Supporting Information

Formal Total Synthesis of (-)-Oseltamivir Phosphate

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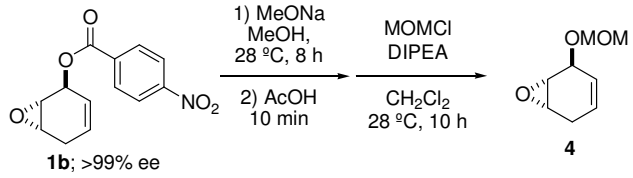
General Methods and Materials

All reactions were performed under argon atmosphere using Schlenk tube techniques and freshly distilled solvents. All melting points were measured on a Yanaco MP-500D and were uncorrected. ^{1}H and ^{13}C NMR spectra (400 and 100.6 MHz, respectively) were recorded on a JEOL JNM-LA 400 using Me_4Si as the internal standard (0 ppm). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Elemental analyses were performed with a Yanaco CHN Corder MT-5. Mass spectra were measured on a Thermo Quest LCQ DECA plus. Optical rotations were measured on a HORIBA SEPA-300 Polarimeter for solution in a 1 dm cell. Preparative column chromatography was carried out on Fuji Silysia BW-820MH or YMC*GEL Silica (6 nm I-40—63 μm). Thin layer chromatography (TLC) was carried out on Merck 25 TLC aluminum sheets silica gel 60 F254. Chiral HPLC was performed on a HITACHI L-2000 series instrument equipped with an L-2455 Diode Array Detector using chiral columns CHIRALPAC AD-H (250mm x 4.6mm x 5•m).

Experimental Procedures and Compounds Characterization Data

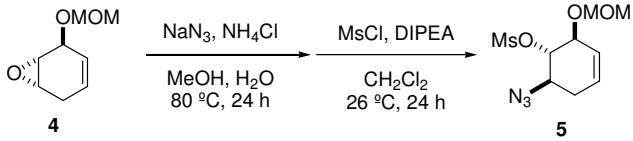
(1*S*,2*S*,3*S*)-3-methoxymethyl-1,2-epoxycyclohex-4-ene (**4**):



1b; >99% ee **4**

To a solution of **1b** (1.5 g, 5.8 mmol) in MeOH (15 mL) was added a 0.5 M NaOMe solution (0.6 mL, 0.3 mmol). After stirring at rt for 8 h, the complete disappearance of starting material was indicated by TLC and acetic acid (18 μL, 0.3 mmol) was added to quench the reaction. Methanol was removed by rotary evaporation and the residue was purified by chromatography (hexane/EtOAc = 4/1 to 2/1) to give the deprotected compound as a colorless liquid. To a solution of the deprotected compound in CH_2Cl_2 (30 mL) was added DIPEA (2.9 mL, 17.3 mmol), followed by addition of MOMCl (1.3 mL, 17.3 mmol). The mixture was stirred for 10 h and H_2O (30 μL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography (hexane/EtOAc = 5/1) to give MOM protected compound **4** as a colorless oil (0.88 g, 99%). R_f = 0.28 (hexane/EtOAc = 3/1); $[\alpha]_D^{17}$ +118.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.6 (br s, 2H), 4.78 (d, *J* = 7.2 Hz, 1H), 4.75 (d, *J* = 7.2 Hz, 1H), 4.4 (br s, 1H), 3.40 (s, 3H), 3.2 (br s, 1H), 3.3 (br s, 1H), 2.63–2.51 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 125.3, 122.8, 95.9, 68.7, 55.5, 52.4, 50.3, 25.1; MS (ESI) m/z 157 $(M + H)^+$; Anal. calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.74; Found: C, 61.25; H, 7.81.

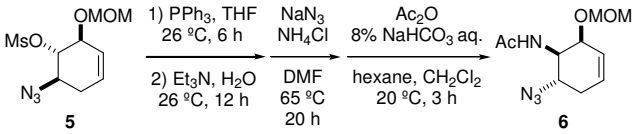
(1*R*,2*S*,3*S*)-1-azido-3-methoxymethyl-2-(methylsulfonyl)oxycyclohex-4-ene (**5**):



