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The First Total Synthesis of 16-Hydroxygeranylgeraniol

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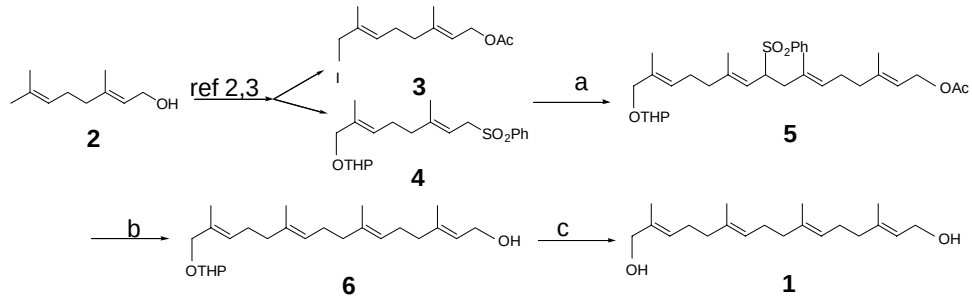
Abstract: Facile synthesis of 16-hydroxygeranylgeranio **1**, a naturally occurring alicyclic diterpene, by alkylation reaction of allylic iodide **3** with phenyl sulfone **4**, is described.

Keywords: Total synthesis, 16-hydroxygeranylgeraniol, diterpene.

The title compound **1**, is a novel oxidative metabolite of the class of alicyclic diterpene derived from geranylgeraniol[1]. Its structure was characterized[1] *via* the corresponding acetic ester of 16-hydroxygeranylgeraniol by extensive spectroscopic analysis. Biological activities of **1** and other members of this class of natural products are unknown. Herein, we report a convenient chemical synthesis of **1** (**Scheme 1**).

Scheme 1



Reagents and conditions: a. *n*-BuLi, THF, -40°C, 94%; b. Na(Hg), MeOH, r.t., 80%; c. *p*-TsOH, MeOH, r.t., 95%.

The allylic iodide **3**[2] and the phenyl sulfone **4**[3] were prepared from geraniol **2** by the usual method. Coupling reaction of iodide **3** with the lithium salt of **4**[4] (formed by treatment with *n*-BuLi in THF at -40°C) in THF at -40°C proceeded smoothly to afford a coupling adduct **5**, which gave the reduced product **6** by treatment with Na(Hg)[4] in methanol. Treatment of **6** with a catalytic amount of *p*-TsOH in methanol gave the title

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compound **1** in good yield (95%). The spectroscopic properties of this material are fully consistent with its assigned structure[5].

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5. Spectral data: **5**, IR (KBr): *v* 3463, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.47-7.90 (m, 5 H, Ar-H), 4.9-5.4 (m, 4 H, 4 CH=), 4.61 (t, 1 H, *J* = 3.6 Hz), 4.50 (d, 2 H, *J* = 7.0 Hz, CH_2O), 4.15 (d, 2 H, *J* = 6.8 Hz), 4.10 (d, 1 H, *J* = 12.4 Hz), 3.89 (m, 1 H), 3.87 (d, 1 H, *J* = 12.4 Hz), 3.50 (m, 1 H), 2.04 (s, 3 H, CH_3), 2.10-1.96 (m, 10 H, 5 CH_2), 1.83-1.46 (m, 6 H, 3 CH_2), 1.75 (s, 3 H, CH_3), 1.71 (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3); EIMS, *m/z*: 429 (M^+-SO_2Ph, 5); **6**, IR (KBr): 3432 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 5.42 (t, 2 H, *J* = 6.4 Hz), 5.11 (t, 2 H, *J* = 6.4 Hz), 4.61 (t, 1H, *J* = 3.6 Hz), 4.15 (d, 2 H, *J* = 6.8 Hz), 4.10 (d, 1 H, *J* = 12.4 Hz), 3.89 (m, 1 H), 3.87 (d, 1 H, *J* = 12.4 Hz), 3.50 (m, 1 H), 2.13-2.00 (m, 12 H), 1.68 (s, 6 H), 1.66 (s, 3 H), 1.59 (s, 3 H), 1.70-1.53 (m, 6 H); EIMS, *m/z*: 288 (M^+-DHP-OH, 15); **1**, IR (KBr): 3328, 2933, 2870, 1669, 1057, 1006, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 5.39 (t, 2 H, *J* = 6.4 Hz), 5.11(t, 2 H, *J* = 6.4 Hz), 4.13 (d, 2 H, *J* = 6.4 Hz), 3.87 (s, 2 H), 2.13-2.00 (m, 12 H), 1.68 (s, 6 H), 1.66 (s, 3 H), 1.59 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 139.5, 137.5, 135.4, 134.7, 126.0, 124.7, 123.8, 123.4, 68.9, 59.3, 42.8, 39.4, 36.8, 31.6, 26.2, 26.0, 25.4, 23.3, 20.8, 16.2; EIMS, *m/z*: 288 (M-18, 9); HRMS (ESI): M^++Na, 329.2450. $C_{20}H_{34}O_2$+Na requires M^++Na 329.2451.

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