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Absolute configurations of 2-methoxy-2-(1-naphthyl)propionic acid and 2-methoxy-2-(2-naphthyl)propionic acid as determined by the phenylglycine methyl ester (PGME) method

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Abstract—The absolute configurations of 2-methoxy-2-(1-naphthyl)propionic acid and 2-methoxy-2-(2-naphthyl)propionic acid were reconfirmed by NMR analyses of phenylglycine methyl ester (PGME) derivatives. Their absolute configurations determined by the PGME method are consistent with those obtained by the ^{1}H NMR anisotropy method and X-ray crystallography.

1. Introduction

The study of single enantiomer drugs is currently of great importance. Novel enantioresolving agents will contribute to racemic switch studies and the structure determination of natural products. We have studied the novel resolving agents, 2-methoxy-2-(1-naphthyl)propionic acid (MαNP acid, **1**)[1–3] and 2-methoxy-2-(2-naphthyl)propionic acid (MβNP acid, **2**) (Fig. 1),[4] which were designed as non-racemizable chiral acids. MαNP acid **1** and MβNP acid **2** are very powerful for the resolution of racemic alcohols and are also useful for the determination of the absolute configuration of homochiral alcohols by the ^{1}H NMR anisotropy method. Goto et al. used acids **1** and **2** for the enantioresolution of amino acid methyl esters.[5,6] The absolute configurations of **1** and **2** were determined by NMR analyses of their precursor (1*R*,2*S*,5*R*)-menthyl esters of the α-hydroxy-carboxylic acids,[1,4] synthesized using the 1,4-chiral induction reactions reported by Prelog[7] (Fig. 1). Using X-ray crystallography, Harada et al.[8] unambiguously determined that the absolute configuration of (+)-**1** is *S*.

Yabuuchi and Kusumi reported the PGME (phenylglycine methyl ester) method[9] to determine the absolute configurations of quaternary α-hydroxy- and α-methoxy-carboxylic acids (Fig. 2 (A)). They proposed the conformations of (*S*)- and (*R*)-PGME amides, where the amide-carbonyl groups were *anti*-periplanar to the ethereal α-methoxyl groups, and the NH amides are *syn*-periplanar to the methoxycarbonyl group, while the amide bonds have *Z* conformation[9] (Fig. 2 (B) and (C)).

This prompted the authors to confirm the absolute configuration of MβNP acid **2** by the PGME method. Herein, we report the application of the PGME method to chiral acids **1** and **2** possessing the aromatic groups.

2. Results and discussion

2.1. (*S*)-MαNP amides of (*S*)- and (*R*)-PGME

Amide **3** (the (*S*)-MαNP amide of (*S*)-PGME) was prepared from (*S*)-(+)-MαNP acid ((*S*)-**1**) and (*S*)-(+)-PGME·HCl using *N*,*N*′-dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP) in dichloromethane. Amide **4** was prepared from (*S*)-(+)-MαNP acid ((*S*)-**1**) and (*R*)-(−)-PGME·HCl by the same method. The ^{1}H NMR spectral signals (600 MHz,

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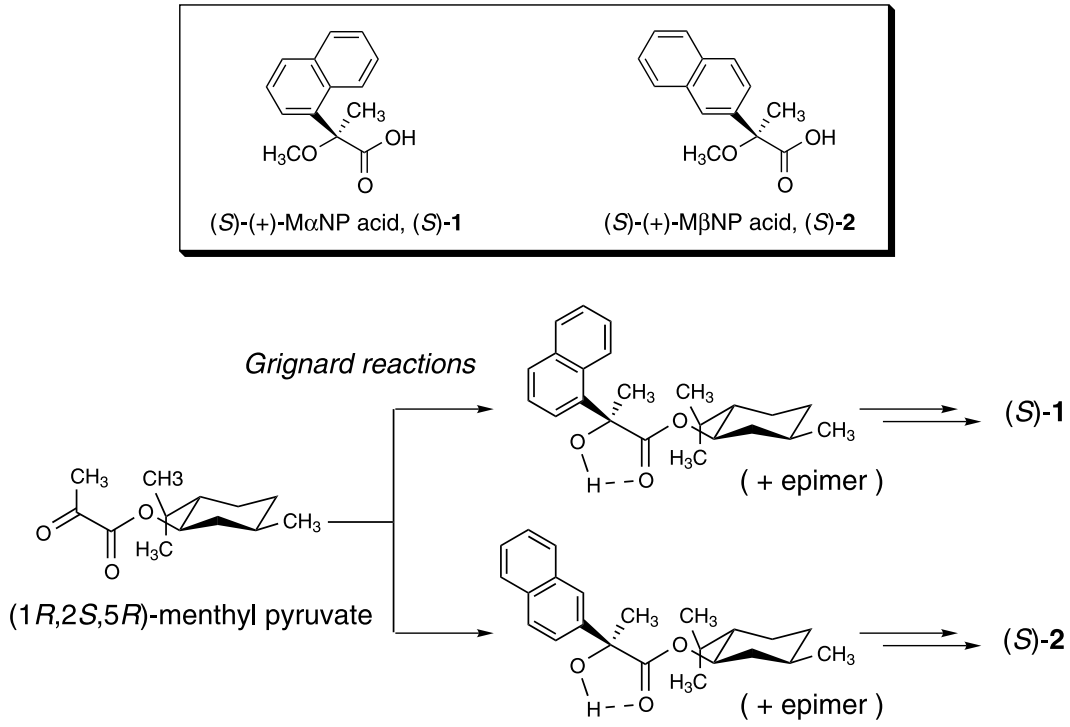

Figure 1. The structures of MαNP and MβNP acids and determination of their absolute configurations by the ^{1}H NMR anisotropy method.[1,4]

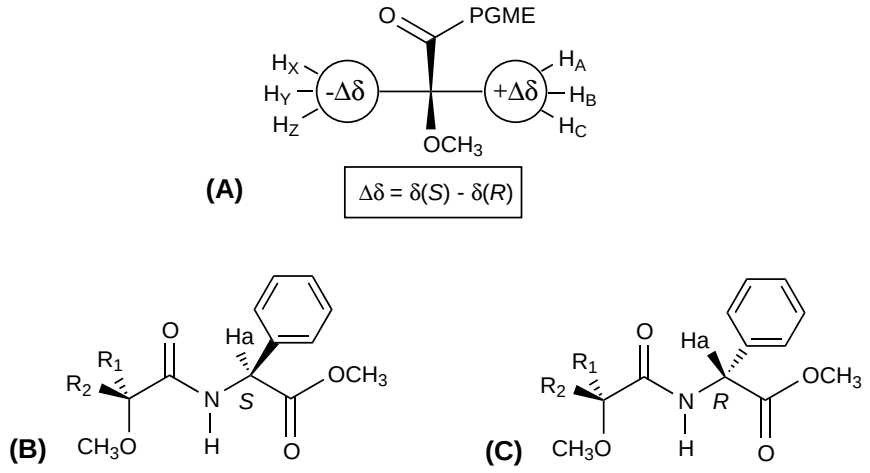

Figure 2. Distribution of $\Delta\delta(=\delta(S)-\delta(R))$ values of PGME amides and their proposed conformations.[9]

$CDCl_3$) of **3** and **4** were fully assigned from the DQF COSY, HSQC, and HMBC spectra.

The $\Delta\delta$ $(=\delta(\mathbf{3})-\delta(\mathbf{4}))$ values in the ^{1}H NMR spectra are shown in Fig. 3. The 1-naphthyl group has negative $\Delta\delta$ values, while the methyl group of MαNP moiety has a positive $\Delta\delta$ value (+0.09). These $\Delta\delta$ values indicate that the absolute configuration of (+)-MαNP acid is *S*. This conclusion is consistent with the previous determination by X-ray crystallography.[8] The PGME method is thus applicable to α-methoxy-carboxylic acids possessing an aromatic group.

2.2. (*R*)- and (*S*)-MβNP amides of (*R*)-PGME

The racemic acid **2** was condensed with (*R*)-PGME using DCC and DMAP in dichloromethane, yielding diastereomeric amides **5** and **6**, which were separated by silica gel chromatography. Alkaline hydrolysis of the first-eluted amide **6** gave acid (+)-**2**. Amide **6** was also

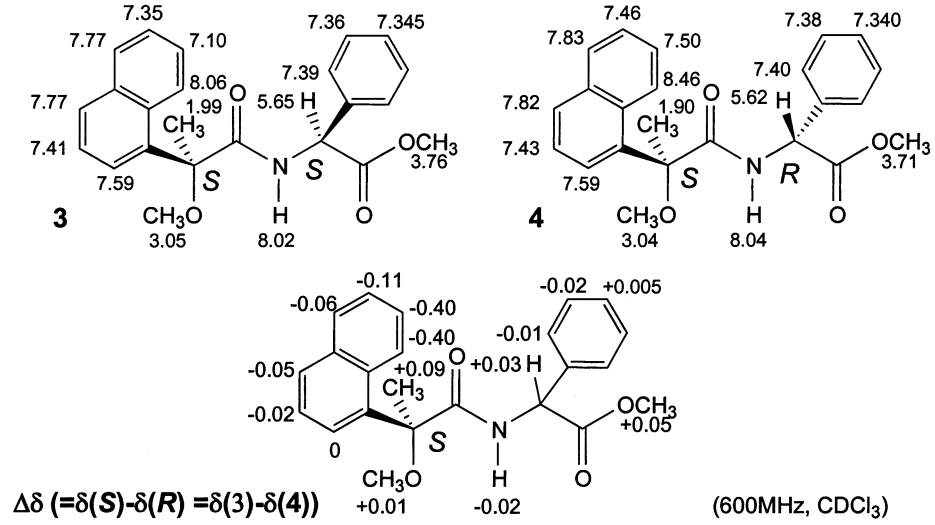

Figure 3. The structures of **3** ((*S*)-MαNP amide of (*S*)-PGME) and **4** ((*S*)-MαNP amide of (*R*)-PGME). The assigned numbers are ^{1}H NMR chemical shifts and their $\Delta\delta$ values.

prepared from (+)-**2** and (*R*)-PGME·HCl using DCC and DMAP in dichloromethane. Compounds **5** and **6** are thus assigned as the (−)- and (+)-MβNP amides of (*R*)-PGME, respectively (Fig. 4).

The ^{1}H NMR signals of **5** and **6** were assigned from the COSY, CH COSY, and HMBC spectra (Fig. 4). The ^{1}H NMR signals for the 2-naphthyl group of **5** were observed at higher field than those of **6**. On the contrary, the signal for the methyl group of **5** (1.90 ppm) was observed at lower field than that of **6** (1.85 ppm). *ent*-**5**, the enantiomer of **5**, was similarly synthesized from acid (+)-**2** and (*S*)-PGME. Since the chemical shift data for the amide **5** and its enantiomer *ent*-**5** are identical to each other, the original equation[9] for defining $\Delta\delta$ value is formulated as follows.

$$\Delta\delta = \delta(S) - \delta(R) = \delta(ent\text{-}\mathbf{5}) - \delta(\mathbf{6}) = \delta(\mathbf{5}) - \delta(\mathbf{6}).$$

The distribution of the positive and negative $\Delta\delta$ values reveals that the absolute configuration of (+)-MβNP acid **2** is *S*. The previous stereochemical assignment, (*S*)-(+)-**2**, determined by Prelog's 1,4-chiral induction reaction and successive ^{1}H NMR anisotropy analyses,[4] was thus corroborated by the PGME method.

Two groups have reported the conformations of the (*S*)- and (*R*)-*O*-methylmandelamides using ^{1}H NMR and other spectroscopic methods.[10,11] They proposed that for both the (*S*)- and (*R*)-amides, the methoxy groups are *anti*-periplanar to the amide-carbonyl groups, and the amides NH protons are *anti*-periplanar to the methine protons (Hb in Fig. 5), while the amide

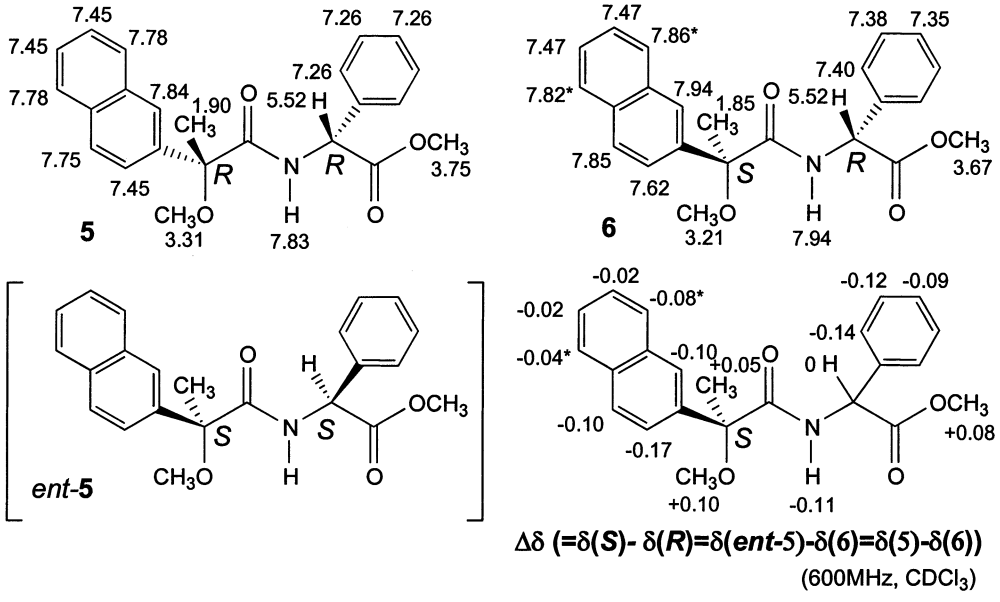

Figure 4. The structures of **5** ((*R*)-MβNP amide of (*R*)-PGME) and **6** ((*S*)-MβNP amide of (*R*)-PGME). The assigned numbers are ^{1}H NMR chemical shifts and their $\Delta\delta$ values. *: Exchangeable.

bonds have the Z conformation in both cases. The $\Delta\delta$ values shown in Figs. 3 and 4 were also explained by the conformations similar to *O*-methylmandelamides that the amide NH protons are *anti*-periplanar to the methine protons (Ha in Fig. 2).

2.3. HPLC analyses

The separation factor (α value, $=(T_2-T_0)/(T_1-T_0)$) for amides **3** and **4** was 1.72 in the normal phase HPLC analysis (SILICA SG80, hexane–ethyl acetate, Fig. 6 (X)). The α value for **3** and **4** was 1.08 in reverse phase HPLC analysis (CAPCELL PAK C18 AG120, methanol–water). For amides **5** and **6**, the α values for the normal and reversed phase HPLC analyses were 1.61 (Fig. 6 (Y)) and 1.09, respectively. As already discussed by Goto et al., MαNP acid is superior to MβNP acid for the enantioresolution of the amino acid methyl ester.[6]

3. Summary

The applicability of the phenylglycine methyl ester (PGME) method was confirmed for (*S*)-(+)-MαNP acid and (*S*)-(+)-MβNP acid. The absolute configurations determined by the PGME method were consistent with those determined by the Prelog's stereoselective Grignard reactions and the ^{1}H NMR anisotropy analyses of the Grignard adducts. These results suggest that the PGME method is applicable to the chiral carboxylic acids possessing the aromatic groups.