4 **5**

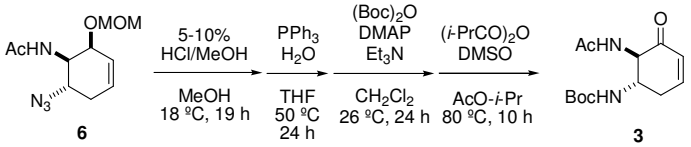
To a solution of **4** (440 mg, 2.8 mmol) in MeOH (15 mL) were added NH_4Cl (450 mg, 8.4 mmol) and NaN_3 (1.27 g, 12.6 mmol) in H_2O (5 mL). The mixture was heated to 80 ºC and stirred for 24 h. After cooling to rt, additional H_2O (20 mL) was added to dissolve the solid and MeOH was removed by rotary evaporation. The aqueous solution was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (15 mL). To the solution, DIPEA (0.70 mL, 4.2 mmol) and MsCl (0.33 mL, 4.2 mmol) were added at 0 ºC. The mixture was stirred for 24 h and aqueous ammonium chloride solution (15 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (30 mL x 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography (hexane/EtOAc = 5/1) to give compound **5** (690 mg, 88%). R_f = 0.17 (hexane/EtOAc = 3/1); m.p. 57–59 ºC; $[\alpha]_D^{28}$ +33.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.72 (m, 2H), 4.81 (d, *J* = 7.2 Hz, 1H), 4.77 (d, *J* = 7.2 Hz, 1H), 4.65 (dd, *J* = 10.4, 7.2 Hz, 1H), 4.32 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.77 (ddd, *J* = 10.4, 10.4, 6.0 Hz, 1H), 3.43 (s, 3H), 3.18 (s, 3H), 2.63 (m, 1H), 2.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 127.3, 125.0, 97.0, 83.5, 76.8, 58.9, 55.9, 39.1, 31.0; MS (ESI) m/z 300 $(M + Na)^+$; Anal. calcd. for $C_9H_{15}N_3O_5S$: C, 38.98; H, 5.45; N, 15.15; Found: C, 38.98; H, 5.45; N, 14.76.

(*1S*,*2R*,*3S*)-2-(acetylamino)-1-azido-3-methoxymethylcyclohex-4-ene (**6**):



A solution of **5** (430 mg, 1.6 mmol) in THF (10 mL) was stirred at 0 ºC. To the solution, PPh_3 (510 mg, 1.95 mmol) was added in three portions. The reaction mixture was stirred at room temperature (20 ºC) for 3 h. After adding Et_3N (0.43 μL, 2.3 mmol) and H_2O (0.7 mL), the solution was stirred vigorously for 12 h. Organic solvent was removed by rotary evaporation, then the residue was extracted with CH_2Cl_2 (30 mL x 3) and brine (20 mL). The combined organic layers were dried over Na_2SO_4. After evaporation of the solvent, $P(O)Ph_3$ and unreacted PPh_3 were removed by chromatography (EtOAc/MeOH = 10/1) to give the aziridine. To a solution of the aziridine in DMF (15 mL) were added NH_4Cl (0.15 g, 2.8 mmol) and NaN_3 (450 mg, 6.9 mmol). The mixture was heated to 65 ºC and stirred for 16 h. After cooling to rt, 5% $NaHCO_3$ aq. (15 mL) was added. The aqueous solution was extracted with hexane (50 mL x 5) and diethyl ether (50 mL x 5). The combined organic layers were dried (Na_2SO_4). After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (1.5 mL) and hexane (1.5 mL). To the solution, 5% $NaHCO_3$ aq. (3.0 mL, 2.8 mmol) and Ac_2O (0.13 mL, 1.4 mmol) were added at 0 ºC. The mixture was stirred for 3 h. The aqueous layer was extracted with diethyl ether (30 mL x 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography (hexane/EtOAc = 1/2) to give compound **6** (220 mg, 67%). R_f = 0.48 (EtOAc); m.p. 82–85 ºC; $[\alpha]_D^{28}$ +101.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.53 (m, 2H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.49 (m, 1H), 3.45 (s, 3H), 2.61 (m, 1H), 2.50–2.43 (m, 1H), 2.40–2.31 (m, 2H), 1.26 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 124.9, 124.0, 95.4, 70.7, 55.5, 33.4, 29.1, 24.7; MS (ESI) m/z 263 $(M + Na)^+$; Anal. calcd. for $C_{10}H_{16}N_4O_3$: C, 49.99; H, 6.71; N, 23.32; Found: C, 50.17; H, 6.85; N, 22.96.

