Supporting Information

Synthesis of Potent Bicyclic Bis-Arylimidazole c-Jun N-Terminal Kinase Inhibitors by Catalytic C-H Bond Activation

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Full Author List for the References from the Article:

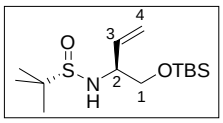
1. Graczyk, P. P.; Khan, A,; Bhatia, G.; Palmer, V.; Medland, D.; Numata, H.; Oinuma, H.; Catchick, J.; Dunne, A.; Ellis, M.; Smales, C.; Whitfield, J.; Neame, S. J.; Shah, B.; Wilton, D.; Morgan, L.; Patel, T.; Chung, R.; Desmond, H.; Staddon, J. M.; Sato, N.; Inoue, A. *Bioorg. & Med. Chem. Lett.* **2005**, *15*, 4666-4670.

General Experimental. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Toluene was dried over alumina under a nitrogen atmosphere, degassed by purging with nitrogen for 5 minutes, and stored in a nitrogen-filled Vacuum Atmosphere inert atmosphere box. Tertahydrofuran (THF), dichloromethane (CH_2Cl_2), and diethyl ether (Et_2O) were dried over alumina under a nitrogen atmosphere. All reactions, unless otherwise stated, were performed under inert atmosphere using syringe and cannula techniques. Flame-dried glassware was used in all cases. All ^{1}H, ^{13}C and ^{19}F NMR spectra were measured with a Bruker AVB-400, AVQ-400 or AV300 spectrometer in $CDCl_3$. NMR chemical shifts are reported in ppm relative to $CHCl_3$ (7.27 ppm for ^{1}H, 77.00 ppm for ^{13}C and -138.9 (1,2-difluorobenzene) for ^{19}F NMR). IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer equipped with an attenuated total reflectance accessor, and only partial data are listed. Elemental analyses and mass spectrometry (HRMS) were carried out by the University of California at Berkeley Mass Spectrometry Facility.

Synthesis of 5:

To a solution of *tert*-butyldimethylsiloxyacetaldehyde (4.50 g, 25.8 mmol) in CH_2Cl_2 (50 mL) was added $CuSO_4$ (12.4 g, 77.7 mmol) followed by the addition of (S_S)-*tert*-butanesulfinamide (6.75g, 38.7 mmol). The reaction mixture was stirred at rt for 12 hours, filtered through a pad of Celite that was then washed with CH_2Cl_2 (20 mL), concentrated under reduced pressure and purified by flash chromatography (20% EtOAc in hexanes) to provide **5** (6.14 g, 86%). Spectral data was identical to literature compound. $[\alpha]^{23}_{D}$ +188 (*c* 1.00, $CHCl_3$).[2]

Synthesis of 6:

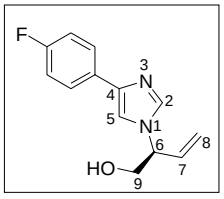


To a solution of **5** (3.93 g, 14.2 mmol) in CH_2Cl_2 (65 mL) cooled to -78 °C was added dropwise vinylmagnesium bromide (1.0 M in THF, 21.2 mL, 21.2 mmol). The reaction mixture was stirred at -78 °C for 5 hours, slowly warmed to rt, and stirred at rt for 8 hours. Saturated aqueous NH_4Cl (20 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, washed with brine (10 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (20% EtOAc in hexanes) to provide the major diastereomer, (S_S,S) 2-methylpropane-2-sulfinic acid [1-(*tert*-butyldimethylsilanyloxymethyl)-allyl]-amide (2.96

g, 69%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68-5.56 (m, 1H, C3-H), 5.35 (d, *J* = 16.8 Hz, 1H, C4-H), 5.24 (d, *J* = 10.2 Hz, 1H, C4-H), 3.98-3.92 (m, 2H, C2-H, N-H), 3.70 (dd, *J* = 9.6, 3.9 Hz, 1H, C1-H), 3.52 (dd, *J* = 9.9, 8.1 Hz, 1H, C1-H), 1.23 (s, 9H, S-C$(CH_3)_3$), 0.90 (s, 9H, Si-C$(CH_3)_3$), 0.08 (s, 3H, Si-CH_3), 0.07 (s, 3H, Si-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5 (C1), 119.0 (C4), 66.0 (C1), 58.4 (C2), 55.2 (-SO*t*Bu), 25.8 (-SO*t*Bu), 22.6 (-OTBS), 18.1 (-OTBS), -5.4 (-OTBS), -5.5 (-OTBS); IR (thin film) 1077, 1108, 2955 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{32}NO_2SSi$ (M+H) 306.192490, found 306.192305; $[\alpha]^{23}_D$ +93.8 (*c* 1.00, $CHCl_3$).

To a solution of (S_S,S) 2-methylpropane-2-sulfinic acid [1-(*tert*-butyldimethylsilanyloxymethyl)-allyl]-amide (1.03 g, 3.38 mmol) in methanol (10 mL) at 0 °C was added 4N HCl in dioxane (4.2 mL, 16.8 mmol). The reaction mixture was warmed to rt and stirred for 2 hours, concentrated under reduced pressure and the resulting oil was washed with ether revealing a yellow solid. The solid was washed with ether (2 x 30 mL) and residual solvent was removed under reduced pressure providing **6** (0.41 g, 99%) as a white solid that was used without further purification. $[\alpha]^{23}_D$ +10.0 (*c* 0.53, CH_3OH) The spectroscopic data for **6** were fully consistent with those previously reported.[3]

Synthesis of 7:



To a solution of **6** (0.375 g, 2.96 mmol) in DMF (12 mL) was added glyoxylic acid monohydrate (0.222 g, 2.36 mmol) followed by K_2CO_3 (1.03 g, 7.44 mmol). The reaction mixture was stirred at rt for 3.5 hours and 4-fluorophenyl tosylmethyl isonitrile[4] (0.559 g, 1.93 mmol) was added, and the reaction mixture was stirred at rt for 8 hours. The reaction was quenched with the addition of H_2O (10 mL) and the resulting mixture was extracted with EtOAc (4 x 10 mL). The organic phases were combined, washed with H_2O (2 x 10 mL) and brine (2 x 10 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (2.0% → 3.5% methanol in CH_2Cl_2 to provide (S)-2-[4-(4-fluorophenyl)-imidazolyl]-but-3-enol (0.414 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.55 (m, 2H, aryl-H), 7.48 (s, 1H, imid.), 7.04 (s, 1H, imid.) 7.06-7.01 (m, 2H, aryl-H), 6.03-5.94 (m, 1H, C7-H), 5.36 (d, *J* = 10.4 Hz, 1H, C8-H), 5.23 (d, *J* = 17.6 Hz, 1H, C8-H), 4.70-4.65 (m, 1H, C6-H), 4.17 (bs, 1H, O-H), 3.97 (dd, *J* = 12.0, 4.0 Hz, 1H, C6-CH), 3.90 (dd, *J* = 12.0, 8.0 Hz, 1H, C6-CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J_{C-F} = 244 Hz, aryl), 140.6 (imid.), 136.8 (C7), 133.0 (imid.), 129.8 (aryl), 126.1 (d, J_{C-F} = 7 Hz, aryl), 119.3 (imid.), 115.2 (d, J_{C-F} = 22 Hz, aryl), 112.8 (C8), 64.7 (C6-C), 62.7 (C6); ^{19}F (377 MHz, $CDCl_3$) δ -116.2; IR (thin film) 3137, 2929, 1558, 1495, 1219 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{14}FN_2O$ (M+H) 233.1086, found 233.1090; $[\alpha]^{23}_D$ -51.4° (*c* 0.56, $CHCl_3$).

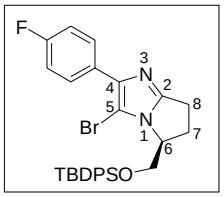
To a solution of (S)-2-[4-(4-fluorophenyl)-imidazolyl]-but-3-enol (0.457 g, 1.97 mmol) in CH_2Cl_2 (9 mL) was added *i*Pr_2NEt (0.563 g, 4.35 mmol) followed by *tert*-butylchlorodiphenylsilane (1.21 g, 4.31 mmol) and a catalytic amount of 4-dimethylaminopyridine. The reaction mixture was stirred at rt for 8 hours, H_2O (5 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (2 x 10 mL). The

organic layers were combined, washed with brine (2 x 5 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (25% EtOAc in hexanes) to provide **7** (0.905 g, 98%, >99% ee). The enantiomeric excess was determined by chiral HPLC [CHIRALPAK^{TM} AD column, detection at 254 nm, flow rate 1.0 mL/min, 85:15 hexane:*i*PrOH → 75:25 hexane:*i*PrOH, T_r(R) 6.7 min. and T_r(S) 9.3 min.] providing the enantiomeric ratio: 6R:6S = 99.9:0.1 (99.8% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.67 (m, 2H, aryl), 7.61-7.56 (m, 3H, aryl, imid.), 7.51-7.49 (m, 2H, aryl), 7.51-7.31 (m, 6H, aryl), 7.16 (s, 1H, imid.), 7.08-7.04 (m, 2H, aryl), 6.06-5.99 (m, 1H, C7-H), 5.33 (d, J = 10.4 Hz, 1H, C8-H), 5.20 (d, J = 17.6 Hz, 1H, C8-H), 4.70-4.66 (m, 1H, C6-H), 3.97 (dd, J = 10.4, 4.0 Hz, 1H, C6-CH), 3.88 (dd, J = 10.8, 7.2 Hz, 1H, C6-CH), 1.07 (s, 9H, OTBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J_{C-F} = 243 Hz, aryl), 141.1 (imid.), 137.0 (C7), 135.6 (aryl), 135.5 (aryl), 133.3 (imid.), 132.7 (aryl), 132.4 (aryl), 130.5 (aryl), 129.9 (aryl), 129.9 (aryl), 127.9 (aryl), 127.8 (aryl), 126.2 (d, J_{C-F} = 8.0 Hz, aryl)), 119.2 (imid.), 115.4 (d, J_{C-F} = 21 Hz, aryl), 113.4 (C8), 66.0 (C6-C), 61.0 (C6), 26.7 (OTBDPS), 19.1 (OTBDPS); ^{19}F NMR (377 MHz, $CDCl_3$) δ -116.2; IR (thin film) 2931, 2857, 1720, 1557, 1491, 1113 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{32}FN_2OSi$ (M+H) 471.227020, found 471.226796; $[\alpha]^{23}_D$ -17.9 (*c* 1.01, $CHCl_3$).

Synthesis of 8:

To a solution of **7** (0.268 g, 0.569 mmol) in toluene (8 mL) in a glove box was added $[RhCl(coe)_2]_2$ (21.4 mg, 0.030 mmol), tricyclohexylphosphine (26.7 mg, 0.095 mmol) and $MgBr_2$ (5.3 mg, 0.030 mmol). The reaction mixture was heated to 180 °C in a sealed high pressure flask for 5.5 hours, cooled to rt, concentrated and purified by flash silica gel chromatography (25% → 50% EtOAc in hexanes) to provide **8** (128 mg, 50%). The enantiomeric purity was evaluated by chiral HPLC [Daicel Chiracel^{TM} OD column, detection at 254 nm, flow rate 1.0 mL/min, 90:10 hexane:*i*PrOH → 75:25 hexane:*i*PrOH, T_r(R) 6.3 and T_r(S) 36.5] providing the enantiomeric ratio: 6R:6S = 4.0:96.0 (92% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.57 (m, 6H, aryl), 7.44-7.33 (m, 6H, aryl), 7.21 (s, 1H, imid.), 7.07-7.02 (m, 2H, aryl), 4.38-4.35 (m, 1H, C6-H), 3.94 (dd, J = 10.8, 4.0 Hz, 1H, C6-CH_2-O), 3.75 (dd, J = 10.8, 6.8 Hz, 1H, C6-CH_2-O), 2.96-2.86 (m, 2H, C8-H), 2.67-2.59 (m, 1H, C7-H), 2.34-2.27 (m, 1H, C7-H), 1.06 (s, 9H, OTBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (d, J_{C-F} = 247 Hz, aryl), 154.5 (imid.), 145.2 (imid.), 135.6 (aryl), 135.5 (aryl), 132.8 (aryl), 132.6 (aryl), 131.2 (aryl), 130.0 (aryl), 129.9 (aryl), 127.9 (aryl), 127.9 (aryl), 126.0 (d, J_{C-F} = 8 Hz, aryl), 115.3 (d, J_{C-F} = 21 Hz, aryl), 110.1 (imid.), 66.4 (C6-C), 58.6 (C6), 28.8 (C8), 26.7 (OTBDPS), 22.9 (C7), 19.1 (OTBDPS); ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.7; IR (thin film) 2931, 2858, 1547, 1492, 1428, 1112 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{32}FN_2OSi$ (M+H) 471.226796, found 471.227910; $[\alpha]^{23}_D$ -25.6 (*c* 0.62 $CHCl_3$).

Synthesis of 9:

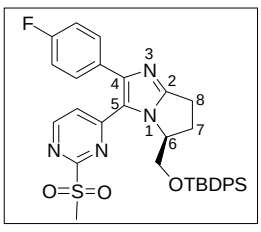


To a solution of **8** (33.3 mg, 0.071 mmol) in CH_2Cl_2 (1.5 mL) at -78 °C was added dropwise a cooled solution of Br_2 (11.9 mg, 0.075 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 15 minutes at -78 °C, and a saturated aqueous solution of $NaHCO_3$ (5 mL) was added. The reaction mixture was warmed to rt and extracted

with CH_2Cl_2 (2 x 5 mL). The organic phases were combined, washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure to provide (S)-5-bromo-9-(*tert*-butyldiphenylsilanyloxymethyl)-4-(4-fluorophenyl)-7,8-dihydro-5H-pyrrolo[1,2-a]imidazole (36.7 mg, 94%) as a colorless foam that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.89 (m, 2H, aryl), 7.62-7.60 (m, 2H, aryl), 7.46-7.36 (m, 6H, aryl), 7.31-7.26 (m, 2H, aryl), 7.12-7.07 (m, 2H, aryl), 4.38-4.34 (m, 1H, C6-H), 4.00 (dd, J = 10.8, 3.6 Hz, 1H, C6-CH_2), 3.83 (dd, J = 10.8, 2.4 Hz, 1H, C6-CH_2), 3.20-3.11 (m, 1H, C8-H), 2.95-2.88 (m, 1H, C8-H), 2.83-2.53 (m, 2H, C7-H), 0.98 (s, 9H, OTBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J_{C-F} = 247 Hz, aryl), 155.1 (imid.), 141.4 (imid.), 135.5 (aryl), 135.5 (aryl), 132.9 (aryl), 132.3 (aryl), 130.0 (d, J_{C-F} = 3 Hz, aryl), 129.9 (aryl), 129.8 (aryl), 128.0 (d, J_{C-F} = 8 Hz, aryl), 127.8 (aryl), 127.8 (aryl), 115.2 (d, J_{C-F} = 21 Hz , aryl), 93.0 (imid), 64.7 (C6-C), 58.6 (C6), 29.5 (C8), 26.6 (OTBDPS), 24.2 (C7), 19.1 (OTBDPS); ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.9; IR (thin film) 2956, 1538, 1426, 1112 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{31}BrFN_2OSi$ (M+H) 549.137307, found 549.136560; $[\alpha]^{23}_D$ -35.1° (*c* 1.09, $CHCl_3$).

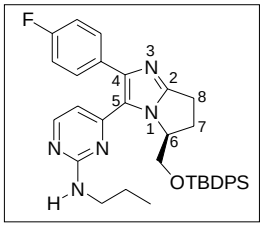
To a solution of (S)-5-bromo-9-(*tert*-butyldiphenylsilanyloxymethyl)-4-(4-fluorophenyl)-7,9-dihydro-5H-pyrrolo[1,2-a]imidazole (0.187 g, 0.340 mmol) in dioxane (6 mL) was added 2-methylsulfanyl-4-trimethylstannanylpyrimidine[5] (0.216 g, 0.750), $Pd_2(dba)_2$•$CHCl_3$ (55.0 mg, 0.034 mmol), triphenylphosphine (17.8 mg, 0.068 mmol), LiCl (50.4 mg, 1.19 mmol), and CuI (33.7 mg, 0.177 mmol). The reaction mixture was heated to 170 °C for 5.5 hours, cooled to rt, filtered through a pad of celite, concentrated under reduced pressure, and purified by flash chromatography (20% EtOAc in hexanes) to provide **9** (0.173 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 5.6 Hz, 1H, pyrim.), 7.53-7.50 (m, 4H, aryl), 7.50-7.27 (m, 6H, aryl), 7.19-7.07 (m, 4H, aryl), 6.71 (d, J = 5.2 Hz, 1H, pyrim.), 5.14 (app d, J = 7.2 Hz, 1H, C6-H), 3.80-3.73 (m, 2H, C6-CH_2), 3.20-3.13 (m, 1H, C8-H), 2.97-2.85 (m, 2H, C8-H, C7-H), 2.71-2.66 (m, 1H, C7-H), 2.44 (s, 3H, S-CH_3), 0.93 (s, 9H, OTBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4 (pyrim.), 164.7 (pyrim.), 163.1 (d, J_{C-F} = 247 Hz, aryl), 158.13 (pyrim.), 156.6 (imid.), 156.2 (imid.), 135.4 (aryl), 135.3 (aryl), 132.9 (aryl), 132.3 (aryl), 131.4 (aryl), 130.6 (d, J_{C-F} = 8 Hz, aryl), 129.8 (aryl), 129.7 (aryl), 127.8 (aryl), 127.6 (aryl), 122.0 (imid.), 115.8 (d, J_{C-F} = 22 Hz, aryl), 112.7 (pyrim.), 65.6 (C6-C), 60.4 (C6), 30.1 (C8), 26.5 (OTBDPS), 23.7 (C7), 19.0 (OTBDPS), 14.0 (S-C); ^{19}F NMR (377 MHz, $CDCl_3$) δ -113.8; IR (thin film) 2928, 1426, 1345, 1209, 1112 cm^{-1}; HRMS (EI) calcd for $C_{34}H_{36}FN_4O_3SSi$ (M+H) 595.2363, found 595.2360.7; $[\alpha]^{23}_D$ -150.9° (*c* 1.80, $CHCl_3$).

Synthesis of 1:



To a solution of **9** (96 mg, 0.16 mmol) in THF (2 mL) and H_2O (4 mL) at rt was added OXONE® (0.39 g, 0.64 mmol). The reaction mixture was stirred at rt for 5 hours and diluted with EtOAc (6 mL). The reaction mixture was washed with 1 N NaOH (3 mL) and brine (2 x 5 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (70% EtOAc in hexanes) to provide (S)-9-(*tert*-butyldiphenylsilanyloxymethyl)-4-(4-fluorophenyl)-5-(3-methanesulfonylphenyl)-7,8-

dihydro-5H-pyrrolo[1,2-a]imidazole (79 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 5.6 Hz, 1H, pyrim.), 7.55-7.47 (m, 4H, aryl), 7.40-7.23 (m, 6H, aryl), 7.19-7.09 (m, 5H, aryl, pyrim.), 5.24 (app d, J = 7.6 Hz, 1H, C6-H), 3.96 (dd, J = 11.2, 2.0 Hz, 1H, C6-CH_2), 3.87 (dd, J = 11.2, 1.6 Hz, 1H, C6-CH_2), 3.27-3.12 (m, 1H, C8-H), 3.09 (s, 3H, S-CH_3), 2.98-2.87 (m, 2H, C8-H, C7-H), 2.51-2.46 (m, 1H, C7-H), 0.94 (s, 9H, OTBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (pyrim.), 163.1 (d, J_{C-F} = 247 Hz, aryl), 160.1 (pyrim.), 157.9 (imid.), 156.7 (pyrim.), 151.5 (imid.), 135.3 (aryl), 135.3 (aryl), 132.8 (aryl), 132.5 (aryl), 131.1 (aryl), 130.6 (d, J_{C-F} = 8 Hz, aryl), 129.8 (aryl), 129.7 (aryl), 127.7 (aryl), 127.4 (aryl), 121.3 (imid.), 118.2 (pyrim.), 116.1 (d, J_{C-F} = 22 Hz, aryl), 65.9 (C6-C), 61.2 (C6), 39.1 (SO_2-C), 30.3 (C8), 26.6 (OTBDPS), 20.7 (C7), 18.9 (OTBDPS); ^{19}F NMR (377 MHz, $CDCl_3$) δ -111.3; IR (thin film) 2913, 1573, 1490, 1428, 1321, 1137, 1112 cm^{-1}; HRMS (EI) calcd for $C_{34}H_{36}FN_4O_3SSi$ (M+H) 627.2261, found 627.2266; $[\alpha]^{23}_D$ -194.3° (*c* 1.30, $CHCl_3$).

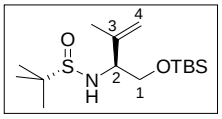


(S)-9-(*tert*-butyldiphenylsilanyloxymethyl)-4-(4-fluorophenyl)-5-(3-methanesulfonylphenyl)-7,8-dihydro-5H-pyrrolo[1,2-a]imidazole (76 mg, 0.12 mmol) was dissolved in propylamine (2 mL) and stirred for 8 hours at rt, concentrated under reduced pressure, and purified by flash chromatography (100% EtOAc) to provide (S)-9-(*tert*-butyldiphenylsilanyloxymethyl)-4-(4-fluorophenyl)-5-(2-methylsulfanylpyrimidin-4-yl)-7,8-dihydro-5H-pyrrolo[1,2-a]imidazole (57 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 5.2 Hz, 1H, pyrim.), 7.57-7.54 (m, 4H, aryl), 7.44-7.26 (m, 6H, aryl), 7.21-7.14 (m, 2H, aryl), 7.10-7.05 (m, 2H, aryl), 6.38 (d, J = 5.2 Hz, 1H, pyrim.), 5.15-5.05 (m, 2H, C6-H. N-H), 3.88-3.84 (m, 1H, C6-CH_2), 3.73 (dd, J = 10.4, 1.6 Hz, 1H, C6-CH_2), 3.22-3.09 (m, 3H, C8-H, N-Pr), 2.95-2.80 (m, 2H, C8-H, C7-H), 2.71-2.65 (m, 1H, C7-H), 1.55-1.45 (m, 2H, N-Pr), 0.94 (s, 9H, OTBDPS), 0.88 (t, J = 7.2 Hz, 3H, N-Pr); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.5 (d, J_{C-F} = 246 Hz, aryl), 162.2 (pyrim.), 157.4 (pyrim.), 157.3 (imid.), 157.2 (imid.), 147.7 (pyrim.), 135.3 (aryl), 135.3 (aryl), 133.0 (aryl), 132.3 (aryl), 131.8 (aryl), 130.6 (d, J_{C-F} = 8 Hz, aryl), 129.7 (aryl), 129.6 (aryl), 127.7 (aryl), 127.6 (aryl), 122.7 (imid), 115.3 (d, J_{C-F} = 21 Hz, aryl), 107.7 (pyrim.), 65.7 (C6-C), 60.0 (C6), 43.1 (N-Pr), 30.0 (C8), 26.5 (OTBDPS), 23.6 (N-Pr), 22.7 (C7), 19.0 (OTBDPS), 11.4 (N-Pr); ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.7; IR (thin film) 3264, 3071, 2959, 2858, 1572, 1529, 1492, 1112 cm^{-1}; HRMS (EI) calcd for $C_{36}H_{41}FN_5OSi$ (M+H) 606.3064, found 606.3072; $[\alpha]^{23}_D$ -173.0° (*c* 1.00, $CHCl_3$).

