Asymmetric Synthesis of (-)-Indolizidine 209D via *B*-Alkyl Suzuki Coupling and Amination Reactions

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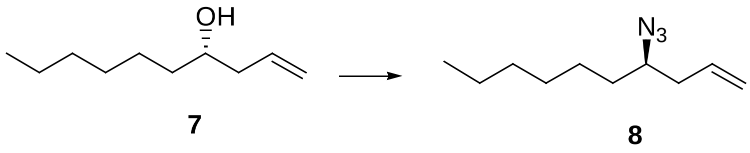
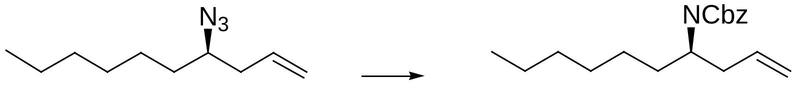
Supporting Information

General Procedures. All reactions were performed in oven-dried glassware with magnetic stirring. Commercial grade reagents and anhydrous solvents were used without further purification expect for chlorotrimethylsilane (TMSCl), which was distilled from calcium hydride.



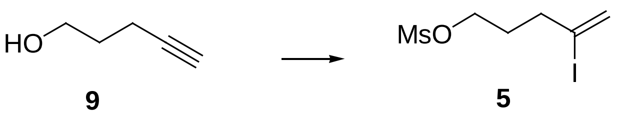
Homoallylic azide 8. A 50-mL, one-necked, round-bottomed flask equipped with a rubber septum pierced with an argon inlet needle was charged with a solution of **7** (0.700 g, 4.49 mmol) in 3 mL of CH_2Cl_2 and 0.5 mL of Et_3N cooled at 0 °C while 0.521 mL of methanesulfonyl chloride was added slowly dropwise by syringe. After the resulting solution was stirred at rt for 2 h, the reaction mixture was diluted with 20 mL of CH_2Cl_2 and washed with three 5-mL portions of water and 10 mL of saturated NaCl solution. The organic layer was then dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on 40 g of silica gel (elution with hexane : EtOAc = 8:1) provided 0.900 g (90%) of a yellow oil. Spectral data for a mesylate intermediate: $[\alpha]^{24}_D$= +25.5 (c 1.17, CH_2Cl_2); IR (thin film) 3854, 3737, 3360, 2925, 2867, 2363, 1697, 1683, 1654, and 1557 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.11-5.18 (m, 2H), 4.72 (apparent quint, *J* = 4.9 Hz, 1H), 2.99 (s, 3H), 2.47 (m, 2H), 1.69 (m, 2H), 1.25-1.49 (m, 8H), and 0.88 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.0, 119.4, 83.4, 39.5, 39.2, 34.6, 32.1, 29.4, 25.4, 23.0, and 14.5. ESIMS *m/z* 257.0 ($M+Na^+$, $C_{11}H_{22}SO_3$ requires 257.1).

A 50-mL, one-necked, round-bottomed flask equipped with a rubber septum pierced with an argon inlet needle was charged with a solution of the mesylate compound (0.800 g, 3.42 mmol) in 4 mL of HMPA and 1.11g of NaN_3 (17.09 mmol) was added. The mixture was stirred at 40 °C for 2 h, and poured into water. The mixture was participated with 20 mL of ether, and washed with brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on 30 g of silica gel (elution with pentane : ether = 20:1) provided 0.600 g (97%) of a colorless oil: IR (thin film) 2944, 2847, 2102, 1731, 1456, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.12-5.18 (m, 2H), 3.33 (apparent quint, *J* = 6.6 Hz, 1H), 2.30 (m, 2H), 1.23-1.56 (m, 8H), and 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 118.3, 62.7, 39.2, 34.3, 32.1, 29.5, 26.4, 23.0, and 14.4. ESIMS *m/z* 182.8 ($M+H^+$, $C_{11}H_{19}N_3$ requires 182.2).

