A Double Ring Closing Metathesis Reaction in the Rapid, Enantioselective Synthesis of NK-1 Receptor Antagonists

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Supplementary Material

Melting points were measured on a Buchi 510 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the sodium D-line. Infra-red spectra were recorded on a Perkin-Elmer 781 spectrophotometer. NMR spectra were recorded on Bruker DRX400 or DPX250 instruments using an internal deuterium lock at ambient probe temperature.
Reactions were carried out under a nitrogen atmosphere unless otherwise stated. Chemicals and solvents were obtained from commercial sources and were used as received. The Grubbs' catalyst was purchased from Fluka or Strem.

Synthesis of ester **9**
To a solution of (*S*)-Phenylglycine methyl ester hydrochloride (12.5 g, 62.0 mmol) in THF (200 mL) under a nitrogen atmosphere was added triethylamine (18.1 mL, 130 mmol) and then *p*-toluenesulfonyl chloride (13.0 g, 68.2 mmol). The mixture was stirred at room temperature for 16 hours and then partitioned between water (100 mL) and IPAC (2 x 100 mL). The organic layers were washed with brine (100 mL), dried over sodium sulfate and concentrated in vacuo. The crude solid was recrystallized from ethanol to give the desired compound **9** (17.0 g, 86%).
^{1}H (250 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.22 (m, 7H), 5.64 (d, *J* = 7.8 Hz, 1H), 5.03 (d, *J* = 7.8 Hz, 1H), 3.54 (s, 3H), 2.35 (s, 3H).

Synthesis of tertiary alcohol **10**
Anhydrous cerium chloride (20.5 g, 83.2 mmol) was heated to 150 ºC under vacuum for 2 hours and then cooled to room temperature under nitrogen. THF (200 mL) was added and the mixture stirred at room temperature overnight and then a solution of ester **9** (5.26 g, 16.5 mmol) in THF (30 mL) was added and stirring continued for one hour before cooling to -10ºC. Freshly prepared vinylmagnesium bromide (68.0 mL, 0.85*M* in THF, 57.8 mmol) was added and the mixture stirred for two hours at the same temperature. The mixture was partitioned between citric acid (100 mL, sat aq) and MeO*t*Bu (2 x 150 mL). The combined organics were washed with brine (100 mL), dried over sodium sulfate and concentrated in vacuo to give a yellow oil which was purified by flash column chromatography (30% EtOAc in hexane) to give the tertiary alcohol **10** (3.39 g, 60%) as an off white solid.
MP (hexane) = 135 – 137 ºC: Rotation α_D = +36.3, c = 1.4 $CHCl_3$: IR (nujol) 3275, 1600, 1495 cm^{-1}: ^{1}H (400 MHz, CD_2Cl_2) δ 7.46 (m, 2H), 7.20-7.10 (m, 3H), 7.10 (m, 2H), 7.06 (m, 2H), 5.81 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.80 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.38 (brd, *J* = 8.1 Hz, 1H), 5.57 (dd, *J* = 17.3, 1.1 Hz), 5.20 (dd, *J* = 17.3, 1.1 Hz, 1H), 5.20 (dd, *J* = 10.7, 1.1 Hz, 1H), 5.12 (dd, *J* = 10.7, 1.1 Hz, 1H), 4.30 (d, *J* = 8.1, 1H), 2.34 (s, 3H): ^{13}C (100.6 MHz, $CDCl_3$) δ 139.4, 138.5, 137.6, 129.4, 129.3, 128.8, 128.1, 127.9, 127.4, 127.3, 116.2, 116.1, 77.9, 65.1, 21.7: MS 326 (MH^+- H_2O) (100%), 260 (60%), 171 (26%), 120 (30%), 155 (74%): HRMS ($C_{19}H_{20}NO_2S$ (MH^+-H_2O) requires 326.12148, found 368.1208.

Tetralkene **7**

A solution of tertiary alcohol **10** (0.954 g, 2.78 mmol) in THF (5.0 mL) and DMPU (5.0 mL) was cooled to 0 ºC and sodium hydride (0.56 g, 60% dispersion, 14.0 mmol) added followed by allyl bromide (2.40 mL, 27.7 mol). The mixture was warmed to room temperature and stirred overnight. The mixture was quenched cautiously with ice cold water (2.0 mL) and then partitioned between water (20 mL) and MeOtBu (2 x 30 mL). The combined organics were washed with brine (20 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc in hexane) afforded **7** as a pale yellow oil (1.14 g, 97%).

Rotation α_D = +17.3, c = 1.5, $CHCl_3$: IR (film) 1640, 1600, 1495 cm^{-1}: ^1H (400 MHz, $CDCl_3$) δ 7.45 (m, 4H), 7.18 (m, 3H), 7.04 (d, 2H, *J* = 8.0 Hz, 1H), 6.04 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.82 (ddt *J* = 17.2, 11.0, 5.3 Hz, 1H), 5.60 (dd, *J* = 17.4, 11.3 Hz, 1H), 5.50 (ddt, *J* = 17.2, 10.2, 6.3 Hz, 1H), 5.31 (dd, *J* = 11.0, 1.3 Hz, 1H), 5.28 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.21 (dq, *J* = 17.2, 1.7, 1H), 5.10 (m, 3H), 5.02 (s, 1H), 4.90 (dq, *J* = 17.2, 1.6 Hz, 1H), 4.79 (dq, *J* = 10.2, 1.6 Hz, 1H), 4.21 (ddt, *J* = 16.5, 6.3, 1.6 Hz, 1H), 3.96 (ddt, *J* = 16.5, 6.3, 1.6 Hz, 1H), 3.81 (ddt, *J* = 12.9, 5.3, 1.7 Hz, 1H), 3.79 (ddt, *J* = 12.9, 5.3, 1.7 Hz, 1H), 2.27 (s, 3H): ^{13}C (100.6MHz, $CDCl_3$) δ 138.3, 137.3, 137.2, 137.1, 136.7, 135.5, 131.5, 130.1, 129.3, 128.4, 128.2, 128.0, 119.0, 118.4, 116.2, 116.1, 86.2, 67.9, 65.9, 49.5, 21.7: MS 366 (MH^+-AllOH) (100%), 211 (40%), 210 (52%), 195 (54%): HRMS $C_{22}H_{24}NSO_2$(MH^+-AllOH) requires 366.1528, found 366.1518.

Double ring closing methathesis of tetralkene **7**

Tetralkene **7** (1.17 g, 2.77 mmol) was dissolved in chloroform (50 mL) which was then degassed and flushed with nitrogen three times. Grubbs' catalyst **11** (89.0 mg, 0.108 mmol) was added portionwise over three hours and the mixture then stirred for a further hour. The reaction was opened to the atmosphere and concentrated in vacuo. The crude oil was purified by column chromatography on Florisil (10% EtOAc in hexane increasing to 20% EtOAc in hexane) to afford two isomers **6** (564 mg, 56%) and (*5-epi*-**6**) (307 mg, 30%). The minor isomer contained about 20% of the major compound.

Major isomer **6** MP (hexane) = 201 – 202 ºC: Rotation α_D = –109, c = 1.2, $CHCl_3$: IR ($CHCl_3$ solution) 1590, 1490 cm^{-1}: ^1H (400 MHz, CD_2Cl_2) δ 7.44 (m, 2H), 7.22 (m, 2H), 7.2-7.1 (m, 5H), 5.98 (dt, *J* = 6.0, 1.6, 1H), 5.85-5.70 (m, 3H), 5.12 (s, 1H), 4.7-4.55 (m, 2H), 4.11 (ddd, *J* = 18.1, 3.0, 1.7 Hz 1H), 3.52 (dt, *J* = 18.1, 1.1 Hz, 1H), 2.73 (s, 3H): ^{13}C (100.6 MHz, $CDCl_3$) δ 143.4, 137.2, 136.7, 132.0, 131.1, 129.5, 129.4, 128.3, 127.9, 127.6, 126.8, 122.3, 88.4, 76.0, 63.0, 42.0, 21.7: MS 368 (MH+) (8%), 213 (26%), 197 (100%), 194 (34%): HRMS $C_{21}H_{22}O_3SN$ (MH^+) requires 368.1320, found 368.1333.

