Design and Synthesis of Florylpicoxamid, a Fungicide Derived from Renewable Raw Materials

Nicholas R. Babij*, Nakyen Choy, Megan A. Cismesia, David J. Couling, Nicole M. Hough, Peter L. Johnson, Jerzy Klosin, Xiaoyong Li, Yu Lu, Elizabeth O. McCusker, Kevin G. Meyer, James M. Renga, Richard B. Rogers, Kenneth E. Stockman, Nicola J. Webb, Gregory T. Whiteker*, and Yuanming Zhu

Corteva Agriscience, 9330 Zionsville Road, Indianapolis, Indiana 46268, United States

Supporting Information

Experimental procedures and characterization data for new compounds.

Table of Contents

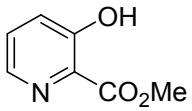
General Information

All of the reagents were commercially available and used as purchased without further purification. Unless otherwise noted, all of the reactions were performed in round-bottom or jacketed cylindrical flasks under nitrogen. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance III HD 500 MHz, a Bruker 400 MHz, or a Varian Gemini 300 MHz spectrometer. Mass spectra were obtained using a Waters Micromass ZQ mass spectrometer. High-resolution mass spectra (HRMS) were obtained on an Agilent 6210 time-of-flight liquid chromatography–mass spectrometry (TOF LC-MS) apparatus or on an Agilent 1290 LC chromatogram interfaced to Quadrupole-Orbitrap Exactive mass spectrometer operated in positive and negative Atmospheric Pressure Chemical Ionization (APCI) modes (the mobile phases were prepared using 0.1 % ammonium acetate in water or methanol). IR spectra were obtained on neat samples using attenuated total reflection (ATR) on a Fisher Scientific Nicolet 6700 Fourier-transform infrared (FT-IR) apparatus. HPLC analysis was performed on an Agilent 1260 chromatograph with an Eclipse Plus C18 column (4.6 mm × 150 mm, 3.5 µm, P/N 959961-902) using a gradient mobile phase comprised of water and acetonitrile unless otherwise noted. Chiral HPLC analysis of chiral alcohol **15** was performed using a Chiralpak IA column (250 x 4.6 mm, P/N: 80325) with isocratic 85% in hexanes (0.1% trifluoroacetic acid)

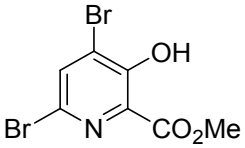
and 15% isopropanol (0.1% trifluoroacetic acid) mobile phase (10 µL injected); using a UV detector set to 265 nm, enantiomer #1 (major) eluted at 6.2 minutes and enantiomer #2 (minor) eluted at 6.8 minutes.

Preparation and Characterization of New Compounds

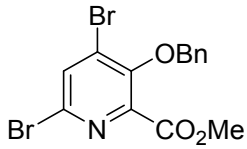
1st Generation Route



Methyl 3-hydroxypyridine-2-carboxylate. A 2-L, 4-neck flask, fitted with overhead stirring, internal temperature probe, reflux condensor and nitrogen gas inlet, was charged with 3-hydroxypicolinic acid (89 g, 640 mmol) and MeOH (1 L). To the resulting slurry was slowly added sulfuric acid (139 mL). The resultant solution was heated at reflux (69 °C) for 19 hours. The reaction was cooled to RT and MeOH was removed under vacuum. The resulting residue was taken up in ethyl acetate (500 mL), and H_2O was added (100 mL). The mixture was cooled in an ice bath and carefully neutralized with 50% NaOH (~160 mL), then with saturated $NaHCO_3$ (~300 mL) until the pH was slightly acidic to pH paper (pH ~6). The phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to yield the title compounds (71 g, 71%) as an off-white solid. Analytical data was consistent with the literature.[1]

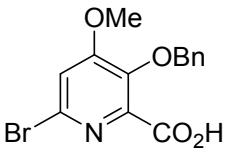


Methyl 4,6-dibromo-3-hydroxypyridine-2-carboxylate (8). To a 2 L, 3-necked flask equipped with a dropping funnel and a mechanical stirrer, was added water (800 mL) and methyl 3-hydroxypyridine-2-carboxylate (15.3 g). To this stirred solution was slowly added bromine (32 g). As the reaction progressed, a solid separated from solution and the reaction mixture became difficult to stir. After the addition was complete, the mixture was vigorously stirred until the bromine color disappeared. ^{1}H-NMR ($CDCl_3$) of a small sample of the crude product showed that it was about a 3:1 mixture of mono to dibrominated product. Sodium carbonate (31.8 g) was carefully added to the reaction mixture and then additional bromine (12 g) was added dropwise. After the bromine color had disappeared, the reaction mixture was adjusted to approximately pH 5 with conc. HCl, and the resulting mixture was extracted with dichloromethane (DCM, 3×150 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated to give an orange solid (14 g, 45%). This material could be recrystallized from methylcyclohexane (after charcoal treatment) to give a white solid: m.p. 181-183 °C. Analytical data was consistent with the literature.[2]

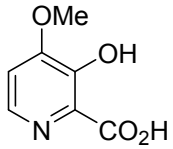


Methyl 4,6-dibromo-3-benzyloxypyridine-2-carboxylate (9). To a stirred mixture of sodium hydride (0.6 g) in DMF (50 mL) was slowly added **8** (7.1 g). After the addition was complete, the mixture was stirred at

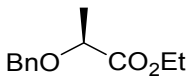
room temperature for 15 minutes, then benzyl chloride (3.05 g) was added all at once. The mixture was then heated at 90 °C for six hours, cooled, poured into water (500 mL) and extracted with ether (2x200 mL). The ether extracts were combined, washed with 2N NaOH (50 mL), dried ($MgSO_4$) and the solvent was evaporated to give product (8.3 g, 91%) as a light yellow solid: m.p. 75-76 °C. Recrystallization from a small volume of methanol gave an analytical sample. Analytical data was consistent with the literature.[2]



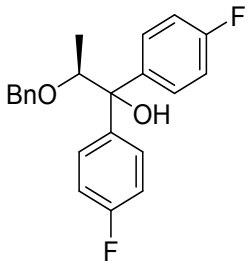
6-bromo-3-benzyloxy-4-methoxypyridine-2-carboxylic acid (10). A vigorously stirred mixture of **9** (25.5 g), potassium carbonate (75 g) and methanol (300 mL) was heated at reflux for 30 hours. The mixture was cooled, poured into water (800 mL), and the pH adjusted to 2 by the addition of conc. HCl. The resulting mixture was extracted with DCM (3×150 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent was evaporated to give a nearly colorless oil (20.5 g) which slowly solidified upon standing. This was recrystallized from methanol (125 mL)/water (40 mL) to afford the product (11.6 g, 54%) as a solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.61 (s, 1H), 7.48 (s, 1H), 7.46 – 7.32 (m, 5H), 5.01 (s, 2H), 3.97 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.3 (CO_2H), 160.8 (C4), 145.6 (C2 or C3), 142.1 (C2 or C3), 136.4 (C6 or Bn-C1), 135.3 (C6 or Bn-C1), 128.2 (Bn-C2 or Bn-C3), 128.1 (Bn-C2 or Bn-C3), 128.1 (Bn-C4), 113.8 (C5), 74.9 (CH_2), 57.0 (OMe); HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{14}H_{12}BrNO_4$, 338.0022. found, 338.0025; m.p. 134-135 °C.



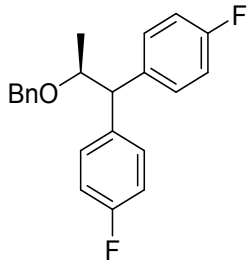
3-Hydroxy-4-methoxypicolinic acid (3). In a 1L Parr reactor, triethylamine (9.1 mL, 65.1 mmol) was added to a suspension of **10** (10 g, 29.6 mmol) in ethanol (74 mL). The head space was flushed with nitrogen and 5% Pd/C (0.17 g, 4.9 mmol) was added and pressurized with hydrogen gas (50 psi H_2). After 1hr, the pressure had been reduced to <10 psi. The bottle was re-pressurized with hydrogen gas (45 psi). After 3 total hrs, the bottle was removed and the solution filtered through Celite®. The ethanol was removed *in vacuo*. The resulting solid was suspended in water (25mL) and 2N HCl (15 mL) was added. A white precipitate formed immediately and the suspension was stirred for 30 min then filtered, washed with water (25 mL), THF (25 mL) and diethyl ether (25 mL) and air dried to give the title compound (4.52 g, 90%) of a white solid: Analytical data was consistent with the 2nd generation route.



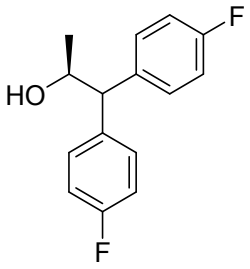
(*S*)-ethyl 2-(benzyloxy)propanoate (**12**). Prepared according to procedure described in the literature.[3]



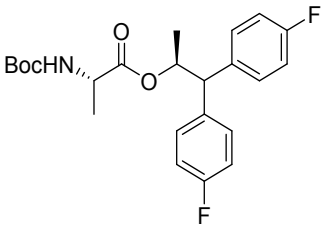
(*S*)-2-(benzyloxy)-1,1-bis(4-fluorophenyl)propan-1-ol (13). To a solution of (*S*)-ethyl 2-(benzyloxy)propanoate (2.08 grams, 10.0 mmol) in tetrahydrofuran (THF; 20 mL) at 0 °C was slowly added (4- fluorophenyl)magnesium bromide (31.3 mL, 25.0 mmol, 0.8 molar (M) in THF) over a 10 min period. The reaction vessel was allowed to warm slowly to room temperature over 2 h, and the reaction mixture was quenched by careful addition of saturated aqueous ammonium chloride (50 mL). The mixture was diluted with diethyl ether (50 mL), the phases were separated, and the aq. phase was extracted with diethyl ether (2 x 50 mL). The combined organic phases were washed with sat. aq. sodium chloride (100 mL), dried over sodium sulfate (Na_2SO_4), filtered, and concentrated. The resulting oil was purified by flash column chromatography to afford the title compound (3.28 g, 93%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.38 (m, 2H), 7.38 – 7.27 (m, 5H), 7.18 – 7.09 (m, 2H), 7.01 – 6.90 (m, 4H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.48 – 4.36 (m, 2H), 3.11 (s, 1H), 1.11 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.7 (d, *J* = 242.2 Hz, Ar-C4), 160.6 (d, *J* = 242.7 Hz, Ar-C4), 142.5 (d, *J* = 3.1 Hz¸ Ar-C1), 141.7 (d, *J* = 3.0 Hz, Ar-C1), 138.4 (Bn-C1), 128.9 – 128.7 (m, Ar-C2), 128.3 – 128.1 (m, Ar-C2), 127.9 (Bn-C2 or Bn-C3), 127.4 (Bn-C2 or Bn-C3), 127.1 (Bn-C4), 114.3 (d, *J* = 21.0 Hz, Ar-C3), 113.9 (d, *J* = 20.8 Hz, Ar-C3), 79.1 (CHMe or $COHAr_2$), 78.5 (CHMe or $COHAr_2$), 70.3 (CH_2), 13.5 (Me); ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.18, - 116.40; HRMS–ESI (*m/z*) $[M+Na]^+$ calcd for $C_{22}H_{20}F_2O_2$, 377.1324; found, 377.1321.



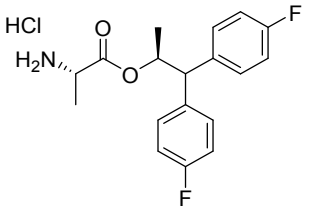
(*S*)-4,4'-(2-(benzyloxy)propane- 1,1- diyl)bis(fluorobenzene) (14). To a solution of (*S*)-2-(benzyloxy)- 1,1-bis(4-fluorophenyl)propan- 1-ol (709 mg, 2.0 mmol) in DCM (20 mL) at 0 °C was added triethylsilane (3.19 mL, 20.0 mmol) followed by 2,2,2-trifluoroacetic acid (1.53 mL, 20.0 mmol). The mixture was stirred at 0 °C for 1h. The resulting solution was quenched by careful addition of sat. aq. sodium bicarbonate (20 mL). The phases were separated, and the aq. phase was extracted with DCM (2 x 30 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated. The resulting oil was purified by flash column to afford the title compound (627 mg, 92%) as a white solid: m.p. 78-82 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 5H), 7.21 – 7.14 (m, 2H), 7.09 – 7.03 (m, 2H), 7.00 – 6.91 (m, 4H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.30 (d, *J* = 11.6 Hz, 1H), 4.18 – 4.09 (m, 1H), 3.93 (d, *J* = 8.1 Hz, 1H), 1.17 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5 (d, *J* = 244.5 Hz, 2C, Ar-C4), 138.5 (d, *J* = 3.3 Hz, Ar-C1), 138.3 (Bn-C1), 137.9 (d, *J* = 3.4 Hz, Ar-C1), 130.3 (d, *J* = 7.7 Hz, Ar-C2), 129.8 (d, *J* = 7.9 Hz, Ar-C2), 128.2 (Bn-C2 or Bn-C3), 127.6 (Bn-C2 or Bn-C3), 127.5 (Bn-C4), 115.3 (d, *J* = 21.0 Hz, Ar-C3), 115.0 (d, *J* = 21.2 Hz, Ar-C3), 77.2 (CHMe), 71.0 (CH_2), 57.1 ($CHAr_2$), 18.3 (Me); ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.56, -117.07; HRMS–ESI (*m/z*) $[M+Na]^+$ calcd for $C_{22}H_{20}F_2O$, 361.1374; found, 361.1410.



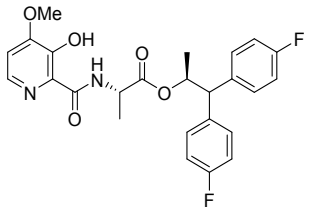
(*S*)-1,1-bis(4-fluorophenyl)propan-2-ol (**15**). To a solution of (*S*)-4,4'-(2-(benzyloxy)propane-1,1-diyl)bis(fluorobenzene) (575 mg, 1.70 mmol) in ethanol (11 mL) and cyclohexene (5.5 mL) at room temperature was added palladium on carbon (362 mg, 0.0850 mmol, 2.5% w/w of Pd). The reaction mixture was stirred at 65 °C for 2 h, cooled to room temperature, filtered through a plug of Celite®, and concentrated to afford the title compound (415 mg, 98%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.29 (m, 2H), 7.25 - 7.18 (m, 2H), 7.09 - 6.93 (m, 4H), 4.47 (dqd, *J* = 8.2, 6.1, 3.3 Hz, 1H), 3.80 (d, *J* = 8.3 Hz, 1H), 1.55 (d, *J* = 3.3 Hz, 1H), 1.19 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) 162.9 (d, *J* = 23.3 Hz, Ar-C4), 160.5 (d, *J* = 23.1 Hz, Ar-C4), 138.2 (d, *J* = 3.1 Hz, Ar-C1), 136.9 (d, *J* = 3.6 Hz, Ar-C1), 130.1 (d, *J* = 7.8 Hz, Ar-C2), 129.6 (d, *J* = 7.8 Hz, Ar-C2), 115.7 (d, *J* = 18.8 Hz, Ar-C3), 115.5 (d, *J* = 18.8 Hz, Ar-C3), 70.1 (CHOH), 58.6 ($CHAr_2$), 21.6 (Me); ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.84, -116.19; HRMS (APCI) m/z $[M+CH_3CO_2]^-$ calcd for $C_{17}H_{17}F_2O_3$ 307.1151, found 307.1152.



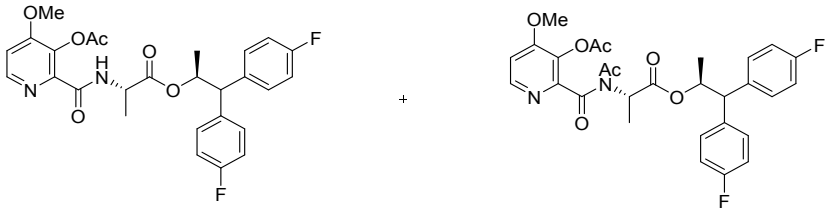
(*S,S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-((*tert*-butoxycarbonyl)amino)propanoate (16). A 3 L, 3-neck flask equipped with overhead mechanical stirring and nitrogen inlet was charged with a solution of (*S*)-1,1-bis(4-fluorophenyl)propan-2-ol (76 g, 297 mmol) and DMAP (3.63 g, 29.7 mmol) in DCM (1650 mL). The mixture was cooled to ~0 °C and (*S*)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (61.8 g, 327 mmol) was added to the flask followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (114 g, 594 mmol). The bath was allowed to expire while the flask was warmed to ambient temperature overnight. The solvent was removed under vacuum and the residue was taken up in ethyl acetate (750 mL). 0.1 N HCl (750 mL) was added and stirred to dissolve the residue. The layers were separated and the organic layer was washed once more with 0.1 N HCl (500 mL) and then saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated to afford the title compound (130 g, 99% yield, 95% purity) of a white, sticky foam. Analytical data was consistent with the 2nd generation route.



(*S,S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-aminopropanoate hydrochloride (4). A 3 L single-neck flask equipped with a stir bar was charged with (*S,S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-((*tert*-butoxycarbonyl)amino)propanoate (130 g, 294 mmol) and dioxane (100 mL). HCl in dioxane (750 mL, 3 mol, 4M solution) was added to the stirring mixture at RT (20 °C). The reaction was stirred overnight and then concentrated in vacuo to yield a sticky, tan foam. Diethyl ether (1.75 L) was added and the heterogeneous mixture was vigorously stirred for 30 min. The mixture was filtered, rinsed with diethyl ether, followed by hexane and vacuum dried under a nitrogen press to afford a white solid (104.7 g, 100%). Analytical data was consistent with the 2nd generation route.



(*S,S*)-1,1-bis(4-fluorophenyl)-propan-2-yl 2-(3-hydroxy-4-methoxypicolinamido)propanoate (2b). A 2 L flask equipped with a stir bar and nitrogen inlet was charged with (*S,S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-aminopropanoate hydrochloride **4** (73 g, 195 mmol), 3-hydroxy-4-methoxypicolinic acid (36.6 g, 214 mmol) and DCM (1000 mL). PyBOP (112 g, 214 mmol) was added to the resulting suspension, followed by *N*,*N*-diisopropylethylamine (113 mL, 643 mmol). After 3.5 hours, most of the solvent was removed and the reaction mixture was purified by flash column chromatography to afford the title compound (66.3 g, 69%) as a white foam. Analytical data was consistent with the 2nd generation route.

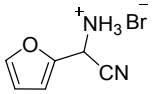


(*S,S*)-1,1-bis(4-fluorophenyl)-propan-2-yl 2-(3-acetoxy-4-methoxypicolinamido)propanoate (2a). A 2 L flask was charged with **2b** (50 g, 102 mmol) in DCM (1000 mL). Triethylamine (28.5 mL, 204 mmol) was added followed by N,N-dimethylpyridin-4-amine (2.5 g, 20.4 mmol) and acetyl chloride (11.1 mL, 153 mmol). The resultant red solution was stirred at ambient temperature (20 °C) for 19 hours. The reaction mixture was poured into saturated NH_4Cl solution (750 mL) and the layers were separated. The aqueous layer was extracted with DCM (1 x 500 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated to a smaller volume. The reaction mixture was purified by flash column chromatography to afford the title compound (47.2 g, 88%) as a white foam and impurity **25** (4.5g, 8%) as a pale yellow solid. Analytical data for **2a** was consistent with the 2nd generation route. Analytical data for **25** is shown below:

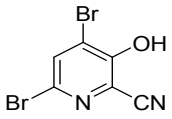
(*S*)-1,1-bis(4-fluorophenyl)propan-2-yl *N*-(3-acetoxy-4-methoxypicolinoyl)-N-acetyl-L-alaninate (25). m.p. 59-65 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.40 (d, *J* = 5.6 Hz, 1H), 7.42 (d, *J* = 5.7 Hz, 1H), 7.40 – 7.31 (m, 4H), 7.14 – 7.02 (m, 4H), 5.54 (dq, *J* = 7.9, 6.1 Hz, 1H), 4.64 (q, *J* = 6.8 Hz, 1H), 4.19 (d, *J* = 8.0 Hz, 1H), 3.93 (s, 3H), 2.21 (s, 3H), 1.93 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.5 (C=O), 169.0 (C=O, 167.6 (C=O), 167.5 (C=O), 160.9 (d, *J* = 242.9 Hz, Ar-C4), 160.8 (d, *J*

= 242.5 Hz, Ar-C4), 158.3 (Py-C4), 148.3 (Py-C2 or Py-C6), 145.7 (Py-C2 or Py-C6), 137.9 (d, *J* = 3.2 Hz, Ar-C1), 137.3 (d, *J* = 3.3 Hz, Ar-C1), 135.0 (Py-C3), 130.3 (d, *J* = 8.0 Hz, Ar-C2), 130.1 (d, *J* = 8.0 Hz, Ar-C2), 115.3 (d, *J* = 21.2 Hz, Ar-C3), 114.9 (d, *J* = 20.9 Hz, Ar-C3), 110.9 (Py-C5), 72.9 (CH-OAla), 56.8 (OMe), 54.1 (CHNAc or $CHAr_2$), 53.2 (CHNAc or $CHAr_2$), 25.7 (N-Ac-Me), 20.0 (O-Ac-Me), 18.4 (Me), 14.3 (Me); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.22, -116.58; HRMS–ESI (*m/z*) $[M+H]^+$ calcd for $C_{29}H_{28}F_2N_2O_7$, 555.1937; found, 555.1954.

2nd Generation Route

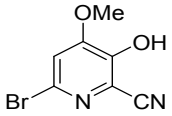


Cyano(furan-2-yl)methanaminium bromide (17). To a magnetically stirred suspension of potassium cyanide (29.3 g, 450 mmol) and ammonium acetate (116 g, 1500 mmol) in methanol (200 mL) was added furan-2-carbaldehyde (28.8 g, 300 mmol) at 0-5 °C. The reaction mixture was stirred at 0-5 °C for 40-50 hours. After the reaction was complete as indicated by HPLC analysis, the reaction mixture was diluted with DCM (300 mL) and 5% $NaHCO_3$ (300 mL). The aqueous layer was extracted with additional DCM (4×150 mL). The organic layers were combined and concentrated under vacuum with ethyl acetate (EtOAc). The resulting residual solution was dissolved in additional EtOAc (600 mL) and cooled to 5 °C. A solution of 33% HBr (66.1 g, 270 mmol) in acetic acid was charged slowly to the EtOAc solution to precipitate a solid. The solid was filtered and washed with EtOAc. The collected solid was dried in air at room temperature to give cyano(furan-2-yl)methanaminium bromide (47 g) in 77% yield: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 3H), 7.94 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.80 (dt, *J* = 3.4, 0.7 Hz, 1H), 6.63 (dd, *J* = 3.4, 1.9 Hz, 1H), 6.29 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.6 (C2 or C5), 142.1 (C2 or C5), 114.3 (CN), 112.4 (C3 or C4), 111.5 (C3 or C4), 37.5 ($CHNH_3$); HBr salt HRMS-ESI (m/z) calc'd for $[C_6H_6N_2O]^+$, 122.048 found, 123.055 $[M+H]^+$; m.p. decomposed >120° C.



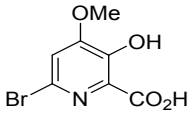
4,6-Dibromo-3-hydroxypicolinonitrile (18). To a magnetically stirred suspension of potassium cyanide (103 g, 1575 mmol) and ammonium acetate (347 g, 4500 mmol) in ethyl acetate (1500 mL) and water (375 mL) was added furan-2-carbaldehyde (144 g, 1500 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight. After the reaction was complete as indicated by ^{1}H NMR analysis, the reaction mixture was diluted with 20% Na_2CO_3 (750 mL). After phase separation, the organic layer was washed with a saturated solution of aqueous NaCl (375 mL). The organic layer containing 2-amino-2-(furan-2-yl)acetonitrile was extracted with 1953 mL of 3.7% aqueous hydrobromic acid (HBr) solution. The organic layer was extracted with additional water (2x200 mL). The combined aqueous layers were cooled to 5 °C, and bromine (959 g, 6000 mmol) was charged slowly via use of a peristaltic pump and Teflon tubing to the HBr solution while maintaining the temperature at <20 °C. The reaction mixture was then warmed and stirred overnight at 25 °C. After the reaction was complete, as indicated by ^{1}H NMR analysis, the reaction mixture was cooled to 5-10 °C, and then an aqueous solution of 40% $NaHSO_3$ (400 mL) was slowly charged while maintaining the temperature at <20 °C. The resulting suspension was stirred for 0.5 hr and then filtered. The filter cake was washed with water (2x200 mL) and dried at ambient temperature in the air to give 4,6-dibromo-3-hydroxypicolinonitrile (251 g) as a tan solid in 60% yield: m.p. 183-185 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.6 (C3), 135.7 (C5 or C6), 129.8 (C5 or C6), 126.0 (C2 or C4), 121.6 (C2 or C4), 114.6 (CN); HRMS-ESI (m/z) calc'd for $[C_6H_2Br_2N_2O]^+$, 275.8534, found, 275.8510. The tan solid was found to contain about 94.5% of 4,6-dibromo-3-hydroxypicolinonitrile and less than about 6% of a mono brominated intermediate product, which was tentatively assigned as either 4-bromo-3-hydroxypicolinonitrile or 6-bromo-3-hydroxypicolinonitrile as determined by MS analysis.

4,6-Dibromo-3-hydroxypicolinonitrile (18) via bromination with HBr and H_2O_2. 53 g of an aqueous solution containing 7.45 g (37 mmol) of cyano(furan-2-yl)methanaminium bromide (14.06 wt % in water) was placed into a 250 mL flask outfitted with a stir bar. 48% HBr (8.2 mL, 73 mmol) was added to the flask with stirring. The flask was placed in an ice bath. After cooling to <5 °C, 6 to 7 mL of 30% hydrogen peroxide was added to the reaction via syringe over 20-30 minutes. This resulted in very little heat evolution. The reaction was allowed to warm to ambient temperature, at which point the reaction started to self heat to about 46-48 °C and became yellow orange in color (homogeneous). The reaction was cooled to 20 °C, and then another 7 mL of the 30% hydrogen peroxide was added via syringe over 15-20 minutes, which resulted in the formation of a precipitate. The reaction was allowed to stir overnight. The reaction was quenched with sodium bisulfite to yield a slightly yellow solution with solids. Peroxide test strips indicated no residual peroxides. The solids were collected by filtration, washed with water, and dried to yield 6.22 grams of a light tan powder. Analytical data matched that from above; ^{1}H NMR analysis indicated that the product consisted of 4,6-dibromo-3-hydroxypicolinonitrile (58.1% yield) and 6-bromo-3-hydroxypicolinonitrile (3.8% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1.00H), 7.75 (d, *J* = 8.9 Hz, 0.064H), 7.44 (d, *J* = 8.9 Hz, 0.064H).

