

Supporting Information

Enantioselective Biginelli Reaction: Crucial Dependence of the Organocatalyst on Sterics, Hydrogen Bonding and Reinforced Chirality

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Supporting Information

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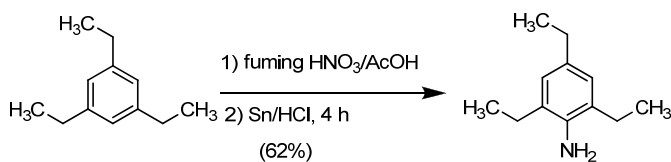
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General Aspects

^1H NMR spectra were recorded on 400 MHz and 500 MHz spectrometers. ^{13}C NMR spectra were recorded with 100/125 MHz NMR spectrometers with complete proton decoupling. IR spectra were recorded on a FT-IR spectrophotometer. Mass spectral analyses were carried out with ESI-Q^{TOF} Instrument. HPLC analyses were performed using OD-H column. Column chromatography was conducted with silica-gel 100-200 μ mesh. Tetrahydrofuran (THF) was freshly distilled over sodium/benzophenone prior to use. DCM was distilled over CaH_2 . Triethylamine and pyridine were distilled from KOH prior to use. 1,3,5-Triethylbenzene was prepared according to the literature reported procedure. Ethyl acetoacetate was distilled prior to use. Fuming HNO_3 was freshly prepared. Pentafluoroaniline, tritylamine, *o*-aminophenol were purchased and used as such.

Synthetic Procedures for the Preparation of the Intermediates and their Characterization Data

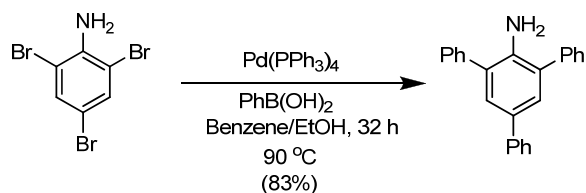
Synthesis of 2,4,6-triethylaniline¹



1,3,5-Triethylbenzene (2.0 g, 12.3 mmol) was taken in 10 mL of glacial AcOH and 5 mL of fuming HNO₃ was slowly added to it under ice cold conditions. The reaction mixture was stirred at rt for 2 h and then poured into crushed ice. The oil was extracted with EtOAc, washed with NaHCO₃, brine, dried and concentrated. Silica-gel column chromatography of the residue led to pure 2,4,6-triethyl nitrobenzene (1.9 g); yield 76%; IR (KBr) cm⁻¹ 1368, 1525, 2878, 2971; ¹H NMR (CDCl₃, 400 MHz) δ 1.19-1.24 (m, 9H), 2.55 (q, 4H, $J = 7.5$ Hz), 2.62 (q, 2H, $J = 7.6$ Hz), 6.95 (s, 2H).

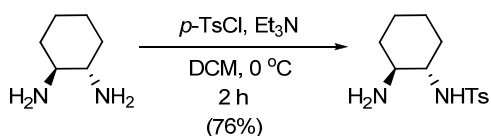
The nitro compound (1.8 g, 8.6 mmol) obtained from the above reaction was dissolved in EtOH and treated with Sn (3.0 g, 25.8 mmol) and Conc HCl (15 mL). The contents were heated at 70 °C for 2 h. Subsequently, the reaction mixture was cooled and the organic matter was extracted with EtOAc. The combined extract was washed with brine, dried and concentrated to get hold of 2,4,6-triethylaniline (1.2 g); yield 82%; IR (KBr) cm⁻¹ 1461, 1478, 1757, 2963, 3385, 3470; ¹H NMR (CDCl₃, 400 MHz) δ 1.06-1.23 (m, 9H), 2.45-2.59 (m, 6H), 6.75 (s, 2H).

Synthesis of 2,4,6-triphenylaniline²



Into an oven-dried 2-necked round bottom flask, cooled under N_2 atmosphere, was introduced 2,4,6-tribromoaniline (1.8 g, 5.4 mmol), phenylboronic acid (3.0 g, 24.5 mmol), NaHCO_3 (9.3 g), $\text{Pd(PPh}_3)_4$ (1.2 g, 1.0 mmol), 40 mL of benzene, 40 mL of ethanol and 20 mL of water. The reaction mixture was heated at $90\text{ }^\circ\text{C}$ for 32 h. The reaction mixture was cooled and the solvent evaporated. The residue was extracted with EtOAc, dried and concentrated to get hold of the crude product, which was further purified by silica gel column chromatography to obtain 2,4,6-triphenylaniline (1.4 g); yield 83%; IR (KBr) cm^{-1} 1155, 1326, 2872, 3269; ^1H NMR (CDCl_3 , 500 MHz) δ 7.22-7.28 (m, 2H), 7.37-7.41 (m, 6H), 7.43-7.49 (m, 3H), 7.53-7.60 (m, 6H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 126.5 \times 2, 127.5, 128.5 \times 2, 128.8, 129.0, 129.5, 131.3, 139.7, 140.2, 140.9.

Synthesis of *N*-((1*S*,2*S*)-2-aminocyclohexyl)-4-methylbenzenesulfonamide³



Trans-cyclohexyl-1,2-diamine (2.0 g, 17.5 mmol) was dissolved in dry DCM, cooled to $0\text{ }^\circ\text{C}$ and Et_3N was added. The reaction mixture was then stirred for 15 min at that temperature and *p*-toluenesulphonyl chloride (3.3 g, 17.5 mmol) was added. The reaction mixture was stirred at rt for 2 h. Subsequently, it was quenched with addition of water and extracted with CHCl_3 . The

combined extract was washed with brine, dried and concentrated to get hold of *N*-((1*S*,2*S*)-2-aminocyclohexyl)-4-methylbenzenesulfonamide (3.5 g); yield 76%; IR (KBr) cm^{-1} 1155, 1326, 2872, 3269; ^1H NMR (CDCl_3 , 500 MHz) δ 0.99-1.23 (m, 4H), 1.54-1.63 (m, 2H), 1.75-1.91 (m, 2H), 2.29-2.34 (m, 1H), 2.41 (s, 3H), 2.57-2.62 (m, 1H), 7.27 (d, 2H, $J = 8.0$ Hz), 7.75 (d, 2H, $J = 8.0$ Hz).

Preparation of Tritylammonium trifluoroacetate

Tritylamine (1.0 g, 3.86 mmol) was dissolved in dry THF (10 mL) and TFA (0.3 mL, 3.86 mmol) was added to it under ice cold condition and the reaction mixture was stirred for 2 h. The solvent was evaporated under reduced pressure, washed thoroughly with petroleum ether and dried in vacuo to obtain the trifluoroacetate salt of the trityl amine as a white hygroscopic solid.

Synthetic Procedures for the Preparation of the Catalysts and the Characterization Data. A representative procedure for the synthesis of (S)-*N*-(2,4,6-triphenylbenzene)pyrrolidine-2-carboxamide, **5** is described below. A similar procedure was followed for the synthesis of the remaining catalysts, i.e., **1**, **2**, **4** and **6-14**.

To a 2-necked round bottom flask containing Boc-L-proline (2.5 g, 11.6 mmol) in 30 mL dry THF was added Et_3N (1.17 g, 11.6 mmol) under N_2 atmosphere. The resultant solution was cooled to 0 °C. Subsequently, ethyl chloroformate (1.2 g, 11.8 mmol) was introduced drop wise over a period of 30 min. After the solution was stirred at this temperature for 1 h, 2,4,6-triphenyl aniline (1.0 g, 3.1 mmol) was added, under N_2 atmosphere, in small portions. The reaction mixture was stirred at 0 °C for 1 h, at rt for 2 h, and heated at reflux for 16 h; the reaction was

continually monitored by TLC analyses. At the end of the reaction, as judged by TLC analysis, the reaction mixture was cooled to rt and filtered. The filtrate was concentrated to get hold of the crude product, which was further purified by silica-gel column chromatography.

The above product (1.5 g, 3.0 mmol) was dissolved in 20 mL of MeOH, 10% Pd/C (0.05 g) was added and stirred under H₂ atm for 6 h. After completion of the reaction, the reaction mixture was filtered through celite and the filtrate was evaporated under reduced pressure to yield (S)-N-(2,4,6-triphenylbenzene)pyrrolidine-2-carboxamide, **5** (1.1 g, 94%) in almost pure form.

(S)-N-(Perfluorophenyl)pyrrolidine-2-carboxamide, 1:⁴ Yield 67 %; mp 82-84 °C; $[\alpha]_D^{27} = -36.46^\circ$ (c = 0.5, EtOH); IR (KBr) cm⁻¹ 1668, 2873, 2967, 3225, 3351; ¹H NMR (CDCl₃, 500 MHz) δ 1.76-1.85 (m, 2H), 2.04-2.07 (m, 1H), 2.19-2.26 (m, 1H), 2.99-3.04 (m, 1H), 3.08-3.13 (m, 1H), 3.96-3.97 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 26.2, 30.9, 47.4, 60.7, 112.0, 112.1, 112.2, 136.8, 138.7, 141.8, 143.8, 174.0; ESI-MS⁺ *m/z* Calcd for C₁₁H₉N₂OF₅ 281.0713 [M+H], found 281.0712.

(S)-N-(2-(*p*-Tosylamido)phenyl)prolinamide 2:⁵ Yield 83%; mp 134 °C; $[\alpha]_D^{27} = -11.87^\circ$ (c = 0.016, MeOH); IR (KBr) cm⁻¹ 1160, 1526, 1650, 2818, 3145, 3339; ¹H NMR (CDCl₃, 500 MHz) δ 1.69-1.75 (m, 2H), 1.88-1.95 (m, 1H), 2.16-2.23 (m, 1H), 2.37 (s, 3H), 2.93-3.01 (m, 1H), 3.03-3.07 (m, 1H), 2.23 (m, 1H), 2.37(s, 3H), 2.88-2.92 (m, 1H), 3.03-3.08 (m, 1H), 3.85 (dd, 1H, *J*₁ = 9.4 Hz, *J*₂ = 5.2 Hz), 7.05-7.09 (m, 1H), 7.14-7.19 (m, 4H), 7.32-7.34 (m, 1H), 7.54 (d, 2H), 9.85 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 21.5, 26.2, 30.7, 47.2, 60.6, 122.5, 125.8, 127.0, 127.4, 127.8, 128.3, 129.4, 132.8, 137.1, 143.3, 174.7; ESI-MS⁺ *m/z* Calcd for C₁₈H₂₁N₃SO₃ 360.1381 [M+H], found 360.1381.

(S)-N-(2-Hydroxyphenyl)pyrrolidine-2-carboxamide 4:⁷ Yield 80%; IR (KBr) cm^{-1} 1530, 1640, 3223, 3354; ^1H NMR (CDCl_3 , 500 MHz) δ 1.77-1.80 (m, 2H), 2.00-2.22 (m, 1H), 2.23-2.26 (m, 1H), 3.00-3.15 (m, 2H), 3.99 (brs, 1H), 6.82 (t, 1H, $J = 8.2$ Hz), 6.94 (d, 1H, $J = 8.2$ Hz), 6.99 (d, 1H, $J = 8.2$ Hz), 7.09 (t, 1H, $J = 8.2$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 26.3, 31.0, 47.4, 60.3, 120.0, 120.1, 122.2, 125.1, 127.2, 149.2, 175.4; ESI-MS⁺ m/z Calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_3$ 264.1348 [M+H], found 264.1348.

(S)-N-(2,4,6-Triphenylbenzene)pyrrolidine-2-carboxamide 5: Yield 68%; mp 160-162 °C; $[\alpha]_D^{27} = -10.0^\circ$ ($c = 0.1$, EtOH); IR (KBr) cm^{-1} 1495, 1677, 3030, 3186, 3474; ^1H NMR (CDCl_3 , 500 MHz) δ 1.18-1.27 (m, 1H), 1.33-1.41 (m, 2H), 1.54 (brs, 1H), 1.72-1.78 (m, 1H), 2.42-2.47 (m, 1H), 2.67-2.72 (m, 1H), 3.35 (dd, 1H, $J_1 = 9.4$ Hz, $J_2 = 4.8$ Hz), 7.24-7.56 (m, 17 H), 9.02 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 25.1, 29.8, 46.8, 59.9, 127.3, 127.4, 127.7, 128.2, 128.6, 128.9, 129.1, 130.4, 139.9, 140.2, 140.6, 141.3, 171.4; ESI-MS⁺ m/z Calcd for $\text{C}_{29}\text{H}_{26}\text{N}_2\text{O}$ 419.2123 [M+H], found 419.2124.

(S)-N-(2,4,6-Triethylbenzene)pyrrolidine-2-carboxamide 6: Yield 75%; mp 158-160 °C; $[\alpha]_D^{27} = -21.5^\circ$ ($c = 0.5$, EtOH); IR (KBr) cm^{-1} 1657, 2861, 2964, 3253; ^1H NMR (CDCl_3 , 400 MHz) δ 1.05-1.21 (m, 9H), 1.74-1.79 (m, 2H), 2.00-2.04 (m, 1H), 2.17-2.24 (m, 1H), 2.43 (q, 4H, $J = 7.5$ Hz), 2.50 (q, 2H, $J = 7.5$ Hz), 2.95-3.10 (m, 2H), 3.94-3.97 (m, 1H), 6.85 (s, 2H), 9.10 (brs, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 14.6, 15.5, 25.0, 26.2, 28.6, 30.9, 47.4, 60.7, 125.9, 130.3, 140.9, 143.4, 173.3; ESI-MS⁺ m/z Calcd for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}$ 275.2123 [M+H], found 275.2124.

(S)-N-Tritylpyrrolidine-2-carboxamide 7: Yield 85%; mp 92-94 °C; $[\alpha]_D^{27} = -10.0^\circ$ ($c = 0.5$, EtOH); IR (KBr) cm^{-1} 1445, 1491, 1674, 3313, 3470; ^1H NMR (CDCl_3 , 500 MHz) δ 1.71-1.75

(m, 2H), 1.91-1.96 (m, 1H), 2.03-2.09 (m, 1H), 2.93-2.98 (m, 1H), 3.03-3.07 (m, 1H), 3.81-3.84 (m, 1H), 7.16-7.30 (m, 15 H), 8.99 (brs, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 26.2, 30.5, 47.3, 61.3, 69.7, 127.0, 128.0, 128.7, 145.0, 173.3; ESI- MS^+ m/z Calcd for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}$ 357.1966 [M+H], found 357.1962.

(2S,4R)-4-Hydroxy-N-phenylpyrrolidine-2-carboxamide, 8:⁸ Yield 88%; mp 120-122 °C; $[\alpha]^{27}_{\text{D}} = -26.0^\circ$ (c = 0.5, EtOH); IR (KBr) cm^{-1} 1553, 1661, 3140, 3288; ^1H NMR (CDCl_3 , 500 MHz) δ 2.00-2.05 (m, 1H), 2.35-2.40 (m, 1H), 2.90 (brs, 1H), 3.11-3.17 (m, 1H), 4.21-4.28 (m, 1H), 4.47 (brs, 1H), 7.07 (t, 1H, $J = 7.3$ Hz), 7.27-7.31 (m, 2H), 7.58 (d, 2H, $J = 8.2$ Hz), 9.83 (d, 1H, $J = 17.9$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 40.1, 55.3, 60.4, 73.4, 120.7, 125.0, 129.3, 137.8, 172.9; ESI- MS^+ m/z Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$ 207.1133 [M+H], found 207.1130.

(2S,4R)-N-Hydroxy-N-(perfluorophenyl)pyrrolidine-2-carboxamide, 9: Yield 74%; mp 128-130 °C; $[\alpha]^{27}_{\text{D}} -18.0^\circ$ (c = 0.5, EtOH); IR (KBr) cm^{-1} 1502, 1690, 3235, 3273; ^1H NMR (CDCl_3 , 500 MHz) δ 2.05-2.11 (m, 1H), 2.35 (dd, 1H, $J_1 = 14.2$ Hz, $J_2 = 8.7$ Hz), 2.89 (dd, 1H, $J_1 = 12.6$, $J_2 = 3.2$ Hz, Hz), 3.11 (dd, 1H, $J_1 = 12.6$ Hz, $J_2 = 1.8$ Hz), 4.17-4.23 (m, 1H), 4.52 (brs, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 40.0, 55.5, 60.0, 73.4, 173.7; ESI- MS^+ m/z Calcd for $\text{C}_{11}\text{H}_9\text{F}_5\text{N}_2\text{O}_2$ 297.0662 [M+H], found 297.0660.

(2S,4R)-4-Hydroxy-N-(2-hydroxyphenyl)pyrrolidine-2-carboxamide, 10: Yield 82%; mp 138-140 °C; $[\alpha]^{27}_{\text{D}} = -19.2^\circ$ (c = 0.5, EtOH); IR (KBr) cm^{-1} 1545, 1661, 3284; ^1H NMR (CDCl_3 , 500 MHz) δ 1.97-2.02 (m, 1H), 2.29-2.34 (m, 1H), 2.82 (dd, 1H, $J_1 = 12.6$ Hz, $J_2 = 3.0$ Hz), 3.06 (d, 1H, $J = 12.6$ Hz), 4.14 (t, 1H, $J = 8.4$ Hz), 4.46 (s, 1H), 6.78 (d, 1H, $J = 7.3$ Hz), 6.86 (d, 1H, $J = 8.0$ Hz), 6.95 (t, 1H, $J = 8.4$ Hz), 7.03 (t, 1H, $J = 8.0$ Hz), 9.91 (brs, 1H); ^{13}C NMR

(CDCl₃, 125 MHz) δ 39.1, 54.6, 59.4, 71.7, 115.1, 118.7, 119.4, 123.6, 125.3, 146.3, 172.8; ESI-MS⁺ m/z Calcd for C₁₁H₁₄N₂O₃ 222.1006 [M⁺], found 222.1004

(2S,4R)-4-Hydroxy-N-((1S,2S)-2-(4-methylphenylsulfonamido)cyclohexyl)-pyrrolidine-2-carboxamide, 11: Yield 85%; mp 190-192 °C; $[\alpha]^{27}_D = +34.0^\circ$ (c = 0.5, EtOH); IR (KBr) cm⁻¹ 1164, 1530, 1636, 2953, 3124, 3288, 3362; ¹H NMR (CDCl₃, 500 MHz) δ 1.08-1.32 (m, 4H), 1.59-1.61 (m, 1H), 1.69 (d, 2H, $J = 11.4$ Hz), 1.99-2.05 (m, 4H), 2.21-2.26 (m, 1H), 2.39 (s, 3H), 2.84 (d, 1H, $J = 3.0$ Hz), 2.85-2.87 (m, 1H), 3.96 (t, 1H, $J = 8.4$ Hz), 4.43 (s, 1H), 7.24 (d, 2H, $J = 6.9$ Hz), 7.69 (d, 2H, $J = 8.4$ Hz), 7.89 (d, 1H, $J = 9.2$ Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 21.6, 24.7 \times 2, 32.5, 33.5, 40.0, 51.7, 55.1, 59.0, 59.6, 73.5, 126.7, 129.6, 139.5, 143.0, 176.5; ESI-MS⁺ m/z Calcd for C₁₈H₂₇N₃O₄S 382.1800 [M+H], found 382.1804.

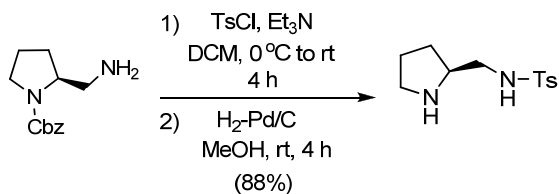
(2S,4R)-4-Hydroxy-N-tritylpyrrolidine-2-carboxamide, 12: Yield 84%; mp 204-206 °C; $[\alpha]^{27}_D = -21.1^\circ$ (c = 0.5, EtOH); IR (KBr) cm⁻¹ 1509, 1664, 3253, 3322, 3465; ¹H NMR (CDCl₃, 500 MHz) δ 1.80 (t, 1H, $J = 13$ Hz), 2.57 (dd, 1H, $J_1 = 13.4$ Hz, $J_2 = 6.9$ Hz), 3.03 (brs, 1H), 3.30 (brs, 1H), 4.45 (brs, 1H), 5.00 (brs, 1H), 7.08-7.10 (m, 6H), 7.24-7.27 (m, 9H), 7.82 (brs, 1H), 9.93 (brs, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 39.7, 55.4, 60.3, 69.8, 73.1, 127.0, 128.0, 144.9, 173.0; ESI-MS⁺ m/z Calcd for C₂₄H₂₄N₂O₂ 373.1916 [M+H], found 373.1914.

(2S,4R)-4-Hydroxy-N-(2,4,6-triethylphenyl)pyrrolidine-2-carboxamide, 13: Yield 76%; mp 154-156 °C; $[\alpha]^{27}_D = +4.0^\circ$ (c = 0.5, EtOH); IR (KBr) cm⁻¹ 1531, 1658, 2930, 2963, 3263; ¹H NMR (CDCl₃, 500 MHz) δ 1.46 (t, 6H, $J = 7.3$ Hz), 1.20 (t, 3H, $J = 7.3$ Hz), 2.10-2.05 (m, 1H), 2.34-2.39 (m, 1H), 2.49 (q, 4H, $J = 7.8$ Hz), 2.58 (q, 2H, $J = 7.8$ Hz), 2.74 (brs, 1H), 2.87-2.90 (m, 1H), 2.08-2.10 (m, 1H), 4.19 (t, 1H, $J = 7.8$ Hz), 4.45 (brs, 1H), 6.91 (s, 2H), 9.13 (brs, 1H);

^{13}C NMR (CDCl_3 , 125 MHz) δ 14.6, 15.6, 25.1, 28.7, 40.2, 55.5, 60.0, 73.3, 126.0, 130.0, 140.9, 143.6, 173.7; ESI- MS^+ m/z Calcd for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_2$ 291.2072 $[\text{M}+\text{H}]$, found 291.2076.

(2S,4R)-4-Hydroxy-N-(2,4,6-triphenylbenzene)pyrrolidine-2-carboxamide, 14: Yield 76%; mp 180-182 °C; $[\alpha]_D^{27} = +5.8^\circ$ ($c = 0.5$, EtOH); IR (KBr) cm^{-1} 1531, 1658, 2930, 2963, 3263; ^1H NMR (CDCl_3 , 400 MHz) δ 1.15-1.18 (m, 1H), 1.87-1.93 (m, 1H), 2.39 (d, 1H, $J = 9.7$ Hz), 2.73 (d, 1H, $J = 11.7$ Hz), 3.87 (t, 1H, $J = 8.2$ Hz), 4.09 (s, 1H), 7.22-7.37 (m, 13 H), 7.50-7.56 (m, 4 H), 9.01 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 37.8, 54.4, 58.9, 70.9, 127.3, 127.6, 128.1, 128.2, 128.6, 128.8, 129.0, 138.6, 139.5, 141.0, 141.2, 142.0, 167.7; ESI- MS^+ m/z Calcd for $\text{C}_{29}\text{H}_{26}\text{N}_2\text{O}_2$ 435.2072 $[\text{M}+\text{H}]$, found 435.2074.

Preparation of (S)-4-methyl-N-(pyrrolidinyl-2-methyl)benzenesulfonamide 3.⁹



The synthesis was done following the literature reported procedure.⁹

(S)-4-Methyl-N-(pyrrolidinyl-2-methyl)benzenesulfonamide 3:⁹ Yield 84%; IR (KBr) cm^{-1} 1155, 1326, 2872, 3269; ^1H NMR (CDCl_3 , 500 MHz) δ 1.23-1.37 (m, 1H), 1.60-1.83 (m, 3H), 2.41 (s, 3H), 2.66 (dd, 1H, $J_1 = 12$ Hz, $J_2 = 7.9$ Hz), 2.71-2.76 (m, 1H), 2.84-2.88 (m, 1H), 2.93 (dd, 1H, $J_1 = 12.0$ Hz, $J_2 = 4.1$ Hz), 3.23-3.28 (m, 1H), 7.28 (d, 2H, $J = 8.2$ Hz), 7.72 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) 21.6, 25.8, 28.9, 46.3, 47.0, 57.5, 127.1, 129.7, 137.1, 143.3.

¹H and ¹³C NMR Spectral Reproductions of the Catalysts 1-16

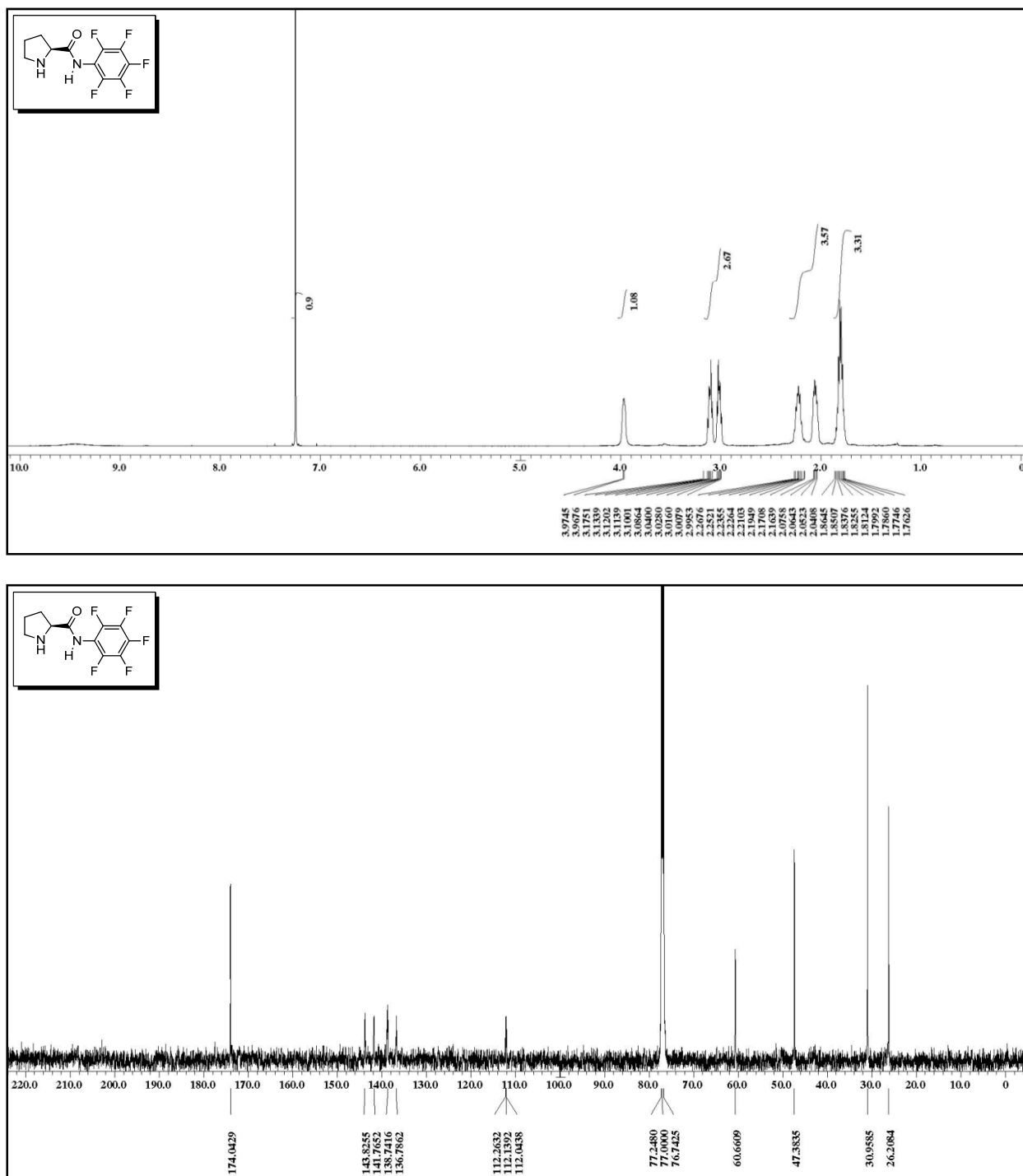


Figure S1. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectra of (S)-N-(perfluorophenyl)pyrrolidine-2-carboxamide, **1**.

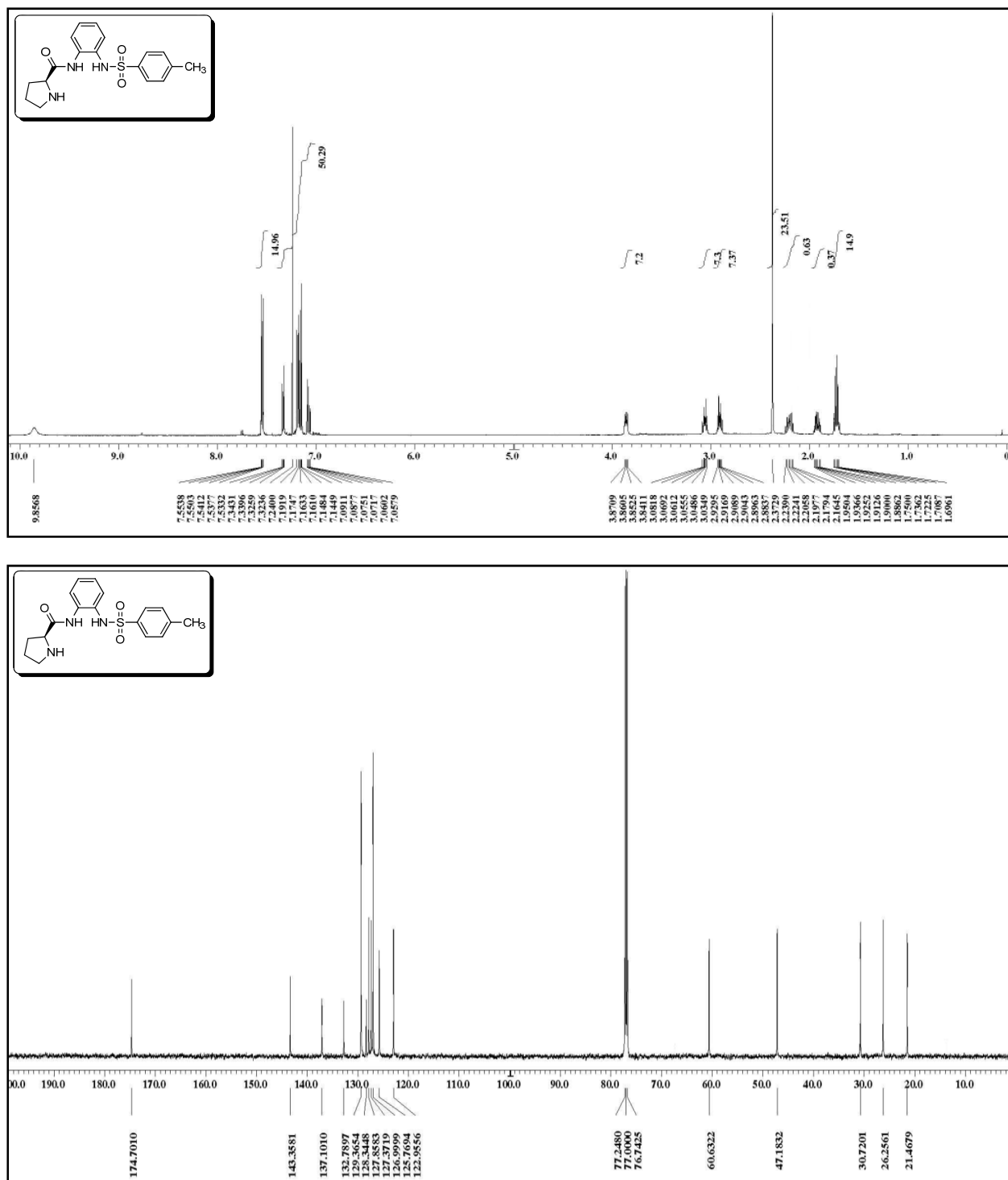


Figure S2. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectra of (S)-N-(2-(p-tosylamido)phenyl)prolinamide **2**.

