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Synthesis of the Racemate and Both Enantiomers of Massoilactone

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A simple and efficient synthesis of (±)-massoilactone (1) as a key substance for the butter and milk flavor was accomplished from *n*-hexanal in only a few steps. Application of its racemic synthesis enabled natural (*R*)-(−)- and unnatural (*S*)-(+)-massoilactone (1a, 1b) to be synthesized by starting from commercially available (*R*)-(+)-1,2-epoxyheptane (5).

Key words: massoilactone; (*R*)-(+)-1,2-epoxyheptane; Mitsunobu inversion; flavor

In 1937, Abe[1)] first found (−)-massoilactone (**1a**) from the bark oil of *Cryptocarya massoia* which grows wild in New Guinea and has been traditionally used for many centuries as a constituent of native medicines. (−)-Massoilactone (**1a**) was later isolated as a defense substance from two species of formicine ants of the genus *Camponotus* collected in Western Australia,[2)] and as a flavor substance from cane molasses[3)] and tuberose flowers.[4)] This lactone **1a** has also been shown to occur in *Hierochloe odorata* and *Hierochloe australis*, both being commonly used in vodka production.[5)] Its structure was confirmed to be **1** by the synthesis of its racemate,[6,7)] and the absolute configuration of natural **1a** was determined as (*R*)-form by the unambiguous synthesis of its unnatural (*S*)-isomer **1b**.[8)] Many reports on the synthesis of the racemate (**1**)[9–14)] and both enantiomers (**1a** and **1b**) have been published. The literature shows that various asymmetric syntheses of both **1a** and **1b** utilized optically active starting materials[15–26)] and optical resolution of the diastereomeric derivatives.[27,28)] Since the industrial use of massoilactone, which is very useful as a butter and milk flavor, has recently been increasing, substantial effort has been devoted to its synthesis. We now describe an efficient and industrial synthesis of **1** starting from *n*-hexanal, and an asymmetric synthesis of **1a** and **1b** starting from commercially available (*R*)-(+)-1,2-epoxyheptane (**5**)[20,21)] that applies the synthetic method for **1**.

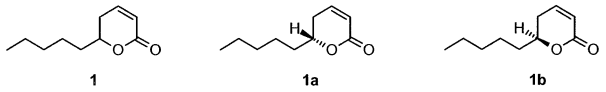

Fig. 1. Structures of the Racemate and Both Enantiomers of Massoilactone.

Results and Discussion

Synthesis of (±)-massoilactone (1)

Our synthetic plan for **1** was based on using economical raw materials and employing a short-step industrial procedure. We therefore selected *n*-hexanal for the C-6 unit, allyl chloride for the C-3 unit and NaCN for the C-1 unit as the raw materials. (±)-1-Nonen-4-ol (**2**), which was easily prepared by Grignard reaction of *n*-hexanal with allyl magnesium chloride[29)] in THF, was used as the starting material. Epoxidation[30)] of homoallylic alcohol **2** was achieved with 40% AcOOH in the presence of NaOAc in toluene to give (±)-epoxy alcohol **3** in a good yield. Subsequent cyanation[31)] of **3** with NaCN/AcOH in EtOH aq. afforded (±)-dihydroxy cyanide **4** as the sole product in a quantitative yield. Finally, the reaction of **4** with 1.2 equivalent of conc. HCl under gentle reflux proceeded smoothly to give the desired (±)-massoilactone (**1**) in a 67% yield. Thus, a simple and industrially suitable synthesis of **1** was established in a 46% overall yield with only four steps from *n*-hexanal.

Synthesis of (R)-(−)- and (S)-(+)-massoilactone (1a and 1b)

The same procedure as that described for **1** was applied to the synthesis of both enantiomers **1a** and **1b** from (*R*)-(+)-1-nonen-4-ol (**2a**).[24)] Grignard reaction of (*R*)-(+)-1,2-epoxyheptane (**5**)[20,21)] with vinylmagnesium chloride in the presence of CuI gave (*R*)-homoallylic alcohol **2a** in an 86% yield. Mitsunobu inversion[32)] of **2a** was employed to obtain corresponding enantiomer (*S*)-**2b**. Treatment of **2a**, using 3,5-dinitrobenzoic acid as a nucleophile,