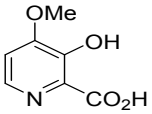


6-Bromo-4-methoxy-3-hydroxypicolinonitrile (19) in DMSO. To a slurry of sodium methoxide (15.2 g, 282 mmol) in 35 mL of anhydrous dimethyl sulfoxide (DMSO) was added a solution of 4,6-dibromo-3-hydroxypicolinonitrile (30 g, 108 mmol) in anhydrous DMSO (30 mL). The solution was added over 30 minutes and the reaction mixture was maintained below 55 °C during the addition. The reaction solution was heated for an additional 1.5 hours after the feed was complete. The resulting reaction mixture was cooled to <30 °C, and then 120 mL of DI water was added. The reaction mixture was allowed to cool to about 25°C. The pH of the reaction mixture was adjusted to about 2 with 40% sulfuric acid, which resulted in the precipitation of a solid. The solid was collected by filtration and washed with 75 mL of pH 1.5 sulfuric acid, followed by 25 mL of DI water. The solid was then allowed to dry to yield 20.7 g (83.7% yield) of desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.47 (s, 1H), 3.98 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.5 (C4), 149.4 (C3), 131.0 (C6), 118.6 (C2), 114.9 (C5 or CN), 114.5 (C5 or CN), 57.2 (OMe); HRMS-ESI (m/z) calc'd for $[C_7H_5\,BrN_2O_2]^+$, 227.9533. found, 227.9534; m.p. 168° C.

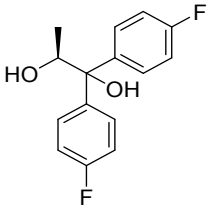
6-Bromo-4-methoxy-3-hydroxypicolinonitrile (19) in PhCN. A 250 mL jacketed reactor equipped w/ a N_2 gas inlet, overhead stirring, and temperature probe was charged with 4,6-dibromo-3-hydroxypicolinonitrile (4.98 g, 17 mmol) and benzonitrile (14.15 g). 25% sodium methoxide in methanol was added (8.45 g, 39 mmol) was loaded and the mixture was heated to 65 °C. Vacuum was pulled and methanol was removed via evaporation. After 16 h, an additional 5.8 g of benzonitrile was added. After 3 additional hours, 2.5 g of 25% sodium methoxide in methanol was added. The reaction was allowed to stir for a total of 33 h. At this point, the reaction was cooled to ambient temperature. Approximately 25 g of 1 M HCl was added to the reaction mixture, and the mixture was analyzed via HPLC. The in-pot yield was determined to be 57%. HPLC analysis was performed with a Waters Xbridge BEH Phenyl column (3.0 mm × 100 mm, 2.5 µm) using a gradient mobile phase comprised of water and acetonitrile (both containing 0.2% trifluoroacetic acid), a UV detector set to 300 nm and an analytical standard of 2-methoxybenzoic acid.



6-Bromo-3-hydroxy-4-methoxypicolinic acid (20). To a magnetically stirred solid sample of 6-bromo-3-hydroxy-4-methoxypicolinonitrile (88 g, 384 mmol) was added 66% H_2SO_4 (384 mL) at room temperature. The resulting mixture was warmed and stirred overnight at 90-95 °C After HPLC analysis indicated the reaction was complete, the reaction mixture was cooled to 30-40 °C and transferred slowly to a flask charged with water (3072 g) to precipitate the product. The resulting suspension was stirred for 0.5 hr. The resulting precipitate was filtered, washed with water, and dried in air overnight to give 6-bromo-3-hydroxy-4-methoxypicolinic acid (95 g) as an off-white solid in 100% yield: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (s, 1H), 3.97 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.1 (CO_2H), 156.6 (C4), 149.1 (C3), 130.2 (C2 or C6), 129.9 (C2 or C6), 114.5 (C5), 56.8 (OMe); HRMS-ESI (m/z) [M+H]+ calcd for $C_7H_6BrNO_4$, 246.948. found, 246.948; m.p. 167-170° C.

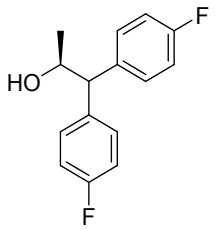


3-Hydroxy-4-methoxypicolinic acid (3). To 6-bromo-3-hydroxy-4-methoxypicolinic acid (47.5 g, 191.5 mmol) and ethanol (576 mL) in a Parr shaker bottle (2 L) was added triethylamine (40.7 g, 402 mmol). Then under a nitrogen atmosphere 5% Pd/C (20 g, 9.6 mmol; 5 mol %) was added to the bottle. The reaction slurry was placed on a Parr shaker and the bottle was placed under hydrogen gas (40-45 psi) and shaken. After completion of the reaction as indicated by HPLC analysis, the hydrogen gas was removed under vacuum and replaced with nitrogen gas. The reaction slurry was filtered through a pad of Celite® and the Celite® pad was washed with fresh ethanol. The ethanolic filtrate was concentrated to give a solid. The solid was diluted with 0.2N HCl (200 mL) to adjust the pH to about 1-2, and the resulting suspension was stirred for 10-15 minutes at room temperature. The solid was then collected by filtration, washed with water, and dried in air for several hours and then placed in a vacuum oven at 50 °C to give 3-hydroxy-4-methoxypicolinic acid (27.5 g) as an off-white solid in 85% yield: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, *J* = 6.4 Hz, 1H), 7.40 (d, *J* = 6.5 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.2 (C4 or CO_2H), 162.0 (C4 or CO_2H), 152.5 (C3), 132.3 (C2 or C6), 126.6 (C2 or C6), 109.1 (C5), 57.4 (OMe); HRMS-ESI (m/z) calcd for $C_7H_7NO_4$, 169.0379. found, 169.0375; m.p. 219° C.



(*S*)-1,1-bis(4-fluorophenyl)propane-1,2-diol (21). A 2-neck 250 mL Schlenk flask equipped with dropping funnel, nitrogen inlet, magnetic stir bar and thermocouple was charged with 90.52 g of (4-fluorophenyl)magnesium bromide solution (1.0 M in THF, 88.65 mmol) under nitrogen. The solution was cooled to 0.7 °C in an ice bath. A solution of 3.03 g (21.0 mmol) of (*S*,*S*)-lactide in THF was added dropwise over 150 min. The addition rate was controlled to keep the reaction temperature below 3.5 °C. The ice bath was removed, and the reaction mixture was allowed to warm. After 2h, the reaction mixture was

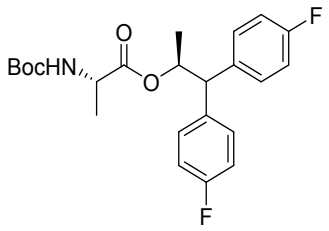
cooled in an ice bath and quenched with 50 mL of saturated NH_4Cl solution. The product was extracted with EtOAc (2 x 50 mL). The extracts were filtered through Celite®, washed with brine and dried (Na_2SO_4). Rotary evaporation gave a yellow oil which was purified by flash chromatography and hexane-EtOAc gradient. Tubes which contained product were rotary evaporated to a colorless oil which was dried in vacuum oven at 50 °C (7.49 g, 67.4% yield). ^{1}H NMR ($CDCl_3$) δ 7.59 – 7.49 (m, 2H), 7.41 – 7.32 (m, 2H), 7.07 – 6.92 (m, 4H), 4.74 (qd, *J* = 6.2, 3.8 Hz, 1H), 3.00 (s, 1H), 1.81 (d, *J* = 3.8 Hz, 1H), 1.08 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9 (d, *J* = 246.8 Hz, Ar-C4), 161.7 (d, *J* = 246.0 Hz, Ar-C4), 141.2 (d, *J* = 3.3 Hz, Ar-C1), 139.6 (d, *J* = 3.2 Hz, Ar-C1), 128.1 (d, *J* = 7.9 Hz, Ar-C2), 127.4 (d, *J* = 8.0 Hz, Ar-C2), 115.4 (d, *J* = 21.3 Hz, Ar-C3), 115.0 (d, *J* = 21.3 Hz, Ar-C3), 79.3 ($COHAr_2$), 71.5 (CHMe), 16.9 (Me); ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.3, -115.9; HRMS (APCI) m/z $[M+CH_3CO_2]^-$ calcd for $C_{17}H_{17}F_2O_4$ 323.1100, found 323.1101.



(*S*)-1,1-bis(4-fluorophenyl)propan-2-ol (15) via reduction with triethylsilane. (*S*)-1,1-bis(4-fluorophenyl)propane-1,2-diol (2.01 g, 7.61 mmol) was dissolved in 25 mL DCM in a 100 mL Schlenk flask. The flask was evacuated/backfilled 3x with nitrogen. The solution was cooled to 0 °C in an ice bath. Neat Et_3SiH (8.76 g, 77 mmol) was added via syringe with no exotherm. Neat trifluoroacetic acid (8.74 g, 75 mmol) was added via syringe over 5 min with an exotherm to 3.0 °C. The reaction mixture was stirred for 1h at 0 °C and then quenched by pouring into 146 g of 1 M NaOH. DCM (50 mL) was added. The aqueous layer was separated and extracted with additional DCM (2 x 50 mL). The combined organics were washed with brine and dried (Na_2SO_4). Rotary evaporation gave 3.17 g of pale yellow oil which was purified by column chromatography. Pure fractions were rotary evaporated to 1.21 g of colorless oil (64% yield). Analytical data was consistent with the 1st generation route. Chiral HPLC analysis was performed using a Chiralpak IA column (250 x 4.6 mm, P/N: 80325) with isocratic 85% in hexanes (0.1% trifluoroacetic acid) and 15% isopropanol (0.1% trifluoroacetic acid) mobile phase (10 µL injected). Using a UV detector set to 265 nm, enantiomer #1 (major) eluted at 6.2 minutes and enantiomer #2 (minor) eluted at 6.8 minutes (see chromatogram below). The enantiopurity was determined to be >99 %ee.

(*S*)-1,1-bis(4-fluorophenyl)propan-2-ol (15) via reduction with PMHS. A 100 mL, three-neck, round bottom flask equipped with a magnetic stirrer, a thermocouple and a nitrogen inlet was charged with (*S*)-1,1-bis(4-fluorophenyl)propane-1,2-diol (1.23 g , 4.67 mmol), and DCM (53 mL), and the resulting solution was cooled to 0 °C. Neat PMHS (M_N = 1700-3200, 2.9 g) was added followed by dropwise addition of neat trifluoroacetic acid (5.4 g, 46.7 mmol). After 80 min, the reaction was quenched by addition to 50 mL of 1 M NaOH. DCM (30 mL) was added. The aqueous layer was separated and extracted with additional DCM (2 x 35 mL). The combined organics were washed with brine, dried (Na_2SO_4) and rotary evaporated. The crude product was purified by column chromatography (SiO_2 , 0 – 45 % EtOAc in hexanes) to give a colorless oil (0.613 g , 53 % yield). Analytical data was consistent with the 1st generation route. Chiral HPLC analysis was performed using a Chiralpak IA column (250 x 4.6 mm, P/N: 80325) with isocratic 85% in hexanes (0.1% trifluoroacetic acid) and 15% isopropanol (0.1% trifluoroacetic acid) mobile phase (10 µL injected). Using a UV detector set to 265 nm, enantiomer #1 (major) eluted at 6.2 minutes and enantiomer

#2 (minor) eluted at 6.8 minutes(see chromatogram below). The enantiopurity was determined to be >99 %ee.

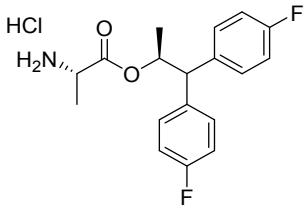


(*S,S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-((*tert*-butoxycarbonyl)amino)propanoate (16) in DCM. A 250 mL flask equipped with a stir bar was charged with (*S*)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (0.91 g, 4.8 mmol) and DCM (20 mL) and cooled to 0 °C. Triethylamine (1.4 mL, 10 mmol) was added to the reaction flask. As pivaloyl chloride (0.59 mL, 4.8 mmol) was slowly added to the reaction mixture a white precipitate began to form. After stirring for 15 min at 0 °C, (*S*)-1,1-bis(4-fluorophenyl)propan-2-ol (993 mg, 4.0 mmol) was added, followed by N,N-dimethylpyridin-4-amine (49 mg, 0.4 mmol), and the reaction was stirred overnight at RT. The reaction was quenched with water, and the layers were separated. The aqueous layer was extracted once with DCM. The combined organic layers were dried with Na_2SO_4, filtered and concentrated to afford a colorless oil. The crude material was purified via silica gel chromatography by eluting with an ethyl acetate/hexane gradient to afford the title compound as a white foam (1.4 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.17 (m, 4H), 7.03 – 6.92 (m, 4H), 5.71 (dq, *J* = 9.8, 6.2 Hz, 1H), 4.94 (d, *J* = 8.0 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 1H), 4.02 (d, *J* = 9.9 Hz, 1H), 1.42 (s, 9H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.84 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8 (CO_2R), 161.7 (d, *J* = 246.1 Hz, Ar-C4), 161.7 (d, *J* = 245.6 Hz, Ar-C4), 154.9 (CO_2tBu), 137.0 (d, *J* = 3.3 Hz, Ar-C1), 136.8 (d, *J* = 3.4 Hz, Ar-C1), 129.5 (d, *J* = 7.9 Hz, Ar-C2), 129.5 (d, *J* = 7.8 Hz, Ar-C2), 115.7 (d, *J* = 21.3 Hz, Ar-C3), 115.4 (d, *J* = 21.3 Hz, Ar-C3), 79.8 ($(CH_3)_3$), 72.9 (CH-OAla), 56.2 ($CHAr_2$), 49.2 (CHNH), 28.3 ($C(\underline{C}H_3)_3$), 19.2 (Me), 18.1 (Me); ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.56, -115.97; HRMS–ESI (*m/z*) $[M+H]^+$ calcd for $C_{23}H_{27}F_2NO_4$, 442.1800; found, 442.1790.

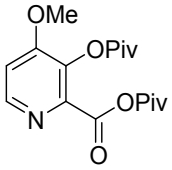
(*S,S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-((*tert*-butoxycarbonyl)amino)propanoate (16) in 2-MeTHF. A 100 mL flask equipped with a stir bar was charged with (*S*)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (0.91 g, 4.8 mmol) and 2-MeTHF (20 mL) and cooled to 0 °C. Triethylamine (1.4 mL, 10 mmol) was added to the reaction flask. As pivaloyl chloride (0.59 mL, 4.8 mmol) was slowly added to the reaction mixture a white precipitate began to form. After stirring for 15 min at 0 °C, (*S*)-1,1-bis(4-fluorophenyl)propan-2-ol (1.0 g, 4.0 mmol) was added, followed by N,N-dimethylpyridin-4-amine (67 mg, 0.5 mmol), and the reaction was stirred overnight at RT. The reaction was quenched with water, and the layers were separated. The aqueous layer was extracted once with 2-MeTHF. The combined organic layers were dried with Mg_2SO_4, filtered and concentrated to afford a colorless oil. The crude material was purified via silica gel chromatography by eluting with an ethyl acetate/hexanes gradient to afford the title compound as a white foam (1.5 g, 90%). Analytical data matched that from above.

(*S,S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-((*tert*-butoxycarbonyl)amino)propanoate (16) in CPME. A 100 mL flask equipped with a stir bar was charged with (*S*)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (0.91 g, 4.8 mmol) and CPME (20 mL) and cooled to 0 °C. Triethylamine (1.4 mL, 10 mmol) was added to the reaction flask. As pivaloyl chloride (0.59 mL, 4.8 mmol) was slowly added to the reaction mixture a white precipitate began to form. After stirring for 15 min at 0 °C, (*S*)-1,1-bis(4-fluorophenyl)propan-2-ol

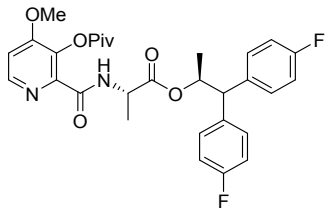
(1.0 g, 4.0 mmol) was added, followed by N,N-dimethylpyridin-4-amine (52 mg, 0.4 mmol), and the reaction was stirred overnight at RT. The reaction was quenched with water, and the layers were separated. The aqueous layer was extracted once with CPME. The combined organic layers were dried with Mg_2SO_4, filtered and concentrated to afford a colorless oil. The crude material was purified via silica gel chromatography by eluting with an ethyl acetate/hexanes gradient to afford the title compound as a white foam (1.65 g, 98%). Analytical data matched that from above.



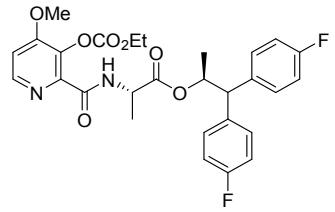
(*S,S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-aminopropanoate hydrochloride (4). A 30 mL vial equipped with a stir bar was charged with (*S,S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-((*tert*-butoxycarbonyl)amino)propanoate (1.0 g, 2.4 mmol) and CPME (1 mL). HCl in CPME (8 mL, 24 mmol, 3M solution) was added to the stirring mixture at RT (20 °C). The reaction was stirred overnight and then sparged with nitrogen. Hexane (9 mL) was added and the heterogeneous mixture was vigorously stirred for 10 min. The mixture was filtered, rinsed with hexanes and vacuum dried under nitrogen to afford a white solid (0.81 g, 94%): m.p. 152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 3H), 7.25 – 7.18 (m, 4H), 7.02 – 6.93 (m, 4H), 5.70 (dq, *J* = 12.5, 6.6 Hz, 1H), 4.09 – 4.02 (m, 2H), 1.23 (d, *J* = 6.1 Hz, 3H), 1.14 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8 (C=O), 161.8 (d, *J* = 246.2 Hz, Ar-C4), 161.7 (d, *J* = 245.7 Hz, Ar-C4), 136.7 (d, *J* = 3.6 Hz, Ar-C1), 136.5 (d, *J* = 3.4 Hz, Ar-C1), 129.6 (d, *J* = 8.1 Hz, Ar-C2), 129.5 (d, *J* = 7.8 Hz, (Ar-C2), 115.8 (d, *J* = 22.1 Hz, Ar-C3), 115.6 (d, *J* = 21.9 Hz, Ar-C3), 74.5 (CH-OAla), 56.0 ($CHAr_2$), 49.2 ($CHNH_3$), 19.0 (Me), 15.5 (Me); ^{19}F NMR (471 MHz, $CDCl_3$) δ -115.15, -115.56; HRMS–ESI (*m/z*) $[M+H]^+$ calcd for $C_{18}H_{19}F_2NO_2$, 320.1457; found, 320.1448.



4-methoxy-3-(pivaloyloxy)picolinic pivalic anhydride (22). A 250 mL rbf equipped with stir bar was charged with 3-hydroxy-4-methoxypicolinic acid (2 g, 11.8 mmol) and DCM (60 mL) and cooled to 0 °C. Triethylamine (3.5 mL, 24.8 mmol) was slowly added, followed by slow addition of Piv-Cl (3.0 mL, 24.2 mmol). The reaction was stirred at 0 °C for 30 min. The reaction was quenched with 0.5 M HCl. The organic layer was concentrated to afford a pale yellow oil. The crude material was purified via silica gel chromatography by eluting with an ethyl acetate/hexane gradient to afford the title compound as a colorless oil (3.2 g, 79%): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.40 (d, *J* = 5.4 Hz, 1H), 7.03 (d, *J* = 5.4 Hz, 1H), 3.90 (s, 3H), 1.39 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4 (C=O*t*Bu), 174.7 (C=O*t*Bu), 160.6 (C4 or CO_2Piv), 159.0 (C4 or CO_2Piv), 147.6 (C6), 140.4 (C2 or C3), 139.5 (C2 or C3), 110.6 (C5), 56.4 (OMe), 39.9 ($\underline{C}(CH_3)_3$), 39.2 ($\underline{C}(CH_3)_3$), 27.1 ($(CH_3)_3$), 26.7 ($(CH_3)_3$); HRMS–ESI (*m/z*) $[M+H]^+$ calcd for $C_{17}H_{23}NO_6$, 338.1598; found, 338.1604.

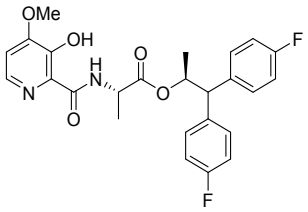


(*S*,*S*)-2-((-1-((-1,1-bis(4-fluorophenyl)propan-2-yl)oxy)-1-oxopropan-2-yl)carbamoyl)-4-methoxypyridin-3-yl pivalate (23). A flask equipped with a stir bar and nitrogen inlet was charged with 3-hydroxy-4-methoxypicolinic acid (1 g, 5.9 mmol) and DCM (29.6 mL) and cooled to 0 °C. Triethylamine (2.6 mL, 18.3 mmol) was slowly added, followed by slow addition of pivaloyl chloride (1.5 mL, 12.1 mmol). The reaction was stirred at 0 °C for 30 min. (S)-1-(((S)-1,1-bis(4-fluorophenyl)propan-2-yl)oxy)-1-oxopropan-2-aminium chloride (2.1 g, 5.9 mmol) was added and the reaction was stirred at 0 °C for 30 min at which point LCMS indicated full consumption of starting material. The reaction mixture was quenched with water and 10 drops of concentrated HCl. The biphasic mixture was diluted with DCM and the organic layer was separated and concentrated to give a yellow oil. The crude material was purified *via* silica gel chromatography by eluting with an ethyl acetate/hexane gradient to afford the title compound as a white foam (2.7 g, 82%): mp 52–65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 5.5 Hz, 1H), 8.29 (br s, 1H), 7.26 – 7.18 (m, 4H), 7.01 – 6.90 (m, 5H), 5.70 (dq, *J* = 9.5, 6.1 Hz, 1H), 4.61 – 4.50 (m, 1H), 4.04 (d, *J* = 9.5 Hz, 1H), 3.88 (s, 3H), 1.39 (s, 9H), 1.22 (d, *J* = 6.1 Hz, 3H), 0.99 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0 (C=O*t*Bu), 172.3 (CO_2R), 162.2 (CONH), 161.7 (d, *J* = 245.8 Hz, Ar-C4), 161.6 (d, *J* = 245.6 Hz, Ar-C4), 159.4 (Py-C4), 146.5 (Py-C2 or Py-C6), 142.1 (Py-C2 or Py-C6), 137.8 (Py-C3), 136.9 (Ar-C1), 136.8 (Ar-C1), 129.6 (d, *J* = 8.1 Hz, Ar-C2), 129.5 (d, *J* = 7.8 Hz, Ar-C2), 115.7 (d, *J* = 21.3 Hz, Ar-C3), 115.4 (d, *J* = 21.3 Hz, Ar-C3), 109.5 (Py-C5), 73.0 (CH-OAla), 56.3 (OMe), 56.1 ($CHAr_2$), 47.8 (CHNH), 39.1 ($\underline{C}(CH_3)_3$), 27.2 ($(CH_3)_3$), 19.1 (Me), 18.1 (Me); ^{19}F NMR (471 MHz, $CDCl_3$) δ -115.65, -115.99; HRMS–ESI (*m/z*) $[M+H]^+$ calcd for $C_{30}H_{32}F_2N_2O_6$, 555.2301; found, 555.2311.

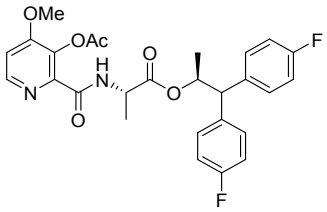


(*S*,*S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-(3-((ethoxycarbonyl)oxy)-4-methoxypicolinamido)propanoate (24). A 250 mL flask equipped with a stir bar was charged with 3-hydroxy-4-methoxypicolinic acid (0.846 g, 5 mmol) and backfilled with nitrogen. DCM (25 mL) was added to the reaction flask and the resulting white heterogeneous mixture was cooled to 0 °C. Triethylamine (2.3 mL, 16.5 mmol) was added and the reaction mixture became a homogeneous solution over the course of ten minutes of vigorous stirring. Ethyl chloroformate (1.0 mL, 10.5 mmol) was slowly added to the reaction mixture and a white precipitate began to form. After stirring for 15 min at 0 °C, (*S*, *S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-aminopropanoate hydrochloride (1.78 g, 5.0 mmol) was added to the flask in one portion. The reaction mixture was stirred at 0 °C for 3 min, at which time the reaction was quenched with 20 mL of water and 5 mL of 2N HCl. The biphasic mixture was diluted with DCM and transferred to a separatory funnel. The layers were separated, and the organic layer was dried with Na_2SO_4, filtered and concentrated to afford a pale yellow oil. The crude material was purified *via* silica gel chromatography by eluting with an ethyl acetate/hexane gradient to afford the title compound as a white solid (2.3 g, 85%):

mp 48–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 - 8.25 (m, 2H), 7.38 - 7.12 (m, 4H), 7.09 - 6.85 (m, 5H), 5.71 (dq, *J* = 9.7, 6.2 Hz, 1H), 4.67 - 4.54 (m, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.04 (d, *J* = 9.6 Hz, 1H), 3.92 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.99 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 (CO_2R), 162.2 (CONH), 161.7 (d, *J* = 246.0 Hz, Ar-C4), 161.6 (d, *J* = 245.6 Hz, Ar-C4), 159.4 (Py-C4), 152.5 (OCO_2Et), 146.8 (Py-C2 or Py-C6), 141.7 (Py-C2 or Py-C6), 137.7 (Py-C3), 136.9 (Ar-C1), 136.8 (Ar-C1), 129.6 (d, *J* = 7.8 Hz, Ar-C2), 129.5 (d, *J* = 7.8 Hz, Ar-C2), 115.7 (d, *J* = 21.4 Hz, Ar-C3), 115.4 (d, *J* = 21.2 Hz, Ar-C3), 110.0 (Py-C5), 73.1 (CH-OAla), 65.4 ($CH_3\underline{C}H_2O$), 56.3 (OMe), 56.1 ($CHAr_2$), 47.8 (CHNH), 19.1 (Me), 18.1 (Me), 14.1 ($\underline{C}H_3CH_2O$); ^{19}F NMR (471 MHz, $CDCl_3$) δ -115.59, -115.95; HRMS–ESI (*m/z*) $[M+H]^+$ calcd for $C_{28}H_{28}F_2N_2O_7$, 543.1937; found, 543.1932.



