

# Supporting Information

## Direct Synthesis of Free $\alpha$ -Amino Acids by Telescoping Three-Step Process from 1,2-Diols

Haruki Inada, Masatoshi Shibuya,\* and Yoshihiko Yamamoto

Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, Nagoya University,  
Furo-cho, Chikusa, Nagoya 464-8601, Japan

Corresponding author, Email: m-shibu@ps.nagoya-u.ac.jp

1.	General considerations	S2
2.	Preparation of 1,2-diols	S3
3.	Transamination of $\alpha$ -keto acids to $\alpha$ -amino acids	S15
4.	Three-step synthesis of $\alpha$ -amino acids from 1,2-diols	S18
5.	Derivatization of $\alpha$ -amino acids	S23
6.	Synthesis of $^{15}\text{N}$ -labeled $\alpha$ -amino acid	S24
7.	Synthesis of bicyclic $\alpha$ -amino acids	S26
8.	Kinetic resolution of <i>N</i> -acetyl $\alpha$ -amino acids	S28
9.	Single crystal X-ray diffraction study	S60
10.	References	S61
11.	NMR spectra	S62

## 1. General considerations

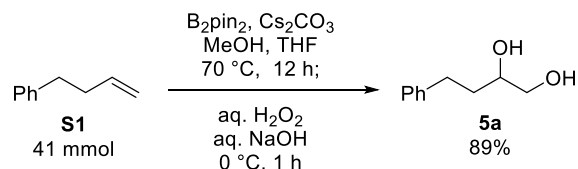
All reactions were carried out under an argon atmosphere, stirred magnetically, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC: Merck Silica Gel 60 F<sub>254</sub>). Column chromatography was carried out using neutral silica gel (Cica silica gel 60N, particle size 0.040-0.050 mm, neutral, KANTO CHEMICAL CO., INC.). NMR spectra were measured by JEOL ECS-400 (400 MHz) in CDCl<sub>3</sub>, chemical shifts are expressed in parts per million (ppm,  $\delta$  scale) relative to tetramethylsilane (TMS) as 0.00 ppm or residual CHCl<sub>3</sub> (7.26 ppm) for <sup>1</sup>H NMR and 77.00 ppm for CDCl<sub>3</sub> for <sup>13</sup>C NMR as an internal reference. In CD<sub>3</sub>OD, chemical shifts are expressed relative to residual CH<sub>3</sub>OH (3.31 ppm for <sup>1</sup>H NMR). In D<sub>2</sub>O, DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) was used as an internal reference. <sup>1</sup>H and <sup>13</sup>C NMR spectra were reported in terms of chemical shift ( $\delta$ , ppm) relative to the singlet at  $\delta$  0.00 ppm for DSS. Coupling constants (*J*) are reported in Hz. Multiplicities are reported using the following abbreviations; s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broad. Infrared (IR) spectra were recorded on a JASCO FT-IR-4200 at 4.0 cm<sup>-1</sup> resolution and reported in wavenumbers. Mass spectra were measured by JEOL JMS-T100LP using Electrospray Ionization (ESI) and Direct Analysis in Real Time (DART). Elemental analyses were performed using Yanaco CHN CORDER MT-6.

L-Aminoacylase (Acylase H “Amano”, >30 kunits/g, mixture of 15% of enzyme and 85% of sodium sulfate) and D-aminoacylase (D-Aminoacylase “Amano”, >10.2 Munits/g) were used for chemoenzymatic resolution. 2-Oxo-4-phenylbutyric acid (**1a**) (TCI), 4-methyl-2-oxovaleric acid (**1b**) (TCI), pyruvic acid (**S29**) (Wako), 2-oxobutyric acid (**S31**) (Aldrich), phenylpyruvic acid (**S33**) (TCI), 4-hydroxyphenylpyruvic acid (**S37**) (TCI), 3-methyl-2-oxovaleric acid (**S39**) (TCI), oxaloacetic acid (**S41**) (TCI), and 2-oxoglutaric acid (**S42**) (TCI) were purchased and used as received.  $\alpha$ -Keto acid **S35** was prepared by the oxidation of the corresponding  $\alpha$ -hydroxy acid according to our previous report.<sup>1</sup> <sup>13</sup>C NMR spectra of  $\alpha$ -amino acids **3g-3l**, **8**, **11**, and **S45** could not be collected owing to their low solubility.

## 2. Preparation of 1,2-diols.

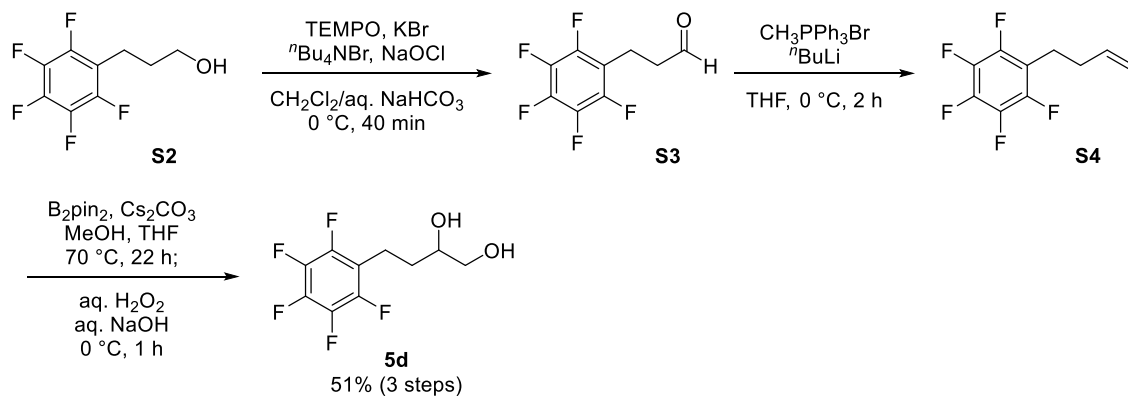
1,2-Diols **5a**, **5d**, **5f**, **5h**, **5i**, **5l**, and **5m** were synthesized from corresponding terminal olefins according to the previous reports.<sup>2, 3</sup>

### Typical procedure for synthesis of 1,2-diols from terminal olefins.



To a solution of olefin **S1** (5.4 g, 41 mmol) in THF (74 mL) were added bis(pinacolato)diboron (20.8 g, 81.7 mmol),  $Cs_2CO_3$  (4.08 g, 12.5 mmol), and MeOH (8.3 mL, 204 mmol) at 0 °C. After the reaction mixture was stirred for 12 h at 70 °C, it was cooled to 0 °C. After the addition of THF (74 mL), aq.  $H_2O_2$  (30%, 20.9 mL, 204 mmol), and aq. NaOH (10%, 73.5 mL, 204 mmol) were added. After 30 min, additional aq.  $H_2O_2$  (30%, 20.9 mL, 204 mmol) and aq. NaOH (10%, 73.5 mL, 204 mmol) were added and the reaction mixture was stirred for 30 min. Then, it was quenched with saturated aq.  $Na_2S_2O_3$  and extracted with AcOEt. The organic layer was dried over  $MgSO_4$ , filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 2/1 to AcOEt only) to afford 1,2-diol **5a** (6.1 g, 89%) as a pale yellow oil.

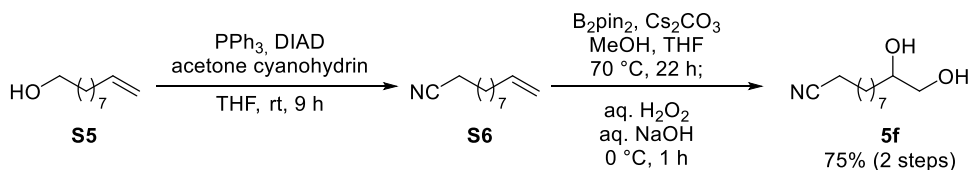
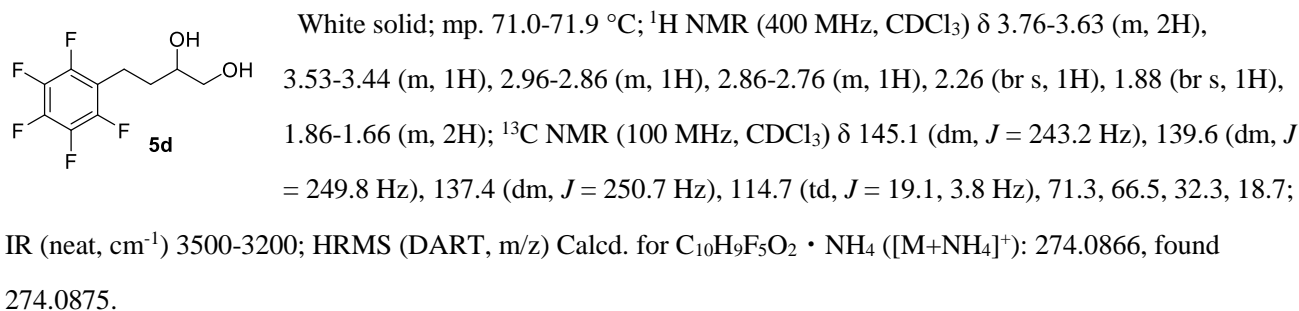
Analytical data of **5a** was shown in ref 3.



To a solution of alcohol **S2** (1.36 g, 6.02 mmol), TEMPO (28.4 mg, 0.182 mmol), KBr (72.5 mg, 0.609 mmol), and  $nBu_4NBr$  (98.6 mg, 0.306 mmol) in  $CH_2Cl_2$  (16 mL) and saturated aq.  $NaHCO_3$  (8.1 mL) was added a solution of aq. NaOCl (1.77 M, 4.42 mL, 7.82 mmol) and saturated aq.  $NaHCO_3$  (8.1 mL) dropwise at 0 °C. After 40 min, it was quenched with saturated aq.  $NaHCO_3$  and saturated aq.  $Na_2S_2O_3$  and extracted with AcOEt. The organic layer was dried over  $MgSO_4$ , filtered, and concentrated in vacuo to provide crude aldehyde **S3**, which was used to the next reaction without any further purification.

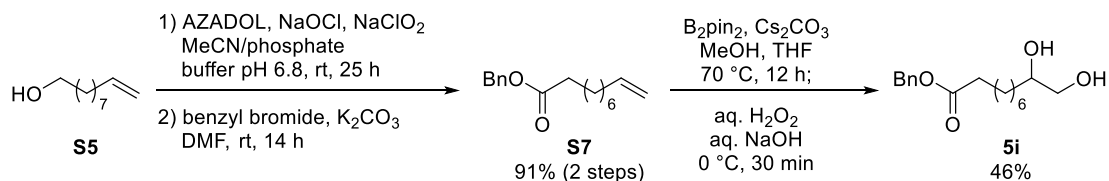
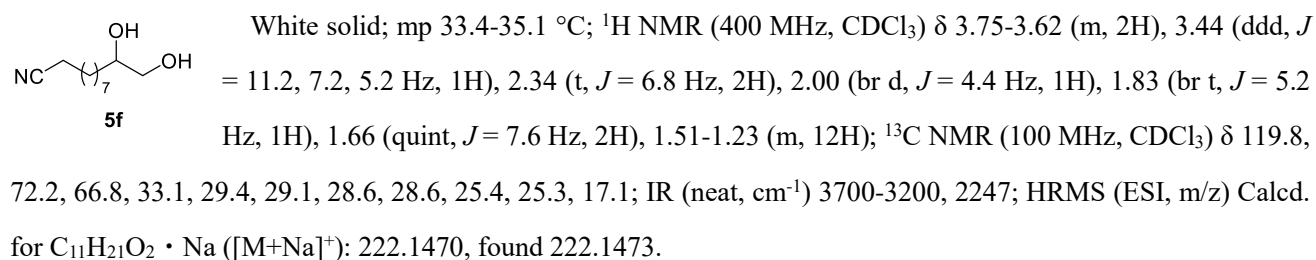
To a well-dried round-bottom flask charged with  $\text{CH}_3\text{PPh}_3\text{Br}$  (2.58 g, 7.23 mmol) and dry THF (15 mL) was added  $n\text{BuLi}$  (15wt%, 4.24 mL, 7.22 mmol) dropwise at 0 °C. After 20 min, a solution of aldehyde **S3** (0.5 M) in THF was added at -78 °C and the reaction mixture was stirred for 2 h at 0 °C. Then, it was quenched with saturated aq.  $\text{NH}_4\text{Cl}$  and extracted with  $\text{Et}_2\text{O}$ . The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo to provide crude olefin **S4**. It was used to the next reaction without any further purification.

1,2-Diol **5d** was prepared from olefin **S4** according to the preparation procedure of **5a**. 1,2-Diol **5d** was afforded as a white solid (0.784 g, 51%, 3 steps) after purification by temporary acetone-protecting and washing by hexane to remove an impurity originated from the boron reagent.



To a solution of alcohol **S5** (52.5 mg, 0.336 mmol),  $\text{PPh}_3$  (104 mg, 0.450 mmol), and DIAD (84.6  $\mu\text{L}$ , 0.437 mmol) in THF (1.7 mL) was added acetone cyanohydrin (36.9  $\mu\text{L}$ , 0.403 mmol) at 0 °C. The reaction mixture was stirred for 9 h at room temperature and concentrated in vacuo. The residue was passed through flash column chromatography on silica gel (hexane/ $\text{AcOEt} = 30/1$ ) to afford olefin **S6** including impurities.

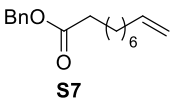
1,2-Diol **5f** was prepared from olefin **S6** according to the preparation procedure of **5a**.



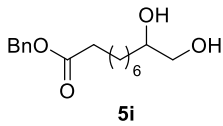


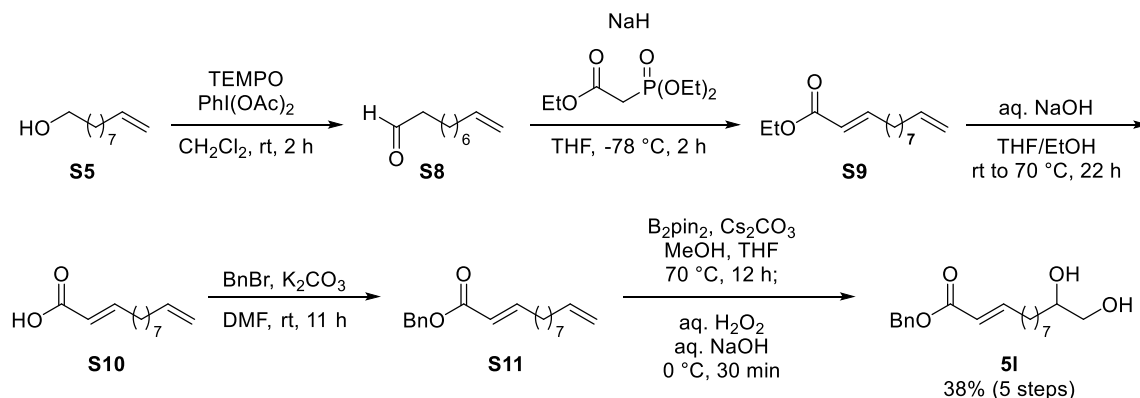
To a solution of alcohol **S5** (1.76 g, 11.3 mmol) and AZADOL (79.8 mg, 0.511 mmol) in MeCN (51 mL) and sodium phosphate buffer (1 M, pH = 6.8, 36 mL) were added a NaOCl aqueous solution (0.20 M, 2.53 mL, 0.506 mmol) and a NaClO<sub>2</sub> aqueous solution (20.2 mmol of 80% NaClO<sub>2</sub> dissolved into 19 mL of water) simultaneously dropwise at room temperature. After 25 h, the reaction mixture was quenched with sodium phosphate buffer (1 M, pH = 2.1, 7.2 mL) and extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to provide crude carboxylic acid which was used to the next reaction without any further purification.

To a solution of carboxylic acid and K<sub>2</sub>CO<sub>3</sub> (3.50 g, 25.3 mmol) in DMF (14 mL) was added benzyl bromide (1.80 mL, 15.2 mmol) at 0 °C. After the reaction mixture was stirred for 14 h at room temperature, it was quenched with H<sub>2</sub>O and extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane only to hexane/AcOEt = 30/1) to afford ester **S7** (2.67 g, 91%, 2 steps) as a colorless oil.

 Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40-7.29 (m, 5H), 5.80 (ddt, *J* = 17.6, 10.0, 6.8 Hz, 1H), 5.11 (s, 2H), 4.99 (dq, *J* = 17.6, 1.6 Hz, 1H), 4.93 (dm, *J* = 10.0 Hz, 1H), 2.35 (t, *J* = 7.6 Hz, 2H), 2.03 (qt, *J* = 6.8, 1.6 Hz, 2H), 1.70-1.60 (m, 2H), 1.42-1.18 (m, 8H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 173.7, 139.1, 136.1, 128.5 (2C), 128.2 (3C), 114.2, 66.0, 34.3, 33.7, 29.1 (2C), 28.9, 28.8, 24.9; IR (neat, cm<sup>-1</sup>) 1738, 1641; HRMS (ESI, *m/z*) Calcd. for C<sub>17</sub>H<sub>24</sub>O<sub>2</sub> • Na ([M+Na]<sup>+</sup>): 283.1674, found 283.1683.

1,2-Diol **5i** was prepared from olefin **S7** according to the preparation procedure of **5a**. 1,2-Diol **5i** was afforded as a white solid (1.40 g, 46%) after purification by temporary acetonide-protection to remove an impurity originated from the boron reagent.

 White solid; mp. 51.3-52.1 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.42-7.28 (m, 5H), 5.11 (s, 2H), 3.74-3.62 (m, 2H), 3.43 (ddd, *J* = 10.8, 7.6, 5.2 Hz, 1H), 2.35 (t, *J* = 7.2 Hz, 2H), 1.95 (d, *J* = 4.4 Hz, 1H), 1.79 (t, *J* = 5.2 Hz, 1H), 1.68-1.60 (m, 2H), 1.48-1.22 (m, 10H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 173.7, 136.1, 128.5 (2C), 128.1 (3C), 72.2, 66.8, 66.1, 34.3, 33.1, 29.3, 29.1, 28.9, 25.4, 24.8; IR (neat, cm<sup>-1</sup>) 3600-3200, 2929, 2850, 1736; HRMS (ESI, *m/z*) Calcd. for C<sub>17</sub>H<sub>26</sub>O<sub>4</sub> • Na ([M+Na]<sup>+</sup>): 317.1729, found 317.1715.



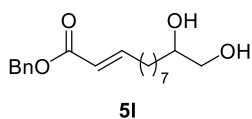
To a solution of alcohol **S5** (1.57 g, 10.1 mmol), TEMPO (158 mg, 1.01 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and was added iodobenzene diacetate (3.41 g, 10.6 mmol) at 0 °C. After the reaction mixture was stirred for 2 h at room temperature, it was quenched with saturated aq. NaHCO<sub>3</sub> and saturated aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to provide crude aldehyde **S8**, which was used to the next reaction without any further purification.

To a well-dried round-bottom flask charged with NaH (60%, 443 mg, 11.1 mmol) and dry THF (50 mL) was added triethyl phosphonoacetate (2.21 mL, 11.1 mmol) dropwise at 0 °C. After 30 min, a solution of aldehyde **S8** (0.5 M) in THF was added at -78 °C. After 2 h, the reaction mixture was quenched with saturated H<sub>2</sub>O and extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to provide crude ester **S9**, which was used to the next reaction without any further purification.

To a solution of ester **S9** in THF (11 mL) and EtOH (2.7 mL) was added aq. NaOH (2.5 M, 13.3 mL, 33.2 mmol) at room temperature. After 12 h, aq. NaOH (2.5 M, 14.2 mL, 35.5 mmol) was added and stirred for 4 h. Then, the reaction mixture was warmed up to 70 °C and stirred for 6 h at the same temperature. After the reaction mixture was cooled to room temperature, AcOEt was added and the resultant mixture was separated into the organic layer and the aqueous layer. The aqueous layer was acidified with aq. HCl (2 M) and extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to provide crude carboxylic acid **S10**, which was used to the next reaction without any further purification.

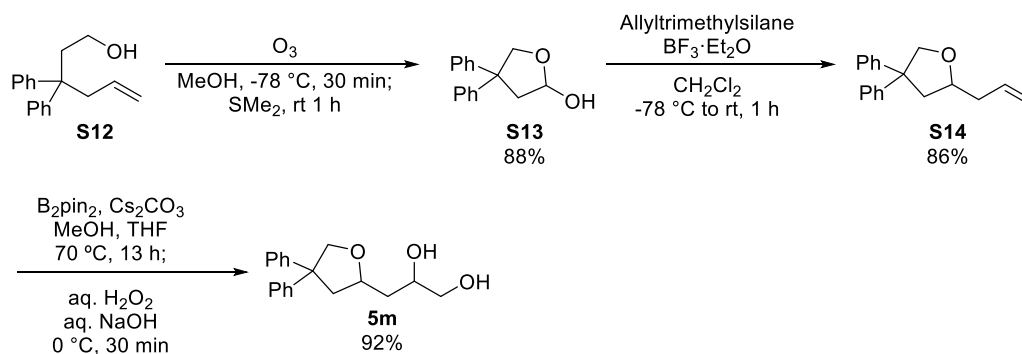
To a solution of carboxylic acid **S10** and K<sub>2</sub>CO<sub>3</sub> (4.88 g, 35.3 mmol) in DMF (14 mL) was added benzyl bromide (2.39 mL, 20.1 mmol) at 0 °C. After the reaction mixture was stirred for 11 h at room temperature, it was quenched with saturated H<sub>2</sub>O and extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was passed through a flash column chromatography on silica gel (hexane/AcOEt = 20/1) to afford ester **S11** including impurities.

1,2-Diol **5I** was prepared from ester **S11** according to the preparation procedure of **5a**. 1,2-Diol **5I** was afforded as a white solid (1.22 g, 38%, 5 steps) after purification by temporary acetonide-protection to remove an impurity originated from the boron reagent.



White solid; mp. 50.2-51.4 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40-7.30 (m, 5H), 7.01 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.86 (dt, *J* = 15.6, 1.2 Hz, 1H), 5.12 (s, 2H), 3.75-3.62 (m, 2H), 3.47-3.40 (m, 1H), 2.20 (qd, *J* = 6.8 Hz, 1.2 Hz, 2H), 1.98 (d, *J* = 4.4 Hz, 1H), 1.83 (t, *J* =

5.2 Hz, 1H), 1.50-1.23 (m, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.5, 150.1, 136.0, 128.4 (2C), 128.0 (3C), 120.8, 72.2, 66.6, 65.9, 32.9, 32.1, 29.4, 29.1, 28.9, 27.8, 25.4; IR (neat, cm<sup>-1</sup>) 3700-3200, 1718, 1653; HRMS (ESI, *m/z*) Calcd. for C<sub>19</sub>H<sub>28</sub>O<sub>4</sub> • Na ([M+Na]<sup>+</sup>): 343.1885, found 343.1876.



After a solution of alcohol **S12** (286 mg, 1.20 mmol) in MeOH (6.0 mL) was cooled to  $-78 ^\circ\text{C}$ , ozone gas was bubbled into the solution until the color of the reaction mixture turned to deep blue. After 30 min, air was bubbled into the reaction mixture until a blue color disappeared. Then, dimethyl sulfide (0.877 mL, 12.0 mmol) was added at the same temperature. After the reaction mixture was stirred for 1 h at room temperature, it was concentrated in vacuo and purified by flash column chromatography on silica gel (hexane only to hexane/AcOEt = 4/1) to afford hemiacetal **S13** (254 mg, 88%) as a white solid.