Minor isomer 5-*epi*-**6**

MP (hexane) = 166 – 167 ºC: Rotation α_D = –64.9, c = 2.12, $CHCl_3$: IR ($CHCl_3$ solution) 1590, 1490 cm^{-1}: ^1H (400 MHz, CD_2Cl_2) δ 7.47 (m, 2H), 7.20-7.10 (m, 5H), 7.05 (m, 2H), 5.92 (ddd, *J* = 10.1, 4.2, 2.4 Hz, 1H), 5.87 (dt, *J* = 6.2, 1.8 Hz, 1H), 5.75 (ddt, *J* = 10.1, 2.4, 0.8 Hz, 1H), 5.13 (dt, *J* = 6.2, 3.5 Hz, 1H), 5.03 (s, 1H), 4.60 (ddd, *J* = 13.3, 2.6, 1.1 Hz, 1H), 4.54 (ddd, *J* = 13.3, 2.3, 1.8 Hz, 1H), 3.91 (ddd, *J* = 18.3, 4.2, 2.3 Hz, 1H), 3.47 (dt, *J* =18.3, 2.4 Hz, 1H), 2.26 (s, 3H): ^{13}C (100.6 MHz, $CDCl_3$) δ 143.2, 137.6, 137.1, 130.2, 129.6, 129.4, 129.0, 128.8, 128.7, 128.2, 127.9, 127.3, 87.3, 74.3, 63.6, 41.4, 21.8: MS 368 (MH+) (100%), 350 (44%), 213 (14%), 194 (26%): HRMS $C_{21}H_{22}O_3SN$ (MH^+) requires 368.1320, found 368.1317.

Isolation of intermediates.

To a solution of Tetralkene **7** (440 mg, 1.04 mmol) in degassed dichloromethane (10 mL) was added Grubbs' catalyst **11** (8.0 mg, 0.0097 mmol) and the mixture stirred for 30 minutes. This solution was concentrated under vacuum and then the ruthenium residues removed by filtration through florisil. The resulting mixture was separated by preparative HPLC on a 25 x 250mm RX C8 column to give the four reaction intermediates **14a**, **14b**, **15a** and **16** all as colourless oils.

14a

Rotation α_D = –23.5, c = 0.5, $CHCl_3$: ^1H (400 MHz, CD_2Cl_2) δ 7.48 (dt, *J* = 6.6, 1.7 Hz, 2H), 7.40 (m, 2H), 7.25 (m, 3H), 7.15 (d, *J* = 6.7 Hz, 2H), 6.10 (dd, *J* = 17.0, 10.6 Hz, 1H), 5.68 (ddt, J = 17.0, 10.2, 5.9 Hz, 1H), 5.64 (dt, *J* = 6.0, 2.4 Hz), 5.58 (dt, *J* = 6.0, 1.5 Hz, 1H), 5.40 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.19 (s, 1H), 5.10 (dd, *J* = 10.6, 1.8 Hz, 1H), 5.01 (dq, *J* = 17.0, 1.5 Hz, 1H), 4.90 (dq, *J* = 10.2, 1.5 Hz, 1H), 4.60 (ddd, *J* = 13.6, 2.4, 1.5 Hz, 1H), 4.40 (ddd, J = 13.6, 2.4, 1.5 Hz, 1H), 4.37 (ddt, *J* = 16.5, 5.9, 1.5 Hz, 1H), 4.12 (ddt, *J* = 16.5, 5.9, 1.5 Hz, 1H), 2.33 (s, 3H): ^{13}C (100.6 MHz, CD_2Cl_2) δ 143.3, 140.3, 138.0, 137.9, 137.1, 131.3, 130.2, 129.2, 128.1, 128.0, 127.9, 126.5, 115.8, 114.1, 96.7, 76.8, 66.7, 49.4, 21.4: HRMS $C_{23}H_{26}NO_2S$ (MH^+) requires 396.1633, found 396.1624.

14b

Rotation α_D = +96.4, c = 0.4, $CHCl_3$: ^1H (400 MHz, CD_2Cl_2) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.43 (m, 2H), 7.24 (m, 2H), 7.19 (m, 3H), 5.96 (dt, *J* = 6.1, 2.3 Hz, 1H), 5.92 (dt, *J* = 6.1, 1.6 Hz, 1H), 5.79 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.22 (s, 1H), 5.19 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.07 (dddd, *J* = 17.5, 10.0, 6.5, 6.0 Hz, 1H), 4.92 (dd, *J* = 10.7, 1.6 Hz, 1H), 4.85 (dq, *J* = 17.5, 1.6 Hz, 1H), 4.83 (ddd, *J* = 12.5, 2.3, 1.6 Hz, 1H), 4.70 (m, 2H), 4.02 (m, 2H), 2.44 (s, 3H): ^{13}C (100.6 MHz, $CDCl_3$) δ 143.6, 140.2, 138.8, 136.8, 136.3, 132.8, 131.5, 129.5, 128.3, 128.2, 128.0, 125.9, 115.7, 114.0, 97.4, 75.6, 65.0, 48.6, 21.5: HRMS $C_{23}H_{25}NO_2SNa$ ($M+Na^+$) requires 418.1453, found 418.1447.

15a

Rotation α_D = –55.8, c = 1.1, $CHCl_3$: ^1H (400 MHz, CD_2Cl_2) δ 7.48 (d, *J* = 6.6 Hz, 2H), 7.30 (m, 2H), 7.18 (m, 3H), 7.08 (d, *J* = 6.6 Hz, 2H), 5.97 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.92 (m, 2H), 5.54 (dddd, *J* = 17.5, 10.5, 5.1, 4.8 Hz), 5.28 (dt, *J* = 10.6, 1.2 Hz, 1H), 5.24 (dt, *J* = 17.3, 1.2 Hz, 1H), 5.23 (s, 1H), 4.91 (dq, *J* = 17.3, 1.9 Hz, 1H), 4.88 (ddd, *J* = 10.5, 2.1, 1.9 Hz, 1H), 3.97 (ddd, *J* = 18.5, 2.8, 1.5 Hz, 1H), 3.87 (ddt, *J* = 13.1, 5.1, 1.7 Hz, 1H), 3.73 (ddt, *J* = 13.2, 4.8, 1.7 Hz, 1H), 3.48 (dt, *J* = 17.6, 1.9 Hz, 1H).2.31 (s, 3H): ^{13}C (100.6 MHz, CD_2Cl_2) δ 143.6, 140.1, 137.0, 136.6, 135.5, 130.0, 129.4, 128.0, 127.9, 127.8, 127.7, 124.0, 118.1, 115.3, 78.1, 64.1, 62.0, 42.2, 21.4.

16

Rotation α_D = -10.7, c = 0.7, $CHCl_3$: ^1H (400 MHz, CD_2Cl_2) δ 7.41 (m, 2H), 7.40 (m, 2H), 7.15 (m, 5H), 6.37 (dd, *J* = 17.5, 10.5 Hz), 5.70 (m, 1H), 5.54 (m, 1H), 5.49 (dd, *J* = 17.0, 10.5 Hz, 1H), 5.38 (dd, *J* = 10.5, 1.5 Hz, 1H), 5.28 (dd, *J* = 17.5, 1.5 Hz, 1H), 5.22 (dd, *J* = 17.0, 2.0 Hz, 1H), 4.98 (dd, *J* = 10.5, 2.,0 Hz, 1H), 4.80 (s, 1H), 4.50 (dq, *J* = 18.5, 1.5 Hz, 1H), 4.40 (ddq, *J* = 15.5, 7.5, 1.5 Hz, 1H), 4.23 (ddt, *J* = 18.5, 3.5, 1.5 Hz, 1H), 3.40 (dd, *J* = 15.5, 7.5 Hz, 1H), 2.35 (s, 3H). ^{13}C (100.6 MHz, $CDCl_3$) δ 142.5, 138.4, 137.0, 136.9, 135.3, 133.5, 129.9, 128.5, 127.0, 126.9, 126.6, 124.8, 120.4, 114.3, 84.7, 64.2, 63.8, 39.2, 20.4: HRMS $C_{23}H_{26}NO_2S$ (MH^+) requires 396.1633, found 396.1629.

Reductive Heck reaction

A solution of spirodiene **6** (437 mg, 1.19 mmol), aryl iodide **12** (1.40 g, 3.55 mmol), Bu_4NCl (396 mg, 1.42 mmol), LiCl (500 mg, 11.8 mmol), potassium formate (300 mg, 3.57 mmol) and triethylamine (0.5 mL, 3.59 mmol) in DMF:H_2O 15:1 (5.0 mL) was degassed and flushed with nitrogen. Palladium acetate (120 mg, 0.535 mmol) was added, the solution degassed again and then heated to 40 ºC for five days. The mixture was filtered through celite and then partitioned between IPAC (2 x 20 mL) and water (20 mL). The combined organics were washed with brine (20 mL), dried over sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography (10% EtOAc in hexane increasing to 20% EtOAc in hexane) to give **13** (453 mg, 60%) as a pale yellow oil.

