Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2669–2675

TETRAHEDRON: *ASYMMETRY*

Absolute configuration of 2-methoxy-2-(2-naphthyl)propionic acid as determined by the ^{1}H NMR anisotropy method

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Received 21 March 2000; accepted 8 June 2000

Abstract

2-Methoxy-2-(2-naphthyl)propionic acid **1** and 2-hydroxy-2-(2-naphthyl)propionic acid **2** were prepared by the Grignard reaction of 2-naphthylmagnesium bromide with (1*R*,2*S*,5*R*)-(–)-menthyl pyruvate. The absolute configurations of (+)-**1** and (+)-**2** were determined to be *S* by the ^{1}H NMR anisotropy method.

1. Introduction

The importance of single-enantiomer drugs is increasing today. Novel enantiomeric resolution reagents are useful for 'racemic switch' applications and structure determination of biologically active natural products. In 1989, Terunuma and Nohira stated the requirements for an enantiomeric resolution reagent:[1] (A) high enantiomeric purity; (B) chemically stable stereogenic center; (C) equal reactivity for both enantiomers; and (D) suitable separation ability. Considering these requirements, 2-methoxy-2-(2-naphthyl)propionic acid (MβNP acid, **1**) and 2-methoxy-2-(1-naphthyl)propionic acid (MαNP, **3**) were designed as enantiomeric resolution reagents that possess high resolution characteristics and a stable stereogenic center (Fig. 1). Goto et al. synthesized both enantiomers of **1** and **3**, and used them for the enantiomeric resolution of methyl esters of aminoic acids.[2,3] One of the authors used **3** for the enantiomeric resolution of monoterpene alcohols.[4] The absolute configuration of **3** was determined by X-ray crystallography[5] and the ^{1}H NMR anisotropy method,[6] along with that of 2-hydroxy-2-(1-naphthyl)propionic acid (HαNP acid, **4**).[6] This paper reports the absolute configuration of 2-methoxy-2-(2-naphthyl)propionic acid (MβNP, **1**) and 2-hydroxy-2-(2-naphthyl)propionic acid (HβNP acid, **2**) as determined by the ^{1}H NMR anisotropy acid method (Fig. 1).

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0957-4166/00/$ - see front matter
PII: S0957-4166(00)00233-0

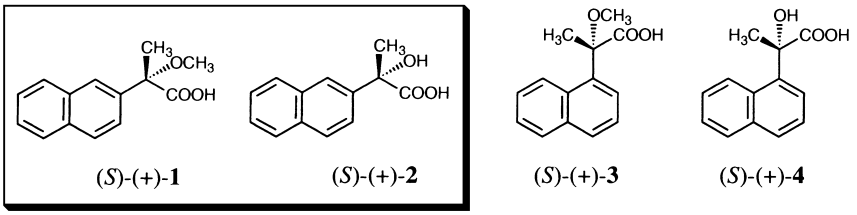
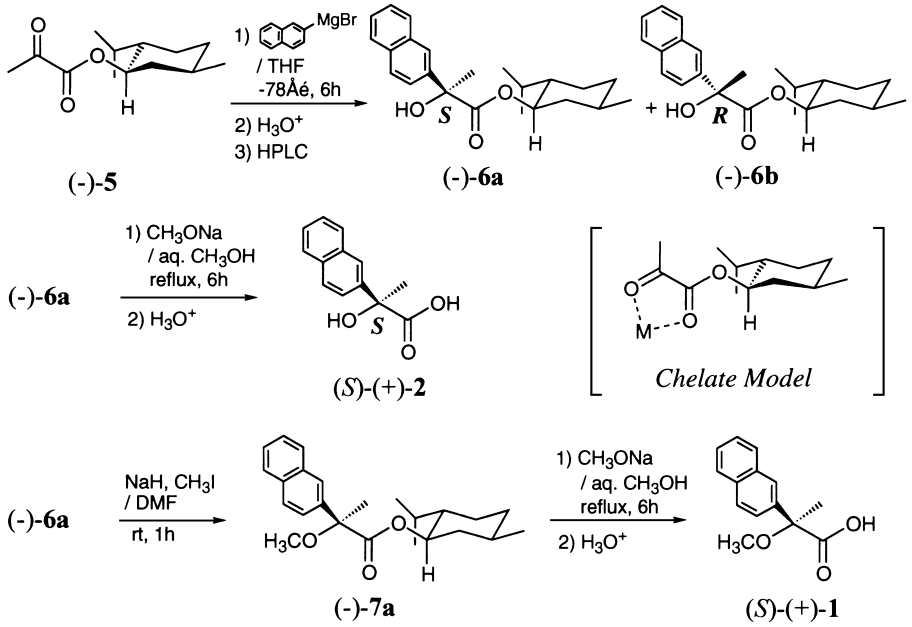