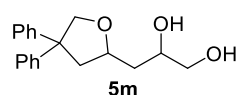
CC1(Cc2ccccc2)C(Cc3ccccc3)C(O)C1O (**S13**) White solid; mp  $108.9\text{--}109.7 ^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34–7.16 (m, 10H), 5.62 (ddd,  $J = 6.0, 5.6, 4.0$  Hz, 1H), 4.55 (d,  $J = 8.8$  Hz, 1H), 4.44 (dd,  $J = 8.8, 0.8$  Hz, 1H), 2.93 (ddd,  $J = 13.6, 6.0, 0.8$  Hz, 1H), 2.62 (dd,  $J = 13.6, 4.0$  Hz, 1H), 2.50 (d,  $J = 6.0$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  146.2, 145.0, 128.6, 128.4, 127.2, 126.8, 126.7, 126.4, 99.5, 75.9, 55.4, 46.9; IR (neat,  $\text{cm}^{-1}$ ) 3700–3200; HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{16}\text{H}_{16}\text{O}_2 \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 263.1048, found 263.1031.

To a well-dried round-bottom flask charged with hemiacetal **S13** (29.9 mg, 0.124 mmol), allyltrimethylsilane (39.7  $\mu\text{L}$ , 0.249 mmol), and dry  $\text{CH}_2\text{Cl}_2$  (300  $\mu\text{L}$ ) was added boron trifluoride - ethyl ether complex (46.9  $\mu\text{L}$ , 0.373 mmol) dropwise at  $-78 ^\circ\text{C}$ . The reaction mixture was warmed up to room temperature over a period of 1 h. Then, it was quenched with  $\text{H}_2\text{O}$  and extracted with AcOEt. The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 30/1) to afford olefin **S14** (28.3 mg, 86%) as a colorless oil.

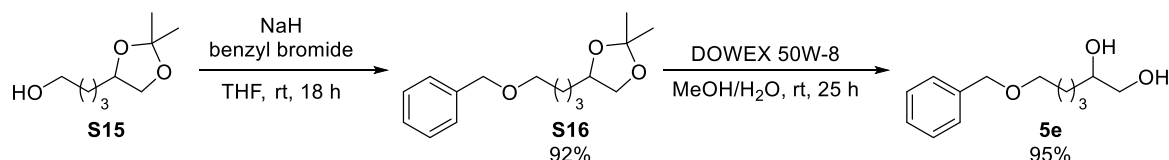
CC1(Cc2ccccc2)C(Cc3ccccc3)C(O)C1C=C (**S14**) Colorless oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32–7.15 (m, 10H), 5.81 (ddt,  $J = 17.6, 10.8, 7.6$  Hz, 1H), 5.10 (dq,  $J = 17.6, 1.2$  Hz, 1H), 5.06 (dm,  $J = 10.8$  Hz, 1H), 4.62 (dd,  $J = 8.8, 1.2$  Hz, 1H), 4.13 (d,  $J = 8.8$  Hz, 1H), 4.13–4.06 (m, 1H), 2.59 (ddd,  $J = 12.4, 5.6, 1.2$  Hz, 1H), 2.45–2.27 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  146.3, 145.9, 134.7, 128.4, 128.3, 127.2, 127.1, 126.4, 126.2, 117.2, 78.0, 76.9, 56.0, 44.3, 40.3; IR (neat,  $\text{cm}^{-1}$ ) 1072; HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{19}\text{H}_{20}\text{O} \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 287.1412, found 287.1392.

1,2-Diol **5m** was prepared from olefin **S14** according to the preparation procedure of **5a**. 1,2-Diol **5m** was

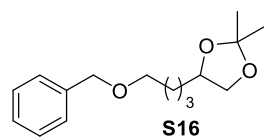
afforded as a white amorphous (644 mg, 92%).



White amorphous;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32-7.16 (m, 20H), 4.66 (d,  $J = 9.6$  Hz, 1H), 4.63 (d,  $J = 9.6$  Hz, 1H), 4.32-4.23 (m, 2H), 4.15 (dd,  $J = 9.6, 2.0$  Hz, 2H), 3.98-3.89 (m, 2H), 3.69-3.59 (m, 3H), 3.57-3.46 (m, 2H), 2.81 (br d,  $J = 9.2$  Hz, 1H), 2.70 (dd,  $J = 12.0, 5.6$  Hz, 1H), 2.65 (dd,  $J = 12.4, 6.0$  Hz, 1H), 2.40 (dd,  $J = 12.0, 9.6$  Hz, 1H), 2.36 (dd,  $J = 12.4, 9.6$  Hz, 1H), 2.23 (br t,  $J = 6.4$  Hz, 1H), 2.09 (br t,  $J = 5.6$  Hz, 1H), 1.85 (ddd,  $J = 14.0, 7.6, 3.2$  Hz, 1H), 1.77-1.66 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  145.8, 145.7, 145.5, 145.3, 128.5 (2C), 128.43 (2C), 128.37 (2C), 128.35 (2C), 127.02 (4C), 126.96 (4C), 126.6, 126.5, 126.4, 126.3, 78.2, 77.2, 76.6, 76.0, 71.6, 69.9, 66.8, 66.4, 55.7, 55.4, 45.4, 44.8, 38.7, 38.5; IR (neat,  $\text{cm}^{-1}$ ) 3700-3200; HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{19}\text{H}_{22}\text{O}_3 \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 321.1467, found 321.1449.

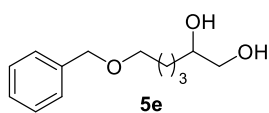


To a well-dried round-bottom flask charged with NaH (60%, 166 mg, 4.16 mmol) and dry THF (5.5 mL) was added a solution of alcohol **S15** (0.7 M, 481 mg, 2.76 mmol) in THF (5.5 mL) at 0 °C. After the mixture was stirred for 30 min at room temperature, benzyl bromide (492  $\mu\text{L}$ , 4.14 mmol) was added dropwise at 0 °C. After the reaction mixture was stirred for 18 h at room temperature, it was quenched with  $\text{H}_2\text{O}$  and extracted with AcOEt. The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane only to hexane/AcOEt = 10/1) to afford ether **S16** (672 mg, 92%) as a colorless oil.

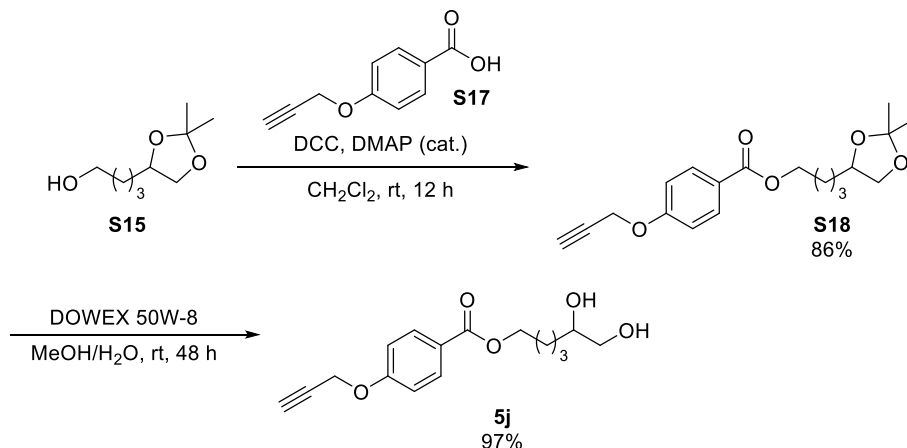


Colorless oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39-7.26 (m, 5H), 4.50 (s, 2H), 4.08 (quin,  $J = 7.2$  Hz, 1H), 4.03 (t,  $J = 7.2$  Hz, 1H), 3.50 (t,  $J = 7.2$  Hz, 1H), 3.48 (t,  $J = 6.4$  Hz, 2H), 1.71-1.59 (m, 3H), 1.57-1.42 (m, 3H), 1.40 (s, 3H), 1.35 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  138.5, 128.3, 127.6, 127.5, 108.6, 76.0, 72.9, 70.1, 69.4, 33.4, 29.7, 26.9, 25.7, 22.5; IR (neat,  $\text{cm}^{-1}$ ) 1101; HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{16}\text{H}_{24}\text{O}_3 \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 287.1622, found 287.1623.

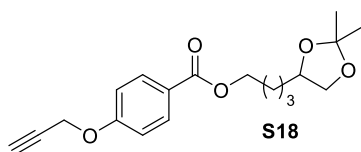
To a solution of ether **S16** (1.11 g, 4.19 mmol) in MeOH (17 mL) and  $\text{H}_2\text{O}$  (4.2 mL) was added DOWEX 50W-8 (200-400 mesh, 120 mg) at room temperature. After 25 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/2) to afford 1,2-diol **5e** (0.897 g, 95%) as a pale yellow oil.



Pale yellow oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38-7.26 (m, 5H), 4.50 (s, 2H), 3.76-3.60 (m, 2H), 3.49 (t,  $J$  = 6.4 Hz, 2H), 3.47-3.39 (m, 1H), 2.13 (br s, 1H), 1.88 (br s, 1H), 1.73-1.39 (m, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  138.4, 128.4, 127.7, 127.6, 73.0, 72.1, 70.1, 66.8, 32.9, 29.6, 22.3; IR (neat,  $\text{cm}^{-1}$ ) 3700-3200, 2937, 2862, 1099; HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{13}\text{H}_{20}\text{O}_3 \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 247.1310, found 247.1310.

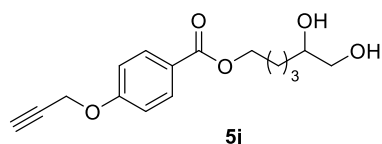


To a solution of alcohol **15** (1.75 g, 10.1 mmol), DCC (2.29 g, 11.1 mmol) and DMAP (246 mg, 2.02 mmol) in  $\text{CH}_2\text{Cl}_2$  (40 mL) was added carboxylic acid **17** (1.78 g, 10.1 mmol) at room temperature. After 12 h, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 8/1) to afford ester **18** (2.87 g, 86%) as a colorless oil.

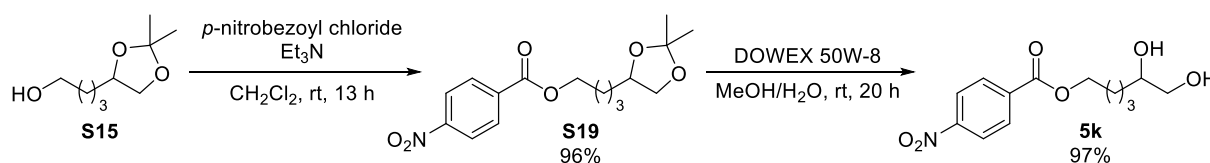


$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.00 (dt,  $J$  = 8.8, 2.8 Hz, 2H), 7.00 (dt,  $J$  = 8.8, 2.8 Hz, 2H), 4.75 (d,  $J$  = 2.0 Hz, 2H), 4.30 (t,  $J$  = 6.4 Hz, 2H), 4.13-4.07 (m, 1H), 4.04 (dd,  $J$  = 7.6, 6.0 Hz, 1H), 3.52 (t,  $J$  = 7.6 Hz, 1H), 2.54 (t,  $J$  = 2.0 Hz, 1H), 1.80 (quint,  $J$  = 7.6 Hz, 2H), 1.73-1.44 (m, 4H), 1.41 (s, 3H), 1.35 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.1, 161.1, 131.5, 123.6, 114.4, 108.7, 77.8, 76.0, 75.8, 69.3, 64.5, 55.8, 33.2, 28.7, 26.9, 25.7, 22.3; IR (KBr,  $\text{cm}^{-1}$ ) 1712; HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{19}\text{H}_{24}\text{NO}_5 \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 355.1514, found 355.1521.

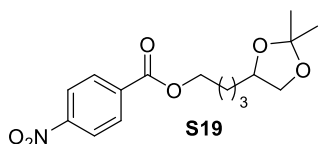
To a solution of ester **18** (1.75 g, 10.1 mmol) in MeOH (34 mL) and  $\text{H}_2\text{O}$  (8.6 mL) was added DOWEX 50W-8 (200-400 mesh, 292 mg) at room temperature. After 14 h, additional DOWEX 50W-8 (200-400 mesh, 287 mg) was added and the reaction mixture was stirred for 34 h. Then, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/1 to AcOEt only) to afford 1,2-diol **5j** (2.44 g, 97%) as a white solid.



White solid; mp. 75.2-77.1 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.98 (dt,  $J = 8.8, 2.8$  Hz, 2H), 7.06 (dt,  $J = 8.8, 2.8$  Hz, 2H), 4.82 (d,  $J = 2.8$  Hz, 2H), 4.31 (t,  $J = 6.4$  Hz, 2H), 3.63-3.57 (m, 1H), 3.48 (dd,  $J = 10.8, 4.4$  Hz, 1H), 3.44 (dd,  $J = 10.8, 6.4$  Hz, 1H), 2.99 (t,  $J = 2.8$  Hz, 1H), 1.87-1.72 (m, 2H), 1.71-1.39 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  167.9, 163.0, 132.4, 124.5, 115.7, 79.1, 77.3, 73.1, 67.3, 65.9, 56.7, 34.0, 29.9, 23.3; IR (KBr,  $\text{cm}^{-1}$ ) 3700-3200, 2360, 1707; HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{16}\text{H}_{20}\text{NO}_5 \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 315.1199, found 315.1208.

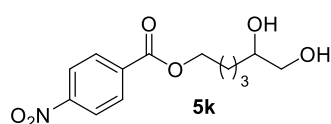


To a solution of alcohol **S15** (1.73 g, 9.96 mmol) and  $\text{Et}_3\text{N}$  (5.52 mL, 4.80 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) was added *p*-nitrobenzoyl chloride (4.82 g, 26.0 mmol) at room temperature. After 13 h, the reaction mixture was quenched with saturated aq.  $\text{NaHCO}_3$  and extracted with  $\text{AcOEt}$ . The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/ $\text{AcOEt} = 4/1$ ) to afford ester **S19** (3.10 g, 96%) as a pale yellow oil.

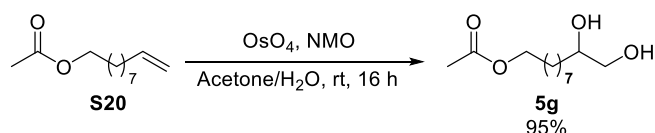


Pale yellow solid; mp 29.7-30.5 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.29 (dt,  $J = 9.2, 2.0$  Hz, 2H), 8.21 (dt,  $J = 9.2, 2.0$  Hz, 2H), 4.39 (t,  $J = 6.4$  Hz, 2H), 4.14-4.08 (m, 1H), 4.05 (dd,  $J = 7.6, 6.0$  Hz, 1H), 3.53 (t,  $J = 7.6$  Hz, 1H), 1.85 (quin,  $J = 6.8$  Hz, 2H), 1.74-1.44 (m, 4H), 1.41 (s, 3H), 1.36 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  164.7, 150.5, 135.7, 130.6, 123.5, 108.8, 75.8, 69.3, 65.7, 33.2, 28.6, 26.9, 25.7, 22.3; IR (neat,  $\text{cm}^{-1}$ ) 1724, 1527, 1275, 1103; HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{16}\text{H}_{21}\text{NO}_6 \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 346.1267, found 346.1263.

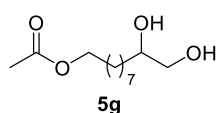
To a solution of ester **S19** (2.96 g, 9.15 mmol) in  $\text{MeOH}$  (37 mL) and  $\text{H}_2\text{O}$  (9.2 mL) was added DOWEX 50W-8 (200-400 mesh, 604 mg) at room temperature. After 20 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/ $\text{AcOEt} = 1/1$  to  $\text{AcOEt}$  only) to afford 1,2-diol **5k** (2.51 g, 97%) as a white solid.



White solid; mp 61.9-64.3 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.29 (dt,  $J = 9.2, 2.0$  Hz, 2H), 8.21 (dt,  $J = 9.2, 2.0$  Hz, 2H), 4.39 (t,  $J = 6.4$  Hz, 2H), 3.79-3.72 (m, 1H), 3.68 (dd,  $J = 11.2, 2.4$  Hz, 1H), 3.47 (dd,  $J = 10.4, 7.2$  Hz, 1H), 1.89-1.73 (m, 2H), 1.71-1.47 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  164.7, 150.5, 135.7, 130.7, 123.5, 71.9, 66.7, 65.7, 32.6, 28.6, 22.1; IR (neat,  $\text{cm}^{-1}$ ) 3800-3100, 1722, 1527, 1279; HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{13}\text{H}_{17}\text{NO}_6 \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 306.0954, found 306.0946.

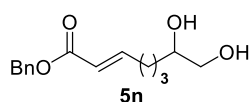


To a solution of olefin **S20** (1.08 g, 5.47 mmol) and *N*-methylmorpholine *N*-oxide (541 mg, 4.62 mmol) in acetone (27 mL) and H<sub>2</sub>O (3.0 mL) was added osmium tetroxide (4% in H<sub>2</sub>O, 185  $\mu$ L, 30.3  $\mu$ mol) at 0 °C. After the reaction mixture stirred for 14 h at room temperature, additional *N*-methylmorpholine *N*-oxide (368 mg, 3.14 mmol) was added and the reaction mixture was stirred for 3 h. Then, it was quenched with saturated aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane only to hexane/AcOEt = 1/1 to AcOEt only) to afford 1,2-diol **5g** (1.21 g, 95%) as a white solid.

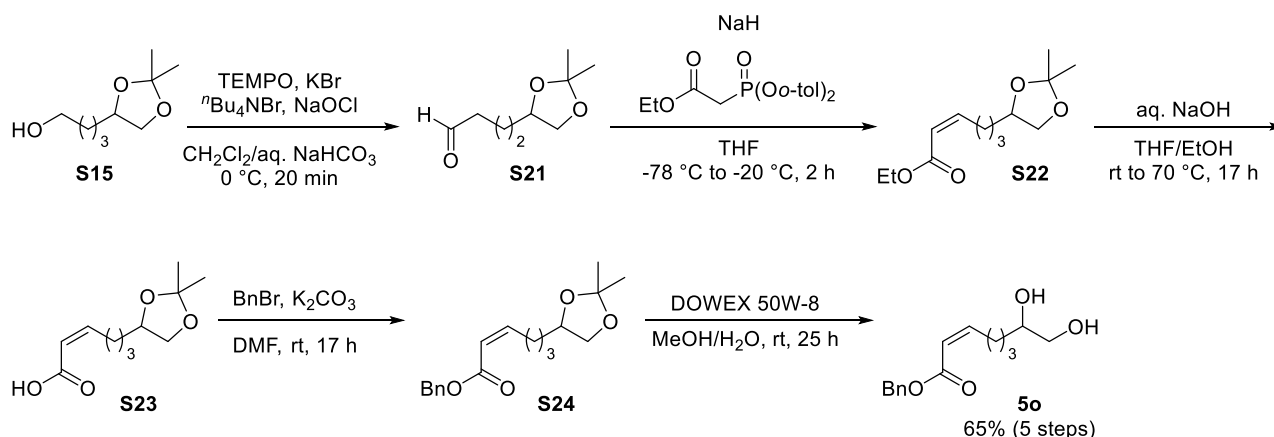


White solid; mp. 31.0-32.3 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.05 (t, *J* = 7.2 Hz, 2H), 3.75-3.62 (m, 2H), 3.48-3.39 (m, 1H), 2.05 (s, 3H), 1.99 (br d, *J* = 4.0 Hz, 1H), 1.84 (br t, *J* = 5.6 Hz, 1H), 1.62 (quin, *J* = 6.8 Hz, 2H), 1.50-1.23 (m, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.3, 72.2, 66.8, 64.6, 33.1, 29.5, 29.3, 29.1, 28.5, 25.8, 25.4, 21.0; IR (neat, cm<sup>-1</sup>) 3700-3200, 1739; HRMS (ESI, *m/z*) Calcd. for C<sub>12</sub>H<sub>24</sub>O<sub>4</sub> • Na ([M+Na]<sup>+</sup>): 255.1572, found 255.1564.

1,2-Diol **5n** was prepared according to our previous report<sup>1</sup>.



Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.39-7.29 (m, 5H), 7.00 (dt, *J* = 16.0, 7.2 Hz, 1H), 5.88 (dt, *J* = 16.0, 1.2 Hz, 1H), 5.17 (s, 2H), 3.75-3.62 (m, 1H), 3.66 (dd, *J* = 10.8, 3.2 Hz, 1H), 3.44 (dd, *J* = 10.8, 7.6 Hz, 1H), 2.25 (qd, *J* = 7.2, 1.2 Hz, 2H), 2.03 (br s, 1H), 1.79 (br s, 1H), 1.72-1.61 (m, 1H), 1.60-1.42 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  166.5, 149.4, 136.0, 128.5 (2C), 128.2 (3C), 121.3, 71.8, 66.7, 66.1, 32.4, 32.0, 23.9; IR (neat, cm<sup>-1</sup>) 3700-3200, 1716, 1653; HRMS (ESI, *m/z*) Calcd. for C<sub>15</sub>H<sub>20</sub>O<sub>4</sub> • Na ([M+Na]<sup>+</sup>): 287.1259, found 287.1233.



To a solution of alcohol **S15** (904 mg, 5.19 mmol), TEMPO (8.8 mg, 0.056 mmol), KBr (62.8 mg, 0.528 mmol), and  $n\text{Bu}_4\text{NBr}$  (85.9 mg, 0.266 mmol) in  $\text{CH}_2\text{Cl}_2$  (14 mL) and saturated aq.  $\text{NaHCO}_3$  (7.0 mL) was added a solution of aq.  $\text{NaOCl}$  (1.77 M, 3.81 mL, 6.75 mmol) and saturated aq.  $\text{NaHCO}_3$  (5.3 mL) dropwise at  $0^\circ\text{C}$ . After 20 min, the reaction mixture was quenched with saturated aq.  $\text{NaHCO}_3$  and saturated aq.  $\text{Na}_2\text{S}_2\text{O}_3$  and extracted with  $\text{AcOEt}$ . The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo to provide crude aldehyde **S21**, which was used to the next reaction without any further purification.

Next Z-selective Horner-Wadsworth-Emmons reaction was carried out according to Ando's report.<sup>4</sup> To a well-dried round-bottom flask charged with  $\text{NaH}$  (60%, 207 mg, 5.18 mmol) and dry THF (26 mL) was added ethyl di-*o*-tolylphosphonoacetate (1.80 mL, 5.18 mmol) dropwise at  $0^\circ\text{C}$ . After 30 min, a solution of aldehyde **S21** (0.5 M) in THF was added to the reaction mixture at  $-78^\circ\text{C}$ . After 1 h, the reaction mixture was warmed up to  $-20^\circ\text{C}$  over a period of 1 h. Then, it was quenched with saturated aq.  $\text{NH}_4\text{Cl}$  and extracted with  $\text{AcOEt}$ . The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo to provide crude ester **S22**, which was used to the next reaction without any further purification.

