

Supporting Information

Asymmetric Formal Synthesis of the Long-acting DPP-4 Inhibitor Omarigliptin

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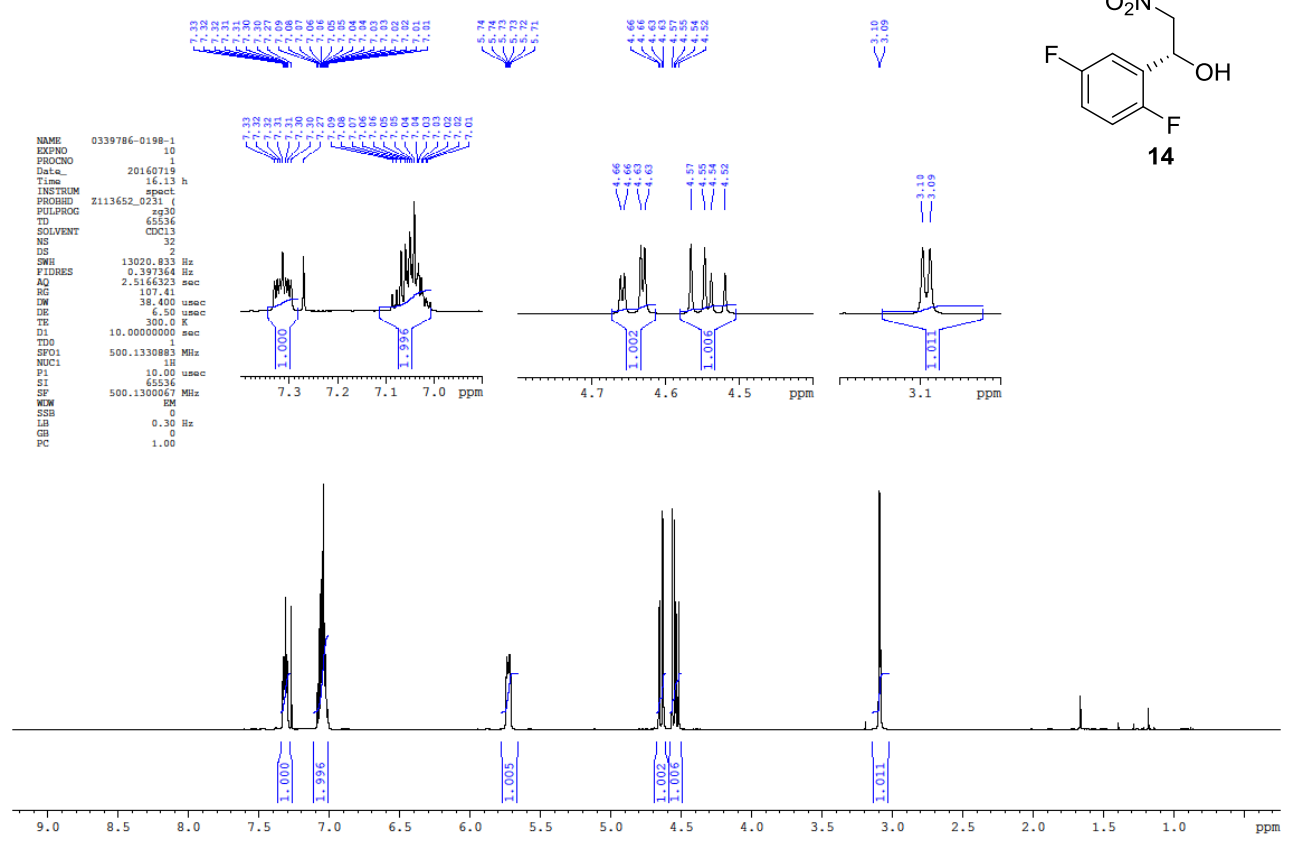
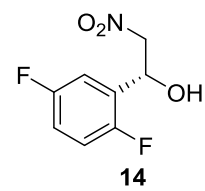
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```

Current Data Parameters
NAME      0339786-0198-2
EXPNO     10
PROCNO    1

F2 - Acquisition Parameters
Date_     20160719
Time      16.25 h
INSTRUM   spect
PROBHD    Z113652_0231 (
PULPROG   zgfhigqn.2
TD        131072
SOLVENT   CDCl3
NS        32
DS        4
SWH       147058.828 Hz
FIDRES    2.243940 Hz
AQ        0.4456948 sec
RG        187.85
DW        3.400 usec
DE        6.50 usec
TE        300.0 K
D1        10.00000000 sec
D11       0.03000000 sec
D12       0.00002000 sec
TD0       1
SFO1      470.5217884 MHz
NUC1      19F
P1        15.00 usec

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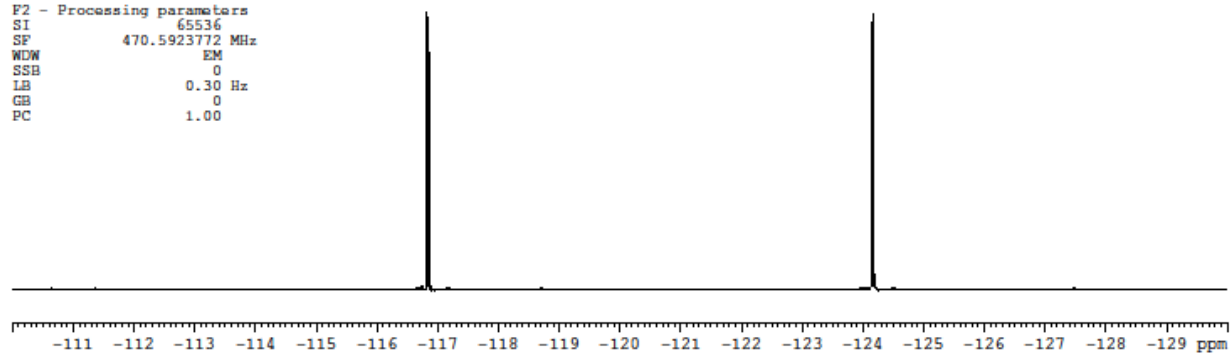
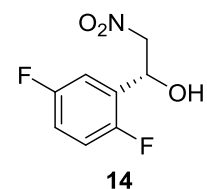
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F2 - Processing parameters
SI        65536
SF        470.5923772 MHz
WDW       EM
SSB       0
LB        0.30 Hz
GB        0
PC        1.00

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-116.82
-116.86

-124.15
-124.18

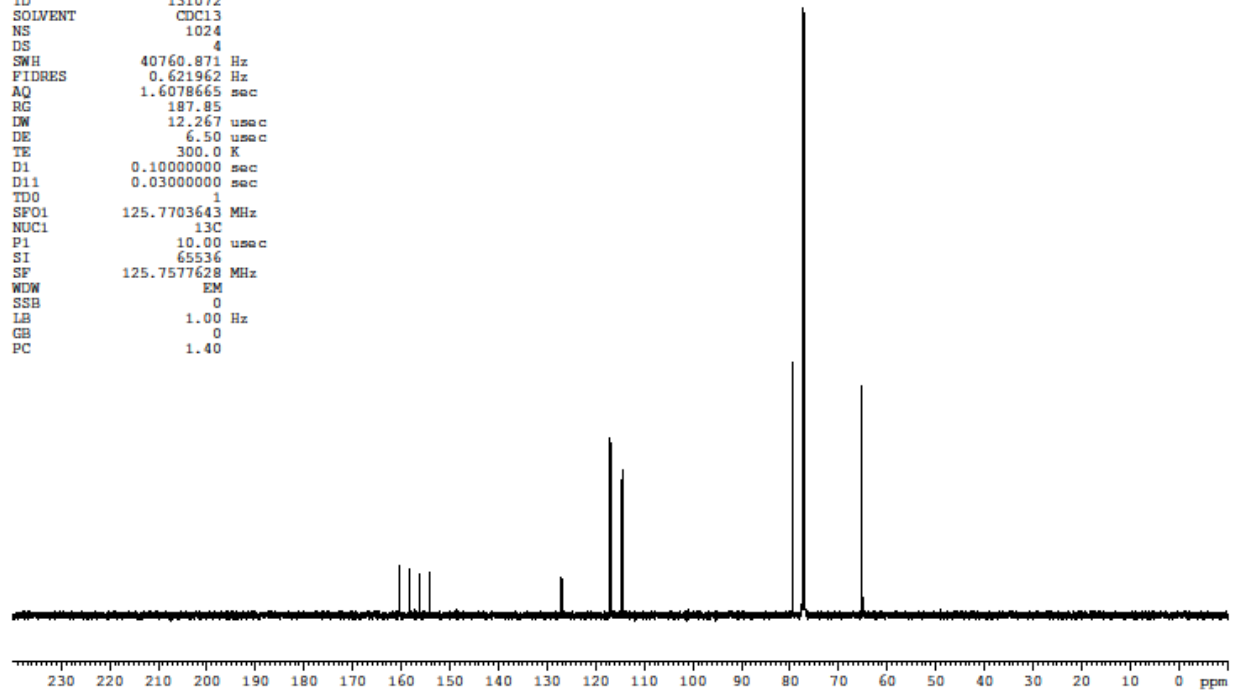
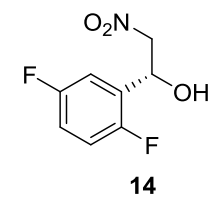


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PROCNO    1
Date_     20160719
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PROBHD    Z113652_0231 (
PULPROG   zgpg30
TD         131072
SOLVENT   CDC13
NS         1024
DS         4
SWH        40760.871 Hz
FIDRES    0.621962 Hz
AQ         1.6078665 sec
RG         187.85
DW         12.267 usec
DE         6.50 usec
TE         300.0 K
D1         0.10000000 sec
D11        0.03000000 sec
TD0        1
SFO1      125.7703643 MHz
NUC1       13C
P1         10.00 usec
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WDW        EM
SSB        0
LB         1.00 Hz
GB         0
PC         1.40

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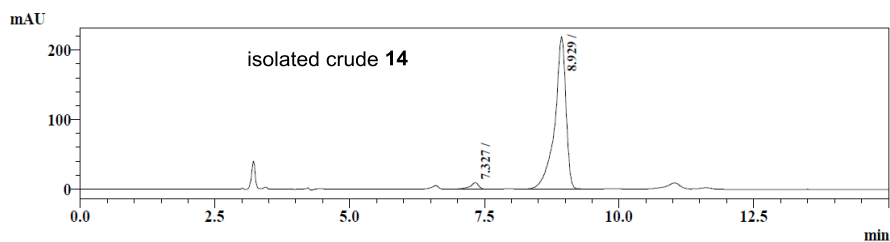
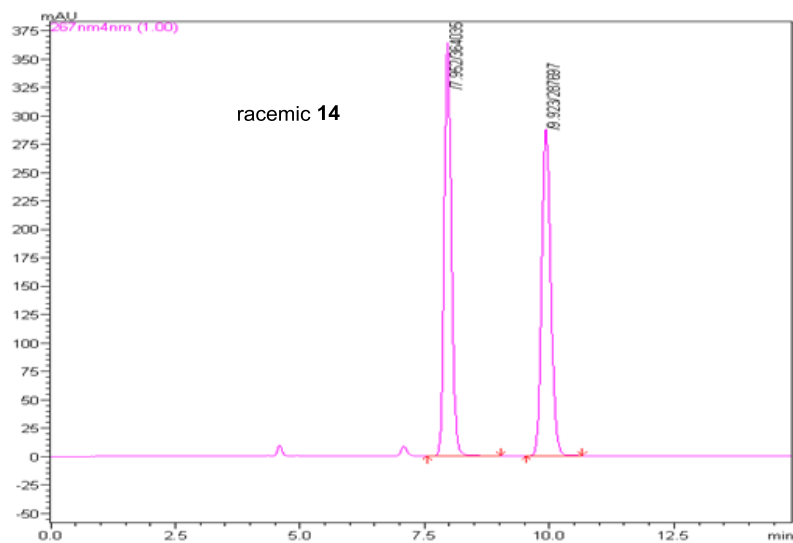
160.32
 158.30
 158.18
 158.16
 156.22
 156.20
 154.30
 154.27
 127.16
 127.10
 127.03
 126.97
 117.13
 117.12
 117.06
 117.05
 116.94
 116.92
 116.87
 116.86
 114.72
 114.69
 114.51
 114.48
 79.53
 79.52
 77.48
 77.23
 76.98
 65.16
 65.15



Chiral LC Assay of 14

Column	IA (25cm×4.6mm ID×5.0μm)
Mobile phase A	Hexane
Mobile phase B	EtOH
Temperature	40 °C
Gradient	Hold 15min at 10% B
Wavelength	267nm
Flow rate	1.0 mL/min
Injection Volume	3 μL
Solution preparation	5mg/mL
Diluent	Methanol
Chiral marker	14+enantiomer

Compound ID	Retention Time (min)	Relative Retention Time (RRT)
Enantiomer of 14	8.0	0.81
14	9.9	1.00



1 PDA Multi 1 / 267nm 4nm

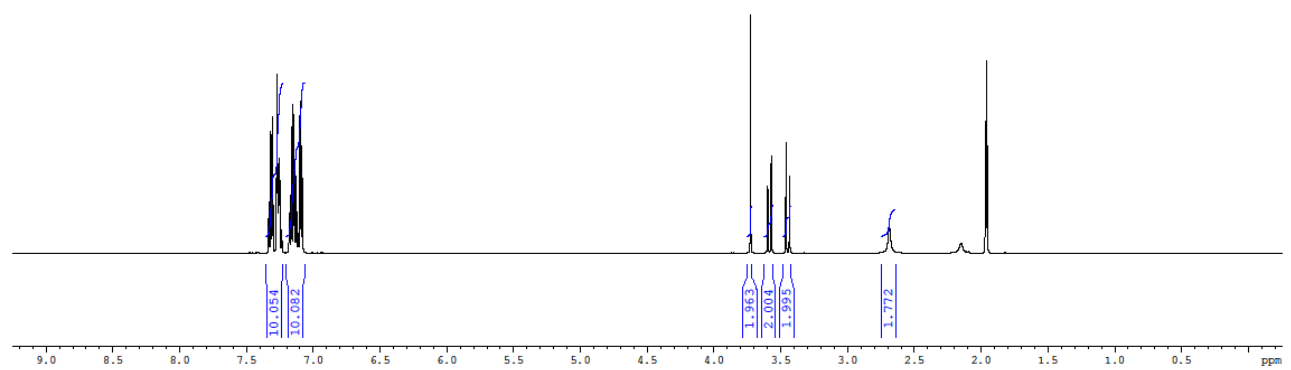
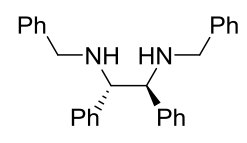
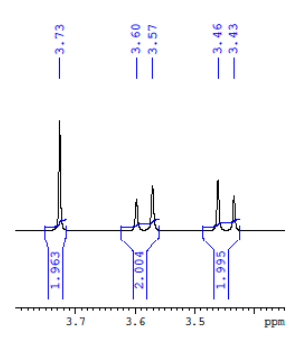
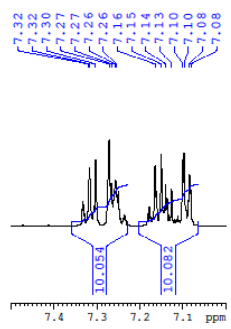
PDA Ch1 267nm 4nm

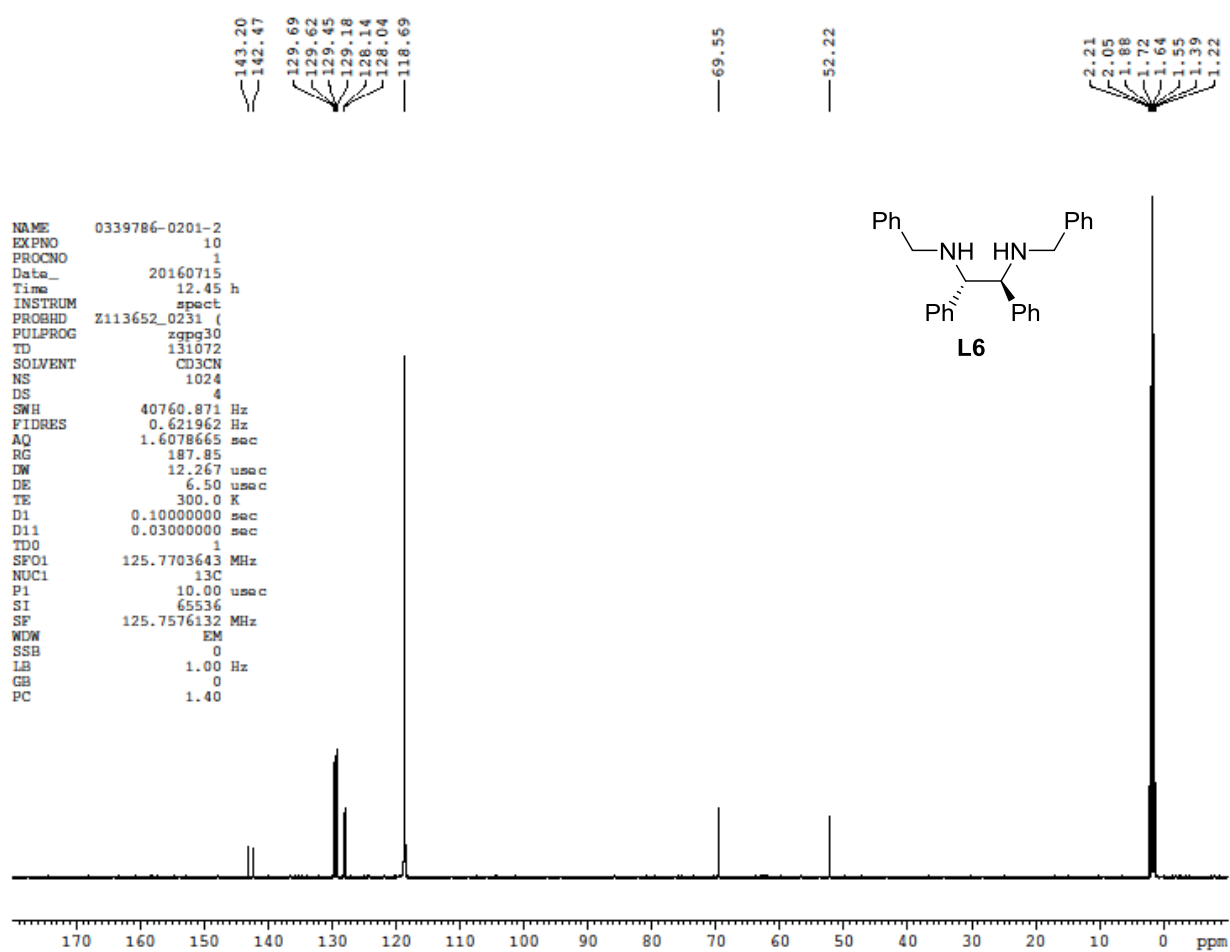
Peak#	Ret. Time	Name	Area	Height	Area %	Resolution	Tailing Factor
1	7.327		104227	9413	3.193	0.000	0.747
2	8.929		3160038	218498	96.807	5.140	0.753
Total					100.000		

