

Supplementary Information

**Enantioselectivity switch in copper-catalyzed conjugate addition
reaction under influence of a chiral N-heterocyclic carbene-silver
complex**

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1. General Method

Et₂Zn and Me₂Zn were purchased from Aldrich and used without further purification. Dry THF was purchased from Wako Pure Chemical Industries, Ltd. and used without further purification. All other chemical reagents and solvents were obtained from commercial sources and used without further purification. All non-commercially available compounds were prepared and characterized as described in Sections 2 and 3 of this ESI. Column chromatographies were performed with silica gel 60 (63-210 μm) purchased from Kanto Chemical Co., Inc. ¹H NMR spectra were recorded on JEOL ECA400 (400 MHz for ¹H NMR and 100 MHz for ¹³C NMR) spectrometer. Chemical shifts were reported downfield from TMS (δ= 0 ppm) for ¹H NMR. For ¹³C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. Elemental analyses were performed at Osaka University. Enantiomeric excesses were measured using gas chromatography (capillary column - Supelco β- or γ-Dex225, 30 m x 0.25 mm id, 0.25 μm).

General procedure for method A: The reaction was performed under argon atmosphere. A flask, under argon atmosphere, was charged with (CuOTf)₂•C₆H₆ (15 mg, 0.03 mmol, 6 mol %) and NHC-Ag complex **2b** (23 mg, 0.04 mmol, 4 mol %). Then, a solution of enone **3** (96 mg, 1 mmol) in anhydrous THF (9 mL) was added. The resulting mixture was stirred at room temperature for 1 h. After the mixture was cooled to -20 °C, a solution of Et₂Zn (**4**) (3 mmol, 1 M in hexanes, 3 mL) was added dropwise over a period of 10 min. The reaction mixture was stirred at -20 °C for 3 h. The reaction was quenched by adding 10% aq. HCl. The resulting mixture was extracted with diisopropyl ether and dried over Na₂SO₄. The product was purified by silica gel column chromatography using a mixture of hexane/EtOAc). The enantiomeric excess was measured using a chiral GLC.

General procedure for method B: The reaction was performed under open-air conditions. $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (10 mg, 0.02 mmol, 4 mol %) and NHC-Ag complex **2b** (59 mg, 0.10 mmol, 10 mol %) were added to anhydrous THF (5.5 mL). After stirring at room temperature for 1 h, the mixture was cooled to 0 °C. Then, Et_2Zn (**4**) (3 mmol, 1 M in hexanes, 3 mL) was added to the reaction vessel. After the resulting mixture was stirred at room temperature for 30 min, a solution of enone **3** (96 mg, 1 mmol) in anhydrous THF (1.5 mL) was added dropwise over a period of 10 min. The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by adding 10% aq. HCl.

2. Ligand Synthesis

Azolium salts **1a**, **1b**, and *ent*-**1b** was synthesized from the corresponding azole and benzyl iodide according to our previously reported procedure.¹

The NHC-Ag complex was prepared by the Ag_2O method. The reaction mixture of azolium salt (1.0 mmol) and Ag_2O (0.5 mmol) in CH_2Cl_2 (12 mL) was stirred for 1 day under open-air conditions. After the reaction, a white precipitate was filtered with suction and washed with CH_2Cl_2 to form the desired silver complex.

3. Characterization of Target Compounds

1a¹: ¹H-NMR (CDCl₃, 400 MHz): δ 10.45 (s, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.59 (m, 5H), 7.41-7.31 (m, 4H), 5.77 (s, 2H), 4.96-4.85 (m, 2H), 3.94-3.93 (br, 1H), 3.46-3.37 (m, 4H), 3.16-3.09 (m, 1H), 1.42-1.30 (m, 2H), 1.22-1.10 (m, 1H), 0.75 (dd, J₁ = 19.0 Hz, J₂ = 6.2 Hz, 6H). ¹³C-NMR (CDCl₃, 100 MHz): δ 169.2, 142.0, 132.3, 131.8, 130.9, 129.4, 129.3, 128.3, 127.3, 127.2, 113.7, 113.4, 64.6, 51.9, 50.4, 44.1, 39.7, 35.5, 24.7, 22.8, 22.1.

1b¹: ¹H-NMR (CDCl₃, 400 MHz): δ 10.51 (s, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.62-7.57 (m, 1H), 7.52-7.48 (m, 4H), 7.44 (d, J = 8.2 Hz, 1H), 7.40-7.33 (m, 3H), 5.77 (dd, J₁ = 21.5 Hz, J₂ = 15.1 Hz, 2H), 4.99-4.93 (m, 1H), 4.88-4.81 (m, 1H), 3.77-3.69 (m, 1H), 3.51-3.44 (m, 3H), 3.31 (br, 1H), 3.16-3.09 (m, 1H), 1.47-1.34 (m, 2H), 0.75 (t, J = 7.3 Hz, 3H). ¹³C-NMR (CDCl₃, 100 MHz): δ 169.3, 141.8, 132.2, 131.8, 130.9, 129.3, 129.3, 128.3, 127.3, 127.2, 113.7, 113.3, 63.6, 53.8, 51.8, 44.1, 35.4, 23.7, 10.4.

ent-**1b**: ¹H-NMR (CDCl₃, 400 MHz): δ 10.52 (s, 1H), 7.89 (d, J = 8.7 Hz, 1H), 7.64-7.57 (m, 1H), 7.54-7.48 (m, 4H), 7.43 (d, J = 8.7 Hz, 1H), 7.40-7.33 (m, 3H), 5.77 (dd, J₁ = 21.5 Hz, J₂ = 15.1 Hz, 2H), 5.00-4.93 (m, 1H), 4.88-4.82 (m, 1H), 3.77-3.69 (m, 1H), 3.52-3.42 (m, 3H), 3.29 (br, 1H), 3.16-3.10 (m, 1H), 1.47-1.36 (m, 2H), 0.75 (t, J = 7.5 Hz, 3H). ¹³C-NMR (CDCl₃, 100 MHz): δ 169.4, 141.9, 132.3, 131.8, 130.9, 129.4, 129.3, 128.3, 127.3, 127.2, 113.7, 113.4, 63.7, 53.8, 51.9, 44.1, 35.5, 23.8, 10.5.

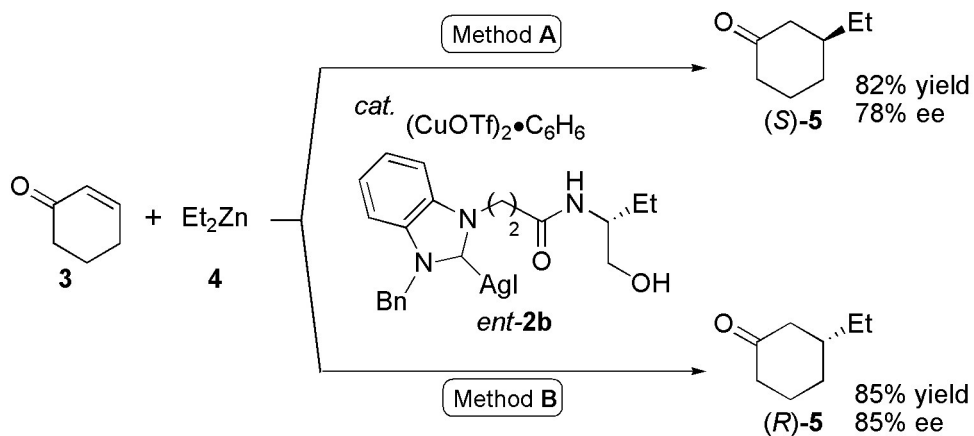
2a: ¹H-NMR (DMSO, 400 MHz): δ 7.81 (d, J = 8.2 Hz, 1H), 7.64 (t, J = 8.5 Hz, 2H), 7.44-7.35 (m, 4H), 7.29-7.26 (m, 3H), 5.79 (dd, J₁ = 19.0 Hz, J₂ = 16.3 Hz, 2H), 4.89-4.77 (m, 2H), 4.55 (br, 1H), 3.67 (br, 1H), 3.16 (br, 1H), 3.06 (br, 1H), 2.85-2.78 (m, 1H), 2.74-2.69 (m, 1H), 1.13-1.06 (m, 2H), 1.01 (t, J = 8.9 Hz, 1H), 0.61 (dd, J₁ = 9.4 Hz, J₂ = 5.7 Hz, 6H). ¹³C-NMR (DMSO, 100 MHz): δ 190.9, 168.9, 136.3, 133.4, 133.1, 128.6,

127.8, 127.3, 123.9, 112.4, 112.2, 63.6, 51.7, 48.7, 45.1, 36.4, 23.9, 23.2, 21.7. Anal. Calc. for $C_{23}H_{29}AgIN_3O_2 \cdot 0.5 H_2O$: C, 44.11; H, 4.67; N, 6.68. Found: C, 44.32; H, 4.85; N, 6.74%.

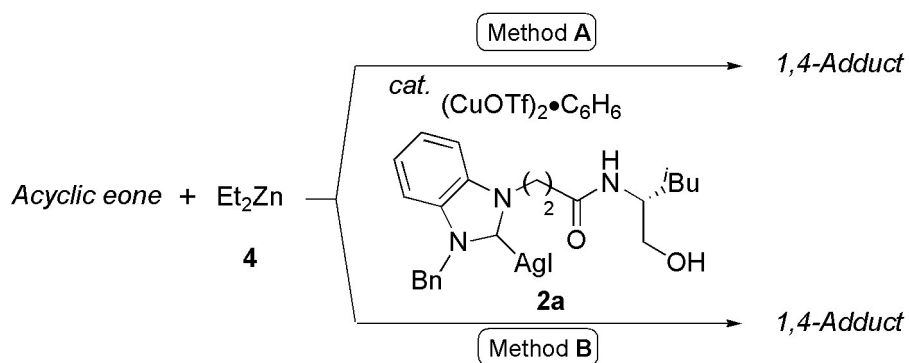
2b: 1H -NMR (DMSO, 400 MHz): δ 7.82 (d, $J = 8.2$ Hz, 1H), 7.66 (d, $J = 7.7$ Hz, 2H), 7.45-7.36 (m, 4H), 7.30-7.26 (m, 3H), 5.81 (s, 2H), 4.91-4.75 (m, 2H), 4.54 (br, 1H), 3.56-3.46 (m, 1H), 3.22-3.20 (br, 1H), 3.11-3.10 (br, 1H), 2.85-2.69 (m, 2H), 1.42-1.32 (m, 1H), 1.14-1.05 (m, 1H), 0.50 (t, $J = 7.5$ Hz, 3H). ^{13}C -NMR (DMSO, 100 MHz): δ 190.8, 169.1, 136.3, 133.3, 133.1, 128.6, 127.8, 127.3, 123.9, 123.9, 112.3, 112.2, 62.6, 52.1, 51.7, 45.1, 36.3, 23.3, 10.0. Anal. Calc. for $C_{21}H_{24}AgIN_3O_2 \cdot 0.5 H_2O$: C, 42.37; H, 4.40; N, 7.06. Found: C, 42.59; H, 4.51; N, 7.11%.

ent-**2b**: 1H -NMR (DMSO, 400 MHz): δ 7.82 (d, $J = 7.7$ Hz, 1H), 7.66 (d, $J = 7.7$ Hz, 2H), 7.46-7.36 (m, 4H), 7.30-7.26 (m, 3H), 5.81 (s, 2H), 4.91-4.74 (m, 2H), 4.54 (br, 1H), 3.53-3.46 (m, 1H), 3.25-3.16 (br, 1H), 3.10 (br, 1H), 2.85-2.69 (m, 2H), 1.42-1.32 (m, 1H), 1.14-1.03 (m, 1H), 0.50 (t, $J = 7.3$ Hz, 3H). ^{13}C -NMR (DMSO, 100 MHz): δ 169.1, 136.3, 133.3, 133.1, 128.6, 127.8, 127.3, 123.9, 123.9, 112.3, 112.2, 62.6, 52.1, 51.7, 45.1, 36.3, 23.3, 10.0, the carbene ^{13}C NMR resonance was not observed.

