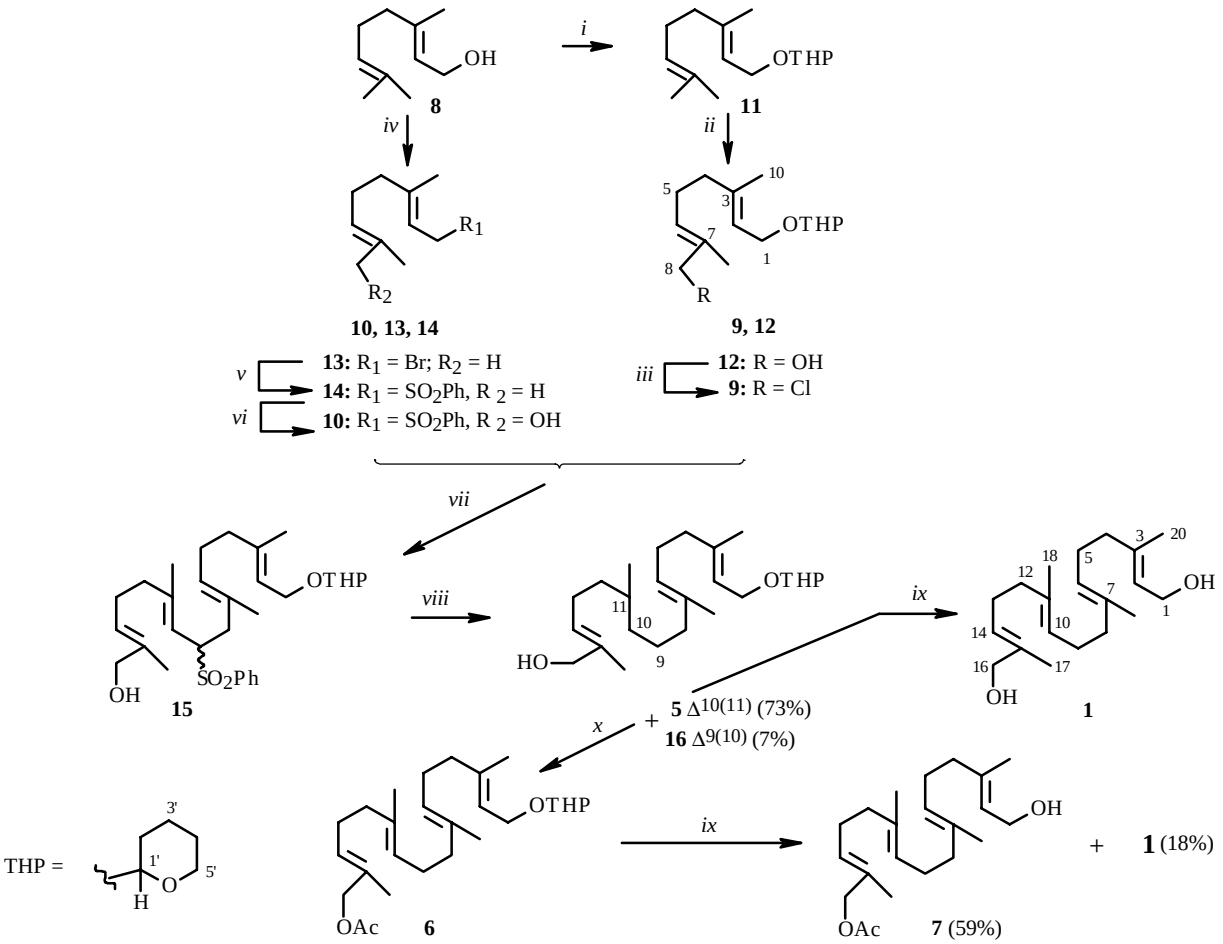

i. DHP, CH_2Cl_2, PyTs, 94%; *ii*. SeO_2, EtOH/Py, 58; *iii*. TsCl, DMAP, Et_3N, CH_2Cl_2, LiCl 93%; *iv*. PBr_3, Et_2O, Py, 0° C; *v*. $NaSO_2Ph$, DMF, 84%, after two steps; *vi*. SeO_2, EtOH, 54%; *vii*. *n*-BuLi, THF, -78C to 0°C, 1.5 h, 91%; *viii*. Na/Hg (6%), Na_2HPO_4, MeOH, 73%; *ix*. *p*-TsOH, MeOH; *x*. Ac_2O, Py, 99%

Scheme 1.

The second synthon **10** was synthesized from **8** also in three steps. Geraniol (**8**) was brominated by phosphorus tribromide to **13**, which was used without further purification to give geranylphenylsulfone (**14**) in ~84% yield [3-5]. The sulfone was selectively oxidized by selenium dioxide in 54% yield into hydroxysulfone **10**. The PMR spectrum of **10** contained signals for two methyls on double bonds, two vinyl protons, >C–CH_2O– and –CH_2– groups next to a –SO_2Ph group, a vinyl proton, and signals characteristic of five aromatic protons. These spectral data agreed with those published [5].

