Supporting Information

$FeCl_3$-Mediated Synthesis of Polysubstituted Tetrahydroquinolines *via* Domino Mannich/ Friedel-Crafts Reactions of Aldehydes and Amines

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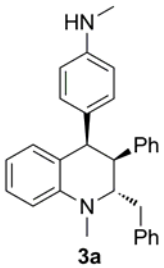
Experimental Section

1. General Information: Column chromatography was carried out on silica gel. Solvents were dried under standard method. ^{1}H NMR spectra were recorded on 400 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded on 100 MHz in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on a FT-IR spectrometer and only major peaks are reported in cm^{-1}. Melting points were determined on a microscopic apparatus and were uncorrected. High-resolution mass spectral analysis (HRMS) data were measured on the Bruker ApexII by means of the ESI technique. Diastereomeric ratio was determined by ^{1}H NMR. Enantioselectivities were determined by high performance liquid chromatography (HPLC) analysis employing on a Darcel Chiralpak IC column.

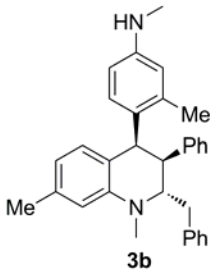
2. General Procedure for the synthesis of 3a-3k, 4a-4f′: To a solution of **1** (1.2 mmol), **2** (0.4 mmol) and 4Å MS 50mg in dry anisole (3 mL) was added $FeCl_3$ (19.5 mg, 0.12 mmol). The mixture was stirred under argon at 60°C. On completion of the reaction as shown by the TLC analysis, the reaction mixture was filtered and partitioned between sat.aq $NaHCO_3$ and ethyl acetate. The aqueous layer was further extracted with ethyl acetate (3×20 mL). The combined organic extracts was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using petroleum ether/ethyl acetate as eluent on alkalescent silica gel to give the desired product.

3. Characterization data of products 3a-3k, 4a-4f′:



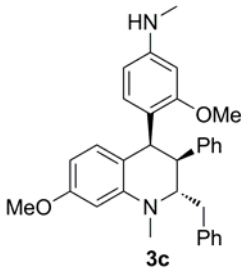
3a

Synthesis of product 3a. Yellow solid; yield 78%; mp: 67-69°C; 88:12 mixture of two isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 1 H), 7.21-7.07 (m, 4 H), 7.06-7.01 (m, 3 H), 6.96-6.78 (m, 3 H), 6.72-6.68 (m, 3 H), 6.58-6.49 (m, 3 H), 6.34-6.32 (m, 1 H) 4.39-4.38 (d, *J* = 5.6 Hz, 1 H), 3.65-3.62 (m, 1 H), 3.49 (s, 1 H), 3.09-3.04 (m, 1 H), 3.02 (s, 3 H), 2.98-2.73 (m, 2 H), 2.71 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 145.4, 142.2, 138.7, 130.9, 130.1, 130.0, 129.5, 129.4, 129.4, 129.1, 128.4, 128.1, 127.7, 127.4, 126.2, 126.1, 124.4, 115.8, 112.3, 111.7, 110.8, 65.2, 46.4, 44.9, 39.7, 39.0, 30.8; IR (KBr, cm^{-1}) 3025, 2919, 1711, 1615, 1600, 1521, 1497, 1451, 1322, 1220, 822, 749, 700; HRMS (ESI) m/z: calcd for $C_{30}H_{30}N_2$: $[M+H]^+$: 419.2482; found: 419.2477.



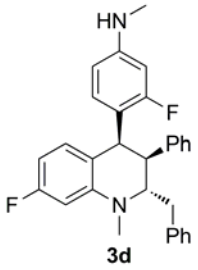
3b

Synthesis of product 3b. Yellow solid; yield 72%; mp: 60-62°C; ^{1}H NMR (400 MHz, $CDCl_3$, 72:28 mixture of two isomers): δ 7.28-6.99 (m, 8 H), 6.92-6.65 (m, 4 H), 6.56-6.02 (m, 4 H), 4.67-4.65 (d, *J* = 5.6 Hz, 1 H), 3.72-3.71 (d, *J* = 4.0 Hz, 1 H), 3.11-3.07 (m, 1 H), 3.09-3.07 (m, 1 H), [3.04 (s), 2.97 (s), 3 H], 3.02-2.92 (m, 2 H), [2.78 (s), 2.71 (s), 3 H], [2.37 (s), 2.34 (s), 3 H], [2.09 (s), 2.05 (s), 3 H]; ^{13}C NMR (100 MHz, $CDCl_3$, 72:28 mixture of two isomers): δ 147.4, 147.1, 146.2, 145.5, 142.6, 139.3, 138.9, 137.7, 137.4, 136.7, 131.3, 129.4, 129.2, 128.7, 128.4, 128.1, 127.7, 126.2, 126.0, 125.8, 122.0, 117.5, 114.2, 113.4, 112.2, 111.8, 110.1, 109.8, 68.0, 65.2, 48.6, 44.8, 39.5, 39.2, 39.0, 38.3, 38.0, 30.9, 30.8, 26.9, 21.7, 19.9; IR (KBr, cm^{-1}) 3405, 2917, 2362, 1609, 1505, 1321, 1067, 1028,700; HRMS (ESI) m/z: calcd for $C_{32}H_{34}N_2$: $[M+H]^+$: 447.2795; found: 447.2784.



3c

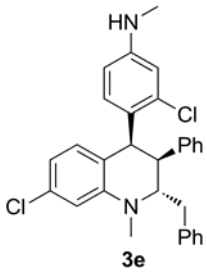
Synthesis of product 3c. Yellow solid; yield 42%; mp: 66-68°C; ^{1}H NMR (400 MHz, $CDCl_3$, 75:25 mixture of two isomers): δ 7.36-7.25 (m, 4 H), 7.13-6.95 (m, 4 H), 6.83-6.82 (d, *J* = 8.4 Hz, 1 H), 6.82-6.65 (m, 2 H), 6.26 (s, 1 H), 6.19-6.14 (t, *J* = 8.4 Hz, 2 H), 6.08 (s, 1 H); 5.79-5.77 (d, *J* = 8.4 Hz, 1 H), 5.12-5.10 (d, *J* = 6.0 Hz, 1 H), 4.29 (s, 1 H), [3.83 (s), 3.81 (s), 3 H], [3.76 (s), 3.72 (s), 3 H], 3.56-3.55 (m, 2 H), 3.09-3.08 (m, 2 H), [3.00 (s), 2.97 (s), 3 H], [2.83 (s), 2.74 (s), 3 H]; ^{13}C NMR (100 MHz, $CDCl_3$, 75:25 mixture of two isomers): δ 159.1, 158.5, 148.5, 146.6, 143.1, 139,1, 131.7, 129.8, 129.6, 129.3, 128.5, 128.2, 128.0, 127.5, 127.4, 126.9, 126.1, 125.7, 118.7, 116.8, 103.8, 99.7, 97.4, 95.0, 66.5, 55.2, 55.0, 43.3, 39.4, 38.9, 30.8; IR (KBr, cm^{-1}) 3402, 2919, 2362, 1609, 1505, 1315, 1207, 1035, 816, 699; HRMS (ESI) m/z: calcd for $C_{32}H_{34}N_2O_2$: $[M+H]^+$: 479.2693; found: 479.2685.



3d

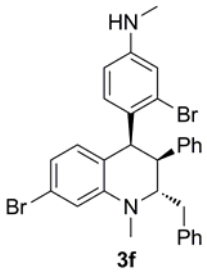
Synthesis of product 3d. Yellow solid; yield 69%; mp: 146-148°C; 90:10 mixture of two isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.28 (d, *J* = 3.6 Hz, 2 H), 7.24-7.21 (m, 3 H), 7.06-6.99 (m, 3 H), 6.81-6.77 (t, *J* = 8 Hz, 1 H), 6.72-6.70 (d, *J* = 6.8 Hz, 2 H), 6.40-6.39 (d, *J* = 2.4 Hz, 1 H), 6.29-6.19 (m, 2 H), 6.14-6.10 (t, *J* = 8.8 Hz, 1 H), 5.95-5.92 (dd, *J* = 2.4 Hz, 8.4 Hz, 1 H), 4.93-4.92 (d, *J* = 6 Hz, 1 H), 3.62-3.58 (m, 2 H), 3.14-3.10 (dd, *J* = 5.6 Hz, 13.6 Hz, 1 H), 3.07-3.04 (dd, *J* = 2.4 Hz, 5.6 Hz, 1 H), 2.98 (s, 3 H), 2.96-2.92 (m, 1 H), 2.73 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9 (d, *J* = 48 Hz), 161.5 (d, *J* = 49 Hz), 149.1 (d, *J* = 12 Hz), 146.8 (d, *J* = 10 Hz), 142.0, 138.5, 131.8, 130.1, 130.0, 129.5, 129.2, 128.5, 127.8, 126.4, 126.3, 118.1, 115.8 (d, *J* = 13 Hz), 108.0, 101.8 (d, *J* = 21 Hz), 97.9 (d, *J* = 27 Hz), 97.6 (d, *J* = 26 Hz), 66.2, 44.2, 40.0, 39.0, 34.6, 30.6; IR (KBr, cm^{-1}) 3410, 2921, 2362, 1613, 1499, 1089, 820, 696; HRMS (ESI) m/z: calcd for $C_{30}H_{28}F_2N_2$: $[M+H]^+$: 455.2293; found: 455.2288.



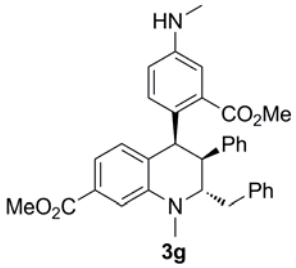
3e

Synthesis of product 3e. Yellow solid; yield 65%; mp: 167-169°C; 86:14 mixture of two isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.21 (m, 5 H), 7.06-6.98 (m, 3 H), 6.75-6.70 (m, 3 H), 6.64 (s, 1 H), 6.56-6.54 (m, 2 H), 6.08-6.06 (d, *J* = 8.4 Hz, 1 H), 6.00-5.98 (dd, *J* = 2 Hz, 8.4 Hz, 1 H), 5.12-5.11 (d, *J* = 6 Hz, 1 H), 3.66-3.62 (t, *J* = 6.4 Hz, 1 H), 3.58 (s, 1 H), 3.18-3.16 (d, *J* = 6 Hz, 1 H), 3.14-2.96 (m, 2 H), 2.94 (s, 3 H), 2.73 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 146.1, 142.1, 138.6, 135.4, 133.0, 132.2, 130.4, 129.5, 129.1, 128.5, 127.8, 126.4, 126.3, 121.1, 115.4, 111.3, 110.9, 110.3, 66.9, 43.1, 40.4, 39.1, 38.7, 30.5; IR (KBr, cm^{-1}) 3411, 2918, 2361, 1708, 1594, 1497, 1409, 1316, 1218, 1032, 822, 699; HRMS (ESI) m/z: calcd for $C_{30}H_{28}Cl_2N_2$: $[M+H]^+$: 487.1702; found: 487.1708.



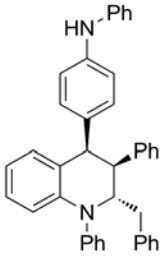
3f

Synthesis of product 3f. Yellow solid; yield 56%; mp: 86-88°C; 89:11 mixture of two isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.21 (m, 5 H), 7.04-6.97 (m, 3 H), 6.78 (s, 1 H), 6.73-6.71 (m, 3 H), 6.68-6.67 (d, *J* = 1.6 Hz, 2 H), 6.02 (s, 2 H), 5.07-5.05 (d, *J* = 6.4 Hz, 1 H), 3.67-3.63 (m, 1 H), 3.56 (s, 1 H), 3.23-3.21 (dd, *J* = 1.6 Hz, 6 Hz, 1 H), 3.18-3.13 (m, 1 H), 3.02-2.96 (m, 1 H), 2.91 (s, 3 H), 2.72 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 146.3, 142.1, 138.8, 132.3, 130.7, 129.6, 129.1, 128.5, 127.9, 127.8, 126.5, 126.4, 126.3, 121.7, 121.3, 118.4, 114.6, 113.1, 111.5, 67.1, 43.3, 41.8, 40.7, 39.2, 30.5; IR (KBr, cm^{-1}) 3432, 2361, 1643, 1498, 1316, 1025, 668; HRMS (ESI) m/z: calcd for $C_{30}H_{28}Br_2N_2$: $[M+H]^+$: 575.0692; found: 575.0704.



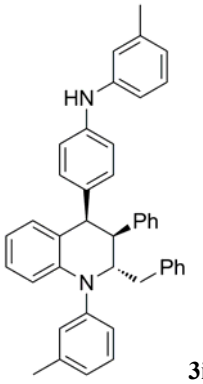
3g

Synthesis of product 3g. Yellow solid; yield 47%; mp: 124-126°C; 87:13 mixture of two isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.11 (m, 10 H), 7.06 (s, 1 H), 7.00-6.97 (d, *J* = 7.6 Hz, 1 H), 6.93-6.91 (d, *J* = 6.8 Hz, 1 H), 6.84-6.82 (d, *J* = 7.2 Hz, 1 H), 6.62-6.58 (m, 1 H), 6.09 (s, 1 H), 4.08 (s, 1 H), 4.03-4.01 (d, *J* = 8.8 Hz, 1 H), 3.93 (s, 3 H), 3.89 (s, 3 H), 3.79-3.75 (m, 1 H), 3.10-3.03 (m, 2 H), 3.00 (s, 3 H), 2.87-2.85 (m, 1 H), 2.78 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 167.3, 147.1, 146.7, 144.3, 138.8, 137.2, 135.1, 130.9, 129.6, 129.3, 128.9, 128.5, 128.2, 128.1, 127.0, 126.3, 126.0, 119.5, 118.3, 117.8, 113.9, 113.3, 67.2, 62.7, 52.0, 48.4, 38.3, 38.2, 37.0, 26.9; IR (KBr, cm^{-1}) 3401, 2948, 1716, 1599, 1445, 1266, 1110, 753, 698; HRMS (ESI) m/z: calcd for $C_{34}H_{34}N_2O_4$: $[M+H]^+$: 535.2590; found: 535.2685.



3h

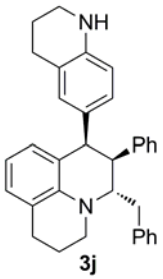
Synthesis of product 3h. Yellow solid; yield 58%; mp: 80-82°C; 86:14 mixture of two isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.12 (m, 7 H), 7.07-7.04 (m, 9 H), 7.00-6.91 (m, 8 H), 6.88-6.86 (m, 4 H), 5.61 (s, 1 H), 4.31-4.28 (m, 1 H), 4.21-4.19 (d, *J* = 7.2 Hz, 1 H), 3.36-3.33 (m, 1 H), 2.98-2.93 (m, 1 H), 2.80-2.75 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 144.9, 143.7, 143.4, 141.2, 138.7, 135.5, 130.7, 130.3, 129.4, 129.3, 128.2, 127.8, 127.0, 126.1, 122.0, 121.5, 120.6, 120.5, 119.8, 118.0, 117.3, 66.7, 54.7, 48.0, 40.1; IR (KBr, cm^{-1}) 3492, 2920, 1595, 1493, 1450, 1312, 1067, 1033, 750, 699; HRMS (ESI) m/z: calcd for $C_{40}H_{34}N_2$: $[M+H]^+$: 543.2795; found: 543.2807.



3i

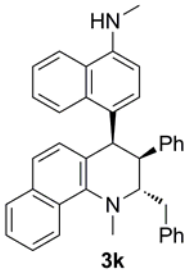
Synthesis of product 3i. Yellow solid; yield 47%; mp: 84-86°C; 79:21 mixture of two isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.13 (m, 3 H), 7.11-7.02 (m, 7 H), 6.97-6.91 (m, 7 H), 6.87-6.84 (m, 6 H), 6.76-6.68 (m, 3 H), 5.58 (s, 1 H), 4.28-4.21 (m, 1 H), 4.18-4.16 (d, *J* = 7.2 Hz, 1 H), 3.34-3.29 (m, 1 H), 3.03-2.93 (m, 1 H), 2.84-2.74 (m, 1 H), 2.29 (s, 3 H), 2.27 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 145.1, 143.5, 143.4, 141.2, 139.1, 138.9, 138.8, 136.7, 135.8, 130.3, 129.8, 129.4, 129.3, 129.2, 129.1, 129.0,

128.7, 128.4, 128.2, 127.8, 127.7, 127.5,126.0, 122.1, 122.0, 121.7, 121.5, 121.4, 120.5, 120.1, 118.1, 118.0, 117.3, 115.7, 114.4, 66.9, 54.5, 47.6, 40.1, 21.5, 21.3; IR (KBr, cm^{-1}) 3391, 3027, 2920, 1710, 1598, 1495, 1317, 750, 699; HRMS (ESI) m/z: calcd for $C_{42}H_{38}N_2$: $[M+H]^+$: 571.3108; found: 571.3100.



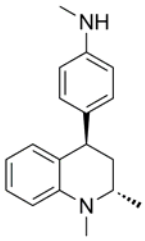
3j

Synthesis of product 3j. Yellow solid; yield 38%; mp: 74-76°C; ^{1}H NMR (400 MHz, $CDCl_3$, 1:1 mixture of two isomers): δ 7.29-7.13 (m, 5 H), 7.11-6.97 (m, 4 H), 6.92-6.88 (m, 2 H), 6.80-6.76 (m, 2 H), 6.71-6.16 (m, 4 H), [4.36(s), 4.13(s), 1 H], 3.52-3.42 (m, 2 H), 3.30-3.27 (m, 2 H), 3.23-3.17 (m, 2 H), 2.96-2.79 (m, 4 H), 2.72-2.50 (m, 2 H), 2.00-1.80 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$, 1:1 mixture of two isomers): δ 150.4, 147.0, 142.9, 142.8, 142.6, 141.9, 141.3, 139.5, 139.0, 136.0, 135.2, 131.5, 130.3, 129.6, 129.5, 129.4, 129.3, 128.6, 128.4, 128.2, 128.0, 127.8, 127.6, 127.5, 127.1, 126.5, 126.2, 126.0, 125.8, 125.7, 122.7, 121.6, 121.4, 121.2, 121.1, 120.6, 115.1, 114.8, 114.0, 113.4, 66.0, 64.8, 49.6, 49.1, 47.9, 46.4, 45.5, 44.1, 42.1, 42.0, 39.5, 37.2, 28.6, 28.4, 27.1, 26.7, 22.4, 22.3, 22.1; IR (KBr, cm^{-1}) 3392, 2920, 2835, 2362, 1707, 1594, 1488, 1454, 1311, 741, 698; HRMS (ESI) m/z: calcd for $C_{34}H_{34}N_2$: $[M+H]^+$: 471.2795; found: 471.2783.



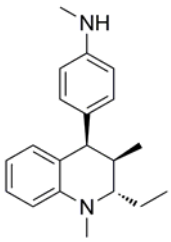
3k

Synthesis of product 3k. Yellow solid; yield 10%; mp: 86-88°C; 67:33 mixture of two isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13-6.58 (m, 22 H), 5.63-5.59 (m, 1 H), 4.28-4.21 (m, 1 H), 4.18-4.16 (d, *J* = 7.2 Hz, 1 H), 3.34-3.28 (m, 1 H), 3.03-2.93 (m, 1 H), 2.84-2.74 (m, 1 H), 2.30 (s, 3 H), 2.26 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 143.5, 143.4, 139.2, 135.9, 130.3, 129.4, 129.3, 129.2, 129.1, 128.2, 127.8, 127.7, 127.5, 126.0, 122.0, 121.6, 121.5, 121.4, 120.5, 120.1, 118.1, 117.3, 114.4, 66.9, 54.5, 47.6, 40.1, 21.5, 21.3; IR (KBr, cm^{-1}) 3400, 2922, 2317, 1591, 1390, 1066, 758, 700, 610; HRMS (ESI) m/z: calcd for $C_{38}H_{34}N_2$: $[M+H]^+$: 519.2795; found: 519.2803.



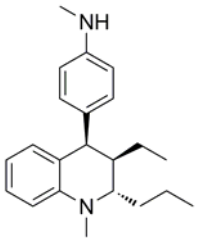
4a

Synthesis of product 4a. Yellow solid; yield 38%; mp: 61-63°C; 90:10 mixture of two isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10-7.06 (t, *J* = 7.2 Hz, 1 H), 7.03-7.00 (d, *J* = 8.8 Hz, 2 H), 6.70-6.68 (d, *J* = 7.6 Hz, 1 H), 6.60-6.57 (dd, *J* = 2.4Hz, 8.8 Hz, 3 H), 6.53-6.49 (t, *J* = 7.6 Hz, 1 H), 3.99-3.95 (dd, *J* = 5.2 Hz, 11.2Hz, 1 H), 3.44-3.39 (m, 1 H), 3.93 (s, 3 H), 2.83 (s, 3 H), 2.19-2.12 (m, 1 H), 1.96-1.91 (m, 1 H), 1.22-1.20 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 145.7, 134.5, 129.5, 129.2, 127.2, 126.1, 115.6, 112.5, 110.7, 53.3, 39.2, 38.0, 37.2, 30.9, 18.1; IR (KBr, cm^{-1}) 3405, 2926, 1607, 1493, 1320, 1044, 820, 747; HRMS (ESI) m/z: calcd for $C_{18}H_{22}N_2$: $[M+H]^+$: 267.1856; found: 267.1876.



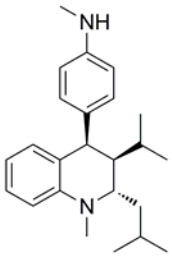
4b

Synthesis of product 4b. Yellow solid; yield 48%; mp: 72-74°C; 94:6 mixture of two isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.14 (t, *J* = 7.6 Hz, 1 H), 7.07-7.05 (d, *J* = 8 Hz, 2 H), 6.98-6.96 (d, *J* = 7.6 Hz, 1 H), 6.62-6.56 (m, 4 H), 4.15-4.14 (d, *J* = 4.4 Hz, 1 H), 3.65 (s, 1 H), 3.06 (s, 3 H), 2.95-2.93 (m, 1 H), 2.88 (s, 3 H), 2.08-2.04 (m, 1 H), 1.80-1.71 (m, 1 H), 1.66-1.59 (m, 1 H), 1.00-0.96 (t, *J* = 7.2 Hz, 3 H), 0.87-0.85 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 145.3, 131.5, 130.8, 129.4, 127.1, 123.5, 115.0, 112.0, 110.5, 66.8, 44.0, 38.8, 33.8, 30.9, 24.5, 16.1, 9.8; IR (KBr, cm^{-1}) 3410, 2961, 1615, 1498, 1322, 1052, 818, 746; HRMS (ESI) m/z: calcd for $C_{20}H_{26}N_2$: $[M+H]^+$: 295.2169; found: 295.2165.



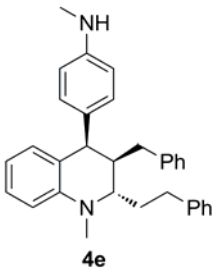
4c

Synthesis of product 4c. Yellow solid; yield 40%; mp: 58-60°C; 88:12 mixture of two isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16-7.12 (t, *J* = 7.2 Hz, 1 H), 7.09-7.07 (d, *J* = 8.4 Hz, 2 H), 7.00-6.99 (d, *J* =7.6 Hz, 1 H), 6.63-6.55 (m, 4 H), 4.31-4.30 (d, *J* = 4.4 Hz, 1 H), 3.65 (s, 1 H), 3.25 (s, 1 H), 3.05 (s, 3 H), 2.86 (s, 3 H), 1.78-1.70 (m, 2 H), 1.60-1.15 (m, 5 H), 1.02-0.99 (t, *J* = 7.2 Hz, 3 H), 0.83-0.79 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 145.4, 131.4, 131.1, 129.4, 127.0, 123.4, 114.9, 112.0, 110.3, 60.8, 43.3, 41.5, 38.9, 34.0, 30.9, 20.4, 19.1, 14.3, 11.9; IR (KBr, cm^{-1}) 3406, 2957, 2869, 2362, 1608, 1498, 1316, 1052, 746, 672; HRMS (ESI) m/z: calcd for $C_{22}H_{30}N_2$: $[M+H]^+$: 323.2482; found: 323.2480.



