Asymmetric Protonation of Cumulenolates: Synthesis of Allenyl Aldehydes Facilitated by an Organomanganese Auxiliary

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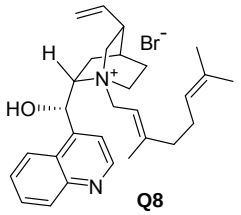
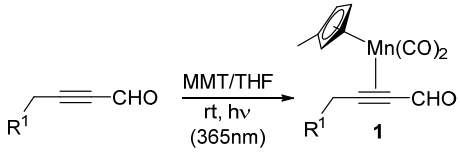
General Information. Reactions were carried out under an argon atmosphere (unless otherwise stated) in oven-dried glassware with magnetic stirring. Purification of reaction products was performed using flash silica gel 40 − 63 μm. Analytical thin-layer chromatography was performed on 200 μm silica gel 60 F-254 plates. Visualization of TLC plates was accomplished with UV light, followed by staining with vanillin or potassium permanganate and drying with a heat gun.^{1}H NMR spectra were recorded on a 400 MHz spectrometer and are reported in ppm (parts per million) using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). ^{13}C NMR spectra were recorded on a 100 MHz spectrometer. High-resolution mass spectra were recorded using an ESI-TOF MS spectrometer. Geranyl bromide and cinchonine was purchased and were used without further purification. Catalyst **1d**, **2**, **3** were purchased; the rest were prepared following previously reported procedures.

Synthesis of catalyst Q8a: This compound was prepared adapting a reported method.[1] Cinchona alkaloid and alkylating agent (1.2 equiv) were dissolved in MeCN (0.1 M) in a flame-dried flask followed by purging with argon. The reaction mixture was heated to 35 °C and allowed to proceed until judged to be complete (usually 16 h) by TLC-analysis (CH_2Cl_2 /MeOH, 9:1) and then cooled to room temperature. Acetonitrile was removed and a minimum amount of methanol was added to dissolve the solid product. It was then transferred dropwise to ethyl ether with stirring. The resulting suspension was stirred for 1 h and the precipitated solids were isolated by filtration. The solid was dried under vacuum and used without any further purification to give a yellowish powder (87% yield): ^{1}H NMR (400 MHz, CD_3OD) δ 8.93 (d, *J* = 4.4 Hz, 1H) 8.12 - 8.09 (m, 2H), 7.91 - 7.90 (m, 1H), 7.86 - 7.82 (m, 1H), 7.76 - 7.71 (m, 1H), 6.34 (m, 1H), 6.10 - 6.01 (m, 1H), 5.78 - 5.74 (t, *J* = 7.6 Hz, 1H), 5.32 - 5.27 (m, 2H), 4.60 (s, 1H), 4.45 - 4.30 (m, 4H), 3.88 - 3.74 (m, 2H), 3.58 - 3.42 (m, 3H), 2.82 - 2.75 (m, 1H), 2.42 - 2.27 (m, 6H), 1.99 - 1.96 (m, 2H), 1.92 (s, 3H), 1.87 - 1.81 (m, 1H), 1.69 (s, 3H), 1.65 (s, 3H), 1.02 - 0.93 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.1, 149.7, 149.6, 147.3, 146.0, 136.2, 132.0, 129.7, 128.9, 127.5, 124.7, 123.2, 122.5, 119.7, 116.5, 111.4, 65.6, 65.2, 57.8, 56.5, 56.3, 39.8, 38.0, 25.7, 24.5, 23.4, 20.5, 16.5, 15.8; $[\alpha]_D^{20}$ 68.0 (c 0.35 g/100 mL, MeOH); HRMS (ESI) calc. for $C_{29}H_{39}N_2O^+$: 431.3057, found 431.3071.

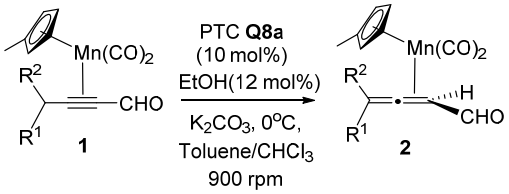


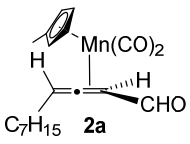
Q8

General procedure for complexing MMD to conjugated alkynal aldehyde: Tricarbonyl (2-methylcyclopentadienyl) manganese (MMT; CAS-12108-13-3) (3.80 mL, 24.2 mmol) and alkynyl aldehyde (2.00 mL, 16.1 mmol) were dissolved in THF (0.1 M in alkynal) in an oven dried glass reactor (see schematic on page S8). The reactor was covered with aluminum foil and the solution was irradiated with ultraviolet light (365 nm) at ambient temperature for 20 h with stirring under constant flow of argon to produce complex **1**. Solvent was removed and the resulting oil was then purified over silica (1-5% hexanes/ethyl acetate, blue color on vanillin TLC strain). MMD-alkyne complex **1** was dissolved in toluene, purged with argon, and stored at 8 °C (or cooler).



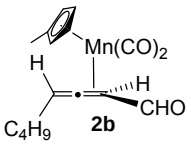
General procedure for catalytic enantioselective allene synthesis: Catalyst **Q8a** (4.0 mg, 0.0080 mmol, 10 mol %) and ethanol (0.0010 mL, 0.01 mmol, 12 mol %) were added to a vial equipped with a stir bar; a toluene solution of MMD complex alkyne aldehyde **1** (30.0 mg, 0.084 mmol) was then added and the resulting mixture was cooled to −5 °C. After 15 min, solid K_2CO_3 (30.0 mg, 0.30 mmol, 3.0 eq) was added and the reaction was stirred overnight. After complete conversion was noticed, confirmed by TLC (vanillin strain, blue color), the reaction mixture was filtered through a pad of silica gel. Solvent was removed and enantioselectivity was measured by HPLC equipped with a chiral column ((*R,R*)-Whelk-O-1) with a flow rate of 2.0 mL/min using hexanes/isopropanol (90:10) as eluent.



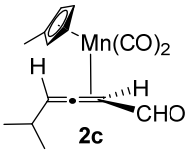


η²-MMD-(R)-undeca-2, 3-dienal (2a): Yellow oil (84% yield, 83% ee); $[\alpha]_D^{20}$ -344.3 (c 0.42 g/100ml, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 1H), 6.19 - 6.15 (dt, *J* = 8.0 Hz, 4.0Hz 1H), 4.73 - 4.68 (m, 2H), 4.54 (m, 1H), 2.87 - 2.85 (d, *J* = 8.0 Hz, 1H), 2.42 - 2.37 (m, 2H), 1.87 (s, 3H), 1.46 - 1.39 (m, 2H), 1.31 - 1.26 (m, 9H), 0.87 (t, *J* = 7.2 Hz, 3H). ^{13}CNMR (100 MHz, $CDCl_3$) δ197.1, 159.9, 129.0, 127.0, 103.2, 87.5, 86.4, 85.6, 84.9, 37.8, 32.0, 30.2, 29.25, 29.20, 27.9, 22.8, 14.2, 12.9. IR (ATR) 1638 nm^{-1} (aldehyde carbonyl), 1908 nm^{-1} (MMD CO), 1976 nm^{-1} (MMD CO). HPLC analysis: (R, R)-Whelk-O 1 column (250 × 4.6 mm) (254 nm), rt , method: *n*-Hex: IPA = 90:10, flow 2.0 ml/min, t(*R-exo*) = 10.6 min (91.3%), t(*S-exo*) = 12.1 min (8.7%). HRMS (ESI) calc. for $C_{19}H_{25}MnO_3$, $[M+H]^+$: 357.1262. Found: 357.1266

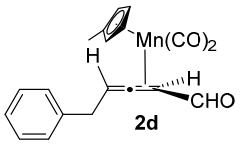
[1] E. Denmark, S.; C. Weintraub, R. *Heterocycles* **2010**, *82*, 1527.



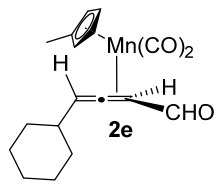
η²-MMD-(R)-octa-2, 3-dienal (2b): Yellow oil (82% yield, 79% ee); $[\alpha]_D^{20}$ -398.8 (c 0.42g/100ml, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 1H), 6.19 - 6.15 (dt, *J* = 8.0 Hz, 4.0Hz 1H), 4.73 - 4.68 (m, 2H), 4.54 (m, 1H), 2.87 - 2.85 (d, *J* = 8.0 Hz, 1H), 2.42 - 2.37 (m, 2H), 1.87 (s, 3H), 1.49 - 1.24 (m, 6H), 0.91, 0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 159.9, 129.0, 127.0, 103.2, 87.5, 86.4, 85.6, 84.9, 37.4, 32.2, 27.8, 22.2, 14.0, 12.8. IR (ATR) 1638 nm^{-1} (aldehyde carbonyl), 1908 nm^{-1} (MMD CO), 1976 nm^{-1} (MMD CO). HPLC analysis: (R, R)-Whelk-O 1 column (250 × 4.6 mm) (254 nm), rt, method: *n*-Hex: IPA = 90:10, flow 2.0 ml/min, t(*R-exo*) = 10.4 min (90%), t(*S-exo*) = 11.9 min (10%).



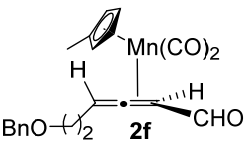
η²-MMD-(R)-5-phenylpenta-2, 3-dienal (2c): Yellow oil (86% yield, 66% ee); $[\alpha]_D^{20}$ -179.2 (c 0.30 g/100ml, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88(d, *J* = 8.0 Hz, 1H), 7.33 - 7.28 (m 2H), 7.23 - 7.15 (m, 3H), 6.35 - 6.31(dt, *J* = 8.0 Hz, 4.0Hz 1H), 4.73 - 4.71 (m, 1H), 4.69 - 4.68 (m, 1H), 4.54 (t, *J* = 4.0Hz, 2H), 3.73 - 3.71 (m, 2H), 2.84 - 2.82 (m, 1H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 162.1, 140.5, 128.7, 128.6, 127.3, 126.4, 87.4, 86.6, 85.7, 85.1, 43.9, 28.0, 12.8. IR (ATR) 1638 nm^{-1} (aldehyde carbonyl), 1908 nm^{-1} (MMD CO), 1976 nm^{-1} (MMD CO). HPLC analysis: (R, R)-Whelk-O 1 column (250 × 4.6 mm) (254 nm), rt, method: *n*-Hex: IPA = 90:10, flow 2.0 ml/min, t(*R-exo*) = 20.0 min (83.2%), t(*S-exo*) = 22.7 min (16.8%).



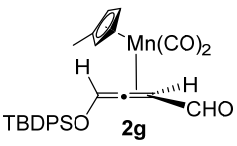
η²-MMD-(R)-4-isopropyl-buta-2,3-dienal (2d): Yellow oil (92% yield, 83% ee); $[\alpha]_D^{20}$ -434.6 (c 0.30 g/100ml, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) 7.90 (d, *J* = 8.0 Hz, 1H), 6.17 - 6.15 (dt, *J* = 8.0 Hz, 4.0Hz 1H), 4.74 - 4.67 (m, 2H), 4.53 - 4.50 (m, 2H), 2.94 - 2.92 (m, 1H), 2.65 - 2.56 (m, 1H), 1.82 (s, 3H), 1.08 - 1.06 (dd, J= 8.0Hz, 4.0Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 157.7, 135.6, 87.6, 86.6, 85.6, 84.6, 36.0, 29.0, 23.5, 23.2, 12.7. IR (ATR) 1638 nm^{-1} (aldehyde carbonyl), 1908 nm^{-1} (MMD CO), 1976 nm^{-1} (MMD CO). HPLC conditions: HPLC analysis: (R, R)-Whelk-O 1 column (250 × 4.6 mm) 254 nm), rt, method: *n*-Hex: IPA = 90:10, flow 2.0 ml/min, t(*R-exo*) = 11.0 min (91.5%), t(*S-exo*) = 12.4 min (8.5%). HRMS (ESI) calc. for $C_{15}H_{17}MnO_3$, $[M+H]^+$: 301.0636. Found: 301.0634.



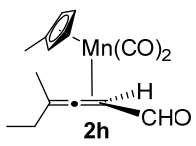
η²-MMD-(R)-4-cylohexyl-buta-2,3-dienal (2e): Yellow oil (91% yield, **75**% ee); $[\alpha]_D^{20}$ -414.2 (c 0.35 g/100ml, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 1H), 6.16 - 6.14 (dt, *J* = 8.0 Hz, 4.0Hz 1H), 4.74 - 4.73 (m, 1H), 4.68 - 4.66 (m, 1H), 4.52 - 4.49 (m, 2H), 2.92 - 2.90 (d, *J* = 8.0 Hz, 1H), 2.28 - 2.25 (m, 1H), 1.81 (s, 3H), 1.75 - 1.62 (m, 5H), 1.30 - 1.13 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 158.3, 134.5, 103.3, 87.6, 86.6, 85.6, 84.5, 45.36, 34.0, 33.7, 29.0, 26.2, 26.2, 26.2, 12.7, IR (ATR) 1638 nm^{-1} (aldehyde carbonyl), 1908 nm^{-1} (MMD CO), 1976 nm^{-1} (MMD CO). HPLC analysis: (R, R)-Whelk-O 1 column (250 × 4.6 mm) (254 nm), rt , method: *n*-Hex: IPA = 90:10, flow 2.0 ml/min, t(*R-exo*) = 12.7 min (87.6%), t(*S-exo*) = 16.2 min (12.4%). HRMS (ESI) calc. for $C_{18}H_{21}MnO_3$, $[M+H]^+$: 341.0949. Found: 341.0944.



η²-MMD-(R)-6-(benzyloxy)hexa-2,3-dienal (2f): Yellow oil (77% yield, 58% ee); $[\alpha]_D^{20}$ -328.2 (c 0.44 g/100ml, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91(d, *J*= 8.0 Hz, 1H), 7.89, 7.35 - 7.33 (m, 5H), 6.25 - 6.21(dt, *J* = 8.0 Hz, 4.0Hz 1H), 4.53 - 4.50 (m, 4H), 3.59 - 3.56(t, *J* = 4Hz, 2H), 2.87 - 2.84 (m, 1H), 2.72-2.66 (m, 2H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 197.0, 138.5, 128.5, 127.8, 127.7, 125.2, 110.1, 87.5, 86.6, 85.7, 85.2, 73.0, 70.0, 37.8, 34.1, 27.8, 12.8. IR (ATR) 1638 nm^{-1} (aldehyde carbonyl), 1908 nm^{-1} (MMD CO), 1976 nm^{-1} (MMD CO). HPLC analysis: (R, R)-Whelk-O 1 column (250 × 4.6 mm) (254 nm), rt, method: n-Hex: IPA = 90:10, flow 2.0 ml/min, t(R-exo) = 26.2 min (79.3%), t(S-exo) = 29.1 min (20.7%). HRMS (ESI) calc. for $C_{21}H_{21}MnO_4$, $[M+H]^+$: 393.0899. Found: 393.0897.

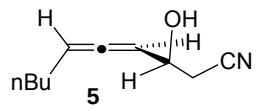


η²-MMD-(R)-4-((tert-butyldiphenylsilyl)oxy)buta-2,3-dienal (2g): Yellow oil (65% yield, 60% ee); $[\alpha]_D^{20}$ -107.7 (c 0.50 g/100ml, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 - 7.69 (m, 4H), 7.59 - 7.57 (m, 1H), 7.44 - 7.37 (m, 6H), 6.58 - 6.57 (m, 1H), 4.52 (m, 2H), 4.40 (m, 2H), 2.71 - 2.69(m, 1H), 1.78 (s, 3H), 1.07(S, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 142.1, 135.7, 133.1, 132.8, 130.1, 127.9, 103.2, 87.5, 86.5, 85.6, 85.4, 31.5, 26.6, 19.4, 13.0; IR (ATR) 1638 nm^{-1} (aldehyde carbonyl), 1908 nm^{-1} (MMD CO), 1976 nm^{-1} (MMD CO); HPLC analysis: (R, R)-Whelk-O 1 column (250 × 4.6 mm) (254 nm), rt, method: n-Hex: IPA = 90:10, flow 2.0 ml/min, t(R-exo) = 13.3 min (78.6%), t(S-exo) = 15.5 min (21.4%). This compound was too unstable for MS analysis.



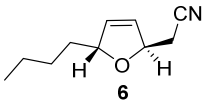
2h

η²-MMD-(R)-4-methylhexa-2,3-dienal (2h): Yellow oil (55% yield, 54% ee); $[\alpha]_D^{20}$ -520.9 (c 0.10 g/100ml, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83(m, 1H), 4.69 - 4.56 (m, 4H), 2.43 - 2.41(m, 2H), 2.19 (s, 3H), 1.25 - 1.23(m, 3H),1.07 (t, *J* = 7.6Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 150.5, 135.0, 85.5, 85.5, 85.1, 84.9, 36.8, 28.6, 21.7, 14.0; HPLC analysis: (R, R)-Whelk-O 1 column (250 × 4.6 mm) (254 nm), rt, method: n-Hex: IPA = 90:10, flow 2.0 ml/min, t(R-exo) = 14.2 min (77.0%), t(S-exo) = 14.9 min (23.0%). HRMS (ESI) calc. for $C_{15}H_{17}MnO_3$, $[M+H]^+$: 301.0636. Found: 301.0640.



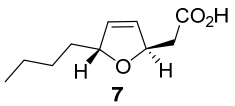
5

***(3R, 5R)-3-hydroxydeca-4,5-dienenitrile (5)*:** Prepared according to a previously reported racemic procedure.[2] To a precooled (for 10 min) Et_2O solution of iodoacetonitrile (0.12 mL, 1.25 mmol) was added ^{i}PrMgCl (2M in THF, 1.42 mL, 2.80 mmol) followed by MMD-complexed allenyl aldehyde **2b** (0.50 g, 1.3 mmol) at -78 ºC. In this mixture, the concentration of Mg and ICH_2CN were 0.11 M and 0.05 M respectively. Allenyl aldehyde was fully consumed after 20 min as confirmed by TLC whereupon saturated aqueous NH_4Cl (10 mL) was added. The aqueous layer was then extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was dissolved again in dry acetone (10 mL) under an argon atmosphere and treated with $PhI(OAc)_2$ (650 mg, 2.03 mmol). After 2 h (completion of reaction as determined by TLC), the solvent was evaporated. The crude product (now decomplexed) was purified by flash chromatography using 10% EtOAc/hexanes to afford 0.08 g (60% yield) of pure product as a liquid; $[\alpha]_D^{20}$ -44.6 (c 0.83 mg/mL, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 - 5.42 (m, 1H), 5.33 - 5.28(m, 1H), 4.48 - 4.45 (m, 1H), 2.69 - 2.56 (m, 2H), 2.08 - 2.05 (m, 2H), 1.40 - 1.33 (m, 4H), 0.91(t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 117.3, 96.5, 93.2, 65.9, 31.2, 28.3, 26.2, 22.3, 14.0.; HRMS calc. for $C_{10}H_{15}NO$ $[M+H]^+$: 166.1232, $[M+NH_4]^+$:183.1492 Found:166.1232.



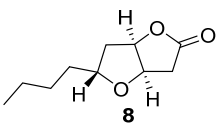
6

(3aR, 5R, 6aR)-5-butyltetrahydrofuro[3,2-b]furan-2(3H)-one (6): To a solution of allenol **5** (50 mg, 0.30 mmol) in acetone/water (3:2, v/v, 2.0 mL) was added $AgNO_3$ (10 mg, 0.06 mmol, 0.2 eq) and the reaction mixture was stirred at room temperature for about 24 h. After the reaction was compete (as confirmed by TLC), the solvent was removed under reduced pressure and the crude reaction mixture was subjected to column chromatography using hexanes/EtOAc to give pure **6**, 43 mg (86% yield). Colorless oil: $[\alpha]_D^{20}$ -151.4 (c 0.7 mg/ml, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 - 5.12 (t, *J* = 4.7 Hz, 1H), 4.83 - 4.80 (dt, *J* = 6.7, 5.1,1H), 4.11 - 4.04 (m, 1H), 2.74 (dd, *J* = 18.8, 6.7 Hz, 1H), 2.6 (d, *J* = 18.8 Hz, 1H), 2.41 - 2.36 (dd, *J* = 14.0, 4.7 Hz, 1H), 1.71 - 1.60 (m, 2H), 1.56 -1.47 (m, 1H), 1.41 - 1.27 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 85.1, 78.4, 77.5, 38.9, 36.8, 34.5, 28.3, 22.8, 14.1. HRMS calc. for $C_{10}H_{16}O_3$, $[M+NH4]^+$: 202.1438. Found: 202.1436



7

((2R, 5R)-5-butyl-2,5-dihydrofuran-2-yl)acetic acid (7): A solution of **6** (30 mg, 0.18 mmol) dissolved in an acetic acid/HCl mixture (4:1, v/v, 2 mL) was heated at 100 °C for 6 hours. After the reaction was completed (as monitored by TLC), the reaction mixture was partitioned between water and ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane/EtOAc to give pure **7**, 25 mg (75% yield); $[\alpha]_D^{20}$ -81.0 (c 0.1 mg/ml, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 - 5.84 (m, 2H), 5.23 - 5.18 (m, 1H), 4.94 - 4.90 (m, 1H), 2.65 - 2.54 (m, 2H), 1.59 - 1.56 (m, 2H), 1.34 - 1.32 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 131.4, 128.5, 86.3, 81.7, 41.0, 35.6, 27.3, 22.9, 14.2. HRMS calc. for $C_{10}H_{16}O_3$, $[M-H]^-$:183.1027, found: 183.1036



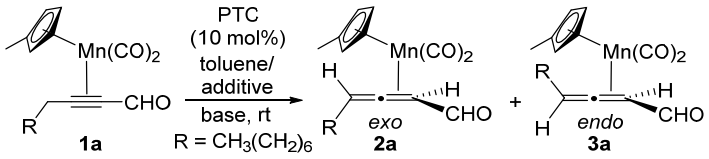
8

(3aR, 5R, 6aR)-5-butyltetrahydrofuro[3,2-b]furan-2(3H)-one (Hagen's Gland lactone **8**): To a solution of **7** (20 mg, 0.11 mmol) in MeCN (2 mL) was added sequentially $NaHCO_3$ (28 mg, 0.33 mmol, 3.0 eq) and iodine (42 mg, 0.33 mmol, 3.0 eq) at 0 °C and the reaction mixture was stirred at rt for 2 to 3 h. The reaction was quenched with aqueous $Na_2S_2O_3$, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. The latter was passed through a short celite pad and solvent evaporated under reduced pressure to give crude iodolactone product which was used for the next reaction without further purification. To a stirred solution of iodolactone (25 mg, 0.080 mmol) in benzene (5.0 mL) was added *n*-Bu_3SnH (44 mg, 0.16 mmol, 2.0 eq) and AIBN (10 mg, 0.064 mmol, 0.40 equiv). The reaction was refluxed for 6 h, cooled to room temperature and volatiles were evaporated. The residue was purified through silica gel chromatography using hexane/EtOAc to give pure **8** (12 mg, 60 %, over two steps) as a colorless oil:

[2] P. Knochel, Z. Zhang, F. F. Fleming, *Org. Lett.*, **2004**, 6, 501

$[\alpha]_D^{20}$ -24.5 (c 0.2 mg/mL, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 - 5.12 (t, *J* = 4.7 Hz, 1H), 4.83 - 4.80 (dt, *J* = 6.7, 5.1,1H), 4.11 - 4.04 (m, 1H), 2.74 (dd, *J* = 18.8, 6.7 Hz, 1H), 2.6 (d, *J* = 18.8 Hz, 1H), 2.41 - 2.36 (dd, *J* = 14.0, 4.7 Hz, 1H), 1.71 - 1.60 (m, 2H), 1.56 - 1.47 (m, 1H), 1.41 - 1.27 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 85.1, 78.4, 77.5, 38.9, 36.8, 34.5, 28.3, 22.8, 14.1. HRMS calc. for $C_{10}H_{16}O_3$, $[M+NH_4]^+$: 202.1438. Found: 202.1436

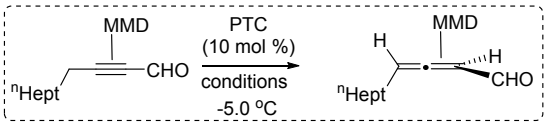
Table 1 - expanded. Optimization of isomerization conditions (including yields)

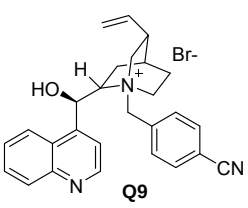


entry	cat.	base	additive[a]	% yield **2a** (reaction time in h)	**2a**:**3a**	ee (%)[b] of **2a**
1	**Q1a**	1 M KOH		62 (16)	4:1	-58
2	**Q1c**	1 M KOH		61 (16)	4:1	+55
3	**Q1d**	0.1 M KOH	Et_2O	77 (16)	4:1	-79
4	**Q1e**	10 M KOH	Et_2O	75 (10)	4:1	-80
5	**Q1f**	0.1 M KOH	Et_2O	62 (16)	5:1	-64
6	**Q1g**	0.1 M KOH	Et_2O	66 (16)	5:1	-79
7	**Q1h**	0.1 M KOH	Et_2O	58 (14)	3:1	-79
8	**Q1b**	0.1 M KOH	Et_2O	52 (16)	2:1	rac
9	**Q2**	1 M KOH		48 (10)	2:1	-40
10	**Q3**	1 M KOH		46 (16)	4:1	rac
11	**Q4**	K_2CO_3		69 (10)	5:1	-78
12	**Q6a**	0.1 M KOH	Et_2O	66 (16)	6.5:1	-70
13	**Q6b**	10 M KOH	Et_2O	60 (16)	5:1	-71
14	**Q6c**	10 M KOH	Et_2O	65 (16)	7:1	-69
15	**Q6d**	10 M KOH	Et_2O	60 (16)	7:1	-65
16	**Q7**	10 M KOH	Et_2O	48 (16)	4:1	rac
17	**Q8a**	0.1 M KOH	Et_2O	76 (12)	6.4:1	-77
18	**Q8a**	aq K_2CO_3		81 (16)	7:1	-80
19	**Q8a**	K_2CO_3			-	-
20[c]	**Q8a**	K_2CO_3	$CHCl_3$/EtOH	85 (16)	7:1	-83
21	**Q5**	10 M KOH	Et_2O	64 (16)	7:1	-72

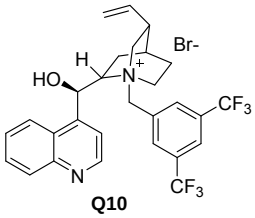
[a]Reactions were performed with base (3 eq) in toluene/additive (3:1) (0.10 M with respect to substrate) at rt (unless indicated otherwise). [b]The enantiomeric excess was determined by chiral HPLC analysis of MMD-allene **2a**. [c]Reaction conducted at -5 °C in toluene/$CHCl_3$ (3:1) with EtOH (0.12 eq).