The combination of structural fragments **9** and **10** under mild conditions [6] formed racemic diterpene derivative **15** (91% overall yield). The PMR spectrum of the combination product had signals for four methyls on double bonds, four vinyl and five aromatic protons, and two hydroxymethylene groups, one of which was isolated and the other, next to a vinyl proton. The spectral data confirmed the structure of **15**.

Reduction of the phenylsulfone in **15** by sodium amalgam as before [6] produced target α,ω-bifunctional diterpenoid **5** and a small (~10%) quantity of its isomer **16** in which the double bond migrated from the C10–C11 position to the C9–C10 position. Compound **5** was purified by semi-preparative HPLC.

The structure of reduction product **5** was established using spectral data. The PMR spectrum of **5** contained signals for four methyls on double bonds, four vinyl protons, two –CH_2O– groups, and the tetrahydropyranyl protons. The spectral data and elemental analysis confirmed the structure of **5**. The tetrahydropyranyl group of **5** was removed by acid hydrolysis as before [7] to produce 16-hydroxygeranylgeraniol (**1**). Its spectral data (PMR and ^{13}C NMR) agreed with those published [8] and confirmed its structure.

Acetylation of **5** under standard conditions with acetic anhydride in pyridine gave in quantitative yield **6**, the structure of which was confirmed by spectral data and elemental analysis. The THP protection in **6** was removed as before [7] to give monoacetate **7** (59%) and a small (18%) amount of diol **1**.

Thus, we developed for the first time a nine-step original method for synthesizing the natural product exclusively *trans*-16-hydroxygeranylgeraniol (**1**). This α,ω-bifunctionalized diterpenoid **1** was prepared from commercially available geraniol (**8**) in 12% overall yield.

α,ω-Bifunctionalized derivatives **5**-**7** were synthesized under standard conditions. They were suitable synthons for preparing difficultly accessible biologically active natural aliphatic diterpenoids.

EXPERIMENTAL

IR spectra were recorded on a Bio-Rad FTS 7 spectrometer; PMR and ^{13}C NMR spectra in $CDCl_3$, on Bruker AC 80 (80 MHz), Bruker WM 300 (300 MHz), and Bruker AM 400 (400 MHz) spectrometers. Chemical shifts are given in ppm. Assignments were made relative to $CHCl_3$ as an internal standard (δ_H 7.26 and δ_C 77.0). Semi-preparative HPLC was performed on a Gilson liquid chromatograph. Column chromatography used Merck 60 silica gel (70-230 mesh, ASTM) and neutral aluminum oxide (activity level II). TLC used Merck plates. Chromatograms were developed by spraying with $Ce(SO_4)_2$ solution (0.1%) in H_2SO_4 (2 N) and heating for 5 min at 80°C. Reaction mixtures in organic solvents were worked up by extracting with diethylether, washing the extract with water until the rinsings were neutral, drying over anhydrous Na_2SO_4, filtering, and removing solvent in vacuo.

Geraniol Tetrahydropyranyl Ether (11). A solution of geraniol (**8**, 4.393 g, 28.53 mmol) in CH_2Cl_2 (59 mL) was treated with dihydropyran (4.2 mL, 45.65 mmol) and pyridinium *p*-toluenesulfonate (PyTs, 0.325 g, 1.29 mmol). The mixture was stirred for 12 h at room temperature. The usual work up gave crude product (6.431 g), which was chromatographed over a column of Al_2O_3 (40 g) with gradient elution by petroleum ether:AcOEt to afford **11** (6.395 g, 94%) as a colorless liquid. The spectral data (IR and PMR) were identical with those published [6].

8-Hydroxygeraniol Tetrahydropyranyl Ether (12). Selenium dioxide (415 mg, 3.74 mmol) was added to a solution of **11** (1.802 g, 8.04 mmol) in ethanol (15 mL) and pyridine (0.4 ml, 4.82 mmol). The mixture was stirred for 20 h at room temperature, diluted with water (100 mL), and extracted with AcOEt (3 × 50 mL). The extract was washed with NaCl solution (2 × 50 mL) and concentrated in vacuo to give a yellow oil (1.908 g). The product was chromatographed over a column of Al_2O_3 (54 g) with gradient elution by petroleum ether:AcOEt to afford starting **11** (502 mg, 28%) and 8-hydroxygeraniol tetrahydropyranyl ether (**12**, 810 mg, 58% counting returned **11**) as a colorless oil. Spectral data of **12** were identical with those published [6].

