Asymmetric Synthesis of Protected Arylglycines by Rhodium-Catalyzed Addition of Arylbronic Acids to *N*-*tert*-butanesulfinyl Imino Esters.

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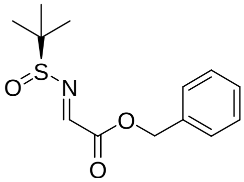
Supporting Information

General Procedure Methods. Arylboronic acids were purchased from commercial sources and purified directly before use by recrystallization from water.[1] Acetylacetonatobis(cyclooctene)rhodium and 1,2-bis(diphenylphosphino)benzene were purchased from Strem and used without further purification. *tert*-Butanesulfinamide[2] and $[Rh(cod)(MeCN)_2]BF_4$[3] were synthesized according to the literature procedures. 4 M HCl (solution in 1,4-dioxane) was purchased from Aldrich. Extra dry 1,4-Dioxane (< 50 ppm water) was purchased from Acros and passed through a column of dry, activated, basic alumina and stored over 3 Å MS in a glove box or it was distilled from sodium/benzophenone ketyl. Methanol, CH_2Cl_2, CH_3CN and NEt_3 were freshly distilled over CaH_2 prior to use. Column chromatography was carried out using Merck 60 230-240 mesh silica gel according to the general procedure of Still.[4] 3 Å MS and 4 Å MS were purchased from Aldrich and were dried according to the method of Burfield and Smithers.[5] *N*-sulfinyl imino esters **1**[6], **2**[7], and **4**[8] were synthesized according to literature procedure and stored in a glovebox at -30 ˚C. Arylboronic acid reactions were carried out in Kimble 5 mL microvials (Kimble product number 60700-5) using PTFE stir-vanes (Kimble product number 749060-0003) and capped with mini-inert seals (Kimble product number 749110-0022) and blue nylon caps (Kimble product number 410119-2015). The reaction vials were heated in a custom-made aluminum heating block drilled to fit the vials (UC machine shop) and the temperature was maintained by placing the block on an IKA stirrer/hotplate (RCT basic model) with a thermistor controller (ETS-D4 fuzzy). Diastereoselectivity determinations were performed using either an Agilent 1100 series LC equipped with a silica normal phase column (Microsorb Si 100 A packing) with a multiwavelength detector or an Agilent 7683 series GC equipped with an Ultra-II column. IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer and only partial data are listed. Chemical shifts for ^{1}H and ^{13}C NMR spectra were recorded in ppm and referenced to either the residual solvent peak (^{1}H, ^{13}C) or TMS (^{1}H) as an internal standard. Mass spectra were obtained from the Microanalytical Laboratory at the University of California, Berkeley.

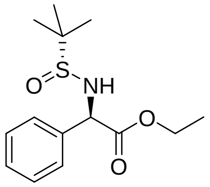


(*R*)-*N*-(*t*-butanesulfinyl)iminoacetic acid, benzyl ester 3. Benzyl glyoxylate[9] (2.95 g, 18.0 mmol, 1.0 equiv) was added to a round-bottom flask containing 4 Å molecular sieves (activated powder which had been dried overnight at 300 ˚C under vacuum) in CH_2Cl_2 (168 mL). To this rapidly stirring solution was added (*R*)-*tert*-butanesulfinamide (2.18 g, 18.0 mmol, 1.0 equiv) and the resulting mixture was stirred at room temperature for 4 days.[6] The reaction mixture was filtered through a pad of Celite and washed with EtOAc (3 x 70 mL). The filtrate was dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (25% EtOAc:hexanes) to yield **3** (2.8 g, 43 % yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (s, 9H), 5.31 (s, 2 H), 7.33-7.38 (m, 5H), 8.02 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 58.8, 67.7, 126.3, 128.4, 128.6, 134.7, 155.2, 160.7. IR: 3301, 2966, 1732, 1176, 1093, 696 cm $^{-1}$. Exact mass calcd for $C_{13}H_{18}NO_3S$ requires m/z 300.1269, found m/z 300.1260 (MH^+, FAB).

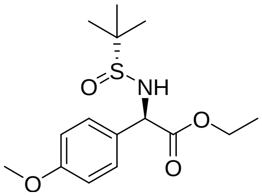
General Procedure for the Addition of Arylboronic Acids to *N-tert*-Butanesulfinyl Imines. Reactions were set up in a glovebox. To a vial containing a stir-vane and the appropriate arylboronic acid (0.500 mmol, 2.0 equiv) was added the appropriate sulfinyl imine (0.250 mmol, 1.0 equiv) in 1.0 mL of dioxane. 1,2-Bis(diphenylphosphino)benzene (6.2 mg, 0.014 mmol, 0.055 equiv) was dissolved in 1.0 mL of dioxane and added to a vial containing acetylacetonatobis(cyclooctene)rhodium (5.3 mg, 0.013 mmol, 0.050 equiv), and the resulting mixture of catalyst and ligand was added to the sulfinyl imine mixture. The reaction vial was capped, removed from the glovebox, and placed in a heating block on the benchtop with stirring. The reaction mixture was heated to 70 ˚C (aluminum block temperature) and stirred for 14-19 h. The reaction mixture was allowed to cool to rt and diluted with EtOAc (4 mL). The organic layer was washed with brine (2 mL) and the aqueous layer was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The products were isolated by silica gel chromatography using EtOAc:hexanes mixtures and were visualized with CMA stain.

General Procedure for the Preparation of (+) and (-) α-Methoxy-α-trifluoromethylphenylacetamides (MTPA amides) from *N*-sulfinyl arylglycine esters. Cleavage of the sulfinyl group was carried out according to the literature procedure.[10] Specifically, the *N*-sulfinyl arylglycine esters were treated with a 1:1 mixture of MeOH and 4 M HCl in dioxane (0.06 M). The reaction mixture was stirred at rt, concentrated, and the desired product was precipitated with diethyl ether. The resulting amine hydrochloride (1.0 equiv) was dissolved in CH_2Cl_2 (0.1 M) and Hunig's base (4.0 equiv) was added dropwise. >99% ee (+) or >99% (-) MTPA chloride (~ 2.0 equiv) was added to the reaction mixture, and the resulting mixture was stirred for 16 h at room temperature. The reaction mixture was quenched with 1 N sodium bisulfate and diluted with Et_2O. The organic layer was removed, and the remaining aqueous layer was extracted with Et_2O (2x). The combined organic layers were dried over Na_2SO_4, concentrated, and filtered through a short plug of silica gel with EtOAc eluent.

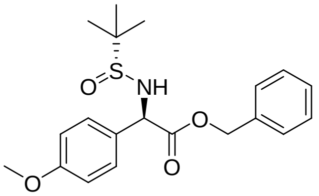
General Procedure for Epimerizations to Obtain an Authentic Mixture of Diastereomers. *N*-Sulfinyl arylglycines (1.0 equiv) were dissolved in CH_2Cl_2 (0.75 M) and NEt_3 (7.0 equiv) was added dropwise. The resulting mixture was stirred for 1-24 h at room temperature or 30 ˚C. The reaction mixture was quenched with 1 N sodium bisulfate and diluted with EtOAc. The organic layer was removed and the remaining aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine (1 x), dried over Na_2SO_4, and concentrated. The obtained product was analyzed without further purification.



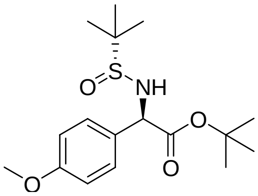
***N*-sulfinyl arylglycine ether ester.** The general procedure was followed with stirring for 19 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (66.1 mg, 93% yield). 97:3 dr. The MTPA derivatives of this compound were prepared according to the general procedure and the diastereomeric ratio was determined by GC analysis (Agilent Ultra II column, 100-300 ˚C, 5 deg/min, 20 psi; (*R*)-MTPA derivative of major diastereomer t_R = 29.33 min, minor diasteromer t_R = 28.84 min). ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, *J* = 7.2, 3H), 1.24 (s, 9H), 4.11 - 4.25 (m, 2H), 4.60 (d, *J* = 4.0, 1H), 5.06 (d, *J* = 4.4, 1H), 7.31-7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.5, 55.9, 60.4, 62.1, 127.7, 128.4, 128.6, 137.2, 171.4. Spectroscopic data corresponds to that reported in literature.[6]



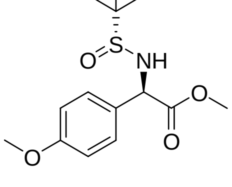
***N*-sulfinyl 4-methoxyarylglycine ethyl ester.** The general procedure was followed with stirring for 19 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (70.0 mg, 89% yield). 98:2 dr. The MTPA derivatives of this compound were prepared according to the general procedure and the diastereomeric ratio was determined by GC analysis (Agilent Ultra II column, 100-300 ˚C, 5 deg/min, 20 psi; (*R*)-MTPA derivative of major diastereomer t_R = 33.49 min, minor diasteromer t_R = 32.95 min).^{1}H NMR (400 MHz, CDCl$_3$): δ 1.21 (t, *J* = 2.8, 3H), 1.22 (s, 9H), 3.80 (s, 3H), 4.13-4.27 (m, 2H), 4.5 (d, *J* = 4 Hz, 1 H), 5.15 (d, *J* = 4 Hz, 1H), 6.88 (d, *J* = 9 Hz, 2H), 7.34 (d, *J* = 9 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.9, 22.5. 55.2, 55.8, 59.7, 62.0, 113.9, 128.9, 129.2, 159.6, 171.5. IR: 3281, 3202, 2966, 1733, 1070 cm $^{-1}$. Exact mass calcd for $C_{15}H_{24}NO_4S$ requires m/z 314.1426, found m/z 314.1435 (MH$^+$, FAB).



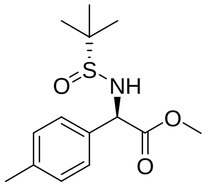
***N*-sulfinyl 4-methoxyarylglycine benzyl ester.** The general procedure was followed with stirring for 18 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a white solid (80.0 mg, 85% yield). mp 76-78 ˚C. 98:2 dr. The MTPA derivatives of this compound were prepared according to the general procedure and the diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 99:1 hexanes: iPrOH, 1.0 mL/min, λ= 230 nm; (*R*)-MTPA derivative of major diasteromer t_R = 10.95 min, minor diasteromer t_R = 9.69 min). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.23 (s, 9H), 3.80 (s, 3H), 4.54 (d, *J* = 3.9 Hz, 1H), 5.08 (d, *J* = 4.0 Hz, 1 H), 5.09 – 5.19 (dd, *J* = 12.3 Hz, 2H), 6.88 (d, *J* = 7.7 Hz, 2H), 7.27 (m, 2H), 7.28-7.30 (m, 5H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 22.5, 55.2, 55.9, 59.8, 67.5, 114.0, 127.9, 128.3, 128.5, 128.9, 129.1, 135.1, 159.7, 171.4. IR: 3301, 2965, 1734, 1068, 735 cm $^{-1}$. Exact mass calcd for $C_{20}H_{26}NO_4S$ requires m/z 376.1582, found m/z 376.1580 (MH$^+$, FAB).



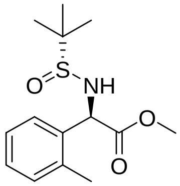
***N*-sulfinyl 4-methoxyarylglycine *tert*-butyl ester.** The general procedure was followed with stirring for 19 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a white solid (66.0 mg, 78% yield). mp 67-69 ˚C. 98:2 dr. The MTPA derivatives of this compound were prepared according to the general procedure and the diastereomeric ratio was determined by ^{19}F NMR (376 MHz, CDCl$_3$): (*R*)-MTPA derivative of major diastereomer δ =-68.29, minor diasteromer δ = -68.01. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.20 (s, 9H), 1.38 (s, 9H), 3.81 (s, 3H), 4.53 (d, *J* = 3.6 Hz, 1H), 4.91 (d, *J* = 4.0 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 22.5, 27.7, 55.2, 55.7, 60.1, 82.7, 113.8, 128.8, 129.8, 159.4, 170.6. IR: 3230, 2966, 1731, 1055 cm $^{-1}$. Exact mass calcd for $C_{17}H_{28}NO_4S$ requires m/z 342.1739, found m/z 342.1727 (MH$^+$, FAB).



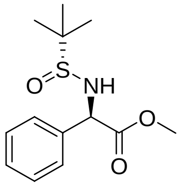
***N*-sulfinyl 4-methoxyarylglycine methyl ester 5a.** The general procedure was followed with stirring for 18 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (67.0 mg, 90% yield). 99:1 dr. The MTPA derivatives of **5a** were prepared according to the general procedure and the diastereomeric ratio was determined by GC analysis (Agilent Ultra II column, 100-300 ˚C, 5 deg/min, 20 psi; (*R*)-MTPA derivative of major diastereomer t_R = 32.25 min, minor diasteromer t_R = 32.74 min). $[\alpha]^{25}_D$ = -127.0 (c =1.0, EtOH) as the free amine after sulfinyl group removal. Lit. value : 84% ee, $[\alpha]^{25}_D$ = -117.3 (c =1.0, EtOH).[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ1.23 (s, 9H), 3.72 (s, 3H), 3.81 (s, 3H), 4.55 (s, 1H), 5.04 (d, *J* = 2.6 Hz, 1 H), 6.89 (d, *J* = 7.0 Hz, 2H), 7.29 (d, *J* = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, MeOD): δ 21.5, 51.7, 54.3, 55.8, 60.4, 113.7, 128.5, 128.8, 159.4, 172.0. IR: 3292, 2957, 1737, 1063 cm $^{-1}$. Exact mass calcd for $C_{14}H_{22}NO_4S$ requires m/z 300.1269, found m/z 300.1260 (MH^+, FAB).



***N*-sulfinyl arylglycine methyl ester 5b.** The general procedure was followed with stirring for 16 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (64.0 mg, 90% yield). 98:2 dr. The MTPA derivatives of **5b** were prepared according to the general procedure and the diastereomeric ratio was determined by GC analysis (Agilent Ultra II column, 100-300 ˚C, 5 deg/min, 20 psi; (*R*)-MTPA derivative of major diastereomer t_R = 30.18 min, minor diasteromer t_R = 29.59 min).^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 9H), 2.35 (s, 3H), 3.72 (s, 3H), 4.55 (d, *J* = 4.0 Hz, 1H), 4.5 (d, *J* = 4.2 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 22.6. 53.0, 56.0, 60.1, 127.7, 129.5, 134.1, 138.4, 172.1. IR: 3282, 2955, 1739, 1066 cm $^{-1}$. Exact mass calcd for $C_{14}H_{22}NO_3S$ requires m/z 284.1320, found 284.1325 (MH$^+$, FAB).

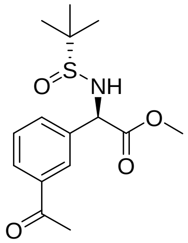


N-sulfinyl arylglycine methyl ester 5c. The general procedure was followed with stirring for 16 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (43.0 mg, 61% yield). 99:1 dr. The MTPA derivatives of **5c** were prepared according to the general procedure and the diastereomeric ratio was determined by GC analysis (Agilent Ultra II column, 100-300 ˚C, 5 deg/min, 20 psi; (*R*)-MTPA derivative of major diastereomer t_R = 29.34 min, minor diasteromer t_R = 28.72 min).^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H), 2.48 (s, 3H), 3.78 (s, 3H), 4.56 (d, *J* = 3.4 Hz, 1H), 5.27 (d, *J* = 4.9 Hz, 1 H), 7.19-7.27 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 22.5, 53.0, 55.8, 57.4, 126.3, 128.2, 128.4, 130.9, 135.2, 136.8, 172.2. IR: 3284, 3199, 2966, 1736, 1067 cm $^{-1}$. Exact mass calcd for $C_{14}H_{22}NO_3S$ requires m/z 284.1320, found m/z 284.1322 (MH$^+$, FAB).

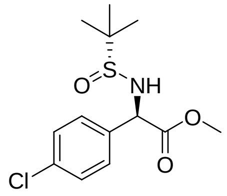


N-sulfinyl arylglycine methyl ester 5d. The general procedure was followed with stirring for 16 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (53.0 mg, 79% yield). 99:1 dr. An authentic mixture of diastereomers of **5d** were prepared according to the general procedure and the diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 95:5 hexanes: iPrOH, 1.0 mL/min,

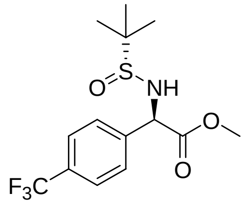
λ= 230 nm; major diastereomer t_R = 18.24 min, minor diastereomer t_R = 13.54 min). $[\alpha]^{25}_D$ = -135.2 (c =1.0, MeOH) as the amine hydrochloride salt after sulfinyl group cleavage. Lit. value: $[\alpha]^{25}_D$ = -132.0 (c =1.0, MeOH).[12] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H), 3.72 (s, 3H), 4.58 (d, *J* = 4.0 Hz, 1H), 5.08 (d, *J* = 4.3 Hz, 1 H), 7.33-7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 53.0, 55.9, 60.3, 127.7, 128.5, 128.7, 137.0, 171.8. IR: 3197, 2966, 1739, 1066, 698 cm $^{-1}$. Exact mass calcd for $C_{13}H_{20}NO_3S$ requires m/z 270.1164, found m/z 270.1161 (MH^+, FAB).



N-sulfinyl arylglycine methyl ester 5e. The general procedure was followed with stirring for 16 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (68.0 mg, 87% yield). 99:1 dr. An authentic mixture of diastereomers of **5e** were prepared according to the general procedure and the diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 90:10 hexanes: iPrOH, 1.0 mL/min, λ= 254 nm; major diastereomer t_R = 22.96 min, minor diastereomer t_R = 20.21 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (s, 9H), 2.61 (s, 3H), 3.74 (s, 3H), 4.66 (d, *J* = 3.5 Hz, 1H), 5.17 (d, *J* = 3.8 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 26.6, 53.2, 56.1, 59.9, 127.6, 128.5, 129.0, 132.4, 137.5, 137.7, 171.3 197.4. IR: 3198, 2966, 1740, 1684, 1067, 691 cm $^{-1}$. Exact mass calcd for $C_{15}H_{22}NO_4S$ requires m/z 312.1269, found m/z 312.1270 (MH^+, FAB).

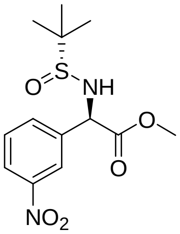


N-sulfinyl arylglycine methyl ester 5f. The general procedure was followed with stirring for 16 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (62.0 mg, 82% yield). 99:1 dr. An authentic mixture of diastereomers of **5f** were prepared according to the general procedure and the diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 95:5 hexanes: iPrOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 17.95 min, minor diasteromer t_R = 12.08 min). $[\alpha]^{25}_D$ = -122.3 (c =1.0, MeOH) as the free amine after sulfinyl group cleavage. Lit. value : $[\alpha]^{25}_D$ = -129.0 (c =1.0, MeOH).[13] ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.24 (s, 9H), 3.73 (s, 3H), 4.58 (d, J = 3.5 Hz, 1H), 5.06 (d, J = 3.8 Hz, 1 H), 7.28-7.36 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 22.5, 53.2, 56.0, 59.6, 128.9, 129.2, 134.4, 135.5, 171.4. IR: 3285, 2956, 1741, 1075 cm $^{-1}$. Exact mass calcd for $C_{13}H_{19}ClNO_3S$ requires m/z 304.0774, found m/z 304.0779 (MH$^+$, FAB).

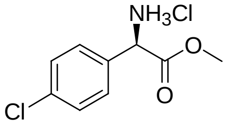


N-sulfinyl arylglycine methyl ester 5g. The general procedure was followed with stirring for 14 h. The product was isolated by chromatography (40:60 EtOAc:hexanes) as a yellow oil (62.5 mg, 74% yield). 98.5:1.5 dr. An authentic mixture of diastereomers of **5g** were prepared according to the general procedure with stirring for 1 h and the diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 95:5

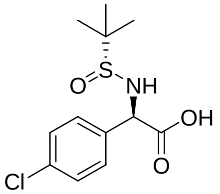
hexanes: iPrOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 18.96 min, minor diasteromer t_R = 12.36 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 9H), 3.73 (s, 3H), 4.64 (d, *J* = 3.7 Hz, 1H), 5.15 (d, *J* = 3.9 Hz, 1 H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7, 53.5, 56.4, 60.0, 125.4 (q, *J* = 272 Hz) 125.9 (q, *J* = 3.7 Hz), 128.4 (2 overlapping C's), 130.8 (q, *J* = 32 Hz), 141.2, 171.3. ^{19}F NMR (376 MHz, $CDCl_3$) -61.87. IR: 3286, 2959, 1743, 1326, 1067 cm $^{-1}$. Exact mass calcd for $C_{14}H_{19}F_3NO_3S$ requires m/z 338.1038, found m/z 338.1046 (MH^+, FAB).



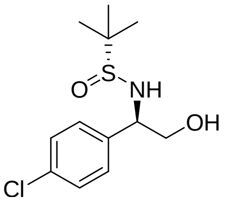
***N*-sulfinyl arylglycine methyl ester 5h.** The general procedure was followed with stirring for 16 h. The product was isolated by chromatography (40:60 EtOAc:hexanes) as a yellow oil (53.9 mg, 69% yield). 99:1 dr. An authentic mixture of diastereomers of **5h** were prepared according to the general procedure with stirring for 1 h and the diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 93:7 hexanes: iPrOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 22.84 min, minor diasteromer t_R = 17.56 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 9H), 3.76 (s, 3H), 4.71 (d, *J* = 3.0 Hz, 1H), 5.22 (d, *J* = 3.5 Hz, 1 H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.75 (d, *J* = 7.7 Hz , 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 8.29(s, 1 H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 53.7, 56.4, 59.5, 122.9, 123.7, 129.9, 134.2, 139.3, 148.6, 171.7. IR: 3295, 2988, 2870, 1740, 1529, 1349, 1066 cm $^{-1}$. Exact mass calcd for $C_{13}H_{18}N_2O_5S$ requires m/z 315.1015, found m/z 315.1010 (MH^+, FAB).



4-chloro phenylglycine methyl ester hydrochloride 6. *N*-sulfinyl arylglycine derivative **5f** (29.0 mg, 0.096 mmol, 1.0 equiv) was taken up in MeOH (0.640 mL, 0.15 M) and was treated with 4.0 M HCl in dioxane (0.120 mL, 5.0 equiv. HCl) at room temperature for 3 h. The reaction mixture was concentrated *en vacuo*, and the amine hydrochloride was precipitated with dry diethyl ether.**[1]** The precipitate was collected by filtration and washed with diethyl ether to yield the amine hydrochloride (21.4 mg, 95%) as a white solid. mp 169-171 ˚C. 98% ee. The MTPA derivatives of **6** were prepared according to the general procedure with stirring for 1 H at -78 ˚C, and the diastereomeric ratio was determined by GC analysis (Agilent Ultra II column, 100-300 ˚C, 5 deg/min, 20 psi; (*R*)-MTPA derivative of major diastereomer t_R = 31.37 min, minor diasteromer t_R = 30.67 min).^{1}H NMR (400 MHz, MeOD): δ 3.82 (s, 3H), 5.27 (s, 1H), 7.47- 7.53 (m, 4H). ^{13}C NMR (100 MHz, MeOD): δ 54.1, 56.8, 130.7, 131.0, 132.0, 137.3, 169.7. IR: 2988, 2869, 1737, 1234, 1138, 765 cm $^{-1}$. Exact mass calcd for $C_9H_{11}ClNO_2$ requires m/z 200.0478, found m/z 200.0482 (MH$^+$, FAB).

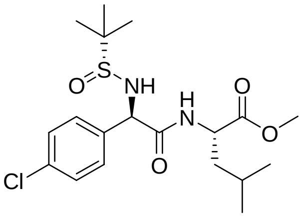


***N*-sulfinyl arylglycine 7** To a round bottomed flask containing LiOH (34.2 mg, 0.990 mmol, 10 equiv) was added distilled H_2O (5.0 mL, 2.0 M), and the resulting solution was cooled to 0 ˚C. A solution of **5f** (30.0 mg, 0.099 mmol, 1.0 equiv) in dioxane (5.0 mL, 0.02 M) was cannulated into the reaction flask. The resulting solution was stirred at 0° C for 5.5 h. The reaction mixture was then concentrated to remove the dioxane, and the remaining material was diluted with distilled H_2O (3 mL) and EtOAc (3 mL) and placed in a seperatory funnel. 1 N $NaHSO_4$ (2 mL) was added and the aqueous layer was extracted with EtOAc (5 x 4 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated with no further purification (26.1 mg, 91%) as a white solid. mp 142-144 ˚C. 99:1 dr. To determine the diastereomeric purity of **7**, the product **7** was treated with diazomethane to afford the *N*-sulfinyl arylglycine methyl ester **5f**. An authentic mixture of diastereomers was made by stirring **5f** with NEt_3 according to the general procedure for 1.5 h at 30 ˚C followed by column chromatography (1:1 EtOAc:hexanes). The diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 95:5 hexanes: iPrOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 17.81 min, minor diasteromer t_R = 11.83 min). ^1H NMR (400 MHz, MeOD): δ 1.23 (s, 9H), 5.03 (s, 1H), 7.36-7.43 (m, 4H). ^{13}C NMR (100 MHz, MeOD): δ 22.9, 61.3, 129.8, 130.6, 135.2, 137.7, 173.6. IR: 3261, 2988, 2870, 1721, 1254, 1007, 887 cm $^{-1}$. Exact mass calcd for $C_{12}H_{16}ClNO_3S$ requires m/z 290.0618, found m/z 290.0622 (MH^+, FAB).



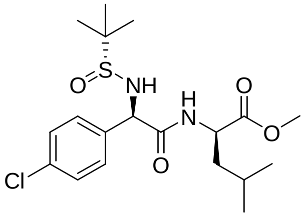
Alcohol 8. To a Kontes vial containing a stir vane was added **7** (30.0 mg, 0.099 mmol, 1.0 equiv) in MeOH (0.250 mL, 0.4 M). The resulting solution was cooled to 0 ˚C and $NaBH_4$ was added in one portion (19.1 mg, 0.50 mmol, 5.0 equiv). The reaction mixture

was stirred at 0 °C for 1 h. The reaction mixture was diluted with EtOAc (3 mL) and was washed with distilled water. The aqueous layer was extracted with EtOAc (3 x), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated with no further purification (22.0 mg, 81%) as an off-white solid. mp 96-98 °C. 99:1 dr. To determine the diastereomeric purity of **8**, epimerized **5f** was reduced with $NaBH_4$ according to the procedure presented above. The diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 90:10 hexanes: EtOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 7.95 min, minor diasteromer t_R = 11.24 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 9H), 3.60 (m, 1H), 3.89 (m, 1 H), 4.28 (m, 1 H), 4.52 (m, 1H), 7.27-7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 56.1, 61.1, 67.2, 128.9, 129.0, 133.9, 137.6. IR: 3277, 2924, 1039, 1012, 825 cm $^{-1}$**.** Exact mass calcd for $C_{12}H_{18}ClNO_2S$ requires m/z 276.0825, found m/z 276.0820 (MH^+, FAB).

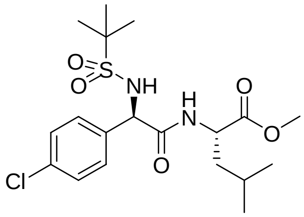


***N*-sulfinyl dipeptide 9.** To a vial containing a stir-vane was added **7** (25.8 mg, 0.089 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 M) and the resulting suspension was cooled to 0 °C. Proton sponge was subsequently added in one portion (57.4 mg, 0.27 mmol, 3.0 equiv.) followed by addition of HOAT (15.8 mg, 0.12 mmol, 1.3 equiv). L-Leucine methyl ester was added to the reaction mixture (48.6 mg, 0.27 mmol, 3.0 equiv), and the reaction mixture was allowed to stir at 0 °C for 1 h and was then warmed to rt and stirred for an additional 2 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with 1

N $NaHSO_4$. The aqueous layer was back-extracted with EtOAc (3 x 5 mL), and the combined organics were then washed with 1 N $NaHCO_3$. The aqueous layer was back-extracted with EtOAc (3 x 5 mL) and combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated by column chromatography (12% EtOAc: hexanes – 100% EtOAc) as a viscous clear oil (30.7 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.933 (d, *J* = 5.1 Hz, 6H), 1.24 (s, 9H), 1.62 (m, 3H), 3.70 (s, 3H), 4.22 (d, *J* = 4.2 Hz, 1H) 4.62 (m, 1H), 5.03 (d, *J* = 4.3 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 7.34 (m, 4H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.7, 22.8, 24.9, 41.1, 51.4, 52.6, 56.2, 60.8, 129.4, 129.7, 134.8, 136.6, 169.9, 173.1. IR: 3267, 2988, 2956, 2870, 1740, 1679, 1144, 1049, 827 cm $^{-1}$. Exact mass calcd for $C_{19}H_{29}ClN_2O_4S$ requires m/z 423.1697, found m/z 423.1712 (MLi^+, FAB).

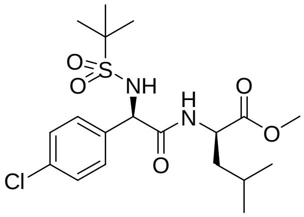


***N*-sulfinyl dipeptide 10.** To a vial containing a stir-vane was added **7** (22.6 mg, 0.078 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 M) and the resulting suspension was cooled to 0 ˚C. Proton sponge was subsequently added in one portion (50.3 mg, 0.24 mmol, 3.0 equiv.) followed by addition of HOAT (13.8 mg, 0.10 mmol, 1.3 equiv). D-Leucine methyl ester was added to the reaction mixture (42.6 mg, 0.24 mmol, 3.0 equiv), and the reaction mixture was allowed to stir at 0 ˚C for 1 h and was then warmed to rt and stirred for an additional 2 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with 1 N $NaHSO_4$. The aqueous layer was back-extracted with EtOAc (3 x 5 mL), and the combined organics were then washed with 1 N $NaHCO_3$. The aqueous layer was back-extracted with EtOAc (3 x 5 mL) and combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated by column chromatography (12% EtOAc: hexanes – 100% EtOAc) as a white solid (15.4 mg, 78 %). mp 102-104 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, *J* = 6.2 Hz, 6H), 1.21 (s, 9H), 1.45-1.62 (m, 3H), 3.66 (s, 3H), 4.55 (m,1H), 4.89 (d, *J* = 2.3 Hz, 1H), 4.95 (d, *J* = 2.6 Hz, 1H), 6.04 (d, *J* = 8.0 Hz, 1H), 7.37 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 22.7, 22.8, 25.0, 41.2, 51.4, 52.5, 56.1, 60.3, 129.5, 130.0, 135.1, 136.0, 169.9, 172.8. IR: 3272, 3067, 2957, 2871, 2870, 1744, 1663, 1201, 1060, 866 cm $^{-1}$. Exact mass calcd for $C_{19}H_{29}ClN_2O_4S$ requires m/z 417.1615, found m/z 417.1616 (MH^+, FAB).



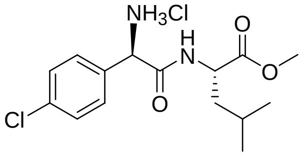
***N*-sulfonyl dipeptide 11.** A vial was charged with **9** (17.0 mg, 0.041 mmol, 1.0 equiv.) in CH_2Cl_2 (0.12 mL, 0.33 M). CH_3CN (0.12 mL, 0.33 M) and H_2O (0.19 mL, 0.22M) were subsequently added to the reaction vial. The reaction mixture was cooled to 0˚C and $NaIO_4$ was added (13.1 mg, 0.061 mmol, 1.5 equiv) followed by a catalytic amount of $RuCl_3$ (0.06 mg, 0.0003 mmol). The reaction mixture was stirred at 0 ˚C for 1 h and then warmed to rt and stirred for an additional 30 minutes. The reaction mixture was diluted with EtOAc (4 mL) and washed with brine. The aqueous layer was extracted with EtOAc (3 x 4 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated after trituration with 95%

hexanes:isopropanol as a white solid (14.4 mg, 81%). dr 99:1. An authentic mixture of diastereomers was prepared by mixing **11** with **12**. The diastereomeric ratio was determined by HPLC analysis of the crude product (HPLC, silica column, 97:3 hexanes: EtOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 15.60 min, minor diasteromer t_R = 12.59 min).^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, *J* = 6.6 Hz, 6H), 1.28 (s, 9H), 1.42 (m, 1H), 1.55 (m, 2H), 3.74 (s, 3H), 4.60 (m, 1H), 5.11 (d, *J* = 6.6 Hz, 1H), 5.54 (d, *J* = 6.5 Hz, 1H), 6.07 (d, J = 8.3 Hz, 1H), 7.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 22.8, 24.2, 24.9, 41.4, 51.4, 52.7, 60.2 (2 overlapping carbons), 128.9, 129.5, 134.9, 136.9, 169.2, 172.9. IR: 3324, 3261, 1728, 1651, 1305, 1136, 1120, 1090, 1015 cm $^{-1}$. Exact mass calcd for $C_{19}H_{29}ClN_2O_5S$ requires m/z 433.1564, found m/z 433.1559 (MH^+, FAB).

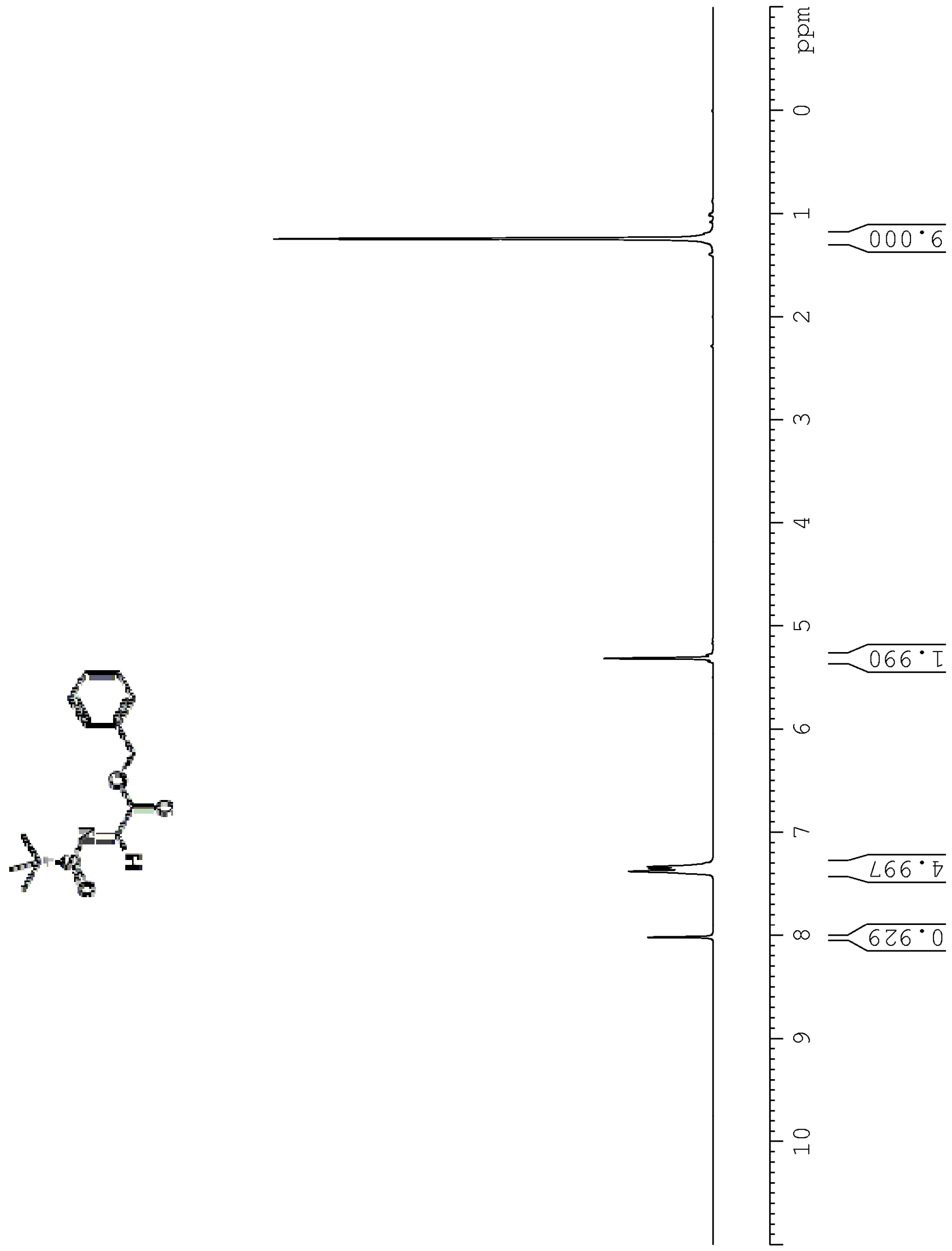


***N*-sulfonyl dipeptide 12.** A vial was charged with **10** (17.4 mg, 0.042 mmol, 1.0 equiv) in CH_2Cl_2 (0.13 mL, 0.33M). CH_3CN (0.13 mL, 0.33M) and H_2O (0.19 mL, 0.22M) were subsequently added to the reaction vial. The reaction mixture was cooled to 0 ˚C and $NaIO_4$ was added (13.4 mg, 0.063 mmol, 1.5 equiv) followed by a catalytic amount of $RuCl_3$ (0.06 mg, 0.0003 mmol). The reaction mixture was stirred at 0 ˚C for 1 h and then warmed to rt and stirred for an additional 30 minutes. The reaction mixture was diluted with EtOAc (4 mL) and washed with brine. The aqueous layer was extracted with EtOAc (3 x 4 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated after trituration with 95%

hexanes:isopropanol as a white solid (12.6 mg, 70%). dr 99:1. An authentic mixture of diastereomers was prepared by mixing **11** with **12**. The diastereomeric ratio was determined by HPLC analysis of the crude product (HPLC, silica column, 97:3 hexanes: EtOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 12.68 min, minor diasteromer t_R = 15.65 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (m, 6H), 1.27 (s, 9H), 1.50-1.65 (m, 3H), 3.66 (s, 3H), 4.62 (m, 1H), 5.10 (d, *J* = 6.7 Hz, 1H), 5.44 (d, *J* = 6.5 Hz, 1H), 5.91 (d, J = 4.3 Hz), 7.31 (m, 4H).^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.9, 24.1, 25.0, 41.4, 51.5, 52.6, 60.1, 60.2, 129.1, 129.5, 135.0, 136.3, 169.5, 172.7. IR: 3282, 2951, 1739, 1651, 1303, 1133, 1091, 684 cm $^{-1}$. Exact mass calcd for $C_{19}H_{29}ClN_2O_5S$ requires m/z 433.1564, found m/z 433.1555 (MH^+, FAB).



Cleavage of the sulfinyl group to yield dipeptide hydrochloride. Dipeptide **9** (17.4 mg, 0.042 mmol, 1.0 equiv) was taken up in dioxane (0.280 mL) and MeOH (0.280 mL) and was treated with 4.0 M HCl in dioxane (0.280 mL, 27 equiv HCl). The reaction mixture was stirred at rt for 3 h. The reaction mixture was concentrated *in vacuo*, and the amine hydrochloride was washed with a 2:1 mixture of pentane:dry diethyl ether (3x). The precipitate was collected by filtration and dried overnight *in vacuo* to yield the amine hydrochloride (13.6 mg, 93%) as a white solid. mp 53-55 ˚C. ^{1}H NMR (400 MHz, MeOD): δ 0.76 (m, 6H), 1.24 (m, 1H), 1.55 (m, 2H), 3.72 (s, 1H), 5.04 (s, 1H), 7.48- 7.54 (m, 4H). ^{13}C NMR (100 MHz, MeOD): δ 21.3, 23.1, 25.9, 41.1, 52.3, 52.9, 57.1, 130.5, 131.0, 133.2, 137.2, 168.6, 174.1. IR: 2957, 1733, 1678, 1494, 1437, 1014 cm $^{-1}$. Excat mass calcd for $C_{15}H_{21}ClN_2O_3$ requires m/z 313.1319, found m/z 313.1320 (MH^+, FAB).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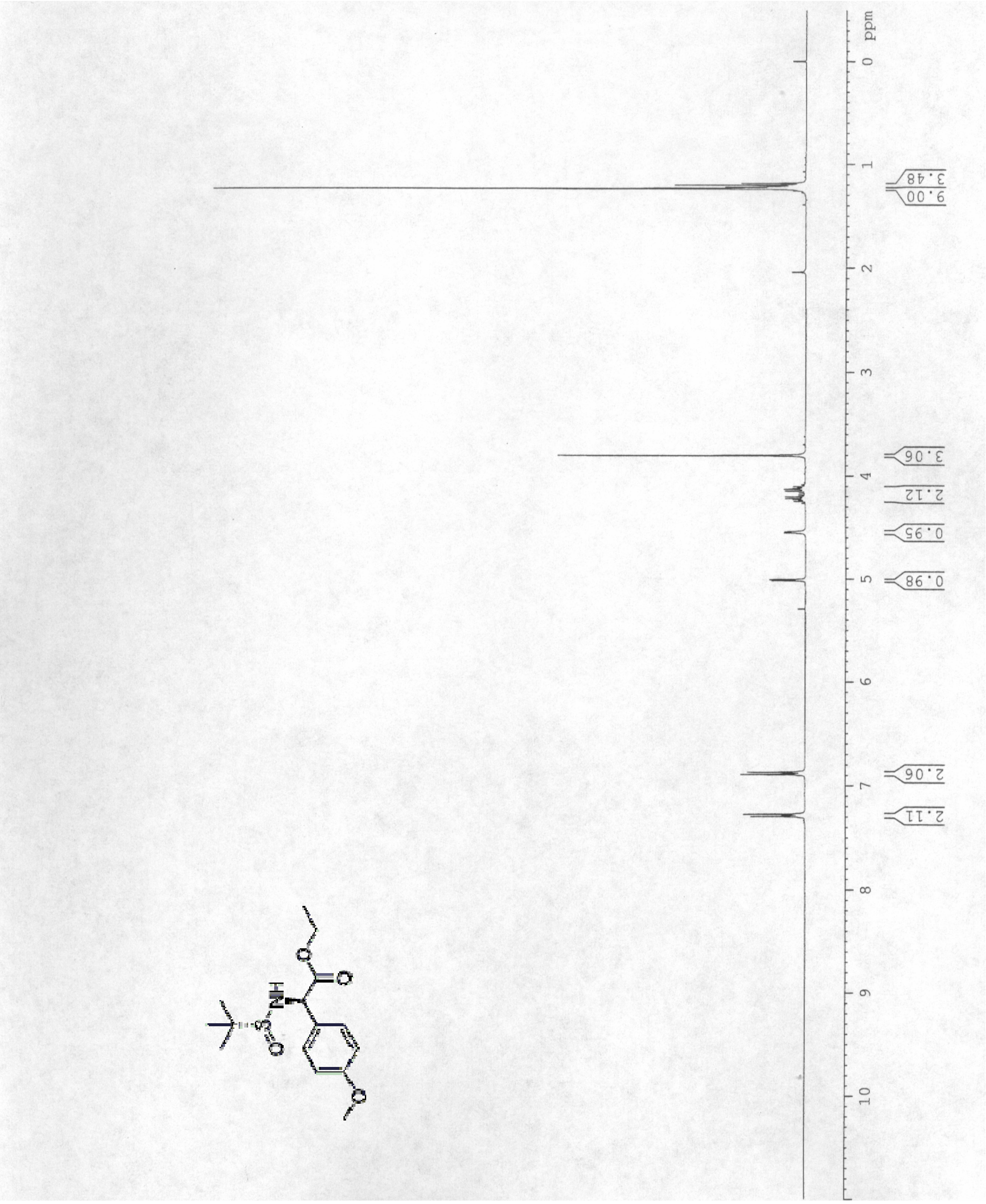
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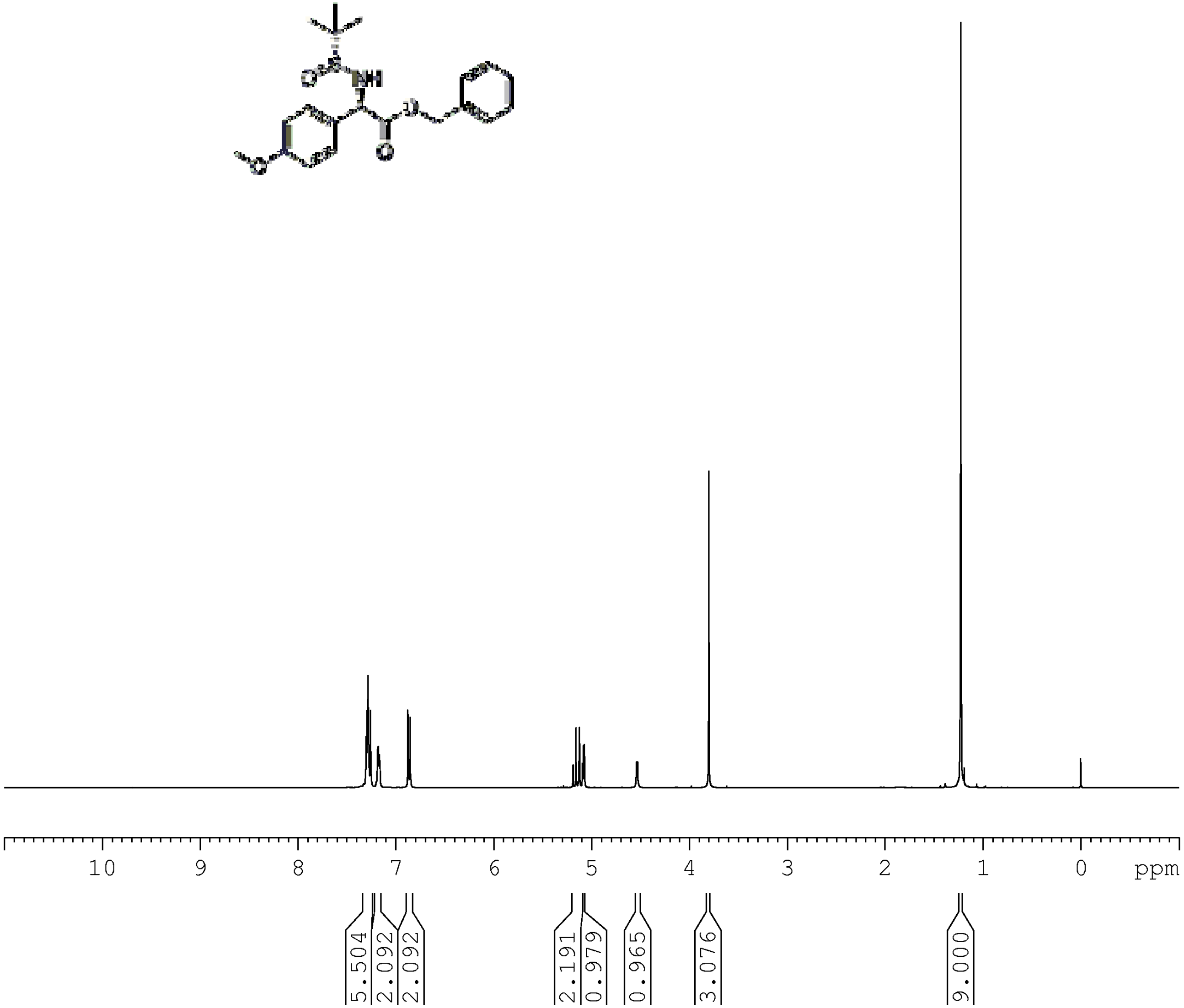
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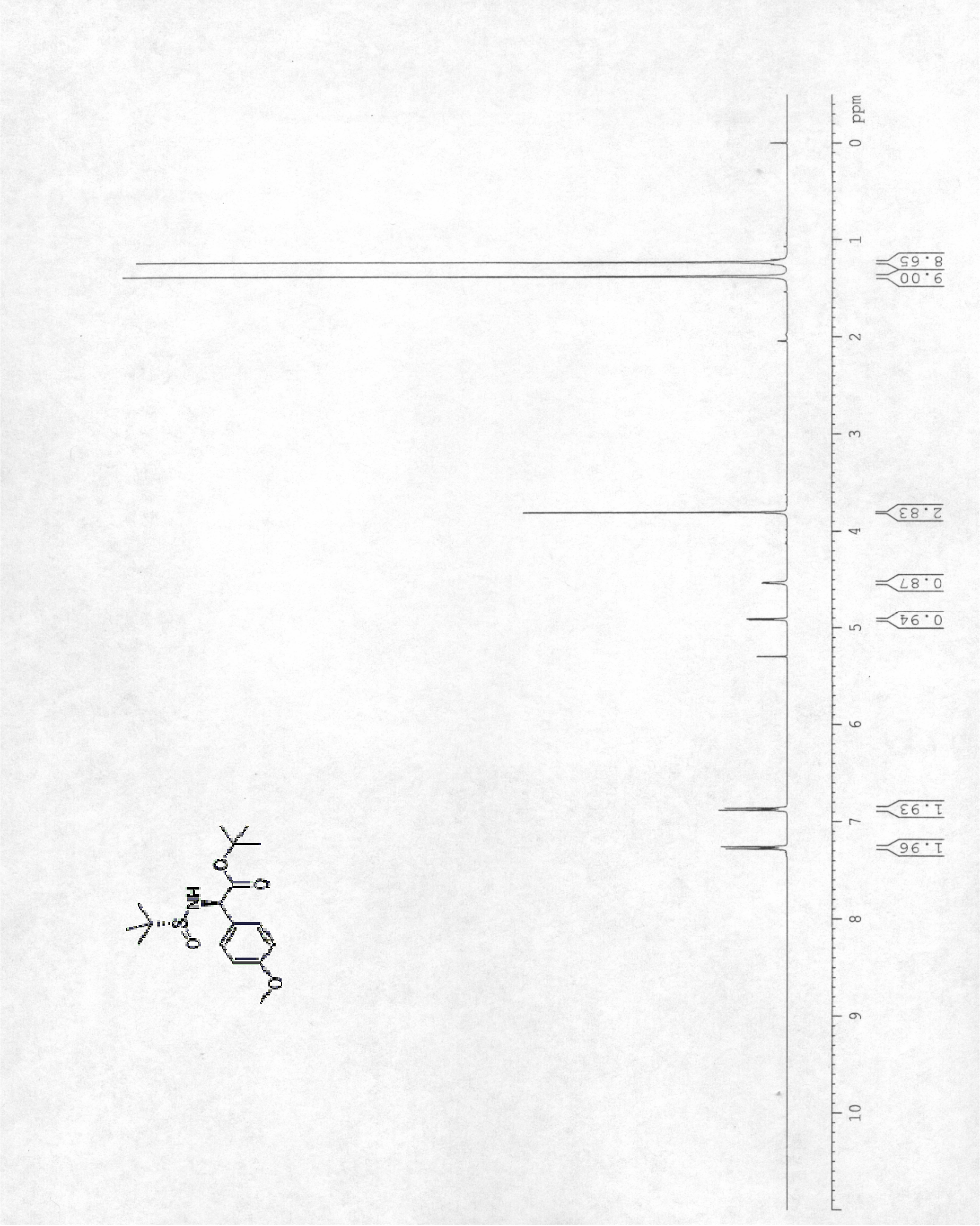
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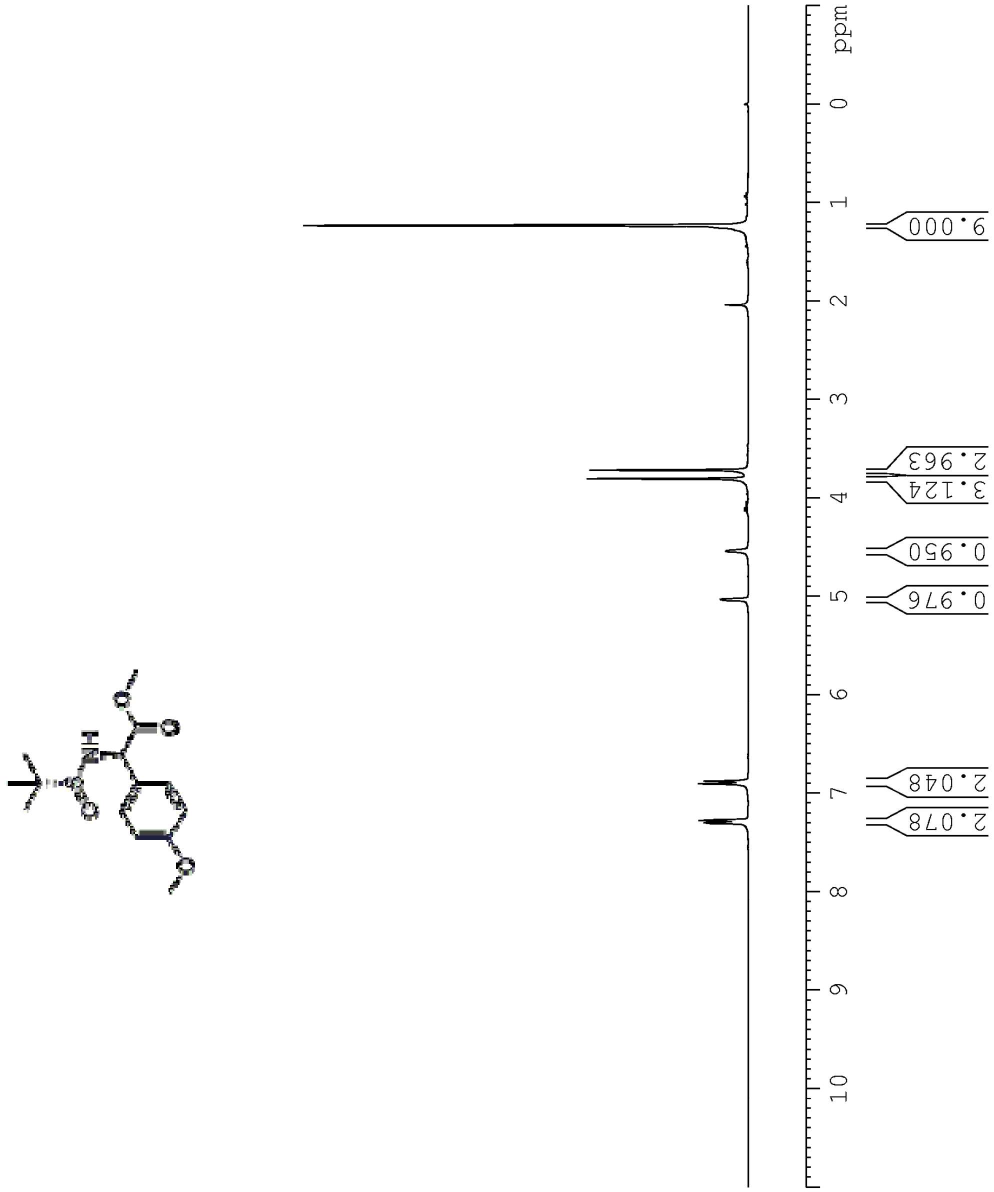
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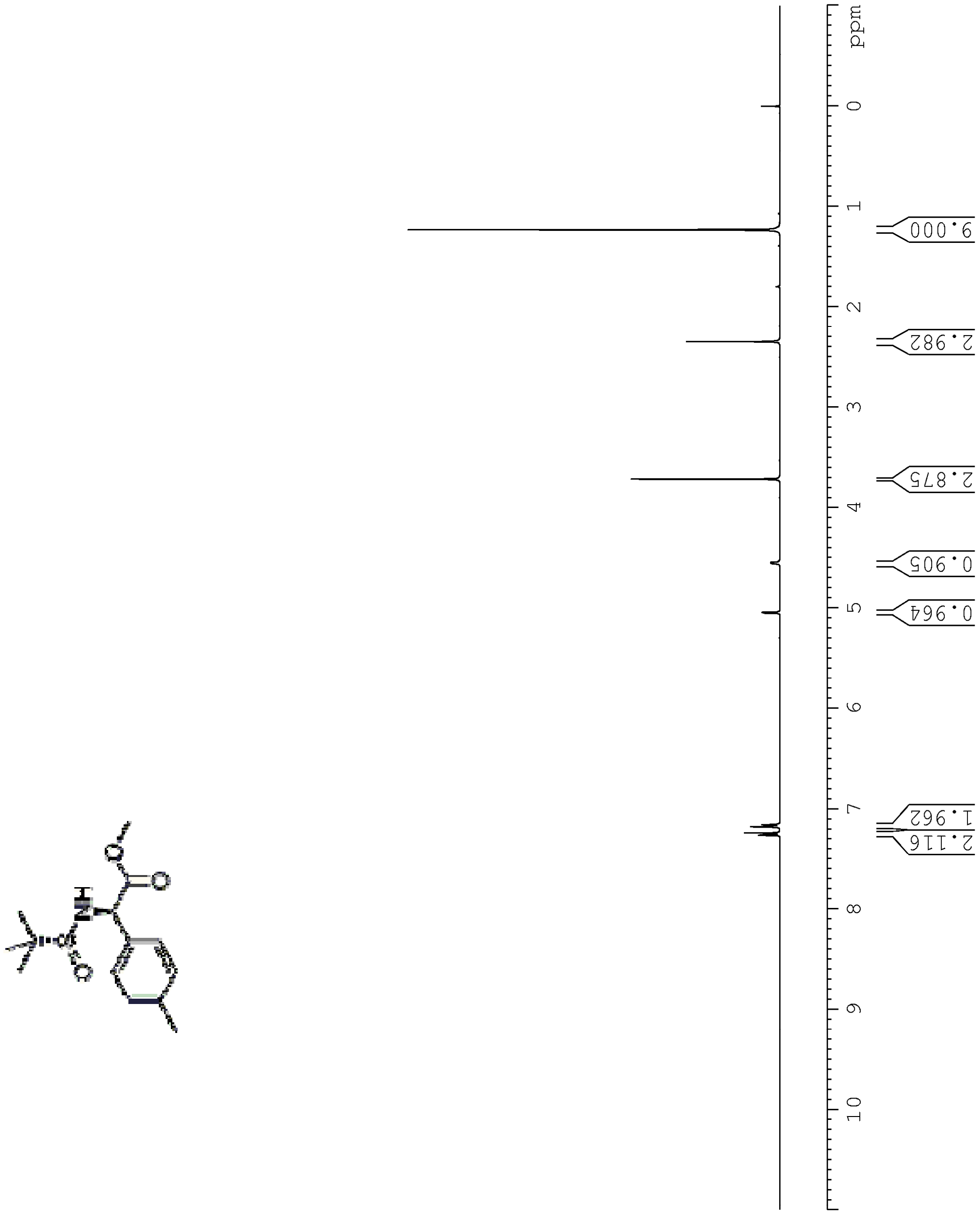

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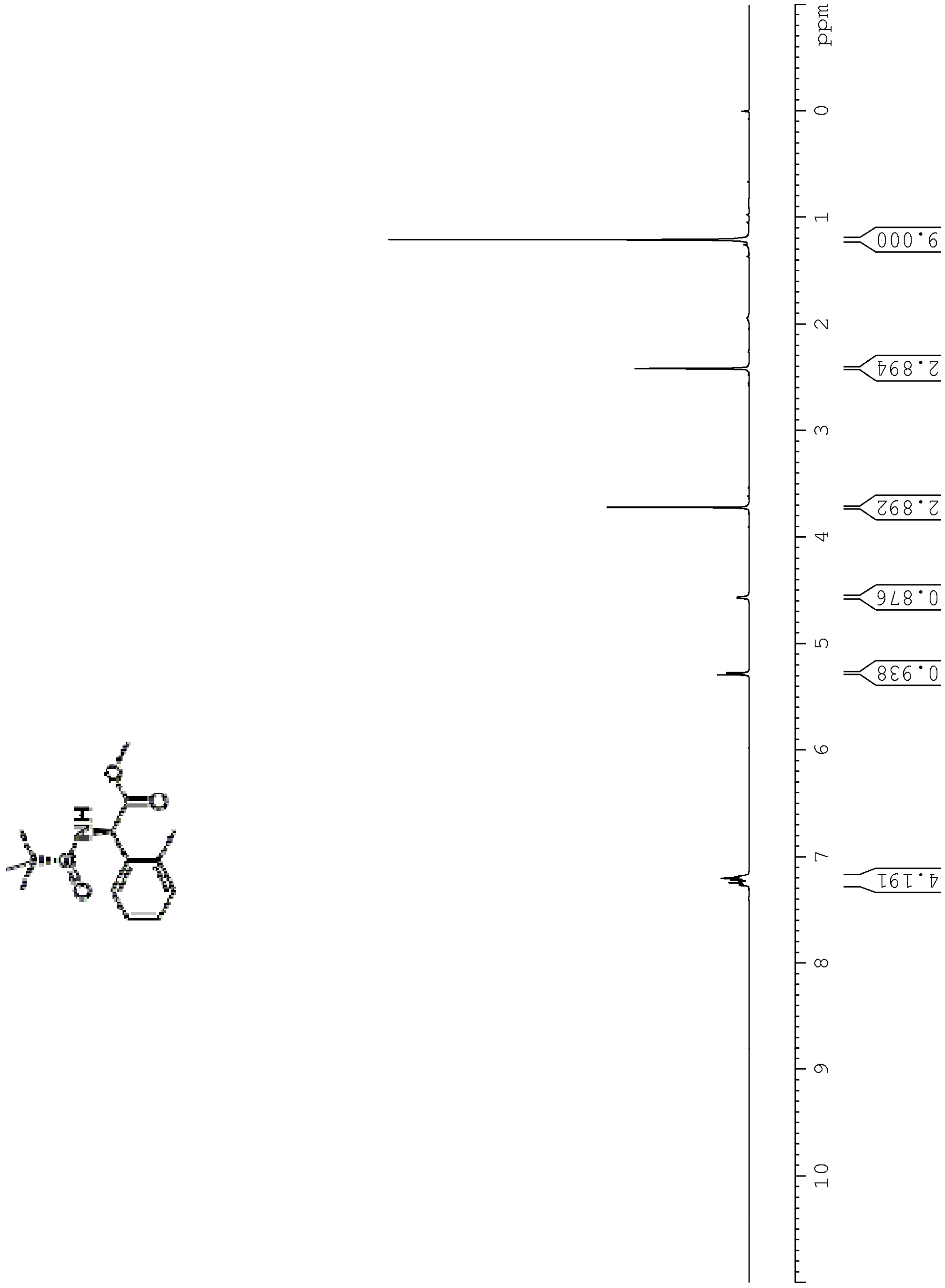
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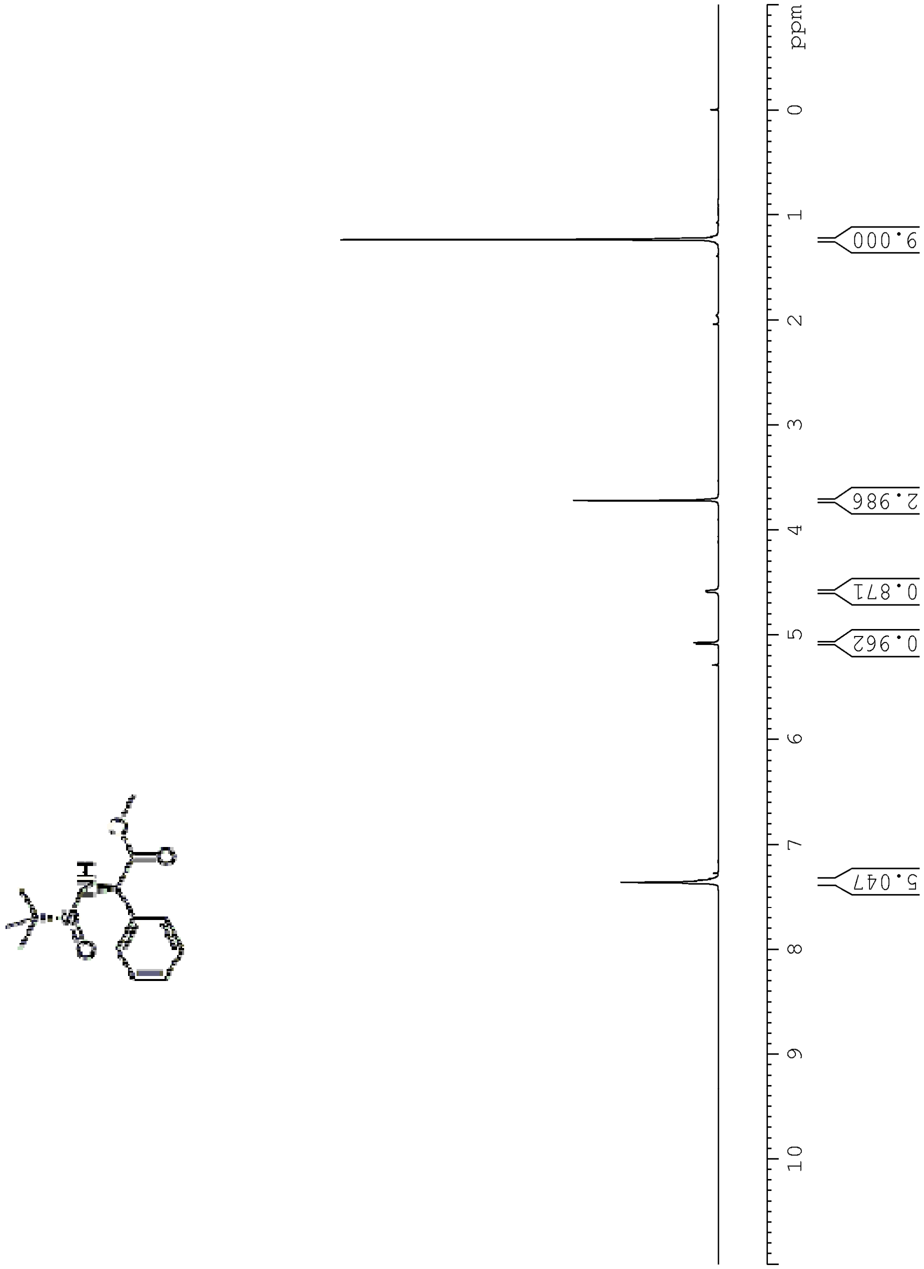
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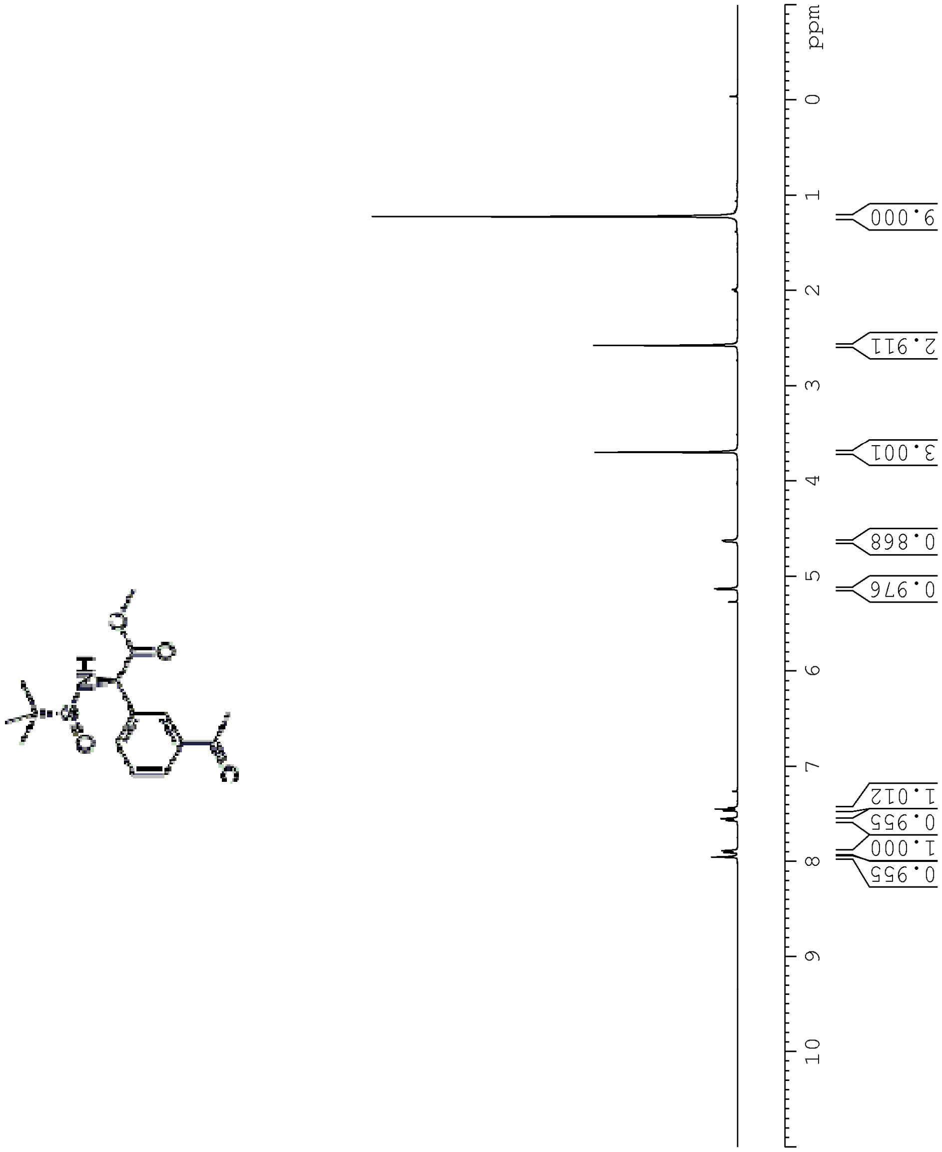

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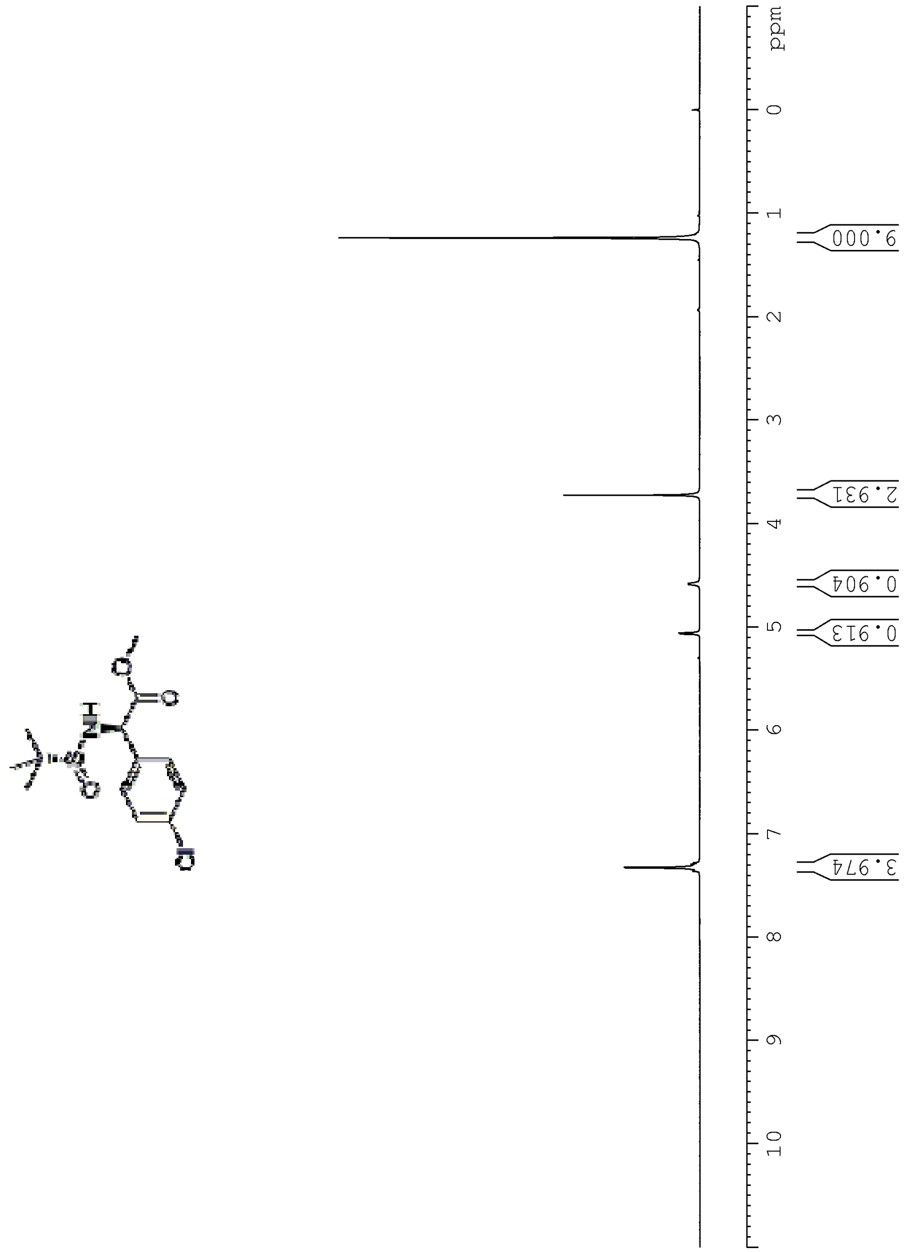
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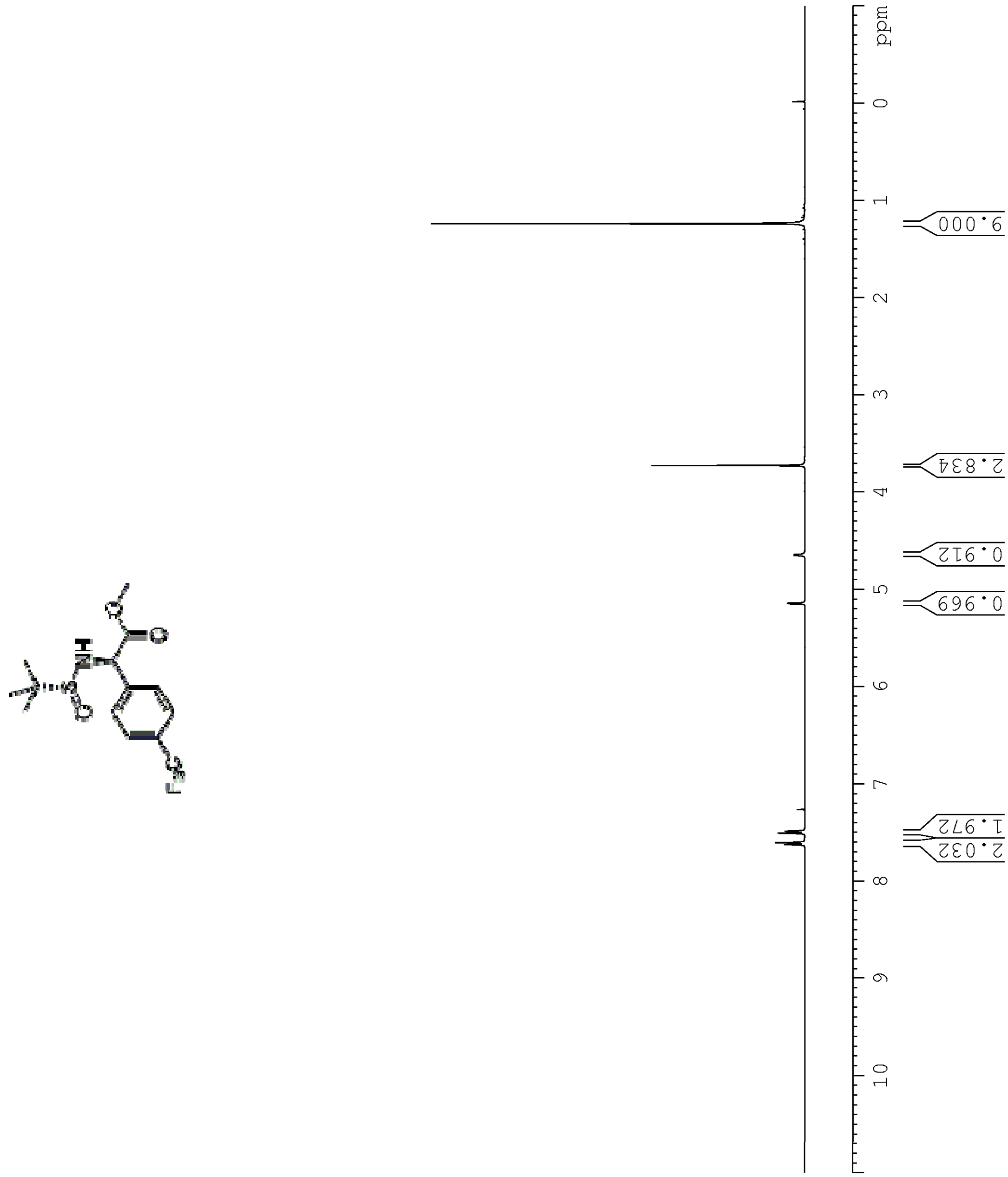
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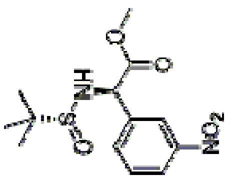
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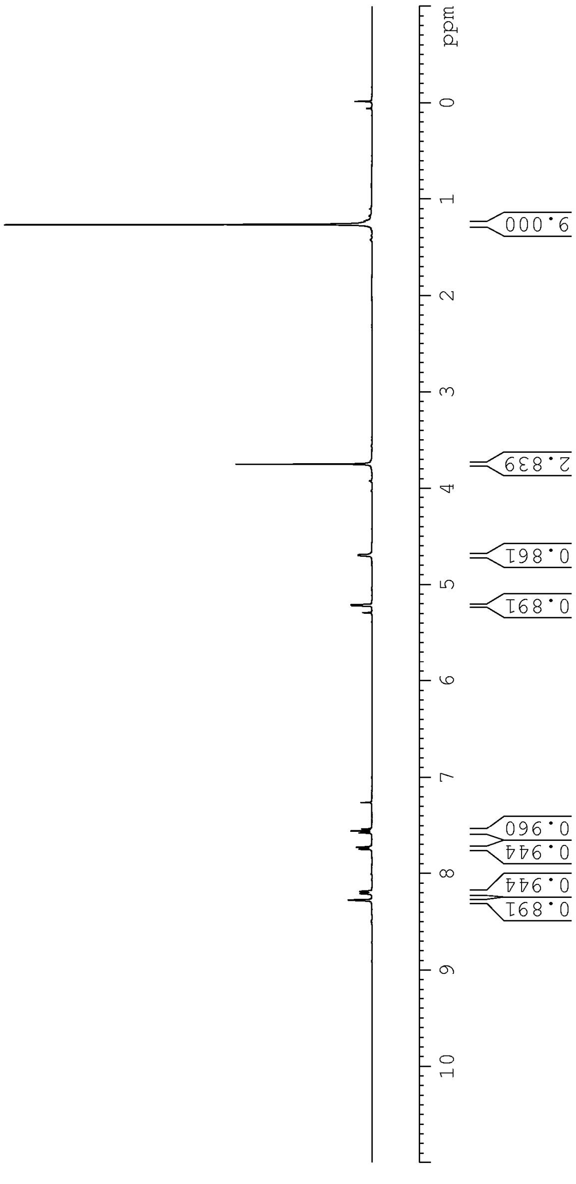
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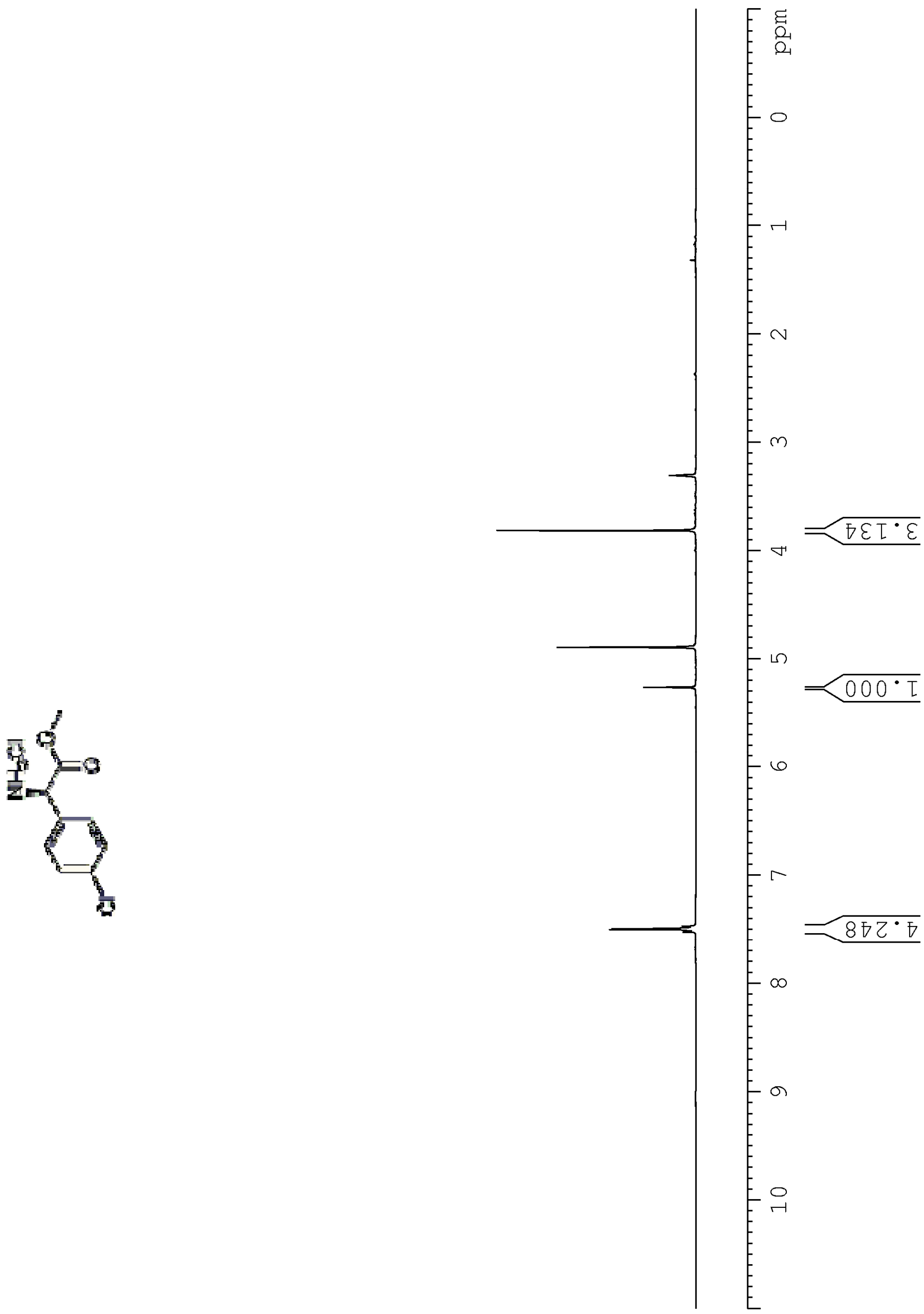
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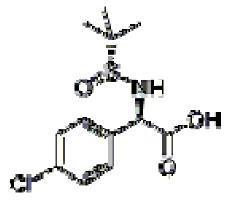
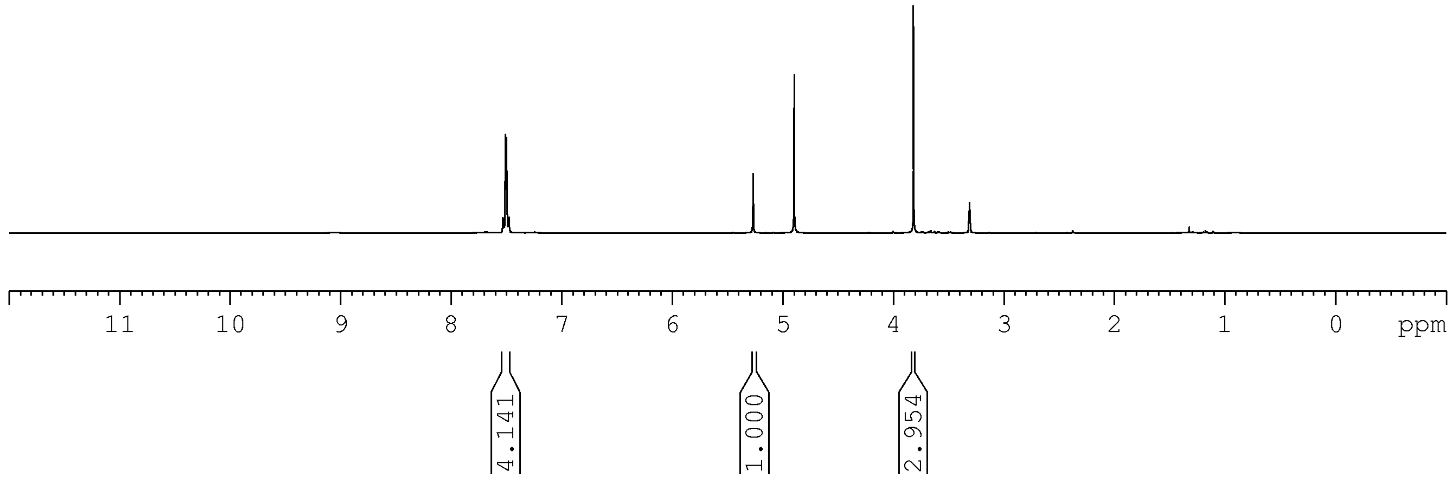
O
Cl
4.248
1.000
3.134
ppm
0
1
2
3
4
5
6
7
8
9
10


Cl
O
S
NH
OH
O


11
10
9
8
7
6
5
4
3
2
1
0
ppm
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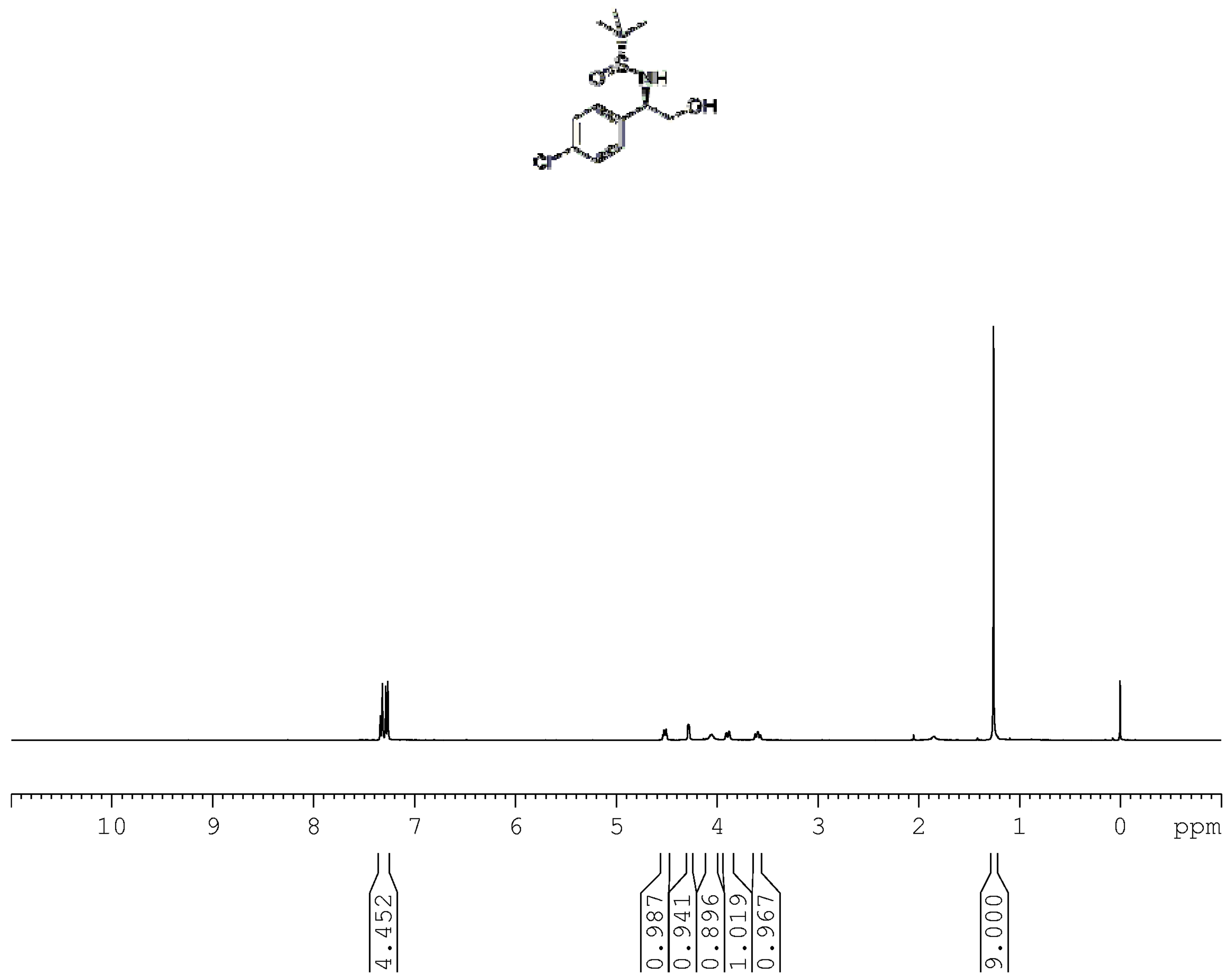
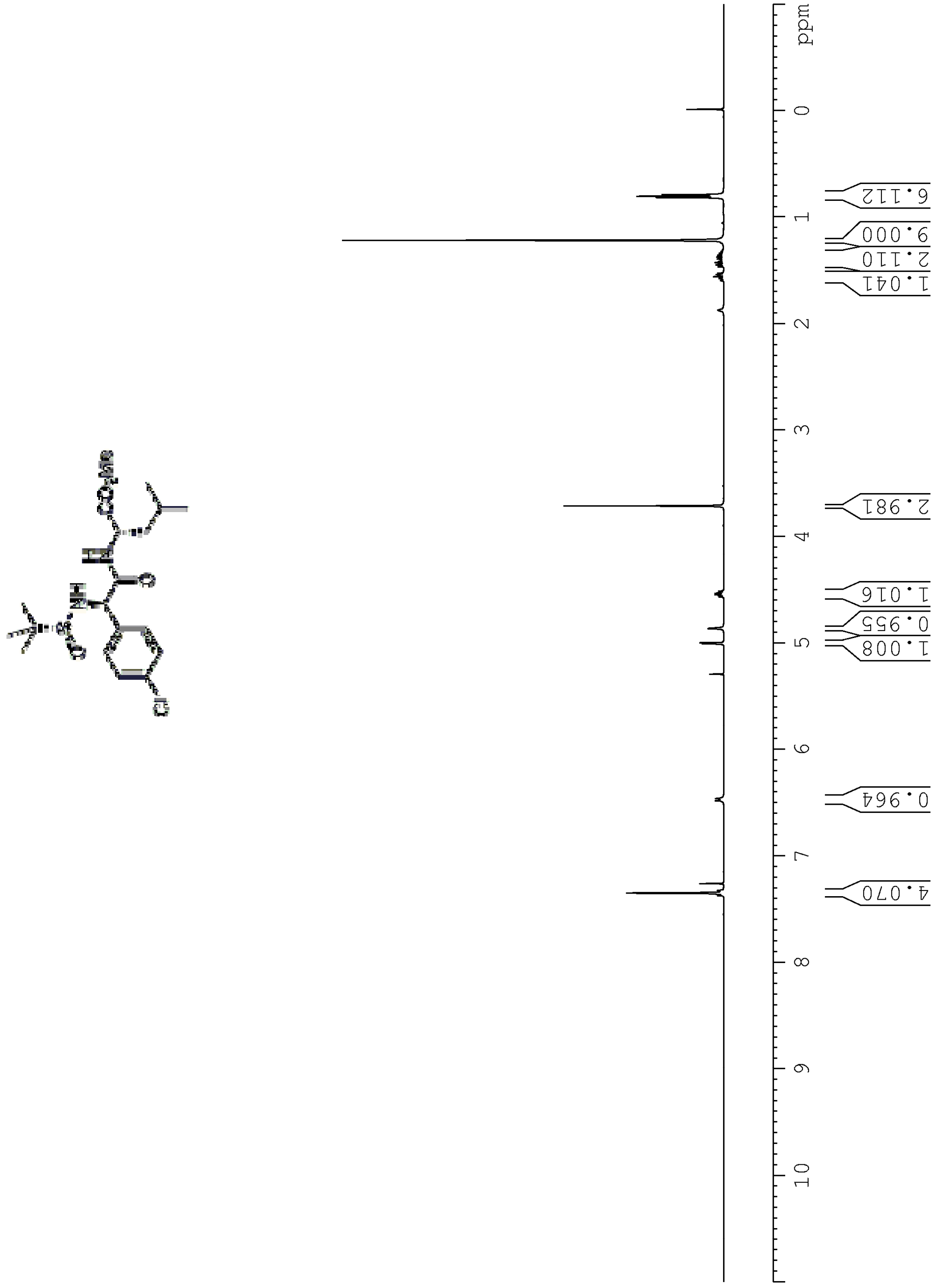
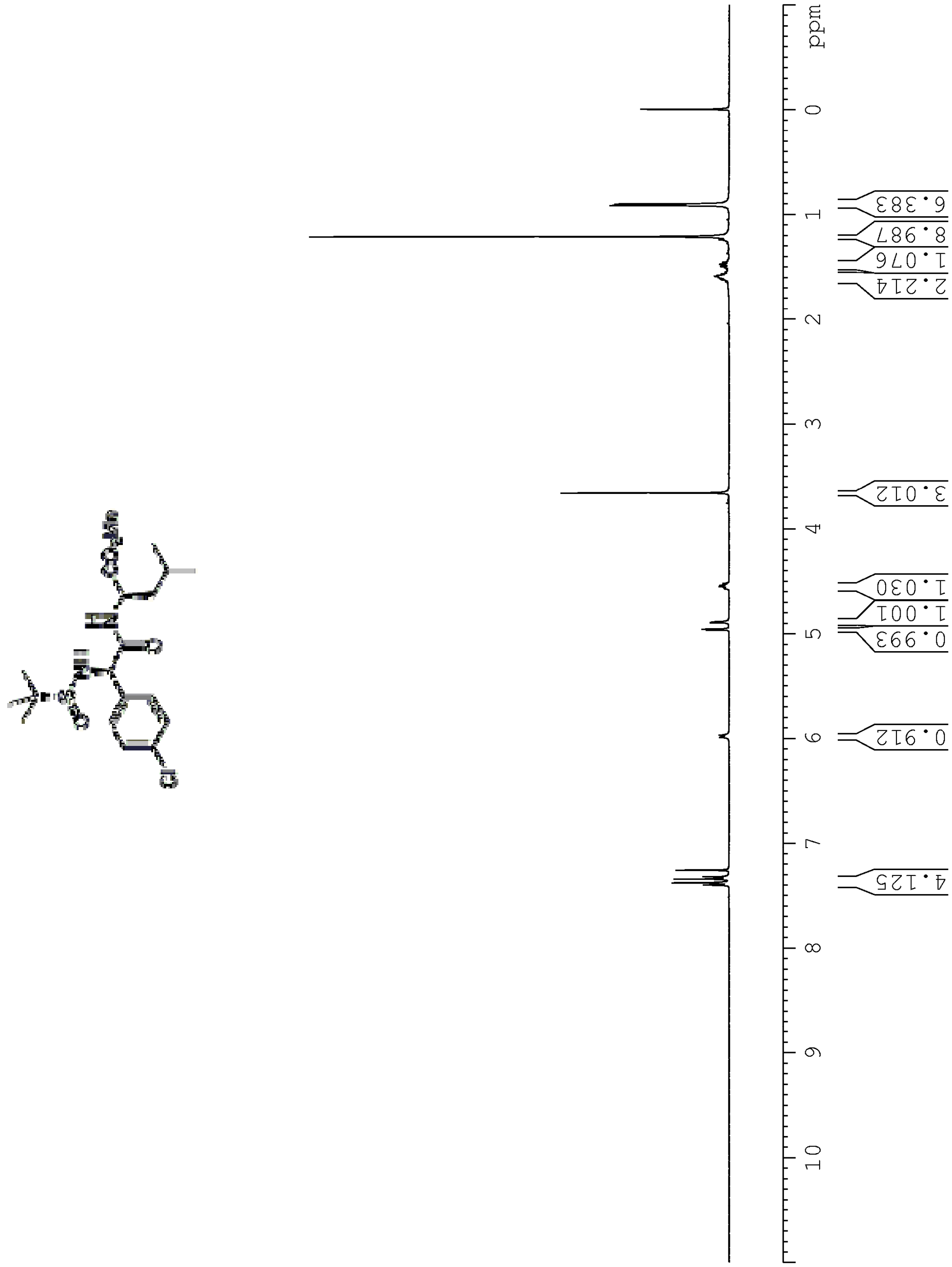
1.000
2.954

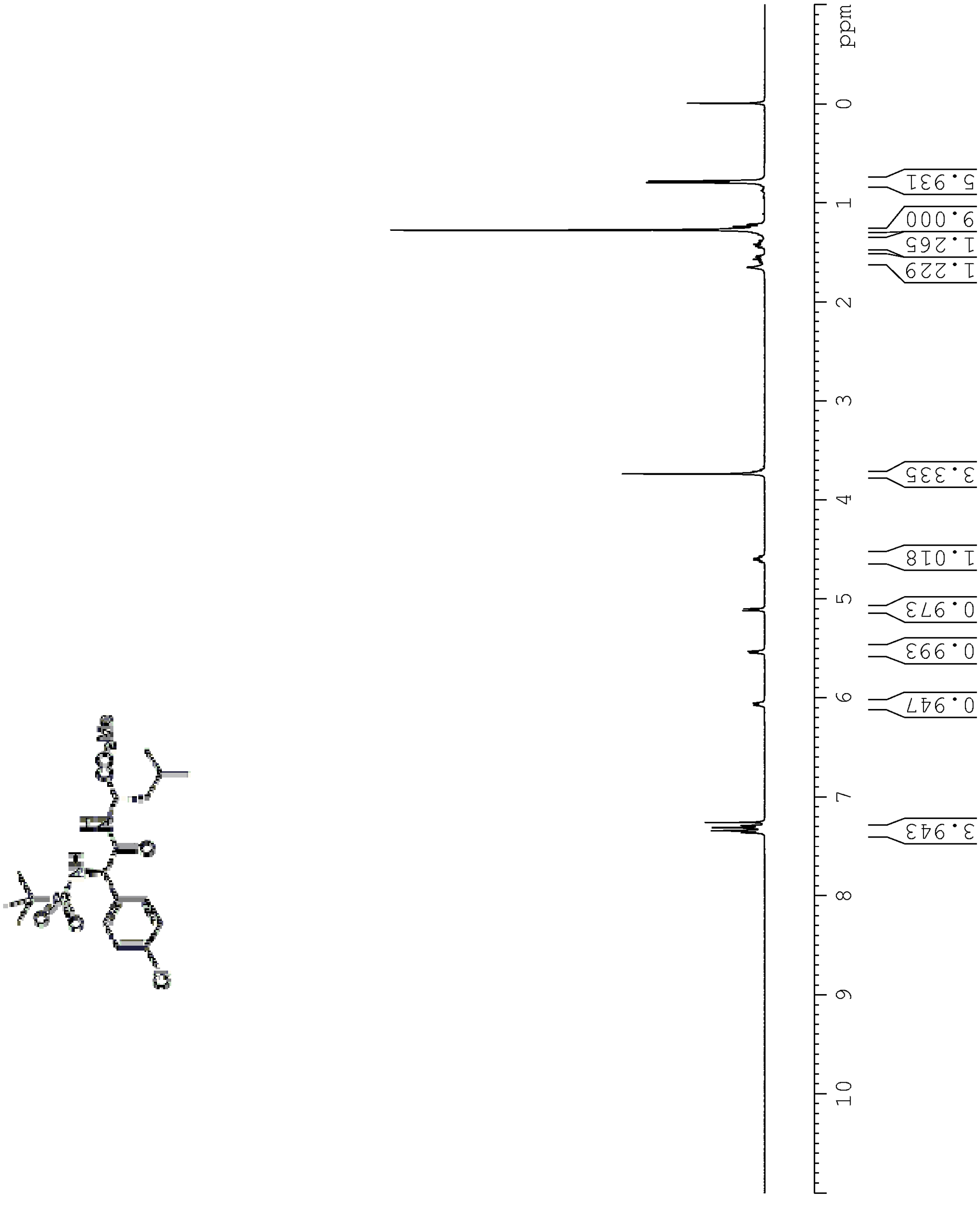


Cl
NH
OH
O
S
10
9
8
7
6
5
4
3
2
1
0
ppm
4.452
0.987
0.941
0.896
1.019
0.967
9.000


ppm
0
1
2
3
4
5
6
7
8
9
10
6.112
9.000
2.110
1.041
2.981
1.016
0.955
1.008
0.964
4.070
Cl
O
S
NH
H
N
O
CO2Me



ppm
0
1
2
3
4
5
6
7
8
9
10
6.383
8.987
1.076
2.214
3.012
1.030
1.001
0.993
0.912
4.125
O
S
NH
O
HN
CO2Me
Cl



ppm
0
1
2
3
4
5
6
7
8
9
10
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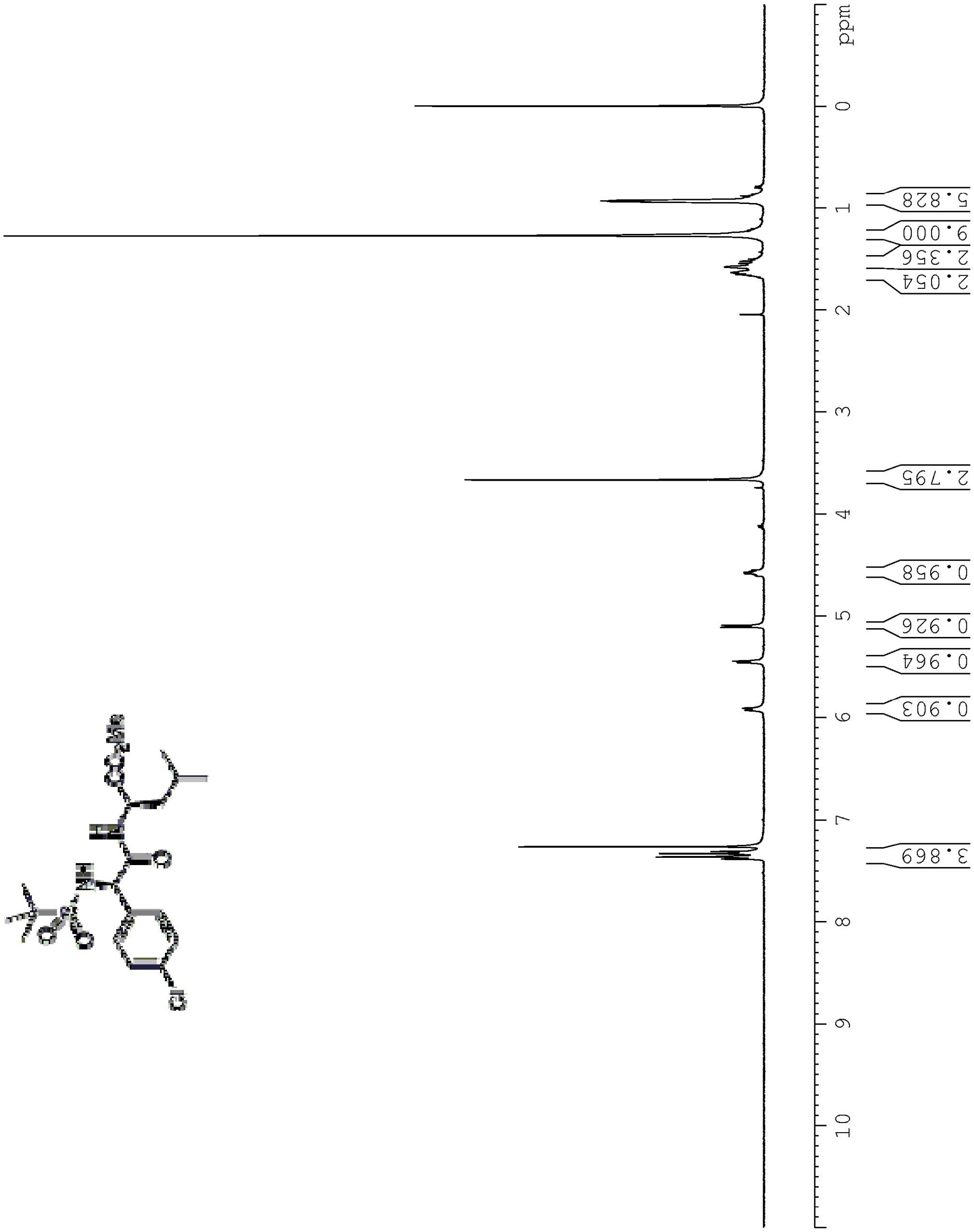
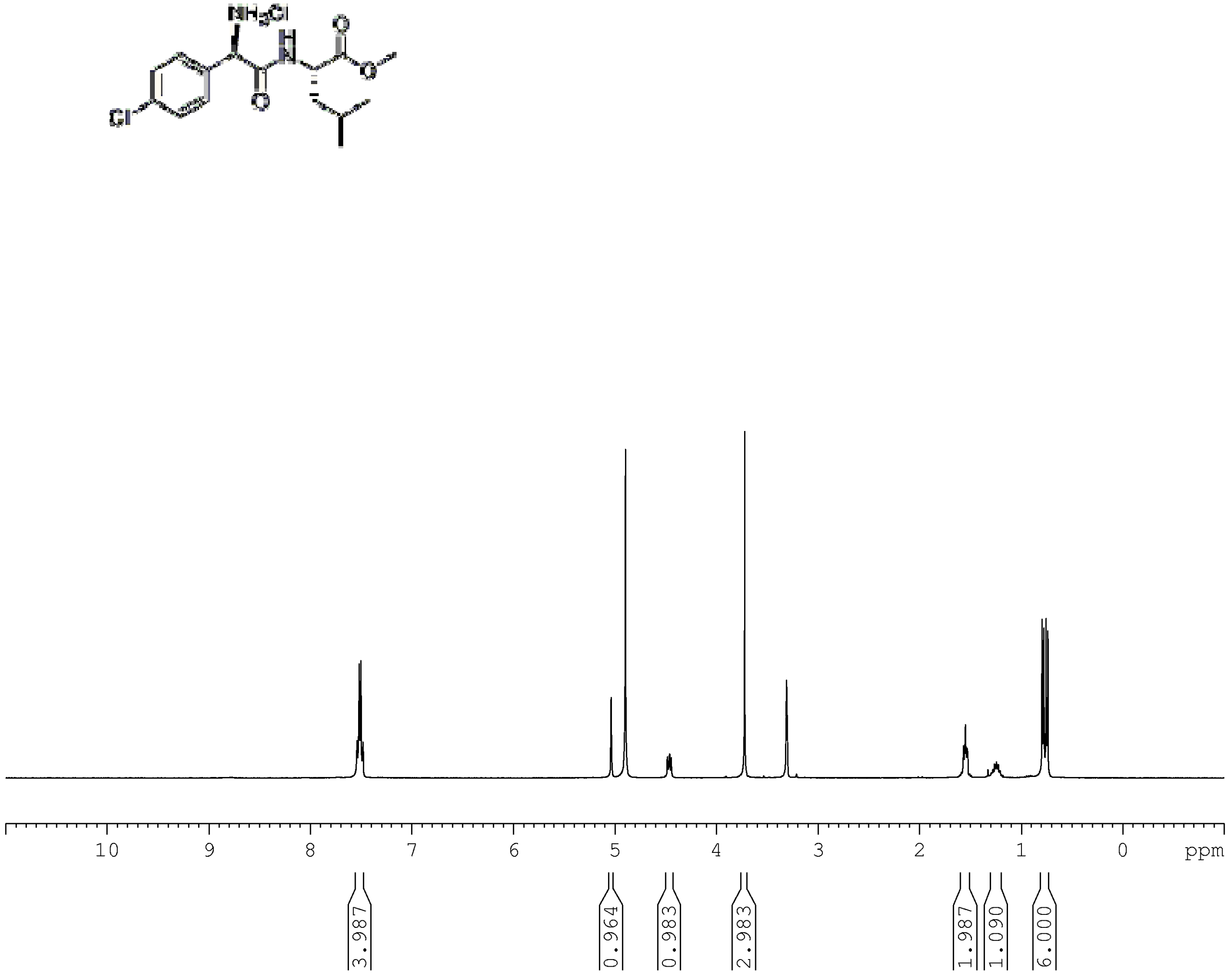
9.000
1.265
1.229
3.335
1.018
0.973
0.993
0.947
3.943
Cl
NH
S
O
O
HN
O
CO2Me


Cl
O
S
O
NH
O
H
N
CO2Me
ppm
0
1
2
3
4
5
6
7
8
9
10
5.828
9.000
2.356
2.054
2.795
0.958
0.926
0.964
0.903
3.869


NH3Cl
H
N
O
O
O
Cl
10
9
8
7
6
5
4
3
2
1
0
ppm
3.987
0.964
0.983
2.983
1.987
1.090
6.000

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