4d

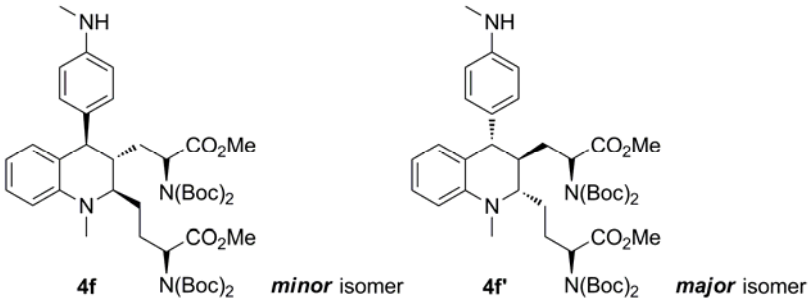
Synthesis of product 4d. Yellow solid; yield 38%; mp: 79-81°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04-7.00 (t, *J* = 7.2 Hz, 1 H), 6.97-6.95 (d, *J* = 8.4 Hz, 2 H), 6.66-6.64 (d, *J* = 7.6 Hz, 1 H), 6.55-6.52 (t, *J* = 6.8 Hz, 3 H), 6.49-6.46 (t, *J* = 7.2 Hz, 1 H), 3.87-3.84 (d, *J* = 11.6 Hz, 1 H), 3.58 (s, 1 H), 3.40-3.37 (m, 1 H), 3.07 (s, 3 H), 2.81 (s, 3 H), 2.14-2.09 (m, 1 H), 1.71-1.66 (m, 1 H), 1.59-1.47 (m, 2 H), 1.25-1.18 (m, 1 H), 1.00-0.99 (d, *J* = 6.8 Hz, 3 H), 0.90-0.88 (d, *J* = 7.2 Hz, 3 H), 0.84-0.83 (d, *J* = 6.4 Hz, 3 H), 0.78-0.77 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 145.0, 135.5, 130.5, 130.1, 128.3, 126.5, 115.9, 112.4, 112.1, 58.9, 48.5, 44.4, 40.6, 38.8, 30.9, 28.7, 25.9, 24.2, 21.9, 21.8, 19.8; IR (KBr, cm^{-1}) 3408, 2953, 1608, 1519, 1317, 805, 747; HRMS (ESI) m/z: calcd for $C_{24}H_{34}N_2$: $[M+H]^+$: 351.2795; found: 351.2793.



4e

Synthesis of product 4e. Yellow solid; yield 70%; mp: 66-68°C; ^{1}H NMR (400 MHz, $CDCl_3$, 1:1 mixture of two isomers): δ 7.27-7.05 (m, 10 H), 7.01-6.96 (m, 4 H), 6.69-6.49 (m, 4 H), [4.40-4.39 (d, *J* = 5.2 Hz), 3.70-3.67 (d, *J* = 11.6 Hz), 1 H], 3.62 (s, 1 H), [2.97 (s), 2.87 (s), 3 H], [2.85 (s), 2.81(s), 3 H], 2.66-2.22 (m, 5 H), 1.94-1.79 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, 1:1 mixture of two isomers): δ 147.9, 147.8, 145.2, 145.0, 133.9, 131.2, 131.0, 130.5, 130.1, 129.8, 129.2, 128.8, 128.4, 128.3, 128.1, 127.3, 127.0, 126.5, 125.8,

125.7,125.6, 122.4, 116.0, 115.3, 112.6, 112.2, 111.9, 110.4, 60.2, 60.0, 46.3, 45.8, 43.2, 41.9, 40.8, 38.6, 36.6, 34.4, 34.3, 33.0, 32.1, 30.9, 30.6; IR (KBr, cm^{-1}) 3407, 2923, 2362, 1602, 1493, 1384, 1051, 748, 699; HRMS (ESI) m/z: calcd for $C_{32}H_{34}N_2$: $[M+H]^+$: 447.2795; found: 447.2789.



Synthesis of product 4f and 4f'. Yellow solid; yield 42 % (combined yield); 3:1 dr value. (Note: major isomer and minor isomer could be partially separated by column chromatography on silica gel with elution of hexanes/EtOAc.); mp: 40-42°C; For the minor diastereoisomer product **4f** indicated here: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.19 (t, *J* = 8 Hz, 2 H), 7.13-7.09 (t, *J* = 7.2 Hz, 1 H), 6.95-6.93 (d, *J* = 7.2 Hz, 1 H), 6.88-6.84 (m, 2 H), 6.70-6.61 (m, 1 H), 6.59-6.53 (m, 1 H), 4.99-4.93 (m, 2 H), 4.77-4.73 (t, *J* = 6.8 Hz, 1 H), 3.65(s, 3 H), 3.64 (s, 3 H), 3.29-3.26 (m, 1 H), 3.06 (s, 3 H), 2.63 (s, 3 H), 2.52-2.50 (m, 1 H), 2.44-2.29 (m, 2 H), 1.92-1.83 (m, 1 H), 1.68-1.62 (m, 3 H), 1.47 (s, 18 H), 1.41 (s, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 171.0, 152.0, 151.9, 129.3, 128.2, 127.4, 121.6, 116.3, 116.0, 112.1, 111.9, 83.2, 83.1, 62.5, 58.4, 57.7, 55.8, 52.1, 40.6, 37.2, 30.9, 29.1 25.9; $[\alpha]^{17}_D$ = +5 (*c* 0.20, CH_3OH). For the minor diastereoisomer product, enantiomeric excess is higher than 99% determined by HPLC (Chiralpak IC, Hexane/Isopropanol/DEA = 98/1.9/0.1, flow rate = 1.0 mL/min, 254 nm): major isomer: t_R = 15.18 min; minor isomer: t_R = 22.02 min. For the major diastereoisomer product **4f'** indicated here: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.18 (t, *J* = 7.6 Hz, 2 H), 7.09-7.06 (t, *J* = 7.2 Hz, 1 H), 6.89-6.87 (d, *J* = 7.6 Hz, 1 H), 6.82-6.80 (d, *J* = 7.6 Hz, 1 H), 6.55-6.51 (d, *J* = 7.2 Hz, 1 H), 6.49-6.47 (d, *J* = 8 Hz, 1 H), 5.06-5.03 (dd, *J*

= 3.2 Hz, 11.2 Hz, 1 H), 4.90 (s, 1 H), 4.86-4.83 (m, 1 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.52-3.49 (m, 1 H), 3.03 (s, 3 H), 2.49 (s, 3 H), 2.27-2.18 (m, 2 H), 2.11-1.95 (m, 2 H), 1.67-1.47 (m, 2 H), 1.41 (s, 36 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 152.1, 151.9, 145.2, 129.3, 128.2, 127.4, 121.3, 116.2, 116.1, 112.0, 111.9, 83.2, 83.1, 61.5, 58.2, 55.6, 52.2, 52.1, 40.7, 28.9, 28.8, 27.8, 25.2; IR (KBr, cm^{-1}) 3418, 2980, 1747, 1599, 1501, 1368, 1248, 1129, 854, 750; HRMS (ESI) m/z: calcd for $C_{46}H_{69}N_4O_{12}$: $[M+H]^+$: 869.4907; found: 869.4916. $[\alpha]^{17}_D = -50$ (*c* 0.20, CH_3OH). For the major diastereoisomer product, enantiomeric excess is higher than 99% determined by HPLC (Chiralpak IC, Hexane/Isopropanol/DEA = 95/4.9/0.1, flow rate = 1.0 mL/min, 254 nm): major isomer: t_R = 10.06 min; minor isomer: t_R = 11.25 min.

4. References:

1. For the preparation of 2-Aryl-1,2,3,4-tetrahydro-isoquinolines, *N*-Aryl-benzenamine **1b-1i, 1k** see:

   (a) Iranpoor, N.; Firouzabadi, H.; Nowrouzi, N.; Khalili, D. *Tetrahedron* **2009**, *65*, 3893.

   (b) Peng, Y.-Y.; Liu, H.-L.; Tang, M.; Cai, L.-S.; Pike, V. *Chinese Journal of Chemistry*, **2009**, *27*, 1339.

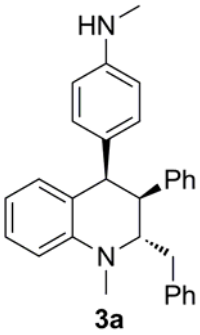
   (c) Zhu, X.-Q.; Dai, Z.; Yu, A.; Wu, S.; Cheng, J.-P. *J. Phys. Chem. B.* **2008**, *112*, 11694.

2. For the preparation of **2f**, see:

   (a) Kokotos, G.; Padrón, J. M.; Martín, T.; Gibbons, W. A.; Martín, V. S. *J. Org. Chem.* **1998**, *63*, 3741.

   (b) Padrón, J. M.; Kokotos, G.; Martín, T.; Markidis, T.; Gibbons, W. A.; Martín, V. S. *Tetrahedron: Asymmetry* **1998**, *9*, 3381.

5. ^{1}H NMR and ^{13}C NMR spectra for compounds 3a-3k, 4a-4f′:



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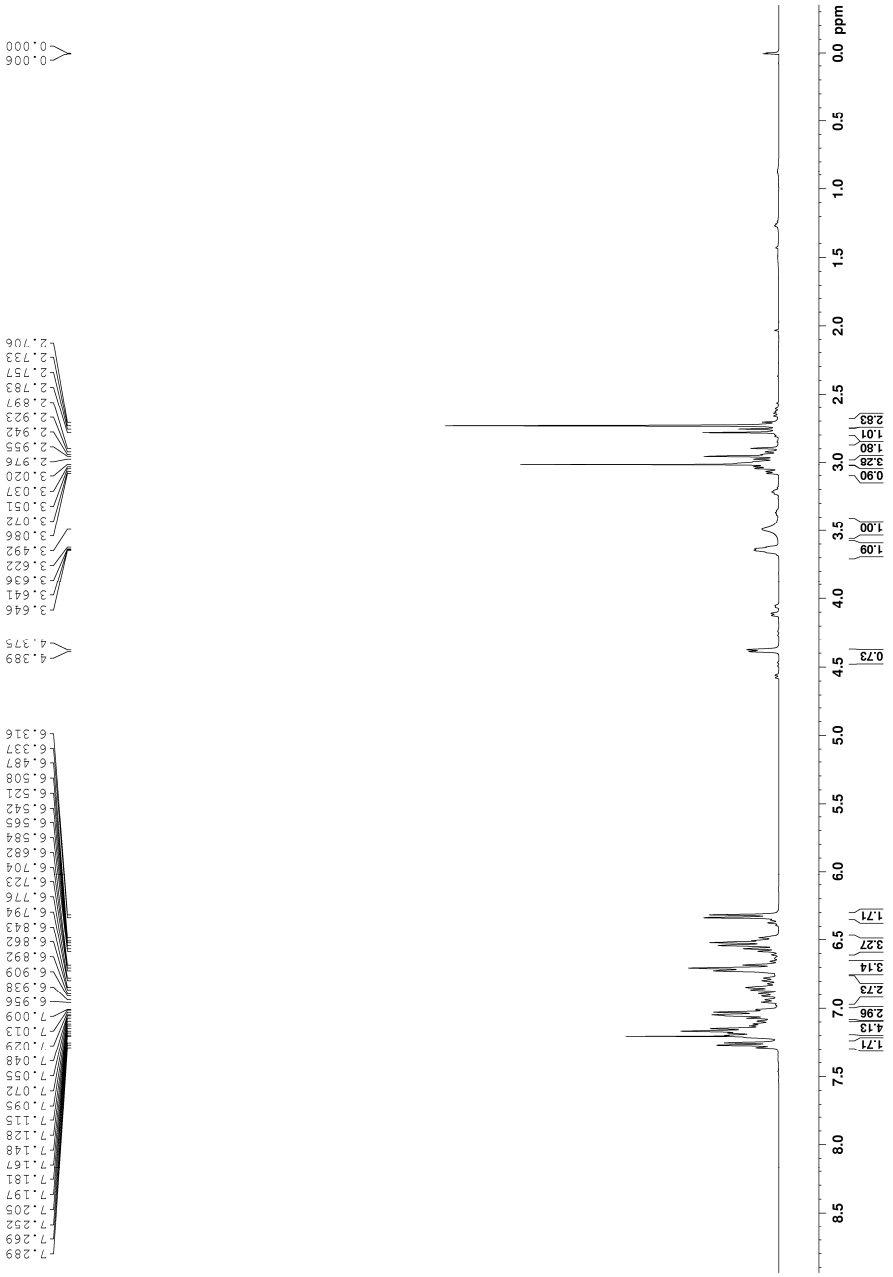

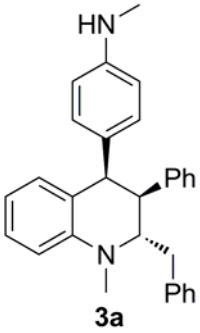

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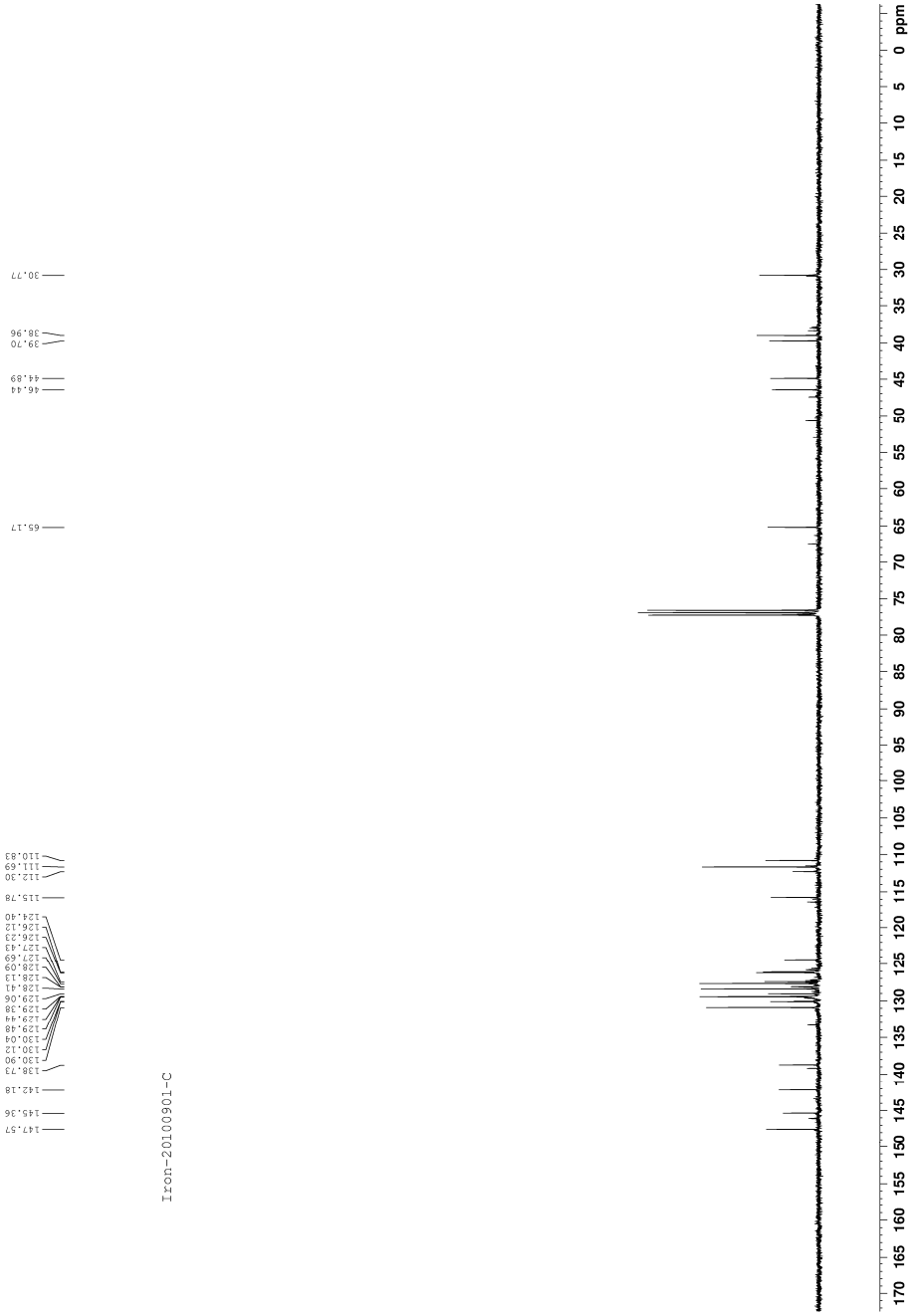

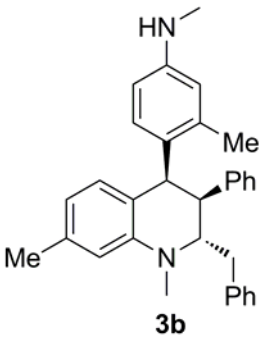

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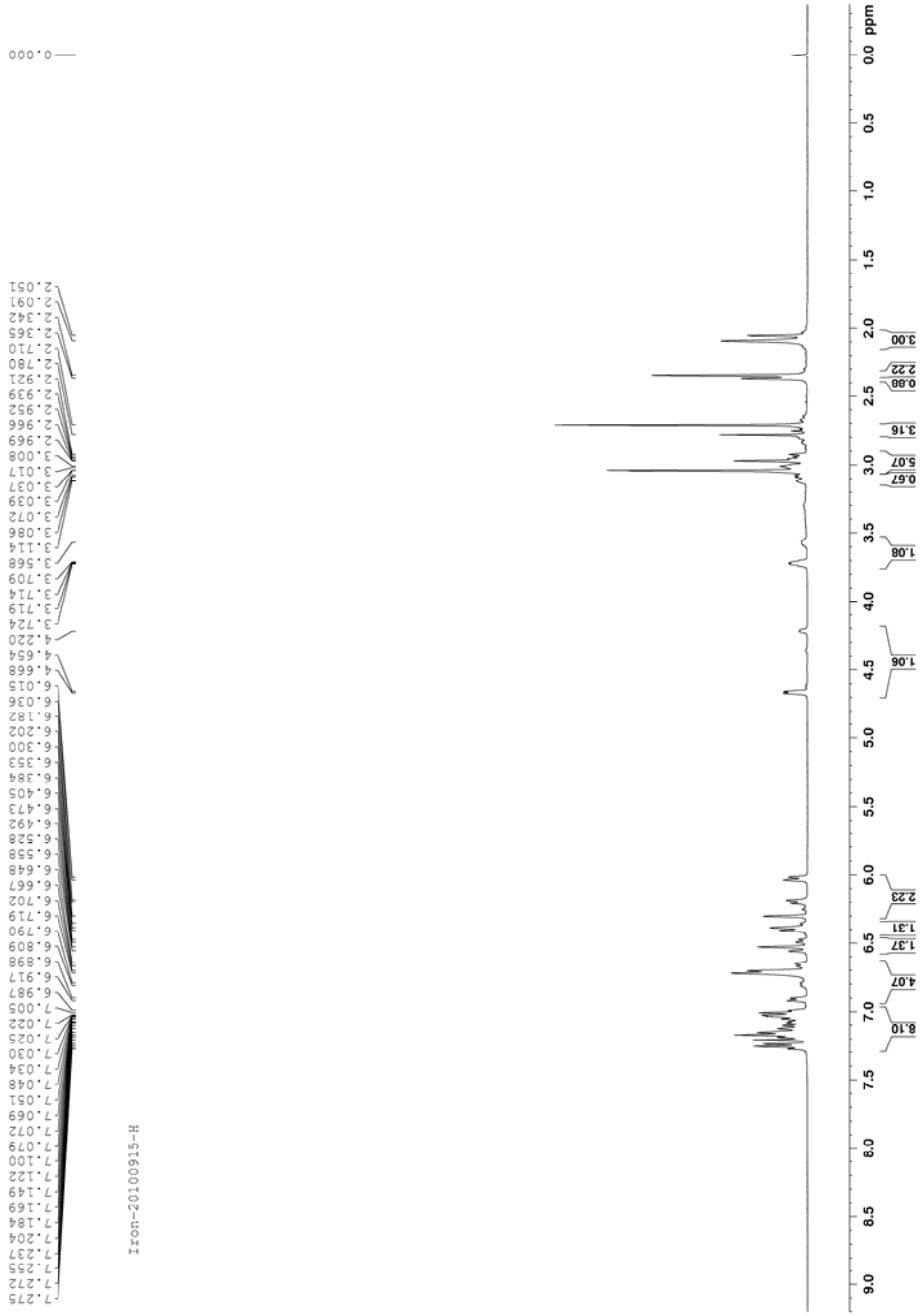

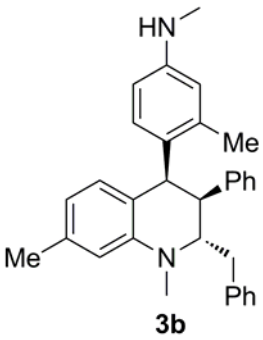

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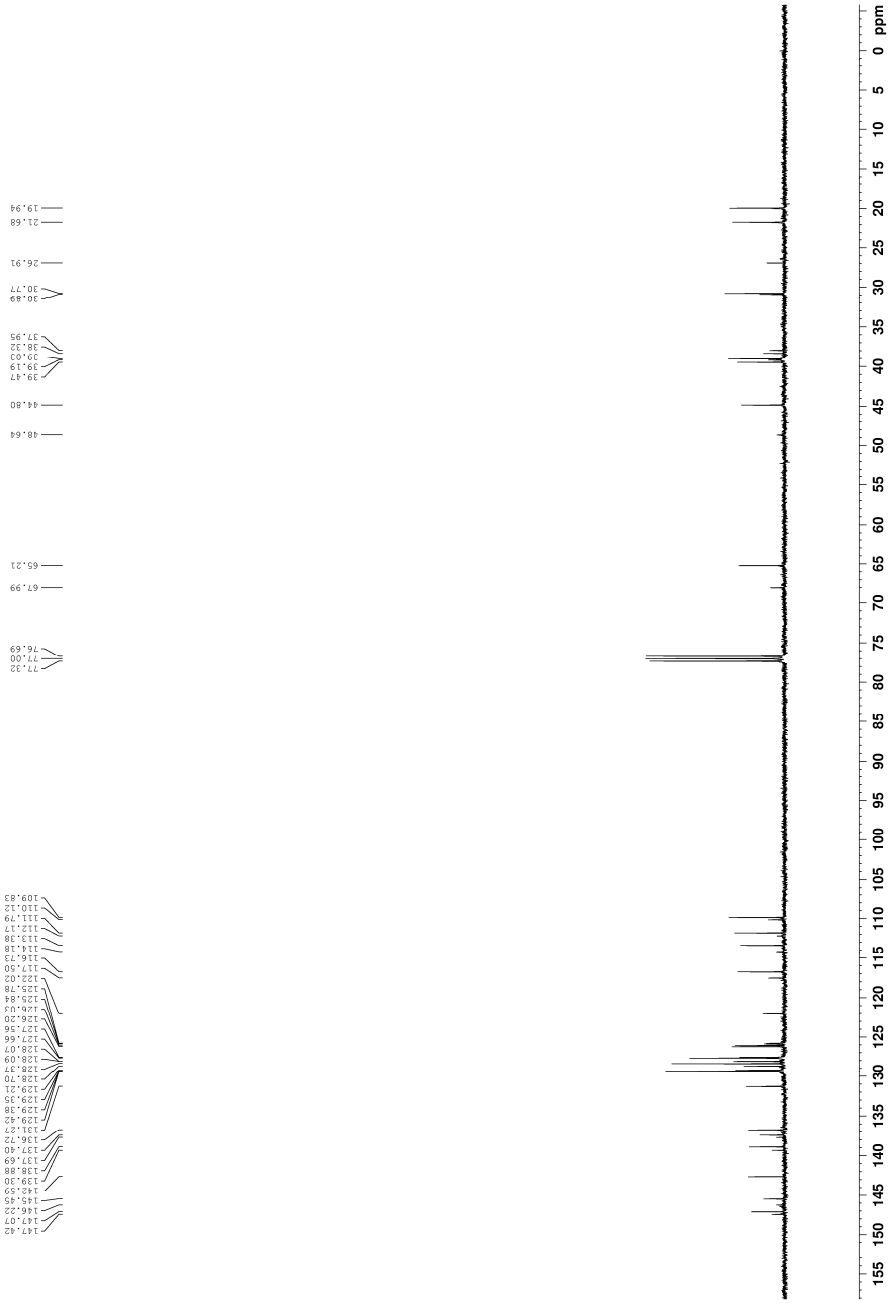

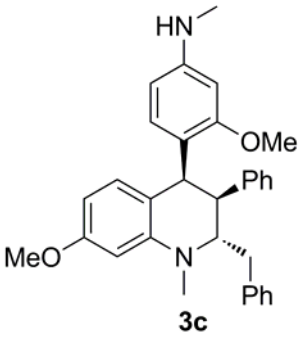

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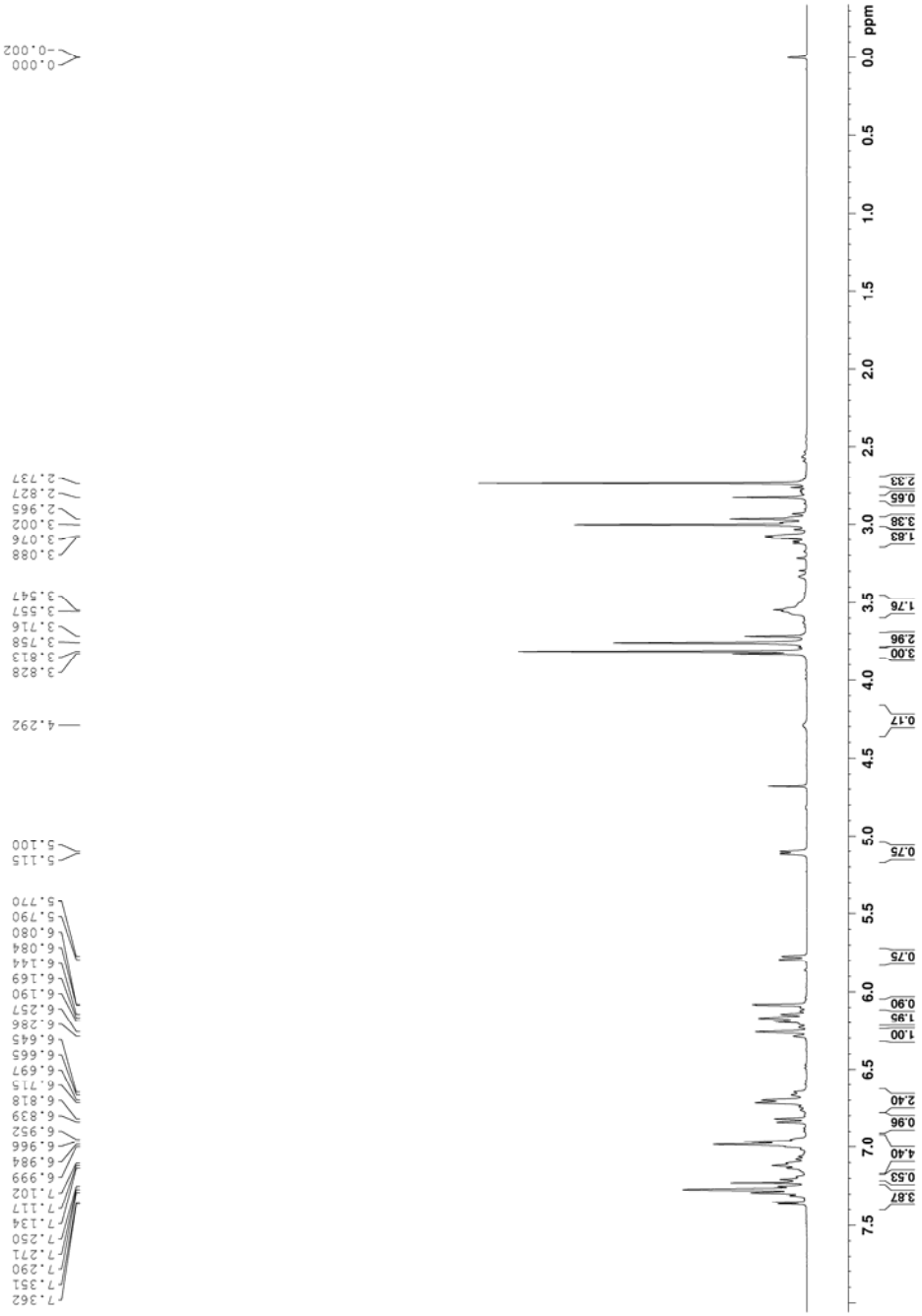

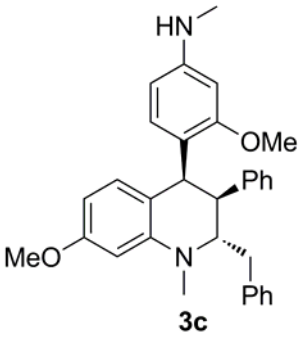

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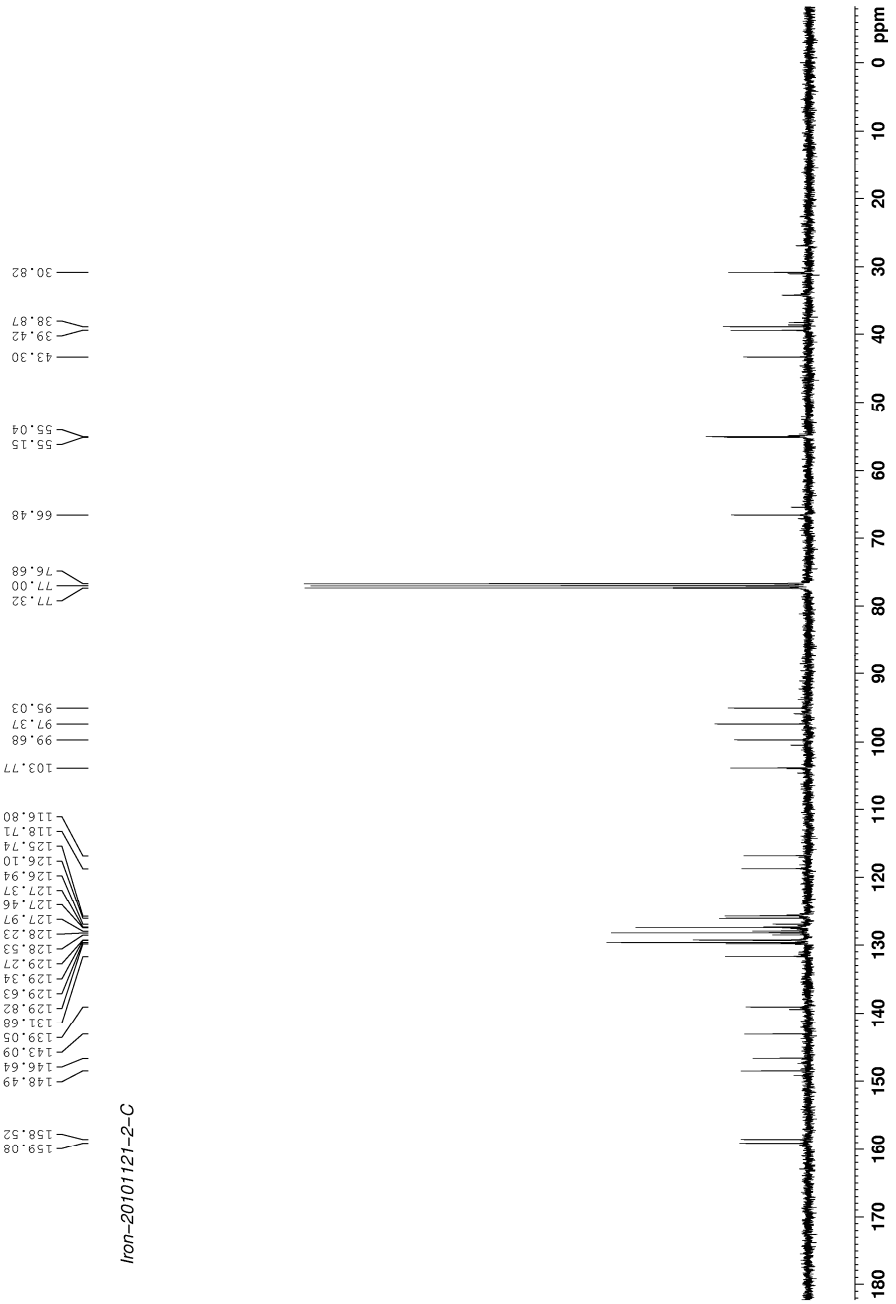

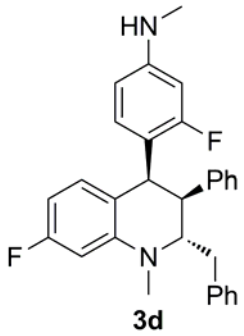

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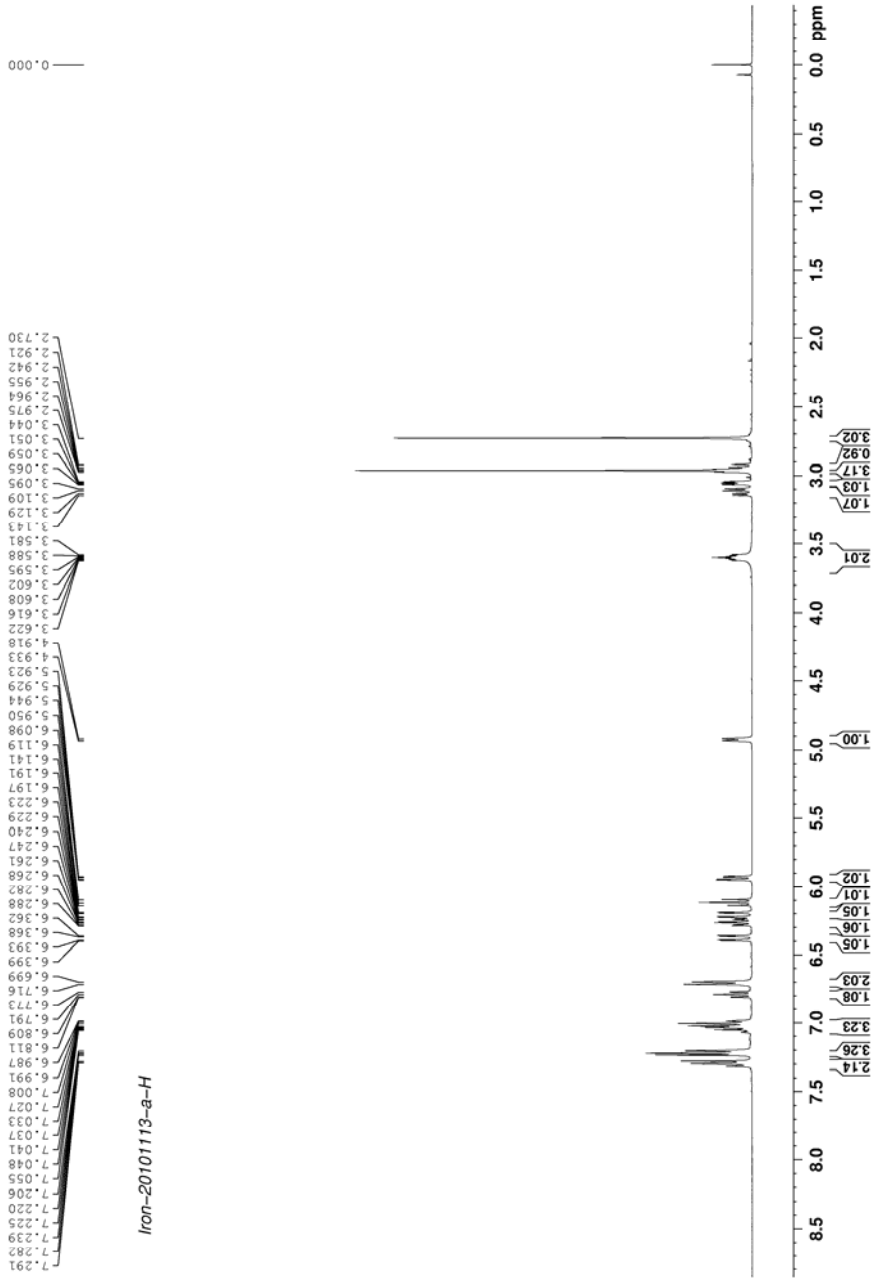

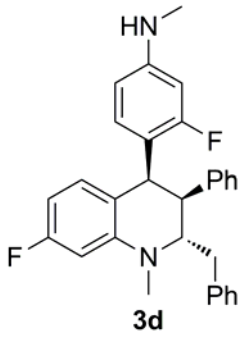

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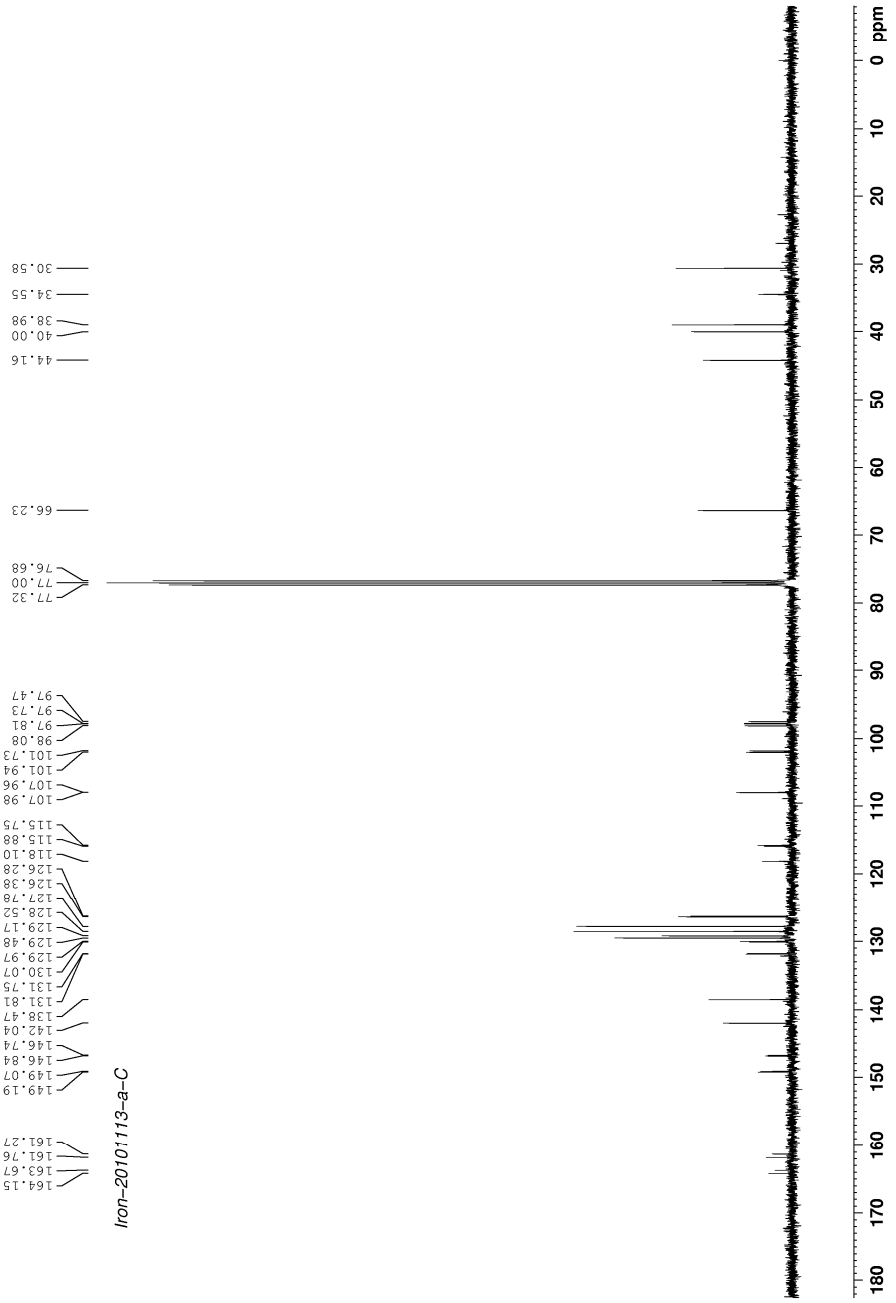

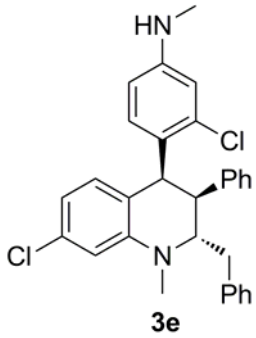

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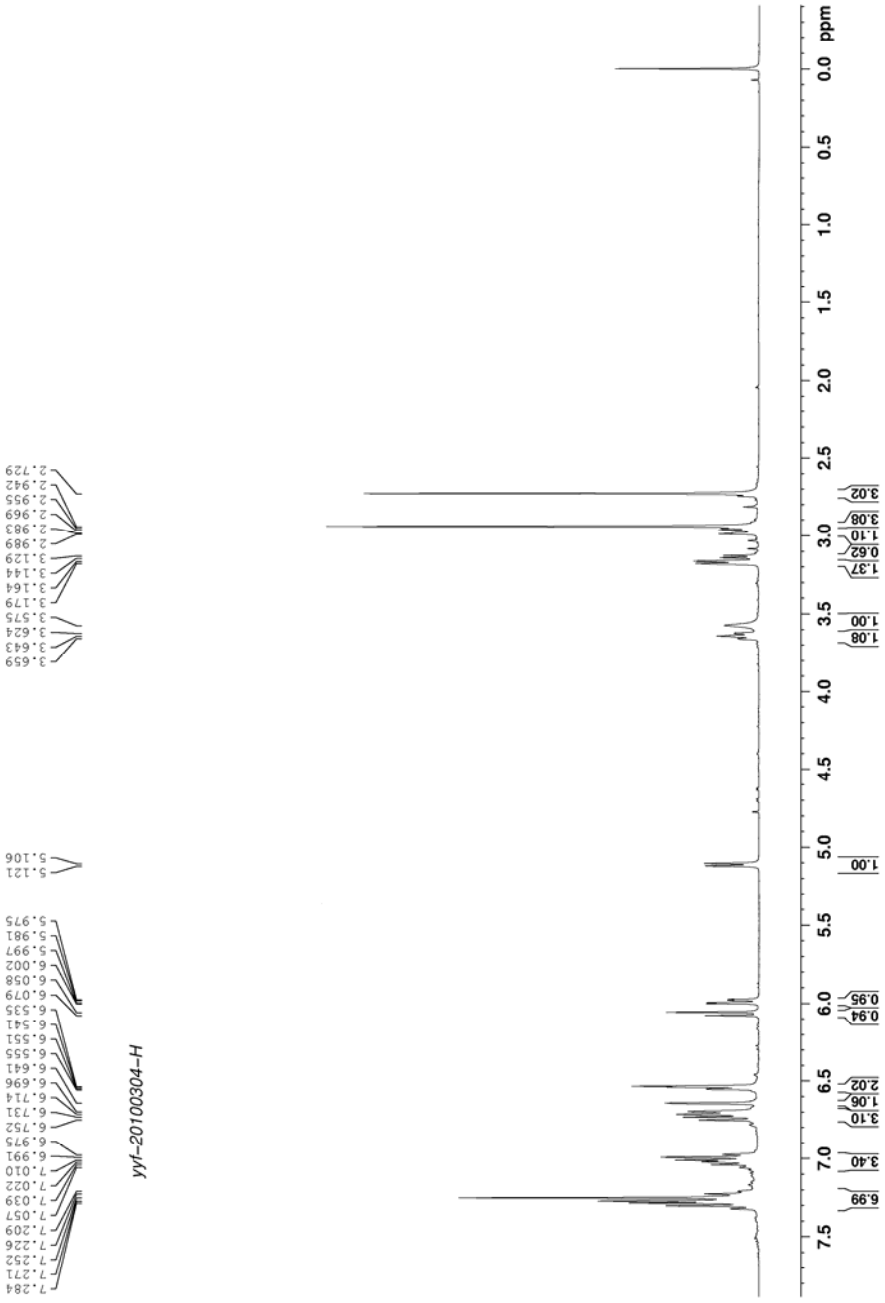

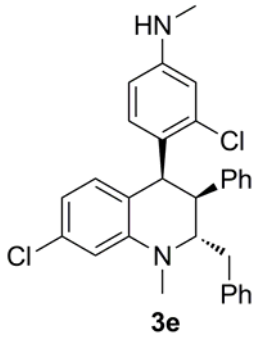

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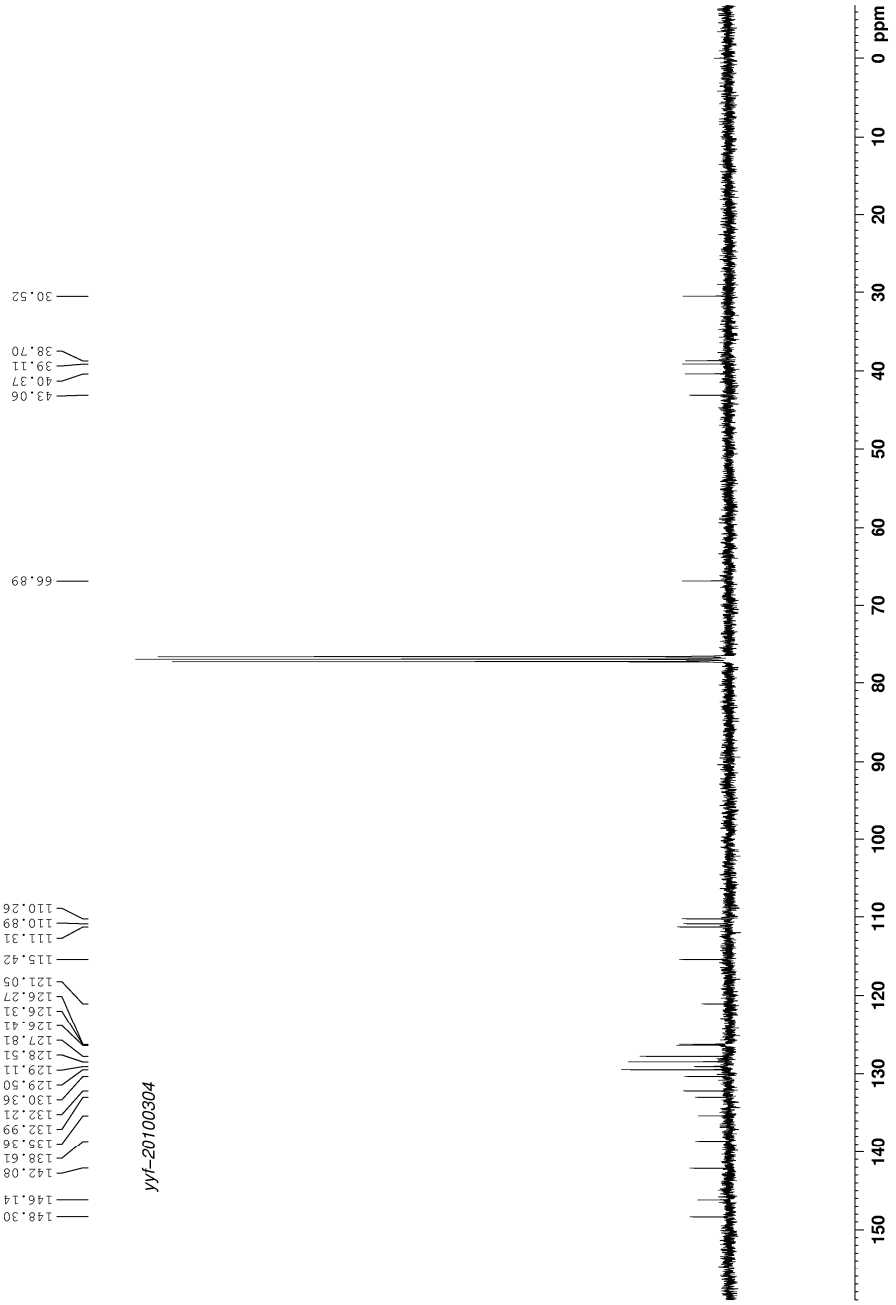

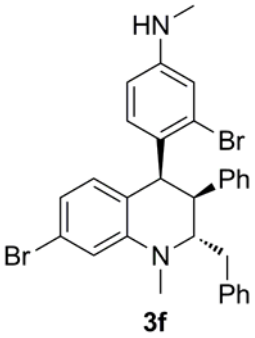

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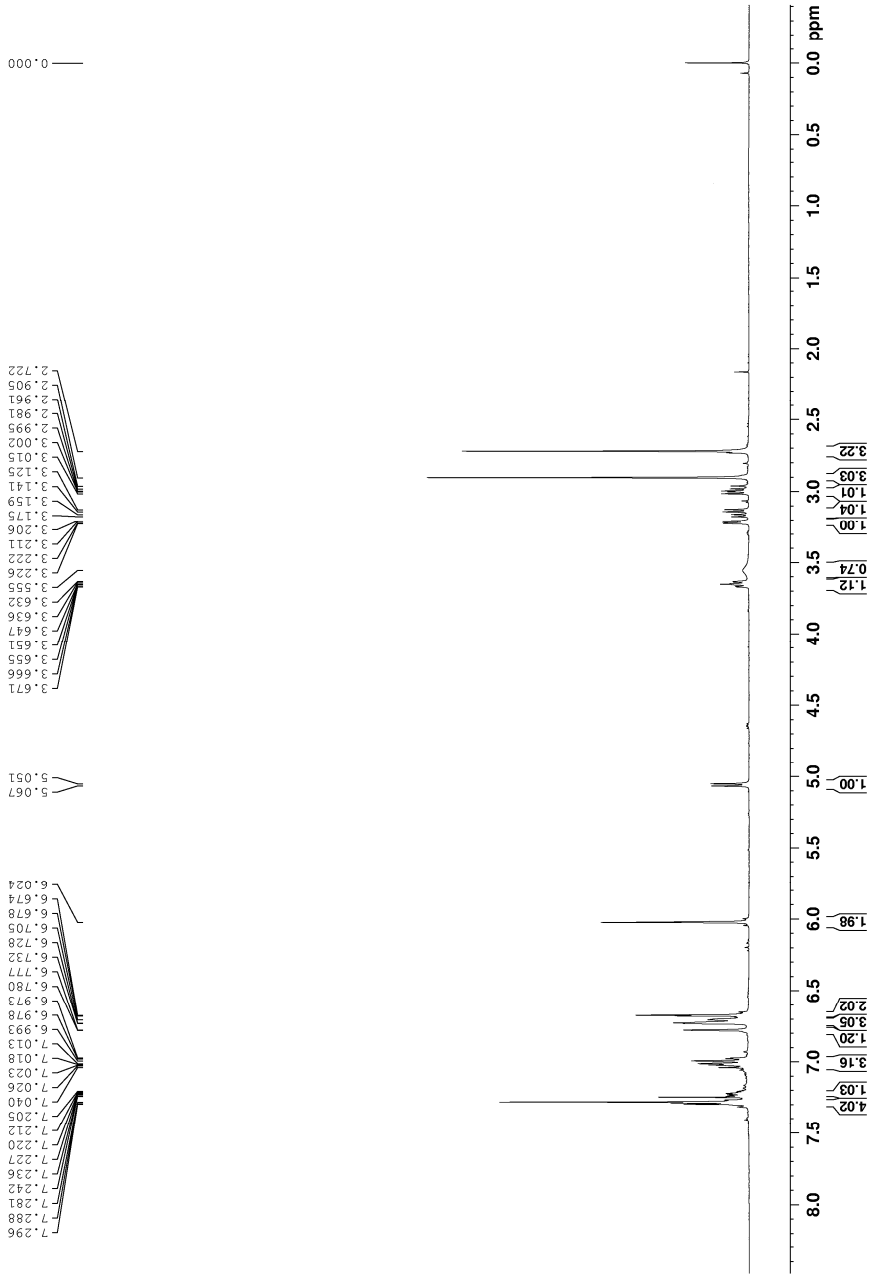

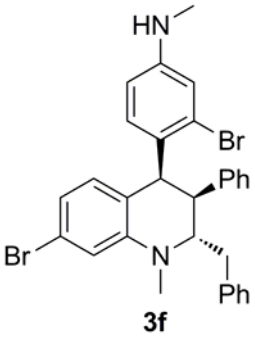

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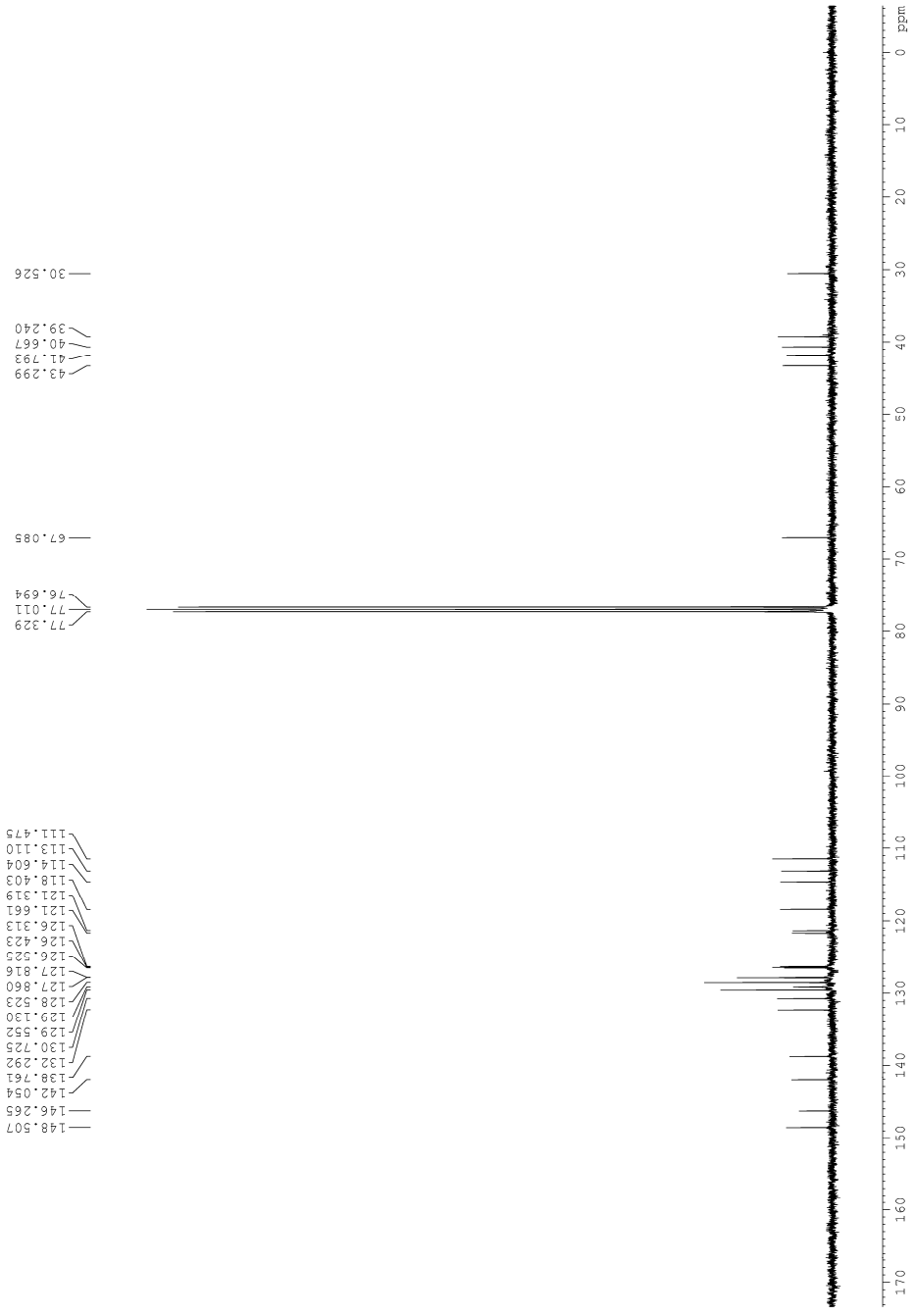

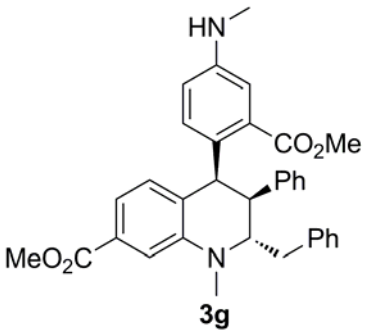

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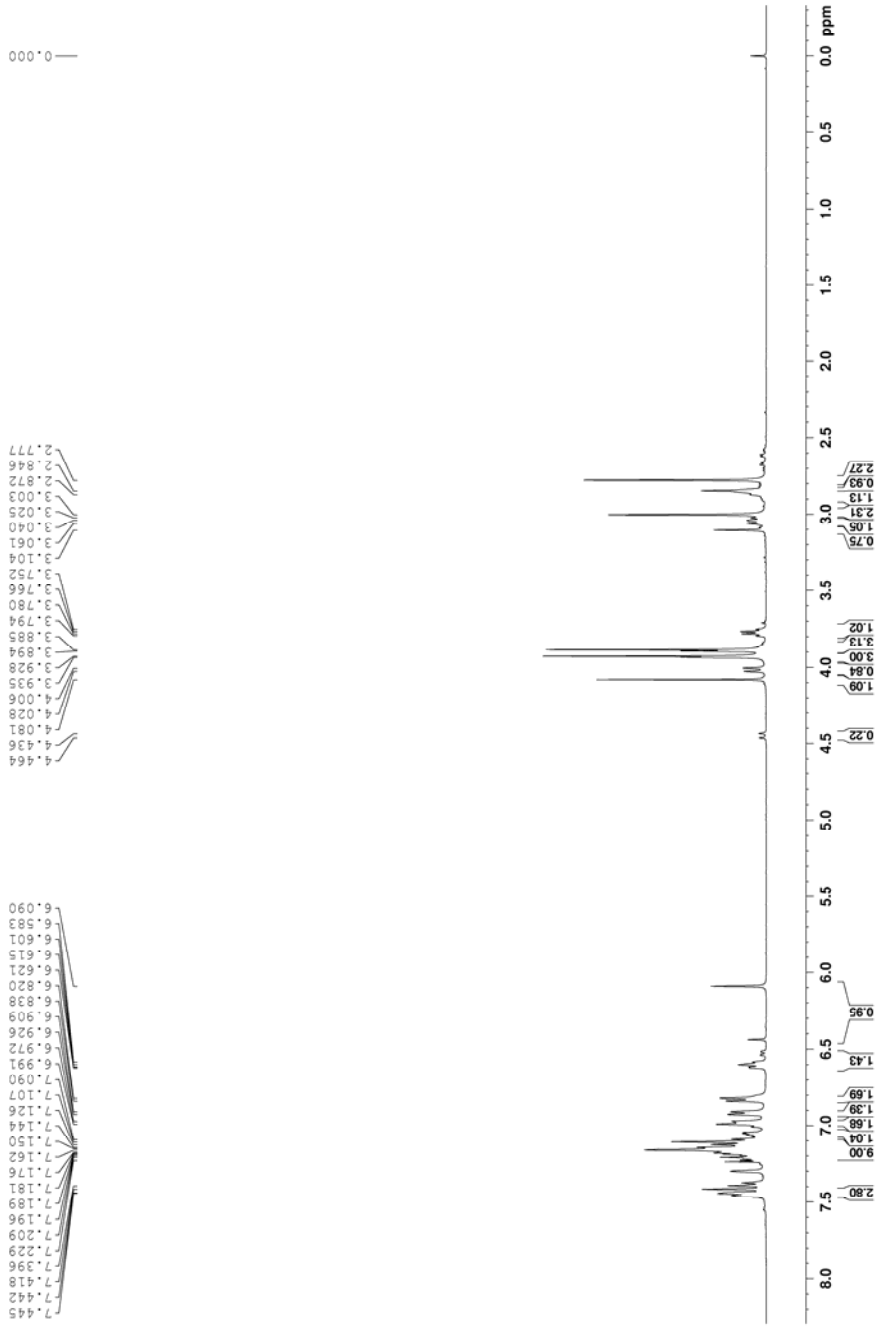

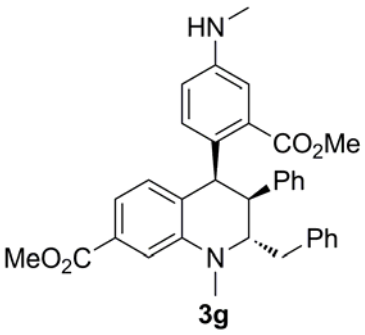

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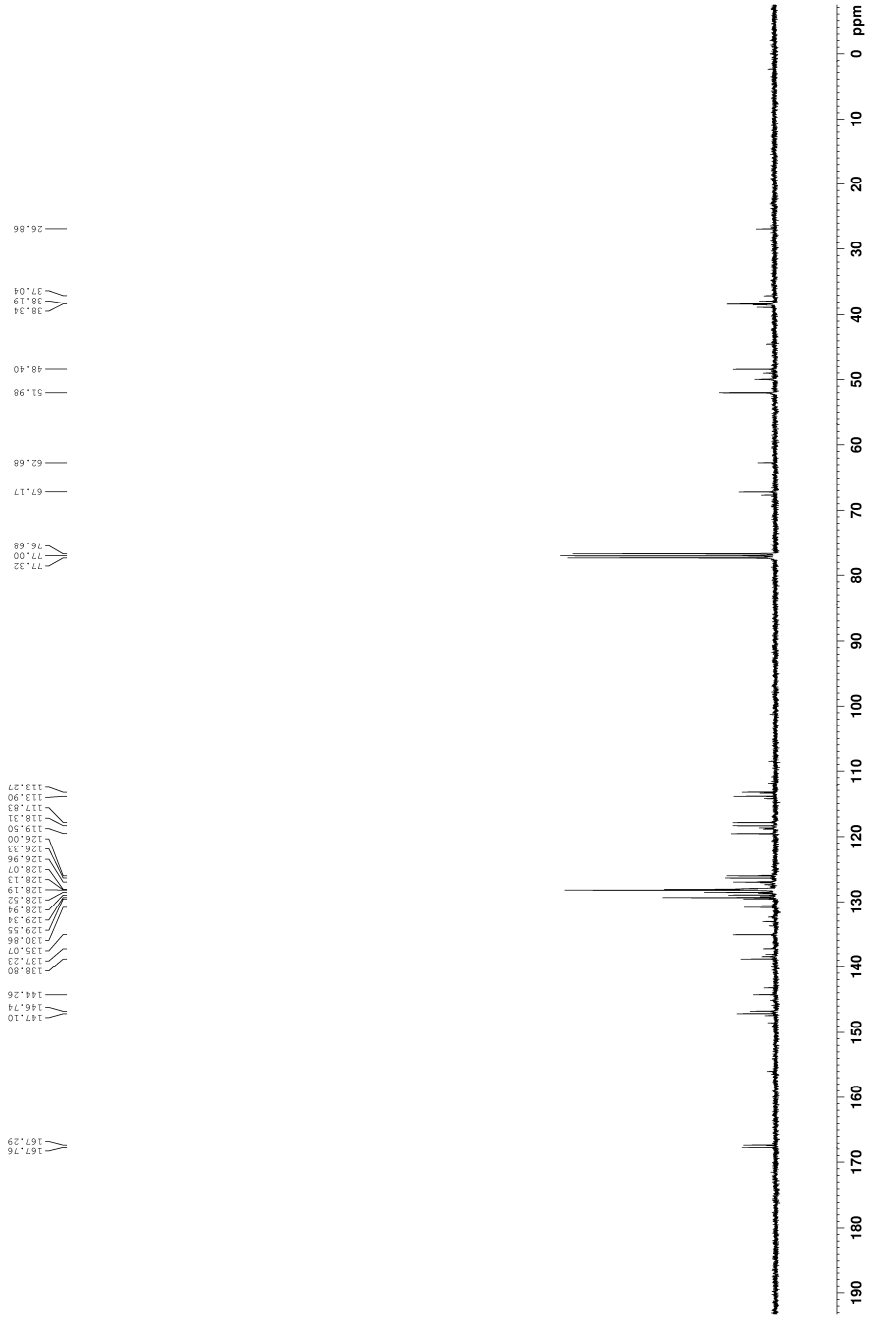

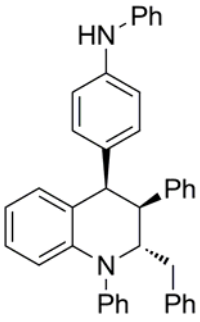

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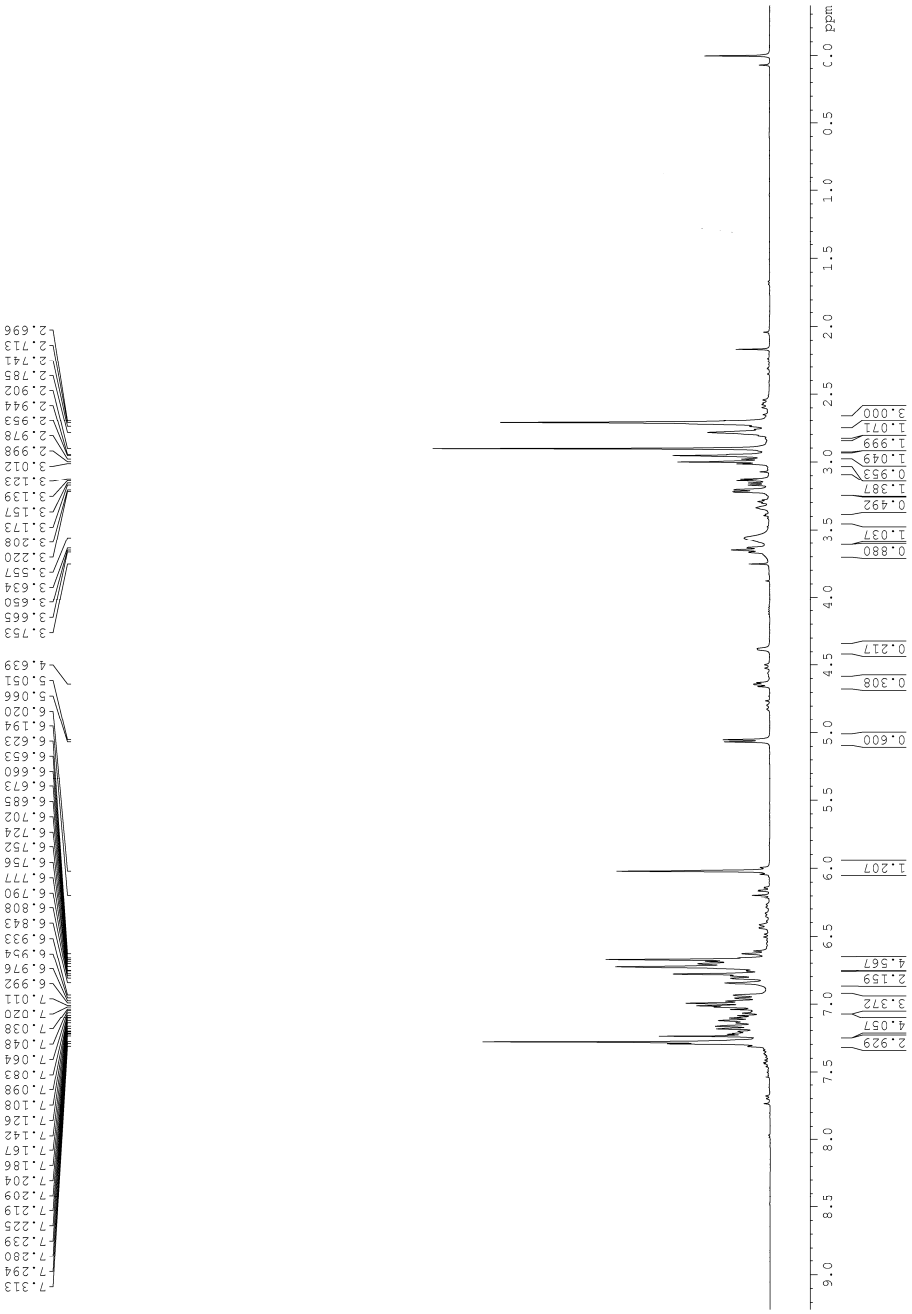

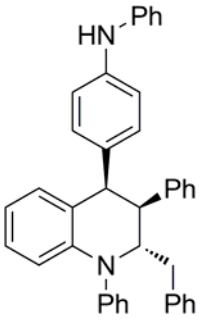

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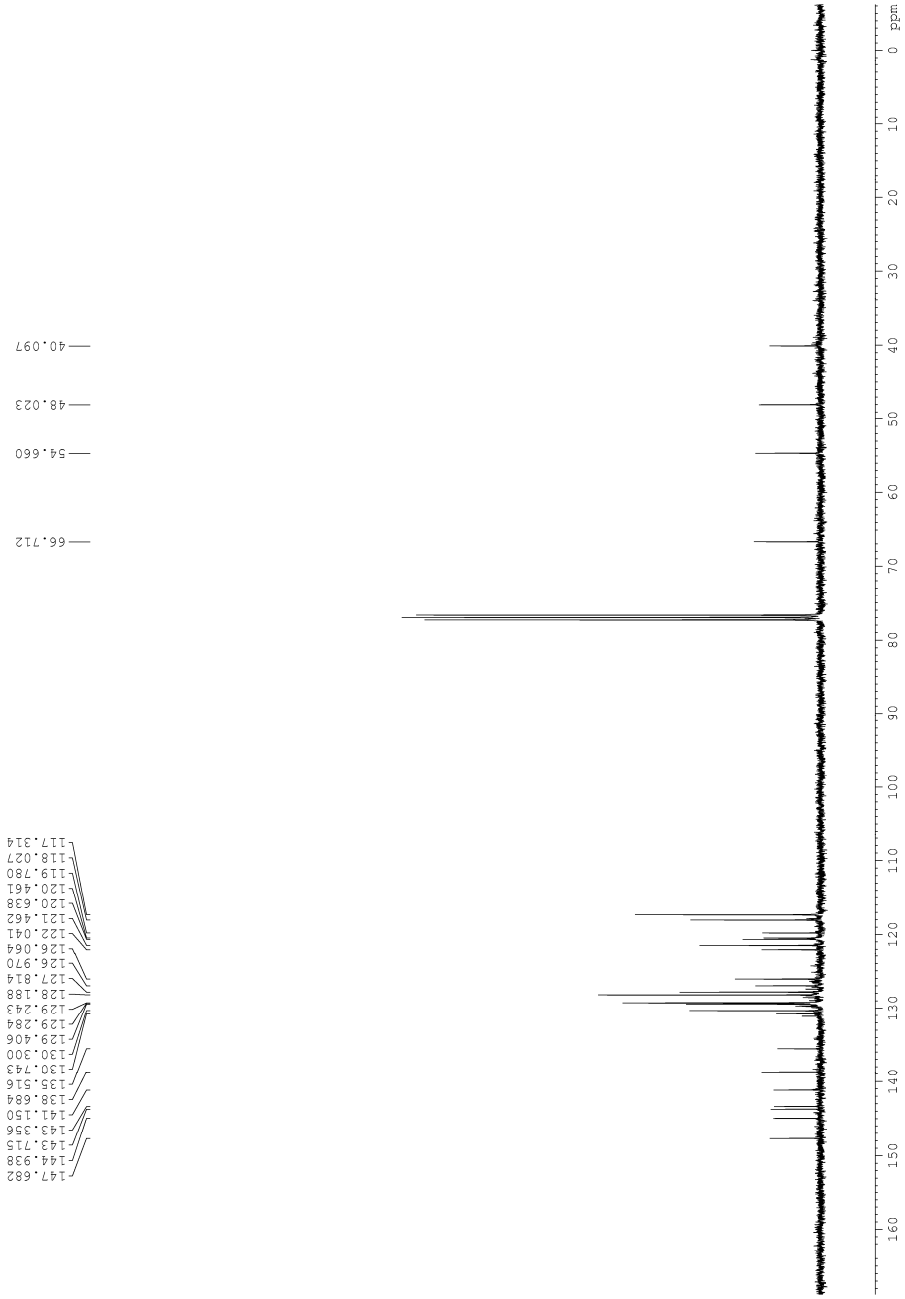

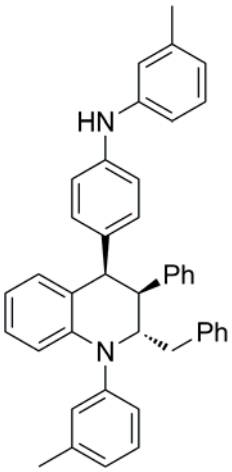

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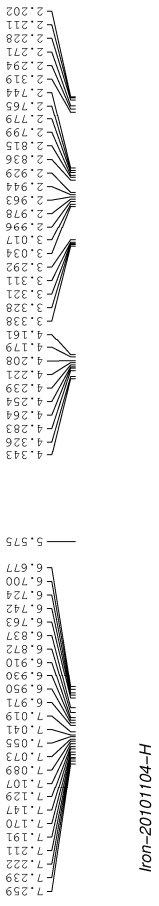

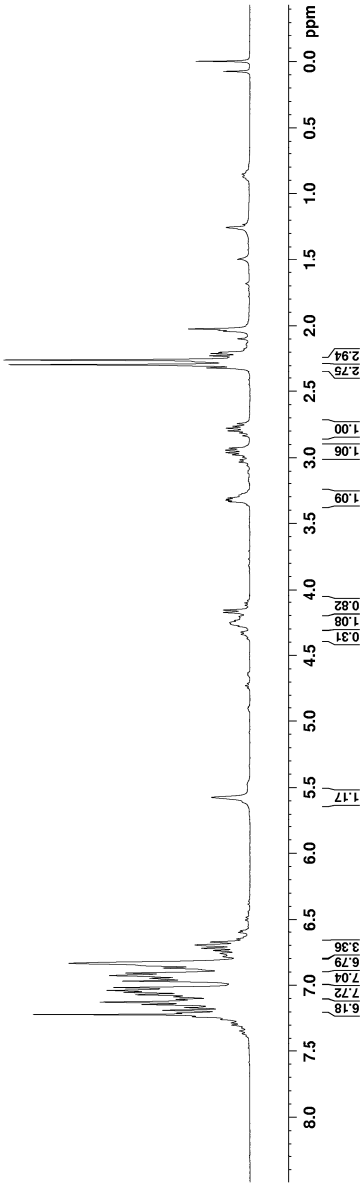

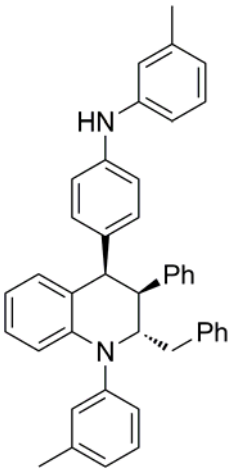

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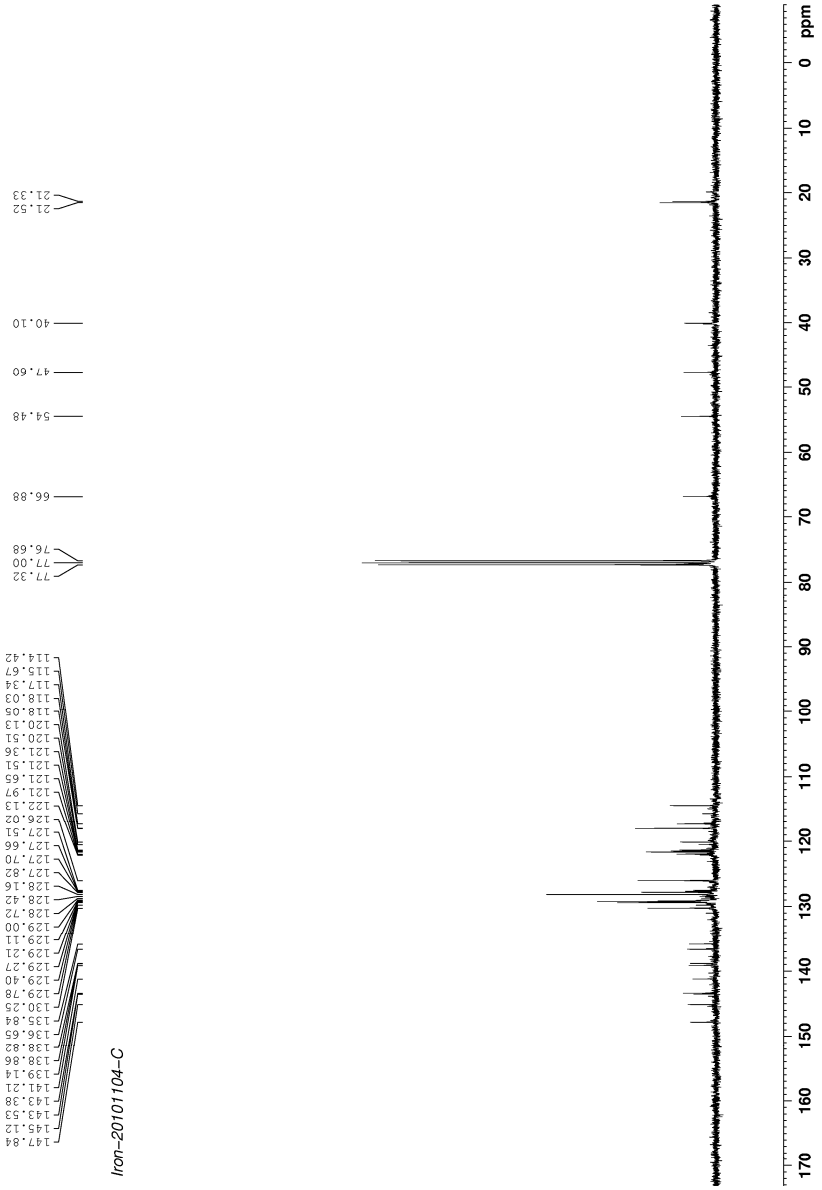

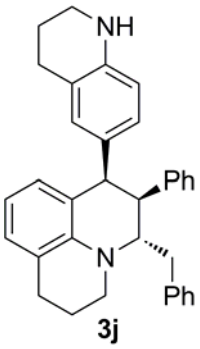

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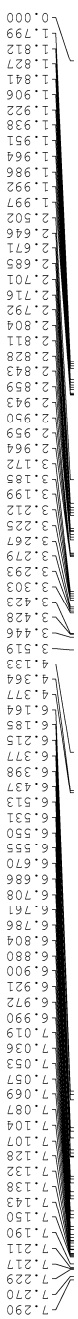

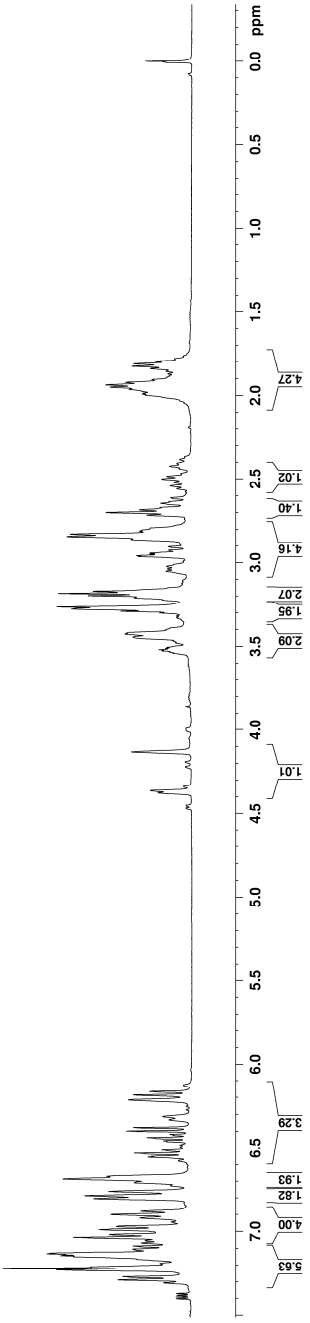

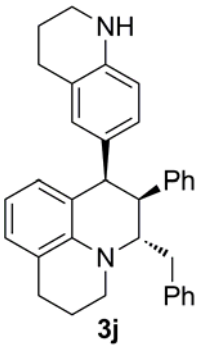

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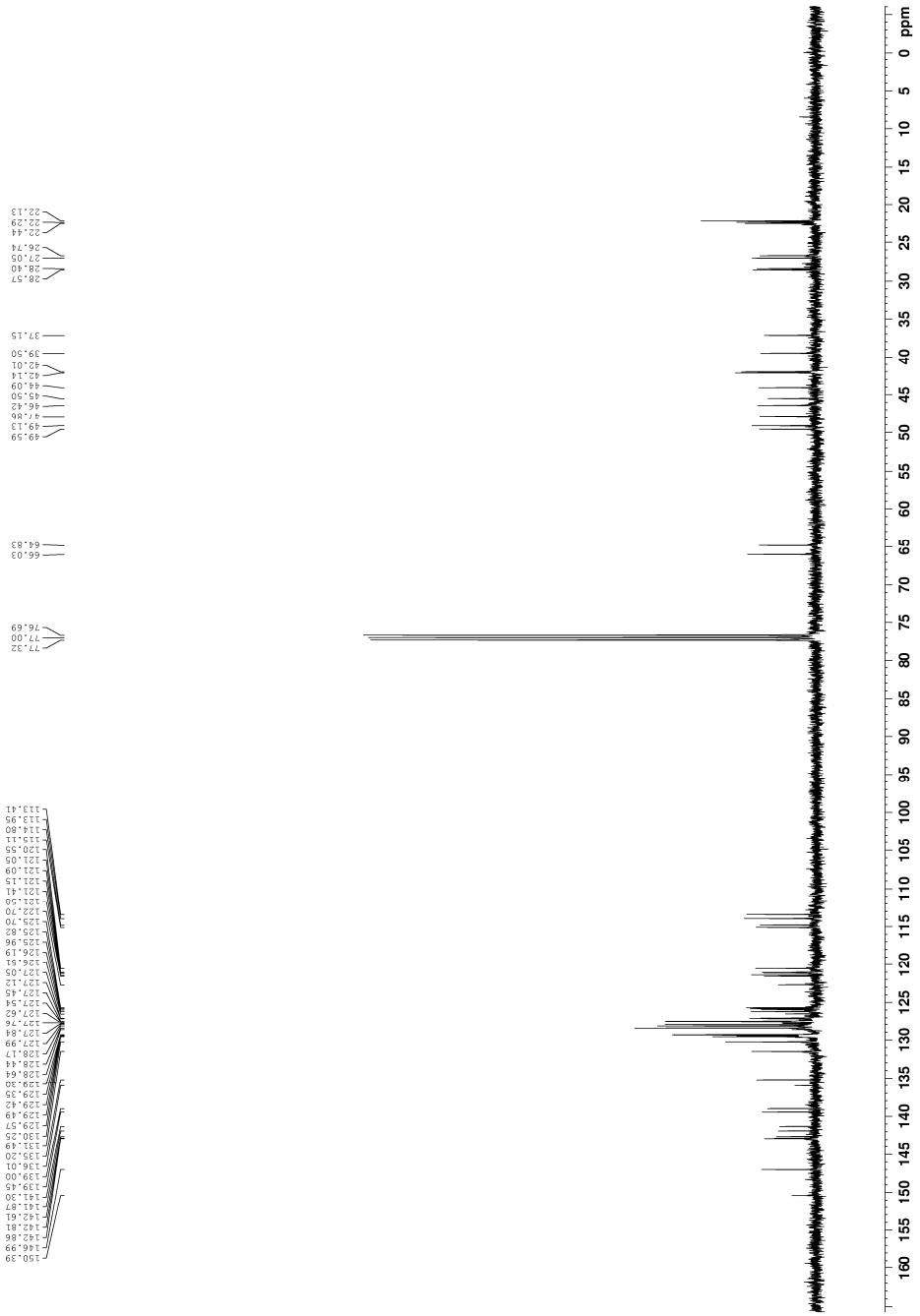

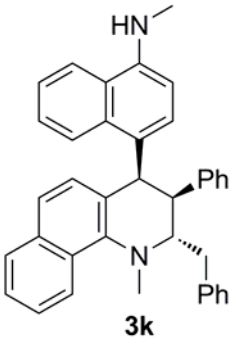

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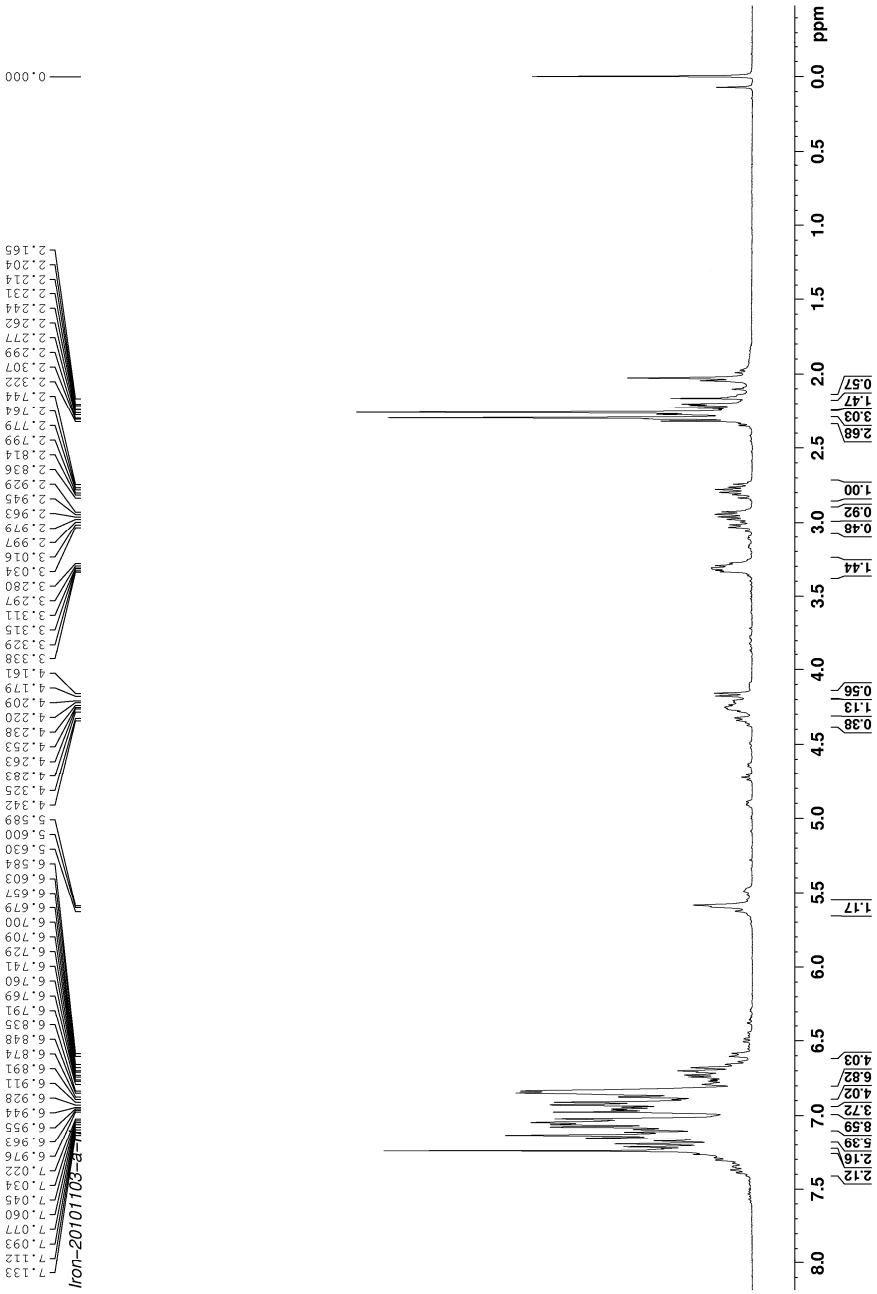

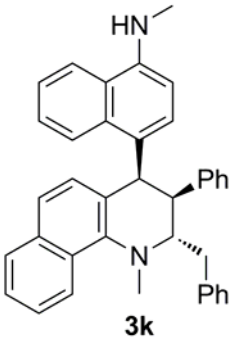

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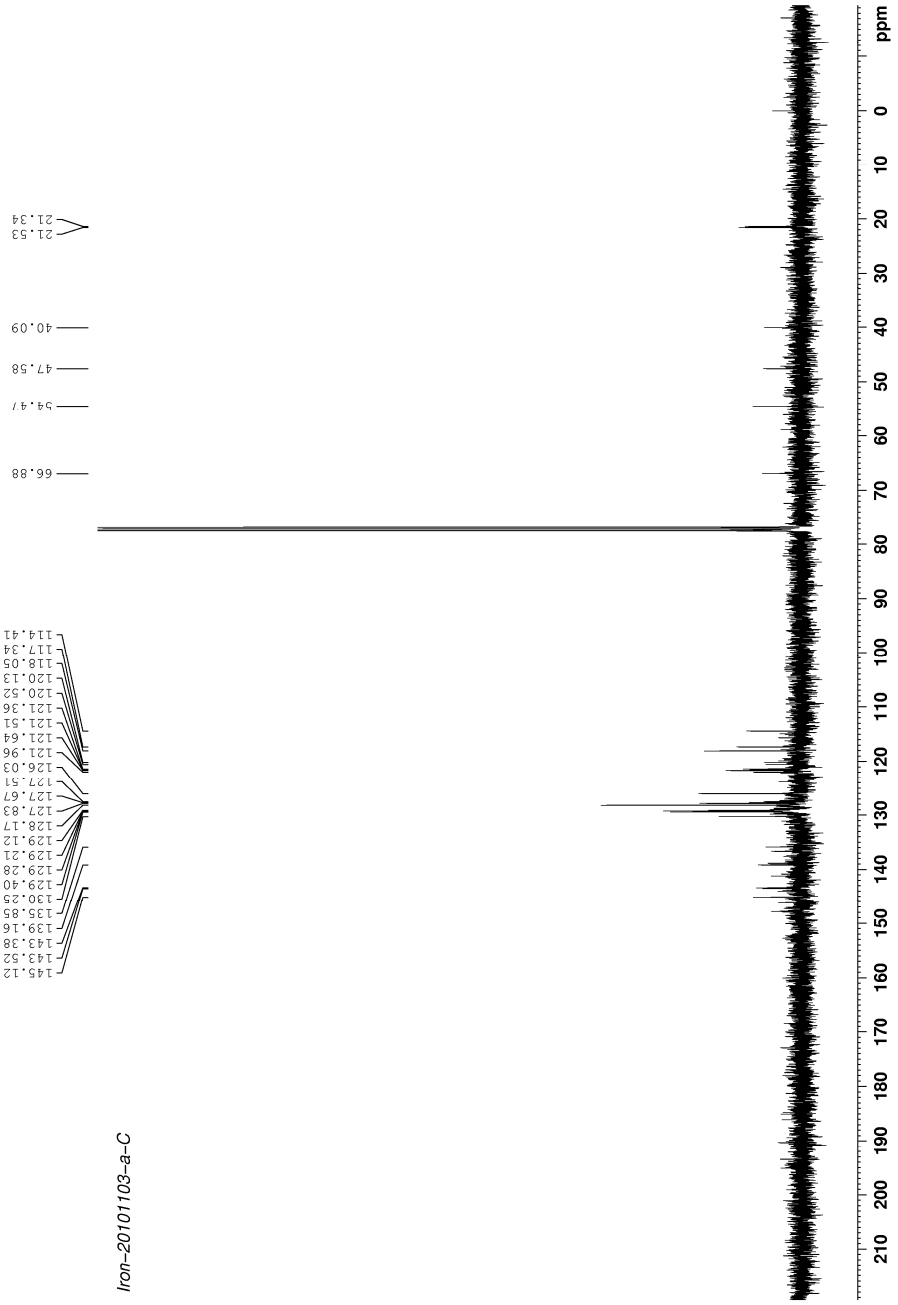

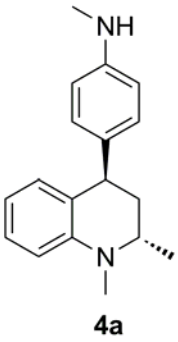

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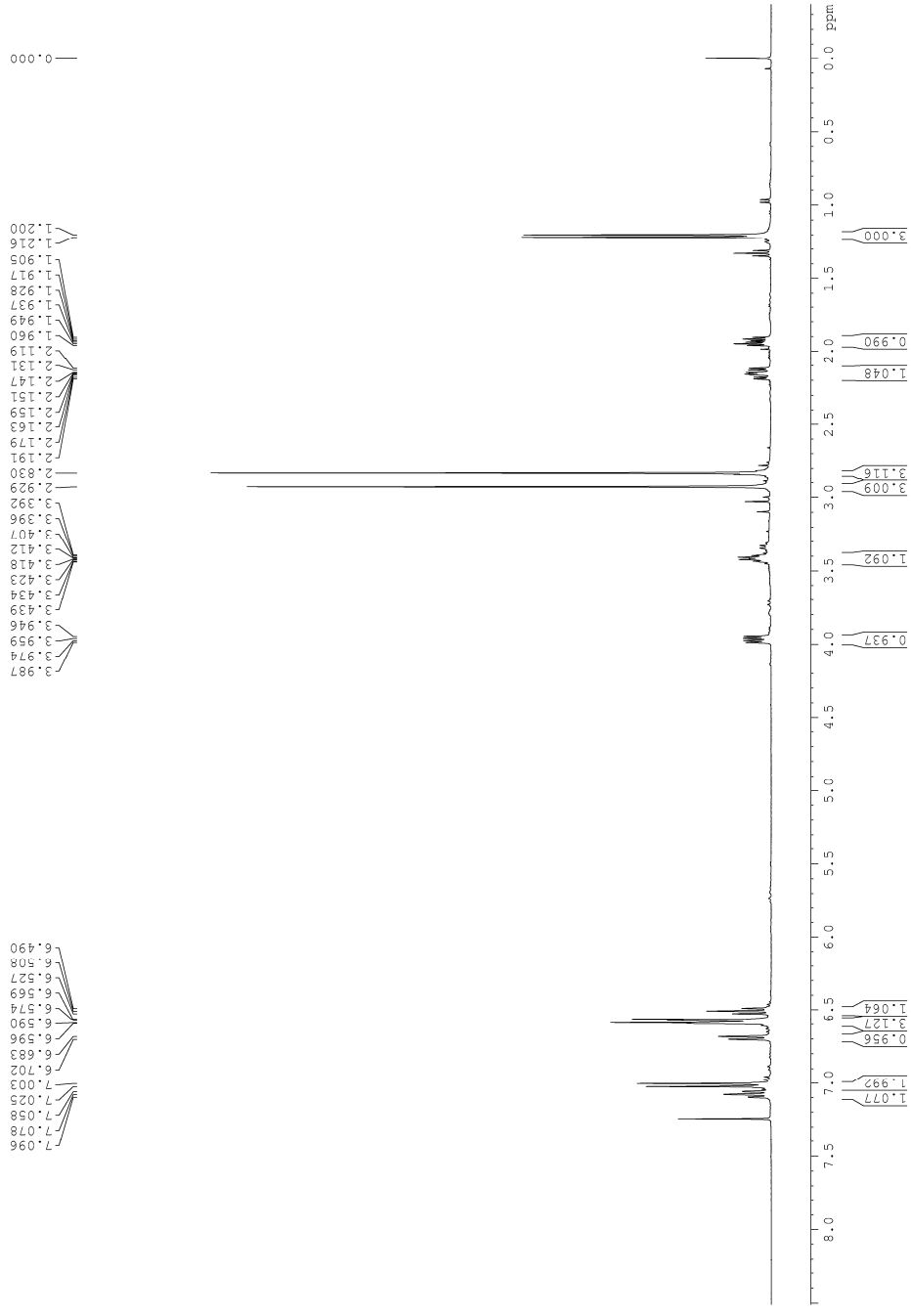

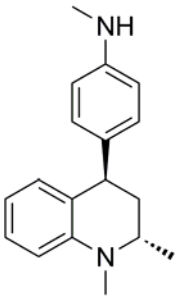

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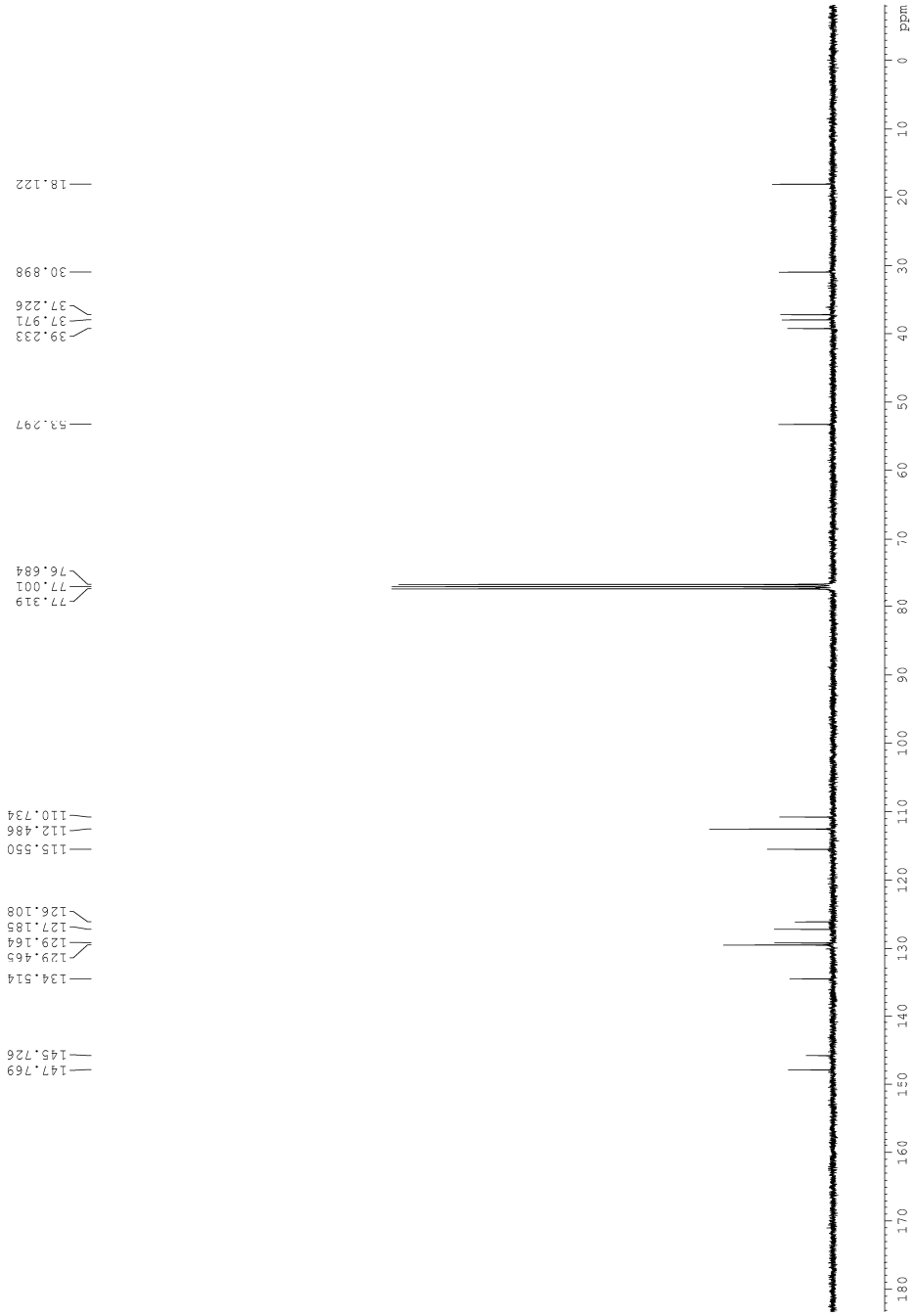

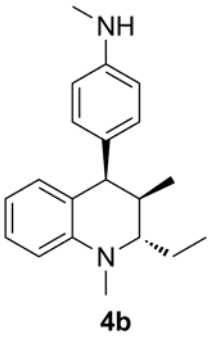

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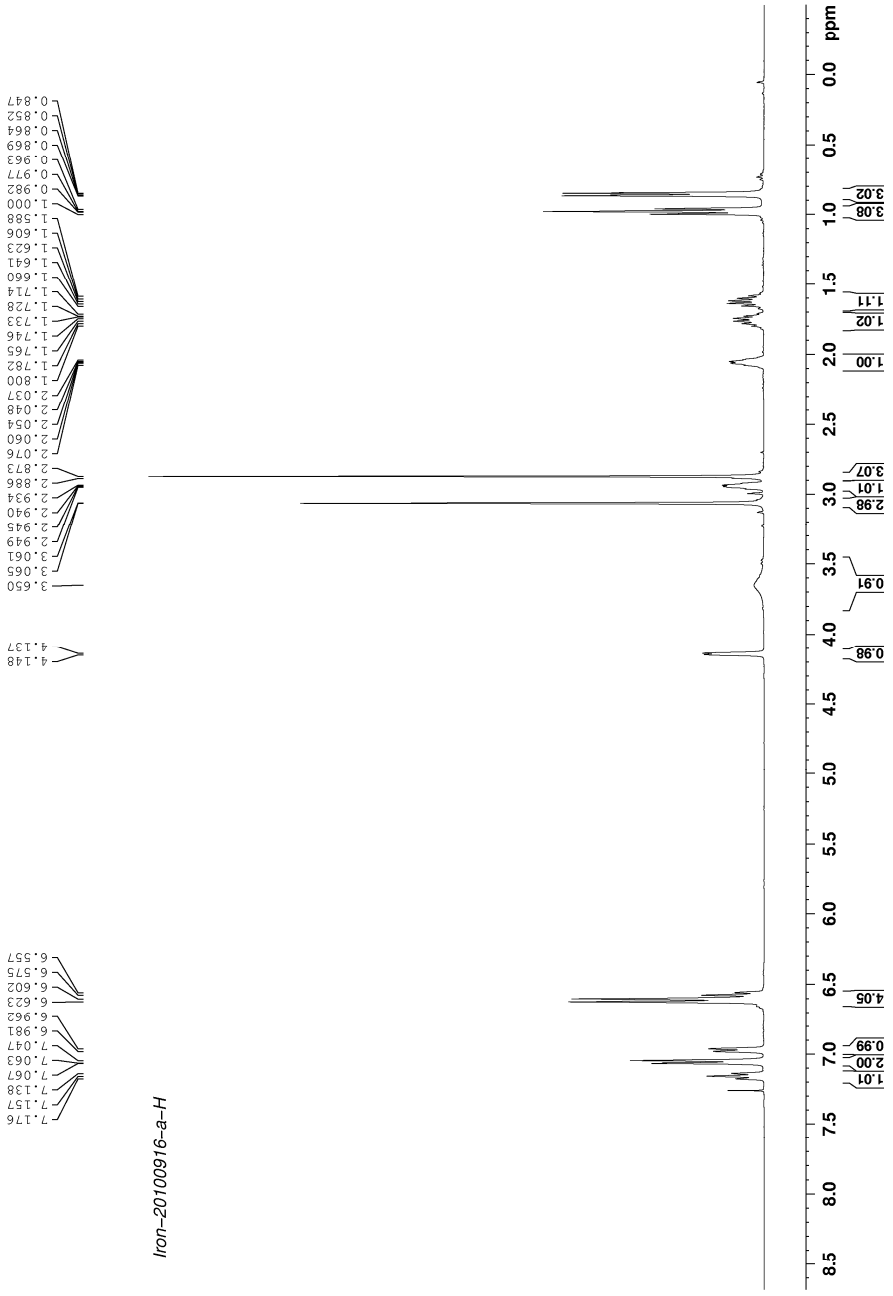

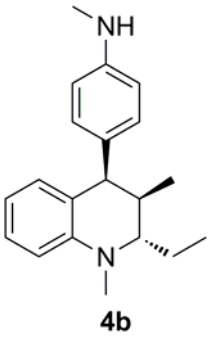

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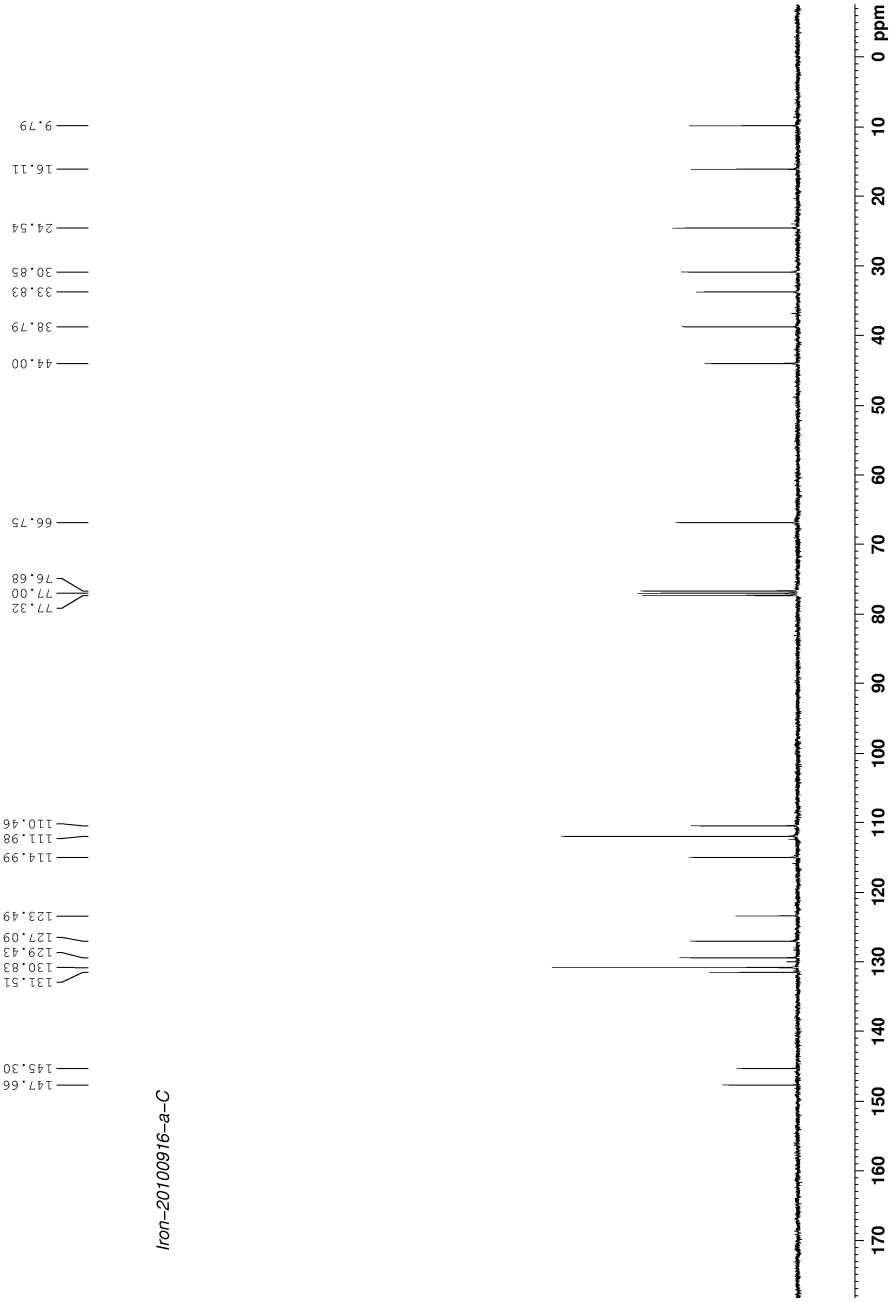

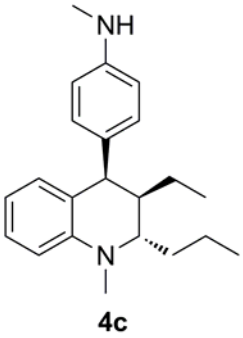

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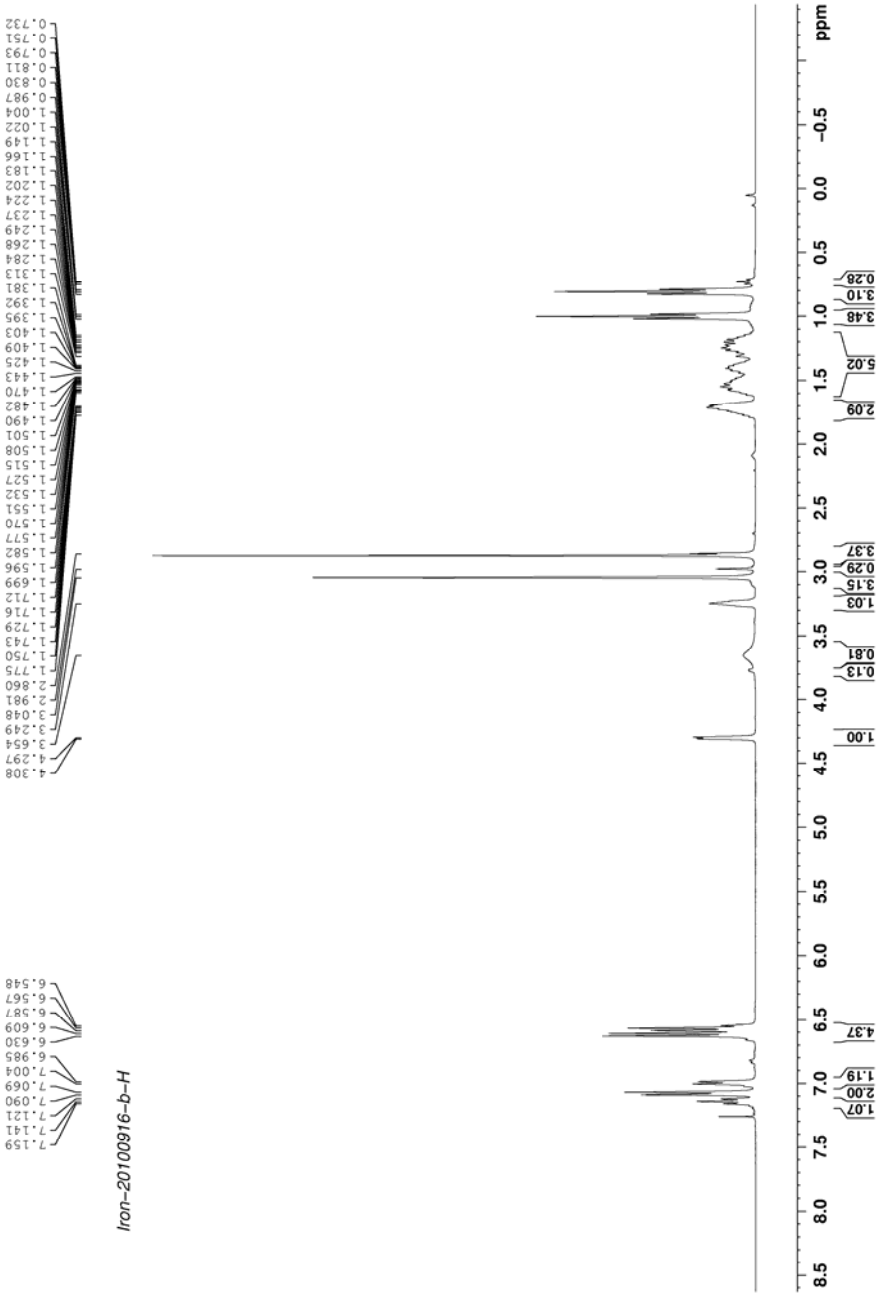
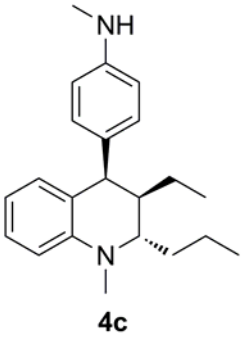
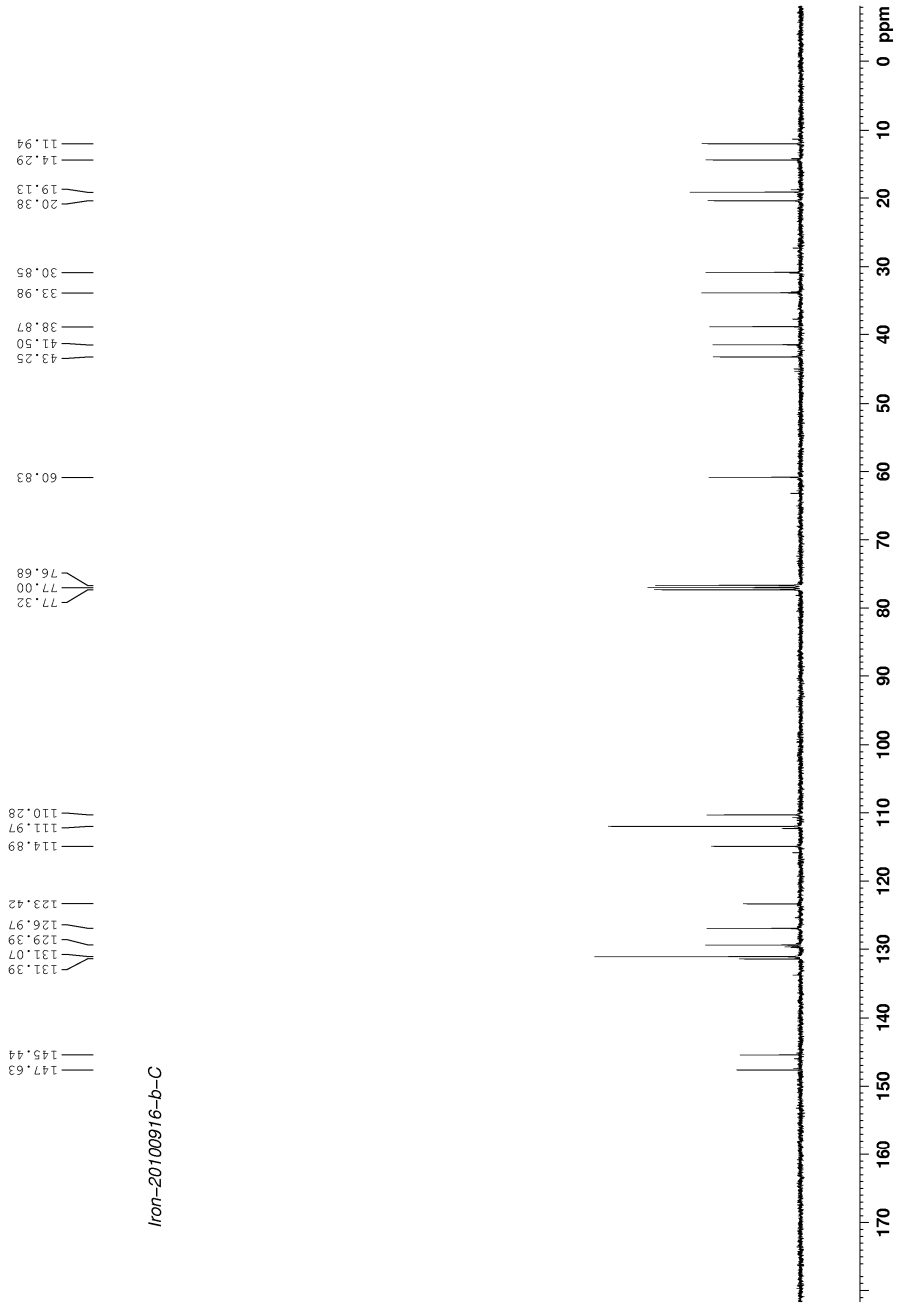



NH
N

4c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20.38
30.85
33.98
38.87
41.50
43.25
60.83
76.68
77.00
77.32
110.28
111.97
114.89
123.42
126.97
129.39
131.07
131.39
145.44
147.63
Iron-20100916-b-C
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120
130
140
150
160
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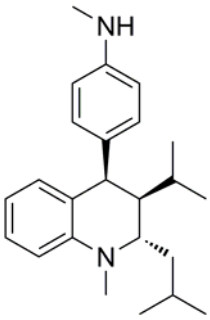
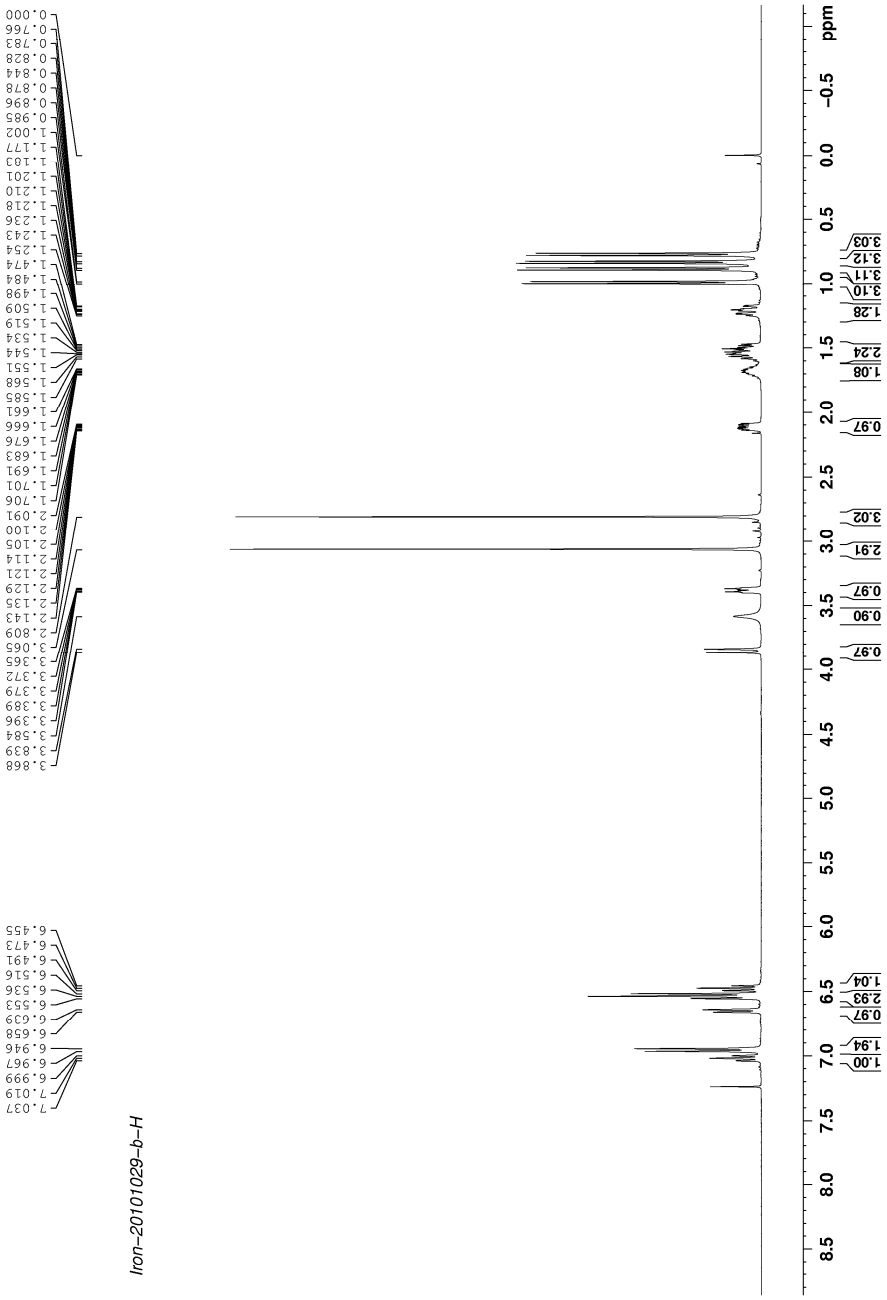
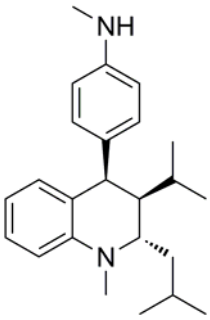


4d



Iron–20101029–b–H



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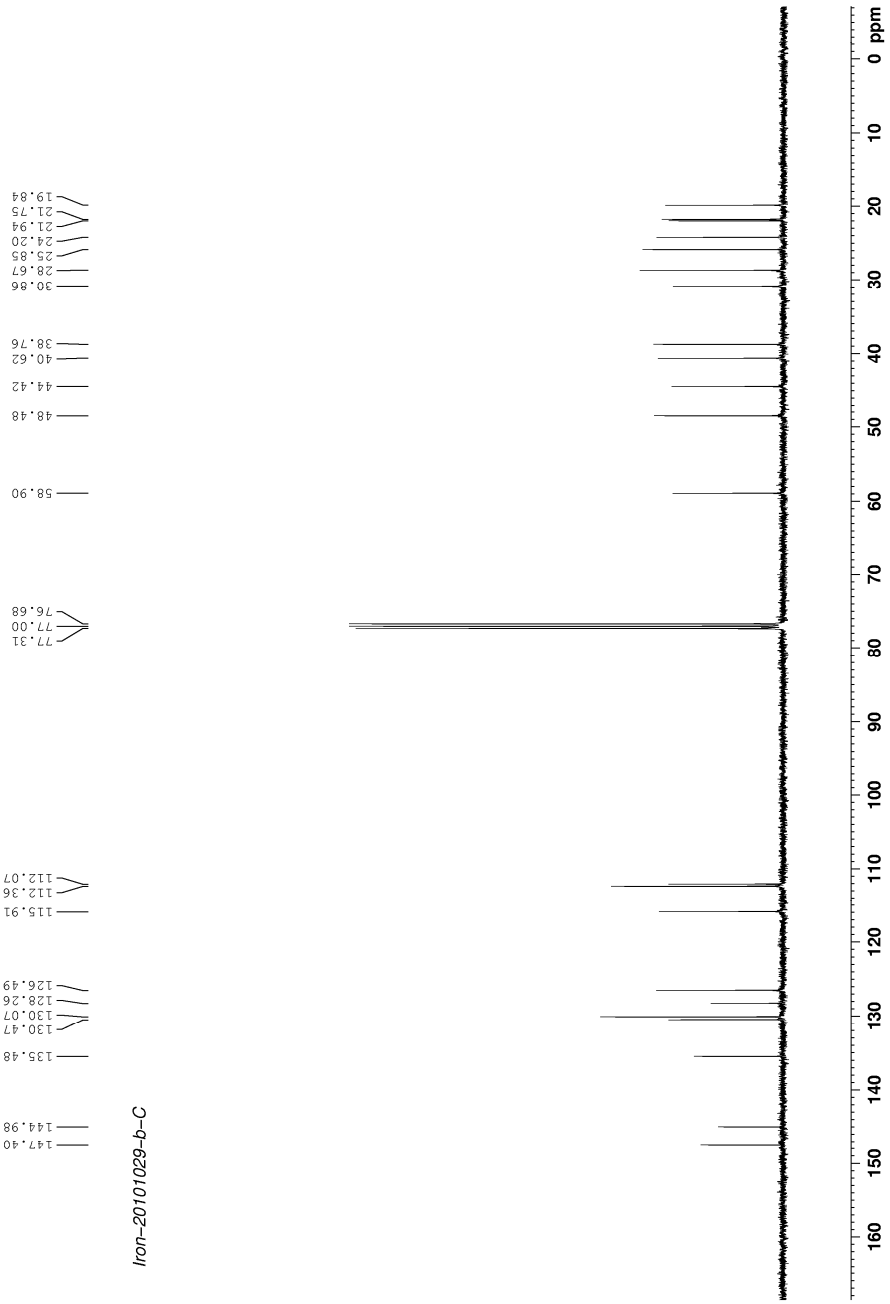