(*S,S*)-1,1-bis(4-fluorophenyl)-propan-2-yl 2-(3-hydroxy-4-methoxypicolinamido)propanoate (2b). A vial equipped with a stir bar was charged with (*S*,*S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-(3-((ethoxycarbonyl)oxy)-4-methoxypicolinamido)propanoate (543 mg, 1 mmol, employed as an 8:1 mixture of the title starting material to product: (*S*,*S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-(3-hydroxy-4-methoxypicolinamido)propanoate) and THF (5 mL). Lithium hydroxide hydrate (71 mg, 1.69 mmol) was dissolved in a separate vial, dissolved in water (2.5 mL) and added to the reaction flask. The reaction immediately turned from clear colorless to yellow. The reaction was allowed to stir for 3h at RT. The reaction was acidified to pH of 2 with 2N HCl (0.8 mL) and diluted with 25 mL of ethyl acetate. The organic layer was concentrated to give a yellow oil. The crude material was purified *via* silica gel chromatography by eluting with an ethyl acetate/hexane gradient to afford the title compound as a white foam (397 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.06 (s, 1H), 8.32 (dd, *J* = 6.7, 4.3 Hz, 1H), 7.98 (d, *J* = 5.2 Hz, 1H), 7.32 - 7.14 (m, 4H), 7.03 - 6.89 (m, 4H), 6.87 (d, *J* = 5.2 Hz, 1H), 5.73 (dq, *J* = 9.8, 6.2 Hz, 1H), 4.61 - 4.47 (m, 1H), 4.05 (d, *J* = 9.8 Hz, 1H), 3.94 (s, 3H), 1.25 (d, *J* = 6.1 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (CO_2R), 168.6 (CONH), 161.8 (d, *J* = 246.1 Hz, Ar-C4), 161.7 (d, *J* = 245.7 Hz, Ar-C4), 155.4 (Py-C4), 148.8 (Py-C3), 140.4 (Py-C6), 136.8 (d, *J* = 3.4 Hz, Ar-C1), 136.7 (d, *J* = 3.4 Hz, Ar-C1), 130.4 (Py-C2), 129.5 (d, *J* = 7.8 Hz, Ar-C2), 129.5 (d, *J* = 7.8 Hz, Ar-C2), 115.7 (d, *J* = 21.3 Hz, Ar-C3), 115.4 (d, *J* = 21.3 Hz, Ar-C3), 109.5 (Py-C5), 73.3 (CH-OAla), 56.1 (OMe or $CHAr_2$), 56.1 (OMe or $CHAr_2$), 47.9 (CHNH), 19.1 (Me), 17.7 (Me); ^{19}F NMR (471 MHz, $CDCl_3$) δ -115.46, -115.80; HRMS–ESI (*m/z*) $[M+H]^+$ calcd for $C_{25}H_{24}F_2N_2O_5$, 471.1726; found, 471.1724.



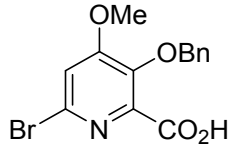
(*S,S*)-1,1-bis(4-fluorophenyl)-propan-2-yl 2-(3-acetoxy-4-methoxypicolinamido)propanoate (2a). A 2 L flask equipped with a stir bar was charged with (*S,S*)-1,1-bis(4-fluorophenyl)-propan-2-yl 2-(3-hydroxy-4-methoxypicolinamido)propanoate (25 g, 51.0 mmol), pyridine (250 mL) and acetic anhydride (250 mL,

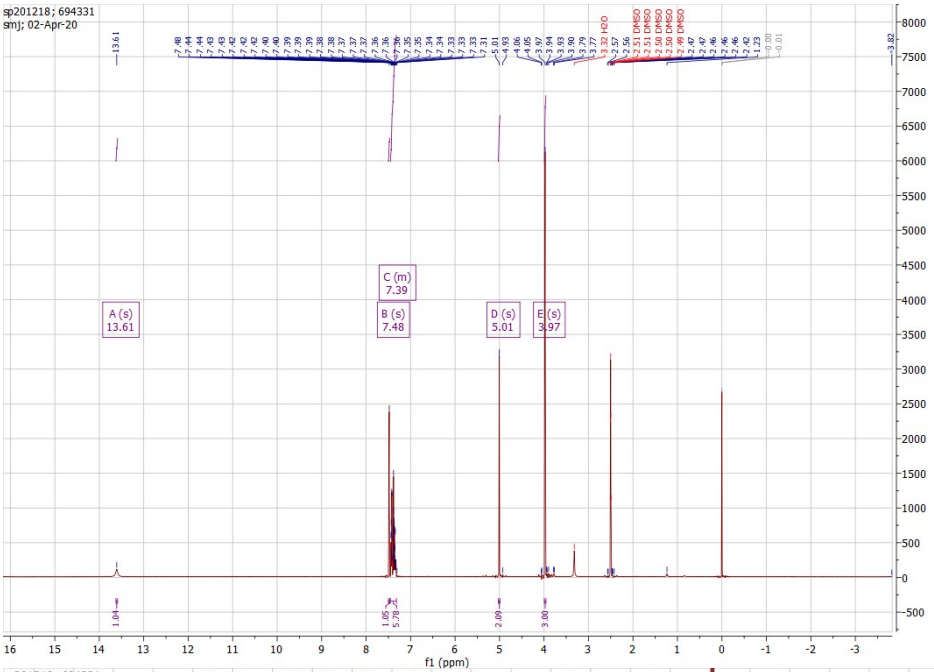
2.65 mol). The reaction was stirred for 1h at RT and then the solvents were removed under vacuum. Heptane was added and the mixture was concentrated. This step was repeated to ensure complete azeotropic removal of any residual solvent. DCM and sat. aqueous ammonium chloride were added to the residue and the layers were separated. The aqueous layer was extracted with DCM (1x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to yield an off-white foam. The crude material was purified via silica gel chromatography by eluting with an ethyl acetate/hexane gradient to afford the title compound as a white foam (25.1 g, 95%): m.p. 50-55 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, br, 1H), 8.32 (d, *J* = 5.4 Hz, 1H), 7.26 – 7.19 (m, 4H), 7.04 – 6.88 (m, 5H), 5.71 (dq, *J* = 9.6, 6.1 Hz, 1H), 4.62 – 4.49 (m, 1H), 4.04 (d, *J* = 9.6 Hz, 1H), 3.90 (s, 3H), 2.38 (s, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.99 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1 (CO_2R), 168.9 (COMe), 162.3 CONH), 161.7 (d, *J* = 246.1 Hz, Ar-C4), 161.6 (d, *J* = 245.6 Hz, Ar-C4), 160.3 (Py-C4), 146.7 (Py-C2 or Py-C6), 141.4 (Py-C2 or Py-C6), 137.5 (Py-C3), 136.9 (d, *J* = 3.3 Hz, Ar-C1), 136.8 (d, *J* = 3.4 Hz, Ar-C1), 129.6 (d, *J* = 5.9 Hz, Ar-C2), 129.5 (d, *J* = 5.8 Hz, Ar-C2), 115.7 (d, *J* = 21.3 Hz, Ar-C3), 115.4 (d, *J* = 21.1 Hz, Ar-C3), 109.8 (Py-C5), 73.0 (CH-OAla), 56.3 (OMe or $CHAr_2$), 56.1 (OMe or $CHAr_2$), 47.9 (CHNH), 20.7 (Ac-Me), 19.1 (Me), 18.0 (Me); ^{19}F NMR (471 MHz, $CDCl_3$) δ -115.60, -115.96; HRMS–ESI (*m/z*) $[M+H]^+$ calcd for $C_{27}H_{26}F_2N_2O_6$, 513.1832; found, 513.1849.

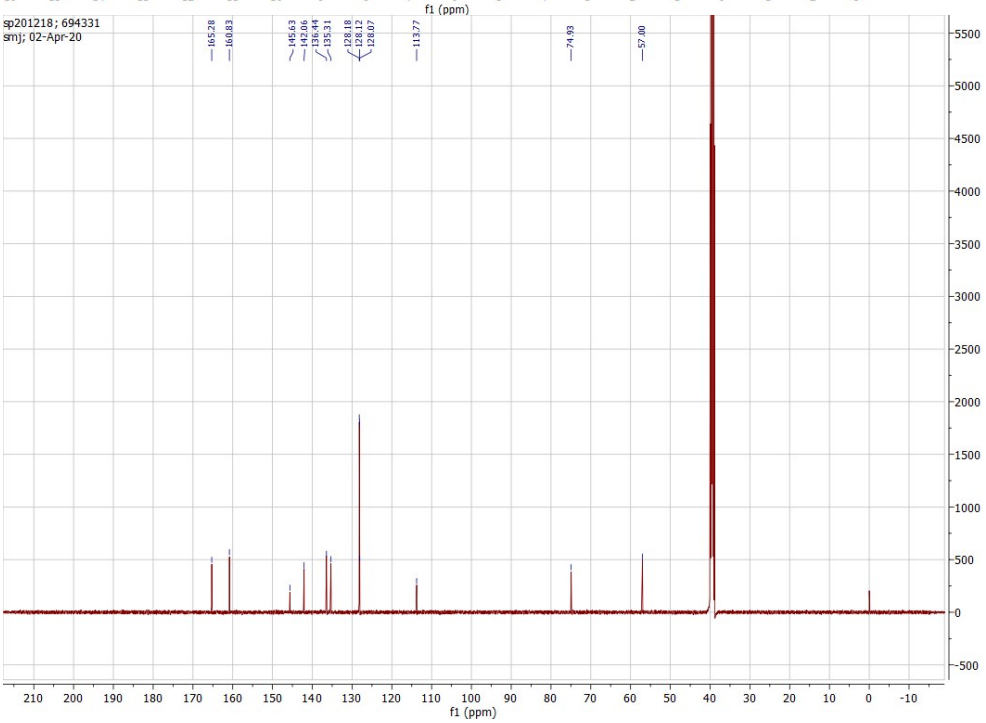
Copies of NMR Spectra

1st Generation Route

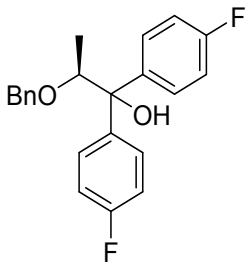
6-bromo-3-benzyloxy-4-methoxypyridine-2-carboxylic acid (10)

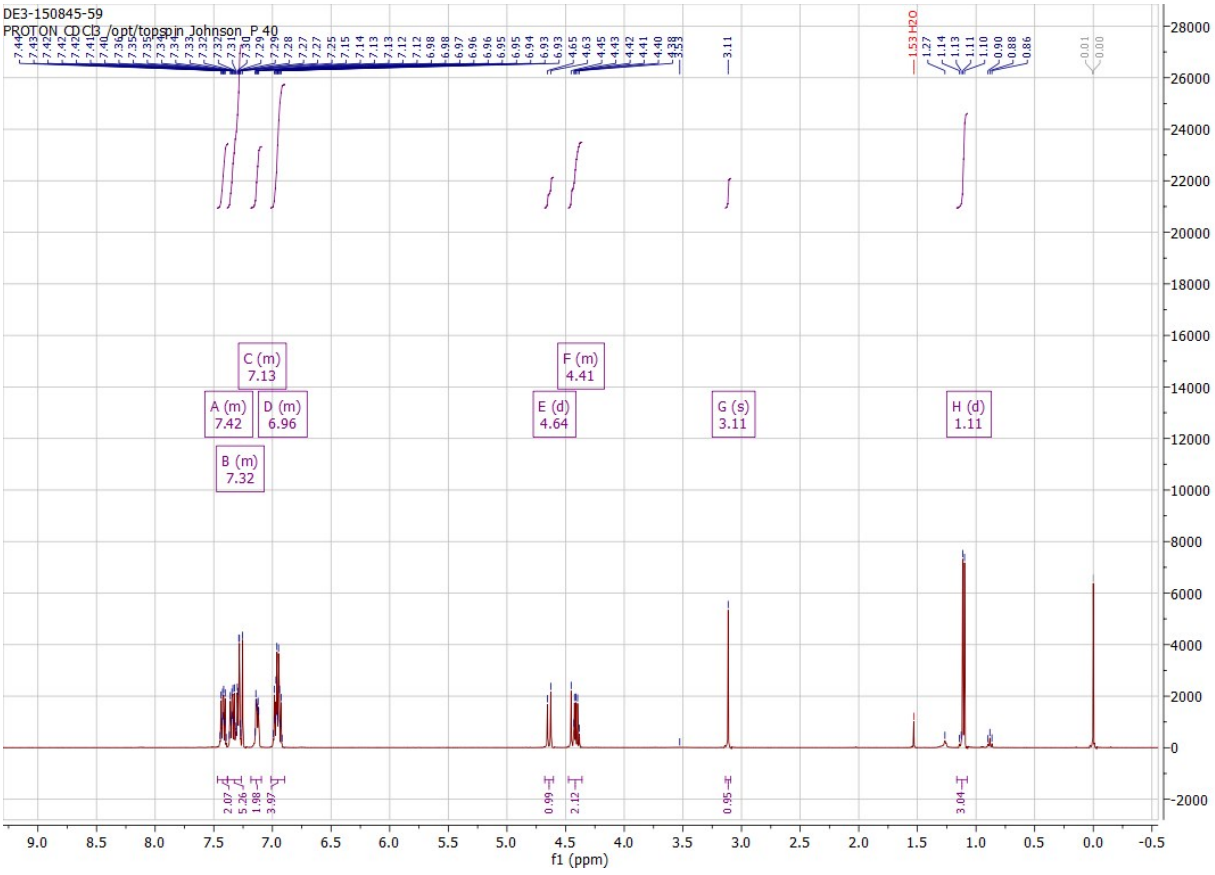




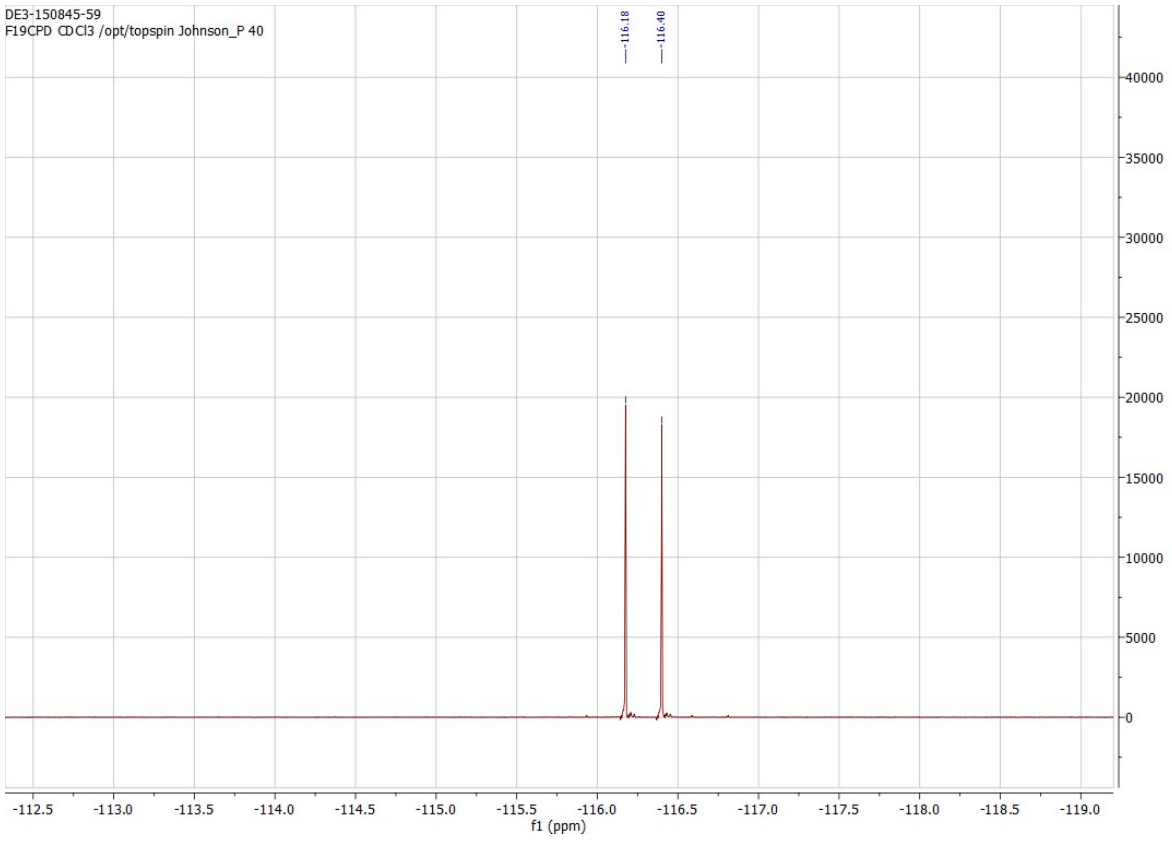


(*S*)-2-(benzyloxy)-1,1-bis(4-fluorophenyl)propan-1-ol (13)

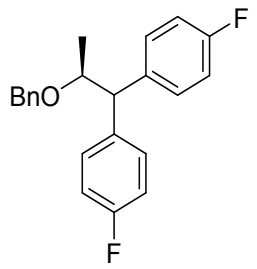


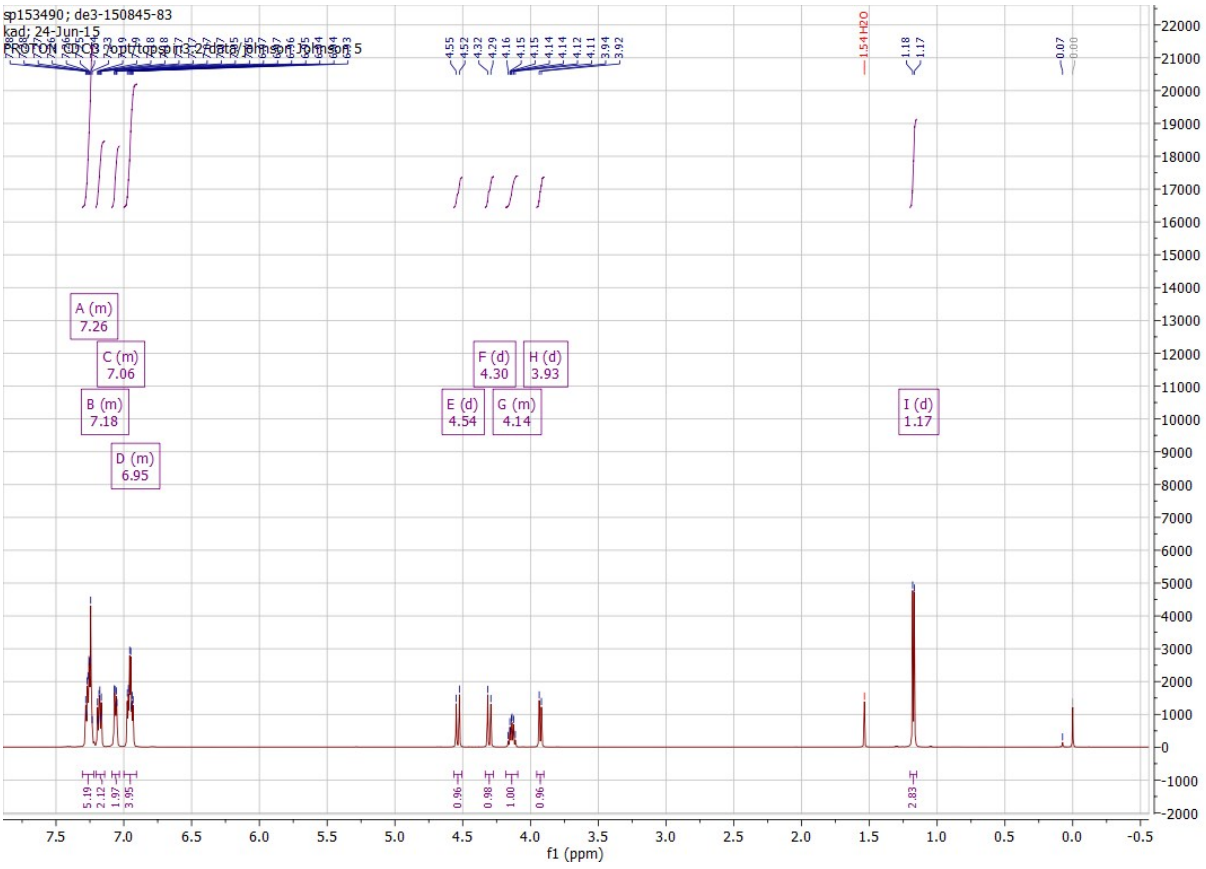


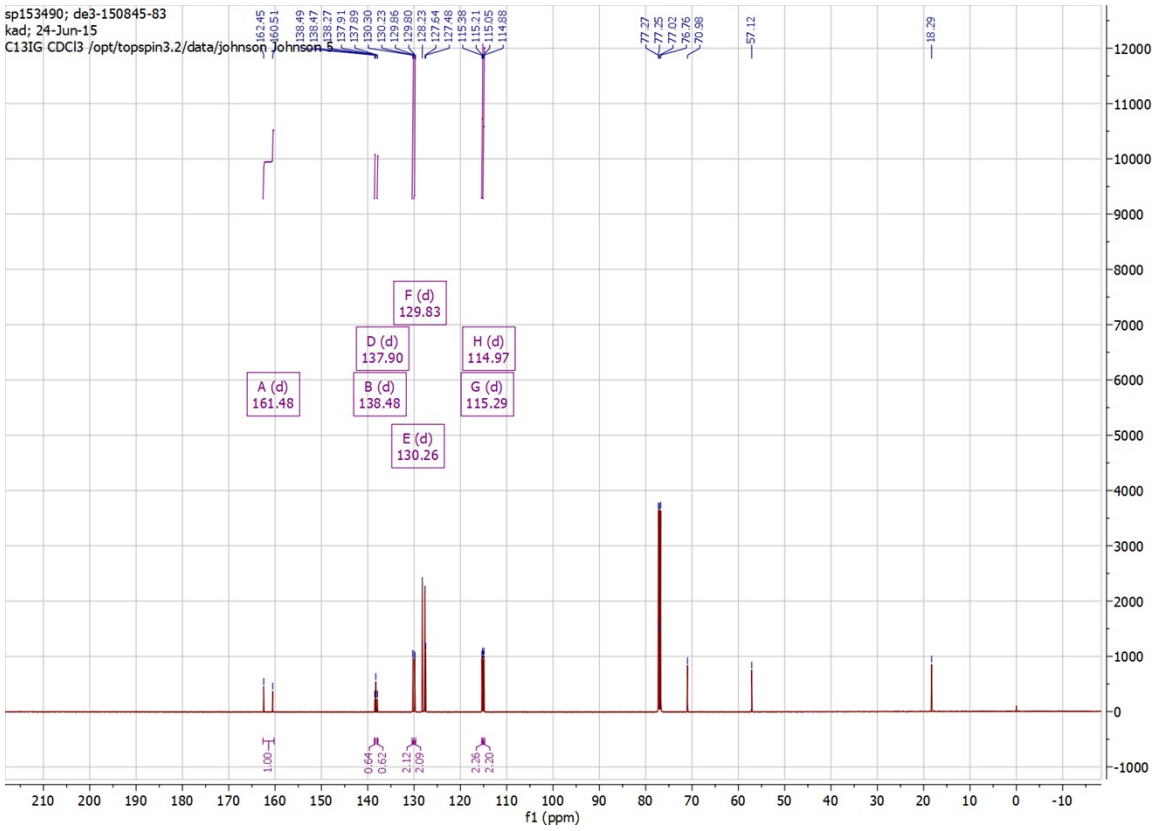

sp151962; de3-150845-59
kad; 24-Mar-15
C13IG CDCl3 /opt/topspin3.2/data/johnson/Johnson_4
B (d) 160.63
A (d) 160.68
D (d) 141.73
C (d) 142.49
F (m) 128.19
E (m) 128.80
H (d) 113.85
G (d) 114.25
f1 (ppm)

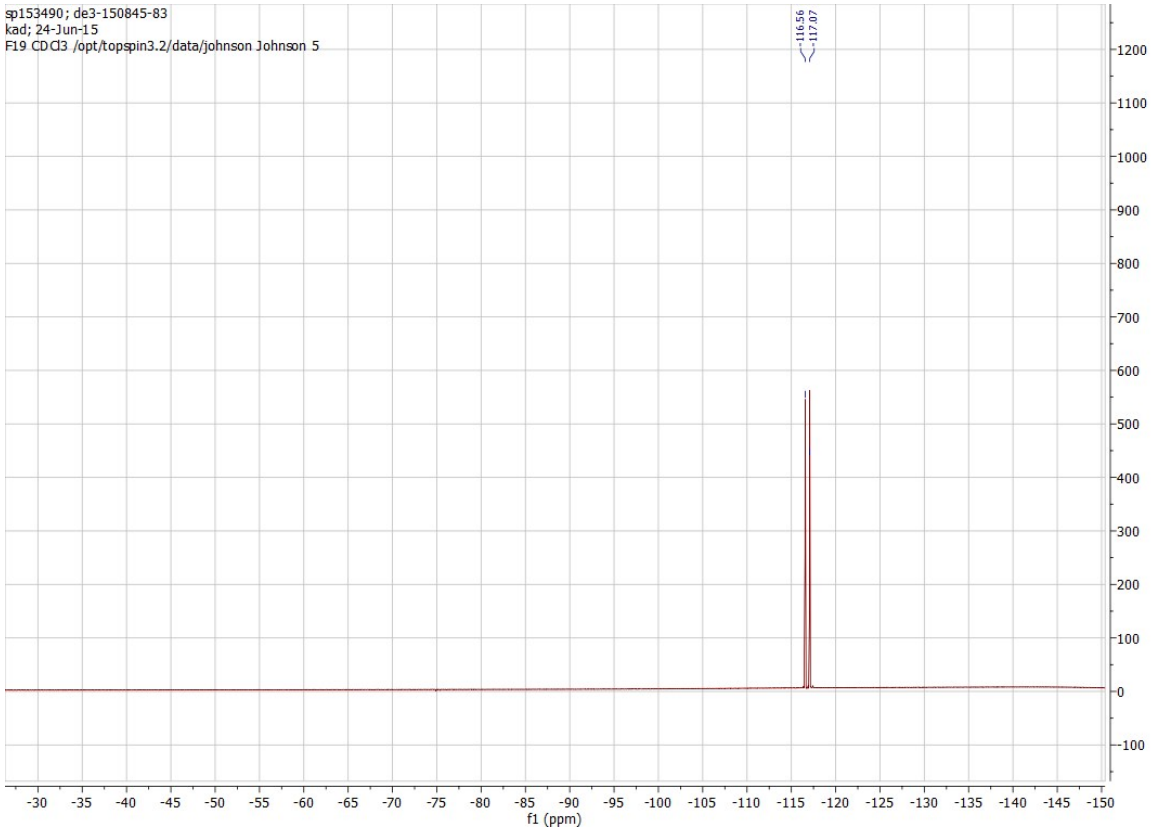

DE3-150845-59
F19CPD CDCl3 /opt/topspin Johnson_P 40
-116.18
-116.40
f1 (ppm)

(*S*)-4,4'-(2-(benzyloxy)propane- 1,1- diyl)bis(fluorobenzene) (14)

