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Supporting Information

Enantiodiscrimination of carboxylic acids using the NMR chiral solvating agent diphenylprolinols

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1. Experimental Section

1.1. General

Melting points were determined using YRT-3 melting point apparatus and are uncorrected. Optical rotations were measured with Perkin Elmer, model 341 Polarimeter at 20 °C in CH_3OH or CH_2Cl_2. NMR spectra were recorded on a Bruker Avance spectrometer for ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz). All spectra were recorded using 16 scans at 298 K. A full spectrum of each sample was recorded referenced to TMS. An exponential window function with a line-broadening factor of 1 Hz was applied to the FID before Fourier transformation. The compounds **2-19** were purchased from J&K China Chemical Ltd. without purification.

Compounds **1a-1b** were synthesized according to the literature procedure. [22]

1.1.1. *N*-Benzyl-(*S*)-diphenyl(pyrrolidin-2-yl)methanol (1a)

White solid, yield 70%, m. p. = 112.3-114.1 °C; $[\alpha]_D^{20}$ = +68.7 (*c* 0.86, in CH_2Cl_2) , (lit. [1] m. p. = 115-116 °C; $[\alpha]_D^{20}$ = +67.0 (*c* 1.00, in CH_2Cl_2)); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.78 (d, *J* = 7.5 Hz, 2H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.38-7.18 (m, 9H), 7.17-7.06 (m, 3H), 4.99 (s, 1H), 4.03 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.29 (d, *J* = 12.6 Hz, 1H), 3.08 (d, *J* = 12.6 Hz, 1H), 2.98-2.95 (m, 1H), 2.43-2.37 (m, 1H), 2.03-1.97 (m, 1H), 1.87-1.76 (m, 1H), 1.75-1.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 148.1, 146.7, 139.7, 128.6, 128.6, 128.2, 128.1, 128.0, 126.8, 126.4, 126.2, 125.7, 125.6, 70.7, 60.6, 55.5, 29.8, 24.1.

1.1.2. (*S*)-diphenyl(pyrrolidin-2-yl)methanol (1b)

In a 100-mL Schlenk tube were placed *N*-benzyl-(*S*)-diphenyl(pyrrolidin-2-yl)methanol **1a** (3.43 g, 10 mmol), palladium hydroxide on carbon (10 wt %, 400 mg), acetic acid (0.7 mL, 12 mmol), dichloromethane (10 mL), and methanol (20 mL). The mixture was stirred under a hydrogen atmosphere at room temperature for 48 h, filtered, and concentrated in vacuo. To liberate the free base, the salt was suspended in ether (40 mL) and 1 M aqueous NaOH (40 mL), and then the resulting mixture was stirred vigorously until the salt was completely dissolved. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by recrystallization with petroleum ether gave (*S*)-diphenyl(pyrrolidin-2-yl)methanol **1b** as a white solid. White solid, yield 90%, m. p. = 76.6-77.9 °C; $[\alpha]_D^{20}$ = -58.5 (*c* 0.394, in CH_3OH), (lit.[1] $[\alpha]_D^{20}$ = -54.3 (*c* 0.261, in CH_3OH)); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.59 (d, *J* = 7.6 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.34 - 7.25 (m, 4H), 7.19-7.15 (m, 2H), 4.28 (t, *J* = 7.6 Hz, 1H), 3.04-3.01 (m, 1H), 2.96 (dd, *J* = 16.6, 7.6 Hz, 1H), 1.69-1.54 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 148.1, 145.4, 128.2, 127.9, 126.5, 126.4, 125.8, 125.5, 64.5, 46.7, 26.3, 25.5.

1.1.3. (*R*)-diphenyl(pyrrolidin-2-yl)methanol (1b)

The (*R*)-CSA **1b** was purchased from J&K China Chemical Ltd.

1.2. Determination of the stoichiometry by ^1H NMR titrations (Job plots)

The (*S*)-CSA **1b**, (*R*)- and (*S*)-mandelic acid **2** was dissolved, respectively, with a concentration of 10 mM in $CDCl_3$. These solutions were distributed among fifteen NMR tubes with the mole ratio of the (*S*)-CSA **1b** and guest [(*R*)- or (*S*)-mandelic acid **2**] of the 15 tubes increasing from 0.1 to 0.9, keeping the total concentration of host and guest 10 mM. Job plots of $\Delta\delta^*X$ versus the molar fraction (*X*) of (*S*)-CAS **1b** in the mixture showed a maximum at *X* = 0.5 which indicated that (*S*)-CAS **1b** and the acid **2** bind in a 1:1 complex under these conditions.

1.3. Determination of enantiomeric purity of mandelic acid

To determine the enantiomeric purity of the carboxylic acids, ten *p*-methoxymandelic acid **7**

samples with -80%, -60%, -40%, -20%, 0%, 20%, 40%, 60%, 80%, 100% ee were prepared at a concentration of 10 mM in $CDCl_3$, respectively, expressed as % *S* in the data. The (*S*)-CAS **1b** was also dissolved in $CDCl_3$ at a concentration of 10 mM. Then 250 μL of (*S*)-CAS **1b** and 250 μL of *p*-methoxymandelic acid **7** with different ee's were mixed in the NMR tube generating a total concentration of 10 mM with a molar ratio of 1:1. Then the enantiomeric purity of the carboxylic acids was determined by ^{1}H NMR method. The plotting of gravimetry ee value (y axis) versus NMR observed *ee* value (x axis) presented excellent linearity with $R^2 = 0.9995$.

1.4. Discrimination ability of (*S*)-CSA 1b toward racemic guests 2-20

At first, (*S*)-CSA **1b**, and the guests were separately dissolved in $CDCl_3$ with a concentration of 10 mM. Then, 0.25 mL of (*S*)-CSA **1b** and 0.25 mL guest were added to NMR tubes, so that the total volume was 0.5 mL, and the concentration of (*S*)-CSA **1b** and guest was 10 mM. The ^{1}H NMR spectra of all samples were recorded on a 500 MHz spectrometer.

All experiment was carried out in oven dried NMR tubes unless otherwise noted. The carboxylic acids were commercially available and used as received. NMR spectra were recorded on a Bruker Avance spectrometer for ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz). All spectra were recorded using 16 scans at 298K. A full spectrum of each sample was recorded referenced to TMS. An exponential window function with a line-broadening factor of 1Hz was applied to the FID before Fourier transformation.

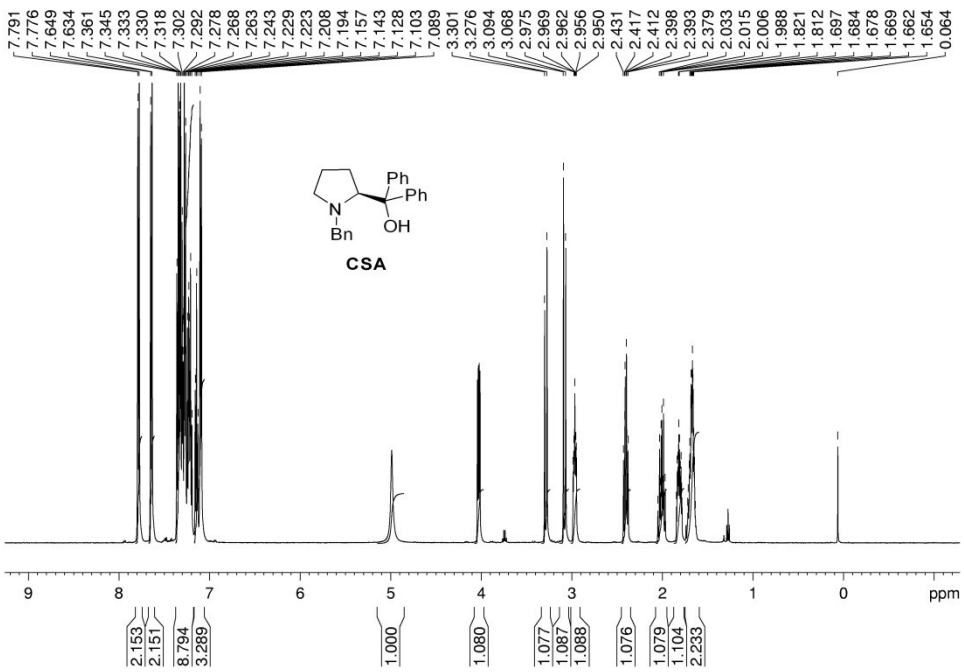
1.5. Correlation between chemicals shifts and absolute configuration of chiral carboxylic acids in the presence of (*S*)-CSA 1b and (*R*)-CSA 1b

^{1}H NMR spectra of the mixture of (*R*)-CSA **1b**/(*S*)-MA and a mixture of (*S*)-CSA **1b**/(*S*)-MA were recorded. By comparison of the chemical shifts of α-H signals of (*S*)-MA in the two mixtures, it was found the $\Delta\delta_{\alpha\text{-H}}{}^{R,S}$ ($\delta_{\alpha\text{-H}}$ of carboxylic acids with (*R*)-CSA **1b**- $\delta_{\alpha\text{-H}}$ of carboxylic acids with (*S*)-CSA **1b**) is - 0.027 ppm. Changing the carboxylic acid to *(R)*-MA, we repeated the process and $\Delta\delta_{\alpha\text{-H}}{}^{R,S}$ was obtained at + 0.026 ppm. Other chiral carboxylic acids were determined by the similar methods. The $\Delta\delta_{\alpha\text{-H}}{}^{R,S}$ sign is characteristic for this enantiomeric series and can be used for the assignment of absolute configuration.

References

[1] (*a*) D.J. Mathre, T.K. Jones, L.C. Xavier, T.J. Blacklock, R.A. Reamer, J.J. Mohan, E.T.T. Jones, K. Hoogsteen, M.W. Baum, and E.J.J. Grabowski, *J. Org. Chem.*, 1991, ***56***, 751; (*b*) Q. Xu, G. Zhu, X. Pan, and A.S.C. Chan, *Chirality*, 2002, **14**, 716.

^{1}H NMR (500 MHz, $CDCl_3$, TMS) of (*S*)-CSA 1a:



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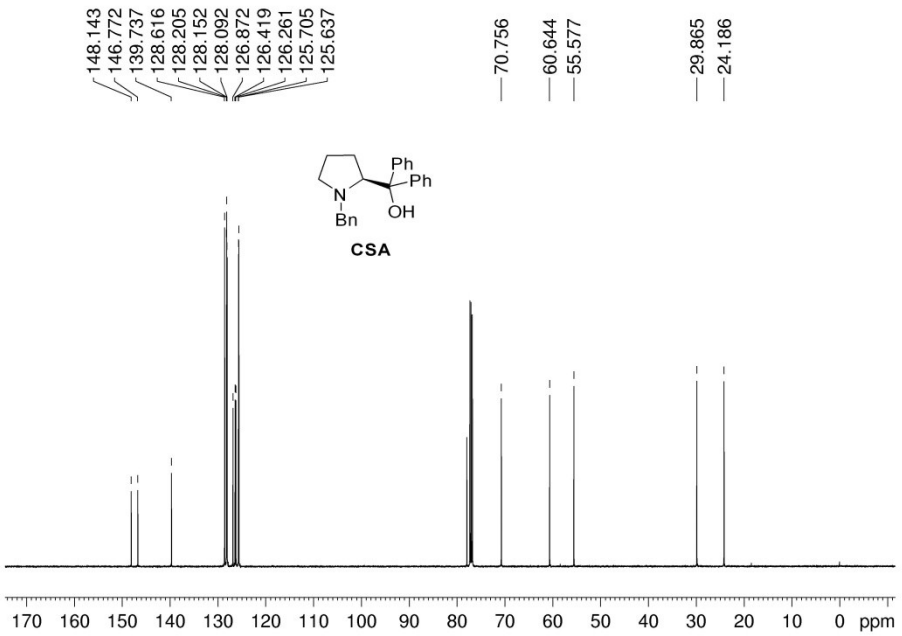

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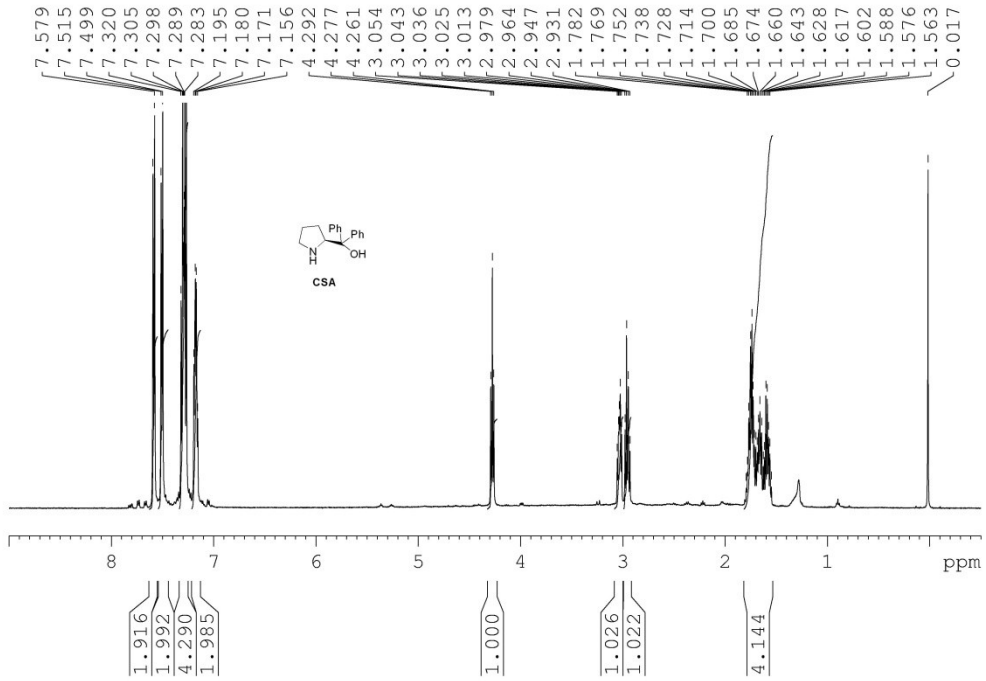