8-Chlorogeraniol Tetrahydropyranyl Ether (9). A solution of **12** (437 mg, 1.71 mmol) in dry CH_2Cl_2 (4.3 mL) was treated under Ar at ambient temperature with 4-dimethylaminopyridine (DMAP, 131 mg, 1.07 mmol), tosylchloride (408 mg, 2.14 mmol), and triethylamine (0.24 mL, 1.71 mmol). The mixture was stirred for 3 h at room temperature, treated with LiCl (145 mg, 3.40 mmol), and stirred for another 2 h at the same temperature. CH_2Cl_2 was removed in vacuo. The residue was treated with water (10 mL) and extracted with ether (3 × 5 mL). The combined ether extract was washed with NaCl solution (2 × 5 mL) and evaporated in vacuo to afford 8-chlorogeraniol tetrahydropyranyl ether (**9**, 411 mg) as a yellow oil that was used without further purification. Spectral data of **9** were identical with those published [6].

Geranylphenylsulfone (14). Phosphorus tribromide (4.3 mL, 12.255 g, 45.29 mmol) was dissolved in dry ether (16 mL) and added dropwise to a stirred solution of **8** (5.120 g, 33.25 mmol) in dry ether (47 mL) with cooling on an ice bath. The mixture was stirred for 12 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 liquid product was added to a solution of sodium benzenesulfonate (6.55 g, 39.90 mmol) in dry DMF (46 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 column of SiO_2 (260 g) with gradient elution by petroleum ether:AcOEt to afford a colorless oil (7.39 g, 84% yield in two steps). Spectral data of **14** were identical with those published [3-5].

8-Hydroxygeranylphenylsulfone (10). A suspension of selenium dioxide (1.84 g, 16.55 mmol) in ethanol (15 mL) was added to a solution of **14** (9.20 g, 33.09 mmol) in ethanol (25 mL). The mixture was stirred at 40°C for 4 h, cooled to 0°C, treated with $NaBH_4$ (670 mg, 16.50 mmol), stirred at the same temperature for 30 min, diluted with water (100 mL), and

extracted with AcOEt (3 × 50 mL). The extract was washed with saturated NaCl solution (2 × 50 mL) and evaporated in vacuo. The resulting liquid product (9.5 g) was chromatographed over a column of SiO_2 (200 g) with gradient elution by petroleum ether:AcOEt to afford starting **14** (1.7 g, 18%) and liquid 8-hydroxygeranylphenylsulfone (**10**, 4.03 g, 54% counting returned **14**). IR spectra and PMR spectra were identical with those published [5].

16-Hydroxy-9-phenylsulfonylgeranylgeraniol Tetrahydropyranyl Ether (15). A stirred solution of **10** (611 mg, 2.08 mmol) in dry THF (9 mL) and hexamethylphosphortriamide (HMPA, 1 mL) was treated at -78°C under Ar with *n*-BuLi (4.16 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 **9** (471 mg, 1.73 mmol) in dry THF (8 mL) and HMPA (0.8 mL). The temperature was gradually increased to room temperature. The mixture was stirred at this temperature overnight and worked up as usual. The product was chromatographed over a column of SiO_2 (46 g) with gradient elution by petroleum ether:AcOEt to afford 16-hydroxy-9-phenylsulfonylgeranylgeraniol tetrahydropyran ether (**15**, 834 mg, 91%) as a colorless oil, $C_{31}H_{46}SO_5$.

IR spectrum (liquid film, ν, cm^{-1}): 3450, 1665, 1582, 1310, 1140.

PMR spectrum (80 MHz, δ_H, ppm): 1.50 (3H, s, H_3-19), 1.52 (3H, s, H_3-18), 1.64 (3H, s, H_3-17), 1.66 (3H, s, H_3-20), 3.58-3.75 (3H, m, H-9 and H_2-5′), 4.87 (1H, m, H-1′), 5.00 (2H, m, H-6 and H-10), 5.33 (2H, m, H-2 and H-14), 7.40-7.90 (5H, m, Ar–H).

16-Hydroxygeranylgeraniol Tetrahydropyranyl Ether (5). A mixture of **15** (530 mg, 1.0 mmol) and Na_2HPO_4 (568 mg, 4 mmol) in dry methanol (11 mL) was treated at 0°C with an excess of freshly prepared sodium amalgam (4 g) and stirred at the same temperature overnight. The excess of the amalgam was decomposed with cold water. The mixture was extracted with ether. The extract was worked up as usual. The product (378 mg) was chromatographed over a column of SiO_2 (4 g) with gradient elution by petroleum ether:AcOEt to afford a product (357 mg) containing traces of other compounds. Then this product was purified by semi-preparative HPLC over a Nova-Pack C-18 column (MeOH:H_2O, 95:5, elution flow rate 1.5 mL/min) to afford 16-hydroxygeranylgeraniol THP ether (**5**, 284 mg, 73%) as a colorless oil, $C_{25}H_{42}O_3$.