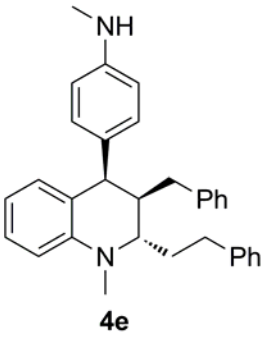

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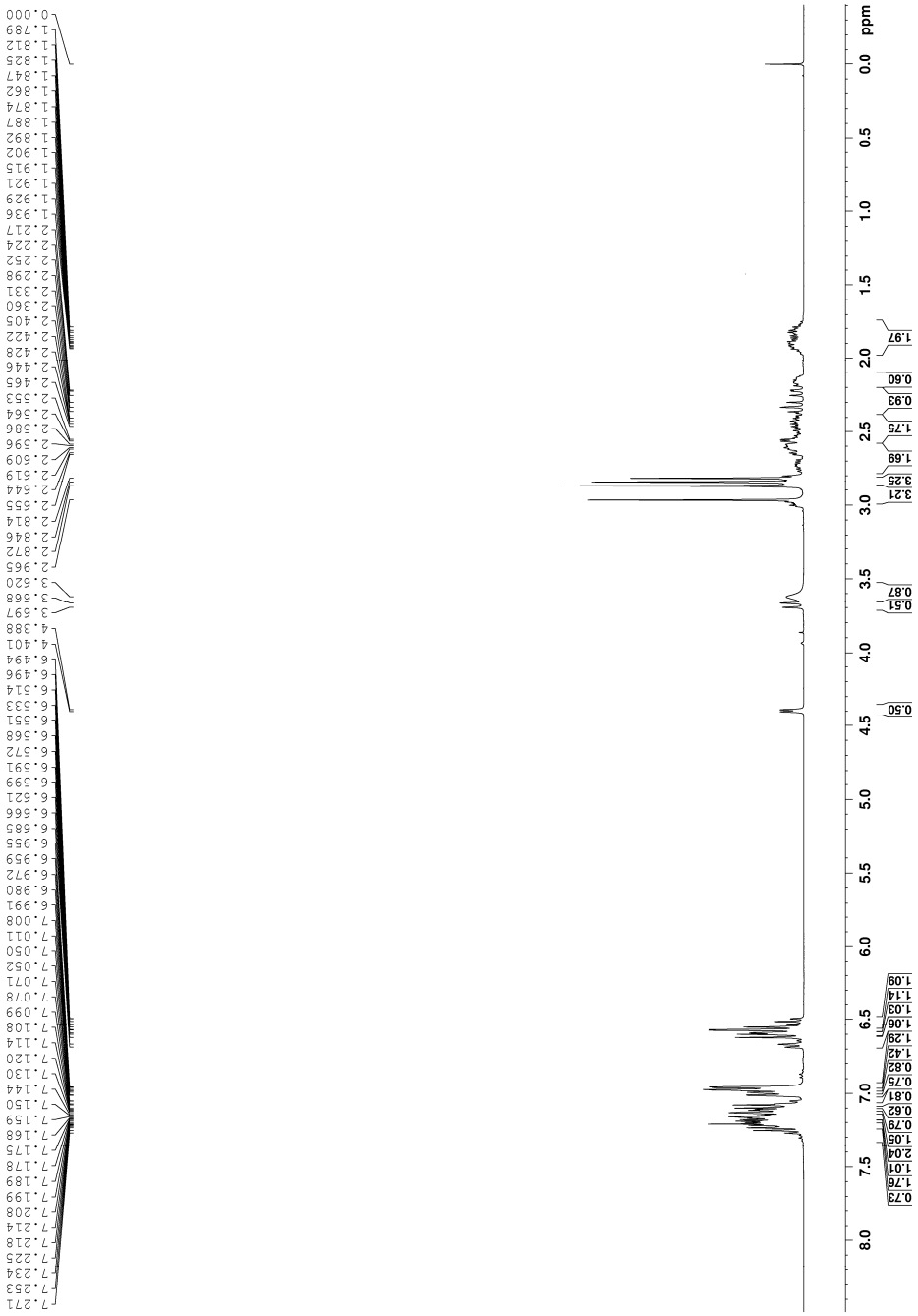
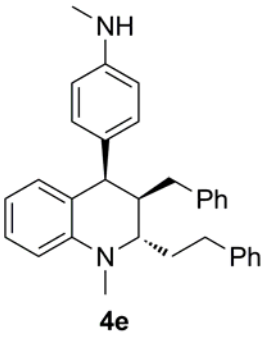
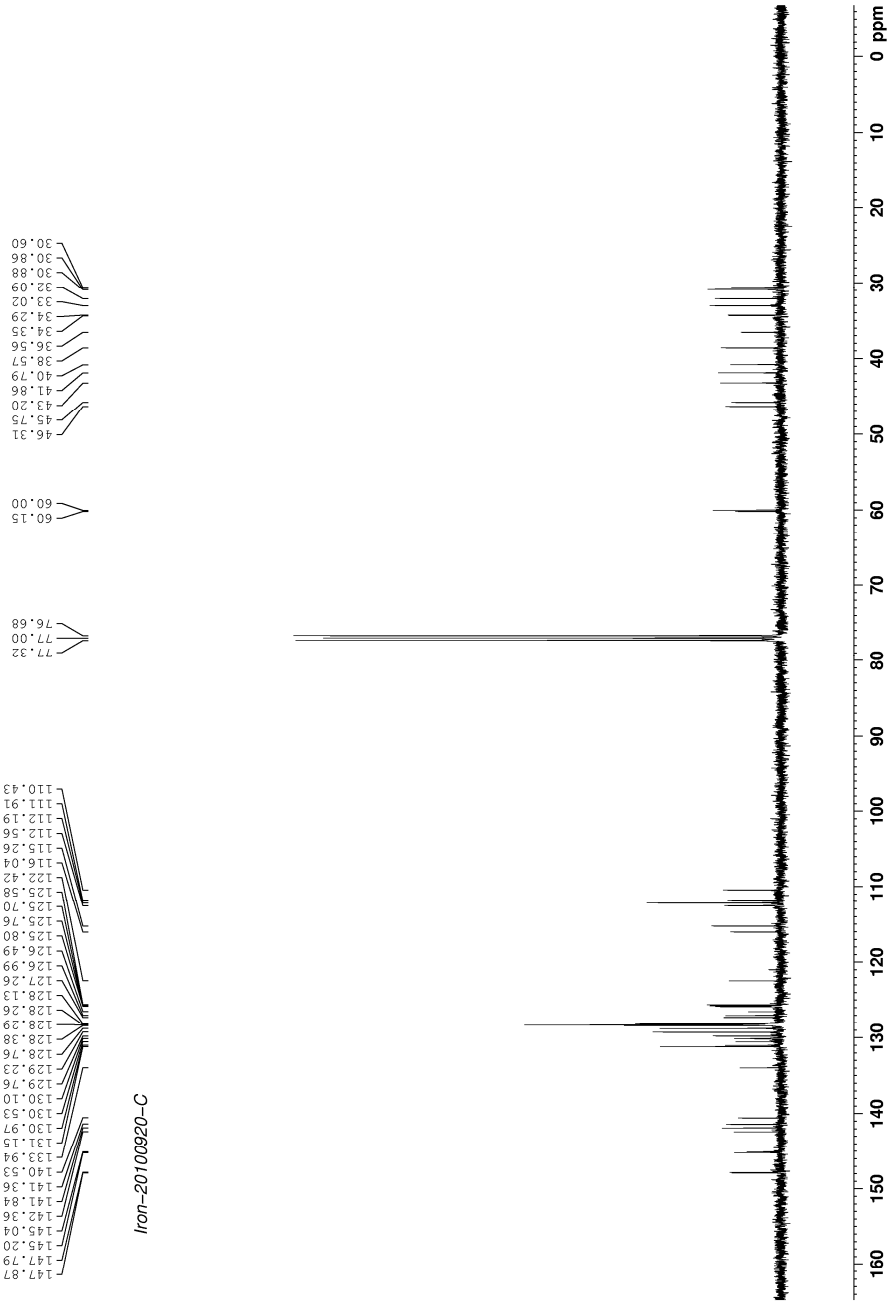
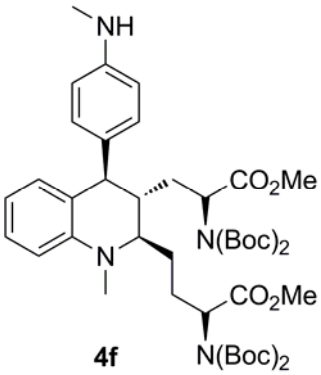


