Synthesis of the Racemate and Both Enantiomers of Massoilactone

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A simple and efficient synthesis of (±)-massoilactone (1l) as a key substance for the butter and milk flavor was accomplished from n-hexanal in only a few steps. Application of its racemization 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 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 formic ants of the genus Camponotus collected in Western Australia, and as a flavor substance from cane molasses and tuberose flowers. This lactone 1a has also been shown to occur in Hierchlooe odorata and Hierchlooe australis, both being commonly used in vodka production. Its structure was confirmed to be 1 by the synthesis of its racemate and the absolute configuration of natural 1a was determined as (R)-form by the unambiguous synthesis of its unnatural (S)-isomer 1b. Many reports on the synthesis of the racemate (1) 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 and optical resolution of the diastereomeric derivatives. 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) that applies the synthetic method for 1.

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 in THF, was used as the starting material. Epoxidation of homoallylic alcohol 2 was achieved with 40% AcOIn in the presence of NaOAc in toluene to give (±)-epoxy alcohol 3 in a good yield. Subsequent cyanation of 3 with NaCN/AcOH in EtOHaq 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-nonene-4-ol (2a). Grignard reaction of (R)-(−)-1,2-epoxyheptane (5) with vinylmagnesium chloride in the presence of CuI gave (R)-Homoallylic alcohol 2a in an 86% yield. Mitsunobu inversion of 2a was employed to obtain corresponding enantiomer (S)-2b. Treatment of 2a, using 3,5-dinitrobenzoic acid as a nucleophile,
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 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 NaN₃/ 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. As reported, 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. ¹H-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. ¹³C-NMR spectra were recorded at 100 MHz by a Jeol JNM-
(4R)-1-Nonen-4-ol (2a). To a stirred mixture of Cul (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 vinlymagnesium 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 NH₄Cl aq. and extracted with ether. The extract was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue by SiO₂ (150 g) chromatography, eluting with n-hexane-ethyl acetate (95:5), gave 2a (6.1 g, 86%). \([\delta]_{D}^{B} + 7.96 (c 1.080, \text{EtOH})\). Its IR and NMR spectra were identical with those of racemate 2. HRMS m/z (M⁺): calcd. for C₇H₁₀O₂, 142.1358; found, 142.1349. The enantiomeric purity of resuting 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 Ph₃P (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 SiO₂ (130 g) chromatography, eluting with n-hexane-ethyl acetate (25:1), gave (4S)-benzoate (11.2 g, 83%) as light yellow crystals. Mp: 37.5-38.0°C. \([\delta]_{D}^{B} - 9.43 (c 1.123, \text{EtOH})\). IR νmax (KBr) cm⁻¹: 1716 (s, C = O), 1631 (m, CH₂ = CH-), 1546, 1346 (s, N-O). NMR δH (400 MHz, CDCl₃): 8.70-9.09 (3H, t, J = 6.6 Hz, 9-CH₃), 1.30-1.42 (6H, m, 6-, 7- and 8-CH₂), 1.74-1.80 (3H, m, 5-CH₂), 2.50-2.55 (2H, m, 3-CH₃), 5.10 and 5.14 (total 2H, each dd, J = 17.2, 10.4, 1.2 Hz, 1-CH₂), 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 δC (100 MHz, CDCl₃): 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 (4S)-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 ether layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue by SiO₂ (50 g) chromatography, eluting with n-hexane-ethyl acetate (20:1), gave 2b (4.4 g, 95%). \([\delta]_{D}^{B} + 8.74 (c 1.075, \text{EtOH})\). Its IR and NMR spectra were identical with those of racemate 2. HRMS m/z (M⁺): calcd. for C₇H₁₀O₂, 142.1358; found, 142.1372. The enantiomeric purity of resuling 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-Epoxyynonan-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% AcOH (9.1 g, 48 mmol) and sodium acetate (1.1 g, 13 mmol) in toluene (20 ml). The residue by SiO₂ (50 g) chromatography, eluting with n-hexane-ethyl acetate (20:1), gave 3a as unseparable diastereomers (4.3 g, 68%). \([\delta]_{D}^{B} - 9.87 (c 1.215, \text{EtOH})\). Its IR and NMR spectra were identical with those of racemate 3. HRMS m/z (M⁺): calcd. for C₇H₁₄O₂, 158.1307; found, 158.1330.

(4S)-1,2-Epoxyynonan-4-ol (3b). In the same manner as that just described, 2b (4.3 g, 30 mmol) gave 3b (3.5 g, 74%). \([\delta]_{D}^{B} + 8.57 (c 1.065, \text{EtOH})\). Its IR and NMR spectra were identical with those of 3 and 3a. HRMS m/z (M⁺): calcd. for C₇H₁₂O₂, 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 CH₂Cl₂. The extract was washed with brine, dried over MgSO₄ and concentrated in vacuo to give crude 4 (56.0 g, q.y.). IR νmax (film) cm⁻¹: 3406 (brm, OH), 2253 (m, CN). NMR δH (400 MHz, CDCl₃): 0.88-0.90 (3H, m, 9-CH₃), 1.24-1.82 (10H, m, 4-, 6-, 7-, 8- and 9-CH₂), 2.51-2.60 (2H, dd, J = 16.0, 5.8 Hz , 2-CH₂), 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 Na₂CO₃ aq. and brine, dried over MgSO₄, and concentrated in vacuo. The residue was distilled to give 1 (28.2 g, 67%). Bp: 111–112°C at 0.5 kPa. IR νₘₐₓ (film) cm⁻¹: 1724 (s, C = O), 1252 (s, C – O). NMR δₖ (400 MHz, CDCl₃): 0.90 (3H, t, J = 6.9 Hz, 10-CH₃), 1.28–1.78 (8H, m, 6-, 7-, 8 and 9-CH₃), 2.31–2.36 (2H, m, 4-CH₂), 4.40–4.45 (1H, m, 5-CH), 6.02 (1H, dt, J = 10.0, 2.0 Hz, 3-CH₃), 6.88 (1H, ddd, J = 10.0, 3.6 Hz, 2-CH₂). NMR δₑ (100 MHz, CDCl₃): 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 C₁₀H₁₆O₂, 168.1150; found, 168.1162.

(R)-(-)-Massoioalactone (1a). In the same manner as that described for the preparation of 1, 3a (1.6 g, 10 mmol) was treated with 95% NaN₃ (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). [α]₆₀° = –117.3 (c 1.045, CHCl₃); ref. 26 [α]₆₀° = –109.7 (c 3.9, CHCl₃). Its IR and NMR spectra were identical with those of racemate 1. HRMS m/z (M⁺): calcd. for C₁₀H₁₆O₂, 168.1150; found, 168.1142. The enantiomeric purity of resulting 1a was found to be 93.4% e.e. by a GLC analysis: tᵣ 117.90 min [3.3%, 1b], tᵣ 118.96 min [96.7%, 1a].

(S)-(+)-massoioalactone (1b). In the same manner as that just described, 3b (3.5 g, 22 mmol) gave 1b (2.5 g, 68%). [α]₆₀° + 109.0 (c 1.125, CHCl₃); ref. 23 [α]₆₀° + 110.5 (c 2.4, CHCl₃). Its IR and NMR spectra were identical with those of 1 and 1a. HRMS m/z (M⁺): calcd. for C₁₀H₁₆O₂, 168.1150; found, 168.1152. The enantiomeric purity of resulting 1b was found to be 93.0% e.e. by a GLC analysis: tᵣ 117.90 min [96.5%, 1b], tᵣ 118.96 min [3.5%, 1a].

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