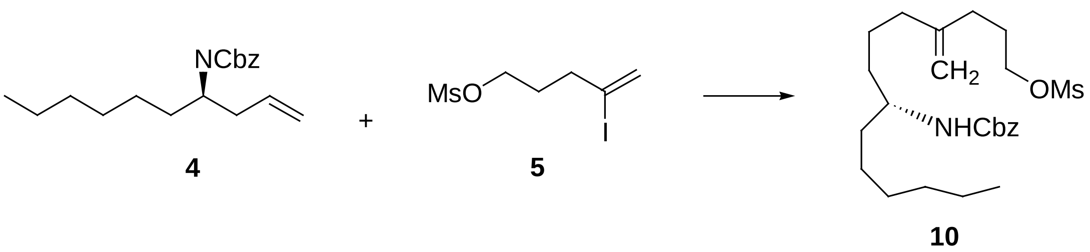


8 **4**

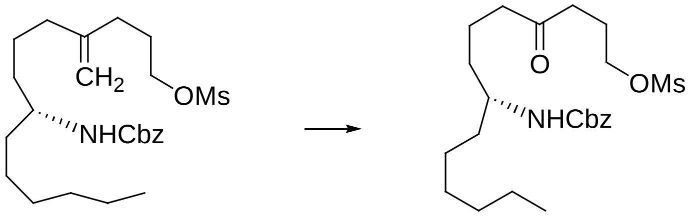
N-Cbz-homoallylic amine 4. A 15-mL, three-necked, round-bottomed flask was charged with a solution of **8** (0.300 g, 1.66 mmol) in 3 ml ether. LAH (3 mL, 1.0 M in ether, 3.0 mmol) was added dropwise, and the resulting mixture was stirred at rt for 30 min, then quenched with 10% of NaOH solution. After the precipitate was filtered, the organic layer was dried over $MgSO_4$, filtered, and concentrated to give 0.260 g of a colorless oil. This crude product was dissolved in THF, and to the solution were added 0.456 g of K_2CO_3 (3.3 mmol) and 0.353 ml of benzyl chloroformate (2,48 mmol). The mixture was stirred at rt for 3h, and diluted with 30 mL of ethyl acetate. The organic layer was washed with 10 ml of water and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on 30 g of silica gel (elution with hexane : ethyl acetate = 10:1) provided 0.446 g (94%) of a yellow solid: mp 47.0-48.8 ^{o}C; $[\alpha]^{24}_{D}$= +22.1 (c 1.07, $CHCl_3$); IR (thin film) 3310, 2924, 1658, 1539, 1468, 1265, 1239, and 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.40 (m, 5H), 5.81 (m, 1H), 5.08-5.19 (m, 2H), 4.66 (d, *J* = 8.4 Hz, 1H), 3.74 (m, 1H), 2.18-2.33 (m, 2H), 1.30-1.52 (m, 8H), and 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 137.1, 134.7, 128.9(3), 128.4(2), 118.2, 66.9, 51.1, 39.9, 35.0, 32.2, 29.6, 26.2, 23.0, and 14.5. ESIMS *m/z* 290.0 ($M+H^+$, $C_{18}H_{27}NO_2$ requires 290.2).



Iodomesylate 5. A 100-mL, one-necked, round-bottomed flask equipped with an argon inlet was charged with a solution of NaI (6.4 g, 42.79 mmol) in 25 mL of CH_3CN, and TMSCl (5.43 mL, 42.79 mmol) was added. The resulting mixture was stirred at rt for 5 min and cooled to 0 °C. To the solution was added water (0.385 mL, 21.40 mmol), and the solution was stirred for 10 min, and warmed to rt. 4-Butyn-1-ol (1.66 mL, 17.83 mmol) was added to the resulting mixture, and the mixture was stirred at rt for 2h. After dilution of the solution with 100 ml of ether, the organic layer was washed with water (30 mL) and saturated $NaHCO_3$ solution (40 mL), dried over $MgSO_4$, filtered, and concentrated to provide 1.80 g of crude product. The crude product (0.972 g, 4.8 mmol) was dissolved in CH_2Cl_2 (3 mL) containing 0.5 mL of Et_3N. To the solution was added MsCl (0.560 mL, 7.2 mmol) slowly at 0 °C. The mixture was warmed to rt, stirred for 1 h, and diluted with 15 mL of CH_2Cl_2.The organic layer was washed with water (10 mL), and brine, dried over $MgSO_4$. After filtration and concentration, the crude product was separated by column chromatography using 50 g of silica gel and eluting solvents hexane : EtOAc = 2:1 to afford 1 g (36%) of **5** as a reddish oil: IR (thin film) 3838, 3747, 3026, 2945, 2357, 2326, 1717, 1684, 1616, 1473, 1358, 1339, and 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 1H), 5.77 (s, 1H), 4.23 (t, J = 6.1 Hz, 2H), 3.02 (s, 3H), 2.55 (t, J = 6.3 Hz, 2H), and 1.97 (q, J = 6.5 Hz, 2H); ^{13}C NMR δ 129.8, 127.7, 68.4, 41.4, 37.9, and 28.8; ESIMS *m/z* 312.7 ($M+Na^+$, $C_6H_{11}O_3SI$ requires 312.9).

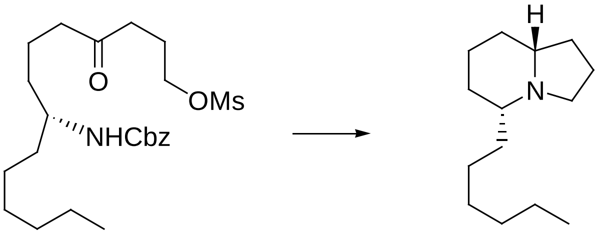


N-Cbz-methyleneamine 10. A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum pierced with an argon inlet needle was charged with a solution of **4** (250 mg, 0.864 mmol) in 5 mL of THF, and 9-BBN dimer (158 mg, 0.648 mmol) was added at rt. The solution was stirred at rt for 1.5 h, and water (155 μL, 8.64 mmol) was added. After 10 min, the resulting solution was cannulated to a solution of **5** (301 mg, 1.037 mmol), Pd(dppf)Cl_2:CH_2Cl_2 (70 mg, 0.086 mmol), Ph_3As (26 mg, 0.086 mmol), Cs_2CO_3 (563 mg, 1.728 mmol), and water (155 μL, 8.64 mmol) in 10 mL of DMF in 50-mL, one-necked, round-bottomed flask. The combined mixture was stirred at rt for 4h, and diluted with 40mL of EtOAc. The organic layer was washed with saturated NH_4Cl solution (20 mL), saturated $NaHCO_3$ solution (20 mL), water (10 mL), brine, and dried over $MgSO_4$. After filtration and concentration, the crude product was separated by column chromatography using 60 g of silica gel and eluting solvents, hexane : EtOAc = 10:1, to afford 250 mg (64%) of **10** as a pale brown solid: mp 52.0-53.5 °C; $[\alpha]^{25}_{D}= +17.5$ (c 1.16, $CHCl_3$); IR (thin film) 3390, 3328, 2929, 2856, 1719, 1700, 1521, 1456, 1354, 1238, 1174, 973, and 927 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.34 (m, 5H), 5.07 (s, 2H), 4.76 (s, 1H), 4.73 (s, 1H), 4.66 (d, *J* = 9.3 Hz, 1H), 4.19 (t, *J* = 9.0 Hz, 2H), 3.61 (broad s, 1H), 2.95 (s, 3H), 1.80-2.10 (m, 6H), 1.20-1.45 (m, 16H), and 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 147.7, 137.2, 128.9(3), 128.4(2), 110.7, 70.3, 70.0, 51.6, 39.7, 37.7, 35.9, 35.5, 32.0, 31.8, 28.4, 26.2, 24.3, 24.2, 23.0, and 14.5. ESIMS *m/z* 454.1 ($M+H^+$, $C_{24}H_{39}NO_5S$ requires 454.2).



