Following an ISES Lead: The First Examples of Asymmetric Ni(0)-Mediated Allylic Amination.

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SUPPORTING INFORMATION

Experimental Section

General. All reactions were conducted under argon atmosphere using oven-dried glassware. Methylene chloride and diisopropylamine were distilled from CaH_2. THF and Et_2O were distilled from sodium benzophenone ketyl. HMPA was distilled from Na under reduced pressure. Methanol was distilled from Mg. Lithium bis(trimethyl)silylamide in hexane was purchased from Aldrich. Yeast alcohol dehydrogenase (EC 1.1.1.1; lyophilized powder, 358 units/mg solid), β-NAD^+ (disodium salt, 95%) were purchased from Sigma and yeast aldehyde dehydrogenase (EC 1.2.1.5; lyophilized powder, 20 units/mg enzyme protein) was purchased from Boehringer-Mannheim. Other reagents were obtained from commercial sources and used without further purification. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). ^1H NMR spectra were recorded on a Bruker 600, 500 or 400 MHz instruments with chemical shifts reported relative to residual $CHCl_3$ (7.25 ppm). Proton-decoupled ^{13}C NMR spectra were acquired on the same instruments with chemical shifts reported relative to $CDCl_3$ (77.0 ppm). Mass spectra were acquired at the Nebraska Center for Mass Spectrometry (University of Nebraska-Lincoln). GC-MS runs wer performed on an HP model 5890 GC with model 5972 MS. Optical rotations @589 nm were measured in an Autopol polarimeter. Enantiomeric excess was determined using a Chiralcel OD (0.46 mm x 25 cm) chiral column. Enzyme assays and ISES runs were carried out on a Shimadzu UV-2101 PC UV/vis spectrophotometer equipped with a CPS-260 six cell positioner with thermoelectric temperature control (set at 25 °C for all experiments reported) using quartz cuvets (from Hellma) of 1 cm path length and a nominal volume of 1 mL.

Standardization of Enzymes for ISES

Yeast Alcohol Dehydrogenase: The final concentration of the reagents in the assay cuvet were as follows: 100 mM ethanol, 7.2 mM NAD^+, 50 mM sodium pyrophosphate. The final pH of the assay was 8.6.

Assay procedure: Typically, the stock solution of ADH was prepared by dissolving 0.9 mg solid of the commercial enzyme lyophilisate in 500 μl of 25 mM $NaPO_4$ buffer, pH 7.0. A 1:20 diluted stock was made (40 μl of the enzyme stock in 760 μl of 25 mM $NaPO_4$ buffer, pH 7.0.). Addition of 0.5 μl of the 1:20 diluted stock (typically 5 μl of 1:200 diluted stock) to a 1mL standard assay solution gives rise to an absorbance change of 95.6 mAbs/min at 340 nm. This indicates the presence of 0.015 U/μl of the 1:20 stock solution.

Definition of one Unit : One unit of enzyme is taken as the amount of enzyme catalyzing the formation of one μmol of NADH per minute. In a 1 mL final cuvet volume, this amounts to an absorbance change of 6.22 min^{-1} when followed at 340 nm.

Yeast Aldehyde Dehydrogenase: : The final concentrations of the reagents in the assay cuvet were as follows: 400 μM acetaldehyde, 7.2 mM NAD^+, 10 mM KCl, 50 mM sodium pyrophosphate. The final pH of the assay was 8.6.

Assay procedure: Typically, the stock solution of AlDH was prepared by dissolving 8.2 mg solid of the commercial enzyme lyophilisate in 900 μl of 25 mM $NaPO_4$ buffer, pH 7.0. Addition of 1μL of this solution (or 5 μL of a 1:5 dilution) to a 1mL standard assay solution gives rise to an absorbance change of 128 m Abs/min at 340 nm. This indicates the presence of 0.01 U/μl of stock solution.

Definition of one Unit: One unit of enzyme is taken as the amount of enzyme catalyzing the formation of one μmol of NADH per minute. In a 1 mL final cuvet volume, this amounts to an absorbance change of 6.22 min^{-1} when followed at 340 nm.

ISES Procedure

The aqueous layers were first prepared in 1.6 mL microcentrifuge tubes and added to the cuvets. A typical aqueous layer composition is given below.

Stock solution	**Vol pipetted**	**Final concentration**
40 mM NAD^+, in 25 mM $NaPO_4$ buffer, pH 7.0	162 μl	7.2 mM
Yeast ADH (0.015U/μl) in 25 mM $NaPO_4$ buffer, pH 7.0	85 μl	(1.3 U)
Yeast AlDH (0.01U/μl) in 25 mM $NaPO_4$ buffer, pH 7.0	12 μl	(0.12 U)
100 mM, KCl solution in dd H_2O	90 μl	10 mM
50 mM sodium pyrophosphate buffer, pH 8.8	551μl	
Total aqueous volume:	**900μl**	

The final pH of the aqueous layer was 8.6.
Each cuvet was sealed with a truncated septum (no. 4 as defined by Aldrich, p. T590 in the 2003-2004 catalogue). ***Note:*** A buffer blank cuvet (double beam instrument) was used, as well, in all runs. This cuvet contained 1 mL of 50 mM sodium pyrophosphate buffer, pH 8.8.

The organic layers were prepared according to the procedure given below, using septum sealed vials. The total organic volume was chosen as 500 μL (300 μL THF + 100 μL toluene +100 μL hexanes)

1. The substrate (100 μmol, 31 mg of **1**) was dissolved by vortexing in 100 μL of distilled toluene in a 750 μL microcentrifuge tube.

2. Ligand and $Ni(cod)_2$ were weighed under argon and added into a vial (charged with a spin bar) which was then sealed with a septum. Then, the contents of this vial were dissolved in 300 μL of freshly distilled THF and stirred under argon for 10 minutes to ensure the complex formation.

3. The substrate (as a solution in toluene) was added (via syringe) to this complex, followed by the addition (via syringe) of 100 μL of LiHMDS (1M in hexanes).

4. Immediately, the contents were pulled into a 1 mL syringe and loaded over the aqueous layer along the walls of the cuvet by piercing the septum.

5. The rate of formation of NADH in the aqueous layer was monitored at 340 nm for up to six such cells in parallel using the thermostatted (25 °C), automatic, six–cell positioner.

Synthesis of Substrates for Allylic Amination (Toward Vinylglycinol)

Ethyl (2Z)-4-[(p-Methoxyanilino)carbonyloxy]-2-butenyl Carbonate (1). To a solution of ethyl (2Z)-4-hydroxy-2-butenyl carbonate[1] (5.13 g, 32 mmol) in THF (40 mL) at 0° C were added, sequentially, pyridine (3.89 mL, 48 mmol) and p-methoxyphenyl isocyanate (6.23 mL, 48 mmol), via syringe. The solution was allowed to warm slowly to rt for 12 h. Following dilution with diethyl ether (100 mL), the organic layer was washed with saturated $CuSO_4$ (aq), followed by water. After drying ($MgSO_4$), filtration and evaporation of the solvent, in vacuo, flash chromatography (40% EtOAc-hexane) afforded **1**[2] (9.67 g, 98%) as a solid, mp 53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7 Hz, 3H), 3.76 (s, 3H), 4.18 (q, *J* = 7 Hz, 2H), 4.72-4.78 (m, 4H), 5.74-5.84 (m, 2H), 6.61 (br s, 1H), 6.81-6.84 (m, 2H), 7.26 (br d, *J* = 10 Hz, 2H).

OMP-Protected Analog of 1

Ethyl (2Z)-4-[(o-Methoxyanilino)carbonyloxy]-2-butenyl Carbonate (23). To a solution of ethyl (2Z)-4-hydroxy-2-butenyl carbonate[1] (1.6 g, 10 mmol) in THF (20 mL) at 0 °C were added, sequentially, pyridine (1.6 mL, 20 mmol) and o-methoxyphenyl isocyanate (1.46 mL, 11 mmol), via syringe. The same procedure as for **1**, with purification by SiO_2 flash chromatography (30% EtOAc-hexane), provided **23** (2.90 g, 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7 Hz, 3H), 3.84 (s, 3H) 4.19 (q, *J* = 7 Hz, 2H), 4.75-4.78 (m, 4H), 5.75-5.87 (m, 2H), 6.84 (dd, *J* = 2, 8 Hz, 1H), 6.91-7.00 (m, 2H), 7.25 (m, 1H), 8.05 (br s, 1H); ^{13}C NMR (100 MHz) δ 14.2, 55.6, 60.4, 62.9, 64.1, 109.9, 118.1, 121.0, 122.8, 127.3, 127.4, 128.8, 129.1, 147.5, 152.9, 154.9; HRMS (FAB, 3-NOBA) calcd for $C_{15}H_{19}O_6N$ ($M+H^+$) 310.1292, obsd 310.1274.

TMP-Protected Analog of 1

Ethyl (2Z)-4-[(3',4',5'-Trimethoxyanilino)carbonyloxy]-2-butenyl Carbonate (24). To a solution of ethyl (2Z)-4-hydroxy-2-butenyl carbonate[1] (1.6 g, 10 mmol) in THF (20 mL) at 0 °C were added, sequentially, pyridine (1.6 mL, 20 mmol) and 3,4,5-trimethoxyphenyl isocyanate (2.3 g, 11 mmol), via syringe. The same procedure as for **1**, with purification by SiO_2 flash chromatography (30% EtOAc-hexane), gave **24** (3.45 g, 93%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 3.78 (s, 3H), 3.81 (s, 6H), 4.18 (q, *J* = 7 Hz, 2H), 4.74 (d, *J* = 5 Hz, 4H), 5.78-5.81 (m, 2H), 6.65 (br s, 2H), 6.71 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 56.0, 60.5, 60.9, 62.9, 64.1, 66.9, 96.4, 127.2, 127.5, 128.6, 133.8, 134.1, 153.1, 153.4, 154.9; HRMS (FAB, 3-NOBA) calcd for $C_{17}H_{23}O_8N$ ($M+H^+$) 370.1504, obsd 370.1473.

Synthesis of Substrate 19 for Allylic Amination (Toward Vigabatrin)

(4Z)-6-(Tetrahydro-2'H-pyran-2'-yloxy)-4-hexenoic Acid, p-Methoxyanilide (25). To a stirred solution of diisopropylamine (4.10 mL, 29.3 mmol) in THF (40 mL) at –78°C was added n-butyllithium (19.6 mL of a 1.5 M solution in hexane, 29.3 mmol). The resulting solution was slowly warmed to 0 °C and stirred for 30 min, then cooled to –78° C. A solution of p-methoxyacetanilide (**17**) (2.2 gm, 13.3 mmol) in THF (10 mL) was then slowly added, via syringe. After stirring for 30 min at –78 °C, a solution of (Z)-1-bromo-4 (tetrahydro-2H-pyran-2yl)oxy 2-butene (**18**)[3] (2.82 g, 11.99 mmol) in THF (15 mL) was added. The reaction mixture was allowed to slowly warm to rt and was then quenched after 1.5 h with NH_4Cl (aq), and extracted with ether. The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Flash chromatography over SiO_2 (35→50% EtOAc-hexane) gave **25** (2.65 g, 70%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48-1.56 (m, 4H), 1.66-1.71 (m, 1H), 1.76-1.80 (m, 1H), 2.36-2.39 (m, 2H), 2.46-2.51 (m, 2H), 3.47-3.51 (m, 1H), 3.75 (s, 3H), 3.83-3.87 (m, 1H), 4.09 (dd, *J* = 6, 12 Hz, 1H), 4.27 (dd, *J* = 5, 12 Hz, 1H) 4.63 (t, *J* = 4 Hz, 1H), 5.60-5.64 (m, 2H), 6.80 (d, *J* = 9 Hz, 2H), 7.37 (d, *J* = 9 Hz, 2H), 7.57 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5, 23.6, 25.4, 30.6, 37.0, 55.4, 62.3, 62.5, 97.9, 114.0, 121.8, 127.4, 131.1, 131.7, 156.3, 170.4; HRMS (FAB, 3-NOBA) calcd for $C_{18}H_{25}O_4N$ ($M+H^+$) 320.1864, obsd 320.1866.

(4Z)-6-Hydroxy-4-hexenoic Acid, p-Methoxyanilide (26). To a stirred solution of protected alcohol **25** (2.10 g, 6.58 mmol) in MeOH (40 mL) was added p-toluenesulfonic acid (125 mg, 0.66 mmol) at rt. After 3 h, the reaction was quenched with saturated $NaHCO_3$(aq). Methanol was evaporated under reduced pressure, followed by extraction with EtOAc, drying ($MgSO_4$), filtration and concentration, to obtain the crude product. Silica gel chromatography (EtOAc) afforded pure **26** (1.45 g, 94%) as a colorless solid, mp 78-80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37-2.41 (m, 2H), 2.46 (app q, *J* = 7 Hz, 2H), 3.12 (brs, 1H), 3.73 (s, 3H), 4.14 (d, *J*= 7 Hz, 2H), 5.46-5.53 (m, 1H), 5.66-5.72 (m, 1H), 6.78 (d, *J* = 9 Hz, 2H), 7.36 (d, *J* = 9 Hz, 2H), 7.91 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 36.4, 55.4, 57.8,, 114.0, 121.9, 129.9, 130.8, 131.0, 156.3, 170.9; HRMS (FAB, 3-NOBA) calcd for $C_{13}H_{17}O_3N$ ($M+H^+$) 236.1288, obsd 236.1286.

(4Z)-6-Ethoxycarbonyloxy-4-hexenoic Acid, p-Methoxyanilide (19). To a stirred solution of alcohol (1.30 g, 5.52 mmol) in CH_2Cl_2 (20 mL) and pyridine (3 mL) was added ethyl chloroformate (0.79 mL, 8.29 mmol), slowly at 0 °C over 10 min. The reaction mixture was allowed to warm to rt and stirred for 4 h. Dilution with ether was followed by washing, sequentially, with 1N HCl and brine, drying ($MgSO_4$), filtration and concentration. Purification by flash chromatography (30→40% EtOAc-hexane) afforded **19** (1.25 g, 74%) as a solid, mp 55-56 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27

(t, J = 7 Hz, 3H), 2.37 (t, J = 7 Hz, 2H), 2.51 (app q, J = 7 Hz, 2H), 3.75 (s, 3H), 4.16 (q, J = 7 Hz, 2H), 4.68 (d, J = 7 Hz, 2H), 5.56-5.63 (m, 1H), 5.65-5.71 (m, 1H), 6.80 (d, J = 9 Hz, 2H), 7.37 (d, J = 9 Hz, 2H), 7.59 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 23.6, 36.8, 55.4, 63.1, 64.0, 114.0, 121.8, 124.3, 131.0, 133.7, 155.1, 156.3, 170.1; HRMS (FAB, 3-NOBA) calcd for $C_{16}H_{21}O_5N$ ($M+H^+$) 308.1501, obsd 308.1504.

Ni(0)-Mediated Asymmetric Allylic Aminations

N-(p-Methoxyphenyl)-4-vinyl-2-oxazolidinone (2): *Small Scale*. A solution of $Ni(cod)_2$ (2.8 mg, 10 μmol) and (*S*) MeO-BIPHEP (12 mg, 20 μmol) in THF (1 mL) was stirred for 30 min, followed by addition of **1** (31 mg, 0.10 mmol) in THF (0.5 mL), slowly, via syringe. After 4 h, the reaction was quenched with saturated NH_4Cl (aq) followed by extraction (3 x) with ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by SiO_2 flash chromatography (30% EtOAc-hexane) gave **2** (19 mg, 86%, 74% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 4.07 (dd, J = 7, 9 Hz, 1H), 4.55 (t, J = 9 Hz, 1H), 4.71-4.77 (m, 1H), 5.27 (d, J = 10 Hz, 1H), 5.29 (d, J = 15 Hz, 1H), 5.76 (ddd, J = 7, 10. 15 Hz, 1H), 6.87 (d, J = 9 Hz, 2H), 7.27 (d, J =. 9 Hz, 2H). The ee was determined by chiral HPLC (Chiralcel OD; 2-propanol/hexane (4:1); 1mL/min)

N-(p-Methoxyphenyl)-4-vinyl-2-oxazolidinone (2): *Larger Scale*. Following the same protocol described above for the synthesis of **2**, a thirteen-fold scale-up was performed. Thus, starting from (400 mg, 1.30 mmol), $Ni(cod)_2$ (36 mg, 0.13 mmol), (*R*)-MeO-BIPHEP (152 mg, 0.26 mmol) was obtained after 6 h, cyclization product **2** (250 mg, 88%, 75% ee). This compound was recrystallized from ether-hexane with a few drops of CH_2Cl_2, followed by addition of a seed crystal to give **2** (181 mg, 64% overall, 97% ee). A second recrystallization from the same solvent system gave scalemic (*S*)-(2) (127 mg, 45%), mp 85 °C; $[\alpha]^{23}_D$ (>99% ee) –1.0 ($CHCl_3$, *c* 3.4). For chiral HPLC traces of the initial product and of the first and second crops from the recrystallization, see below.