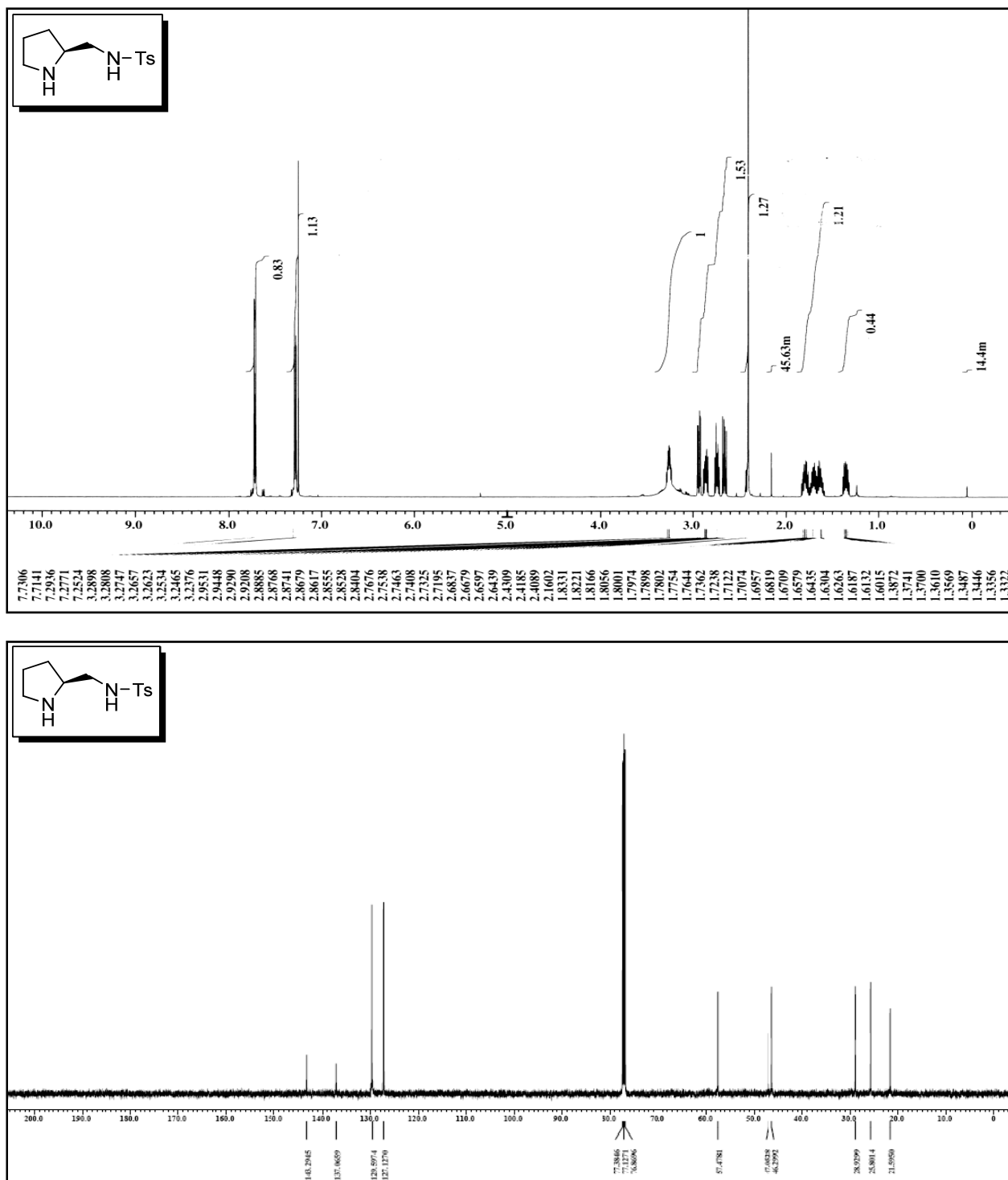


Figure S3. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 Hz) spectrum of (S)-4-methyl-N-(pyrrolidin-2-yl)methylbenzenesulfonamide **3**.

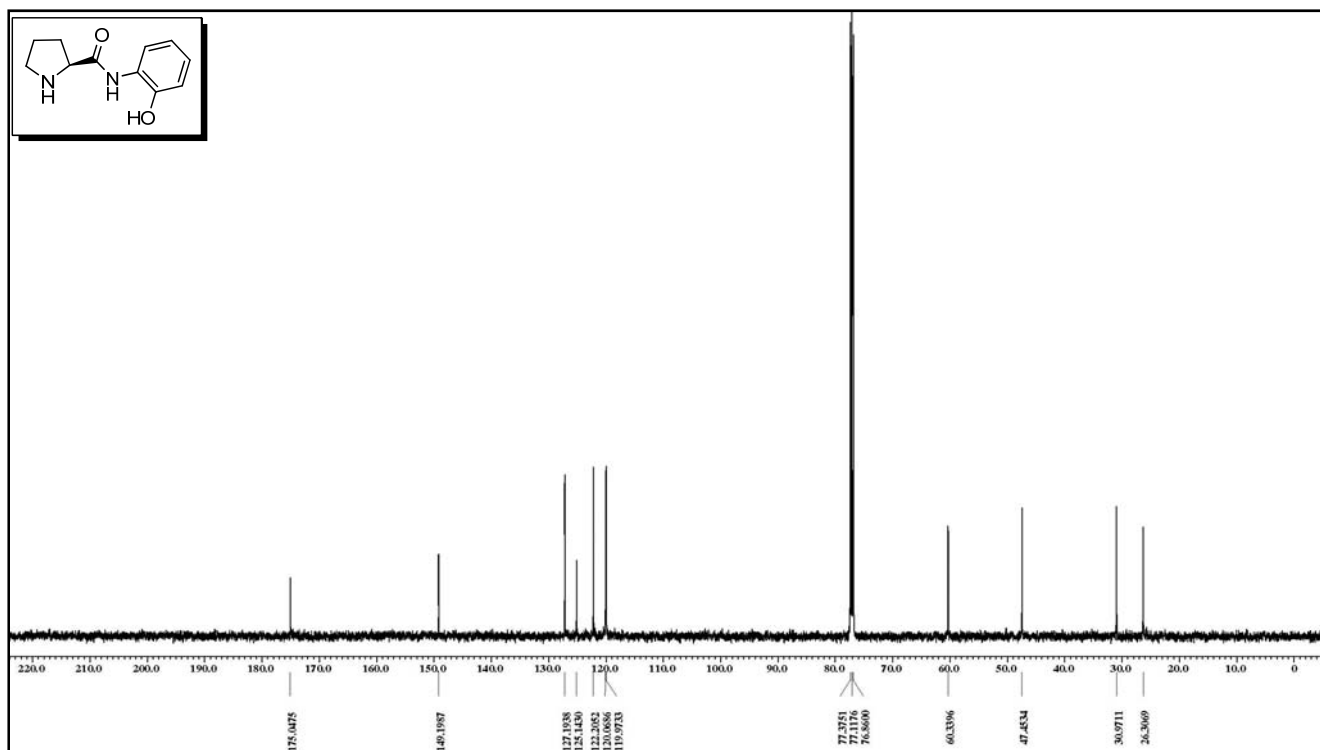
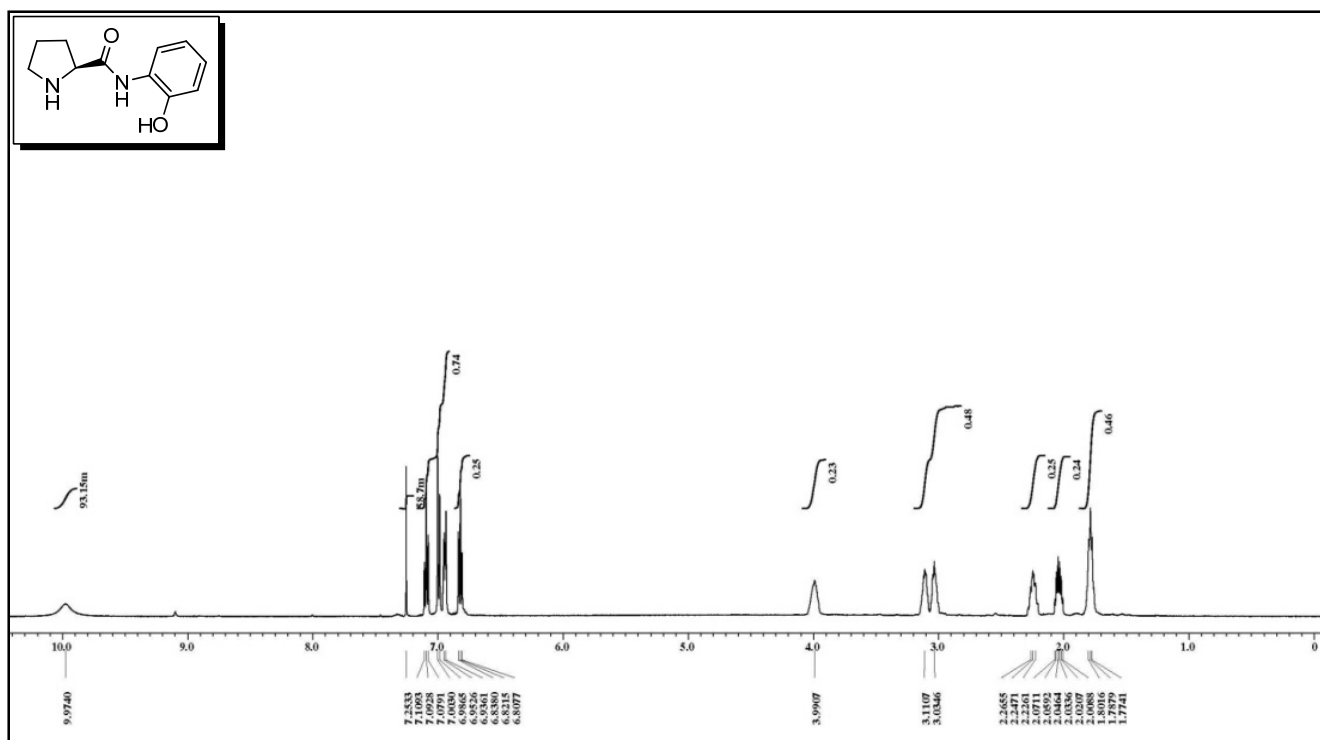


Figure S4. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectra of (S)-N-(2-hydroxyphenyl)pyrrolidine-2-carboxamide **4**.

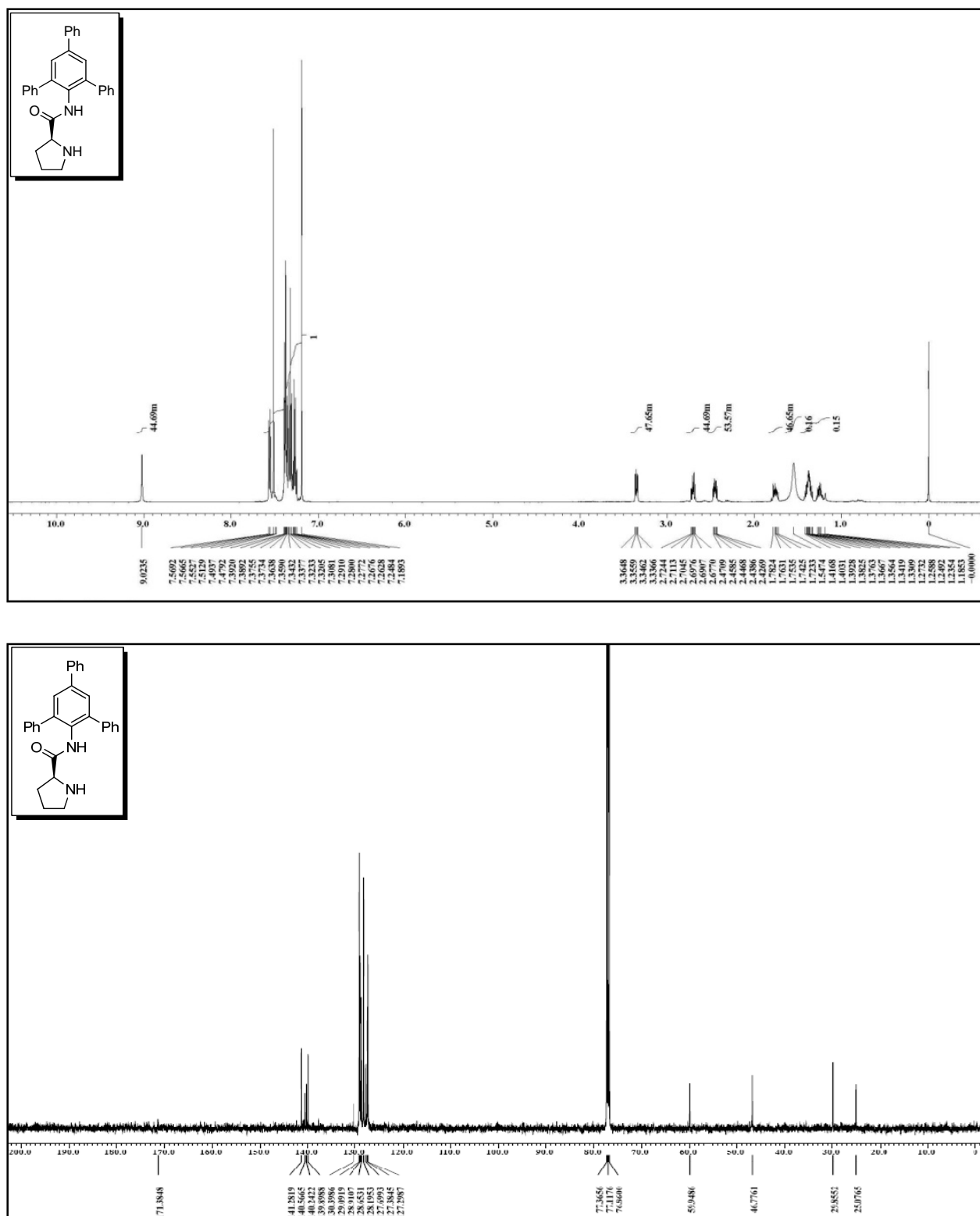


Figure S5. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 100 MHz) spectra of (S)-N-(2,4,6-triphenylphenyl)pyrrolidine-2-carboxamide **5**.

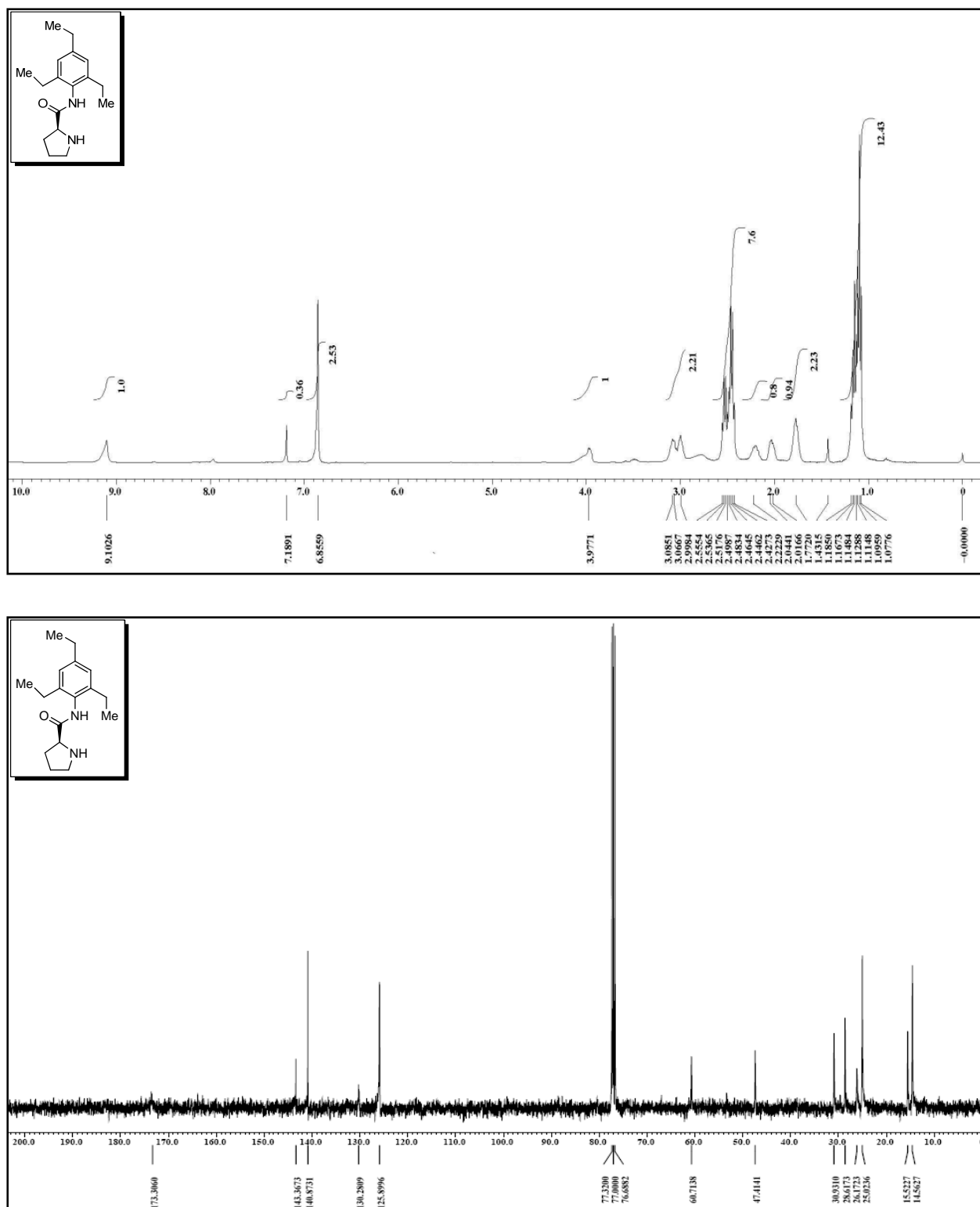


Figure S6. ¹H NMR (CDCl₃, 400 MHz) and ¹³C NMR (CDCl₃, 100 MHz) spectra of (S)-N-(2,4,6-triethylbenzene)pyrrolidine-2-carboxamide **6**.

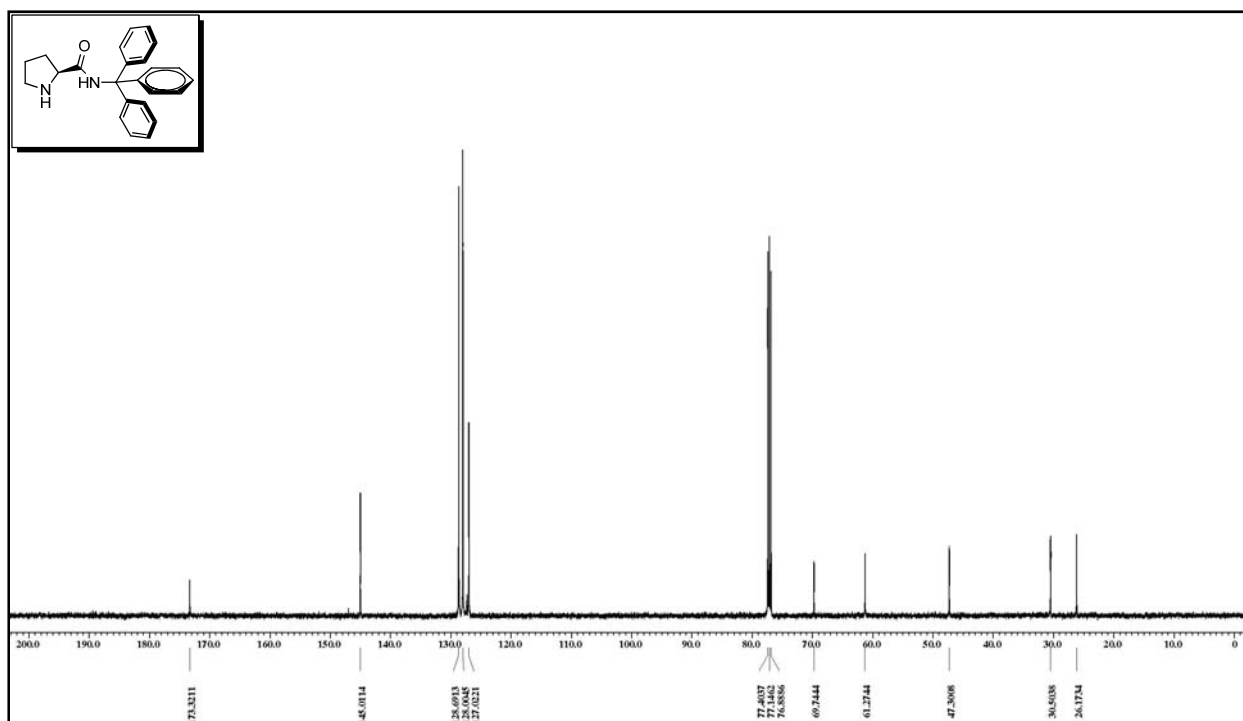
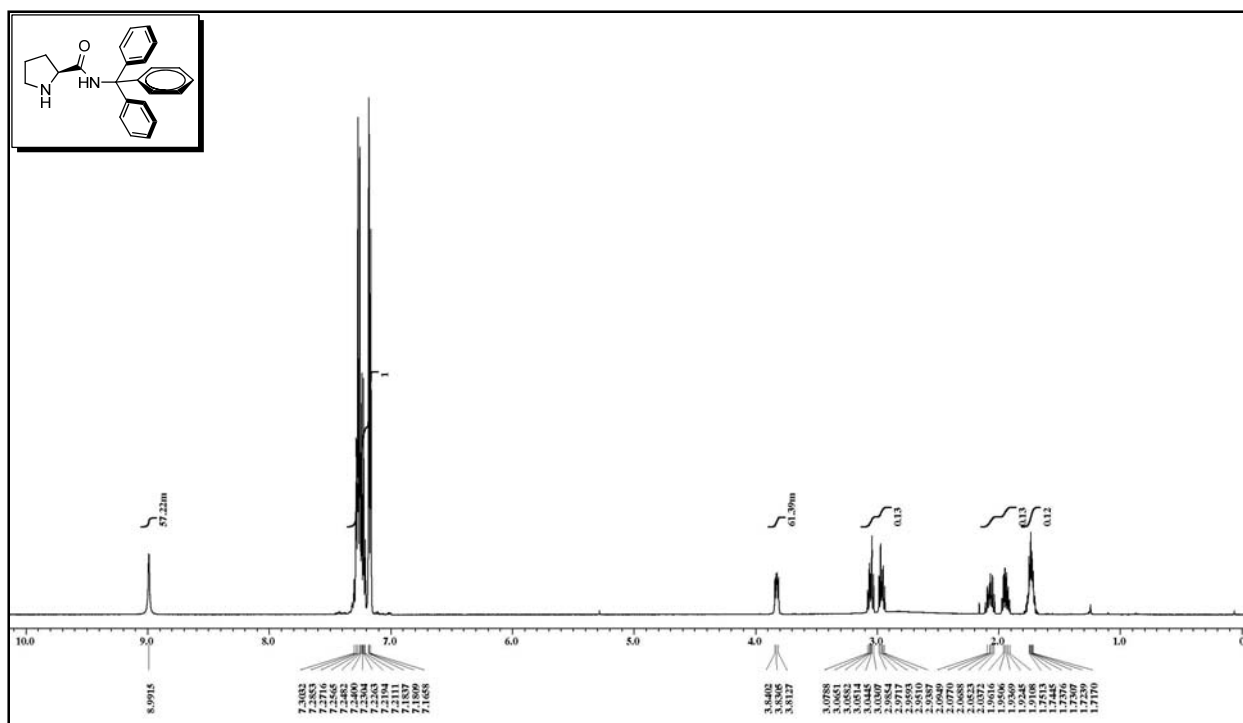


Figure S7. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectra of (S)-N-tritylpyrrolidine-2-carboxamide **7**.

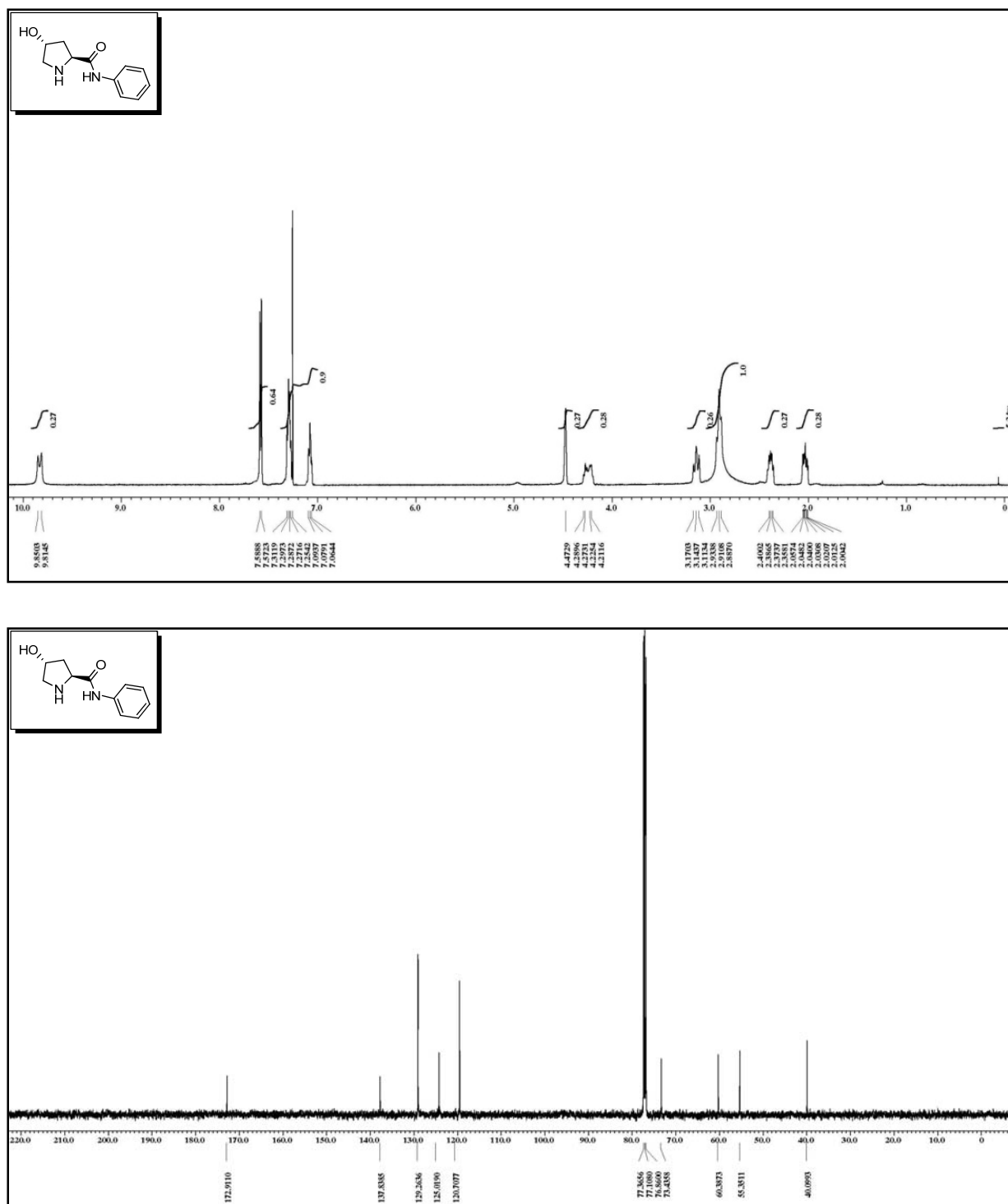


Figure S8. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectra of (2S,4R)-4-hydroxy-N-phenylpyrrolidine-2-carboxamide **8**.

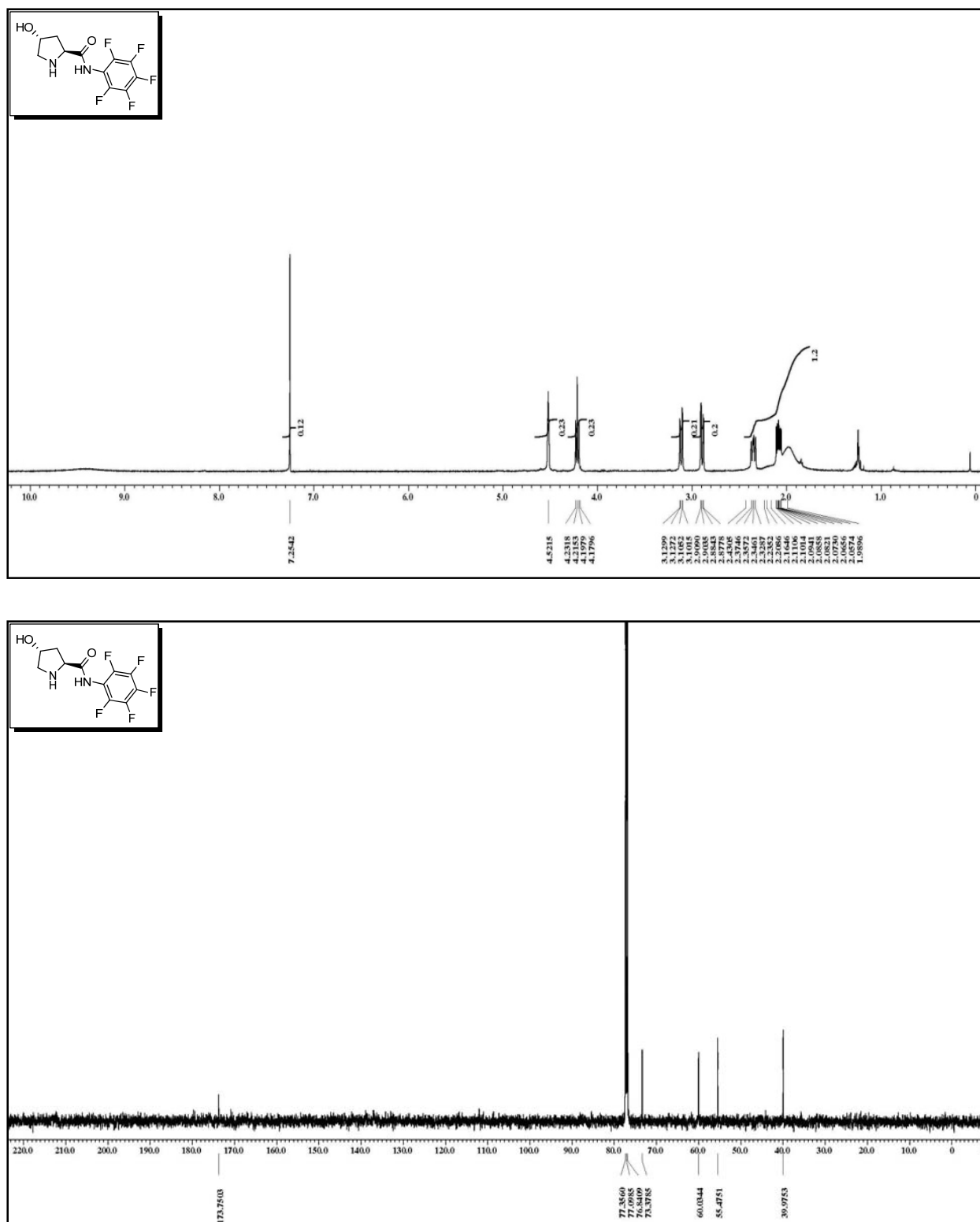


Figure S9. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectra of (2S,4R)-N-hydroxy-N-(perfluorophenyl)pyrrolidine-2-carboxamide **9**.

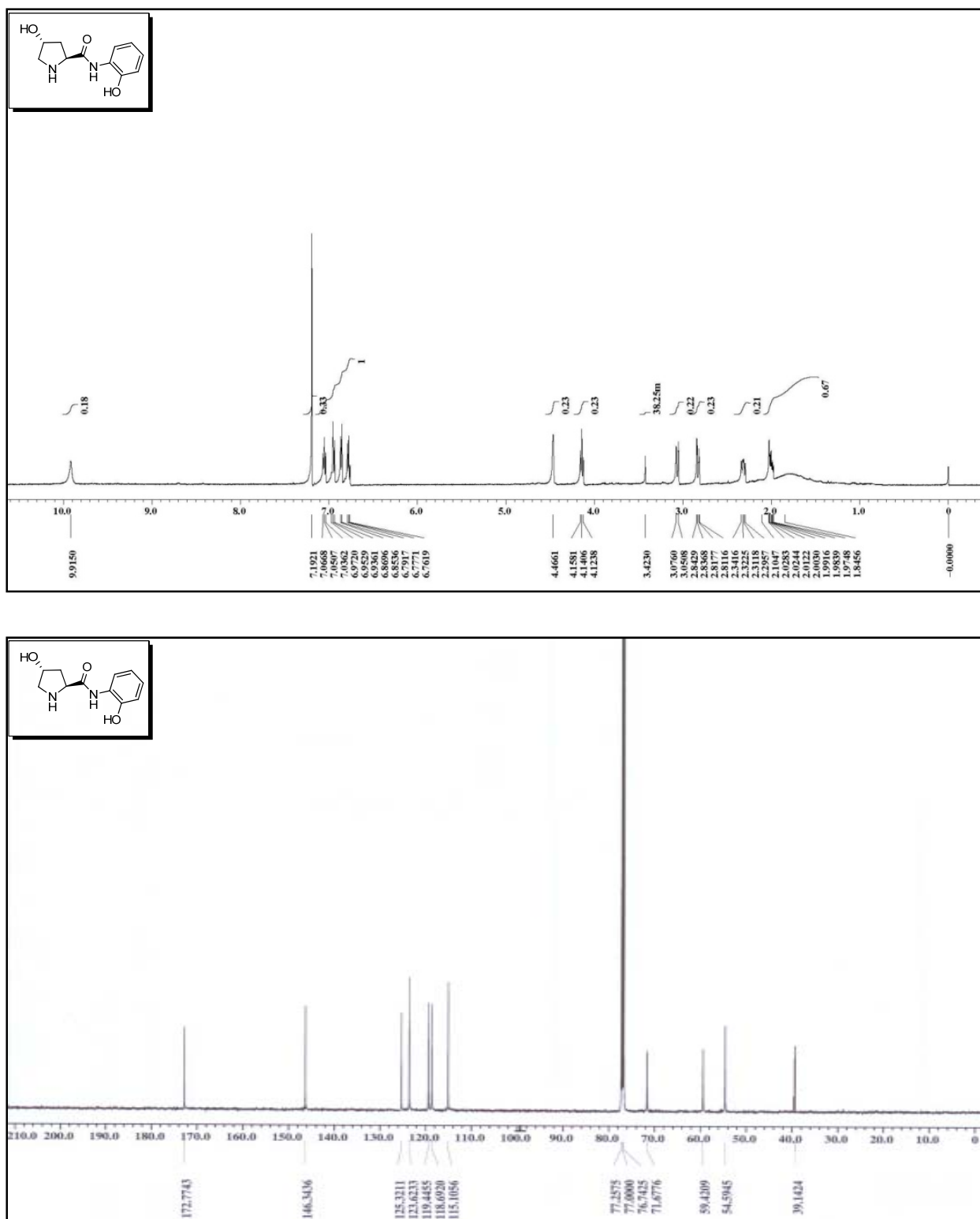


Figure S10. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectra of (2S,4R)-4-hydroxy-N-(2-hydroxyphenyl)pyrrolidine-2-carboxamide **10**.

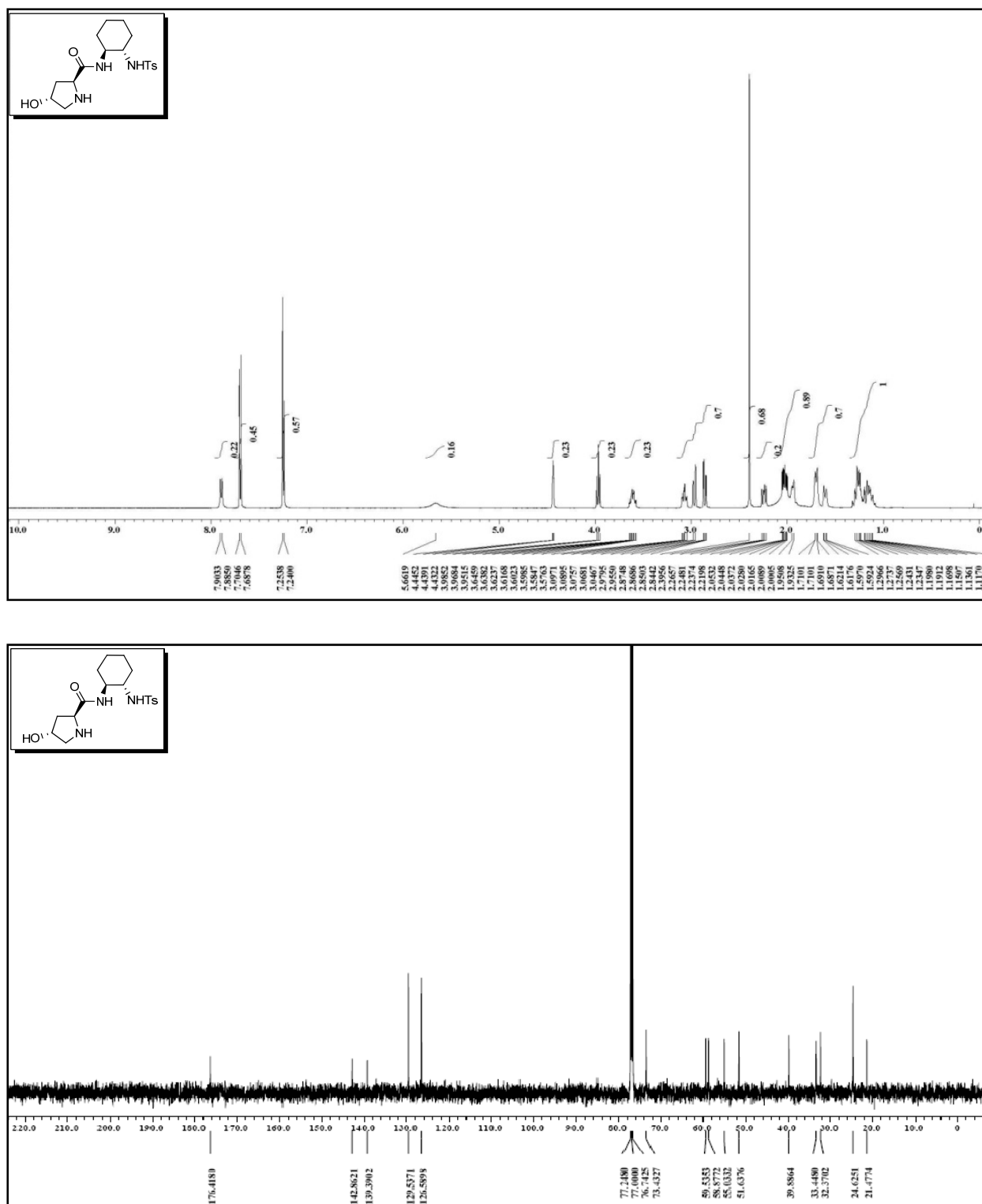


Figure S11. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectra of (2S,4R)-4-hydroxy-N-((1S,2S)-2-(4-methylphenylsulfonamido)-cyclohexyl)pyrrolidine-2-carboxamide

11.

S21

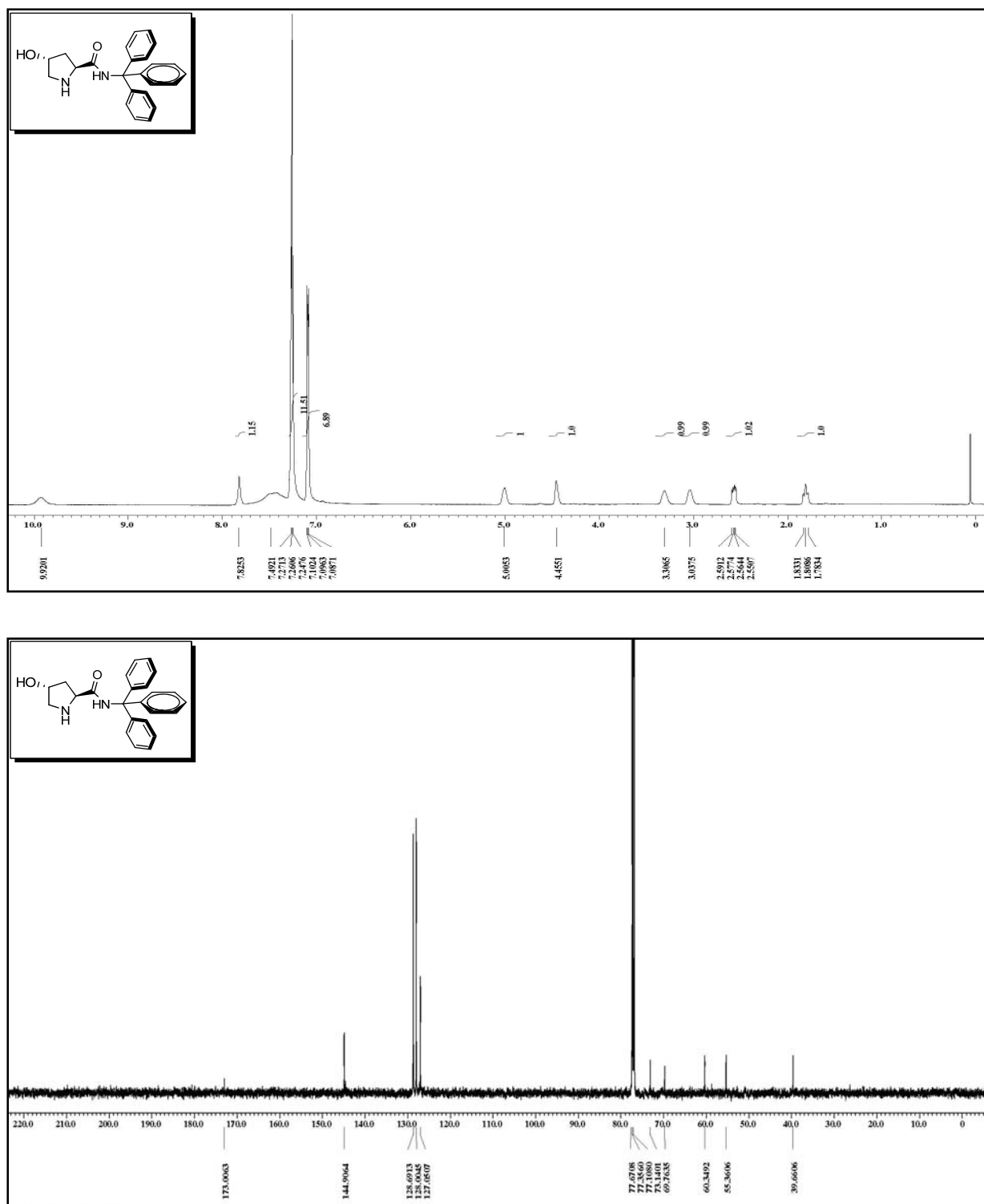


Figure S12. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectra of (2S,4R)-4-hydroxy-*N*-tritylpyrrolidine-2-carboxamide **12**.

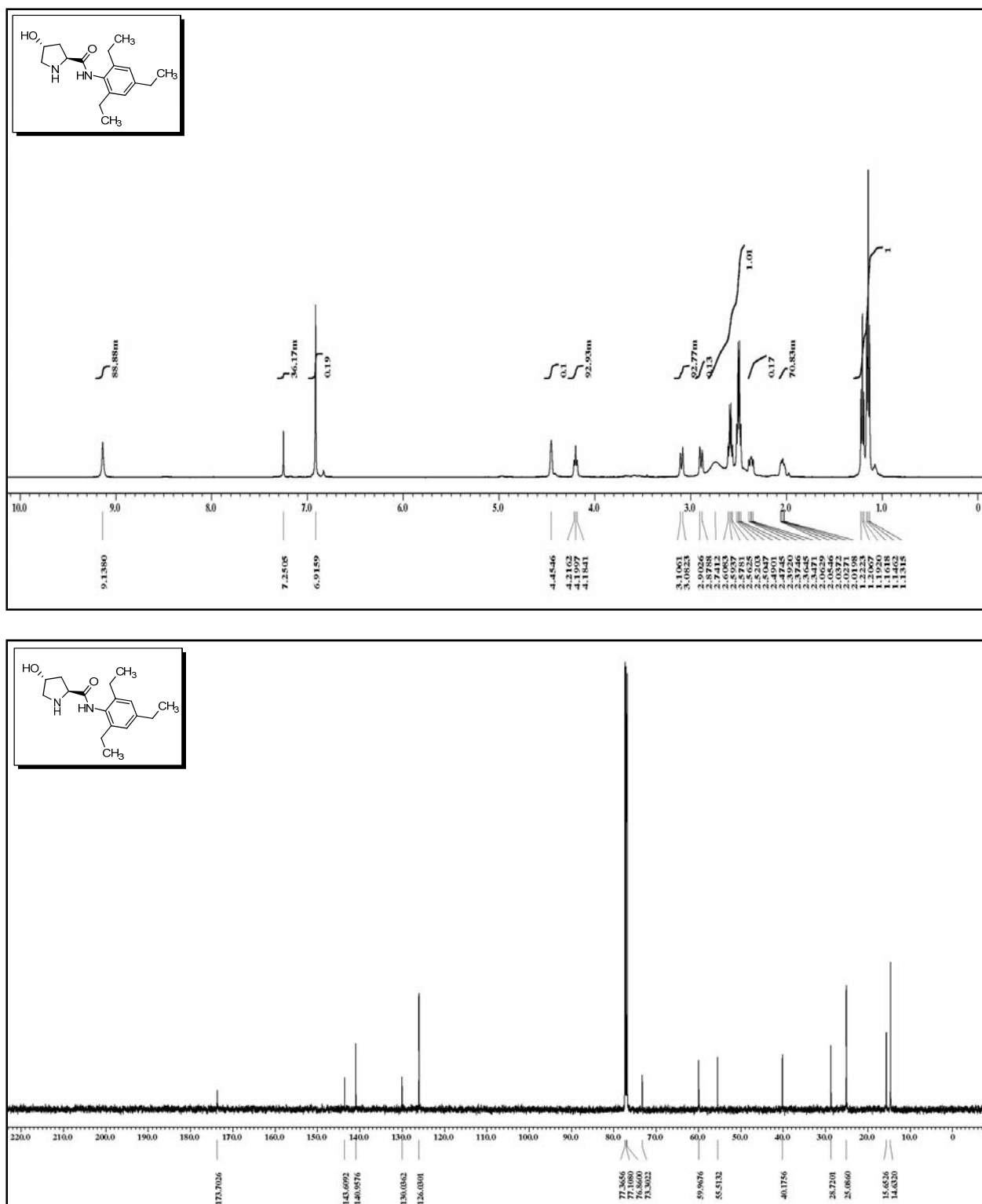


Figure S13. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectra of (2S,4R)-4-hydroxy-N-(2,4,6-triethylphenyl)pyrrolidine-2-carboxamide **13**.

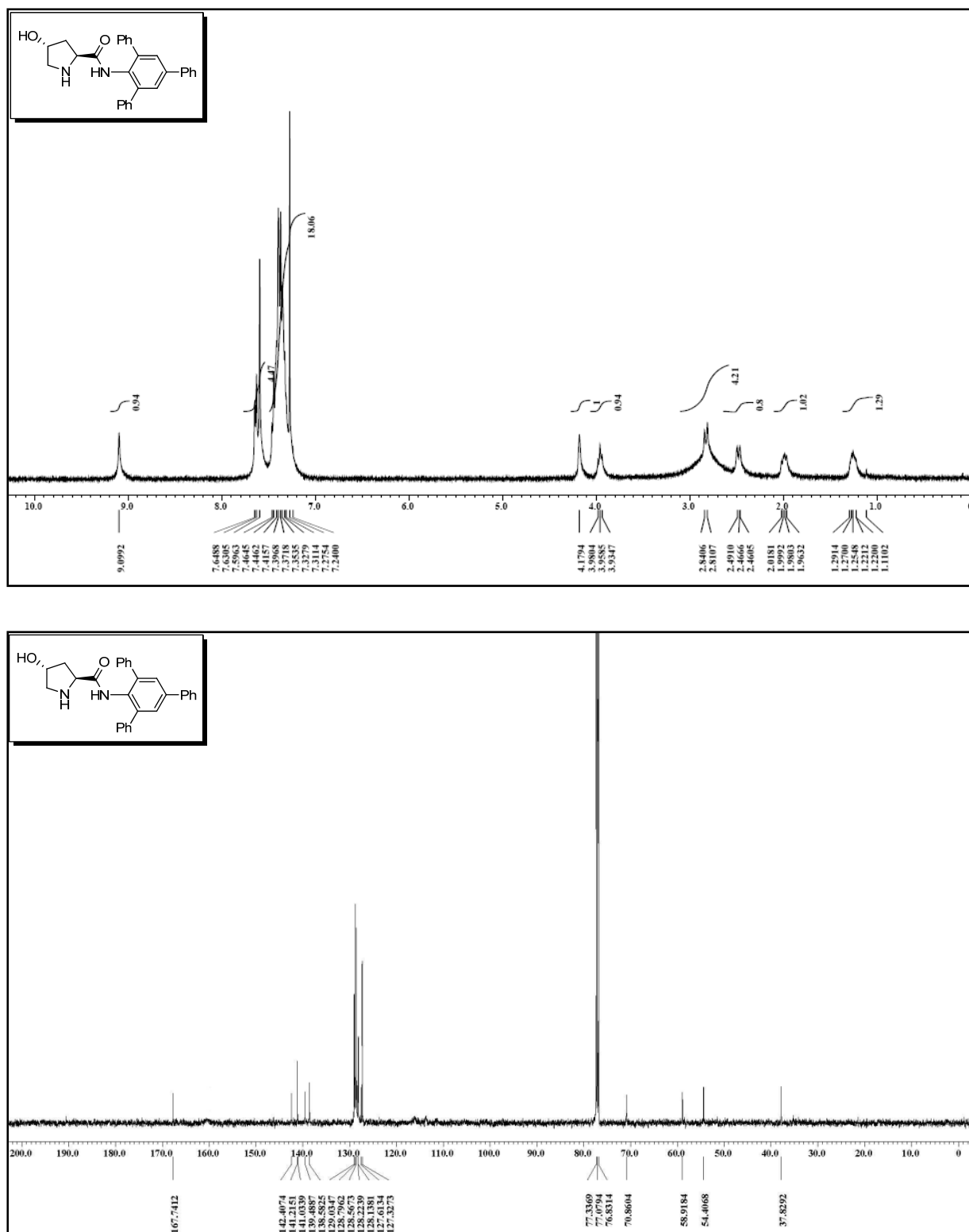


Figure S14. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectra of (2S,4R)-4-hydroxy-N-(2,4,6-triphenylbenzene)pyrrolidine-2-carboxamide **14**.

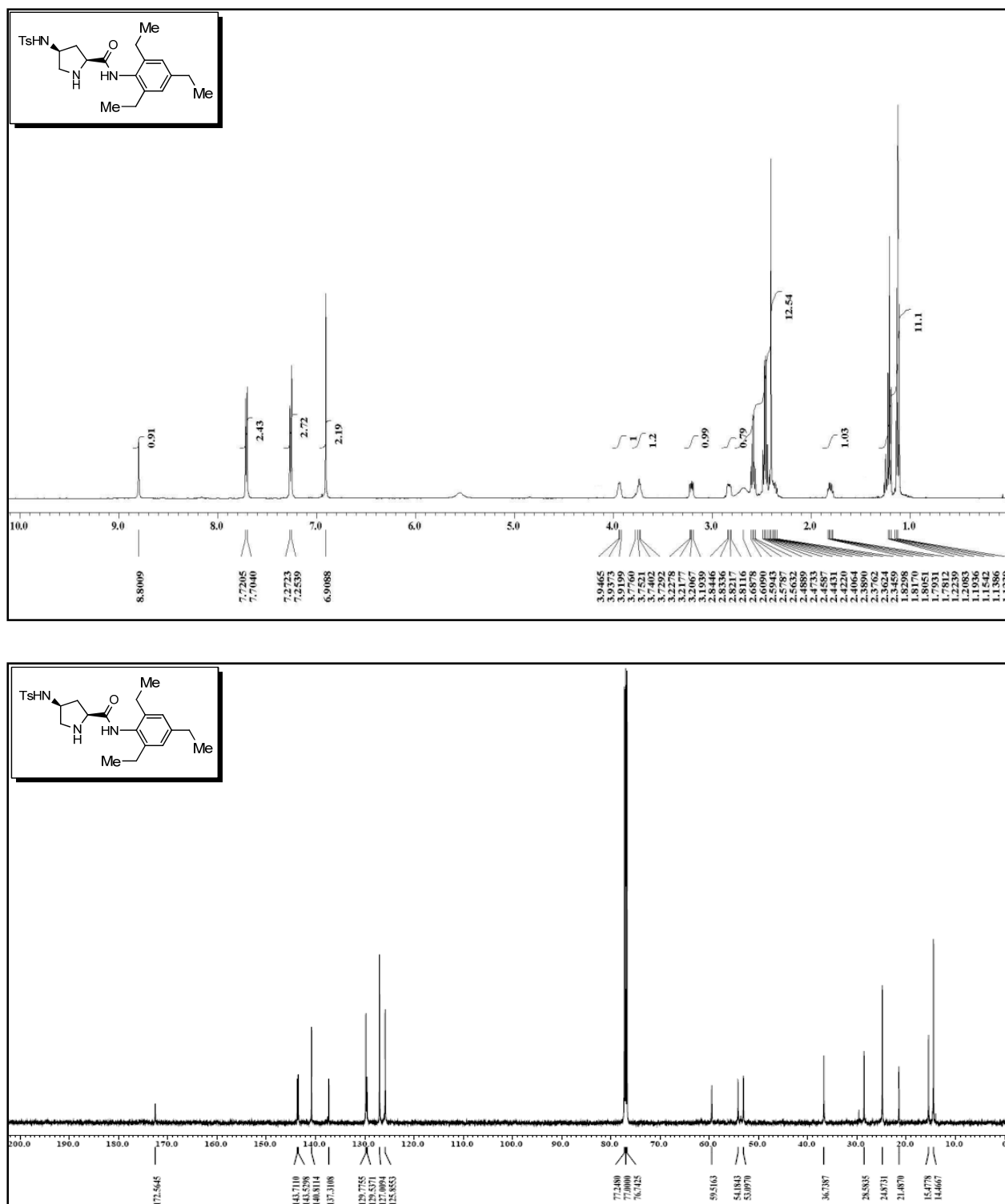


Figure S15. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectra of (2S,4R)-4-tosylamido-*N*-(2,4,6-triethylphenyl)pyrrolidine-2-carboxamide **15**.

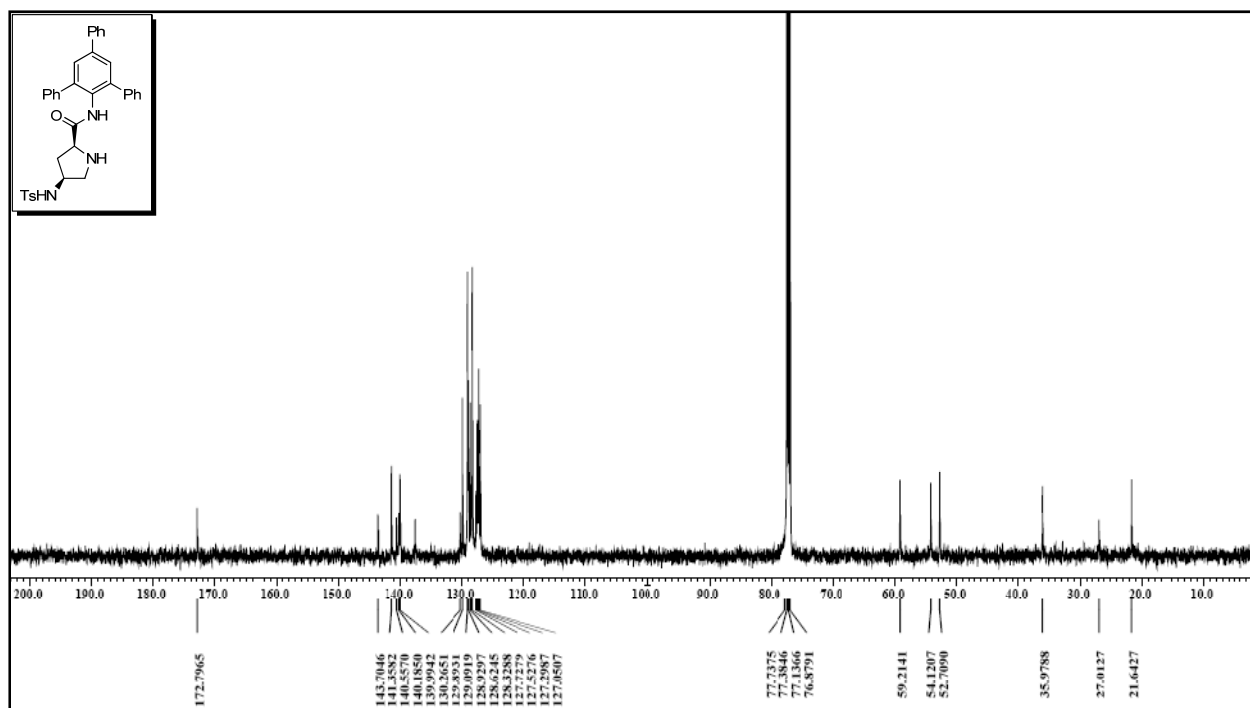
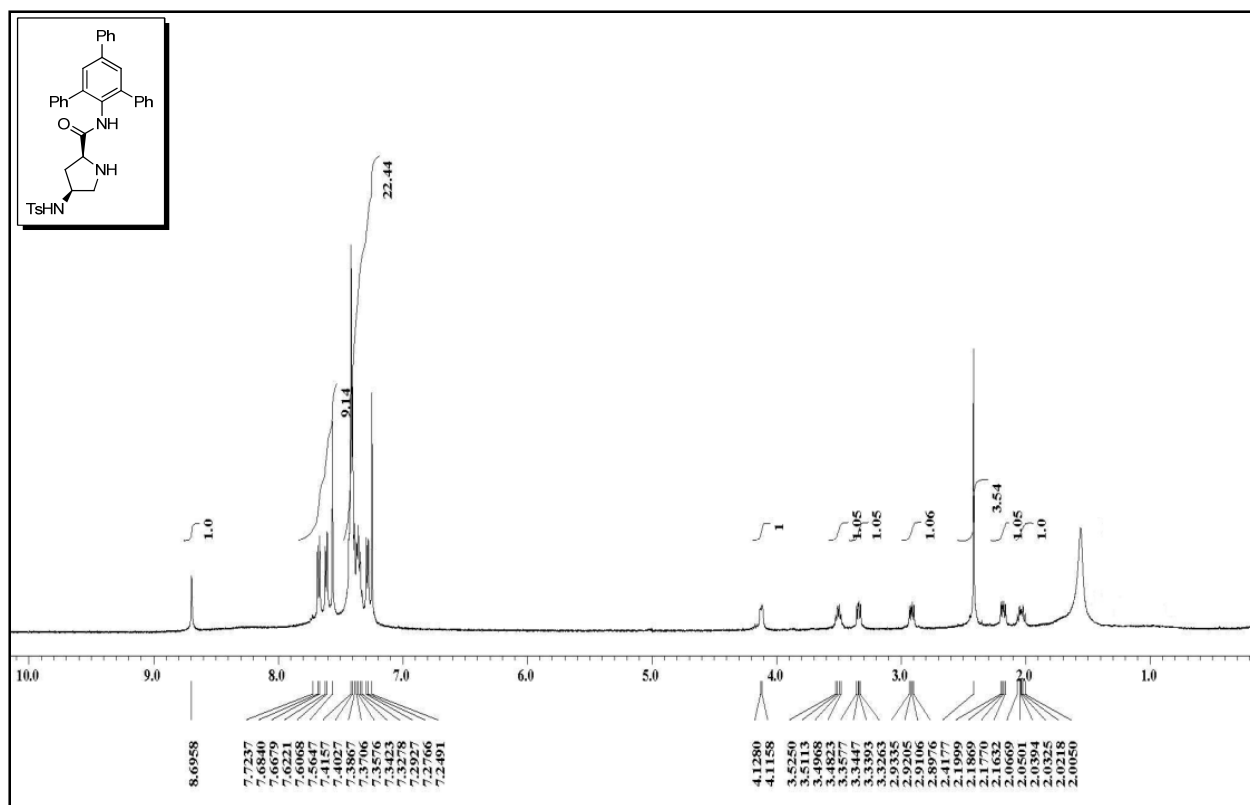


Figure S16. ¹H NMR (CDCl₃, 500 MHz) and ¹³C NMR (CDCl₃, 125 MHz) spectra of (2S,4R)-4-tosylamido-*N*-(2,4,6-triphenylbenzene)pyrrolidine-2-carboxamide **16**.

¹H NMR Spectral Reproductions for the Representative Biginelli Products.¹⁰

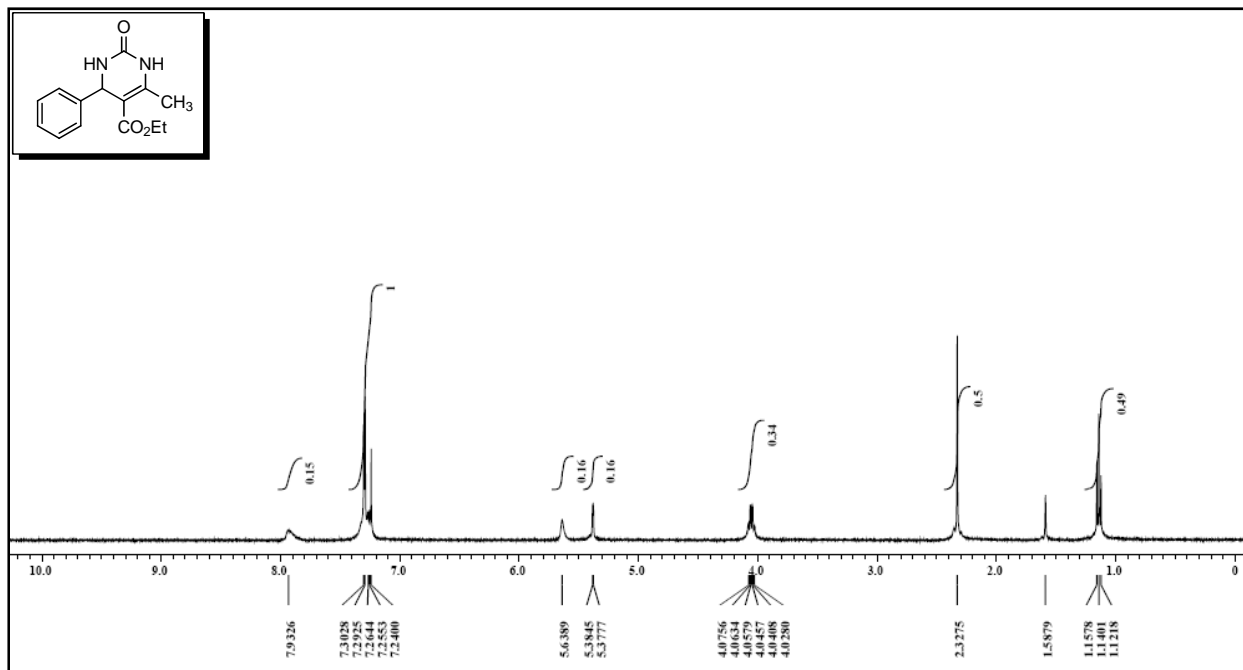


Figure S17. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (entry 1, Table 3).

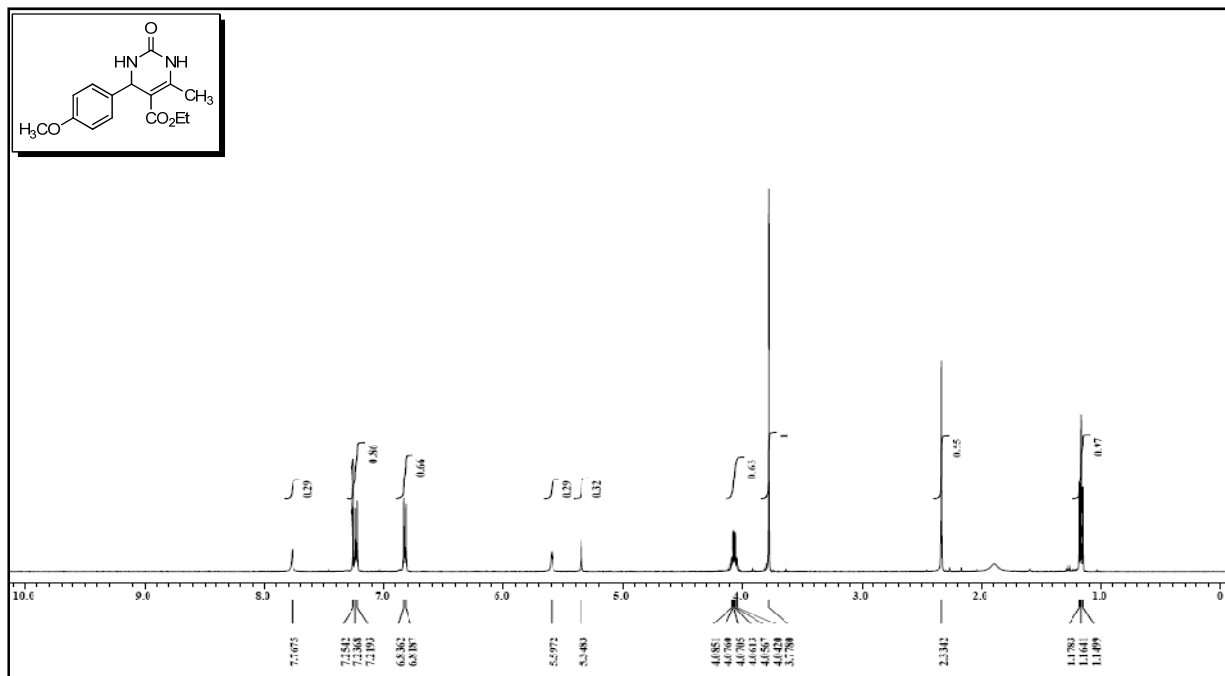


Figure S18. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (entry 2, Table 3).

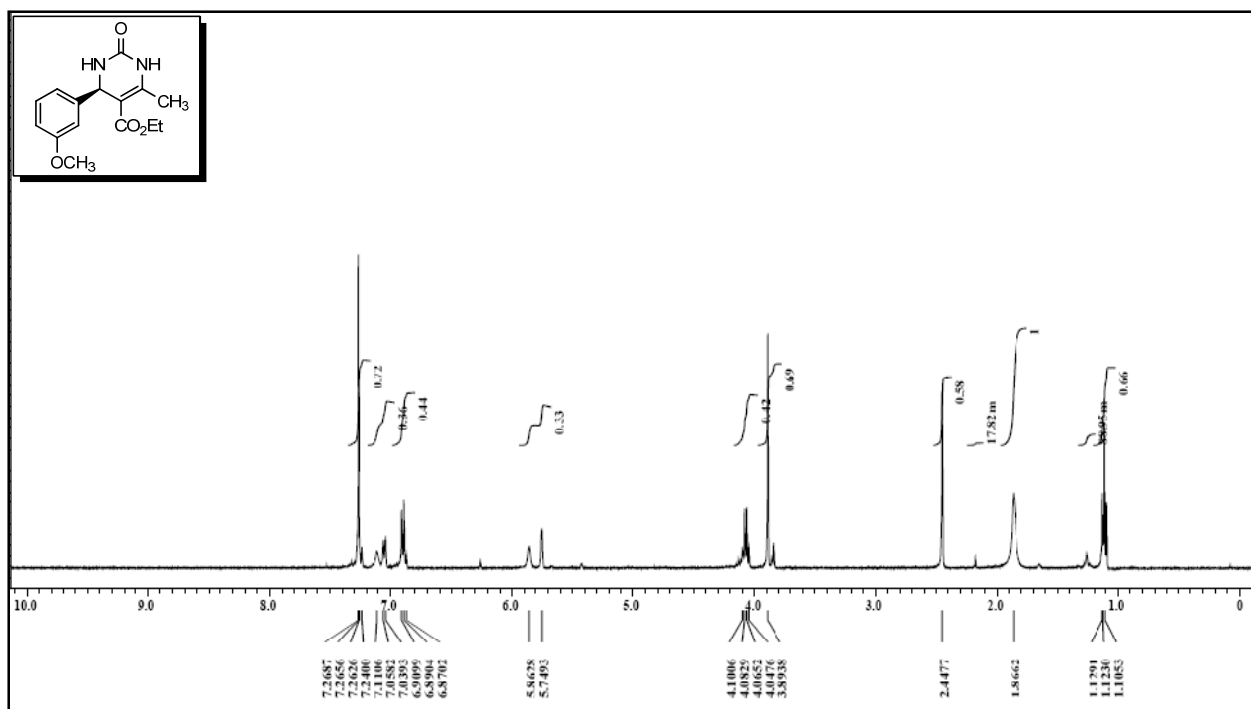


Figure S19. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-(3-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (entry 3, Table 3).

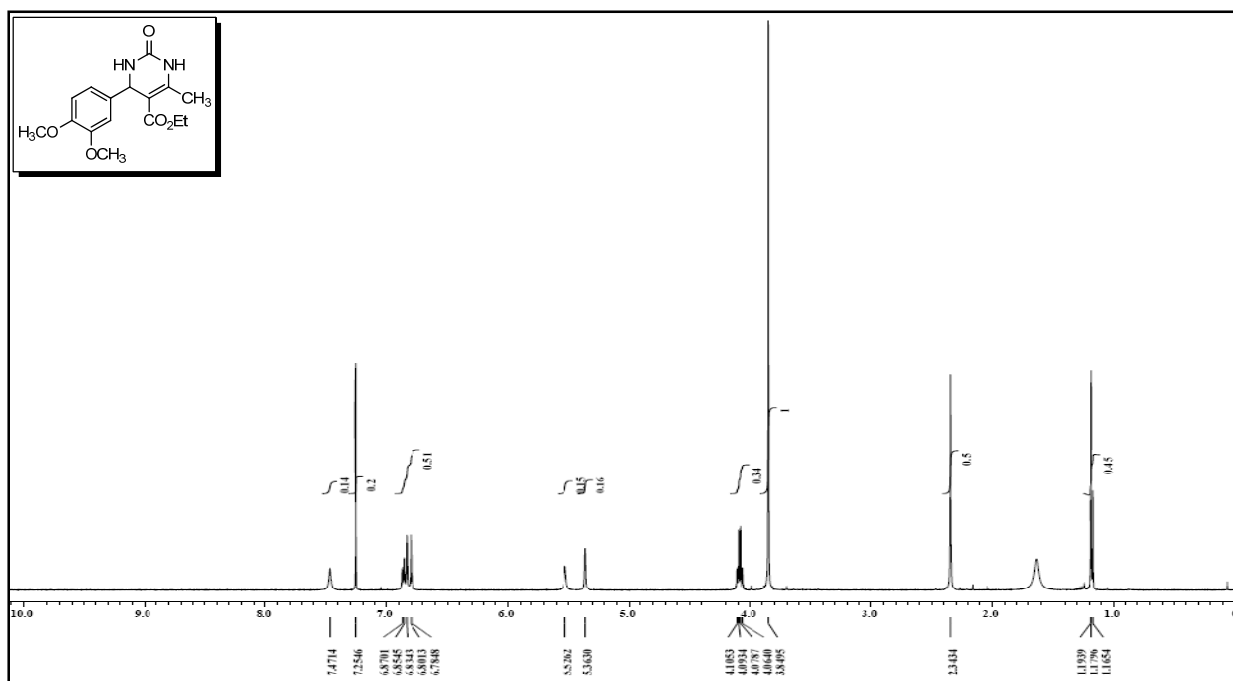


Figure S20. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-(3,4-dimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (entry 4, Table 3).

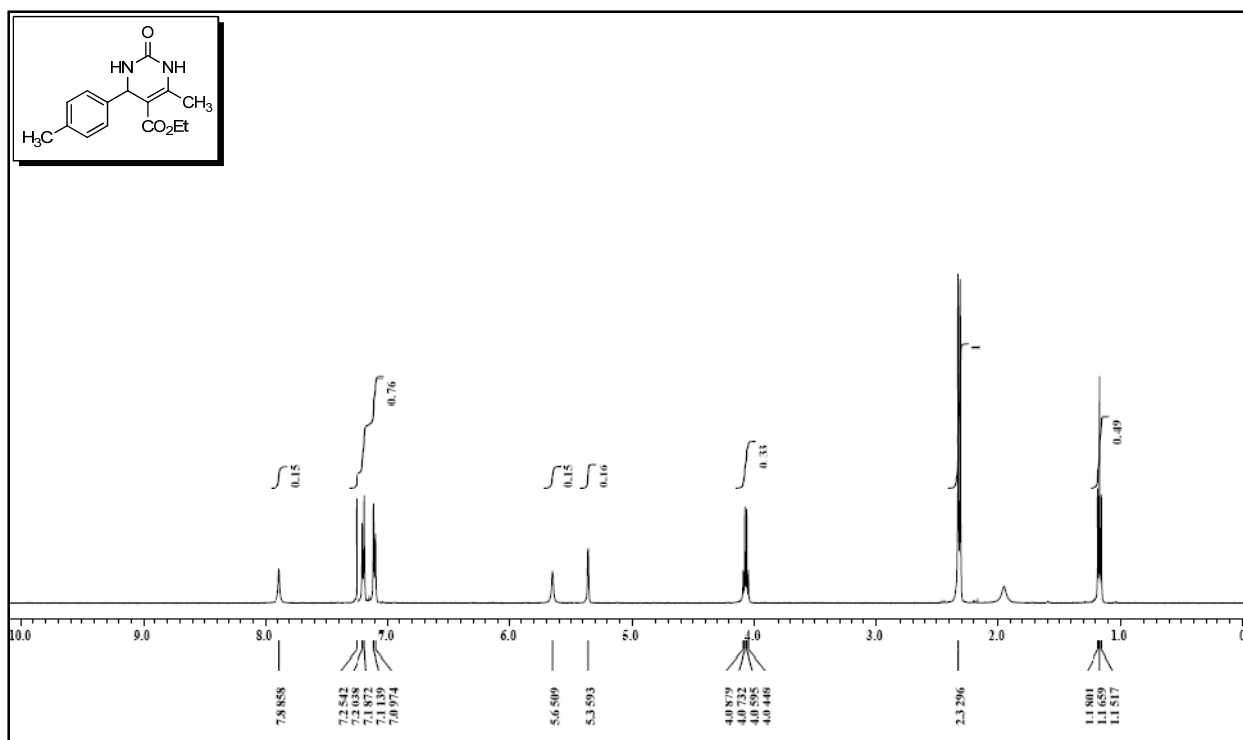


Figure S21. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (entry 6, Table 3).

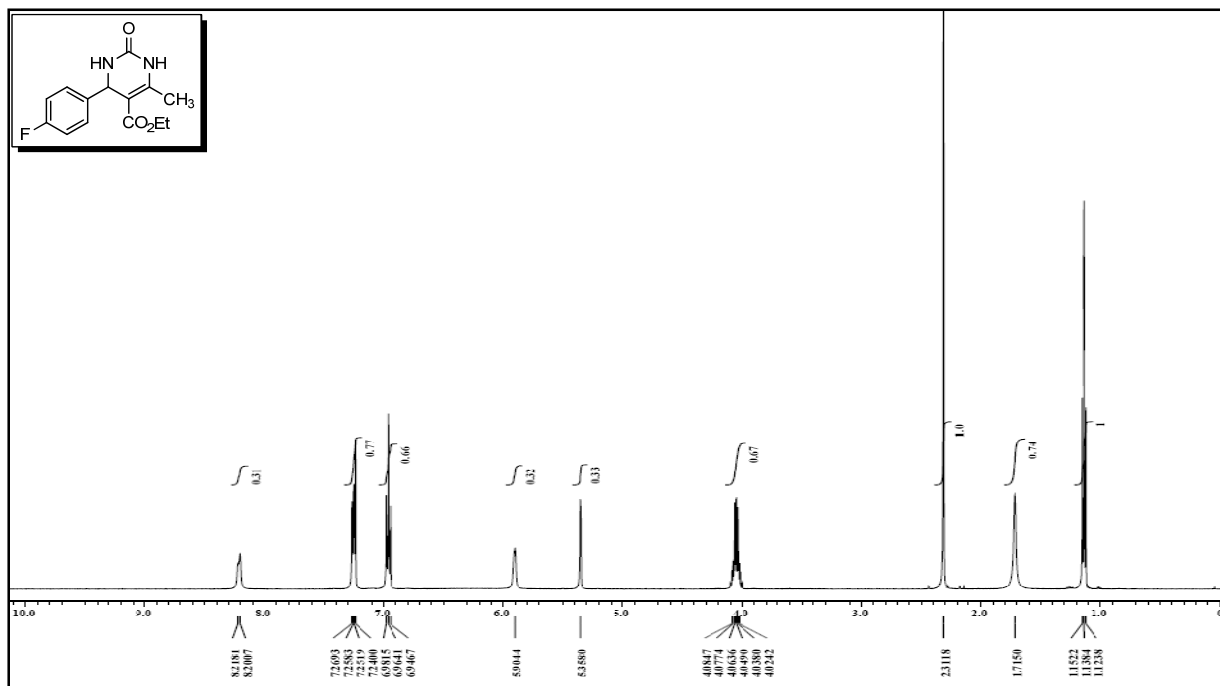


Figure S22. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-(4-fluorophenyl)-3,4-dihydropyrimidin-2(1H)-one (entry 7, Table 3).

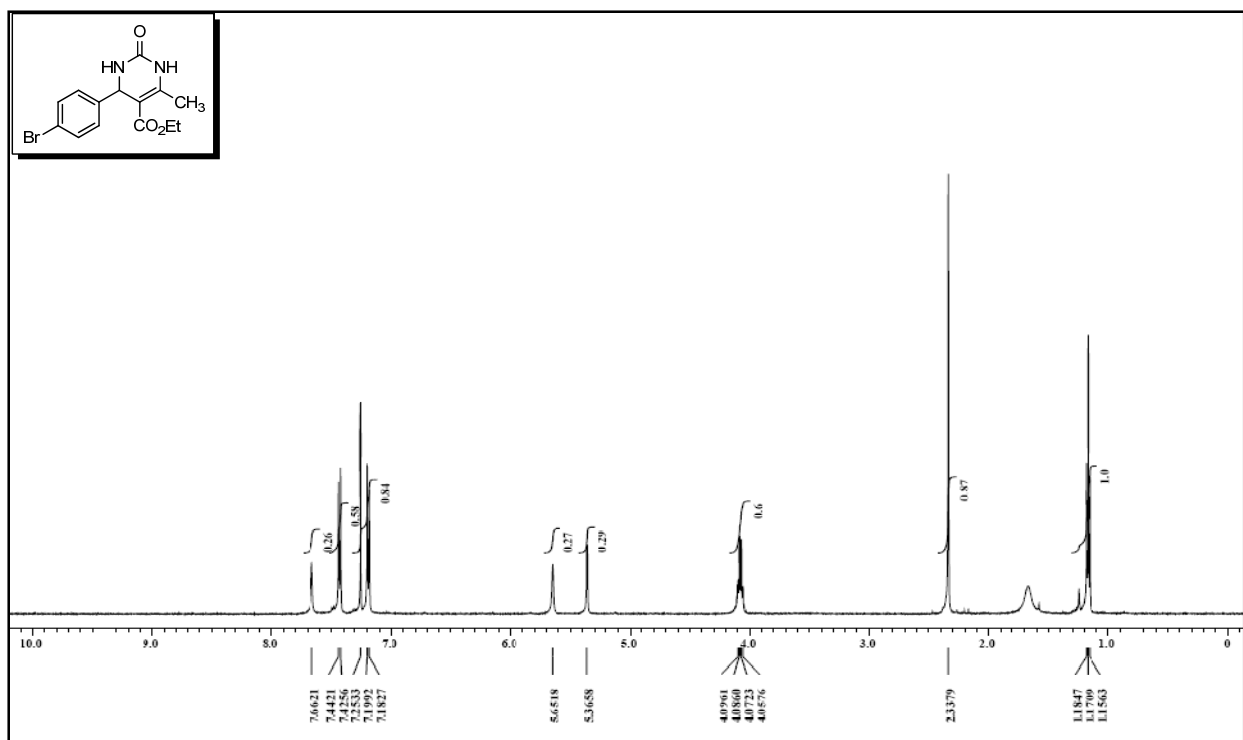


Figure S23. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-(4-bromophenyl)-3,4-dihydropyrimidin-2(1H)-one (entry 8, Table 3).

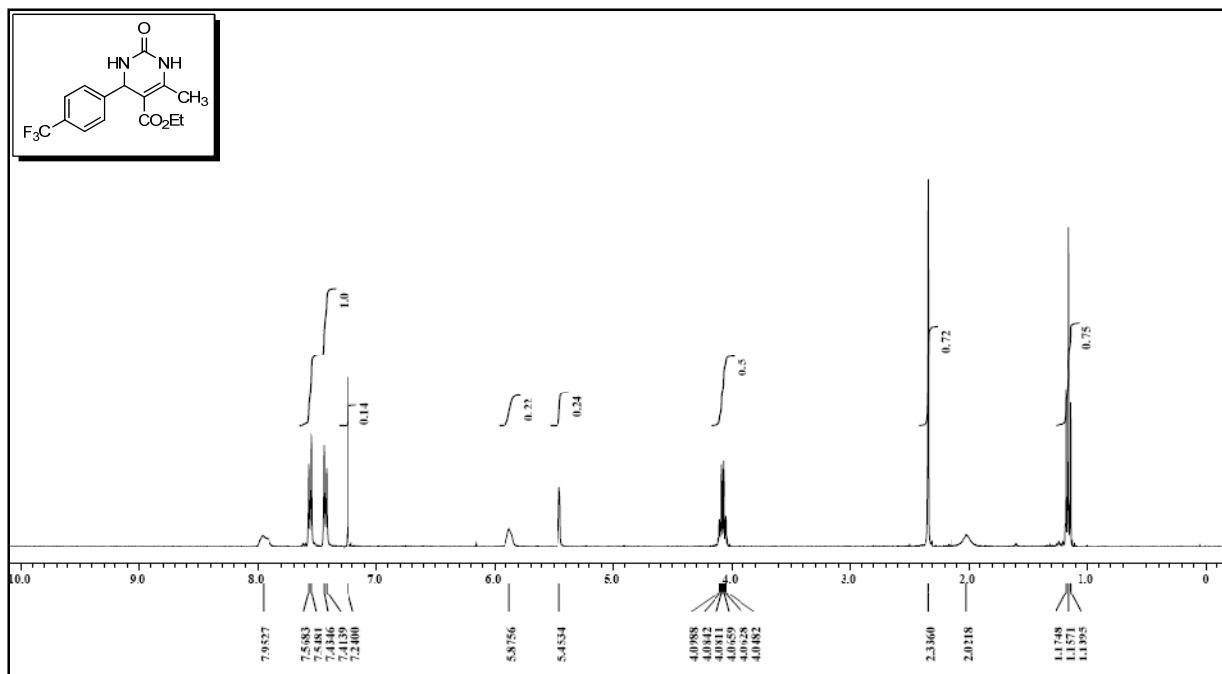


Figure S24. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-(4- α,α,α -trifluoromethylphenyl)-3,4-dihydropyrimidin-2(1H)-one (entry 10, Table 3).

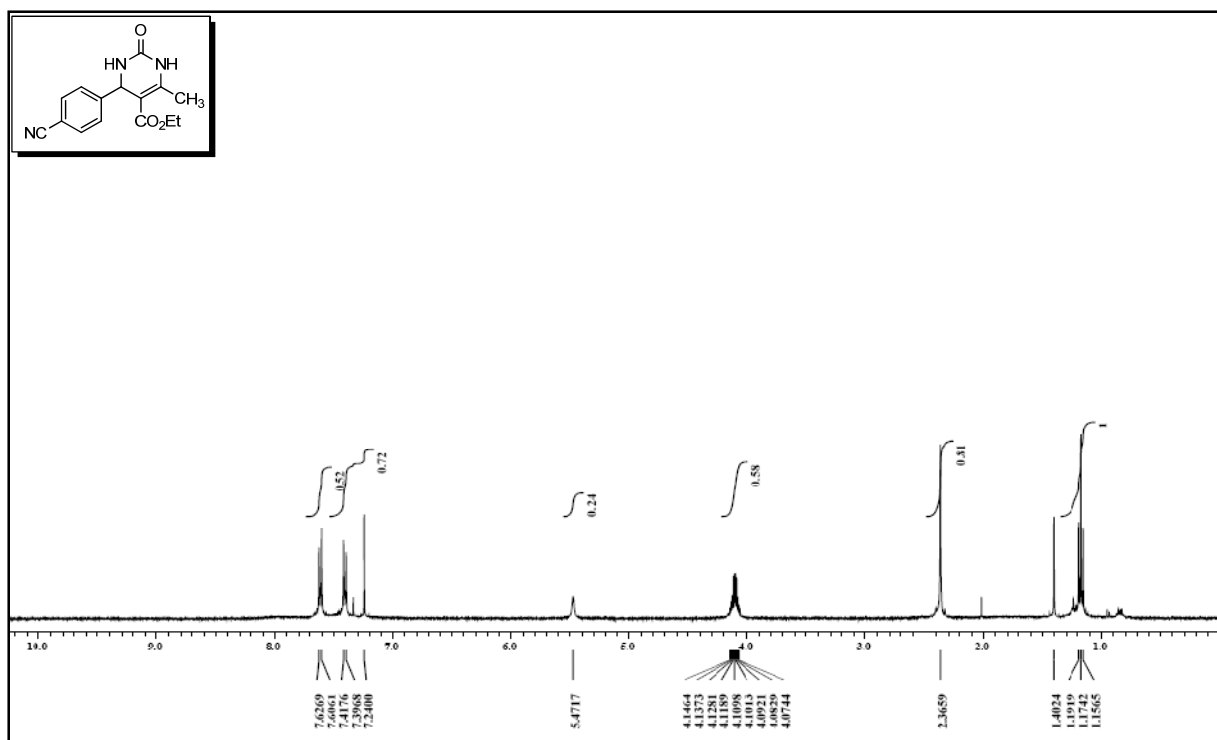


Figure S25. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-(4-cyanophenyl)-3,4-dihydropyrimidin-2(1H)-one (entry 11, Table 3).

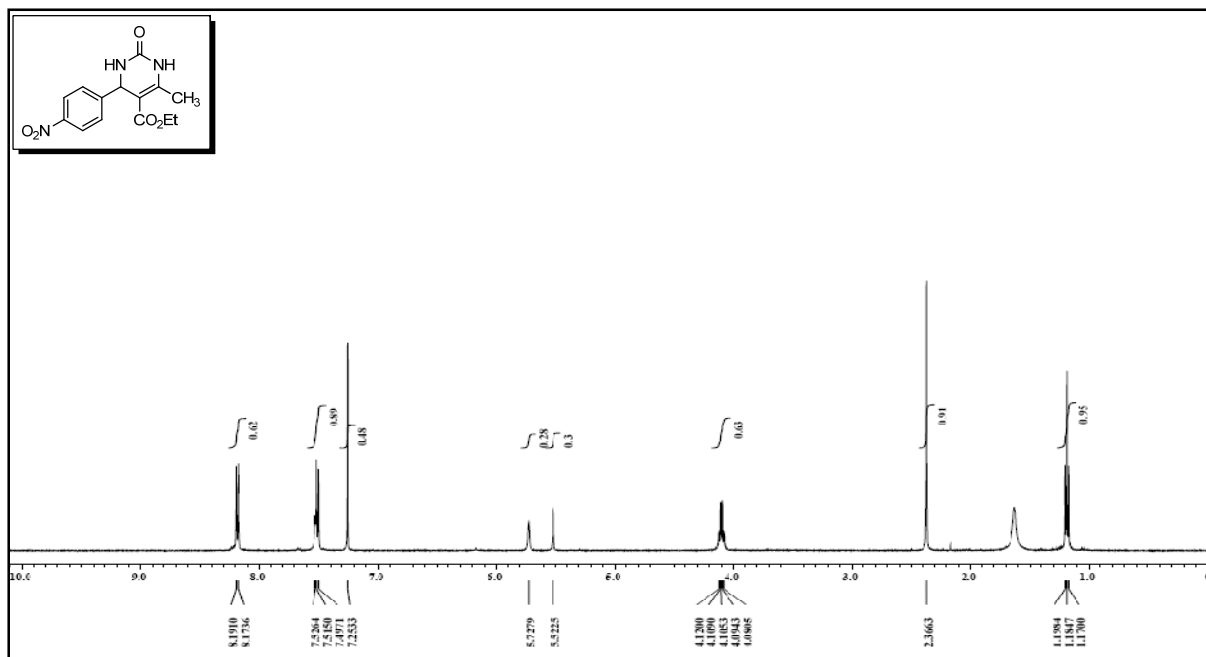


Figure S26. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (entry 12, Table 3).

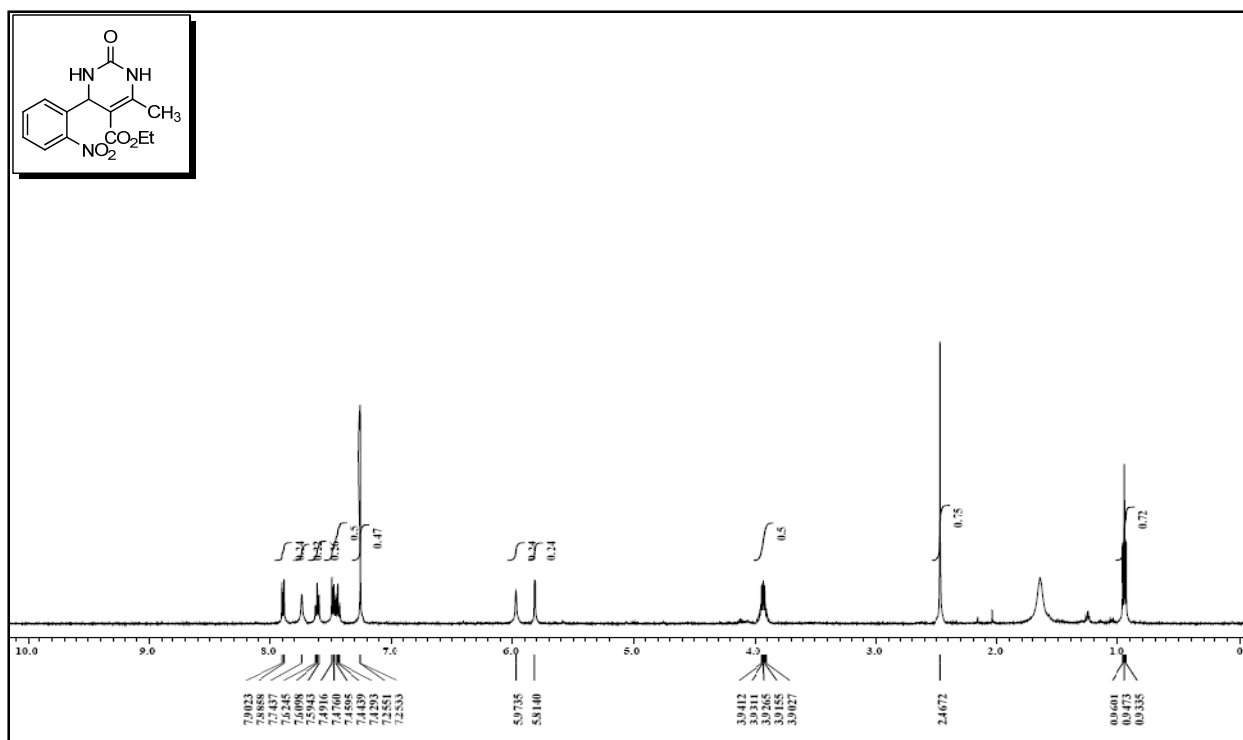


Figure S27. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (entry 13, Table 3).

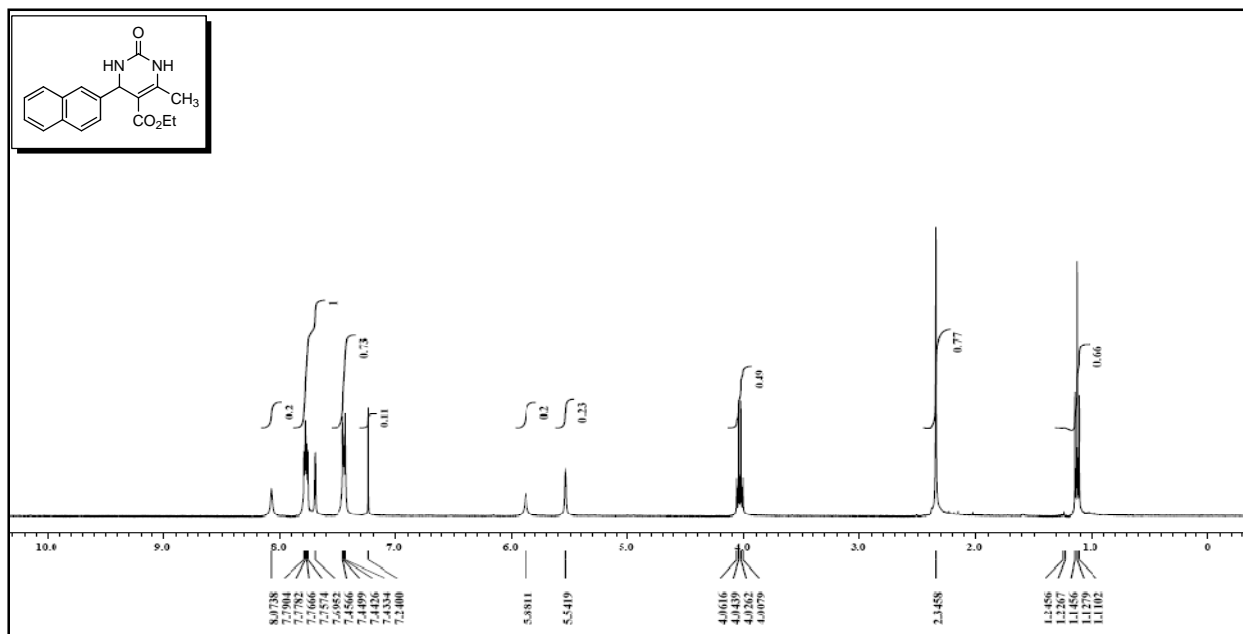


Figure S28. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-naphthyl-3,4-dihydropyrimidin-2(1H)-one (entry 14, Table 3).

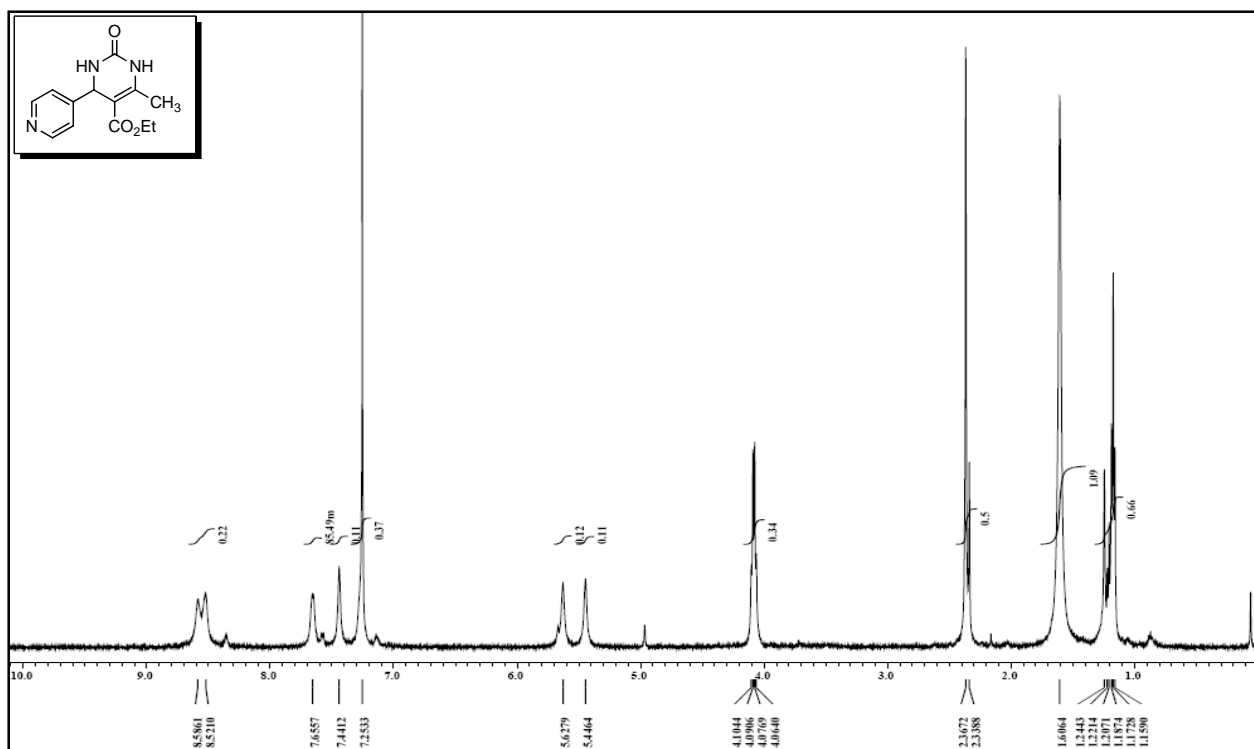


Figure S29. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-pyridyl-3,4-dihydropyrimidin-2(1H)-one (entry 15, Table 3).

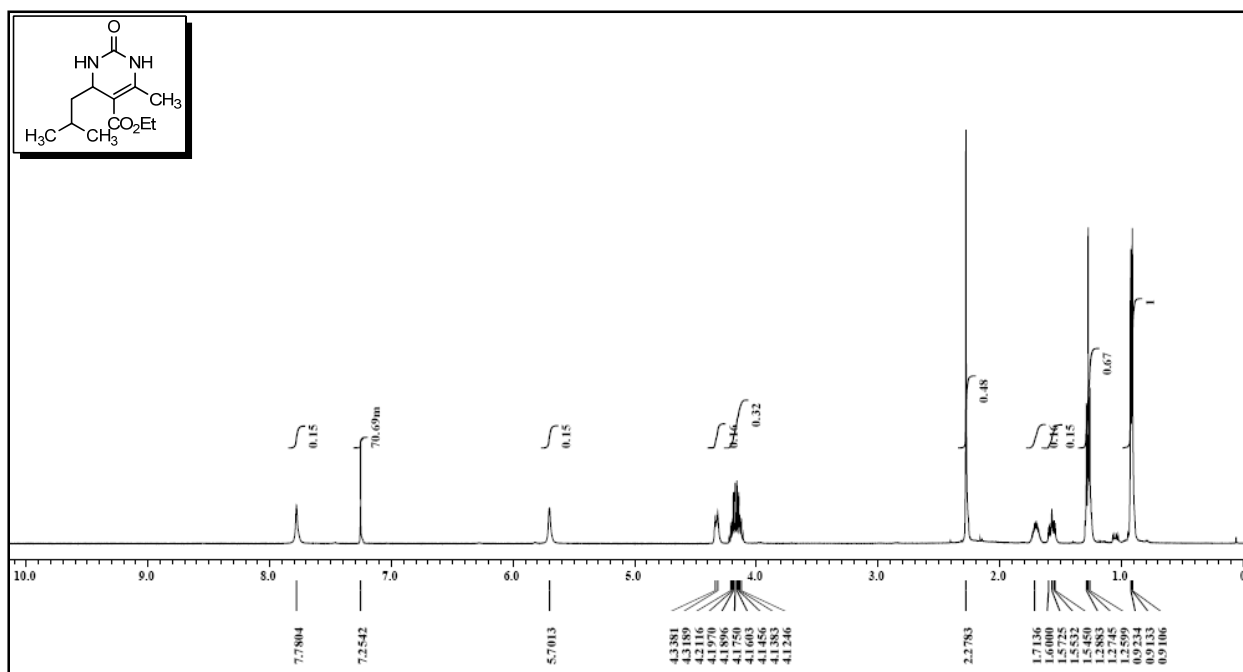


Figure S30. ¹H NMR (CDCl₃, 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-isobutyl-3,4-dihydropyrimidin-2(1H)-one (entry 16, Table 3).

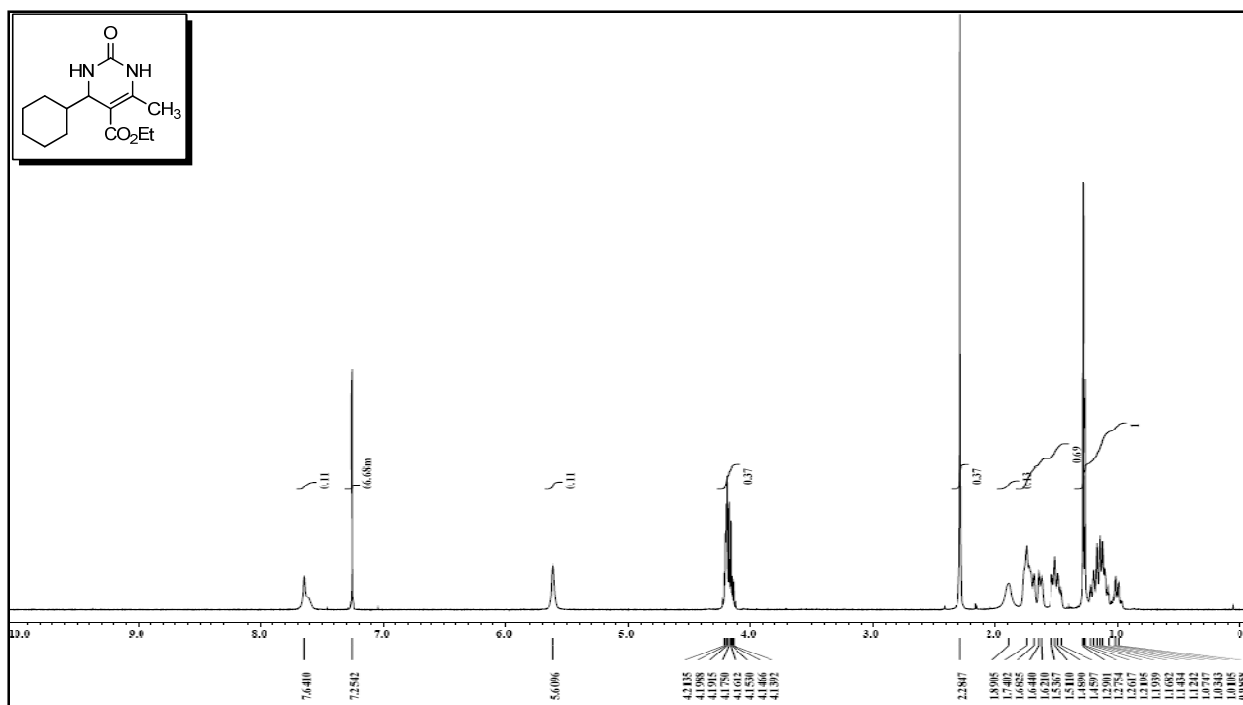
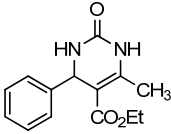
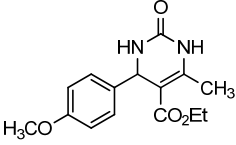
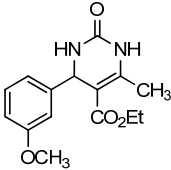
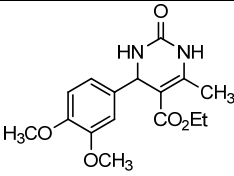
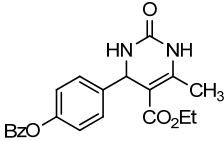
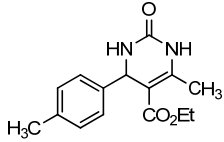
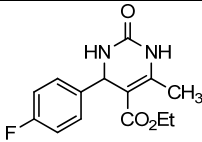
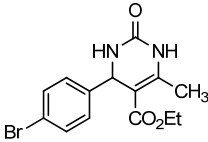
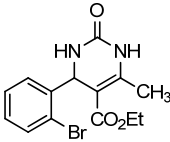
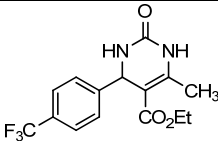
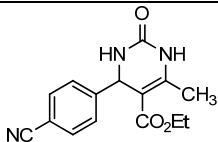
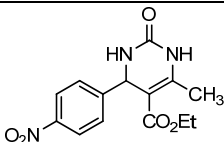
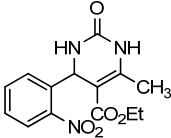
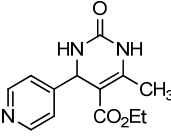
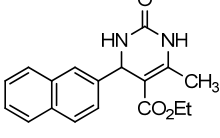
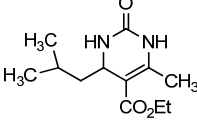
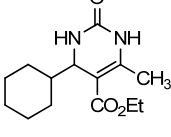


Figure S31. ^1H NMR (CDCl_3 , 500 MHz) spectrum of 5-ethoxycarbonyl-6-methyl-4-cyclohexyl-3,4-dihydropyrimidin-2(1H)-one (entry 17, Table 3).

Table S1. The HPLC Resolution Conditions for the DHPM Products.

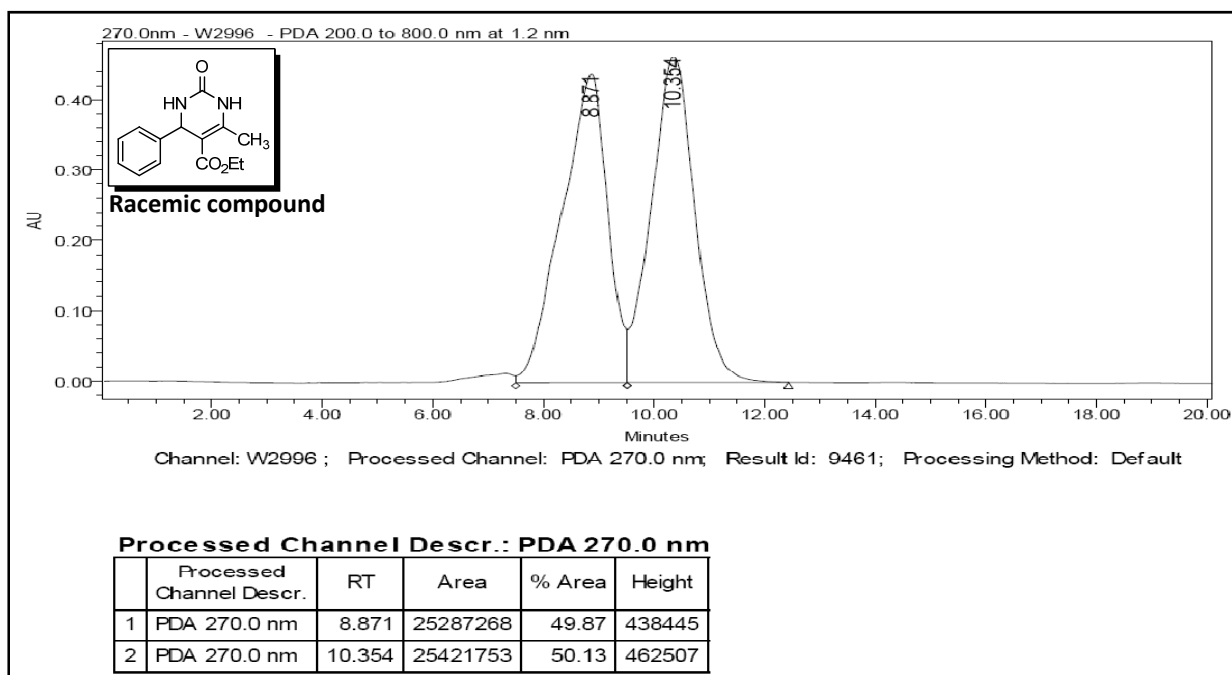
entry	product ^a	HPLC resolution conditions ^b	retention times ^c
1		OD-Column, Hex:IPA = 85:15 1.0 ml/min, 254 nm	t_{R1} = 8.8 t_{R2} = 10.3
2		OD-Column, Hex:IPA = 85:15 1.0 ml/min, 217 nm	t_{R1} = 11.6 t_{R2} = 14.6
3		OD-Column, Hex:IPA = 85:15 1.0 ml/min, 213 nm	t_{R1} = 12.9 t_{R2} = 14.4

4		OD-Column, Hex:IPA = 50:50 1.0 ml/min, 254 nm	t_{R1} = 9.1 t_{R2} = 16.7
5		OD-Column, Hex:IPA = 85:15 1.0 ml/min, 254 nm	t_{R1} = 19.1 t_{R2} = 23.0
6		OD-Column, Hex:IPA = 70:30 1.0 ml/min, 254 nm	t_{R1} = 6.0 t_{R2} = 6.7
7		OD-Column, Hex:IPA = 85:15 1.0 ml/min, 210 nm	t_{R1} = 9.6 t_{R2} = 11.7
8		OD-Column, Hex:IPA = 85:15 1.0 ml/min, 234 nm	t_{R1} = 9.9 t_{R2} = 12.7
9		OD-Column, Hex:IPA = 85:15 1.0 ml/min, 225 nm	t_{R1} = 9.9 t_{R2} = 12.1
10		OD-Column, Hex:IPA = 85:15 1.0 ml/min, 254 nm	t_{R1} = 8.2 t_{R2} = 9.5
11		OD-Column, Hex:IPA = 85:15 1.0 ml/min, 254 nm	t_{R1} = 34.6 t_{R2} = 49.9
12		OD-Column, Hex:IPA = 85:15 1.0 ml/min, 254 nm	t_{R1} = 14.6 t_{R2} = 16.8

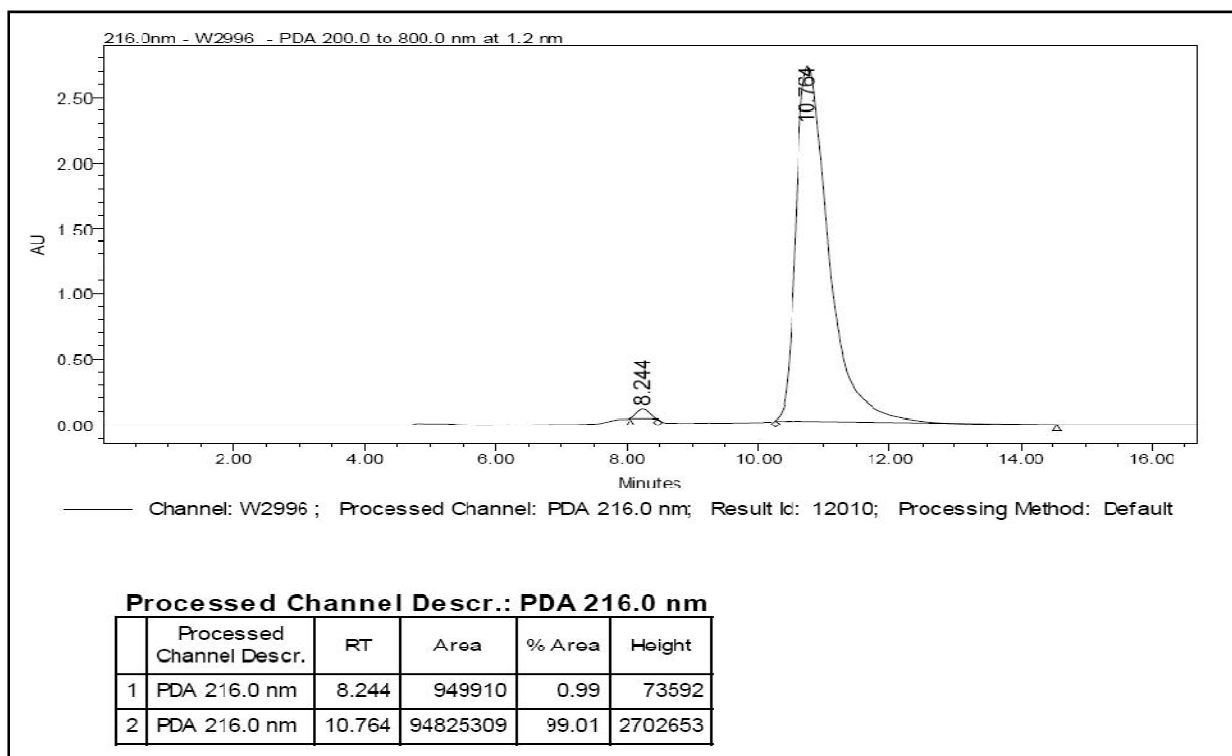
13		OD-Column, Hex:IPA = 85:15 1.0 ml/min, 252 nm	t_{R1} = 12.4 t_{R2} = 15.2
14		OD-Column, Hex:IPA = 90:10 1.0 ml/min, 254 nm	t_{R1} = 19.9 t_{R2} = 42.9
15		OD-Column, Hex:IPA = 85:15 1.0 ml/min, 260 nm	t_{R1} = 42.7 t_{R2} = 43.5
16		OD-Column, Hex:IPA = 85:15 1.0 ml/min, 268 nm	t_{R1} = 30.3 t_{R2} = 31.8
17		OD-Column, Hex:IPA = 95:05 1.0 ml/min, 254 nm	t_{R1} = 14.9 t_{R2} = 16.6

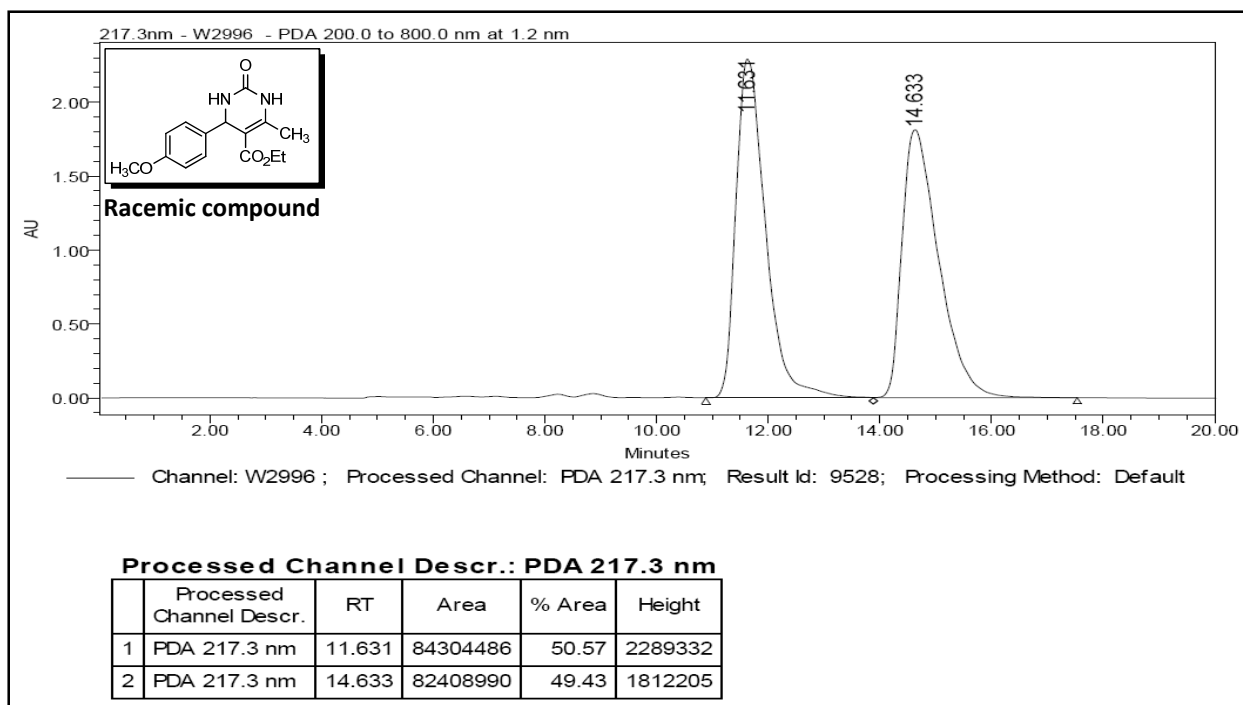
^a Racemic molecules were prepared following the literature reported procedure using Conc HCl under reflux in EtOH. ^b Hex = *n*-hexane and IPA = isopropyl alcohol. ^c t_{R1} and t_{R2} = Retention times for S and R isomer of DHPMs.

HPLC Chromatograms of the Biginelli Products¹⁰

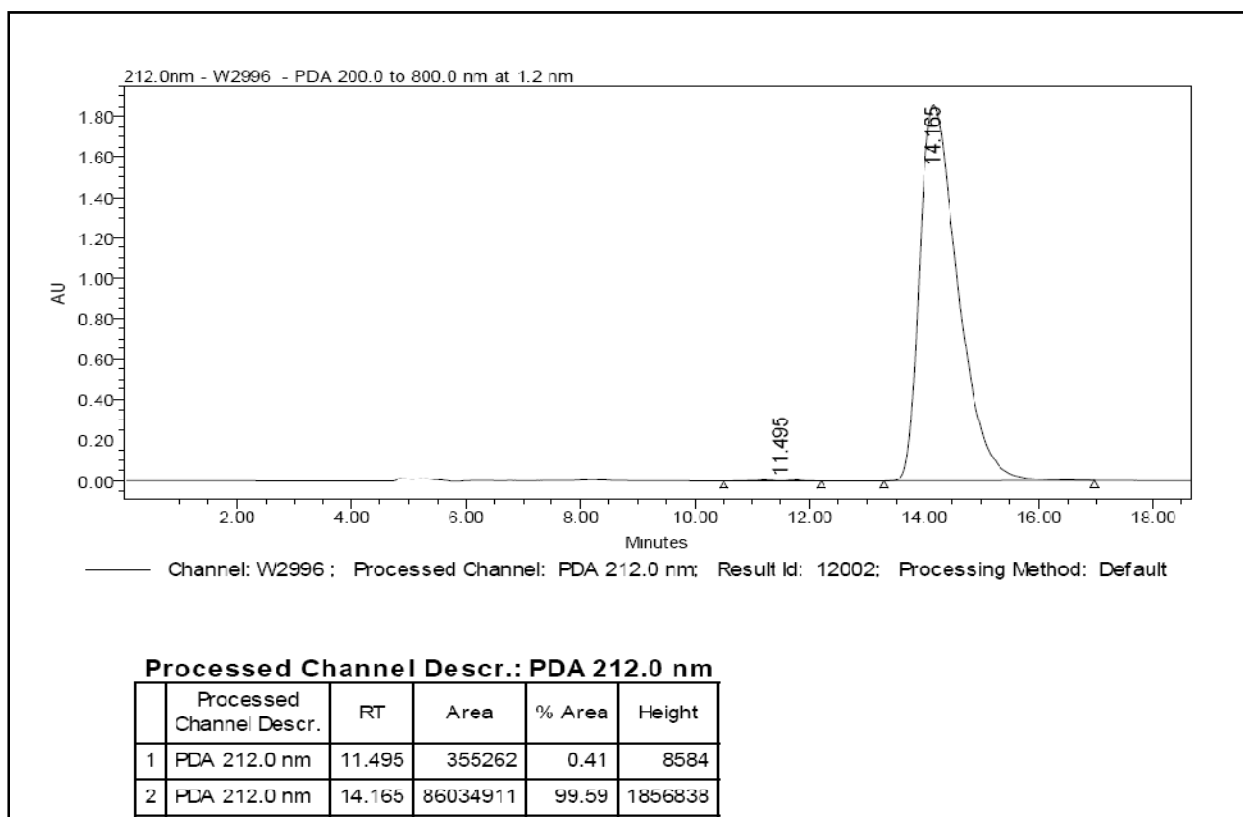


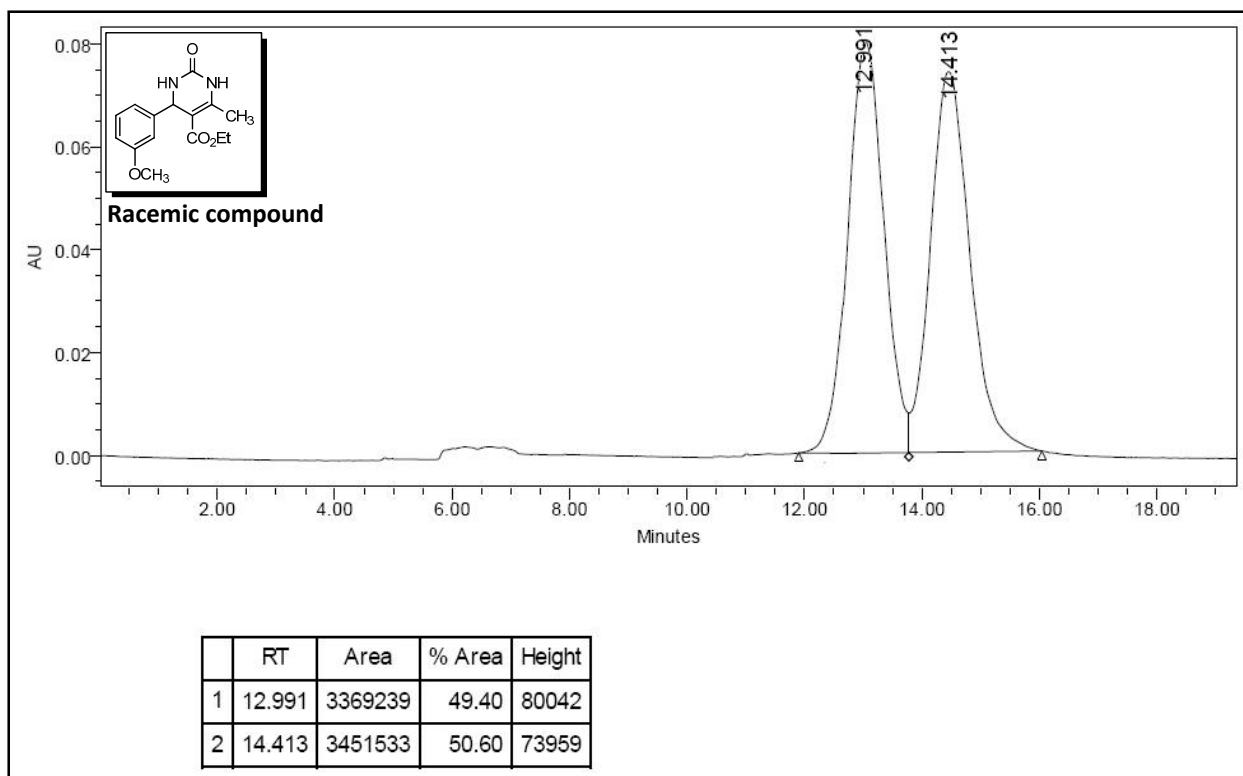
HPLC Profile for Entry 1, Table 3, 98% ee



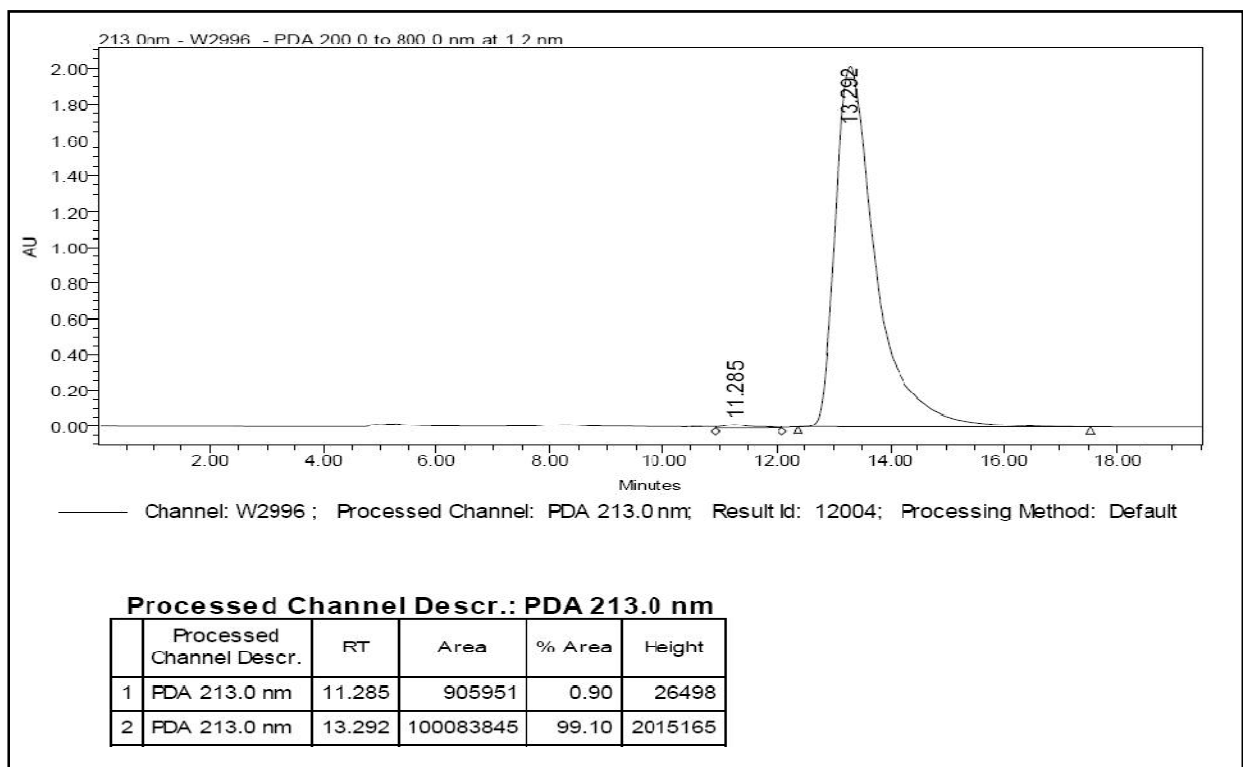


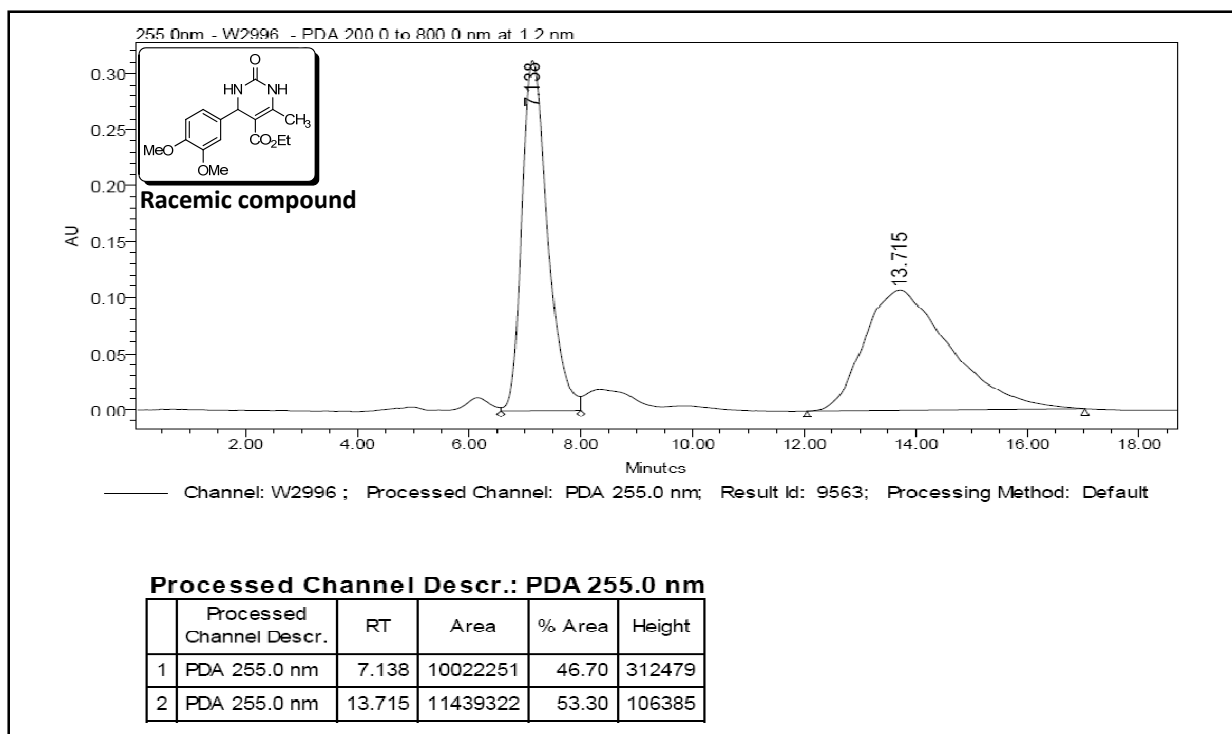
HPLC Profile for Entry 2, Table 3, 99% ee



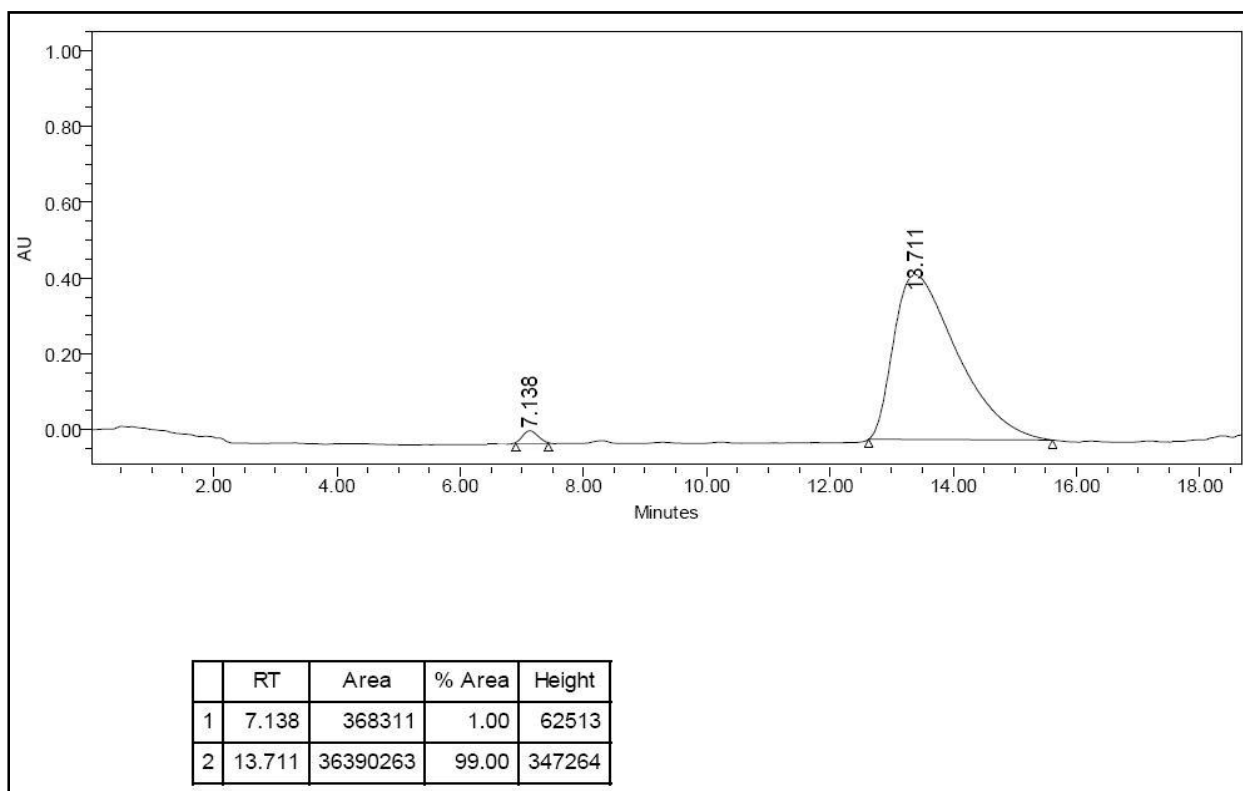


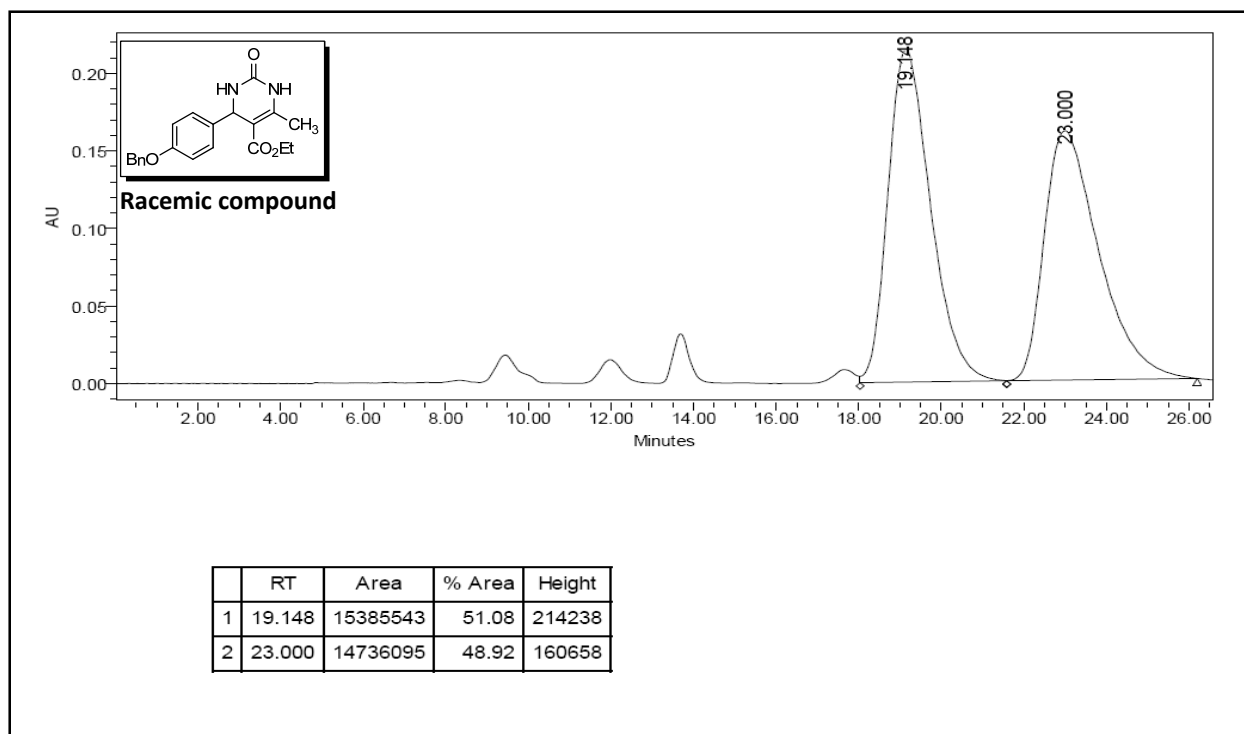
HPLC Profile for Entry 3, Table 3, 98% ee



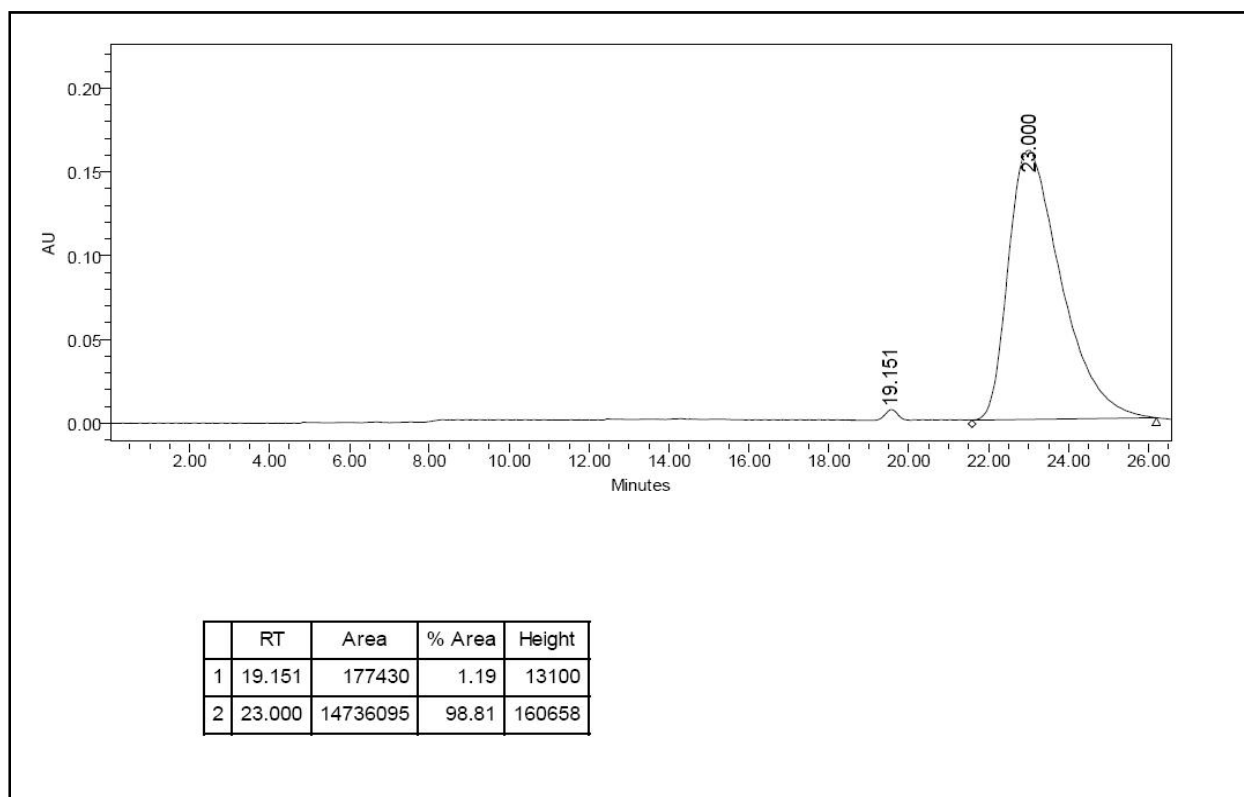


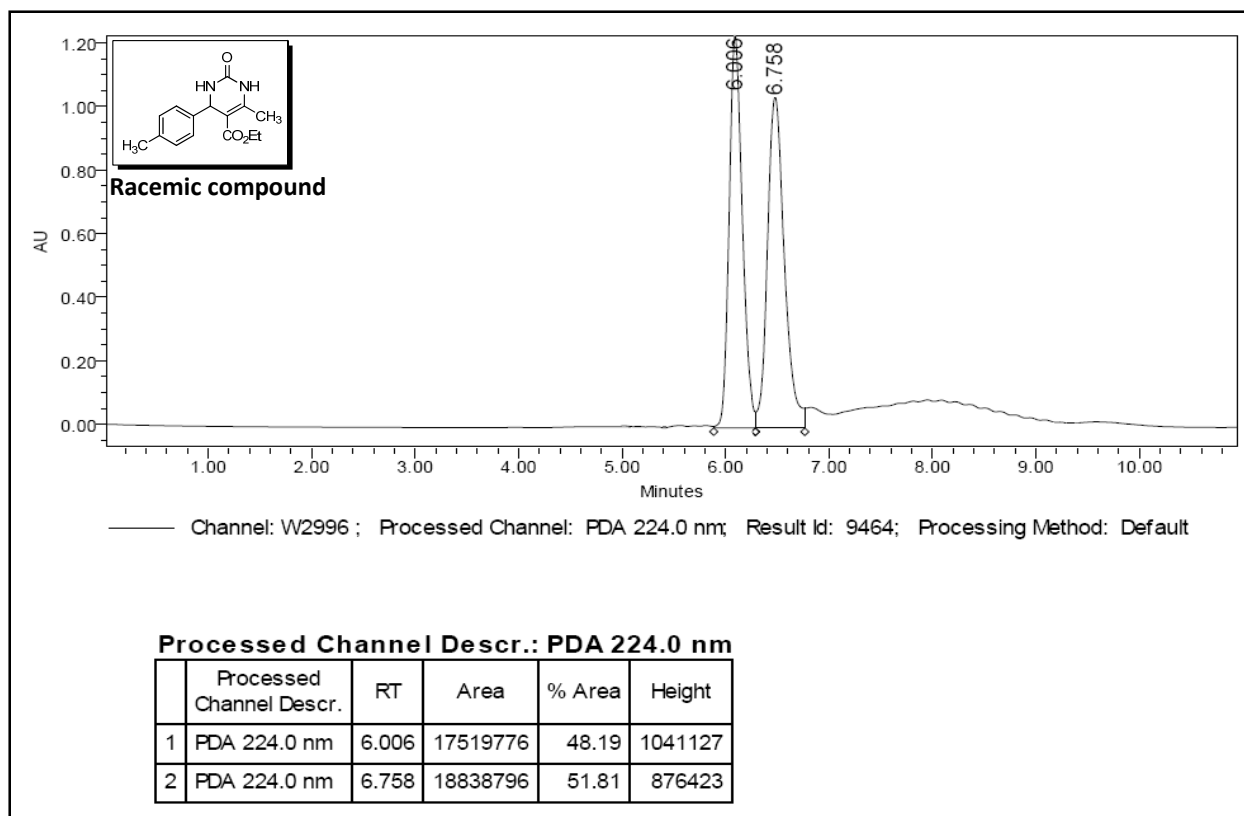
HPLC Profile for Entry 4, Table 3, 98% ee



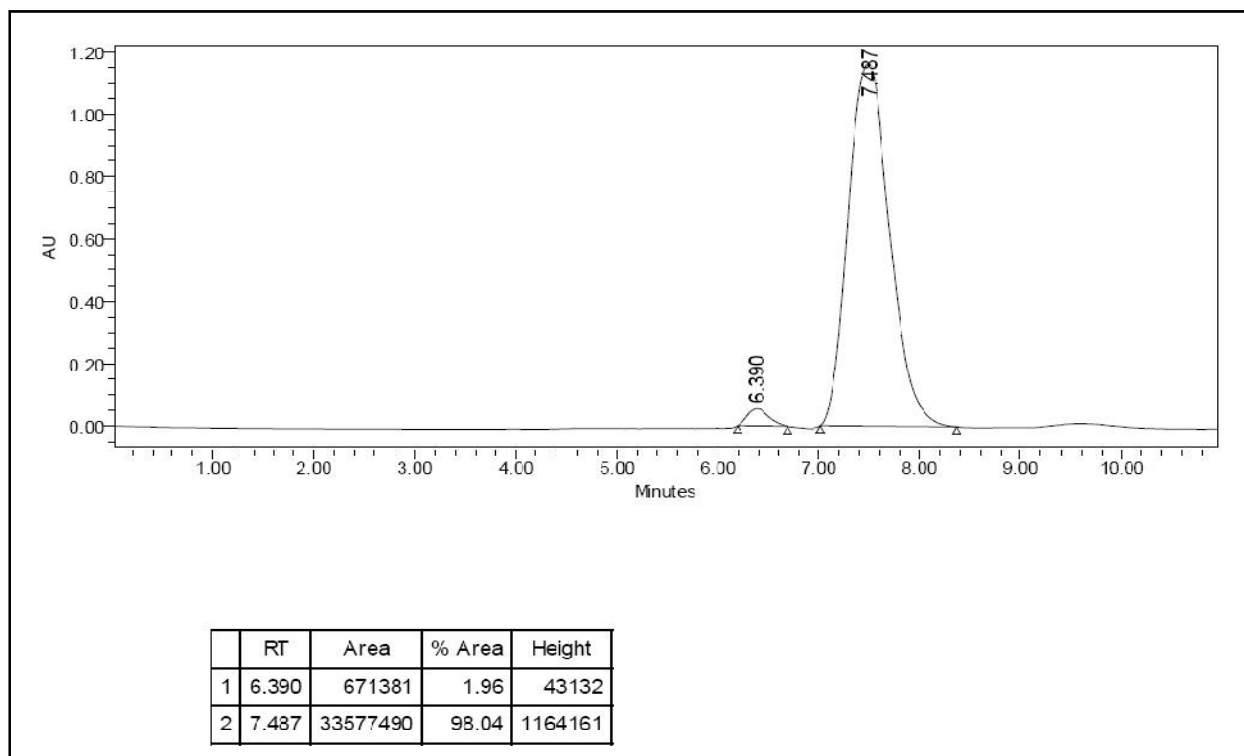


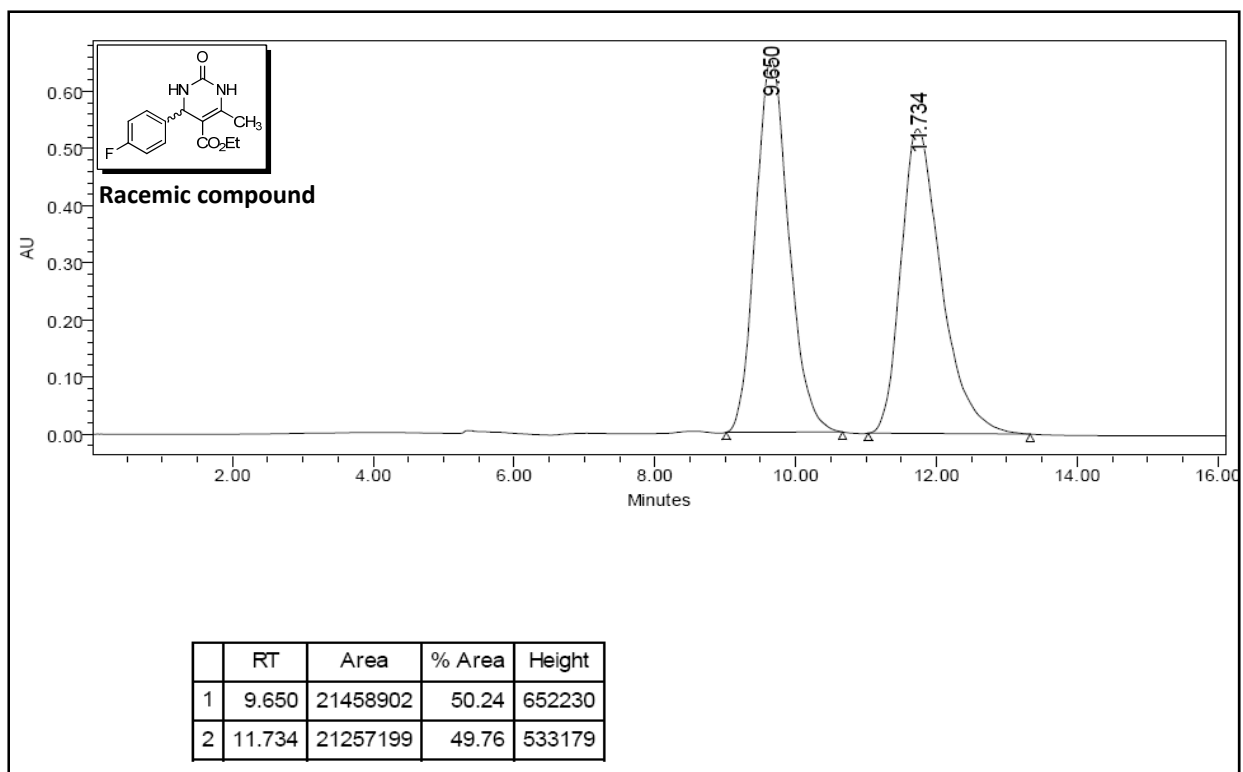
HPLC Profile for Entry 5, Table 3, 98% ee



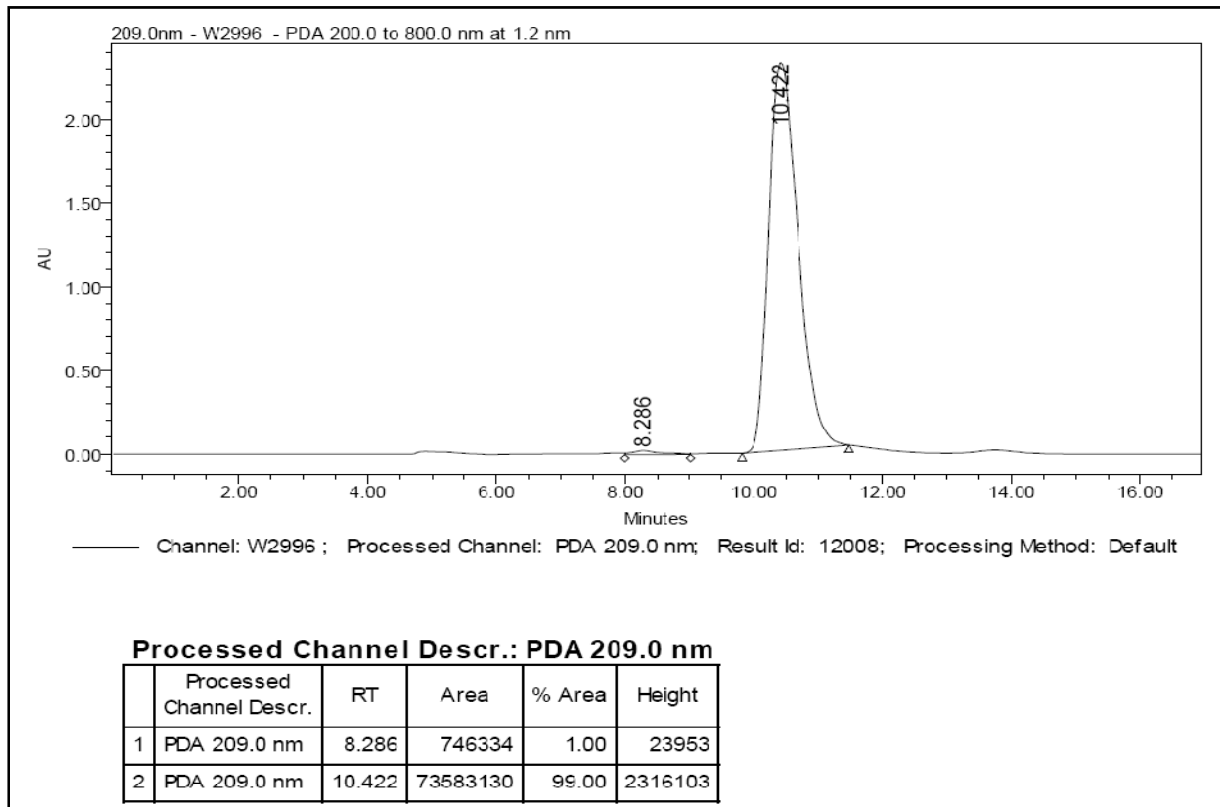


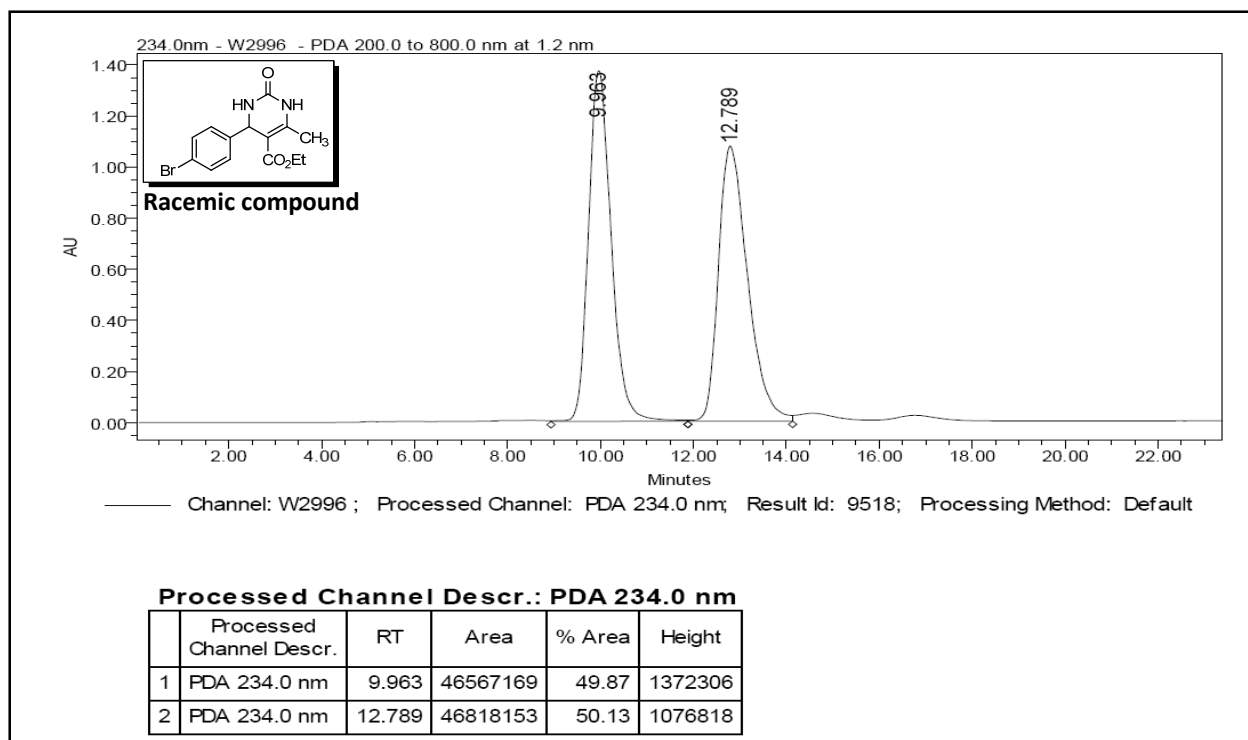
HPLC Profile for Entry 6, Table 3, 96% ee



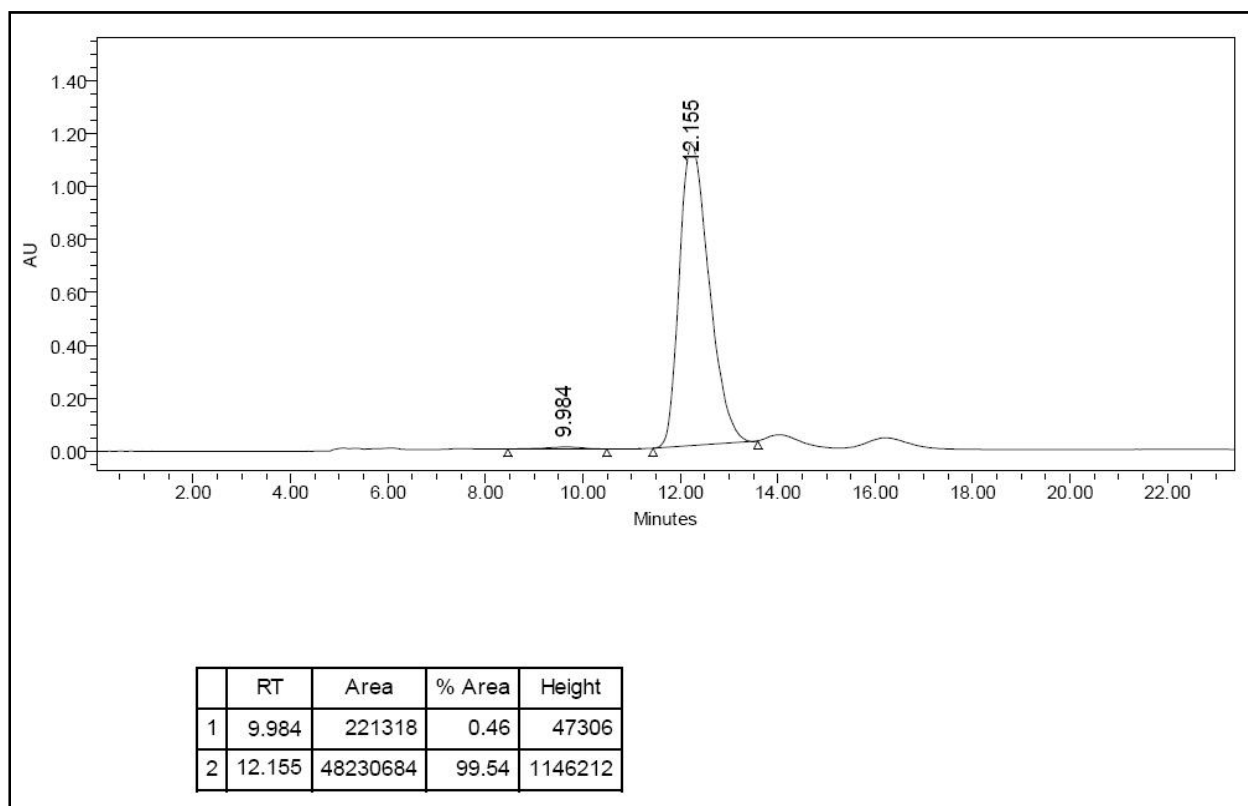


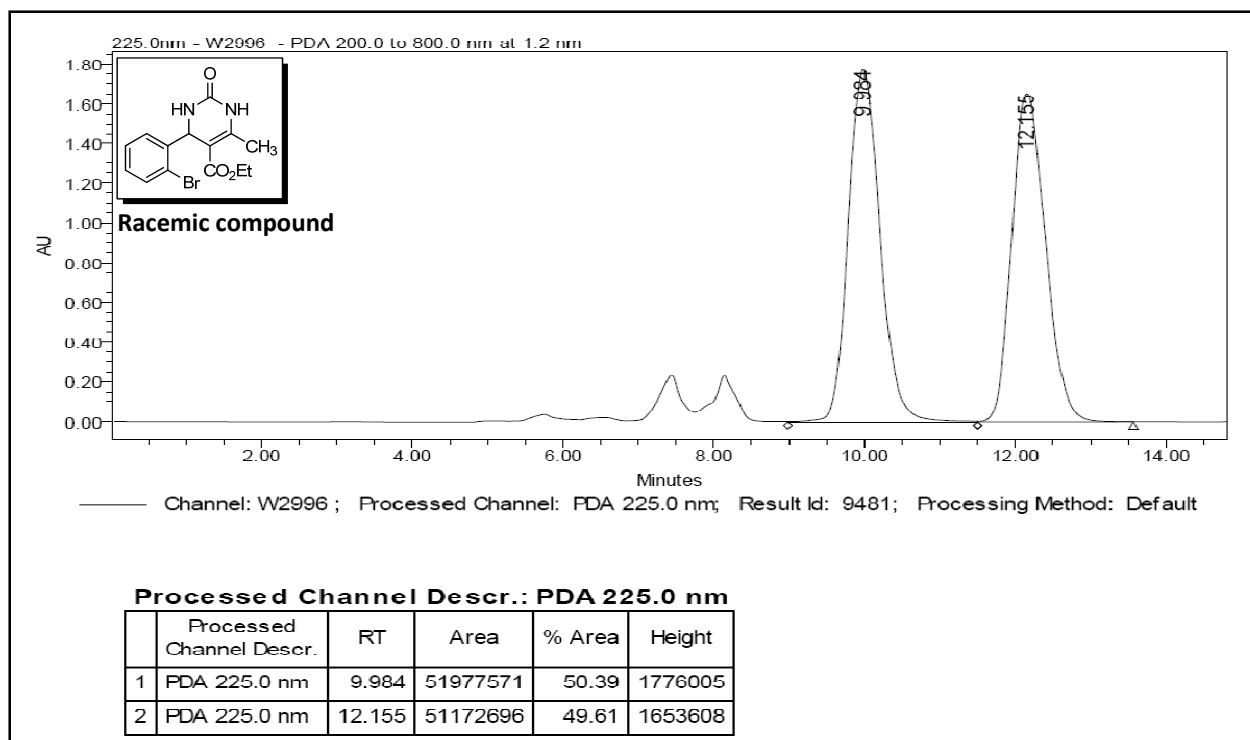
HPLC Profile for Entry 7, Table 3, 98% ee



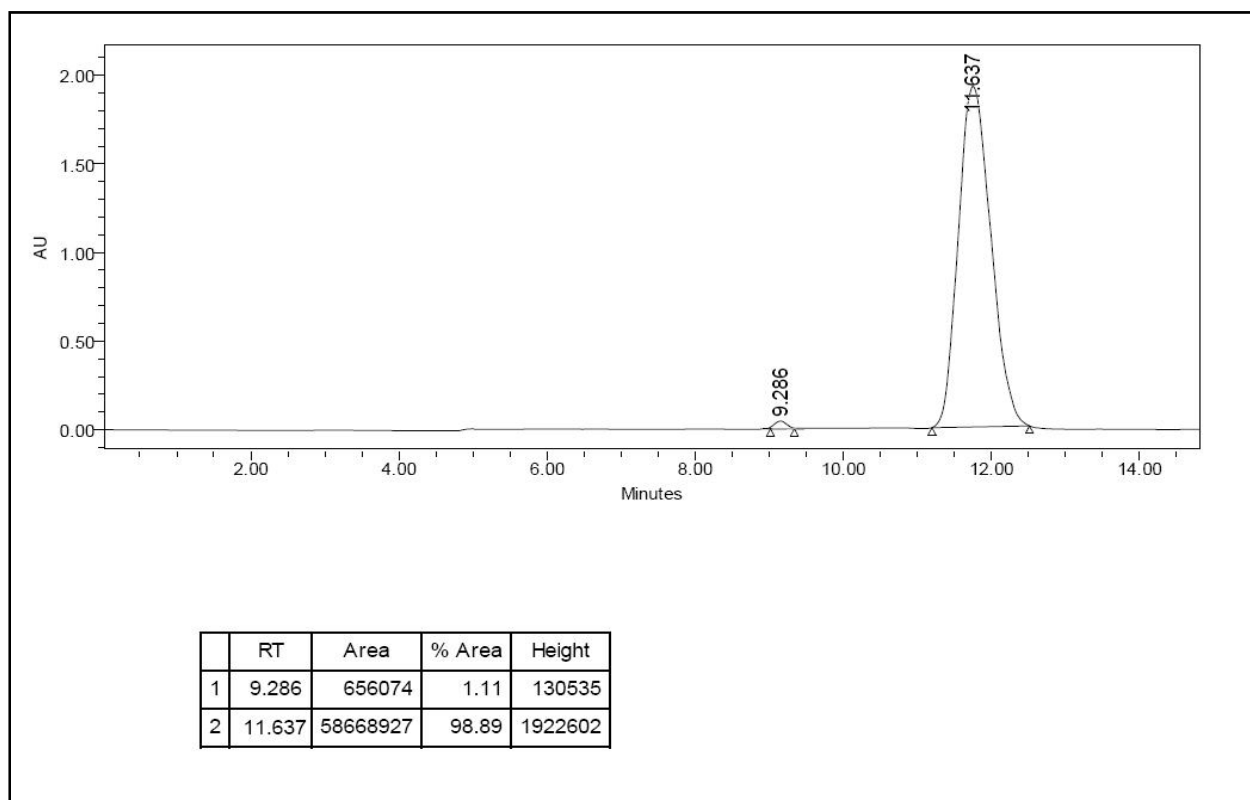


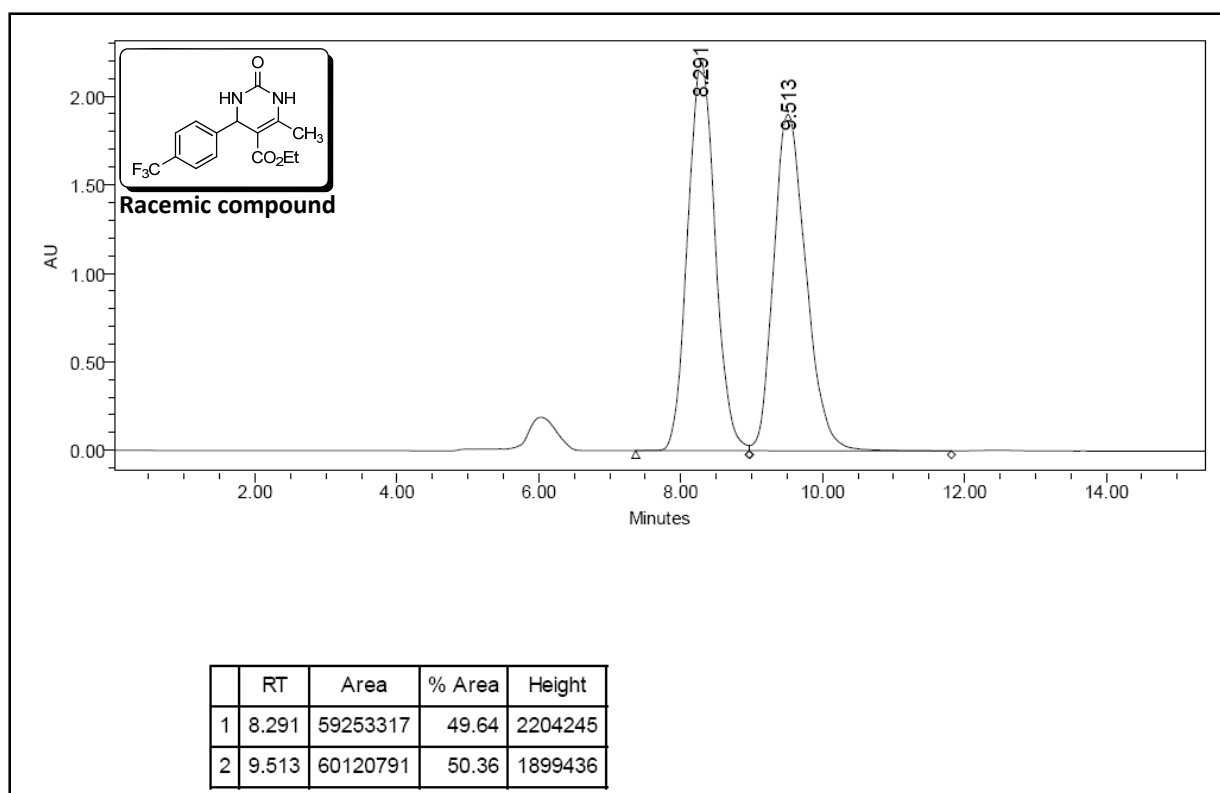
HPLC Profile for Entry 8, Table 3, 99% ee



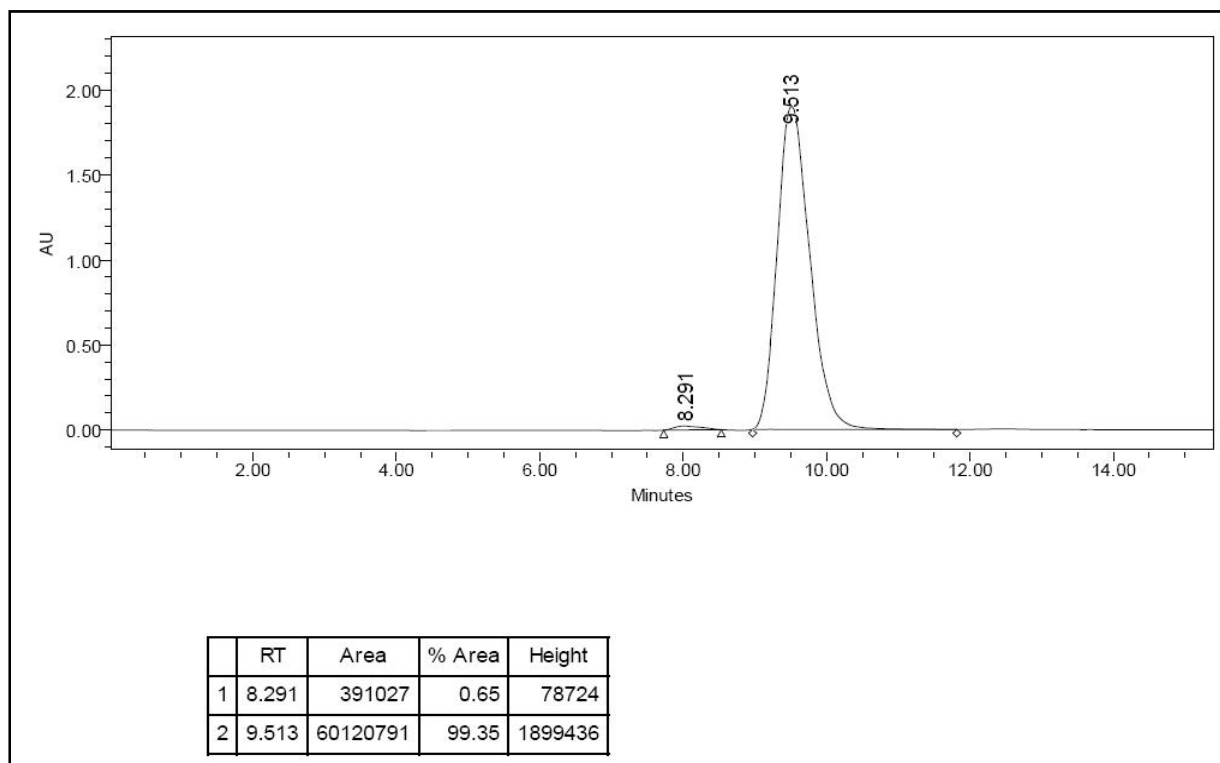


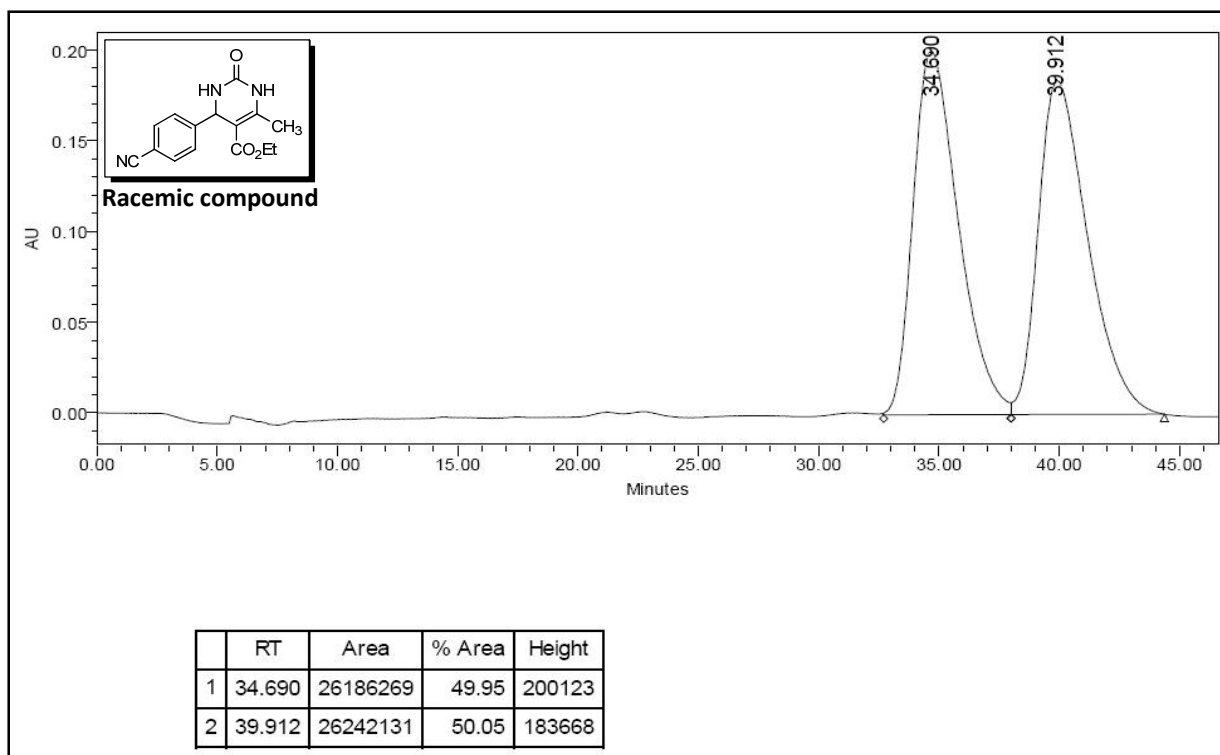
HPLC Profile for Entry 9, Table 3, 98% ee



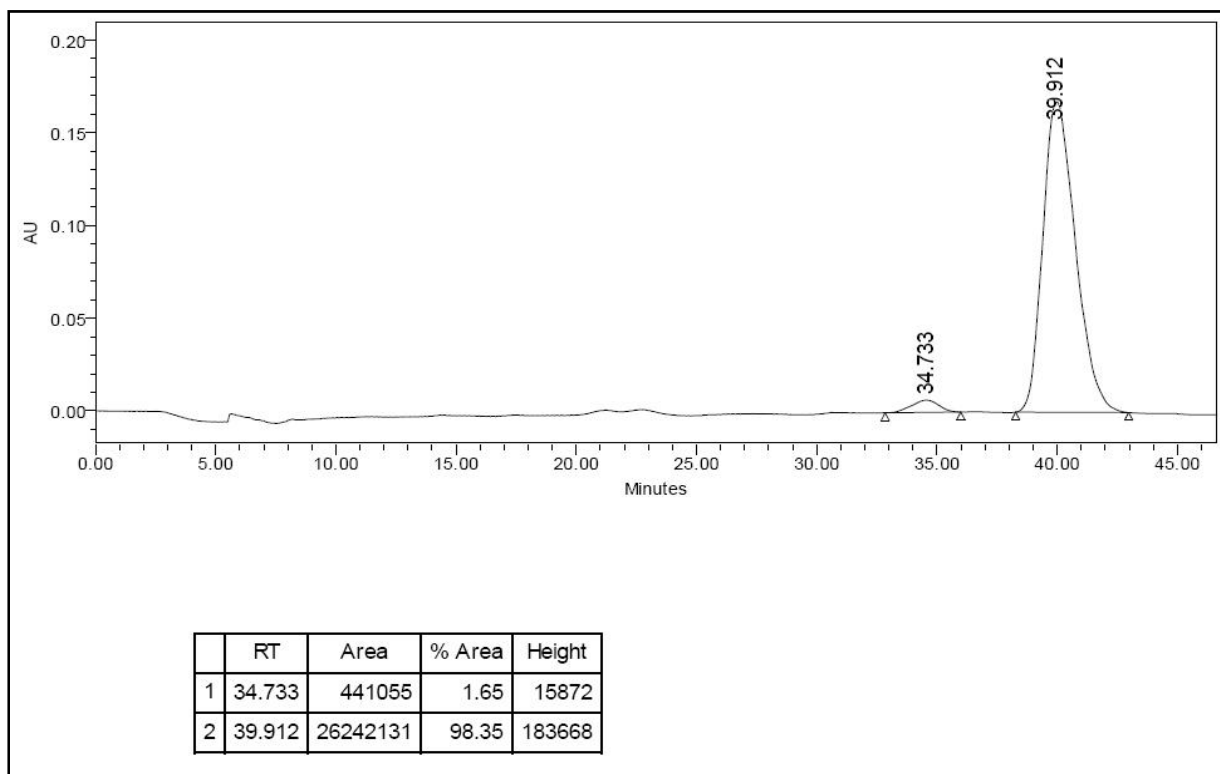


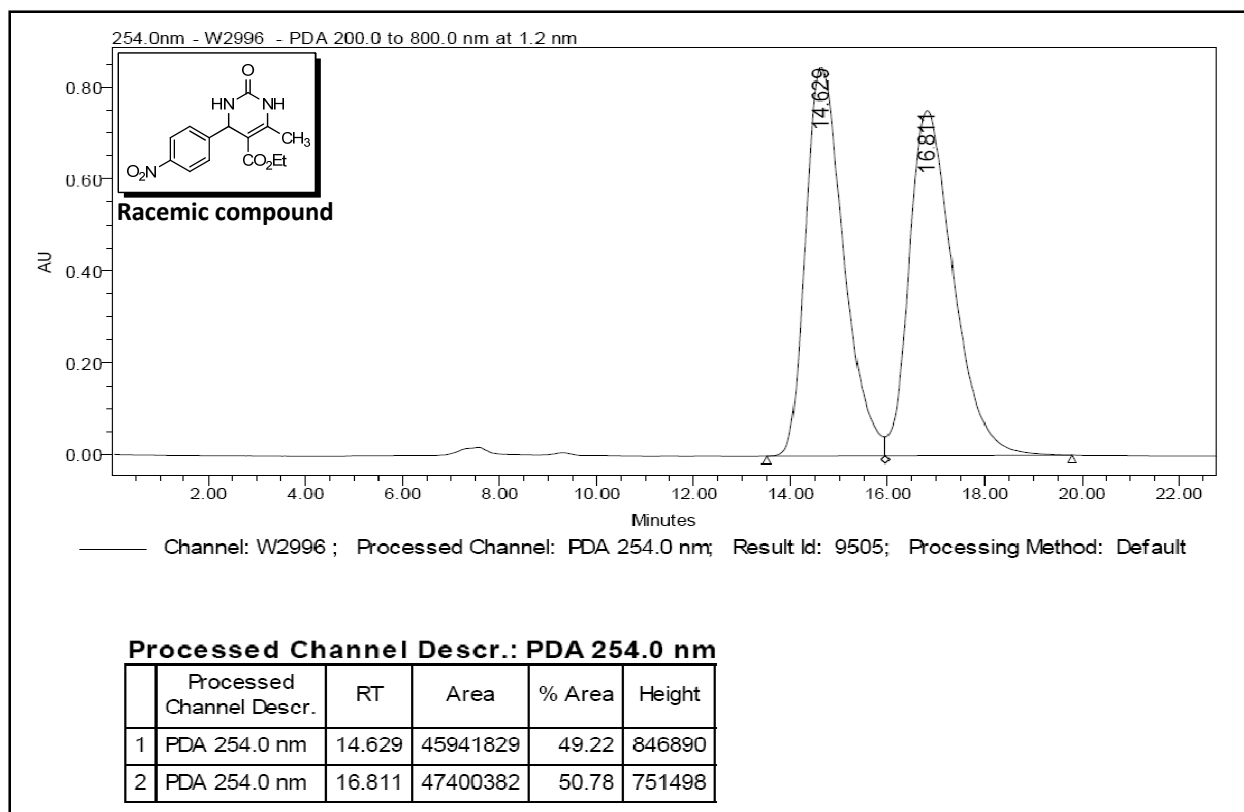
HPLC Profile for Entry 10, Table 3, 98% ee



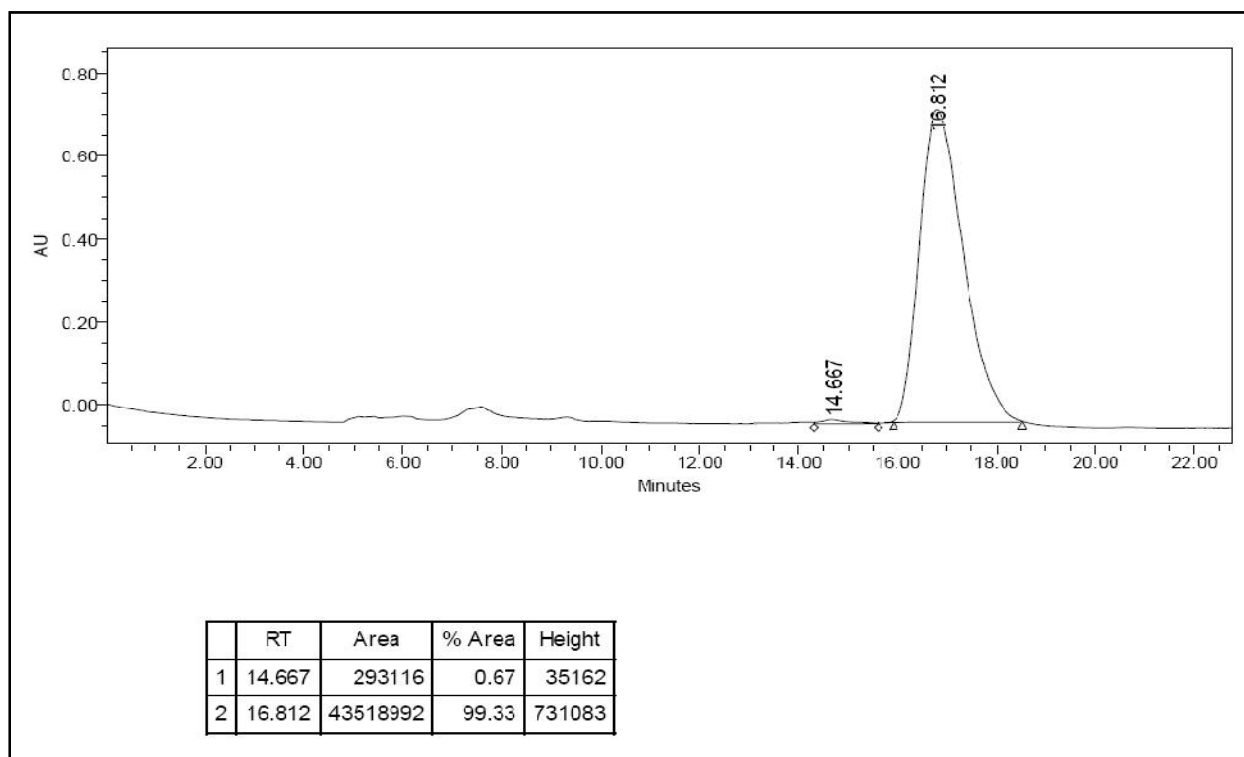


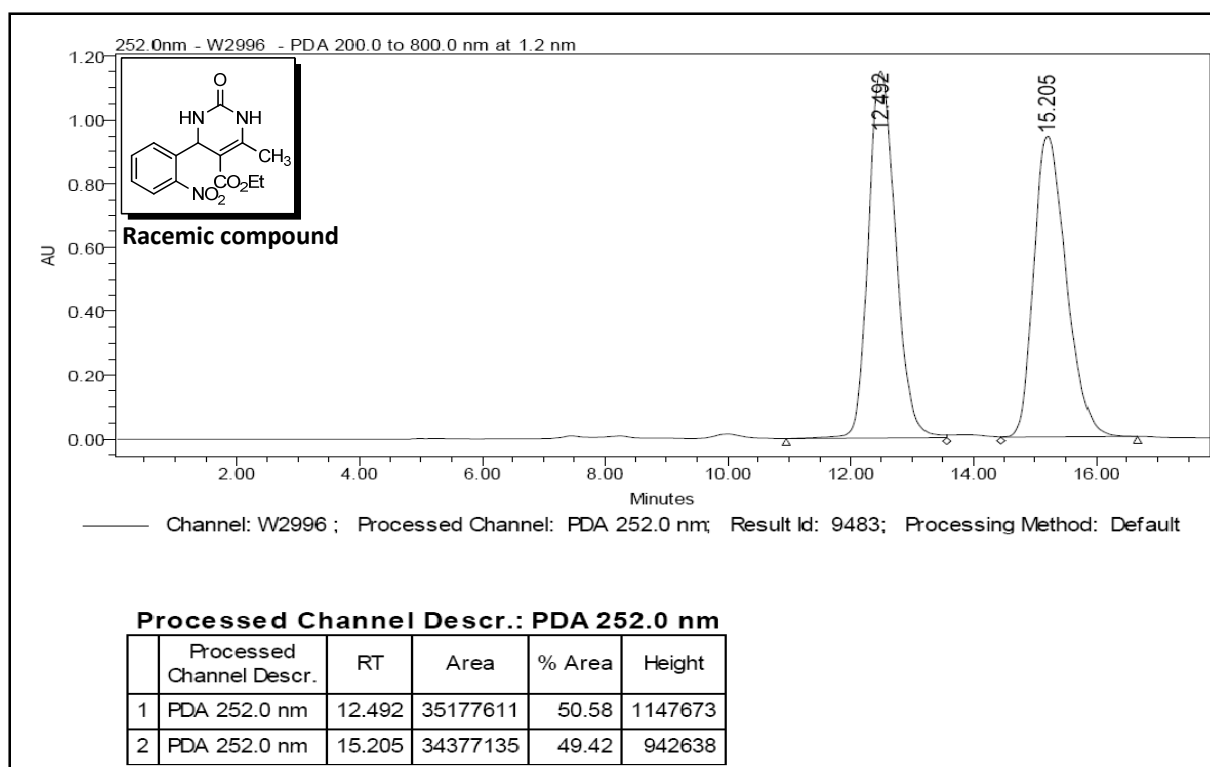
HPLC Profile for Entry 11, Table 3, 97% ee



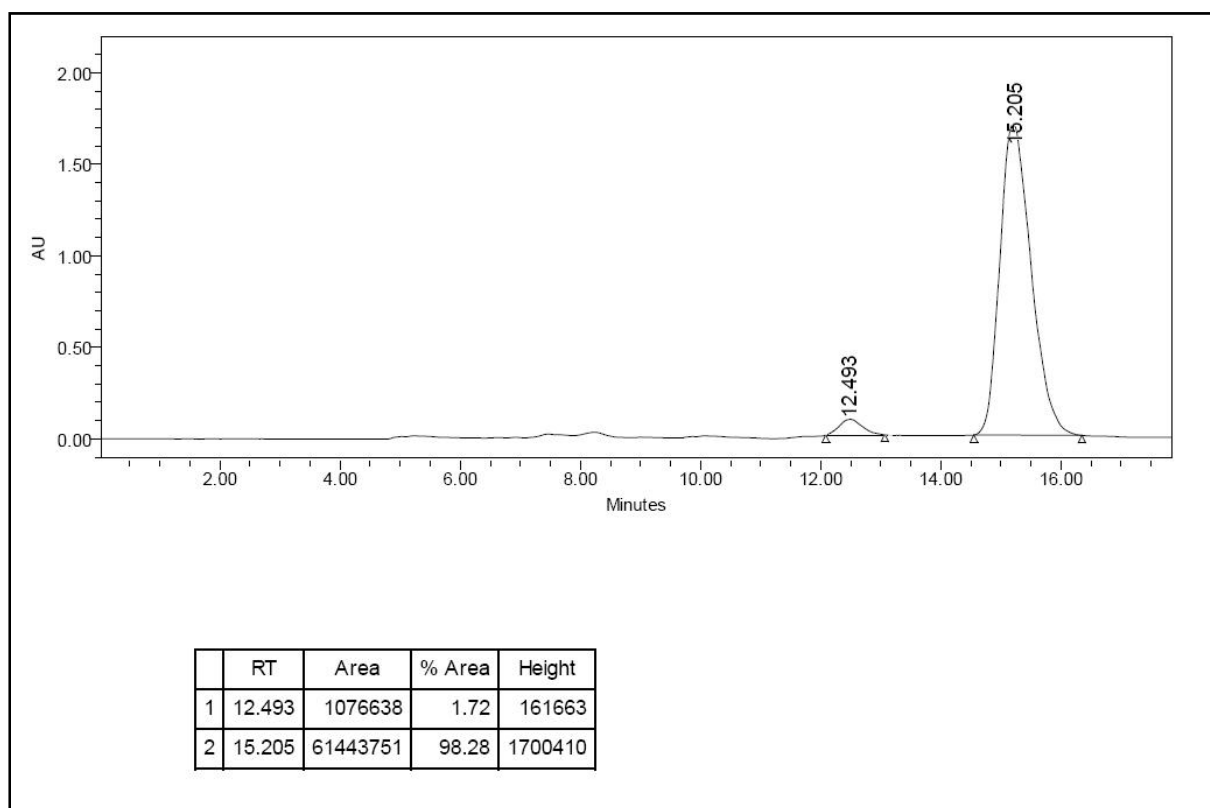


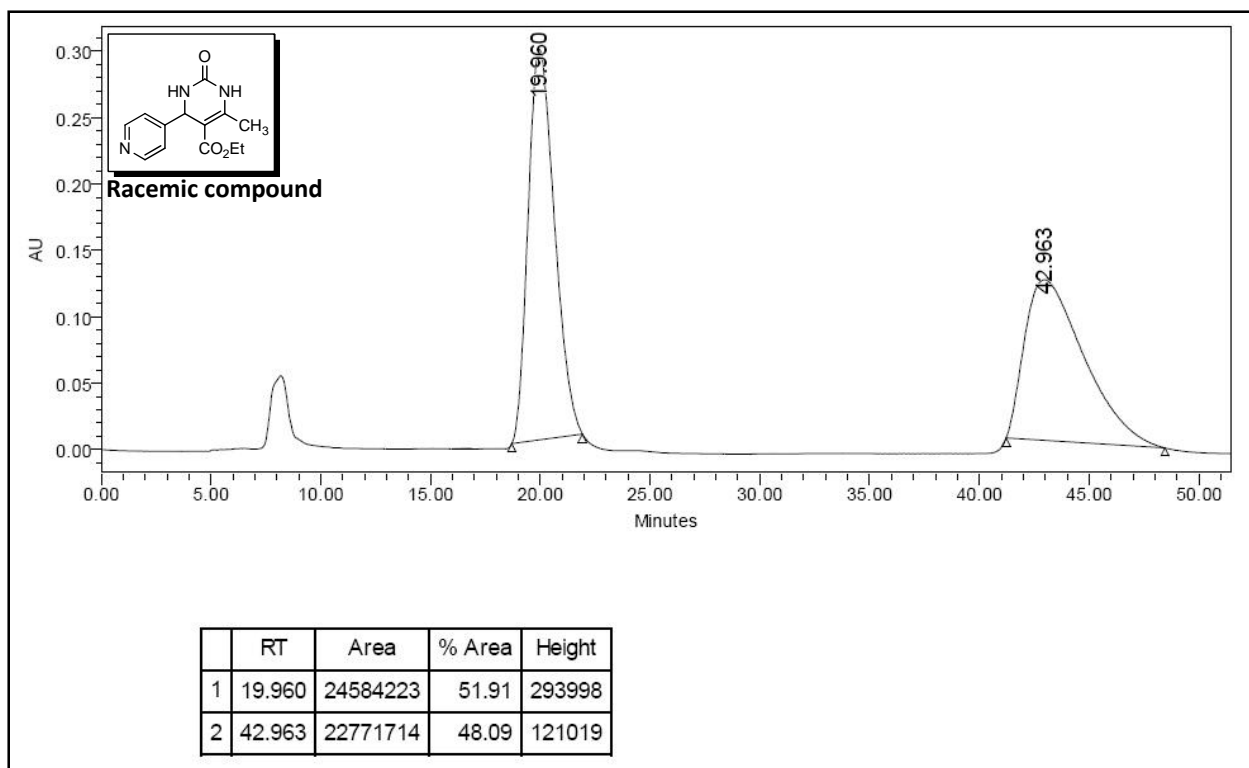
HPLC Profile for Entry 12, Table 3, 99% ee



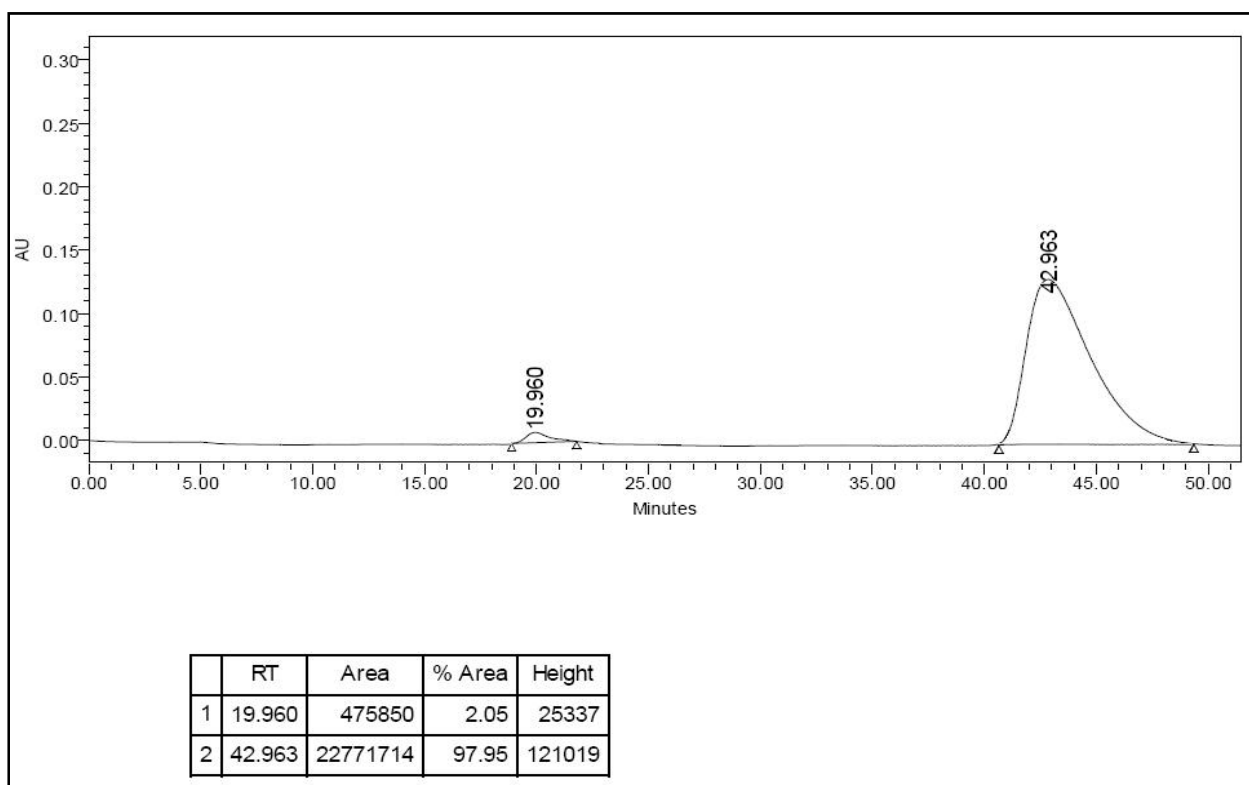


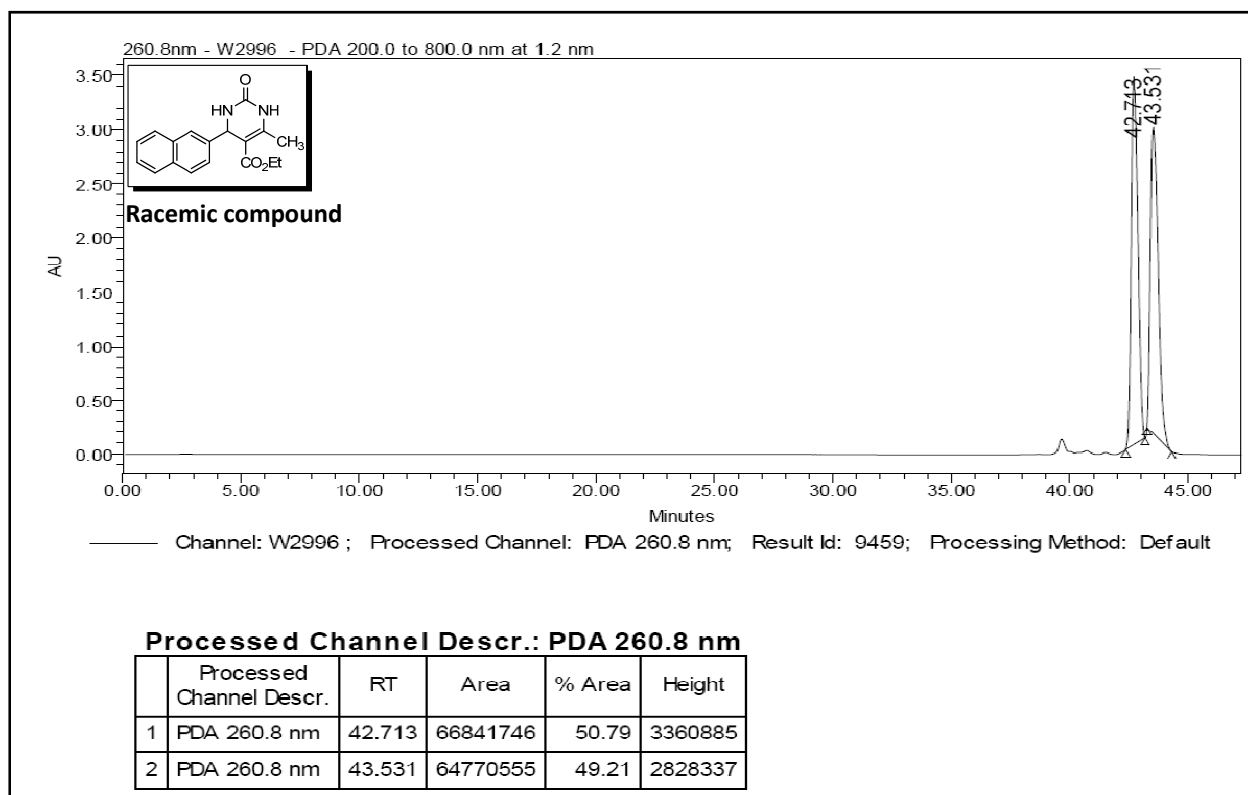
HPLC Profile for Entry 13, Table 3, 96% ee



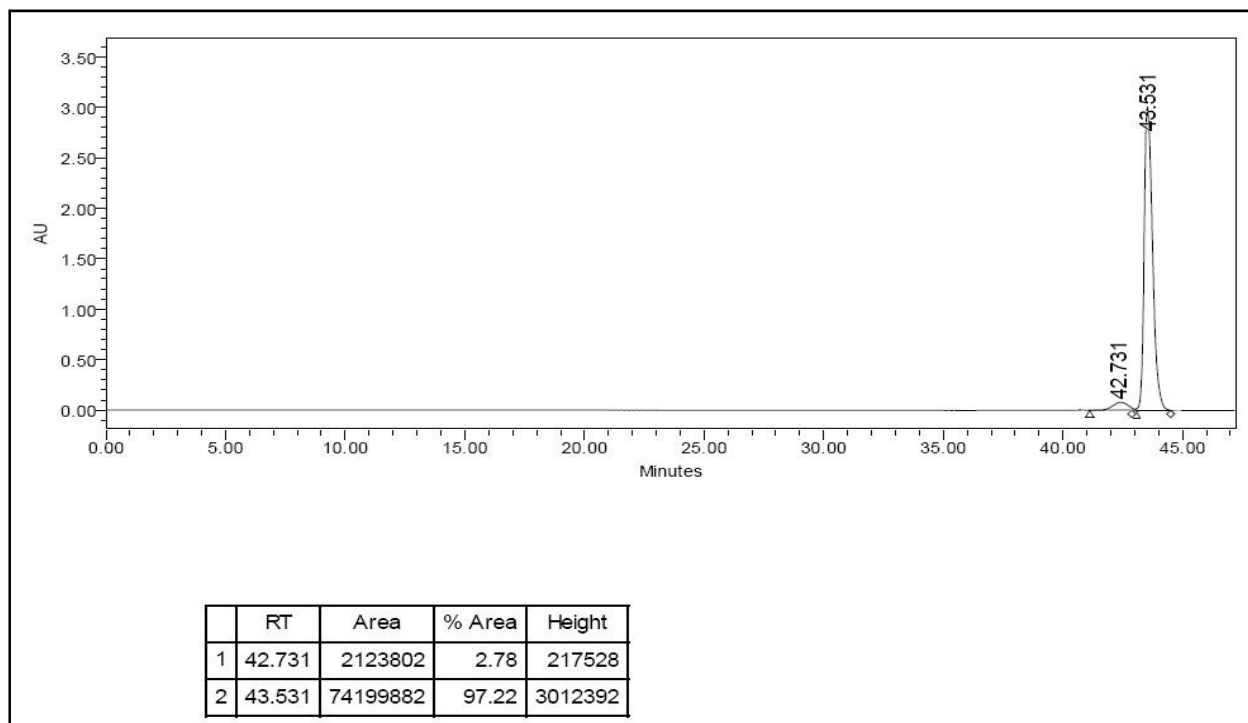


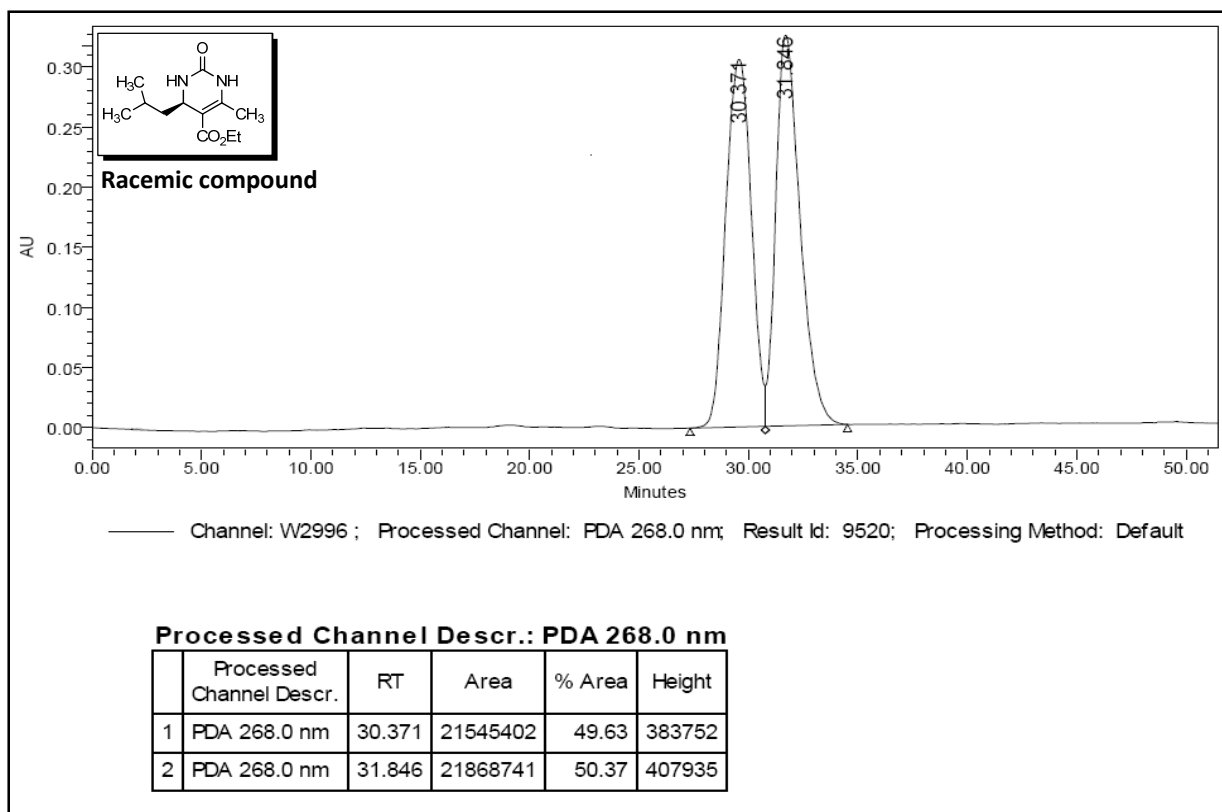
HPLC Profile for Entry 14, Table 3, 96% ee



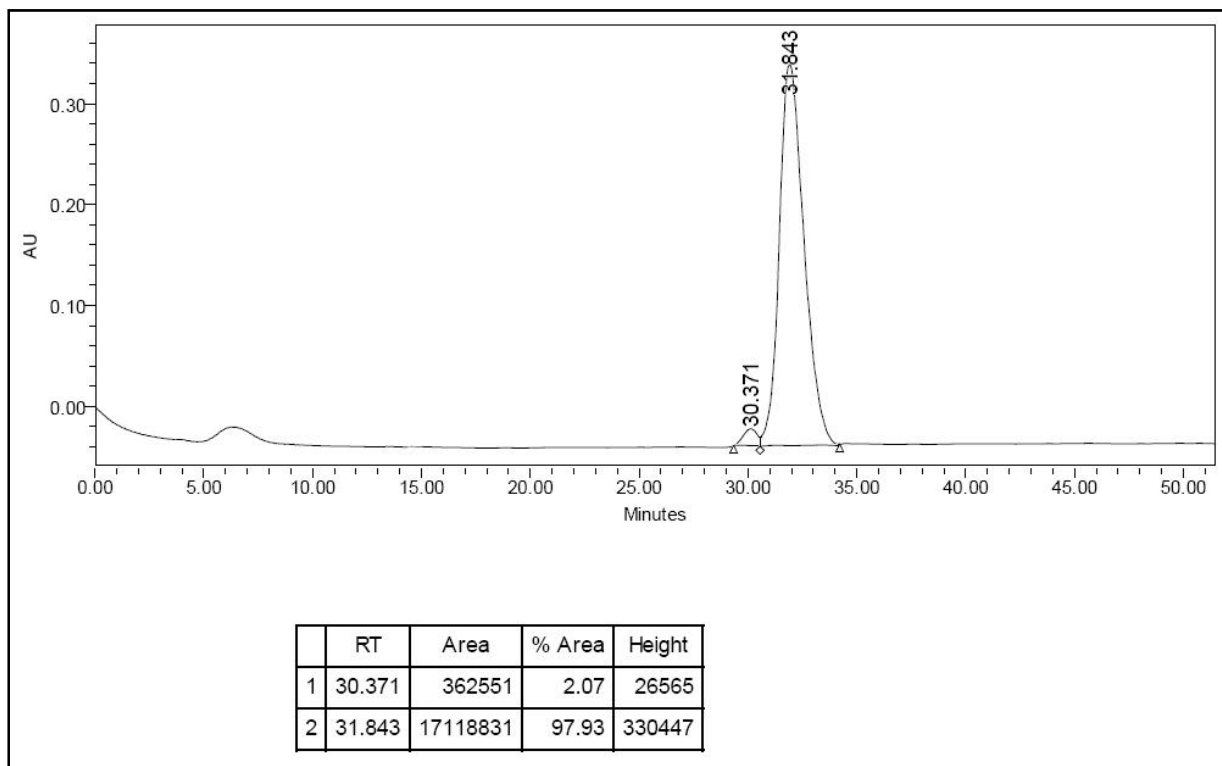


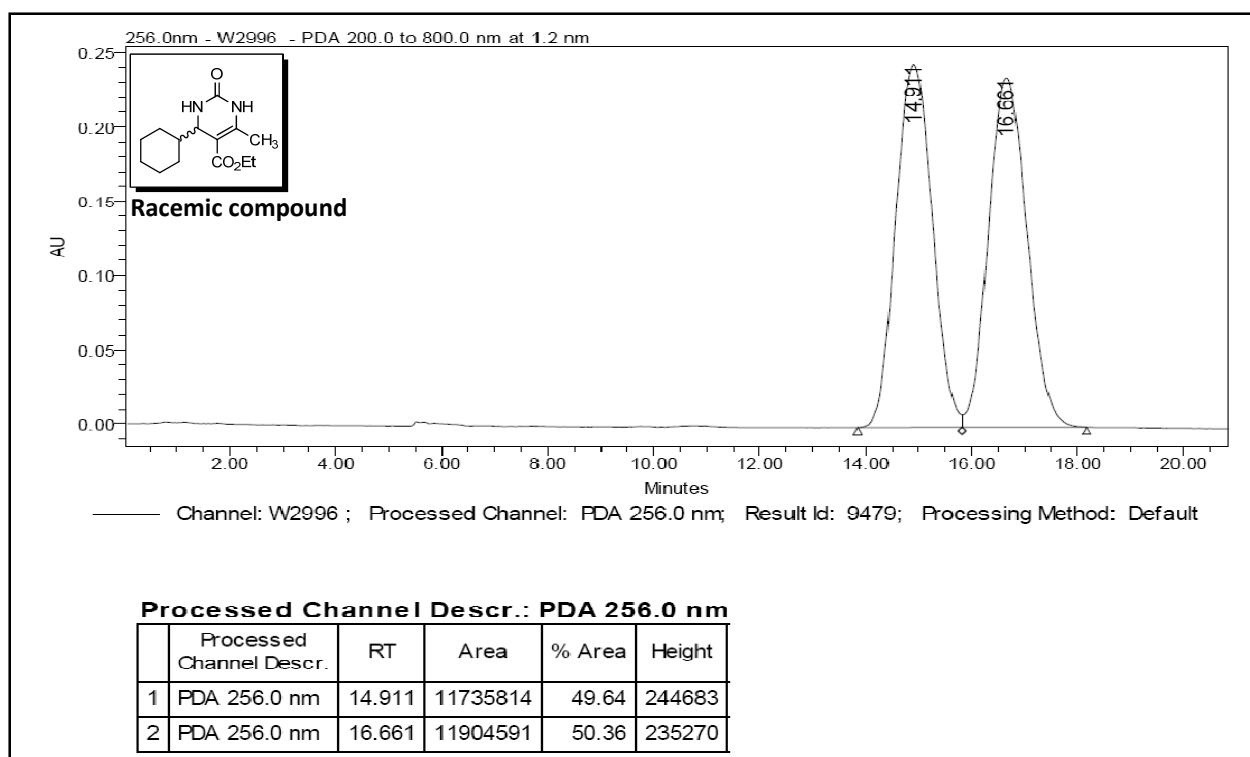
HPLC Profile for Entry 15, Table 3, 94% ee



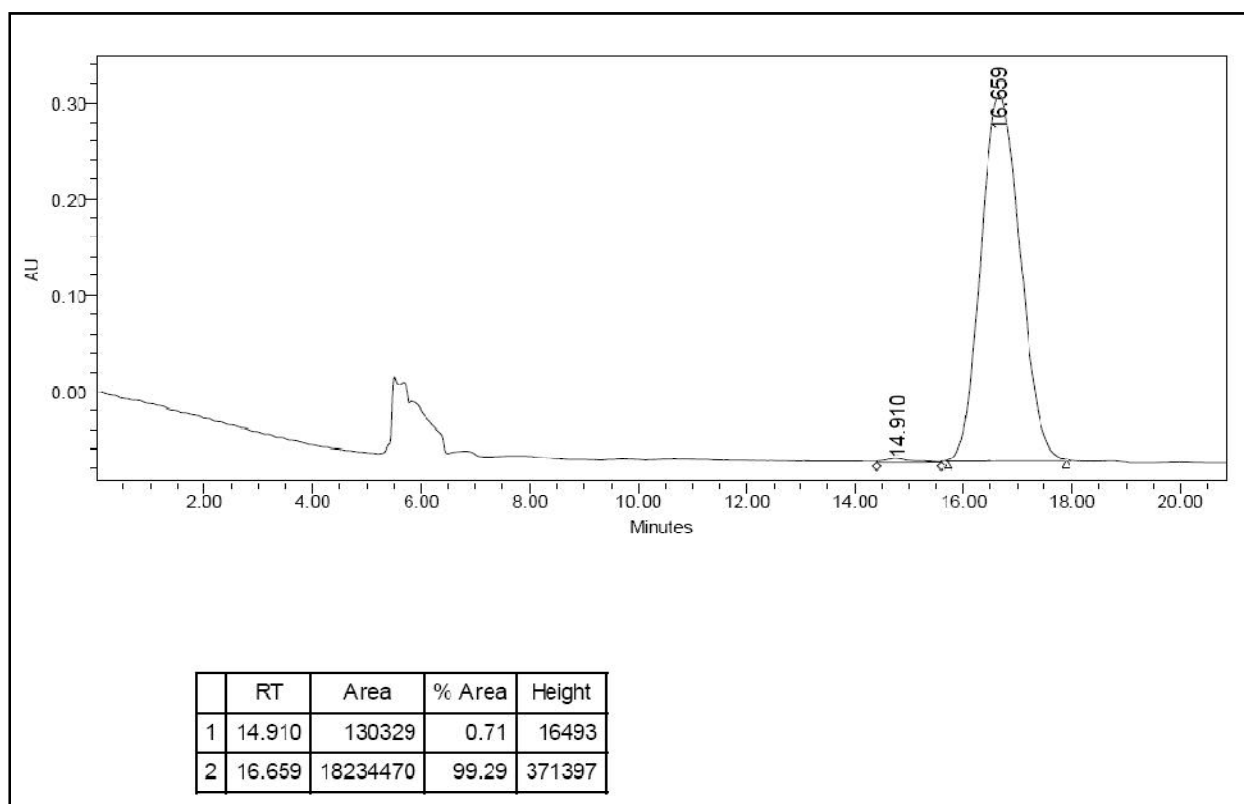


HPLC Profile for Entry 16, Table 3, 96% ee





HPLC Profile for Entry 17, Table 3, 98% ee



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