

Synthesis and Reduction Reactions of Pyridones and 5-Acyl-2-Methoxypyridines

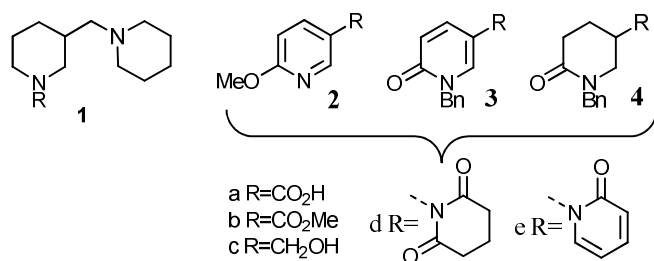
Alexander A. Bisset,^a Allan Dishington,^b Teyrnnon Jones,^b Guy J. Clarkson^a and Martin Wills^{a*}

^a *Department of Chemistry, The University of Warwick, Coventry, CV4 7AL UK.*

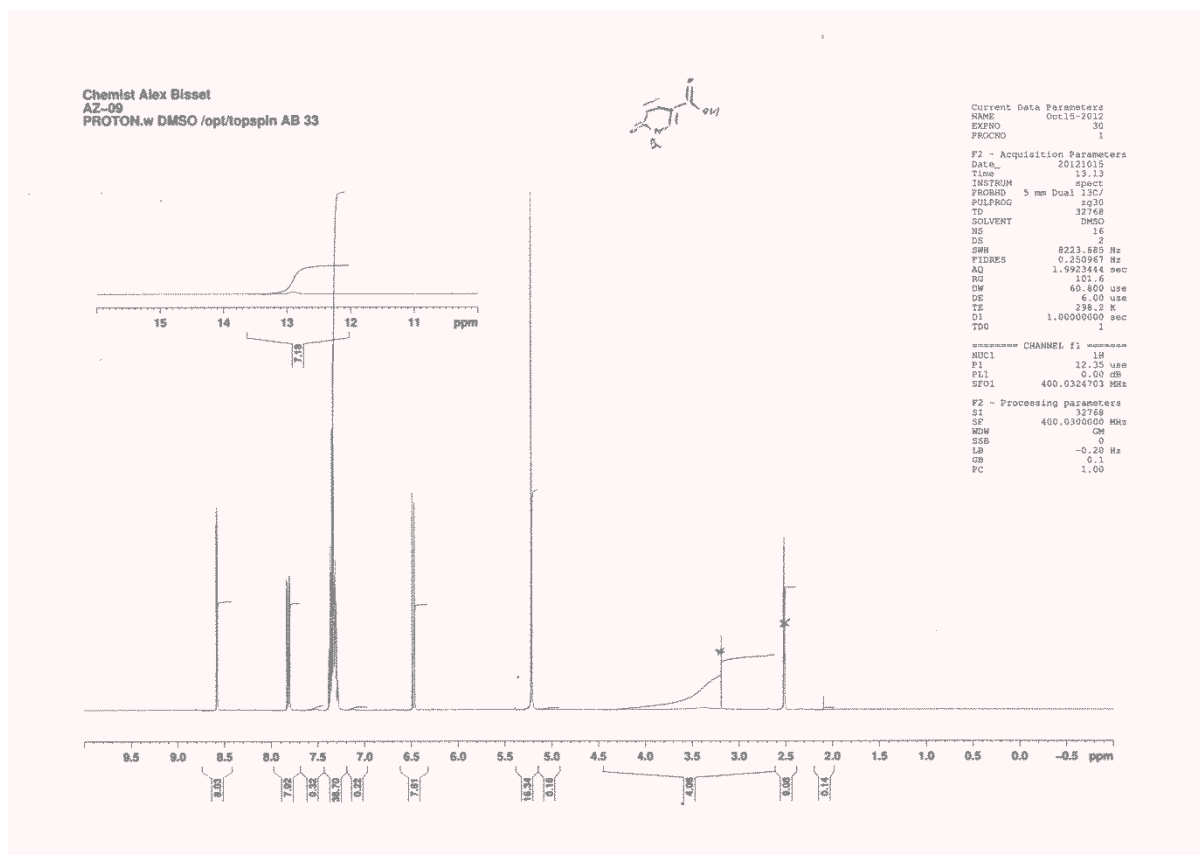
^b *AstraZeneca, Oncology Innovative Medicines, Alderley Park, Macclesfield, Cheshire, England. SK10 4TG, UK*

* Corresponding author. Tel: (+44) 24 7652 3260; Fax: (+44) 24 7652 4112; E-mail: m.wills@warwick.ac.uk.

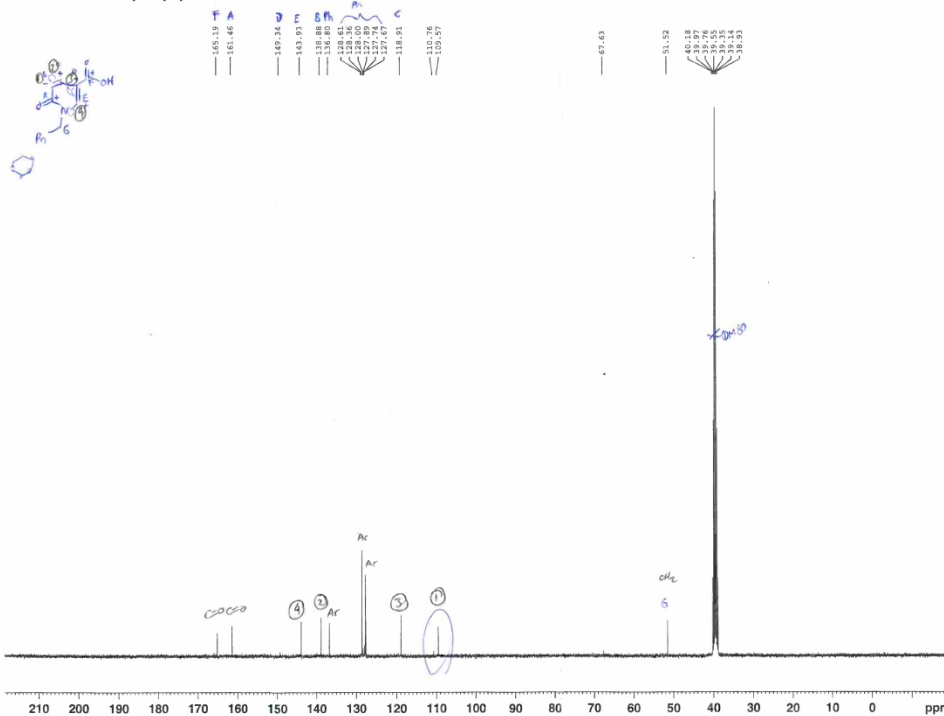
NMR spectra of intermediates and products.



1-Benzyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid, **3a**.



Name A Bisset
 M No krtw983
 Notebook Ref EN05661-09
 carbon.az DMSO /opt/topspin2.1 chem 30



AstraZeneca

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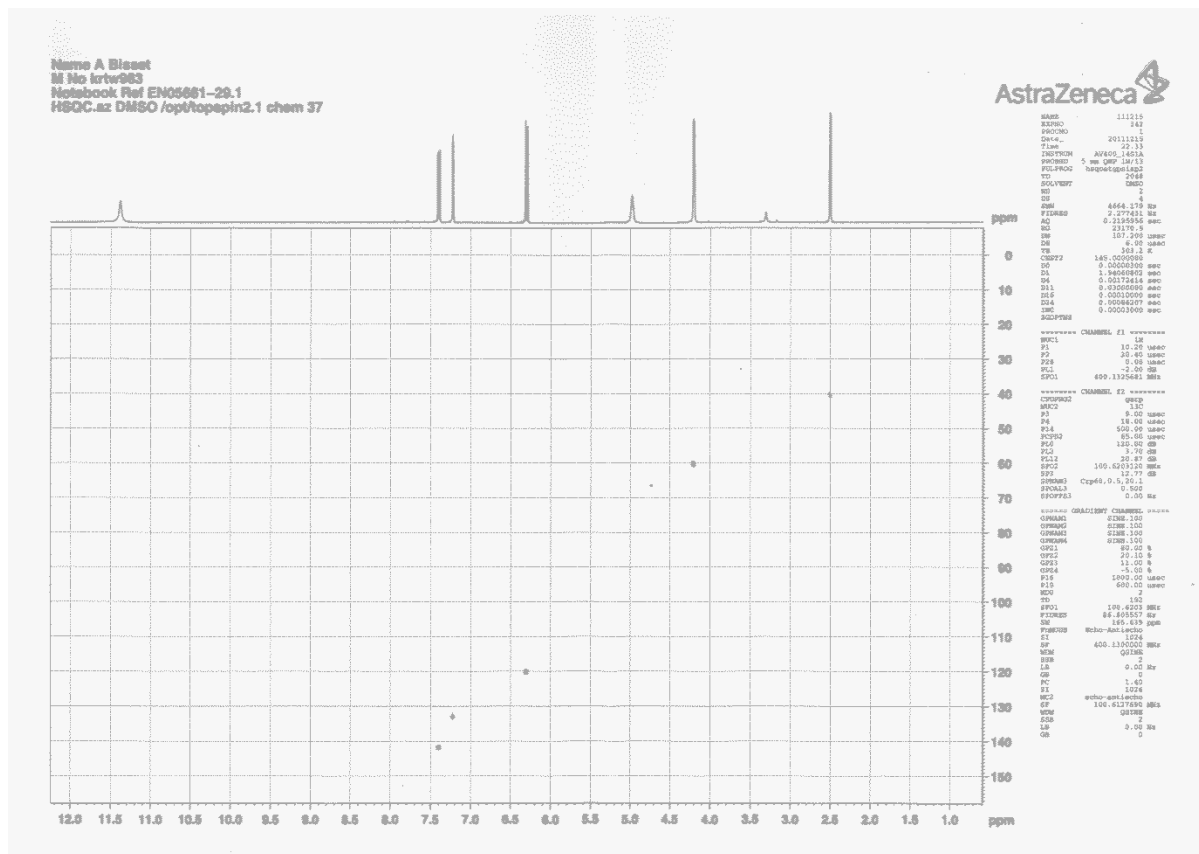
NAME      111007
EXPNO    300
PROCNO   1
PROCNO   20111007
Time     20.44
INSTRUM  AV400_1401A
PROBHD   5 mm QNP 1H/13
PULPROG  zgpg30
TD        65536
SOLVENT  DMSO
NS        800
DS        4
SWH       23980.814 Hz
FIDRES   0.365918 Hz
AQ        1.3664756 sec
RG        26008
DW        20.850 usec
DE        20.00 usec
TE        303.2 K
D1        2.0000000 sec
D11       0.0300000 sec
TDO       10

===== CHANNEL f1 =====
NUC1      13C
P1        9.00 usec
PL1       3.70 dB
SFO1     100.6282028 MHz

===== CHANNEL f2 =====
CPDPRG2  waltz16
NUC2      1H
PCPD2    80.00 usec
PL2       -2.00 dB
PL12     15.89 dB
PL13     15.00 dB
SFO2     400.1316005 MHz
SI        32768
SF        100.6182193 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40

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Methyl 6-methoxynicotinate, **2b** in DMSO.



AstraZeneca

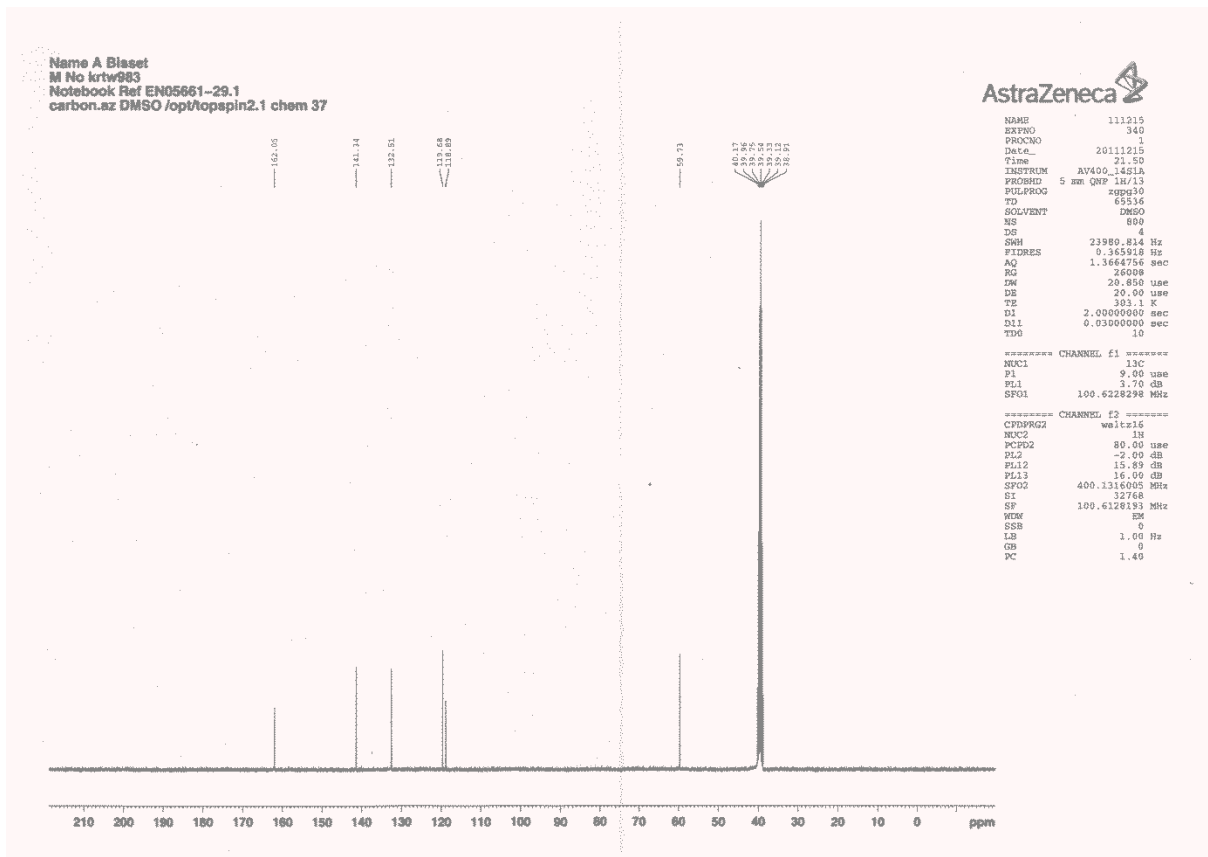
Name A Bisset
 M No krtw983
 Notebook Ref EN05661-20.1
 HSQC.az DMSO /opt/topspin2.1 chem 37

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NAME      111115
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PROCNO   1
PROCNO   20111115
Time     20.44
INSTRUM  AV400_1401A
PROBHD   5 mm QNP 1H/13
PULPROG  zgpg30
TD        65536
SOLVENT  DMSO
NS        800
DS        4
SWH       4644.179 Hz
FIDRES   0.2195956 Hz
AQ        0.2195956 sec
RG        151.208 usec
DW        6.00 usec
DE        383.1 K
TE        303.2 K
D1        145.0000000 sec
D11       0.0300000 sec
D12       1.3400000 sec
D13       0.03176416 sec
D14       0.03000000 sec
D15       0.00010000 sec
D16       0.00088207 sec
D17       0.00013000 sec
D18       0.00013000 sec
D19       0.00013000 sec
D20       0.00013000 sec
===== CHANNEL f1 =====
NUC1      13C
P1        15.00 usec
PL1       3.70 dB
SFO1     100.6282028 MHz

===== CHANNEL f2 =====
CPDPRG2  waltz16
NUC2      1H
PCPD2    80.00 usec
PL2       -2.00 dB
PL12     15.89 dB
PL13     15.00 dB
SFO2     400.1316005 MHz
SI        32768
SF        100.6182193 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40

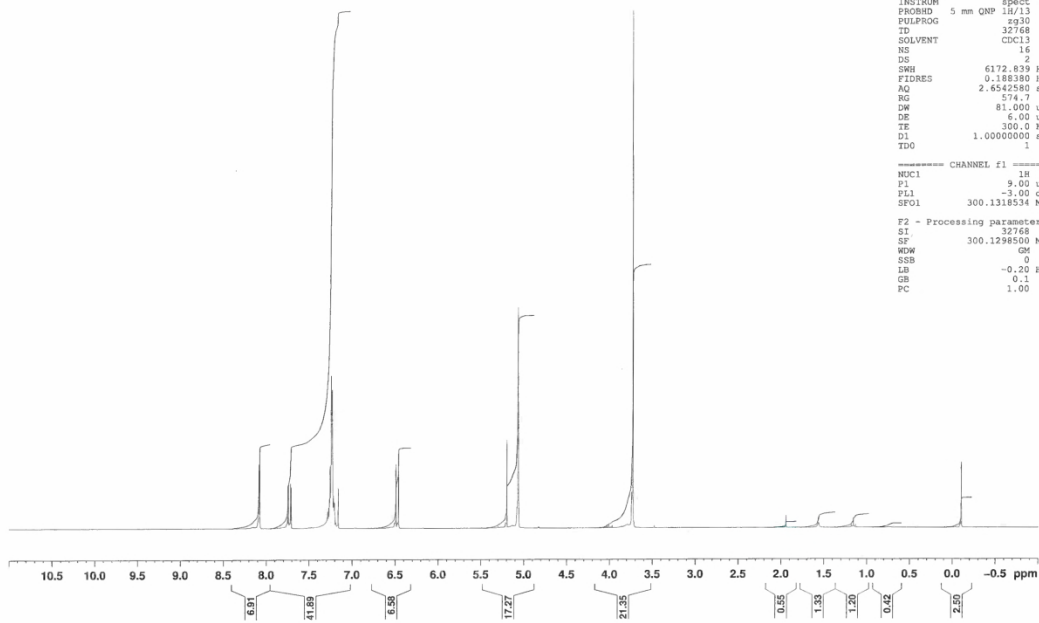
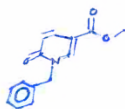
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Methyl 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylate, **3b**.

Chemist Alex Bisset
ALX365
PROTON.w CDCI3 /opt/topspin AB 46

purified.



```
Current Data Parameters
NAME      Feb09-2012
EXPNO    00
PROCNO    1

F2 - Acquisition Parameters
Date_     20120209
Time      14.38
INSTRUM   spect
PROBHD    5 mm QNP 1H/13
PULPROG   zg30
TD         32768
SOLVENT   CDCl3
NS         16
DS         2
SWH        6172.839 Hz
FIDRES     0.188280 Hz
AQ         2.8542580 sec
RG         574.7
DW         81.000 use
DE         6.00 use
TE         300.0 K
D1         1.0000000 sec
TDO        1

----- CHANNEL f1 -----
NUC1       1H
P1         9.00 use
PL1        -3.00 dB
SFO1       300.1318534 MHz

F2 - Processing parameters
SI         32768
SF         300.1298500 MHz
WDW        EM
SSB        0
LB         -0.20 Hz
GB         0.1
PC         1.00
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Chemist Alex Bisset
ALX365
C13depiq.w CDCI3 /opt/topspin AB 14

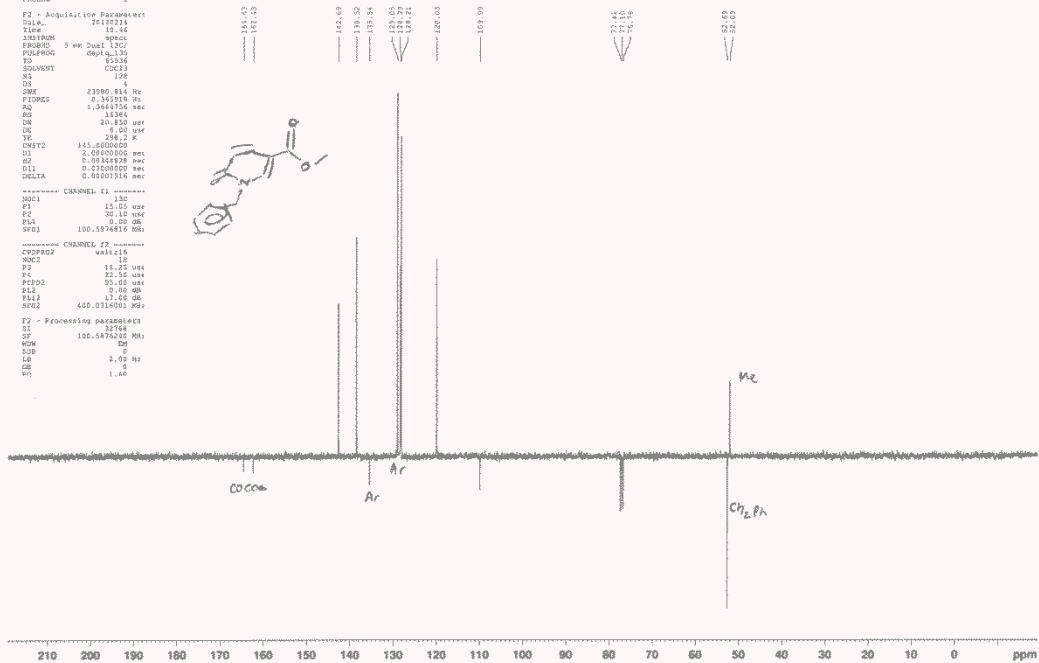
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EXPNO    10
PROCNO    10

F2 - Acquisition Parameters
Date_     20120216
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INSTRUM   spect
PROBHD    5 mm QNP 1H/13
PULPROG   dprg13
TD         65536
SOLVENT   CDCl3
NS         16
DS         4
SWH        23980.814 Hz
FIDRES     0.365310 Hz
AQ         1.3664756 sec
RG         1284
DW         20.830 use
DE         6.00 use
TE         298.2 K
CNET2     145.0000000
D1         2.0000000 sec
d2         0.0938428 sec
D11        0.0100000 sec
DELTA     0.0000314 sec

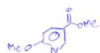
----- CHANNEL f1 -----
NUC1       13C
P1         15.00 use
PL1        0.00 dB
SFO1       100.627616 MHz

----- CHANNEL f2 -----
CPDPRG2   waltz16
NUC2       13C
P2         15.25 use
PL2        21.50 use
P3         95.00 use
PL3        0.00 dB
PL4        17.50 dB
SFO2       125.7611701 MHz

F2 - Processing parameters
SI         65536
SF         100.627616 MHz
WDW        EM
SSB        0
LB         2.00 Hz
GB         0
PC         1.60
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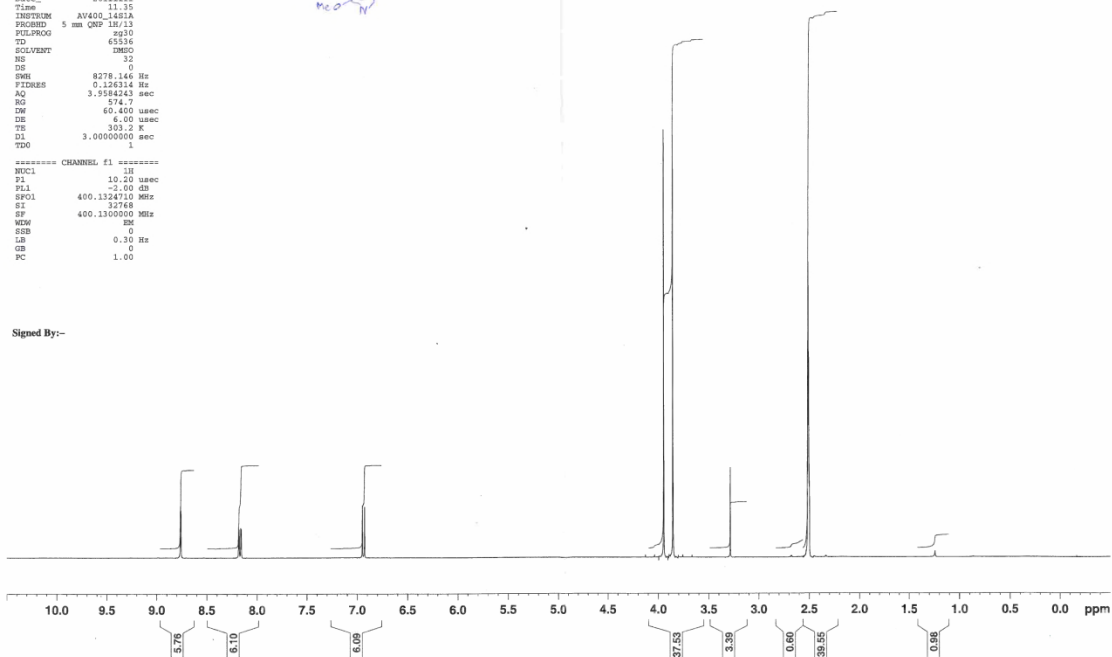
(6-Methoxyphenyl)pyridin-3-ylmethanol, 2c.



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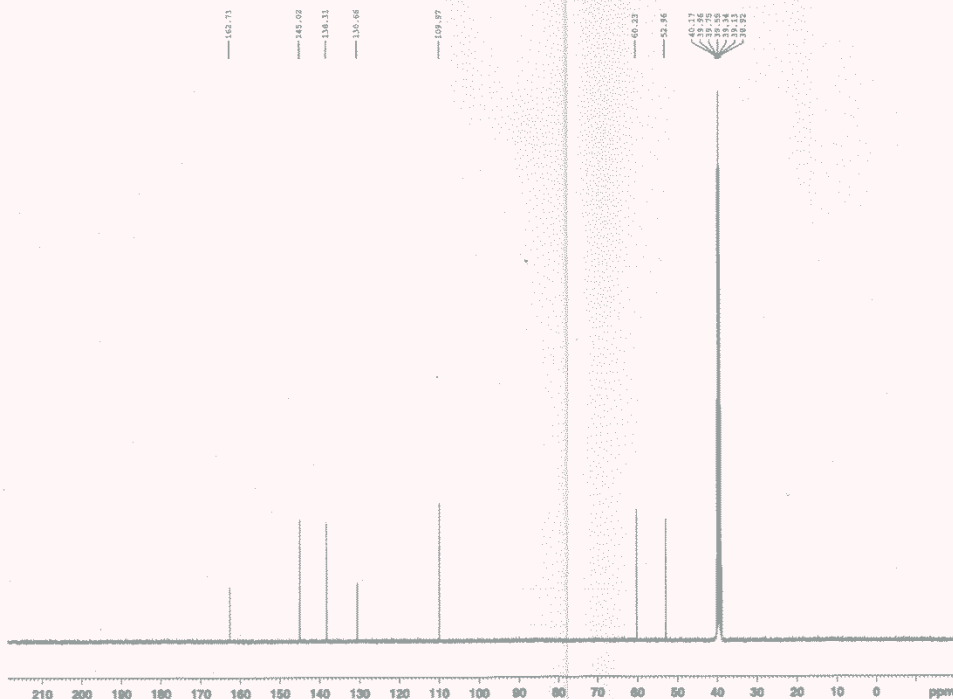
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EXPNO         70
PROCNO        1
Date_         20111111
Time         11.35
INSTRUM       AV400_14651A
PROBHD        5 mm QNP 1H/13
PULPROG       zgpg30
TD            65536
SOLVENT       DMSO
NS            32
DS            0
SWH           8278.146 Hz
FIDRES        0.126314 Hz
AQ           3.9594243 sec
RG            574.7
DM           60.400 usec
DE           6.00 usec
TE           303.2 K
D1           3.0000000 sec
TDO          1
===== CHANNEL f1 =====
NUC1          1H
P1           10.20 usec
PL1          -2.00 dB
SFO1         400.1324710 MHz
SI           32768
SF           400.1300000 MHz
WDW          EM
SSB          0
LB           0.30 Hz
GB           0
PC           1.00
    
```

Signed By:-



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NAME          111214
EXPNO         220
PROCNO        1
Date_         20111214
Time         20.29
INSTRUM       AV400_14651A
PROBHD        5 mm QNP 1H/13
PULPROG       zgpg30
TD            65536
SOLVENT       DMSO
NS            4
DS            4
SWH           23980.814 Hz
FIDRES        0.365918 Hz
AQ           1.3648756 sec
RG           26008
DM           20.850 usec
DE           20.00 usec
TE           303.2 K
D1           2.0000000 sec
D11          0.0300000 sec
TDO          10
===== CHANNEL f1 =====
NUC1          13C
P1           9.00 usec
PL1          3.70 dB
SFO1         100.6228298 MHz
===== CHANNEL f2 =====
CPDPRG2       waltz16
NUC2          1H
PCPD2         80.00 usec
PL2          -2.00 dB
PL12         15.89 dB
PL13         16.00 dB
SFO2         400.1316005 MHz
SI           32768
SF           100.6129193 MHz
WDW          EM
SSB          0
LB           1.00 Hz
GB           0
PC           1.40
    
```



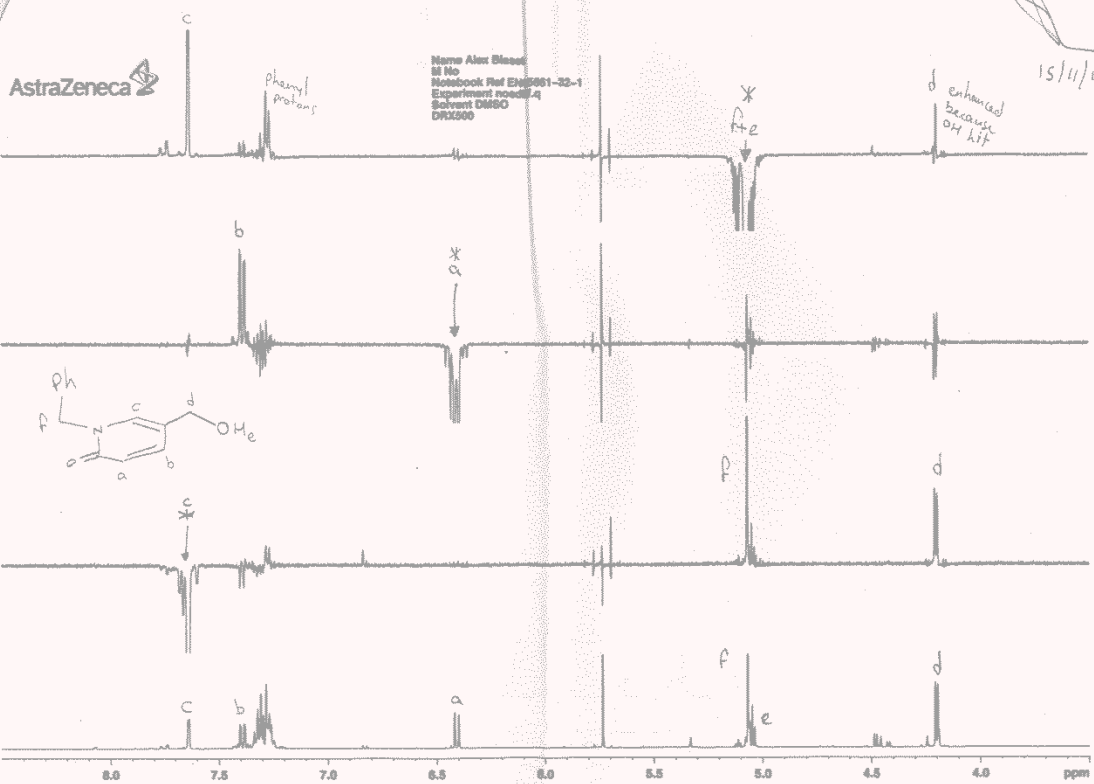
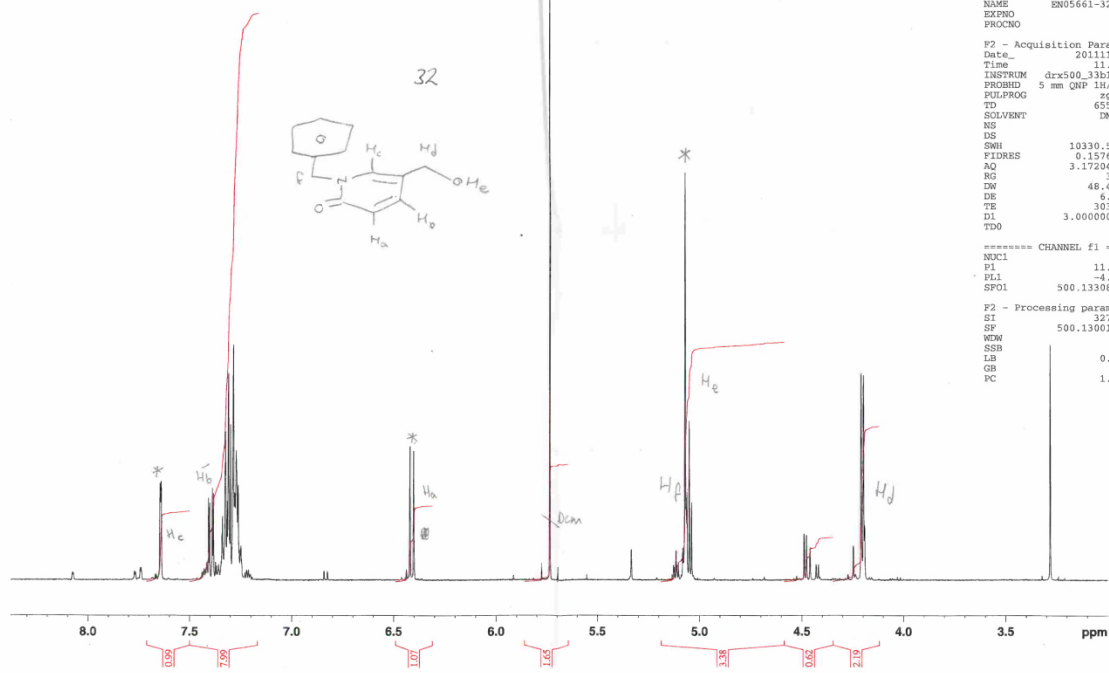
1-Benzyl-5-(hydroxymethyl)pyridin-2(1H)-one, 3c .

Current Data Parameter
NAME EN05661-32-
EXPNO
PROCNO

F2 - Acquisition Param
Date_ 201111
Time 11.2
INSTRUM drx500_33b15
PROBHD 5 mm QNP 1H/1
PULPROG zg3
TD 6552
SOLVENT DMS
NS 1
DS
SWH 10330.57
FIDRES 0.15765
AQ 3.17294C
RG 36
DW 48.4C
DE 8.4
TE 303.
DL 3.000000C
TDO

===== CHANNEL f1 ==
NUC1 1
P1 11.5
PL1 -1.5
SFO1 500.133086

F2 - Processing param
SI 3276
SF 500.13001C
WDW F
SSB 0.0
LB GB
PC 1.0



Chemist Alex Bisset
ALX443
C13deptq.w CDCI3 /opt/topspin AB 18

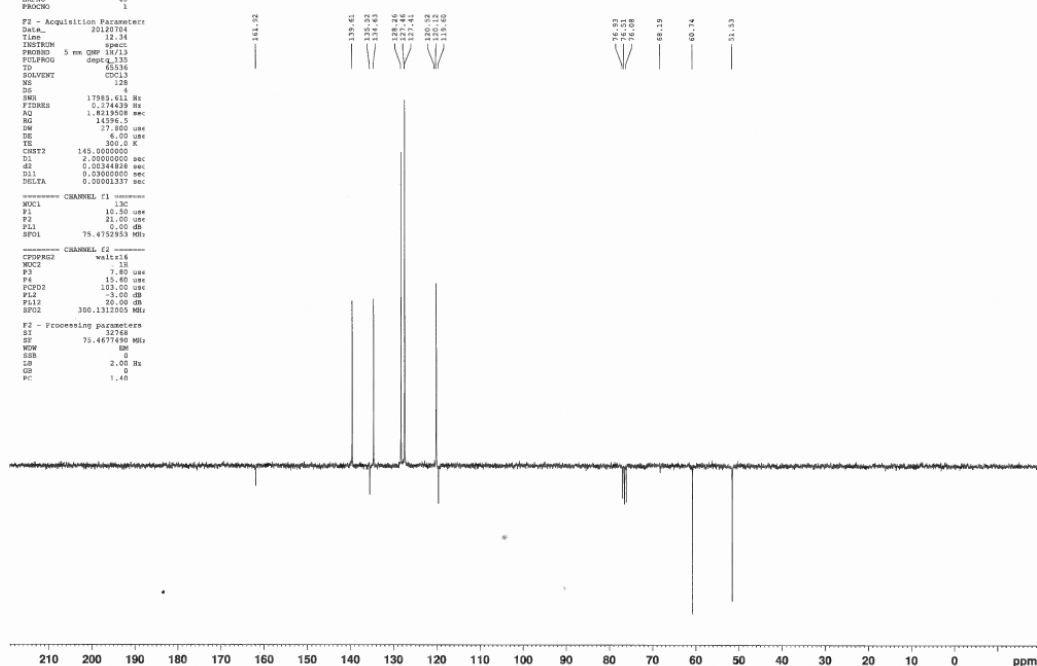
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Current Data Parameters
NAME      Jan07-2012
EXPNO    40
PROCNO   1
F2 - Acquisition Parameters
Date_    20120704
Time     12.34
INSTRUM  spect
PROBHD   5 mm QNP 1H/13
PULPROG  zgpg30
TD        65536
SOLVENT  CDCl3
NS        128
DS        4
SWH       17989.611 Hz
FIDRES   0.274428 Hz
AQ        1.8218500 sec
RG         345
DM         27.800 use
DE         6.00 use
TE        300.2 K
C13T2    2.0000000 sec
d2        0.0034828 sec
d31       0.0000000 sec
DELTA     0.0001337 sec

===== CHANNEL f1 =====
NUC1      13C
P1        10.50 use
PC1       21.00 use
PL1       0.00 dB
SFO1      75.4750263 MHz

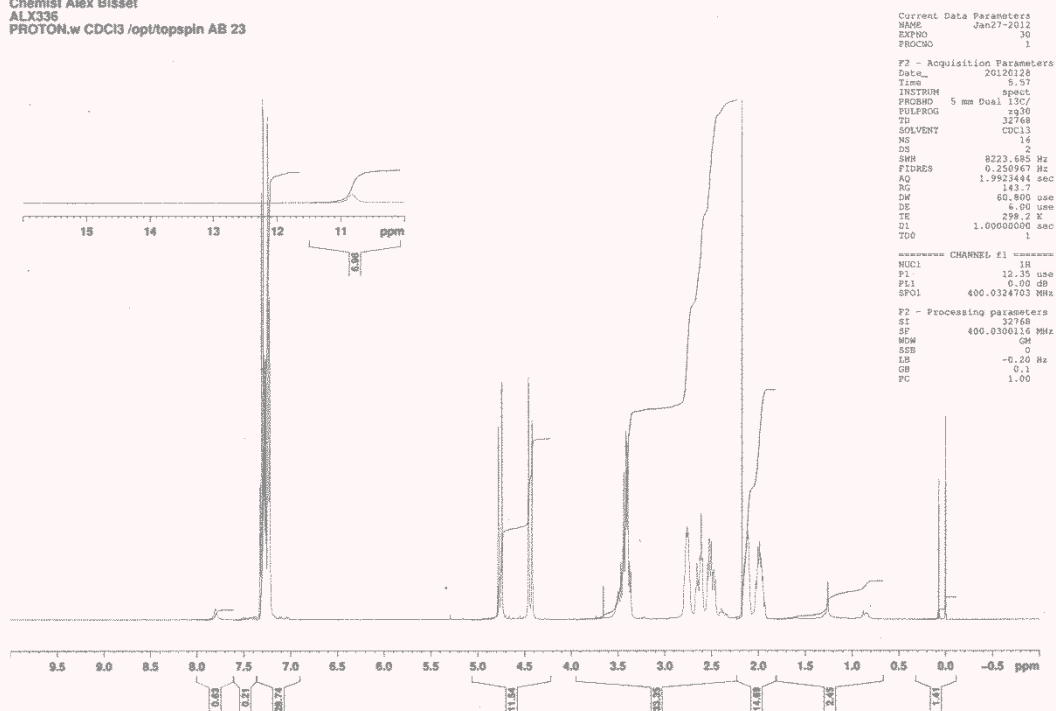
===== CHANNEL f2 =====
CFOPROG2  waltz16
NUC2      1H
P2        7.80 use
PC2       13.00 use
PL2       0.00 dB
PL12      3.00 dB
PL13      20.00 dB
SFO2      300.1312004 MHz

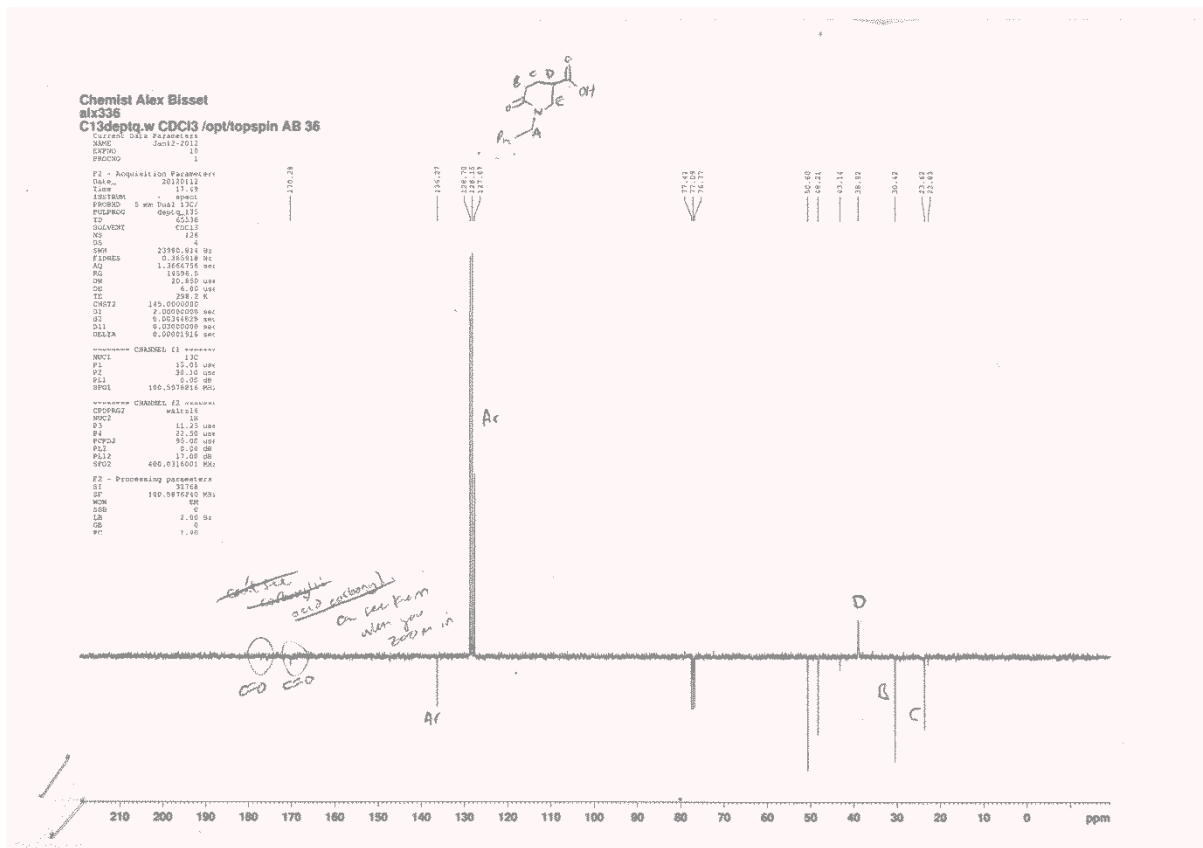
F2 - Processing parameters
SI        32768
SF        400.0324703 MHz
WDW       EM
SSB       0
LB        -0.20 Hz
GB        0.1
PC        1.00
  
```



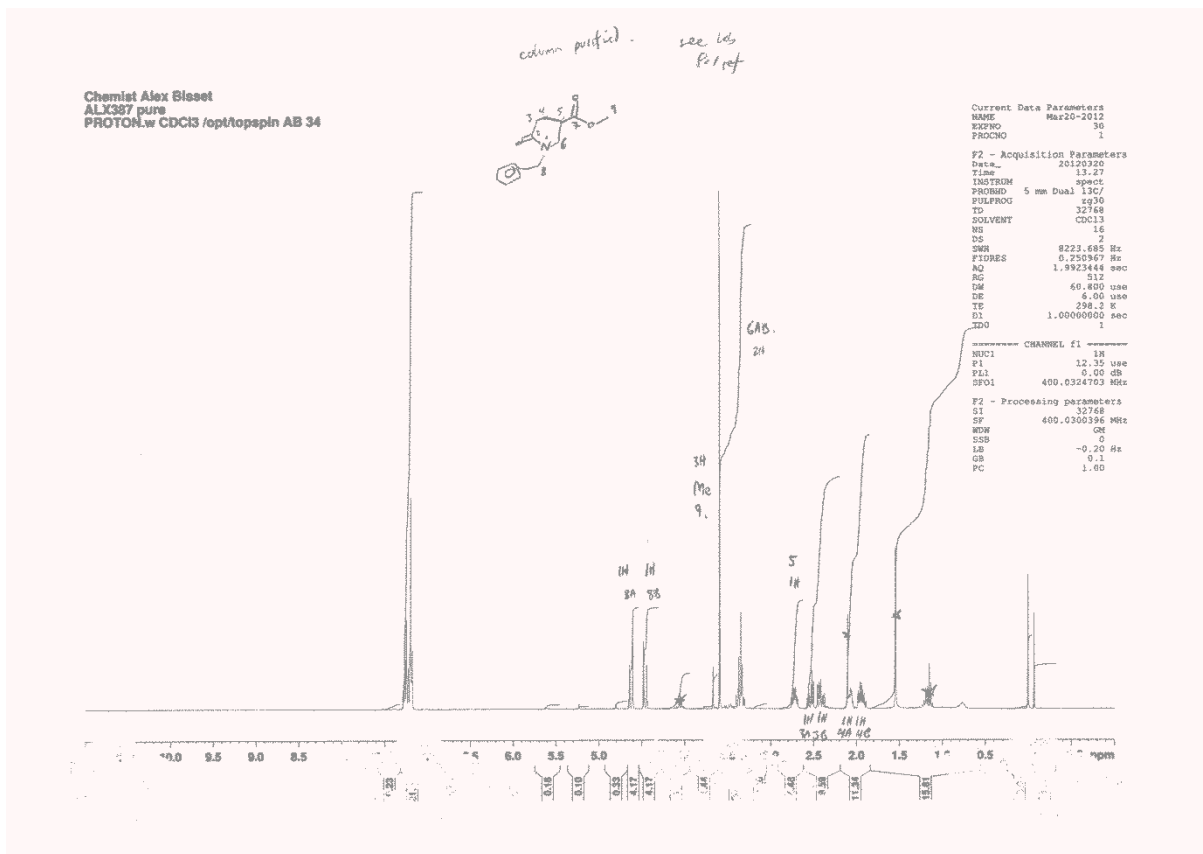
1-Benzyl-6-oxopiperidine-3-carboxylic acid, (\pm)-4a.