To a solution of ester **S22** in THF (5.5 mL) and EtOH (1.4 mL) was added aq.  $\text{NaOH}$  (5.0 M, 7.27 mL, 36.4 mmol) at room temperature. After 13 h, aq.  $\text{NaOH}$  (5.3 M, 7.27 mL, 38.8 mmol) was added to the reaction mixture. After 3 h, the reaction mixture was warmed up to  $70^\circ\text{C}$  and stirred for 1 h at the same temperature. After the reaction mixture was cooled to room temperature,  $\text{AcOEt}$  was added and the resultant mixture was separated into the organic layer and the aqueous layer. The aqueous layer was acidified with aq.  $\text{HCl}$  (2M) and extracted with  $\text{AcOEt}$ . The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo to provide crude carboxylic acid **S23**, which was used to the next reaction without any further purification.

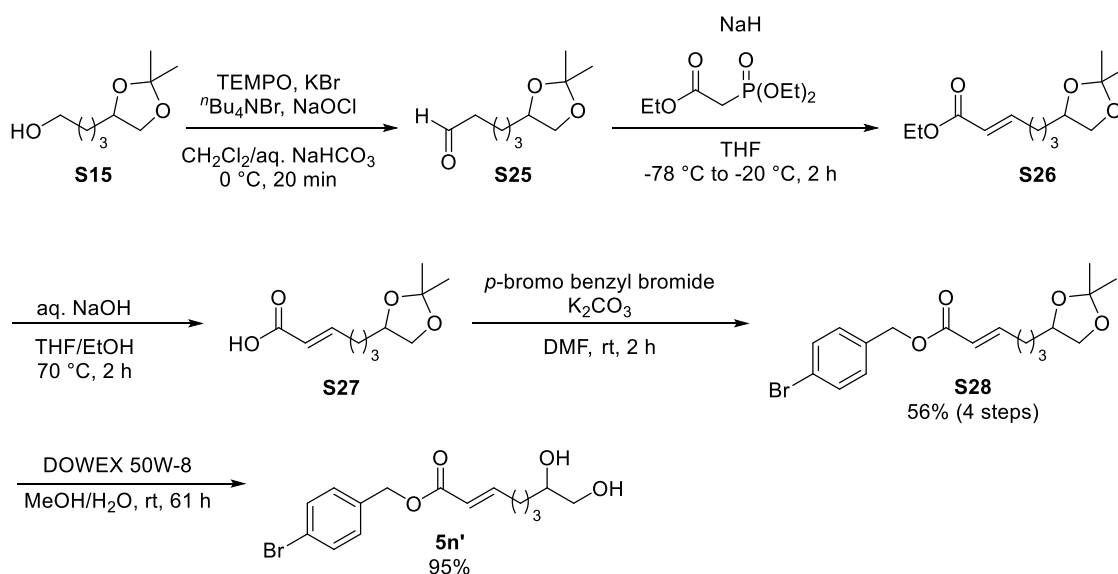
To a solution of carboxylic acid **S23** and  $\text{K}_2\text{CO}_3$  (2.54 g, 18.3 mmol) in DMF (7.4 mL) was added benzyl bromide (1.23 mL, 10.4 mmol) at  $0^\circ\text{C}$ . After the reaction mixture was stirred for 4 h at room temperature, additional  $\text{K}_2\text{CO}_3$  (0.718 g, 5.20 mmol) and benzyl bromide (0.615 mL, 5.19 mmol) were added and stirred for 13 h. Then, it was quenched with saturated aq.  $\text{Na}_2\text{S}_2\text{O}_3$  and extracted with  $\text{AcOEt}$ . The organic layer was dried over



MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was passed through a flash column chromatography on silica gel (hexane/AcOEt = 10/1) to afford ester **S24** including impurities.

To a solution of ester **S24**, in MeOH (16 mL) and H<sub>2</sub>O (3.9 mL) was added DOWEX 50W-8 (200-400 mesh, 240 mg) at room temperature. After 36 h, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/1 to AcOEt only) to afford 1,2-diol **5o** (898 mg, 65%, 5 steps) as a white solid.

White solid; mp 26.1-27.0 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39-7.29 (m, 5H), 6.28 (dt, *J* = 11.2, 7.2 Hz, 1H), 5.85 (dt, *J* = 11.2 Hz, 1.6 Hz, 1H), 5.15 (s, 2H), 3.78-3.70 (m, 1H), 3.67-3.60 (m, 1H), 3.47-3.39 (m, 1H), 2.80-2.69 (m, 1H), 2.69-2.57 (m, 1H), 2.23 (br d, *J* = 4.0 Hz, 1H), 1.86 (br t, *J* = 5.6 Hz, 1H), 1.69-1.40 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.2, 150.6, 136.0, 128.6, 128.2, 128.2, 119.8, 71.7, 66.8, 65.8, 32.4, 28.7, 24.8; IR (neat, cm<sup>-1</sup>) 3700-3200, 1718; HRMS (ESI, *m/z*) Calcd. for C<sub>15</sub>H<sub>20</sub>O<sub>4</sub> • Na ([M+Na]<sup>+</sup>): 287.1259, found 287.1252.



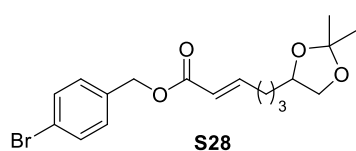
To a solution of alcohol **S15** (1.74 g, 10.0 mmol), TEMPO (15.7 mg, 0.100 mmol), KBr (122 mg, 1.03 mmol) and *t*Bu<sub>4</sub>NBr (163 mg, 0.504 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (26 mL) and saturated aq. NaHCO<sub>3</sub> (14 mL) was added a solution of aq. NaOCl (1.77 M, 7.35 mL, 13.0 mmol) and saturated aq. NaHCO<sub>3</sub> (10 mL) dropwise at 0 °C. After 20 min, it was quenched with saturated aq. NaHCO<sub>3</sub> and saturated aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to provide crude aldehyde **S25**, which was used to the next reaction without any further purification.

To a well-dried round-bottom flask charged with NaH (60%, 441 mg, 11.0 mmol) and dry THF (50 mL) was added triethyl phosphonoacetate (2.19 mL, 11.0 mmol) dropwise at 0 °C. After 40 min, a solution of aldehyde **S25** (0.5 M) in THF was added at -78 °C. After 2 h, the reaction mixture was quenched with saturated H<sub>2</sub>O and extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to provide

crude ester **S26**, which was used to the next reaction without any further purification.

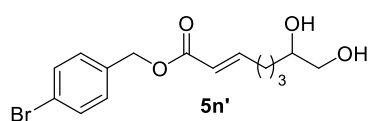
To a solution of ester **S26** in THF (11 mL) and EtOH (2.7 mL) was added aq. NaOH (5.1 M, 14.0 mL, 70.8 mmol) at room temperature. After the reaction mixture was stirred for 3 h at 70 °C, it was cooled to room temperature. Then, AcOEt was added and the resultant mixture was separated into the organic layer and the aqueous layer. The aqueous layer was acidified with aq. HCl (2 M) and extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to provide crude carboxylic acid **S27**, which was used to the next reaction without any further purification.

To a solution of carboxylic acid **S27** and K<sub>2</sub>CO<sub>3</sub> (4.84 g, 35.0 mmol) in DMF (14 mL) was added *p*-bromobenzyl bromide (5.00 g, 20.1 mmol) at 0 °C. After the reaction mixture was stirred for 2 h at room temperature, it was quenched with saturated H<sub>2</sub>O and extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was passed through a flash column chromatography on silica gel (hexane/AcOEt = 10/1) to afford ester **S28** (2.16 g, 56%, 4 steps) as a colorless oil.



Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.49 (dt, *J* = 8.0, 1.6 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.00 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.87 (dt, *J* = 15.6, 1.2 Hz, 1H), 5.11 (s, 2H), 4.11-4.00 (m, 2H), 3.50 (t, *J* = 7.2 Hz, 1H), 2.25 (qd, *J* = 6.8, 1.2 Hz, 2H), 1.68-1.43 (m, 4H), 1.40 (s, 3H), 1.35 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.1, 149.5, 135.1, 131.6, 129.8, 122.1, 121.2, 108.7, 75.6, 69.3, 65.2, 33.0, 32.0, 26.9, 25.7, 24.1; IR (neat, cm<sup>-1</sup>) 1720, 1653; HRMS (ESI, *m/z*) Calcd. for C<sub>18</sub>H<sub>23</sub>BrO<sub>4</sub> · Na ([M+Na]<sup>+</sup>): 405.0677, found 405.0663.

To a solution of ester **S28** (2.13 g, 5.57 mmol) in MeOH (22 mL) and H<sub>2</sub>O (5.6 mL) was added DOWEX 50W-8 (200-400 mesh, 227 mg) at room temperature. After 61 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 1/1) to afford 1,2-diol **5n'** (1.82 g, 95%) as a white solid.



White solid; mp 36.7-38.4 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.49 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.00 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.87 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.12 (s, 2H), 3.75-3.63 (m, 2H), 3.44 (dd, *J* = 11.2, 8.0 Hz, 1H), 2.25 (qd, *J* = 7.2, 1.6 Hz, 2H), 2.03 (br s, 1H), 1.77 (br s, 1H), 1.72-1.42 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.2, 149.7, 134.8, 131.4, 129.7, 122.0, 120.8, 71.7, 66.4, 65.1, 32.1, 31.9, 23.8; IR (neat, cm<sup>-1</sup>) 3700-3200, 1718, 1651; HRMS (ESI, *m/z*) Calcd. for C<sub>15</sub>H<sub>19</sub>BrO<sub>4</sub> · Na ([M+Na]<sup>+</sup>): 365.0364 found 365.0353.

### 3. Transamination of $\alpha$ -keto acids to $\alpha$ -amino acids.

Table S1. Optimizing the reaction conditions of transamination using 2,2-diphenylglycine (**2**)

$\text{1a}$  (1.0 mmol) +  $\text{2}$  (x eq)  $\xrightarrow[\text{temp., time}]{\text{THF/H}_2\text{O (7/3, 0.1 M)}}$   $\text{3a}$

entry	x [eq]	temp. [°C]	time [h]	yield [%]	recovered N-source [%]
1	1.0	reflux	24	63 <sup>a</sup>	2 <sup>a</sup>
2	0.9	reflux	24	66	0
3 <sup>b</sup>	0.9	50	72	38 <sup>a</sup>	21 <sup>a</sup>
4 <sup>c</sup>	0.9	reflux	24	0	—
5 <sup>d</sup>	0.9	reflux	24	2	0

<sup>a</sup>An inseparable mixture. <sup>b</sup>0.2 mmol of **1a** was used. <sup>c</sup>Benzylamine was used instead of **2**. <sup>d</sup>Pyridoxamine dihydrochloride monohydrate was used instead of **2**.

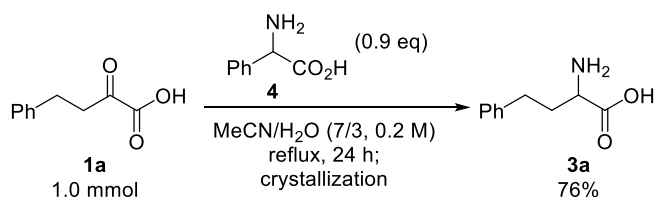
Table S2. Substrate scope of transamination of  $\alpha$ -keto acids

$\text{1}$  +  $\text{4}$  (0.9 eq)  $\xrightarrow[\text{reflux, 24 h}]{\text{MeCN/H}_2\text{O (7/3, 0.2 M)}}$   $\text{3}$

$\alpha$ -keto acid	$\alpha$ -amino acid	yield [%] <sup>a</sup>	$\alpha$ -keto acid	$\alpha$ -amino acid	yield [%] <sup>a</sup>
		76			80
		90 <sup>b</sup>			8 <sup>d</sup>
		86 <sup>b</sup>			88
		52			19
		73			31 <sup>c</sup>

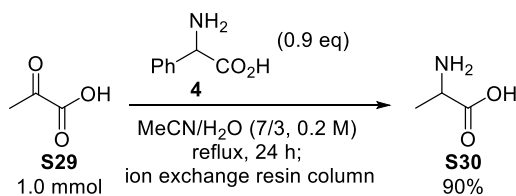
<sup>a</sup>Isolated yield. <sup>b</sup>Ion-exchange chromatography (Dowex 50W-8) was used for the purification. <sup>c</sup>NMR yield. <sup>d</sup>Inseparable mixture with **4**.

### Representative procedure of transamination of $\alpha$ -keto acids to $\alpha$ -amino acids (method A).

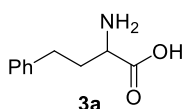


To a solution of  $\alpha$ -keto acid **1a** (178 mg, 1.00 mmol) in MeCN (3.5 mL) and H<sub>2</sub>O (1.5 mL) was added DL-2-phenylglycine (**4**) (136 mg, 0.900 mmol) at room temperature. After the reaction mixture was refluxed for 24 h, it was cooled to room temperature. After Et<sub>2</sub>O (5.0 mL) was added, the desired  $\alpha$ -amino acid was fully precipitated, the reaction mixture was filtrated. The precipitate was washed with Et<sub>2</sub>O and dried under reduced pressure to afford  $\alpha$ -amino acid **3a** (136 mg, 76%).

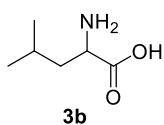
### Representative procedure of transamination of $\alpha$ -keto acids to $\alpha$ -amino acids (method B).



To a solution of  $\alpha$ -keto acid **S29** (88.4 mg, 1.00 mmol) in MeCN (3.5 mL) and H<sub>2</sub>O (1.5 mL) was added DL-2-phenylglycine (**4**) (137 mg, 0.904 mmol) at room temperature. After the reaction mixture was refluxed for 24 h, it was cooled to room temperature, Then, CH<sub>2</sub>Cl<sub>2</sub> was added and the resultant mixture was separated into organic layer and aqueous layer. The organic layer was extracted with H<sub>2</sub>O and the two aqueous layers were combined. The resultant aqueous layer was charged on a cationic ion exchange chromatography (DOWEX 50W-8, 200-400 mesh). The product was eluted with aq. NH<sub>3</sub> (3%). The eluent was concentrated by freeze-dry to afford  $\alpha$ -amino acid **S30** (79.8 mg, 90%).

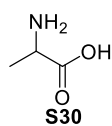


115 mg (76% yield); method A; Spectra data is described in p. 19.

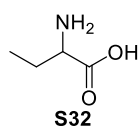


90.8 mg (68% yield); method A; White solid; mp. 260.5-263.2 °C; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O with 4 eq of KOH)  $\delta$  3.24 (t,  $J$  = 6.8 Hz, 1H), 1.69-1.59 (m, 1H), 1.49-1.32 (m, 2H), 0.89 (t,  $J$  = 6.8 Hz, 6H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O with 4 eq of KOH)  $\delta$  187.2, 57.3, 46.9, 27.1, 25.1, 24.0; IR (KBr,

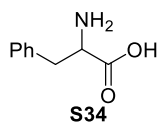
cm<sup>-1</sup>) 3300-1800, 1618, 1587, 1508; HRMS (DART, m/z) Calcd. for C<sub>6</sub>H<sub>13</sub>NO<sub>2</sub> • H ([M+H]<sup>+</sup>): 132.1022, found 132.1025; Anal. Calcd. for C<sub>6</sub>H<sub>13</sub>NO<sub>2</sub>: C, 54.94; H, 9.99; N, 10.68. Found: C, 54.89; H, 9.94; N, 10.60.



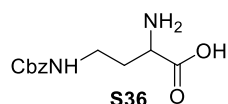
79.8 mg (90% yield); method B; White solid; 176 °C decomp.; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 3.77 (q, *J* = 6.8 Hz, 1H), 1.47 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O) δ 178.5, 53.2, 18.8; IR (KBr, cm<sup>-1</sup>) 3300-1800, 1593; HRMS (DART, m/z) Calcd. for C<sub>3</sub>H<sub>7</sub>NO<sub>2</sub> • H ([M+H]<sup>+</sup>): 90.0559, found 90.0555.



91.4 mg (86% yield); method B; White solid; mp. 236.6-238.3 °C; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 3.69 (t, *J* = 6.0 Hz, 1H), 1.94-1.83 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O) δ 177.6, 58.6, 26.4, 11.2; IR (KBr, cm<sup>-1</sup>) 3300-2000, 1654, 1577, 1508; HRMS (DART, m/z) Calcd. for C<sub>4</sub>H<sub>9</sub>NO<sub>2</sub> • H ([M+H]<sup>+</sup>): 104.0684, found 104.0712.



85.6 mg (52% yield); method A; Precipitation was carried out using MeCN instead of Et<sub>2</sub>O.; White solid; 204 °C decomp.; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O with 4 eq of KOH) δ 7.37 (t, *J* = 7.2 Hz, 2H), 7.31-7.26 (m, 3H), 3.49 (dd, *J* = 7.2, 5.6 Hz, 1H), 2.98 (dd, *J* = 13.2, 5.6 Hz, 1H), 2.83 (dd, *J* = 13.2, 7.2 Hz, 1H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O with 4 eq of KOH) δ 185.1, 141.0, 132.1, 131.2, 129.3, 60.1, 43.4; IR (KBr, cm<sup>-1</sup>) 3300-2300, 1619, 1588, 1506; HRMS (DART, m/z) Calcd. for C<sub>9</sub>H<sub>11</sub>NO<sub>2</sub> • H ([M+H]<sup>+</sup>): 166.0894, found 166.0868; Anal. Calcd. for C<sub>9</sub>H<sub>11</sub>NO<sub>2</sub>: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.45; H, 6.75; N, 8.40.



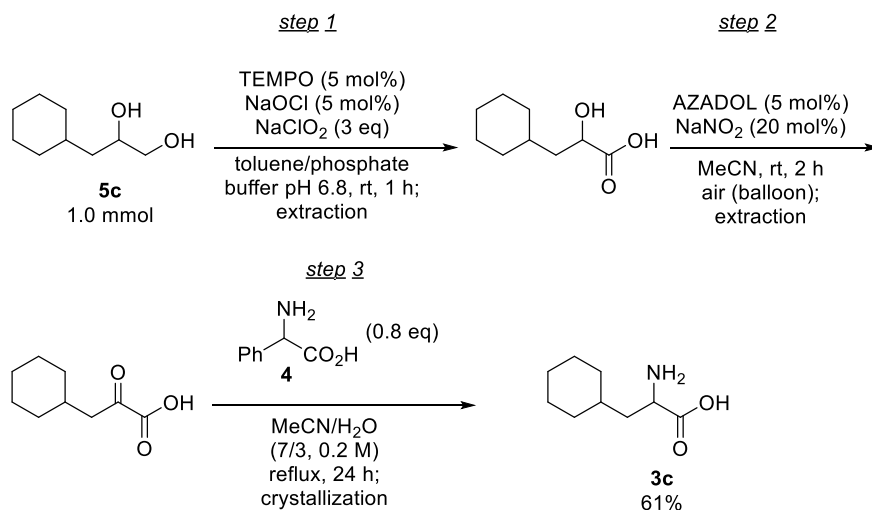
185.1 mg (73% yield); method A; White solid; 229 °C decomp.; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O with 4 eq of KOH) δ 7.45-7.37 (m, 5H), 5.09 (s, 2H), 3.24-3.16 (m, 3H), 1.87-1.79 (m, 1H), 1.69-1.60 (m, 1H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O with 4 eq of KOH) δ 185.5, 161.0, 139.2, 131.5, 131.0, 130.3, 69.5, 56.5, 40.3, 37.3; IR (KBr, cm<sup>-1</sup>) 3305, 3200-1800, 1687, 1654, 1583, 1545; HRMS (DART, m/z) Calcd. for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> • H ([M+H]<sup>+</sup>): 253.1182, found 253.1188; Anal. Calcd. for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.02; H, 6.45; N, 10.93.



144.9 mg, (80% yield); method A; White solid; 234 °C decomp.; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O with 4 eq of KOH) δ 6.98 (d, *J* = 8.0 Hz, 2H), 6.57 (d, *J* = 8.0 Hz, 2H), 3.39 (dd, *J* = 7.2, 5.2 Hz, 1H), 2.84 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.66 (dd, *J* = 13.6, 7.2 Hz, 1H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O with 4 eq of KOH) δ 185.6, 167.3, 133.4, 126.4, 121.3, 60.3, 42.6; IR (KBr, cm<sup>-1</sup>) 3400-2300, 1628, 1588, 1513; HRMS (DART, m/z) Calcd. for C<sub>9</sub>H<sub>11</sub>NO<sub>3</sub> • H ([M+H]<sup>+</sup>): 182.0812, found 182.0817; Anal. Calcd. for C<sub>9</sub>H<sub>11</sub>NO<sub>3</sub>: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.67; H, 6.29; N, 7.43.

#### 4. Three-step synthesis of $\alpha$ -amino acids from 1,2-diols.

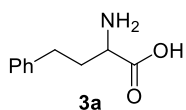
##### Typical procedure of synthesis of $\alpha$ -amino acids from 1,2-diols



**Step1:** To a solution of 1,2-diol **5c** (158.7 mg, 1.00 mmol) and TEMPO (7.8 mg, 0.05 mmol) in toluene (5.0 mL) and sodium phosphate buffer (1 M, pH = 6.8, 3.6 mL) were added a NaOCl aqueous solution (0.20 M, 251  $\mu$ L, 0.05 mmol) and a NaClO<sub>2</sub> aqueous solution (3.0 mmol of 80% NaClO<sub>2</sub> dissolved into 1.4 mL of water) simultaneously dropwise at room temperature. The color of the reaction mixture turned to deep red indicating the formation of charge-transfer complex TEMPO-ClO<sub>2</sub>. After 1 h, sodium phosphate buffer (1 M, pH = 2.1, 7.2 mL) was added. The aqueous layer was extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to provide crude  $\alpha$ -hydroxy acid.

**Step 2:** To a solution of crude  $\alpha$ -hydroxy acid and AZADOL (7.7 mg, 0.05 mmol) in MeCN (5.0 mL) was added NaNO<sub>2</sub> (13.8 mg, 0.20 mmol) at room temperature. (The flask size should be ten times bigger than the solution's volume. The reaction mixture should be stirred vigorously.) After the reaction mixture was stirred under air (balloon) for 2 h, it was quenched with sodium phosphate buffer (1 M, pH = 2.1, 5.0 mL) was added. The aqueous layer was extracted with AcOEt. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to provide crude  $\alpha$ -keto acid.

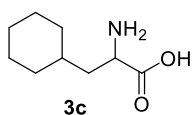
**Step 3:** To a solution of crude  $\alpha$ -keto acid in MeCN (3.5 mL) and H<sub>2</sub>O (1.5 mL) was added DL-2-phenylglycine (**4**) (121 mg, 0.802 mmol) at room temperature. The reaction mixture was refluxed for 24 h and cooled to room temperature. After Et<sub>2</sub>O (5.0 mL) was added to the reaction mixture, the solution was stirred until  $\alpha$ -amino acid was fully precipitated. After filtration, the precipitate was washed with Et<sub>2</sub>O and dried under reduced pressure to afford  $\alpha$ -amino acid **3c** (105 mg, 61%) with high purity.



1.0 mmol-scale synthesis; 115 mg (63% yield); An additional NaOCl aqueous solution (0.20 M, 251  $\mu$ L, 0.05 mmol) was added after 3 h in step 1.

20 mmol-scale synthesis; 2.52 g (70% yield); In step 1, the reaction mixture was stirred using a mechanical stirrer. An additional NaOCl aqueous solution (0.20 M, 2.51 mL, 0.50 mmol) was added after 3 h.

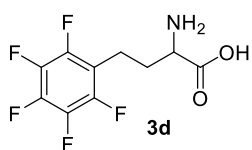
White solid; 261 °C decomp.;  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$  with 4 eq of KOH)  $\delta$  7.37 (t,  $J$  = 6.8 Hz, 2H), 7.31 (d,  $J$  = 6.8, 2H), 7.26 (t,  $J$  = 6.8, 1H), 3.25 (dd,  $J$  = 6.8, 6.0 Hz, 1H), 2.64 (t,  $J$  = 8.0 Hz, 2H), 1.95-1.79 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$  with 4 eq of KOH)  $\delta$  186.0, 145.1, 131.4, 131.2, 128.7, 58.5, 39.6, 34.2; IR (KBr,  $\text{cm}^{-1}$ ) 3300-1800, 1654, 1625, 1582; HRMS (DART,  $m/z$ ) Calcd. for  $\text{C}_{10}\text{H}_{13}\text{NO}_2 \cdot \text{H}$  ( $[\text{M}+\text{H}]^+$ ): 180.1034, found 181.1025; Anal. Calcd. for  $\text{C}_{10}\text{H}_{13}\text{NO}_2$ : C, 67.02; H, 7.31; N, 7.82. Found: C, 67.12; H, 7.42; N, 7.51.



105 mg (61% yield); White solid; mp. 240.1-240.7 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$  with 4 eq of KOH)  $\delta$  3.27 (dd,  $J$  = 7.6, 5.6 Hz, 1H), 1.75-1.56 (m, 5H), 1.52-1.42 (m, 1H), 1.39-1.29 (m, 2H),

1.29-1.10 (m, 3H), 0.98-0.81 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$  with 4 eq of KOH)  $\delta$  187.2,

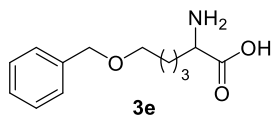
56.6, 45.5, 36.5, 36.1, 35.0, 28.8, 28.5, 28.4; IR (KBr,  $\text{cm}^{-1}$ ) 3300-1800, 1625, 1583, 1518; HRMS (DART,  $m/z$ ) Calcd. for  $\text{C}_9\text{H}_{17}\text{NO}_2 \cdot \text{H}$  ( $[\text{M}+\text{H}]^+$ ): 172.1354, found 172.1338.



164 mg (61% yield); In step 1, the reaction was carried out at 50 °C. An additional NaOCl aqueous solution (0.20 M, 250  $\mu$ L, 0.05 mmol) was added after 1 h in step 1.;

White solid; mp. 266.0-266.5 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$  with 4 eq of KOH)  $\delta$  3.25 (t,  $J$  = 6.0 Hz, 1H), 2.77 (t,  $J$  = 8.0 Hz, 2H), 1.94-1.76 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$  with

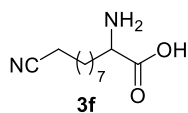
4 eq of KOH)  $\delta$  185.3, 147.7 (dm,  $J$  = 241.2 Hz), 142.0 (dm,  $J$  = 246.9 Hz), 139.9 (dm,  $J$  = 247.0 Hz), 117.3 (td,  $J$  = 19.1, 2.9 Hz), 58.3, 36.8, 21.1; IR (KBr,  $\text{cm}^{-1}$ ) 3300-1900, 1626, 1579, 1504; HRMS (DART,  $m/z$ ) Calcd. for  $\text{C}_{10}\text{H}_8\text{F}_5\text{NO}_2 \cdot \text{H}$  ( $[\text{M}+\text{H}]^+$ ): 270.0553, found 270.0536; Anal. Calcd. for  $\text{C}_{10}\text{H}_8\text{F}_5\text{NO}_2$ : C, 44.62; H, 3.00; N, 5.20. Found: C, 44.71; H, 3.36; N, 5.01.



144 mg (61% yield); White solid; 218 °C decomp.;  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$  with 4 eq of KOH)  $\delta$  7.46-7.36 (m, 5H), 4.54 (s, 2H), 3.57 (t,  $J$  = 6.4 Hz, 2H), 3.20 (dd,  $J$  = 6.8,

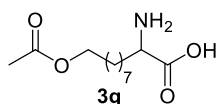
6.0 Hz, 1H), 1.66-1.48 (m, 4H), 1.39-1.30 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$  with 4 eq

of KOH)  $\delta$  186.3, 140.1, 131.4, 131.2, 130.9, 75.1, 72.8, 58.6, 37.1, 31.3, 24.3; IR (KBr,  $\text{cm}^{-1}$ ) 3300-1900, 1654, 1581, 1514; HRMS (DART,  $m/z$ ) Calcd. for  $\text{C}_{13}\text{H}_{19}\text{NO}_3 \cdot \text{H}$  ( $[\text{M}+\text{H}]^+$ ): 238.1443, found 238.1451; Anal. Calcd. for  $\text{C}_{13}\text{H}_{19}\text{NO}_3$ : C, 65.80; H, 8.07; N, 5.90. Found: C, 65.66; H, 8.12; N, 6.00.



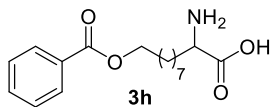
124 mg (58% yield), An additional NaOCl aqueous solution (0.20 M, 251  $\mu$ L, 0.05 mmol) was added after 1.5 h in step 1; MeCN was used for the precipitation instead of Et<sub>2</sub>O in step 3;

White solid; 214 °C decomp.; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O with 4 eq of KOH)  $\delta$  3.20 (t,  $J$  = 6.8 Hz, 1H), 2.45 (t,  $J$  = 7.6 Hz, 2H), 1.68-1.47 (m, 4H), 1.45-1.37 (m, 2H), 1.36-1.22 (m, 8H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O with 4 eq of KOH)  $\delta$  186.6, 125.1, 58.7, 37.4, 31.3, 30.9, 30.5, 30.4, 27.6, 27.1, 18.9; IR (KBr, cm<sup>-1</sup>) 3300-2000, 2247, 1654, 1583, 1516; HRMS (DART, m/z) Calcd. for C<sub>11</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub> • H ([M+H]<sup>+</sup>): 213.1603, found 213.1588; Anal. Calcd. for C<sub>11</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>: C, 62.24; H, 9.50; N, 13.20. Found: C, 62.05; H, 9.53; N, 13.25.



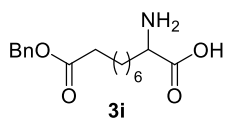
146 mg (59% yield); An additional NaOCl aqueous solution (0.20 M, 51  $\mu$ L, 0.01 mmol) was added after 2.5 h in step 1; White solid; 214 °C decomp.; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$

4.05 (t,  $J$  = 6.8 Hz, 2H), 3.51 (dd,  $J$  = 6.8, 4.8 Hz, 1H), 2.02 (s, 3H), 1.93-1.71 (m, 2H), 1.67-1.58 (m, 2H), 1.50-1.24 (m, 10H); IR (KBr, cm<sup>-1</sup>) 3300-1900, 1730, 1657, 1581, 1508; HRMS (DART, m/z) Calcd. for C<sub>12</sub>H<sub>23</sub>NO<sub>4</sub> • H ([M+H]<sup>+</sup>): 246.1705, found 246.1700; Anal. Calcd. for C<sub>12</sub>H<sub>23</sub>NO<sub>4</sub>: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.74; H, 9.60; N, 5.85.



206 mg (67% yield); White solid; 196 °C decomp.; <sup>1</sup>H NMR (400 MHz, 5wt% deuterium chloride solution in D<sub>2</sub>O)  $\delta$  8.04 (d,  $J$  = 8.0 Hz, 2H), 7.69 (t,  $J$  = 8.0 Hz, 1H), 7.55 (t,  $J$  = 8.0 Hz, 2H), 4.37 (t,  $J$  = 6.8 Hz, 2H), 4.09 (t,  $J$  = 6.8 Hz, 1H), 2.02-1.86 (m,

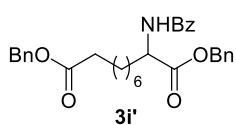
2H), 1.80-1.71 (m, 2H), 1.50-1.31 (m, 10H); IR (KBr, cm<sup>-1</sup>) 3300-2300, 1718, 1643, 1600, 1568; HRMS (DART, m/z) Calcd. for C<sub>17</sub>H<sub>25</sub>NO<sub>4</sub> • H ([M+H]<sup>+</sup>): 308.1867, found 308.1862; Anal. Calcd. for C<sub>17</sub>H<sub>25</sub>NO<sub>4</sub>: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.54; H, 8.28; N, 4.37.



200 mg (65% yield); An additional NaOCl aqueous solution (0.20 M, 250  $\mu$ L, 0.05 mmol) was added after 1 h in step 1; White solid; 215 °C decomp.; <sup>1</sup>H NMR (400 MHz, 5wt% deuterium chloride solution in D<sub>2</sub>O)  $\delta$  7.48-7.39 (m, 5H), 5.17 (s, 2H), 4.10 (t,  $J$  = 6.0 Hz,

1H), 2.42 (t,  $J$  = 7.2 Hz, 2H), 2.03-1.83 (m, 2H), 1.60 (quint,  $J$  = 7.2 Hz, 2H), 1.49-1.21 (m, 8H); IR (KBr, cm<sup>-1</sup>) 3300-2000, 1737, 1657, 1583, 1512; HRMS (DART, m/z) Calcd. for C<sub>17</sub>H<sub>25</sub>NO<sub>4</sub> • H ([M+H]<sup>+</sup>): 308.1863, found 308.1862.

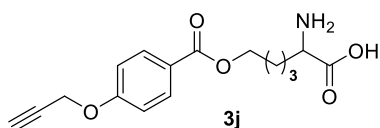
For the characterization, **3i** was converted to the *N*-benzoyl benzyl ester **3i'**.



White solid; mp 65.5-66.7 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.80 (dt,  $J$  = 6.8, 2.0 Hz, 2H), 7.51 (tt,  $J$  = 7.2, 2.0 Hz, 1H), 7.44 (tt,  $J$  = 7.2, 2.0 Hz, 2H), 7.39-7.28 (m, 10H), 6.66 (br d,  $J$  = 8.0, 1H), 5.25 (d,  $J$  = 12.0 Hz, 1H), 5.17 (d,  $J$  = 12.0 Hz, 1H), 5.10 (s, 2H), 4.90-4.83 (m,

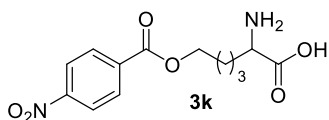


1H), 2.32 (t,  $J = 7.2$  Hz, 2H), 2.01-1.90 (m, 1H), 1.83-1.72 (m, 1H), 1.65-1.53 (m, 2H), 1.43-1.17 (m, 8H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.6, 172.6, 167.0, 136.1, 135.3, 134.0, 131.7, 128.6, 128.6, 128.5, 128.5, 128.3, 128.2, 128.2, 127.0, 67.2, 66.1, 52.6, 34.2, 32.6, 29.0, 28.9, 28.9, 25.0, 24.8; IR (neat,  $\text{cm}^{-1}$ ) 2900-2700, 1738, 1645; HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{31}\text{H}_{35}\text{NO}_5 \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 524.2413, found 524.2416.



163 mg (54% yield); An additional NaOCl aqueous solution (0.20 M, 250  $\mu\text{L}$ , 0.05 mmol) was added after 5 h in step 1; White solid; 201  $^\circ\text{C}$  decomp.;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.99 (dt,  $J = 9.2, 2.0$  Hz, 2H), 7.06 (dt,  $J = 9.2, 2.0$

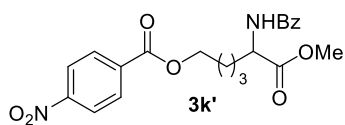
Hz, 2H), 4.82 (d,  $J = 2.4$  Hz, 2H), 4.32 (t,  $J = 6.4$  Hz, 2H), 3.55 (dd,  $J = 6.8, 6.4$  Hz, 1H), 2.99 (t,  $J = 2.4$  Hz, 1H), 2.02-1.78 (m, 4H), 1.65-1.55 (m, 2H); IR (KBr,  $\text{cm}^{-1}$ ) 3284, 3200-1900, 1718, 1620, 1587, 1504; HRMS (DART,  $m/z$ ) Calcd. for  $\text{C}_{16}\text{H}_{19}\text{NO}_5 \cdot \text{H}$  ( $[\text{M}+\text{H}]^+$ ): 306.1336, found 306.1342; Anal. Calcd. for  $\text{C}_{16}\text{H}_{19}\text{NO}_5$ : C, 62.94; H, 6.27; N, 4.59. Found: C, 62.97; H, 6.38; N, 4.25.



199 mg (67% yield); In step 1, the reaction was carried out at 50  $^\circ\text{C}$ . An additional NaOCl aqueous solution (0.20 M, 250  $\mu\text{L}$ , 0.05 mmol) was added after 1 h; Pale brown solid; 148  $^\circ\text{C}$  decomp.;  $^1\text{H}$  NMR (400 MHz, 5wt% deuterium

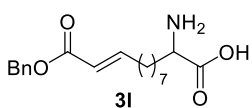
chloride solution in  $\text{D}_2\text{O}$ )  $\delta$  8.34 (dt,  $J = 8.8, 2.0$  Hz, 2H), 8.21 (dt,  $J = 8.8, 2.0$  Hz, 2H), 4.43 (t,  $J = 6.8$  Hz, 2H), 4.17 (t,  $J = 6.0$  Hz, 1H), 2.16-1.98 (m, 2H), 1.90 (t,  $J = 6.8$  Hz, 2H), 1.76-1.53 (m, 2H); IR (KBr,  $\text{cm}^{-1}$ ) 3500-2000, 1720, 1589, 1541, 1527, 1500, 1279; HRMS (DART,  $m/z$ ) Calcd. for  $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}_6 \cdot \text{H}$  ( $[\text{M}+\text{H}]^+$ ): 297.1093, found 297.1087.

For the characterization, **3k** was converted to the *N*-benzoyl methyl ester **3k'**.



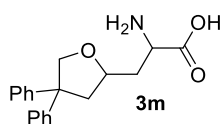
Pale yellow oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (dt,  $J = 9.2, 2.0$  Hz, 2H), 8.15 (dt,  $J = 9.2, 2.0$  Hz, 2H), 7.80 (dt,  $J = 7.2, 2.0$  Hz, 2H), 7.54 (tt,  $J = 7.2, 2.0$

Hz, 1H), 7.45 (tt,  $J = 8.0, 2.0$  Hz, 2H), 6.71 (d,  $J = 7.2$  Hz, 1H), 4.89 (td,  $J = 7.2, 5.2$  Hz, 1H), 4.38 (td,  $J = 6.4, 1.6$  Hz, 2H), 3.79 (s, 3H), 2.13-2.03 (m, 1H), 1.95-1.78 (m, 3H), 1.67-1.46 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.0, 167.0, 164.7, 150.5, 135.6, 133.7, 131.9, 130.6, 128.6, 127.0, 123.5, 65.3, 52.6, 52.2, 32.3, 28.1, 21.8; IR (neat,  $\text{cm}^{-1}$ ) 3400-3200, 1724, 1645, 1527, 1277; HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{21}\text{H}_{22}\text{NO}_7 \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 437.1325, found 437.1329.



206 mg (62% yield); In step 1, the reaction was carried out at 50  $^\circ\text{C}$ . An additional NaOCl aqueous solution (0.20 M, 250  $\mu\text{L}$ , 0.05 mmol) was added after 1 h; White solid; 213  $^\circ\text{C}$  decomp.;  $^1\text{H}$  NMR (400 MHz, 5wt% deuterium chloride solution in  $\text{D}_2\text{O}$ )  $\delta$

7.47-7.39 (m, 5H), 7.09 (ddd,  $J = 15.2, 6.4, 6.4$  Hz, 1H), 5.94 (d,  $J = 15.2$  Hz, 1H), 5.22 (s, 2H), 4.10 (t,  $J = 6.0$  Hz, 1H), 2.28-2.21 (m, 2H), 2.10-1.86 (m, 2H), 1.50-1.26 (m, 10H); IR (KBr,  $\text{cm}^{-1}$ ) 3300-1800, 1718, 1652, 1581, 1512; HRMS (DART,  $m/z$ ) Calcd. for  $\text{C}_{19}\text{H}_{27}\text{NO}_4 \cdot \text{H}$  ( $[\text{M}+\text{H}]^+$ ): 334.2018, found 334.2022; Anal. Calcd. for  $\text{C}_{19}\text{H}_{27}\text{NO}_4$ : C, 68.44; H, 8.16; N, 4.20. Found: C, 68.20; H, 8.18; N, 4.23.

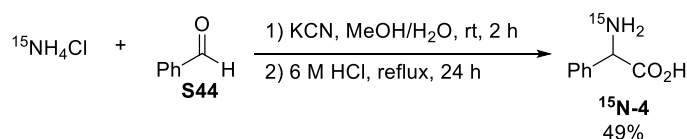


49.9 mg (16% yield), An additional NaOCl aqueous solution (0.20 M, 50  $\mu\text{L}$ , 0.01 mmol) was added after 1 h in step 1. Due to the high solubility, **3m** was purified by the following procedure. aq. HCl (1 M) was poured into the reaction mixture and it was washed with

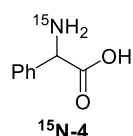
$\text{CH}_2\text{Cl}_2$ . After the aqueous layer was brought to pH 12 with aq. NaOH (10%), it was washed with  $\text{CH}_2\text{Cl}_2$  and charged on cationic ion exchange chromatography (DOWEX 50W-8, 200-400 mesh). The product was eluted with aq.  $\text{NH}_3$  (3%). The eluent was concentrated by freeze-dry to afford  $\alpha$ -amino acid **3m**;  $dr = 1/1$ ; White solid; 172  $^\circ\text{C}$  decomp.;  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$  with 5 eq of KOH)  $\delta$  7.44-7.22 (m, 20H), 4.66 (d,  $J = 9.2$  Hz, 2H), 4.16 (dd,  $J = 9.2, 2.4$  Hz, 2H), 4.16-4.09 (m, 2H), 3.30 (dd,  $J = 8.4, 4.8$  Hz, 1H), 3.25 (dd,  $J = 8.0, 6.0$  Hz, 1H), 3.02-2.93 (m, 2H), 2.37-2.28 (m, 2H), 2.03-1.65 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$  with 4 eq of KOH)  $\delta$  185.0, 184.6, 147.9, 131.0, 130.9, 129.5, 129.3, 128.9, 80.1, 78.6, 78.0, 77.9, 58.0, 57.9, 57.3, 56.3, 46.4, 46.3, 43.8, 43.5; IR (KBr,  $\text{cm}^{-1}$ ) 3900-2800, 1601, 1493, 1404; HRMS (DART,  $m/z$ ) Calcd. for  $\text{C}_{19}\text{H}_{21}\text{N}_1\text{O}_3 \cdot \text{H}$  ( $[\text{M}+\text{H}]^+$ ): 312.1600, found 312.1596.



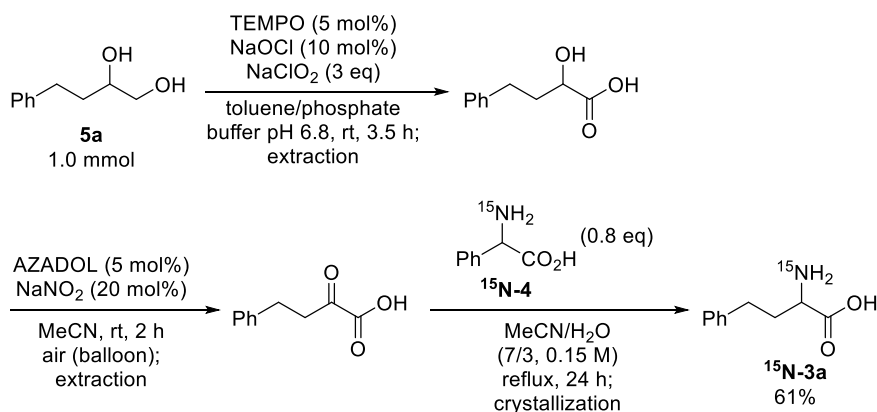
## 6. Synthesis of $^{15}\text{N}$ -labeled $\alpha$ -amino acid



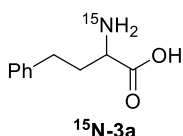
To a solution of KCN (657 mg, 10.1 mmol) and  $^{15}\text{NH}_4\text{Cl}$  (545 mg, 10.0 mmol) in  $\text{H}_2\text{O}$  (2.0 mL) was added benzaldehyde (**S44**) (1.38 g, 13.0 mmol) in MeOH (2.0 mL) at 0 °C. The reaction mixture was stirred for 2 h. After  $\text{H}_2\text{O}$  was added to the reaction mixture, the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  and then the organic layer was extracted with aq. HCl (6 M, 10 mL $\times$ 3). The resultant aqueous layer was refluxed for 24 h. After it was cooled to room temperature, the solution was neutralized to pH 7 with aq. NaOH (20%) and  $\text{Et}_2\text{O}$  was added. After it was stirred for several minutes at room temperature,  $^{15}\text{N}$ -phenylglycine ( **$^{15}\text{N-4}$** ) appeared as a precipitate. It was washed with  $\text{H}_2\text{O}$ , MeOH, and  $\text{Et}_2\text{O}$  and dried under reduced pressure to afford  $^{15}\text{N}$ -phenylglycine ( **$^{15}\text{N-4}$** ) (571 mg, 38%) as a white solid. After that, the filtrate was basified with aq. NaOH (1 M) until pH 9 and washed with  $\text{CH}_2\text{Cl}_2$ . Then, the aqueous layer was neutralized with aq. HCl (1 M) to pH 8. The resultant aqueous layer was charged on a cationic ion exchange chromatography (DOWEX 50W-8, 200-400 mesh). The  $^{15}\text{N}$ -phenylglycine was eluted with aq.  $\text{NH}_3$  (3%). The eluent was concentrated in vacuo to afford  $^{15}\text{N}$ -phenylglycine ( **$^{15}\text{N-4}$** ) (170 mg, 11%) as a pale brown solid. The combined yield was 49%.



White solid; mp 211.5-212.2 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$  with 4 eq of KOH)  $\delta$  7.43-7.30 (m, 5H), 4.34 (d,  $J$  = 2.0 Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$  with 4 eq of KOH)  $\delta$  183.8, 144.8, 131.5, 130.2, 129.5, 63.2 (d,  $J$  = 4.8 Hz); IR (KBr,  $\text{cm}^{-1}$ ) 3300-2400, 1657, 1630, 1585; HRMS (DART,  $m/z$ ) Calcd. for  $\text{C}_8\text{H}_9^{15}\text{NO}_2 \cdot \text{H}$  ( $[\text{M}+\text{H}]^+$ ): 153.0682, found 153.0677.



