Pd(II)-Catalyzed Asymmetric Addition Reaction of Malonates to Dihydroisoquinolines

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Supporting Information

(A) General

(B) Preparation of imines used in this work

(C) A representative procedure for the catalytic asymmetric addition reaction of malonates to dihydroisoquinolines and analytical data of the products

(D) Asymmetric synthesis of calycotomine

(E) Procedure for dehydrogenative addition reaction of malonate

(F) NMR spectra

(A) General

Catalysts used in this paper were prepared according to the reported procedure.[1] NMR spectra were recorded on a JEOL JNM-LA400 spectrometer, operating at 400 MHz for ^{1}H-NMR, 100.4 MHz for ^{13}C-NMR, or a JEOL JAM-LA300 spectrometer, operating at 300 MHz for ^{1}H-NMR, 75.0 MHz for ^{13}C-NMR. Chemical shifts were reported downfield from TMS (= 0) for ^{1}H-NMR. For ^{13}C-NMR, chemical shifts were reported in the scale relative to $CDCl_3$ as an internal reference. FAB-LRMS was taken on JEOL JMS GCmate II or JEOL Mstation JMS-700 using *m*-nitrobenzyl alcohol (*m*NBA) as matrix. Optical rotations were measured on a JASCO DIP-370 polarimeter. IR was measured on Thermo Nicolet AVATAR 370 FT-IR equipped with DuraScope™. Melting points were measured using Yanaco MP-J3. Flash column chromatography was performed with silica gel 60 (40-100 μm) purchased from KANTO CHEMICAL Co. In some cases, purification was carried out using Medium Pressure Liquid Chromatography (MPLC) consisting of the followings: Shimadzu MPLC systems [pump, LC-6AD; UV-detector, SPD-10A; RI-detector, RID-10A; column, Yamazen ULTRA SI-40A; eluent, *n*-hexane/ethyl acetate]. The enantiomeric excesses (ees) were determined by chiral HPLC analysis, which was performed on JASCO Borwin Ver.1.5 systems consisting of the followings: pump, PU-2080 Plus; detector, CD-2095 Plus measured at 254 nm or 280 nm; column, DAICEL CHIRALPAK AD-H, AS-H, IA; mobile phase, hexane/2-propanol (IPA). Solvents used in this paper were purchased and used directly. Other reagents were purified by usual methods.

(B) Preparation of imines used in this work

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[1] a) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450-5458. b) Hamashima, Y. Yagi, K.; Takano, H.; Tamás, L. Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530-14531.

All DHIQs were prepared by oxidation of the corresponding secondary amines or classical Bischler-Napieralski reaction according to the reported procedure.[2,3] Imines **2a**, **2c**, and **2d** are known compounds and the synthesized compounds were found identical by comparison of ^{1}H NMR. These methods were applied to the syntheses of other DHIQs **2b**, **2e**, **2f**, and **2g**. Electron-deficient substrate **2 h** was prepared according to the literature.[4] The obtained imines were stored in a fridge (4 °C) and passed through neutral alumina (eluent: hexane/ethyl acetate = 1/1) before use.

2a[2]: white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.73 (t, *J* = 7.8 Hz, 2H), 3.76 (td, *J* = 7.8, 2.1 Hz, 2H), 7.13-7.37 (m, 4H), 8.32 (t, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 25.0, 47.4, 127.1, 127.2, 127.4, 128.5, 131.0, 136.2, 160.3.

2b: yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.67-2.70 (m, 2H), 3.75-3.79 (m, 2H), 3.83 (s, 3H), 6.83 (d, *J* = 2.4 Hz, 1H), 6.92 (dd, *J* = 2.4, 8.3 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 8.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 24.2, 47.9, 55.4, 112.2, 116.6, 128.1, 129.0, 158.4, 160.0.

2c[5]: yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.60-2.70 (m, 2H), 3.64-3.73 (m, 2H), 5.98 (s, 2H), 6.62 (s, 1H), 6.75 (s, 1H), 8.16 (t, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 25.3, 47.2, 101.2, 107.5, 108.0, 122.7, 131.7, 146.4, 149.3, 159.4.

2d[4]: yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.57-2.66 (m, 2H), 3.62-3.70 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 6.60 (s, 1H), 6.74 (s, 1H), 8.16 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.7, 47.3, 56.0, 56.1, 110.3, 110.4, 121.5, 129.8, 147.8, 151.2, 159.6.

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[2] Pelletier, J. C.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 616-622.

[3] Rohluff, J. C.; Dyson, N. H.; Gardner, J. O.; Alfredson, T. V.; Sparacino, M. L.; Robinson III, J. *J. Org. Chem.* **1993**, *58*, 1935-1938.

[4] Fecik, R. A.; Devasthale, P.; Pillai, S.; Keschavarz-Shokri, A.; Shen, L.; Mitscher, L. A. *J. Med. Chem.* **2005**, *48*, 1229-1236.

[5] Huang, W.-J.; Singh, O. V.; Chen, C.-H.; Chiou, S.-Y.; Lee, S.-S. *Helv. Chem. Acta* **2002**, *85*, 1069-1078.

2e: yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.74 (t, *J* = 7.5 Hz, 2H), 3.65-3.73 (m, 2H), 3.78 (s, 3H), 3.87 (s, 3H), 6.79 (d, *J* = 8.3 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 8.21 (t, *J* = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 18.9, 46.8, 55.7, 60.6, 109.7, 122.7, 124.0, 130.1, 145.2, 155.0, 159.6.

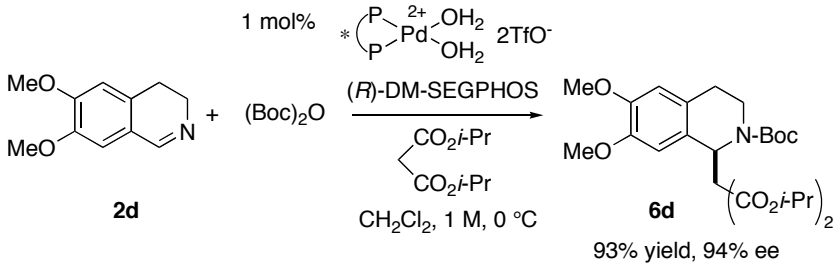
2f: pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.65 (t, *J* = 8.1 Hz, 2H), 3.68 (dt, *J* = 2.1, 8.1 Hz, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 6.72 (d, *J* = 9.0 Hz, 1H), 6.88 (t, *J* = 9.0 Hz, 1H), 8.69 (t, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 18.5, 46.4, 55.9, 56.0, 108.9, 113.9, 117.9, 126.4, 149.6, 151.4, 155.7.

2g: yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.29 (s, 3H), 2.64 (t, *J* = 7.7 Hz, 2H), 3.65-3.72 (m, 2H), 6.96-7.16 (m, 3H), 8.23 (t, *J* = 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.0, 24.6, 47.5, 127.2, 127.9, 128.3, 131.7, 133.3, 136.7, 160.6.

2h: white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.67 (t, *J* = 7.8 Hz, 2H), 3.69 (dt, *J* = 2.0, 7.9 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 1H), 7.25 (brs, 1H), 7.36 (dd, *J* = 1.5, 8.3 Hz, 1H), 8.24 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 24.8, 46.9, 125.2, 126.9, 128.6, 130.2, 130.5, 138.2, 159.2.

(C) A representative procedure for the catalytic asymmetric addition reaction of malonates to dihydroisoquinolines and analytical data of the products

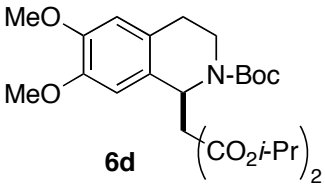
A representative procedure



The imine **2d** (300 mg, 1.57 mmol) and $(Boc)_2O$ (513 mg, 2.35 mmol, 1.5 eq) were dissolved in CH_2Cl_2 (1.6 mL). The resulting mixture was stirred for 30 minutes at ambient temperature. Under ice-

bath cooling, diisopropyl malonate (446 μL, 2.35 mmol, 1.5 eq) and the Pd complex **1c** (18.2 mg, 0.0156 mmol, 1 mol%) were added successively. The reaction mixture was stirred at the same temperature for additional 3 h. After completion of the reaction, ethyl acetate (5 mL) and brine (5 mL) were added for quenching. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure, followed by flash column chromatography (SiO_2, hexane-ethyl acetate or hexane-ether system, ~6/1) afforded the desired product **6d** as a white solid (718 mg, 93% yield). The ee was determined to be 94% by chiral HPLC analysis.

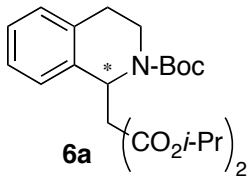
6d: This compound exists as a mixture of rotamers in a ratio of 1.5/1 in $CDCl_3$ at 22 ºC



6d

White solid; m.p. 112-113 ℃; IR (neat) ν 2979, 2936, 1726, 1694, 1248, 1160, 1099 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.4 Hz, 1.8H [major]), 1.09 (d, *J* = 6.4 Hz, 1.8H [major]), 1.10 (d, *J* = 6.3 Hz, 1.2H [minor]), 1.14 (d, *J* = 6.3Hz, 1.2H [minor]), 1.24-1.30 (m, 6H), 1.44 (s, 3.6H [minor]), 1.47 (s, 5.4H [major]), 2.67-2.76 (m, 1H), 2.79-2.92 (m, 1H), 3.36-3.44 (m, 0.6H [major]), 3.48-3.55 (m, 0.4H [minor]), 3.69-3.72 (m, 1H), 3.81 (s, 1.2 H [minor]), 3.83 (s, 1.8 H [major]), 3.84 (s, 3H), 3.86-3.92 (m, 0.4H [minor]), 4.11-4.16 (m, 0.6H [major]), 4.82-5.11 (m, 2H), 5.82 (d, *J* = 5.6 Hz, 0.6H [major]), 5.94 (d, *J* = 8.3 Hz, 0.4H [minor]), 6.60 (s, 1H), 6.92 (s, 0.6H [major]), 6.97 (s, 0.4H [minor]); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 21.4, 21.4, 21.5, 21.6, 21.6, 21.6 (These peaks are so close each other and are difficult to identify.), 27.5, 28.3, 28.3, 37.8, 39.6, 52.3, 53.1, 55.8, 59.6, 60.4, 68.9, 69.1, 69.2, 79.8, 80.5, 110.2, 111.0, 111.2, 126.4, 126.6, 127.4, 147.0, 147.0, 148.1, 154.2, 154.6, 166.6, 167.1, 167.3, 167.4; FAB-LRMS (*m*NBA) m/z 480 $[M+1]^+$; $[\alpha]_D^{26}$ +66.0 (c = 1.62, $CHCl_3$) (94% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 9/1, 1.0 mL/min., 280 nm, τ_{major} 8.5 min., τ_{minor} 6.3 min.)

