

# A Practical Synthesis of Enantiomerically Pure (-)-Geosmin *via* Highly Diastereoselective Reduction of (4a*S*, 8*S*)-4,4a,5,6,7,8-Hexahydro-4a,8-dimethyl-2(3H)-naphthalenone

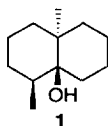
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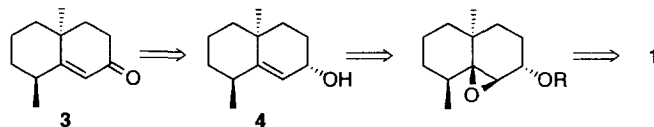
**Abstract:** An asymmetric synthesis of (-)-geosmin **1** *via* highly diastereoselective reduction of the enantiomerically pure title ketone **3** is described. Diisobutylaluminum hydride reduction of **3** in a mixed solvent of tetrahydrofuran and 1,2-dimethoxyethane led to allylic alcohol **4** in 96% d.e., which by recrystallization from hexane, afforded a diastereomerically pure sample. This was then converted to **1** in high overall yield through a five-step reaction sequence including a completely stereoselective epoxidation of silyl ether **6** and a one-pot process of epoxy silyl ether **7** to mesylate **9**.

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(-)-Geosmin **1**, first isolated by Gerber and Lechevalier in 1965<sup>1</sup>, is a neutral oil with a very strong earthy-musty odor at extremely high dilution. This is a metabolite of many *Actinomycetes*, several blue-green algae and some fungi, and is known as an off-flavor contaminant of water supplies as well as a trace constituent of several foodstuffs.<sup>2,3</sup> Removal of this earthy-musty odor component, together with 2-methylisoborneol from drinking water has recently become a matter of great interest. However, it is difficult to remove by conventional water treatment methods such as coagulation-sedimentation and rapid sand filtration. In association with our work on the biodegradation of these off-flavor substances,<sup>4</sup> which is one of the most effective means for this purpose, we needed multi-gram quantity of enantiomerically pure (-)-geosmin **1**. A number of methods for synthesizing **1** in racemic or optically active form have appeared in the literature.<sup>5</sup> Among them, a combination of Reviel's protocol<sup>5d</sup> based on asymmetric Michael-type alkylation of chiral imines leading to (+)-octalone **3** and

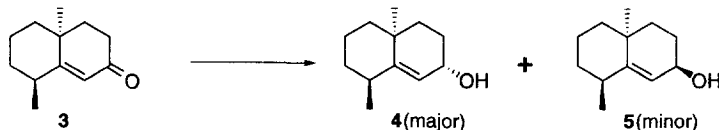


Gosselin's racemic geosmin synthesis<sup>5c</sup> is virtually the sole practical method for obtaining optically active geosmin. In order to access enantiomerically pure (-)-geosmin **1** in much higher overall yield, we developed a six-step reaction process starting from (+)-octalone **3**. In this paper, we describe a new, effective synthesis of (-)-geosmin **1** using a highly diastereoselective reduction of **3** as the key reaction. Our synthetic strategy is outlined in Scheme 1.



Scheme 1

The known starting (+)-octalone **3** was prepared by the Revial's procedure<sup>5d</sup> in an enantiomerically pure form. Diastereoselective reduction of **3** with various reagents and solvents was examined (Table 1). The best result (96% d.e.) was obtained when diisobutylaluminum hydride in a mixed solvent of tetrahydrofuran and 1,2-dimethoxyethane was employed. Recrystallization of this sample from hexane at  $-78^{\circ}\text{C}$  gave diastereomerically pure **4**.<sup>6</sup>