4. Scheme S1. Switching of enantioselectivity on the ACA reaction using *ent-2b*



5. Scheme S2. ACA reaction of several acyclic enones using 2a



| Acyclic enone | with Method A | with Method B |
|---------------|---------------|---------------|
| | | |
| | | |
| | | |

6. Data for Figure 1

with method A

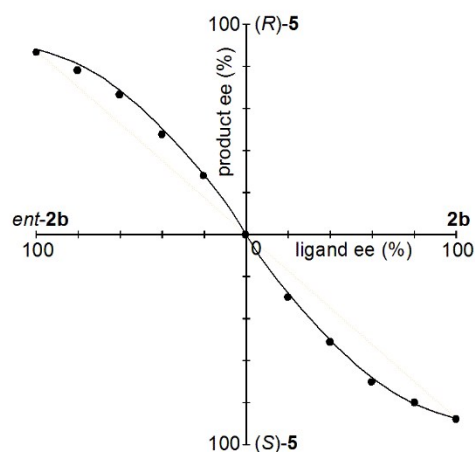
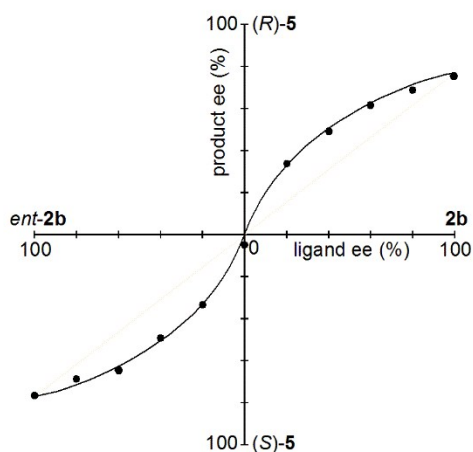
| entry | 2b : ent-2b | major product | yield (%) | ee (%) |
|-------|-------------|---------------|-----------|--------|
| 1 | 10 : 0 | (R)-5 | 84 | 74 |
| 2 | 9 : 1 | (R)-5 | 85 | 68 |
| 3 | 8 : 2 | (R)-5 | 82 | 62 |
| 4 | 7 : 3 | (R)-5 | 85 | 50 |
| 5 | 6 : 4 | (R)-5 | 86 | 34 |
| 6 | 5 : 5 | (±)-5 | 85 | 4 |
| 7 | 4 : 6 | (S)-5 | 84 | 34 |
| 8 | 3 : 7 | (S)-5 | 81 | 50 |
| 9 | 2 : 8 | (S)-5 | 80 | 64 |
| 10 | 1 : 9 | (S)-5 | 83 | 68 |
| 11 | 0 : 10 | (S)-5 | 82 | 78 |

Reaction conditions: see Table 1, entry 11.

with method B

| entry | 2b : ent-2b | major product | yield (%) | ee (%) |
|-------|-------------|---------------|-----------|--------|
| 1 | 10 : 0 | (S)-5 | 84 | 87 |
| 2 | 9 : 1 | (S)-5 | 79 | 80 |
| 3 | 8 : 2 | (S)-5 | 71 | 70 |
| 4 | 7 : 3 | (S)-5 | 73 | 52 |
| 5 | 6 : 4 | (S)-5 | 75 | 30 |
| 6 | 5 : 5 | (±)-5 | 71 | 0 |
| 7 | 4 : 6 | (R)-5 | 65 | 28 |
| 8 | 3 : 7 | (R)-5 | 70 | 48 |
| 9 | 2 : 8 | (R)-5 | 71 | 66 |
| 10 | 1 : 9 | (R)-5 | 83 | 78 |
| 11 | 0 : 10 | (R)-5 | 85 | 86 |

Reaction conditions: see Table 1, entry 15.



7. References

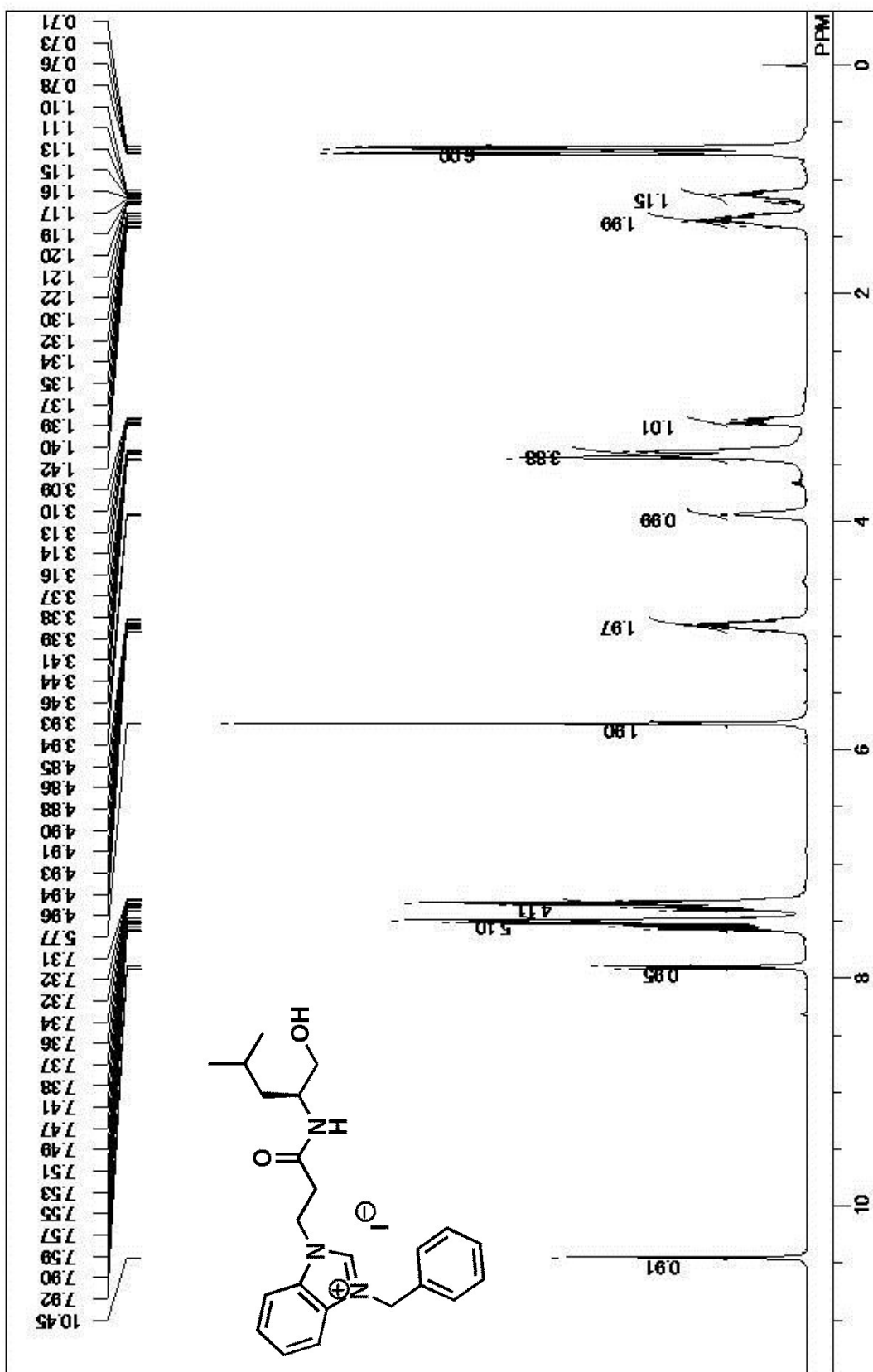
- 1 N. Shibata, M. Yoshimura, H. Yamada, R. Arakawa and S. Sakaguchi, *J. Org. Chem.*, 2012, **77**, 4079.
- 2 Y. Matsumoto, K.-i. Yamada and K. Tomioka, *J. Org. Chem.*, 2008, **73**, 4578.
- 3 K. Kawamura, H. Fukuzaw and M. Hayashi, *Org. Lett.*, 2008, **10**, 3509.

8.

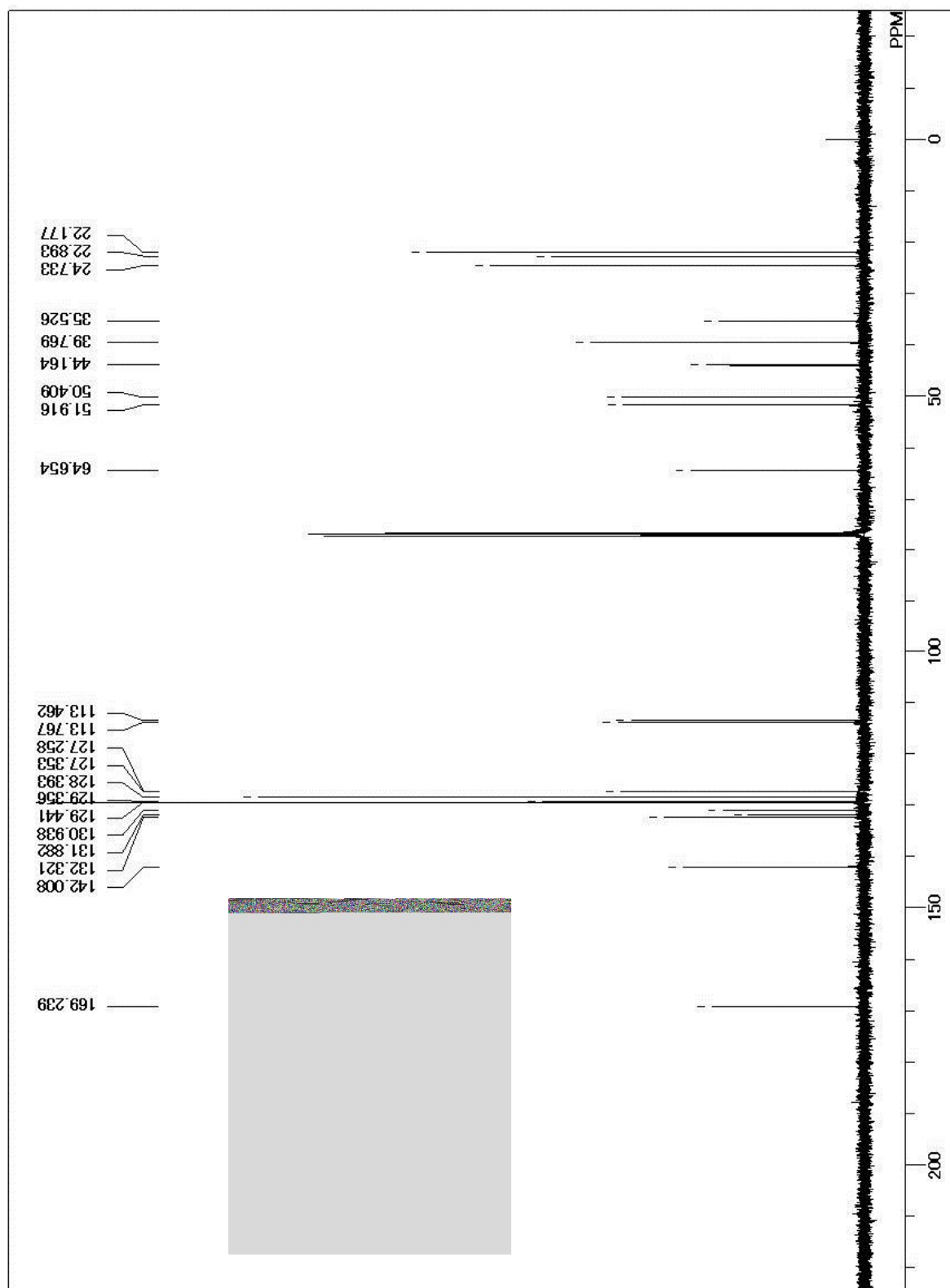
NMR

Charts

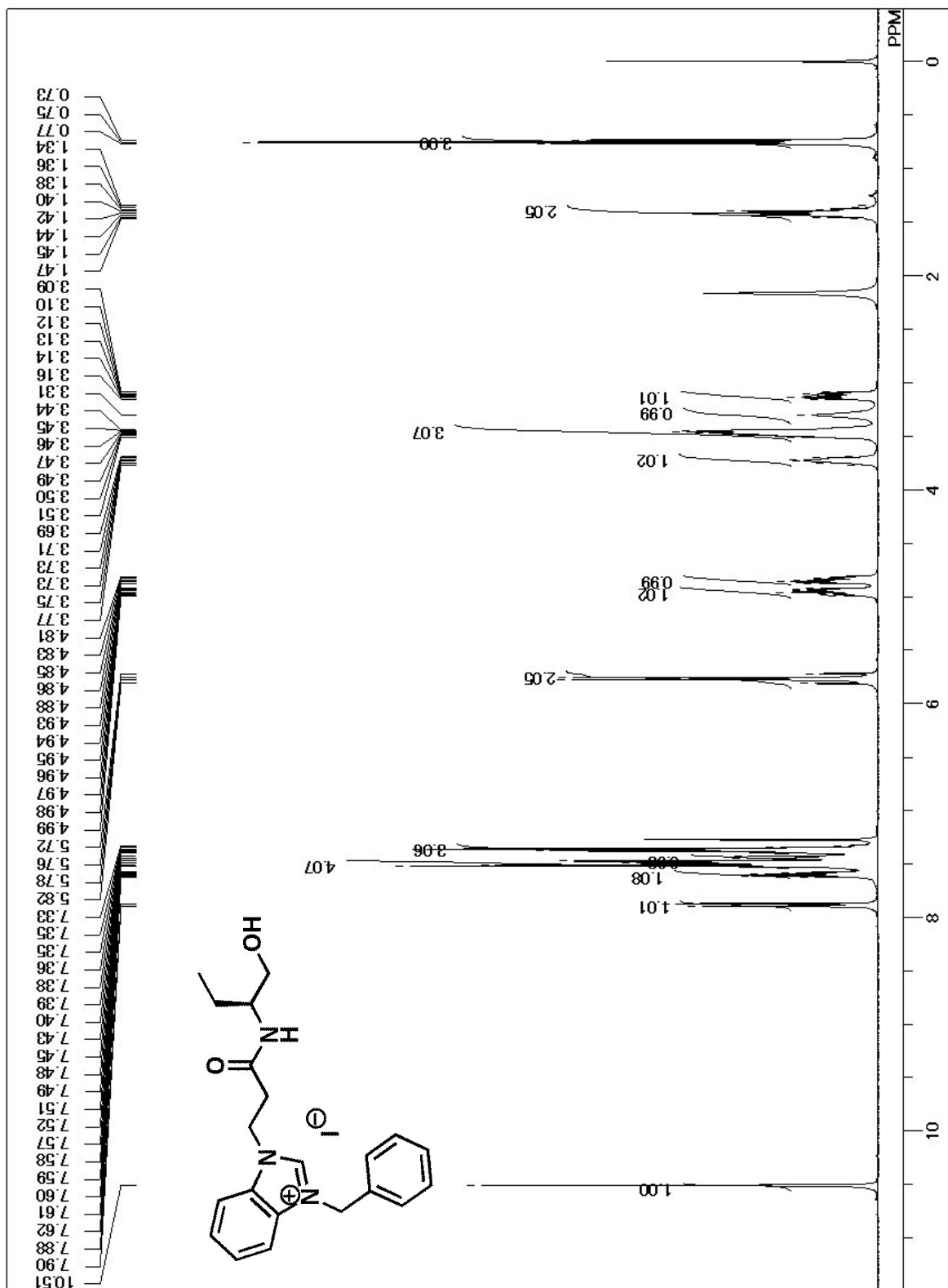
¹H-NMR Spectra for 1a



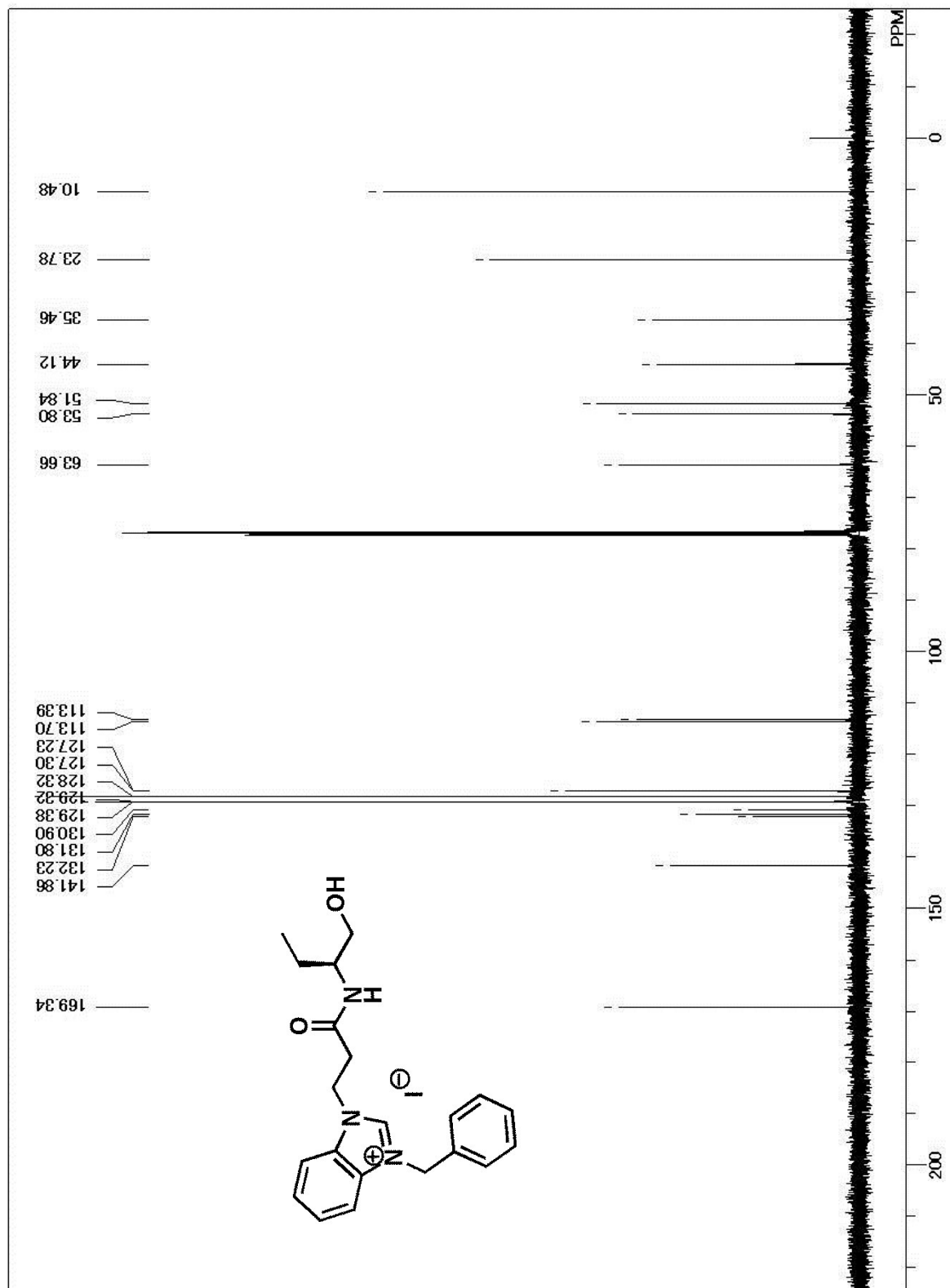
¹³C-NMR Spectra for **1a**



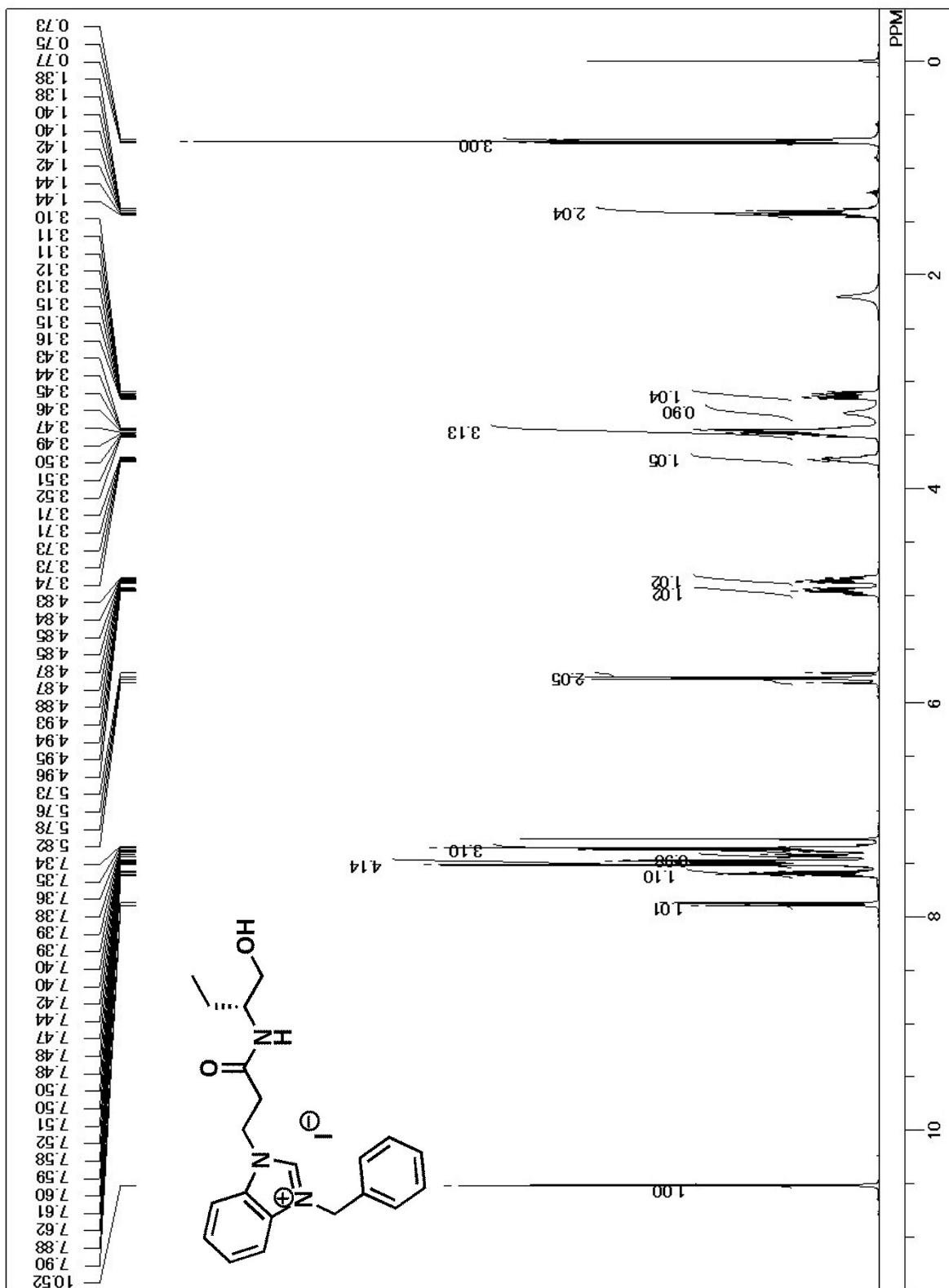
¹H-NMR Spectra for **1b**



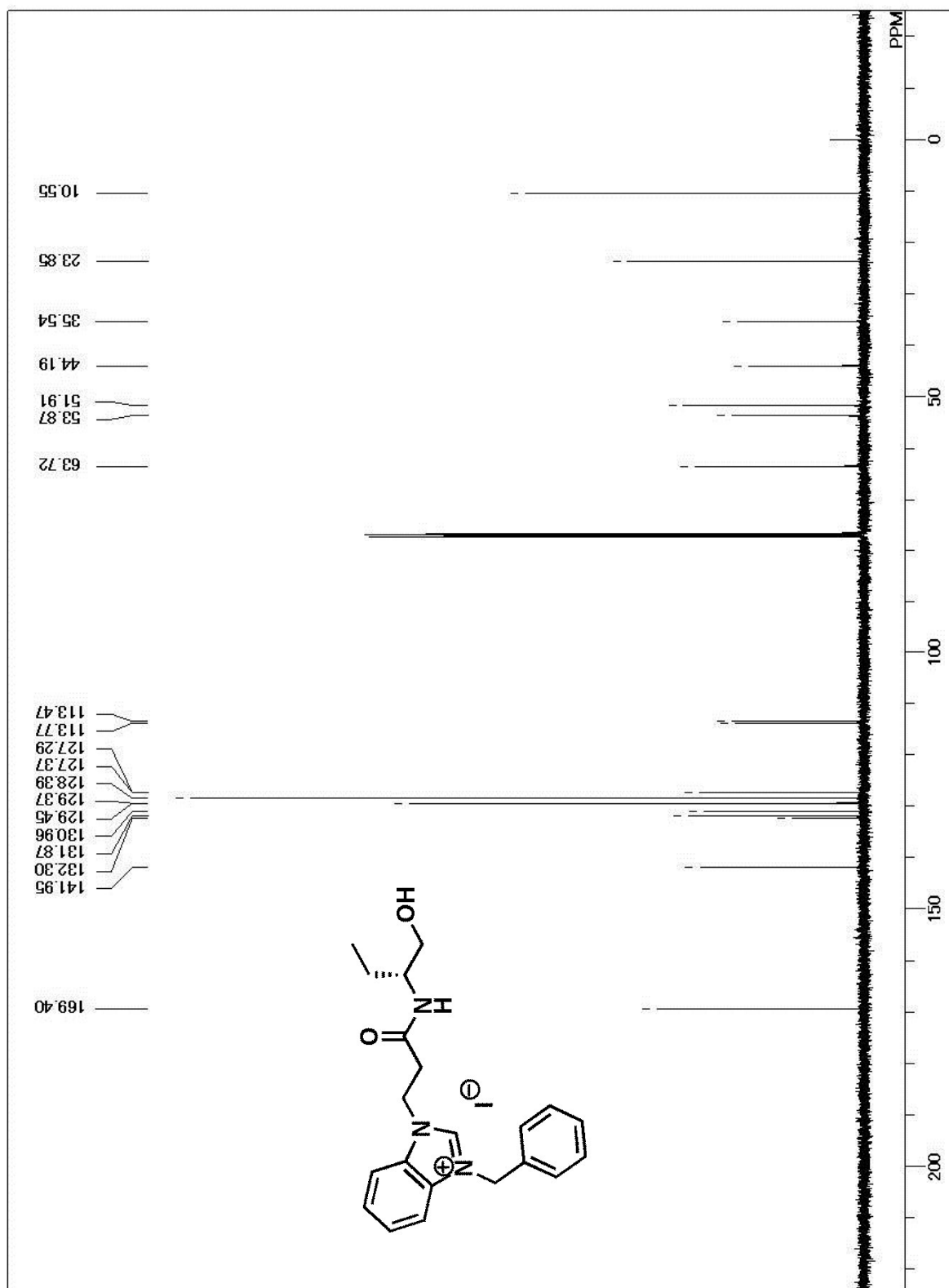
¹³C-NMR Spectra for **1b**



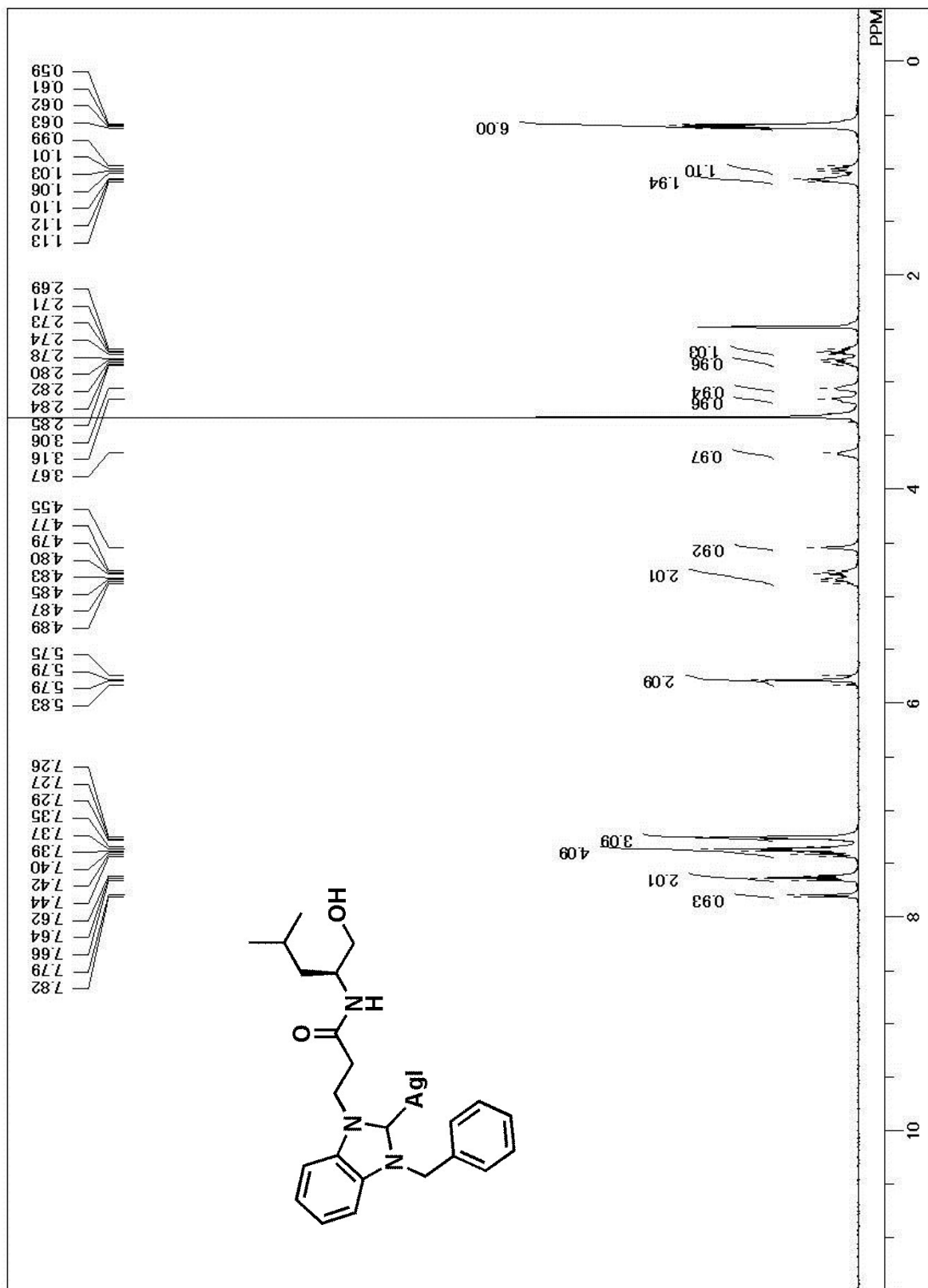
¹H-NMR Spectra for *ent-1b*



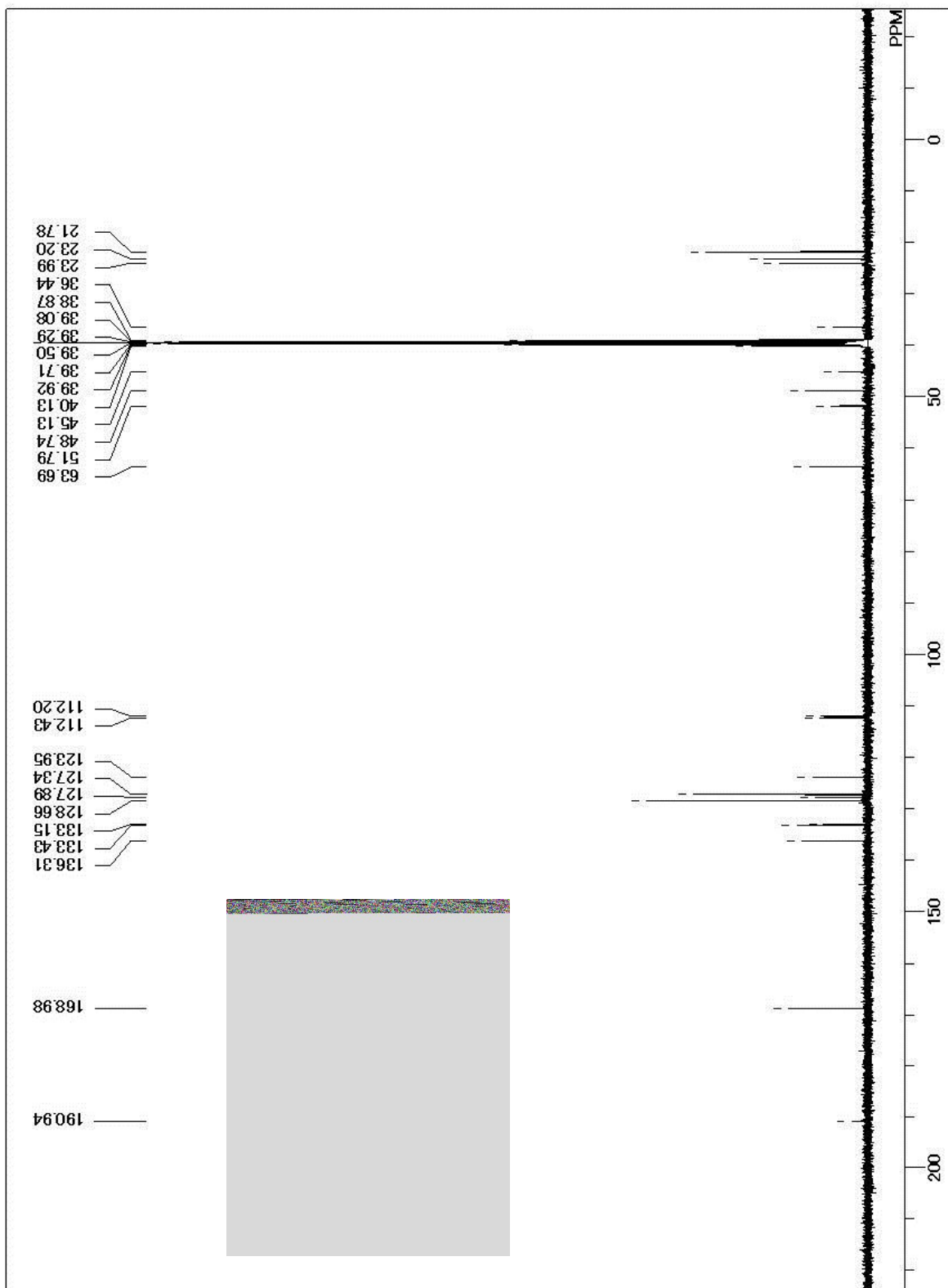
¹³C-NMR Spectra for *ent-1b*



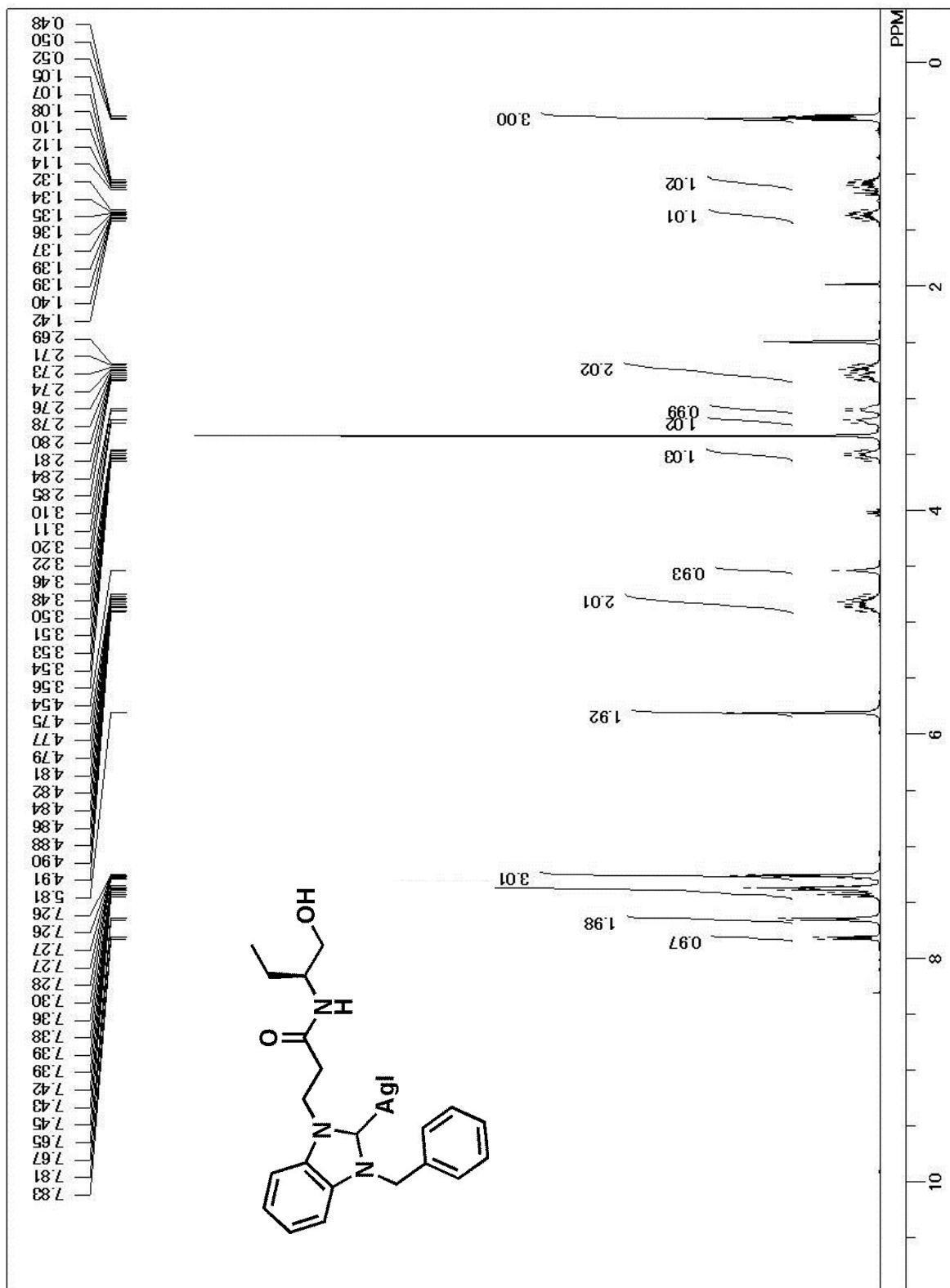
¹H-NMR Spectra for 2a



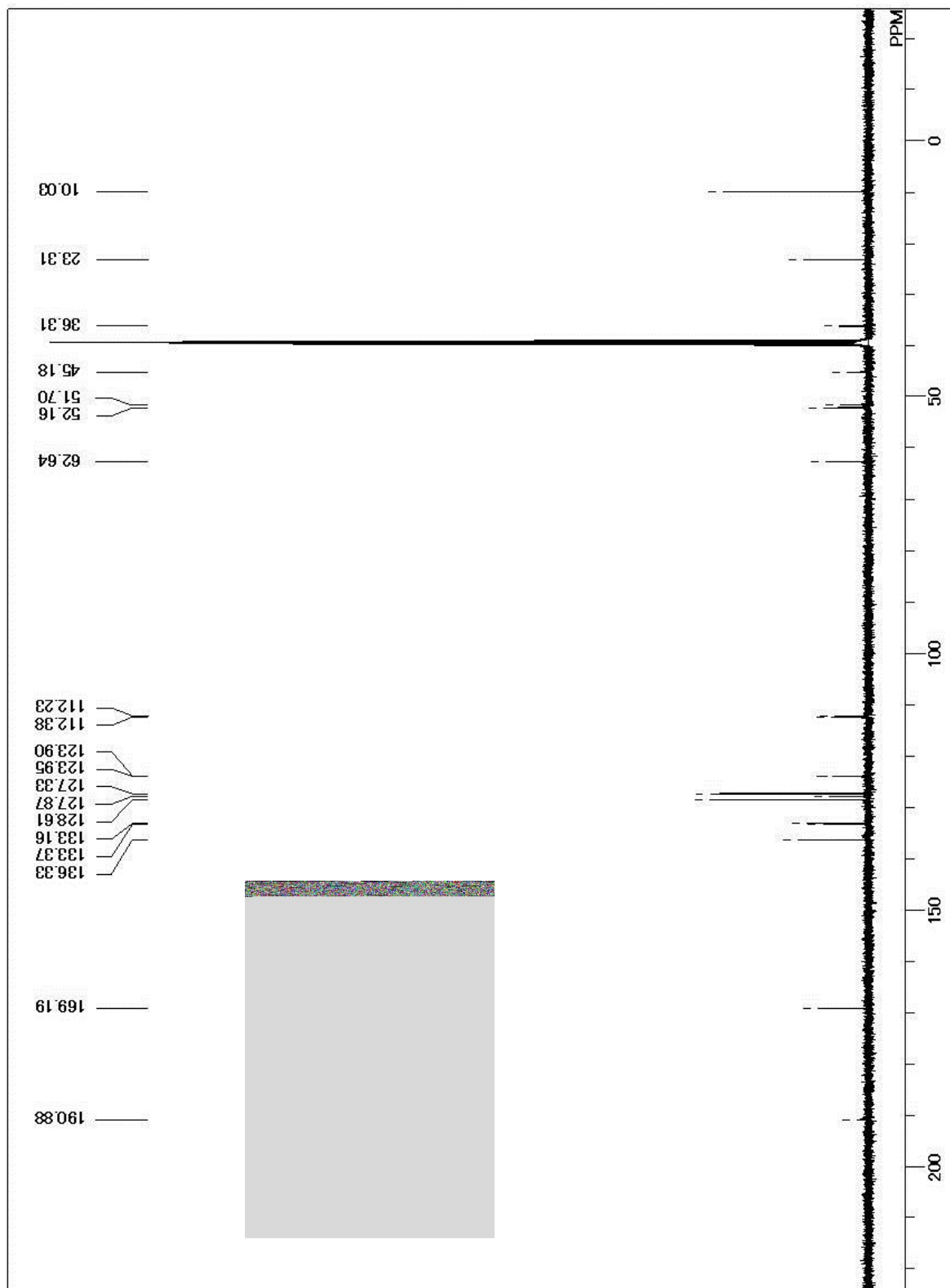
¹³C-NMR Spectra for **2a**



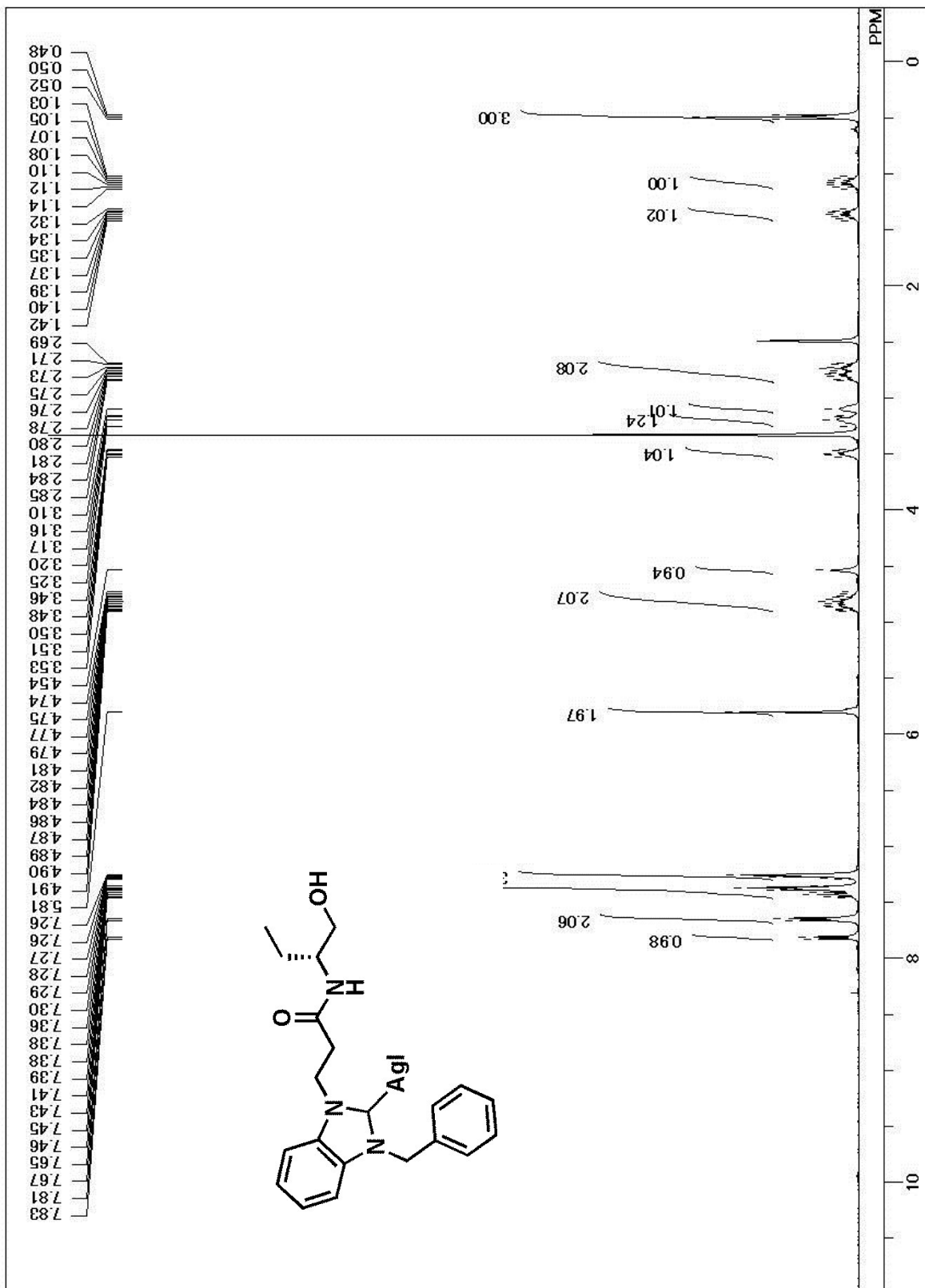
¹H-NMR Spectra for **2b**



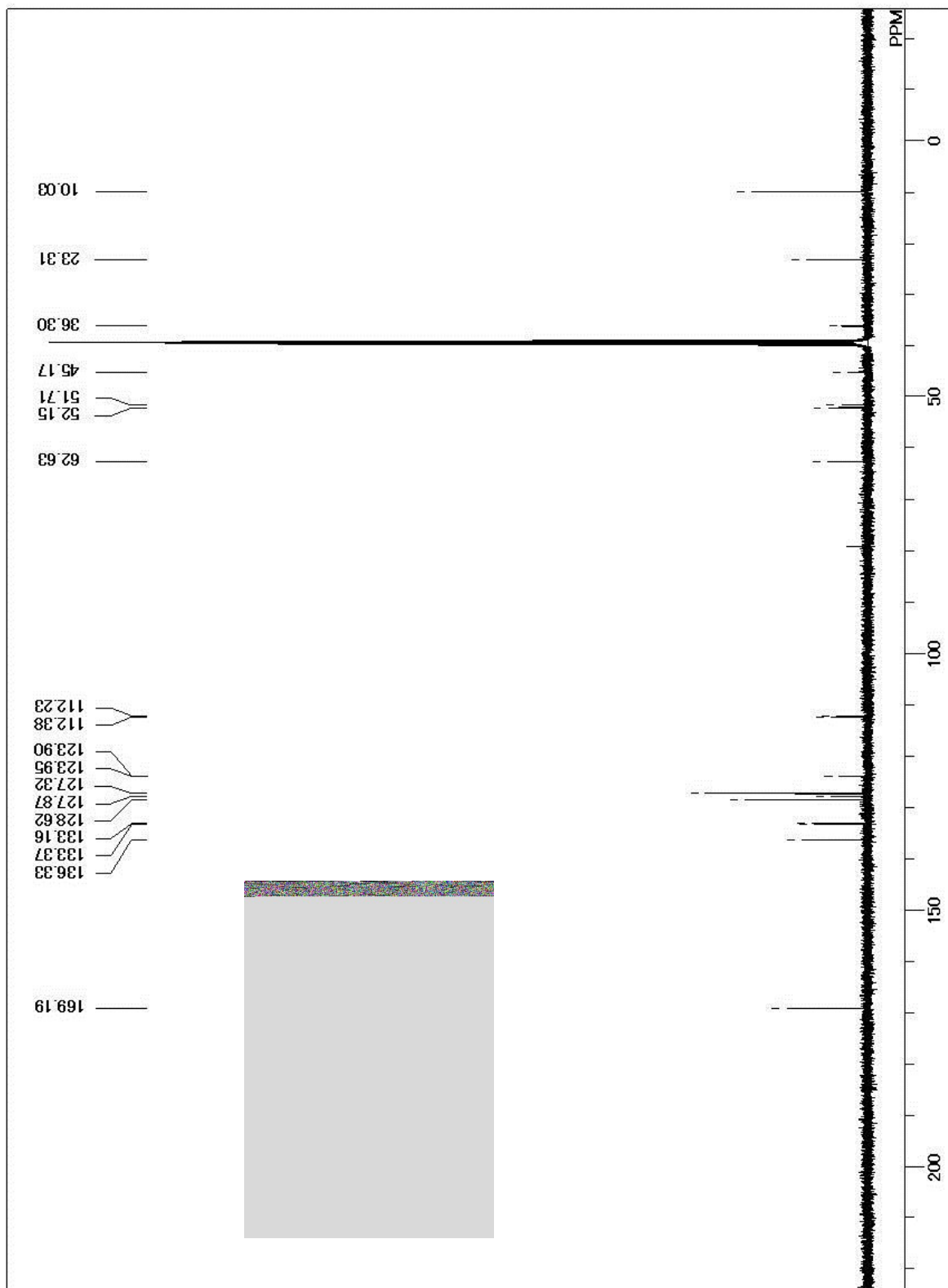
¹³C-NMR Spectra for **2b**



¹H-NMR Spectra for *ent-2b*



¹³C-NMR Spectra for *ent-2b*



9. Selected Chiral GC Traces in the ACA Reaction

Enantiomeric excesses were measured using gas chromatography according to our previously reported procedure.¹

3-Ethylcyclohexanone (5): Supelco γ -Dex225, 70 °C, N₂ gas, linear velocity of 27.5 cm/s, Rt = 59 min (*S*), 62 min (*R*).^{2,3}

3-Ethylcycloheptanone (7): Supelco β -Dex225, 80 °C, N₂ gas, linear velocity of 27.5 cm/s, Rt = 57 min (*S*), 61 min (*R*).³

3-Methylcycloheptanone (9): Supelco β -Dex225, 70 °C, N₂ gas, linear velocity of 27.5 cm/s, Rt = 56 min (*S*), 72 min (*R*).³

3-Methylcyclohexanone (10): Supelco γ -Dex225, 60 °C, N₂ gas, linear velocity of 27.5 cm/s, Rt = 53 min (*S*), 61 min (*R*).³

3-Ethyl-4,4-dimethylcyclohexanone (12): Supelco γ -Dex225, 85 °C, N₂ gas, linear velocity of 27.5 cm/s, Rt = 58 min (*R*), 60 min (*S*).³

3-Ethylcyclopentanone (14): Supelco γ -Dex225, 70 °C, N₂ gas, linear velocity of 27.5 cm/s, Rt = 45 min (*S*), 48 min (*R*).^{2,3}

Table 1, Entry 3, (*R*)-**5** (72% *ee*) [method A]

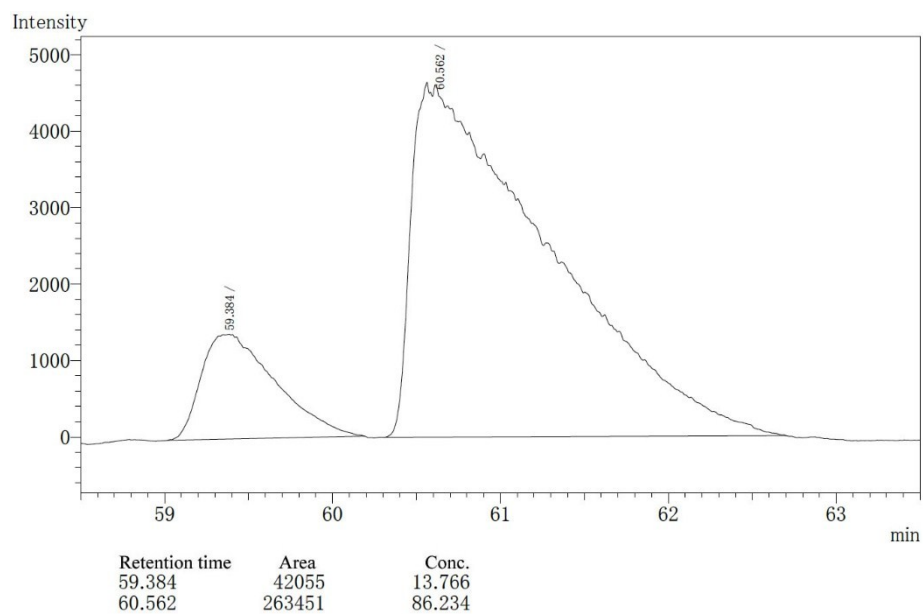


Table 1, Entry 7, (*S*)-**5** (88% *ee*) [method B]

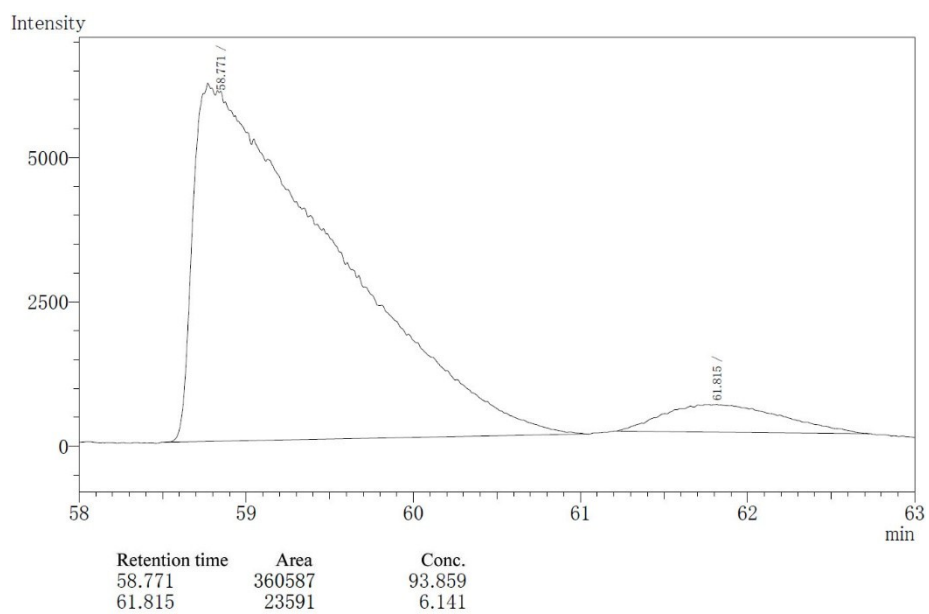


Table 1, Entry 11, (*R*)-**5** (74% *ee*) [method A]

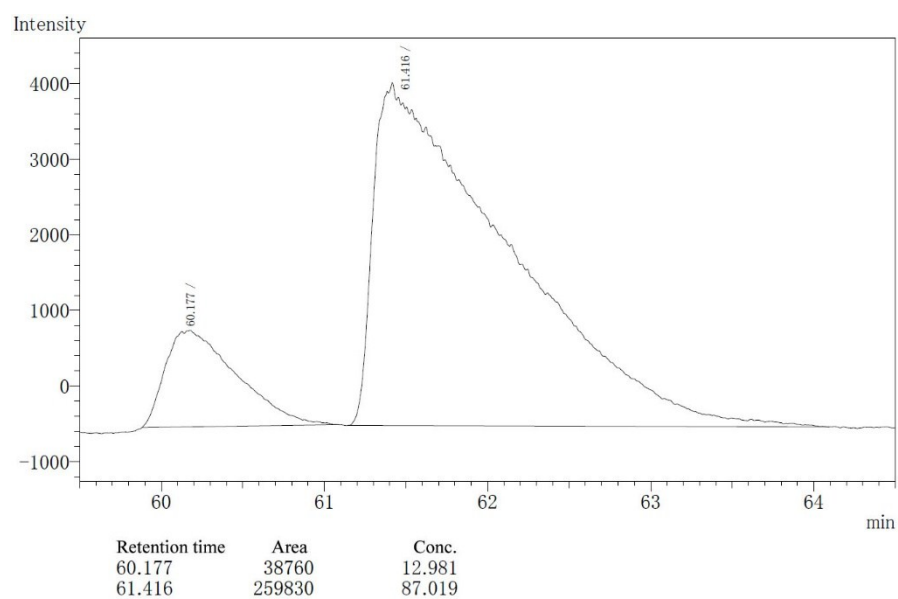
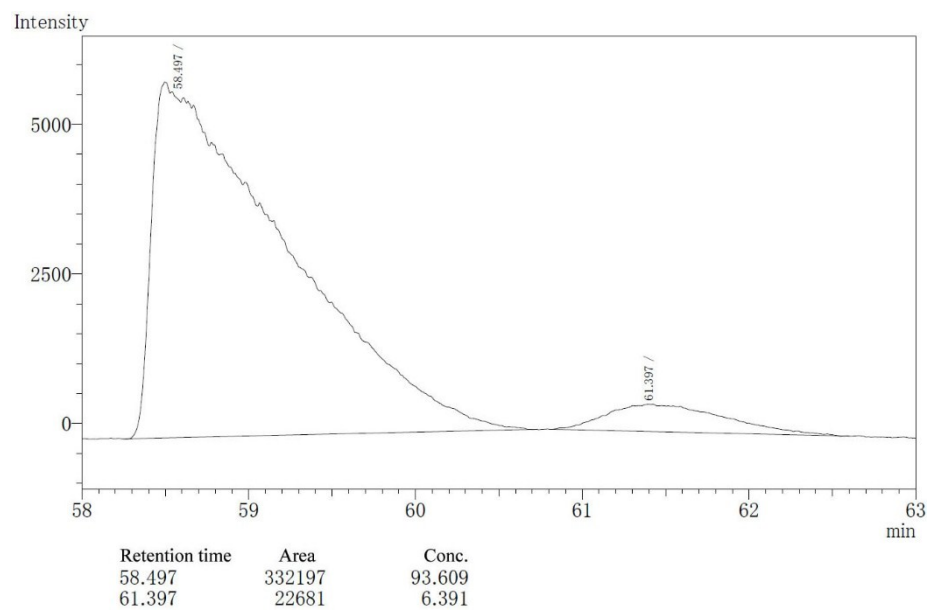
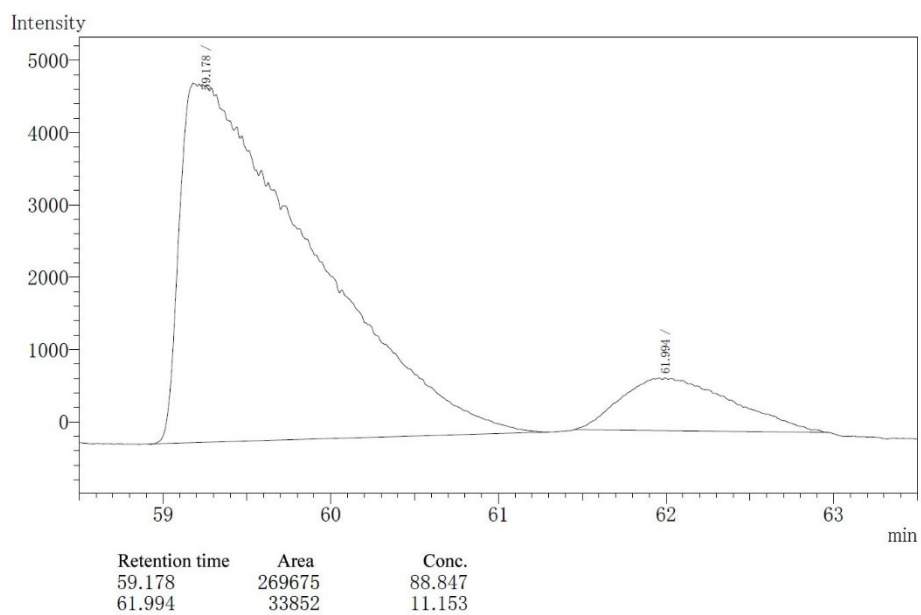


Table 1, Entry 15, (*S*)-**5** (87% *ee*) [method B]



Scheme S1, method A, (*S*)-**5** (78% *ee*)



Scheme S1, method B, (*R*)-**5** (85% *ee*)

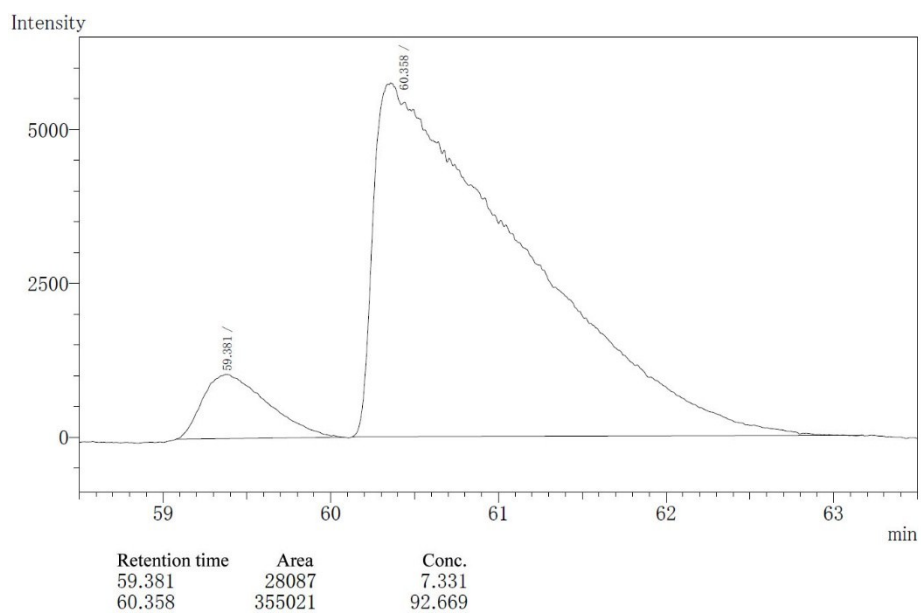


Table 2, Entry 2, (*R*)-7 (83% *ee*) [method A]

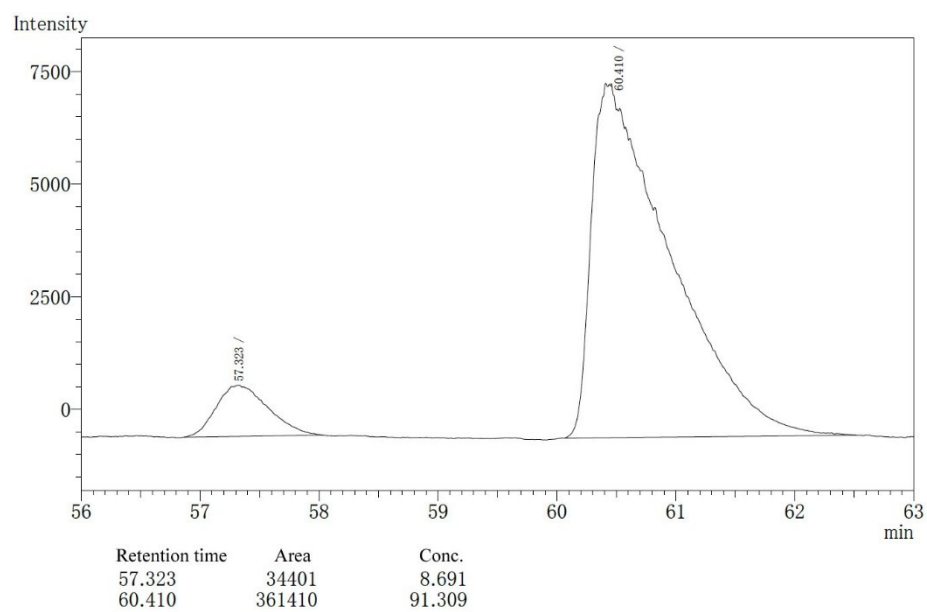


Table 2, Entry 4, (*S*)-7 (86% *ee*) [method B]

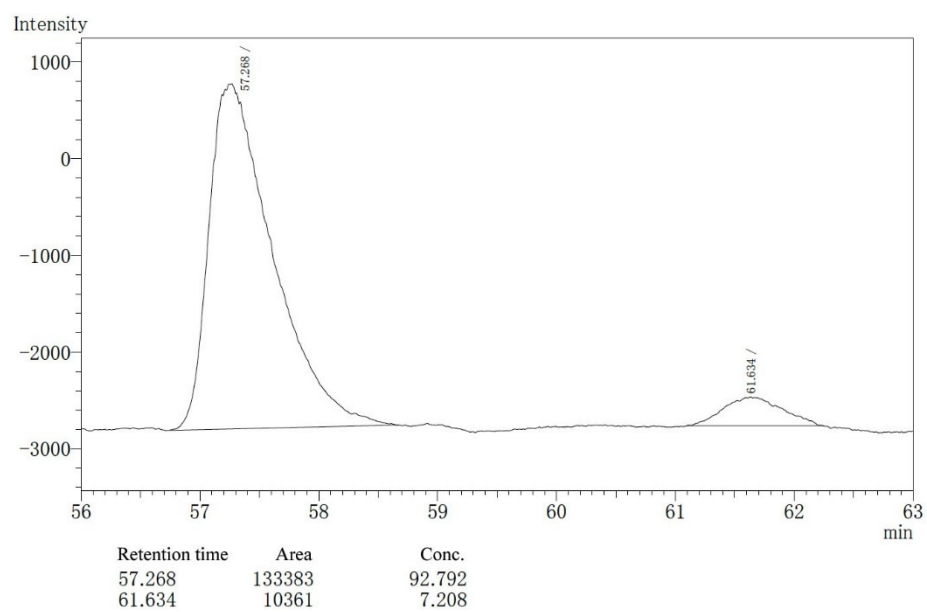


Table 2, Entry 6, (S)-9 (95% ee) [method B]

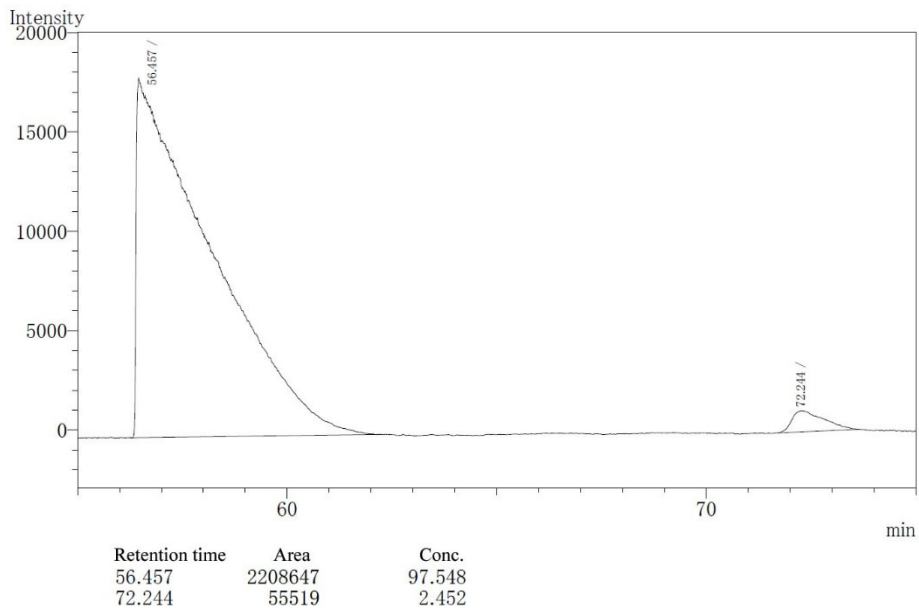


Table 2, Entry 9, (S)-10 (95% ee) [method B]

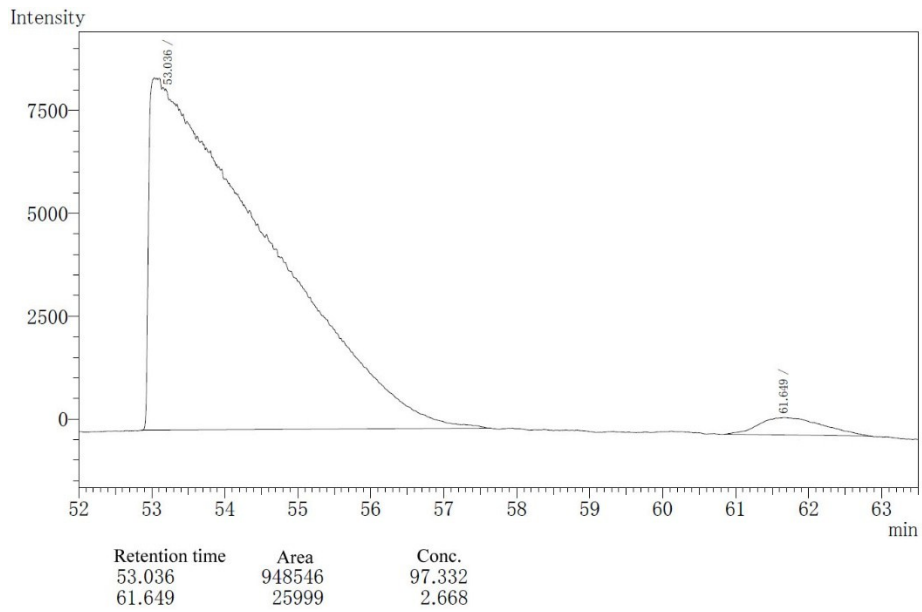


Table 2, Entry 10, (*S*)-**12** (71% *ee*) [method A]

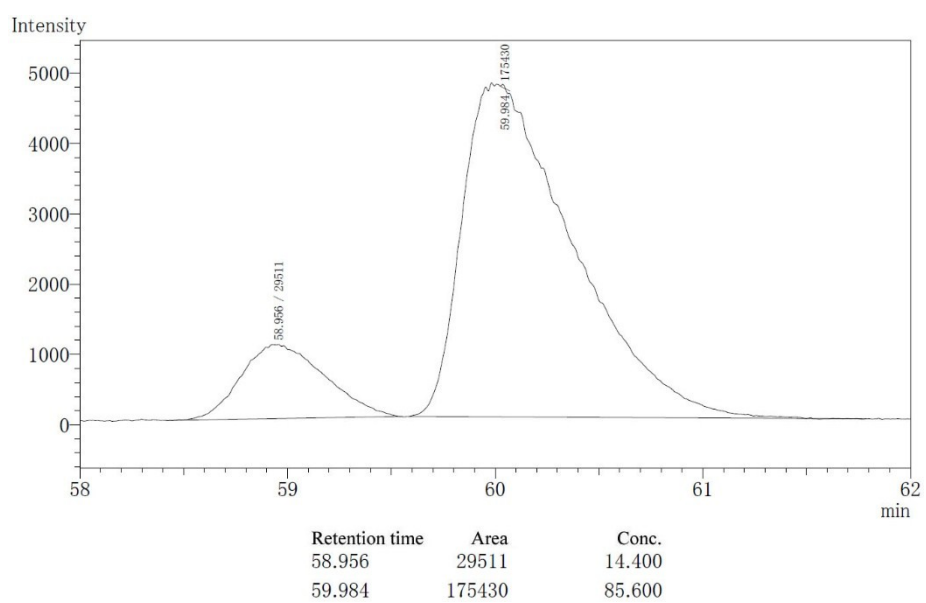


Table 2, Entry 13, (*R*)-**12** (96% *ee*) [method B]

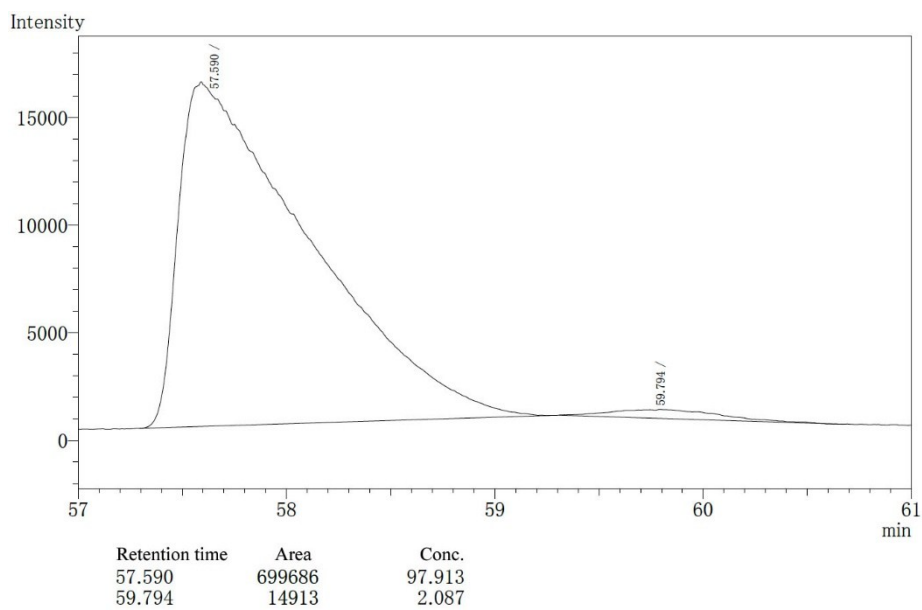


Table 2, Entry 14, (*S*)-**14** (9% *ee*) [method A]

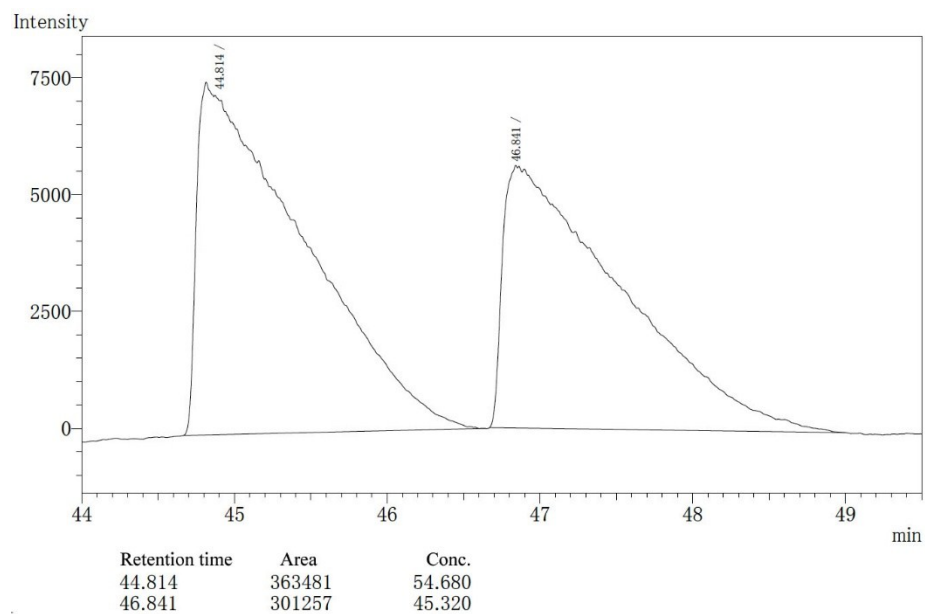


Table 2, Entry 15, (*S*)-**14** (80% *ee*) [method B]

