Enantioconvergent Synthesis of (+)-Aphanorphine via Asymmetric Pd-Catalyzed Alkene Carboamination.

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Supporting Information

Experimental procedures, characterization data for new compounds, and copies of NMR spectra.

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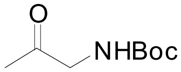
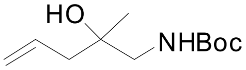
General: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. Tris(dibenzylideneacetone)dipalladium and (*R)*-Siphos-PE were purchased from Strem Chemical Co. and used without further purification. All reagents were obtained from commercial sources and were used as obtained. Toluene, THF, methylene chloride and diethyl ether were purified using a GlassContour solvent purification system. The yields reported in the Supporting Information describe the result of a single experiment, whereas the yields reported in Schemes 1–4 are average yields of two or more experiments. Thus, the yields reported in the Supporting Information may differ from those shown in Schemes 1–4.

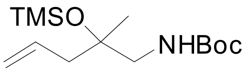
Experimental Procedures and Compound Characterization Data.



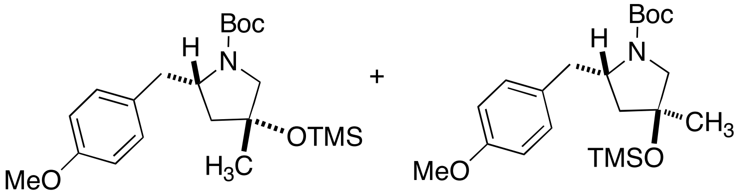
***tert*-Butyl (2-oxopropyl)carbamate (10).**[1] A flame-dried flask was cooled under a stream of nitrogen and charged with pyridinium chlorochromate (12.3 g, 57 mmol) and CH_2Cl_2 (50 mL). The flask was cooled in an ice-water bath and (±)-*tert*-butyl (2-hydroxypropyl)carbamate (5.0 g in 10 mL CH_2Cl_2, 28.5 mmol) was added to the solution. The resulting mixture was stirred overnight at rt, then Et_2O (100 mL) was added. The resulting black tar was filtered through a plug of silica gel and concentrated. The crude product was purified by flash chromatography on silica gel to afford 4.7 g (96%) of the title compound as a yellow oil. Spectroscopic properties were consistent with those reported in the literature.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (s, br, 1 H), 4.03 (d, *J* = 4.5 Hz, 2 H), 2.18 (s, 3 H), 1.44 (s, 9 H).



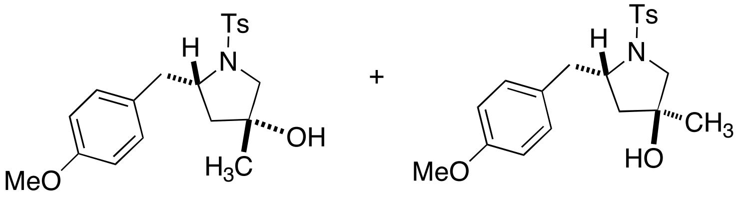
(±)-*tert*-Butyl (2-hydroxy-2-methylpent-4-en-1-yl)carbamate (11). A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of allylmagnesium bromide (92 mL, 1 M in Et_2O) and additional Et_2O (25 mL). The resulting solution was cooled in an ice-water bath and a solution of *tert*-butyl (2-oxopropyl)carbamate (8.0 g, 46 mmol) in Et_2O (25 mL) was added slowly via syringe. The resulting mixture was warmed to rt and stirred until the starting material was consumed as judged by TLC analysis (ca. 1.5 h). The mixture was then cooled in an ice-water bath and the reaction was quenched by the slow addition of water (100 mL). The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 100 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to afford 9.3 g (94%) of the title compound as a brown oil that was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95–5.81 (m, 1 H), 5.21–5.07 (m, 2 H), 4.90 (s, br, 1 H), 3.13 (d, *J* = 6.2 Hz, 2 H), 2.40 (s, 1 H), 2.23 (d, *J* = 7.4 Hz, 2 H), 1.45 (s, 9 H), 1.16 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 133.4, 118.3, 79.1, 72.2, 49.6, 44.2, 28.1, 24.1; IR (film) 3369, 1694 cm^{-1}; MS (ESI): 238.1417 (238.1419 calc for $C_{11}H_{21}NO_3$, M + Na^+).



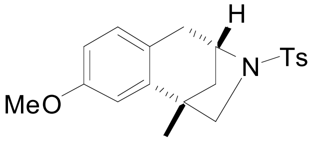
(±)-*tert*-Butyl {2-methyl-2-[(trimethylsilyl)oxy]pent-4-en-1-yl}carbamate (5). A flame-dried round bottom flask equipped with a stirbar was cooled under a stream of nitrogen and charged with (±)-*tert*-butyl (2-hydroxy-2-methylpent-4-en-1-yl)carbamate (5.0 g, 23 mmol). Neat 1-(trimethylsilyl)-1H-imidazole (6.8 mL, 46 mmol) was added and the resulting mixture was stirred at rt until the starting material had been consumed as judged by TLC analysis (ca. 4 h). Water (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to afford 6.0 g (90%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87–5.73 (m, 1 H), 5.09–5.01 (m, 2 H), 4.74 (s, br, 1 H), 3.16–2.99 (m, 2 H), 2.23 (d, $J = 7.2$ Hz, 2 H), 1.45 (s, 9 H), 1.19 (s, 3 H), 0.13 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 133.9, 117.9, 79.0, 75.7, 50.0, 45.2, 28.3, 24.9, 2.5; IR (film) 3368, 1720 cm^{-1}; MS (ESI): 310.1815 (311.1833 calcd for $C_{14}H_{29}NO_3Si$, M + Na$^+$).



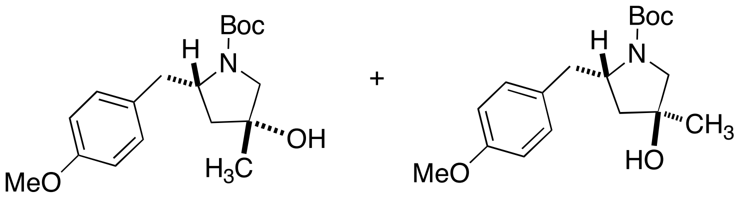
(+)-(2*S*,4*RS*)-*tert*-Butyl 2-(4-methoxybenzyl)-4-methyl-4-[(trimethylsilyl)oxy]pyrrolidine-1-carboxylate (6a-b). A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (191 mg, 0.2 mmol), (*R*)-Siphos-PE (303 mg, 0.06 mmol) and NaO^{t}Bu (960 mg, 0.5 mmol). The tube was evacuated and backfilled with nitrogen three times, then a solution of (±)-*tert*-butyl {2-methyl-2-[(trimethylsilyl)oxy]pent-4-en-1-yl}carbamate (3.0 g, 10 mmol) and 4-bromoanisole (3.74 g, 20 mmol) in toluene (30 mL) was added via syringe. The resulting mixture was stirred at rt for 1 min then was immersed in 90 °C oil bath and stirred overnight (ca 14 h). The mixture was then cooled to room temperature and saturated aqueous ammonium chloride (10 mL) was added. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to afford 3.1 g (75%) of the title compound as a pale yellow oil. The product was judged to be a 1:1 mixture of rotamers and a 1:1 mixture of diastereomers by ^{1}H NMR analysis. Data are for the mixture. $[\alpha]^{23}_D$ +18.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.03 (m, 2 H), 6.86–6.78 (m, 2 H), 4.19–3.82 (m, 1 H), 3.79 (s, 3 H), 3.76–3.10 (m, 2 H), 2.93–2.54 (m, 2 H), 1.94–1.79 (m, 1 H), 1.77–1.66 (m, 1 H), 1.55–1.47 (m, 9 H), 1.33–1.26 (m, 3 H), 0.14 (s, 4.5 H), 0.07 (s, 4.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 157.7, 154.9, 154.7, 154.3, 130.8, 130.5, 130.3, 130.2, 130.0, 126.5, 113.6, 113.5, 113.4, 113.3, 79.0, 78.9, 78.8, 78.6, 78.0, 77.8, 77.6, 59.9, 59.7, 59.1, 59.0, 58.8, 58.2, 57.9, 54.7, 46.6, 45.5, 44.5, 43.4, 39.6, 39.4, 38.3, 38.2, 28.3, 28.1, 28.0, 26.6, 26.5, 24.8, 24.7, 2.2, 1.9, 1.8, 1.7; IR (film) 2972, 1699, 1684 cm^{-1}; MS (ESI): 416.2228 (416.2233 calcd for $C_{21}H_{35}NO_4Si$, M + Na$^+$).



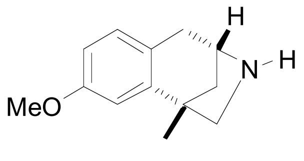
(+)-(5*S*,3*RS*)-5-(4-Methoxybenzyl)-3-methyl-1-tosylpyrrolidin-3-ol (12a-b).[2] A round bottomed flask equipped with a stirbar was charged with (+)-(2*S*,4*RS*)-*tert*-Butyl 2-(4-methoxybenzyl)-4-methyl-4-[(trimethylsilyl)oxy]pyrrolidine-1-carboxylate and CH_2Cl_2 (7.6 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (5.7 mL, 76.2 mmol) was added, and the solution was warmed to rt and stirred until the starting material had been consumed as judged by TLC analysis (ca. 10 min). The reaction mixture was diluted with water, basified with NH_4OH, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was dissolved in THF (5 mL) and the resulting solution was added to a stirring solution of triethylamine (3.2 mL, 22.9 mmol), tosyl chloride (2.18 mg, 11.4 mmol) and THF (10 mL). The reaction mixture was stirred overnight at rt, then saturated $NaHCO_3$ (10 mL) was added. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to afford 2.3 g (80%) of the title compound as a colorless oil.[2] The product was judged to be a 1:1 mixture of diastereomers by ^{1}H NMR analysis. Data are for the mixture. $[\alpha]^{23}{}_D$ +65.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.73 (m, 2 H), 7.36–7.30 (m, 2 H), 7.20 (d, *J* = 8.0 Hz, 1.2 H), 7.14 (d, *J* = 8.4 Hz, 0.8 H), 6.88–6.80 (m, 2 H), 4.02–3.94 (m, 0.5 H), 3.83–3.75 (m, 3.5 H), 3.42–3.37 (m, 1 H), 3.30–3.21 (m, 1 H), 3.18–3.07 (m, 1 H), 3.03 (d, *J* = 10.4 Hz, 0.6 H), 2.83 (dd, *J* = 9.2, 13.6 Hz, 0.4 H), 2.44–2.41 (m, 3 H), 1.84–1.74 (m, 1 H), 1.64–1.54 (m, 2 H), 1.19 (m, 1 H), 1.09 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 143.7, 143.6, 133.9, 130.9, 130.6, 130.0, 129.8, 129.7, 129.6, 127.8, 127.7, 113.9, 113.7, 76.1, 76.0, 61.7, 61.6, 61.5, 61.0, 55.2, 45.5, 43.2, 41.1, 41.0, 25.4, 24.1, 21.5 (5 peaks are incidentally equivalent).