Table A. Isomerization reaction with various other catalysts

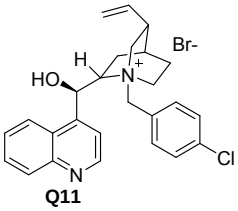




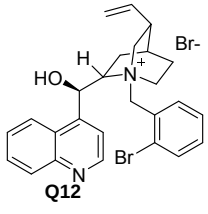
Q9



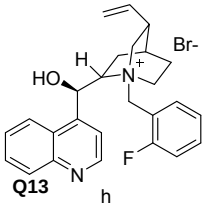
Q10



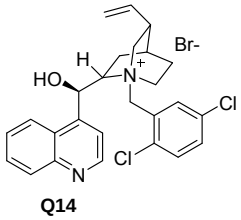
Q11



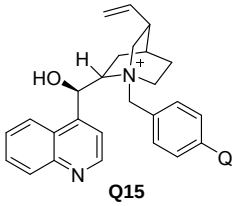
Q12



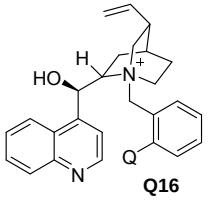
Q13 h



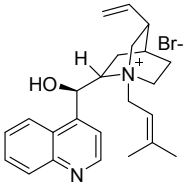
Q14



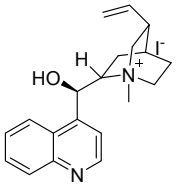
Q15



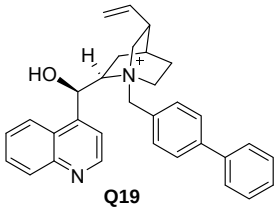
Q16



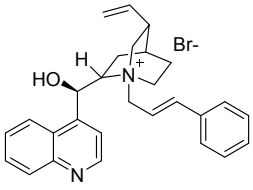
Q17



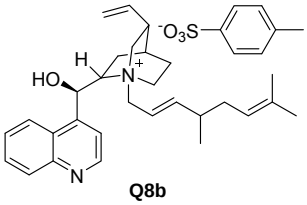
Q18



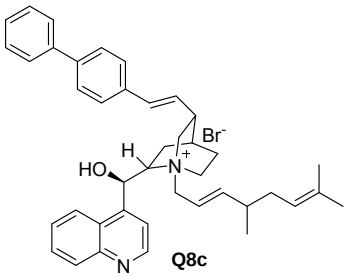
Q19



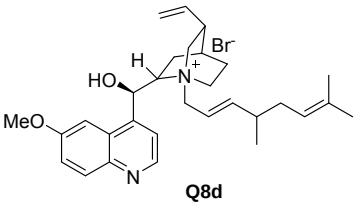
Q20



Q8b



Q8c

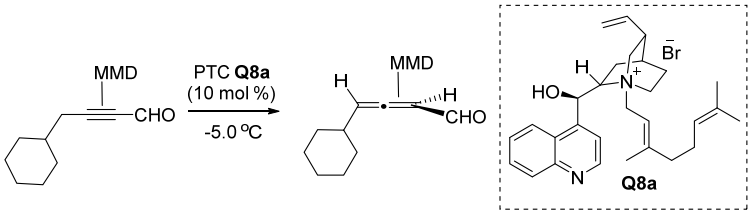


Q8d

catalyst	condition	ee (%)	dr
Q9	0.1M KOH/Tol-$CHCl_3$(3:1)	69	5:1
Q10	0.1M KOH/Tol-$CHCl_3$(3:1)	80	4:1
Q11	0.1M KOH/Tol-$CHCl_3$(3:1)	79	4:1
Q12	0.1M KOH/Tol-$CHCl_3$(3:1)	74	4:1
Q13	0.1M KOH/Tol-$CHCl_3$(3:1)	73	4:1
Q14	0.1M KOH/Tol-$CHCl_3$(3:1)	77.7	3:1
Q15	0.1M KOH/Tol-$CHCl_3$(3:1)	52	5:1
Q16	0.1M KOH/Tol-$CHCl_3$(3:1)	50	5:1
Q17	0.1M KOH/Tol-$CHCl_3$(3:1)	72.6	6:1
Q18	1.0 M KOH/Tol-$CHCl_3$(3:1)	65	6:1
Q19	1M KOH/Tol-$CHCl_3$(3:1)	70	5:1
Q20	aq K_2CO_3/Tol	74	6:1
Q8b	aq K_2CO_3/Tol	81.6	5:1
Q8c	aq K_2CO_3/Tol	79	6:1
Q8d	1.0 M KOH/Tol-$CHCl_3$(3:1)	72	5.6:1
Q8a	***K_2CO_3/tol/$CHCl_3$/EtOH/-5°C***	***83***	***7:1***

Changing counter ion, substitution on cinchonidine vinyl group, or the presence of a methoxy group on **Q8a** did not improve ee.

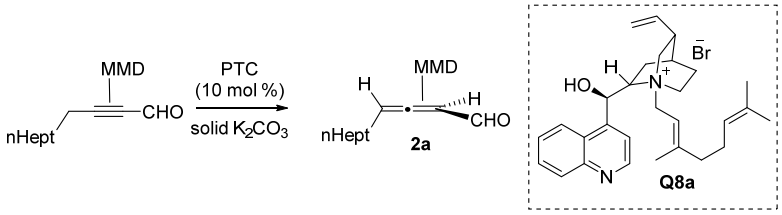
Table B. Comparison of different isomerization condition for allene **2e**



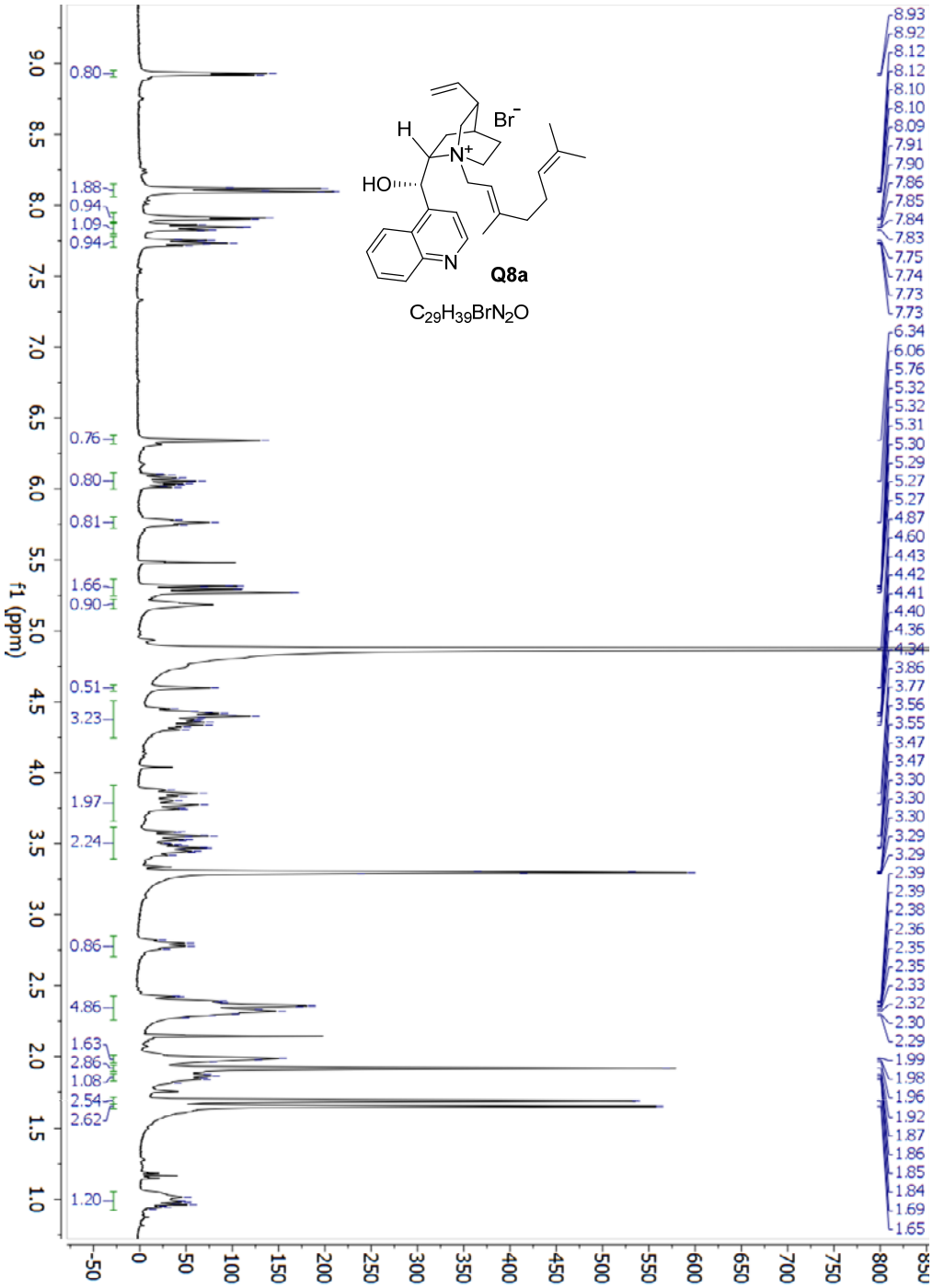
entry	condition	ee (%)		comment
1	Solid K_2CO_3 / EtOH /Tol-$CHCl_3$/ rt	71		
2	***Solid K_2CO_3 / EtOH/ Tol-$CHCl_3$/-5.0 °C***	***75***	***Exo only***	
3	Solid K_2CO_3 / EtOH /Tol-$CHCl_3$/-5.0 °C	74		counter ion sulfonate/ **Q8b**
4	aq 100% K_2CO_3 /Tol	72		
5	1M KOH/ Tol-$CHCl_3$/-5.0 °C	40		

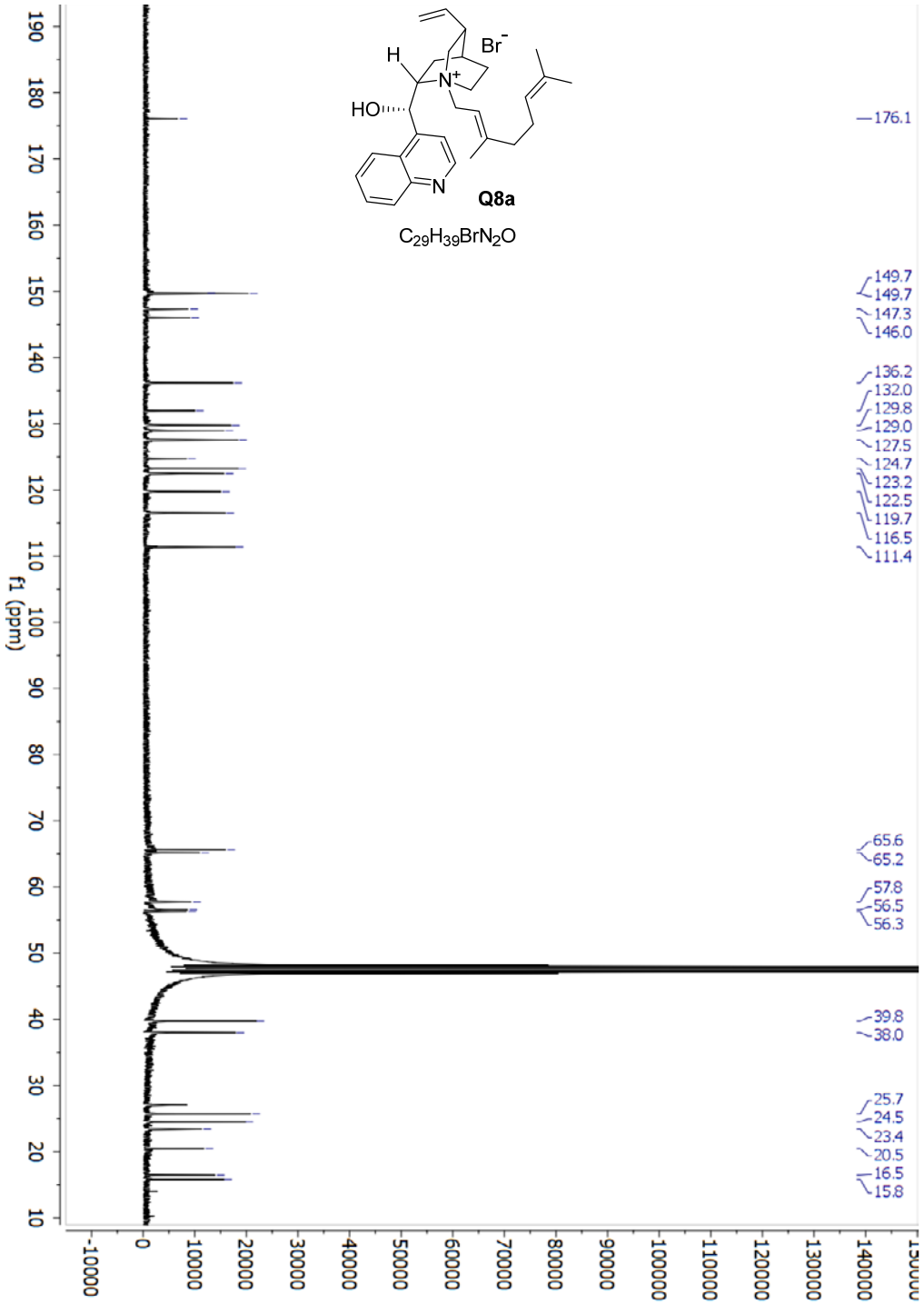
Condition 1 and 4 produces similar ee. Reducing temp to -5.0 °C increases ee slightly. Changing counter ion (**Q8b**) to sulfonate did not improve ee.

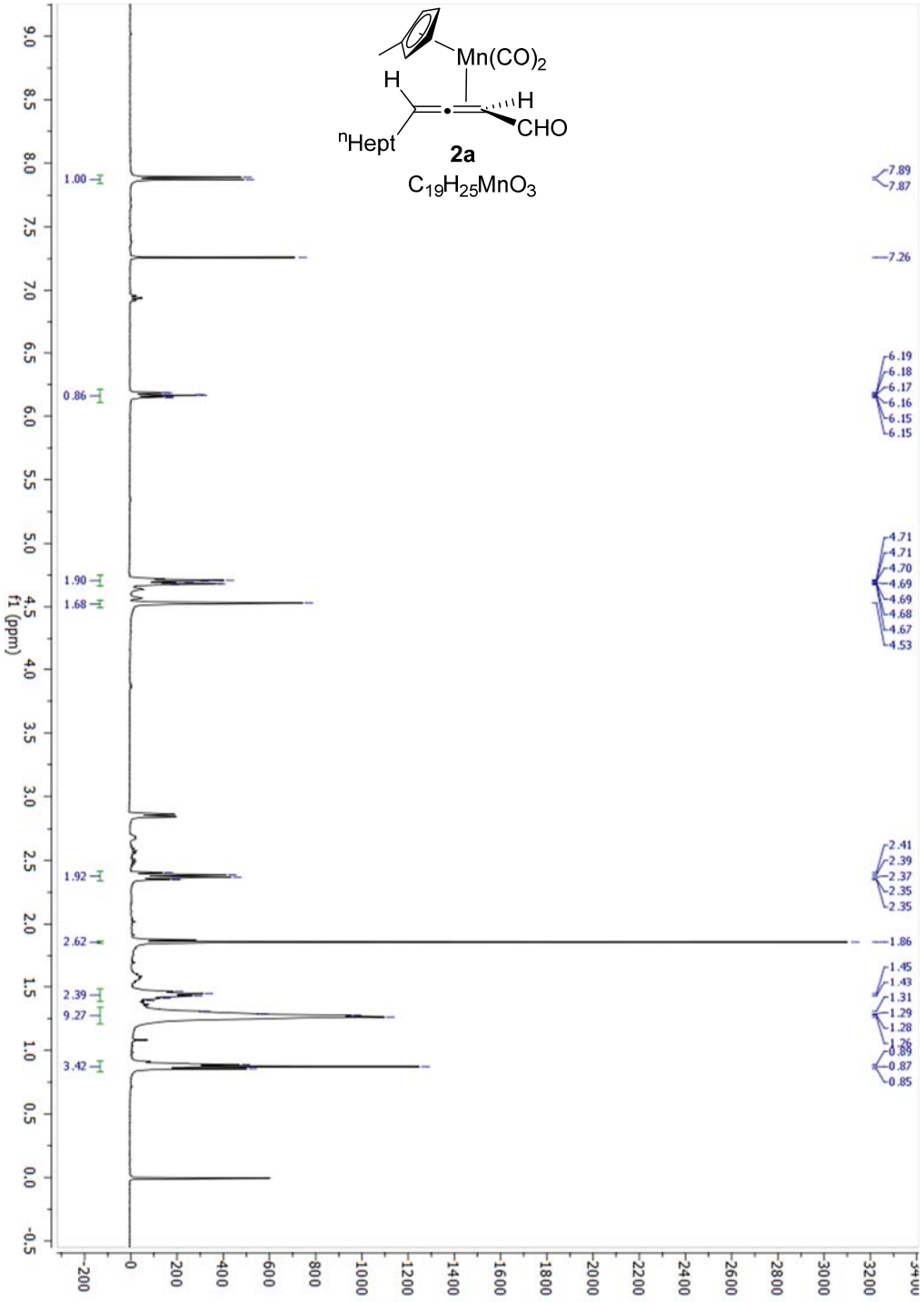
Table C. Other alcohol screened for isomerization reaction to **2a**