Rotation α_D = –102, c = 1.8, $CHCl_3$: IR ($CHCl_3$ solution) 1605, 1500 cm^{-1}: ^1H (400 MHz, $CDCl_3$) δ 7.30 (m, 7H), 7.10 (m, 6H), 6.95 (m, 3H), 6.82 (d, *J* = 8.9 Hz, 1H), 5.85 (m, 1H), 5.71 (m, 1H), 5.13 (s, 1H), 5.06 (d, *J* = 11.8 Hz, 1H), 5.03 (d, *J* = 11.8 Hz, 1H), 4.13 (t, *J* = 8.0 Hz, 1H), 4.04 (dddd, *J* = 17.5, 6.1, 3.7, 2.3 Hz, 1H), 3.93 (dq, *J* = 9.9, 8.0 Hz, 1H), 3.71 (t, *J* = 8.0 Hz, 1H), 3.39 (dt, *J* = 17.5, 2.4, 1H), 2.64 (dd, *J* = 12.9, 8.0, 1H), 2.22 (s, 3H), 2.03 (dd, *J* = 12.9, 9.9, 1H): ^{13}C (100.6MHz $CDCl_3$) δ 155.5, 143.3, 137.0, 136.9, 136.3, 132.9, 131.7, 129.6, 129.5, 129.4, 129.1, 128.5, 128.3, 128.0, 127.7, 127.6, 122.4, 121.1, 121.0 (q), 120.5, 112.8, 82.0, 73.4, 71.1, 52.5, 44.8, 41.9, 39.0, 21.7: MS 636 (MH+) (100%), 618 (10%), 528 (10%). HRMS $C_{35}H_{33}F_3NO_5S$ (MH+) requires 636.20315, found 633.2049.

Hydrogenation

A solution of Heck product **13** (180 mg, 0.338 mmol) and palladium hydroxide on carbon (25.0 mg) in ethanol (5.0 mL) was flushed with nitrogen and then hydrogen and left to stir under a hydrogen atmosphere for 18 hours. The mixture was flushed with nitrogen, filtered through celite and concentrated in vacuo. The crude mixture was purified by flash column chromatography (30% EtOAc in hexane) to afford the phenol as a colorless oil (140 mg, 90%).

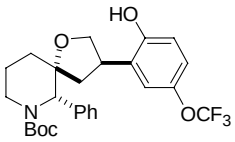
Rotation α_D = –64.7, c = 1.9, EtOH: IR ($CHCl_3$ solution) 3440, 1605, 1515, 1495 cm^{-1}: ^1H (400 MHz, $CDCl_3$) δ 7.25 (m, 3H), 7.19 (m, 1H), 7.14 (d, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 7.6 Hz, 2H), 6.94 (m, 1H), 6.86 (m, 2H), 6.67 (d, *J* = 8.6 Hz, 1H), 5.06 (s, 1H), 4.22 (dd, *J* = 8.6, 7.4 Hz, 1H), 3.85 (m, 1H), 3.80 (m, 2H), 3.19 (td, *J* = 12.5, 3.6 Hz, 1H), 2.86 (dd, *J* = 13.0, 8.3 Hz, 1H), 2.27 (s, 3H), 2.18 (td, *J* = 13.0, 4.5 Hz, 1H), 1.88 – 1.70 (m, 4H): ^{13}C (100.6 MHz, $CDCl_3$) δ 153.2, 143.3, 137.3, 136.6, 129.8, 129.5, 128.4, 127.9, 127.3, 122.2 (q), 121.5, 120.8, 117.0, 84.7, 67.7, 63.6, 43.9, 41.6, 40.1, 31.5, 23.7, 21.7: MS (548 (MH+) (100%), 530 (6%). HRMS $C_{28}H_{29}F_3NO_5S$ (MH^+) requires 548.17186, found 548.1732.

Sodium Naphthalide reduction.

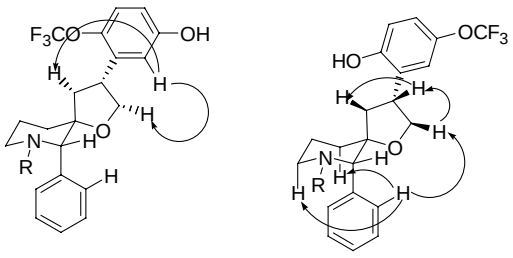
A solution of the above phenol (110 mg, 0.200 mmol) in DME (3.0 mL) was degassed and cooled to –78 ºC under a nitrogen atmosphere. Freshly prepared sodium naphthalide was added until the blue color remained in the solution. The mixture was quenched with ammonium chloride (1.0 mL, sat. aq) and acidified with 2.0*N* HCl solution. This was then extracted with ether (1 x 10 mL) to remove the naphthalide and other organic impurities. The aqueous layer was then brought to pH12 with aqueous Na_2CO_3 and then extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over sodium sulfate and concentrated in vacuo to give the desired amine **1** as a pale yellow oil (69 mg, 87%).

Rotation α_D = –10.0, c = 1.0, $CHCl_3$: IR ($CHCl_3$ 3080, 1615, 1515, 1500 cm^{-1}: ^1H (400 MHz, CD_2Cl_2) δ 7.42 (m, 2H), 7.31 (m, 3H), 6.80 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.77 (d, *J* = 2.2, 1H), 6.52 (d, *J*= 8.7 Hz, 1H), 3.91 (t, *J* = ~8.0 Hz, 1H), 3.62 (t, *J*= ~8.0 Hz, 1H), 3.55 (s, 1H), 3.15 (d, *J*= ~12 Hz, 1H), 2.72 (t, *J*= ~12 Hz, 1H), 2.25-2.10 (m, 2H), 2.00 (d, *J*= ~12 Hz, 1H), 1.75-1.55 (m, 4H.: ^{13}C (100.6 MHz, CD_2Cl_2) δ 153.8, 142.4, 141.4, 129.5, 128.4, 128.1, 121.0, 120, 116.5, 83.5, 72.1, 70.1, 47.8, 42.3, 39.2, 38.0, 24.7: MS 394 (MH^+) (100%). HRMS $C_{21}H_{23}F_3NO_3$ (MH^+) requires 394.1630, found 394.1630.

Boc-Protected **1**



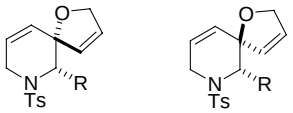
Rotation α_D = +15.7, c = 0.9, EtOH: ^1H (400 MHz, CD_2Cl_2) δ 7.95 (brs, 1H), 7.58 (m, 2H), 7.31 (m, 2H), 7.25 (m, 1H), 7.03 (d, *J* = 2.7 Hz, 1H), 6.92 (m, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 5.76 (s, 1H), 4.32 (dd, *J* = 7.5, 8.5, 7.5 Hz, 1H), 4.00 (dd, *J* = 13.3, 4.1 Hz, 1H), 3.94 (qn, *J* = 8.5 Hz, 1H), 3.83 (t, *J* = 8.5 Hz, 1H), 2.85 (dt, *J* = 13.3, 3.5 Hz, 1H), 2.64 (dd, *J* = 12.8, 8.5 Hz, 1H), 2.24 (dt, *J* = 17.1, 4.9 Hz, 1H), 1.89 (dd, *J* = 12.8, 8.5 Hz, 1H), 1.85-1.60 (m, 3H), 1.51 (s, 9H): ^{13}C (100.6 MHz, CD_2Cl_2) δ 156.3, 153.8, 142.3, 138.9, 130.3, 129.4, 128.4, 127.2, 121.2, 120.5, 119.8, 119.5 (q, *J* = 255.4), 85.1, 80.9, 72.4, 59.8, 43.9, 39.9, 39.6, 32.7, 28.5, 24.2.



Molecular Modeling Studies

Calculations were carried out using the MM2* force field as implemented in Macromodel 5.5. Monte Carlo searches were performed to ensure that all low energy conformations had been included in the calculation. Ratios were calculated by summing the Boltzmann factors of all the minima found by Monte Carlo searches. For the spirocyclic compounds **6**, **5a**, **5b** and their C_5-epimers the results are shown in **Table 1** (energies quoted in $kJmol^{-1}$). As noted in the text the only substrate to show a significant energy difference between the two is **6**, which experimentally shows the lowest selectivity.

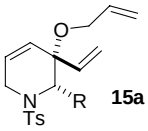
Table 1



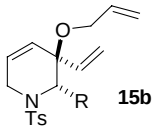
	R	Major isomer	Minor isomer	difference
5a	Me	79.77	80.48	0.7
5b	iPr	99.34	100.14	0.8
6	Ph	70.24	81.22	11.0

Studies were also carried out on the intermediate compounds in which only one ring was formed as outlined in **Table 2**. These results suggest that for the studied case of R = Ph, compound **15a** should be significantly favored over compound **15b**. Experimentally (based on LC analysis) **15b** is not seen at all. In contrast, the theoretical ratio for the two five membered rings **14a** and **14b** is predicted to be low, again in agreement with experiment where a ca 1:1 ratio is seen during the reaction.

