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Synthesis of optically active *S*-methylthio-2-methylbutanoate, an excellent smelling compound

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Synthesis of optically active *S*-methylthio-2-methylbutanoate, an excellent smelling compound

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Optically active *S*-methylthio-2-methylbutanoate **3**, which has been found in hops, cheese and melon as a tropical fruit-type flavor, was synthesized from the corresponding optically active 2-methylbutanoic acid **1** by the asymmetric hydrogenation of tiglic acid, conversion to the acid chloride **2**, followed by treatment with the methylmercaptan sodium salt in a 15% water solution in good yield. The naturally occurring **3** is suggested to be the (*S*)-form.

Keywords: optically active *S*-methylthio-2-methylbutanoate; 2-methylbutanoic acid; asymmetric hydrogenation; tiglic acid; fruit-type flavor compound

1. Introduction

S-Methylthio-2-methylbutanoate (**3**) has been found in hops, cheese and melon, and has a tropical fruit-type flavor (*1–3*). However, the absolute configuration of the 2-methyl group in naturally occurring **3** has not been determined, and a synthesis of optically active **3** has not been reported. On the other hand, asymmetric hydrogenation with Ru-BINAP complex catalyst, which has been discovered by Noyori, is one of the most powerful tools for the synthesis of optically active compounds (*4–8*). In particular, asymmetric hydrogenation of 3-substituted-2-propenic acids and substituted alkylidensuccinic acids are well known (*9–11*). Moreover, the syntheses of optically active 2-methylbutanoic acid by asymmetric hydrogenation using Ru-BINAP or Rh complex catalyst with other atropisomeric ligands are reported (*12–18*).

We now report the synthesis of optically active **3** with asymmetric hydrogenation as the key step. The synthetic route is shown in Scheme 1. Optically active 2-methylbutanoic acid *i.e.*, the (*S*)-(+)-2-methylbutanoic acid (**1a**) and (*R*)-(−)-2-methylbutanoic acid (**1b**), were derived from asymmetric hydrogenation of tiglic acid by a previously reported method (*12–18*). Next, **1a** and **1b** were converted to the corresponding acid chlorides **2a** and **2b**. Treatment of the acid chlorides with the methylmercaptan sodium salt in a 15% water furnished *S*-methylthio esters (*S*)-(+)-**3a** and (*R*)-(−)-**3b**, respectively.

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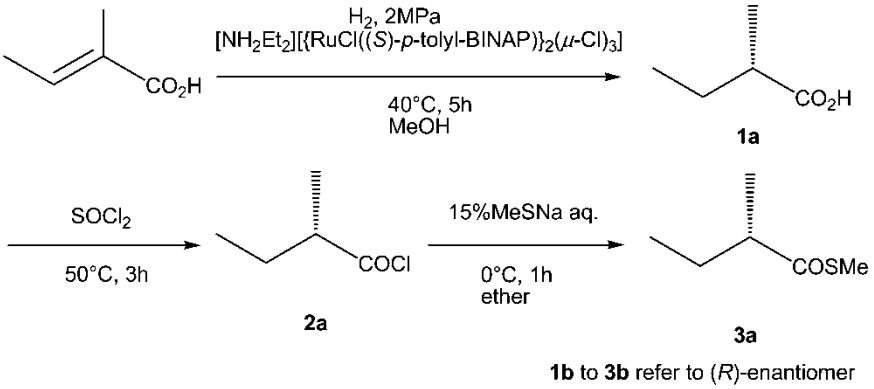

Scheme 1. Synthetic route of optically active S-Methylthio-2-methylbutanoate (3) from tiglic acid.

2. Results and discussion

The (*S*)-(+)-2-methylbutanoic acid **1a** and (*R*)-(−)-**1b** can be obtained from tiglic acid by asymmetric hydrogenation using (*S*)-*p*-tolyl-BINAP and (*R*)-*p*-tolyl-BINAP as the catalysts, respectively (*12, 13*). Derivatization to the corresponding (*R*)-1-(1-naphthyl)ethylamide (*12, 13*), followed by GLC analysis using a chiral column (Figure 1), showed the optical purities of **1a** and **1b** to be 88% ee and 91% ee, respectively.