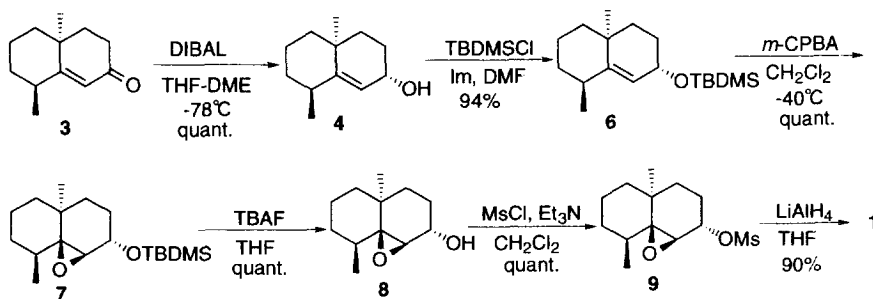
Table 1. Stereoselective Reduction of (+)-Octalone **3**

Reagent	Solvent	Temp. ( $^{\circ}\text{C}$ )	Time	Selectivity (% d.e.) <sup>a</sup>	Yield (%) <sup>b</sup>
$\text{NaBH}_4$ , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	MeOH	r.t.	4 h	43	95
$\text{NaBH}_3\text{CN}$	EtOH	r.t.	2 d	70	93
$[\text{t-BuC}(\text{C}_2\text{H}_5)_2\text{O}]_3\text{AlH}$	THF	$-78$	1 d	60	88
9-BBN	THF	r.t.	NR	–	–
Catecholborane	THF	$-78$	decomp.	–	–
DIBAL	$\text{CH}_2\text{Cl}_2$	$-78$	10 min	64	50 <sup>c</sup>
DIBAL	Toluene	$-78$	10 min	76	52 <sup>d</sup>
DIBAL	$\text{Et}_2\text{O}$	$-78$	5 min	83	quant.
DIBAL	THF	$-78$	5 min	88	quant.
<b>DIBAL</b>	<b>THF-DME</b>	<b><math>-78</math></b>	<b>5 min</b>	<b>96</b>	<b>quant.</b>

a) Diastereomeric excess was determined by  $^1\text{H-NMR}$ . b) Isolation yield. c), d) 1,4-Reduction (c : 10%, d : 37%) was observed.

As shown in Scheme 2, transformation of **4** into (-)-geosmin **1** was performed through a five-step sequence of reactions. After protecting **4** as a *tert*-butyldimethylsilyl ether **6**, epoxidation reaction of **6** with *m*-chloroperbenzoic acid at  $-40^{\circ}\text{C}$  completely stereoselectively proceeded to afford the requisite epoxide **7**. Stereoselectivity in this reaction was dependent upon the temperature conditions. Thus, when this reaction was

performed above  $-20^{\circ}\text{C}$ , the unwanted diastereoisomer was also detected. Deprotection of the *tert*-butyldimethylsilyl group of **7** with tetra(*n*-butyl)ammonium fluoride furnished epoxy alcohol **8**, which on treatment with methanesulfonyl chloride and triethylamine, gave mesylate **9**. In practice, it was more efficient to carry out the above two reactions in one-pot. Thus, After treating **7** with pre-dried tetra(*n*-butyl)ammonium fluoride<sup>7</sup> in tetrahydrofuran, excess methanesulfonyl chloride and triethylamine were added to this solution as monitored by TLC. The usual work-up and preparative thin layer chromatography gave **9** in a quantitative yield. Finally, reductive elimination of the mesylate and subsequent cleavage of the oxirane ring with lithium aluminum hydride in tetrahydrofuran afforded (-)-geosmin **1** in good yield. The IR,  $^1\text{H-NMR}$  and GC-MS spectra were identical with those of an authentic sample of ( $\pm$ )-**1**.<sup>8</sup> The specific rotation value of the synthetic sample was  $-15.8$  (lit.<sup>1</sup>  $-16.5$ ).



Scheme 2

## Experimental

All melting points (mp) are uncorrected. Optical rotation was measured with a JASCO DIP-4 spectrometer. IR spectra were taken with a JASCO IR-810 infrared spectrometer, and  $^1\text{H-NMR}$  spectra were measured with JEOL GSX-270 (270 MHz), GSX-400 (400 MHz) and Varian GEMINI 2000/300 (300 MHz) spectrometers. Mass spectra were recorded with a JEOL JMS-HX-105 instrument.

**(4*aS*, 8*S*)-4, 4*a*, 5, 6, 7, 8-Hexahydro-4*a*, 8-dimethyl-2(3*H*)-naphthalenone 3**. This compound was prepared in 60% overall yield from 2,6-dimethylcyclohexanone according to the Reviel's procedure.<sup>6d</sup> Recrystallization from pentane afforded enantiomerically pure **3**, mp  $57.5\text{--}59^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{22} +195$  (*c* 1.00,  $\text{CHCl}_3$ ) {lit. mp  $57^{\circ}\text{C}$ ;  $[\alpha]_{\text{D}}^{20} +203$  (*c* 2,  $\text{CHCl}_3$ )}. Enantiomeric purity ( $>98\%$  ee) of this sample was checked by HPLC using a chiral column (DAICEL CHIRALCELL OD).

**(2*S*, 4*aS*, 8*S*)-2, 3, 4, 4*a*, 5, 6, 7, 8-Octahydro-4*a*, 8-dimethyl-2-naphthalenol 4**. To a solution of **3** (2.65 g, 14.9 mmol) in THF/DME (1 : 1, 300 mL) was added DIBAL (20.0 mL of a 1.0 M solution in hexane,

20.0 mmol) at  $-78^{\circ}\text{C}$ . After stirring for 5 min at  $-78^{\circ}\text{C}$ , the reaction mixture was quenched with MeOH (1 mL). The mixture was diluted with  $\text{Et}_2\text{O}$  (100 mL), washed with sat. aq. sodium potassium tartrate (10 mL), and dried ( $\text{MgSO}_4$ ). Filtration, concentration and silica gel column chromatography (hexane–AcOEt = 6 : 1) afforded alcohol **4** (2.68 g, 14.9 mmol, 100%, 96% d.e.). Recrystallization of this sample from hexane at  $-78^{\circ}\text{C}$  gave pure **4** (100% d.e.) as a white powder, mp  $49 - 50^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{22} +67.5$  (*c* 3.11,  $\text{CHCl}_3$ ). IR (film)  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ : 3330, 3050, 2925, 2850, 1658, 1460, 1375, 1055, 1050.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.28 (1H, d,  $J = 1.1$  Hz), 4.25–4.20 (1H, m), 2.22–2.14 (1H, m), 1.95–1.88 (1H, m), 1.81–1.75 (1H, m), 1.74–1.62 (1H, m), 1.58–1.46 (4H, m), 1.42 (1H, s,  $-\text{OH}$ ), 1.37 (1H, dd,  $J = 2.5, 12.8$  Hz), 1.18 (1H, dt,  $J = 4.0, 12.8$  Hz), 1.11 (3H, s), 0.99 (3H, d,  $J = 6.5$  Hz), 0.95 (1H, dt,  $J = 4.0, 12.8$  Hz). HREIMS:  $m/z$  ( $M^+$ ) Calcd. for  $\text{C}_{17}\text{H}_{20}\text{O}$ , 180.1514; Found, 180.1552.

**(2S, 4aS, 8S)-2, 3, 4, 4a, 5, 6, 7, 8-Octahydro-2-tert-butyl dimethylsilyloxy-4a, 8-dimethylnaphthalene 6**. A solution of the alcohol **4** (2.12 g, 11.7 mmol) in DMF (10 mL) was treated with imidazole (2.39 g, 34.1 mmol) and *tert*-butyldimethylsilyl chloride (2.65 g, 17.3 mmol) at room temperature and the mixture was stirred overnight. The reaction mixture was diluted with ether (20 mL), washed with sat. aq.  $\text{NH}_4\text{Cl}$  solution (5 mL) and brine (5 mL), and dried ( $\text{MgSO}_4$ ). Filtration, concentration and silica gel column chromatography (hexane–AcOEt = 15 : 1) gave silyl ether **6** (3.22 g, 10.9 mmol, 94%) as a colorless oil.  $[\alpha]_{\text{D}}^{22} +16.8$  (*c* 3.00,  $\text{CHCl}_3$ ). IR (film)  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ : 2930, 2855, 1460, 1250, 1080, 895, 875, 835, 775.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.17 (1H, d,  $J = 1.1$  Hz), 4.26 (1H, m), 2.21–2.11 (1H, m), 1.81–1.73 (2H, m), 1.69–1.62 (1H, m), 1.62–1.47 (5H, m), 1.43–1.25 (2H, m), 1.10 (3H, s), 0.98 (3H, d,  $J = 6.5$  Hz), 0.91 (9H, s), 0.09 (3H, s), 0.08 (3H, s). HREIMS:  $m/z$  ( $M^+$ ) Calcd. for  $\text{C}_{18}\text{H}_{34}\text{OSi}$ , 294.2379; Found, 294.2354.

**(1R, 2S, 4aS, 8S, 8aS)-Decahydro-2-tert-butyl dimethylsilyloxy-4a, 8-dimethyl-1, 8a-epoxynaphthalene 7**. A solution of silyl ether **6** (3.11 g, 10.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) was treated with *m*-chloroperbenzoic acid (*ca.* 70%, 3.45 g, 14.0 mmol) at  $-40^{\circ}\text{C}$  and the reaction mixture was stirred overnight. To this mixture was added aq.  $\text{Na}_2\text{S}_2\text{O}_3 / \text{NaHCO}_3$  (1 : 1) solution and after stirring for 1 h at room temperature, the aqueous solution was extracted with  $\text{Et}_2\text{O}$ , the extract being dried ( $\text{MgSO}_4$ ). Filtration, concentration and silica gel column chromatography (hexane–AcOEt = 10 : 1) afforded epoxide **7** (3.30 g, 10.6 mmol, 100%) as a colorless oil.  $[\alpha]_{\text{D}}^{22} +30.3$  (*c* 2.31,  $\text{CHCl}_3$ ). IR (film)  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ : 2930, 2850, 1480, 1250, 1095, 1080, 860, 840, 775.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.93 (1H, dd,  $J = 7.7, 9.2$  Hz), 2.99 (1H, s), 2.15–2.06 (1H, m), 1.77–1.65 (2H, m), 1.60–1.52 (3H, m), 1.47–1.22 (5H, m), 1.44 (3H, s), 0.90 (9H, s), 0.67 (3H, d,  $J = 6.6$  Hz), 0.09 (3H, s), 0.08 (3H, s). HREIMS:  $m/z$  ( $M^+$ ) Calcd. for  $\text{C}_{18}\text{H}_{34}\text{O}_2\text{Si}$ , 310.2328; Found, 310.2328.

**(1R, 2S, 4aS, 8S, 8aS)-Decahydro-4a, 8-dimethyl-1, 8a-epoxy-2-naphthalenol 8**. To a stirred solution of silyl ether **7** (3.30 g, 10.6 mmol) in THF (5 mL) was added dropwise tetra(*n*-butyl)ammonium fluoride (14.0 mL of a 1.0 M solution, 14.0 mmol) at room temperature. After stirring overnight, the reaction mixture was diluted with  $\text{Et}_2\text{O}$  (50 mL), washed with brine (5 mL), and dried ( $\text{MgSO}_4$ ). Filtration, concentration and silica gel column chromatography (hexane–AcOEt = 6 : 1) gave alcohol **8** (2.08 g, 10.6 mmol, 100%) as a colorless needles, mp  $127 - 128^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{22} +48.3$  (*c* 2.00,  $\text{CHCl}_3$ ). IR (film)  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ : 3490, 3010, 2960, 2945, 2850, 1460, 1440, 1270, 1255, 1090, 1065, 1040, 1000, 960, 940, 800, 650, 630.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.05 (1H, m), 3.07 (1H, s), 2.14–2.05 (1H, m), 1.90–1.81 (1H, m), 1.77–1.65 (1H, m), 1.61–1.53 (2H, m), 1.46–1.23 (6H, m), 1.15 (3H, s), 0.99–0.88 (1H, m), 0.68 (3H, d,  $J = 6.6$  Hz). *Anal.* Calcd. for  $\text{C}_{12}\text{H}_{20}\text{O}_2$ : C, 73.43; H, 10.27; Found: C, 73.71; H, 10.23%.

**(1R, 2S, 4aS, 8S, 8aS)-Decahydro-4a, 8-dimethyl-1, 8a-epoxy-2-naphthyl methanesulfonate**

**9. a) From alcohol 8.** To a mixture of **8** (300 mg, 1.53 mmol) and  $\text{Et}_3\text{N}$  (0.43 mL, 3.06 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added methanesulfonyl chloride (0.18 mL, 1.84 mmol) at  $-20^\circ\text{C}$ . After the reaction had been completed, the mixture was diluted with ether and washed with sat. aq.  $\text{NH}_4\text{Cl}$  (5 mL) and brine (5 mL), and dried ( $\text{MgSO}_4$ ). Filtration and concentration provided a colorless oil, which on purification by preparative TLC, furnished **9** (419 mg, 1.53 mmol, 100%).  $[\alpha]_D^{22} +22.5$  (*c* 1.49,  $\text{CHCl}_3$ ). IR (film)  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ : 2930, 2870, 1455, 1440, 1420, 1360, 1340, 1170, 1080, 1000, 940, 890, 860, 800, 750, 630.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.88 (1H, t,  $J = 8.8$  Hz), 3.22 (1H, s), 3.06 (3H, s), 2.18-2.07 (1H, m), 2.07-1.96 (1H, m), 1.80-1.54 (4H, m), 1.49-1.25 (4H, m), 1.16 (3H, s), 1.12 (1H, dt,  $J = 3.8, 13.5$  Hz), 0.67 (3H, d,  $J = 6.9$  Hz). HREIMS:  $m/z$  ( $M^+$ ) Calcd. for  $\text{C}_{13}\text{H}_{22}\text{O}_4\text{S}$ , 274.1239; Found, 274.1257.

**b) In one-pot from 7.** To a solution of **7** (200 mg, 0.64 mmol) in THF (20 mL) was added at  $0^\circ\text{C}$  tetra(*n*-butyl)ammonium fluoride (0.65 mL of a 1.0 M solution, 0.65 mmol), which had been dried over molecular sieves 4A, and the mixture was allowed to warm to room temperature. After stirring for 1 hr, methanesulfonyl chloride (0.20 mL, 2.56 mmol) and  $\text{Et}_3\text{N}$  (0.72 mL, 5.12 mmol) were added to this solution at  $-10$ – $-5^\circ\text{C}$ . The reaction mixture was stirred for 2 hr and treated with sat.  $\text{NaHCO}_3$  (5 mL) and diluted with  $\text{Et}_2\text{O}$ . The organic layer was washed with sat. aq.  $\text{NH}_4\text{Cl}$  (5 mL) and brine (5 mL), and dried ( $\text{MgSO}_4$ ). Filtration, concentration and preparative TLC of the crude residue afforded **9** (176 mg, 0.64 mmol, 100%).

**(-)-Geosmin 1.** A solution of mesylate **9** (430 mg, 1.53 mmol) in THF (5 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (148 mg, 3.90 mmol) in THF (5 mL) at  $0^\circ\text{C}$ . The reaction mixture was refluxed for 3 h and excess reagent was hydrolyzed by dropwise addition of water (0.15 mL), followed by 2 N NaOH (0.15 mL) and water (0.60 mL). Filtration, concentration and short-path distillation gave (-)-geosmin **1** (251 mg, 1.38 mmol, 90%) as a colorless oil.  $[\alpha]_D^{22} -15.8$  (*c* 1.80,  $\text{CHCl}_3$ ) {lit.  $[\alpha]_D^{25} -16.5$  (*c* 0.5,  $\text{CHCl}_3$ )}. The IR,  $^1\text{H-NMR}$ , GC-MS spectra of this synthetic sample were identical with those of authentic ( $\pm$ )-geosmin.

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