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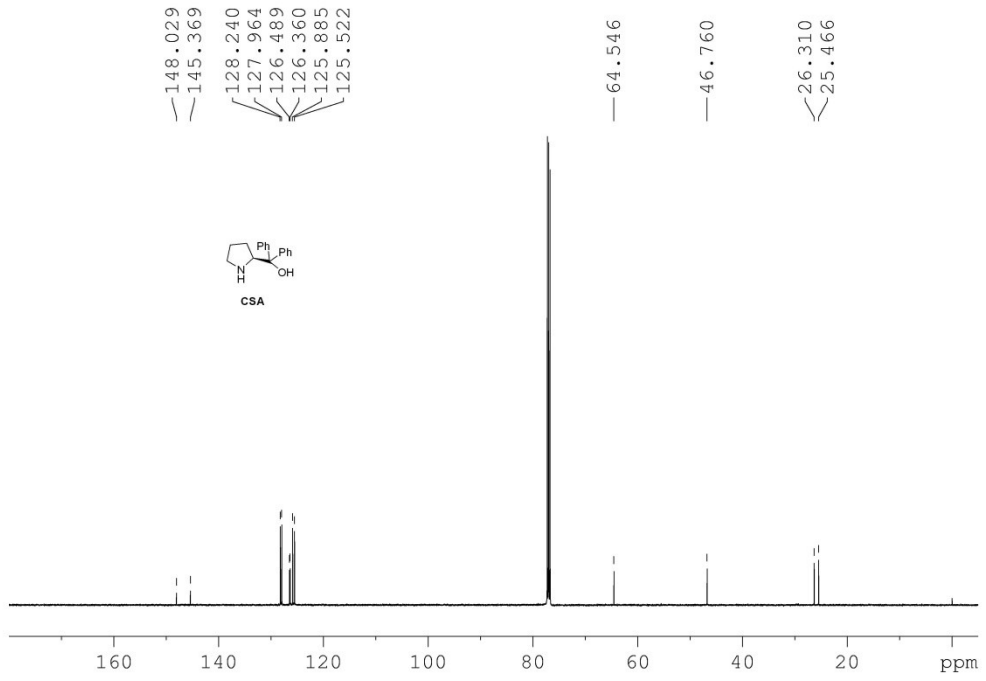
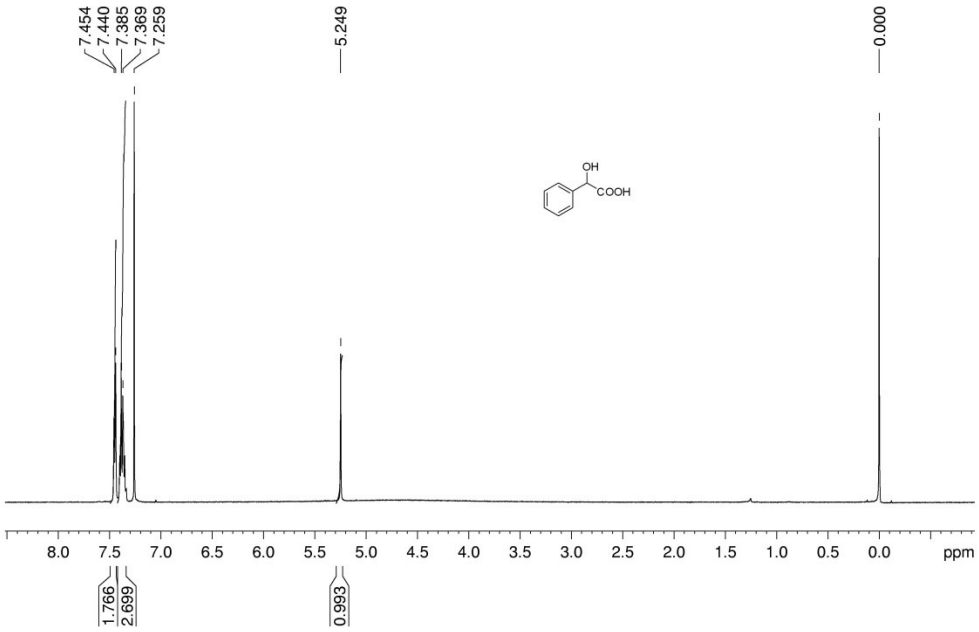


^{1}H NMR (500 MHz, $CDCl_3$, TMS) of (±)-Mandelic Acid:



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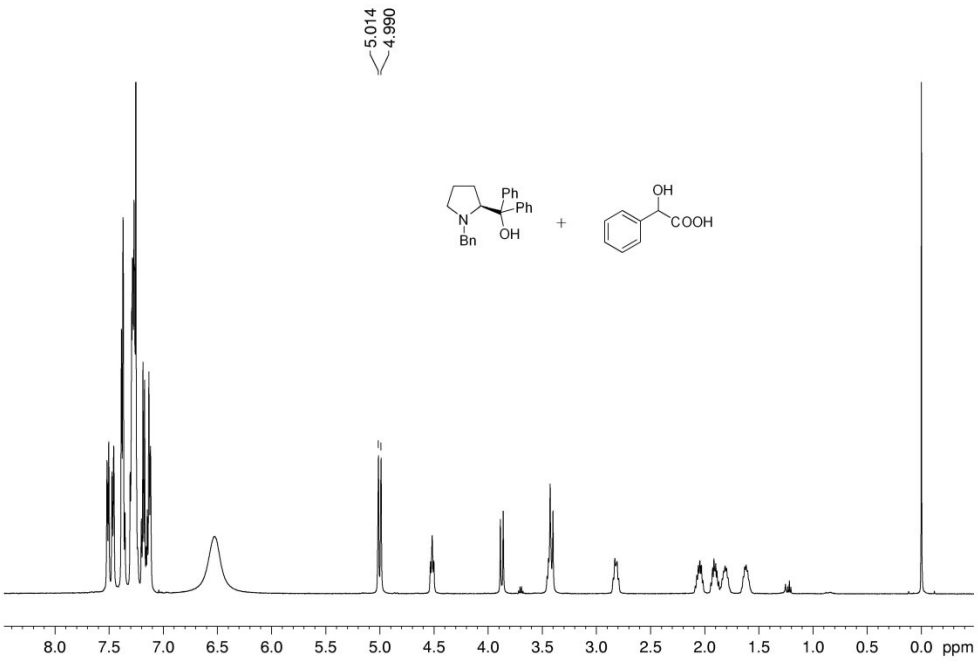

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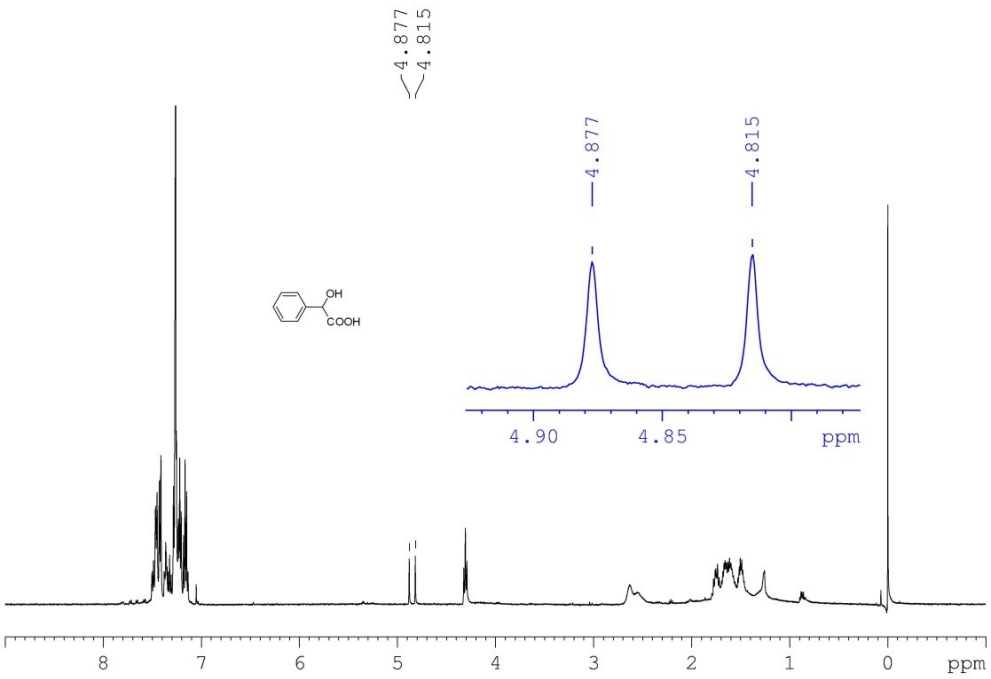

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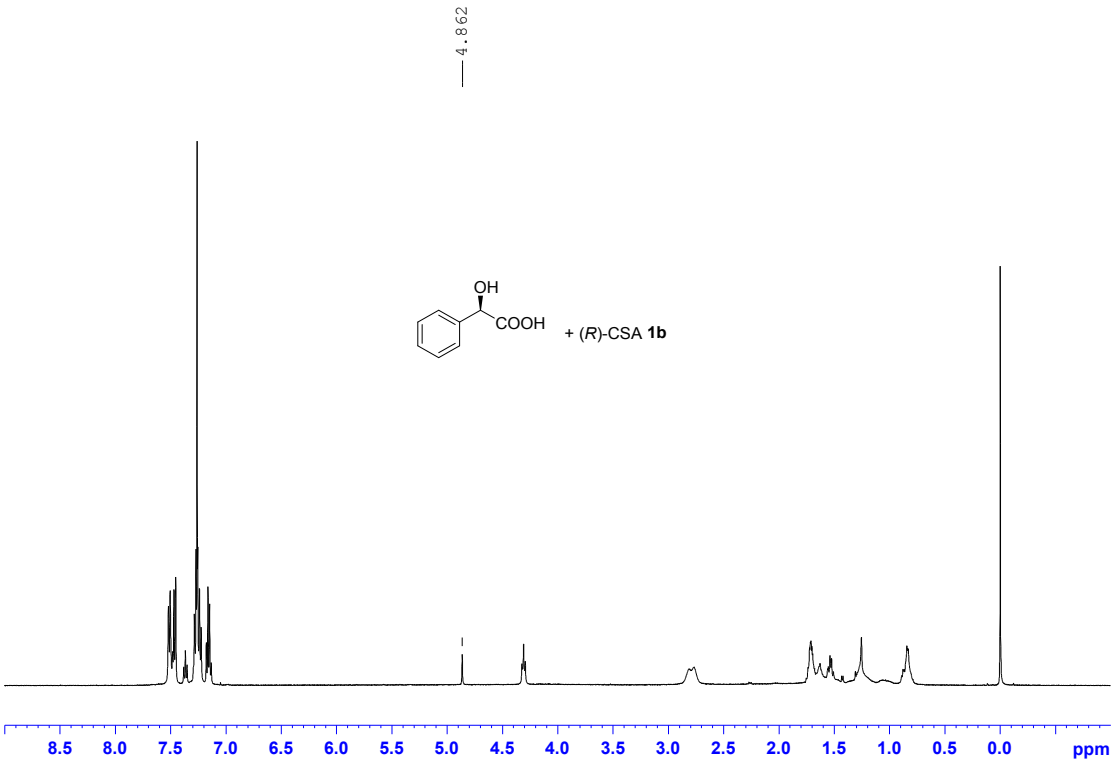

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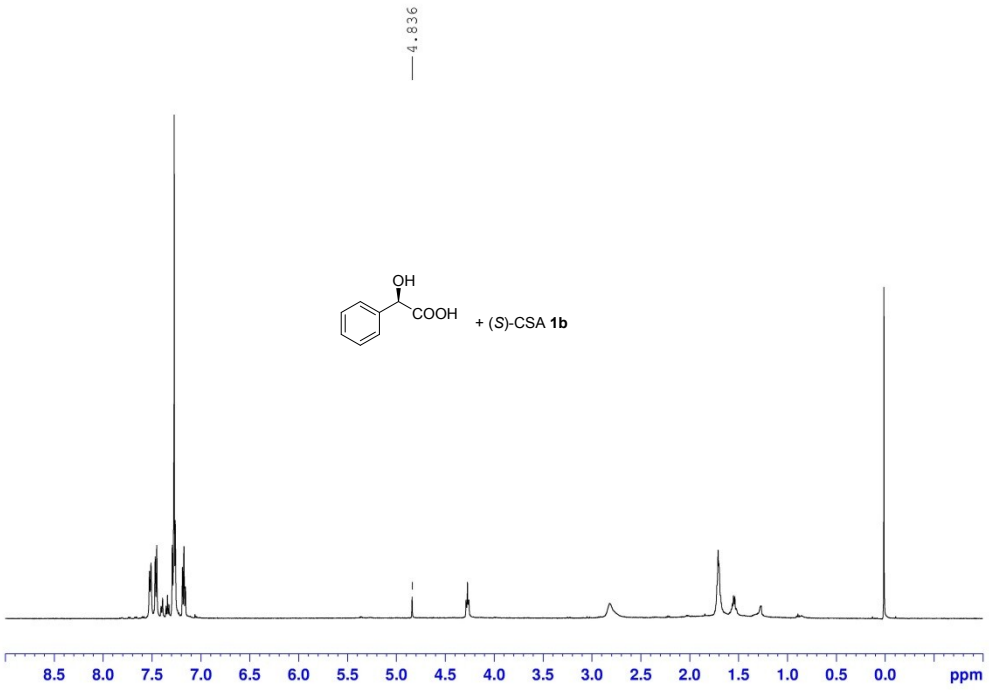

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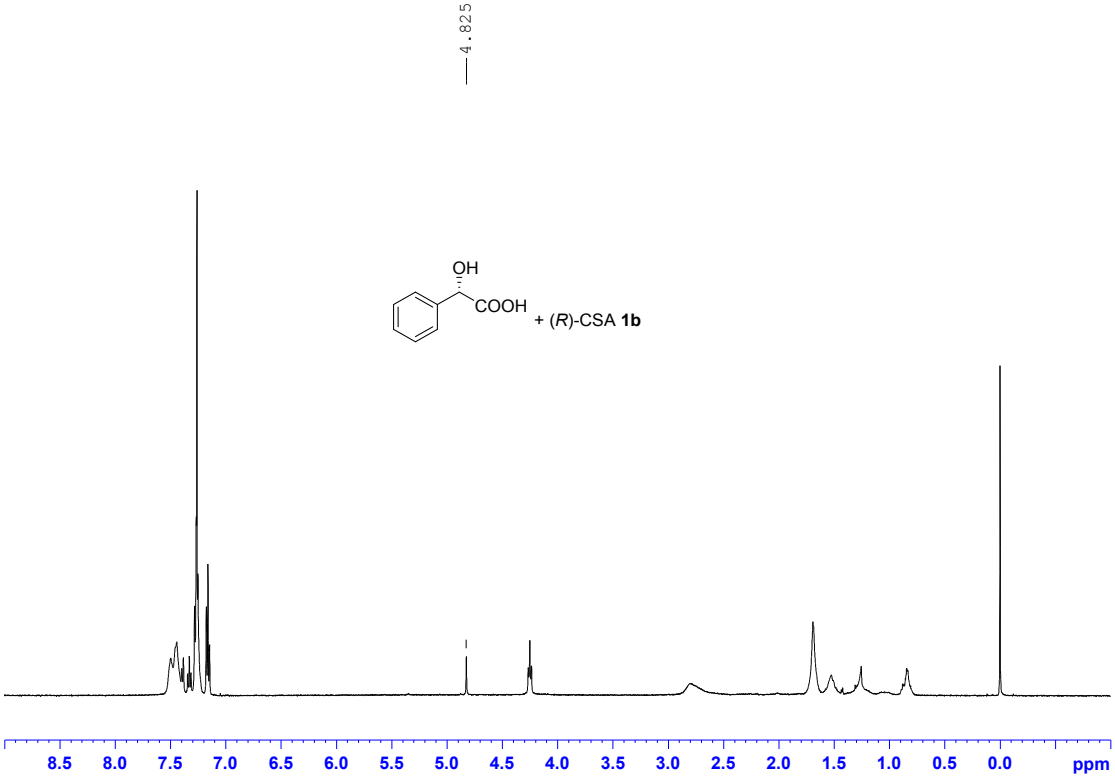