To a solution of (S)-9-(*tert*-butyldiphenylsilanyloxymethyl)-4-(4-fluorophenyl)-5-(2-methylsulfanylpyrimidin-4-yl)-7,8-dihydro-5H-pyrrolo[1,2-a]imidazole (45 mg, 0.07 mmol) in THF (2 mL) was added tetrabutylammonium fluoride (70 mg, 0.22 mmol) and the reaction mixture was stirred at rt for 2 hours. H_2O (4 mL) was added and the reaction mixture was extracted with EtOAc (3 x 5 mL). The organic phases were combined, washed with brine (5 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (2% *i*PrOH in EtOAc) to provide **1** (27 mg, 100%). ^{1}H NMR (377 MHz, $CDCl_3$) δ 8.05 (d, J = 4.8 Hz, 1H, aryl), 7.54 (dd, J = 8.4, 6.0 Hz, 2H, aryl), 7.06 (app t, J = 8.8 Hz, 2H, aryl), 6.41 (d, J = 5.2 Hz, 1H, aryl), 5.16-5.10 (m, 1H, N-H), 4.93 (bs, 1H, C6-H), 3.95 (dd, J = 11.2, 3.6 Hz, 1H, C6-CH_2),

3.84-3.79 (m, 1H, C6-CH_2), 3.39 (dd, J = 13.2, 5.6 Hz, 2H, N-Pr), 3.10-3.01 (m, 1H, C8-H), 2.91-2.75 (m, 2H, C8-H, C7-H), 2.43-2.36 (m, 1H, C7-H), 1.66 (q, J = 7.2 Hz, 2H, N-Pr), 1.60 (bs, 1H, O-H) 1.01 (t, J = 7.2 Hz, 3H, N-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, J_{C-F} = 246 Hz, aryl), 161.8 (pyrim.), 158.0 (pyrim.), 157.0 (imid.), 156.5 (imid.), 147.5 (pyrim.), 131.2 (aryl), 130.6 (d, J_{C-F} = 8 Hz, aryl), 122.9 (imid.), 115.4 (d, J_{C-F} = 21 Hz, aryl), 108.2 (pyrim.), 65.3 (C6-C), 60.6 (C6), 43.3 (N-Pr), 30.6 (C8), 23.0 (N-Pr), 22.8 (C7), 11.4 (N-Pr); ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.2; IR (thin film) 3261, 2962, 2872, 1570, 1493, 1221 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{23}FN_5O$ (M+H) 368.1887, found 368.1897; $[\alpha]^{23}{}_D$ = -166.5° (c = 0.37, MeOH).

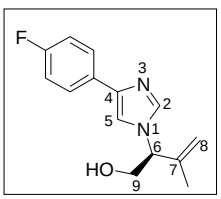
Synthesis of 10:



To a solution of **5** (5.00 g, 18.0 mmol) in CH_2Cl_2 (100 mL) cooled to -78 °C was added dropwise isopropenylmagnesium bromide (0.6 M in ether, 60.0 mL, 36.0 mmol). The reaction mixture was stirred at -78 °C for 5 hours, slowly warmed to rt and stirred for 8 hours. Saturated aqueous NH_4Cl (20 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, washed with brine, dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (15% EtOAc in hexanes) to provide (S_S,S)-2-methylpropane-2-sulfinic acid [1-(*tert*-butyldimethylsilanyloxymethyl)-2-methylallyl]-amide (5.16 g, 90%) as a single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (s, 1H, C4-H), 5.00 (s, 1H, C4-H), 3.98-3.94 (m, 2H, C2-H, N-H), 3.73 (dd, J = 9.6, 4.0 Hz, 1H, C1-H), 3.58 (dd, J = 9.6, 8.4 Hz, 1H, C1-H), 1.78 (s, 3H, C3-CH_3), 1.24 (s, 9H, S-C(CH_3)$_3$), 0.90 (s, 9H, OTBS), 0.08 (s, 3H, OTBS), 0.08 (s, 3H, OTBS); ^{13}C NMR (400 MHz, $CDCl_3$) 141.7 (C3), 115.6 (C4), 65.2 (C1), 60.8 (C2), 55.2 (SO*t*Bu), 25.8 (SO*t*Bu), 22.7 (OTBS), 18.6 (C3-C), 18.1 (OTBS), -5.4 (OTBS), -5.5 (OTBS); IR (thin film) 3450, 3282, 3203, 2955, 1650, 1472, 1363, 1256, 1078 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{34}FNO_2Si$ (M+H) 320.2080, found 320.2079; (S_S,S) $[\alpha]^{23}{}_D$ +89.5° (c 1.05, $CHCl_3$), (R_S,R) $[\alpha]^{25}{}_D$ -85.5° (c 1.10, $CHCl_3$).

To a solution of (S_S,6S)-2-methylpropane-2-sulfinic acid [1-(*tert*-butyldimethylsilanyloxymethyl)-2-methylallyl]-amide (0.28 g, 0.88 mmol) in methanol (5 mL) was added 4N HCl in dioxane (2.2 mL, 8.80 mmol). The reaction mixture was stirred at rt for 2 hours, concentrated under reduced pressure and the resulting oil was washed with ether revealing a yellow solid. The solid was washed with ether (2 x 15 mL) and the residual solvent was removed under reduced pressure providing **10** (0.12 g, 96%) as a white solid that was used without further purification; ^{1}H NMR (400 MHz, CD_3OD) δ 5.15 (d, J = 1.6 Hz, 1H, C4-H), 5.08 (s, 1H, C4-H), 3.80 (dd, J =11.2, 4.0 Hz, 1H, C1-H), 3.76-3.73 (m, 1H, C2-H), 3.64 (dd, J = 11.2, 4.7 Hz, 1H, C1-H), 1.85 (s, 3H, C3-CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 140.2 (C3), 115.7 (C4), 62.1 (C1), 58.9 (C2), 20.2 (C3-C); (S) $[\alpha]^{23}{}_D$ +2.94° (c 1.02, CH_3OH), (R) $[\alpha]^{23}{}_D$ -2.79° (c 1.04, CH_3OH).

Synthesis of 11:



To a solution of **10** (93 mg, 0.68 mmol) in DMF (3.5 mL) was added glyoxylic acid monohydrate (53 mg, 0.58 mmol) followed by K_2CO_3

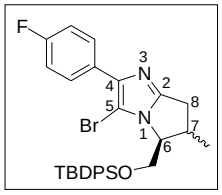
(0.253 g, 1.84 mmol). The reaction mixture was stirred at rt for 3.5 hours and 4-fluorophenyl tosylmethyl isonitrile[4] (0.140 g, 0.48 mmol) was added and the reaction mixture was stirred at rt for 8 hours. The reaction was quenched with the addition of H_2O (5 mL), and the resulting mixture was extracted with EtOAc (4 x 5 mL). The organic phases were combined, washed with H_2O (2 x 5 mL), brine (2 x 5 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (2.0% → 3.5% methanol in CH_2Cl_2 to provide (6S)-2-[4-(4-fluorophenyl)-imidazol-1-yl]-3-methylbut-3-en-1-ol containing residual DMF. The mixture was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.8, 5.6 Hz, 2H, aryl), 7.39 (d, *J* = 1.2 Hz, 1H, imid), 7.02 (app t, *J* = 6.8 Hz, 2H, aryl), 6.91 (d, *J* = 1.2 Hz, 1H, imid.), 5.55 (bs, 1H, O-H), 5.04 (s, 1H, C8-H), 4.90 (s, 1H, C8-H), 4.45 (dd, *J* = 8.4, 3.2 Hz, 1H, C6-H), 4.05 (dd, *J* = 12.0, 3.6 Hz, 1H, C6-CH_2), 3.96 (dd, *J* = 12.0, 8.8 Hz, 1H, C6-CH_2), 1.65 (s, 3H, C7-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J_{C-F} = 244 Hz, aryl), 140.6 (imid.), 140.6 (C7), 137.2 (imid.) 129.8 (aryl), 126.1 (d, J_{C-F} = 8 Hz, aryl), 115.2 (d, J_{C-F} = 22 Hz, aryl), 114.3 (C8), 112.8 (imid.), 64.9 (C6-C), 63.0 (C6), 20.8 (C7-C); ^{19}F NMR (400 MHz, $CDCl_3$) δ -115.3; IR (thin film) 3208, 2941, 2873, 1656, 1494, 1454, 1220 cm^{-1}; HRMS (EI) Calcd for $C_{14}H_{16}FN_2O$ (M+H) 247.1267, found 247.1246; (6S) $[\alpha]^{23}_D$ +52.3° (*c* 1.11, $CHCl_3$), (6R) $[\alpha]^{23}_D$ -46.6° (*c* 1.20, $CHCl_3$).

To a solution of (6S)-2-[4-(4-fluorophenyl)-imidazol-1-yl]-3-methylbut-3-en-1-ol (104 mg (with minor amount of DMF), 0.422 mmol) in CH_2Cl_2 (4 mL) was added *i*Pr_2NEt (255 mg, 1.27 mmol), followed by *tert*-butylchlorodiphenylsilane (255 mg, 0.93 mmol) and a catalytic amount of 4-dimethylaminopyridine. The reaction mixture was stirred at rt for 8 hours, H_2O (5 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with brine (2 x 5 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (30% EtOAc in hexanes) to provide **11** (176 mg, 86% over 2 steps). The enantiomeric excess was determined by chiral HPLC [CHIRALPAK™ AD column, detection at 254 nm, flow rate 1.0 mL/min, 85:15 hexane:*i*PrOH → 75:25 hexane:*i*PrOH, T_r(R) 5.2 min. and T_r(S) 6.9 min.] providing the enantiomeric ratio: 6R:6S = 99.3:0.7 (98.6% ee) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.69 (m, 2H, aryl), 7.63-7.59 (m, 3H, aryl, imid.), 7.52-7.49 (m, 2H, aryl), 7.47-7.31 (m, 6H, aryl), 7.15 (d, *J* = 1.2 Hz, 1H, imid.), 7.09-7.04 (m, 2H, aryl), 5.05 (s, 1H, C8-H), 4.90 (s, 1H, C8-H), 4.54 (dd, *J* = 7.6, 4.0 Hz, 1H, C6-H), 4.09 (dd, *J* = 10.8, 4.0 Hz, 1H, C6-CH_2), 4.01 (dd, *J* = 10.8, 7.6 Hz, 1H, C6-CH_2), 1.80 (s, 3H, C7-CH_3), 1.04 (s, 9H, OTBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J_{C-F} = 243 Hz, aryl), 141.0 (imid.), 140.7 (C7), 137.4 (imid.), 135.6 (aryl), 135.5 (aryl), 132.8 (aryl), 132.4 (aryl), 130.6 (d, J_{C-F} = 3 Hz, aryl), 129.9 (aryl), 129.9 (aryl), 127.8 (aryl), 127.8 (aryl), 126.2 (d, J_{C-F} = 8 Hz, aryl), 115.3 (d, J_{C-F} = 22 Hz, aryl), 114.6 (C8), 113.6 (imid.), 64.6 (C6-C), 64.0 (C6), 29.7 (OTBDPS), 20.5 (C7-C), 19.1 (OTBDPS); ^{19}F NMR (377 MHz, $CDCl_3$) δ -116.8; IR (thin film) 2931, 1557, 1496, 1471, 1427 1113 cm^{-1}; HRMS (EI) calcd for $C_{30}H_{34}FN_2OSi$ (M+H) 485.2424, found 485.2450; (S) $[\alpha]^{23}_D$ +19.9° (*c* 1.19, $CHCl_3$), (R) $[\alpha]^{23}_D$ -20.3° (*c* 1.06, $CHCl_3$).

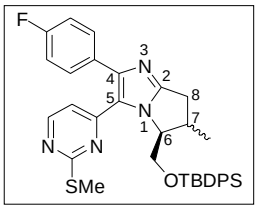
Synthesis of 12:

To a solution of **11** (0.660 g, 1.36 mmol) in toluene (18 mL) in a glove box was added $[RhCl(coe)_2]_2$ (48.8 mg, 0.068 mmol), tricyclohexylphosphine (57.2 mg, 0.204 mmol) and $MgBr_2$ (12.5 mg, 0.068 mmol). The reaction mixture was heated to 180 °C in a sealed high pressure flask for 40 hours, cooled to rt, concentrated and purified by flash silica gel chromatography (25% → 50% EtOAc in hexanes) to provide **12** (402 mg, 61%**)**. The enantiomeric purity was evaluated by chiral HPLC [Daicel Chiracel™ OD column, flow rate 1.0 mL/min, 90:10 hexane:*i*PrOH → 75:25 hexane:*i*PrOH, T_r(6R,7R) 5.73, T_r(6S,7S) 6.33, T_r(6R,7S) 10.44 and T_r(6S,7R) 28.05] providing the enantiomeric ratio: 6R:6S = 4.0:96.0 (92% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.66 (m, 5.25H), 7.48-7.35 (m, 6H), 7.30-7.27 (m, 0.75H), 7.20 (s, 0.75H), 7.08-7.02 (m, 2.25H), 4.12-4.19 (ddd, *J* = 8.0, 4.0, 4.0 Hz, 0.25H), 3.90-3.76 (m, 2.75H), 3.19-3.10 (m, 1H), 3.03 (dd, *J* = 15.2, 8.0 Hz, 0.25H), 2.73-2.65 (m, 1H), 2.51 (dd, *J* = 16.0, 6.4 Hz, 0.75H), 1.29 (d, *J* = 6.8 Hz, 0.75H), 1.19 (d, *J* = 6.8 Hz, 2.25H), 1.08 (s, 6.75H), 1.00 (s, 2.25H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -117.06 (0.75H), -117.17 (0.25H); HRMS (EI) calcd for $C_{30}H_{34}FN_2OSi$ (M+H) 485.2424, found 485.2424.

Synthesis of 13:

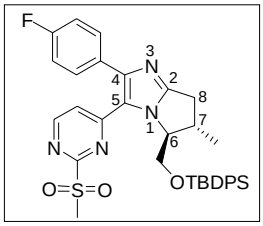


To a solution of **12** (215 mg, 0.440 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added dropwise a cooled solution of Br_2 (73.5 mg, 0.46 mmol) in CH_2Cl_2 (0.5 mL) (*The slow addition of the bromine solution is imperative for optimal yields*). The reaction mixture was stirred for 15 minutes at -78 °C and a saturated aqueous solution of $NaHCO_3$ (5 mL) was added. The reaction mixture was warmed to rt and extracted with CH_2Cl_2 (2 x 5 mL). The organic phases were combined, washed with brine, dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (20% EtOAc in hexanes) to provide 3-bromo-5-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-6-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (238.1 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.90 (m, 2H), 7.63-7.61 (m, 2H), 7.48-7.22 (m, 8H), 7.15-7.09 (m, 2H), 4.18-4.15 (m, 0.25H), 4.04-3.99 (m, 1H), 3.91-3.86 (m, 1.75H), 3.36 (dd, *J* = 16.0, 8.0 Hz, 0.75H), 3.21-3.06 (m, 1.25H), 3.01-2.94 (m, 0.25H), 2.55 (dd, *J* = 16.0, 2.4 Hz, 0.75H), 1.48 (d, *J* = 8 Hz, 0.75H), 1.29 (d, *J* = 8, 2.25H), 0.99 (s, 6.75H), 0.95 (s, 2.25H); HRMS (EI) calcd for $C_{30}H_{33}BrFN_2OSi$ (M+H) 563.1530, found 563.1530.

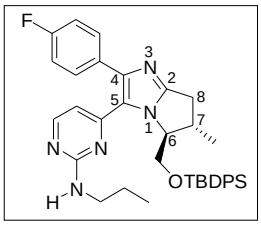


To a solution of 3-bromo-5-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluoro-phenyl)-6-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (0.220 g, 0.390 mmol) in dioxane (6 mL) was added 2-methylsulfanyl-4-trimethylstannanylpyrimidine[5] (0.248 g, 0.860), $Pd_2(dba)_2$•$CHCl_3$ (41.0 mg, 0.040 mmol), triphenylphosphine (21.0 mg, 0.080 mmol), LiCl (50.4 mg, 1.19 mmol), and CuI (33.7 mg, 0.177 mmol). The reaction mixture was heated to 170 °C for 12 hours, cooled to rt, filtered through a pad of celite, concentrated under reduced pressure, and purified by flash chromatography (20% EtOAc in hexanes) to provide 5-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-6-methyl-3-(2-

methylsulfanylpyrimidin-4-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (0.144 g, 66%). HRMS (EI) calcd for $C_{35}H_{38}FN_4OSiS$ (M+H) 609.2520, found 609.2526.



To a solution of 5-(*tert*-Butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-6-methyl-3-(2-methylsulfanylpyrimidin-4-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (50 mg, 0.08 mmol) in THF (2 mL) and H_2O (4 mL) at rt was added OXONE® (196 mg, 0.32 mmol). The reaction mixture was stirred at rt for 8 hours and diluted with EtOAc (6 mL). The reaction mixture was washed with 1 N NaOH (3 mL) and brine (2 x 5 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (50% EtOAc in hexanes) to provide (6S,7S)-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)-6-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (40.4 mg, 77%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 5.6, 1H, pyrim.), 7.60-7.52 (m, 2H, aryl), 7.48-7.47 (m, 2H, aryl), 7.43-7.25 (m, 6H, aryl), 7.23-7.14 (m, 3H, aryl, pyrim.), 7.11-7.08 (m, 2H, aryl), 4.73 (s, 1H, C6-H), 4.04 (dd, J = 11.2, 2.8 Hz, 1H, C6-CH_2), 3.93 (dd, J = 11.2, 1.6 Hz, 1H, C6-CH_2), 3.43 (dd, J = 16.8, 8.4 Hz, 1H, C8-H), 3.17-3.10 (m, 1H, C8-H), 3.07 (s, 3H, SO_2-CH_3), 2.56 (dd, J = 16.8, 1.6 Hz, 1H, C7-H), 1.34 (d, J = 7.2 Hz, 3H, C7-CH_3), 0.91 (s, 9H, OTBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 (pyrim.), 163.1 (d, J_{C-F} = 247 Hz, aryl), 159.3 (pyrim.), 157.9 (imid.), 156.7 (imid.), 151.4 (pyrim.), 135.4 (aryl), 135.3 (aryl), 132.8 (aryl), 132.5 (aryl), 131.1 (d, J_{C-F} = 3 Hz, aryl), 130.6 (d, J_{C-F} = 8 Hz, aryl), 129.8 (aryl), 129.7 (aryl), 127.7 (aryl), 127.4 (aryl), 121.4 (imid.), 118.2 (pyrim.), 116.1 (d, J_{C-F} = 22 Hz, aryl), 68.9 (C6-C), 65.3 (C6), 39.1 (SO_2-C), 38.8 (C8), 32.6 (OTBDPS), 26.6 (C7), 22.0 (C7-C), 18.9 (OTBDPS); ^{19}F NMR (377 MHz, $CDCl_3$) δ -112.6; IR (thin film) 2959, 1573, 1357, 1321, 1137, 1112 cm^{-1}; HRMS (EI) calcd for $C_{35}H_{38}FN_4O_3SiS$ (M+H) 641.2418, found 641.2427; (6S,7S) $[\alpha]^{23}_D$ -161.8° (c 1.61, $CHCl_3$), (6R,7R) $[\alpha]^{23}_D$ +163.0° (c 1.20, $CHCl_3$).

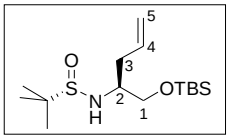


(6S,7S)-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)-6-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (60 mg, 0.09 mmol) was dissolved in propylamine (2 mL) and stirred for 8 hours at rt, concentrated under reduced pressure, and purified by flash chromatography (30% EtOAc in hexanes) to provide (6S,7S)-{4-[5-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-6-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl]-pyrimidin-2-yl}-propylamine (54 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 5.2 Hz, 1H, pyrim.), 5.57-7.53 (m, 4H, aryl), 7.44-7.29 (m, 6H, aryl), 7.26-7.19 (m, 2H, aryl), 7.11-7.05 (m, 2H, aryl), 6.38 (d, J= 5.2 Hz, 1H, pyrim.), 5.01 (bs, 1H, N-H), 4.64 (s, 1H, C6-H), 3.86 (dd, J = 10.4, 3.6 Hz, 1H, C6-CH_2) , 3.77 (dd, J = 10.8, 2.4 Hz, 1H, C6-CH_2), 3.33 (dd, J = 16.4, 8.4 Hz, 1H, C8-H), 3.23-3.08 (m, 3H, C8-H, N-Pr), 2.52 (dd, J = 16.4, 2.0 Hz, 1H, C7-H), 1.47-1.47 (m, 2H, N-Pr), 1.34 (d, J = 7.2 Hz, 3H, C7-CH_3), 0.93 (s, 9H, OTBDPS), 0.88 (t, J = 7.2 Hz, 3H, N-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, J_{C-F} = 246 Hz, aryl), 162.1 (pyrim.), 157.4 (pyrim.), 157.3 (imid.), 156.4 (imid.), 147.7 (pyrim.), 135.3 (aryl), 135.3 (aryl), 133.1 (aryl), 132.2 (aryl), 131.8 (aryl), 130.6 (d, J_{C-F} = 8 Hz, aryl), 129.8 (aryl), 129.7

(aryl), 127.7 (aryl), 127.6 (aryl), 122.8 (imid.), 115.3, (d, $J_{C\text{-}F}$ = 22 Hz, aryl), 107.7 (pyrim.), 67.8 (C6-C), 65.2 (C6), 43.2 (N-Pr), 38.4 (C8), 32.0 (OTBDPS), 22.7 (N-Pr), 26.5 (C7), 22.0 (C7-CH_3), 19.0 (OTBDPS), 11.4 (N-Pr): ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.7; IR (thin film) 3264, 2959, 1569, 1523, 1492, 1112 cm^{-1}; HRMS (EI) calcd for $C_{37}H_{42}FN_5OSi$ (M^+) 619.3142, found 619.3126; (6S,7S) $[\alpha]^{23}_D$ -152.8° (c 1.11, $CHCl_3$), (6R,7R) $[\alpha]^{23}_D$ +150.2° (c 1.08, $CHCl_3$).

To a solution of (6S,7S)-{4-[5-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-6-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl]-pyrimidin-2-yl}-propylamine (33.2 mg, 0.054 mmol) in THF (2 mL) was added tetrabutylammonium fluoride (78.2 mg, 0.216 mmol), and the reaction mixture was stirred at rt for 3 hours. H_2O (4 mL) was added, and the reaction mixture was extracted with EtOAc (3 x 5 mL). The organic phases were combined, washed with brine (5 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (2% *i*PrOH in EtOAc) to provide **13** (17.2 mg, 87%). H^1 NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 5.2 Hz, 1H, pyrim.), 7.58 (dd, *J* = 8.8, 5.6 Hz, 2H, aryl), 7.10 (dd, *J* = 8.8, 8.4 Hz, 2H, aryl), 6.46 (d, *J* = 5.2 Hz, 1H, pyrim.), 5.20-5.17 (m, 1H, N-H), 4.47-4.40 (m, 1H, C6-H), 4.03-4.00 (m, 1H, C6-CH_2), 3.85-3.81 (m, 1H, C6-CH_2), 3.46-3.41 (m, 2H, N-Pr), 3.26 (dd, *J* = 16.4, 7.6 Hz, 1H, C8-H), 2.82-2.78 (m, 1H, C7-H), 2.54 (d, *J* = 16.4 Hz, 1H, C8-H), 1.76-1.64 (m, 2H, N-Pr), 1.64 (bs, 1H, O-H), 1.29 (d, *J* = 7.2 Hz, 3H, C7-CH_3), 1.05 (t, *J* = 7.2 Hz, 3H, N-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, $J_{C\text{-}F}$ = 246 Hz, aryl), 161.7 (pyrim.), 158.0 (pyrim.), 156.9 (imid.), 155.7 (imid.), 147.4 (pyrim.), 131.1 (aryl), 130.5 (d, $J_{C\text{-}F}$ = 9 Hz, aryl), 122.9 (imid.), 115.4 (d, $J_{C\text{-}F}$ = 22 Hz, aryl), 108.4 (imid.), 68.2 (C6-C), 64.6 (C6), 43.3 (N-Pr), 38.8 (C8), 31.2 (N-Pr), 22.8 (C7), 14.1 (C7-C), 11.4 (N-Pr); ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.3; IR (thin film) ; HRMS (EI) calcd for $C_{21}H_{25}FN_5O$ (M+H) 382.2043, found 382.2050; (6S,7S) $[\alpha]^{23}_D$ -107.8° (*c* 0.71, $CHCl_3$), (6R,7R) $[\alpha]^{23}_D$ +101.9° (*c* 1.29, $CHCl_2$).

