

# Chemo and Enantioselective Routes to Chiral Fluorinated Hydroxyketones Using Ketoreductases

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## Supplemental Information

### Sections:

1. Analytical methods
2. Synthesis of methyl/trifluoromethyl diketone substrates (**1**, **2**, **3**)
3. Analysis of *para*-diketone **1**
4. Analysis of *meta*-diketone **2**
5. Analysis of *ortho*-diketone **3a**
6. Synthesis of racemic trifluoromethyl hydroxyketones (**4**, **5**)
7. Analysis of *para*-trifluoromethyl hydroxyketone **4**
8. Analysis of *meta*-trifluoromethyl hydroxyketone **5**
9. Synthesis of racemic methyl hydroxyketones (**7**, **8**)
10. Analysis of *para*-methyl hydroxyketone **7**
11. Analysis of *meta*-methyl hydroxyketone **8**
12. Synthesis of bis-alcohols (**10**, **11**)
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## Section 1: Analytical Methods

### RP-HPLC method:

All chemical reactions for synthesis of diketone and product standards were monitored by reverse phase HPLC using a Zorbax Rx-C8 (4.6mm X 25cm, 5µm) column at 25°C and a detection wavelength of 210nm. The mobile phase was 50% acetonitrile and 50% 0.1% H<sub>3</sub>PO<sub>4</sub> H<sub>2</sub>O. Samples were prepared using acetonitrile or acetonitrile:H<sub>2</sub>O (1:1) as diluent.

### Achiral GC method:

All screening reactions of the catalysts were monitored by GC using a Restek Rtx-1701 (30m X 320µm, 1µm film thickness) column with a split injector (10:1) and a linear velocity of 45cm/sec using helium as the makeup gas. The inlet and detector temperatures were set to 275°C using a FID detector. The compounds were eluted with the following temperature gradient, 200°C hold for 2 minutes, ramp temperature to 275°C at 25°C/min and hold for 1 min.

### Chiral HPLC method:

Reaction samples were extracted with 2 volumes MTBE, dried under N<sub>2</sub> purge and resuspended in isopropanol. Chiral separation of the enantiomers of trifluoromethyl hydroxyketones **4** and **5** was achieved on normal phase HPLC using a Chiralcel OJ-H column with 10% MeOH in heptane at 1mL/min and a detection wavelength of 210nm.

### Chiral GC method:

Reaction samples were extracted with 2 volumes MTBE, dried under N<sub>2</sub> purge and resuspended in isopropanol. Chiral separation of the enantiomers of methyl hydroxyketones **7** and **8** was achieved on chiral GC using a Chirasil-dex CB (25m X 320µm, 0.25µm film thickness) column with a split injector (10:1) and a linear velocity of 60cm/sec using helium as the makeup gas. The inlet and detector temperatures were set to 200°C using a FID detector. Compound **7** was eluted with an isothermal method at 130°C. Compound **8** was eluted with an isothermal method at 100°C.

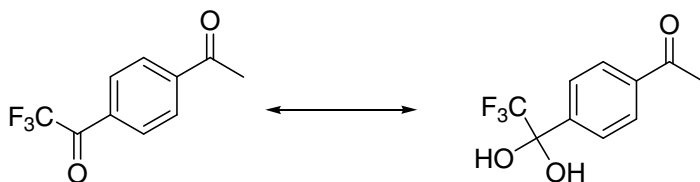
## Section 2: Synthesis of methyl/trifluoromethyl diketone substrates

To a solution of bromo-acetophenone (10g) in toluene (70mL) at 25C was added ethylene glycol (1.5 equivalents) and a catalytic amount of *p*-toluene sulfonic acid. The solution was refluxed overnight with a Dean-Stark trap. Due to the observed distillation of ethylene glycol, an additional 2 equivalents of the reagent was added in order to form the ketal. The toluene solution was cooled to 25C, washed with brine (1/2 volume), dried over MgSO<sub>4</sub>, and concentrated on a rotary evaporator. The *p*-bromo-ketal (99% conversion, 96% yield) was isolated as a fine white solid while the *m*-bromo-ketal (97% conversion, 93% yield) and *o*-bromo-ketal (98% conversion, 94% yield) were yellow oils.

The reaction from the ketal to the diketone was modified from the method in the literature reference<sup>2</sup>. 1.1 equivalents n-hexyl lithium (2.3M in hexanes) was added to a solution of bromo-ketal (10g) in THF (100mL) at -78C and aged to completion. Methyl trifluoroacetate (1.2 equivalents) was added to quench and the solution was aged. Upon completion, the solution was warmed to 25C and the ketal was deprotected by addition of 1N HCl. The deprotection of the *meta* and *ortho* compounds required reflux overnight. The THF solution was extracted into t-butyl methyl ether (MTBE, 2 vol.) and the organic layer was washed with brine (1 vol.), dried over MgSO<sub>4</sub> and concentrated to a crude waxy solid on the rotary evaporator. The crude solids were dissolved in ethyl acetate (EtOAc) and the *p*-diketone **1** (65% yield), *m*-diketone **2** (58% yield), and *o*-diketone **3** (80% yield) crystallized as a fine white solid upon addition of heptane.

### Section 3: *para*-diketone **1**

#### **1**: *p*-diketone



**1**: diketone form

**1**: mono-hydrate form

#### *Para*-diketone **1**

(mono-hydrate form):  $^1\text{H}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 8.00 (m, 2H), 7.78 (m, 2H), 5.40 (s, 2H), 2.59 (s, 3H) ppm.  $^{13}\text{C}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 198.78, 142.83, 139.20, 128.92, 128.68, 124.19 (q,  $J_{\text{CF}}$  = 287.3 Hz), 94.13 (q,  $J_{\text{CF}}$  = 32.0 Hz), 27.24 ppm.  $^{19}\text{F}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = -85.29 ppm.

(diketone form):  $^1\text{H}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 8.18 (m, 2H), 8.13 (m, 2H), 2.64 (s, 3H) ppm.  $^{19}\text{F}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = -73.40 ppm.

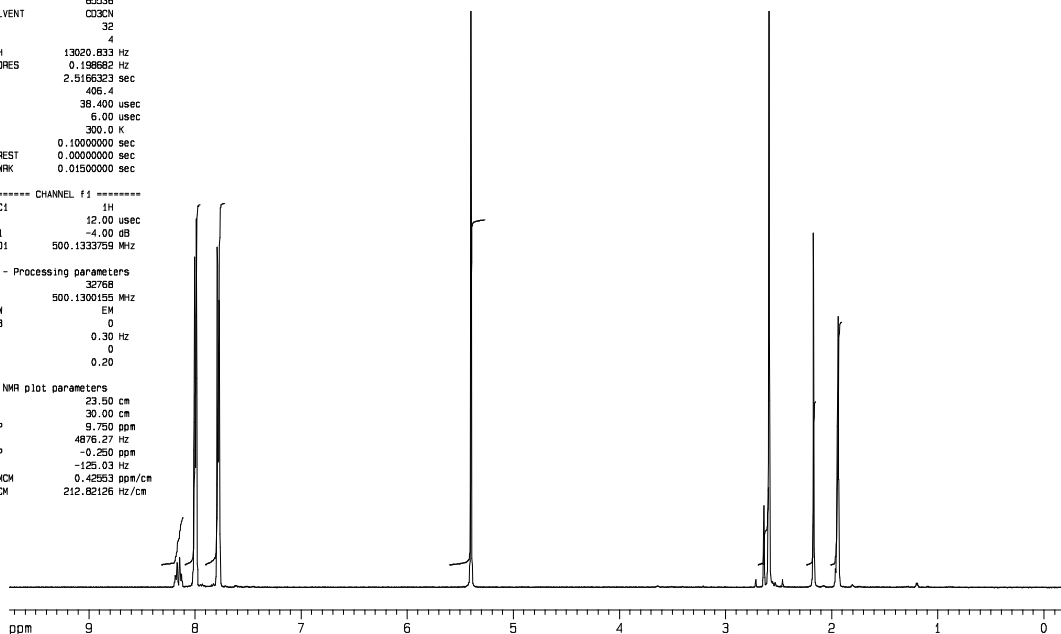
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PROCNO 1

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SOLVENT CD3CN  
NS 32  
DS 4  
SWH 13020.833 Hz  
FIDRES 0.196662 Hz  
AQ 2.5166323 sec  
RG 406.4  
DM 38.400 usec  
DE 6.00 usec  
TE 300.0 K  
D1 0.10000000 sec  
WCREST 0.00000000 sec  
WCMRK 0.01500000 sec

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PL1 -4.00 dB  
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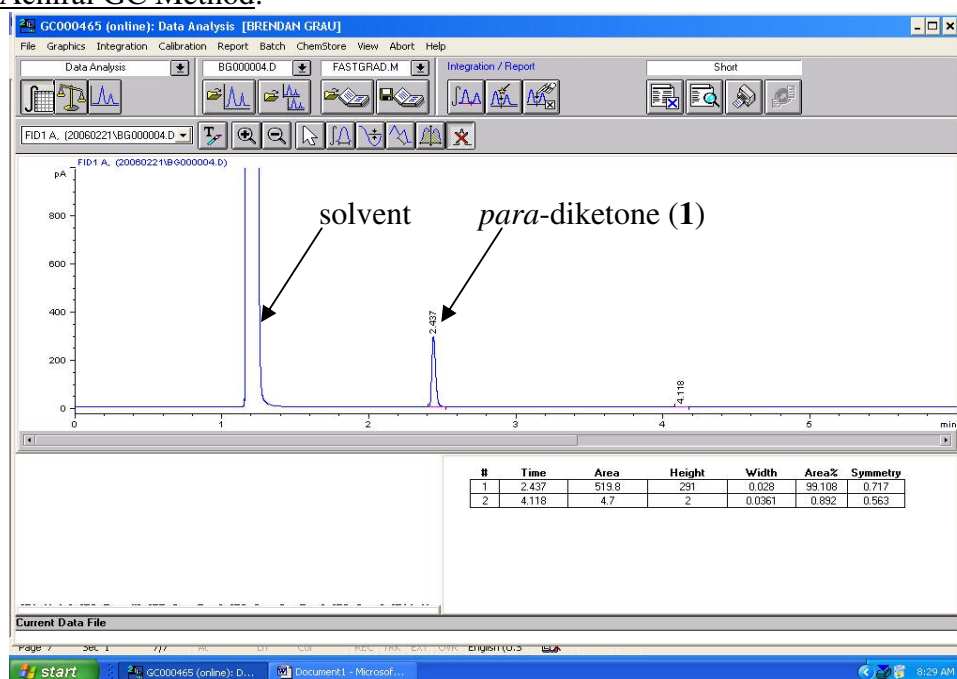
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CY 30.00 cm  
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F2P -0.250 ppm  
F2 -125.03 Hz  
PPMCM 0.42553 ppm/cm  
HZCM 212.82126 Hz/cm



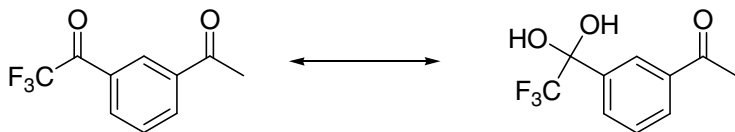


## Achiral GC Method:



## Section 4: *meta*-diketone **2**

### **2**: *m*-diketone



#### **2**: diketone form

#### **2**: mono-hydrate form

##### *Meta*-diketone **2**

(mono-hydrate form):  $^1\text{H}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 8.21 (s, 1H), 8.03 (d,  $J$  = 7.95 Hz, 1H), 7.89 (d,  $J$  = 7.95 Hz, 1H), 7.57 (t,  $J$  = 7.95 Hz, 1H), 5.43 (s, 2H), 2.59 (s, 3H) ppm.  $^{13}\text{C}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 198.71, 139.03, 138.20, 132.82, 130.56, 129.62, 127.83, 124.26 (q,  $J_{\text{CF}}$  = 286.7 Hz), 94.09 (q,  $J_{\text{CF}}$  = 32.0 Hz), 27.17 ppm.  $^{19}\text{F}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = -85.44 ppm.

(diketone form):  $^1\text{H}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 8.56 (s, 1H), 8.35 (d,  $J$  = 7.95 Hz, 1H), 8.27 (d,  $J$  = 7.95 Hz, 1H), 7.76 (t,  $J$  = 7.95 Hz, 1H), 2.64 (s, 3H) ppm.  $^{19}\text{F}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = -72.97 ppm.

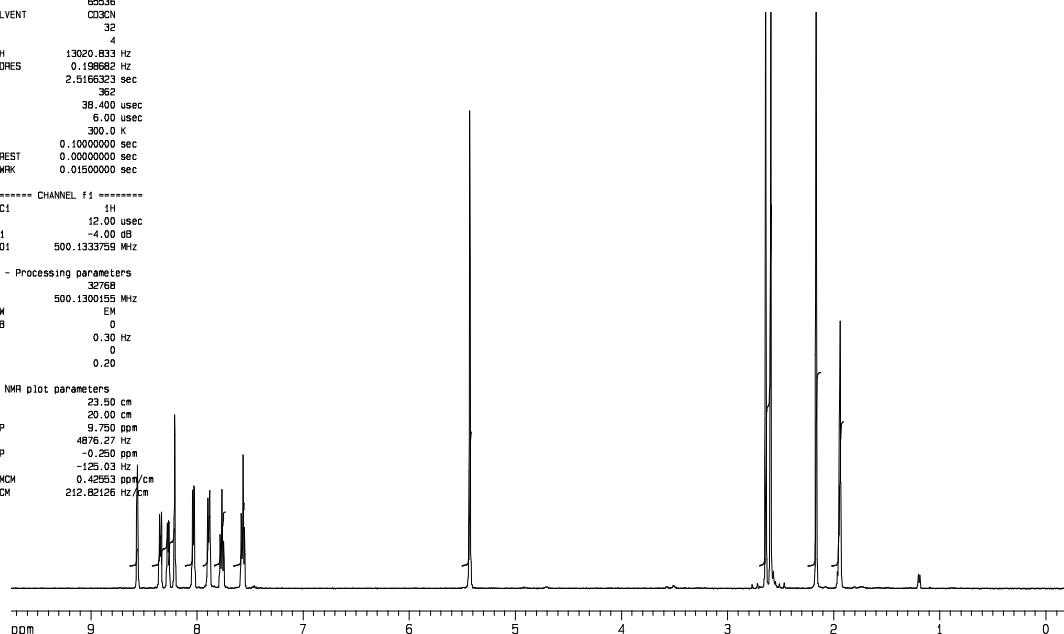
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NS 32  
DS 4  
SWH 13020.833 Hz  
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AQ 2.5166323 sec  
RG 362  
DM 38.400 usec  
DC 6.00 usec  
TE 300.0 K  
D1 0.10000000 sec  
MCREST 0.00000000 sec  
MCWRR 0.01500000 sec

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F2 - Processing parameters  
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LB 0.30 Hz  
GB 0  
PC 0.20

1D NMR plot parameters  
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CY 20.00 cm  
F1P 9.750 ppm  
F1 4876.27 Hz  
F2P -0.250 ppm  
F2 -125.03 Hz  
PPMDH 0.42553 ppm/cm  
HZDM 212.82126 Hz/cm



Current Data Parameters  
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PROCNO 1

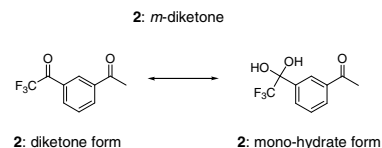
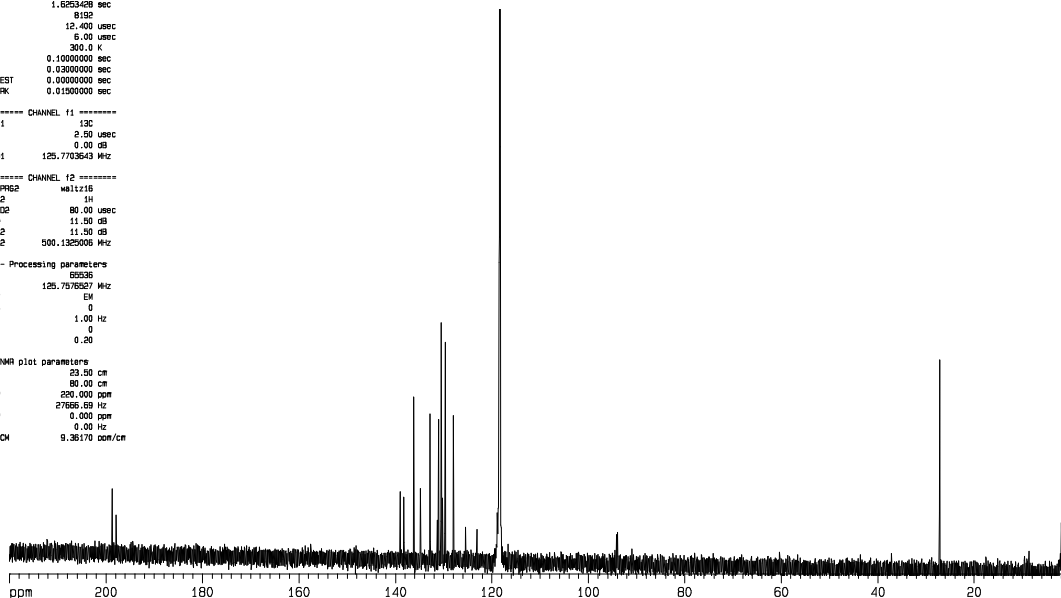
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SOLVENT CDCl3  
NS 710  
DS 4  
SWH 49322.562 Hz  
FIDRES 0.307637 Hz  
AQ 1.625328 sec  
RG 8192  
DM 15.400 usec  
DE 6.00 usec  
TE 300.0 K  
D1 0.10000000 sec  
S11 0.03000000 sec  
KCHST 0.00000000 sec  
KCHCK 0.01000000 sec

===== CHANNEL f1 =====  
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P1 2.50 usec  
PL1 0.00 dB  
SFO1 125.770543 MHz

===== CHANNEL f2 =====  
DPRG22 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 11.50 dB  
PL12 11.50 dB  
SFO2 500.1325006 MHz

F2 - Processing parameters  
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SSB 0  
LB 1.00 Hz  
GB 0  
PC 0.20

1D NMR plot parameters  
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CY 80.00 cm  
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F1 27666.89 Hz  
F2P 0.000 ppm  
F2 0.00 Hz  
PPMCH 9.36170 ppm/cm



Current Data Parameters  
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PROCNO 1

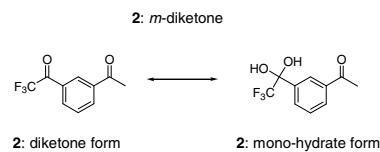
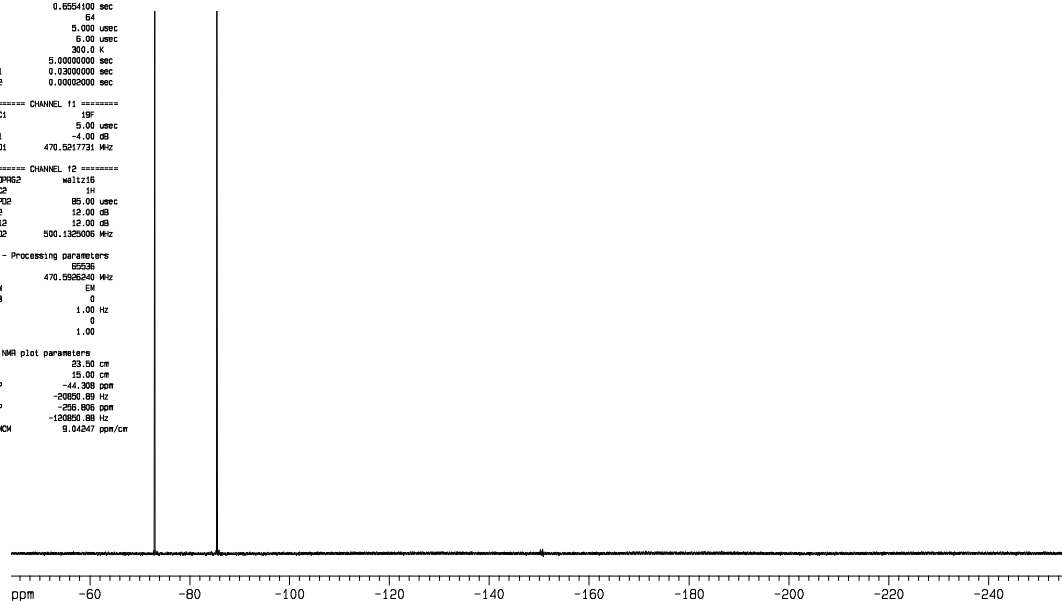
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TD 131072  
SOLVENT CDCl3  
NS 16  
DS 4  
SWH 100000.000 Hz  
FIDRES 0.762626 Hz  
AQ 0.6524100 sec  
RG 64  
DM 5.000 usec  
DE 6.00 usec  
TE 300.0 K  
D1 5.00000000 sec  
S11 0.03000000 sec  
S12 0.00020000 sec

===== CHANNEL f1 =====  
NUC1 19F  
P1 5.00 usec  
PL1 -1.00 dB  
SFO1 470.5217731 MHz

===== CHANNEL f2 =====  
DPRG22 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 12.00 dB  
PL12 12.00 dB  
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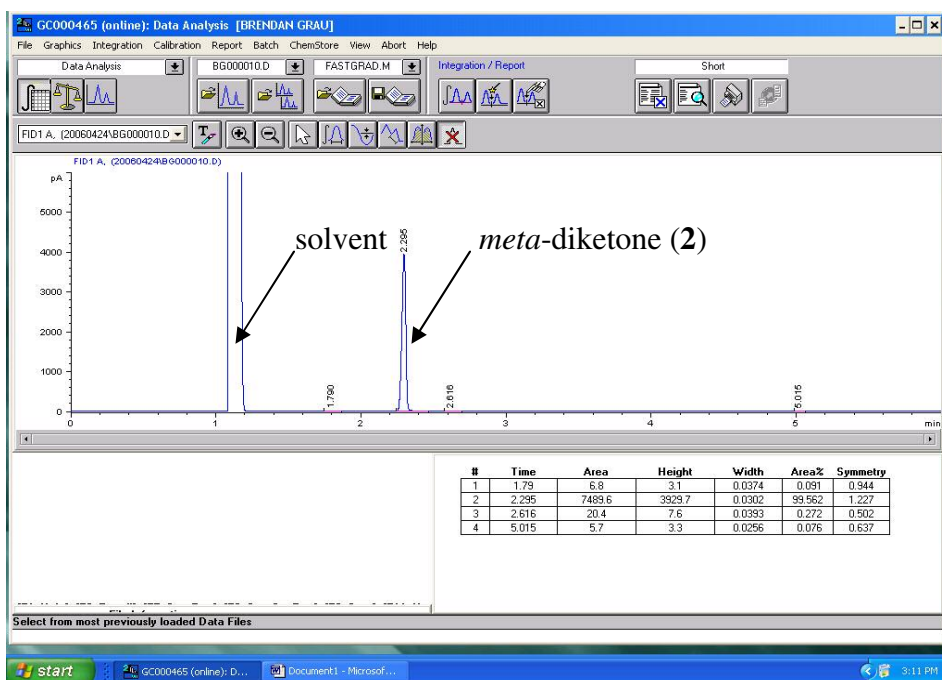
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F1 -20080.88 Hz  
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PPMCH 9.04247 ppm/cm



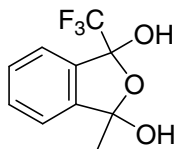


## Achiral GC Method:



## Section 5: *ortho*-diketone **3a**

**3a**: *o*-diketone (dihydrate form)



### Ortho-diketone **3a**

(cyclized di-hydrate form):  $^1\text{H}$  NMR (400.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = ):  $^1\text{H}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = [7.60–7.56 (om, 1H), 7.53–7.50 (om, 2H), 7.47–7.60 (om, 1H), 5.37 (brs, 1H), 4.62 (s, 1H), 1.76 (s, 3H) and 7.60–7.56 (om, 1H), 7.53–7.50 (om, 2H), 7.47–7.60 (om, 1H), 5.37 (brs, 1H), 4.73 (brs, 1H), 1.70 (s, 3H) ppm.  $^{13}\text{C}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = [145.17, 135.85, 132.41, 130.94, 124.10 (q,  $J_{\text{CF}}$  = 286.0 Hz), 123.34, 109.26, 102.58 (q,  $J_{\text{CF}}$  = 33.6 Hz), 27.31 ppm.  $^{19}\text{F}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = [-84.37 and -84.15] ppm.

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EXPNO     1
PROCNO    1

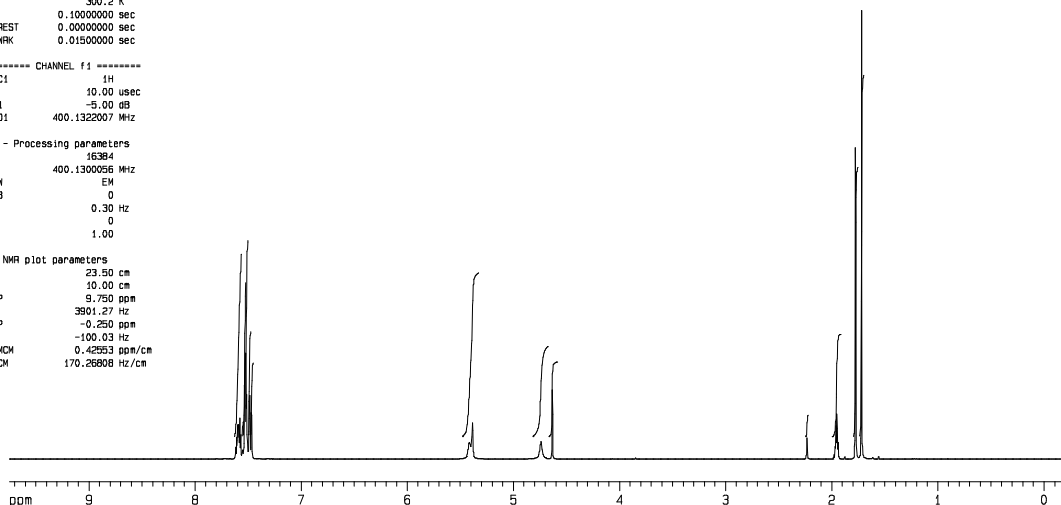
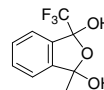
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FIDRES     0.200247 Hz
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RG         256
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WCMRK      0.01500000 sec

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PL1        -5.00 dB
SFO1       400.132007 MHz

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GB         0
PC         1.00

1D NMR plot parameters
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CY         10.00 cm
F1P        5.750 ppm
F1         3901.27 Hz
F2P        -0.250 ppm
F2         -100.03 Hz
PPMCH      0.42553 ppm/cm
HZCM       170.26808 Hz/cm
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**3a**: *o*-diketone (dihydrate form)



Current Data Parameters  
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EXPNO 2  
PROCNO 1

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SOLVENT CDCl3  
NS 1188  
DS 0  
SWH 26246.719 Hz  
FIDRES 0.400433 Hz  
AQ 1.2485108 sec  
RG 8192  
DM 19.050 usec  
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dCREST 0.00000000 sec  
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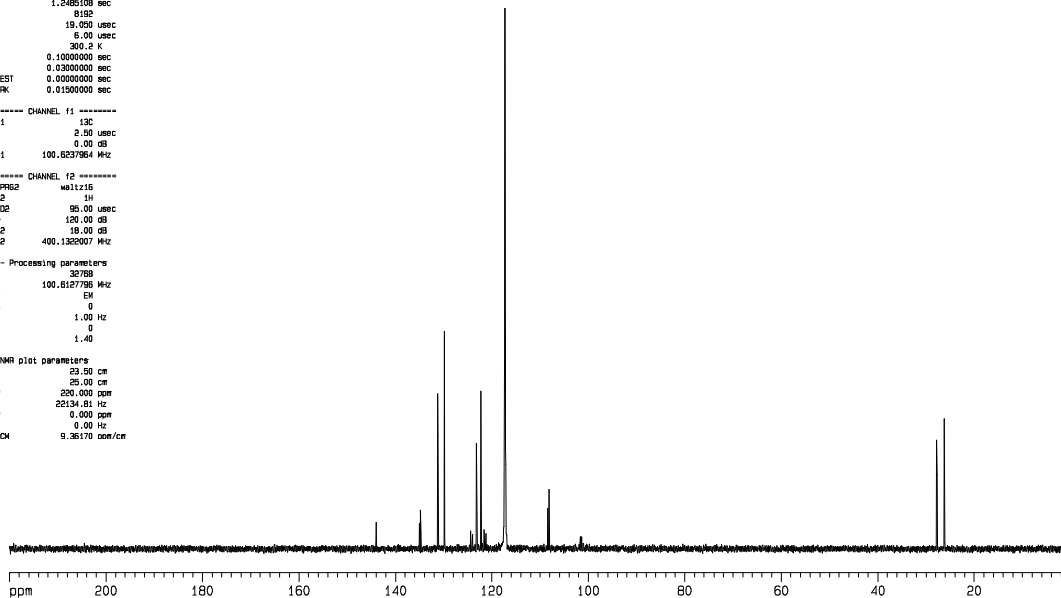
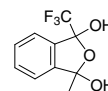
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NUC2 1H  
PCPD2 86.00 usec  
PL2 19.00 dB  
PL12 19.00 dB  
SFO2 400.1320007 MHz

F2 - Processing parameters  
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GB 0  
PC 1.40

1D NMR plot parameters  
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CY 25.00 cm  
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F1 20134.81 Hz  
F2P 0.000 ppm  
F2 0.00 Hz  
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3a: o-diketone (dihydrate form)



Current Data Parameters  
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PROCNO 1

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SOLVENT CDCl3  
NS 243  
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SWH 112994.352 Hz  
FIDRES 0.862078 Hz  
AQ 0.5800436 sec  
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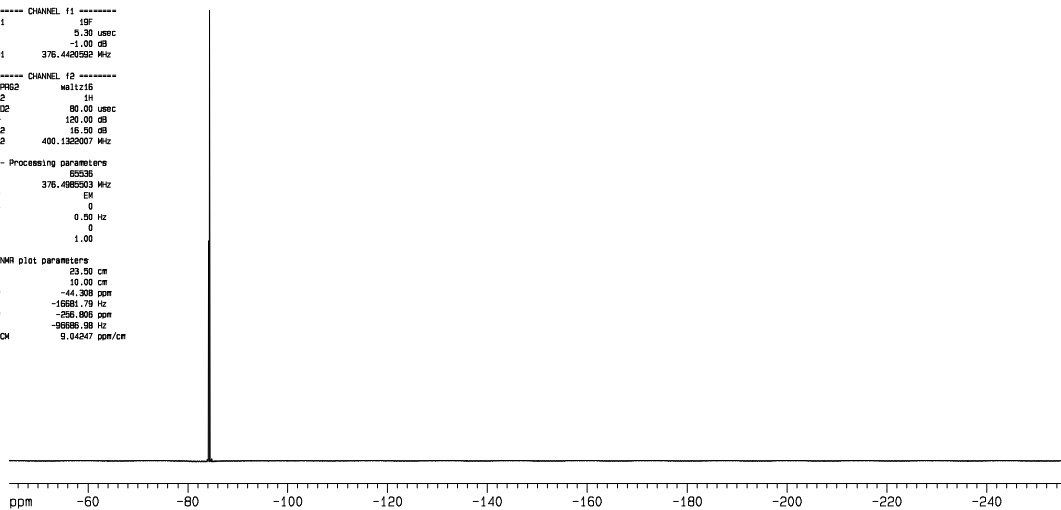
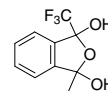
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PL12 19.00 dB  
SFO2 400.1320007 MHz

F2 - Processing parameters  
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GB 0  
PC 1.00

1D NMR plot parameters  
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3a: o-diketone (dihydrate form)



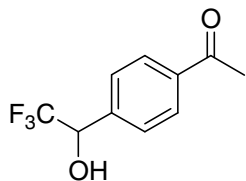
Section 6: Synthesis of racemic trifluoromethyl hydroxyketones **4** and **5**.

To a solution of diketone **1**, **2**, and **3a** (1g) in toluene (20mL) was added ethylene glycol (4 equivalents) and a catalytic amount of *p*-toluene sulfonic acid. The solution was refluxed overnight with a Dean-Stark to afford the ketal. No reaction was observed on compound **3a**. The toluene solution was cooled to 25C and washed with brine (1/2 vol.). The organic layer was dried over MgSO<sub>4</sub> and concentrated on a rotary evaporator to afford the crude ketal.

Sodium borohydride (1 equivalent) was added to a solution of ketal (1g) in THF:H<sub>2</sub>O (10:1) at 25C and aged 0.5hr. Upon completion the solution was quenched with 1N HCl and aged. The THF solution was extracted into MTBE (2 vol.). The organic layer was washed with brine (1 vol.), dried over MgSO<sub>4</sub> and concentrated on a rotary evaporator to yield the crude racemic trifluoromethyl hydroxyketone **4** and **5**.

## Section 7: *para*-trifluoromethyl hydroxyketone **4**

### **4**: *p*-trifluoromethyl hydroxyketone



**4**:  $^1\text{H}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 8.00 (m, 2H), 7.62 (m, 2H), 5.20 (q,  $J$  = 7.15, 1H), 2.58 (s, 3H) ppm.  $^{13}\text{C}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 198.71, 141.04, 139.88, 129.29 (2C), 128.87 (2C), 125.80 (q,  $J_{\text{CF}}$  = 281.8 Hz), 71.98 (q,  $J_{\text{CF}}$  = 31.4 Hz), 27.18 ppm.  $^{19}\text{F}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = -79.11 ppm.

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PROCNO    1

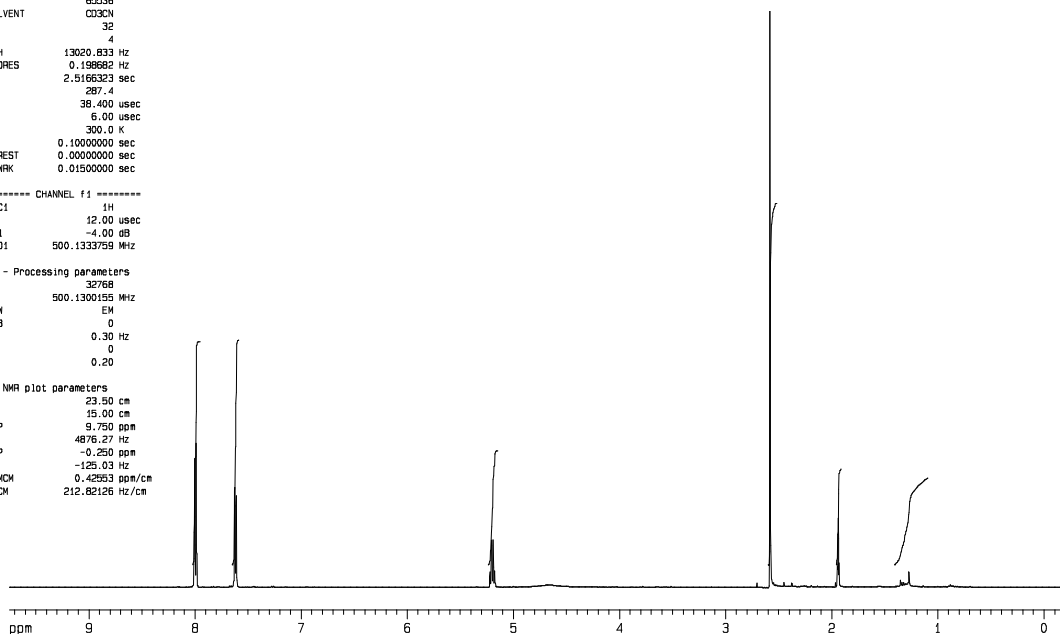
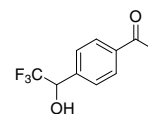
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FIDRES     0.198682 Hz
AQ         2.5166323 sec
RG         287.4
DW         38.400 usec
DE         6.00 usec
TE         300.0 K
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MCREST    0.00000000 sec
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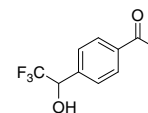
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CY         15.00 cm
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F1         4876.27 Hz
F2P        -0.250 ppm
F2         -125.03 Hz
PPMCM      0.42553 ppm/cm
HZCM       212.82126 Hz/cm
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**4**: *p*-trifluoromethyl hydroxyketone



4: *p*-trifluoromethyl hydroxyketone



Current Data Parameters  
NAME 232427-999-h  
EXPNO 3  
PROCNO 1

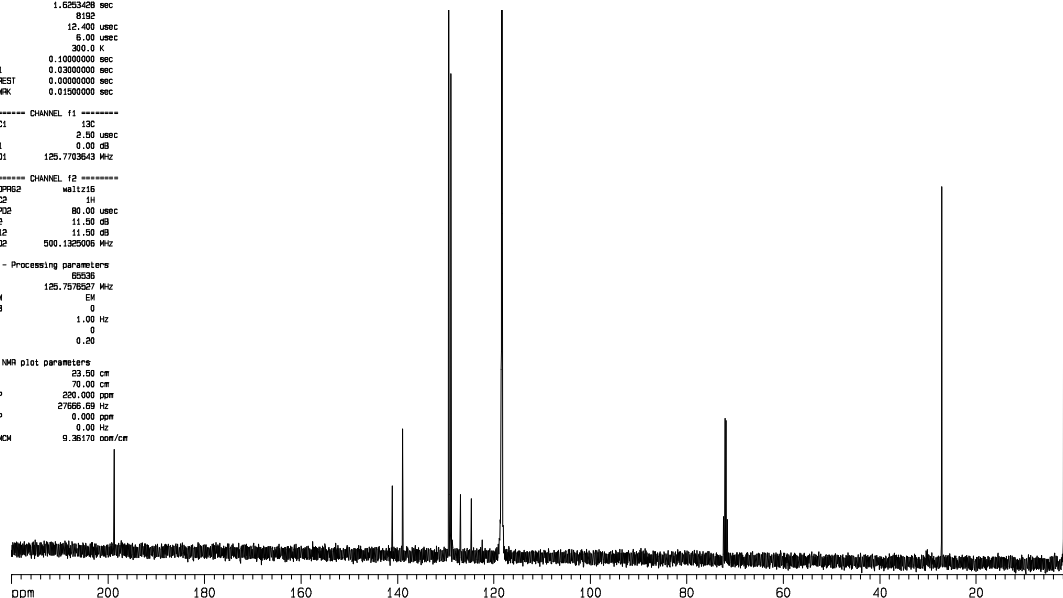
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FIDRES 0.307637 Hz  
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ICREST 0.00000000 sec  
ICORR 0.01000000 sec

===== CHANNEL f1 =====  
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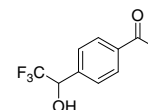
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F2 - Processing parameters  
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1D NMR plot parameters  
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F2 0.00 Hz  
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4: *p*-trifluoromethyl hydroxyketone



Current Data Parameters  
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EXPNO 2  
PROCNO 1

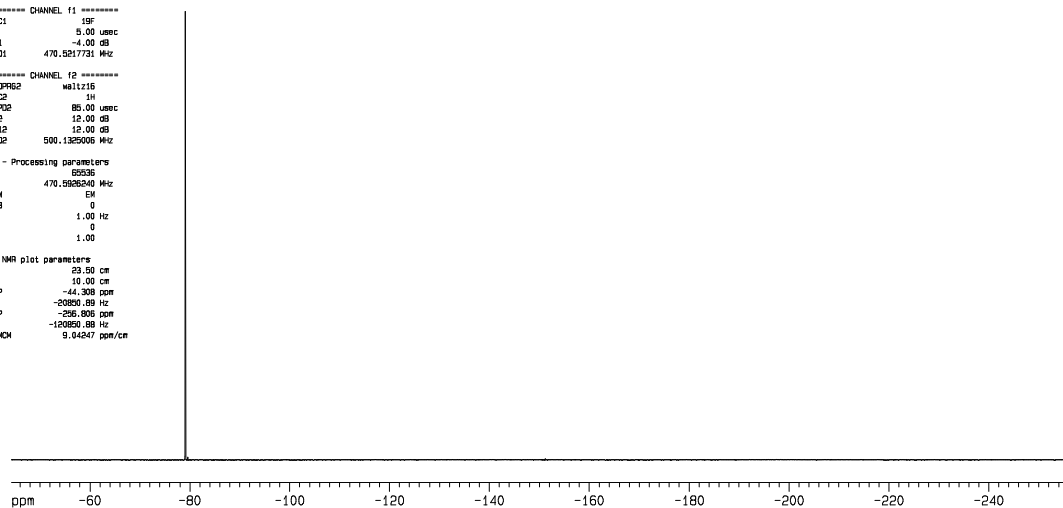
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NS 116  
DS 4  
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AQ 0.6954100 sec  
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d11 0.03000000 sec  
d12 0.00000000 sec

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===== CHANNEL f2 =====  
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F2P -256.896 ppm  
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GC000465 (online): Data Analysis [BRENDAN GRAU]

File Graphics Integration Calibration Report Batch ChemStore View Abort Help

Data Analysis BG000002.D FASTGRAD.M Integration / Report Short

FID1 A, (20061020\BG000002.D)

Reaction isolate from KRED-112  
solvent *para*-trifluoromethyl hydroxyketone (4)

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2	3.923	1.7	1.2	0.0215	0.461	0.98
3	4.111	366.7	293.7	0.0194	98.745	0.999

Specify Report Calculation and Print Style

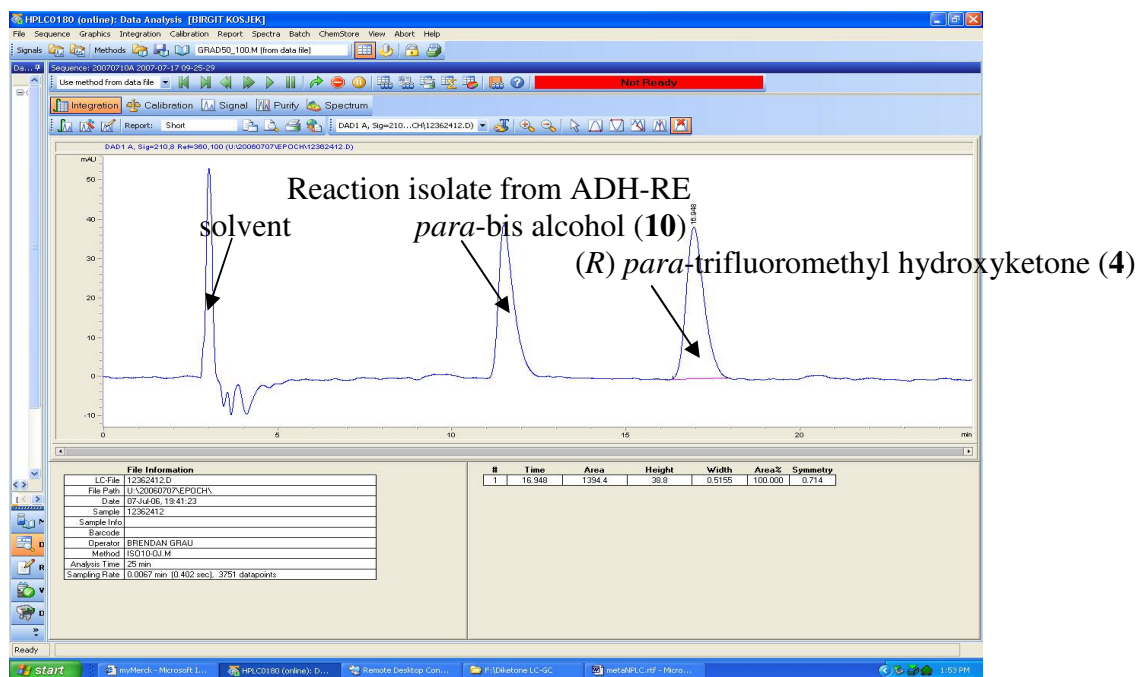
Page 3 361 379 381 382 383 384 385 386 387 388 389 390 391 392 393 394 395 396 397 398 399 400 401 402 403 404 405 406 407 408 409 410 411 412 413 414 415 416 417 418 419 420 421 422 423 424 425 426 427 428 429 430 431 432 433 434 435 436 437 438 439 440 441 442 443 444 445 446 447 448 449 450 451 452 453 454 455 456 457 458 459 460 461 462 463 464 465 466 467 468 469 470 471 472 473 474 475 476 477 478 479 480 481 482 483 484 485 486 487 488 489 490 491 492 493 494 495 496 497 498 499 500 501 502 503 504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546 547 548 549 550 551 552 553 554 555 556 557 558 559 560 561 562 563 564 565 566 567 568 569 570 571 572 573 574 575 576 577 578 579 580 581 582 583 584 585 586 587 588 589 590 591 592 593 594 595 596 597 598 599 600 601 602 603 604 605 606 607 608 609 610 611 612 613 614 615 616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657 658 659 660 661 662 663 664 665 666 667 668 669 670 671 672 673 674 675 676 677 678 679 680 681 682 683 684 685 686 687 688 689 690 691 692 693 694 695 696 697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715 716 717 718 719 720 721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745 746 747 748 749 750 751 752 753 754 755 756 757 758 759 760 761 762 763 764 765 766 767 768 769 770 771 772 773 774 775 776 777 778 779 780 781 782 783 784 785 786 787 788 789 790 791 792 793 794 795 796 797 798 799 800 801 802 803 804 805 806 807 808 809 810 811 812 813 814 815 816 817 818 819 820 821 822 823 824 825 826 827 828 829 830 831 832 833 834 835 836 837 838 839 840 841 842 843 844 845 846 847 848 849 850 851 852 853 854 855 856 857 858 859 860 861 862 863 864 865 866 867 868 869 870 871 872 873 874 875 876 877 878 879 880 881 882 883 884 885 886 887 888 889 890 891 892 893 894 895 896 897 898 899 900 901 902 903 904 905 906 907 908 909 910 911 912 913 914 915 916 917 918 919 920 921 922 923 924 925 926 927 928 929 930 931 932 933 934 935 936 937 938 939 940 941 942 943 944 945 946 947 948 949 950 951 952 953 954 955 956 957 958 959 960 961 962 963 964 965 966 967 968 969 970 971 972 973 974 975 976 977 978 979 980 981 982 983 984 985 986 987 988 989 990 991 992 993 994 995 996 997 998 999 1000 1001 1002 1003 1004 1005 1006 1007 1008 1009 1010 1011 1012 1013 1014 1015 1016 1017 1018 1019 1020 1021 1022 1023 1024 1025 1026 1027 1028 1029 1030 1031 1032 1033 1034 1035 1036 1037 1038 1039 1040 1041 1042 1043 1044 1045 1046 1047 1048 1049 1050 1051 1052 1053 1054 1055 1056 1057 1058 1059 1060 1061 1062 1063 1064 1065 1066 1067 1068 1069 1070 1071 1072 1073 1074 1075 1076 1077 1078 1079 1080 1081 1082 1083 1084 1085 1086 1087 1088 1089 1090 1091 1092 1093 1094 1095 1096 1097 1098 1099 1100 1101 1102 1103 1104 1105 1106 1107 1108 1109 1110 1111 1112 1113 1114 1115 1116 1117 1118 1119 1120 1121 1122 1123 1124 1125 1126 1127 1128 1129 1130 1131 1132 1133 1134 1135 1136 1137 1138 1139 1140 1141 1142 1143 1144 1145 1146 1147 1148 1149 1150 1151 1152 1153 1154 1155 1156 1157 1158 1159 1160 1161 1162 1163 1164 1165 1166 1167 1168 1169 1170 1171 1172 1173 1174 1175 1176 1177 1178 1179 1180 1181 1182 1183 1184 1185 1186 1187 1188 1189 1190 1191 1192 1193 1194 1195 1196 1197 1198 1199 1200 1201 1202 1203 1204 1205 1206 1207 1208 1209 1210 1211 1212 1213 1214 1215 1216 1217 1218 1219 1220 1221 1222 1223 1224 1225 1226 1227 1228 1

The chromatogram displays detector response (mAU) over time (minutes). The x-axis ranges from 0 to 22.5 minutes, and the y-axis ranges from 0 to 1400 mAU. Three peaks are identified:

- DMF**: A sharp peak at approximately 6.5 minutes.
- 14.461**: A peak at 14.461 minutes, labeled with its retention time.
- 19.461**: A peak at 19.461 minutes, labeled with its retention time.

The baseline is relatively flat with minor noise. The peak at 19.461 minutes is the most prominent.

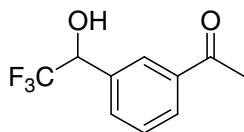
## Chiral NP-HPLC Method:





## Section 8: *meta*-trifluoromethyl hydroxyketone **5**

### **5**: *m*-trifluoromethyl hydroxyketone



**5**:  $^1\text{H}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 8.06 (s, 1H), 8.00 (d,  $J$  = 7.55, 1H), 7.73 (d,  $J$  = 7.55, 1H), 7.56 (t,  $J$  = 7.55, 1H), 5.21 (m, 1H), 2.58 (s, 3H) ppm.  $^{13}\text{C}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 198.73, 138.47, 136.98, 133.05, 130.11, 129.93, 128.15, 125.80 (q,  $J_{\text{CF}}$  = 281.8 Hz), 72.00 (q,  $J_{\text{CF}}$  = 31.4 Hz), 27.15 ppm.  $^{19}\text{F}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = -79.34 ppm.

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EXPNO 1  
PROCNO 1

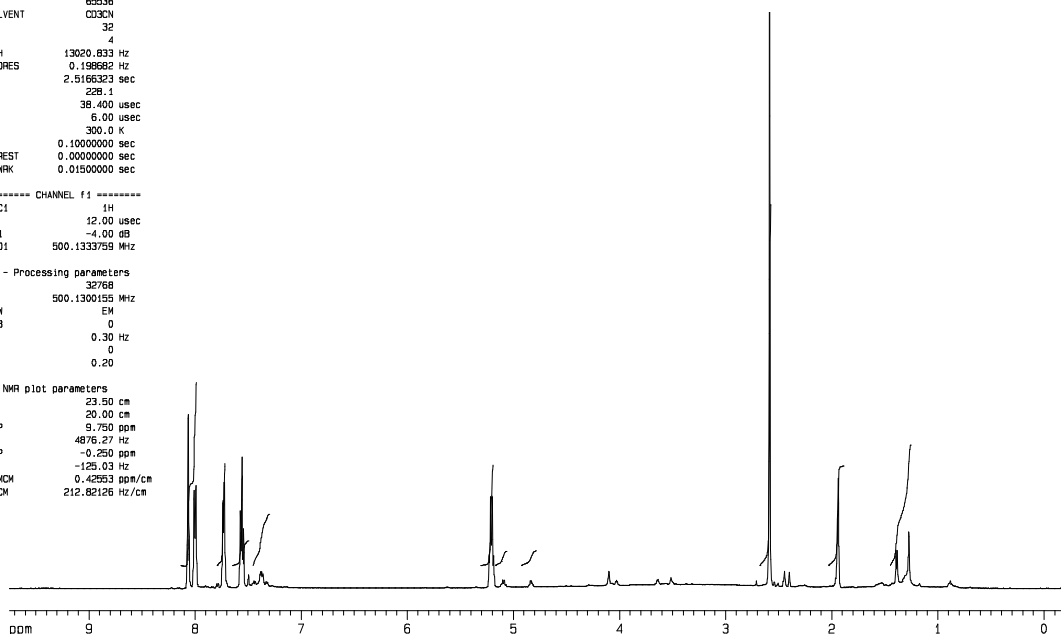
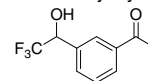
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NS 32  
DS 4  
SWH 13020.833 Hz  
FIDRES 0.198682 Hz  
AQ 2.5166323 sec  
RG 228.1  
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DE 5.00 usec  
TE 300.0 K  
D1 0.10000000 sec  
MCREST 0.00000000 sec  
MCWRK 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 1H  
P1 12.00 usec  
PL1 -4.00 dB  
SFO1 500.133759 MHz

F2 - Processing parameters  
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SF 500.1300155 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 0.20

1D NMR plot parameters  
CX 23.50 cm  
CY 20.00 cm  
F1P 9.750 ppm  
F1 4876.27 Hz  
F2P -0.250 ppm  
F2 -125.03 Hz  
PPHOM 0.42553 ppm/cm  
HZOM 212.82126 Hz/cm

**5**: *m*-trifluoromethyl hydroxyketone



Current Data Parameters  
NAME 232427-999-d  
EXPNO 3  
PROCNO 1

F2 - Acquisition Parameters  
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PULPROG zgpg30  
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NS 500  
DS 4  
SWH 49382.562 Hz  
FIDRES 0.307637 Hz  
AQ 1.6203428 sec  
RG 8182  
DM 12.400 usec  
DE 6.00 usec  
TE 300.0 K  
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ICORR 0.01500000 sec

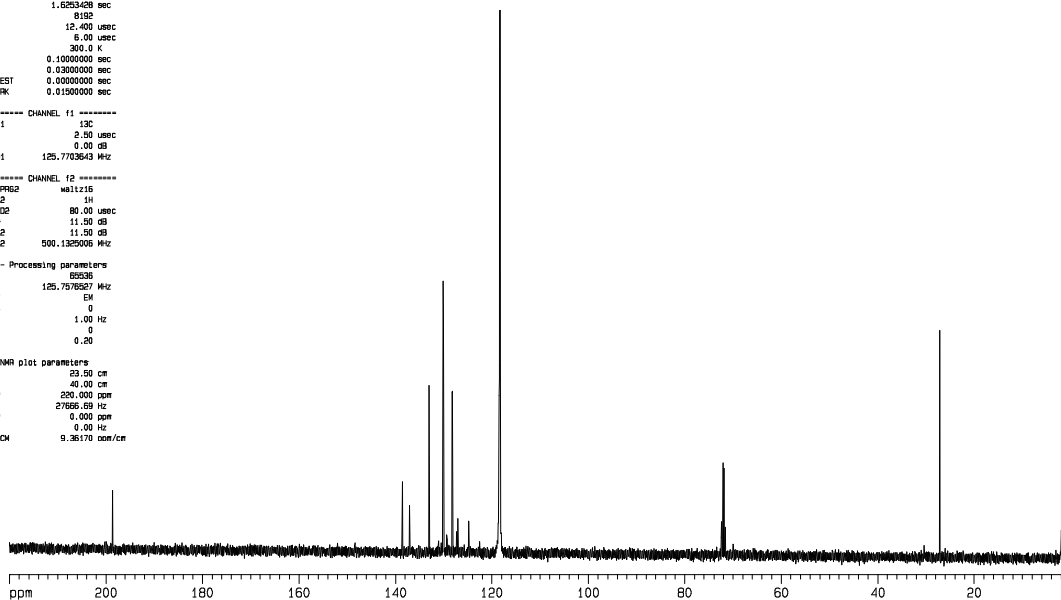
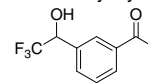
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PL1 0.00 dB  
SFO1 125.7703645 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 11.50 dB  
PL12 11.50 dB  
SFO2 500.1325006 MHz

F2 - Processing parameters  
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SF 125.757657 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 0.20

1D NMR plot parameters  
CX 23.50 cm  
CY 40.00 cm  
F1P 200.000 ppm  
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F2P 0.000 ppm  
F2 0.00 Hz  
PPMCH 9.36170 ppm/cm

5: *m*-trifluoromethyl hydroxyketone



Current Data Parameters  
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EXPNO 2  
PROCNO 1

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PULPROG zgpg30  
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SOLVENT CDCl3  
NS 16  
DS 4  
SWH 100000.000 Hz  
FIDRES 0.762939 Hz  
AQ 0.6954100 sec  
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d12 0.00000000 sec

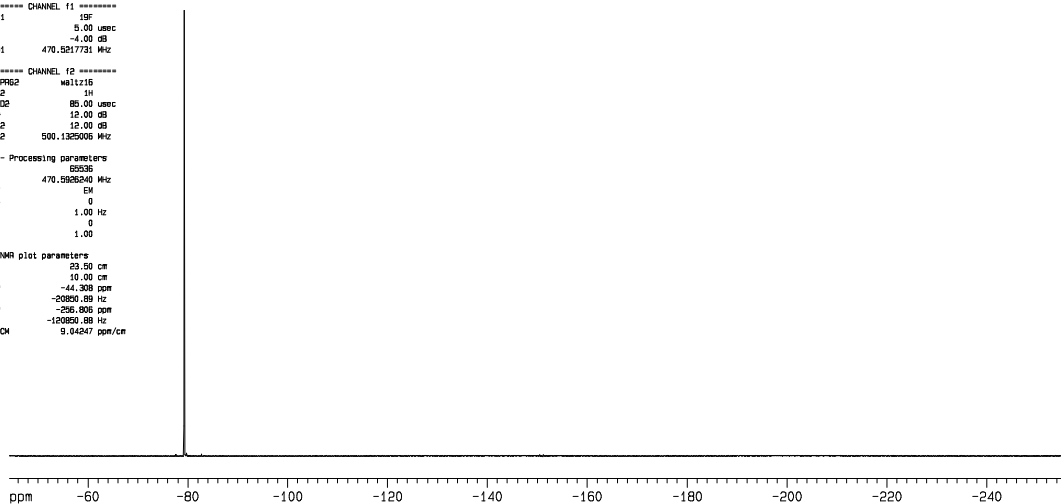
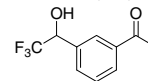
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SFO1 470.5217731 MHz

===== CHANNEL f2 =====  
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PL12 12.00 dB  
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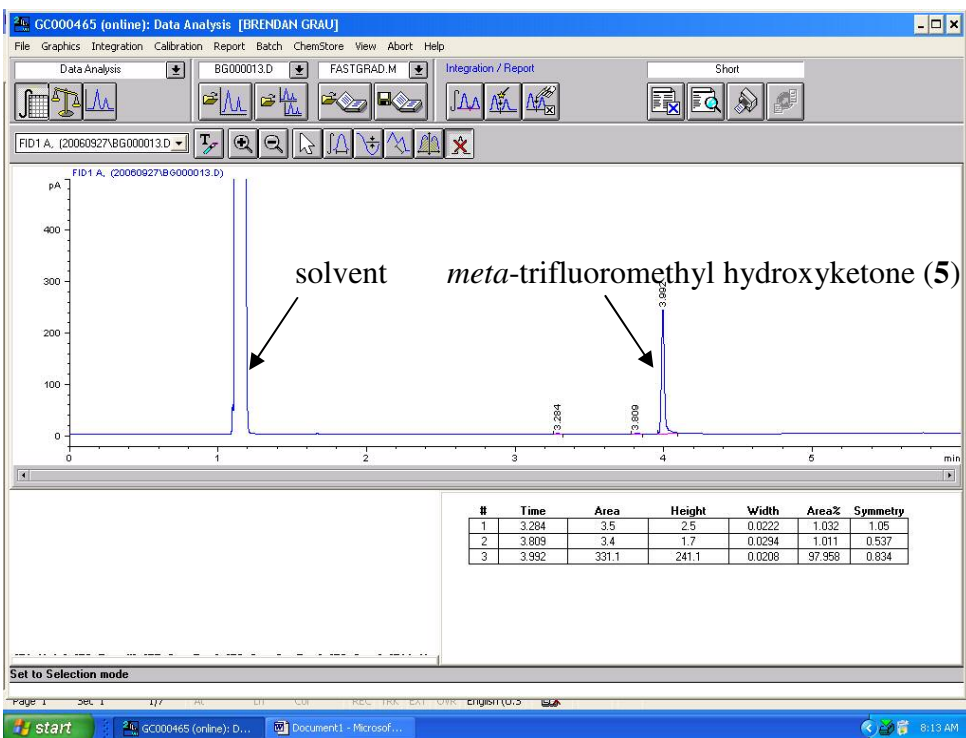
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LB 1.00 Hz  
GB 0  
PC 1.00

1D NMR plot parameters  
CX 23.50 cm  
CY 10.00 cm  
F1P -44.300 ppm  
F1 -20800.89 Hz  
F2P -256.896 ppm  
F2 -100800.88 Hz  
PPMCH 9.04247 ppm/cm

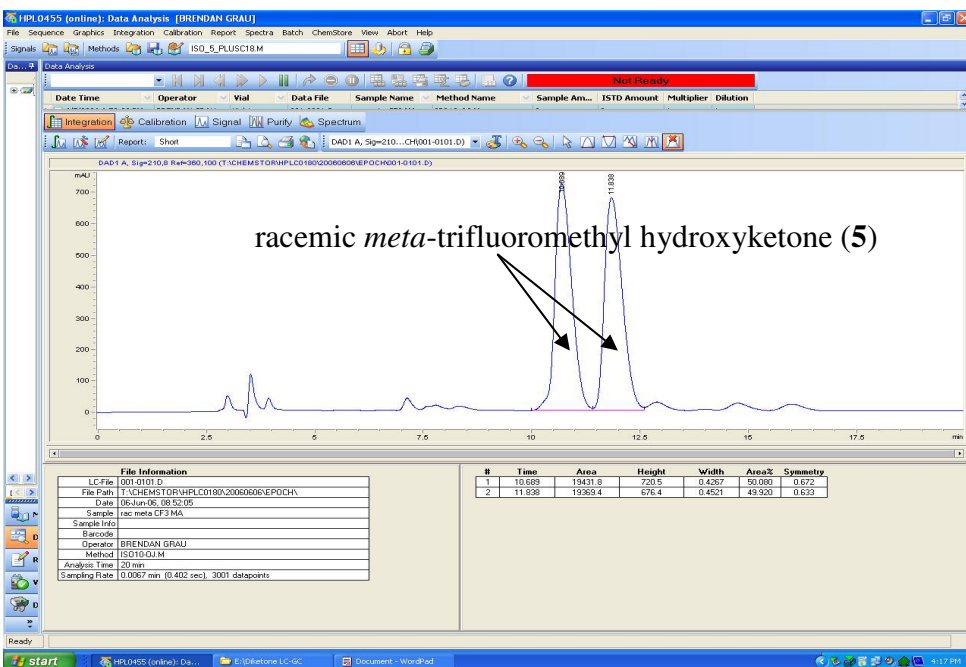
5: *m*-trifluoromethyl hydroxyketone



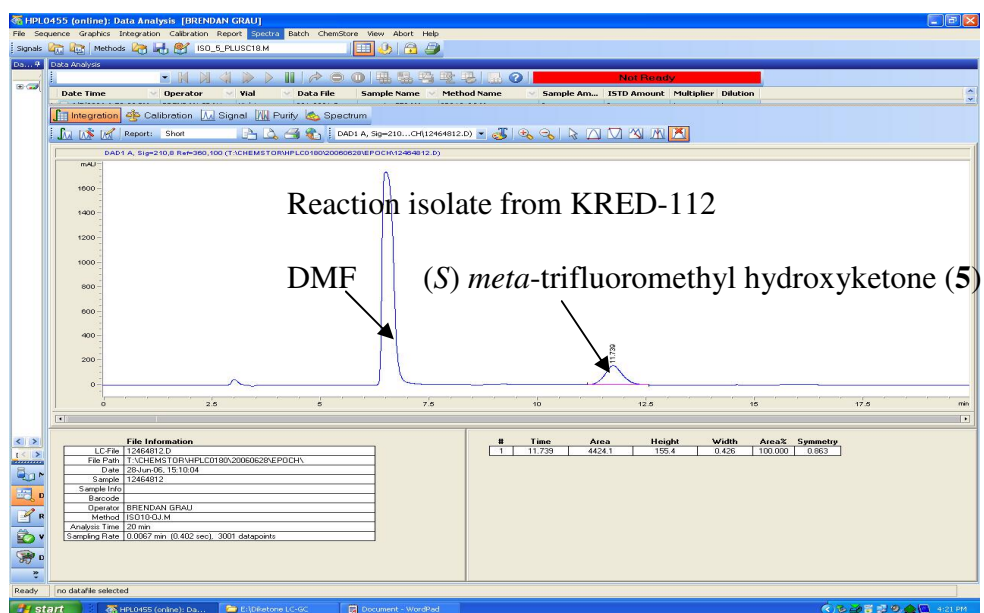
## Achiral GC Method:



## Chiral NP-HPLC Method:



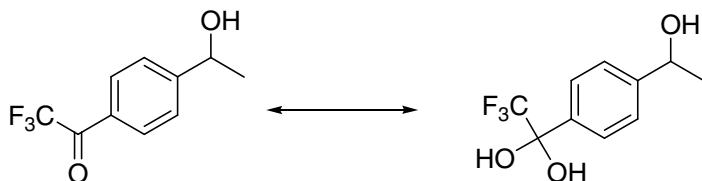
## Chiral NP-HPLC Method:



Section 9: Synthesis of racemic methyl hydroxyketones **7** and **8**.

The racemic standards for the methyl hydroxyketones **7** and **8** were subjected to modified reaction conditions listed in the literature reference<sup>2</sup> by using THF/H<sub>2</sub>O as solvent. No reaction was observed on compound **3a**. The THF solution was extracted with MTBE (2 vol.) and the organic layer was washed with brine (1/2 vol.). The organic layer was dried over MgSO<sub>4</sub> and concentrated on a rotary evaporator to yield the crude racemic methyl hydroxyketones of **7** and **8**.

Section 10: *para*-methyl hydroxyketone **7**  
**7**: *p*-methyl hydroxyketone



**7**: ketone form

**7**: hydrate form

(hydrate form):  $^1\text{H}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 7.61 (m, 2H), 7.41 (m, 2H), 5.25 (s, 2H), 4.84 (m, 1H), 3.31 (brs, 1H), 1.39 (d,  $J$  = 6.36, 3H) ppm.  $^{13}\text{C}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 149.49, 136.90, 128.22 (2C), 126.06 (2C), 124.40 (q,  $J_{\text{CF}}$  = 287.3 Hz), 94.24 (q,  $J_{\text{CF}}$  = 32.0 Hz), 69.86, 25.93 ppm.  $^{19}\text{F}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = -85.39 ppm.

```

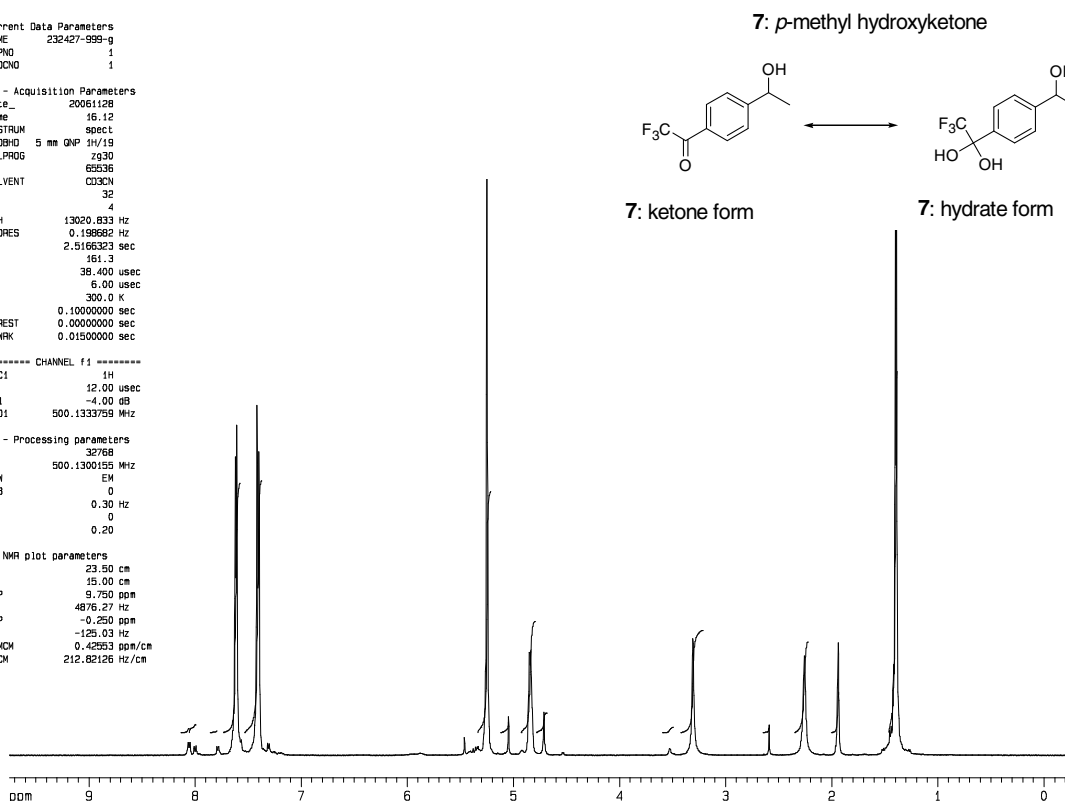
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PROCNO    1

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PULPROG    zg30
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SOLVENT    CD3CN
NS         32
DS         4
SWH         13020.833 Hz
FIDRES     0.198682 Hz
AQ         2.5166323 sec
RG         161.3
DM         38.400 usec
DE         6.00 usec
TE         300.0 K
D1         0.10000000 sec
WCREST     0.00000000 sec
WCHWK      0.01500000 sec

***** CHANNEL f1 *****
NUC1       1H
P1         12.00 usec
PL1        -4.00 dB
SFO1       500.1333759 MHz

F2 - Processing parameters
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PC         0.20

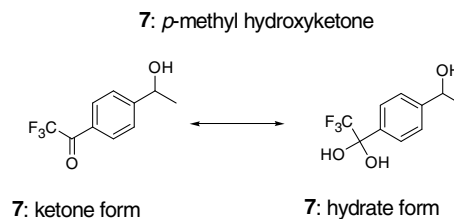
1D NMR plot parameters
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CY         15.00 cm
F1P        47.750 ppm
F1         4876.27 Hz
F2P        -0.250 ppm
F2         -125.03 Hz
PPHOM      0.42553 ppm/cm
HZOM       212.82126 Hz/cm
    
```



```

ID NMR plot parameters
CX                23.50 cm
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F2P              0.000 ppm
F2               0.00 Hz
PPHMOD           9.36170 ppm/cm

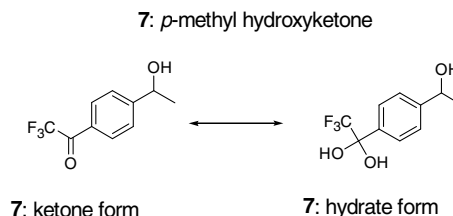
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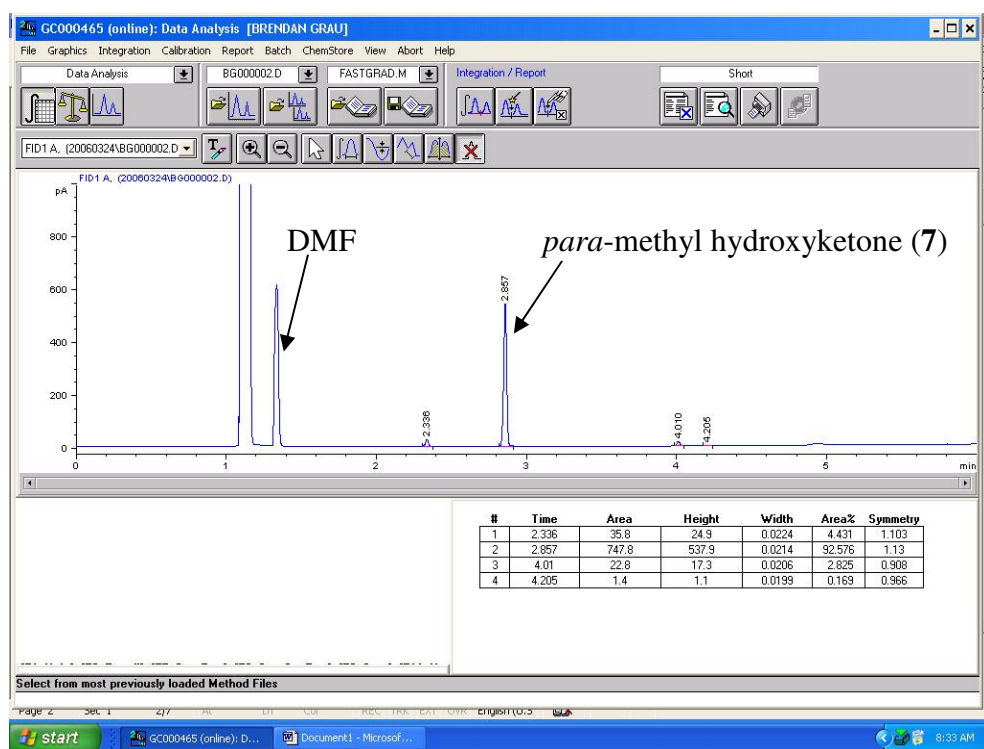
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1D NMR plot parameters
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F1         -20850.89 Hz
F2P        -256.806 ppm
F2         -120850.88 Hz
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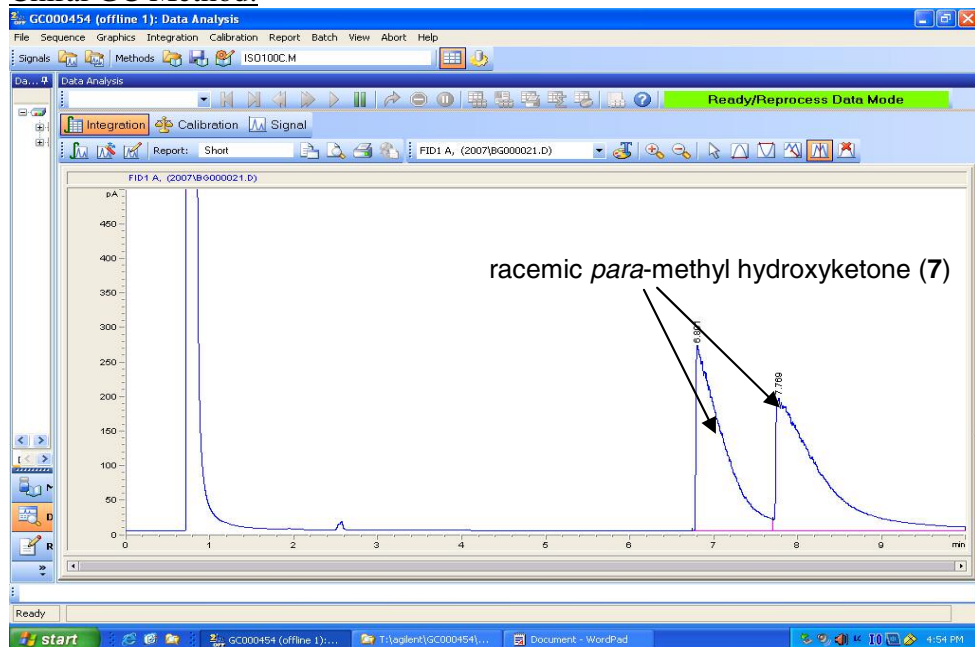
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## Achiral GC Method:

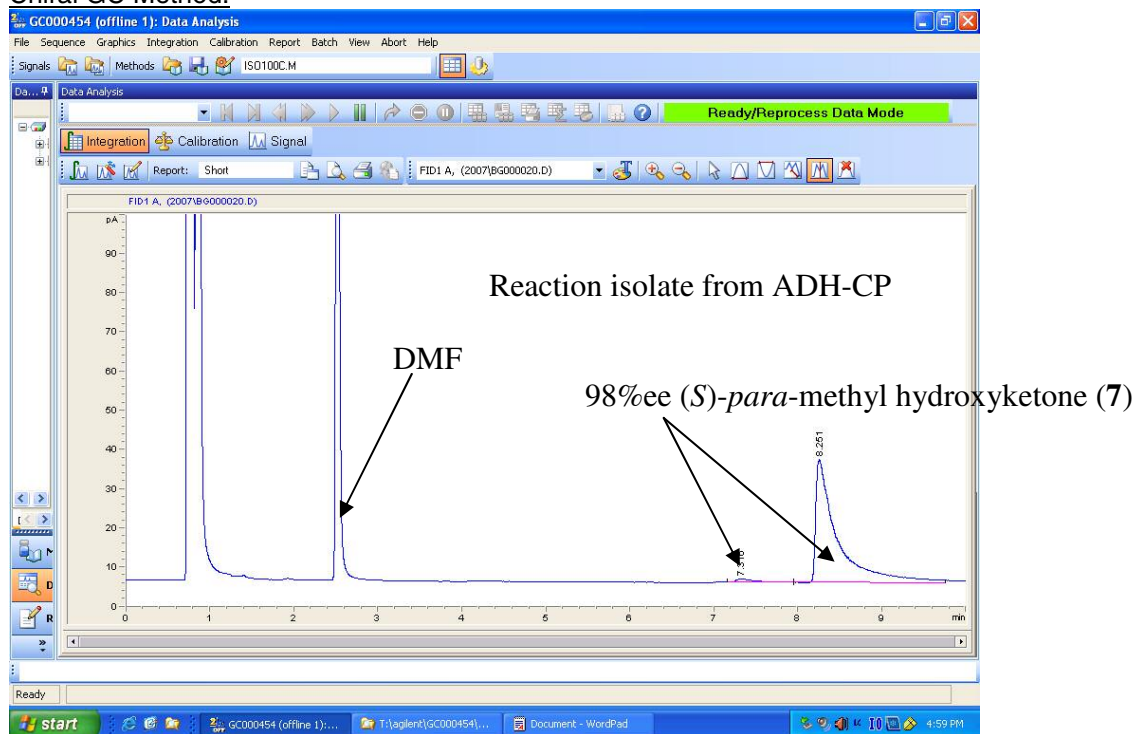


## Chiral GC Method:

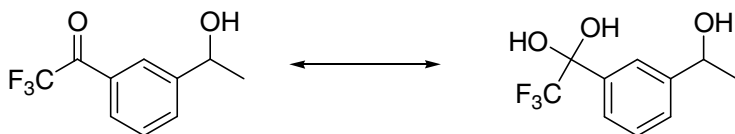




### Chiral GC Method:



Section 11: *meta*-methyl hydroxyketone **8**  
**8**: *m*-methyl hydroxyketone



**8**: ketone form

**8**: hydrate form

(hydrate form):  $^1\text{H}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 7.66 (s, 1H), 7.53 (d,  $J$  = 7.55, 1H), 7.41 (m, 1H), 7.39 (d,  $J$  = 7.55, 1H), 4.85 (q,  $J$  = 6.36, 1H), 3.64 (m, 2H), 1.39 (m, 3H) ppm.  $^{13}\text{C}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 147.92, 138.33, 130.39, 128.99, 127.84, 126.84, 125.32, 94.50 (q,  $J_{\text{CF}}$  = 32.4 Hz), 69.5, 26.0 ppm.  $^{19}\text{F}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = -85.36 ppm.

(ketone form):  $^1\text{H}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 8.08 (s, 1H), 7.96 (d,  $J$  = 7.55, 1H), 7.78 (d,  $J$  = 7.55, 1H), 7.59 (m, 1H), 4.92 (q,  $J$  = 6.36, 1H), 3.64 (m, 2H), 1.39 (m, 3H) ppm.  $^{19}\text{F}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = -72.70 ppm.

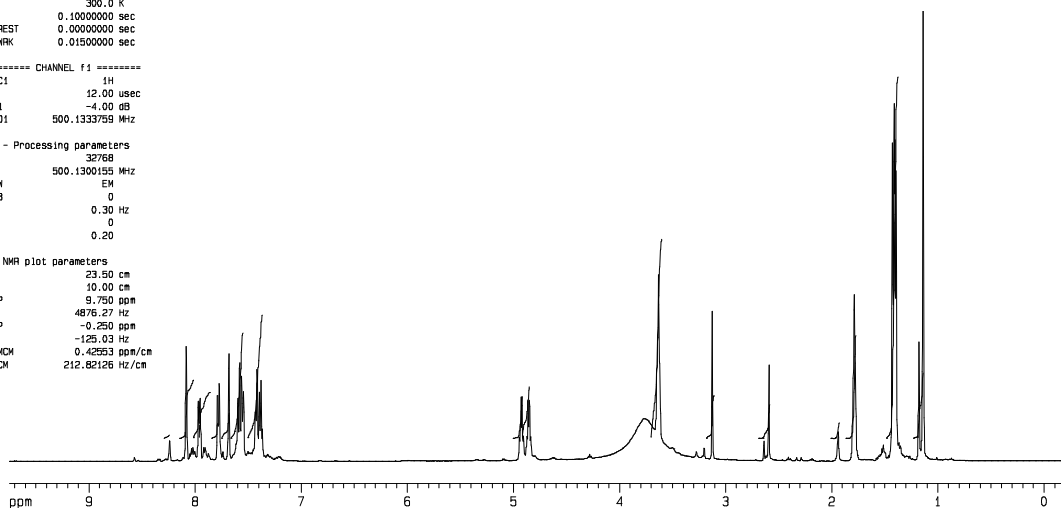
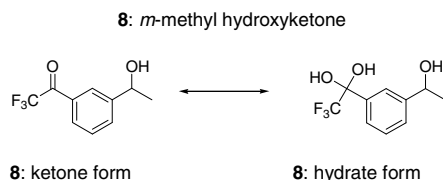
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Current Data Parameters
NAME      232427-999-e
EXPNO     4
PROCNO    1

F2 - Acquisition Parameters
Date_     20061128
Time      12.10
INSTRUM   spect
PROBHD    5 mm GNP 1H/19
PULPROG   zg30
TD         65536
SOLVENT   CD3CN
NS         32
DS         4
SWH        13020.833 Hz
FIDRES     0.198682 Hz
AQ         2.5166323 sec
RG          32
DM         38.400 usec
DE         6.00 usec
TE         300.0 K
D1         0.10000000 sec
MCREST    0.00000000 sec
MCWRK     0.01500000 sec

***** CHANNEL f1 *****
NUC1       1H
P1         12.00 usec
PL1        -4.00 dB
SFO1       500.1333759 MHz

F2 - Processing parameters
SI         32768
SF         500.1300155 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
PC         0.20

1D NMR plot parameters
CX         23.50 cm
CY         10.00 cm
F1P        9.750 ppm
F1         4876.27 Hz
F2P        -0.250 ppm
F2         -125.03 Hz
PPM0M      0.42553 ppm/cm
HZ0M       212.82126 Hz/cm
```



Current Data Parameters  
NAME 232427-999-e  
EXPNO 5  
PROCNO 1

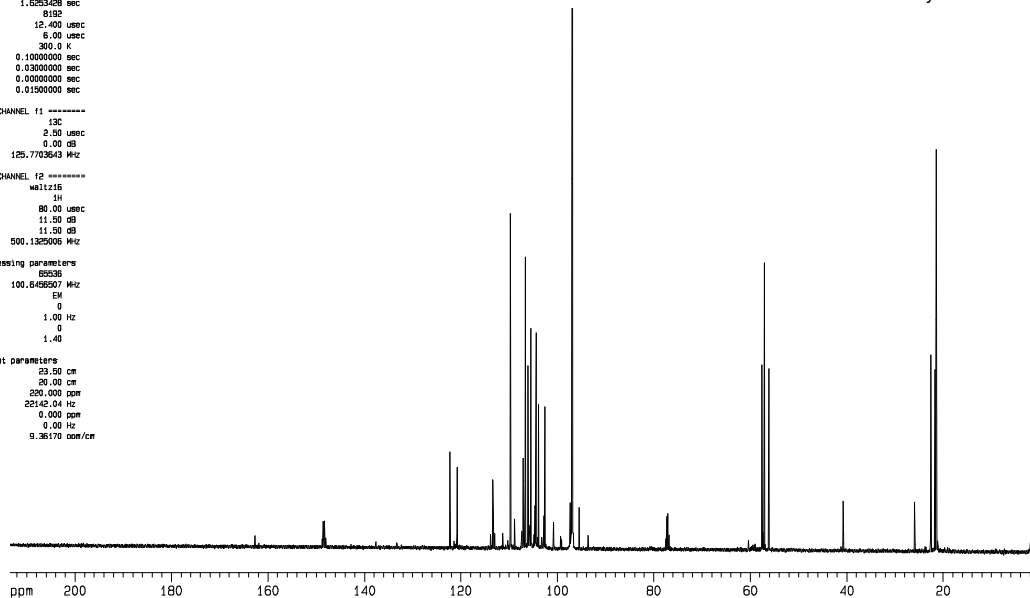
F2 - Acquisition Parameters  
Date\_ 20061208  
Time 12.13  
INSTRUM spect  
PROBHD 5 mm QNP 1H/19  
PULPROG zgpg30  
TD 131072  
SOLVENT CDCl3  
NS 1695  
DS 4  
SWH 49389.562 Hz  
FIDRES 0.307637 Hz  
AQ 1.6203428 sec  
RG 8182  
DM 12.400 usec  
DE 6.00 usec  
TE 300.0 K  
D1 0.10000000 sec  
d11 0.03000000 sec  
dREST 0.00000000 sec  
dCHCK 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 13C  
P1 2.50 usec  
PL1 0.00 dB  
SFO1 125.7703645 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 11.50 dB  
PL12 11.50 dB  
SFO2 500.1325006 MHz

F2 - Processing parameters  
SI 65536  
SF 100.6465957 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

1D NMR plot parameters  
CX 23.50 cm  
CY 30.00 cm  
F1P 200.000 ppm  
F1 201.4204 Hz  
F2P 0.000 ppm  
F2 0.00 Hz  
PPMCH 9.36170 ppm/cm



Current Data Parameters  
NAME 232427-999-e  
EXPNO 2  
PROCNO 1

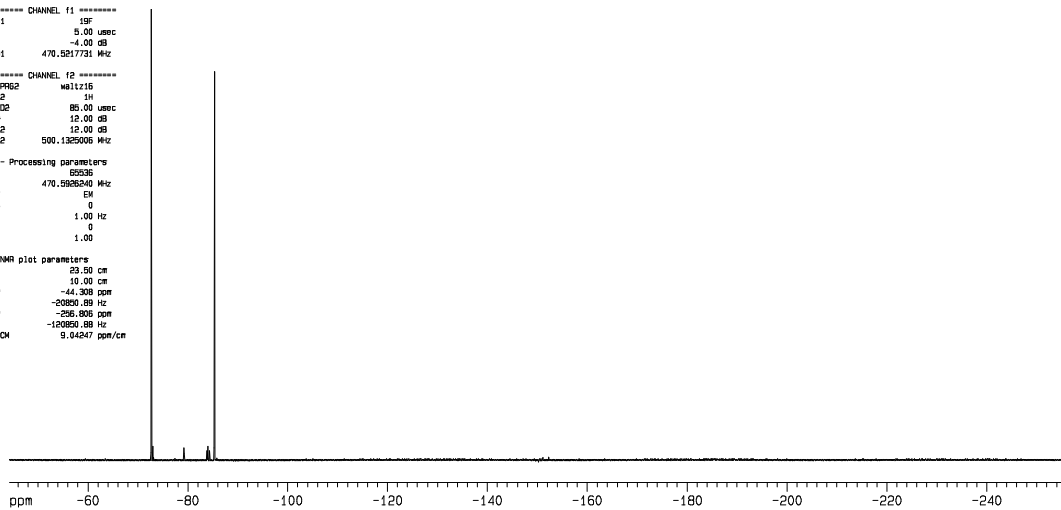
F2 - Acquisition Parameters  
Date\_ 20061208  
Time 0.47  
INSTRUM spect  
PROBHD 5 mm QNP 1H/19  
PULPROG zgpg30  
TD 131072  
SOLVENT CDCl3  
NS 16  
DS 4  
SWH 100000.000 Hz  
FIDRES 0.762939 Hz  
AQ 0.6504100 sec  
RG 64  
DM 5.000 usec  
DE 6.00 usec  
TE 300.0 K  
D1 5.00000000 sec  
d11 0.03000000 sec  
d12 0.00000000 sec

===== CHANNEL f1 =====  
NUC1 19F  
P1 5.00 usec  
PL1 -4.00 dB  
SFO1 470.5217731 MHz

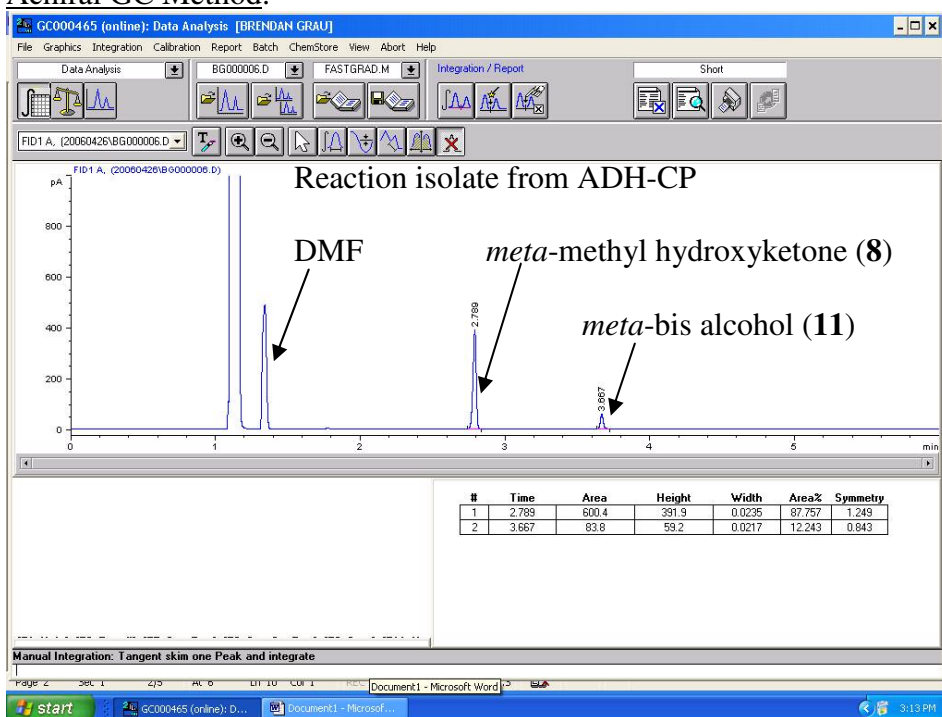
===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 12.00 dB  
PL12 12.00 dB  
SFO2 500.1325006 MHz

F2 - Processing parameters  
SI 65536  
SF 470.5982640 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.00

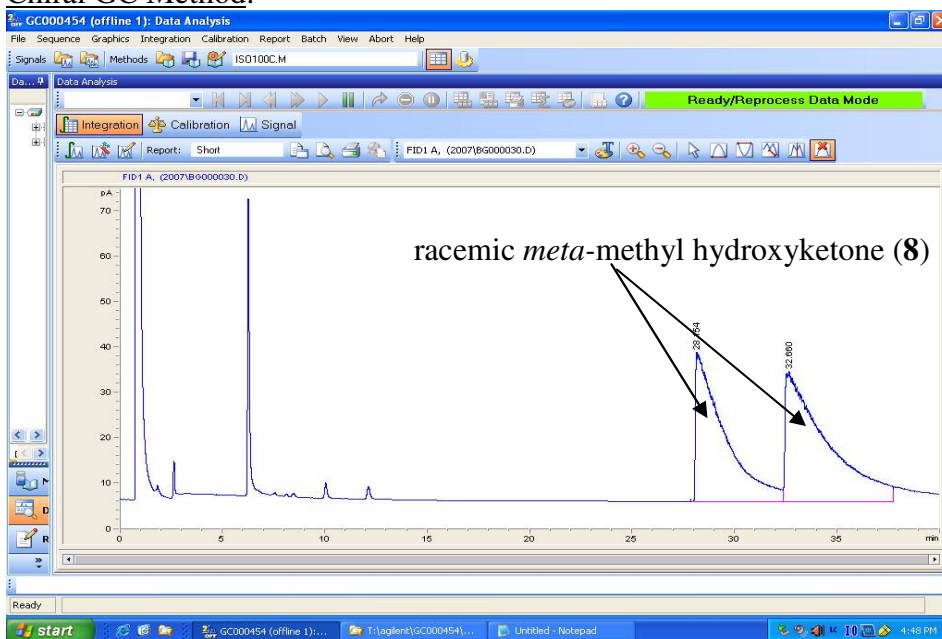
1D NMR plot parameters  
CX 23.50 cm  
CY 30.00 cm  
F1P -44.300 ppm  
F1 -20800.89 Hz  
F2P -206.896 ppm  
F2 -100800.00 Hz  
PPMCH 9.04247 ppm/cm



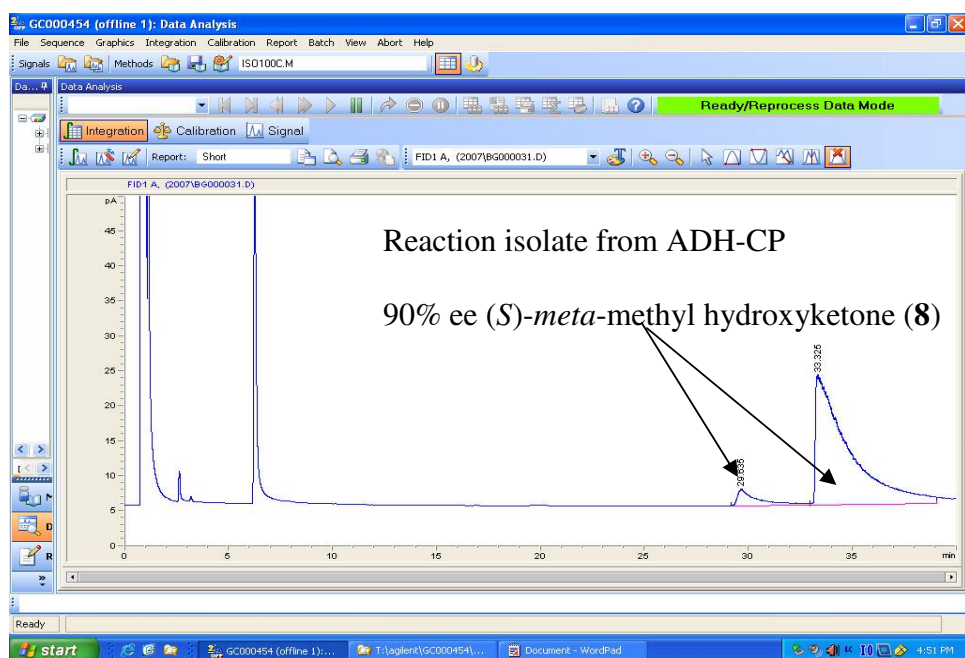
## Achiral GC Method:



## Chiral GC Method:



## Chiral GC Method:

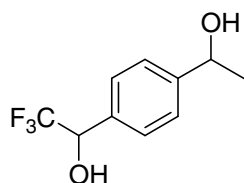


## Section 12: Synthesis of bis alcohol **10** and **11**.

The bis alcohol standards for **10** and **11** were made by reacting the diketones with excess sodium borohydride. No reaction was observed on compound **3a**.

## Section 13: *para* bis alcohol **10**

### **10**: *p*-bis-alcohol



**10**:  $^1\text{H}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 7.45 (m, 2H), 7.40 (m, 2H), 5.08 (m, 1H), 4.83 (m, 1H), 4.52 (brs, 1H), 3.26 (brs, 1H), 1.39 (d,  $J$  = 6.36, 3H) ppm.  $^{13}\text{C}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 148.04 [148.04], 133.79 [133.79], 127.45 (2C) [127.45 (2C)], 125.37 (2C) [125.37 (2C)], 125.00 (q,  $J_{\text{CF}}$  = 281.2 Hz) [125.00 (q,  $J_{\text{CF}}$  = 281.2 Hz)], 71.22 (q,  $J_{\text{CF}}$  = 31.4 Hz) [71.20 (q,  $J_{\text{CF}}$  = 30.8 Hz)], 68.81 [68.78], 24.90 [24.90] ppm.  $^{19}\text{F}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = -79.28 ppm.

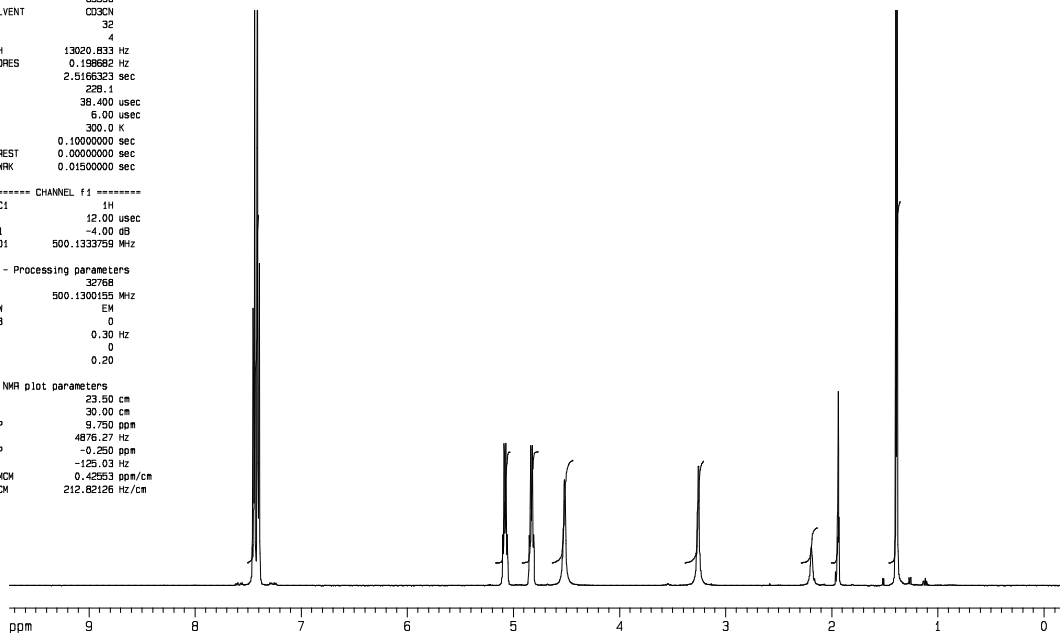
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Current Data Parameters
NAME      232427-999-1
EXPNO     1
PROCNO    1

F2 - Acquisition Parameters
Date_     20061129
Time      8.23
INSTRUM   spect
PROBHD    5 mm QNP 1H/19
PULPROG   zg30
TD         65536
SOLVENT   CD3CN
NS         32
DS         4
SWH        13020.833 Hz
FIDRES     0.198682 Hz
AQ         2.5166323 sec
RG         256.1
DM         36.400 usec
DE         6.00 usec
TE         300.0 K
D1         0.10000000 sec
WCREST     0.00000000 sec
WCMRK      0.01500000 sec

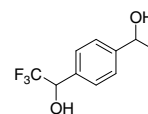
===== CHANNEL f1 =====
NUC1       1H
P1         12.00 usec
PL1        -4.00 dB
SFO1       500.133759 MHz

F2 - Processing parameters
SI         32768
SF         500.1300195 MHz
WDW        EM
SSB         0
LB         0.30 Hz
GB         0
PC         0.20

1D NMR plot parameters
CX         23.50 cm
CY         30.00 cm
F1P        9.750 ppm
F1         4876.27 Hz
F2P        -0.250 ppm
F2         -125.03 Hz
PPHOM      0.42553 ppm/cm
HZCM       212.82126 Hz/cm
```



**10**: *p*-bis-alcohol



Current Data Parameters  
NAME 232427-999-1  
EXPNO 3  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20061209  
Time 8.36  
INSTRUM spect  
PROBHD 5 mm QNP 1H/19  
PULPROG zgpg30  
TD 131072  
SOLVENT CDCl3  
NS 675  
DS 4  
SWH 49389.562 Hz  
FIDRES 0.307637 Hz  
AQ 1.6203428 sec  
RG 8182  
DM 12.400 usec  
DE 6.00 usec  
TE 300.0 K  
D1 0.10000000 sec  
d11 0.03000000 sec  
ICREST 0.00000000 sec  
KICK 0.01500000 sec

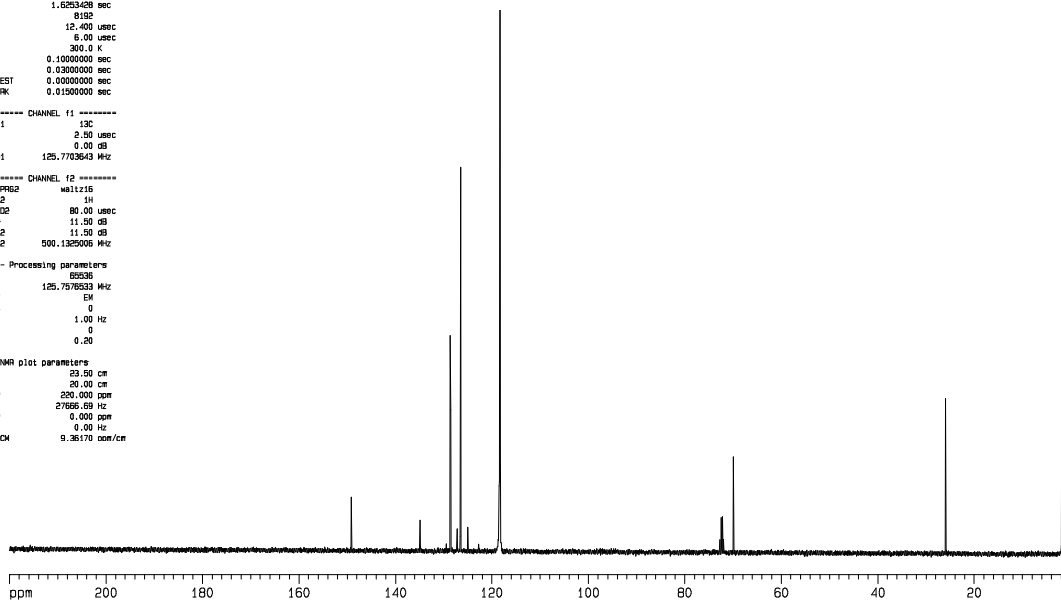
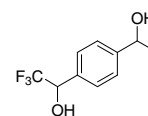
===== CHANNEL f1 =====  
NUC1 13C  
P1 2.50 usec  
PL1 0.00 dB  
SFO1 125.7703645 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 11.50 dB  
PL12 11.50 dB  
SFO2 500.1325006 MHz

F2 - Processing parameters  
SI 65536  
SF 125.7576533 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 0.20

1D NMR plot parameters  
CX 23.50 cm  
CY 30.00 cm  
F1P 200.000 ppm  
F1 27866.89 Hz  
F2P 0.000 ppm  
F2 0.00 Hz  
PPMCH 9.36170 ppm/cm

10: *p*-bis-alcohol



Current Data Parameters  
NAME 232427-999-1  
EXPNO 2  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20061209  
Time 8.36  
INSTRUM spect  
PROBHD 5 mm QNP 1H/19  
PULPROG zgpg30  
TD 131072  
SOLVENT CDCl3  
NS 16  
DS 4  
SWH 100000.000 Hz  
FIDRES 0.762939 Hz  
AQ 0.6954100 sec  
RG 64  
DM 5.000 usec  
DE 6.00 usec  
TE 300.0 K  
D1 5.00000000 sec  
d11 0.03000000 sec  
d12 0.00000000 sec

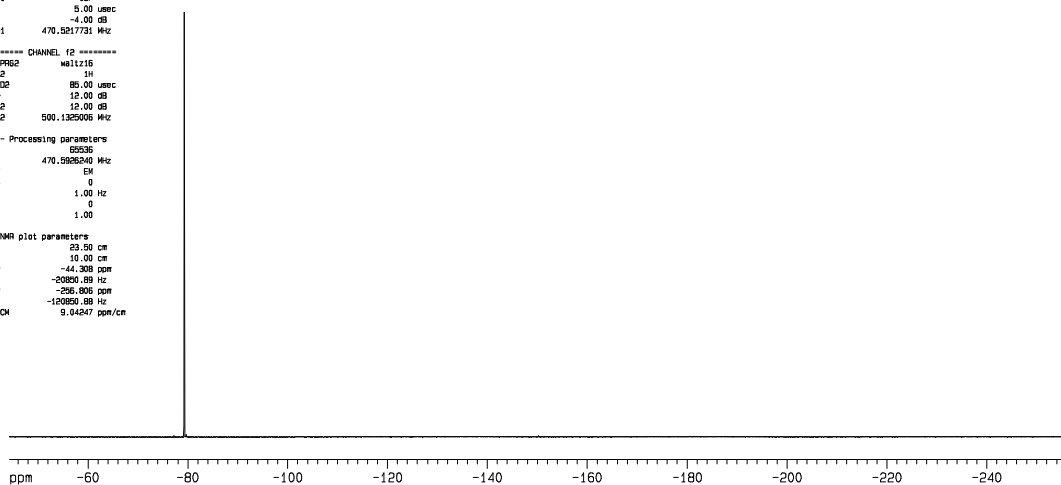
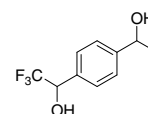
===== CHANNEL f1 =====  
NUC1 19F  
P1 5.00 usec  
PL1 -4.00 dB  
SFO1 470.5217731 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 12.00 dB  
PL12 12.00 dB  
SFO2 500.1325006 MHz

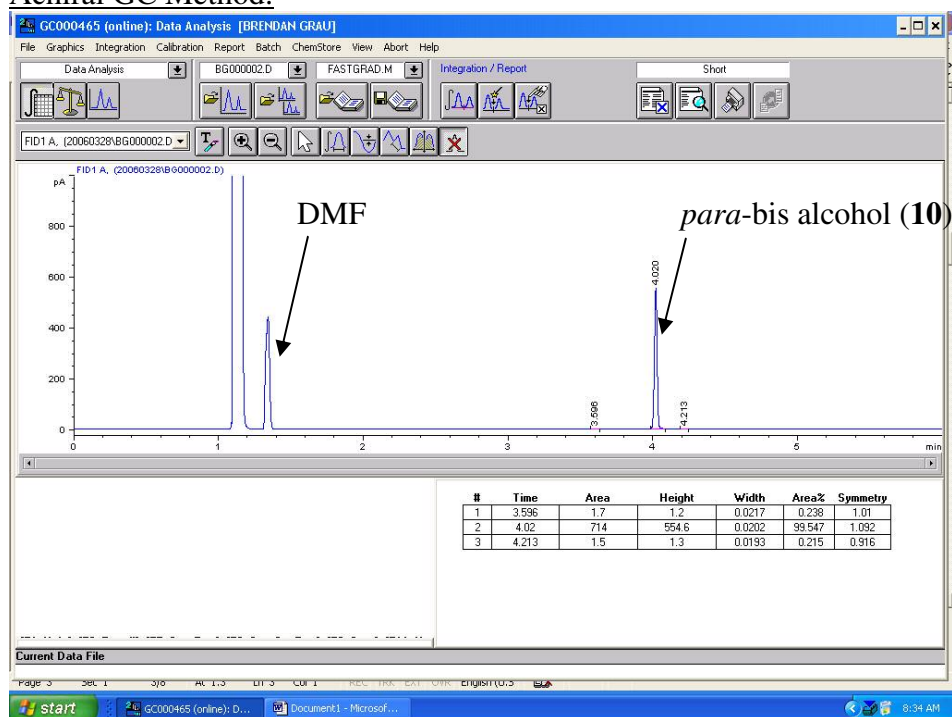
F2 - Processing parameters  
SI 65536  
SF 470.5986640 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.00

1D NMR plot parameters  
CX 23.50 cm  
CY 30.00 cm  
F1P -44.300 ppm  
F1 -20800.89 Hz  
F2P -296.896 ppm  
F2 -100860.88 Hz  
PPMCH 9.04247 ppm/cm

10: *p*-bis-alcohol



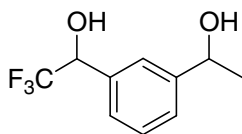
## Achiral GC Method:





# Section 14: *meta* bis-alcohol **11**

## **11**: *m*-bis-alcohol



**11**:  $^1\text{H}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 7.50 (s, 1H), 7.38 (m, 3H), 5.10 (m, 1H), 4.84 (m, 1H), 4.64 (d,  $J$  = 5.56, 1H), 3.37 (d,  $J$  = 3.58, 1H), 1.39 (d,  $J$  = 6.36, 3H) ppm.  $^{13}\text{C}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 148.28 [148.28], 136.30 [136.30], 129.37 (2C) [129.37 (2C)], 127.26 [127.19], 125.67 [125.63], 126.08 (q,  $J_{\text{CF}}$  = 281.8 Hz) [126.08 (q,  $J_{\text{CF}}$  = 281.8 Hz)], 70.03 [70.00], 72.52 (q,  $J_{\text{CF}}$  = 30.8 Hz) [72.52 (q,  $J_{\text{CF}}$  = 30.8 Hz)], 26.04 [26.02] ppm.  $^{19}\text{F}$  NMR (500.13 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = -79.20 ppm.

Current Data Parameters  
NAME 232427-999-f  
EXPNO 1  
PROCNO 1

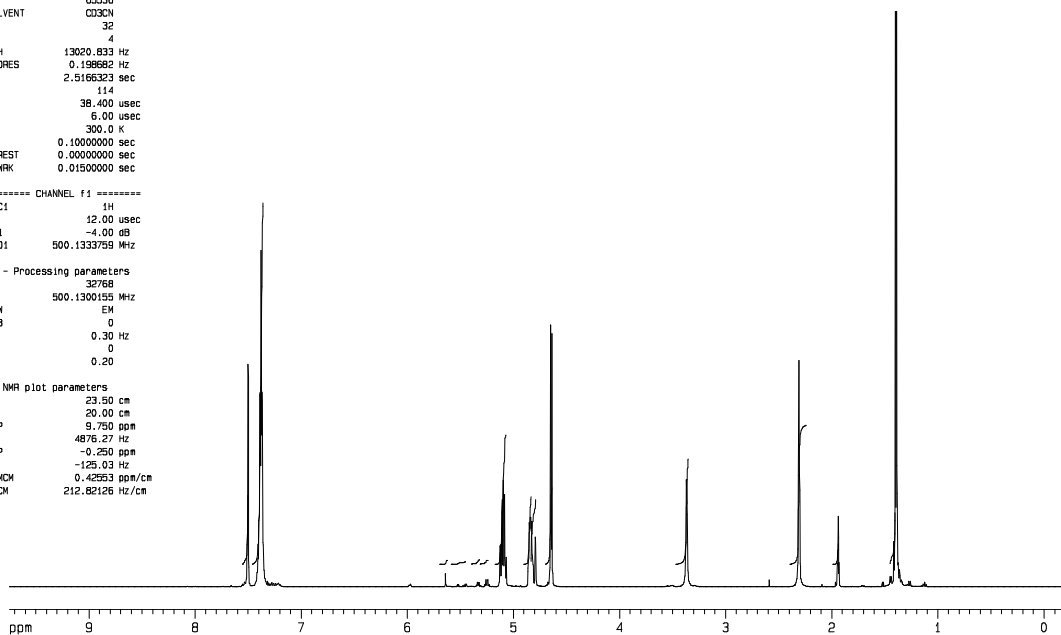
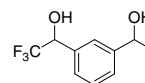
F2 - Acquisition Parameters  
Date\_ 20061129  
Time 8.52  
INSTRUM spect  
PROBHD 5 mm QNP 1H/19  
PULPROG zgpg30  
TD 65536  
SOLVENT CD3CN  
NS 32  
DS 4  
SWH 13020.833 Hz  
FIDRES 0.198682 Hz  
AQ 2.5166323 sec  
RG 114  
DM 38.400 usec  
DE 6.00 usec  
TE 300.0 K  
D1 0.10000000 sec  
MCREST 0.00000000 sec  
MCWRR 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 1H  
P1 12.00 usec  
PL1 -4.00 dB  
SFO1 500.133759 MHz

F2 - Processing parameters  
SI 32768  
SF 500.1300155 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 0.20

1D NMR plot parameters  
CX 23.50 cm  
CY 20.00 cm  
FIP 9.750 ppm  
F1 4876.27 Hz  
F2 -0.250 ppm  
F2 -125.03 Hz  
PPHOM 0.42553 ppm/cm  
HZCM 212.82126 Hz/cm

**11**: *m*-bis-alcohol



Current Data Parameters  
NAME 232427-999-f  
EXPNO 3  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20061129  
Time 9.02  
INSTRUM spect  
PROBHD 5 mm QNP 1H/19  
PULPROG zgpg30  
TD 131072  
SOLVENT CDCl3  
NS 675  
DS 4  
SWH 49389.562 Hz  
FIDRES 0.307637 Hz  
AQ 1.6203428 sec  
RG 8182  
DM 12.400 usec  
DE 6.00 usec  
TE 300.0 K  
D1 0.10000000 sec  
d11 0.03000000 sec  
ICREST 0.00000000 sec  
KICK 0.01000000 sec

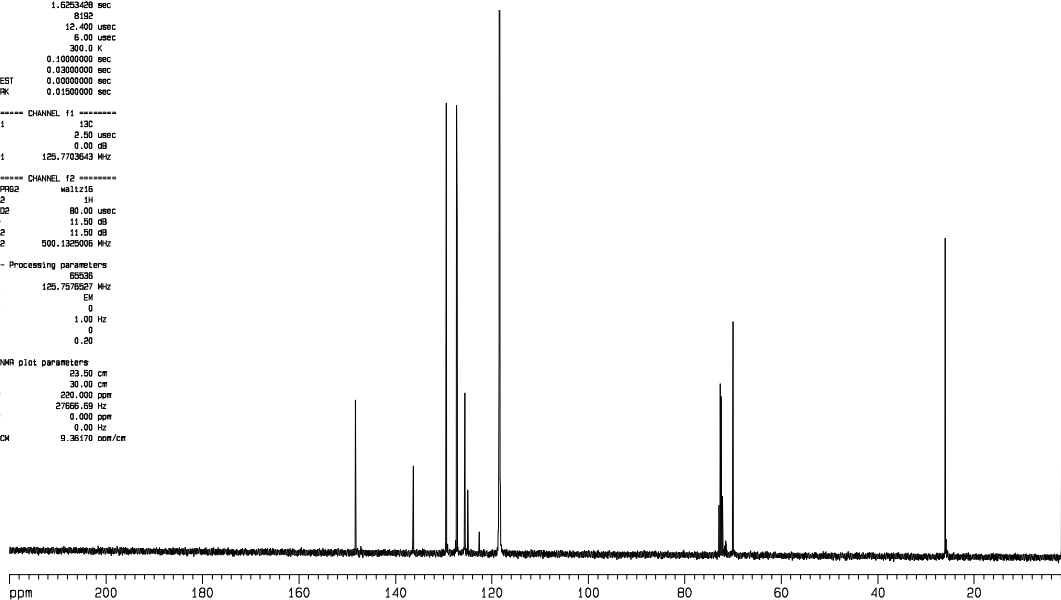
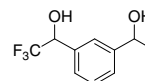
===== CHANNEL f1 =====  
NUC1 13C  
P1 2.50 usec  
PL1 0.00 dB  
SFO1 125.7703643 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 11.50 dB  
PL12 11.50 dB  
SFO2 500.1325006 MHz

F2 - Processing parameters  
SI 65536  
SF 125.757657 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 0.20

1D NMR plot parameters  
CX 23.50 cm  
CY 30.00 cm  
F1P 200.000 ppm  
F1 27866.89 Hz  
F2P 0.000 ppm  
F2 0.00 Hz  
PPMCH 9.36170 ppm/cm

11: *m*-bis-alcohol



Current Data Parameters  
NAME 232427-999-f  
EXPNO 2  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20061129  
Time 9.05  
INSTRUM spect  
PROBHD 5 mm QNP 1H/19  
PULPROG zgpg30  
TD 131072  
SOLVENT CDCl3  
NS 16  
DS 4  
SWH 100000.000 Hz  
FIDRES 0.762939 Hz  
AQ 0.6504100 sec  
RG 64  
DM 5.000 usec  
DE 6.00 usec  
TE 300.0 K  
D1 5.00000000 sec  
d11 0.03000000 sec  
d12 0.00000000 sec

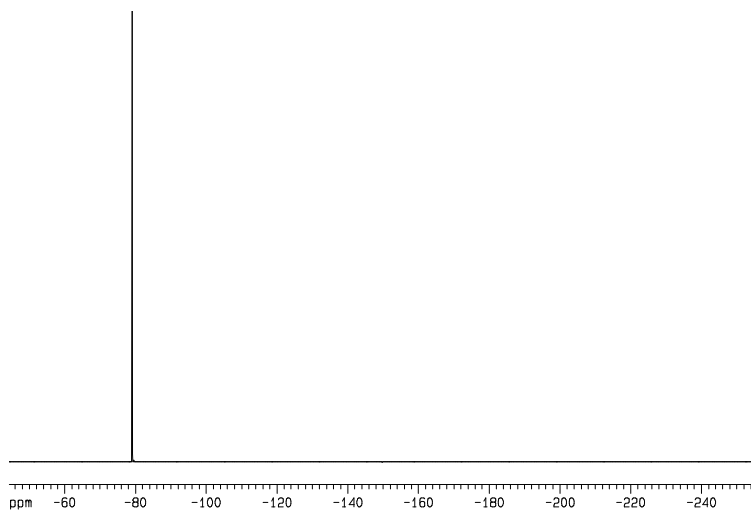
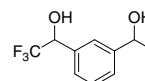
===== CHANNEL f1 =====  
NUC1 19F  
P1 5.00 usec  
PL1 -4.00 dB  
SFO1 470.5217731 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 12.00 dB  
PL12 12.00 dB  
SFO2 500.1325006 MHz

F2 - Processing parameters  
SI 65536  
SF 470.592640 MHz  
WDW DM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.00

1D NMR plot parameters  
CX 23.50 cm  
CY 10.00 cm  
F1P 0.000 ppm  
F1 0.00 Hz  
F2P -300.000 ppm  
F2 -141177.78 Hz  
PPMCH 12.76596 ppm/cm

11: *m*-bis-alcohol



## Achiral GC Method:

