Synthesis of enantiopure 6-methoxy-2-naphthylglycolic acid and its application as a resolving agent

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Abstract— As a novel acidic resolving agent, 6-methoxy-2-naphthylglycolic acid (6-**MNGA**) was designed on the model of 2-naphthylglycolic acid (2-**NGA**). Enantiopure 6-**MNGA** was easily obtained from commercially available 2-bromo-6-methoxynaphthalene through four steps and was found to show a better chiral recognition ability for racemic 1-arylethylamines than did the prototype 2-**NGA**. The X-ray crystallographic analyses of the less-soluble diastereomeric salts revealed that the introduction of a methoxy group at the 6-position of the 2-**NGA** skeleton made CH/π interaction(s) effective between 6-**MNGA** molecules and between 6-**MNGA** molecule and the target amine molecule. The methoxy group was also found to contribute to the realization of effective van der Waals interaction. These interactions played important roles for the stabilization of the less-soluble diastereomeric salts to improve the chiral recognition ability of 6-**MNGA**, compared to that of 2-**NGA**.

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1. Introduction

Enantioseparation via the diastereomeric salt formation is one of the most practical methods for obtaining enantiopure compounds because of its simplicity of operation and its applicability to an industrial scale-operation. However, the choice of a suitable resolving agent for a given racemate has been carried out by a time-consuming trial-and-error procedure even at present.[1] Such situation prompted us to develop effective resolving agents, which are able to apply to a wide range of racemates, and to propose criteria for the proper choice of a suitable resolving agent. Our continuous studies on the development of resolving agents revealed that the formation of 2_1 columns in the corresponding less-soluble diastereomeric salt crystals is essential and that favorable is a resolving agent, of which the molecular length is similar to that of a target racemate to make van der Waals interaction between the columns effective and/or in which there exists a naphthyl group to achieve effective CH/π interaction(s) in the crystals.[1] As one of tailored resolving agents designed on the basis of the knowledge, we have previously reported the synthesis of enantiopure 2-naphthylglycolic acid (2-**NGA**) and its application to enantioseparation as a resolving agent.[2] 2-**NGA** showed a moderate to good chiral recognition ability for racemic 1-arylethylamines; the origin of the ability was found to be effective CH/π interactions between the aryl groups in 2-**NGA** and the racemate on the basis of the X-ray crystallographic analyses of the less-soluble diastereomeric salts. This result prompted us to improve the chiral recognition ability of 2-**NGA** for a wide variety of racemic 1-arylethylamines. Thus, we designed a novel acidic resolving agent, 6-methoxy-2-naphthylglycolic acid (6-**MNGA**), which has a methoxy group at the 6-position of the naphthyl group of 2-**NGA**, with an expectation that the methoxy group would make the molecular length longer to contribute to the realization of effective van der Waals interaction and would enhance the effect of CH/π interaction(s) owing to its electron-donating characteristic. In this paper, we report the synthesis of enantiopure 6-**MNGA** and its performance as a superior resolving agent for racemic 1-phenylethylamines, which are important chiral compounds from pharmaceutical point of view.[3]

2. Results and discussion

The key material, ethyl 6-methoxy-2-naphthylglyoxylate (**2**), was obtained in 98% yield by the reaction of diethyl glyoxylate with the Grignard reagent, prepared from commercially available 2-bromo-6-methoxynaphthalene (**1**), and the reduction of **2** with $NaBH_4$/AcOH gave racemic ethyl 6-methoxy-2-naphthylglycolate (**3**) in 98% yield, which was hydrolyzed under basic conditions to afford racemic 6-**MNGA**. A mixture of the diastereomeric salts of racemic 6-**MNGA** with commercially

available (*R*)-1-phenylethylamine ((*R*)-**PEA**) was crystallized and then recrystallized from EtOH/H_2O to give the diastereopure less-soluble salt. The X-ray crystallographic analysis for a needle-like single crystal of the less-soluble salt revealed that its absolute configuration was (*R*)-6-**MNGA**•(*R*)-**PEA**. The decomposition of the less-soluble salt with 1M HCl aq., followed by extraction with 2-butanone, afforded (*R*)-6-**MNGA** in 8% overall yield (from racemic 6-**MNGA**; based on the amount of racemic 6-**MNGA** used).

Although enantiopure 6-**MNGA** was obtained, the overall yield was unsatisfactory from the viewpoint of its practical use. Then, we next tried to successively apply the simple and large scale-applicable asymmetric reduction of the keto group of **2** and the enantioseparation of the resultant enantio-enriched **3** with enantiopure **PEA** in order to achieve high overall yield: The asymmetric reduction of **2** with $NaBH_4$/(L)-tartaric acid, according to the procedure reported by Yatagai and Ohnuki,[4] gave (*R*)-enriched **3** in 98% yield with 74% enantiomeric excess (ee). Although the ee of the resulting 6-**MNGA** was unfortunately diminished to 39% during the hydrolysis of the (*R*)-enriched **3** under basic conditions, the successive enantioseparation with (*R*)-**PEA** (crystallized from EtOH/H_2O), followed by recrystallization twice from EtOH/H_2O and usual salt decomposition, gave (*R*)-6-**MNGA** in 49% overall yield from (*R*)-enriched 6-**MNGA** (based on the amount of (*R*)-enriched 6-**MNGA** used; 71% recovery from (*R*)-6-**MNGA** contained in (*R*)-enriched 6-**MNGA** used). Moreover, the antipode, (*S*)-6-**MNGA**, was obtained in 20% overall yield (based on (*R*)-enriched 6-**MNGA** used; 68% recovery from (*S*)-6-**MNGA** contained in (*R*)-enriched 6-**MNGA** used) by the enantioseparation of 6-**MNGA**, which was recovered from the mother liquor of the first enantioseparation, with (*S*)-**PEA** (crystallized and then recrystallized once from EtOH/H_2O). These results clearly indicate that the enantioseparation of the enantio-enriched form, which is obtained by simple and large scale-applicable asymmetric synthesis, is advantageous, compared to that of the completely racemic form, from the viewpoint of yield and operational simplicity.

The chiral recognition ability of enantiopure 6-**MNGA** for racemic 1-arylethylamines **4** was determined as follows: An alcohol or aqueous alcohol solution of the racemic 1-arylethylamine and 6-**MNGA** (molar ratio=1:1) was cooled down from the reflux temperature to 30 °C in order to make the conditions constant and to avoid the problem of polymorphism as far as possible. Moreover, the ratio of water/alcohol and the amount of the solvent were adjusted so as to control the yield of the precipitated salt to be as close as possible to a range of 50-90% (based on a half amount of the racemic amine used), and only crystallization was performed in order to compare the results with each other and to discuss the difference in chiral recognition ability between 6-**MNGA** and 2-**NGA**. The results are summarized in Table 1.

As can be seen from Table 1, the chiral recognition ability of 6-**MNGA** is, in general, superior to 2-**NGA**: In the cases of entries 1 and 4-9, 6-**MNGA** achieved high resolution efficiencies as well as did 2-**NGA**. Moreover, 6-**MNGA** could effectively recognize the chirality of *o*-substituted 1-phenyethylamines and 1-arylethylamines with a longer molecular length, for which 2-**NGA** showed very low chiral recognition ability (entries 2, 3, 9, and 11). Thus, 6-**MNGA** was found to show a chiral recognition ability better than 2-**NGA**; 6-**MNGA** was applicable for a wide variety of racemic 1-arylethylamines.

In the next stage, we carried out X-ray crystallographic analyses of the less-soluble diastereomeric salts in order to clarify the origin of the wide-spread chiral recognition ability of 6-**MNGA**. We could fortunately obtained the single crystals of the less-soluble diastereomeric salts, (*R*)-6-**MNGA•4a**, (*R*)-6-**MNGA•4b**, and (*S*)-6-**MNGA•4j**, suitable for X-ray crystallography. In all of the crystals, a columnar hydrogen-bonding network (2_1 column), consisting of ammonium cations and carboxylate anions with a 2-fold screw axis in the center, was commonly constructed, and the hydroxy group in 6-**MNGA** molecule linked the columns by another kind of hydrogen bond with the vacant site of the carboxylate molecule to form a supramolecular sheet, as was observed for the less-soluble salts of 1-arylethylamines with enantiopure arylglycolic acids, such as mandelic acid,[1,5] substituted mandelic acids,[1,5] and 2-**NGA**.[2]

The crystal structure and partial molecular arrangement of the less-soluble diastereomeric (*R*)-6-**MNGA•**(*R*)-**4a** salt is shown in Figures 1a and 1b with those of (*R*)-2-**NGA•**(*R*)-**4a** (Figures 1c and 1d)[2] for comparison. Although on first viewing, the crystal structures seem to be similar to each other, a precise study on the crystal structures revealed that the molecular arrangement of (*R*)-6-**MNGA** and (*R*)-**4a** in the (*R*)-6-**MNGA•**(*R*)-**4a** crystal is different from that of (*R*)-2-**NGA** and (*R*)-**4a** in the (*R*)-2-**NGA•**(*R*)-**4a** crystal. The naphthyl groups of (*R*)-6-**MNGA** and (*R*)-2-**NGA** are located almost perpendicularly to four surrounding phenyl groups of (*R*)-**4a** molecules to form four kinds of T-shaped CH(sp^2)/π interactions, respectively. In the formation of the T-shaped CH(sp^2)/π interactions, the naphthyl groups of (*R*)-6-**MNGA** and (*R*)-2-**NGA** play both roles of a proton donor and a proton acceptor in a similar manner. The proton donating abilities of the naphtyl groups of (*R*)-6-**MNGA** and (*R*)-2-**NGA** in the crystals, however, would be low, because the protons of the naphtyl groups of (*R*)-6-**MNGA** and (*R*)-2-**NGA** are located not to sufficiently overlap with the π orbital of the phenyl group of (*R*)-**4a**. This means that both pairs of CH(sp^2)/π interactions are similarly weak to give almost no influence to the difference in stability between the (*R*)-6-**MNGA•**(*R*)-**4a** and (*R*)-2-**NGA•**(*R*)-**4a** crystals. In contrast, the proton accepting abilities of the naphtyl groups of (*R*)-6-**MNGA** and (*R*)-2-**NGA** in the crystals should be different from each other. One of the distances between the C atoms of the phenyl groups (proton donors)

of the surrounding (*R*)-**4a** molecules and the π plane of the naphthyl group (proton acceptor) of (*R*)-6-**MNGA** in the (*R*)-6-**MNGA**•(*R*)-**4a** crystal (3.88 Å) is obviously shorter than that in the (*R*)-2-**NGA**•(*R*)-**4a** crystal (3.96 Å). Thus, the electron-donating methoxy group strengthened the proton accepting ability of the naphthyl group of (*R*)-6-**MNGA** for the T-shaped CH(sp^2)/π interaction in the less-soluble diastereomeric salts, as was expected, although the chiral recognition ability of 6-**MNGA** to **4a** was comparable to that of 2-**NGA**.

Figure 2 shows the crystal structure and partial molecular arrangement of the less-soluble diastereomeric (*R*)-6-**MNGA**•(*R*)-**4b** salt. As shown in Figure 2a, the surfaces of the sheet are not planar but uneven, due to the significant difference in molecular length between (*R*)-6-**MNGA** and (*R*)-**4b**. Such a packing pattern is known to be disadvantageous for the stabilization of less-soluble diastereomeric salts to result in low efficiency in enantioseparation.[5] However, the efficiency of the enantioseparation of **4b** with (*R*)-6-**MNGA** was high (0.69), compared to that with 2-**NGA** (0.05). The large difference in efficiency between the enantioseparations with enantiopure 6-**MNGA** and 2-**NGA** would arise from the effectively engaged stack of the sheets in the (*R*)-6-**MNGA**•(*R*)-**4b**; the projected parts of the sheet occupy the apertures of the neighboring sheet. The (*R*)-6-**MNGA**•(*R*)-**4b** crystal also has characteristic features. There exists somewhat short CH(sp^2)/π interaction (3.45 Å) between the neighbored phenyl group (proton donor) of (*R*)-**4b** and naphthyl group (proton acceptor) of (*R*)-**MNGA**. Moreover, short CH(sp^3)/π interaction is observed between the methyl group on the phenyl ring of (*R*)-**4b** and the naphthyl group of (*R*)-6-**MNGA** (Figure 2b); the distance between the C atom and the π plane is only 3.42 Å, which is unusually short as CH(sp^3)/π interaction.[6] The efficient CH(sp^2)/π and CH(sp^3)/π interactions would originate from the naphthyl group of (*R*)-6-**MNGA**, which is electron-enriched by the electron-donating methoxy group at the 6-position, to effectively stabilize the supramolecular sheet. The methoxy groups of 6-**MNGA** molecules in the supramolecular sheets interpenetrate each other at the boundary of the surfaces to make van der Waals interaction effective and to realize close packing in the crystal. These characteristics would contribute to the stabilization of the less-soluble salt of (*R*)-6-**MNGA**•(*R*)-**4b** crystal. Although the structure of the corresponding (*R*)-2-**NGA**•(*R*)-**4b** salt crystal is not solved, it is deduced that the less-soluble (*R*)-2-**NGA**•(*R*)-**4b** salt is stabilized less sufficiently than is the less-soluble (*R*)-6-**MNGA**•(*R*)-**4b** salt, because of the luck of an electron-enriched π plane and no effect of the interpenetration. The crystal structure of (*R*)-6-**MNGA**•(*R*)-**4b** salt strongly indicates that our design of 6-**MNGA** is adequate to improve the chiral recognition ability of 2-**NGA**.

Figure 3 shows the crystal structure and partial molecular arrangement of the less-soluble diastereomeric (*S*)-6-**MNGA**•(*S*)-**4j** crystal. In contrast to the less-soluble diastereomeric (*R*)-6-**MNGA**•(*R*)-**4a** and (*R*)-6-**MNGA**•(*R*)-**4b** crystals, the surfaces of the supramolecular sheet in the (*S*)-6-**MNGA**•(*S*)-**4j** crystal are rather planar owing to the similarity in molecular length between 6-**MNGA** and **4j**, as shown in Figure 3a. The planar surfaces would bring effective van der Waals interaction between the sheets to make the stack of the sheets sufficient. Moreover, efficient T-shaped CH(sp^2)/π interactions are achieved between the naphthyl groups of 6-**MNGA** and **4j** (Figure 3b). In the supramolecular sheet, simultaneous cooperative CH(sp^2)/π interaction effectively stabilizes the sheet as well as intercolumnar hydrogen bonds.

3. Conclusion

A novel resolving agent, enantiopure 6-**MNGA**, was prepared in high yield by employing the simple and large scale-applicable asymmetric reduction of ethyl 6-methoxy-2-naphthylglyoxylate, followed by enantioseparation. A systematic study on the enantioseparation of 1-arylethylamines **4** with enantiopure 6-**MNGA** revealed that 6-**MNGA** had a high chiral recognition ability for a variety of 1-arylethylamines wider than did the prototype 2-**NGA**. The X-ray crystallographic analyses of the less-soluble salt clarified that there exists a supramolecular sheet, consisting of 2_1 columns, as observed in the less-soluble diastereomeric salts of 1-arylethylamines with enantiopure arylglycolic acids, and that the methoxy group at the 6-position of the 6-**MNGA** played a significant role in making CH/π interactions between 6-**MNGA** and the target amine sufficient in the sheet and/or in making van der Waals interaction between the sheets effective.

4. Experimental

NMR spectra were recorded on a Varian Mercury 300 instrument. IR spectra were recorded on a Jasco FT/IR-480. HPLC analyses were performed on Daicel Chiralcel columns using a Jasco PU-2080i pump, a Jasco PU-2075 UV detector and a Hitachi D-2500 Chromato-Integrator.

Ethyl 6-methoxy-2-naphthylglyoxylate, 2

To a suspension of Mg (1.10 g, 45.2 mmol) in THF (5 mL) was slowly added

2-bromo-6-methoxynaphthalene (8.19 g, 34.5 mmol) in THF (20 mL) under Ar atmosphere, and the mixture was stirred at rt for 30 min. To the mixture, cooled down to 0 °C, was added a solution of diethyl oxalate (15.32 g, 104.8 mmol) in THF (40 mL) at -78 °C drop by drop over a period of 1 h. The mixture was stirred at -78 °C for 2 h and then at 0 °C for 2 h. Saturated NH_4Cl aq. (50 mL) was added to the solution, and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with sat. NaCl aq. (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude ethyl 6-methoxy-2-naphthylglycoxylate (**2**) as a yellow oil. The precipitation of the oil with hexane/AcOEt (20/1, 630 mL) and the successive silica gel chromatography (eluent, hexane/AcOH = 10/1 – 9/1) of the residue, recovered upon concentrating the filtrate, afforded **2** (8.77 g, 34.0 mmol, 98%) as a white solid. An aliquot was distilled by using a kugelrohr for the following analyses (3 mmHg; oven temperature, 120 °C). IR (KBr) cm^{-1}: 3070-2840, 1725, 1680, 1619, 1198, 1175, 1154, 1127, 1095, 1022, 923, 910, 854, 836. ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, *J* = 7 Hz, 3H), 3.97 (s, 3H), 4.49 (q, *J* = 7 Hz, 2H), 7.18 (s, 1H), 7.23 (d, *J* = 9 Hz, 1H), 7.81 (d, *J* = 9 Hz, 1H), 7.78 (d, *J* = 9 Hz, 1H), 8.03 (d, *J* = 9 Hz, 1H), 8.48 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.11, 55.45, 62.25, 105.91, 120.05, 124.80, 127.55, 127.58, 127.79, 131.59, 133.23, 138.27, 160.61, 164.13, 186.01. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.82; H, 5.55.

(*R*)-Enriched ethyl 6-methoxy-2-naphthylglycolate, 3

To a suspension of $NaBH_4$ (11.38 g, 300.9 mmol) in THF (60 mL) was added (L)-tartaric acid (45.09 g, 300.4 mmol) at rt, and the mixture was refluxed for 4 h. The mixture, cooled down to rt, was added a solution of **2** (19.50 g, 75.5 mmol) in THF (160 mL) at -78 °C, and the mixture was stirred for 1 h at -78 °C. To the mixture was added 1M HCl aq. (100 mL) at -78 °C, and the resultant mixture was stirred for 15 min at rt. After removal of THF under reduced pressure, the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with NaCl aq. (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude ethyl 6-methoxy-2-naphthylglycolate (**3**) (19.29 g, 74.1 mmol, 98%) as a white solid. The ee of **3** was determined by a HPLC analysis (Daicel CHIRALCEL OJ; eluent, hexane/2-propanol = 9/1; flow rate, 1.0 mL/min; t_1 (*S*-isomer) = 56.2 min, t_2 (*R*-isomer) = 42.1 min; the

enantiomeric excess, 74%). An aliquot (100 mg) was recrystallized from hexane/ethyl acetate (8/1, 4 mL/0.5 mL) for the following analyses. Mp 88.5-90.5 °C; IR (KBr) cm^{-1}: 3421, 3050-2900, 1737, 1631, 1607, 1487, 1453, 1271, 1064, 1031, 861, 824. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7 Hz, 3H), 3.52 (d, *J* = 6 Hz, 1H), 3.92 (s, 3H), 4.17 (dq, *J* = 7 Hz, *J'* = 11 Hz, 1H), 4.28 (dq, *J* = 7 Hz, *J'* = 11 Hz, 1 H), 5.29 (d, *J* = 6 Hz, 1H), 7.14 -7.18 (m, 2H), 7.47 (d, *J* = 8 Hz, 1H), 7.74 (d, *J* = 8 Hz, 2H), 7.82 (s, 1H).). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.20, 55.47, 62.44, 73.14, 105.77, 119.31, 124.82, 125.89, 127.39, 128.77, 129.74, 133.65, 134.63, 158.14, 173.97. Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.31; H, 6.43.

(*R*)-Enriched 6-methoxy-2-naphthylglycolic acid, (*R*)-enriched 6-MNGA

A solution of crude **3** (19.40 g, 74.5 mmol) in a mixture of 12 M KOH aq. (10 mL) and 2-propanol (250 mL) was stirred at 50 °C for 10 min. The solution was concentrated under reduced pressure in order to remove 2-propanol, acidified with 3 M HCl aq. (200 mL), and extracted with 2-butanone (3 x 400 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to (*R*)-enriched give 6-**MNGA** (16.91 g, 72.8 mmol, 98%) as a pale yellow solid. The ee of (*R*)-enriched 6-**MNGA** was determined by a HPLC analysis (Daicel CHIRALCEL OJ-RH; eluent, $HClO_4$ aq. (pH 2):CH_3CN = 8:2; flow rate, 0.5 mL/min; t_1 (*S*-isomer) = 45.1 min, t_2 (*R*-isomer) = 39.3 min; the enantiomeric excess, 39%).

Enantiopure (*R*)-6-methoxy-2-naphthylglycolic acid, (*R*)-6-MNGA

To a solution of (*R*)-enriched 6-**MNGA** (1.69 g, 7.3 mmol, 39% ee) in a mixture of H_2O (3 mL) and EtOH (7 mL) was added (*R*)-1-phenylethylamine (**PEA**) (0.88 g, 7.3 mmol), and the mixture was stirred under reflux for 6 h. After being cooled to rt, the mixture was standed overnight, and the deposited colorless crystals were collected by filtration. The salt thus obtained was recrystallized twice with a mixture of H_2O/EtOH (3/7; 8 and then 5 mL) to afford the diastereopure (*R*)-6-**MNGA** •(*R*)-**PEA** salt (1.26 g, 3.6 mmol, 49% based on the amount of (*R*)-enriched 6-**MNGA** used) as white crystals. To the diastereomeric salt was added 1M HCl aq. (100 mL), and the mixture was stirred 1 h and extracted with 2-butanone (3 x 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford enantiopure (*R*)-6-**MNGA** (0.83g, 3.6 mmol,

quant.; 71% recovery from (*R*)-6-**MNGA** contained in (*R*)-enriched 6-**MNGA** used) as a white solid. The ee of (*R*)-6-**MNGA** was determined by a HPLC analysis. Mp 173.5-174.0 °C; $[\alpha]_D^{25}$ = -144 (*c* 1.018 in MeOH). IR (KBr) cm^{-1}: 3361, 3276, 3080-2840, 1721, 1689, 1633, 1605, 1392, 1227, 1166, 1040, 852, 815. ^1H NMR (300 MHz, DMSO-d6) δ 3.87 (s, 3H), 5.14 (s, 1H), 7.14-7.18 (m, 1H), 7.30 (s, 1H), 7.49-7.51 (m, 1H), 7.77-7.84 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d6) δ 55.19, 72.48, 105.80, 118.77, 125.31, 125.59, 126.62, 128.07, 129.37, 133.84, 135.40, 157.34, 174.20. Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.09; H, 5.39.

Enantiopure (*S*)-6-methoxy-2-naphthylglycolic acid, (*S*)-6-MNGA

After concentration of the mother liquor of the enantioseparation described above under reduced pressure, 1 M HCl aq. (50 mL) was added to the residue, and the aqueous layer was extracted with 2-butanone (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-enriched 6-**MNGA** (0.75g, 3.2 mmol). Crystallization of (*S*)-enriched 6-**MNGA** (0.75g, 3.2 mmol) with (*S*)-**PEA** (0.40 g, 3.3 mmol) from a mixture of H_2O/EtOH = (3/7, 5 mL), followed by recrystallization from H_2O/EtOH (3/7, 4 mL), afforded diastereopure (*S*)-6-**MNGA** •(*S*)-**PEA** salt (0.60 g, 1.5 mmol) as white crystals. To the diastereomeric salt thus obtained was added 1M HCl aq. (50 mL), and the mixture was stirred for 1 h and extracted with 2-butanone (3 x 50 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford enantiopure (*S*)-6-**MNGA** (0.34 g, 1.46 mmol, 20% total yield from (*R*)-enriched 6-**MNGA** used; 68% recovery from (*S*)-6-**MNGA** contained in (*R*)-enriched 6-**MNGA** used) as a white solid. The ee of (*S*)-6-**MNGA** was determined by a HPLC analysis. The IR, ^1H NMR, and ^{13}C NMR spectra were the same as those of (*R*)-6-**MNGA**. Mp 171.5-172.0 °C; $[\alpha]_D^{25}$= +143 (*c* 0.941 in MeOH). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.11; H, 5.42.

A typical procedure for the enantioseparation of racemic amines with enantiopure 6-MNGA.

To a solution of (*R*)-**MNGA** (121.1 mg, 0.5 mmol) in EtOH/H_2O (9/1, 4 mL) was added racemic 1-phenylethylamine (**4a**) (60.5 mg, 0.5 mmol), and the mixture was refluxed for 6 h. The solution was

then slowly cooled to 30 °C and left standing for 12 h in a water bath kept at 30 °C. The deposited powder was collected by filtration, washed with EtOH/H_2O (8/1, 0.5 mL), and dried under reduced pressure. The salt was dissolved in 1M KOH aq. (20 mL), and the aqueous solution was extracted with chloroform (3 x 20 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give enantio-enriched **4a** (20.9 mg, 69% based on a half amount of **4a** used).

The enantiomeric excesses of the amines were determined by HPLC analyses on a Daicel Chiralcel CrownPak CR(+) for **4a, 4d, 4e, 4f, 4g, 4h, 4i,** and **4k**, and on a Daicel Chiralcel OJ-RH for **4b**, **4c** and **4j**, respectively.

Crystal data for (*R*)-6-MNGA•(*R*)-4a salt

FW = 353.42, Monoclinic, Space group $P2_1$, *a* = 8.365(2), *b* = 6.8230(13), *c* = 16.988(5) Å, β = 103.245(8), *V* = 943.8(4) Å^3, *Z* = 2, *R* = 0.0790, *Rw* = 0.0960. The dihedral angle between the carboxylate and the hydroxy group of (*R*)-6-**MNGA**: -170.6 °(CCDC 279953).

Mp 182.5-187.5 °C (decomp.); $[\alpha]_D^{25}$= + 75.9 (*c* = 0.1961 in MeOH). IR (KBr) cm^{-1}: 3363, 3100-2830, 1607, 1573, 1533, 1386, 1255, 1213, 1169, 1029, 861, 765, 704, 475. ^{1}H NMR (300 MHz, CD_3OD) δ 1.61 (d, *J* = 7 Hz, 3H), 3.89 (s, 3H), 4.40 (q, *J* = 7 Hz, 1H), 4.98 (s, 1H), 7.07-7.11 (m, 1H), 7.20 (d, *J* = 2 Hz, 1H), 7.40-7.44 (m, 5H), 7.54-7.57 (m, 1H), 7.69-7.73 (m, 2H), 7.83 (s, 1H).

Crystal data for (*R*)-6-MNGA•(*R*)-4b salt

FW = 367.44, Monoclinic, Space group $P2_1$, *a* = 8.6250(8), *b* = 6.7910(4), *c* = 16.882(3) Å, β = 97.308(3), *V* = 980.8(2) Å^3, *Z* = 2, *R* = 0.0520, *Rw* = 0.0600. The dihedral angle between the carboxylate and the hydroxy group of (*R*)-6-**MNGA**: -172.0 °(CCDC 279954).

Mp 195.5-198.0 °C (decomp.); $[\alpha]_D^{25}$= +57.8 (*c* = 0.2068 in MeOH). IR (KBr) cm^{-1}: 3398, 3100-2800, 1607, 1576, 1533, 1387, 1257, 1216, 1169, 1071, 1029, 860, 768, 460. ^{1}H NMR (300 MHz, CD_3OD) δ 1.56 (d, *J* = 7 Hz, 3H), 2.39 (s, 3H), 3.89 (s, 3H), 4.68 (q, *J* = 7 Hz, 1H), 4.98 (s, 1H), 7.07-7.11 (m, 1H), 7.20 (d, *J* = 2 Hz, 1H), 7.25-7.33 (m, 3H), 7.41-7.43 (m, 1H), 7.54-7.57 (m, 1H), 7.69-7.74 (m, 2H), 7.83 (s, 1H).

Crystal data for (*S*)-6-MNGA•(*S*)-4j salt

FW = 403.48, Monoclinic, Space group $P2_1$, *a* = 8.3320(8), *b* = 6.9090(5), *c* = 18.378(2) Å, β =

92.771(4), V = 1056.7(2) Å^3, Z = 16, R = 0.0570, Rw = 0.0680. The dihedral angle between the carboxylate and the hydroxy group of (*R*)-6-**MNGA**: -170.3 °(CCDC 279955).

Mp 210.5-2137.0 °C (decomp.); $[\alpha]_D^{25}$= -42.0 (c = 0.1666 in MeOH). IR (KBr) cm^{-1}: 3408, 3100-2800, 1606, 1543, 1509, 1466, 1389, 1267, 1214, 1168, 1072, 1029, 858, 818, 749, 480. ^{1}H NMR (300 MHz, CD_3OD) δ 1.71 (d, J = 7 Hz, 3H), 3.89 (s, 3H), 4.59 (q, J = 6 Hz, 1H), 4.98 (s, 1H), 7.07-7.11 (m, 1H), 7.19 (d, J = 3 Hz, 1H), 7.53-7.57 (m, 4H), 7.69-7.74 (m, 2H), 7.83 (s, 1H), 7.88-7.95 (m, 3H), 7.98 (s, 1H).

Acknowledgments

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References

1. (a) Kinbara, K.; Saigo, K. In *Topics in Stereochemistry*; Denmark, S. C., Ed. Wiley & Sons: New York, 2003, Chapter 4. (b) Kinbara, K. *Synlett*. **2005**, *5*, 732-743.
2. (a) Kinbara, K.; Harada, Y.; Saigo, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2219-2222; (b) Kinbara, K.; Harada, Y.; Saigo, K. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1339-1347.
3. (a) Freeman, S.; Alder, J. F. *Eur. J. Med. Chem.* **2002**, 527-539; (b) Choi, S.-K.; Moran, E. J. *USP* **2003**, No. 323,939.
4. Yatagai, M.; Ohnuki, T. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1826-1827.
5. Kinbara, K.; Sakai, K.; Hashimoto, Y.; Nohira, H.; Saigo, K. *J. Chem. Soc. Perkin Trans. 2* **1996**, 2615-2622.
6. (a) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2000**, *122*, 3746-3753; (b) Kobayashi, Y.; Kurasawa, T.; Kinbara, K.; Saigo, K. *J. Org. Chem.* **2004**, *69*, 7436-7441.

Scheme 1. Synthesis of enantiopure 6-**MNGA**.

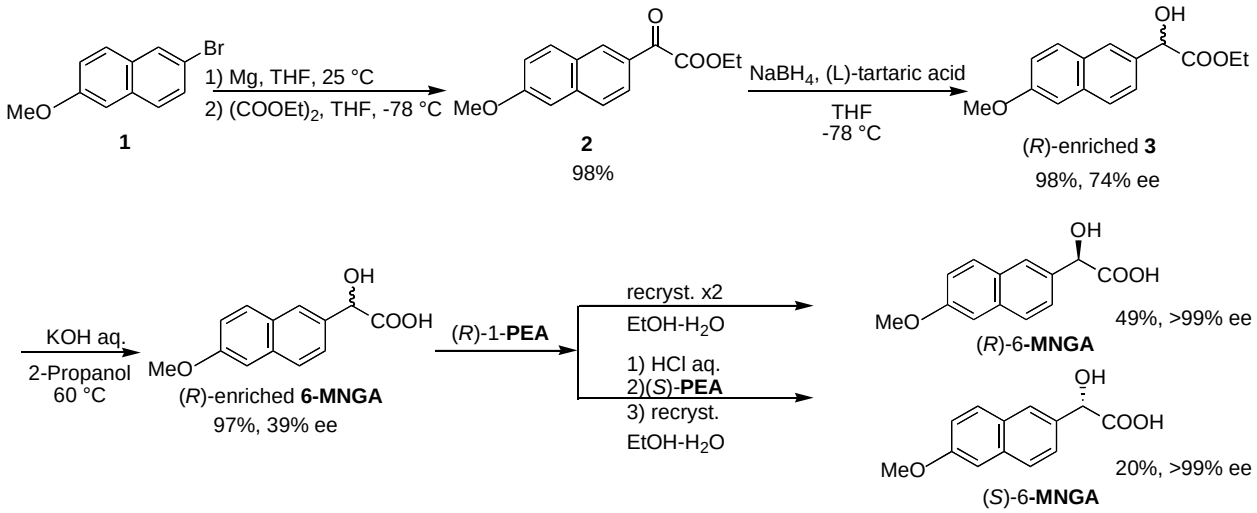
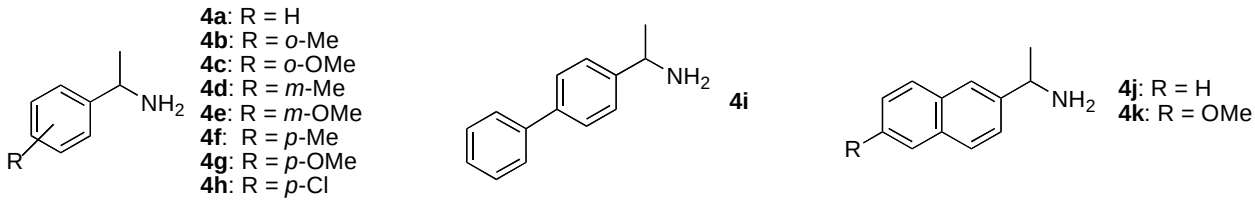


Table 1. Enantioseparation of 1-arylethylamines **4a-k** with enantiopure 6-**MNGA**.

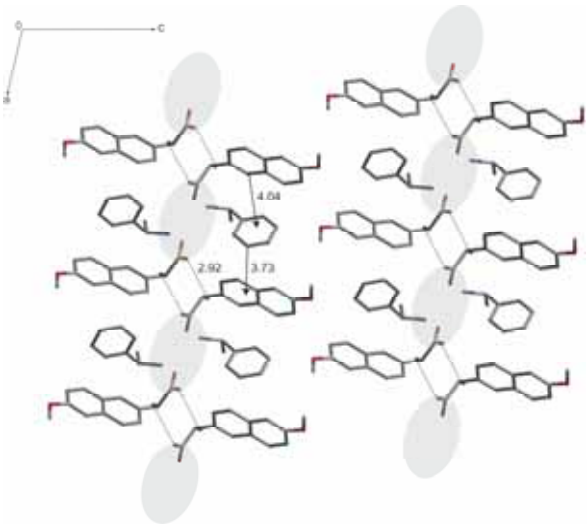


Entry	Racemic amine	Solvent	Amount of solvent[a]	Yield (%)[b]	Ee (%)[c]	Efficiency[d]
1[e]	**4a**	EtOH/H_2O	3.6/0.4	69	>99 (*R*)[f]	0.68 (0.70)
2[e]	**4b**	MeOH/H_2O	7.0/2.0	70	99 (*R*)	0.69 (0.05)
3[g]	**4c**	EtOH	3.5	54	90 (*S*)	0.49 (-)[h]
4[g]	**4d**	iPrOH	8.0	75	96 (-)[i]	0.72 (0.75)
5[e]	**4e**	MeOH	7.0	81	81 (-)[i]	0.66 (0.65)
6[e]	**4f**	MeOH/H_2O	10.0/2.0	70	>99 (*R*)	0.69 (0.65)
7[e]	**4g**	MeOH	7.0	86	56 (-)[i]	0.48 (0.52)
8[g]	**4h**	MeOH/H_2O	10.0/0.5	77	97 (*S*)	0.74 (0.74)
9[g]	**4i**	iPrOH	12.0	77	29 (-)[i]	0.22 (0.08)
10[g]	**4j**	EtOH/H_2O	12.0/3.0	87	>99 (*S*)	0.86 (0.72)
11[g]	**4k**	MeOH	10.0	69	>99 (*S*)	0.68 (0.14)

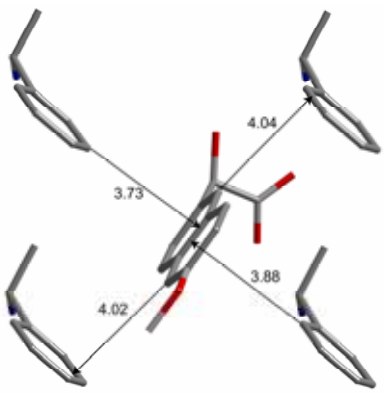
[a] The weight (g) of the solvent normalized to a 0.5 mmol-scale. [b] Yield of the crystallized diastereomeric salt based on a half amount of the racemic amine.
[c] Enantiomeric excess (ee) of the liberated amine, which was determined by a HPLC analysis. [d] Efficiency is the product of the yield and the ee. The value in the parenthesis is the efficiency in enantioseparation with 2-**NGA**. [e] (*R*)-6-**MNGA** was used. [f] Absolute configuration of the major enantiomer, which was determined by a X-ray crystallographic analysis and/or deduced on the basis of the elution order in the HPLC analysis. [g] (*S*)-6-**MNGA** was used.
[h] Not crystallized. [i] Not determined.

Figure 1. Crystal structures; a) top view and b) molecular arrangement at the proximity of the naphthyl group of the (*R*)-6-**MNGA**•(*R*)-**4a** salt, and c) and d) those of the (*R*)-6-**MNGA**•(*R*)-**4a** salt. The gray circles mean columnar hydrogen-bonding networks. The dotted lines and arrows show intercolumnar hydrogen bonds and T-shaped CH(sp^2)/π interactions, respectively. The bond distances are in angstrom.

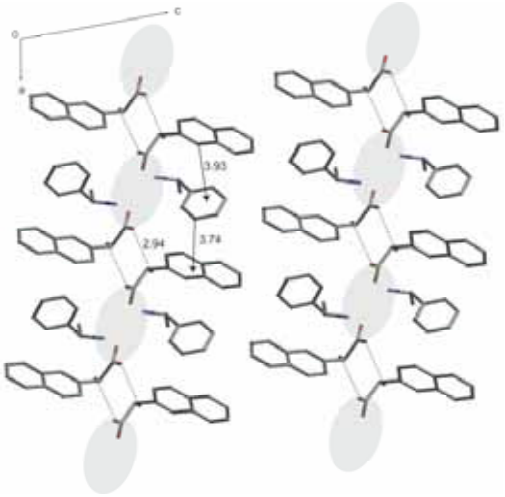
a)



b)



c)



d)

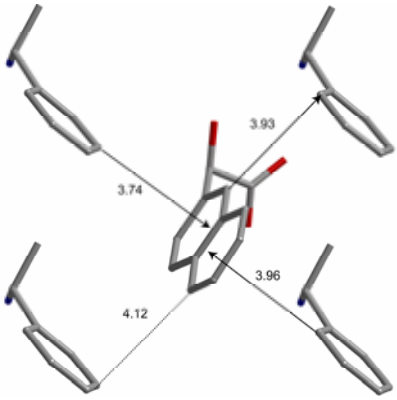


Figure 2. Crystal structure of the less-soluble (*R*)-6-**MNGA**•(*R*)-**4b** salt; a) top view and b) molecular arrangement at the proximity of the naphthyl group. The gray circles and lines mean columnar hydrogen-bonding networks and boundary surfaces interacting by van der Waals interaction, respectively. The dotted lines and arrows show hydrogen bonds and T-shaped CH(sp^2)/π and CH(sp^3)/π interactions, respectively. The bond distances are in angstrom.

a) b)

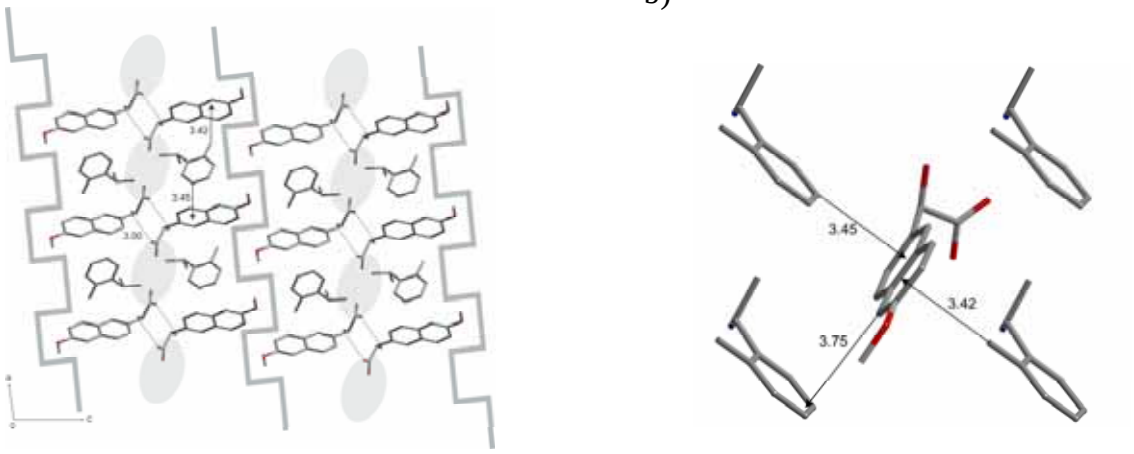
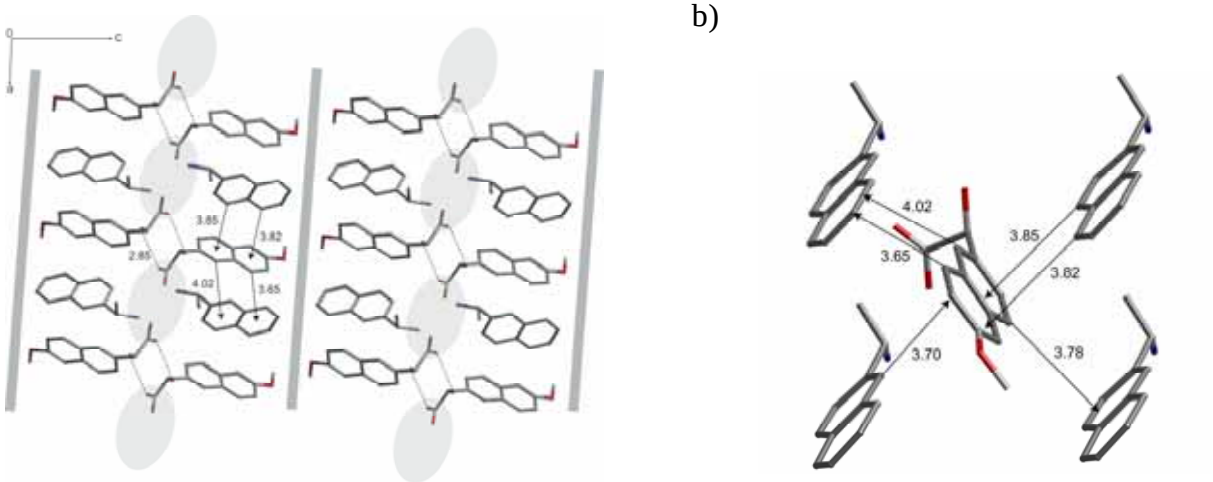


Figure 3. Crystal structure of the less-soluble (*S*)-6-**MNGA**•(*S*)-**4j** salt; a) top view and b) molecular arrangement at the proximity of the naphthyl group. The gray circles and lines mean hydrogen-bonding networks and boundary surfaces interacting with van der Waals interaction, respectively. The dotted lines and arrows show hydrogen bonds and T-shaped CH(sp^2)/π interactions, respectively. The bond distances are in angstrom.

a) b)



Graphical Abstract

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Synthesis of enantiopure 6-methoxy-2-naphthylglycolic acid and its application as a resolving agent

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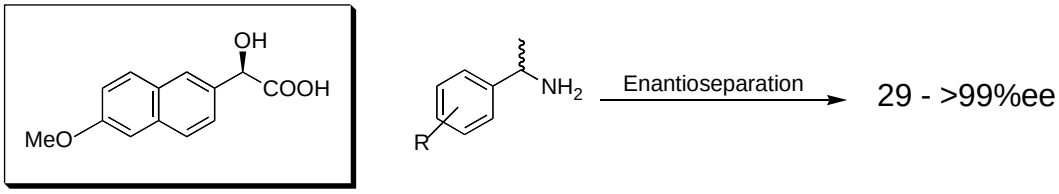
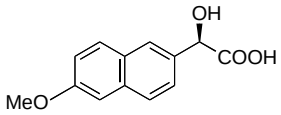
Takayoshi Shimada, Yuka Kobayashi, and Kazuhiko Saigo*



Stereochemistry Abstract

Takayoshi Shimada, Yuka Kobayashi, Kazuhiko Saigo*



$C_{13}H_{12}O_4$

(*R*)-6-Methoxy-2-naphthylglicolic acid

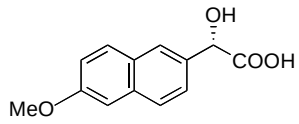
Ee >99%

$[\alpha]^{25}_D$ = -144 (*c* 1.018, MeOH)

Source of chirality: (*R*)-phenylethylamine

Absolute configration: *R*

Takayoshi Shimada, Yuka Kobayashi, Kazuhiko Saigo*



$C_{13}H_{12}O_4$

(*S*)-6-Methoxy-2-naphthylglicolic acid

Ee >99%

$[\alpha]^{25}_D$ = +143 (*c* 0.941, MeOH)

Source of chirality: (*S*)-phenylethylamine

Absolute configration: *S*