Synthesis of 14:

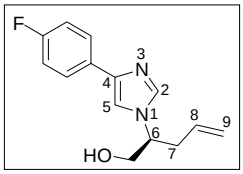


To a solution of **5** (2.00 g, 7.21 mmol) in CH_2Cl_2 (30 mL) cooled to -78 °C was added drop wise allylmagnesium bromide (1.0 M in ether, 14.4 mL, 14.4 mmol). The reaction mixture was stirred at -78 °C for 5 hours and slowly warmed to rt. Saturated aqueous NH_4Cl (20 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, washed with brine, dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (20% EtOAc in hexanes) to provide (S_S,S)-2-methylpropane-2-sulfinic acid [1-(*tert*-butyldimethylsilanyloxymethyl)-but-3-enyl]-amide (2.12 g, 92%) as a single diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81-5.75 (m, 1H, C4-H), 5.17-5.12 (m, 2H, C5-H), 3.66 (dd, *J* = 10.0, 4.4 Hz, 1H, C1-H), 3.53 (dd, *J* = 9.6, 5.2 Hz, 1H, C1-H), 3.49 (d, *J* = 6.4 Hz, 1H, N-H), 3.38-3.30 (m, 1H, C2-H), 2.55-2.48 (m, 1H, C3-H), 2.43-2.36 (m, 1H, C3-H), 1.20 (s, 9H, SO*t*Bu), 0.90 (s, 9H, OTBS), 0.05 (s, 6H, OTBS); ^{13}C (100 MHz, $CDCl_3$) δ 134.3 (C4), 118.5 (C5), 64.9 (C1), 56.4 (C2), 55.8 (SO*t*Bu), 37.0 (C3), 25.8 (SO*t*Bu), 22.5 (OTBS), 18.2 (OTBS), -5.5 (OTBS), -5.5 (OTBS); IR (thin film) 3222, 2955, 2857, 1640, 1472, 1254, 1058 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{34}NO_2S$

(M+H) 320.2080, found 320.2085; (S_S,S) $[\alpha]^{23}_D$ +57.8° (*c* 1.15, $CHCl_3$), (R_S,R) $[\alpha]^{23}_D$ -56.8° (*c* 1.02, $CHCl_3$).

To a solution of (S_S,S)-2-methylpropane-2-sulfinic acid [1-(*tert*-butyldimethylsilanyloxymethyl)-but-3-enyl]-amide (1.72 g, 5.38 mmol) in methanol (20 mL) at 0 °C was added 4N HCl in dioxane (6.73 mL, 26.9 mmol). The reaction mixture was warmed to rt and stirred for 2 hours, concentrated under reduced pressure and the resulting oil was washed with ether (20 mL) revealing a yellow solid. The solid was washed with ether (2 x 30 mL) and residual solvent was removed under reduced pressure providing **14** (0.70 g, 94%) as a white solid that was used without further purification. ^{1}H NMR (400 MHz, CD_3OD) δ 5.78-5.68 (m, 1H, C4-H), 5.18-5.11 (m, 2H, C5-H), 3.67 (dd, *J* = 11.6, 3.6 Hz, 1H, C1-H), 3.47 (dd, *J* = 11.6, 6.8 Hz, 1H, C1-H), 3.19-3.14 (m, 1H, C2-H), 2.39-2.52 (m, 2H, C3-H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.5 (C4), 150.4 (C5), 92.1 (C1), 84.1 (C2), 65.0 C3); (S) $[\alpha]^{25}_D$ +14.1° (*c* 0.64, CH_3OH), (R) $[\alpha]^{25}_D$ -12.2 (*c* 1.09, CH_3OH).

Synthesis of 15:



To a solution of **14** (0.287 g, 2.09 mmol) in DMF (10 mL) was added glyoxylic acid monohydrate (0.165 g, 1.79 mmol) followed by K_2CO_3 (1.10 g, 7.94 mmol). The reaction mixture was stirred at rt for 3.5 hours and 4-fluorophenyl tosylmethyl isonitrile[4] (0.430 g, 1.49 mmol) was added, and the reaction mixture was stirred at rt for 8 hours. The reaction was quenched with the addition of H_2O (10 mL) and the resulting mixture was extracted with EtOAc (4 x 10 mL). The organic phases were combined, washed with H_2O (2 x 10 mL), brine (2 x 10 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (2.0% → 3.5% methanol in CH_2Cl_2 to provide (S)-2-[4-(4-fluorophenyl)-imidazol-1-yl]-pent-4-en-1-ol with residual DMF as a minor impurity. This sample was carried forward without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.41 (m, 2H, aryl), 7.31 (d, *J* = 1.2 Hz, 1H, imid.), 7.03-6.98 (m, 2H, aryl), 6.87 (d, *J* = 0.8 Hz, 1H, imid.), 5.63-5.53 (m, 1H, C8-H), 5.30 (bs, 1H, O-H), 5.07-5.00 (m, 2H, C9-H), 4.05-3.98 (m, 1H, C6-H), 3.80 (dd, *J* = 12.0, 3.2 Hz, 1H, C6-CH_2), 3.72 (dd, *J* = 12.4, 8.0 Hz, 1H, C6-CH_2), 2.54-2.39 (m, 2H, C7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, J_{C-F} = 244 Hz, aryl), 140.5 (imid.), 136.7 (imid.), 132.5 (C8), 128.7 (d, J_{C-F} = 3 Hz, aryl), 126.0 (d, J_{C-F} = 8 Hz, aryl), 118.7 (C9), 115.2 (d, J_{C-F} = 21 Hz), 112.1 (imid.), 64.8 (C6-C), 61.0 (C6), 35.5 (C7); ^{19}F NMR (377 MHz, $CDCl_3$) δ -116.2; IR (thin film) 3226, 2837, 1639, 1550, 1221 cm^{-1}; HRMS calcd for $C_{14}H_{16}FN_2O$ (M+H) 247.1247, found 247.1243; (S) $[\alpha]^{23}_D$ +28.8° (*c* 1.04, $CHCl_3$), (R) $[\alpha]^{23}_D$ -29.6°.

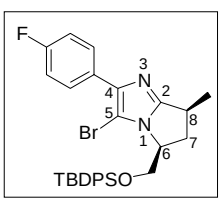
To a solution of (S)-2-[4-(4-fluorophenyl)-imidazol-1-yl]-pent-4-en-1-ol (1.49 mmol) in CH_2Cl_2 (5 mL) was added *i*Pr_2NEt (0.577 g, 4.47 mmol), followed by *tert*-butylchlorodiphenylsilane (0.90 g, 3.29 mmol) and a catalytic amount of 4-dimethylaminopyridine. The reaction mixture was stirred at rt for 8 hours, H_2O (5 mL) was added, and then the reaction mixture was extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with brine (2 x 5 mL), dried with Na_2SO_4, filtered,

concentrated under reduced pressure, and purified by flash chromatography (20% EtOAc in hexanes) to provide **15** (0.566 g, 78% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.69 (m, 2H, aryl), 7.57-7.50 (m, 5H, aryl, imid.), 7.44-7.40 (m, 2H, aryl), 7.37-7.31 (m, 4H, aryl), 7.18 (d, *J* = 0.8 Hz, 1H, imid.), 7.09-7.05 (m, 2H, aryl), 5.69-5.59 (m, 1H, C8-H), 5.12-5.05 (m, 2H, C9-H), 4.15-4.08 (m, 1H, C6-H), 3.87 (dd, *J* = 10.8, 4.0 Hz, 1H, C6-CH_2), 3.78 (dd, *J* = 10.8, 6.0 Hz, 1H, C6-CH_2), 2.69-2.56 (m, 2H, C7-CH_2), 1.04 (s, 9H, OTBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, $J_{C\text{-}F}$ = 244 Hz, aryl), 141.1 (imid.), 137.0 (imid.), 135.5 (aryl), 135.4 (aryl), 132.8 (C8), 132.6 (aryl), 132.4 (aryl), 130.6 (d, $J_{C\text{-}F}$ = 3 Hz, aryl), 129.9 (aryl), 129.9 (aryl), 127.8 (aryl), 127.8 (aryl), 126.3, (d, $J_{C\text{-}F}$ = 8 Hz, aryl), 118.8 (C9), 115.3 (d, $J_{C\text{-}F}$ = 22 Hz), 113.0 (imid.), 66.0 (C6-C), 59.8 (C6), 35.6 (C7), 26.7 (OTBDPS), 19.1 (OTBDPS); ^{19}F NMR (377 MHz, $CDCl_3$) δ -116.7; IR (thin film) 2931, 1557, 1496, 1471, 1427 1113 cm^{-1}; HRMS (EI) calcd for $C_{30}H_{34}FN_2OSi$ (M+H) 485.2424, found 485.2425; (S) $[\alpha]^{23}_D$ -2.3° (*c* 1.10, $CHCl_3$), (R) $[\alpha]^{23}_D$ +0.9° (*c* 1.27, $CHCl_3$).

Synthesis of 16:

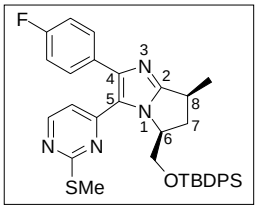
To a solution of **15** (0.05 g, 0.10 mmol) in toluene (1 mL) in a glove box was added $[RhCl(coe)_2]_2$ (3.7 mg, 5.0 μmol), tricyclohexylphosphine (5.8 mg, 21 μmol) and $MgBr_2$ (1.0 mg, 5.0 μmol). The reaction mixture was heated to 180 °C in a sealed high pressure flask for 20 hours, cooled to rt and an additional loading of catalyst ($[RhCl(coe)_2]_2$ (3.7 mg, 5.0 μmol), tricyclohexylphosphine (5.8 mg, 21 μmol) and $MgBr_2$ (1.0 mg, 5.0 μmol) in 0.2 mL toluene) was added. The reaction mixture was heated to 180 °C and stirred for an additional 20 hours, cooled to rt, concentrated and purified by flash silica gel chromatography (25% → 50% EtOAc in hexanes) to provide **16** (26.2 mg, 52%, 92% ee). The enantiomeric purity was evaluated by chiral HPLC [Daicel Chiracel™ OD column, flow rate 1.0 mL/min, 90:10 hexane:*i*PrOH → 75:25 hexane:*i*PrOH, T_r 6.31 (6S,8S) and 19.47 (6R,8R)] providing the enantiomeric ratio: (6S,7S):(6R,7R) = 4.1:95.9 (92% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.63 (m, 6H, aryl), 7.45-7.37 (m, 6H, aryl), 7.21 (s, 1H, imid.), 7.08-7.02 (m, 2H, aryl), 4.38-4.28 (m, 1H, C6-H), 3.85 (dd, *J* = 10.8, 3.6 Hz, 1H, C6-CH_2), 3.76 (dd, *J* = 10.8, 7.6 Hz, 1H, C6-CH_2), 3.31-3.18 (m, 1H, C8-H), 2.77 (ddd, *J* = 13.2, 7.6, 7.6 Hz, 1H, C7-H), 1.79 (ddd, *J* = 12.8, 7.6, 7.6 Hz, 1H, C7-H) 1.39 (d, *J* = 7.2 Hz, 3H, C8-CH_3), 1.09 (s, 9H, OTBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, $J_{C\text{-}F}$ = 244 Hz, aryl), 157.9 (imid.), 145.0 (imid.), 135.7 (aryl), 135.6 (aryl), 132.8 (aryl), 132.7 (aryl), 131.1 (d, $J_{C\text{-}F}$ = 3 Hz, aryl), 130.1 (aryl), 130.0 (aryl) 127.9 (aryl), 127.9 (aryl), 126.4 (d, $J_{C\text{-}F}$ = 8 Hz, aryl), 115.3 (d, $J_{C\text{-}F}$ = 22 Hz, aryl), 110.0 (imid.), 66.7 (C6-C), 58.1 (C6), 37.7 (C8), 30.6 (OTBDPS), 26.9 (C7), 19.3 (C8-C), 19.2 (OTBDPS); ^{19}F (377 MHz, $CDCl_3$) δ -117.07; IR (thin film) 2931, 2858, 1547, 1492, 1428, 1112 cm^{-1}; HRMS (EI) calcd for $C_{30}H_{34}FN_2OSi$ (M+H) 485.2424, found 485.2415; (6S,8S) $[\alpha]^{23}_D$ +18.1° (*c* 3.37, $CHCl_3$), (6R,8R) $[\alpha]^{23}_D$ -19.6° (*c* 2.83, $CHCl_3$).

Synthesis of 17:

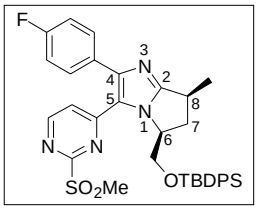


To a solution of **15** (84 mg, 0.17 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added dropwise a cooled solution of Br_2 (0.1 M in CH_2Cl_2, 1.7 mL, 0.17 mmol) in CH_2Cl_2 (17 mL) (*The slow addition of the bromine solution is imperative for optimal yields*). The reaction mixture was

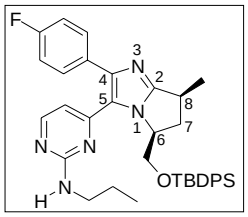
stirred for 15 minutes at -78 °C and a saturated aqueous solution of $NaHCO_3$ (10 mL) was added. The reaction mixture was warmed to rt and extracted with CH_2Cl_2 (2 x 5 mL). The organic phases were combined, washed with brine, dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (20% EtOAc in hexanes) to provide (6S,8S)-3-bromo-5-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-7-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (76.1 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.81 (m, 2H, aryl), 7.65-7.62 (m, 2H, aryl), 7.59-7.57 (m, 2H, aryl), 7.44-7.32 (m, 6H, aryl), 7.09-7.02 (m, 2H, aryl), 4.34-4.29 (m, 1H, C6-H), 4.06 (dd, J = 10.8, 5.6 Hz, 1H, C6-CH_2), 3.95 (dd, J = 10.4, 2.8 Hz, 1H, C6-CH_2), 3.27-3.18 (m, 1H, C8-H), 2.95 (ddd, J = 13.2, 9.2, 9.2 Hz, 1H, C7-H), 2.32 (ddd, J = 13.6, 4.8, 4.8 Hz, 1H, C7-H), 1.43 (d, J = 7.2 Hz, 3H, C8-CH_3), 1.03 (s, 9H, OTBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, $J_{C\text{-}F}$ = 244 Hz, aryl), 158.6 (imid.), 141.7 (imid.), 135.6 (aryl), 135.5 (aryl), 132.9 (aryl), 132.7 (aryl), 129.9 (d, $J_{C\text{-}F}$ = 3 Hz, aryl), 129.9 (aryl), 129.8 (aryl), 129.3 (d, $J_{C\text{-}F}$ = 8 Hz, aryl), 127.9 (aryl), 127.7 (aryl), 115.0 (d, $J_{C\text{-}F}$ = 22 Hz, aryl), 92.8 (imid.), 64.1 (C6-C), 58.1 (C6), 37.2 (C8), 30.5 (OTBDPS), 26.8 (C7), 19.8 (C8-C), 19.2 (OTBDPS); ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.8; IR (thin film) 2959, 2857, 1540, 1113 cm^{-1}; HRMS (EI) calcd for $C_{30}H_{33}BrFN_2OSi$ (M+H) 563.1530, found 563.1543; (6S,8S) $[\alpha]^{23}_D$ +21.7°, (6R,8R) $[\alpha]^{23}_D$ -23.1° (*c* 0.95, $CHCl_3$).



To a solution of (6S,8S)-3-bromo-5-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-7-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (60 mg, 0.11 mmol) in dioxane (3 mL) was added 2-methylsulfanyl-4-trimethylstannanylpyrimidine[5] (67 mg, 0.23 mmol), $Pd_2(dba)_2$•$CHCl_3$ (12 mg, 0.01 mmol), triphenylphosphine (6.0 mg, 0.02 mmol), LiCl (16 mg, 0.37 mmol), and CuI (10 mg, 0.05 mmol). The reaction mixture was heated to 170 °C for 12 hours, cooled to rt, filtered through a pad of celite, concentrated under reduced pressure, and purified by flash chromatography (30% EtOAc in hexanes) to provide (6S,8S)-5-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-7-methyl-3-(2-methylsulfanylpyrimidin-4-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (0.54 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 5.2 Hz, 1H, pyrim.), 7.50-7.46 (m, 4H, aryl), 7.41-7.31 (m, 6H, aryl), 7.26-7.21 (m, 2H, aryl), 7.08 (app t, J = 8.4 Hz, 2H, aryl), 6.64 (d, J = 5.2, 1H, pyrim.), 5.05-5.04 (m, 1H, C6-H), 3.79-3.72 (m, 2H, C6-CH_2), 3.30-3.27 (m, 1H, C8-H), 3.07 (ddd, J = 13.2, 9.2, 9.2 Hz, 1H, C7-H), 2.48 (s, 3H, S-CH_3), 2.36 (ddd, J = 13.2, 4.0, 4.0 Hz, 1H, C8-H), 1.46 (d, J = 7.2 Hz, 3H, C8-CH_3), 0.97 (s, 9H, OTBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3 (pyrim.), 162.6 (d, $J_{C\text{-}F}$ = 241 Hz, aryl), 161.0 (pyrim.), 156.6 (pyrim.), 156.2 (imid.), 148.8 (imid.), 135.4 (aryl), 135.4 (aryl), 132.9 (aryl), 132.5 (aryl), 131.4 (aryl), 130.6 (d, $J_{C\text{-}F}$ = 8 Hz, aryl), 129.8 (aryl), 129.8 (aryl), 127.7 (aryl), 127.6 (aryl), 121.9 (imid.), 115.6 (d, $J_{C\text{-}F}$ = 22 Hz, aryl), 113.0 (pyrim.), 64.9 (C6-C), 59.5 (C6), 37.5 (S-C), 30.0 (C8), 26.7 (OTBDPS), 19.6 (C7), 19.1 (C7-C), 14.0 (OTBDPS); ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.0; IR (thin film) 2959, 1540, 1427 cm^{-1}; HRMS (EI) calcd for $C_{35}H_{38}FN_4OSSi$ (M+H) 609.2520, found 609.2543; (6S,8S) $[\alpha]^{23}_D$ +176.4° (*c* 1.51, $CHCl_3$), (6R,8R) $[\alpha]^{23}_D$ -186.7° (*c* 1.09, $CHCl_3$).



To a solution of (6S,8S)-5-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)-7-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (105 mg, 0.17 mmol) in THF (4 mL) and H_2O (6 mL) at rt was added OXONE® (627 mg, 1.02 mmol). The reaction mixture was stirred at rt for 8 hours and diluted with EtOAc (10 mL). The reaction mixture was washed with 1 N NaOH (6 mL) and brine (2 x 5 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure to provide (6S,8S)-{4-[5-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-7-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl]-pyrimidin-2-yl}-propylamine, which was taken on without purification. The product can be purified by flash chromatography (50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 5.6 Hz, 1H, pyrim.), 7.49-7.36 (m, 5H, aryl), 7.31-7.27 (m, 5H, aryl), 7.18-7.12 (m, 4H, aryl), 7.10 (d, *J* = 5.6 Hz, 1H, pyrim.), 5.16-5.14 (m, 1H, C6-H), 4.01 (dd, *J* = 11.2, 3.6 Hz, 1H, C6-CH_2), 3.80 (dd, *J* = 11.2, 1.6 Hz, 1H, C6-CH_2), 3.38-3.29 (m, 1H, C8-H), 3.13 (ddd, *J* = 13.2, 9.6, 9.6 Hz, 1H, C7-H), 3.08 (s, 3H, SO_2-C), 2.39 (ddd, *J* = 13.2, 4.4, 4.4 Hz, 1H, C7-H), 1.52 (d, *J* = 7.2 Hz, 3H, C8-C), 0.93 (s, 9H, OTBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 (pyrim.), 164.1 (d, J_{C-F} = 243 Hz, aryl), 161.7 (pyrim.), 157.9 (pyrim.), 156.7 (imid.), 151.5 (imid.), 135.3 (aryl), 135.3 (aryl), 132.8 (aryl), 132.6 (aryl), 131.0 (d, J_{C-F} = 4 Hz, aryl), 130.4, (d, J_{C-F} = 8 Hz, aryl), 129.7 (aryl), 129.7 (aryl), 127.7 (aryl), 127.5 (aryl), 121.2 (imid.), 118.4 (pyrim.), 116.0 (d, J_{C-F} = 21 Hz, aryl), 64.6 (C6-C), 60.2 (C6), 39.0 (SO_2-C), 37.4 (C8), 26.7 (OTBDPS), 19.1 (C7), 19.0 (C8-C), 14.1 (OTBDPS); ^{19}F NMR (377 MHz, $CDCl_3$) δ -112.8; IR (thin film) 2959, 1573, 1357, 1321, 1137, 1112 cm^{-1}; HRMS (EI) calcd for $C_{35}H_{38}FN_4O_3SSi$ (M+H), found 641.2421; (6S,8S) $[\alpha]^{23}_D$ +190.4° (*c* 1.06, $CHCl_3$), (6R,8R) $[\alpha]^{23}_D$ -206.1° (*c* 0.98, $CHCl_3$).



(6S,8S)-5-(*tert*-Butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)-7-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (0.17 mmol) was dissolved in propylamine (2 mL) and stirred for 8 hours at rt, concentrated under reduced pressure, and purified by flash chromatography (30% EtOAc in hexanes) to provide (6S,8S)-{4-[5-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-7-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl]-pyrimidin-2-yl}-propylamine (96 mg, 91% over two steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 5.6 Hz, 1H, pyrim.), 7.63-7.48 (m, 4H, aryl), 7.42-7.31 (m, 6H, aryl), 7.25-7.22 (m, 2H, aryl), 7.07-7.02 (m, 2H, aryl), 6.29 (d, *J* = 5.2 Hz, 1H, pyrim.), 5.20-4.95 (m, 2H, C6-H, N-H), 3.81-3.74 (m, 2H, C6-CH_2), 3.34-3.23 (m, 3H, C8-H, N-Pr), 3.06 (ddd, *J* = 12.8, 9.6, 9.6 Hz, 1H, C7-H), 2.35 (ddd, *J* = 13.2, 4.4 Hz, 1H, C7-H), 1.58-1.45 (m, 2H, N-Pr), 1.45 (d, *J* = 6.9 Hz, 3H, C8-C), 0.97 (s, 9H, OTBDPS), 0.90 (t, *J* = 7.6 Hz, 3H, N-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, J_{C-F} = 246 Hz, aryl), 162.1 (pyrim.), 160.2 (pyrim.), 157.4 (pyrim.), 157.3 (imid.), 147.6 (imid.), 135.4 (aryl), 135.3 (aryl), 133.1 (aryl), 132.6 (aryl), 131.7 (d, J_{C-F} = 3 Hz, aryl), 130.7 (d, J_{C-F} = 8 Hz, aryl), 129.7 (aryl), 129.7 (aryl), 127.7 (aryl), 127.6 (aryl), 122.6 (imid.), 115.3 (d, J_{C-F} = 21 Hz, aryl), 108.0 (pyrim.), 65.2 (C6-C), 59.2 (C6), 43.2 (N-Pr), 37.5 (C8), 30.0 (N-Pr), 26.7 (OTBDPS), 23.6 (N-Pr), 19.7 (C7), 19.1 (C8-C), 11.4 (OTBDPS); ^{19}F (377 MHz, $CDCl_3$) δ -114.8; IR (thin film) 3264, 2959, 1569, 1523,

1492, 1112 cm^{-1}; HRMS (EI) calcd for $C_{37}H_{43}FN_5OSi$ (M+H) 620.3221, found 620.3211; (6S,8S) $[\alpha]^{23}_D$ +176.5° (*c* 2.21, $CHCl_3$), (6R,8R) $[\alpha]^{23}_D$ -178.8° (*c* 1.00, $CHCl_3$).

To a solution of (6S,8S)-{4-[5-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-fluorophenyl)-7-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl]-pyrimidin-2-yl}-propylamine (54.0 mg, 0.087 mmol) in THF (2 mL) was added tetrabutylammonium fluoride (1 M THF, 0.17 mL, 0.17 mmol) and the reaction mixture was stirred at rt for 3 hours. H_2O (4 mL) was added, and the reaction mixture was extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with brine (5 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (2% *i*PrOH in EtOAc) to provide **17** (32.8 mg, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 5.2 Hz, 1H, pyrim.), 7.52-7.49 (m, 2H, aryl), 7.07-7.02 (m, 2H, aryl), 6.35 (d, *J* = 5.2 Hz, 1H, aryl), 5.24 (bs, 1H, N-H), 4.80 (bs, 1H, C6-H), 3.94 (dd, *J* = 11.6, 3.6 Hz, 1H, C6-CH_2), 3.82 (dd, *J* = 11.2, 6.4 Hz, 1H, C6-CH_2), 3.41-3.36 (m, 2H, N-Pr), 3.26-3.21 (m, 1H, C8-H), 3.02 (ddd, *J* = 13.2, 9.2, 9.2 Hz, 1H, C7-H), 2.06-2.01 (m, 1H, C8-H), 1.70-1.61 (m, 2H, N-Pr), 1.48 (d, *J* = 7.2 Hz, 3H, C8-CH_3), 1.00 (d, *J* = 7.2 Hz, 3H, N-Pr), 3.00-0.50 (very bs, 1H, O-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.6 (d, J_{C-F} = 246 Hz, aryl), 161.7 (pyrim.), 160.3 (pyrim.), 158.1 (pyrim.), 157.1 (imid.), 147.9 (imid.), 131.2 (aryl), 130.7 (d, *J* = 9 Hz, aryl), 122.6 (imid.), 115.4 (d, J_{C-F} = 21 Hz, aryl), 108.8 (pyrim.), 66.3 (C6-C), 60.5 (C6), 43.3 (N-Pr), 38.4 (C8), 29.9 (N-Pr), 22.8 (N-Pr), 20.1 (C8-C), 11.4 (N-Pr); ^{19}F NMR (377 MHz, $CDCl_3$) δ -113.0; IR (thin film) 3261, 2962, 2872, 1570, 1493, 1221 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{25}FN_5O$ (M+H) 382.2043, found 382.2045; (6S,7S) $[\alpha]^{23}_D$ -172.8 (*c* 0.91, CH_3OH), (6R,7R) $[\alpha]^{23}_D$ +163.9° (*c* 0.59, CH_3OH).

Assay Data

Homogeneous time resolved fluorescence assay

Enzyme inhibition studies were performed in 384-well polystyrene HTRF plates (Grainier) for 15 min at ambient temperature (~ 22 °C) with , 0.2 μM biotinylated GST-ATF2, 1 μM ATP, 0.3 nM activated JNK3α1 (with a control in the absence of kinase for determining the basal signal) in 10 μL volumes containing the final concentrations of the following: 50 mM Hepes, pH 7.0, 2.5 mM $MgCl_2$, 0.1 mg/ml bovine serum albumin, 1 mM DL-dithiothreitol, 0.01% Triton X-100 (all from Sigma-Aldrich), and 5% DMSO (with or without compound). A 10 point titration of all compounds was carried out in 3–fold dilutions from 10pM –2000 nM. After 15 min, the kinase reaction was terminated by addition of 10 μl of quenching solution [50 mM Hepes, pH 7.0, with 14 mM EDTA, 0.01% Triton X-100, 200 mM KF (all from Sigma-Aldrich)]. The detection reagents, streptavidin-xlAPC (400 nM) and europium cryptate-labeled rabbit polyclonal anti-phospho-ATF2 (0.43 ng/well), were from Cis-Bio. The HTRF signal was detected using a viewlux plate reader (Perkin Elmer) 1h post-quenching. The data from four different experiments were averaged and presented as the mean ± standard deviation. IC_{50} values were determined by fitting the data to the equation for a four-parameter logistic.

Compound	IC_{50} curve fit 1 (nM)	IC_{50} curve fit 1 (nM)	IC_{50} curve fit 1 (nM)	IC_{50} curve fit 1 (nM)	Avg. JNK3 IC_{50} (nM)
1	4.47	4.30	7.35	5.40	5.38 ± 1.4
13	3.42	5.82	6.03	5.90	5.29 ± 1.25
ent-13	1.30	1.60	2.09	1.53	1.63 ± 0.34
17	5.10	5.23	5.03	4.06	4.85 ± 0.54
***ent*-17**	5.59	9.87	8.85	8.09	8.10 ± 1.82

Radioactivity Assay Data

Enzyme inhibition studies were performed at 27 °C-32 °C for 60 min with 0.5 μM biotinylated GST-ATF2, 1 μM ATP, 0.5 nM activated JNK3α1 in 50 μL volumes containing the final concentrations of the following: 50mM HEPES (Sigma), pH 7.4, 10 mM $MgCl_2$ (Sigma); 1 mM DTT (Sigma), 2 μCi [γ-^{33}P]ATP (3000 Ci/mmol; 1 Ci = 37 GBq) Amersham). A 10 point titration of all compounds was carried out in 3-fold dilutions from 30pM – 1000 nM. Reactions were stopped by addition of 25 μL 8 M guanidine HCl. Incorporation of [^{33}P]phosphate into biotinylated GST-ATF2 was measured by capture onto streptavidin membrances (SAM^2; Promega) following the manufacturer's instructions and as previously described.[6] 15 μL of stopped reaction was spotted on each 1 cm^2 SAM^3 membrane. Data are from an average of two replicate experiments ± SE. IC_{50} values were determined by fitting the data to the equation for a four-parameter logistic[7] (assay references will be included at the end of the experimental section).

References:

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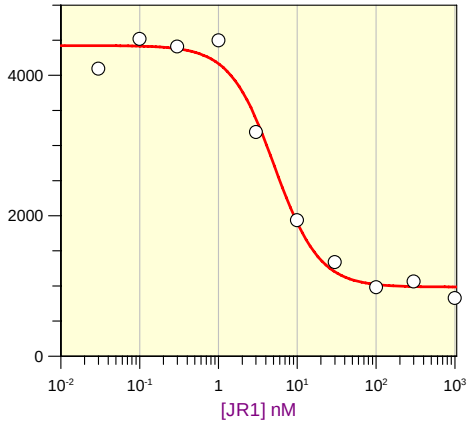
7. Leatherbarrow, R.J. (1992) *GraFit*, Version 3.0, Erithacus Software Ltd. Staines, UK.

1 = JR1



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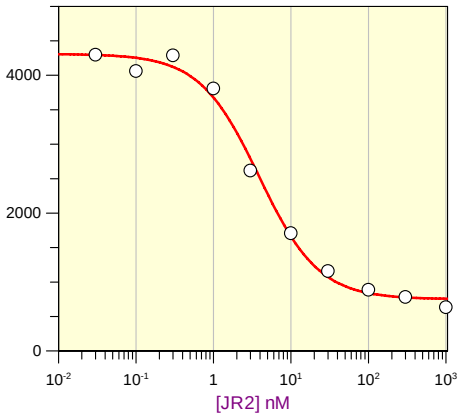
Y Range	3439.4372	202.4983
IC 50	5.1514	0.9244
Slope factor	1.5311	0.3406
Background	984.3799	134.4669

13 = JR2



Parameter	Value	Std. Error
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Slope factor	1.1291	0.1612
Background	751.5210	99.1372

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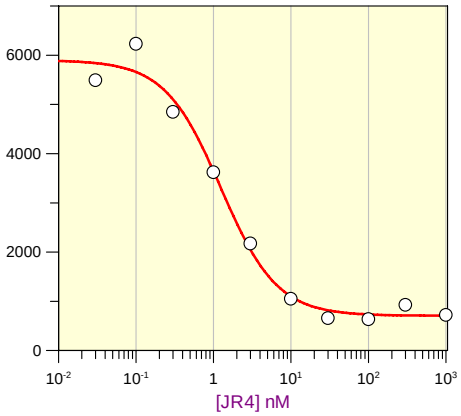

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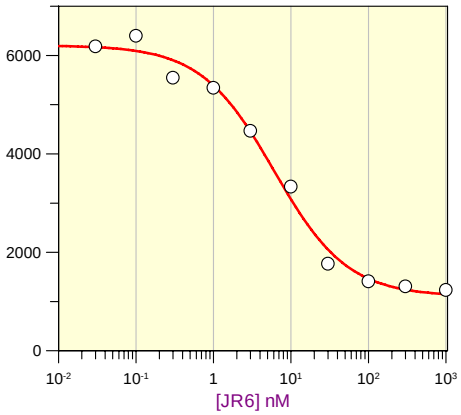
17 = JR6



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Slope factor	0.9193	0.1640
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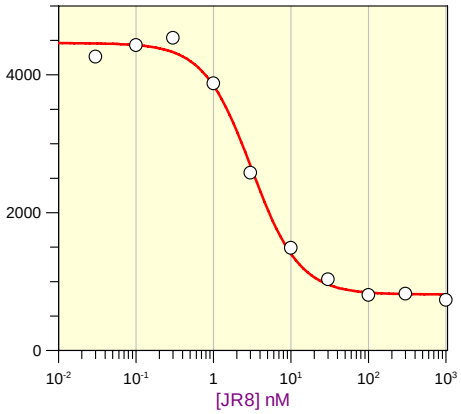
***ent*-17 = JR8**



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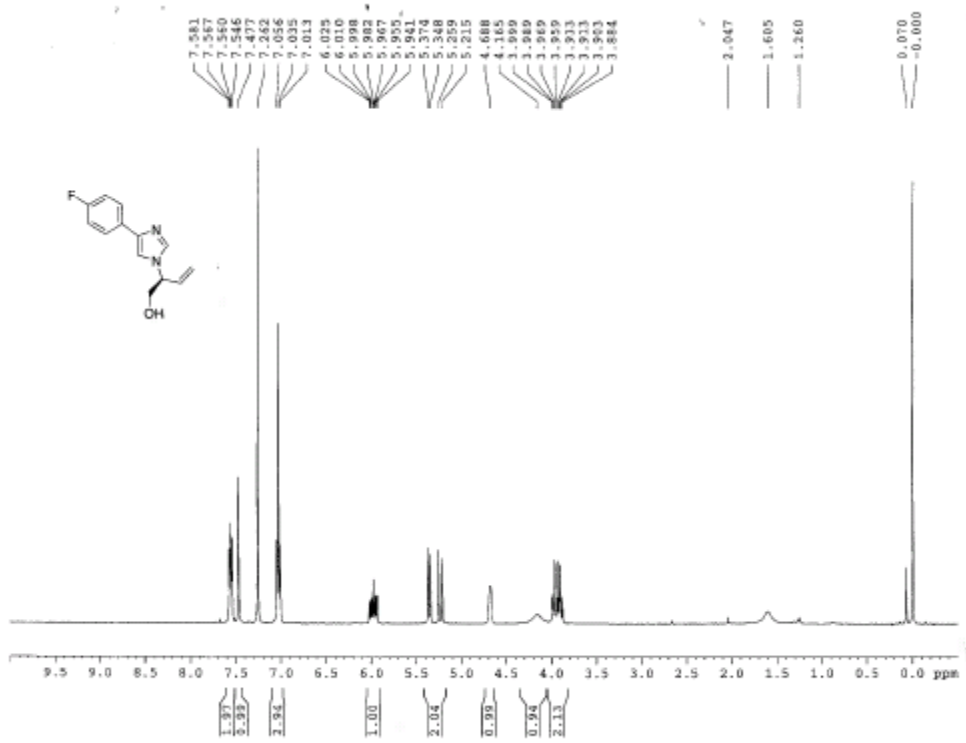
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N
N
OH
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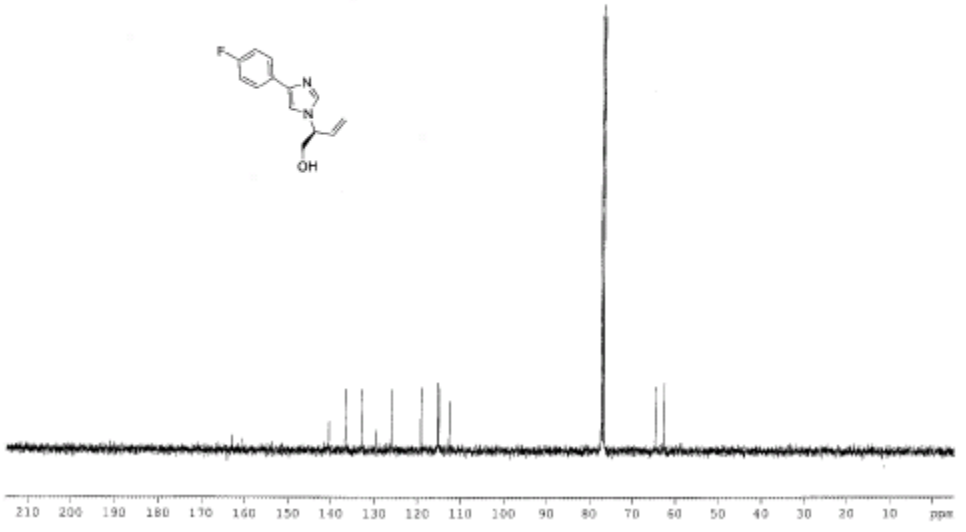
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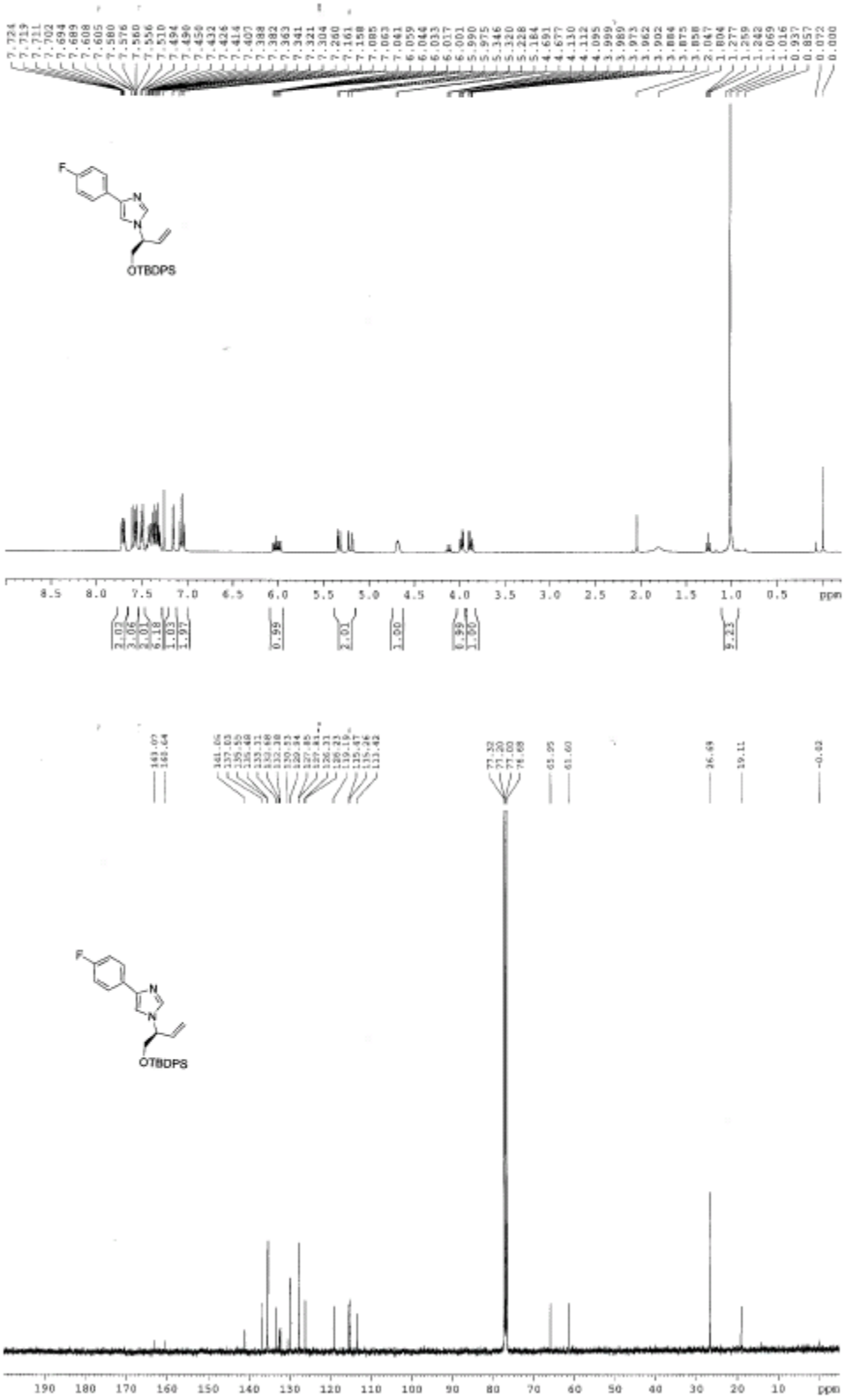
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N
OTBDPS
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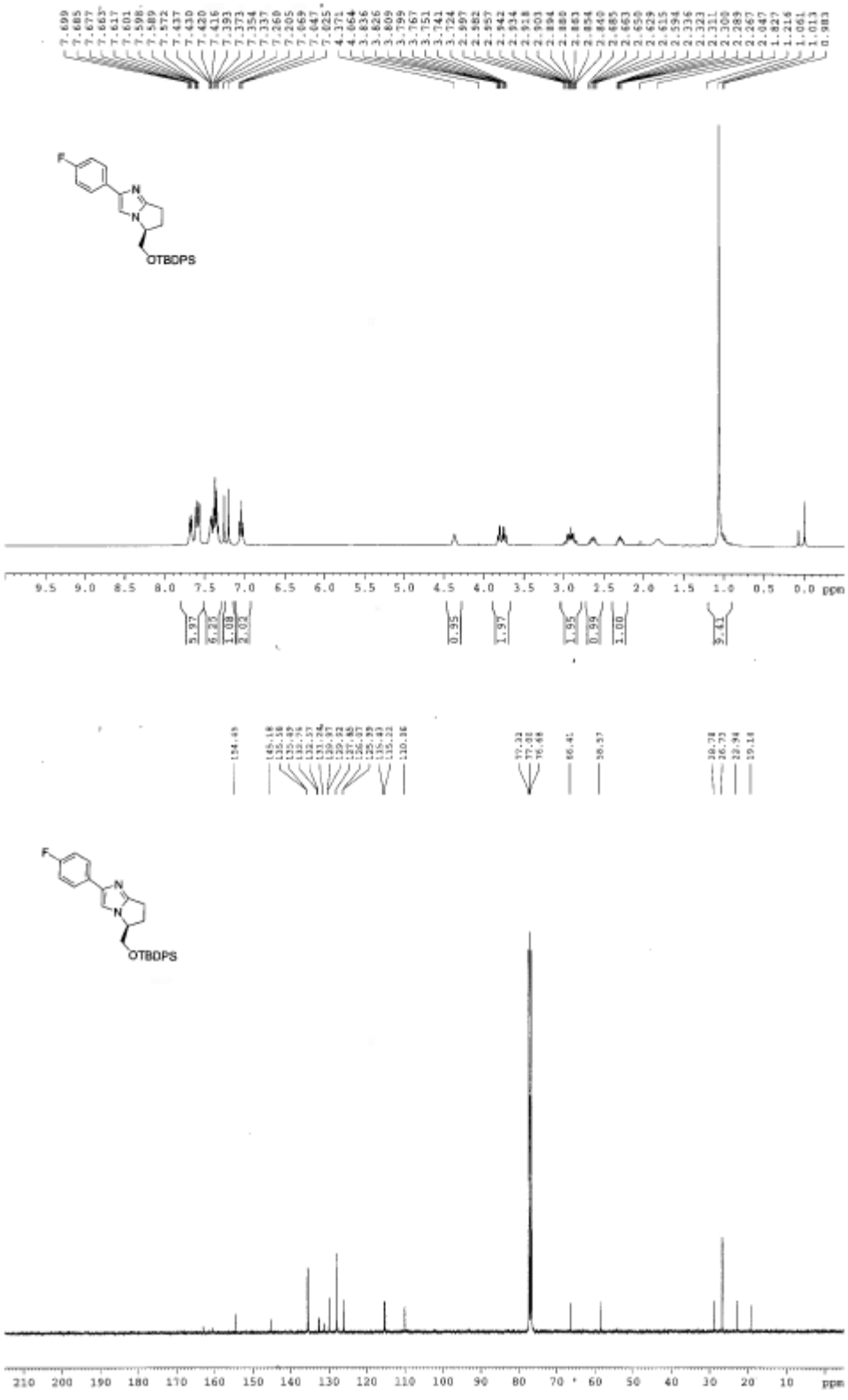
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N
N
OTBDPS
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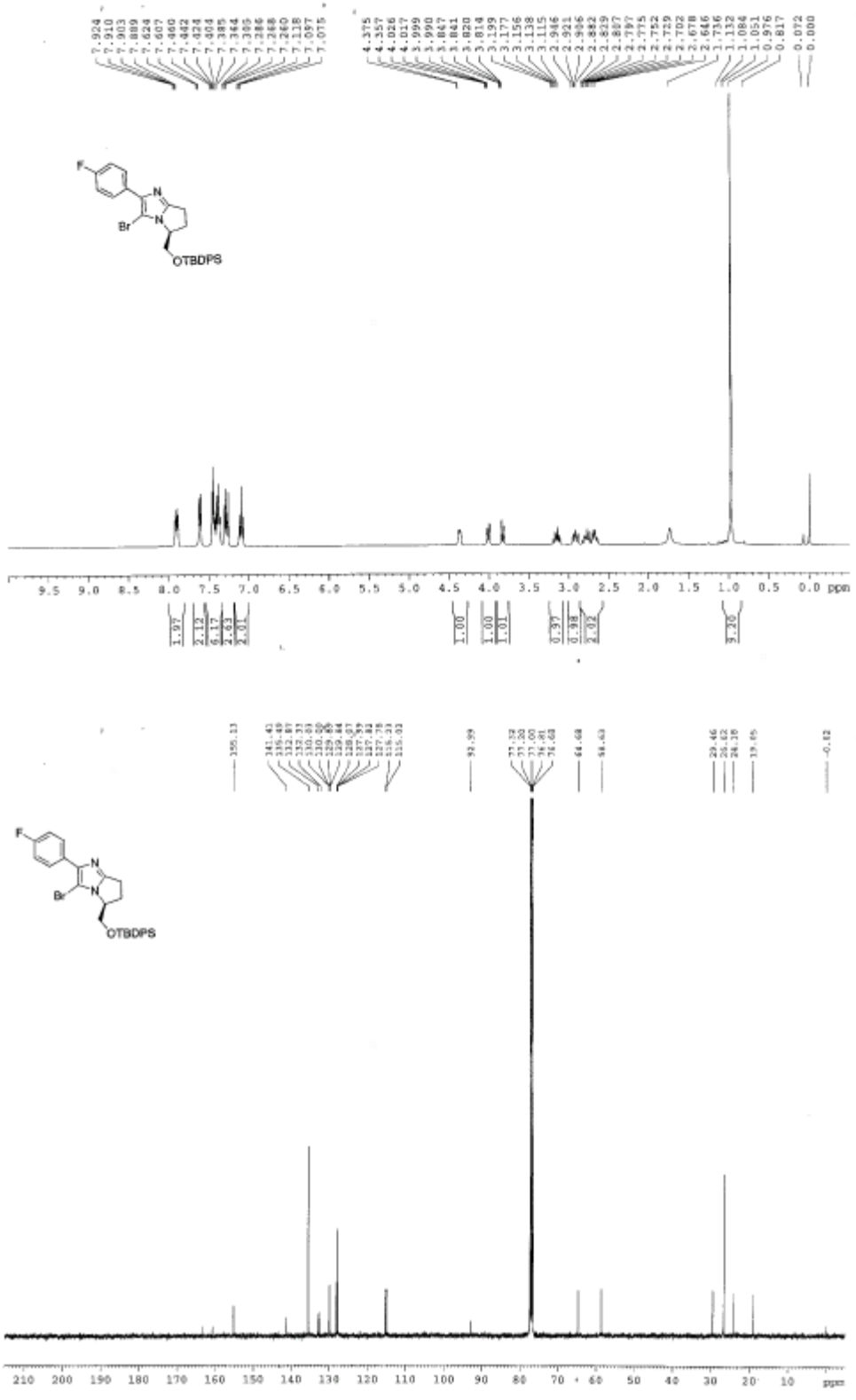
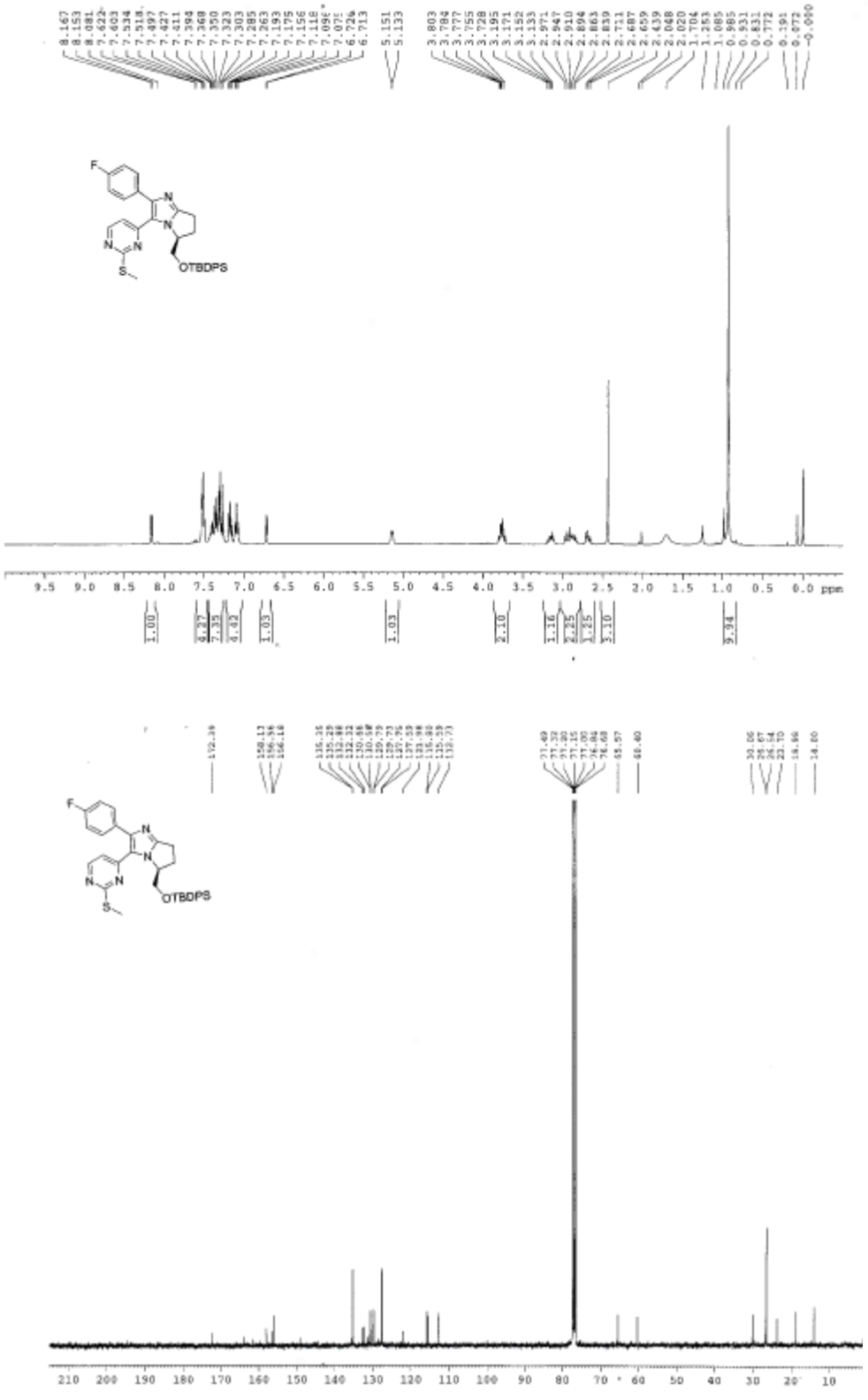
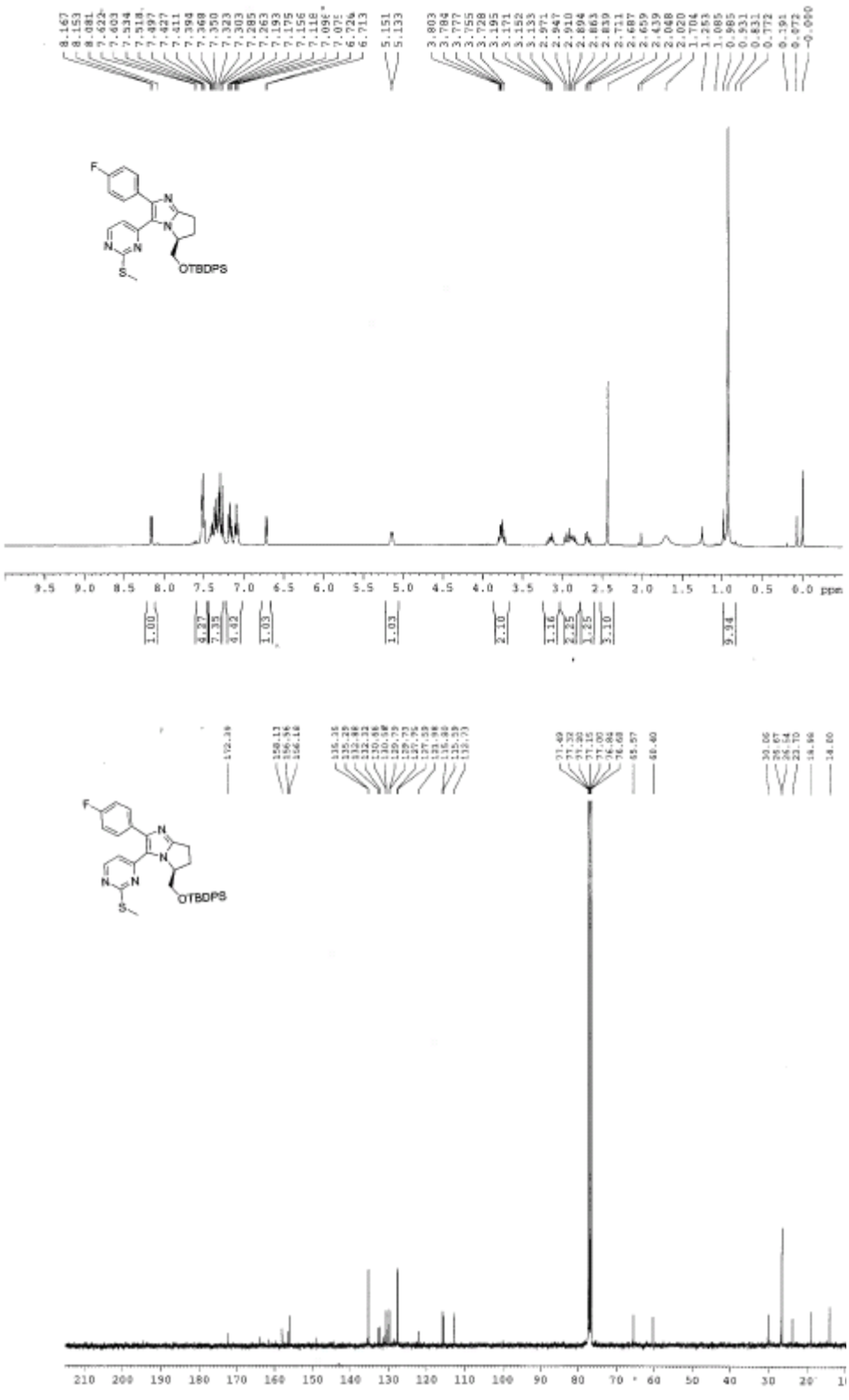
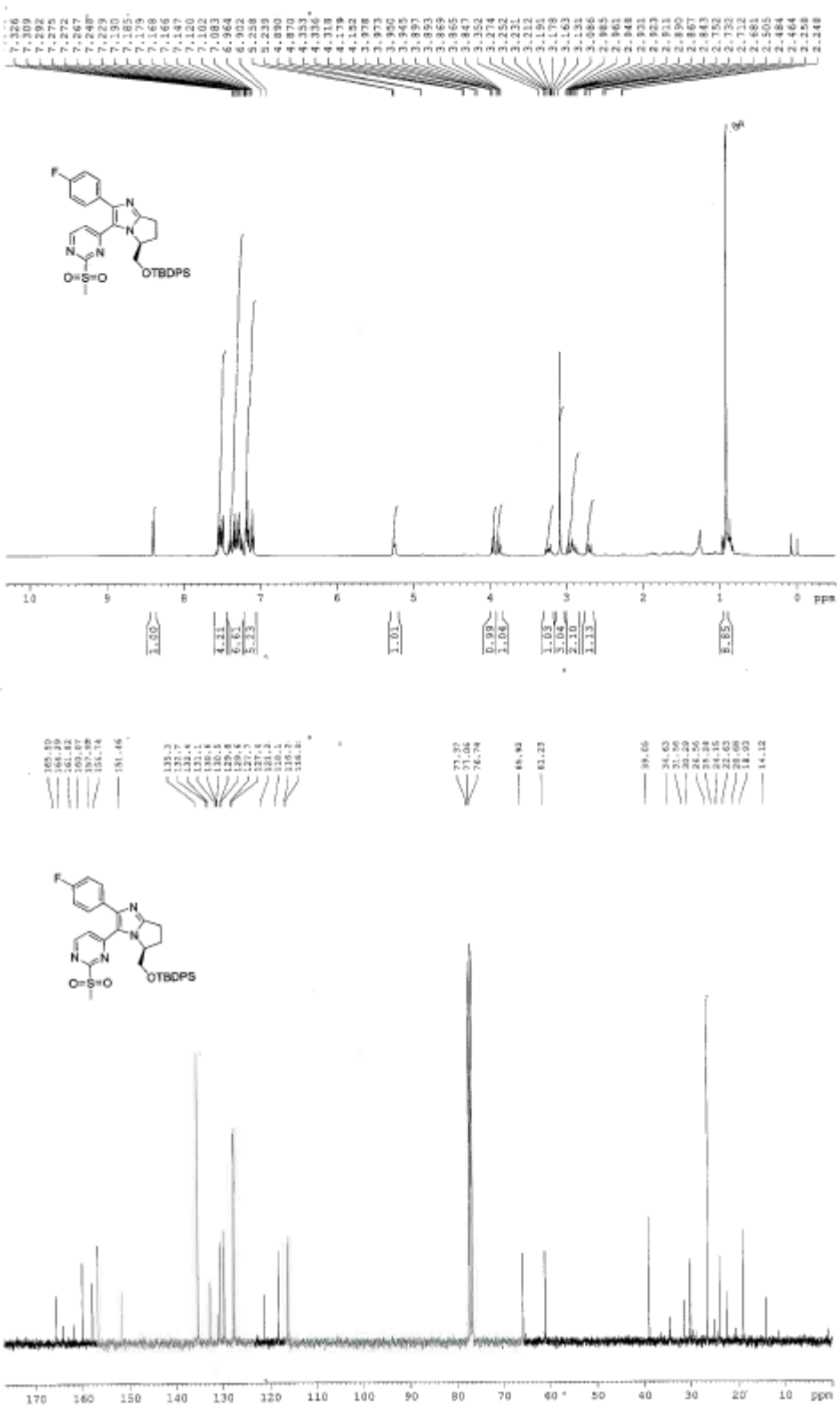
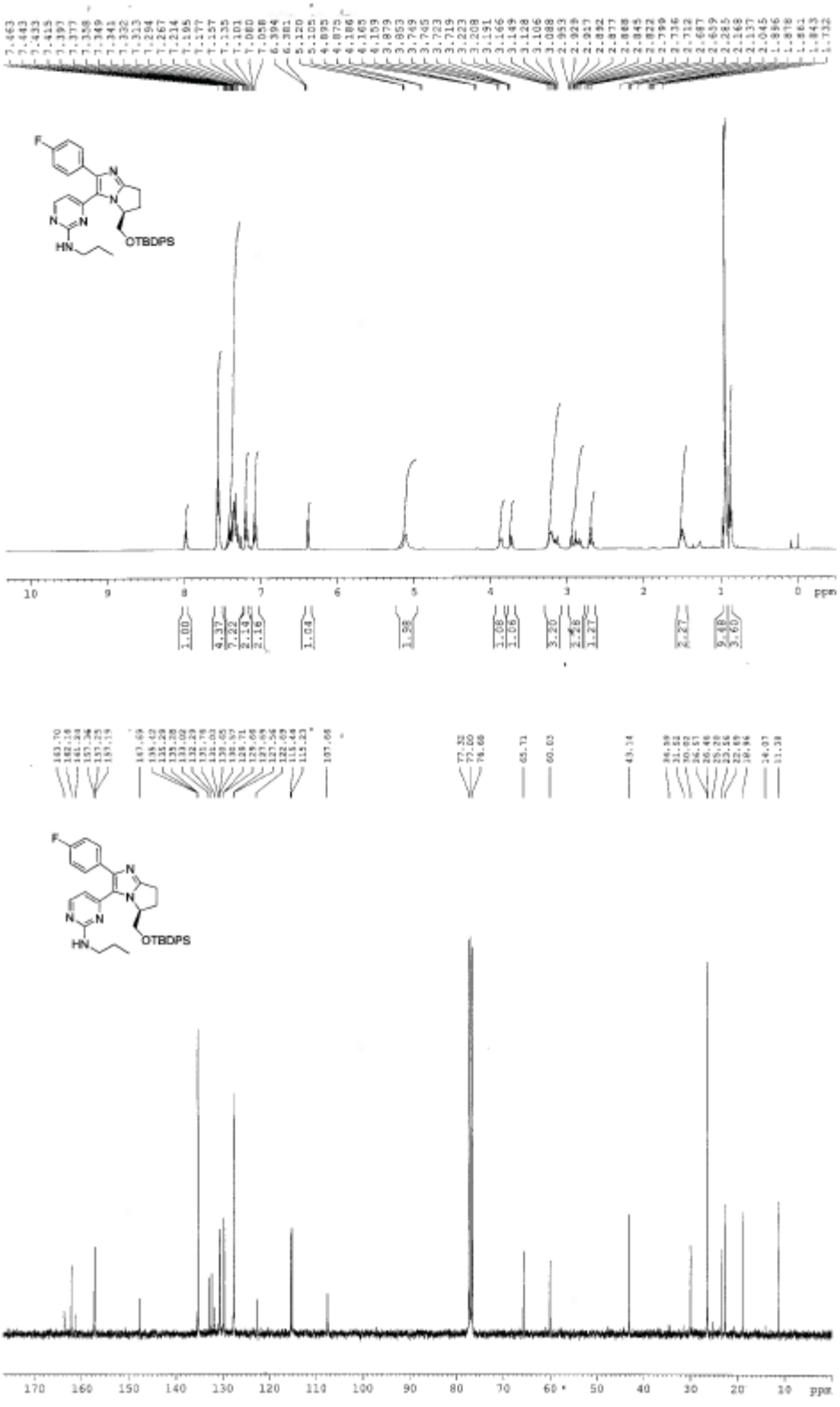
5.97
6.20
1.08
8.02
0.95
1.97
1.95
0.99
1.00
9.41
F
N
N
OTBDPS
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

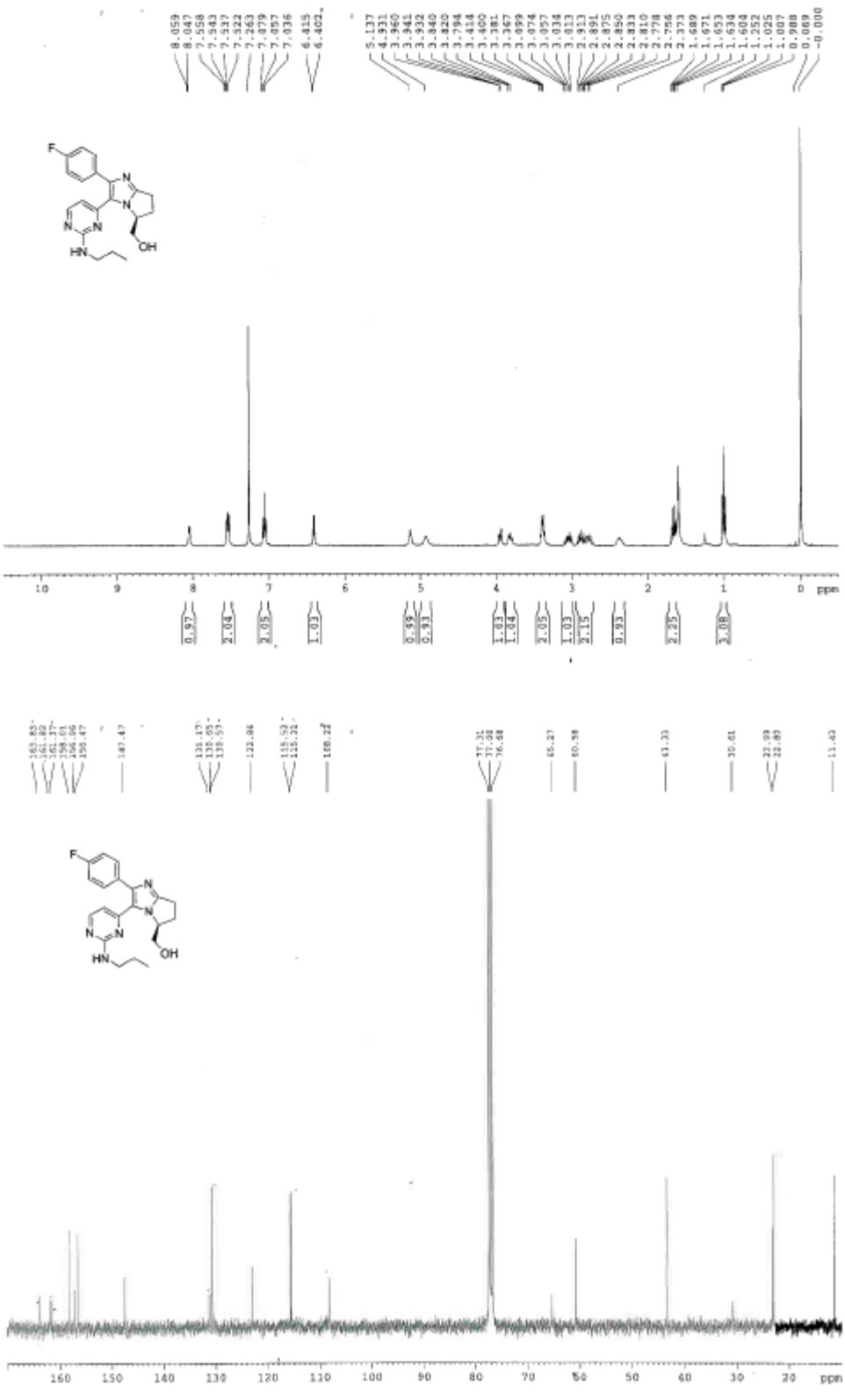

F
N
Br
N
OTBDPS
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
F
N
Br
N
OTBDPS
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