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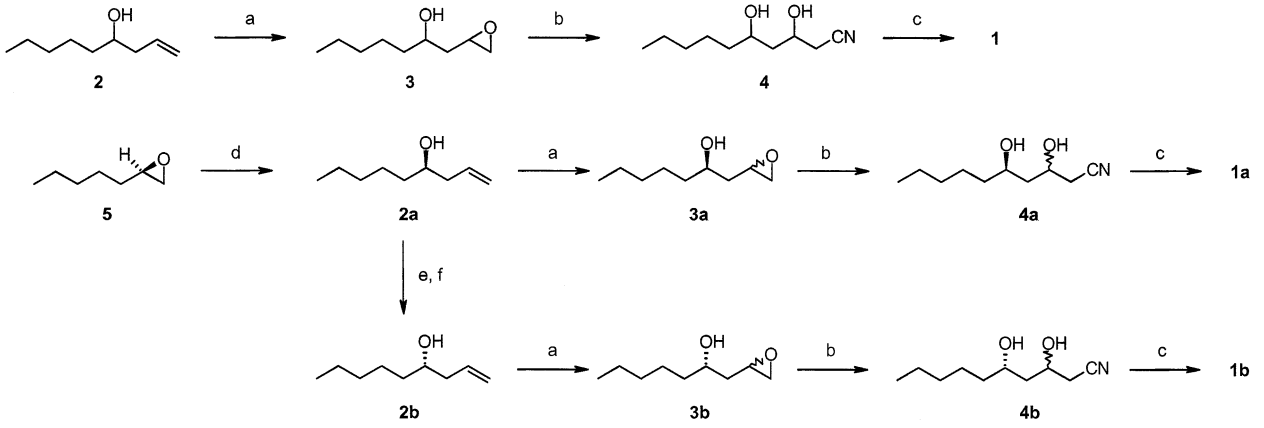

Scheme 1. Synthesis of the Racemate and Both Enantiomers of Massoilactone.
Reagents: (a) 40% AcOOH, NaOAc; (b) NaCN, AcOH; (c) conc. HCl; (d) vinylmagnesium chloride, CuI; (e) PPh_3, 3,5-dinitrobenzoic acid, diethyl azodicarboxylate; (f) KOH, MeOH.

afforded (*S*)-**2b** in a 79% yield upon transesterification of the resulting 3,5-dinitrobenzoate. The optical purity of starting material **5** and resulting **2a** and **2b** were respectively evaluated to be 94.1% *e.e.*, 93.8% *e.e.* and 93.5% *e.e.* by a GLC analysis using a chiral GLC column[33] with cyclodextrin derivatives. Similarly, epoxidation of both homoallylic alcohols **2a** and **2b** with 40% AcOOH gave diastereomeric mixtures of epoxy alcohols **3a** and **3b** in 68% and 73% yields, which were then cyanated with NaCN/AcOH to afford crude dihydroxy cyanides **4a** and **4b**. Finally, **4a** and **4b** were each hydrolyzed with conc. HCl under reflux to give the desired (*R*)-(−)-massoilactone (**1a**) and (*S*)-(+)-massoilactone (**1b**) in 65% and 68% yields from **3a** and **3b**, respectively. These synthetic **1a** and **1b** enantiomers were completely identical with racemic massoilactone (**1**) in their IR and NMR spectral properties, while the optical purity values for **1a** and **1b** were shown to be 93.4% *e.e.* and 93.0% *e.e.* by a GLC analysis.[33] As reported,[28] natural **1a** was found to have a fresher and stronger milk-butter-coconut-like flavor than unnatural **1b**. In summary, an efficient synthesis of both enantiomers **1a** and **1b** was achieved in 38% and 34% respective overall yields in only 4–5 steps from **5**.

Experimental

(*R*)-(+)-1,2-Epoxyheptane was purchased from Japan Energy Corporation, all other chemicals being of technical grade and commercially available. All boiling point (bp) data are uncorrected. Melting point (mp) data were measured with a Büchi B-545 instrument and are uncorrected. IR spectra were measured with a Jasco IR-5000 spectrometer. ^{1}H-NMR spectra were recorded at 400 MHz by a Jeol JNM-LA400 spectrometer, the peak for TMS (at δ 0.00) being used as the internal standard. ^{13}C-NMR spectra were recorded at 100 MHz by a Jeol JNM-LA400 spectrometer, the peak for $CDCl_3$ (at δ 77.0) being used as the internal standard. MS spectra were obtained with a Hitachi M-80B spectrometer at 70 eV, and optical rotation values were measured with a Horiba SEPA-2000 polarimeter. GLC analyses were performed by a Hewlett-Packard 5890 gas chromatograph with a 0.25 mm i.d. × 50 m capillary column coated with a mixture of heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-β-CD, octakis-(2,6-di-*O*-methyl-3-trifluoroacetyl)-γ-CD and OV-1701 (2:1:7) (column temp., 70°C to 160°C, programmed at 0.7°C/min; carrier gas, He at 0.9 ml/min). Column chromatography was carried out on Merck Kieselgel 60 Art 7734.