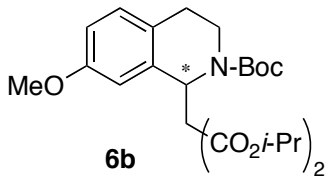
6a: This compound exists as a mixture of rotamers in a ratio of 1.44/1 in $CDCl_3$ at 22 ºC.



6a

Colorless oil; IR (neat) ν 2978, 2936, 1727, 1696, 1366, 1291, 1248, 1161, 1101, 935, 754 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.98 (d, *J* = 6.3 Hz, 1.77H [major]), 1.09 (d, *J* = 6.1 Hz, 3H), 1.15 (d, *J* = 6.1 Hz, 1.23H [minor]), 1.24-1.29 (m, 6H), 1.44 (s, 3.69H [minor]), 1.47 (s, 5.31H [major]), 2.81-3.00 (m, 2H), 3.41-3.48 (m, 0.59H [major]), 3.55-3.62 (m, 0.41H [minor]), 3.67-3.72 (m, 1H), 3.77-3.83 (m, 0.41H [minor]), 4.05-4.11 (m, 0.59H [major]), 4.82-5.11 (m, 2H), 5.91 (d, *J* = 6.1 Hz, 0.59H [major]), 6.02 (d, *J* = 8.3 Hz, 0.41H [minor]), 7.11-7.20 (m, 3H), 7.32 (d, *J* = 7.4 Hz, 0.59H [major]), 7.37 (d, *J* = 7.3 Hz, 0.41H [minor]); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.2, 21.3, 21.4, 21.6, 27.9, 28.2, 28.3, 38.1, 39.9, 52.8, 53.5, 59.4, 60.1, 68.9, 69.1, 69.2, 79.8, 80.4, 126.0, 126.1, 127.2, 127.3, 127.4, 127.8, 128.5, 128.8, 134.5, 134.5, 134.7, 135.4, 154.3, 154.7, 166.6, 166.8, 167.0, 167.2; FAB-LRMS (*m*NBA) m/z 420 $[M+1]^+$; $[\alpha]_D^{26}$ +48.6 (c = 0.51, $CHCl_3$) (85% ee); HPLC (DAICEL CHIRALPAK IA, *n*-hexane/IPA = 99/1, 0.5 mL/min., 280 nm, τ_{major} 17.6 min., τ_{minor} 22.3 min.)

6b: This compound exists as a mixture of rotamers in a ratio of 1.33/1 in $CDCl_3$ at 22 ºC.

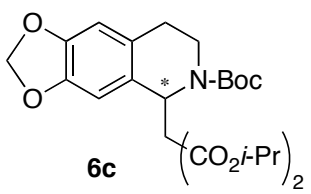


6b

Colorless oil; IR (neat) ν 2980, 2931, 1727, 1696, 1254, 1158, 1105 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.4 Hz, 1.71H [major]), 1.09-1.12 (m, 3H), 1.16 (d, *J* = 6.1 Hz, 1.29H [minor]), 1.24-1.29 (m, 6H), 1.44 (s, 3.86H [minor]), 1.47 (s, 5.14H [major]), 2.72-2.91 (m, 2H), 3.37-3.44 (m, 0.57H [major]), 3.50-3.57 (m, 0.43H), 3.68-3.72 (m, 1H), 3.75 (s, 3H), 3.77-3.83 (m, 0.43H [minor]), 4.05-4.10 (m, 0.57H [major]), 4.84-5.11 (m, 2H), 5.88 (d, *J* = 5.88 Hz, 0.57H [major]), 6.00 (d, *J* = 8.32 Hz, 0.43H [minor]), 6.74 (d, *J* = 2.7 Hz, 0.43 H [minor]), 6.76 (d, *J* = 2.7 Hz, 0.57H [major]), 6.90 (brd, *J* = 1.9 Hz, 0.57 H [major]), 6.96 (brs, 0.43 H [minor]), 7.01-7.04 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 21.4, 21.5, 21.6, 27.1, 28.3, 28.3, 38.3, 40.1, 52.9, 53.6, 55.2, 59.4, 60.2, 69.0, 69.2, 79.9, 80.5, 111.8, 112.5, 114.0, 126.3, 126.5, 129.4, 129.7, 135.6, 136.4, 154.3, 157.7, 166.6, 166.9, 167.1, 167.2; FAB-LRMS (*m*NBA)

m/z 450 $[M+1]^+$; $[\alpha]_D^{27}$ +50.7 (c = 1.71, $CHCl_3$) (81% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 95/5, 0.5 mL/min., 280 nm, τ_{major} 9.8 min., τ_{minor} 11.5 min.)

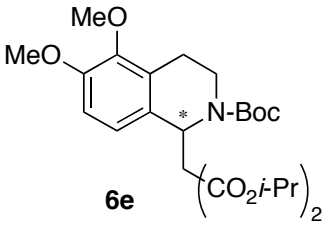
6c: This compound exists as a mixture of rotamers in a ratio of 1.33/1 in $CDCl_3$ at 22 ºC.



6c

Colorless oil; IR (neat) ν 2980, 2936, 1725, 1694, 1484, 1366, 1247, 1160, 1101, 1038, 940, 757cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.4 Hz, 1.71H [major]), 1.12 (d, *J* = 6.4 Hz, 1.71H [major]), 1.15 (d, *J* = 6.1 Hz, 1.29H [minor]) 1.18 (d, *J* = 6.1 Hz, 1.29H [minor]), 1.24-1.28 (m, 6H), 1.44 (s, 3.86H [minor]), 1.46 (s, 5.14H [major]), 2.69-2.89 (m, 2H), 3.37-3.44 (m, 0.57H [major]), 3.49-3.55 (m, 0.43H [minor]), 3.63-3.68 (m, 1H), 3.71-3.78 (m, 0.43H [minor]), 3.98-4.04 (m, 0.57H [major]), 4.87-5.10 (m, 2H), 5.78 (d, *J* = 6.1 Hz, 0.57H [major]), 5.88-5.90 (s, 2H and d, 0.43H [minor]), 6.58 (s, 1H), 6.83 (s, 0.57H [major]), 6.89 (s, 0.43H [minor]); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 21.6, 27.9, 28.3, 28.4, 38.2, 39.9, 52.8, 53.6, 59.5, 60.2, 69.0, 69.2, 79.9, 80.5, 100.8, 107.6, 108.3, 108.4, 108.6, 127.6, 127.9, 128.0, 128.6, 145.8, 146.8, 154.2, 154.6, 166.6, 166.9, 167.1, 167.1; FAB-LRMS (*m*NBA) m/z 463 $[M]^+$; $[\alpha]_D^{26}$ +29.9 (c = 1.47, $CHCl_3$) (88% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 95/5, 1.0 mL/min., 280 nm, τ_{major} 9.8 min., τ_{minor} 12.0 min.)

6e: This compound exists as a mixture of rotamers in a ratio of 1.3/1 in $CDCl_3$ at 22 ºC.

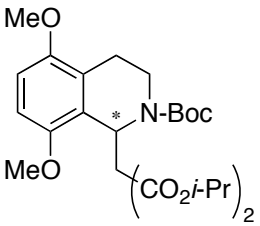


6e

Colorless oil; IR (neat) ν 2974, 2930, 2831, 1728, 1693, 1492, 1453, 1413, 1389, 1364, 1274, 1160, 1098 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.98 (d, *J* = 6.1 Hz, 1.69H [major]), 1.09-1.12 (m, 3H), 1.16 (d, *J* = 6.1Hz, 1.31H [minor]), 1.22-1.28 (m, 6H), 1.42 (s, 3.9H [minor]), 1.45 (s, 5.1H [major]), 2.75-2.95 (m, 2H), 3.30-3.38 (m, 0.57 H [major]), 3.40-3.52 (m, 0.43H [minor]), 3.60-3.70 (m, 1H), 3.77 (s, 3H), 3.81 (s, 3H), 4.03-4.13 (m, 1H), 4.80-4.5.10 (m, 2H), 5.84 (d, *J* = 6.4 Hz, 0.56 H [major]), 5.93 (d, *J* = 8.8 Hz, 0.44 H [minor]), 6.67-6.72 (m, 1H), 7.01-7,08 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.2, 21.4, 21.6, 21.8, 22.0, 28.2, 28.3, 37.5, 39.2, 52.2, 53.0, 55.7, 59.4, 60.0, 60.1, 60.2, 68.9,

69.0, 69.1, 79.8, 80.4, 109.9, 110.0, 122.7, 123.4, 127.7, 128.4, 128.6, 129.0, 146.0, 146.2, 151.5, 151.5, 154.2, 154.6, 166.5, 166.9, 167.1; FAB-LRMS (*m*NBA) m/z 480 $[M+1]^+$; $[\alpha]_D^{26}$ +24.6 (c = 1.35, $CHCl_3$) (97% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 98/2, 1.0 mL/min., 280 nm, τ_{major} 18.2 min., τ_{minor} 20.6 min.).

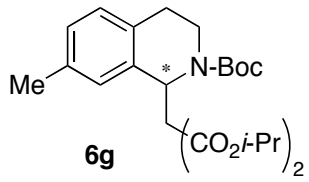
6f: This compound exists as a mixture of rotamers in a ration of about 1.28 : 1 in $CDCl_3$ at 23 °C.



6f

Colorless oil; IR (neat) ν 2978, 2935, 2835, 1754, 1725, 1692, 1481, 1416, 1365, 1255, 1162, 1102 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.96-1.18 (m, 12H [major + minor]), 1.36 (s, ca. 5H, [major]), 1.40 (s, ca. 4H, [minor]), 2.50-2.72 (m, 2H), 3.10-3.25 (m, 0.44H [minor]), 3.50-3.59 (m, 0.56H, [major]), 3.67 + 3.69 (2 x s, 6H [major + minor]), 3.78 (d, *J* = 5.6 Hz, 0.56H [major]), 3.96-4.01 (m, 0.44H [minor]), 4.10-4.17 (m, 1H), 4.75-4.94 (m, 2H), 5.97-6.03 (m, 1H), 6.50-6.55 (m, 1H), 6,58-6.62 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 21.5, 21.6, 21.7, 22.0, 22.1, 22.1, 22.2, 28.4, 36.9, 38.0, 48.7, 49.5, 55.3, 55.6, 55.7, 56.5, 58.2, 68.3, 68.5, 68.6, 68.7, 77.2, 79.6, 80.2, 106.9, 107.2, 108.3, 108.4, 124.7, 125.1, 125.2, 125.5, 149.6, 149.7, 150.8, 151.0, 154.2, 154.5, 166.5, 166.7, 167.1 ; FAB-LRMS (*m*NBA) m/z 479 $[M]^+$; $[\alpha]_D^{31}$ +55.9 (c = 1.31, $CHCl_3$) (82% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 95/5, 1.0 mL/min., 280 nm, τ_{major} 14.0 min., τ_{minor} 11.6 min.).

6g: This compound exists as a mixture of rotamers in a ratio of 1.44/1 in $CDCl_3$ at 22 ºC.

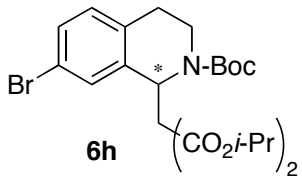


6g

Colorless oil; IR (neat) ν 2979, 2936, 1728, 1697, 1366, 1252, 1164, 1102 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.4 Hz, 1.77H [major]), 1.10-1.12 (m, 3H), 1.69 (d, *J* = 6.1Hz, 1.23H [minor]), 1.24-1.29 (m, 6H), 1.43 (s, 3.7H [minor]), 1.47 (s, 5.3H [major]), 2.27 (s, 3H), 2.76-2.94 (m, 2H), 3.37-3.44 (m, 0.59H [major]), 3.52-3.58 (m, 0.41H [minor]), 3.66-3.71 (m, 1H), 3.75-3.81 (m, 0.41H [minor]), 4.03-4.09 (m, 0.59H [major]), 4.85-5.10 (m, 2H), 5.88 (d, *J* = 6.6 Hz, 0.59H [major]), 5.97 (d, *J* = 8.8 Hz, 0.41H [minor]), 6.97-7.02 (m, 2H), 7.09 (s, 0.59H [major]), 7.16 (s, 0.41 H [minor]); ^{13}C-NMR (100 MHz, $CDCl_3$) δ

21.0, 21.3, 21.4, 21.4, 21.6, 27.5, 28.3, 28.4, 38.3, 40.1, 52.9, 53.6, 59.4, 60.0, 69.0, 69.1, 69.2, 79.8, 80.4, 127.6, 128.2, 128.3, 128.4, 128.7, 131.4, 131.5, 134.6, 135.3, 135.5, 135.6, 154.3, 166.6, 166.8, 167.1; FAB-LRMS (*m*NBA) m/z 434 $[M+1]^+$; $[\alpha]_D^{26}$ +39.1 (c = 0.985, $CHCl_3$) (96% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 95/5, 1.0 mL/min., 280 nm, τ_{major} 5.3 min., τ_{minor} 6.3 min.)

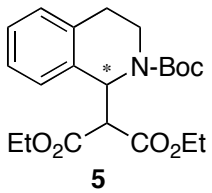
6h: This compound exists as a mixture of rotamers in a ratio of 1.40/1 in $CDCl_3$ at 24 ºC.



6h

Colorless oil; IR (neat) ν 2979, 2934, 1725, 1694, 1390, 1365, 1282, 1246, 1159, 1098 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.98 (d, *J* = 6.1 Hz [major]) , 1.05-1.12 (m, 4.25H), 1.20-1.26 (m, 6H), 1.42 (s, 3.75H [minor]), 1.44 (s, 5.25H [major]), 2.74-2.90 (m, 2H), 3.30-3.43 (m, 0.58H [major]), 3.46-3.58 (m, 0.42H [minor]), 3.62-3.69 (m, 1H), 3.76-3.84 (m, 0.42H [minor]), 4.01-4.10 (m, 0.58H [major]), 4.81-5.09 (m, 2H), 5.81 (d, *J* = 5.6 Hz, 0.58H [major]), 5.94 (d, *J* = 8.3 Hz, 0.42H [minor]), 7.18-7.28 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 21.5, 21.6, 21.7, 27.9, 28.3, 28.4, 37.7, 39.5, 52.4, 53.2, 59.2, 60.0, 69.2, 69.4, 77.2, 80.2, 80.8, 121.0, 121.0, 128.9, 129.0, 129.5, 131.3, 131.5, 133.5, 134.3, 136.7, 136.9, 154.0, 154.4, 166.3, 166.6, 166.7, 166.9; FAB-LRMS (*m*NBA) m/z 498 $[M]^+$, 500 $[M+2]^+$; $[\alpha]_D^{26}$ +32.9 (c = 2.35, $CHCl_3$) (90% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 95/5, 1.0 mL/min., 254 nm, τ_{major} 18.0 min., τ_{minor} 14.8 min.)

5: This compound exists as a mixture of rotamers in a ratio of 1.2/1 in $CDCl_3$ at 22 ºC.



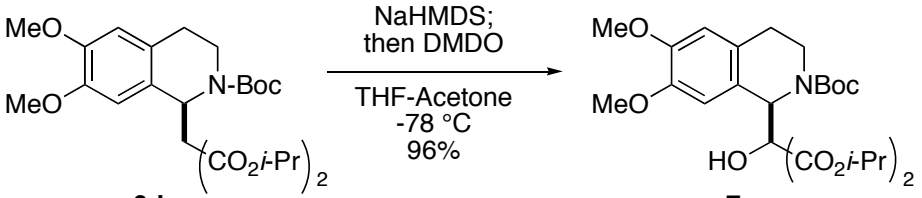
5

White solid; IR (solid) ν 2975, 2936, 1747, 1713, 1688, 1397, 1366, 1170, 1144, 1116 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.08-1.19 (m, 3H), 1.27-1.35 (m, 3H), 1.47 and 1.49 (s x 2, 9H), 2.80-3.10 (m, 2H), 3.40-3.51 (m, 0.55H [major]), 3.58-3.70 (m, 0.45H [minor]), 3.72-3.80 (m, 1.5H), 3.94-4.32 (m, 4.5H), 5.94 (d, *J* = 7.0 Hz, 0.55H [major]), 6.02 (d, *J* = 8.4 Hz, 0.44 Hz [minor]), 7.10-7.40 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.8, 13.9, 14.0, 14.0, 27.9, 28.0, 28.3, 28.3, 38.4, 40.2, 53.1, 53.8, 59.0, 59.4, 61.4, 61.5, 61.6, 80.0, 80.6, 126.1, 126.2, 127.1,

127.5, 127.7, 128.5, 128.9, 134.6, 134.8, 135.3, 154.3, 154.8, 167.1, 167.3, 167.4, 167.5; FAB-LRMS (*m*NBA) m/z 434 $[M+1]^+$; $[\alpha]_D^{26}$ +32.7 (c = 0.87, $CHCl_3$) (73% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 98/2, 1.0 mL/min., 280 nm, τ_{major} 19.6 min., τ_{minor} 17.7 min.)

(D) Asymmetric synthesis of calycotomine

Conversion of **6d** to **8** was carried out based on similar transformation reported by Terada *et al.*[6]



6d **7**

To a solution of **6d** (250 mg, 0.52 mmol, 94% ee) in THF (5 mL) was added NaHMDS (1 M in THF, 574 μL, 0.57 mmol) at -78 °C. After 10 minutes, a solution of dimethyldioxirane (DMDO) in acetone (~0.06 M, ~10 mL) was added until completion of the reaction. Solvent was evaporated 1/5 concentrated, and saturated aqueous NH_4Cl and ethyl acetate were added. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, and dried over Na_2SO_4. Further purification was carried out by flash column chromatography (SiO_2, hexane/ethyl acetate = 4/1) to give **7** as a white solid (248 mg, 96% yield). The ee was determined to be 94% by chiral HPLC analysis.

7: This compound exists as a mixture of rotamers in a ratio of 2.3/1 in $CDCl_3$ at 23 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.20-1.35 (m, 12H), 1.42 (s, 9H), 2.52-3.00 (m, 2H), 3.65-4.25 (m, 8H), 4.95-5.19 (m, 2H), 6.05 (s, 0.3H [minor]), 6.24 (s, 0.7H [major]), 6.57 (s, 1H), 6.74-6.79 (m, 1H); $[\alpha]_D^{30}$ +92.0 (c = 1.0, $CHCl_3$) (94% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 9/1, 1.0 mL/min., 280 nm, τ_{major} 39.5 min., τ_{minor} 53.4 min.).

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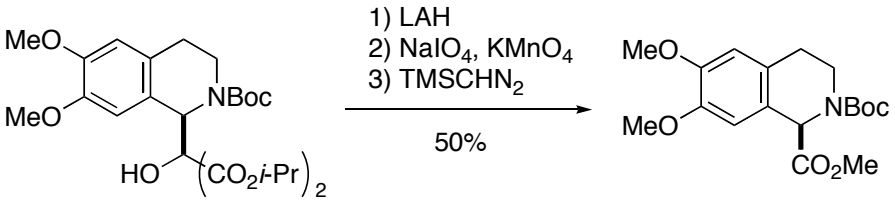
[6] Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356-5357.



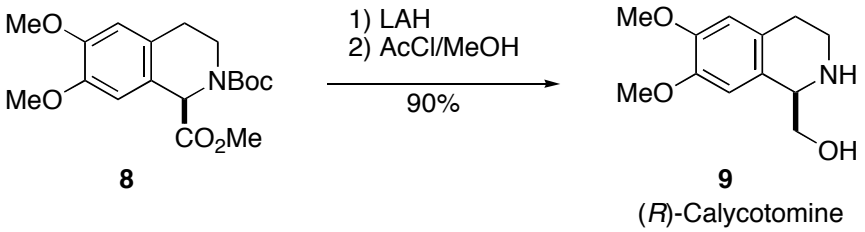
7 **8**

To a stirred solution of $LiAlH_4$ (113 mg, 2.97 mmol) in THF (4 mL) was added a solution of **7** (184 mg, 0.371 mmol) in THF (3 mL) at -78 °C. The reaction mixture was stirred under ice-bath cooling for 3 h and at room temperature for additional 3 h. Saturated aqueous Rochelle salt was added under ice-bath cooling, and the mixture was stirred until the solution became clear. The aqueous layer was extracted with ethyl acetate (4 x 10 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was used in the next step.

The obtained triol was dissolved in THF-H_2O (1:1, 4 mL), and Na_2CO_3 (20 mg, 0.19 mmol), $NaIO_4$ (400 mg, 1.86 mmol), $KMnO_4$ (12 mg, 0.074 mmol) were added successively under ice-bath cooling. After stirring at room temperature for 30 minutes, 0.5 N H_2SO_4 was added until pH value became 3~4. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were washed with water and brine and dried over Na_2SO_4. Evaporation of the dried solvent gave the crude mixture, which was treated with saturated aqueous $NaHCO_3$. After extraction with ether, the aqueous layer was acidified with 0.5N H_2SO_4 and extracted with ethyl acetate (3 x 10 mL). After washing with brine, the organic phase was concentrated under reduced pressure. The resulting crude product was dissolved in MeOH-ether (1:1, 2 mL), and $TMSCHN_2$ (2 M in ether, 0.2 mL) was added at 0 °C. After completion, the reaction mixture was concentrated, and purification by flash column chromatography was performed (SiO_2, hexane/ethyl acetate = 3/1) to afford the desired methyl ester **8** as colorless oil (65 mg, 50% yield for 3 steps, not optimized). The ee was determined to be 93% by chiral HPLC analysis.

8: This compound exists as a mixture of rotamers in a ratio of 1.45/1 in $CDCl_3$ at 23 ºC.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 3.7H [minor]), 1.50 (s, 5.3H [major]), 2.75-2.90 (m, 2H), 3.66-3.90 (m, 11H), 5.36 (s, 0.59H [major]), 5.47 (s, 0.41H [minor]), 6.64 (s, 1H), 6.99 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.6, 28.7, 28.7, 39.9, 41.1, 52.6, 52.7, 53.8, 56.2, 56.3, 56.4, 57.5, 58.5, 80.7, 80.9, 110.7, 111.2, 111.3, 111.5, 121.9, 122.8, 127.9, 128.1, 148.0, 148.9, 155.0, 155.7, 172.3, 172.7; $[\alpha]_D^{26}$ +2.63 (c = 2.17, $CHCl_3$) (93% ee); HPLC (DAICEL CHIRALPAK AS-H, *n*-hexane/IPA = 98/2, 1.0 mL/min., 280 nm, τ_{major} 19.6 min., τ_{minor} 16.2 min.)



8 **9**

(*R*)-Calycotomine

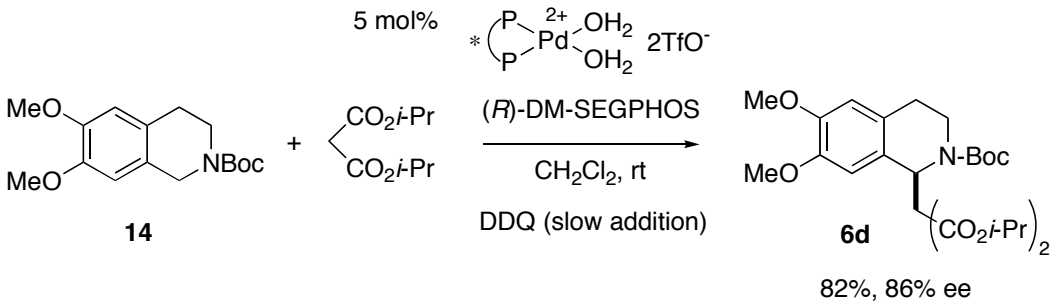
To a suspension of $LiAlH_4$ (13 mg, 0.342 mmol) in THF (1 mL) was added a solution of **8** (40 mg, 0.114 mmol) in THF (1 mL) under ice-bath cooling. After completion of reduction, the reaction was stopped by addition of H_2O-15% aq. NaOH-H_2O (1:1:3 to LAH). The resulting suspension was diluted with ethyl acetate and passed through Celite with ethyl acetate as an eluent. Further purification was carried out using flash column chromatography (SiO_2, hexane/ethyl acetate = 1/1): ^{1}H NMR was unclear due to broadening. HPLC (DAICEL CHIRALPAK AS-H, *n*-hexane/IPA = 9/1, 1.0 mL/min., 280 nm, τ_{major} 12.4 min., τ_{minor} 8.7 min.); $[\alpha]_D^{27}$ +69.1 (c = 1.85, $CHCl_3$) (93% ee).

Removal of the *N*-Boc group was carried out as follows: AcCl (120 μL, 1.7 mmol) was added into anhydrous MeOH (2 mL) under ice-bath cooling and the mixture was stirred at room temperature for 1 h. To this solution was added a solution of the obtained alcohol in MeOH (2 mL), and the mixture was stirred at 40 °C for 3 h. After evaporation, the crude product was treated with 1N NaOH. The aqueous layer was extracted with $CHCl_3$ (5 x 10 mL), and the combined organic layers were dried over Na_2SO_4. Evaporation gave the desired (*R*)-calycotomine as pale yellow oil with purity sufficient for ^{1}H-NMR analysis (22.9 mg, 90% yield for 2 steps). For optical rotation, recrystallization from toluene was

carried out to obtain the pure compound (a white solid, 50% yield). This compound was found identical to the reported material by comparison of NMR data.[7]

(*R*)-Calycotomine (**9**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.55 (brs, 2H), 2.62-2.73 (m, 2H), 3.00-3.11 (m, 2H), 3.62 (dd, *J* = 9.0, 11.0 Hz, 1H), 3.76 (dd, *J* = 4.0, 11.0 Hz, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 3.96 (dd, *J* = 4.0, 9.0 Hz, 1H), 6.57 (s, 1H), 6.59 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.0, 38.7, 55.7, 55.9, 55.9, 64.0, 108.9, 111.7, 126.7, 127.4, 147.2, 147.5; $[\alpha]_D^{32}$ +11.1 (c = 0.37, $CHCl_3$) (93% ee) {Lit.[6] -13.7 (c = 0.38, $CHCl_3$), *S*-enantiomer}.

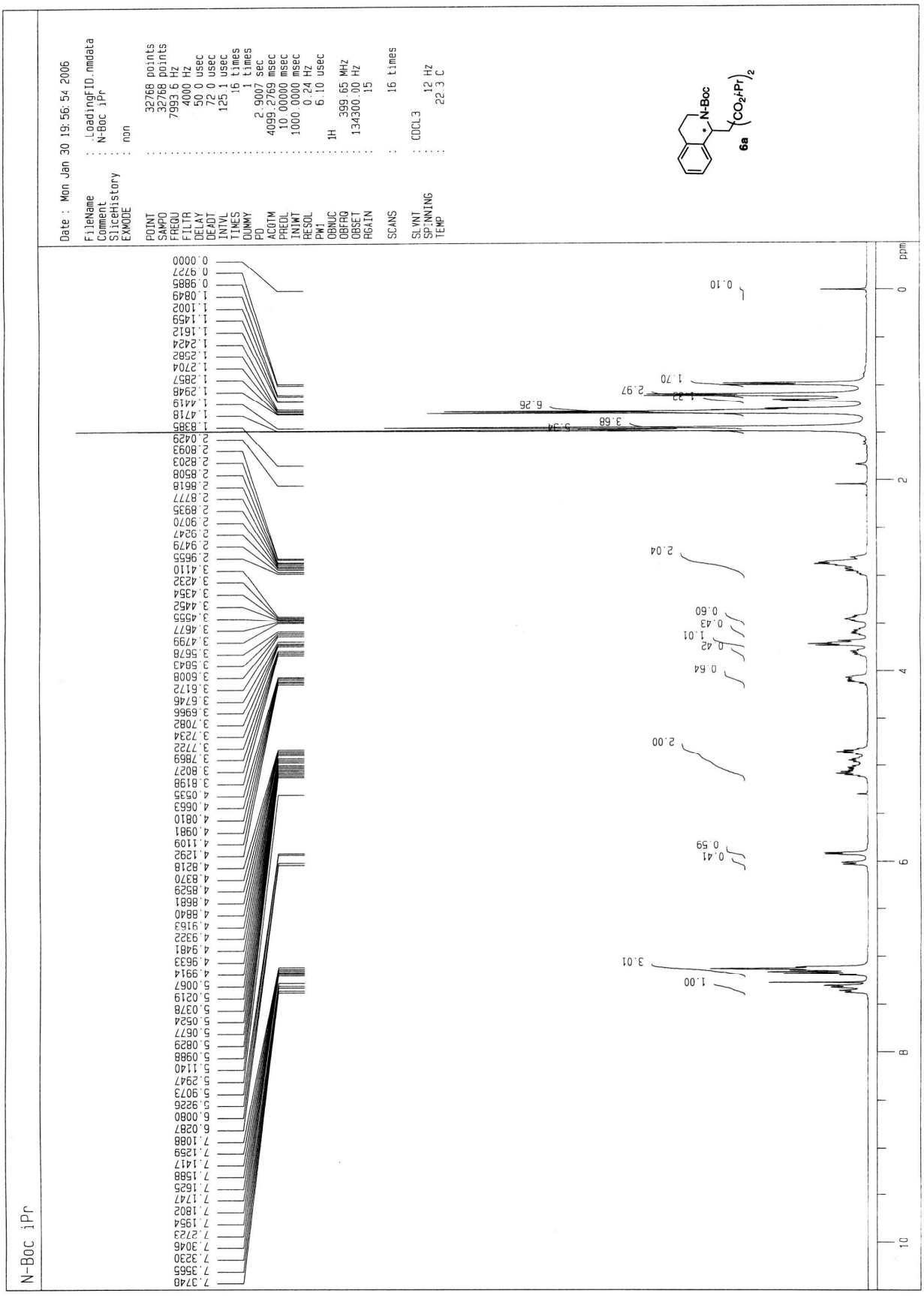
(E) Procedure for dehydrogenative addition reaction of malonate



The *N*-Boc-amine **14** (29.3 mg, 0.1 mmol), diisopropyl malonate (28.5 μL, 0.15 mmol), and **1c** (5.3 mg, 4.6 mol%) were dissolved in CH_2Cl_2 (0.2 mL). DDQ (25 mg, 0.11 mmol) in CH_2Cl_2 (1.5 mL) was slowly added over 5 hours to the reaction mixture with a syringe pump (addition speed: 0.3mL/h). After the addition was completed, the reaction was stirred for additional 2 h. The mixture was diluted with ether (4 mL) and filtered through a silica pad with ether as an eluent. The obtained yellow solution was evaporated under reduced pressure and the remaining yellow oil was purified by flash column chromatography (hexane/ether = 5/1 to 4/1) to give the desired product **6d** (39.8 mg, 0.83 mmol, 83% yield, 86% ee).

(F) NMR spectra

[7] Pedrosa, R.; Andrés, C.; Iglesias, J. M. *J. Org. Chem.* **2001**, *66*, 243-250.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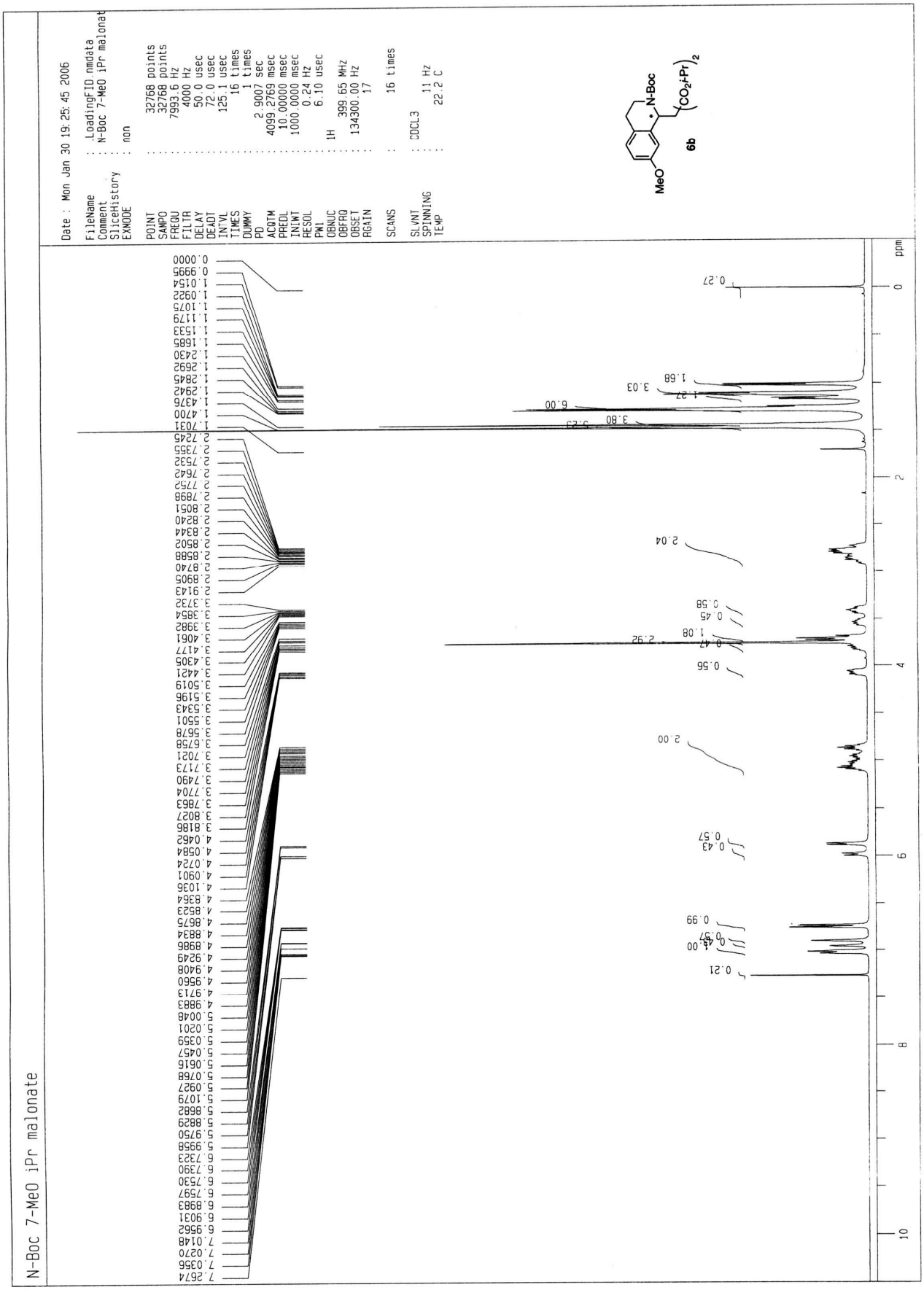
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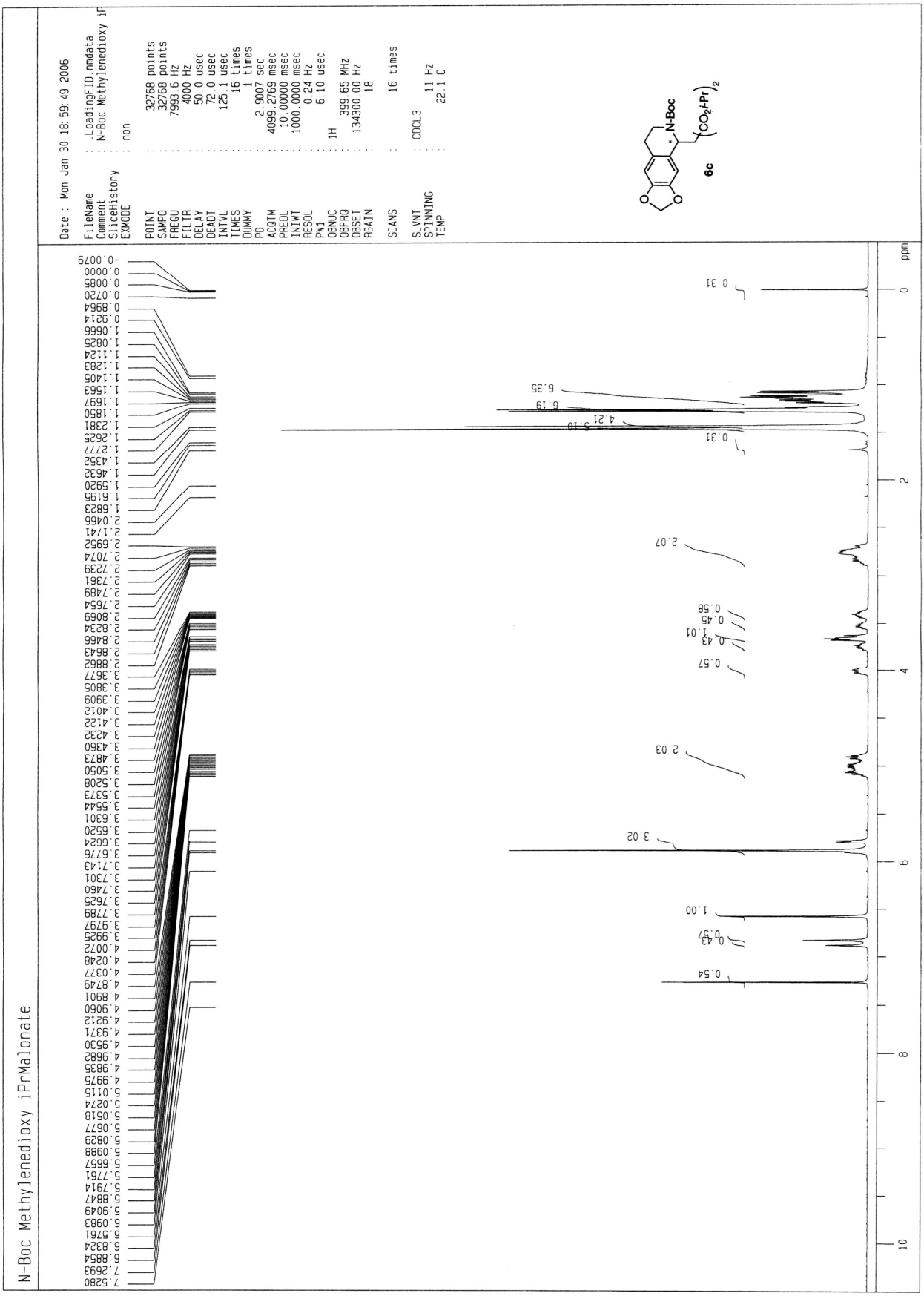
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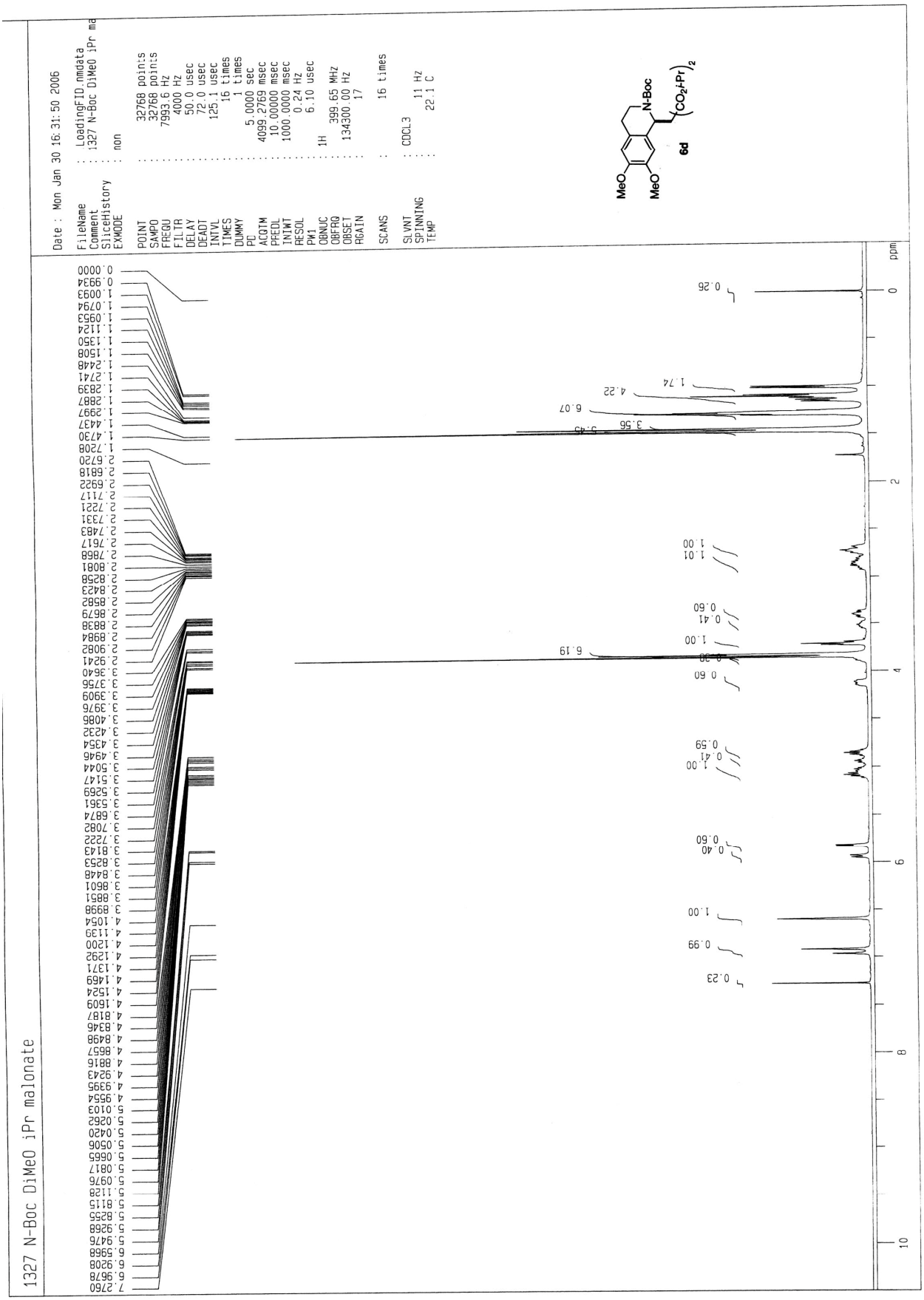
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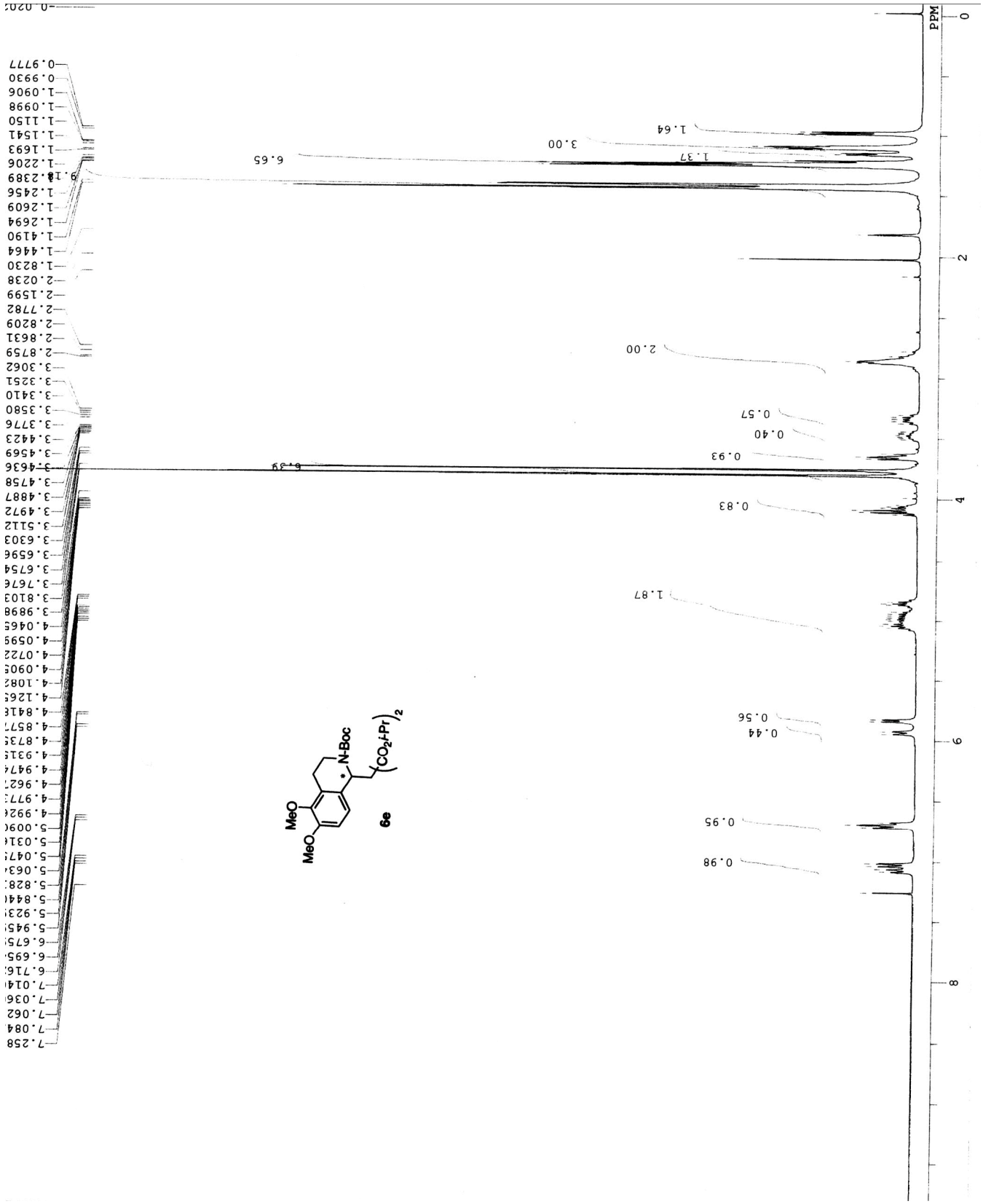
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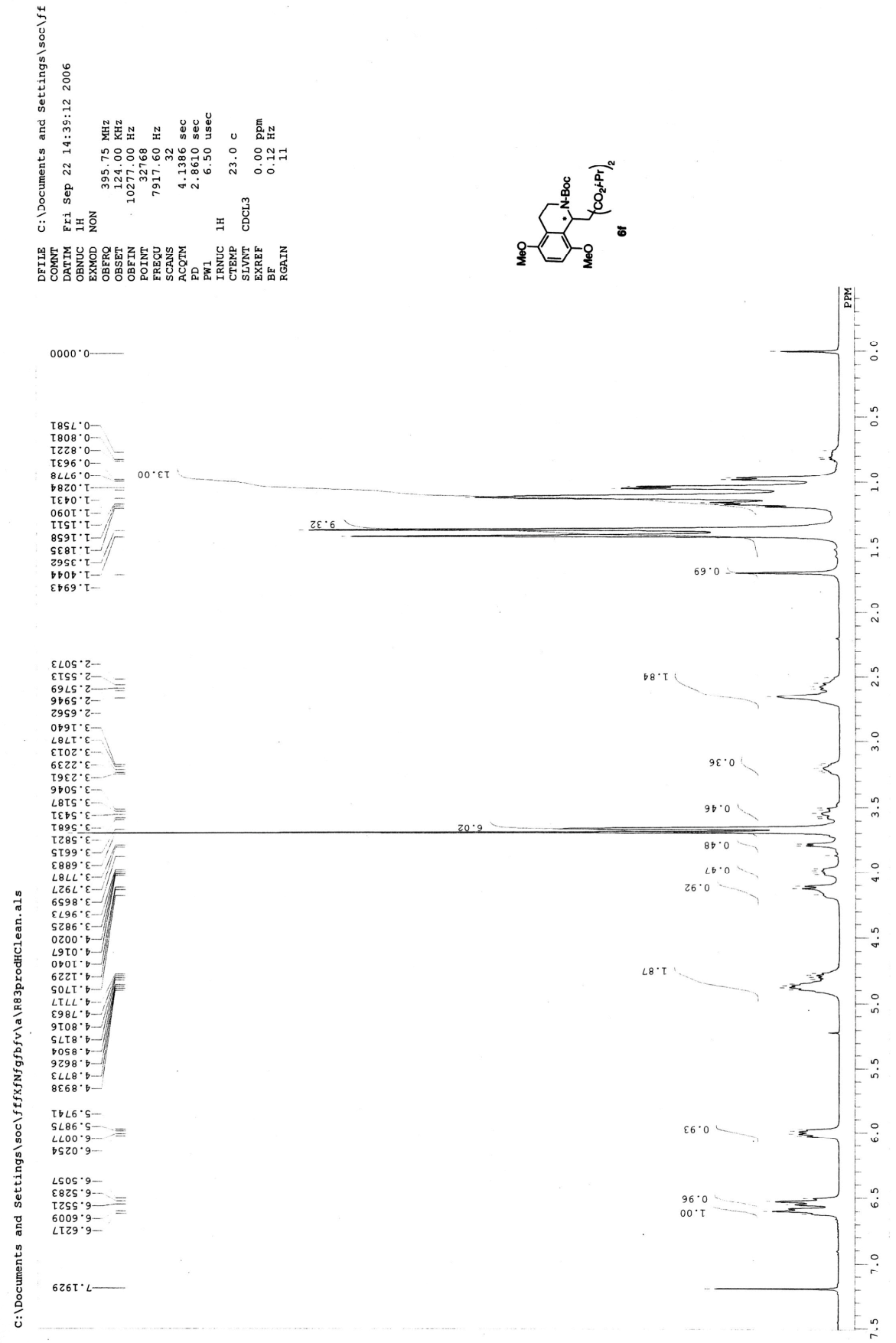
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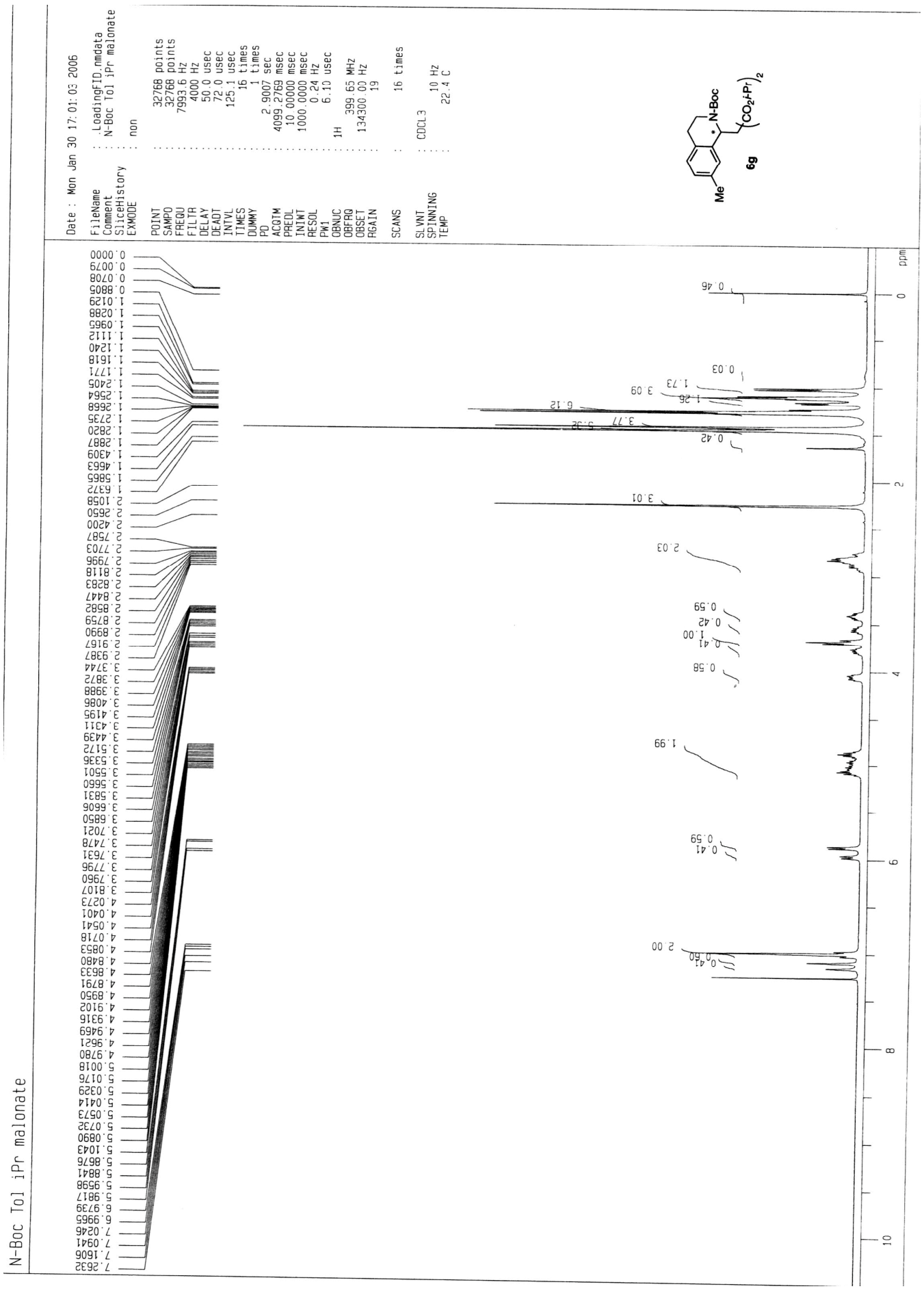
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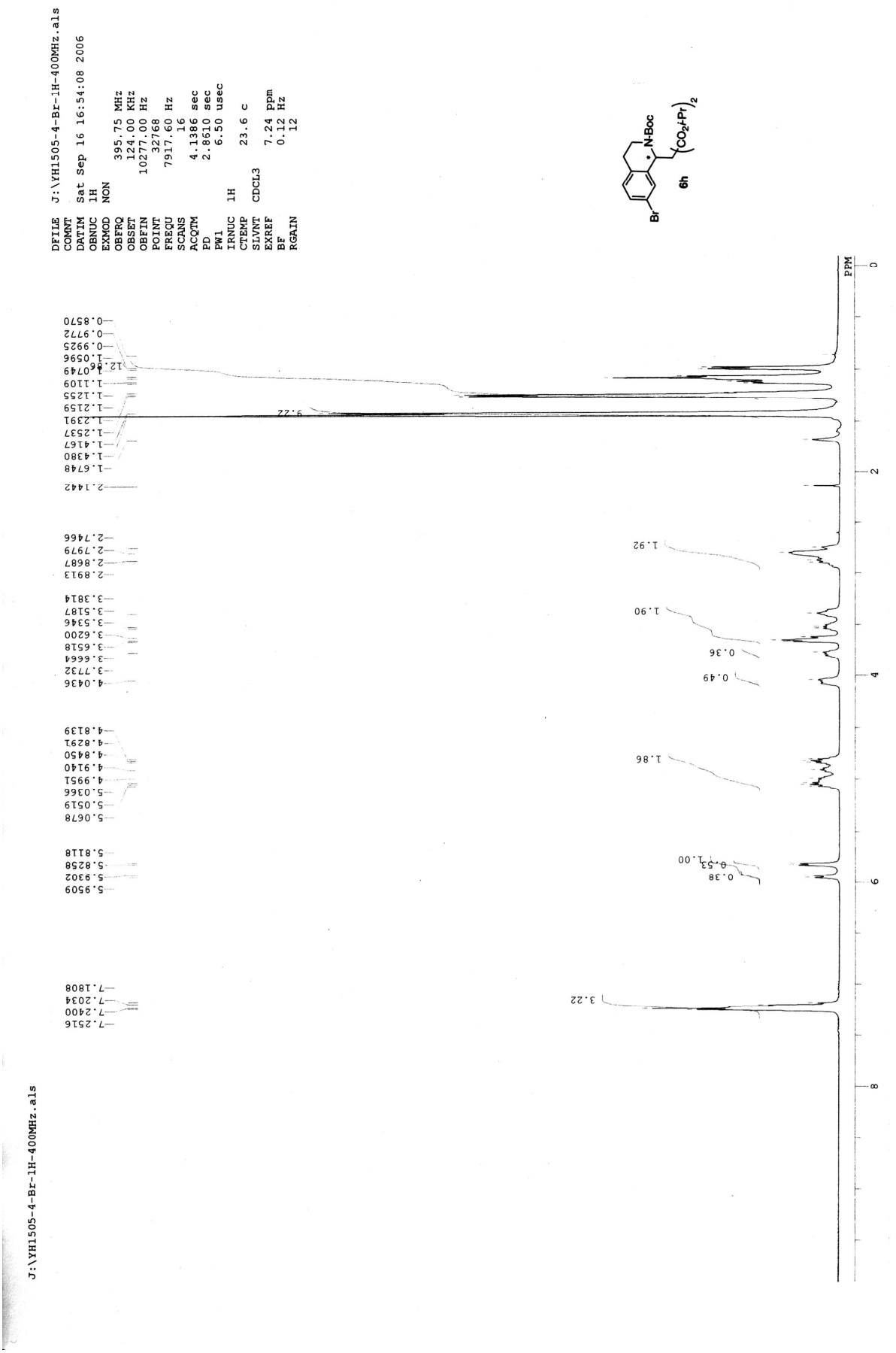
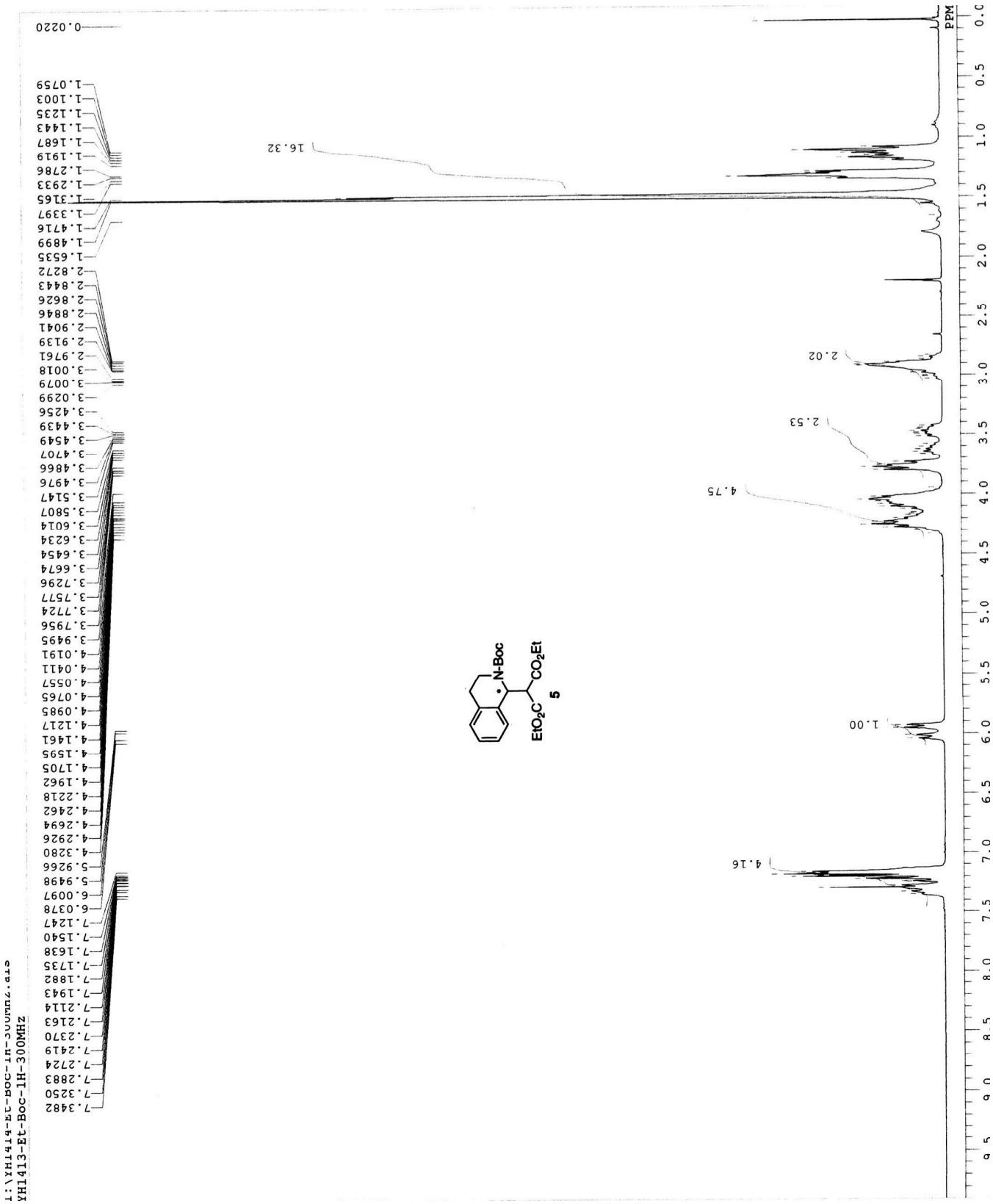
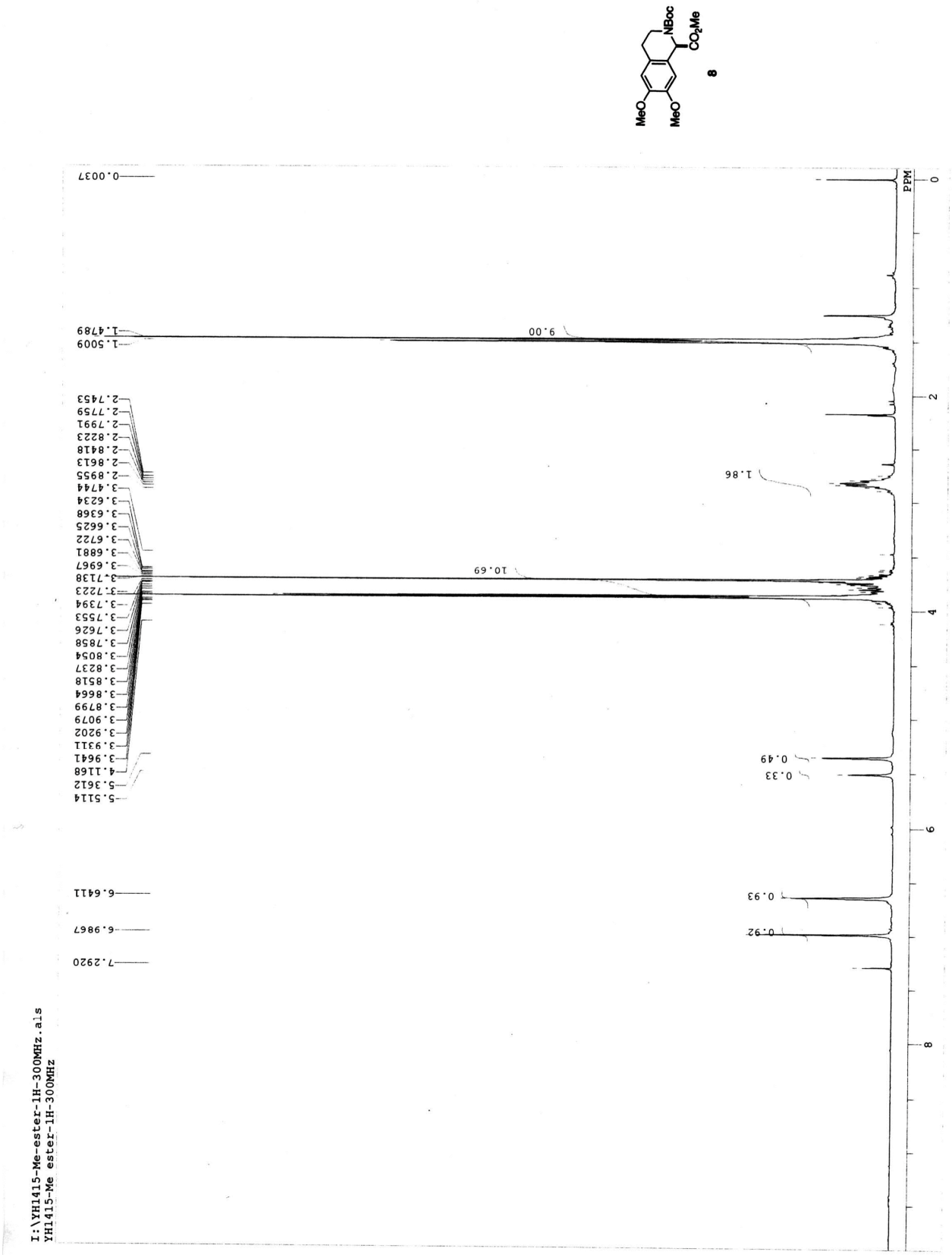
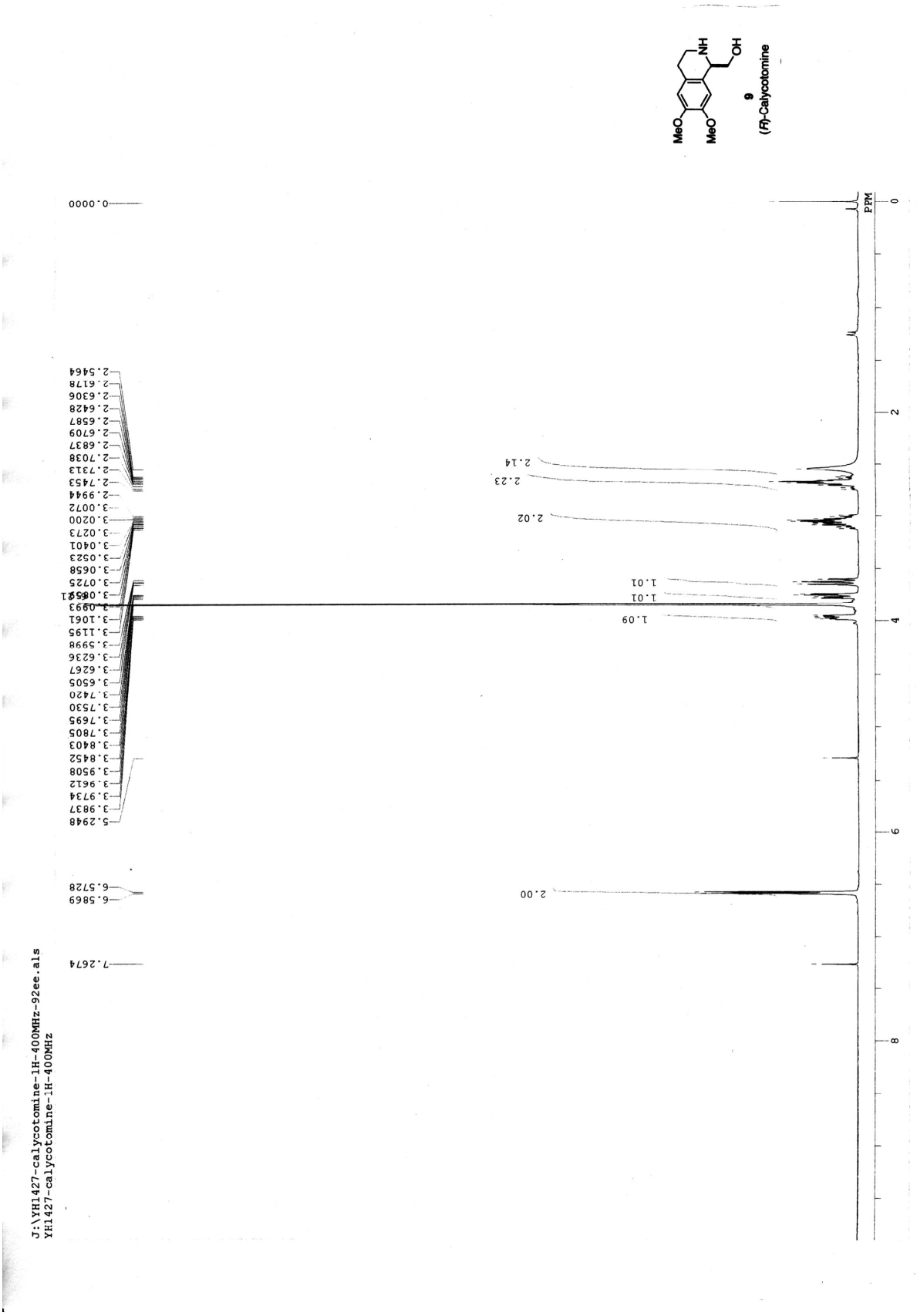
SLVNT : CDCL3
SPINNING : 10 Hz
TEMP : 22.4 C
Me
N-Boc
(CO2iPr)2
6g
ppm



J:\YH1505-4-Br-1H-400MHz.als


N-Boc
CO2Et
EtO2C
5
16.32
4.75
2.53
2.02
1.00
4.16
PPM
D:\YH1414-Et-Boc-1H-300MHz.dat
YH1413-Et-Boc-1H-300MHz


NBoc
CO2Me
MeO
MeO
8
I:\YH1415-Me-ester-1H-300MHz.als
YH1415-Me ester-1H-300MHz
PPM
0.0037
1.4789
1.5009
9.00
1.86
10.69
0.49
0.33
0.93
0.92
6.6411
6.9867
7.2920


MeO
MeO
NH
OH
9
(R)-Calycotomine
PPM
0
2
4
6
8
2.14
2.23
2.02
1.01
1.01
1.09
2.00
7.2674
6.5869
6.5728
5.2948
3.9837
3.9734
3.9612
3.9508
3.8452
3.8403
3.7805
3.7695
3.7530
3.7420
3.6505
3.6267
3.6236
3.5998
3.1195
3.1061
3.0993
3.0725
3.0658
3.0523
3.0401
3.0273
3.0200
3.0072
2.9944
2.7453
2.7313
2.7038
2.6837
2.6709
2.6587
2.6428
2.6306
2.6178
2.5464
0.0000
J:\YH1427-calycotomine-1H-400MHz-92ee.als
YH1427-calycotomine-1H-400MHz