Electronic supplementary information (ESI)

General comments: *p*-Tolualdehyde, benzhydrylamine, DBU and methanol were used after the distillation of commercial sources. Hydrogen cyanide was prepared from H_2SO_4 and KCN in water and isolated by the distillations. Melting points were recorded on an AS one ATM-01 apparatus and are uncorrected. Diffraction data were obtained on a Rigaku, R-Axis Rapid-F imaging plate diffractometer using a graphite monochromated Mo-Kα radiation and data was processed using RAPID-AUTO. 1H spectra were recorded using a JEOL JNM-ECX500II FT NMR system. The chemical sifts δ are given in parts per million (ppm) and the coupling constants J in hertz (Hz). Optical rotations were measured using a JASCO P-2100 digital polarimeters using 5.0 cm cells.

Materials and Methods: To a 1 M 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) solution of methanol were added *p*-tolualdehyde (80 μL, 0.68 mmol), benzhydrylamine (117 μL, 0.68 mmol) and excess amount of hydrogen cyanide at room temperature. After *ca*. 0.5–72 h (the appearance of crystalline product) and additional 6–8 h, the powder-like crystal was filtered off, dissolved in ether, and then filtered through silica gel. The solvent was removed under reduced pressure to give amino nitrile **1** originated from the product in solid phase.

The initial filtrate was purified by passing through silica gel with the mixed solvent of *n*-hexane / ether (3/1, *v*/*v*). The solvents were evaporated in *vacuo* to give amino nitrile **1** originated from the product in solution phase.

To a reaction suspension of **1** was added dichloromethane (*ca*. 2.5 mL) to dissolve the crystalline product and filtered through silica gel with the mixed solvent of *n*-hexane / ether (3/1, *v*/*v*). The solvent was removed under reduced pressure to give amino nitrile **1** originated from the products in both solid and solution phases.

Hydrolysis was performed based on the reported procedure.[S1] The solid product 1 was dissolved in the mixed solvent of concentrated HCl and trifluoroacetic acid (1:1, *v*/*v*). The reaction solution was heated at 80 °C for a period of 18 h in sealed vial. The reaction mixture was diluted with water and was washed with ether (3 times). The aqueous phase

was concentrated in *vacuo* and the residue was purified by passage through a column of Dowex 50W-X8 ion exchange resin to afford α-(*p*-tolyl)glycine (**2**) as white solid. (*R*)-amino nitrile **1** with 18.1% ee was hydrolyzed to afford (*R*)-amino acid **2** with 17.9% ee in 79% isolated yield.

Amplification of enantiomeric enrichment of solid state **1**: To a 1 M DBU solution of methanol (2.0 mL) were added *rac*-**1** (80 mg) and excess amount of HCN at room temperature. After the saturation of the solution by **1**, powder-like crystal of (*R*)-amino nitrile **1** (140 mg, 7.0% ee) was added and vigorously stirred in the presence of glass beads (2.0 g). After 98 h, powder-like crystal was filtered off then the typical purification afforded (*R*)-**1** (100 mg, 93% ee).

***N*-Benzhydryl-α-*p*-tolylglycine nitrile (1)**[15]: Colorless crystal. ^{1}H-NMR (500 MHz, methanol-d_4, C*H*D$_2$OD = 3.30 ppm) δ = 7.52–7.19 (m, 14H), 5.09 (s, 1H), 4.53 (s, 1H), 2.35 (s, 3H). HPLC analysis: Daicel Chiralpak IA-3 (4.6 × 250 mm), *n*-hexane/2-propanol = 80/20 (*v*/*v*), 1.5 mL/min, room temperature, 220 nm, *t* = 6.3 min (*R*-isomer), *t* = 10.3 min (*S*-isomer). M.p. 131–132 °C (homochiral crystal), 107–121 °C (*ca*. 50% ee), 107–110 °C (near racemic conglomerate). $[\alpha]_D^{25}$ +44.9 (*c* = 1.01, $CHCl_3$, *R*-isomer with 94% ee from HPLC analysis), $[\alpha]_D^{25}$ –47.3 (*c* = 0.99, $CHCl_3$, *S*-isomer with 98% ee from HPLC analysis) [literature values: $[\alpha]_D^{22}$ –41.8 (*c* = 1.05, $CHCl_3$, *S*-isomer),[S1] $[\alpha]_D^{22}$ +41.0 (*c* = 1.13, $CHCl_3$, *R*-isomer)[S2]].

α-(*p*-Tolyl)glycine (2): White solid. $[\alpha]_D^{23}$ –152.8 ° (*c* = 0.20, 1 M HCl, *R*-isomer with 96% ee) [literature value[S3]: $[\alpha]_D^{23}$ +149 (*c* = 0.50, 1 M HCl, *S*-isomer with > 99% ee)]. ^{1}H-NMR (500 MHz, methanol-d_4, C*H*D$_2$OD = 3.30 ppm) δ = 7.35 (d, *J* = 8.0, 2H), 7.22 (d, *J* = 8.0, 2H), 4.52 (s, 1H), 2.33 (s, 3H). HPLC analysis: Daicel Chiralpak CR-I(+) (4 × 150 mm), aqueous $HClO_4$ (pH 1.5)/CH_3CN = 70/30 (*v*/*v*), 0.5 mL/min, room temperature, 220 nm, *t* = *ca*. 2.4 min (*R*-isomer), *t* = *ca*. 10 min (*S*-isomer).

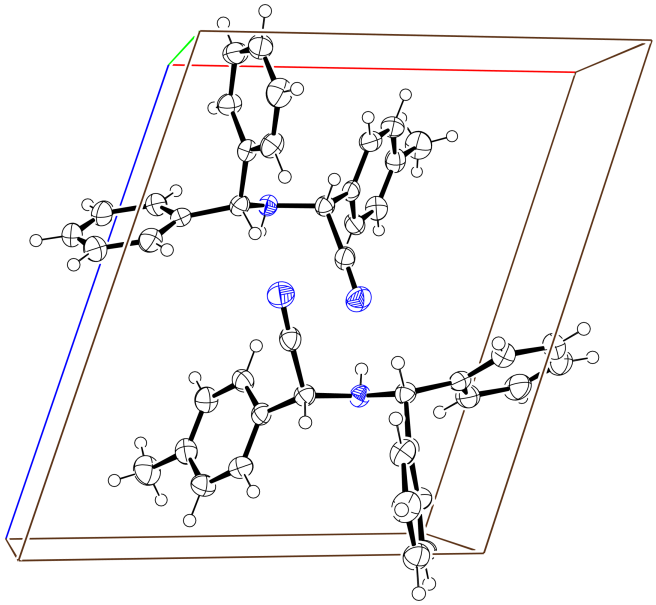
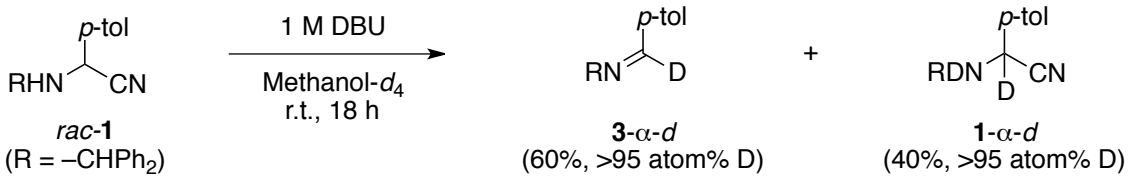


Figure S1. X-ray single crystal structure of (*R*)-1. Monoclinic space group $P2_1$, a = 10.8234(4) Å, b = 6.6783(3) Å, c = 12.8182(4) Å, β = 108.8990(10), V = 876.576 Å^3, Z = 2, ρ = 1.184 g/cm^3, μ(Mo$_{K\alpha}$) = 0.71 cm^{-1}, R = 0.0372, wR2 = 0.1155 for 3857 reflections. The single crystal was obtained from the reaction mixture under unstirred condition was submitted to X-ray structural analysis. The absolute configuration was determined to be *R* from chiral HPLC analysis of the same source of single crystal. The conglomerate of **1** with almost same crystal structure was obtained from saturated solution of *rac*-**1** in CH_3CN.



Scheme S1. Reverse reaction and deuterium substitution of amino nitrile 1 in a 1 M DBU solution of methanol-d_4. Racemate **1** (12.3 mg) was completely dissolved in 1 M DBU in methanol-d_4 (1.15 mL) at room temperature. After 18 h, DBU was removed by the filtration through silica gel. After the removal of the solvents in *vacuo*, the crude products were submitted to ^{1}H-NMR experiment. As a result, formations of **3**-α-*d* in the ratio of 60%

and **1**-α-*d* in 40% have been observed from the integration of methine protons at the benzhydryl groups. No other product could be detected. The α-protons of both compounds **3** and **1** were substituted by the deuterium in >95 atom%. Non-labelled imine **3** was prepared by the reported method[S5] to compare the ^{1}H-NMR spectrum with **3**-α-*d*. ***N*-(4-Methylbenzylidene)benzhydrylamine (3)**: Colorless crystal. ^{1}H-NMR (500 MHz, methanol-d_4, C*H*D$_2$OD = 3.30 ppm) δ = 8.44 (s, 1H), 7.71 (d, *J* = 8.0, 2H), 7.34–7.28 (m, 8H), 7.25–7.21 (m, 4H), 5.64 (s, 1H), 2.36 (s, 3H).

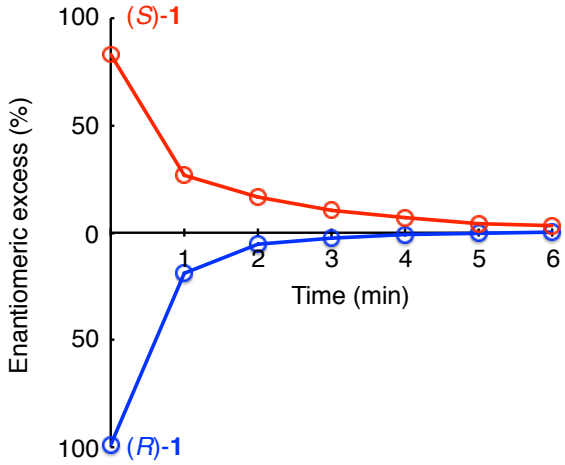


Figure S2. Racemization of amino nitrile 1 in a 1 M DBU solution of methanol against time. The powdered single crystals of (*S*)-**1** (11.4 mg, 0.036 mmol) and (*R*)-**1** (7.8 mg, 0.025 mmol) were dissolved in 1 M DBU solution of methanol (2.0 mL) at room temperature, respectively. The initial ee was determined by the analysis of the ethereal solution of a part of powdered single crystal **1**. The time (t = 0) started after the complete dissolution of powdered crystal in the solvent. The enantiomeric excess of **1** was monitored by using HPLC on a chiral stationary phase. Without DBU, the racemization half-life ($t_{1/2}$) has been observed *ca*. 11 h in methanol and in other solvents, no racemization has been observed under present time scale.[S4]

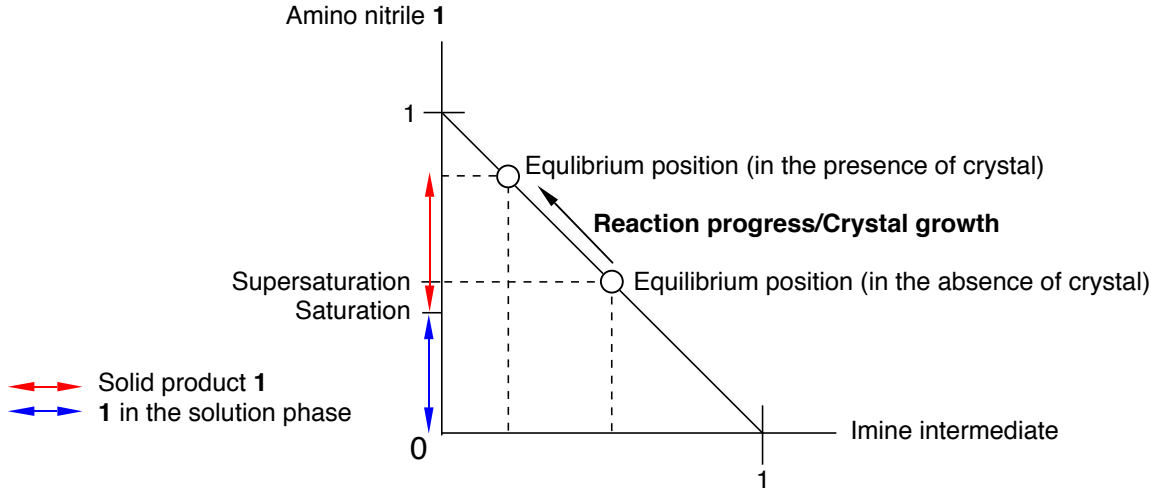


Figure S3. Proposed equilibrium shift before and after the crystal formation and the following reaction progress and crystal growth. Horizontal axis: relative ratio of imine intermediate. Vertical axis: relative ratio of amino nitrile **1**.

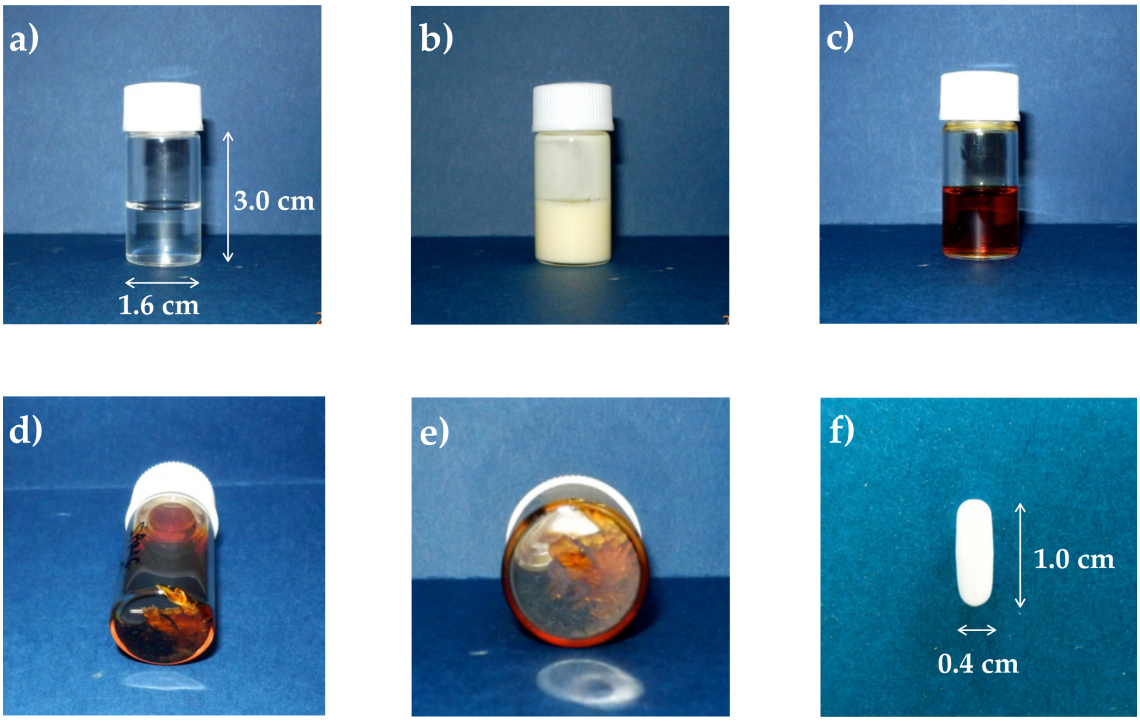


Figure S4. Photos of reaction mixtures in vials. (a) Initial reaction solution of HCN, *p*-tolualdehyde and benzhydrylamine in 1 M DBU solution of methanol. (b) Powder-like

crystal of **1** spontaneously formed under stirred condition. (c) Reaction solution without crystallization among 1 week. (d, e) Water clear crystals of **1** obtained from unstirred condition which were taken from different angles. (f) Stir-bar used in the reaction under stirred condition.

References

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S2. S. Wuennemann, R. Froehlich and D. Hoppe, *Eur. J. Org. Chem.,* 2008, 684.

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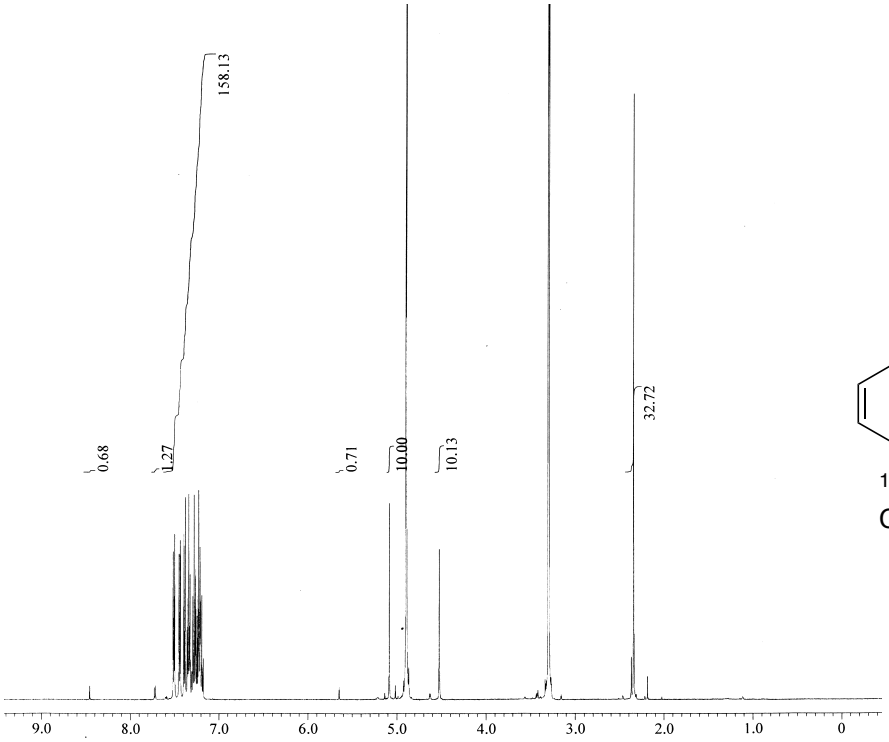
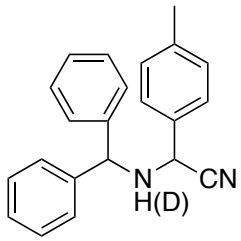
S4. B. Vorawit, M. Woraluk, B. Worawan and V. Tirayut, *Tetrahedron,* 2009, **65**, 5849.

S5. Y. Zhang, A. Desai, Z. Lu, G. Hu, Z. Ding and W. D. Wulff, *Chem. Eur. J.,* 2008, **14**, 3785.