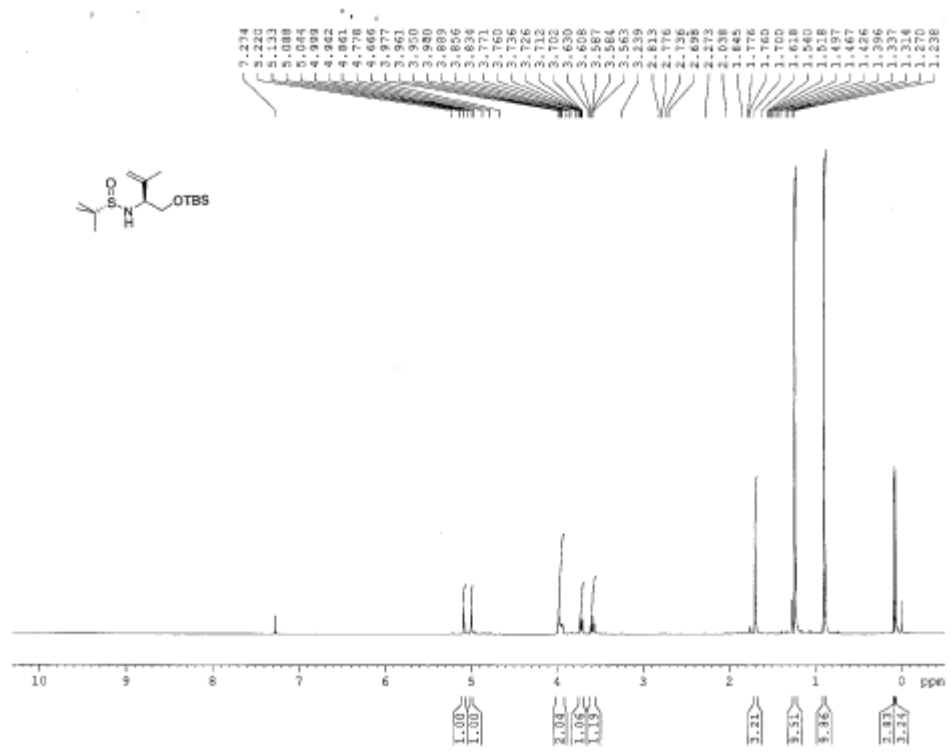

F
N
N
N
S
OTBDPS
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

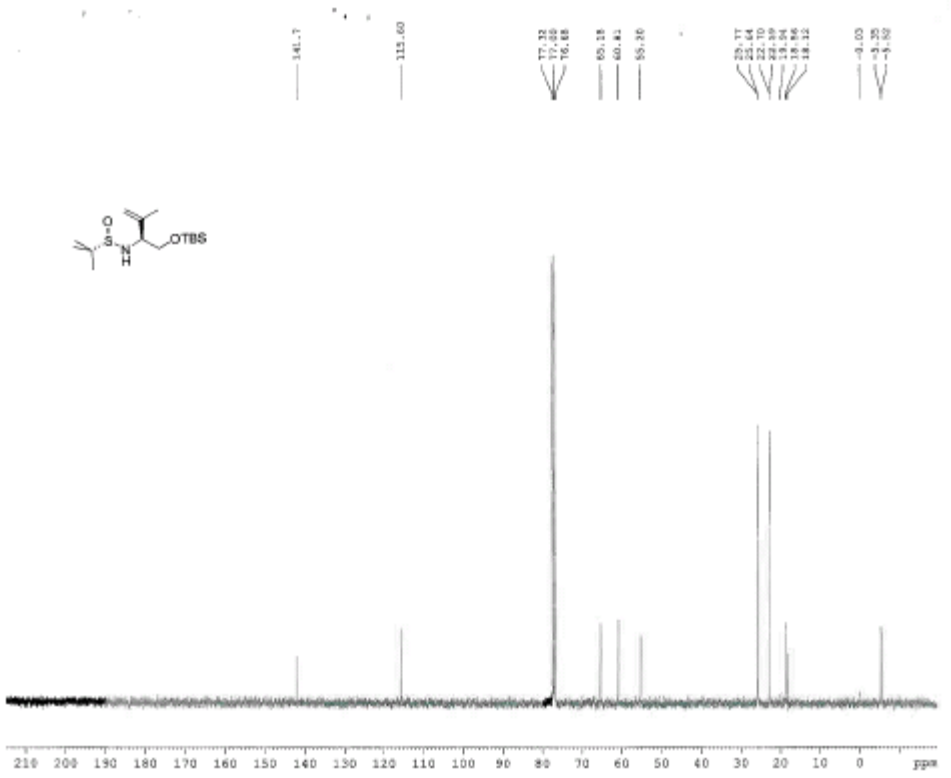

F
N
N
N
S
OTBDPS
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20

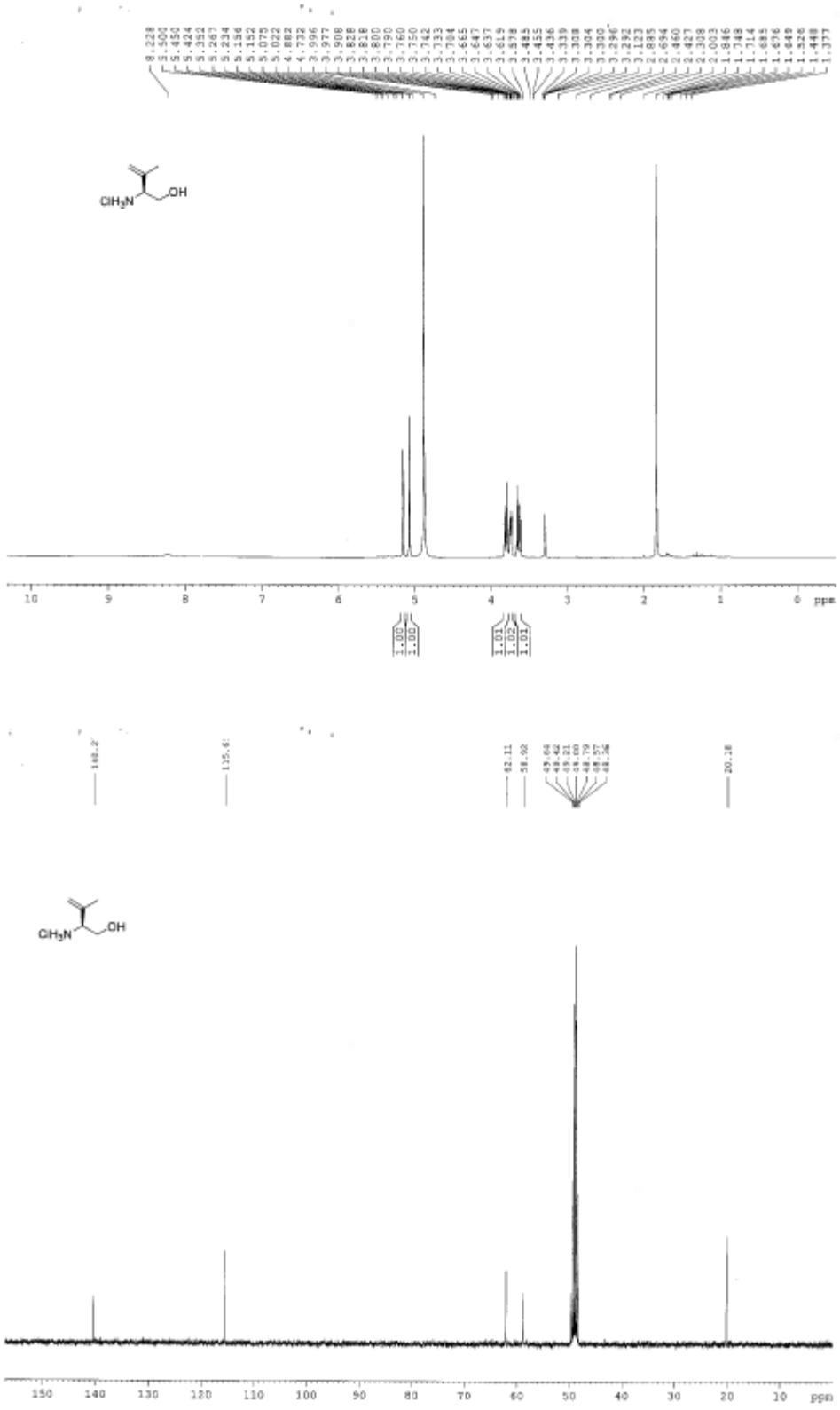

F
N
N
N
O=S=O
OTBDPS
9.85
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
4.21
6.61
5.23
1.01
0.99
1.04
1.05
3.04
2.10
3.13
8.85
77.37
77.06
76.74
65.93
61.23
39.66
34.63
31.56
30.20
28.96
28.34
24.15
22.63
18.08
14.12
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

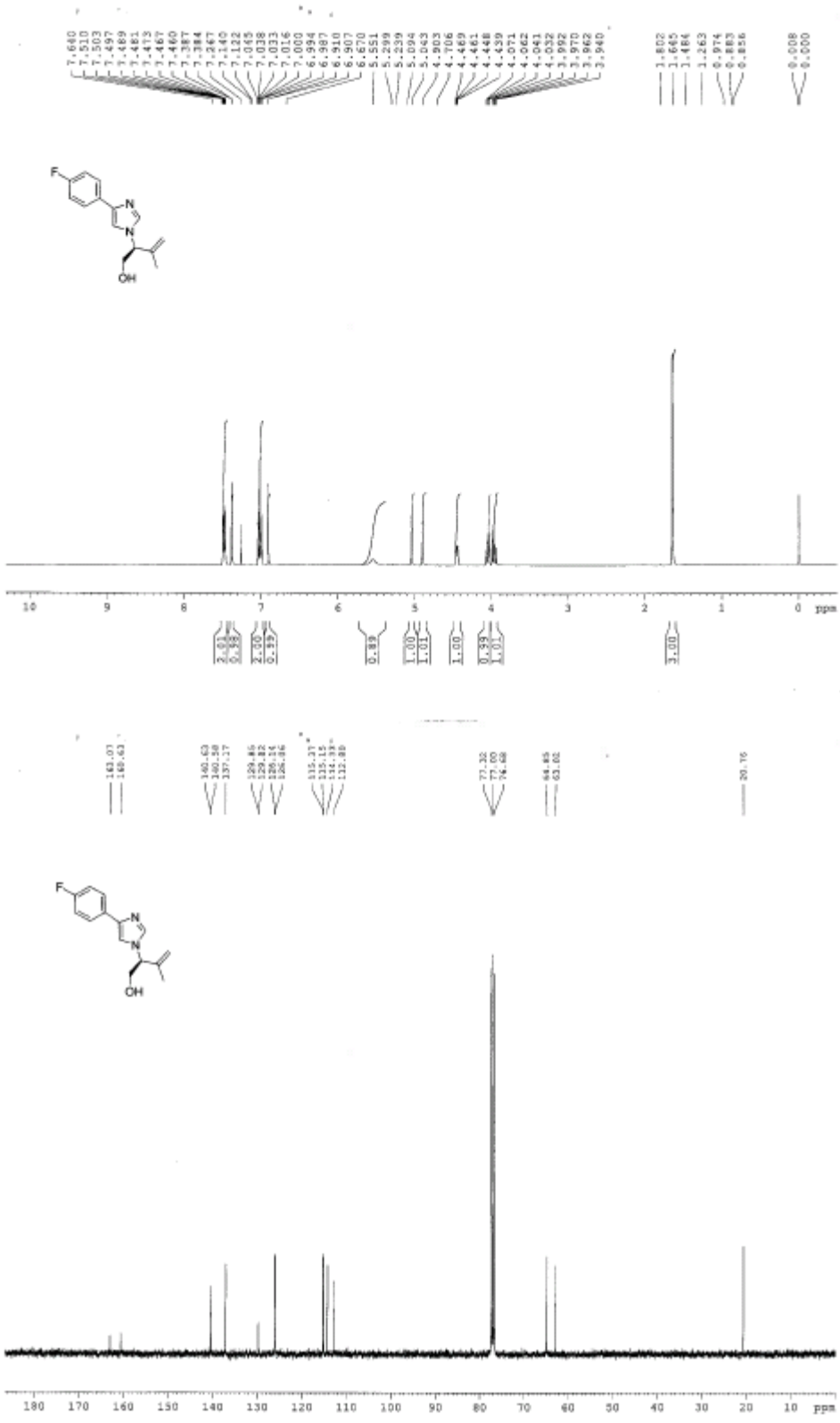

F
N
N
N
HN
OTBDPS
ppm
F
N
N
N
HN
OTBDPS
ppm

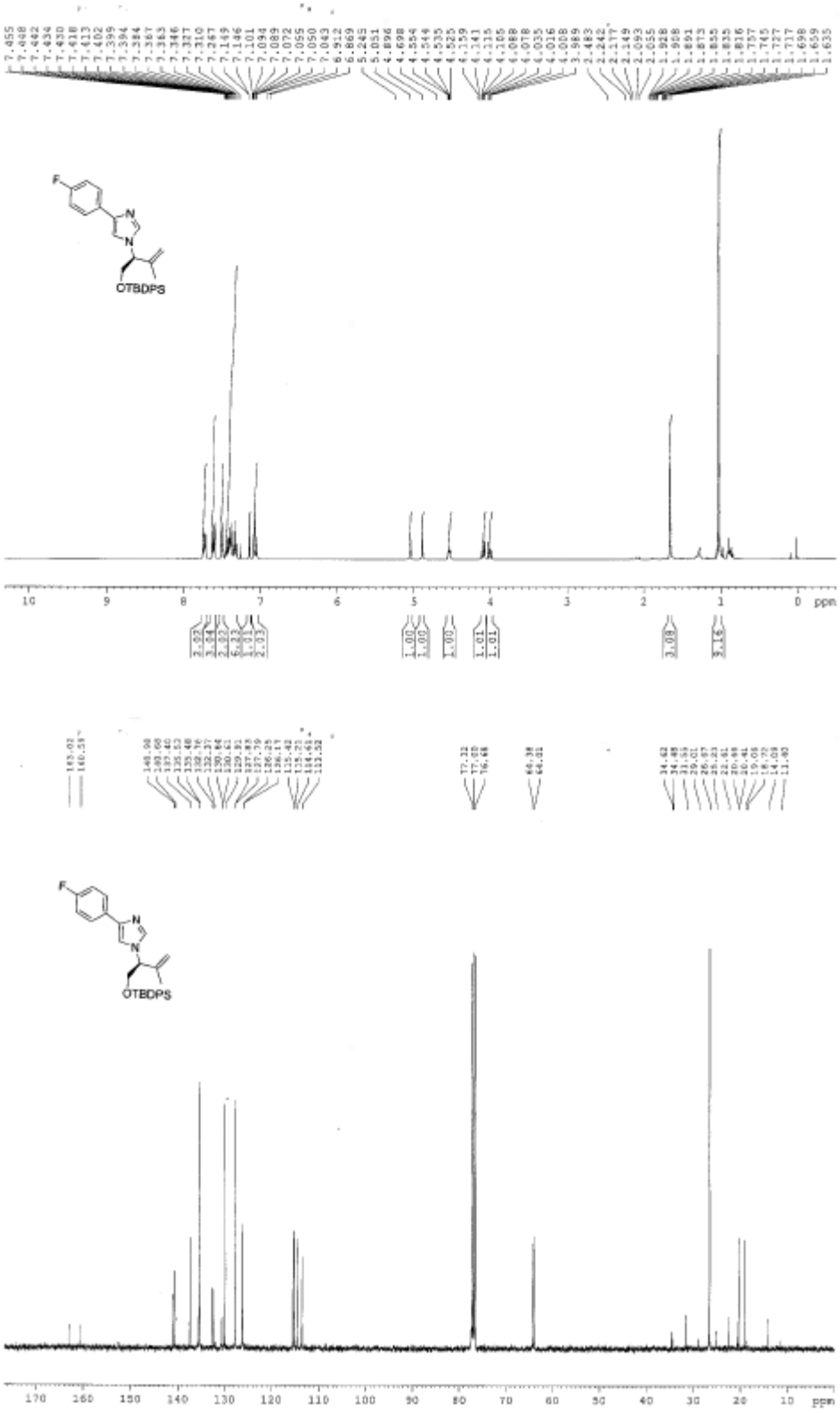


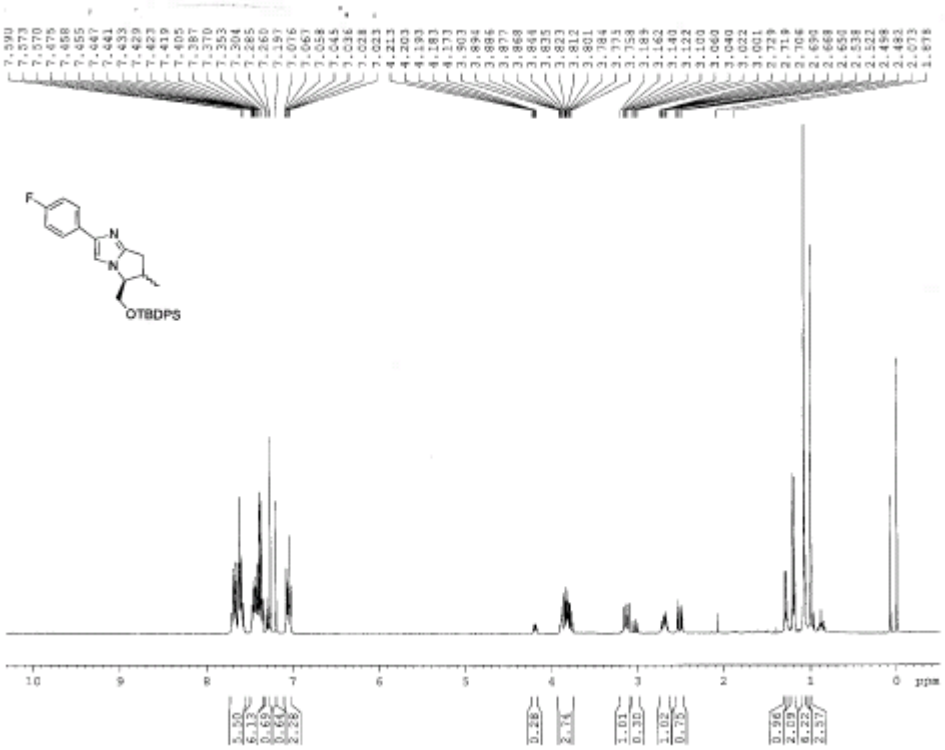

OTBS
ppm

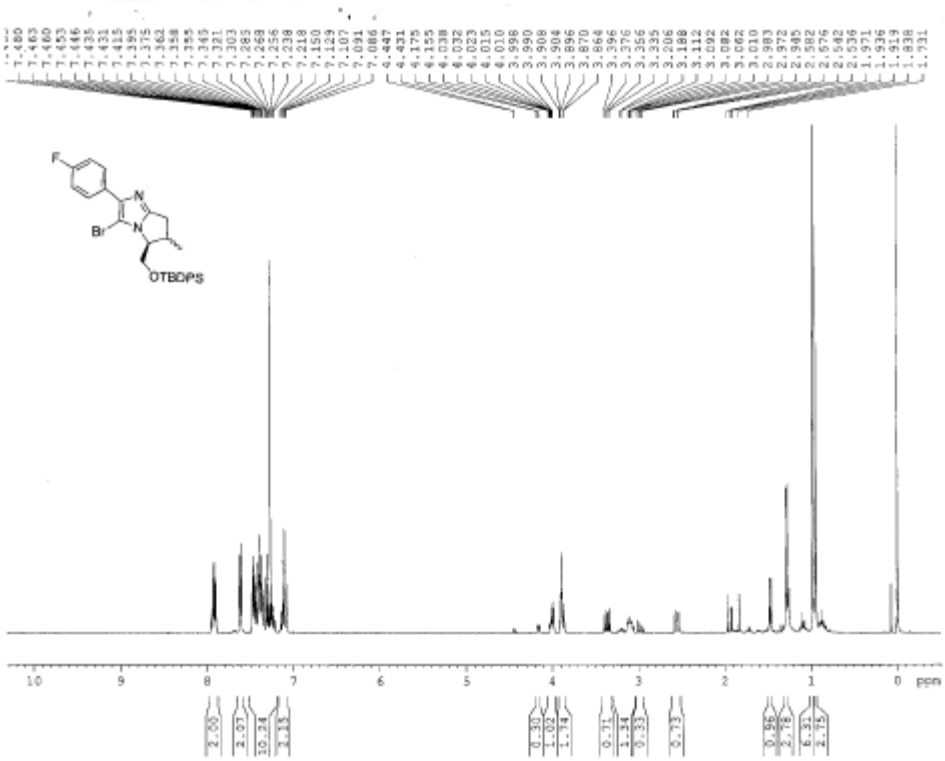

OTBS
ppm

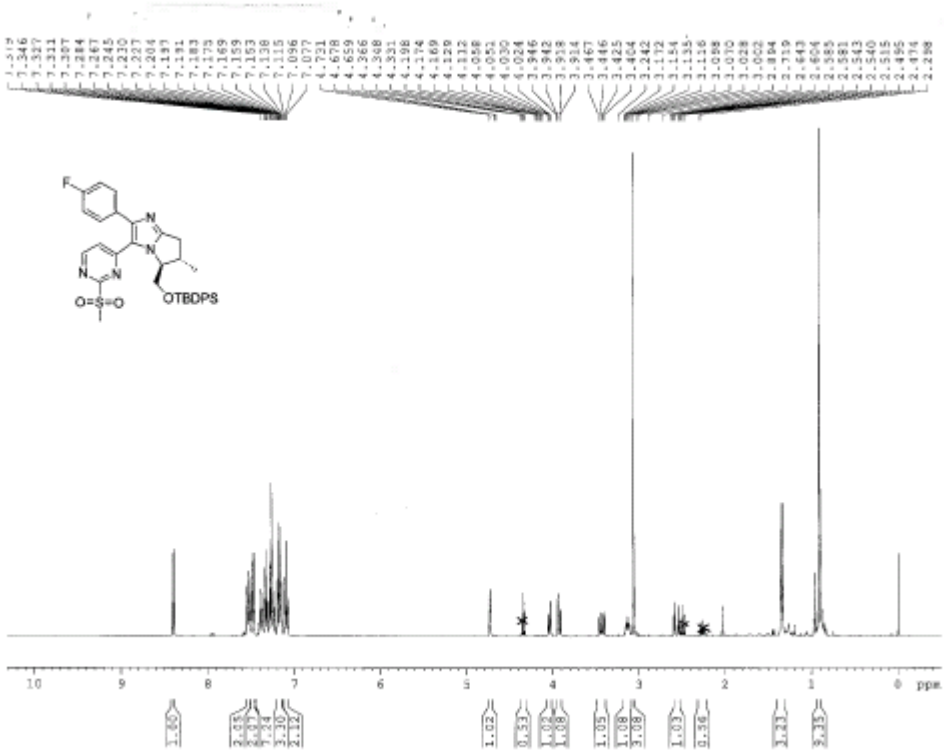


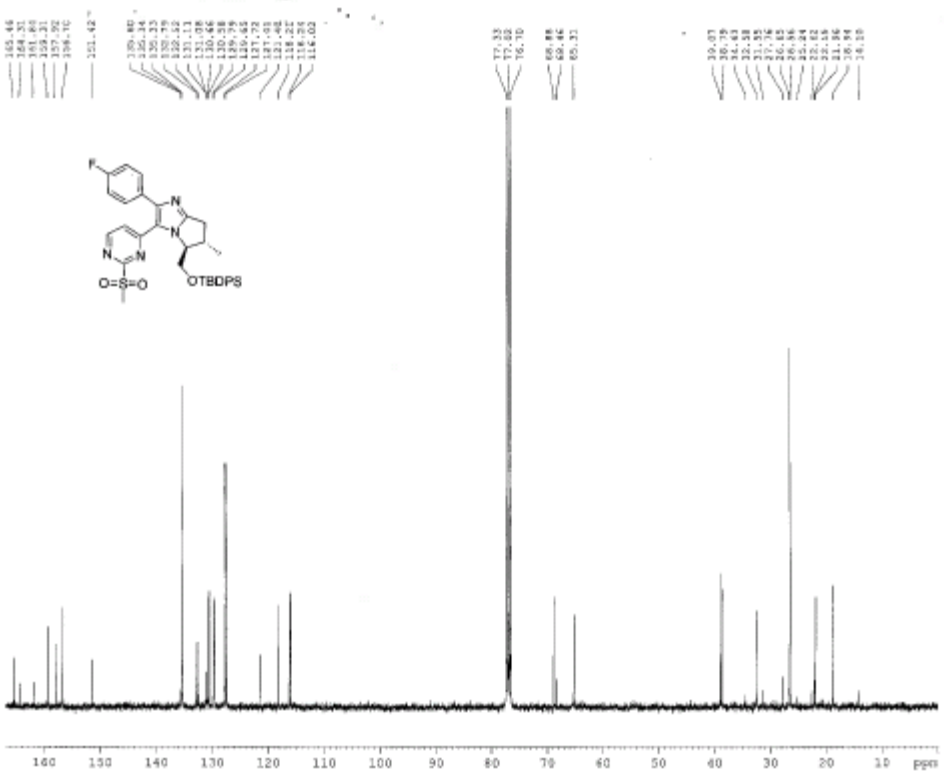


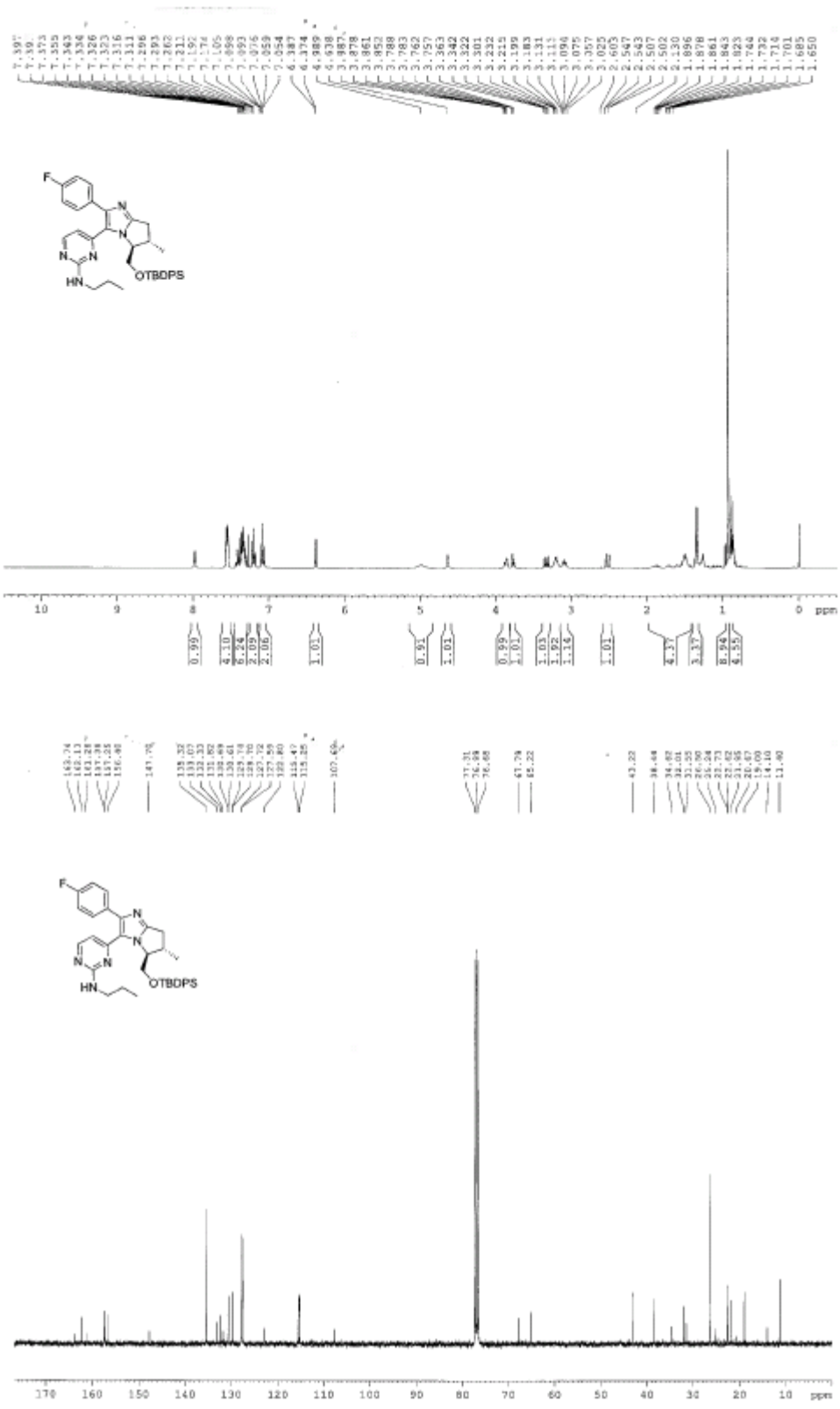

F
N
N
OTBDPS
10
9
8
7
6
5
4
3
2
1
0
ppm
F
N
N
OTBDPS
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

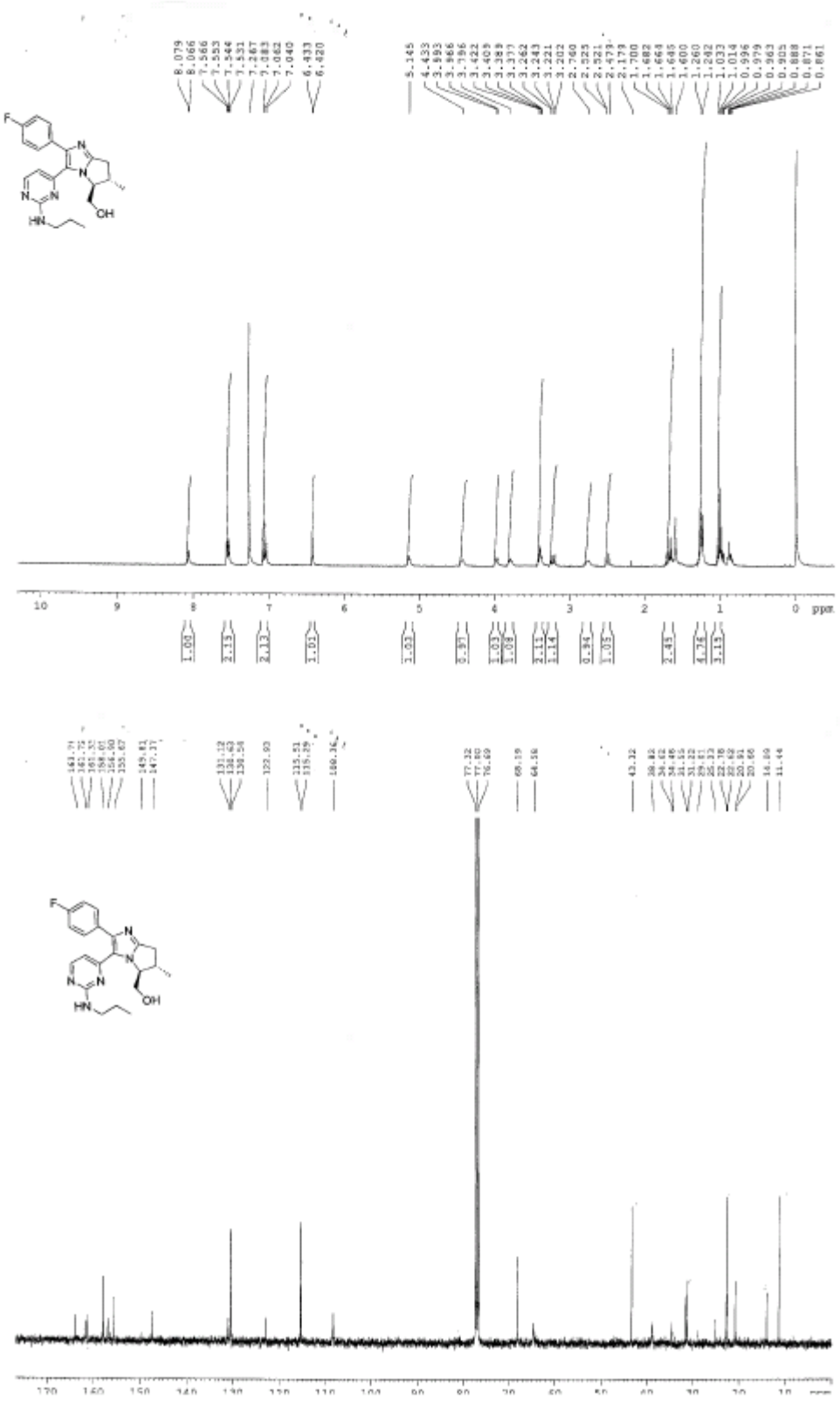

F
N
N
OTBDPS
10
9
8
7
6
5
4
3
2
1
0
ppm

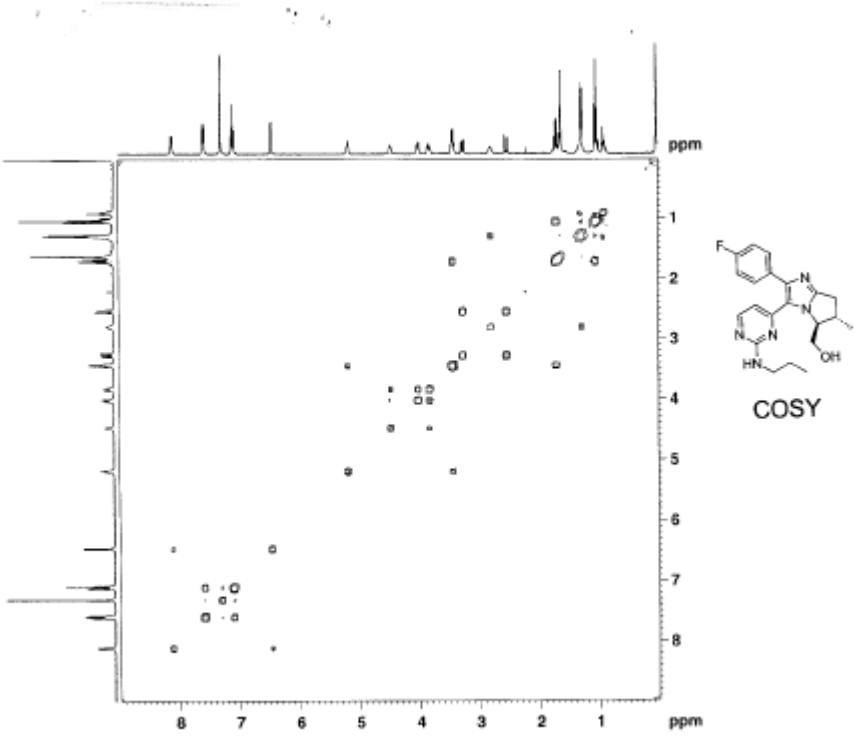

F
Br
N
N
OTBDPS
10
9
8
7
6
5
4
3
2
1
0
ppm


F
N
N
N
O=S=O
OTBDPS
10
9
8
7
6
5
4
3
2
1
0
ppm

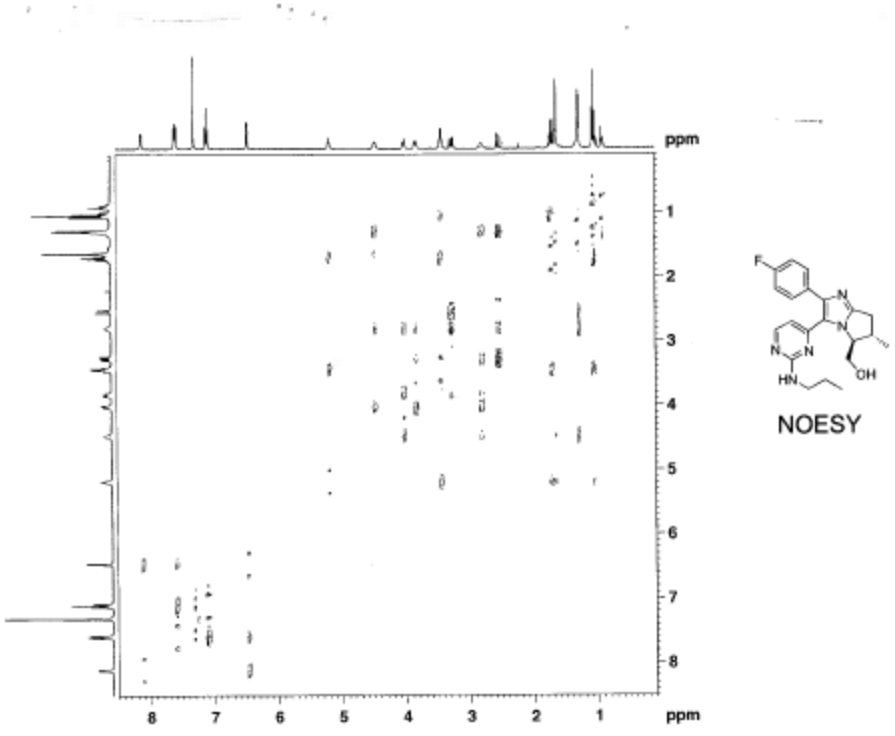

F
N
N
N
O=S=O
OTBDPS
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


F
N
N
N
HN
OTBDPS
ppm
F
N
N
N
HN
OTBDPS
ppm

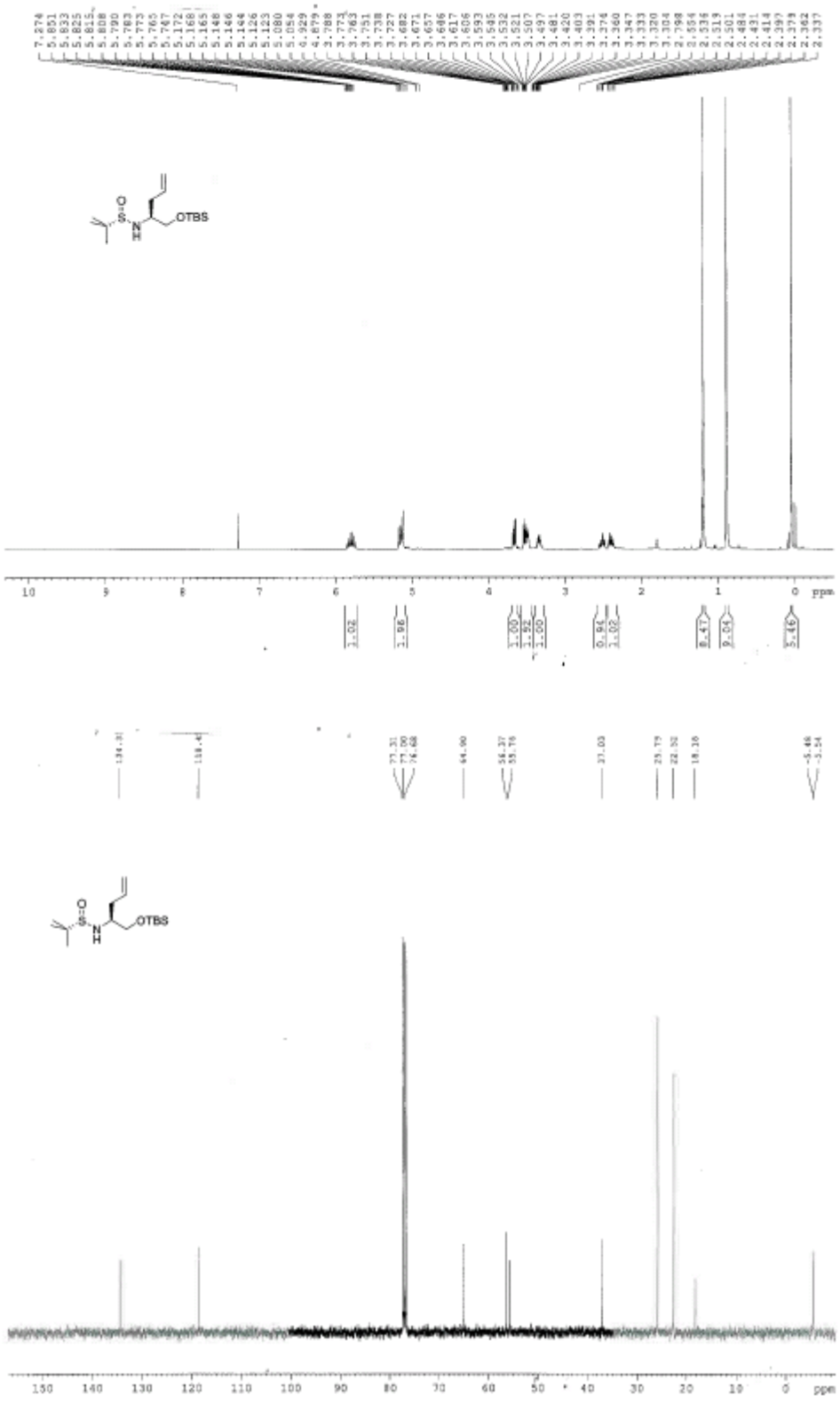


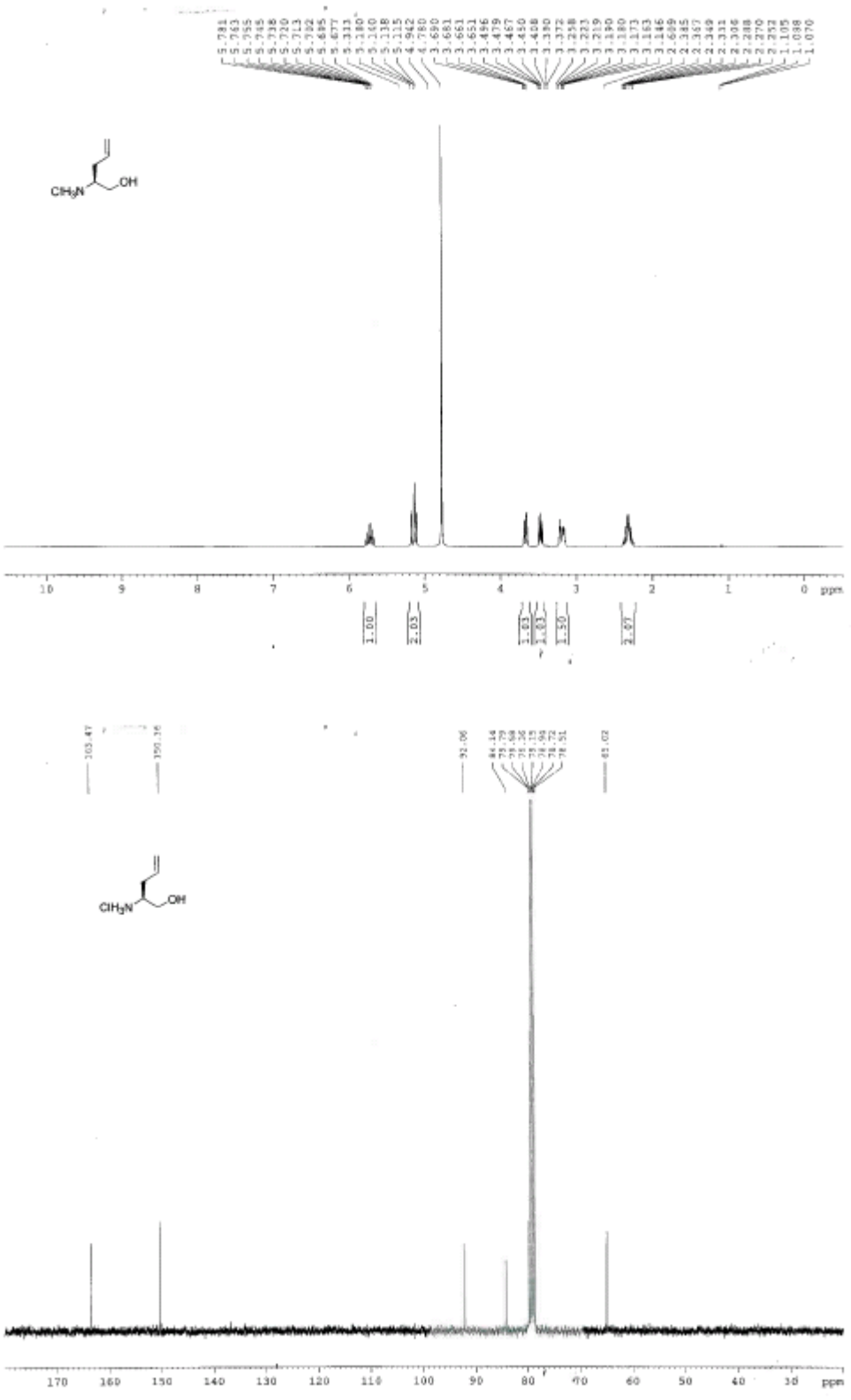

ppm
1
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
ppm
F
N
N
N
HN
OH

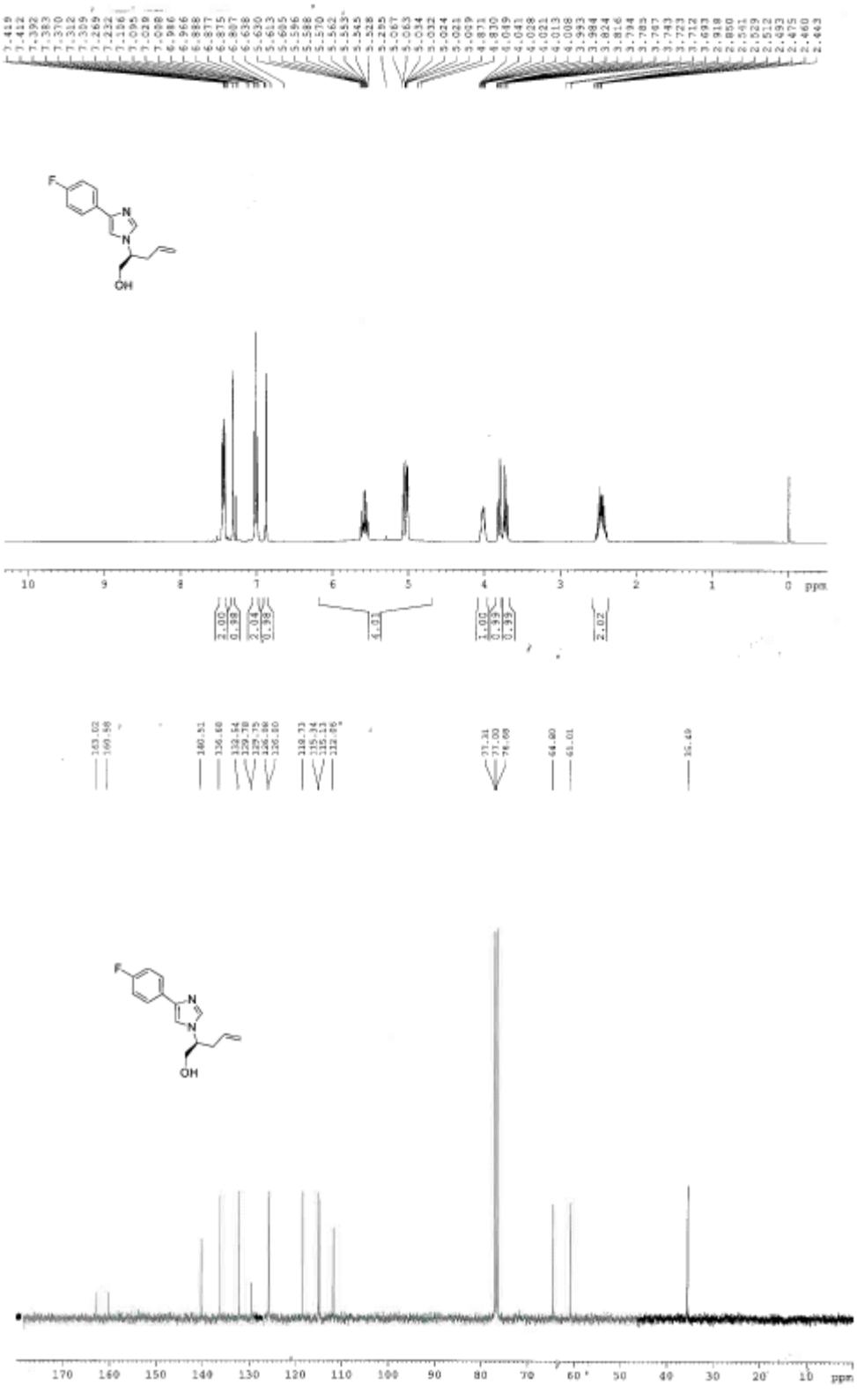
COSY

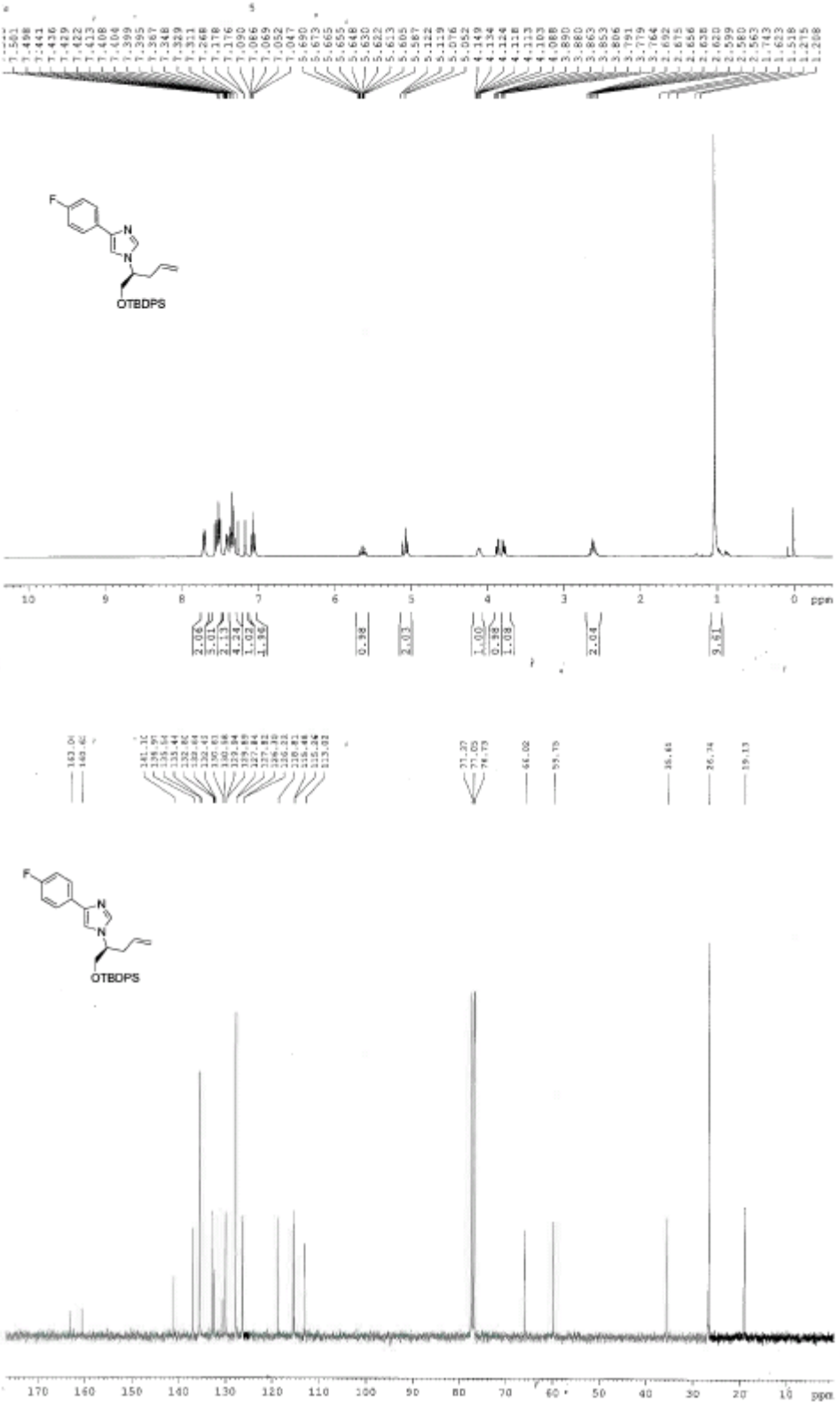

ppm
1
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
ppm
F
N
N
N
HN
OH

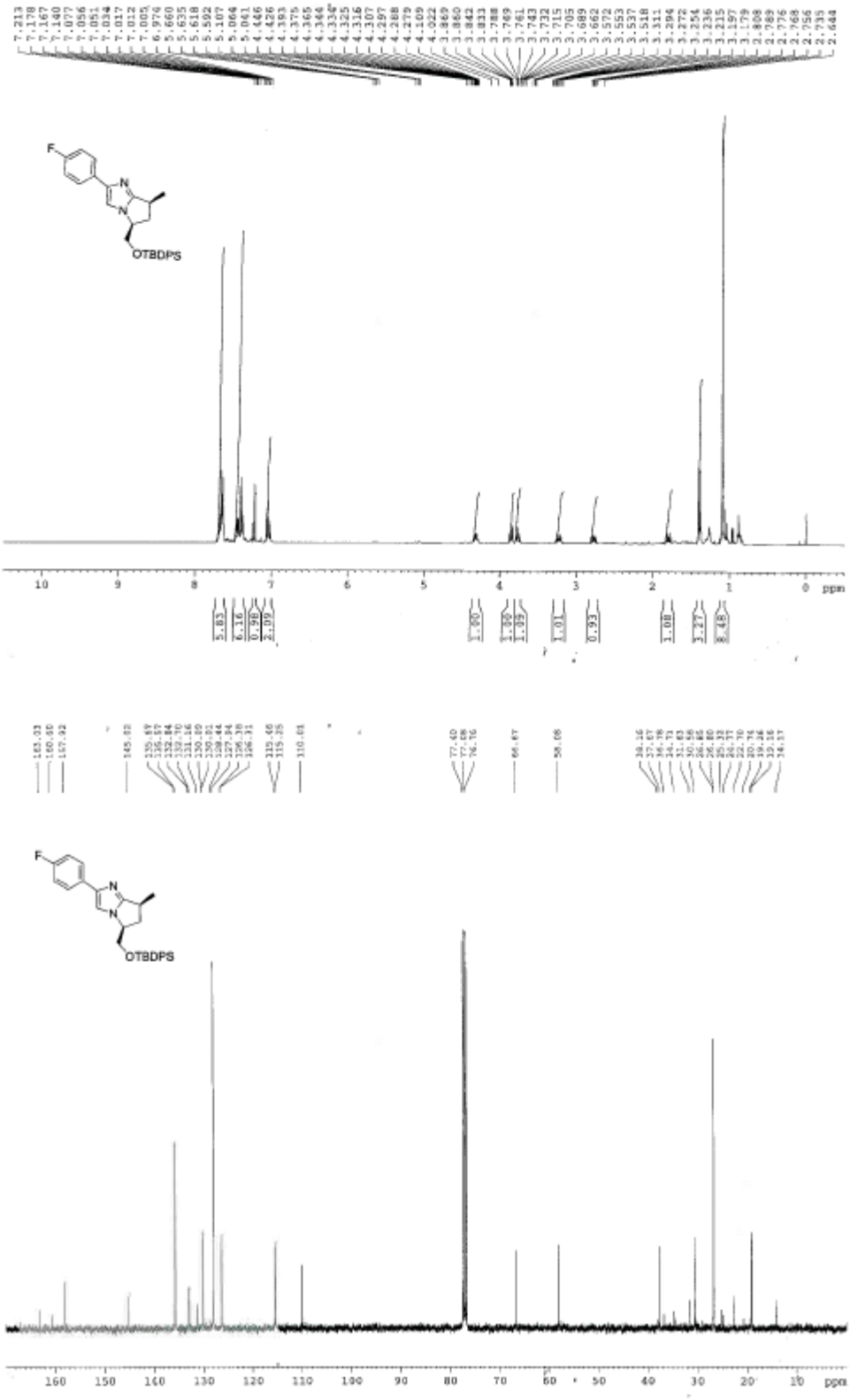
NOESY

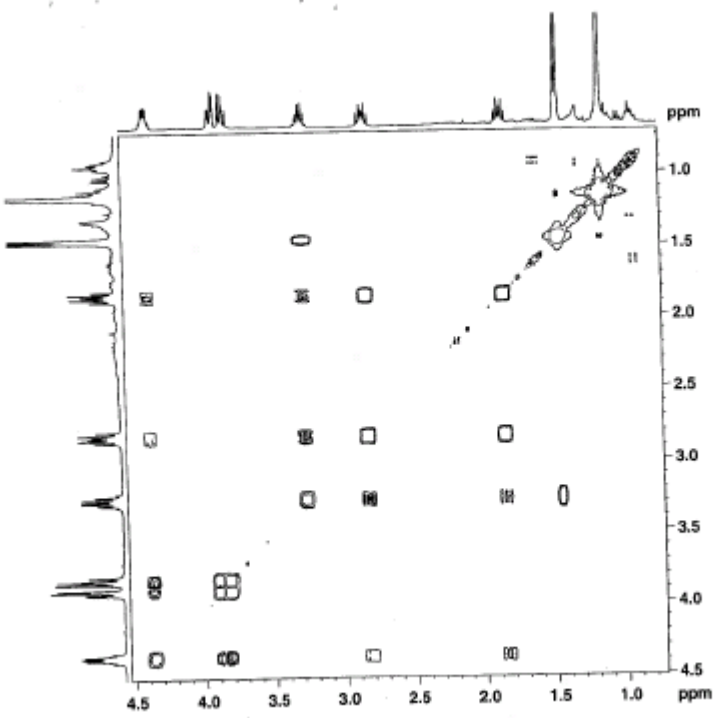

OTBS
ppm
OTBS
ppm


CH3N
OH
ppm
CH3N
OH
ppm

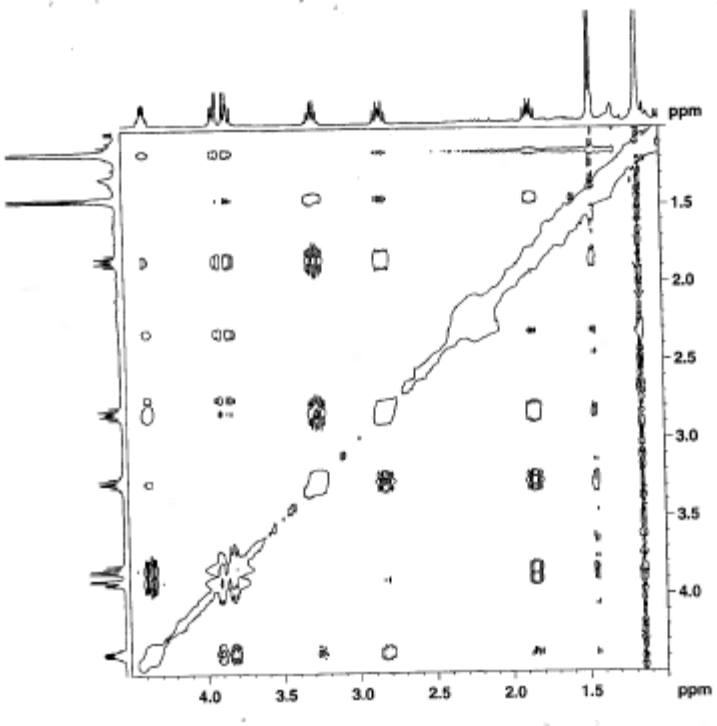

F
N
N
OH
10 9 8 7 6 5 4 3 2 1 0 ppm
F
N
N
OH
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


F
N
N
OTBDPS
10
9
8
7
6
5
4
3
2
1
0
ppm
F
N
N
OTBDPS
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

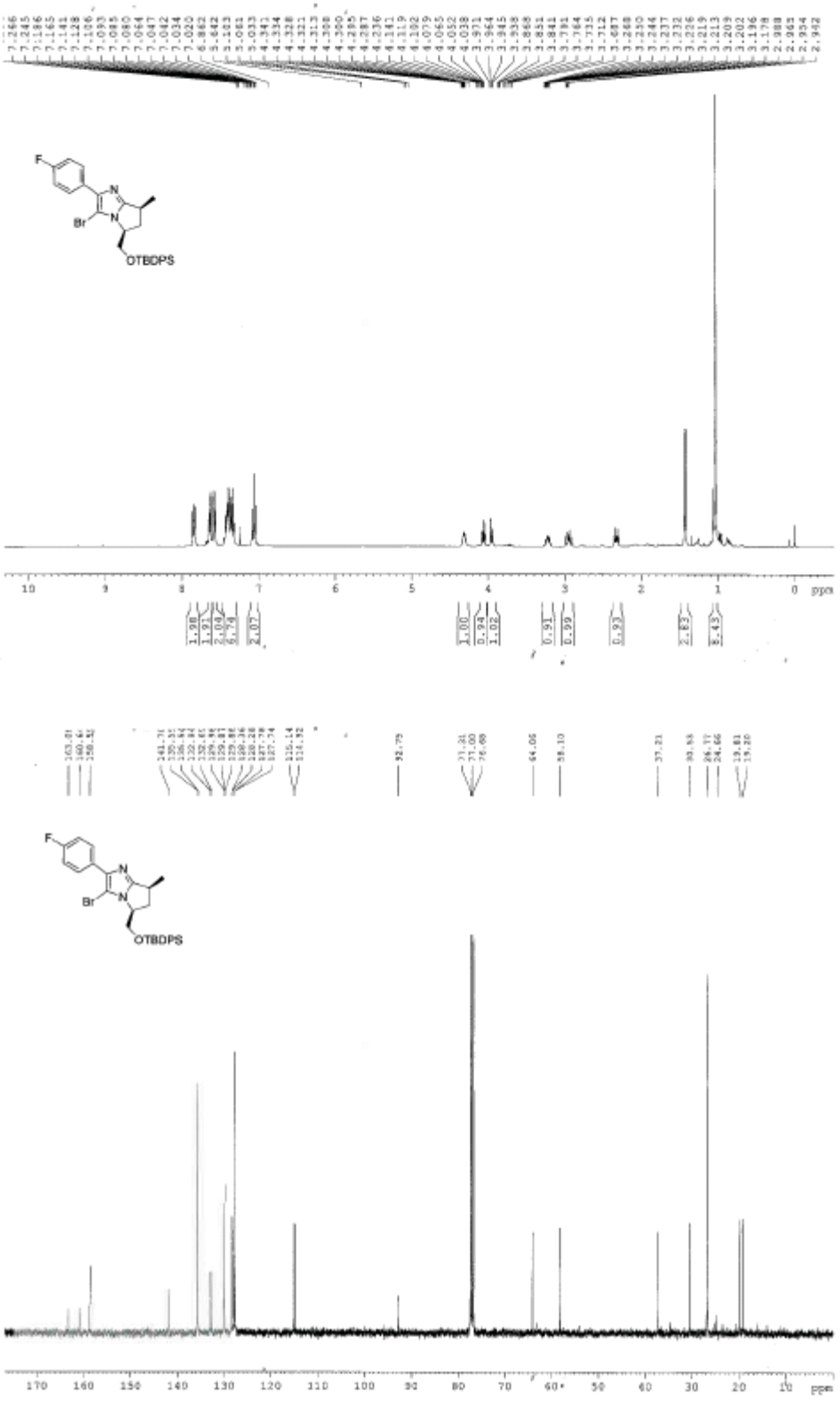

F
N
N
OTBDPS
ppm
F
N
N
OTBDPS
ppm

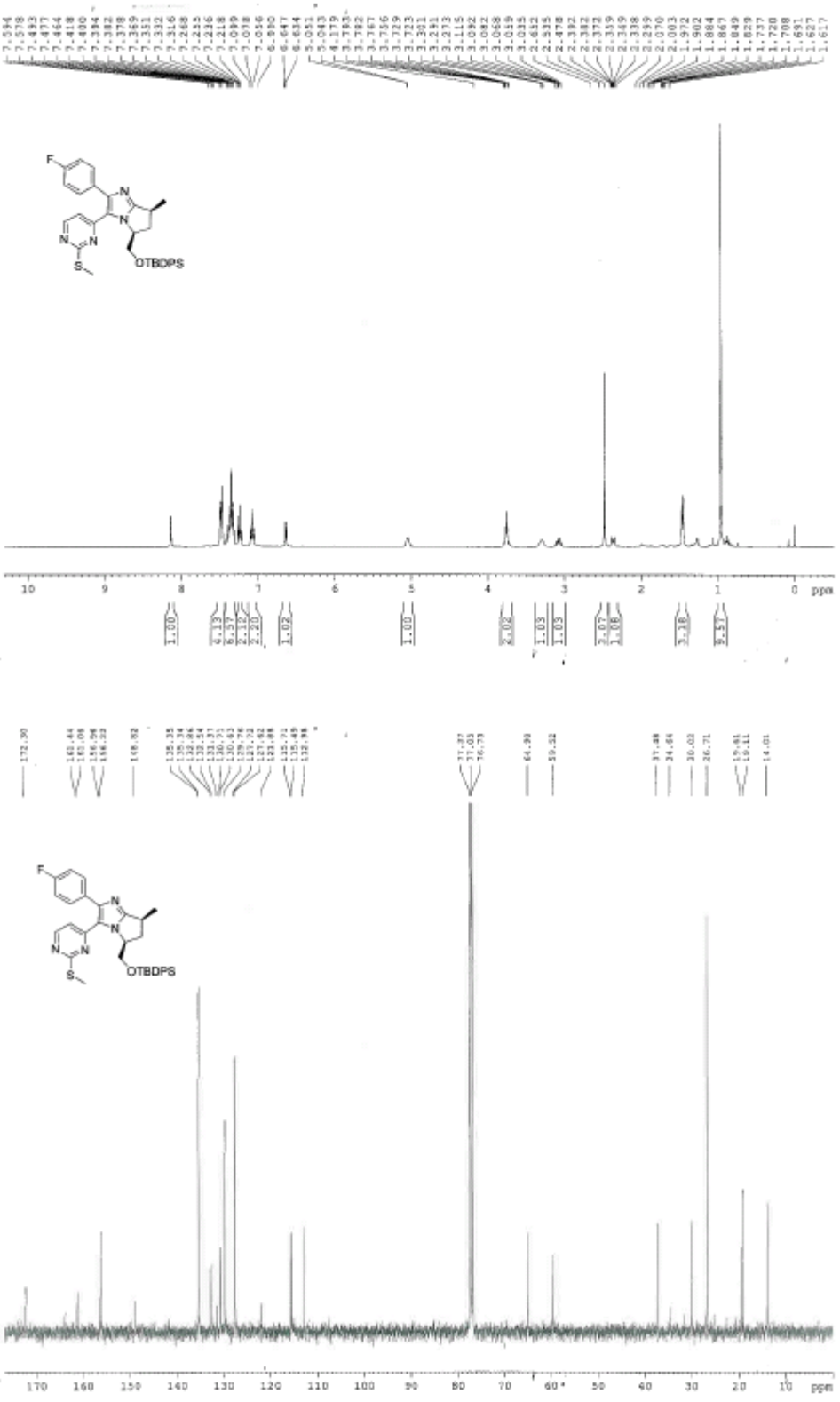

ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
F
N
N
OTBDPS

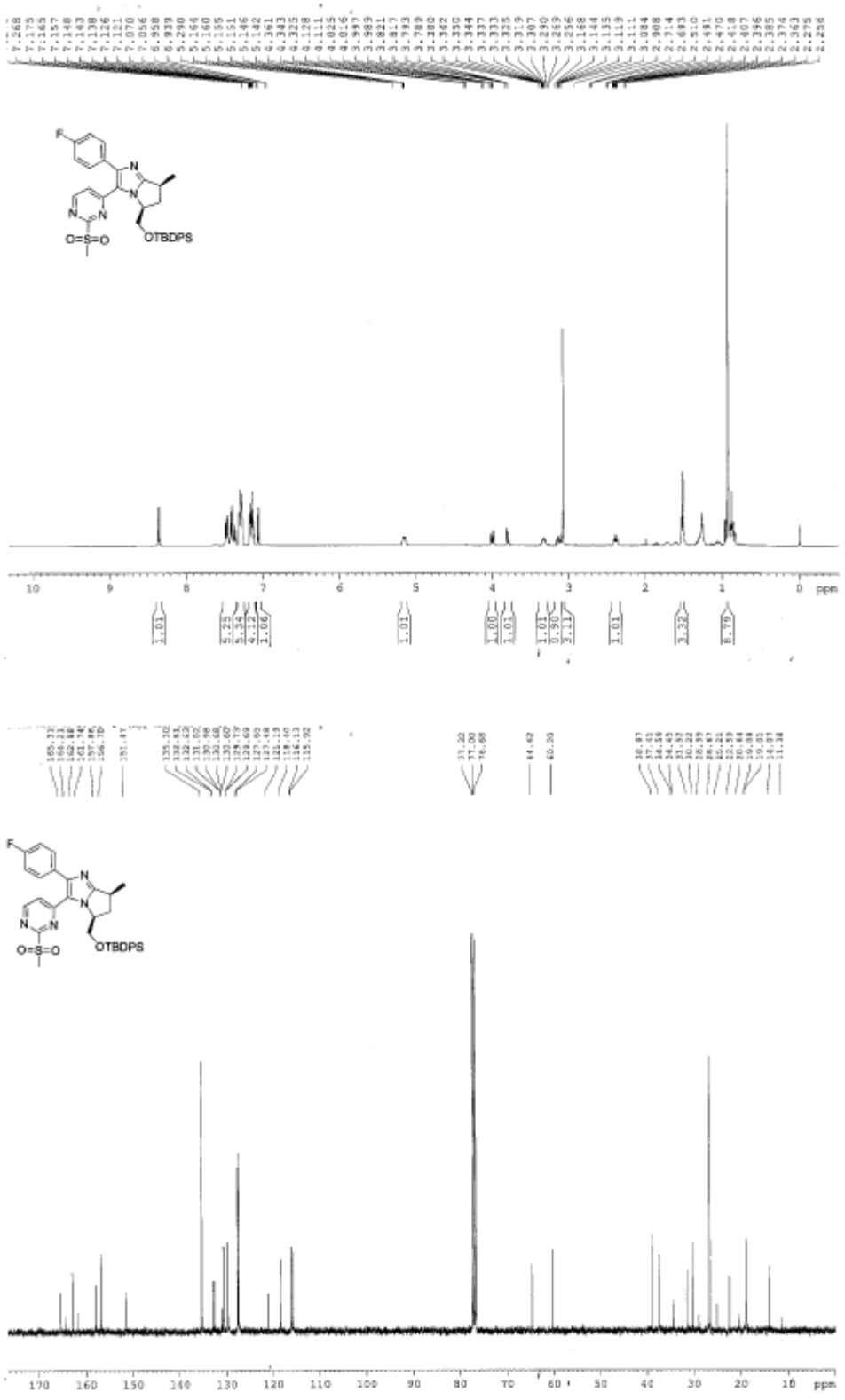
COSY

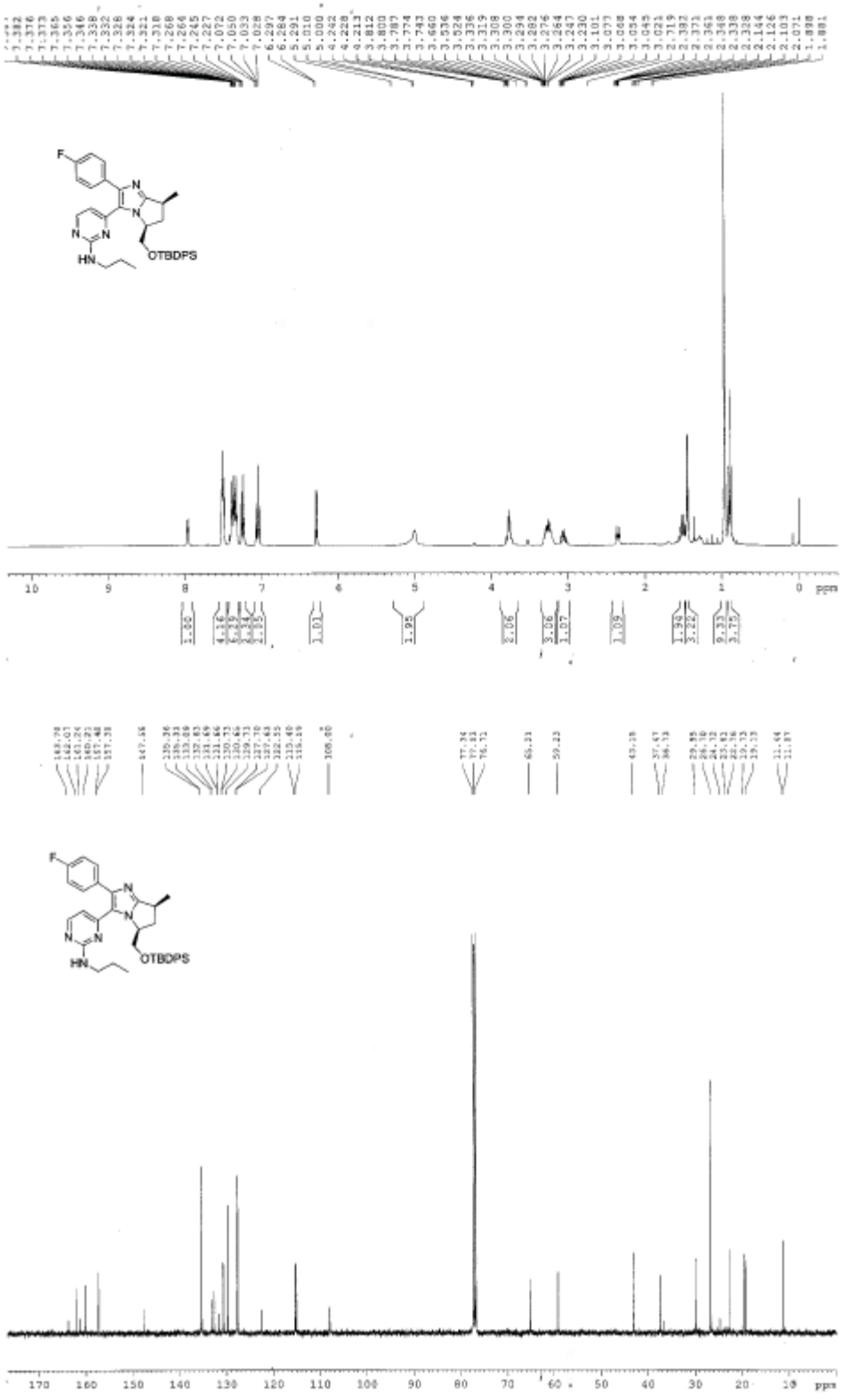

ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.0
3.5
3.0
2.5
2.0
1.5
ppm
F
N
N
OTBDPS

NOESY


F
N
Br
N
OTBDPS
ppm
F
N
Br
N
OTBDPS
ppm


F
N
N
N
S
OTBDPS
ppm
F
N
N
N
S
OTBDPS
ppm


F
N
N
N
O=S=O
OTBDPS
10
9
8
7
6
5
4
3
2
1
0
ppm
F
N
N
N
O=S=O
OTBDPS
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


F
N
N
N
HN
OTBDPS
ppm