Next, chiral acids **1a/b** were converted to the corresponding acid chlorides **2a/b** by the usual method using thionyl chloride, and then the distilled chiral acid chlorides in ether were treated with the methylmercaptan sodium salt in a 15% water solution to give optically active 2-methylbutanoic acid methylthio esters **3a** and **3b** good yield (82–86%) without racemization. The optical rotations of (*S*)-(+)-**3a** and (*R*)-(−)-**3b** are observed to be +34.3 and −36.7 respectively. Moreover, the optical purities of **3a** and **3b** as determined by GLC using a chiral column (Chiraldex G-TA, Figure 2), were 86% ee and 90.5% ee, respectively. Therefore, the optical purity of **3a/b** remained similar to that of the precursor acid **1a/b**.

Compound **3a** possesses a sharp, clean, strong top note reminiscent of grapefruit, whereas **3b** has a strong long lasting, fresh scent.

3. Experimental

All reagents and solvents were obtained from commercial sources and used without further purification. Boiling points are uncorrected. The optical rotations were recorded using a JASCO DIP-4 digital polarimeter. NMR spectra were obtained using a Bruker DRX-500. The ^{1}H and ^{13}C NMR spectra were measured at 500 MHz and 125 MHz, respectively. The NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard. The chemical shifts are given in δ (ppm). IR spectra were measured using a Nicolet Avatar 360 FT-IR. MS spectra were recorded using an Hitachi M-80A mass spectrometer at 70 eV. GLC experiments were done using a Shimadzu GC-17A equipped with an FID detector. The column specifications and experimental conditions for the GLC experiments are as follows: Column-1, Neutrabond-1 produced by GL Sciences, Inc., Japan, df = 0.25 μm, 0.25 mm ID × 30 m; carrier gas N_2, 0.1 MPa, oven temperature, 80–230 °C programmed at 5 °C/min; injection temperature, 230 °C, detector temperature, 250 °C. **1** *tr*: 5.2 min., **2** *tr*: 4.1 min., **3** *tr*: 6.7 min. For the (*R*)-(+)-α-(1-Naphthyl)ethylamide of (*S*)-**1a** *tr*: 18.5 min.

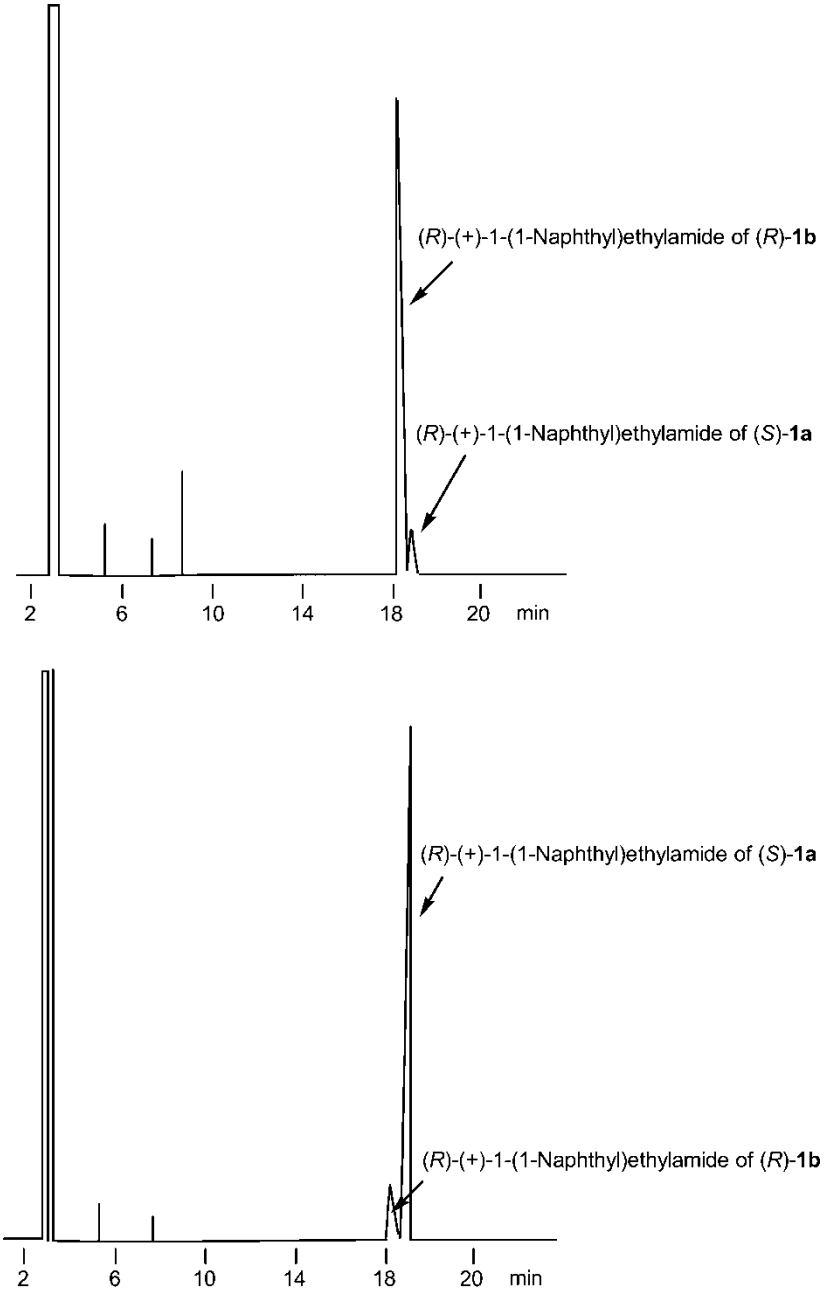

Figure 1. GC chromatogram of chirality of (**1**). GC conditions are described in the Experimental Section.

For the (*R*)-(+)-α-(1-Naphthyl)ethylamide of (*R*)-**1a** *tr*: 18.2 min. Column-2, Chiraldex G-TA produced by Advanced Separation Technologies, Inc. (ASTEC), USA, df = 0.25 μm, 0.25 mm ID × 30 m; carrier gas He, 0.1 MPa, oven temperature, 70 °C (10 min) and 70–150 °C programmed at 1 °C/min; injection temperature, 230 °C, detector temperature, 250 °C. (*S*)-**3a** *tr*: 23.7 min. (*R*)-**3b** *tr*: 23.4 min.

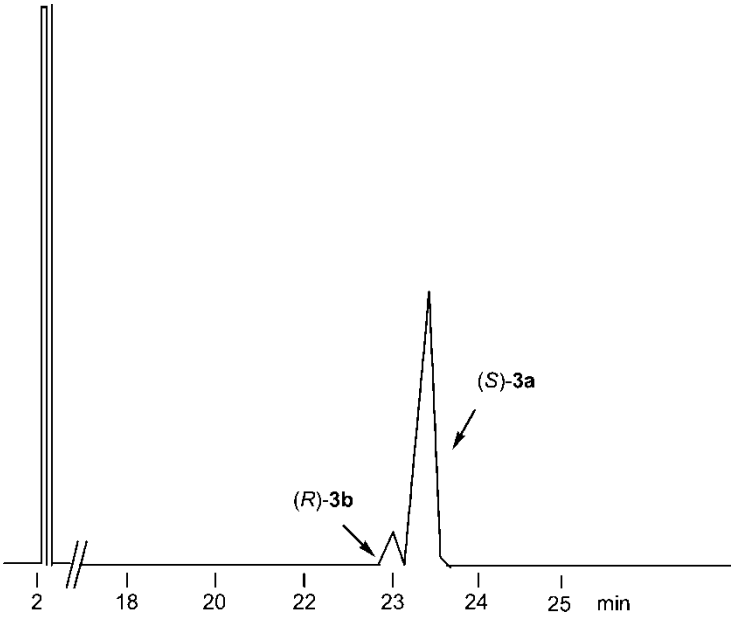

Figure 2. GC chromatogram of chirality of (**3**). GC conditions are described in the Experimental Section.

3.1. *(S)-(+)-2-Methylbutanoic acid (1a)*

Into a 500 mL autoclave were added tiglic acid (100 g, 1.0 mol) in MeOH (200 mL) and $[NH_2Et_2][\{RuCl((S)\text{-}p\text{-tolyl-BINAP})\}_2(\mu\text{-Cl})_3]$ (*19*) (120 mg, 0.132 mmol) under an atmosphere of N_2. The atmosphere was then replaced with H_2 at a pressure of 2 MPa. The reaction mixture was stirred for 5 h at 40 °C. The reaction solution was concentrated *in vacuum* and the residue was distilled under reduced pressure to give **1a** as a colourless oil (96 g, 93.5%, bp. 45 °C/0.1 torr). For measurement of the enantiomeric purity by GC, **1a** was converted into the corresponding (*R*)-(+)-α-(1-naphthyl)ethylamide. The optical purity was 87% ee. $[\alpha]_D^{20}$: = +16.3 (neat). IR (neat) νcm^{-1}: 2972, 2939, 2880, 1708, 1465, 1418, 1229 cm^{-1}. ^{1}H NMR: 0.95 (t, J = 7.5 Hz, 3H), 1.18 (d, J = 7 Hz, 3H), 1.48–1.53 (m, 1H), 1.69–1.74 (m, 1H), 2.38–2.43 (m, 1H). ^{13}C NMR: 11.5 (CH_3), 16.3 (CH_3), 26.5 (CH_2), 40.9 (CH), 183.2 (CO).

3.2. *(R)-(−)-2-Methylbutanoic acid (1b)*

Following a method similar to that described for **1a**, the (*R*)-enantiomer **1b** was prepared from tiglic acid (94% yield). The optical purity was 91% ee. $[\alpha]_D^{20} = -17.2$ (neat). The NMR spectra data were identical to that observed for **1a**.

3.3. *(S)-2-Methylbutanoic acid chloride (2a)*

In a 200 mL flask was added **1a** (35 g, 350 mmol) under N_2. Thionyl chloride (50.0 g, 420 mmol) was added over 3 h at 50°C. The reaction temperature was raised to 80 °C and the solution stirred for 1 h. The excess thionyl chloride was evaporated off and the residue was distilled under reduced pressure to give **2a** as colourless oil (40.4 g, 96%, bp. 35°C/0.1 torr). IR (neat) νcm^{-1}: 2974, 2940, 2881, 1794, 1460, 1384, 1139, 924 cm^{-1}. ^{1}H NMR: 0.98 (t, J = 7.5 Hz, 3H), 1.29 (d, J = 6.9 Hz, 3H), 1.58–1.66 (m, 1H), 1.79–1.87 (m, 1H), 2.78–2.85 (m, 1H). ^{13}C NMR: 11.5 (CH_3), 16.9

(CH_3), 26.9 (CH_2), 53.3 (CH), 178.1(CO). MS: (m/z, relative intensity) 123 ($M^+ + 3$, 3%), 121 ($M^+ + 1$, 2) 105 (2), 94 (7), 92 (21), 85 (52), 57 (100), 41 (39), 29 (30).

3.4. *(R)-2-Methylbutanoic acid chloride (2b)*

Following a method similar to that described for the synthesis of **2a**, the (*R*)-enantiomer **2b** was prepared from (*R*)-(+)-2-methylbutanoic acid **1b** (92% yield). The spectral data were identical to that observed for **2a**.

3.5. *S-Methylthio-(S)-(+)-2-methylbutanoate (3a)*

Into a 200 mL flask were added the methylmercaptan sodium salt in a 15% water solution (75 g) and ether (100 mL). To this solution, **2a** (16.1 g, 121 mmol) was dropwise added over 1 h at 0 °C with vigorous stirring under N_2. The reaction mixture was separated and washed with brine. The ether was removed and the residue was distilled under reduced pressure to give **3a** as colourless oil (15.1 g, 86%, bp. 32°C/5 torr). $[\alpha]_D^{20} = +34.3$ (neat). IR (neat) νcm^{-1}: 2974, 2940, 2881, 1794, 1460, 1384, 1139, 924 cm^{-1}. ^{1}H NMR: 0.98 (t, $J = 7.5$ Hz, 3H), 1.29 (d, $J = 6.9$ Hz, 3H), 1.58–1.66 (m, 1H), 1.79–1.87 (m, 1H), 2.78–2.85 (m, 1H). ^{13}C NMR: 11.5 (CH_3), 16.9 (CH_3), 26.9 (CH_2), 53.3 (CH), 178.1 (CO). MS: (m/z, relative intensity) 133 ($M^+ + 1$, 5%), 132 (M^+, 6) 117 (9), 85 (84), 75 (13), 57 (100), 41 (36), 29 (22).

3.6. *S-Methylthio-(R)-(−)-2-methylbutanoate (3b)*

Following that the method described for the synthesis of **3a**, the (*R*)-enantiomer **3b** was prepared from the (*R*)-(+)-2-methylbutanoic acid chloride **2b** (82% yield). $[\alpha]_D^{20} = -36.7$ (neat). The spectral data were identical to that observed for **3a**.

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