# Continuous flow conditions for high temperature formation of a benzodioxan pharmaceutical intermediate: Rapid scaleup for early phase material delivery

*AUTHOR NAMES*

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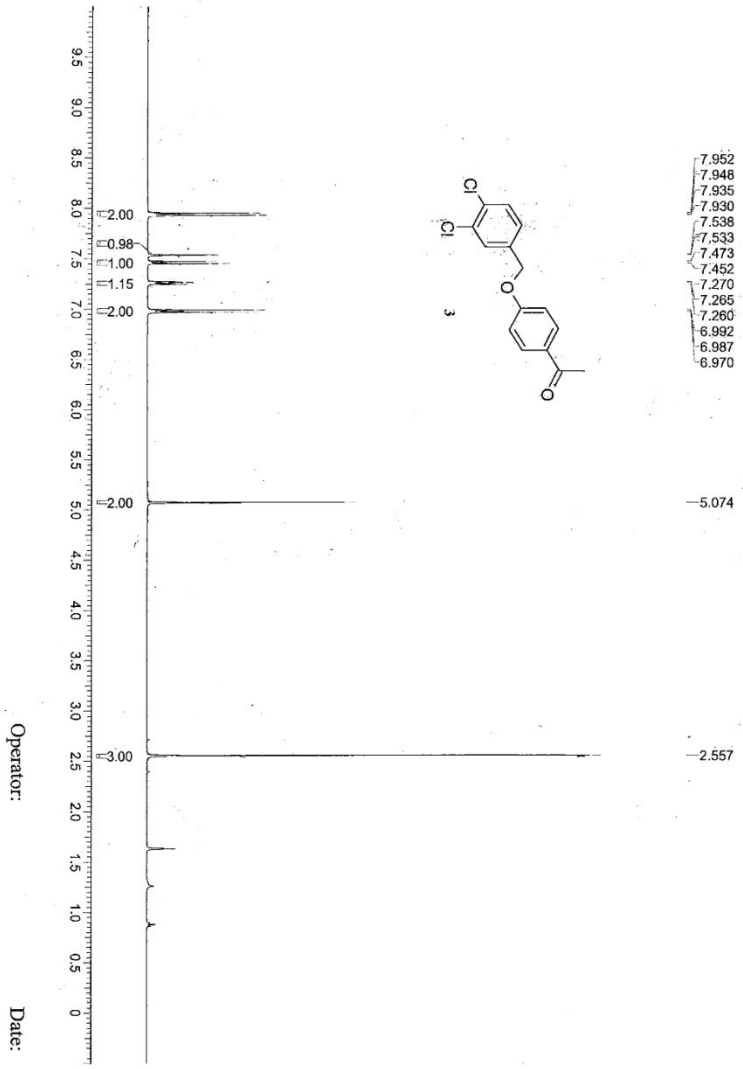
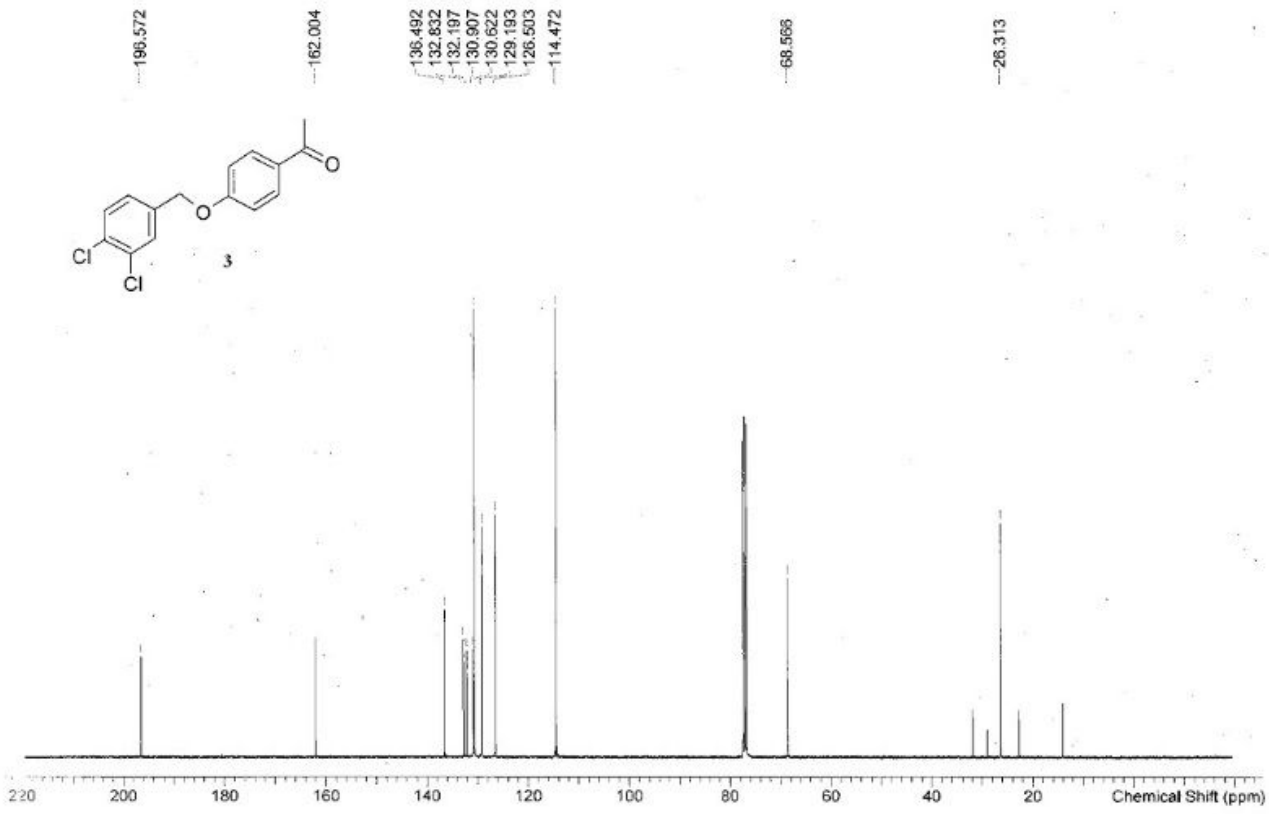
# Index

# 1. $^{1}$H NMR and $^{13}$ C NMR

## 1) 1-(4-((3,4-dichlorobenzyl)oxy)phenyl)ethan-1-one (3)



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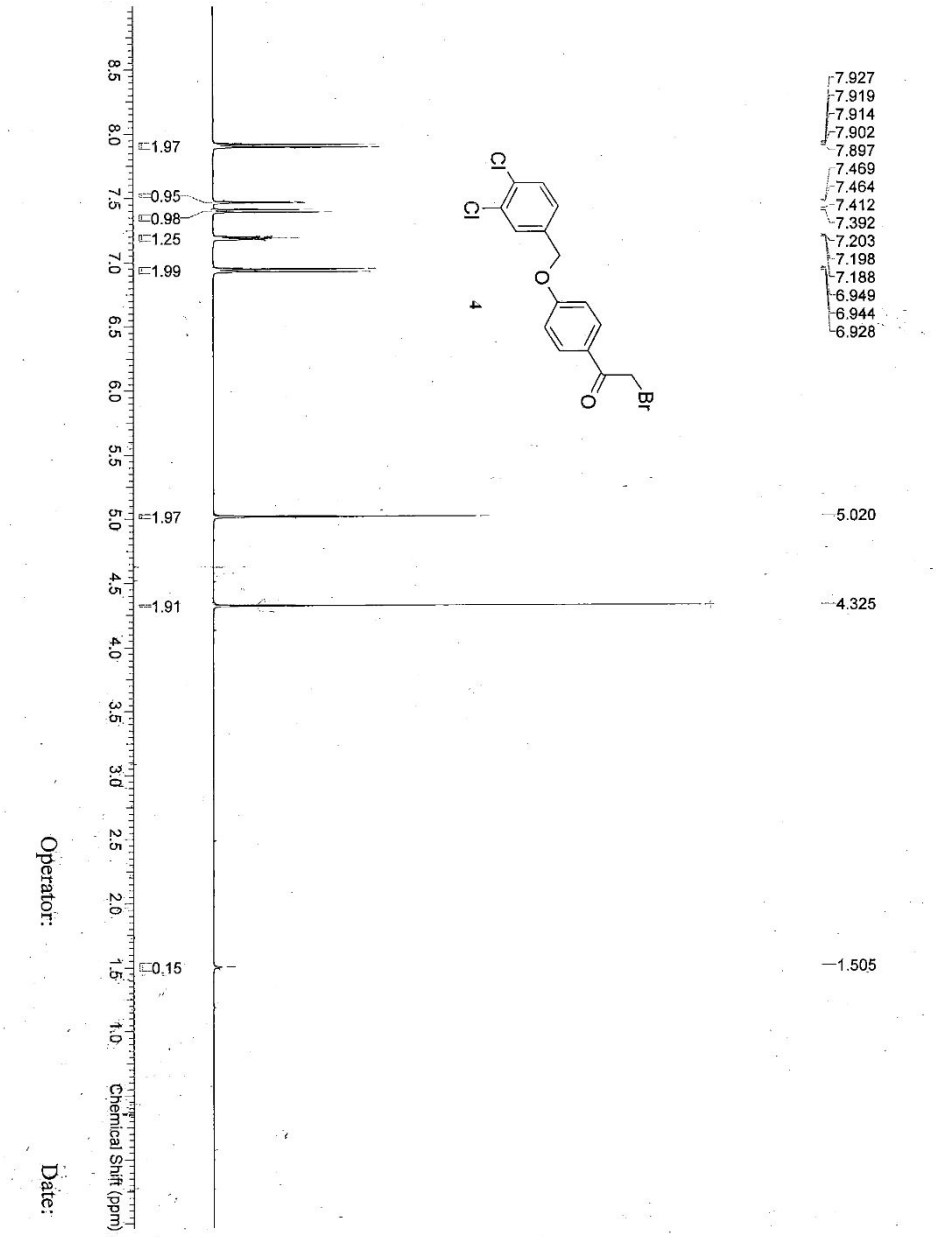
| Date | 19 Mar 2019 23:04:15 |
| Frequency (MHz) | 100.6128 |
| Nucleus | 13C |
| Number of Transients | 1024 |
| Origin | spect |
| Original Points Count | 32768 |
| Owner | NMRSU |
| Points Count | 32768 |
| Pulse Sequence | zgpg30 |
| Receiver Gain | 2050.00 |
| SW(cyclical) (Hz) | 24038.46 |
| Solvent | CHLOROFORM-d |
| Spectrum Offset (Hz) | 10060.8047 |
| Spectrum Type | standard |
| Sweep Width (Hz) | 24037.73 |
| Temperature (degree C) | 27.000 |