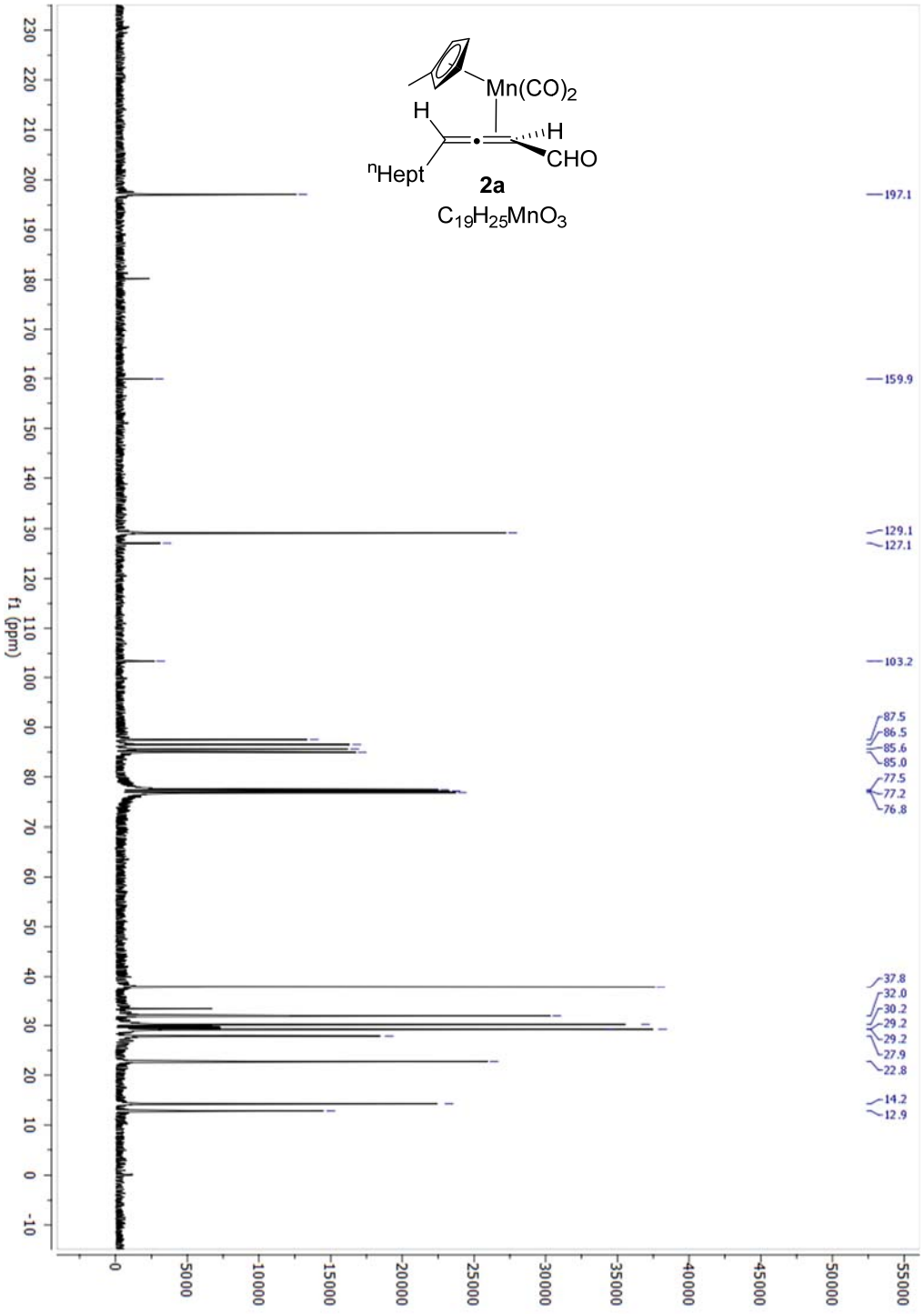


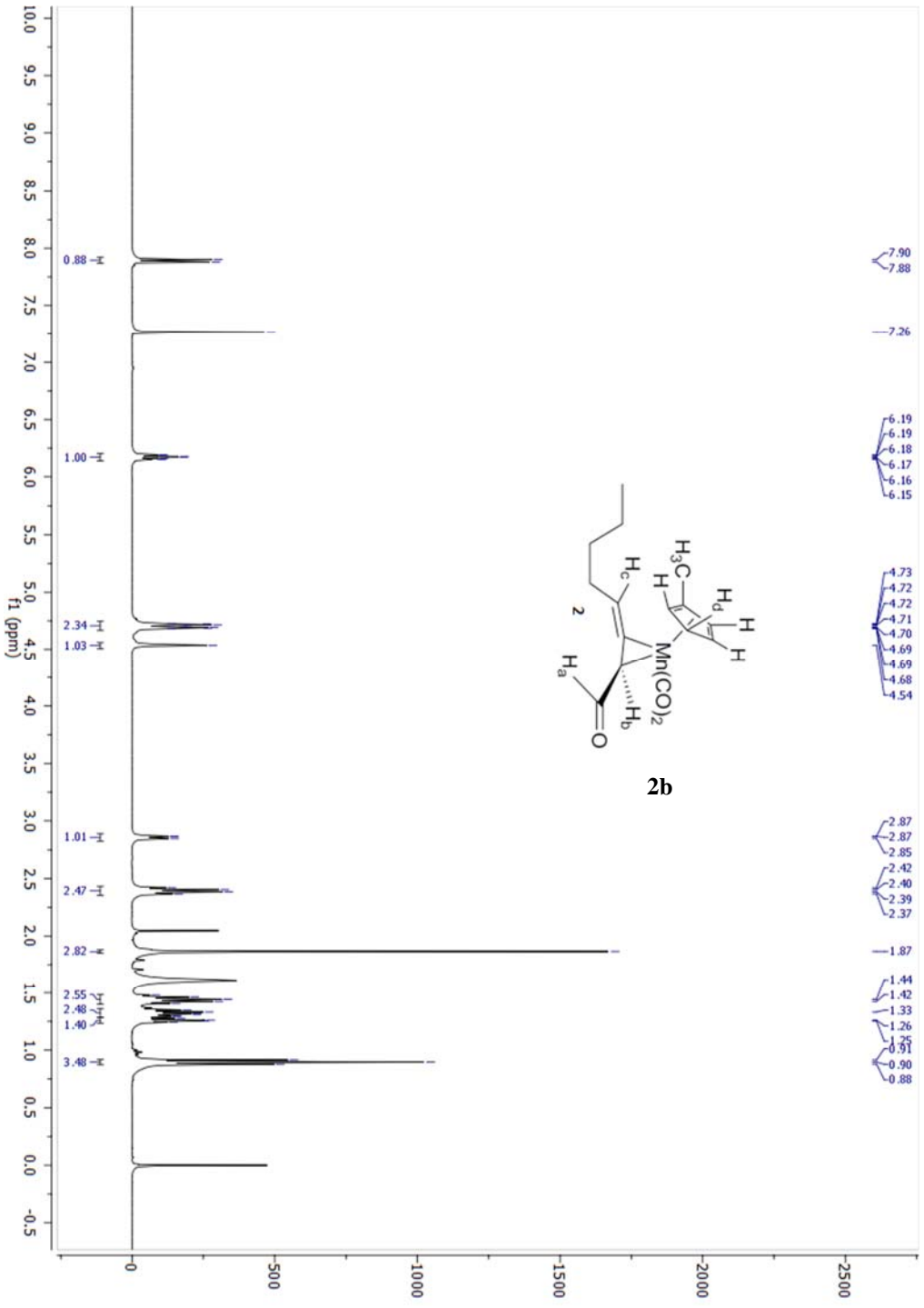
entry	alcohol	ee (%)	dr	comment
1	2-methoxyethanol			no conv
2	neopentyl alchol			no conv
3	4-Bromobenzyl alcohol			no conv
4	(2-benzyloxy) ethanol	80	6.4:1	
5	2-mercaptoethanol			poor conv
6	SDS			poor conv
7	tetraethylene glycol	49	5:1	
8	1-phenyl 1,2 ethane diol	70	7:1	
9	propargyl alcohol	33	11:1	
10	5-hexyne-1-ol			no conv
11	1-hetadecanol			no conv
12	1-hexanol	75	5.5	
13	cyclopentanol	80	6:1	
14	trans-2-methylcyclohexanol			poor conversion
15	trans-3-methylcyclohexanol			poor conversion
16	trans-4-methylcyclohexanol			poor conversion
17	EtOH	82	7:1	
18	CF_3CH_2OH	30	20:1	
19	***EtOH /Tol: $CHCl_3$ (3:1)***	***82***	***8:1***	
20	EtOH / Tol: $CHCl_3$ (3:1) (-50°C)			no conv
21	2-benzyloxyethanol/ Tol: $CHCl_3$ (-50°C)			no conv


Br⁻
H
N⁺
HO
N
Q8a
C29H39BrN2O
f1 (ppm)

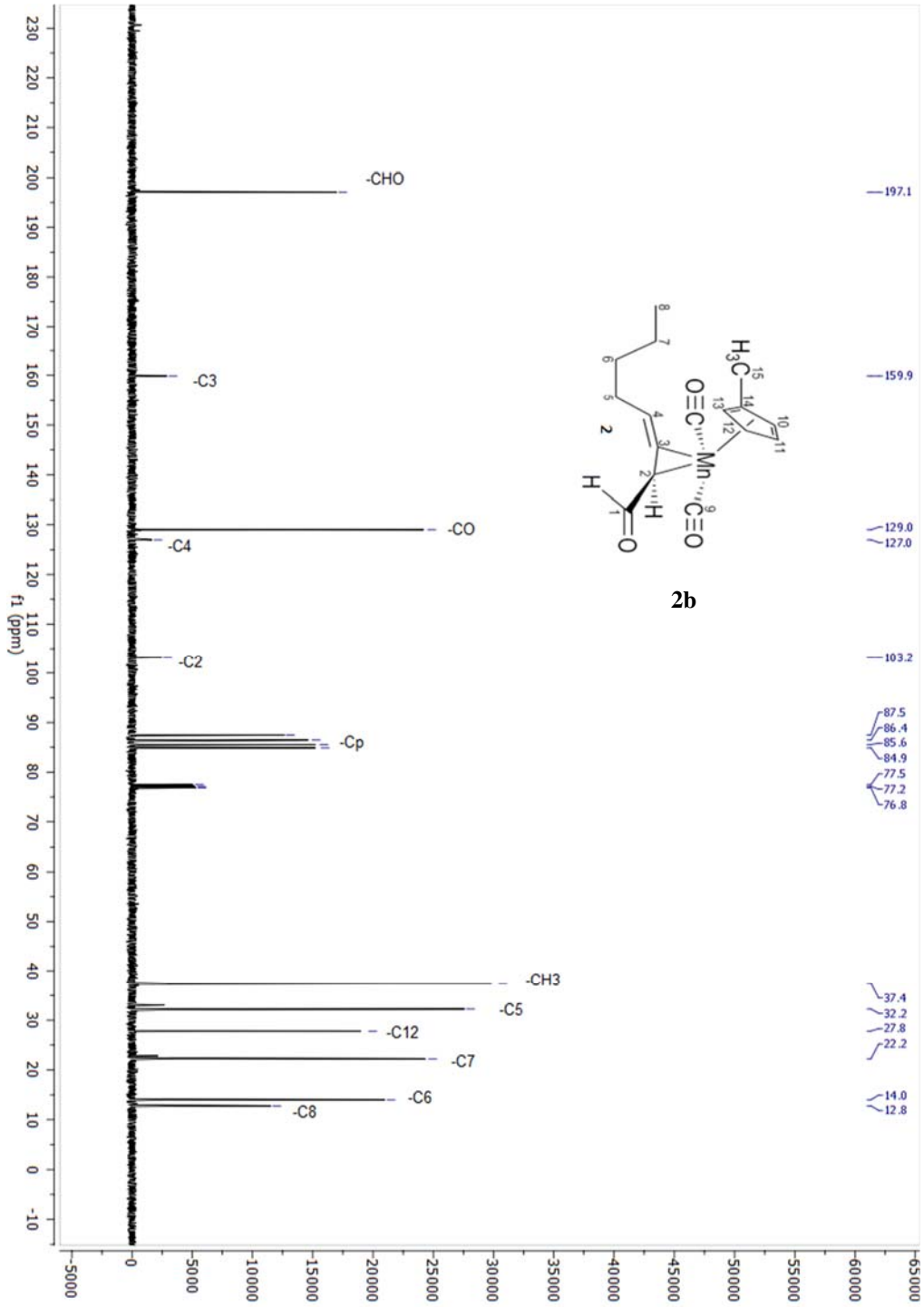

Br-
H
N+
HO
N
Q8a
C29H39BrN2O
176.1
149.7
149.7
147.3
146.0
136.2
132.0
129.8
129.0
127.5
124.7
123.2
122.5
119.7
116.5
111.4
65.6
65.2
57.8
56.5
56.3
39.8
38.0
25.7
24.5
23.4
20.5
16.5
15.8
f1 (ppm)


Mn(CO)2
H
H
CHO
nHept
2a
C19H25MnO3
f1 (ppm)
1.00
0.86
1.90
1.68
1.92
2.62
2.39
9.27
3.42
7.89
7.87
7.26
6.19
6.18
6.17
6.16
6.15
6.15
4.71
4.71
4.70
4.69
4.69
4.68
4.67
4.53
2.41
2.39
2.37
2.35
2.35
1.86
1.45
1.43
1.31
1.29
1.28
1.26
0.89
0.87
0.85

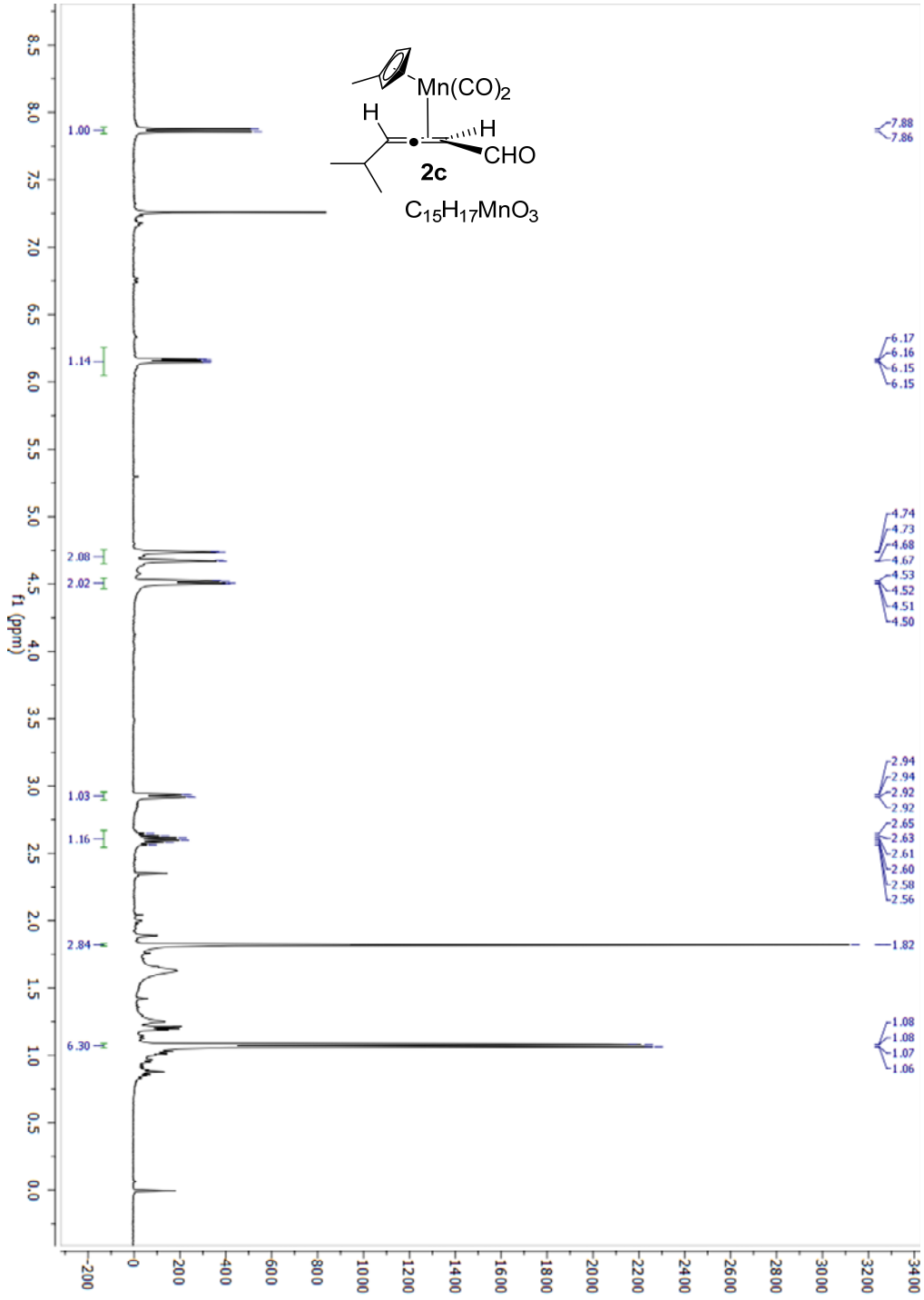

Mn(CO)2
H
H
CHO
nHept
2a
C19H25MnO3
f1 (ppm)
197.1
159.9
129.1
127.1
103.2
87.5
86.5
85.6
85.0
77.5
77.2
76.8
37.8
32.0
30.2
29.2
29.2
27.9
22.8
14.2
12.9

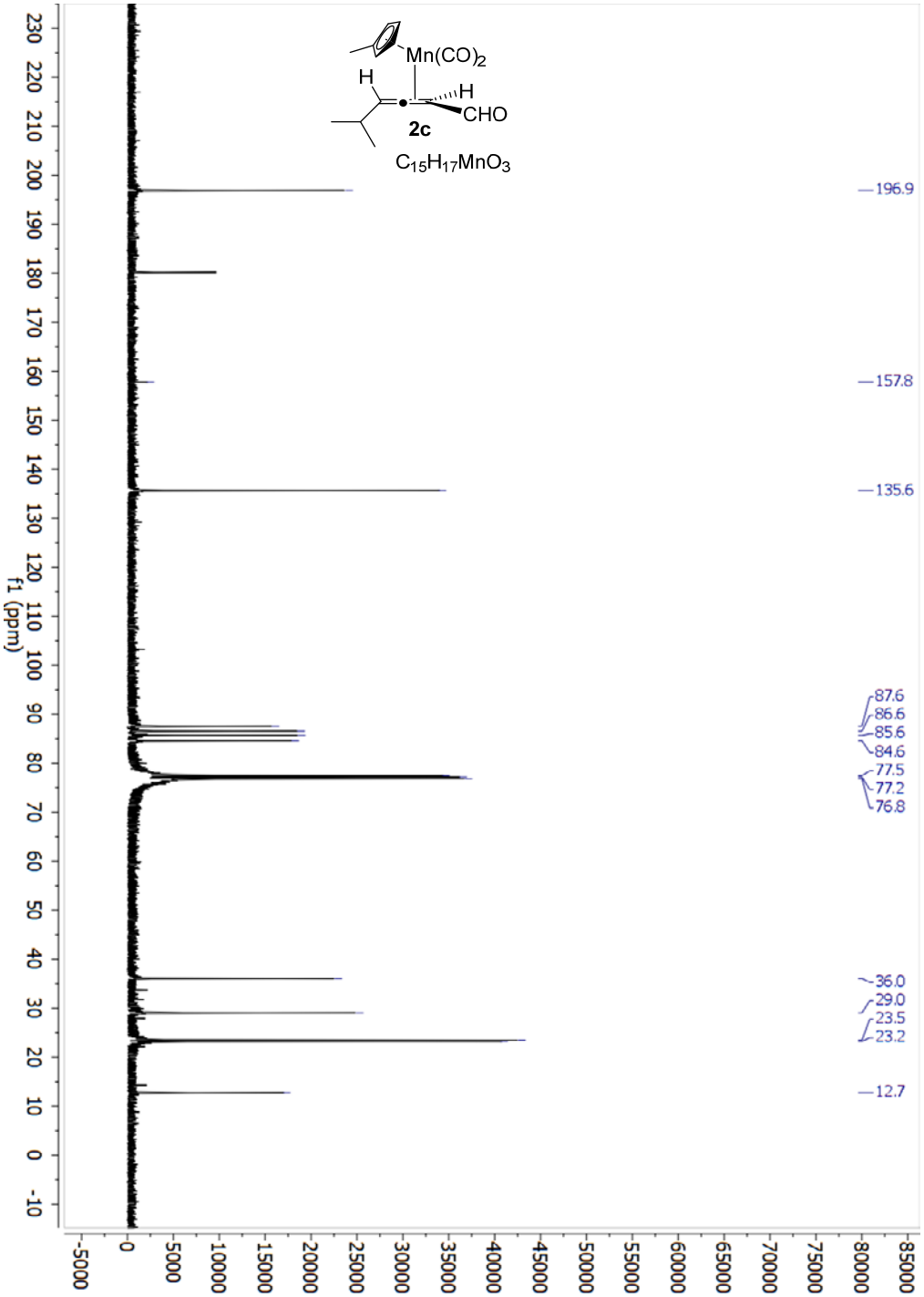

f1 (ppm)
0.88
1.00
2.34
1.03
1.01
2.47
2.82
2.55
2.48
1.40
3.48
7.90
7.88
7.26
6.19
6.19
6.18
6.17
6.16
6.15
4.73
4.72
4.72
4.71
4.70
4.69
4.69
4.68
4.54
2.87
2.87
2.85
2.42
2.40
2.39
2.37
1.87
1.44
1.42
1.33
1.26
0.91
0.90
0.88
Hc
H3C
H
Hd
H
H
2
Mn(CO)2
Ha
Hb
O

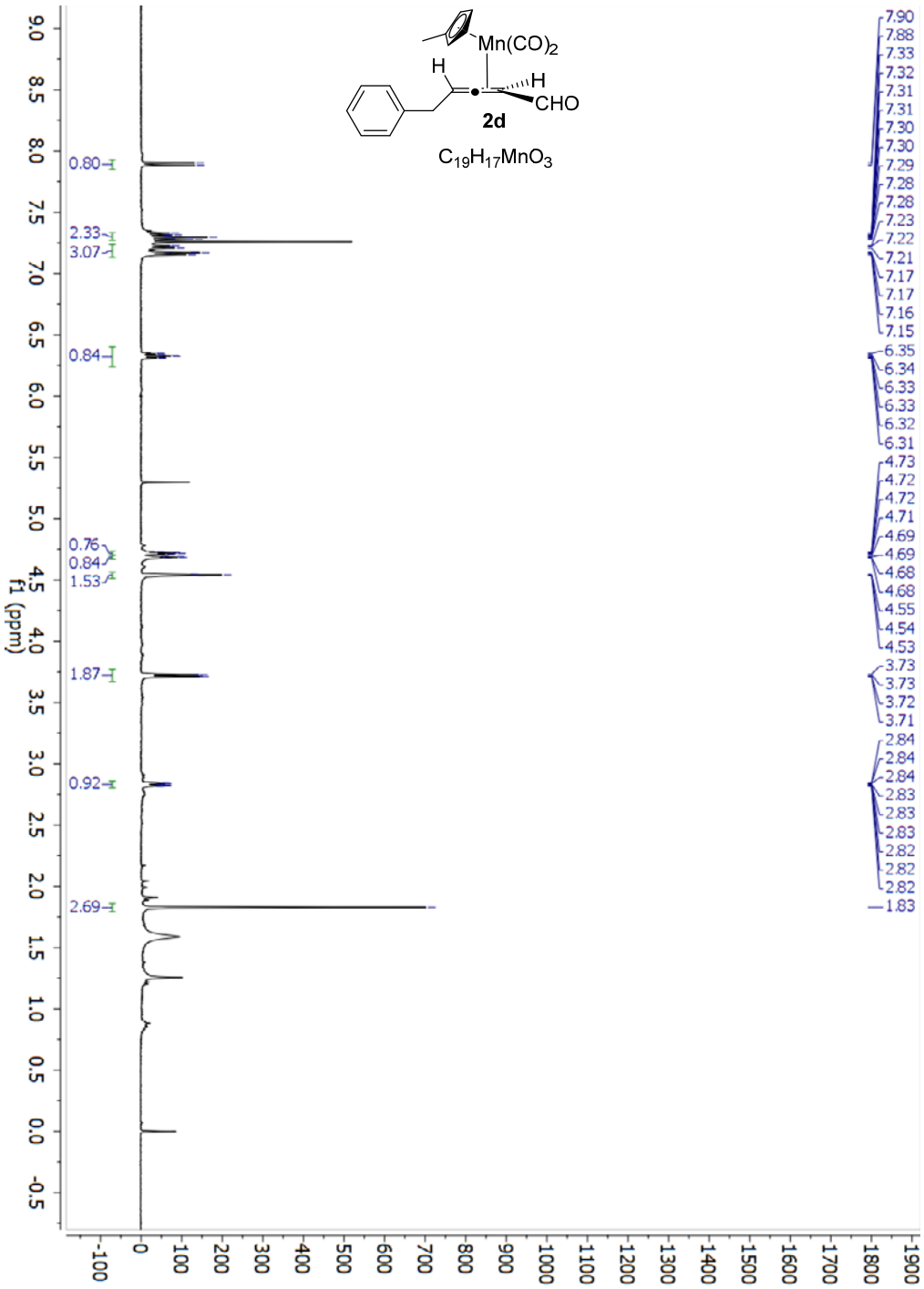
2b


-CHO
-C3
-CO
-C4
-C2
-Cp
-CH3
-C5
-C12
-C7
-C6
-C8
197.1
159.9
129.0
127.0
103.2
87.5
86.4
85.6
84.9
77.5
77.2
76.8
37.4
32.2
27.8
22.2
14.0
12.8
f1 (ppm)

2b


Mn(CO)2
H
H
CHO
2c
C15H17MnO3
f1 (ppm)
1.00
1.14
2.08
2.02
1.03
1.16
2.84
6.30
7.88
7.86
6.17
6.16
6.15
6.15
4.74
4.73
4.68
4.67
4.53
4.52
4.51
4.50
2.94
2.94
2.92
2.92
2.65
2.63
2.61
2.60
2.58
2.56
1.82
1.08
1.08
1.07
1.06


Mn(CO)2
H
H
CHO
2c
C15H17MnO3
196.9
157.8
135.6
87.6
86.6
85.6
84.6
77.5
77.2
76.8
36.0
29.0
23.5
23.2
12.7
f1 (ppm)


Mn(CO)2
H
H
CHO
2d
C19H17MnO3
f1 (ppm)
0.80
2.33
3.07
0.84
0.76
0.84
1.53
1.87
0.92
2.69
7.90
7.88
7.33
7.32
7.31
7.31
7.30
7.30
7.29
7.28
7.28
7.23
7.22
7.21
7.17
7.17
7.16
7.15
6.35
6.34
6.33
6.33
6.32
6.31
4.73
4.72
4.72
4.71
4.69
4.69
4.68
4.68
4.55
4.54
4.53
3.73
3.73
3.72
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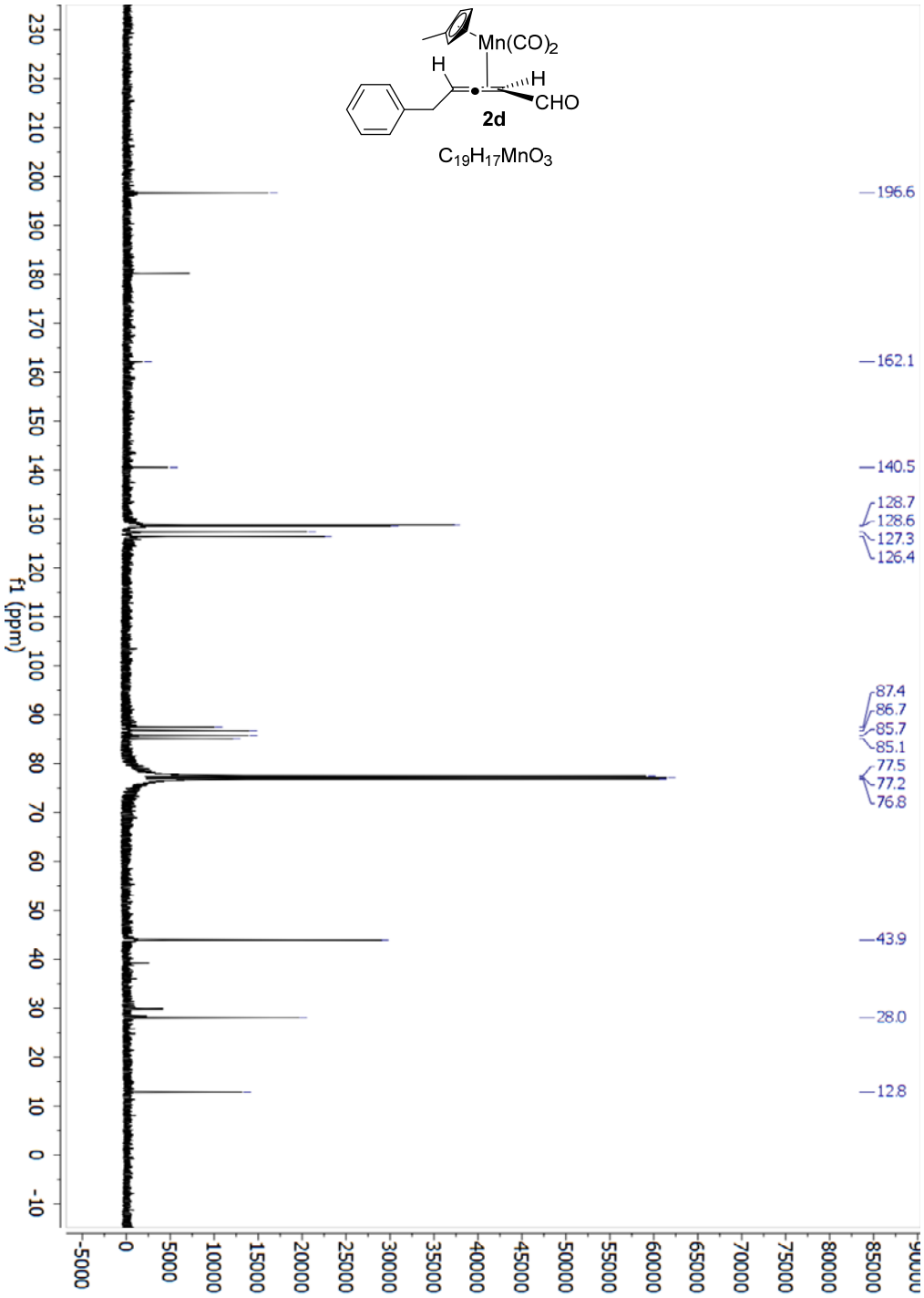
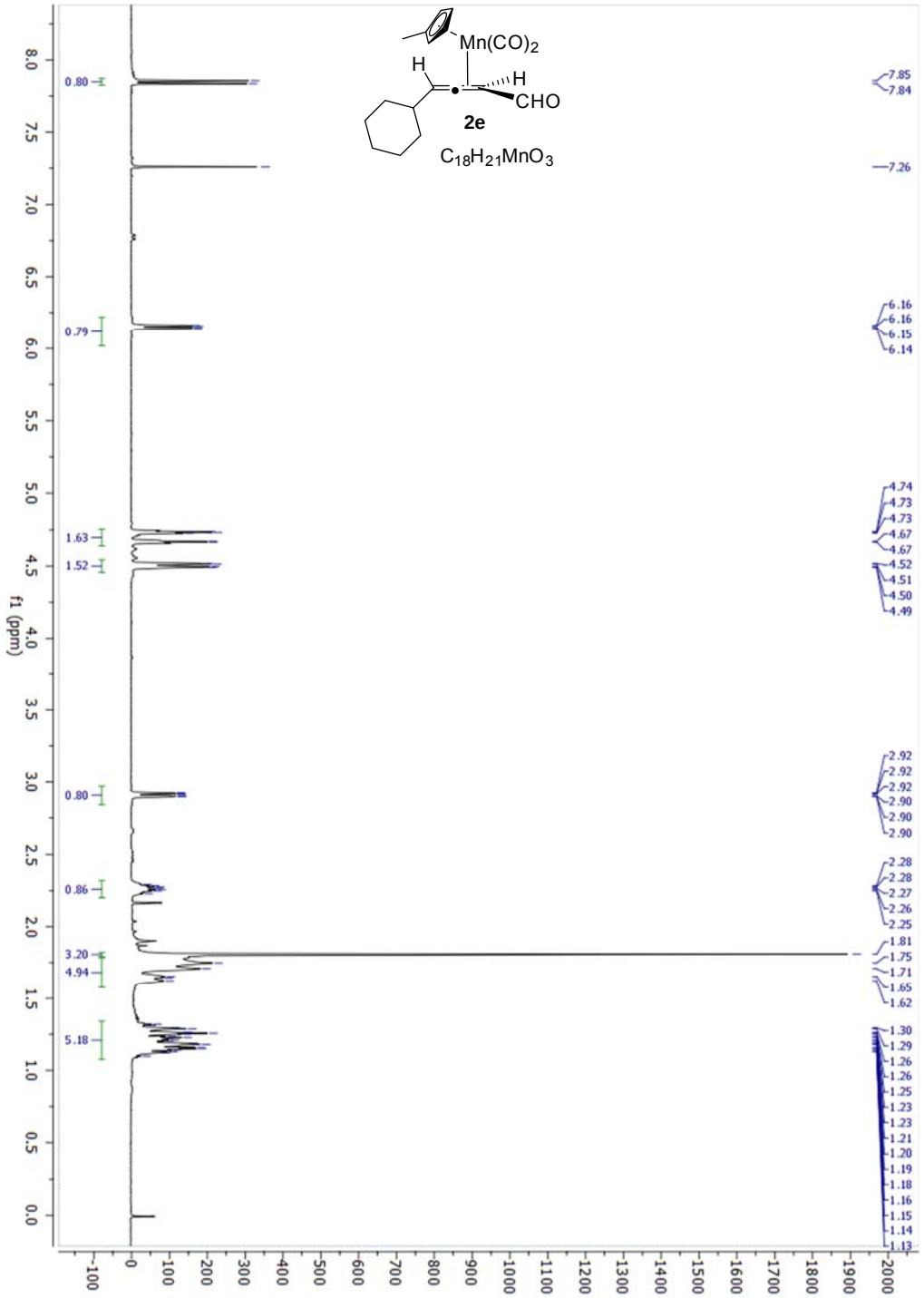
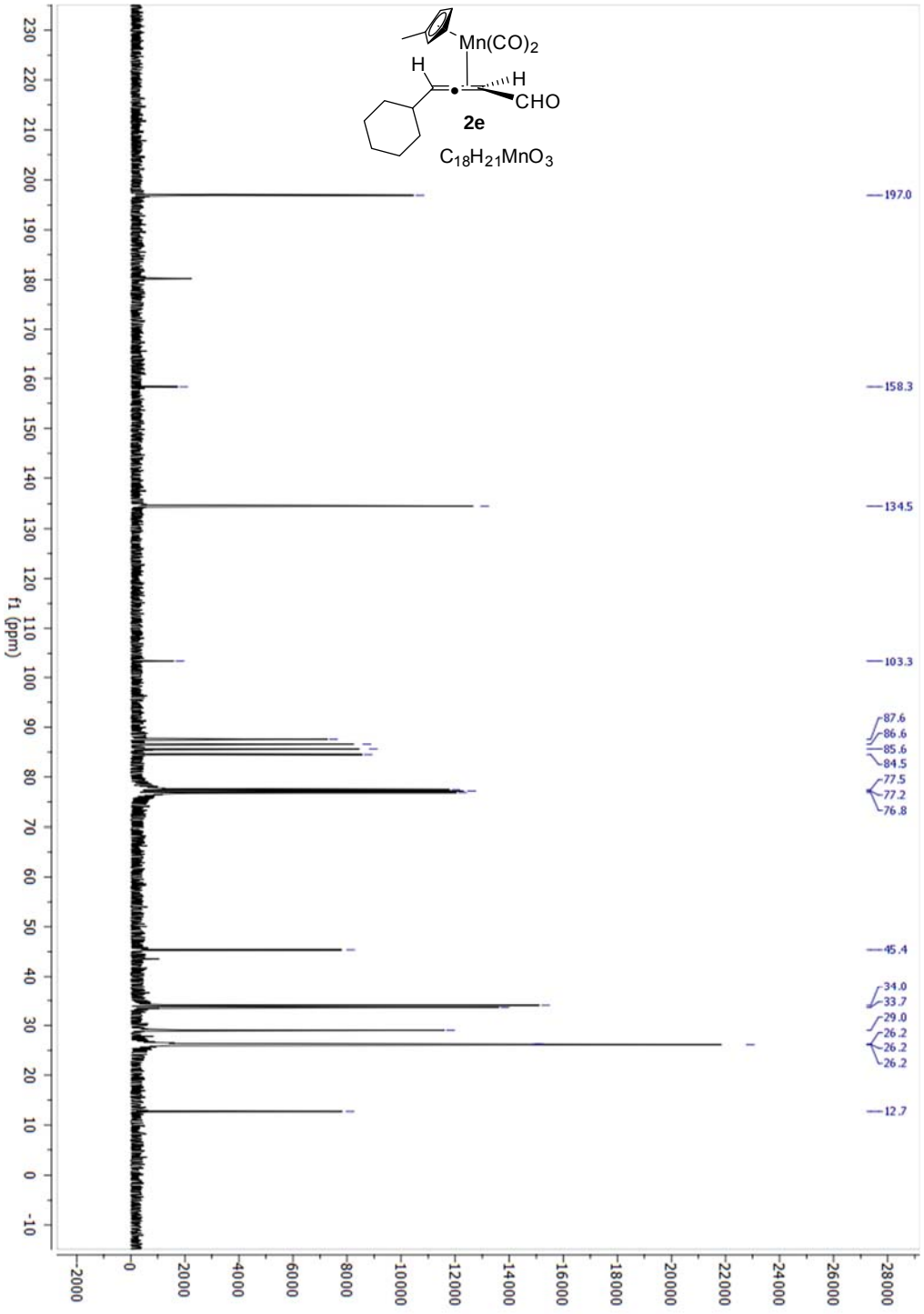
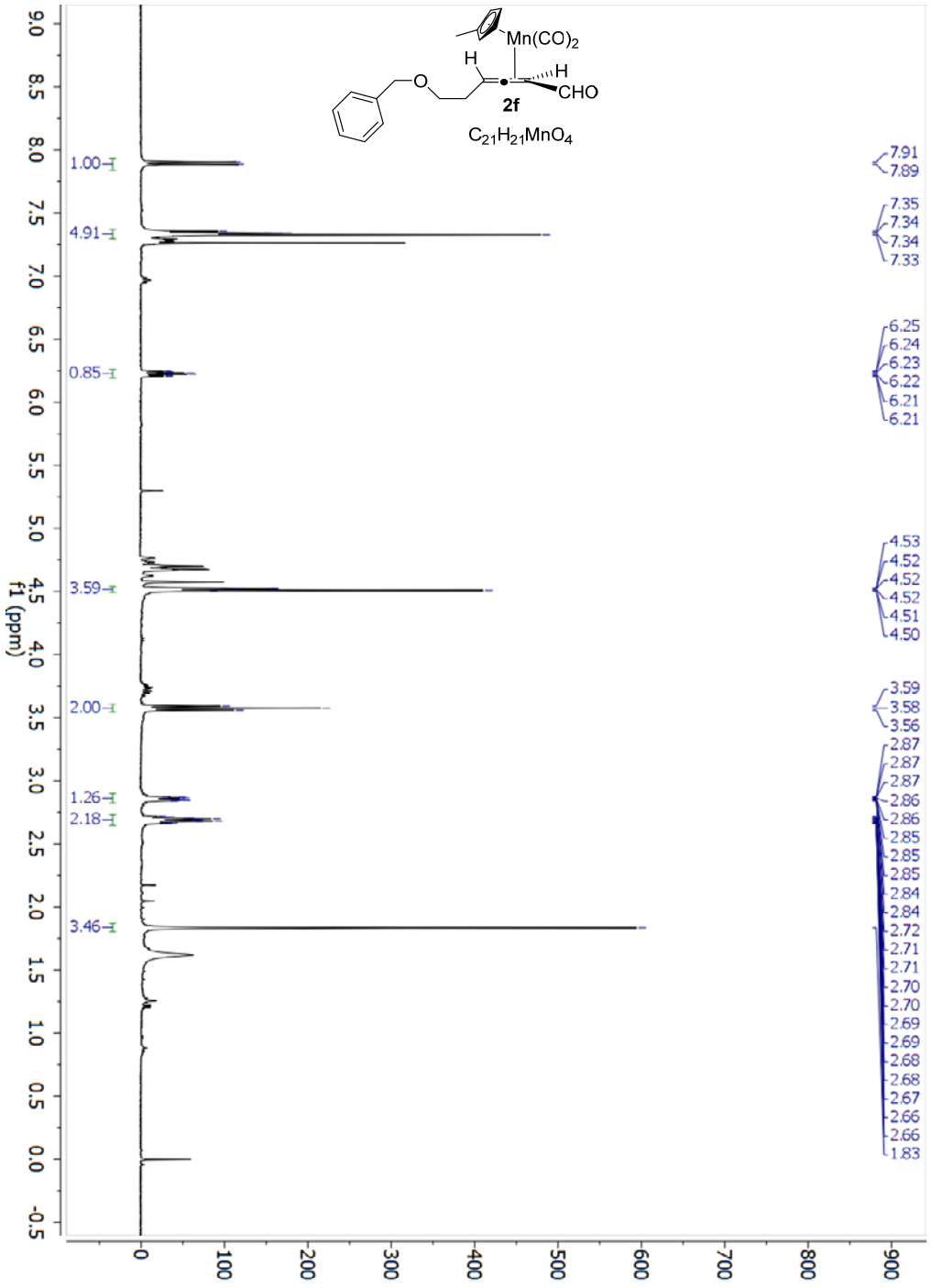
2.83
2.83
2.82
2.82
2.82
1.83


Mn(CO)2
H
H
CHO
2d
C19H17MnO3
196.6
162.1
140.5
128.7
128.6
127.3
126.4
87.4
86.7
85.7
85.1
77.5
77.2
76.8
43.9
28.0
12.8
f1 (ppm)


Mn(CO)2
H
H
CHO
2e
C18H21MnO3
f1 (ppm)
0.80
0.79
1.63
1.52
0.80
0.86
3.20
4.94
5.18
7.85
7.84
7.26
6.16
6.16
6.15
6.14
4.74
4.73
4.73
4.67
4.67
4.52
4.51
4.50
4.49
2.92
2.92
2.92
2.90
2.90
2.90
2.28
2.28
2.27
2.26
2.25
1.81
1.75
1.71
1.65
1.62
1.30
1.29
1.26
1.26
1.25
1.23
1.23
1.21
1.20
1.19
1.18
1.16
1.15
1.14
1.13


Mn(CO)2
H
H
CHO
2e
C18H21MnO3
197.0
158.3
134.5
103.3
87.6
86.6
85.6
84.5
77.5
77.2
76.8
45.4
34.0
33.7
29.0
26.2
26.2
26.2
12.7
f1 (ppm)


Mn(CO)2
H
H
CHO
O
2f
C21H21MnO4
f1 (ppm)
1.00
4.91
0.85
3.59
2.00
1.26
2.18
3.46
7.91
7.89
7.35
7.34
7.34
7.33
6.25
6.24
6.23
6.22
6.21
6.21
4.53
4.52
4.52
4.52
4.51
4.50
3.59
3.58
3.56
2.87
2.87
2.87
2.86
2.86
2.85
2.85
2.85
2.84
2.84
2.72
2.71
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2.70
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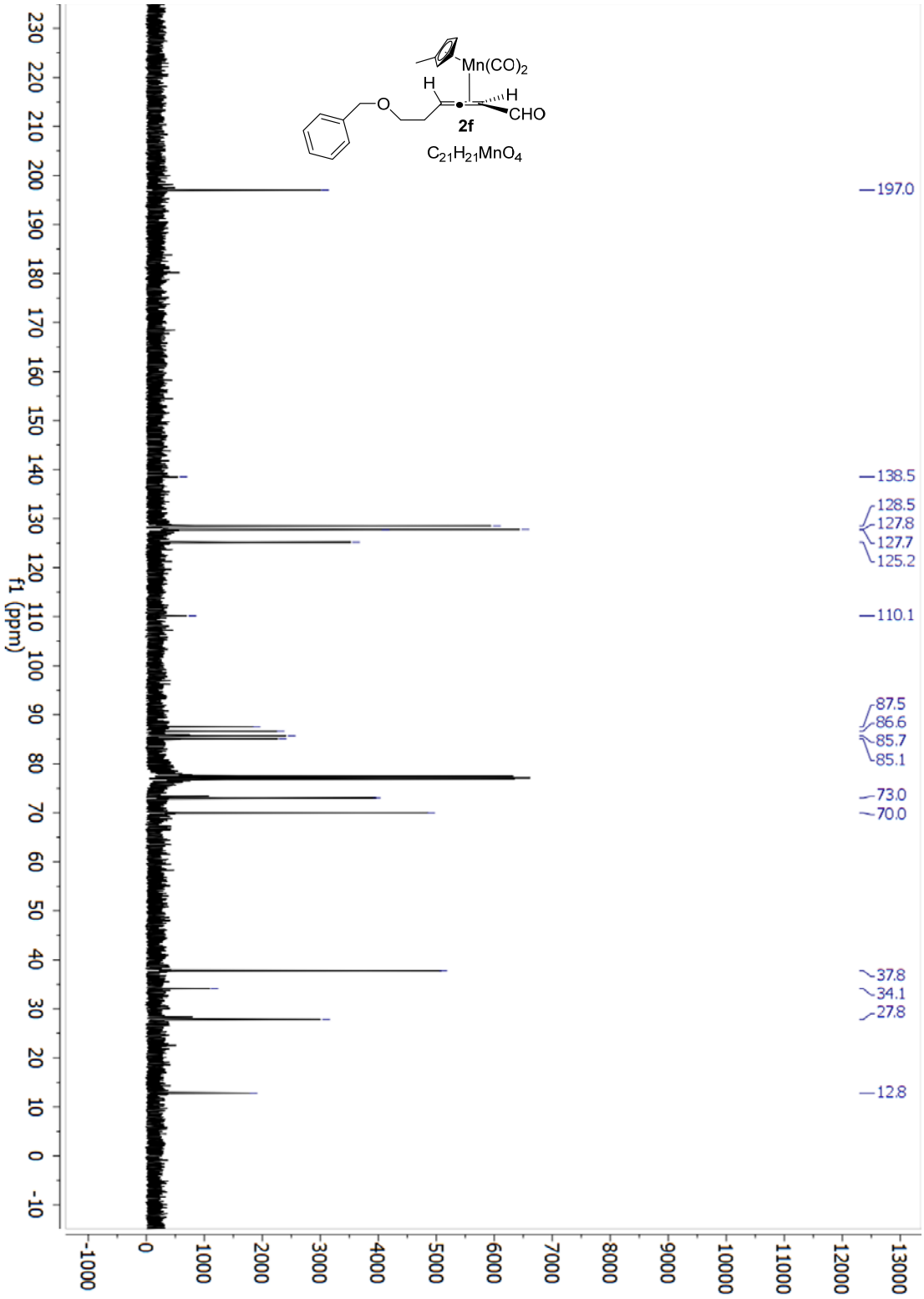
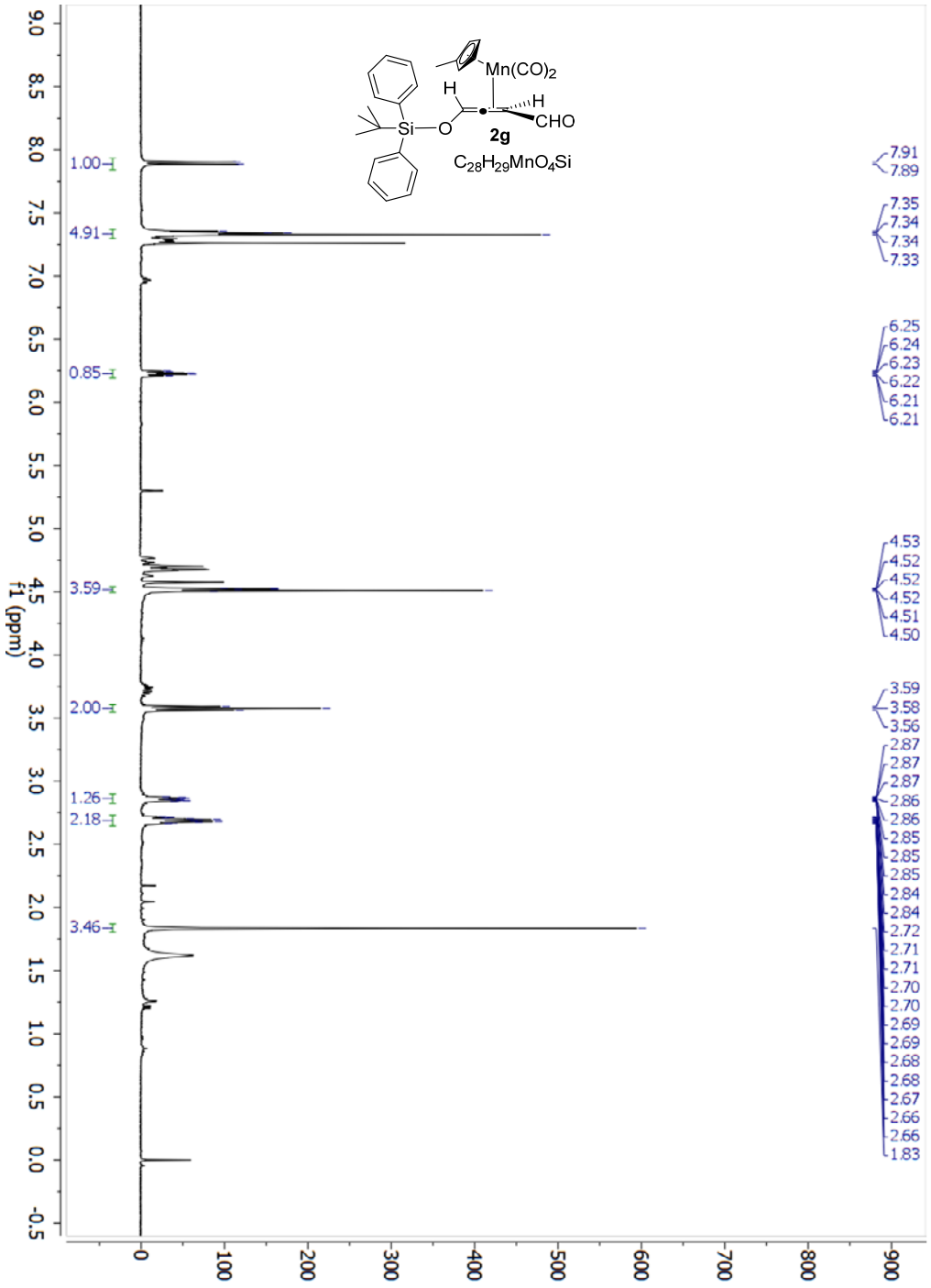
2.69
2.68
2.68
2.67
2.66
2.66
1.83


Mn(CO)2
H
H
CHO
O
2f
C21H21MnO4
197.0
138.5
128.5
127.8
127.7
125.2
110.1
87.5
86.6
85.7
85.1
73.0
70.0
37.8
34.1
27.8
12.8
f1 (ppm)


Mn(CO)2
H
H
CHO
Si
O
2g
C28H29MnO4Si
f1 (ppm)
1.00
4.91
0.85
3.59
2.00
1.26
2.18
3.46
7.91
7.89
7.35
7.34
7.34
7.33
6.25
6.24
6.23
6.22
6.21
6.21
4.53
4.52
4.52
4.52
4.51
4.50
3.59
3.58
3.56
2.87
2.87
2.87
2.86
2.86
2.85
2.85
2.85
2.84
2.84
2.72
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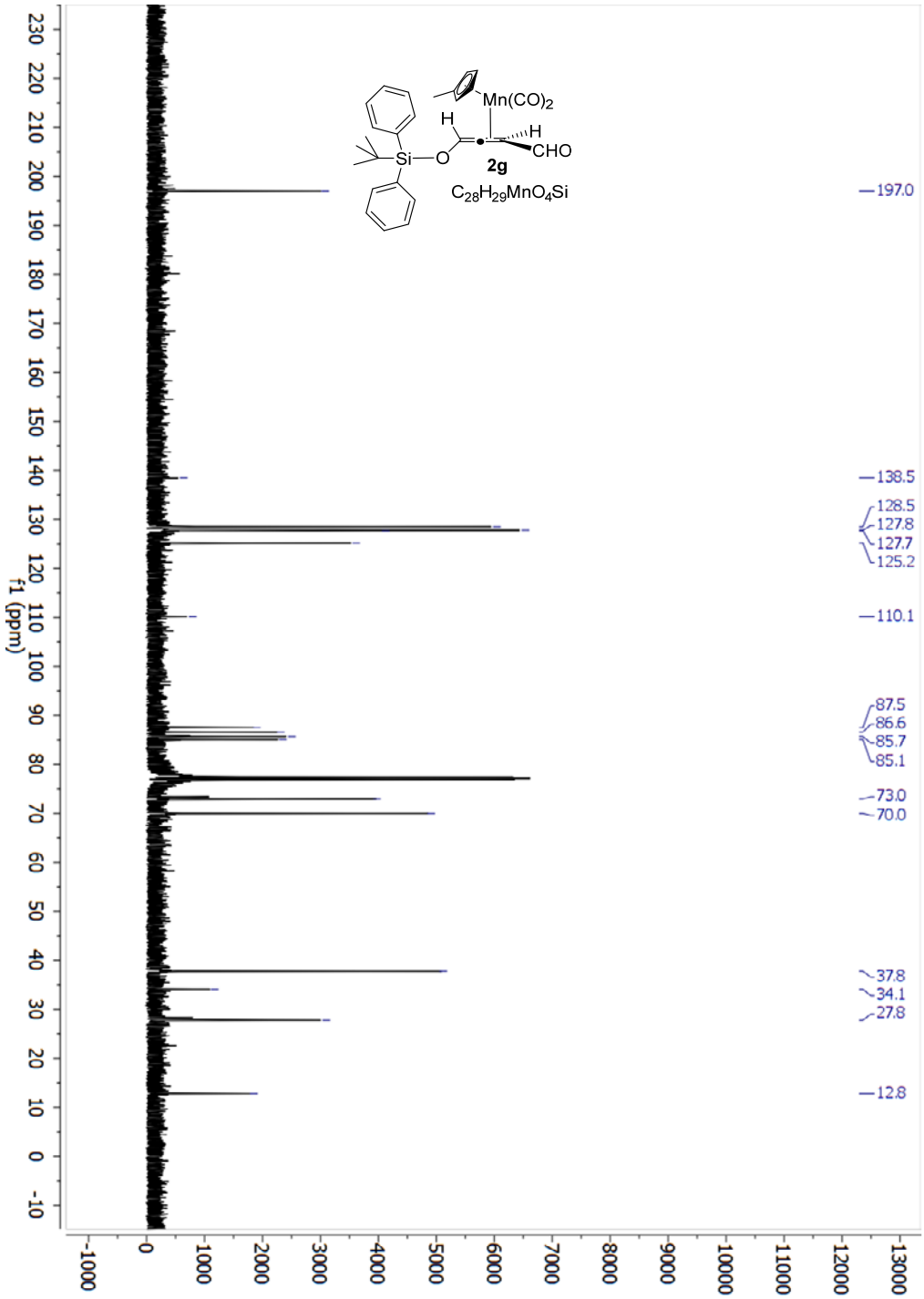
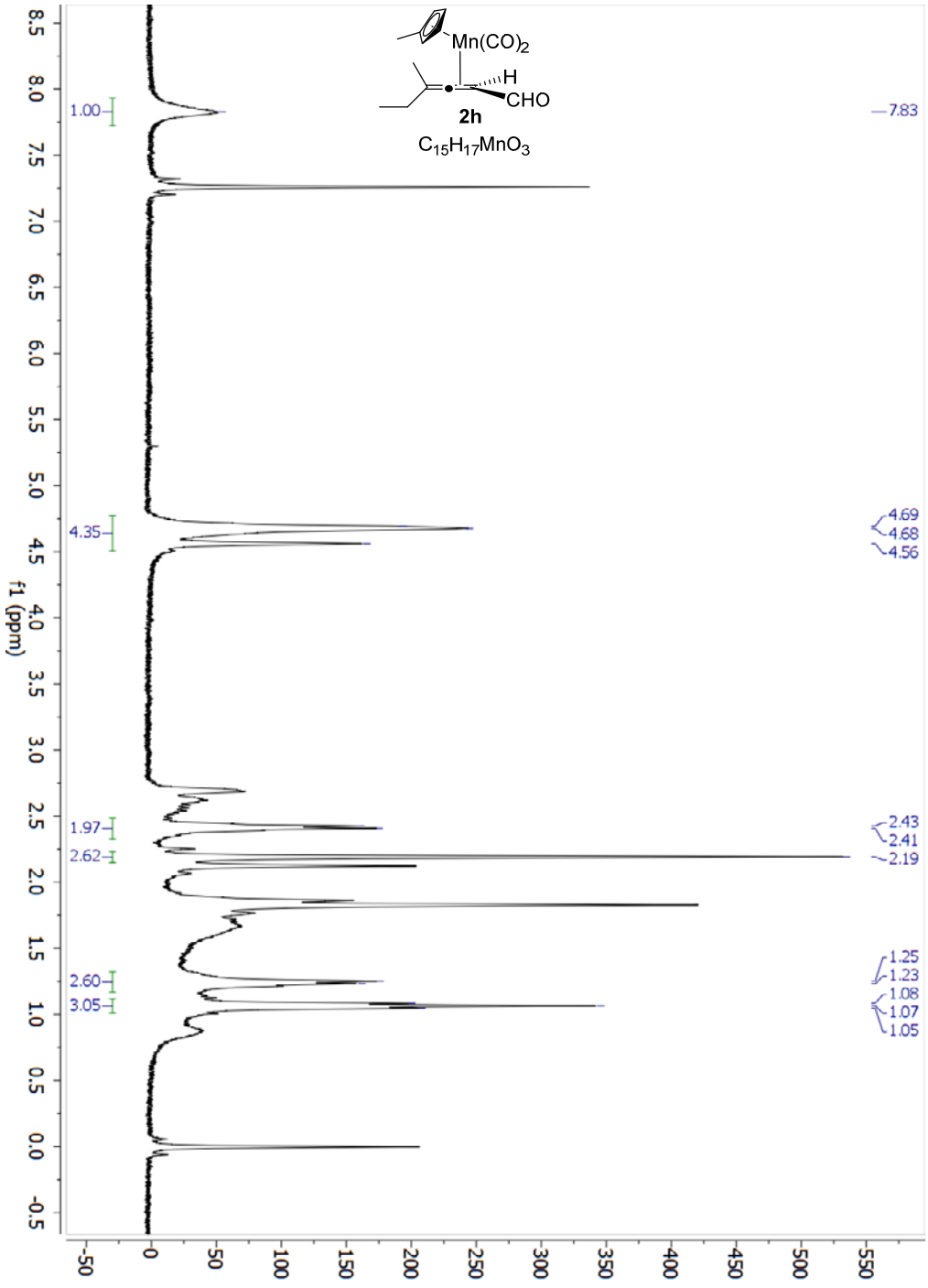
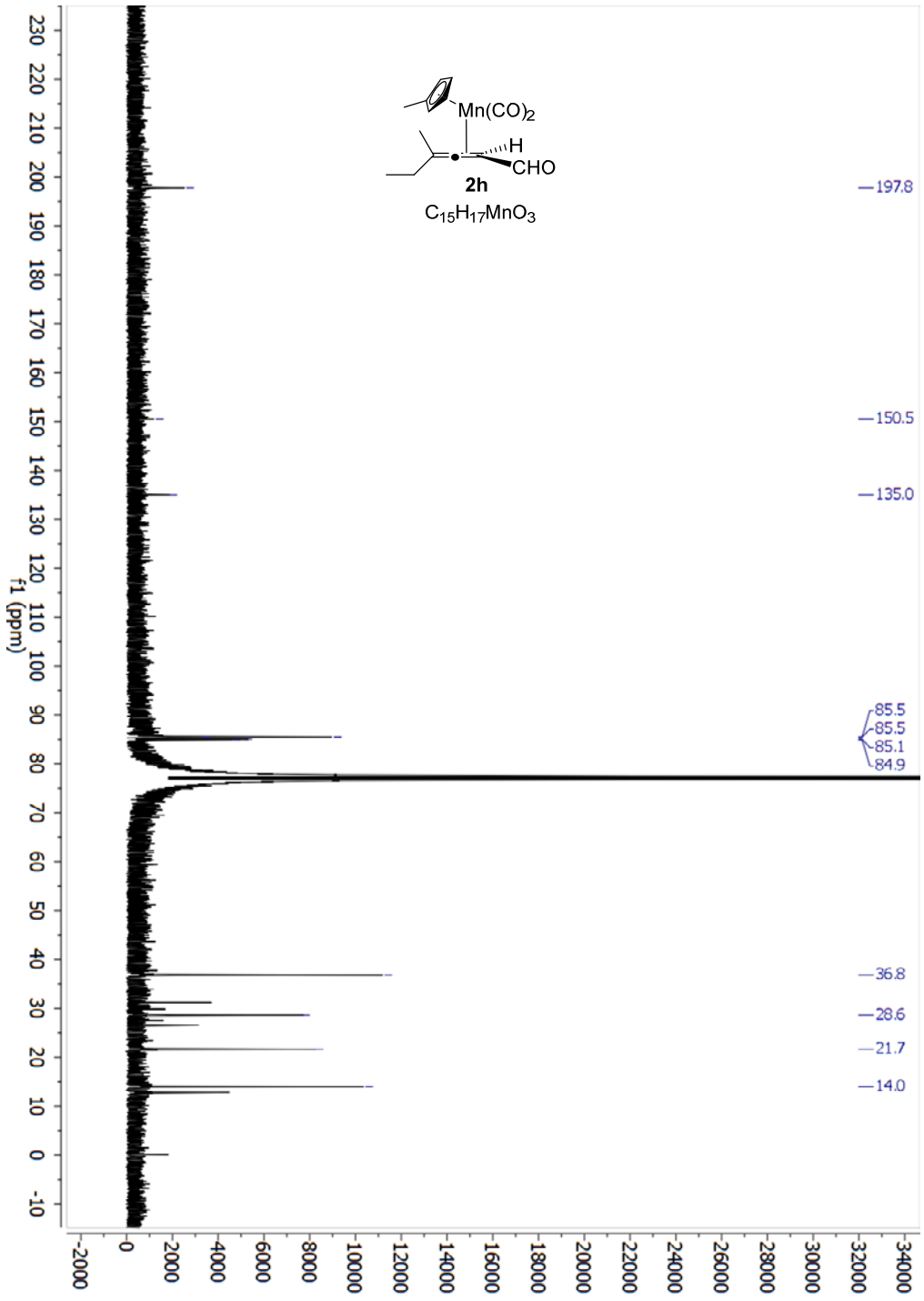
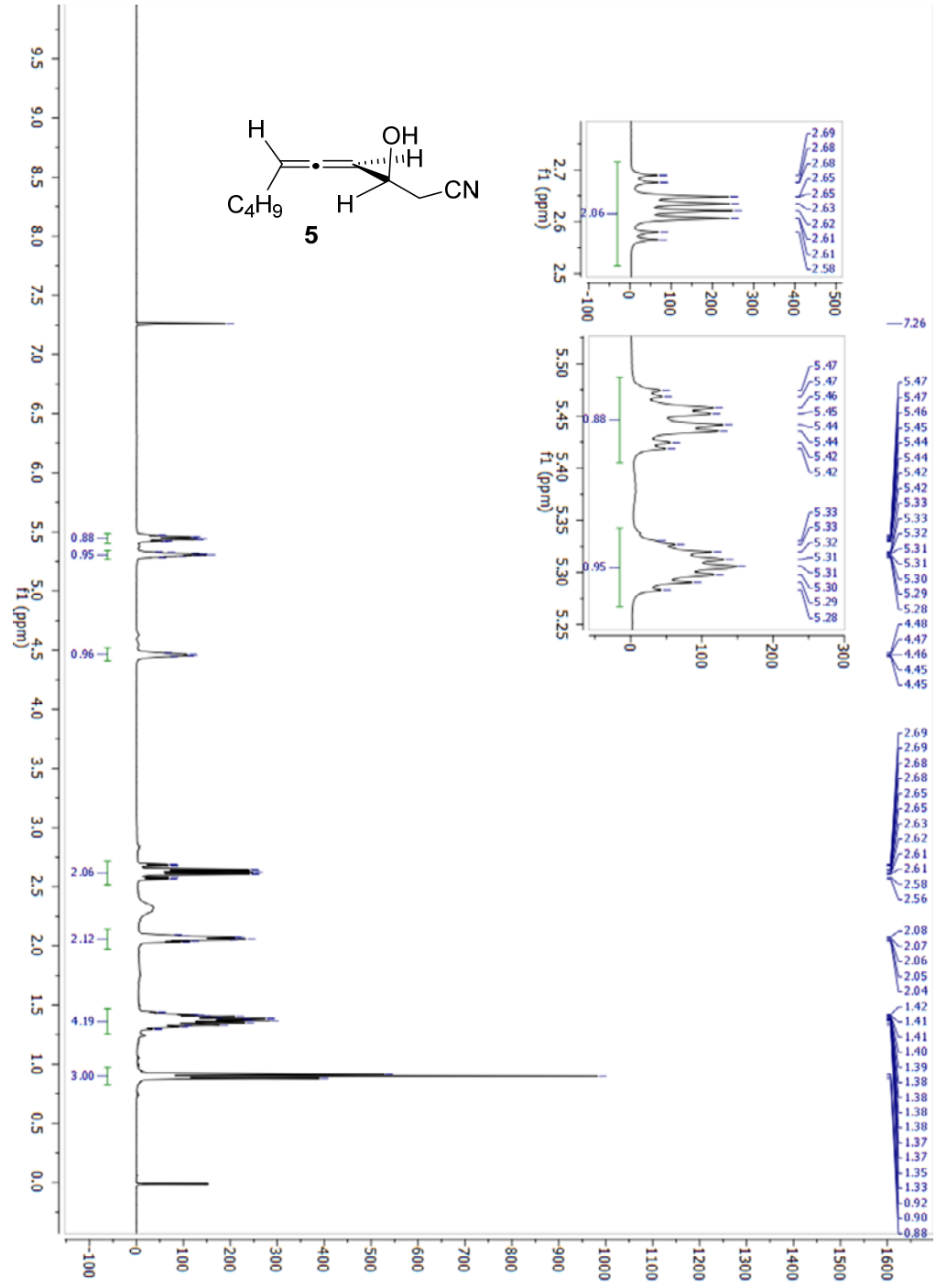
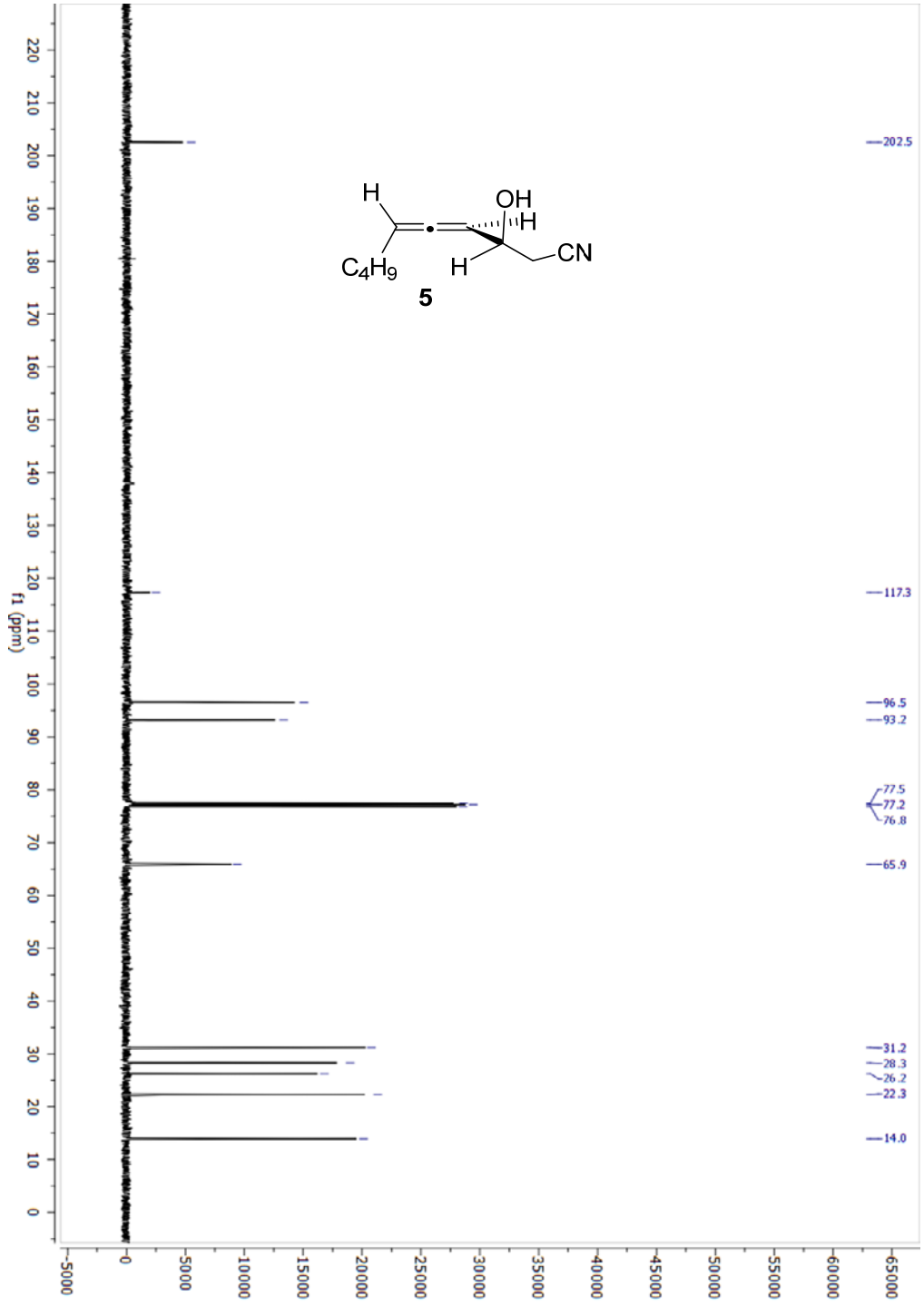
2.69
2.68
2.68
2.67
2.66
2.66
1.83

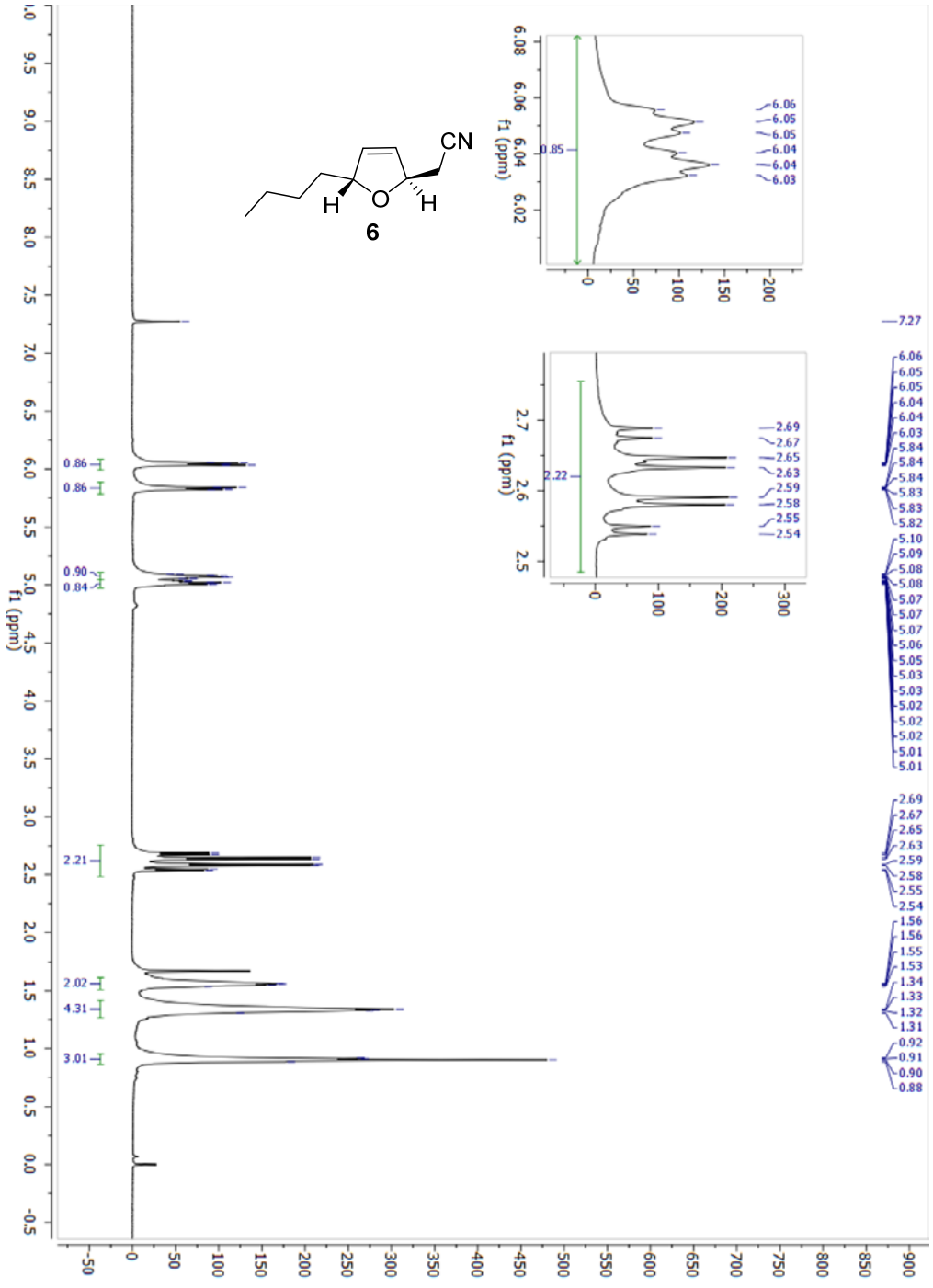

Mn(CO)2
H
H
Si
O
CHO
2g
C28H29MnO4Si
197.0
138.5
128.5
127.8
127.7
125.2
110.1
87.5
86.6
85.7
85.1
73.0
70.0
37.8
34.1
27.8
12.8
f1 (ppm)

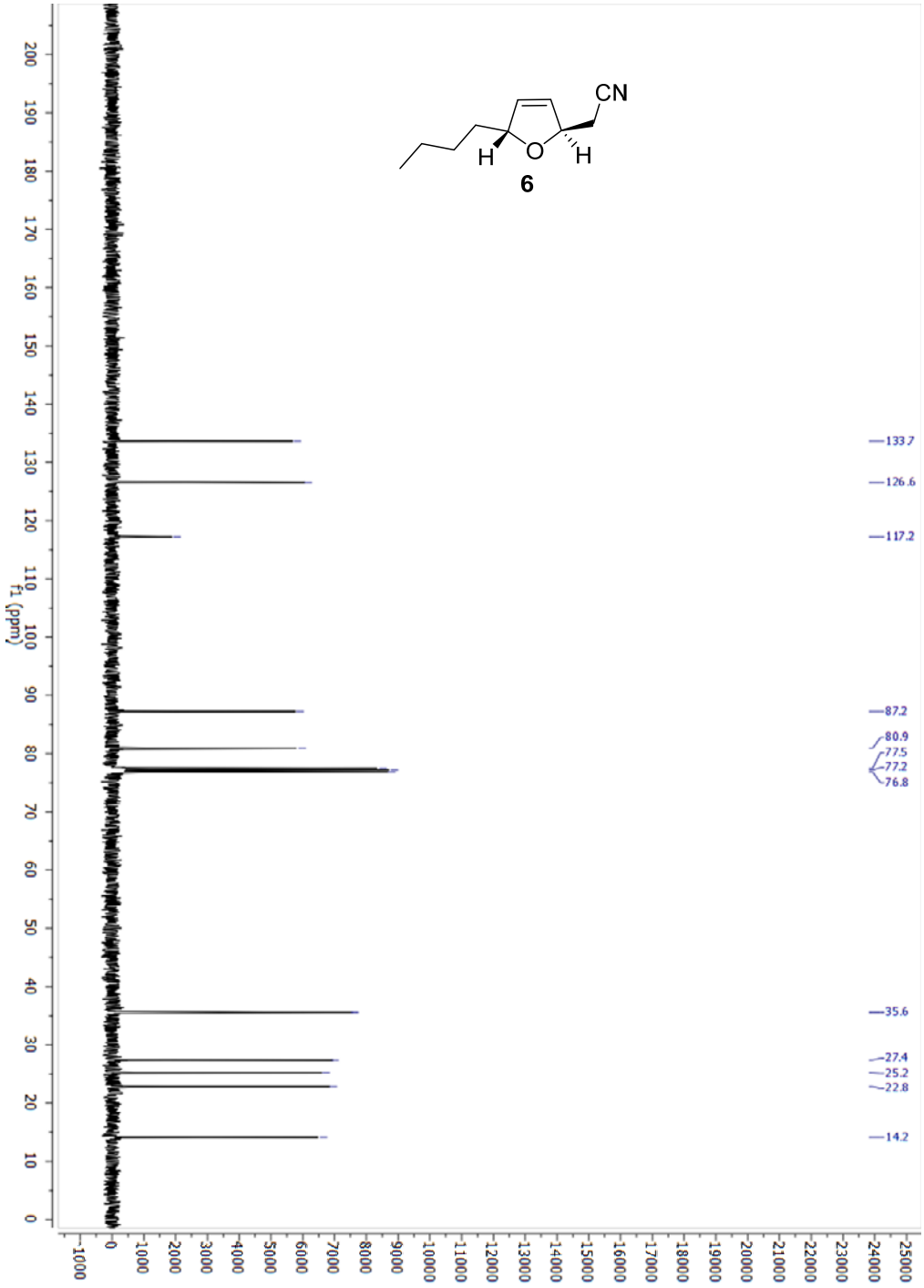

Mn(CO)2
H
CHO
2h
C15H17MnO3
f1 (ppm)
1.00
4.35
1.97
2.62
2.60
3.05
7.83
4.69
4.68
4.56
2.43
2.41
2.19
1.25
1.23
1.08
1.07
1.05

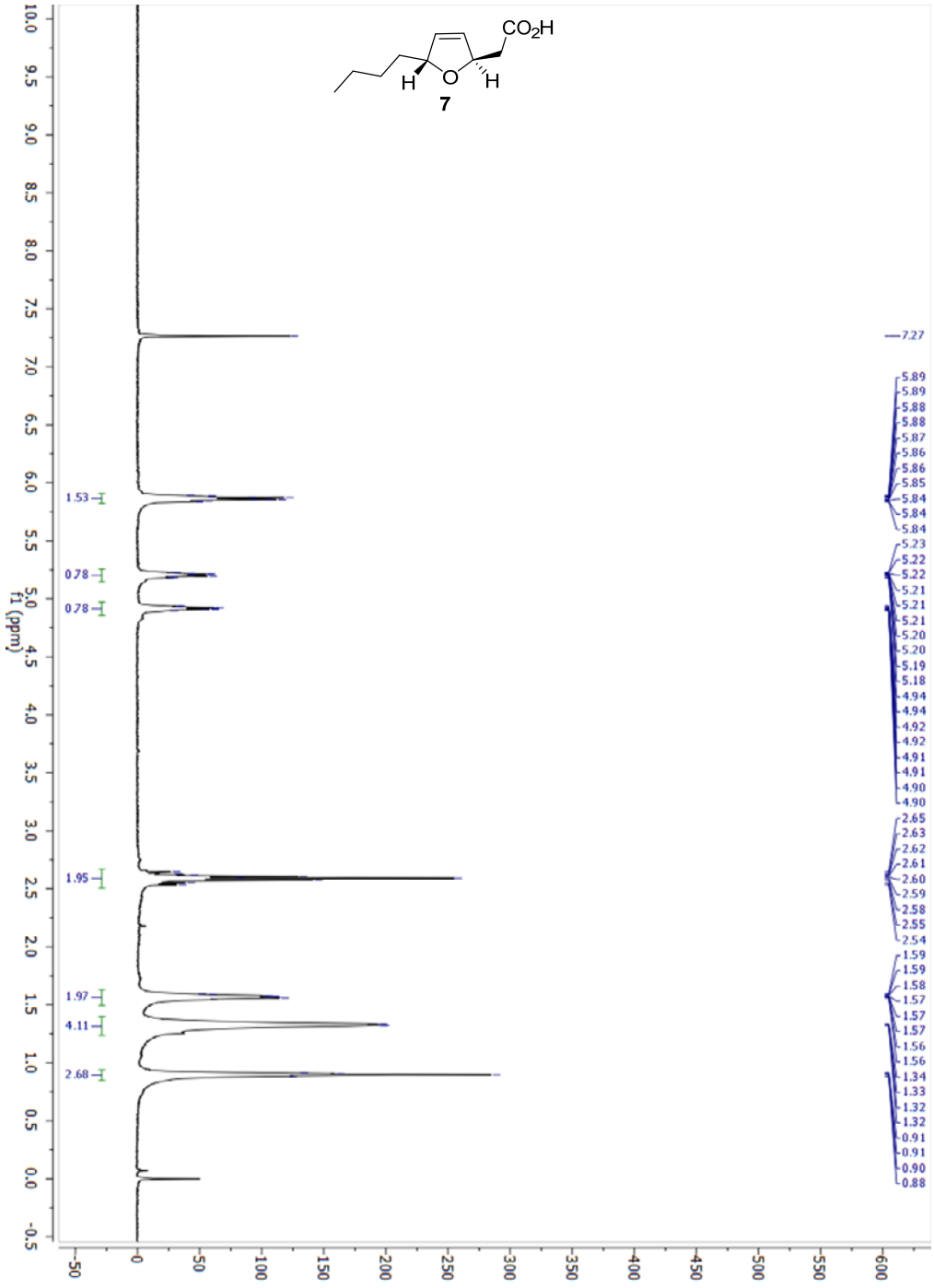

Mn(CO)2
H
CHO
2h
C15H17MnO3
197.8
150.5
135.0
85.5
85.5
85.1
84.9
36.8
28.6
21.7
14.0
f1 (ppm)

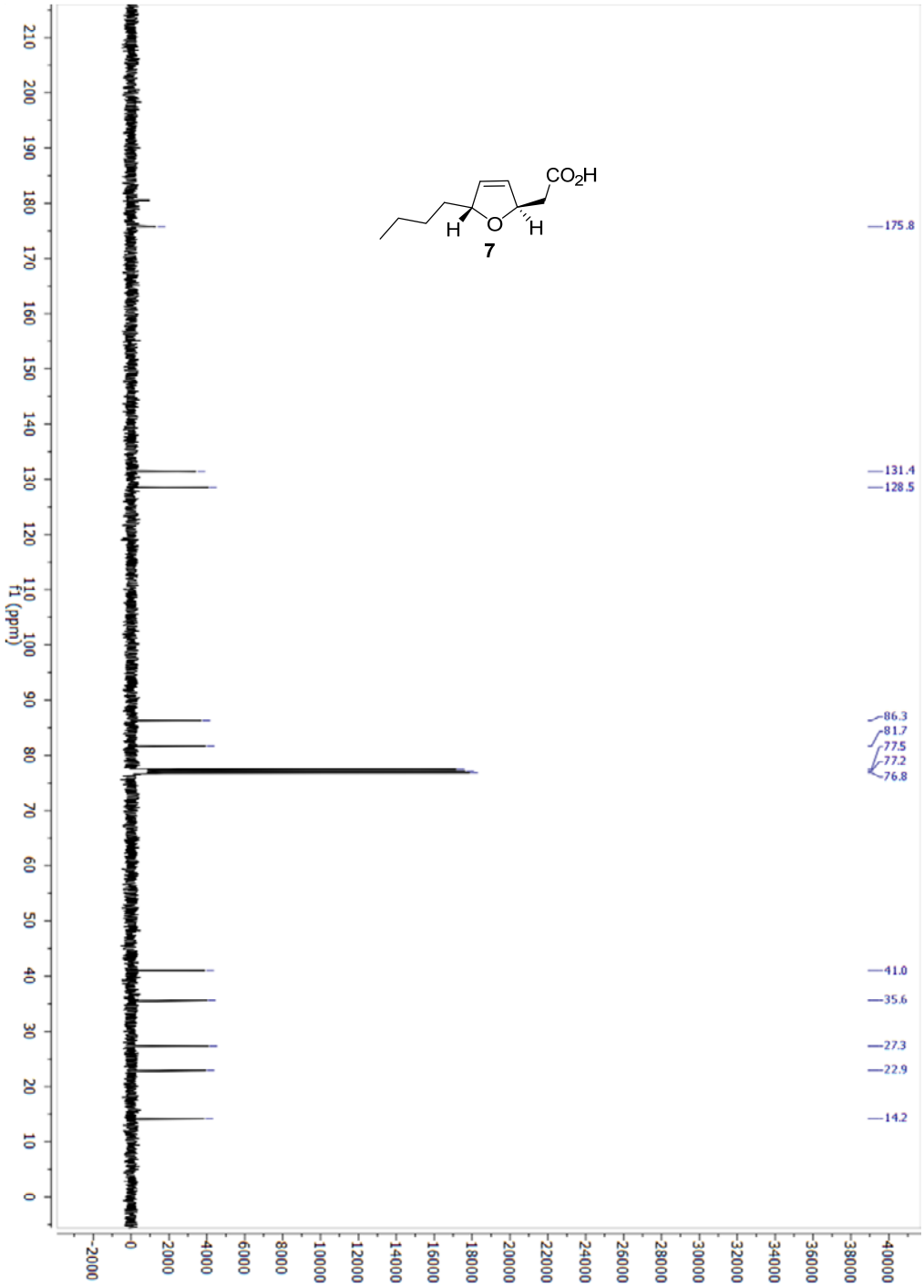

H
OH
H
C4H9
H
CN
5
f1 (ppm)
0.88
0.95
0.96
2.06
2.12
4.19
3.00
2.06
0.88
0.95
7.26

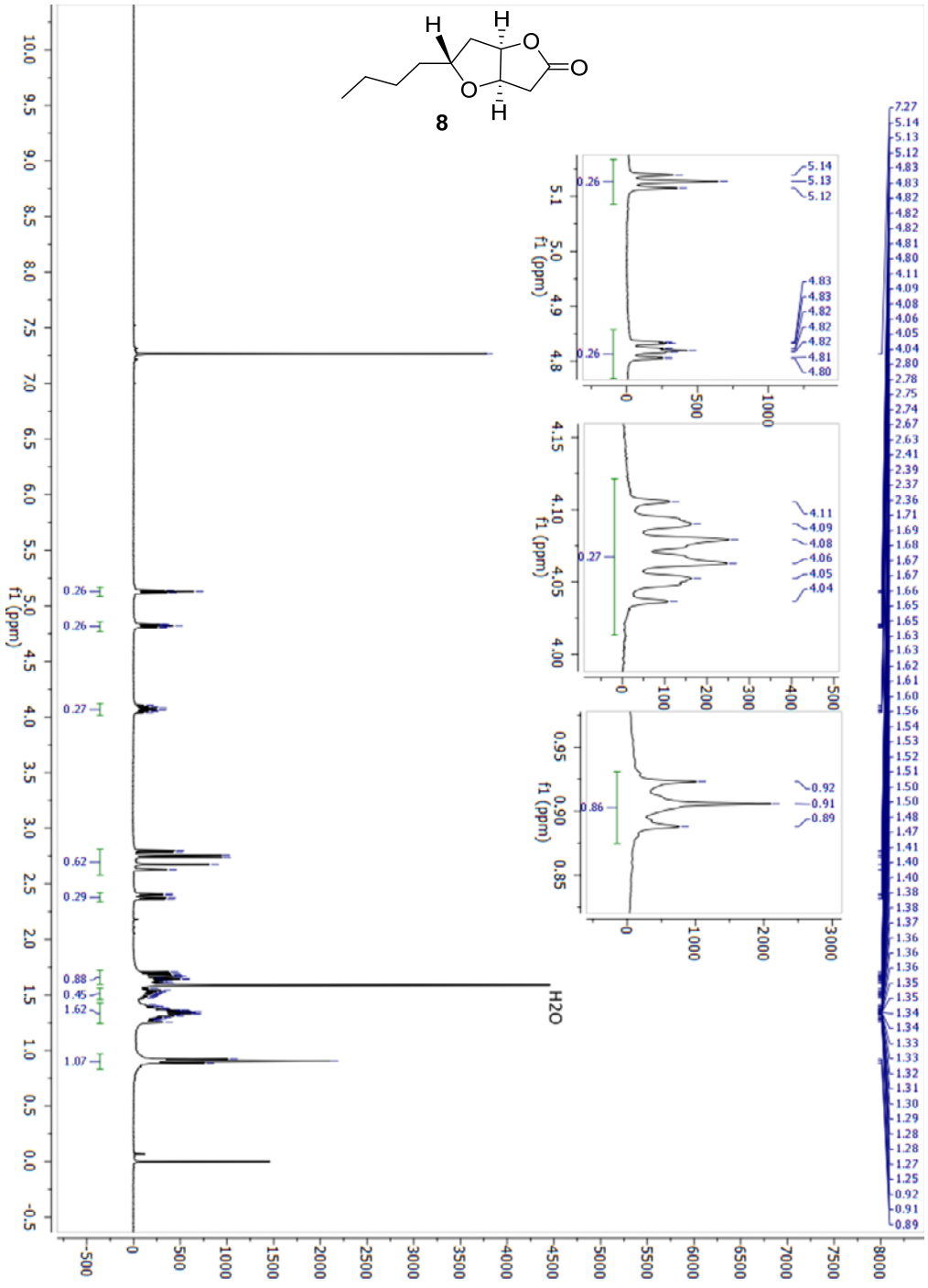

H
OH
H
C_4H_9
H
CN
5
202.5
117.3
96.5
93.2
77.5
77.2
76.8
65.9
31.2
28.3
26.2
22.3
14.0
f1 (ppm)

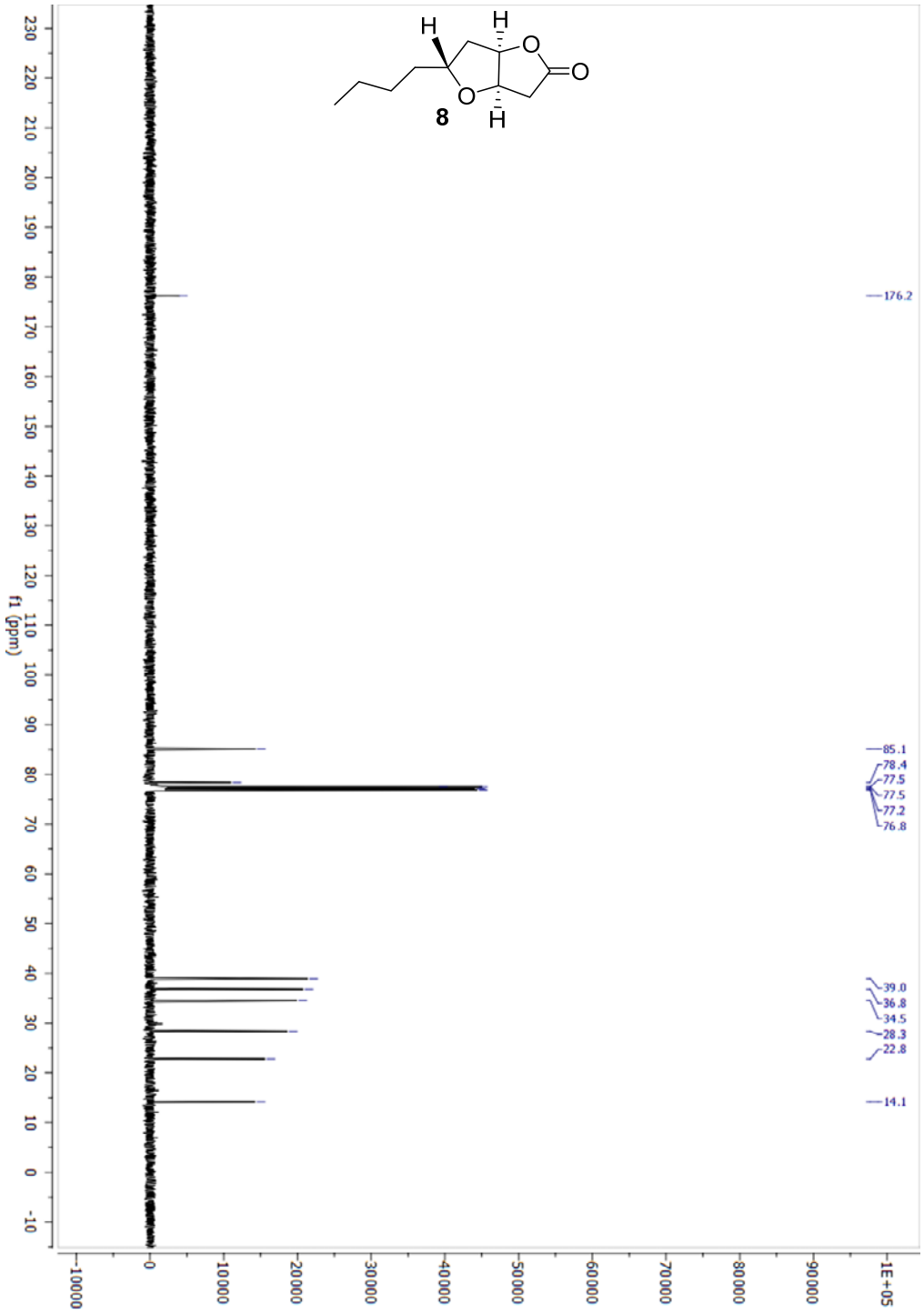

CN
H
O
H
6
f1 (ppm)
0.85
2.22
7.27
0.86
0.86
0.90
0.84
2.21
2.02
4.31
3.01

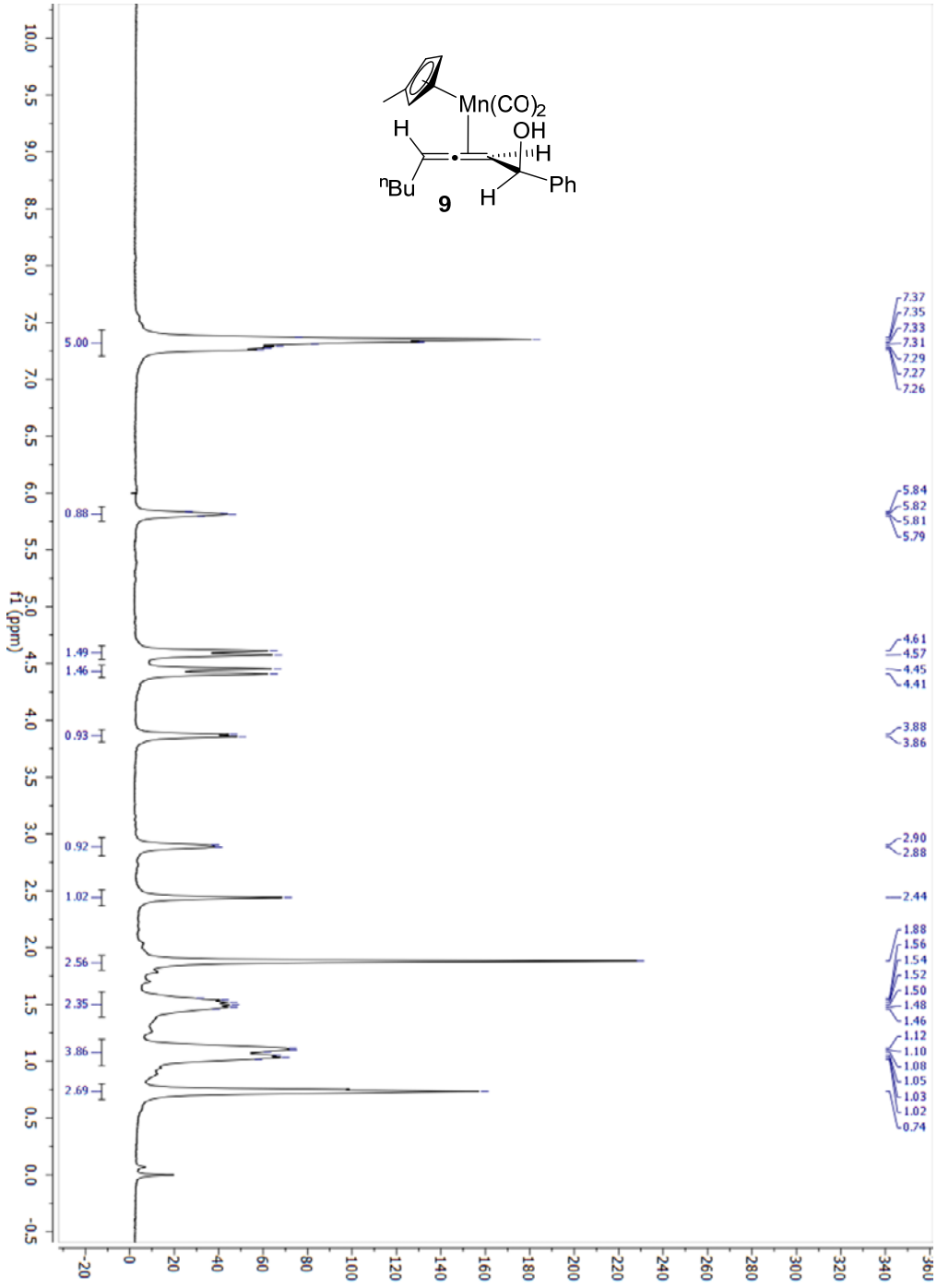

CN
H
O
H
6
133.7
126.6
117.2
87.2
80.9
77.5
77.2
76.8
35.6
27.4
25.2
22.8
14.2
f1 (ppm)

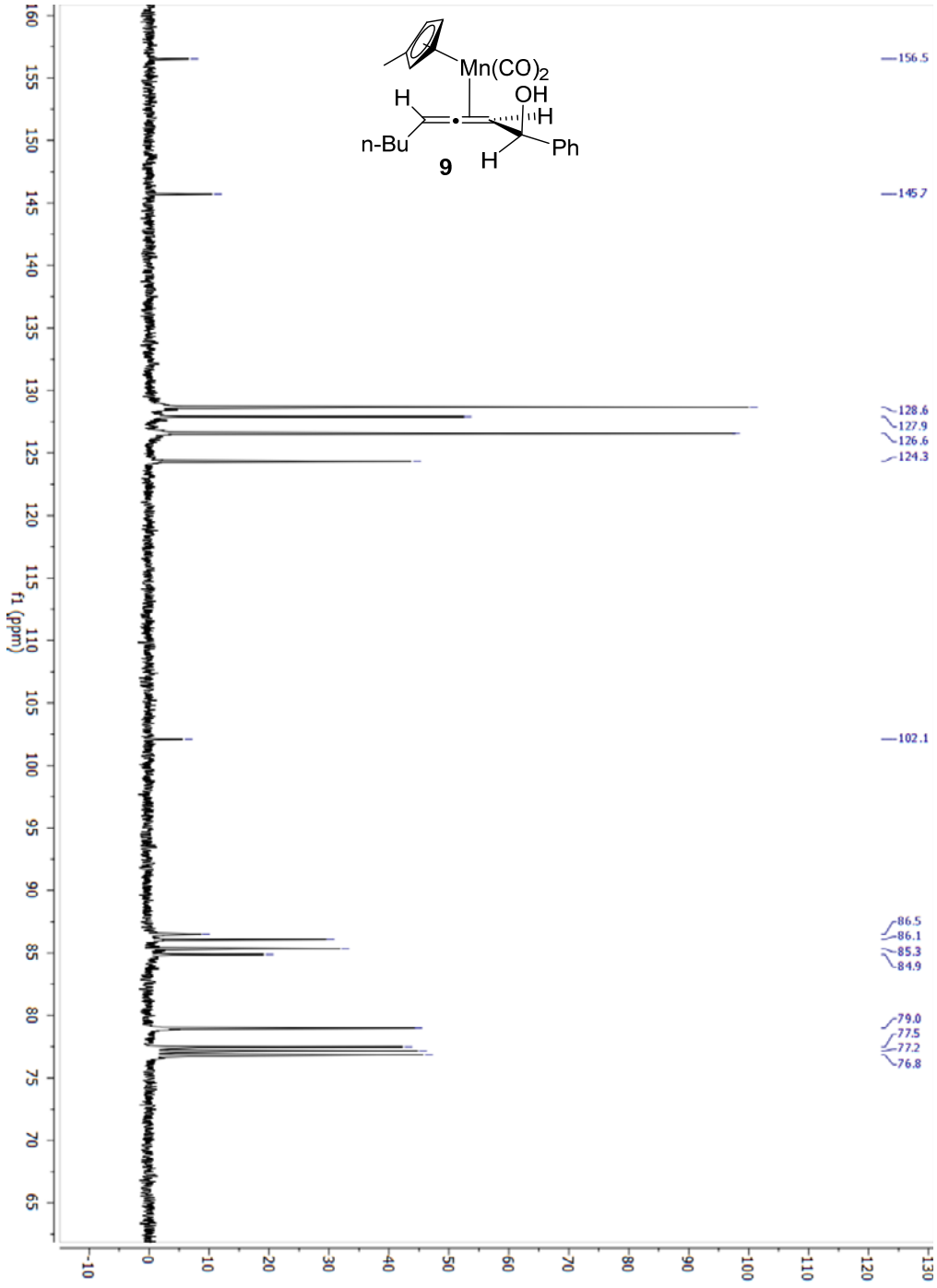

CO2H
H
O
H
7
f1 (ppm)
1.53
0.78
0.78
1.95
1.97
4.11
2.68
7.27
5.89
5.89
5.88
5.88
5.87
5.86
5.86
5.85
5.84
5.84
5.84
5.23
5.22
5.22
5.21
5.21
5.21
5.20
5.20
5.19
5.18
4.94
4.94
4.92
4.92
4.91
4.91
4.90
4.90
2.65
2.63
2.62
2.61
2.60
2.59
2.58
2.55
2.54
1.59
1.59
1.58
1.57
1.57
1.57
1.56
1.56
1.34
1.33
1.32
1.32
0.91
0.91
0.90
0.88

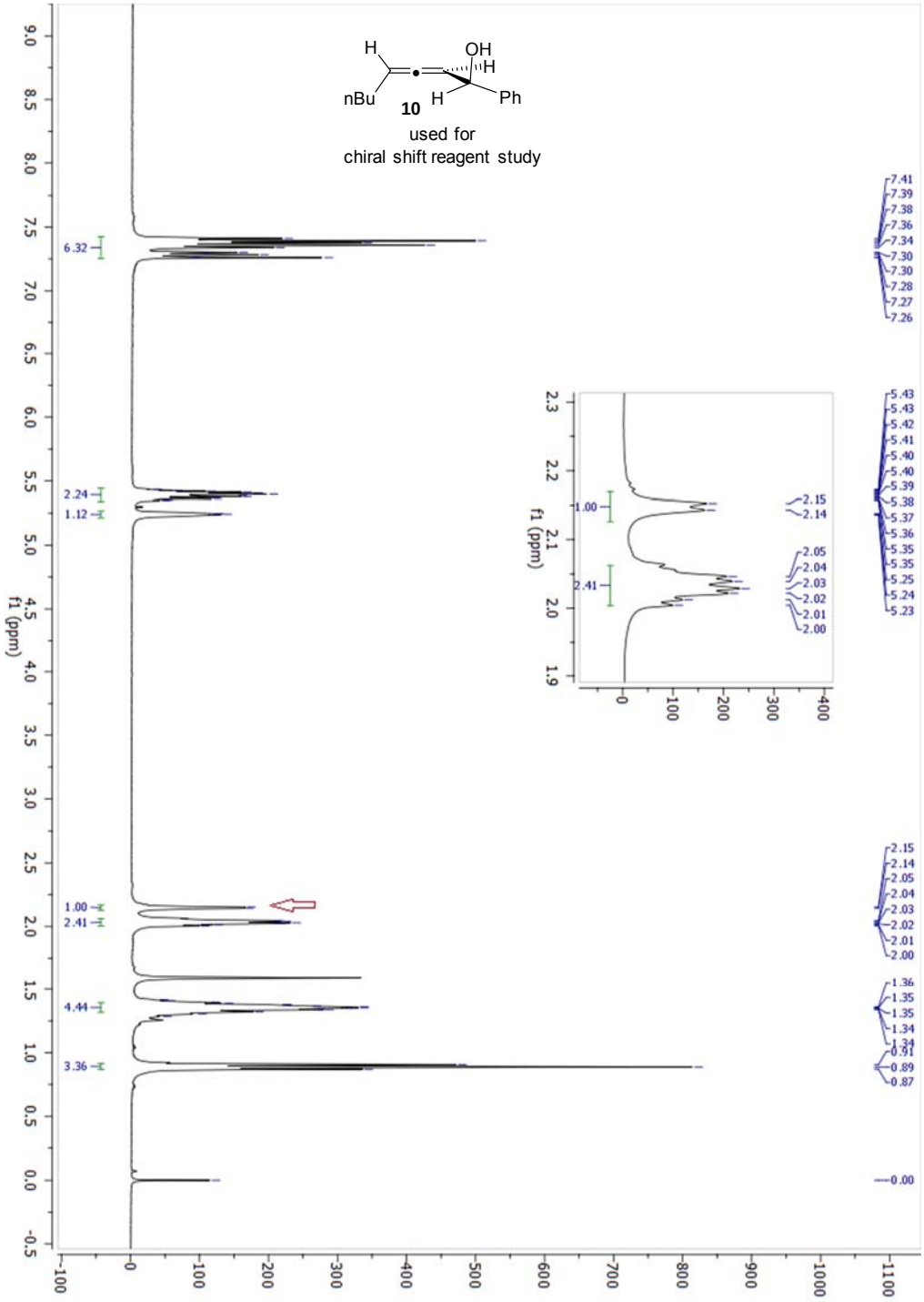

CO2H
H
O
H
7
175.8
131.4
128.5
86.3
81.7
77.5
77.2
76.8
41.0
35.6
27.3
22.9
14.2
f1 (ppm)


8
H2O
f1 (ppm)


H
H
O
O
O
H
8
176.2
85.1
78.4
77.5
77.5
77.2
76.8
39.0
36.8
34.5
28.3
22.8
14.1
f1 (ppm)

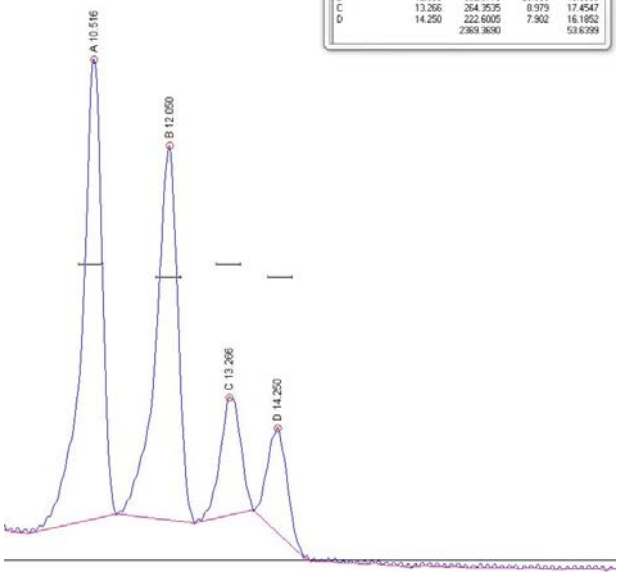

Mn(CO)2
H
OH
H
nBu
Ph
H
9
f1 (ppm)
5.00
0.88
1.49
1.46
0.93
0.92
1.02
2.56
2.35
3.86
2.69
7.37
7.35
7.33
7.31
7.29
7.27
7.26
5.84
5.82
5.81
5.79
4.61
4.57
4.45
4.41
3.88
3.86
2.90
2.88
2.44
1.88
1.56
1.54
1.52
1.50
1.48
1.46
1.12
1.10
1.08
1.05
1.03
1.02
0.74

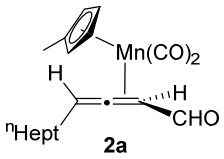

Mn(CO)2
H
OH
H
n-Bu
Ph
H
9
156.5
145.7
128.6
127.9
126.6
124.3
102.1
86.5
86.1
85.3
84.9
79.0
77.5
77.2
76.8
f1 (ppm)


H
OH
H
nBu
H
Ph
10
used for
chiral shift reagent study
f1 (ppm)
6.32
2.24
1.12
1.00
2.41
4.44
3.36
7.41
7.39
7.38
7.36
7.34
7.30
7.30
7.28
7.27
7.26
5.43
5.43
5.42
5.41
5.40
5.40
5.39
5.38
5.37
5.36
5.35
5.35
5.25
5.24
5.23
2.15
2.14
2.05
2.04
2.03
2.02
2.01
2.00
1.36
1.35
1.35
1.34
1.34
0.91
0.89
0.87
0.00

Results

Component	Retention	Area	Height	External
A	10.516	999.5380	34.787	10.0000
B	12.050	882.8770	28.336	10.0000
C	13.266	264.3535	0.979	17.4547
D	14.250	222.6005	7.902	16.1852
		2369.3690		53.6299



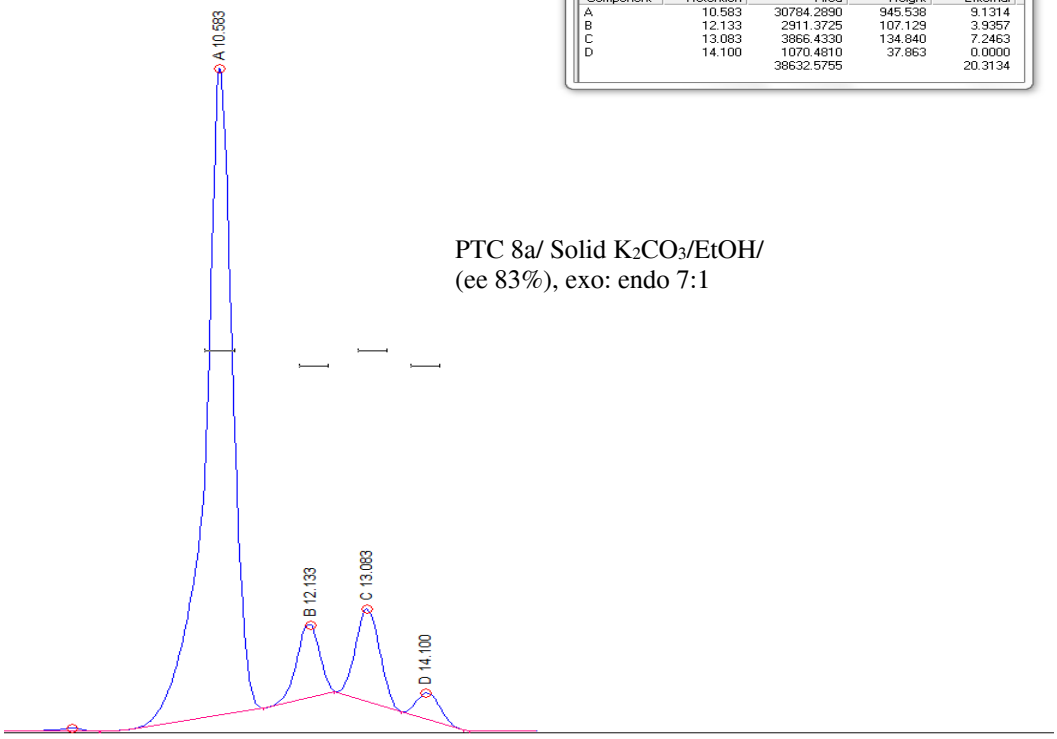


2a

TBAB/K2CO3/EtOH/RT; rac

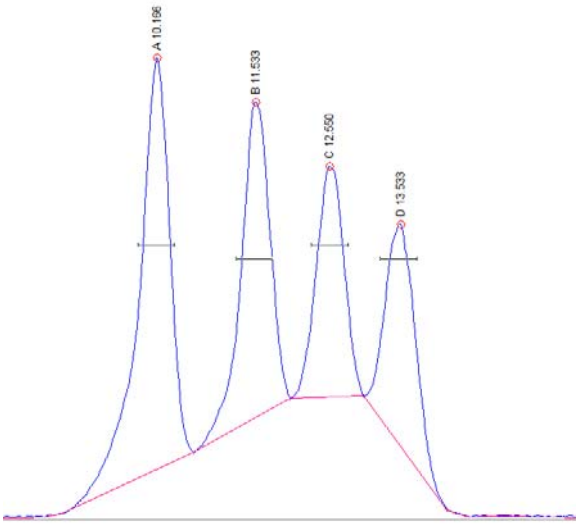
Results

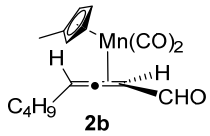
Component	Retention	Area	Height	External
A	10.583	30784.2890	945.538	9.1314
B	12.133	2911.3725	107.129	3.9357
C	13.083	3866.4330	134.840	7.2463
D	14.100	1070.4810	37.863	0.0000
		38632.5755		20.3134



PTC 8a/ Solid K_2CO_3/EtOH/
(ee 83%), exo: endo 7:1

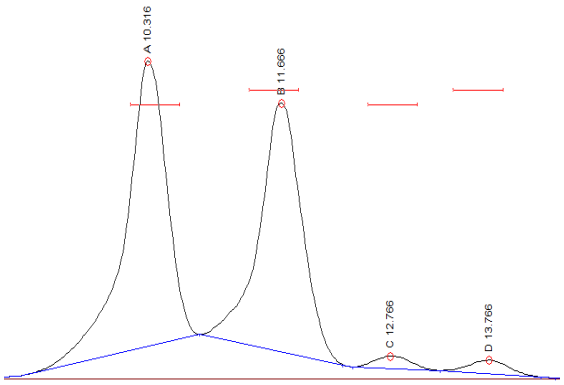
TBAB/ Solid K_2CO_3/EtOH/
Rac, exo: endo 1:1

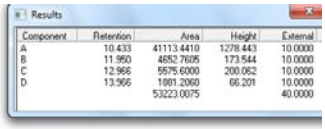




2b

DBU; rac
High exo:endo ratio

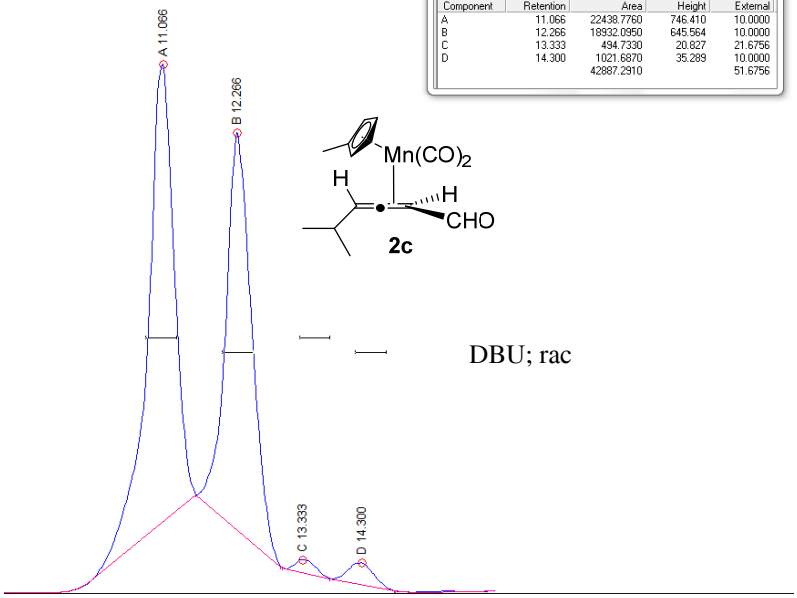




PTC 8a/ Solid K_2CO_3/EtOH/
(ee 79%), exo: endo 6:1

Results

Component	Retention	Area	Height	External
A	11.066	22438.7760	746.410	10.0000
B	12.266	18932.0950	645.564	10.0000
C	13.333	494.7330	20.827	21.6756
D	14.300	1021.6870	35.289	10.0000
		42887.2910		51.6756

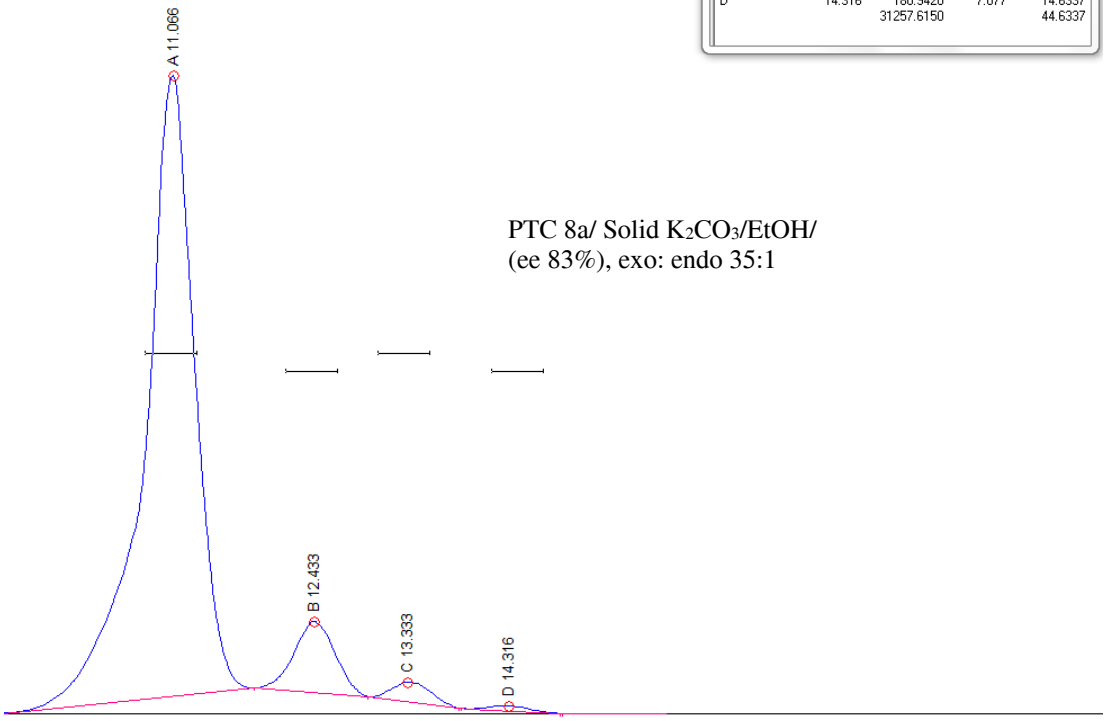


2c

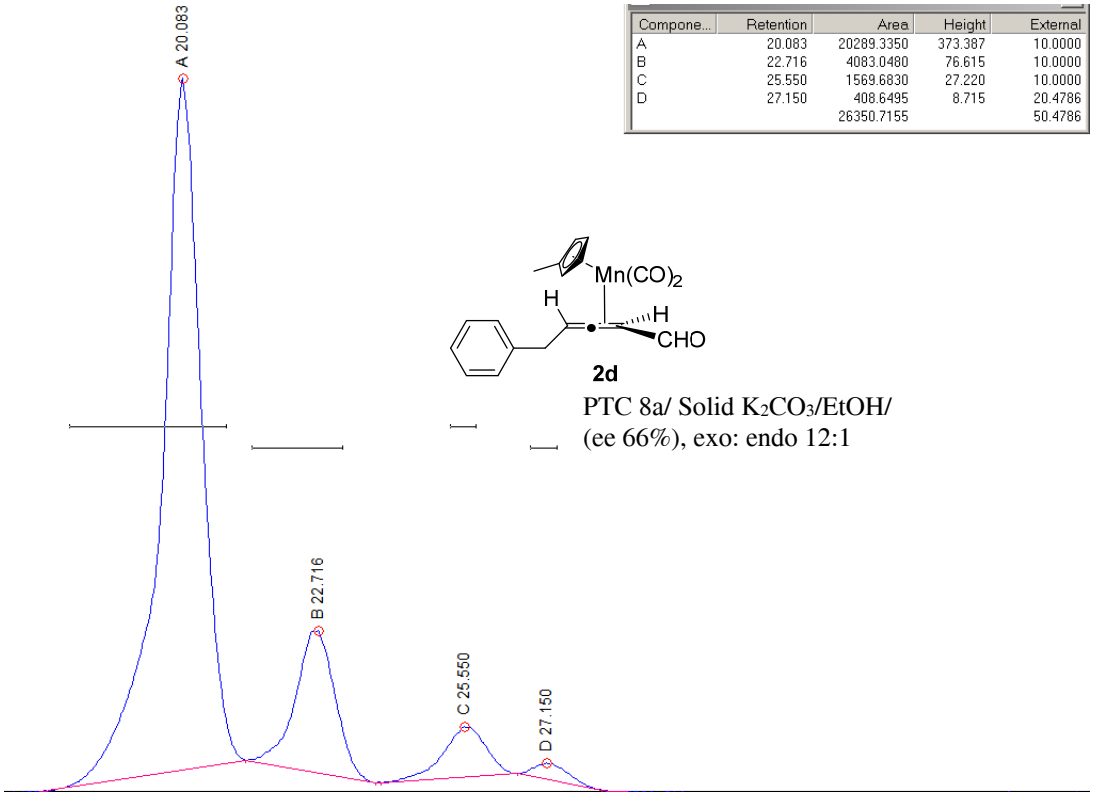
DBU; rac

Results

Component	Retention	Area	Height	External
A	11.066	27817.7970	823.338	10.0000
B	12.433	2579.4900	94.384	10.0000
C	13.333	679.3860	25.743	10.0000
D	14.316	180.9420	7.077	14.6337
		31257.6150		44.6337



PTC 8a/ Solid K_2CO_3/EtOH/
(ee 83%), exo: endo 35:1



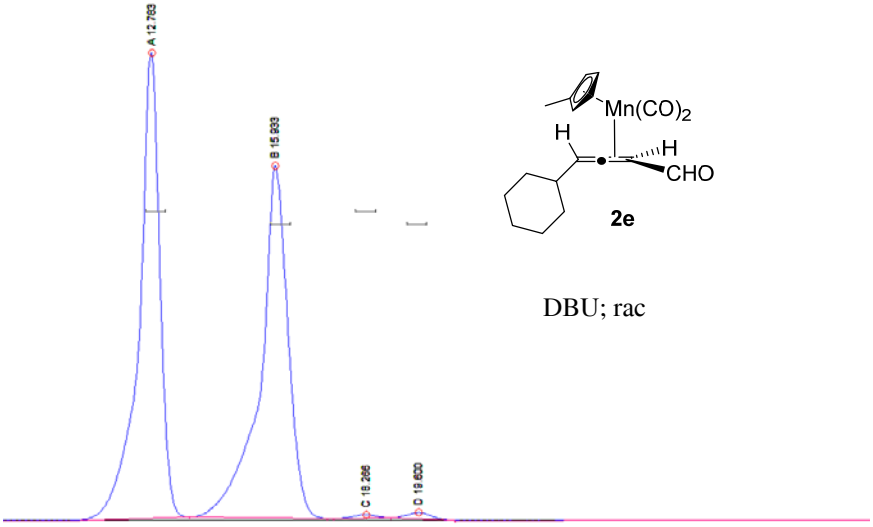
Compone...	Retention	Area	Height	External
A	20.083	20289.3350	373.387	10.0000
B	22.716	4083.0480	76.615	10.0000
C	25.550	1569.6830	27.220	10.0000
D	27.150	408.6495	8.715	20.4786
		26350.7155		50.4786

2d

PTC 8a/ Solid K_2CO_3/EtOH/
(ee 66%), exo: endo 12:1

Results

Component	Retention	Area	Height	External
A	12.783	17827.9260	484.160	10.0000
B	15.933	17943.7370	366.624	10.0000
C	18.266	130.6000	3.010	12.6647
D	19.600	279.6740	6.830	17.8629
		36190.1450		50.5286

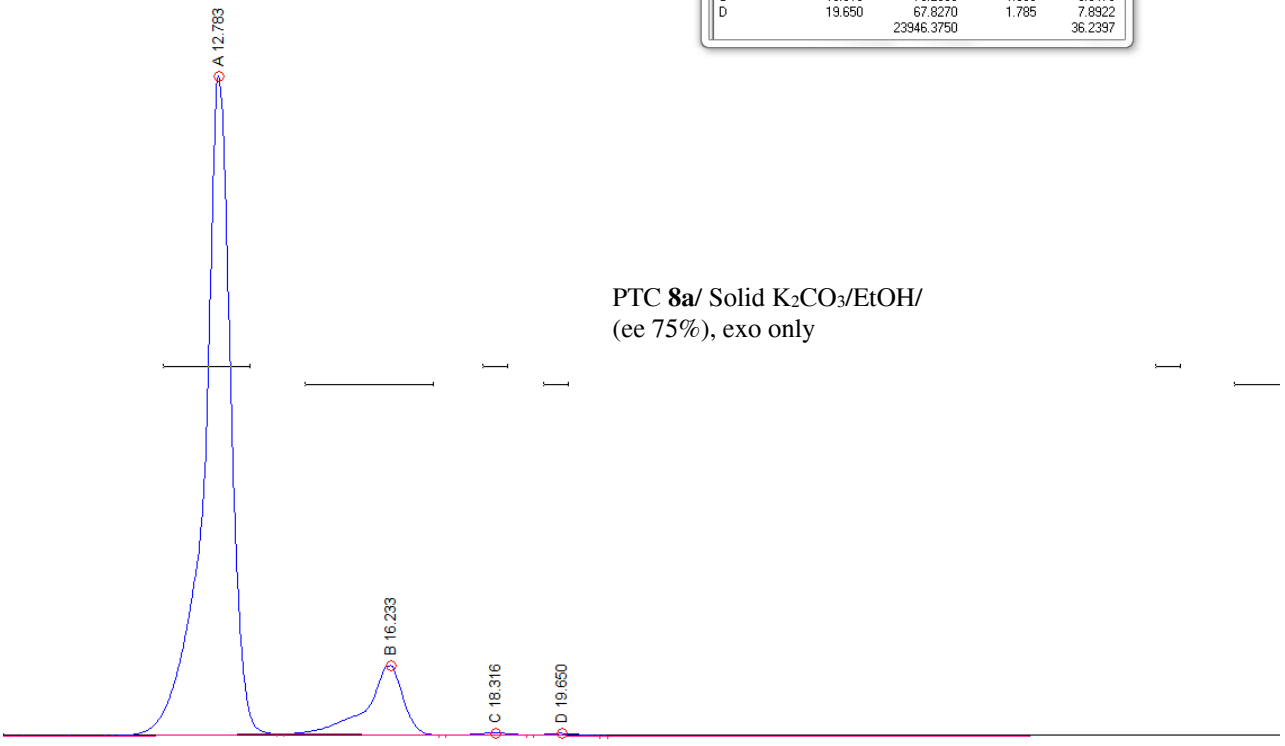


2e

DBU; rac

Results

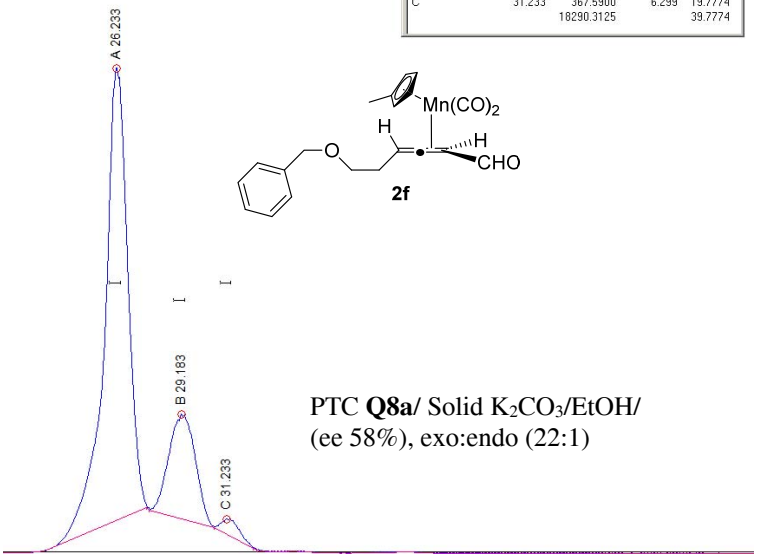
Component	Retention	Area	Height	External
A	12.783	20855.1290	562.654	10.0000
B	16.233	2950.1690	58.929	10.0000
C	18.316	73.2500	1.935	8.3476
D	19.650	67.8270	1.785	7.8922
		23946.3750		36.2397



PTC **8a/** Solid K_2CO_3/EtOH/
(ee 75%), exo only

Results

Component	Retention	Area	Height	External
A	26.233	14224.0100	196.989	10.0000
B	29.183	3698.7125	45.134	10.0000
C	31.233	367.5900	6.299	19.7774
		18290.3125		39.7774

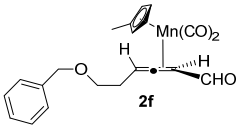


2f

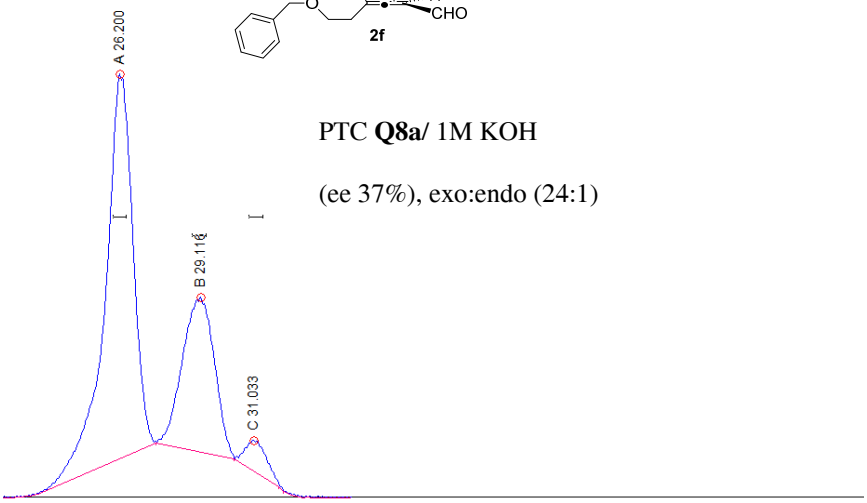
PTC **Q8a/** Solid K_2CO_3/EtOH/
(ee 58%), exo:endo (22:1)

Results

Component	Retention	Area	Height	External
A	26.200	4193.1060	60.426	10.0000
B	29.116	1919.3535	24.239	10.0000
C	31.033	249.4640	4.660	17.0297
		6361.9235		37.0297

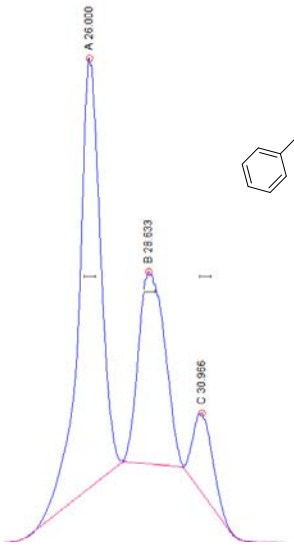


2f



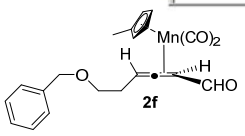
PTC **Q8a/** 1M KOH

(ee 37%), exo:endo (24:1)



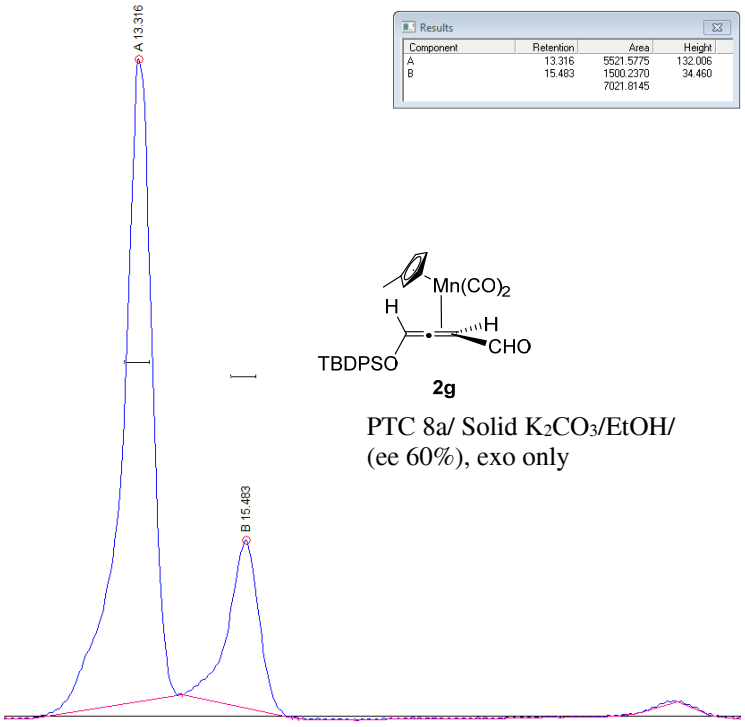
Results

Compone...	Retention	Area	Height	External
A	26.000	17398.6515	261.559	10.0000
B	28.633	9288.9015	116.771	10.0000
C	30.966	2812.3570	47.843	10.0000
		29499.9100		30.0000



2f

PTC **Q1D**/ 1M KOH
(ee 30%), exo:endo (9:1)



Results

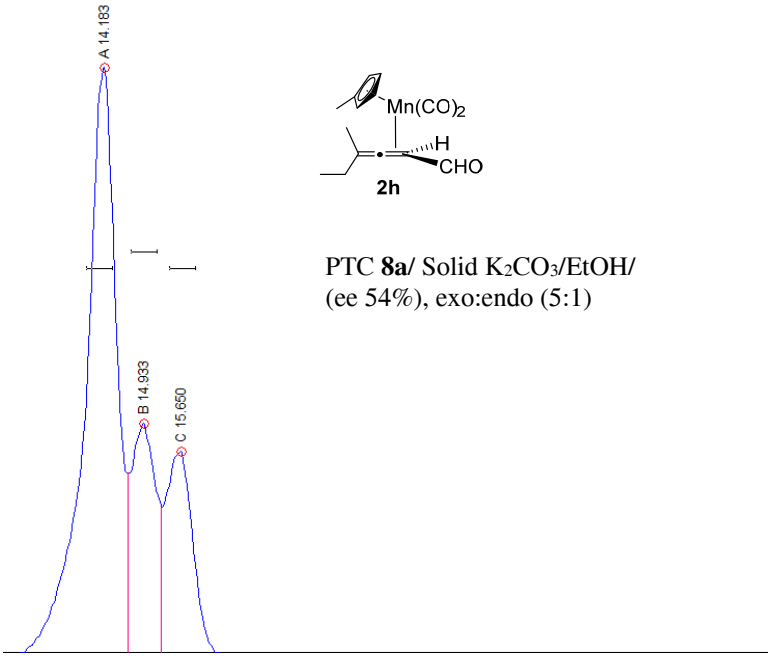
Component	Retention	Area	Height
A	13.316	5521.5775	132.006
B	15.483	1500.2370	34.460
		7021.8145	

2g

PTC 8a/ Solid K_2CO_3/EtOH/
(ee 60%), exo only

Results

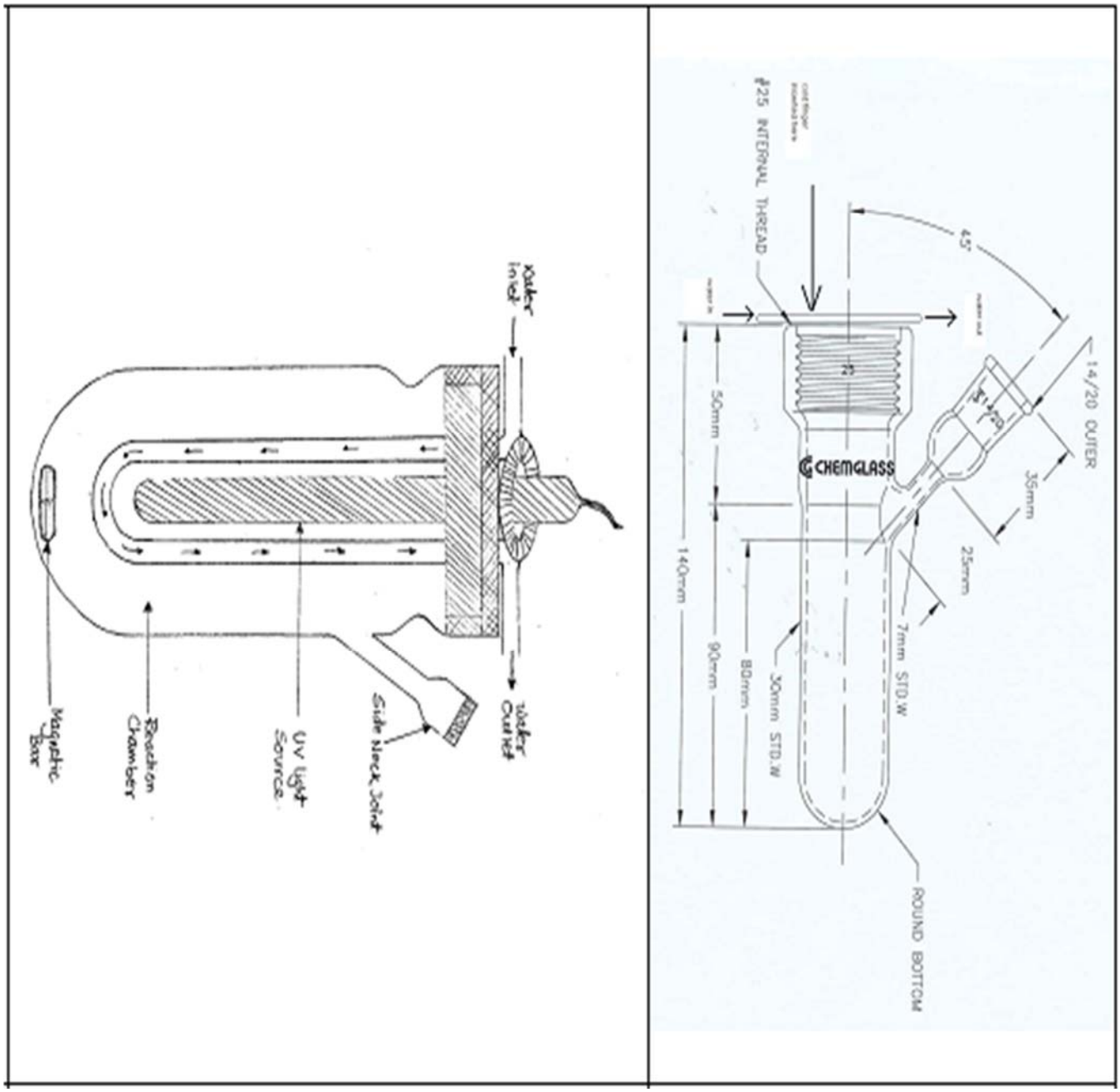
Component	Retention	Area	Height	External
A	14.183	3494.9555	81.543	10.0000
B	14.933	1045.9630	32.423	10.0000
C	15.650	1028.1025	28.578	10.0000
		5569.0210		30.0000



2h

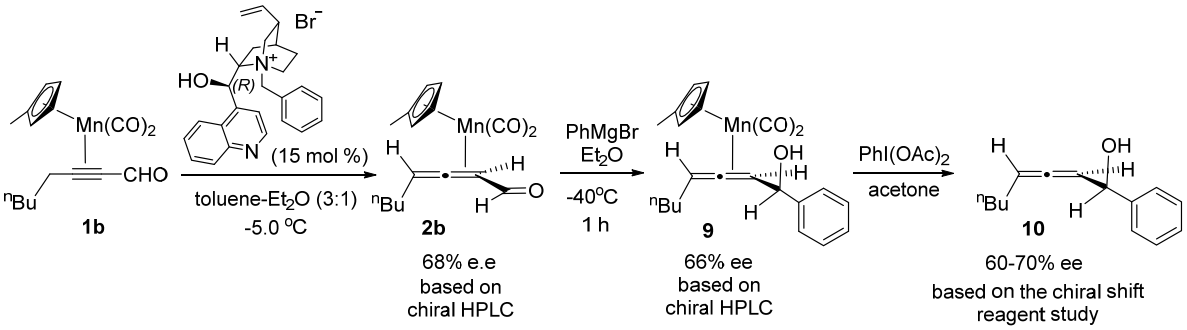
PTC **8a/** Solid K_2CO_3/EtOH/
(ee 54%), exo:endo (5:1)

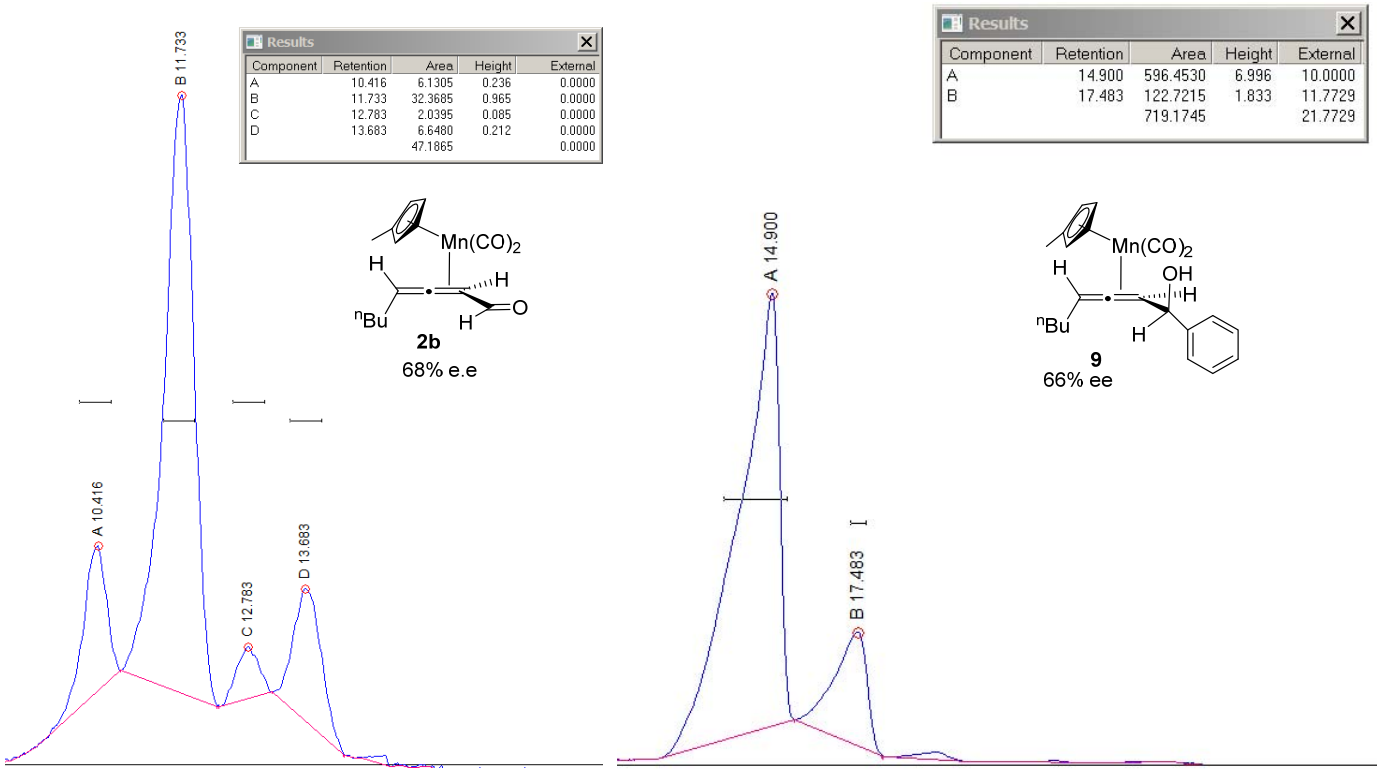
Schematic of photoreactor and sketch of setup for MMD-complexation reaction.

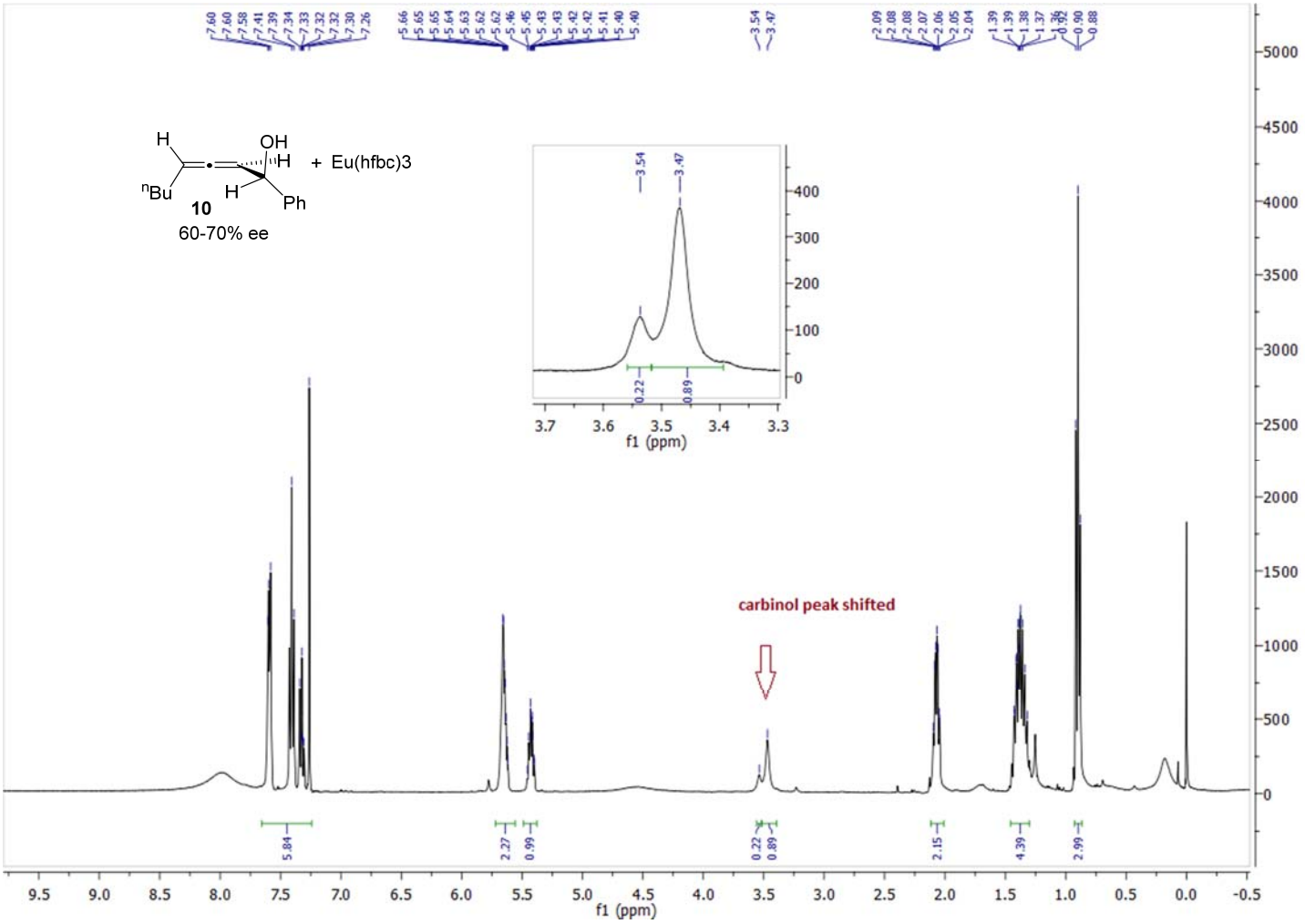


Calibrating enantiomeric excess measurement via chiral shift reagent study:

Compound **2b** (68% ee) was reacted with Grignard reagent to prepare **9** (66% ee). It was decomplexed and enantiomeric excess was determined via chiral shit reagent study (see pages S46 and S47).






+ Eu(hfbc)3
10
60-70% ee
carbinol peak shifted
f1 (ppm)

NMR experiment with shift reagent to determine enantiomeric excess of allenol **10:**

Dry $CDCl_3$ solution of shift reagent (europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]) was added dropwise to a dry $CDCl_3$ solution of allenol **10** and NMR spectra were recorded until hydroxyl peak at 2.15 ppm were resolved (see page S46). When 20 drops of shift reagent was added, carbinol peak was mostly resolved. Integration is in the range of 60-70% ee