IR spectrum (liquid film, ν, cm^{-1}): 3423, 2920, 2850, 1450, 1370, 1210, 1020, 838.

PMR spectrum (80 MHz, δ_H, ppm): 1.52 (6H, s, H_3-18 and H_3-19), 1.59 (6H, s, H_3-17 and H_3-20), 2.57 (1H, br.s, O<u>H</u>), 3.49-3.82 (2H, m, H_2-5′), 3.90 (2H, br.s, H_2-16), 4.09 (2H, d, J = 7, H_2-2), 4.54 (1H, m, H-1′), 5.04 (2H, m, H-6 and H-10), 5.23 (2H, m, H-2 and H-14).

16-Hydroxygeranylgeraniol (1). A solution of **5** (105 mg, 0.269 mmol) in methanol (1.6 mL) was treated at room temperature under Ar with *p*-toluenesulfonic acid (1.5 mg, 0.0087 mmol). The mixture was stirred for 12 h and worked up as usual. The product (79 mg) was chromatographed over a column of SiO_2 (3 g) with gradient elution by petroleum ether:AcOEt to afford **1** (68 mg, 83%) as a colorless oil. Spectra data (IR and PMR) were identical to those published [8].

16-Acetoxygeranylgeraniol Tetrahydropyranyl ether (6). A solution of **5** (480 mg, 1.23 mmol) in pyridine (2.5 mL) was treated at room temperature with acetic anhydride (0.24 mL, 2.55 mmol). The mixture was held overnight at the same temperature, poured onto ice, and extracted with ether. The extract was worked up as usual. The product (564 mg) was chromatographed over a column of SiO_2 (16 g) with gradient elution by petroleum ether:AcOEt to afford 16-acetoxygeranylgeraniol THP ether (**6**, 530 mg, 99%) as a colorless oil, $C_{27}H_{44}O_4$.

IR spectrum (liquid film, ν, cm^{-1}): 1725, 1660, 1440, 1360, 1230, 1020, 845.

PMR spectrum (400 MHz, δ_H, ppm, J/Hz): 1.59 (6H, s, H_3-18 and H_3-19), 1.64 (3H, s, H_3-17), 1.67 (3H, s, H_3-20), 2.06 (3H, s, OAc), 2.62 (1H, br.s, O<u>H</u>), 3.50 (1H, m, H_A-5′), 3.89 (1H, m, H_B-5′), 4.02 (1H, dd, J_1 = 7.3, J_2 = 12.0, H_A-2), 4.23 (1H, dd, J_1 = 6.4, J_2 = 12.0, H_B-2), 4.44 (1H, s, H_2-16), 4.62 (1H, dd, J_1 = 3.1, J_2 = 3.9, H-1′), 5.11 (1H, m, H-6), 5.28 (1H, m, H-10), 5.35 (1H, t, J = 7, H-2), 5.44 (1H, t, J = 7, H-14).

16-Acetoxygeranylgeraniol (7). A solution of **6** (509 mg, 1.18 mmol) in methanol (7 mL) was treated at room temperature under Ar with *p*-toluenesulfonic acid (7 mg, 0.041 mmol), stirred for 12 h, and worked up as usual. The residue (440 mg) was chromatographed over a column of SiO_2 (15 g) with gradient elution by petroleum ether:AcOEt to afford 16-acetoxygeranylgeraniol (**7**, 240.7 mg, 59%) and 16-hydroxygeranylgeraniol (**1**, 64 mg, 18%).

Compound 7, $C_{22}H_{26}O_3$, colorless oil. IR spectrum (liquid film, ν, cm^{-1}): 3423, 2920, 2850, 2360, 1730, 1670, 1445, 1380, 1235, 1023, 840.

PMR spectrum (300 MHz, δ_H, ppm, J/Hz): 1.60 (6H, s), 1.65 (3H, s), 1.68 (3H, s), 2.07 (3H, s), 4.15 (2H, d, J = 6.6), 4.44 (2H, s), 5.11 (1H, m), 5.42 (2H, m).

^{13}C NMR spectrum (75.5 MHz, δ_C, ppm): 170.0 (s, O<u>C</u>OCH_3), 140.2 (s, C-3), 135.7 (s, C-15), 134.8 (s, C-11), 128.4 (s, C-7), 128.0 (d, C-14), 125.1 (d, C-2), 124.2 (d, C-10), 123.7 (d, C-6), 69.8 (t, C-16), 62.4 (t, C-1), 40.1 (t, C-4), 39.5 (t, C-8

and C-12), 27.0 (t, C-5), 26.8 (t, C-13), 26.7 (t, C-9), 21.5 (q, OCO<u>C</u>H_3), 16.7 (q, C-17), 16.4 (q, C-18 and C-20), 14.4 (q, C-19).

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