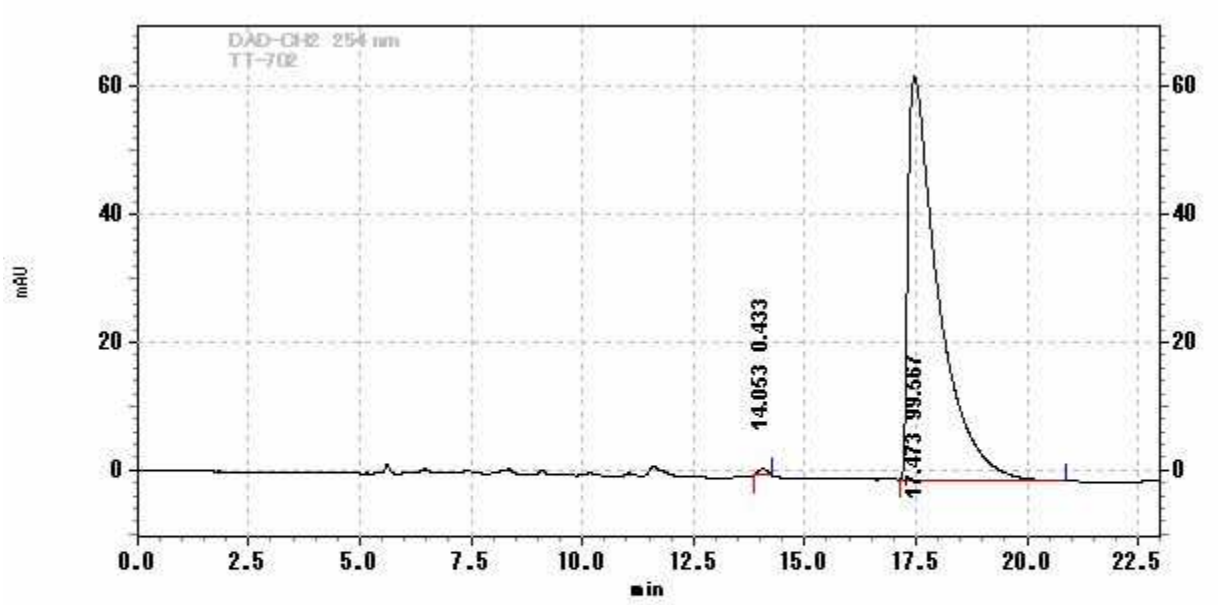
(1*S*,2*R*,3*S*)-2-(acetylamino)-1-(*tert*-butoxycarbonylamino) -4-cyclohexen-3-one (**3**):



A solution of **6** (230 mg, 0.9 mmol) in MeOH (1 mL) was stirred at 0 ºC. To the solution, 5–10% HCl in MeOH (5 mL) was added slowly. The reaction mixture was stirred at room temperature (20 ºC) for 20 h. Organic solvent was removed by rotary evaporation. Further removal of HCl gas was carried out by passing air over the solution for 1 h. The residue was dissolved in THF (10 mL). To this solution, PPh_3 (370 mg, 1.4 mmol) was added in three portions. The reaction mixture was stirred at room temperature (20 ºC) for 1 h. After adding H_2O (1 mL), the solution was stirred vigorously at 50 ºC for 24 h. Organic solvent was removed by rotary evaporation and the residue was dissolved in CH_2Cl_2 (10 mL). To the solution, Boc_2O (21 mg, 0.9 mmol) and Et_3N (0.66 mL, 4.8 mmol) were added. After adding 4-dimethylaminopyridine (6.1 mg, 0.05 mmol), the solution was stirred at 26 ºC for 24 h. Sat. NH_4Cl aq. (2 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (30 mL x 3). The combined organic layers were dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography (EtOAc) to give the crude allylic alcohol. This allylic alcohol was dissolved in *i*-PrOAc (1.5 mL) and DMSO (135 μL) to which was added isobutyric anhydride (150 μL). The reaction mixture was stirred at 80 ºC for 5 h. The mixture was diluted with 10 mL of EtOAc. The

