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

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Abstract

Enantiopure 2-hydroxy-2-(1-naphthyl)propionic acid (+)-**2** was prepared by the stereoselective Grignard reaction of 1-naphthylmagnesium bromide with (1*R*,3*R*,4*S*)-menthyl pyruvate **3** or (1*R*,3*R*,4*S*)-8-phenylmenthyl pyruvate **4**, and the absolute configuration of acid (+)-**2** was unambiguously determined to be *S* by the ^{1}H NMR anisotropy method.

2-Methoxy-2-(1-naphthyl)propionic acid **1** (αMNPA) had been designed as a chiral auxiliary useful for enantioresolution of various alcohols (Fig. 1).[1,2] Namely, diastereomeric esters prepared from enantiopure acid **1** and racemic alcohol were separated by HPLC, and from the diastereomer separated, enantiopure alcohol was recovered. One of the authors has succeeded in the enantioresolution of (±)-citronellol and (±)-3,7-dimethyl-1-octanol by this method.[3] The merit of this chiral auxiliary is that the α-position of the carboxylic acid group, the stereogenic center of acid **1**, is fully substituted and is, therefore, inert towards racemization. In addition, αMNPA **1** may be useful as a chiral auxiliary[4] for determining the absolute stereochemistry of chiral alcohols by ^{1}H NMR anisotropy methods.[5,6] On the other hand, 2-hydroxy-2-(1-naphthyl)propionic acid **2** (αHNPA) may be another possible chiral auxiliary for the ^{1}H NMR anisotropy method. In this paper, we report the preparation of enantiopure 2-hydroxy-2-(1-naphthyl)propionic acid (+)-**2** and the determination of its absolute configuration by the ^{1}H NMR anisotropy method.

(1*R*,3*R*,4*S*)-(−)-Menthyl pyruvate **3** ($[\alpha]_D^{30}$ −94.0 (*c* 1.14, $CHCl_3$)) was prepared by heating a mixture of (1*R*,3*R*,4*S*)-(−)-menthol and pyruvic acid with *p*-toluenesulfonic acid in toluene. The reaction of 1-naphthylmagnesium bromide (1.0 equiv.) with (−)-menthyl pyruvate **3** in tetrahydrofuran (THF) at −40°C yielded a diastereomeric mixture of menthyl 2-hydroxy-2-(1-naphthyl)propionate **4** (65%) together with

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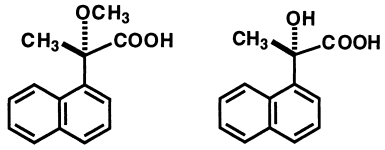
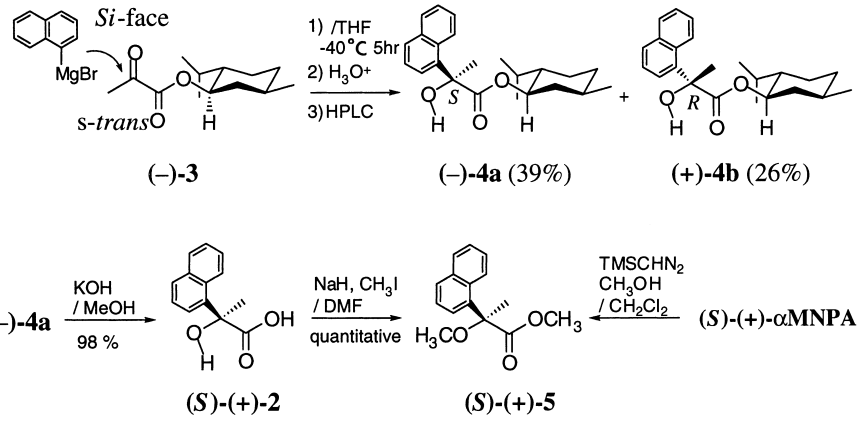


(*S*)-(+)-**1** (*S*)-(+)-**2**

Figure 1. (*S*)-(+)-2-Methoxy-2-(1-naphthyl)propionic acid **1** and (*S*)-(+)-2-methoxy-2-(1-naphthyl)propionic acid **2**

recovered **3** (16%) (Scheme 1).[7] The diastereomeric mixture of **4** was separated by reverse phase HPLC (CAPCELL PAK C18 AG120/5 μm, MeOH:H_2O, 85:15) giving the first-eluted ester (−)-**4a** (39%, $[\alpha]_D^{29}$ −84.0 (*c* 0.48, $CHCl_3$)) and the second-eluted (+)-**4b** (26%, $[\alpha]_D^{30}$ +7.6 (*c* 0.32, $CHCl_3$)). The configuration and conformation of esters (−)-**4a** and (+)-**4b** were determined as follows: the two-dimensional (2D) NMR spectra including COSY, CH-COSY, HOHAHA, HMBC, and NOESY were measured leading to the full assignment of all signals as shown in Fig. 2. The hydroxyl proton peaks of esters (−)-**4a** and (+)-**4b** appeared as sharp singlet peaks at δ 3.67 and 3.78 ppm, respectively, indicating intramolecular hydrogen bonding with the ester carbonyl oxygen. The hydrogen bonding was also supported by the lower shift of the carbonyl stretching bands in IR spectra; both hydroxyl esters (−)-**4a** and (+)-**4b** exhibit C=O bands in $CHCl_3$ at 1713 and 1716 cm^{-1}, respectively: in KBr, both exhibit at 1720 cm^{-1}. On the other hand, (1*R*,3*R*,4*S*)-menthyl 2-methoxy-2-(1-naphthyl)propionates prepared from (−)-menthol and 2-methoxy-2-(1-naphthyl)propionic acid (±)-**1** exhibit the corresponding bands at 1750 cm^{-1} in KBr. The rotational conformation around the C1′–C2′ single bond is thus fixed in esters (−)-**4a** and (+)-**4b** as illustrated in Fig. 2.



Scheme 1. Preparation of (*S*)-(+)-αHNPA and related compounds

In the ^1H NMR spectra, the 2-axial proton of diastereomer (−)-**4a** appears at δ 0.51 ppm, while that of (+)-**4b** appears at δ 0.87 ppm (Fig. 2). Namely, a high field shift of 0.36 ppm is observed in (−)-**4a**, because the 2-axial proton is above the naphthalene plane and subject to the diamagnetic ring current effect. In addition, the NOESY data shown in Fig. 2 indicate that the methyl group of the acid moiety is close to the isopropyl group at the 4-position in (−)-**4a**. On the other hand, protons of the isopropyl group of (+)-**4b** appear at a higher field than those of (−)-**4a**: for (+)-**4b**, 8-CH_3, δ 0.13 and 0.26 ppm, 8-H, δ 0.46 ppm; for (−)-**4a**, 8-CH_3, δ 0.67 and 0.77 ppm, 8-H, δ 1.65 ppm. Therefore, the naphthyl group of (+)-**4b** is close to the isopropyl group at the 4-position. From these results, the absolute configurations of the acid moieties in esters (−)-**4a** and (+)-**4b** are unambiguously determined as *S* and *R*, respectively. The stereochemical assignment obtained is consistent with that derived from Prelog's rule.[7]

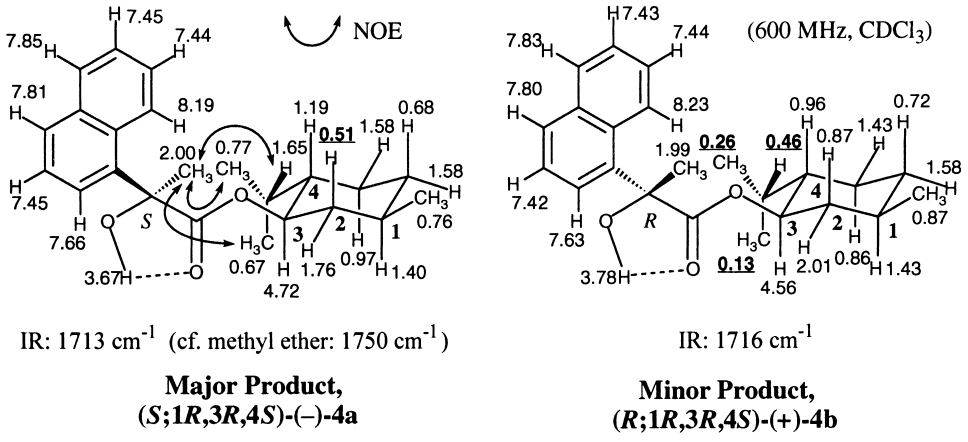
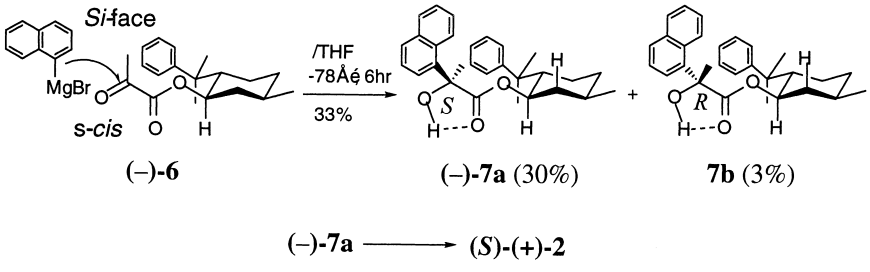


Figure 2. The NMR chemical shift and NOE data of esters (−)-**4a** and (+)-**4b**

Alkaline hydrolysis of ester (−)-**4a** gave enantiopure 2-hydroxy-2-(1-naphthyl)propionic acid (*S*)-(+)-**2** (98%, $[\alpha]_D^{29}$ +40 (*c* 0.21, $CHCl_3$)) (Scheme 1). Methylation of hydroxyl and carboxylic acid groups of (+)-**2** with sodium hydride in dimethyl formamide (DMF) and iodomethane yielded (*S*)-(+)-methyl 2-methoxy-2-(1-naphthyl)propionate **5** (93%, $[\alpha]_D^{30}$ +31 (*c* 0.22, $CHCl_3$)), which was identical to the authentic sample of **5** ($[\alpha]_D^{25}$ +34.8 (*c* 2.62, $CHCl_3$)).[7] The *S* absolute configuration of the authentic methyl ester (+)-**5** had been established by X-ray crystallography and chemical correlation.[8]

The Grignard reaction of 1-naphthylmagnesium bromide (1.0 equiv.) was similarly applied to (1*R*,3*R*,4*S*)-(−)-8-phenylmenthyl pyruvate **6** ($[\alpha]_D^{31}$ −5.2 (*c* 1.04, $CHCl_3$)) at −78°C in THF yielding a diastereomeric mixture of esters **7** (33%), which was separated by reverse phase HPLC (CAPCELL PAK C18 AG120/5 μm, CH_3CN:H_2O, 4:1) giving the first-eluted major ester (−)-**7a** (30%, $[\alpha]_D^{30}$ −51.0 (*c* 0.13, $CHCl_3$)) and the second-eluted minor ester **7b** (3%), while the starting material **6** was also recovered (32%) (Scheme 2). As in the case of esters **4a** and **4b**, most proton NMR peaks of the major product (−)-**7a** were assigned by 2D NMR spectra. The hydroxyl proton captured in the intramolecular hydrogen bonding appeared as a sharp singlet at δ 3.25 ppm. The IR band at 1715 cm^{-1} in $CHCl_3$ also confirmed the intramolecular hydrogen bonding. Since the 2β axial proton of the major ester appeared at δ 0.42 ppm, the absolute configuration of the major product was determined as *S*, which agrees with the reaction mechanism proposed by Whitesell et al.[9] Hydrolysis of ester (−)-**7a** with NaOMe in MeOH afforded α-hydroxy acid (+)-**2** (38%, $[\alpha]_D^{31}$ +35 (*c* 0.02, $CHCl_3$)), which was identical to (*S*)-(+)-**2** derived from ester (−)-**4a**.

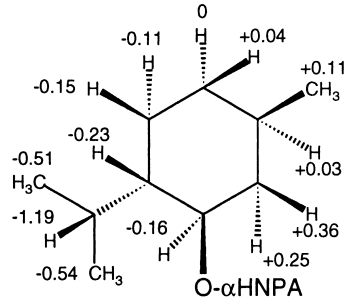


Scheme 2. Preparation of (*S*)-(+)-αHNPA using ester (−)-**6**

As discussed above, the absolute configuration of α-hydroxy acid (+)-**2** was unambiguously determined to be *S* by the ^1H NMR anisotropy method, which was in agreement with the determination using

X-ray crystallography.[8] In light of the present results, the absolute configuration of acid **1** previously reported by one of the authors[3] should be revised.

The data of chemical shift difference ($\Delta\delta=\delta(R)-\delta(S)$) between (*R*)-(+)-**4b** and (*S*)-(−)-**4a** are listed in Fig. 3; based on these anisotropy data and the known absolute configuration of (−)-menthol, the absolute configuration of α-hydroxy acid **2** was determined. These $\Delta\delta$ values are much larger than those reported for (1*R*,3*R*,4*S*)-menthyl α-methoxy-2-naphthylacetates.[5] Therefore, if each enantiomer of α-hydroxy acid **2** can be used for esterification of chiral alcohols, this acid would become a chiral auxiliary powerful enough to determine the absolute configuration of alcohols by the ^{1}H NMR anisotropy data.



$\Delta\delta = \delta(R) - \delta(S)$

Figure 3. The $\Delta\delta$ values for (1*R*,3*R*,4*S*)-(−)-menthol using 2-hydroxy-2-(1-naphthyl)propionic acid: $\Delta\delta=\delta((R)$-(+)-**4b**$)-\delta((S)$-(−)-**4a**$)$ (600 MHz, $CDCl_3$)

Further studies along this methodology are now in progress.

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