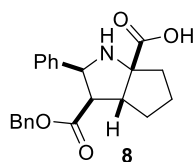
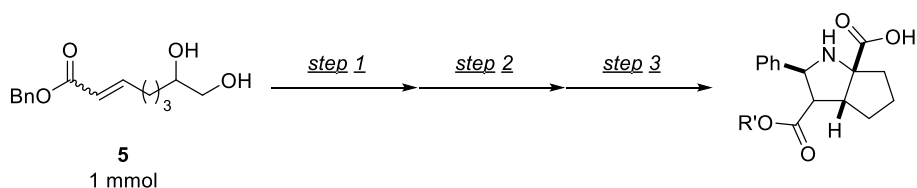
$\alpha$ -Amino acid  **$^{15}\text{N-3a}$**  was synthesized from 1,2-diol **5a** (171 mg, 1.03 mmol) according to the synthetic procedure of **3a** and afforded  $\alpha$ -amino acid  **$^{15}\text{N-3a}$**  as a white solid (113 mg, 61%).



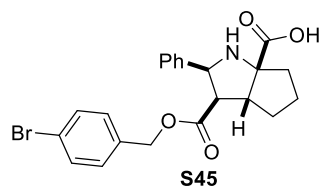
White solid;  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$  with 4 eq of KOH)  $\delta$  7.37 (t,  $J$  = 6.8 Hz, 2H), 7.31 (d,  $J$  = 6.8, 2H), 7.26 (t,  $J$  = 6.8, 1H), 3.25 (ddd,  $J$  = 7.6, 6.0, 2.4 Hz, 1H), 2.64 (t,  $J$  = 8.4 Hz, 2H), 1.95-1.79 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$  with 4 eq of KOH)  $\delta$  186.0, 145.1, 131.4, 131.2, 128.7, 58.4 (d,  $J$  = 4.7 Hz), 39.6, 34.2; HRMS (DART,  $m/z$ ) Calcd. for  $\text{C}_{10}\text{H}_{13}^{15}\text{NO}_2 \cdot \text{H}$

([M+H]<sup>+</sup>): 181.0995, found 181.0996; Anal. Calcd. for C<sub>10</sub>H<sub>13</sub><sup>15</sup>NO<sub>2</sub>: C, 66.65; H, 7.27; <sup>15</sup>N, 8.32. Found: C, 66.49; H, 7.37; <sup>15</sup>N, 7.97.

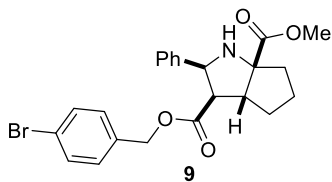
## 7. Synthesis of bicyclic $\alpha$ -amino acids

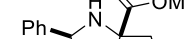


240 mg (65% yield); The synthesis of **8** was carried out according to the typical procedure of three-step  $\alpha$ -amino acid synthesis except the following point. An additional NaOCl aqueous solution (0.20 M, 252  $\mu$ L, 0.05 mmol) was added after 2 h in step 1.; White solid; 238  $^{\circ}$ C decomp.;  $^1\text{H}$  NMR (400 MHz, 5wt% deuterium chloride solution in  $\text{D}_2\text{O}$ )  $\delta$  7.47-7.29 (m, 8H), 7.06 (d,  $J$  = 6.4 Hz, 2H), 5.45 (d,  $J$  = 6.4 Hz, 1H), 5.01 (d,  $J$  = 12.4 Hz, 1H), 4.96 (d,  $J$  = 12.4 Hz, 1H), 3.68 (dd,  $J$  = 6.4, 2.0 Hz, 1H), 3.56 (td,  $J$  = 8.4, 2.0 Hz, 1H), 2.59-2.51 (m, 1H), 2.42-2.22 (m, 2H), 2.11-1.82 (m, 3H); IR (KBr,  $\text{cm}^{-1}$ ) 3200-1900, 1741, 1616; HRMS (DART,  $m/z$ ) Calcd. for  $\text{C}_{22}\text{H}_{23}\text{NO}_4 \cdot \text{H}$  ( $[\text{M}+\text{H}]^+$ ): 366.1705, found 366.1696; Anal. Calcd. for  $\text{C}_{22}\text{H}_{23}\text{NO}_4$ : C, 72.31; H, 6.34; N, 3.83. Found: C, 72.16; H, 6.44; N, 3.96.

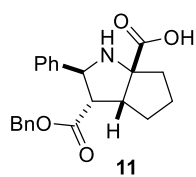


317 mg (71% yield); The synthesis of **S45** was carried out according to the typical procedure of three-step  $\alpha$ -amino acid synthesis except the following point. An additional NaOCl aqueous solution (0.20 M, 252  $\mu$ L, 0.05 mmol) was added after 2 h in step 1.; White solid; 248  $^{\circ}$ C decomp.;  $^1$ H NMR (400 MHz, 5wt% deuterium chloride solution in D<sub>2</sub>O)  $\delta$  7.45 (d,  $J$  = 8.0 Hz, 2H), 7.42 (t,  $J$  = 8.4 Hz, 1H), 7.33 (t,  $J$  = 8.4 Hz, 2H), 7.26 (d,  $J$  = 8.0 Hz, 2H), 6.94 (d,  $J$  = 8.4 Hz, 2H), 5.45 (d,  $J$  = 6.0 Hz, 1H), 5.00 (d,  $J$  = 12.0 Hz, 1H), 4.90 (d,  $J$  = 12.0 Hz, 1H), 3.68 (d,  $J$  = 6.0, 1.2 Hz, 1H), 3.57 (t,  $J$  = 8.0 Hz, 1H), 2.58-2.51 (m, 1H), 2.40-2.23 (m, 2H), 2.10-1.81 (m, 3H); IR (KBr,  $\text{cm}^{-1}$ ) 3200-2800, 1747, 1595; HRMS (DART,  $m/z$ ) Calcd. for C<sub>22</sub>H<sub>22</sub>BrNO<sub>4</sub>  $\cdot$  H ([M+H]<sup>+</sup>): 444.0811, found 444.0806; Anal. Calcd. for C<sub>22</sub>H<sub>22</sub>BrNO<sub>4</sub>: C, 59.47; H, 4.99; N, 3.15. Found: C, 59.48; H, 5.04; N, 2.86.



  
**9**

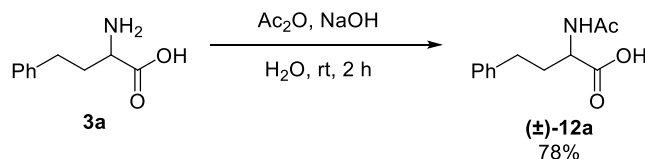
White solid; mp 128.3-128.9 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 (d,  $J$  = 8.4 Hz, 2H), 7.27-7.21 (m, 5H), 6.75 (d,  $J$  = 8.4 Hz, 2H), 4.66 (d,  $J$  = 12.0 Hz, 1H), 4.62 (d,  $J$  = 6.4 Hz, 1H), 4.57 (1H,  $J$  = 12.0 Hz), 3.77 (s, 3H), 3.43 (br s, 1H), 3.17 (t,  $J$  = 8.8 Hz, 1H), 3.00 (d,  $J$  = 6.4 Hz, 1H), 2.29-2.13 (m, 2H), 1.92-1.73 (m, 3H), 1.61-1.51 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  176.6, 172.6, 137.8, 134.3, 131.4, 130.0, 128.3, 127.5, 126.3, 122.1, 65.3, 64.7, 57.3, 53.3, 52.4, 41.1, 33.1, 26.6; IR (neat,  $\text{cm}^{-1}$ ) 1732; HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{23}\text{H}_{24}\text{BrNO}_4 \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 480.0786, found 480.0795.



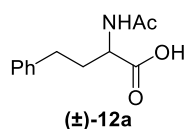
138 mg (38% yield); The synthesis of **11** was carried out according to the typical procedure of three-step  $\alpha$ -amino acid synthesis except the following point. An additional NaOCl aqueous solution (0.20 M, 251  $\mu$ L, 0.05 mmol) was added after 2 h in step 1.; White solid; 206  $^{\circ}$ C decomp.;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.59-7.53 (m, 2H), 7.49-7.43 (m, 3H), 7.33-7.28 (m, 3H), 7.27-7.22 (m, 2H), 5.17 (d,  $J$  = 12.0 Hz, 1H), 5.02 (d,  $J$  = 12.0 Hz, 1H), 4.95 (d,  $J$  = 12.0 Hz, 1H), 3.70 (dd,  $J$  = 12.0, 7.2 Hz, 1H), 3.29 (q,  $J$  = 7.2 Hz, 1H), 2.50 (quint,  $J$  = 6.8 Hz, 1H), 2.07-1.80 (m, 4H), 1.68-1.57 (m, 1H); IR (KBr,  $\text{cm}^{-1}$ ) 3300-1900, 1730, 1620; HRMS (DART,  $m/z$ ) Calcd. for  $\text{C}_{22}\text{H}_{23}\text{NO}_4 \cdot \text{H}$  ( $[\text{M}+\text{H}]^+$ ): 366.1705, found 366.1717; Anal. Calcd. for  $\text{C}_{22}\text{H}_{23}\text{NO}_4$ : C, 72.31; H, 6.34; N, 3.83. Found: C, 72.23; H, 6.36; N, 3.72.

## 8. Kinetic resolution of *N*-acetyl $\alpha$ -amino acid

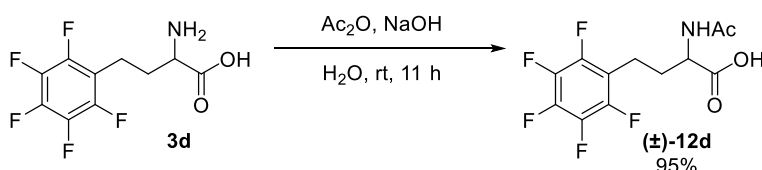
### Preparation of *N*-acetyl $\alpha$ -amino acids ( $\pm$ )-12



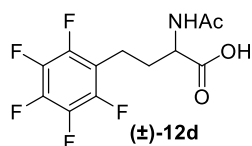
To a solution of  $\alpha$ -amino acid **3a** (100 mg, 0.558 mmol) in aq.  $\text{NaOH}$  (0.56 M, 1.0 mL) were added  $\text{Ac}_2\text{O}$  (69  $\mu\text{L}$ , 0.730 mmol) and aq.  $\text{NaOH}$  (36%, 0.20 mL) at room temperature. After 1 h,  $\text{Ac}_2\text{O}$  (70  $\mu\text{L}$ , 0.741 mmol) and aq.  $\text{NaOH}$  (36%, 0.20 mL) were added and the reaction mixture was stirred for 1 h. Then, the reaction mixture was acidified with aq.  $\text{HCl}$  (10%) to pH 1 and filtration of a precipitation afforded *N*-acetyl L-homophenylalanine [( $\pm$ )-**12a**] (95.9 mg, 78%) as a white solid.



White solid; mp 117.5–118.1  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31–7.25 (m, 2H), 7.22–7.15 (m, 3H), 6.09 (d,  $J$  = 7.6 Hz, 1H), 4.64 (td,  $J$  = 7.6, 5.6 Hz, 1H), 2.77–2.64 (m, 2H), 2.31–2.21 (m, 1H), 2.11–1.97 (m, 1H), 2.00 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  175.4, 173.4, 142.2, 129.5 (2C), 127.1, 53.3, 34.5, 33.1, 22.3; IR (KBr,  $\text{cm}^{-1}$ ) 3345, 1714, 1597, 1545; HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{12}\text{H}_{15}\text{NO}_3 \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 244.0950, found 244.0927.

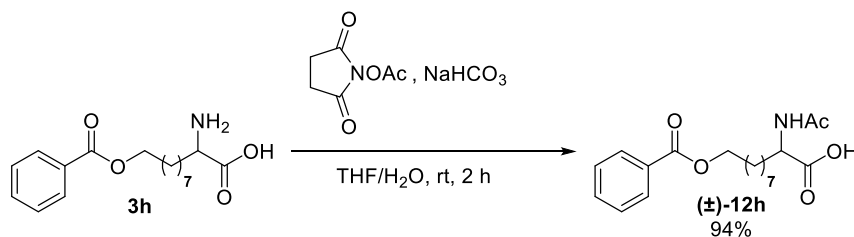


To a solution of  $\alpha$ -amino acid **3d** (23.1 mg, 0.0858 mmol) in  $\text{H}_2\text{O}$  (1.0 mL) was added aq.  $\text{NaOH}$  (10%, 127  $\mu\text{L}$ ) at room temperature. Then,  $\text{Ac}_2\text{O}$  (20.3  $\mu\text{L}$ , 0.215 mmol) and aq.  $\text{NaOH}$  (10%, 127  $\mu\text{L}$ , 0.343 mmol) were added at 0  $^{\circ}\text{C}$ . After the reaction mixture was stirred for 11 h at room temperature, it was acidified with aq.  $\text{HCl}$  (10%) to pH 1 and extracted with  $\text{Et}_2\text{O}$ . The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo to afford *N*-acetyl  $\alpha$ -amino acid ( $\pm$ )-**12d** (25.4 mg, 95%) as a white solid.



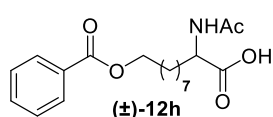
White solid; mp 173.9–175.4  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  4.37 (dd,  $J$  = 9.2, 4.4 Hz, 1H), 2.92–2.78 (m, 2H), 2.24–2.14 (m, 1H), 2.05–1.92 (m, 1H), 2.01 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  174.6, 173.5, 146.6 (dm,  $J$  = 241.2 Hz), 141.2 (dm,  $J$  = 243.1 Hz), 138.8 (dm,  $J$  = 233.6 Hz), 115.5 (t,  $J$  = 16.2 Hz), 53.0, 31.6, 22.3, 19.8; IR (KBr,  $\text{cm}^{-1}$ ) 3354, 1707, 1624 HRMS (ESI,  $m/z$ ) Calcd. for  $\text{C}_{12}\text{H}_{10}\text{F}_5\text{NO}_3 \cdot \text{Na}$  ( $[\text{M}+\text{Na}]^+$ ): 334.0479, found 334.0477.



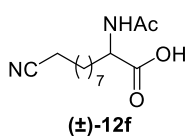


For the *N*-acetylation of  $\alpha$ -amino acid **3f**, **3h**, and **3i**, the method using *in situ* prepared *N*-acetyl succinimide was employed.<sup>5</sup>

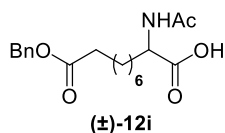
To a well-dried round-bottom flask charged with *N*-hydroxysuccinimide (8.1 mg, 0.070 mmol) and *N,N*-diisopropylethylamine (13.4  $\mu$ L, 0.0781 mmol) and dry THF (0.50 mL) was added AcCl (5.1  $\mu$ L, 0.072 mmol) dropwise at 0 °C. The solution was stirred for 3 h at room temperature. The solution was added to a solution of  $\alpha$ -amino acid **3h** and NaHCO<sub>3</sub> (10.0 mg, 0.119 mmol) in H<sub>2</sub>O (0.50 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. Then, it was acidified with aq. HCl (1 M) to pH 3 and extracted with Et<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to afford *N*-acetyl  $\alpha$ -amino acid (±)-**12h** (21.5 mg, 94%) as a white solid.



White solid; mp 95.1-96.1 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.05-8.01 (m, 2H), 7.55 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 2H), 6.33 (d, *J* = 7.2 Hz, 1H), 4.58 (ddd, *J* = 7.2, 4.8 Hz, 1H), 4.31 (t, *J* = 6.4 Hz, 2H), 2.05 (s, 3H), 1.93-1.82 (m, 1H), 1.79-1.64 (m, 3H), 1.50-1.20 (m, 10H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  175.5, 171.0, 166.8, 132.9, 130.4, 129.5, 128.3, 65.1, 52.4, 31.9, 29.1, 29.0, 29.0, 28.6, 25.9, 25.1, 22.9; IR (neat, cm<sup>-1</sup>) 3500-3300, 1718, 1657, 1630, 1277; HRMS (ESI, *m/z*) Calcd. for C<sub>19</sub>H<sub>27</sub>O<sub>5</sub> · Na ([M+Na]<sup>+</sup>): 372.1787, found 372.1787.

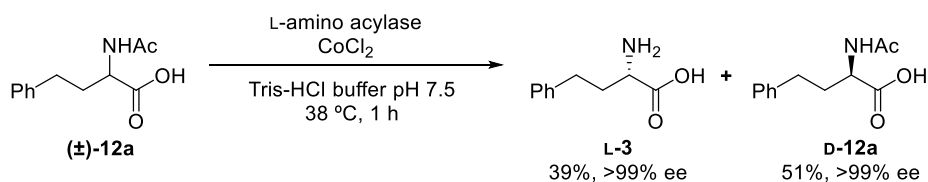


293 mg (97% yield); Yellow solid; mp 57.9-59.6 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.98 (br s, 1H), 4.57 (ddd, *J* = 7.6, 7.6, 5.6 Hz, 1H), 2.34 (t, *J* = 7.6 Hz, 2H), 2.06 (s, 3H), 1.97-1.85 (m, 1H), 1.76-1.61 (m, 3H), 1.50-1.26 (m, 10H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  175.5, 171.1, 119.8, 52.4, 31.9, 28.9, 28.48, 28.46, 25.2, 25.0, 22.9, 17.1; IR (neat, cm<sup>-1</sup>) 3500-3300, 2247, 1728, 1649, 1630, 1549; HRMS (ESI, *m/z*) Calcd. for C<sub>13</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub> · Na ([M+Na]<sup>+</sup>): 277.1528, found 277.1508.



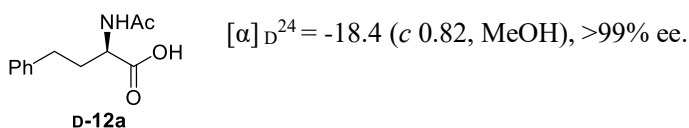
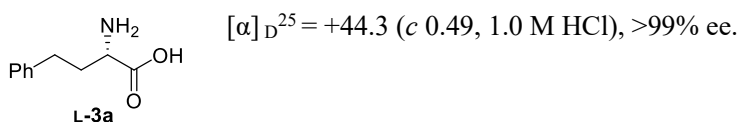
50.8 mg (79%); White solid; mp 88.2-90.0 °C <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.39-7.29 (m, 5H), 6.18 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 2H), 4.57 (td, *J* = 8.0, 8.0, 5.2 Hz, 1H), 2.35 (t, *J* = 7.6 Hz, 2H), 2.05 (s, 3H), 1.93-1.82 (m, 1H), 1.74-1.57 (m, 3H), 1.40-1.20 (m, 8H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  175.2, 173.9, 170.9, 136.0, 128.5, 128.2, 128.2, 66.2, 52.4, 34.2, 31.9, 28.8 (3C), 25.0, 24.8, 23.0; IR (neat, cm<sup>-1</sup>) 3500-3300, 1731, 1651, 1628; HRMS (ESI, *m/z*) Calcd. for C<sub>19</sub>H<sub>27</sub>NO<sub>5</sub> · Na ([M+Na]<sup>+</sup>): 372.1787, found 372.1781.

### Typical procedure of kinetic resolution of *N*-acetyl $\alpha$ -amino acid using L-amino acylase



To a solution of *N*-acetyl homophenylalanine [(±)-**12a**] (30.5 mg, 0.138 mmol) and aq.  $\text{CoCl}_2$  (0.01 M, 17.2  $\mu\text{L}$ , 172 nmol) in Tris-HCl buffer (1 M, pH 7.5, 1.4 mL) was added L-aminoacylase (10.2 mg) at room temperature. After the reaction mixture was stirred for 1 h at 38  $^\circ\text{C}$ ,  $\text{Et}_2\text{O}$  (5 mL) was added. After 5 min, L-homophenylalanine (**L-3**) was precipitated. The precipitate was filtered, washed with  $\text{Et}_2\text{O}$  and water, and dried under reduced pressure. L-Homophenylalanine (**L-3**) (9.6 mg, 39%) was obtained. The filtrate was acidified with sodium phosphate buffer (1 M, pH = 2.1, 2.8 mL) and extracted with  $\text{Et}_2\text{O}$ . The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo to afford *N*-acetyl D-homophenylalanine (**D-12a**) (15.6 mg, 51%).

Enantiomeric excess was measured as the *N*-acetyl ethyl ester of homophenylalanine by chiral HPLC. The absolute configuration was determined by comparing optical rotations with a previous report.<sup>6</sup>



### HPLC Conditions

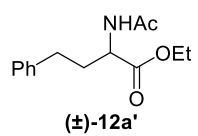
Column: Chiralcel OD-H, Daicel Chemical Industries, Ltd.

Eluent: hexane/isopropanol (90:10)

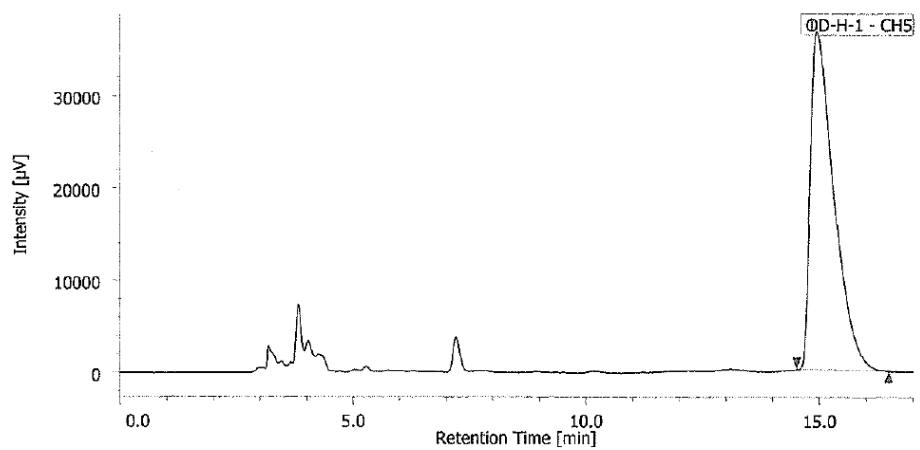
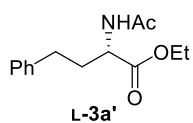
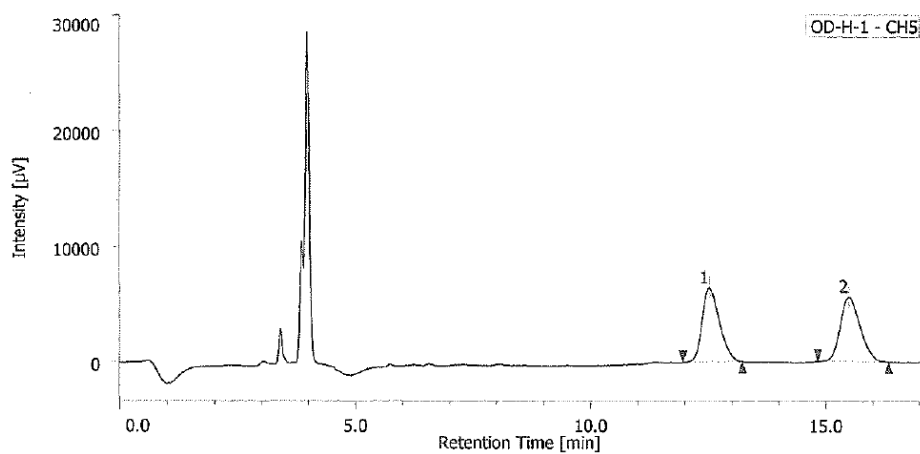
Flow rate: 1.0 mL/min

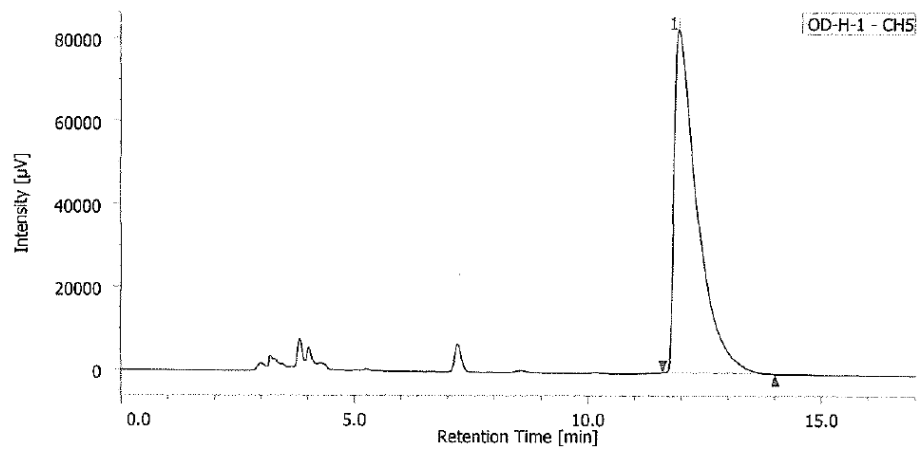
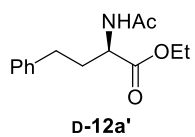
Detection: UV 230 nm

Retention time: D-isomer: 12.5 min, L-isomer: 15.5 min.

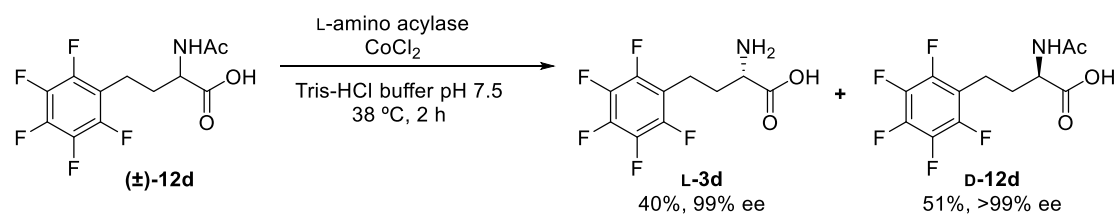


Racemate



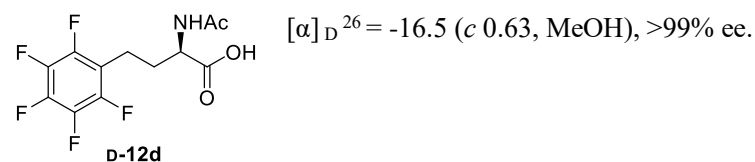
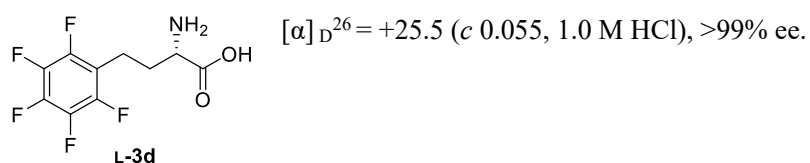


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	11.965	2811072	82824	100.000



Kinetic resolution of *N*-acetyl  $\alpha$ -amino acid (**(±)-12d**) (20.1 mg, 0.0646 mmol) was carried out according to the typical procedure. L-aminoacylase (5.0 mg) and aq.  $\text{CoCl}_2$  (0.01 M, 8.1  $\mu\text{L}$ , 81 nmol) were used.

Enantiomeric excess was measured as the *N*-acetyl ethyl ester by chiral HPLC. The absolute configuration was determined by comparing optical rotations with a previous report.<sup>7</sup>



### HPLC Conditions

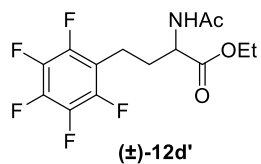
Column: Chiralcel OD-H, Daicel Chemical Industries, Ltd.

Eluent: hexane/isopropanol (90:10)

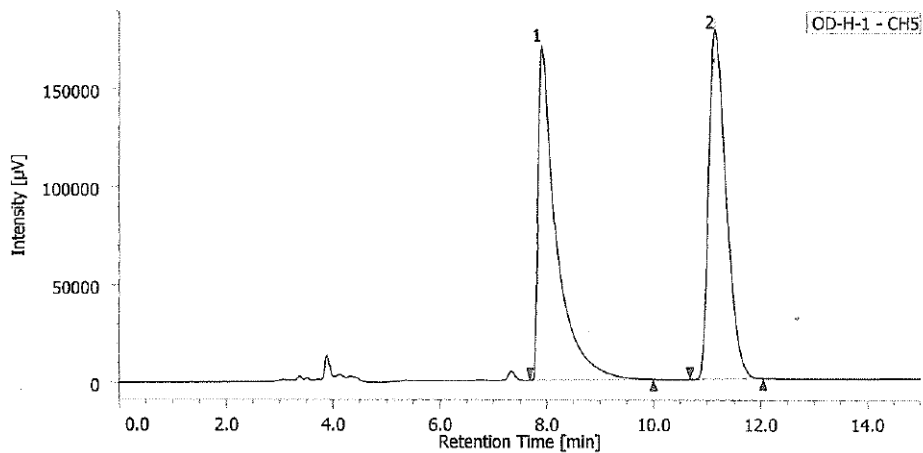
Flow rate: 1.0 mL/min

Detection: UV 230 nm

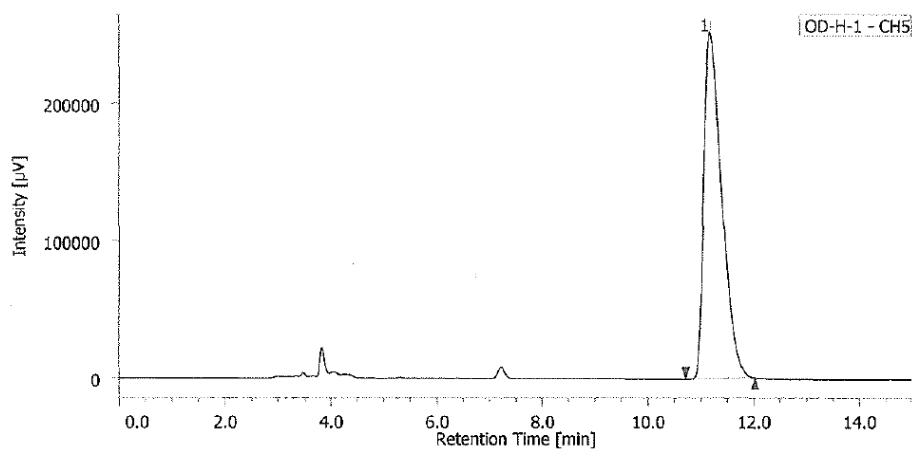
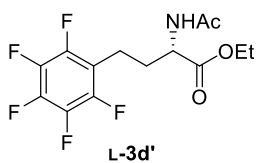
Retention time: 7.9 min, 11.1 min.



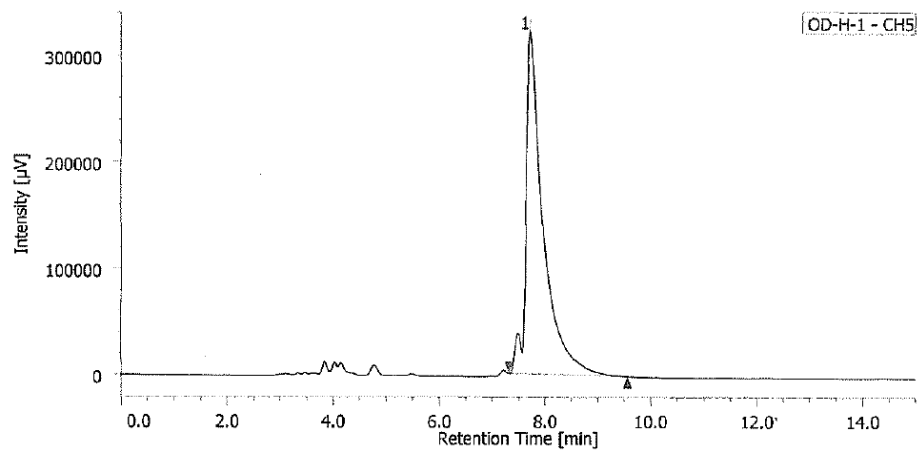
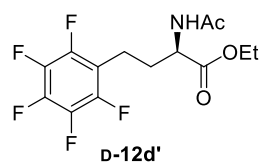
Racemate



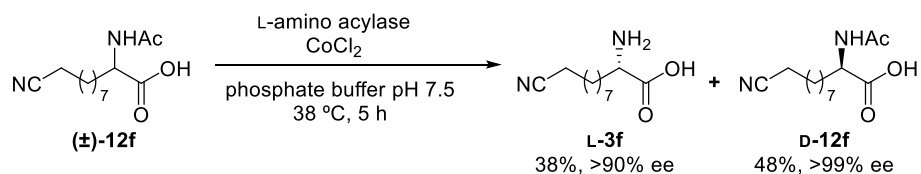
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	7.905	4058644	171011	50.097
2	Unknown	5	11.142	4042879	176831	49.903



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	11.167	5958592	252543	100.000



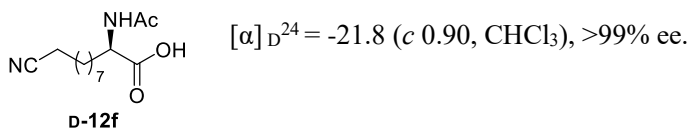
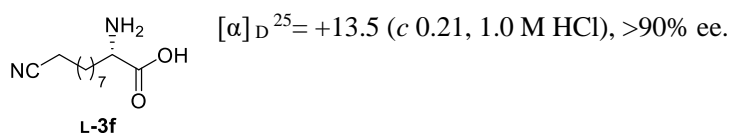
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	7.717	7363789	324126	100.000



Kinetic resolution of *N*-acetyl  $\alpha$ -amino acid ( $\pm$ )-**12f** was carried out according to the following procedure.

To a solution of *N*-acetyl  $\alpha$ -amino acid ( $\pm$ )-**12f** (24.8 mg, 0.0975 mmol) and aq.  $\text{CoCl}_2$  (0.01 M, 12.2  $\mu\text{L}$ , 122 nmol) in phosphate buffer (1 M, pH 7.5, 0.98 mL) was added L-aminoacylase (15.0 mg) at room temperature. After the reaction mixture was stirred for 5 h at 38  $^\circ\text{C}$ , it was acidified with aq.  $\text{HCl}$  (1 M) and extracted with  $\text{Et}_2\text{O}$ . The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo to afford *N*-acetyl  $\alpha$ -amino acid (**D-12f**) (11.8 mg, 48%). The resultant aqueous layer was basified with aq.  $\text{NaOH}$  (1 M) until pH 9 and charged on a cationic ion exchange chromatography (DOWEX 50W-8, 200-400 mesh). The product was eluted with aq.  $\text{NH}_3$  (3%). The eluent was concentrated by freeze-dry to afford  $\alpha$ -amino acid **L-3f** (7.8 mg, 38%).

Enantiomeric excess was measured as the *N*-acetyl benzyl ester by chiral HPLC.



### HPLC Conditions

Column: Chiralcel IC, Daicel Chemical Industries, Ltd.

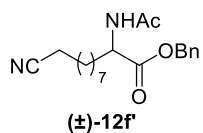
Eluent: hexane/isopropanol (70:30)

Flow rate: 1.0 mL/min

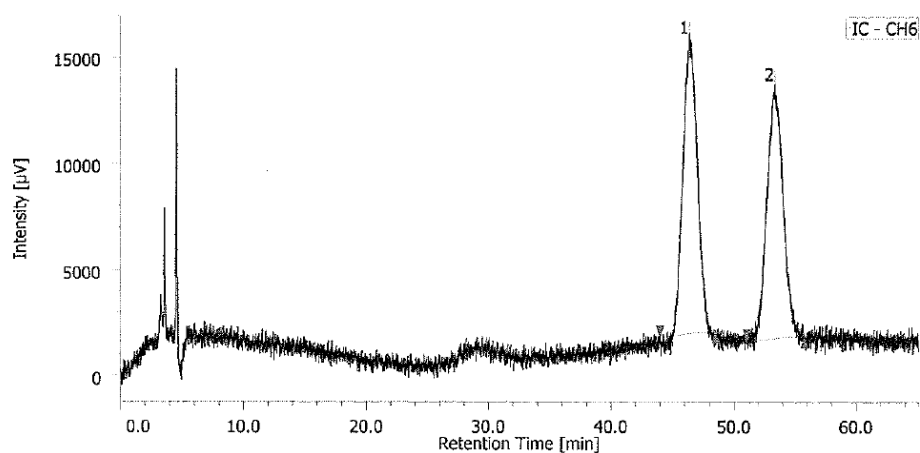
Detection: UV 200 nm

Retention time: 46.4 min, 53.3 min.

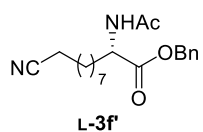




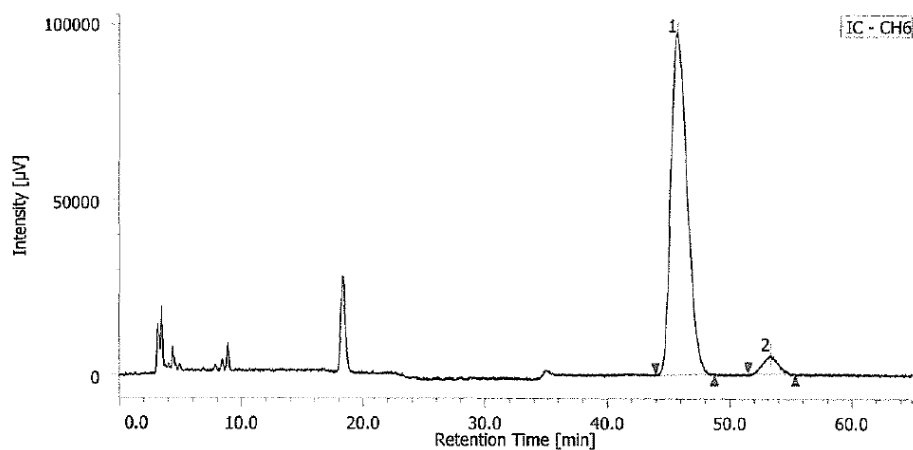
Racemate



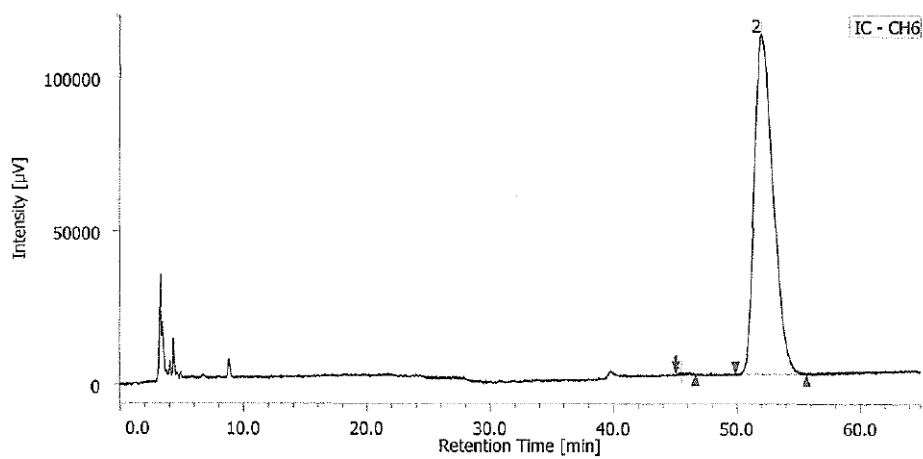
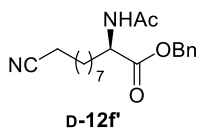
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	6	46.397	1116344	14107	50.123
2	Unknown	6	53.332	1110858	11975	49.877



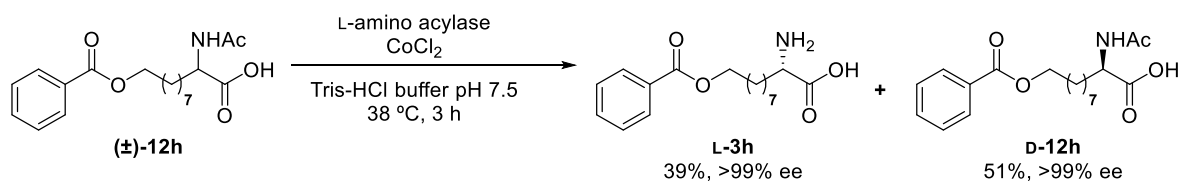
HPLC analysis using photodiode array detector suggests that the peak of minor enantiomer includes impurity.



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	6	45.713	8988953	97744	95.113
2	Unknown	6	53.307	461874	5524	4.887

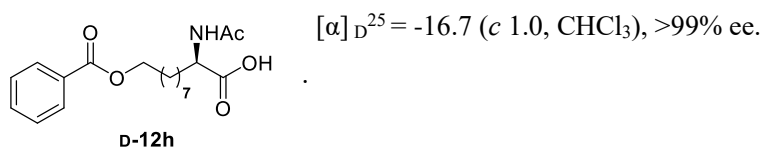
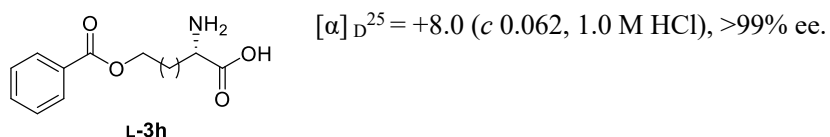


#	Peak Name	CH	tR [min]	Area [µV-sec]	Height [µV]	Area%
1	Unknown	G	45.495	6135	488	0.052
2	Unknown	G	51.992	11851979	111299	99.948



Kinetic resolution of *N*-acetyl  $\alpha$ -amino acid ( $\pm$ )-**12h** (25.2 mg, 0.0721 mmol) was carried out according to the typical procedure. L-Aminoacylase (17.4 mg) and aq.  $\text{CoCl}_2$  (0.01 M, 18.0  $\mu\text{L}$ , 180 nmol) were used.

Enantiomeric excess was measured as the *N*-acetyl benzyl ester by chiral HPLC.



#### HPLC Conditions

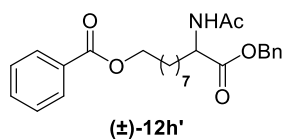
Column: Chiralcel IC, Daicel Chemical Industries, Ltd.

Eluent: hexane/isopropanol (80:20)

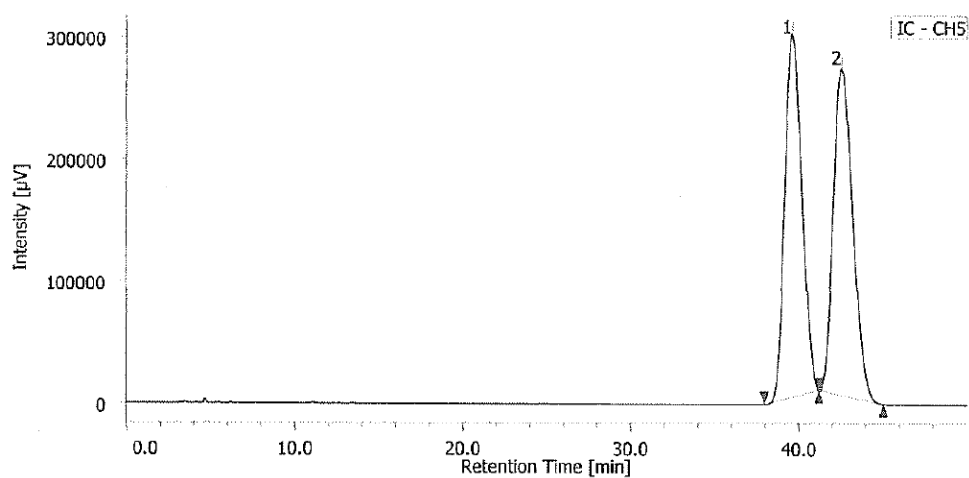
Flow rate: 1.0 mL/min

Detection: UV 230 nm

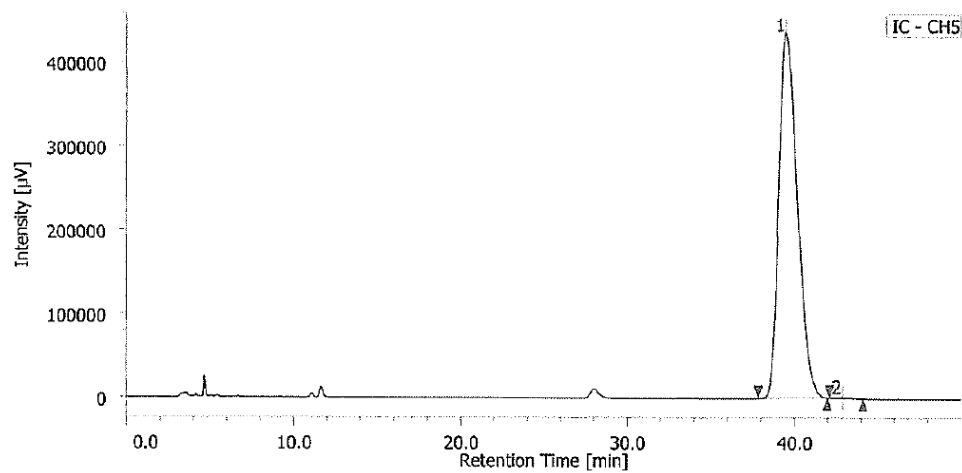
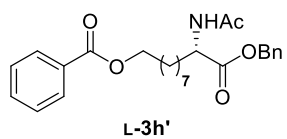
Retention time: 39.6 min, 42.5 min.



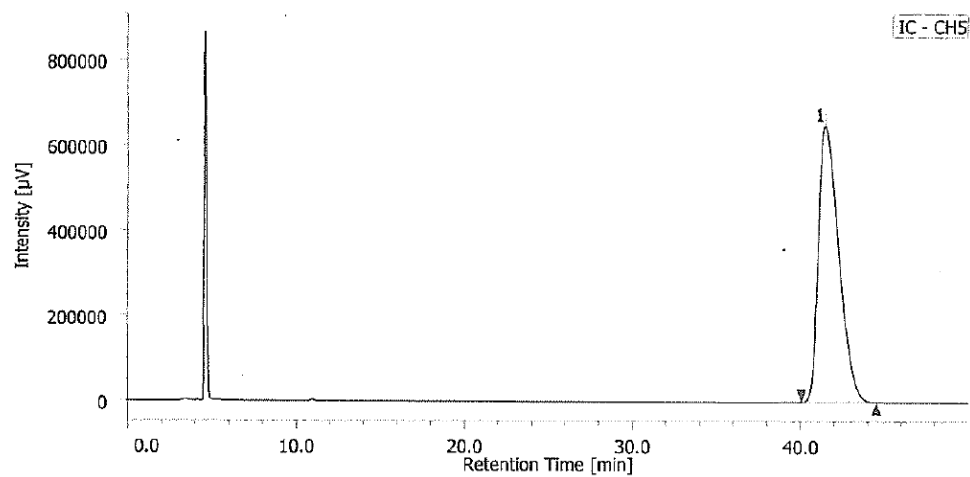
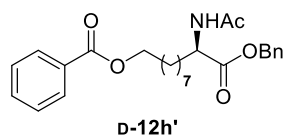
Racemate



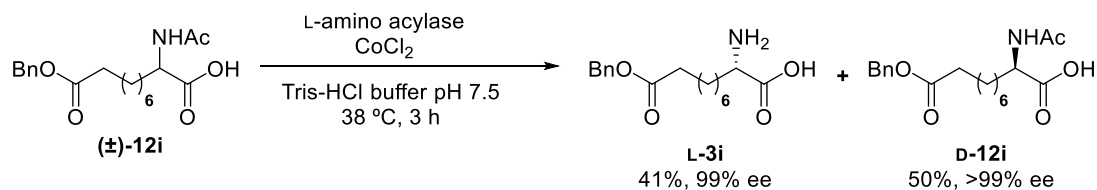
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	39.590	21350600	297593	49.912
2	Unknown	5	42.547	21426014	267839	50.088



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	39.480	33766041	437073	99.884
2	Unknown	5	42.847	39368	676	0.116

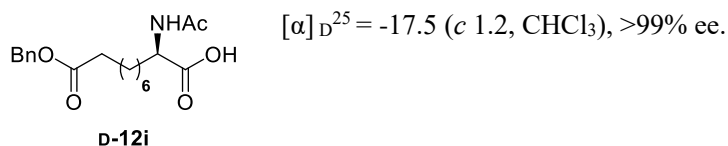
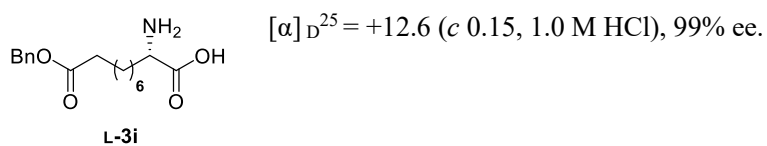


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	41.488	55023047	648878	100.000



Kinetic resolution of *N*-acetyl  $\alpha$ -amino acid ( $\pm$ )-**12i** (31.4 mg, 0.0899 mmol) was carried out according to the typical procedure. L-Aminoacylase (20.2 mg) and aq.  $\text{CoCl}_2$  (0.01 M, 33.7  $\mu\text{L}$ , 337 nmol) were used.

Enantiomeric excess was measured as the *N*-acetyl benzyl ester by chiral HPLC.



#### HPLC Conditions

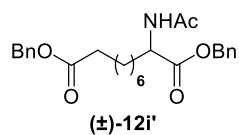
Column: Chiralcel IC, Daicel Chemical Industries, Ltd.

Eluent: hexane/isopropanol (80:20)

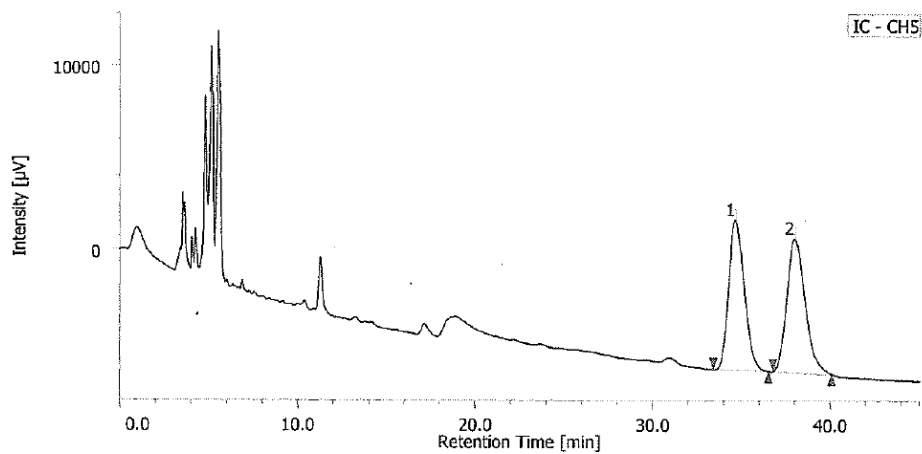
Flow rate: 1.0 mL/min

Detection: UV 230 nm

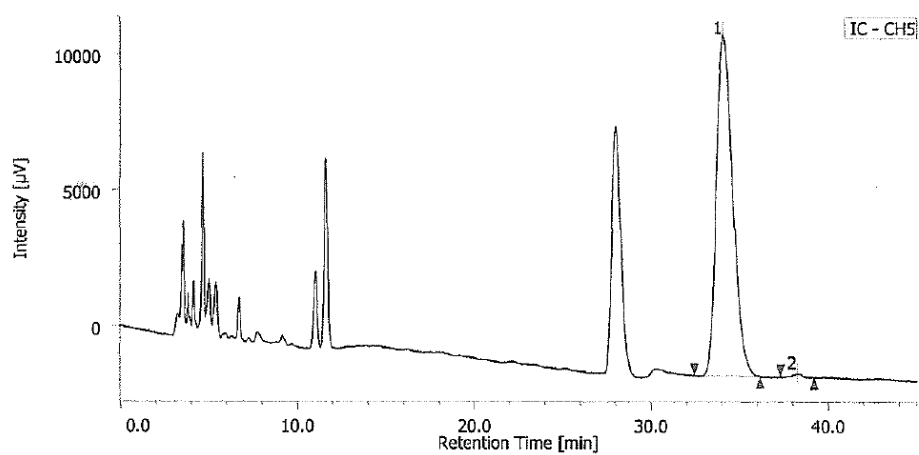
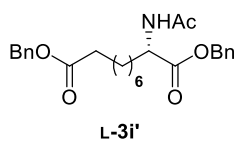
Retention time: 34.6 min, 38.0 min.



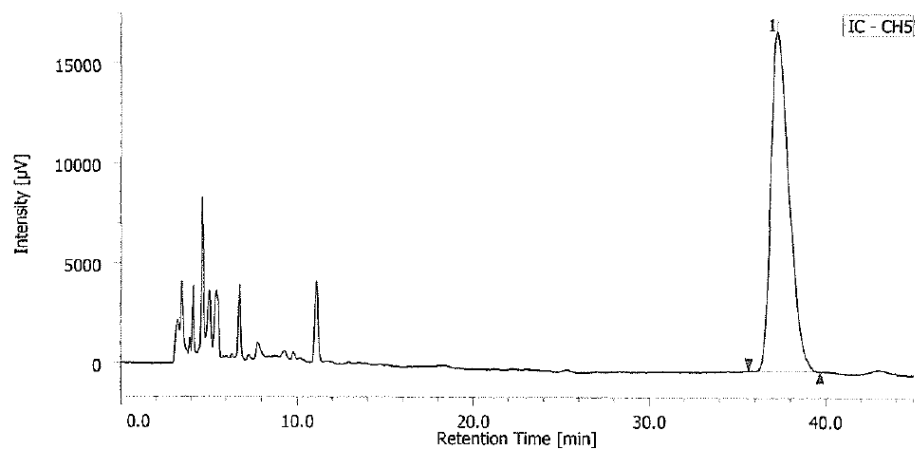
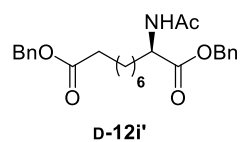
Racemate



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	34.643	499836	8173	48.237
2	Unknown	5	37.982	536363	7328	51.763



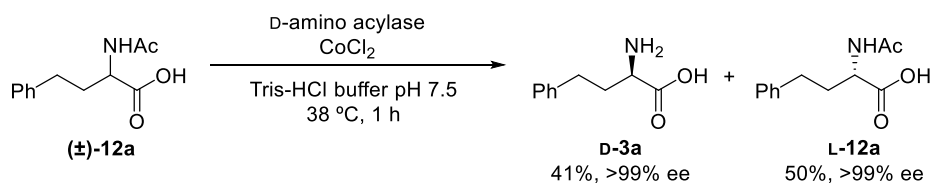
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	34.037	802409	12560	99.412
2	Unknown	5	38.255	4747	147	0.588



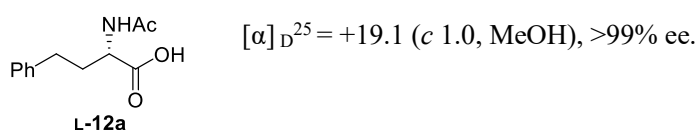
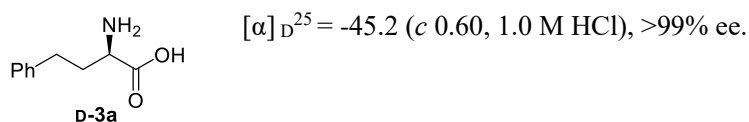
#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%
1	Unknown	5	37.263	1224248	16999	100.000



### Typical procedure of kinetic resolution of *N*-acetyl $\alpha$ -amino acid using D-aminoacylase.



To a solution of *N*-acetyl homophenylalanine [ $(\pm)$ -12a] (102 mg, 0.461 mmol) and aq.  $\text{CoCl}_2$  (0.01 M, 57.6  $\mu\text{L}$ , 576 nmol) in Tris-HCl buffer (1 M, pH 7.5, 4.6 mL) was added D-aminoacylase (3.52 mg) at room temperature. After the reaction mixture was stirred for 1 h at 38 °C,  $\text{Et}_2\text{O}$  (5 mL) was added. After 5 min, D-homophenylalanine (**D-3a**) was precipitated. The precipitate was filtered, washed with  $\text{Et}_2\text{O}$  and water, and dried under reduced pressure. D-Homophenylalanine (**D-3a**) (33.5 mg, 41%) was afforded. Then, the filtrate was acidified with sodium phosphate buffer (1 M, pH = 2.1, 4.6 mL) and extracted with  $\text{Et}_2\text{O}$ . The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo to afford *N*-acetyl L-homophenylalanine (**L-12a**) (50.7 mg, 50%).



### HPLC Conditions

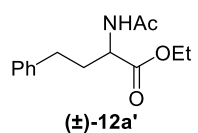
Column: Chiralcel OD-H, Daicel Chemical Industries, Ltd.

Eluent: hexane/isopropanol (90:10)

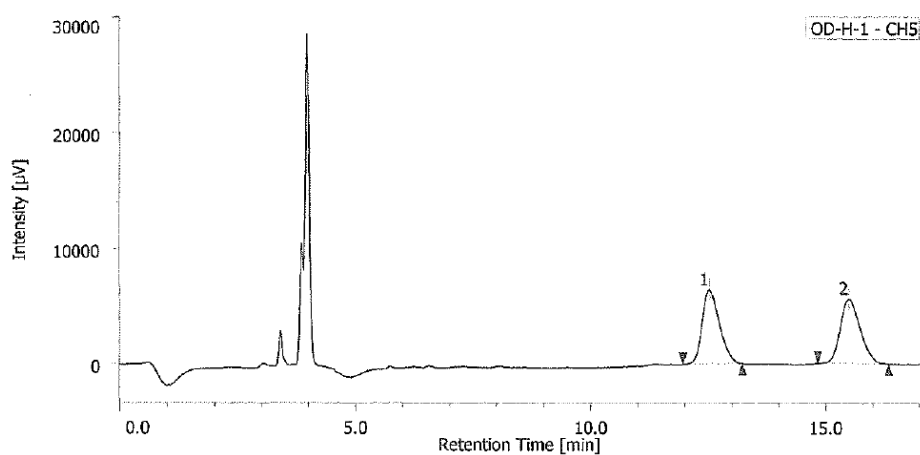
Flow rate: 1.0 mL/min

Detection: UV 230 nm

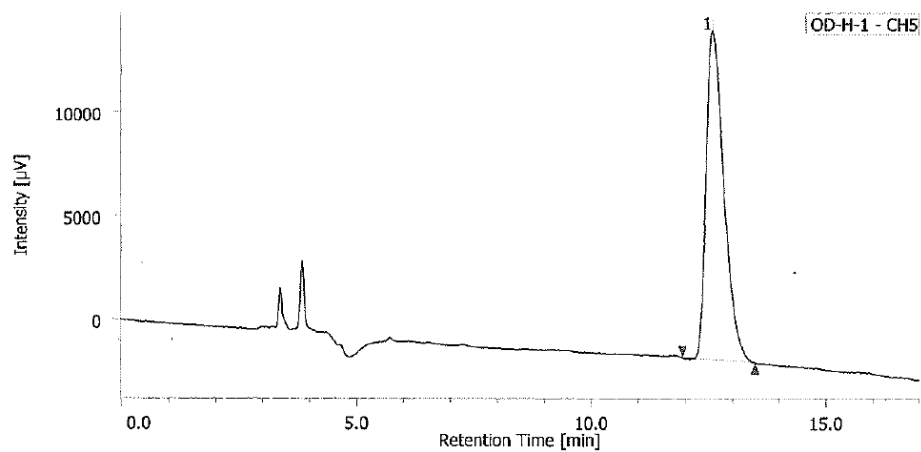
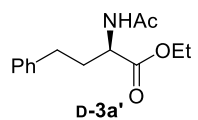
Retention time: D-isomer: 12.5 min, L-isomer: 15.5 min.



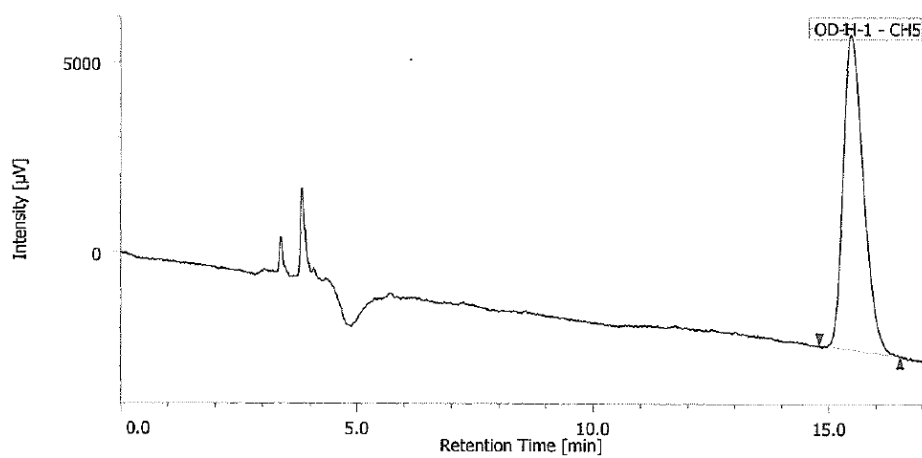
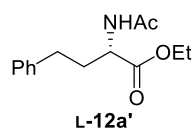
Racemate



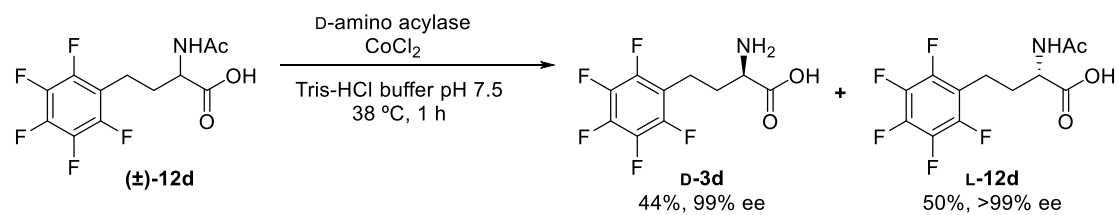
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	12.522	166256	6475	50.047
2	Unknown	5	15.482	165943	5616	49.953



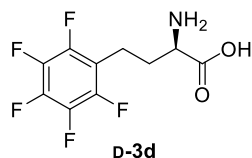
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	12.578	416901	15920	100.000



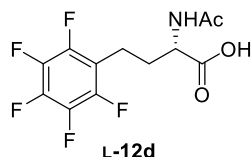
#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%
1	Unknown	5	15.470	249574	8282	100.000



Kinetic resolution of *N*-acetyl  $\alpha$ -amino acid  $(\pm)$ -**12d** (24.7 mg, 0.0794 mmol) was carried out according to the typical procedure. D-Aminoacylase (0.65 mg) and aq.  $\text{CoCl}_2$  (0.01 M, 9.9  $\mu\text{L}$ , 99 nmol) were used.



$[\alpha]_{\text{D}}^{25} = -25.3$  (*c* 0.052, 1.0 M HCl), 99% ee.



$[\alpha]_{\text{D}}^{25} = +16.7$  (*c* 0.74, MeOH), >99% ee.

#### HPLC Conditions

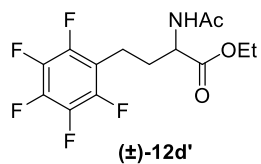
Column: Chiralcel OD-H, Daicel Chemical Industries, Ltd.

Eluent: hexane/isopropanol (90:10)

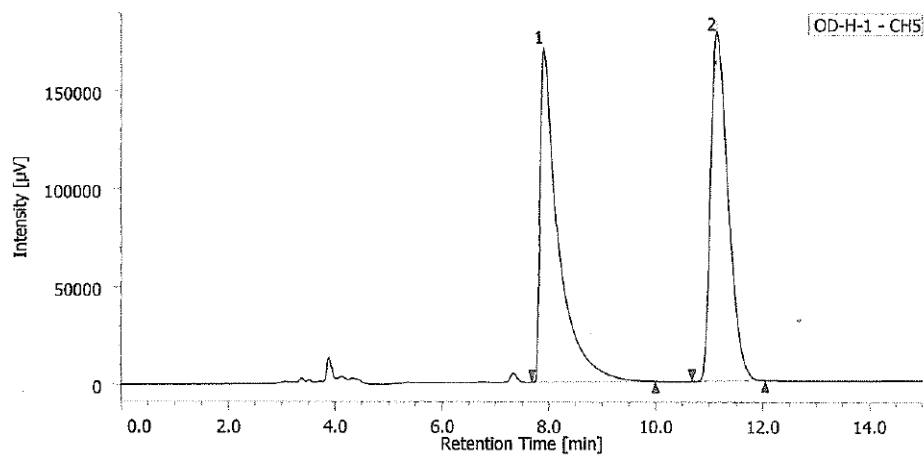
Flow rate: 1.0 mL/min

Detection: UV 230 nm

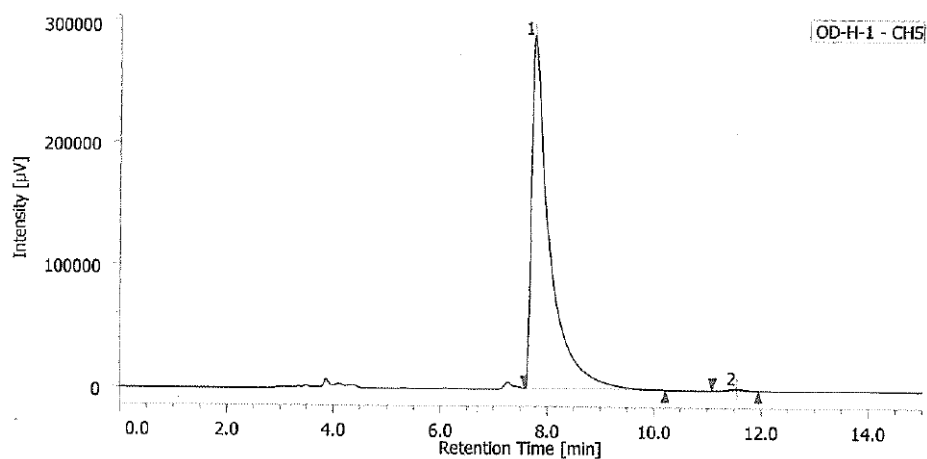
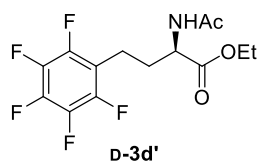
Retention time: 7.9 min, 11.1 min.



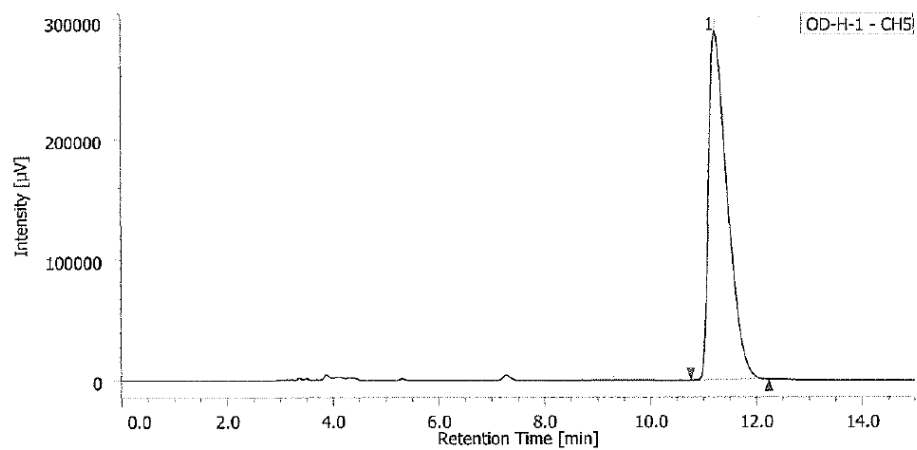
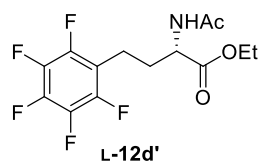
Racemate



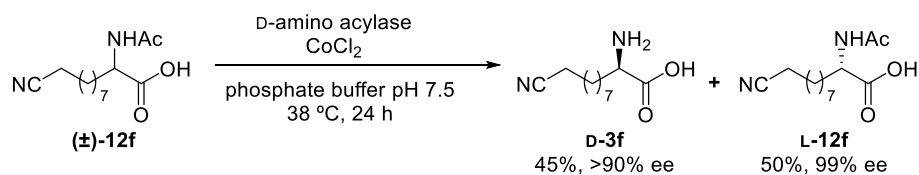
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	7.905	4058644	171011	50.097
2	Unknown	5	11.142	4042879	178831	49.903



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	7.753	6734890	288397	99.511
2	Unknown	5	11.535	33101	1588	0.489

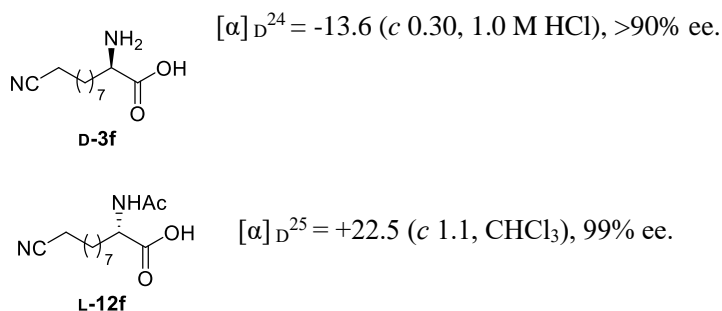


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	11.212	7137769	289770	100.000



Kinetic resolution of *N*-acetyl  $\alpha$ -amino acid ( $\pm$ )-**12f** was carried out according to the following procedure.