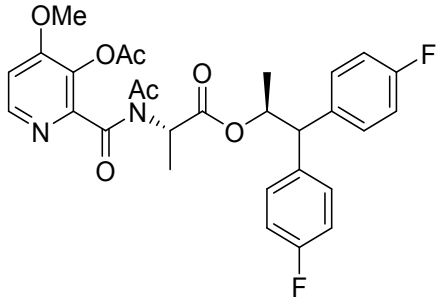


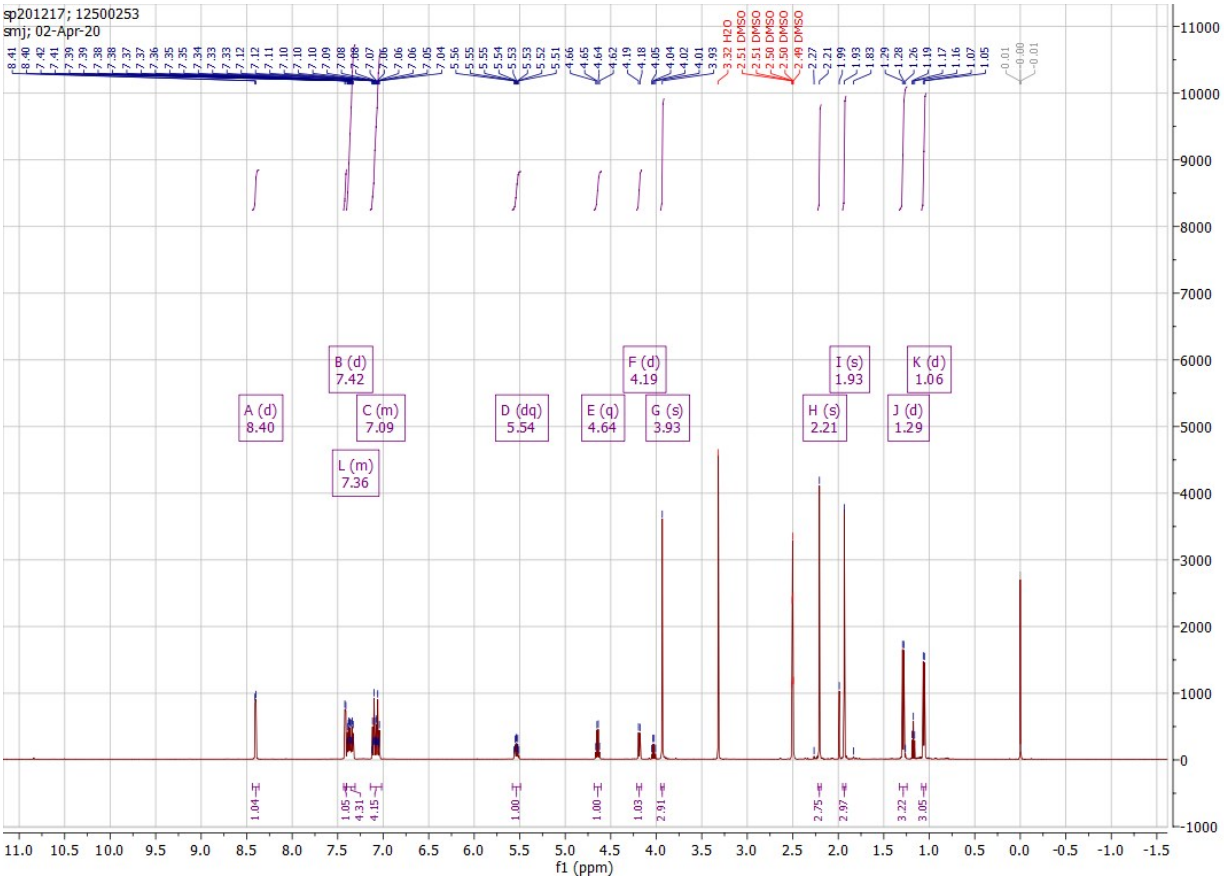


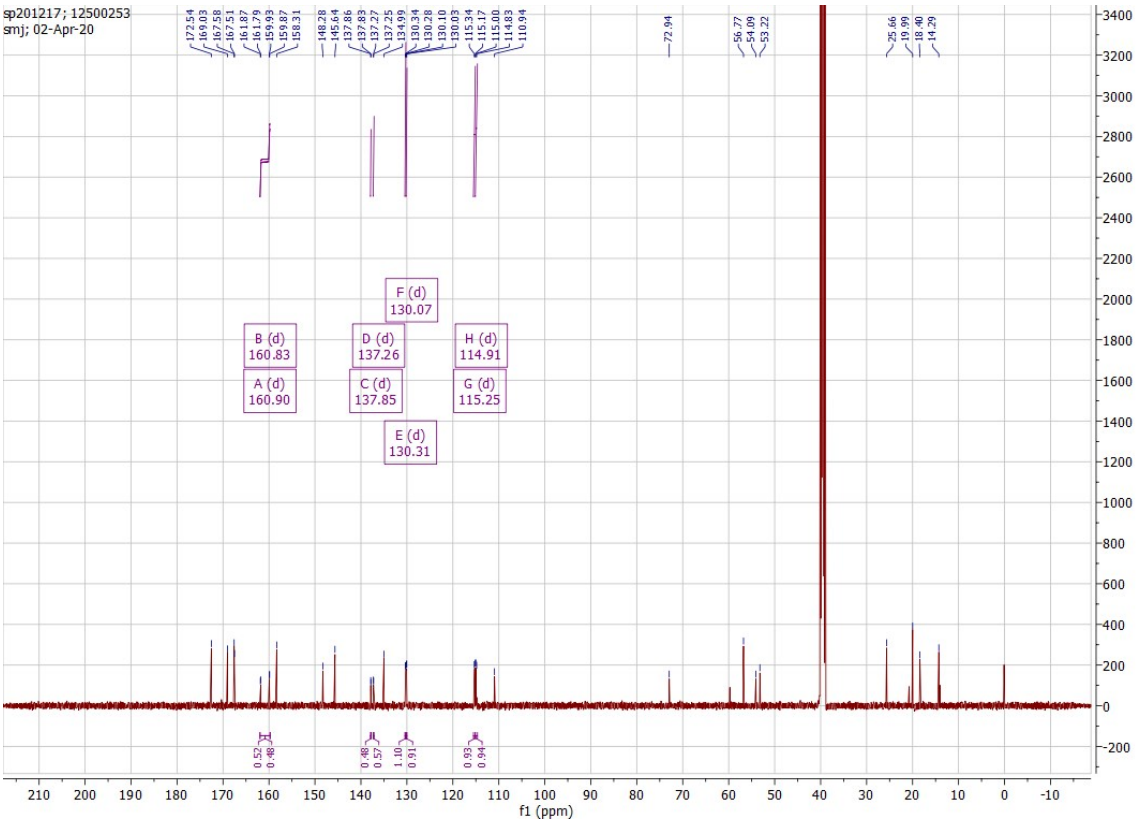

sp153490; de3-150845-83
kad; 24-Jun-15
C13IG CDCl3 /opt/topspin3.2/data/johnson johnson 5
162.45
160.51
138.49
138.47
138.27
137.91
137.89
130.30
130.23
129.86
129.80
128.23
127.64
127.48
115.38
115.21
115.05
114.88
77.27
77.25
77.02
76.76
70.98
57.12
18.29
F (d)
129.83
D (d)
137.90
H (d)
114.97
A (d)
161.48
B (d)
138.48
G (d)
115.29
E (d)
130.26
1.00
0.64
0.62
2.12
2.09
2.26
2.20
f1 (ppm)

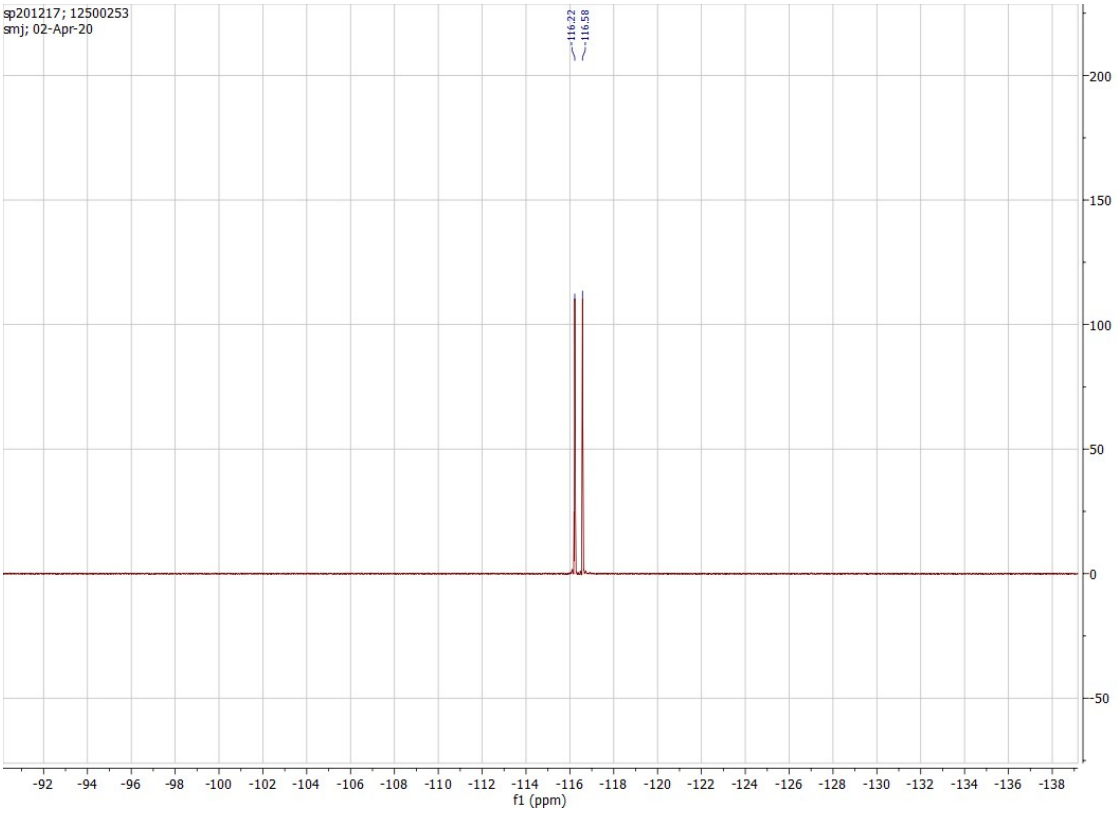

sp153490; de3-150845-83
kad; 24-Jun-15
F19 CDCl3 /opt/topspin3.2/data/johnson Johnson 5
116.56
117.07
f1 (ppm)

(*S*)-1,1-bis(4-fluorophenyl)propan-2-yl N-(3-acetoxy-4-methoxypicolinoyl)-N-acetyl-L-alaninate (25)



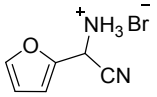


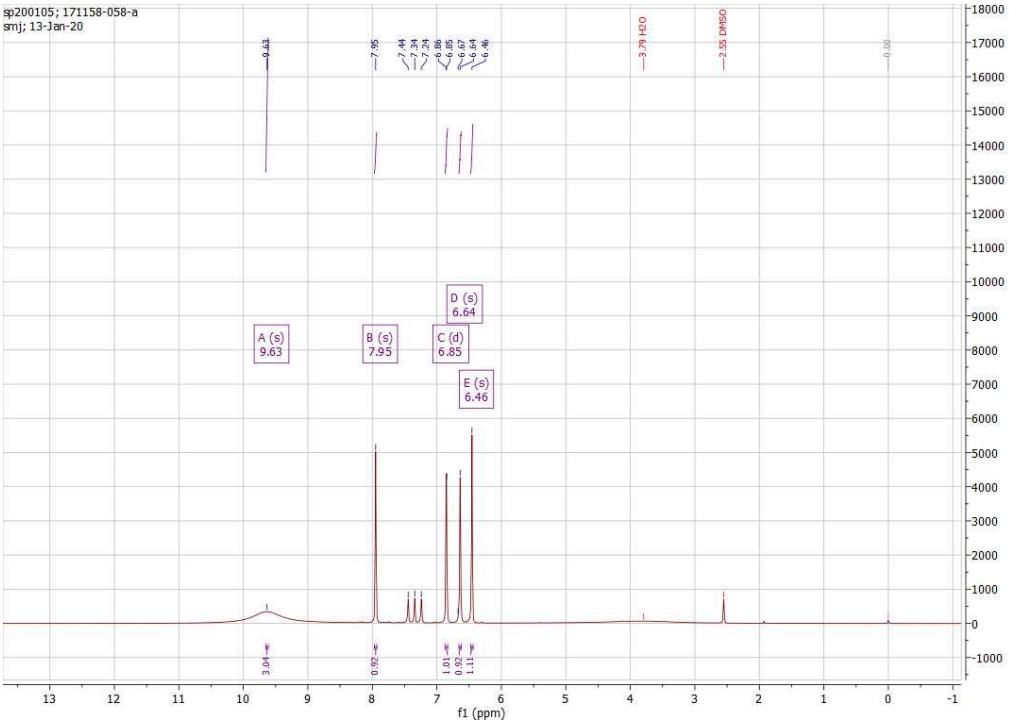

sp201217; 12500253
smj; 02-Apr-20
F (d)
130.07
B (d)
160.83
D (d)
137.26
H (d)
114.91
A (d)
160.90
C (d)
137.85
G (d)
115.25
E (d)
130.31
f1 (ppm)

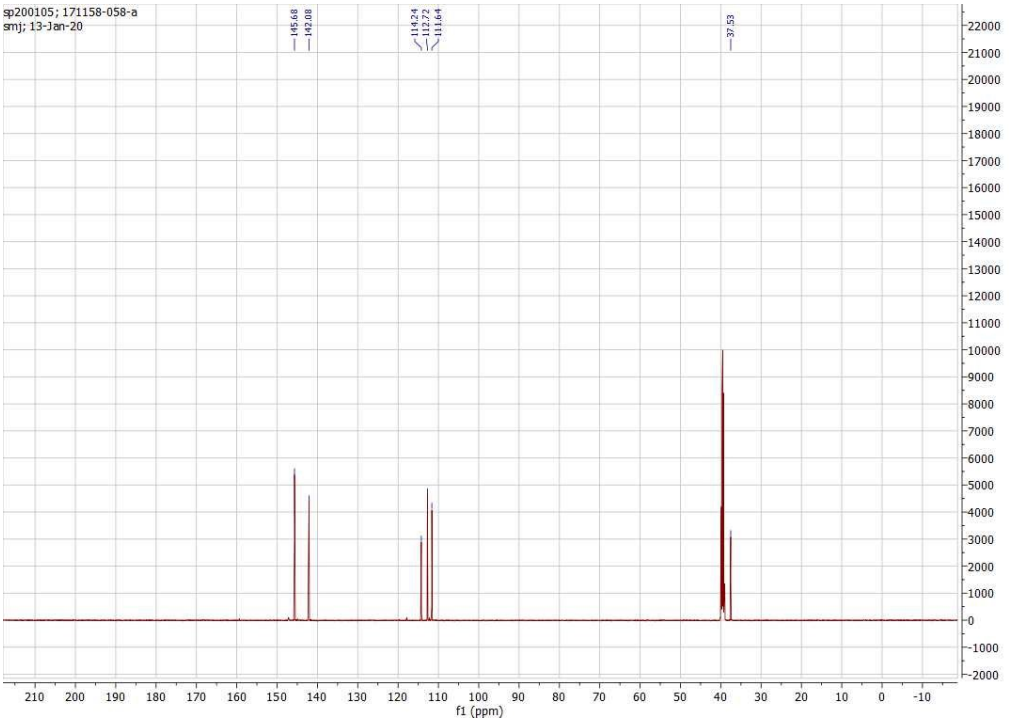

sp201217; 12500253
smj; 02-Apr-20
-116.22
-116.58
f1 (ppm)

2nd Generation Route

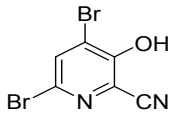
Cyano(furan-2-yl)methanaminium bromide (17)

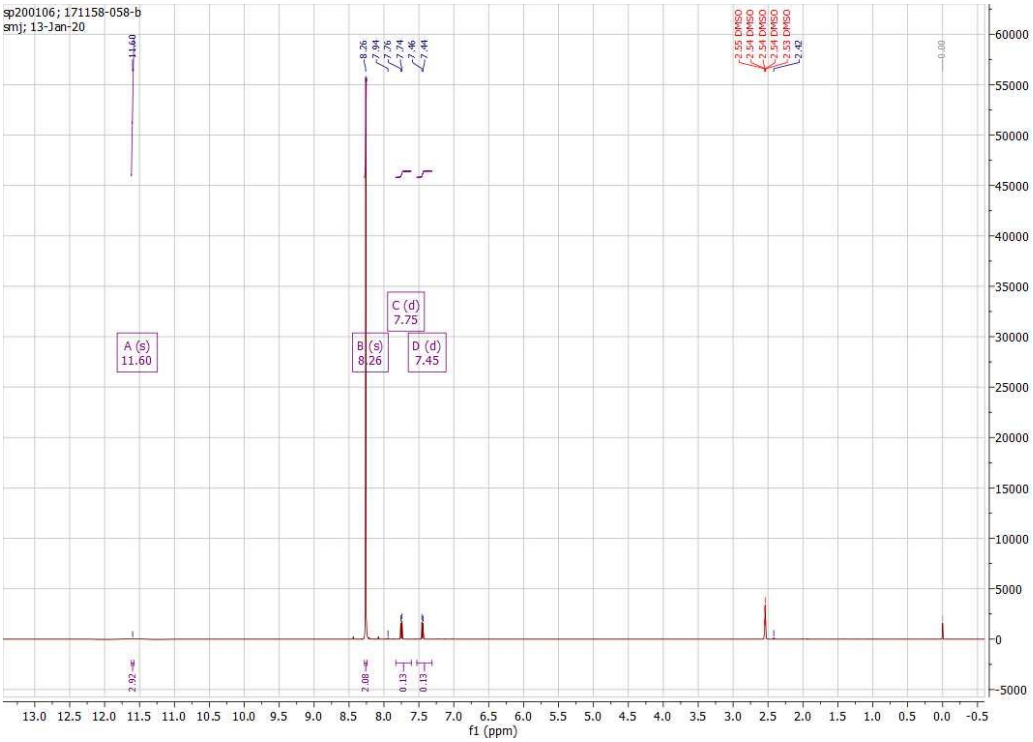


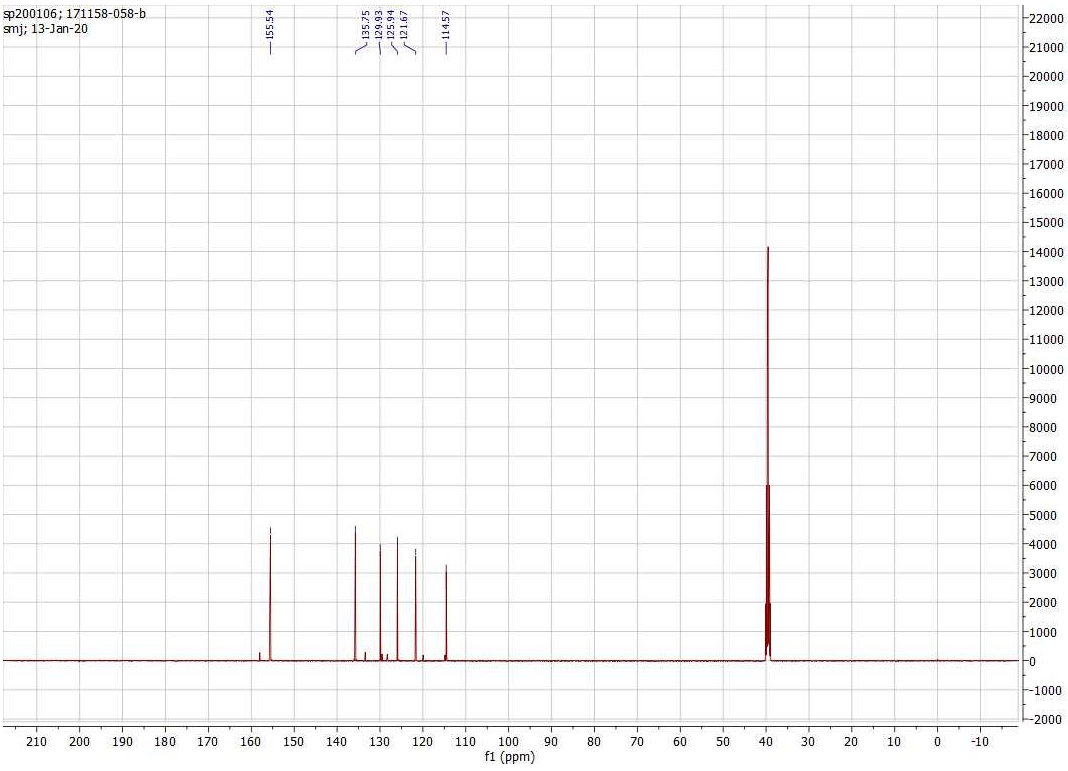




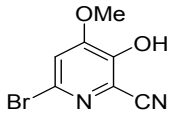
4,6-Dibromo-3-hydroxypicolinonitrile (18)

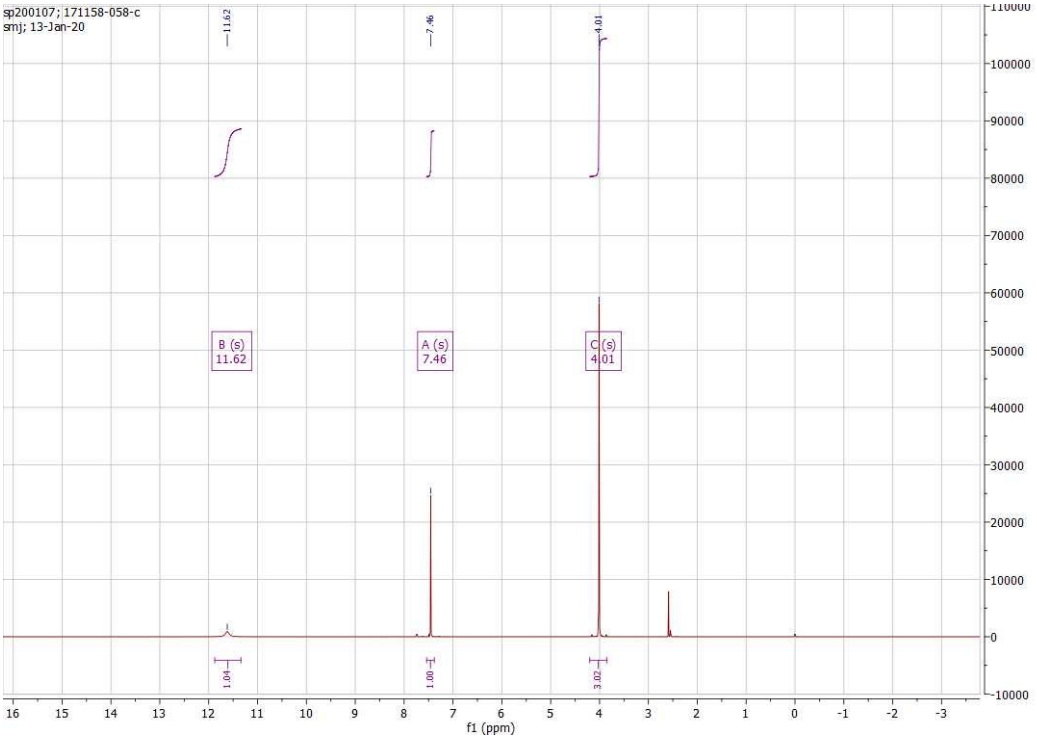


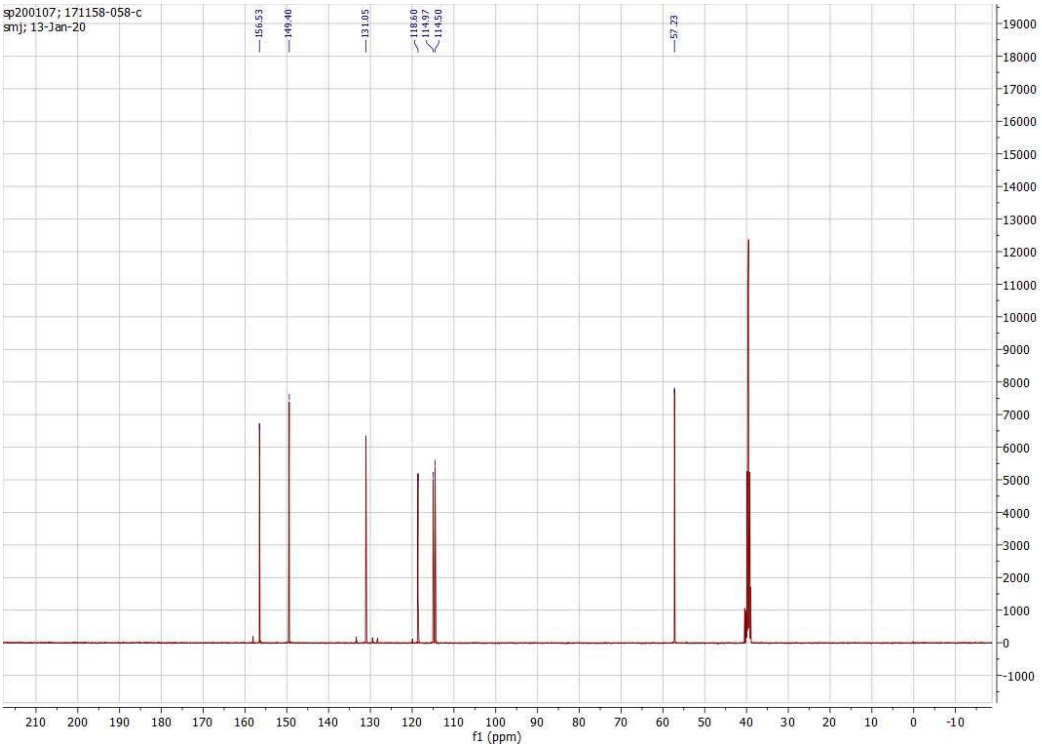




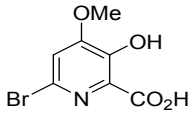
6-Bromo-4-methoxy-3-hydroxypicolinonitrile (19)