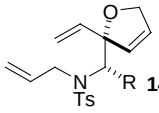
Table 2



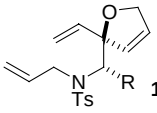
15a



15b



14a



14b

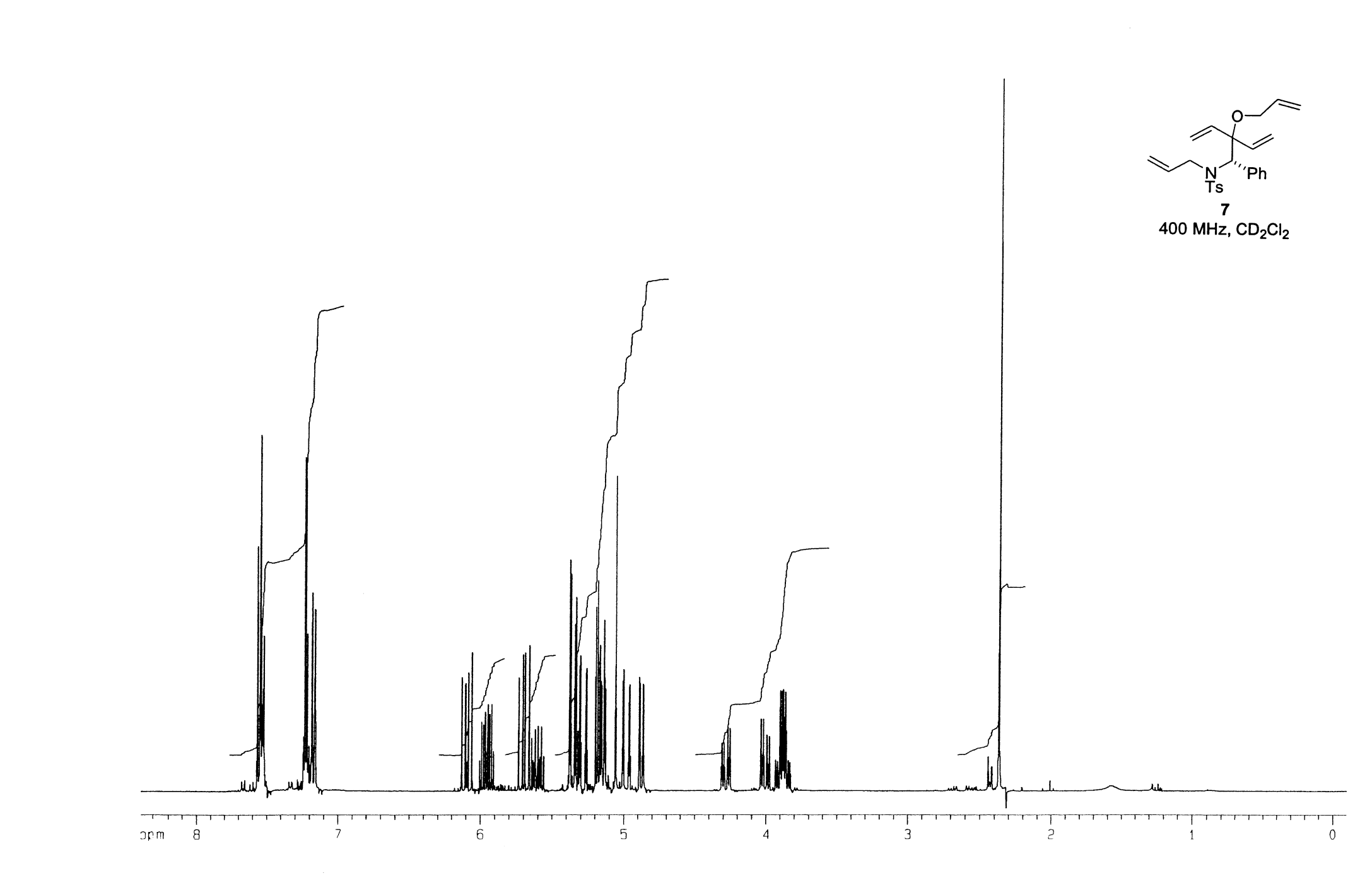
R	**15a**	**15b**	difference 6-membered ring	**14a**	**14b**	difference 5-membered ring
Ph	54.98	60.37	5.39	68.27	69.28	1.01
Me	62.39	56.90	-5.49	73.28	76.25	2.97

In the case of the substrate with R = Me these calculations predict a larger energy difference between the two dihydrofurans in favor of **14a** over **14b**. As we believe this pathway to be the predominant one operating during the reaction, and that **14a** directly forms the major double metathesis isomer this could explain the higher selectivity obtained for this reaction. It is notable that the predicted relative energies of the tetrahydropyridines is reversed in this case, but as formation of these intermediates is not favored this is unlikely to have a significant contribution. Studies are underway to provide experimental evidence for this theory.

In order to obtain an idea of the kinetic effects in these reactions a simple model of the transitions state was created by constraining the reacting ends of the double bonds to be 2 A apart, and re-minimising the results of the previous searches. This crude model ignores the effect of the metal, but allows for the ring strain which must be overcome to bring the reacting carbon atoms together. For the starting material the phenyl group was replaced with a methyl group.

These calculations suggest that it is easier to form the five membered rings than the six membered rings, with the eight membered ring being hardest of all to form.

Formation of the major methathesis isomer from **14a** and **15a** requires less energy than the formation of the minor isomer from **14b** or **15b** for both studied cases of R = Me and Ph. For these later compounds an inversion reaction (eg **14b** to **15a**) becomes more likely. Experimentally we have observed that **14a** and **15a** (R = Ph) react to form solely the major isomer as predicted, but that **14b** gives a 2:1 mixture of minor to major isomer suggesting some inversion has taken place.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Ts
Ph
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ppm
8
7
6
5
4
3
2
1
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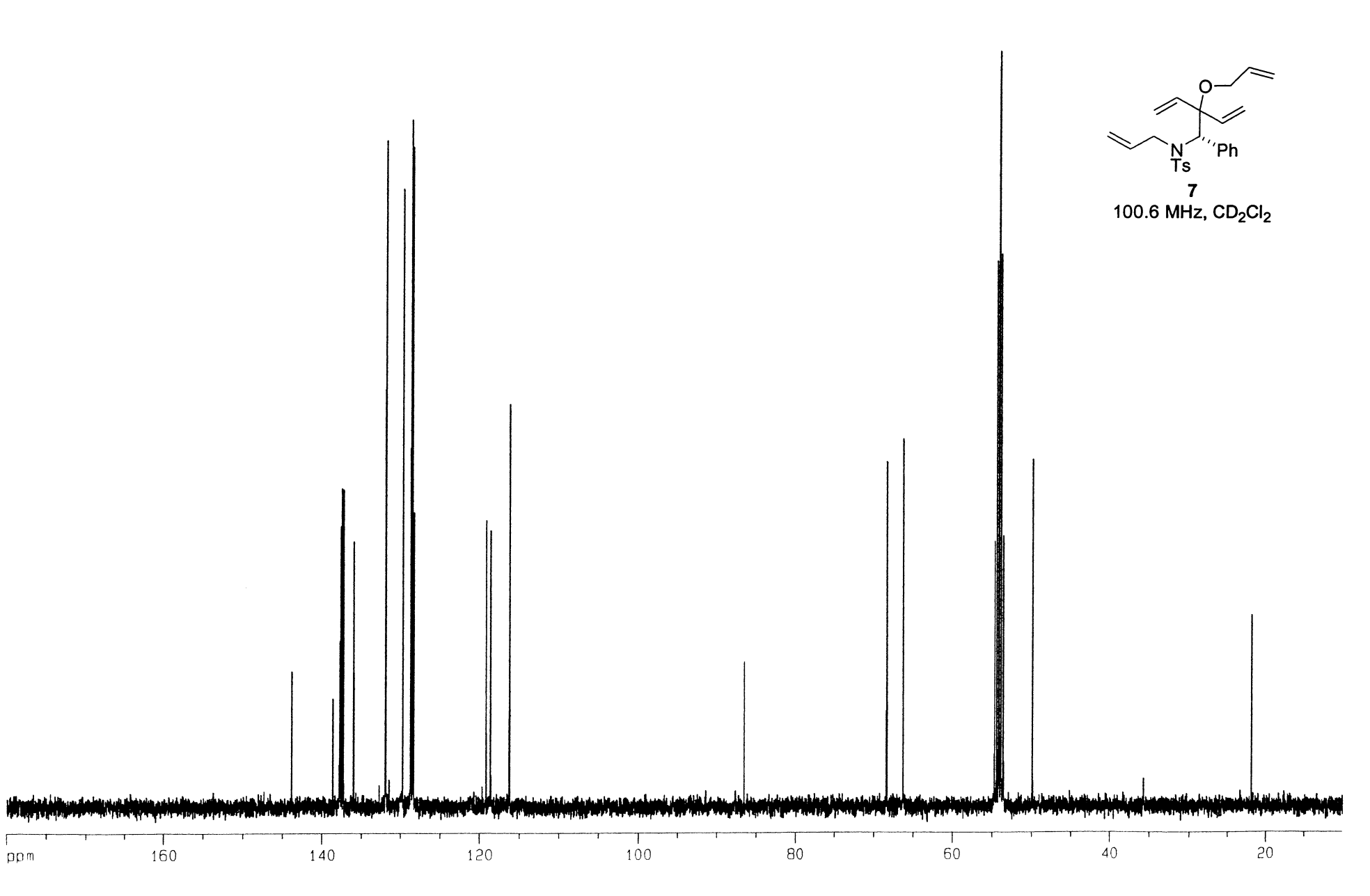
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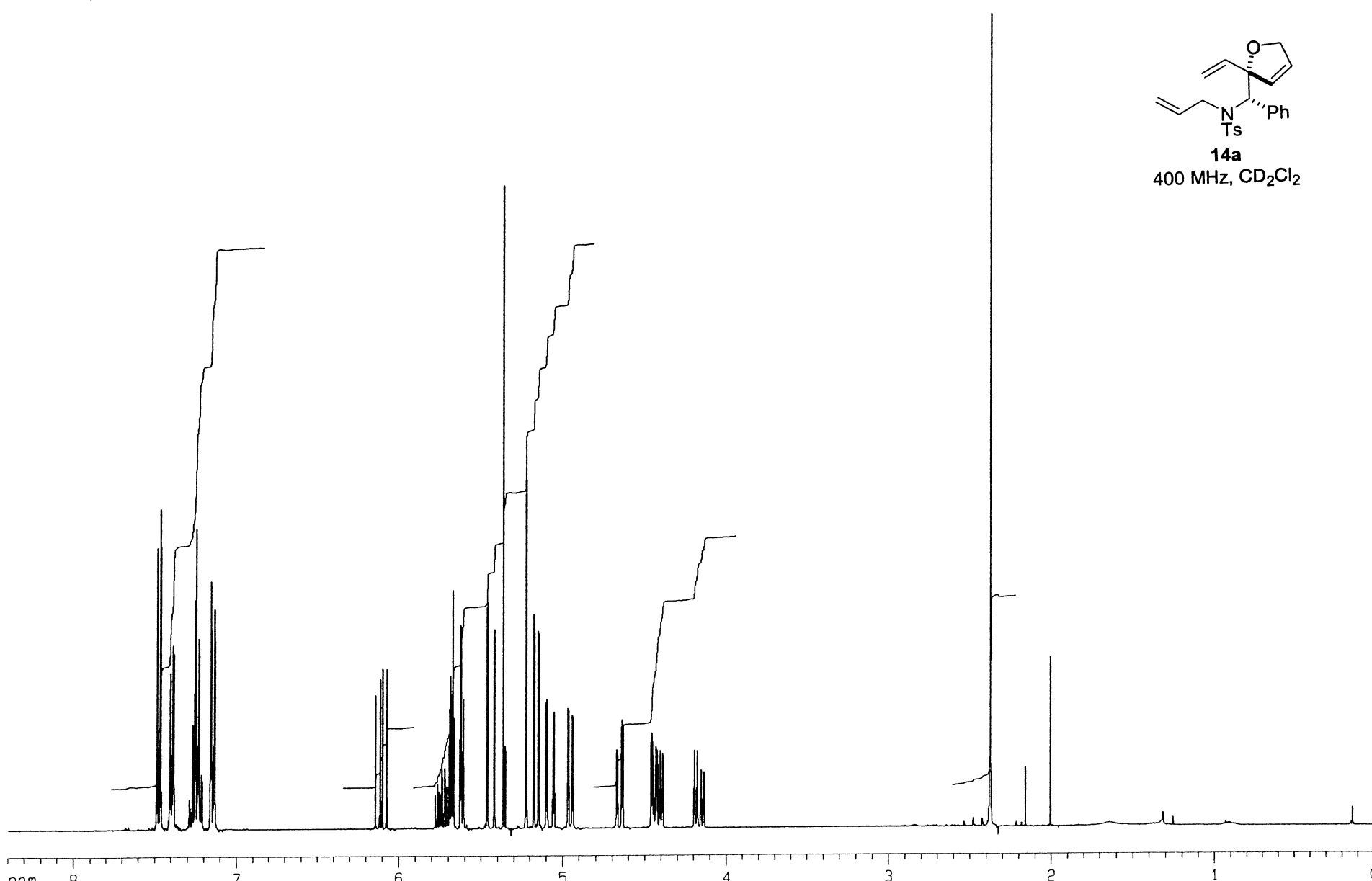
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Ph
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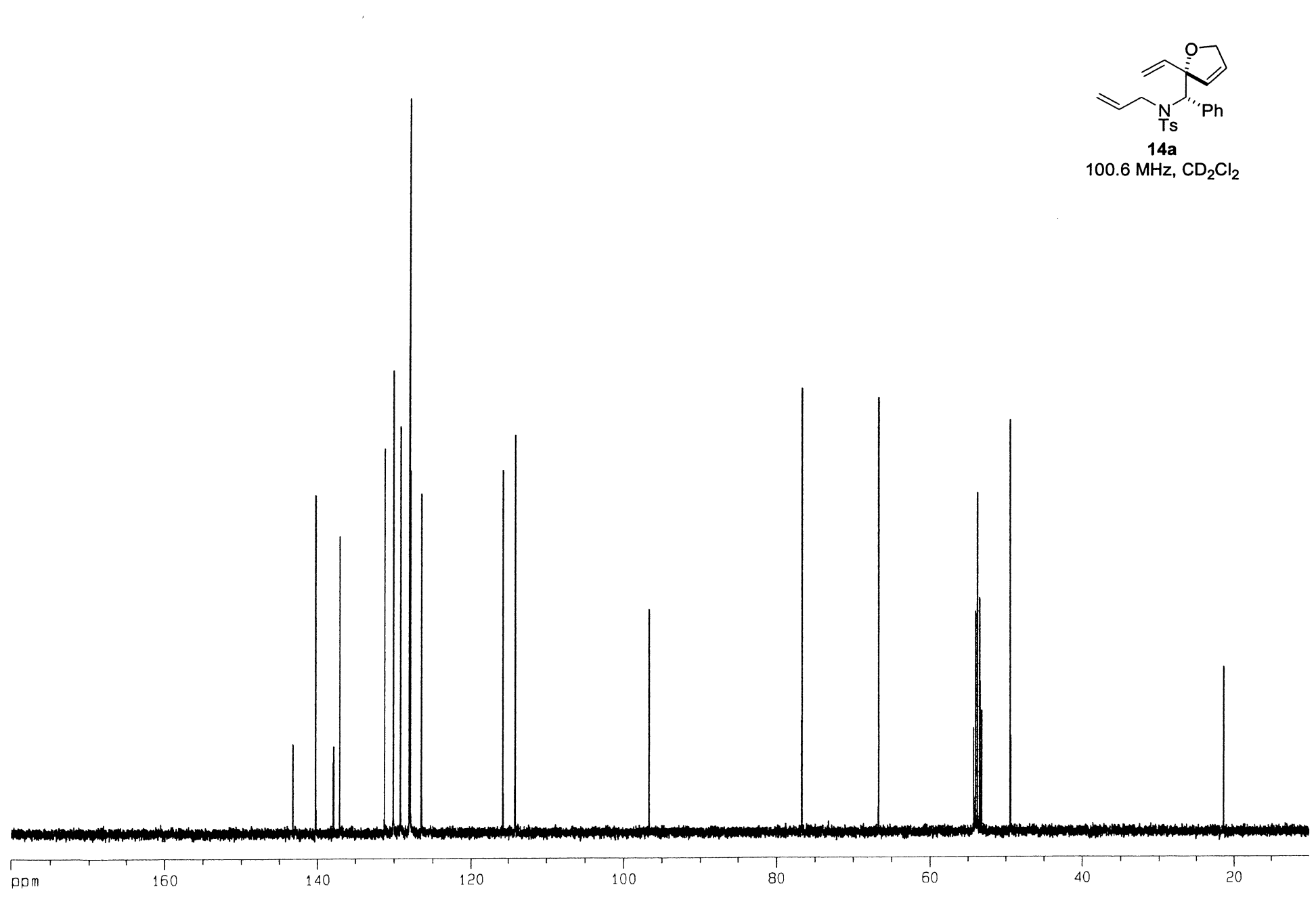