To a solution of *N*-acetyl  $\alpha$ -amino acid ( $\pm$ )-**12f** (30.1 mg, 0.118 mmol) and aq.  $\text{CoCl}_2$  (0.01 M, 14.8  $\mu\text{L}$ , 148 nmol) in phosphate buffer (1 M, pH 7.5, 1.2 mL) was added D-aminoacylase (0.90 mg) at room temperature. After the reaction mixture was stirred for 24 h at 38  $^\circ\text{C}$ , it was acidified with aq.  $\text{HCl}$  (1 M) and extracted with  $\text{Et}_2\text{O}$ . The organic layer was dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo to afford *N*-acetyl  $\alpha$ -amino acid (**L-12f**) (15.1 mg, 50%). The resultant aqueous layer was basified with aq.  $\text{NaOH}$  (1 M) until pH 9 and charged on a cationic ion exchange chromatography (DOWEX 50W-8, 200-400 mesh). The product was eluted with aq.  $\text{NH}_3$  (3%). The eluent was concentrated by freeze-dry to afford  $\alpha$ -amino acid **D-3f** (11.3 mg, 45%).



### HPLC Conditions

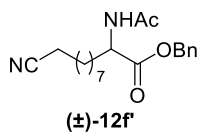
Column: Chiralcel IC, Daicel Chemical Industries, Ltd.

Eluent: hexane/isopropanol (70:30)

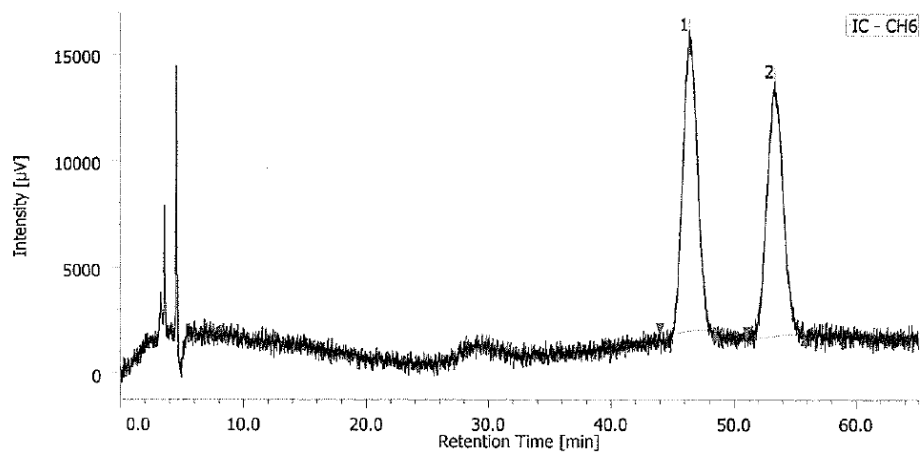
Flow rate: 1.0 mL/min

Detection: UV 200 nm

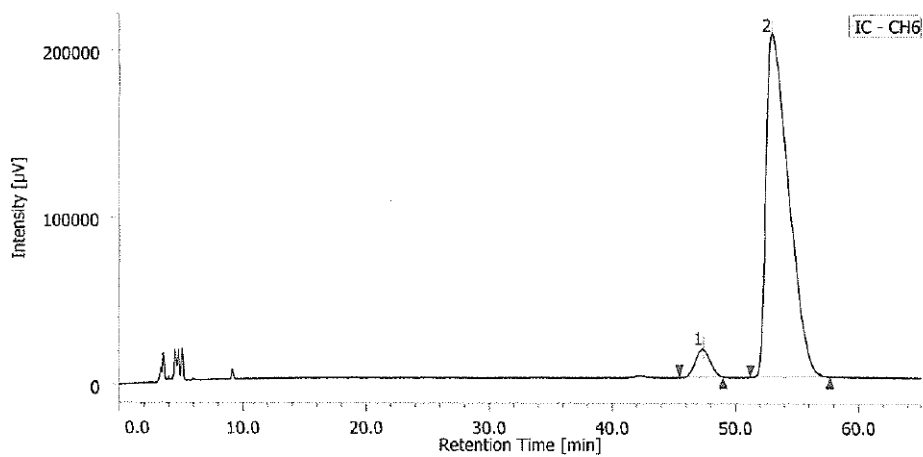
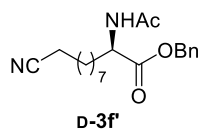
Retention time: 46.4 min, 53.3 min.



Racemate

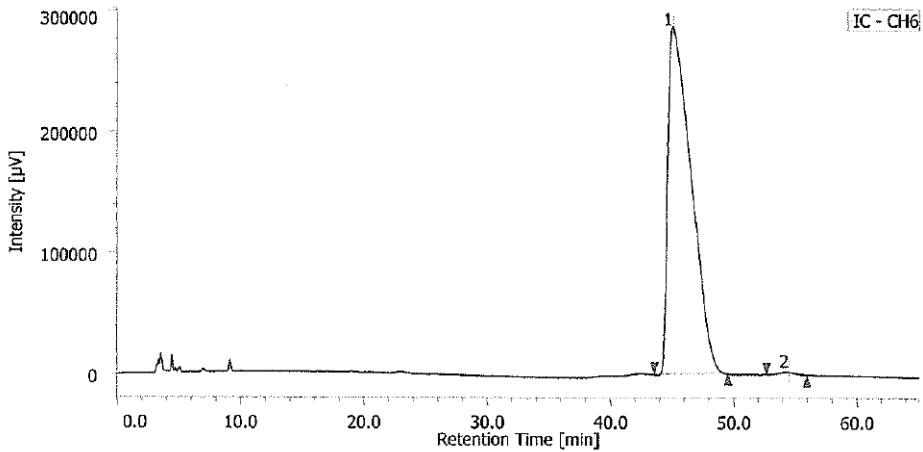


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	6	46.397	1116344	14107	50.123
2	Unknown	6	53.332	1110858	11975	49.877

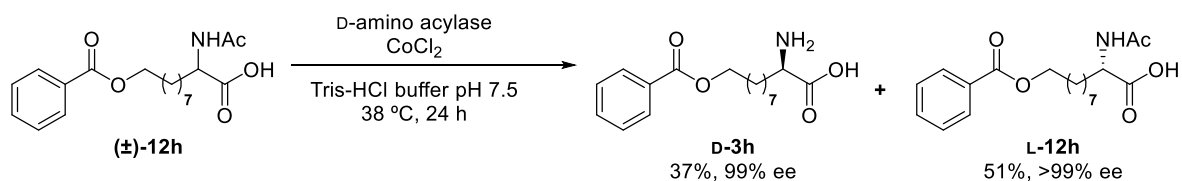


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	6	47.355	1392120	16983	4.992
2	Unknown	6	52.937	26494128	206033	95.008

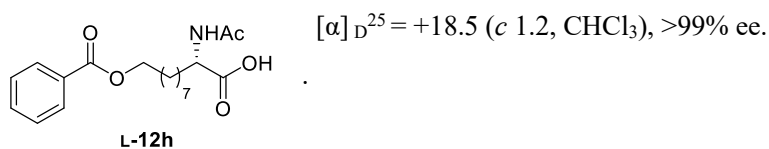
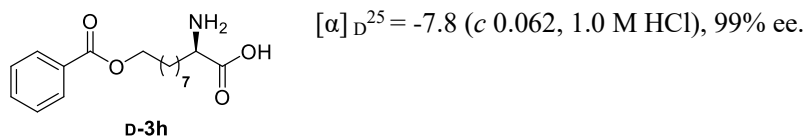




#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%
1	Unknown	6	45.020	37585530	287471	99.459
2	Unknown	6	54.487	204573	2662	0.541



Kinetic resolution of *N*-acetyl  $\alpha$ -amino acid (**(±)-12h**) (36.7 mg, 0.105 mmol) was carried out according to the typical procedure. D-Aminoacylase (2.41 mg) and aq.  $\text{CoCl}_2$  (0.01 M, 26.3  $\mu\text{L}$ , 263 nmol) were used.



#### HPLC Conditions

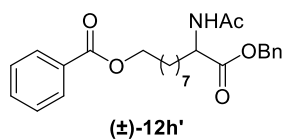
Column: Chiralcel IC, Daicel Chemical Industries, Ltd.

Eluent: hexane/isopropanol (80:20)

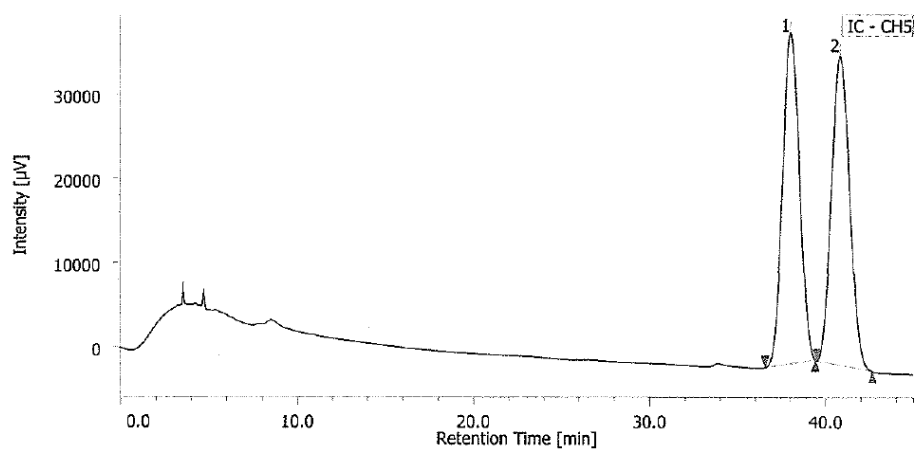
Flow rate: 1.0 mL/min

Detection: UV 230 nm

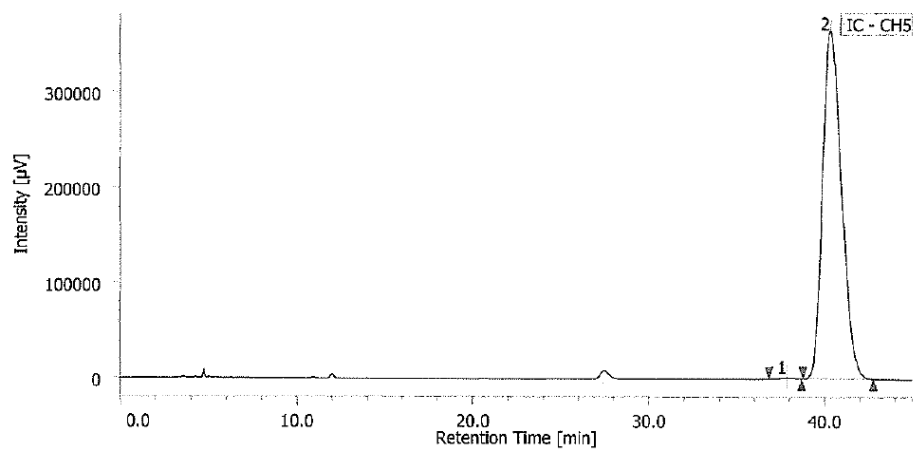
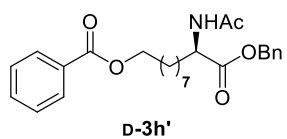
Retention time: 38.0 min, 40.8 min.



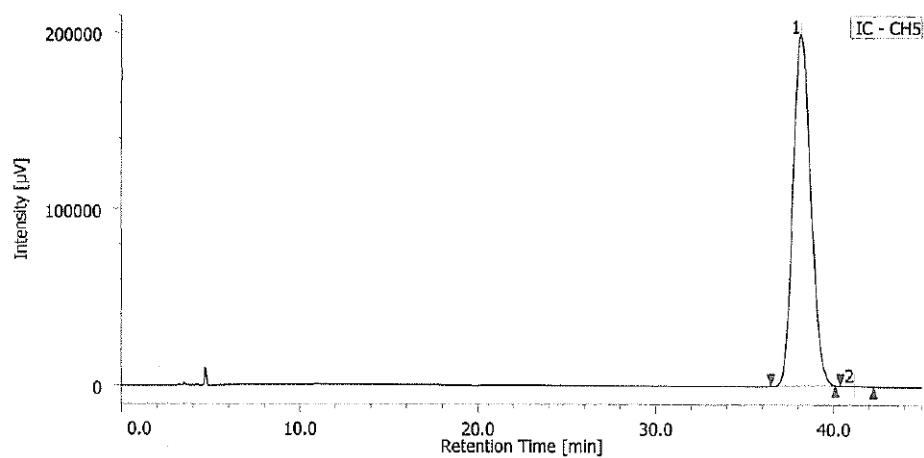
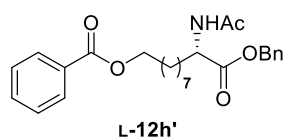
Racemate



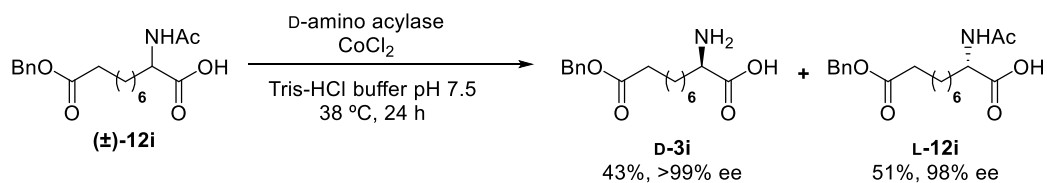
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	38.040	2605661	39409	49.886
2	Unknown	5	40.823	2617576	36800	50.114



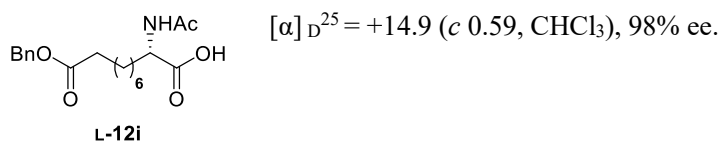
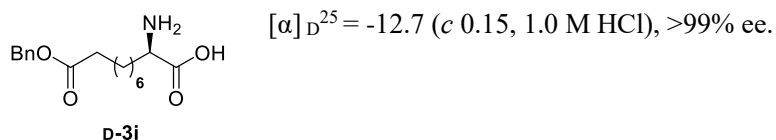
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	37.873	84958	1549	0.311
2	Unknown	5	40.342	27223601	365832	99.689



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%
1	Unknown	5	38.163	13821664	199530	99.877
2	Unknown	5	41.177	17058	342	0.123



Kinetic resolution of *N*-acetyl  $\alpha$ -amino acid  $(\pm)$ -**12i** (20.9 mg, 0.0598 mmol) was carried out according to the typical procedure. D-Aminoacylase (1.44 mg) and aq.  $\text{CoCl}_2$  (0.01 M, 22.4  $\mu\text{L}$ , 224 nmol) were used.



#### HPLC Conditions

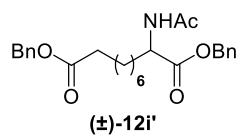
Column: Chiralcel IC, Daicel Chemical Industries, Ltd.

Eluent: hexane/isopropanol (80:20)

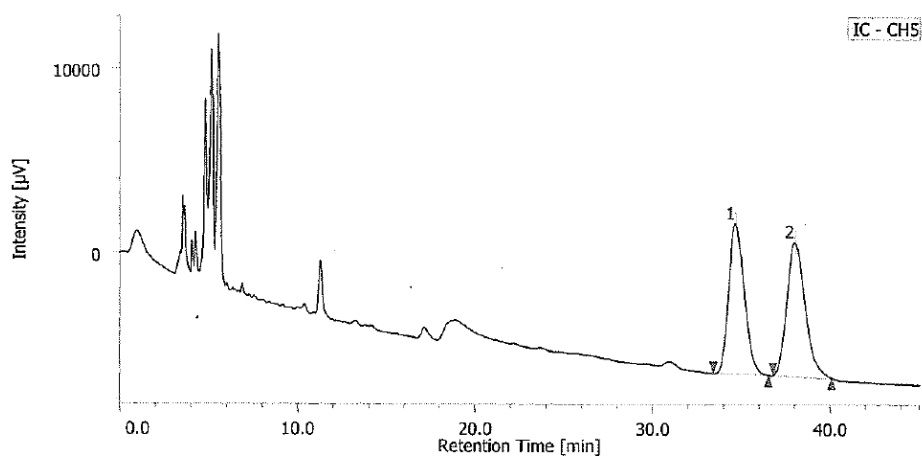
Flow rate: 1.0 mL/min

Detection: UV 230 nm

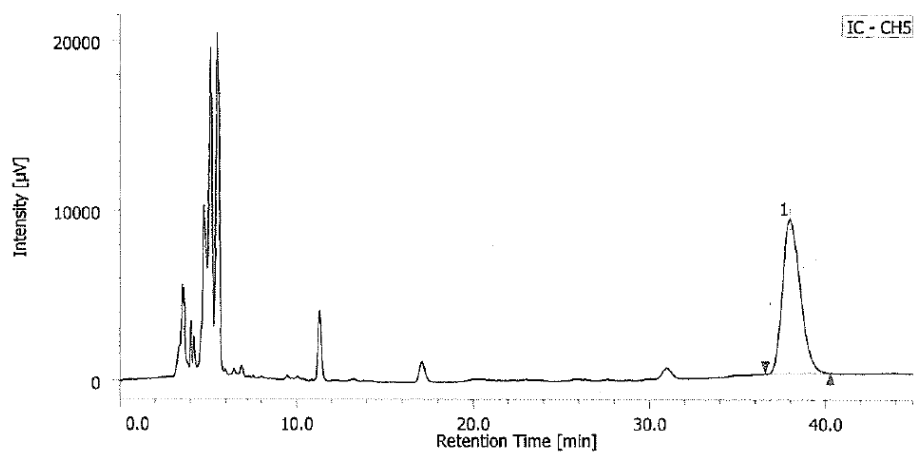
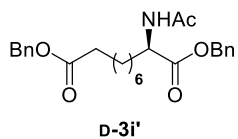
Retention time: 34.6 min, 38.0 min.



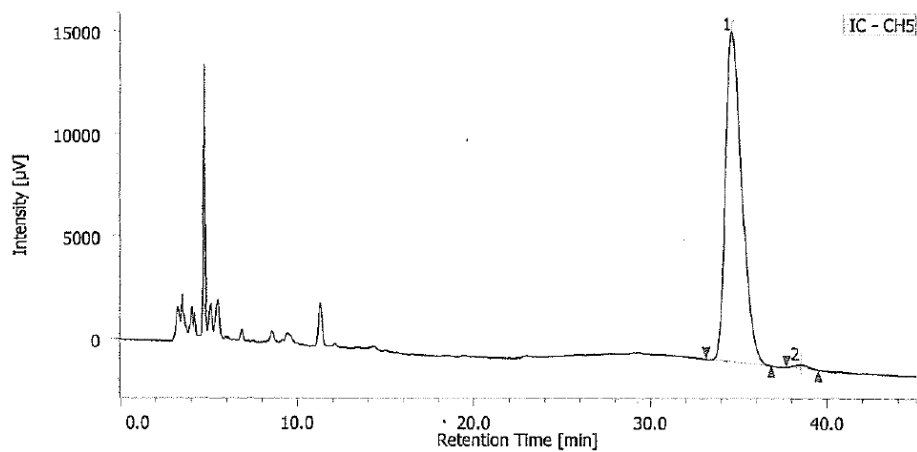
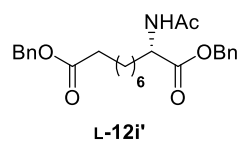
Racemate



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	34.643	499836	8173	48.237
2	Unknown	5	37.982	536363	7328	51.763



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	37.945	633665	9080	100.000



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%
1	Unknown	5	34.595	1047251	16133	98.990
2	Unknown	5	38.507	10683	215	1.010

## 9. Single crystal X-ray diffraction study

A single crystal of **9** was mounted on a glass fiber, and diffraction data were collected in  $\theta$  ranges specified in Table S2 at 93 K on a Bruker D8 QUEST diffractometer with graphite monochromatized Mo K $\alpha$  radiation ( $\lambda = 0.71073$  Å). The absorption correction was made using SADABS. The structure was solved by direct methods and refined by the full-matrix least-squares on  $F^2$  by using SHELXL-2013.<sup>8</sup> All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in calculated positions. Final refinement details are compiled in Table S2. The supplementary crystallographic data for this paper (CCDC 1872155) can also be obtained free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)).

**Table S3. Selected crystallographic data and collection parameters for **9****

formula	C <sub>23</sub> H <sub>24</sub> BrNO <sub>4</sub>
fw	458.34
crystal system	orthorhombic
space group	P 21 21 21
<i>a</i> , Å	6.1363(5)
<i>b</i> , Å	14.6139(10)
<i>c</i> , Å	21.9016(15)
volume, Å <sup>3</sup>	1964.0(2)
<i>Z</i>	4
<i>D</i> (calcd), Mg m <sup>-3</sup>	1.550
$\mu$ , mm <sup>-1</sup>	2.124
<i>F</i> (000)	944
crystal size, mm	0.1 x 0.1 x 0.25
$\theta$ range for data collection, deg	2.32 to 25.07
index ranges	-7 $\leq h \leq$ 7, -17 $\leq k \leq$ 17, -26 $\leq l \leq$ 25
reflections collected	12617
independent reflections [ <i>R</i> (int)]	3327 [ <i>R</i> (int) = 0.0283]
coverage of independent reflections	99.6%
max. and min. transmission	0.8160/0.6190
data / restraints / parameters	3327 / 0 / 264
goodness-of-fit on $F^2$	1.126
<i>R</i> <sub>1</sub> , <i>wR</i> <sub>2</sub> [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )]	0.0227, 0.0625
<i>R</i> <sub>1</sub> , <i>wR</i> <sub>2</sub> (all data)	0.0231, 0.0627
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0173P)^2 + 1.3957P]$ Where $P = (F_o^2 + 2F_c^2)/3$
largest diff. peak and hole, e Å <sup>-3</sup>	0.570 and -0.433



## 10. References

- <sup>1</sup> K. Furukawa, H. Inada, M. Shibuya, Y. Yamamoto *Org. Lett.* **2016**, *18*, 4230.
- <sup>2</sup> a) A. Bonet, C. Pubill-Ulldemolins, C. Bo, H. Gulyás, E. Fernández *Angew. Chem. Int. Ed.* **2011**, *50*, 7158. b) T. P. Blaisdell, T. C. Caya, L. Zhang, A. Sanz-Marco, J. P. Morken *J. Am. Chem. Soc.* **2014**, *136*, 9264.
- <sup>3</sup> K. Furukawa, M. Shibuya, Y. Yamamoto *Org. Lett.* **2015**, *17*, 2282.
- <sup>4</sup> K. Ando *J. Org. Chem.* **1997**, *62*, 1934.
- <sup>5</sup> T. Zhang, W. Song, J. Zhao, J. Liu *Ind. Eng. Chem. Res.* **2017**, *56*, 11697.
- <sup>6</sup> C. W. Bradshaw, C.-H Wong, W. Hummel, M.-R. Kula *Bioorg. Chem.* **1991**, *19*, 29.
- <sup>7</sup> I. R. Babu, E. K. Hamill, K. Kumar *J. Org. Chem.* **2004**, *69*, 5468.
- <sup>8</sup> Sheldrick, G. M. SHELXL-2013, Bruker AXS Inc., Madison, Wisconsin, 2013.

## 11. NMR spectra