7.33
7.33
7.32
7.32
7.31
7.31
7.30
7.27
7.26
7.25
7.24
7.24
7.18
7.18
7.17
7.17
7.16
7.16
7.15
7.15
7.15
7.14
7.14
7.13
7.13
7.12
7.12
7.11
7.11
7.10
7.10
7.09
7.09
7.08
7.08
7.08

3.73
3.60
3.57
3.46
3.43
2.69
2.15
1.97
1.96
1.96
1.95

NAME 0339786-0201-1
EXPNO 10
PROCNO 1
Data_ 20160715
Time 12.13 h
INSTRUM spect
PROBHD Z113652_0231 (4
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 13020.833 Hz
FIDRES 0.397364 Hz
AQ 2.5166523 sec
RG 137.98
DW 38.400 usec
DE 6.50 usec
TE 300.0 K
D1 10.00000000 sec
D10 1
SFO1 500.1330883 MHz
NUC1 1H
P1 10.00 usec
SI 65536
SF 500.1330038 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00





SFC Chiral Assay of L6

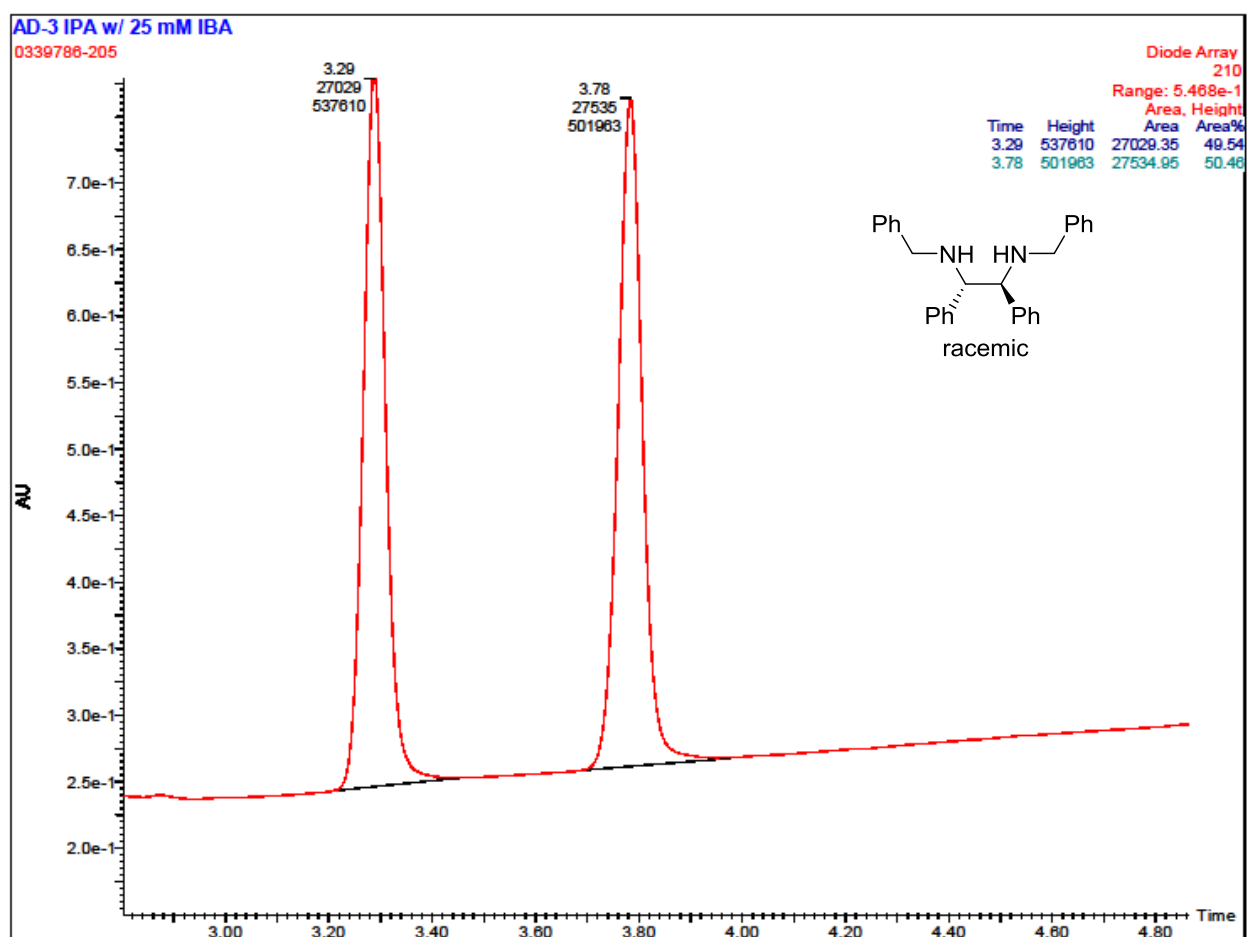
Column:	AD-3, 150 x 4.6 mm, 3 μ m particle size
Detector:	210 nm
Temperature:	40°C
Flow rate:	3.0 mL/min
Mobile Phase:	A: CO ₂ B: IPA with 25 nM IBA

Run Time = 6.6 min, Pressure = 200 (bar), Temperature: 40°C, Column: Chiralpak AD-3

Mobile Phase Program:	Time (min)	%A (CO ₂)	%B
	0	99	01
	5	60	40
	6	60	40
	6.1	99	01

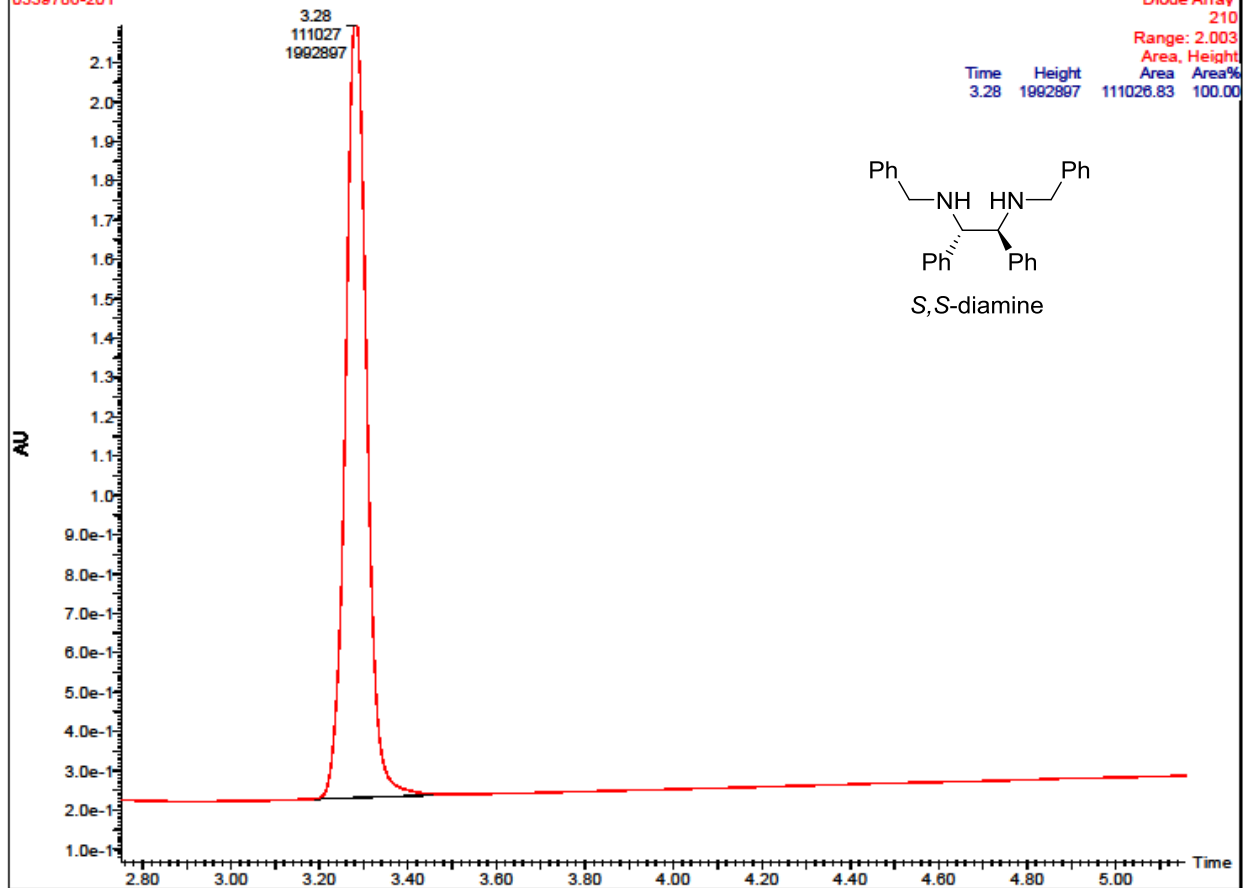
3.29 min = Desired Enantiomer

3.78 min = Undesired Enantiomer

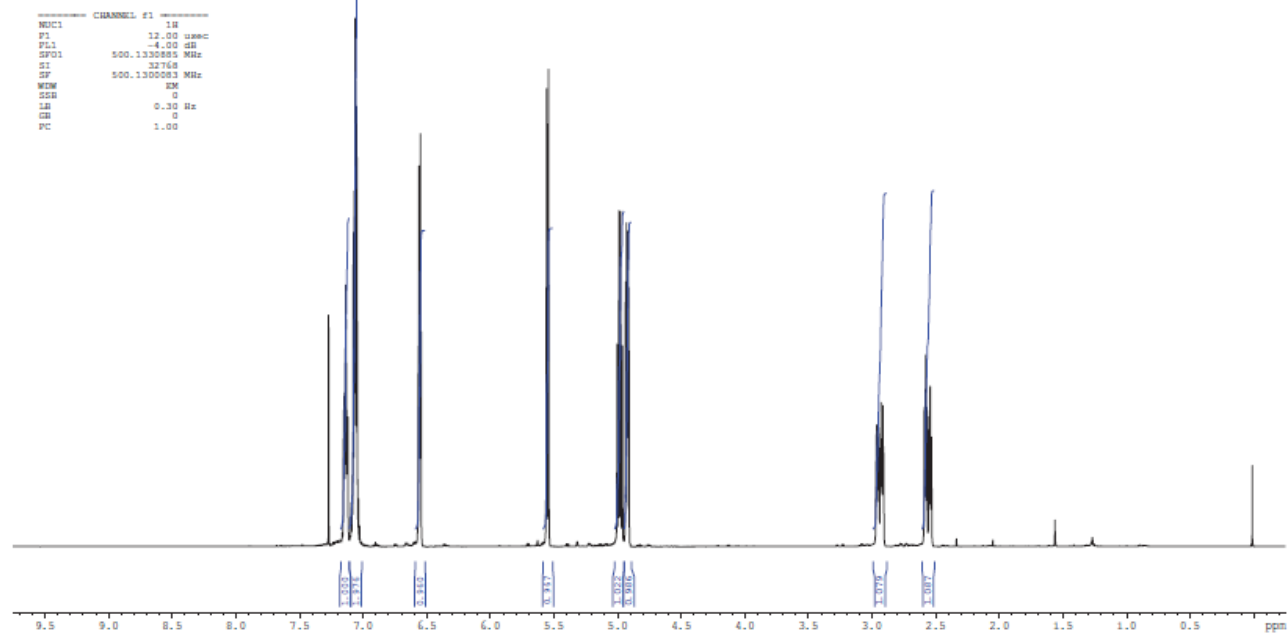
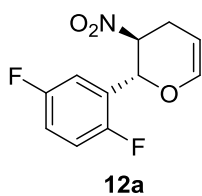


AD-3 IPA w/ 25 mM IBA

0339786-201



NAME 0330738-60-4
 EXPNO 10
 PROCNO 1
 Date_ 20130123
 Time 17.13
 INSTRUM spect
 PROBR0 5 mm QNP 1H/13
 PULPROG zg30
 TD 65536
 SOLVENT CDCl3
 NS 32
 DS 4
 SWH 13020.833 Hz
 FIDRES 0.198682 Hz
 AQ 2.5166707 sec
 RG 128
 EM 38.400 usec
 EK 6.50 usec
 TE 300.0 K
 D1 0.10000000 sec
 TD0 1



NAME 0330738-60-4
 EXPNO 11
 PROCNO 1
 Date_ 20130123
 Time 17.29
 INSTRUM spect
 PROBHD 5 mm QNP 1H/13
 PULPROG zgpg30
 TD 131072
 SOLVENT CDCl3
 NS 512
 DS 4
 SWH 40322.582 Hz
 FIDRES 0.307637 Hz
 AQ 1.629352 sec
 RG 8192
 DW 12.400 usec
 DE 6.50 usec
 TE 300.0 K
 D1 0.1000000 sec
 D11 0.0300000 sec
 TDO 1

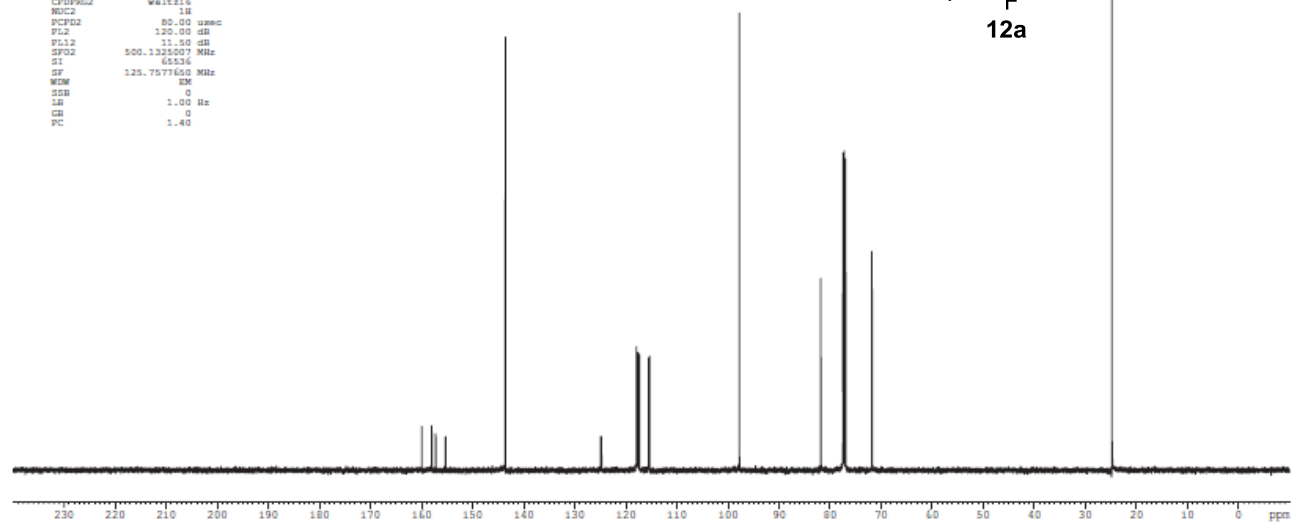
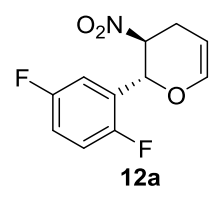
CHANNEL #1
 NUC1 13C
 P1 2.50 usec
 PL1 0.00 dB
 SFO1 125.7703648 MHz

CHANNEL #2
 CPDPRG2 waltz16
 NUC2 1H
 PCPD2 80.00 usec
 PL2 120.00 dB
 PL12 11.50 dB
 SFO2 500.1325007 MHz
 SI 65336
 SF 125.7577650 MHz
 MW XM
 SR 0
 LB 1.00 Hz
 GB 0
 PC 1.40

159.97
158.03
156.01
137.23
135.29
135.27
143.60
134.30
124.90
124.84
124.84
117.90
117.02
117.02
117.02
117.02
117.32
117.32
117.32
115.35
115.35
115.35
97.77

81.85
77.40
77.23
76.88
71.82

24.83



```

NAME      0330738-60-4
EXPNO     12
PROCNO    1
Date_     20120123
Time      11:31
INSTRUM   spect
PROBHD    5 mm QNP 1H/13
PULPROG   zgpg30
TD         131072
SOLVENT   CDCl3
NS         128
DS         4
SWH        141843.969 Hz
FIDRES    1.082184 Hz
AQ         0.4620823 sec
RG         64
DM         3.525 usec
DC         5.04 usec
TE         300.1 K
D1         0.10000000 sec
D11        0.03000000 sec
D12        0.00020000 sec
TD0        1

```

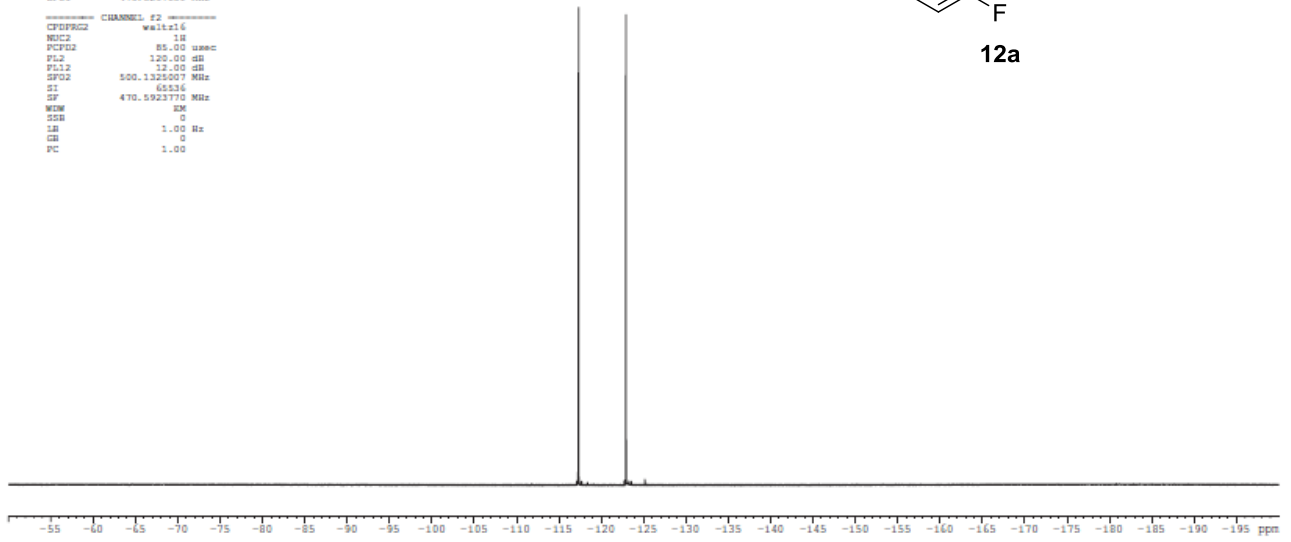
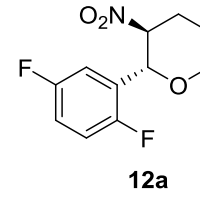
```

===== CHANNEL f1 =====
NUC1       13F
P1         5.00 usec
PL1        -4.00 dB
SFO1       470.527381 MHz

===== CHANNEL f2 =====
CPDPRG2   waltz16
NUC2       1H
PCPD2      85.00 usec
PL2        120.00 dB
PL12       12.00 dB
SFO2       500.1325077 MHz
SI         65516
SF         470.5923770 MHz
NUC#       0M
SSB        0
LB         1.00 Hz
GB         0
PC         1.00

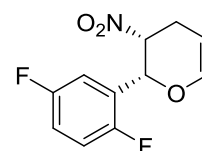
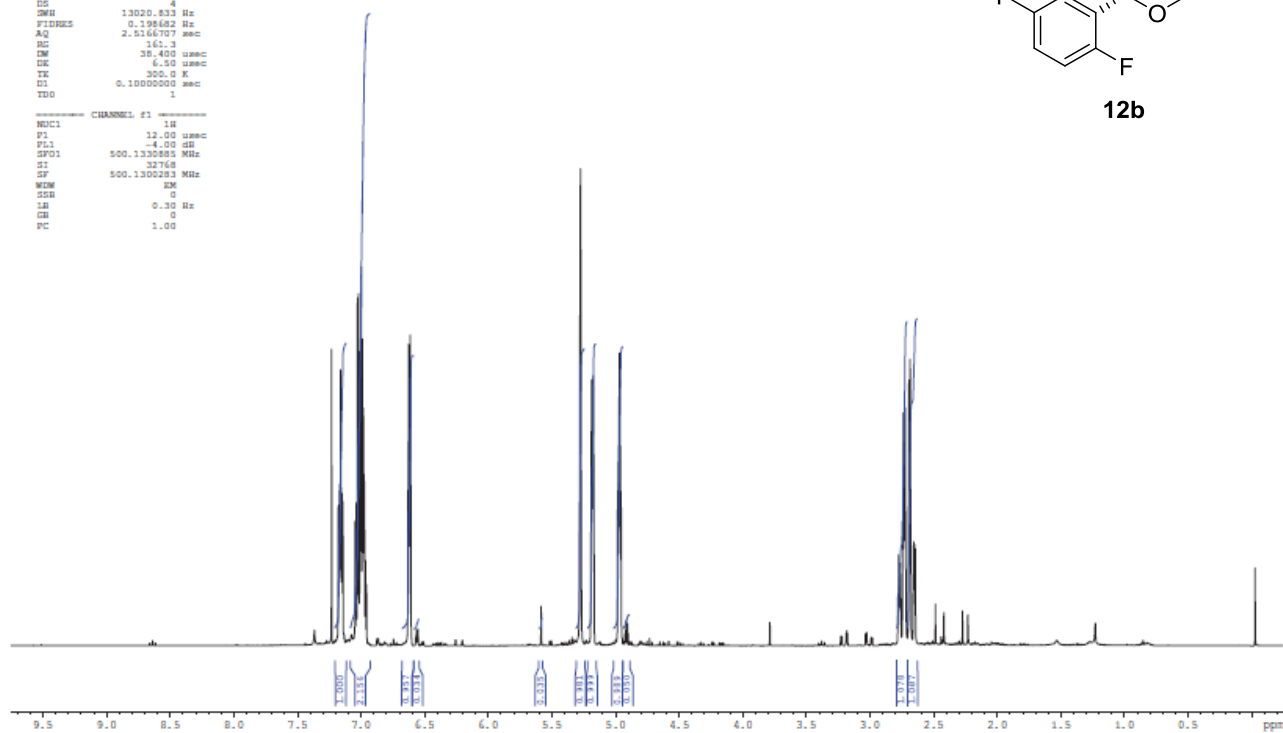
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-117.21
 -117.31
 -122.07
 -122.91

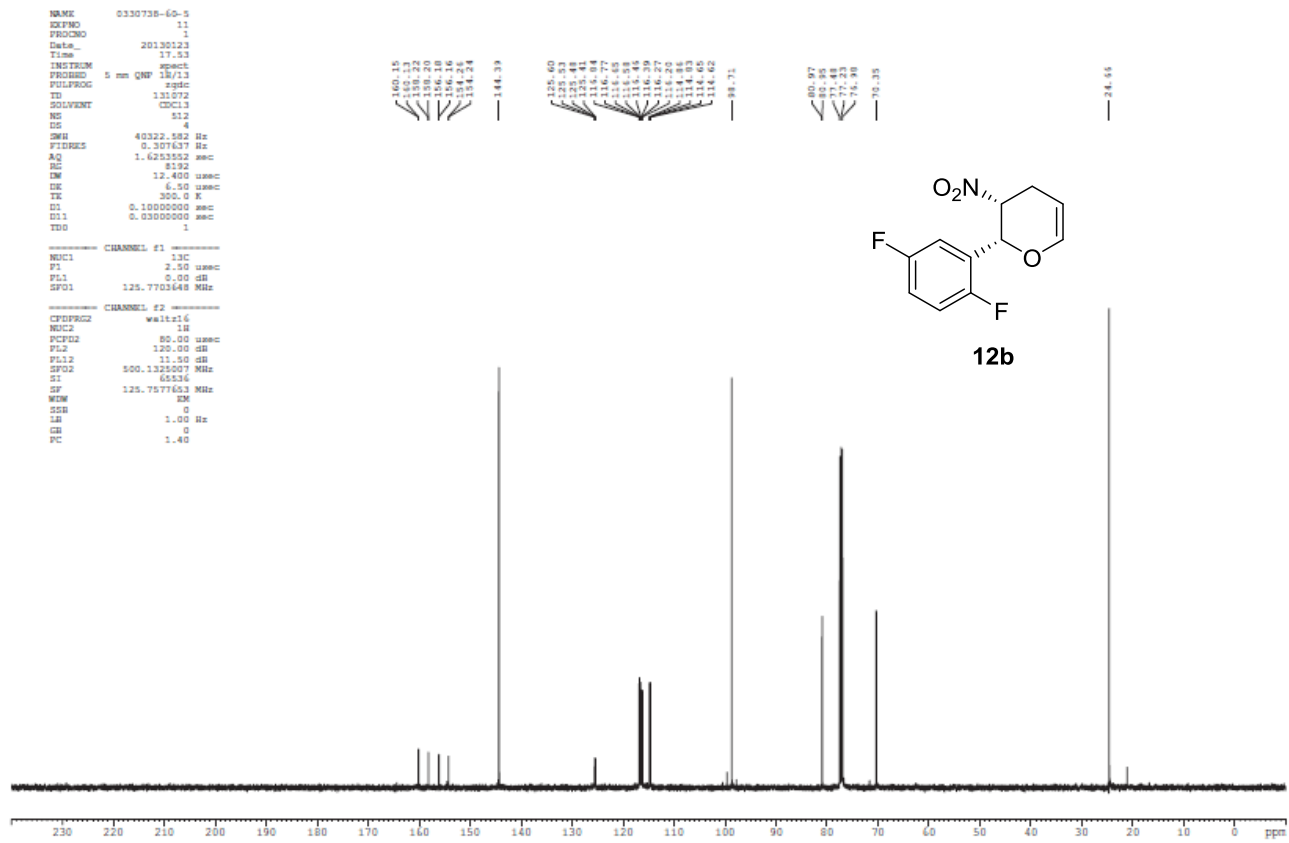


NAME 0330738-60-5
 EXPNO 10
 PROCNO 1
 Date_ 20130123
 Time 17.37
 INSTRUM spect
 PROBRD 5 mm QNP 1H/13
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 32
 DS 4
 SWH 13020.833 Hz
 FIDRES 0.198482 Hz
 AQ 2.5166707 sec
 RG 161.3
 DM 39.400 usec
 DE 6.50 usec
 TE 300.0 K
 D1 0.10000000 sec
 TDO 1

----- CHANNEL f1 -----
 NUC1 13C
 P1 12.00 usec
 PL1 4.00 dB
 SFO1 500.1300851 MHz
 SI 32768
 SF 500.1300283 MHz
 NMR
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00



12b



```

NAME      0330738-60-5
EXPNO     12
PROCNO    1
Date_     20130123
Time      11:55
INSTRUM   spect
PROBHD    5 mm QNP 1H/13
PULPROG   zgpg30
TD         131072
SOLVENT   CDCl3
NS         128
DS         4
SWH        141843.969 Hz
FIDRES    1.082184 Hz
AQ         0.4620823 sec
RG         64
DM         3.525 usec
DE         5.04 usec
TE         300.1 K
D1         0.10000000 sec
D1.1      0.03000000 sec
D1.2      0.00000000 sec
TD0        1

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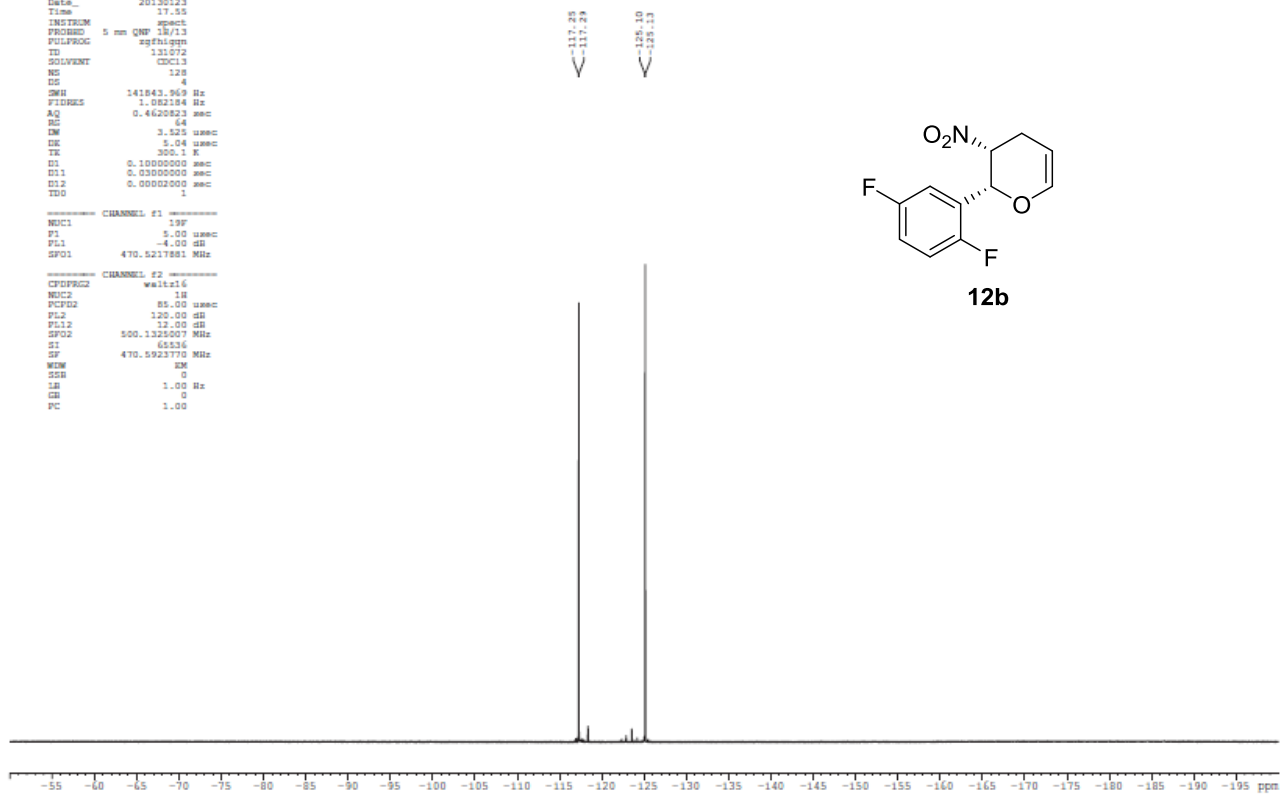
===== CHANNEL f1 =====
NUC1       13F
P1         5.00 usec
PL1        -4.00 dB
SFO1      470.5217881 MHz

```

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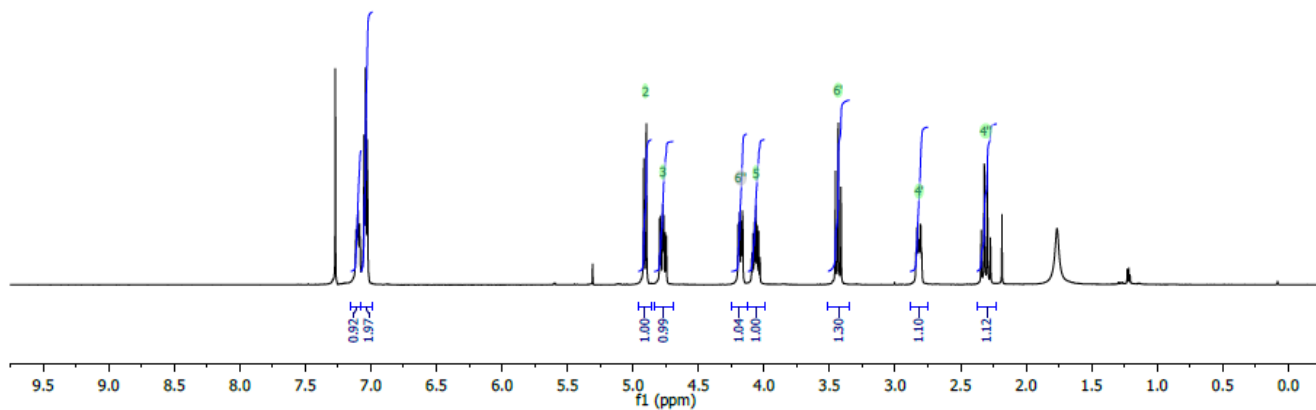
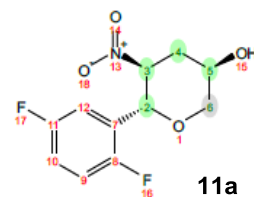
===== CHANNEL f2 =====
CPDPRG2   waltz16
NUC2       1H
PCPD2     85.00 usec
PL2        120.00 dB
PL12      12.00 dB
SFO2      500.1325007 MHz
SI         65536
SF         470.5923770 MHz
NUC3       13C
SSB        0
LB         1.00 Hz
GB         0
PC         1.00

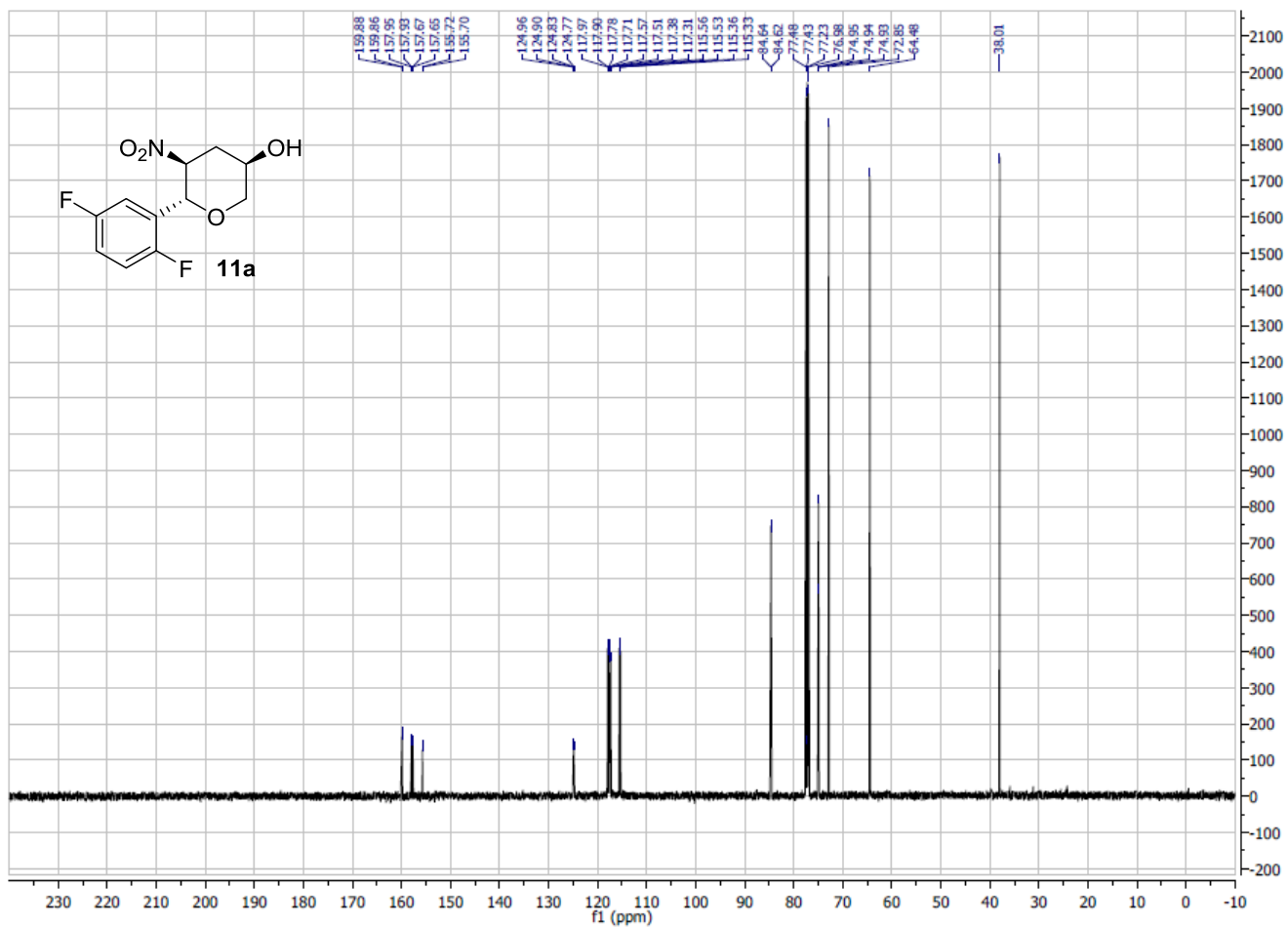
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Parameter	Value
Title	0339786-0185-A.10.fid
Spectrometer	spect
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Probe	5 mm QNP 1H/ 13C/ 31P/ 19F Z-GRD Z8420/ 0073

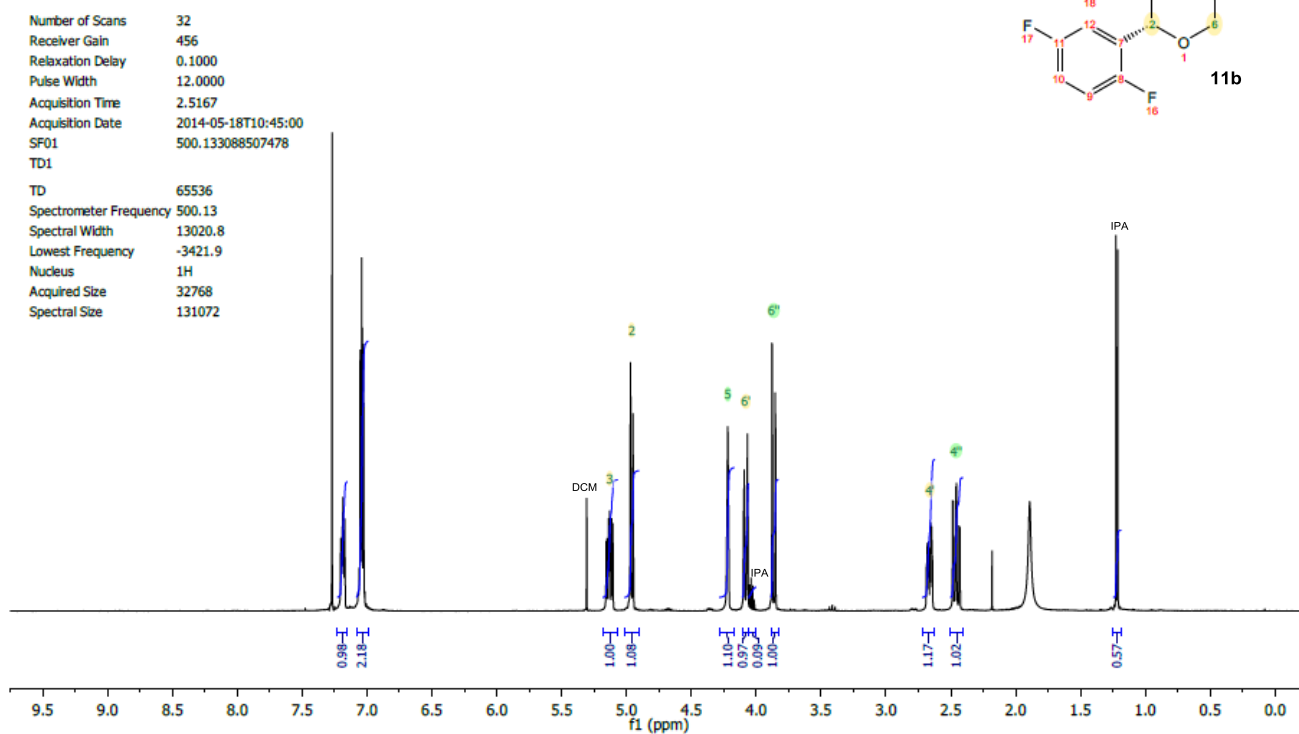
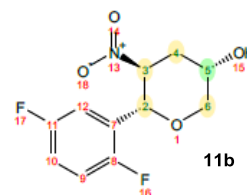
0339786-0185-A/10 kassimam
Pure Diastereomer A (solid)
after SFC Purification



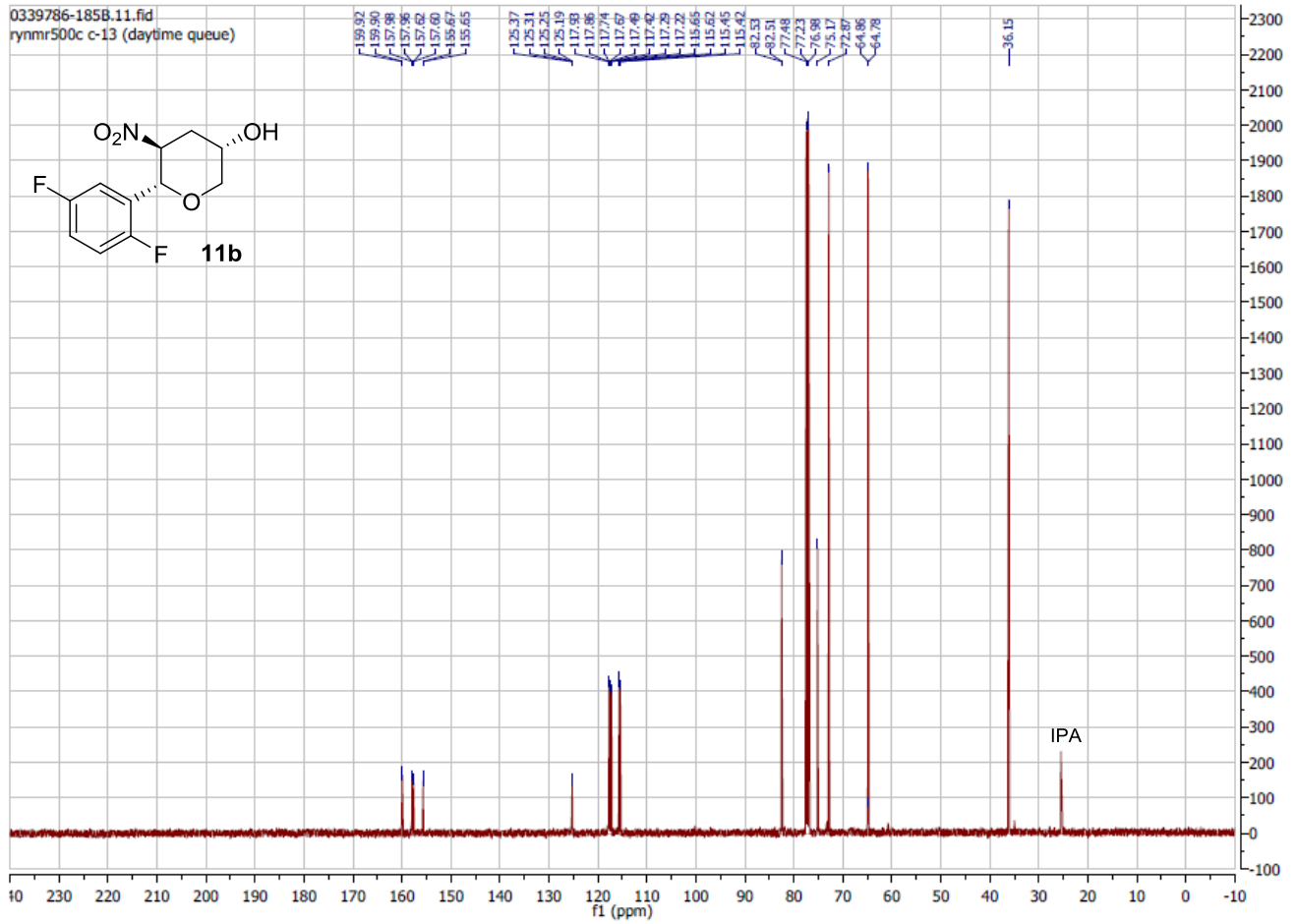


Parameter	Value
Title	0339786-0185-B.10.fid
Spectrometer	spect
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Probe	5 mm QNP 1H/ 13C/ 31P/ 19F Z-GRD Z8420/ 0073

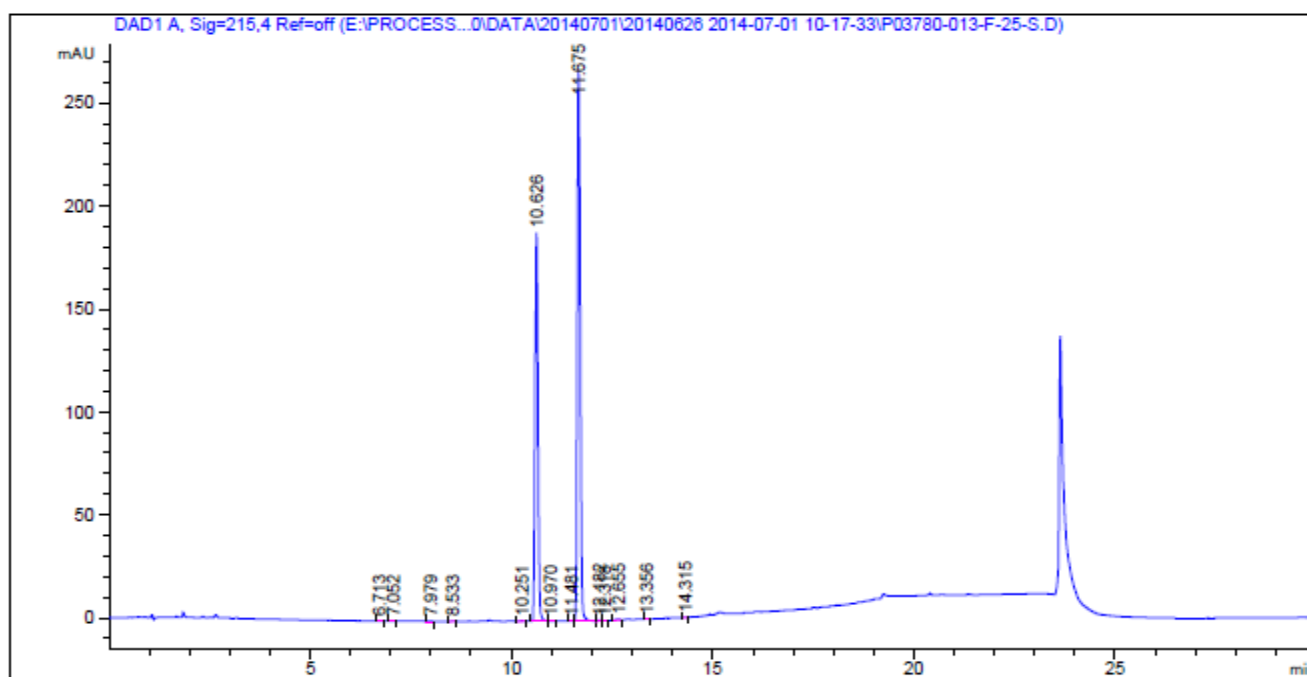
0339786-0185-B/10 kassimam
 Pure Diastereomer B (oil)
 after SFC Purification



0339786-185B.11.fid
rnmr500c c-13 (daytime queue)



HPLC of compound 4



=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=215,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.713	MM	0.0735	7.30334e-1	1.65546e-1	0.0319
2	7.052	MM	0.0726	3.64797e-1	8.37995e-2	0.0159
3	7.979	MM	0.0702	5.55305e-1	1.31890e-1	0.0242
4	8.533	MM	0.0822	8.68835e-1	1.76161e-1	0.0379
5	10.251	MM	0.1099	1.86373	2.82673e-1	0.0814
6	10.626	MF	0.0823	933.84955	189.20198	40.7777
7	10.970	FM	0.1029	1.03617	1.67806e-1	0.0452
8	11.481	MF	0.0801	1.49801	3.11835e-1	0.0654
9	11.675	FM	0.0833	1342.21863	268.61728	58.6096
10	12.182	MF	0.0858	1.52569	2.96277e-1	0.0666
11	12.318	FM	0.0704	2.84962e-1	6.74206e-2	0.0124
12	12.655	MM	0.0915	3.19191	5.81224e-1	0.1394
13	13.356	MM	0.0707	1.52656	3.59626e-1	0.0667
14	14.315	MM	0.0636	5.86546e-1	1.53605e-1	0.0256

Totals : 2290.10101 460.59712

Cartesian Coordinates for minima

Compound 17		M06/6-31G**	M062X/6-31G**	B3LYP/6-31G** w/ D2	M062X/6-31+G**
-NO ₂	-Cl	ΔG	ΔG	ΔG	ΔG
17a	equa axial	0.0	0.0	0.0	0.0
17b	axial axial	2.5	2.4	2.5	2.7
17c	equa equa	3.5	2.6	3.1	2.6
17d	axial equa	7.7	7.0	7.5	7.3

Compound 17a

M06-2X/6-31+G** free energy -1364.893128

6 2.47949 0.744885 -1.07279
6 0.480544 -0.170602 0.17103
6 2.35101 -1.6096 -0.207005
8 0.972891 -1.47823 -0.095754
6 2.93452 -0.698761 -1.27605
6 0.961173 0.766756 -0.961977
1 2.8032 1.37182 -1.90853
1 2.91004 1.15864 -0.156776
1 0.886626 0.195252 1.12344
1 2.53495 -2.66309 -0.411763
1 2.57737 -1.07843 -2.24142
1 4.02415 -0.770745 -1.26934
1 0.463224 0.483287 -1.89292
17 3.16434 -1.29701 1.39669
6 -1.02221 -0.264796 0.243428
6 -3.82981 -0.323508 0.363838
6 -1.74354 0.657333 0.993035
6 -1.73146 -1.23908 -0.459946
6 -3.11447 -1.24617 -0.384904
6 -3.12626 0.648625 1.06893
1 -1.21295 -1.99219 -1.04215
1 -3.63089 1.39876 1.66665
1 -4.91227 -0.372932 0.388313
7 0.471688 2.16091 -0.668078
8 -0.570176 2.50049 -1.19752
8 1.13231 2.83914 0.094042
9 -1.05809 1.60279 1.66771
9 -3.79224 -2.1905 -1.06708

Compound 17b

M06-2X/6-31+G** free energy -1364.888869

6 -2.52035 0.527899 -1.26627
6 -0.41496 -0.428143 -0.250569
6 -2.46316 -0.738029 0.910162
8 -1.09908 -0.514448 0.988866
6 -3.18715 0.316645 0.09356
6 -1.00278 0.670058 -1.16465

1 -2.94261 1.40402 -1.76482
1 -2.7107 -0.339641 -1.90829
1 -0.584757 -1.36211 -0.805612
1 -2.82255 -0.795111 1.93598
1 -3.14851 1.24313 0.671909
1 -4.23284 0.028236 -0.033433
17 -2.80238 -2.41032 0.215085
6 1.06348 -0.323873 0.025907
6 3.82943 -0.147703 0.521396
6 1.58515 0.566768 0.962408
6 1.95863 -1.13745 -0.668699
6 3.31691 -1.0305 -0.415244
6 2.94193 0.664418 1.22234
1 1.60829 -1.86076 -1.3985
1 3.28779 1.38005 1.95925
1 4.89896 -0.102157 0.691205
9 0.745115 1.37695 1.62781
9 4.16514 -1.82443 -1.09753
1 -0.519489 0.584933 -2.13995
7 -0.599571 2.05018 -0.697153
8 0.496148 2.43891 -1.05635
8 -1.37598 2.67932 -0.004856

Compound 17c

M06-2X/6-31+G free energy -1364.888948**

6 2.29328 1.55494 -0.63751
6 0.43136 0.199722 0.409901
6 2.6329 -0.640286 0.457933
8 1.26923 -0.935803 0.282261
6 3.13238 0.27432 -0.644272
6 0.814579 1.19473 -0.715867
1 2.56645 2.20043 -1.47716
1 2.46776 2.12192 0.28267
1 0.597626 0.694673 1.37966
1 3.03731 -0.256323 -1.59767
1 4.18871 0.505409 -0.486296
1 0.534595 0.759431 -1.67806
6 -0.995453 -0.277888 0.307352
6 -3.6806 -1.07828 0.096077
6 -2.02745 0.463042 0.871178
6 -1.32202 -1.45158 -0.373223
6 -2.65329 -1.82352 -0.463288
6 -3.35803 0.09058 0.779637
1 -0.548204 -2.0744 -0.807631
1 -4.1176 0.7139 1.23705
1 -4.70607 -1.41469 -0.003979
7 -0.034924 2.43075 -0.579836
8 -1.03989 2.48463 -1.26259
8 0.322965 3.27349 0.221033
9 -1.71002 1.59455 1.53483
9 -2.96111 -2.9603 -1.11755
1 2.79379 -0.202762 1.45204
17 3.49682 -2.19907 0.444089

Compound 17d**M06-2X/6-31+G** free energy -1364.88144**

6 -2.20888 1.15584 -1.54154
6 -0.247112 -0.234028 -0.764433
6 -2.40558 -1.06698 -0.443868
8 -1.12805 -0.895238 0.119131
6 -3.08927 0.270371 -0.650086
6 -0.747065 1.19261 -1.09825
1 -2.6101 2.17157 -1.58497
1 -2.21021 0.764901 -2.56698
1 -0.255579 -0.753283 -1.7389
1 -3.23491 0.736084 0.326516
1 -4.06556 0.117083 -1.11748
6 1.15787 -0.319107 -0.222745
6 3.79297 -0.474553 0.756095
6 1.46128 -0.040563 1.10877
6 2.20609 -0.680859 -1.06922
6 3.49694 -0.745485 -0.569649
6 2.75145 -0.116419 1.60793
1 2.02847 -0.919398 -2.11339
1 2.92559 0.11626 2.65214
1 4.81661 -0.542621 1.10589
9 0.475159 0.336193 1.93663
9 4.4945 -1.09723 -1.40477
1 -0.095782 1.60787 -1.87011
7 -0.542599 2.1262 0.071035
8 0.568661 2.61143 0.180536
8 -1.47856 2.33557 0.816373
1 -2.31842 -1.63013 -1.38475
17 -3.33044 -2.10362 0.670681