10 **11**

Keto-N-Cbz-amine 11. Ozone was bubbled through the solution of **10** (100 mg, 0.221 mmol) in CH_2Cl_2 (2 mL) / MeOH (2 mL) at –78 °C. After the presence of excess ozone was detected, DMS (200 μL, 2.72 mmol) was added to the solution and immediately diluted with 25 ml of EtOAc. The organic layer was washed two 10 mL portions of water, brine, and dried over $MgSO_4$. After filtration and concentration, the crude product was separated by column chromatography using 20 g of silica gel and eluting solvents, hexane : EtOAc = 5:1, to afford 82 mg (80%) of **11** as an oil: $[\alpha]^{24}_{D}$= +2.0 (c 1.10, CH_2Cl_2); IR (thin film) 3328, 2932, 2853, 1708, 1688, 1534, 1455, 1352, 1257, 1242, and 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.52 (m, 5H), 5.09 (s, 2H), 4.53 (d, *J* = 8.9 Hz, 1H), 4.25 (t, *J* = 6.1 Hz, 2H), 3.66 (broad s, 1H), 3.00 (s, 3H), 2.56 (t, *J* = 6.6 Hz, 2H), 2.37-2.58 (m, 2H), 2.02 (apparent quint, *J* = 6.5 Hz, 2H), 1.26-1.66 (m, 15H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 224.9, 210.7, 157.6, 130.0(3), 129.4(2), 70.6, 68.0, 52.4, 43.8, 39.3, 38.8, 36.8, 36.1, 33.1, 30.6, 27.2, 24.5, 24.0, 21.3, and 15.5. ESIMS *m/z* 456.1 ($M+H^+$, $C_{23}H_{37}NO_6S$ requires 456.2).



11 **2**

(-)-Indolizidine 209D 2. A 15-mL, one-necked, round-bottomed flask equipped with a rubber septum was charged with a solution of **11** (48 mg, 1.054 mmol) in 5 mL of MeOH contaning 0.1 mL of Et$_3$N and 20mg of 10% Pd on carbon. The flask atmosphere was replaced by hydrogen gas via blowing an excess amount of the gas, and the solution was stirred under hydrogen balloon at rt for 15 h. The solution was filtered through fine filter paper under pressure with aid of 20 mL of EtOAc. The filtrate organic layer was washed with water (10 mL), brine, dried over MgSO$_4$. Filtration was followed by concentration to afford 10 mg (77%) of **2** as a yellow oil: $[\alpha]^{24}_{D}$= -77.7 (c 0.70, CH$_2$Cl$_2$); Other spectral data for **2** were consistent with that reported previously for this compound.[1]

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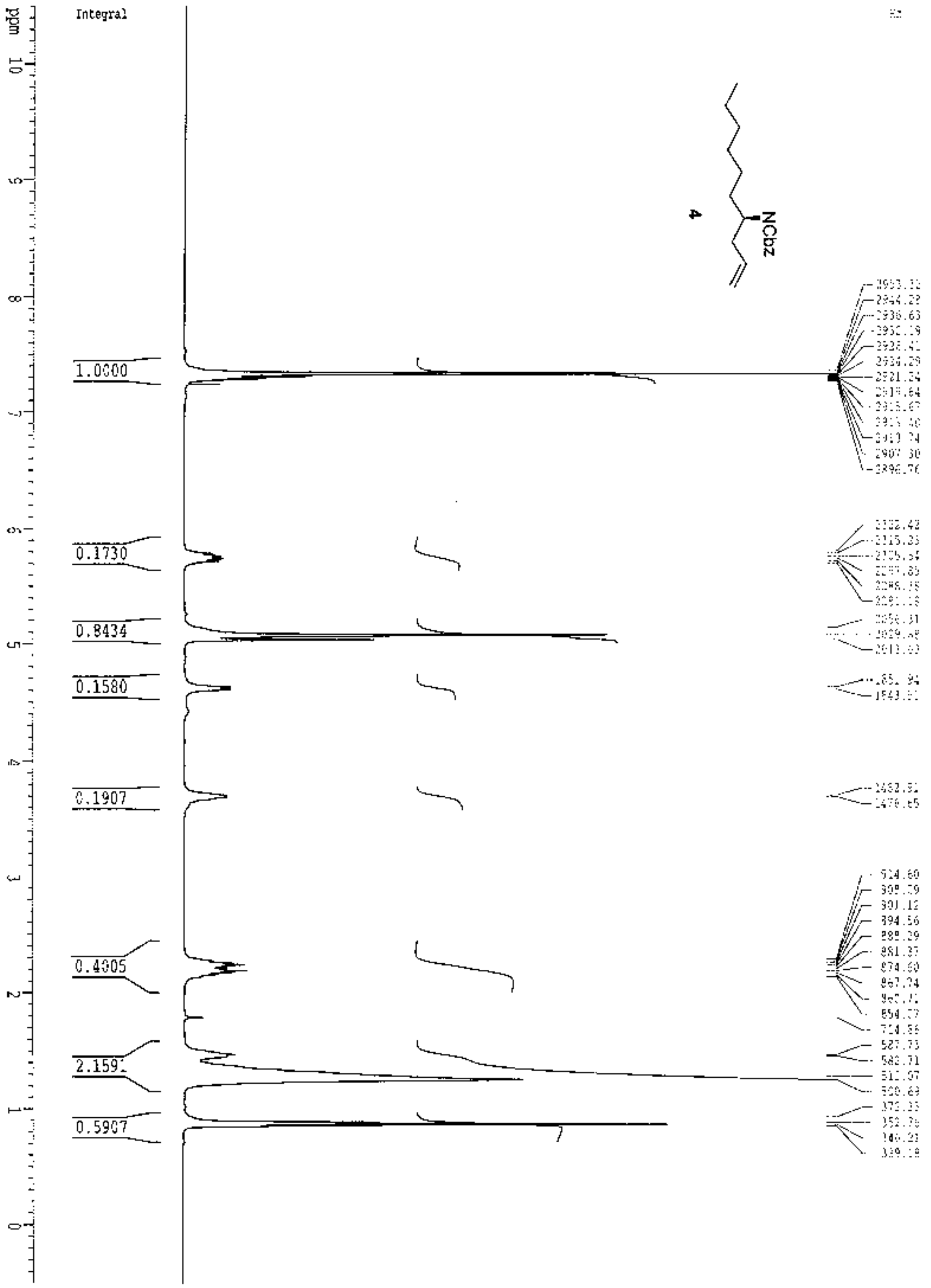
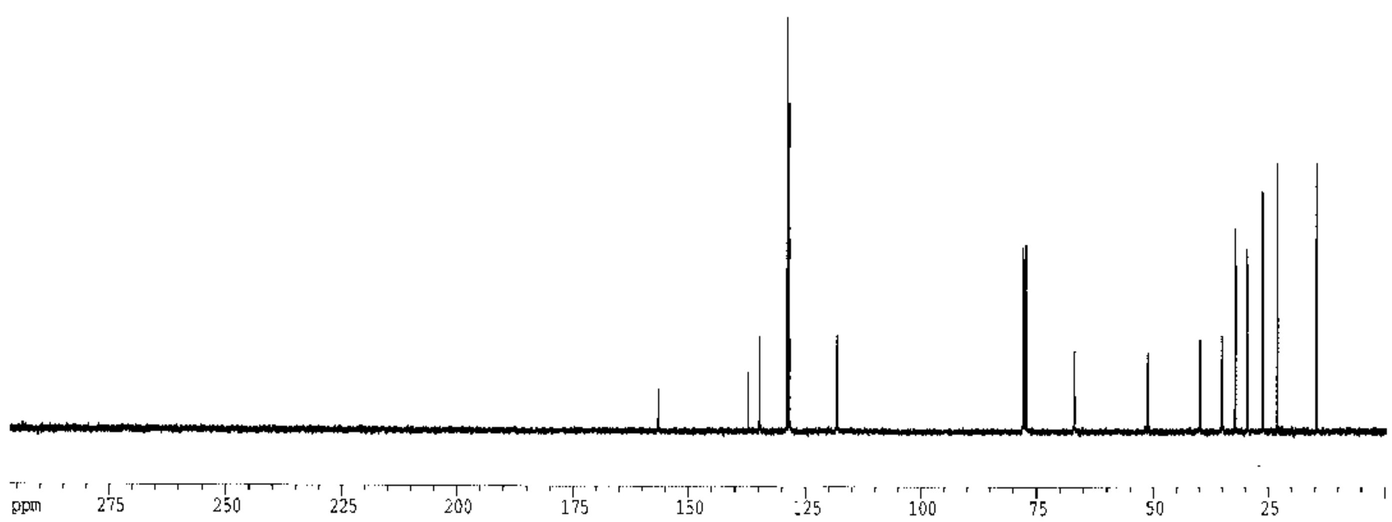
[1] Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688.

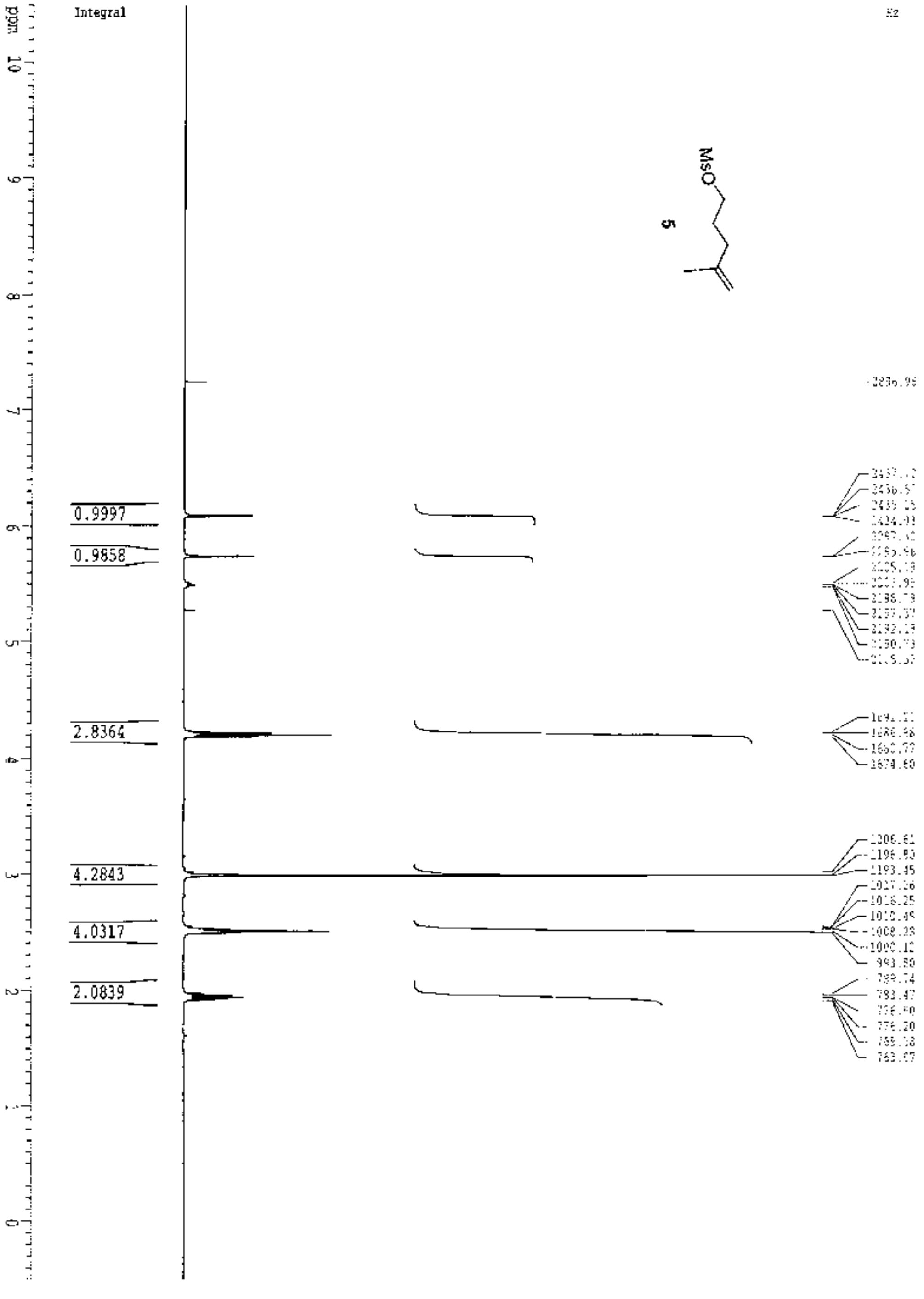


^{1}H NMR of 4 (400MHz, CDCl$_3$)

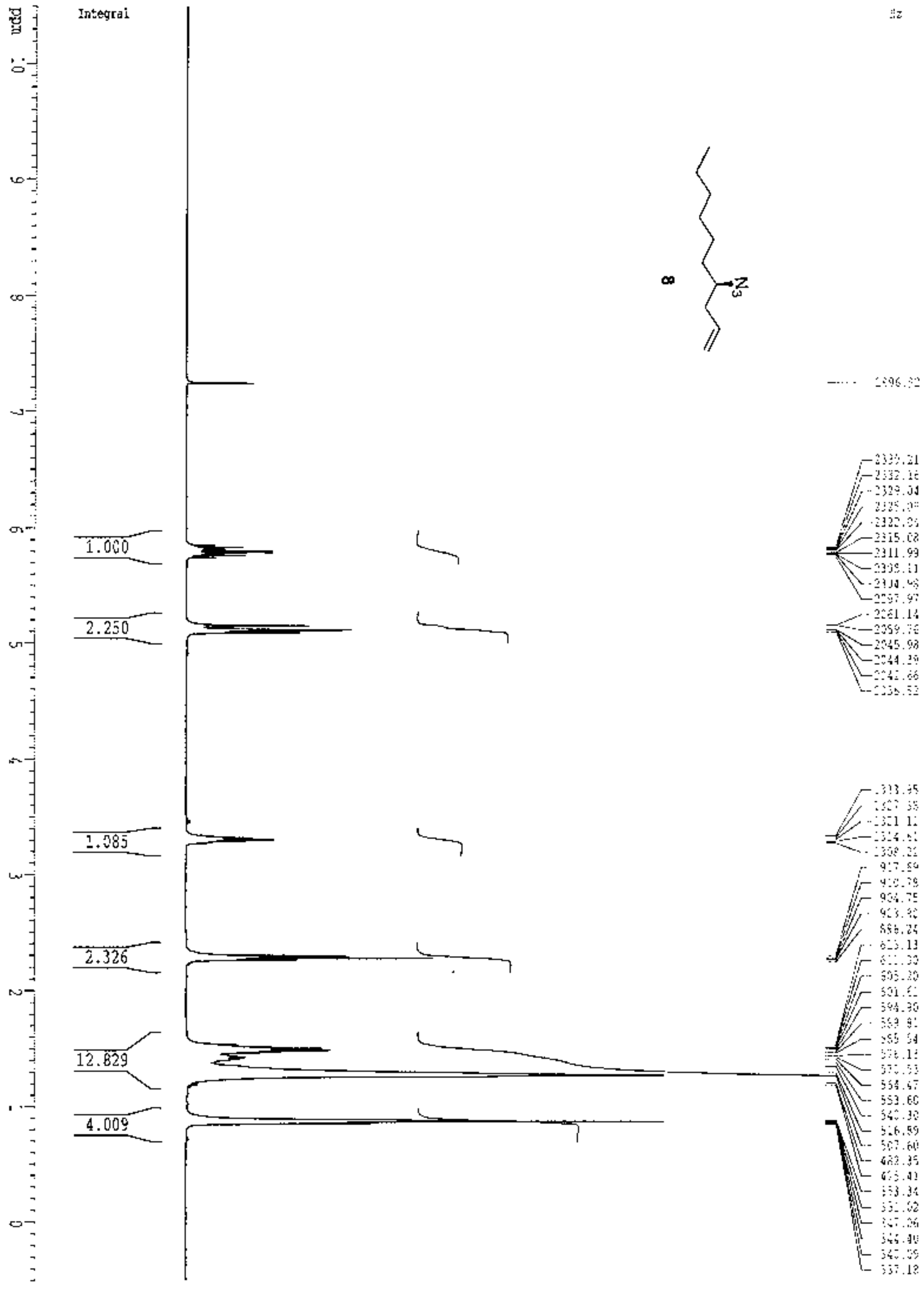
^{13}C NMR of 4 (100MHz, $CDCl_3$)

4



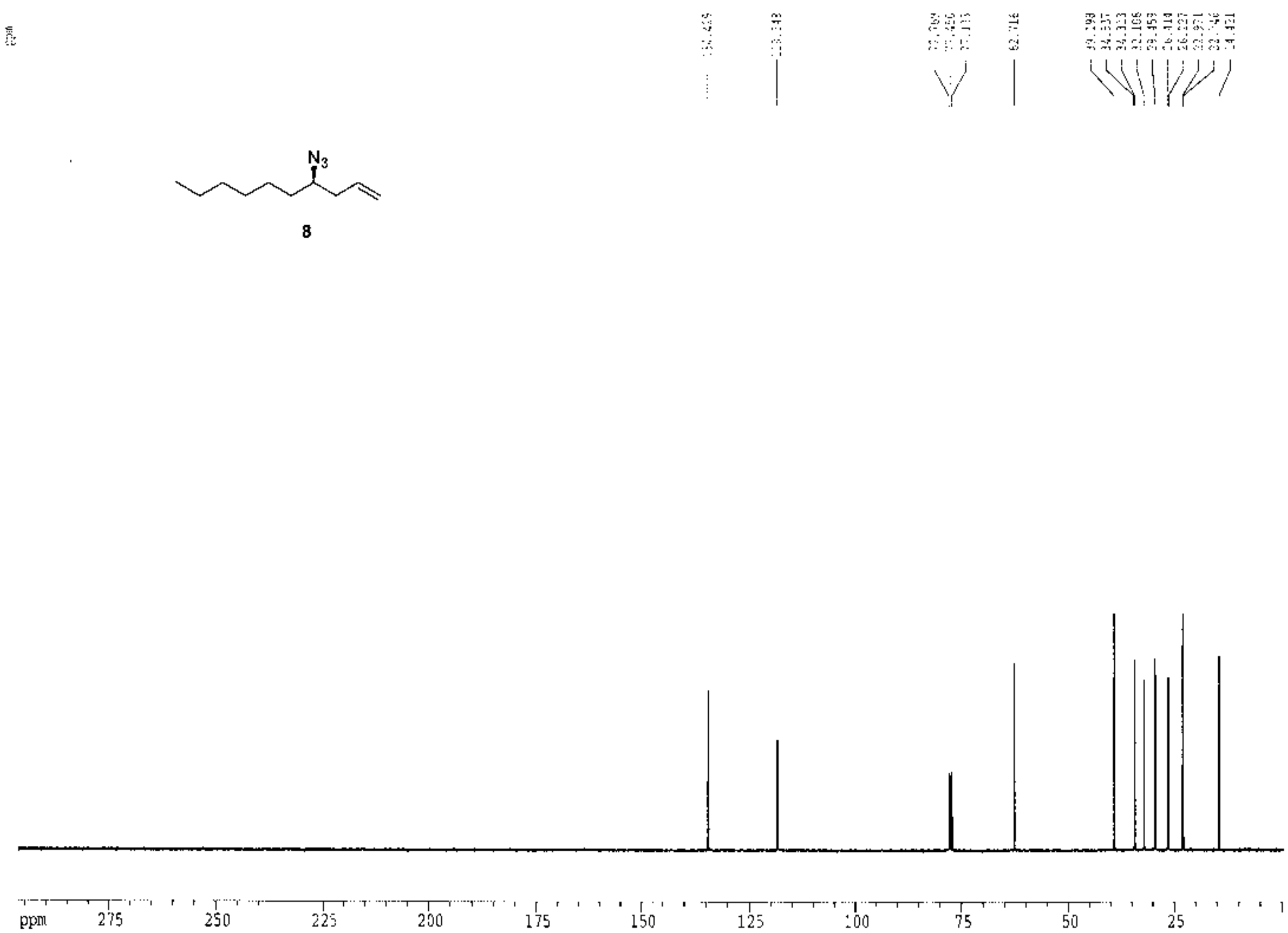


^{1}H NMR of 5 (400MHz, CDCl$_3$)

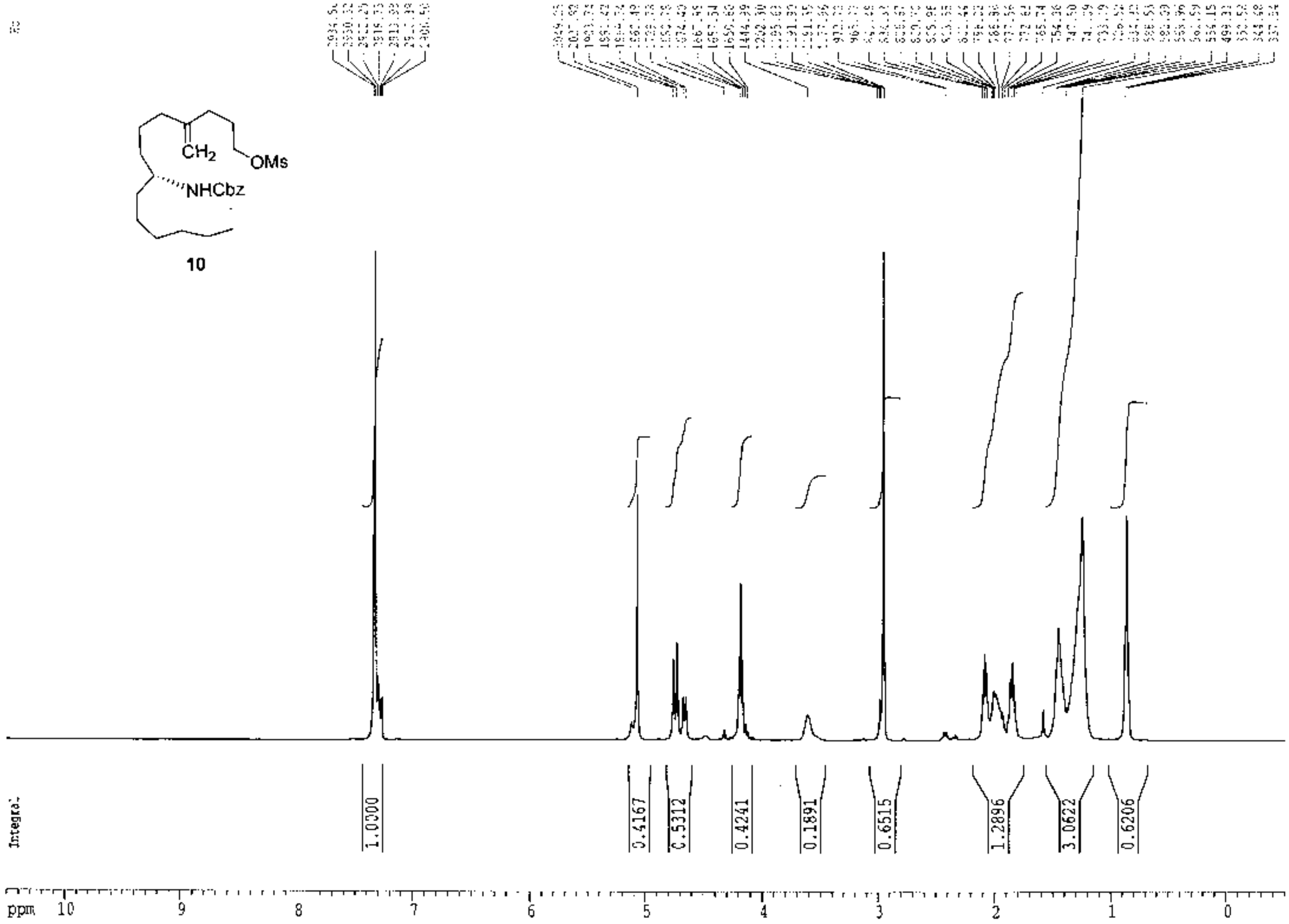


^{1}H NMR of **8** (400MHz, CDCl$_3$)

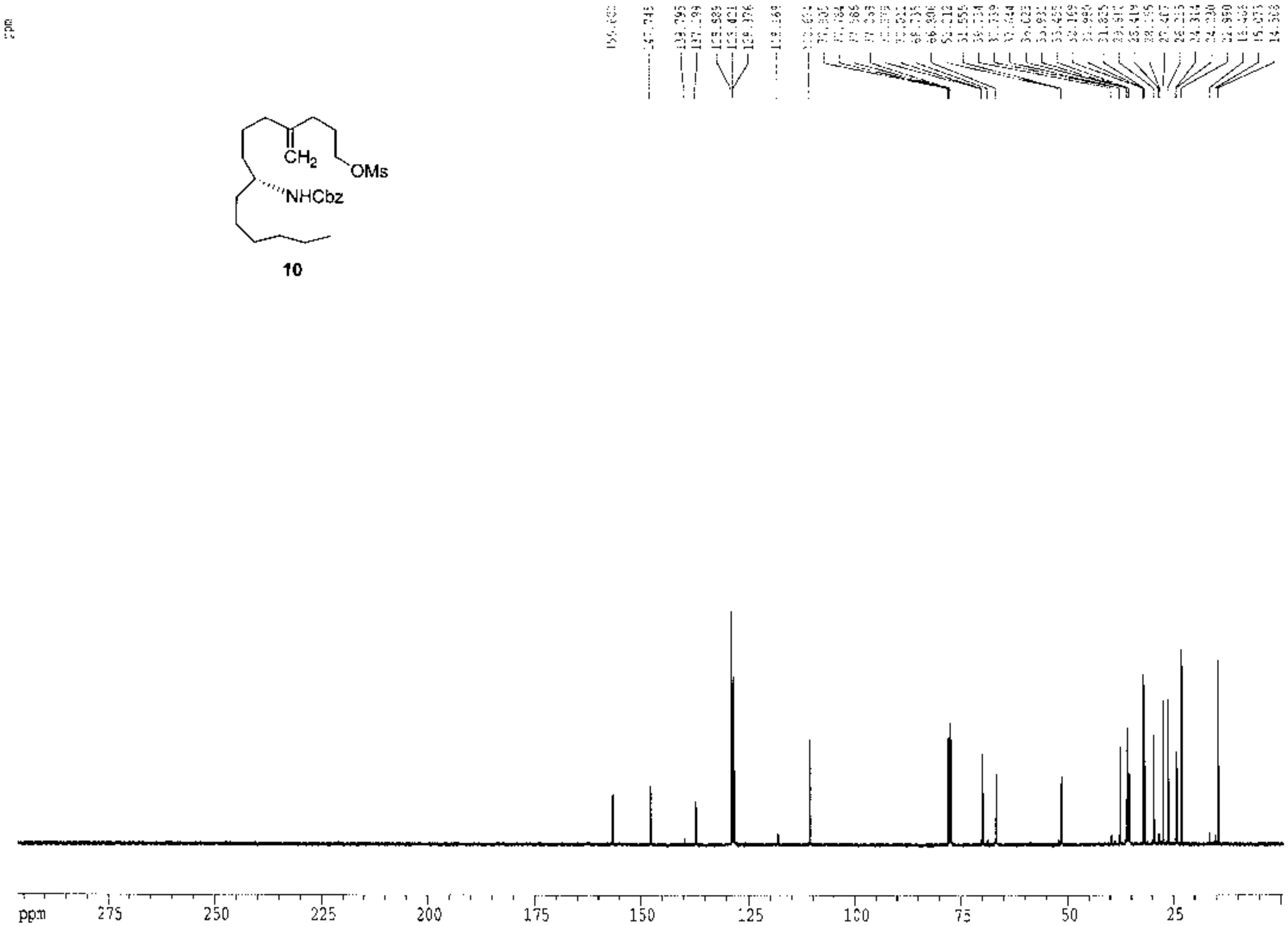
^{13}C NMR of **8** (100MHz, $CDCl_3$)



^{1}H NMR of 10 (400MHz, CDCl$_3$)

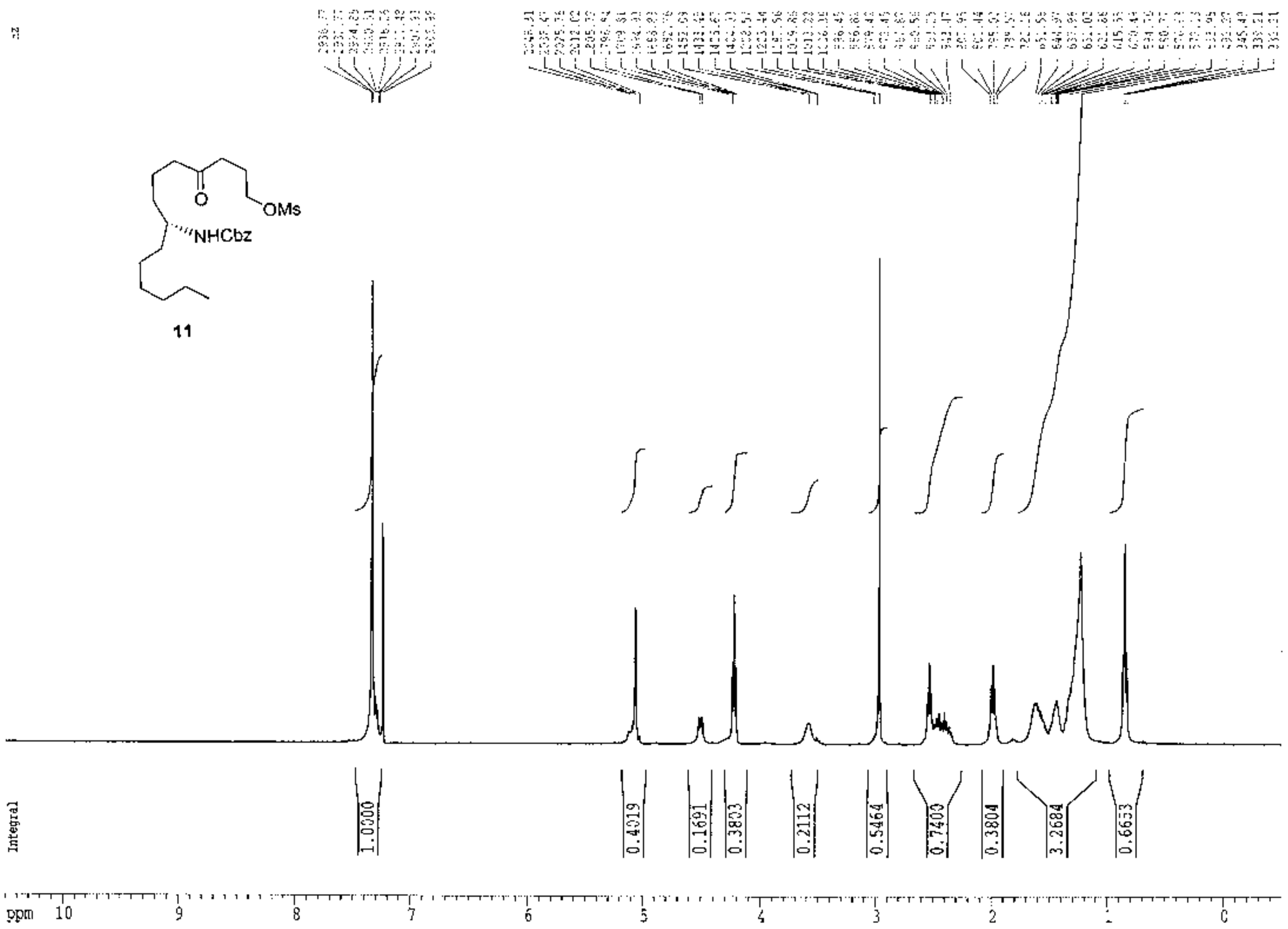


^{13}C NMR of **10** (100MHz, CDCl$_3$)



10

¹H NMR of 11 (400MHz, CDCl$_3$)



^{13}C NMR of 11 (100MHz, CDCl$_3$)