4. Experimental

4.1. General

The NMR spectra were obtained using either a Bruker DRX600, ADVANCE800, or a JEOL JNM α600 in

Figure 5. Proposed conformations of *O*-methylmandelamides.[10,11]

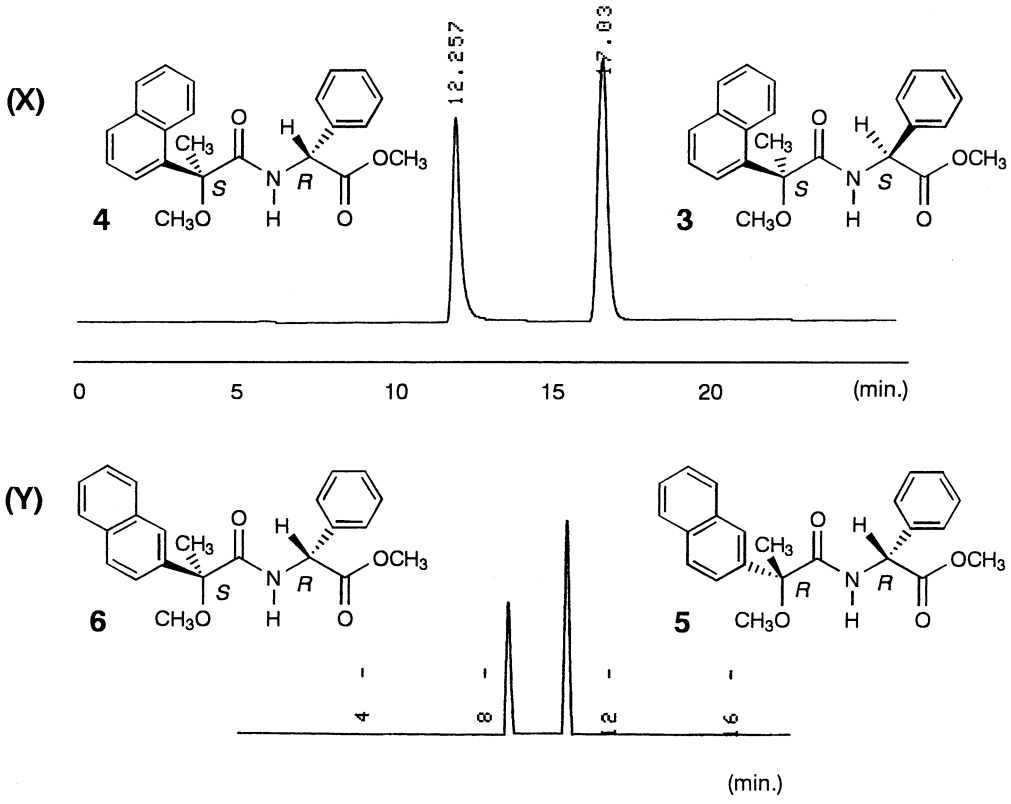

Figure 6. Separation of MαNP/PGME and MβNP/PGME amide diastereomers by normal phase HPLC (Silica SG80, hexane–ethyl acetate, UV: 300 nm).

$CDCl_3$ with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on a Perkin Elmer 1760X. The MS data were obtained with a Hewlett–Packard 1100 LC/MSD system. The optical rotations were determined on a JASCO DIP1000 spectropolarimeter. Kieselgel 60 (Merck KGaA) and Wakogel C-200 (Wako Pure Chemical Industries, Ltd.) were used for the open column chromatography. A C.I.G.® prepacked silica gel column (Kusano Kagakukikai Co., Tokyo) was used for the preparative LC. A CAPCELL PAK C18 AG120/5 μm column (4.6×150 mm, Shiseido Co., Ltd.) and a SILICA SG80 column (4.6×250 mm, Shiseido Co., Ltd.) were used for HPLC. (*S*)-MαNP acid ($[\alpha]_D^{29}$ +72 (*c* 1.53, ethanol)), (*R*)-MαNP acid ($[\alpha]_D^{30}$ −81 (*c* 0.92, ethanol)), (*S*)-MβNP acid ($[\alpha]_D^{27}$ +30 (*c* 0.42, ethanol)), and (*R*)-MβNP acid ($[\alpha]_D^{31}$ −30 (*c* 0.37, ethanol)) were prepared by the enantioresolution of (±)-MαNP and (±)-MβNP acids, respectively, using (1*R*,2*S*,5*R*)-(−)-menthol (Aldrich, M278-0).

4.2. Preparation of amides 3 and 4

A solution of (*S*)-MαNP acid (12 mg), (*S*)-PGME·HCl (Aldrich 30,867-6, 50 mg), DMAP (52 mg), and DCC (38 mg) in dry CH_2Cl_2 (0.5 mL) was allowed to stand for 14 h. The reaction mixture was directly subjected to open column chromatography on silica gel (hexane–ethyl acetate). Further purification by preparative LC gave pure **3** (11 mg). Amide **4** was prepared from (*S*)-MαNP acid (17 mg) and (*R*)-PGME HCl (Aldrich 30,788-2, 44 mg) in the same way (18 mg).

4.2.1. (*S*)-MαNP amide of (*S*)-PGME, compound 3. ^{1}H NMR (600 MHz): 8.06 (1H, dd, J=8.5, 1 Hz), 8.02 (1H, d, J=8 Hz), 7.77 (1H, br d, J=8 Hz), 7.77 (1H, br d, J=8 Hz), 7.59 (1H, dd, J=7.5, 1 Hz), 7.41 (1H, dd, J=8, 7.5 Hz), 7.39 (2H, m), 7.36 (2H, m), 7.35 (1H, m), 7.345 (1H, m), 7.10 (1H, ddd, J=8.5, 7, 1.5 Hz), 5.65 (1H, d, J=8 Hz), 3.76 (3H, s), 3.05 (3H, s), 1.99 (3H, s); ^{13}C NMR (151 MHz): 173.91, 171.33, 136.47, 134.58, 134.21, 131.34, 129.65, 128.98, 128.71, 128.53, 127.58, 127.02, 125.88, 125.43, 125.04, 124.59, 82.52, 56.20, 52.71, 50.70, 22.22; LC-MS (API-ES, methanol–water) m/z: 400 ($[M+Na]^+$, 100%), 346 (50); IR ($CDCl_3$ solution in NaCl cell): 3410 cm^{-1}, 2955, 1745, 1680, 1500, 780; $[\alpha]_D^{31}$ +176 (*c* 0.20, ethanol).

4.2.2. (*S*)-MαNP amide of (*R*)-PGME, compound 4. ^{1}H NMR (600 MHz): 8.46 (1H, br d, J=8.5 Hz), 8.04 (1H, d, J=8 Hz), 7.83 (1H, br d, J=8 Hz), 7.82 (1H, br d, J=8 Hz), 7.59 (1H, dd, J=7.5, 1 Hz), 7.50 (1H, ddd, J=8.5, 7, 1.5 Hz), 7.46 (1H, ddd, J=8, 7, 1.5 Hz), 7.43 (1H, dd, J=8, 7.5 Hz), 7.40 (2H, m), 7.38 (2H, m), 7.340 (1H, m), 5.62 (1H, d, J=8 Hz), 3.71 (3H, s), 3.04 (3H, s), 1.90 (3H, s); ^{13}C NMR (151 MHz): 173.97, 171.21, 136.66, 134.46, 134.26, 131.49, 129.74, 128.98, 128.72, 128.50, 127.33, 127.16, 126.35, 125.62, 125.50, 124.60, 82.52, 56.07, 52.70, 50.70, 20.40; LC-MS (API-ES, methanol–water) m/z: 400 ($[M+Na]^+$, 100%), 346 (34); IR ($CDCl_3$ solution in NaCl cell): 3410 cm^{-1}, 2955, 1740, 1680, 1500, 780; $[\alpha]_D^{30}$ −25 (*c* 0.35, ethanol).

4.3. Preparation of amides 5 and 6

A solution of (±)-MβNP acid (24 mg), (*R*)-PGME·HCl (65 mg), DMAP (90 mg), and DCC (60 mg) in dry CH_2Cl_2 (0.5 mL) was allowed to stand for 14 h. The reaction mixture was directly subjected to open column chromatography on silica gel (hexane–ethyl acetate). Further purification by preparative LC gave pure **5** (17 mg) and **6** (17 mg). The amide **5** was also synthesized from (*R*)-MβNP acid (8 mg) and (*R*)-PGME HCl (35 mg), and *ent*-**5** was prepared from (*S*)-MβNP acid (7 mg) and (*S*)-PGME HCl (30 mg). Amide **6** was prepared from (*S*)-MβNP acid (3 mg) and (*R*)-PGME HCl (16 mg) in the same way.

4.3.1. (*R*)-MβNP amide of (*R*)-PGME, compound 5. ^{1}H NMR (600 MHz): 7.84 (1H, br s), 7.83 (1H, m), 7.78 (2H, m), 7.75 (1H, d, J=9 Hz), 7.45 (3H, m), 7.26 (5H, m), 5.52 (1H, d, J=7 Hz), 3.75 (3H, s), 3.31 (3H, s), 1.90 (3H, s); ^{13}C NMR (151 MHz): 173.03, 171.27, 138.11, 136.20, 133.06, 132.90, 128.87, 128.46, 128.30, 128.10, 127.44, 127.19, 126.16, 126.08, 125.47, 123.81, 82.13, 56.35, 52.72, 51.44, 20.41; IR ($CDCl_3$ solution in NaCl cell): 3410 cm^{-1}, 2955, 1745, 1680, 1500; LC-MS (API-ES, methanol–water) m/z: 400 ($[M+Na]^+$, 7%), 346 (100); $[\alpha]_D^{31}$ −130 (*c* 0.20, ethanol).

4.3.2. (*S*)-MβNP amide of (*S*)-PGME, compound *ent*-5. The ^{1}H NMR spectrum (800 MHz) of *ent*-**5** showed identical chemical shits with compound **5**. $[\alpha]_D^{32}$ +150 (*c* 0.15, ethanol).

4.3.3. (*S*)-MβNP amide of (*R*)-PGME, compound 6. ^{1}H NMR (600 MHz): 7.94 (1H, br s), 7.94 (1H, m, NH), 7.86 (1H, m), 7.85 (1H, d, J=9 Hz), 7.82 (1H, m), 7.62 (1H, dd, J=9, 2 Hz), 7.47 (2H, m) 7.40 (2H, m), 7.38 (2H, m), 7.35 (1H, m), 5.52 (1H, d, J=7 Hz), 3.67 (3H, s), 3.21 (3H, s), 1.85 (3H, s); ^{13}C NMR (151 MHz): 173.01, 171.07, 137.63, 136.61, 133.10, 133.01, 128.99, 128.53, 128.36, 128.20, 127.49, 127.33, 126.21, 126.08, 125.93, 124.23, 81.95, 56.37, 52.64, 51.21, 20.21; IR ($CDCl_3$ solution in NaCl cell): 3410 cm^{-1}, 2955, 1745, 1680, 1505; LC-MS (API-ES, aq. 20 mM ammonium acetate–methanol) m/z: 400 ($[M+Na]^+$, 13%), 346 (100), 318 (15), 286 (33), 225 (12), 195 (13), 196 (14); $[\alpha]_D^{30}$ −18 (*c* 0.69, ethanol).

4.4. HPLC analyses of compounds 3, 4, 5, and 6

Ethanol solutions of **3**, **4**, **5**, and **6** (5 μL, 1–2 mg/mL) were injected to a SILICA SG80 column or a CAPCELL PAK C18 column. The flow rate was 0.5 mL/min, while the UV absorption was monitored at 300 nm.

For SILICA SG80 column (hexane:ethyl acetate, 7:3), the retention times of amides **3** and **4** were 17.03 and 12.26 min, respectively. The retention times of **5** and **6** were 10.63 and 8.73 min, respectively (hexane:ethyl acetate, 6:4). The retention time of octadecylbenzene (5.6 min) was adopted as T_0 for the SILICA SG80 column.

For CAPCELL PAK C18 AG120 column (methanol:water, 7:3), the retention times of amides **3**, **4**, **5**, and **6** were 13.38, 12.62, 17.96, and 16.74 min, respectively. The retention time of uracil (3.2 min) was adopted as the T_0 for the CAPCELL PAK C18 column.

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