(±)-1-Nonen-4-ol (2). To a stirred mixture of Mg turnings (26.7 g, 1.1 g atom) in dry THF (100 ml) was added a small portion (20 ml) of a solution of *n*-hexanal (100.0 g, 1.0 mol) and allyl chloride (91.8 g, 1.2 mol) in dry THF (400 ml). After the reaction had begun at 45°C, the remaining solution was added dropwise over 2 hr at 30°C under ice-cooling, and stirring was continued for 1 hr at room temperature. The reaction mixture was slowly poured into cooled 2.0 M HCl aq. (600 g) and then extracted with toluene. The organic layer was successively washed with Na_2CO_3 aq. and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled to give 134.0 g (94%) of **2**. Bp: 64–65°C at 0.5 kPa. IR ν_{max} (film) cm^{-1}: 3358 (brm, OH), 1641 (m, CH_2=CH-). NMR δ_H (400 MHz, $CDCl_3$): 0.90 (3H, t, J=6.8 Hz, 9-CH_3), 1.20–1.50 (9H, m, 5-, 6-, 7-, 8-CH_2 and OH), 2.10–2.32 (2H, m, 3-CH_2), 3.62–3.66 (1H, m, 4-CH), 5.13 and 5.14 (total 2H, each dd, J=15.6, 12.0, 1.2 Hz, 1-CH_2), 5.70–5.90 (1H, m, 2-CH). NMR δ_C (100 MHz, $CDCl_3$): 14.04, 22.64, 25.36, 31.88, 36.82, 41.97, 70.73, 118.04, 134.95. HRMS m/z (M^+): calcd. for $C_9H_{18}O$, 142.1358; found, 142.1350.

(4R)-1-Nonen-4-ol (2a). To a stirred mixture of CuI (0.95 g, 5.0 mmol) and a solution of (*R*)-(+)-**5** (5.7 g, 50 mmol) in dry THF (50 ml) was added dropwise a solution of vinylmagnesium chloride in THF (1.38 M, 43.5 ml, 60 mmol) over 1 hr at −50°C, stirring being continued for 0.5 hr at 0°C. The mixture was poured into NH_4Cl aq. and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue by SiO_2 (150 g) chromatography, eluting with *n*-hexane-ethyl acetate (95:5), gave **2a** (6.1 g, 86%). $[\alpha]_D^{20}$ +7.96 (*c* 1.080, EtOH). Its IR and NMR spectra were identical with those of racemate **2**. HRMS *m/z* (M^+): calcd. for $C_9H_{18}O$, 142.1358; found, 142.1349. The enantiomeric purity of resulting **2a** was found to be 93.8% *e.e.* by a GLC analysis: t_R 73.64 min [96.9%, **2a**], t_R 74.73 min [3.1%, **2b**].

(4S)-1-Nonen-4-ol (2b). To a stirred solution of Ph_3P (10.5 g, 40 mmol), 3,5-dinitrobenzoic acid (8.5 g, 40 mmol) and **2a** (5.7 g, 40 mmol) in dry THF (150 ml) was added dropwise a 40% solution of diethyl azodicarboxylate in toluene (17.4 g, 40 mmol) over 30 min at room temperature. After being stirred for 16 hr at room temperature, the mixture was concentrated *in vacuo*. The residue by SiO_2 (130 g) chromatography, eluting with *n*-hexane-ethyl acetate (25:1), gave (4*S*)-benzoate (11.2 g, 83%) as light yellow crystals. Mp: 37.5–38.0°C. $[\alpha]_D^{20}$ −9.43 (*c* 1.123, EtOH). IR ν_{max} (KBr) cm^{-1}: 1716 (s, C=O), 1631 (m, CH_2=CH-), 1546, 1346 (s, N-O). NMR δ_H (400 MHz, $CDCl_3$): 0.87–0.90 (3H, t, *J*=6.6 Hz, 9-CH_3), 1.30–1.42 (6H, m, 6-, 7- and 8-CH_2), 1.74–1.80 (3H, m, 5-CH_2), 2.50–2.55 (2H, m, 3-CH_2), 5.10 and 5.14 (total 2H, each dd, *J*=17.2, 10.4, 1.2 Hz, 1-CH_2), 5.28–5.30 (1H, m, 4-CH), 5.77–5.85 (1H, m, 2-H), 9.14 (2H, s, aromatic), 9.22 (1H, s, aromatic). NMR δ_C (100 MHz, $CDCl_3$): 13.98, 14.13, 22.51, 22.68, 25.07, 31.57, 33.62, 38.67, 76.78, 118.47, 122.27, 129.40, 133.10, 134.44, 148.72, 162.19. To a stirred and ice-cooled solution of (4*S*)-benzoate (11.0 g, 33 mmol) in THF (120 ml) was added dropwise a mixture of 1 M KOH aq. (36 ml) and MeOH (70 ml). Stirring was continued for 2 hr at room temperature, and then the mixture was extracted with ether. The ethereal layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue by SiO_2 (50 g) chromatography, eluting with *n*-hexane-ethyl acetate (20:1), gave **2b** (4.4 g, 95%). $[\alpha]_D^{20}$ −8.74 (*c* 1.075, EtOH). Its IR and NMR spectra were identical with those of racemate **2**. HRMS *m/z* (M^+): calcd. for $C_9H_{18}O$, 142.1358; found, 142.1372. The enantiomeric purity of resulting **2b** was found to be 93.6% *e.e.* by a GLC analysis: t_R 73.64 min [3.2%, **2a**], t_R 74.73 min [96.8%, **2b**].

(±)-1,2-Epoxynonan-4-ol (3). To a stirred mixture of **2** (71.0 g, 0.50 mol) and sodium acetate (14.2 g, 0.17 mol) in toluene (250 ml) was added dropwise 40% AcOOH (114.0 g, 0.60 mol) over 2 hr at 40°C. After being stirred for 6 hr at 45°C, the mixture was washed with brine. The organic layer was separated, successively washed with $FeSO_4$ aq., Na_2CO_3 aq. and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled to give **3** (59.2 g, 75%). Bp: 82–83°C at 0.53 kPa. IR ν_{max} (film) cm^{-1}: 3423 (brm, OH), 1258, 843 (m, epoxy). NMR δ_H (400 MHz, $CDCl_3$): 0.89 (3H, t, *J*=6.6 Hz, 9-CH_3), 1.25–2.10 (11H, m, 3-, 5-, 6-, 7-, 8-CH_2 and OH), 2.51 and 2.62 (total 1H, each dd, *J*=4.9, 2.7 Hz, 1-CH), 2.79 and 2.83 (total 1H, each dd, *J*=4.9, 4.3 Hz, 1-CH), 3.00–3.20 (1H, m, 2-CH), 3.78–3.95 (1H, m, 4-CH). NMR δ_C (100 MHz, $CDCl_3$): 14.03, 22.62, 25.20, 31.80, 37.54, 39.03, 39.75, 46.61, 46.87, 50.24, 50.65, 69.33, 70.58. HRMS *m/z* (M^+): calcd. for $C_9H_{18}O_2$, 158.1307; found, 158.1330.

(4R)-1,2-Epoxynonan-4-ol (3a). In the same manner as that described for the preparation of **3**, **2a** (5.7 g, 40 mmol) was treated with 40% AcOOH (9.1 g, 48 mmol) and sodium acetate (1.1 g, 13 mmol) in toluene (20 ml). The residue by SiO_2 (50 g) chromatography, eluting with *n*-hexane-ethyl acetate (20:1), gave **3a** as unseparable diastereomers (4.3 g, 68%). $[\alpha]_D^{20}$ −9.87 (*c* 1.215, EtOH). Its IR and NMR spectra were identical with those of racemate **3**. HRMS *m/z* (M^+): calcd. for $C_9H_{18}O_2$, 158.1307; found, 158.1322.

(4S)-1,2-Epoxynonan-4-ol (3b). In the same manner as that just described, **2b** (4.3 g, 30 mmol) gave **3b** (3.5 g, 74%). $[\alpha]_D^{20}$ +8.57 (*c* 1.065, EtOH). Its IR and NMR spectra were identical with those of **3** and **3a**. HRMS *m/z* (M^+): calcd. for $C_9H_{18}O_2$, 158.1307; found, 158.1319.

(±)-3,5-Dihydroxydecanenitrile (4). To a solution of 95% NaCN (17.0 g, 0.33 mol) in water (60 ml) was added a solution of **3** (47.4 g, 0.30 mol) in 95% EtOH (60 ml). To this mixture was added dropwise AcOH (20.0 g, 0.33 mol) over 1 hr at 35°C under water-cooling, and stirring was continued for 4 hr at 60°C. The mixture was diluted with water and extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give crude **4** (56.0 g, q.y.). IR ν_{max} (film) cm^{-1}: 3406 (brm, OH), 2253 (m, CN). NMR δ_H (400 MHz, $CDCl_3$): 0.88–0.90 (3H, m, 9-CH_3), 1.24–1.82 (10H, m, 4-, 6-, 7-, 8- and 9-CH_2), 2.51–2.60 (2H, dd, *J*=16.0, 5.8 Hz , 2-CH_2), 3.85–4.30 (2H, m, 3-CH and 5-CH).

(±)-Massoilactone (1). A mixture of **4** (46.3 g, 0.25 mol) and conc. HCl (46 g) was heated at 90–

95°C for 3 hr. The cooled mixture was diluted with water and extracted with toluene. The extract was successively washed with Na_2CO_3 aq. and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled to give **1** (28.2 g, 67%). Bp: 111–112°C at 0.5 kPa. IR ν_{max} (film) cm^{-1}: 1724 (s, C=O), 1252 (s, C−O). NMR δ_H (400 MHz, $CDCl_3$): 0.90 (3H, t, J=6.9 Hz, 10-CH_3), 1.28–1.78 (8H, m, 6-, 7-, 8 and 9-CH_2), 2.31–2.36 (2H, m, 4-CH_2), 4.40–4.45 (1H, m, 5-CH), 6.02 (1H, dt, J=10.0, 2.0 Hz, 3-CH_2), 6.88 (1H, ddd, J=10.0, 3.6, 3.6 Hz, 2-CH_2). NMR δ_C (100 MHz, $CDCl_3$): 13.99, 22.51, 24.50, 29.41, 31.54, 34.85, 78.04, 121.45, 145.06, 164.63. These NMR data are in good accord with those reported in ref. 8. HRMS m/z (M^+): calcd. for $C_{10}H_{16}O_2$, 168.1150; found, 168.1162.

(R)-(−)-Massoilactone (1a). In the same manner as that described for the preparation of **1**, **3a** (1.6 g, 10 mmol) was treated with 95% NaCN (0.64 g, 13 mmol) and AcOH (0.75 g, 13 mmol) in EtOH aq. (5.2 ml) to give crude **4a** (1.7 g). **4a** (1.6 g) was then treated with conc. HCl (1.6 g) to give **1a** (1.0 g, 65% from **3a**). $[\alpha]_D^{20}$ −117.3 (*c* 1.045, $CHCl_3$); ref. 26 $[\alpha]_D^{28}$ −109.7 (*c* 3.9, $CHCl_3$). Its IR and NMR spectra were identical with those of racemate **1**. HRMS m/z (M^+): calcd. for $C_{10}H_{16}O_2$, 168.1150; found, 168.1142. The enantiomeric purity of resulting **1a** was found to be 93.4% *e.e.* by a GLC analysis: t_R 117.90 min [3.3%, **1b**], t_R 118.96 min [96.7%, **1a**].

(S)-(+)-massoilactone (1b). In the same manner as that just described, **3b** (3.5 g, 22 mmol) gave **1b** (2.5 g, 68%). $[\alpha]_D^{20}$ +109.0 (*c* 1.125, $CHCl_3$); ref. 23 $[\alpha]_D^{28}$ +110.5 (*c* 2.4, $CHCl_3$). Its IR and NMR spectra were identical with those of **1** and **1a**. HRMS m/z (M^+): calcd. for $C_{10}H_{16}O_2$, 168.1150; found, 168.1152. The enantiomeric purity of resulting **1b** was found to be 93.0% *e.e.* by a GLC analysis: t_R 117.90 min [96.5%, **1b**], t_R 118.96 min [3.5%, **1a**].

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