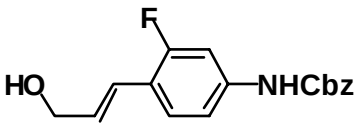
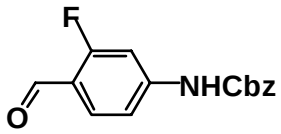
Supplementary materials for the manuscript "Synthesis of Aza-, Oxa-, and Thiabicyclo[3.1.0]hexane Heterocycles from a Common Synthetic Intermediate"
Adam R. Renslo, Hongwu Gao, Priyadarshini Jaishankar, Revathy Venkatachalam, and Mikhail F. Gordeev

Preparation of compound **3**



3

Step 1. Benzyl 3-fluoro-4-formylphenylcarbamate (**2**) (prepared previously using a different route; see Gordeev, M. F.; Luehr, G. L.; Patel, D. V.; Ni, Z.-J.; Gordon, E. U.S. Patent 6,239,152)



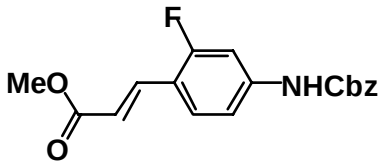
To an oven dried flask was added 4-bromo-2-fluorobenzaldehyde (50 g, 0.247 mol, 1.0 equiv.), benzyl carbamate (45 g, 0.297 mol, 1.2 equiv.), *rac*-BINAP (12.5 g, 0.020 mol, 0.08 equiv.), Cs_2CO_3 (115 g, 0.353 mol, 1.42 equiv.) and $Pd_2(dba)_3$ (9.15 g, 0.01 mol, 0.04 equiv.). The flask was evacuated and refilled with nitrogen. Anhydrous toluene (500 mL) was transferred into the flask by cannula. The resulting suspension was stirred at 95^0-100^0C for 24 hours and then cooled to room temperature. The reaction mixture was diluted with NH_4Cl aqueous (1000 mL) and extracted with EtOAc (3x300 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel, eluting with a gradient increasing in polarity from 0 to 20% ethyl acetate in hexane. Relevant fractions were combined to provide.

Yield 44.7 g (66%)

HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 5 min; 2 mL/min rate): retention time = 2.87 min

^{1}H NMR (300 MHz, $CDCl_3$): 5.23 (s, 2H), 6.98 (bs, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 7.40 (bs, 5H), 7.57 (d, *J*= 12.6 Hz, 1H), 7.80 (t, *J* = 7.8 Hz, 1H), 10.23 (s, 1H)

Step 2. Methyl (2E)-3-(4-{[(benzyloxy)carbonyl]amino}-2-fluorophenyl)acrylate



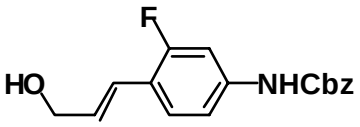
Sodium hydride (7.2 g of a 60% dispersion, 0.188 mol) was placed in a flask, rinsed three times with hexane and the flask evacuated and filled with nitrogen. The resulting solid was suspended in DMF (140 mL) and cooled to 0 °C. Trimethyl phosphonoacetate (30.7 mL, 0.190 mol) was added dropwise to this suspension to produce a clear homogeneous solution. After stirring for another 20 minutes at 0 °C, a solution of benzyl 3-fluoro-4-formylphenylcarbamate (**2**) (48 g, 0.176 mol) in DMF (140 mL) was added dropwise. The resulting orange suspension was allowed to warm slowly to room temperature and stirred for 16 hours. The reaction mixture was poured into 0.5 N HCl (1.5 L) and extracted with three 300 mL portions of dichloromethane. Combined organic phases were washed with saturated $NaHCO_3$, twice with H_2O, brine, and dried (Na_2SO_4). Upon concentration of the solution on a rotary evaporator, the product precipitated from solution. The solids were collected on a filter (providing 33.4 g) and the filtrate was concentrated to afford additional solids that were washed with ether (an additional 8.4 g obtained).

Yield 41.8 g (72%)

^{1}H NMR (300 MHz, d_6-DMSO): 3.71 (s, 3H), 5.17 (s, 2H), 6.55 (dd, *J* = 16, 1 Hz, 1H), 7.26 (d, *J* = 9 Hz, 1H), 7.35-7.50 (m, 6H), 7.63 (d, *J* = 16 Hz, 1H), 7.79 (t, *J* = 9 Hz, 1H), 10.3 (bs, 1 H)

mp = 157-158 °C

Step 3. Benzyl 3-fluoro-4-[(1E)-3-hydroxyprop-1-enyl]phenylcarbamate (**3**)



A THF solution of diisobutylaluminum hydride (522 mL of a 1.0 M solution, 522 mmol) was added to a cooled (-78 °C) solution of methyl (2E)-3-(4-{[(benzyloxy)carbonyl] amino}-2-fluorophenyl)acrylate (43 g, 130 mmol) in THF (900 mL). After stirring for one hour at – 78 °C, additional diisobutylaluminum hydride solution was added (140 mL of a 1.0 M solution, 140 mmol). After another 30 minutes, aqueous citric acid and ethyl acetate were added and the mixture allowed to warm slowly to room temperature. The layers were separated and the aqueous phase extracted with more ethyl acetate. Combined organic phases were washed with water, brine and, dried ($MgSO_4$), filtered, and concentrated to afford a red oil. This crude residue was purified by column chromatography (0-40% ethyl acetate-hexane) to provide **3** as a yellow solid.

Yield 36 g (92%)

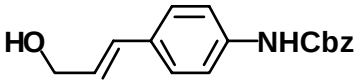
ESI-MS (m/z): $[M+Na]^+ = 324$

^1H NMR (300 MHz, $CDCl_3$): 1.43 (t, J = 6 Hz, 1H), 4.33 (t, J = 6 Hz, 2H), 5.28 (s, 2H), 6.37 (dt, J = 15, 6 Hz, 1H), 6.69 (d, J = 16 Hz, 1H), 6.70 (s, 1H), 6.99 (d, J = 9 Hz, 1H), 7.20-7.39 (m, 7H)

^{13}C NMR (75 MHz, d_6-DMSO): 61.5, 66.0, 104.8 (J_{C-F} = 27 Hz), 114.0, 118.1 (J_{C-F} = 12 Hz), 119.8 (J_{C-F} = 3 Hz), 127.4 (J_{C-F} = 5 Hz), 127.9, 128.0, 128.3, 131.7 (J_{C-F} = 4 Hz), 136.2, 139.4 (J_{C-F} = 11 Hz), 153.0, 159.2 (J_{C-F} = 243 Hz)

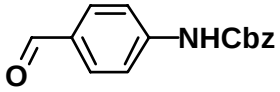
mp = 105-106 °C

Preparation of intermediate **4**



4

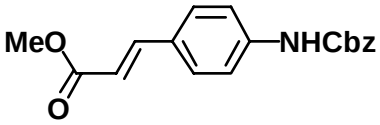
Step 1. benzyl 4-formylphenylcarbamate



Benzyl 4-bromophenylcarbamate (20 g, 65.3 mmol) was dissolved in anhydrous THF (440 mL) and cooled to -78 °C. A *n*-BuLi solution (55 mL, 137.2 mmol) was added dropwise and the reaction mixture stirred for 0.5 h at -78 °C. To this mixture, DMF (7.6 mL) was added dropwise and the reaction mixture allowed to warm to room temperature over a period of 5 h. The reaction mixture was quenched with 1 N HCl, concentrated to remove THF, and diluted with additional water. The mixture was extracted with three portions of ethyl acetate. The combined organic phases were washed with H_2O, brine, and dried ($MgSO_4$), filtered, and concentrated. Trituration of the residue with hexanes and then with 20 % ethyl acetate in hexanes afforded the title compound as a yellow solid that was used in the next step without further purification.

Yield 8.75 g (52%)

Step 2. methyl (2E)-3-(4-{[(benzyloxy)carbonyl]amino}phenyl)acrylate



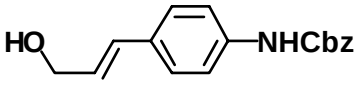
Sodium hydride (0.36 g of a 60% dispersion, 9.0 mmol) was placed in a flask, rinsed three times with hexane and the flask evacuated and filled with nitrogen. The resulting solid was suspended in DMF (7 mL) and cooled to 0 °C. Trimethyl phosphonoacetate (1.53 mL, 9.46 mmol) was added dropwise to this suspension to give a

clear homogeneous solution. After stirring for another 20 minutes at 0 °C, a solution of benzyl 4-formylphenyl-carbamate (2.3 g, 9.0 mmol) in DMF (7 mL) was added dropwise. The resulting orange suspension was allowed to warm slowly to room temperature and stirred for 15 h. The reaction mixture was poured into 0.5 N HCl and extracted with three portions of dichloromethane. Combined organic phases were washed with saturated $NaHCO_3$, H_2O, brine, and dried ($MgSO_4$) filtered and concentrated. Purification by silica gel column chromatography (gradient 0-30% EtOAc in hexanes) provided the title compound.

Yield 2.5 g (89%)

^{1}H NMR (300 MHz, $CDCl_3$): 3.79(s, 3H), 5.21 (s, 2H), 6.33-6.38 (d, *J* = 16 Hz, 1H), 6.78 (s, 1H), 7.31-7.46 (m, 9H), 7.61-7.66 (d, *J* = 16 Hz, 1H)

Step 3. benzyl 4-[(1E)-3-hydroxyprop-1-enyl]phenylcarbamate (**4**)



A THF solution of $LiAlH_4$ (6.75 mL of a 1.0 M solution, 6.75 mmol) was added to a cooled (-78 °C) solution of methyl (2E)-3-(4-{[(benzyloxy)carbonyl] amino}phenyl) acrylate (2.1 g, 6.75 mmol) in THF (34 mL). The solution was allowed to warm slowly to –20 °C and maintained at that temperature for 2 hours. The reaction mixture was quenched by slow addition of saturated NH_4Cl and then treated with dilute citric acid. The resulting solution was stirred for 15 minutes and then extracted with three portions of ethyl acetate. The combined organic phases were washed with H_2O, brine and dried ($MgSO_4$), filtered and concentrated to afford an oil. The crude residue was purified by column chromatography (20-50% ethyl acetate-hexane) to provide **4** as a yellow solid.

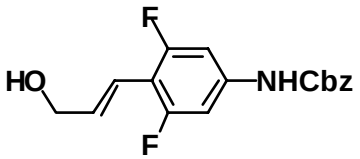
Yield 1.0 g (52%)

ESI-MS (m/z): $[M-H]^-$ = 282

^{1}H NMR (300 MHz, $CDCl_3$): 4.28-4.30 (d, *J* = 6 Hz, 2H), 5.18 (s, 2H), 6.22-6.31 (m, 1H), 6.52-6.57 (d, *J* = 16 Hz, 1H), 6.64 (s, 1H), 7.32-7.40 (m, 9H)

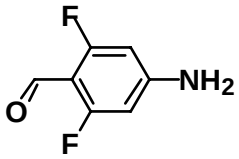
^{13}C NMR (75 MHz, d_6-DMSO): 61.5, 65.7, 118.1, 126.4, 127.9, 127.95, 128.0, 128.3, 128.9, 131.1, 136.4, 138.0, 153.1

Preparation of intermediate **5.**



5

Step 1. 4-Amino-2,6-difluoro-benzaldehyde



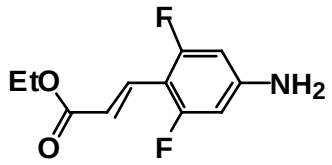
A solution of 3,5-difluoroaniline (12.9 g, 0.1 mol) in anhydrous THF (400 mL) was cooled at –78^{0}C and treated with *n*-butyllithium (2.5 M in hexane, 84 mL, 0.21 mol, 2.1 equv.) dropwise over 25 min. After stirring at –78^{0}C for 30 min, trimethylsilyl chloride (1.0 M in THF, 210 mL, 0.21 mol, 2.1 equiv.) was added dropwise over 30 min. The temperature was allowed to rise to 23^{0}C and the mixture stirred overnight. After re-cooling to –78^{0}C, additional *n*-butyllithium (2.5 M in hexane, 44 mL, 0.11 mol, 1.1 equiv.) was added dropwise over 20 min, and the reaction mixture stirred at that temperature for 5 hours. Then, DMF (11.6 ml, 0.15 mol, 1.5 equiv.) was added dropwise over 20 min. The temperature was allowed to rise to 23^{0}C and stirred overnight. The mixture was cooled in an ice-bah and acidified to pH=1 by slow addition of aqueous HCl (1.0 M, 220 mL, 0.22 mol). After stirring for 15 min, the mixture was extracted with ethyl acetate (3x200 mL). The combined organic layers were washed (brine), dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified by chromatography on a silica gel column, eluting with a gradient increasing in polarity from 0 to 50% ethyl acetate in hexane. Relevant fractions were combined and concentrated to afford the title compound.

Yield 8.5 g (55%)

HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 5 min; 2 mL/min rate): retention time = 1.58 min

^{1}H NMR (300 MHz, DMSO-d_6): 6.19 (d, *J*= 12.3 Hz, 2H), 6.93 (bs, 2H), 9.83 (s, 1H)

Step 2. Ethyl (2E)-3-[4-amino-2,6-difluorophenyl]acrylate



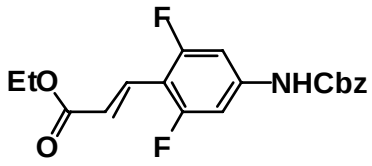
To a solid mixture of 4-amino-2,6-difluoro-benzaldehyde (6.5 g, 41.4 mmol, 1.0 equiv.) and (carbethoxymethylene)triphenylphosphorane (18.75 g, 53.8 mmol, 1.3 equiv.) at room temperature was added ethanol (97 mL). After stirring for 25 min at 23^{0}C, the reaction mixture was concentrated, absorbed to silica gel and purified by flash column chromatography eluting with a gradient increasing in polarity from 0 to 30% ethyl acetate in hexane. Relevant fractions were combined and concentrated to provide the title compound.

Yield 9.0 g (96%)

HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 5 min; 2 mL/min rate): retention time = 2.74 min

^{1}H NMR (300 MHz, $CDCl_3$): 1.32 (t, *J* = 7.2 Hz, 3H), 4.14 (bs, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 6.19 (d, *J* = 10.8 Hz, 2H), 6.50 (d, *J* = 16.2 Hz, 1H), 7.68 (d, *J* = 16.2 Hz, 1H)

Step 3. Ethyl (2E)-3-(4-{[(benzyloxy)carbonyl]amino}-2,6-difluorophenyl)acrylate



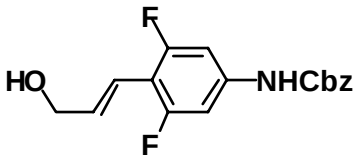
A solution of ethyl (2E)-3-[4-amino-2,6-difluorophenyl]acrylate (1.7 g, 7.5 mmol) in CH_2Cl_2 (100 mL) and pyridine (1.2 mL, 14.8 mmol, 2.0 equiv) was cooled in an ice-bath. The solution was then treated with benzyl chloroformate (1.3 mL, 9.1 mmol, 1.2 eq) dropwise and the solution stirred at 23^0C for 17 hours. The reaction mixture was then diluted with more CH_2Cl_2 and the organic phase was washed with water, brine, and dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on a silica gel column, eluting with a gradient increasing in polarity from 0 to 20% ethyl acetate in hexane. Relevant fractions were combined and concentrated to afford the title compound.

Yield 2.59 g (96%)

HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 5 min; 2 mL/min rate): retention time = 3.55 min

^{1}H NMR (300 MHz, $CDCl_3$): 1.33 (t, *J*=7.2 Hz, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 5.21 (s, 2H), 6.62 (d, *J* = 16.5 Hz, 1H), 6.90 (bs, 1H), 7.07 (d, *J* = 10.8 Hz, 2H), 7.40 (bs, 5H), 7.70 (d, *J* = 16.5 Hz, 1H)

Step 4. Benzyl 2,6-difluoro-4-[(1E)-3-hydroxyprop-1-enyl]phenylcarbamate (**5**)



A solution of diisobutylaluminum hydride (8.3 mL, of 1.0 M hexane solution, 8.3 mmol, 3.0 equiv.) was added to a cooled (-78^{0}C) solution of ethyl (2E)-3-(4-{[(benzyloxy)carbonyl]amino}-2,6-difluorophenyl)acrylate (0.97 g, 2.69 mmol) in THF (20 mL) over 10 min and the cooling bath allowed to warm to -50^{0}C. After stirring at –50^{0}C for 1h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and then treated with aqueous citric acid (100 mL of a 10% solution). The resulting mixture was stirred for 15 min and then extracted with ethyl acetate (3x70 mL). Combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified by chromatography on a silica gel column, eluting with a gradient increasing in polarity from 0 to 30% ethyl acetate in hexane. Relevant fractions were combined and concentrated to provide **5**.

Yield 0.69 g (81%)

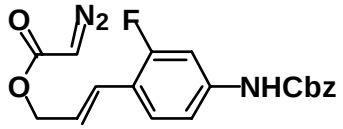
ESI-MS (m/z): $[M-H]^-$ = 318

HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 5 min; 2 mL/min rate): retention time = 2.86 min

^{1}H NMR (300 MHz, $CDCl_3$): 1.54 (t, J = 5.4 Hz, 1H), 4.34 (bs, 2H), 5.21 (s, 2H), 6.58 (m, 2H), 6.77 (bs, 1H), 7.00 (d, J = 10.2 Hz, 2H), 7.39 (bs, 5H)

^{13}C NMR (75 MHz, d_6-DMSO): 61.6, 66.2, 101.1 (J_{C-F} = 30 Hz), 107.5, 113.8, 128.0, 128.1, 128.3, 136.0 (J_{C-F} = 9 Hz), 136.2, 139.1 (t, J_{C-F} = 15 Hz), 152.9, 159.9 (dd, J_{C-F} = 244, 11 Hz)

(**6**) (2E)-3-(4-{[(benzyloxy)carbonyl]amino}-2-fluorophenyl)prop-2-enyl diazoacetate



6

To a suspension of glyoxylic acid *p*-toluenesulfonylhydrazone (24 g, 0.10 mol, prepared as described by C. J. Blankley, F. J. Sauter and H. O. House, *Organic Syntheses*, Coll. Vol. V, p. 258; John Wiley, New York (1973)) in CH_2Cl_2 (600 mL) at 23^0C was added commercially available 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (15 mL, 0.114 mol, 1.14 equiv.) over 5 min. The reaction mixture was stirred at the same temperature for 40 min. The reaction mixture was then cooled to 0 °C and benzyl 3-fluoro-4-[(1E)-3-hydroxyprop-1-enyl]phenylcarbamate (23 g, 0.077 mol) was added in one portion followed by the addition of *N*,*N*-dimethylaniline (12 mL, 0.095 mol). After 30 minutes, triethylamine (53 mL, 0.385 mol) was added and the mixture stirred for 30 minutes at 0 °C and 15 minutes at room temperature. The reaction mixture was then concentrated to a volume of about 100 mL and 500 mL of water added. The mixture was extracted with two portions of diethyl ether and the combined organic solutions washed with saturated $NaHCO_3$, brine, and dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (0-25% ethyl acetate-hexane) provided **6** as a yellow solid.

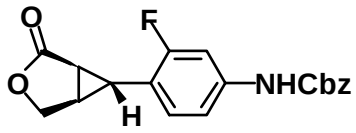
Yield 23.8 g (84%)

^{1}H NMR (300 MHz, $CDCl_3$): 4.80 (s, 2H), 4.83 (s, 1H), 5.21 (s, 2H), 6.29 (dt, J = 16, 6 Hz, 1H), 6.72 (d, J = 16 Hz, 1H), 6.73 (s, 1H), 6.98 (d, J = 8 Hz, 1H), 7.25-7.40 (m, 7H)

^{13}C NMR (75 MHz, $CDCl_3$): 46.3, 65.5, 67.2, 106.0 ($J_{C\text{-}F}$ = 27 Hz), 113.9, 118.8 ($J_{C\text{-}F}$ = 13 Hz), 124.2 ($J_{C\text{-}F}$ = 5 Hz), 126.3 ($J_{C\text{-}F}$ = 3 Hz), 127.8 ($J_{C\text{-}F}$ = 5 Hz), 128.3, 128.4, 128.6, 135.7, 138.9 ($J_{C\text{-}F}$ = 11 Hz), 152.9, 160.5 ($J_{C\text{-}F}$ = 248 Hz), 166.6

mp = 93-96 °C

(**7**) (racemic) benzyl 3-fluoro-4-[*rac*-(1α,5α,6β)-2-oxo-3-oxabicyclo[3.1.0]hex-6-yl]phenylcarbamate



(± **7**)

A solution of (2E)-3-(4-{[(benzyloxy)carbonyl]amino}-2-fluorophenyl)prop-2-enyl diazoacetate (13.9 g, 37.5 mmol) in 1,2-dichloroethane (150 mL) was added via syringe pump over 14 h to a refluxing solution of bis-(*N*-*t*-butylsalicylaldiminato)copper(II) (0.82 g, 1.9 mmol, prepared as described by R. G. Charles, *J. Org. Chem.* **1957**, *22*, 677) in 1.5 L of toluene. After the addition was complete, the reaction mixture was heated another hour at reflux, then cooled, filtered and concentrated to an oil. The crude residue was purified by column chromatography (0-50% ethyl acetate-hexanes) to provide **7** as a yellow solid.

Yield 9.3 g (73%)

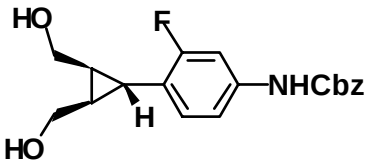
ESI-MS (m/z): $[M+Na]^+ = 364$

^{1}H NMR (300 MHz, $CDCl_3$): 2.33-2.39 (m, 2H), 2.49-2.53 (m, 1H), 4.4 (m, 2H), 5.18 (s, 2H), 6.82 (t, J = 9 Hz, 1H), 7.0 (d, J = 8 Hz, 1H), 7.01 (s, 1H), 7.25-7.38 (m, 6H)

^{13}C NMR (300 MHz, $CDCl_3$): 23.3 (J_{C-F} = 4 Hz), 25.1 (J_{C-F} = 2 Hz), 25.8, 67.3, 69.7, 106.1 (J_{C-F} = 27 Hz), 114.0, 118.6 (J_{C-F} = 14 Hz), 127.2 (J_{C-F} = 5 Hz), 128.2, 128.4, 128.5, 135.5, 138.3 (J_{C-F} = 11 Hz), 152.8, 161.1 (J_{C-F} = 244 Hz), 174.8

mp = 141-142 °C

(**8**) Benzyl 4-[(1α,5α,6β)-2,3-bis(hydroxymethyl)cyclopropyl]-3-fluorophenylcarbamate



8

Solid $LiBH_4$ (2.6 g, 119 mmol) was added in one portion to a solution of benzyl 3-fluoro-4-[*rac*-(1α,5α,6β)-2-oxo-3-oxabicyclo[3.1.0]hex-6-yl]phenylcarbamate (8.3 g, 24.3 mmol) in THF (170 mL) cooled at 0 °C. The solution was allowed to warm to room temperature and stirred for 14 hours. The solution was then re-cooled to 0 °C and quenched by the addition of aqueous citric acid solution. The solution was extracted with three portions of ethyl acetate. The combined organic phases were then washed with water, brine, and dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (20-75% ethyl acetate-hexanes) provided **8** as a white foam.

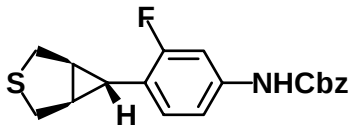
Yield 6.4 g (81%)

ESI-MS (m/z): $[M+Na]^+ = 368$

^{1}H NMR (300 MHz, $CDCl_3$): 1.65-1.72 (m, 2H), 1.90 (t, J = 5 Hz, 1H), 2.72 (bs, 2H), 3.48 (m, 2H), 4.23 (m, 2H), 5.19 (s, 2H), 6.75 (s, 1H), 6.82 (t, J = 8 Hz, 1H), 6.93 (dd, J = 9, 2 Hz, 1H), 7.30-7.41 (m, 6H)

^{13}C NMR (300 MHz, d_6-DMSO): 19.2 (J_{C-F} = 4 Hz), 28.1, 60.0, 65.9, 104.5 (J_{C-F} = 27 Hz), 113.8, 122.7 (J_{C-F} = 15 Hz), 126.5 (J_{C-F} = 6 Hz), 127.9, 128.0, 128.3, 136.3, 137.7 (J_{C-F} = 11 Hz), 153.0, 160.2 (J_{C-F} = 239 Hz)

(**13**) benzyl 3-fluoro-4-[(1α,5α,6β)-3-thiabicyclo[3.1.0]hex-6-yl]phenylcarbamate



13

Methanesulfonic anhydride (1.51 g, 8.7 mmol) was added to a cooled (0°C) solution of benzyl 4-[(1α,5α,6β)-2,3-bis(hydroxymethyl)cyclopropyl]-3-fluorophenylcarbamate (1.0 g, 2.9 mmol) in dichloromethane (36 mL) and triethylamine (1.61 mL, 11.6 mmol). The solution was allowed to warm to room temperature and stirred for 2 h. The solution was then diluted with 30 mL of dichloromethane and washed with two portions of saturated $NaHCO_3$, brine, and dried ($MgSO_4$). The crude product was used directly in the next reaction or first passed through a short pad of SiO_2 (eluting with ethyl acetate) to provide 4-[(1α,5α,6β)-2,3-bis(methanesulfonyloxymethyl)cyclopropyl]-3-fluorophenylcarbamate as a white solid.

Sodium sulfide (0.65 g, 8.4 mmol) was added to a solution of benzyl 4-[(1α,5α,6β)-2,3-bis(methanesulfonyloxymethyl)cyclopropyl]-3-fluorophenylcarbamate (1.4 g, 2.8 mmol) in DMSO (5.5 mL). The reaction mixture was stirred at room temperature for 2 h. The resulting yellow suspension was then diluted with 30 mL of H_2O and extracted with three portions of diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to provide **13** as a white solid.

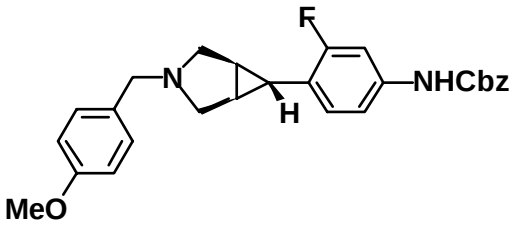
Yield 0.87 g (91%)

ESI-MS (m/z): $[M+Na]^+ = 366$

^1H NMR (300 MHz, $CDCl_3$): 1.91 (m, 2H), 2.44 (m, 1H), 3.09 (d, *J* = 11 Hz, 2H), 3.18 (d, *J* = 11 Hz, 2H), 5.20 (s, 2H), 6.61 (s, 1H), 6.91 (t, *J* = 8 Hz, 1H), 6.94 (d, *J* = 8 Hz, 1H), 7.19-7.40 (m, 6H)

mp = 121-122 °C

(**16**) Benzyl 3-fluoro-4-[(1α,5α,6β)-3-(4-methoxybenzyl)-3-azabicyclo[3.1.0]hex-6-yl]phenylcarbamate



16

Methanesulfonic anhydride (9.85 g, 56.5 mmol) was added to a cooled (0°C) solution of benzyl 4-[(1α,5α,6β)-2,3-bis(hydroxymethyl)cyclopropyl]-3-fluorophenylcarbamate (6.5 g, 18.8 mmol) in dichloromethane (220 mL) and triethylamine (10.6 mL, 76 mmol). The solution was allowed to warm to room temperature and stirred for 1 h. The solution was then diluted with 250 mL of dichloromethane and washed with two portions of saturated $NaHCO_3$, brine, and dried (Na_2SO_4), filtered, and concentrated. The crude product used directly in the next reaction or first passed through a short pad of SiO_2 (eluting with ethyl acetate) to provide the bis-mesylate intermediate as a white solid.

Crude benzyl 4-[(1α,5α,6β)-2,3-bis(methanesulfonyloxymethyl)cyclopropyl]-3-fluorophenylcarbamate (18.8 mmol) was dissolved in 4-methoxybenzylamine (50 g, 360 mmol) and stirred at room temperature for 16 h. The resulting solution was then diluted with ethyl aceate and washed with 2.5% $NaHCO_3$, dilute aqueous HCl (360 mL of a 1 N solution diluted to 1.0 L with H_2O), again with 2.5% $NaHCO_3$, brine, and dried ($MgSO_4$), filtered and concentrated. The crude product was purified by silica gel column chromatography (gradient 0-30% ethyl acetate-hexane – 1% Et_3N) to provide **16** as a white solid.

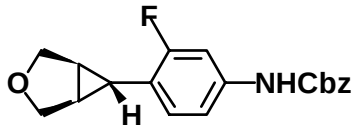
Yield 7.7 g (92% over 2 steps)

ESI-MS (m/z): $[M+H]^+ = 447$

^1H NMR (300 MHz, $CDCl_3$): 1.65 (bs, 2H), 2.44 (d, *J* = 9 Hz, 2H), 2.47 (m, 1H), 3.09 (d, *J* = 9 Hz, 2H), 3.58 (s, 2H), 3.80 (s, 3H), 5.19 (s, 2H), 6.60 (bs, 1H), 6.77-6.93 (m, 4H), 7.21-7.41 (m, 8H)

^{13}C NMR (75 MHz, $CDCl_3$): 16.8 ($J_{C\text{-}F}$ = 4 Hz), 25.7, 54.6, 55.2, 58.2, 67.0, 106.0 ($J_{C\text{-}F}$ = 26 Hz), 113.5, 114.0, 124.4 ($J_{C\text{-}F}$ = 15 Hz), 126.7 ($J_{C\text{-}F}$ = 6 Hz), 128.25, 128.35, 128.6, 129.6, 131.4, 135.8, 136.2 ($J_{C\text{-}F}$ = 11 Hz), 153.1, 158.4, 161.2 ($J_{C\text{-}F}$ = 161 Hz)

(**19**) benzyl 3-fluoro-4-[(1α,5α,6β)-3-oxabicyclo[3.1.0]hex-6-yl]phenylcarbamate



19

A solution of benzyl 4-[(1α,5α,6β)-2,3-bis(hydroxymethyl)cyclopropyl]-3-fluorophenylcarbamate (0.18 g, 0.52 mmol,) in THF (5 mL) was cooled to –50 °C. An *n*-BuLi solution (0.72 mL, 1.14 mmol) was added and the resulting yellow suspension was stirred for 10 min at–50 °C and then treated with methanesulfonyl chloride (0.088 mL, 1.14 mmol). This produced a homogeneous solution that was stirred for another 10 min and then treated with more *n*-BuLi (0.36 mL, 0.57 mmol). The solution was allowed to warm to –30 °C over one hour and then quenched by the addition of water and dilute $NaHCO_3$. The solution was concentrated *in vacuo* to remove THF and the resulting aqueous solution was then extracted with ethyl acetate three times. The combined organic phases were washed with brine and dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by column chromatography (0-30% ethyl acetate/hexane) to provide **19**.

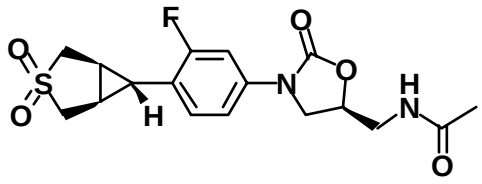
Yield 73 mg (43%)

ESI-MS (m/z): $[M+H]^+$ = 328

^{1}H NMR (300 MHz, $CDCl_3$): 1.89 (m, 2H), 1.98 (t, *J* = 4 Hz, 1H), 3.80 (d, *J* = 8 Hz, 2H), 4.02 (d, *J* = 8 Hz, 2H), 5.20 (s, 2H), 6.63 (bs, 1H), 6.87 (t, *J* = 8 Hz, 1H), 6.95 (d, *J* = 8 Hz, 1H), 7.25 (d, *J* = 12 Hz, 1H), 7.35-7.41 (m, 5H)

mp = 118-119 °C

(**21**) N-[((5S)-3-{4-[(1α,5α,6β)-3,3-dioxido-3-thiabicyclo[3.1.0]hex-6-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide



21

Lithium butoxide solution (3.0 mL of a 1.0 M THF solution, 3.0 mmol) was added to a cooled (0 °C) solution of benzyl 3-fluoro-4-[(1α,5α,6β)-3-thiabicyclo[3.1.0]hex-6-yl]phenylcarbamate (0.35 g, 1.0 mmol) in DMF (0.7 mL) and MeOH (0.081 mL, 2.0 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester (0.39 g, 2.0 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Saturated aqueous ammonium chloride (2 mL) was added, along with 10 mL of H_2O and 10 mL of brine. The solution was extracted with three portions of dichloromethane and the combined organic phases dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by column chromatography (0-3% MeOH- dichloromethane) to provide the sulfide intermediate N-[((5S)-3-{3-fluoro-4-[(1α,5α,6β)-3-thiabicyclo[3.1.0]hex-6-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (0.24 g, 68% yield).

Peracetic acid (0.18 mL of a 32% aqueous solution, 0.856 mmol) was added to a solution of N-[((5S)-3-{3-fluoro-4-[(1α,5α,6β)-3-thiabicyclo[3.1.0]hex-6-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (0.10 g, 0.285 mmol) in THF (9 mL) cooled at 0 °C. The reaction mixture was stirred for 2 h at room temperature, treated with more peracetic acid (0.050 mL) and stirred another 3 h. The reaction was quenched by the addition of saturated $Na_2S_2O_3$ (2 mL) and water (5 mL). The solution was concentrated to remove THF and the resulting aqueous solution extracted with three portions of ethyl acetate. Combined organic extracts were washed with dilute $NaHCO_3$, brine, and dried

($MgSO_4$). The crude product was purified by column chromatography (0-4% MeOH-dichloromethane) to provide **21** as a foam.

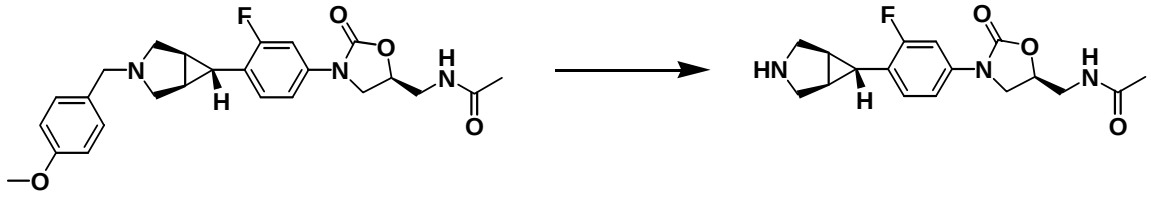
Yield 0.089 g (82%)

ESI-MS (m/z): [M+Na] = 405

^{1}H NMR (300 MHz, d_6-DMSO): 1.82 (s, 3H), 2.10 (m, 2H), 2.33 (t, *J* = 4 Hz, 1H), 3.01 (d, *J* = 13 Hz, 2H), 3.33-3.41 (m, 2H), 3.59 (m, 2H), 3.71 (t, *J* = 7 Hz, 1H), 4.09 (t, *J* = 9 Hz, 1H), 4.71 (m, 1H), 7.12 (t, *J* = 8 Hz, 1H), 7.22 (d, *J* = 8 Hz, 1H), 7.47 (d, *J* = 13 Hz, 1H), 8.24 (t, *J* = 5 Hz, 1H)

Representative procedures for removal of 4-methoxybenzyl (PMB) protection in azabicyclic systems.

N-[((5S)-3-{4-[(1α,5α,6β)-3-azabicyclo[3.1.0]hex-6-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide



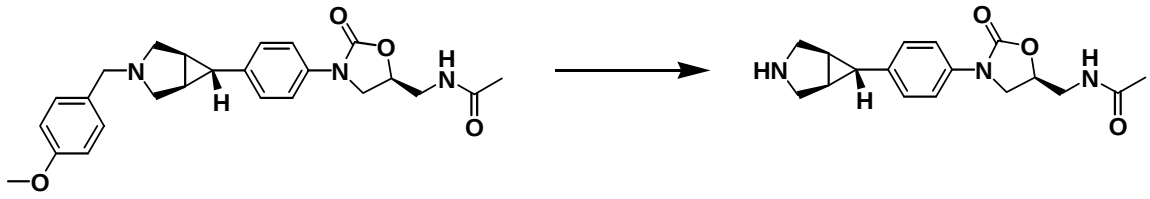
A solution of N-[((5S)-3-{3-fluoro-4-[exo-(1α,5α,6β)-3-(4-methoxybenzyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (0.087 g, 0.19 mmol) in 1:1 ethyl acetate-methanol (5 mL) was stirred under a hydrogen atmosphere in the presence of 20% $Pd(OH)_2/C$ (0.10 g) for 4 h and then filtered through celite. The filtrate was concentrated to provide *N*-[((5S)-3-{4-[(1α,5α,6β)-3-azabicyclo[3.1.0]hex-6-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide which could be used directly in subsequent reactions, or purified by column chromatography (0-6% MeOH-dichloromethane-1% Et_3N).

Yield 0.055 g (86%)

ESI-MS (m/z): [M+H] = 334

^{1}H NMR (300 MHz, CD_3OD): 1.88 (m, 2H), 1.95 (s, 3H), 1.96 (m, 1H), 3.05 (d, *J* = 11 Hz, 2H), 3.22 (d, *J* = 11 Hz, 2H), 3.54 (d, *J* = 5 Hz, 2H), 3.78 (m, 1H), 4.11 (t, *J* = 9 Hz, 1H), 4.78 (m, 1H), 7.03 (t, *J* = 9 Hz, 1H), 7.17 (dd, *J* = 9, 2 Hz, 1H), 7.43 (dd, *J* = 13, 3 Hz, 1H)

N-[((5S)-3-{4-[(1α,5α,6β)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide.



A solution of *N*-[((5S)-3-{4-[(1α,5α,6β)-3-(4-methoxybenzyl)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (0.11 g, 0.25 mmol) in dichloromethane (1.0 mL) and triethylamine (0.035 mL, 0.25 mmol) and stirred at 0 °C. To this, 1-chloroethyl chloroformate (0.055 mL, 0.5 mmol) was added and the reaction mixture stirred at 0 °C for 30 min. The reaction mixture was then concentrated, dissolved in methanol and heated at reflux for 45 min. The reaction mixture was then concentrated and triturated with diethyl ether to provide *N*-[((5S)-3-{4-[(1α,5α,6β)-3-azabicyclo[3.1.0]hex-6-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide hydrochloride as a yellow powder. This material was used directly in subsequent reactions without further purification.

Crude Yield 0.085 g (>95%)

ESI-MS (m/z): [M+H] = 316

451-51

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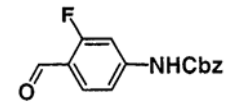

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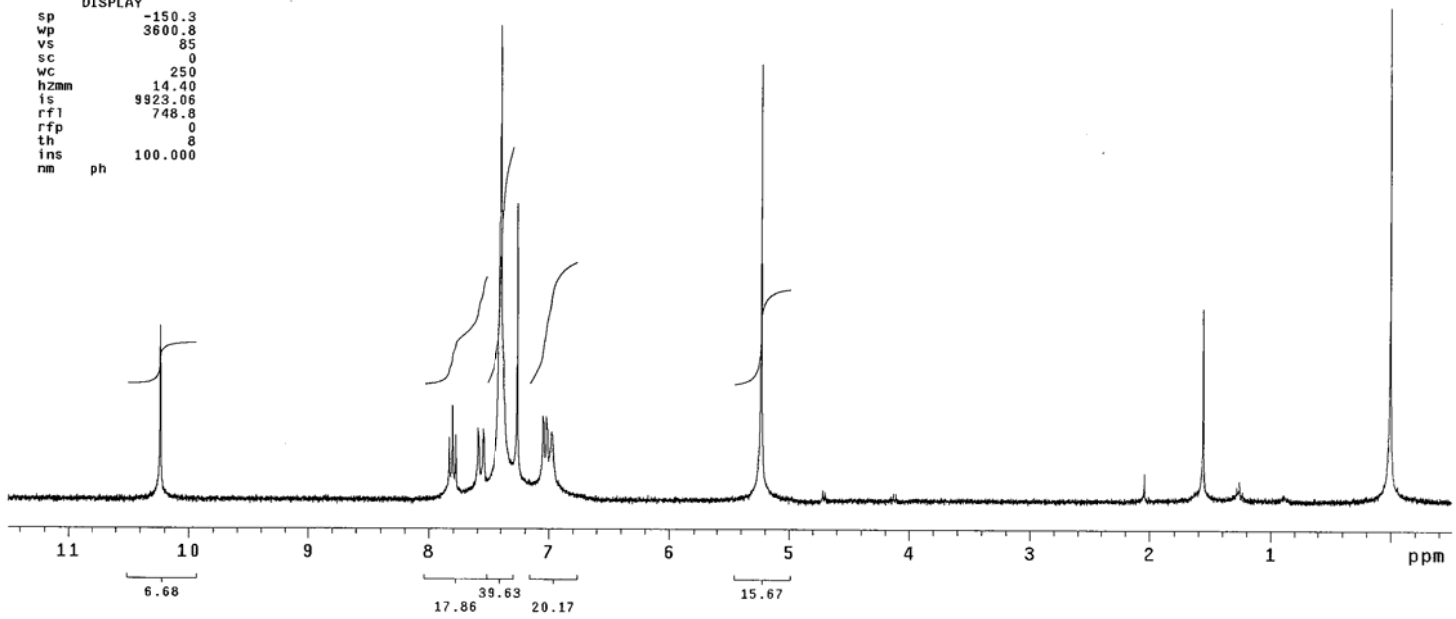

451-60

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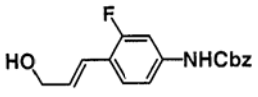
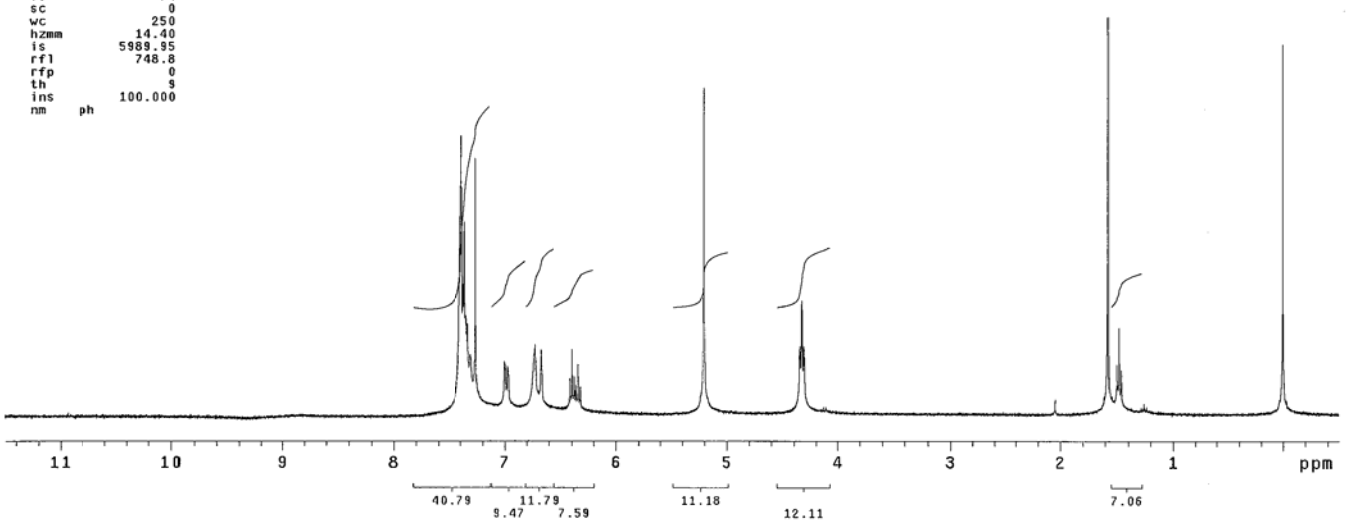


3



rv-273-91
STANDARD 1H OBSERVE

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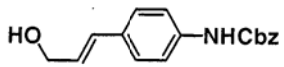

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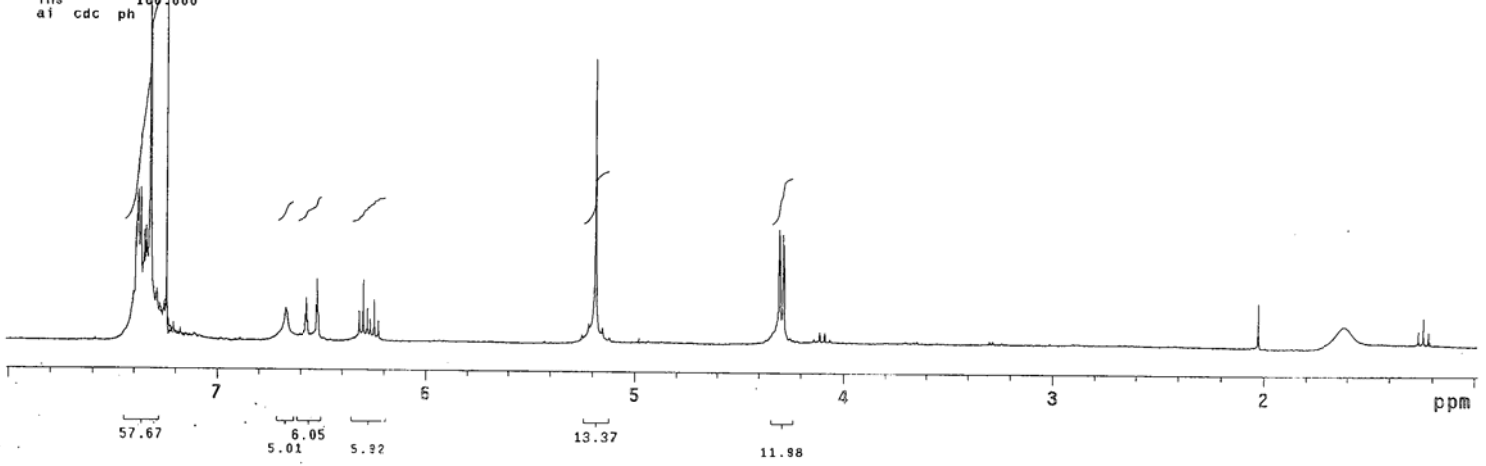

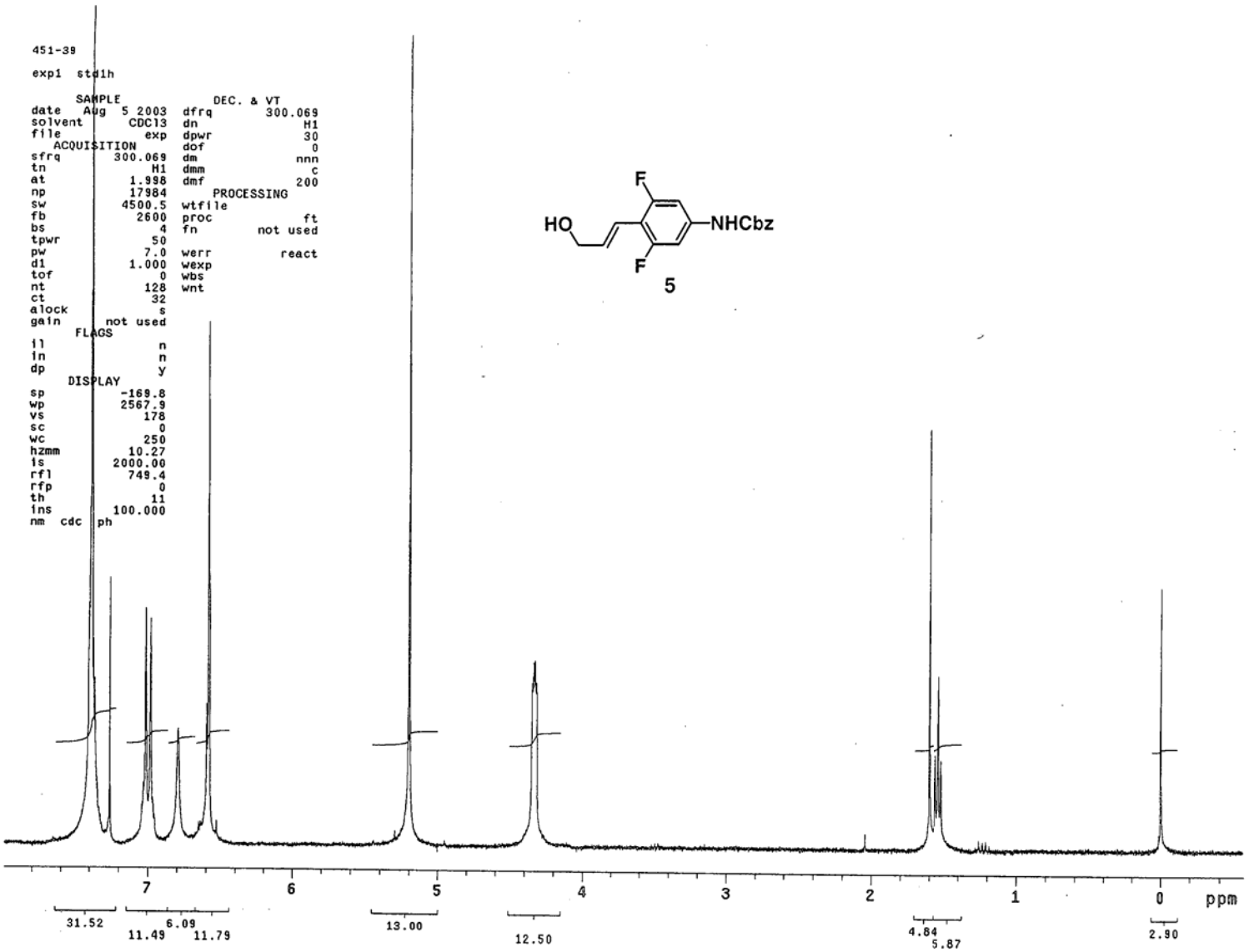
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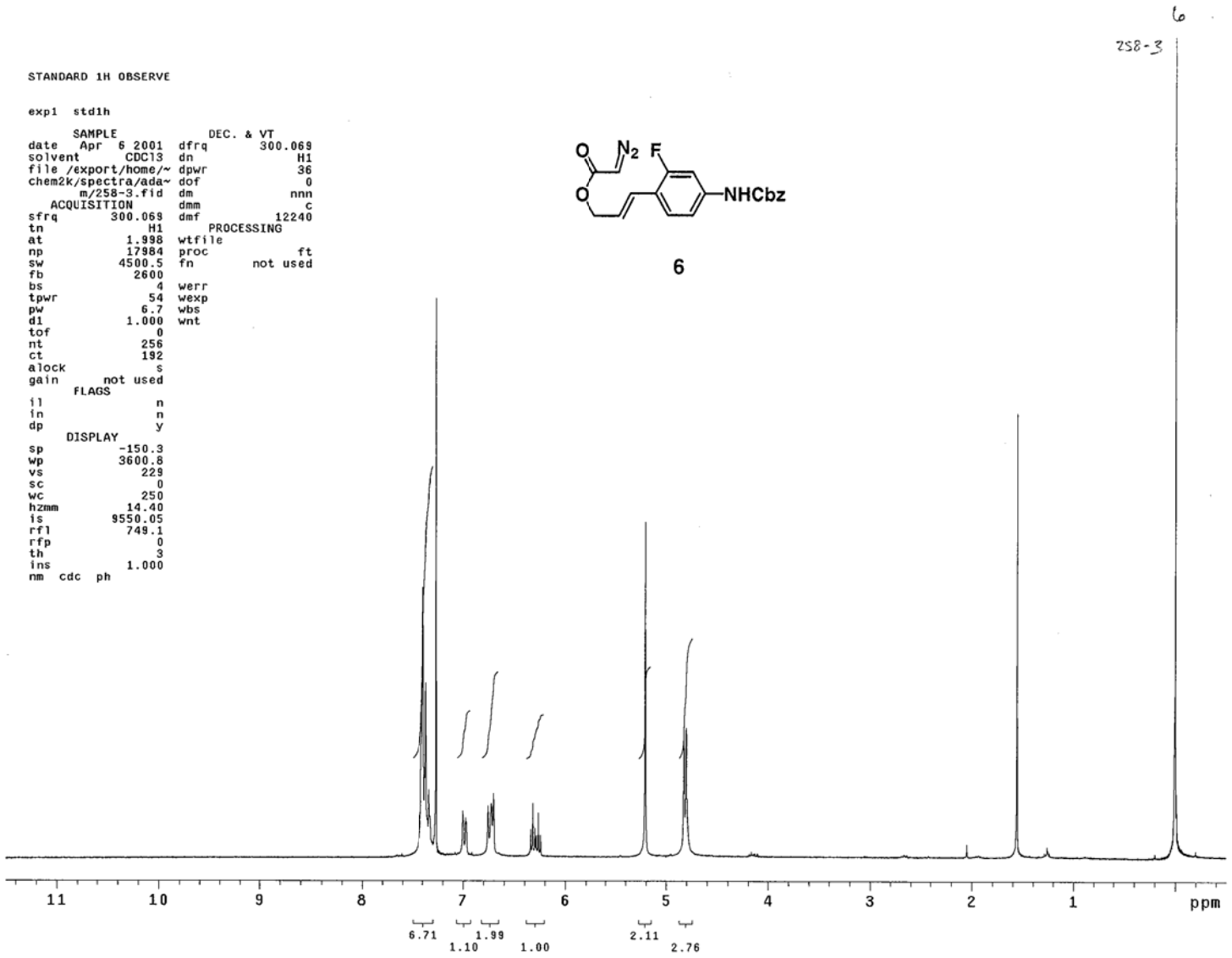
6
258-3
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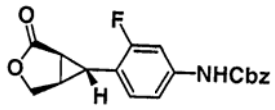
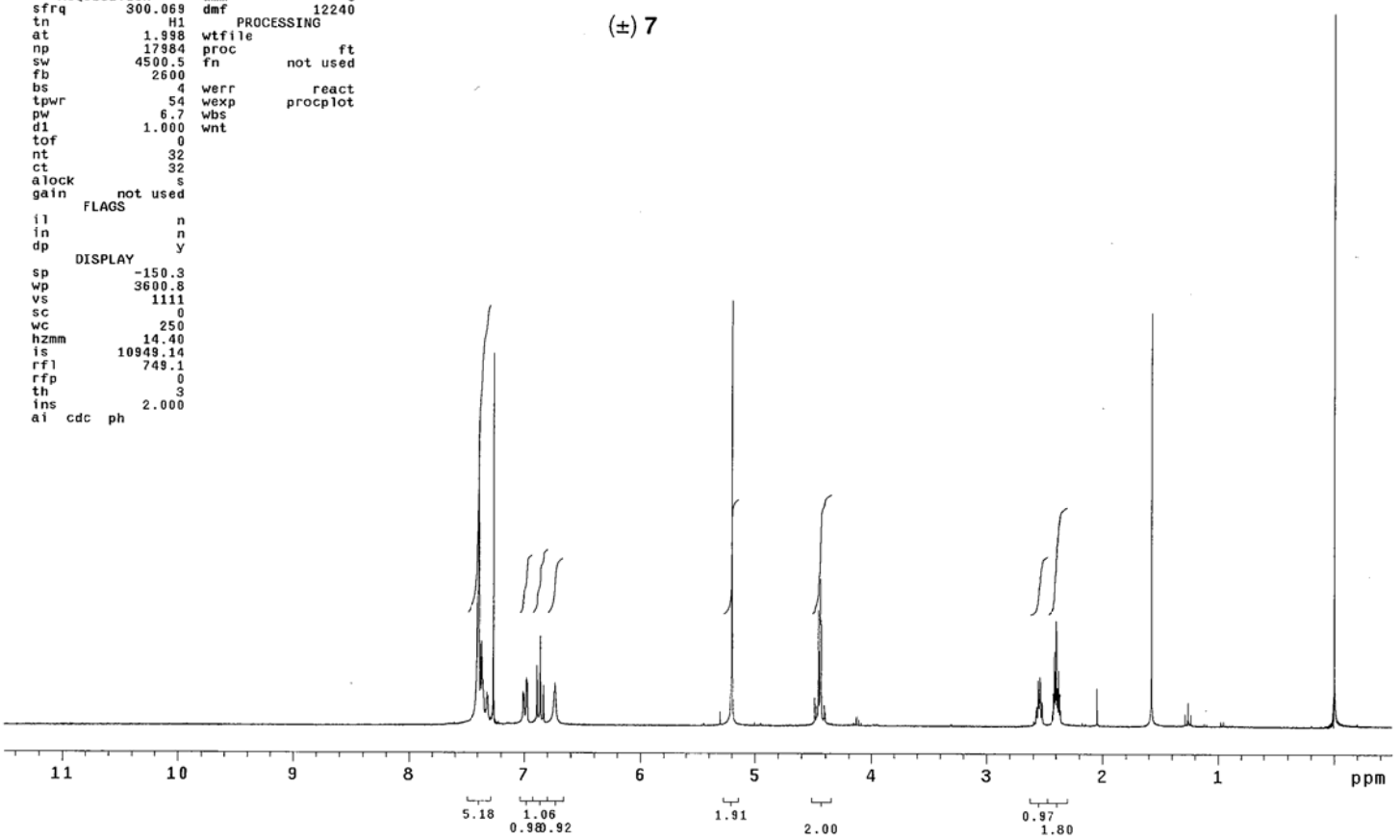
237-92
STANDARD 1H OBSERVE

exp1 std1h

SAMPLE		DEC. & VT	
date	Mar 30 2001	dfrq	300.069
solvent	cdcl3	dn	H1
file	/export/home/~	dpwr	36
chem2k/spectra/ada~		dof	0
	m/237-92.fid	dm	nnn
ACQUISITION		dmm	c
sfrq	300.069	dmf	12240
tn	H1	PROCESSING	
at	1.998	wtfile	
np	17984	proc	ft
sw	4500.5	fn	not used
fb	2600		
bs	4	werr	react
tpwr	54	wexp	procplot
pw	6.7	wbs	
d1	1.000	wnt	
tof	0		
nt	32		
ct	32		
alock	s		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-150.3		
wp	3600.8		
vs	1111		
sc	0		
wc	250		
hzmm	14.40		
is	10949.14		
rfl	749.1		
rfp	0		
th	3		
ins	2.000		
ai cdc ph			



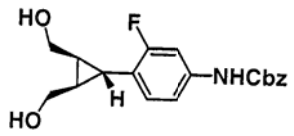
(±) 7



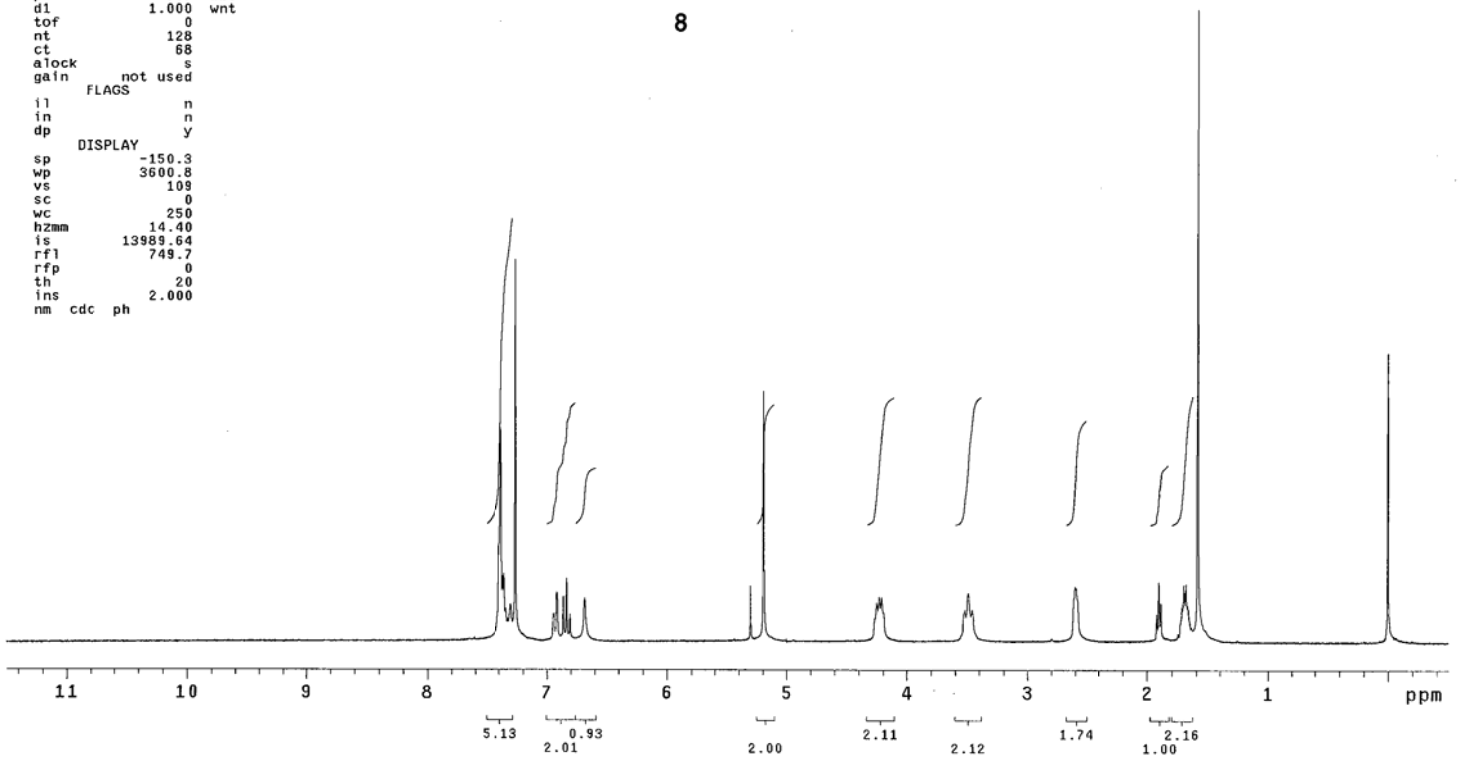
STANDARD 1H OBSERVE

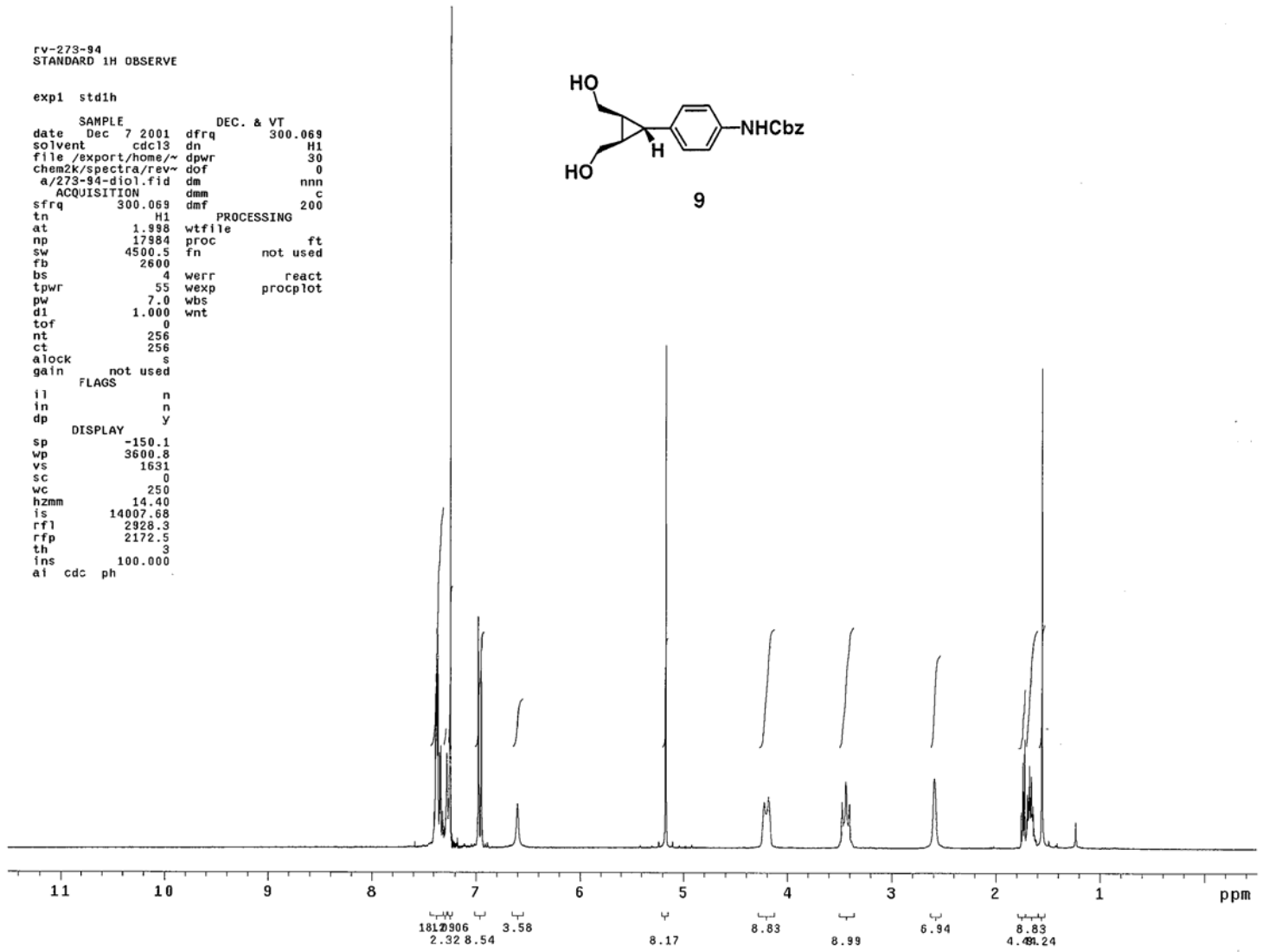
exp1 std1h

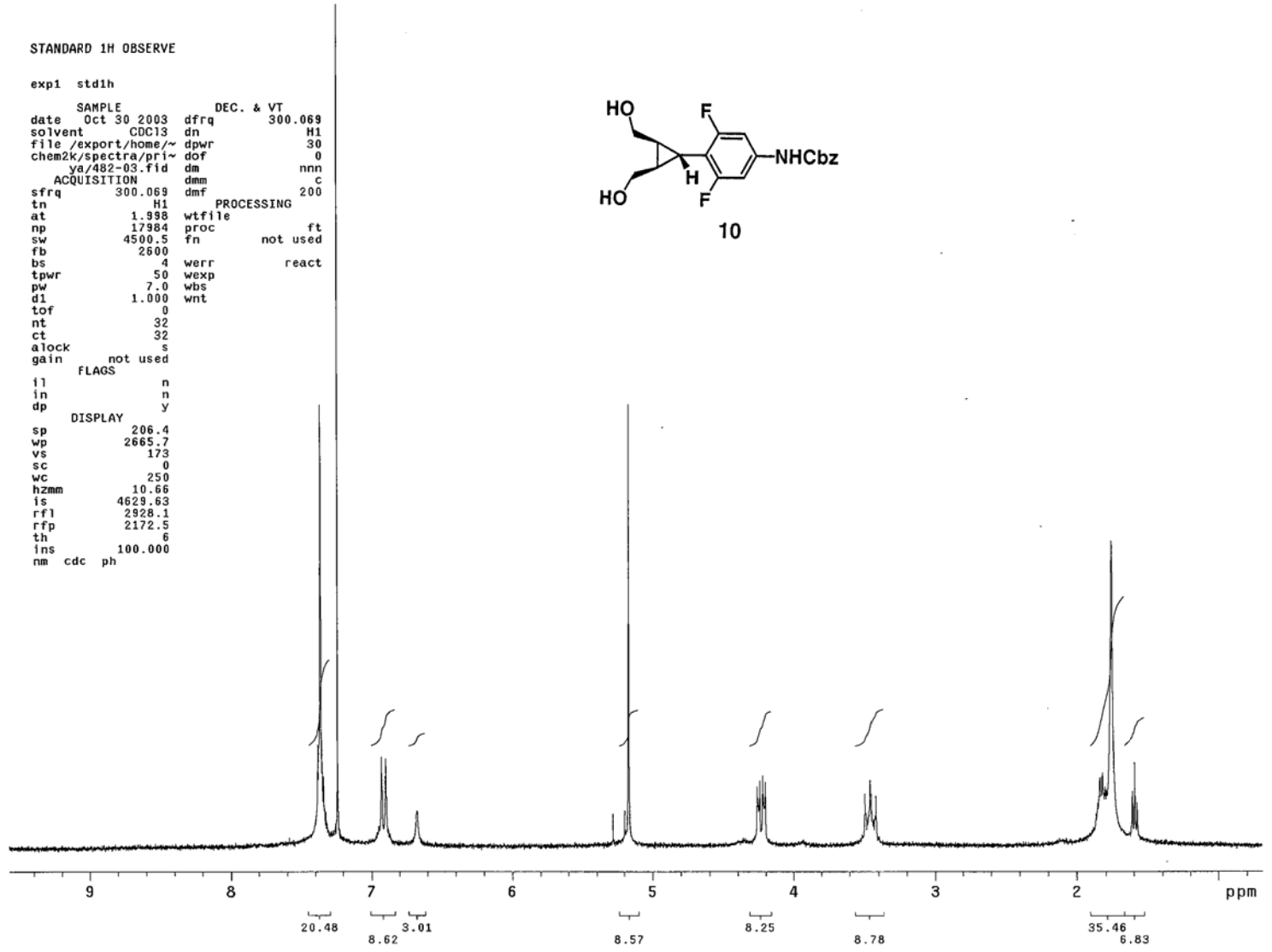
SAMPLE		DEC. & VT	
date	Jul 18 2001	dfrq	300.069
solvent	CDCl3	dn	H1
file	/export/home/~	dpwr	36
chem2k/spectra/ada~		dof	0
	m/258-75.fid	dm	nnn
ACQUISITION		dmm	c
sfrq	300.069	dmf	12240
tn	H1	PROCESSING	
at	1.998	wtfile	
np	17984	proc	ft
sw	4500.5	fn	not used
fb	2600		
bs	4	werr	
tpwr	54	wexp	
pw	6.7	wbs	
d1	1.000	wnt	
tof	0		
nt	128		
ct	68		
alock	s		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-150.3		
wp	3600.8		
vs	109		
sc	0		
wc	250		
hzmm	14.40		
is	13989.64		
rfl	749.7		
rfp	0		
th	20		
ins	2.000		
nm cdc ph			

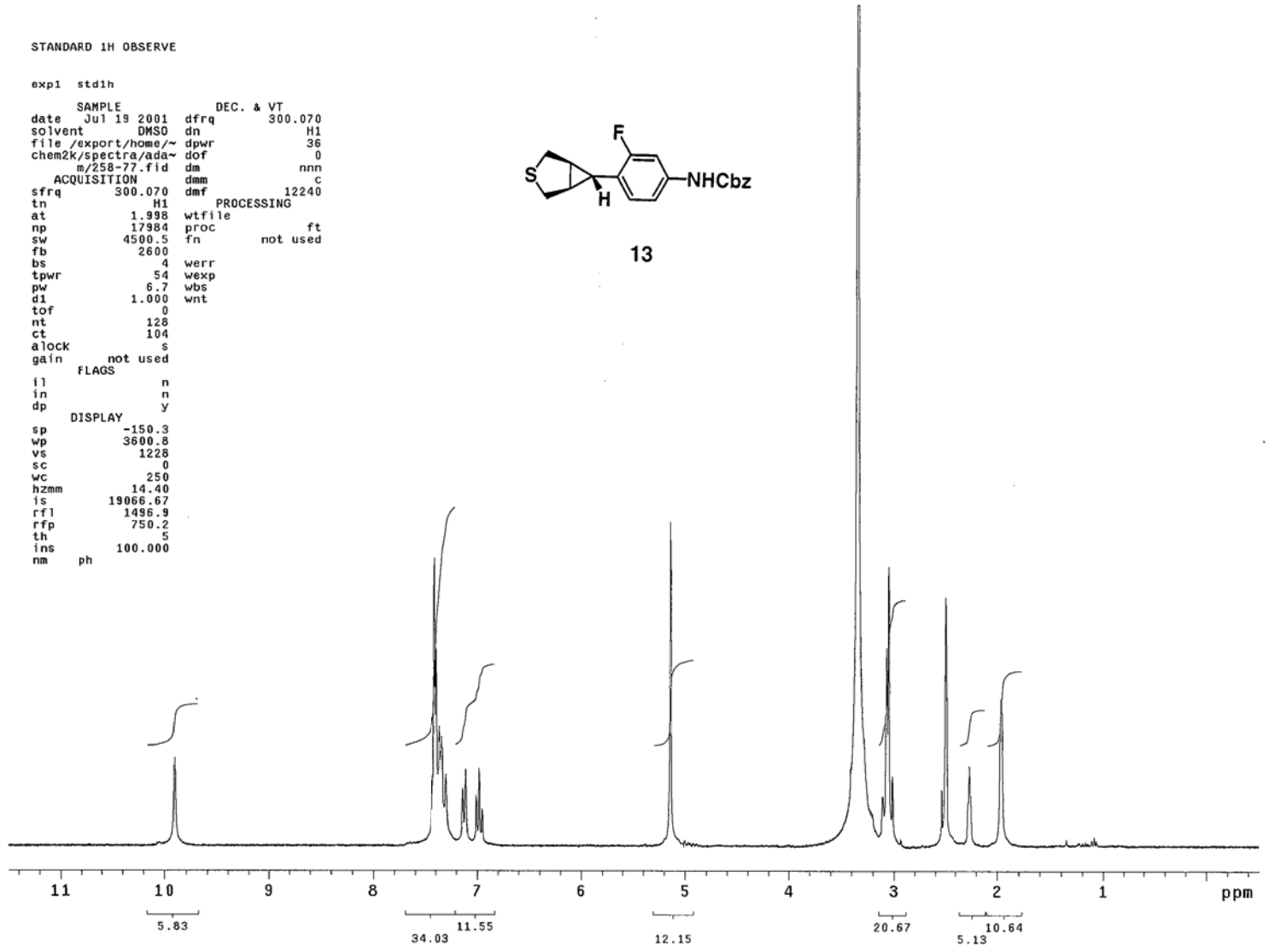


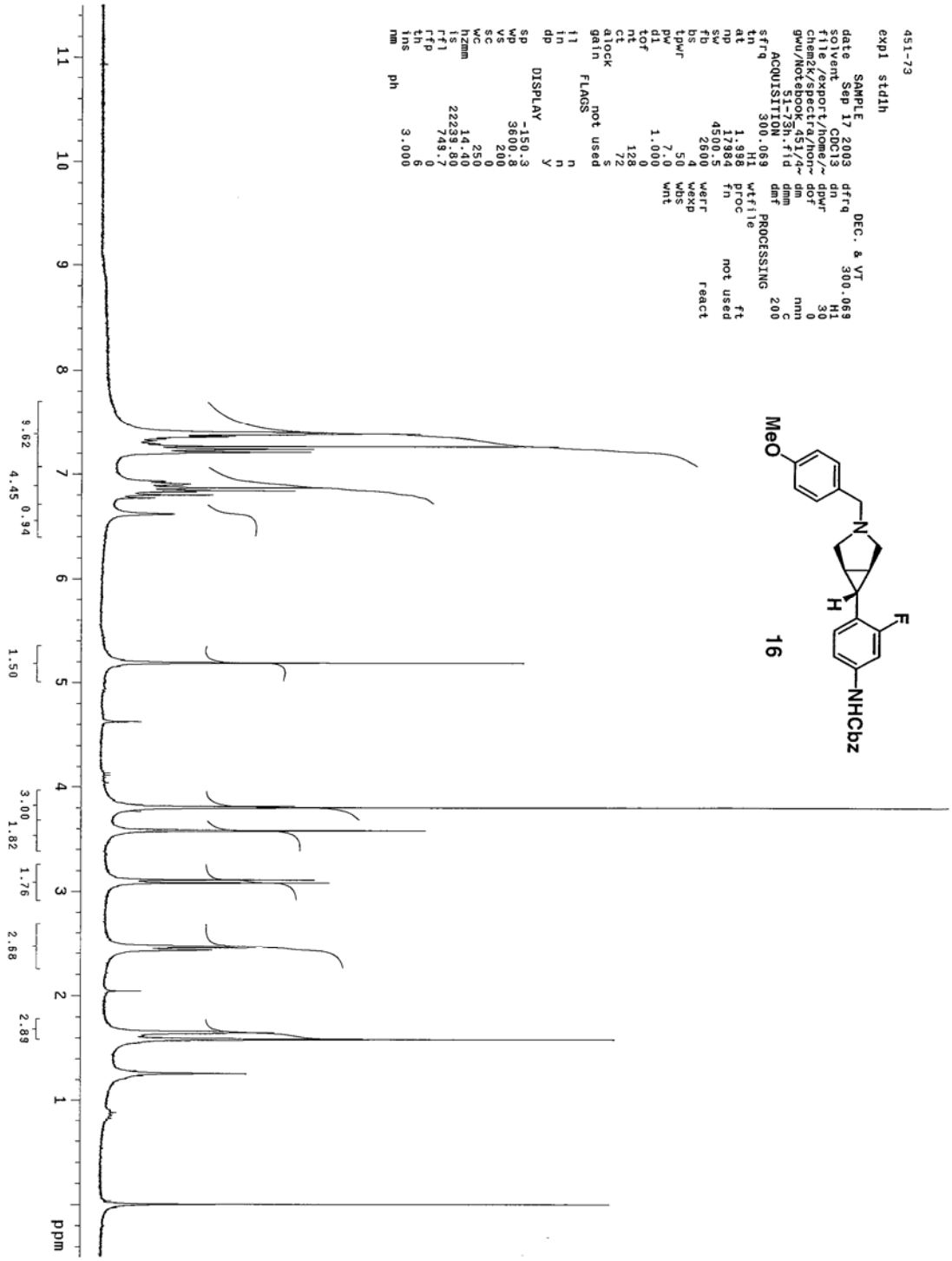
8

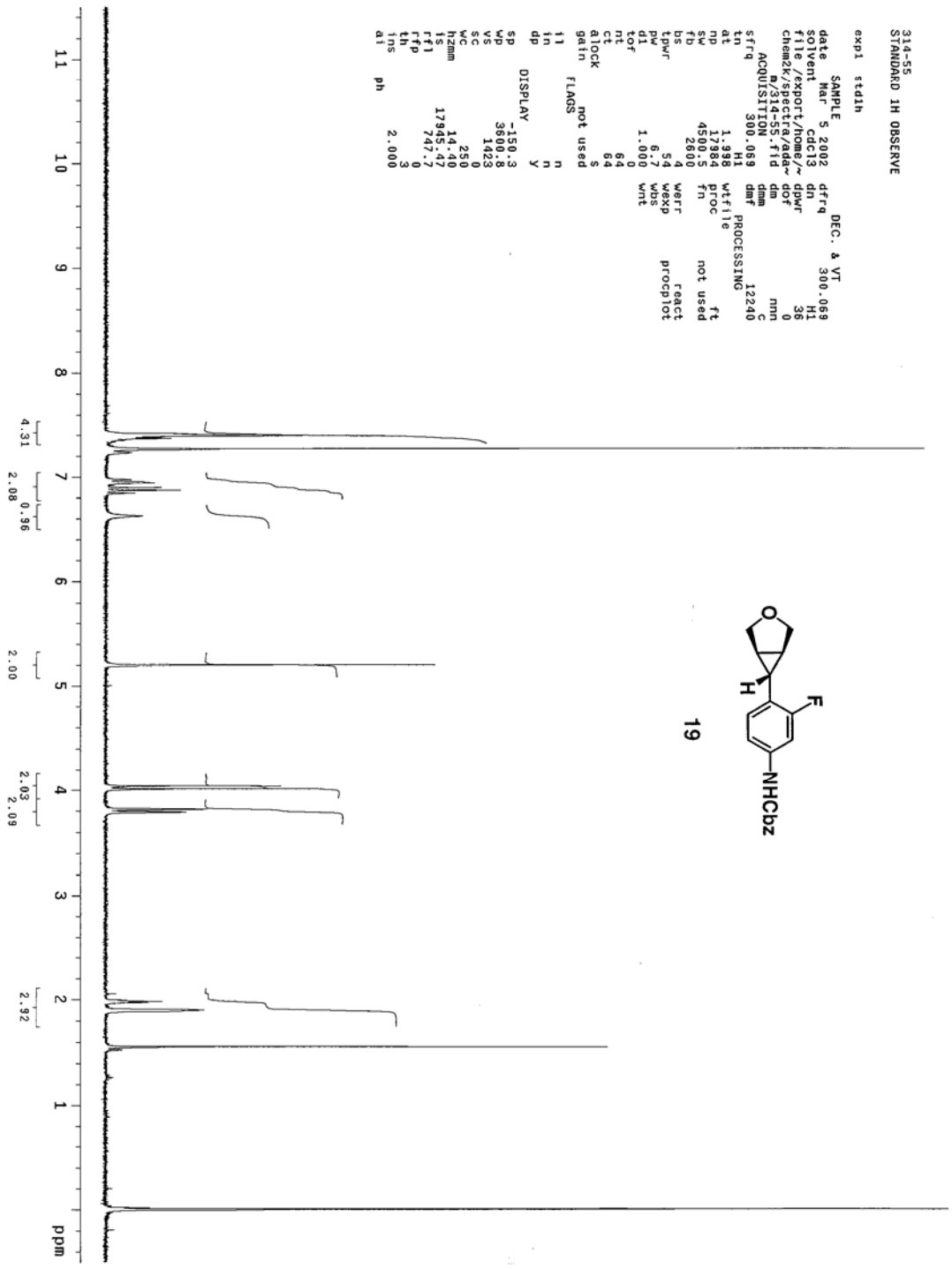



rv-273-94
STANDARD 1H OBSERVE
exp1 std1h
SAMPLE
date Dec 7 2001
solvent cdcl3
file /export/home/~
chem2k/spectra/rev~
a/273-94-diol.fid
ACQUISITION
sfrq 300.069
tn H1
at 1.998
np 17984
sw 4500.5
fb 2600
bs 4
tpwr 55
pw 7.0
d1 1.000
tof 0
nt 256
ct 256
alock s
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -150.1
wp 3600.8
vs 1631
sc 0
wc 250
hzmm 14.40
is 14007.68
rfl 2928.3
rfp 2172.5
th 3
ins 100.000
ai cdc ph
DEC. & VT
dfrq 300.069
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr react
wexp procplot
wbs
wnt
HO
HO
H
NHCbz
9
11
10
9
8
7
6
5
4
3
2
1
ppm
2.32
8.54
3.58
8.17
8.83
8.99
6.94
8.83


STANDARD 1H OBSERVE
exp1 std1h
SAMPLE
date Oct 30 2003
solvent CDCl3
file /export/home/~
chem2k/spectra/pri~
ya/482-03.fid
ACQUISITION
sfrq 300.069
tn H1
at 1.998
np 17984
sw 4500.5
fb 2600
bs 4
tpwr 50
pw 7.0
d1 1.000
tof 0
nt 32
ct 32
alock s
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp 206.4
wp 2665.7
vs 173
sc 0
wc 250
hzmm 10.66
is 4629.63
rfl 2928.1
rfp 2172.5
th 6
ins 100.000
nm cdc ph
DEC. & VT
dfrq 300.069
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr react
wexp
wbs
wnt
HO
F
NHCbz
H
HO
F
10
9
8
7
6
5
4
3
2
ppm
20.48
8.62
3.01
8.57
8.25
8.78
35.46
6.83


STANDARD 1H OBSERVE
exp1 std1h
SAMPLE
date Jul 19 2001
solvent DMSO
file /export/home/~
chem2k/spectra/ada~
m/258-77.fid
ACQUISITION
sfrq 300.070
tn H1
at 1.998
np 17984
sw 4500.5
fb 2600
bs 4
tpwr 54
pw 6.7
d1 1.000
tof 0
nt 128
ct 104
alock s
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -150.3
wp 3600.8
vs 1228
sc 0
wc 250
hzmm 14.40
is 19066.67
rfl 1496.9
rfp 750.2
th 5
ins 100.000
nm ph
DEC. & VT
dfrq 300.070
dn H1
dpwr 36
dof 0
dm nnn
dmm c
dmf 12240
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
F
S
NHCbz
H
13
11
10
9
8
7
6
5
4
3
2
1
ppm
5.83
34.03
11.55
12.15
20.67
5.13
10.64

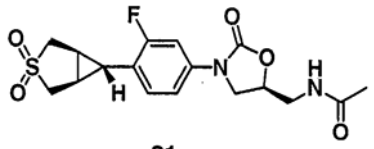

451-73
expl stdlh
SAMPLE
date Sep 17 2003
solvent CDCl3
file /export/home/~
chem2k/spectra/hon~
gwu/Notebook 451/4~
51-73h.fid
ACQUISITION
sfrq 300.069
tn H1
at 1.998
np 17984
sw 4500.5
fb 2600
bs 4
tpwr 50
pw 7.0
d1 1.000
tof 0
nt 128
ct 72
alock s
gain not used
FLAGS
fl n
in n
dp y
DISPLAY
sp -150.3
wp 3600.8
vs 200
sc 0
wc 250
hzmm 14.40
ts 22239.80
rfl 749.7
rfp 0
th 6
ins 3.000
nm ph
DEC. & VT
dfrq 300.069
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr react
wexp
wbs
wnt
MeO
F
NHCbz
16
9.62
4.45
0.94
1.50
3.00
1.82
1.76
2.68
2.89
ppm


314-55
STANDARD 1H OBSERVE
exp1 std1h
SAMPLE
date Mar 5 2002
solvent cdcl3
file /export/home/~
chem2k/spectra/ada~
m/314-55.fid
ACQUISITION
sfrq 300.069
tn H1
at 1.998
np 17984
sw 4500.5
fb 2600
bs 4
tpwr 54
pw 6.7
d1 1.000
tof 0
nt 64
ct 64
alock s
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -150.3
wp 3600.8
vs 1423
sc 0
wc 250
hzmm 14.40
ts 17945.47
rfl 747.7
rfp 0
th 3
ins 2.000
ai ph
DEC. & VT
dfrq 300.069
dn H1
dpwr 36
dof 0
dm nnn
dmm c
dmf 12240
PROCESSING
wtfile
proc ft
fn not used
werr
wexp react
wbs procplot
wnt
F
H
NHCbz
19
4.31
2.08
0.96
2.00
2.03
2.09
2.92
11
10
9
8
7
6
5
4
3
2
1
ppm

STANDARD 1H OBSERVE

exp3 std1h

SAMPLE		DEC. & VT	
date	Apr 19 2001	dfrq	300.070
solvent	DMSO	dn	H1
file	exp	dpwr	36
ACQUISITION		dof	0
sfrq	300.070	dm	nnn
tn	H1	dmm	c
at	1.998	dmf	12240
np	17984	PROCESSING	
sw	4500.5	wtfile	
fb	2600	proc	ft
bs	4	fn	not used
tpwr	54		
pw	6.7	werr	
d1	1.000	wexp	
tof	0	wbs	
nt	256	wnt	
ct	256		
alock	s		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-150.3		
wp	3600.8		
vs	2110		
sc	0		
wc	250		
hzmm	14.40		
is	35000.00		
rfl	1494.7		
rfp	750.2		
th	20		
ins	100.000		
nm cdc ph			



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