

*Supporting Information*

**Large Scale Practical Synthesis of Enantiomerically Pure *cis*-4-Amino-3-fluoro-1-methylpiperidine via Rhodium-Catalyzed Asymmetric Hydrogenation of a Tetrasubstituted Fluoroalkene**

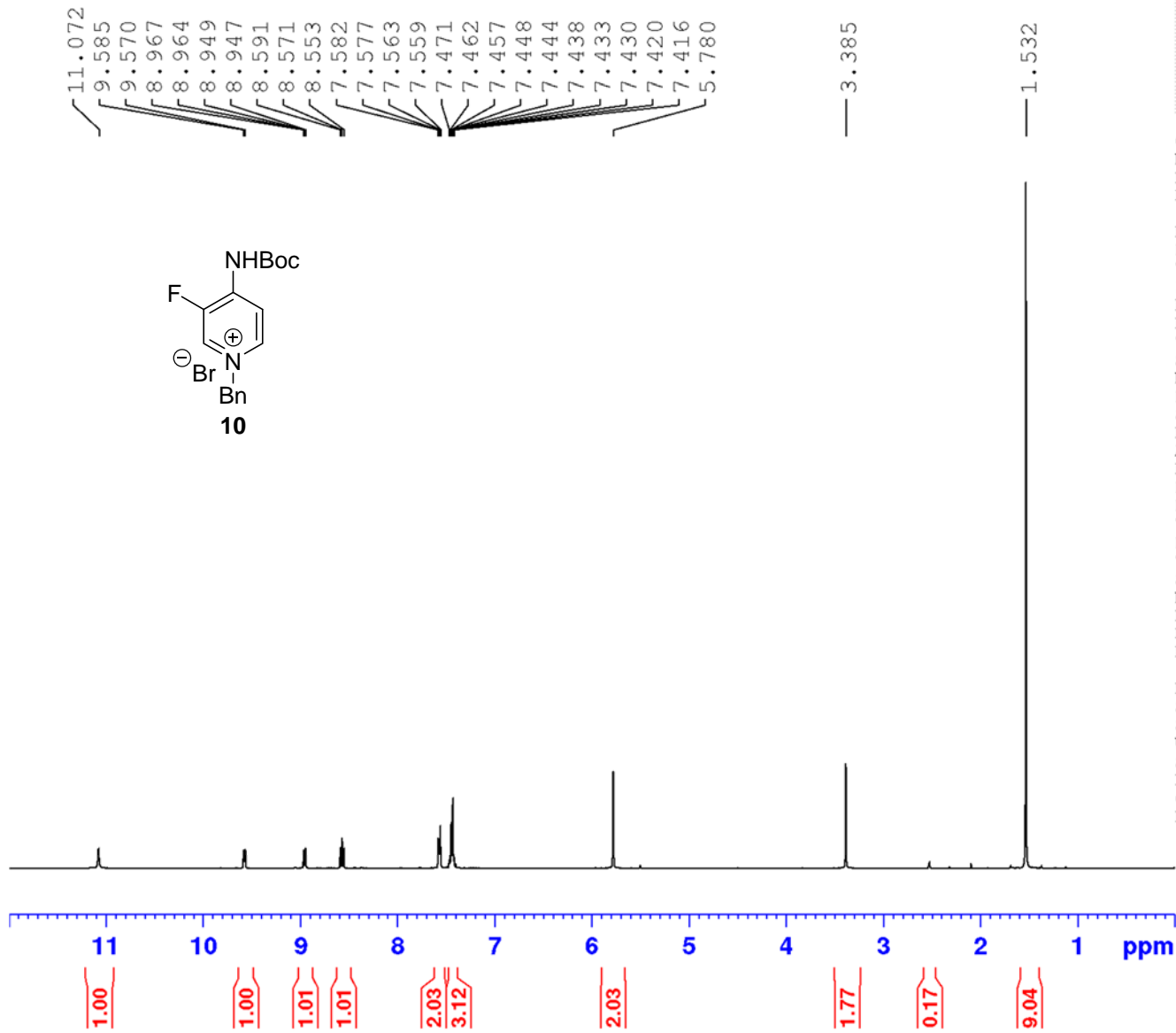
Bo Qu<sup>\*,a</sup>, Anjan Saha<sup>a</sup>, Guisheng Li<sup>a</sup>, Xingzhong Zeng<sup>a</sup>, Xiaojun Wang<sup>a</sup>, Nizar Haddad<sup>a</sup>, Xiaowen Hou<sup>a</sup>,  
Jon C. Lorenz<sup>a</sup>, Lifan Wu<sup>b</sup>, Scott Pennino<sup>b</sup>, Heewon Lee<sup>a</sup>, Jinhua J. Song<sup>a</sup>, Chris H. Senanayake<sup>a,#</sup>

- a. Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road,  
Ridgefield, Connecticut 06877, USA
- b. Material Analytical Sciences, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road,  
Ridgefield, CT 06877, USA

\*bo.qu@boehringer-ingelheim.com

**Table of Content**

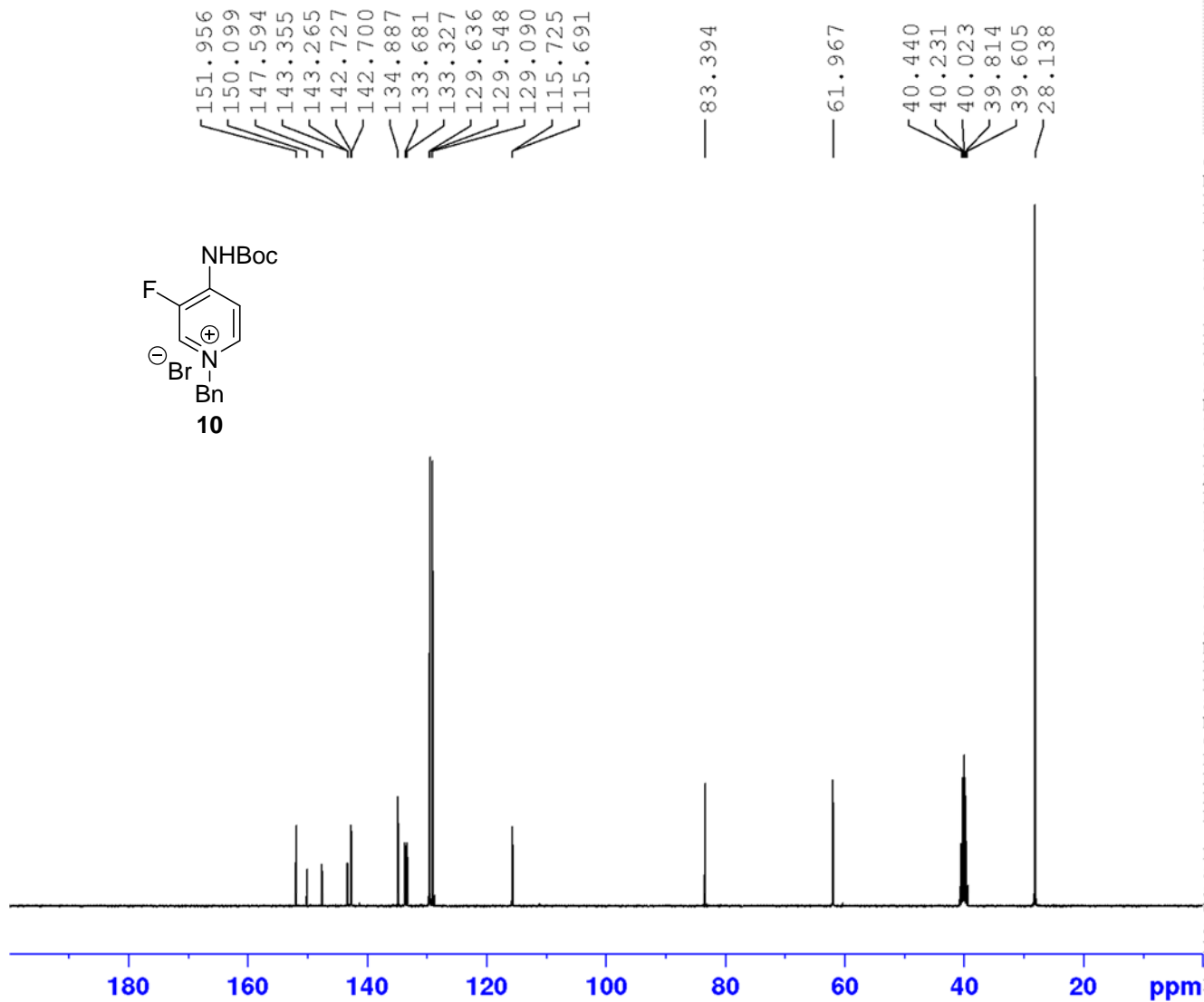
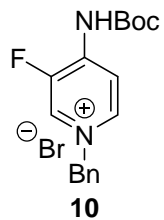
1	<sup>1</sup> H and <sup>13</sup> C NMR Spectra	S2
2	HPLC and GC data	S14