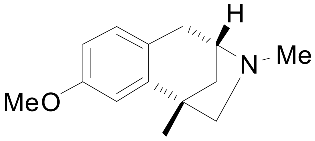
(+)-(*1S,4S*)-8-Methoxy-1-methyl-3-tosyl-2,3,4,5-tetrahydro-1H-1,4-methanobenzo[*d*]azepine (13).[3] A flame-dried round-bottom flask was charged with aluminum trichloride (8.0 g, 60 mmol) and CH_2Cl_2 (100 mL). The flask was cooled to 0 °C and a solution of (+)-(5*S*,3*RS*)-5-(4-methoxybenzyl)-3-methyl-1-tosylpyrrolidin-3-ol (2.15 g, 5.7 mmol) in CH_2Cl_2 (20 mL) was added *via* syringe. The resulting mixture was allowed to slowly warm to rt and was stirred overnight. The reaction mixture was then poured into a solution of saturated aqueous $NaHCO_3$ (50 mL). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to afford 1.2 g (60%) of the title compound as a pale yellow solid. The enantiomeric excess was determined to be 81% ee by chiral HPLC analysis (Chiralpak AD-H 0.46 cm x 25 cm, 1 % *i*PrOH/hexanes, 1 mL/min, λ = 254 nm, RT = 8.0 and 9.8 min). Spectroscopic properties were consistent with those previously reported in the literature. $[\alpha]^{23}{}_D$ +16.0 (*c* 1.0, CH_2Cl_2) [for *ent*-**13** lit.[3] $[\alpha]^{27}{}_D$ –16.9 (*c* 0.89, $CHCl_3$)]; mp: 137–140 °C (lit.[3] mp 136–138 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 6.78 (d, *J* = 2.5 Hz, 1 H), 6.72 (dd, *J* = 2.6, 8.3 Hz, 1 H), 4.41–4.35 (m, 1 H), 3.78 (s, 3 H), 3.40 (dd, *J* = 1.2, 8.7 Hz, 1 H), 3.11 (d, *J* = 16.6 Hz, 1 H), 3.02 (d, *J* = 8.6 Hz, 1 H), 2.93 (dd, *J* = 2.8, 16.5 Hz, 1 H), 2.42 (s, 3 H), 1.79 (d, *J* = 11.5 Hz, 1 H), 1.50–1.38 (m, 4 H).



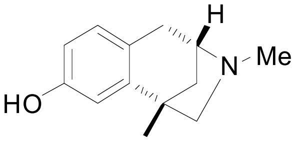
(+)-(*2S,4RS*)-*tert*-Butyl 4-hydroxy-2-(4-methoxybenzyl)-4-methylpyrrolidine-1-carboxylate (14a-b). A round-bottom flask was charged with (+)-(2*S*,4*RS*)-*tert*-butyl 2-(4-methoxybenzyl)-4-methyl-4-[(trimethylsilyl)oxy]pyrrolidine-1-carboxylate (100 mg, 0.254 mmol) and tetrabutylammonium fluoride (0.51 mL, 0.51 mmol) 1 M solution in THF) and the resulting solution was stirred until the starting material had been consumed as judged by TLC analysis (ca. 1 h). The reaction mixture was diluted with water (5 mL) and CH_2Cl_2 (5 mL) then was transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel to afford 73 mg (90%) of the title compound as a colorless viscous oil. The product was judged to be a 1:1 mixture of rotamers and a 1:1 mixture of diastereomers by ^{1}H NMR analysis. Data are for the mixture. $[\alpha]^{23}_D$ +23.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.02 (m, 2 H), 6.84–6.78 (m, 2 H), 4.24–3.88 (m, 1 H), 3.79 (s, 3 H), 3.70–3.08 (m, 2.5 H), 3.00–2.60 (m, 1.5 H), 1.96–1.70 (m, 2 H), 1.51 (s, 9 H), 1.38–1.24 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 155.1, 154.6, 131.1, 130.4, 130.1, 113.7, 79.4, 77.2, 76.1, 75.7, 75.2, 59.9, 59.5, 59.3, 58.2, 57.7, 55.0, 45.1, 44.5, 43.0, 42.5, 39.7, 39.5, 38.5, 38.1, 28.5, 26.7, 24.7; IR (film) 3420, 1682 cm^{-1}; MS (ESI): 344.1833 (344.1838 calcd for $C_{18}H_{27}NO_4$, M + Na$^+$).



(+)- *(*1*S*,4*S*)-8-Methoxy-1-methyl-2,3,4,5-tetrahydro-1*H*-1,4-methanobenzo[*d*]azepine (S1). A flame-dried round-bottom flask was charged with (+)-(1*S*,4*S*)-8-methoxy-1-methyl-3-tosyl-2,3,4,5-tetrahydro-1H-1,4-methanobenzo[*d*]azepine (1.1 g, 3.1 mmol) and xylene (15 mL). A solution of Red-Al was added (3.5 M in toluene, 3.3 mL, 11.4 mmol) and the mixture was heated to reflux for 1 h. The solution was cooled to 0 °C, diluted with ether and quenched with a few drops of water. The solution was filtered through a pad of celite and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 450 mg (71%) of the title compound as a yellow oil. $[\alpha]^{23}_{D}$ +38.2 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.5 Hz, 1 H), 6.82 (d, *J* = 2.5 Hz, 1 H), 6.71 (dd, *J* = 3.0, 8.5 Hz, 1 H), 3.85–3.79 (m, 4 H), 3.11–3.02 (m, 2 H), 2.92 (d, *J* = 10 Hz, 1 H), 2.78 (m, 2 H), 1.96–1.92 (m, 1 H), 1.86 (d, *J* = 11 Hz, 1 H), 1.49 (s, 3 H).



(–)-8-*O*-methylaphanorphine (15). A flame-dried round-bottom flask was charged with (+)-(1*S*,4*S*)-8-methoxy-1-methyl-2,3,4,5-tetrahydro-1*H*-1,4-methanobenzo[*d*]azepine (300 mg, 1.5 mmol), a solution of 37% aqueous formalin (1.8 mL) and formic acid (2.8 mL). The reaction mixture was heated to 100 °C for 1.5 h, then cooled to rt, diluted with water (10 mL), and basified with 10% NaOH solution. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 294 mg (90%) of the title compound as a pale yellow oil. Spectroscopic properties are consistent with those previously reported in the literature. $[\alpha]^{23}_{D}$ –5.8 (*c* 1.0, $CHCl_3$), [lit.[4] $[\alpha]^{27}_{D}$ –7.4 (*c* 0.35, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.4 Hz, 1 H), 6.78 (d, *J* = 2.8 Hz, 1 H), 6.68 (dd, *J* = 2.8, 8.4 Hz, 1 H), 3.78 (s, 3 H), 3.42 (m, 1 H), 3.02 (d, *J* = 16.4 Hz, 1 H), 2.88–2.84 (m, 2 H), 2.82 (d, *J* = 1.2 Hz, 1 H), 2.76 (d, *J* = 9.2 Hz, 1 H), 2.48 (s, 3 H), 2.02 (ddd, *J* = 1.2, 5.6, 10.8 Hz, 1 H), 1.48 (s, 3 H).



(+)-aphanorphine (16). Demethylation of (–)-8-*O*-methylaphanorphine was carried according to reported procedure.[5] A flame-dried round-bottom flask was charged with **15** (40 mg, 0.18 mmol) and CH_2Cl_2 (1 mL) and cooled to –30 ˚C. BBr_3 (1.0 M in CH_2Cl_2, 0.36 mL) was added slowly dropwise. The reaction mixture was stirred for 30 min at –30 ˚C, 30 min at –20 ˚C, 30 min at –10 ˚C and then 30 min at 0 ˚C. The reaction was quenched at 0 °C with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was taken up in 2 mL of 3 M NaOH and heated at 100 °C for 5 min. The solution was acidified with 1 M HCl and basified with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude solid was triturated with acetone to afford 23 mg (63%) of the title compound as a white solid. Spectroscopic properties are consistent with the present literature. $[\alpha]^{23}_{D}$ +28.0 (*c* 0.1, MeOH) [lit.[4] $[\alpha]^{27}_{D}$ +37.5 (*c* 0.16, MeOH)]; mp 202–208 °C (lit.[4] mp 215–222). ^1H NMR (400 MHz, CD_3OD) δ 6.89 (d, *J* = 8 Hz, 1 H), δ 6.67 (d, *J* = 2.4 Hz, 1 H), δ 6.56 (dd, *J* = 2.4, 8.4 Hz, 1 H), 3.38 (m, 1 H), 2.97 (d, *J* = 16.8 Hz, 1 H), 2.85 (m, 2 H), 2.63 (d, *J* = 9.6 Hz, 1 H), 2.40 (s, 3 H), 2.01 (q, *J* = 5.6 Hz, 1 H), 1.83 (d, *J* = 11.2 Hz, 1 H), 1.44 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 156.6, 148.6, 131.2, 125.2, 114.5, 110.9, 72.7, 63.4, 44.3, 42.8, 42.1, 36.7, 21.7.

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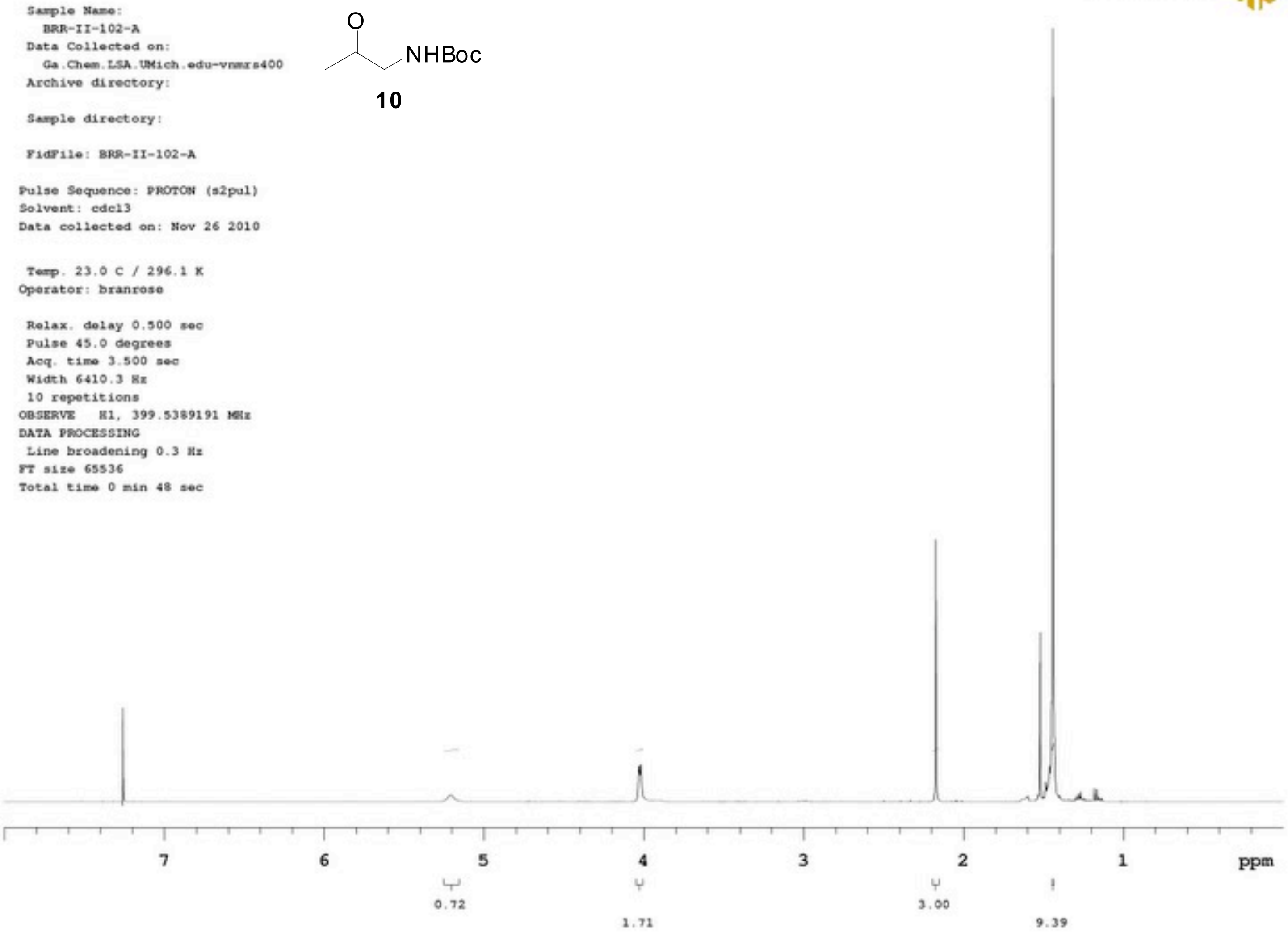
[1] Nagafuji, P.; Cushman, M. *J. Org. Chem.* **1996**, *61*, 4999.

[2] Ma, Z.; Hu, H.; Xiong, W.; Zhai, H. *Tetrahedron* **2007**, *63*, 7523.

[3] For *ent*-**13**, see: Yang, X.; Zhai, H.; Li, Z. *Org. Lett.* **2008**, *10*, 2457.

[4] Takano, S.; Inomata, K.; Sato, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun*. **1989**, 1591.

[5] Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923.



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 Archive directory:

 Sample directory:

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Data collected on: Nov 26 2010

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Operator: branrose

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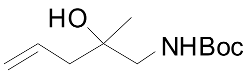

11

Sample Name:

Archive directory:

Sample directory:

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Solvent: cdcl3
Data collected on: Jun 24 2008

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INOVA-500 "Sn.Chem.LSA.UMich.edu"

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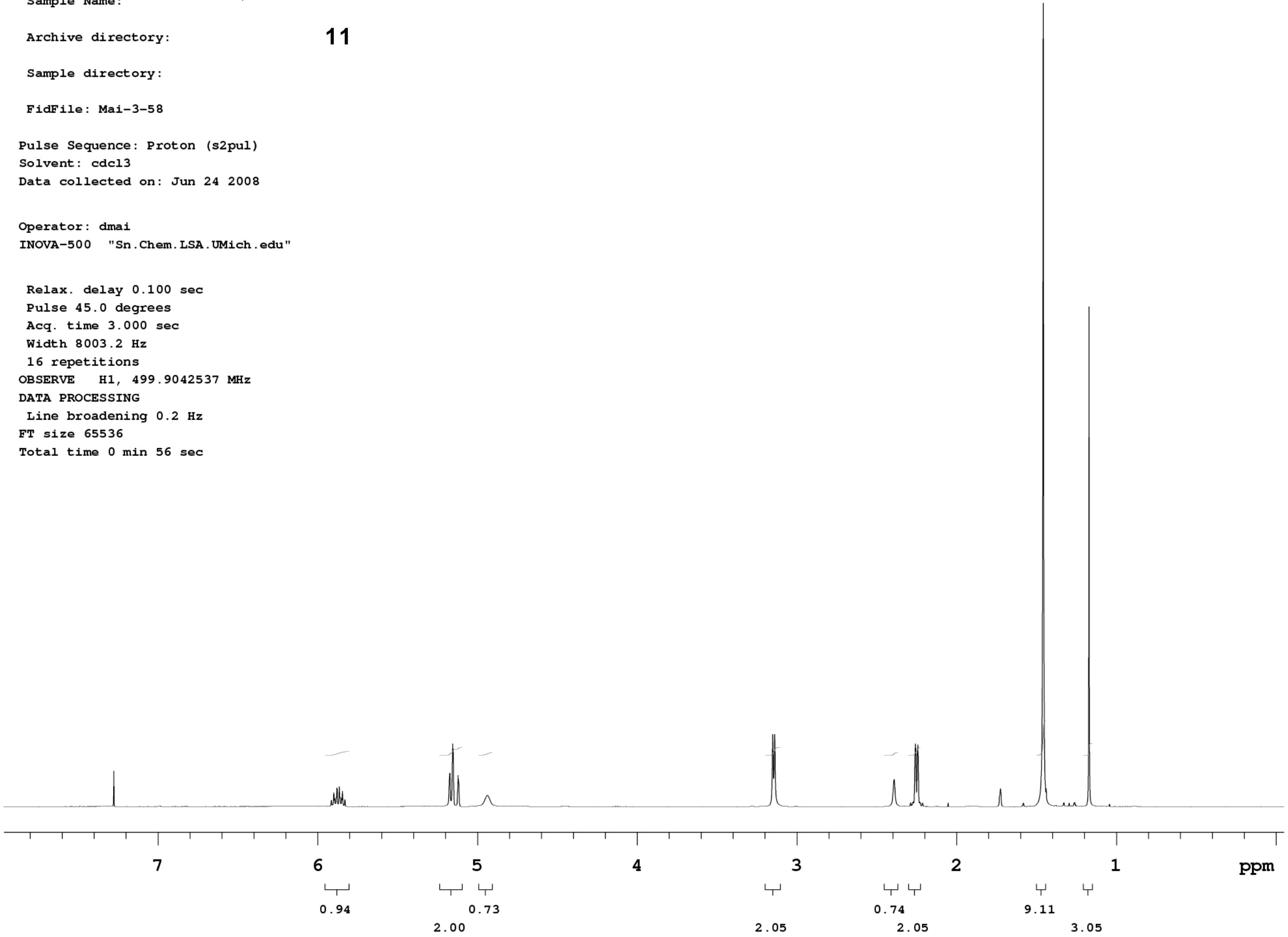

Mai-3-58-CARBON

Sample Name:

Data Collected on:
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Sample directory:

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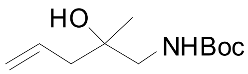
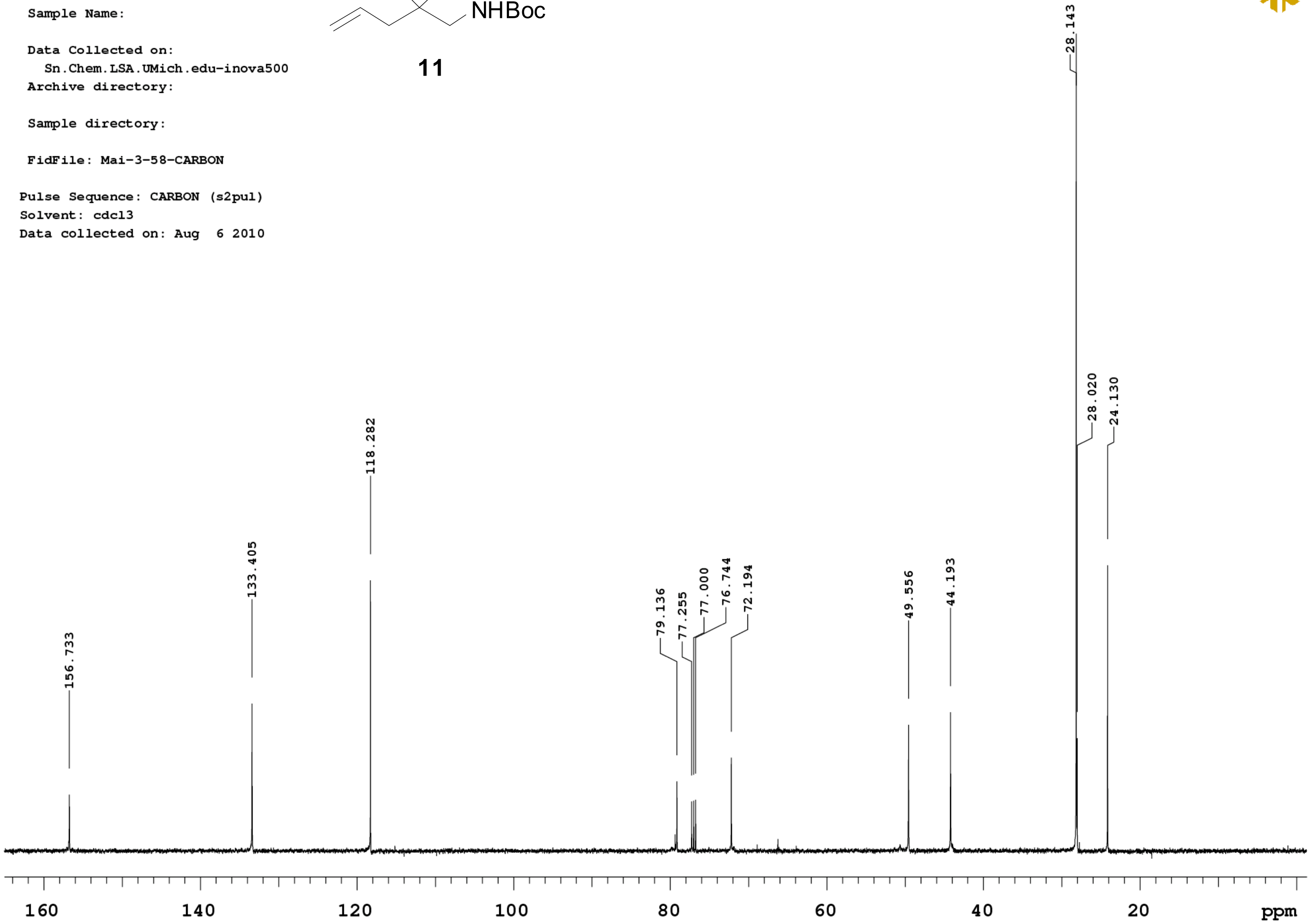
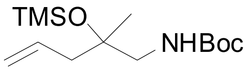
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 6 2010



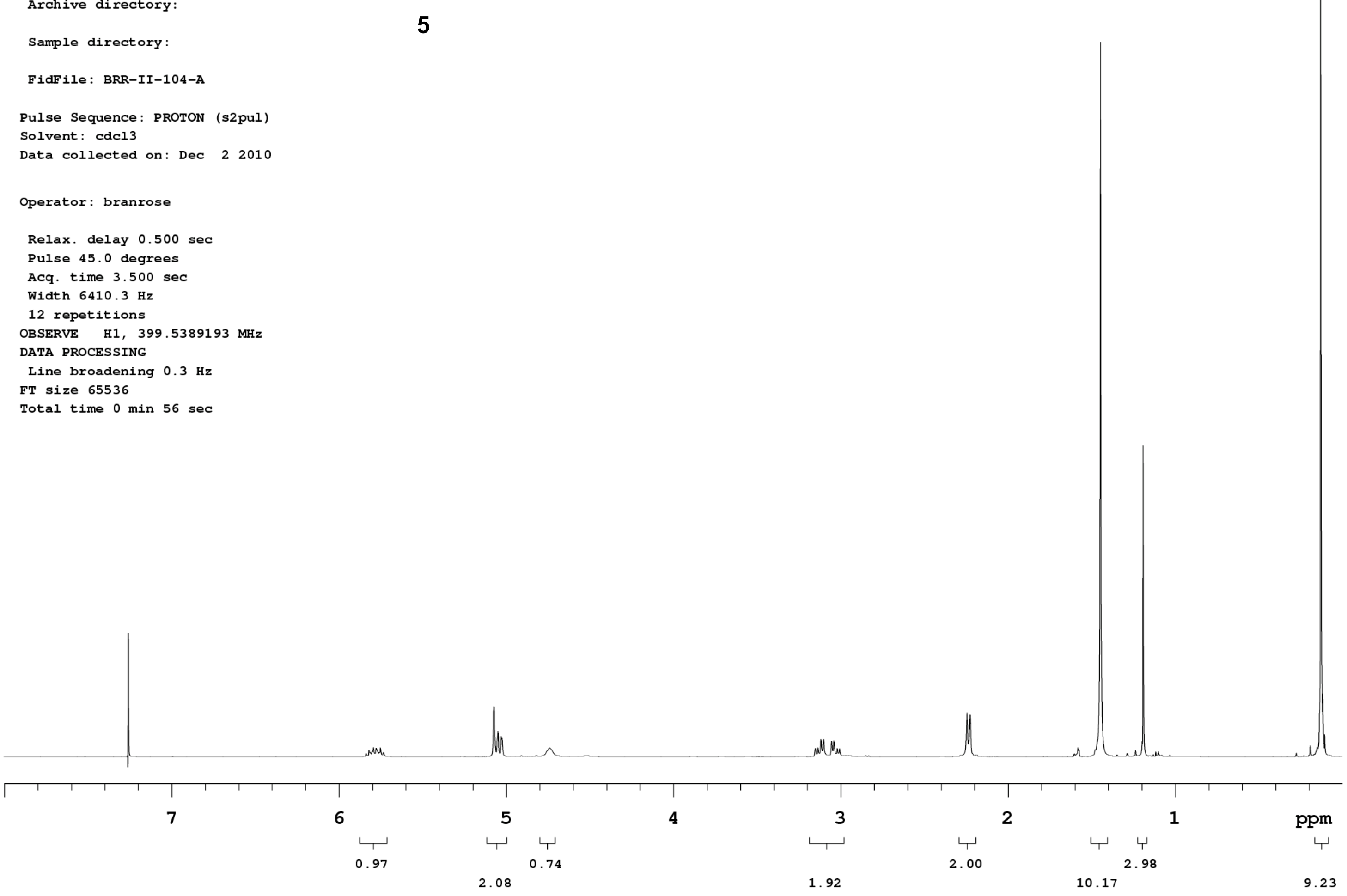
11



```
 Sample Name:
   BRR-II-104-A
 Data Collected on:
   Ga.Chem.LSA.UMich.edu-vnmrs400
 Archive directory:

 Sample directory:

 FidFile: BRR-II-104-A

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec  2 2010


Operator: branrose

 Relax. delay 0.500 sec
 Pulse 45.0 degrees
 Acq. time 3.500 sec
 Width 6410.3 Hz
 12 repetitions
OBSERVE   H1, 399.5389193 MHz
DATA PROCESSING
 Line broadening 0.3 Hz
FT size 65536
Total time 0 min 56 sec
```



5



TMS Substrate CARBON

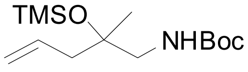
Sample Name:

Data Collected on:
Ga.Chem.LSA.UMich.edu-vnmrs400
Archive directory:

Sample directory:

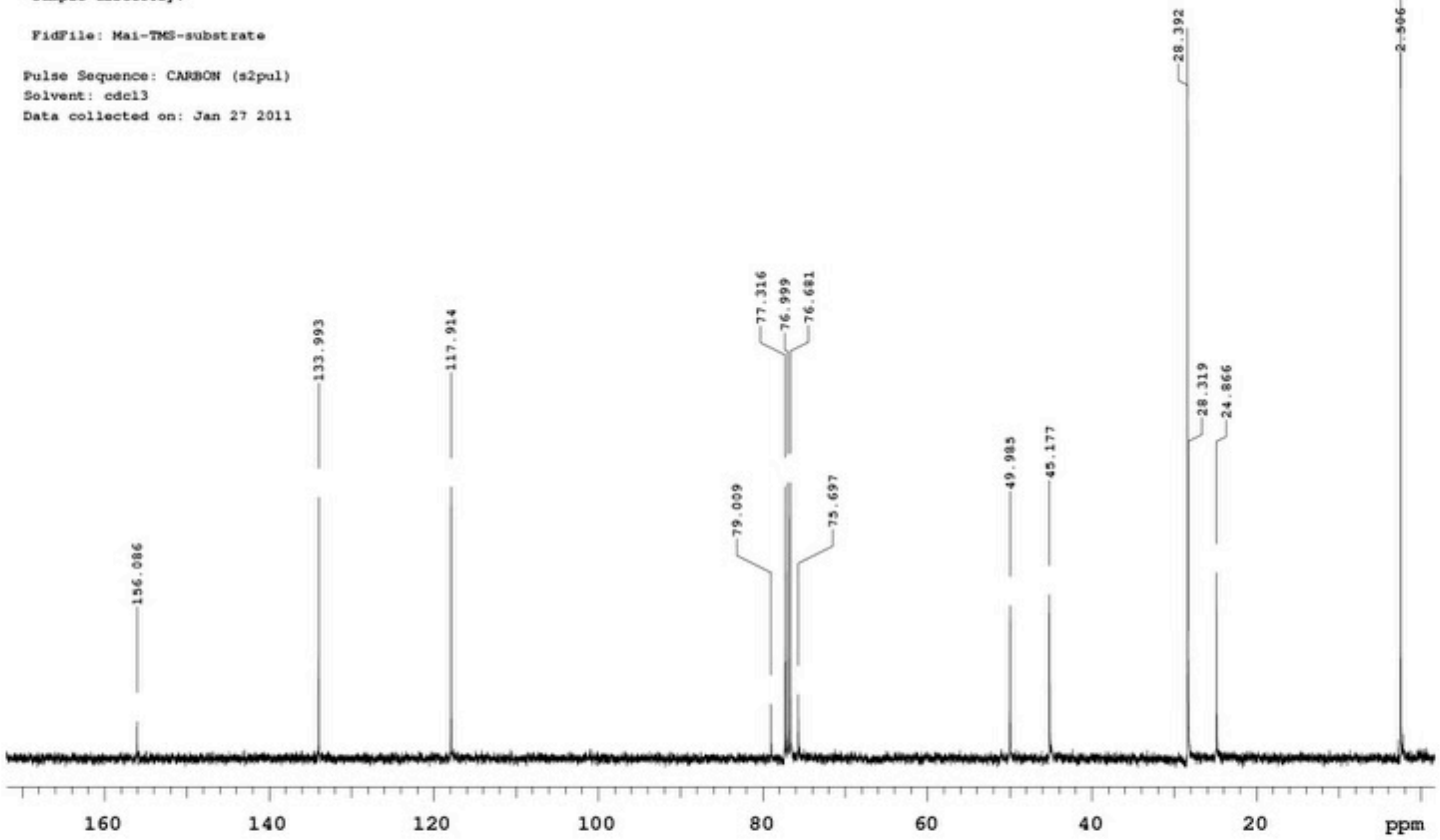
FidFile: Mai-TMS-substrate

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 27 2011

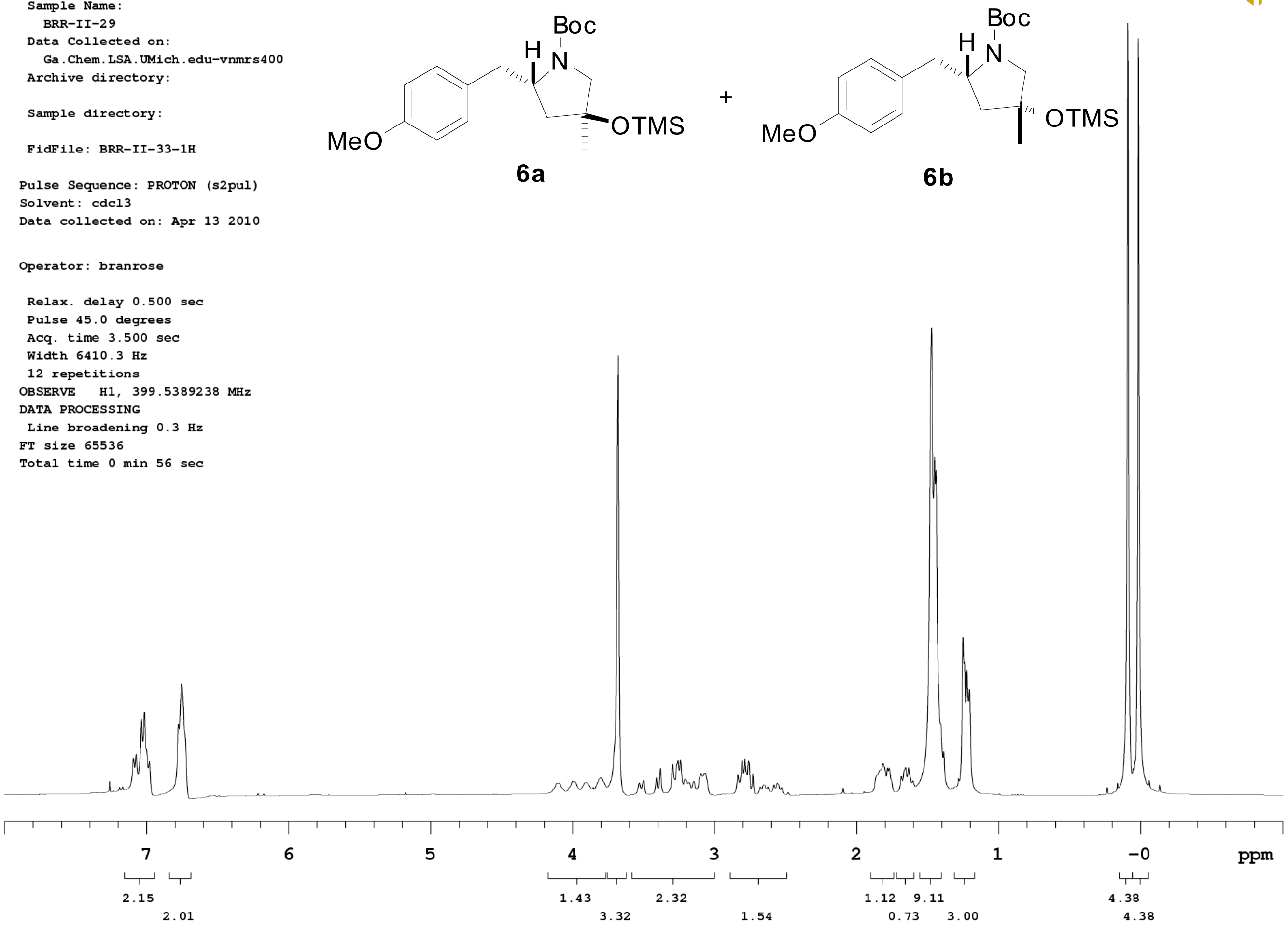


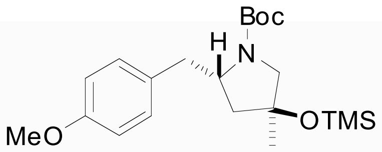
5

VARIAN



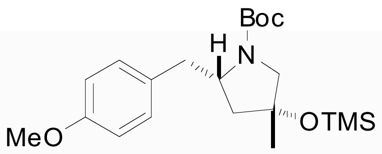
```
 Sample Name:
   BRR-II-29
 Data Collected on:
   Ga.Chem.LSA.UMich.edu-vnmrs400
 Archive directory:

 Sample directory:

 FidFile: BRR-II-33-1H

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 13 2010

Operator: branrose

 Relax. delay 0.500 sec
 Pulse 45.0 degrees
 Acq. time 3.500 sec
 Width 6410.3 Hz
 12 repetitions
OBSERVE   H1, 399.5389238 MHz
DATA PROCESSING
 Line broadening 0.3 Hz
FT size 65536
Total time 0 min 56 sec
```





6a

+



6b

STANDARD PROTON PARAMETERS

Sample Name:

Data Collected on:
Ga.Chem.LSA.UMich.edu-vnmrs400
Archive directory:

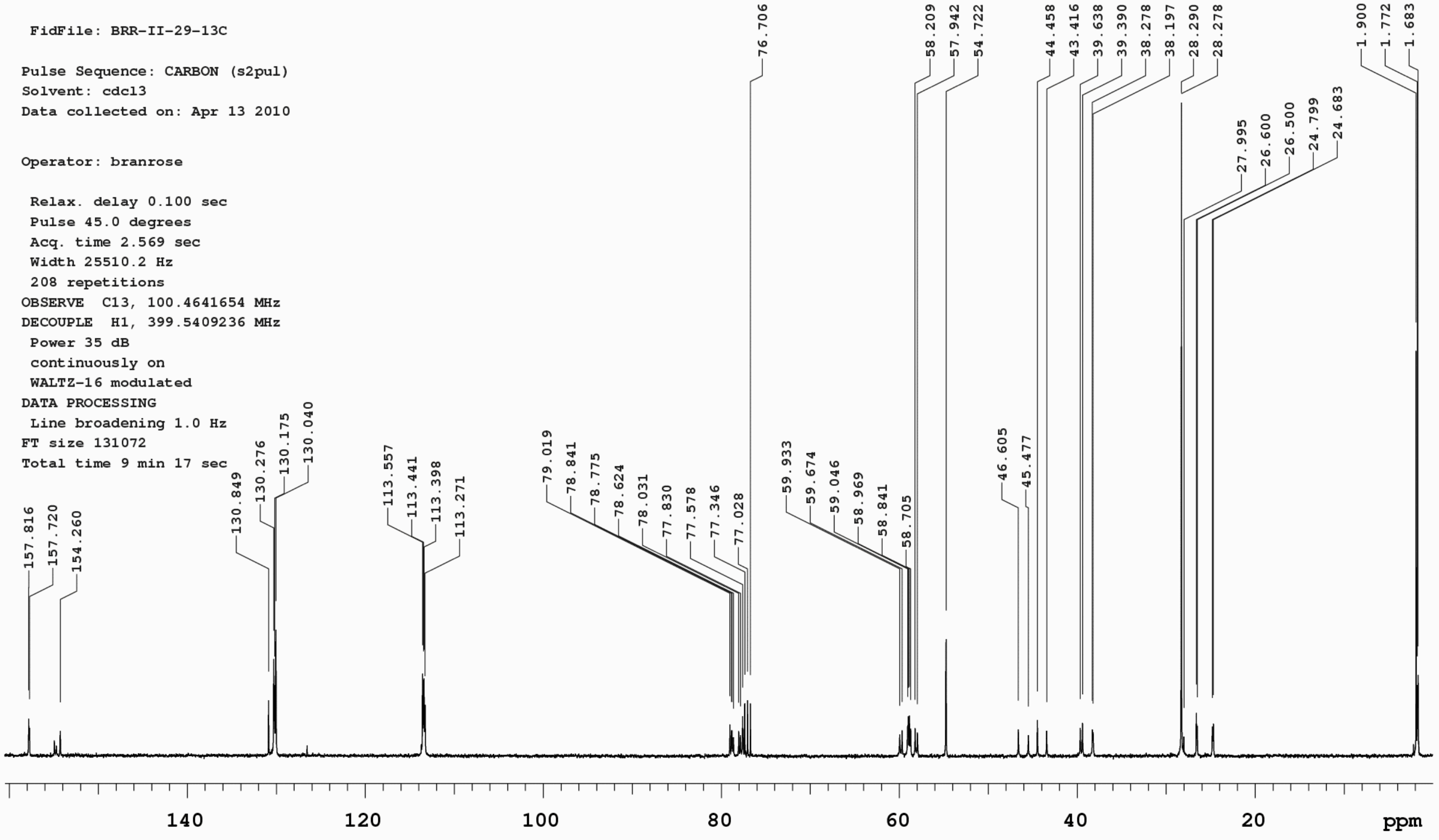
Sample directory:

FidFile: BRR-II-29-13C

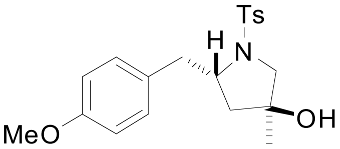
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Apr 13 2010

Operator: branrose

Relax. delay 0.100 sec
Pulse 45.0 degrees
Acq. time 2.569 sec
Width 25510.2 Hz
208 repetitions
OBSERVE C13, 100.4641654 MHz
DECOUPLE H1, 399.5409236 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 9 min 17 sec

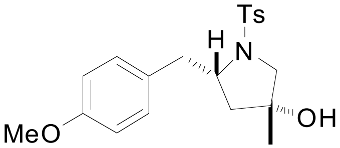


```
Mai-8-103

 Sample Name:

 Data Collected on:
   Ga.Chem.LSA.UMich.edu-vnmrs400
 Archive directory:

 Sample directory:

 FidFile: Mai-8-103

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan  5 2011

Operator: dmai

 Relax. delay 0.500 sec
 Pulse 45.0 degrees
 Acq. time 3.500 sec
 Width 6410.3 Hz
 16 repetitions
OBSERVE   H1, 399.5389200 MHz
DATA PROCESSING
 Line broadening 0.3 Hz
FT size 65536
Total time 1 min 12 sec
```



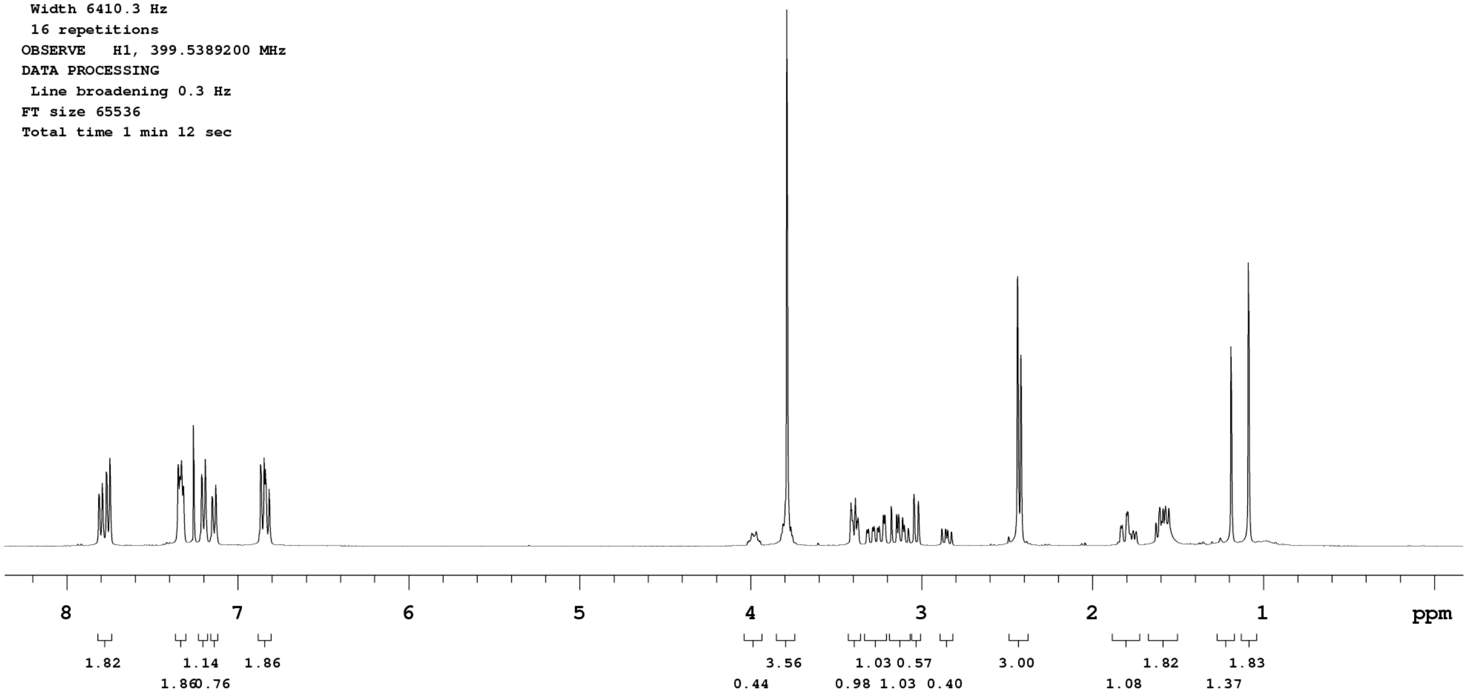
12a

+



12b

VARIAN



Mai-8-103

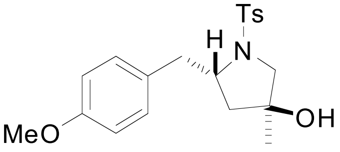
Sample Name:

Data Collected on:
Ga.Chem.LSA.UMich.edu-vnmrs400
Archive directory:

Sample directory:

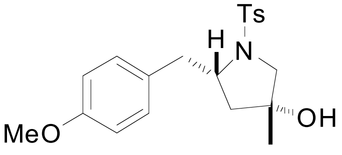
FidFile: Mai-8-103-CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 5 2011

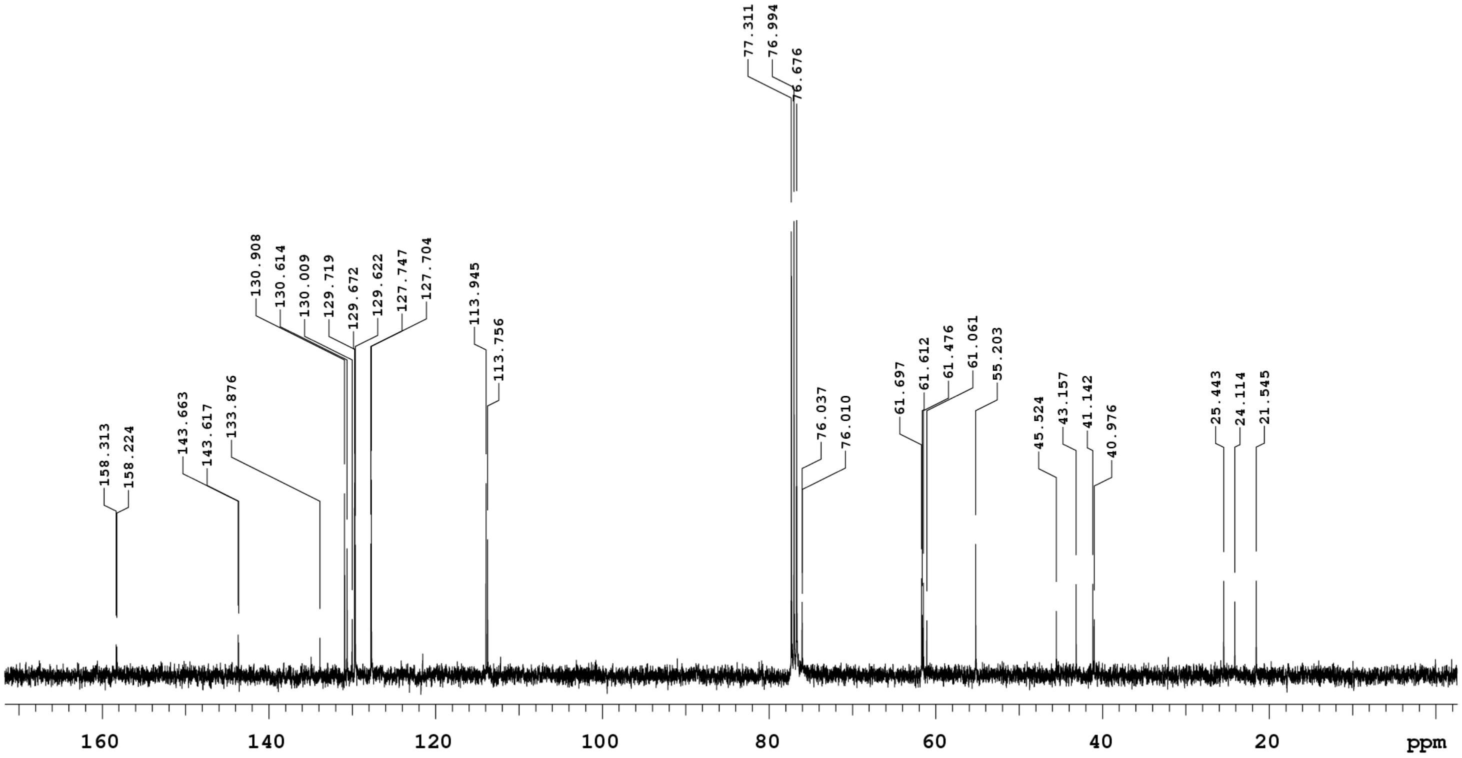


12a

+



12b



Sample Name:
BRR-II-111-A
Data Collected on:
Ga.Chem.LSA.UMich.edu-vnmrs400
Archive directory:

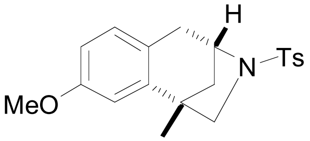
Sample directory:

FidFile: BRR-II-111-A

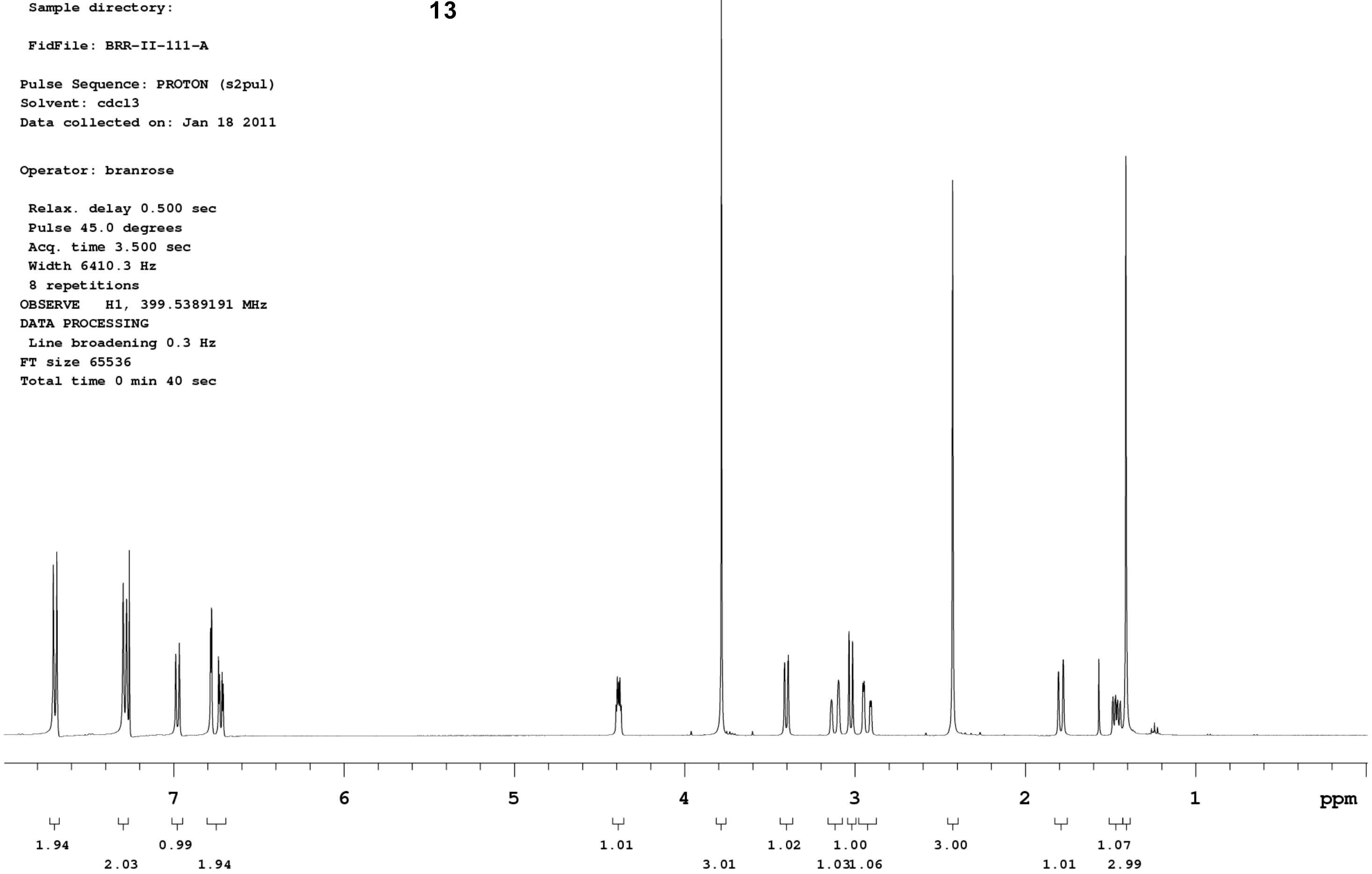
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 18 2011

Operator: branrose

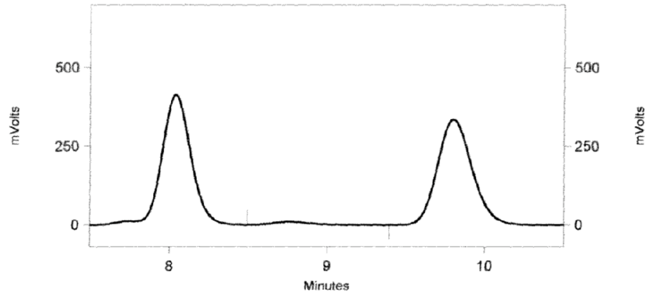
Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 3.500 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.5389191 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 65536
Total time 0 min 40 sec

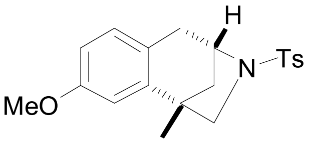


13



C:\CLASS-VP\Enterprise\Projects\Default\Data\Mai\HPLC\Aphanorphine\RAC-Mai-3-54-ADH-25%IPA_1.0mL_min.dat



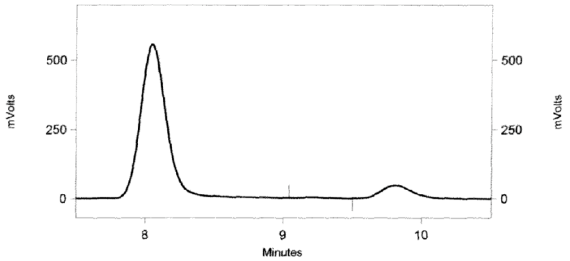


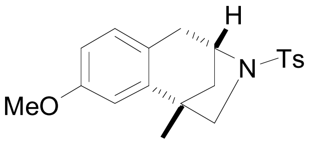
RAC-13

SPD-10Avp Ch2-254nm
Results

Retention Time	Area	Area Percent
8.042	5347671	50.752
9.800	5189148	49.248
Totals	10536819	100.000

C:\CLASS-VP\Enterprise\Projects\Default\Data\Mai\HPLC\Aphanorphine\CHIRAL-Mai-4-201-ADH-25%IPA_1.0mL_min.dat



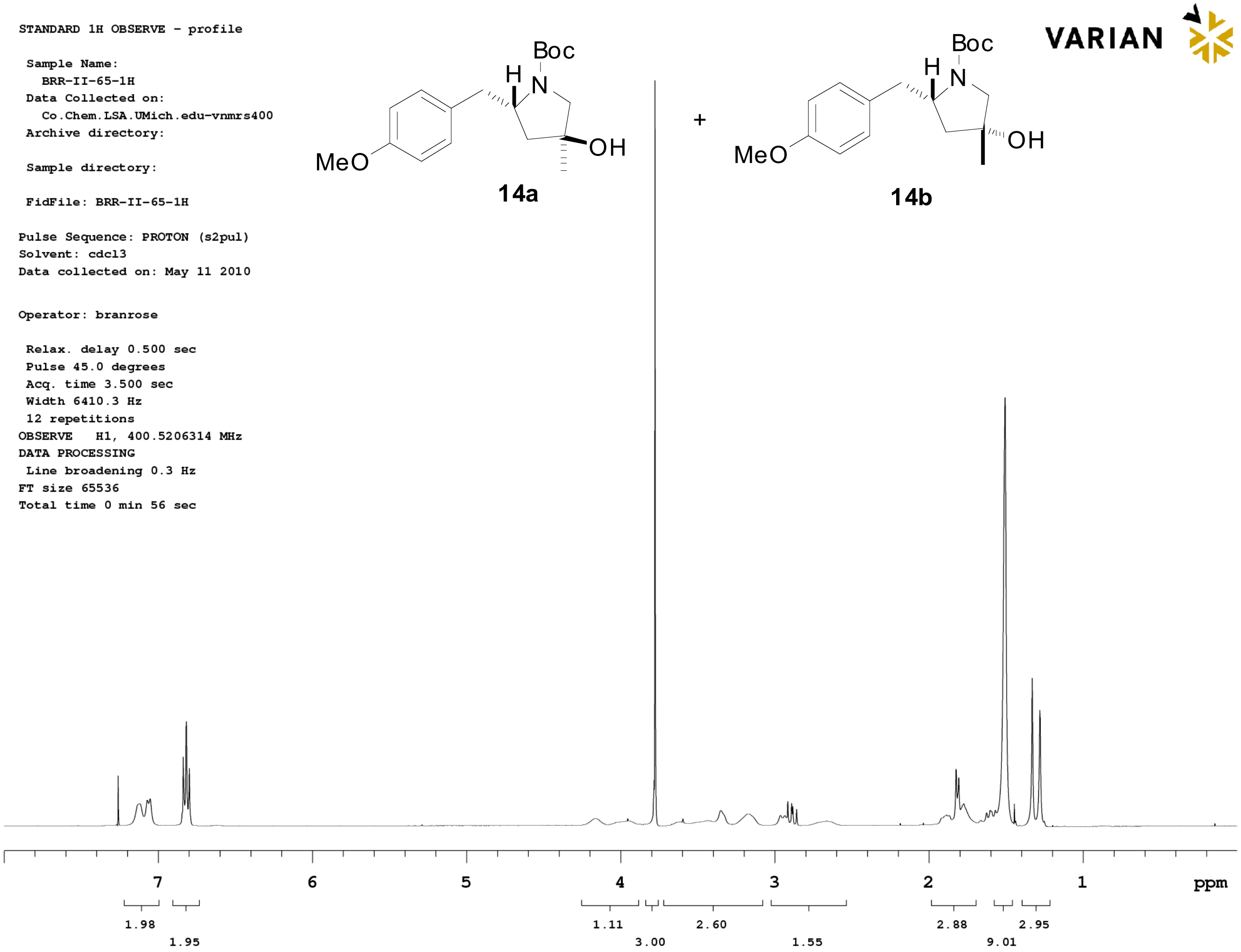


CHIRAL-13

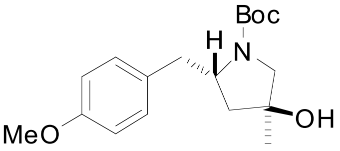
SPD-10Avp Ch2-254nm
Results

Retention Time	Area	Area Percent
8.050	7382399	90.574
9.808	768262	9.426
Totals	8150661	100.000

```
STANDARD 1H OBSERVE - profile

 Sample Name:
   BRR-II-65-1H
 Data Collected on:
   Co.Chem.LSA.UMich.edu-vnmrs400
 Archive directory:

 Sample directory:

 FidFile: BRR-II-65-1H

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 11 2010

Operator: branrose

 Relax. delay 0.500 sec
 Pulse 45.0 degrees
 Acq. time 3.500 sec
 Width 6410.3 Hz
 12 repetitions
OBSERVE   H1, 400.5206314 MHz
DATA PROCESSING
 Line broadening 0.3 Hz
FT size 65536
Total time 0 min 56 sec
```

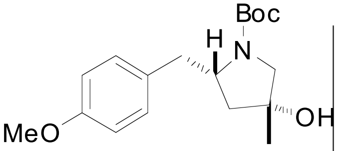


```
STANDARD PROTON PARAMETERS

 Sample Name:

 Data Collected on:
   Co.Chem.LSA.UMich.edu-vnmrs400
 Archive directory:

 Sample directory:

 FidFile: BRR-II-65-13C

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 11 2010

Operator: branrose

 Relax. delay 0.100 sec
 Pulse 45.0 degrees
 Acq. time 2.569 sec
 Width 25510.2 Hz
 452 repetitions
OBSERVE  C13, 100.7110037 MHz
DECOUPLE  H1, 400.5226414 MHz
 Power 41 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 131072
Total time 20 min
```



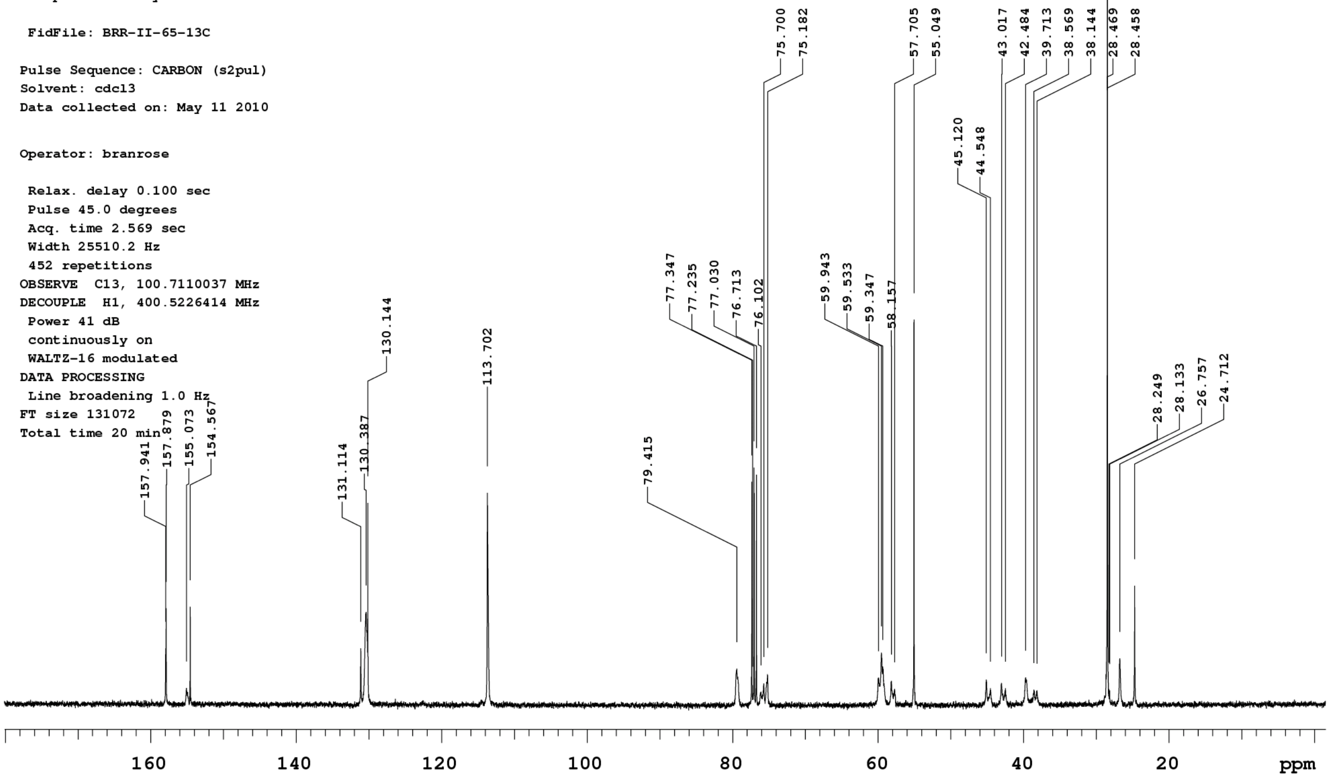
14a

\+



14b

VARIAN



Mai-8-109-FreeAmine

Sample Name:

Data Collected on:
Sn.Chem.LSA.UMich.edu-inova500
Archive directory:

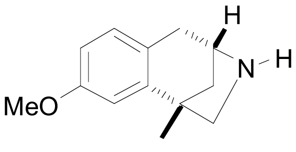
Sample directory:

FidFile: Mai-8-109-FreeAmine

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 24 2010

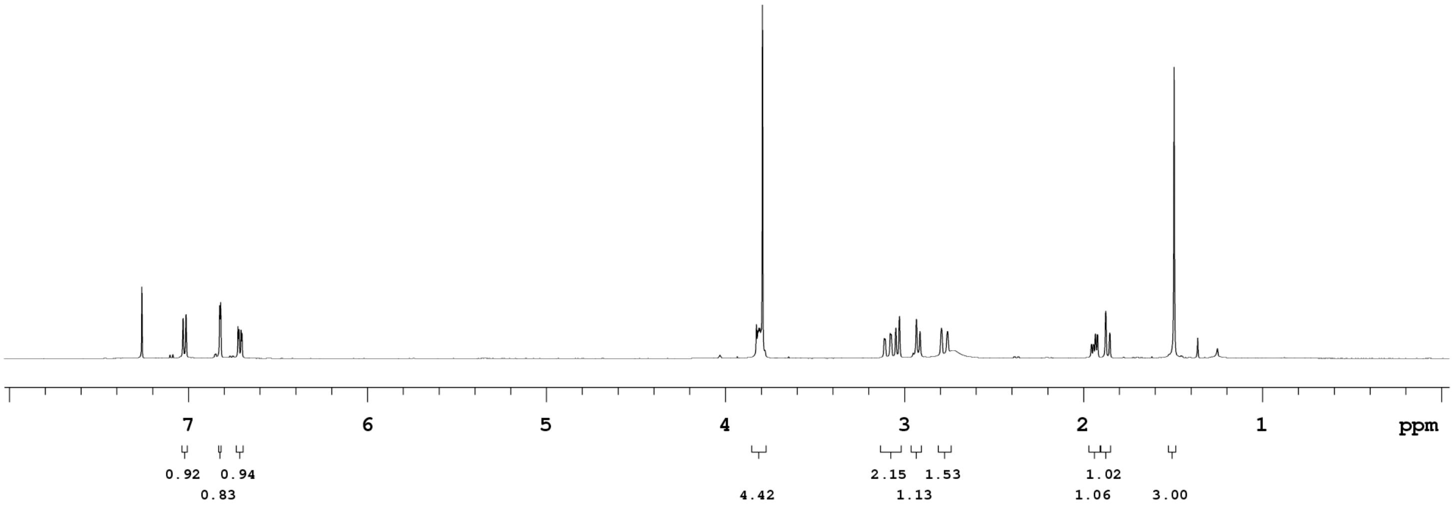
Operator: dmai

Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 3.500 sec
Width 7998.4 Hz
16 repetitions
OBSERVE H1, 499.9042608 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 65536
Total time 1 min 12 sec

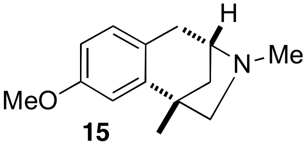


S1

VARIAN

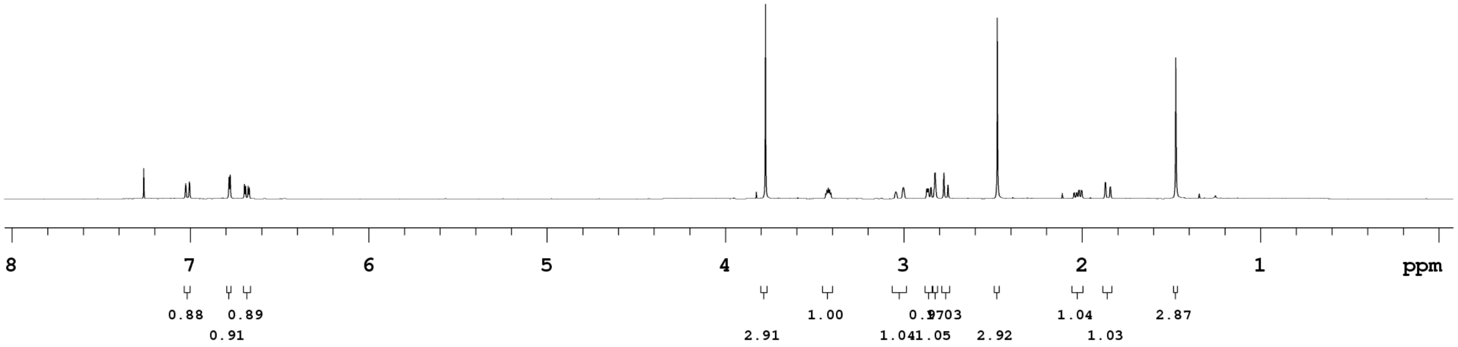


```
Mai-8-21

 Sample Name:

 Data Collected on:
   Zr.Chem.LSA.UMich.edu-inova400
 Archive directory:
   /export/home/chempack/vnmrsys/data
 Sample directory:

 FidFile: Mai-8-21

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Sep 20 2010

 Temp. 25.0 C / 298.1 K
Operator: dmai

 Relax. delay 0.500 sec
 Pulse 45.0 degrees
 Acq. time 3.500 sec
 Width 6399.5 Hz
 16 repetitions
OBSERVE   H1, 399.9649486 MHz
DATA PROCESSING
 Line broadening 0.3 Hz
FT size 65536
Total time 1 min 12 sec
```



15

VARIAN



Mai-8-143-CD3OD

Sample Name:

Data Collected on:
Ga.Chem.LSA.UMich.edu-vnmrs400
Archive directory:

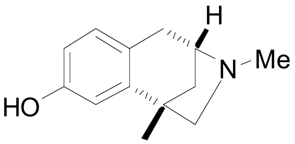
Sample directory:

FidFile: Mai-8-143-CD3OD

Pulse Sequence: PROTON (s2pul)
Solvent: cd3od
Data collected on: Jan 21 2011

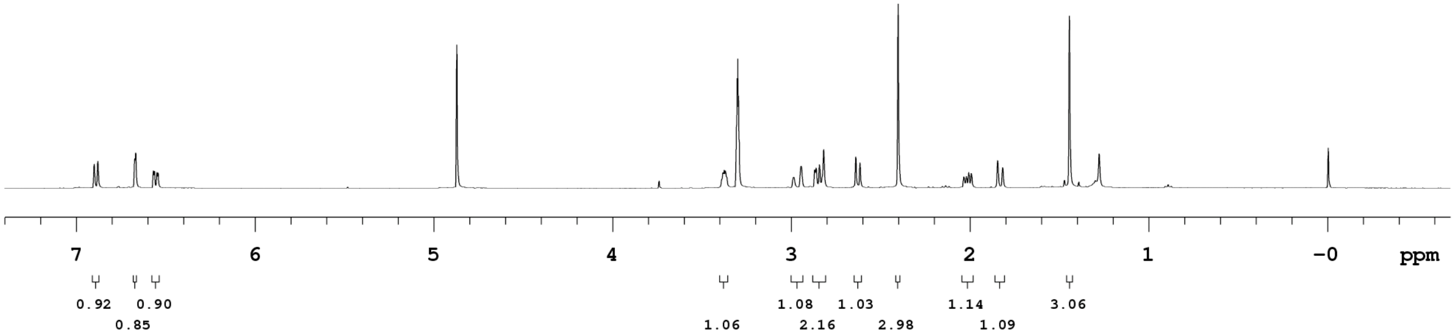
Operator: dmai

Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 3.500 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.5404952 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 65536
Total time 1 min 12 sec



(+)-aphanorphine

VARIAN



Mai-8-143-CARBON

Sample Name:

Data Collected on:
Co.Chem.LSA.UMich.edu-vnmrs400
Archive directory:

Sample directory:

FidFile: Mai-8-143-CARBON2

Pulse Sequence: CARBON (s2pul)
Solvent: cd3od
Data collected on: Jan 21 2011