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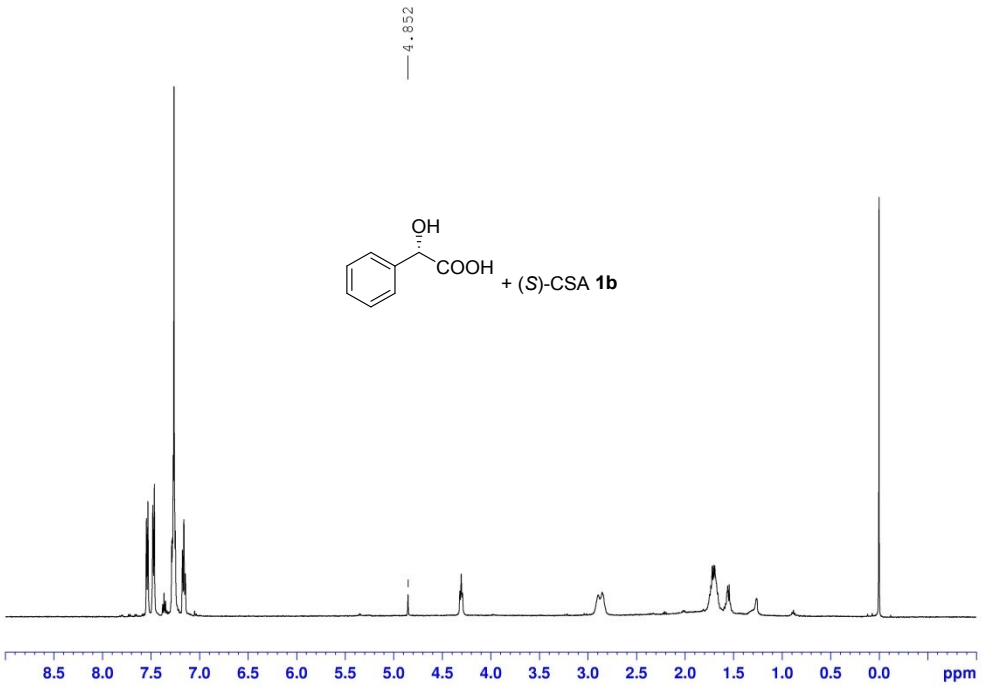

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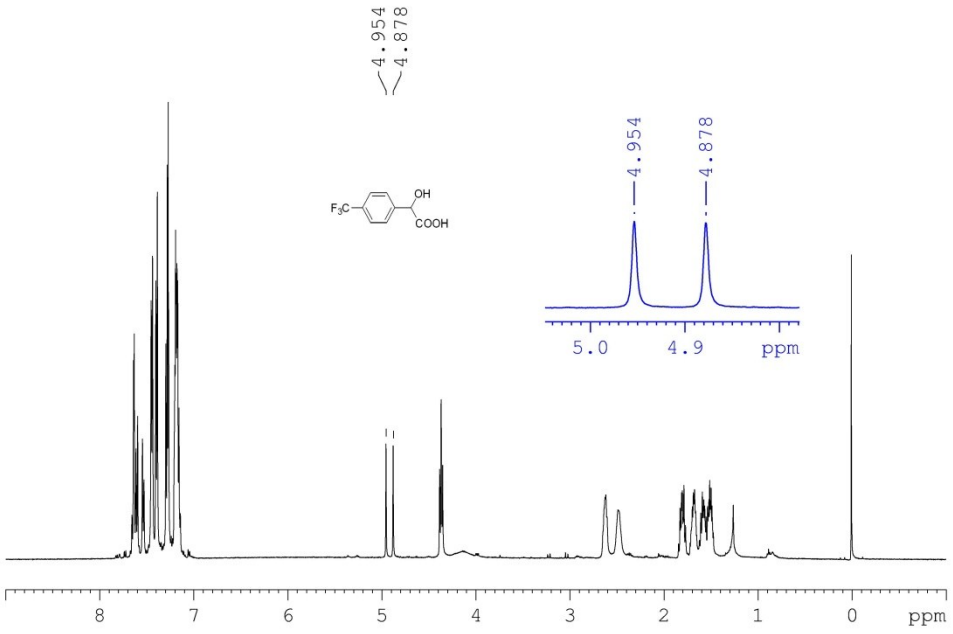

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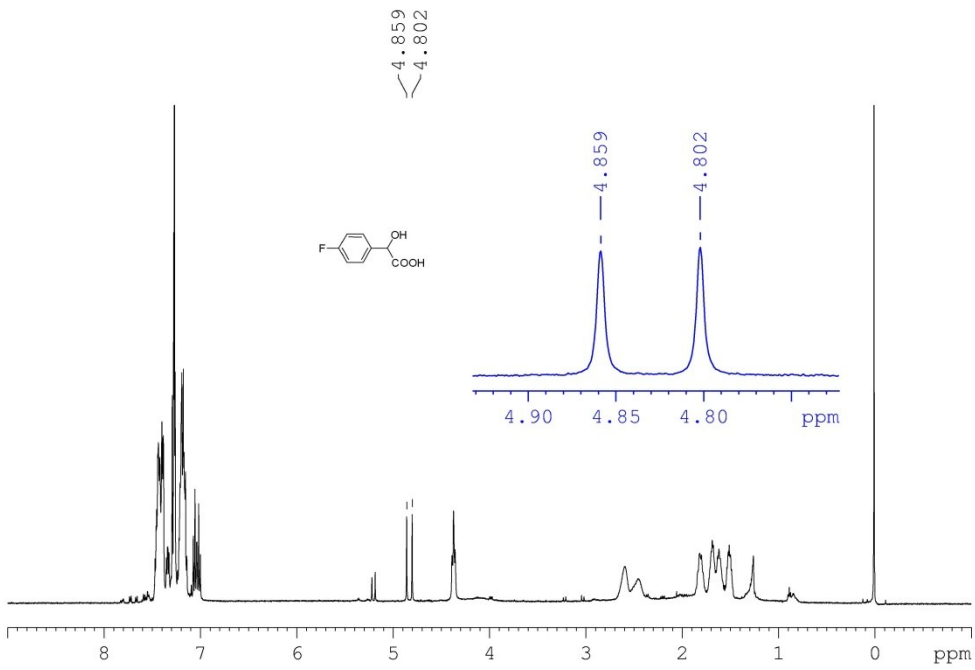

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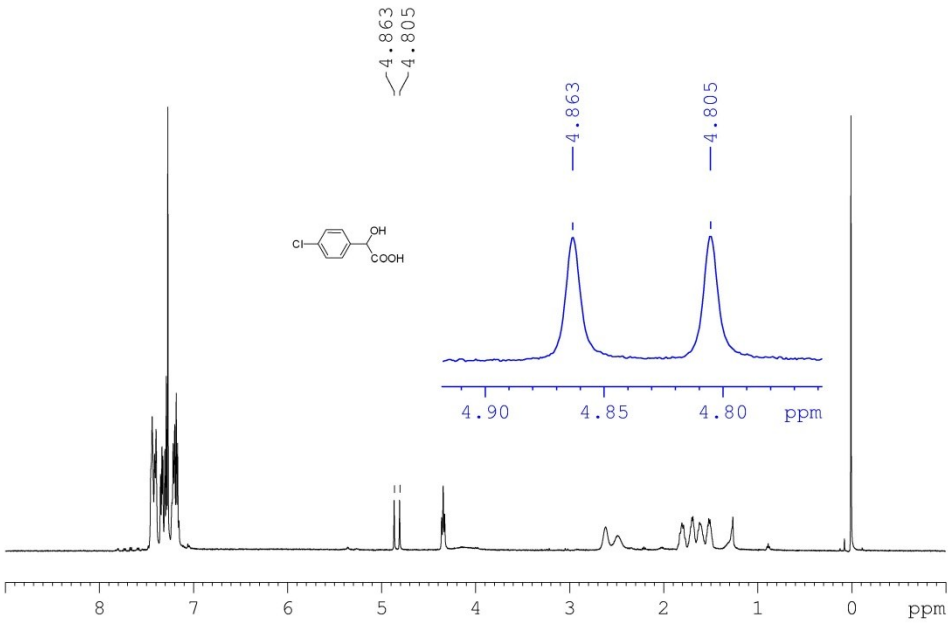

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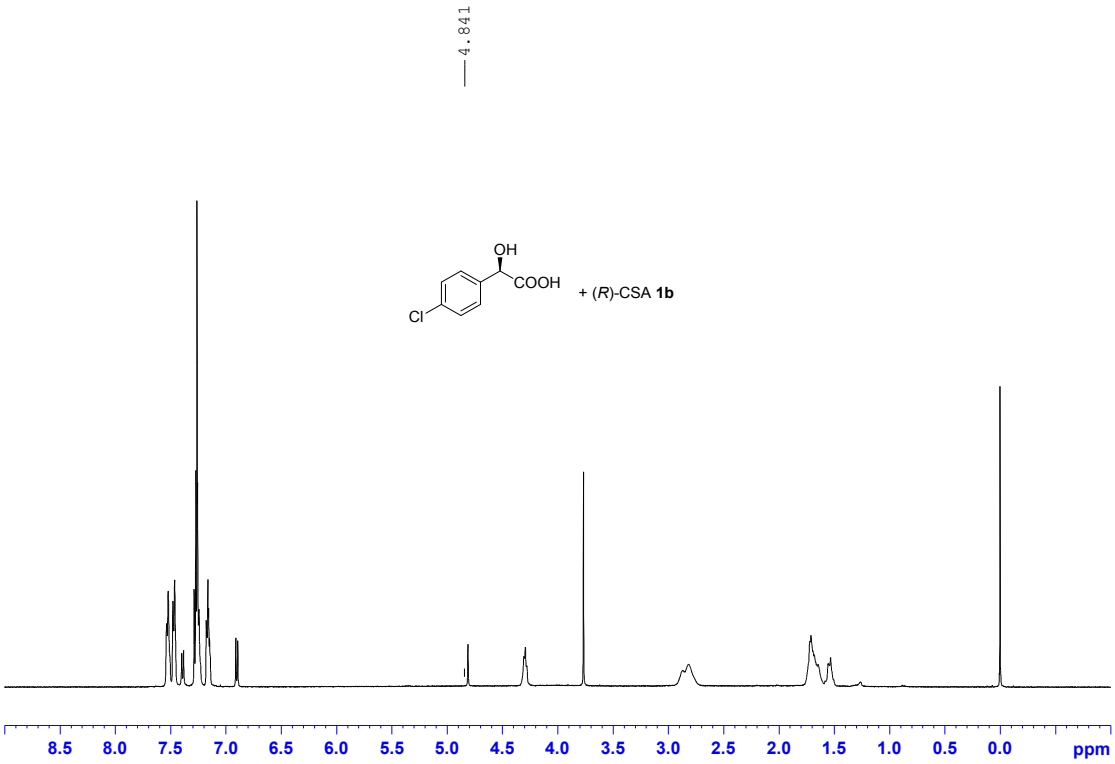

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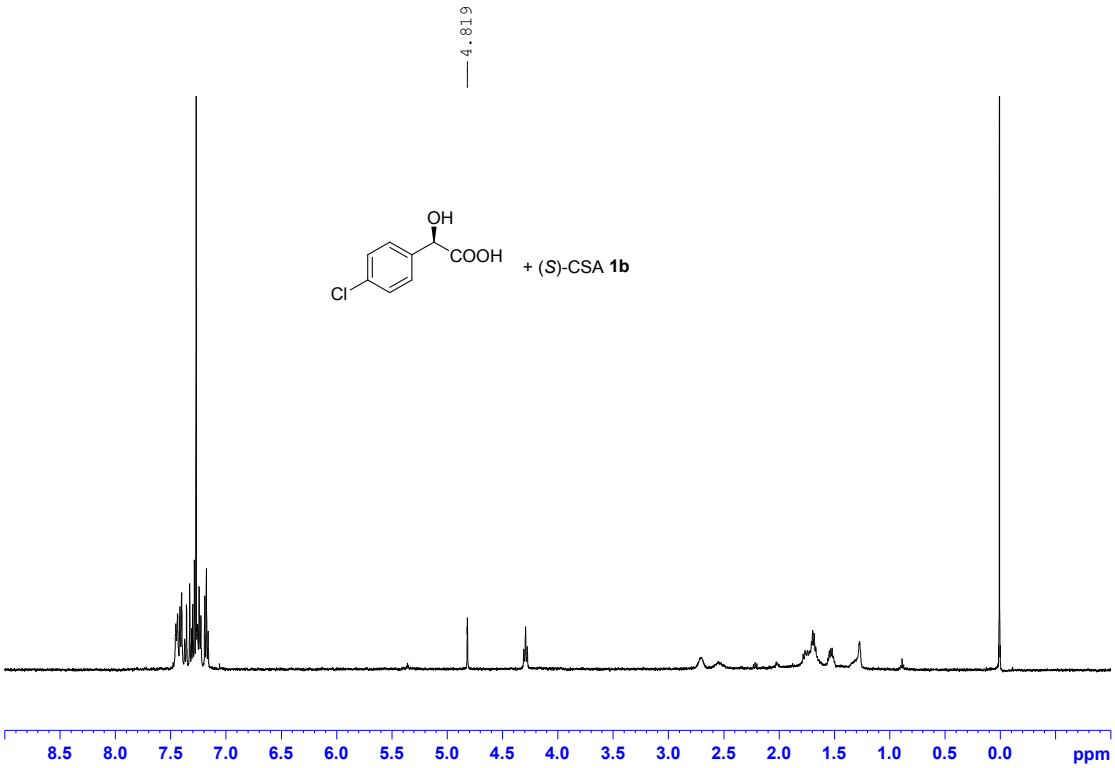

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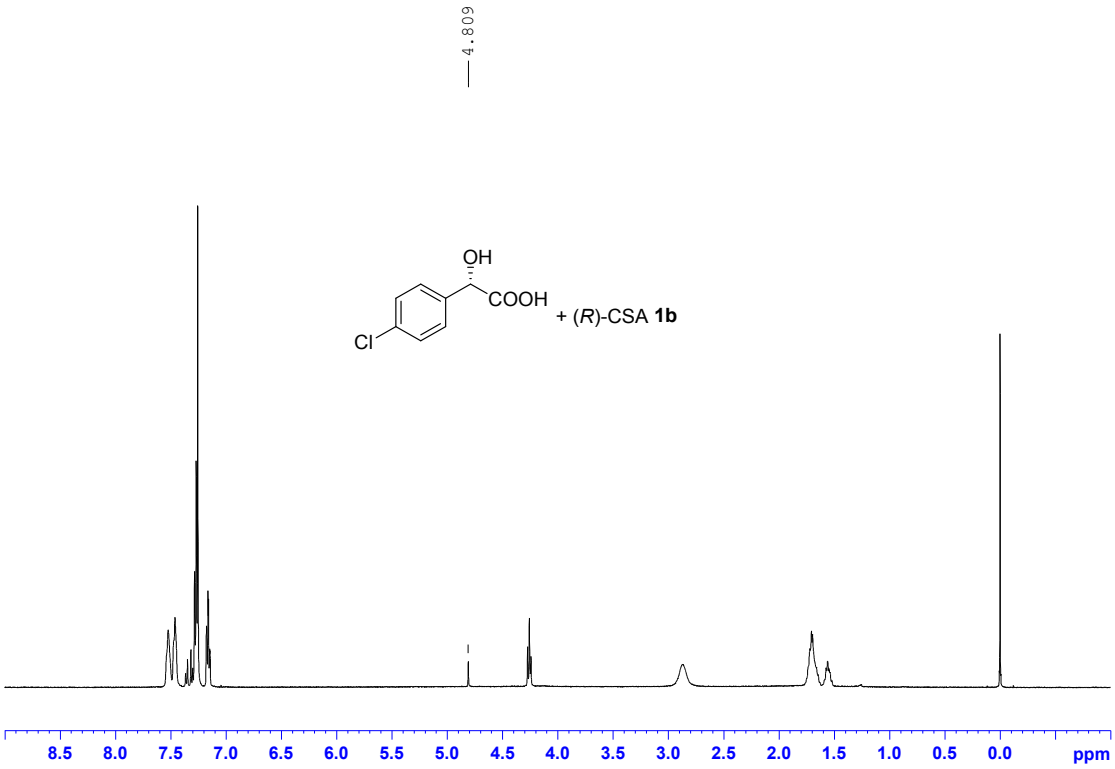

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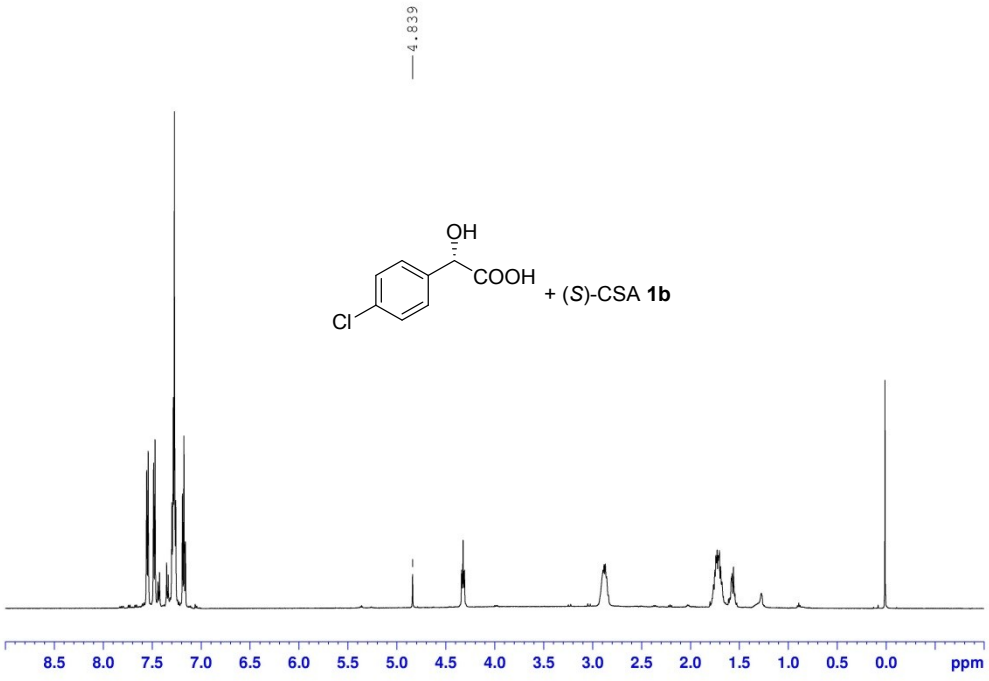

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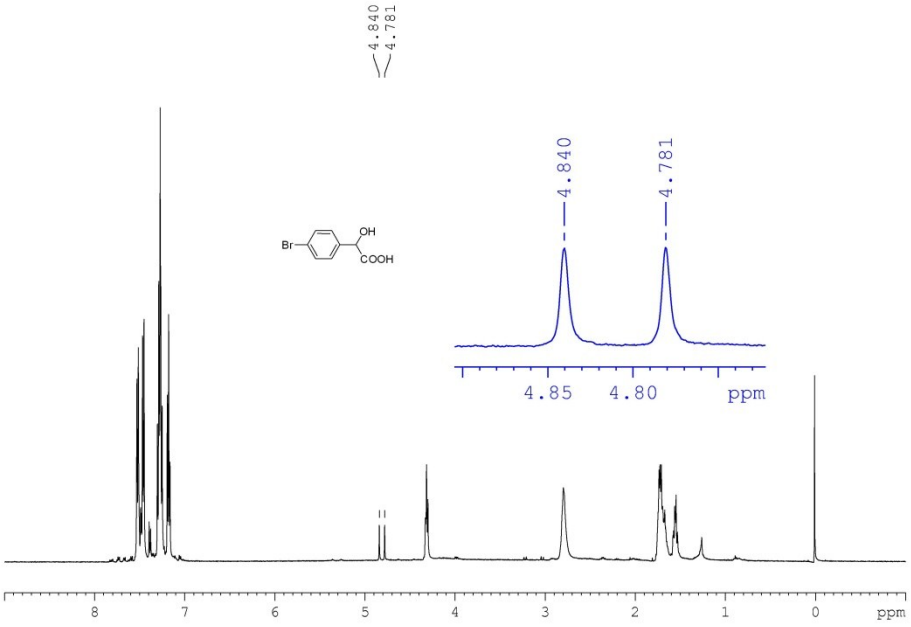

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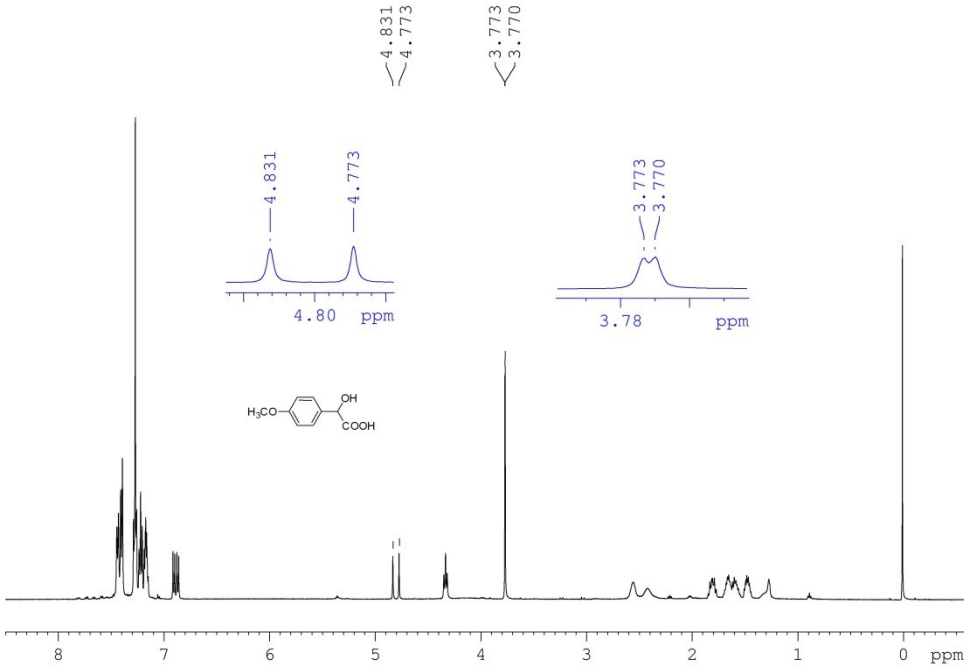

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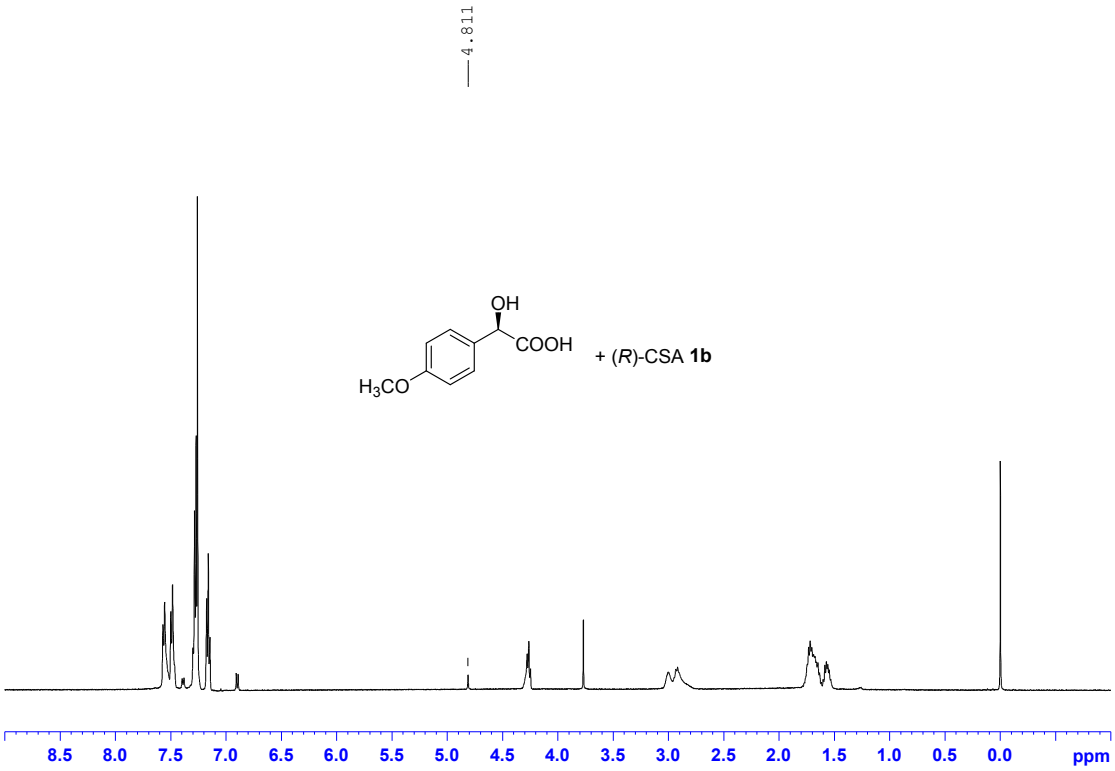

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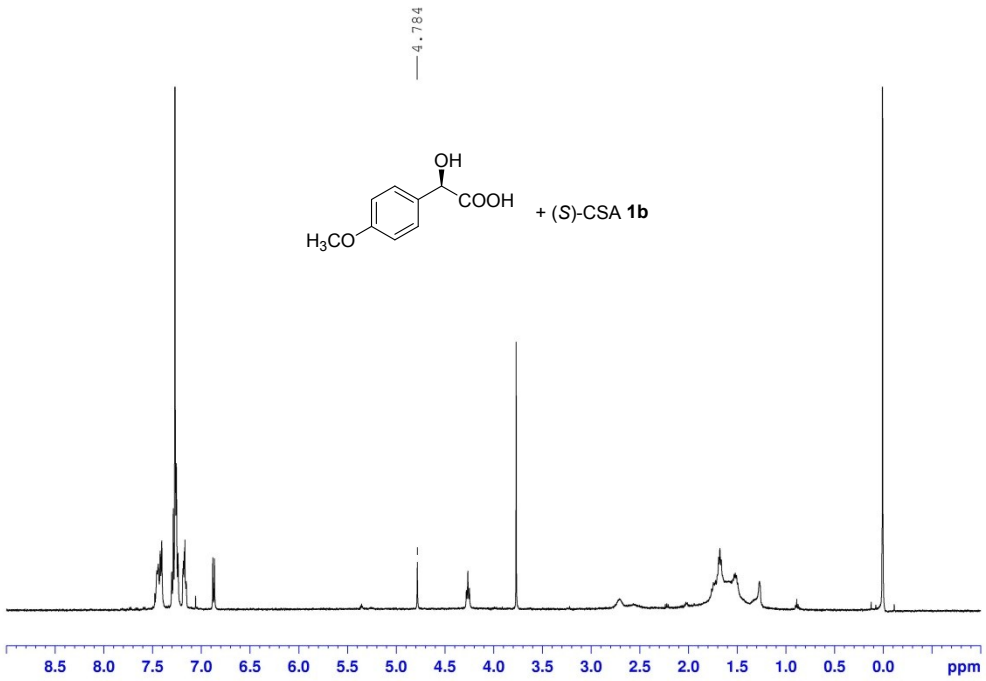

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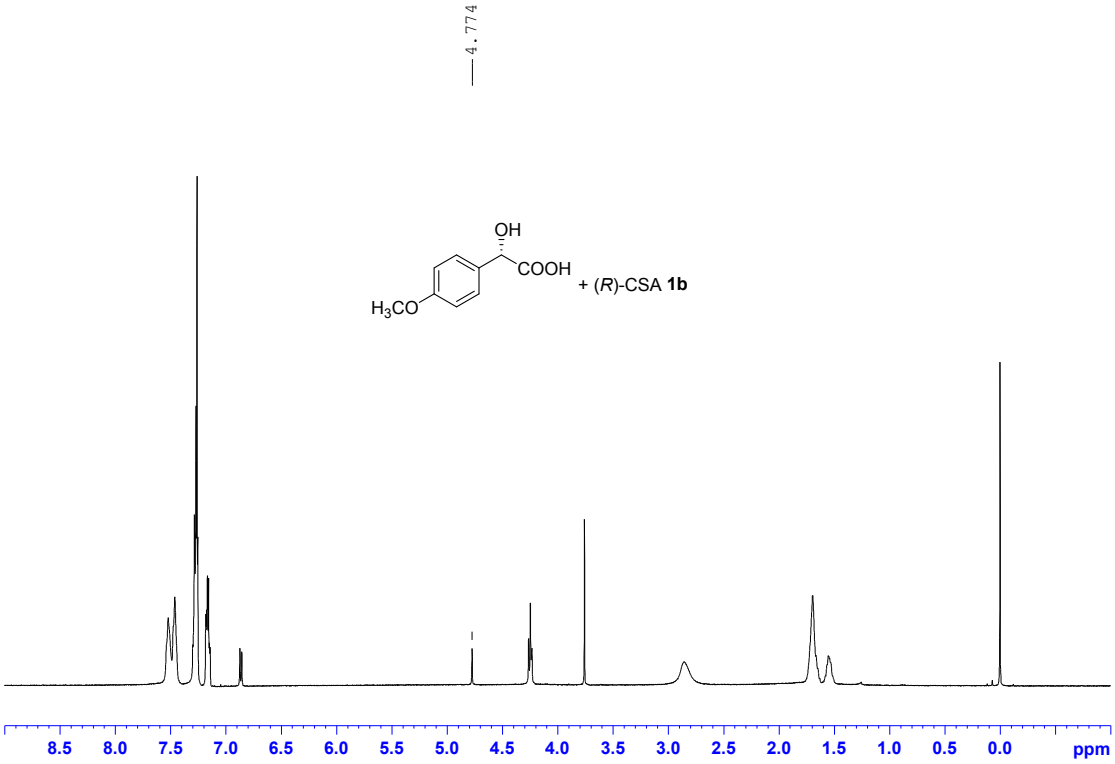

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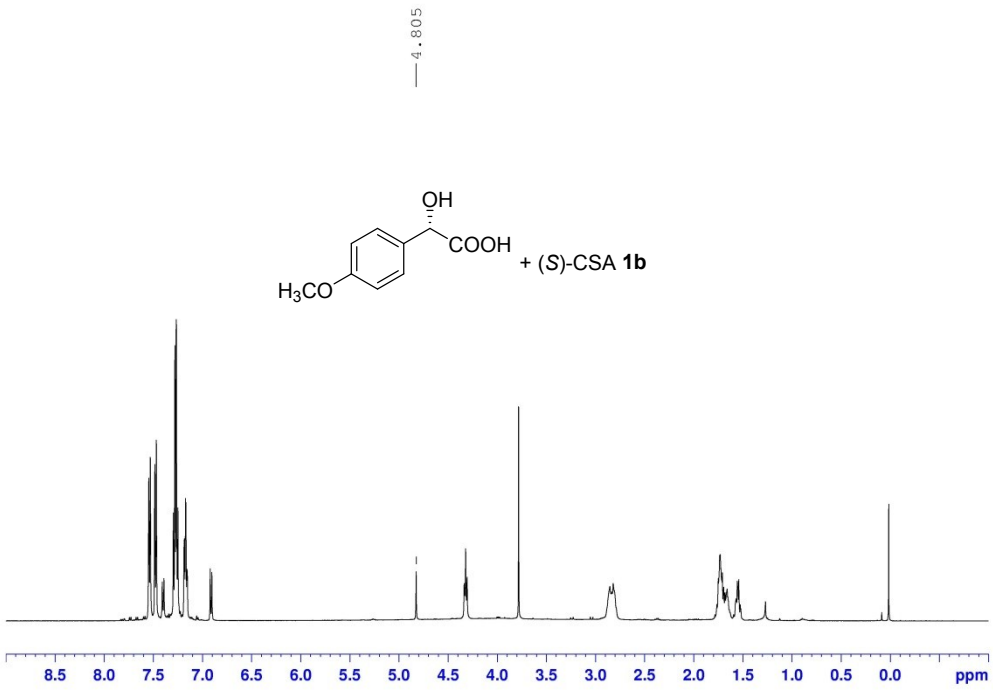