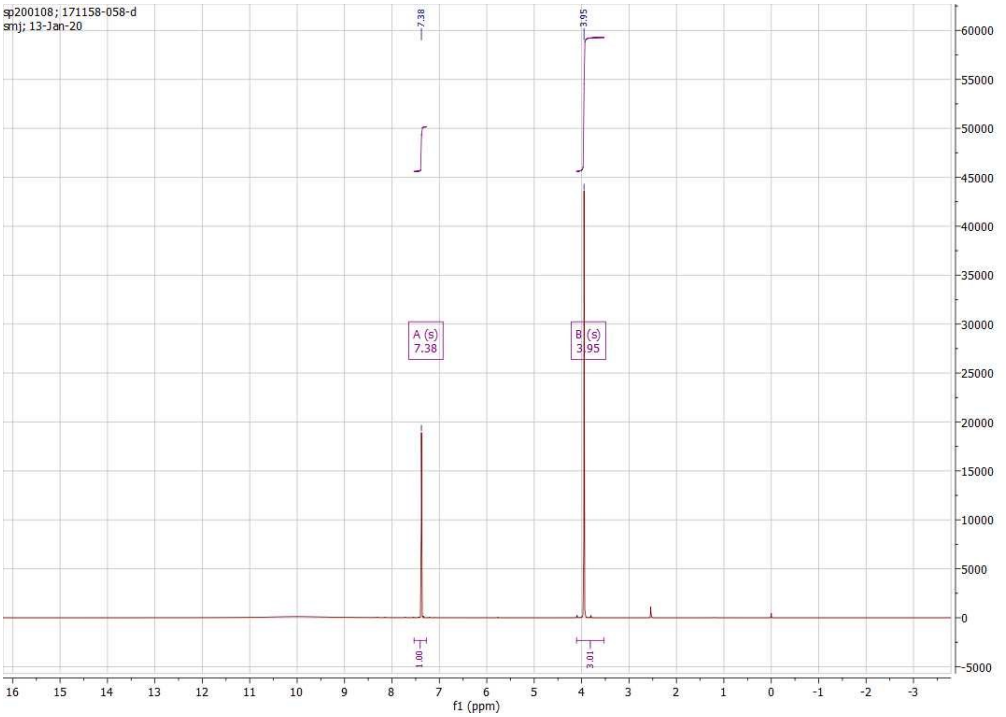


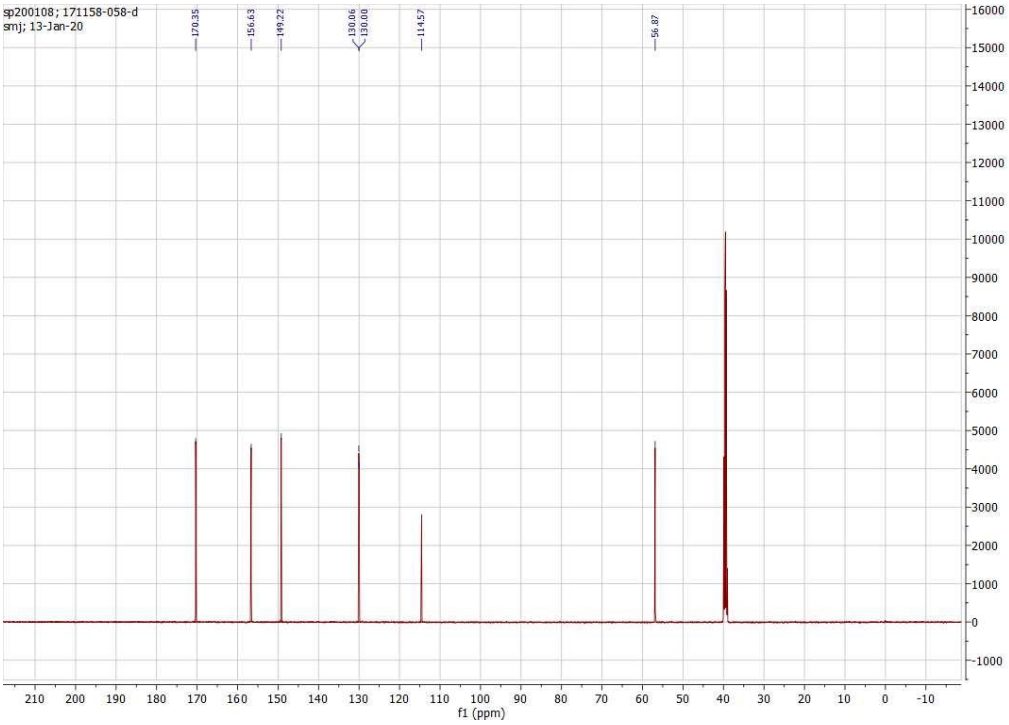




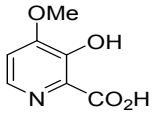
6-Bromo-3-hydroxy-4-methoxypicolinic acid (20)

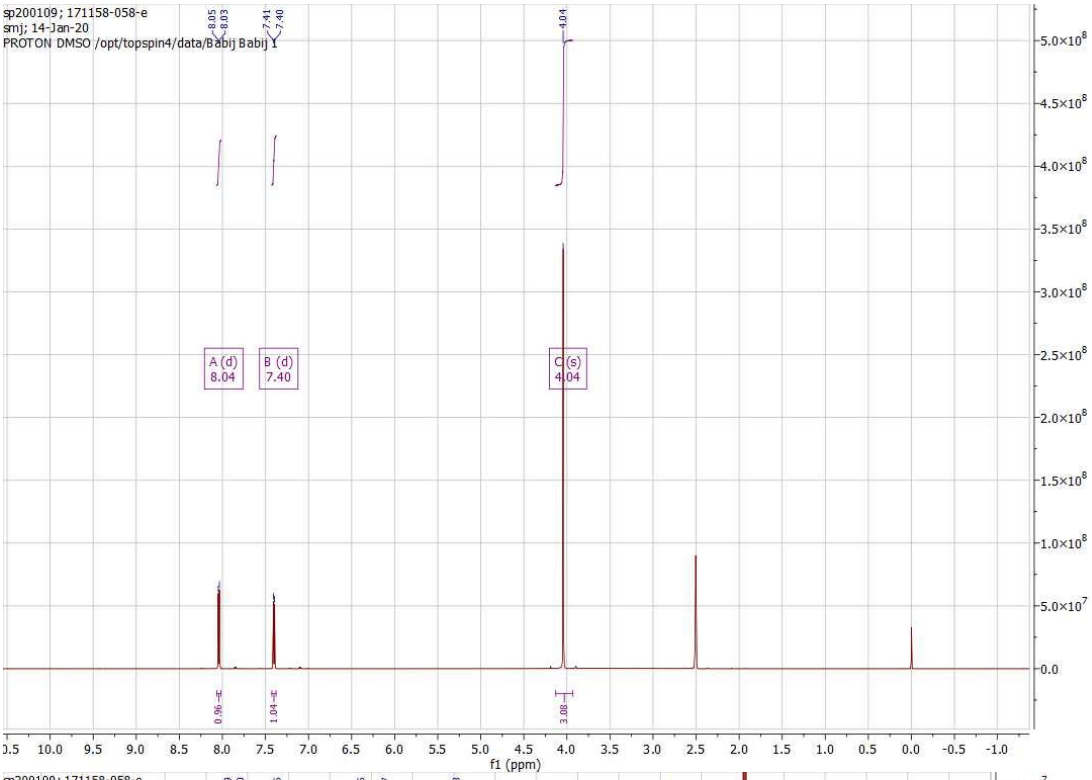


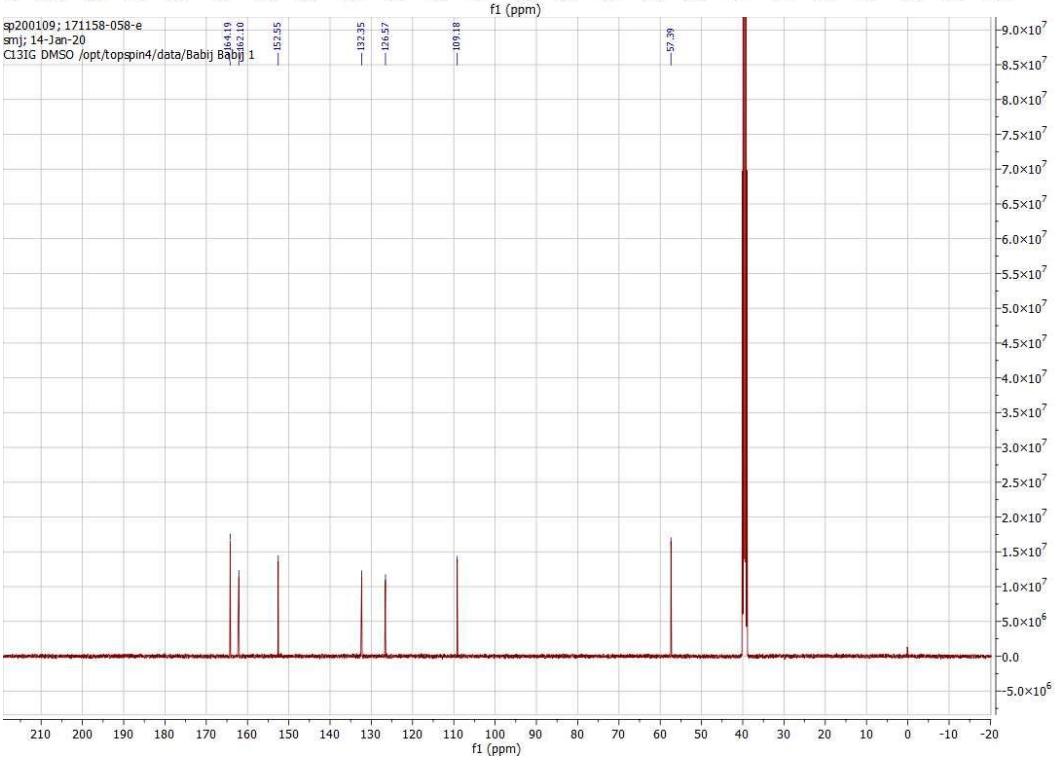




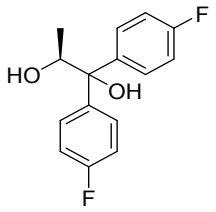
3-Hydroxy-4-methoxypicolinic acid (3)

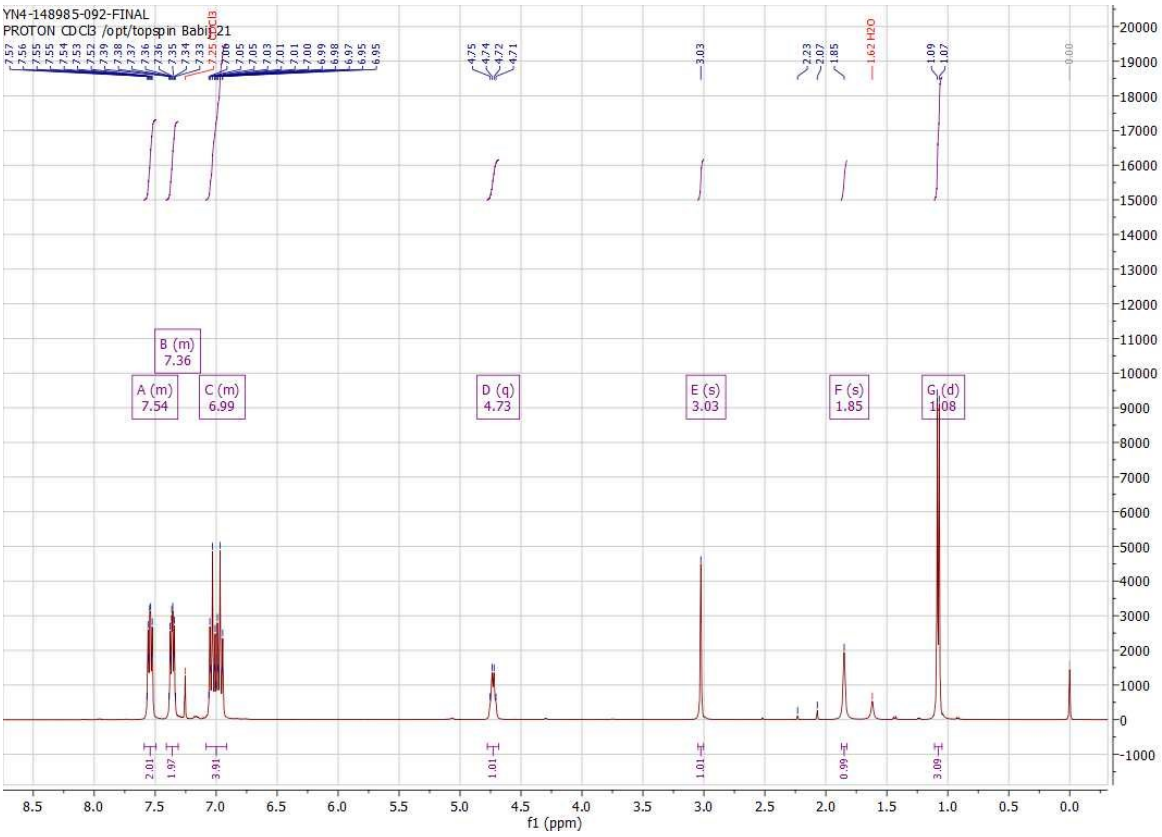


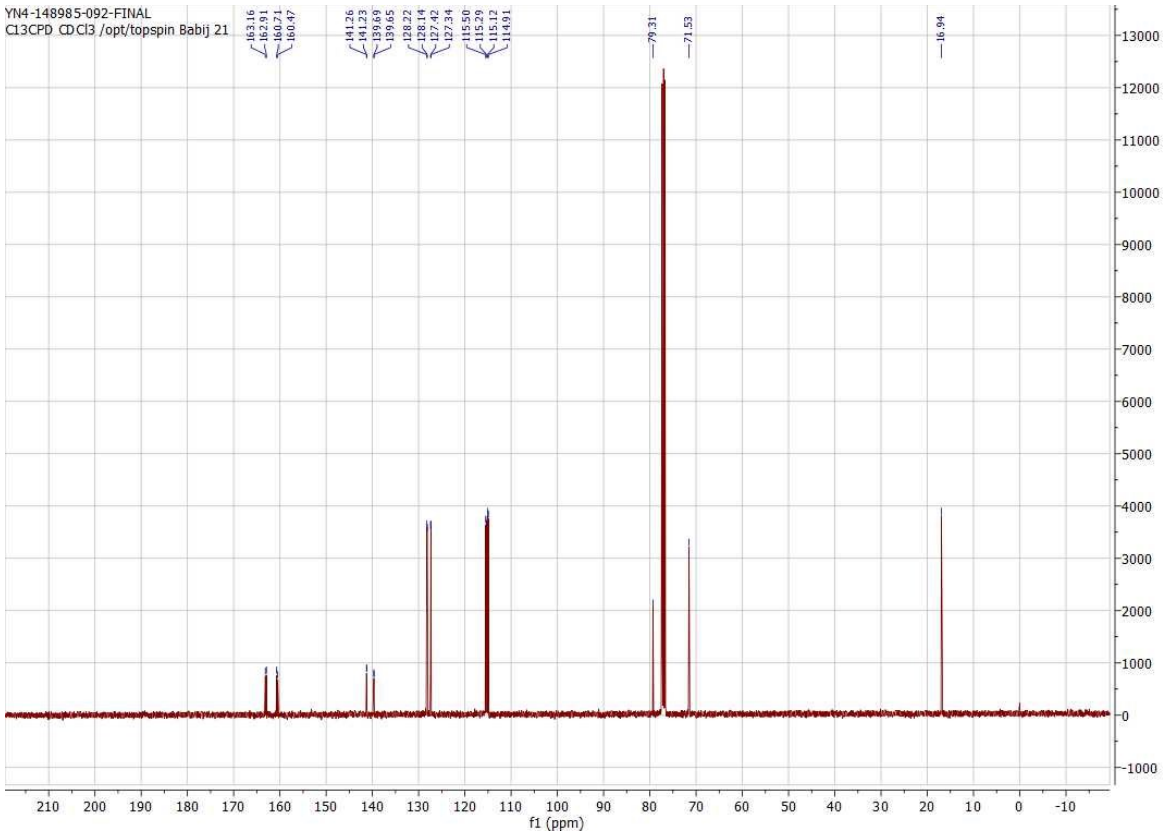


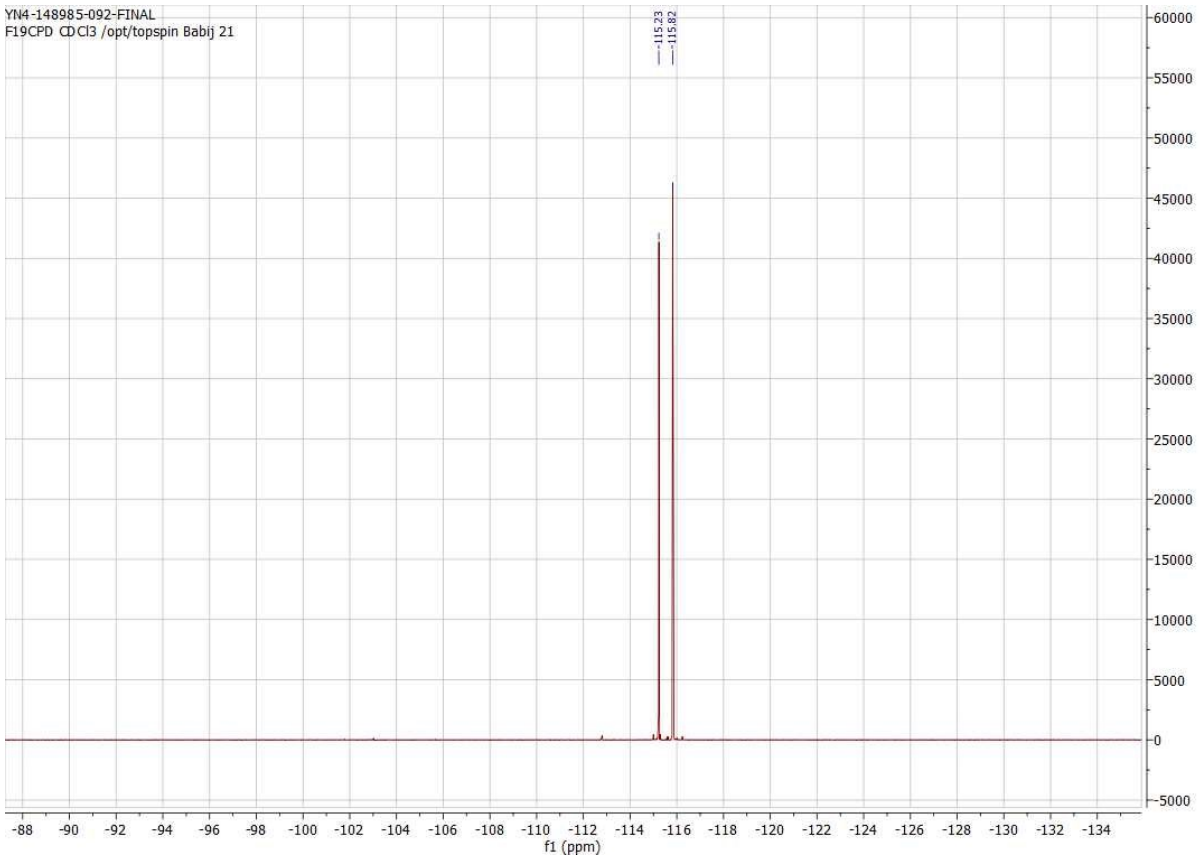


(*S*)-1,1-bis(4-fluorophenyl)propane-1,2-diol (21)

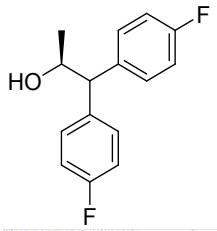


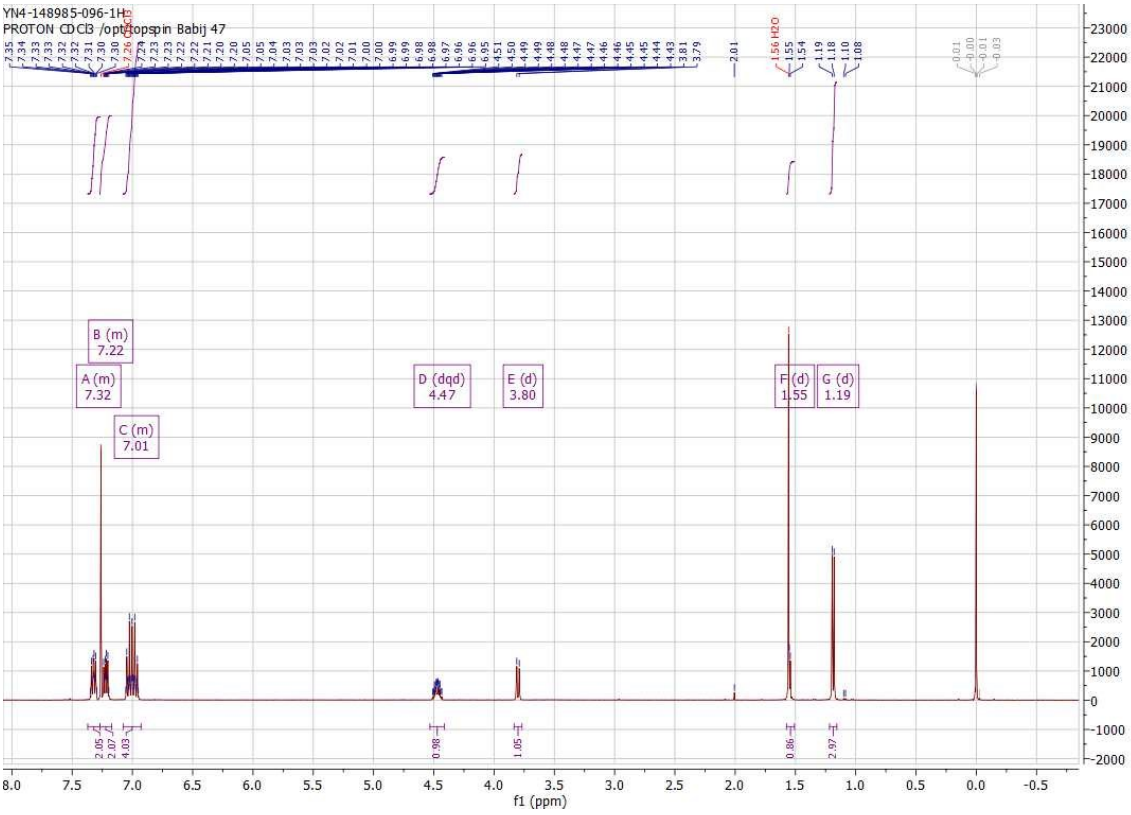


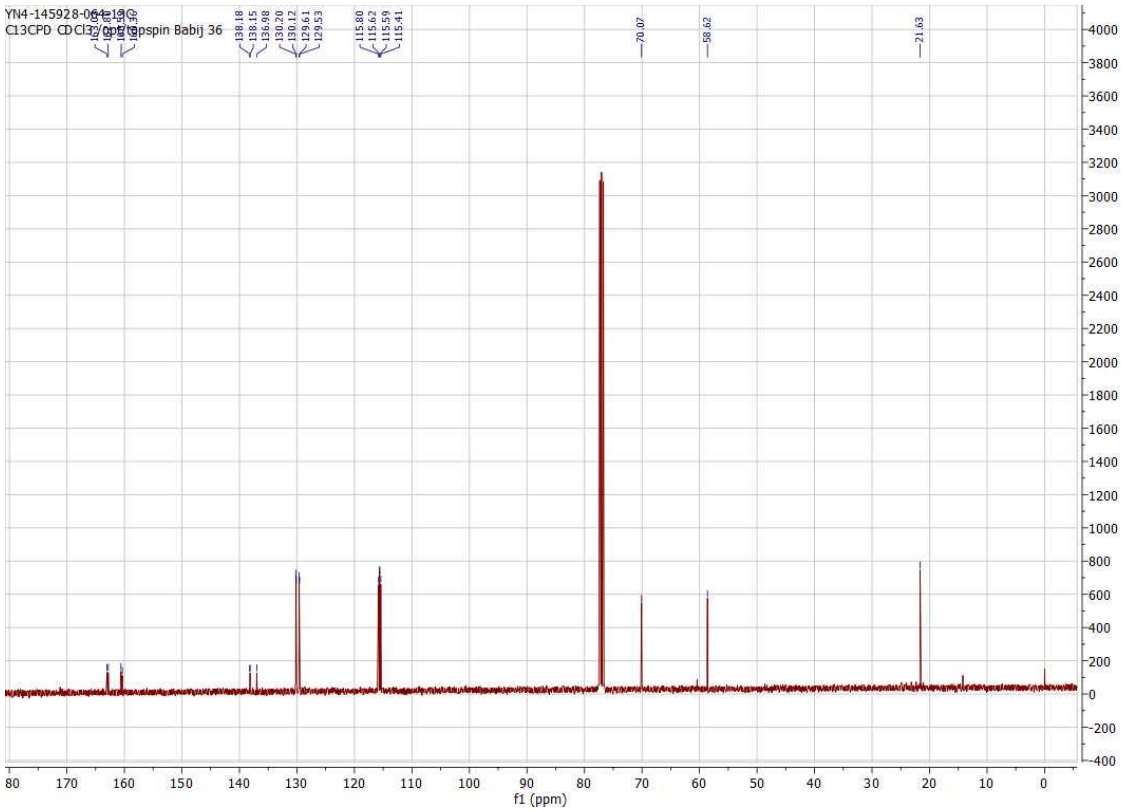

YN4-148985-092-FINAL
C13CPD CDCl3 /opt/topspin Babij 21
163.16
162.91
160.71
160.47
141.26
141.23
139.69
139.65
128.22
128.14
127.42
127.34
115.50
115.29
115.12
114.91
79.31
71.53
16.94
f1 (ppm)

