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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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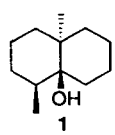
Abstract: An asymmetric synthesis of (–)-geosmin **1** *via* highly diastereoselective reduction of the enantiomerically pure title ketone **3** is described. Diisobutylaluminum hydride reduction of **3** in a mixed solvent of tetrahydrofuran and 1,2-dimethoxyethane led to allylic alcohol **4** in 96% 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**.

(–)-Geosmin **1**, first isolated by Gerber and Lechevalier in 1965[1], 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.[2,3] 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,[4] 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.[5] Among them, a combination of Revial's protocol[5d] based on asymmetric Michael-type alkylation of chiral imines leading to (+)-octalone **3** and



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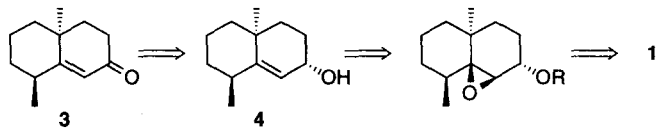
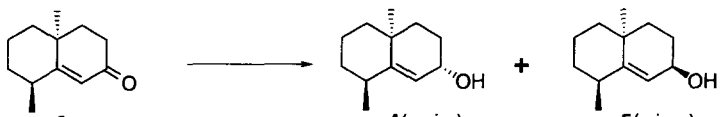
Gosselin's racemic geosmin synthesis[5c] is virtually the sole practical method for obtaining optically active geosmin. In order to access enantiomerically pure (–)-geosmin **1** in much higher overall yield, we developed a six-step reaction process starting from (+)-octalone **3**. In this paper, we 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[5d] 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°C gave diastereomerically pure **4**.[6]

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

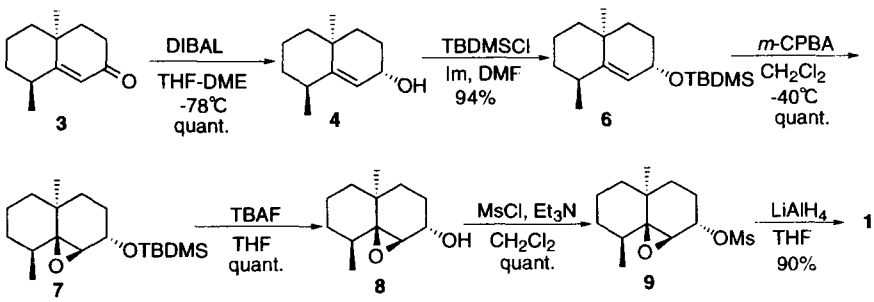


Reagent	Solvent	Temp. (°C)	Time	Selectivity (% d.e.)[a]	Yield (%)[b]
$NaBH_4$, $CeCl_3 \cdot 7H_2O$	MeOH	r.t.	4 h	43	95
$NaBH_3CN$	EtOH	r.t.	2 d	70	93
$[t\text{-}BuC(C_2H_5)_2O]_3AlH$	THF	–78	1 d	60	88
9-BBN	THF	r.t.	NR	–	–
Catecholborane	THF	–78	decomp.	–	–
DIBAL	CH_2Cl_2	–78	10 min	64	50[c]
DIBAL	Toluene	–78	10 min	76	52[d]
DIBAL	Et_2O	–78	5 min	83	quant.
DIBAL	THF	–78	5 min	88	quant.
DIBAL	**THF-DME**	**–78**	**5 min**	**96**	**quant.**

a) Diastereomeric excess was determined by ^{1}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°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°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[7] 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}H-NMR and GC-MS spectra were identical with those of an authentic sample of (±)-**1**.[8] The specific rotation value of the synthetic sample was –15.8 (lit.[1] –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}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.

(4a*S*,8*S*)-4,4a,5,6,7,8-Hexahydro-4a,8-dimethyl-2(3H)-naphthalenone 3. This compound was prepared in 60% overall yield from 2,6-dimethylcyclohexanone according to the Revial's procedure.[6d] Recrystallization from pentane afforded enantiomerically pure **3**, mp 57.5-59°C. $[\alpha]_D^{22}$ +195 (*c* 1.00, $CHCl_3$) {lit. mp 57°C; $[\alpha]_D^{20}$ +203 (*c* 2, $CHCl_3$)}. Enantiomeric purity (>98% ee) of this sample was checked by HPLC using a chiral column (DAICEL CHIRALCELL OD).