organic solution was washed with sat. $NaHCO_3$ aq. (10 mL) and brine (10 mL). The combined organic layers were dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by chromatography (hexane/EtOAc = 1/1) to give compound **3** (96.7 mg, 40%). R_f = 0.50 (EtOAc); m.p. 142–144 ºC; $[\alpha]_D^{28}$ -119.6 (*c* 0.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.98 (ddd, *J* = 10.0, 6.4, 2.0 Hz, 1H), 6.36 (br d, *J* = 6.4 Hz, 1H), 6.15 (dd, *J* = 10.0, 3.6 Hz, 1H), 5.72 (br d, *J* = 7.2 Hz, 1H), 4.61 (dd, *J* = 13.2, 6.8 Hz, 1H), 3.98-3.87 (m, 1H), 2.97 (ddd, *J* = 19.2, 6.4, 4.8 Hz, 1H), 2.48–2.40 (m, 1H), 2.10 (s, 3H), 1.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 194.8, 172.4, 148.7, 132.1, 128.5, 79.5, 59.7, 53.6, 34.2, 28.4, 23.9; MS (ESI) m/z 291 $(M + Na)^+$.

HPLC chart of 3



DAD-CH2 254 nm

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column, CHIRALPAK AD-H (DAICEL): eluent, hexane–2-propanol (90:10): 0.6 mL/min, detection, 254 nm