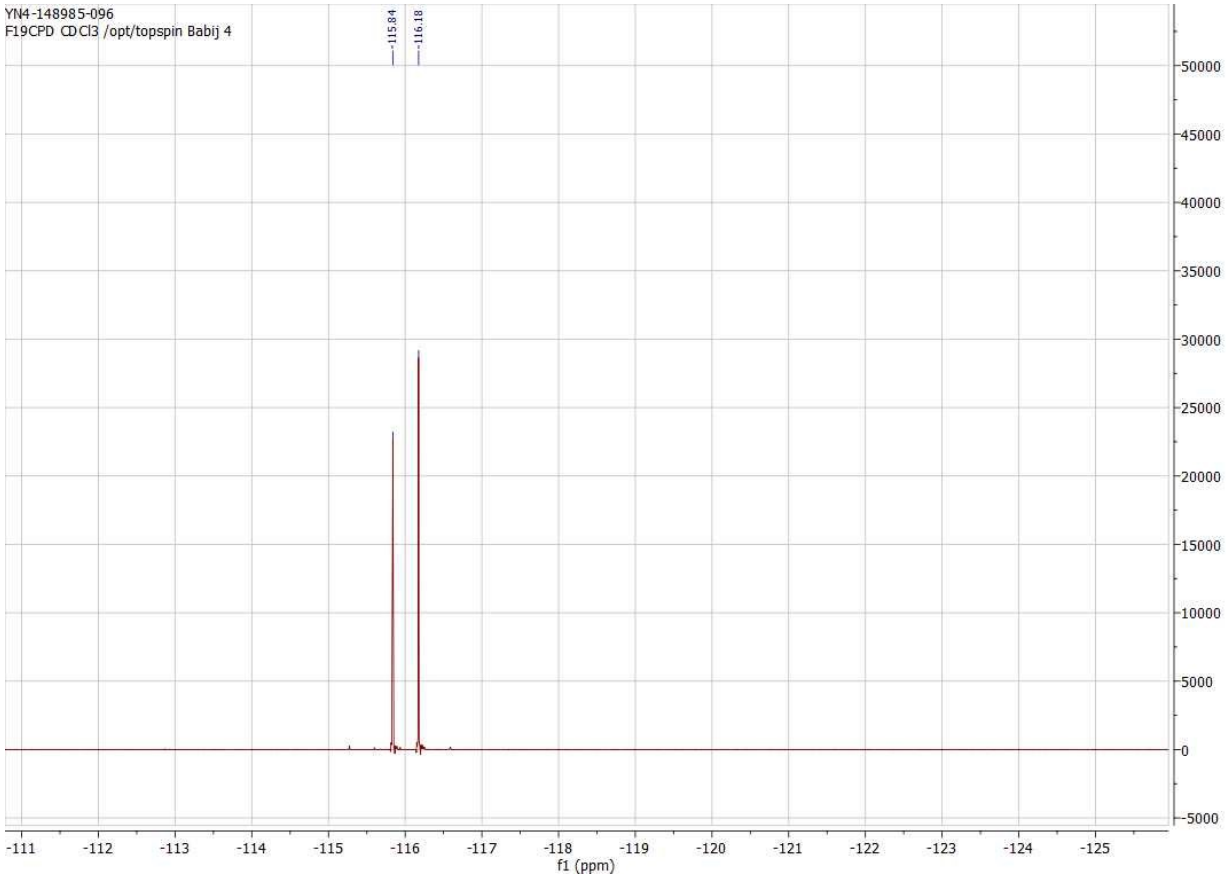

YN4-148985-092-FINAL
F19CPD CDCl3 /opt/topspin Babij 21
-115.23
-115.82
f1 (ppm)

(*S*)-1,1-bis(4-fluorophenyl)propan-2-ol (15)

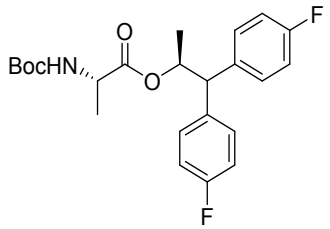


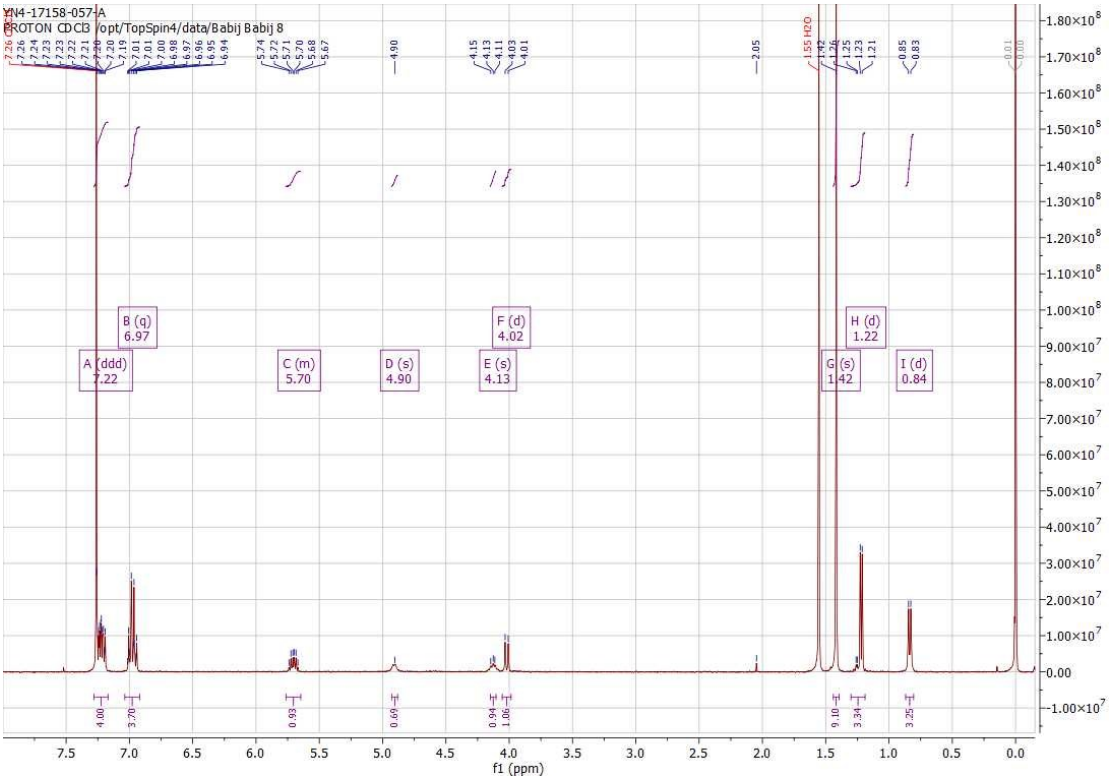


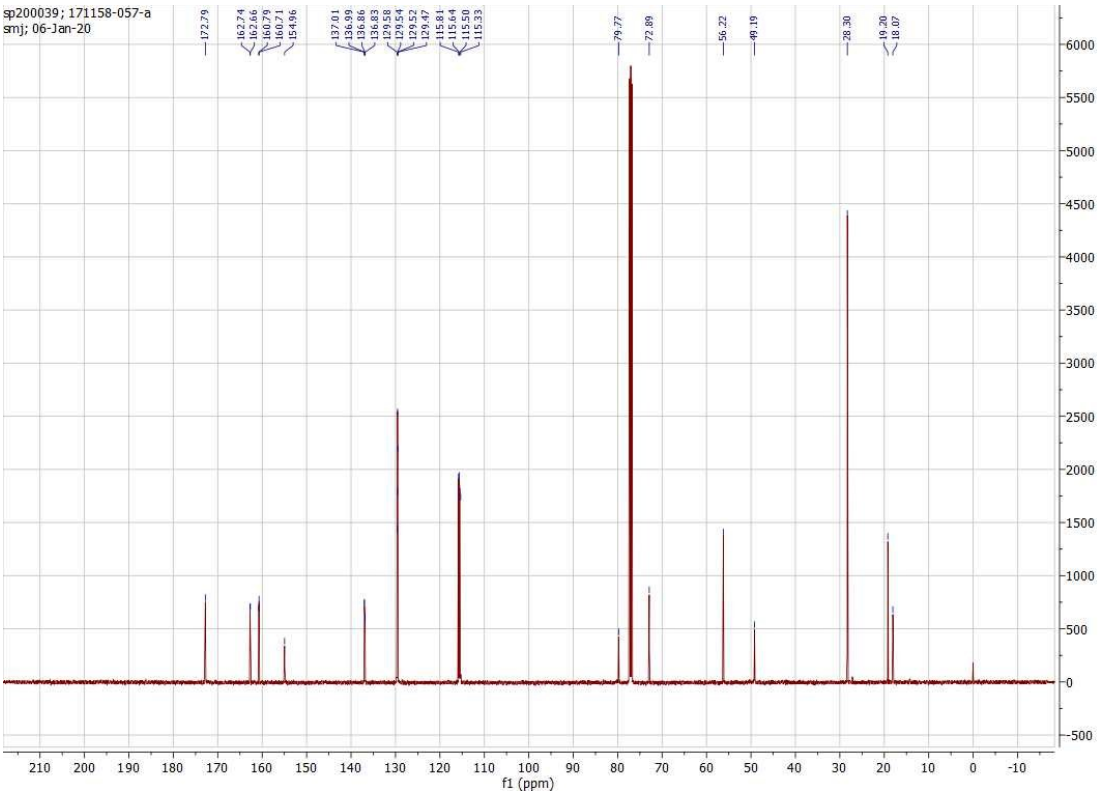

YN4-145928-064e13C
C13CPD CDCl3 /opt/topspin Babij 36
138.18
138.15
136.98
130.20
130.12
129.61
129.53
115.80
115.67
115.59
115.41
70.07
58.62
21.63
f1 (ppm)

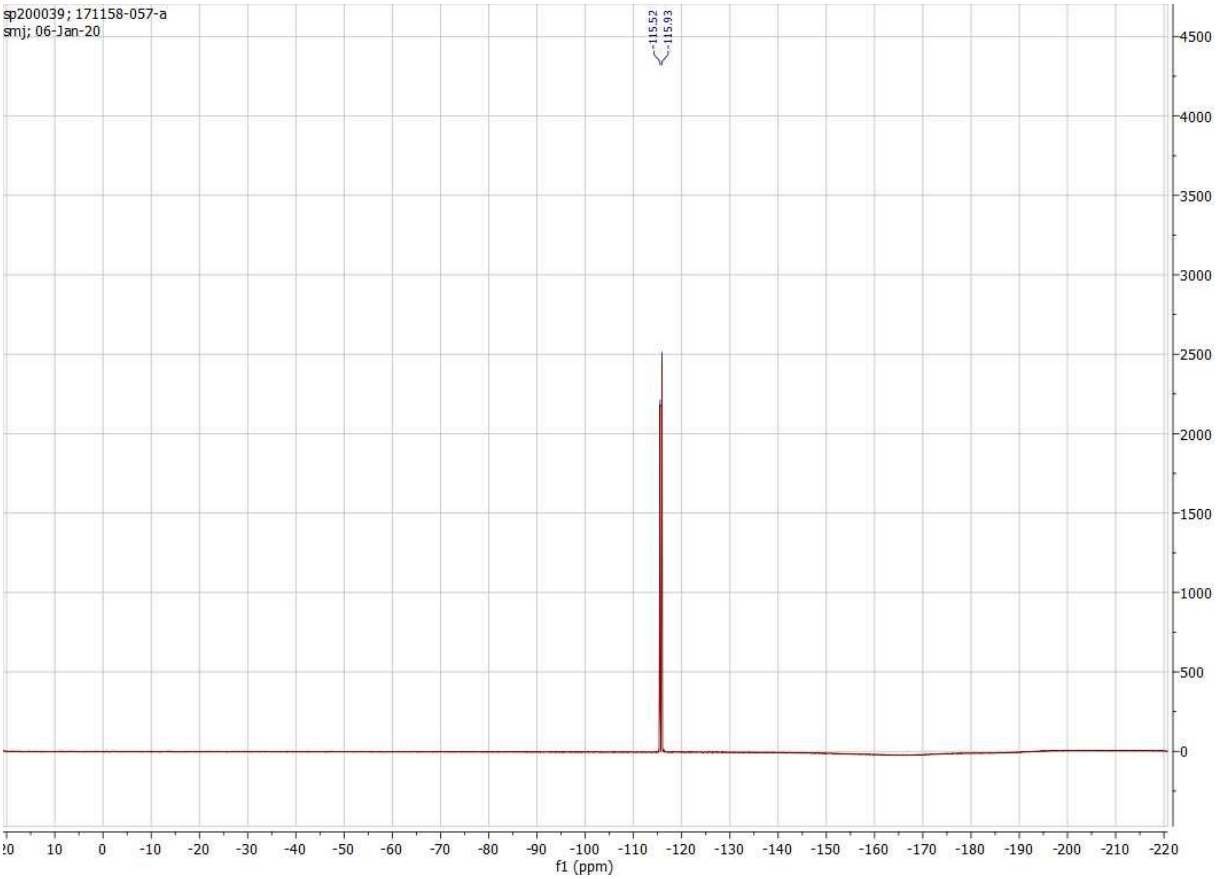

YN4-148985-096
F19CPD CDCl3 /opt/topspin Babij 4
-115.84
-116.18
f1 (ppm)

(*S,S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-((*tert*-butoxycarbonyl)amino)propanoate (16)

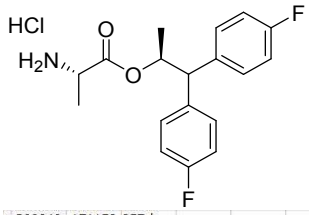


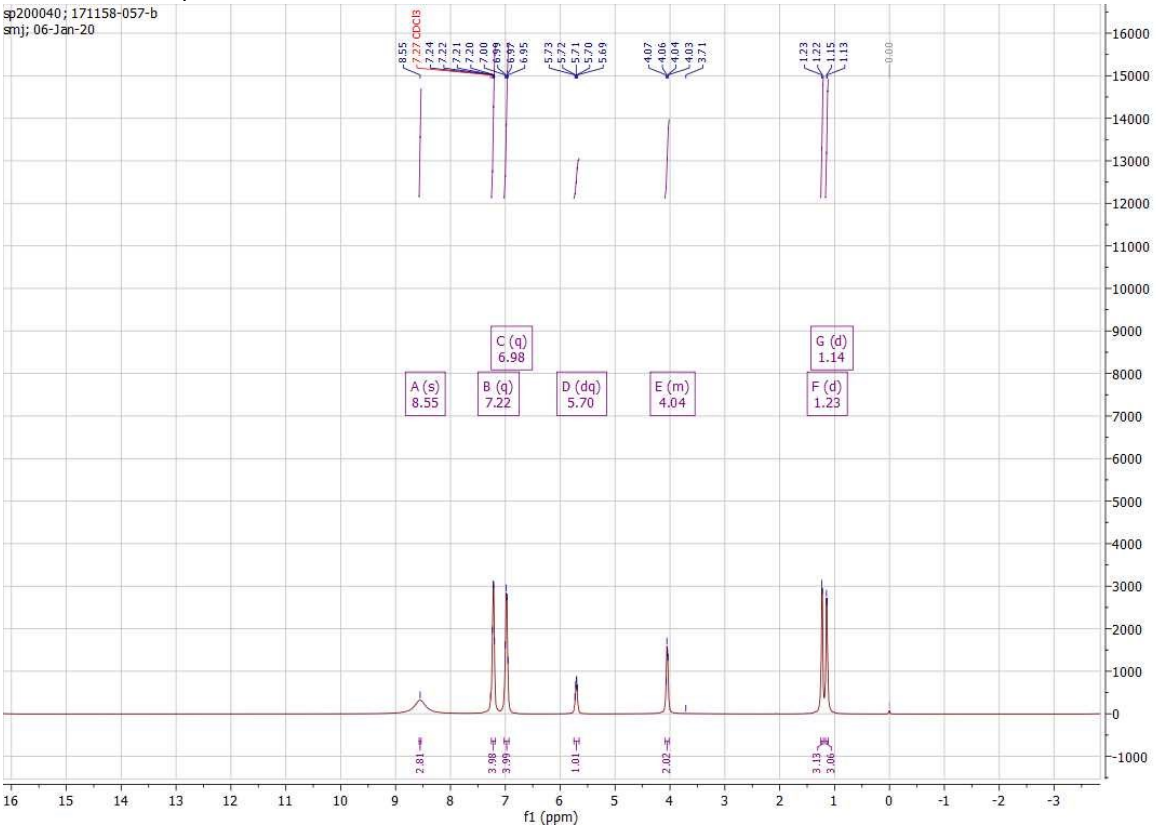


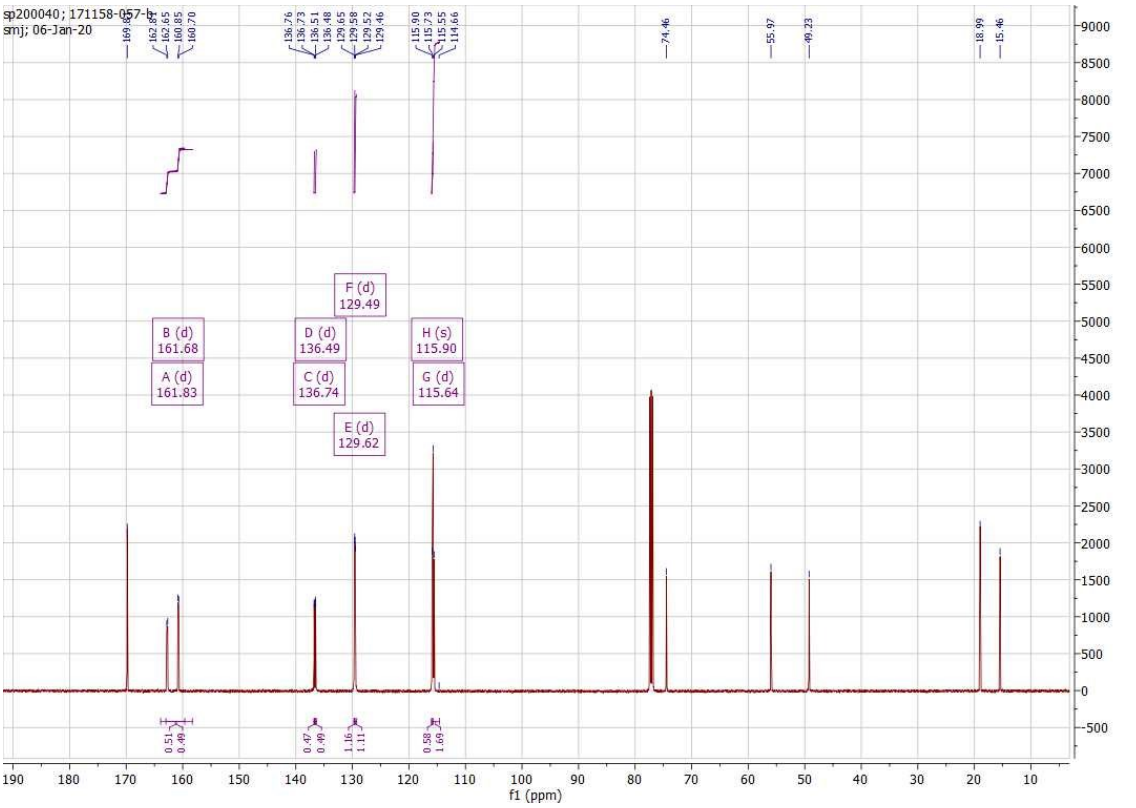

sp200039; 171158-057-a
smj; 06-Jan-20
172.79
162.74
162.66
160.79
160.71
154.96
137.01
136.99
136.86
136.83
129.58
129.54
129.52
129.47
115.81
115.64
115.50
115.33
79.77
72.89
56.22
49.19
28.30
19.20
18.07
f1 (ppm)

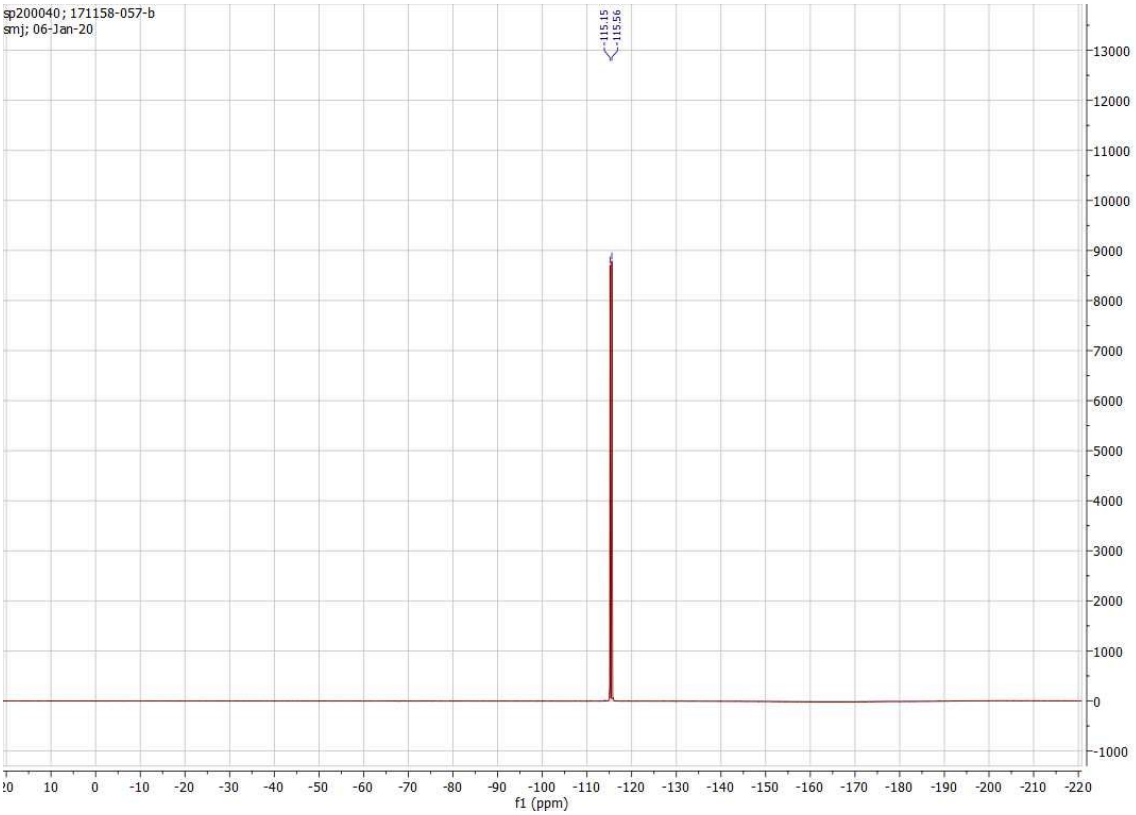

sp200039; 171158-057-a
smj; 06-Jan-20
115.52
115.93
f1 (ppm)

(*S,S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-aminopropanoate hydrochloride (4)

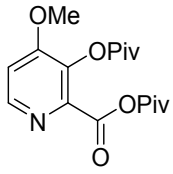


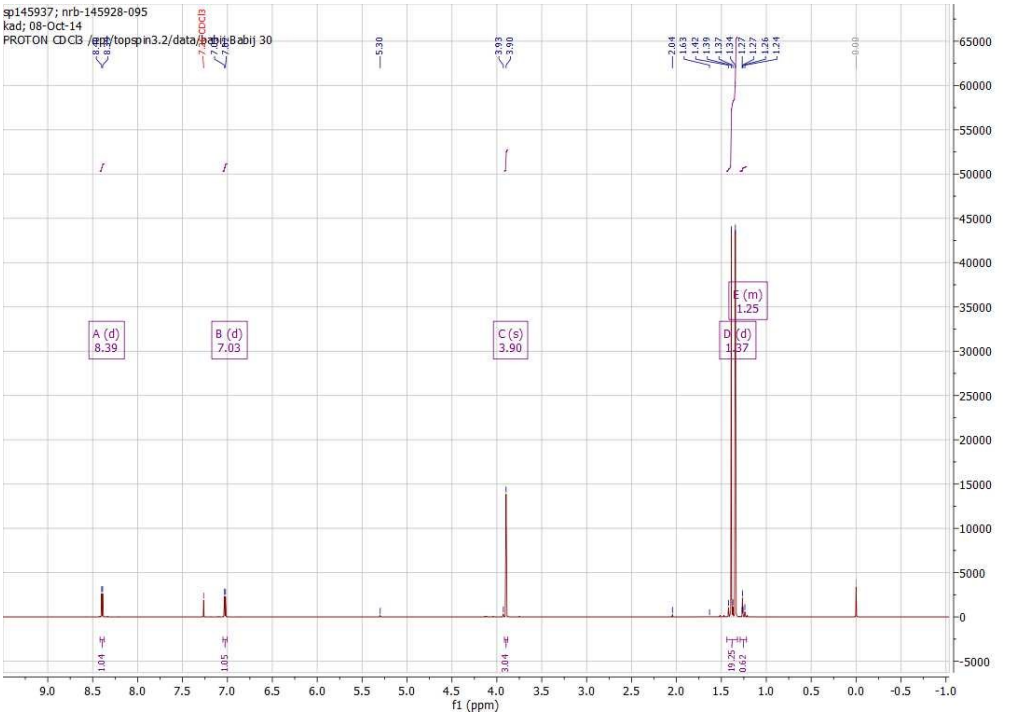


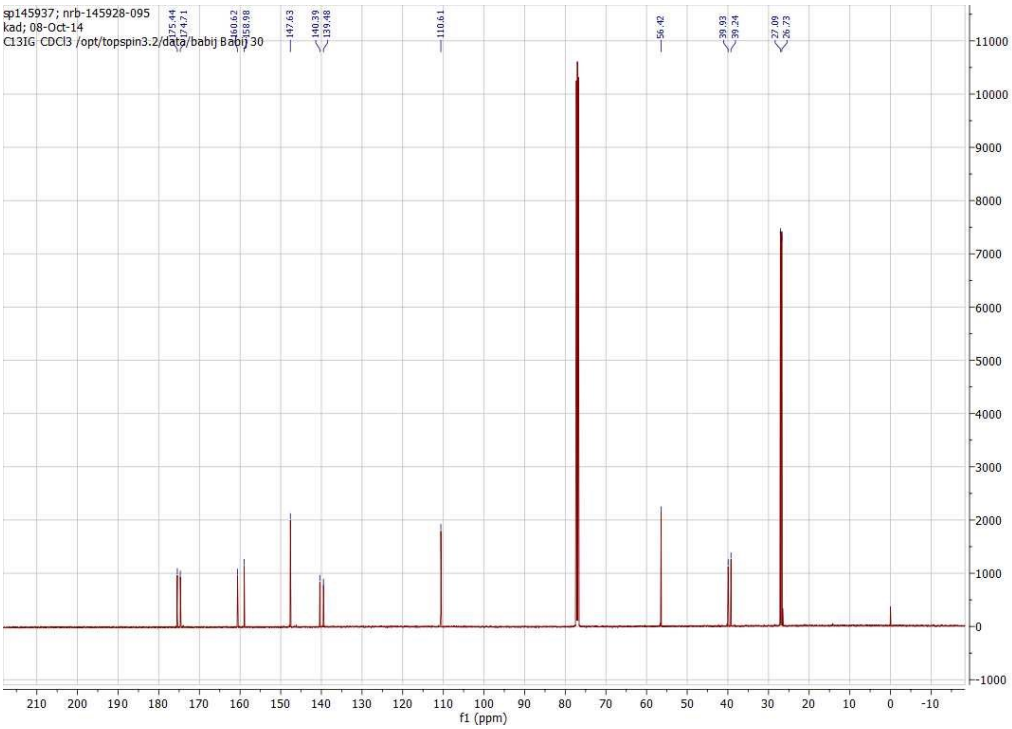

sp200040; 171158-057-b
smj; 06-Jan-20
169.88
162.87
162.65
160.85
160.70
136.76
136.73
136.51
136.48
129.65
129.58
129.52
129.46
115.90
115.73
115.55
114.66
74.46
55.97
49.23
18.99
15.46
F (d)
129.49
B (d)
161.68
D (d)
136.49
H (s)
115.90
A (d)
161.83
C (d)
136.74
G (d)
115.64
E (d)
129.62
0.51
0.49
0.47
0.49
1.16
1.11
0.58
1.63
f1 (ppm)


sp200040; 171158-057-b
smj; 06-Jan-20
115.15
115.56
f1 (ppm)