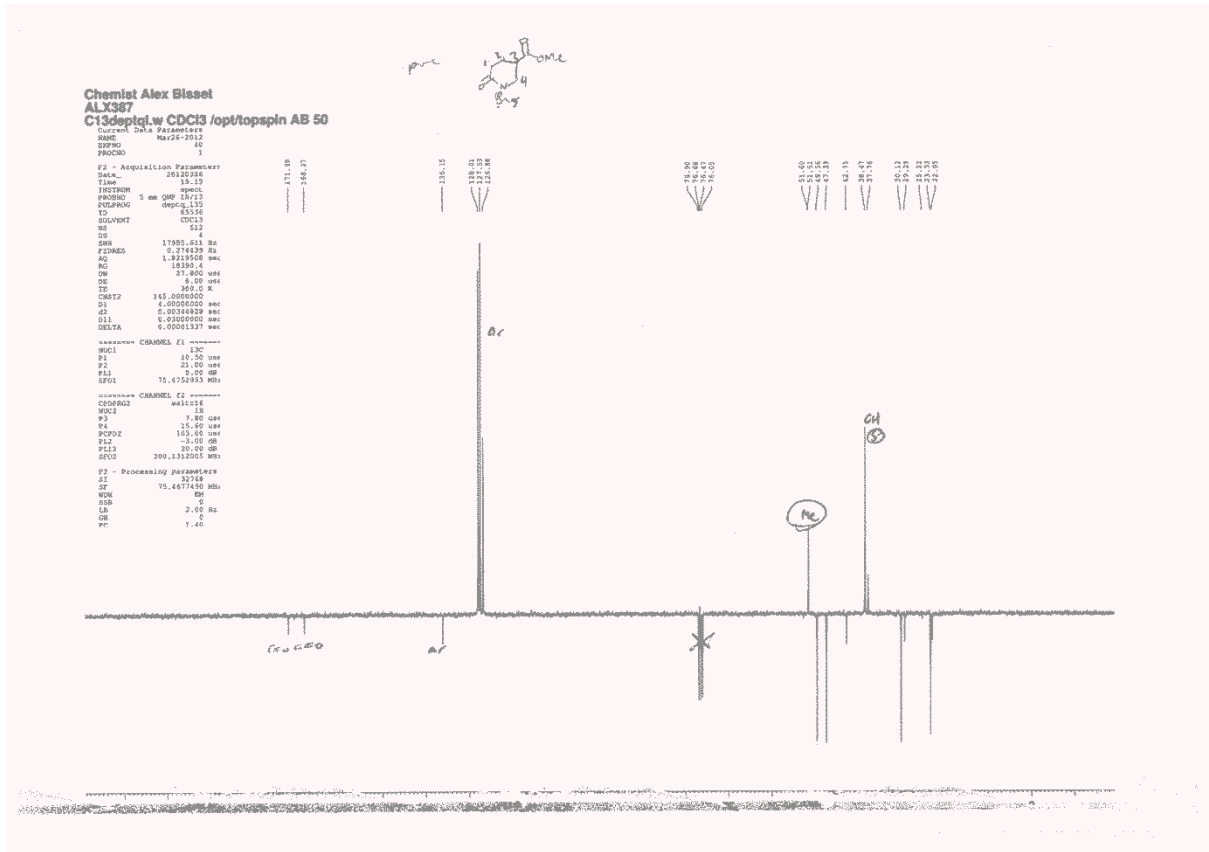
Chemist Alex Bisset
ALX336
PROTON.w CDCI3 /opt/topspin AB 23





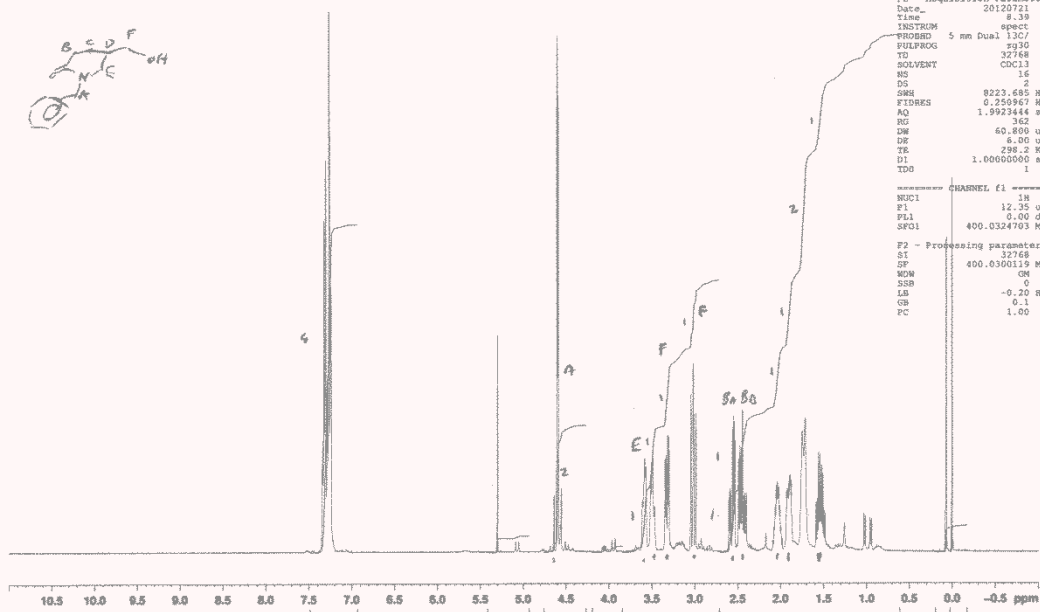
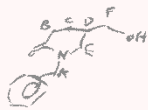
Methyl 1-benzyl-6-oxopiperidine-3-carboxylate, (\pm)-**4b**.





1-Benzyl-3-hydroxymethyl 6-oxopiperidine (±)-4c.

Chemist Alex Bisset
ALX489
PROTON.w CDC13 /opt/topspin AB 43



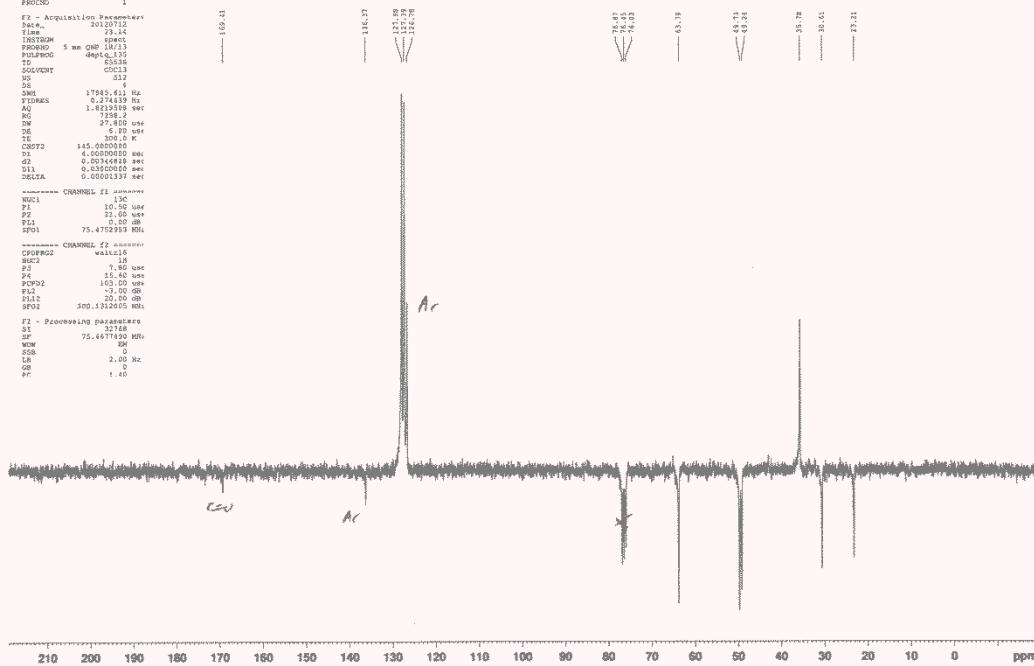
Current Data Parameters
NAME Jul20-2012
EXPNO 20
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120721
Time 4.39
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zg30
TD 32768
SOLVENT CDC13
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.258967 Hz
AQ 1.9923444 sec
RG 362
DM 60.800 use
DE 4.00 use
TE 298.2 K
D1 1.00000000 sec
D11 1

CHANNEL f1 -----
NUC1 1H
P1 12.25 use
PL1 0.00 dB
SFO1 400.0324703 MHz

F2 - Processing parameters
SI 32768
SF 400.0300119 MHz
WDW EM
SSB 0
LB -0.20 Hz
GB 0.1
PC 1.00

Chemist Alex Bisset
ALX Pt hydrog BX
C13depiq.w CDC13 /opt/topspin AB 21



Current Data Parameters
NAME Jul22-2012
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120722
Time 19.14
INSTRUM spect
PROBHD 5 mm QNP 13C/
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 256
DS 4
SWH 17985.411 Hz
FIDRES 0.2744339 Hz
AQ 1.8822039 sec
RG 2598.2
DM 77.000 use
DE 4.00 use
TE 300.2 K
D1 145.0000000 sec
D11 4.00000000 sec
D12 0.20344998 sec
D13 0.03500000 sec
DELTA 0.0000137 sec

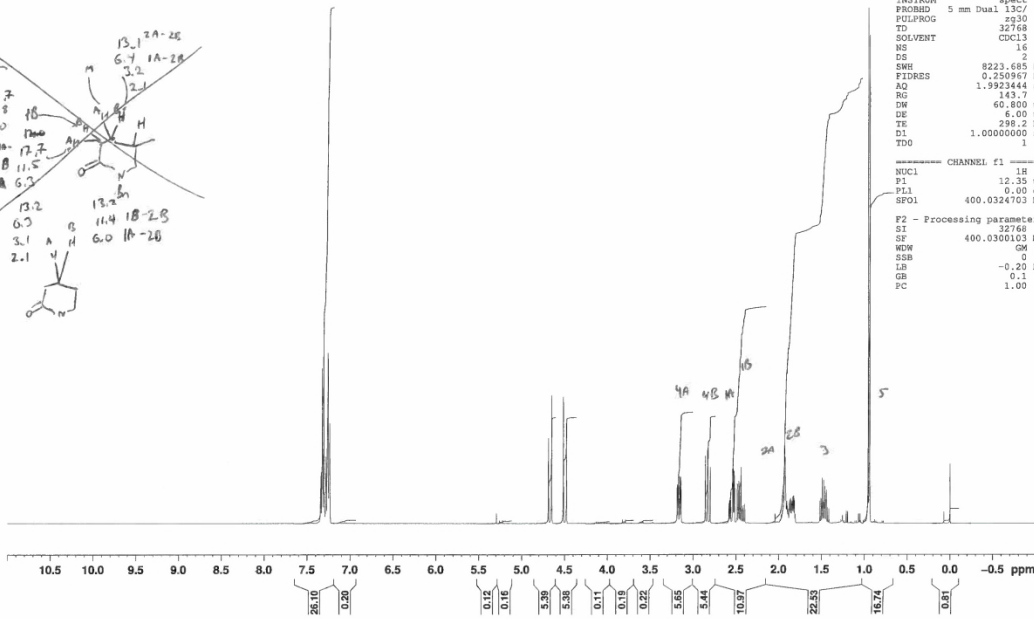
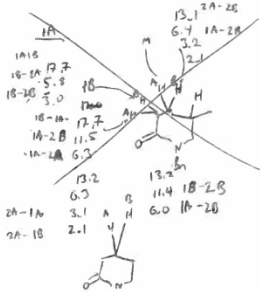
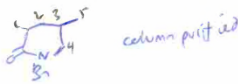
CHANNEL f1 -----
NUC1 13C
P1 10.50 use
PL1 0.00 dB
SFO1 75.4782953 MHz

CHANNEL f2 -----
CPROG2 waltz16
NUC2 1H
P2 1.50 use
PL2 19.00 dB
PCP2 103.00 dB
PL12 20.00 dB
SFO2 500.1320053 MHz

F2 - Processing parameters
SI 65536
SF 75.4677850 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40

1-Benzyl-5-methylpiperidin-2-one, (\pm)-21.

Chemist Alex Bisset
ALX488
PROTON.w CDC13 /opt/topspin AB 46



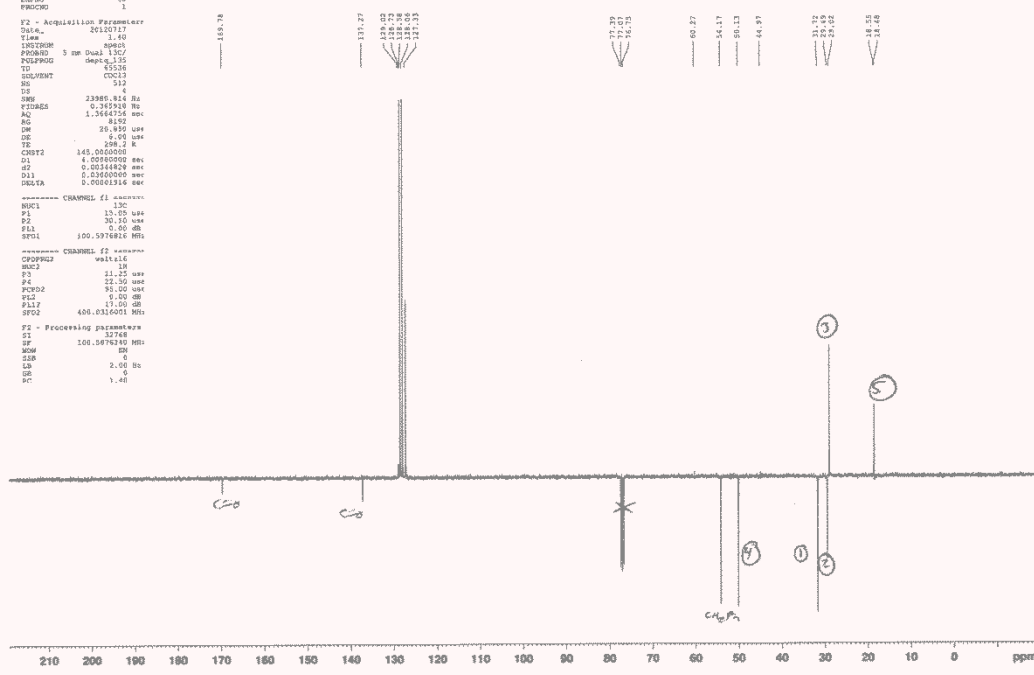
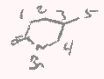
Current Data Parameters
NAME Jul16-2012
EXPNO 20
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120716
Time 15.24
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zg30
TD 32768
SOLVENT CDC13
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 143.7
DM 60.800 use
DE 6.00 use
TE 298.2 K
D1 1.0000000 sec
TD0

CHANNEL f1
NUC1 1H
P1 12.55 use
PL1 0.00 dB
SFO1 400.0324703 MHz

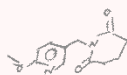
F2 - Processing parameters
SI 32768
SF 400.0306103 MHz
WDW GM
SSB 0
LB -0.20 Hz
GB 0.1
PC 1.00

Chemist Alex Bisset
ALX488
C13dept.w CDC13 /opt/topspin AB 47



1-((6-Methoxypyridin-3-yl)methyl)piperidine-2,6-dione, 2d.

Chemist Alex Bisset
ALX374
PROTON.w CDC13 /opt/topspin AB 2

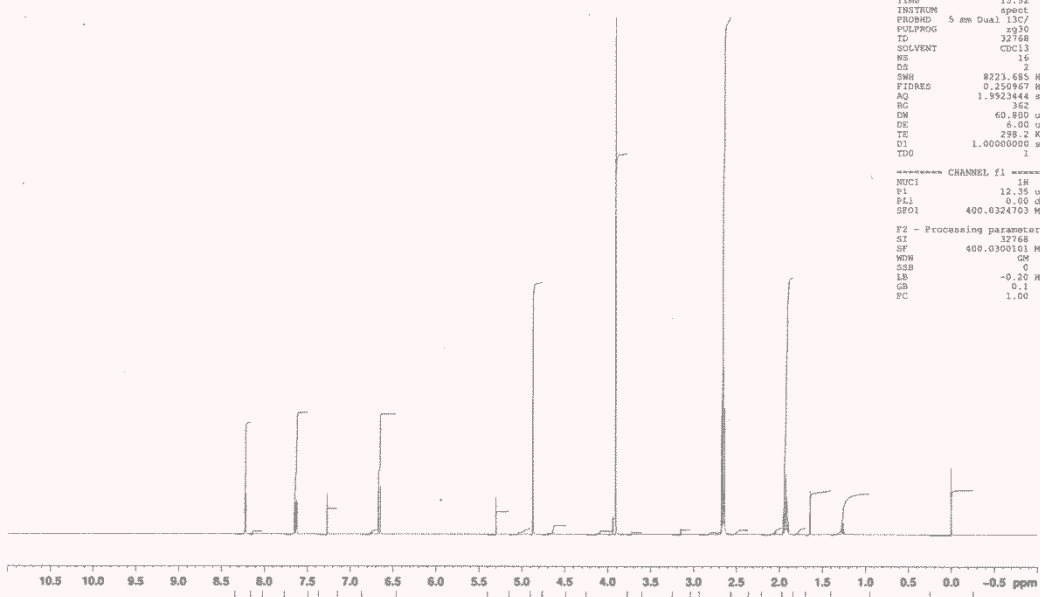


Current Data Parameters
NAME Fab27-0312
EXPNO 20
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120227
Time 19.52
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg30
TD 32768
SOLVENT CDC13
NS 16
DS 2
SWH 8223.655 Hz
FIDRES 0.250967 Hz
AQ 1.9523444 sec
RG 362
DN 60.800 use
DE 8.00 use
TE 298.2 K
D1 1.0000000 sec
TD0

***** CHANNEL f1 *****
NUC1 1H
P1 12.35 use
PL1 0.00 dB
SFO1 400.0324703 MHz

F2 - Processing parameters
SI 32768
SF 400.0300101 MHz
WDW GM
SSB 0
LB -0.20 Hz
GB 0.1
PC 1.00



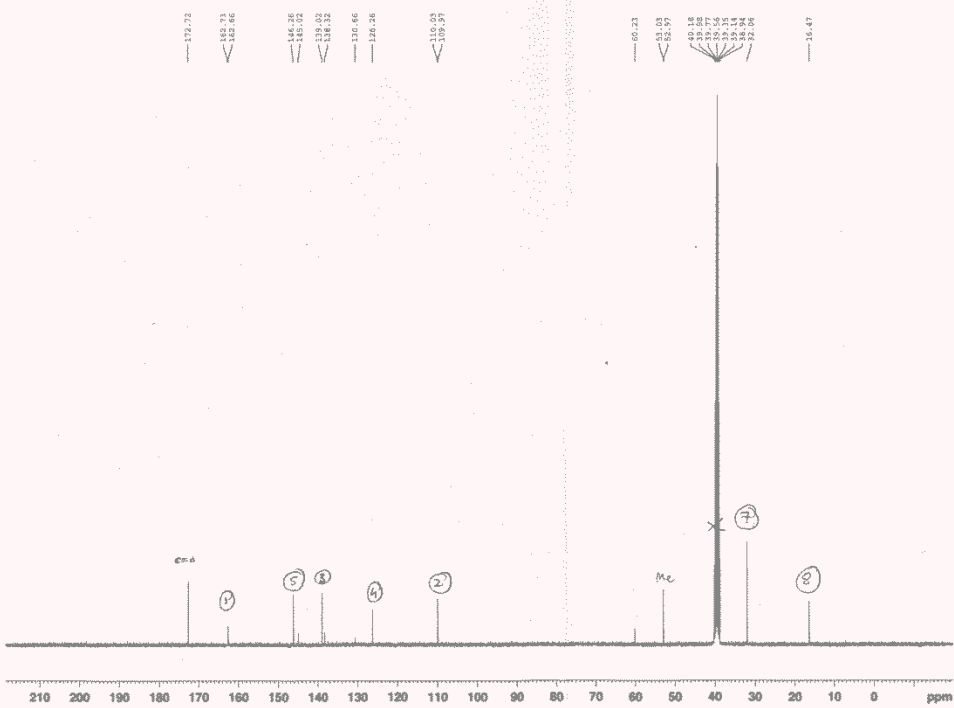
Name A Bisset
M No lrtw983
Notebook Ref EN05661-44
carbon.az DMSO /opt/topspin2.1 chem 24



NAME 111214
EXPNO 230
PROCNO 1
Date_ 20111214
Time 21.34
INSTRUM NV400-1451A
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 4
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 23170.5
DW 20.850 use
DE 20.00 use
TE 303.2 K
D1 2.0000000 sec
D11 0.0388000 sec
TD0 10

***** CHANNEL f1 *****
NUC1 13C
P1 9.00 use
PL1 3.78 dB
SFO1 100.6228298 MHz

***** CHANNEL f2 *****
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 use
PL2 -2.00 dB
PL12 15.89 dB
PL13 16.00 dB
SFO2 400.1316005 MHz
SI 32768
SF 100.6128333 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



1-[(1-Benzyl-6-oxo-1,6-dihydropyridin-3-yl)methyl]piperidine-2,6-dione 3d.

Chemist Alex Bisset
 PROTONight.w CDC13 /opt/topspin AB 21

245

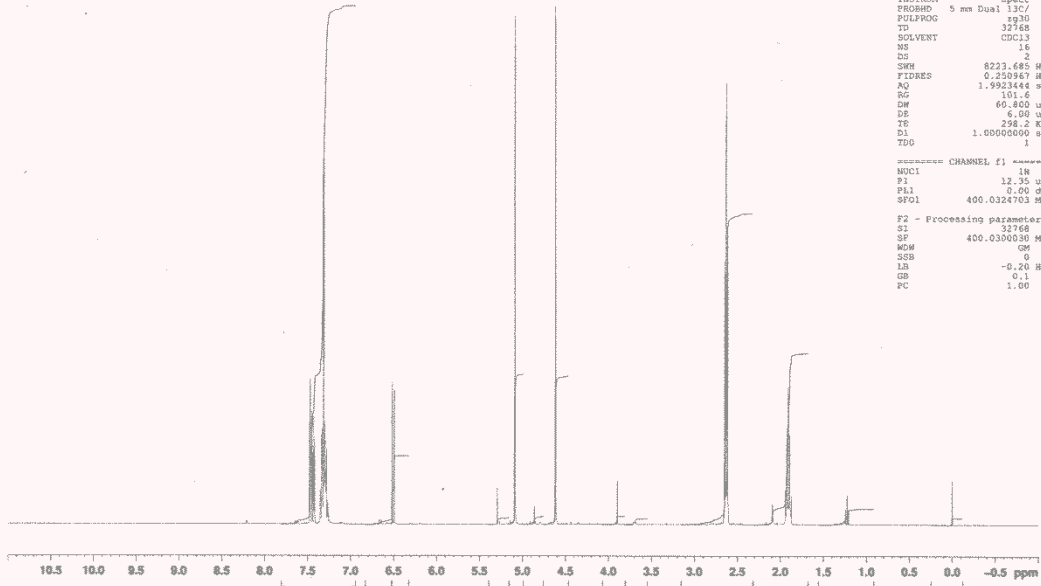


Current Data Parameters
 NAME Jan27-2012
 EXPNO 11
 PROCNO 1

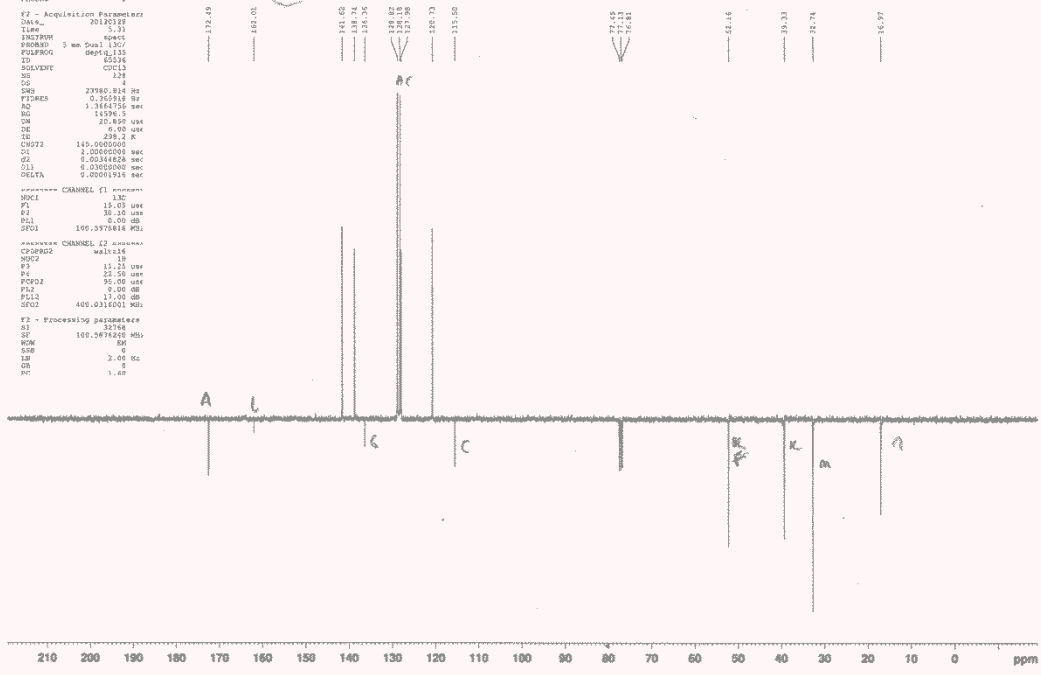
F2 - Acquisition Parameters
 Date_ 20121228
 Time 5.32
 INSTRUM spect
 PROBHD 5 mm Dual 13C/
 PULPROG zgpg30
 TD 32768
 SOLVENT CDC13
 NS 16
 DS 2
 SFO1 400.0324703 MHz
 FIDRES 0.250967 Hz
 AQ 1.9923444 sec
 RG 101.6
 DM 60.800 usec
 DE 6.00 usec
 TE 298.2 K
 D1 1.00000000 sec
 TDD

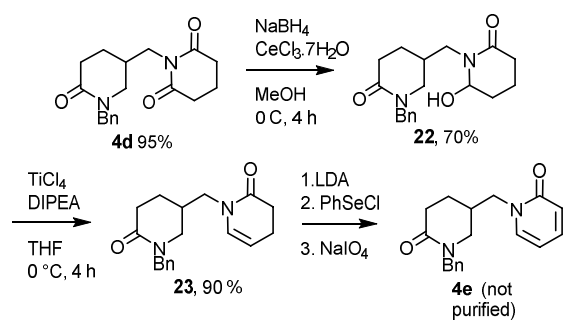
===== CHANNEL f1 =====
 NUCL1 1H
 P1 12.30 usec
 PL1 0.00 dB
 SFO1 400.0324703 MHz

F2 - Processing parameters
 SI 32768
 SF 400.030038 MHz
 MDW 68
 SGB 0
 LB -0.20 Hz
 GB 0.1
 PC 1.00

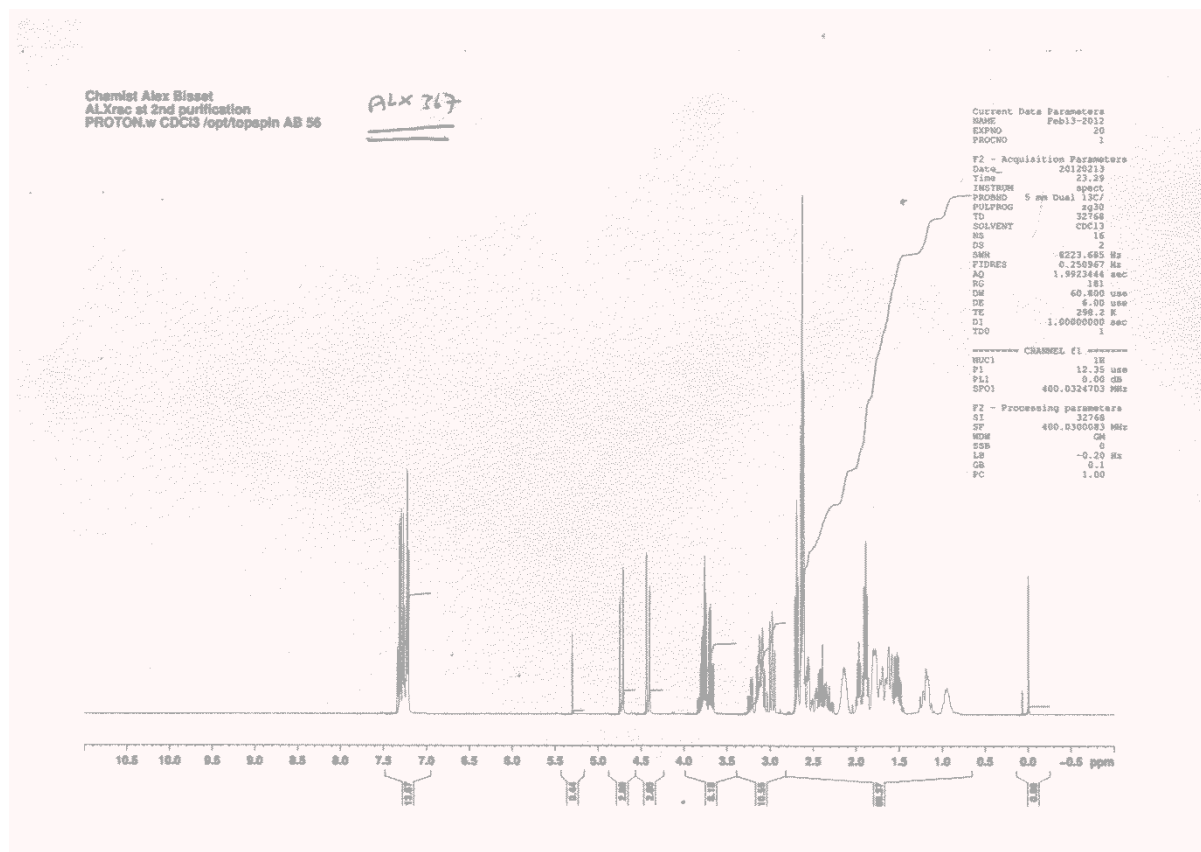


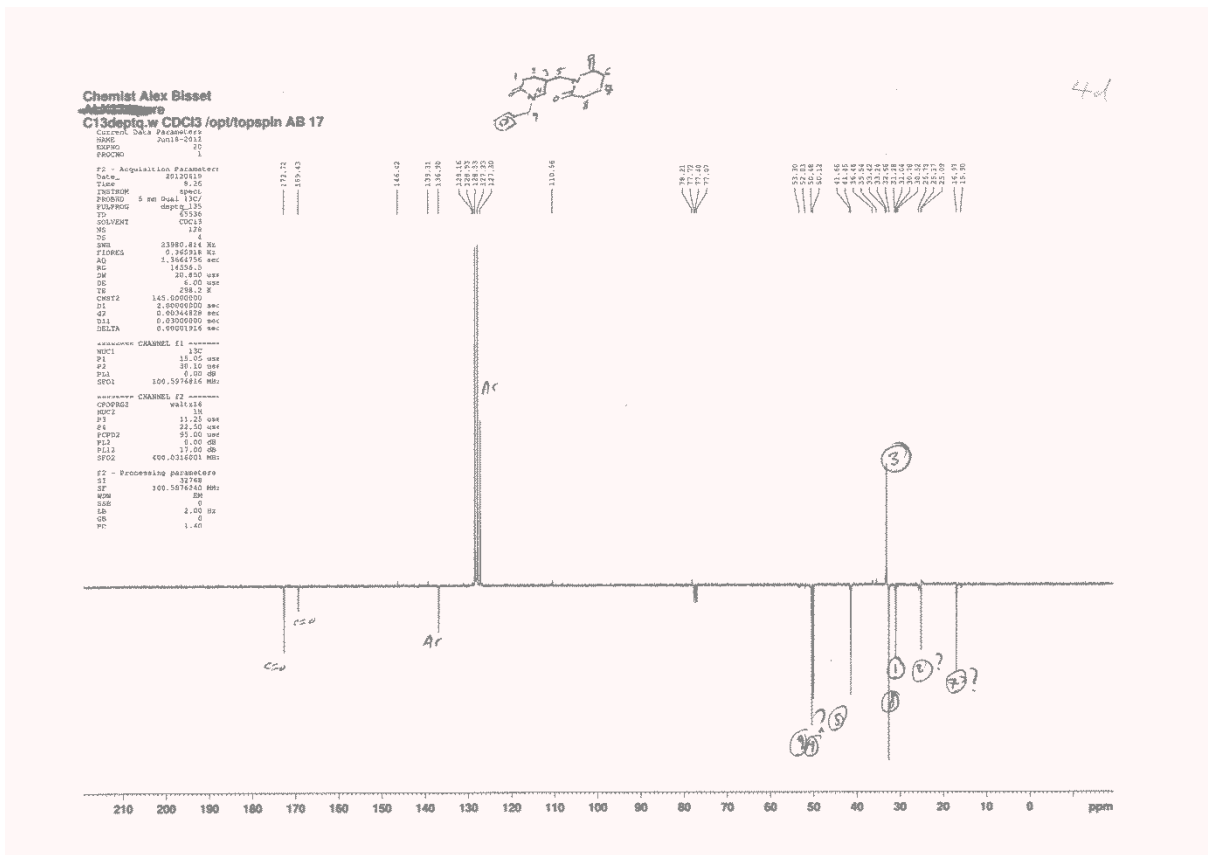
Chemist Alex Bisset
 ALX345
 C13deptq.w CDC13 /opt/topspin AB 21



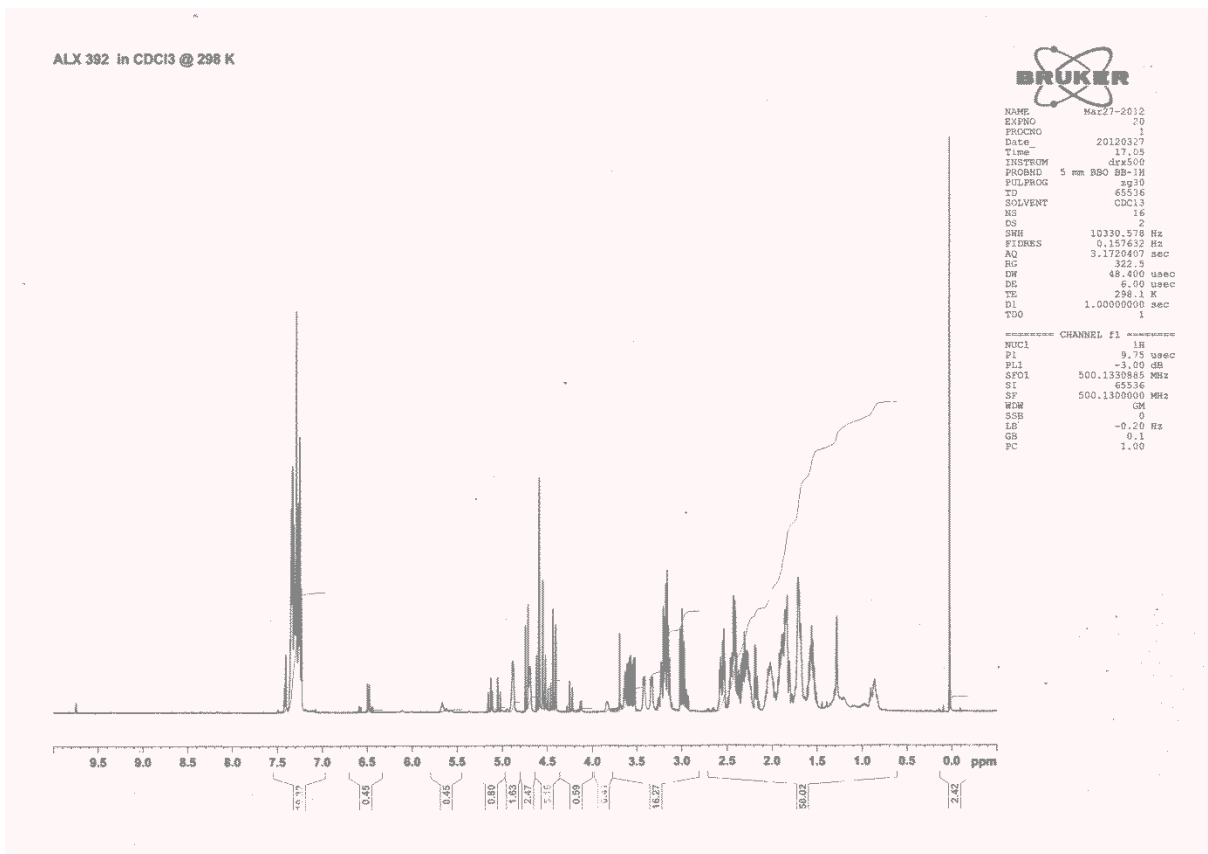


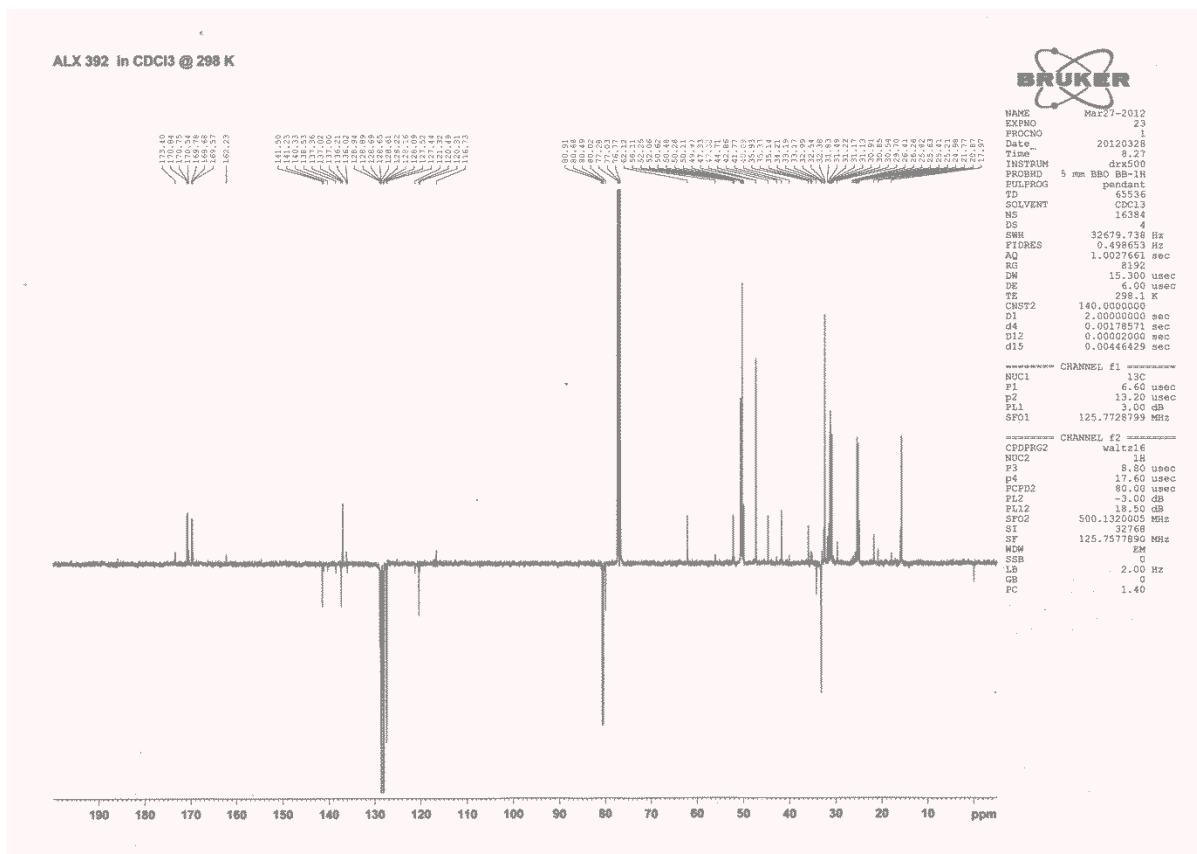
1-[(1-Benzyl-6-oxopiperidin-3-yl)methyl]piperidine-2,6-dione, (\pm)-4d.



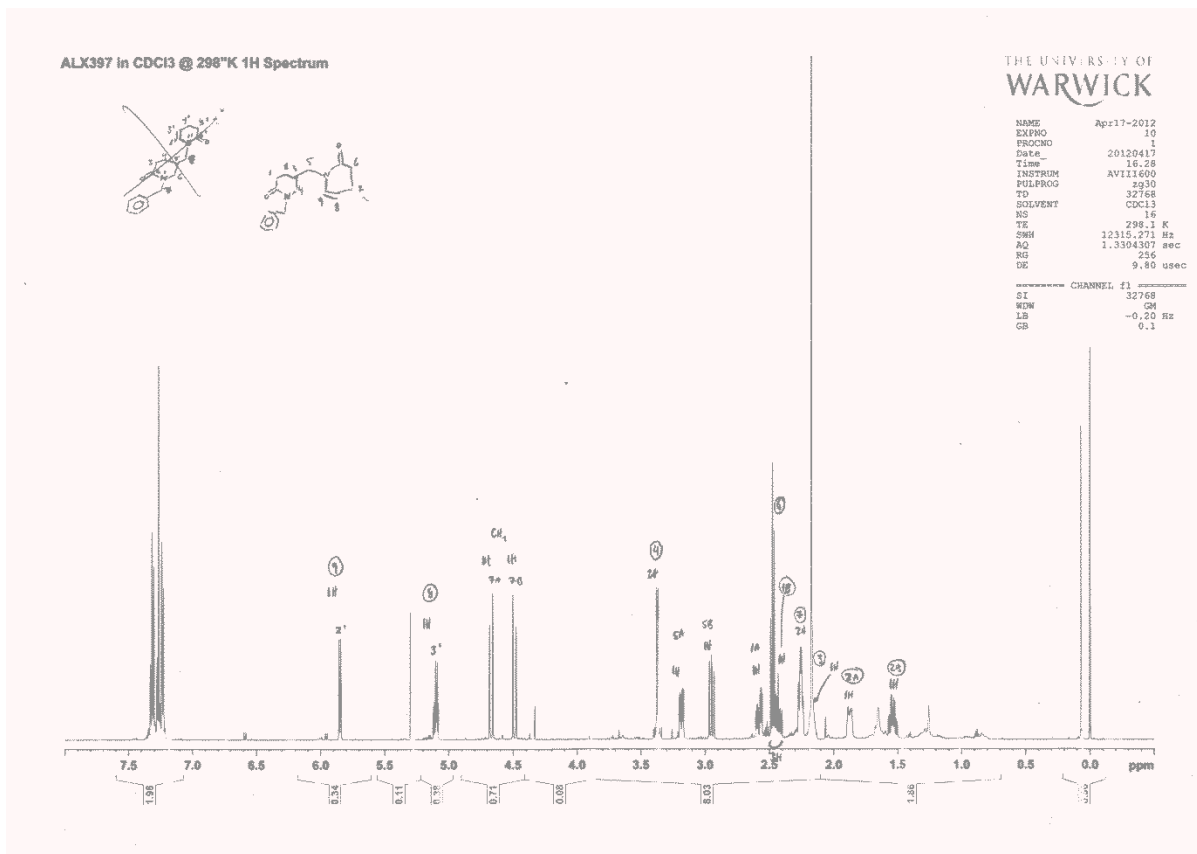


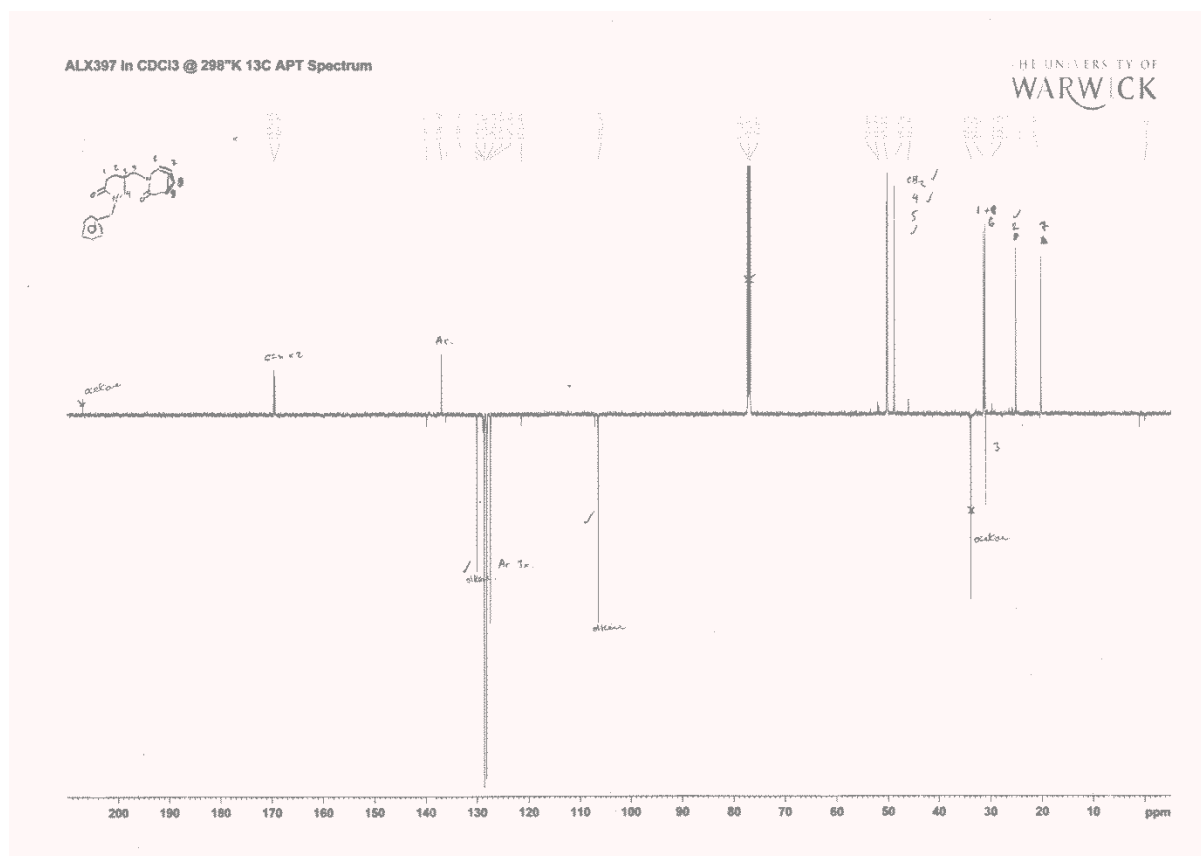
1-Benzyl-5-[(2-hydroxy-6-oxopiperidin-1-yl)methyl]piperidin-2-one, (\pm)-**22**.





1-[(1-Benzyl-6-oxopiperidin-3-yl)methyl]-3,4-dihydropyridin-2(1H)-one, (\pm)-**23**.

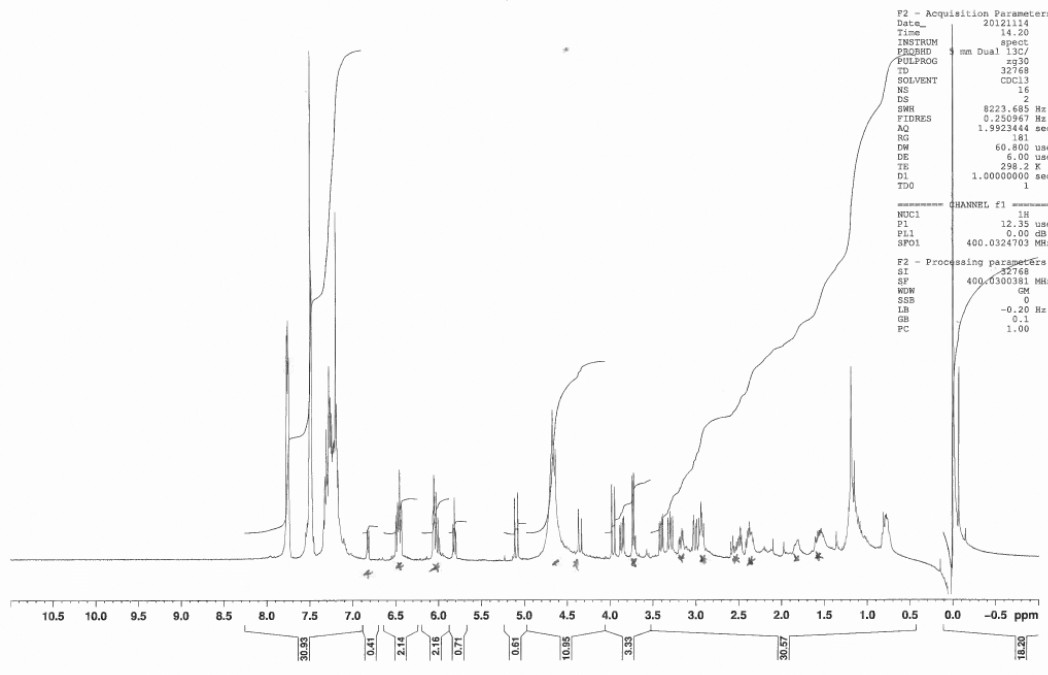




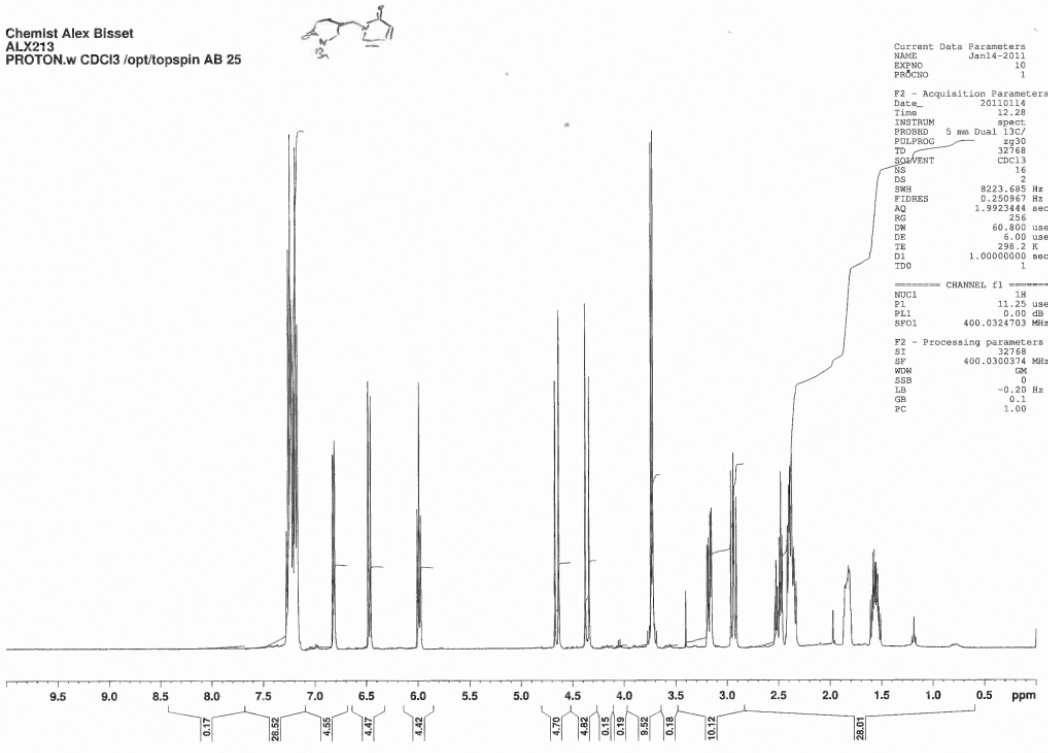
The selenoxide oxidation – elimination of enamide (\pm)-**23**, yielding (\pm)-1-((1-benzyl-6-oxopiperidin-3-yl)methyl)pyridin-2(1H)-one, (\pm)-**4e**.

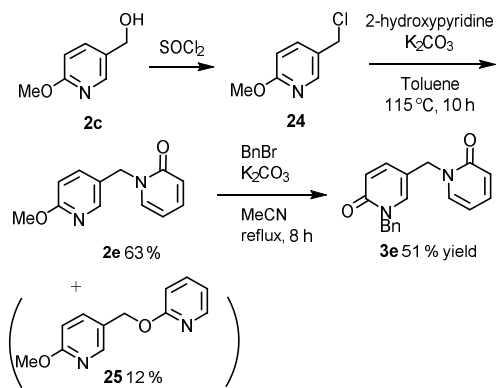
Product from reaction (crude mix with side-product), the position of **4e** is indicated with * and is partly masked by an inseparable by product:

AXS81
Chemist Alex Bisset
ALX598
PROTON.w CDCl3 /opt/topspin AB 56

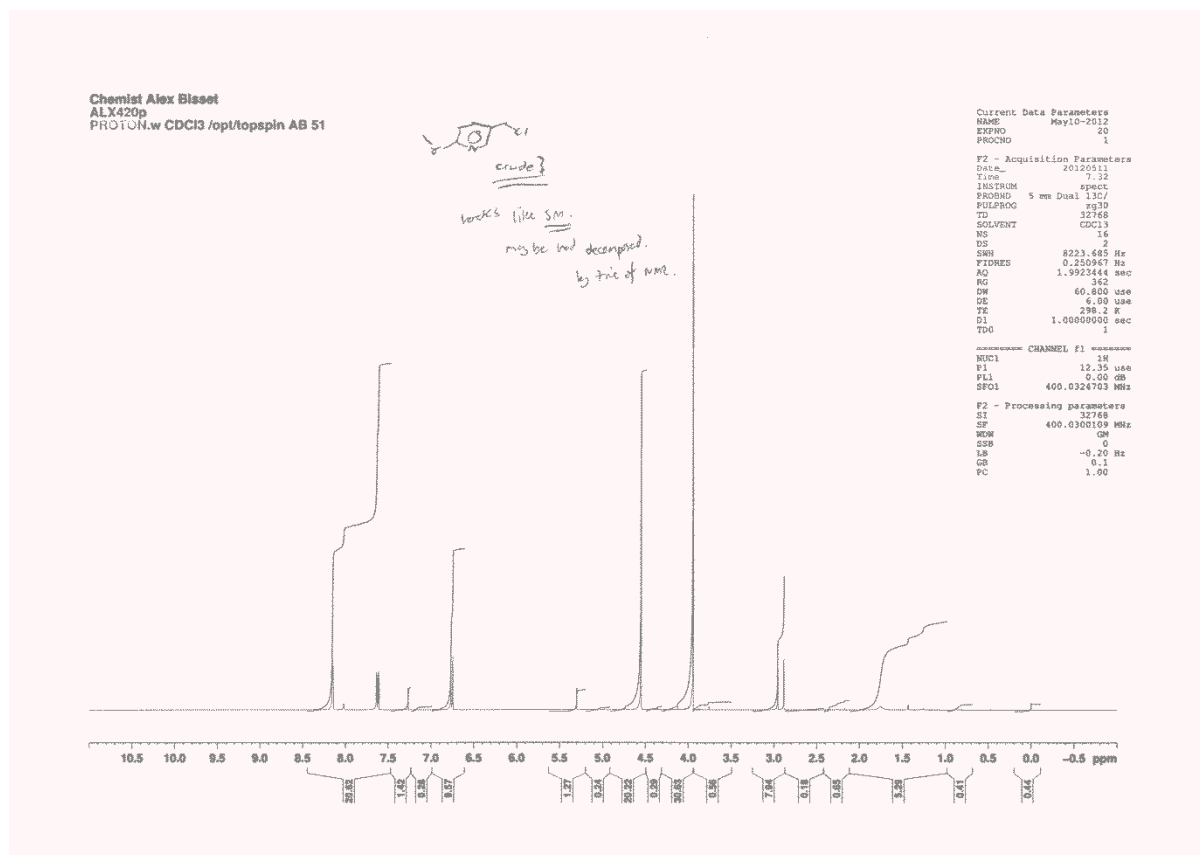


For comparison, a sample of authentic 4e is shown below:

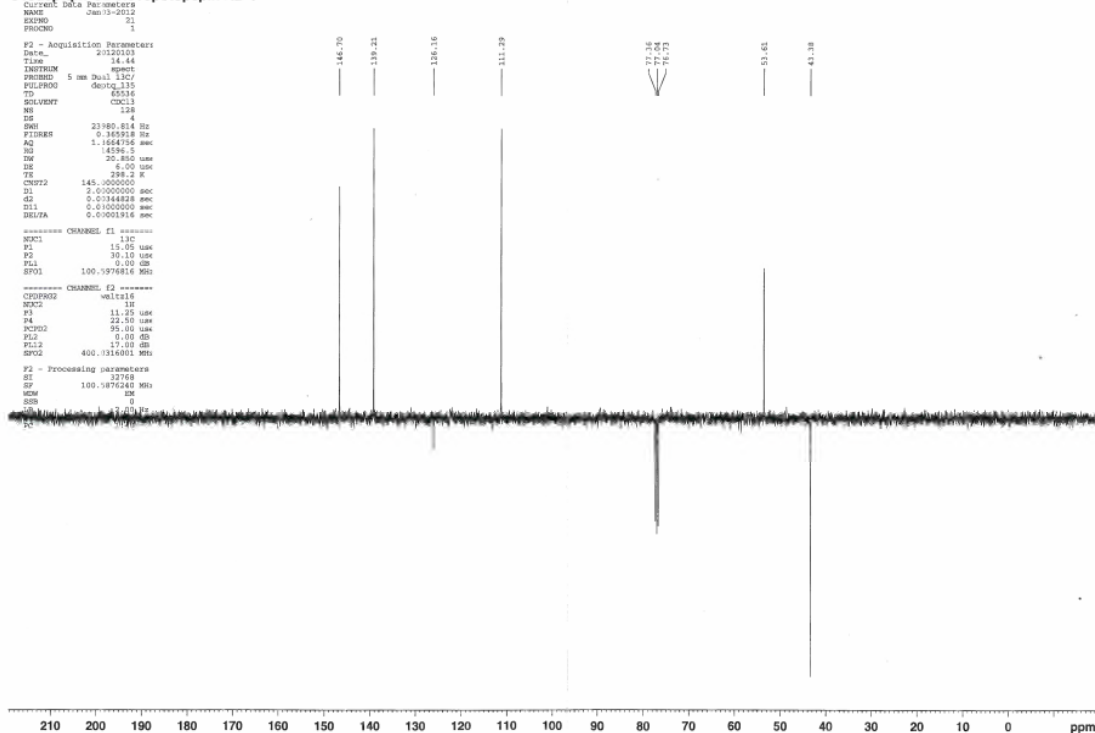




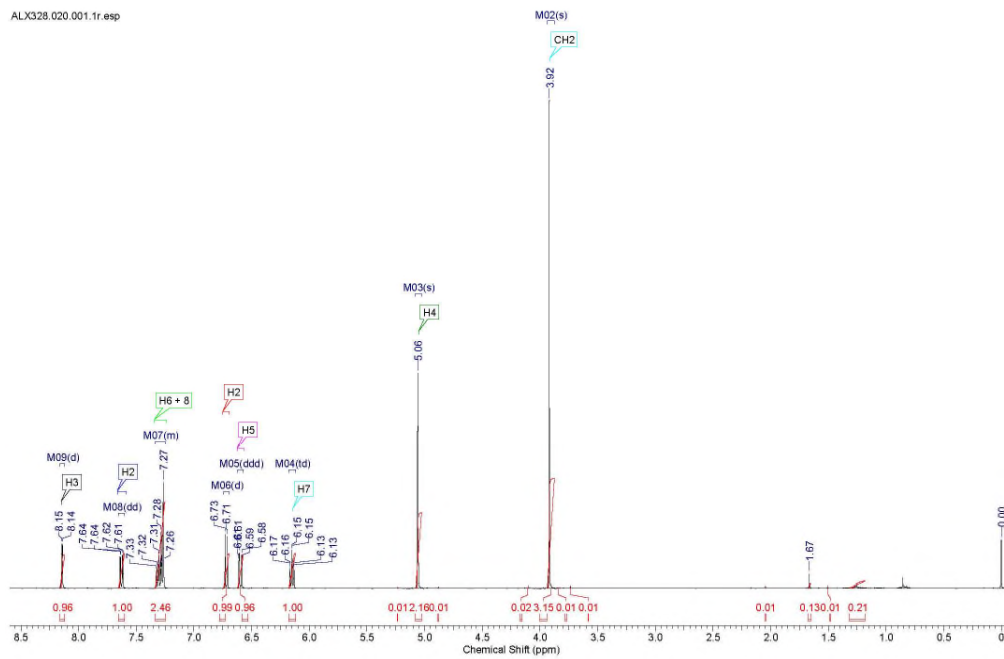
5-Chloromethyl-2-methoxypyridine, 24.

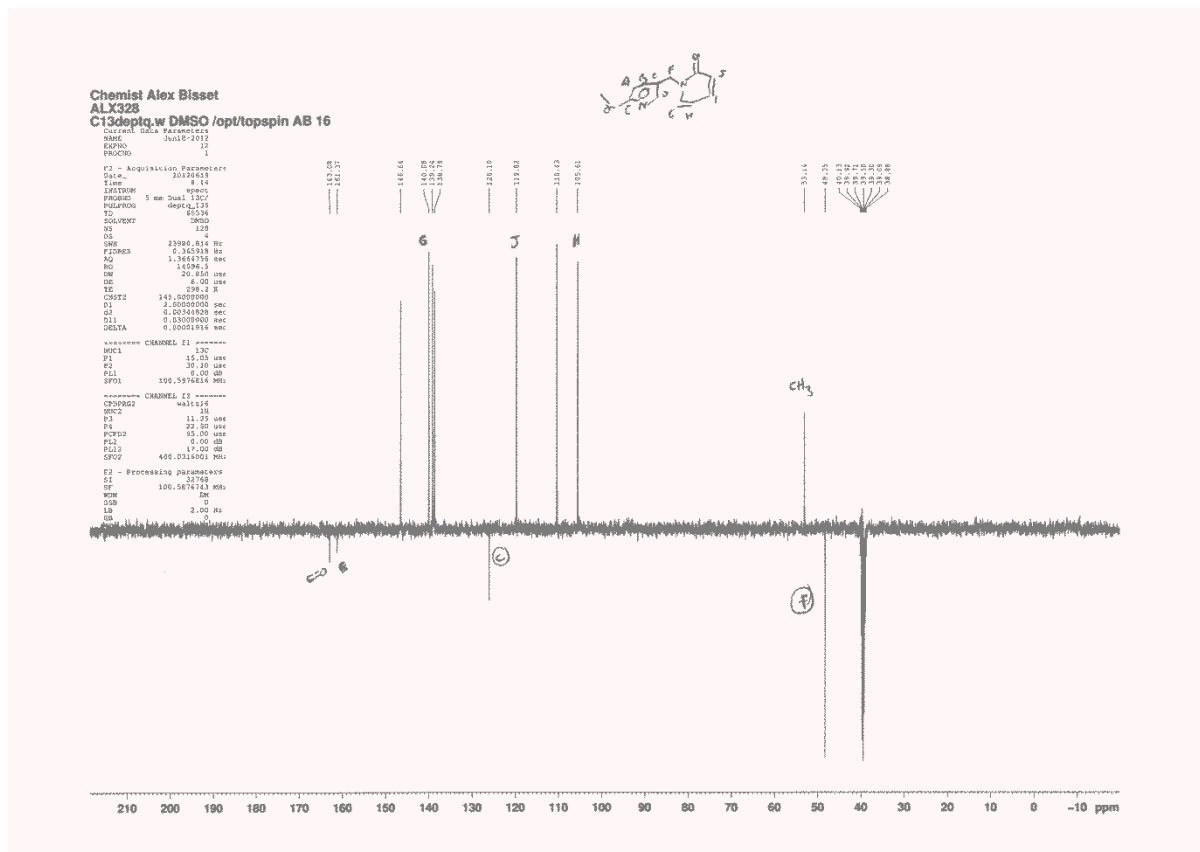
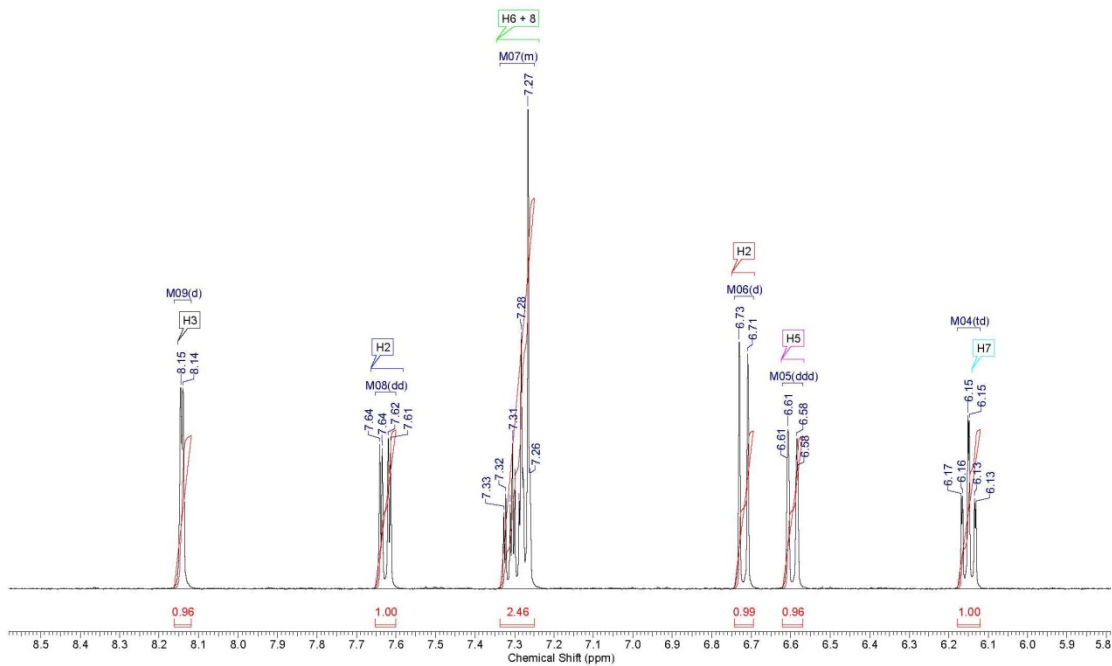


Chemist Alex Bisset
ALX327
C13deptq.w CDC13 /opt/topspin AB 4

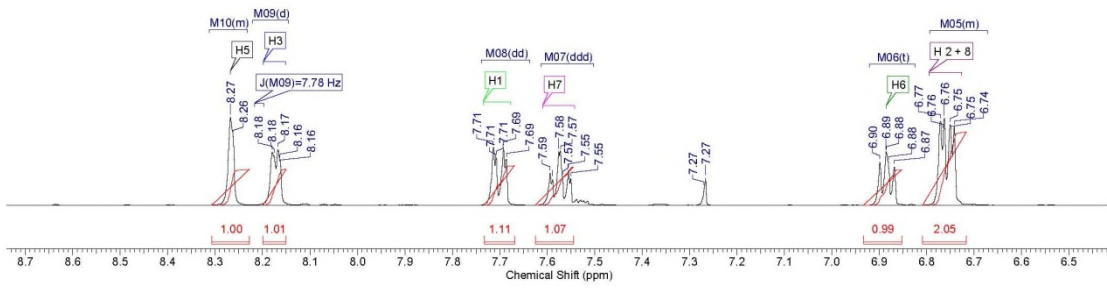
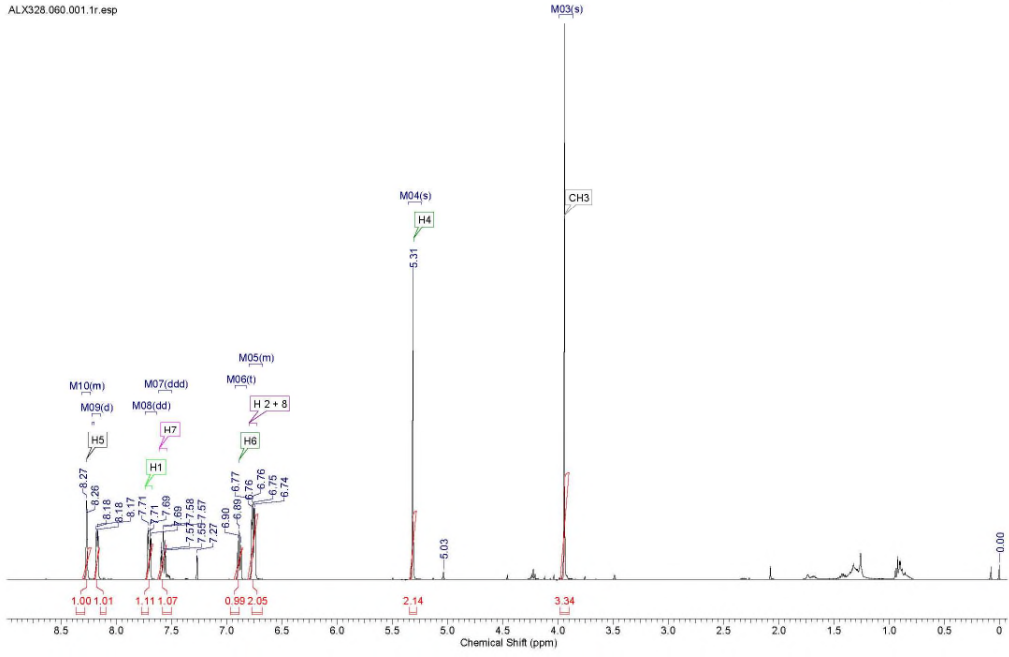


1-((6-methoxy-pyridin-3-yl)methyl)pyridin-2(1H)-one **2e**.



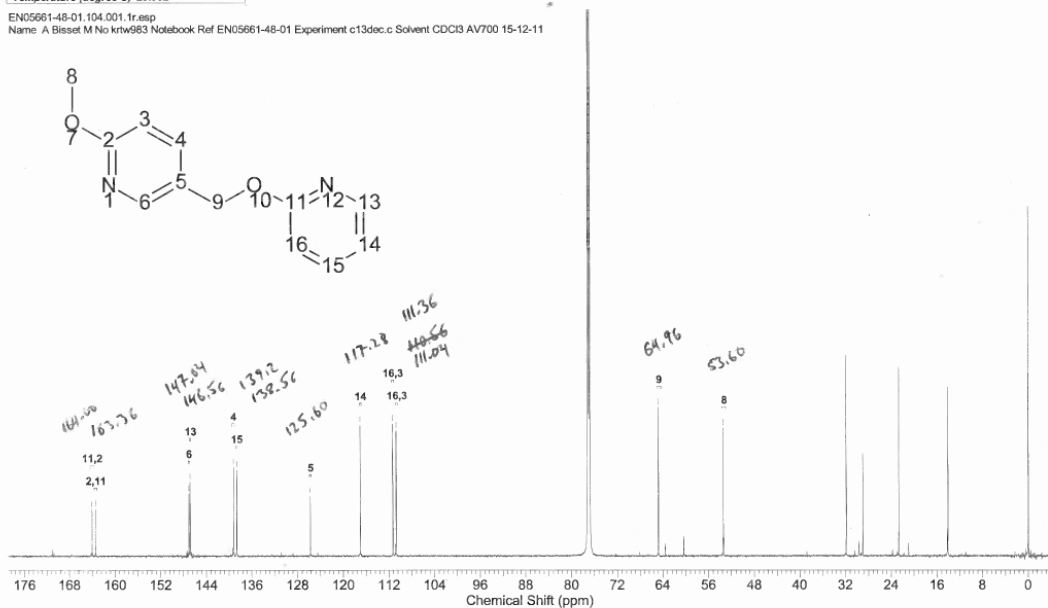


2-methoxy-5-((pyridin-2-yloxy)methyl)pyridine, 25.



Acquisition Time (sec)	0.7846	Comment	Name	A Bisset M No krtw983 Notebook Ref EN05661-48-01 Experiment c13dec.c Solvent CDCl3 AV700 15-12-11
Date	16 Dec 2011 05:13:36	Date Stamp	16 Dec 2011 05:13:36	
File Name	hjakapw069nmr.routine2011\mr\EN05661-48-01\104\pd1st111r	Frequency (MHz)	175.37	Nucleus
Number of Transients	12000	Origin	av700_33b193	Owner
Points Count	65536	Pulse Sequence	zgpg30_b	Receiver Gain
Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	17601.4004	Spectrum Type
Temperature (degree C)	29.982			Sweep Width (Hz)

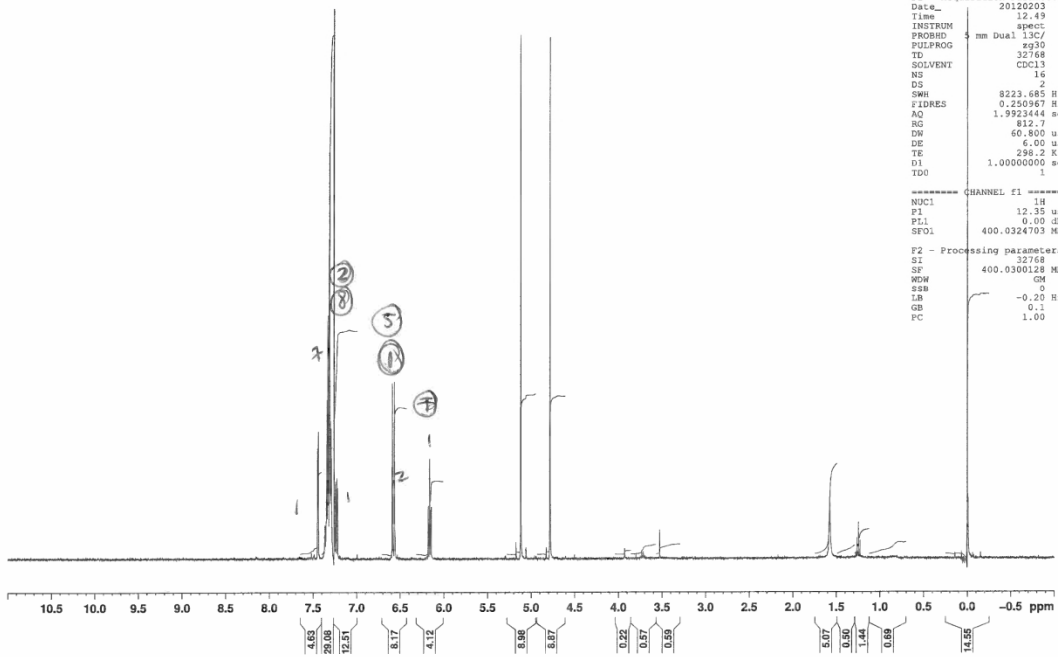
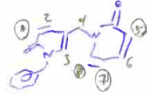
EN05661-48-01.104.001.1r.epp
 Name: A Bisset M No krtw983 Notebook Ref EN05661-48-01 Experiment c13dec.c Solvent CDCl3 AV700 15-12-11



1-Benzyl-5-[(2-oxopyridin-1(2H)-yl)methyl]pyridin-2(1H)-one, 3e.

Chemist Alex Bisset
ALX n-benzylbispyridone pure
PROTON.w CDC13 /opt/topspin AB 32

ALX 357



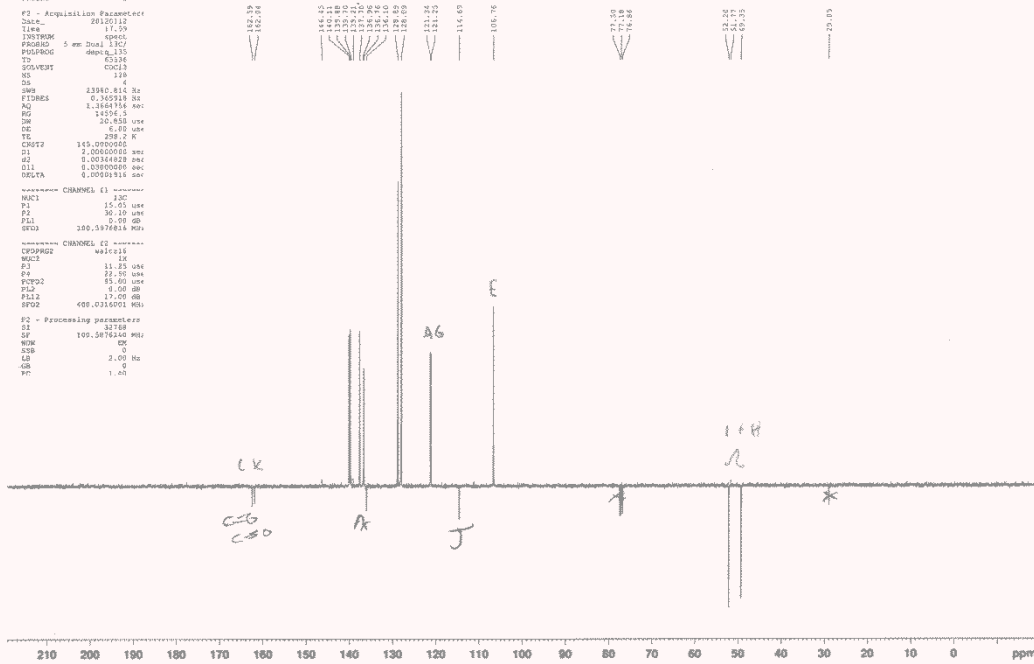
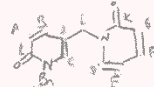
```
Current Data Parameters
NAME      Fes03-2012
EXPNO    30
PROCNO   1

F2 - Acquisition Parameters
Date_    20120203
Time     12.49
INSTRUM  spect
PROBHD   5 mm Dual 13C/
PULPROG  zg30
TD        32768
SOLVENT  CDCl3
NS        16
DS        2
SWH       8223.685 Hz
FIDRES    0.260967 Hz
AQ        1.9923444 sec
RG        812.7
DN        60.800 use
DE        6.00 use
TE        298.2 K
D1        1.0000000 sec
TD0       1

----- CHANNEL f1 -----
NUC1      13
P1        12.35 use
PL1       0.00 dB
SFO1      400.0324703 MHz

F2 - Processing parameters
SI        32768
SF        400.0300128 MHz
WDW       EM
SSB       0
LB        -0.20 Hz
GB        0.1
PC        1.00
```

Chemist Alex Bisset
alx334
C13deptq.w CDC13 /opt/topspin AB 38



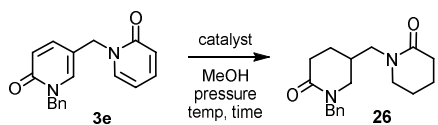
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Current Data Parameters
NAME      alx334
EXPNO    38
PROCNO   1

F2 - Acquisition Parameters
Date_    20120218
Time     11.59
INSTRUM  spect
PROBHD   5 mm Dual 13C/
PULPROG  zgpg30
TD        65536
SOLVENT  CDCl3
NS        128
DS        2
SWH       23980.814 Hz
FIDRES    0.262918 Hz
AQ        1.2684756 sec
RG        32536.5
DN        30.833 use
DE        6.00 use
TE        298.2 K
CNS17    145.0000000 use
SI        2.0000000 use
SF        0.00344028 use
D1        0.0000000 use
DELTA    0.0000115 use

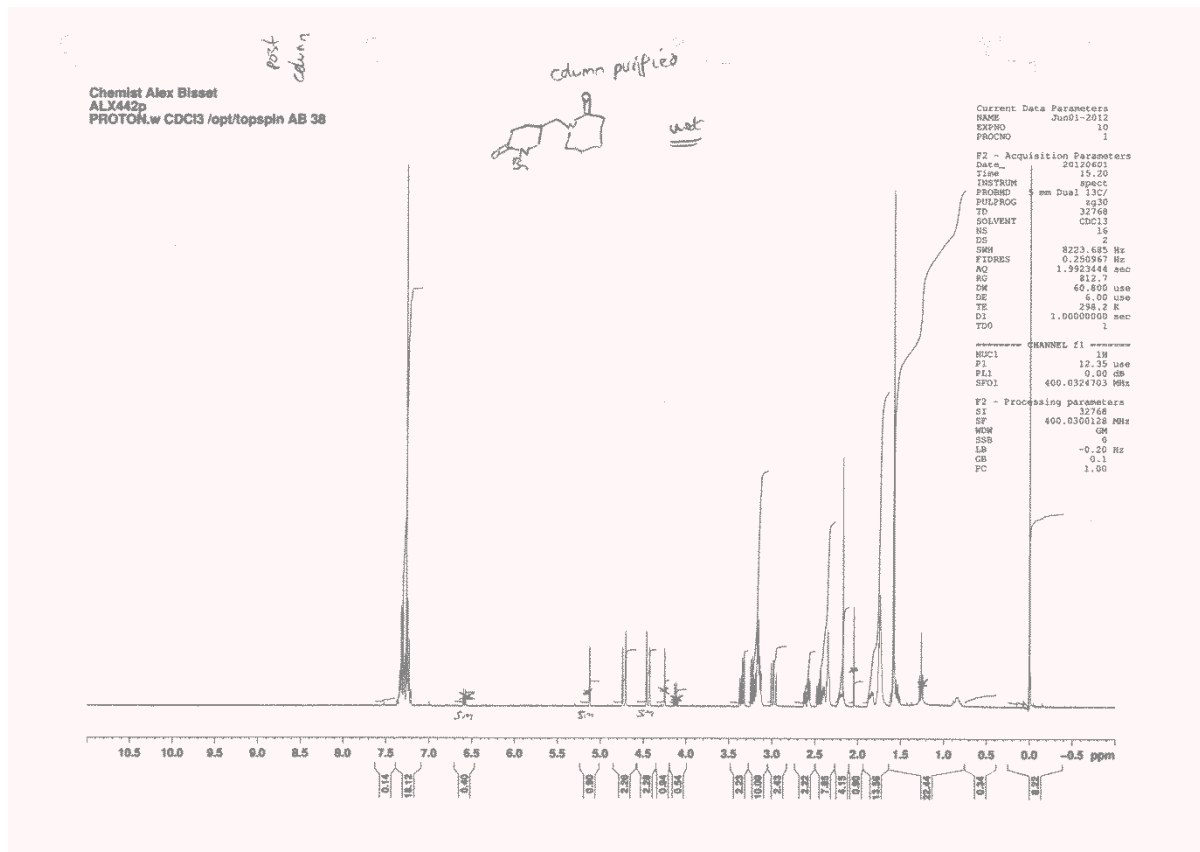
----- CHANNEL f1 -----
NUC1      13
P1        15.05 use
PL1       0.00 dB
SFO1      100.6261818 MHz