N-(o-Methoxyphenyl)-4-vinyl-2-oxazolidinone (27). To a solution of $Ni(cod)_2$ (2.8 mg, 10 μmol) and (*S*)-MeO-BIPHEP (11.6 mg, 20 μmol) in THF (1 mL) that had been stirred for 30 min was added **23** (31.0 mg, 100 μmol) in THF (0.5 mL), via cannula. The reaction mixture was stirred overnight at rt and quenched with saturated NH_4Cl (aq), followed by extraction (3x) with ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography over SiO_2 (30% EtOAc-hexane) gave **27** (10 mg, 79% based on recovered starting material, 64% ee by chiral HPLC – *vide infra*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 4.11 (app t, J = 8 Hz, 1H), 4.60 (t, J = 9 Hz, 1H), 4.78 (app q, J = 8 Hz, 1H), 5.13 (d, J = 11 Hz, 1H), 5.14 (d, J = 17 Hz, 1H), 5.73 (ddd, J = 9, 11, 17 Hz, 1H), 6.92-6.97 (m, 2H), 7.21 (dd, J = 2, 8 Hz,

1H), 7.27-7.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 60.9, 67.6, 76.7, 111.9, 120.7, 120.8, 124.5, 129.2, 130.0, 134.9, 155.3, 157.0; HRMS (FAB, 3-NOBA) calcd for $C_{12}H_{13}NO_3$, (M+H$^+$) 220.0975, obsd 220.0969.

N-(3',4',5'-Trimethoxyphenyl)-4-vinyl-2-oxazolidinone (28). To a solution of $Ni(cod)_2$ (2.8 mg, 10 μmol) and (*S*)-MeO-BIPHEP (11.6 mg, 20 μmol) in THF (1 mL) that had been stirred for 30 min was added **24** (37 mg, 100 μmol) in THF (0.5 mL), via cannula. The reaction mixture was stirred for 4 h at rt and quenched with saturated NH_4Cl (aq) followed by extraction with ether. The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography over SiO_2 (40% EtOAc-hexane) gave **28** (23 mg, 83%): $[\alpha]^{23}_D$ (67% ee) +2.6 ($CHCl_3$, *c* 2.0); $[\alpha]^{23}_D$ (calcd for 100% ee) + 4.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.82 (s, 6H), 4.09 (dd, *J* = 6, 9 Hz, 1H), 4.57 (t, *J* = 9 Hz, 1H), 4.77 (app q, *J* = 8 Hz, 1H), 5.34 (d, *J*= 10 Hz, 1H), 5.37 (d, *J* = 17 Hz, 1H), 5.83 (ddd, *J* = 8, 10, 17 Hz, 1H), 6.68 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.1, 60.2, 60.8, 66.9, 99.6, 120.4, 132.8, 135.1, 135.4, 153.2, 155.6; HRMS (FAB, 3-NOBA) calcd for $C_{14}H_{17}NO_5$ (M+H$^+$) 280.1187, obsd 280.1184.

(5*S*)-N-p-Methoxyphenyl-5-vinylpyrrolidin-2-one (20). To a solution of $Ni(cod)_2$ (2.8 mg, 10 μmol) and (*R,R*)-Me-DUPHOS (5.9 mg, 20 μmol) that had been stirred for 30 min in THF (1 mL) was added **19** (31 mg, 100 μmol) in THF (0.5 mL), via syringe. Then, LiHMDS (0.1 mL of a 1.0 M solution in hexane; 0.1 mmol,) was slowly added, via syringe. The reaction mixture was stirred for 24 h and quenched with saturated NH_4Cl (aq), followed by extraction (3x) with ether. The combined organic layers were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (40→50% EtOAc-hexane) gave pure **20** (20 mg, 93%) as an oil: $[\alpha]^{23}_D$ (66% ee) – 11.5 ($CHCl_3$, *c* 0.10); $[\alpha]^{23}_D$ (calcd for 100% ee) - 17.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84-1.93 (m, 1H), 2.32-2.42 (m, 1H), 2.51 (ddd, *J* = 7, 9, 16 Hz, 1H), 2.62 (ddd, *J* = 7, 9, 17 Hz, 1H), 3.77 (s, 3H), 4.53-4.58 (m, 1H), 5.14 (dd, *J* = 11, 17 Hz, 2H), 5.72 (ddd, *J* = 8, 10, 17 Hz, 1H), 6.87 (d, *J* = 9 Hz, 2H), 7.29 (d, *J* = 9 Hz, 2H), 7.59 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 30.9, 55.4, 63.2, 114, 117.5, 125.0, 130.8, 137.6, 157.2, 174.3; HRMS (FAB, 3-NOBA) calcd for $C_{13}H_{15}O_2N$ (M+H$^+$) 218.1183, obsd 218.1176.

Elaboration of (-)-2 to L-Vinylglycine

(*4S*)-Vinyl-2-oxazolidinone (29). To a stirred solution of **2** (400 mg, 1.83 mmol) in acetonitrile (36 mL) was added CAN (3.0 g, 5.5 mmol) in water (18 mL), dropwise, via syringe at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then quenched with saturated aqueous sodium sulfite followed by extraction (3x) with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered and concentrated, in vacuo. Crude product was purified by SiO_2 flash chromatography (40-50% EtOAc-hexane) to give **29** (156 mg, 75%) as a colorless oil: $[\alpha]^{23}_D$ –24.7 ($CHCl_3$, *c* 1.16); Lit.[4] $[\alpha]^{20}_D$ –17.6 ($CHCl_3$, *c* 1.0); 2nd Lit.[5] $[\alpha]^{28}_D$ –26.2 ($CHCl_3$, *c* 1.03). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (dd, *J* = 7, 9 Hz, 1H), 4.34-4.40 (m, 1H), 4.52 (app t, *J* = 9 Hz, 1H), 5.22 (dt, *J* = 1, 10 Hz, 1H), 5.29 (dt, *J* = 1, 17 Hz), 5.80 (ddd, *J* = 7, 10, 17 Hz, 1H), 6.17 (br s, 1H).

N-(tert-Butoxycarbonyl)-(*4S*)-vinyl-2-oxazolidinone (30). To a solution of vinyl oxazolidinone **29** (134 mg, 1.18 mmol) in CH_2Cl_2 (10 mL) and Et_3N (0.25 mL, 1.77 mmol) was added a solution of Boc_2O (775 mg, 3.58 mmol) in CH_2Cl_2 (5 mL) at rt. The reaction mixture was stirred for 60 h. The reaction was quenched with H_2O (10 mL) and extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash chromatography over SiO_2 (20% EtOAc-hexane) to afford **30**[2] (212 mg, 84%) as a colorless oil: $[\alpha]^{23}_D$ +5.9 ($CHCl_3$, *c* 1.82). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 4.01 (dd, *J* = 4, 9 Hz, 1H), 4.41 (app t, *J* = 9Hz, 1H), 4.69 (dt, *J* = 4, 8 Hz, 1H), 5.30 (d, *J* = 11 Hz, 1H), 5.31 (d, *J* = 17 Hz, 1H), 5.85 (ddd, *J* = 8, 10, 17 Hz, 1H).

N-(tert-Butoxycarbonyl)-(*4S*)-vinylglycinol (21). To a stirred solution of **30** (176 mg, 0.83 mmol) in MeOH (8 mL) was added Cs_2CO_3 (54 mg, 0.17 mmol). The reaction mixture was stirred for 1.5 h, quenched with saturated NH_4Cl (aq), followed by removal of MeOH, and partitioning into CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and evaporated. Flash chromatography (30% EtOAc-hexane) afforded **21** (118 mg, 77%) as a colorless oil: $[\alpha]^{23}_D$ -28.4 ($CHCl_3$, *c* 1.37); Lit.[6] $[\alpha]_D$ –29 ($CHCl_3$, *c* 2.5); 2nd Lit.[7] $[\alpha]_D$ –30.5 ($CHCl_3$, *c* 1.03). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.36 (br s, 1H), 3.60 (dd, *J* = 6, 11 Hz, 1H), 3.69 (dd, *J* = 4, 11 Hz, 1H), 4.22 (br s, 1H), 4.92 (br s, 1H), 5.21 (d, *J* = 11 Hz, 1H), 5.25 (d, *J* = 17 Hz, 1H), 5.79 (ddd, *J* = 5, 11, 17 Hz, 1H).

N-(tert-Butoxycarbonyl)-(*4S*)-vinylglycine (31). To a stirred solution of **21** (110 mg, 0.59 mmol), in acetone (5 mL) was added Jones reagent (4 M, 0.4 mL), slowly at 0 °C, over 10 min. The reaction mixture was stirred for 3 h at rt and the excess Jones reagent quenched with excess *i*-PrOH. The solvent was evaporated, and the residue dissolved in water, and extracted with EtOAc. The organic phase was again extracted with saturated Na_2CO_3 (aq). Acidification of the combined aqueous phases to pH 4 with AcOH,

followed by extraction with ethyl acetate, drying ($MgSO_4$), and removal of the solvent gave clean **31** (95 mg, 80%), as a colorless oil: $[\alpha]^{23}_D$ +2.8 (MeOH, *c* 2.25); Lit.[8] $[\alpha]^{25}_D$ +2.6 (MeOH, *c* 1.5); 2nd Lit.[9] $[\alpha]^{20}_D$ +2.8 (MeOH, *c* 4.0). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.38 (s, 9H), 4.51 (dd, *J* = 6, 7 Hz, 1H), 5.17 (d, *J* = 10 Hz, 1H), 5.29 (d, *J* = 17 Hz, 1H), 5.88 (ddd, *J* = 6, 10, 17 Hz, 1H), 7.31 (d, *J* = 8 Hz, 1H), 12.68 (br s, 1H).

L-α-Vinylglycine, Trifluoroacetate Salt (22). To a solution of Boc-protected vinylglycine **31** (50 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added excess trifluoroacetic acid (1.7 ml). After stirring 3 h at rt, water (10 mL) was added, followed by extraction with CH_2Cl_2 and ether. Evaporation of the aqueous layer, was followed, sequentially, by azeotropic drying with benzene, and then thorough drying with mild heating, in vacuo (P_2O_5 sidearm) to provide **22** (43 mg, 85%): $[\alpha]^{23}_D$ +47 (H_2O, *c* 2.15); Lit.[10] $[\alpha]^{24}_D$ + 42.8 (H_2O, *c* 1.1). ^{1}H NMR (400 MHz, D_2O) δ 4.46 (d, *J* = 7 Hz, 1H), 5.39 (dd, *J* = 1, 16 Hz, 1H), 5.43 (dd, *J* = 2, 12 Hz, 1H), 5.83 (ddd, *J* = 7, 10, 17 Hz, 1H).

References

1. This monocarbonate ester can be synthesized in 82% yield from (2Z)-butene-1,4-diol: Fernandez-Rivas, C.; Mendez, M.; Echavarren, A. M. *J. Am. Chem. Soc*. **2000**, *122*, 1221-1222.
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7. Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1701-1709.
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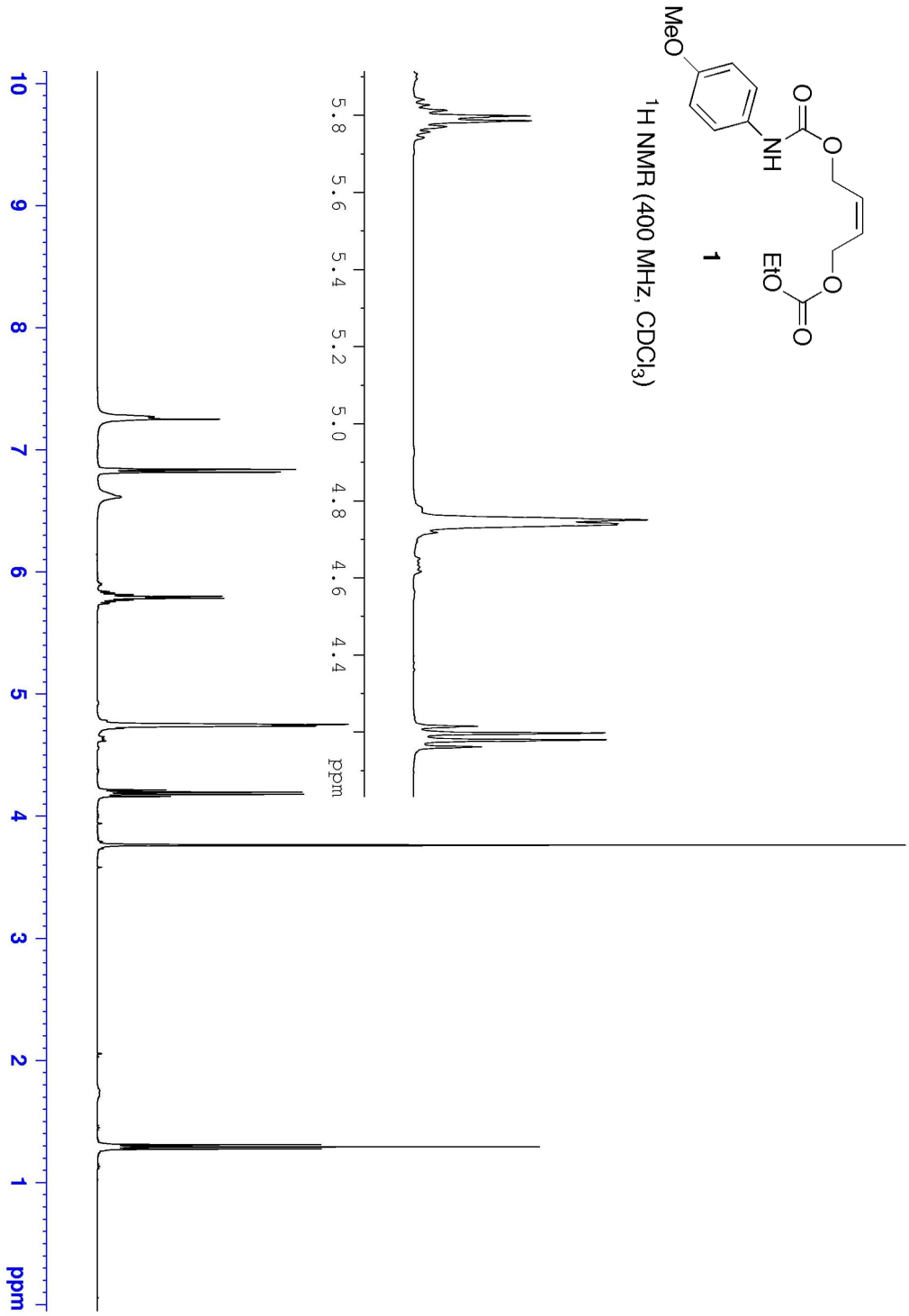
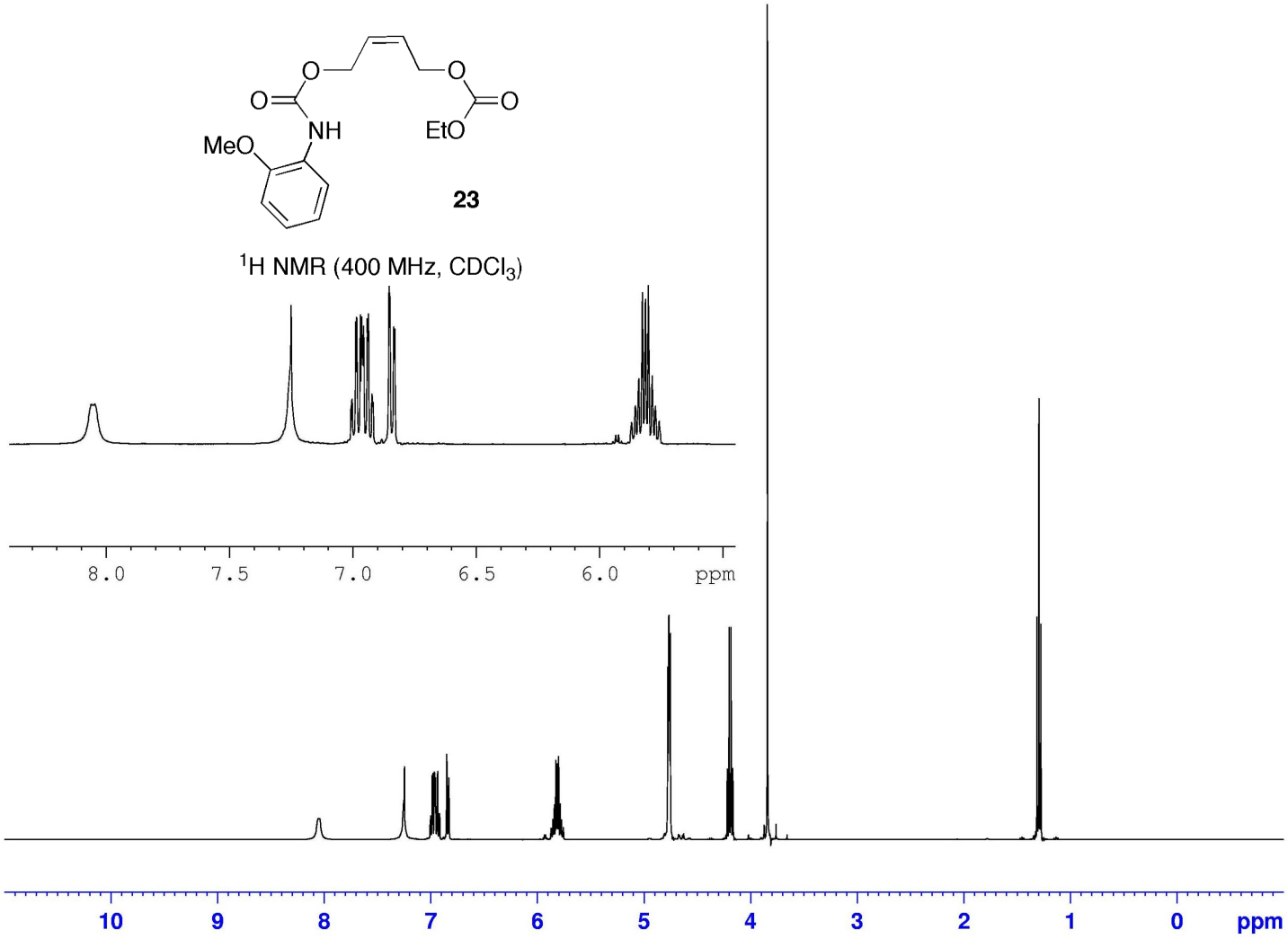
10. Berkowitz, D. B.; Smith, M. K. *Synthesis* **1996**, 39-41.