Operator: Date:

## 2) 2-Bromo-1(4-((3,4-dichlorobenzyl)oxy)phenyl)ethan-1-one (4)




| | |
|---|---|
| Acquisition Time (sec) | 3.9846 |
| Comment | EL-H8145 0-066-B-P CDCl3 Bruker_N_ 400MHz |
| Date | 08 Feb 2018 15:22:18 |
| Frequency (MHz) | 400.1400 |
| Nucleus | 1H |
| Number of Transients | 8 |
| Origin | spect |
| Original Points Count | 32768 |
| Owner | nmrsu |
| Points Count | 32768 |
| Pulse Sequence | zg30 |
| Receiver Gain | 203.00 |
| SW(cyclical) (Hz) | 8223.68 |
| Solvent | TMS |
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| Spectrum Type | standard |
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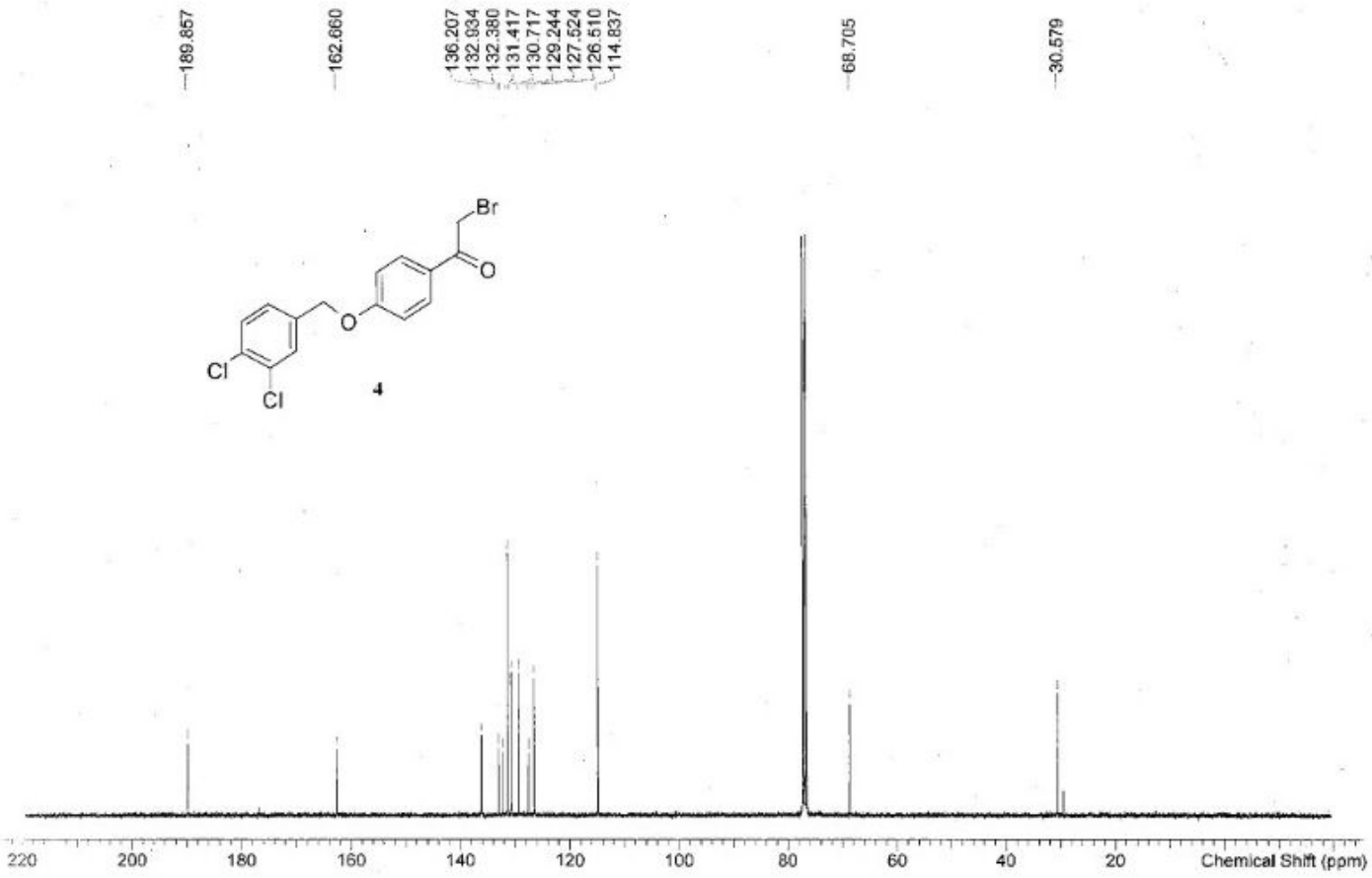
| Temperature (degree C) | 21.560 |

Operator:

Date:




| | |
|---|---|
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| Frequency (MHz) | 100.6128 |
| Nucleus | 13C |
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| Origin | spect |
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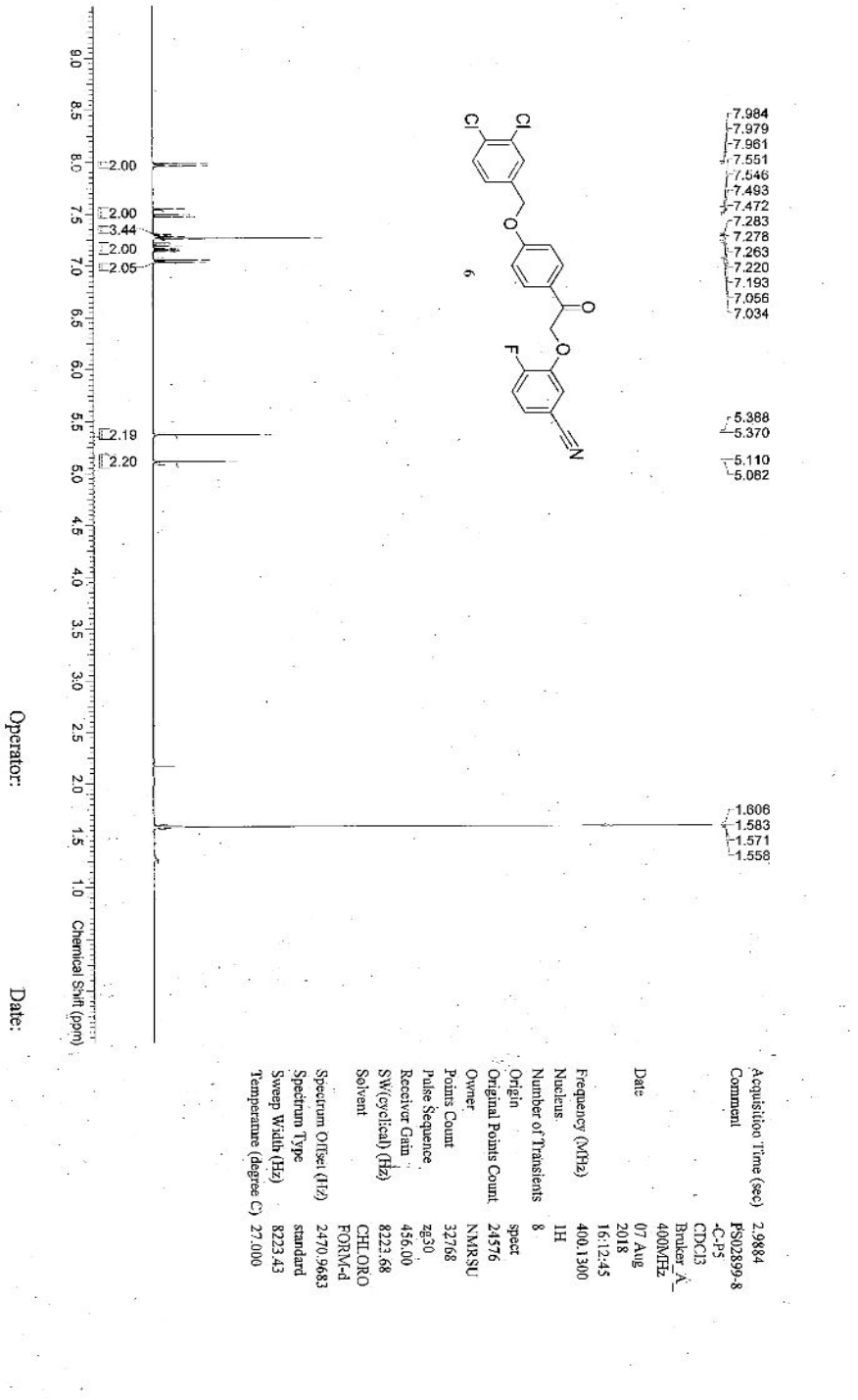
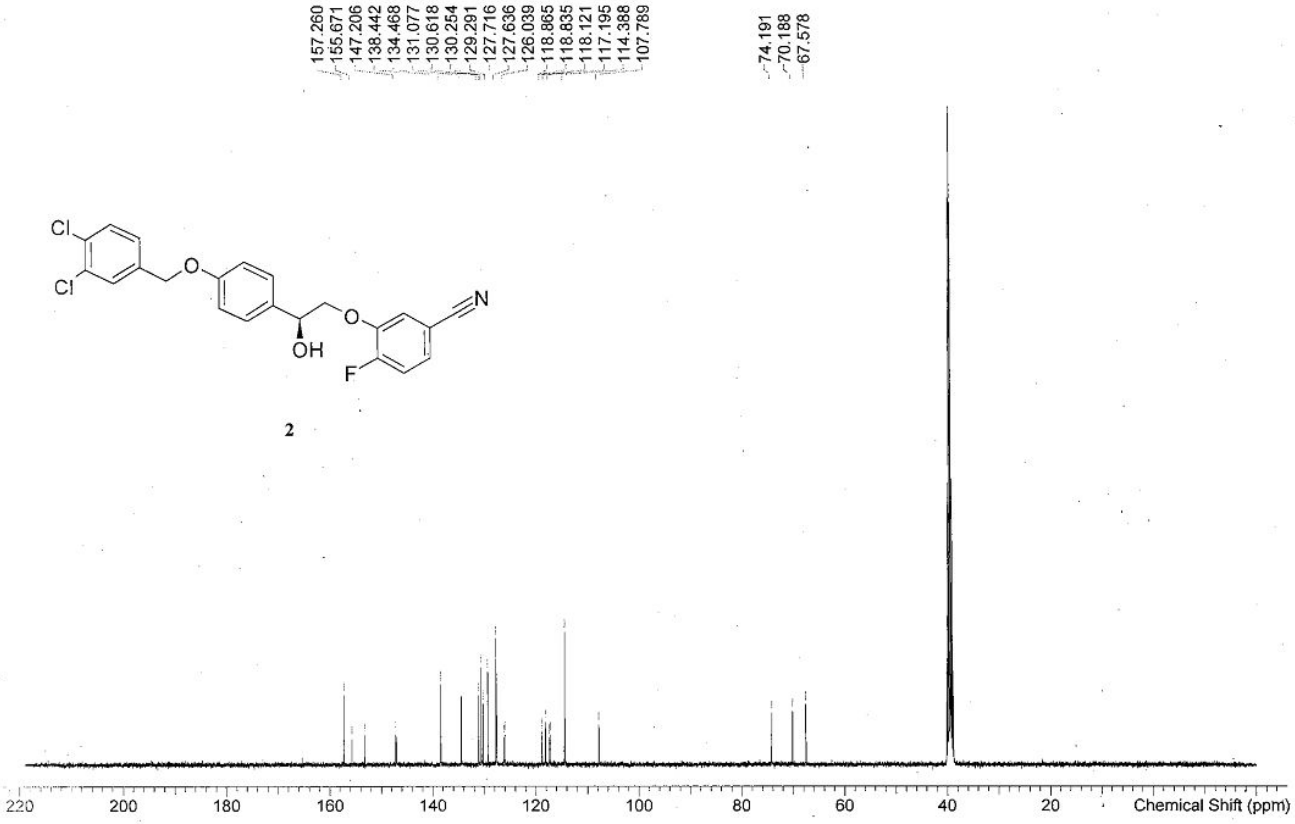
| Owner | NMRSU |
| Points Count | 32768 |
| Pulse Sequence | zgpg30 |
| Receiver Gain | 2050.00 |
| SW(cyclical) (Hz) | 24038.46 |
| Solvent | CHLOROFORM-d |
| Spectrum Offset (Hz) | 10060.8047 |
| Spectrum Type | standard |
| Sweep Width (Hz) | 24037.73 |
| Temperature (degree C) | 27.000 |

Operator: Date:

## 3) 3-(2-(4-((3,4-dichlorobenzyl)oxy)phenyl-2-oxoethoxy)-4-fluorobenzonitrile (6)






**2**

| | |
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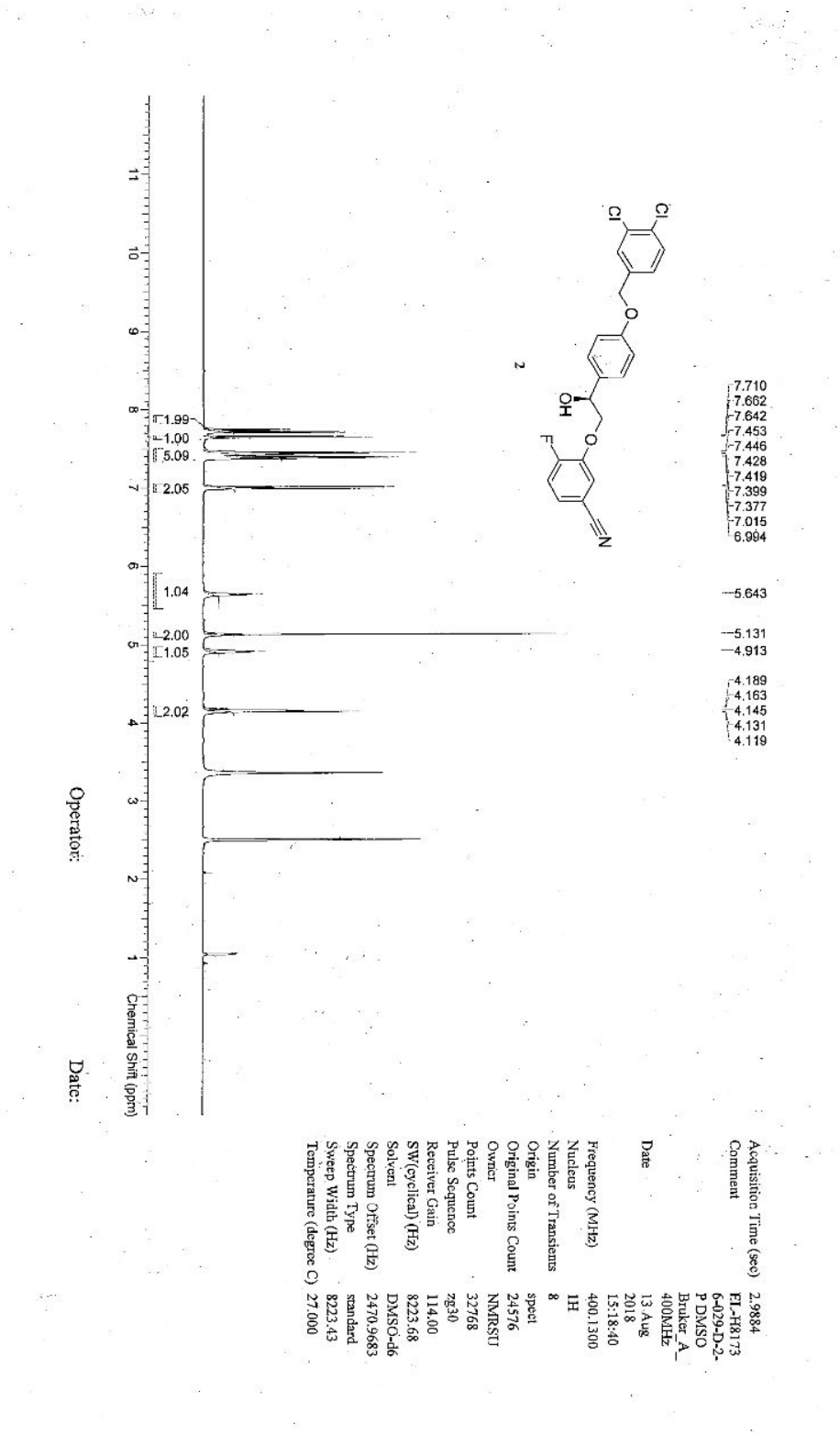
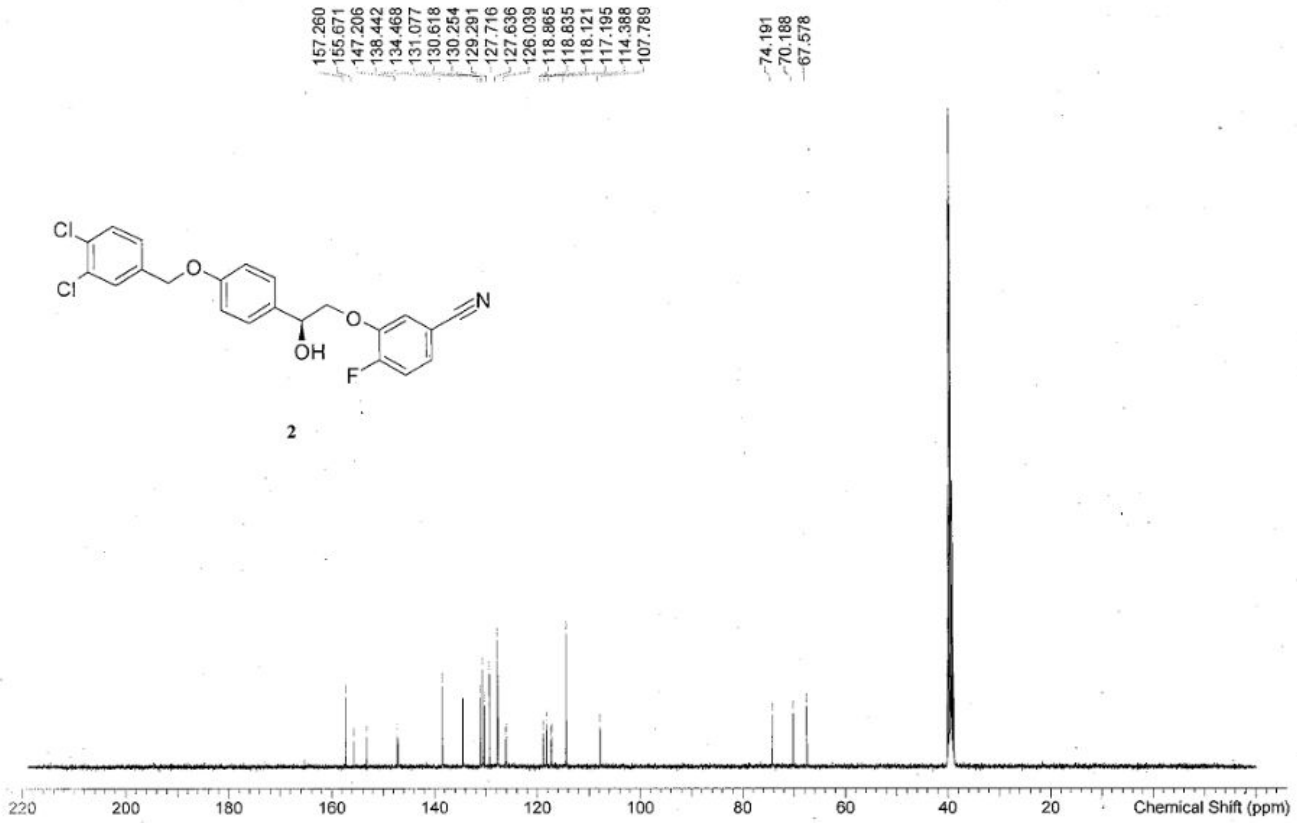
| Owner | NMRSU |
| Points Count | 32768 |
| Pulse Sequence | zgpg30 |
| Receiver Gain | 2050.00 |
| SW(cyclical) (Hz) | 24038.46 |
| Solvent | DMSO-d6 |
| Spectrum Offset (Hz) | 10010.4990 |
| Spectrum Type | standard |
| Sweep Width (Hz) | 24037.73 |
| Temperature (degree C) | 27.000 |

Operator: Date:

**4) (*S*)-3-(2-(4-((3,4-dichlorobenzyl)oxy)-2-hydroxyethoxy)-4-fluorobenzonitrile (2)**






2

| | |
|---|---|
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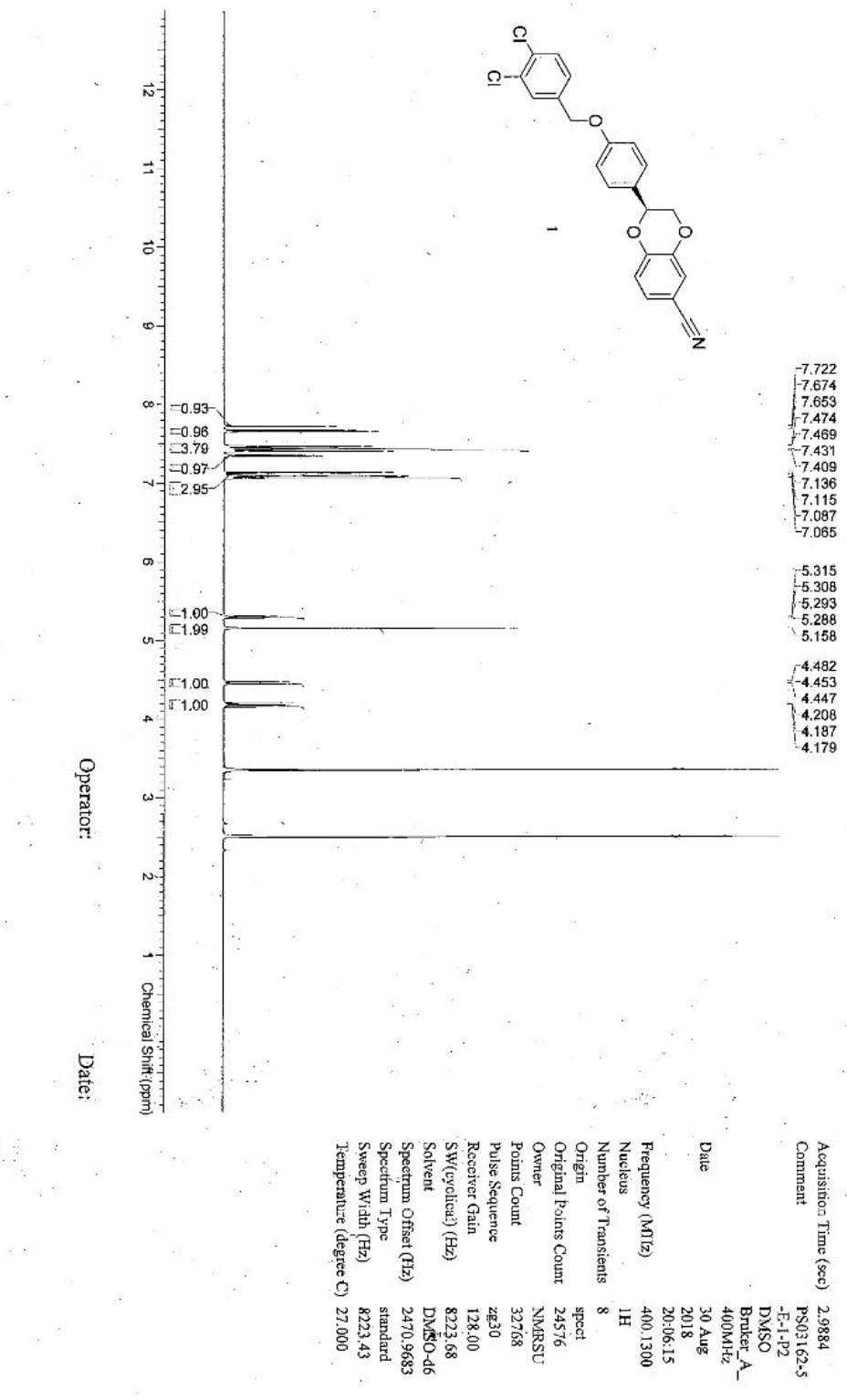
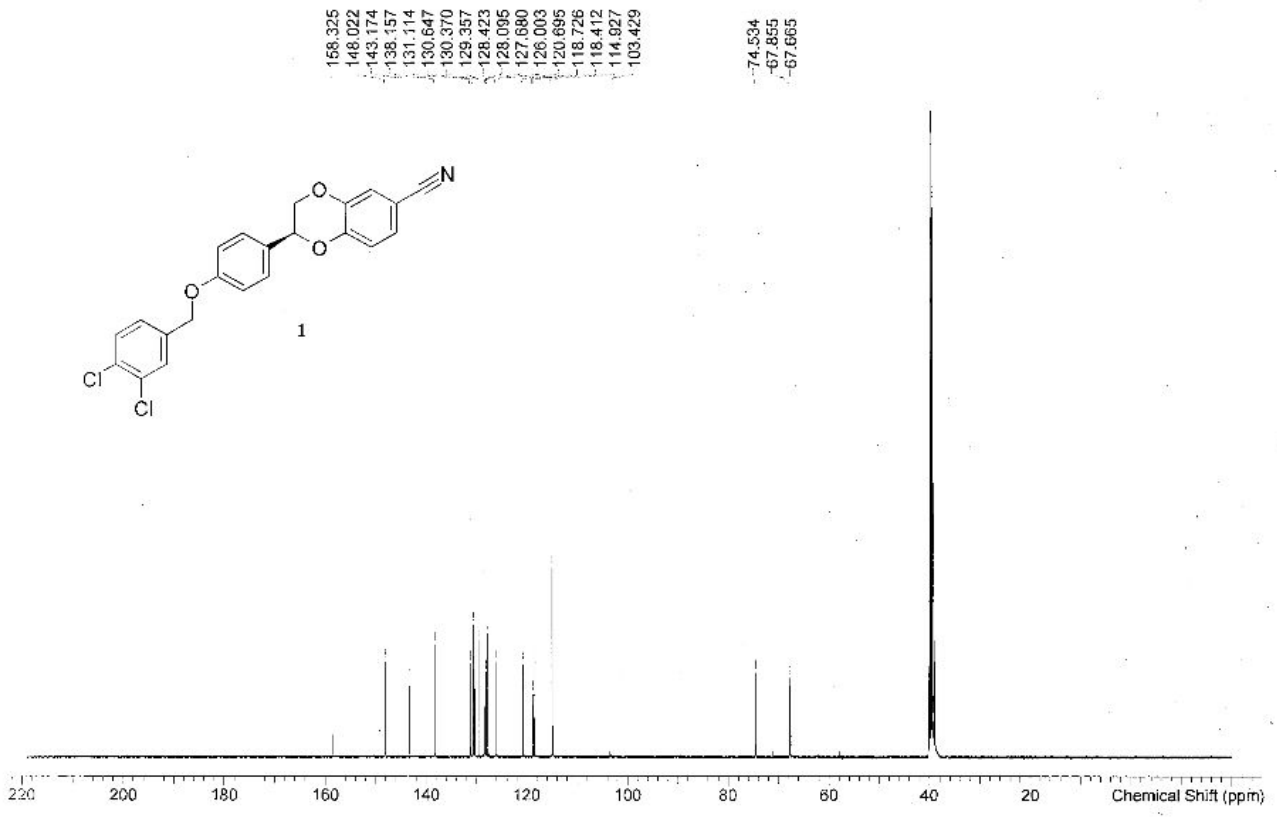
| Nucleus | 13C |
| Number of Transients | 1024 |
| Origin | spect |
| Original Points Count | 32768 |
| Owner | NMRSU |
| Points Count | 32768 |
| Pulse Sequence | zgpg30 |
| Receiver Gain | 2050.00 |
| SW(cyclical) (Hz) | 24038.46 |
| Solvent | DMSO-d6 |
| Spectrum Offset (Hz) | 10010.4990 |
| Spectrum Type | standard |
| Sweep Width (Hz) | 24037.73 |
| Temperature (degree C) | 27.000 |

Operator: Date:

**5) (*S*)-2-(4-((3,4-dichlorobenzyl)oxy)phenyl)-2,3-dihydrobenzo [b][1,4]dioxine-6-carbonitrile (1)**






| | |
|---|---|
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| Nucleus | 13C |
| Number of Transients | 3000 |
| Origin | spect |
| Original Points Count | 32768 |
| Owner | NMRSU |
| Points Count | 32768 |
| Pulse Sequence | zgpg30 |
| Receiver Gain | 2050.00 |
| SW(cyclical) (Hz) | 24038.46 |
| Solvent | DMSO-d6 |
| Spectrum Offset (Hz) | 10010.4990 |
| Spectrum Type | standard |
| Sweep Width (Hz) | 24037.73 |
| Temperature (degree C) | 27.000 |

Operator: Date:

## 2. Chromatogram of the racemate and the enantiomerically pure compound

### 1) (*S*)-3-(2-(4-((3,4-dichlorobenzyl)oxy)-2-hydroxyethoxy)-4-fluorobenzonitrile (2)

**HPLC REPORT**

Sample Information @D:\...\EL-Process\2018\EL-V20171211A\Data\20180917\H81755-007-D-P2.lcd

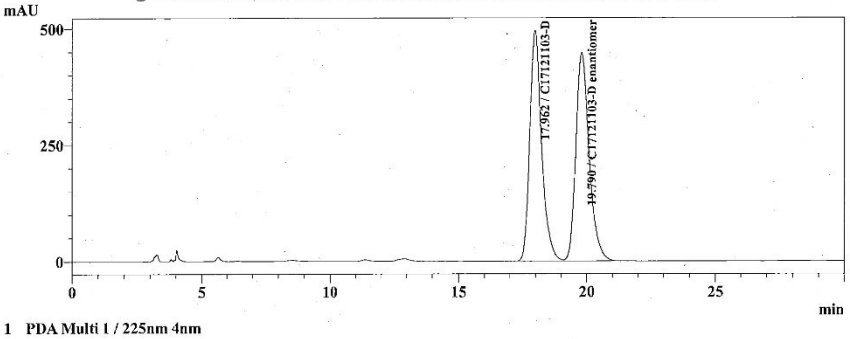
| | |
|---|---|
| Project No.: | EL-V20171211A |
| Compound ID: | C17121103-D |
| Sample ID: | H81755-007-D-P2 |
| Vail# : | 9 |
| Injection Volume: | 5 uL |
| Test Items: | Chiral |
| Operator: | GZh |
| Notebook Reference: | H81592-031 |

| | |
|---|---|
| Data Filename: | D:\Raw Data\EL-Process\2018\EL-V20171211A\Data\20180917\H81755-007-D-I |
| Method Filename: | D:\Raw Data\EL-Process\2018\EL-V20171211A\Method\AM-20%B-35C-1.0-30 |
| Date Acquired: | 9/17/2018 4:00:24 PM |
| Data Processed: | 9/17/2018 4:30:26 PM |

System Configuration @D:\...\EL-Process\2018\EL-V20171211A\Data\20180917\H81755-007-D-P2.lcd

| | |
|---|---|
| Instrument Name: | ADS-HPLC-734 |
| Column Name: | Chiralpak IC 250*4.6mm 5 um ADS-HPC-25-505 |

@D:\Raw Data\EL-Process\2018\EL-V20171211A\Data\20180917\H81755-007-D-P2.lcd




1 PDA Multi 1 / 225nm 4nm

PeakTable @D:\Raw Data\EL-Process\2018\EL-V20171211A\Data\20180917\H81755-007-D-P2.lcd

PDA Ch1 225nm 4nm

| No. | Ret. Time | Name | Area | Height | Area % | Resolution | Tailing Factor | Theoretical Plate |
|---|---|---|---|---|---|---|---|---|
| 1 | 17.962 | C17121103-D | 16016668 | 494973 | 49.9250 | 0.000 | 1.339 | 7539 |
| 2 | 19.790 | C17121103-D enantiomer | 16064810 | 447627 | 50.0750 | 2.098 | 1.341 | 7480 |
| Tota | | | | | 100.0000 | | | |

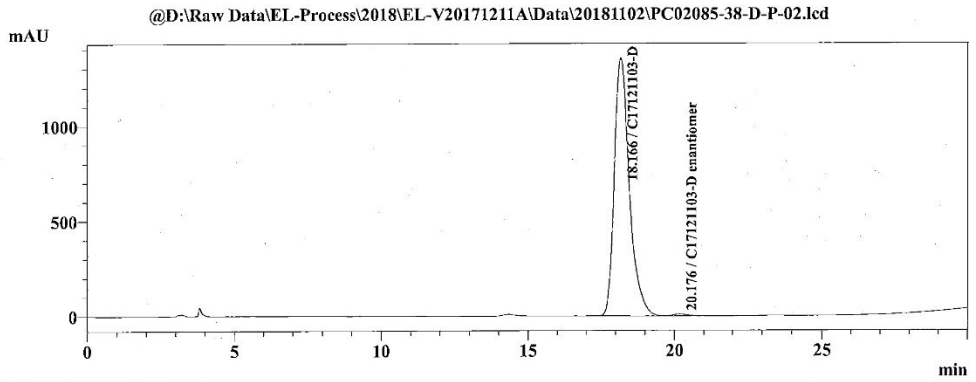
# HPLC REPORT

**Sample Information @D:\...\EL-Process\2018\EL-V20171211A\Data\20181102\PC02085-38-D-P-02.lcd**

| | |
|---|---|
| **Project No.:** | **EL-V20171211A** |
| **Compound ID:** | **C17121103-D** |
| **Sample ID:** | **PC02085-38-D-P** |
| **Vail# :** | **10** |
| **Injection Volume:** | **10 uL** |
| **Test Items:** | **Chiral** |
| **Operator:** | **GZh** |
| **Notebook Reference:** | **H81592-050** |
| **Data Filename:** | **D:\Raw Data\EL-Process\2018\EL-V20171211A\Data\20181102\PC02085-38-D-I** |
| **Method Filename:** | **D:\Raw Data\EL-Process\2018\EL-V20171211A\Method\AM-20%B-35C-1.0-30** |
| **Date Acquired:** | **11/2/2018 6:45:09 PM** |
| **Data Processed:** | **11/5/2018 9:33:58 AM** |

**System Configuration @D:\...\EL-Process\2018\EL-V20171211A\Data\20181102\PC02085-38-D-P-02.lcd**

| | |
|---|---|
| **Instrument Name:** | **ADS-HPLC-734** |
| **Column Name:** | **Chiralpak IC 250*4.6mm 5 um ADS-HPC-25-505** |




1 PDA Multi 1 / 225nm 4nm

**PeakTable @D:\Raw Data\EL-Process\2018\EL-V20171211A\Data\20181102\PC02085-38-D-P-02.lcd**

**PDA Ch1 225nm 4nm**

| Peak# | Ret. Time | Name | Area | Height | Area % | Resolution | Tailing Factor | Theoretical Plate |
|---|---|---|---|---|---|---|---|---|
| 1 | 18.166 | C17121103-D | 48555041 | 1356244 | 99.2983 | 0.000 | 1.399 | 6554 |
| 2 | 20.176 | C17121103-D enantiome | 343115 | 9153 | 0.7017 | 2.178 | 0.000 | 7249 |
| Total | | | | | 100.0000 | | | |

## 2) (*S*)-2-(4-((3,4-dichlorobenzyl)oxy)phenyl)-2,3-dihydrobenzo [b][1,4]dioxine-6-carbonitrile (1)

**HPLC REPORT**

Sample Information @D:\...\2018\EL-V20171211A\Data\20180917\H81755-008-E-P3-IPA-IA868.lcd

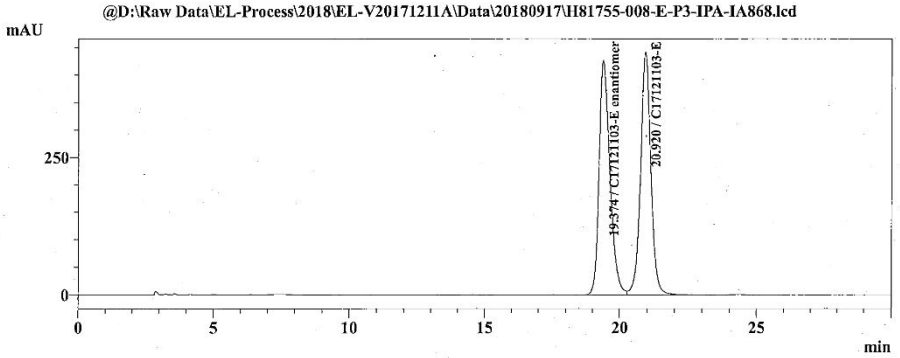
| | |
|---|---|
| Project No.: | EL-V20171211A |
| Compound ID: | C17121103-E |
| Sample ID: | H81755-008-E-P3 |
| Vail# : | 6 |
| Injection Volume: | 5 uL |
| Test Items: | Chiral |
| Operator: | GZh |
| Notebook Reference: | H81592-031 |

| | |
|---|---|
| Data Filename: | D:\Raw Data\EL-Process\2018\EL-V20171211A\Data\20180917\H81755-008-E-I |
| Method Filename: | D:\Raw Data\EL-Process\2018\EL-V20171211A\Method\AM-10%B-35C-1.0-30 |
| Date Acquired: | 9/19/2018 11:11:49 AM |
| Data Processed: | 9/21/2018 5:13:55 PM |

System Configuration @D:\...\2018\EL-V20171211A\Data\20180917\H81755-008-E-P3-IPA-IA868.lcd

| | |
|---|---|
| Instrument Name: | ADS-HPLC-734 |
| Column Name: | Chiralpak IA 250*4.6mm ADS-HPLC-25-868 |

@D:\Raw Data\EL-Process\2018\EL-V20171211A\Data\20180917\H81755-008-E-P3-IPA-IA868.lcd




1 PDA Multi 1 / 225nm 4nm

PeakTable @D:\Raw Data\EL-Process\2018\EL-V20171211A\Data\20180917\H81755-008-E-P3-IPA-IA868.lcd

PDA Ch1 225nm 4nm

| No. | Ret. Time | Name | Area | Height | Area % | Resolution | Tailing Factor | Theoretical Plate |
|---|---|---|---|---|---|---|---|---|
| 1 | 19.374 | C17121103-E enantiomer | 11815408 | 427591 | 49.5638 | 0.000 | 1.444 | 11717 |
| 2 | 20.920 | C17121103-E | 12023387 | 442149 | 50.4362 | 2.184 | 1.113 | 14312 |
| Tota | | | | | 100.0000 | | | |

# HPLC REPORT

Sample Information @D:\...\EL-Process\2018\EL-V20171211A\Data\20181127\PS03110-33-E-dry-02.lcd

| | |
|---|---|
| Project No.: | EL-V20171211A |
| Compound ID: | C17121103-E |
| Sample ID: | PS03110-33-E-dry |
| Vail# : | 24 |
| Injection Volume: | 1 uL |
| Test Items: | Chiral |
| Operator: | GZh |
| Notebook Reference: | H81592-058 |
| Data Filename: | D:\Raw Data\EL-Process\2018\EL-V20171211A\Data\20181127\PS03110-33-E-d |
| Method Filename: | D:\Raw Data\EL-Process\2018\EL-V20171211A\Method\AM-15%B-35C-1.0-30 |
| Date Acquired: | 11/27/2018 4:10:08 PM |
| Data Processed: | 11/27/2018 5:01:43 PM |

System Configuration @D:\...\2018\EL-V20171211A\Data\20181127\PS03110-33-E-dry-02.lcd

| | |
|---|---|
| Instrument Name: | ADS-HPLC-734 |

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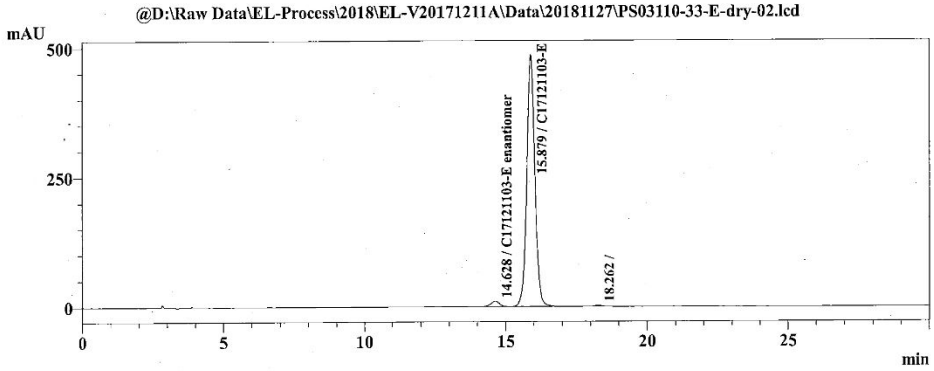



1 PDA Multi 1 / 225nm 4nm

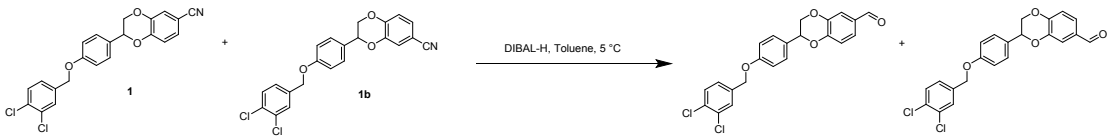
PeakTable @D:\Raw Data\EL-Process\2018\EL-V20171211A\Data\20181127\PS03110-33-E-dry-02.lcd

PDA Ch1 225nm 4nm

| Peak# | Ret. Time | Name | Area | Height | Area % | Resolution | Tailing Factor | Theoretical Plate |
|---|---|---|---|---|---|---|---|---|
| 1 | 14.628 | C17121103-E enantiome | 220600 | 10331 | 2.1845 | 0.000 | 0.927 | 11082 |
| 2 | 15.879 | C17121103-E | 9825908 | 485836 | 97.2999 | 2.308 | 1.057 | 14496 |
| 3 | 18.262 | | 52070 | 2463 | 0.5156 | 4.335 | 1.084 | 16305 |
| Total | | | | | 100.0000 | | | |

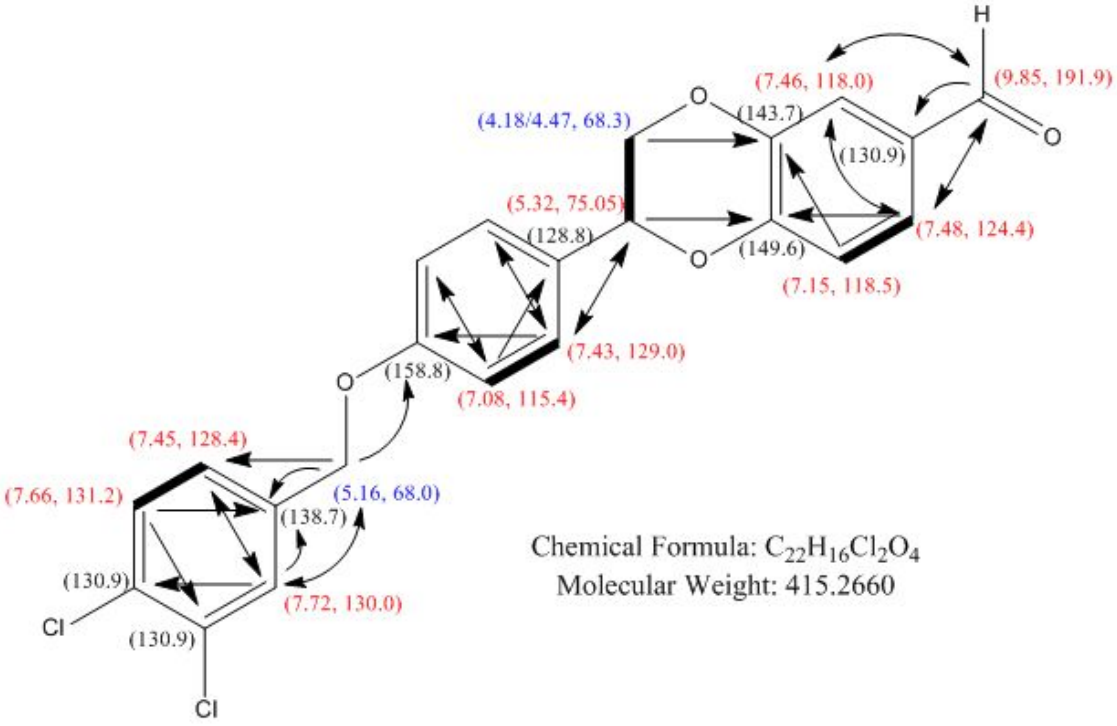
## 3. Characterization of regioisomer 1b

The regioisomers **1** and **1b** could not be separated by flash column chromatography. Identification of the product regioisomer **1b** was achieved by product derivatization. The mixture of **1** and **1b** were converted to the aldehyde via treatment with DIBAL-H according to the procedure below. The isomers were separated by flash column chromatography and analyzed by 2D NMR spectroscopy to confirm the regioisomer **1b**.




To a 100 mL 3-necked RBF was added the mixture of **1** and **1b** (3.6 g, 8.7 mmol, 1.0 eq.), toluene (28 mL, 8 mL/g)**.** After the suspension was cooled to 5 $^{o}$C, DIBAL-H (8 mL, 150 mmol, 1.5 eq., in 1M toluene solution) was added into the reaction mixture dropwise. The reaction mixture was stirred for 2 h at 5 $^{o}$C. After which time, it was quenched with potassium tartrate (25 g, 20 wt%, aq.) and stirred at RT for 1h. The solid was removed by filtration through a pad of celite, then the organic layer was separated and washed with 2 M HCl. The volatiles were removed, and the residue was purified via column chromatography to separate the two product regioisomers.

Desired Regioisomer




(#.##, ##.#) ($^{1}H$, $^{13}C$, $^{19}F$, or $^{15}N$) chemical shift assignments based on a variety of 1D and 2D data

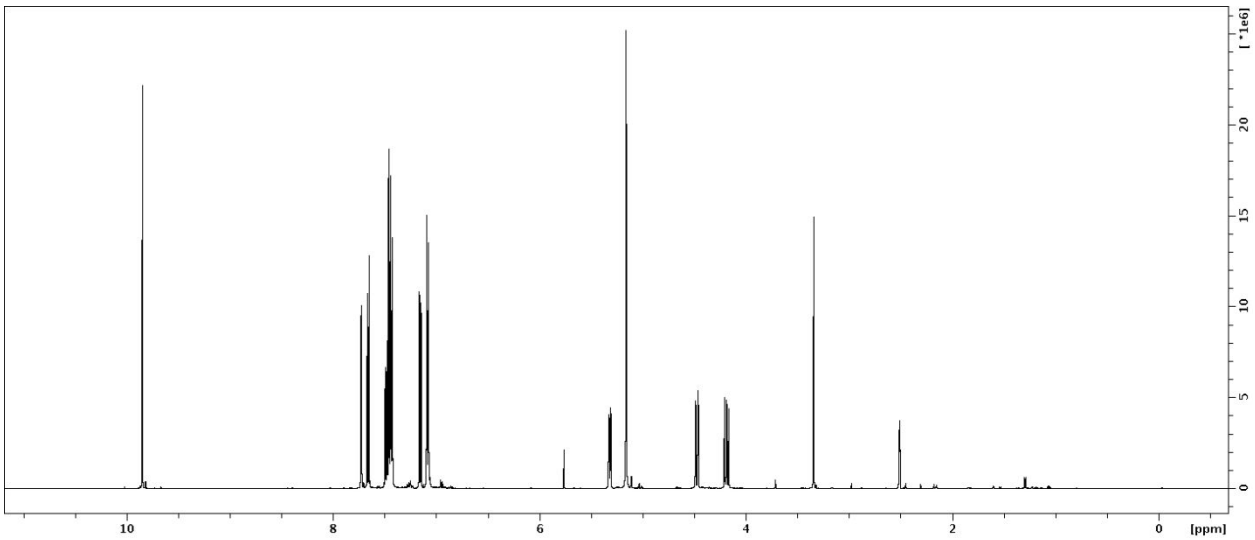
(#.##, ##.#) ($^{1}H$, $^{13}C$) chemical shift assignments of positive correlation in HSQC (with multiplicity editing) CH or $CH_3$

(#.##, ##.#) ($^{1}H$, $^{13}C$) chemical shift assignments of negative correlation in HSQC (with multiplicity editing) $CH_2$

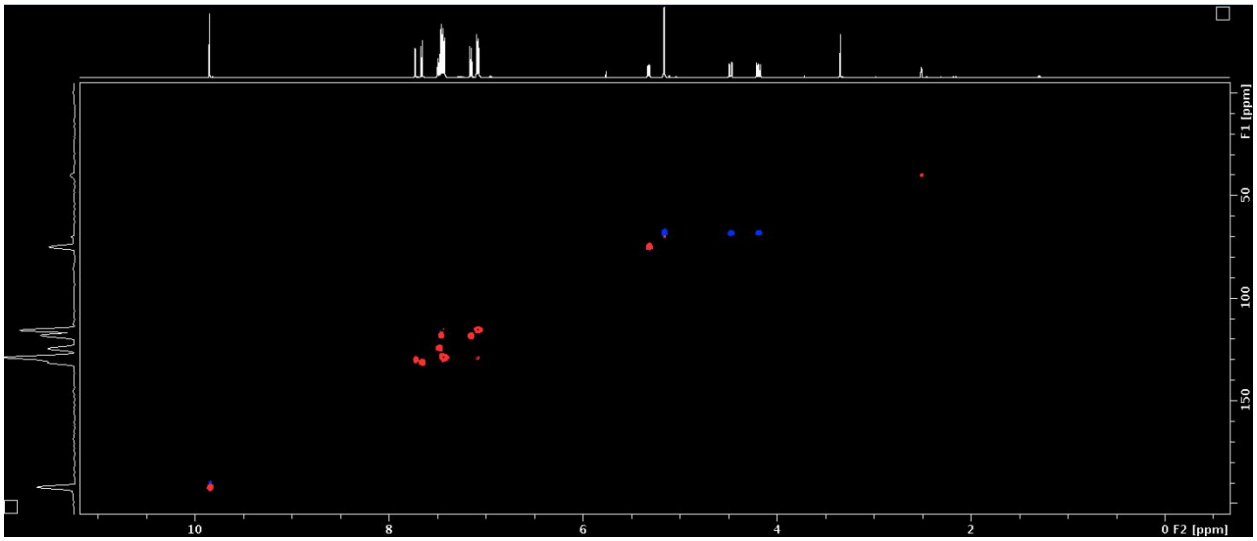
Represents an HMBC long range correlation (LRC) was observed ($^{1}H$ to $^{13}C$) or ($^{1}H$ to $^{15}N$)

Represents an COSY correlation was observed between proton resonances

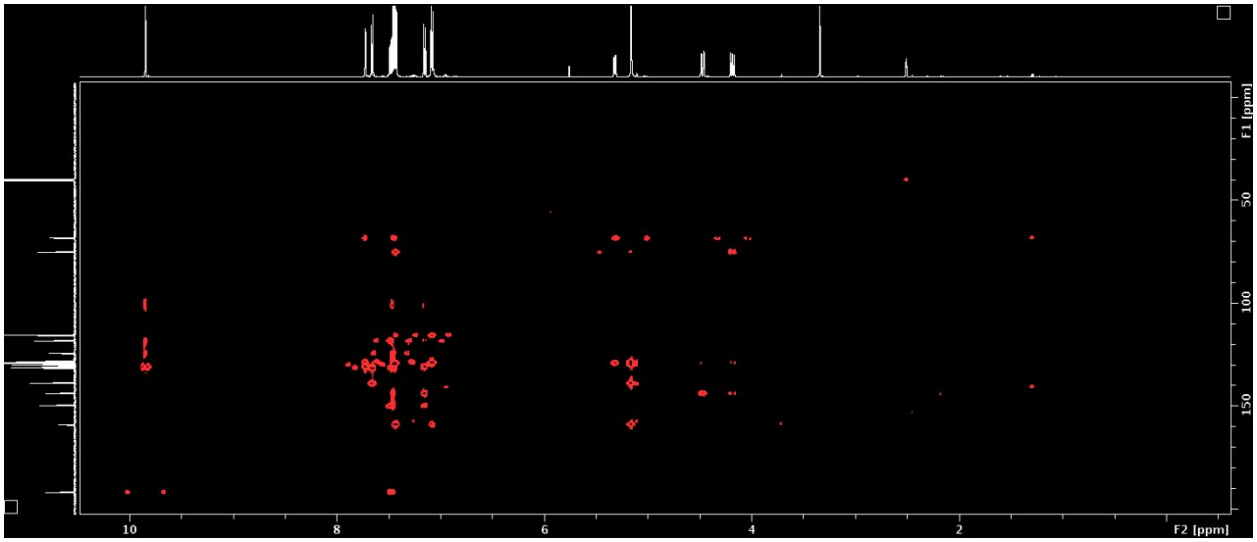
1H



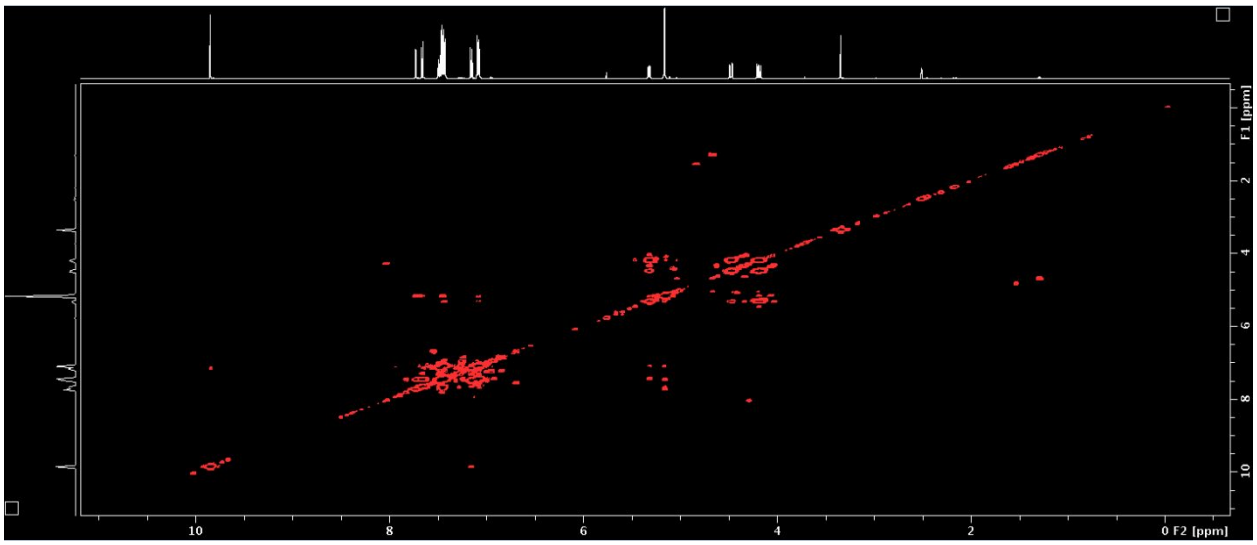
HSQC



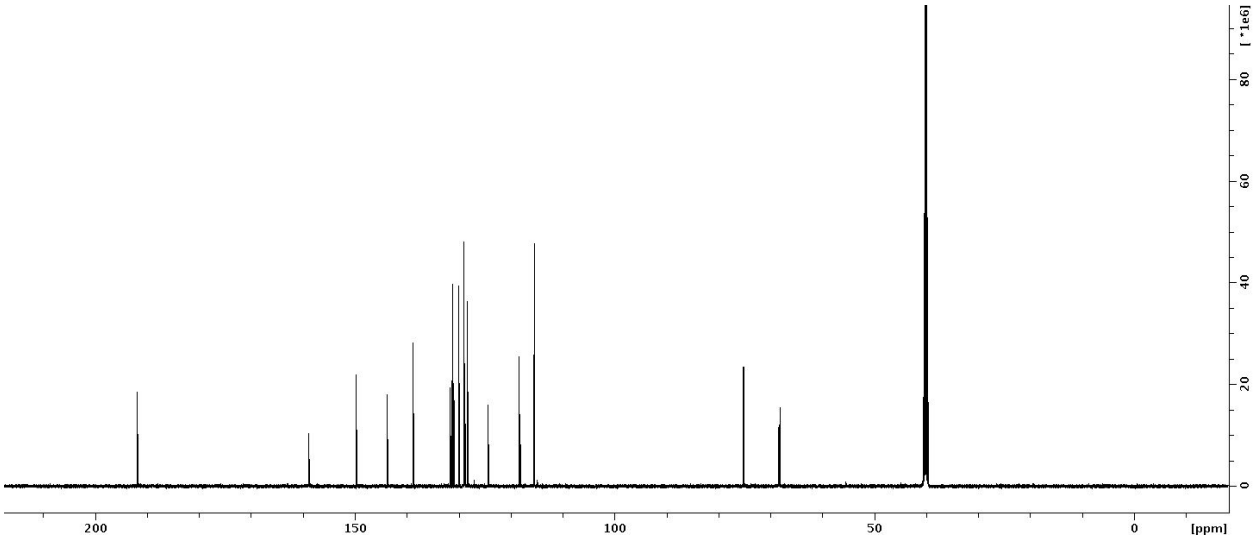

HMBC



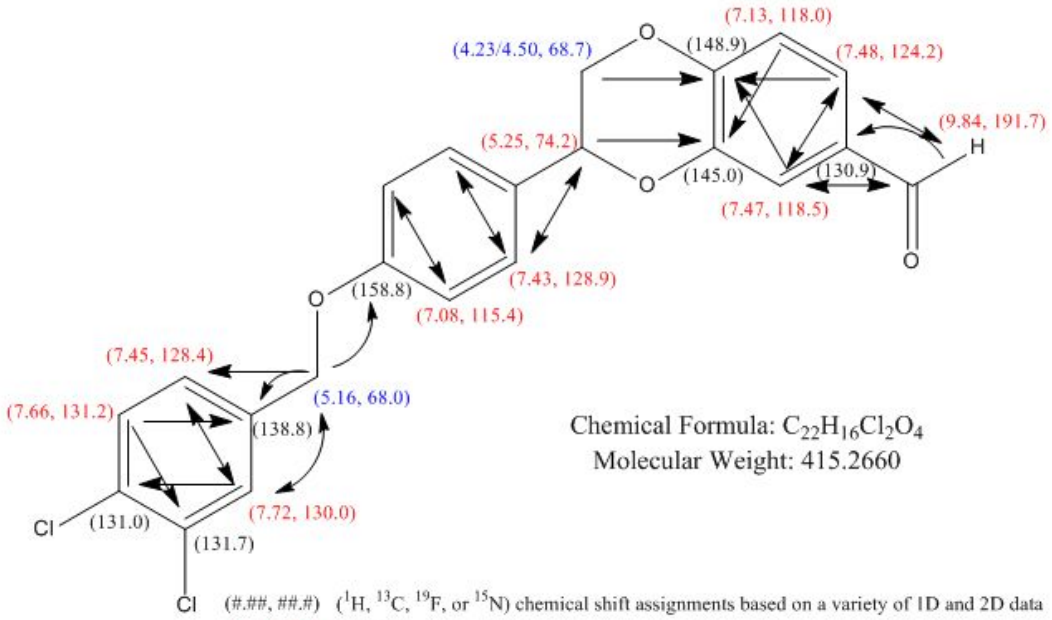
COSY



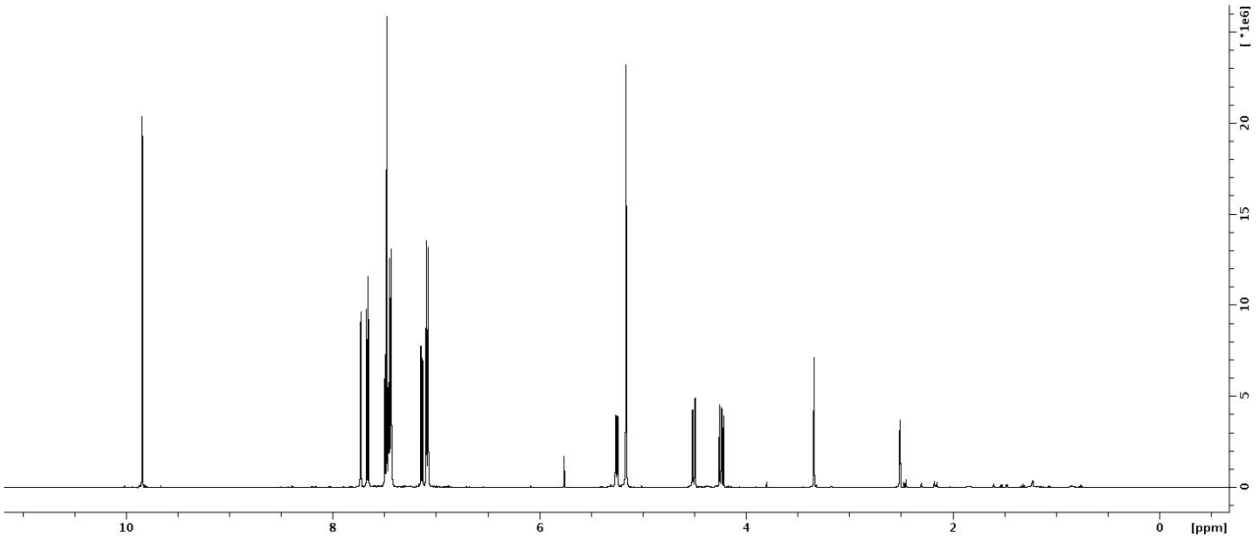

CARBON



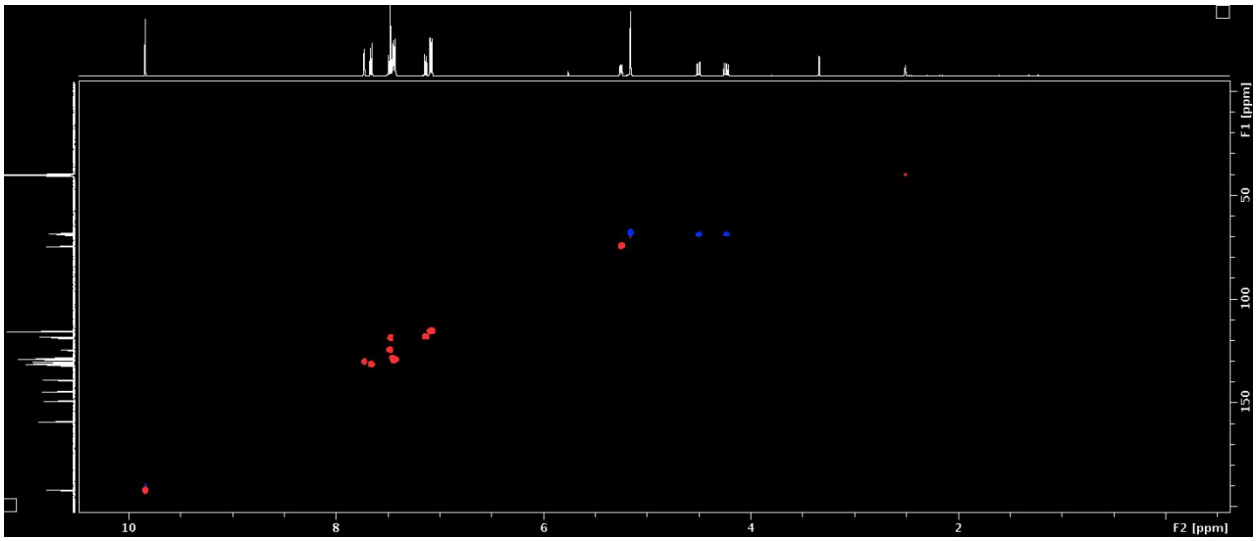

Undesired Regioisomer


(7.13, 118.0)
(4.23/4.50, 68.7)
(148.9)
(7.48, 124.2)
(9.84, 191.7)
(5.25, 74.2)
(145.0)
(130.9)
(7.47, 118.5)
(158.8)
(7.43, 128.9)
(7.08, 115.4)
(7.45, 128.4)
(5.16, 68.0)
(7.66, 131.2)
(138.8)
(7.72, 130.0)
(131.0)
(131.7)
Cl
Cl
Chemical Formula: $C_{22}H_{16}Cl_2O_4$
Molecular Weight: 415.2660
(#.##, ##.#) ($^1$H, $^{13}$C, $^{19}$F, or $^{15}$N) chemical shift assignments based on a variety of 1D and 2D data
(#.##, ##.#) ($^1$H, $^{13}$C) chemical shift assignments of positive correlation in HSQC (with multiplicity editing) CH or $CH_3$
(#.##, ##.#) ($^1$H, $^{13}$C) chemical shift assignments of negative correlation in HSQC (with multiplicity editing) $CH_2$
Represents an HMBC long range correlation (LRC) was observed ($^1$H to $^{13}$C) or ($^1$H to $^{15}$N)
Represents an COSY correlation was observed between proton resonances

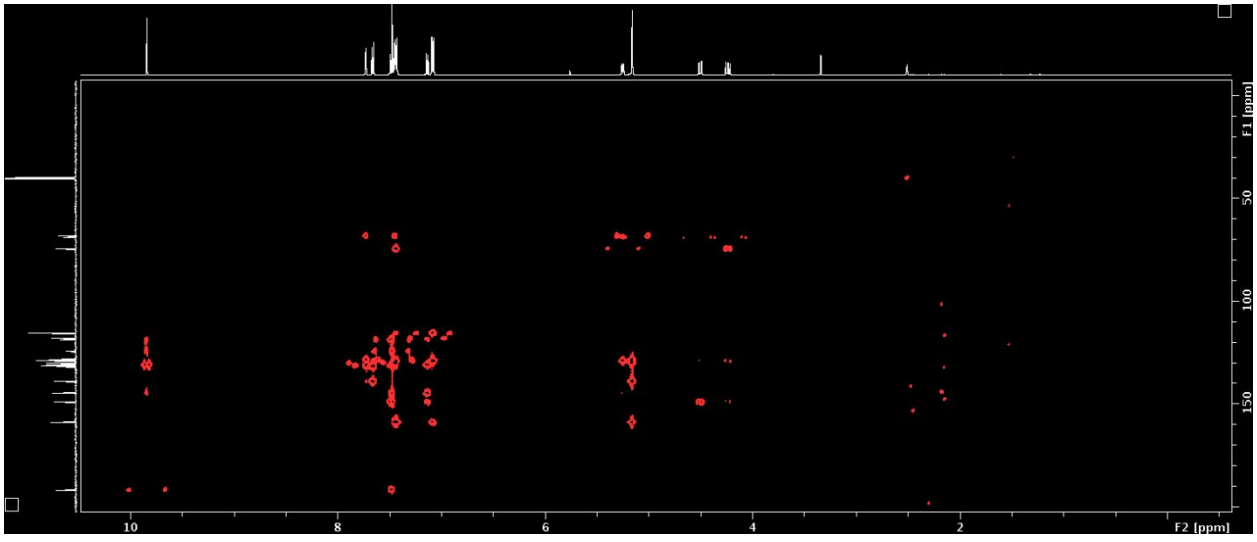
1H


[1e6]
20
15
10
5
0
10
8
6
4
2
0
[ppm]

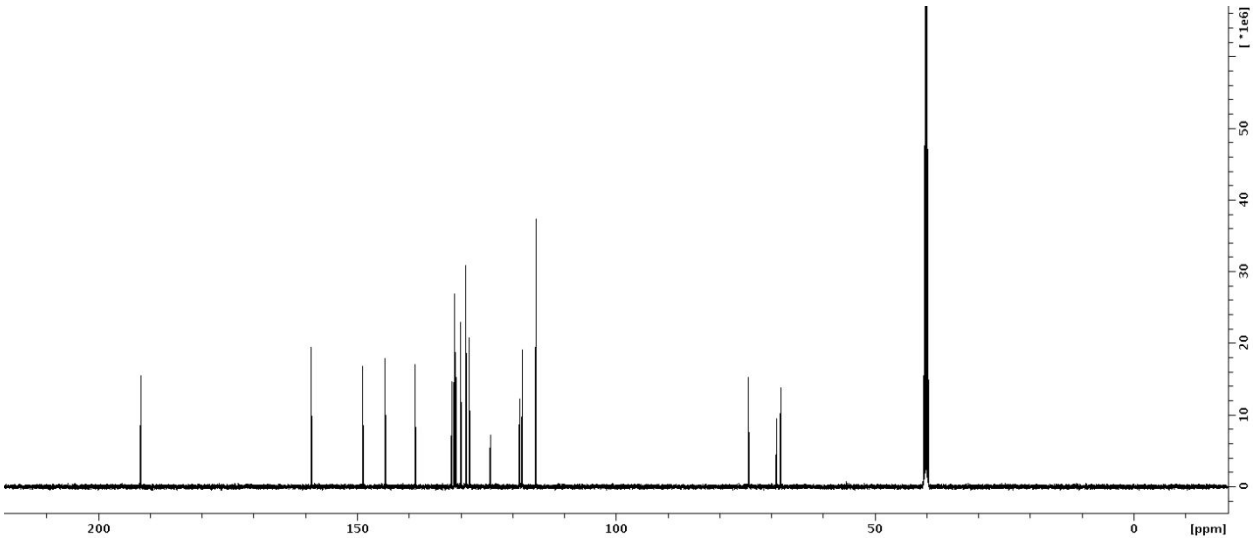
HSQC




HMBC

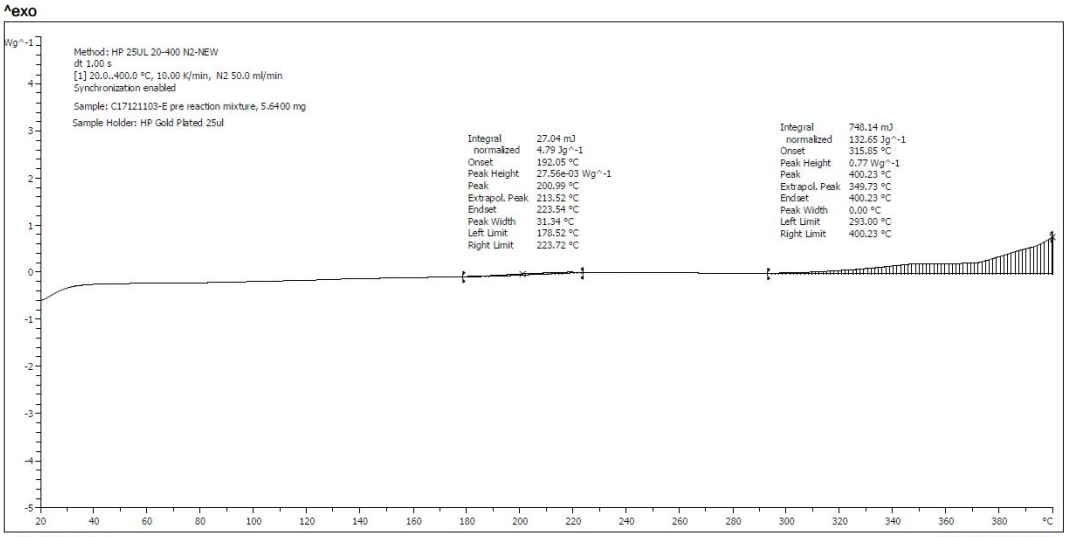


CARBON

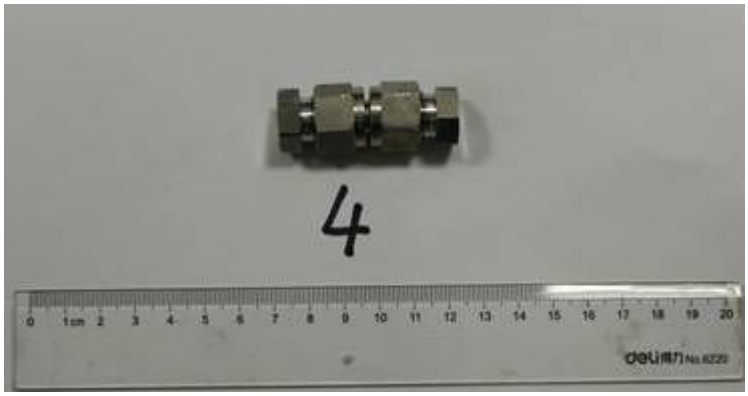



# 4. Safety Analysis of the high temperature $S_NAr$ Cyclization Conditions

DSC was completed on a representative reaction mixture for the $S_NAr$ cyclization of **2**. The reaction mixture consisted of **2**, in 10 mL/mg of diglyme with 3.2 equivalent of DBU.




# 5. Port Connector reactors for Small Scale Screening of High Temperature Conditions




## Swagelok port connector reactors are sealed and heated in a GC oven.

These small port connector reactors do not have pressure safety relief. Therefore, an internal safety group in each organization should set safety guidelines based on volume, thermal expansion, % liquid filled, and potential thermal decomposition to prevent port connector rupture, and shielding for protection in the event of rupture.