Current Data Parameters  
 NAME aks1-00024-1112  
 EXPNO 1  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20201112  
 Time 19.22 h  
 INSTRUM Avance  
 PROBHD Z108618\_0981 {  
 PULPROG zg10  
 TD 32768  
 SOLVENT DMSO  
 NS 16  
 DS 4  
 SWH 5882.353 Hz  
 FIDRES 0.359030 Hz  
 AQ 2.7852800 sec  
 RG 101  
 DW 85.000 usec  
 DE 6.50 usec  
 TE 300.0 K  
 D1 2.00000000 sec  
 TD0 1  
 SFO1 400.1327209 MHz  
 NUC1 1H  
 P0 1.56 usec  
 P1 14.00 usec  
 PLW1 15.73099995 W

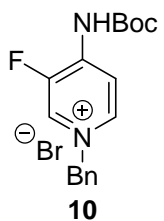
F2 - Processing parameters  
 SI 65536  
 SF 400.1299929 MHz  
 WDW EM  
 SSB 0  
 LB 0.05 Hz  
 GB 0  
 PC 1.00



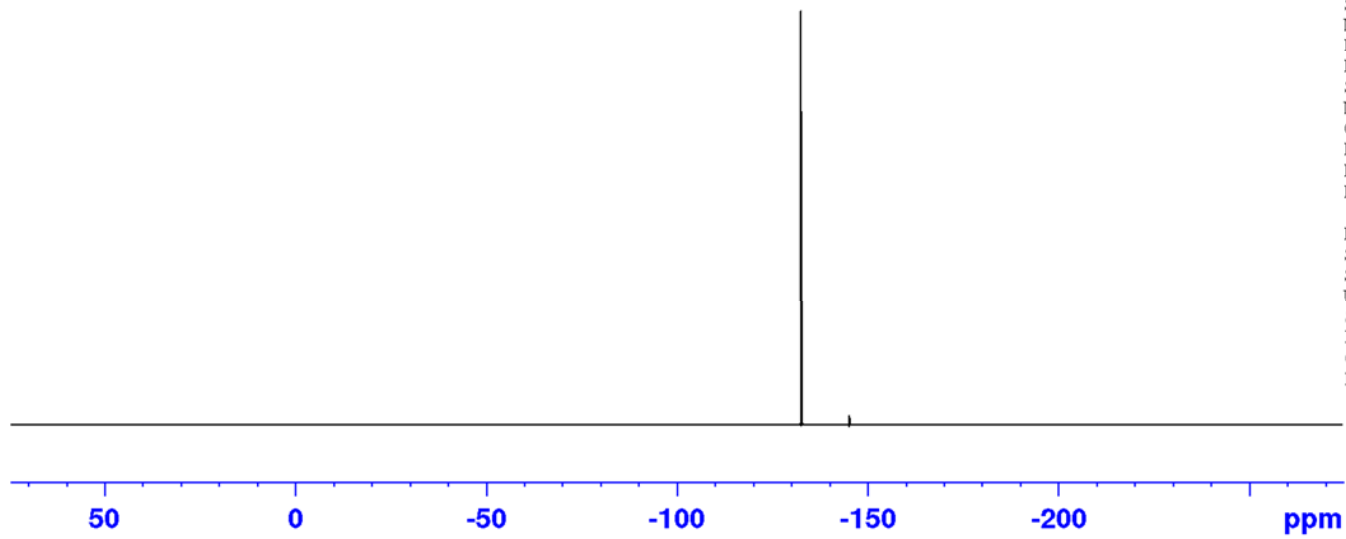
Current Data Parameters  
NAME aks1-00024-1112  
EXPNO 4  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20201112  
Time 21.05 h  
INSTRUM Avance  
PROBHD Z108618\_0981 {  
PULPROG zgpg  
TD 32768  
SOLVENT DMSO  
NS 2048  
DS 4  
SWH 23809.523 Hz  
FIDRES 1.453218 Hz  
AQ 0.6881280 sec  
RG 101  
DW 21.000 usec  
DE 6.50 usec  
TE 300.0 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1  
SFO1 100.6243395 MHz  
NUC1 13C  
P1 10.00 usec  
PLW1 53.94300079 W  
SFO2 400.1316005 MHz  
NUC2 1H  
CPDPRG[2] waltz16  
PCPD2 90.00 usec  
PLW2 15.73099995 W  
PLW12 0.38064000 W  
PLW13 0.19146000 W

F2 - Processing parameters  
SI 65536  
SF 100.6127690 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40



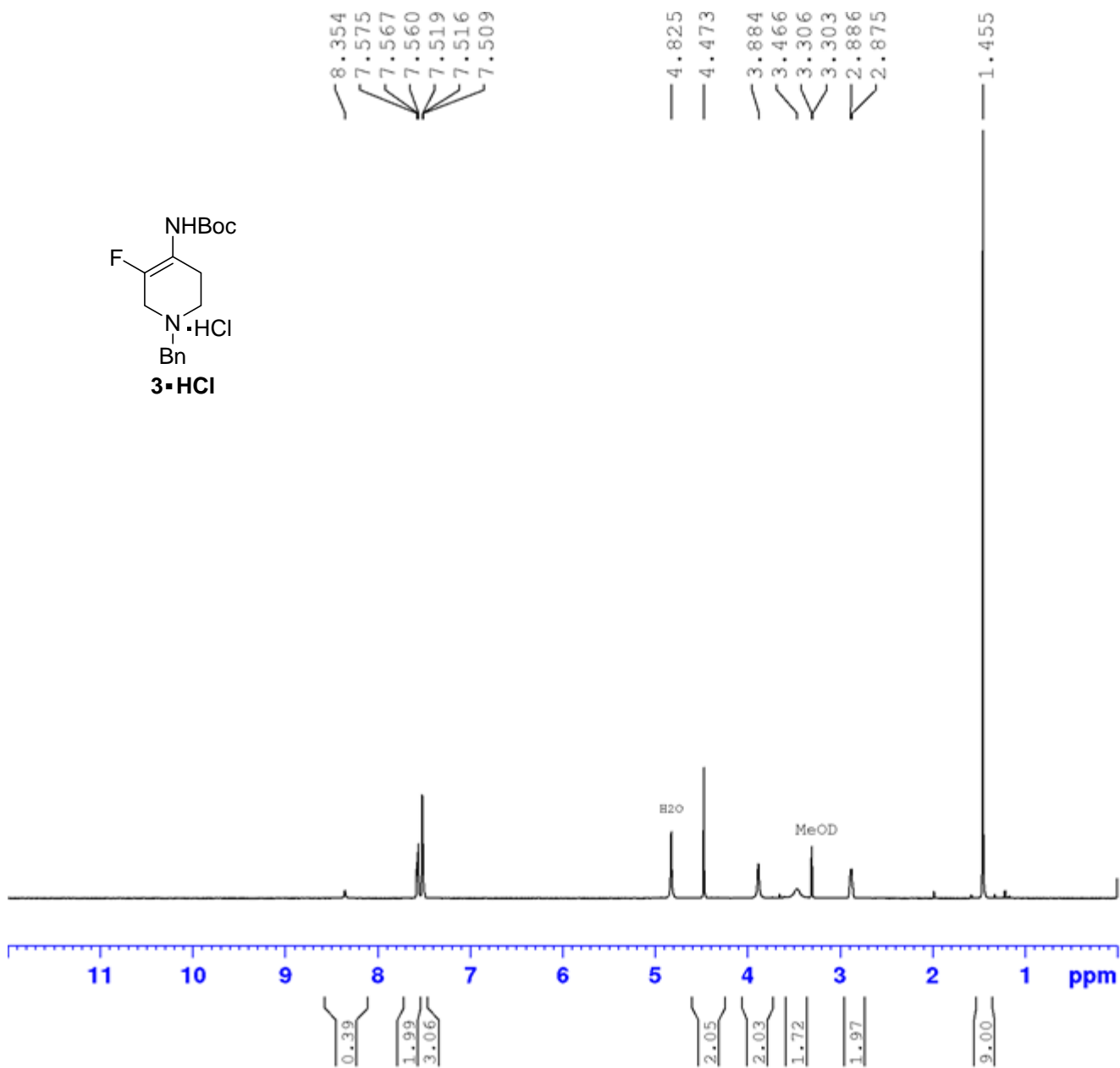
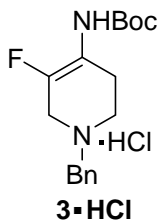
— -132.72



Current Data Parameters  
 NAME aks1-00024-1112  
 EXPNO 2  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20201112  
 Time 19.24 h  
 INSTRUM Avance  
 PROBHD Z108618\_0981 (  
 PULPROG zgig  
 TD 131072  
 SOLVENT DMSO  
 NS 16  
 DS 4  
 SWH 131578.953 Hz  
 FIDRES 2.007735 Hz  
 AQ 0.4980736 sec  
 RG 101  
 DW 3.800 usec  
 DE 6.50 usec  
 TE 300.1 K  
 D1 1.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 376.4607164 MHz  
 NUC1 19F  
 P1 15.00 usec  
 PLW1 17.84399986 W  
 SFO2 400.1316005 MHz  
 NUC2 1H  
 CPDPRG[2] waltz16  
 PCPD2 90.00 usec  
 PLW2 15.73099995 W  
 PLW12 0.38064000 W

F2 - Processing parameters  
 SI 262144  
 SF 376.4983660 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.00

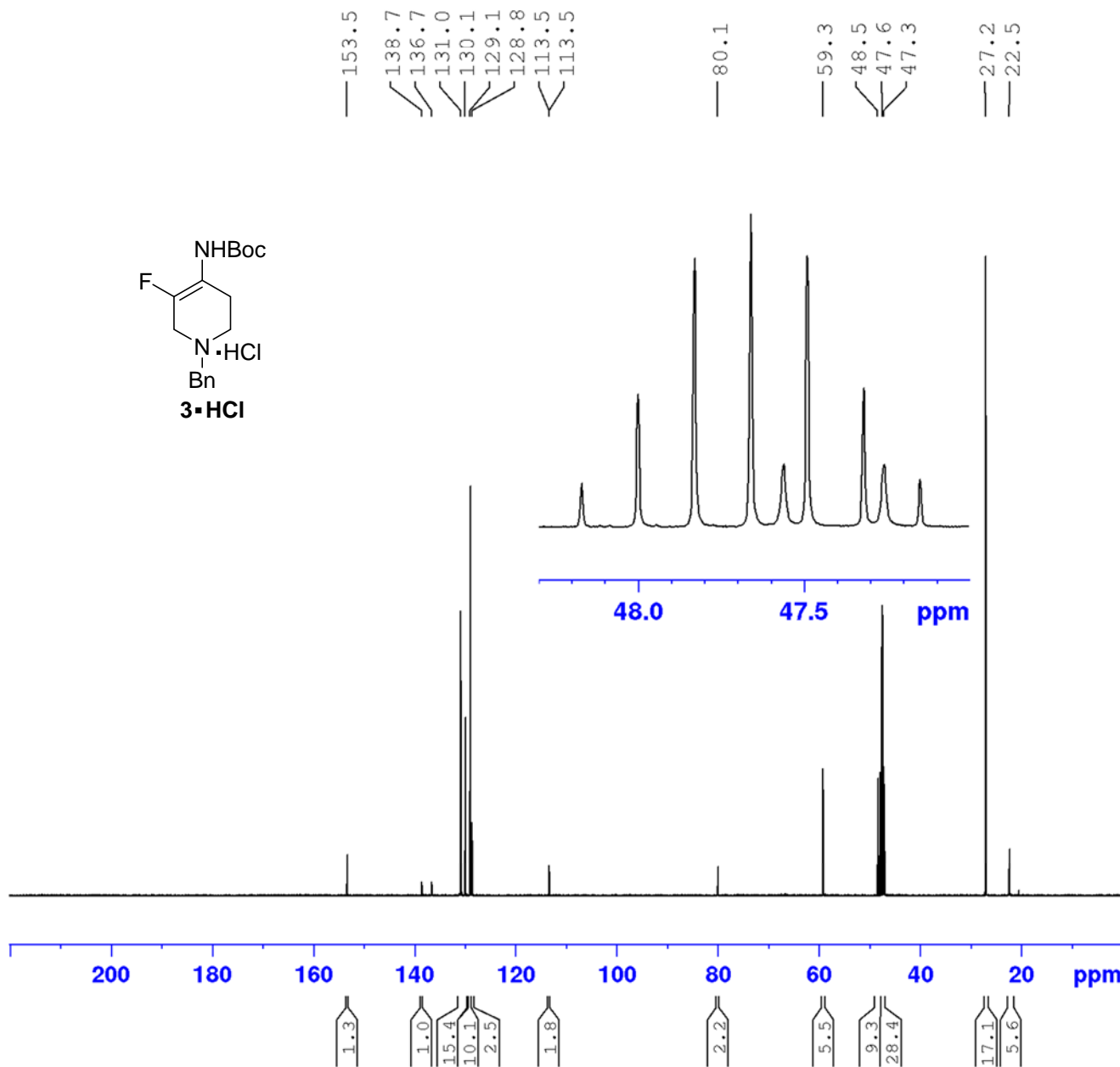
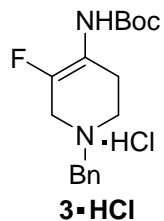


Current Data Parameters  
 NAME klp01417-meod  
 EXPNO 1  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20201121  
 Time\_ 15.16  
 INSTRUM spect  
 PROBHD 5 mm PABBO BB/  
 PULPROG zg10  
 TD 32768  
 SOLVENT MeOD  
 NS 16  
 DS 0  
 SWH 7500.000 Hz  
 FIDRES 0.228882 Hz  
 AQ 2.1845334 sec  
 RG 456  
 DW 66.667 usec  
 DE 6.50 usec  
 TE 300.0 K  
 D1 1.00000000 sec  
 TD0 1

----- CHANNEL f1 -----  
 SFO1 500.1325007 MHz  
 NUC1 1H  
 P1 13.65 usec  
 PLW1 16.79999924 W

F2 - Processing parameters  
 SI 16384  
 SF 500.1300114 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.00



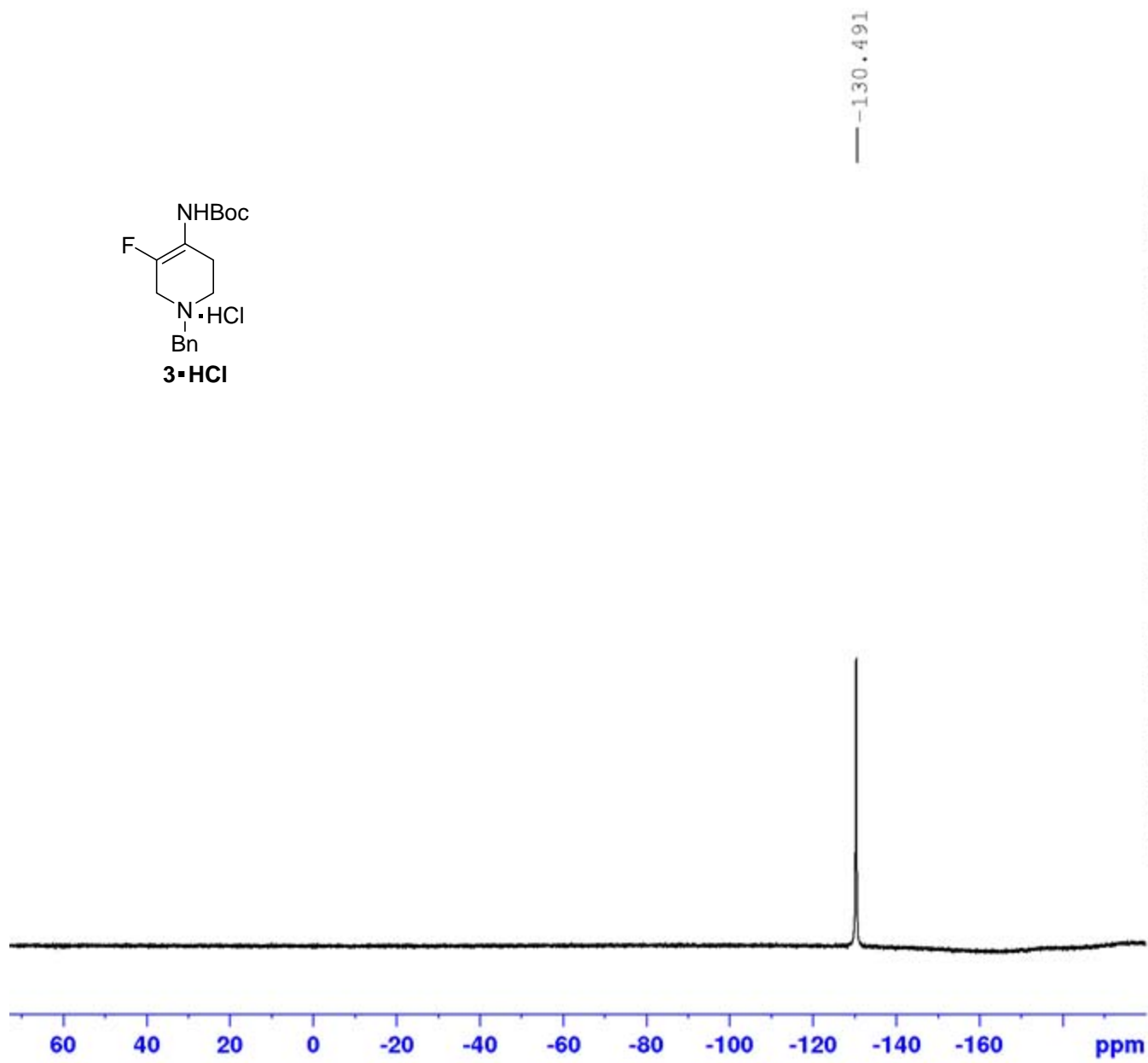
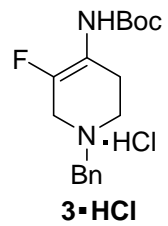
Current Data Parameters  
 NAME klp01417-meod  
 EXPNO 4  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20201121  
 Time\_ 19.54  
 INSTRUM spect  
 PROBHD 5 mm PABBO BB/  
 PULPROG zgpg  
 TD 262144  
 SOLVENT MeOD  
 NS 1024  
 DS 0  
 SWH 31250.000 Hz  
 FIDRES 0.119209 Hz  
 AQ 4.1943040 sec  
 RG 2050  
 DW 16.000 usec  
 DE 6.50 usec  
 TE 300.1 K  
 D1 1.00000000 sec  
 D11 0.03000000 sec  
 TDO 1