Spectral Data

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O
O
O
NH
EtO
MeO
23
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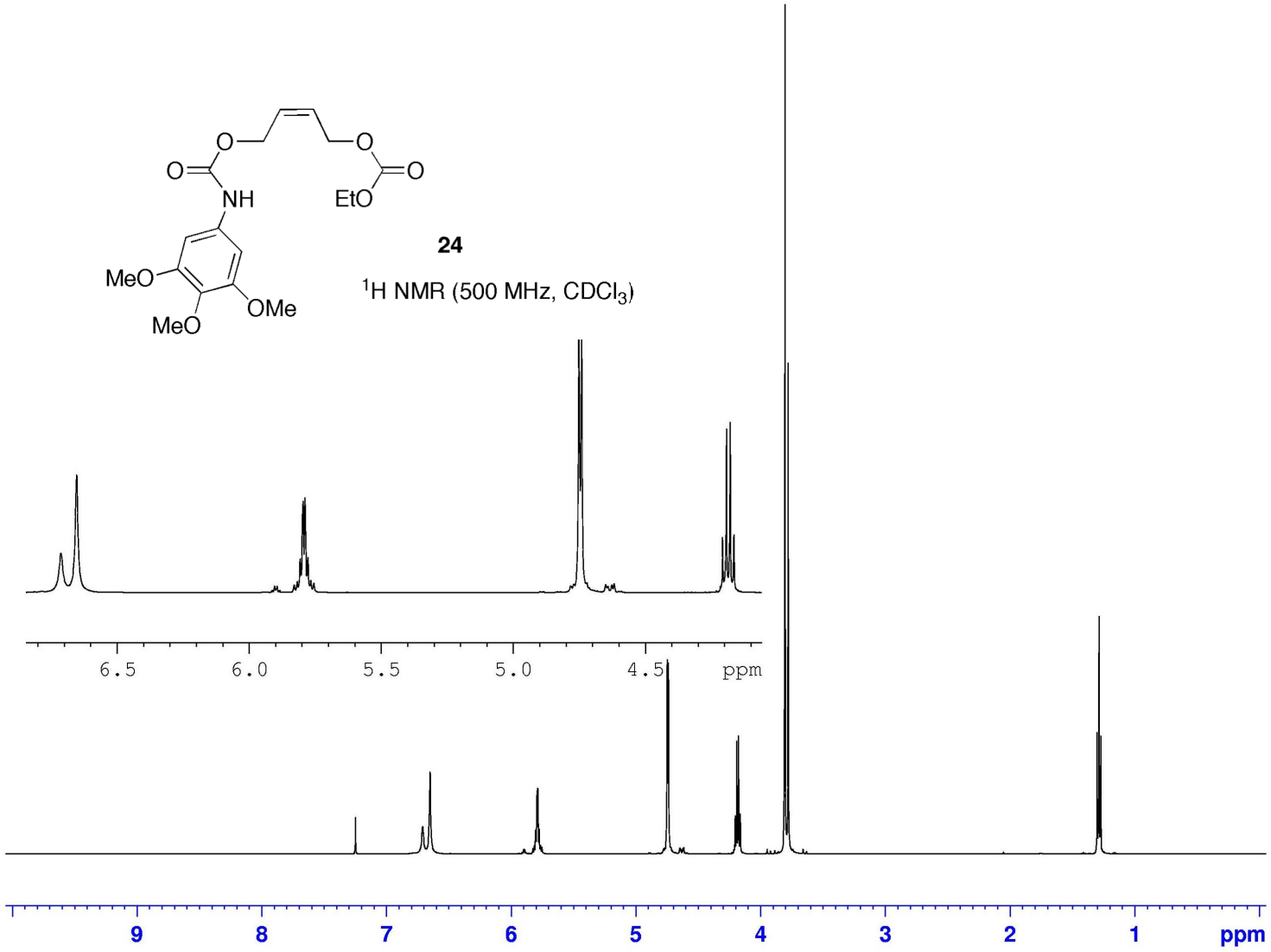
7.5
7.0
6.5
6.0
ppm
10
9
8
7
6
5
4
3
2
1
0
ppm


O
O
O
O
NH
EtO
MeO
MeO
OMe
24
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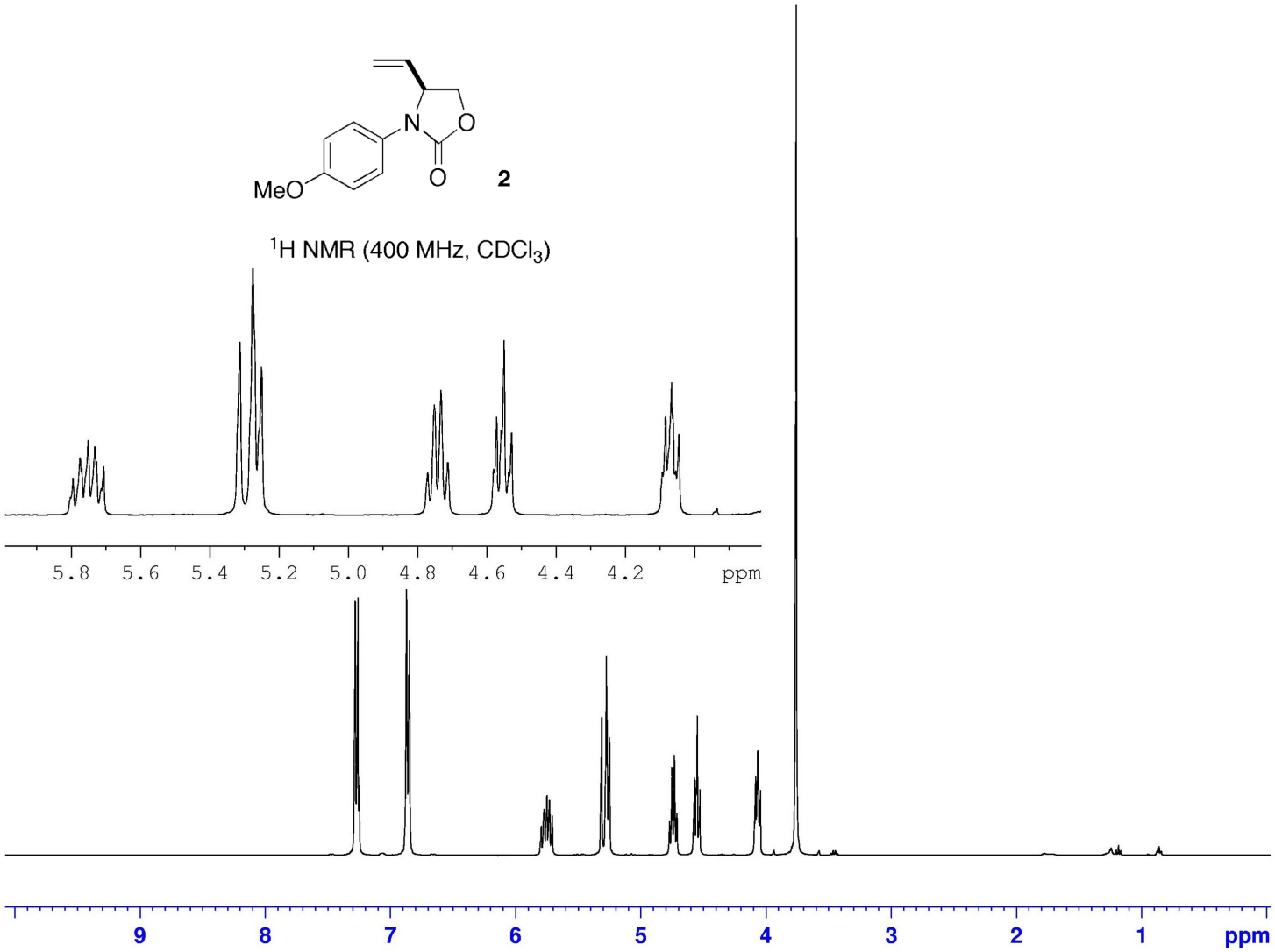
9
8
7
6
5
4
3
2
1
ppm


MeO
N
O
O
2
^{1}H NMR (400 MHz, $CDCl_3$)
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5.6
5.4
5.2
5.0
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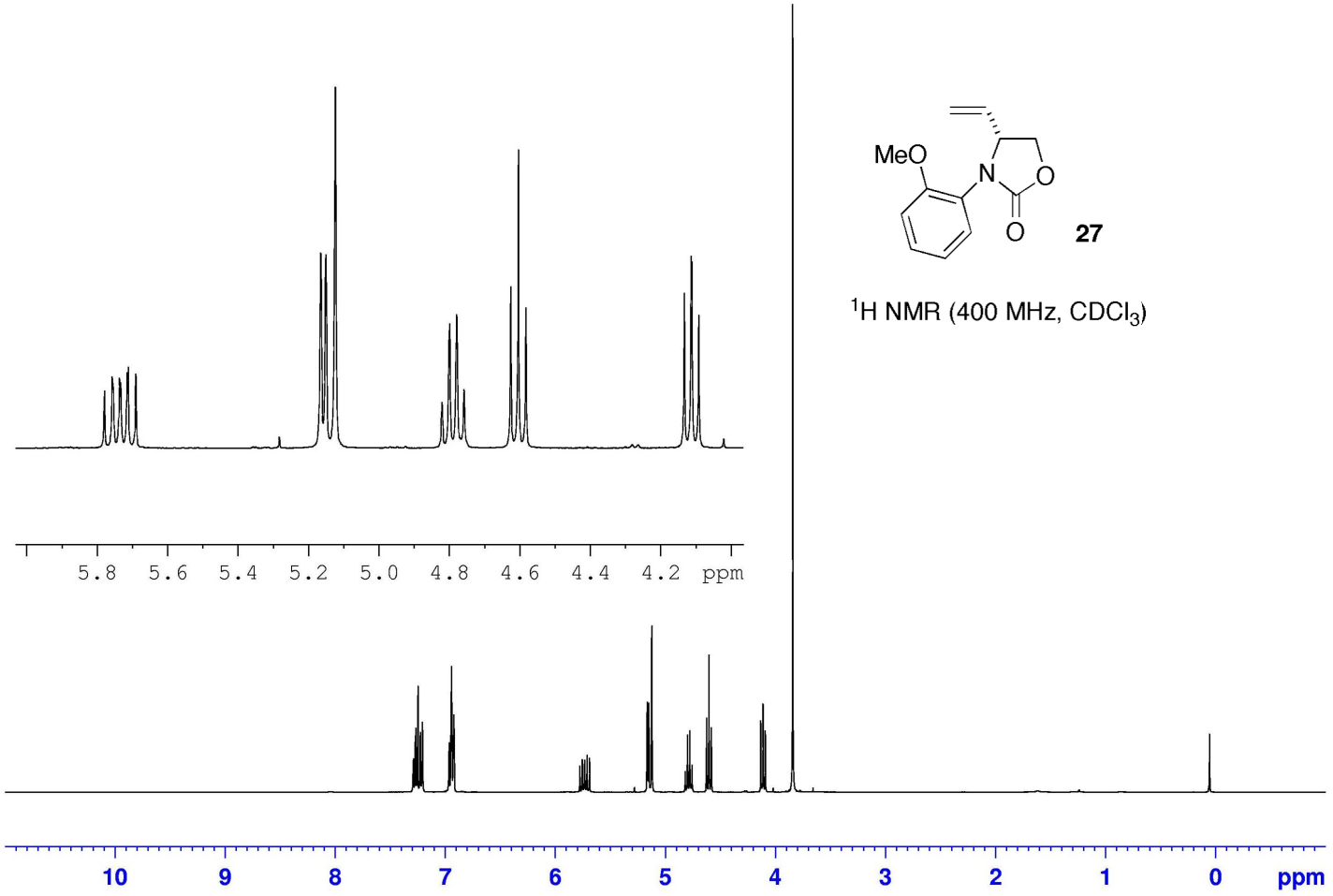
4.6
4.4
4.2
ppm
9
8
7
6
5
4
3
2
1
ppm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N
O
O
27
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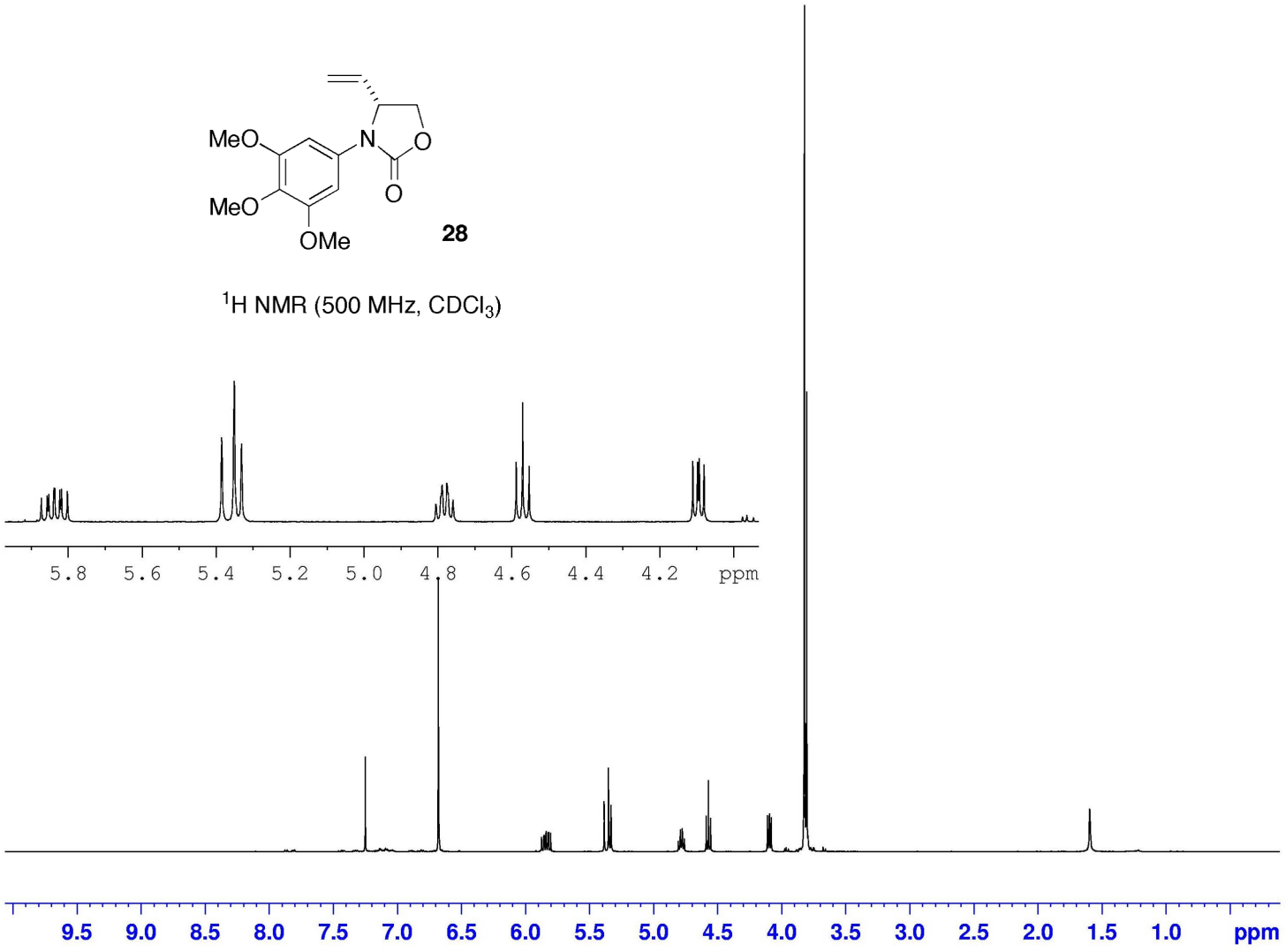
10 9 8 7 6 5 4 3 2 1 0 ppm


MeO
MeO
OMe
N
O
O
28
^{1}H NMR (500 MHz, $CDCl_3$)
5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 ppm
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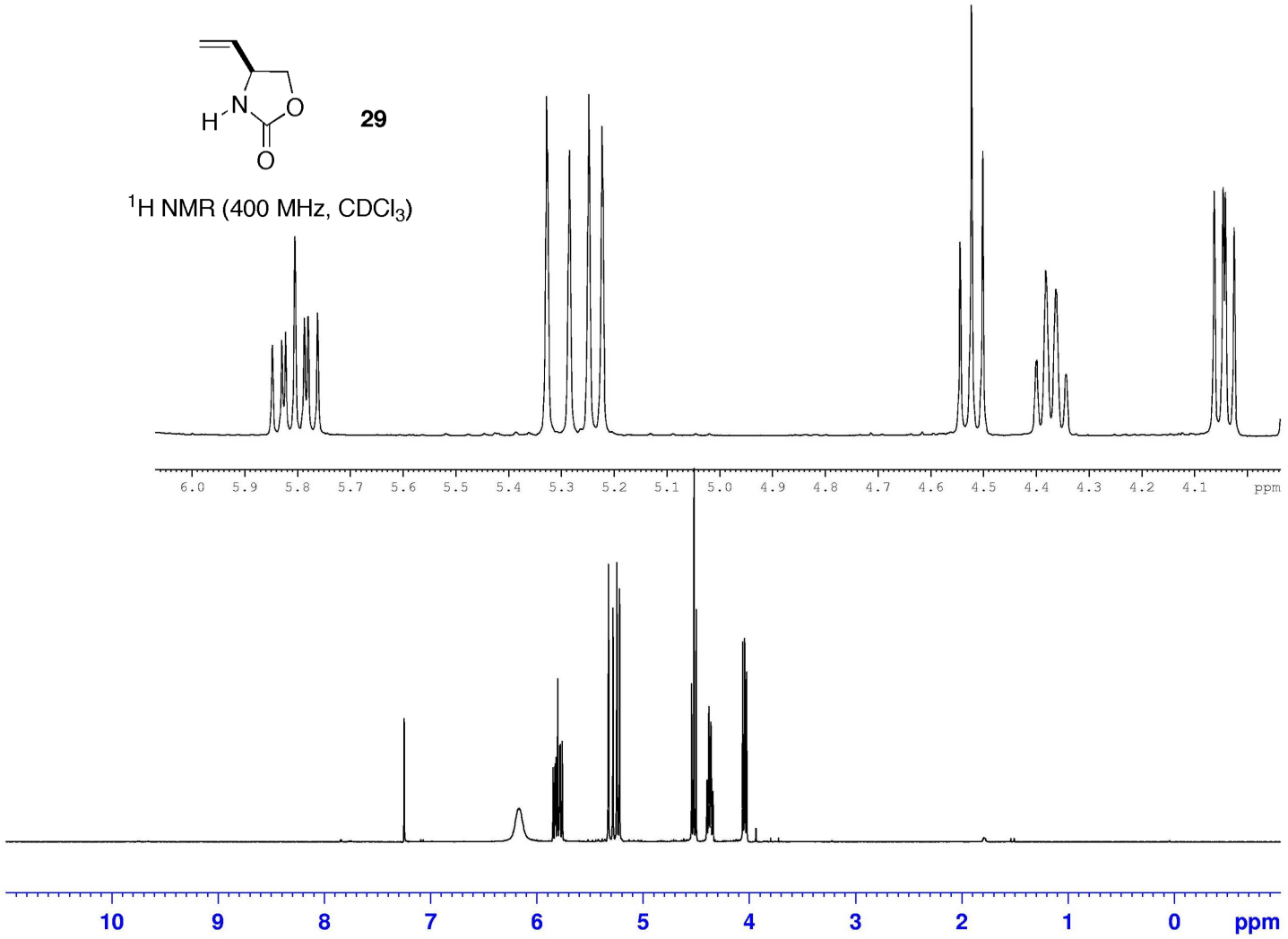
29
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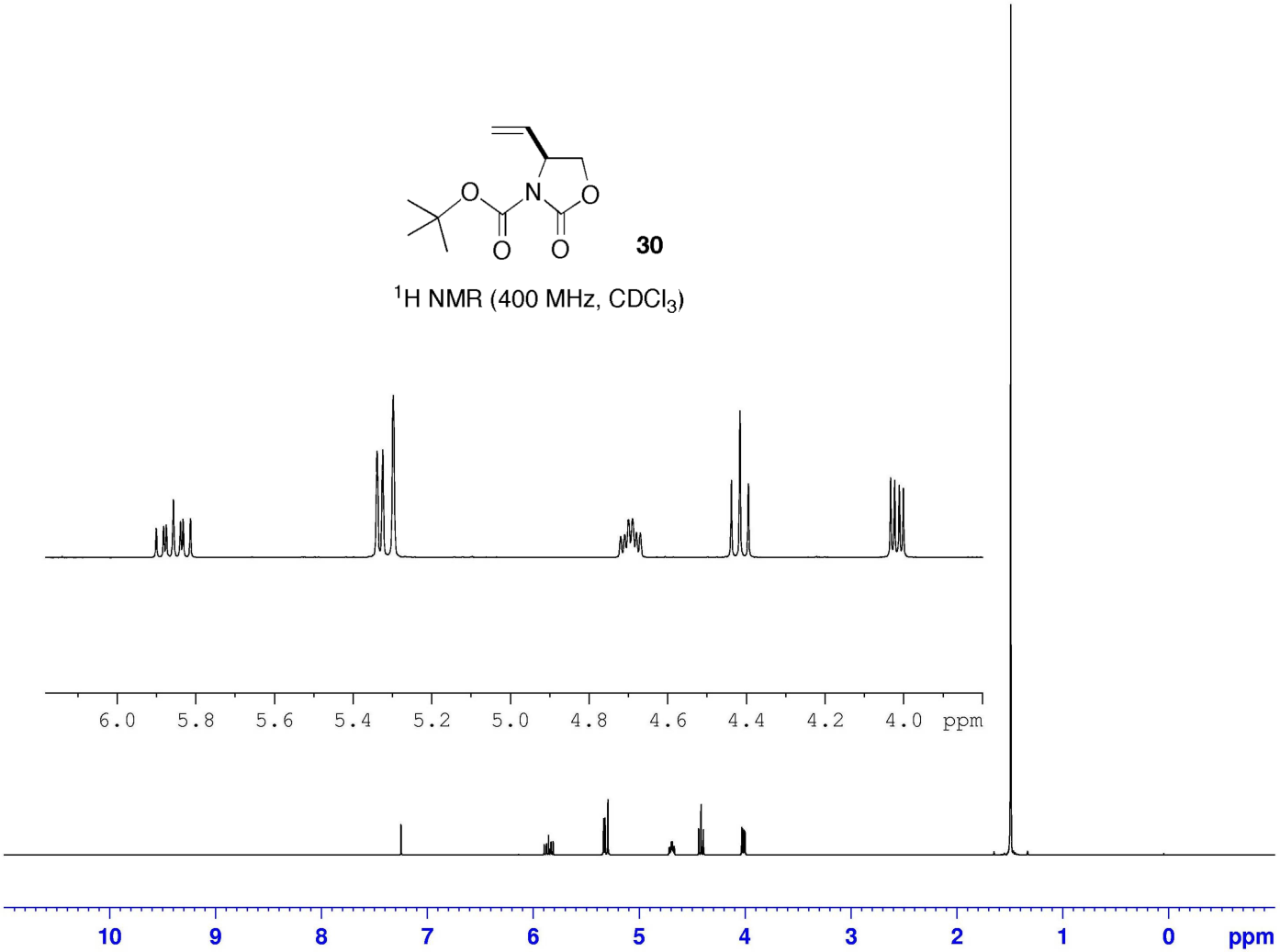
10 9 8 7 6 5 4 3 2 1 0 ppm


O
N
O
O
O
30
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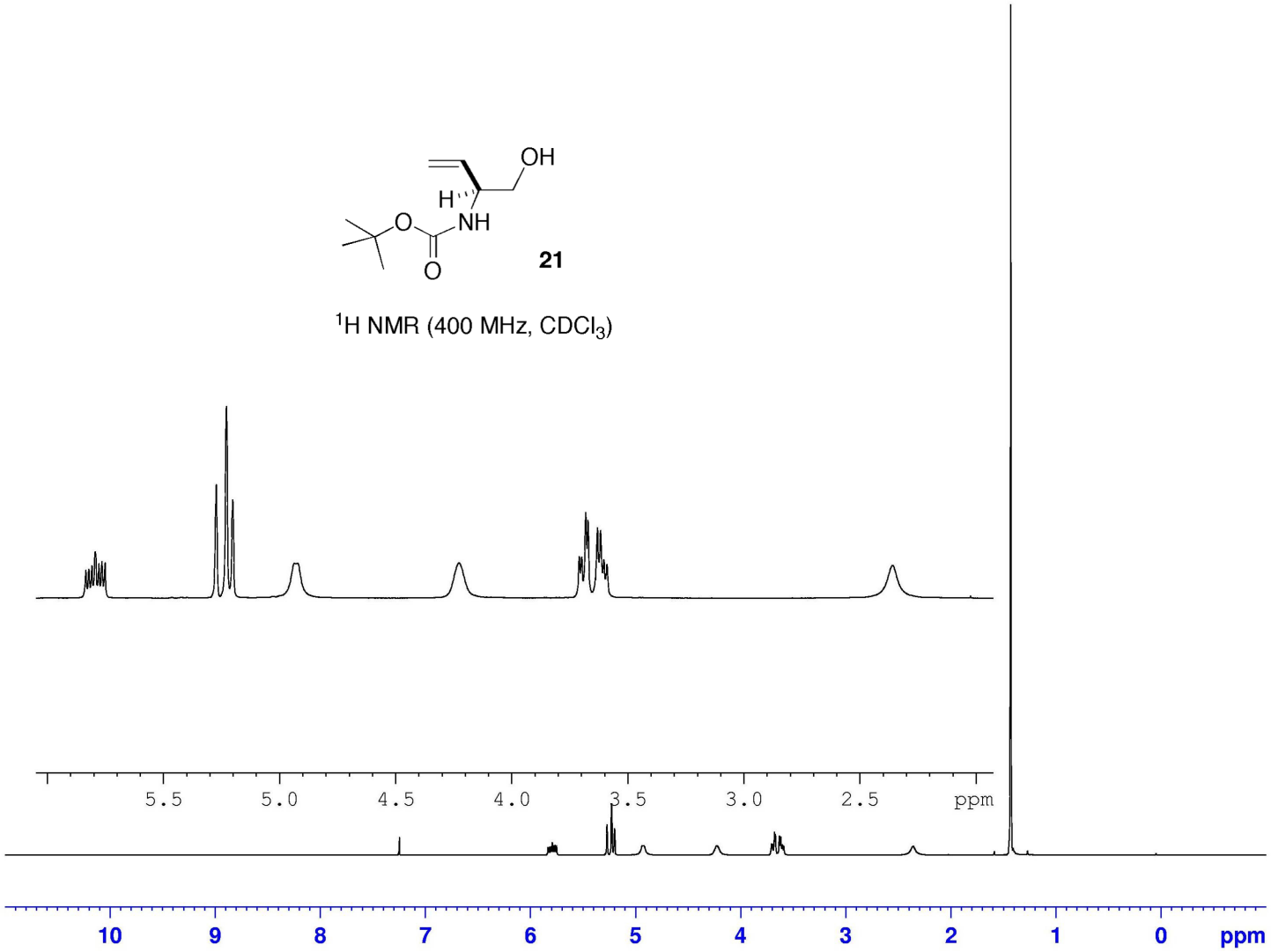
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
ppm
10
9
8
7
6
5
4
3
2
1
0
ppm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H
NH
O
O
21
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4.5
4.0
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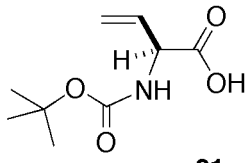
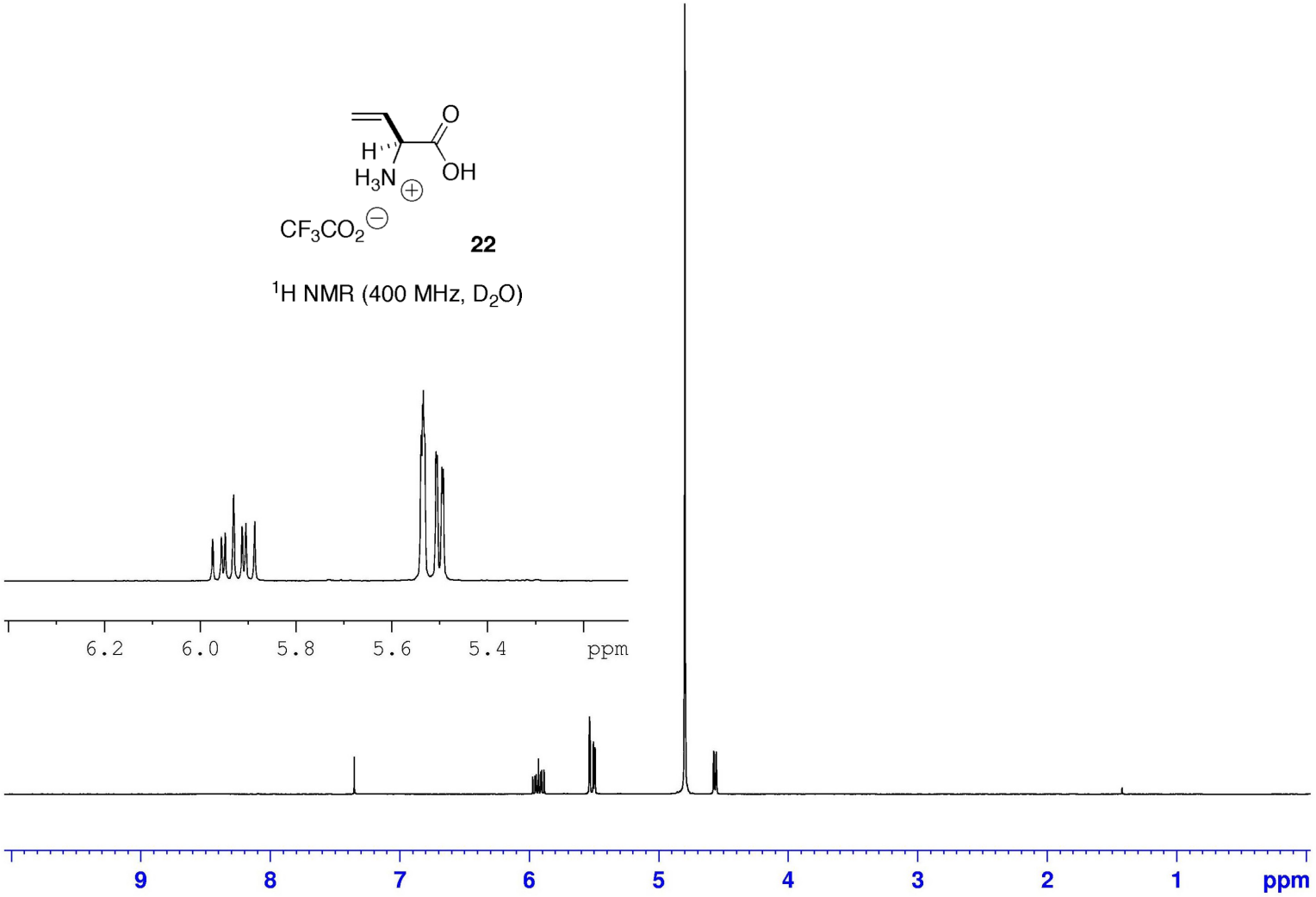
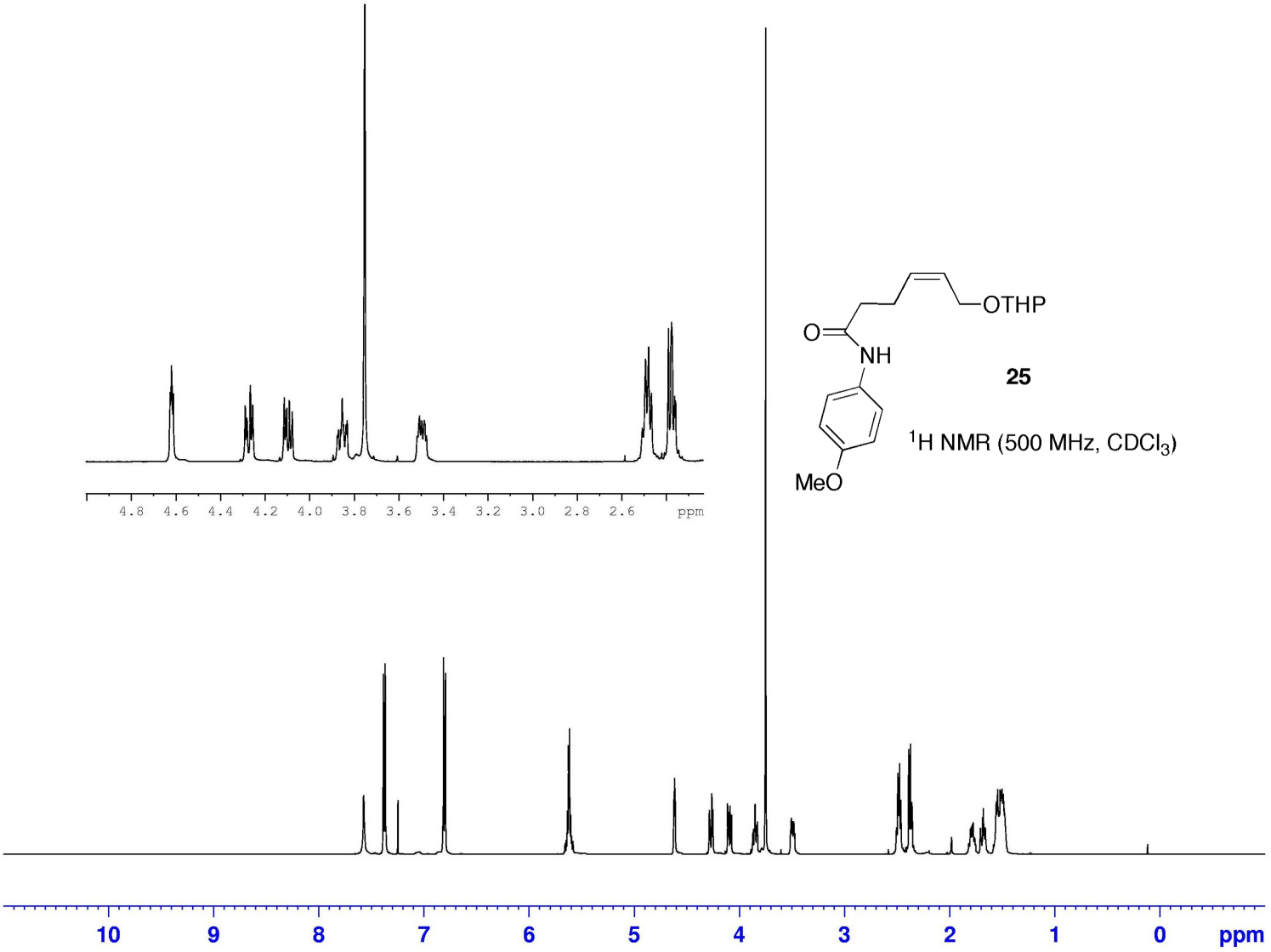
3.0
2.5
ppm
10
9
8
7
6
5
4
3
2
1
0
ppm



31

^{1}H NMR (500 MHz, DMSO-d_6)


O
H
H3N
OH
CF3CO2
22
1H NMR (400 MHz, D2O)
6.2
6.0
5.8
5.6
5.4
ppm
9
8
7
6
5
4
3
2
1
ppm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O
NH
MeO
25
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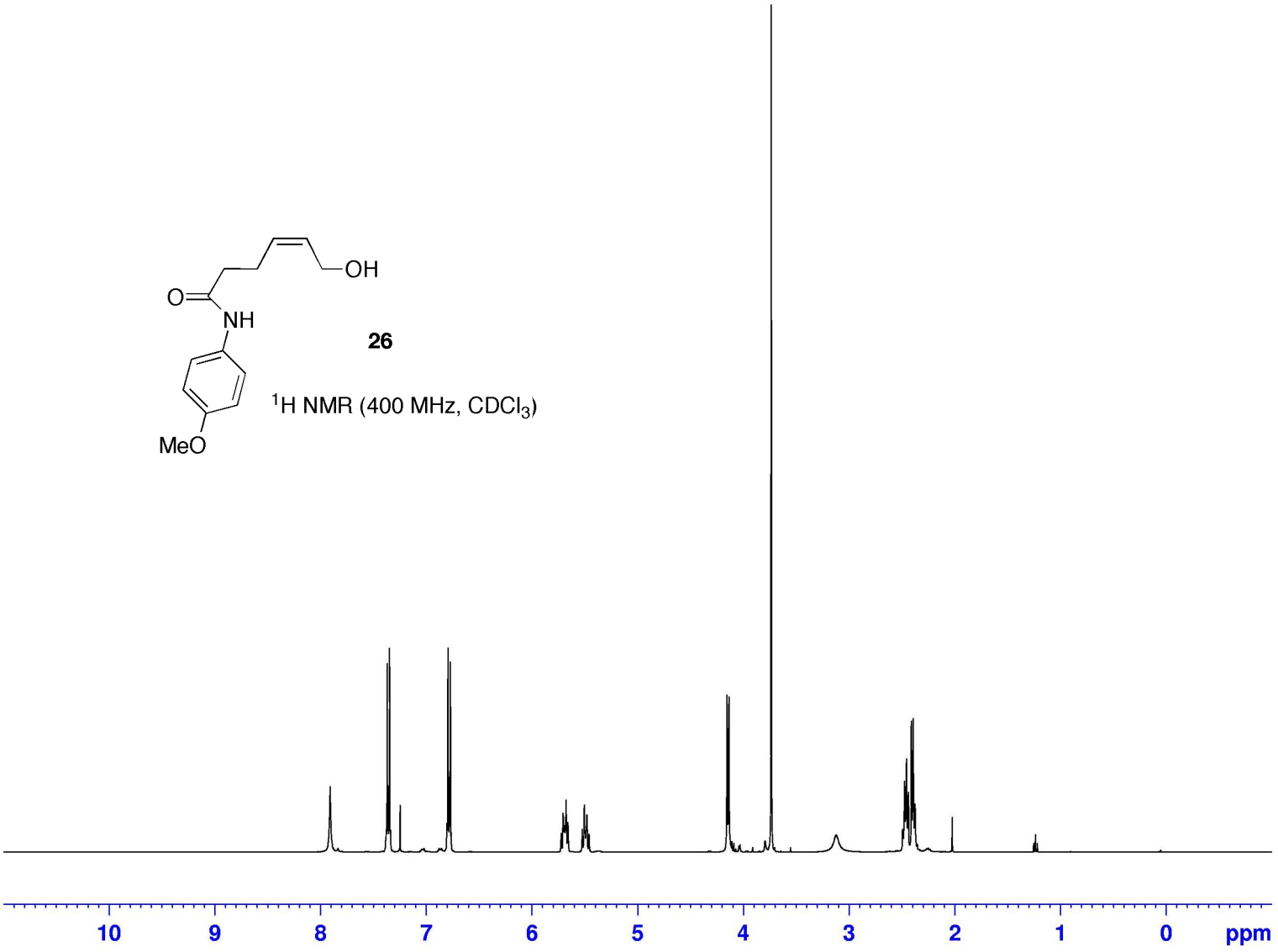
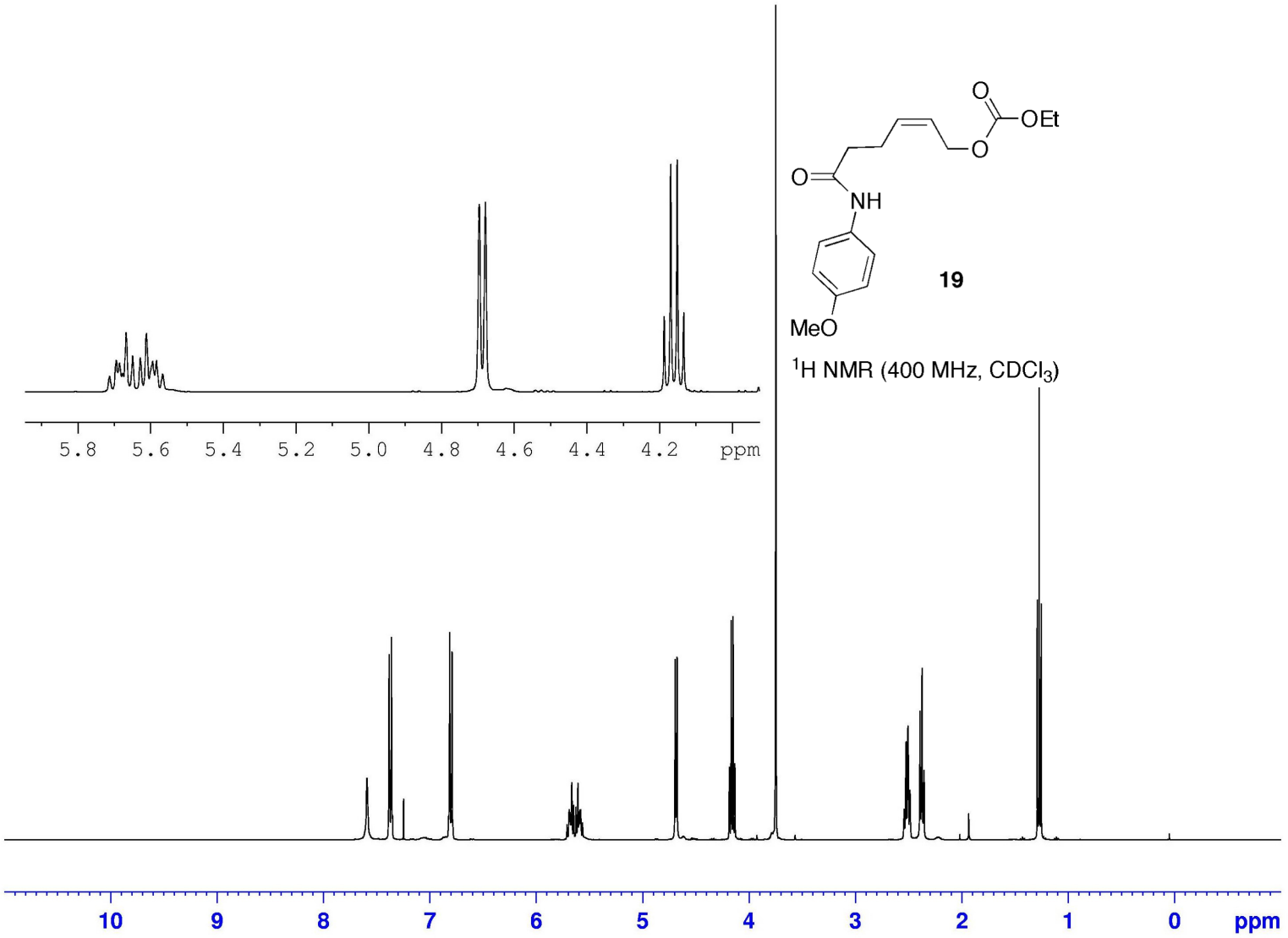
10 9 8 7 6 5 4 3 2 1 0 ppm



26

^{1}H NMR (400 MHz, $CDCl_3$)


O
OEt
O
O
NH
MeO
19
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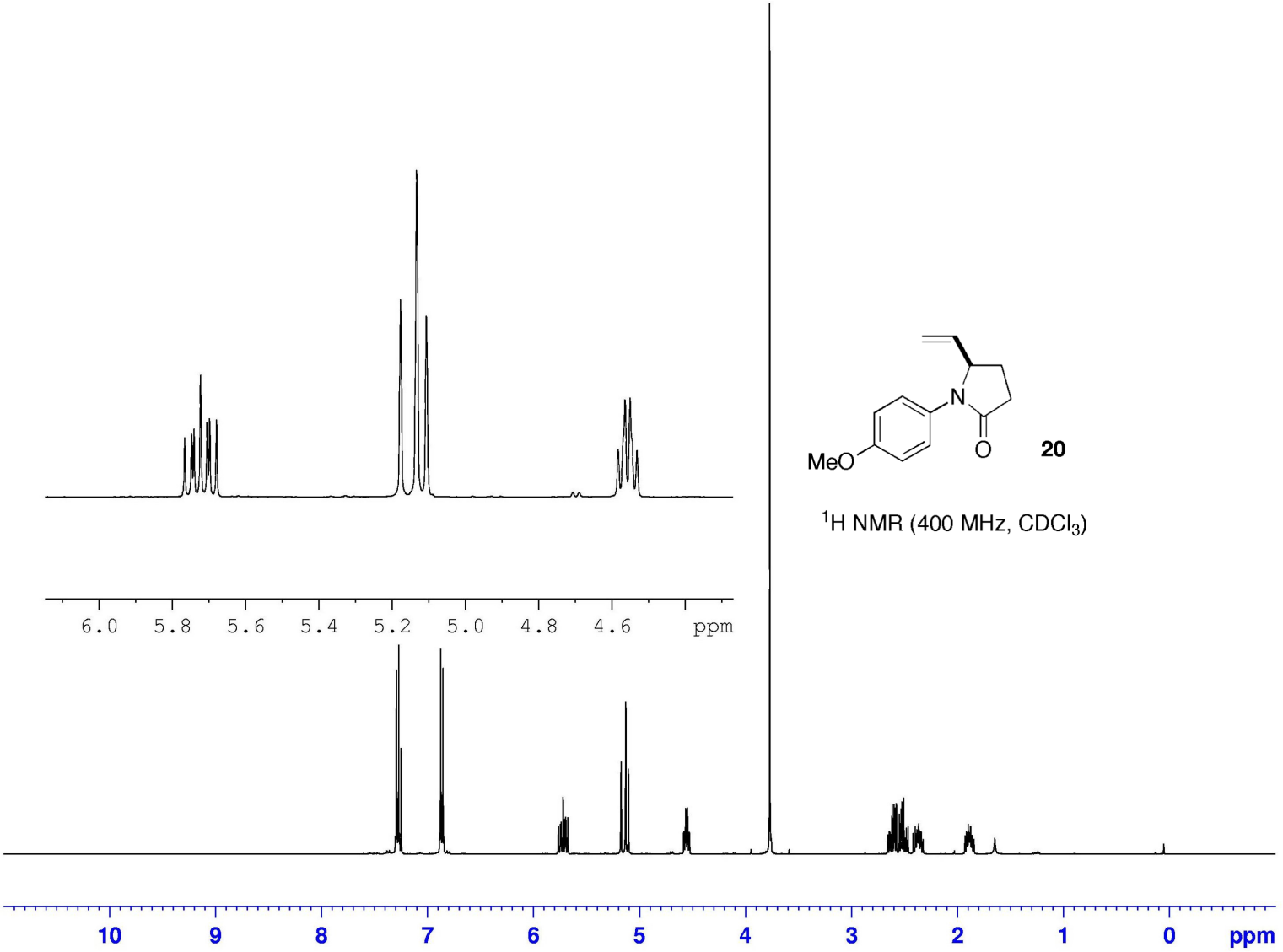
10 9 8 7 6 5 4 3 2 1 0 ppm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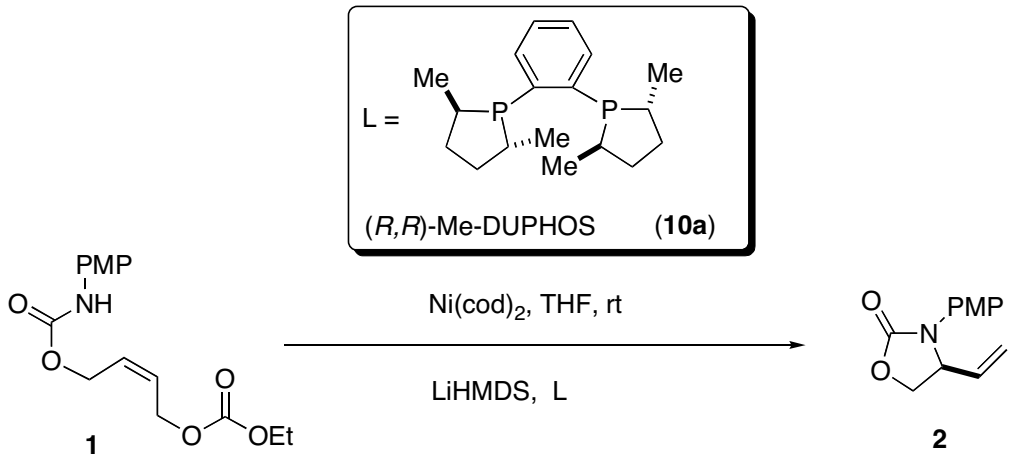
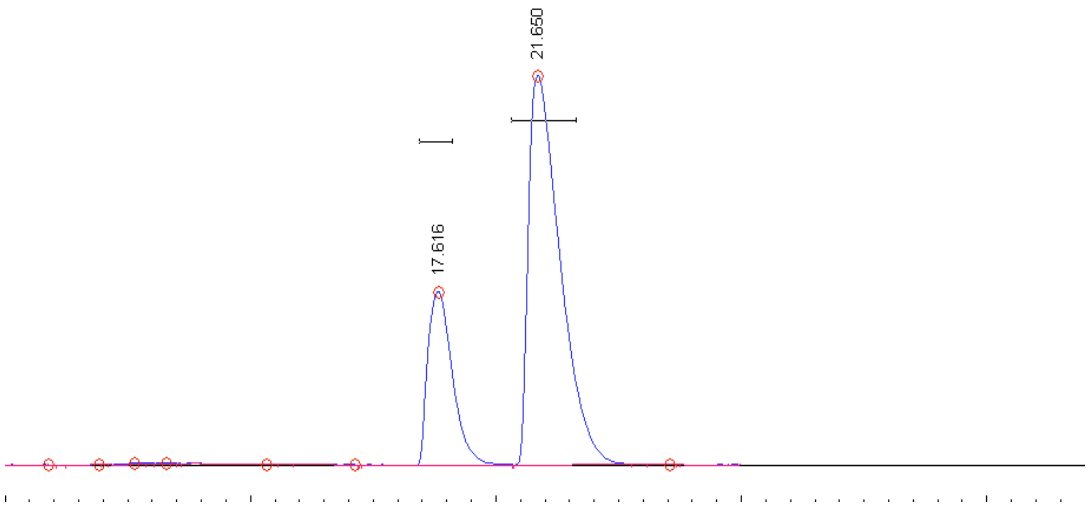
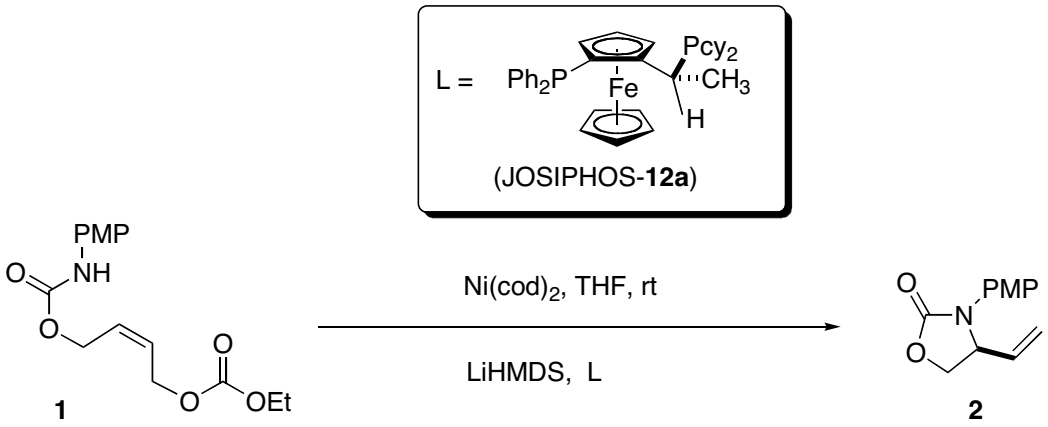
5.8
5.6
5.4
5.2
5.0
4.8
4.6
ppm
MeO
N
O
20
^{1}H NMR (400 MHz, $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
0
ppm

Representative Chiral HPLC Traces

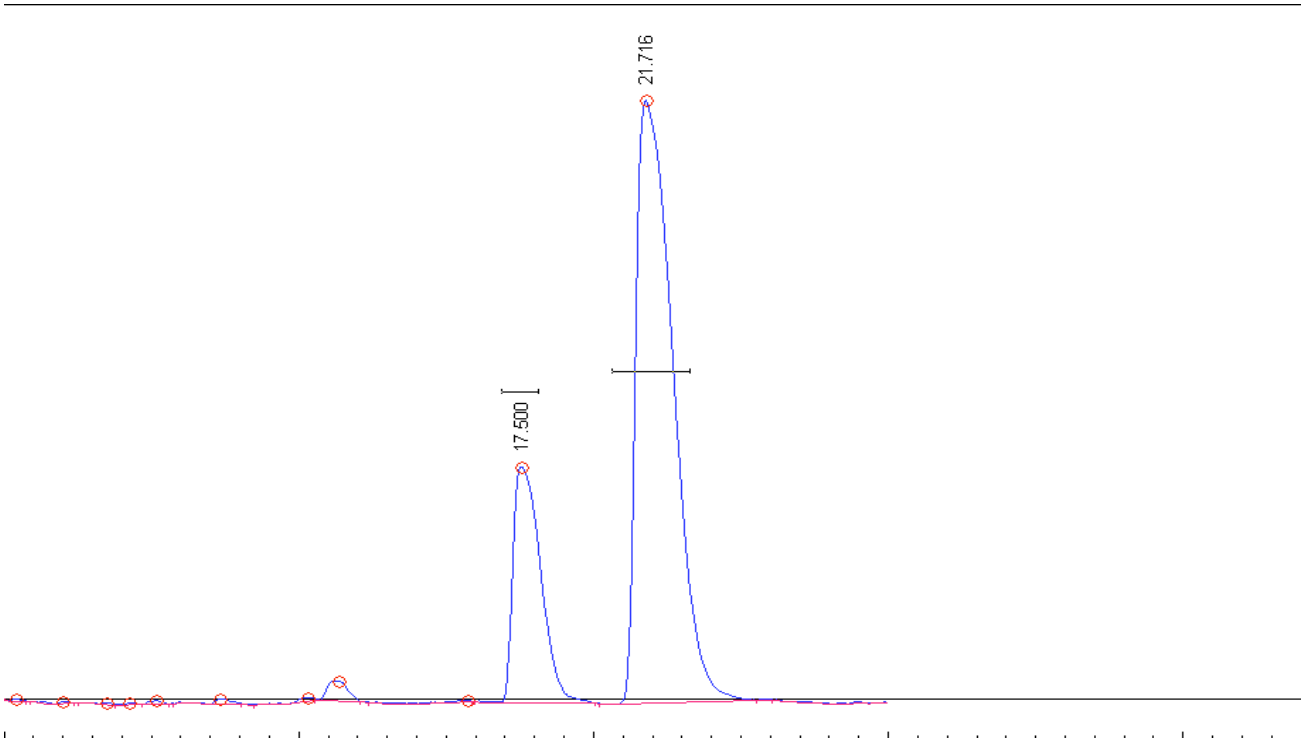


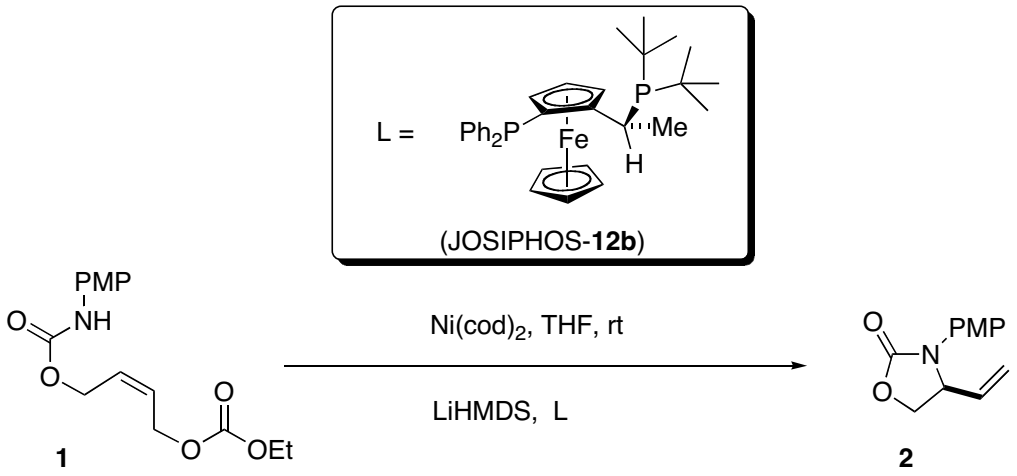
Solvent: *i*-PrOH/hexane (1:4) *Flow rate* = 1 mL/min
Retention time: 17.6 (*R*) and 21.7 (*S*)
Integration = 26:74 (48% ee)



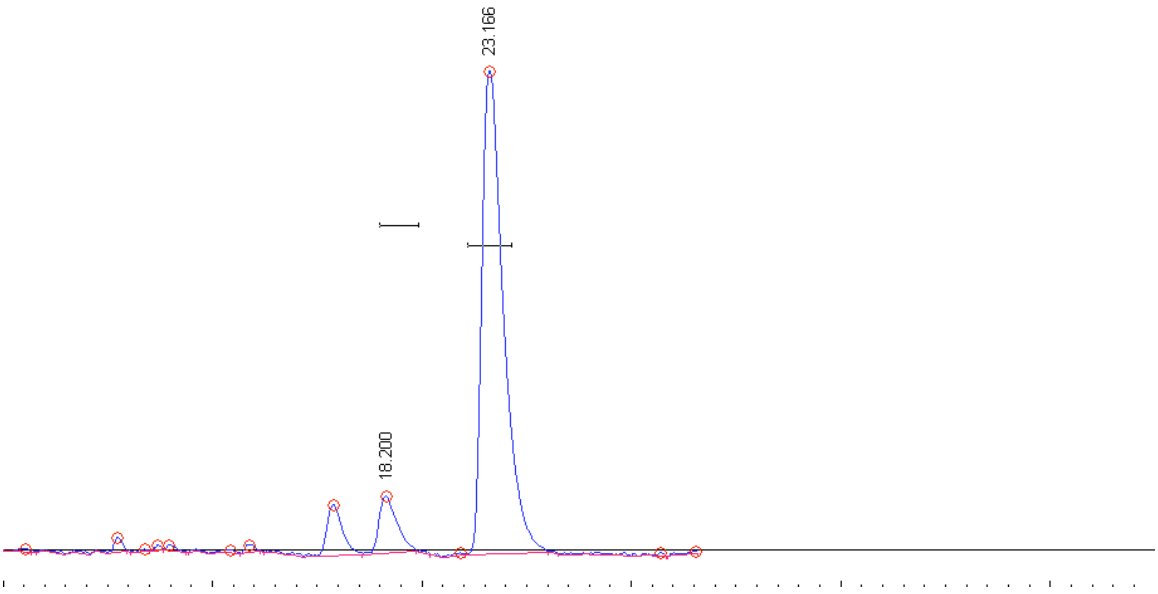


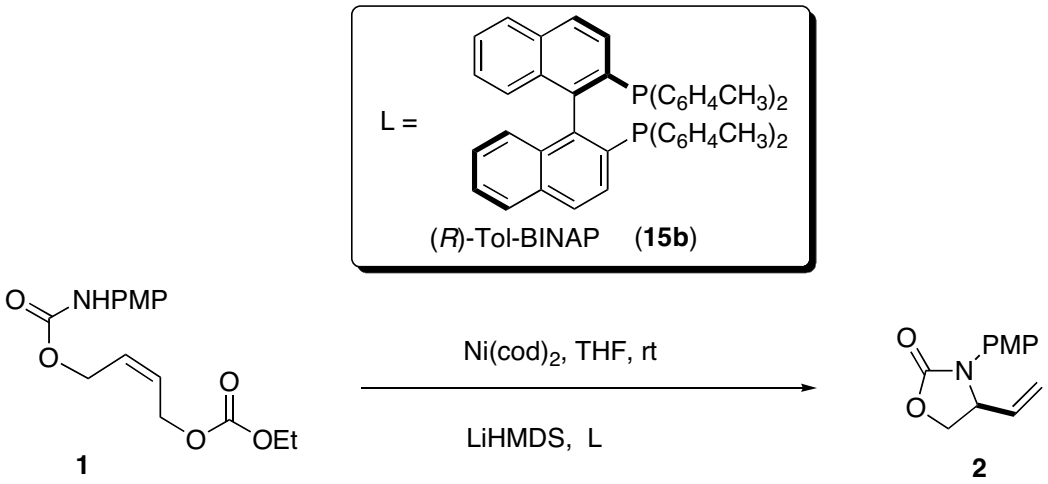
Solvent: *i*-PrOH/hexane (1:4) *Flow rate* = 1 mL/min
Retention time: 17.5 (*R*) and 21.7 (*S*)
Integration = 22:78 (56% ee)





Solvent: *i*-PrOH/hexane (1:4) *Flow rate*= 1 mL/min
Retention time: 18.2 (*R*) and 23.1 (*S*) min
Integration = 9:91 (82% ee)

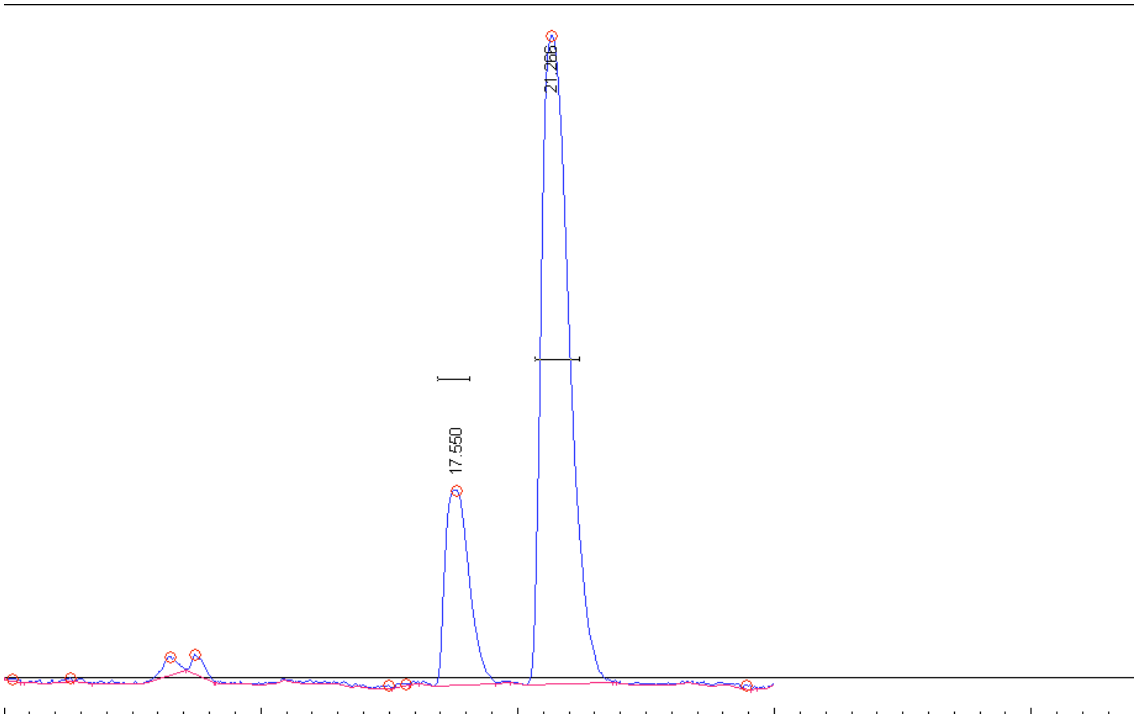


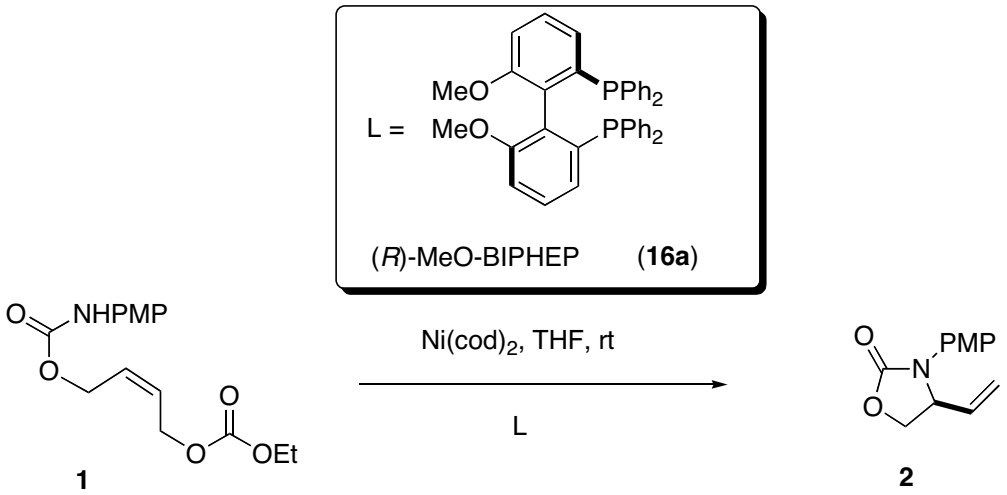


Solvent: *i*-PrOH/hexane (1:4); *Flow rate* = 1 mL/min.

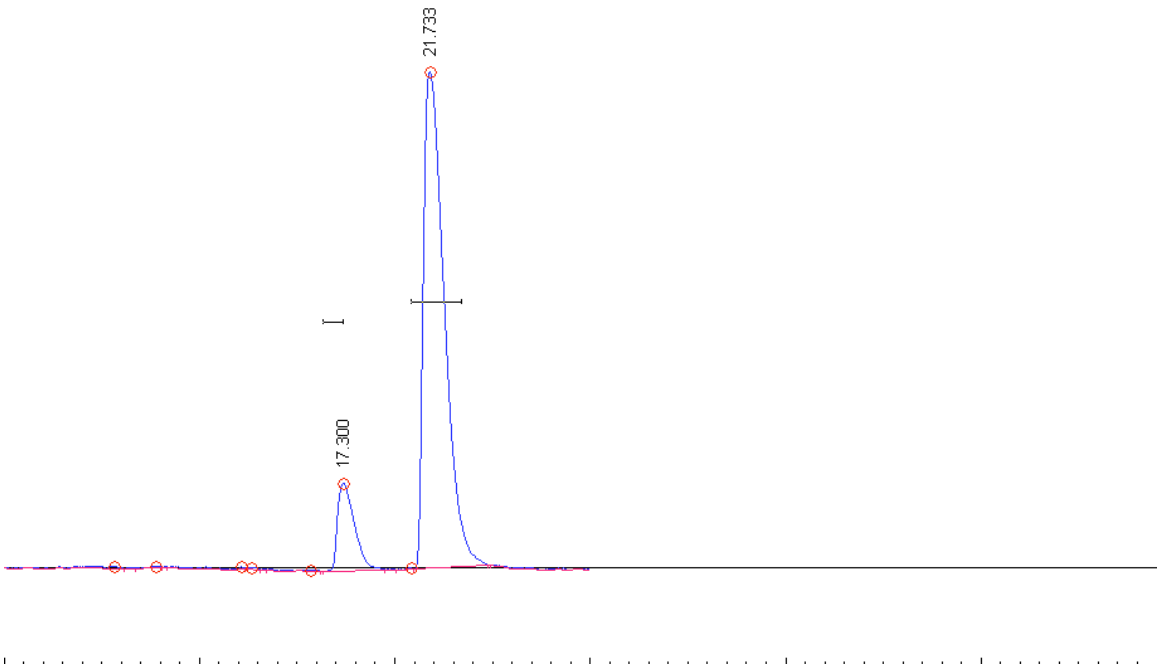
Retention time: 17.6 (*R*) and 21.3 (*S*) min

Integration = 20.6:79.6 (59% ee)





Solvent: *i*-PrOH/hexane (1:4) *Flow rate* = 1 mL/min
Retention time: 17.3 (*R*) and 21.7 (*S*) min
Integration = 12.5:87.5 (75% ee)

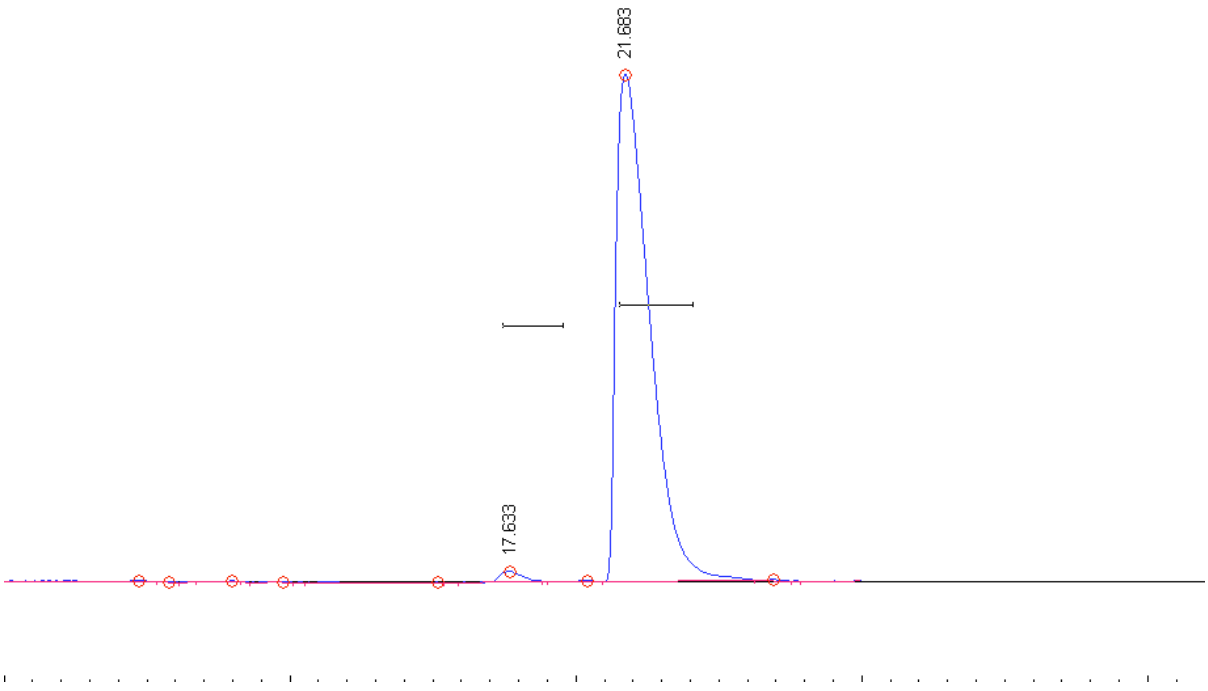


Results of the1st crystallization of **2** from the (*R*)-MeO-BIPHEP reaction using ether-hexane (and a few drops of methylene chloride) solvent:

Solvent: *i*-PrOH/hexane (1:4); *Flow rate* = 1 mL/min

Retention time: 17.6 (*R*) and 21.6 (*S*) min

Integration = 1.3:98.7 (97.4% ee)

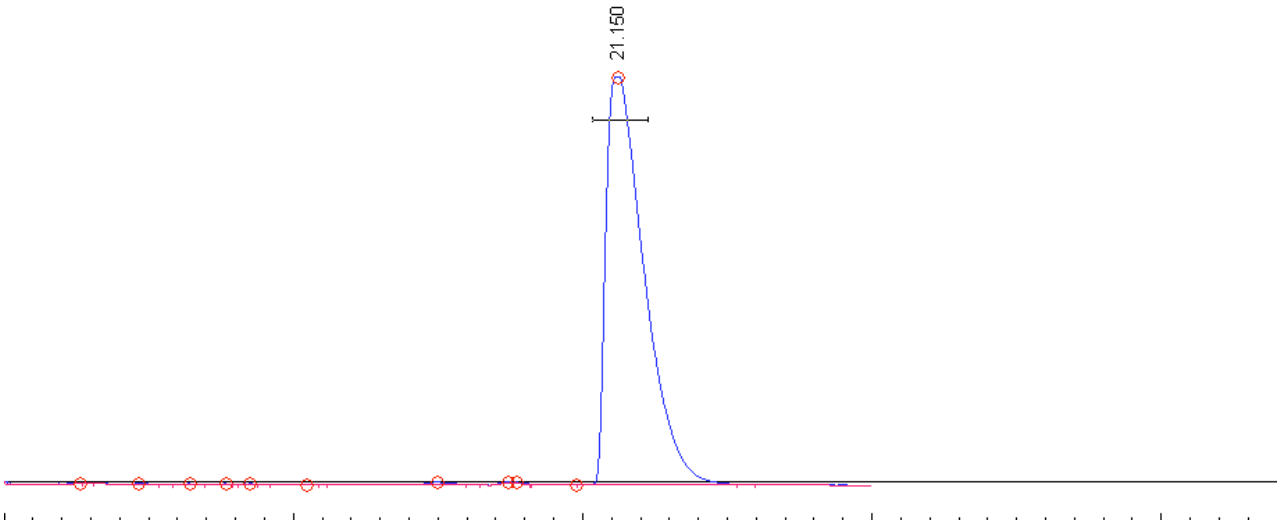


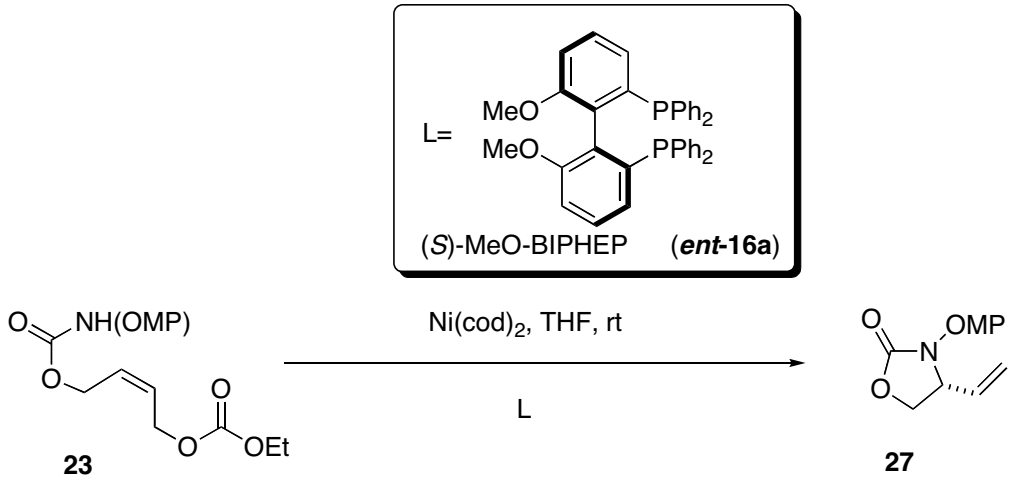
Results of the 2nd crystallization of **2** from the (*R*)-MeO-BIPHEP reaction:

Solvent: *i*-PrOH/hexane (1:4); *Flow rate* = 1 mL/min.

Retention time: 21.2 (*S*) min

Integration = (>99% ee)





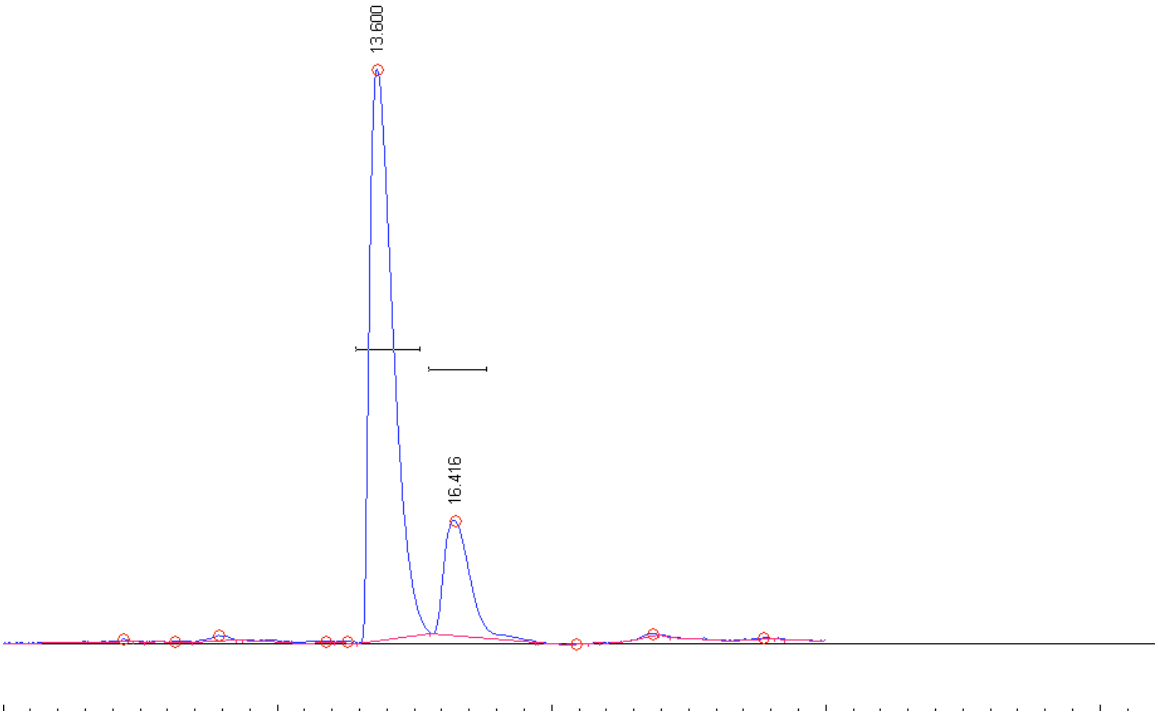
OMP= *o*-methoxyphenyl

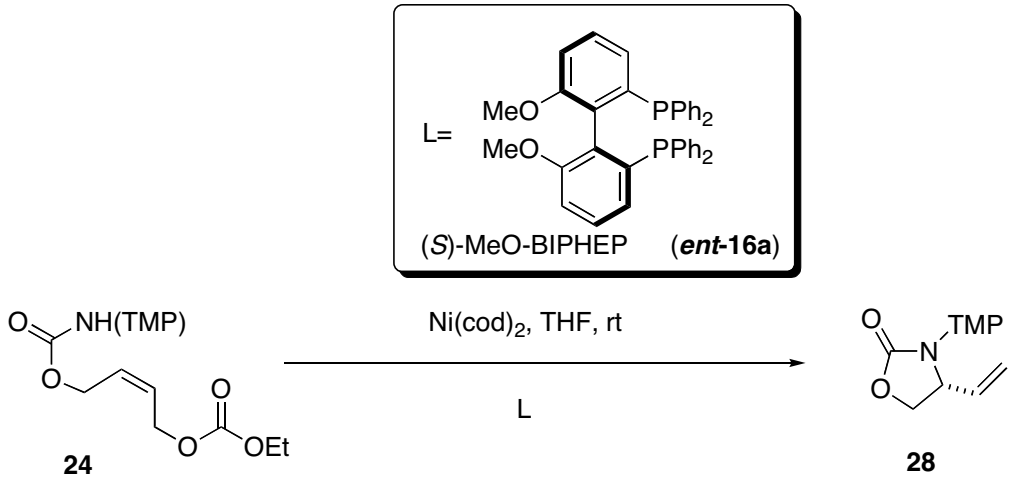
Note: (S)-Absolute stereochemistry assumed by analogy with the elution profile of the antipodes of the PMP-protected oxazolidinone (i.e. (R)-antipode elutes first).

Solvent: *i*-PrOH/hexane (1:4); *Flow rate* = 1 mL/min.

Retention time: 13.6 (*R*) and 16.4 (*S*) min

Integration = 82:18 (64% ee)





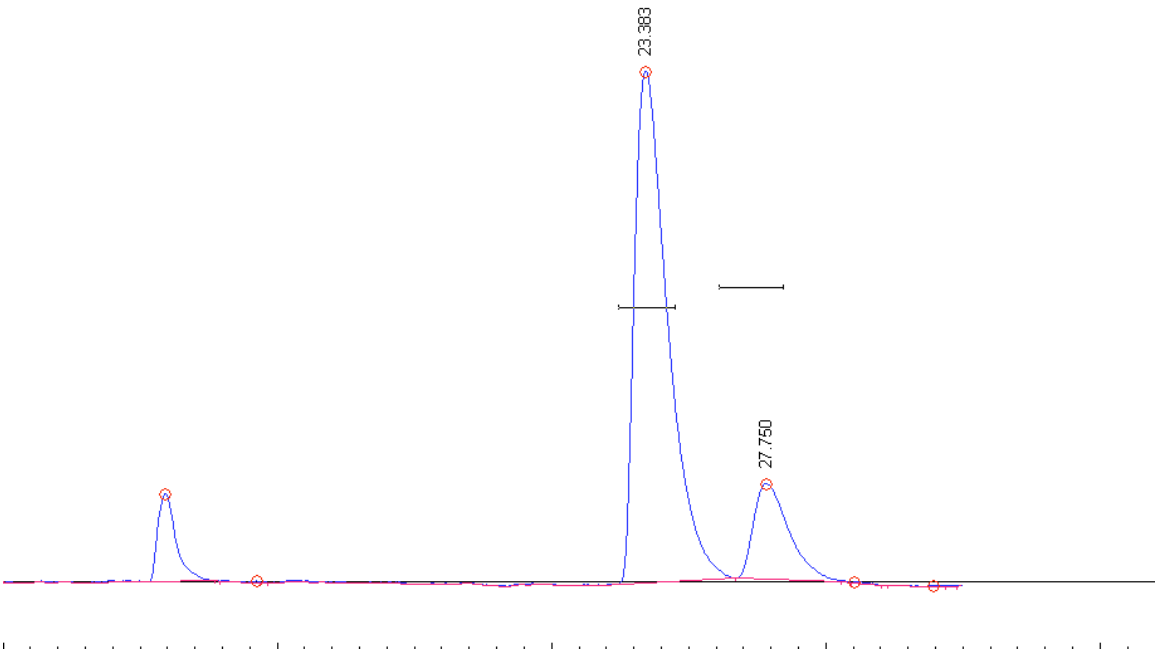
TMP= 3,4,5-trimethoxyphenyl

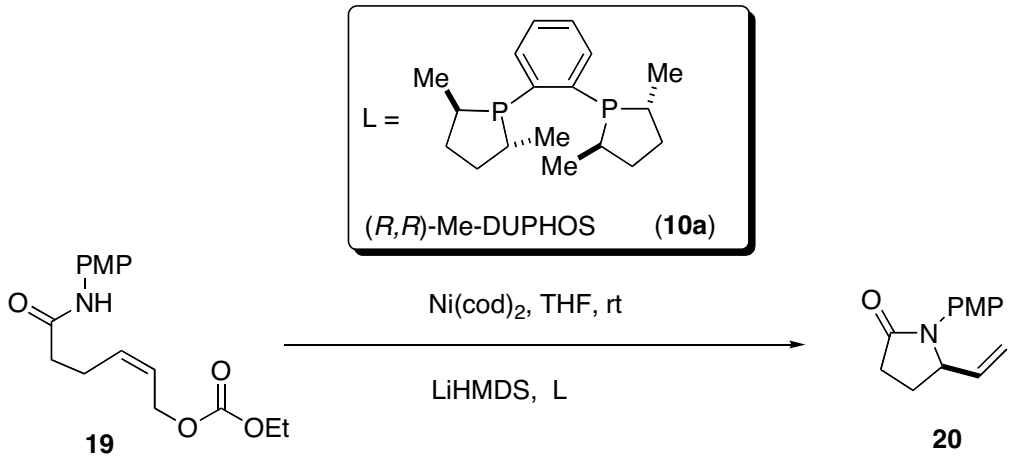
Note: (S)-Absolute stereochemistry assumed by analogy with the elution profile of the antipodes of the PMP-protected oxazolidinone (i.e. (R)-antipode elutes first).

Solvent: *i*-PrOH/hexane (1:4); *Flow rate* = 1 mL/min.

Retention time: 21.8 (*R*) and 24.6 (*S*) min

Integration = 16.5:83.5 (67% ee)



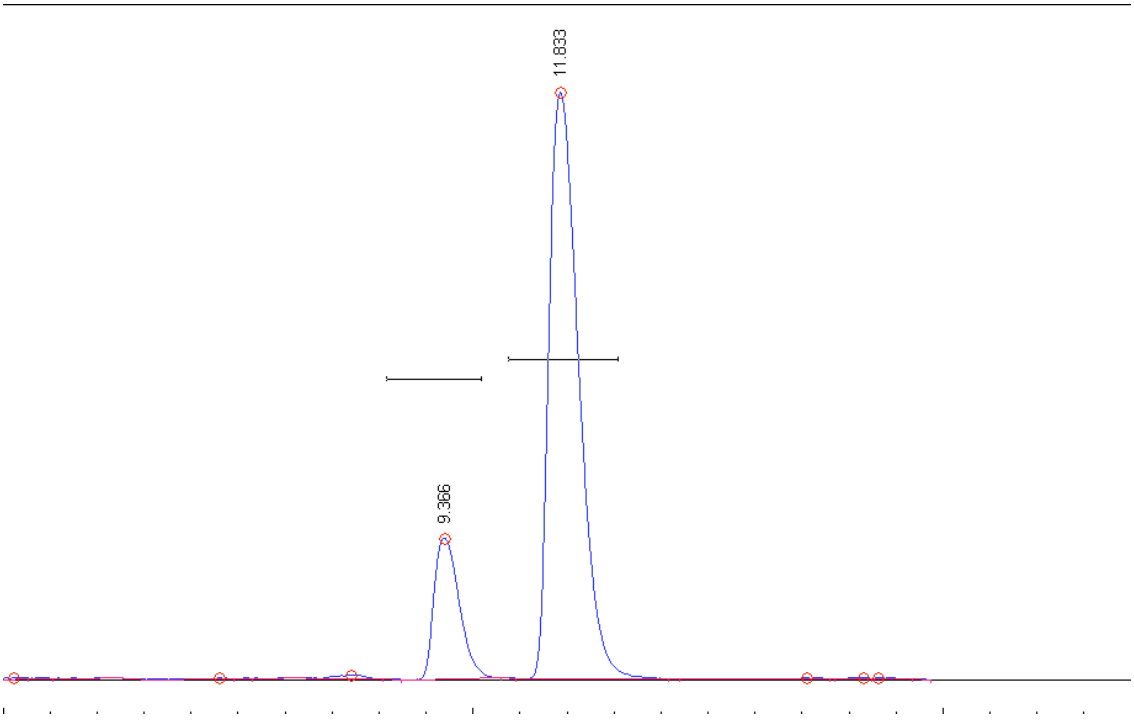


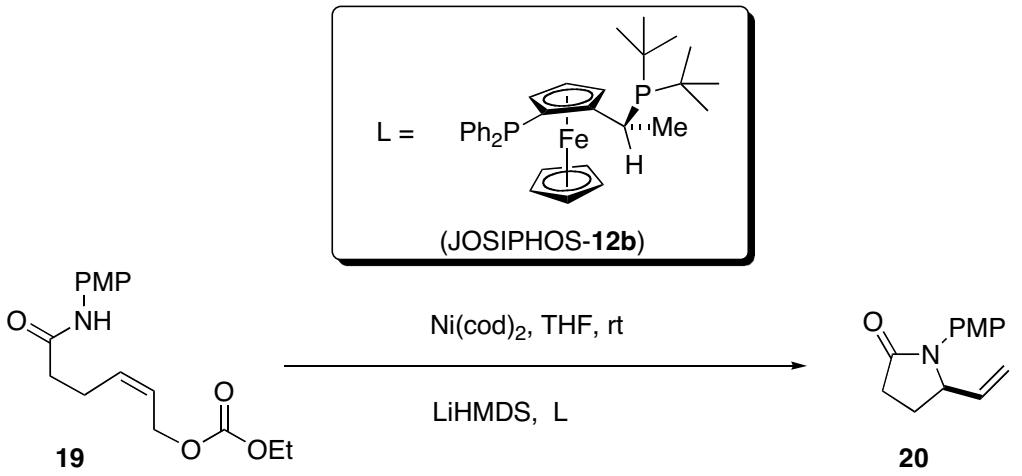
(Absolute stereochemistry determined by chemical correlation with the known γ-lactam, following PMP deprotection – see manuscript for details.)

Solvent: *i*-PrOH/hexane (27:73); *Flow rate* = 1 mL/min.

Retention time: 9.37(*S*) and 11.83 (*R*) min

Integration = 17:83 (66% ee)



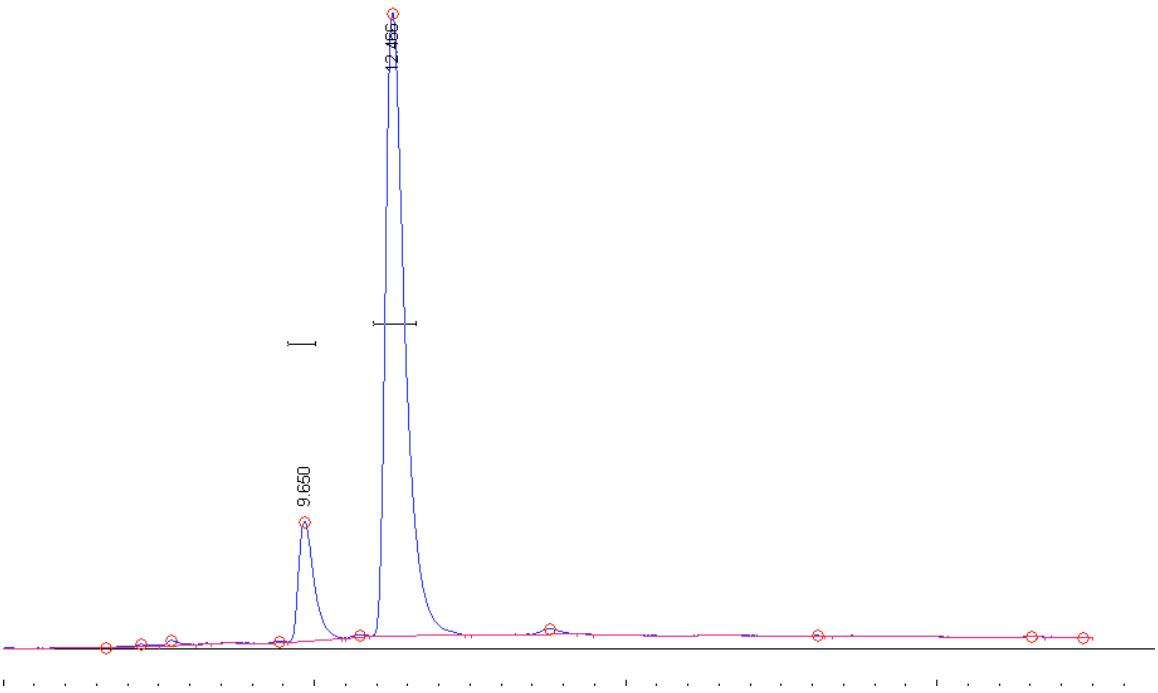


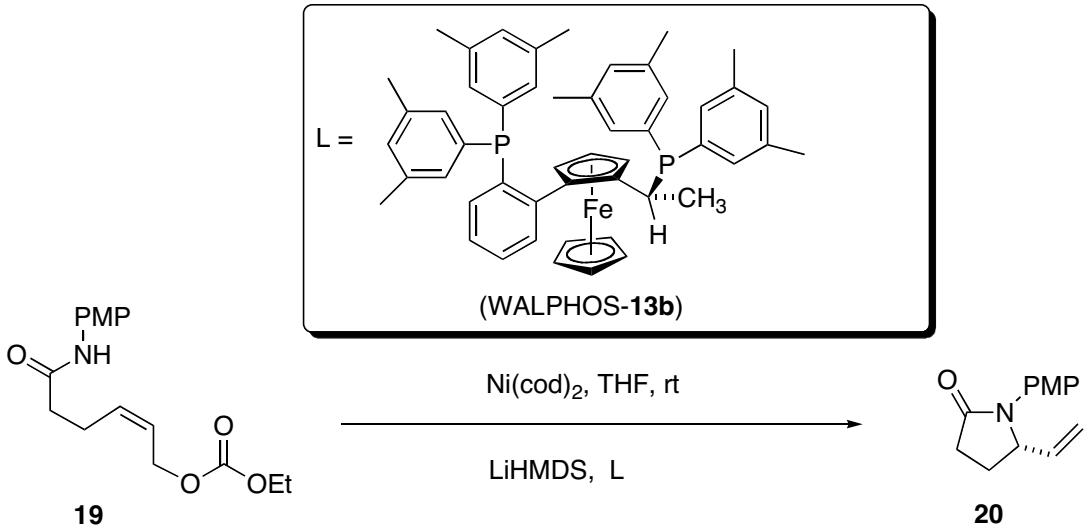
(Absolute stereochemistry determined by chemical correlation with the known γ-lactam, following PMP deprotection – see manuscript for details.)

Solvent: *i*-PrOH/hexane (27:73); *Flow rate* = 1 mL/min.

Retention time: 9.65(*S*) and 12.5 (*R*) min

Integration = 13:87 (74% ee)





(Absolute stereochemistry determined by chemical correlation with the known γ-lactam, following PMP deprotection – see manuscript for details.)

Solvent: *i*-PrOH/hexane (27:73); *Flow rate* = 1 mL/min.

Retention time: 9.11 (*S*) and 11.6 (*R*) min

Integration = 76:24 (52% ee)