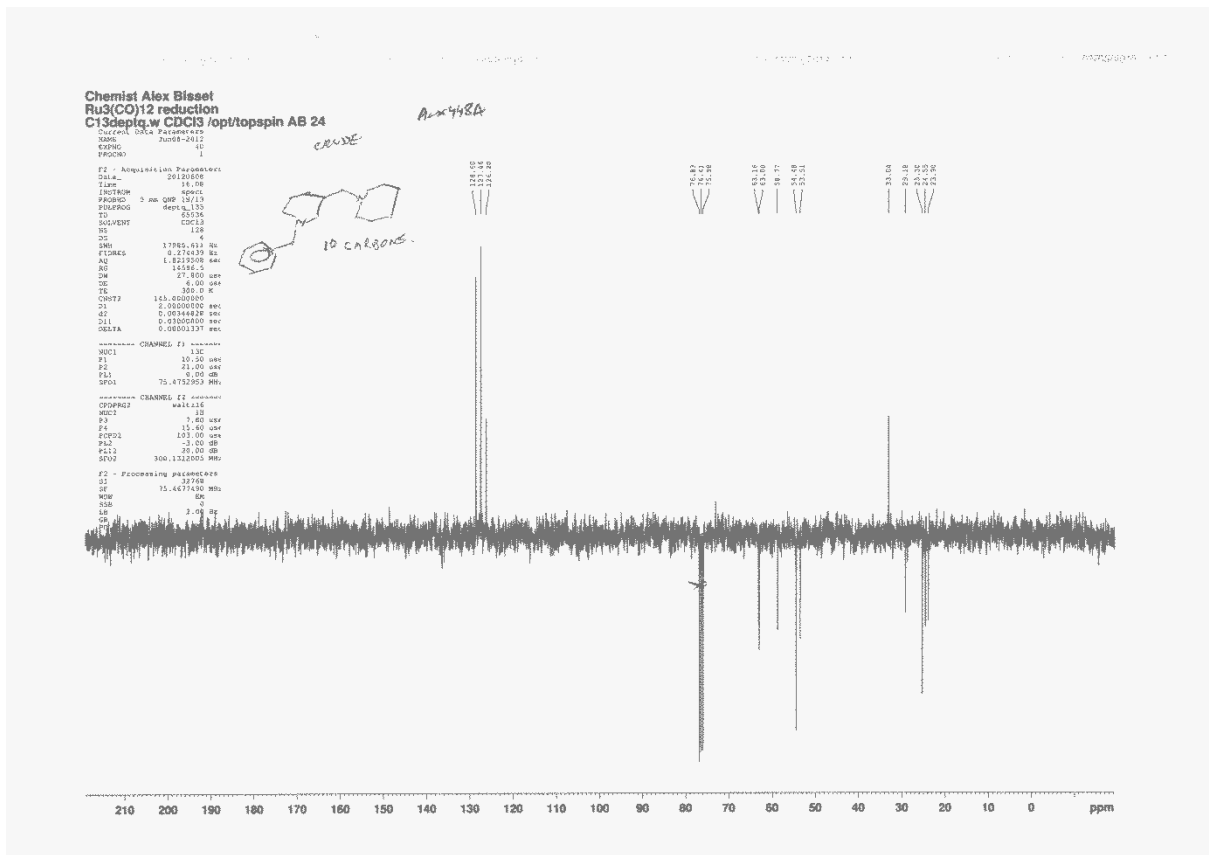
----- CHANNEL f2 -----
CPDPRG2  waltz16
NUC2      13
P2        31.25 use
PL2       22.35 use
PCPD2    95.00 use
PL4       0.00 dB
PL12     0.17.00 dB
RF02     400.0140001 MHz

F2 - Processing parameters
SI        65536
SF        100.6261818 MHz
WDW       EM
SSB       0
LB        2.00 Hz
GB        0
PC        1.00
```

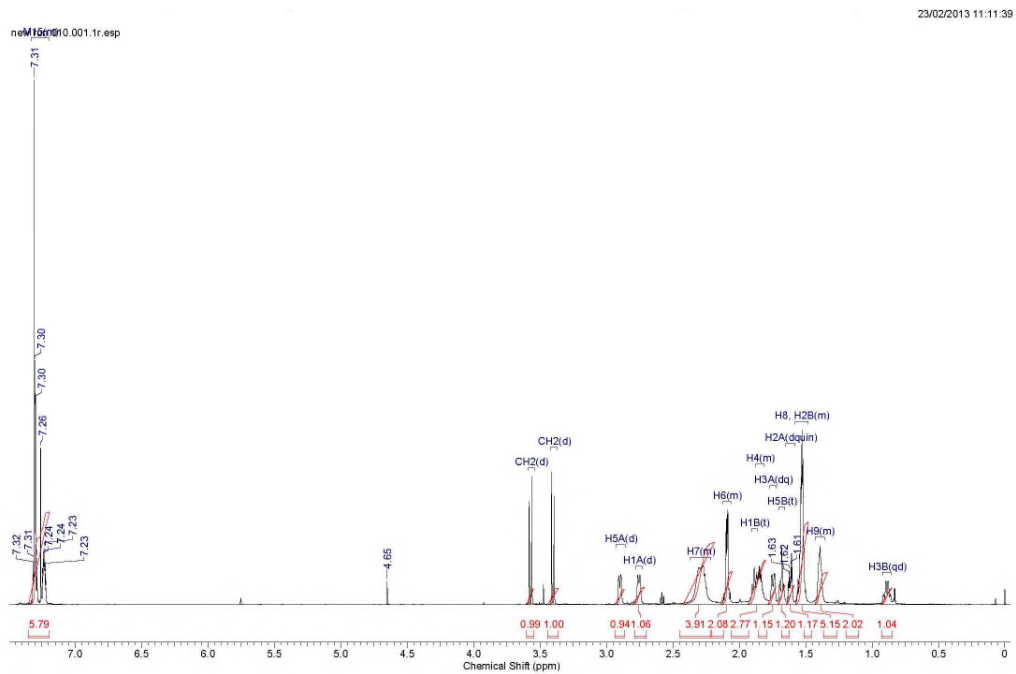


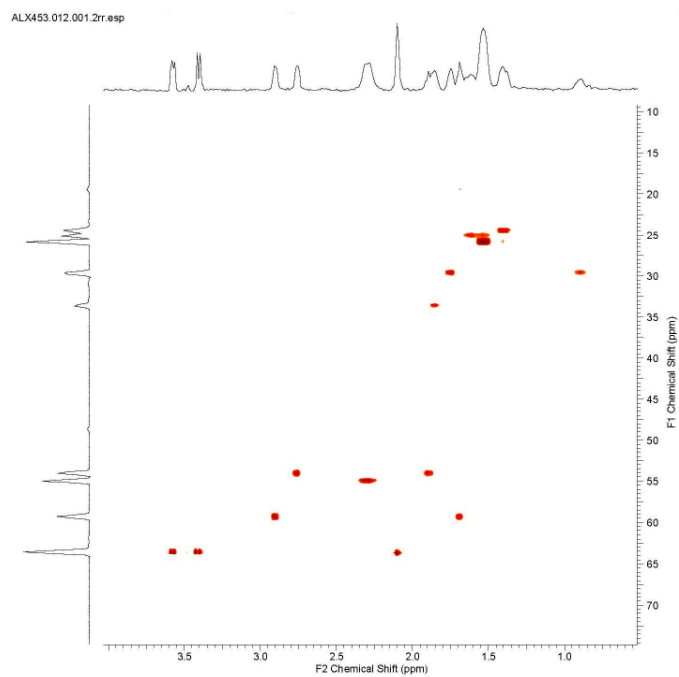
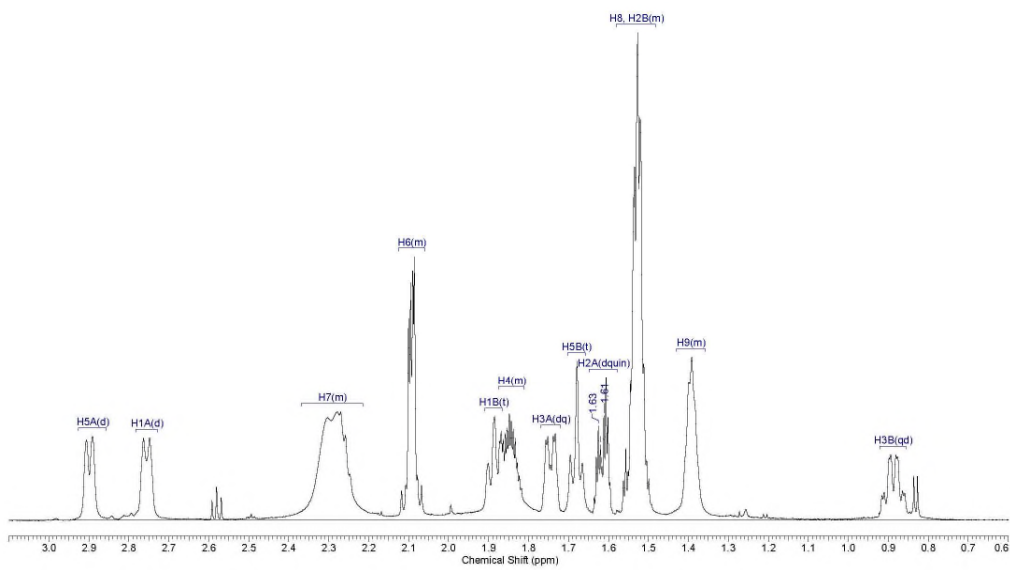
1-((1-Benzyl-6-oxopiperidin-3-yl)methyl)piperidin-2-one, (\pm)-**26**.



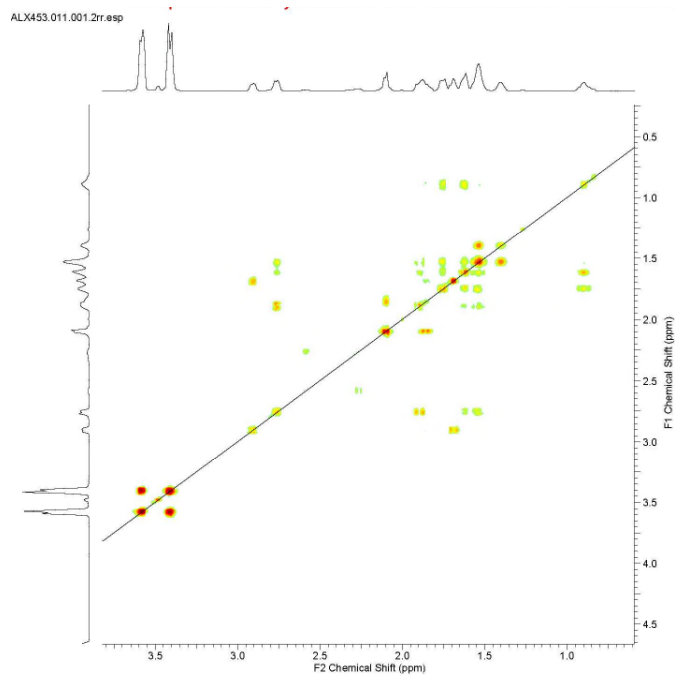


1-Benzyl-3-(piperidin-1-ylmethyl)piperidine, (\pm)-1 (R=Bn).



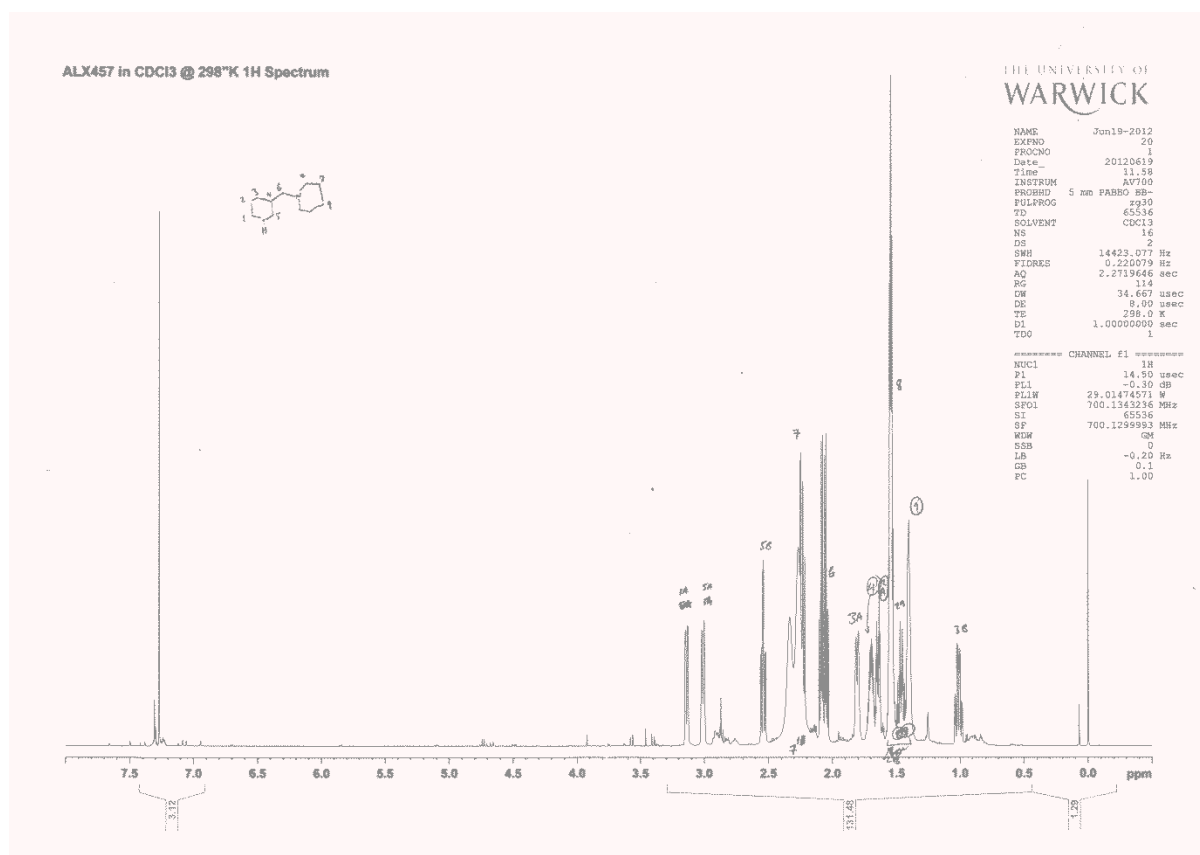


HMQC spectra of **1** (R=Bn), 700 MHz (^1H), 176 MHz (^{13}C) CDCl_3 .



COSY **1** (R=Bn), 700 MHz ($^1\text{H}_1, ^1\text{H}_2$), CDCl_3 .

1-(Piperidin-3-ylmethyl)piperidine, (\pm)-**1** (R=H).



Chemist Alex Bisset
ALX457
C13deptq.w CDC13 /opt/topspin AB 41

post-polymer



```

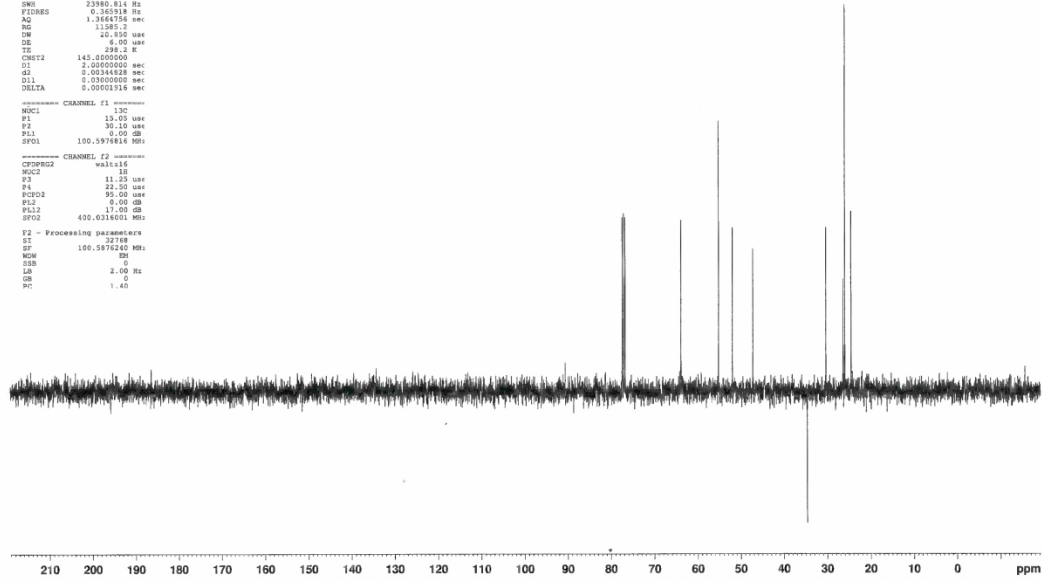
F2 - Acquisition Parameters
Date_ 20120813
Time 16.23
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 128
DS 4
SWH 23980.814 Hz
FIDRES 0.365318 Hz
AQ 1.3664756 sec
RG 31285.0
DM 20.850 usec
DE 6.00 usec
TE 298.2 K
CHET2 145.000000
G1 2.00000000 sec
G2 0.00000000 sec
G13 0.00000000 sec
DELTA 0.00001916 sec

===== CHANNEL f1 =====
NUC1 13C
P1 10.00 usec
P2 30.00 usec
SFO1 100.5974818 MHz

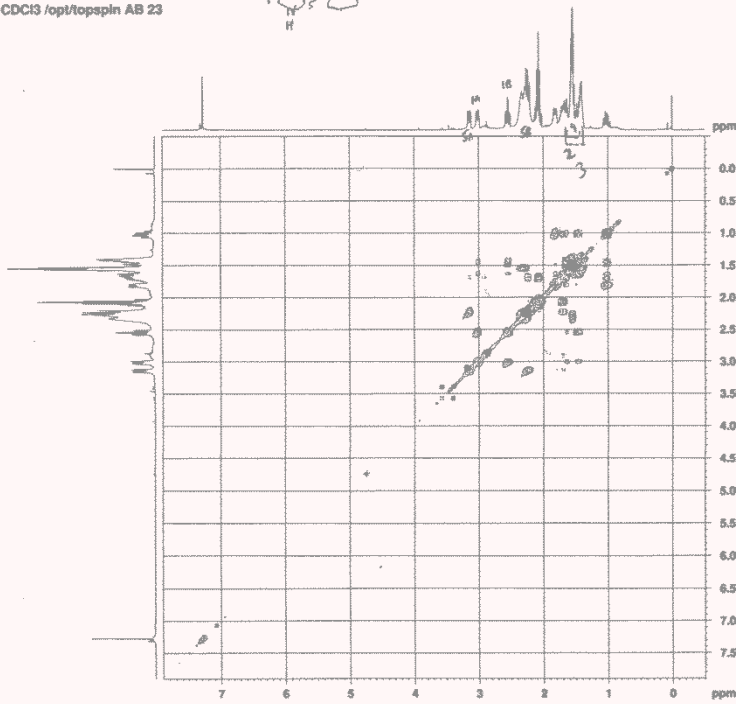
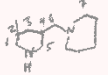
===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
P3 11.20 usec
P4 21.00 usec
PULP2 90.00 usec
PFL 0.00 dB
PFL2 17.00 dB
SFO2 400.0116051 MHz

F2 - Processing parameters
SI 32768
SF 100.5974240 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
  
```

77.26
77.24
63.84
55.17
51.96
47.21
34.62
26.40
24.22
21.14



Chemist Alex Bisset
ALX457
COSY.w CDC13 /opt/topspin AB 23



```

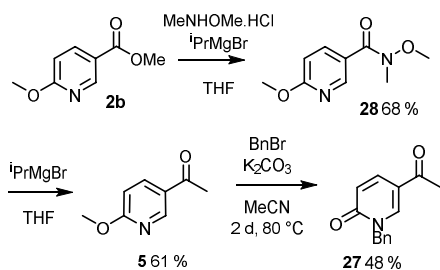
Current Data Parameters
Date_ 20120813
Time 17.20
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 128
DS 4
SWH 23980.814 Hz
FIDRES 0.365318 Hz
AQ 1.3664756 sec
RG 31285.0
DM 20.850 usec
DE 6.00 usec
TE 298.2 K
CHET2 145.000000
G1 2.00000000 sec
G2 0.00000000 sec
G13 0.00000000 sec
DELTA 0.00001916 sec

===== CHANNEL f1 =====
NUC1 13C
P1 10.00 usec
P2 30.00 usec
SFO1 100.5974818 MHz

===== GRADIENT CHANNEL =====
CPDPRG1 zgpg30
NUC1 13C
P1 10.00 usec
SFO1 100.5974818 MHz

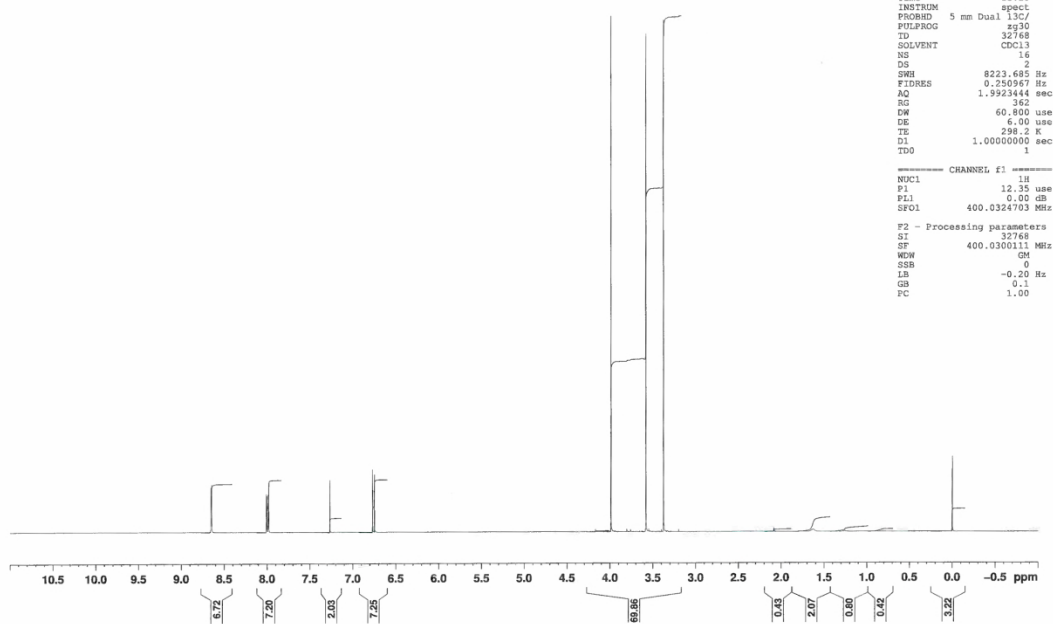
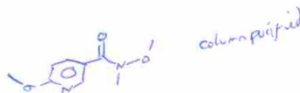
F2 - Acquisition parameters
SI 32768
SF 100.5974240 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 1.40

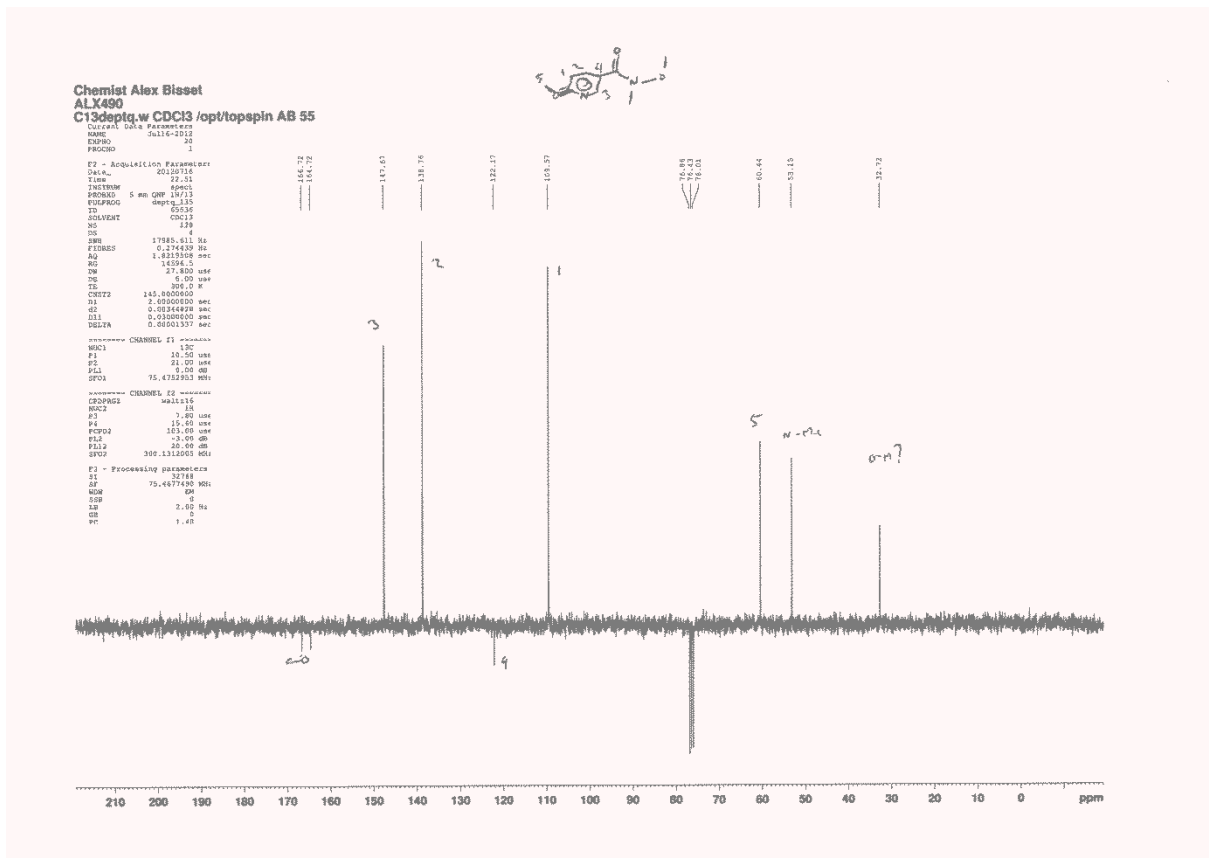
F2 - Processing parameters
SI 32768
SF 100.5974240 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
  
```



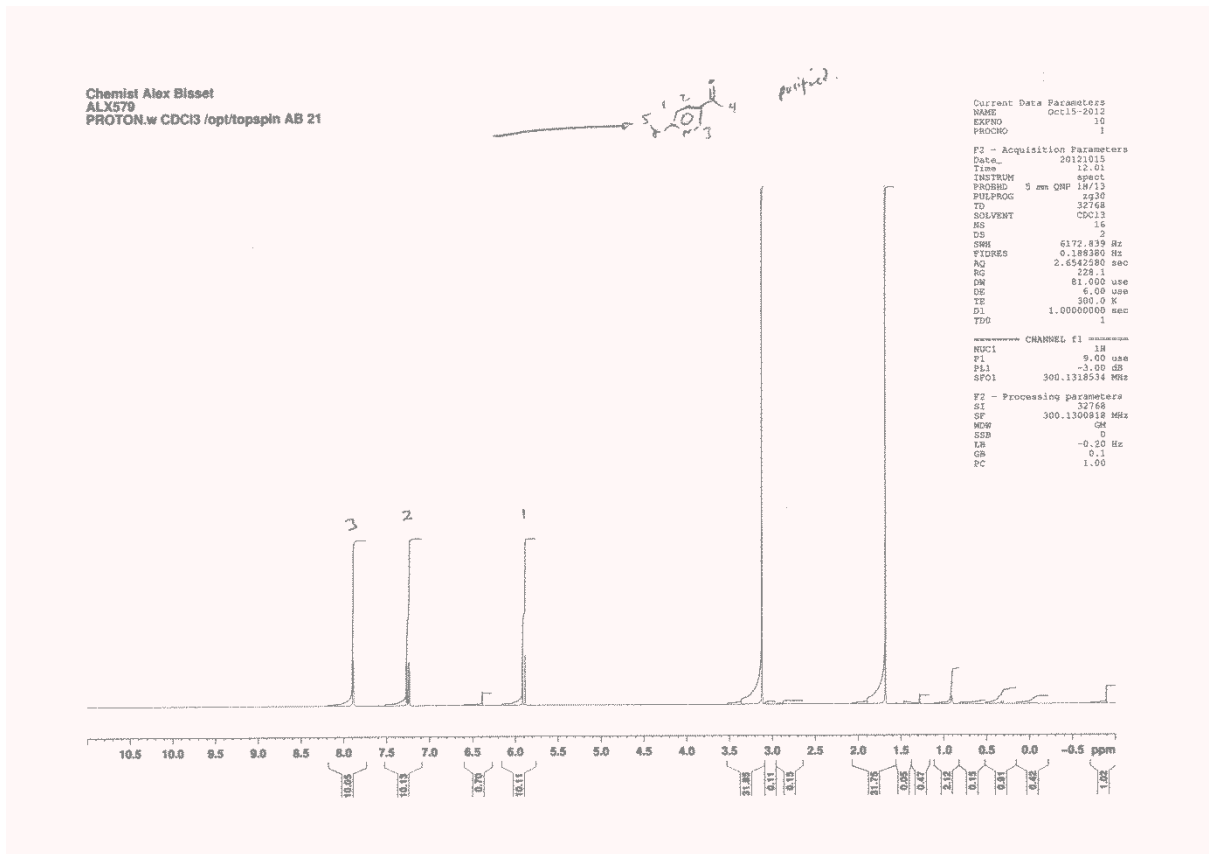
N,6-Dimethoxy-*N*-methylpyridine-3-carboxamide, **28**.

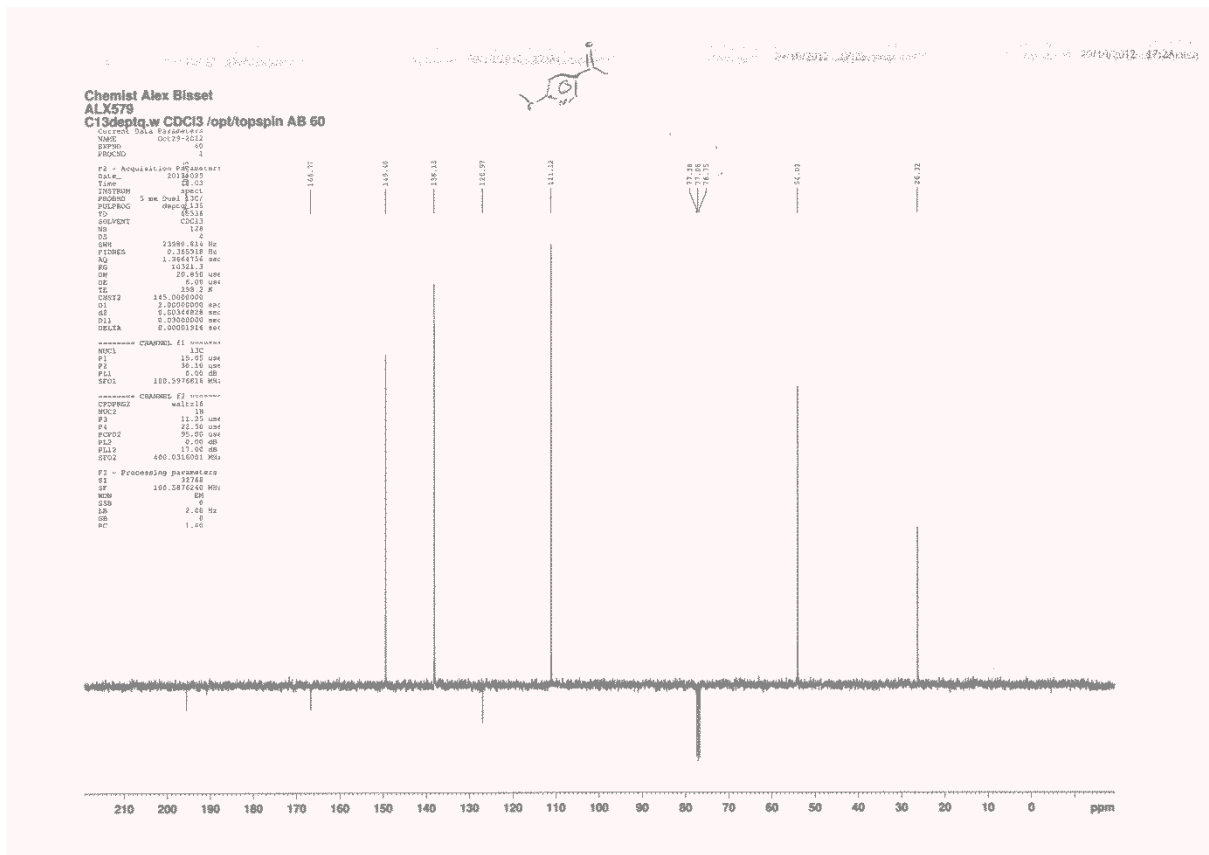
Chemist Alex Bisset
ALX480
PROTON.w CDCI3 /opt/topspin AB 47



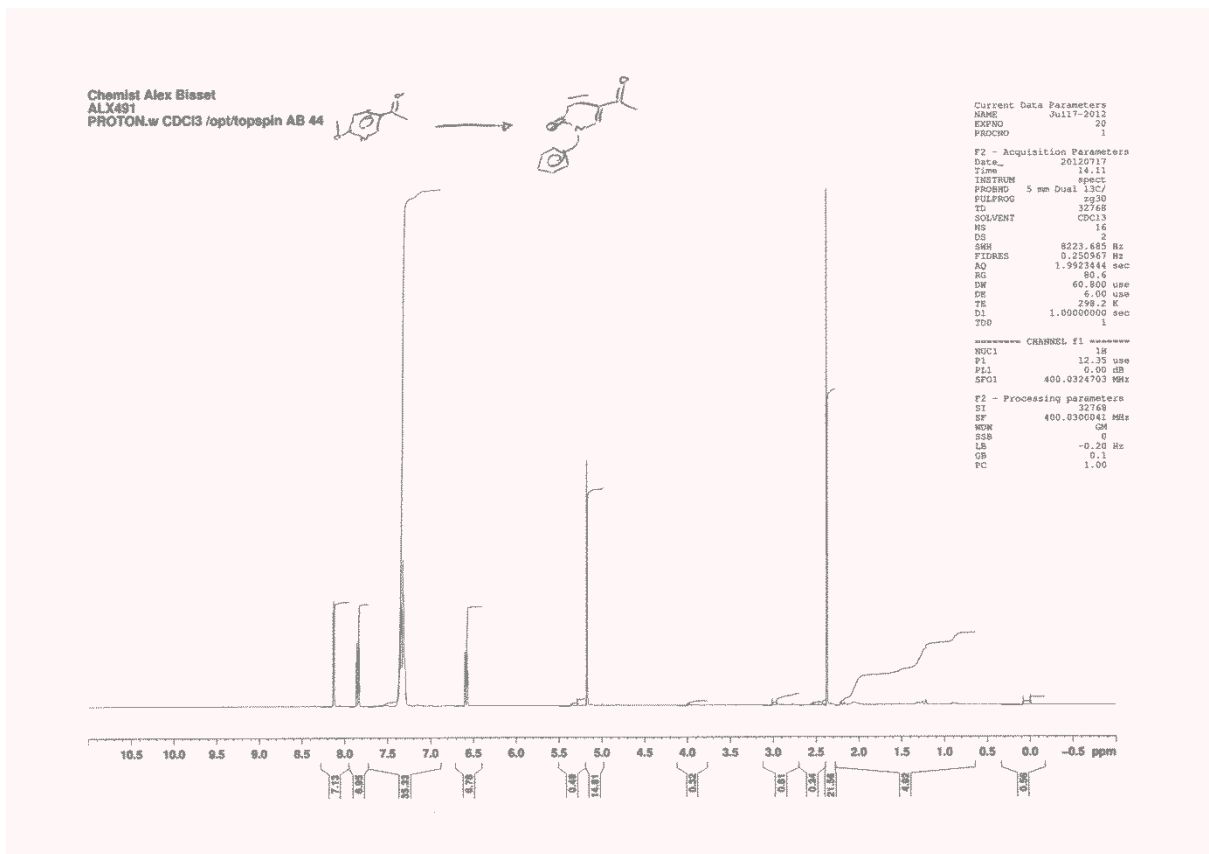


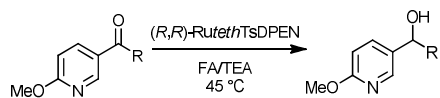
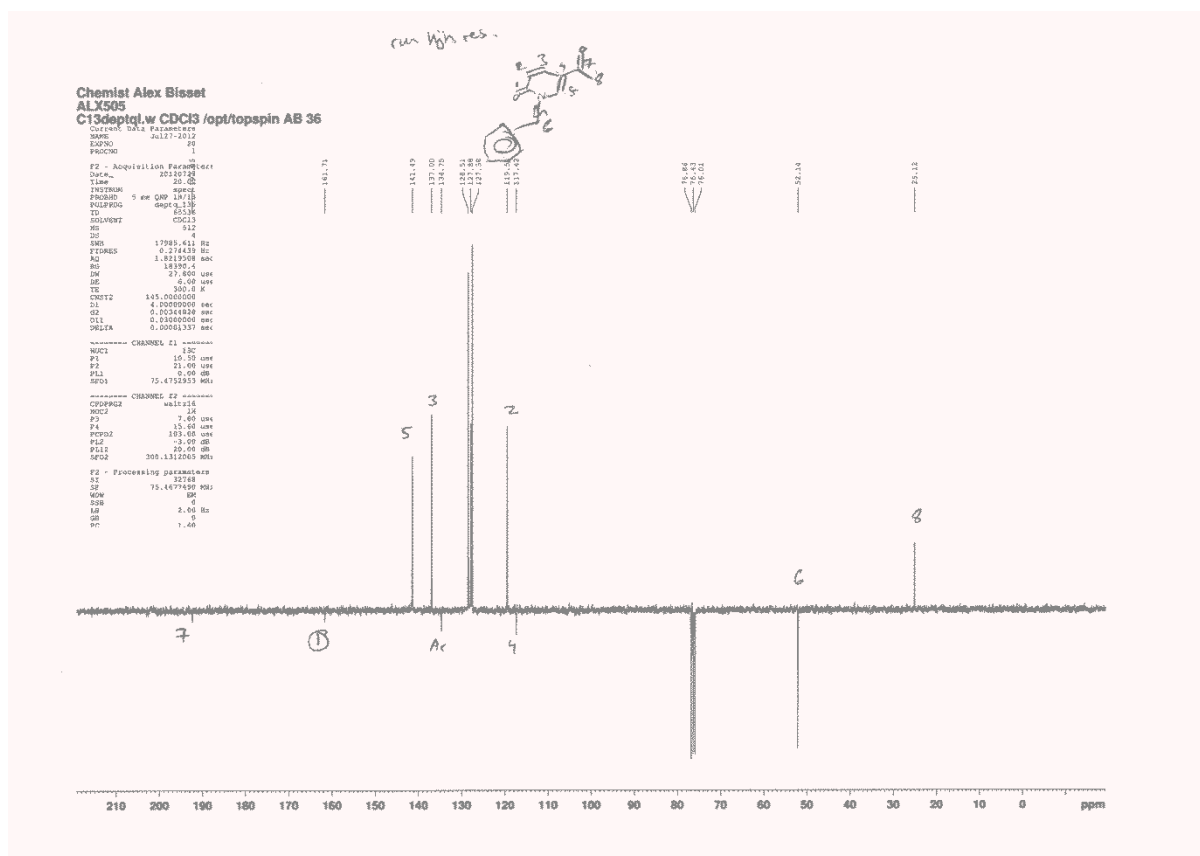
1-(6-Methoxypyridin-3-yl)ethanone, **5**.





5-Acetyl-1-benzylpyridin-2(1H)-one, 27.

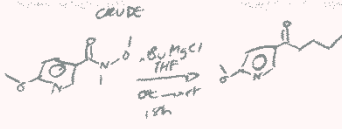




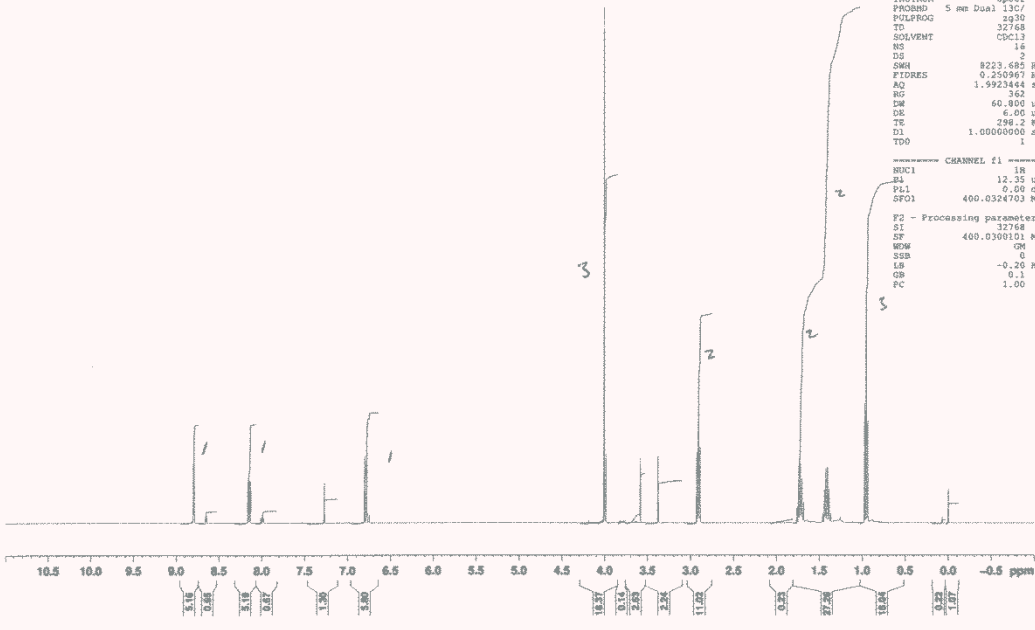
Entry	ketone ^a	R	t / h ^b	Prod.	Ee / %
1	5 ^b	Methyl	21	(<i>R</i>)- 10 ^h	83 ^d
2	6	<i>n</i> -butyl	20	(<i>R</i>)- 11 ⁱ	76 ^d
3	7	<i>i</i> -propyl	22	(<i>R</i>)- 12 ⁱ	53 ^c
4	8	Cyclohexyl	24	(<i>R</i>)- 13 ⁱ	35 ^f
5	9	Phenyl	24	(-)- 14	48 ^e

1-(4-Methoxyphenyl)pentan-1-one, **6**.

ALX517
 Chemist Alex Bisset
 ALX517
 PROTON.w CDC13 /opt/topapin AB 41

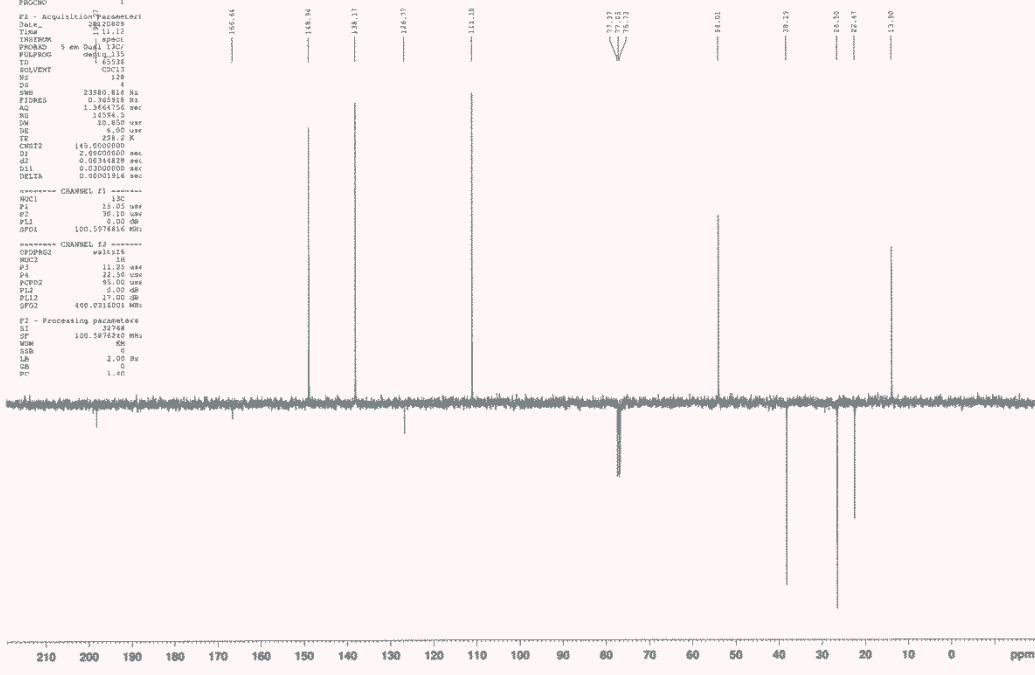


Current Data Parameters
 NAME Aug07-2011
 EXPR0 10
 PROCNO 1
 F2 - Acquisition Parameters
 Date_ 20120801
 Time 13.39
 INSTRUM spect
 PROBHD 5 mm Dual 13C/
 PULPROG zgpg30
 TD 32768
 SOLVENT CDCl3
 NS 16
 DS 2
 SWS 8223.688 Hz
 FIDRES 0.250967 Hz
 AQ 1.9920444 sec
 RG 362
 DW 60.800 usec
 DE 6.00 usec
 TE 298.2 K
 D1 1.0000000 sec
 TDO 1



----- CHANNEL f1 -----
 NUC1 1H
 P1 12.00 usec
 PL1 0.00 dB
 SFO1 400.0324703 MHz
 F2 - Processing parameters
 SI 32768
 SF 400.0300101 MHz
 WDW GM
 SSB 0
 LB -0.20 Hz
 GB 0.1
 PC 1.00

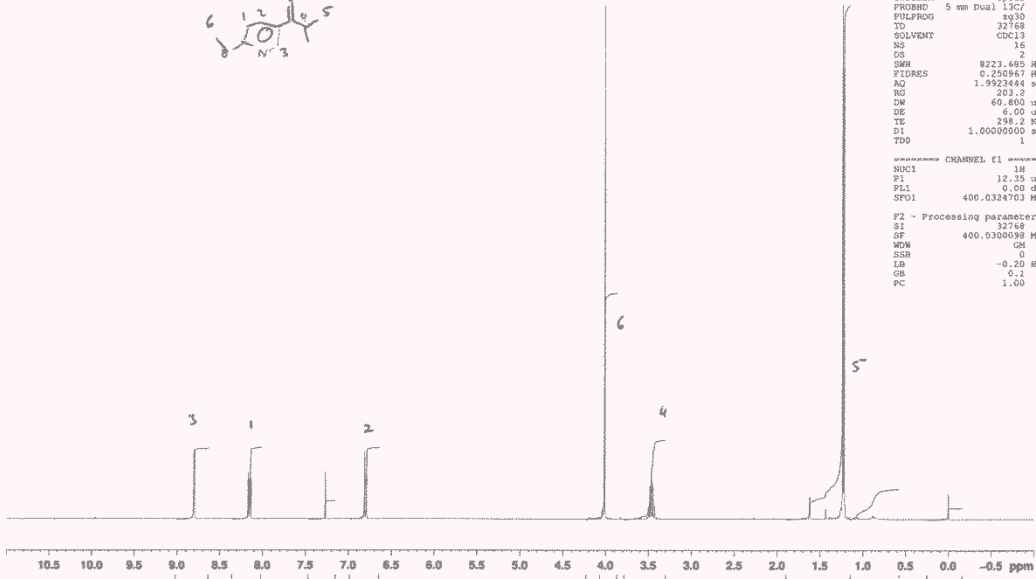
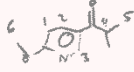
ALX517
 Chemist Alex Bisset
 ALX517
 C13deptq.w CDC13 /opt/topapin AB 21



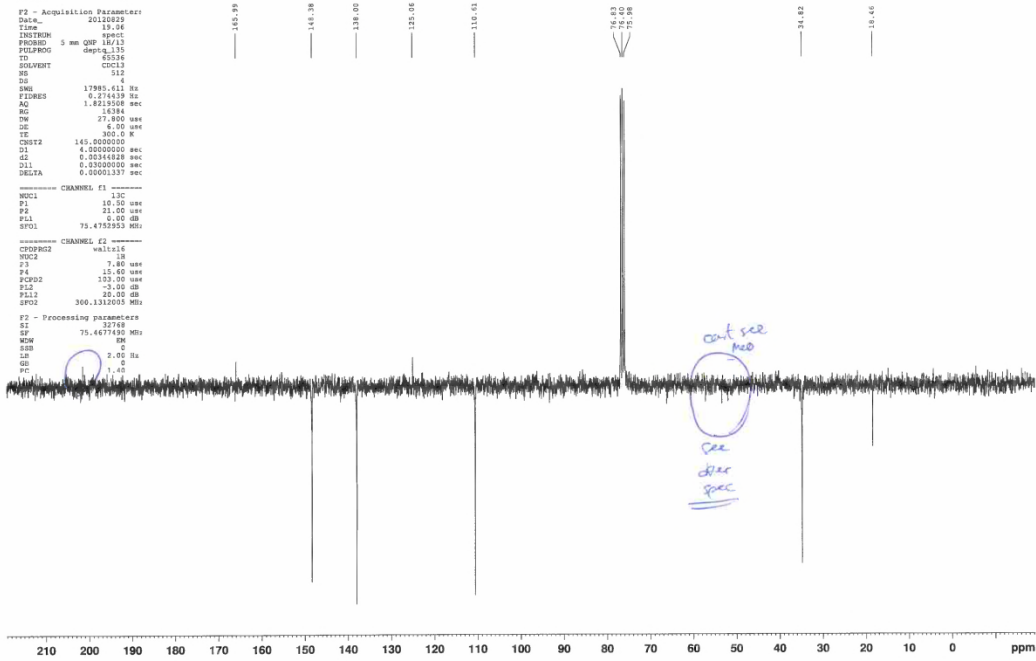
Current Data Parameters
 NAME Aug07-2011
 EXPR0 11
 PROCNO 1
 F2 - Acquisition Parameters
 Date_ 20120801
 Time 11.12
 INSTRUM spect
 PROBHD 5 mm Dual 13C/
 PULPROG zgpg30
 TD 32768
 SOLVENT CDCl3
 NS 16
 DS 2
 SWS 23380.612 Hz
 FIDRES 0.260918 Hz
 AQ 1.9849756 sec
 RG 362
 DW 60.800 usec
 DE 6.00 usec
 TE 298.2 K
 D1 1.0000000 sec
 TDO 1
 F2 - Processing parameters
 SI 32768
 SF 100.5076416 MHz
 WDW GM
 SSB 0
 LB 2.00 Hz
 GB 0
 PC 1.40

1-(6-Methoxy-3-pyridinyl)-2-methylpropan-1-one, 7.

Chemist Alex Bisset
ALX522
PROTON.w CDC13 /opt/topspin AB 52



Chemist Alex Bisset
ALX522
C13deptql.w CDC13 /opt/topspin AB 20



Cyclohexyl(6-methoxypyridin-3-yl)methanone, **8**.

Chemist Alex Bisset
 ALX609 pure
 PROTON.w CDC13 /opt/topspin AB 51

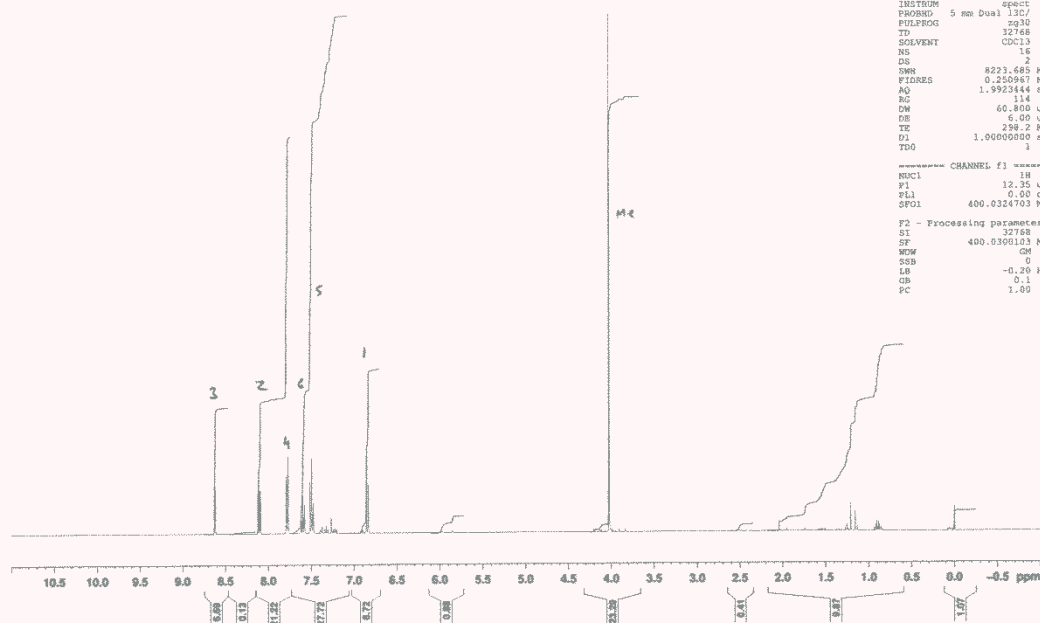


Current Data Parameters
 NAME Nov09-2012
 EXPNO 40
 PROCNO 1

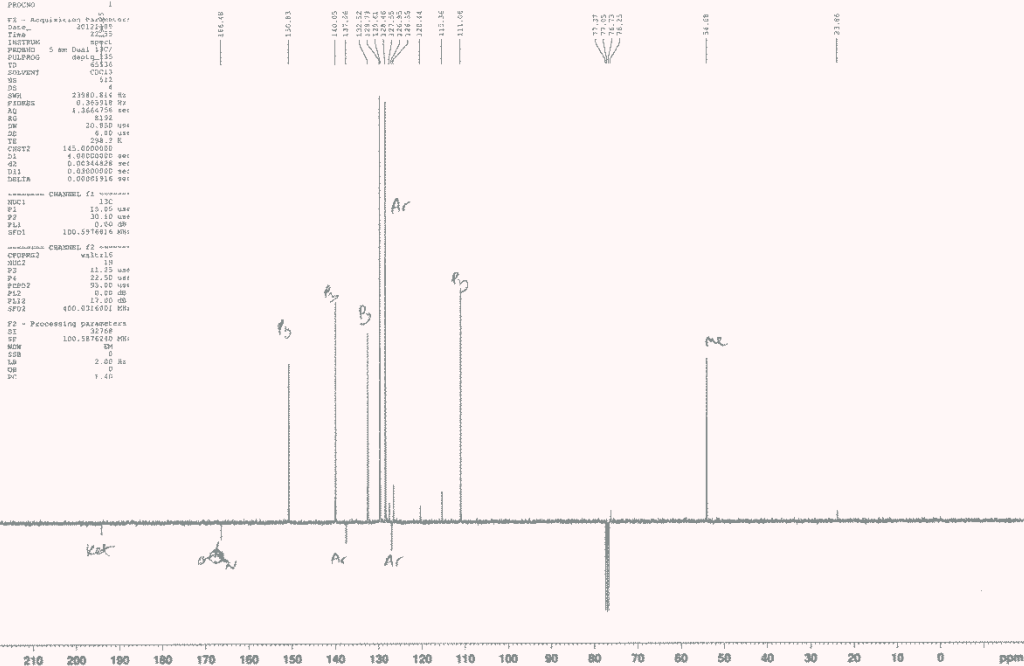
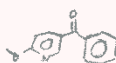
F2 - Acquisition Parameters
 Date_ 2012109
 Time 16.38
 INSTRUM spect
 PROBRD 5 mm Dual 13C/
 PULPROG zgpg30
 TD 32768
 SOLVENT CDC13
 NS 16
 DS 2
 SWS 8223.485 Hz
 FIDRES 0.250967 Hz
 AQ 1.9923444 sec
 RG 114
 DM 60.800 usec
 DE 6.00 usec
 TE 298.2 K
 D1 1.0000000 sec
 TSD 1

----- CHANNEL f1 -----
 NUC1 1H
 P1 12.35 usec
 PL1 0.00 dB
 SFO1 400.0324703 MHz

F2 - Processing parameters
 SI 32768
 SF 400.0301103 MHz
 MDW GM
 SGB 0
 LB -0.20 Hz
 GB 0.1
 PC 1.00

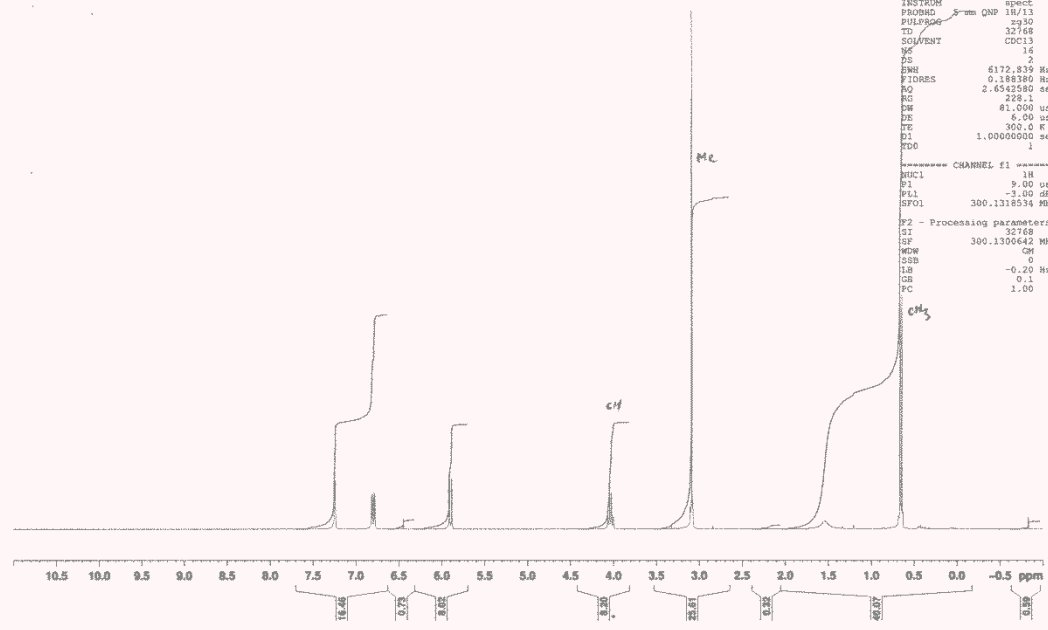
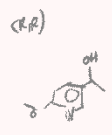


Chemist Alex Bisset
 ALX609 pure
 C13deptgt.w CDC13 /opt/topspin AB 51



(S)-1-(6-Methoxy-pyridin-3-yl)ethanol, (S)-10.

Chemist Alex Bisset
 ALX584c
 PROTON.w CDC13 /opt/topspin AB 18



Current Data Parameters
 NAME Oct16-2012
 EXPNO 10
 PROCNO 1

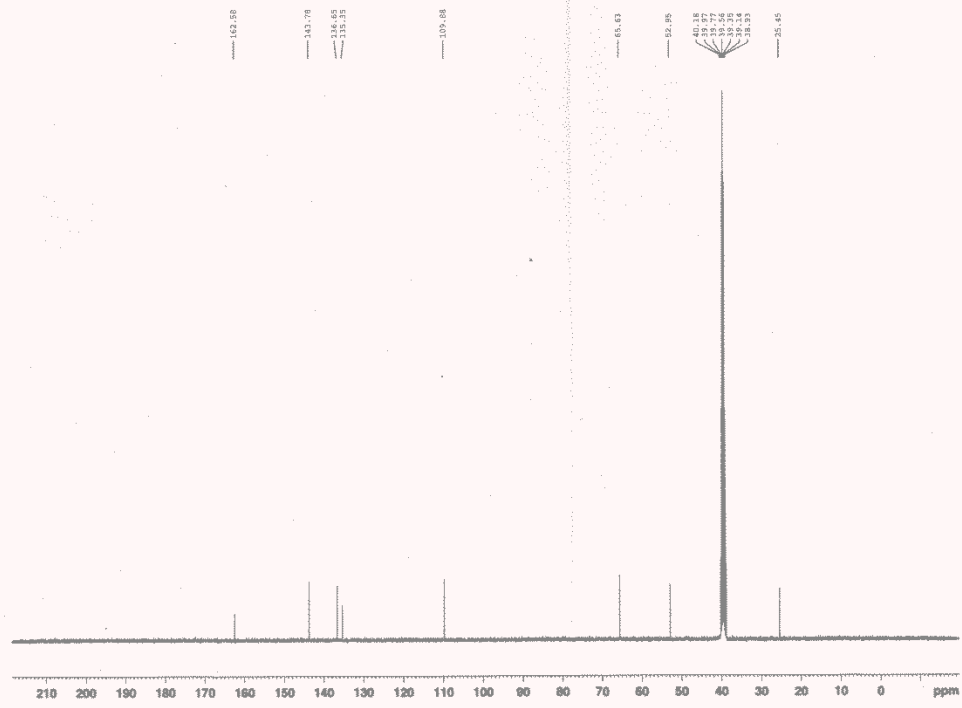
F2 - Acquisition Parameters
 Date_ 20111216
 Time 16.05
 INSTRUM spect
 PROBHD 5 mm QNP 1H/13
 PULPROG zg30
 TO 32768
 SOLVENT CDC13
 NS 14
 DS 2
 SWH 5172.839 Hz
 FIDRES 0.188395 Hz
 AQ 2.6542580 sec
 RG 423.1
 SW 81.000 use
 DE 8.00 use
 TE 303.2 K
 D1 1.0000000 sec
 FID 1

===== CHANNEL f1 =====
 NUC1 1H
 P1 9.00 use
 PL1 -3.00 dB
 SFO1 300.1318534 MHz

F2 - Processing parameters
 SI 32768
 SF 300.1300642 MHz
 WDR CM
 ZSB 0
 LB -0.20 Hz
 GB 0.1
 PC 1.00

Name A Bisset
 N No krw983
 Notebook Ref EN05661-36
 carbon.az DMSO /opt/topspin2.1 chem 36

5-10

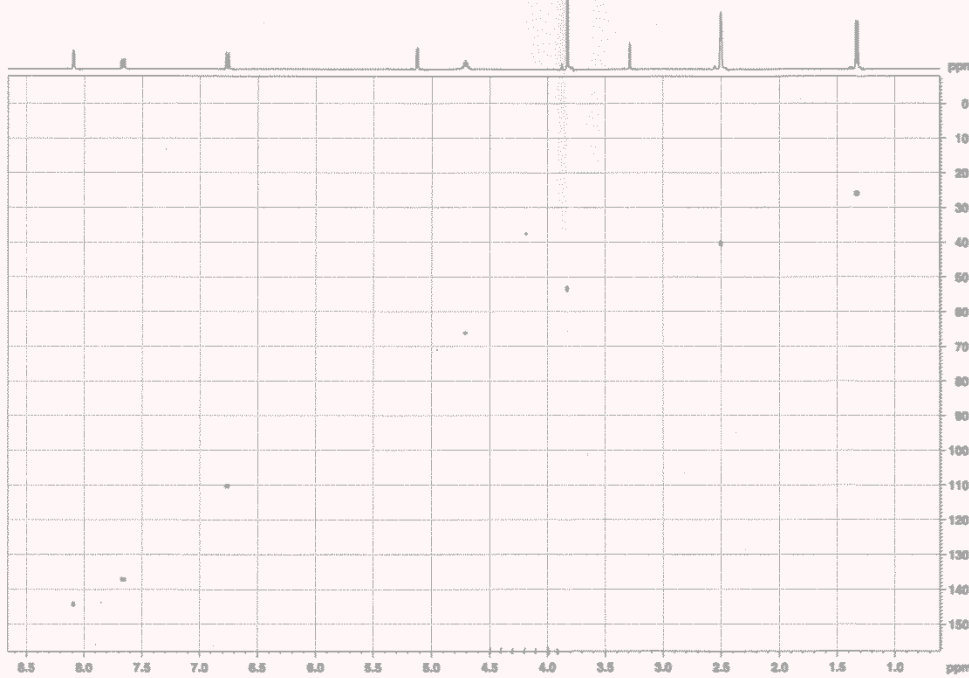


NAME 111215
 EXPNO 330
 PROCNO 1
 Date_ 20111215
 Time 20.44
 INSTRUM AV400-1481A
 PROBHD 5 mm QNP 1H/13
 PULPROG zgpg30
 TO 65536
 SOLVENT DMSO
 NS 800
 DS 4
 SWH 23960.814 Hz
 FIDRES 0.365918 Hz
 AQ 1.3664756 sec
 RG 23170.5
 DW 20.850 use
 DE 20.00 use
 TE 303.2 K
 D1 2.0000000 sec
 D11 0.0300000 sec
 TDO 10

===== CHANNEL f1 =====
 NUC1 13C
 P1 9.00 use
 PL1 1.70 dB
 SFO1 100.6228298 MHz

===== CHANNEL f2 =====
 CPDPRG2 waltz16
 NUC2 1H
 PCPD2 80.00 use
 PL2 -2.00 dB
 PL12 15.89 dB
 PL13 16.00 dB
 SFO2 400.1316005 MHz
 SI 32768
 SF 100.6128193 MHz
 WDR EM
 ZSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

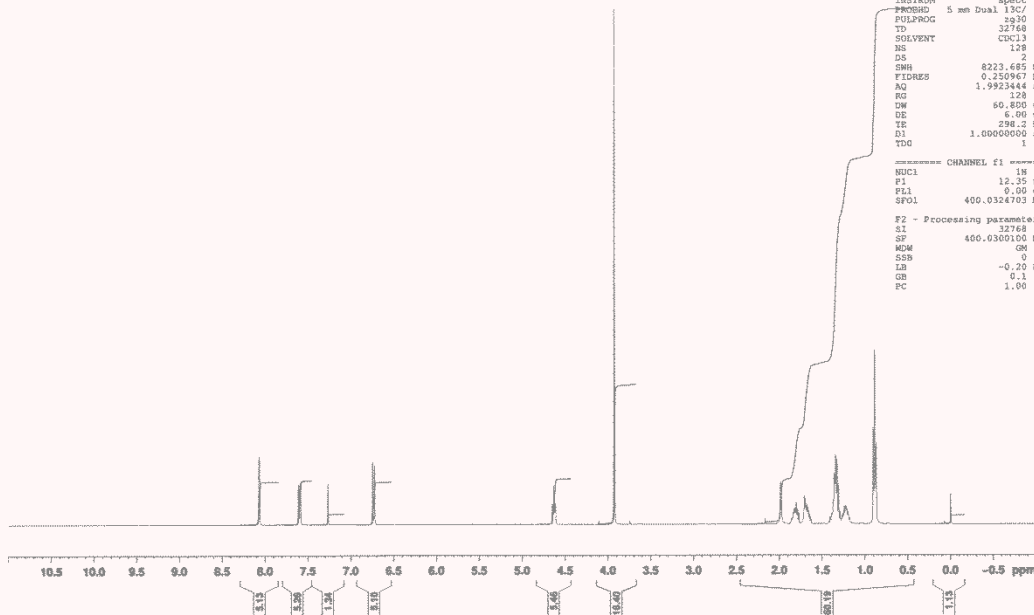
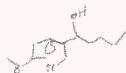
Name A Bisset
M No krtw983
Notebook Ref EN05661-36
HSQC.sz DMSO /opt/topspin2.1 chem 36



```
NAME          311213
EXPNO         1
PROCNO        1
Date_         20111211
Time          21.27
INSTRUM      AV400 14614
PROBHD       5 mm QNP 1H/13
PULPROG      zgpg30
SOLVENT      DMSO
NS           1248
DS           4
SWH          3221.640 Hz
FIDRES      0.1418971 Hz
AQ          0.7117896 sec
RG           313.53
DW          6.02 usec
DE          197.150 usec
TE          300.2 K
NUC1         13C
NUC2         1H
PCPD2        140.000000 sec
D1          0.00000000 sec
D11         1.84230788 sec
D4          0.00176416 sec
SLS         0.00000000 sec
SLS2        0.00000000 sec
SLS3        0.00000000 sec
SLS4        0.00000000 sec
===== CHANNEL f1 =====
NUC1         1H
P1          10.00 usec
P2          20.00 usec
PC1         0.00 dB
PC2         -2.00 dB
SFO1        400.131809 MHz
===== CHANNEL f2 =====
CPDPRG2      gpcgpg2
NUC2         13C
PC2          8.00 usec
P4          18.00 usec
P8          80.00 usec
PCPD2       80.00 usec
PCPD3       120.00 dB
PL2         3.70 dB
PL3         30.87 dB
SFO2        100.6203100 MHz
=====
SFO          Cmp86.0.9, 70.1
SFO2         0.500
SFO3         0.500
===== GRABBER CHANNEL =====
CPDPRG1      gpcgpg1
NUC1         13C
PC1          8.00 usec
P2          18.00 usec
P4          80.00 usec
PCPD1       80.00 usec
PCPD2       120.00 dB
PL1         3.70 dB
PL2         30.87 dB
SFO1        100.6203100 MHz
=====
SFO          Cmp86.0.9, 70.1
SFO2         0.500
SFO3         0.500
=====
===== GRABBER CHANNEL =====
CPDPRG1      gpcgpg1
NUC1         13C
PC1          8.00 usec
P2          18.00 usec
P4          80.00 usec
PCPD1       80.00 usec
PCPD2       120.00 dB
PL1         3.70 dB
PL2         30.87 dB
SFO1        100.6203100 MHz
=====
SFO          Cmp86.0.9, 70.1
SFO2         0.500
SFO3         0.500
=====
===== GRABBER CHANNEL =====
CPDPRG1      gpcgpg1
NUC1         13C
PC1          8.00 usec
P2          18.00 usec
P4          80.00 usec
PCPD1       80.00 usec
PCPD2       120.00 dB
PL1         3.70 dB
PL2         30.87 dB
SFO1        100.6203100 MHz
=====
SFO          Cmp86.0.9, 70.1
SFO2         0.500
SFO3         0.500
=====
```

(R)-1-(6-Methoxypyridin-3-yl)pentan-1-ol, (R)-11.

Chemist Alex Bisset
ALX526
PROTONweak.w CDC13 /opt/topspin AB 32

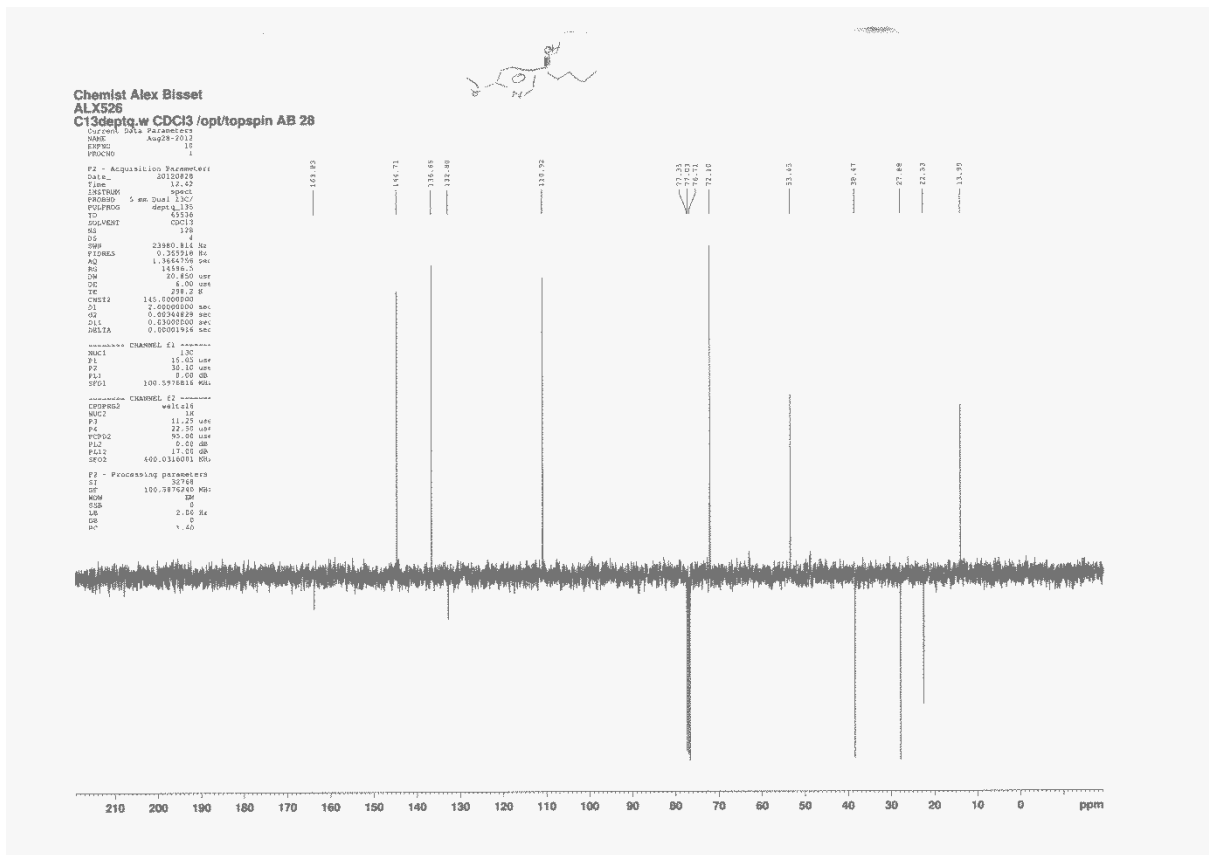


```
Current Data Parameters
NAME          Aug03-2012
EXPNO         70
PROCNO        1

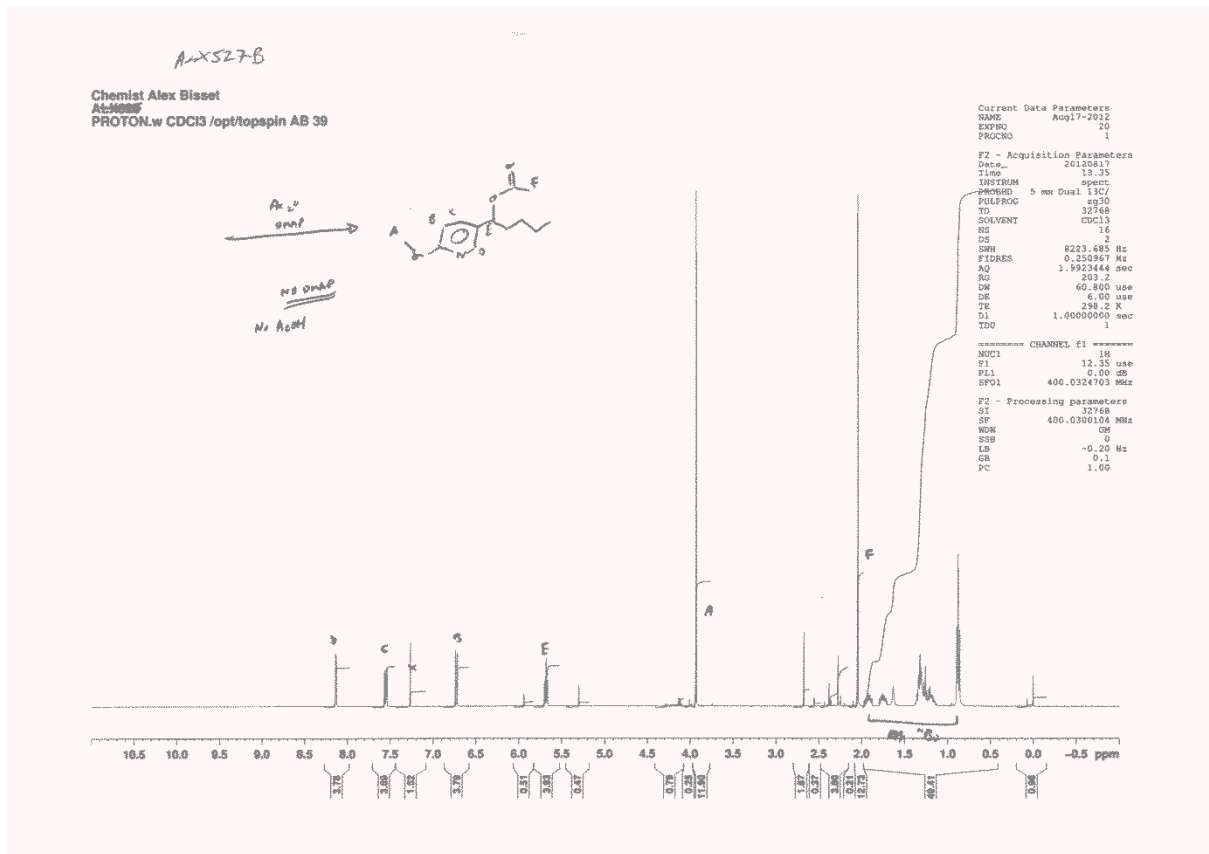
F2 - Acquisition Parameters
Date_         20120828
Time          16.26
INSTRUM      spect
PROBHD       5 mm Dual 13C/
PULPROG      zg30
TD           32768
SOLVENT      CDC13
NS           128
DS           2
SWH          8223.680 Hz
FIDRES      0.250967 Hz
AQ          1.9923444 sec
RG           128
DW          60.800 usec
DE          6.500 usec
TE          298.2 K
D1          1.0000000 sec
TD0         1

===== CHANNEL f1 =====
NUC1         1H
P1          12.35 usec
PC1         0.00 dB
SFO1        400.0324703 MHz

F2 - Processing parameters
SI           32768
SF          400.0300100 MHz
MDW         GM
SSB         0
LB          -0.20 Hz
GB          0.1
PC          1.00
```

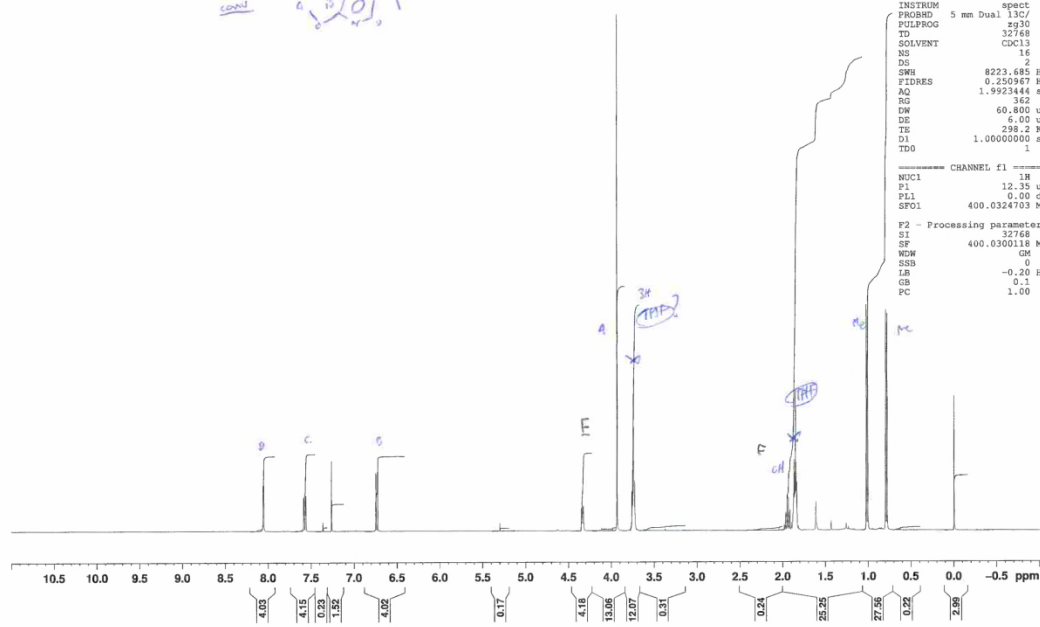
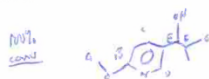



Acetate derivative for ee determination:



(R)-1-(6-Methoxypyridin-3-yl)-2-methylpropan-1-ol, (R)-12.

Chemist Alex Bisset
ALX531
PROTON.w CDC13 /opt/topspin AB 47



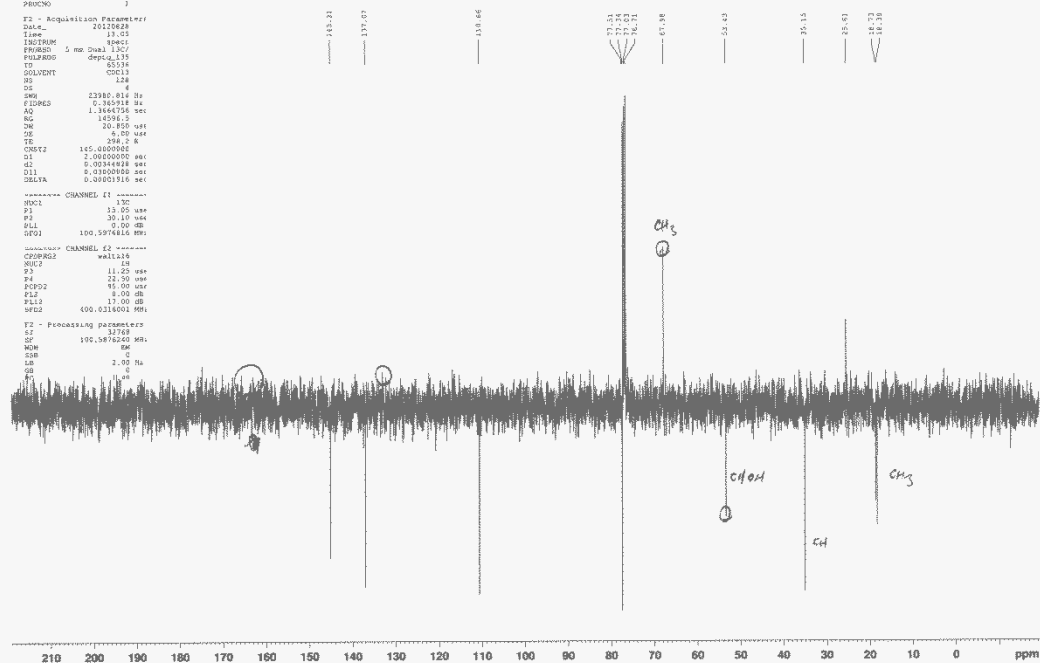
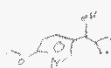
Current Data Parameters
NAME Aug23-2012
EXPRM 30
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120823
Time 15:35
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zg30
TD 32768
SOLVENT CDC13
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 362
DM 60.800 use
DE 6.00 use
TE 298.2 K
D1 1.0000000 sec
TDO 1

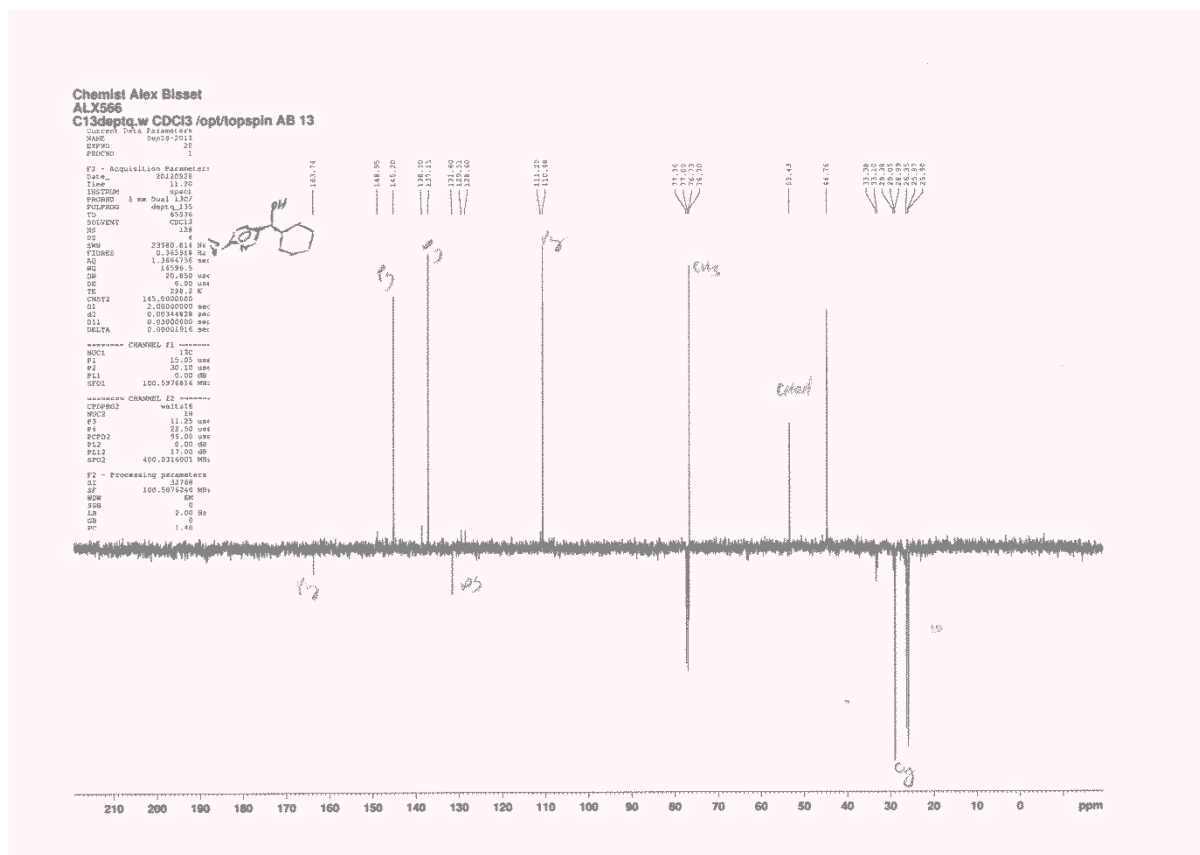
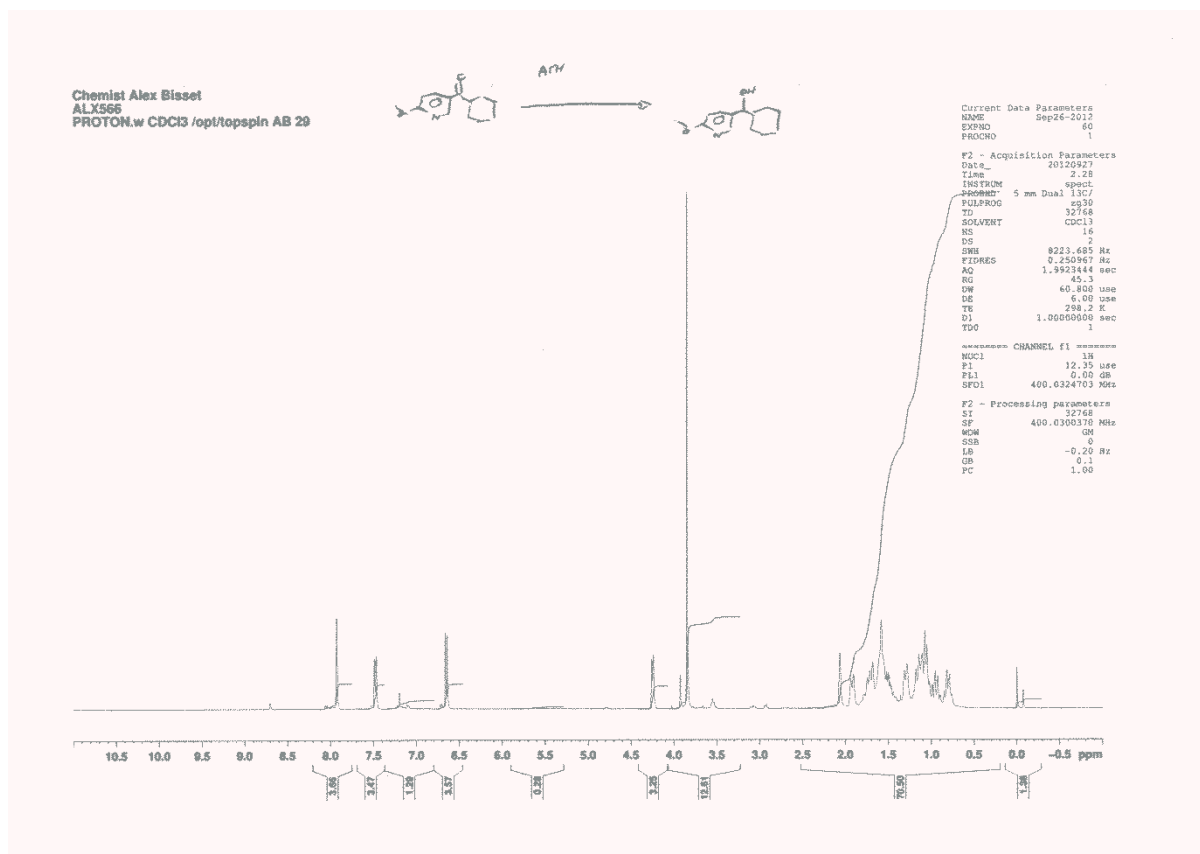
CHANNEL f1
NUC1 1H
P1 12.35 use
PL1 0.00 dB
SFO1 400.0324703 MHz

F2 - Processing parameters
SI 32768
SF 400.030118 MHz
WDW EM
SSB 0
LB -0.20 Hz
GB 0.1
PC 1.00

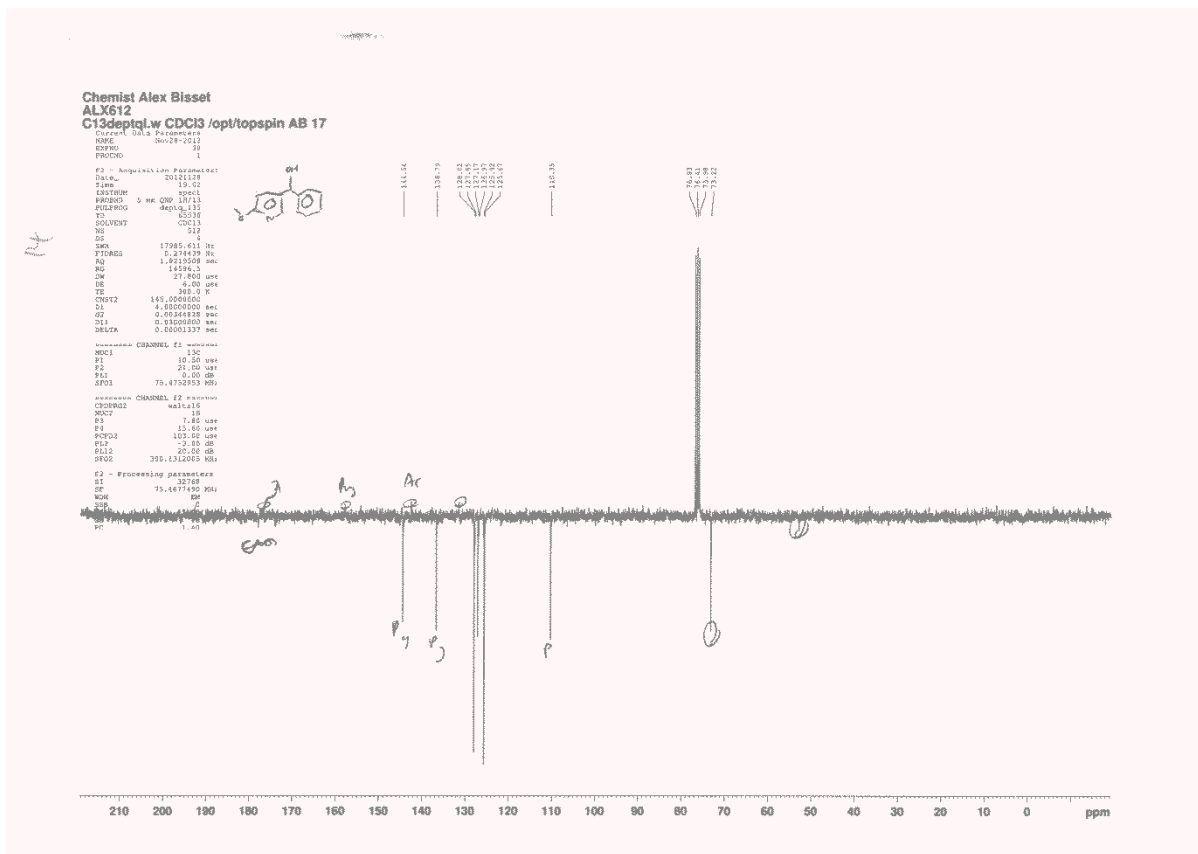
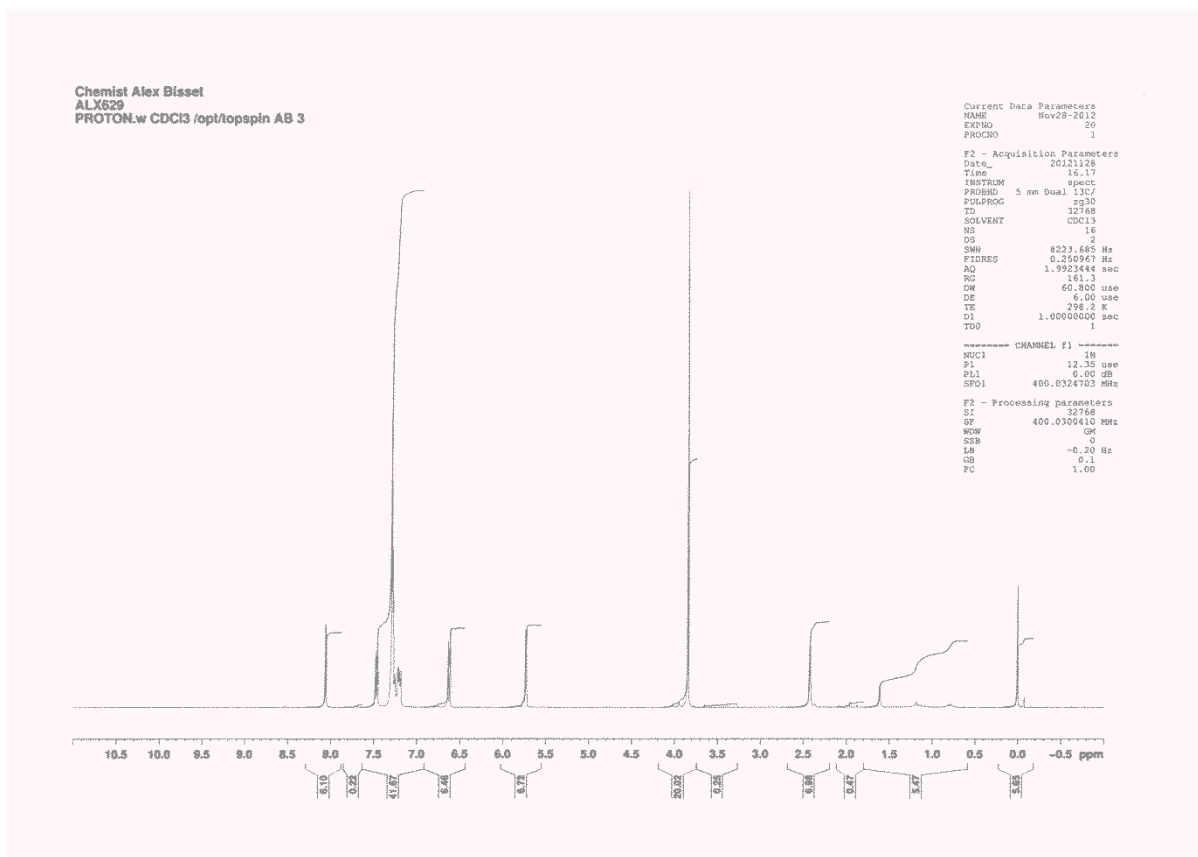
Chemist Alex Bisset
ALX531
C13dept.w CDC13 /opt/topspin AB 30



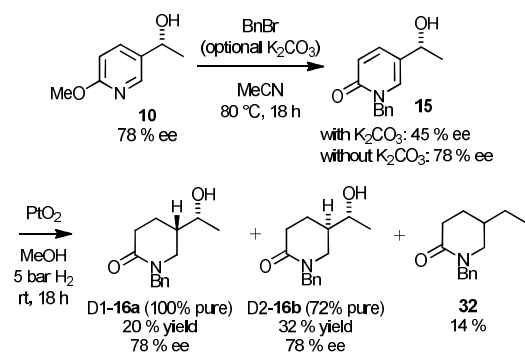
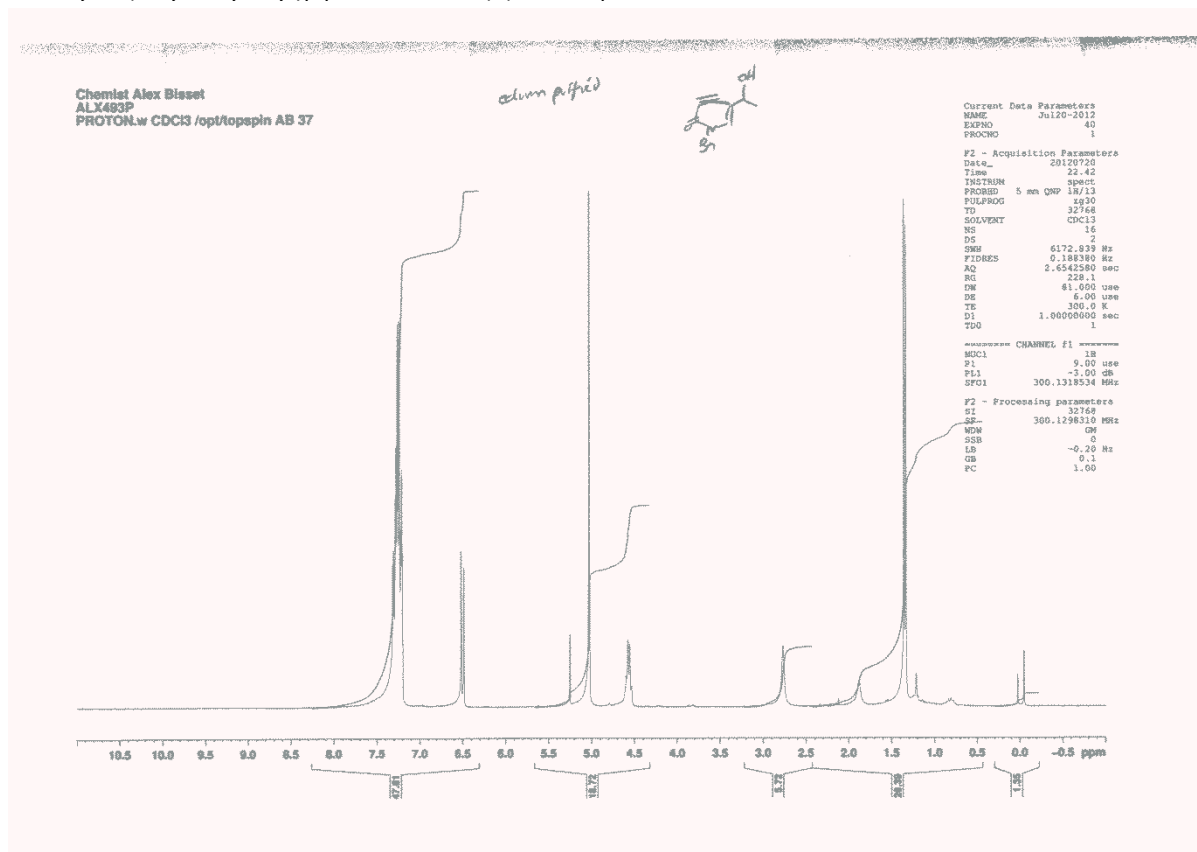
(R)-Cyclohexyl(6-methoxypyridin-3-yl)methanol, (R)-13.



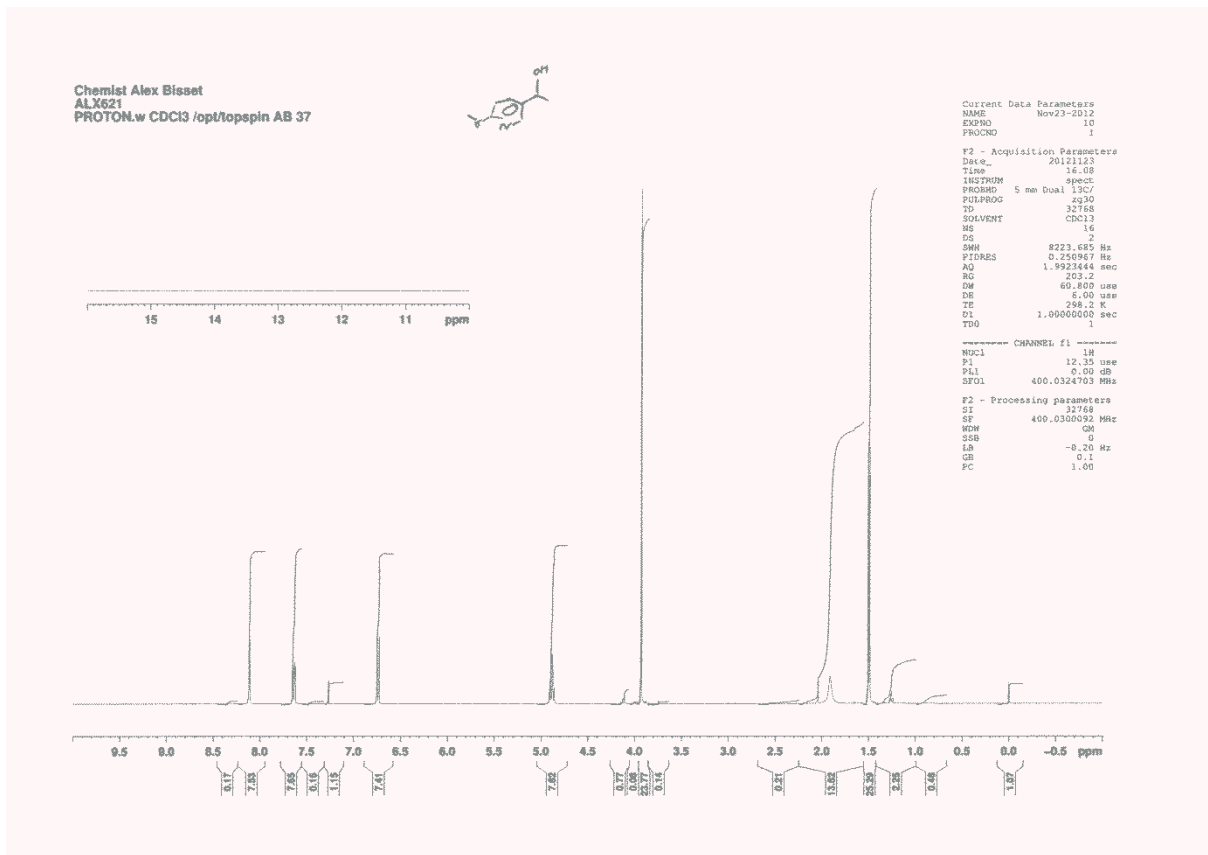
(6-Methoxyphenyl)(phenyl)methanol, (-)-14.



1-Benzyl-5-(1-hydroxyethyl)piperidin-2-one, (R)-**15** sample from reduction of **27** in 42% ee.

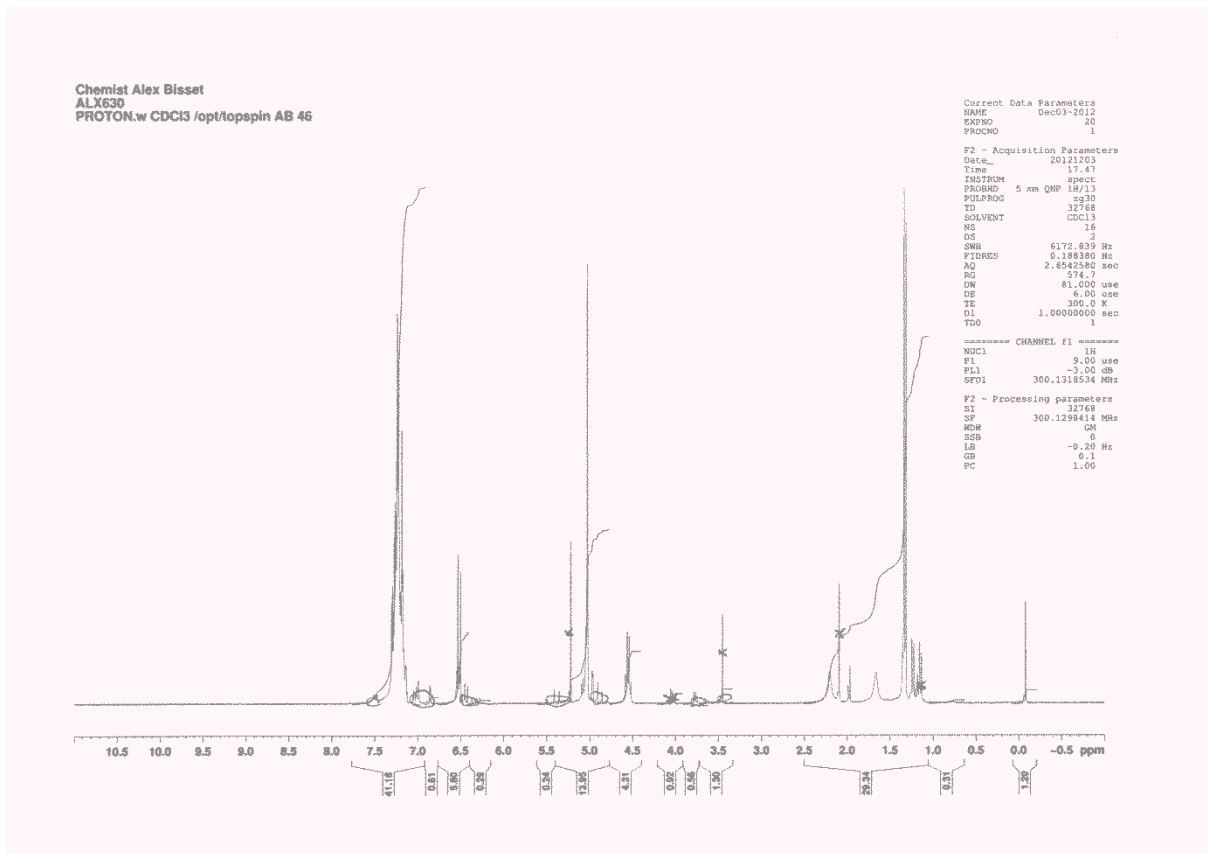


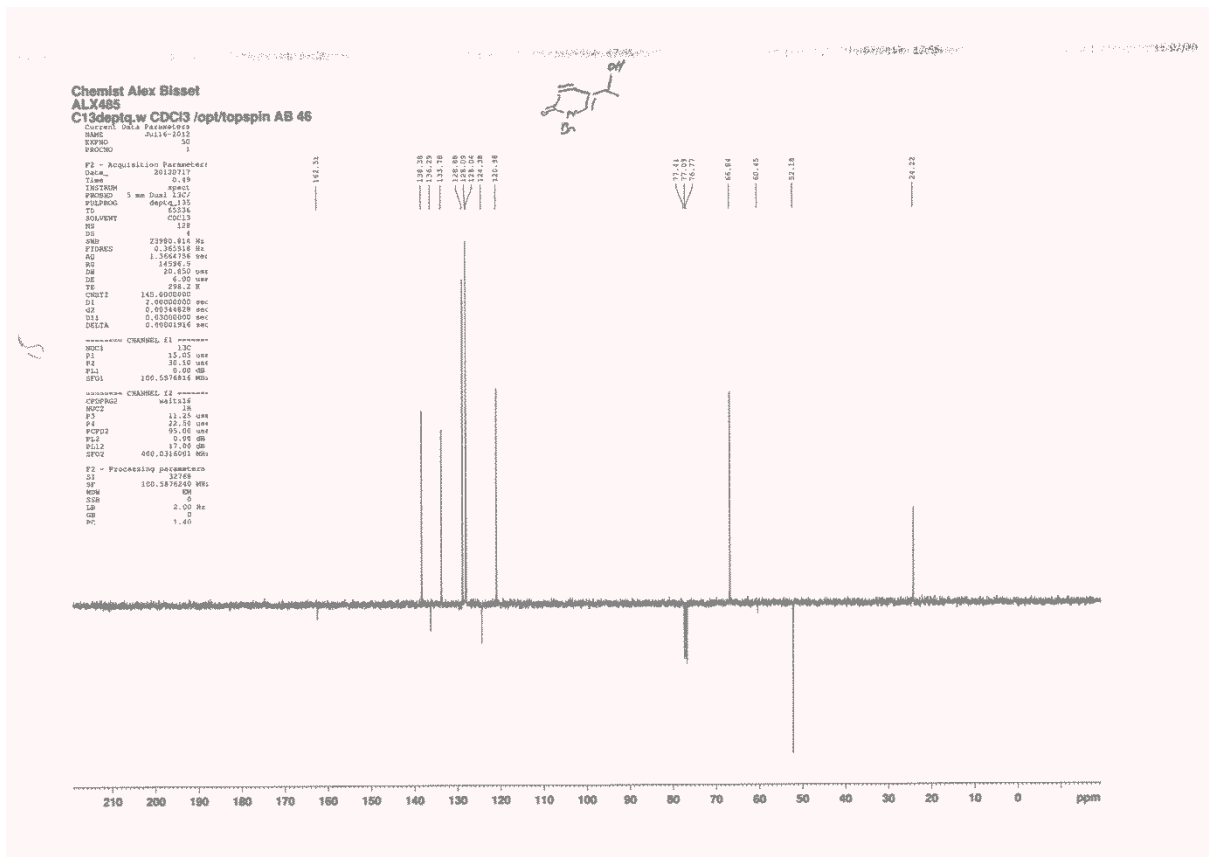
(R)-1-(6-Methoxypyridin-3-yl)ethanol, (R)-**10** (larger scale preparation).



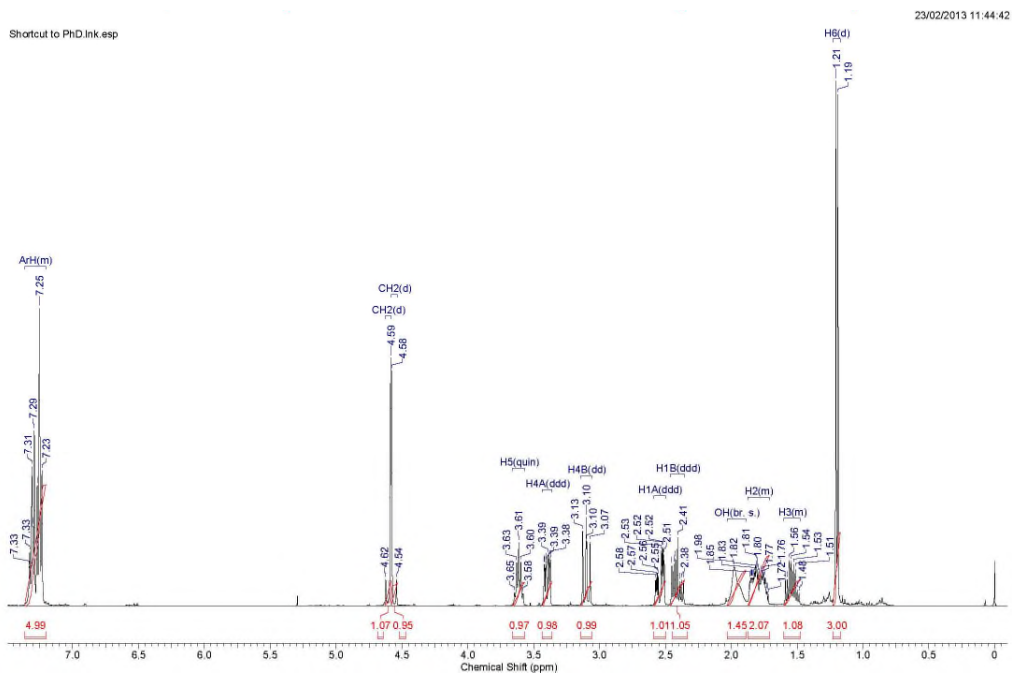
1-Benzyl-5-(1-hydroxyethyl)pyridin-2(1H)-one, (R)- **15** made from the pyridine **10**.

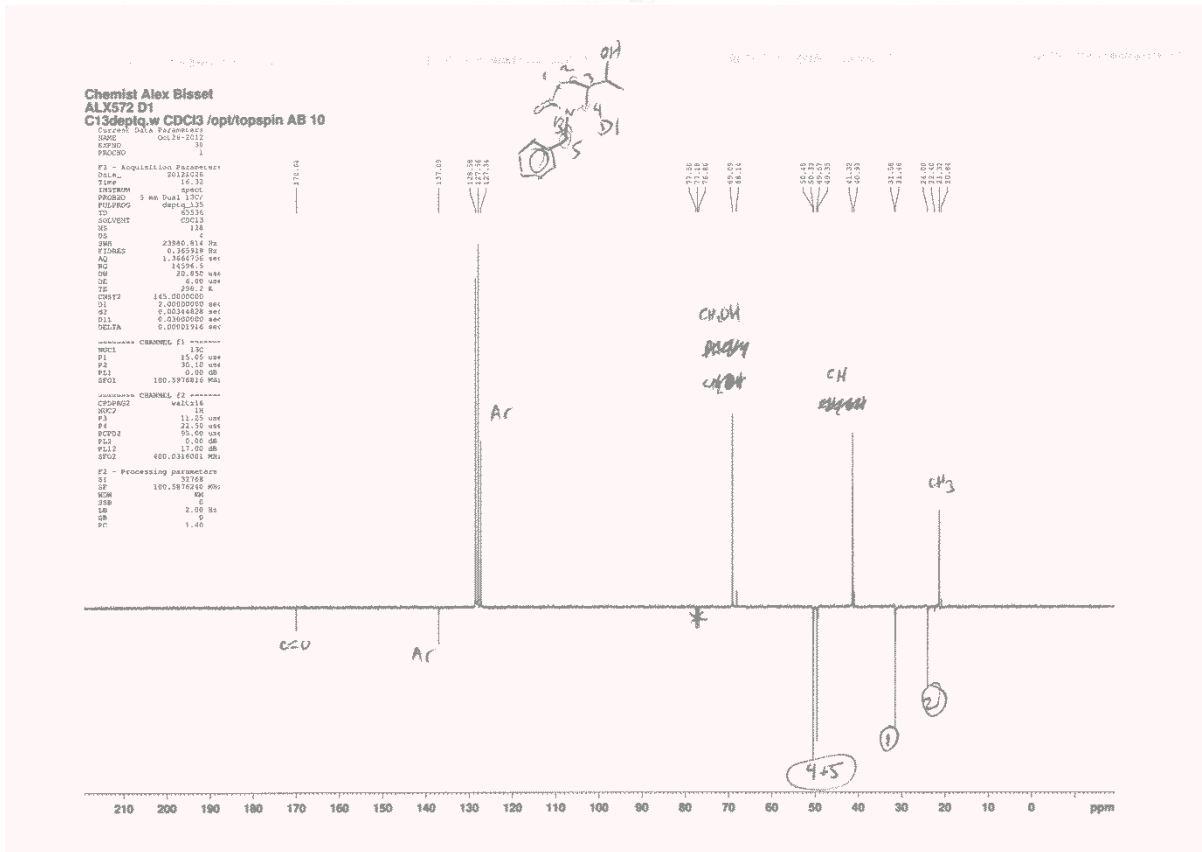
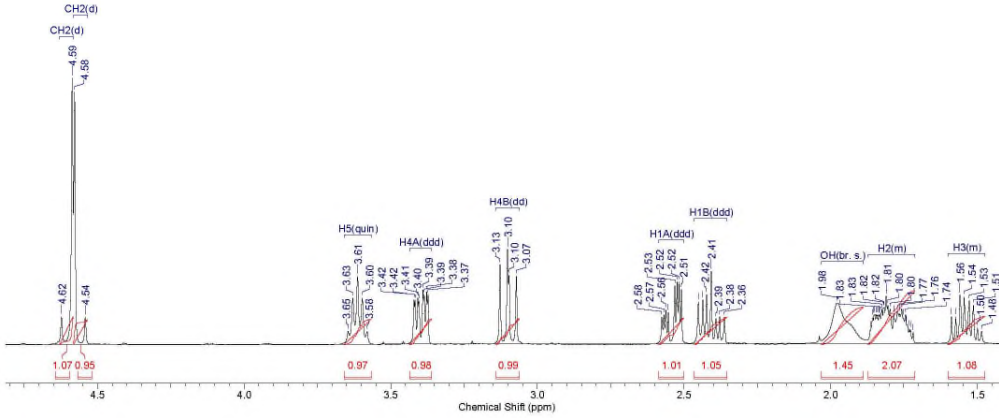
Crude product:



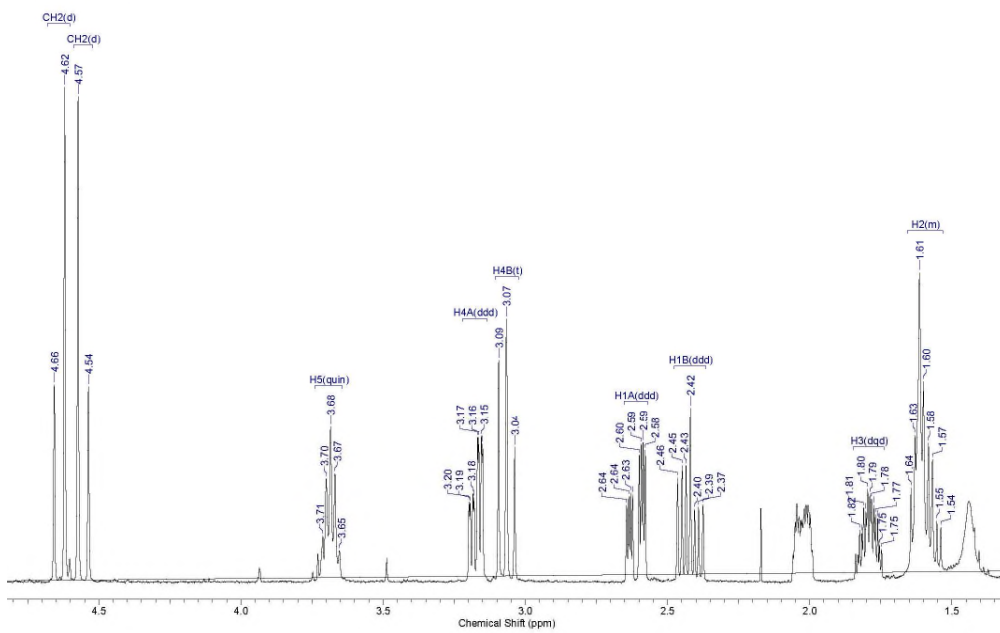
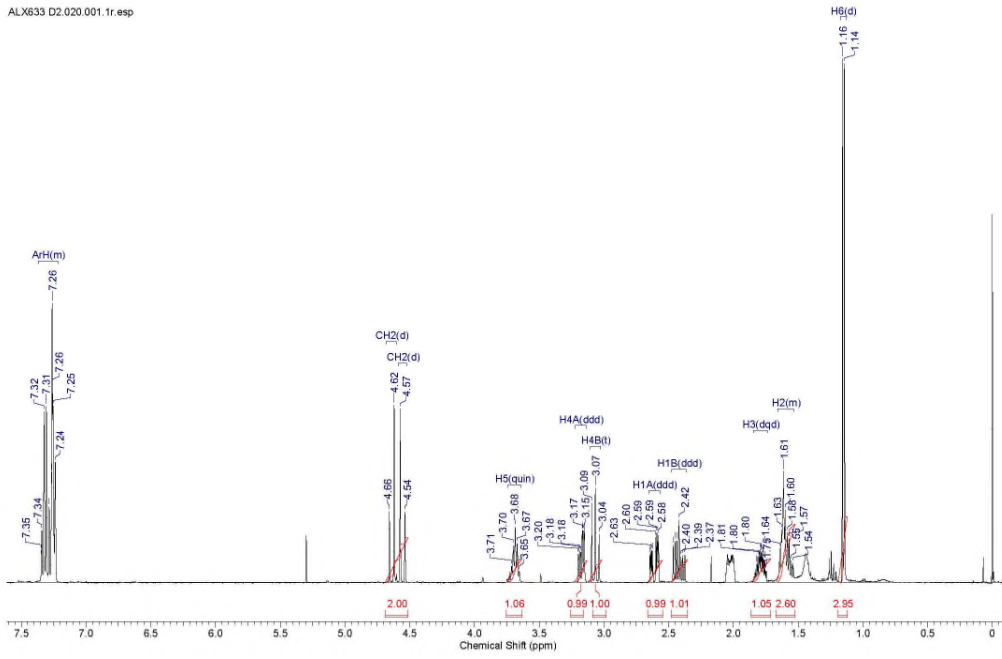


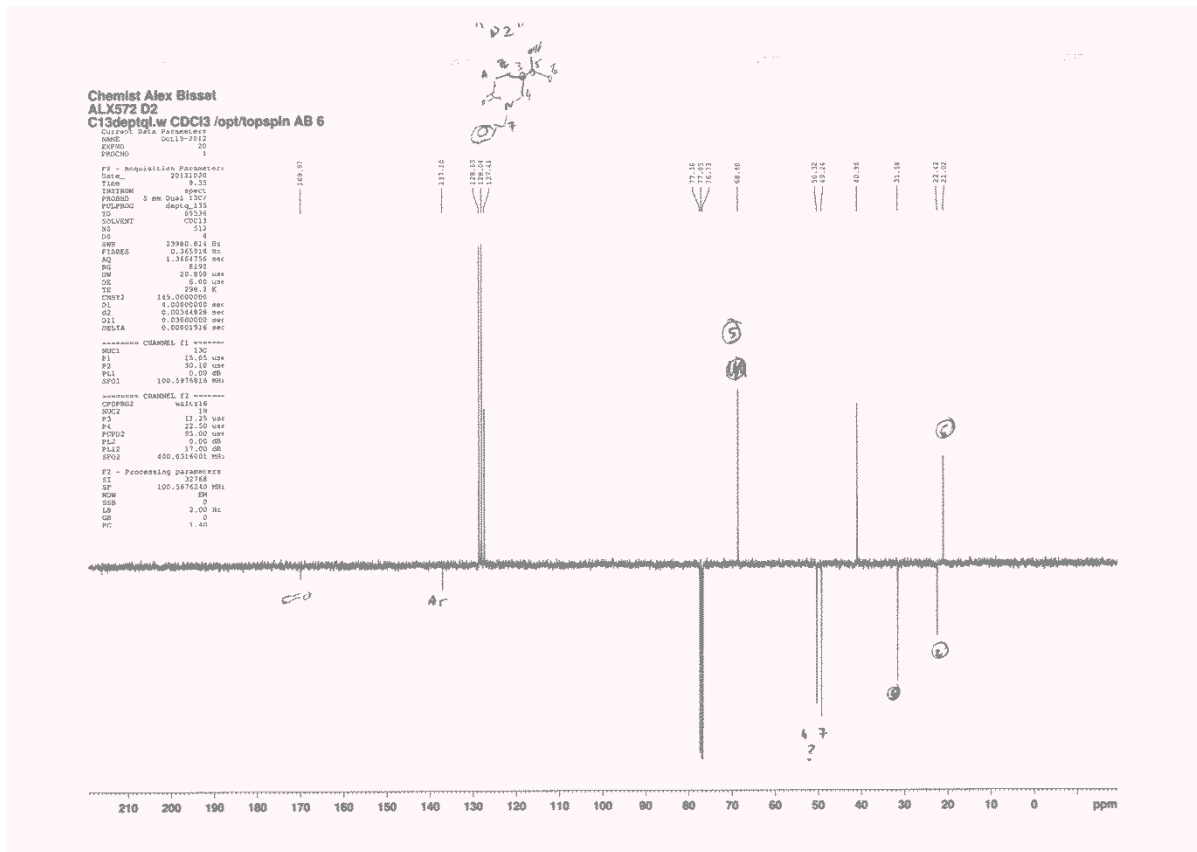
1-benzyl-5-(1-hydroxyethyl)piperidin-2-one, D1- 16a.





1-benzyl-5-(1-hydroxyethyl)piperidin-2-one, D2-16b.





The hydrogenolysis product 1-benzyl-5-ethylpiperidin-2-one, **32**.

Chemist Alex Bisset
ALX484
PROTON w CDC13 /opt/topspin AB 54

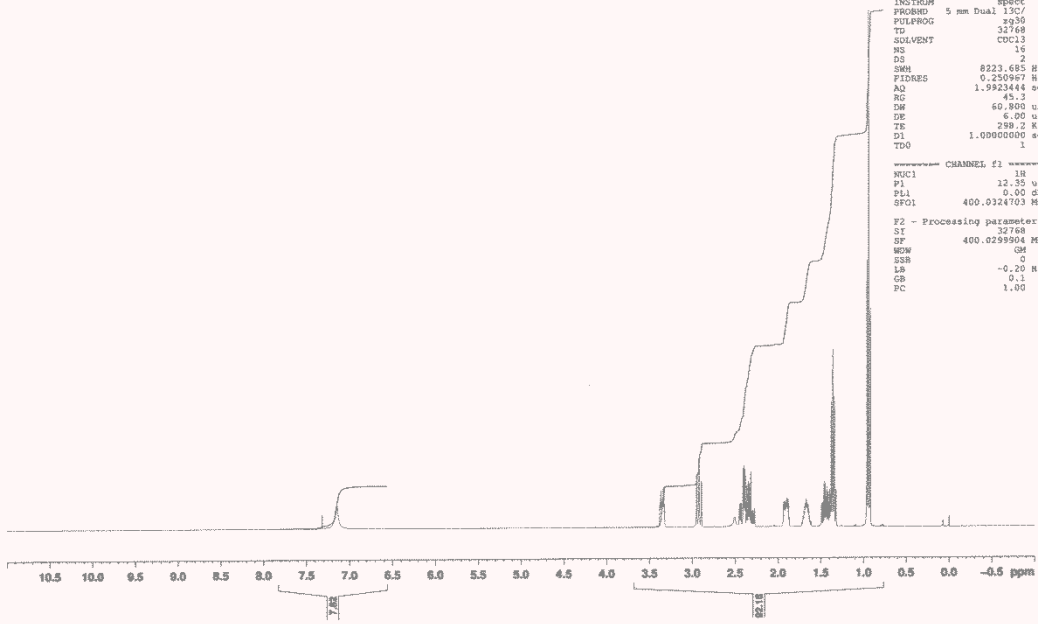


Current Data Parameters
NAME Jul25-2012
EXPNO 30
PROCNO 1

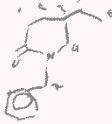
F2 - Acquisition Parameters
Date_ 20120725
Time 12.47
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg30
TD 32768
SOLVENT cdcl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9933444 sec
RG 43.3
DM 60.800 um
DE 6.00 um
TE 298.2 K
D1 1.0000000 sec
TDO 1

===== CHANNEL f1 =====
NUC1 1H
P1 12.50 usec
PL1 0.00 dB
SFO1 400.0324703 MHz

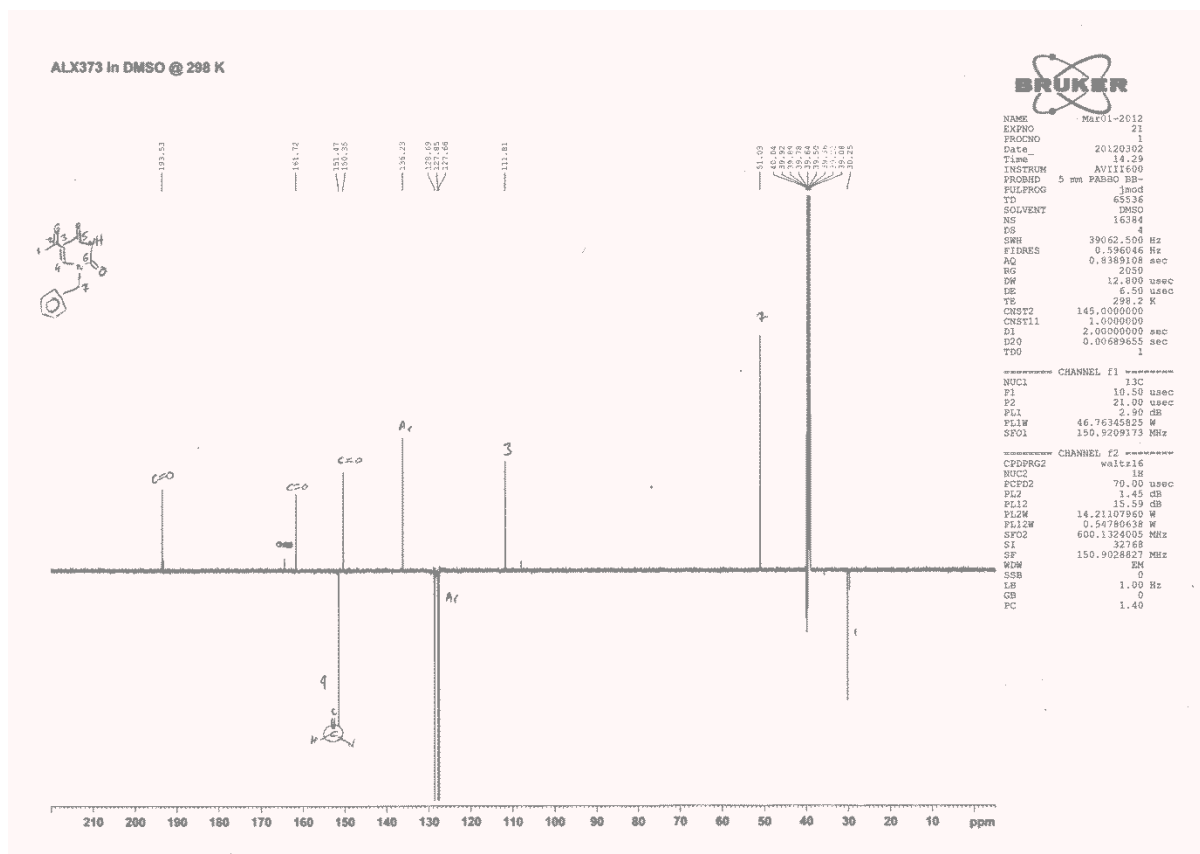
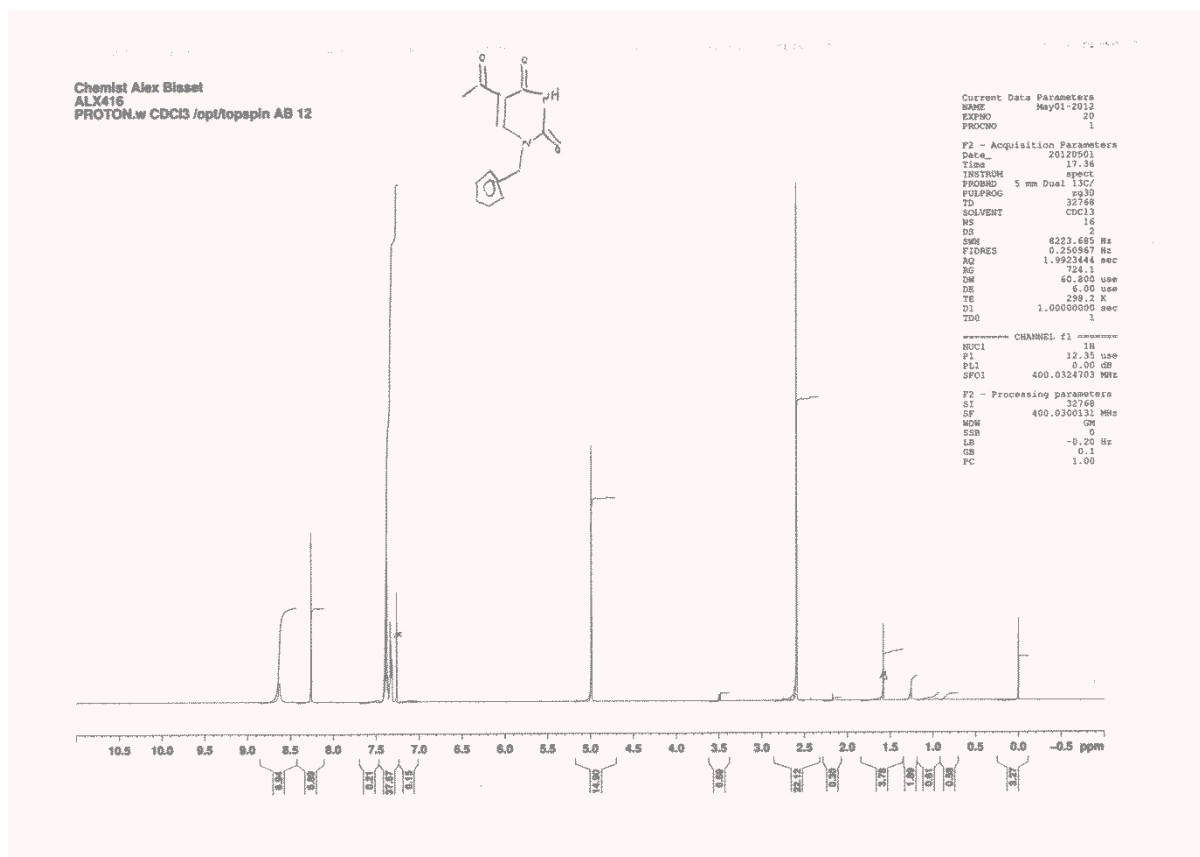
F2 - Processing parameters
SI 32768
SF 400.0299904 MHz
WDW EM
SSB 0
LB -0.20 Hz
GB 0.1
PC 1.00



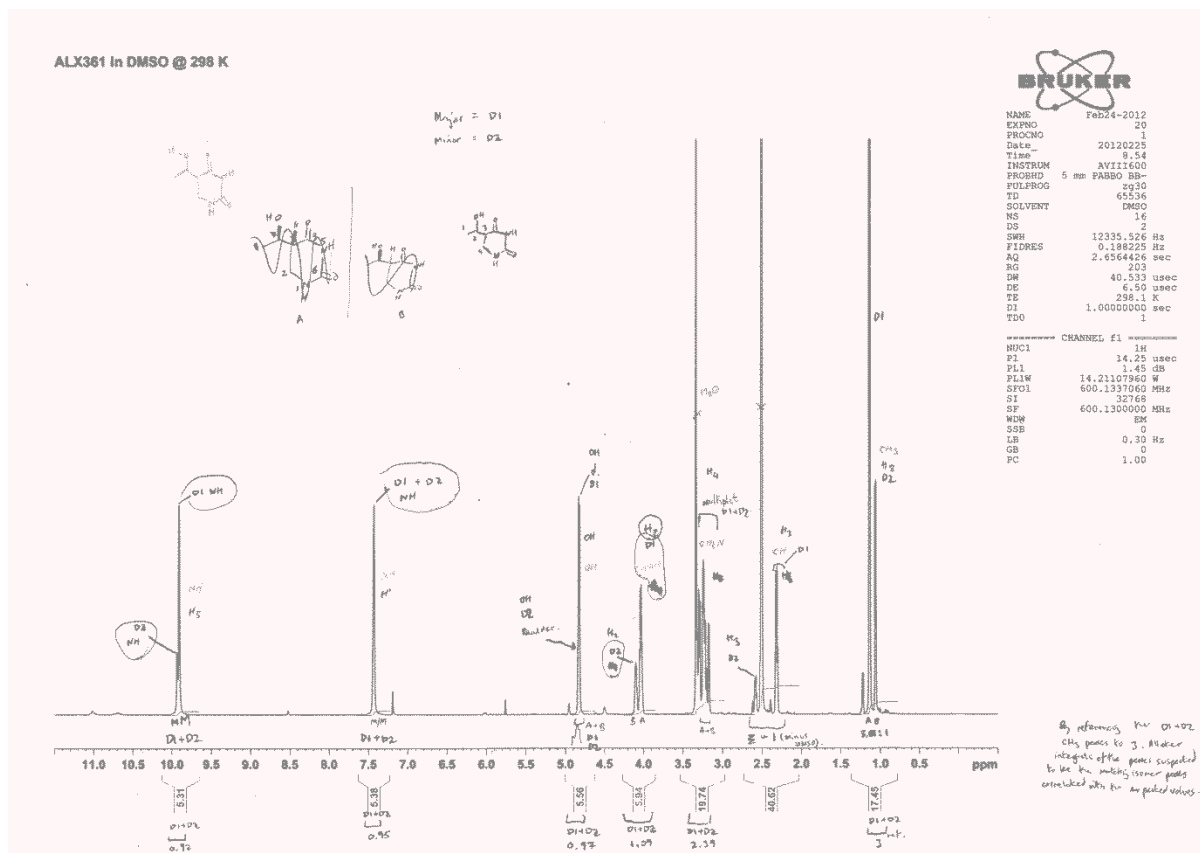
Chemist Alex Bisset
ALX533 ethyl product
C13deptq w CDC13 /opt/topspin AB 42

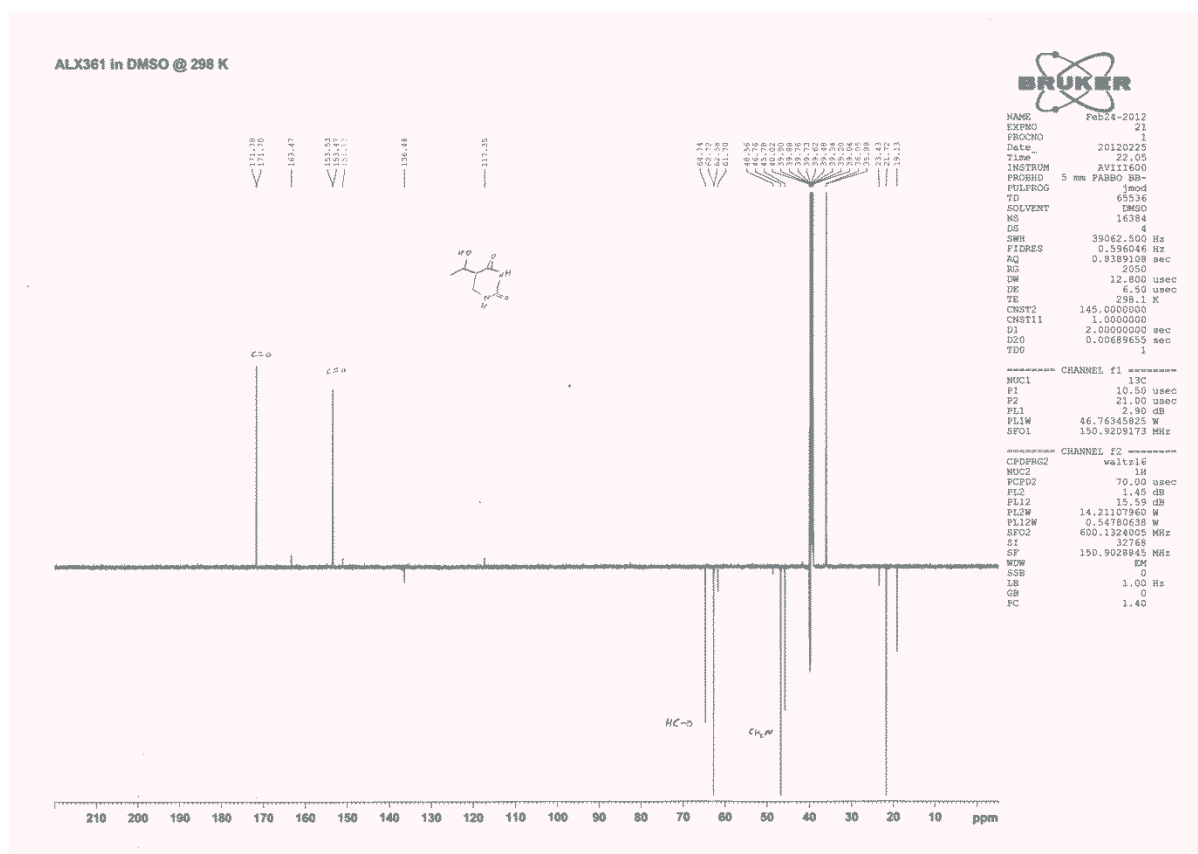


5-Acetyl-1-benzylpyrimidine-2,4(1H,3H)-dione, **34**.



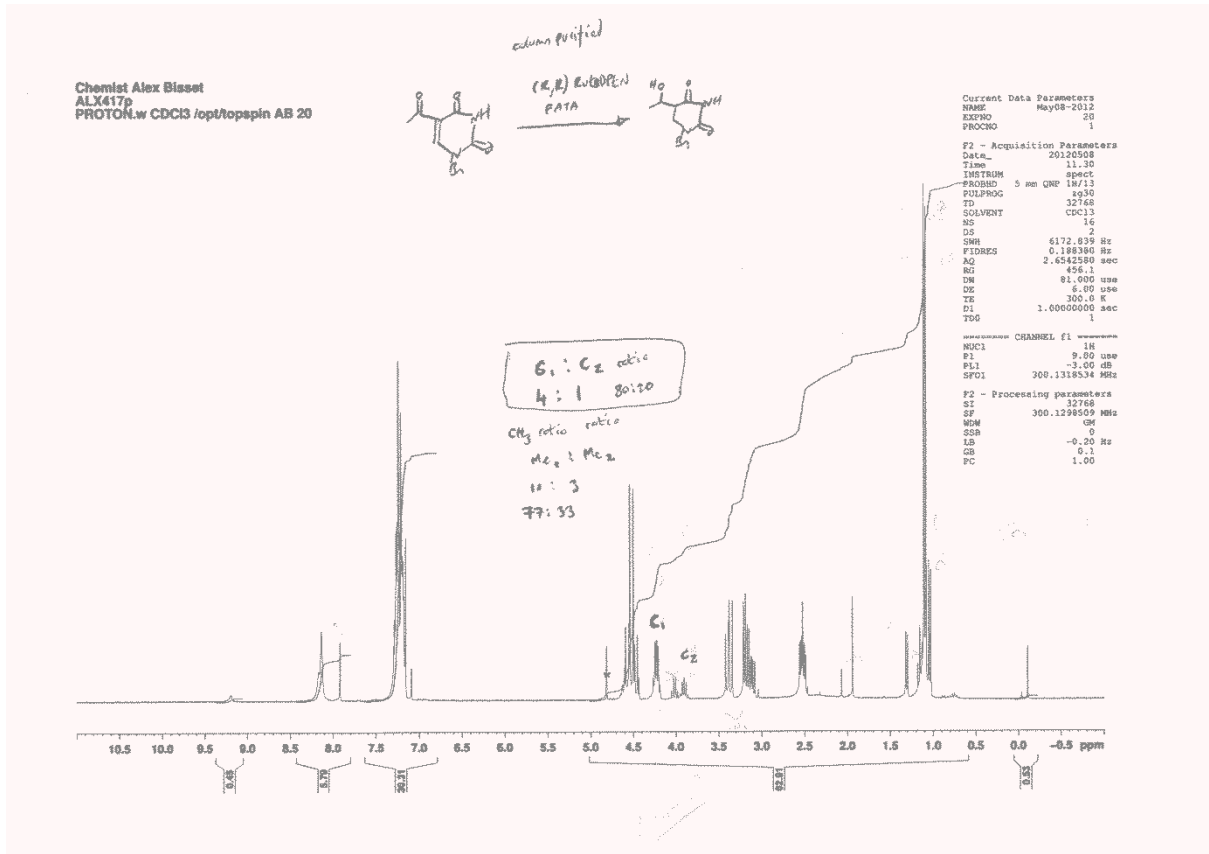
5-(1-hydroxyethyl)dihydropyrimidine-2,4(1H,3H)-dione, 35.



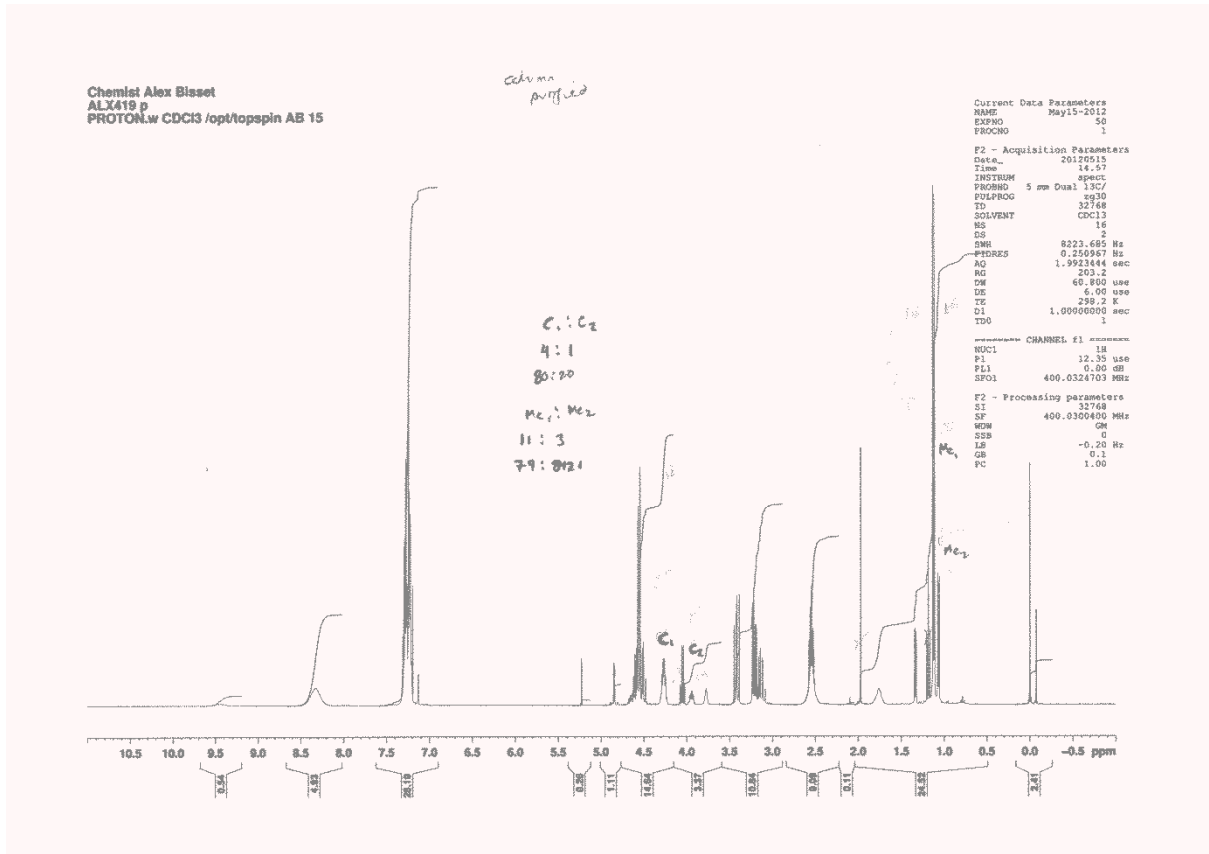


1-Benzyl-5-(1-hydroxyethyl)dihydropyrimidine-2,4(1H,3H)-dione, **37a and b**.

With (*R,R*)-catalyst **19**:



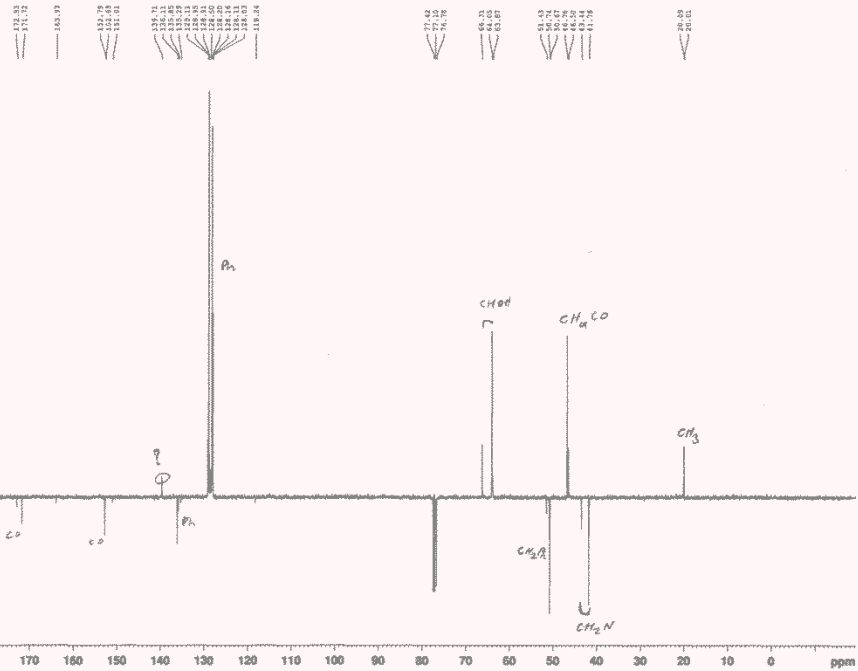
With (S,S)-catalyst 19:



Chemist Alex Bisset
 ALX404
 C13 labeled w CDC13 /opt/topopin AB 38



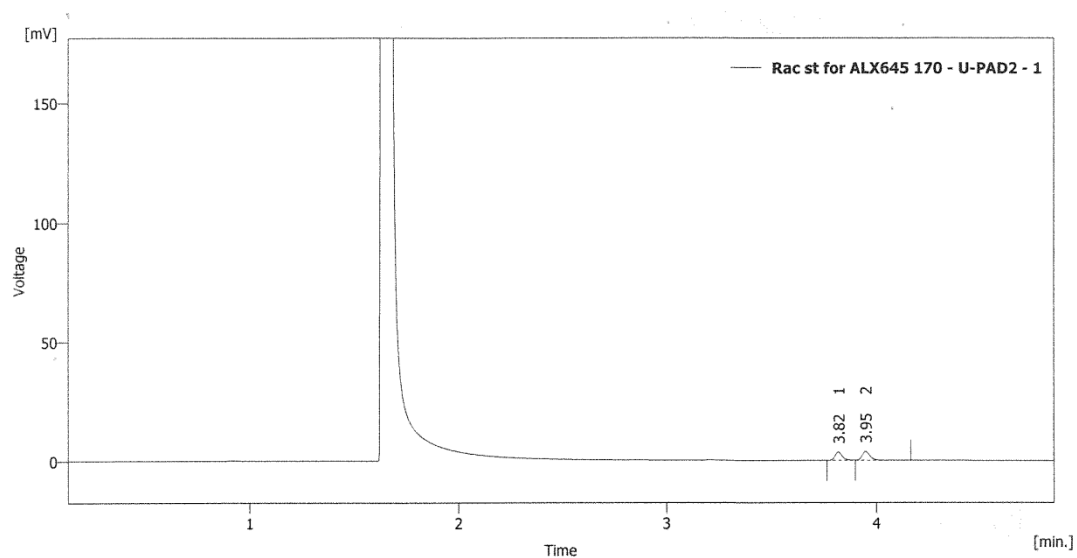
----- Acquisition Parameters -----
 Date_ 20180419
 Time 9:02
 INSTRUM spect
 PROGRAM 1 am Dual 13C13
 POLPROG zgpg30
 ID 45536
 SOLVENT CDC13
 NS 4
 DS 4
 SWH 23980.814 Hz
 FIDRES 0.265918 Hz
 AQ 1.266156 sec
 RG 1304
 SW 20.450 use
 DE 6.00 use
 TE 299.2 K
 CBST2 140.000000 use
 D1 4.0000000 sec
 d3 0.0344478 sec
 D11 0.0300000 sec
 DELTA 0.0001316 sec
 ----- CHANNEL f1 -----
 NUC1 13C
 P1 15.00 use
 P2 30.10 use
 PL1 0.00 dB
 PL2 100.000000 dB
 ----- CHANNEL f2 -----
 CPDPRG2 waltz16
 NUC2 15N
 P1 11.00 use
 P2 22.00 use
 P3 80.00 use
 PL1 0.00 dB
 PL2 17.00 dB
 PL3 400.000000 dB
 ----- Processing parameters -----
 SI 32768
 SF 101.587440 MHz
 SFO 500.136200 MHz
 LB 2.00 Hz
 GB 0
 PC 1.40



Chiral HPLC and GC Traces.

Compound (S)-**10** (acetate derivative).

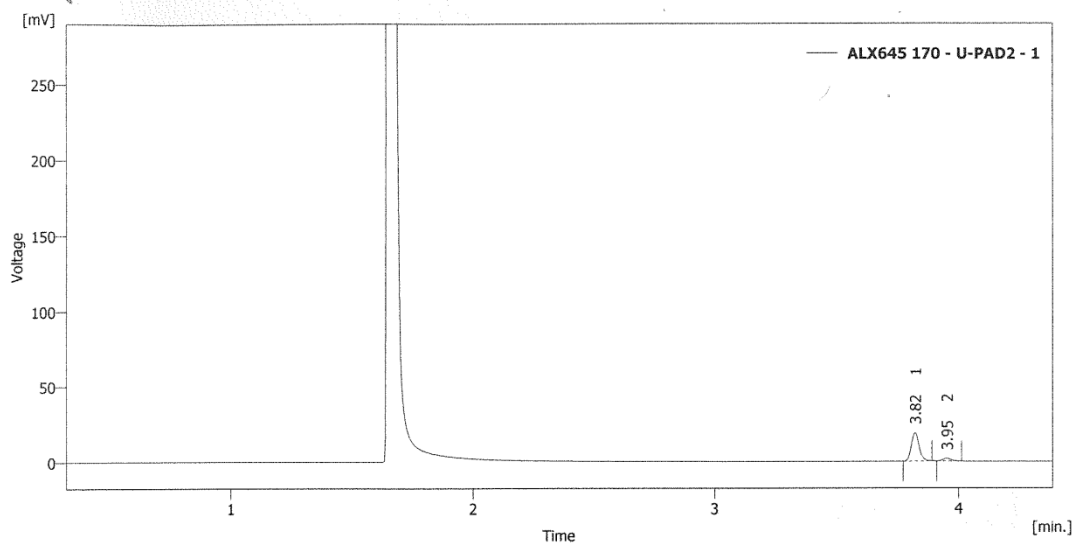
Racemic:



Result Table (Uncal - Rac st for ALX645 170 - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	3.820	8.695	3.464	46.2	47.4	0.04	
2	3.948	10.123	3.837	53.8	52.6	0.04	
	Total	18.818	7.301	100.0	100.0		

Sample of 82% ee (S):

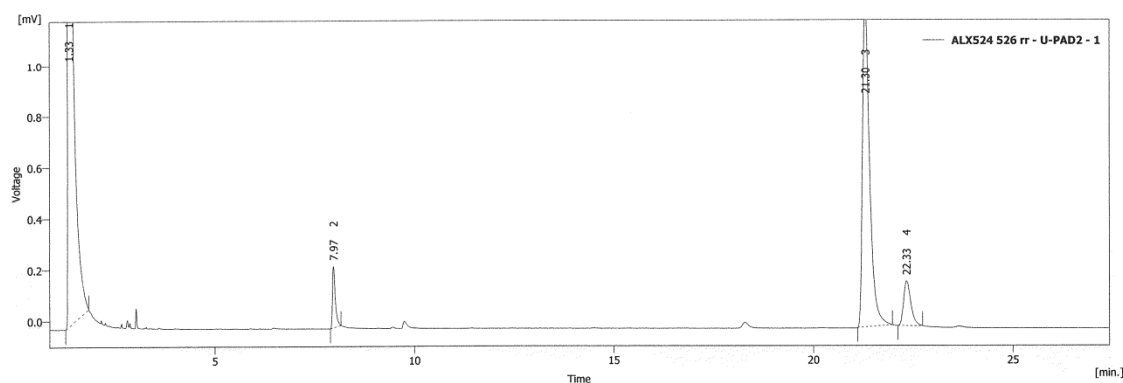


Result Table (Uncal - ALX645 170 - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	3.820	41.994	18.920	91.1	91.2	0.04	
2	3.952	4.126	1.830	8.9	8.8	0.04	
	Total	46.121	20.750	100.0	100.0		

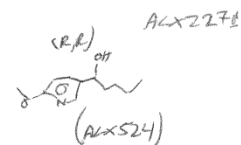
Compound **11** (rather than forming a racemate, reduction by each catalyst enantiomer was carried out independently).

(R)-enantiomer 76% ee compound **11** (under conditions given in Table 5):

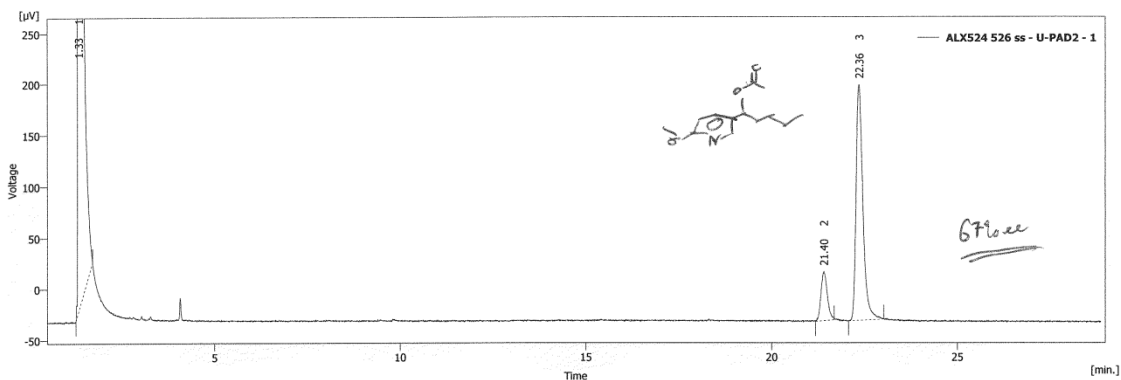


Result Table (Uncal - ALX524 526 rr - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	1.332	3048.204	986.417	99.4	99.8	0.05	
2	7.968	1.186	0.240	0.0	0.0	0.08	
3	21.304	15.818	1.269	0.5	0.1	0.19	
4	22.328	2.206	0.175	0.1	0.0	0.19	
	Total	3067.414	988.101	100.0	100.0		



(S) enantiomer 67% ee:



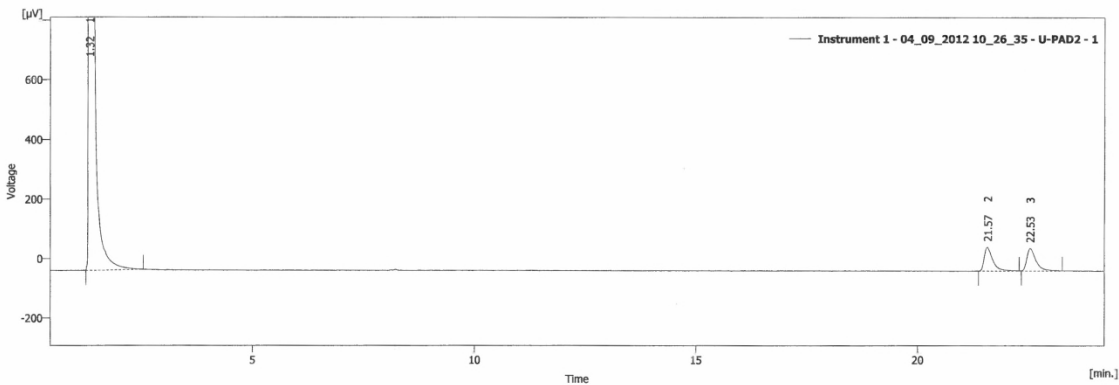
Result Table (Uncal - ALX524 526 ss - U-PAD2 - 1)

Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	2902.984	986.394	99.9	100.0	0.05	
2	21.404	0.569	0.048	0.0	0.18	
3	22.360	2.943	0.230	0.1	0.19	
Total	2906.496	986.673	100.0	100.0		

ALX528
(ALX526)
110°C
He
18 psi

Compound 12:

Racemic:

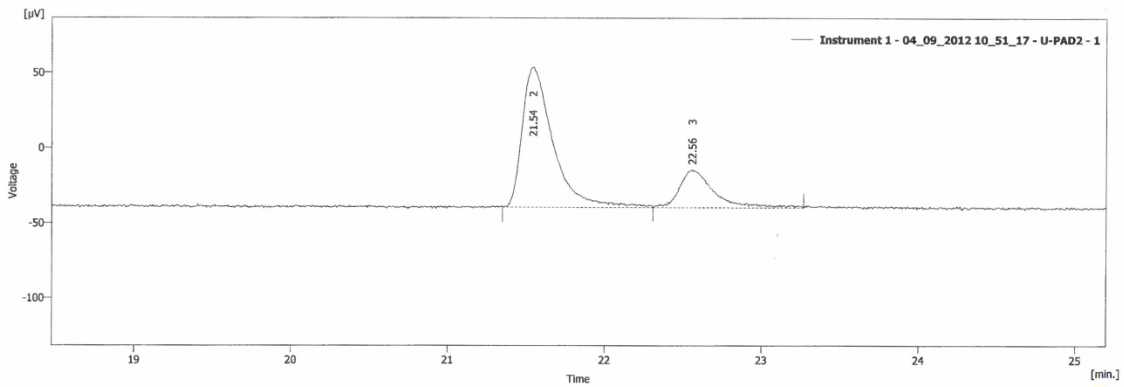


Result Table (Uncal - Instrument 1 - 04_09_2012 10_26_35 - U-PAD2 - 1)

Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	2967.323	986.455	99.9	100.0	0.05	
2	21.572	1.090	0.080	0.0	0.20	
3	22.528	1.095	0.076	0.0	0.21	
Total	2969.508	986.611	100.0	100.0		

Racemic
GC1
det 220°C
inj 220°C
(He) (chiral)

(R)-product, 53% ee



Result Table (Uncal - Instrument 1 - 04_09_2012 10_51_17 - U-PAD2 - 1)

Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	3094.362	986.463	99.9	100.0	0.05	
2	1.281	0.093	0.0	0.0	0.20	
3	0.393	0.025	0.0	0.0	0.22	
Total	3096.036	986.581	100.0	100.0		

$\frac{0.888}{1.676} = 53\% ee$

an 40%
 Ret 2200
 GC 1
 Ho 18 psi
 Anx 531
 free alcohol
 (molecular)

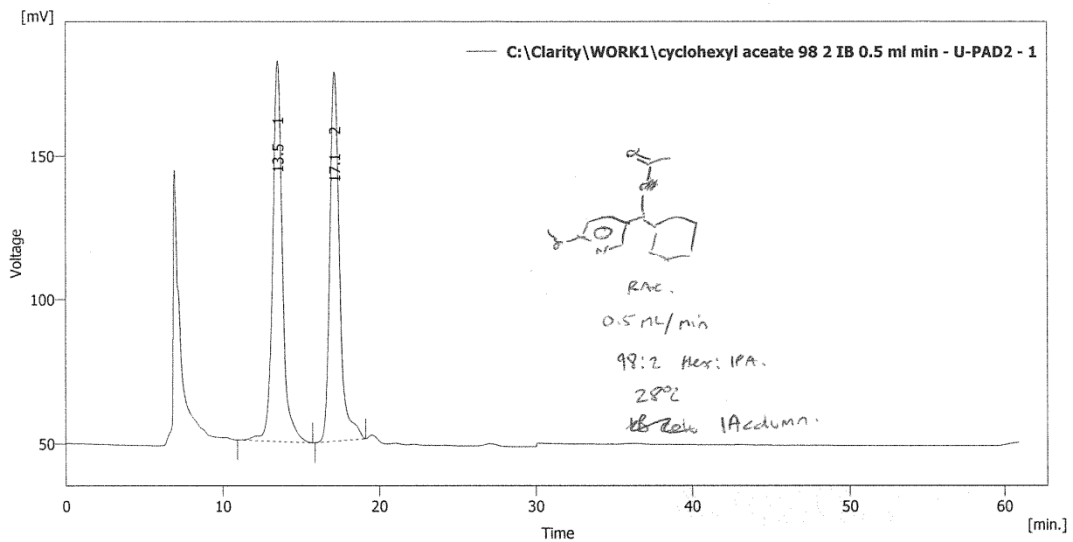
Compound 13

racemic:



Clarity - Chromatography SW

DataApex 2006
 www.dataapex.com



Result Table (Uncal - C:\Clarity\WORK1\cyclohexyl aceate 98 2 IB 0.5 ml min - U-PAD2 - 1)

Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	5720.937	132.321	50.8	50.8	0.61	
2	5540.240	128.312	49.2	49.2	0.62	
Total	11261.176	260.632	100.0	100.0		

(R)-product, 35 % ee:

15/11/2012 12:44

Chromatogram C:\Clarity\WORK1\asym cyclohexyl acetate 982 0.5 ml min IA 28C.PRM

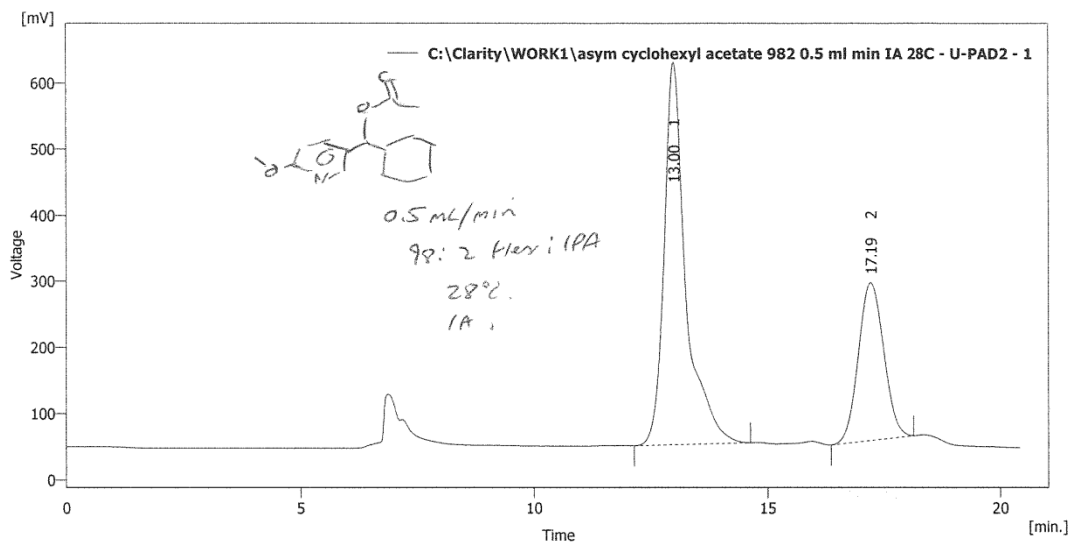
Page 1 of 1



Clarity - Chromatography SW

DataApex 2006

www.dataapex.com



Result Table (Uncal - C:\Clarity\WORK1\asym cyclohexyl acetate 982 0.5 ml min IA 28C - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	12.996	18643.845	578.542	67.6	70.9	0.42	
2	17.188	8950.634	237.999	32.4	29.1	0.60	
	Total	27594.479	816.541	100.0	100.0		

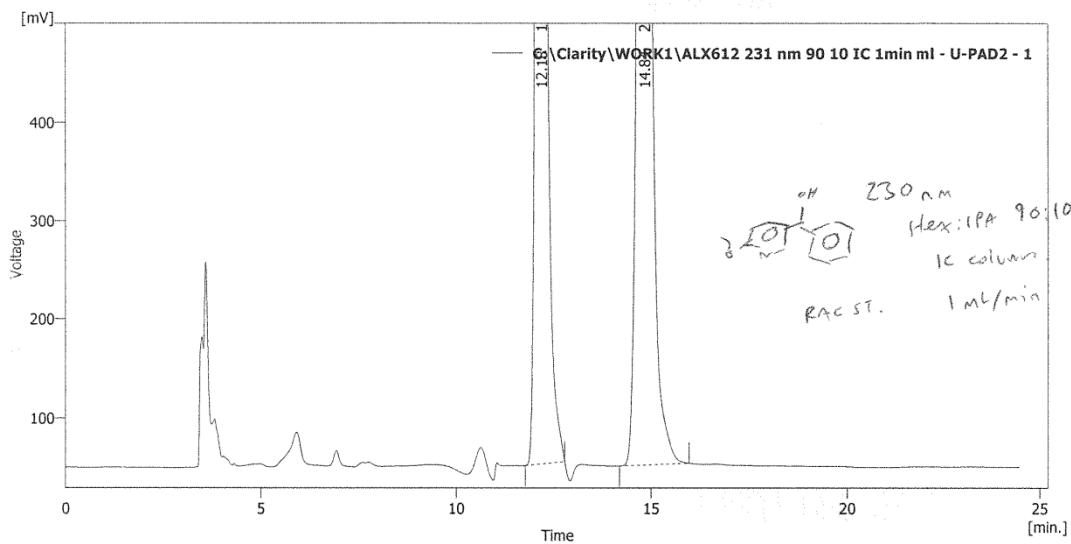
Compound 14

racemic



Clarity - Chromatography SW

DataApex 2006
www.dataapex.com



Result Table (Uncal - C:\Clarity\WORK1\ALX612 231 nm 90 10 IC 1min ml - U-PAD2 - 1)

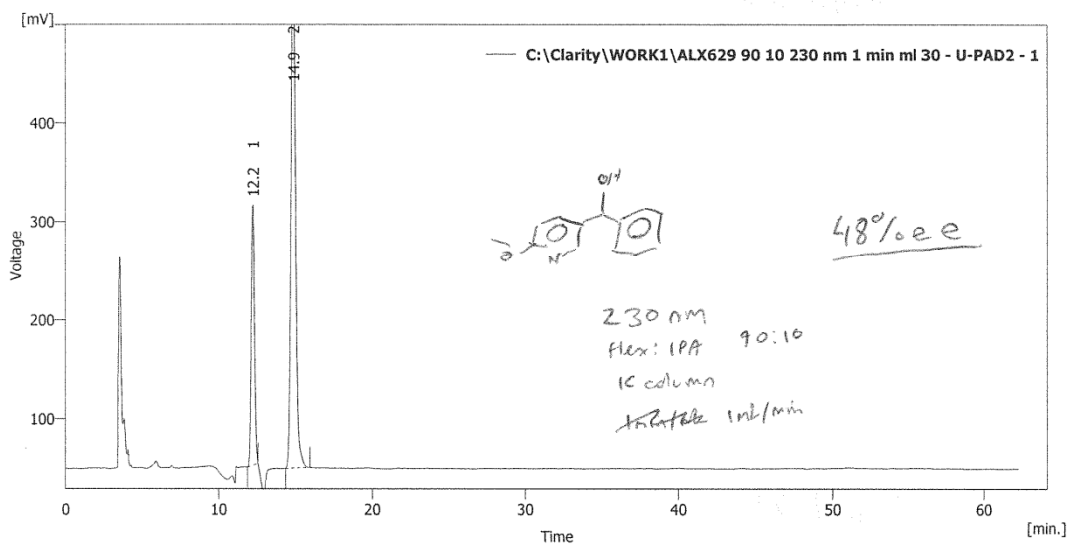
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	12.184	22901.444	1104.474	46.3	51.1	0.32	
2	14.836	26613.840	1055.027	53.7	48.9	0.40	
	Total	49515.284	2159.501	100.0	100.0		

Of 48% ee:



Clarity - Chromatography SW

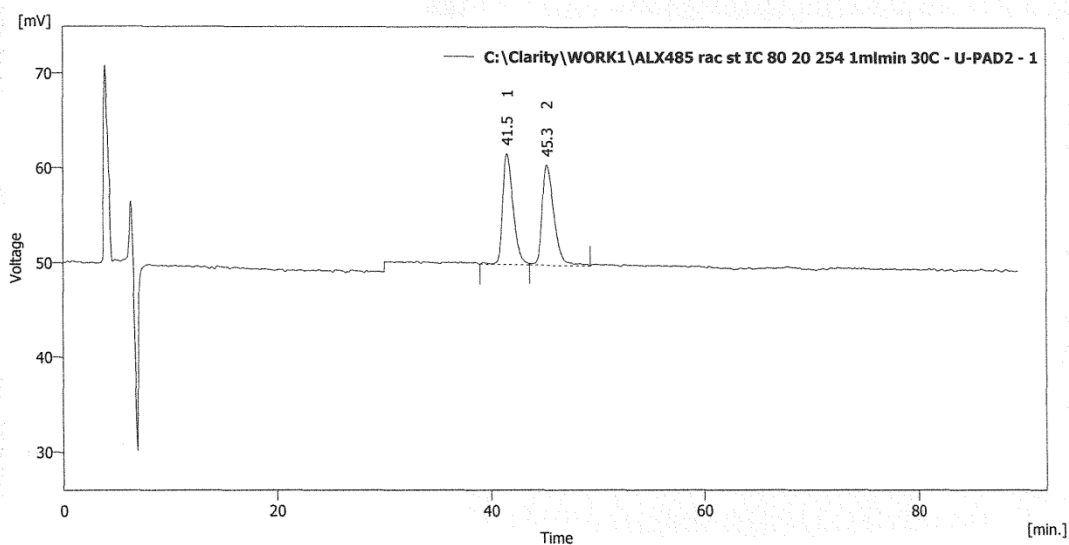
DataApex 2006
www.dataapex.com



Result Table (Uncal - C:\Clarity\WORK1\ALX629 90 10 230 nm 1 min ml 30 - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	12.228	3793.274	263.645	26.2	33.5	0.23	
2	14.856	10712.084	522.455	73.8	66.5	0.31	
	Total	14505.359	786.100	100.0	100.0		

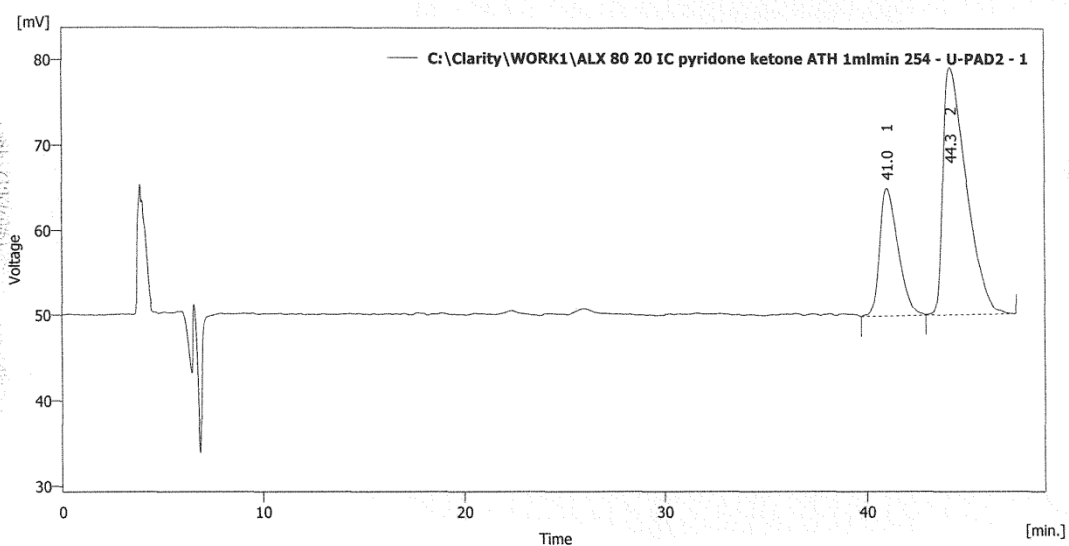
Compound 15 racemic



Result Table (Uncal - C:\Clarity\WORK1\ALX485 rac st IC 80 20 254 1mlmin 30C - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	41.532	797.035	11.691	49.0	52.5	1.04	
2	45.280	828.430	10.559	51.0	47.5	1.16	
	Total	1625.465	22.250	100.0	100.0		

Of 42% ee formed by reduction of **27**:



Result Table (Uncal - C:\Clarity\WORK1\ALX 80 20 IC pyridone ketone ATH 1mlmin 254 - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	41.020	970.590	15.101	29.0	34.2	0.99	
2	44.256	2379.758	29.103	71.0	65.8	1.27	
	Total	3350.348	44.203	100.0	100.0		

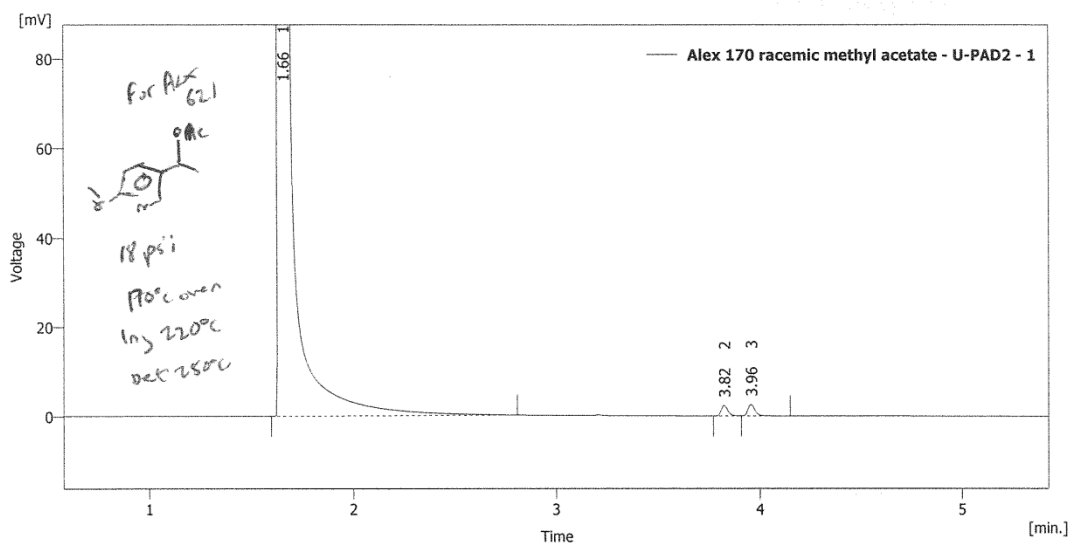
Large scale reduction of **10** to give **15** in 78% ee (GC of acetate derivative):

Racemic standard:

26/11/2012 12:32

Chromatogram C:\Clarity\WORK1\DATA\Alex 170 racemic methyl acetate.prm

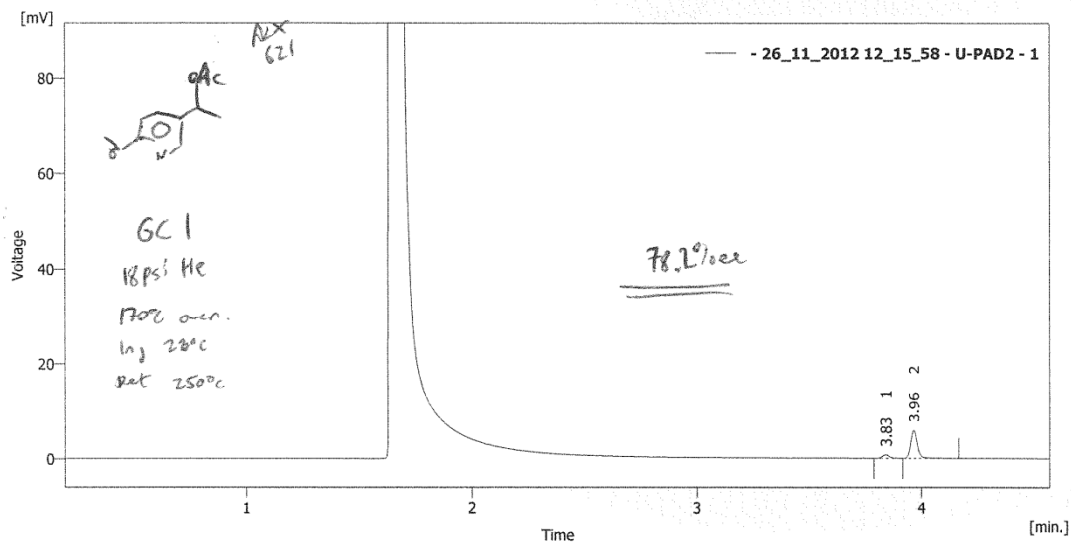
Page 2 of 2



Result Table (Uncal - Alex 170 racemic methyl acetate - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	1.656	3156.224	1093.924	99.6	99.6	0.04	
2	3.824	5.383	2.338	0.2	0.2	0.04	
3	3.956	6.298	2.569	0.2	0.2	0.04	
	Total	3167.905	1098.831	100.0	100.0		

78% ee sample (R) formed from **10**:

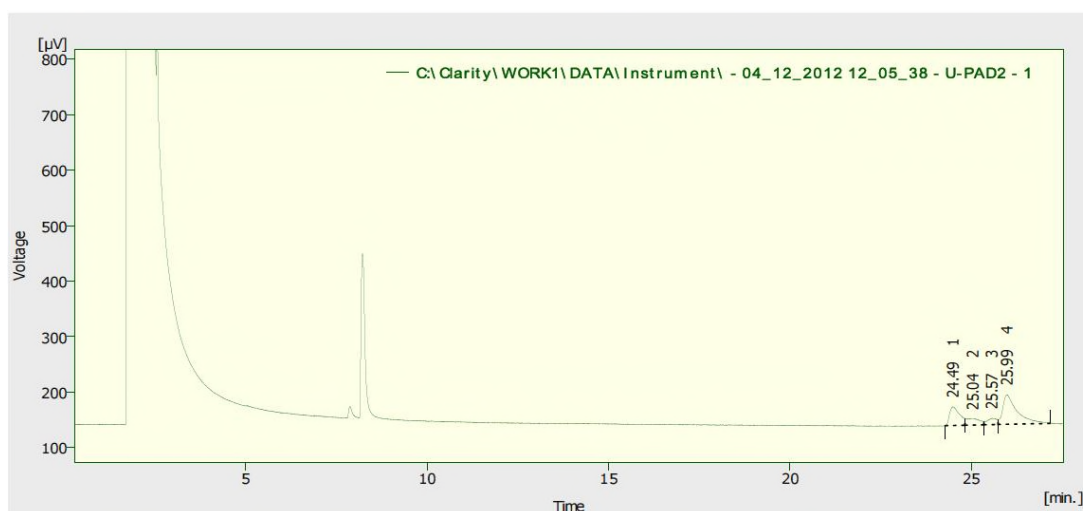


Result Table (Uncal - - 26_11_2012 12_15_58 - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	3.832	1.677	0.755	10.9	11.3	0.04	
2	3.960	13.752	5.919	89.1	88.7	0.04	
	Total	15.429	6.674	100.0	100.0		

crude reduction mixture of **16a** and **16b**

This GC trace was obtained from the crude reaction mixture of (D1)-**16a** and (D2)-**16b** resulting from the PtO₂ reduction of pyridone (R)-**15** (78 % ee). This was used to determine the dr of the reaction. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 μm, gas: He, T = 200 °C, P = 18 psi He, det = 250 °C, inj = 220 °C, (S,R) isomer 24.49 min., (R,S) isomer 25.04 min., (S,S) isomer 25.57 min., (R,R) isomer 25.99 min.) 31 % de.

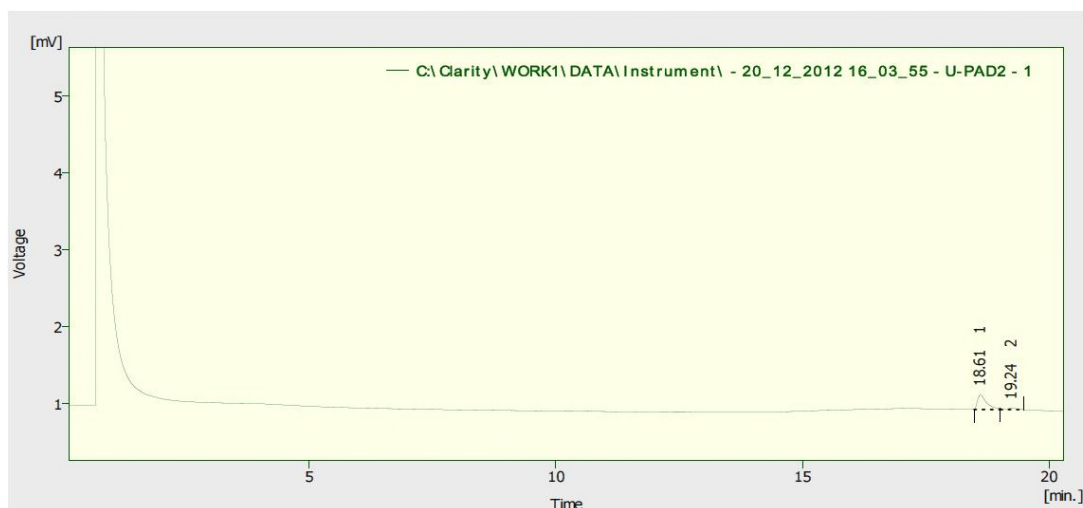


	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	24.492	0.652	0.034	24.6	30.8	0.34
2	25.044	0.310	0.012	11.7	10.6	0.52
3	25.572	0.213	0.012	8.0	10.5	0.33
4	25.988	1.479	0.053	55.7	48.1	0.37
	Total	2.654	0.111	100.0	100.0	

Following chromatography of this crude mixture, the diastereomers D1-**16a** and D2-**16b** were separated. The GC traces of these isomers are shown below.

D1-16a, 78 % ee.

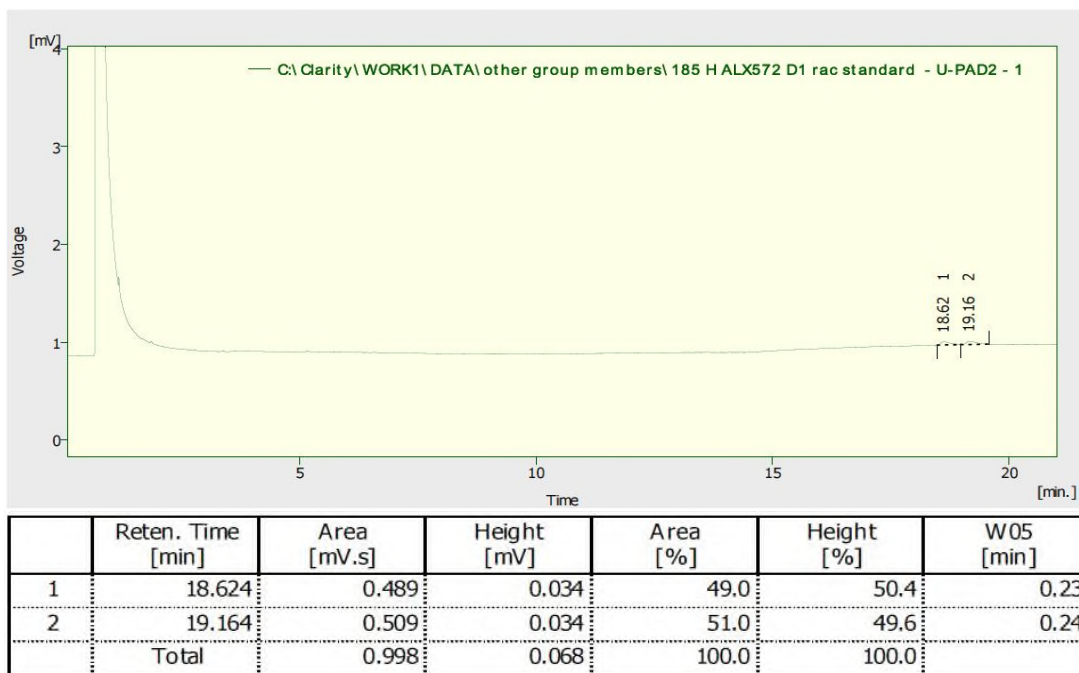
This GC trace was obtained from a chromatographically separated sample of D1-**16a**. Different GC conditions (to those in GC trace 1) were required for adequate separation. The racemic standard for this run is shown in GC trace 3. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 μ m, gas: H, T = 185 °C, P = 18 psi H, det = 250 °C, inj = 220 °C, (*S,R*) isomer 18.61 min., (*R,S*) isomer 19.24 min.) 78 % ee.



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	18.608	2.437	0.189	89.4	91.2	0.19
2	19.236	0.289	0.018	10.6	8.8	0.22
	Total	2.726	0.207	100.0	100.0	

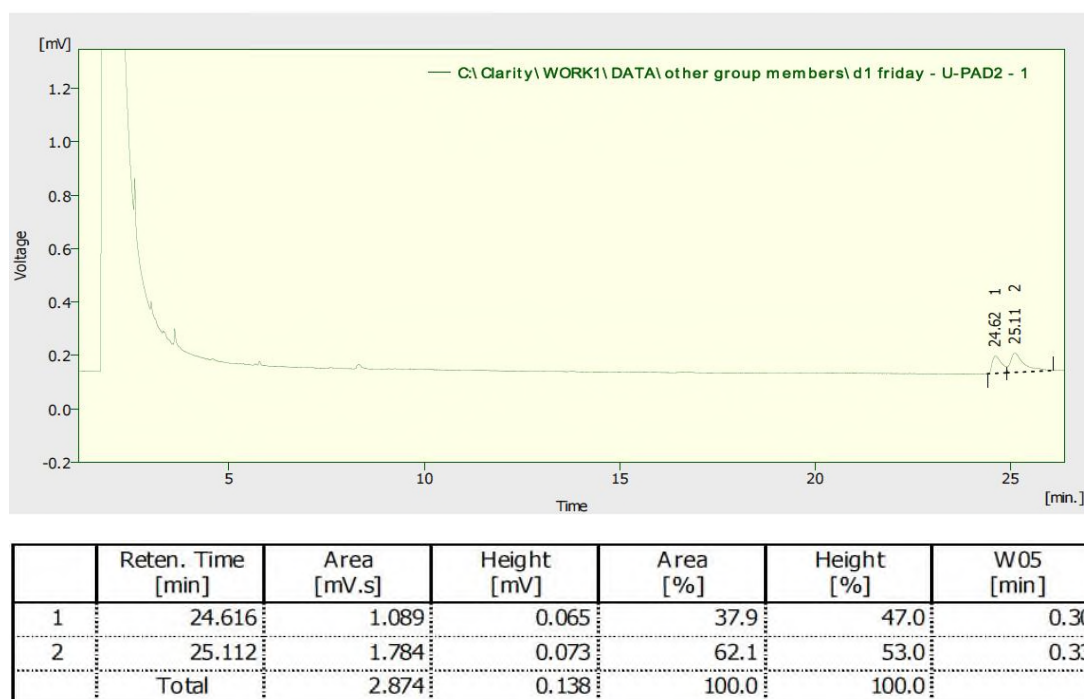
(\pm)-(*D1*)-**16a** (racemic standard).

This GC trace of (*D1*)- **16a** was used as a racemic standard for GC trace 2: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 μ m, gas: H, T = 185 °C, P = 18 psi H, det = 250 °C, inj = 220 °C, (*S,R*) isomer 18.64 min., (*R,S*) isomer 19.16 min.).



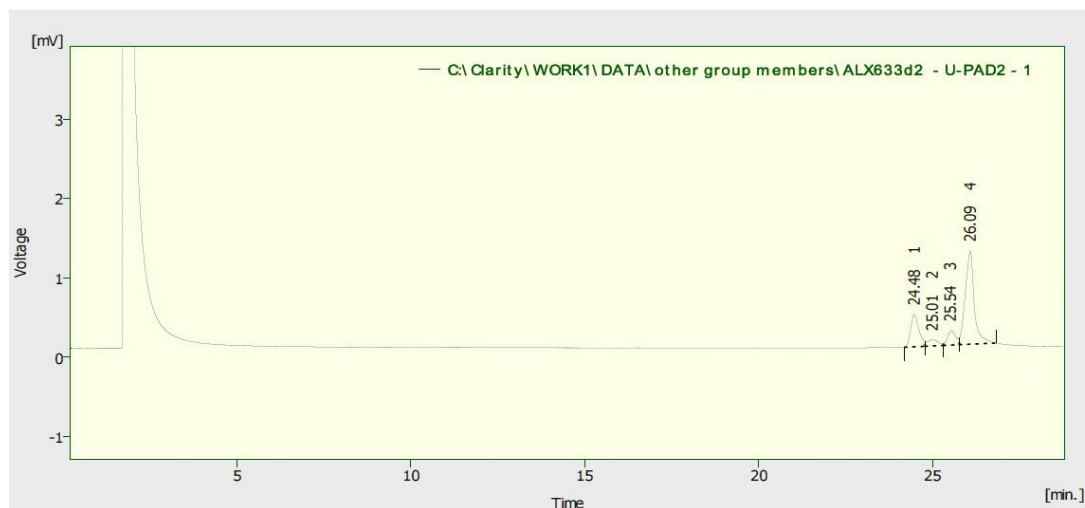
(±)-D1-16a (in reference to GC 1).

This GC trace of racemic (D1)-16a was run at the same conditions as GC trace 1 to enable comparison. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 μm, gas: He, T = 200 °C, P = 18 psi He, det = 250 °C, inj = 220 °C, (S,R) isomer 24.62 min., (R,S) isomer 25.11 min.).



GC trace 5: D2-16b, 78 % ee.

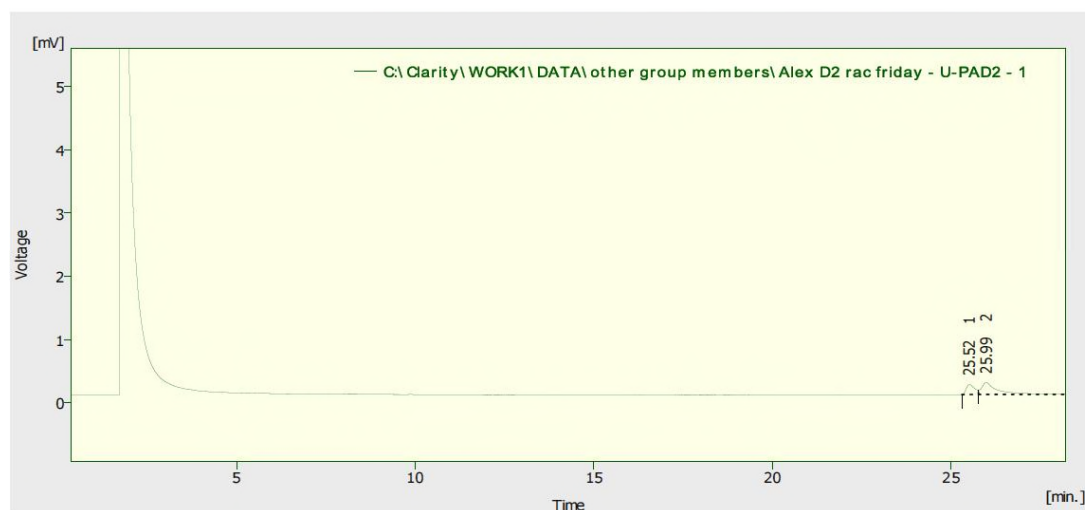
This GC trace was obtained from a chromatographically enriched sample of D2-**16b** (72 % D2). The racemic standard is shown in GC trace 6. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 μ m, gas: H, T = 200 $^{\circ}$ C, P = 18 psi He, det = 250 $^{\circ}$ C, inj = 220 $^{\circ}$ C, (*S,R*) isomer 24.48 min., (*R,S*) isomer 25.00 min. (*S,S*) isomer 25.54 min., (*R,R*) isomer 26.09 min.) 78 % ee.



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	24.480	6.773	0.409	20.8	22.2	0.26
2	25.008	1.692	0.081	5.2	4.4	0.40
3	25.536	2.993	0.180	9.2	9.7	0.28
4	26.088	21.105	1.174	64.8	63.7	0.26
	Total	32.564	1.843	100.0	100.0	

GC trace 6: (\pm)-D2-16b**.**

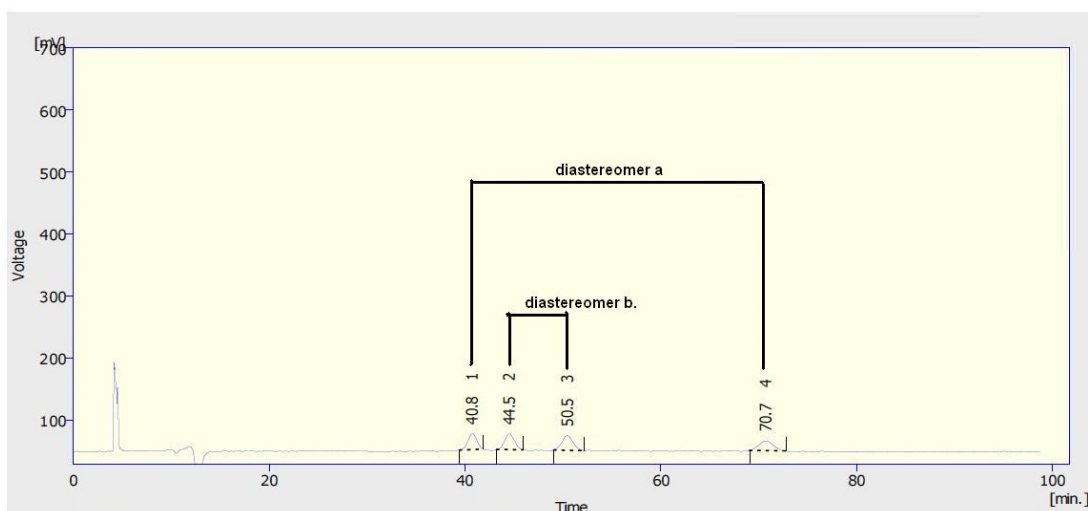
This GC trace of (\pm)-D2-**16b** was used as a racemic standard for GC trace 5. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 μ m, gas: He, T = 200 $^{\circ}$ C, P = 18 psi He, det = 250 $^{\circ}$ C, inj = 220 $^{\circ}$ C, (*S,S*) isomer 25.52 min., (*R,R*) isomer 25.99 min.).



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	25.524	2.612	0.155	30.1	45.2	0.31
2	25.992	6.066	0.189	69.9	54.8	0.36
	Total	8.678	0.344	100.0	100.0	

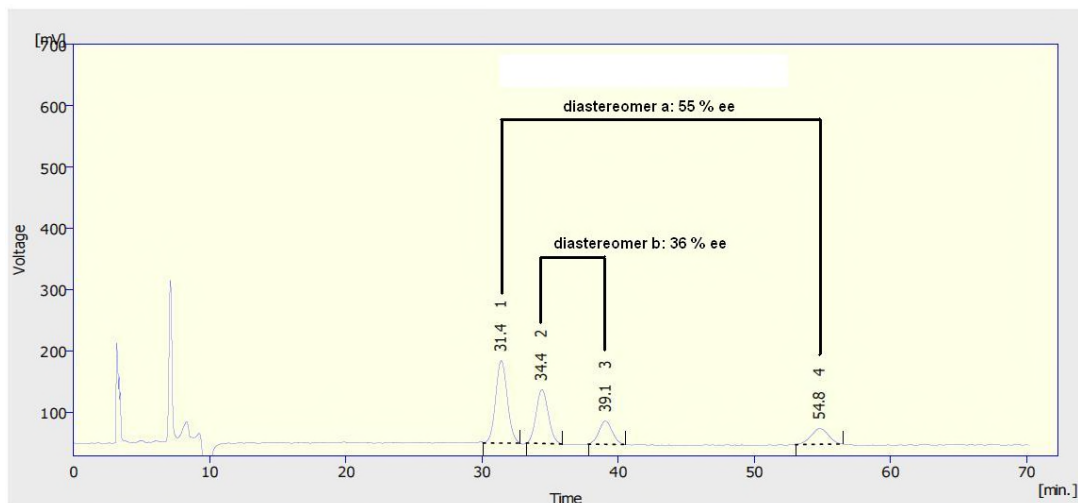
ATH of *N*-benzyl-5-acetyluracil **34**.

Reduction with the racemic catalyst, RuTsEN **36**, (entry 2, Table 6); chiral separation details: (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 90 : 10, 1 mL/min, T = 30 °C, minor isomer 46.0 min, major isomer 51.9 min.) **37a**:**37b** dr = 1:1.



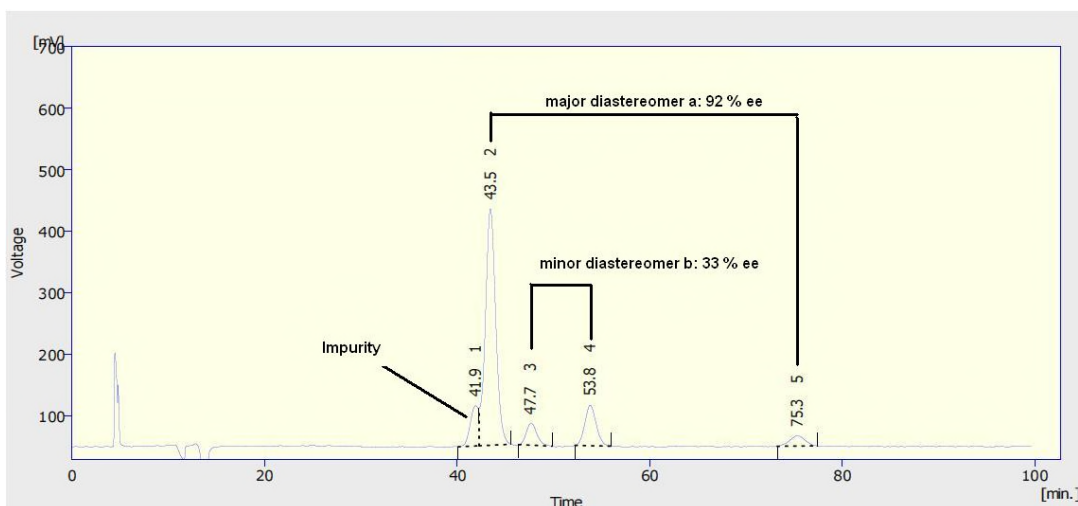
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	40.752	1615.491	25.718	23.6	28.3	1.00	diastereomer a; enantiomer a.
2	44.544	1758.386	25.366	25.7	28.0	1.12	diastereomer b; enantiomer a.
3	50.468	1889.580	23.823	27.6	26.3	1.22	diastereomer b; enantiomer b.
4	70.728	1585.524	15.830	23.1	17.4	1.62	diastereomer a; enantiomer b.
	Total	6848.981	90.737	100.0	100.0		

Reduction with catalyst (*R,R*)-**20**, (entry 3, Table 6); chiral separation details: (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 90 : 10, 1 mL/min, T = 30 °C) **37a**: 55 % ee; **37b**: 36 % ee. a : b dr = 1.3:1.



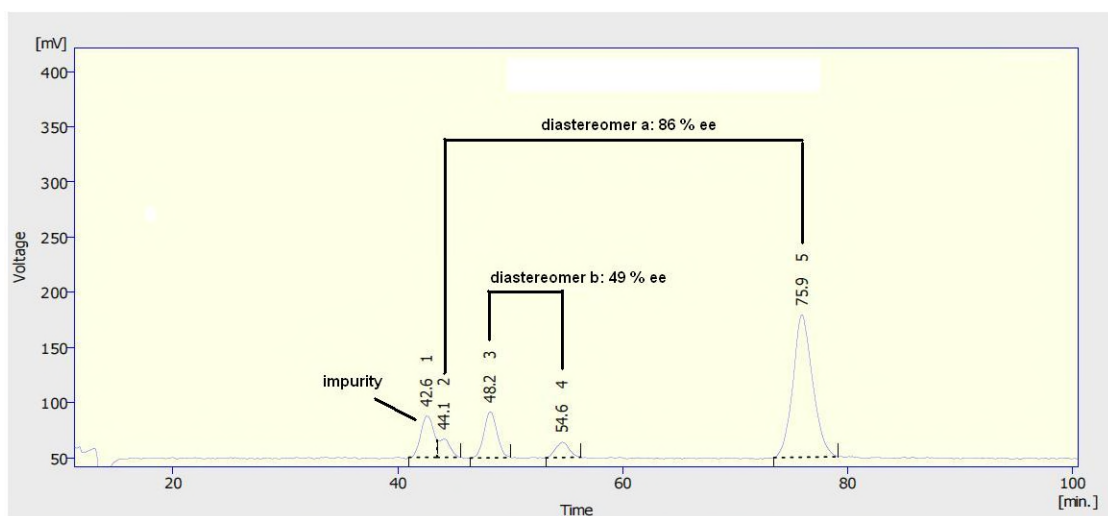
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	31.416	7997.752	134.399	43.6	46.9	0.92	diastereomer a; enantiomer a.
2	34.404	5467.036	87.831	29.8	30.7	0.97	diastereomer b; enantiomer a.
3	39.076	2577.286	37.902	14.1	13.2	1.06	diastereomer b; enantiomer b.
4	54.792	2298.262	26.173	12.5	9.1	1.40	diastereomer a; enantiomer b.
	Total	18340.336	286.305	100.0	100.0		

Reduction with (*R,R*)-RutethTsDPEN, (*R,R*)-**19**, (entry 4, Table 6); chiral separation details: (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 90 : 10, 1 mL/min, T = 30 °C) **37a**: 92 % ee; **37b**: 33 % ee. a : b dr = 4:1.



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	41.936	3870.949	65.238	9.0	11.5	0.97	impurity
2	43.460	28903.698	384.210	67.6	67.7	1.14	diastereomer a; enantiomer a.
3	47.676	2752.056	35.332	6.4	6.2	1.18	diastereomer b; enantiomer a.
4	53.832	5388.335	65.920	12.6	11.6	1.27	diastereomer a; enantiomer b.
5	75.316	1871.360	16.953	4.4	3.0	1.74	diastereomer b; enantiomer b.
	Total	42786.397	567.652	100.0	100.0		

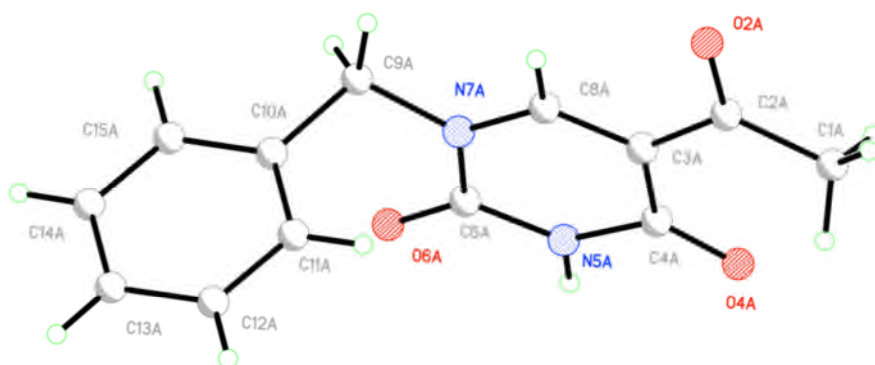
Reduction with (*S,S*)-RutethTsDPEN, (*S,S*)- **19**, (entry 5, Table 6); chiral separation details: (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 90 : 10, 1 mL/min, T = 30 °C) **37a**: 86 % ee; **37b**: 49 % ee. **a** : **b** dr = 4:1.



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	42.604	2946.792	37.572	12.1	15.8	1.35	impurity
2	44.116	1223.431	16.495	5.0	6.9	1.24	diastereomer a; enantiomer a.
3	48.228	3379.271	41.556	13.8	17.4	1.26	diastereomer b; enantiomer a.
4	54.616	1159.484	13.825	4.7	5.8	1.34	diastereomer b; enantiomer b.
5	75.940	15722.951	128.948	64.4	54.1	1.84	diastereomer a; enantiomer b.
	Total	24431.929	238.395	100.0	100.0		

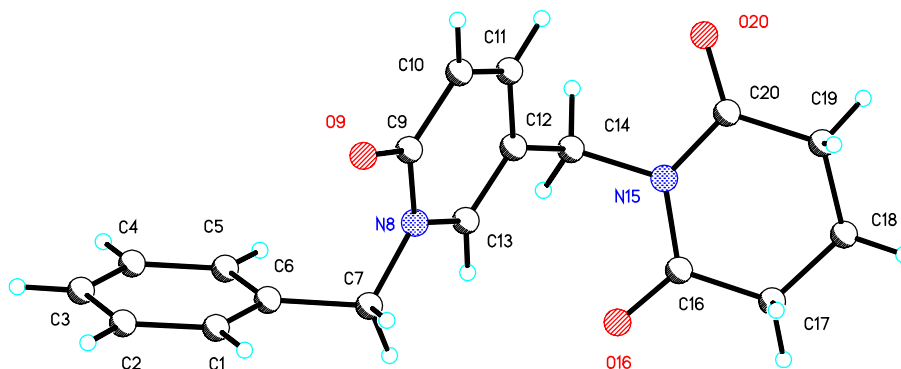
X-ray crystallographic structures.

5-Acetyl-1-benzylpyrimidine-2,4(1H,3H)-dione, **34**. CCDC 992397.



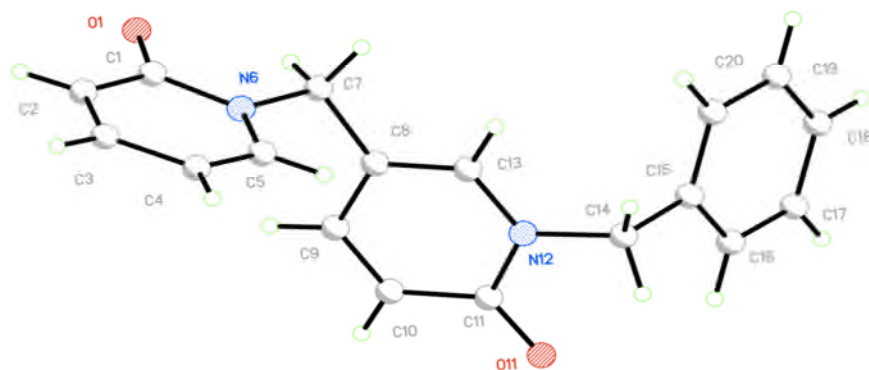
This structure was determined by the EPSRC Crystallographic Service. Crystallographic data for **34**: $C_{13}H_{12}N_2O_3$, $M = 244.25$, Monoclinic, space group $P2(1)/n$, $a = 9.680(15)$, $b = 23.71(3)$, $c = 10.025(13)$ Å, $\alpha = 90$ deg., $\beta = 97.78(3)$ deg., $\gamma = 90$ deg., $U = 2280(5)$ Å³ (by least squares refinement on 453 reflection positions), $T = 100(2)$ K, $\lambda = 0.71075$ Å, $Z = 8$, $D(\text{cal}) = 1.423$ Mg/m³, $F(000) = 1024$. $mv(\text{MoK-}\alpha) = 0.103$ mm⁻¹. Crystal character: colourless needle. Crystal dimensions $0.20 \times 0.01 \times 0.01$ mm, 25462 reflections measured, 5220 unique [$R(\text{int}) = 0.0623$].

1-[(1-Benzyl-6-oxo-1,6-dihydropyridin-3-yl)methyl]piperidine-2,6-dione, **3d**. CCDC 992395.



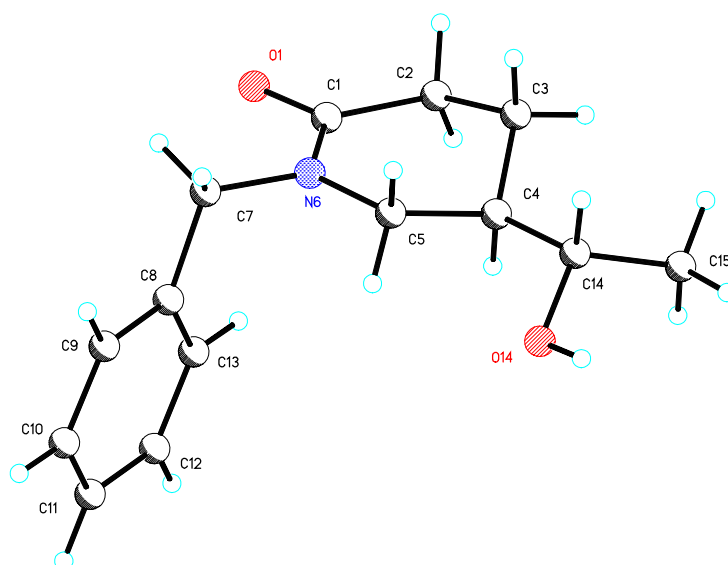
Crystallographic data for **3d**: $C_{18}H_{18}N_2O_3$, $M = 310.34$, Orthorhombic, space group $Pbca$, $a = 8.60003(9)$, $b = 17.41730(19)$, $c = 20.1379(3)$ Å, $\alpha = 90$ deg., $\beta = 90$ deg., $\gamma = 90$ deg., $U = 3016.45(6)$ Å³ (by least squares refinement on 9775 reflection positions), $T = 100(2)$ K, $\lambda = 1.54184$ Å, $Z = 8$, $D(\text{cal}) = 1.367$ Mg/m³, $F(000) = 1312$. $mv(\text{MoK-}\alpha) = 0.766$ mm⁻¹. Crystal character: colourless block. Crystal dimensions $0.40 \times 0.40 \times 0.28$ mm, 15826 reflections measured, 2892 unique [$R(\text{int}) = 0.0173$].

1-Benzyl-5-[(2-oxopyridin-1(2H)-yl)methyl]pyridin-2(1H)-one, **3e**. CCDC 992396.



Crystallographic data for **3e**. $C_{18}H_{16}N_2O_2$, $M = 292.33$, Monoclinic, space group $P2(1)/n$, $a = 13.0964(3)$, $b = 7.73187(14)$, $c = 15.1103(3)$ Å, $\alpha = 90$ deg., $\beta = 108.983(2)$ deg., $\gamma = 90$ deg., $U = 1446.85(5)$ Å³ (by least squares refinement on 2682 reflection positions), $T = 150(2)$ K, $\lambda = 1.54184$ Å, $Z = 4$, $D(\text{cal}) = 1.342$ Mg/m³, $F(000) = 616$. μ (MoK- α) = 0.714 mm⁻¹. Crystal character: colourless plate. Crystal dimensions $0.20 \times 0.20 \times 0.01$ mm. 5296 reflections measured, 2543 unique [$R(\text{int}) = 0.0216$].

1-benzyl-5-(1-hydroxyethyl)piperidin-2-one, *anti*-D1-**16a**. CCDC 992398.



Crystal Data for **16a**: $C_{14}H_{19}NO_2$, $M = 233.30$, Orthorhombic, space group $Pna2(1)$, $a = 10.7915(2)$, $b = 21.1078(5)$, $c = 5.64620(18)$ Å, $\alpha = 90$ deg., $\beta = 90$ deg., $\gamma = 90$ deg., $U = 1286.11(6)$ Å³ (by least squares refinement on 5741 reflection positions), $T = 150(2)$ K, $\lambda = 1.54184$ Å, $Z = 4$, $D(\text{cal}) = 1.205$ Mg/m³, $F(000) = 504$. μ (MoK- α) = 0.638 mm⁻¹. Crystal character: colourless needle. Crystal dimensions $0.50 \times 0.01 \times 0.01$ mm, 10079 reflections measured, 2146 unique [$R(\text{int}) = 0.0250$].