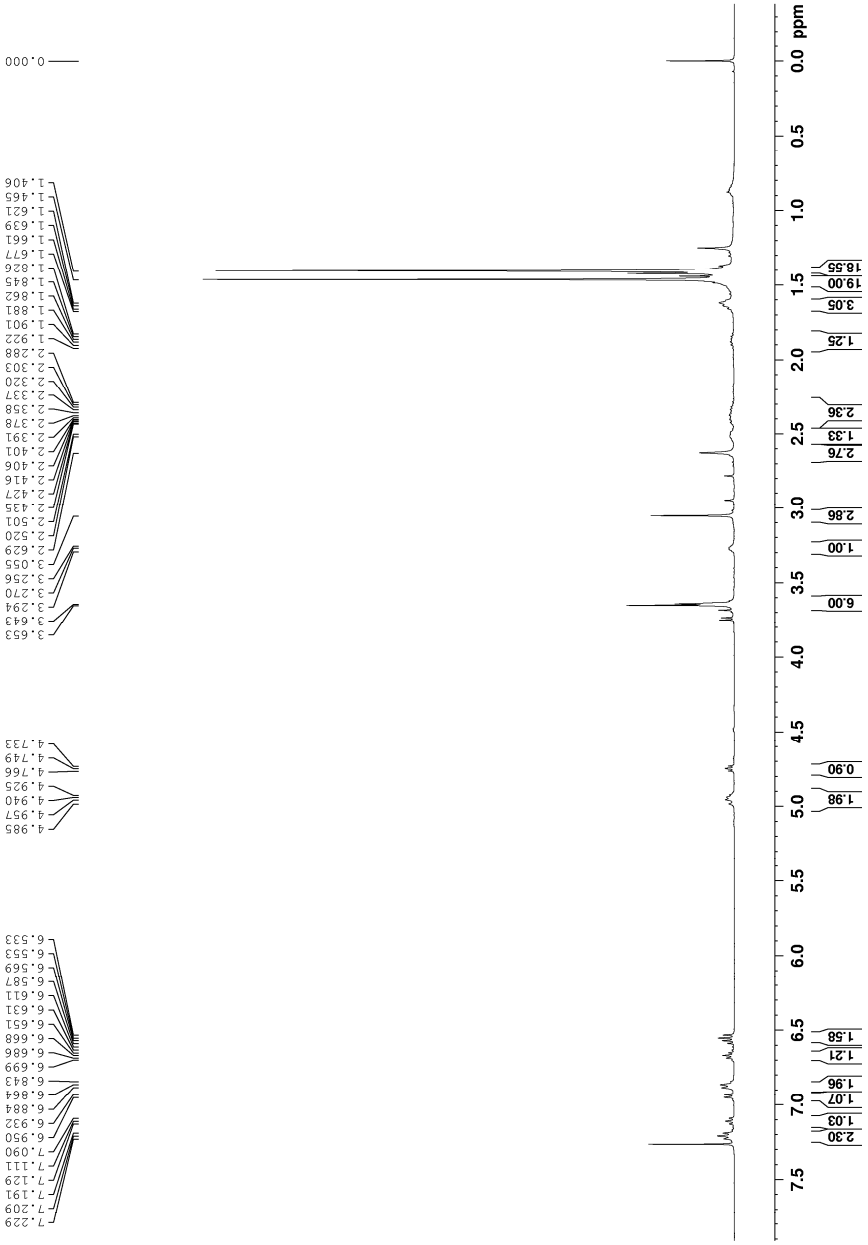


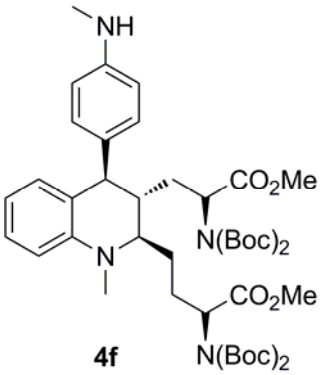
4e



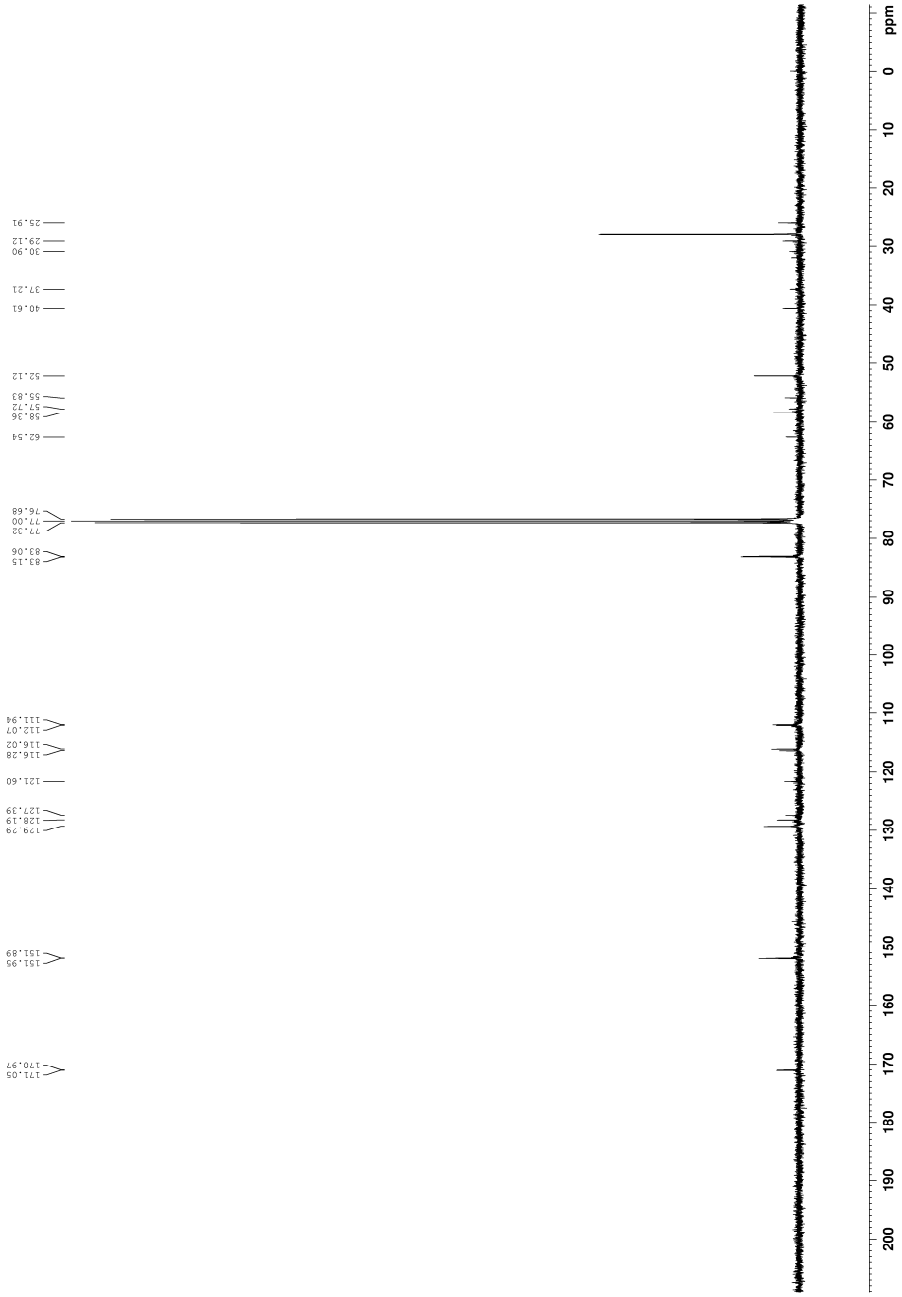


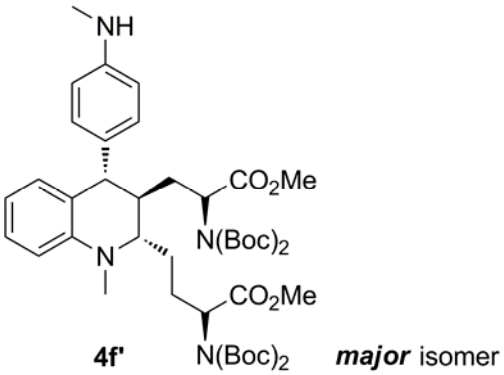
4f ***minor*** isomer



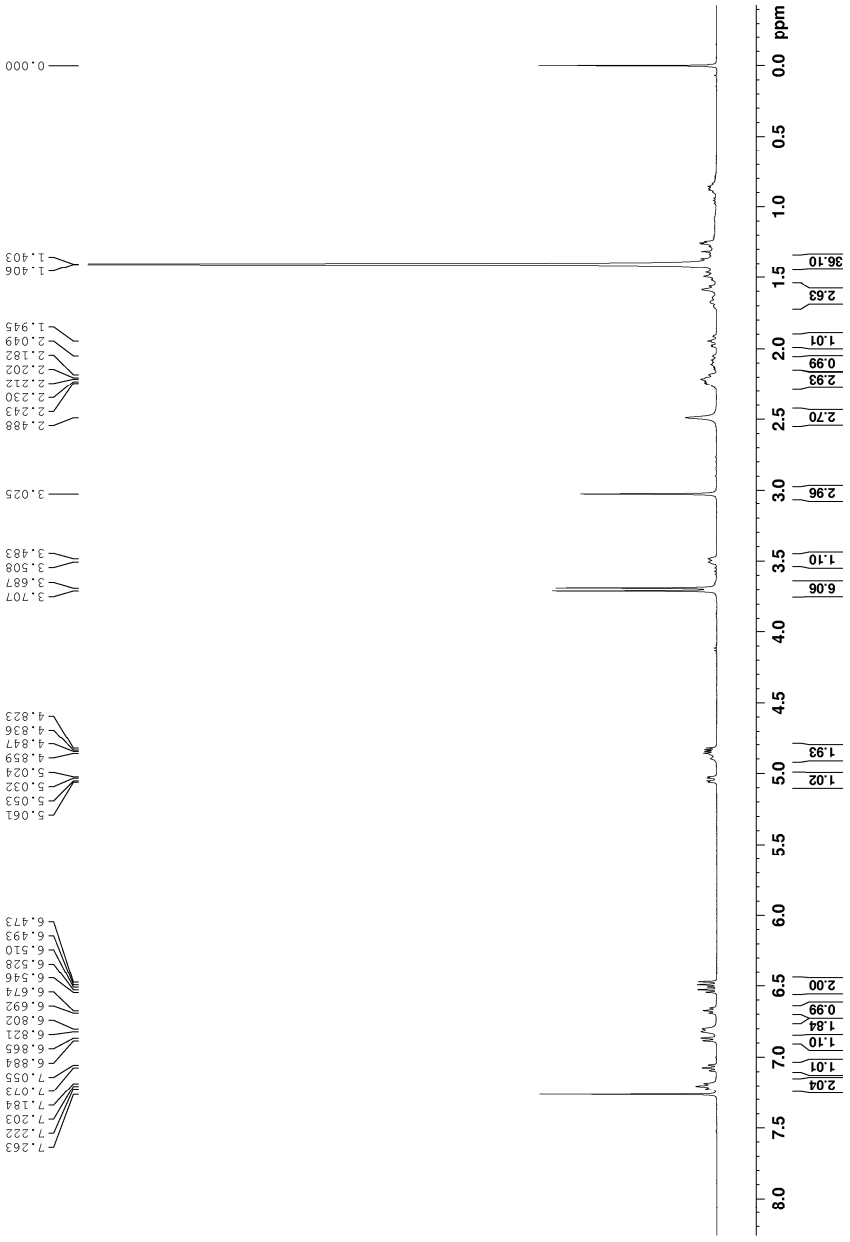


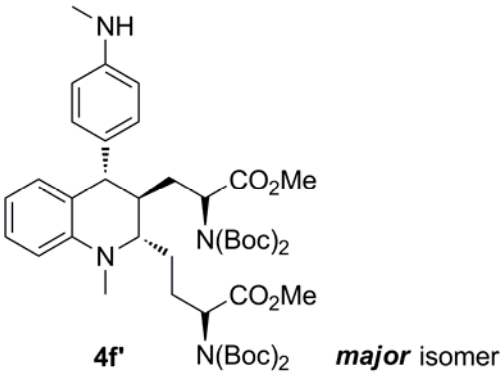
4f ***minor*** isomer



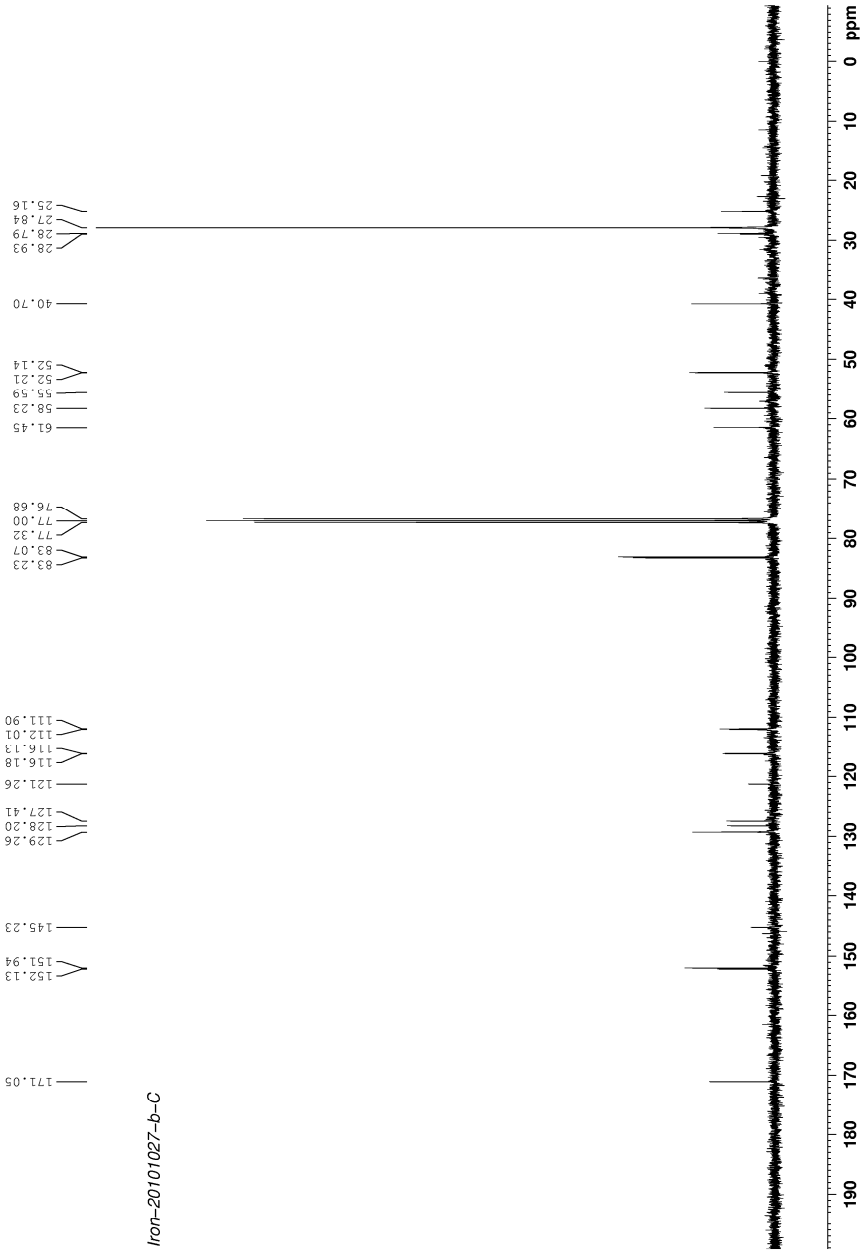


4f' ***major*** isomer

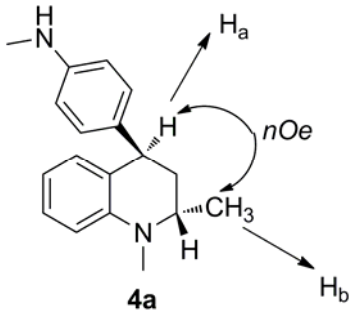




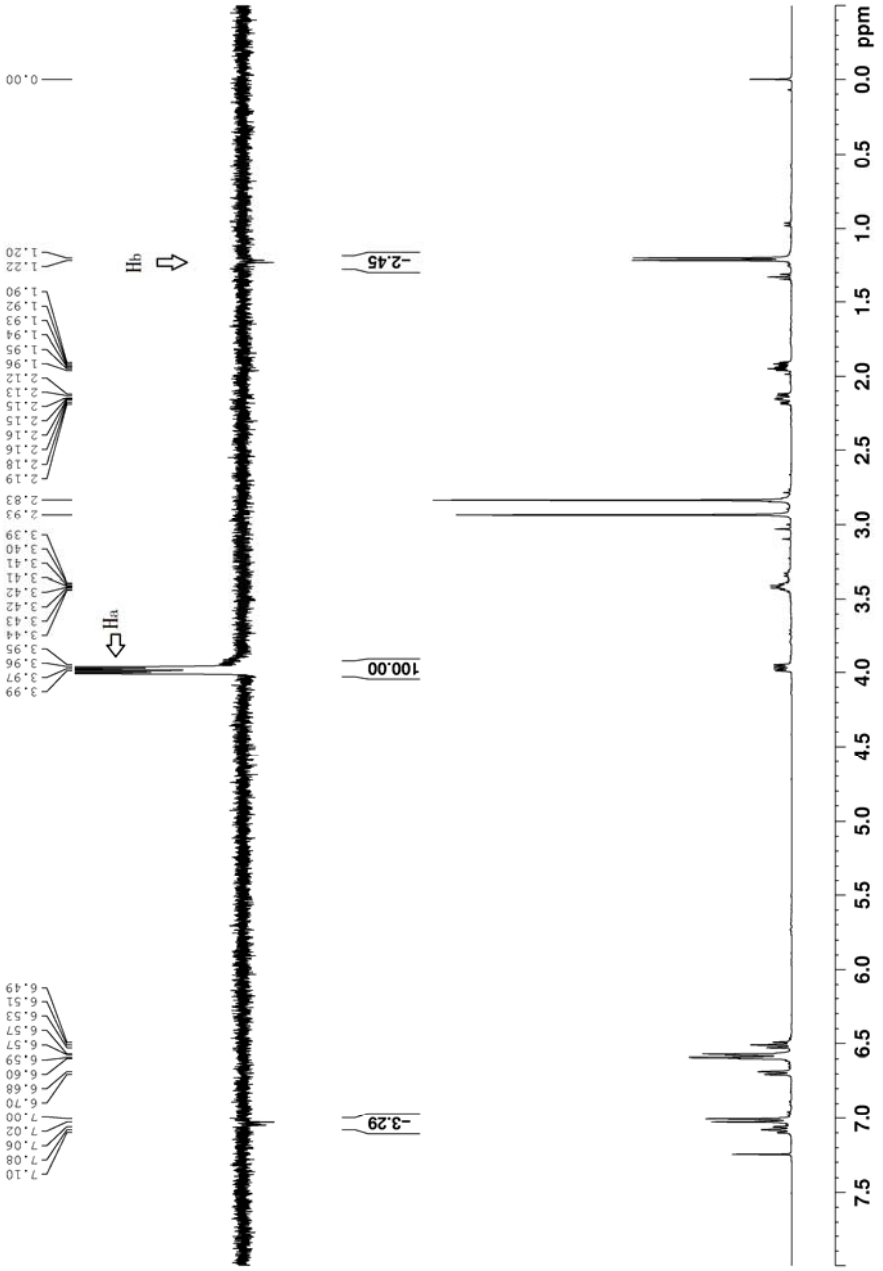
4f' ***major*** isomer

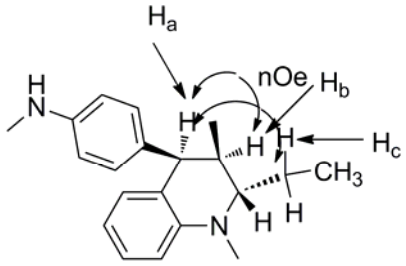


6. NOE spectra for compounds 4a, 4b, 4f and 4f′:

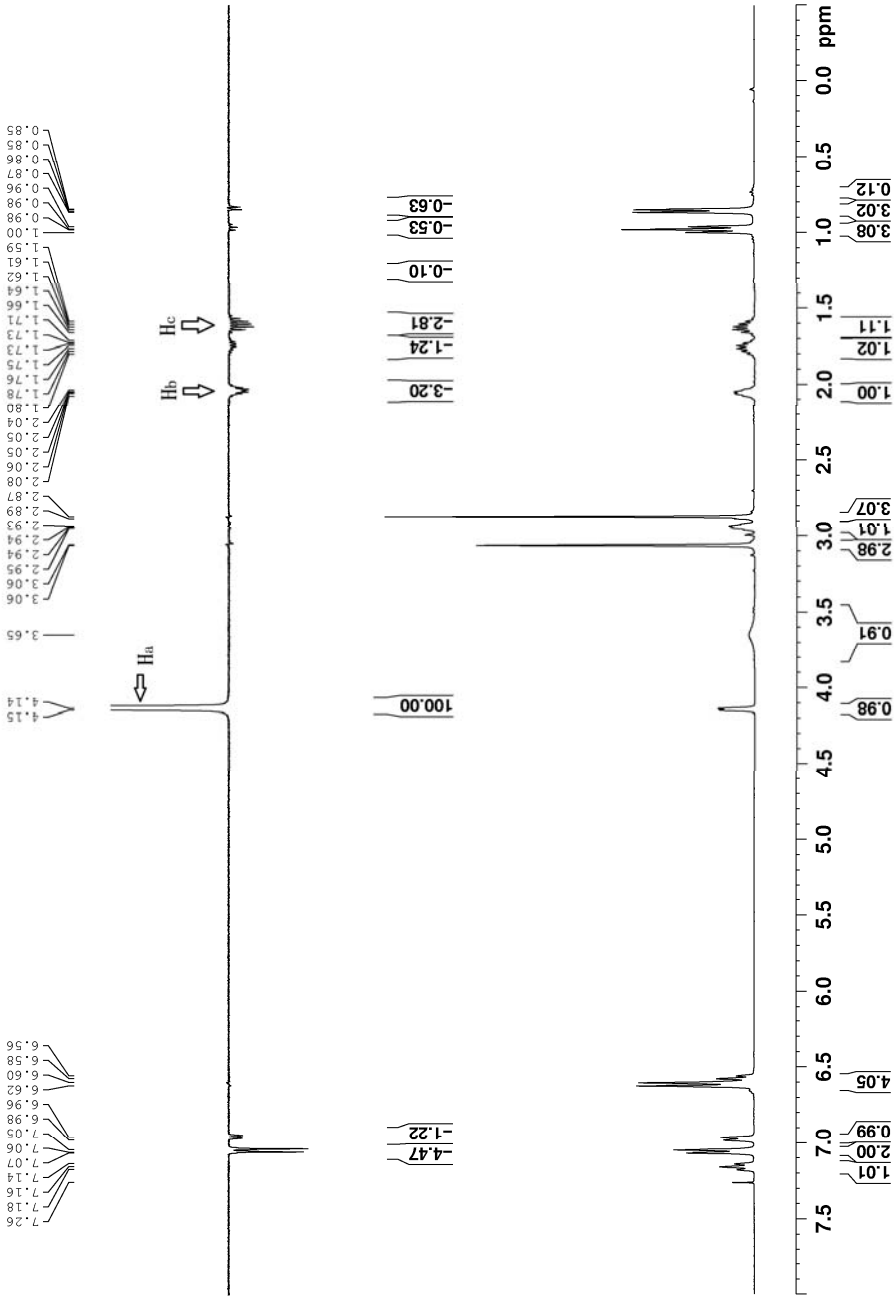


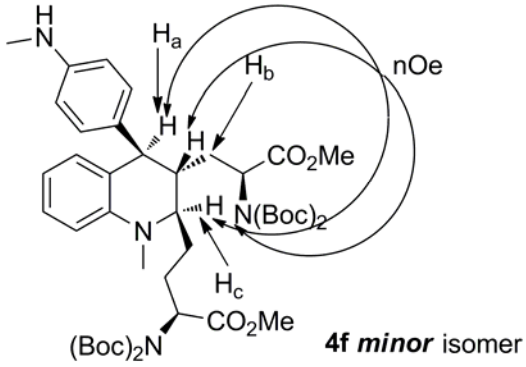
4a



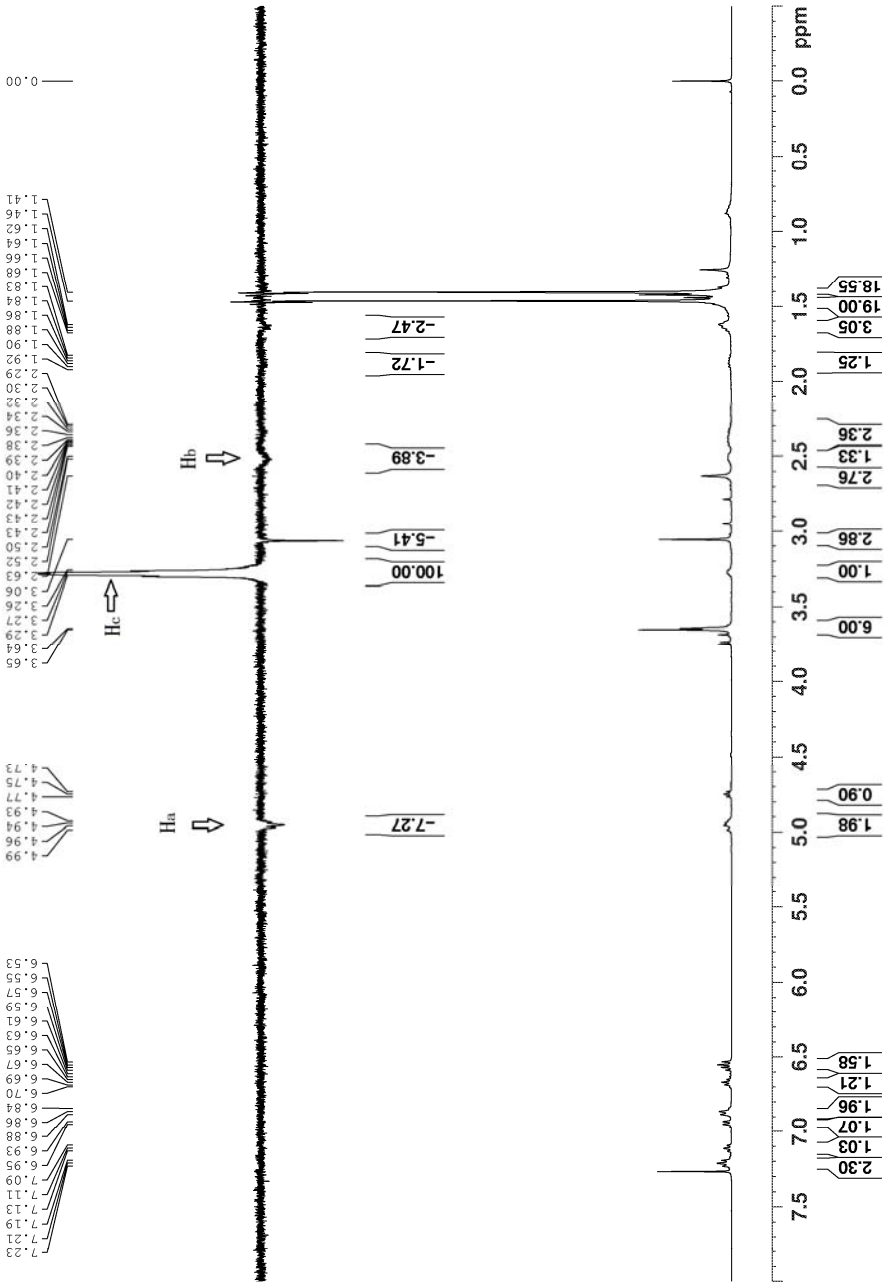


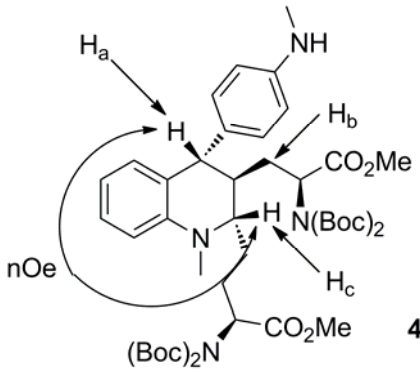
4b



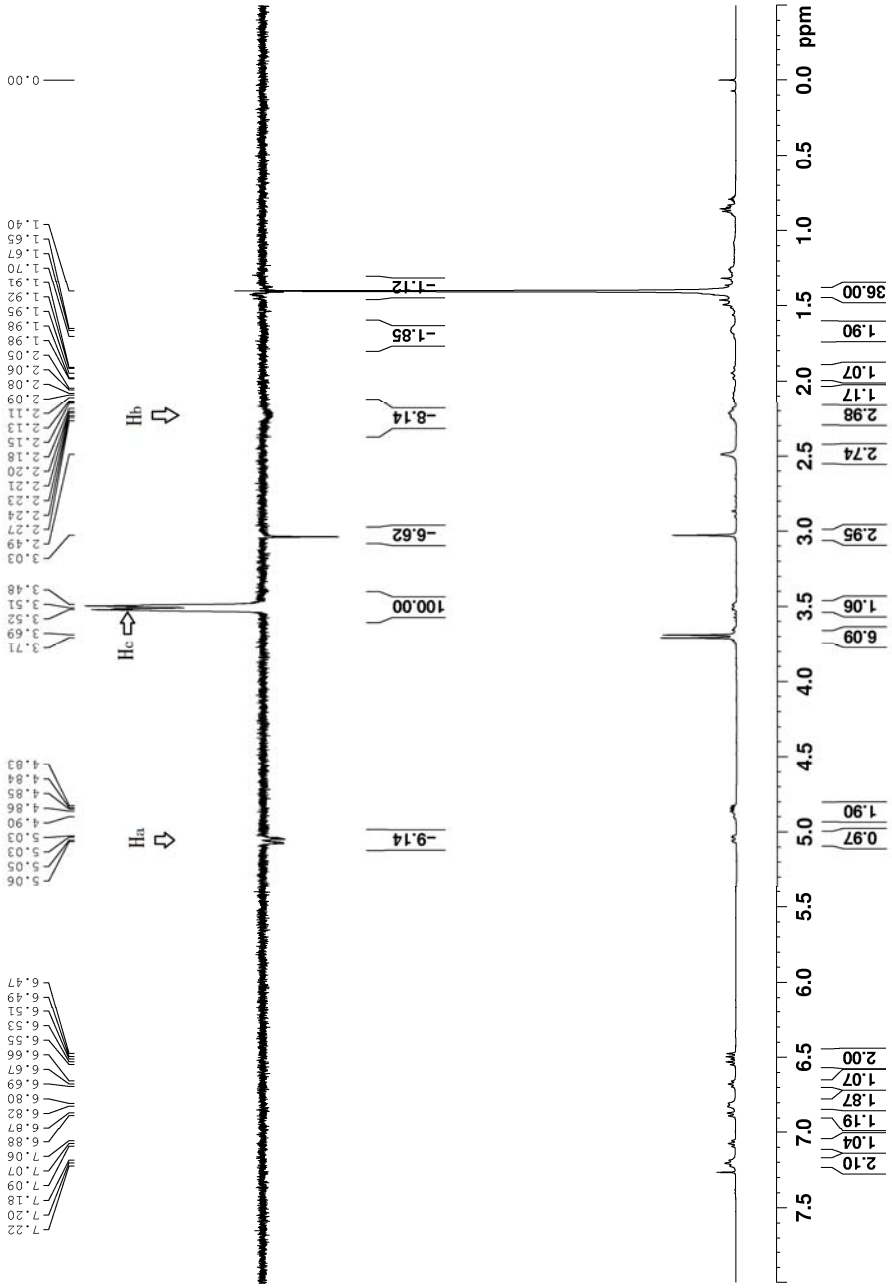


4f *minor* isomer





4f' *major* isomer



7. Copies of HPLC spectra for product 4f and 4f′:

Data File C:\HPCHEM\1\DATA\YANGMING\YM000317.D Sample Name: yangyanfang-rac1
IC hex:ipr:DEA=98:1.9:0.1 1ml/min

```
Injection Date  : 1/17/2011 9:04:41 PM
Sample Name     : yangyanfang-rac1              Location : Vial 1
Acq. Operator   : yangming
Acq. Method     : C:\HPCHEM\1\METHODS\ZHANGQW.M
Last changed    : 1/17/2011 8:48:24 PM by yangming
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\ZHANGQW.M
Last changed    : 1/18/2011 8:19:38 PM by yangming
                  (modified after loading)
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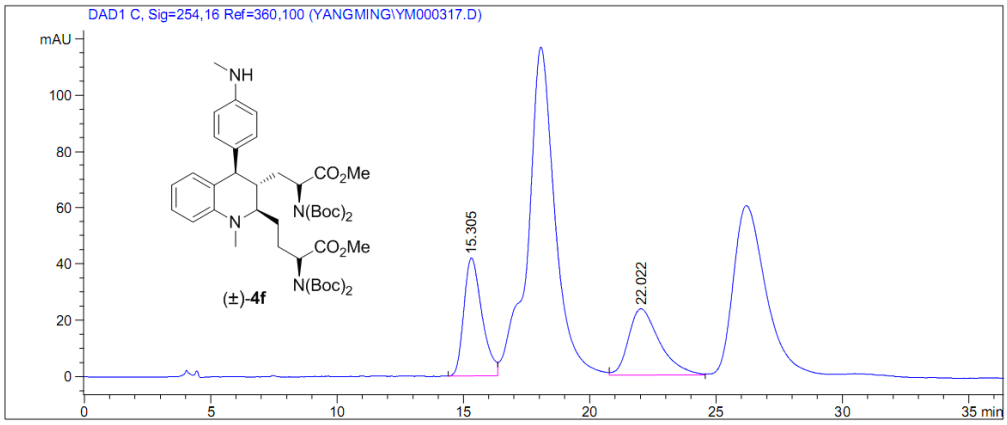


```
                          Area Percent Report

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 C, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  15.305 BV    0.7688 2099.78003   41.88745  50.9055
   2  22.022 VB    1.2500 2025.08032   23.57991  49.0945

Totals :                  4124.86035   65.46736

 Results obtained with enhanced integrator!

                          Summed Peaks Report

Signal 1: DAD1 C, Sig=254,16 Ref=360,100

                       Final Summed Peaks Report

Signal 1: DAD1 C, Sig=254,16 Ref=360,100
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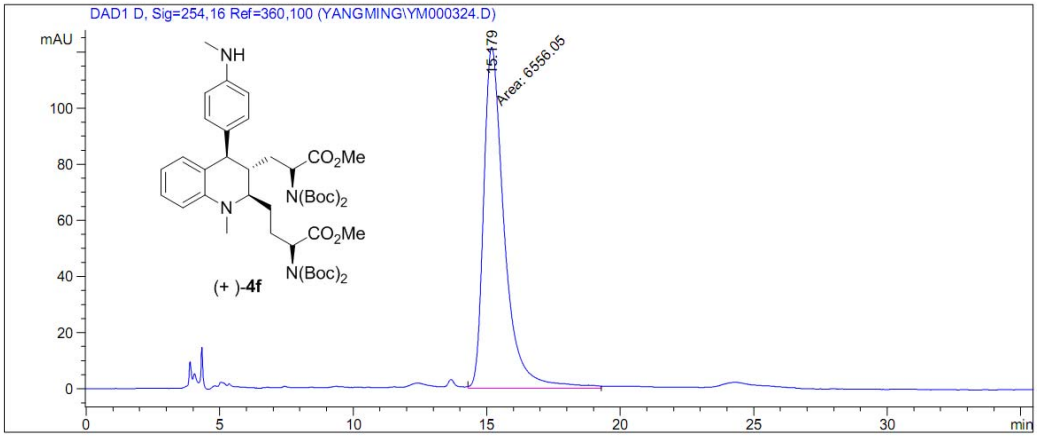
Data File C:\HPCHEM\1\DATA\YANGMING\YM000324.D Sample Name: yangyanfang-1
IC hex:ipr:DEA=98:1.9:0.1 1ml/min

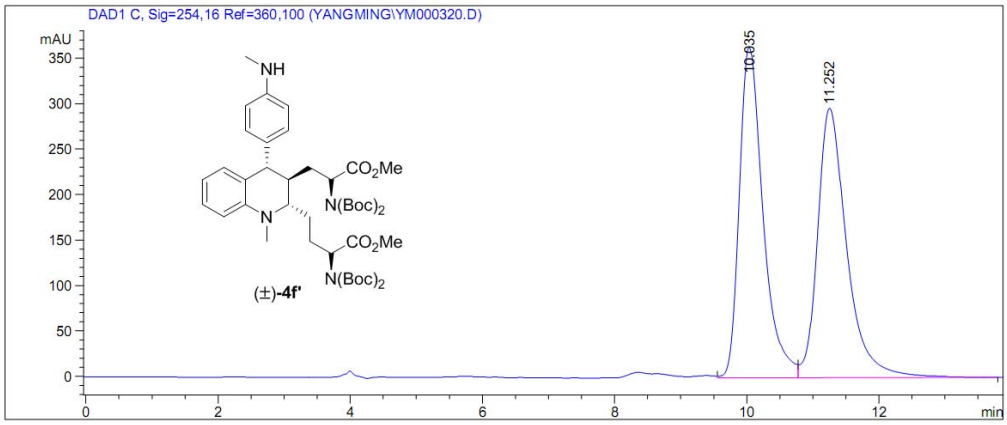
```
==========================================================================
Injection Date  : 1/18/2011 8:29:16 PM
Sample Name     : yangyanfang-1                  Location : Vial 1
Acq. Operator   : yangming
Acq. Method     : C:\HPCHEM\1\METHODS\ZHANGQW.M
Last changed    : 1/18/2011 9:04:00 PM by yangming
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\ZHANGQW.M
Last changed    : 1/18/2011 9:06:36 PM by yangming
                  (modified after loading)
==========================================================================
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: DAD1 D, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  15.179 MM    0.8995 6556.04932  121.47272 100.0000

Totals :                  6556.04932  121.47272

 Results obtained with enhanced integrator!
==========================================================================
                        Summed Peaks Report
==========================================================================

Signal 1: DAD1 D, Sig=254,16 Ref=360,100
==========================================================================
                      Final Summed Peaks Report
==========================================================================

Signal 1: DAD1 D, Sig=254,16 Ref=360,100
```

Data File C:\HPCHEM\1\DATA\YANGMING\YM000320.D Sample Name: yangyanfang-rac2
IC hex:ipr:DEA=95:4.9:0.1 1ml/min

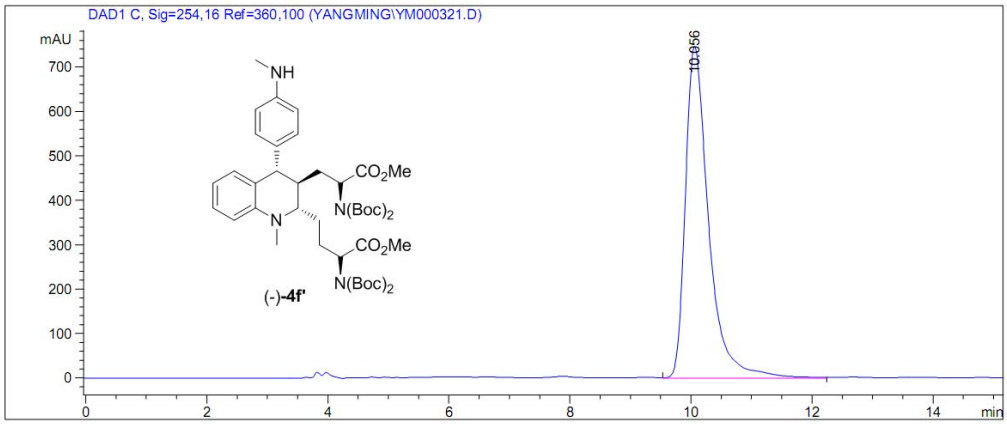
```
==========================================================================
Injection Date  : 1/17/2011 10:59:10 PM
Sample Name     : yangyanfang-rac2              Location : Vial 1
Acq. Operator   : yangming
Acq. Method     : C:\HPCHEM\1\METHODS\ZHANGQW.M
Last changed    : 1/17/2011 10:51:13 PM by yangming
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\ZHANGQW.M
Last changed    : 1/17/2011 11:17:12 PM by yangming
                  (modified after loading)
==========================================================================
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: DAD1 C, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.035 VV    0.3781 9045.56250  363.76901  49.8258
   2  11.252 VB    0.4667 9108.79590  296.27890  50.1742

Totals :                  1.81544e4   660.04791

 Results obtained with enhanced integrator!
==========================================================================
                        Summed Peaks Report
==========================================================================

Signal 1: DAD1 C, Sig=254,16 Ref=360,100
==========================================================================
                      Final Summed Peaks Report
==========================================================================

Signal 1: DAD1 C, Sig=254,16 Ref=360,100
```

Data File C:\HPCHEM\1\DATA\YANGMING\YM000321.D Sample Name: yangyanfang-2
IC hex:ipr:DEA=95:4.9:0.1 1ml/min

```
==========================================================================
Injection Date  : 1/17/2011 11:14:42 PM
Sample Name     : yangyanfang-2                 Location : Vial 1
Acq. Operator   : yangming
Acq. Method     : C:\HPCHEM\1\METHODS\ZHANGQW.M
Last changed    : 1/17/2011 11:17:12 PM by yangming
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\ZHANGQW.M
Last changed    : 1/18/2011 9:04:00 PM by yangming
                  (modified after loading)
==========================================================================
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 C, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.056 VB    0.4031 2.00247e4   746.05157 100.0000

Totals :                  2.00247e4   746.05157

 Results obtained with enhanced integrator!
==========================================================================
                        Summed Peaks Report
==========================================================================

Signal 1: DAD1 C, Sig=254,16 Ref=360,100
==========================================================================
                      Final Summed Peaks Report
==========================================================================

Signal 1: DAD1 C, Sig=254,16 Ref=360,100
```