3
2
1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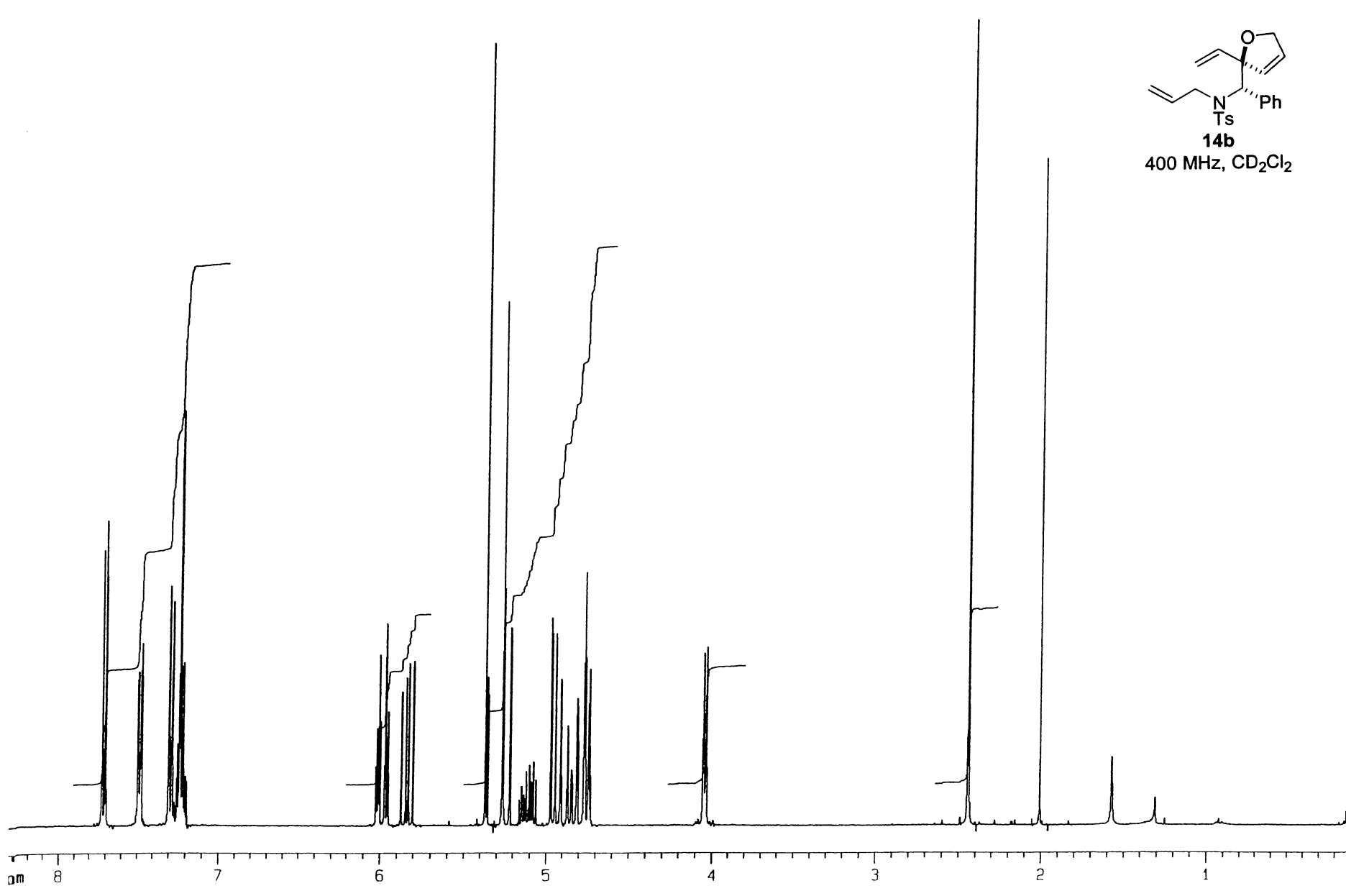
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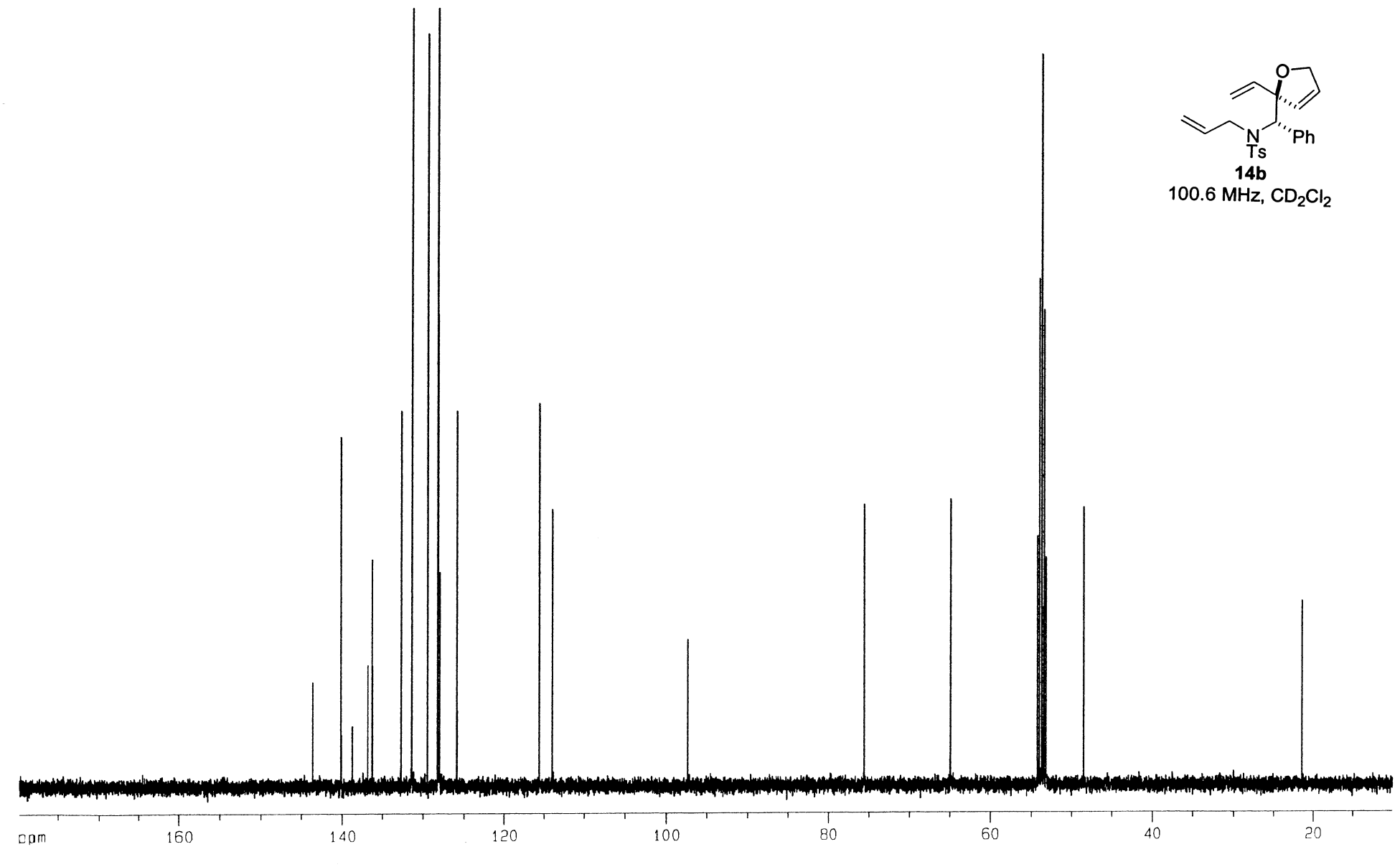
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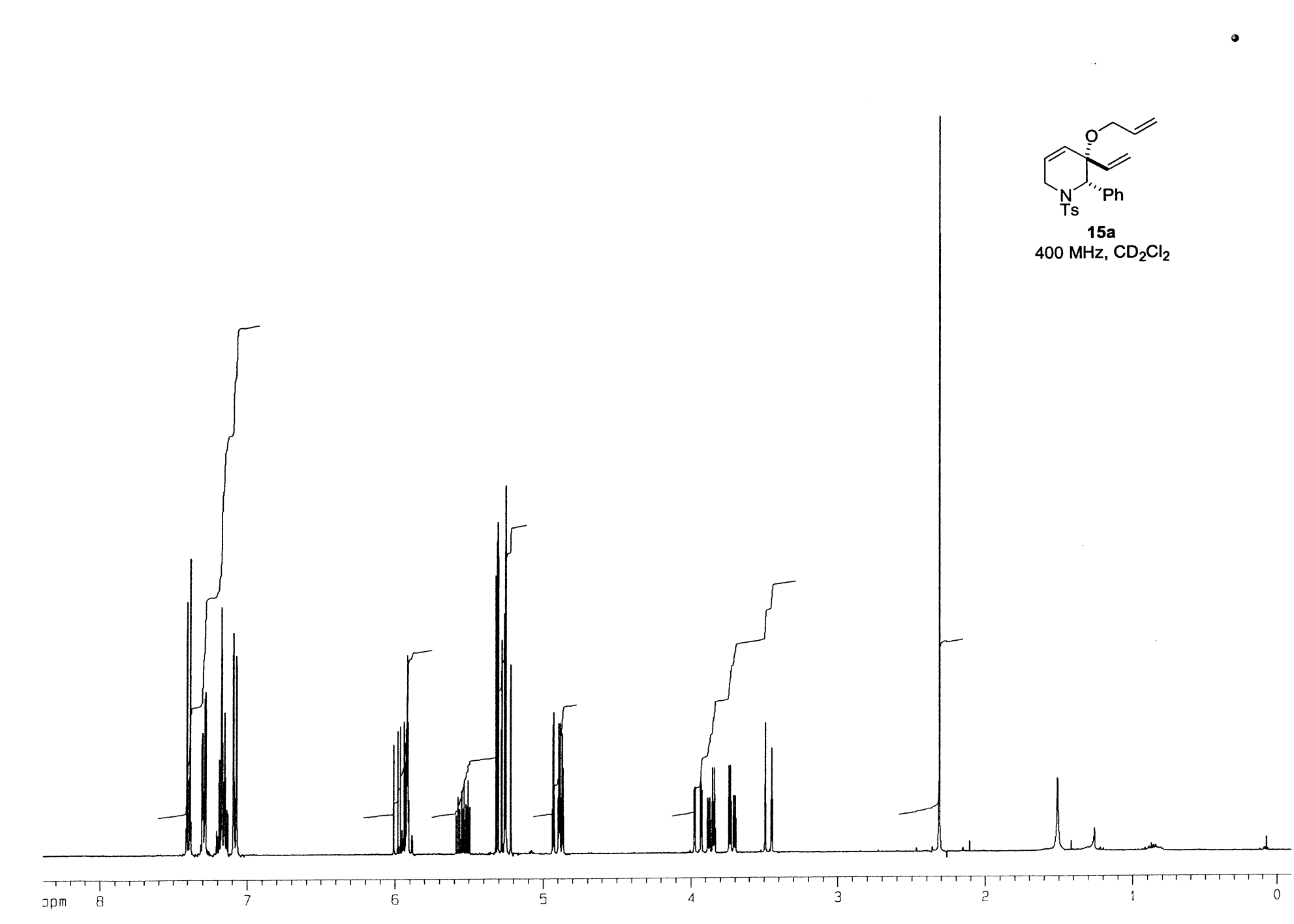
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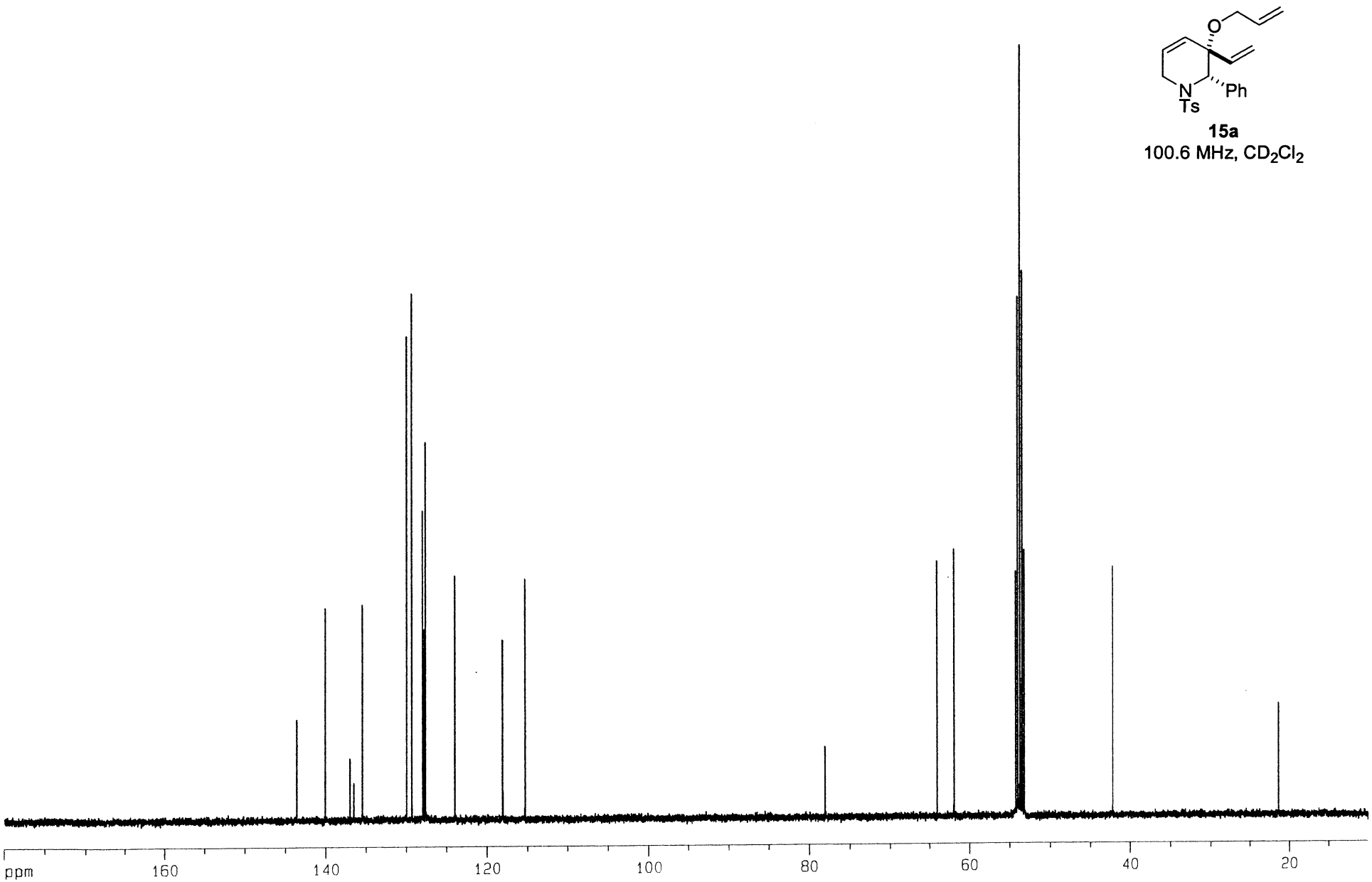
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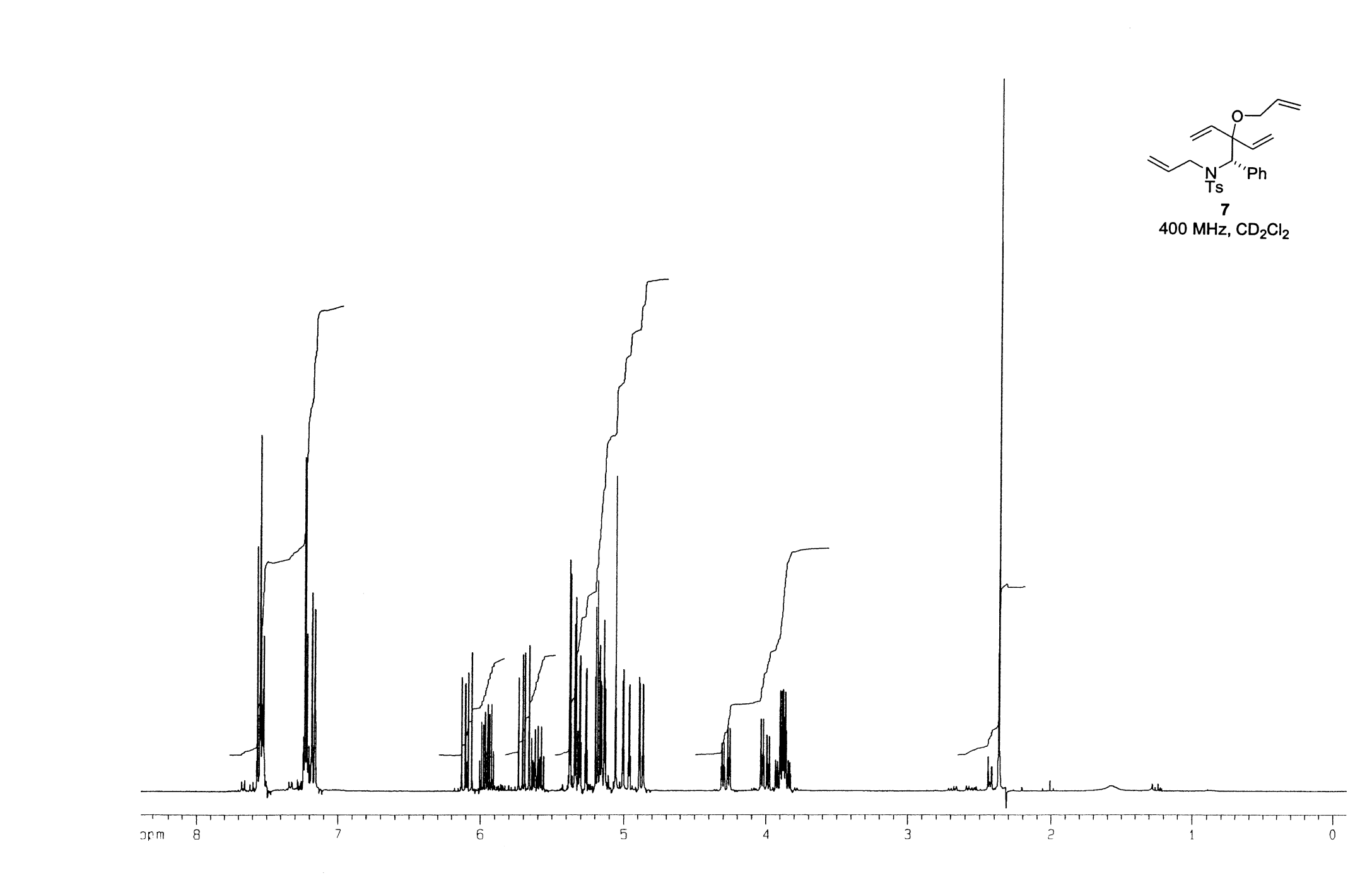