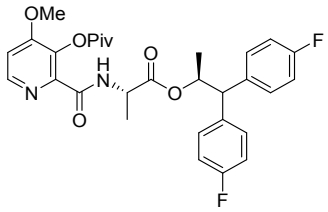
4-methoxy-3-(pivaloyloxy)picolinic pivalic anhydride (22)

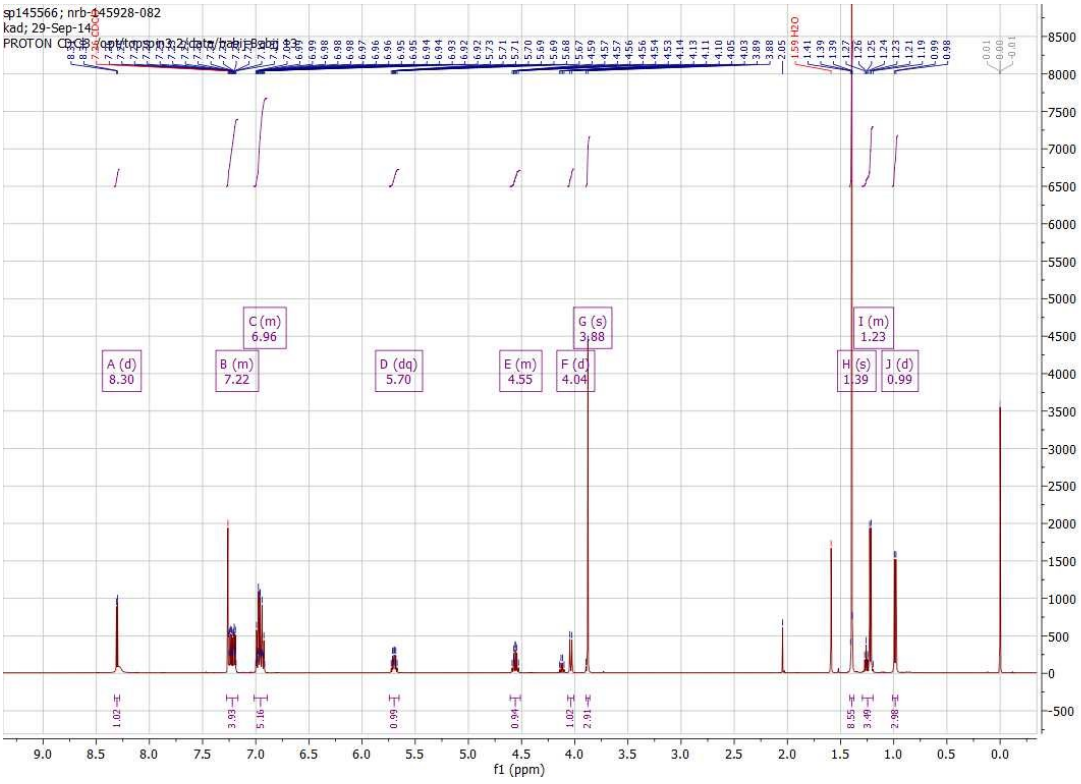


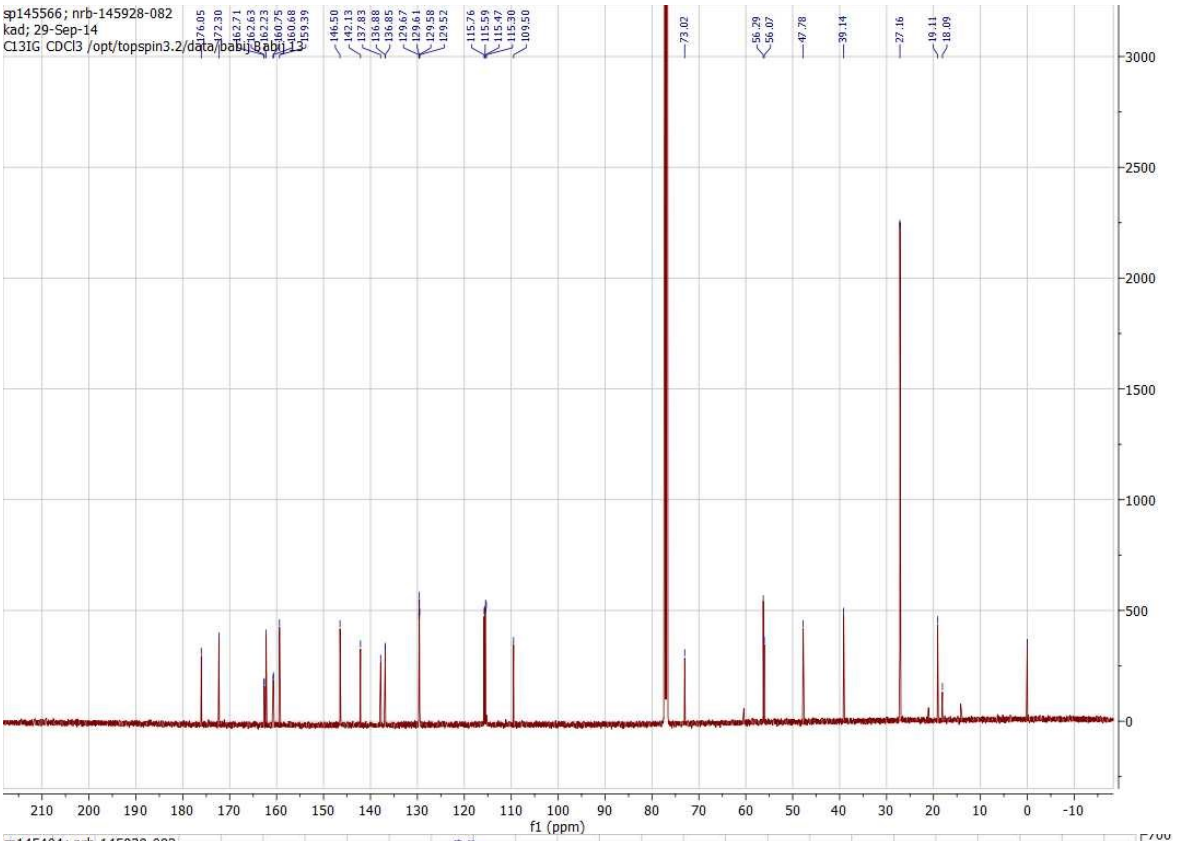


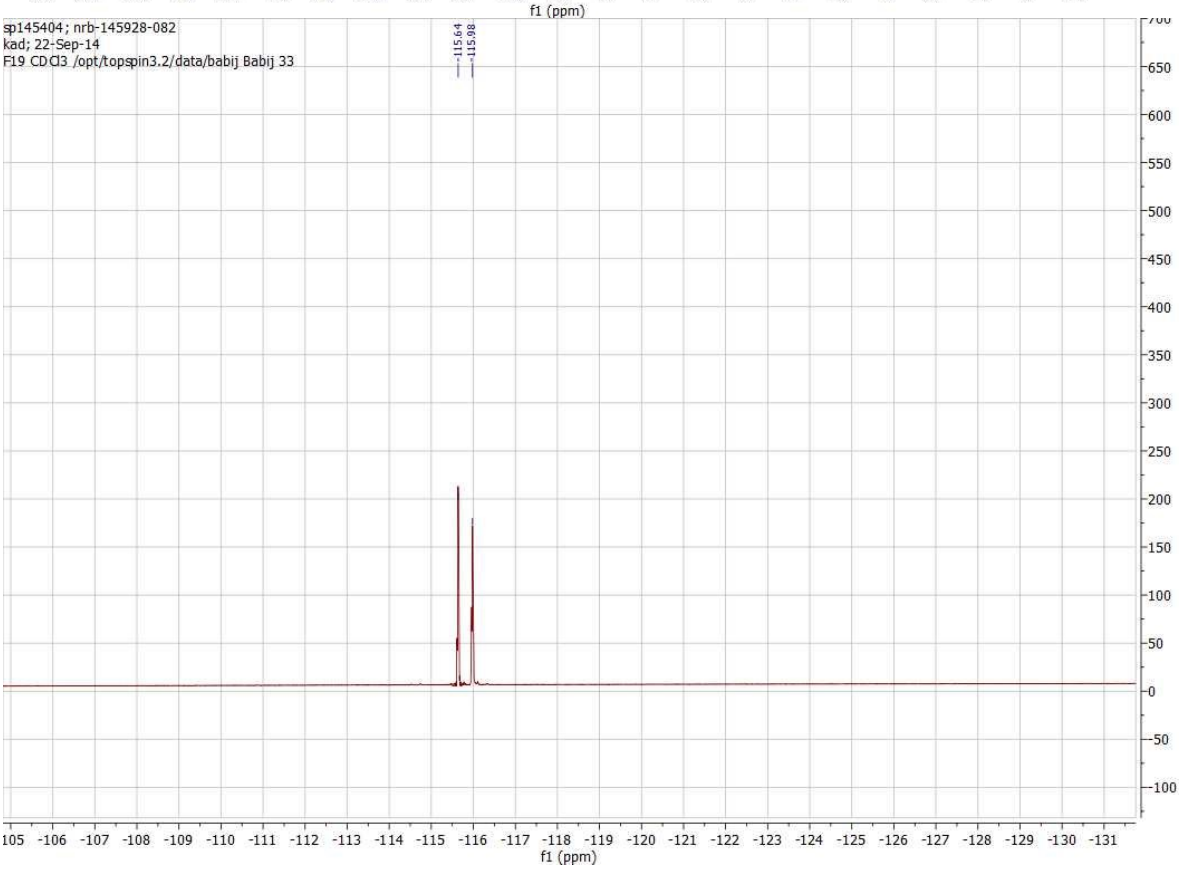


(*S*,*S*)-2-((-1-((-1,1-bis(4-fluorophenyl)propan-2-yl)oxy)-1-oxopropan-2-yl)carbamoyl)-4-methoxypyridin-3-yl pivalate (23)

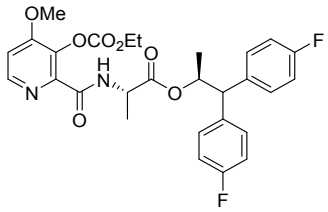


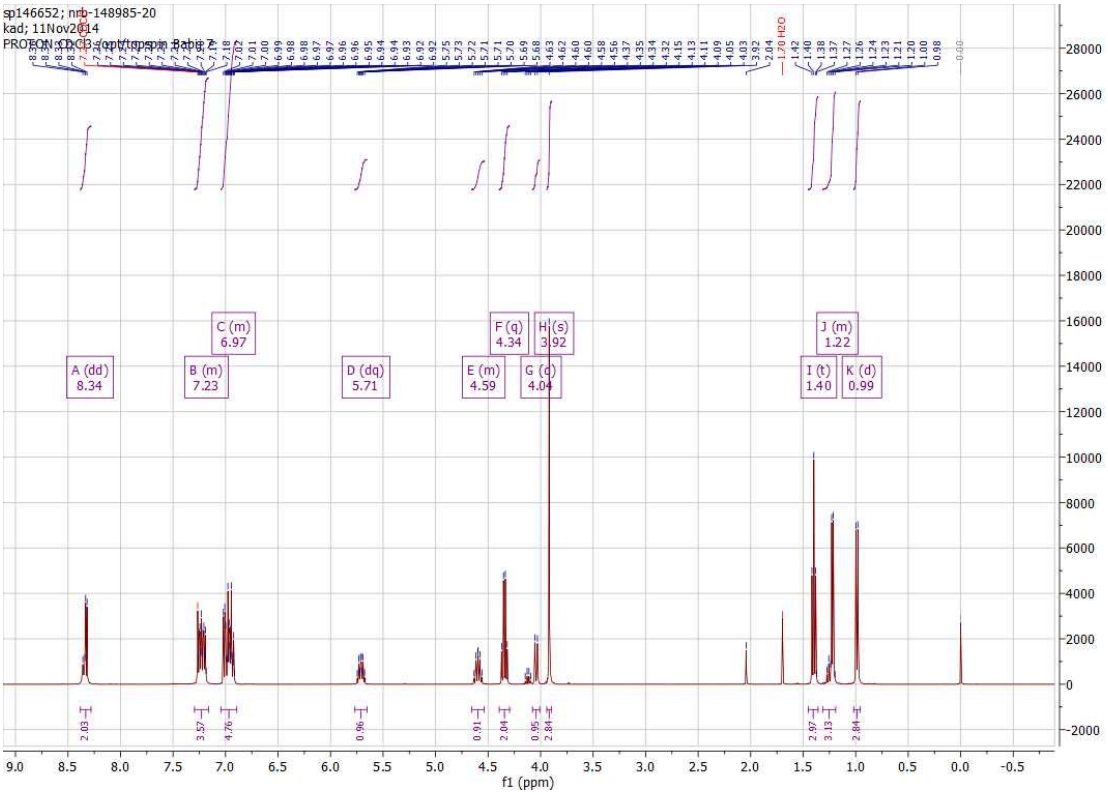


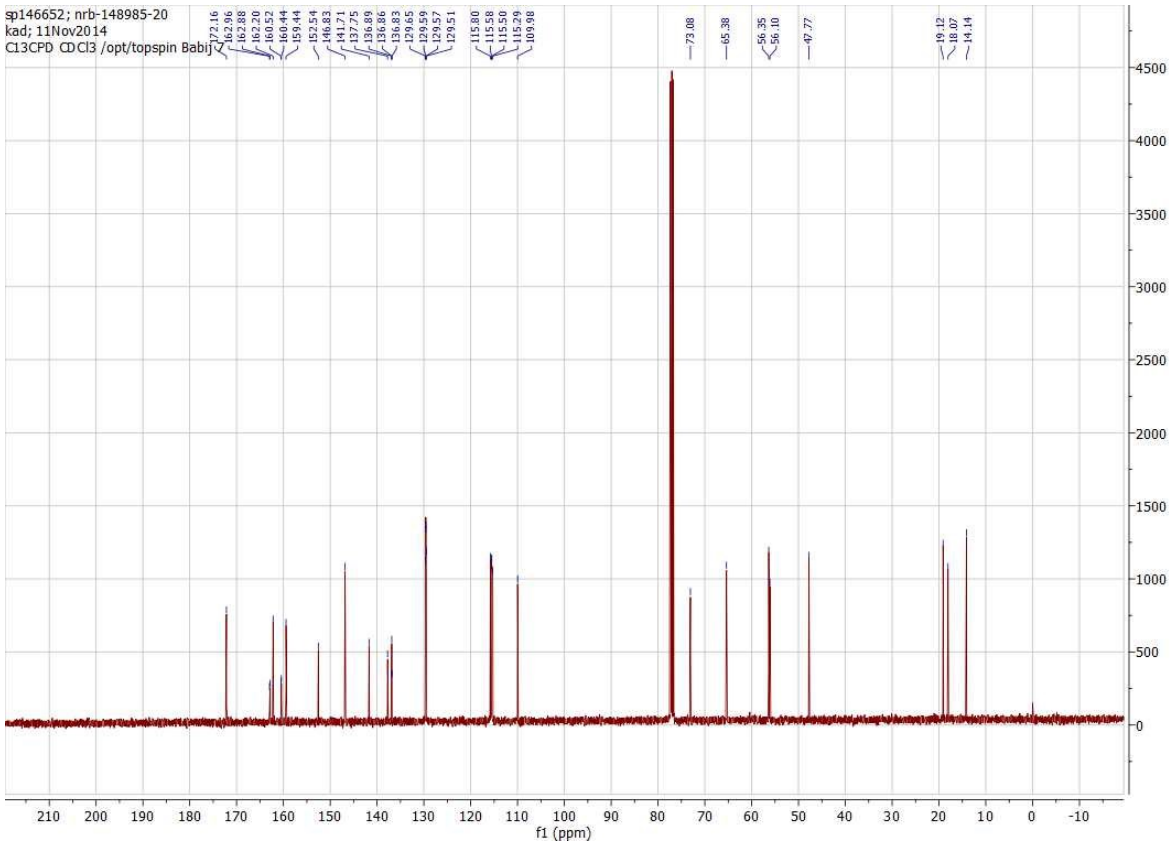

sp145566; nrb-145928-082
kad; 29-Sep-14
C13IG CDCl3 /opt/topspin3.2/data/babij Babij 16
176.05
172.30
162.71
162.63
162.23
160.75
160.68
159.39
146.50
142.13
137.83
136.88
136.85
129.67
129.61
129.58
129.52
115.76
115.59
115.47
115.30
109.50
73.02
56.29
56.07
47.78
39.14
27.16
19.11
18.09
f1 (ppm)

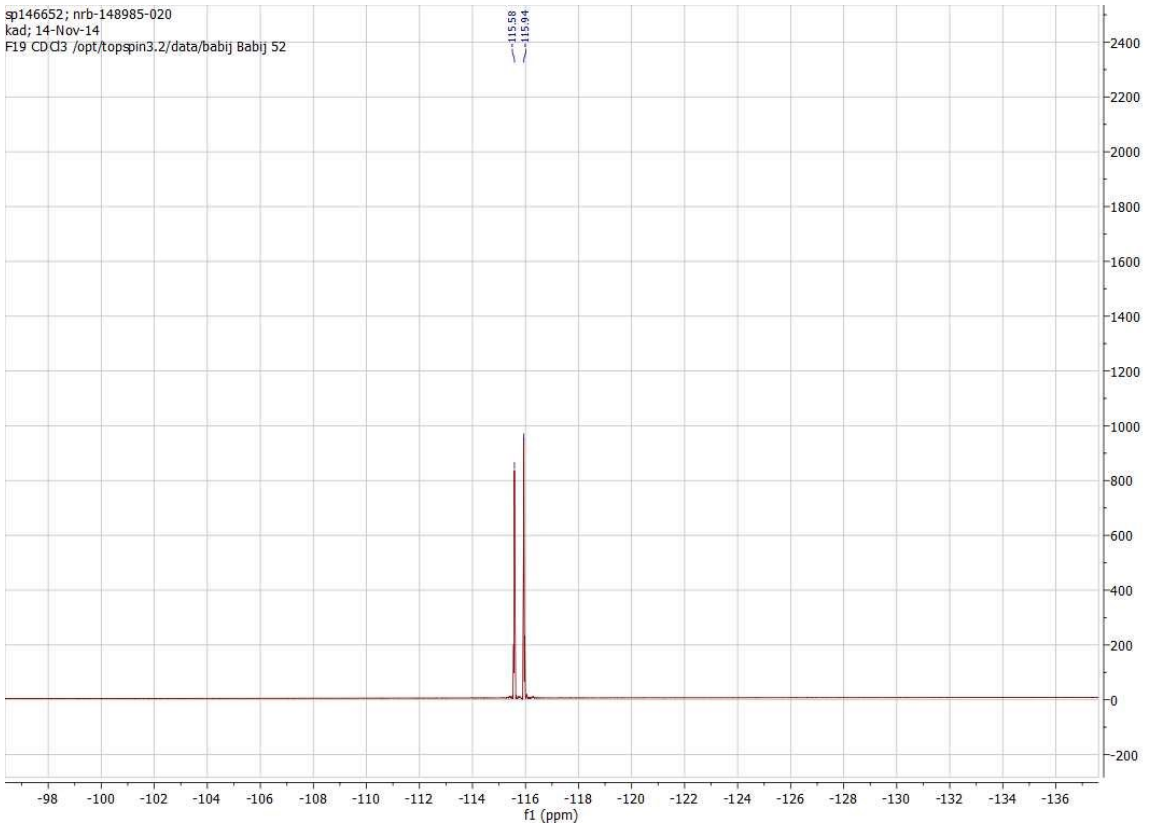

sp145404; nrb-145928-082
kad; 22-Sep-14
F19 CDCl3 /opt/topspin3.2/data/babij Babij 33
115.64
115.98
f1 (ppm)

(*S*,*S*)-1,1-bis(4-fluorophenyl)propan-2-yl 2-(3-((ethoxycarbonyl)oxy)-4-methoxypicolinamido)propanoate (24)

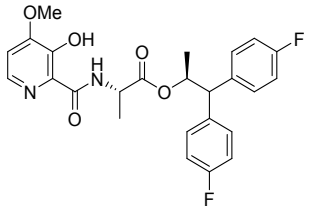


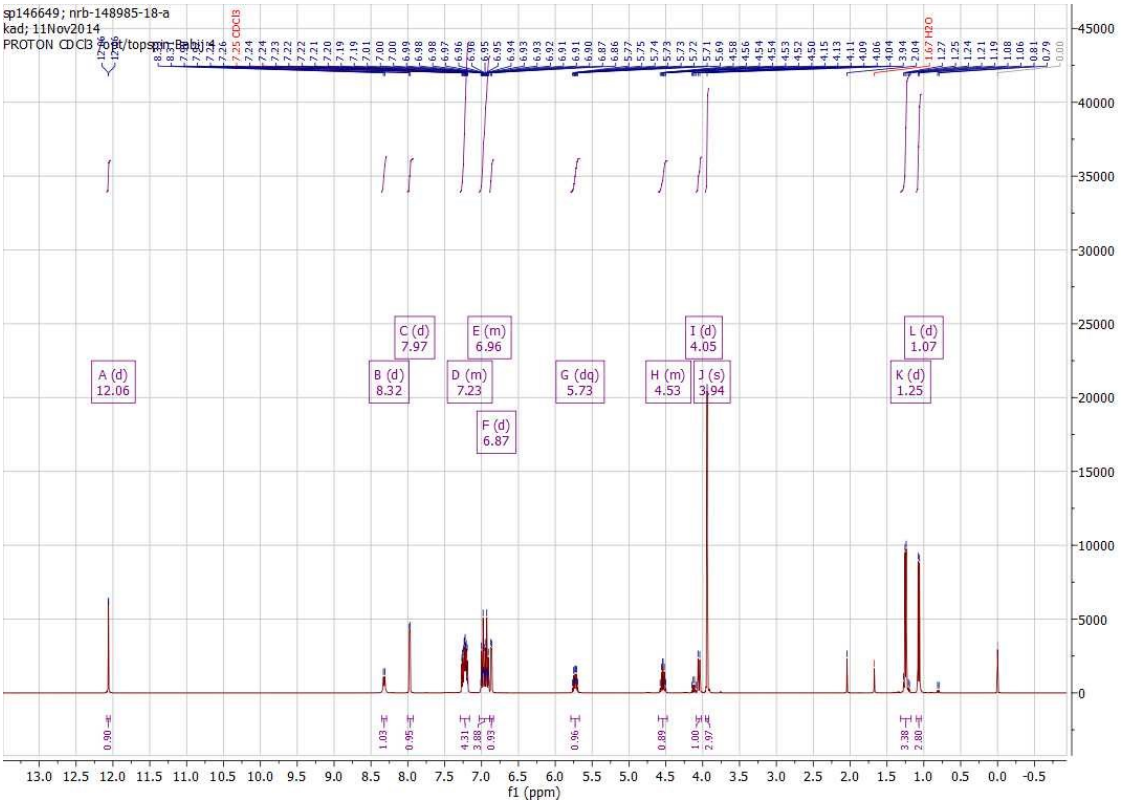


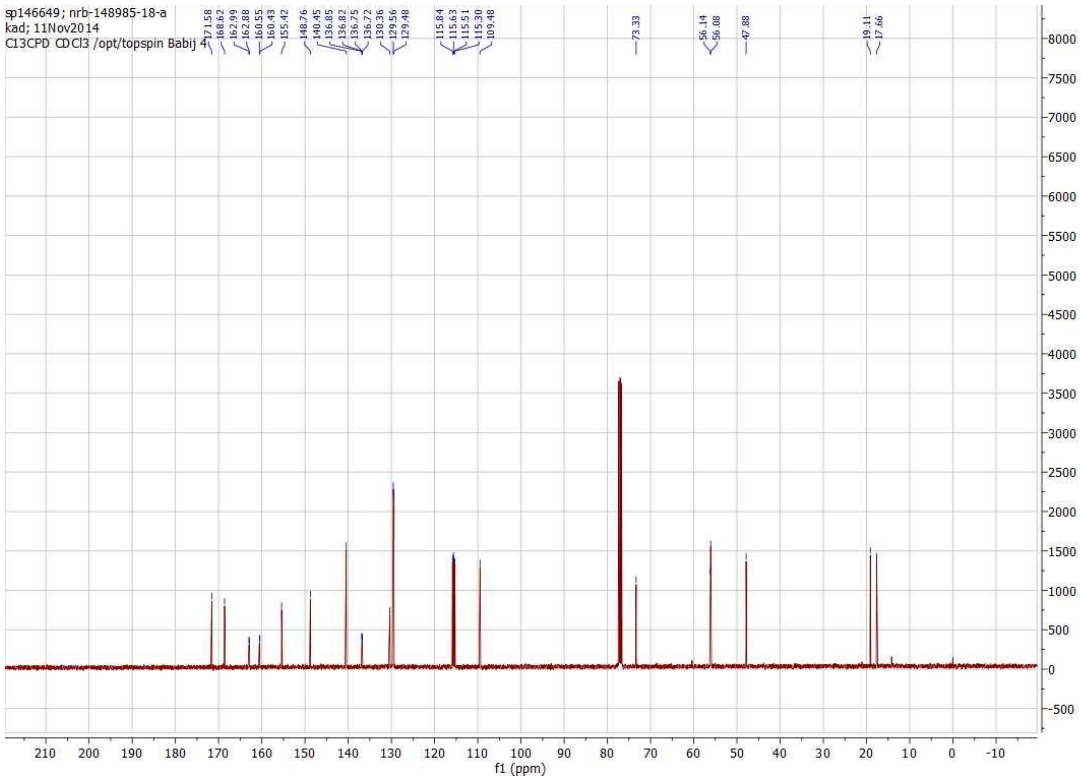

sp146652; nrb-148985-20
kad; 11Nov2014
C13CPD CDCl3 /opt/topspin Babij
172.16
162.96
162.88
162.20
160.52
160.44
159.44
152.54
146.83
141.71
137.75
136.89
136.86
136.83
129.65
129.59
129.57
129.51
115.80
115.58
115.50
115.29
109.98
73.08
65.38
56.35
56.10
47.77
19.12
18.07
14.14
f1 (ppm)