^{1}H-NMR





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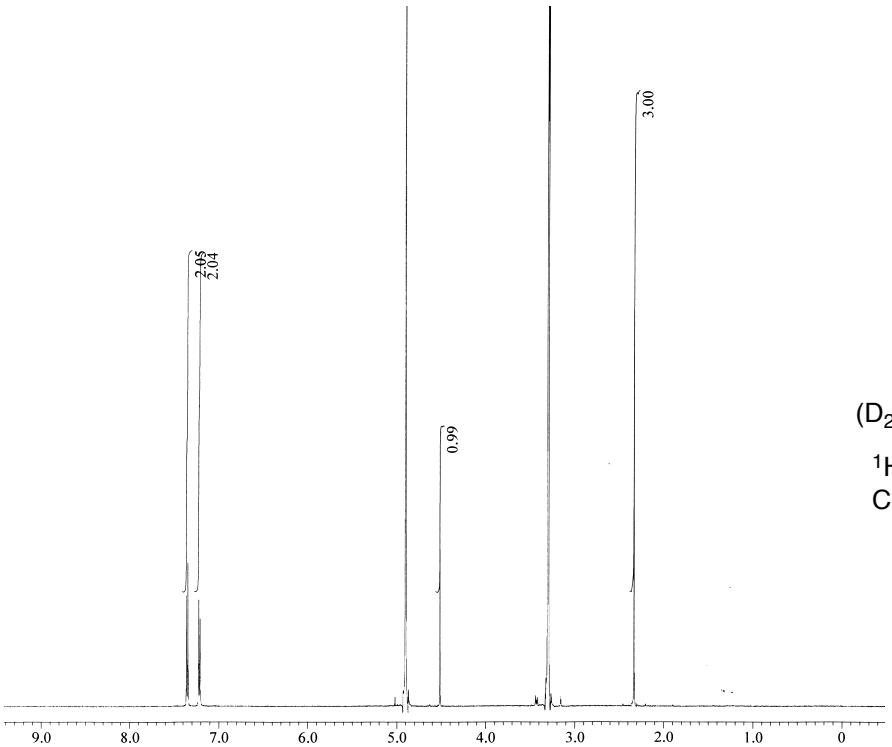
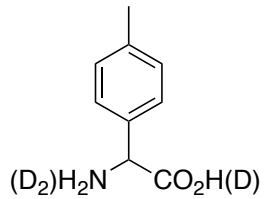
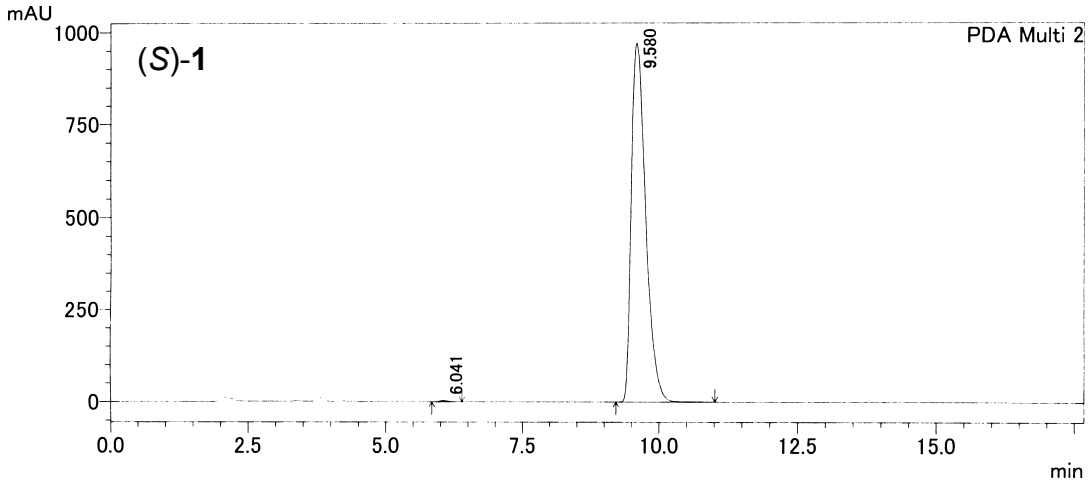
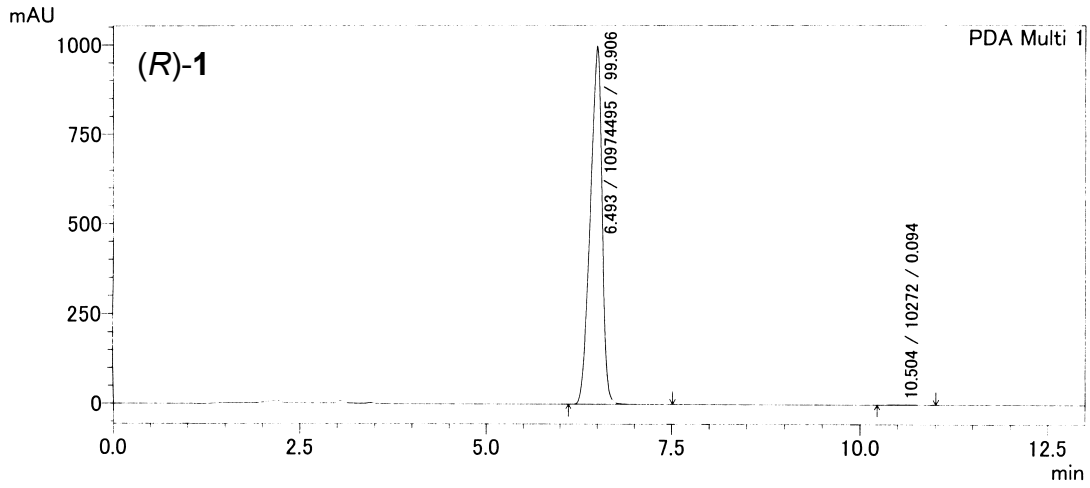


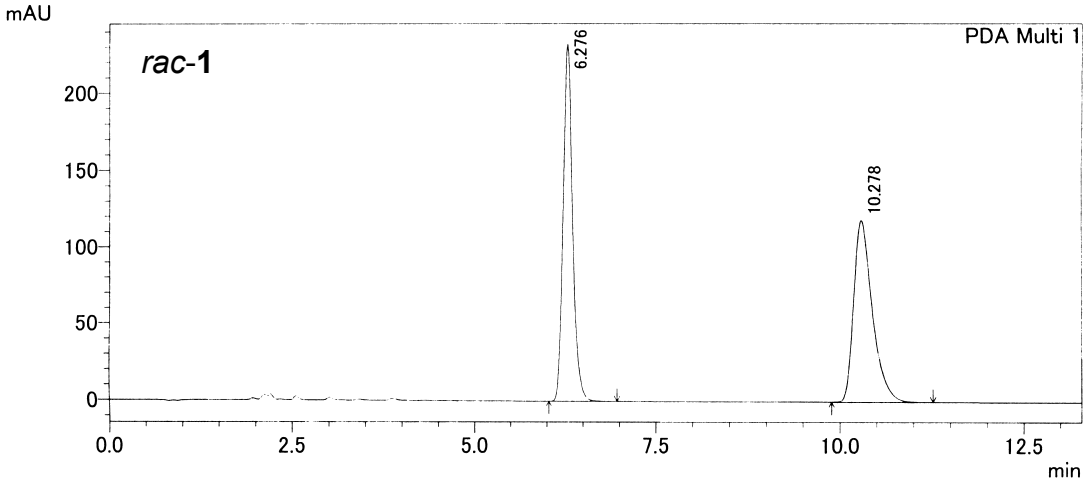


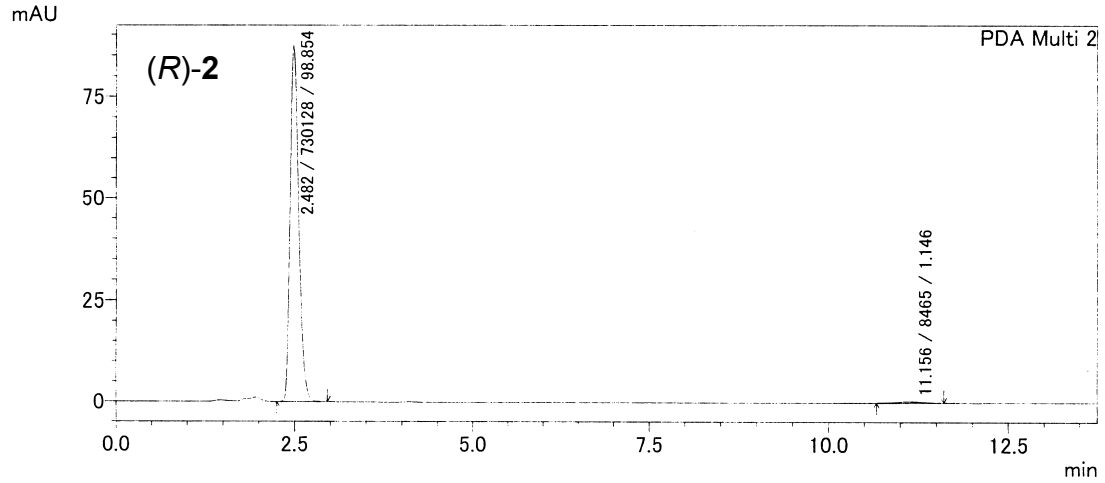
^{1}H-NMR, 500 MHz,
CD_3OD (3.3 ppm)

HPLC analyses





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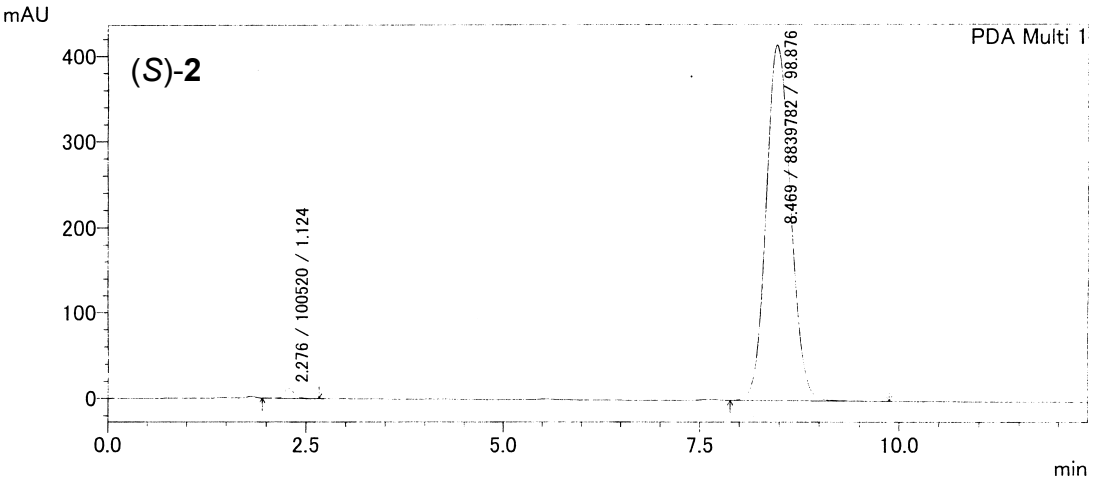
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