^{1}H and ^{13}C NMR spectra


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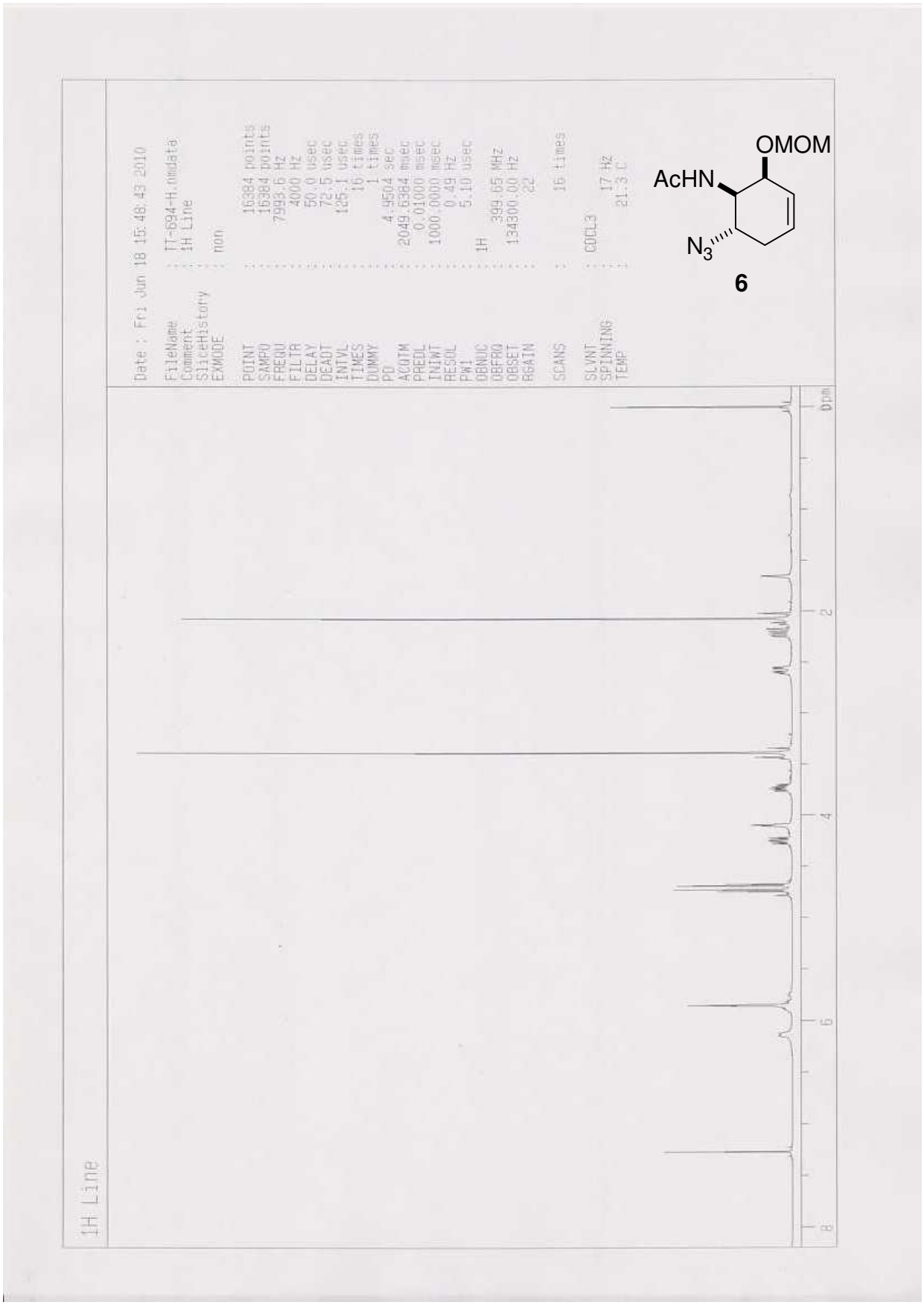
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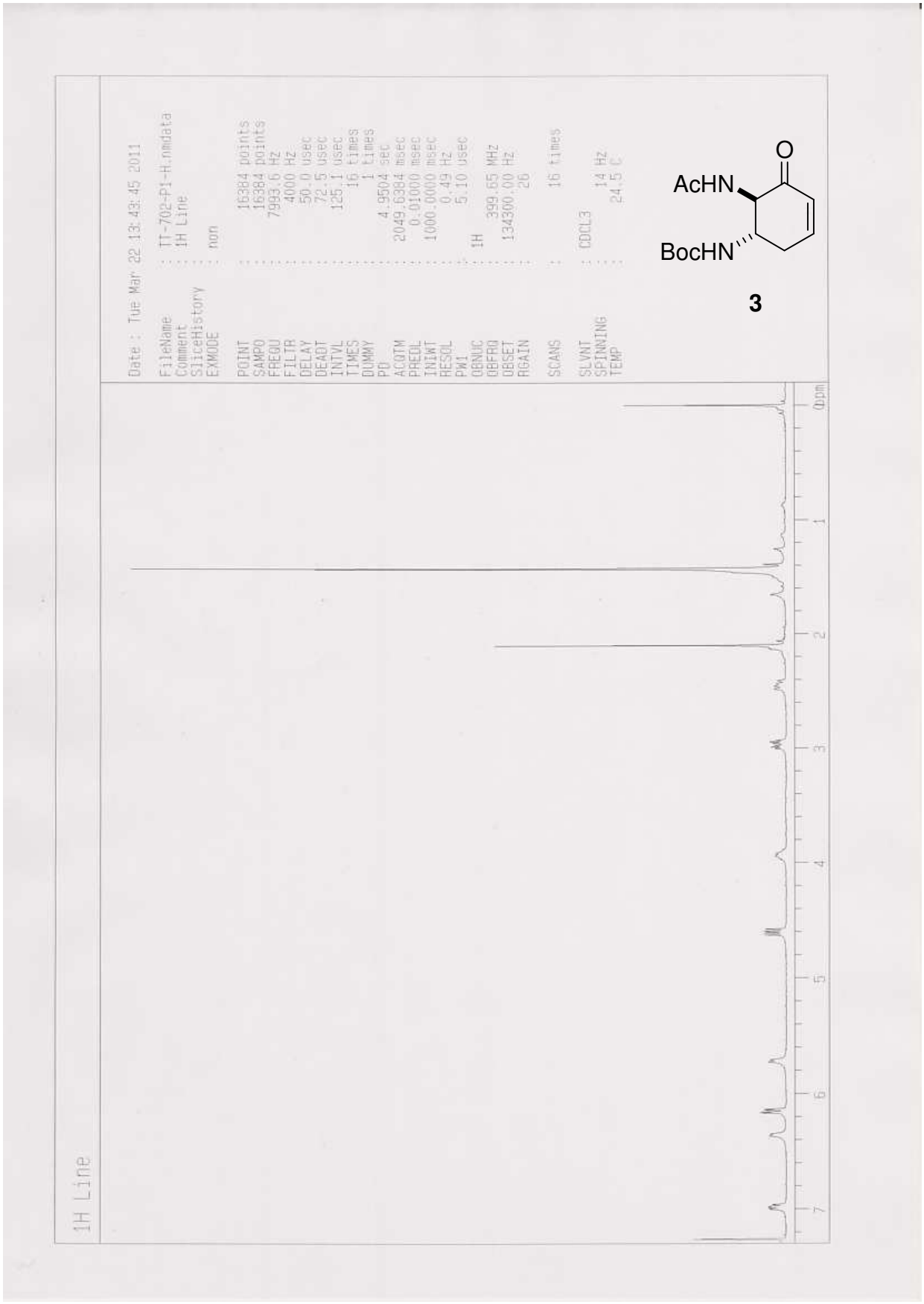
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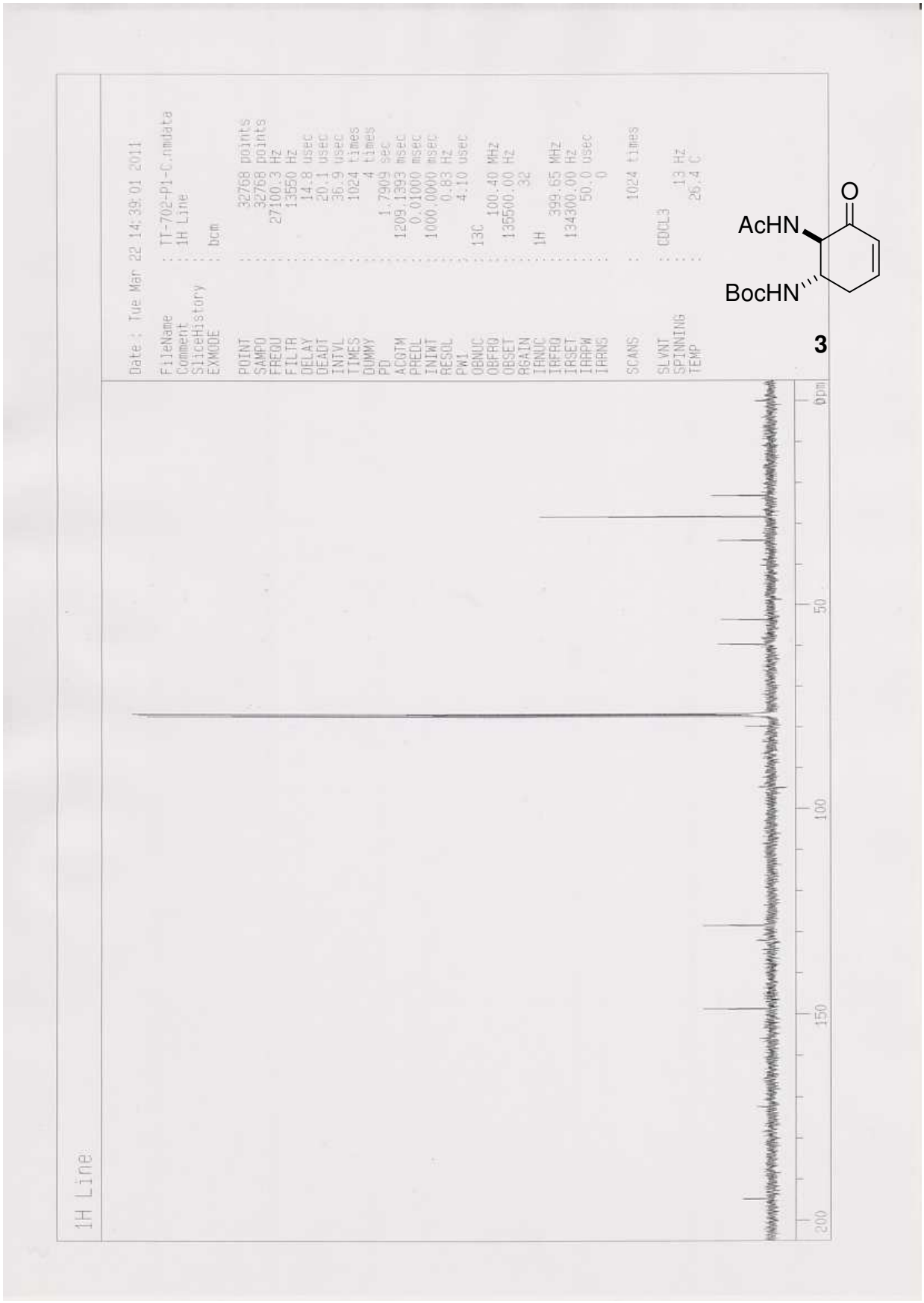
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