(2*S*,4a*S*,8*S*)-2,3,4,4a,5,6,7,8-Octahydro-4a,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°C. After stirring for 5 min at –78°C, the reaction mixture was quenched with MeOH (1 mL). The mixture was diluted with Et_2O (100 mL), washed with sat. aq. sodium potassium tartrate (10 mL), and dried ($MgSO_4$). 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 °C gave pure **4** (100% d.e.) as a white powder, mp 49 - 50°C. $[\alpha]_D^{22}$ +67.5 (*c* 3.11, $CHCl_3$). IR (film)ν_{max} cm^{-1}: 3330, 3050, 2925, 2850, 1658, 1460, 1375, 1055, 1050. ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 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, -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 $C_{12}H_{20}O$, 180.1514; Found, 180.1552.

(2*S*,4a*S*,8*S*)-2,3,4,4a,5,6,7,8-Octahydro-2-*tert*-butyldimethylsilyloxy-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. NH_4Cl solution (5 mL) and brine (5 mL), and dried ($MgSO_4$). 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. $[\alpha]_D^{22}$ +16.8 (*c* 3.00, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2930, 2855, 1460, 1250, 1080, 895, 875, 835, 775. ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 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 $C_{18}H_{34}OSi$, 294.2379; Found, 294.2354.

(1*R*,2*S*,4a*S*,8*S*,8a*S*)-Decahydro-2-*tert*-butyldimethylsilyloxy-4a,8-dimethyl-1,8a-epoxynaphthalene 7. A solution of silyl ether **6** (3.11 g, 10.6 mmol) in CH_2Cl_2 (20 mL) was treated with *m*-chloroperbenzoic acid (*ca.* 70%, 3.45 g, 14.0 mmol) at –40°C and the reaction mixture was stirred overnight. To this mixture was added aq. $Na_2S_2O_3$ / $NaHCO_3$ (1 : 1) solution and after stirring for 1 h at room temperature, the aqueous solution was extracted with Et_2O, the extract being dried ($MgSO_4$). 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. $[\alpha]_D^{22}$ +30.3 (*c* 2.31, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2930, 2850, 1480, 1250, 1095, 1080, 860, 840, 775. ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 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 $C_{18}H_{34}O_2Si$, 310.2328; Found, 310.2328.

(1*R*,2*S*,4a*S*,8*S*,8a*S*)-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 Et_2O (50 mL), washed with brine (5 mL), and dried ($MgSO_4$). 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°C. $[\alpha]_D^{22}$ +48.3 (*c* 2.00, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3490, 3010, 2960, 2945, 2850, 1460, 1440, 1270, 1255, 1090, 1065, 1040, 1000, 960, 940, 800, 650, 630. ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 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 $C_{12}H_{20}O_2$: C, 73.43; H, 10.27; Found: C, 73.71; H, 10.23%.

(1*R*,2*S*,4a*S*,8*S*,8a*S*)-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 Et_3N (0.43 mL, 3.06 mmol) in CH_2Cl_2 (10 mL) was added methanesulfonyl chloride (0.18 mL, 1.84 mmol) at –20°C. After the reaction had been completed, the mixture was diluted with ether and washed with sat. aq. NH_4Cl (5 mL) and brine (5 mL), and dried ($MgSO_4$). 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, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2930, 2870, 1455, 1440, 1420, 1360, 1340, 1170, 1080, 1000, 940, 890, 860, 800, 750, 630. ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 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 $C_{13}H_{22}O_4S$, 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°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 Et_3N (0.72 mL, 5.12 mmol) were added to this solution at –10~–5°C. The reaction mixture was stirred for 2 hr and treated with sat. $NaHCO_3$ (5 mL) and diluted with Et_2O. The organic layer was washed with sat. aq. NH_4Cl (5 mL) and brine (5 mL), and dried ($MgSO_4$). 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°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, $CHCl_3$) {lit.[1] $[\alpha]_D^{25}$ –16.5 (*c* 0.5, $CHCl_3$)}. The IR, ^{1}H-NMR, GC-MS spectra of this synthetic sample were identical with those of authentic (±)-geosmin.

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