Chemo and Enantioselective Routes to Chiral Fluorinated Hydroxyketones Using Ketoreductases

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Supplemental Information
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5. Analysis of *ortho*-diketone **3a**
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8. Analysis of *meta*-trifluoromethyl hydroxyketone **5**
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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, 5um) column at 25C and a detection wavelength of 210nm. The mobile phase was 50% acetonitrile and 50% 0.1%H_3PO_4 H_2O. Samples were prepared using acetonitrile or acetonitrile:H_2O (1:1) as diluent.

Achiral GC method:
All screening reactions of the catalysts were monitored by GC using a Restek Rtx-1701 (30m X 320um, 1um 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 275C using a FID detector. The compounds were eluted with the following temperature gradient, 200C hold for 2 minutes, ramp temperature to 275C at 25C/min and hold for 1 min.

Chiral HPLC method:
Reaction samples were extracted with 2 volumes MTBE, dried under N_2 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_2 purge and resuspended in isopropanol. Chiral separation of the enantiomers of methyl hydroxyketones **7** and **8** was achieved on chiral GC using a Chiralsil-dex CB (25m X 320um, 0.25um 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 200C using a FID detector. Compound **7** was eluted with an isothermal method at 130C. Compound **8** was eluted with an isothermal method at 100C.

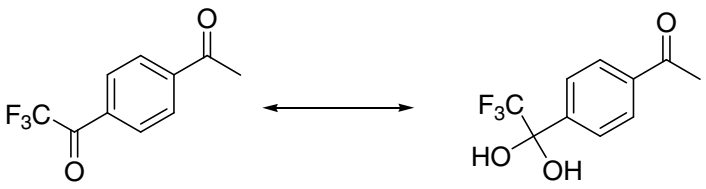
Section 2: Synthesis of methyl/trifluoromethyl diketone substrates

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 $MgSO_4$, 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[2]. 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 $MgSO_4$ 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

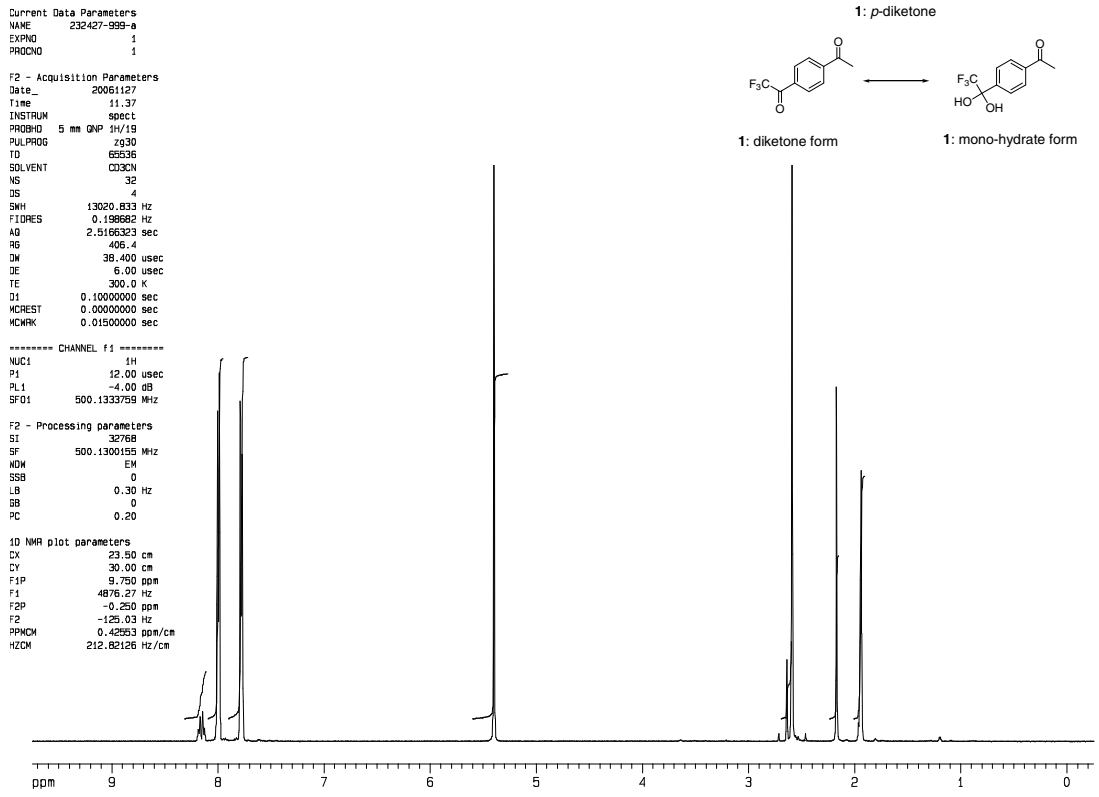


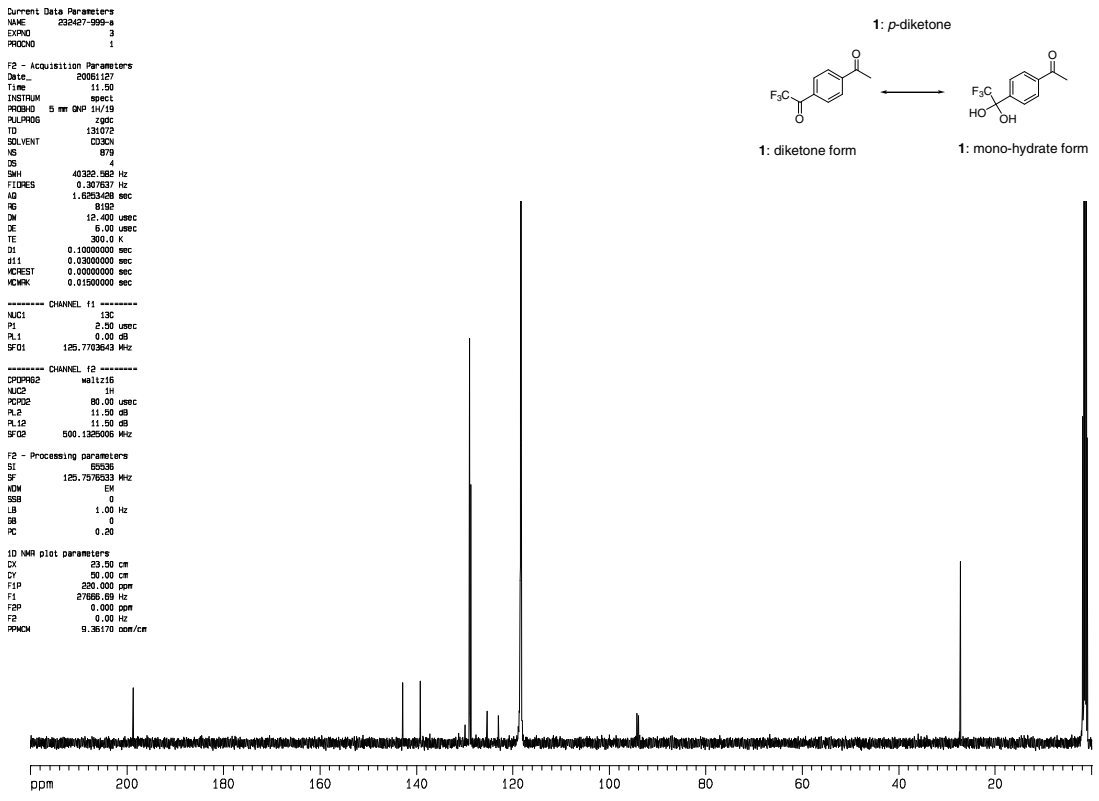
1: diketone form **1**: mono-hydrate form

Para-diketone **1**

(mono-hydrate form): ^{1}H NMR (500.13 MHz, CD_3CN) δ = 8.00 (m, 2H), 7.78 (m, 2H), 5.40 (s, 2H), 2.59 (s, 3H) ppm. ^{13}C NMR (500.13 MHz, CD_3CN) δ = 198.78, 142.83, 139.20, 128.92, 128.68, 124.19 (q, J_{CF} = 287.3 Hz), 94.13 (q, J_{CF} = 32.0 Hz), 27.24 ppm. ^{19}F NMR (500.13 MHz, CD_3CN) δ = -85.29 ppm.

(diketone form): ^{1}H NMR (500.13 MHz, CD_3CN) δ = 8.18 (m, 2H), 8.13 (m, 2H), 2.64 (s, 3H) ppm. ^{19}F NMR (500.13 MHz, CD_3CN) δ = -73.40 ppm.

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F1 27666.69 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 9.35170 ppm/cm
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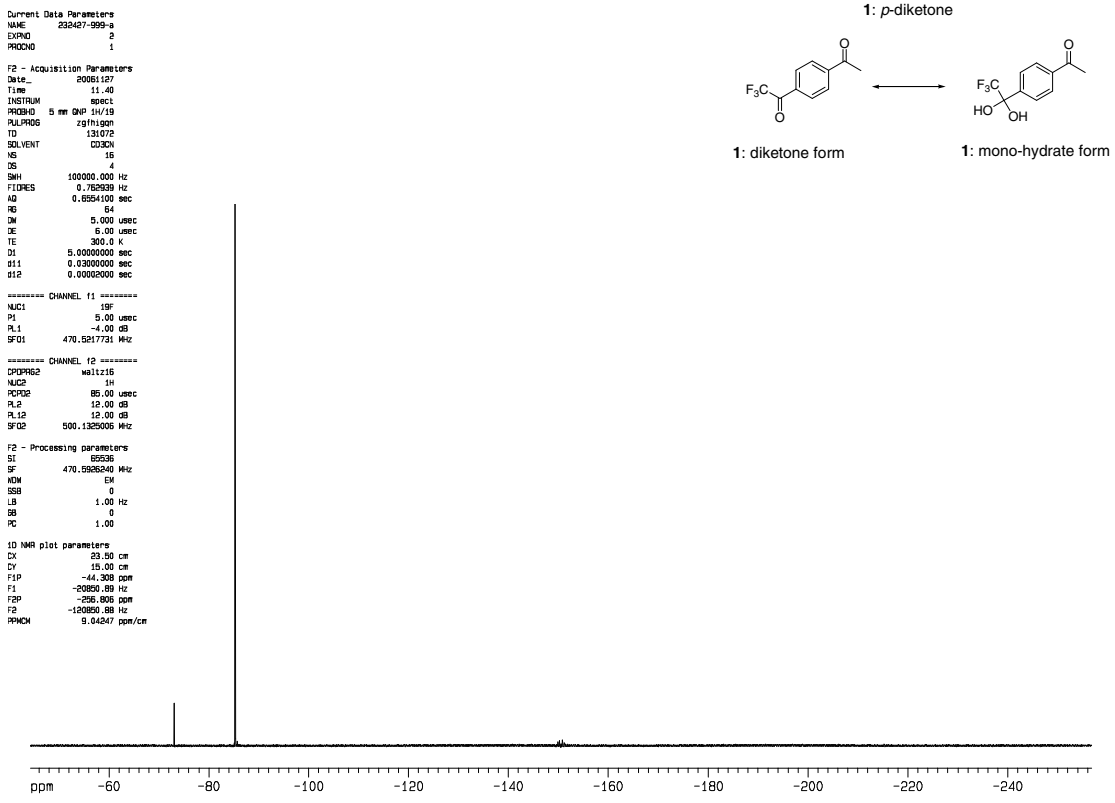
1: diketone form
1: mono-hydrate form
ppm
200
180
160
140
120
100
80
60
40
20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d12 0.00002000 sec
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CY 15.00 cm
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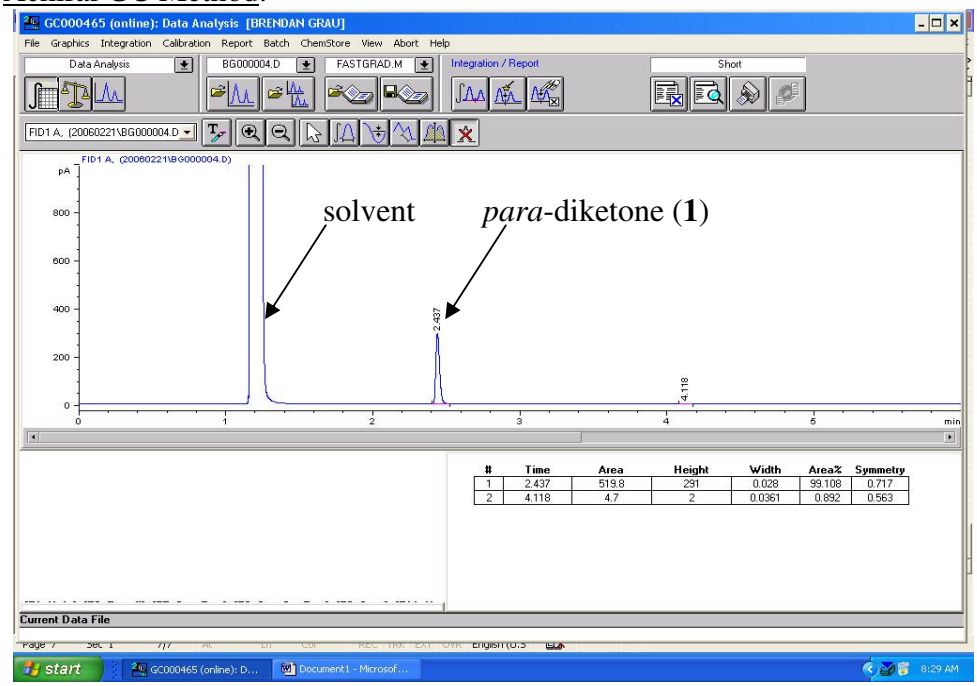
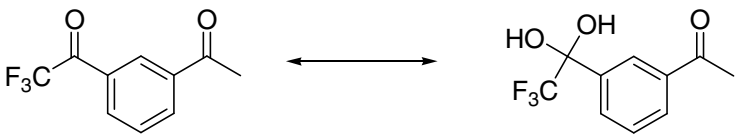
F1 -20850.89 Hz
F2P -255.805 ppm
F2 -120850.88 Hz
PPMCM 9.04247 ppm/cm
1: p-diketone
1: diketone form
1: mono-hydrate form
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240

Achiral GC Method:



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

2: *m*-diketone

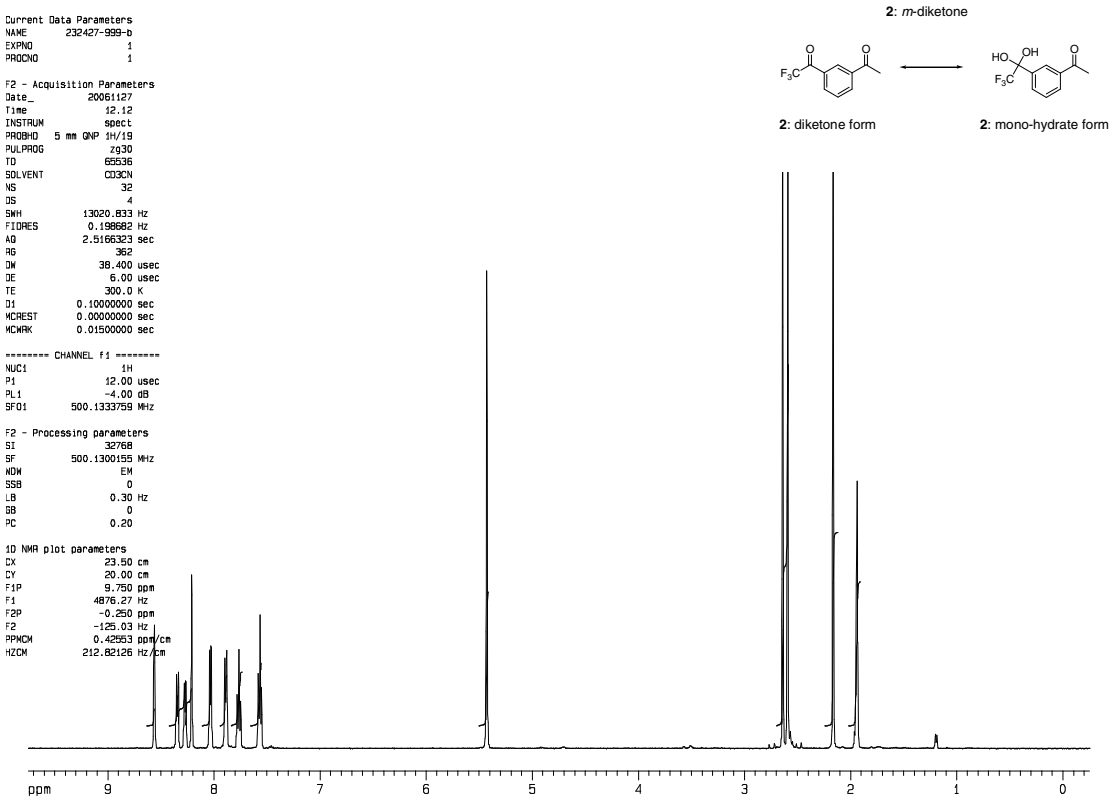


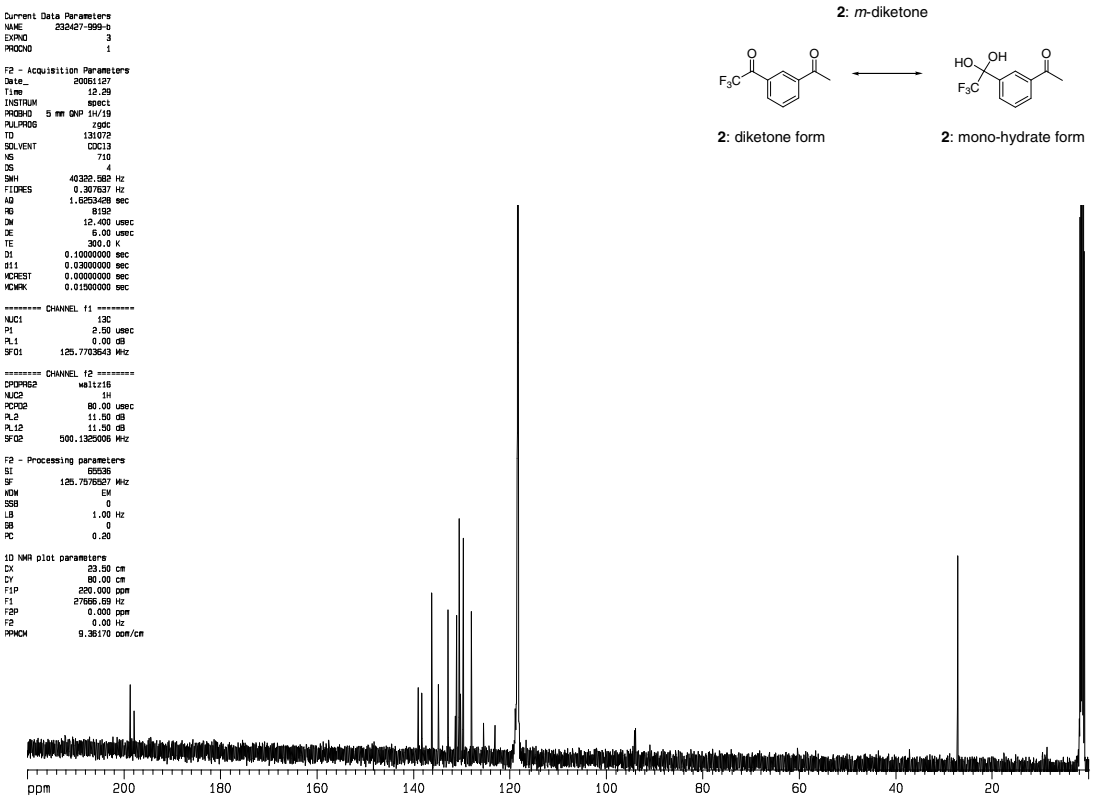
2: diketone form **2**: mono-hydrate form

Meta-diketone **2**

(mono-hydrate form): ^{1}H NMR (500.13 MHz, CD_3CN) δ = 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}C NMR (500.13 MHz, CD_3CN) δ = 198.71, 139.03, 138.20, 132.82, 130.56, 129.62, 127.83, 124.26 (q, J_{CF} = 286.7 Hz), 94.09 (q, J_{CF} = 32.0 Hz), 27.17 ppm. ^{19}F NMR (500.13 MHz, CD_3CN) δ = -85.44 ppm.

(diketone form): ^{1}H NMR (500.13 MHz, CD_3CN) δ = 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}F NMR (500.13 MHz, CD_3CN) δ = -72.97 ppm.

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PL1 0.00 dB
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1D NMR plot parameters
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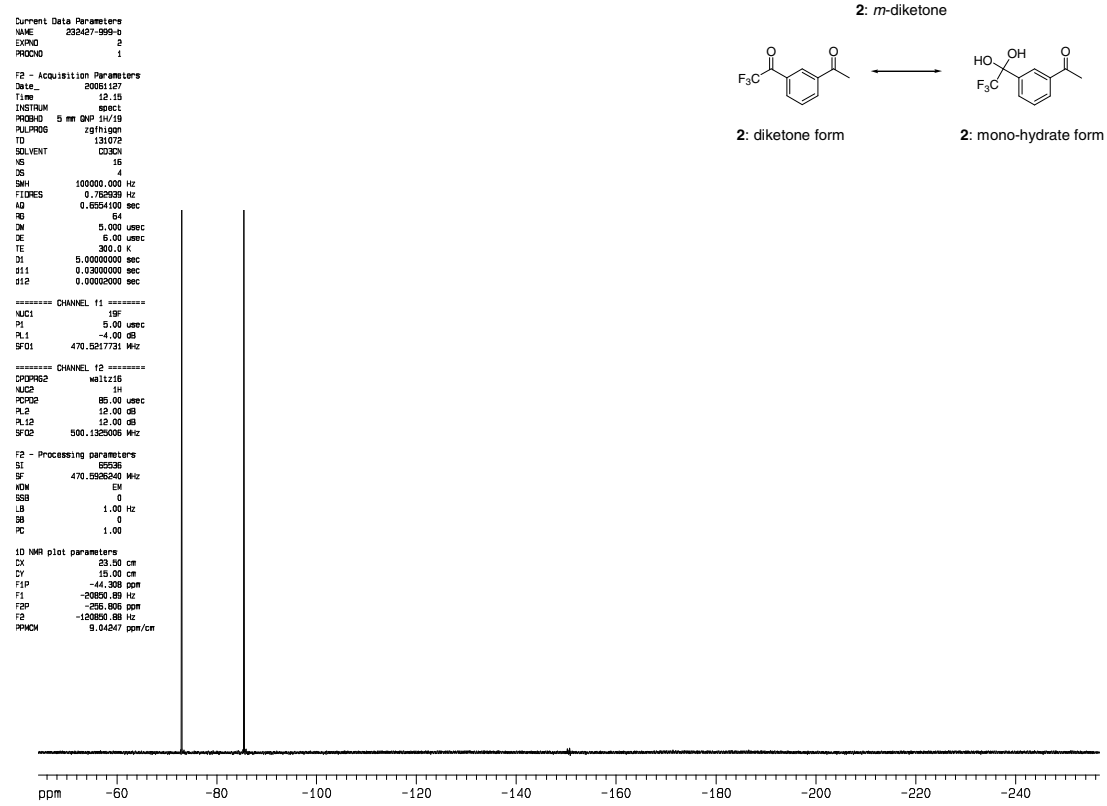
CY 20.00 cm
F1P 220.000 ppm
F1 27666.69 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 9.36170 ppm/cm
2: m-diketone
2: diketone form
2: mono-hydrate form
ppm
200
180
160
140
120
100
80
60
40
20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1D NMR plot parameters
CX 23.50 cm
CY 15.00 cm
F1P -44.308 ppm
F1 -20850.89 Hz
F2P -256.806 ppm
F2 -120850.88 Hz
PPMCM 9.04247 ppm/cm
2: m-diketone
2: diketone form
2: mono-hydrate form
ppm
-60
-80
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-120
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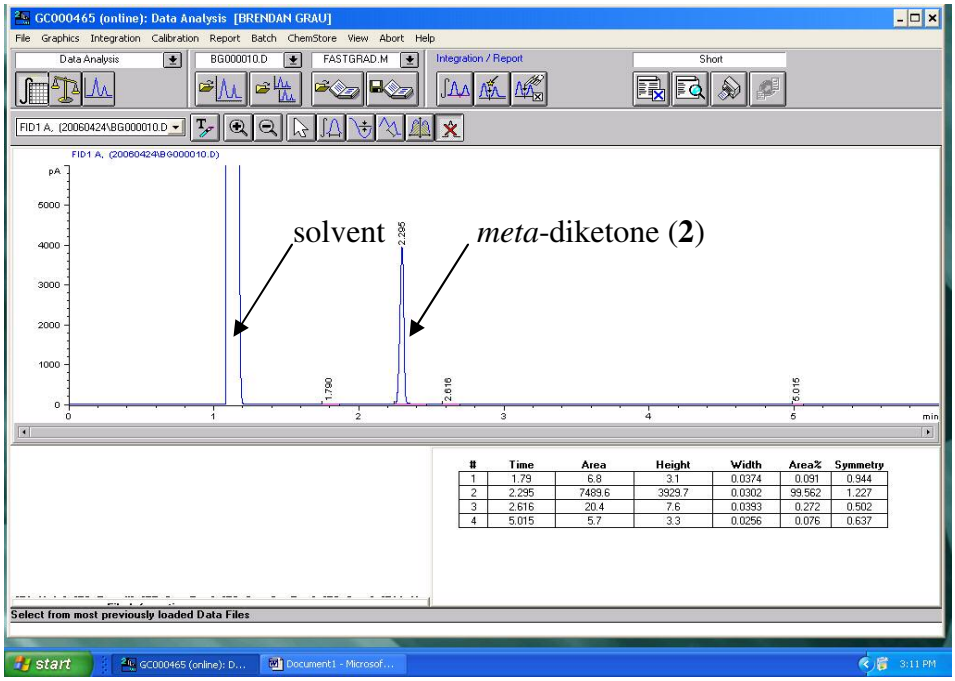
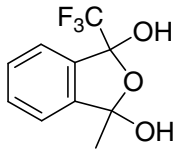
-180
-200
-220
-240

Achiral GC Method:



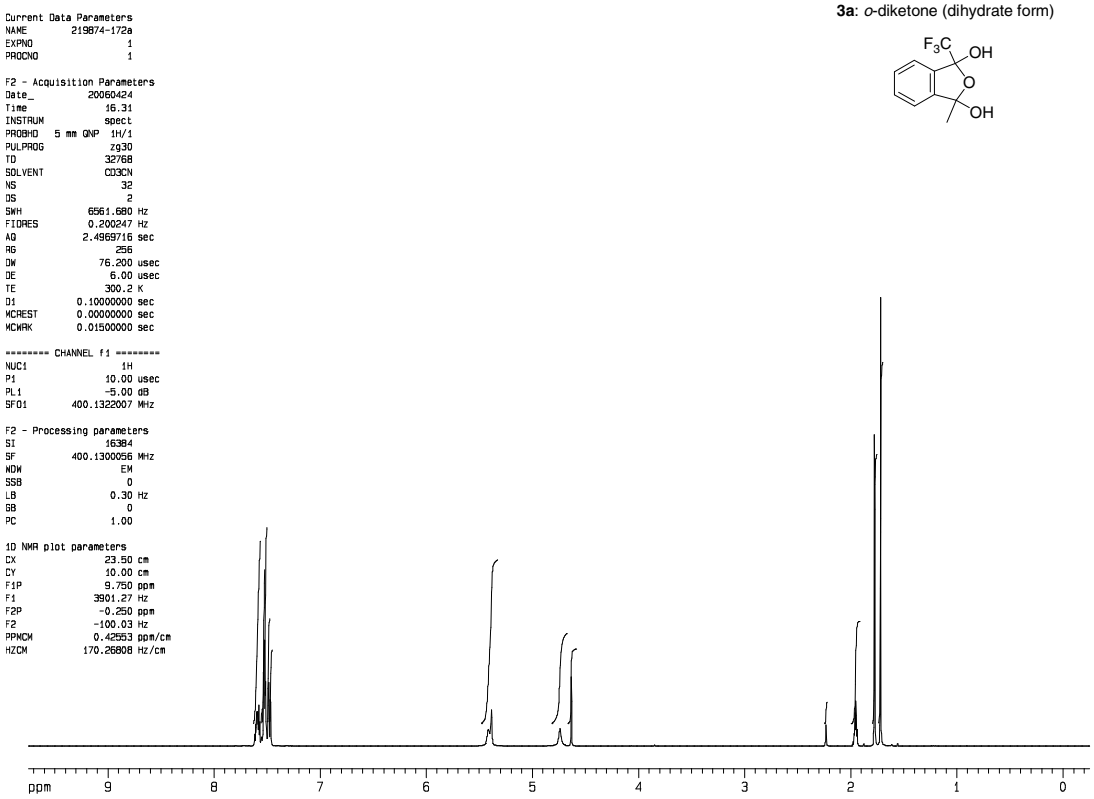
Section 5: *ortho*-diketone **3a**

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



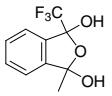
Ortho-diketone **3a**

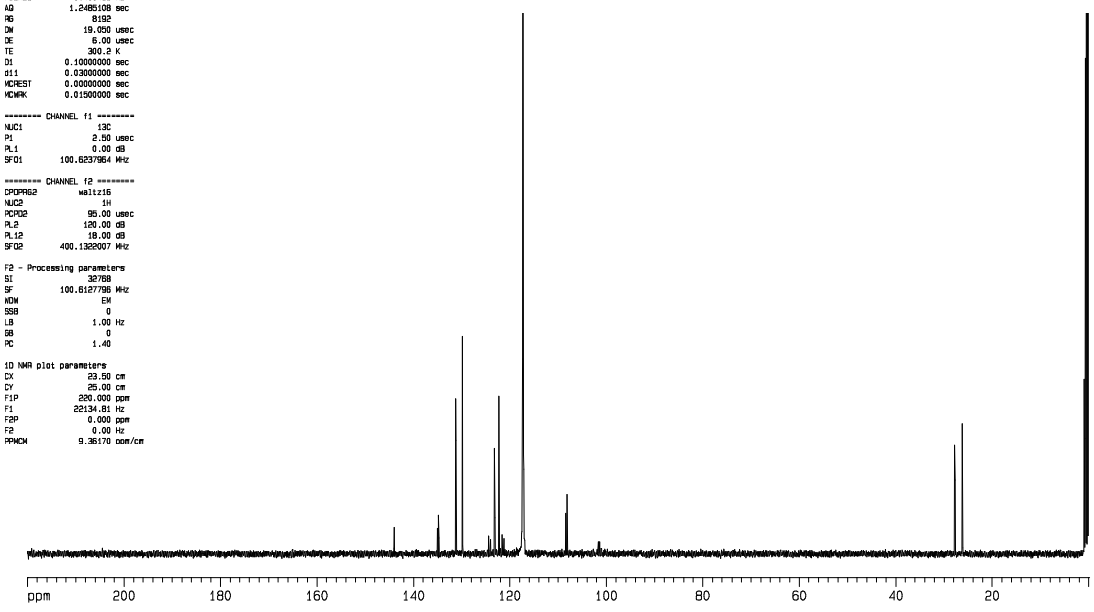
(cyclized di-hydrate form): ^{1}H NMR (400.13 MHz, CD_3CN) δ =): ^{1}H NMR (500.13 MHz, CD_3CN) δ = [7.60–7.56 (om, 1H), 7.53-7.50 (om, 2H), 7.47-7.60 (om, 1H), 5.37 (brs, 1H), 4.62 (s, 1H), 1.76 (s, 3H) and 7.60-7.56 (om, 1H), 7.53-7.50 (om, 2H), 7.47-7.60 (om, 1H), 5.37 (brs, 1H), 4.73 (brs, 1H), 1.70 (s, 3H) ppm. ^{13}C NMR (500.13 MHz, CD_3CN) δ = [145.17, 135.85, 132.41, 130.94, 124.10 (q, J_{CF} = 286.0 Hz), 123.34, 109.26, 102.58 (q, J_{CF} = 33.6 Hz), 27.31 ppm. ^{19}F NMR (500.13 MHz, CD_3CN) δ = [-84.37 and -84.15] ppm.



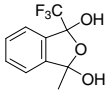
3a: *o*-diketone (dihydrate form)

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





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



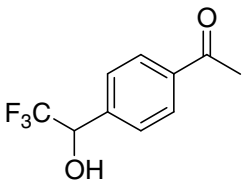
Section 6: Synthesis of racemic trifluoromethyl hydroxyketones **4** and **5**.

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 $MgSO_4$ and concentrated on a rotary evaporator to a crude the crude ketal.

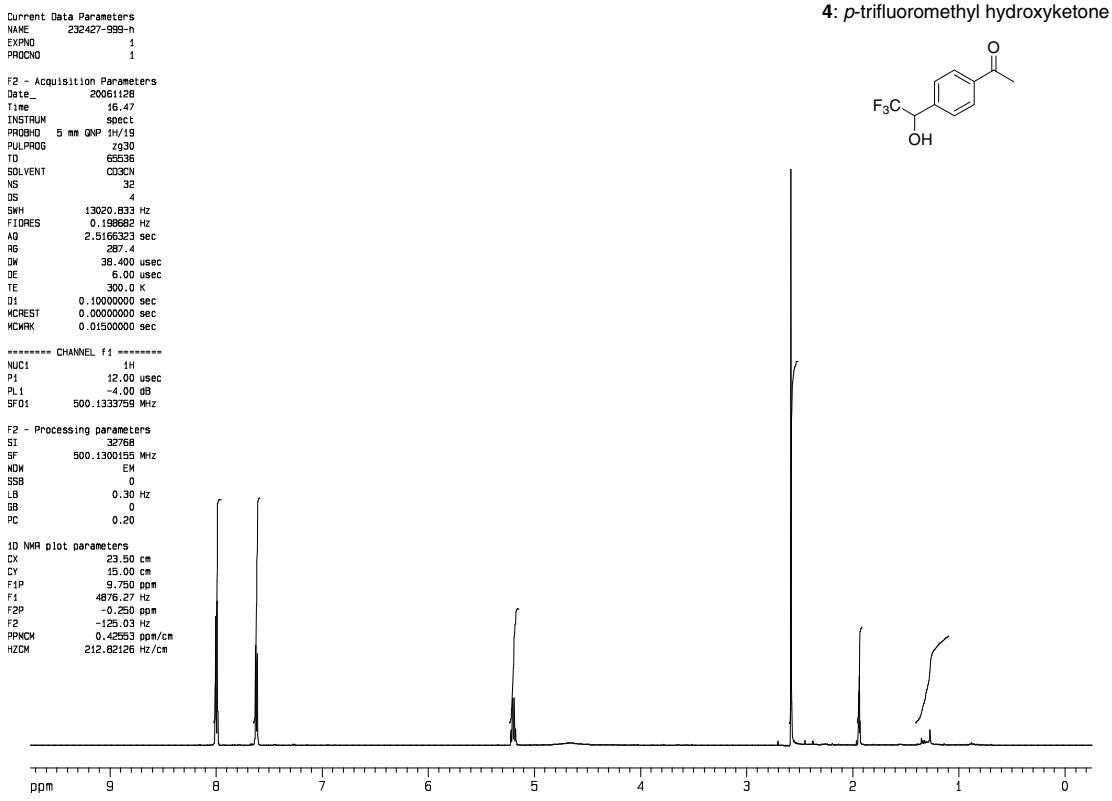
Sodium borohydride (1 equivalent) was added to a solution of ketal (1g) in THF:H_2O (10:1) at 25C and aged 0.5hr. Upon completion the solution was quenched with 1N HCl and aged. The THF solution was extracted into MTBE (2 vol.). The organic layer was washed with brine (1 vol.), dried over $MgSO_4$ and 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}H NMR (500.13 MHz, CD_3CN) δ = 8.00 (m, 2H), 7.62 (m, 2H), 5.20 (q, J = 7.15, 1H), 2.58 (s, 3H) ppm. ^{13}C NMR (500.13 MHz, CD_3CN) δ = 198.71, 141.04, 139.88, 129.29 (2C), 128.87 (2C), 125.80 (q, J_{CF} = 281.8 Hz), 71.98 (q, J_{CF} = 31.4 Hz), 27.18 ppm. ^{19}F NMR (500.13 MHz, CD_3CN) δ = -79.11 ppm.



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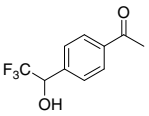
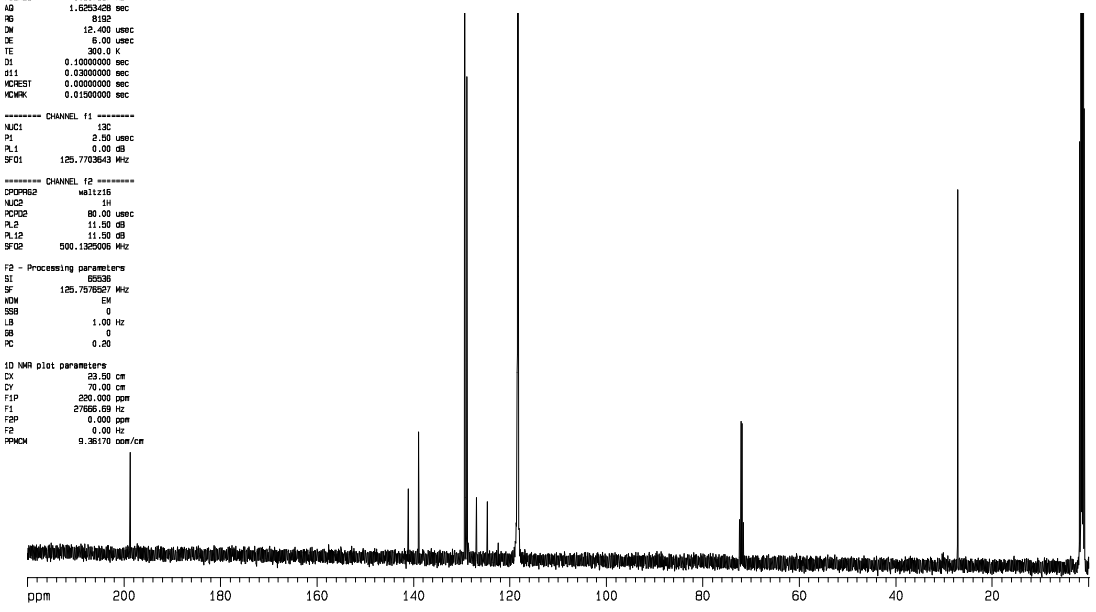
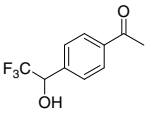




4: *p*-trifluoromethyl hydroxyketone



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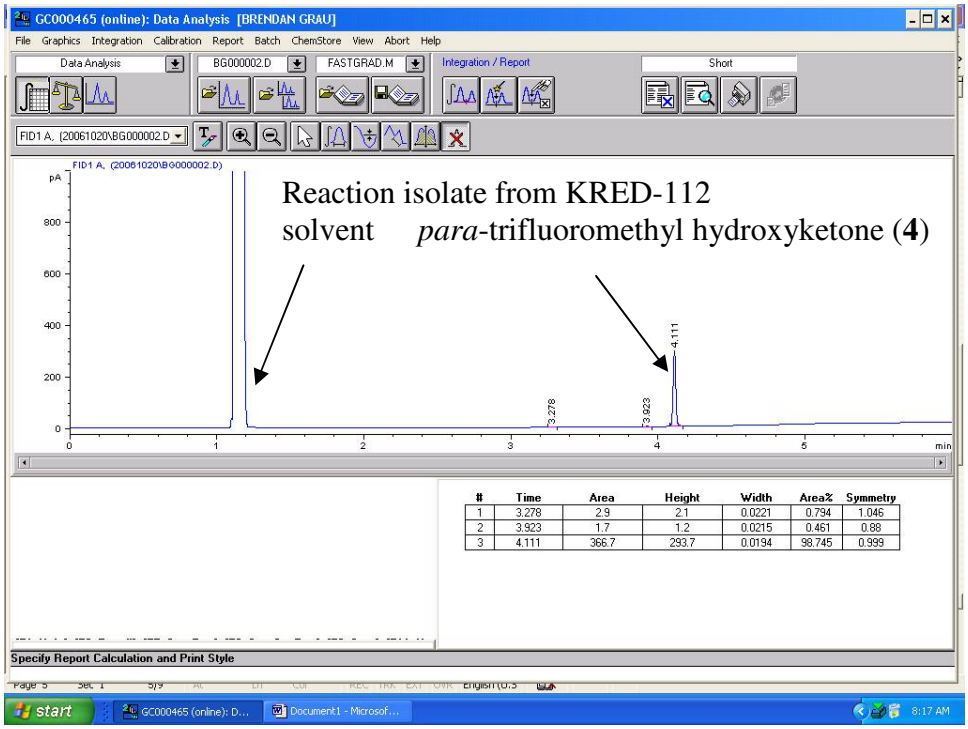

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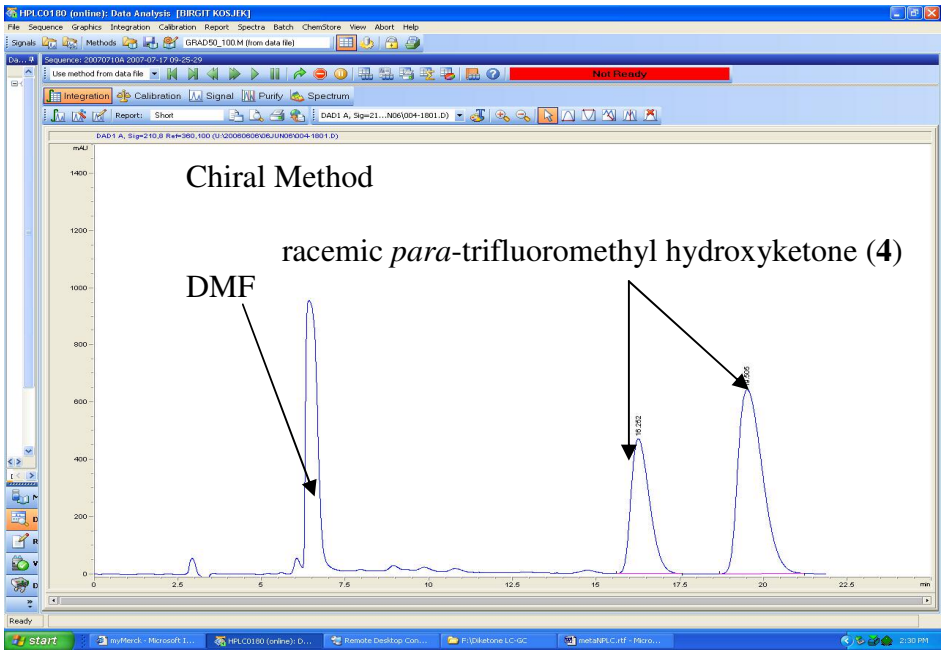
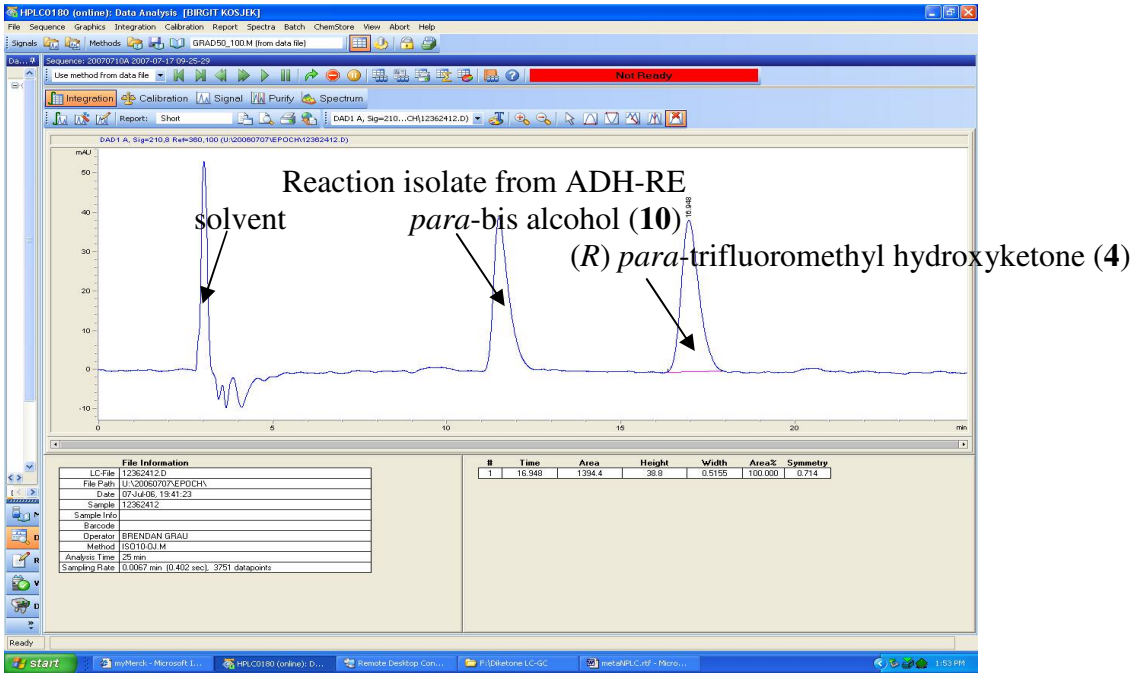
Chiral NP-HPLC Method:

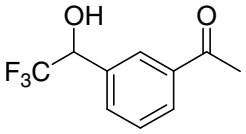


Chiral NP-HPLC Method:

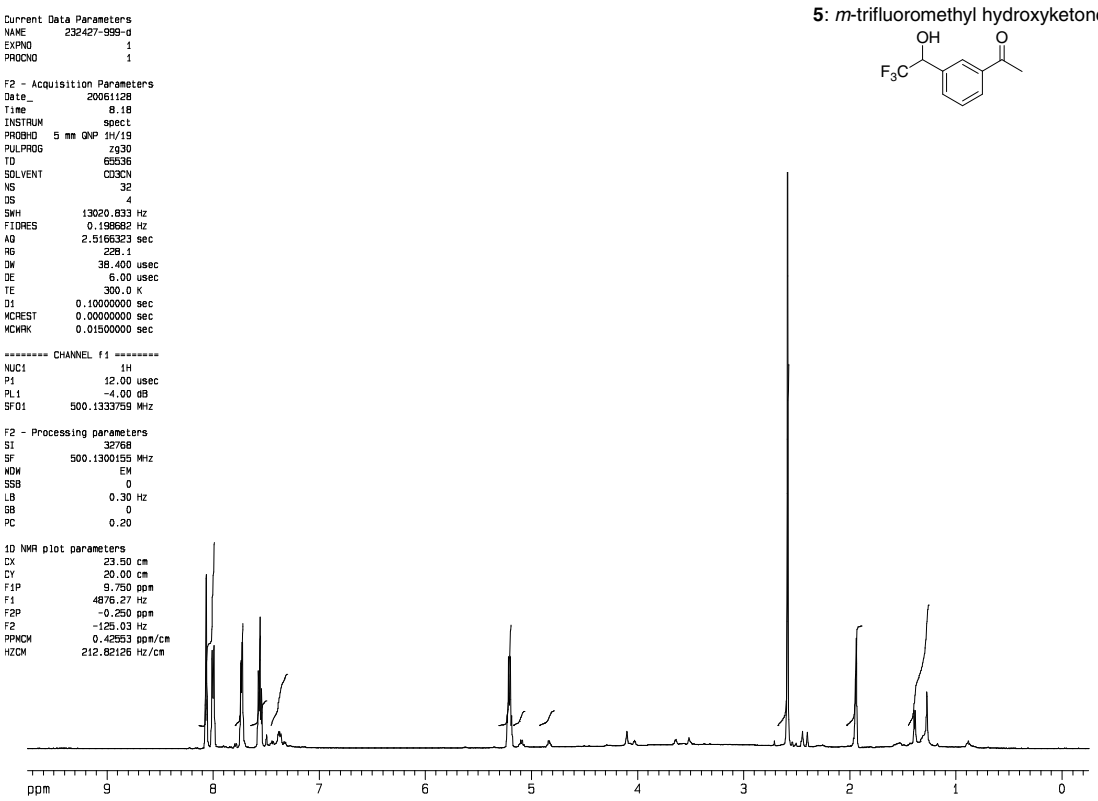


Section 8: *meta*-trfluoromethyl hydroxyketone **5**

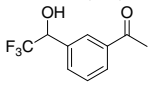
5: *m*-trifluoromethyl hydroxyketone

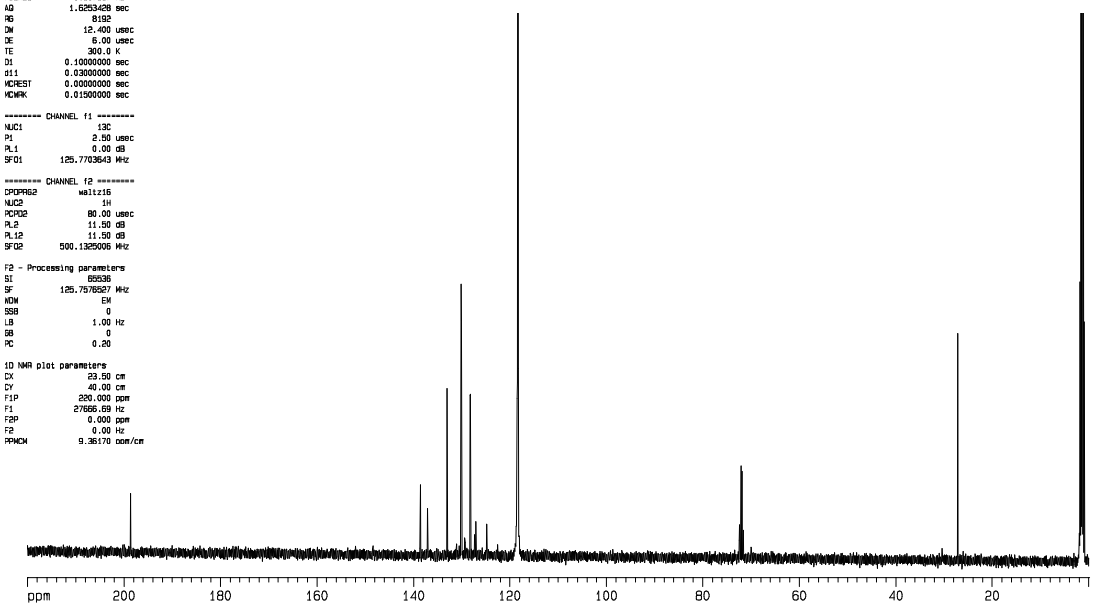


5: ^{1}H NMR (500.13 MHz, CD_3CN) δ = 8.06 (s, 1H), 8.00 (d, J = 7.55, 1H), 7.73 (d, J = 7.55, 1H), 7.56 (t, J = 7.55, 1H), 5.21 (m, 1H), 2.58 (s, 3H) ppm. ^{13}C NMR (500.13 MHz, CD_3CN) δ = 198.73, 138.47, 136.98, 133.05, 130.11, 129.93, 128.15, 125.80 (q, J_{CF} = 281.8 Hz), 72.00 (q, J_{CF} = 31.4 Hz), 27.15 ppm. ^{19}F NMR (500.13 MHz, CD_3CN) δ = -79.34 ppm.

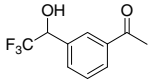


5: *m*-trifluoromethyl hydroxyketone

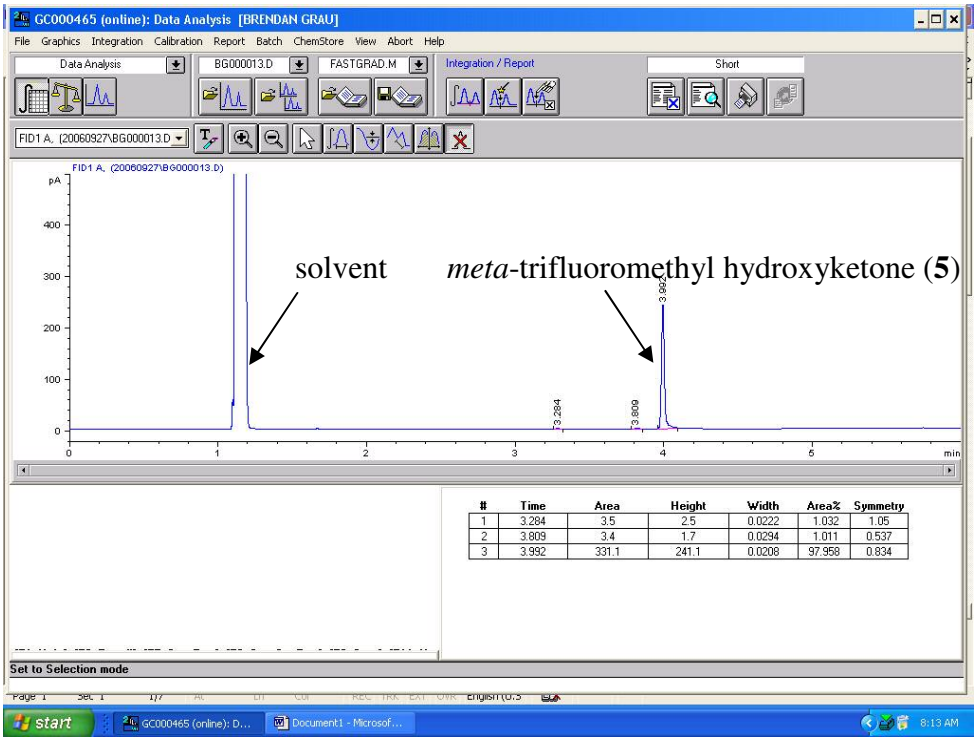




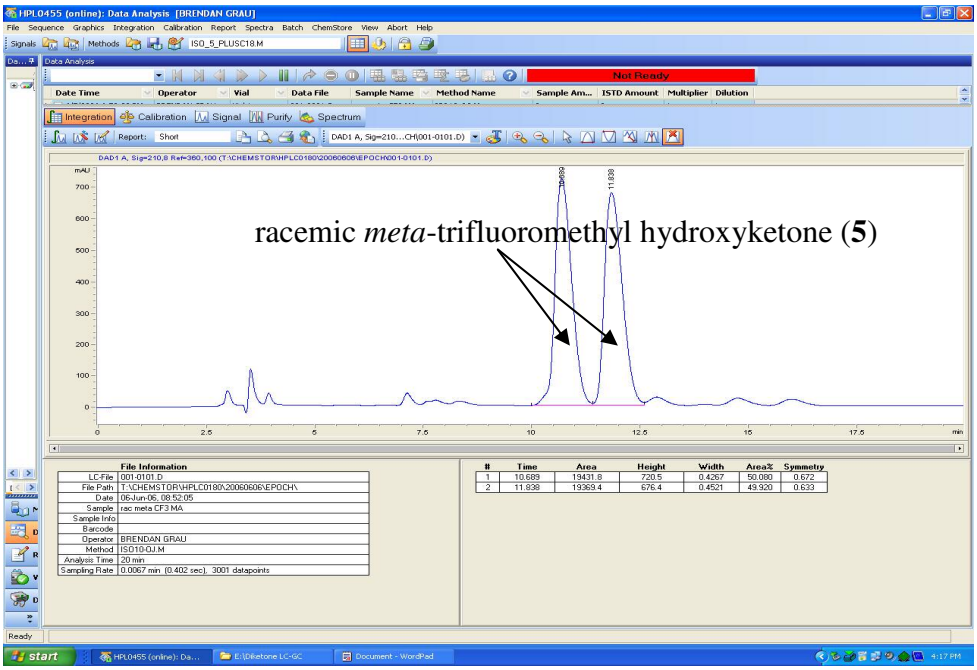
5: *m*-trifluoromethyl hydroxyketone



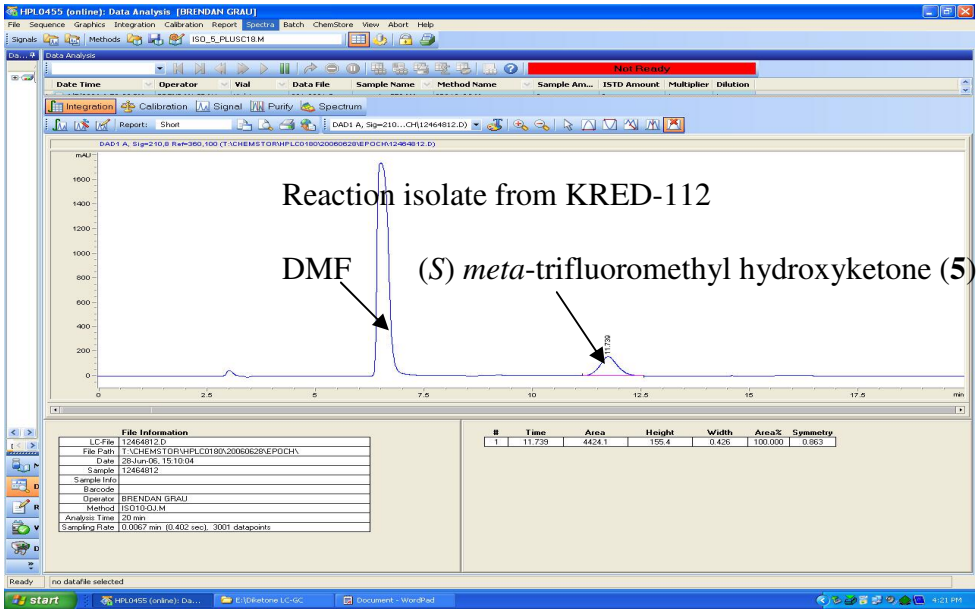
Achiral GC Method:



Chiral NP-HPLC Method:



Chiral NP-HPLC Method:

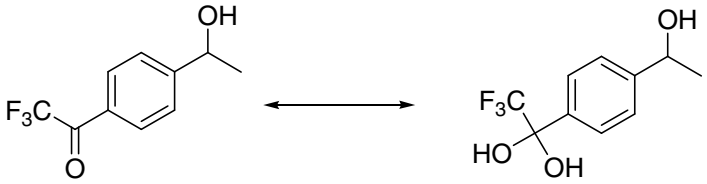


Section 9: Synthesis of racemic methyl hydroxyketones **7** and **8**.

The racemic standards for the methyl hydroxyketones **7** and **8** were subjected to modified reaction conditions listed in the literature reference[2] by using THF/H_2O 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 $MgSO_4$ and concentrated on a rotary evaporator to yield the crude racemic methyl hydroxyketones of **7** and **8**.

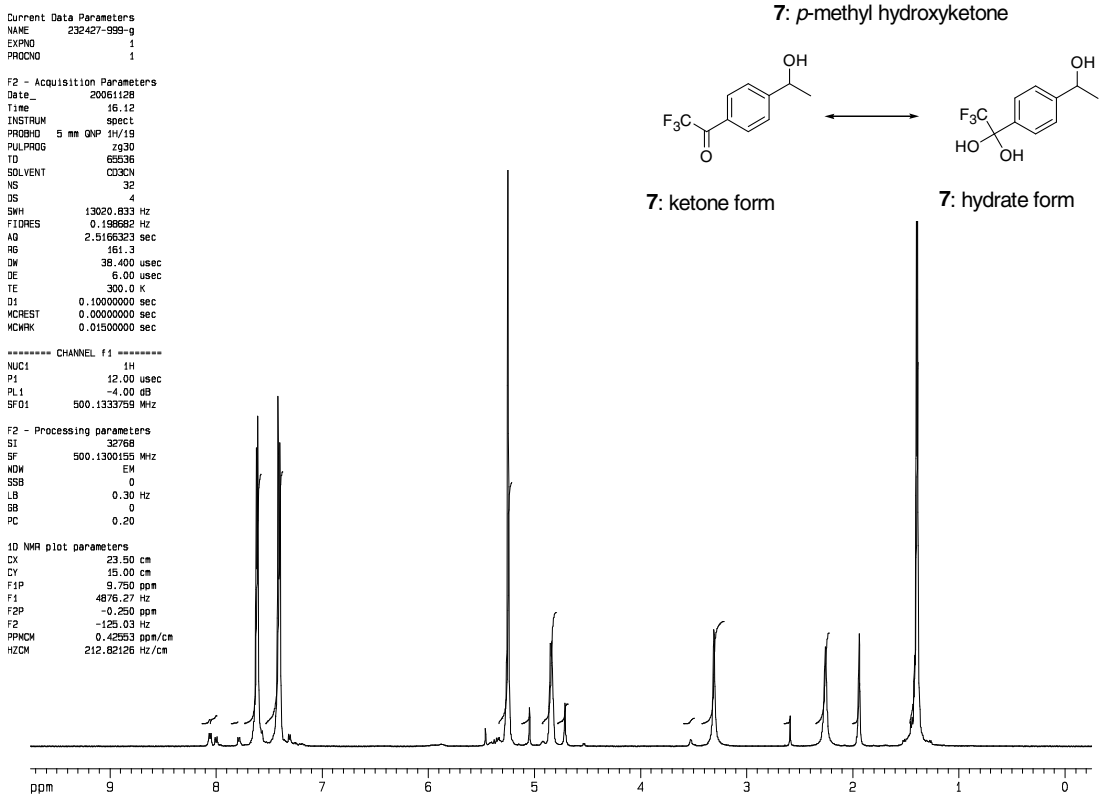
Section 10: *para*-methyl hydroxyketone **7**

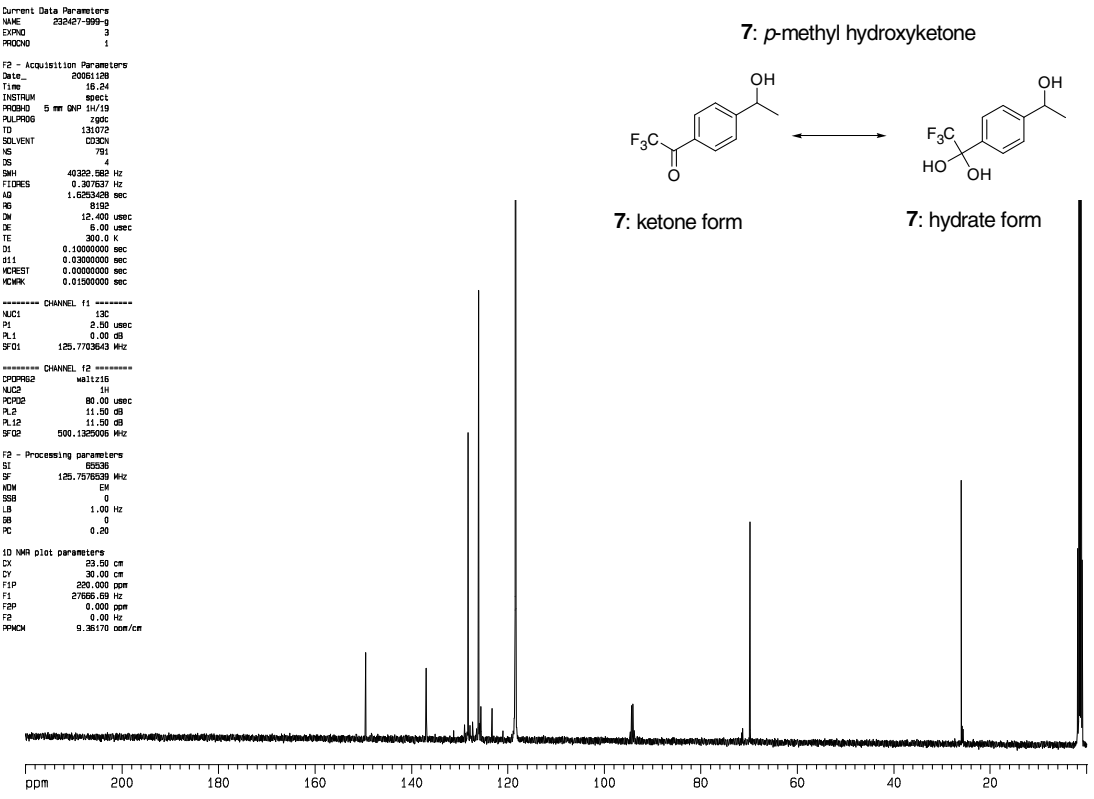
7: *p*-methyl hydroxyketone



7: ketone form **7**: hydrate form

(hydrate form): ^{1}H NMR (500.13 MHz, CD_3CN) δ = 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}C NMR (500.13 MHz, CD_3CN) δ = 149.49, 136.90, 128.22 (2C), 126.06 (2C), 124.40 (q, J_{CF} = 287.3 Hz), 94.24 (q, J_{CF} = 32.0 Hz), 69.86, 25.93 ppm. ^{19}F NMR (500.13 MHz, CD_3CN) δ = -85.39 ppm.

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EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
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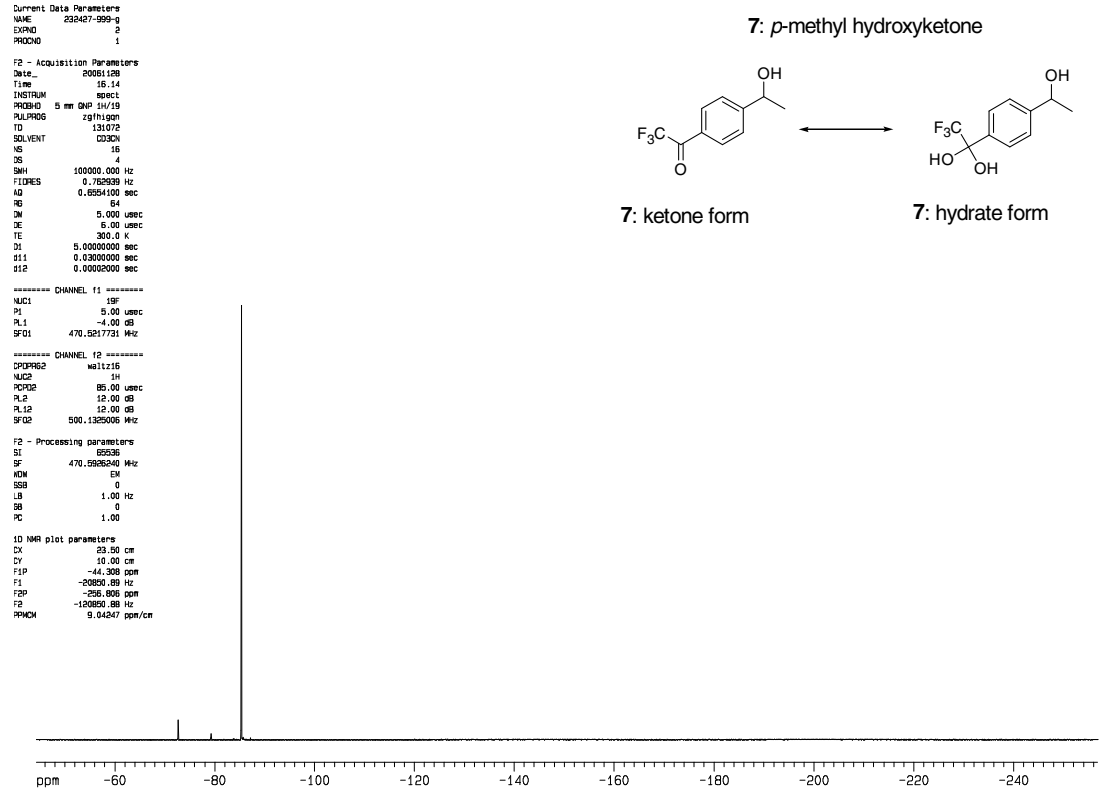
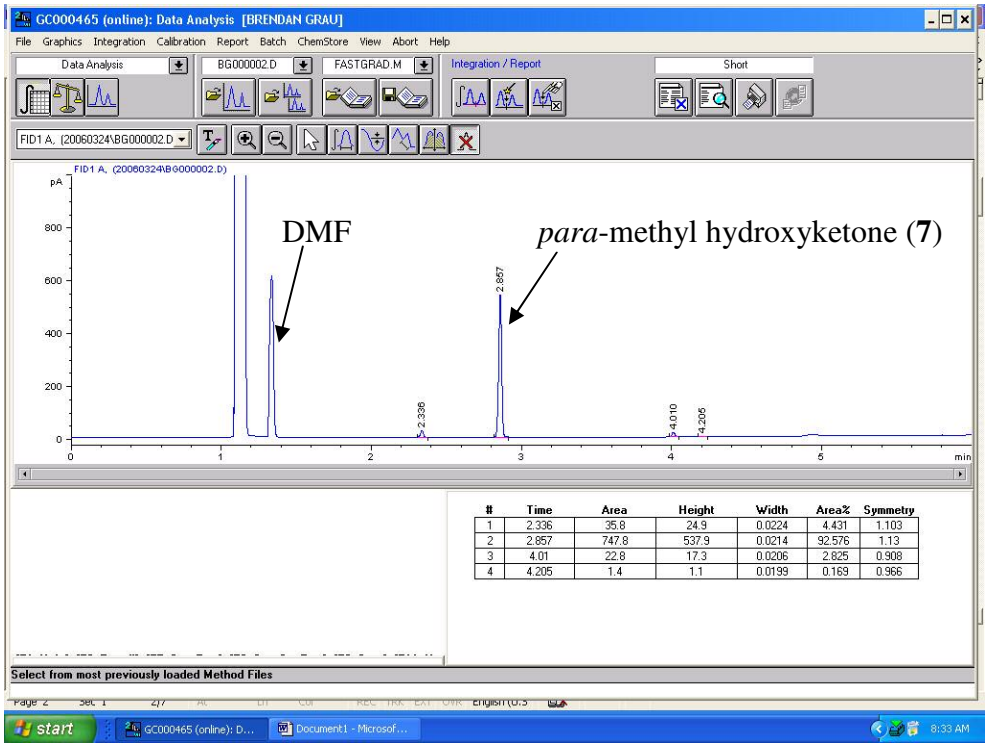
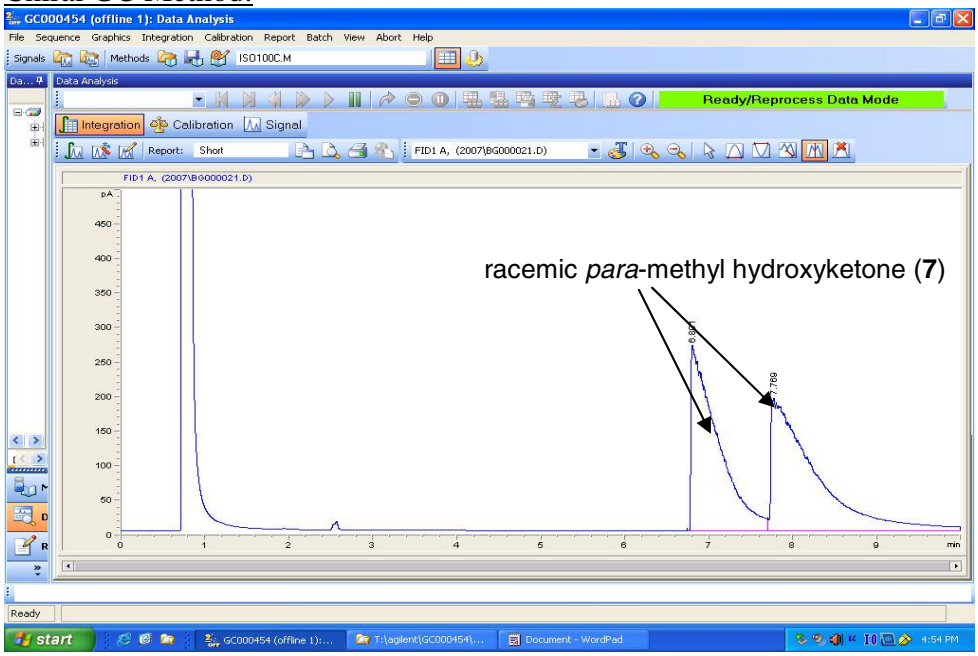
Time 16.24
INSTRUM spect
PROBHD 5 mm QNP 1H/19
PULPROG zgdc
TD 131072
SOLVENT CD3CN
NS 791
DS 4
SWH 40322.582 Hz
FIDRES 0.307637 Hz
AQ 1.6253428 sec
RG 8192
DW 12.400 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
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 125.7576539 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 220.000 ppm
F1 27666.69 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 9.36170 ppm/cm
7: p-methyl hydroxyketone
OH
F3C
O
7: ketone form
OH
F3C
HO
OH
7: hydrate form
ppm
200
180
160
140
120
100
80
60
40
20


Current Data Parameters
NAME 232427-999-g
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20061128
Time 16.14
INSTRUM spect
PROBHD 5 mm QNP 1H/19
PULPROG zgfhigqn
TD 131072
SOLVENT CD3CN
NS 16
DS 4
SWH 100000.000 Hz
FIDRES 0.762939 Hz
AQ 0.6554100 sec
RG 64
DW 5.000 usec
DE 6.00 usec
TE 300.0 K
D1 5.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 19F
P1 5.00 usec
PL1 -4.00 dB
SFO1 470.5217731 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 85.00 usec
PL2 12.00 dB
PL12 12.00 dB
SFO2 500.1325006 MHz
F2 - Processing parameters
SI 65536
SF 470.5926240 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 23.50 cm
CY 10.00 cm
F1P -44.308 ppm
F1 -20850.89 Hz
F2P -256.806 ppm
F2 -120850.88 Hz
PPMCM 9.04247 ppm/cm
7: p-methyl hydroxyketone
OH
F3C
O
7: ketone form
OH
F3C
HO
OH
7: hydrate form
ppm
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240

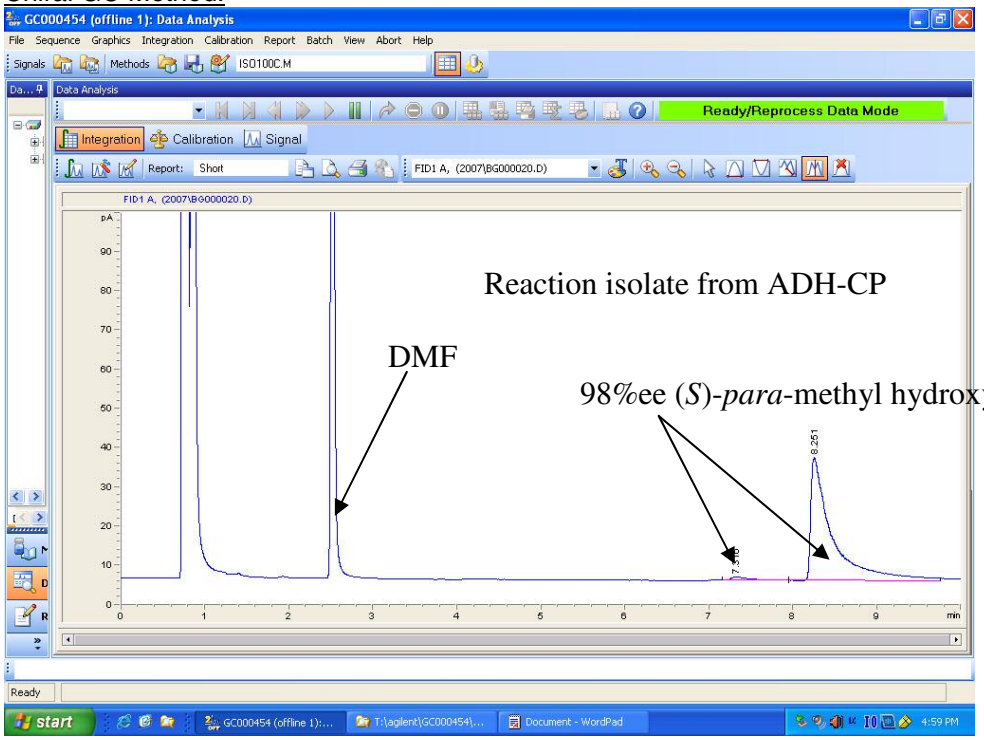
Achiral GC Method:



Chiral GC Method:

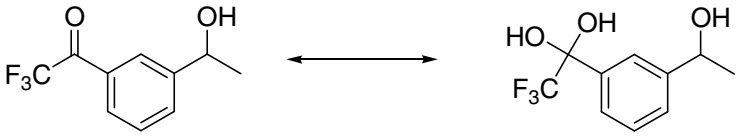


Chiral GC Method:



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

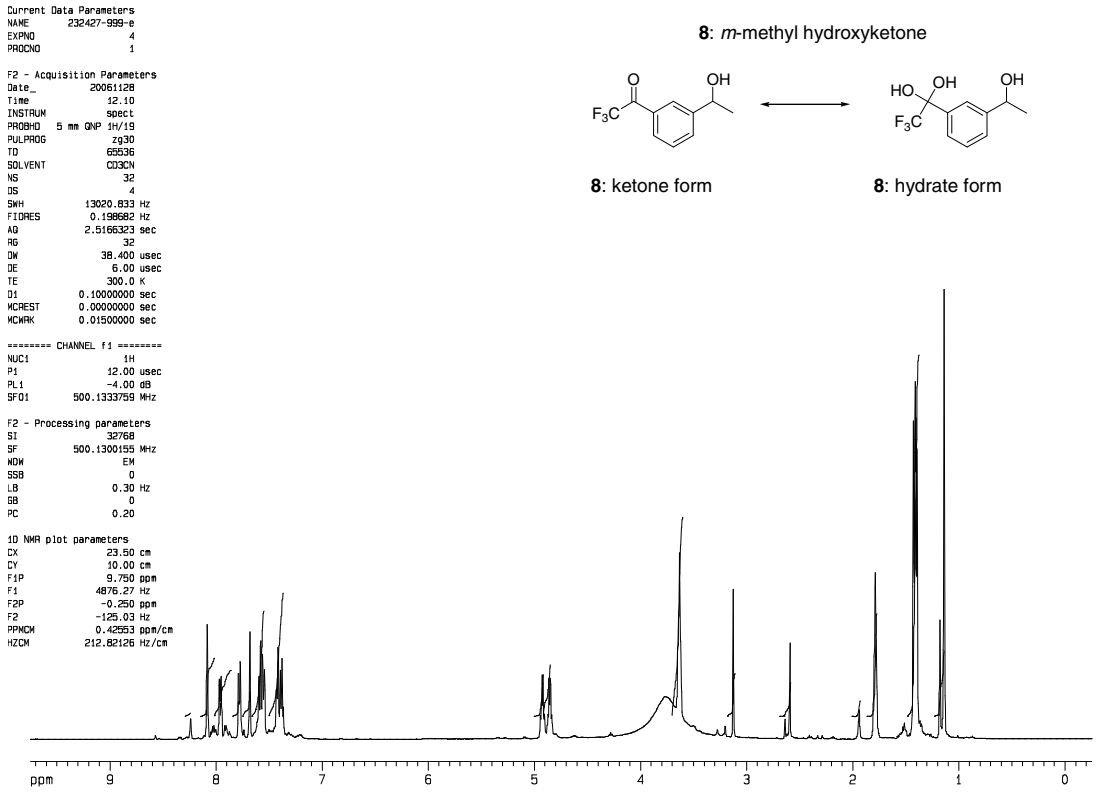
8: *m*-methyl hydroxyketone

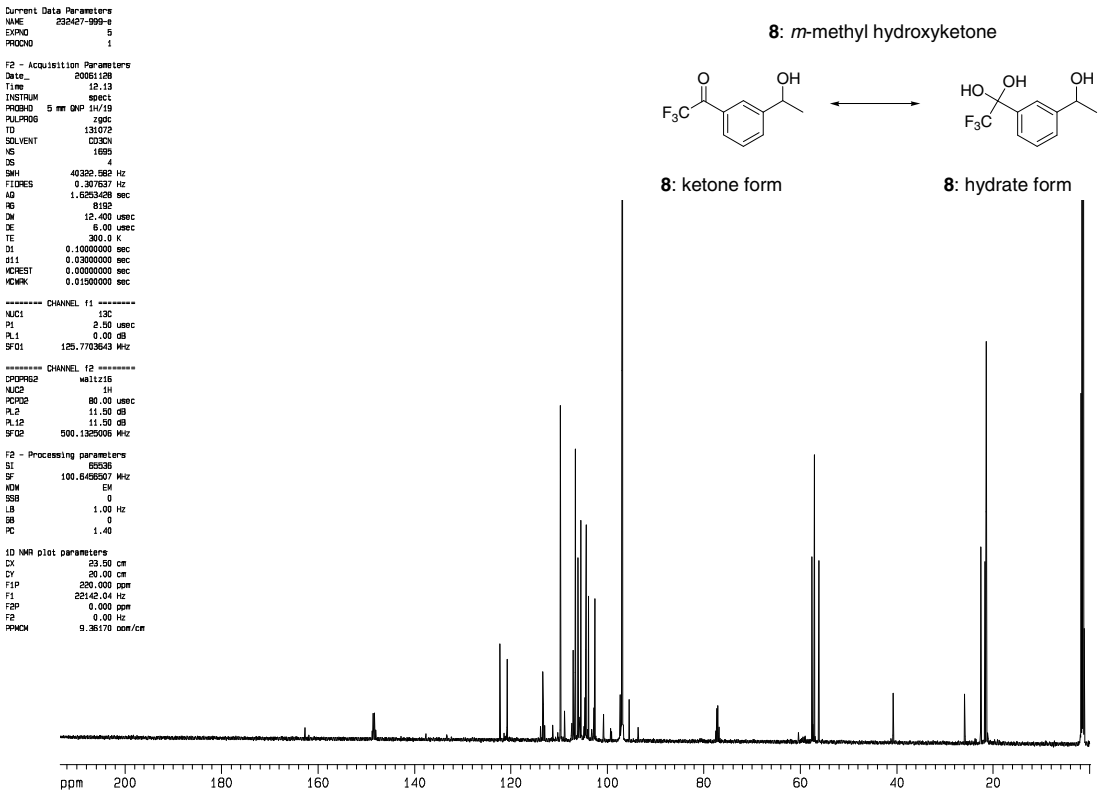


8: ketone form **8**: hydrate form

(hydrate form): ^{1}H NMR (500.13 MHz, CD_3CN) δ = 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}C NMR (500.13 MHz, CD_3CN) δ = 147.92, 138.33, 130.39, 128.99, 127.84, 126.84, 125.32, 94.50 (q, J_{CF} = 32.4 Hz), 69.5, 26.0 ppm. ^{19}F NMR (500.13 MHz, CD_3CN) δ = -85.36 ppm.

(ketone form): ^{1}H NMR (500.13 MHz, CD_3CN) δ = 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}F NMR (500.13 MHz, CD_3CN) δ = -72.70 ppm.

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PROCNO 1
F2 - Acquisition Parameters
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Time 12.13
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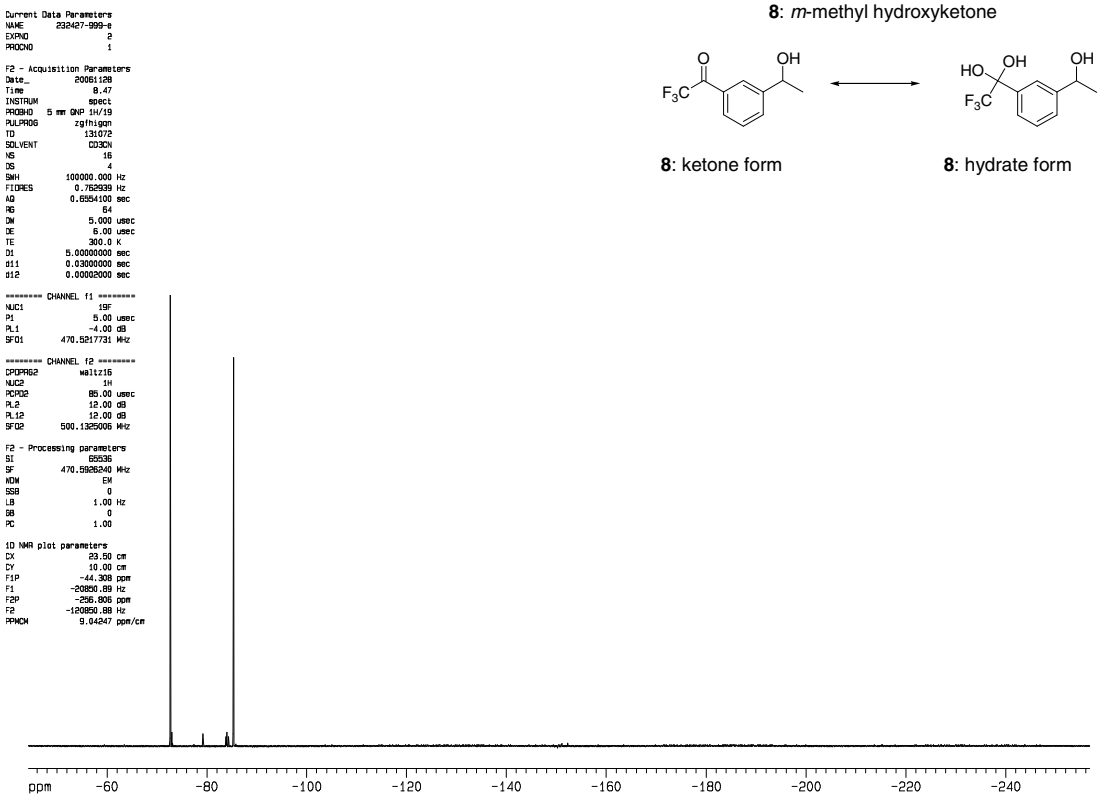
PROBHD 5 mm QNP 1H/19
PULPROG zgdc
TD 131072
SOLVENT CD3CN
NS 1695
DS 4
SWH 40322.582 Hz
FIDRES 0.307637 Hz
AQ 1.6253428 sec
RG 8192
DW 12.400 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 2.50 usec
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 100.6456507 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 23.50 cm
CY 20.00 cm
F1P 220.000 ppm
F1 22142.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 9.36170 ppm/cm
8: m-methyl hydroxyketone
8: ketone form
8: hydrate form
ppm 200 180 160 140 120 100 80 60 40 20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PROCNO 1
F2 - Acquisition Parameters
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Time 8.47
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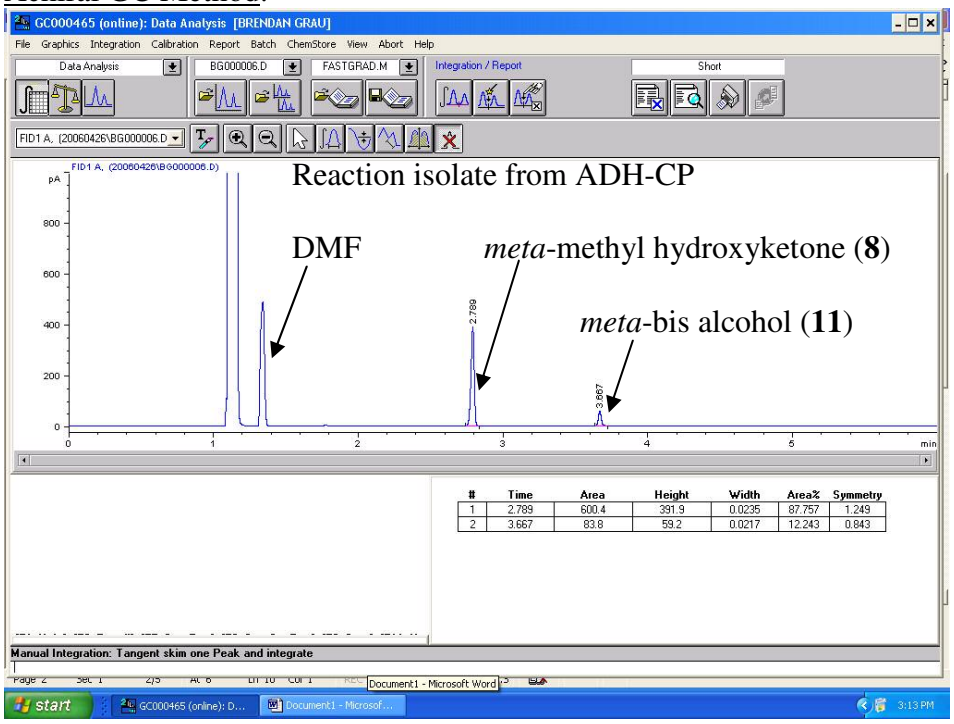
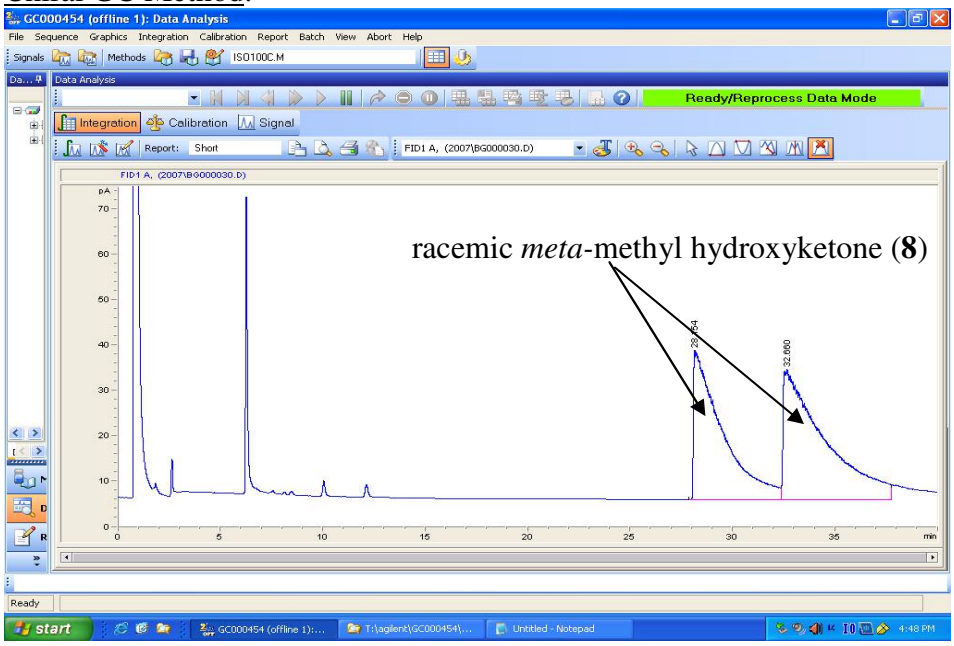
TD 131072
SOLVENT CD3CN
NS 16
DS 4
SWH 100000.000 Hz
FIDRES 0.762939 Hz
AQ 0.6554100 sec
RG 64
DW 5.000 usec
DE 6.00 usec
TE 300.0 K
D1 5.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 19F
P1 5.00 usec
PL1 -4.00 dB
SFO1 470.5217731 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 85.00 usec
PL2 12.00 dB
PL12 12.00 dB
SFO2 500.1325006 MHz
F2 - Processing parameters
SI 65536
SF 470.5926240 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 23.50 cm
CY 10.00 cm
F1P -44.308 ppm
F1 -20850.89 Hz
F2P -256.806 ppm
F2 -120850.88 Hz
PPMCM 9.04247 ppm/cm
8: m-methyl hydroxyketone
8: ketone form
8: hydrate form
ppm -60 -80 -100 -120 -140 -160 -180 -200 -220 -240

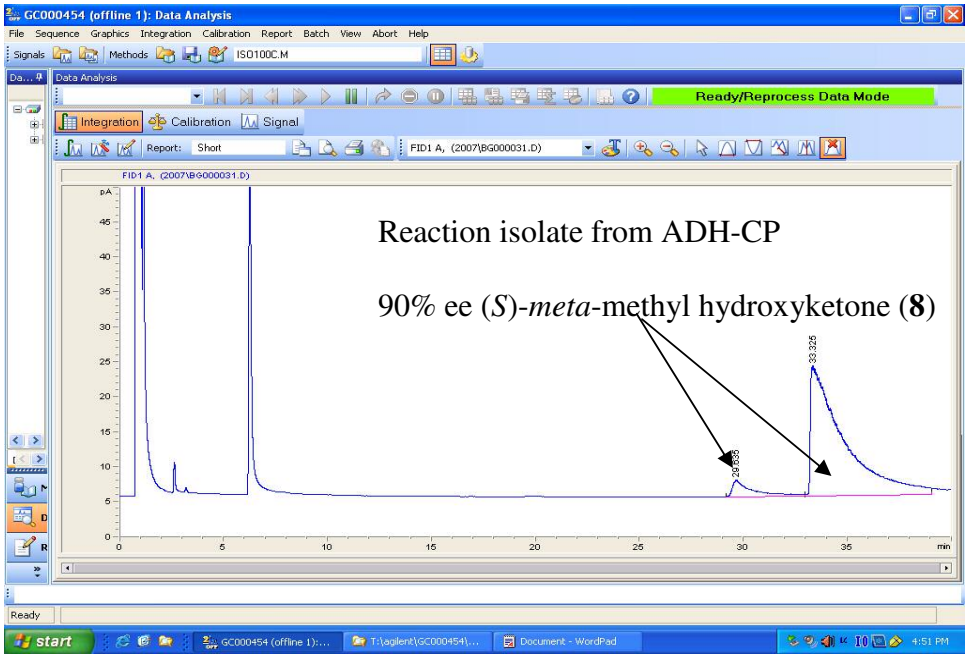
Achiral GC Method:



Chiral GC Method:



Chiral GC Method:

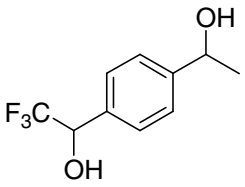


Section 12: Synthesis of bis alcohol **10** and **11**.

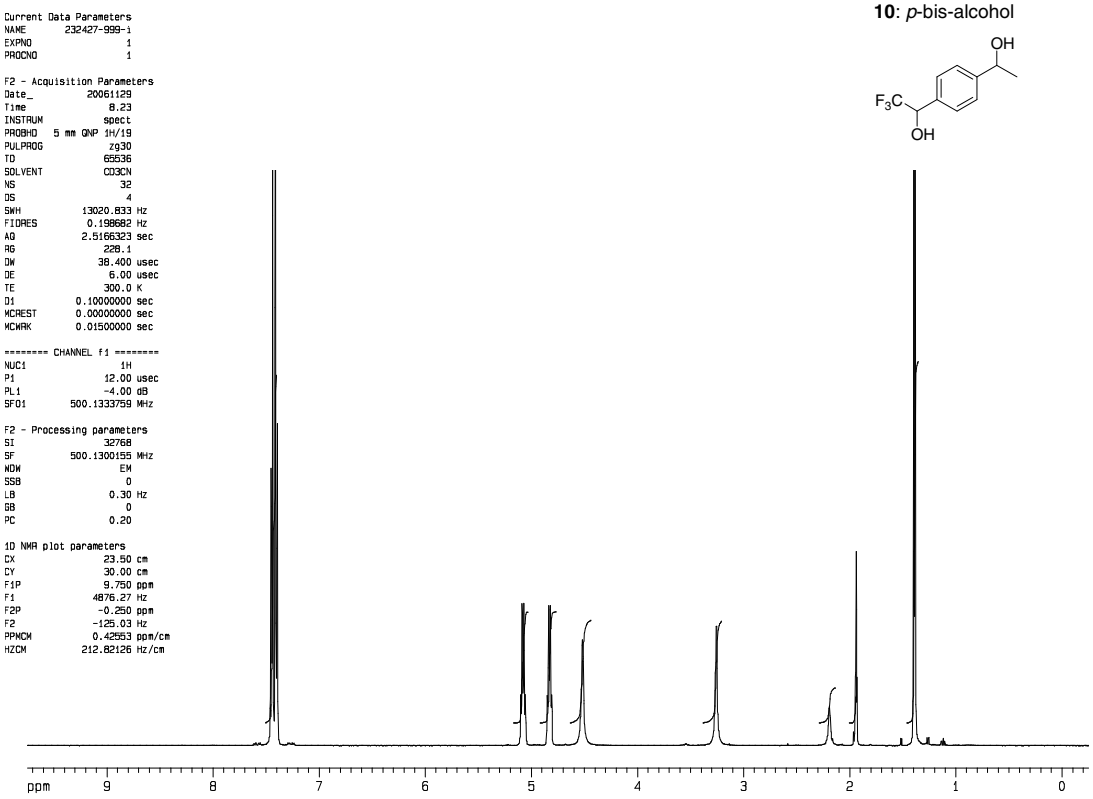
The bis alcohol standards for **10** and **11** were made by reacting the diketones with excess sodium borohydride. No reaction was observed on compound **3a**.

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

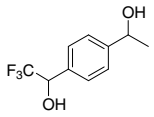
10: *p*-bis-alcohol



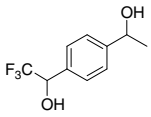
10: ^{1}H NMR (500.13 MHz, CD_3CN) δ = 7.45 (m, 2H), 7.40 (m, 2H), 5.08 (m, 1H), 4.83 (m, 1H), 4.52 (brs, 1H), 3.26 (brs, 1H), 1.39 (d, J = 6.36, 3H) ppm. ^{13}C NMR (500.13 MHz, CD_3CN) δ = 148.04 [148.04], 133.79 [133.79], 127.45 (2C) [127.45 (2C)], 125.37 (2C) [125.37 (2C)], 125.00 (q, J_{CF} = 281.2 Hz) [125.00 (q, J_{CF} = 281.2 Hz)], 71.22 (q, J_{CF} = 31.4 Hz) [71.20 (q, J_{CF} = 30.8 Hz)], 68.81 [68.78], 24.90 [24.90] ppm. ^{19}F NMR (500.13 MHz, CD_3CN) δ = -79.28 ppm.



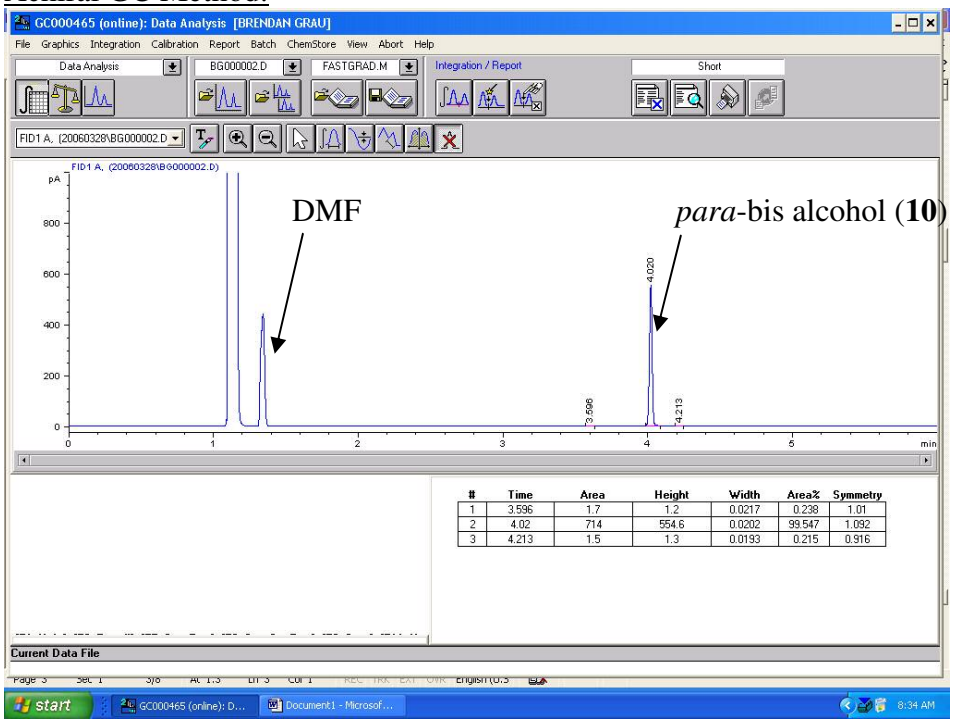
10: *p*-bis-alcohol



10: *p*-bis-alcohol

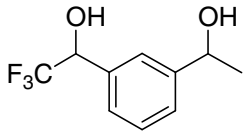


Achiral GC Method:

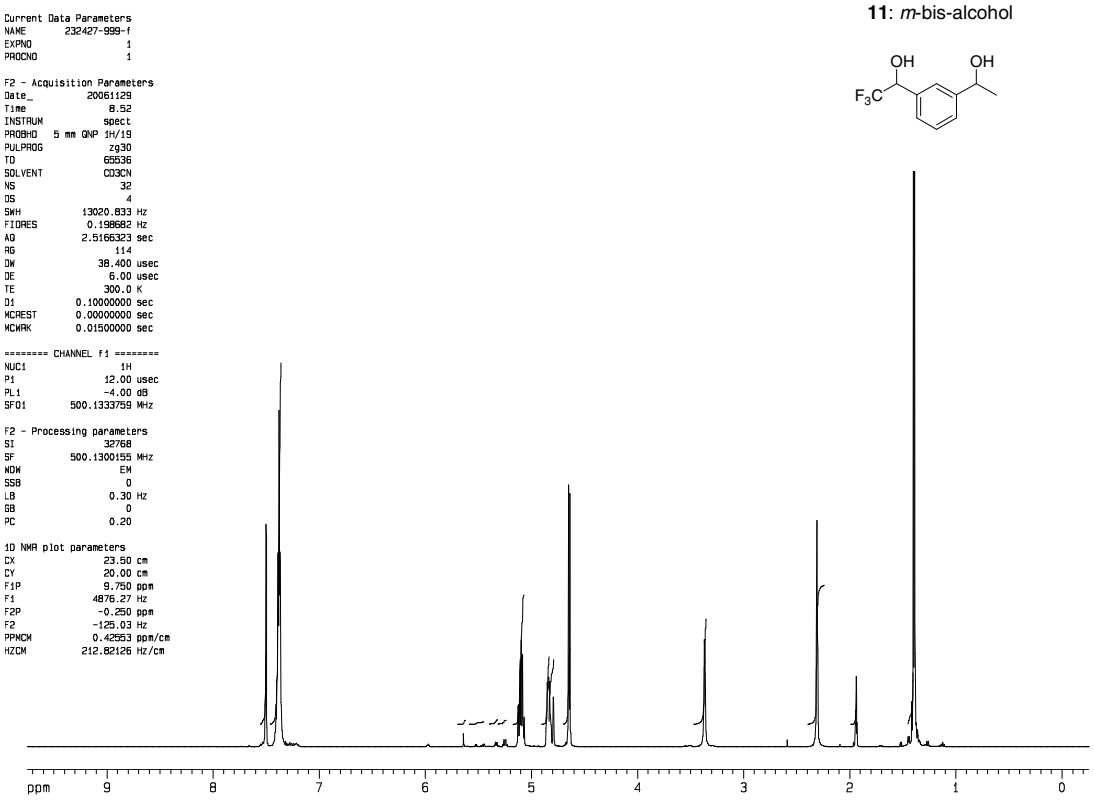


Section 14: *meta* bis-alcohol **11**

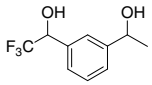
11: *m*-bis-alcohol



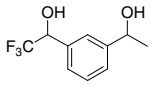
11: ^{1}H NMR (500.13 MHz, CD_3CN) δ = 7.50 (s, 1H), 7.38 (m, 3H), 5.10 (m, 1H), 4.84 (m, 1H), 4.64 (d, J = 5.56, 1H), 3.37 (d, J = 3.58, 1H), 1.39 (d, J = 6.36, 3H) ppm. ^{13}C NMR (500.13 MHz, CD_3CN) δ = 148.28 [148.28], 136.30 [136.30], 129.37 (2C) [129.37 (2C)], 127.26 [127.19], 125.67 [125.63], 126.08 (q, J_{CF} = 281.8 Hz) [126.08 (q, J_{CF} = 281.8 Hz)], 70.03 [70.00], 72.52 (q, J_{CF} = 30.8 Hz) [72.52 (q, J_{CF} = 30.8 Hz)], 26.04 [26.02] ppm. ^{19}F NMR (500.13 MHz, CD_3CN) δ = -79.20 ppm.



11: *m*-bis-alcohol



11: *m*-bis-alcohol



Achiral GC Method: