Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Organocatalytic Formal [2+2] Cycloaddition Initiated by Vinylogous Friedel-Crafts Alkylation: Enantioselective Synthesis of Substituted Cyclobutane Derivatives

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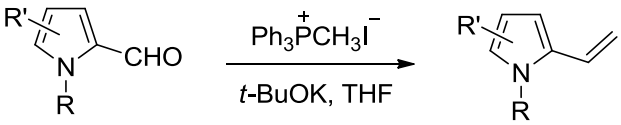
1. General information

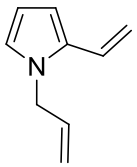
All glassware was thoroughly oven-dried. Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. Thin-layer chromatography plates were visualized by exposure to ultraviolet light and/or staining with phosphomolybdic acid followed by heating on a hot plate. Flash chromatography was carried out using silica gel (200-300 mesh) or aluminum oxide-neutral. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 (400 MHz). Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants *J* are given in Hz. The spectra were recorded in $CDCl_3$ as the solvent at room temperature, TMS served as internal standard (δ = 0 ppm) for ^{1}H NMR and $CDCl_3$ used as an internal standard (δ = 77.00 ppm) for ^{13}C NMR. IR spectra were recorded on a Nicolet NEXUS 670 FT-IR instrument. Optical rotation was measured on the Perkin Elmer 341 polarimeter. HRMS were performed on a Bruker Apex II mass instrument (ESI). Enantiomeric excess values were determined by HPLC with Chiralcel OD-H, AD-H or AS-H columns on Waters 600 Delta eluting with *i*-PrOH and *n*-hexane.

2. General procedure for the preparation of vinyl pyrroles[1] and analytical date:



Potassium *t*-butoxide (3.9 mmol, 1.3 eq) was added slowly to methyltriphenylphosphonium bromide (3.9 mmol, 1.3 eq) in THF (10 mL) at 0 °C under nitrogen, formation of the bright yellow color characteristic of the ylide was observed immediately. The mixture was stirred at RT under nitrogen for 1 h and then cooled to 0 °C. A solution of pyrroles (3.0 mmol, 1.0 eq) in THF (4 mL) was added dropwise over 10 min, and the mixture was stirred at 50 °C until the reaction was completed as indicated by TLC analysis. The mixture was allowed to cool to room temperature and filtered. The filter cake was washed with THF (3×20 mL), the filtrate was then concentrated *in vacuo* and the crude product was purified by flash chromatography on aluminum oxide-neutral (eluting with petroleum ether/ethyl acetate) to afford the pure product.

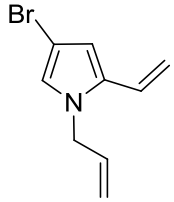
1-allyl-2-vinyl-1H-pyrrole (1a)



Colorless oil (yield: 65%); ^{1}H NMR (400 MHz): δ 6.64 (t, *J* = 2.0 Hz, 1H), 6.55 (dd, *J* = 17.6, 11.2 Hz, 1H), 6.43–6.42 (m, 1H), 6.16 (t, *J* = 3.2 Hz , 1H), 6.00–5.91 (m, 1H), 5.50 (dd, *J* = 21.6, 1.2 Hz, 1H),

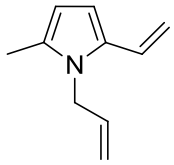
5.20 –5.17(m, 1H), 5.04 (dd, *J* = 11.2, 1.2 Hz, 1H), 5.01–4.96 (m, 1H), 4.54–4.52 (m, 2H); ^{13}C NMR (100 MHz): δ 134.2, 131.7, 125.3, 122.2, 116.7, 111.2, 108.1, 106.4, 49.3.

1-allyl-4-bromo-2-vinyl-1H-pyrrole (1b)[1-2]



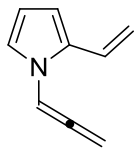
Colorless oil (yield: 55%); ^{1}H NMR (400 MHz): δ 6.60 (d, *J* = 2.0 Hz, 1H), 6.45 (dd, *J* = 17.2, 11.2 Hz, 1H), 6.38 (d, *J* = 2.0 Hz, 1H), 5.95–5.85 (m, 1H), 5.49 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.20 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.08 (dd, *J* = 10.8, 0.8 Hz, 1H), 5.00 (dd, *J* = 16.8, 1.2 Hz, 1H), 4.47–4.45 (m, 2H); ^{13}C NMR (100 MHz): δ 133.4, 132.4, 124.3, 121.4, 117.3, 113.0, 108.6, 95.9, 49.4.

1-allyl-2-methyl-5-vinyl-1H-pyrrole (1c)[1, 3]



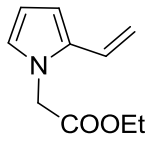
Colorless oil (yield: 62%); ^{1}H NMR (400 MHz): δ 6.49 (dd, *J* = 17.6, 11.2 Hz, 1H), 6.32 (d, *J* = 3.6 Hz, 1H), 5.93–5.86 (m, 2H), 5.44 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.14 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.95 (dd, *J* = 11.2, 1.2 Hz, 1H), 4.77 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.47–4.45 (m, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz): δ 133.9, 131.2, 129.8, 125.8, 116.0, 109.9, 106.9, 105.2, 45.5, 12.2.

1-(propa-1,2-dien-1-yl)-2-vinyl-1H-pyrrole (1d)



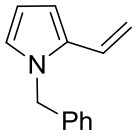
Colorless oil (yield: 68%); ^{1}H NMR (400 MHz): δ 6.95 (t, *J* = 6.4 Hz, 1H), 6.79 (s, 1H), 6.64 (dd, *J* = 17.6, 11.2 Hz, 1H), 6.38 (s, 1H), 6.19 (d, *J* = 2.4 Hz, 1H), 5.51 (d, *J* = 17.2 Hz, 1H), 5.45 (d, *J* = 6.4 Hz, 2H), 5.09 (d, *J* = 11.2 Hz, 1H); ^{13}C NMR (100 MHz): δ 203.6, 131.7, 125.0, 120.3, 112.6, 109.9, 107.7, 97.3, 86.5.

ethyl 2-(2-vinyl-1H-pyrrol-1-yl)acetate (1e)



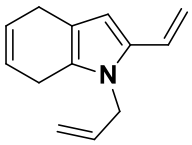
Colorless oil (yield: 57%); ^{1}H NMR (400 MHz): δ 6.62 (d, *J* = 1.6 Hz, 1H), 6.49–6.41 (m, 2H), 6.17 (t, *J* = 3.2 Hz, 1H), 5.48 (d, *J* = 17.2 Hz, 1H), 5.07 (d, *J* = 11.6 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 168.5, 132.1, 124.8, 123.1, 112.1, 108.8, 107.1, 61.6, 48.5, 14.1.

1-benzyl-2-vinyl-1H-pyrrole (1f)



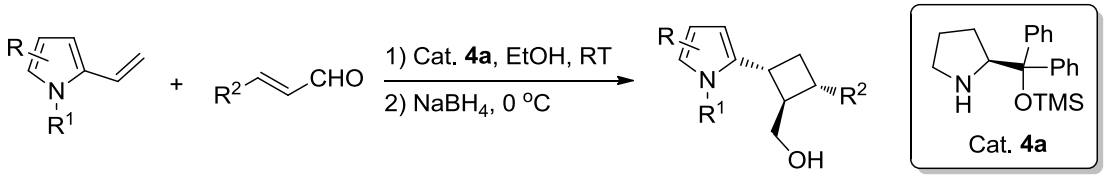
Colorless oil (yield: 70%); ^{1}H NMR (400 MHz): δ 7.31–7.21 (m, 3H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.67–6.66 (t, *J* = 2.0 Hz, 1H), 6.51–6.44 (m, 2H), 6.18–6.17 (t, *J* = 3.2 Hz, 1H), 5.46 (dd, *J* = 17.6, 1.6 Hz, 1H), 5.11 (s, 2H), 4.96 (dd, *J* = 11.2, 1.6 Hz, 1H); ^{13}C NMR (100 MHz): δ 138.1, 131.9, 128.7, 127.4, 126.2, 125.3, 122.8, 111.4, 108.4, 106.7, 50.4.

1-allyl-2-vinyl-4,7-dihydro-1H-indole (1g)[1, 4-5]



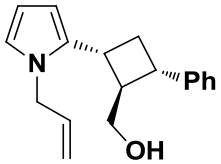
Colorless oil (yield: 72%); ^{1}H NMR (400 MHz): δ 6.51 (dd, *J* = 17.2, 11.2 Hz, 1H), 6.25 (s, 1H), 5.92-5.79 (m, 3H), 5.44 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.11 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.94 (dd, *J* = 11.2, 1.2 Hz, 1H), 4.82 (dd, *J* = 11.2, 1.2 Hz, 1H), 4.43-4.41 (m, 2H), 3.23-3.17 (m, 4H); ^{13}C NMR (100 MHz): δ 134.1, 130.7, 126.3, 125.9, 125.5, 122.2, 115.9, 114.4, 109.8, 104.0, 45.4, 24.9, 23.2.

3. General procedure for the cascade reaction and analytical date:



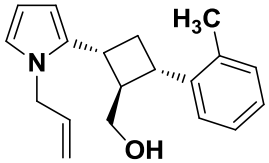
A solution of 1-allyl-2-vinyl-1H-pyrrole (0.15 mmol), (*E*)-Cinnamaldehyde (0.10 mmol) and *α,α*-diphenylprolinol trimethylsilyl ether catalyst (20 mol%, 0.02 mmol) in EtOH (0.5 mL) was stirred at room temperature for indicated time, then $NaBH_4$ (0.12 mmol) was added to the mixture at 0 °C. After the solvent was evaporated under vacuum, the residue was purified by column chromatography on silica gel (eluting with petroleum ether/ethyl acetate) to afford the pure product.

((1R,2R,4S)-2-(1-allyl-1H-pyrrol-2-yl)-4-phenylcyclobutyl)methanol (3a)



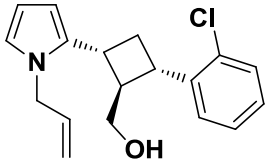
Colorless oil (yield: 76%). $[\alpha]_D^{20}$ = –18 (*c* 1.50, CH_2Cl_2, 93% *ee*); ^{1}H NMR (400 MHz): δ 7.35–7.29 (m, 4H), 7.24–7.20 (m, 1H), 6.61 (t, *J* = 2.4 Hz, 1H), 6.15 (t, *J* = 3.2 Hz, 1H), 6.09 (d, *J* = 1.2 Hz, 1H), 6.02–5.92 (m, 1H), 5.17 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.97 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.54–4.42 (m, 2H), 3.79 (d, *J* = 4.8 Hz, 2H), 3.33–3.21 (m, 2H), 2.81–2.69 (m, 1H), 2.68–2.64 (m, 1H), 2.08 (dd, *J* = 20.0, 10.4 Hz, 1H), 1.42 (s, 1H); ^{13}C NMR (100 MHz): δ 143.9, 135.9, 134.8, 128.4, 126.9, 126,3, 120.7, 116.5, 107.2, 104.8, 64.0, 52.2, 49.1, 38.8, 34.6, 30.0; IR (KBr, cm^{-1}): 3391, 2931, 1644, 1486, 1283, 1076, 1027, 993, 922, 752, 701; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane:*i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 12.6 min, minor enantiomer t_R = 17.3 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{18}H_{22}NO^+$: 268.1696, found: 268.1691.

((1R,2R,4S)-2-(1-allyl-1H-pyrrol-2-yl)-4-(o-tolyl)cyclobutyl)methanol (3b)



Colorless oil (yield: 53%); $[\alpha]_D^{20}$ = –20.5 (*c* 1.35, CH_2Cl_2, 91% *ee*); ^{1}H NMR (400 MHz): δ 7.35 (d, *J* = 8.0 Hz, 1H), 7.24–7.18 (m, 1H), 7.14–7.11 (m, 2H), 6.58 (s, 1H), 6.13 (t, *J* = 3.2 Hz, 1H), 6.07 (s, 1H), 6.00–5.91(m, 1H), 5.16 (d, *J* = 10.0 Hz, 1H), 4.95 (d, *J* = 17.2 Hz, 1H), 4.53–4.41 (m, 2H), 3.77 (d, *J* = 2.0 Hz, 2H), 3.44 (dd, *J* = 18.0, 9.6 Hz, 1H), 3.25 (dd, *J* = 17.6, 9.2 Hz, 1H), 2.97–2.90 (m, 1H), 2.72 (dd, *J* = 18.0, 8.0 Hz, 1H), 2.32 (s, 3H), 1.89 (dd, *J* = 20.4, 10.0 Hz, 1H), 1.39 (s, 1H); ^{13}C NMR (100 MHz): δ 141.5, 136.0, 135.9, 134.8, 130.1, 126.1, 126.0, 125.6, 120.7, 116.4, 107.2, 104.9, 63.8, 50.3, 49.0, 35.6, 35.1, 30.1, 19.7; IR (KBr, cm^{-1}): 3405, 2934, 1643, 1486, 1284, 1076, 923, 755, 710, 615; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 10.6 min, minor enantiomer t_R = 16.7 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{19}H_{24}NO^+$: 282.1852, found: 282.1845.

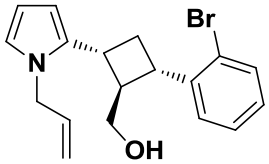
((1R,2R,4S)-2-(1-allyl-1H-pyrrol-2-yl)-4-(2-chlorophenyl)cyclobutyl)methanol (3c)



Colorless oil (yield: 78%); $[\alpha]_D^{20}$ = –18.9 (*c* 1.17, CH_2Cl_2, 95% *ee*); ^{1}H NMR (400 MHz): δ 7.44 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.34 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.28–7.25 (m, 1H), 7.17–7.13 (m, 1H), 6.59 (t, *J* = 2.4 Hz, 1H), 6.13 (t, *J* = 3.2 Hz, 1H), 6.07–6.06 (m, 1H), 5.99–5.91 (m, 1H), 5.17 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.95 (dd, *J* = 17.0, 1.2 Hz, 1H), 4.53–4.45 (m, 2H), 3.79 (d, *J* = 2.4 Hz, 2H), 3.67 (dd, *J* = 9.6 Hz, 1H), 3.28

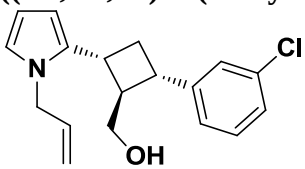
(dd, *J* = 9.6 Hz, 1H), 2.84–2.72 (m, 2H), 1.97 (dd, *J* = 20.4, 10.0 Hz, 1H), 1.53 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz): δ 140.7, 135.7, 134.7, 133.6, 129.4, 127.6, 127.4, 127.0, 120.8, 116.5, 107.1, 104.8, 63.7, 51.1, 49.1, 35.8, 34.2, 29.8; IR (KBr, cm^{-1}): 3410, 2935, 1645, 1478, 1438, 1283, 1034, 924, 754, 710, 614; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 23.1 min, minor enantiomer t_R = 40.7 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{18}H_{21}ClNO^+$: 302.1306, found: 302.1308.

((1R,2R,4S)-2-(1-allyl-1H-pyrrol-2-yl)-4-(2-bromophenyl)cyclobutyl)methanol (3d)



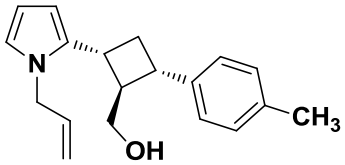
Colorless oil (yield: 63%); $[\alpha]_D^{20}$ = –15.2 (*c* 1.05, CH_2Cl_2, 92% *ee*); ^{1}H NMR (400 MHz): δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 1.6 Hz, 1H), 6.14 (t, *J* = 3.2 Hz, 1H), 6.08 (s, 1H), 6.01–5.92 (m, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 4.96 (d, *J* = 17.2 Hz, 1H), 4.54–4.42 (m, 2H), 3.82–3.74 (m, 2H), 3.65 (dd, *J* = 10.0 Hz, 1H), 3.29 (dd, *J* = 9.6 Hz, 1H), 2.86–2,76 (m, 2H), 1.96 (dd, *J* = 20.0, 10.0 Hz, 1H), 1.55 (t, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz): δ 142.4, 135.7, 134.7, 132.7, 127.8, 127.7, 127.7, 124.3, 120.8, 116.5, 107.2, 104.8, 63.6, 51.3, 49.1, 38.3, 34.5, 29.7; IR (KBr, cm^{-1}): 3416, 2935, 1643, 1474, 1283, 1024, 753, 709; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 12.3 min, minor enantiomer t_R = 20.2 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{18}H_{21}BrNO^+$: 346.0801, found: 346.0809.

((1R,2R,4S)-2-(1-allyl-1H-pyrrol-2-yl)-4-(3-chlorophenyl)cyclobutyl)methanol (3e)



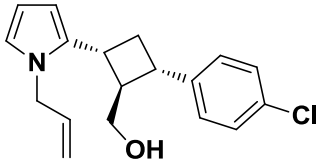
Colorless oil (yield: 68%); $[\alpha]_D^{20}$ = –10.5 (*c* 1.05, CH_2Cl_2, 91% *ee*); ^{1}H NMR (400 MHz): δ 7.25–7.15 (m, 4H), 6.59 (t, *J* = 2.2 Hz, 1H), 6.13 (t, *J* = 3.2 Hz, 1H), 6.06–6.05 (m, 1H), 6.00–5.90 (m, 1H), 5.17 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.95 (dd, *J* = 17.0, 1.2 Hz, 1H), 4.52–4.40 (m, 2H), 3.77 (d, *J* = 10.0 Hz, 2H), 3.31–3.20 (m, 2H), 3.76–2.63 (m, 2H), 2.03 (dd, *J* = 20.4, 10.0 Hz, 1H), 1.40 (s, 1H); ^{13}C NMR (100 MHz): δ 146.0, 135.6, 134.7, 134.2, 129.6, 127.1, 126.4, 125.1, 120.8, 116.5, 107.2, 104.9, 63.7, 52.0, 49.1, 38.4, 34.5, 29.8; IR (KBr, cm^{-1}): 3400, 2934, 1596, 1480, 1077, 780, 710, 616; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 10.1 min, minor enantiomer t_R = 15.9 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{18}H_{21}ClNO^+$: 302.1306, found: 302.1314.

((1R,2R,4S)-2-(1-allyl-1H-pyrrol-2-yl)-4-(p-tolyl)cyclobutyl)methanol (3f)



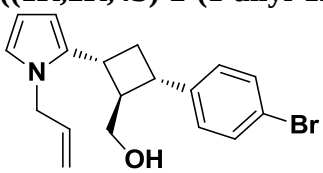
Colorless oil (yield: 62%); $[\alpha]_D^{20}$ = –26.2 (*c* 1.26, CH_2Cl_2, 91% *ee*); ^{1}H NMR (400 MHz): δ 7.19 (d, *J* = 8 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.60 (t, *J* = 2.2 Hz, 1H), 6.14 (t, *J* = 3.2 Hz, 1H), 6.08 (t, *J* = 2.4 Hz, 1H), 6.10–5.92 (m, 1H), 5.19 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.96 (dd, *J* = 16.8, 1.2 Hz, 1H), 4.53–4.41 (m, 2H), 3.78 (s, 2H), 3.27–3.18 (m, 2H), 2.77–2.70 (m, 1H), 2.68–2.33 (m, 1H), 2.33 (s, 3H), 2.05 (dd, *J* = 20.4, 10.4 Hz, 1H), 1.34 (s, 1H); ^{13}C NMR (100 MHz): δ 140.9, 136.0, 135.8, 134.8, 129.1, 126.8, 120.7, 116.5, 107.1, 104.8, 64.1, 52.3, 49.1, 38.5, 34.8, 30.0, 21.0; IR (KBr, cm^{-1}): 3376, 2923, 1652, 1443, 1161, 1026, 810, 706, 664; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 20.1 min, minor enantiomer t_R = 26.9 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{19}H_{24}NO^+$: 282.1852, found $[M+H]^+$: 282.1860.

((1R,2R,4S)-2-(1-allyl-1H-pyrrol-2-yl)-4-(4-chlorophenyl)cyclobutyl)methanol (3g)



Colorless oil (yield: 70%); $[\alpha]_D^{20}$ = –7.1 (*c* 1.57, CH_2Cl_2, 89% *ee*); ^{1}H NMR (400 MHz): δ 7.27 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.59 (t, *J* = 2.2 Hz, 1H), 6.13 (t, *J* = 3.2 Hz, 1H), 6.06–6.05 (m, 1H), 6.00–5.90 (m, 1H), 5.17 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.95 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.52–4.40 (m, 2H), 3.76 (s, 2H), 3.30–3.19 (m, 2H), 2.74–2.63 (m, 2H), 2.01 (dd, *J* = 20.4, 10.0 Hz, 1H), 1.38 (s, 1H); ^{13}C NMR (100 MHz): δ 142.4, 135.7, 134.7, 131.9, 128.5, 128.3, 120.8, 116.5, 107.2, 104.8, 63.8, 52.2, 49.1, 38.2, 34.7, 29.8; IR (KBr, cm^{-1}): 3387, 2918, 1645, 1490, 1072, 1017, 922, 825, 708; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 22.6 min, minor enantiomer t_R = 32.9 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{18}H_{21}ClNO^+$: 302.1306, found : 302.1299.

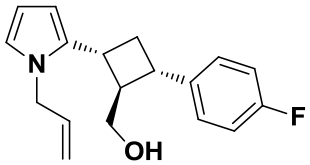
((1R,2R,4S)-2-(1-allyl-1H-pyrrol-2-yl)-4-(4-bromophenyl)cyclobutyl)methanol (3h)



Colorless oil (yield: 65%); $[\alpha]_D^{20}$ = –41.0 (*c* 1.00, CH_2Cl_2, 94% *ee*); ^{1}H NMR (400 MHz): δ 7.43 (dd, *J* = 6.8, 1.6 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.60 (t, *J* = 2.2 Hz, 1H), 6.13 (t, *J* = 3.2 Hz, 1H), 6.06–6.05 (m,

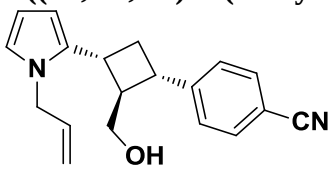
1H), 6.00–5.91 (m, 1H), 5.16 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.95 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.52–4.40 (m, 2 H), 3.77 (s, 2H), 3.28–3.19 (m, 2H), 2.74–2.63 (m, 2H), 2.01 (dd, *J* = 20.4, 10.0 Hz, 1H), 1.35 (s, 1H); ^{13}C NMR (100 MHz): δ 142.9, 135.7, 134.7, 131.4, 128.7, 120.8, 119.9, 116.5, 107.2, 104.8, 63.8, 52.1, 49.1, 38.3, 34.6, 29.8; IR (KBr, cm^{-1}): 3397, 2932, 1643, 1486, 1300, 1073, 1010, 922, 822, 709; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 24.6 min, minor enantiomer t_R = 36.4 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{18}H_{21}BrNO^+$: 346.0801, found $[M+H]^+$: 346.0794.

((1R,2R,4S)-2-(1-allyl-1H-pyrrol-2-yl)-4-(4-fluorophenyl)cyclobutyl)methanol (3i)



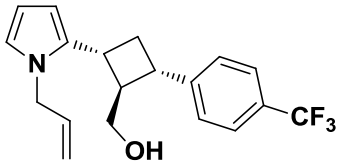
Colorless oil (yield: 72%); $[\alpha]_D^{20}$ = –83.3 (*c* 1.80, CH_2Cl_2, 96% *ee*); ^{1}H NMR (400 MHz): δ 7.24–7.22 (m, 2H), 6.99 (t, *J* = 8.8 Hz, 2H), 6.60 (t, *J* = 2.2 Hz, 1H), 6.14 (t, *J* = 3.2 Hz, 1H), 6.07 (d, *J* = 1.2 Hz, 1H), 6.00–5.91 (m, 1H), 5.17 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.95 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.52–4.41 (m, 2H), 3.77 (s, 2H), 3.30–3.18 (m, 2H), 2.75–2.63 (m, 2H), 2.01 (dd, *J* = 20.4, 10.0 Hz, 1H), 1.35 (s, 1H); ^{13}C NMR (100 MHz): δ 139.6, 135.8, 134.7, 128.3, 120.8, 116.5, 115.2, 115.0, 107.2, 104.8, 63.9, 52.3, 49.1, 38.2, 34.9, 29.8; IR (KBr, cm^{-1}): 3410, 2921, 1711, 1510, 1362, 1224, 912, 737; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 20.7 min, minor enantiomer t_R = 29.4 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{18}H_{21}FNO^+$: 286.1602, found: 286.1599.

4-((1S,2R,3R)-3-(1-allyl-1H-pyrrol-2-yl)-2-(hydroxymethyl)cyclobutyl)benzonitrile (3j)



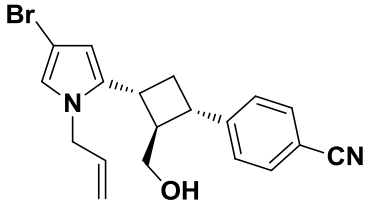
Colorless oil (yield: 79%); $[\alpha]_D^{20}$ = –36.9 (*c* 1.30, CH_2Cl_2, 95% *ee*); ^{1}H NMR (400 MHz): δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 6.60 (t, *J* = 2.4 Hz, 1H), 6.13 (t, *J* = 3.2 Hz, 1H), 6.05–6.04 (m, 1H), 6.00–5.91 (m, 1H), 5.18 (dd, *J* = 9.6, 1.2 Hz, 1H), 4.95 (dd, *J* = 16.8, 1.2 Hz, 1H), 4.52–4.41(m, 2H), 3.78 (m, 2H), 3.38 (dd, *J* = 18.0, 9.6 Hz, 1H), 3.28 (dd, *J* = 9.6 Hz, 1H), 2.78–2.67 (m, 2H), 2.04 (dd, *J* = 20.4, 10.4 Hz, 1H), 1.38 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz): δ 149.6, 135.3, 134.7, 132.2, 127.4, 121.0, 119.1, 116.5, 109.9, 107.2, 104.9, 63.5, 51.9, 49.1, 38.8, 34.4, 29.7; IR (KBr, cm^{-1}): 3434, 2933, 2227, 1606, 1486, 1300, 1075, 922, 835, 710, 558; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 12.6 min, minor enantiomer t_R = 17.2 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{19}H_{21}N_2O^+$: 293.1648, found: 293.1640.

((1R,2R,4S)-2-(1-allyl-1H-pyrrol-2-yl)-4-(4-(trifluoromethyl)phenyl)cyclobutyl)methanol (3k)



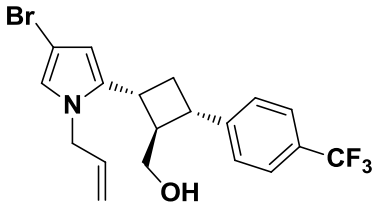
Colorless oil (yield: 71%); $[\alpha]_D^{20}$ = –30.0 (*c* 0.70, CH_2Cl_2, 92% *ee*); ^{1}H NMR (400 MHz): δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 6.60 (t, *J* = 2.4 Hz, 1H), 6.14 (t, *J* = 3.2 Hz, 1H), 6.07–6.05 (m, 1H), 6.01–5.91 (m, 1H), 5.18 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.96 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.52–4.41 (m, 2H), 3.79 (d, *J* = 4.4 Hz, 2H), 3.37 (dd, *J* = 18.4, 9.6 Hz, 1H), 3.27 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.80–2.67 (m, 2H), 2.07 (dd, *J* = 20.4, 10.4 Hz, 1H), 1.38 (s, 1H); ^{13}C NMR (100 MHz): δ 148.0, 135.5, 134.7, 128.3, 127.3, 125.4, 125.3, 120.8, 116.5, 107.2, 104.9, 63.7, 52.0, 49.1, 38.6, 34.5, 29.8; IR (KBr, cm^{-1}): 3406, 2918, 1710, 1326, 1266, 1121, 910, 737; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 9.4 min, minor enantiomer t_R = 13.4 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{19}H_{21}F_3NO^+$: 336.1570, found: 336.1582.

4-((1S,2R,3R)-3-(1-allyl-4-bromo-1H-pyrrol-2-yl)-2-(hydroxymethyl)cyclobutyl)benzonitrile (3l)



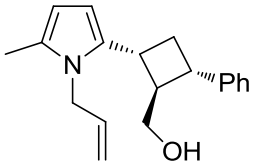
Colorless oil (yield: 70%); $[\alpha]_D^{20}$ = –15.4 (*c* 1.30, CH_2Cl_2, 98% *ee*); ^{1}H NMR (400 MHz): δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.57 (d, *J* = 2.0 Hz, 1H), 6.05 (d, *J* = 1.6 Hz, 1H), 5.95–5.86 (m, 1H), 5.20 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.98 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.47–4.35(m, 2H), 3.76 (d, *J* = 4.8 Hz, 2H), 3.39 (dd, *J* = 18.0, 9.6 Hz, 1H), 3.27 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.72–2.65 (m, 2H), 2.02 (dd, *J* = 20.4, 10.0 Hz, 1H), 1.26 (s, 1H); ^{13}C NMR (100 MHz): δ 149.2, 136.3, 133.9, 132.3, 127.7, 120.3, 119.0, 117.1, 110.0, 107.8, 94.8, 63.1, 51.9, 49.2, 38.5, 34.1, 29.4; IR (KBr, cm^{-1}): 3421, 2928, 2228, 1606, 1414, 1307, 1022, 925, 835, 663; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 22.9 min, minor enantiomer t_R = 19.1 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{19}H_{20}BrN_2O^+$: 371.0754, found: 371.0745.

((1R,2R,4S)-2-(1-allyl-4-bromo-1H-pyrrol-2-yl)-4-(4-(trifluoromethyl)phenyl)cyclobutyl)methanol (3m)



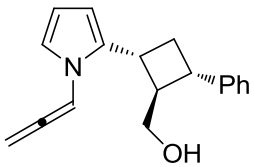
Colorless oil (yield: 65%); $[\alpha]_D^{20}$ = –11.7 (*c* 1.20, CH_2Cl_2, 97% *ee*); ^{1}H NMR (400 MHz): δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 6.57 (d, *J* = 1.6 Hz, 1H), 6.0 (d, *J* = 1.2 Hz, 1H), 5.96–5.87 (m, 1H), 5.20 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.99 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.48–4.36 (m, 2H), 3.77 (d, *J* = 4.4 Hz, 2H), 3.37 (dd, *J* = 18.0, 10.0 Hz, 1H), 3.26 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.72–2.65 (m, 2H), 2.04 (dd, *J* = 20.4, 10.4 Hz, 1H), 1.46 (s, 1H); ^{13}C NMR (100 MHz): δ 147.7, 136.5, 134.0, 127.2, 125.4, 125.3, 120.3, 117.1, 107.7, 94.8, 63.3, 52.0, 49.2, 38.3, 34.2, 29.5; IR (KBr, cm^{-1}): 3384, 2925, 1645, 1415, 1327, 1122, 1067, 926, 838, 600; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 28.4 min, minor enantiomer t_R = 24.6 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{19}H_{20}BrF_3NO^+$: 414.0675, found: 414.0662.

((1R,2R,4S)-2-(1-allyl-5-methyl-1H-pyrrol-2-yl)-4-phenylcyclobutyl)methanol (3n)



Colorless oil (yield: 53%); $[\alpha]_D^{20}$ = –54 (c 1.05, CH_2Cl_2, 65% ee); ^{1}H NMR (400 MHz): δ 7.31–7.26 (m, 4H), 7.22–7.18 (m, 1H), 5.98–5.86 (m, 3H), 5.11 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.72 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.49–4.34 (m, 2H), 3.78 (d, *J* = 4.0 Hz, 2H), 3.29–3.14 (m, 2H), 2.80–2.73 (m, 1H), 2.76–2.61 (m, 1H), 2.18 (s, 3H), 2.03 (dd, *J* = 20.4, 10.4 Hz, 1H), 1.25 (s, 1H); ^{13}C NMR (100 MHz): δ 144.0, 135.3, 134.5, 128.5, 128.4, 127.0, 126.2, 115.5, 105.6, 103.4, 64.2, 51.9, 45.7, 38.9, 35.2, 30.5, 12.1; IR (KBr, cm^{-1}): 3426, 2930, 1643, 1417, 1265, 1028, 737, 700; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane:*i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 10.0 min, minor enantiomer t_R = 14.2 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{19}H_{24}NO^+$: 282.1852, found: 282.1849.

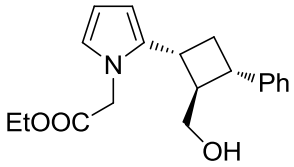
((1R,2S,4R)-2-phenyl-4-(1-(propa-1,2-dien-1-yl)-1H-pyrrol-2-yl)cyclobutyl)methanol (3o)



Colorless oil (yield: 62%); $[\alpha]_D^{20}$ = –65 (c 1.55, CH_2Cl_2, 92% ee); ^{1}H NMR (400 MHz): δ 7.29–7.20 (m, 5H), 6.96 (t, *J* = 6.4 Hz, 1H), 6.79–6.78 (m, 1H), 6.17 (t, *J* = 3.2 Hz, 1H), 6.07 (s, 1H), 5.48 (d, *J* = 6.4 Hz, 2H), 3.85–3.77 (m, 2H), 3.40–3.29 (m, 2H), 2.75–2.66 (m, 2H), 2.13 (dd, *J* = 20.4, 10.4 Hz, 1H), 1.47 (s,

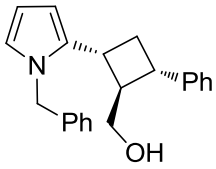
1H); ^{13}C NMR (100 MHz): δ 203.2, 143.7, 135.8, 128.4, 126.9, 126.3, 118.9, 109.1, 106.0, 97.5, 86.7, 63.7, 52.0, 38.8, 33.7, 29.8; IR (KBr, cm^{-1}): 3392, 2934, 1706, 1480, 1266, 1068, 738, 702; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 9.5 min, minor enantiomer t_R = 12.5 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{18}H_{20}NO^+$: 266.1539, found: 266.1534.

ethyl 2-(2-((1R,2R,3S)-2-(hydroxymethyl)-3-phenylcyclobutyl)-1H-pyrrol-1-yl)acetate (3p)



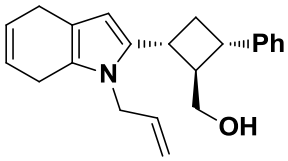
Colorless oil (yield: 68%); $[\alpha]_D^{20}$ = –47 (c 1.18, CH_2Cl_2, 90% ee); ^{1}H NMR (400 MHz): δ 7.33–7.25 (m, 4H), 7.23–7.19 (m, 1H), 6.57 (dd, *J* = 2.4, 2.0 Hz, 1H), 6.17 (t, *J* = 3.2 Hz, 1H), 6.11–6.10 (m, 1H), 4.62 (dd, *J* = 31.6, 17.6 Hz, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.80–3.72 (m, 2H), 3.25 (dd, *J* = 18.0, 9.6 Hz, 1H), 3.14 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.79–2.72 (m, 1H), 2.66–2.60 (m, 1H), 2.08 (dd, *J* = 20.4, 10.4 Hz, 1H), 1.70 (s, 1H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 169.3, 143.7, 136.4, 128.4, 126.9, 126.3, 121.5, 108.1, 105.6, 63.9, 61.7, 52.7, 48.3, 38.5, 34.5, 30.1, 14.2; IR (KBr, cm^{-1}): 3505, 2977, 2935, 1751, 1488, 1303, 1199, 1026, 753, 701; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 16.2 min, minor enantiomer t_R = 28.3 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{19}H_{24}NO_3^+$: 314.1751, found: 314.1755.

((1R,2R,4S)-2-(1-benzyl-1H-pyrrol-2-yl)-4-phenylcyclobutyl)methanol (3q)



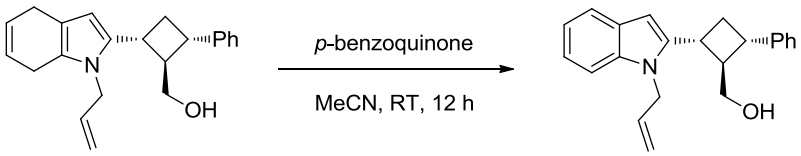
Colorless oil (yield: 72%); $[\alpha]_D^{20}$ = –32 (c 1.25, CH_2Cl_2, 90% ee); ^{1}H NMR (400 MHz): δ 7.31–7.16 (m, 8H), 6.99 (d, *J* = 7.2 Hz, 2H), 6.64 (t, *J* = 2.4, 1H), 6.18 (t, *J* = 3.2 Hz, 1H), 6.14 (d, *J* = 1.2 Hz, 1H), 5.09 (dd, *J* = 28.4, 16.4 Hz, 2H), 3.63–3.55 (m, 2H), 3.20–3.09 (m, 2H), 2.74–2.67 (m, 1H), 2.47–2.40 (m, 1H), 1.97 (dd, *J* = 20.4, 10.0 Hz, 1H), 1.12 (s, 1H); ^{13}C NMR (100 MHz): δ 144.0, 138.8, 136.4, 128.8, 128.5, 127.5, 127.0, 126.3, 121.6, 107.4, 105.5, 63.8, 52.6, 50.5, 38.6, 34.9, 30.0; IR (KBr, cm^{-1}): 3416, 2934, 1603, 1494, 1452, 1296, 1076, 1028, 751, 730, 700; The enantiomeric excess was determined by HPLC with an AS-H column. (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 14.7 min, minor enantiomer t_R = 20.3 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{22}H_{24}NO^+$: 318.1860, found: 318.1852.

((1R,2R,4S)-2-(1-allyl-4,7-dihydro-1H-indol-2-yl)-4-phenylcyclobutyl)methanol (3r)



Colorless oil (yield: 42%); $[\alpha]_D^{20}$ = –68 (c 1.15, CH_2Cl_2, 88% ee); ^{1}H NMR (400 MHz): δ 7.33-7.20 (m, 5H), 5.94-5.80 (m, 4H), 5.10 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.79 (dd, *J* = 16.8, 1.2 Hz, 1H), 4.47-4.32 (m, 2H), 3.79-3.77 (m, 2H), 3.29-3.17 (m, 6H), 2.79-2.72 (m, 1H), 2.69-2.62 (m, 1H), 2.04 (dd, *J* = 20.0, 10.0 Hz, 1H), 1.25 (s, 1H); ^{13}C NMR (100 MHz): δ 144.0, 135.0, 134.8, 128.4, 127.0, 126.2, 125.9, 124.7, 122.5, 115.7, 113.2, 102.6, 64.2, 52.2, 45.6, 38.9, 35.3, 30.1, 25.1, 23.2; IR (KBr, cm^{-1}): 3339, 2930, 1693, 1614, 1492, 1461, 1410, 1314, 1022923, 749, 699; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 14.7 min, minor enantiomer t_R = 24.1 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{22}H_{26}NO^+$: 320.2009, found: 320.2003.

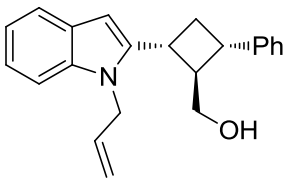
4. Synthesis of Indole-tethered cyclobutanes[6] and analytical date:



3r **3s**

The solution of **3r** (1.0 eq) and *p*-benzoquinone (1.5 eq) in MeCN was stirred at room temperature overnight. After the reaction was completed, the reaction was poured into water, extracted with EtOAc (three times), the combined organic layers were dried over Na_2SO_4, evaporated, and the crude product was purified by flash chromatography on silica gel (eluting with petroleum ether/ethyl acetate) to yield the desired product **3s** (yield: 92%) as a colorless oil.

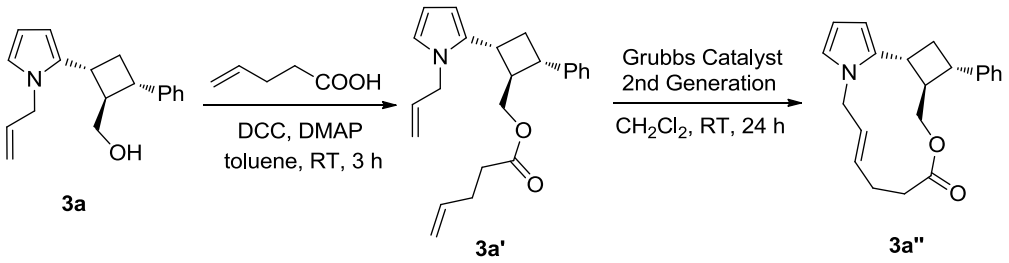
((1R,2R,4S)-2-(1-allyl-1H-indol-2-yl)-4-phenylcyclobutyl)methanol (3s)



Colorless oil (yield: 92%); $[\alpha]_D^{20}$ = –96 (c 0.95, CH_2Cl_2, 85% ee); ^{1}H NMR (400 MHz): δ 7.57 (d, *J* = 7.7 Hz, 1H), 7.35-7.30 (m, 4H), 7.25-7.21 (m, 2H), 7.17-7.13 (m, 1H), 7.10-7.06 (m, 1H), 6.44 (s, 1H), 6.00-5.91 (m, 1H), 5.12 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.85 (dd, *J* = 17.1, 1.2 Hz, 1H), 4.81-4.67 (m, 2H), 3.87-3.81 (m, 2H), 3.47-3.36 (m, 2H), 2.95-2.88 (m, 1H), 2.80-2.74 (m, 1H), 2.17 (dd, *J* = 20.4, 10.2 Hz, 1H), 1.39 (s, 1H); ^{13}C NMR (100 MHz): δ 143.6, 143.5, 137.0, 133.6, 128.5, 127.9, 126.9, 126.4, 121.0, 120.0, 119.5, 116.1, 109.3, 98.2, 63.9, 51.6, 45.5, 38.9, 34.4, 30.3; IR (KBr, cm^{-1}): 3366, 2929, 1644, 1603, 1494, 1462, 1409, 1312, 1016, 922, 748, 700; The enantiomeric excess was determined by HPLC with an AD-H

column. (*n*-hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 8.4 min, major enantiomer t_R = 9.6 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{22}H_{24}NO^+$: 318.1852, found: 318.1848.

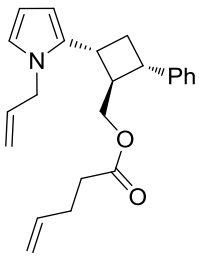
5. Synthesis of the fused 12-membered macrolide and analytical date:



Step 1: The mixture of **3a** (26.7 mg, 0.1 mmol), pent-4-enoic acid (12.2 mg, 0.12 mmol), *N*,*N'*-dicyclohexylcarbodiimide (30.9 mg, 0.15 mmol) and 4-dimethylamiopryidine (2.4 mg, 0.02 mmol) in toluene (1.0 mL) was stirred at room temperature for 3 h. The reaction mixture was evaporated under vacuum; the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the desired product **3a'** (Yield: 96%) as colorless oil.

Step 2: A flame-dried vial was charged with **3a'** (10.5 mg, 0.03 mmol), evacuated with an oil pump and refilled with argon gas, then CH_2Cl_2 (20.0 mL) was added. Finally, Grubbs Catalyst 2nd Generation (1.0 mg, 0.0012 mmol) was added to the above solution under argon gas protection. The resultant solution was stirred at room temperature for 24 h. The reaction solution was then concentrated and the residue was purified by column chromatography on silica gel (eluting with petroleum ether/ethyl acetate) to afford the desired products of **3a''** (Yield: 95%) as colorless oil.

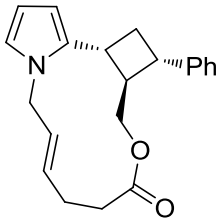
((1R,2R,4S)-2-(1-allyl-1H-pyrrol-2-yl)-4-phenylcyclobutyl)methyl pent-4-enoate (3a')



Colorless oil (yield: 96%); ^{1}H NMR (400 MHz): δ 7.33-7.29 (m, 2H), 7.27 (s, 1H), 7.25 (s, 1H), 7.23-7.19 (m, 1H), 6.58 (t, *J* = 2.1 Hz, 1H), 6.13 (t, *J* = 3.2 Hz, 1H), 6.06-6.05 (m, 1H), 5.98-5.89 (m, 1H), 5.82-5.72 (m, 1H), 5.16 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.04-4.95 (m, 3H), 4.49-4.38 (m, 2H), 4.30-4.19 (m, 2H), 3.27-3.16 (m, 2H), 2.90-2.83 (m, 1H), 2.70-2.64 (m, 1H), 2.36-2.28 (m, 4H), 2.07 (dd, *J* = 20.4, 10.4 Hz, 1H); ^{13}C NMR (100 MHz): δ 173.0, 143.3, 136.7, 135.4, 134.6, 128.4, 126.9, 126.3, 120.7, 116.5, 115.4, 107.2, 104.9, 65.3, 49.1, 48.8, 39.7, 34.7, 33.4, 30.7, 28.7; IR (KBr, cm^{-1}): 3081, 2976, 2940, 1735,

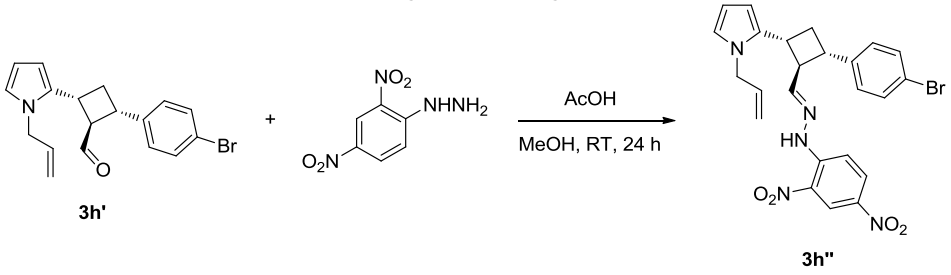
1642, 1486, 1444, 1285, 1245, 1169, 993, 919, 754, 702; ESI-HRMS: calcd. $[M+H]^+$ for $C_{23}H_{28}NO_2^+$: 350.2115, found: 350.2111.

(2S,2aR,14bR,E)-2-phenyl-2a,3,6,7,10,14b-hexahydro-1H-cyclobuta[c]pyrrolo[2,1-e][1,6]oxaazacyclododecin-5(2H)-one (3a'')



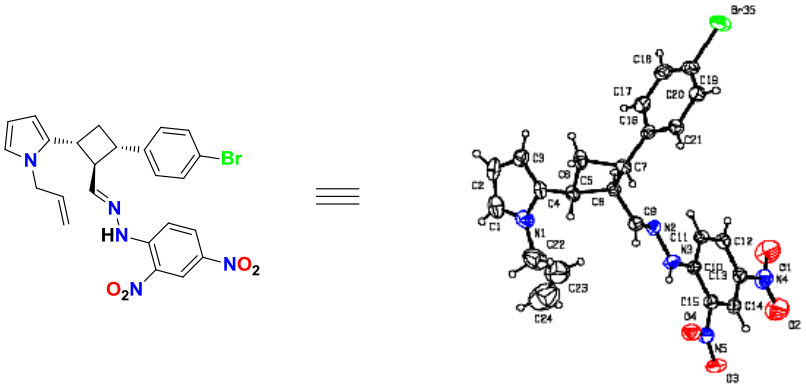
Colorless oil (yield: 95%); $[\alpha]_D^{20}$ = –85 (c 0.85, CH_2Cl_2, 95% ee); ^{1}H NMR (400 MHz): δ 7.37-7.33 (m, 2H), 7.30-7.28 (m, 2H), 7.24-7.22 (m, 1H), 6.52 (t, *J* = 2.0 Hz, 1H), 6.21-6.20 (m, 1H), 6.15-6.14 (m, 1H), 5.53 (ddd, *J* = 15.2, 6.4, 2.8 Hz, 1H), 5.20-5.13 (m, 1H), 4.52-4.40 (m, 2H), 4.13 (m, ddd, *J* = 25.6, 11.6, 3.6 Hz, 2H), 3.19-3.09 (m, 2H), 2.82-2.69 (m, 2H), 2.43-2.30 (m, 4H), 2.10 (dd, *J* = 20.8 10.4 Hz, 1H); ^{13}C NMR (100 MHz): δ 173.4, 143.3, 136.4, 130.6, 128.5, 128.2, 126.8, 126.4, 120.8, 107.0, 106.2, 64.6, 51.8, 49.0, 38.2, 37.3, 35.1, 30.6, 29.6; IR (KBr, cm^{-1}): 2939, 1731, 1479, 1443, 1337, 1248, 1152, 755, 700; The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 11.8 min, minor enantiomer t_R = 14.6 min; ESI-HRMS: calcd. $[M+H]^+$ for $C_{21}H_{24}NO_2^+$: 322.1802, found: 322.1797.

6. Determination of the stereochemistry of the cyclobutane adducts[7]:



2,4-dinitrophenylhydrazine (21.8 mg, 0.11 mmol) was added to a solution of **3h'** (34.4 mg, 0.1 mmol) in MeOH (1.5 mL) and AcOH (a drop) The mixture was stirred at room temperature for 24 h. The reaction mixture was then concentrated *in vacuo* and the residue was purified by column chromatography (petroleum ether/ethyl acetate) to afford pure product of **3h''** (yield: 85%) as a orange solid.

Orange crystal of **3h''** suitable for X-Ray analysis was obtained by recrystallization from petroleum ether /CH_2Cl_2



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alpha=90 beta=90 gamma=90
Temperature: 292 K

	Calculated	Reported
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Hall group	P 2ac 2ab	P 2ac 2ab
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Sum formula	C24 H22 Br N5 O4	C24 H22 Br N5 O4
Mr	524.37	524.38
Dx,g cm-3	1.470	1.470
Z	4	4
Mu (mm-1)	1.775	1.775
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F000’	1071.27	
h,k,lmax	6,20,30	6,20,30
Nref	2613[4490]	4294
Tmin,Tmax	0.556,0.653	0.967,1.000
Tmin’	0.532	

Correction method= MULTI-SCAN
Data completeness= 1.64/0.96 Theta(max)= 25.680
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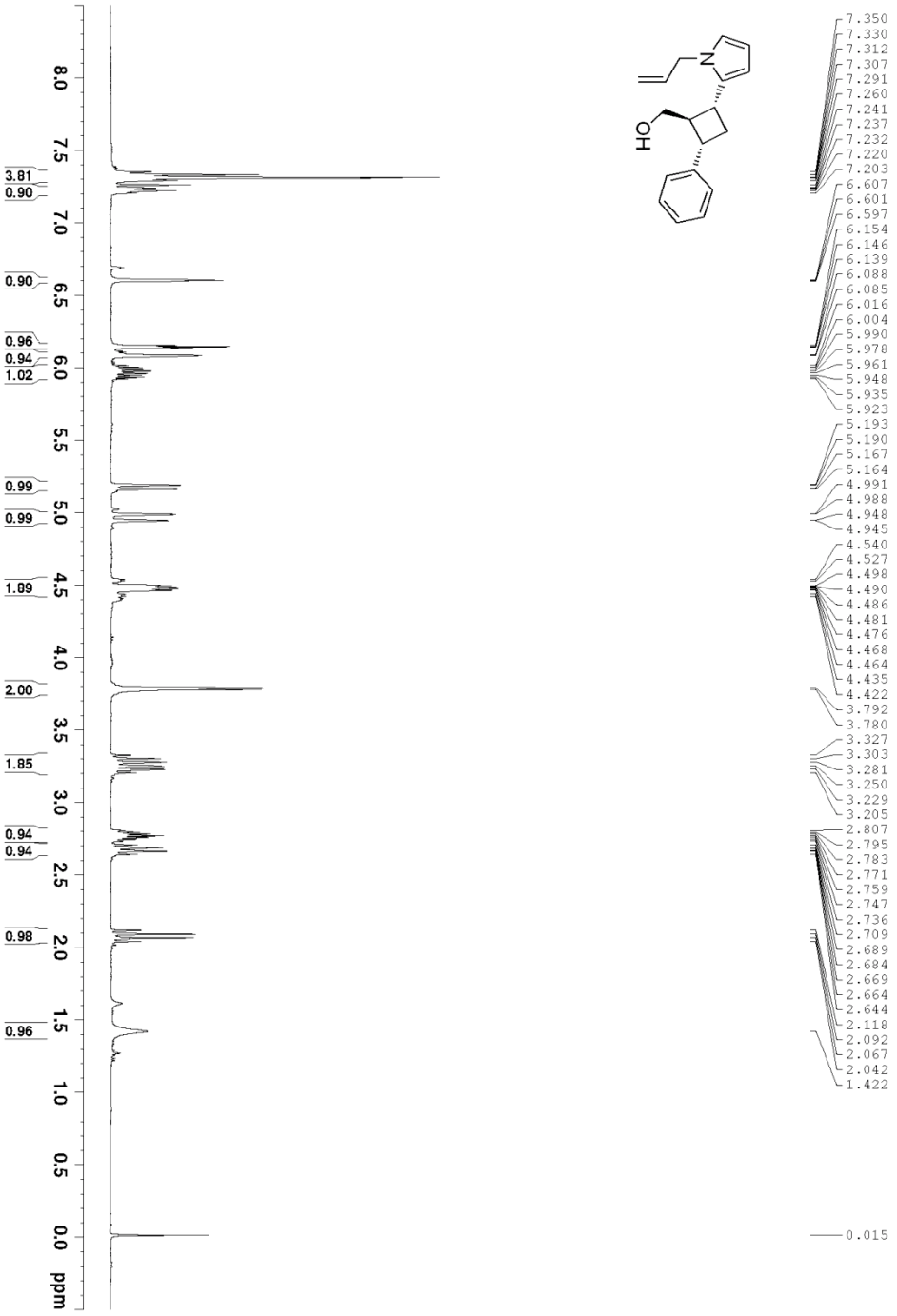
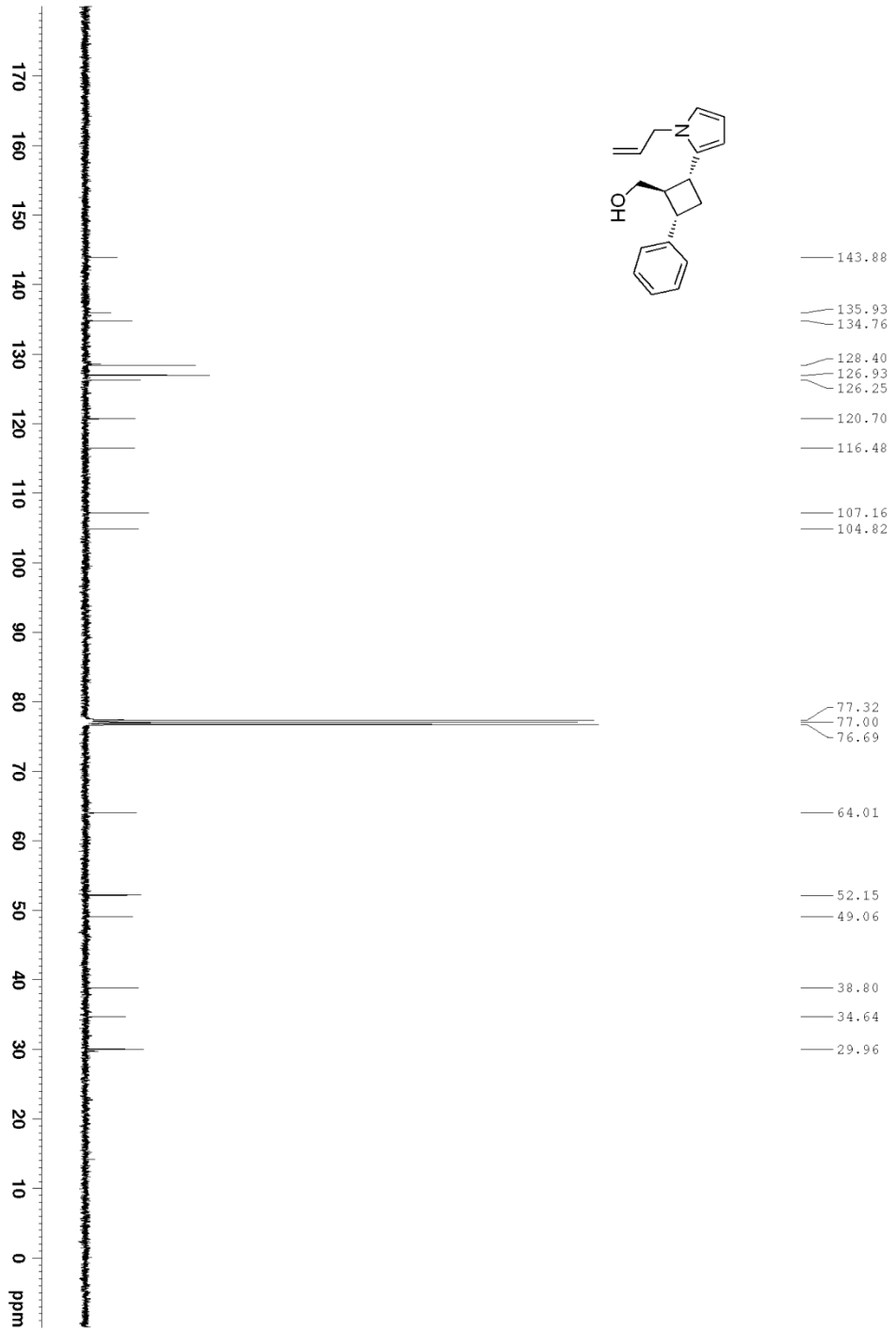
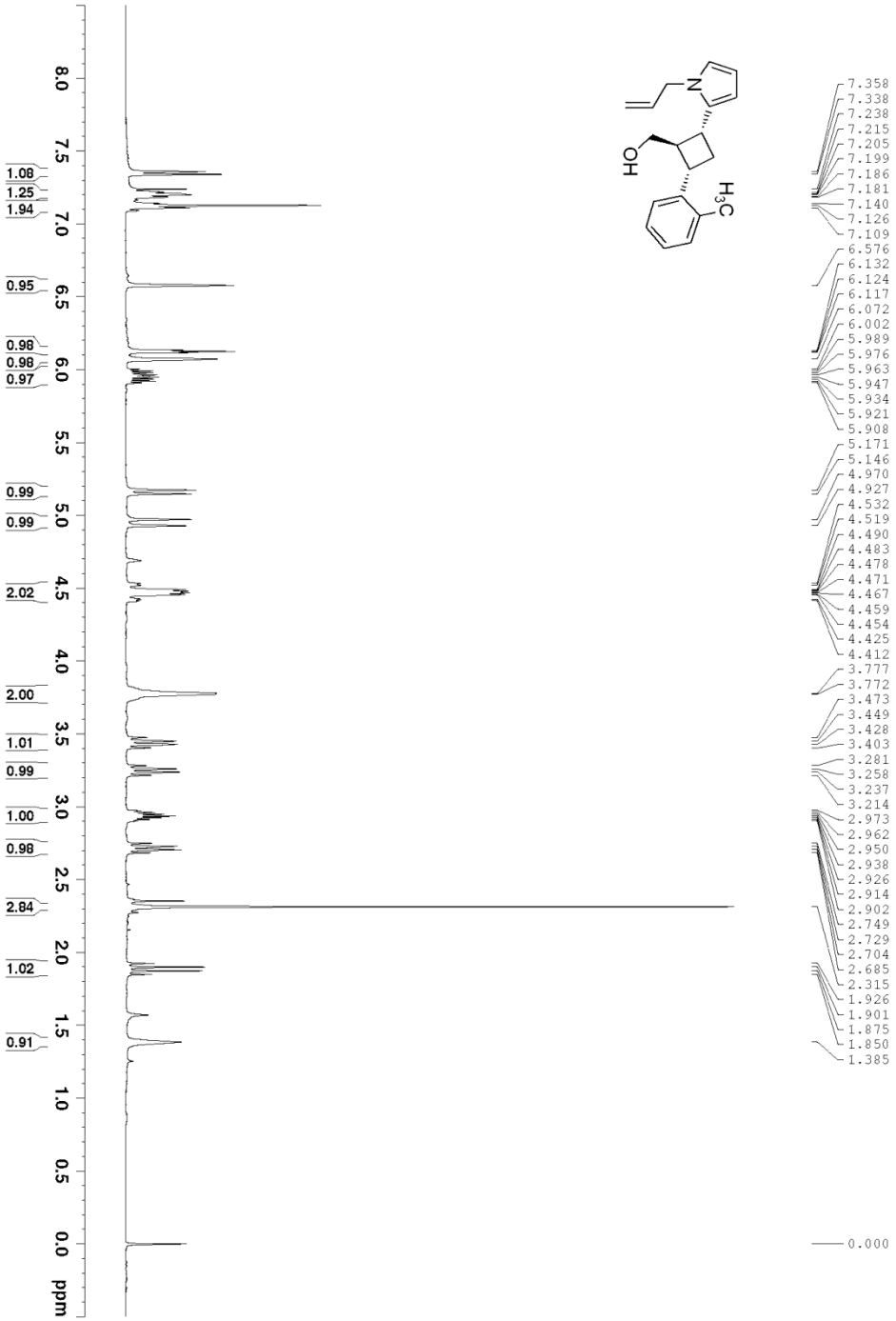
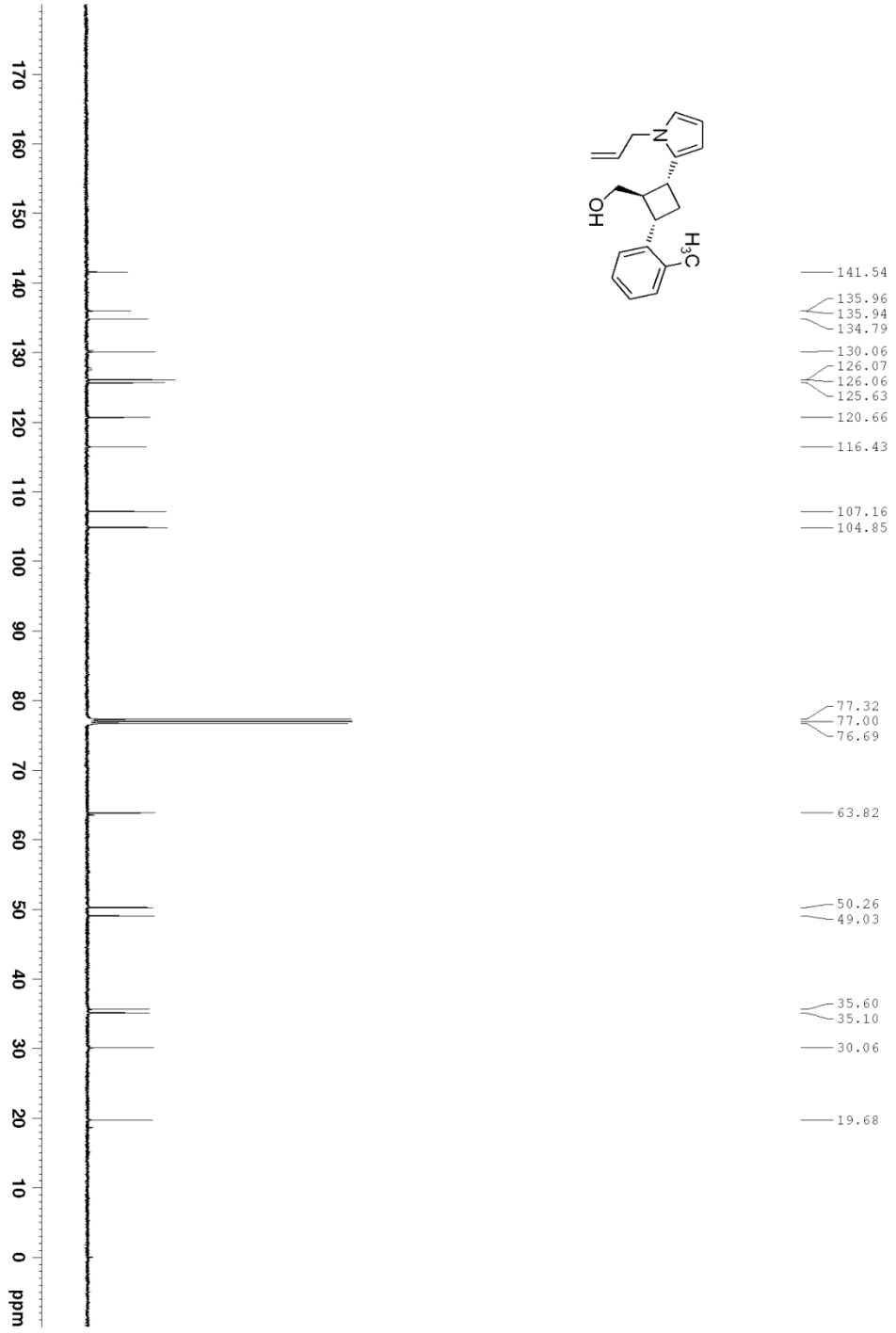
S = 0.928 Npar= 307

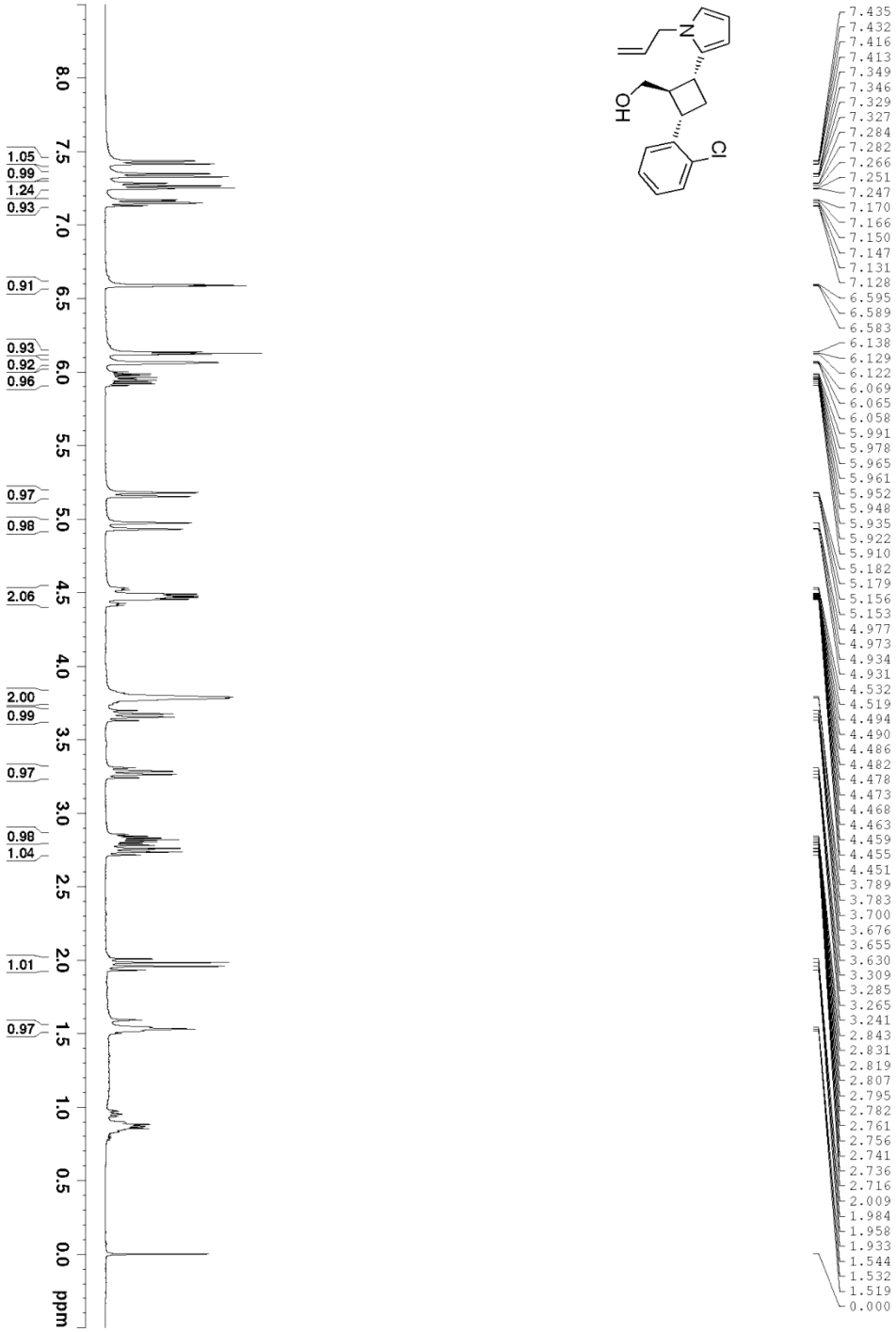
7. NMR Spectrum:

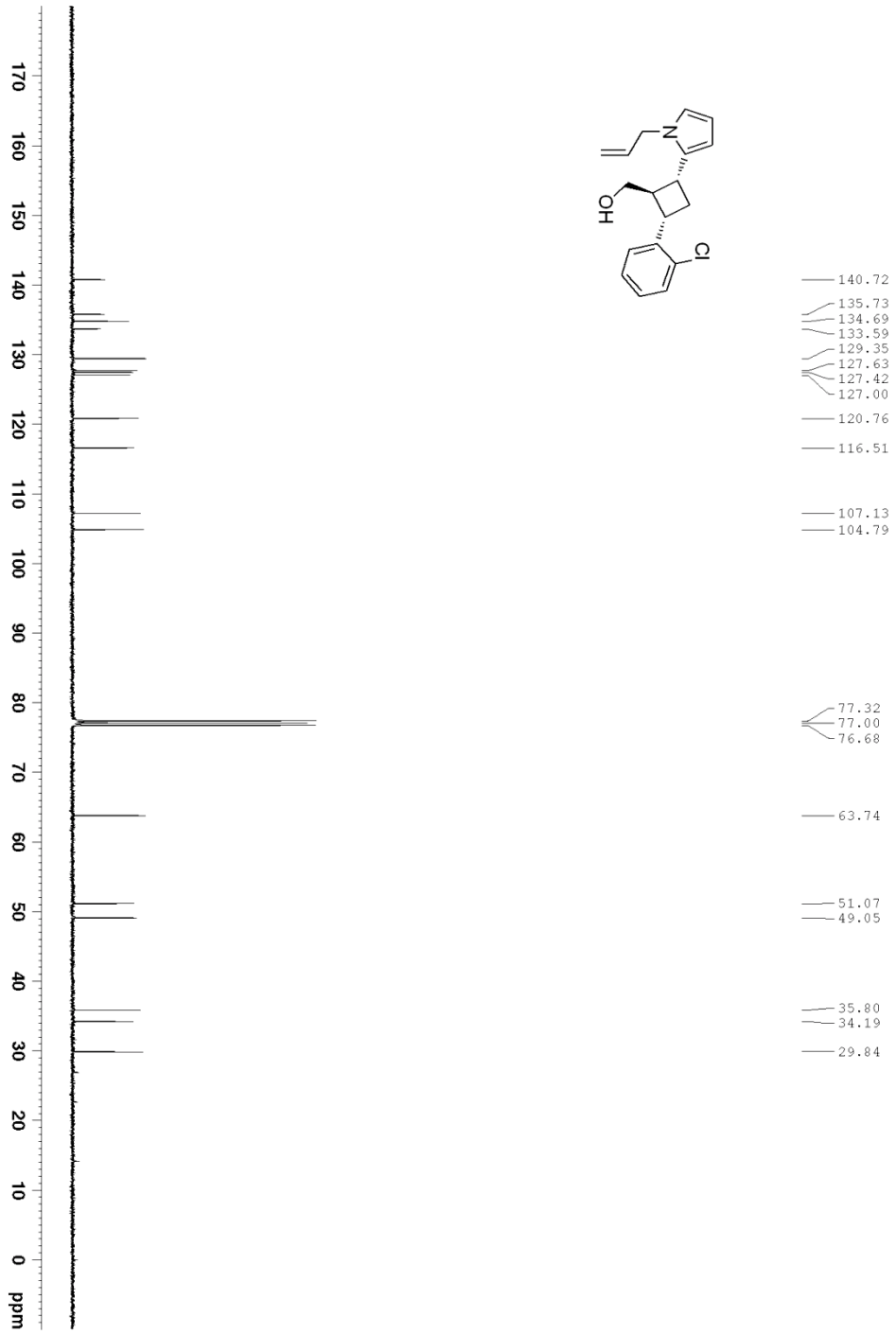


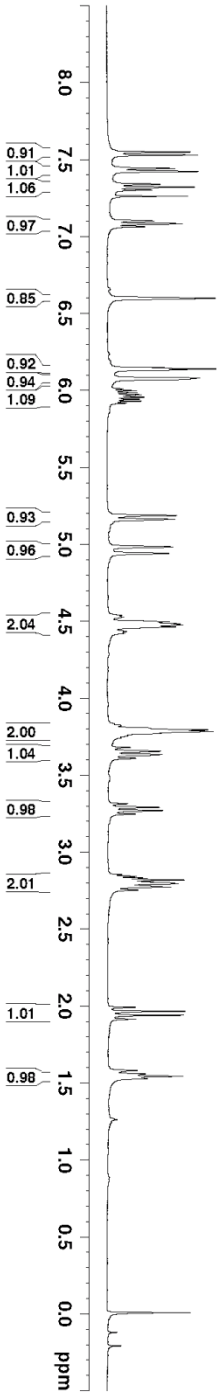


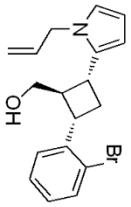


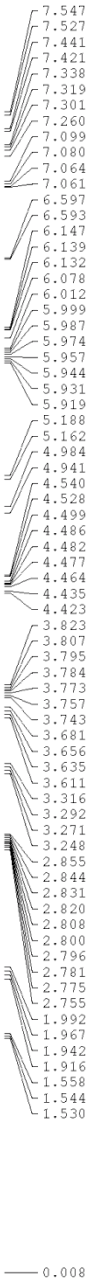


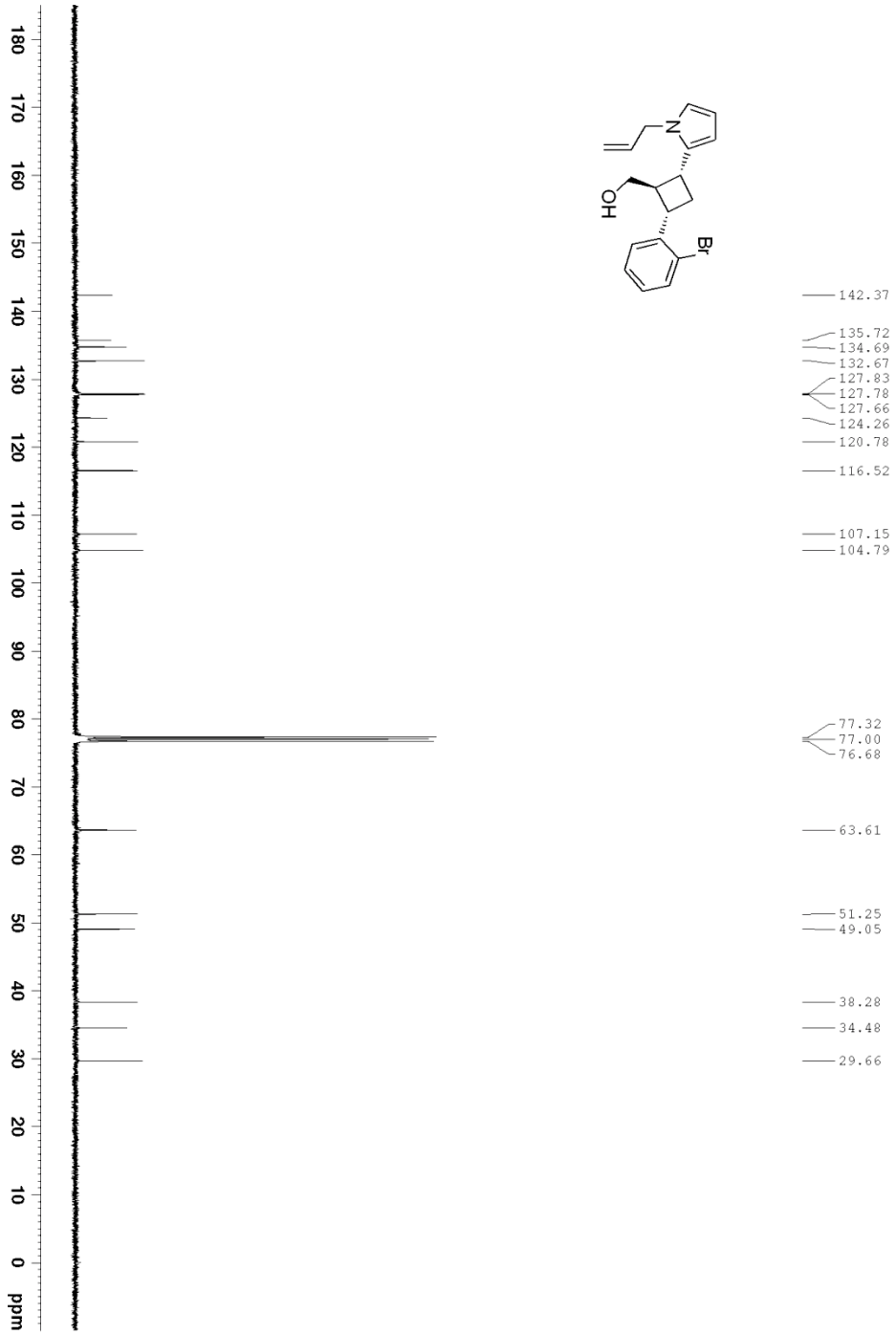


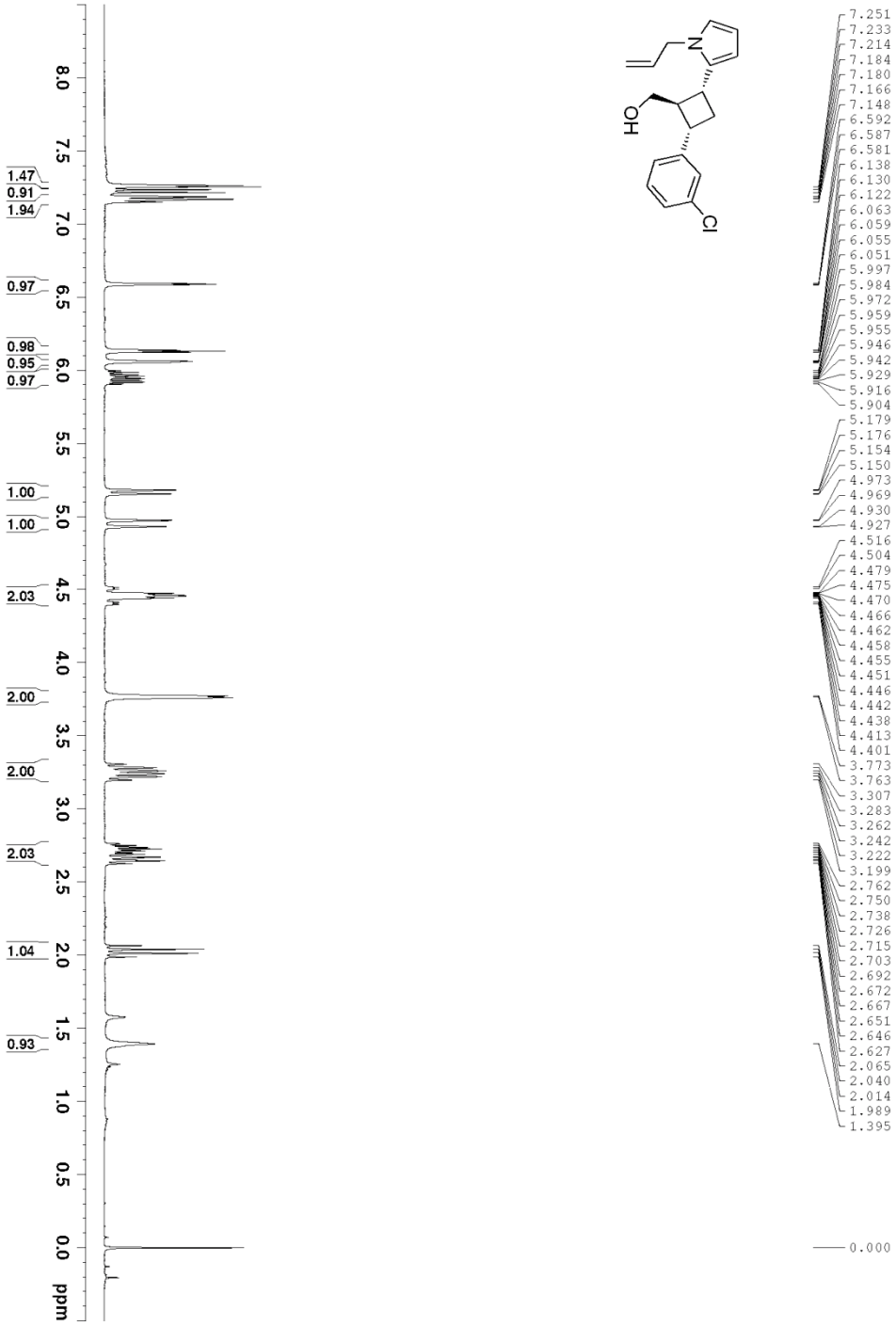


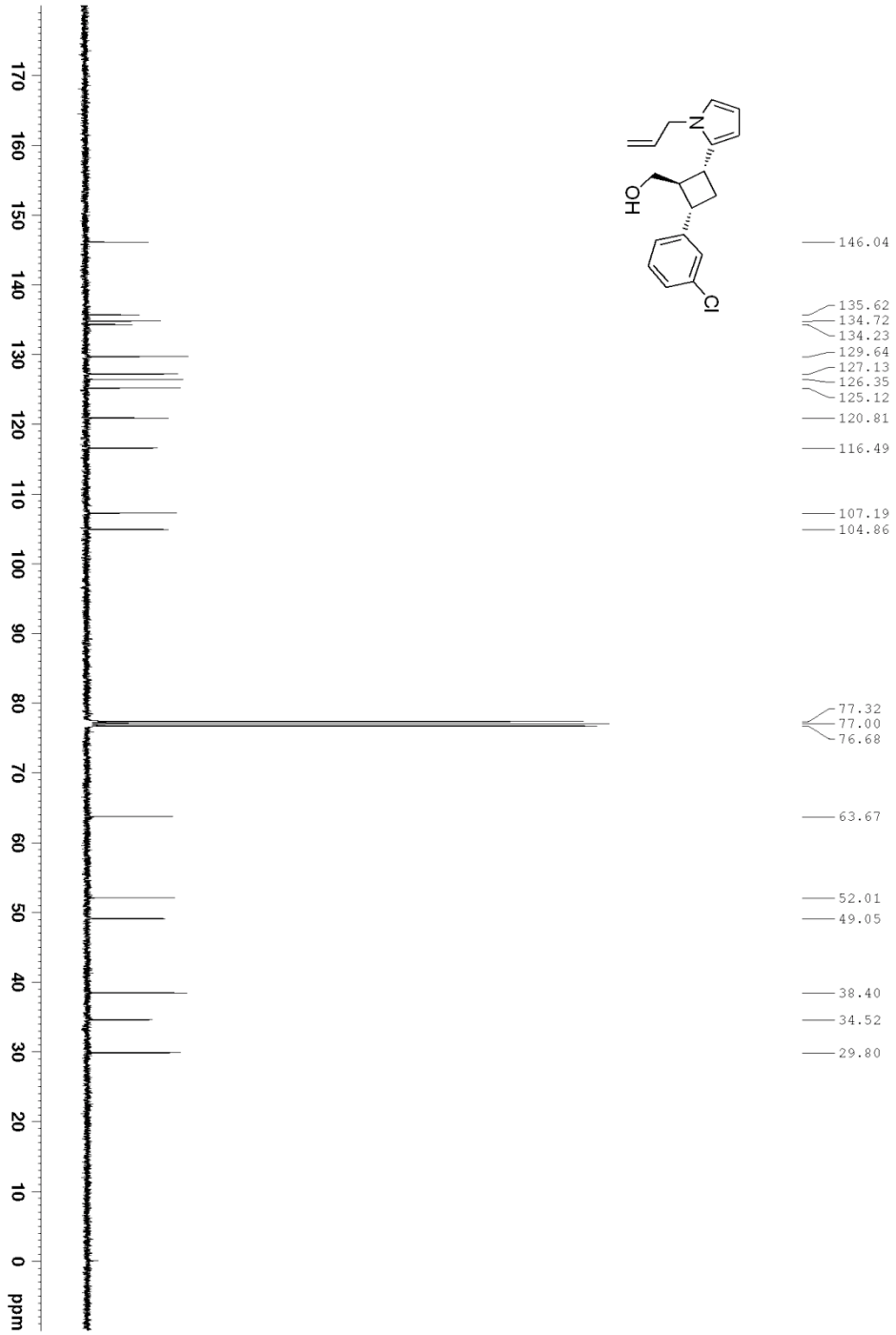


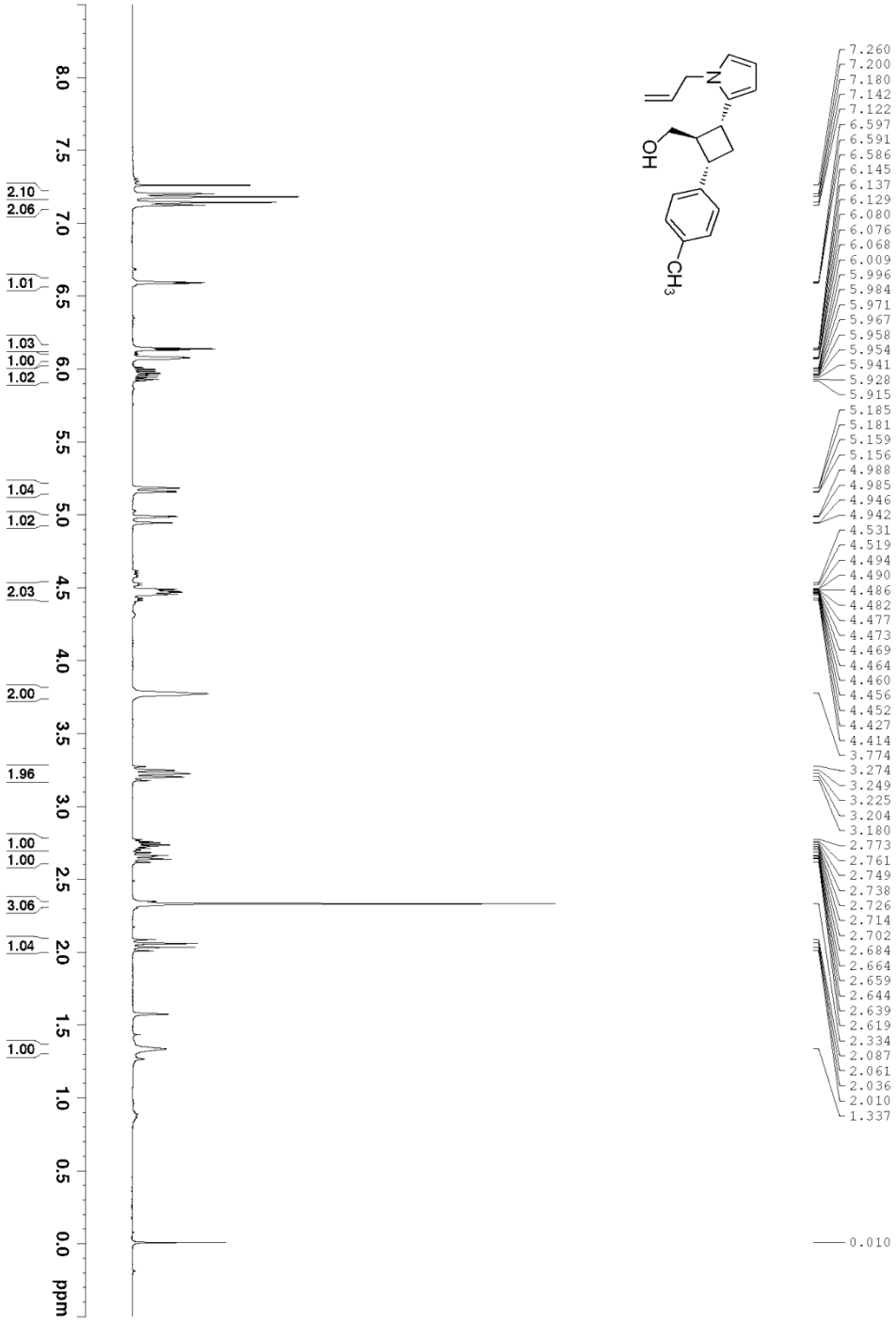


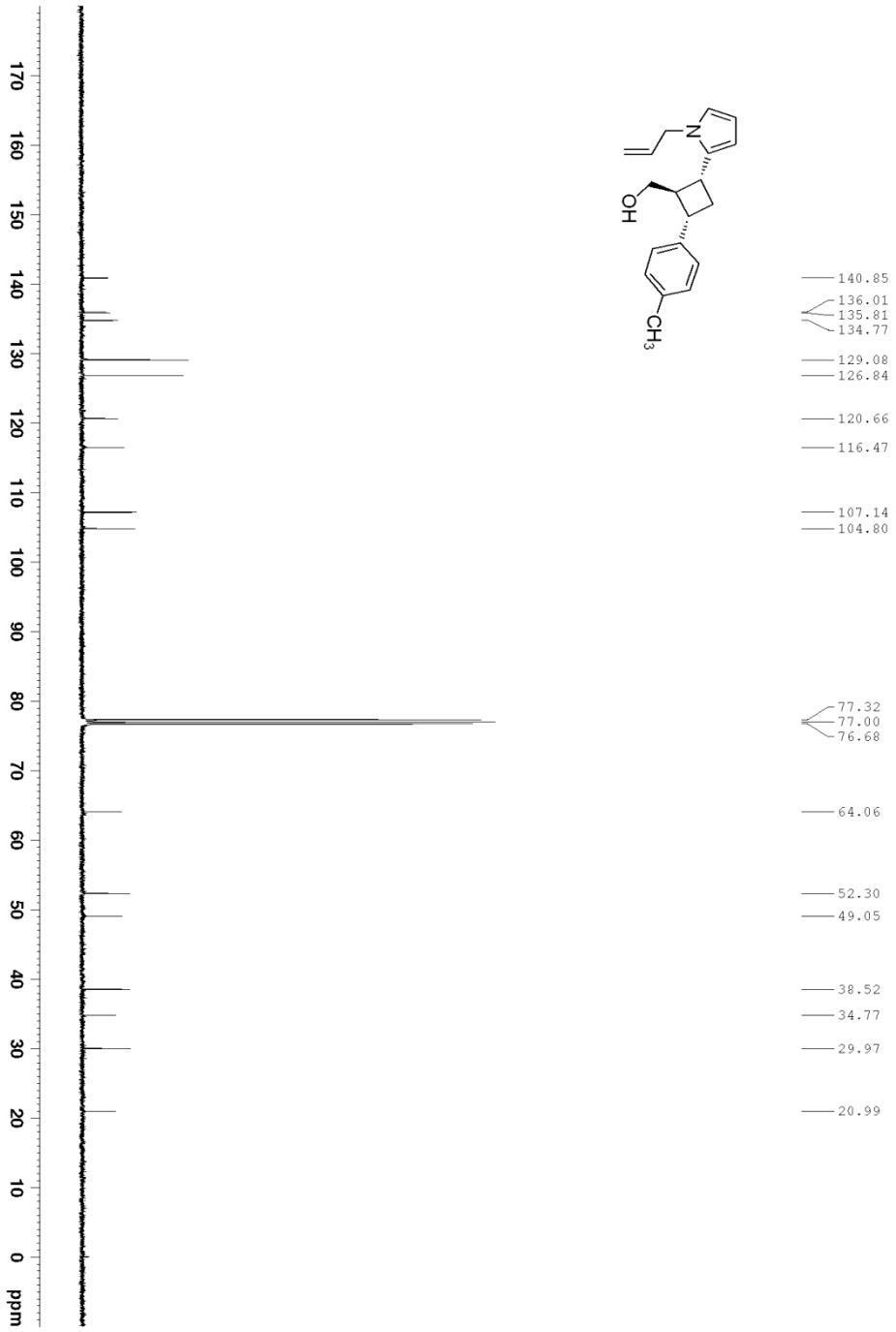


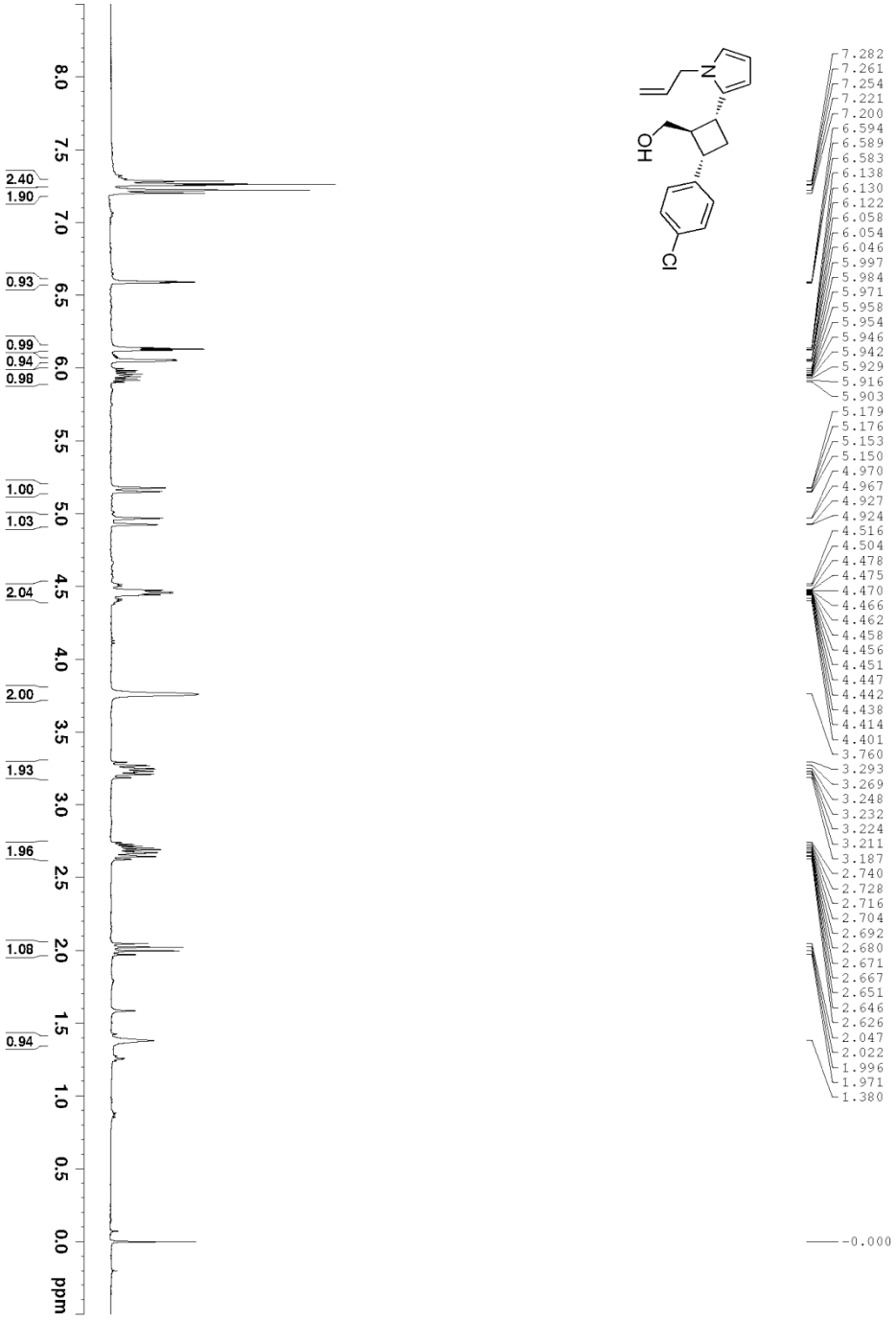


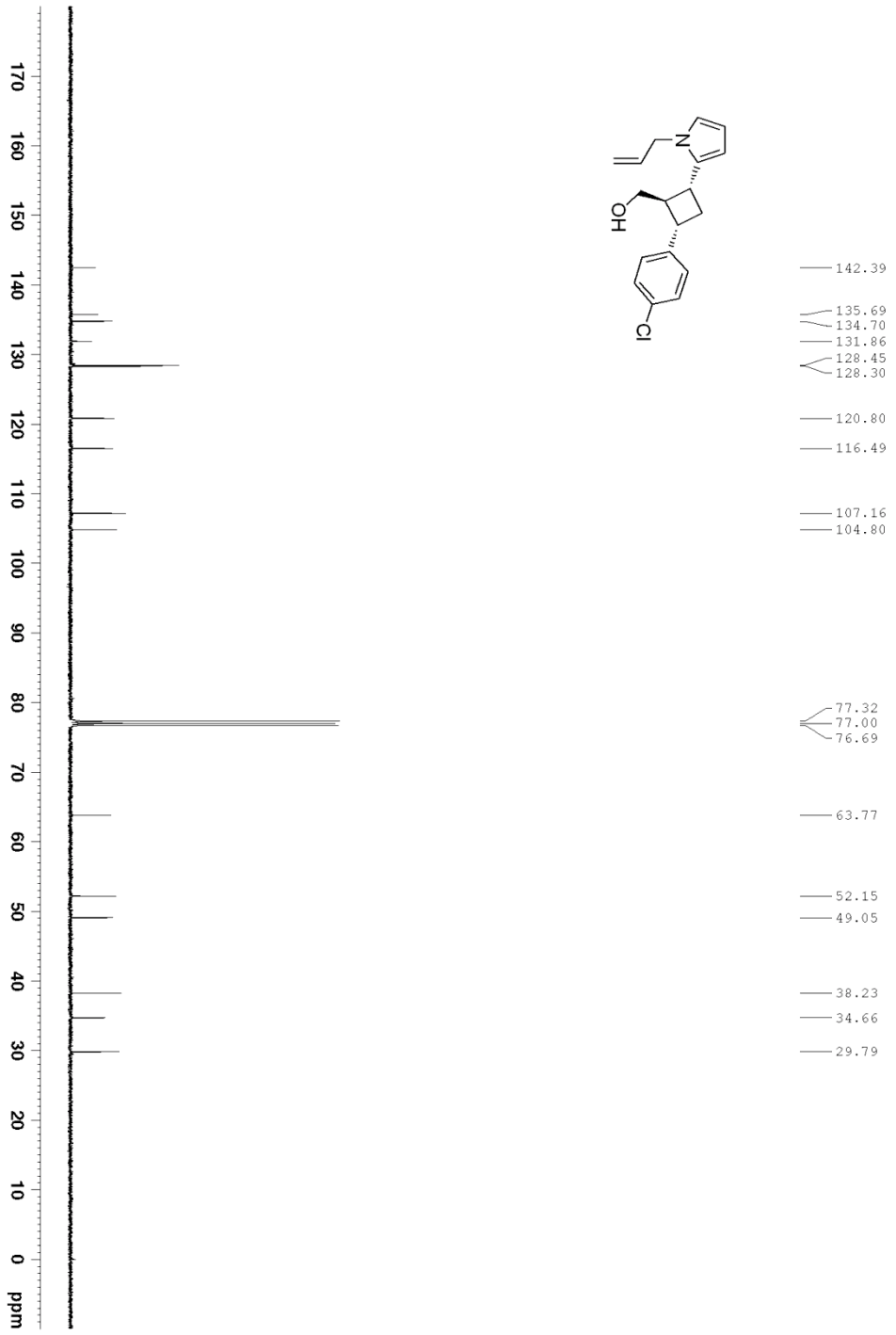


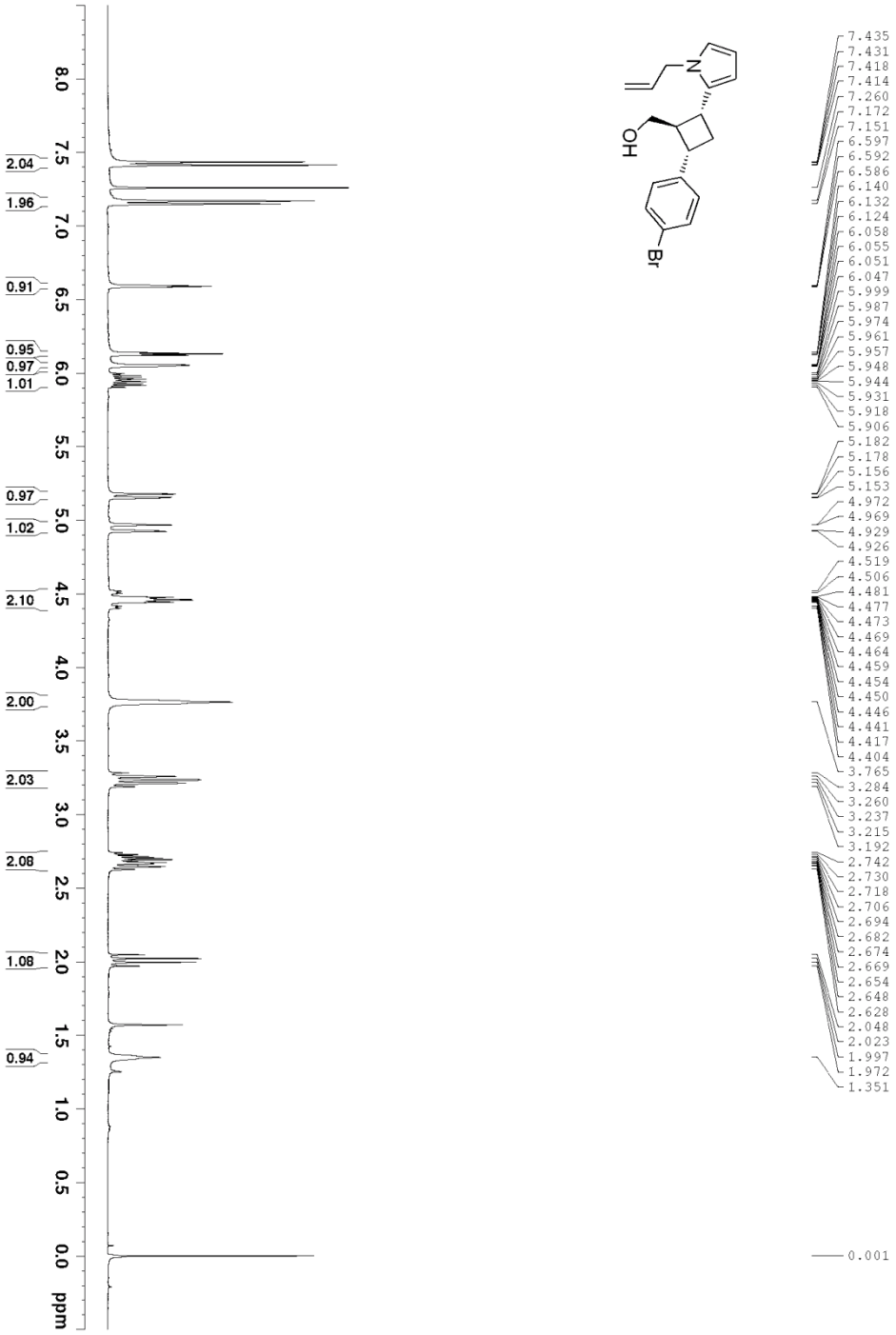


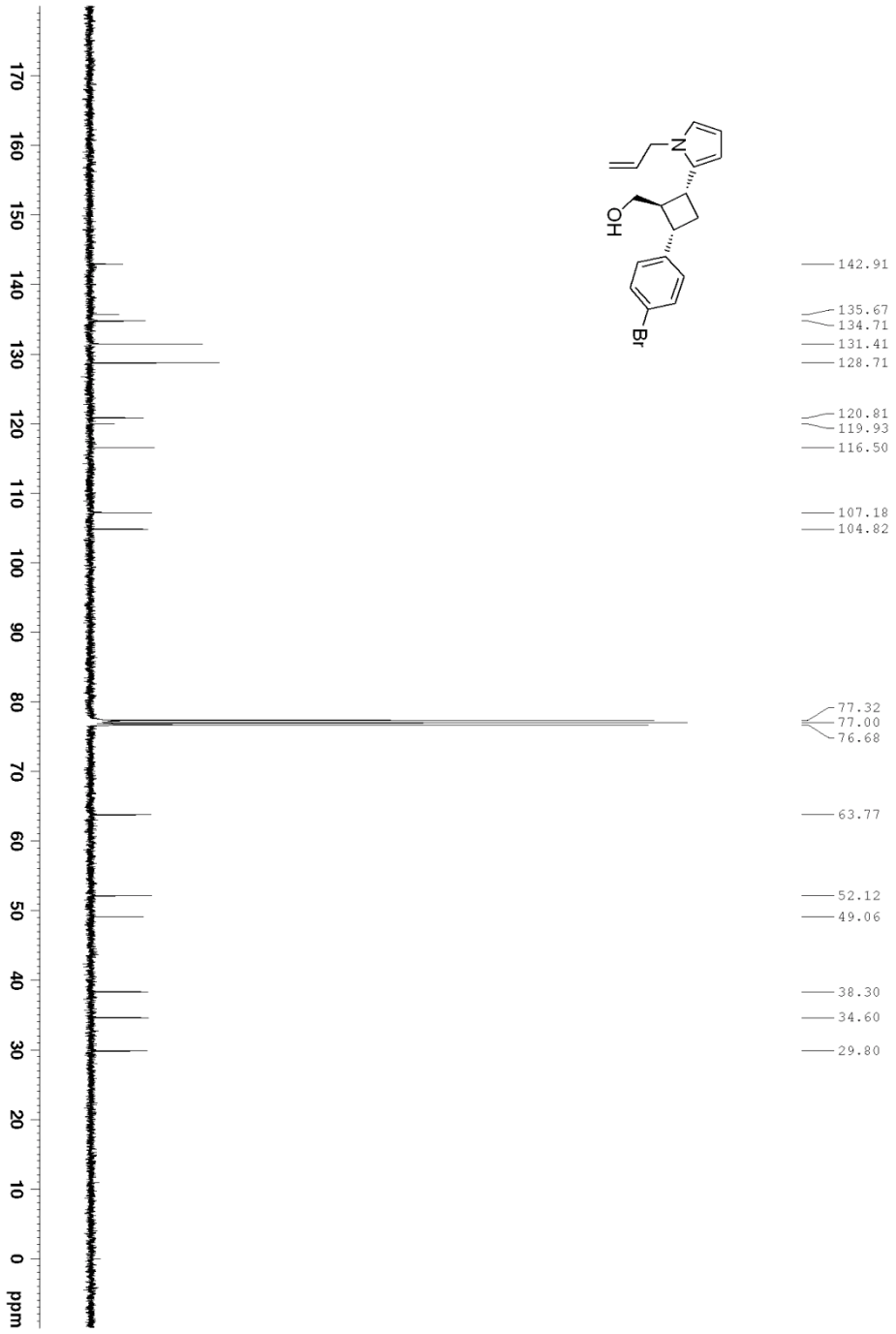


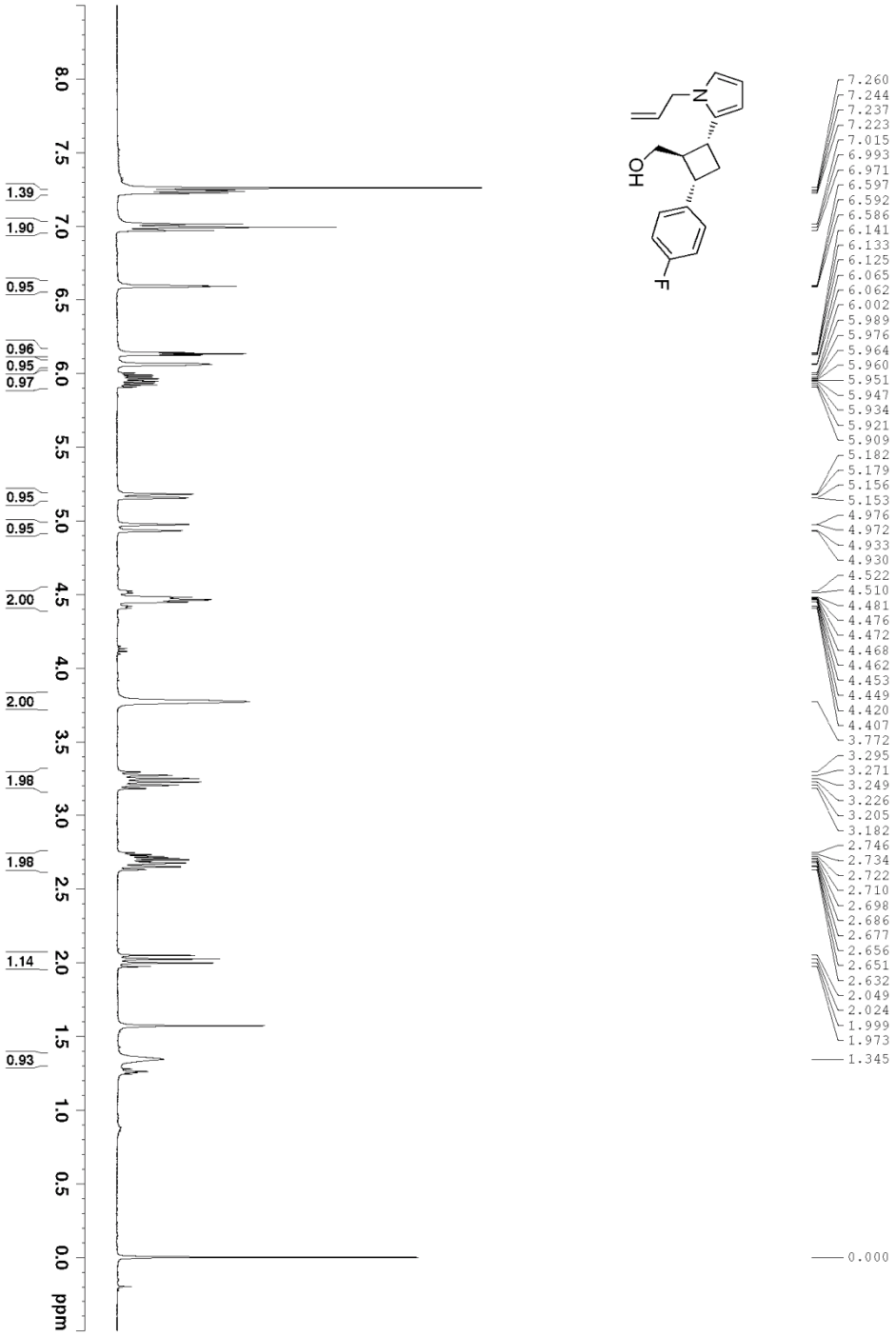


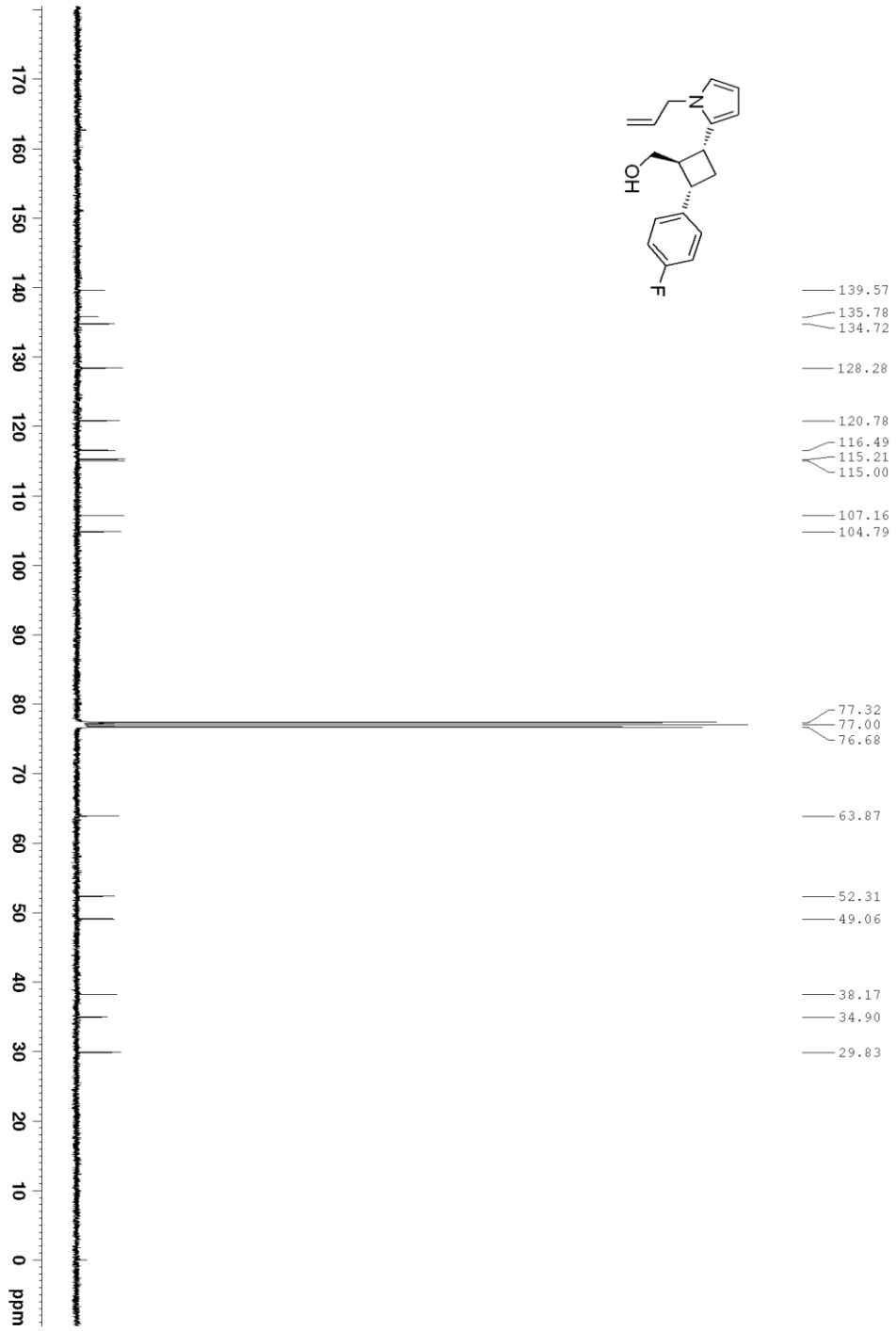


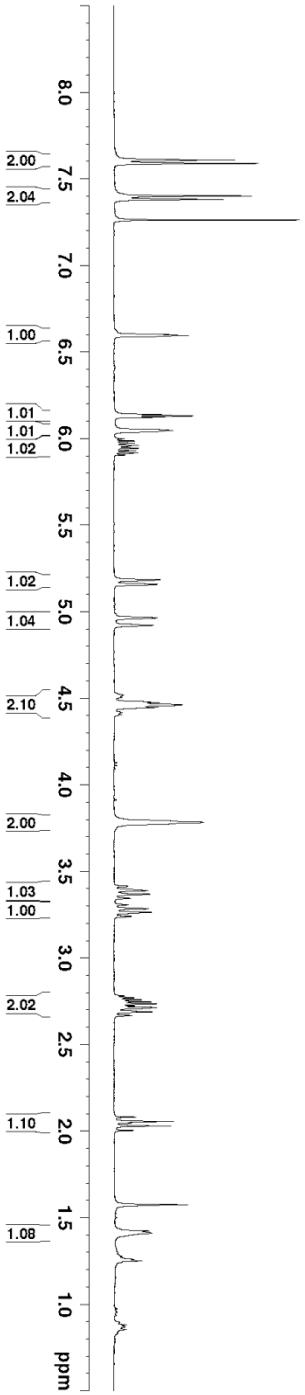


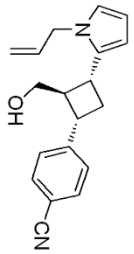


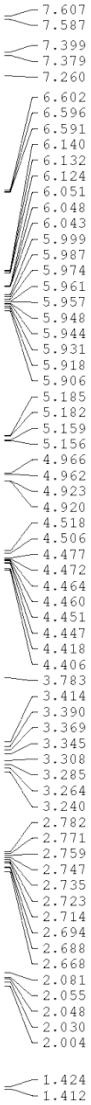


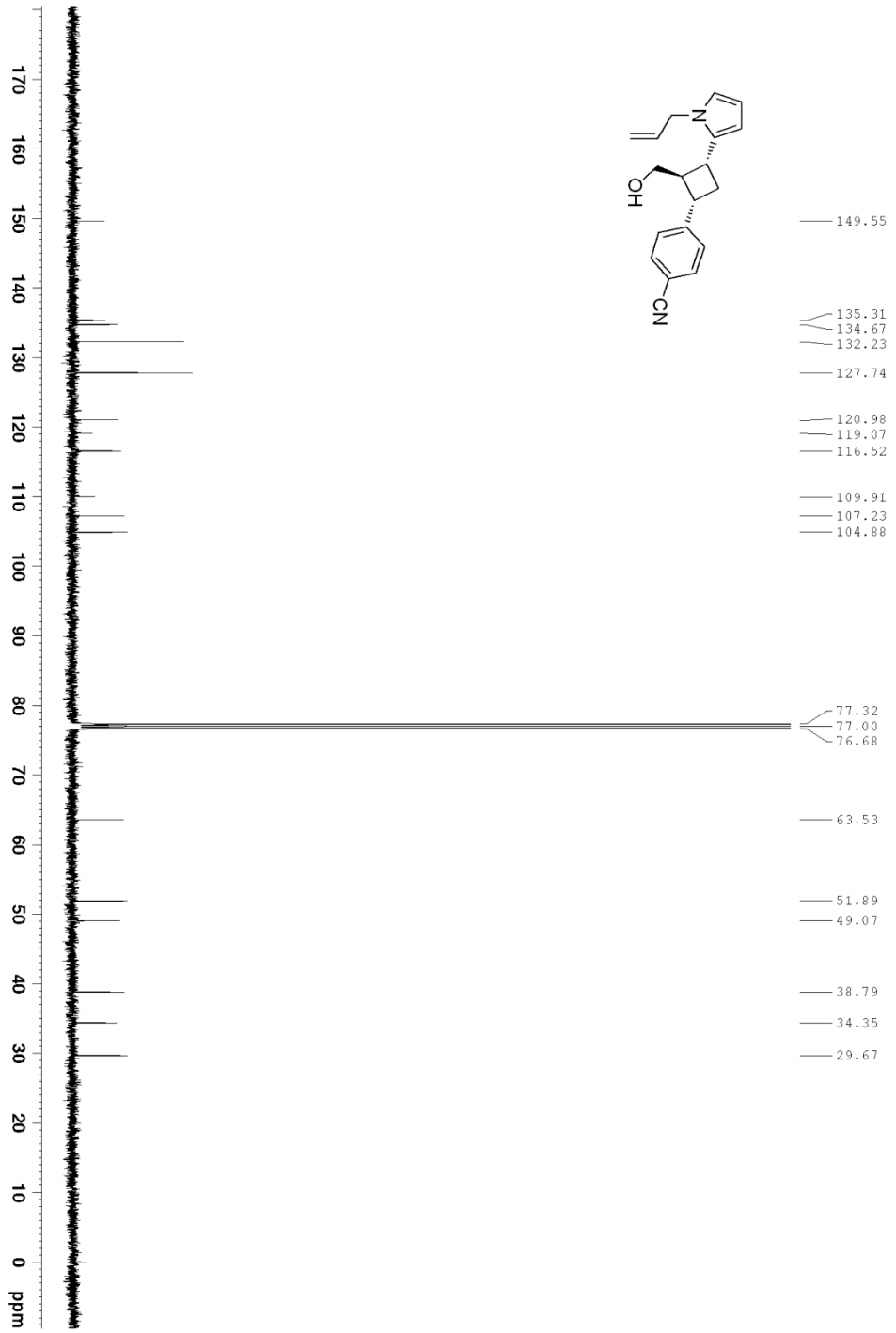


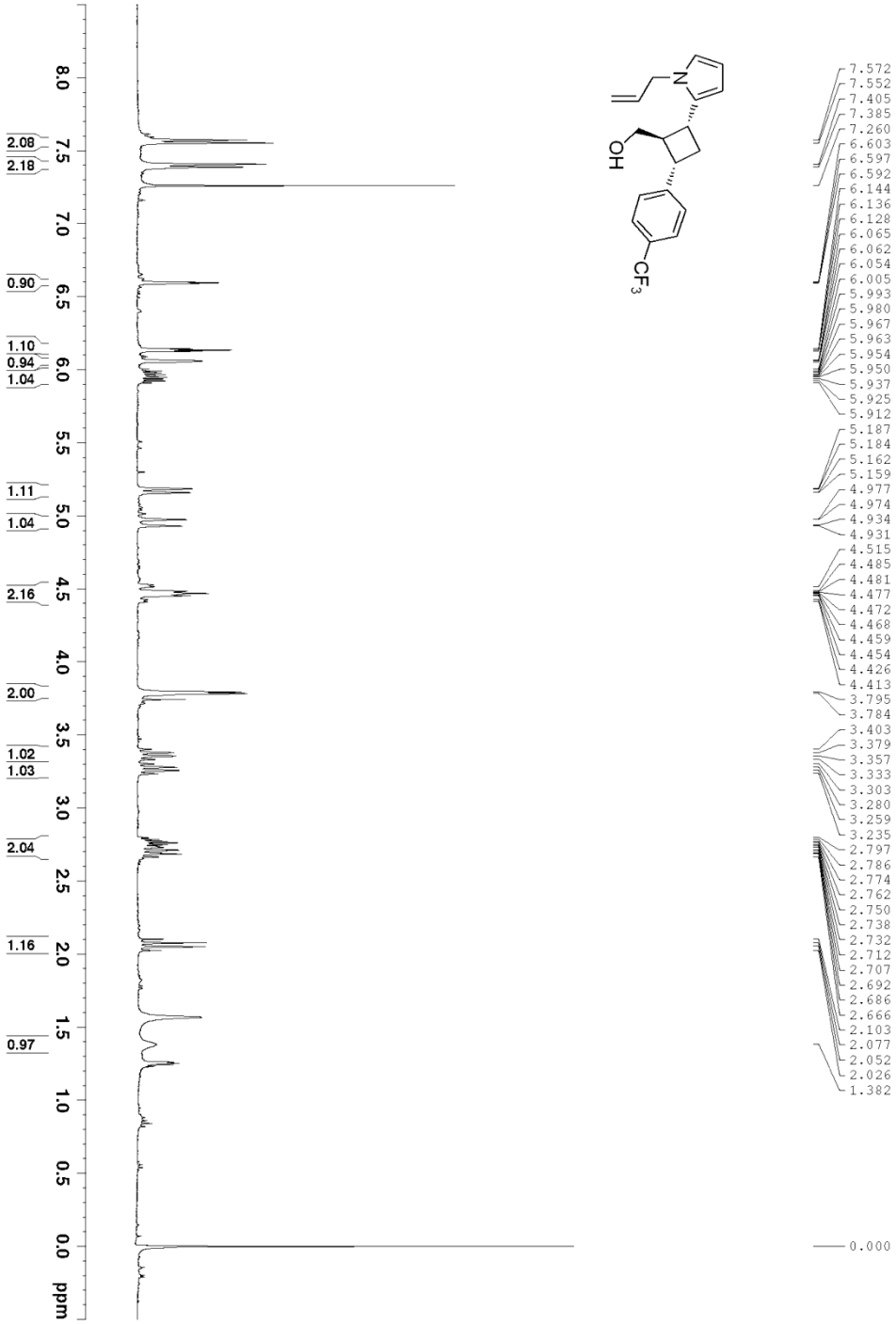








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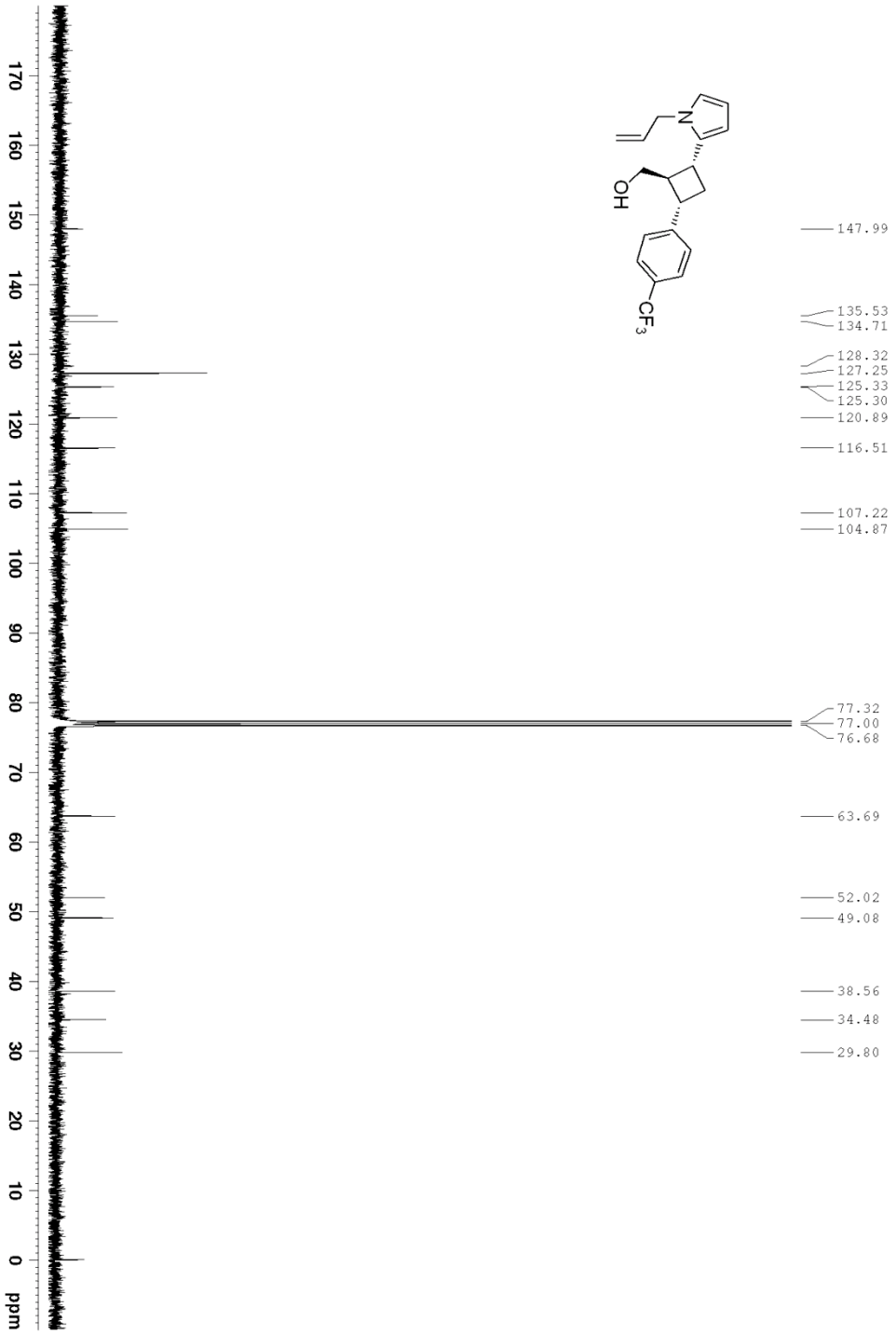

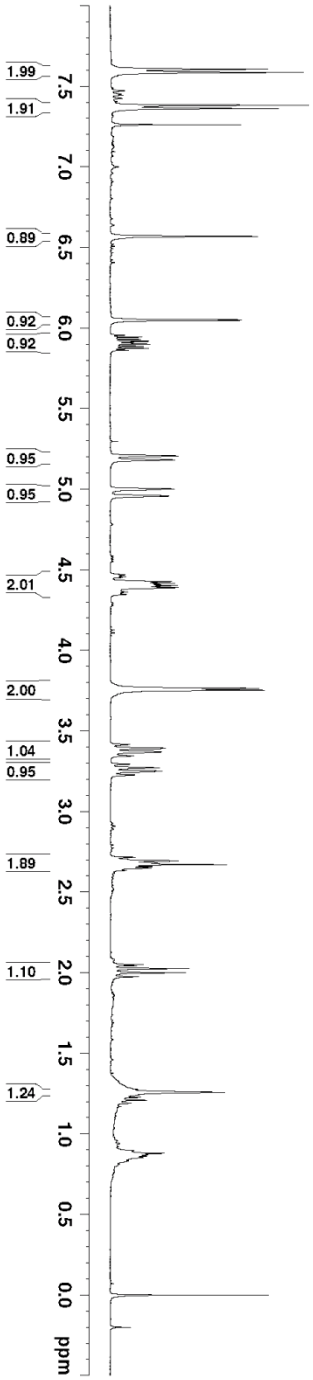

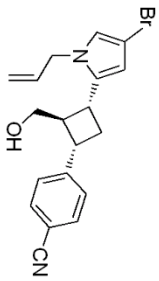

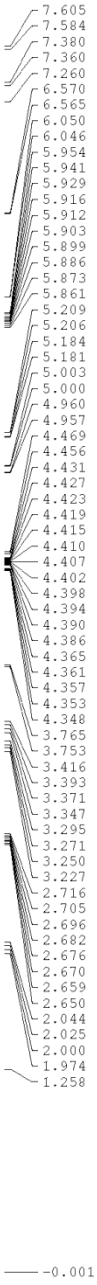

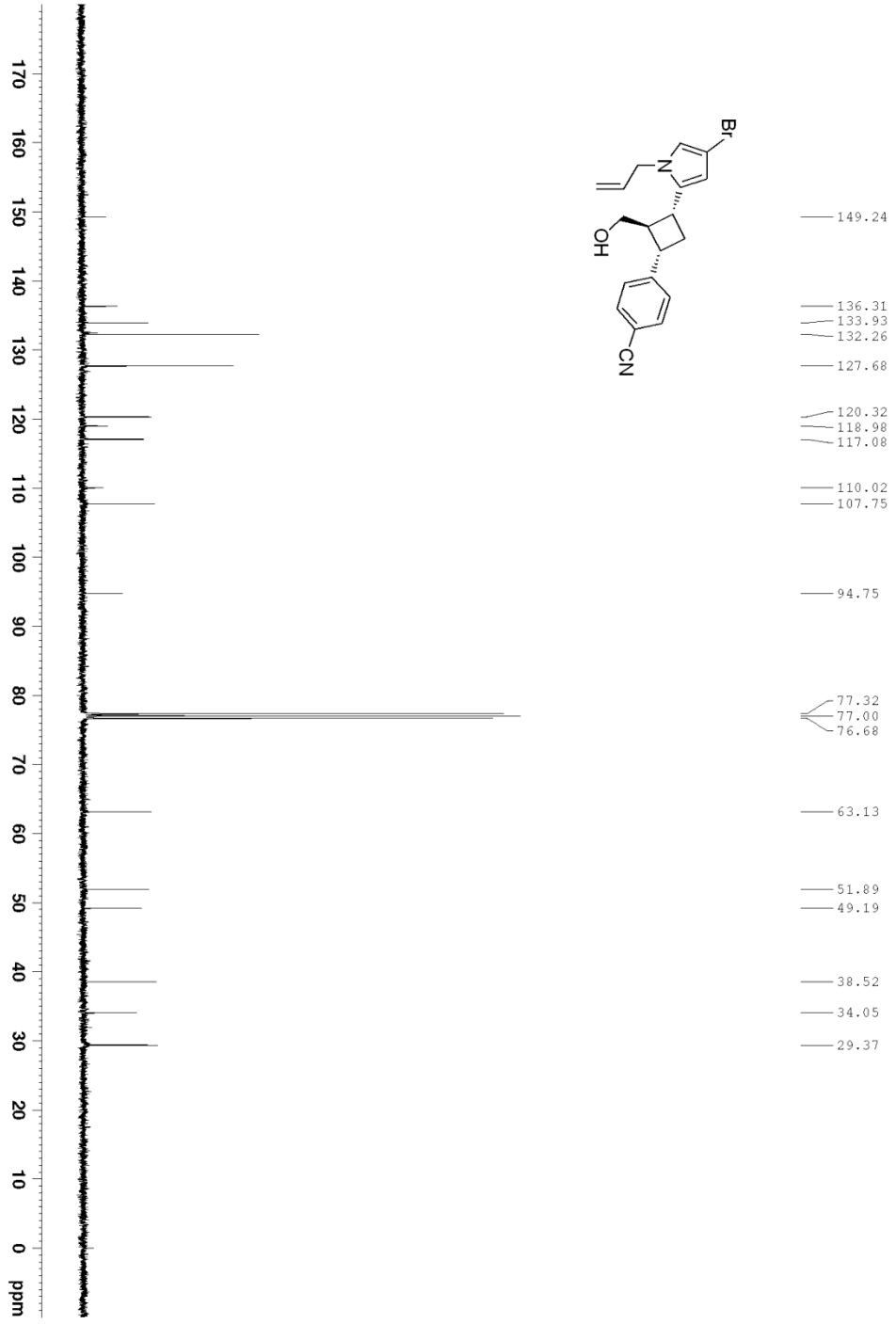

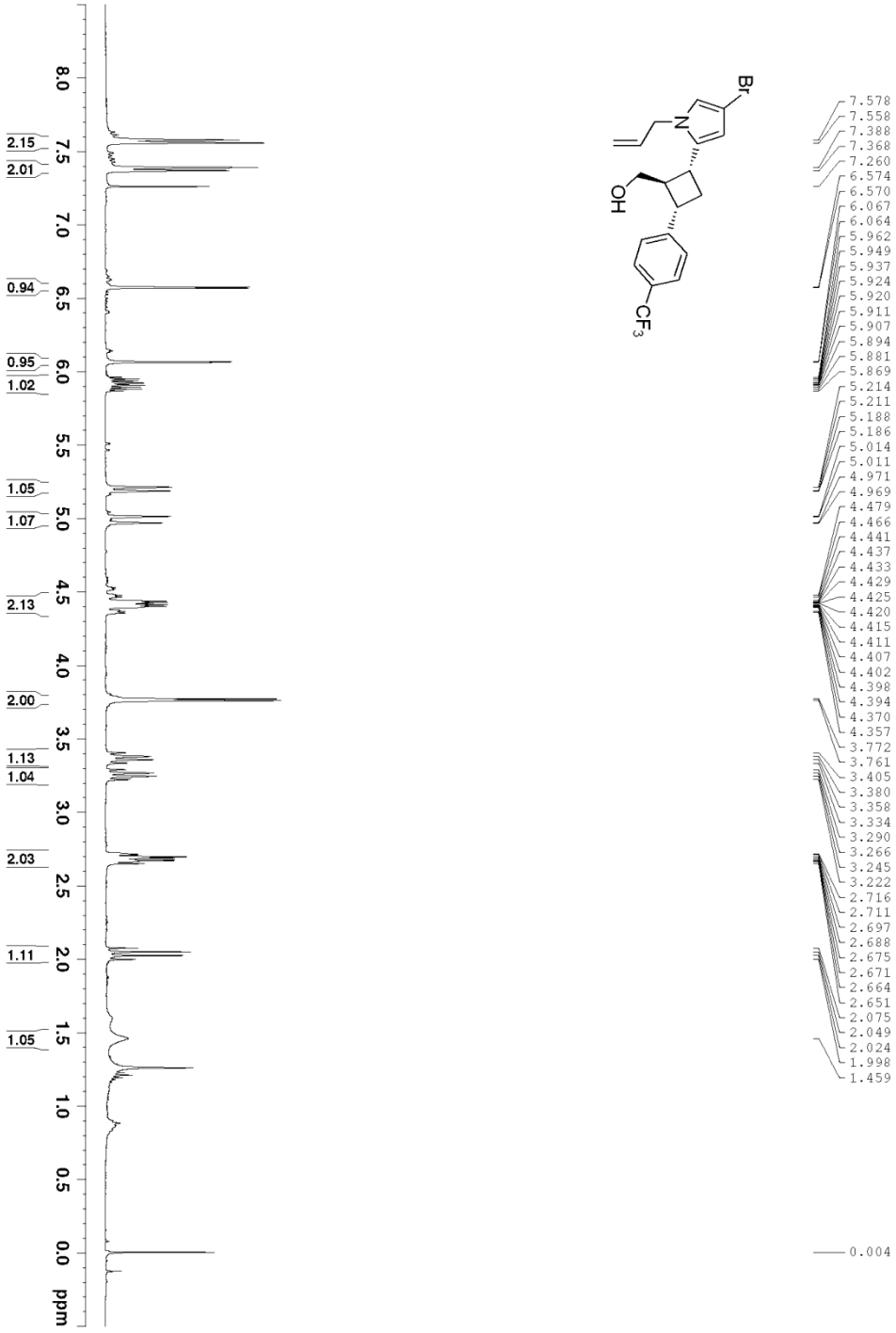

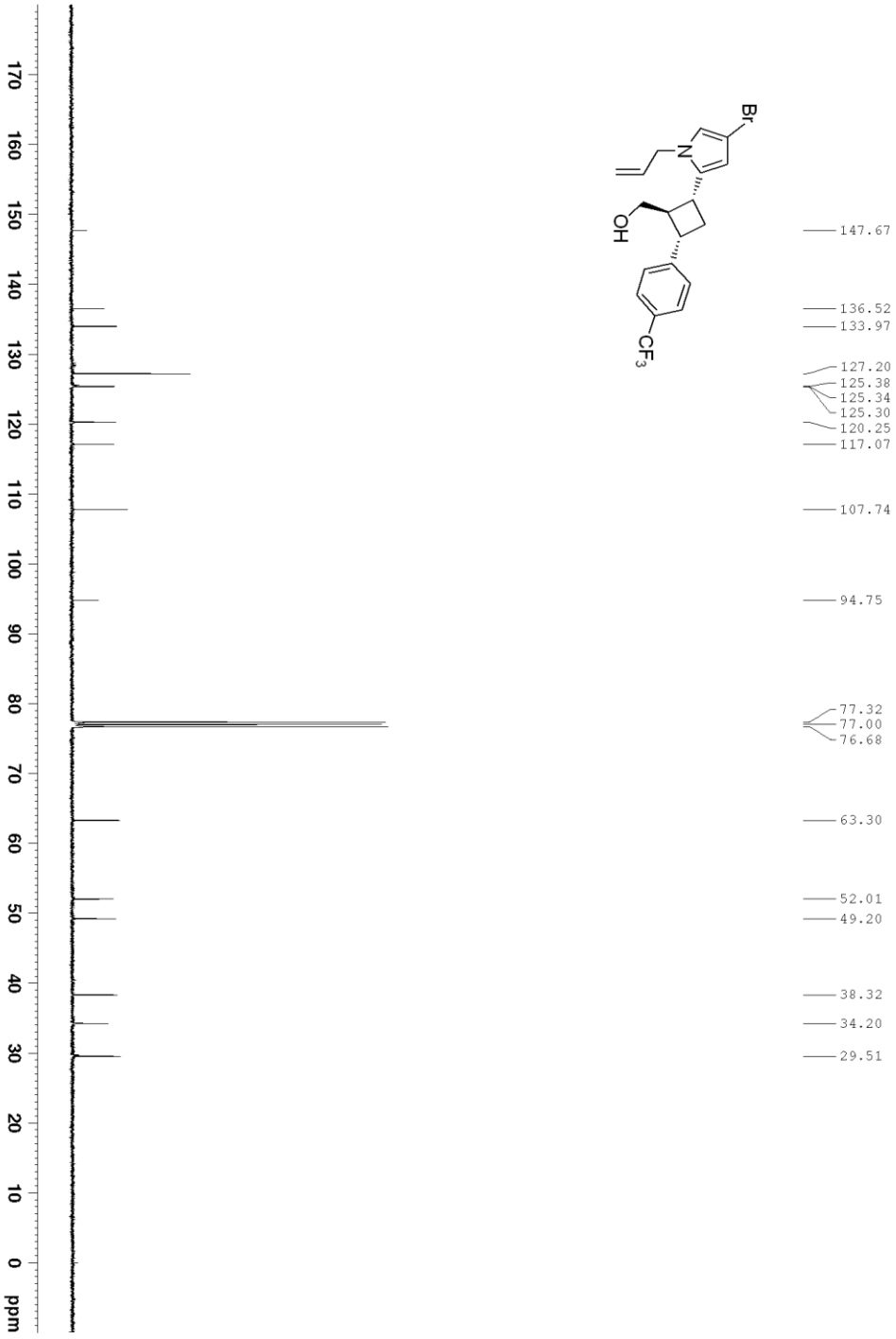

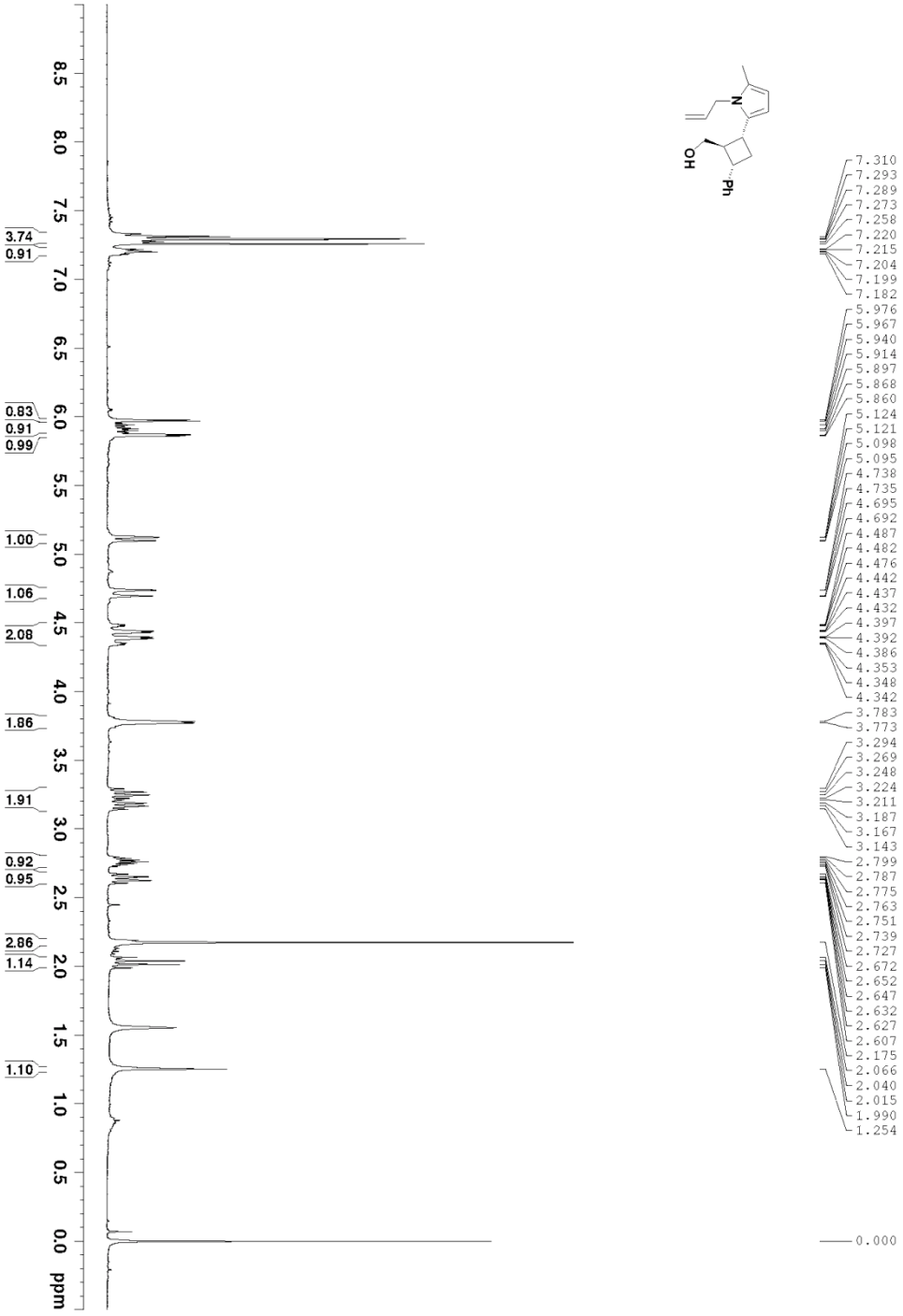

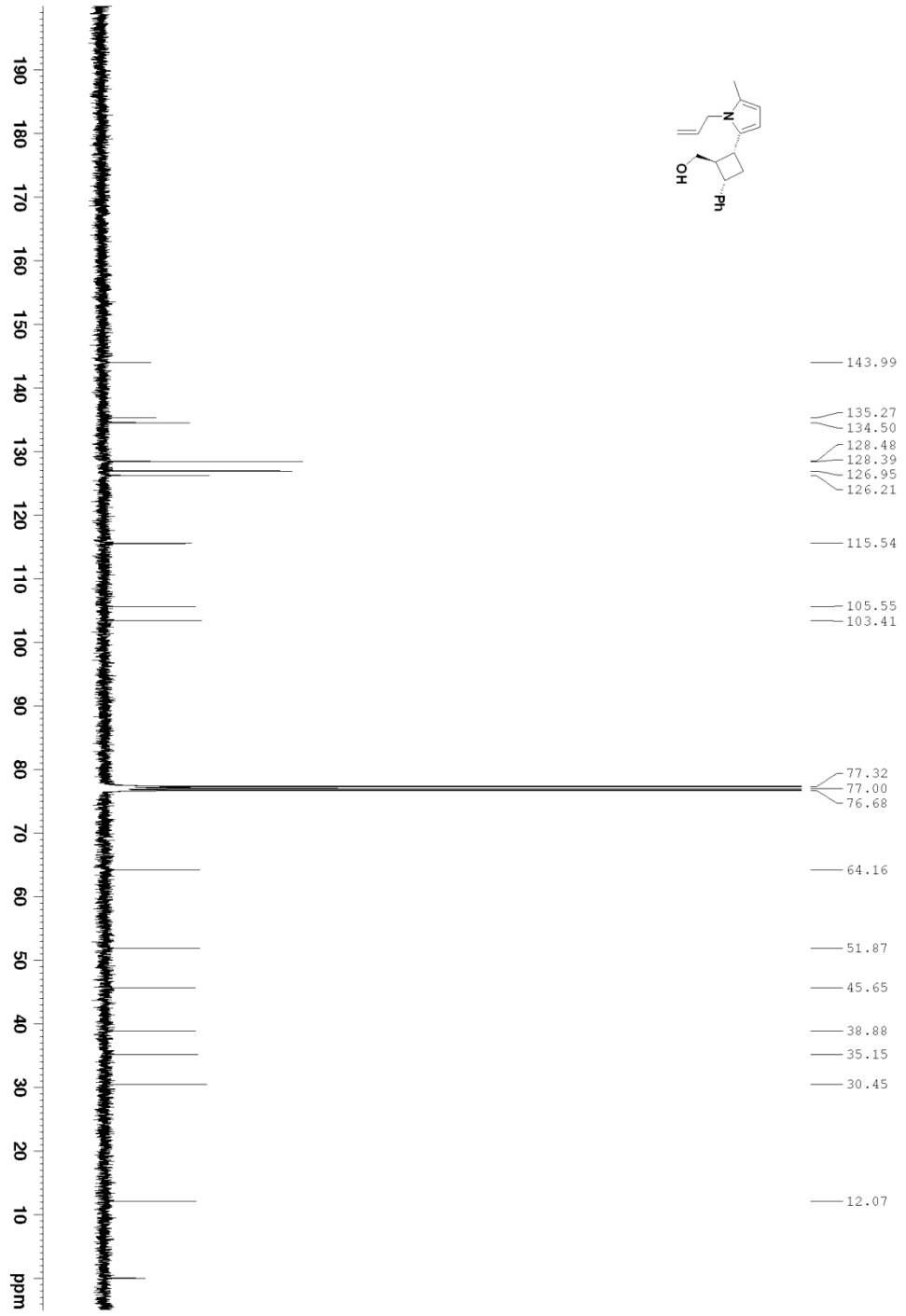

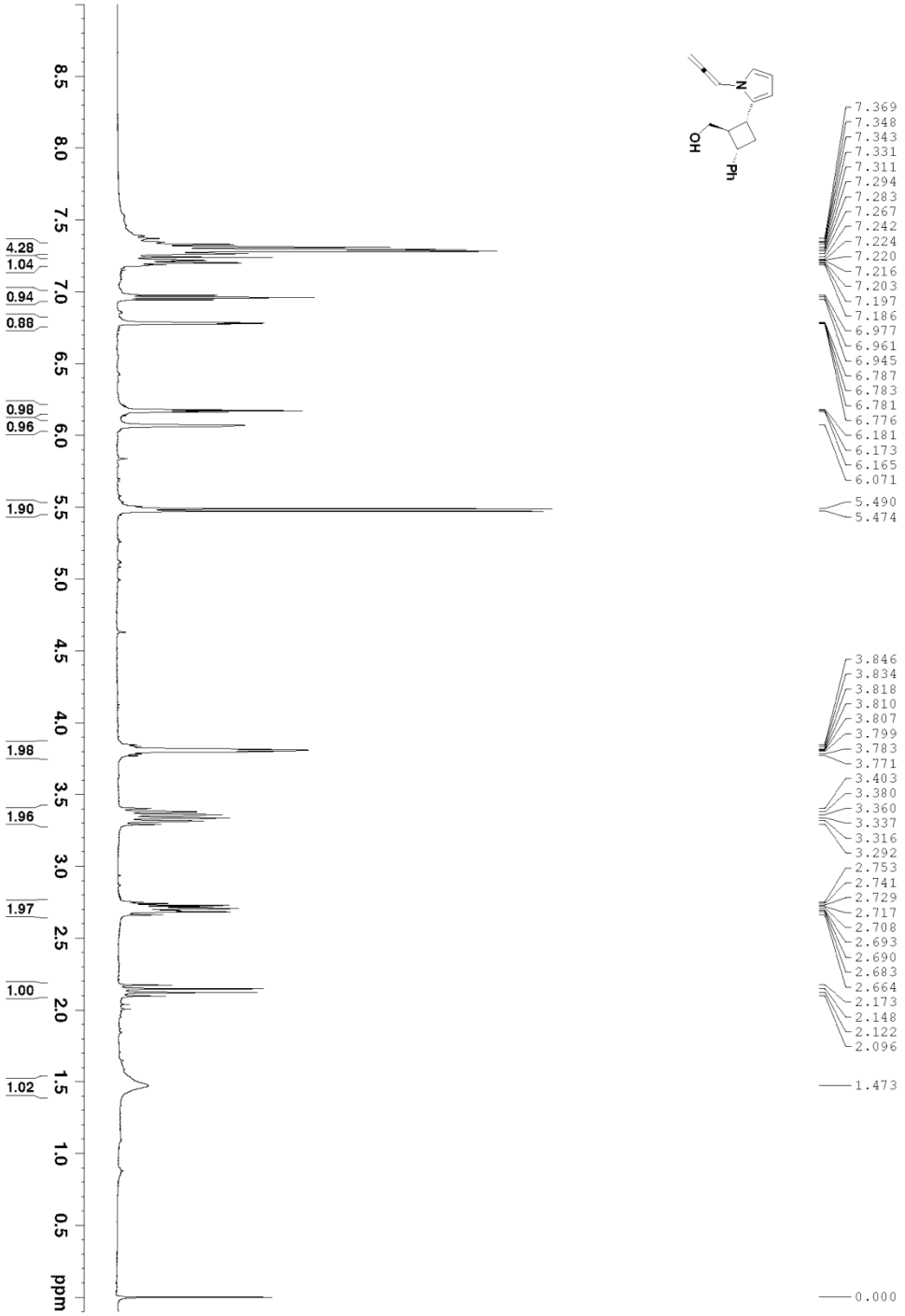

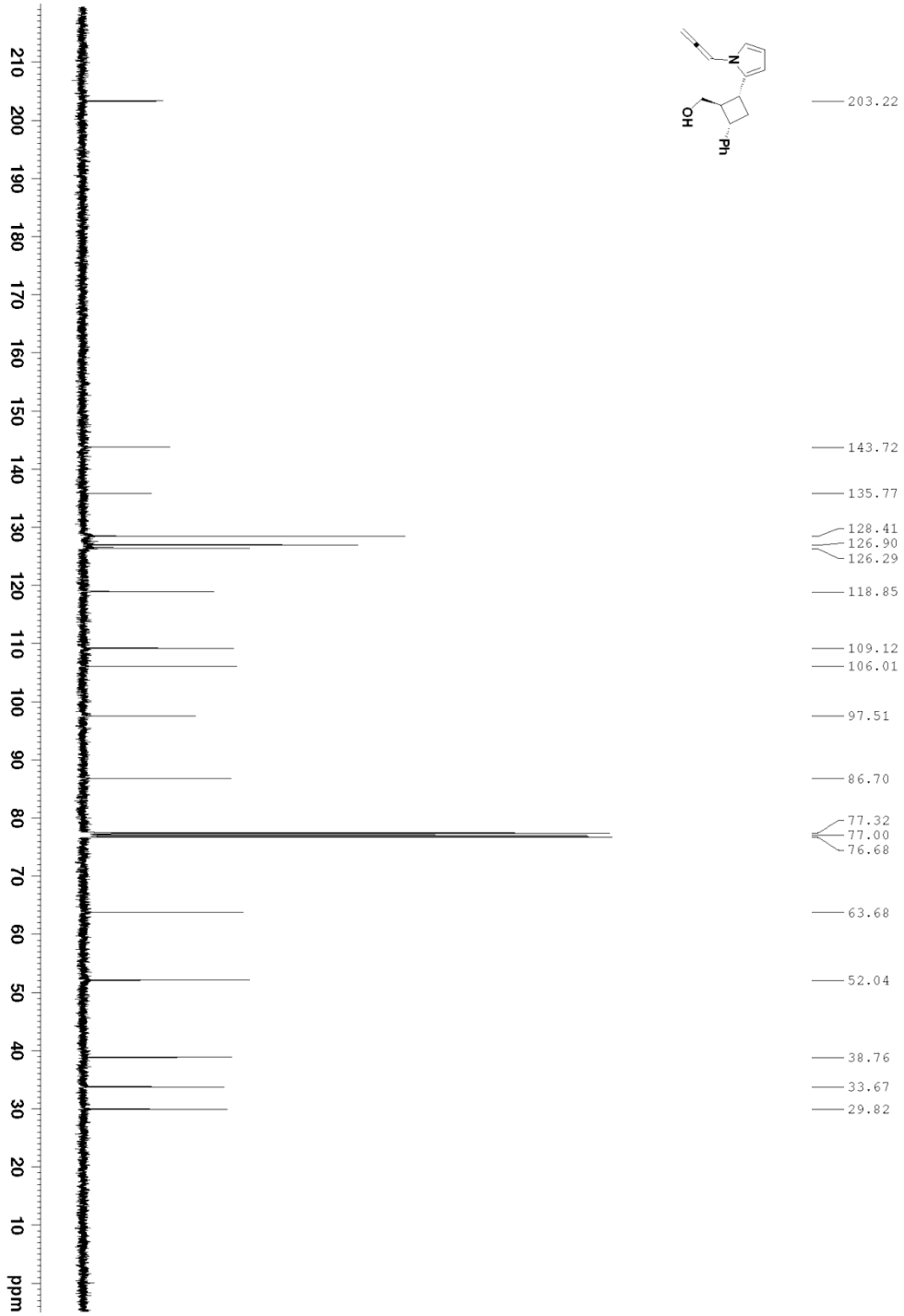

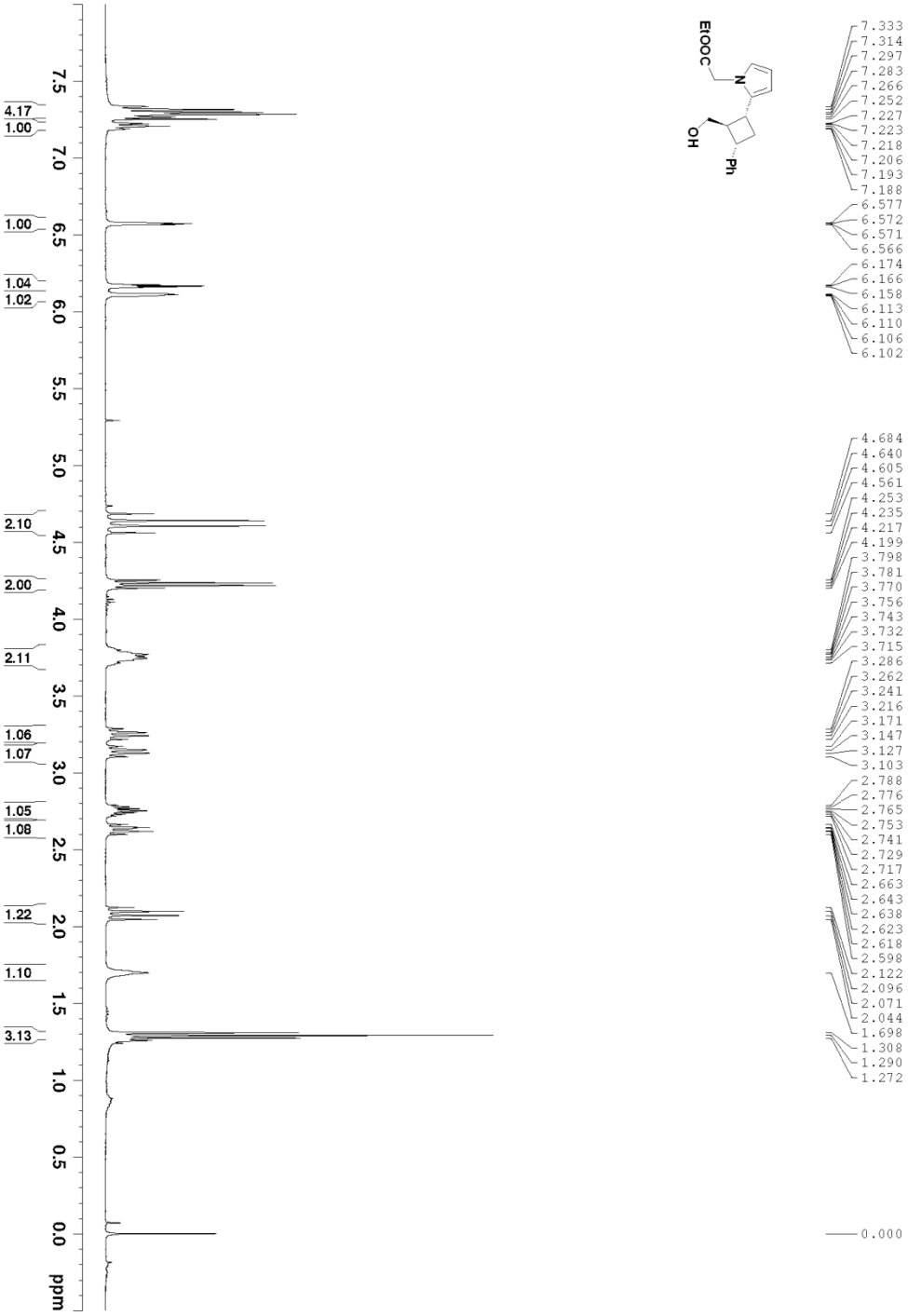

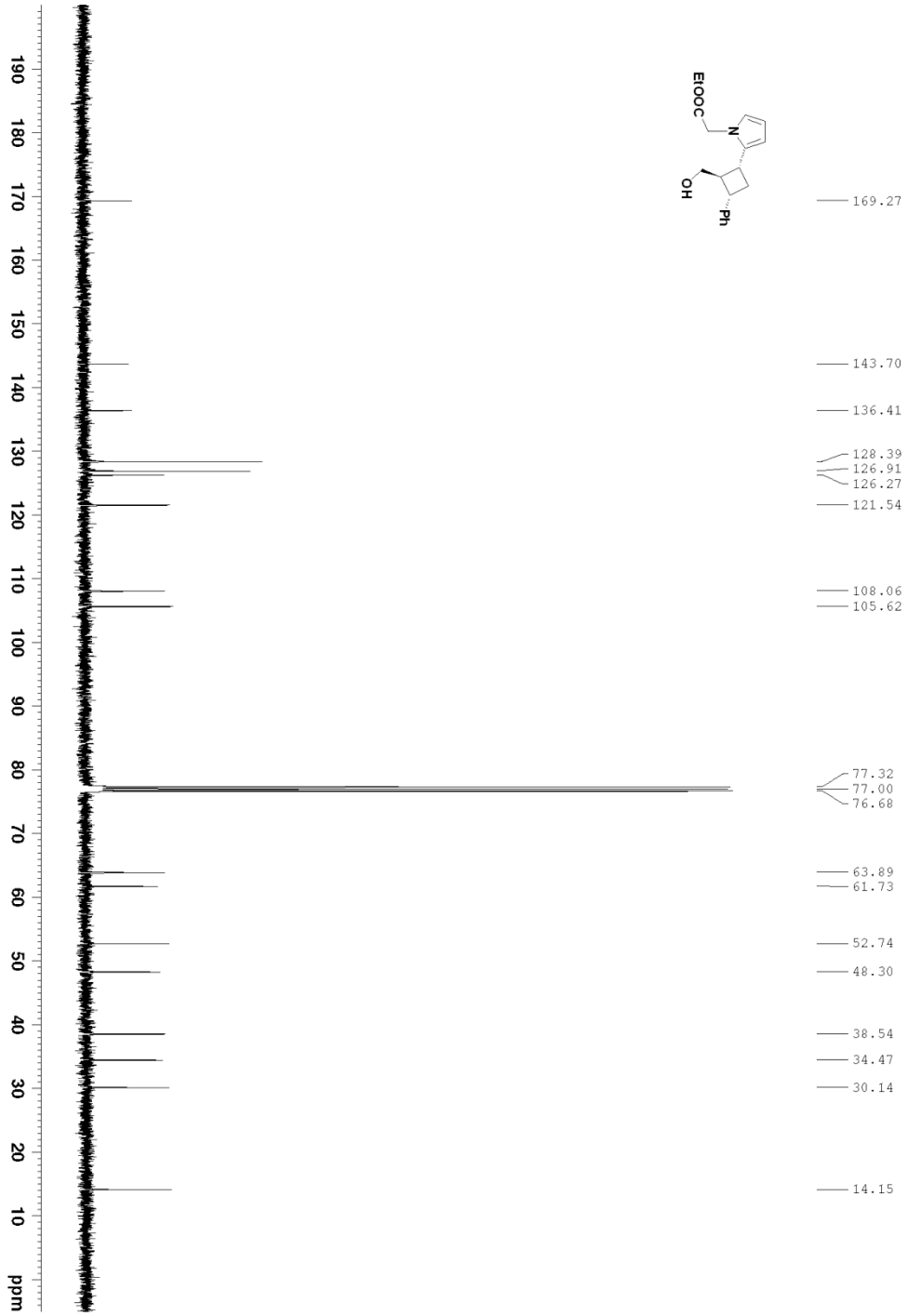

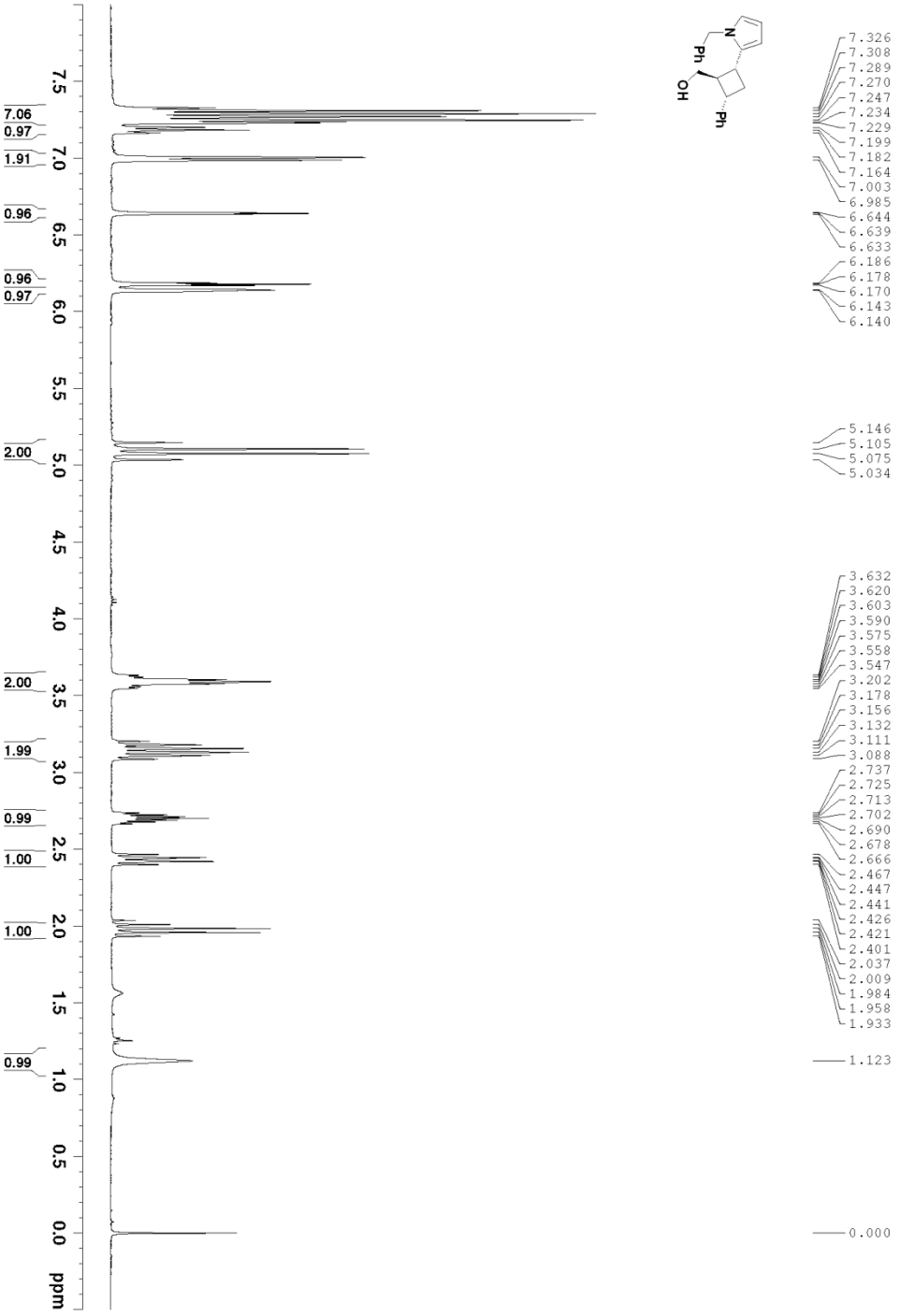

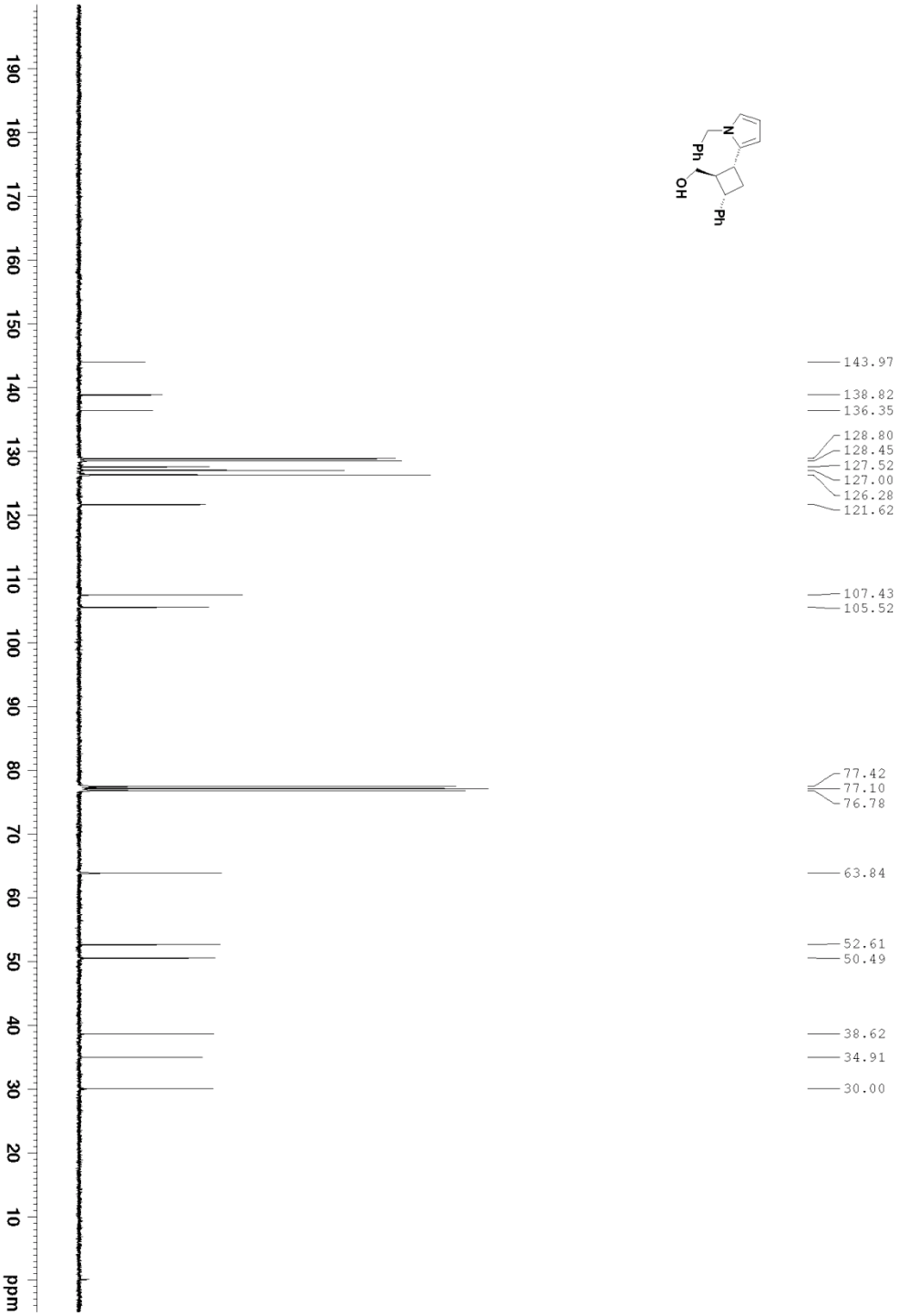

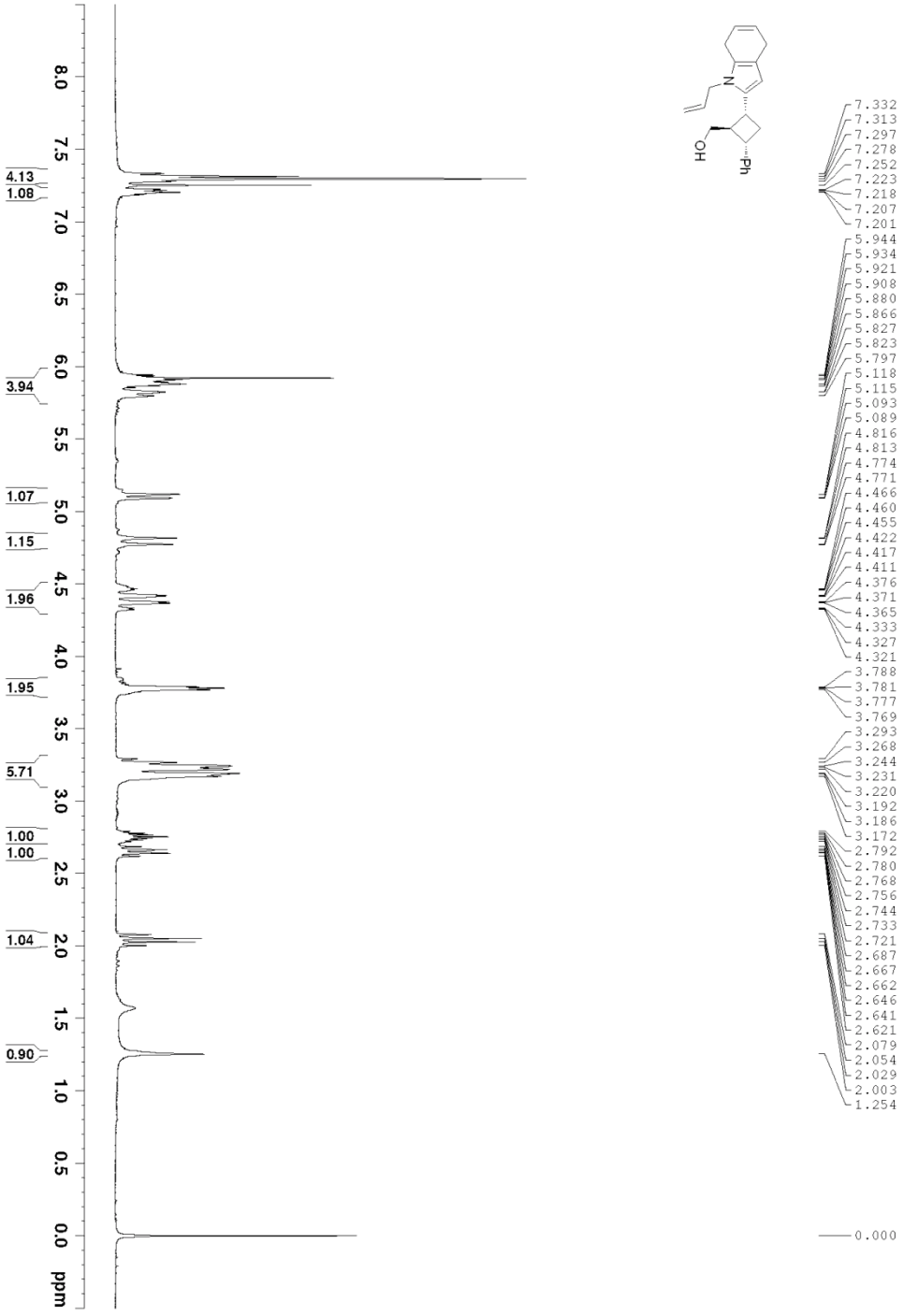

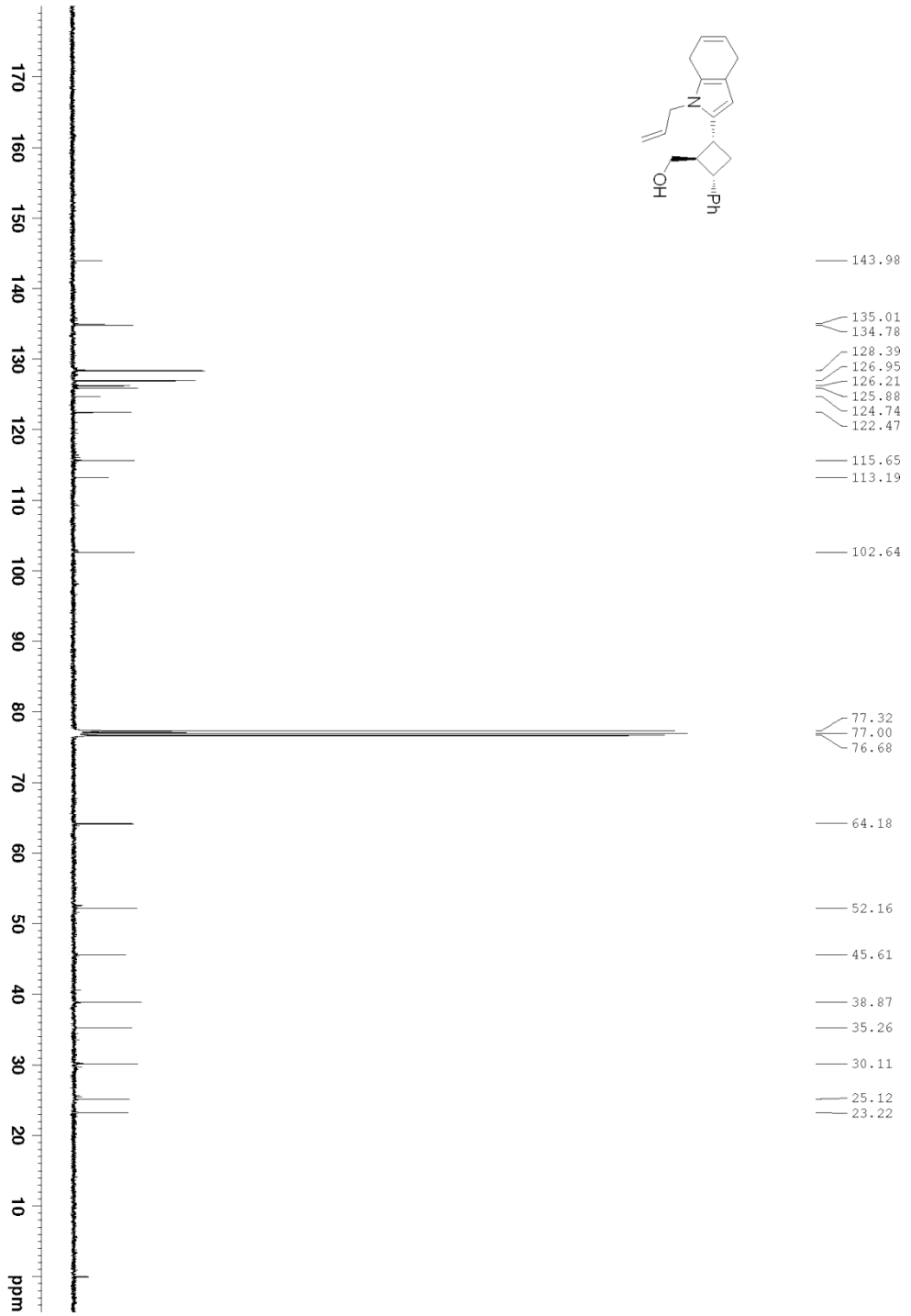

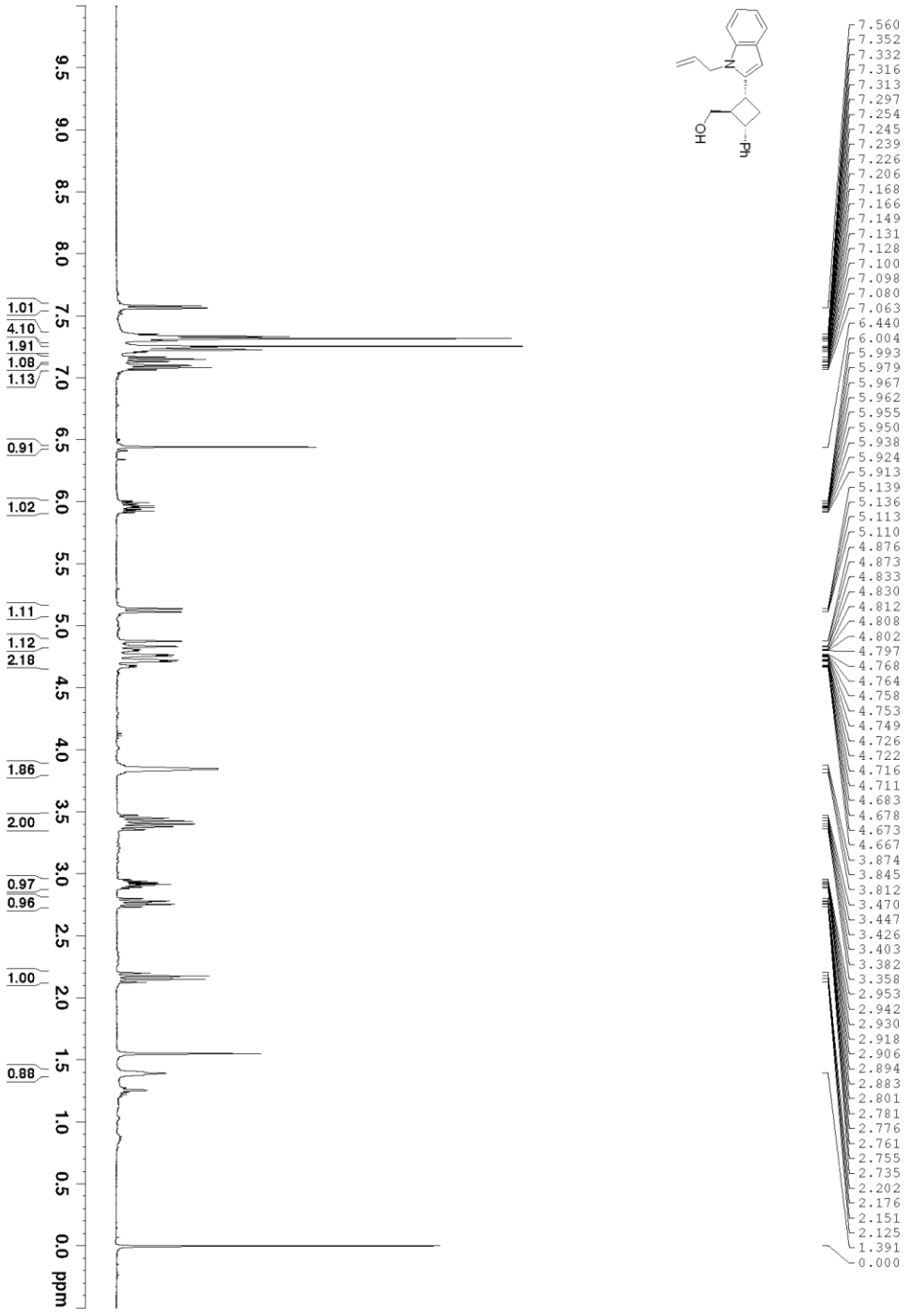

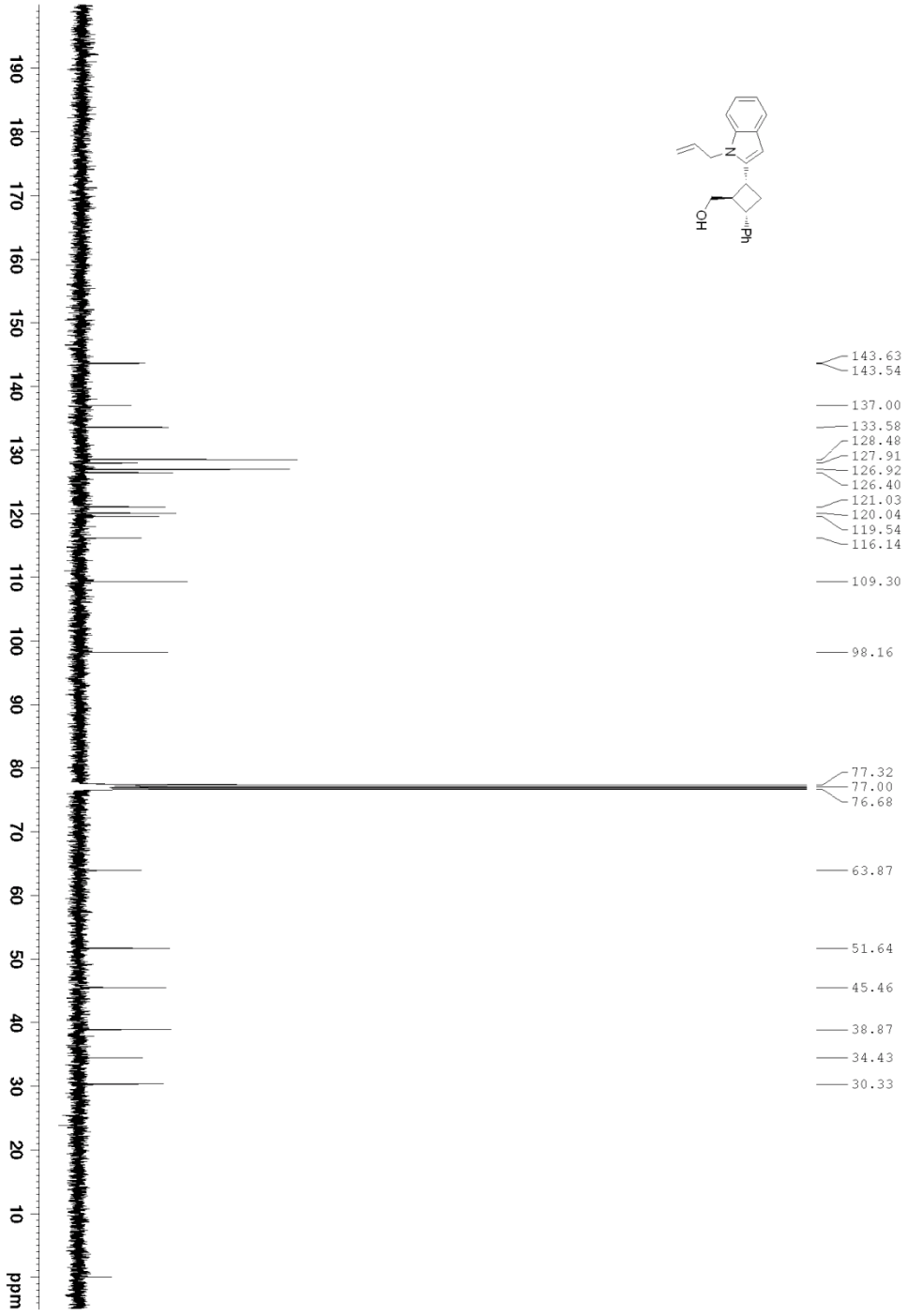

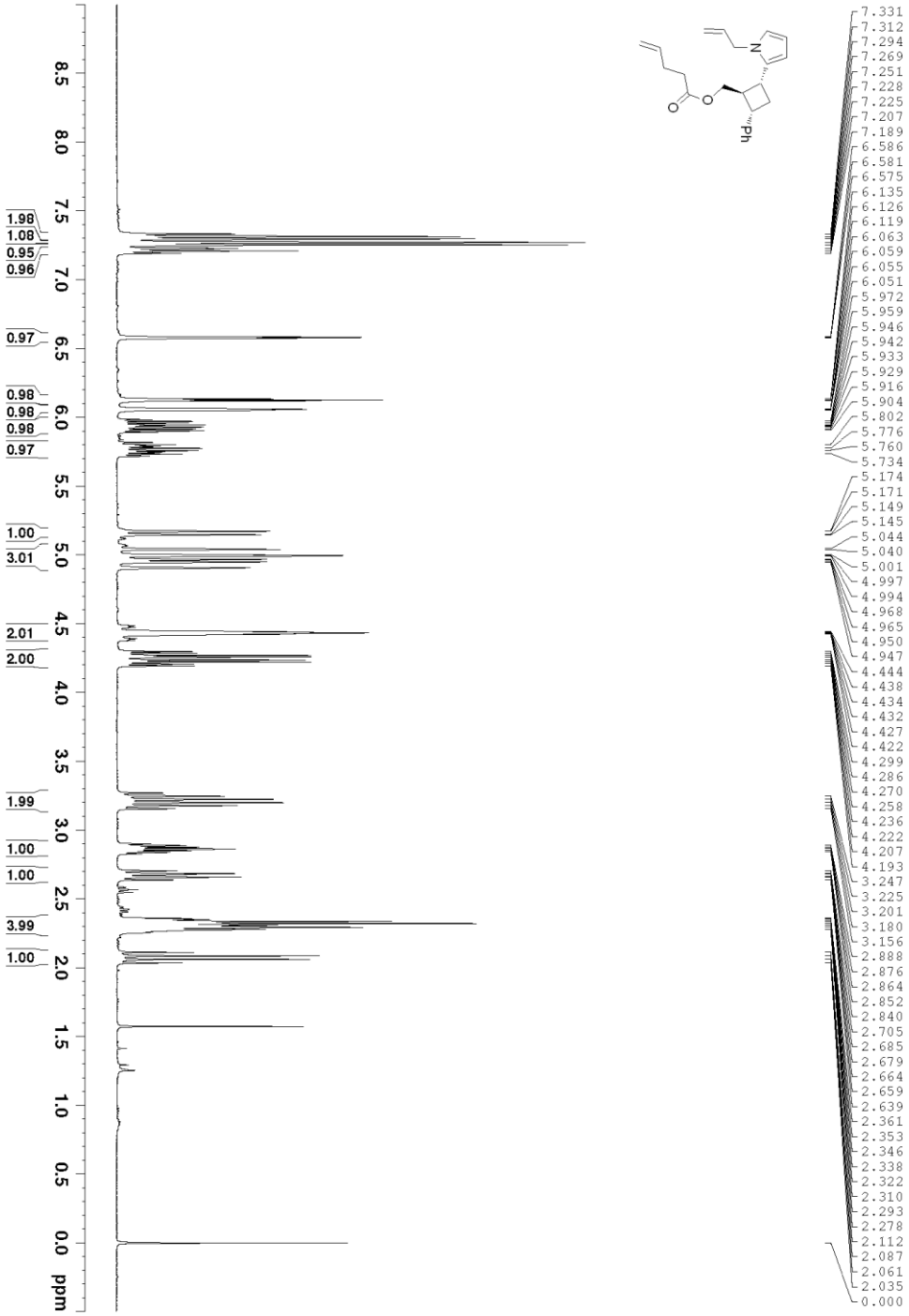

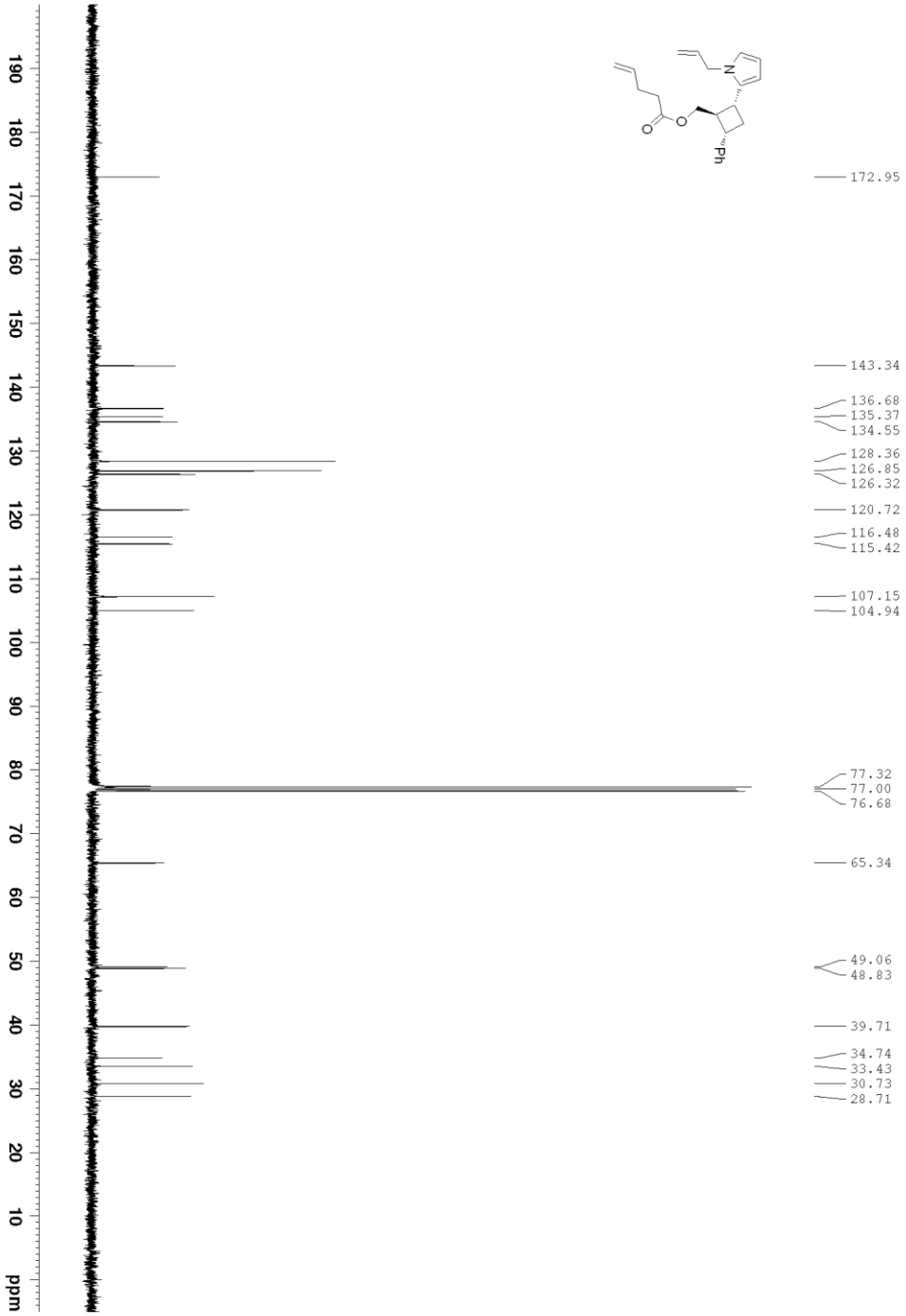

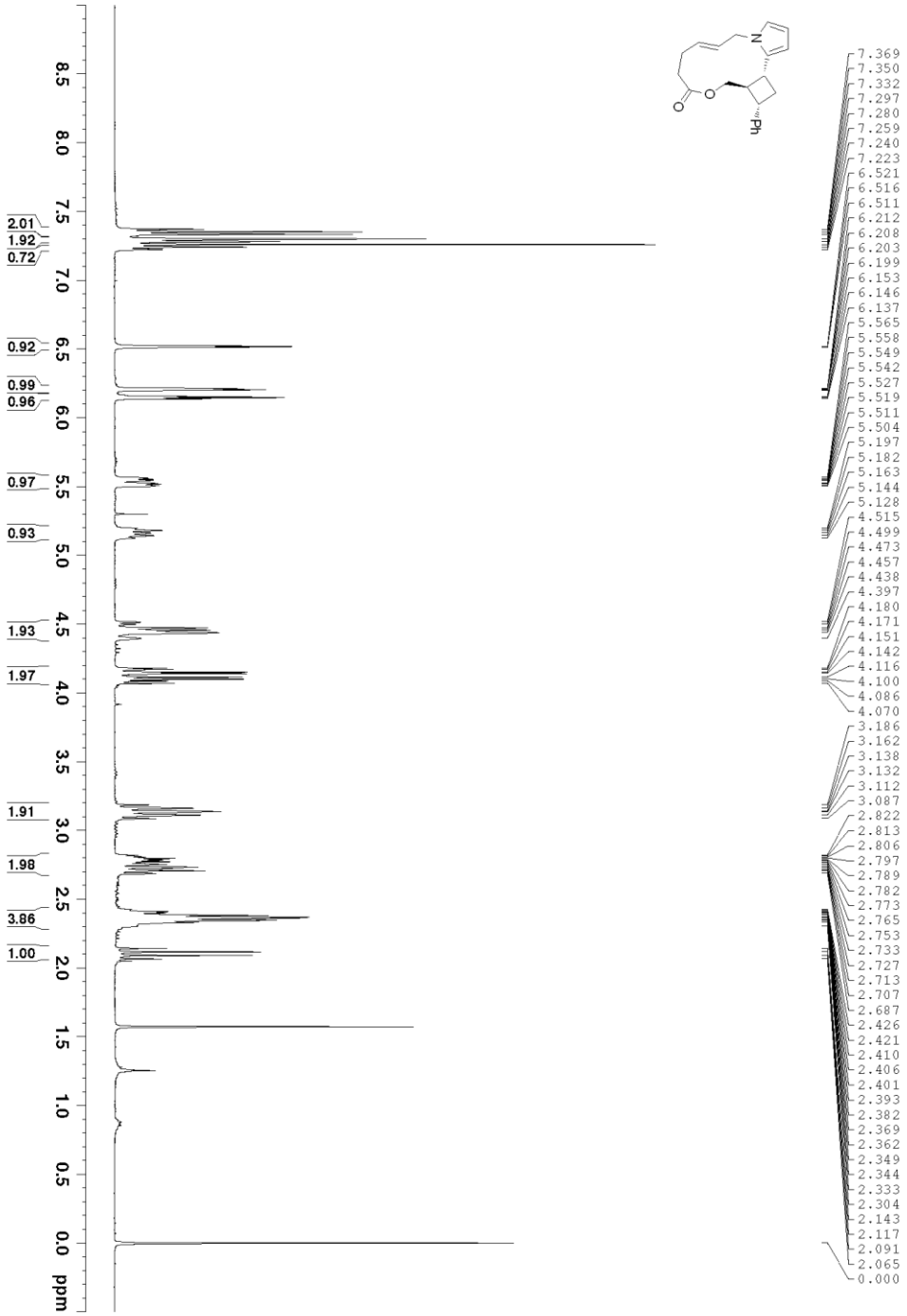
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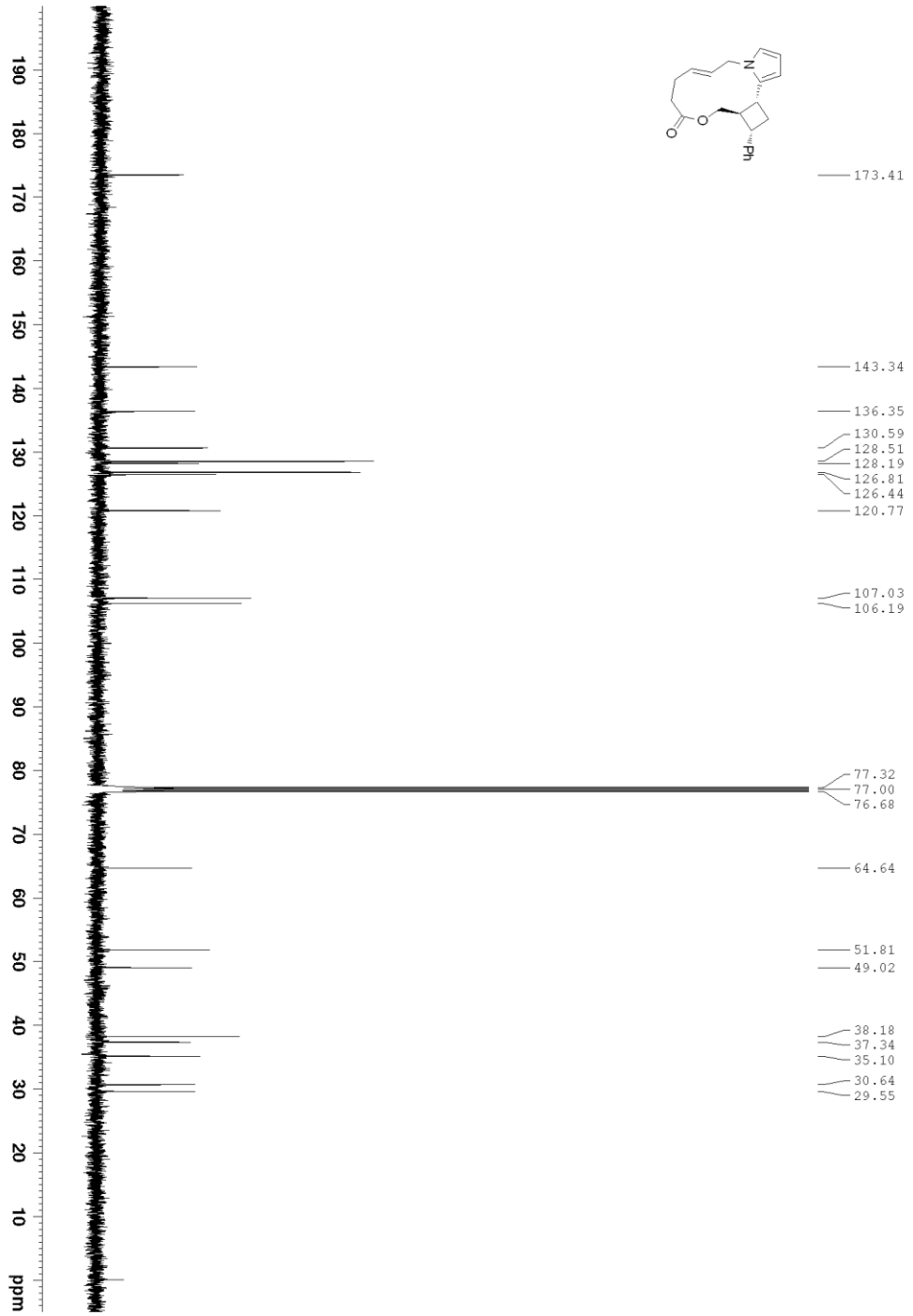
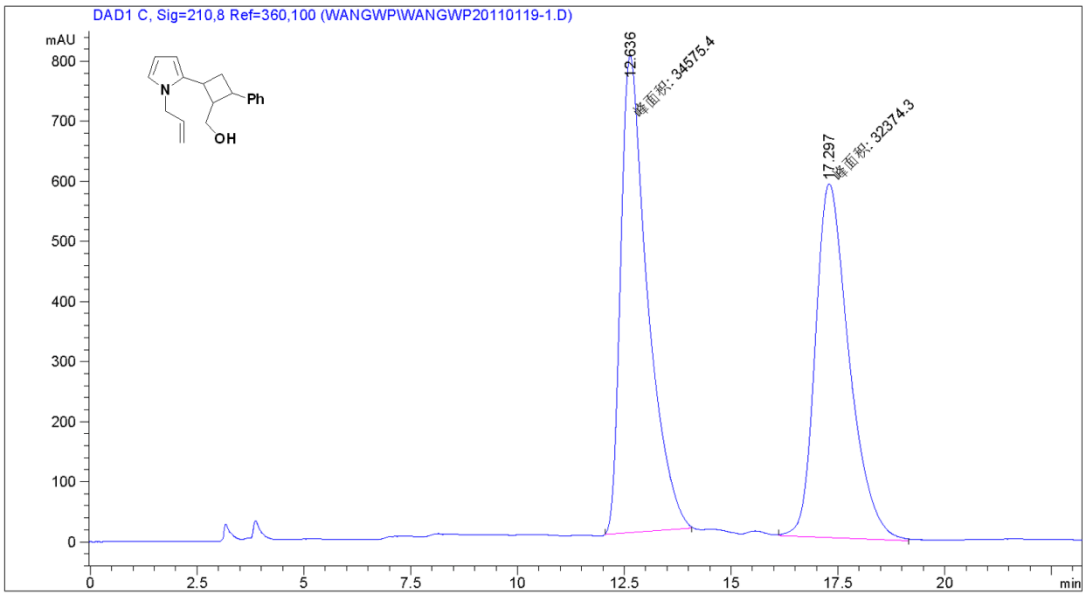