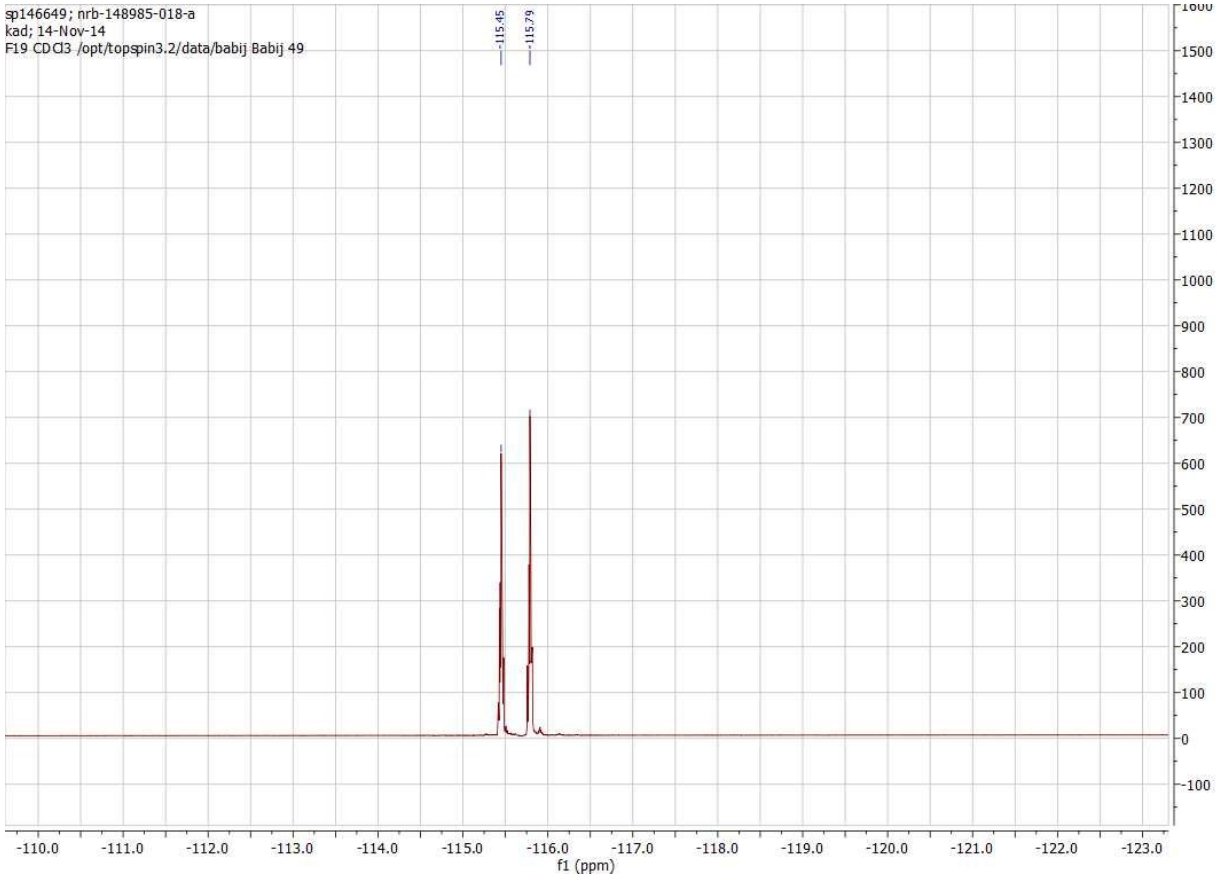

sp146652; nrb-148985-020
kad; 14-Nov-14
F19 CDCl3 /opt/topspin3.2/data/babij Babij 52
115.58
115.94
f1 (ppm)

(*S,S*)-1,1-bis(4-fluorophenyl)-propan-2-yl 2-(3-hydroxy-4-methoxypicolinamido)propanoate (2b)

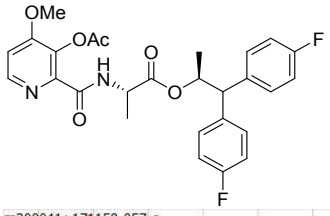


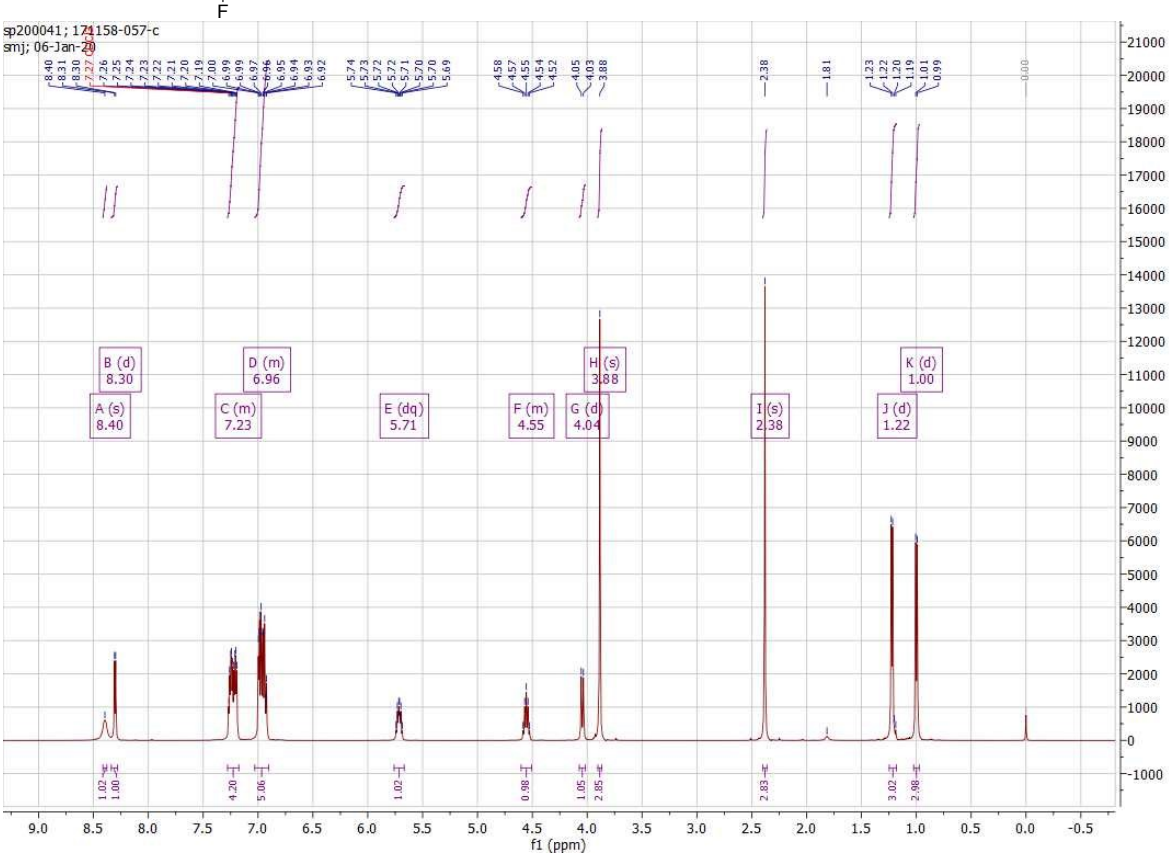


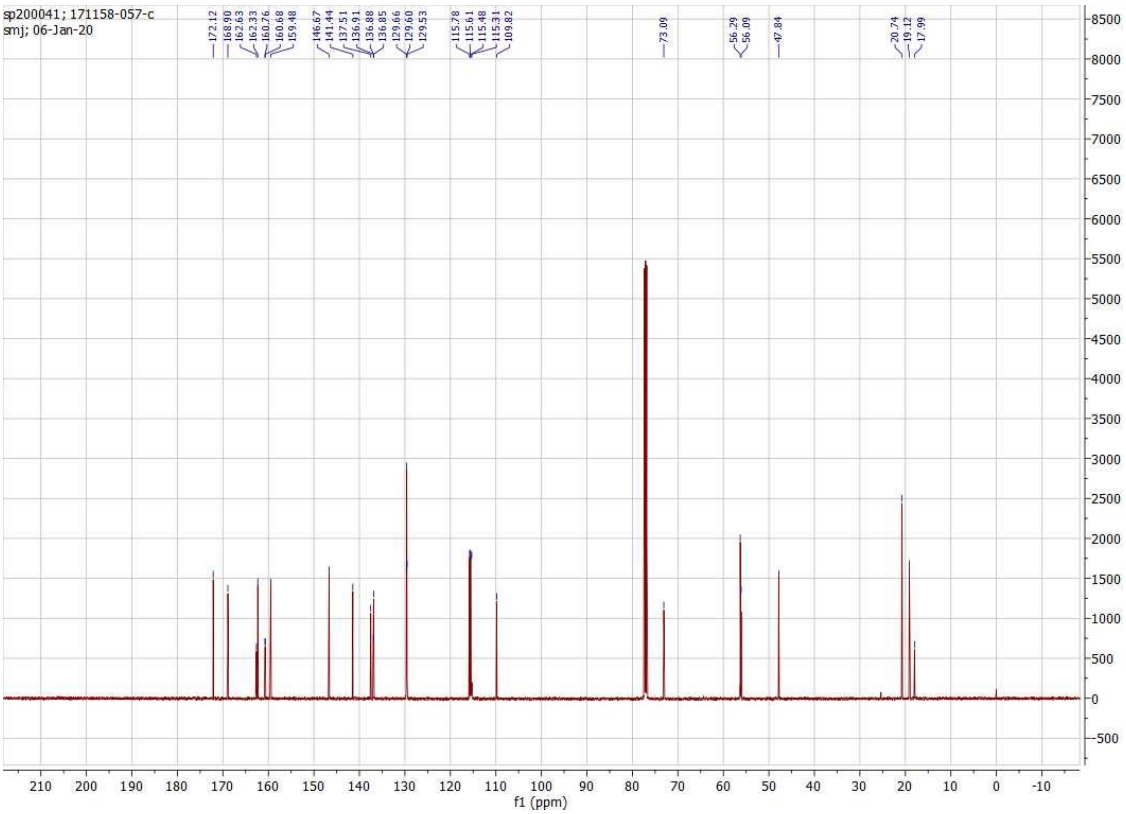

sp146649; nrb-148985-18-a
kad; 11Nov2014
C13CPD CDCl3 /opt/topspin Babij 4
171.58
168.62
162.99
162.88
160.55
160.43
155.42
148.76
140.45
136.85
136.82
136.75
136.72
130.36
129.56
129.48
115.84
115.63
115.51
115.30
109.48
73.33
56.14
56.08
47.88
19.11
17.66
f1 (ppm)

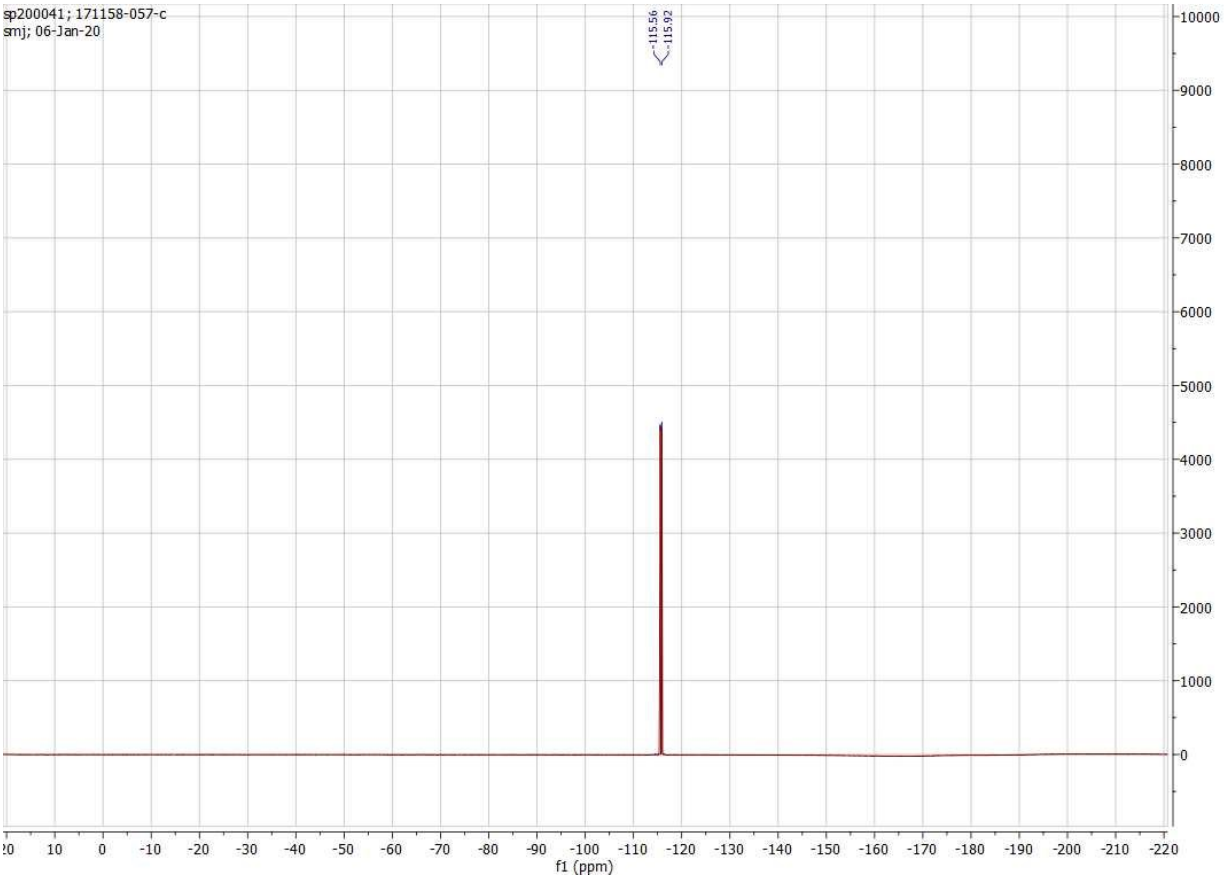

sp146649; nrb-148985-018-a
kad; 14-Nov-14
F19 CDCl3 /opt/topspin3.2/data/babij Babij 49
-115.45
-115.79
f1 (ppm)

(*S,S*)-1,1-bis(4-fluorophenyl)-propan-2-yl 2-(3-acetoxy-4-methoxypicolinamido)propanoate (2a)

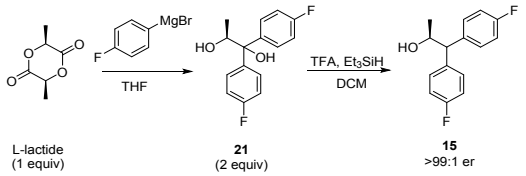





sp200041; 171158-057-c
smj; 06-Jan-20
172.12
168.90
162.63
162.33
160.76
160.68
159.48
146.67
141.44
137.51
136.91
136.88
136.85
129.66
129.60
129.53
115.78
115.41
115.08
115.31
109.82
73.09
56.29
56.09
47.84
20.74
19.12
17.99
f1 (ppm)


sp200041; 171158-057-c
smj; 06-Jan-20
-115.56
-115.92
f1 (ppm)

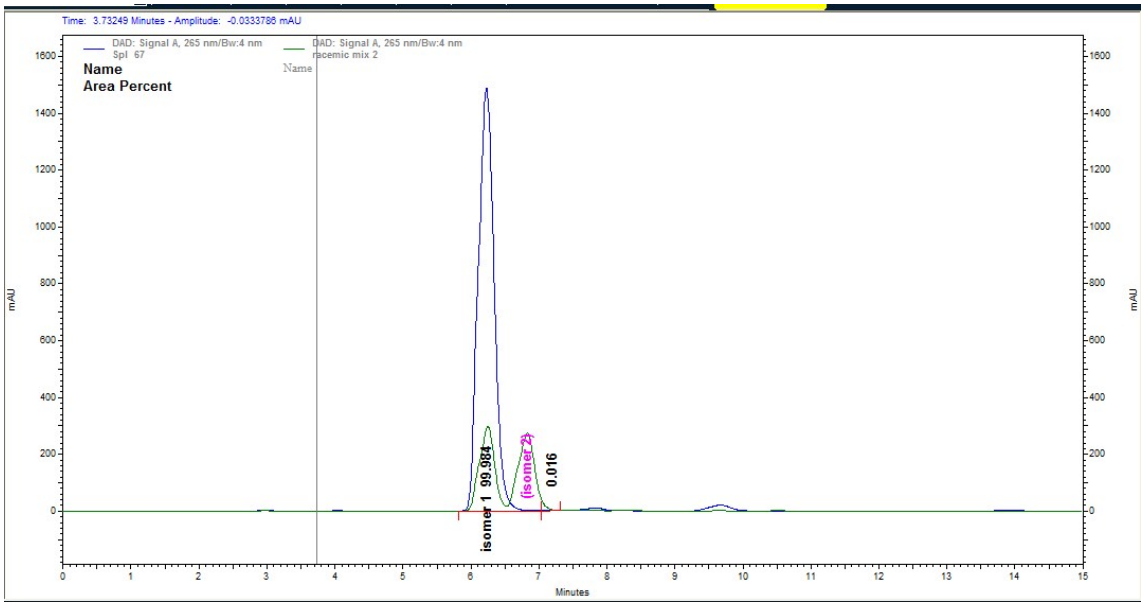
Copies of HPLC traces

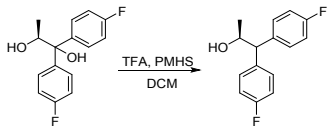


(*S*)-1,1-bis(4-fluorophenyl)propan-2-ol (15) via reduction with triethylsilane.

Chiral HPLC analysis was performed using a Chiralpak IA column (250 x 4.6 mm, P/N: 80325) with isocratic 85% in hexanes (0.1% trifluoroacetic acid) and 15% isopropanol (0.1% trifluoroacetic acid) mobile phase (10 µL injected). Using a UV detector set to 265 nm, enantiomer #1 (major) eluted at 6.2 minutes and enatiomer #2 (minor) eluted at 6.8 minutes. The enantiopurity was determined to be >99% ee.

Overlay of **15** from chiral L-lactide (blue) via reduction with triethylsilane and racemic **15** (green).





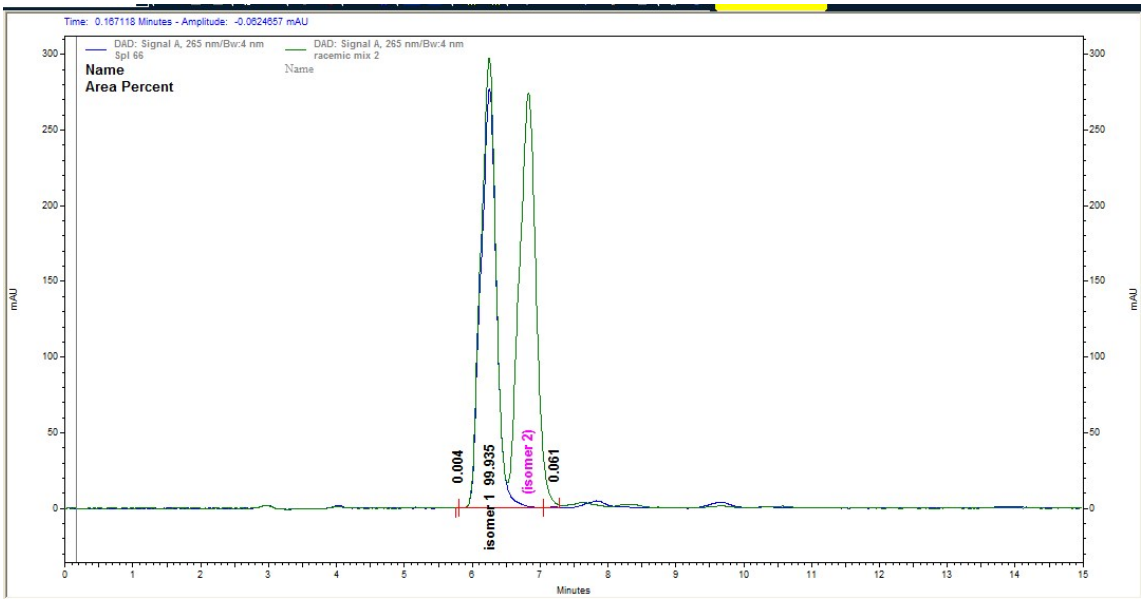
21
(2 equiv)

15
>99:1 er

(*S*)-1,1-bis(4-fluorophenyl)propan-2-ol (15) via reduction with PMHS.

Chiral HPLC analysis was performed using a Chiralpak IA column (250 x 4.6 mm, P/N: 80325) with isocratic 85% in hexanes (0.1% trifluoroacetic acid) and 15% isopropanol (0.1% trifluoroacetic acid) mobile phase (10 µL injected). Using a UV detector set to 265 nm, enantiomer #1 (major) eluted at 6.2 minutes and enatiomer #2 (minor) eluted at 6.8 minutes. The enantiopurity was determined to be >99% ee.

Overlay of **15** from chiral L-lactide (blue) and racemic **15** (green).



Crystallographic Data for amine hydrochloride salt (4)

CCDC 2005099 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

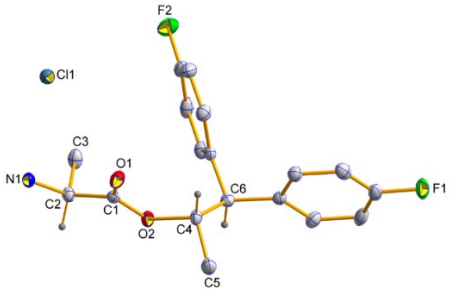


Table 1. Crystal data and structure refinement for **4**

Identification code	Final	
Empirical formula	C24 H36 Cl F2 N O4	
Formula weight	475.99	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.3081(3) Å	□= 90°.
	b = 11.7497(4) Å	□= 90°.
	c = 26.4644(8) Å	□ = 90°.
Volume	2583.39(15) Å^3	
Z	4	
Density (calculated)	1.224 Mg/m^3	
Absorption coefficient	0.190 mm^{-1}	
F(000)	1016	
Crystal size	0.260 x 0.120 x 0.100 mm^3	
Theta range for data collection	1.539 to 27.495°.	
Index ranges	-10<=h<=10, -14<=k<=15, -33<=l<=34	
Reflections collected	13605	
Independent reflections	5864 [R(int) = 0.0246]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.981 and 0.952	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5864 / 0 / 298	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2sigma(I)]	R1 = 0.0373, wR2 = 0.0827	
R indices (all data)	R1 = 0.0463, wR2 = 0.0865	
Absolute structure parameter	0.00(2)	
Largest diff. peak and hole	0.537 and -0.312 e.Å^{-3}	

Crystallographic Data for Florylpicoxamid (2a)

CCDC 2005098 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

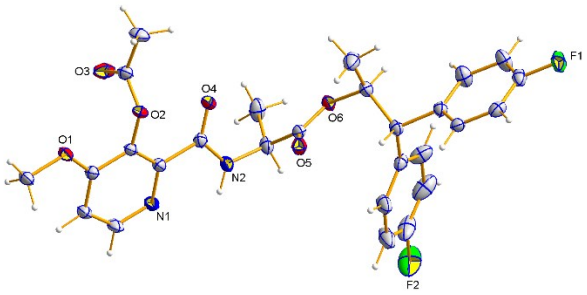


Table 1. Crystal data and structure refinement for **2a**.

Identification code	Final-P1	
Empirical formula	C54 H52 F4 N4 O12	
Formula weight	1024.99	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 8.5574(2) Å	□= 91.4030(10)°.
	b = 9.8938(2) Å	□= 93.6580(10)°.
	c = 14.8351(4) Å	□ = 97.9200(10)°.
Volume	1240.80(5) $Å^3$	
Z	1	
Density (calculated)	1.372 Mg/m^3	
Absorption coefficient	0.107 mm^{-1}	
F(000)	536	
Crystal size	0.360 x 0.310 x 0.230 mm^3	
Theta range for data collection	1.376 to 27.497°.	
Index ranges	-11<=h<=11, -12<=k<=12, -19<=l<=19	
Reflections collected	21191	
Independent reflections	9654 [R(int) = 0.0164]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	multi-scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9654 / 3 / 675	
Goodness-of-fit on F^2	1.090	
Final R indices [I>2sigma(I)]	R1 = 0.0327, wR2 = 0.0890	
R indices (all data)	R1 = 0.0360, wR2 = 0.0973	
Absolute structure parameter	-0.09(17)	
Largest diff. peak and hole	0.215 and -0.243 e.$Å^{-3}$	

Process Mass Intensity (PMI) Summary

The tables below summarize the Process Mass Intensity (PMI) data shown in Figure 2 which compare the 1st (a) and 2nd (b) generation routes to substituted picolinic acid **3**. The convergent PMI calculator tool used to perform these calculations is freely available from the ACS Green Chemistry Institute at https://www.acsgcipr.org/tools-for-innovation-in-chemistry/. For more detailed information see the excel document attached as additional supporting information.

Final Product - PMI Summary Table GEN 1				
Step Name/Number	esterification	Bromination	Bz protection	SNAr + hydrolysis
Mass Substrate (kg)	0.089	0.015	0.007	0.026
Mass Reagents (kg)	1.018	0.076	0.008	0.313
Mass Solvents (kg)	0.950	0.599	0.332	0.698
Mass Aqueous (kg)	0.496	0.800	0.550	0.840
Step PMI	36	106	108	162
Step PMI Substrate, Reagents, Solvents	29	49	42	89
Step PMI Substrates and Reagents	16	7	2	29
Step PMI Solvents	13	43	40	60
Step PMI Water	7	57	66	72
Cumulative PMI	36	145	231	667
Cumulative PMI Substrate, Reagents, Solvents	29	80	109	327
Cumulative PMI Substrates and Reagents	16	22	20	71
Cumulative PMI Solvents	13	57	89	256
Cumulative PMI Water	7	65	122	340

NOTE: DO NOT MODIFY THIS TABLE. All cells have been set to summarize the information in the indiviudal templates. As each template is completed, the appropriate informati
it is recommended that the embedded cell references are still valid.

Final Product - PMI Summary Table GEN 2				
Step Name/Number	Cyclizn/bromination	SNAr	hydrolysis	Reduction
Mass Substrate (kg)	0.14	0.03	0.09	0.05
Mass Reagents (kg)	1.71	0.02	0.46	0.06
Mass Solvents (kg)	1.34	0.03	0.13	0.45
Mass Aqueous (kg)	4.43	0.22	0.00	0.20
Step PMI	32	14	7	28
Step PMI Substrate, Reagents, Solvents	13	4	7	20
Step PMI Substrates and Reagents	8	2	6	4
Step PMI Solvents	6	2	1	17
Step PMI Water	19	10	0	7
Cumulative PMI	32	56	58	127
Cumulative PMI Substrate, Reagents, Solvents	13	20	25	62
Cumulative PMI Substrates and Reagents	8	11	15	29
Cumulative PMI Solvents	6	9	10	34
Cumulative PMI Water	19	36	33	64

References

[1] L. Louise-Leriche, E. Păunescu, G. Saint André, R. Baati, A. Romieu, A. Wagner and P.-Y. Renard, *Chem. Eur. J*., 2010, **16**, 3510-3523.
[2] T. Verdelet, G. Mercey, N. Correa, L. Jean and P.-Y. Renard, *Tetrahedron,* 2011, **67**, 8757-8762.
[3] D. Enders, S. von Berg, and B. Jandeleit, *Organic Syntheses*, 2004, **10**, 66; 2002, **78** 177.