Figure 1. The absolute configurations of the naphthylpropionic acid derivatives **1**, **2**, **3** and **4**

2. Results and discussion

In 1953, Prelog reported that the Grignard addition to (1*R*,2*S*,5*R*)-(–)-menthyl pyruvate (–)-**5** prefers the *Si*-face.[7] This stereoselectivity is rationalized by 'Prelog's rule', which has been cited as the basic rule for the 1,4-asymmetric induction reaction. The *s-trans* conformation[7] had been adopted to explain the stereoselectivity of the Grignard reaction preferring the *Si* face of (–)-**5**. Recent studies on the reduction of pyruvate esters have proposed the *s-cis* chelate models[8,9] to explain the *Si*-face selectivity (Scheme 1). The Grignard reaction of 2-naphthylmagnesium bromide with (–)-**5** gave two diastereomers of (1*R*,2*S*,5*R*)-menthyl 2-hydroxy-2-(2-naphthyl)propionate **6a** (15%) and **6b** (10%) together with recovered (–)-**5** (63%) (Scheme 1). The separation was achieved by preparative reversed phase HPLC (Capcellpak C18 AG120/5 μm, acetonitrile:water, 9:1), giving the first and second eluted esters, (–)-**6a** (95% d.e. (determined by the ^{1}H NMR spectrum), $[\alpha]_D^{30}$ =–52 (*c* 0.75, ethanol)) and (–)-**6b** (97% d.e., $[\alpha]_D^{30}$ =–85 (*c* 0.28, ethanol)). The hydroxyl protons of (–)-**6a** and (–)-**6b** in the ^{1}H NMR spectra (3.96 ppm and 4.01 ppm, respectively) and their absorption maxima in the IR spectra (1715 cm^{-1}) reveal intramolecular hydrogen



Scheme 1. Preparation of MβNP and related compounds

bonds. The ^{1}H NMR chemical shifts of the Grignard adducts (–)-**6a** and (–)-**6b** are assigned in Fig. 2 by the two-dimensional NMR spectra (COSY, CH-COSY, HMBC, HOHAHA, and NOESY). The $\Delta\delta$ ($=\delta R-\delta S$) values are shown in Fig. 3. The distribution of the $\Delta\delta$ values shows that the absolute configuration of HβNP in the major diastereomer, (–)-**6a**, is the *S*-configuration (Fig. 2). This stereoselectivity coincides with the early observation by Prelog (vide ante). The alkaline hydrolysis of the major Grignard adduct (–)-**6a** gave (*S*)-(+)-2-hydroxy-2-(2-naphthyl)-propionic acid ((*S*)-(+)-**2**, $[\alpha]_D^{29}=+38$ (*c* 0.07, ethanol)).

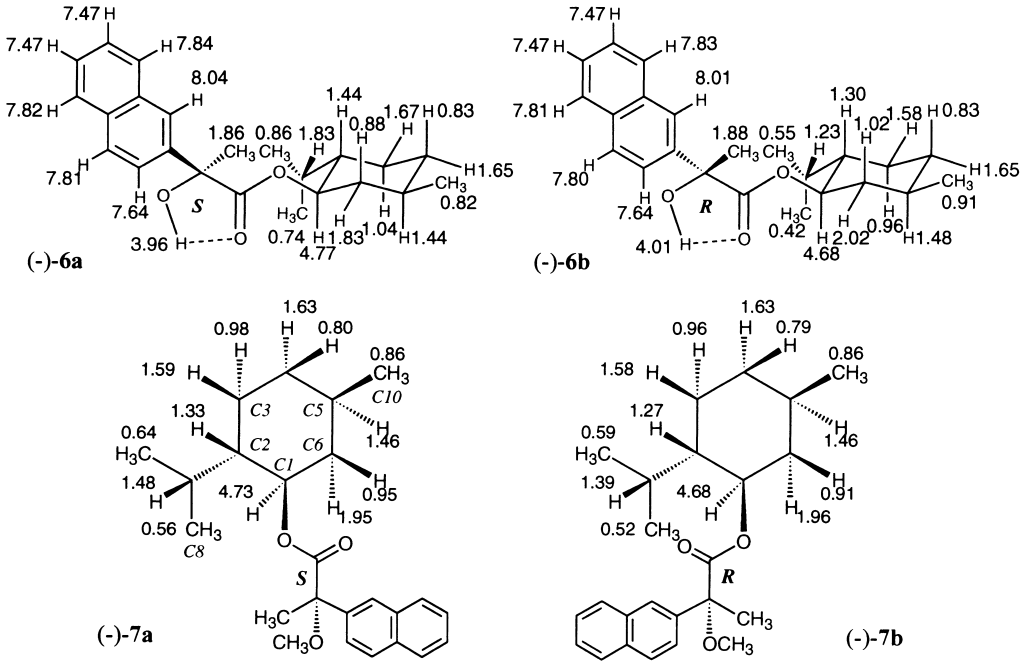


Figure 2. The ^{1}H NMR chemical shifts of Grignard adducts (–)-**6a** and (–)-**6b** and their methyl ethers (–)-**7a** and (–)-**7b** (600 MHz, $CDCl_3$)

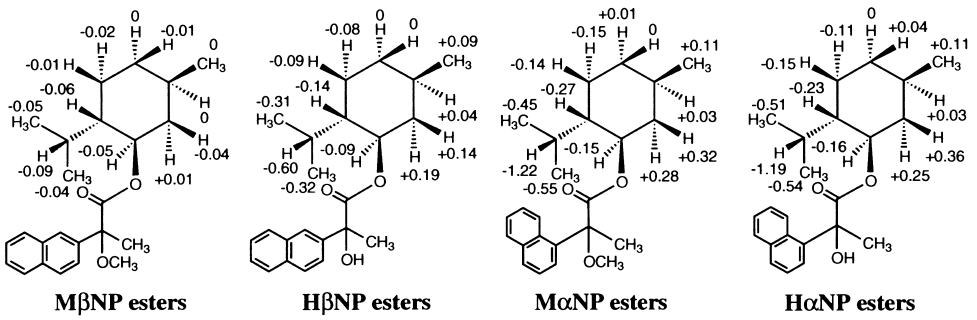


Figure 3. The ^{1}H NMR $\Delta\delta$ ($=\delta(R)-\delta(S)$) values of MβNP, HβNP, MαNP, and HαNP esters of (1*R*,2*S*,5*R*)-(–)-menthol (600 or 400 MHz, $CDCl_3$)

The hydroxyl groups of the major Grignard adduct (–)-**6a** were methylated by NaH and CH_3I in DMF, giving (–)-**7a** ($[\alpha]_D^{29} = -49$ (*c* 0.29, ethanol)). The minor Grignard adduct (–)-**6b** gave (–)-**7b** ($[\alpha]_D^{30} = -89$ (*c* 0.17, ethanol)) by the same methylation reaction. The ^{1}H NMR signals of (–)-**7a** and (–)-**7b** were assigned from two-dimensional NMR spectra (COSY, CH-COSY, HMBC, HOHAHA, and NOESY) as shown in Fig. 2. There was no systematic rule for the distribution of $\Delta\delta$ ($=\delta R-\delta S$) values obtained from the two methyl ethers (–)-**7a** and (–)-**7b**. Their ^{1}H NMR chemical shifts were close: ((–)-**7a**) C2β proton; 0.95 ppm, isopropyl group; 0.56 ppm, 0.64 ppm, 1.48 ppm ((–)-**7b**) C2β proton; 0.91 ppm, isopropyl group; 0.52 ppm, 0.59 ppm, 1.39 ppm. These chemical shifts show that the methyl ethers (–)-**7a** and (–)-**7b** are the conformational mixtures for the C(=O)–Cα bonds. The $\Delta\delta$ values obtained for (*S*)- and (*R*)-MβNP esters of (1*R*,2*S*,5*R*)-(–)-menthol suggest that MβNP acid is not suitable for Mosher–Trost-type analyses[10,11] of the absolute configurations of secondary alcohols. Compounds (–)-**7a** and (–)-**7b** can be separated by reversed phase HPLC analysis (Capcellpak C18 AG120 /5 μm, methanol:water, 8:1) and normal phase HPLC analysis (Silica SG80, hexane:ethanol, 199:1). The alkaline hydrolysis of (–)-**7a** gave 2-methoxy-2-(2-naphthyl)propionic acid (*S*)-(+)-**1**, $[\alpha]_D^{30} = +47$ (*c* 0.14, ethanol).

Fig. 3 shows the $\Delta\delta$ ($=\delta R-\delta S$) values of the MβNP, HβNP, MαNP, and HαNP esters of (1*R*,2*S*,5*R*)-(–)-menthol in the ^{1}H NMR spectra. The $\Delta\delta$ values of the HαNP esters and the HβNP esters are positive at the C5 and C6 positions of the menthyl group, and negative at C2, C3, and the isopropyl group. These phenomena show that the methine protons at C1 position of the menthyl group, the carbonyl group, and the hydroxyl group are located in the same plane in the HβNP esters and the HαNP esters (see Fig. 2). The $\Delta\delta$ values of the MαNP esters are very close to those of the HαNP esters, suggesting that the MαNP esters' conformations are similar to those of the HαNP esters, in spite of the absence of hydrogen bonds. As already discussed, the MβNP esters of (1*R*,2*S*,5*R*)-(–)-menthol are the conformational mixtures.

In this paper, the absolute configurations of (+)-2-methoxy-2-(2-naphthyl)propionic acid (+)-**1** and (+)-2-hydroxy-2-(2-naphthyl)propionic acid (+)-**2** were determined to be *S*. In addition, the conformations of the HβNP esters of (1*R*,2*S*,5*R*)-(–)-menthol (–)-**6a** and (–)-**6b** were determined by the ^{1}H NMR anisotropy method. MβNP acid will contribute to the exploratory research of agrochemicals and medicines, along with MαNP acid.

3. Experimental

3.1. General

The NMR spectra were obtained using either a JEOL JNM α 600 or a Bruker ARX 400, in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. The IR spectra were recorded on a Perkin–Elmer 1760X. The MS data were obtained with a JEOL JMS SX102A. 3-Nitrobenzyl alcohol was used as the matrix for FAB-MS measurement. The optical rotations were determined on a JASCO DIP1000 spectropolarimeter. Kieselgel 60 (Merck) and Wakogel C-200 (Wako) were used for the open column chromatography.

3.2. Grignard reaction

A solution of (–)-**5** (430 mg, 1.9 mmol) in 2 ml of THF in a dried flask, under nitrogen, was cooled to –78°C and treated with 2-naphthylmagnesium bromide (1.9 mmol in 2 ml of THF,

uncorrected). After 6 h, the reaction mixture was quenched by addition of 2.5 ml of 5% HCl, worked up with AcOEt and water, and dried (Na_2SO_4). The solution was evaporated, and the residue was purified by open column chromatography to give the mixture of (–)-**6a** and (–)-**6b** (15 and 10%, respectively). The adducts (–)-**6a** and (–)-**6b** were separated by preparative reversed phase HPLC.

*3.2.1. (1*R*,2*S*,5*R*)-Menthyl (*S*)-2-hydroxy-2-(2-naphthyl)propionate (–)-**6a***

^{1}H NMR (600 MHz): 8.04 (1H, br s), 7.84 (1H, m), 7.82 (1H, m), 7.81 (1H, d, J=9 Hz), 7.64 (1H, dd, J=9, 1.5 Hz), 7.47 (2H, m), 4.77 (1H, td, J=11, 4 Hz), 3.96 (1H, s), 1.86 (3H, s), 1.83 (2H, m), 1.67 (1H, m), 1.65 (1H, m), 1.44 (1H, tt, J=11, 4 Hz), 1.44 (1H, m), 1.04 (1H, qd, J=11, 4 Hz), 0.88 (1H, m), 0.86 (3H, d, J=6.5 Hz), 0.83 (1H, m), 0.82 (3H, d, J=6.5 Hz), 0.74 (3H, d, J=6.5 Hz); ^{13}C NMR (151 MHz): 175.2 (s, C1′), 140.3 (s, C2″), 133.0 (s, C8″a), 132.8 (s, C4″a), 128.3 (d, C8″), 127.9* (d, C5″), 127.5* (d, C4″), 126.1 (d, C6″), 126.1 (d, C7″), 124.0 (d, C1″), 123.5 (d, C3″), 76.8 (d, C1), 75.9 (s, C2′), 47.0 (d, C2), 40.2 (t, C6), 34.1 (t, C4), 31.3 (d, C5), 26.5 (q, C3′), 26.1 (d, C7), 23.2 (t, C3), 21.8 (q, C10), 20.7 (q, C9), 16.0 (q, C8), *: exchangable; IR ($CHCl_3$ solution in NaCl cell): 3525 cm^{-1}, 2950, 2920, 2870, 1715, 1455, 1375, 1260, 1245, 1180, 1140, 955, 905, 815; MS (FAB) m/z: 377 ([M+Na]$^{+1}$, 12%), 337 (12), 224 (5), 221 (7), 199 (88), 171 (100), 155 (16), 153 (16), 139 (20); $[\alpha]_D^{30}$ =–52 (c 0.75, ethanol).

*3.2.2. (1*R*,2*S*,5*R*)-Menthyl (*R*)-2-hydroxy-2-(2-naphthyl)propionate (–)-**6b***

^{1}H NMR (600 MHz): 8.01 (1H, br s), 7.83 (1H, m), 7.81 (1H, m), 7.80 (1H, d, J=9 Hz), 7.64 (1H, dd, J=9, 1.5 Hz), 7.47 (2H, m), 4.68 (1H, td, J=12, 3 Hz), 4.01 (1H, s), 2.02 (1H, br d, J=12 Hz), 1.88 (3H, s), 1.65 (1H, br d, J=12 Hz), 1.58 (1H, dq, J=12, 3 Hz), 1.48 (1H, tt, J=12, 4 Hz), 1.30 (1H, tt, J=12, 3 Hz), 1.23 (1H, m), 1.02 (1H, q, J=12 Hz), 0.96 (1H, qd, J=12, 4 Hz), 0.91 (3H, d, J=6.5 Hz), 0.83 (1H, qd, J=12, 3 Hz), 0.55 (3H, d, J=6.5 Hz), 0.42 (3H, d, J=6.5 Hz); ^{13}C NMR (151 MHz): 175.5 (s, C1′), 140.1 (s, 2″), 133.0 (s, C8″a), 132.8 (s, C4″a), 128.2 (d, C8″), 127.8* (d, C5″), 127.5* (d, C4″), 126.1 (d, C6″), 126.1 (d, C7″), 124.3 (d, C1″), 123.6 (d, C3″), 76.8 (d, C1), 75.7 (s, C2′), 47.1 (d, C2), 40.6 (t, C6), 34.1 (t, C4), 31.4 (d, C5), 26.1 (q, C3′), 25.6 (d, C7), 23.0 (t, C3), 21.9 (q, C10), 20.5 (q, C9), 15.6 (q, C8), *: exchangable; IR ($CHCl_3$, NaCl): 3565 cm^{-1}, 2960, 2930, 2870, 1715, 1540, 1510, 1450, 1375, 1260, 1245, 1180, 1140, 955, 815; MS (FAB) m/z: 377 ([M+Na]$^{+1}$, 42%), 354 (8), 337 (25), 221 (10), 216 (6), 199 (80), 171 (100), 139 (19); $[\alpha]_D^{30}$ =–85 (c 0.28, ethanol).

*3.3. Methylation of (–)-**6a**; preparation of (–)-**7a***

NaH (60% in oil,188 mg) was washed with THF (0.5 ml×3) and suspended in DMF (1 ml). The suspension was added to (–)-**6a** (9 mg) and an excess of CH_3I (0.5 ml) followed. The mixture was stirred for 60 min, then CH_3I was removed by nitrogen. The mixture was diluted with ice-water (5 ml), and extracted with AcOEt (0.5 ml×3). The solution was washed with brine and dried over Na_2SO_4. After concentration in vacuo, the residual DMF solution was subjected to SiO_2 column chromatography to afford (–)-**7a**. The yield was 60%.

*3.3.1. (1*R*,2*S*,5*R*)-Menthyl (*S*)-2-methoxy-2-(2-naphthyl)propionate (–)-**7a***

^{1}H NMR (600 MHz): 7.95 (1H, br s), 7.83 (1H, m), 7.81 (2H, m), 7.57 (1H, dd, J=9, 1 Hz), 7.47 (2H, m), 4.73 (1H, td, J=12, 4 Hz), 3.35 (3H, s), 1.95 (1H, br d, J=12 Hz), 1.86 (3H, s), 1.63 (1H, br d, J=12 Hz), 1.59 (1H, dq, J=12, 3 Hz), 1.48 (1H, m), 1.46 (1H, m), 1.33 (1H, tt, J=12, 3 Hz), 0.98 (1H, m), 0.95 (1H, q, J=12 Hz), 0.86 (3H, d, J=6.5 Hz), 0.80 (1H, qd, J=12, 3 Hz),

0.64 (3H, d, $J=6.5$ Hz), 0.56 (3H, d, $J=6.5$ Hz); ^{13}C NMR (151 MHz): 172.5 (s, C1′), 138.7 (s, C2″), 133.0 (s, C8″a), 132.8 (s, C4″a), 128.3 (d, C8″), 127.9* (d, C5″), 127.5* (d, C4″), 126.1 (d, C6″), 126.1 (d, C7″), 124.8 (d, C1″), 123.7 (d, C3″), 82.0 (s, C2′), 75.5 (d, C1), 52.1 (q, -OCH_3), 46.9 (d, C2), 40.5 (t, C6), 34.2 (t, C4), 31.4 (d, C5), 25.6 (d, C7), 23.0 (t, C3), 22.2 (q, C3′), 22.0 (q, C10), 20.6 (q, C9), 15.7 (q, C8), *: exchangable; IR ($CHCl_3$, NaCl): 3000 cm^{-1}, 2960, 2930, 2870, 1725, 1450, 1370, 1265, 1185, 1135, 955, 820; MS (EI): 368 (M^+, 3%), 186 (13), 185 (100), 155 (18), 127 (2); $[\alpha]_D^{29}=-49$ (*c* 0.29, ethanol).

*3.4. Methylation of (–)-**6b**; preparation of (–)-**7b***

Compound (–)-**7b** was prepared from (–)-**6b** (12 mg) by the method used for the preparation of (–)-**7a**. The yield was 60%.

*3.4.1. (1*R*,2*S*,5*R*)-Menthyl (*R*)-2-methoxy-2-(2-naphthyl)propionate (–)-**7b***

^{1}H NMR (600 MHz): 7.93 (1H, br s), 7.83 (1H, m), 7.82 (2H, m), 7.58 (1H, br d, $J=9$ Hz), 7.48 (2H, m), 4.68 (1H, td, $J=12$, 4 Hz), 3.32 (3H, s), 1.96 (1H, br d, $J=12$ Hz), 1.88 (3H, s), 1.63 (1H, br d, $J=12$ Hz), 1.58 (1H, dq, $J=12$, 3 Hz), 1.46 (1H, m), 1.39 (1H, m), 1.27 (1H, tt, $J=12$, 3 Hz), 0.96 (1H, m), 0.91 (1H, m), 0.86 (3H, d, $J=6.5$ Hz), 0.79 (1H, qd, $J=12$, 3 Hz), 0.59 (3H, d, $J=6.5$ Hz), 0.52 (3H, d, $J=6.5$ Hz); ^{13}C NMR (151 MHz): 172.6 (s, C1′), 138.3 (s, C2″), 133.1 (s, C8″a), 132.9 (s, C4″a), 128.2 (d, C8″), 127.9* (d, C5″), 127.5* (d, C4″), 126.2** (d, C6″), 126.1** (d, C7″), 125.3 (d, C1″), 124.1 (d, C3″), 81.7 (s, C2′), 75.5 (d, C1), 52.0 (q, -OCH_3), 46.9 (d, C2), 40.5 (t, C6), 34.2 (t, C4), 31.4 (d, C5), 25.6 (d, C7), 23.0 (t, C3), 22.0 (q, C10), 21.7 (q, C3′), 20.5 (q, C9), 15.6 (q, C8), * and **: exchangable; IR ($CHCl_3$, NaCl): 3000 cm^{-1}, 2960, 2930, 2870, 1725, 1450, 1370, 1265, 1185, 1140, 960, 825; MS (EI): 368 (M^+, 3%), 186 (13), 185 (100), 155 (18), 127 (2); $[\alpha]_D^{30}=-89$ (*c* 0.17, ethanol).

*3.5. Alkaline hydrolysis of (–)-**6a**; preparation of (S)-(+)-2-hydroxy-2-(2-naphthyl)propionic acid (+)-**2***

The solution of sodium methoxide (250 mg) in aqueous methanol (2 ml) was added to (–)-**6a** (16 mg), and the mixture was heated to reflux for 6 h. After elimination of the solvent at reduced pressure, the residue was diluted with water, and washed with AcOEt (3 ml×3). The aqueous solution was acidified by 5% HCl and extracted with AcOEt (5 ml×3). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. Filtration through a short silica gel column afforded (+)-**2**. The yield was 99%. $[\alpha]_D^{29}=+38$ (*c* 0.07, ethanol).

*3.6. Alkaline hydrolysis of (–)-**7a**; preparation of (S)-(+)-2-methoxy-2-(2-naphthyl)propionic acid (+)-**1***

Compound (+)-**1** was prepared from (–)-**7b** (12 mg) by the method used for the preparation of (+)-**2** in 89% yield. $[\alpha]_D^{30}=+47$ (*c* 0.14, ethanol).

Acknowledgements

A.I. would like to thank Dr. T. Nishide, Dr. H. Kato, and Dr. Y. Magoshi for their support.

References

1. Terunuma, D.; Nohira, H. In *Methods of Determining Optical Purity*; Okamoto, Y.; Osa, T.; Nakai, T.; Nohira, H.; Murakami, N.; Yamada, H., Eds.; Kikan Kagaku Sosetsu, Vol. 6. Resolution of optical isomers (in Japanese with English summaries). Japan Scientific Societies Press: Tokyo, 1989; pp. 188–197.
2. Goto, J.; Hasegawa, M.; Nakamura, S.; Shimada, K.; Nambara, T. *Chem. Pharm. Bull.* **1977**, *25*, 847.
3. Goto, J.; Hasegawa, M.; Nakamura, S.; Shimada, K.; Nambara, T. *J. Chromatogr.* **1978**, 152.
4. Ichikawa, A. *Chirality* **1999**, *11*, 70.
5. Kuwahara, S.; Fujita, K.; Watanabe, M.; Harada, N.; Ishida, T. *Enantiomer* **1999**, *4*, 141.
6. Ichikawa, A.; Hiradate, S.; Sugio, A.; Kuwahara, S.; Watanabe, M.; Harada, N. *Tetrahedron*: *Asymmetry* **1999**, *10*, 4075; Harada, N.; Watanabe, M.; Kuwahara, S.; Sugio, A.; Kasai, Y.; Ichikawa, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1249.
7. Prelog, V. *Helv. Chim. Acta* **1953**, *36*, 308.
8. Akiyama, T.; Nishimoto, H.; Kuwata, T.; Ozaki, S. *Bull. Chem. Soc. Japan* **1994**, *67*, 180.
9. Xiang, Y. B.; Snow, K.; Belley, M. *J. Org. Chem.* **1993**, *58*, 993.
10. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
11. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.