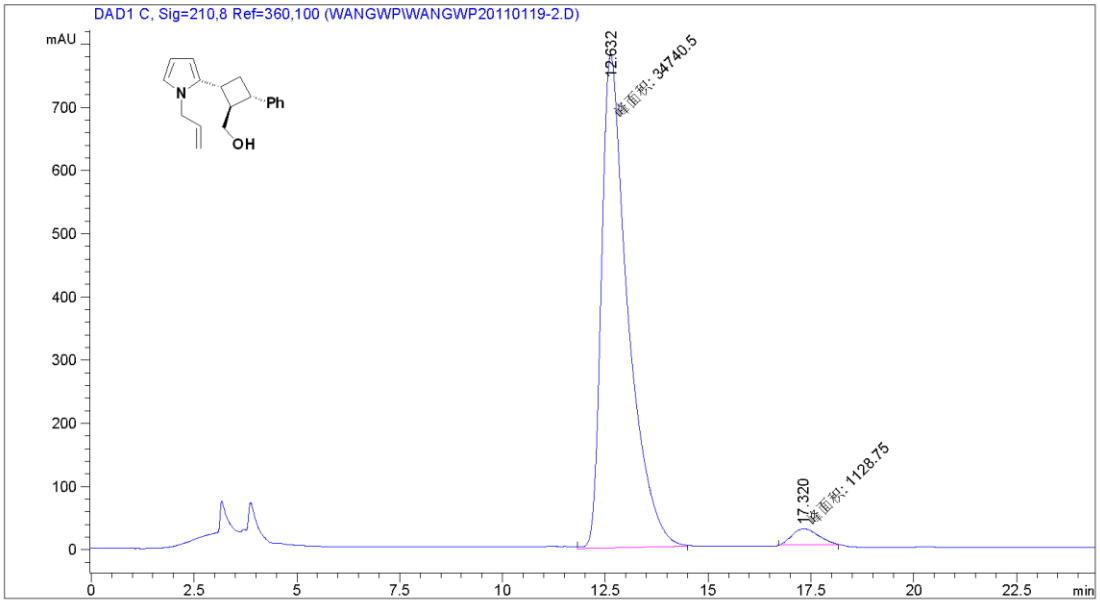


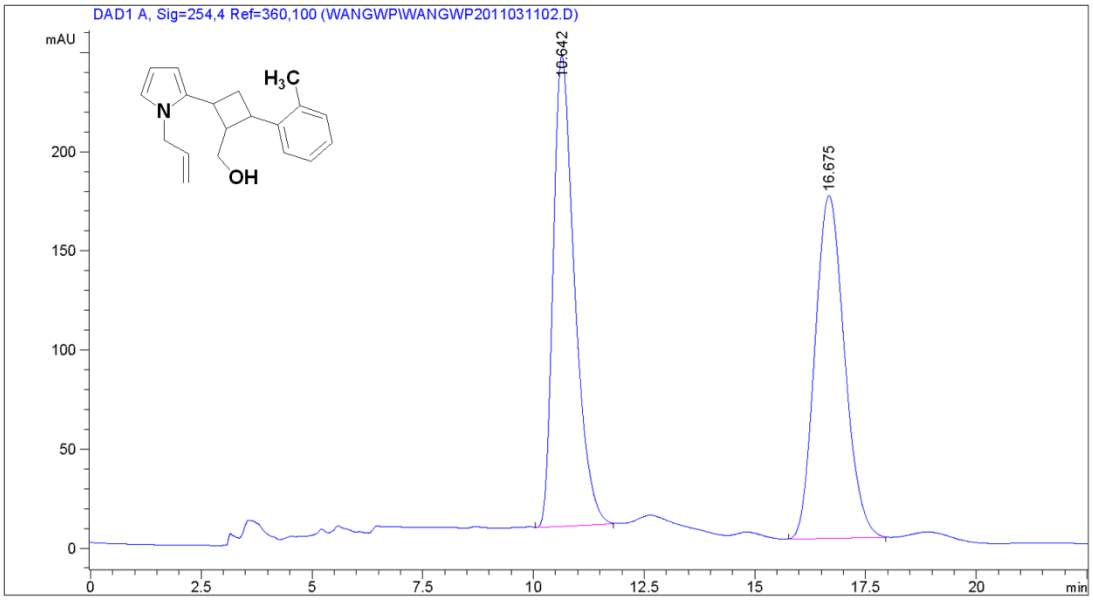
8. HPLC Data:



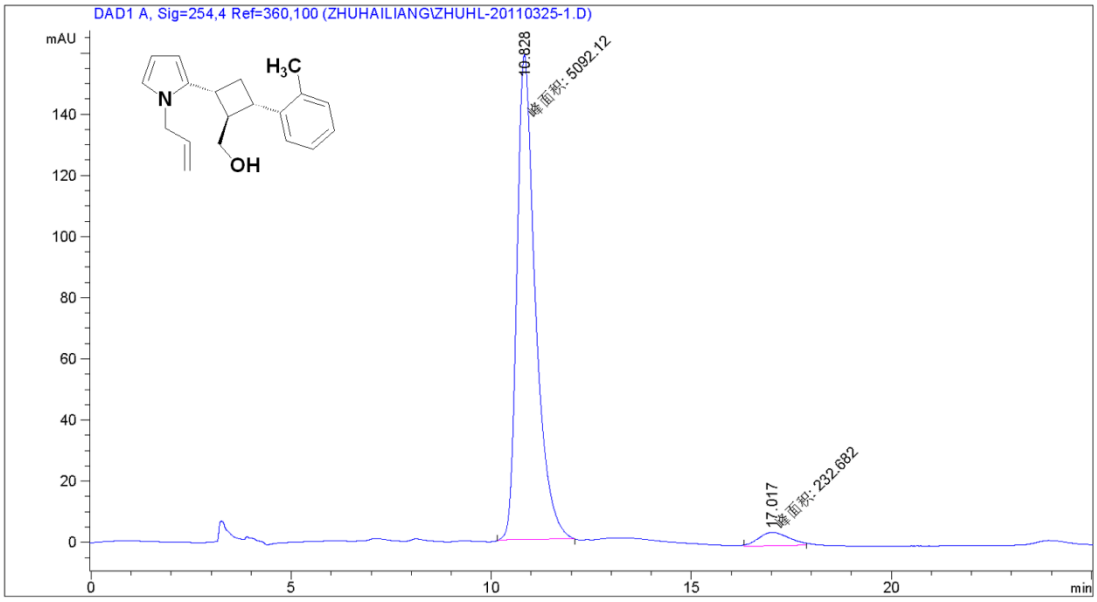
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	12.636	3.45754e4	793.64252	51.6438
2	DAD 210.8 nm	17.297	3.23743e4	588.82086	48.3562



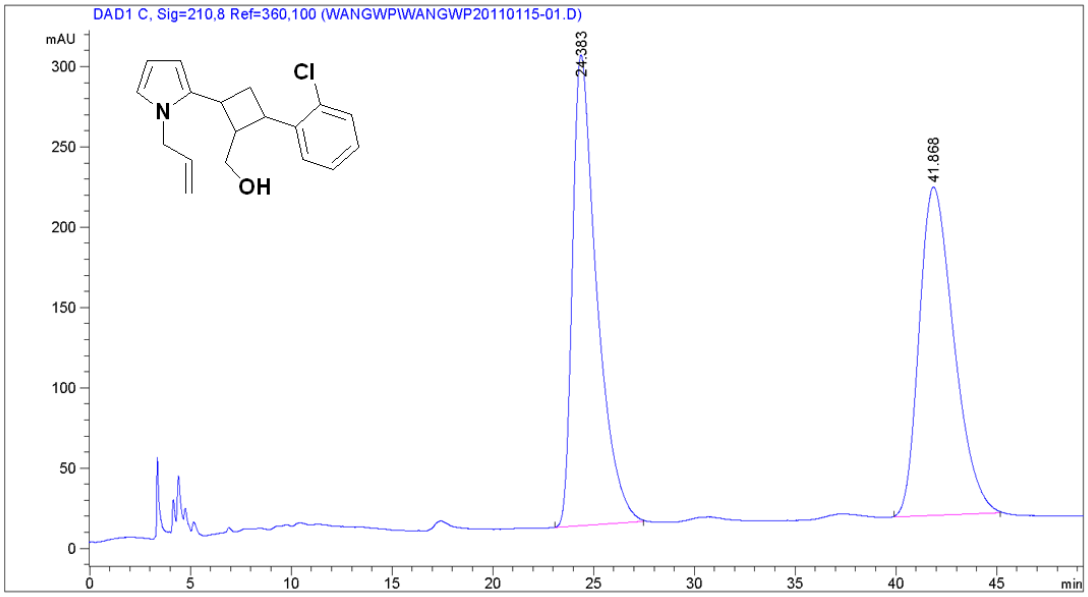
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	12.632	3.47405e4	779.61511	96.8531
2	DAD 210.8 nm	17.320	1128.75403	25.41377	3.1469



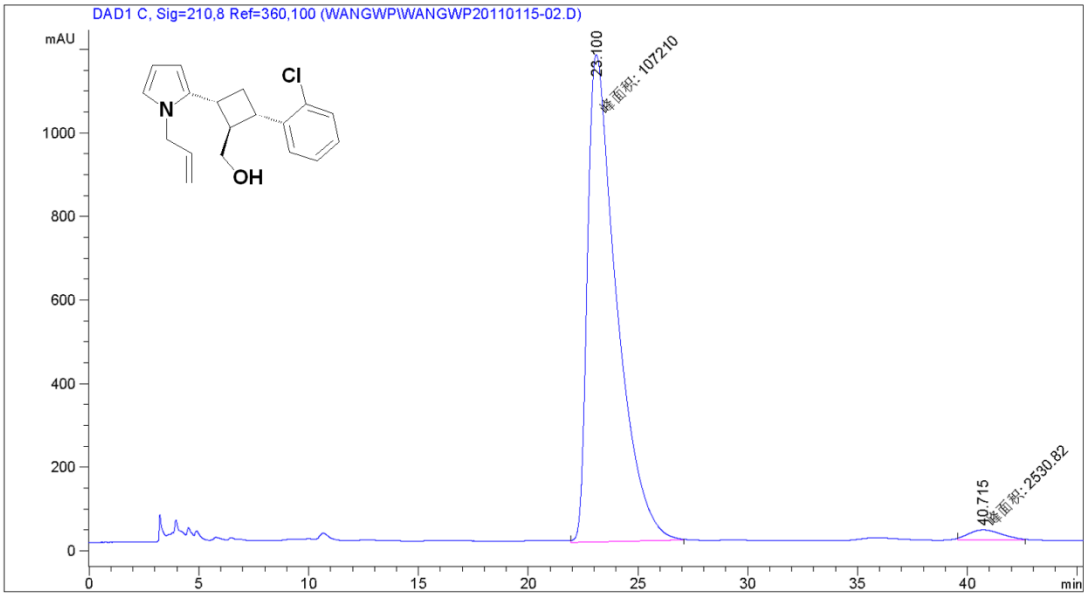
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	10.642	7954.28906	237.54878	49.8655
2	DAD 254.4 nm	16.675	7997.18750	172.76445	50.1345



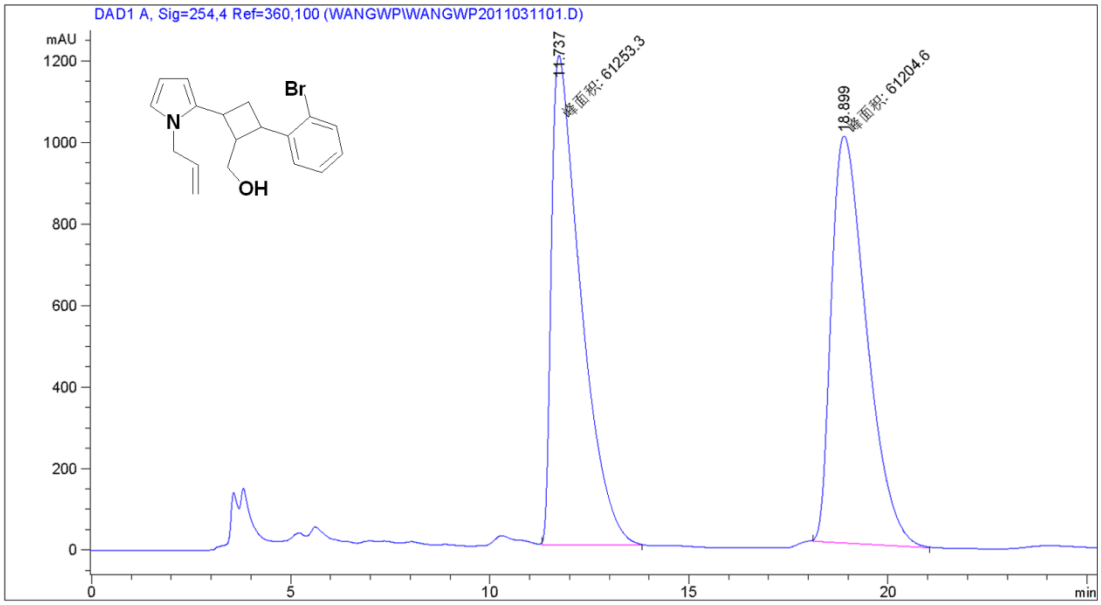
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	10.828	5092.11719	158.45110	95.6302
2	DAD 254.4 nm	17.017	232.68246	4.35654	4.3698



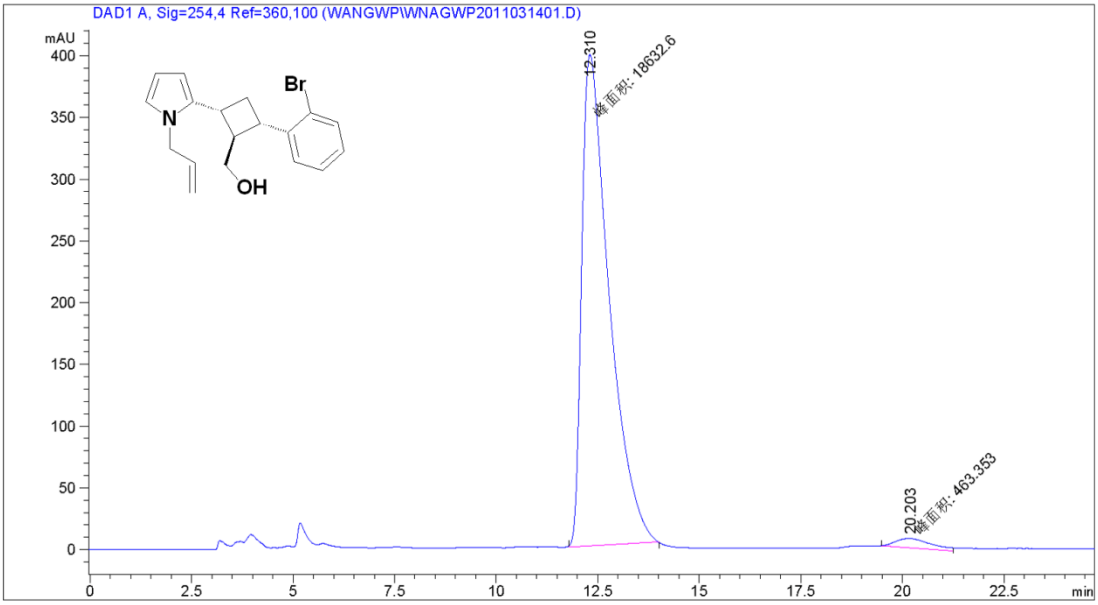
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	24.383	2.45484e4	292.96021	50.1230
2	DAD 210.8 nm	41.868	2.44279e4	204.32729	49.8770



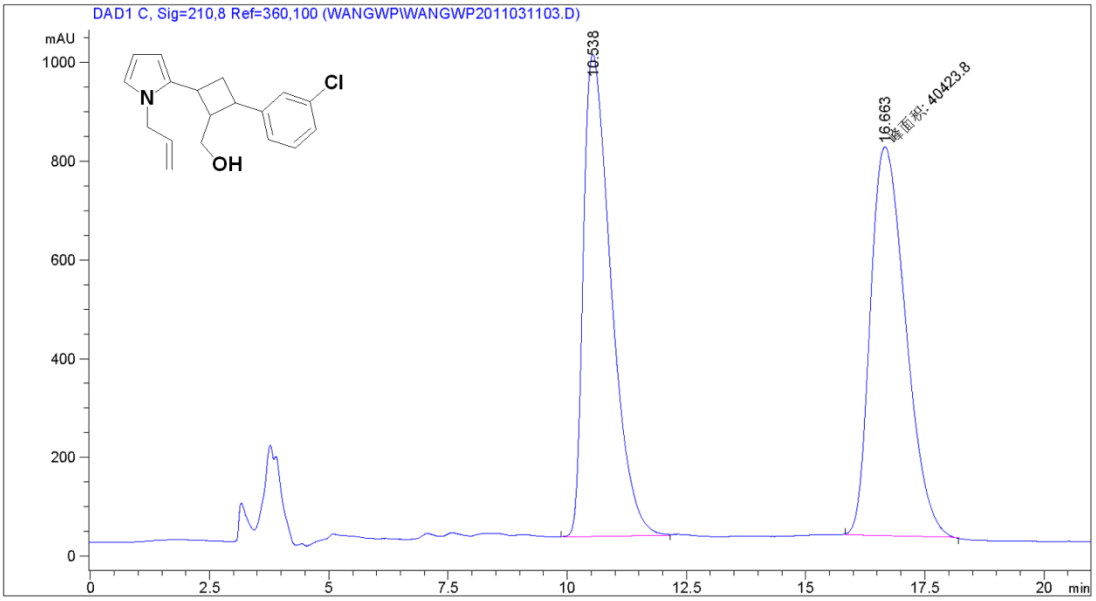
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	23.100	1.07210e5	1165.34705	97.6938
2	DAD 210.8 nm	40.715	2530.82275	24.09236	2.3062



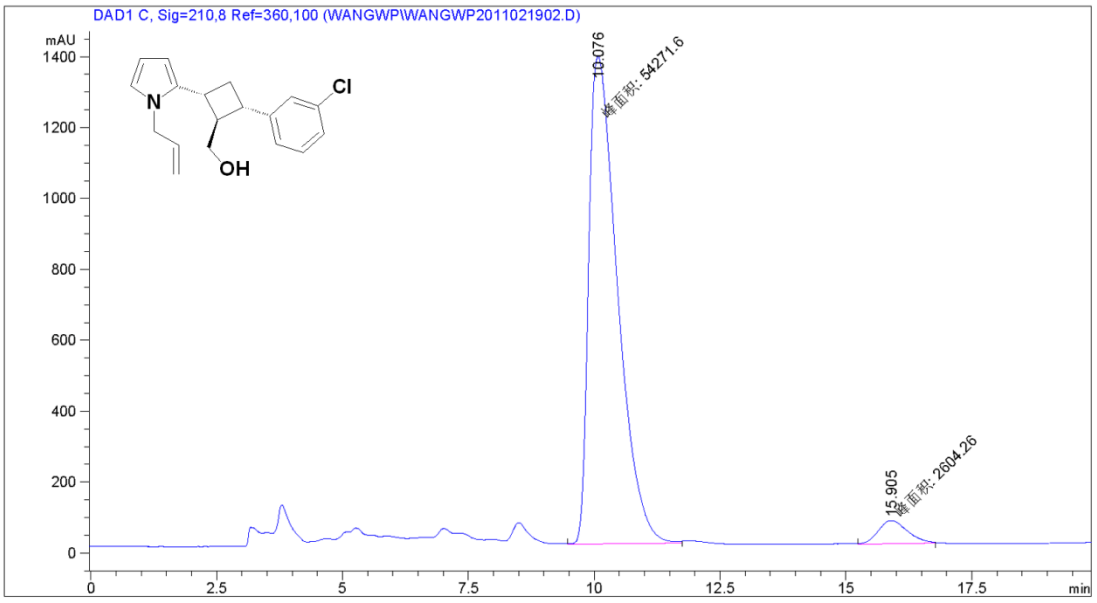
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	11.737	6.12533e4	1200.85352	50.0199
2	DAD 254.4 nm	18.899	6.12046e4	997.54089	49.9801



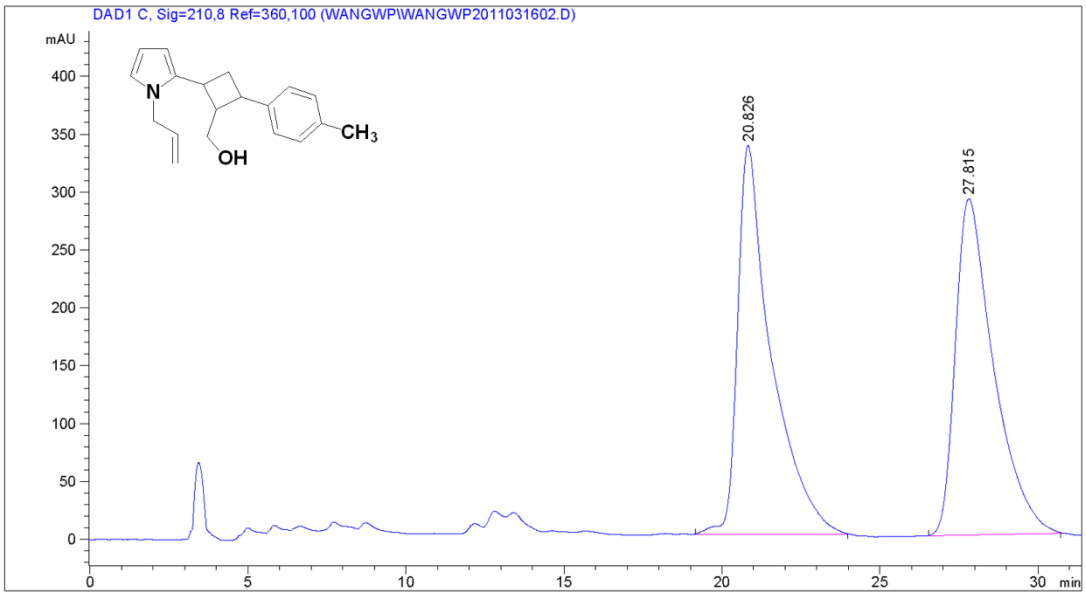
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	12.310	1.86326e4	397.88040	97.5736
2	DAD 254.4 nm	20.203	463.35272	7.50532	2.4264



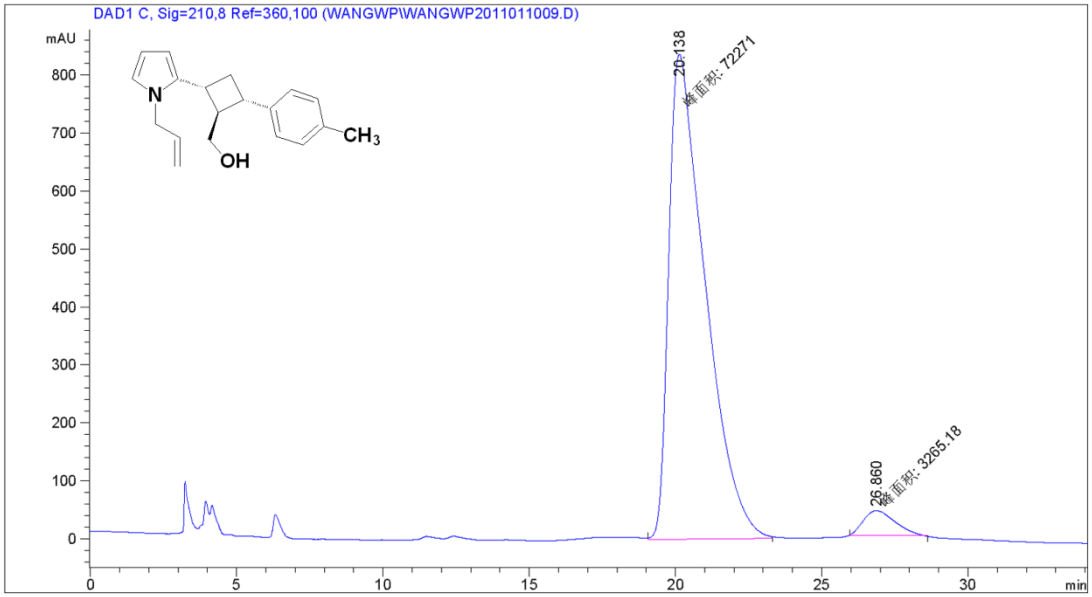
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	10.538	3.93419e4	975.06042	49.3218
2	DAD 210.8 nm	16.663	4.04238e4	787.07544	50.6782



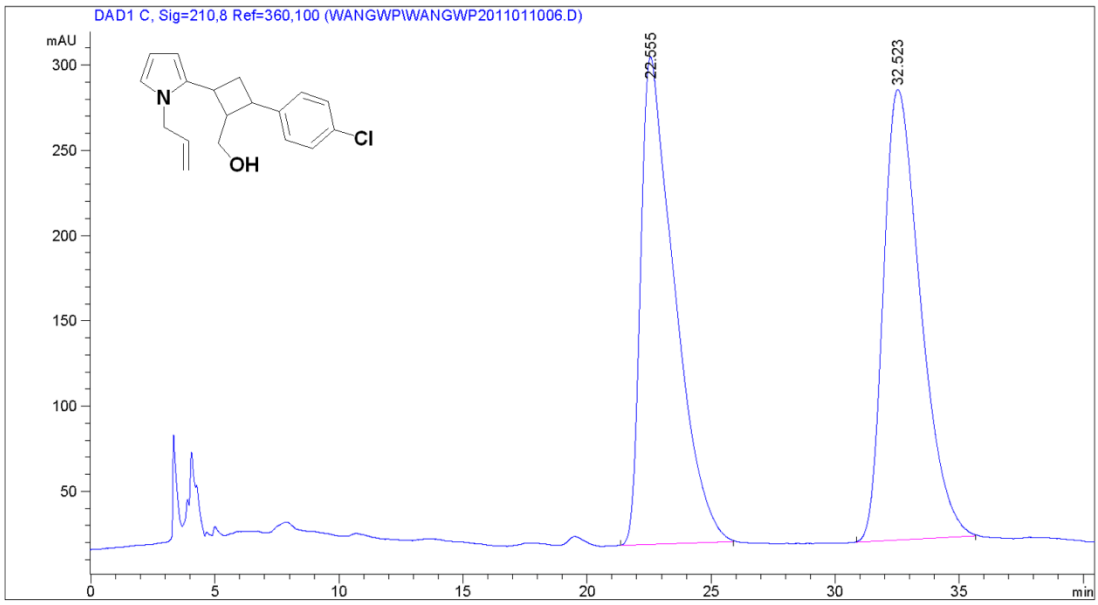
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	10.076	5.42716e4	1375.37927	95.4211
2	DAD 210.8 nm	15.905	2604.26392	65.19234	4.5789



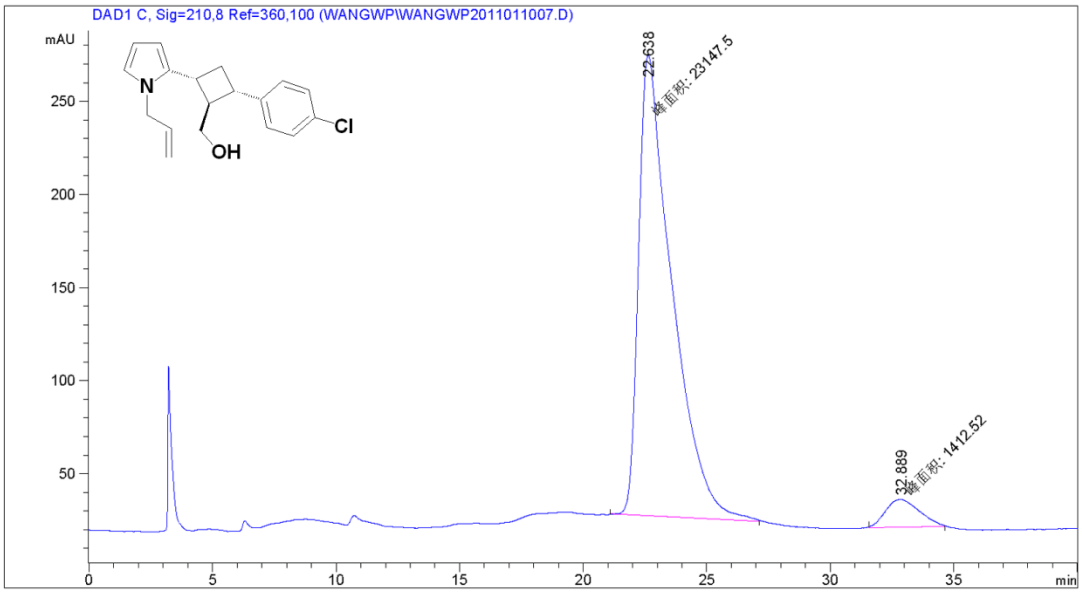
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	20.826	2.49617e4	335.94046	50.5582
2	DAD 210.8 nm	27.815	2.44105e4	290.61996	49.4418



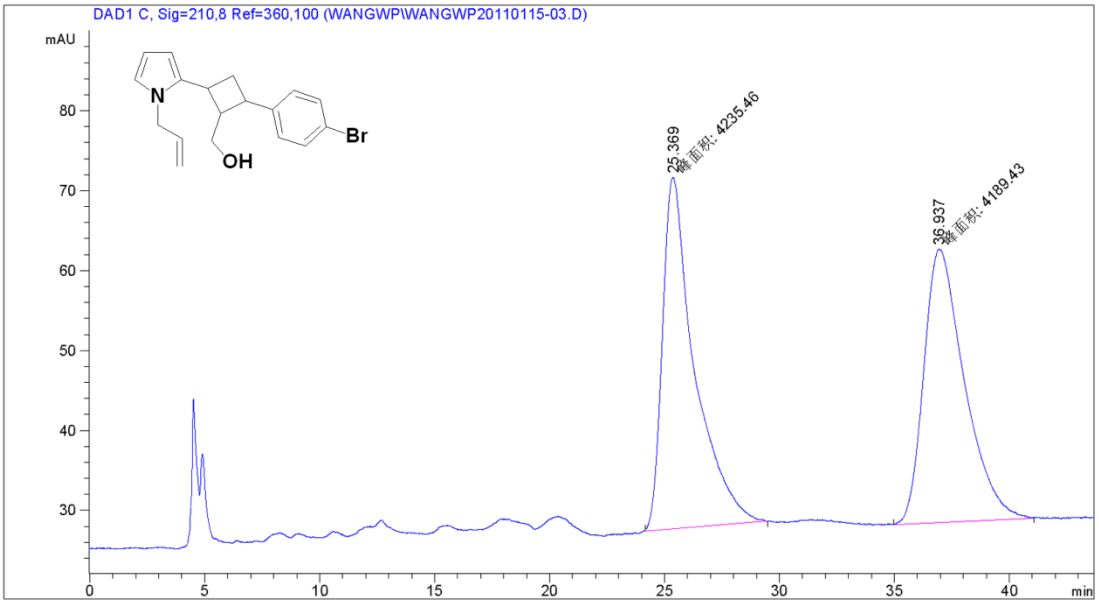
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	20.138	7.22710e4	836.29038	95.6773
2	DAD 210.8 nm	26.860	3265.18188	43.13464	4.3227



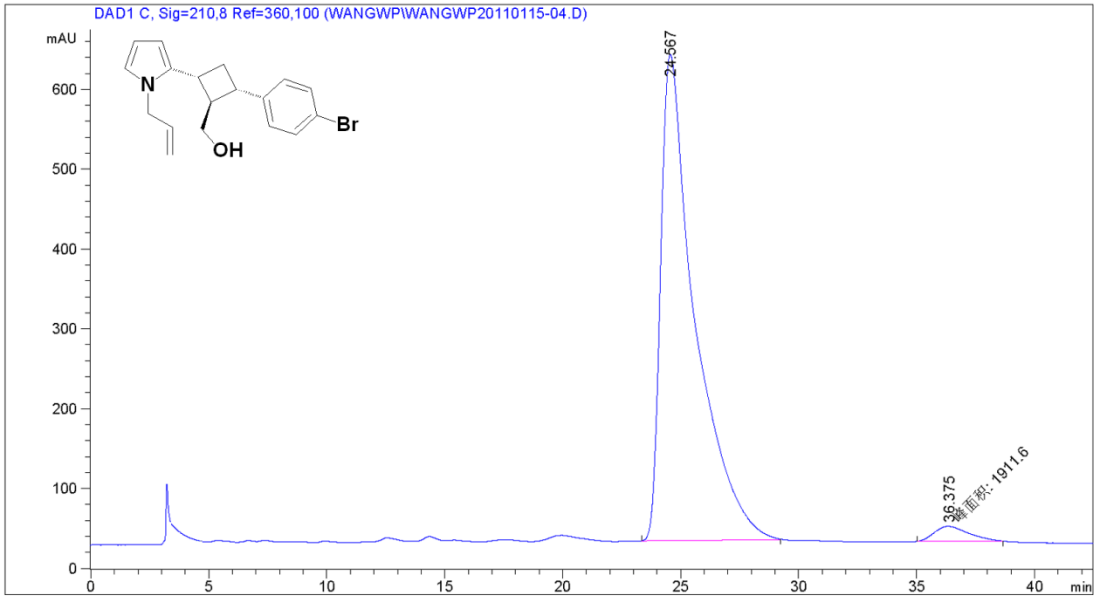
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	22.555	2.70532e4	285.97119	49.6723
2	DAD 210.8 nm	32.523	2.74101e4	264.13980	50.3277



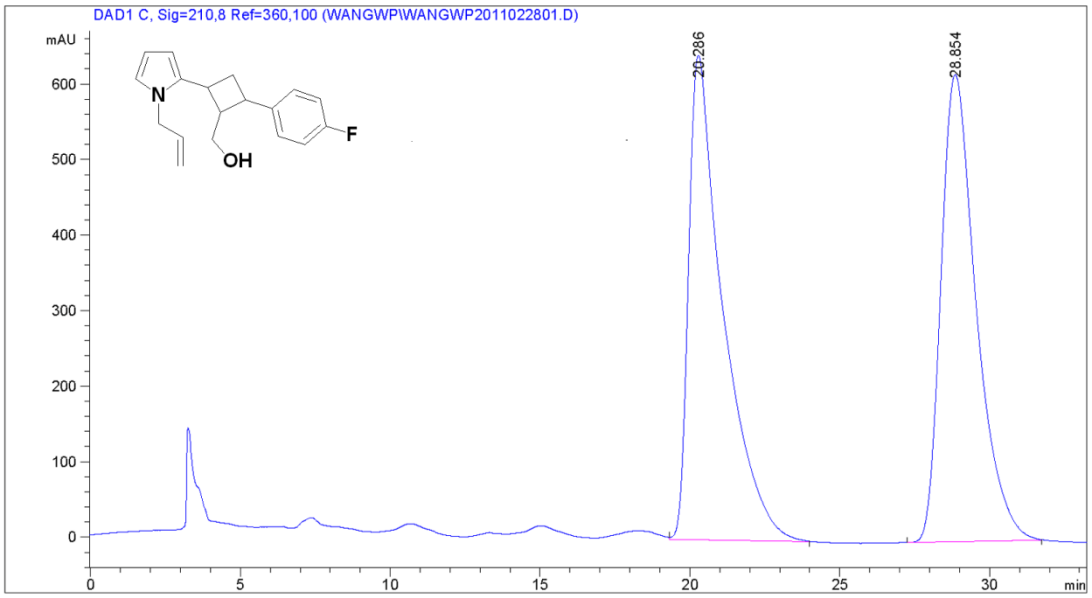
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	22.638	2.31475e4	247.2093	94.2487
2	DAD 210.8 nm	32.889	1412.52405	14.95035	5.7513



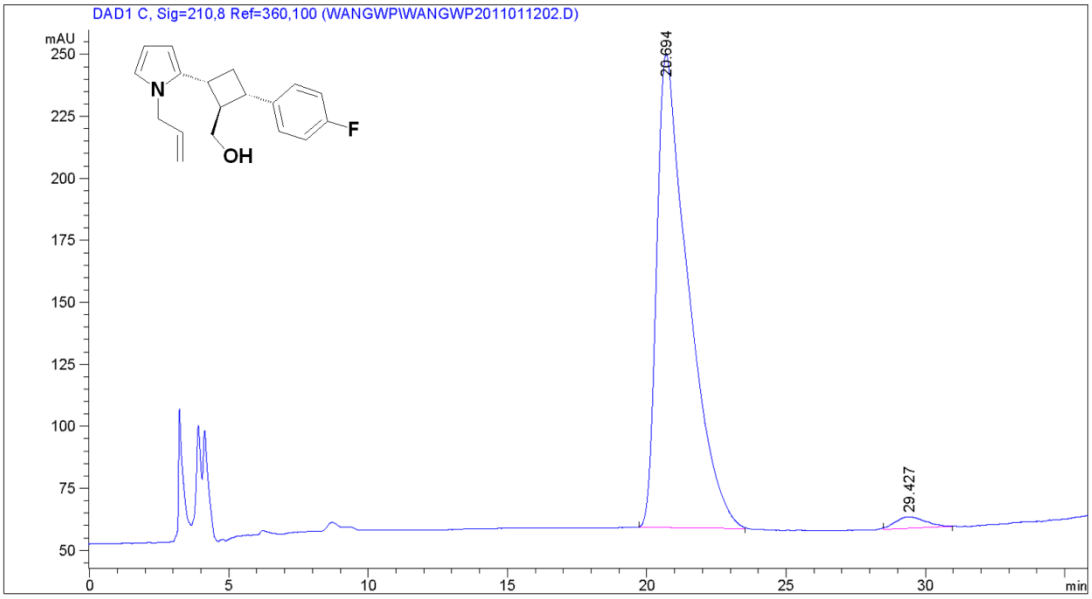
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	25.369	4235.46484	43.98576	50.2732
2	DAD 210.8 nm	36.937	4189.42773	34.20866	49.7268



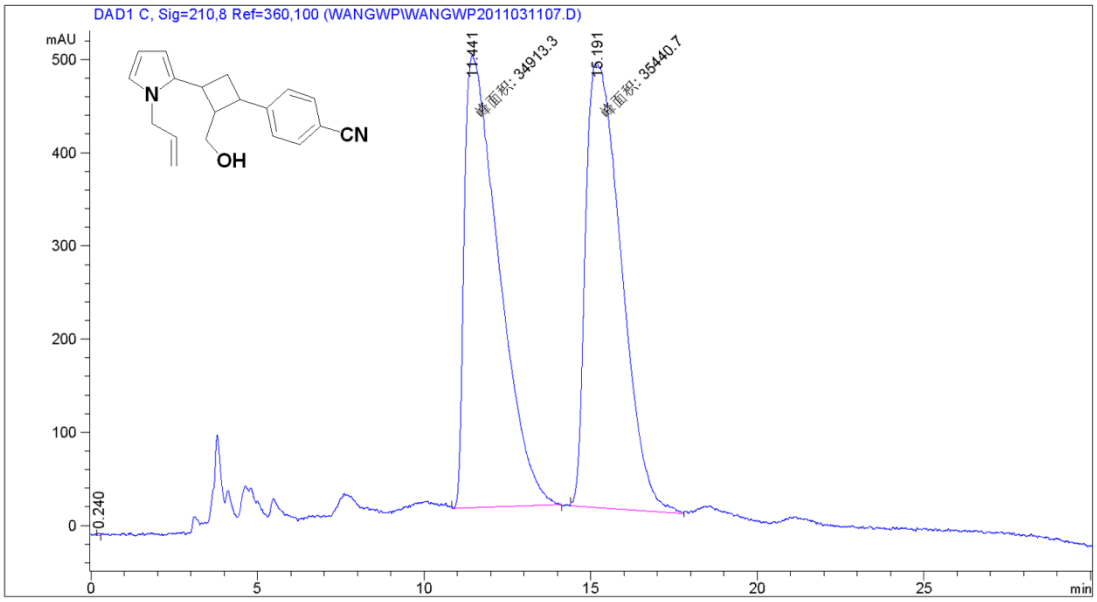
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	24.567	6.13112e4	608.82935	96.9764
2	DAD 210.8 nm	36.375	1911.59692	18.87424	3.0236



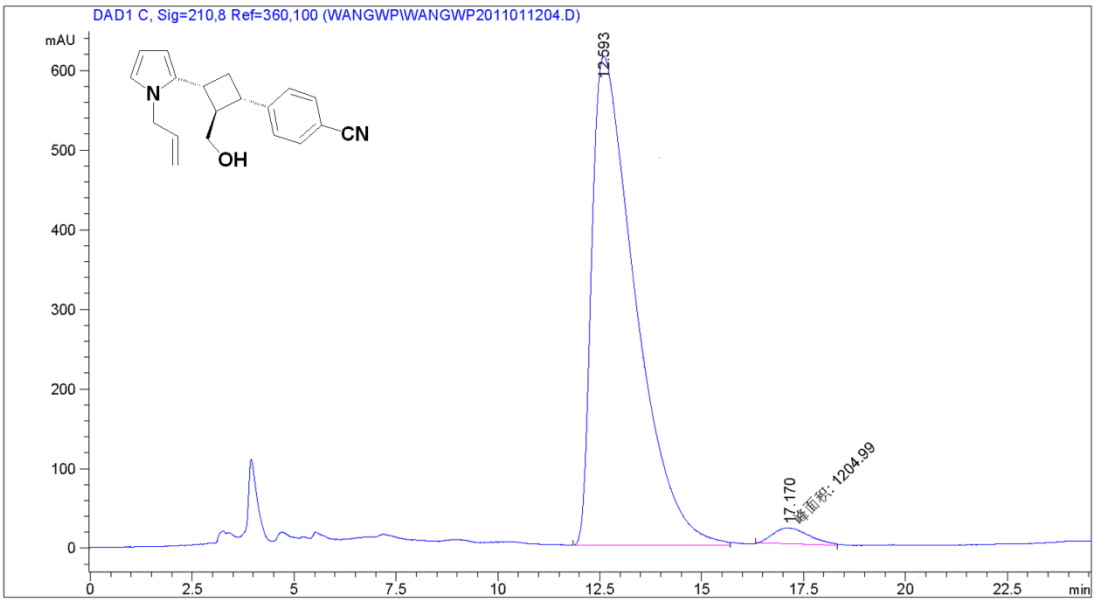
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	20.286	5.09481e4	640.84088	50.2910
2	DAD 210.8 nm	28.854	5.03585e4	618.26849	49.7090



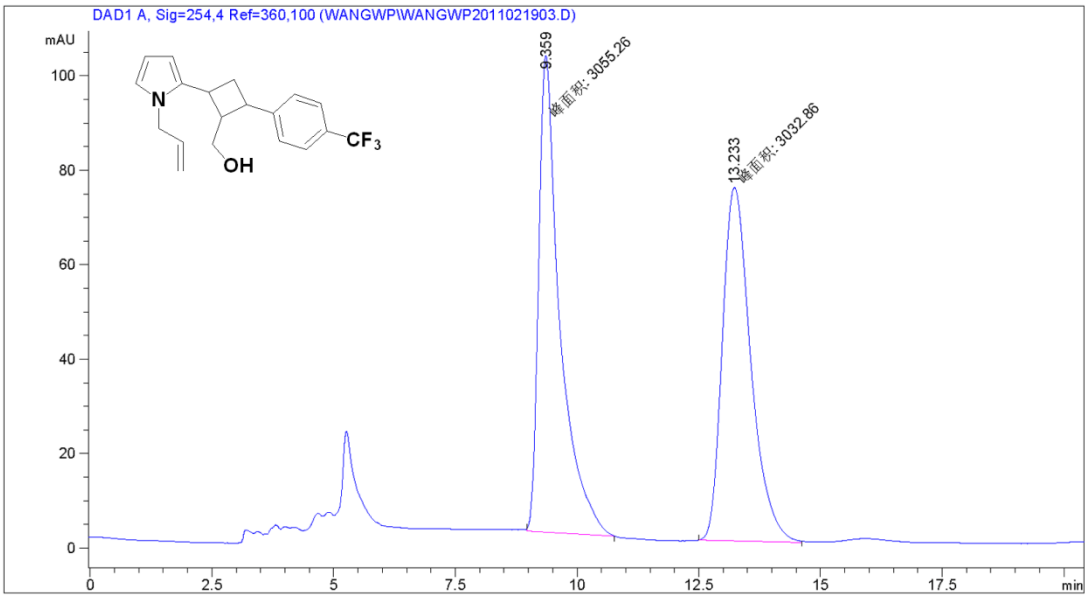
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	20.694	1.49598e4	190.64757	97.7465
2	DAD 210.8 nm	29.427	344.88440	4.62198	2.2535



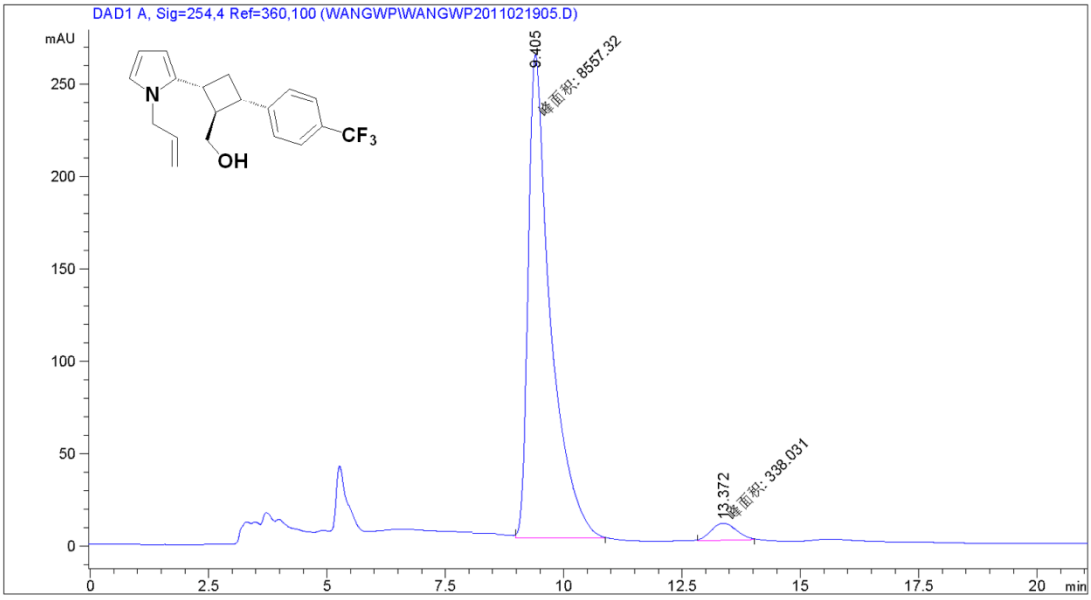
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	11.441	3.49133e4	485.29037	49.6159
2	DAD 210.8 nm	15.191	3.54407e4	478.16608	50.3654



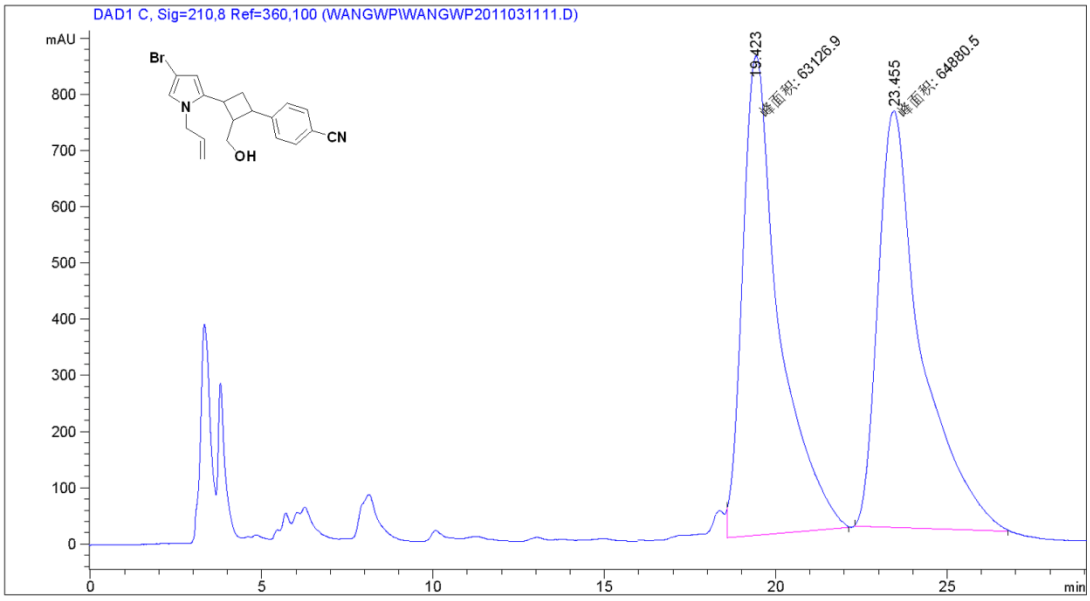
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	12.593	4.53944e4	614.14490	97.4142
2	DAD 210.8 nm	17.170	1204.98926	19.83750	2.5858



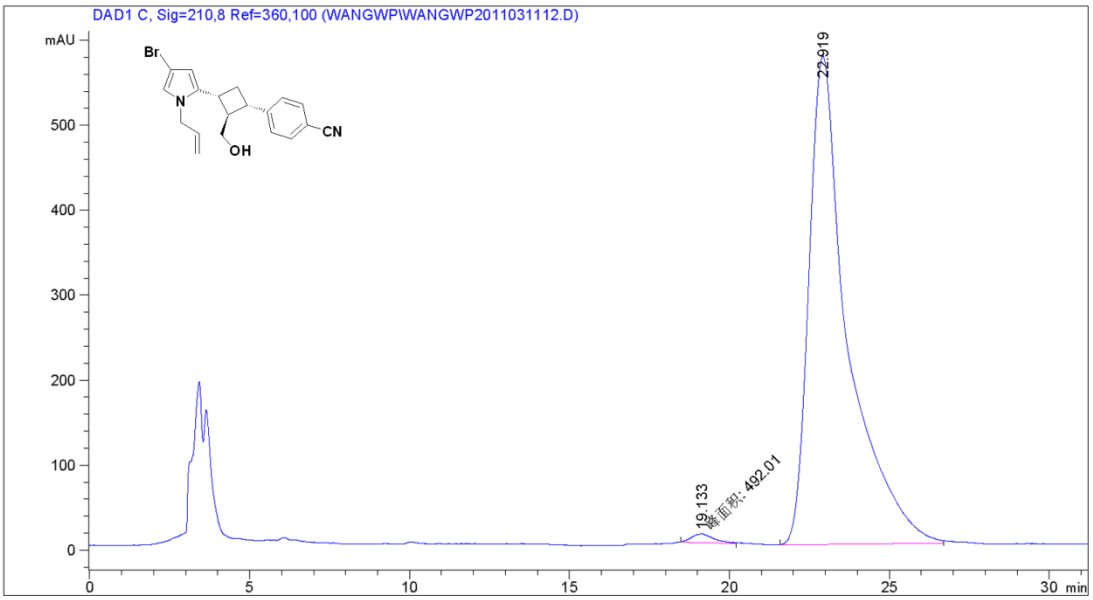
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	9.359	3055.26367	100.90082	50.1840
2	DAD 254.4 nm	13.233	3032.86133	74.84806	49.8160



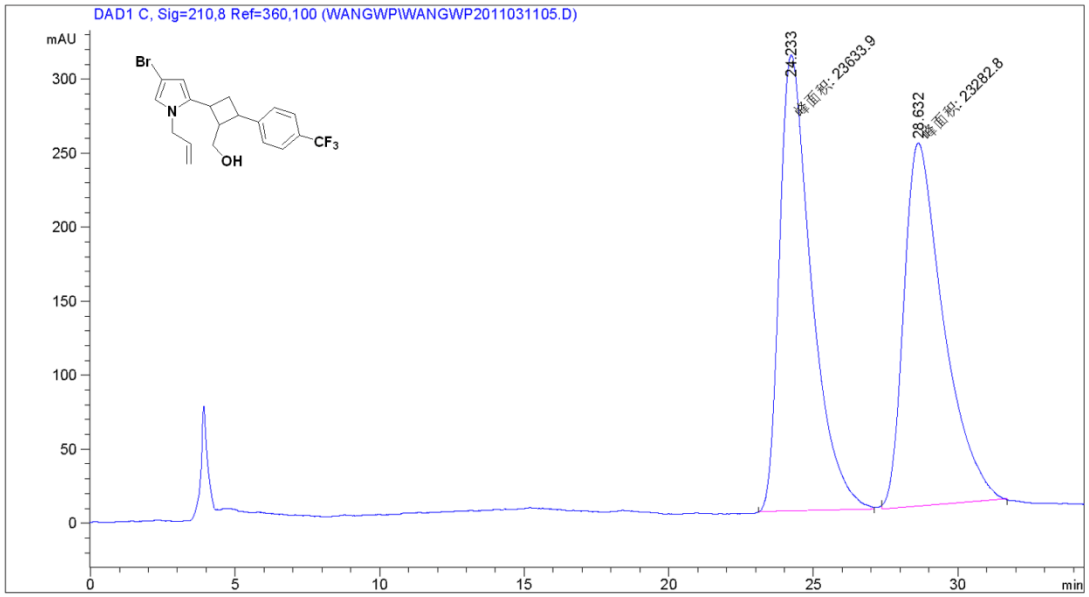
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	9.405	8557.31641	261.84277	96.1999
2	DAD 254.4 nm	13.372	338.03052	9.16491	3.8001



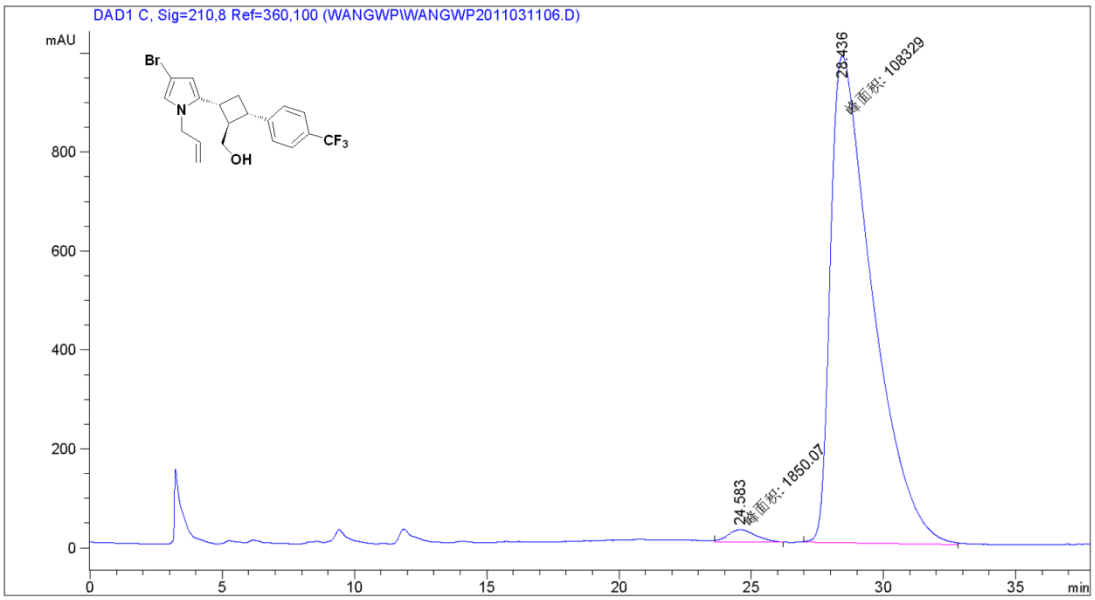
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	19.423	6.31269e4	853.27728	49.3150
2	DAD 210.8 nm	23.455	6.48805e4	741.45447	50.6850



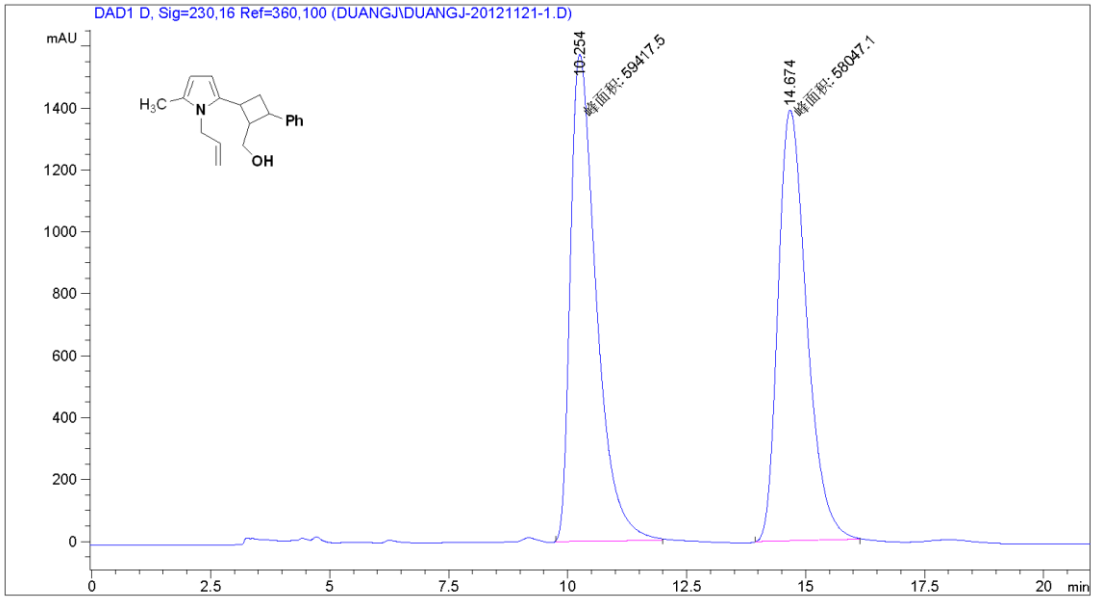
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	19.133	492.01031	10.39235	1.0055
2	DAD 210.8 nm	22.919	4.84421e4	574.87585	98.9945



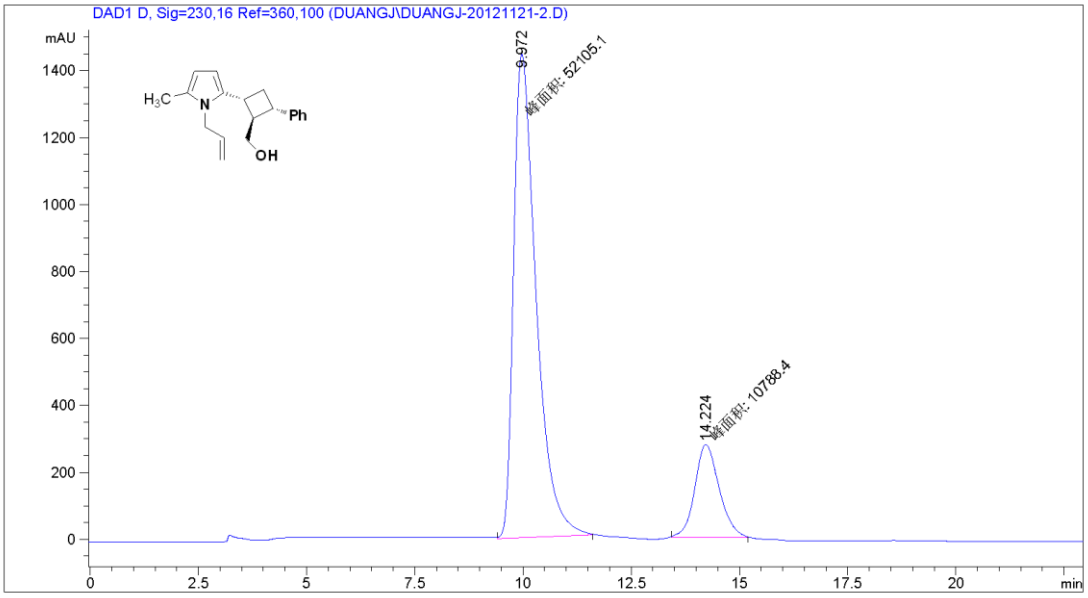
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	24.233	2.36339e4	307.88058	50.3742
2	DAD 210.8 nm	28.632	2.32828e4	245.36508	49.6258



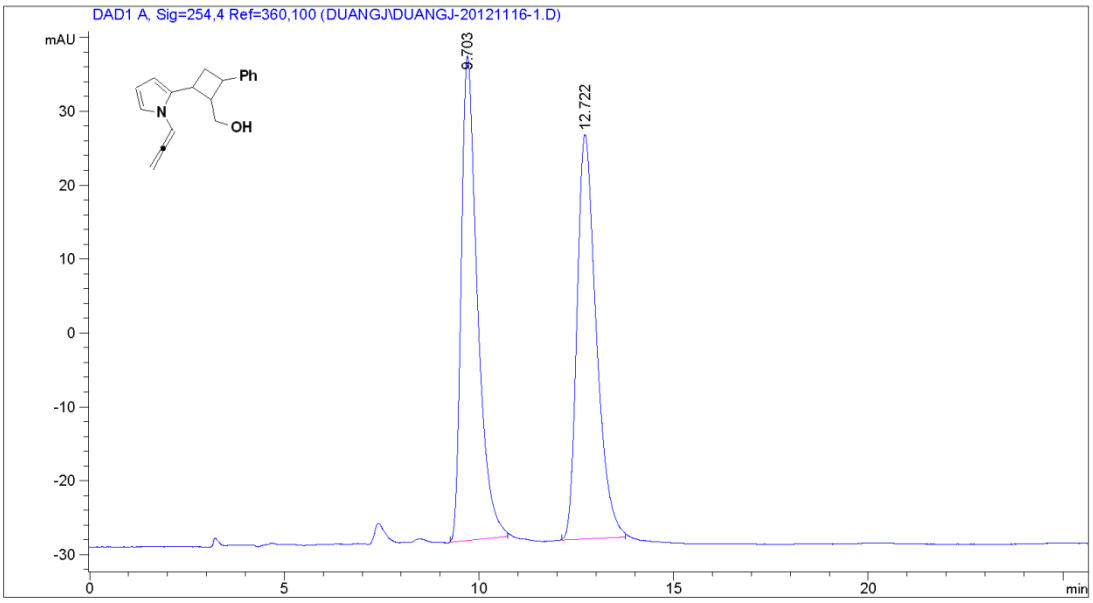
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 210.8 nm	24.583	1850.07068	25.57025	1.6792
2	DAD 210.8 nm	28.436	1.08329e5	983.88000	98.3208



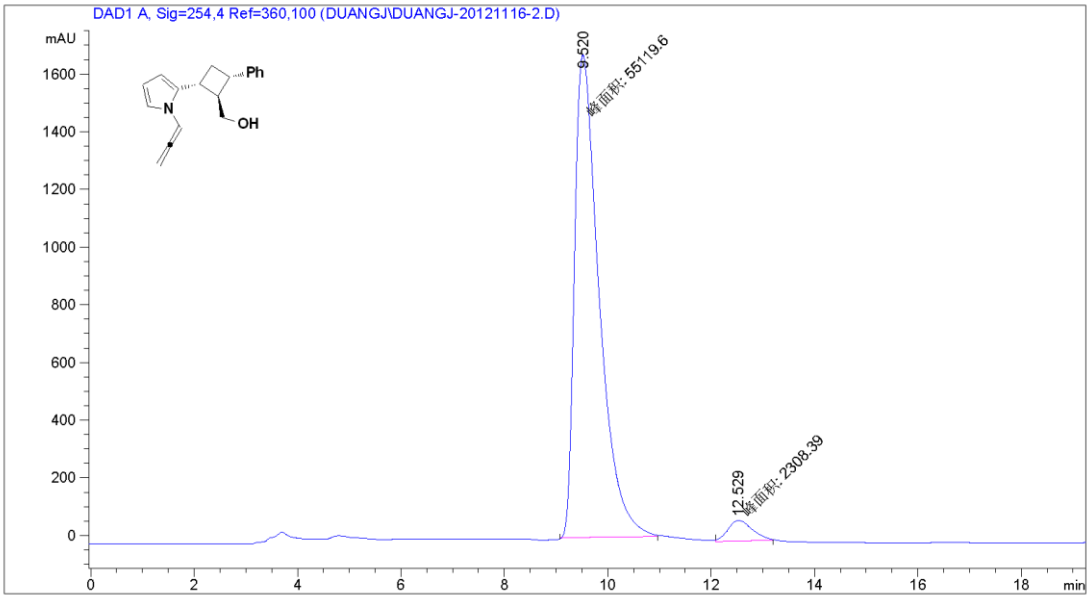
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 230.16 nm	10.254	5.94175e4	1572.84021	50.5833
2	DAD 230.16 nm	14.674	5.80471e4	1391.37183	49.4167



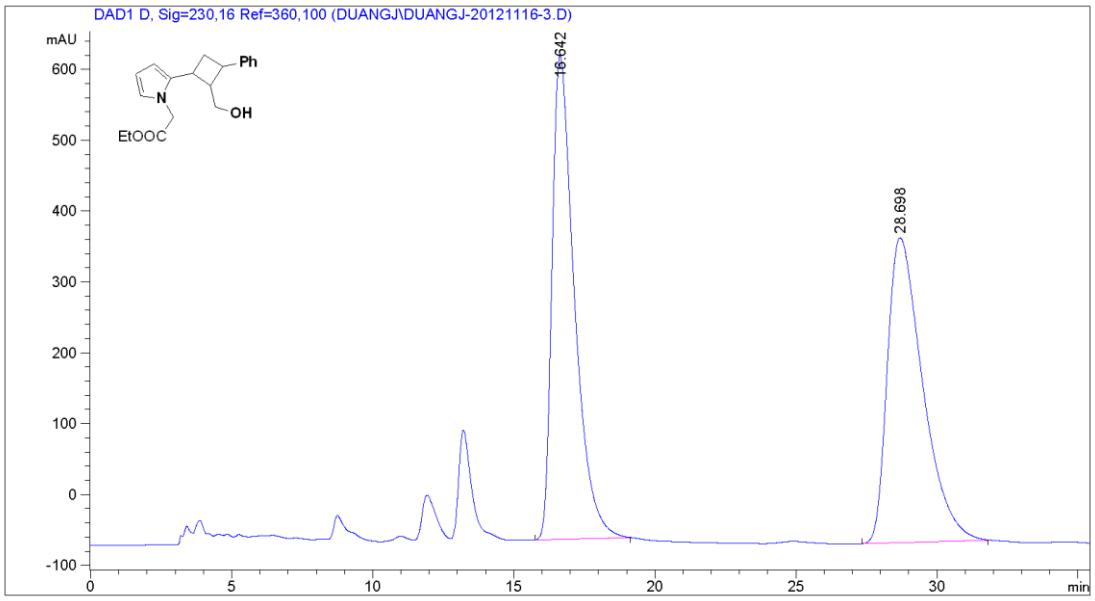
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 230.16 nm	9.972	5.21051e4	1444.06213	82.8465
2	DAD 230.16 nm	14.224	1.07884e4	276.25937	17.1535



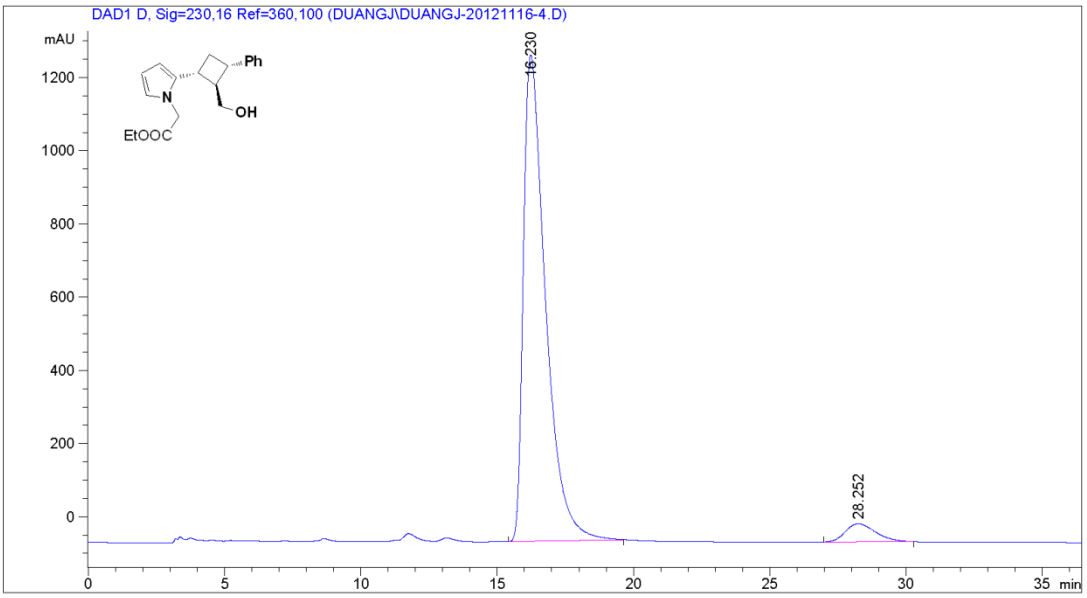
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	9.703	1891.20056	65.55125	50.1905
2	DAD 254.4 nm	12.722	1876.84521	54.71827	49.8095



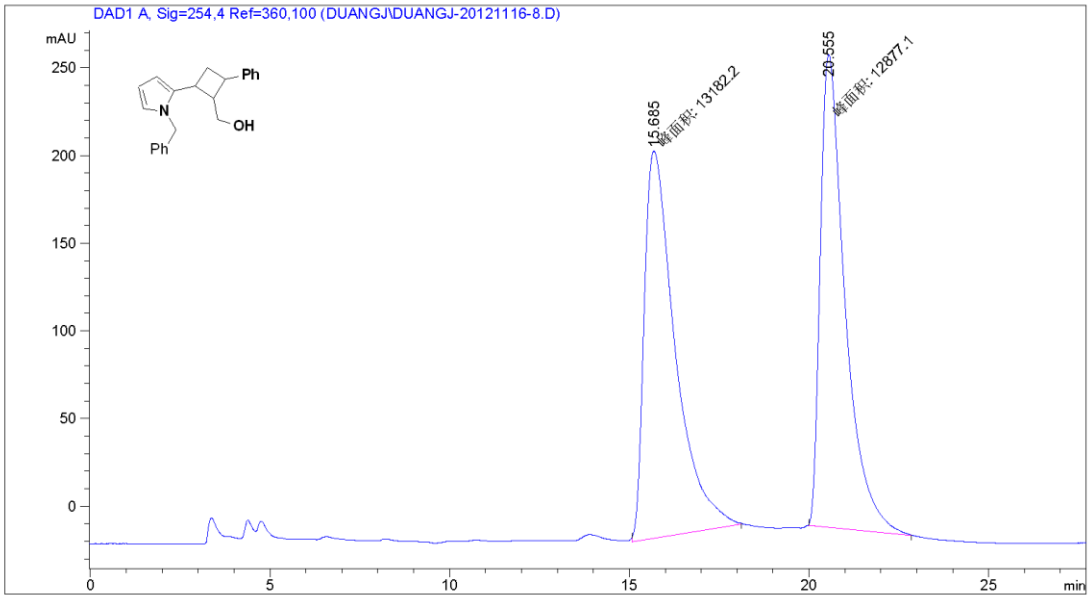
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	9.520	5.51196e4	1673.75598	95.9804
2	DAD 254.4 nm	12.529	2308.38916	71.02544	4.0196



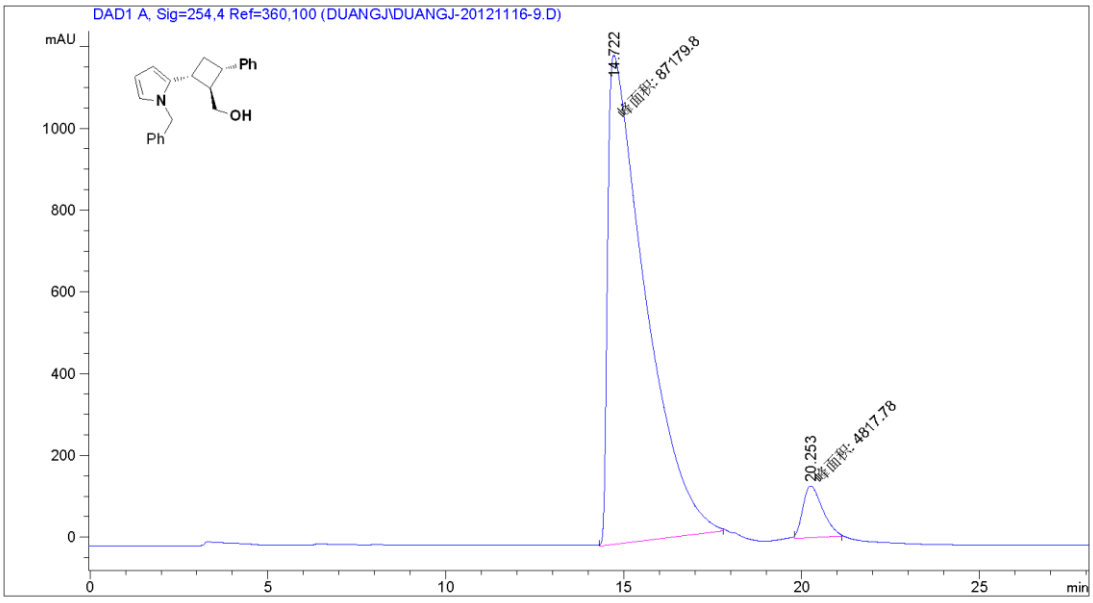
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 230.16 nm	16.642	3.74961e4	682.27606	50.0543
2	DAD 230.16 nm	28.698	3.74147e4	430.18222	49.9457



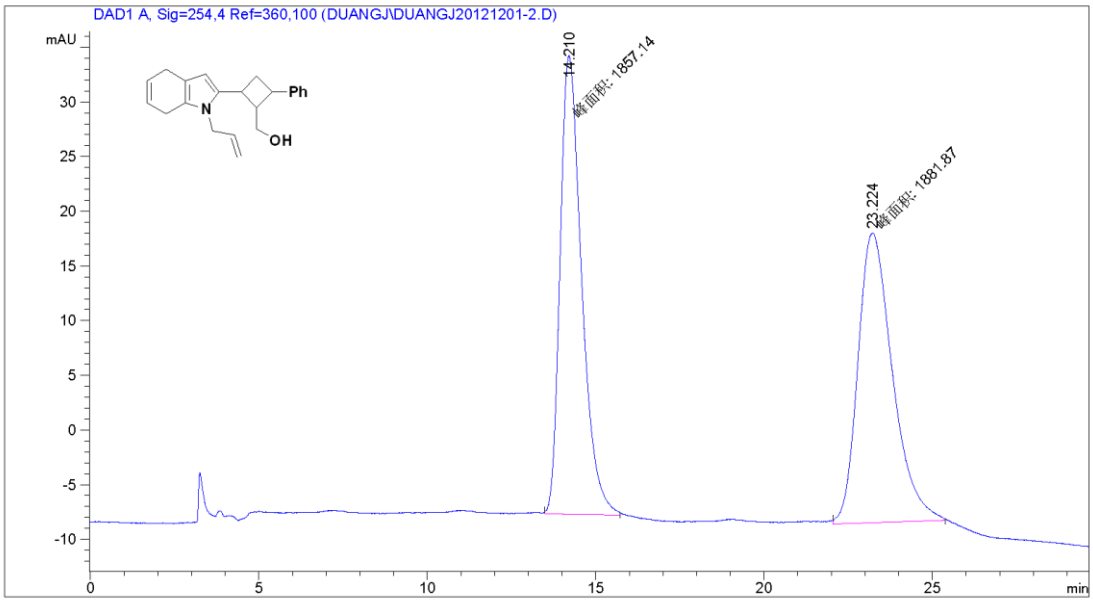
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 230.16 nm	16.230	7.47050e4	1327.39063	95.1180
2	DAD 230.16 nm	28.252	3834.27832	49.64068	4.8820



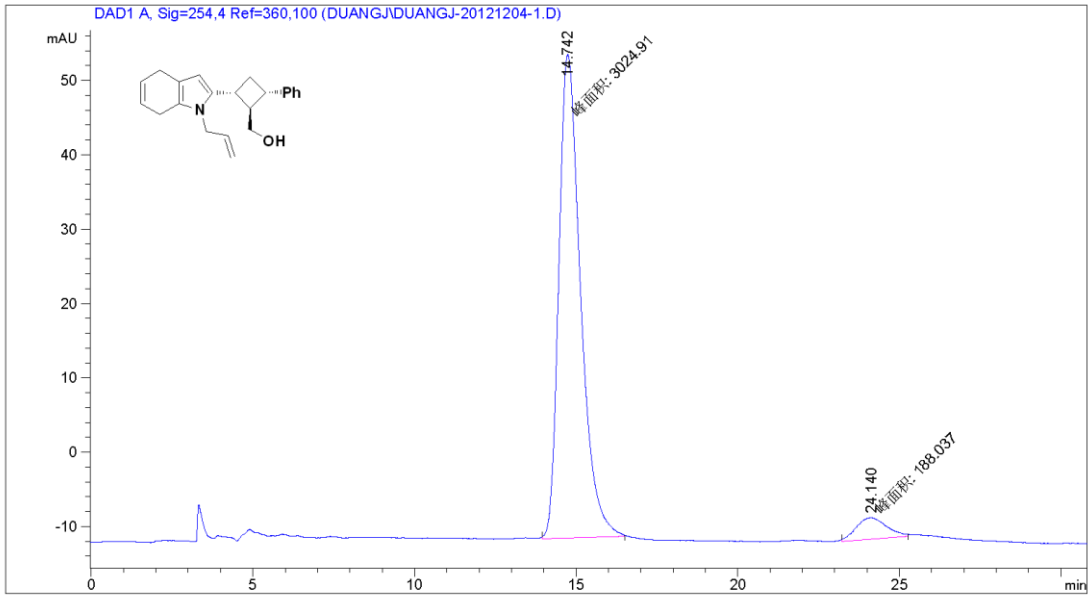
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	15.685	1.31822e4	220.67876	50.5853
2	DAD 254.4 nm	20.555	1.28771e4	269.34744	49.4147



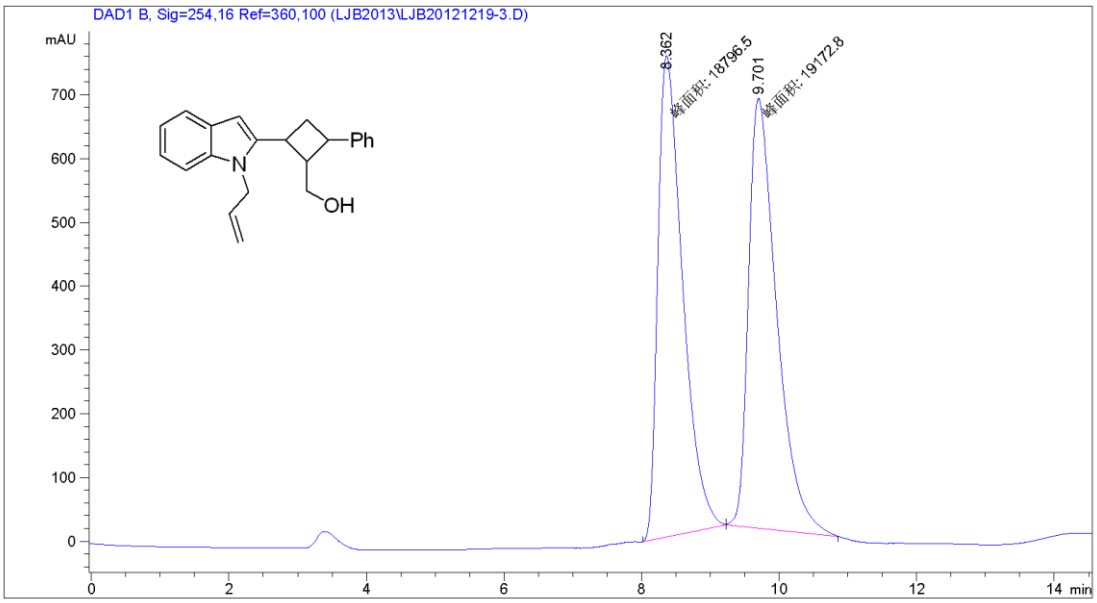
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	14.722	8.71798e4	1195.40088	94.7631
2	DAD 254.4 nm	20.253	4817.78125	126.40548	5.2369



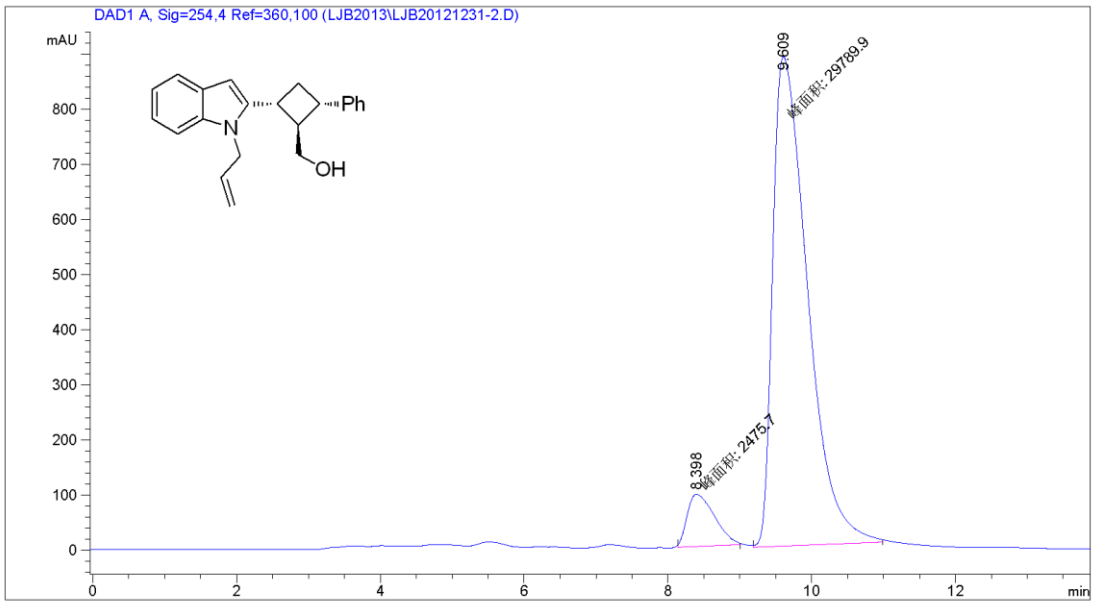
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	14.210	1857.14258	41.92830	49.6693
2	DAD 254.4 nm	23.224	1881.87476	26.49141	50.3307



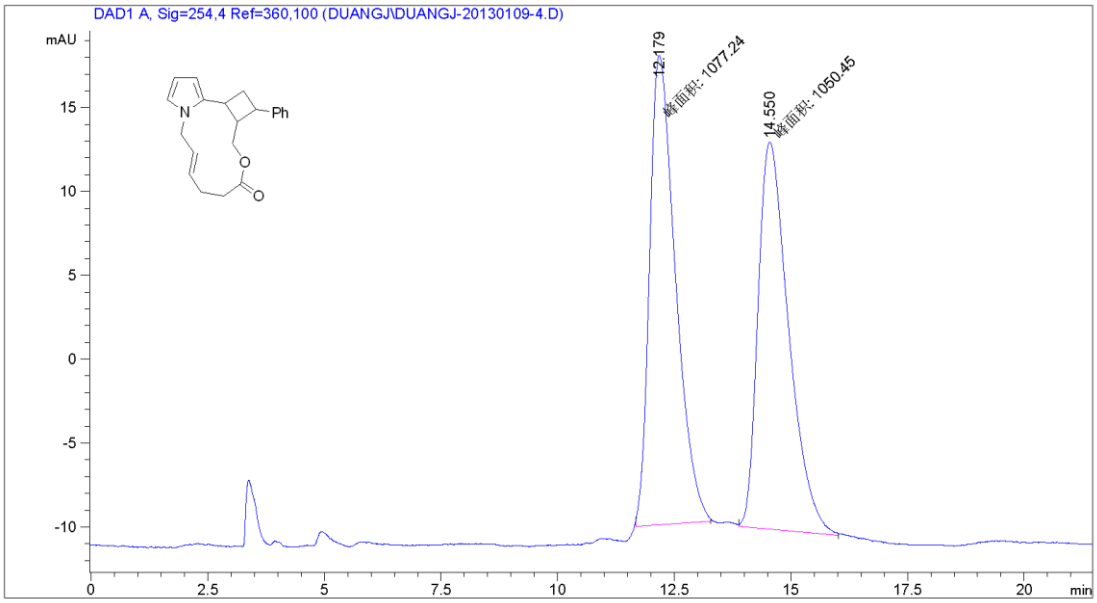
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	14.742	3024.91211	65.01622	94.1475
2	DAD 254.4 nm	24.140	188.03696	2.87063	5.8525



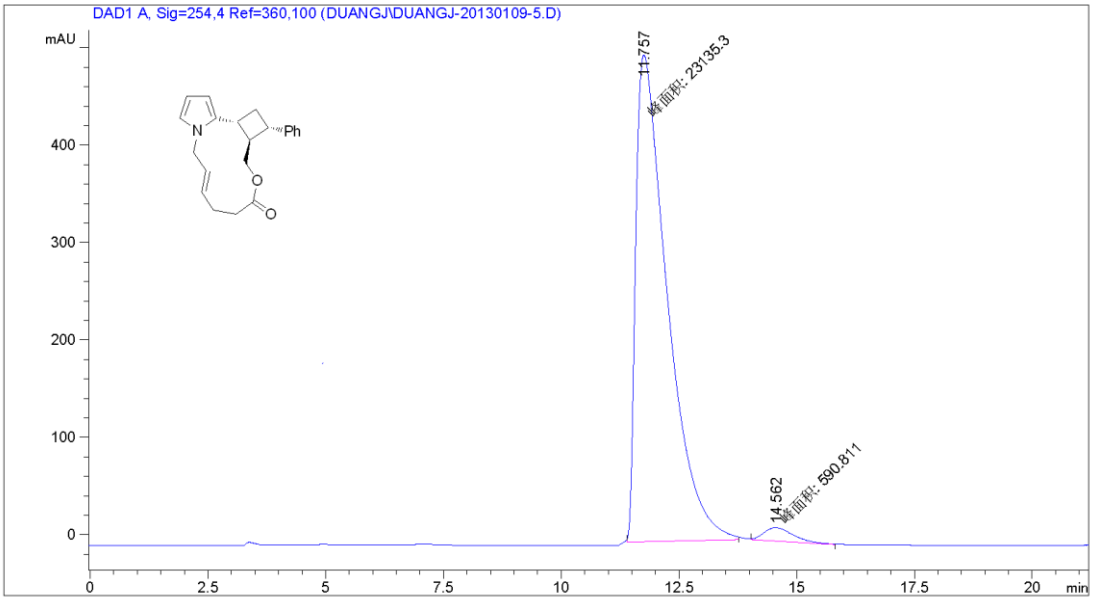
Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	8.362	1.87965e4	754.09204	49.5044
2	DAD 254.4 nm	9.701	1.91728e4	673.86755	50.4956



Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	8.398	2475.69946	94.52950	7.6729
2	DAD 254.4 nm	9.609	2.97899e4	889.34247	92.3271



Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	12.179	1077.23547	27.96583	50.6295
2	DAD 254.4 nm	14.550	1050.44958	23.06739	49.3705



Peak	Processed Channel	Retention Time (min)	Peak Area (mAU*s)	Peak Height (mAU)	Peak Area (%)
1	DAD 254.4 nm	11.757	2.31353e4	499.74982	97.5099
2	DAD 254.4 nm	14.562	590.81116	13.68974	2.4901

9. References:

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[5] D. J. Zack, T. Bannister, T. Vojkovsky, Z. –Y. Yang, C. Berlinicke, WO2011119777 A2, 2011.

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