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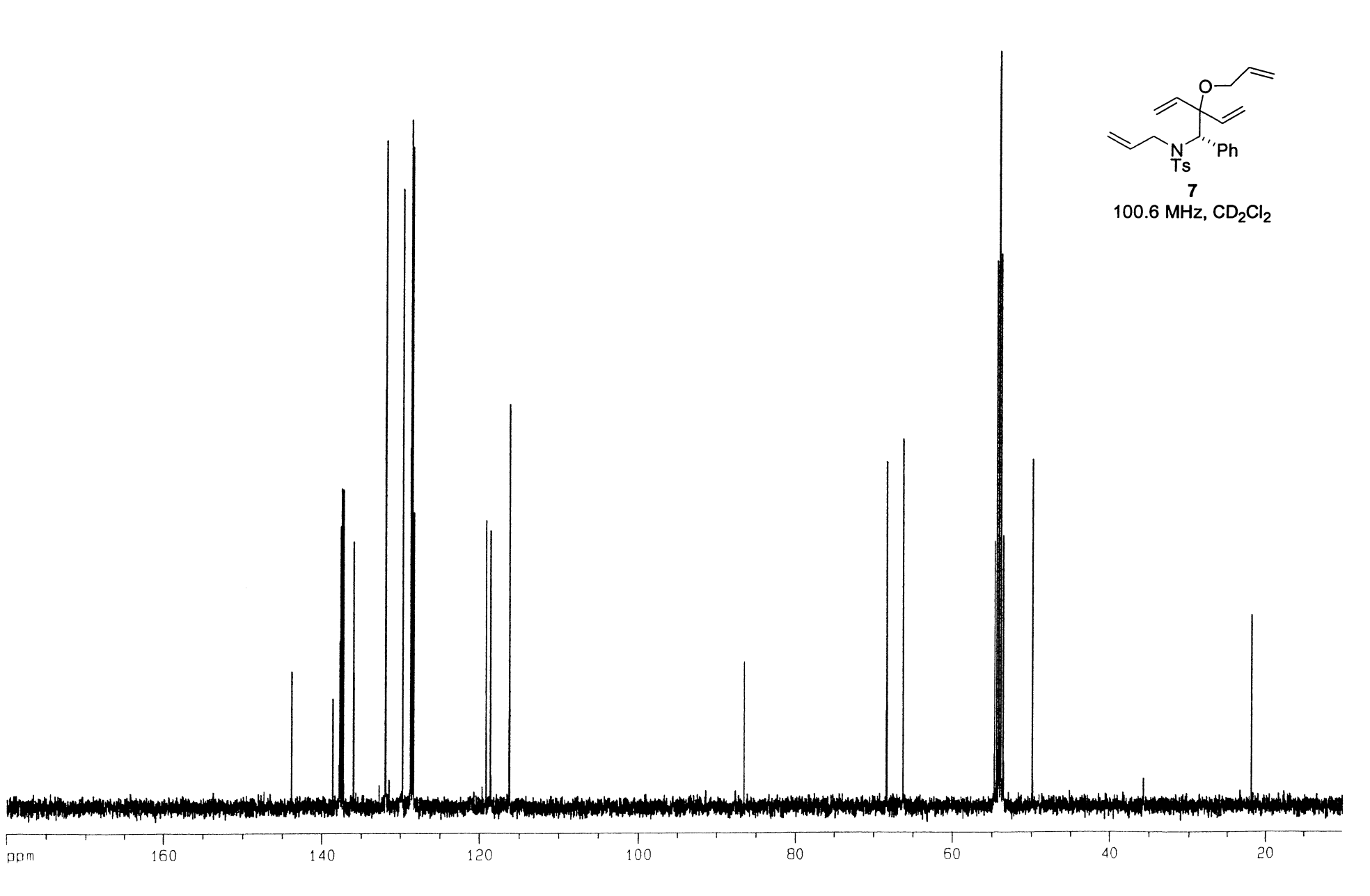
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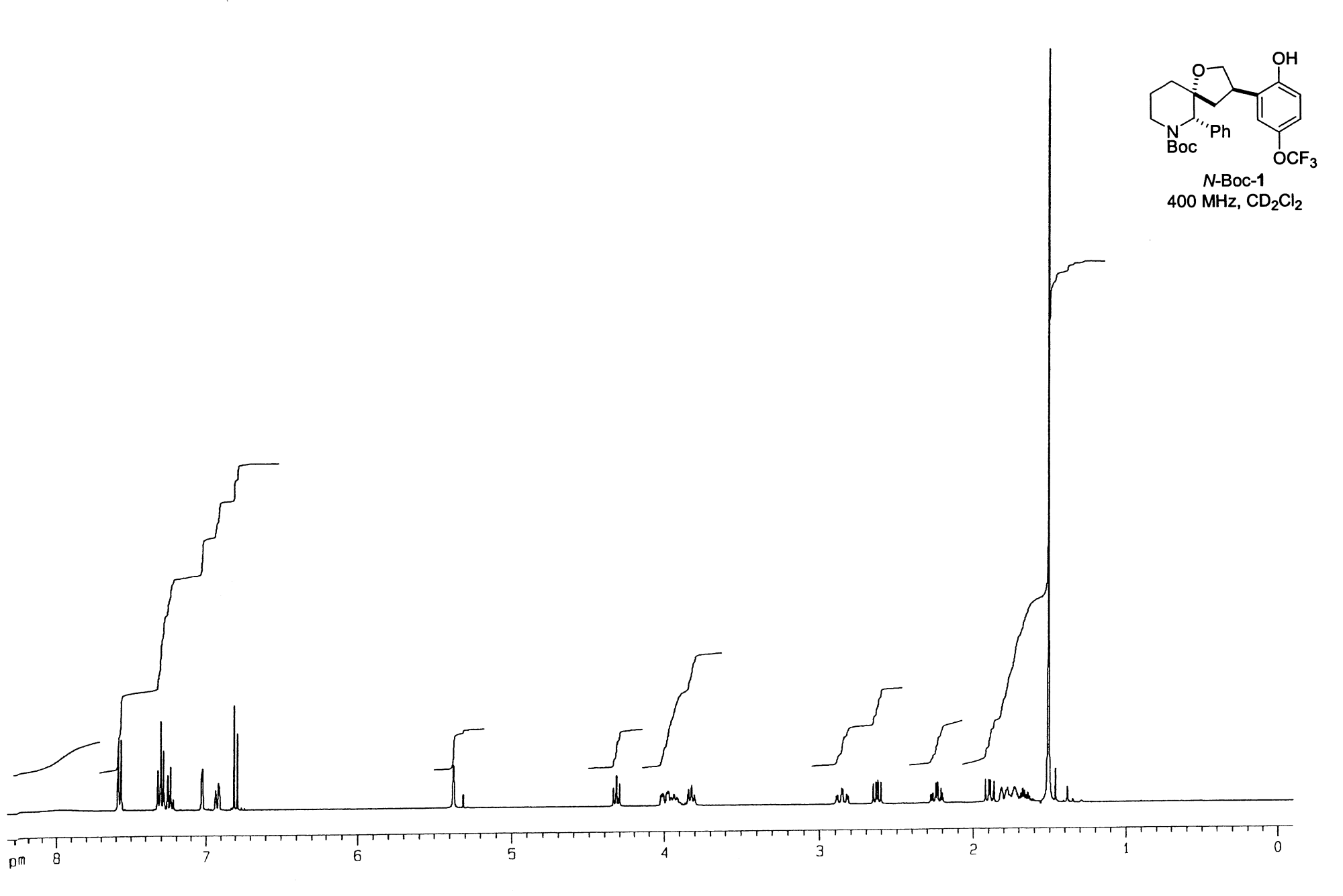
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Boc
Ph
OCF3
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pm
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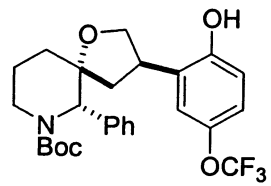
7
6
5
4
3
2
1
0



N-Boc-**1**
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