===== CHANNEL f1 =====  
 SFO1 125.7698617 MHz  
 NUC1 13C  
 P1 9.80 usec  
 PLW1 99.50000000 W

===== CHANNEL f2 =====  
 SFO2 500.1325007 MHz  
 NUC2 1H  
 CPDPRG[2] waltz16  
 PCPD2 80.00 usec  
 PLW2 16.79999924 W  
 PLW12 0.48910001 W  
 PLW13 0.24601001 W

F2 - Processing parameters  
 SI 131072  
 SF 125.7577890 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.40



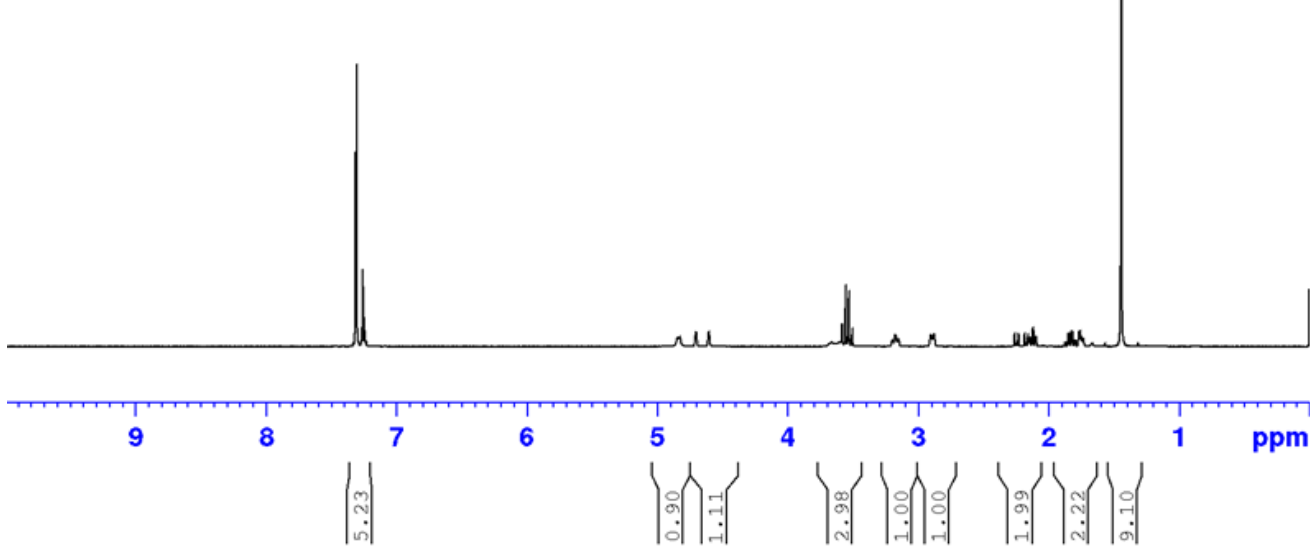
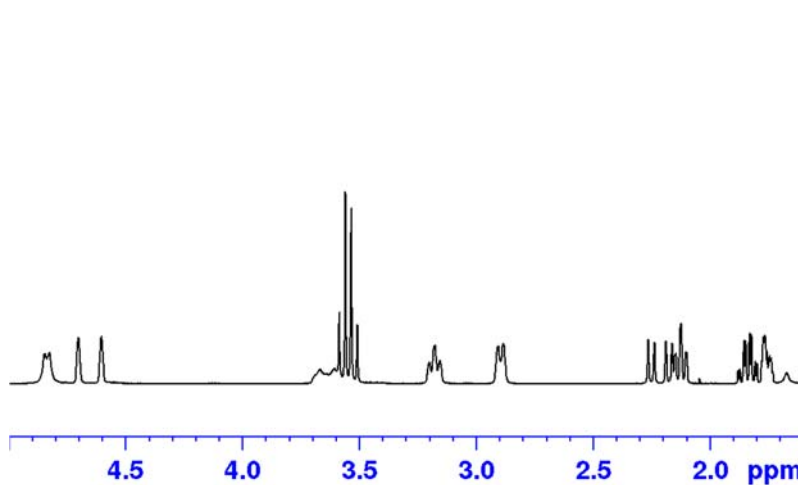
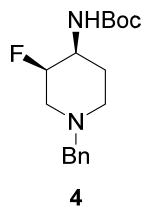
Current Data Parameters  
 NAME klp01417-meod  
 EXPNO 3  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20201121  
 Time 15.54  
 INSTRUM spect  
 PROBHD 5 mm PABBO BB/  
 PULPROG zg10flqn  
 TD 159766  
 SOLVENT MeOD  
 NS 96  
 DS 0  
 SWH 163043.484 Hz  
 FIDRES 1.020514 Hz  
 AQ 0.4899491 sec  
 RG 812  
 DW 3.067 usec  
 DE 6.50 usec  
 TE 300.0 K  
 D1 10.00000000 sec  
 TDO 1

----- CHANNEL f1 -----  
 SFO1 470.5457864 MHz  
 NUC1 19F  
 P1 13.80 usec  
 PLW1 30.00000000 W

F2 - Processing parameters  
 SI 16384  
 SF 470.5923770 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.00

7.315  
7.306  
7.298  
7.266  
7.258  
7.249  
7.239  
4.844  
4.827  
4.703  
4.604  
3.583  
3.556  
3.531  
3.505  
3.176  
3.172  
3.151  
2.905  
2.901  
2.882  
2.878  
2.259  
2.233  
2.183  
2.157  
2.145  
2.141  
2.121  
2.118  
2.098  
2.095  
1.849  
1.841  
1.825  
1.817  
1.766  
1.762  
1.758  
1.750  
1.740  
1.737  
1.733  
1.443



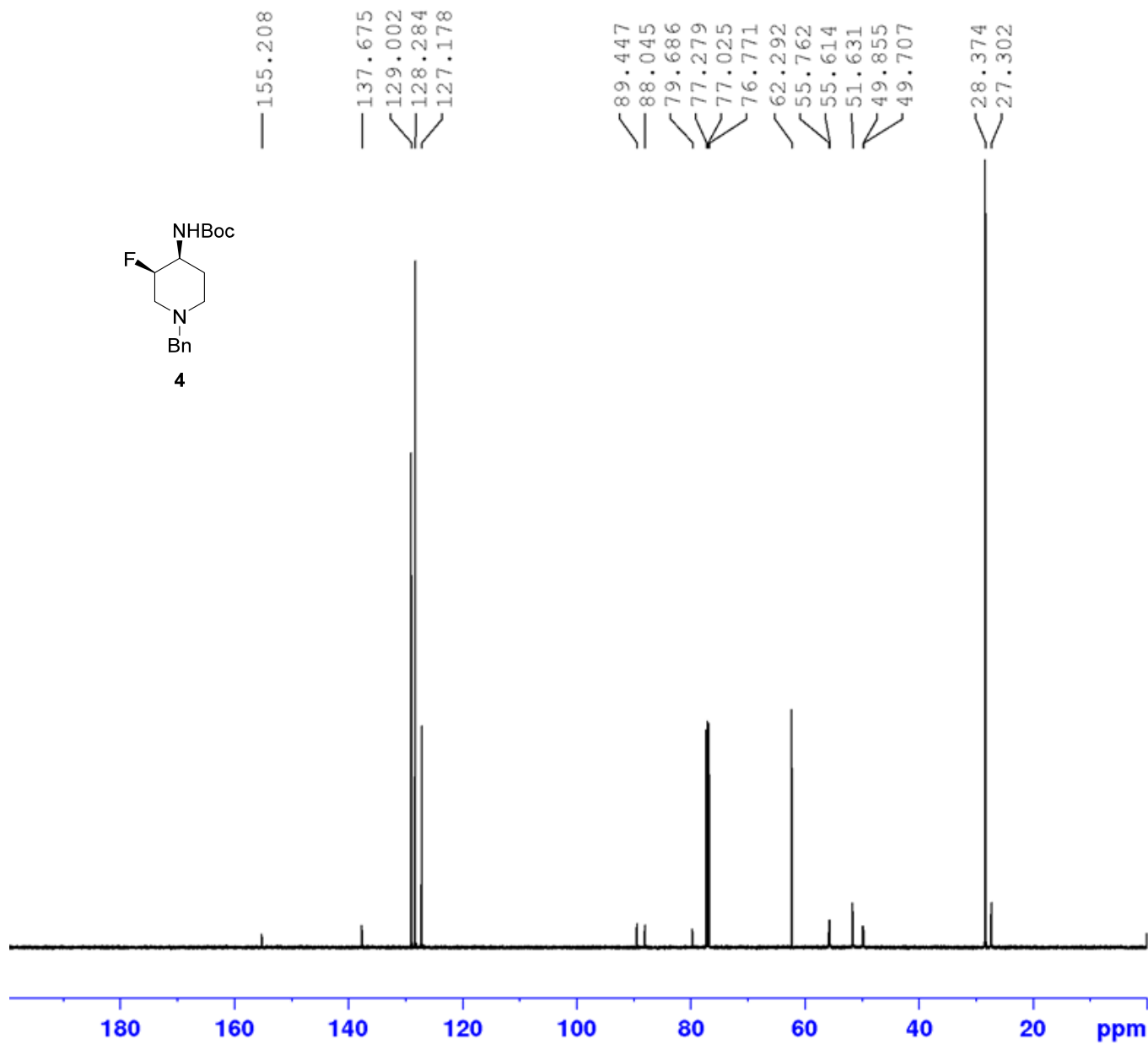
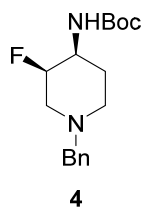
Current Data Parameters  
NAME bqu1-00624-pp  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20201201  
Time 22.12  
INSTRUM spect  
PROBHD 5 mm PABBO BB/  
PULPROG zg10  
TD 32768  
SOLVENT CDC13  
NS 16  
DS 0  
SWH 7500.000 Hz  
FIDRES 0.228882 Hz  
AQ 2.1845334 sec  
RG 406  
DW 66.667 usec  
DE 6.50 usec  
TE 300.0 K  
D1 1.00000000 sec  
TD0 1

----- CHANNEL f1 -----  
SFO1 500.1325007 MHz  
NUC1 1H  
P1 13.65 usec  
PLW1 16.79999924 W

F2 - Processing parameters  
SI 16384  
SF 500.1300132 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00





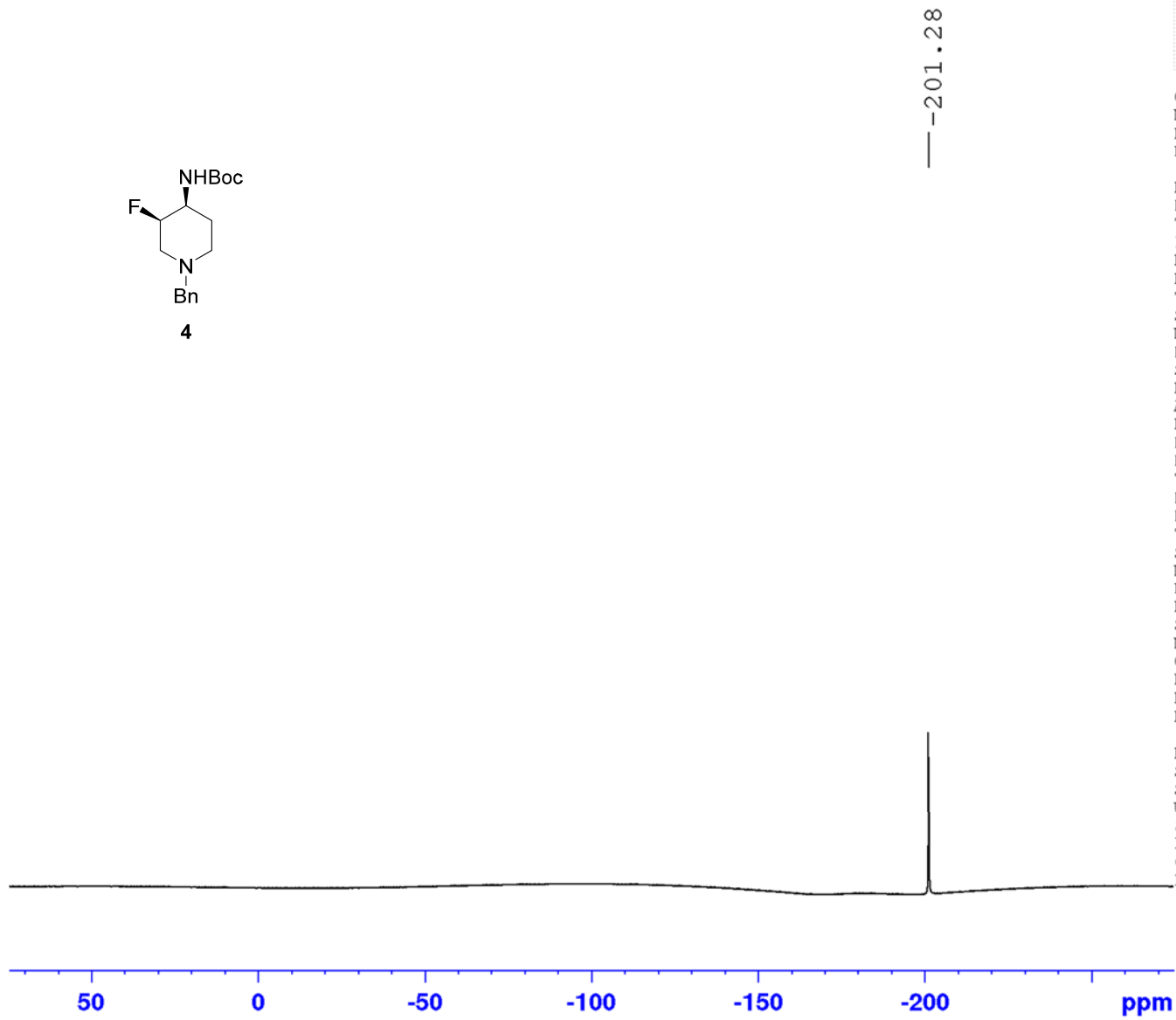
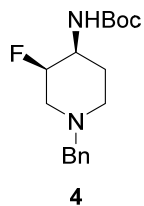
Current Data Parameters  
 NAME bqul-00624-pp  
 EXPNO 2  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20201202  
 Time 1.13  
 INSTRUM spect  
 PROBHD 5 mm PABBO BB/  
 PULPROG zgpg  
 TD 262144  
 SOLVENT CDC13  
 NS 2048  
 DS 0  
 SWH 31250.000 Hz  
 FIDRES 0.119209 Hz  
 AQ 4.1943040 sec  
 RG 2050  
 DW 16.000 usec  
 DE 6.50 usec  
 TE 300.0 K  
 D1 1.00000000 sec  
 D11 0.03000000 sec  
 TD0 1

----- CHANNEL f1 -----  
 SFO1 125.7698617 MHz  
 NUC1 13C  
 P1 9.80 usec  
 PLW1 99.50000000 W

----- CHANNEL f2 -----  
 SFO2 500.1325007 MHz  
 NUC2 1H  
 CPDPRG[2] waltz16  
 PCPD2 80.00 usec  
 PLW2 16.79999924 W  
 PLW12 0.48910001 W  
 PLW13 0.24601001 W

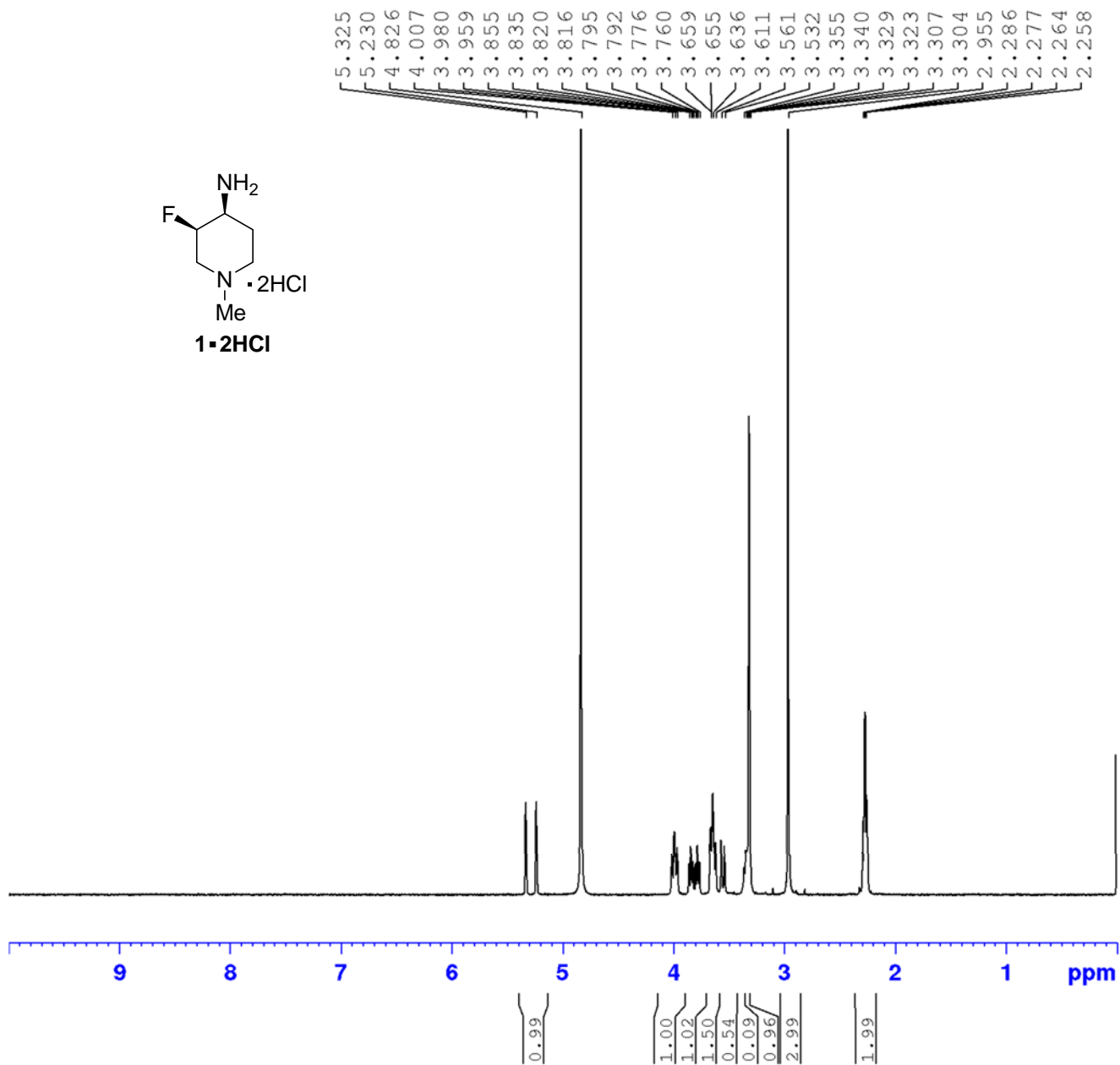
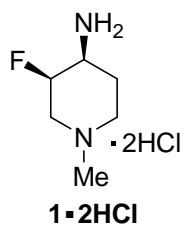
F2 - Processing parameters  
 SI 131072  
 SF 125.7577887 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.40



Current Data Parameters  
 NAME bqu1-00624-p  
 EXPNO 2  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20201130  
 Time 19.29 h  
 INSTRUM Avance  
 PROBHD Z108618\_0981 (  
 PULPROG zgig  
 TD 131072  
 SOLVENT CDCl3  
 NS 320  
 DS 4  
 SWH 131578.953 Hz  
 FIDRES 2.007735 Hz  
 AQ 0.4980736 sec  
 RG 101  
 DW 3.800 usec  
 DE 6.50 usec  
 TE 300.0 K  
 D1 1.00000000 sec  
 D11 0.03000000 sec  
 TD0 1  
 SFO1 376.4607164 MHz  
 NUC1 19F  
 P1 15.00 usec  
 PLW1 17.84399986 W  
 SFO2 400.1316005 MHz  
 NUC2 1H  
 CPDPRG[2] waltz16  
 PCPD2 90.00 usec  
 PLW2 15.73099995 W  
 PLW12 0.38064000 W

F2 - Processing parameters  
 SI 262144  
 SF 376.4983660 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.00

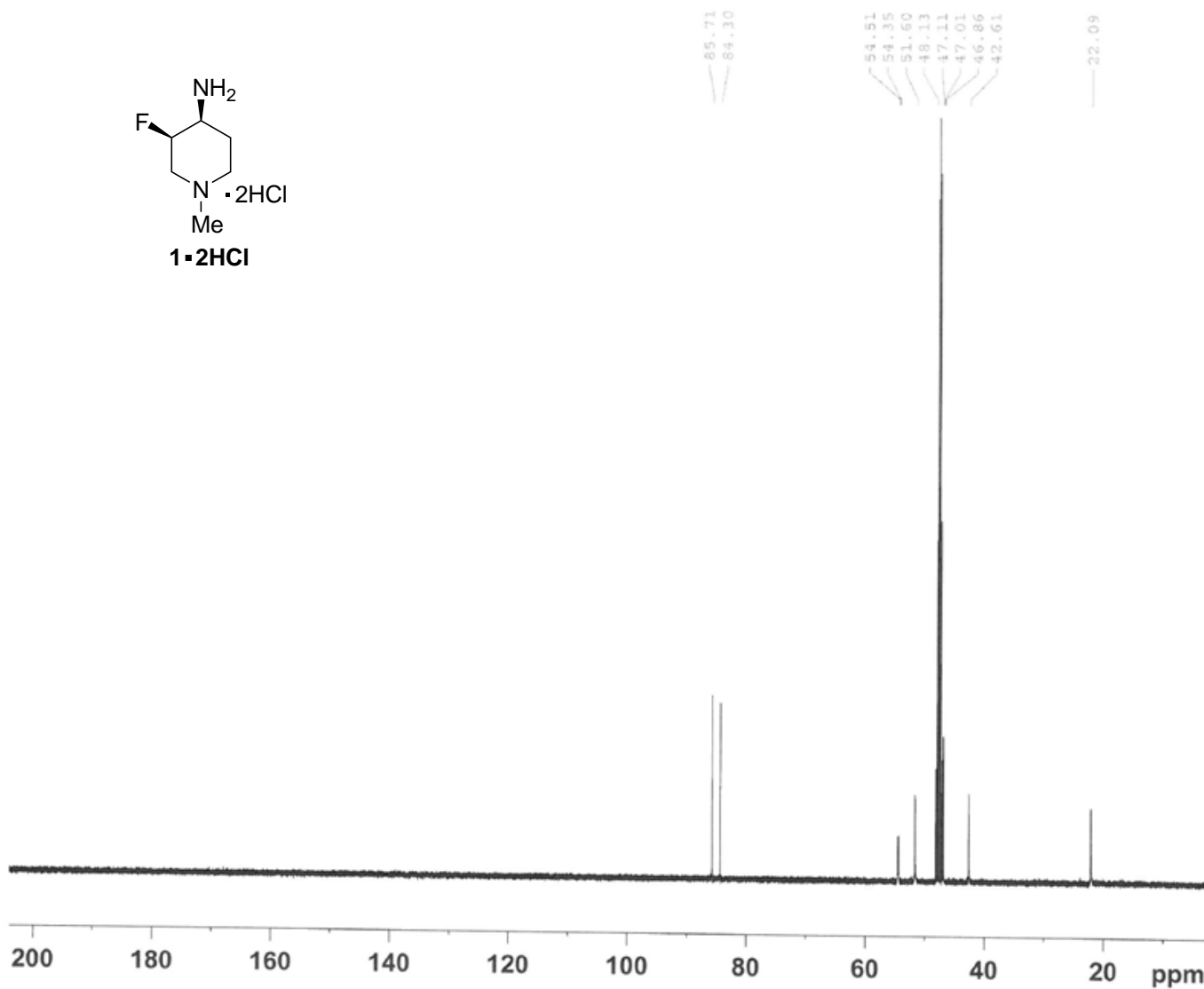
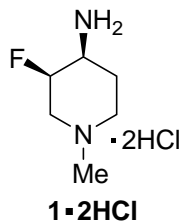


Current Data Parameters  
 NAME klp04917-112120  
 EXPNO 1  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20201121  
 Time 14.31  
 INSTRUM spect  
 PROBHD 5 mm PABBO BB/  
 PULPROG zg10  
 TD 32768  
 SOLVENT MeOD  
 NS 16  
 DS 0  
 SWH 7500.000 Hz  
 FIDRES 0.228882 Hz  
 AQ 2.1845334 sec  
 RG 645  
 DW 66.667 usec  
 DE 6.50 usec  
 TE 300.0 K  
 D1 1.00000000 sec  
 TD0 1

===== CHANNEL f1 =====  
 SFO1 500.1325007 MHz  
 NUC1 1H  
 P1 13.65 usec  
 PLW1 16.79999924 W

F2 - Processing parameters  
 SI 16384  
 SF 500.1300110 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.00



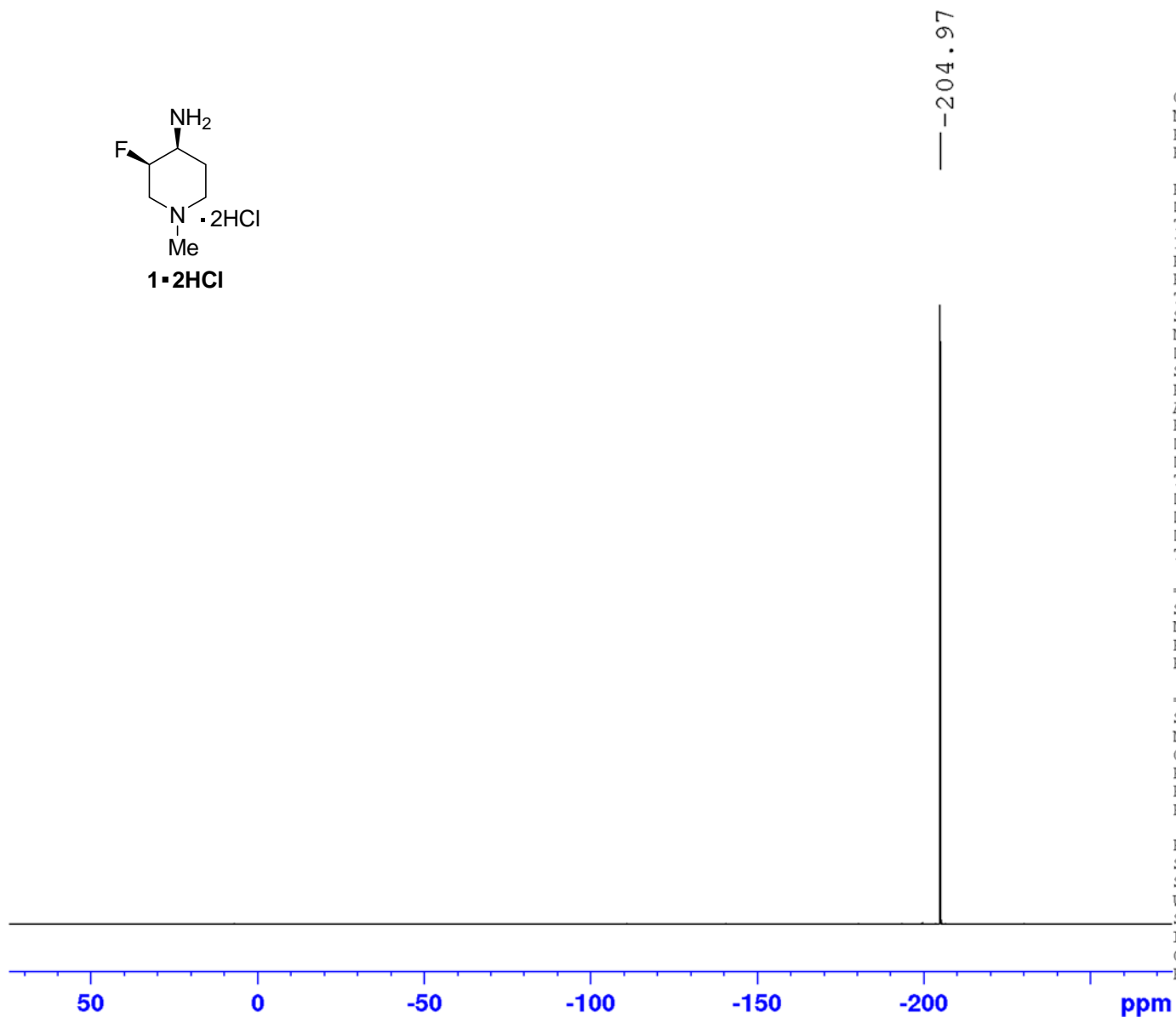
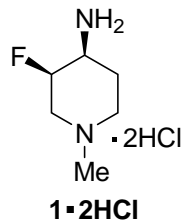
Current Data Parameters  
 NAME klp159  
 EXPNO 2  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20170907  
 Time 9.51  
 INSTRUM spect  
 PROBHD 5 mm PABBO BB-  
 PULPROG zgpg  
 TD 262144  
 SOLVENT MeOD  
 NS 256  
 DS 0  
 SWH 31250.000 Hz  
 FIDRES 0.119209 Hz  
 AQ 4.1943040 sec  
 RG 2050  
 DW 16.000 usec  
 DE 6.50 usec  
 TE 299.0 K  
 D1 1.00000000 sec  
 D11 0.03000000 sec  
 TD0 1

==== CHANNEL f1 =====  
 SFO1 125.7698617 MHz  
 NUC1 13C  
 P1 9.75 usec  
 PLW1 126.00000000 W

==== CHANNEL f2 =====  
 SFO2 500.1325007 MHz  
 NUC2 1H  
 CPDPRG[2] waltz16  
 PCPD2 80.00 usec  
 PLW2 18.39999962 W  
 PLW12 0.41056001 W  
 PLW13 0.20651001 W

F2 - Processing parameters  
 SI 131072  
 SF 125.7577890 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.40



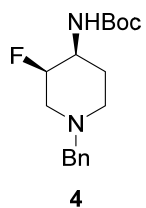
Current Data Parameters  
 NAME klp15917  
 EXPNO 2  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20170906  
 Time 18.34  
 INSTRUM spect  
 PROBHD 5 mm PABBO BB-  
 PULPROG zgfhigqn  
 TD 131072  
 SOLVENT MeOD  
 NS 256  
 DS 4  
 SWH 131578.953 Hz  
 FIDRES 1.003868 Hz  
 AQ 0.4980736 sec  
 RG 2050  
 DW 3.800 usec  
 DE 6.50 usec  
 TE 298.0 K  
 D1 1.00000000 sec  
 D11 0.03000000 sec  
 D12 0.00002000 sec  
 TD0 1

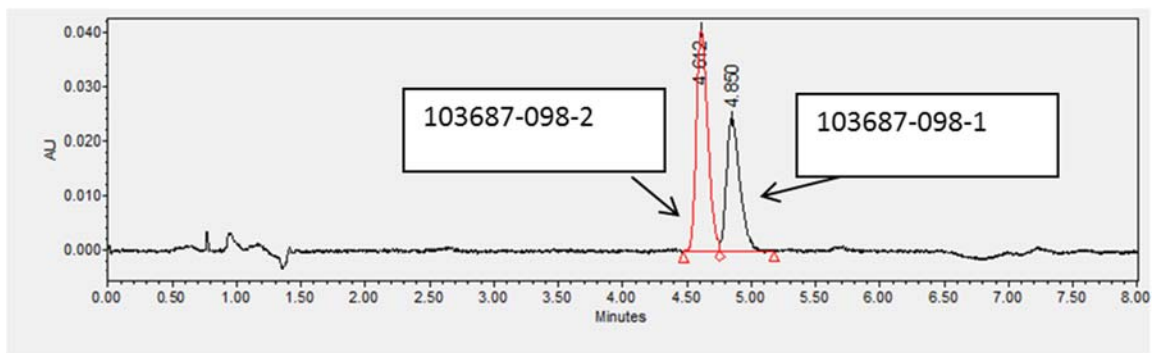
----- CHANNEL f1 -----  
 SFO1 376.4607164 MHz  
 NUC1 19F  
 P1 15.10 usec  
 PLW1 13.19999981 W

----- CHANNEL f2 -----  
 SFO2 400.1316005 MHz  
 NUC2 1H  
 CPDPRG[2] waltz16  
 PCPD2 90.00 usec  
 PLW2 10.50000000 W  
 PLW12 0.29166999 W

F2 - Processing parameters  
 SI 262144  
 SF 376.4983660 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.00

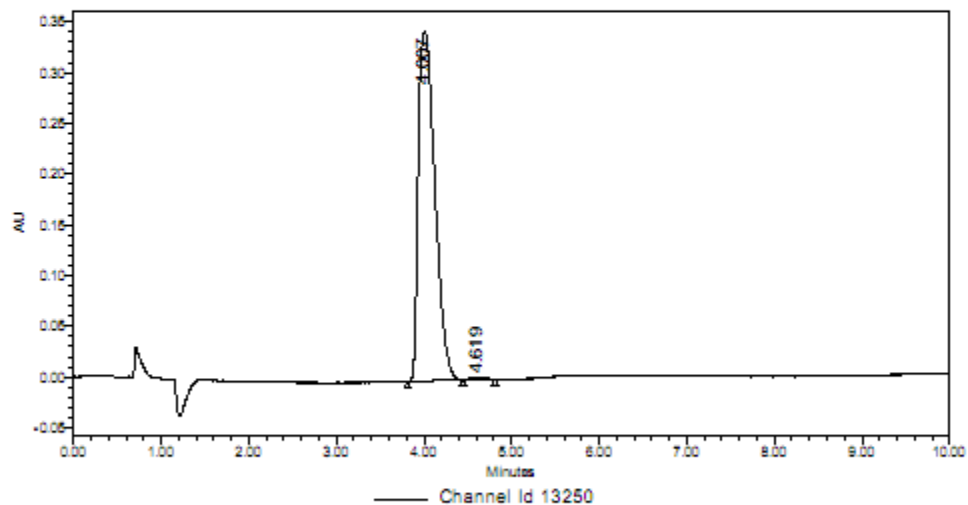


Chiral SFC spectrum of free base **4** from co-injecting of purified asymmetric hydrogenation mixtures of **3**•HCl starting from W003-1 and W003-2.



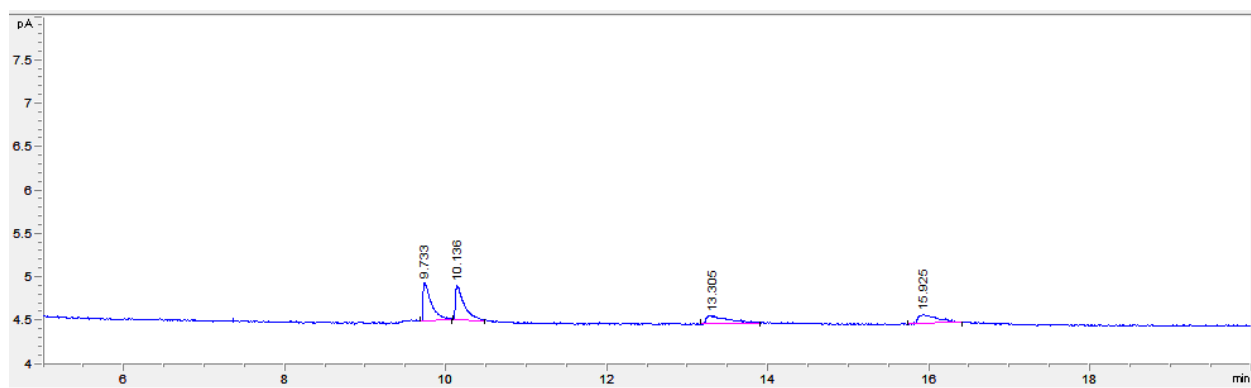
Enantiomeric ratio analysis of crude reactions mixture of the free base **4**

SAMPLE INFORMATION			
Sample Name:	KLP00417-14-1	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	KLP
Vial:	1:E,7	Acq. Method Set:	Anjan_Bo_Fluoroamine
Injection #:	1	Processing Method:	KLP000417
Injection Volume:	3.00 ul	Channel Name:	PDA Ch1 220nm@4.8nm
Run Time:	10.0 Minutes	Proc. Chnl. Descr.:	PDA Ch1 220nm@4.8nm
Date Acquired:	1/11/2017 10:44:09 AM EST		
Date Processed:	1/16/2017 1:14:45 PM EST		

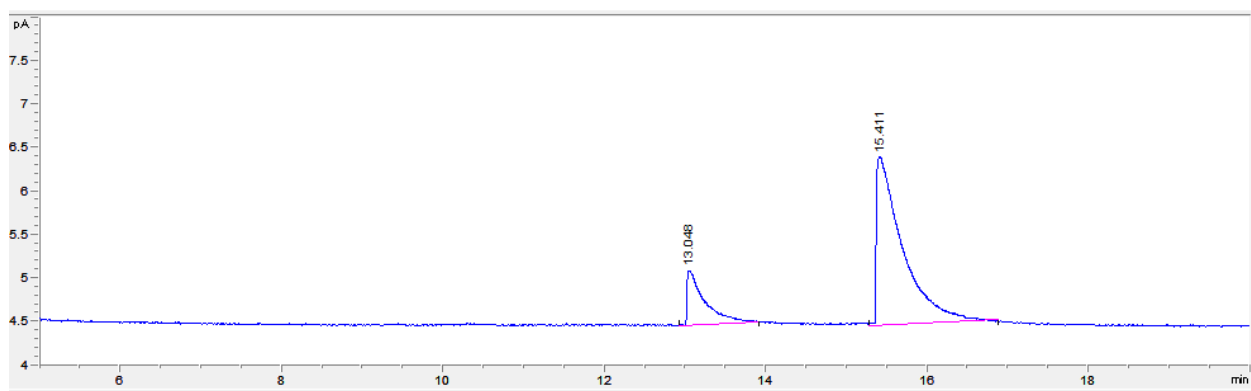


	RT	Area	% Area	Height
1	4.007	4524484	99.52	344660
2	4.619	21978	0.48	2112

GC spectrum of free base sample of racemic *cis*-, and *trans*-**1**

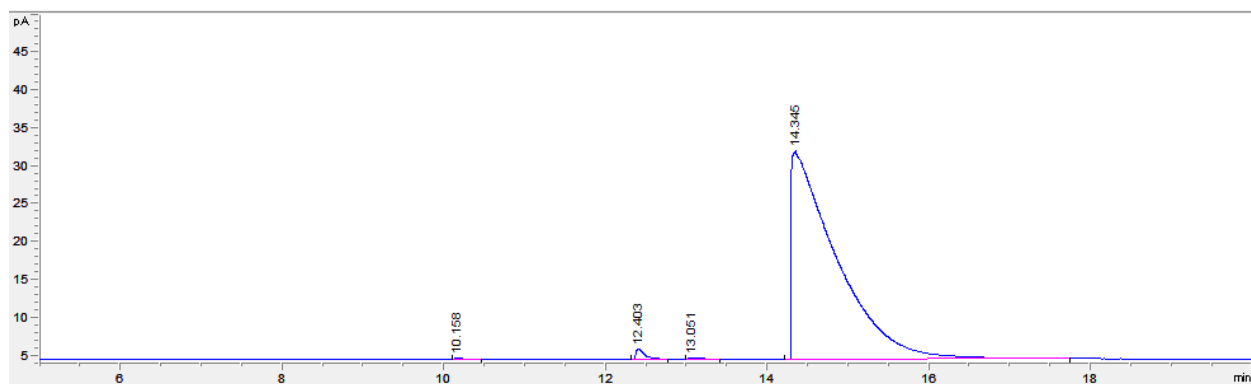


GC spectrum of purified free base **1** starting from asymmetric hydrogenation using 75% W003-1 and 25% W003-2





GC spectrum of free base **1** after free basing of **1**•2HCl from kilo lab sample (an unidentified peak at 12.4 min). Des-F impurity was not detectable by comparing to the authentic sample.



GC purity

#	Time	Area	Height	Width	Area%	Symmetry
1	10.158	1.3	1.9E-1	0.1208	0.126	0.262
2	12.403	9.6	1.4	0.1154	0.902	0.407
3	13.051	1.6	1.5E-1	0.1774	0.148	0.283
4	14.345	1056.4	27.4	0.6416	98.824	9.28E-2

Enantiomeric ratio

#	Time	Area	Height	Width	Area%	Symmetry
1	13.052	1.6	1.5E-1	0.1824	0.155	0.277
2	14.345	1056.4	27.5	0.6413	99.845	9.29E-2