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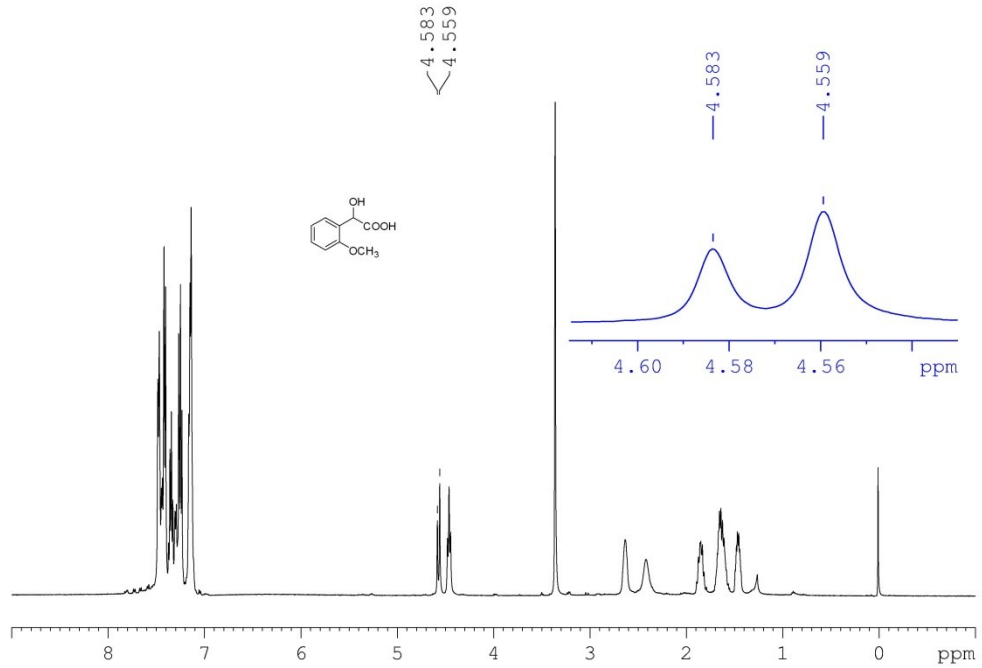

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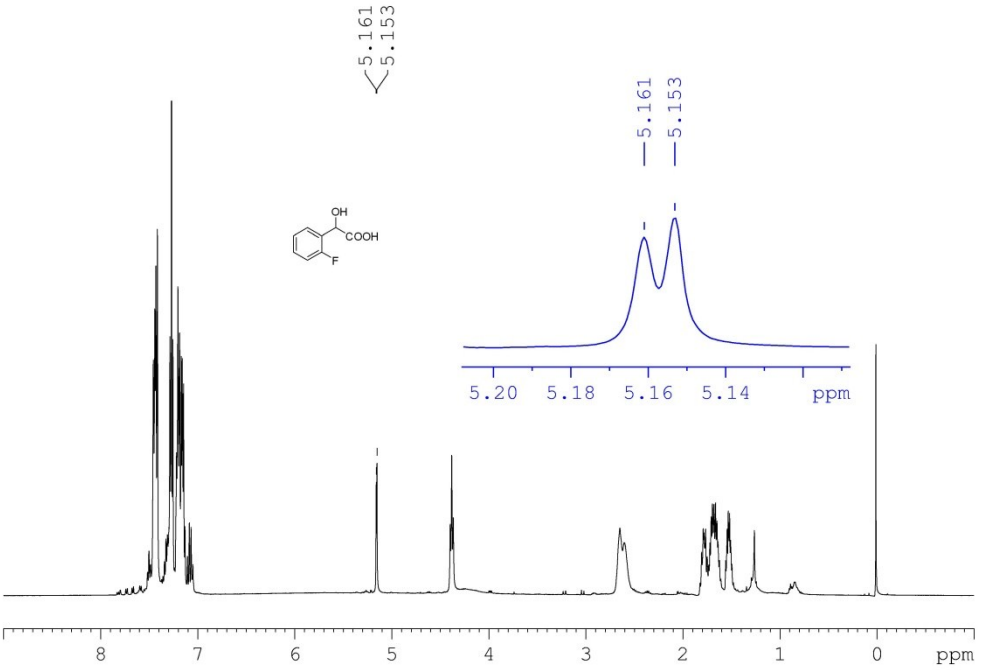

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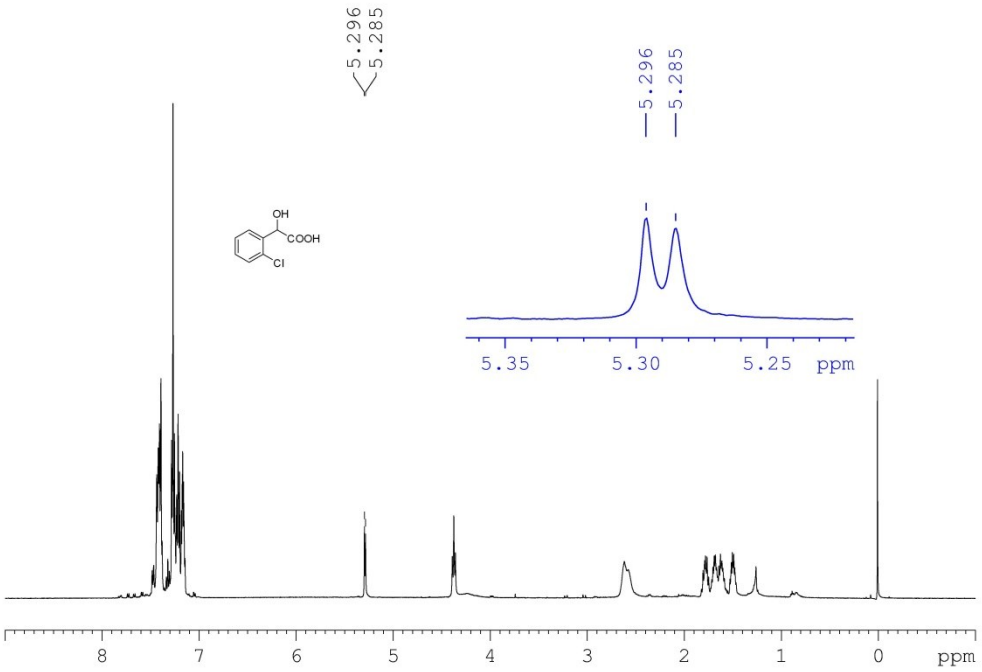

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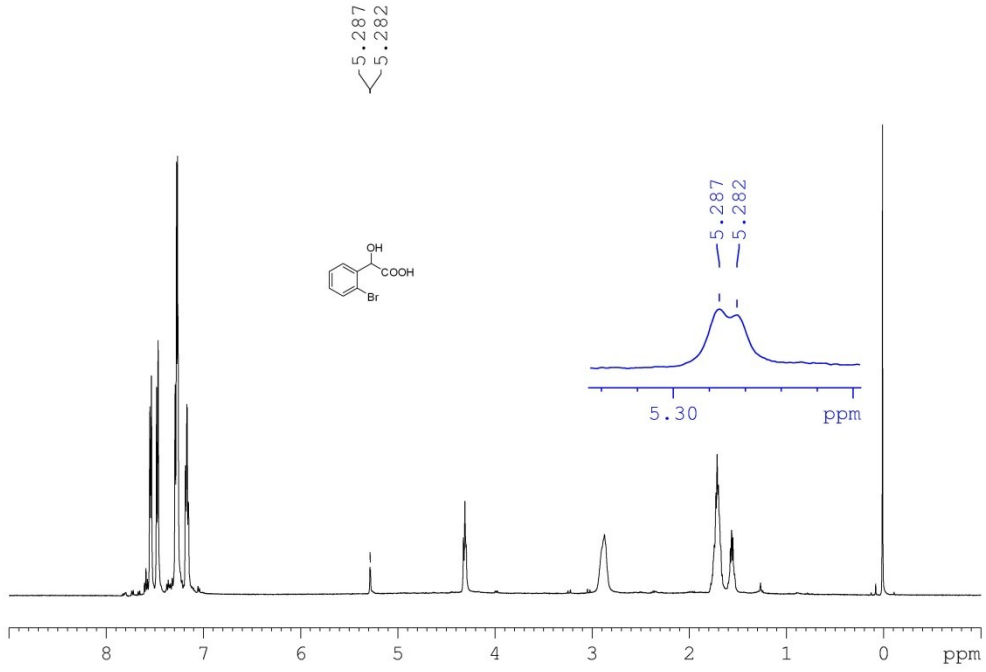

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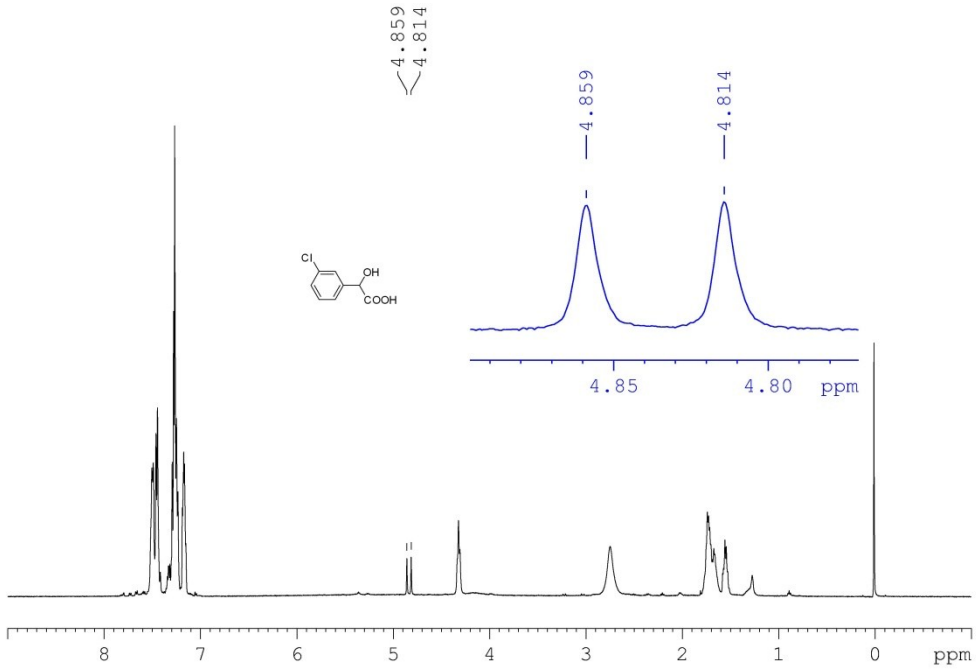

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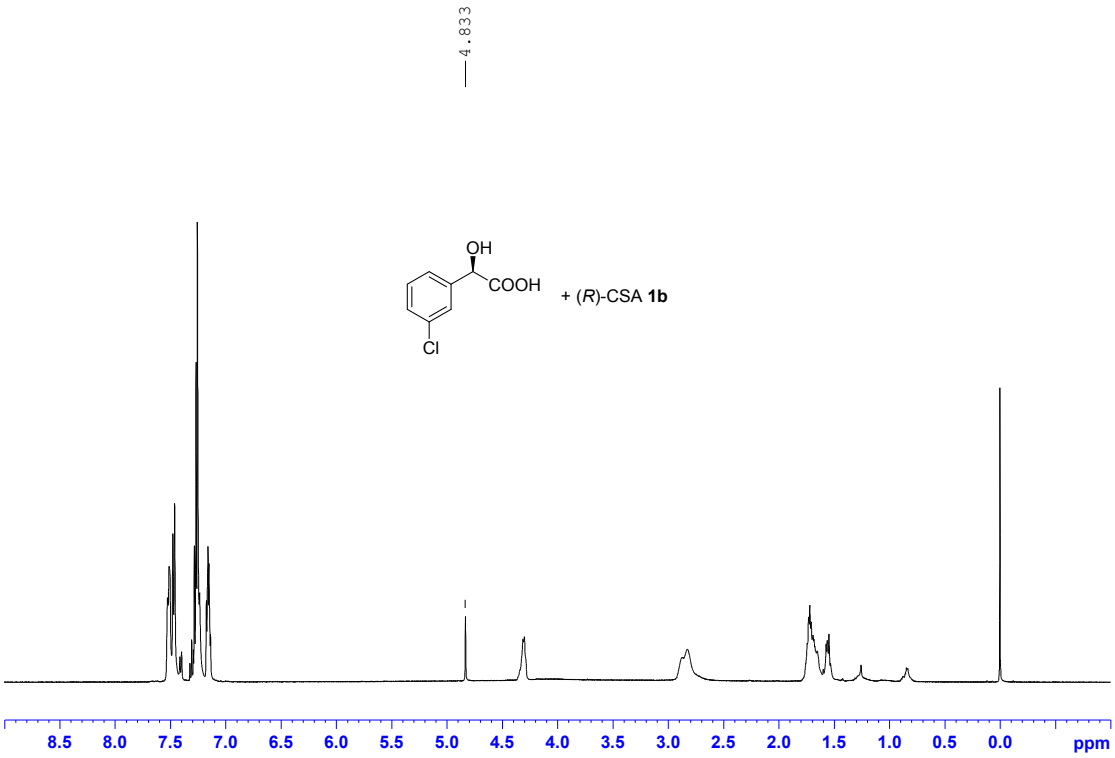

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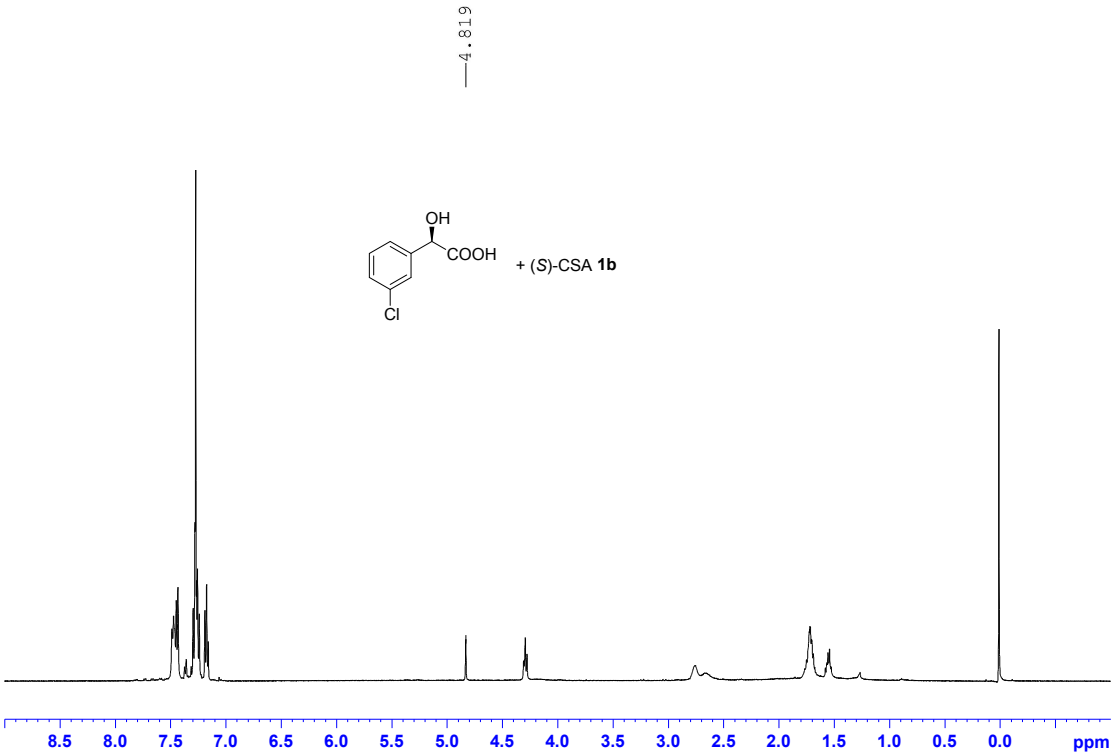

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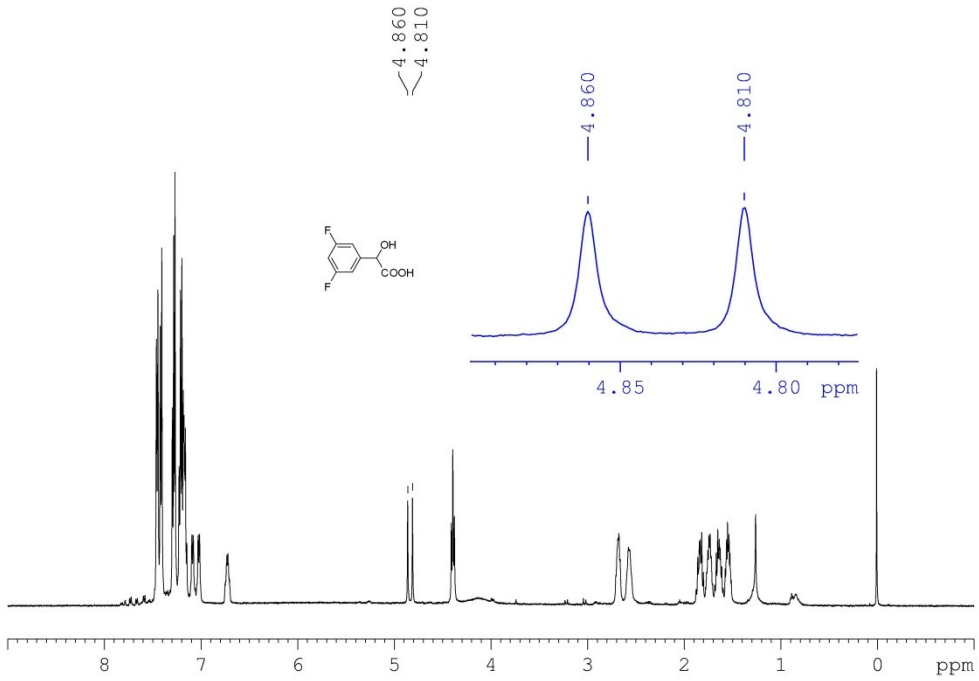
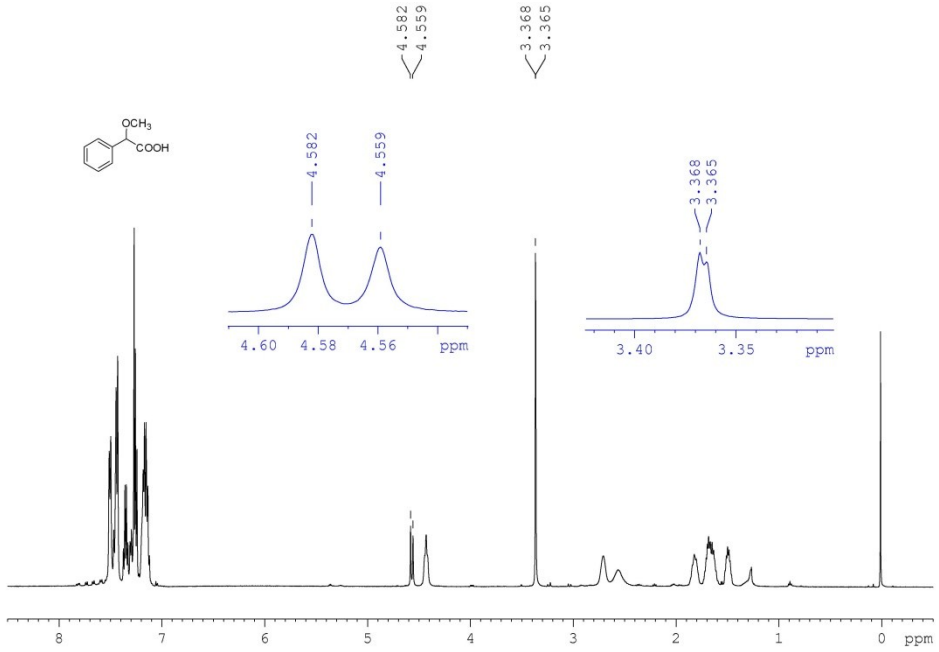
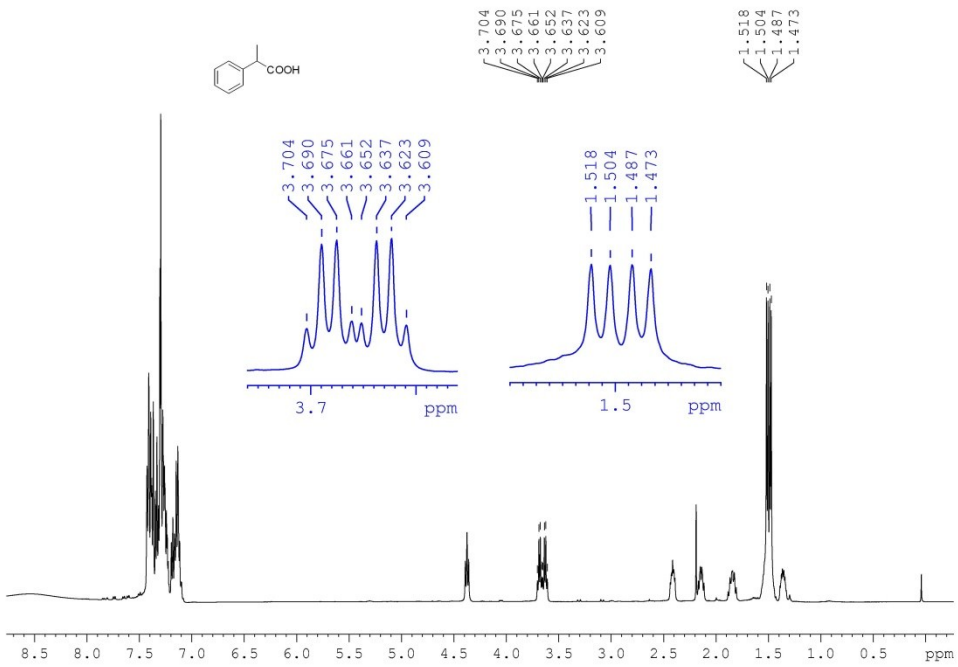


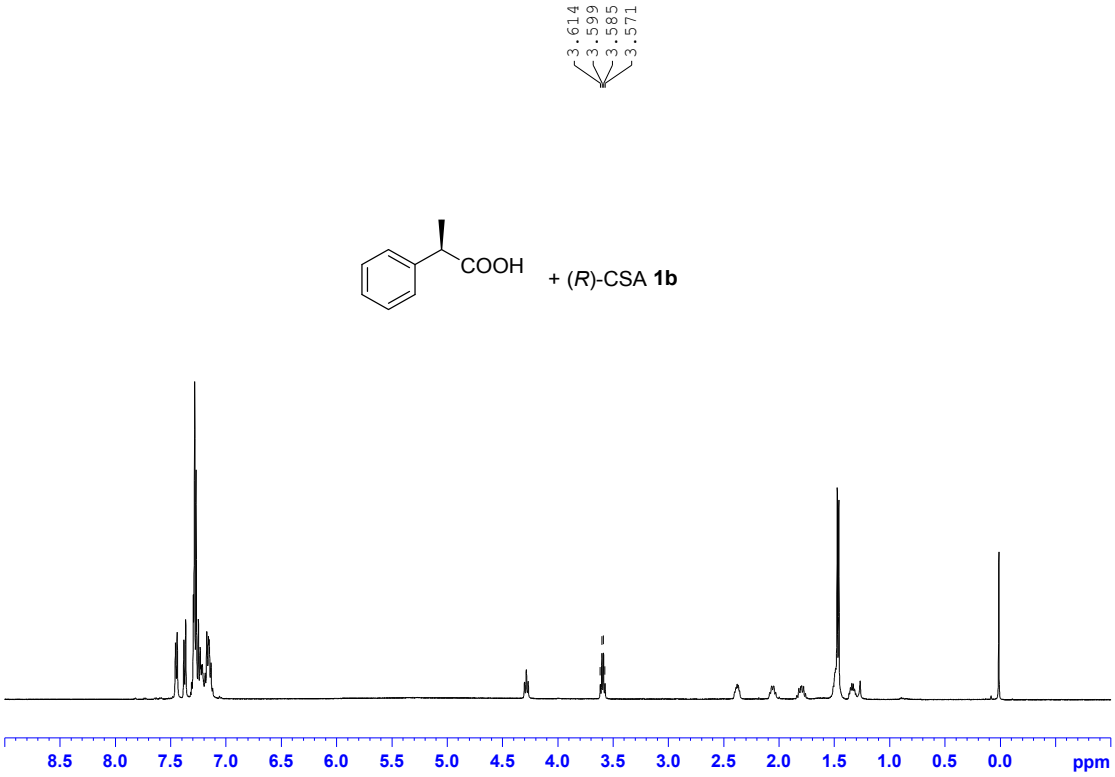
^{1}H NMR Spectra of (*S*)-CSA 1b and (±)-α-Methoxyphenylacetic Acid:



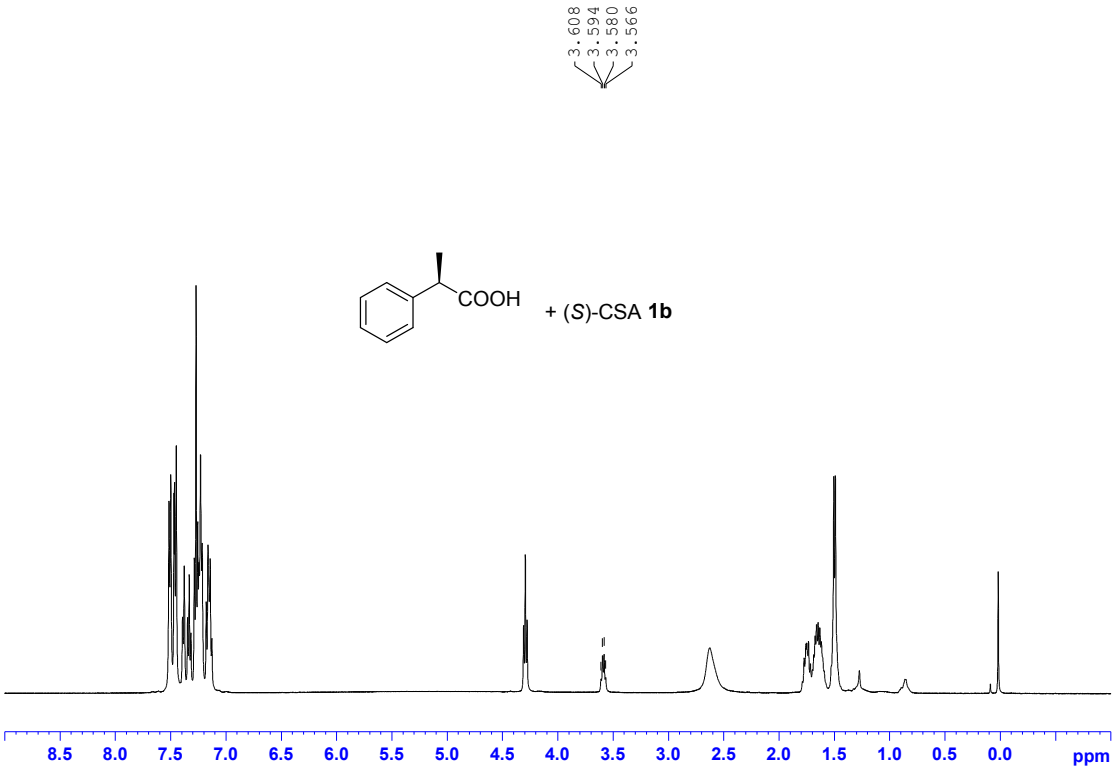
^{1}H NMR Spectra of (*S*)-CSA 1b and (±)-2-Phenylpropionic Acid:



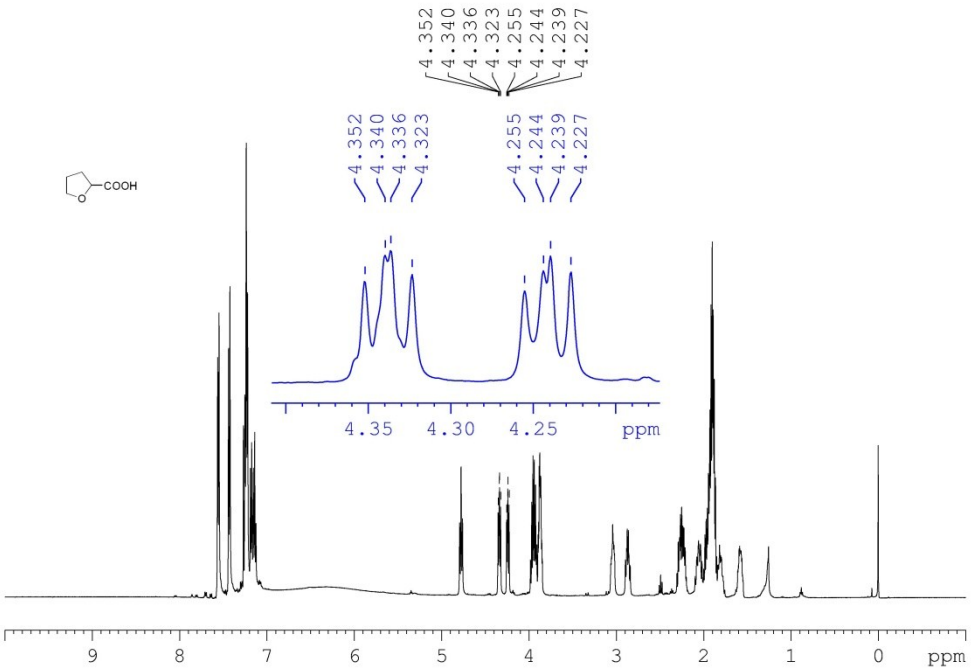
^{1}H NMR Spectra of (*R*)-CSA 1b and (*R*)-2-Phenylpropionic Acid:



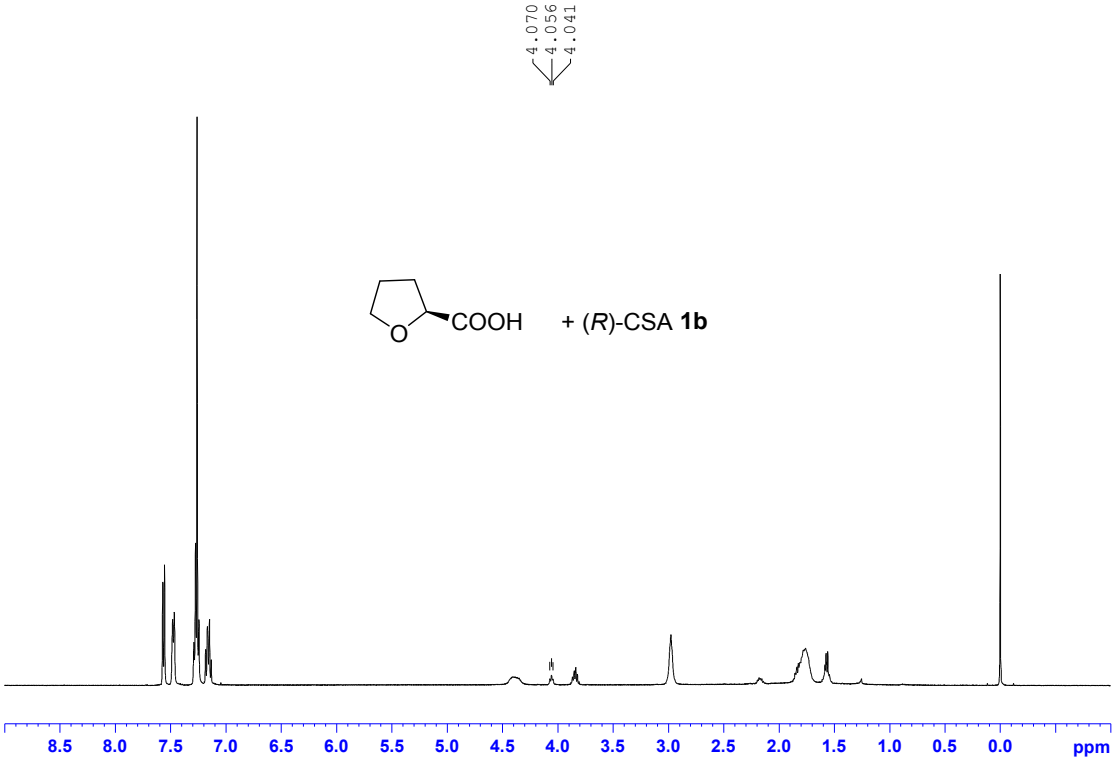
^{1}H NMR Spectra of (*S*)-CSA 1b and (*R*)-2-Phenylpropionic Acid:



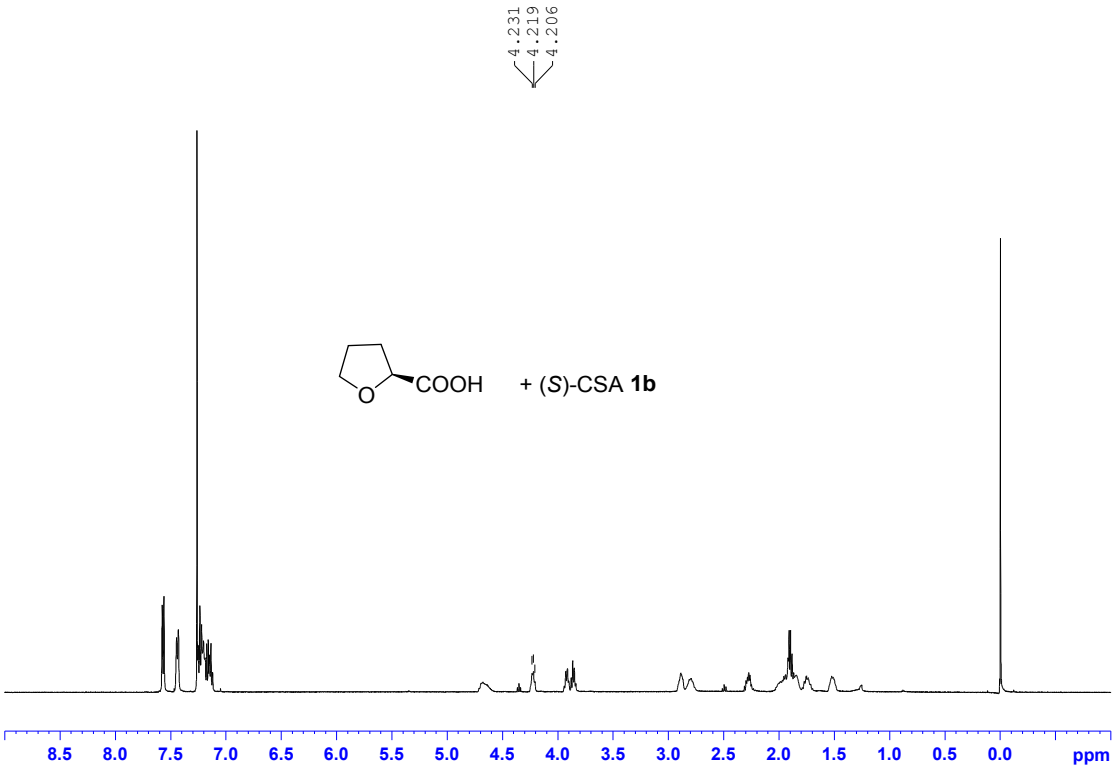
^{1}H NMR Spectra of (S)-CSA 1b and (±)-2-Tetrahydrofuroic Acid:



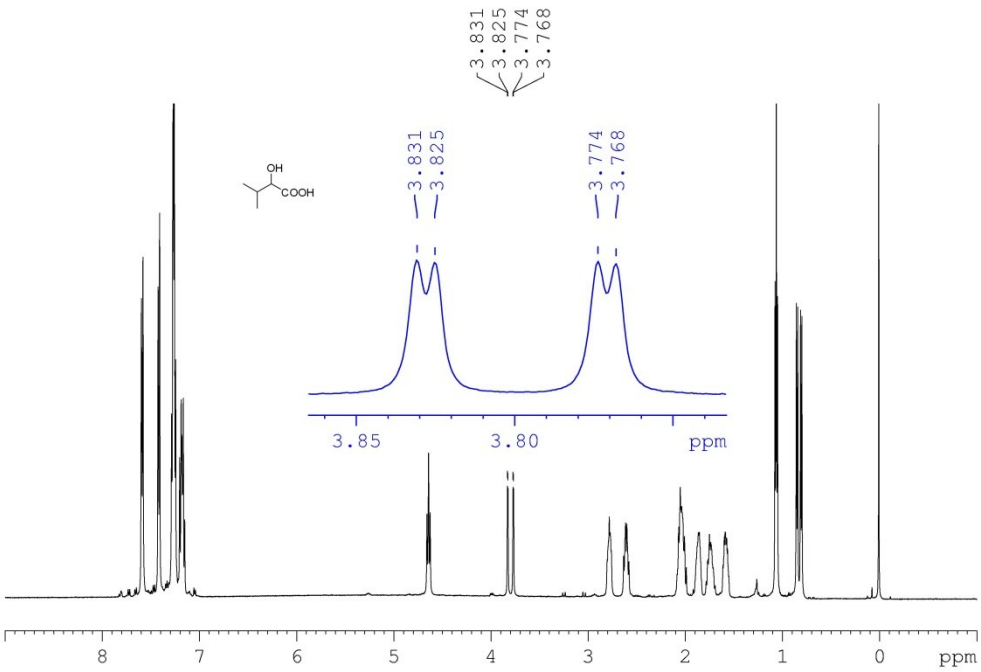
^{1}H NMR Spectra of (*R*)-CSA 1b and (*S*)-2-Tetrahydrofuroic Acid:



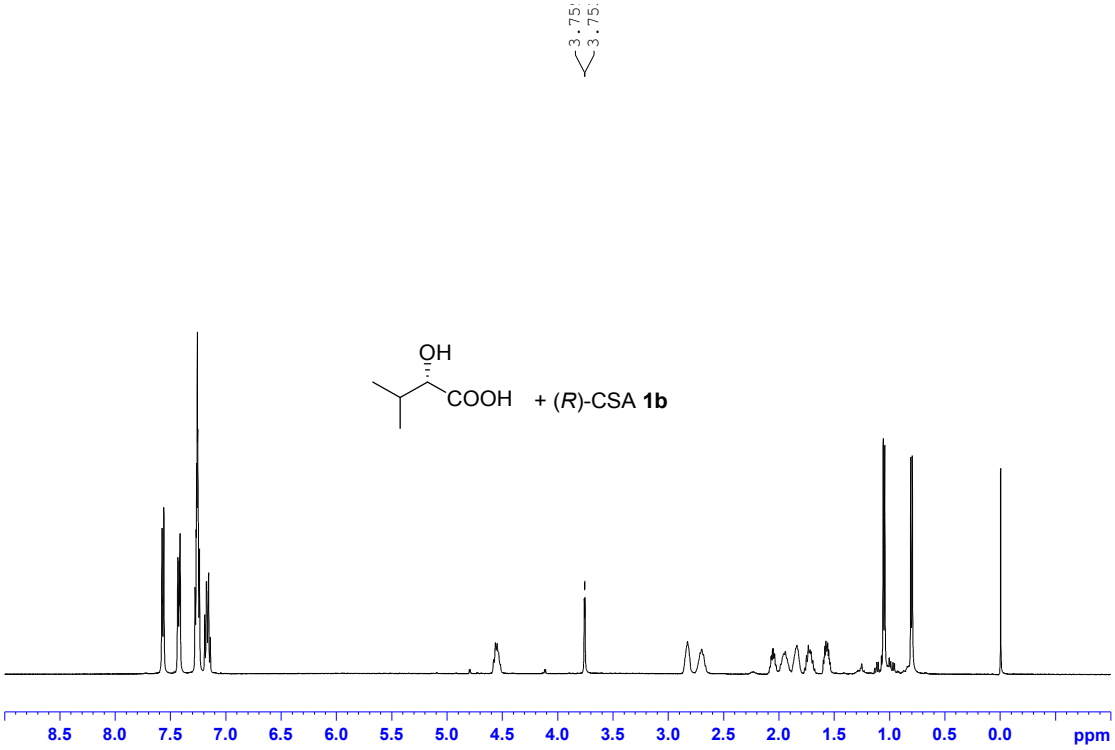
^{1}H NMR Spectra of (*S*)-CSA 1b and (*S*)-2-Tetrahydrofuroic Acid:



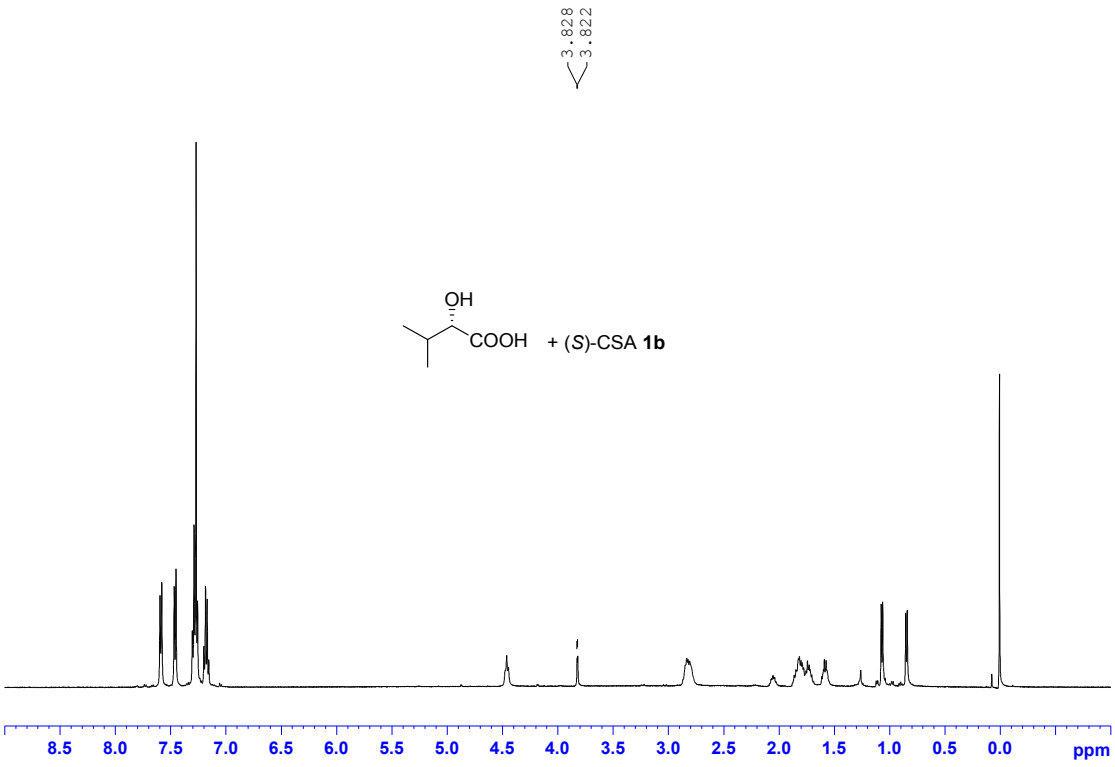
^{1}H NMR Spectra of (*S*)-CSA 1b and (±)-2-Hydroxy-3-methylbutanoic Acid:



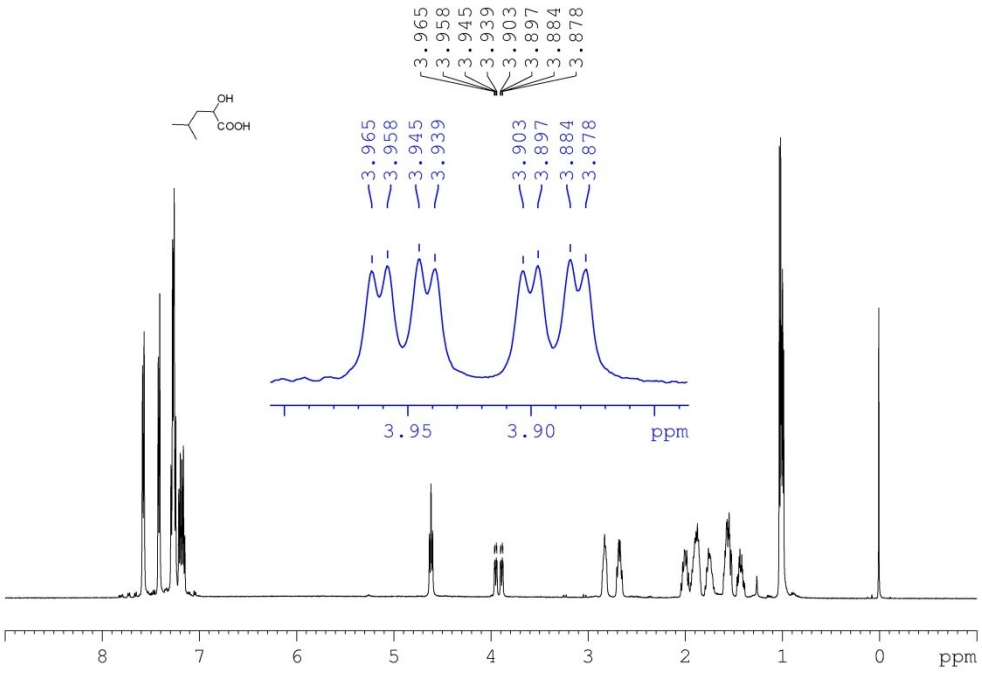
^{1}H NMR Spectra of (*R*)-CSA 1b and (*S*)-2-Hydroxy-3-methylbutanoic Acid:



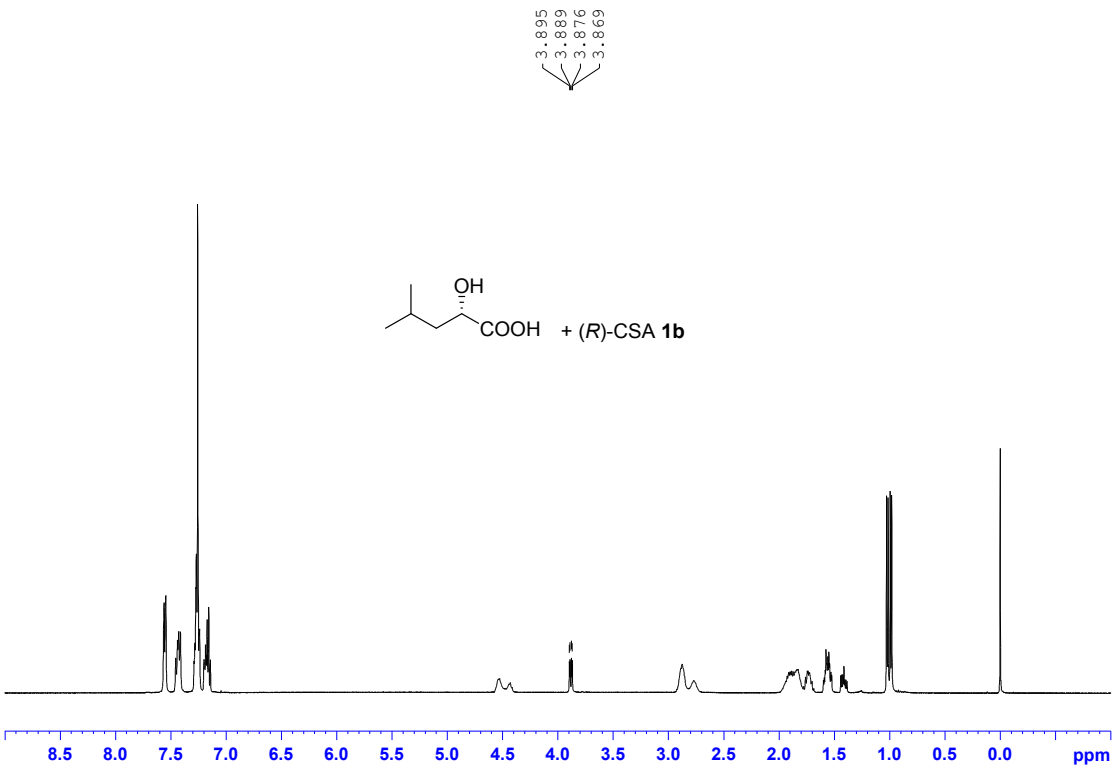
^{1}H NMR Spectra of (*S*)-CSA 1b and (*S*)-2-Hydroxy-3-methylbutanoic Acid:



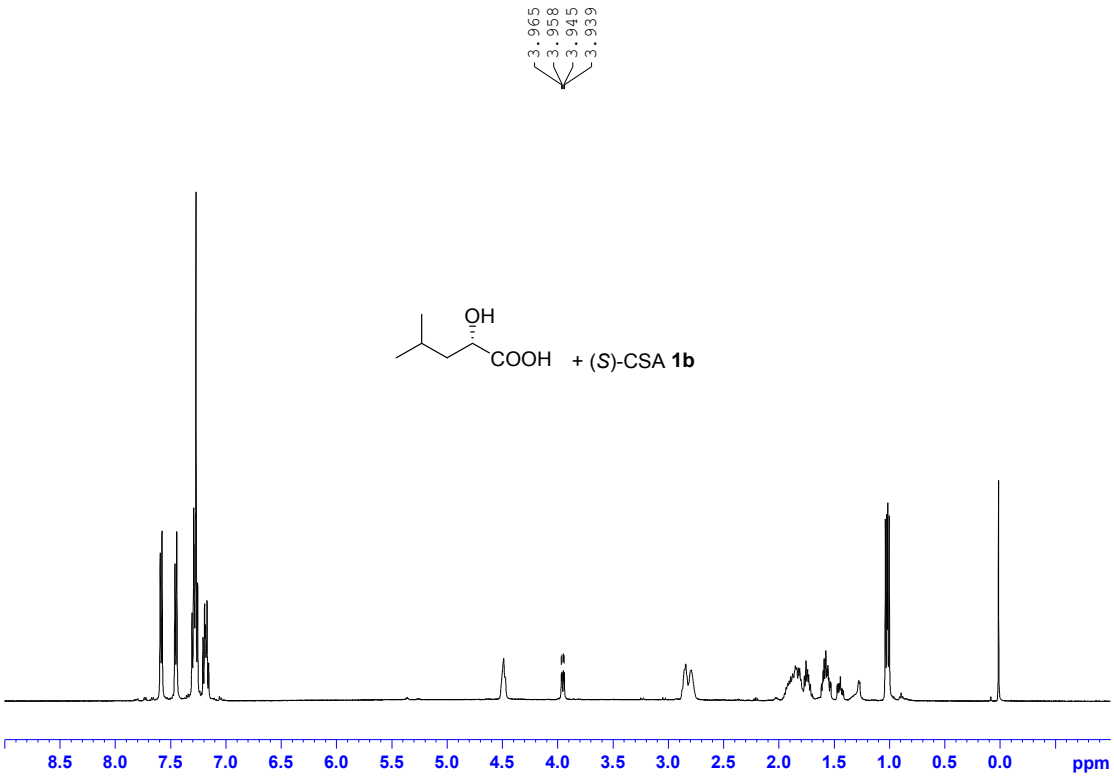
^{1}H NMR Spectra of (*S*)-CSA 1b and (±)-2-Hydroxy-4-methylpentanoic Acid:



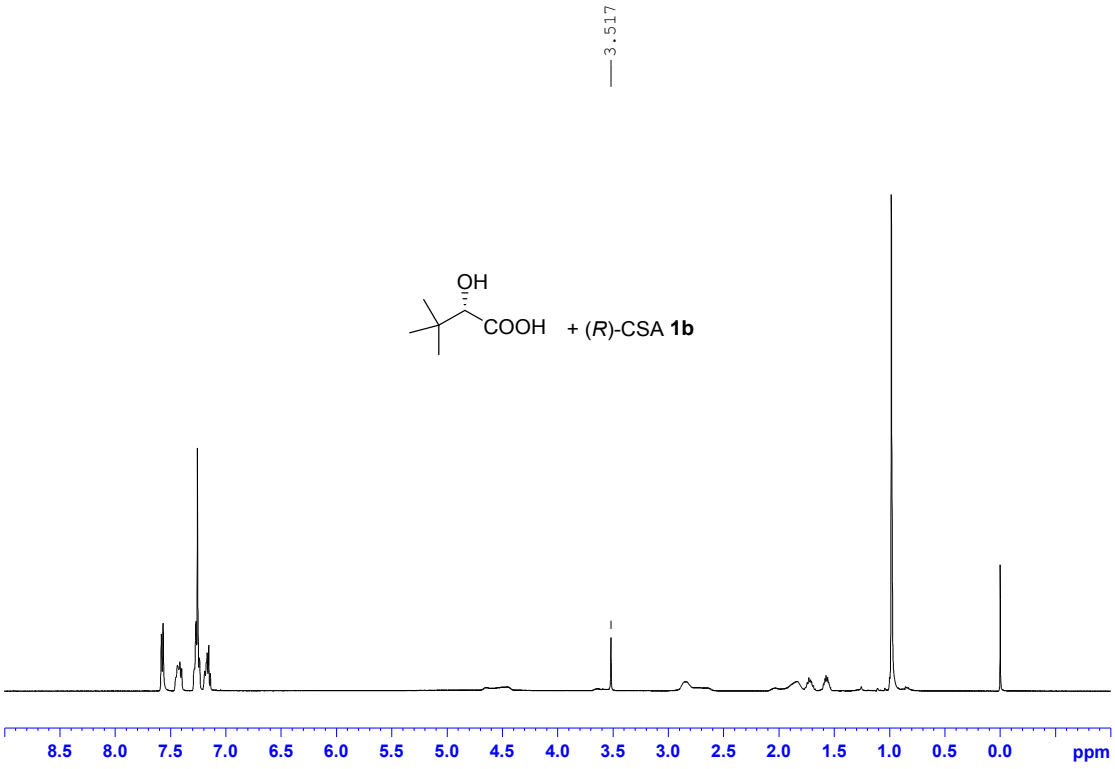
^{1}H NMR Spectra of (*R*)-CSA 1b and (*S*)-2-Hydroxy-4-methylpentanoic Acid:



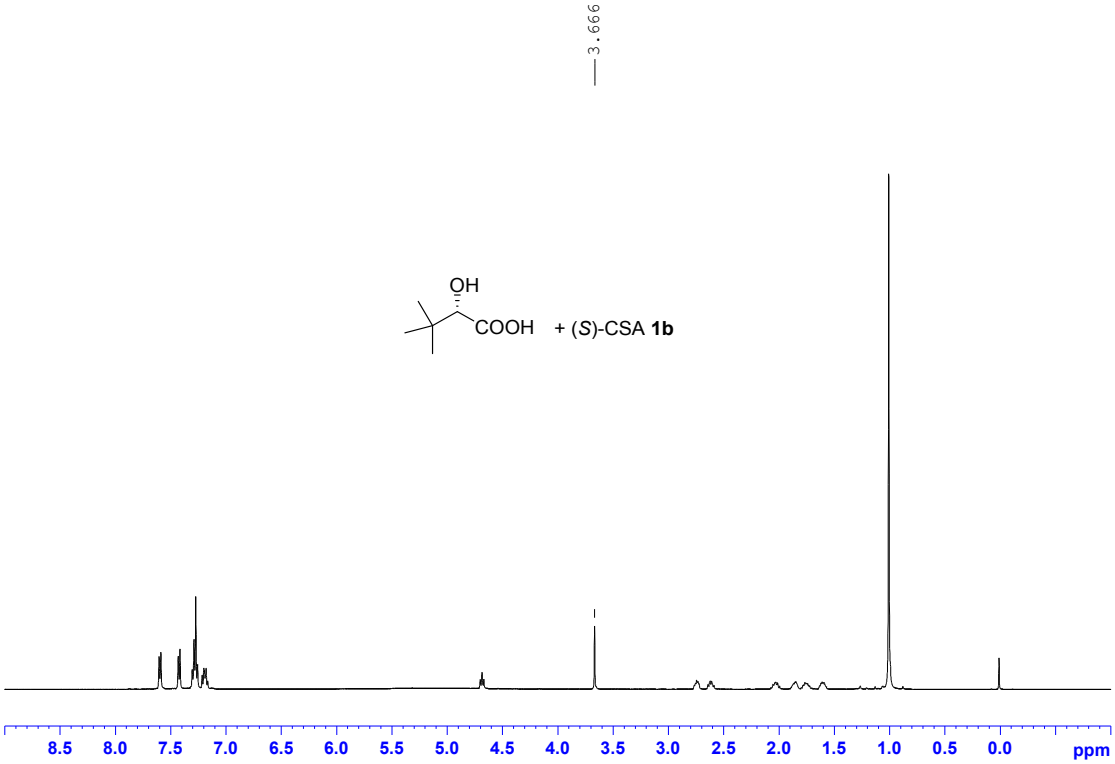
^{1}H NMR Spectra of (*S*)-CSA 1b and (*S*)-2-Hydroxy-4-methylpentanoic Acid:



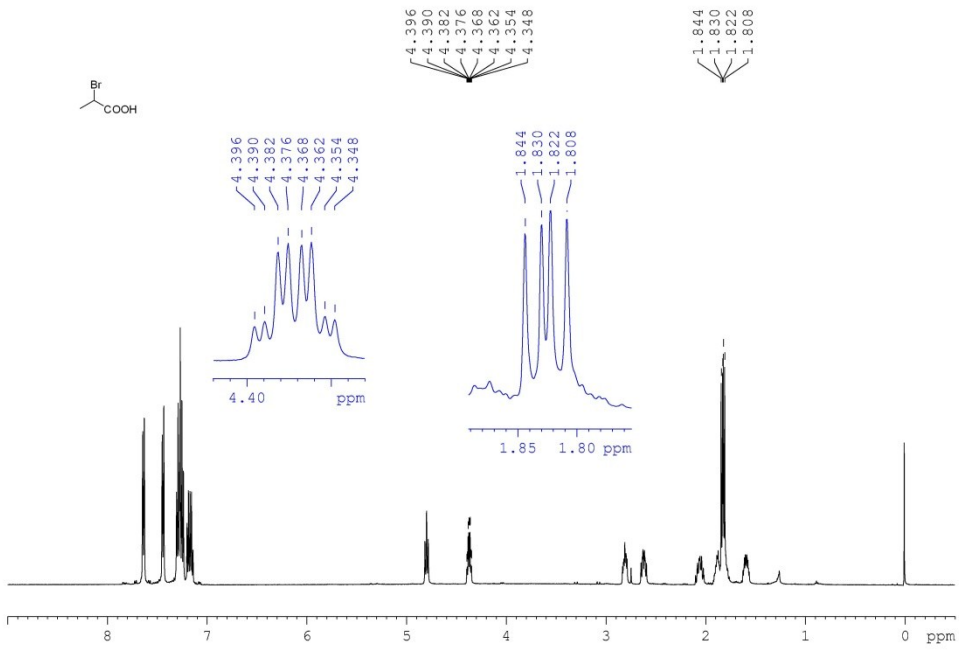
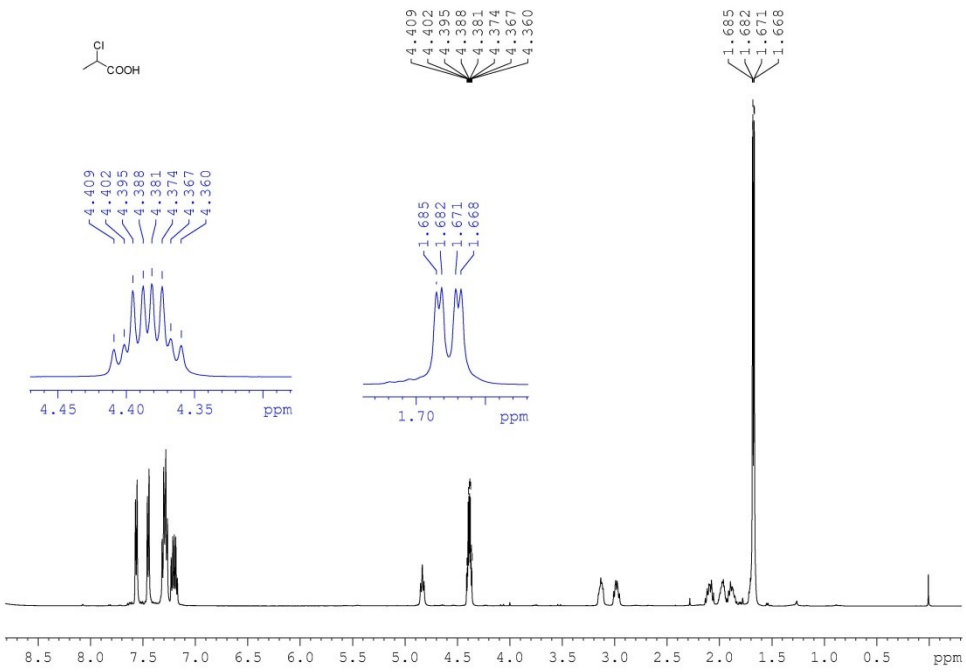
^{1}H NMR Spectra of (*R*)-CSA 1b and (*S*)-2-Hydroxy-3,3-dimethylbutyric Acid:



^{1}H NMR Spectra of (*S*)-CSA 1b and (*S*)-2-Hydroxy-3,3-dimethylbutyric Acid:



^{1}H NMR Spectra of (*S*)-CSA 1b and (±)-2-Bromopropionic Acid:



^{1}H NMR Spectra of (*S*)-CSA 1b and (±)-2-Chloropropionic Acid: