

**Supporting Information for**  
**HYBRID CATALYSIS OF 8-QUINOLINECARBOXALDEHYDE AND BRØNSTED ACID**  
**FOR EFFICIENT RACEMIZATION OF  $\alpha$ -AMINO AMIDES AND ITS APPLICATION IN**  
**CHEMOENZYMATIC DYNAMIC KINETIC RESOLUTION**

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### **General Information**

<sup>1</sup>H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) and JEOL JNM-ECA600II (600 MHz) spectrometer. Chemical shifts are reported in ppm from the tetramethylsilane (0.0 ppm) resonance as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, and br = broad) and coupling constants (Hz). <sup>13</sup>C NMR spectra were recorded on a JEOL JNM-ECA600II (151 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance as the internal standard (CDCl<sub>3</sub>; 77.23 ppm or CD<sub>3</sub>OD; 49.15 ppm). Optical rotations were measured on a HORIBA SEPA-500 polarimeter. The high-resolution mass spectra were measured on Thermo Fisher Scientific Exactive Plus (ESI). Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Flash column chromatography was performed on Silica gel 60 N (spherical, neutral, 40~50 $\mu$ m; Kanto Chemical Co., Inc.). Enantiomeric excesses were determined by HPLC analysis using chiral columns ( $\phi$  4.6 mm x 250 mm, DAICEL CHIRALPAK AZ-3 (AZ3) and CHIRALPAK IB N-3 (IBN3)) with hexane (H), isopropyl alcohol (IPA), and ethanol (EtOH) as eluent.

Toluene was supplied from Kanto Chemical Co., Inc. as “Dehydrated” and further purified by both A2 alumina and Q5 reactant using a GlassContour solvent dispensing system. Water was deionized with a Millipore system as a Milli-Q grade. Immobilized CALB was purchased from Sigma-Aldrich (Lipase acrylic resin,  $\geq$ 5,000 U/g, recombinant, expressed in *Aspergillus niger*) and used as such. Phenylglycine derivatives were synthesized by following the literature methods.<sup>1</sup>

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<sup>1</sup> H. L. van Lingen, J. K. W. van de Mortel, K. F. W. Hekking, F. L. van Delft, T. Sonke, F. P. J. T. Rutjes, *Eur. J. Org. Chem.* **2003**, 317.

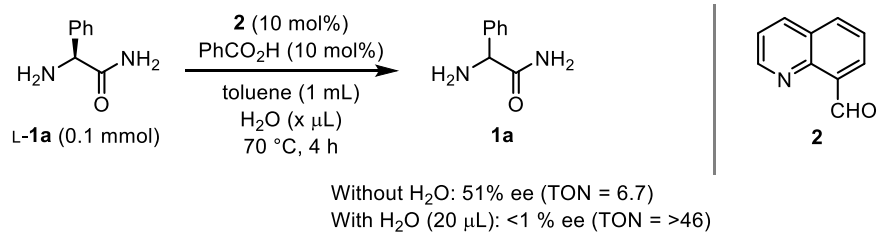
### Procedure for catalytic racemization of $\alpha$ -amino amides

8-Quinolinecarboxaldehyde (1.6 mg, 0.01 mmol), benzoic acid (1.2 mg, 0.01 mmol), and L-phenylglycine amide (15.0 mg, 0.1 mmol) were placed in a test tube and dissolved in toluene (1.0 mL). The resulting solution was heated to 70 °C and stirred for 24 h. After cooling to room temperature, triethylamine (28  $\mu$ L, 0.2 mmol) and acetic anhydride (19  $\mu$ L, 0.2 mmol) were successively added to the reaction solution, and the stirring was maintained for additional 4 h at room temperature. The mixture was then poured into water, and the extractive work-up was performed with EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Filtration, evaporation for solvent removal, and purification of the resulting crude material by column chromatography (CHCl<sub>3</sub>/MeOH = 20:1 to 10:1 as eluent) gave *N*-acetyl phenylglycine amide (**3a**, 17.9 mg, 0.093 mmol, 93%) in a racemic form. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.42-7.32 (5H, m), 6.80 (1H, br), 5.63 (1H, br), 5.47 (1H, d, *J* = 7.2 Hz), 5.43 (1H, br), 2.03 (3H, s); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  172.1, 169.8, 138.0, 129.4, 128.8, 127.6, 57.0, 23.4; HRMS (ESI) Calcd for C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>Na<sup>+</sup> ([M+Na]<sup>+</sup>) 215.0791, Found 215.0792; HPLC using DAICEL CHIRALPAK IB N-3, H/IPA = 10:1, flow rate = 1.0 mL/min,  $\lambda$  = 210 nm, 23.4 min (L), 31.7 min (D).

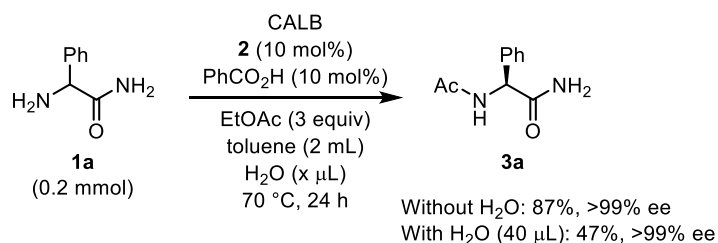
### General procedure for DKR of $\alpha$ -amino amides

CALB (10 mg), 8-quinolinecarboxaldehyde (3.1 mg, 0.02 mmol), benzoic acid (2.4 mg, 0.02 mmol), and racemic **1a** (30.0 mg, 0.2 mmol) were placed in a test tube and dissolved in toluene (2.0 mL). Then, EtOAc (59  $\mu$ L, 0.6 mmol) was added, and the whole mixture was heated to 70 °C and stirred for 24 h. The reaction mixture was cooled to room temperature and filtered through a pad of celite with the aid of MeOH. The resulting filtrate was concentrated under reduced pressure and purified by column chromatography (CHCl<sub>3</sub>/MeOH = 20:1 to 10:1 as eluent) to afford **3a** (33.5 mg, 0.17 mmol, >99% ee); [ $\alpha$ ]<sub>D</sub><sup>26</sup> = +207.6 (c = 1.0, MeOH).

## Effect of water on catalytic racemization and chemoenzymatic kinetic resolution

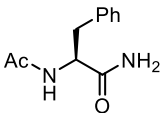


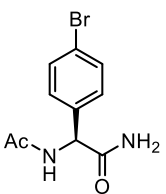
As described in Table 1 in the main manuscript, moderate turnover number (TON = 6.7) was observed when the racemization of L-**1a** was conducted with the optimal catalyst combination, 8-quinolinecarboxaldehyde (**2**) and benzoic acid, in toluene for 4 h. However, the addition of water as a co-solvent (the ratio of toluene to water was 50:1) led to significant improvement in the reaction efficiency: entirely racemic **1a** was obtained under otherwise identical reaction conditions.

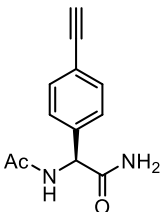


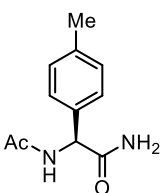
On the other hand, water was found to have a negative effect on the chemoenzymatic kinetic resolution of amino amides. For instance, the reaction of racemic **1a** with ethyl acetate under the influence of CALB, **2**, and benzoic acid in toluene and water (50:1) resulted in the formation of *N*-acetyl amide **3a** in much lower yield (47%) than that of the reaction without water (87%) probably due to the rapid hydrolysis of ethyl acetate.

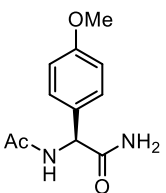
## Characterization of *N*-Acetyl $\alpha$ -Amino Amides

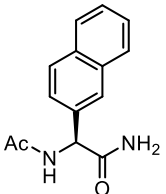
 **3b:**  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.29-7.17 (5H, m), 4.60 (1H, dd,  $J = 9.2, 5.6$  Hz), 3.13 (1H, dd, 14.0, 5.6 Hz), 2.86 (1H, dd, 14.0, 9.2 Hz), 1.89 (3H, s);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  176.5, 173.2, 138.8, 130.4, 129.5, 127.9, 56.0, 39.2, 22.5; HRMS (ESI) Calcd for  $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2\text{Na}^+$  ( $[\text{M}+\text{Na}]^+$ ) 279.0948, Found 279.0942; HPLC AZ3, H/IPA = 10:1, flow rate = 1.0 mL/min,  $\lambda = 210$  nm, 13.1 min (D), 18.1 min (L);  $[\alpha]_{\text{D}}^{26} = +26.5$  ( $c = 1.0$ , MeOH).

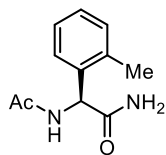
 **3c:**  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.51 (2H, d,  $J = 8.8$  Hz), 7.35 (2H, d,  $J = 8.8$  Hz), 5.40 (1H, s), 2.00 (3H, s);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  174.7, 173.0, 138.5, 133.0, 130.8, 123.2, 58.1, 22.5; HRMS (ESI) Calcd for  $\text{C}_{10}\text{H}_{11}\text{BrN}_2\text{O}_2\text{Na}^+$  ( $[\text{M}+\text{Na}]^+$ ) 292.9897, Found 292.9895; HPLC IBN3, H/IPA = 85:15, flow rate = 1.0 mL/min,  $\lambda = 210$  nm, 12.5 min (major), 22.3 min (minor);  $[\alpha]_{\text{D}}^{26} = +134.1$  ( $c = 1.0$ , MeOH).

 **3d:**  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.46 (2H, d,  $J = 8.4$  Hz), 7.42 (2H, d,  $J = 8.4$  Hz), 5.43 (1H, s), 3.50 (1H, s), 2.00 (3H, s);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  174.7, 173.0, 139.8, 133.4, 129.0, 123.8, 84.1, 79.4, 58.4, 22.6; HRMS (ESI) Calcd for  $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2\text{Na}^+$  ( $[\text{M}+\text{Na}]^+$ ) 239.0791, Found 239.0788; HPLC IBN3, H/IPA = 85:15, flow rate = 1.0 mL/min,  $\lambda = 210$  nm, 13.1 min (major), 23.6 min (minor);  $[\alpha]_{\text{D}}^{25} = +207.4$  ( $c = 1.0$ , MeOH).

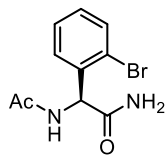
 **3e:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 (2H, d,  $J = 8.0$  Hz), 7.18 (2H, d,  $J = 8.0$  Hz), 6.76 (1H, br), 5.63 (1H, br), 5.43 (1H, d,  $J = 6.4$  Hz), 5.42 (1H, br), 2.34 (3H, s), 2.02 (3H, s);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  172.4, 169.8, 138.7, 135.1, 130.0, 127.5, 56.8, 23.4, 21.4; HRMS (ESI) Calcd for  $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2\text{Na}^+$  ( $[\text{M}+\text{Na}]^+$ ) 229.0948, Found 229.0947; HPLC IBN3, H/IPA = 10:1, flow rate = 1.0 mL/min,  $\lambda = 210$  nm, 20.6 min (major), 35.6 min (minor);  $[\alpha]_{\text{D}}^{26} = +202.3$  ( $c = 1.0$ , MeOH).

 **3f:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 (2H, d,  $J = 8.8$  Hz), 6.89 (2H, d,  $J = 8.8$  Hz), 6.74 (1H, br), 5.61 (1H, br), 5.42 (1H, d,  $J = 6.8$  Hz), 5.41 (1H, br), 3.80 (3H, s), 2.02 (3H, s);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  172.4, 169.7, 160.0, 130.1, 129.0, 114.7, 56.5, 55.6, 23.4; HRMS (ESI) Calcd for  $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_3\text{Na}^+$  ( $[\text{M}+\text{Na}]^+$ ) 245.0897, Found 245.0887; HPLC IBN3, H/IPA = 85:15, flow rate = 1.0 mL/min,  $\lambda = 210$  nm, 17.7 min (major), 21.6 min (minor);  $[\alpha]_{\text{D}}^{26} = +180.7$  ( $c = 1.0$ , MeOH).

 **3g:**  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.92 (1H, d,  $J = 1.6$  Hz), 7.88-7.83 (3H, m), 7.54 (1H, dd,  $J = 8.8, 2.0$  Hz), 7.51-7.46 (2H, m), 5.60 (1H, s), 2.03 (3H, s);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  175.3, 173.1, 136.5, 134.9, 134.7, 129.7, 129.2, 128.8, 128.1, 127.6, 127.5, 126.4, 58.9, 22.6; HRMS (ESI) Calcd for  $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2\text{Na}^+$  ( $[\text{M}+\text{Na}]^+$ ) 265.0948, Found 265.0948; HPLC IBN3, H/IPA = 85:15, flow rate = 1.0 mL/min,  $\lambda = 210$  nm, 17.9 min (major), 28.8 min (minor);  $[\alpha]_{\text{D}}^{26} = +162.2$  ( $c = 1.0$ , MeOH).

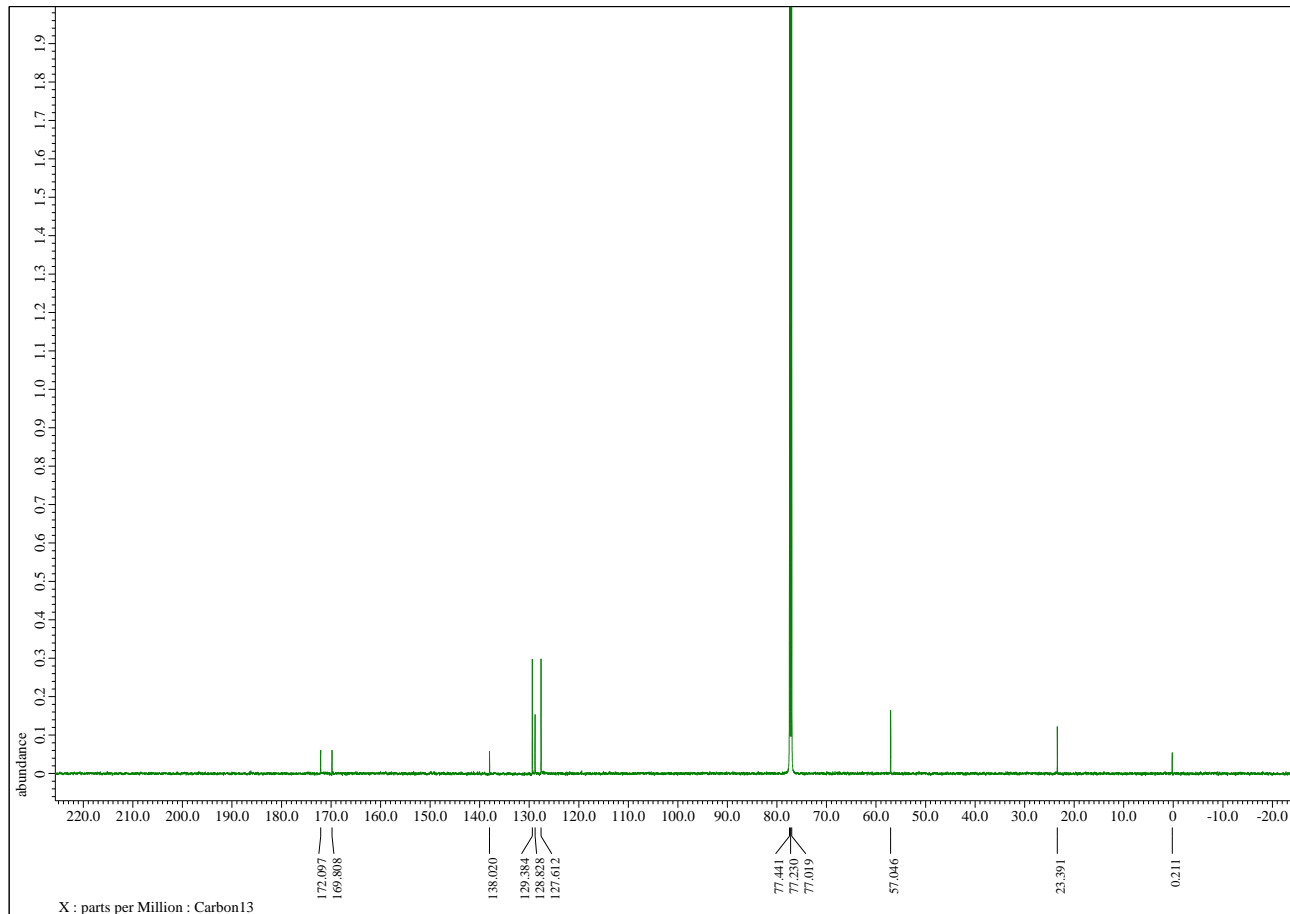
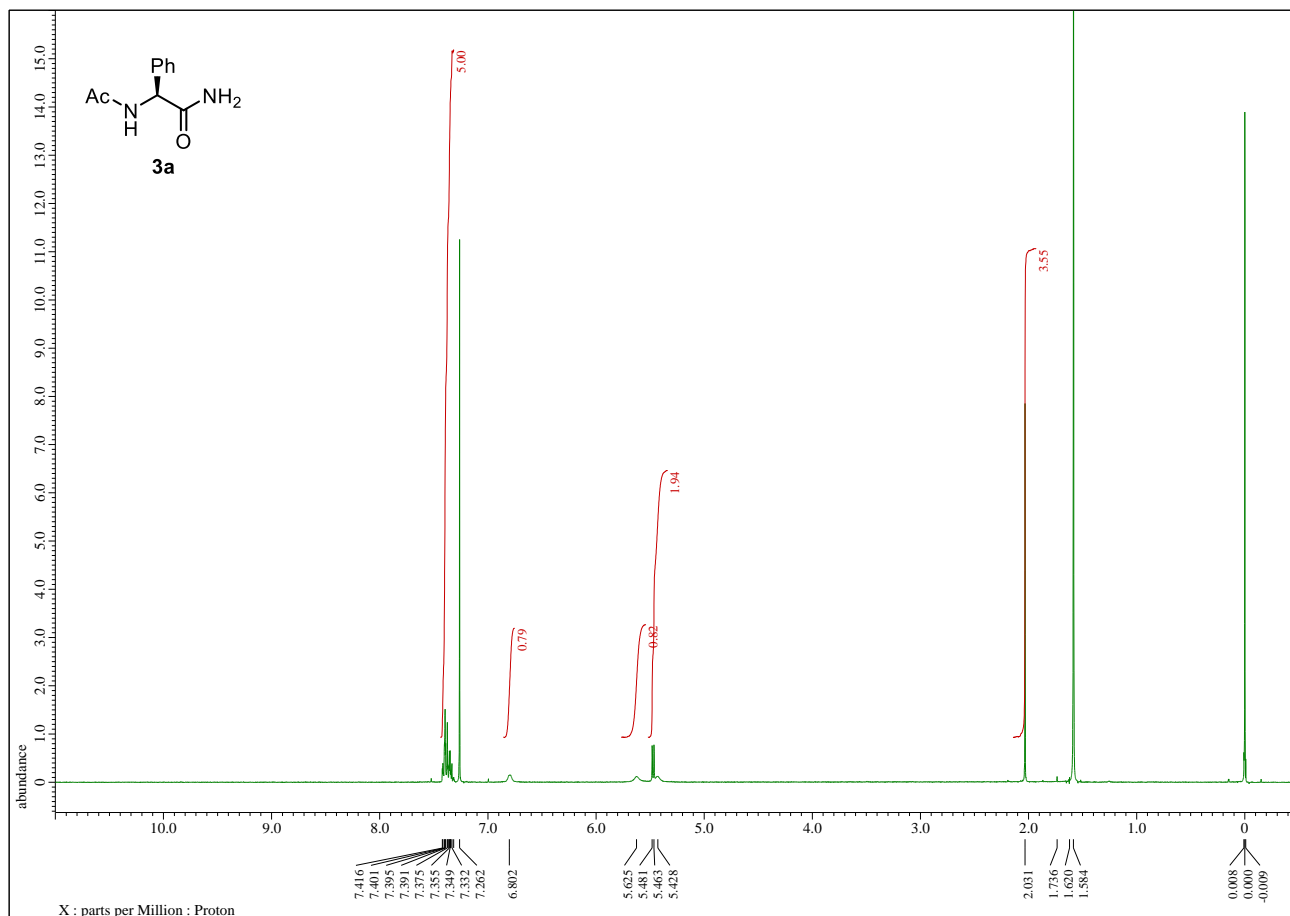


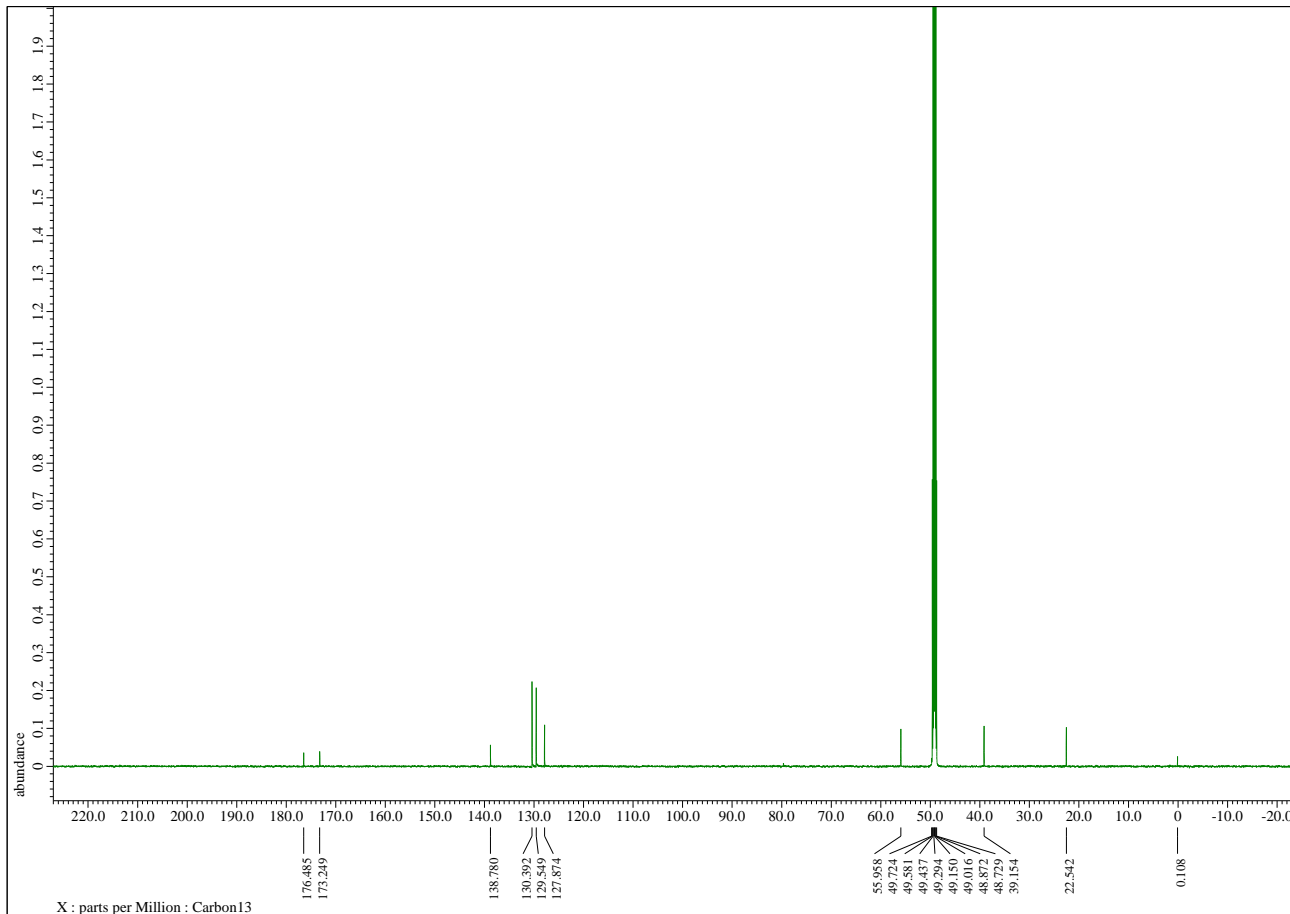
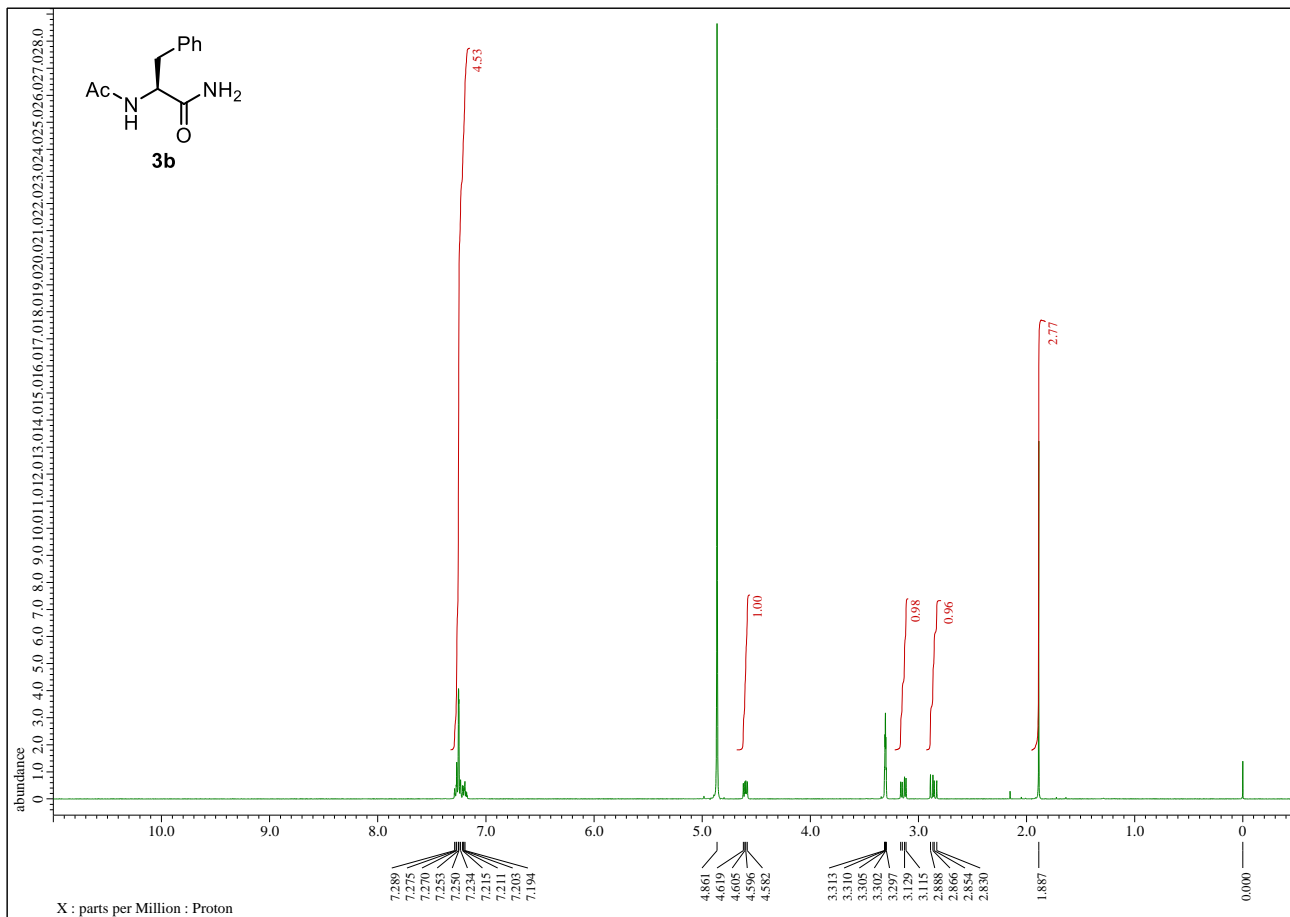
**3h:**  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.33 (1H, d,  $J = 6.8$  Hz), 7.23-7.16 (3H, m), 5.64 (1H, s), 2.39 (3H, s), 1.99 (3H, s);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  176.0, 173.2, 138.6, 137.0, 131.9, 129.6, 127.5, 55.8, 22.4, 19.5; HRMS (ESI) Calcd for  $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2\text{Na}^+$  ( $[\text{M}+\text{Na}]^+$ ) 229.0948, Found 229.0936; HPLC IBN3, H/IPA = 10:1, flow rate = 1.0 mL/min,  $\lambda = 210$  nm, 21.0 min (major), 26.6 min (minor);  $[\alpha]_{\text{D}}^{25} = +137.9$  ( $c = 1.0$ , MeOH).

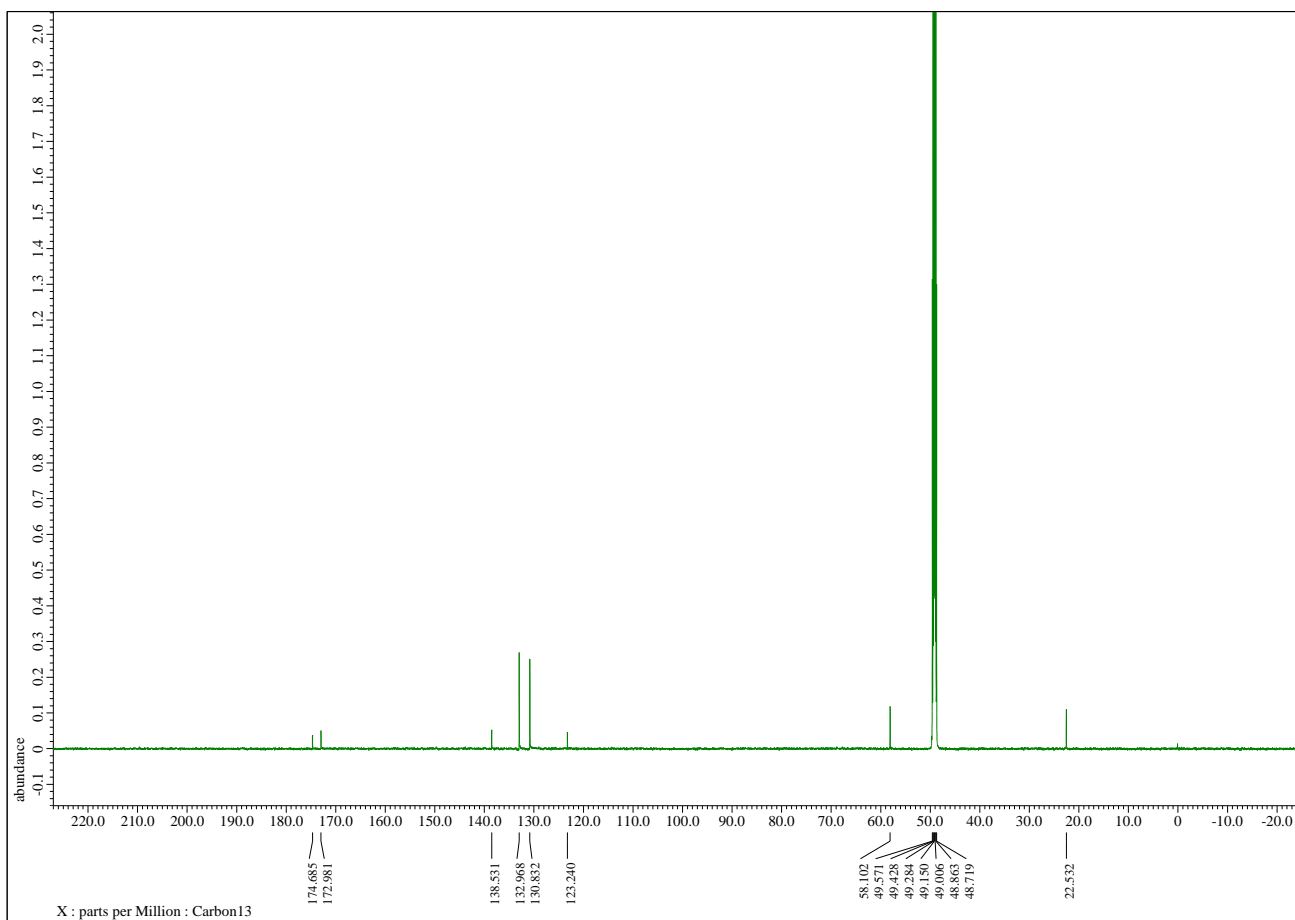
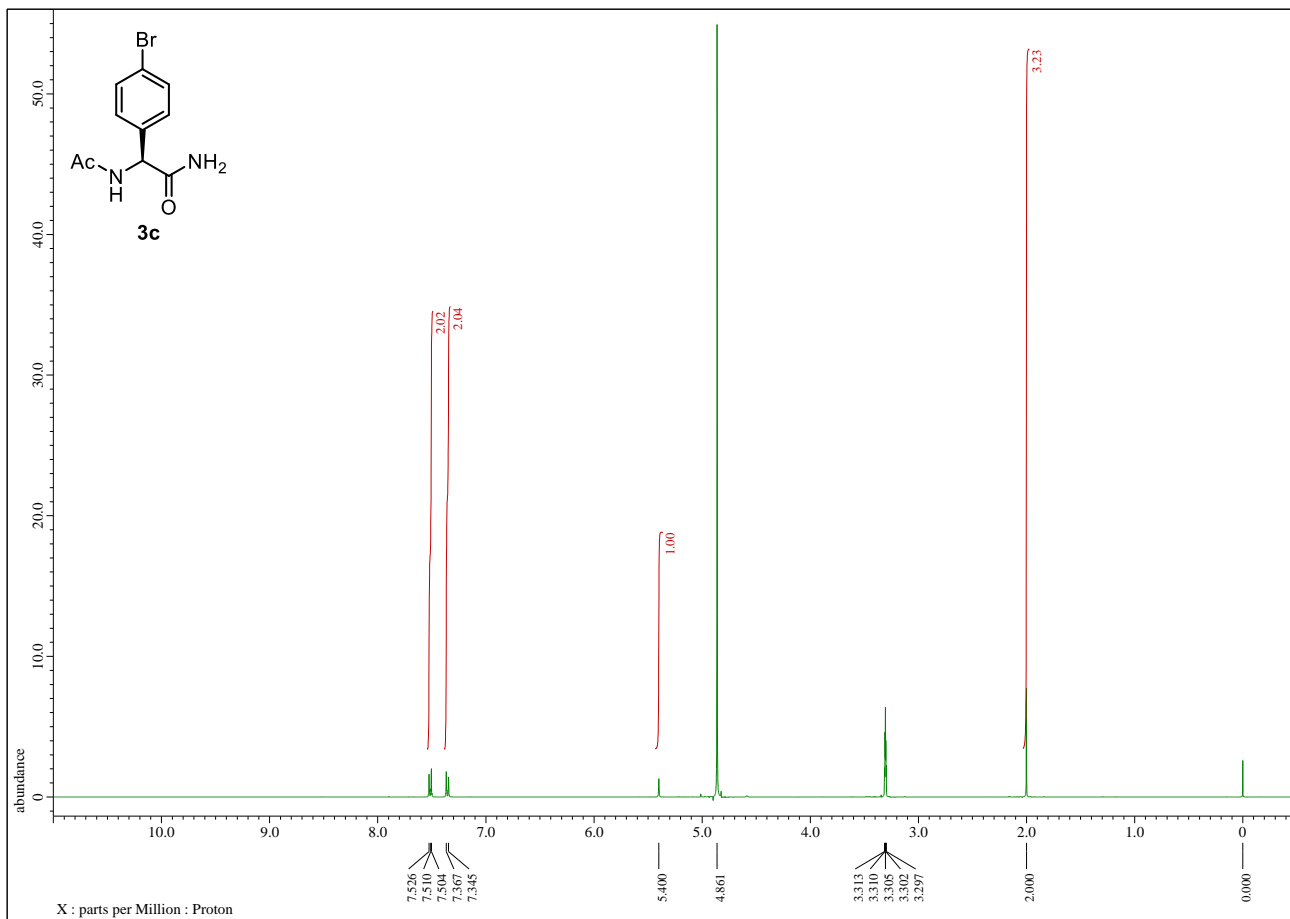


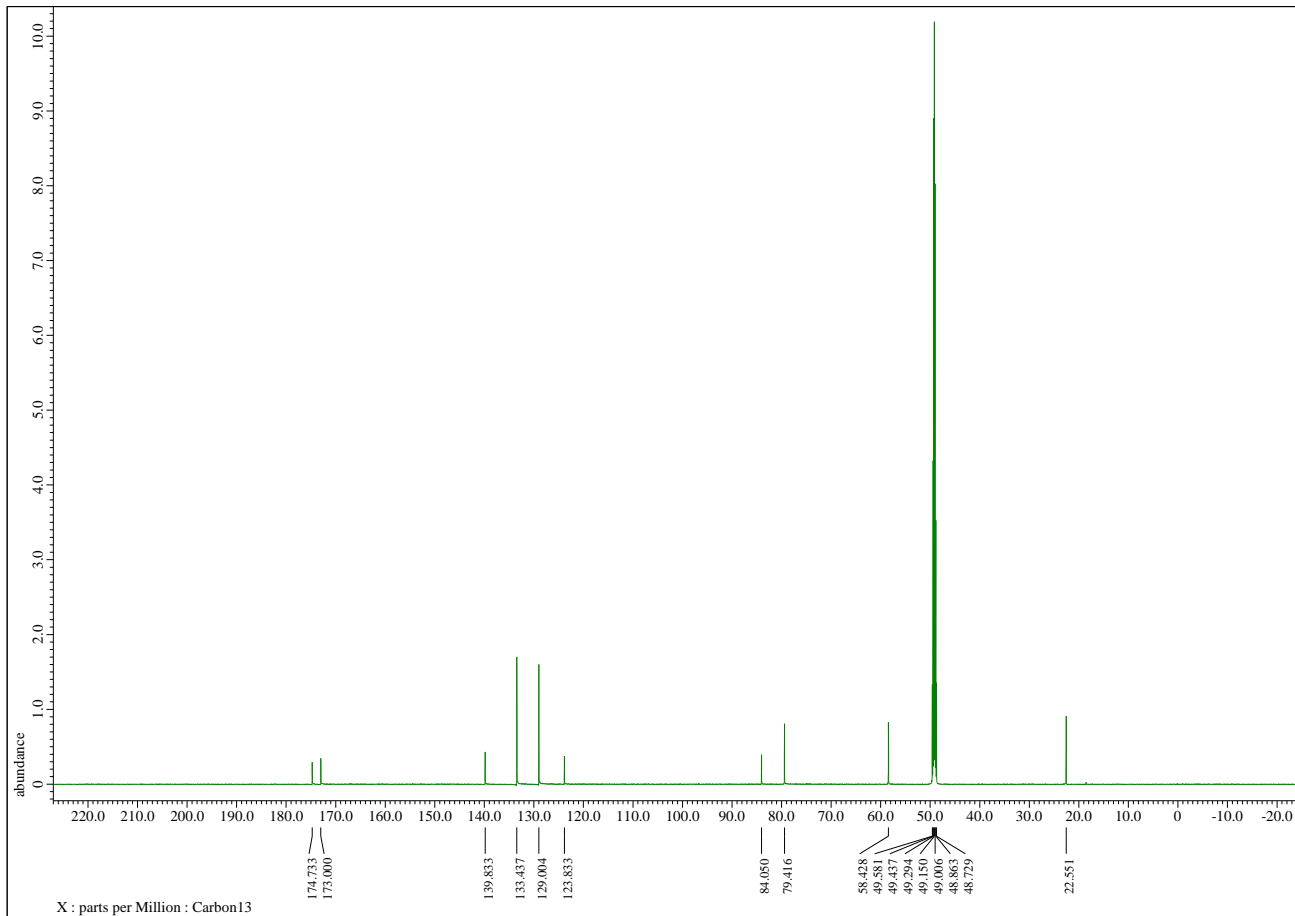
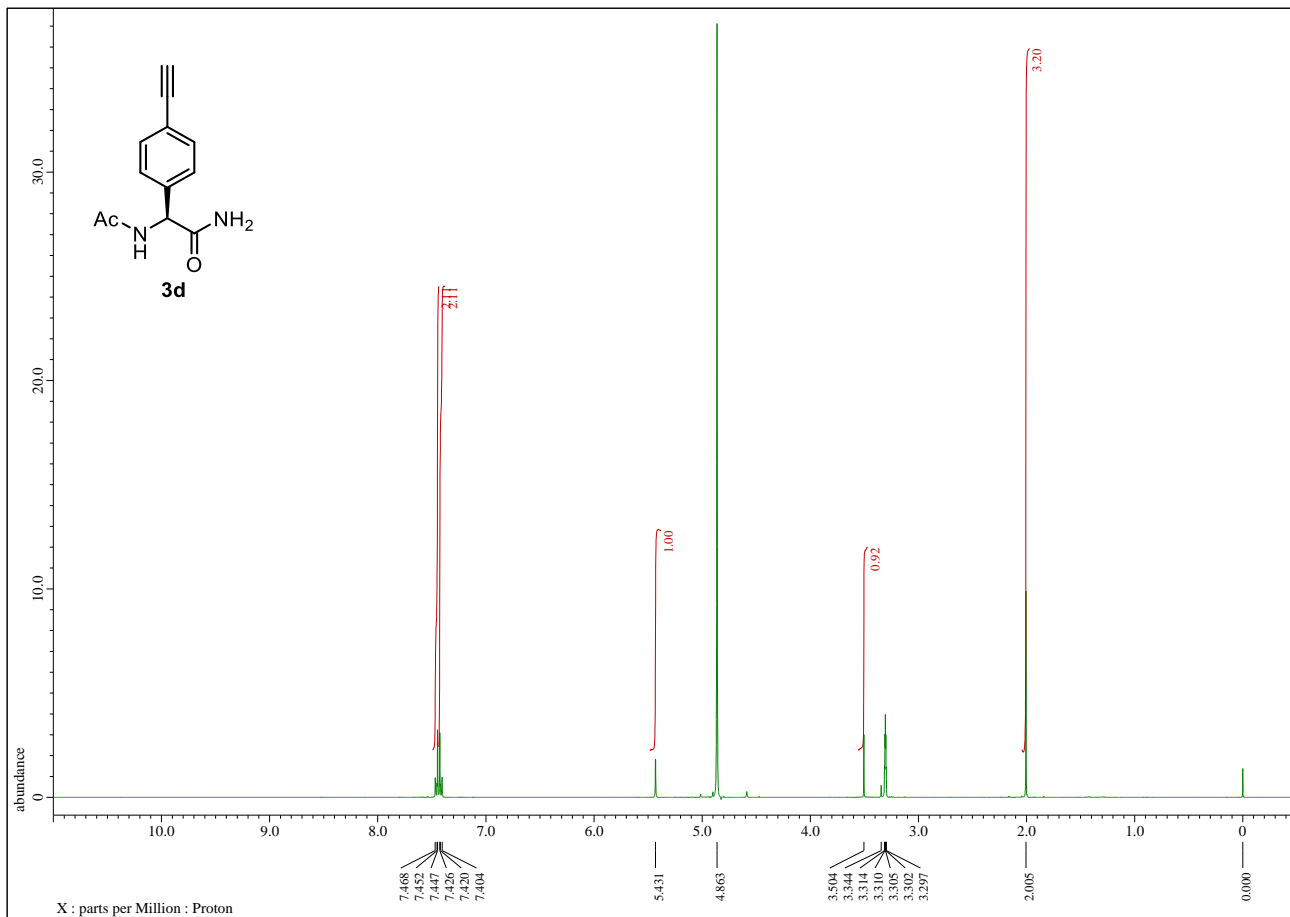
**3i:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59 (1H, d,  $J = 8.0$  Hz), 7.41 (1H, d,  $J = 8.0$  Hz), 7.33 (1H, t,  $J = 8.0$  Hz), 7.20 (1H, t,  $J = 8.0$  Hz), 6.99 (1H, br), 5.88 (1H, br), 5.87 (1H, d,  $J = 6.4$  Hz), 5.44 (1H, br), 2.05 (3H, s);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  171.1, 169.6, 137.5, 133.6, 130.2, 129.2, 128.6, 123.4, 56.5, 23.2; HRMS (ESI) Calcd for  $\text{C}_{10}\text{H}_{11}\text{BrN}_2\text{O}_2\text{Na}^+$  ( $[\text{M}+\text{Na}]^+$ ) 292.9897, Found 292.9888; HPLC IBN3, H/IPA = 85:15, flow rate = 1.0 mL/min,  $\lambda = 210$  nm, 17.1 min (major), 22.1 min (minor);  $[\alpha]_{\text{D}}^{26} = +115.6$  ( $c = 1.0$ , MeOH).

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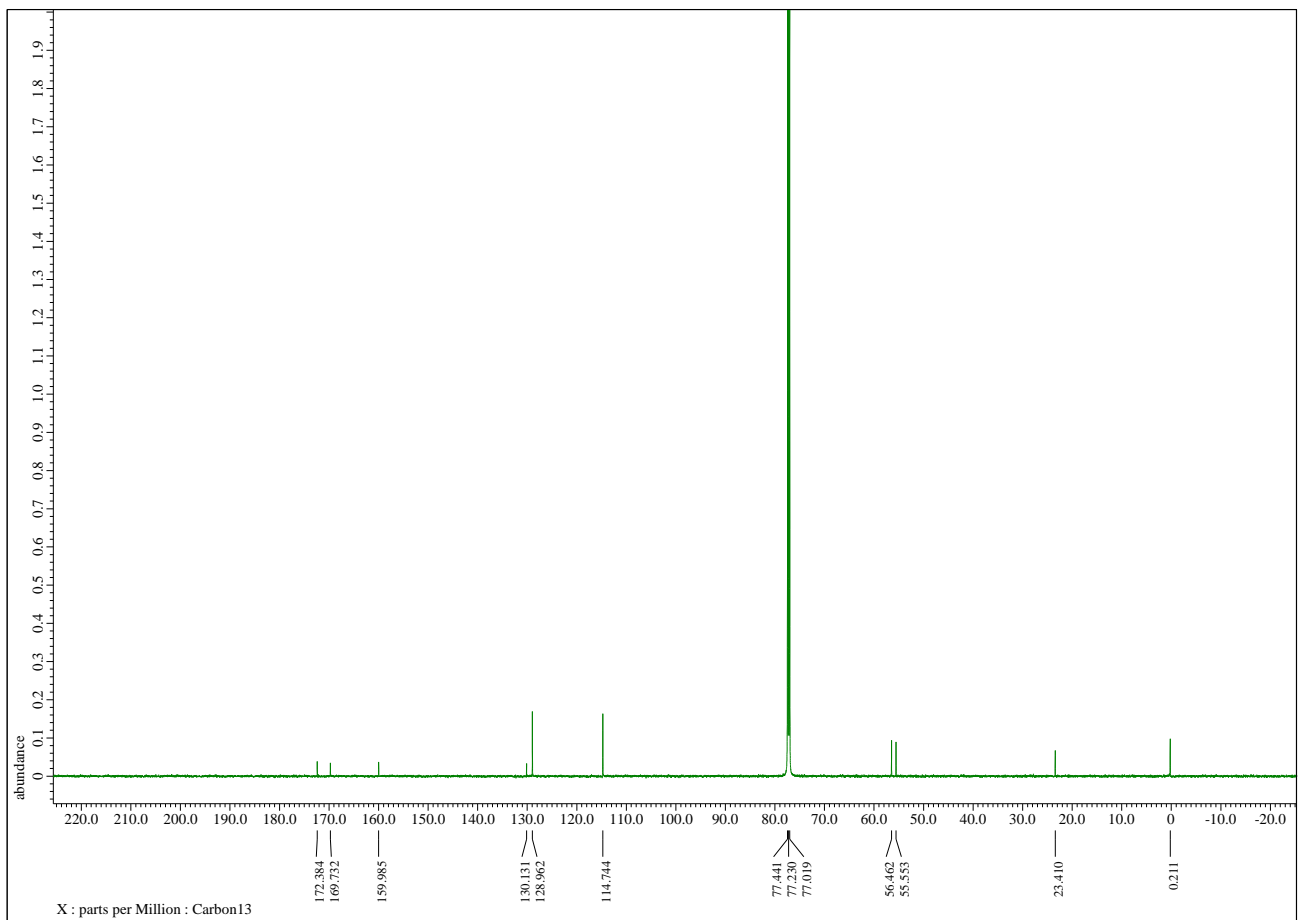
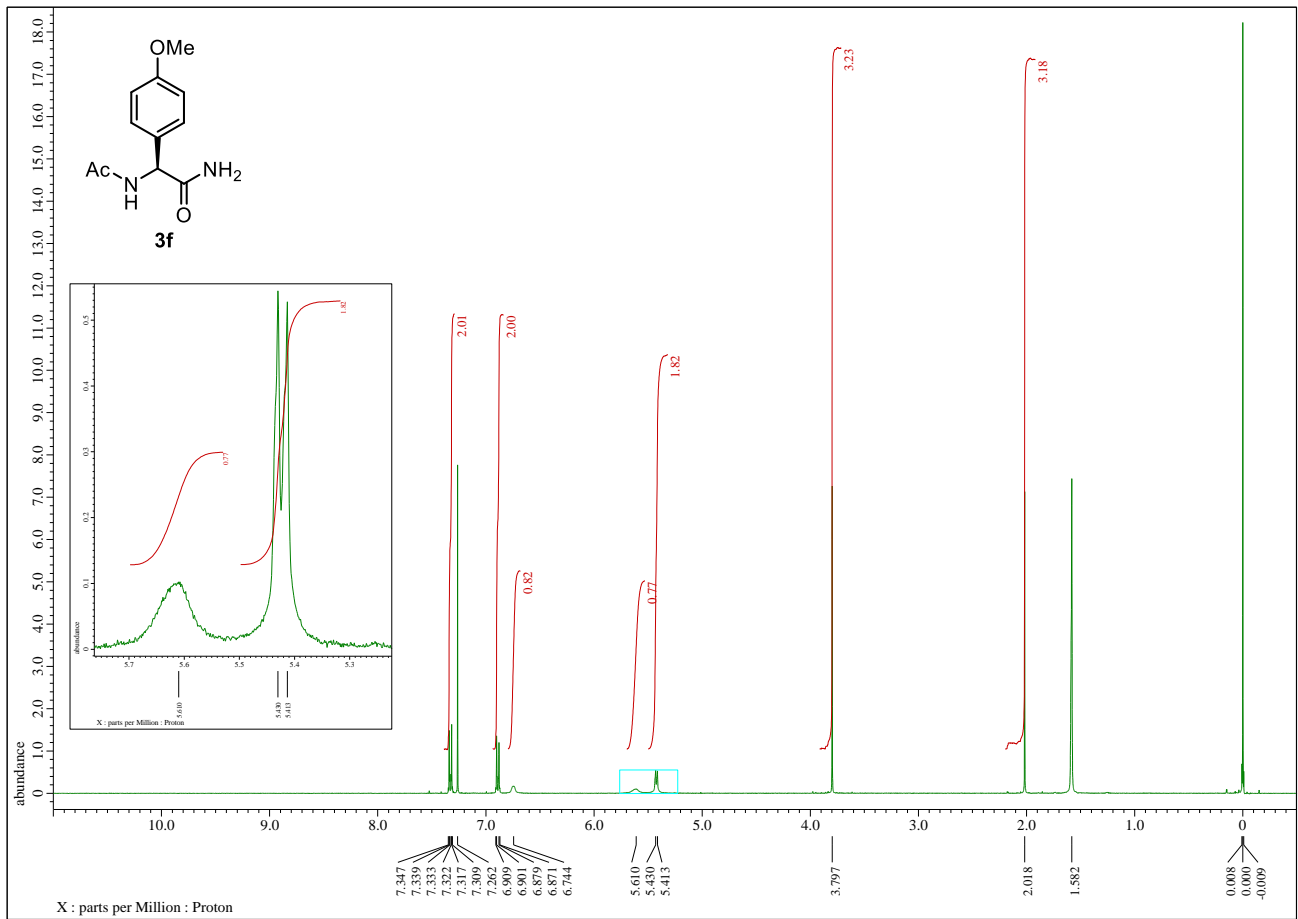


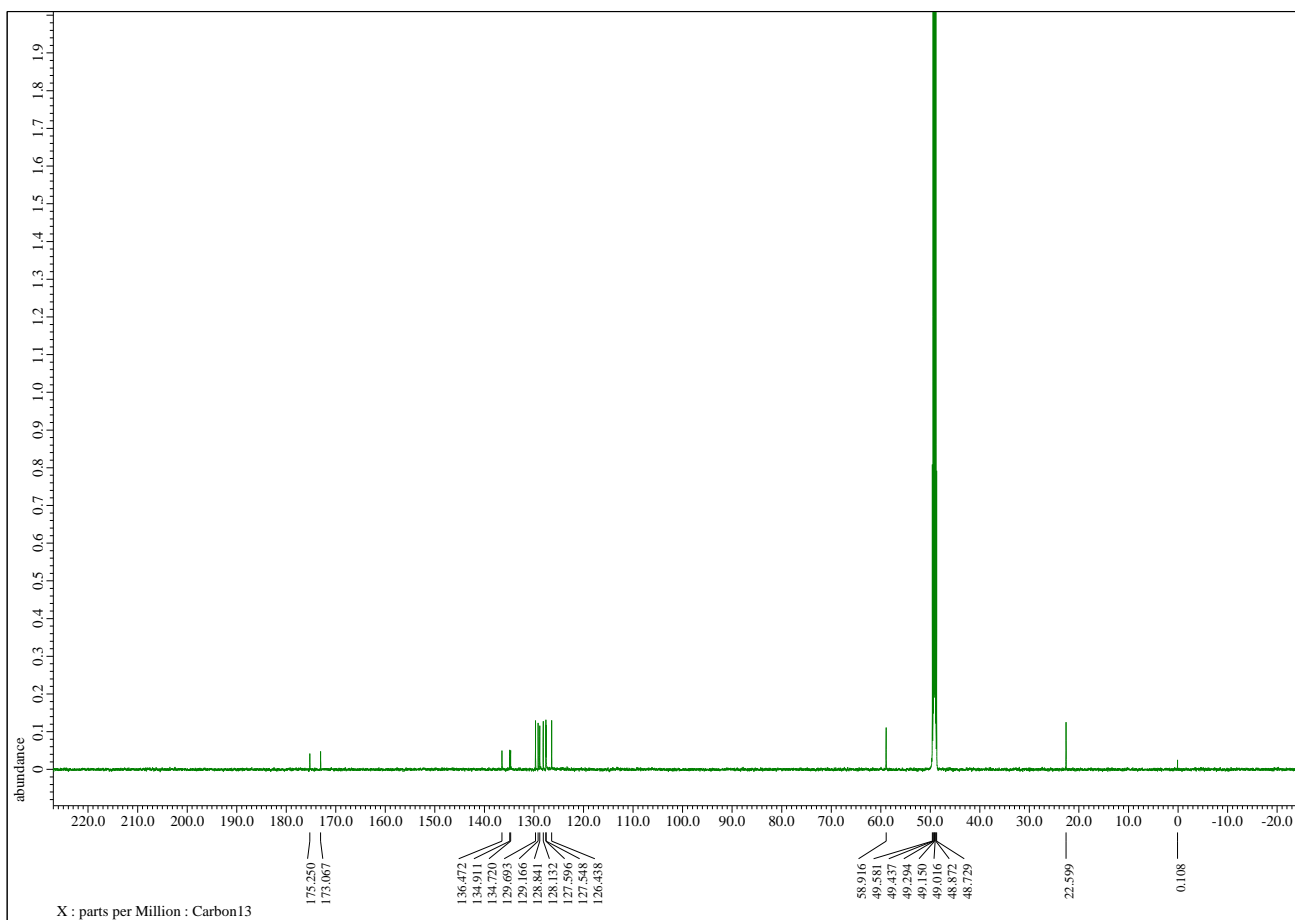
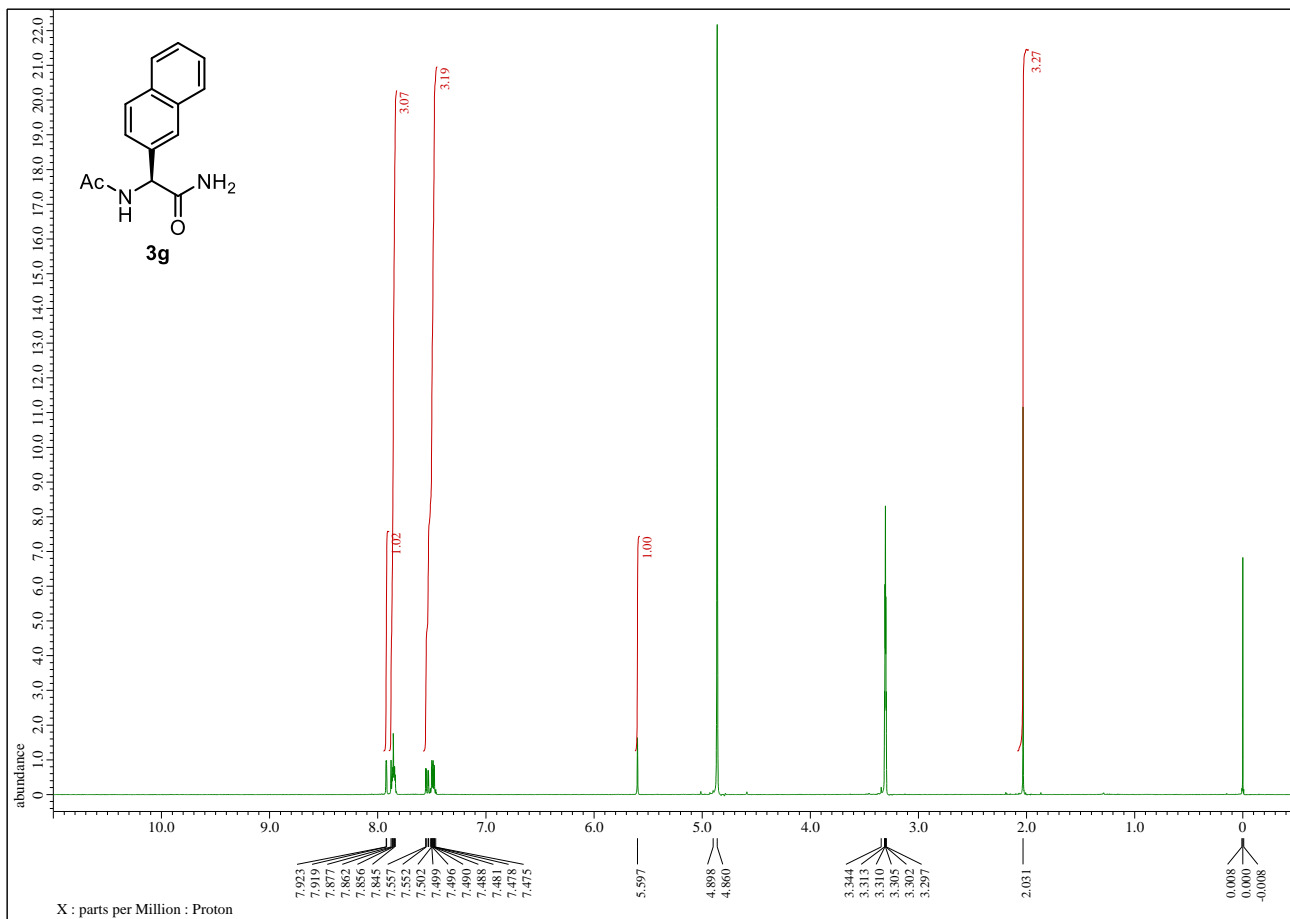


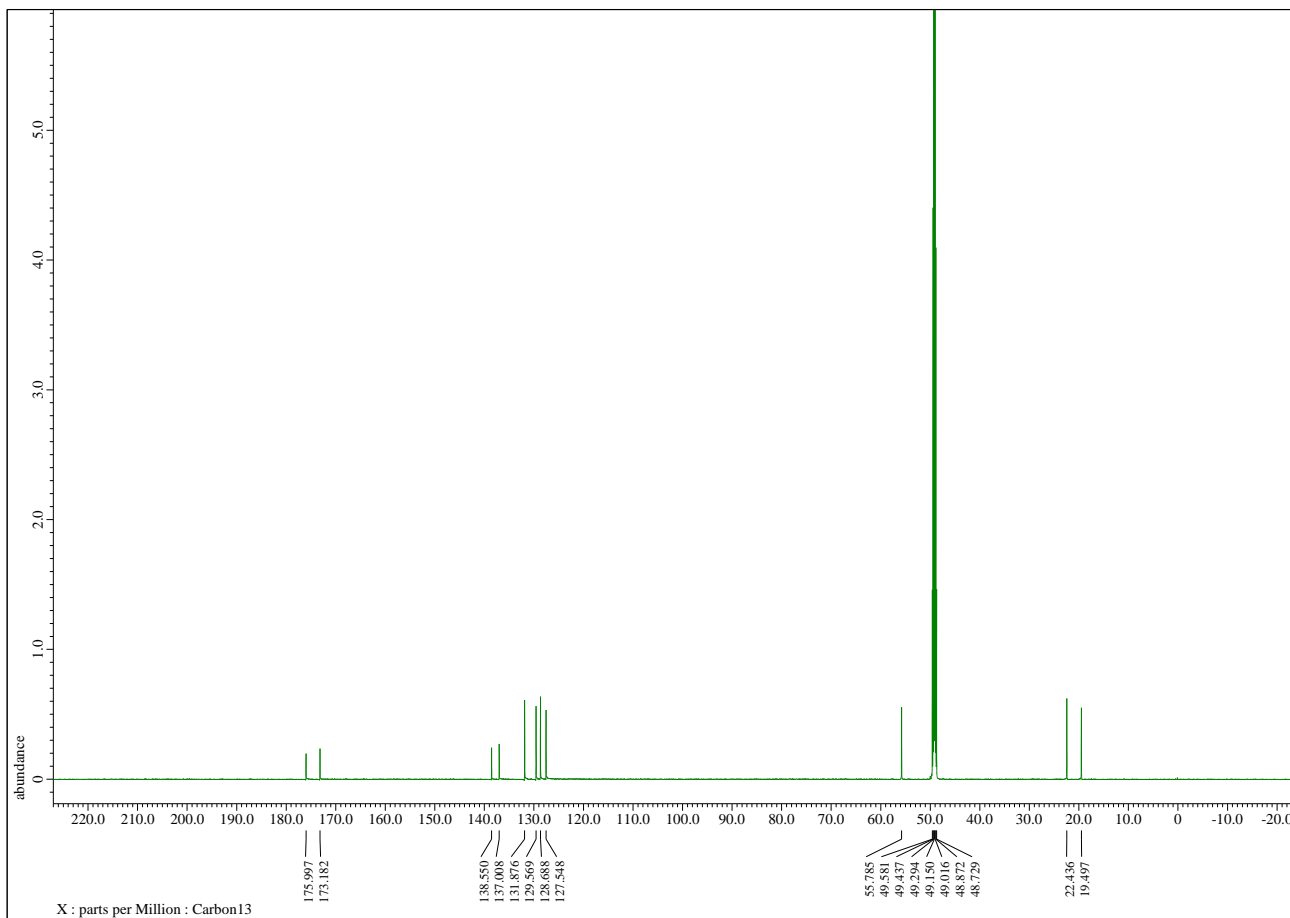
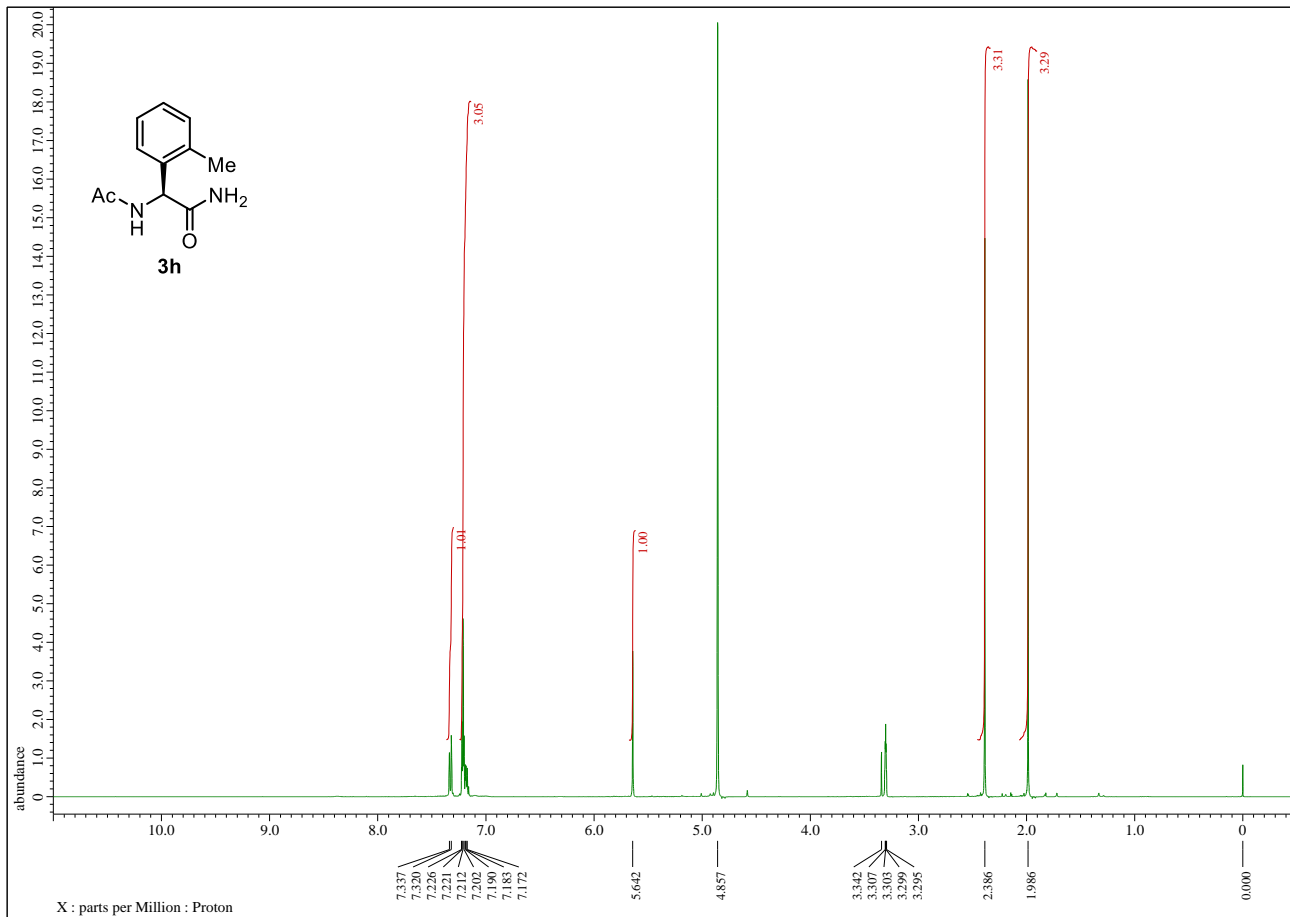


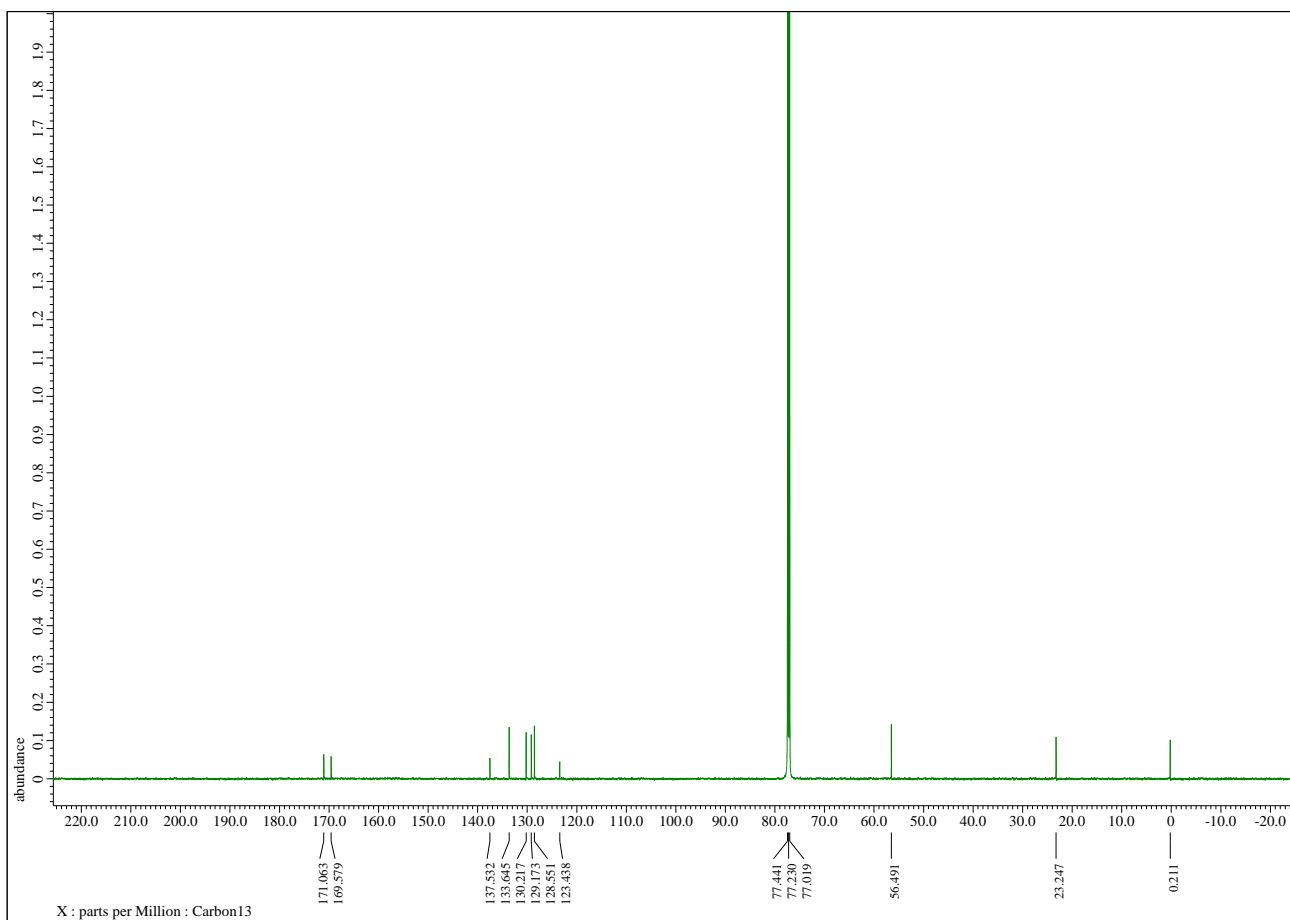
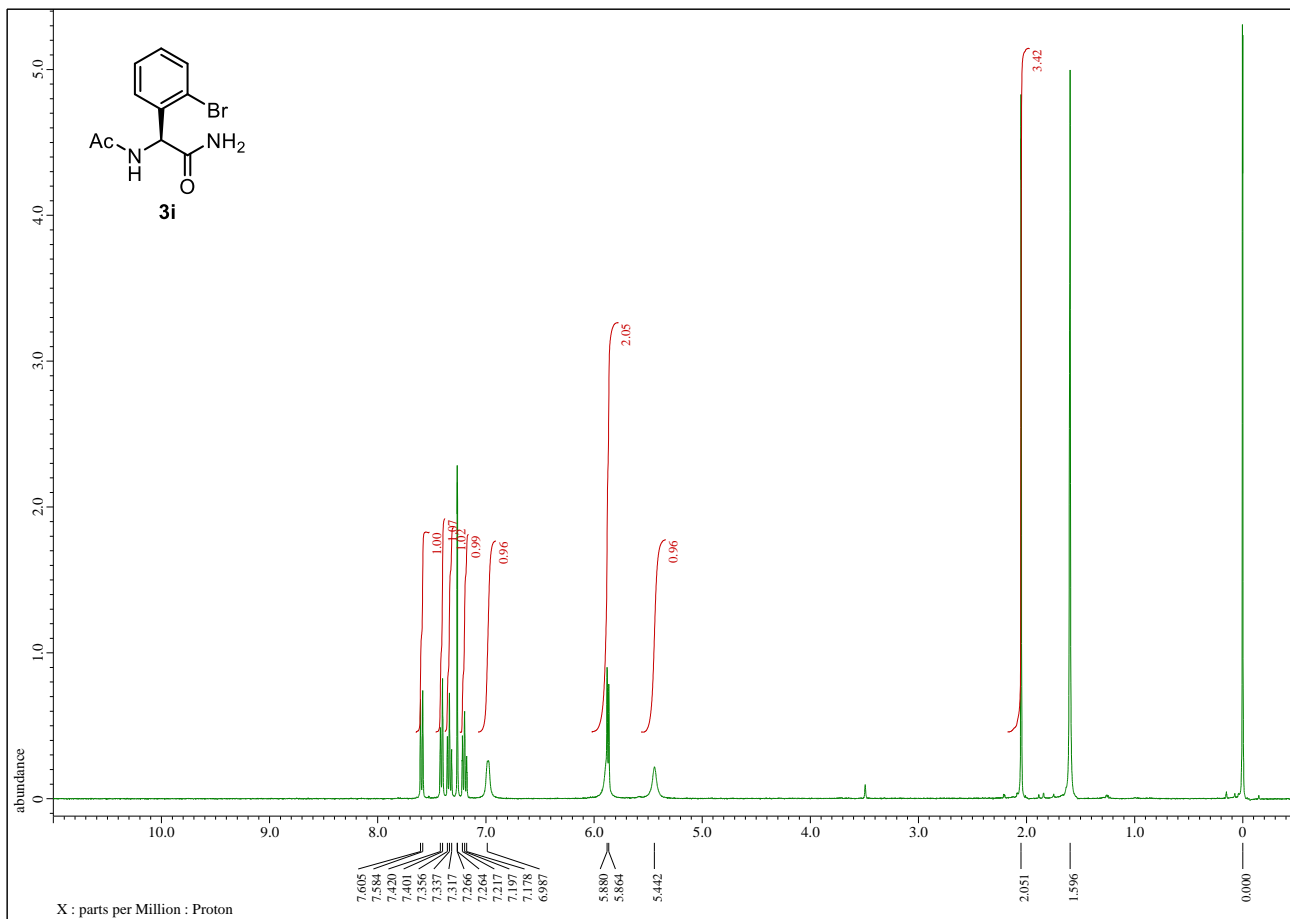




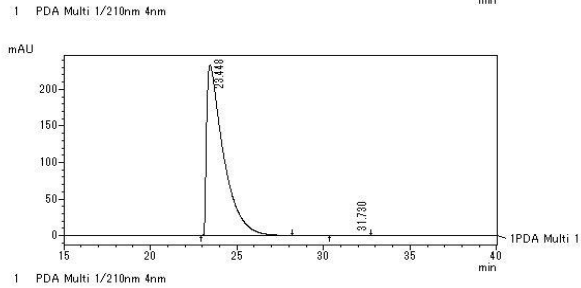
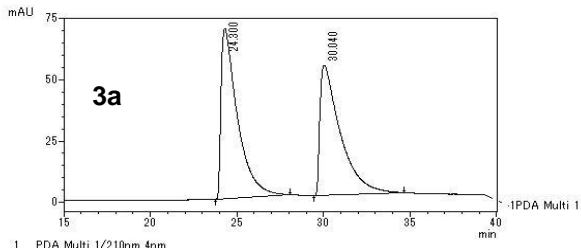






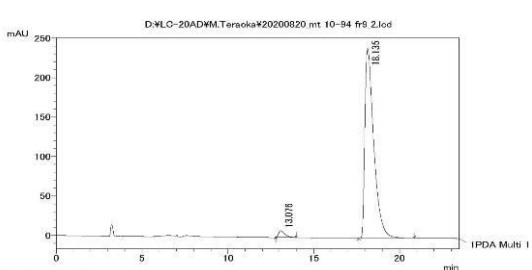
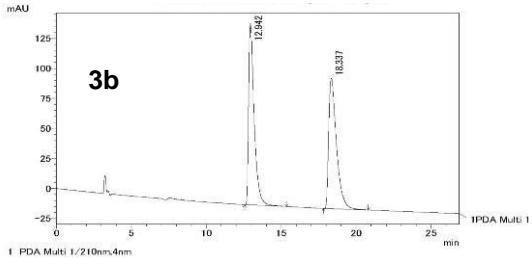


HPLC spectral date:



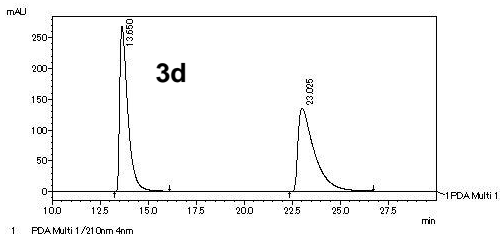
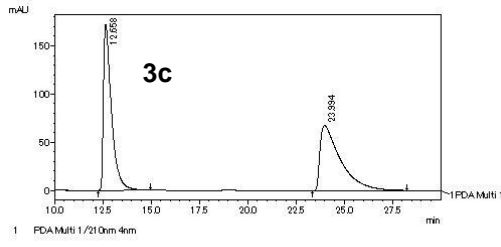
ピークデータ

ピーク番号	保持時間	面積	高さ	面積%	λmax
1	23.448	15830945	233309	89.904	206/258
2	31.730	15167	265	0.096	
合計		15846112	233574	100.000	



ピークデータ

ピーク番号	保持時間	面積	高さ	面積%	λmax
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2	18.136	2405	100.000		
合計		18136	2405	100.000	

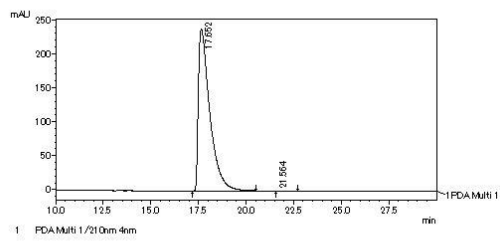
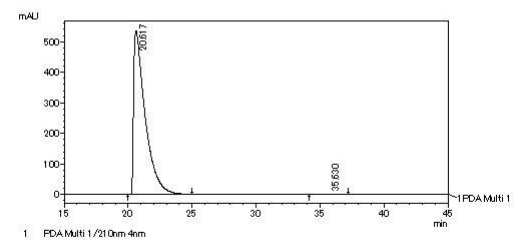
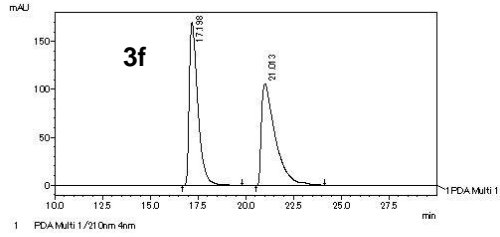
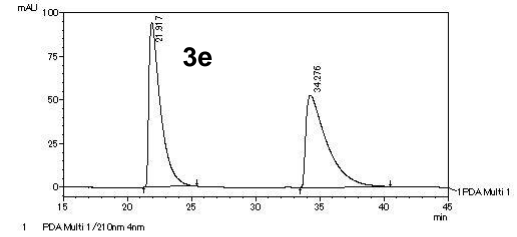


ピークデータ

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2	22.286	3204	69	0.026	246
合計		12118626	411343	100.000	

ピークデータ

ピーク番号	保持時間	面積	高さ	面積%	λmax
1	13.143	35112048	1110942	99.812	135/241/208
2	23.588	67964	1281	0.188	242/206
合計		35180011	1112223	100.000	

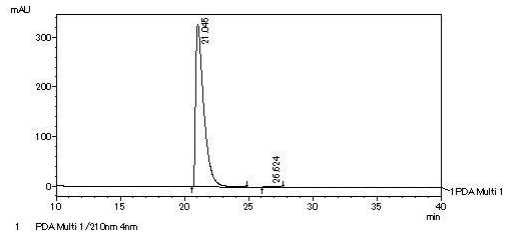
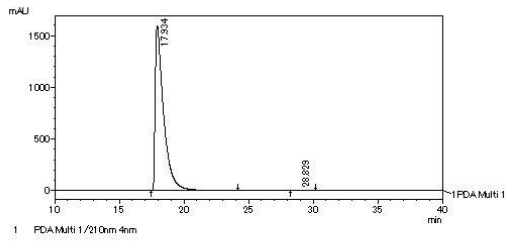
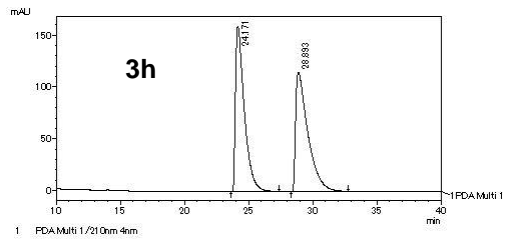
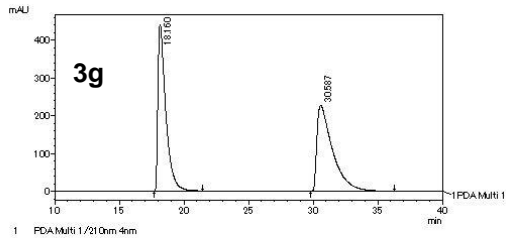


ピークデータ

ピーク番号	保持時間	面積	高さ	面積%	λmax
1	20.617	33708815	536067	89.833	206/263
2	35.630	39671	323	0.061	223
合計		33728486	536390	100.000	

ピークデータ

ピーク番号	保持時間	面積	高さ	面積%	λmax
1	17.652	3955282	238824	99.992	204/229/274
2	21.854	812	11	0.008	
合計		3956094	238835	100.000	

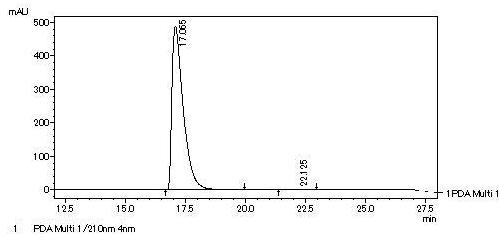
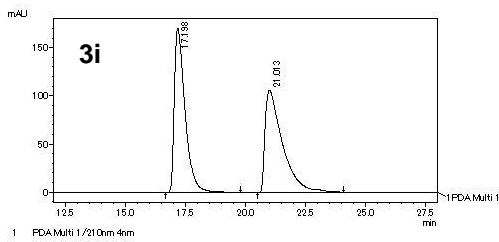


ピーク-7/L

ピーク	保持時間	面積	高さ	面積%	λmax
1	17.934	726827.75	153771.6	99.995	202/218/275/267
2	28.829	3734	73	0.005	206
合計		726831.0	153775.0	100.000	

ピーク-7/L

ピーク	保持時間	面積	高さ	面積%	λmax
1	21.006	1446173	338422	85.220	205/254
2	26.624	99118	2132	0.680	214/265/200
合計		14560846	338555	100.000	



ピーク-7/L

ピーク	保持時間	面積	高さ	面積%	λmax
1	17.065	18063467	489275	89.674	206/267
2	221.95	52467	1448	0.326	
合計		18063535	490724	100.000	