Supporting information

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

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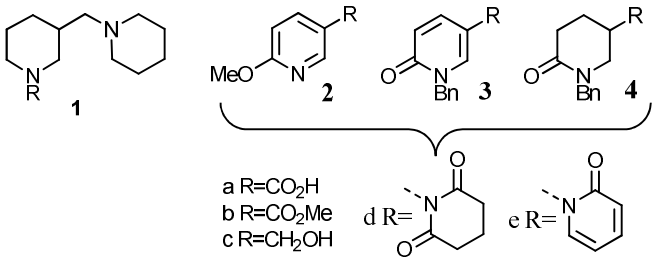
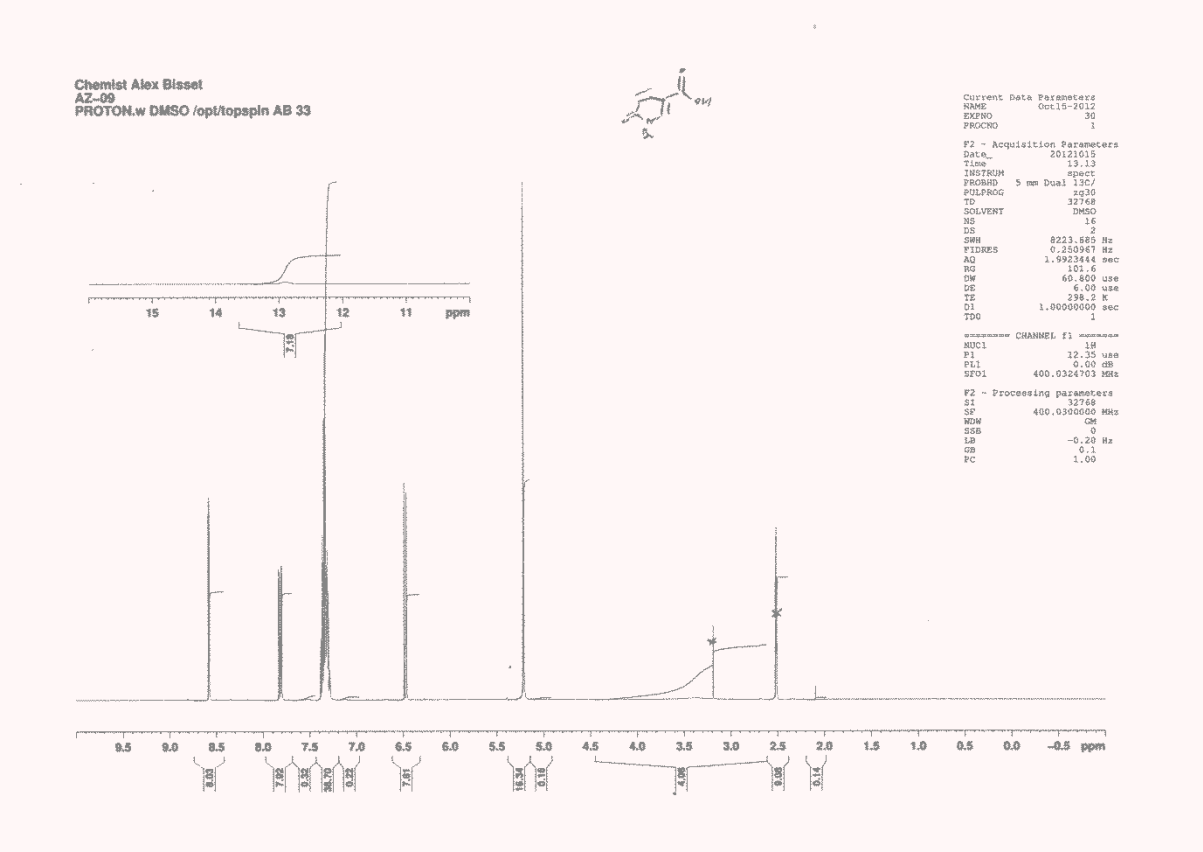
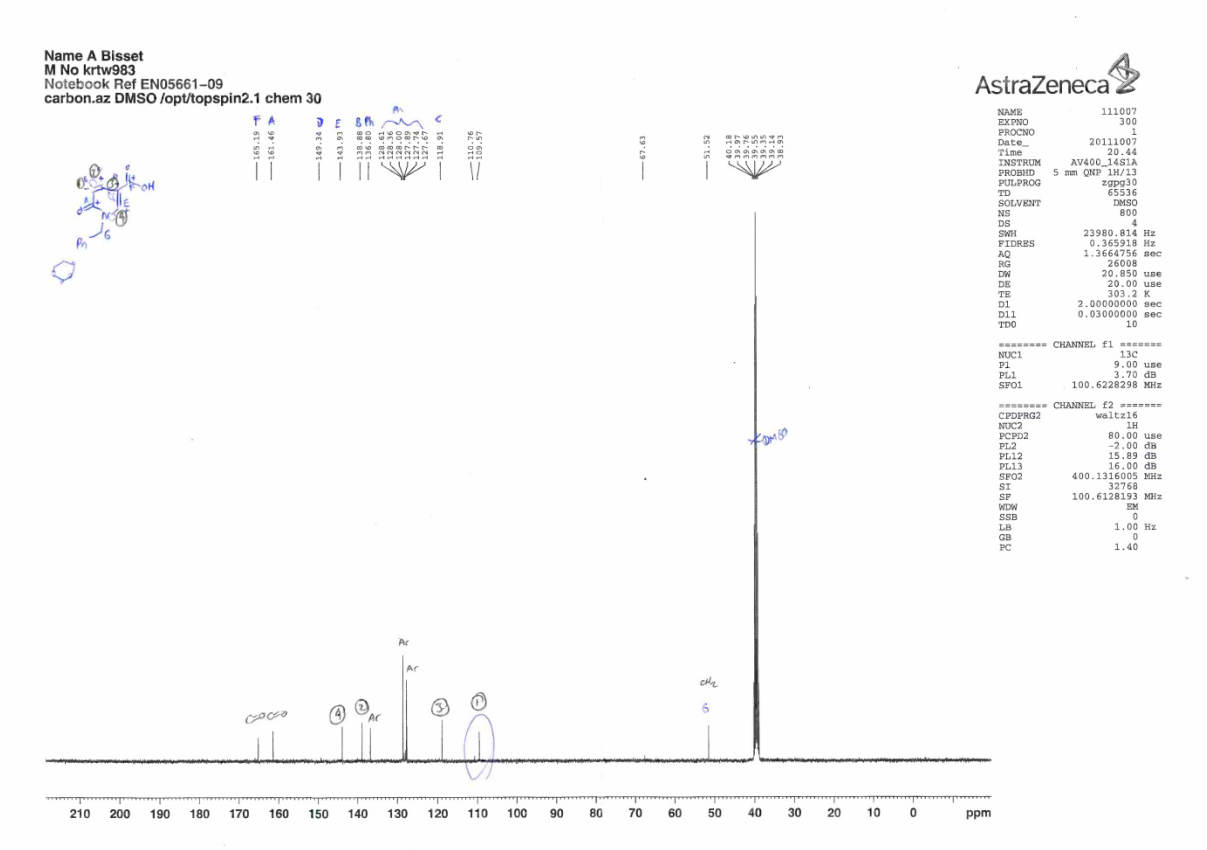
NMR spectra of intermediates and products.

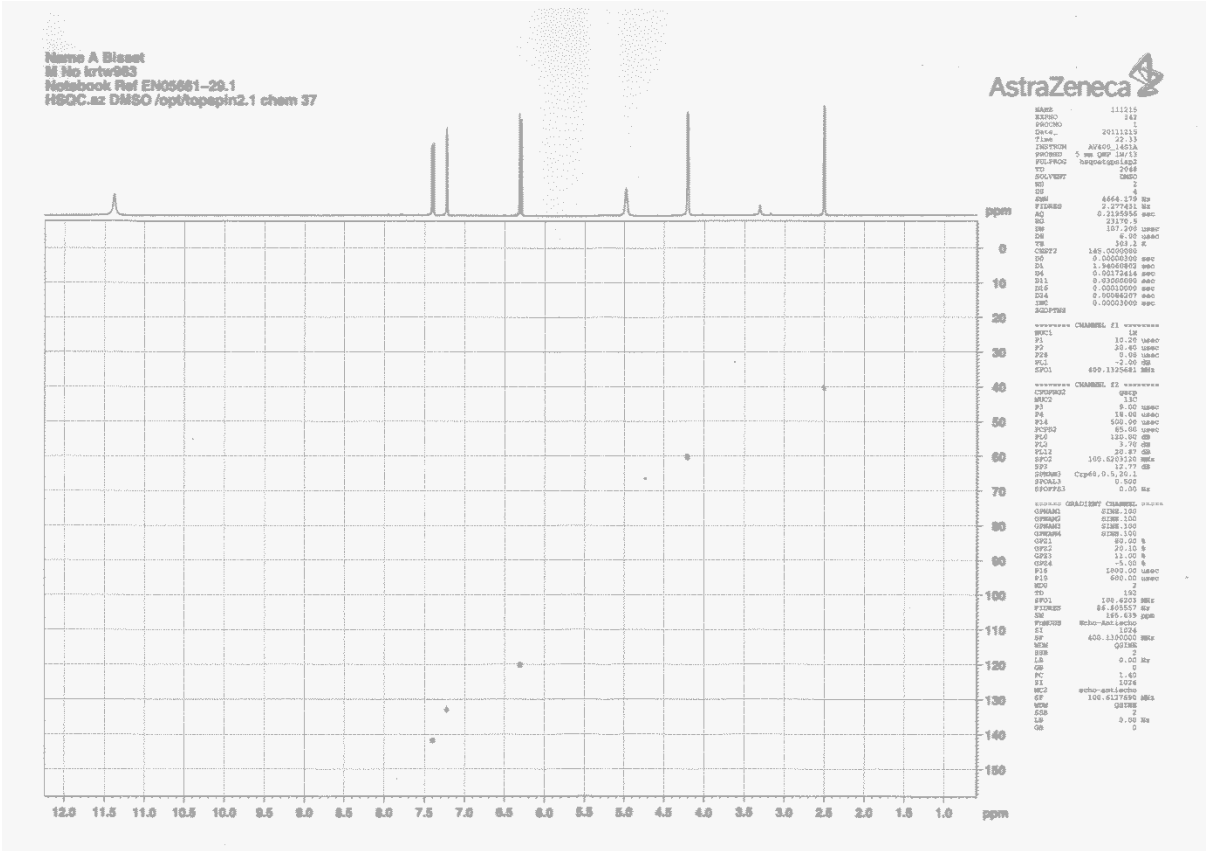


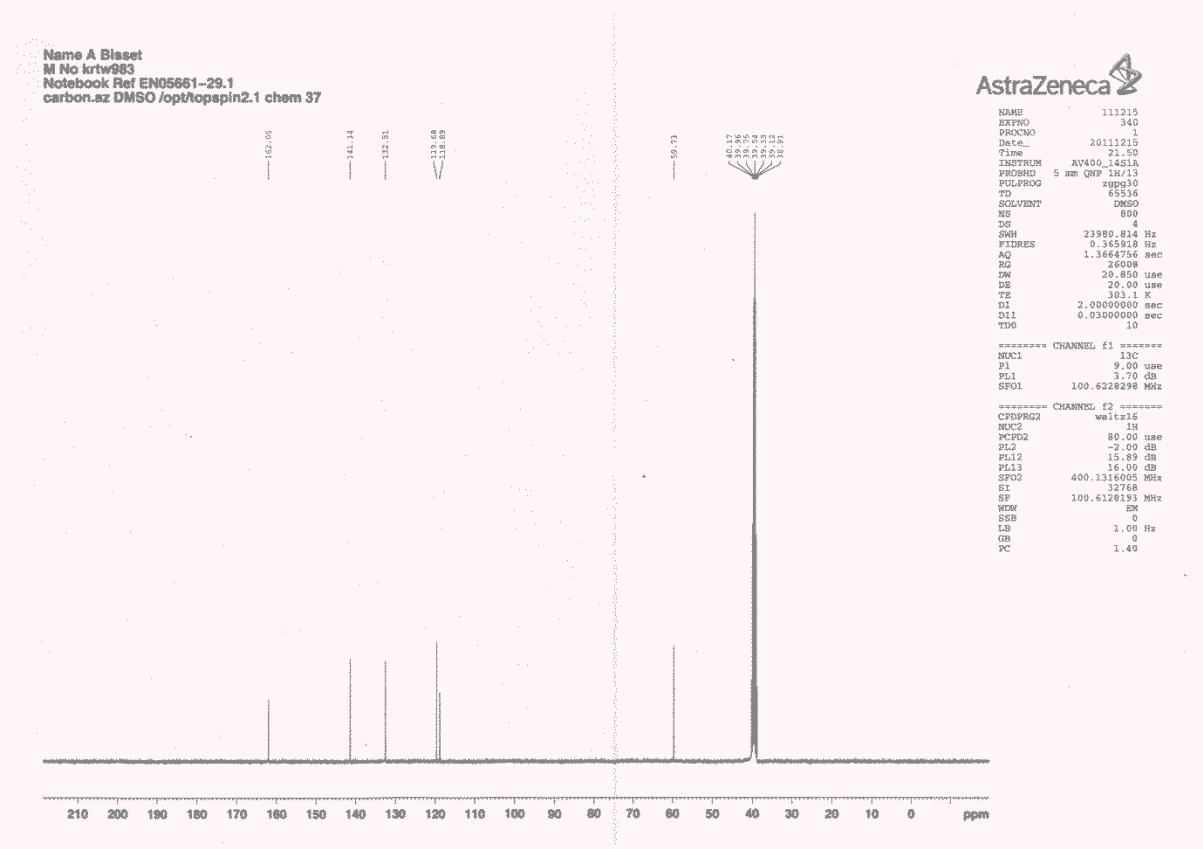
1-Benzyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid, ***3a.***



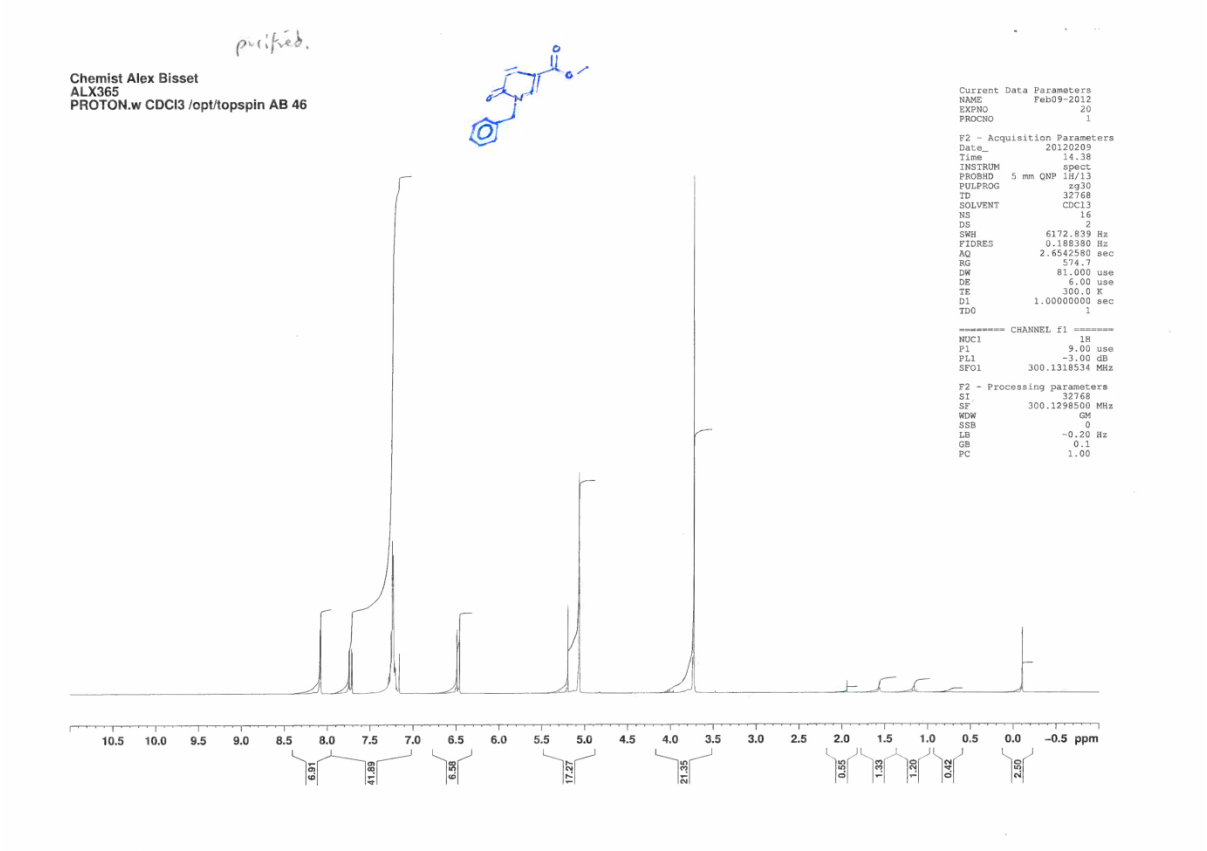


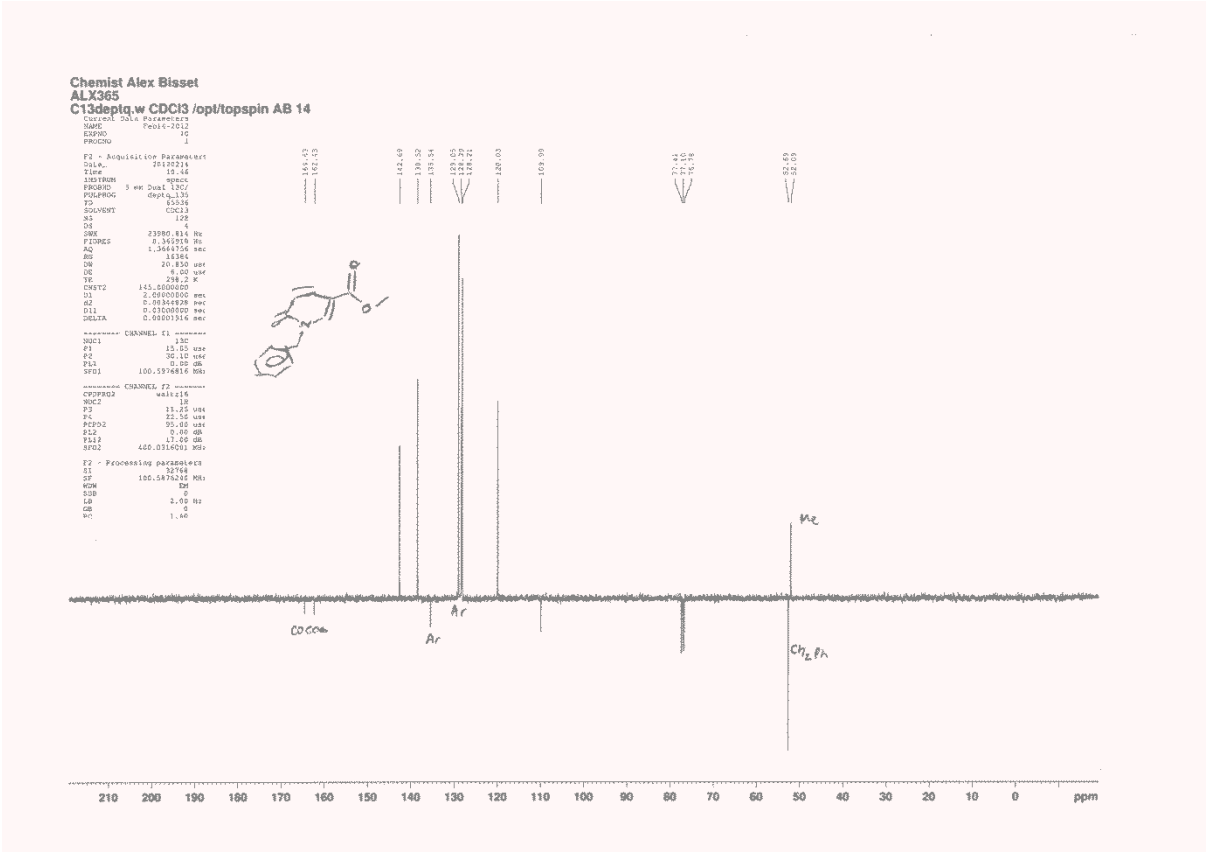
Methyl 6-methoxynicotinate, ***2b*** *in DMSO****.***



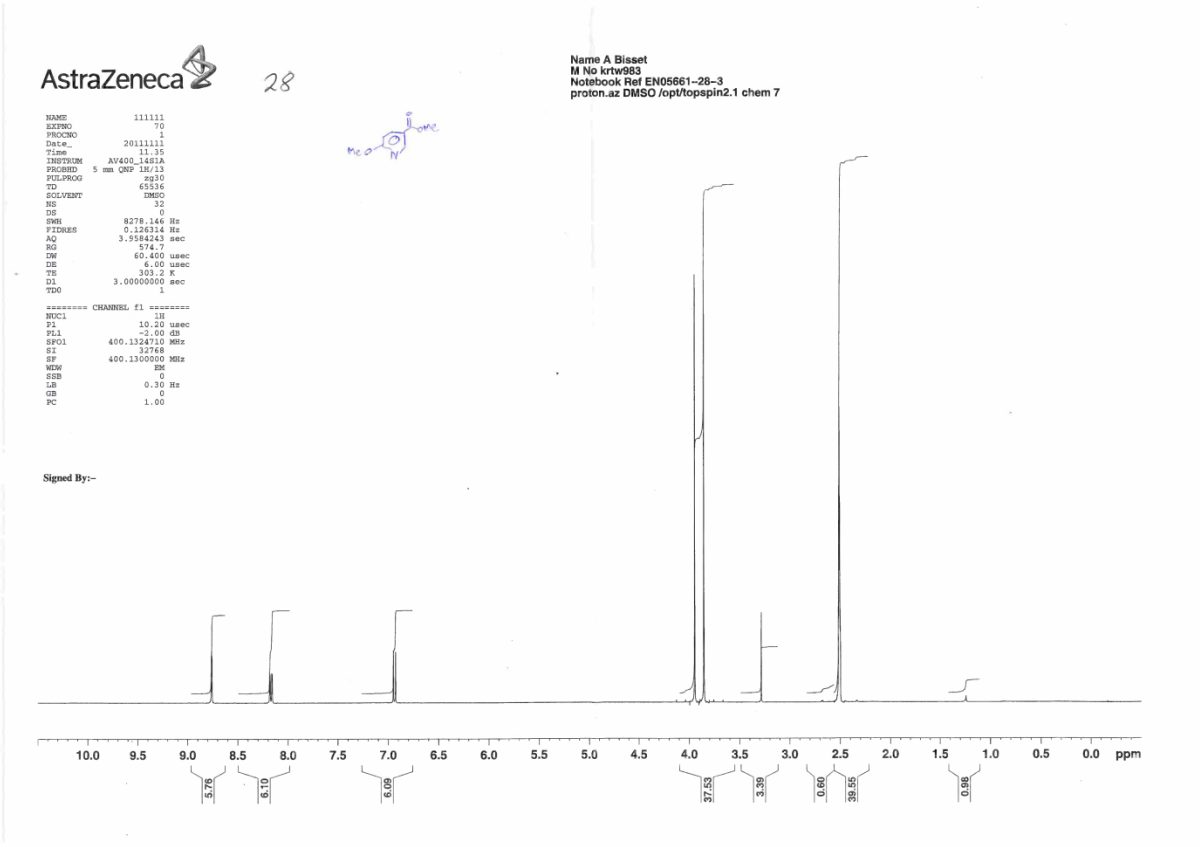


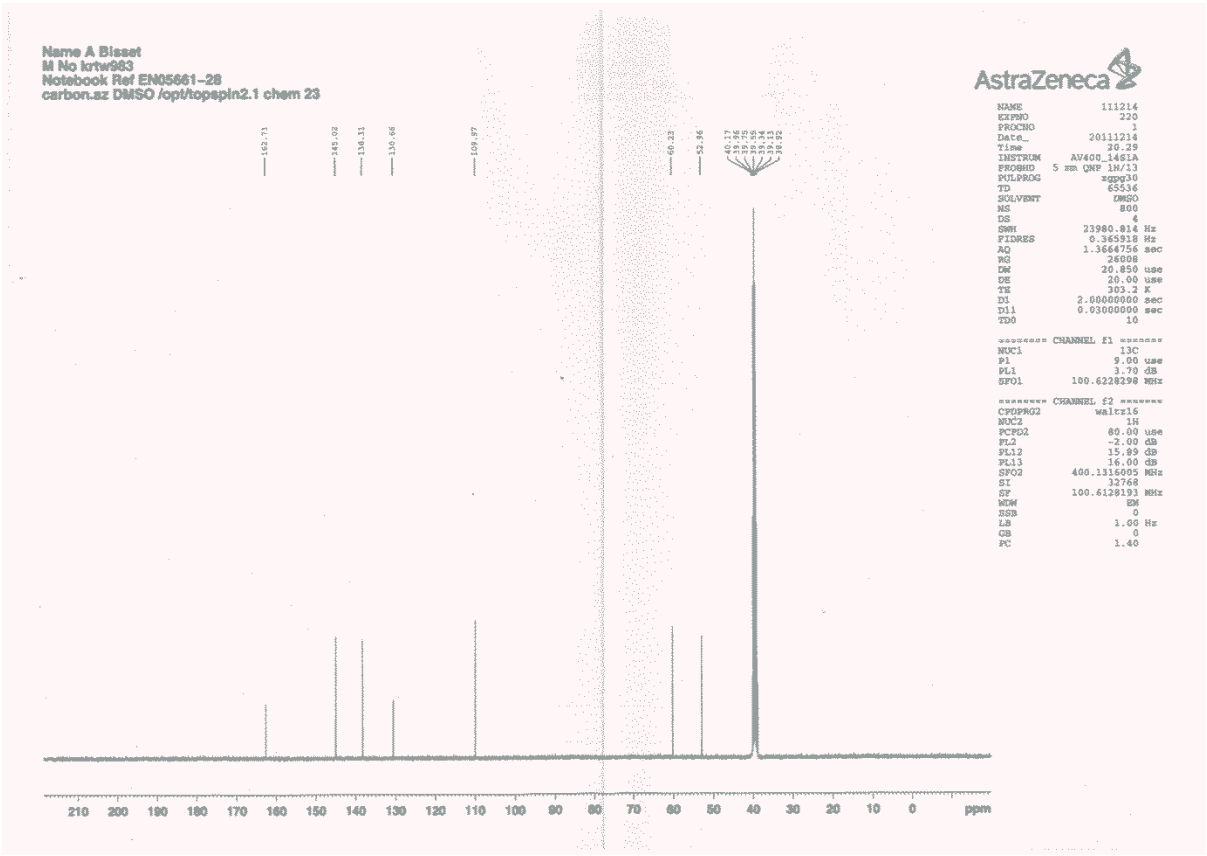
Methyl 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylate, ***3b.***



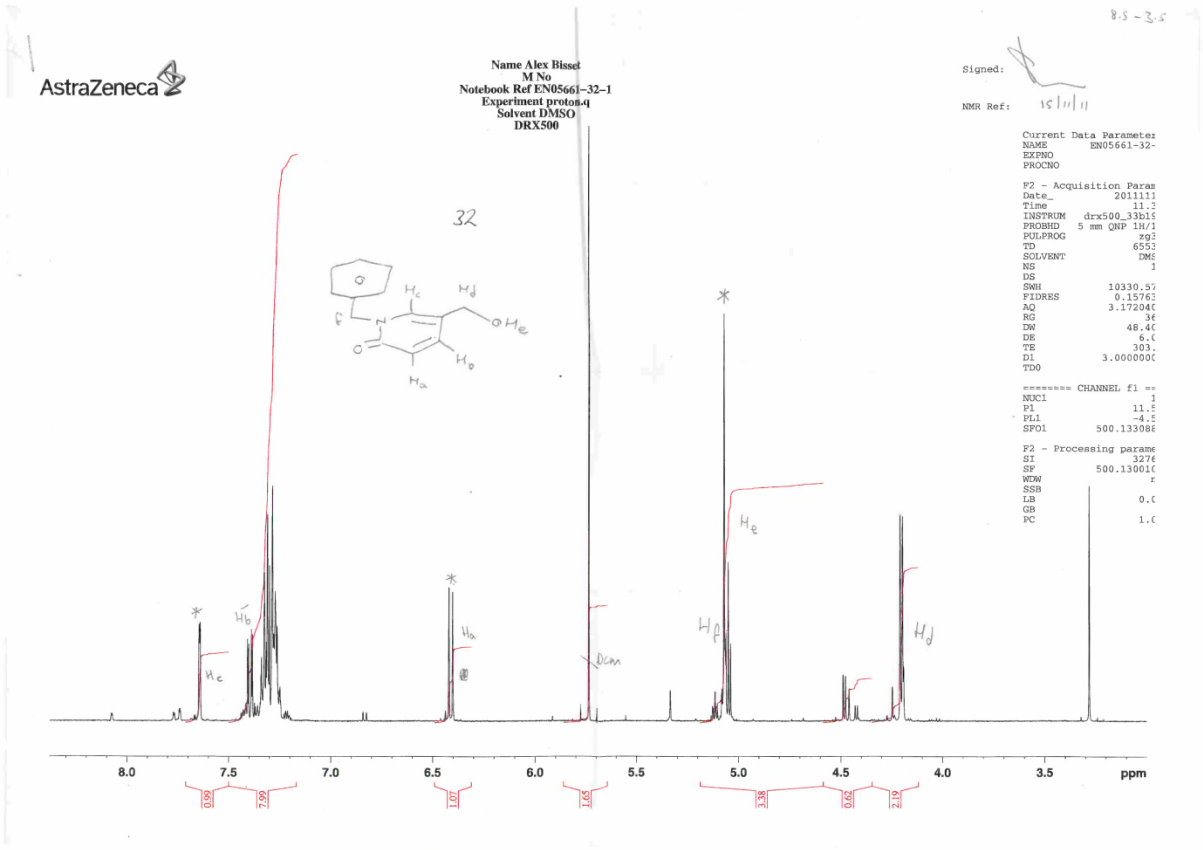


(6-Methoxypyridin-3-yl)methanol, ***2c.***





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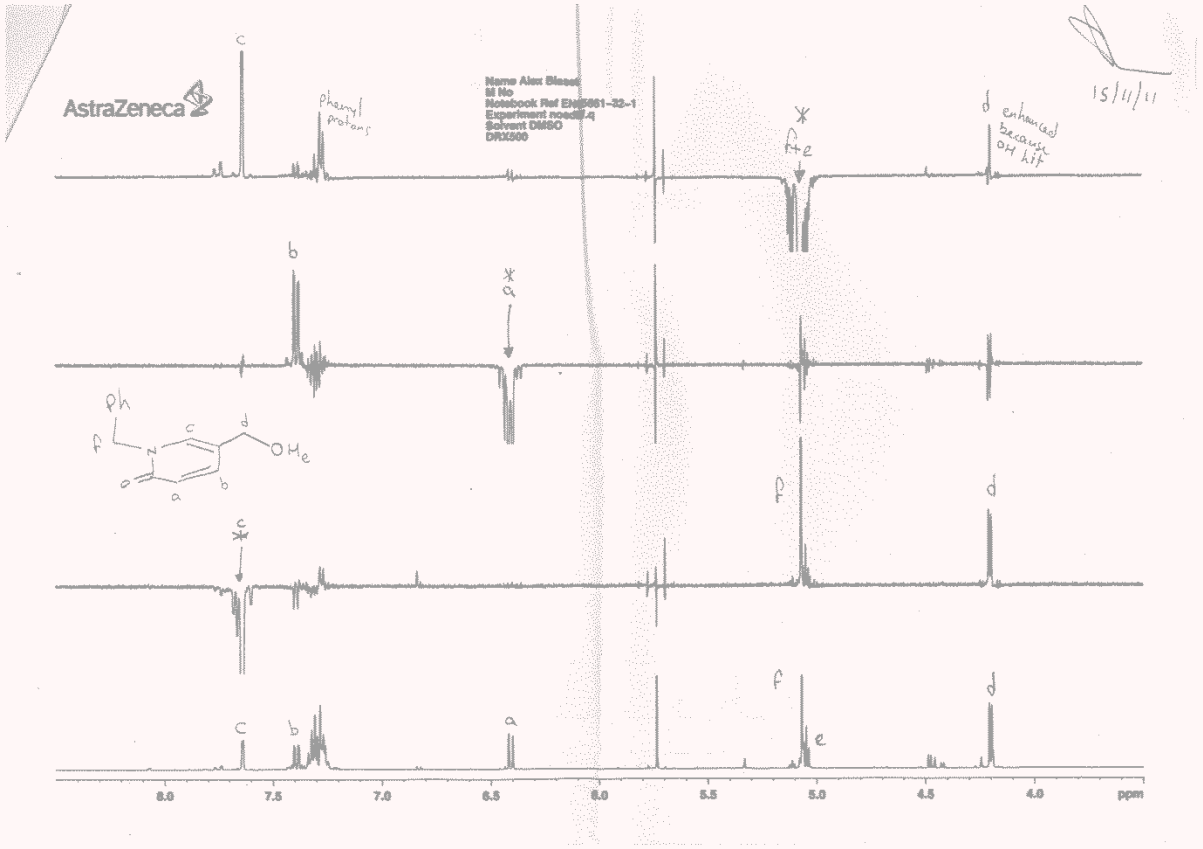
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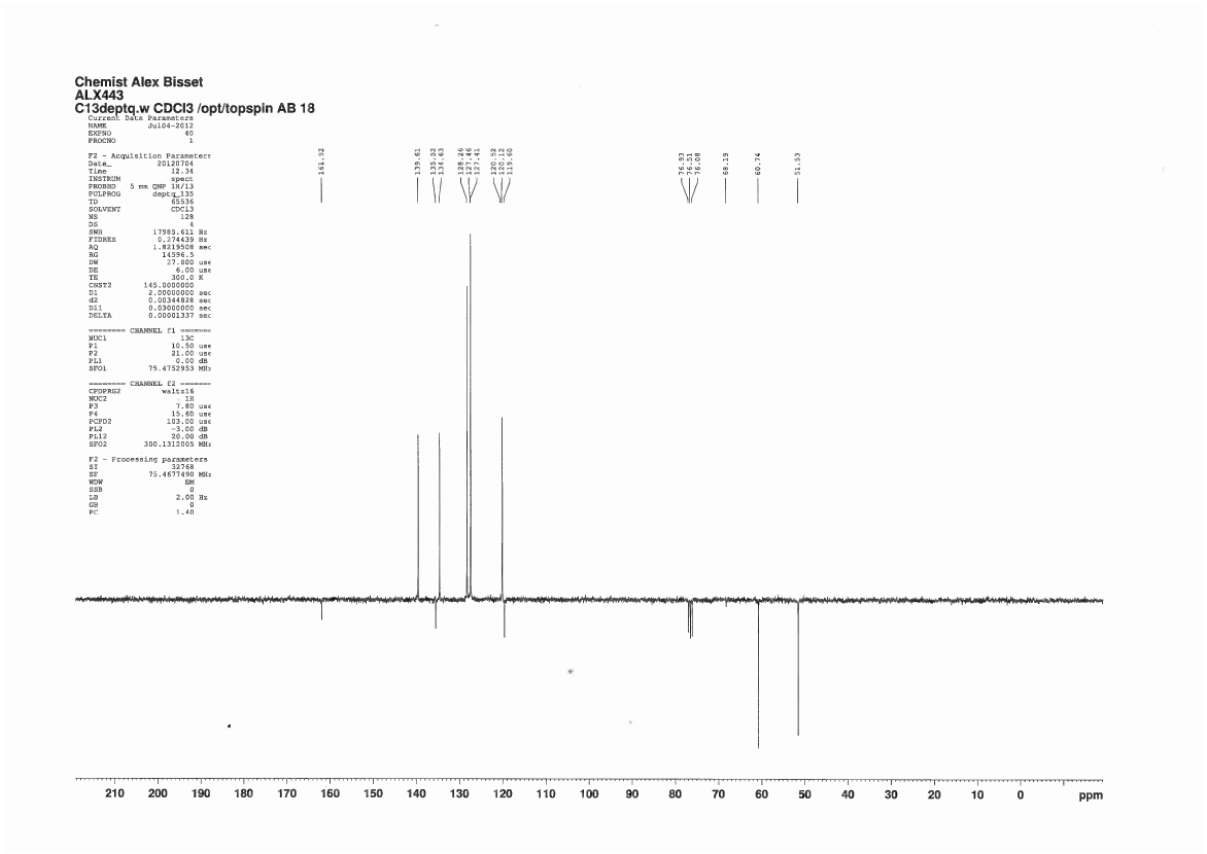
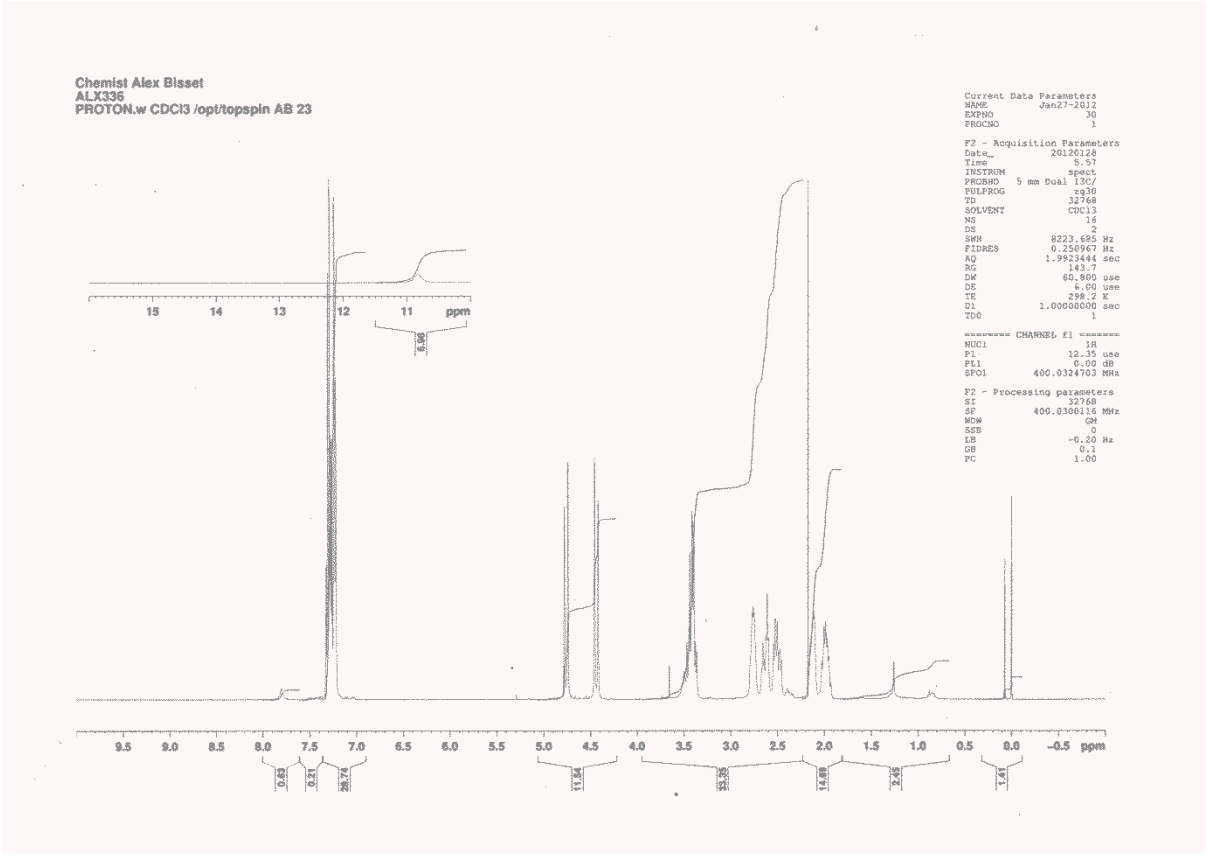
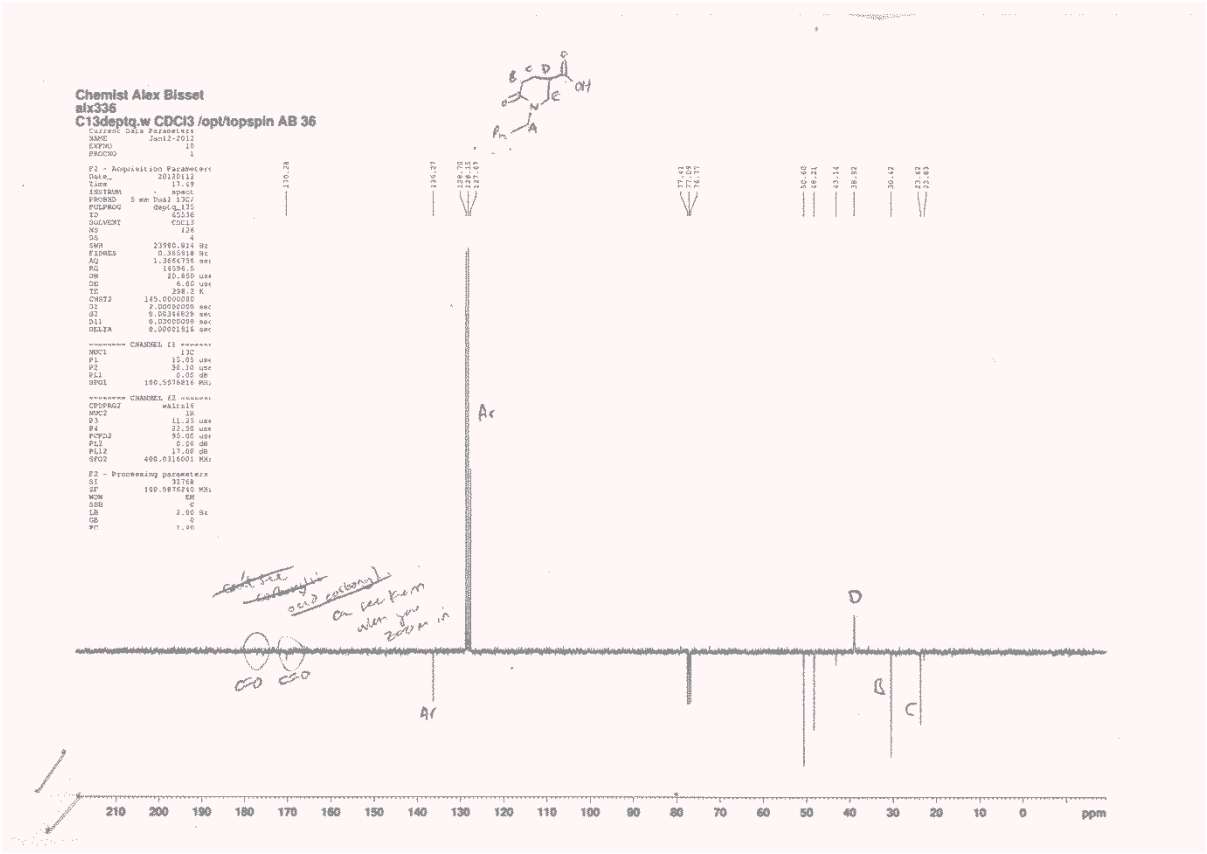
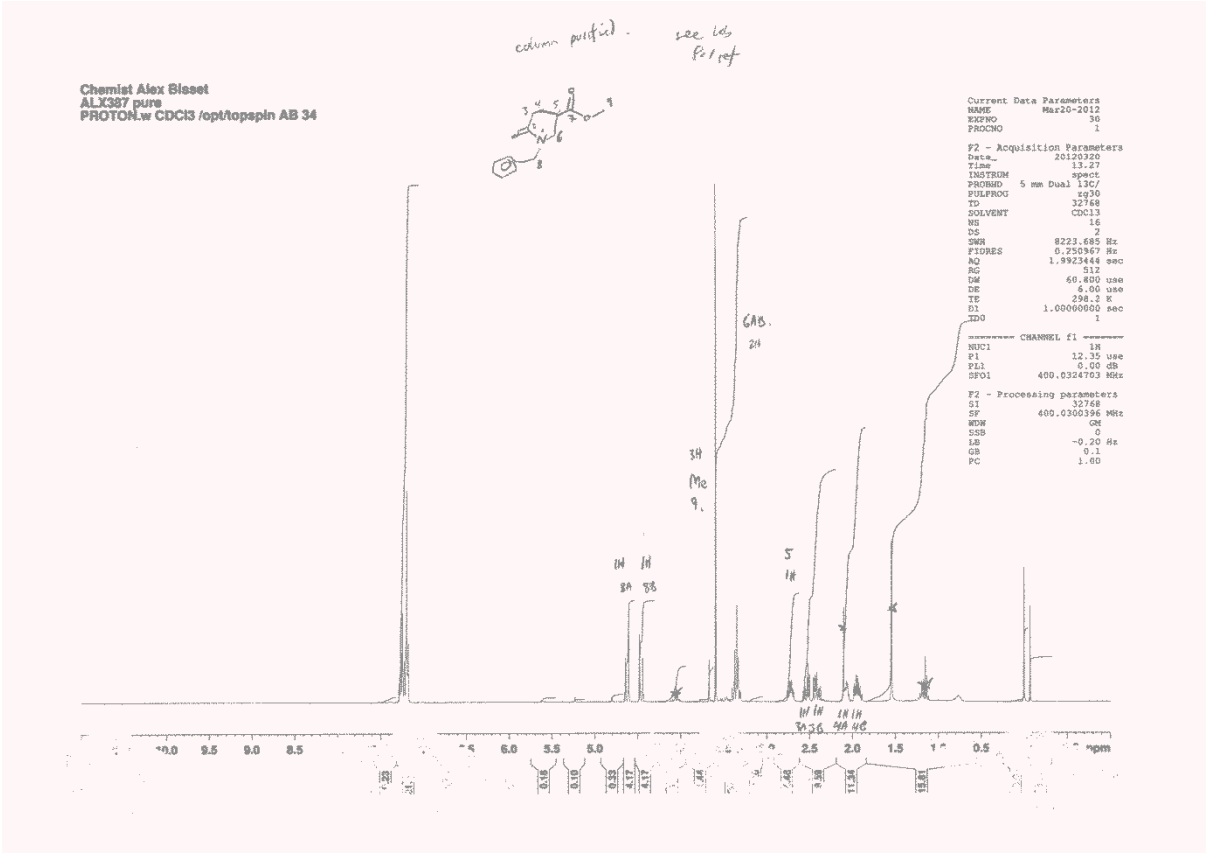


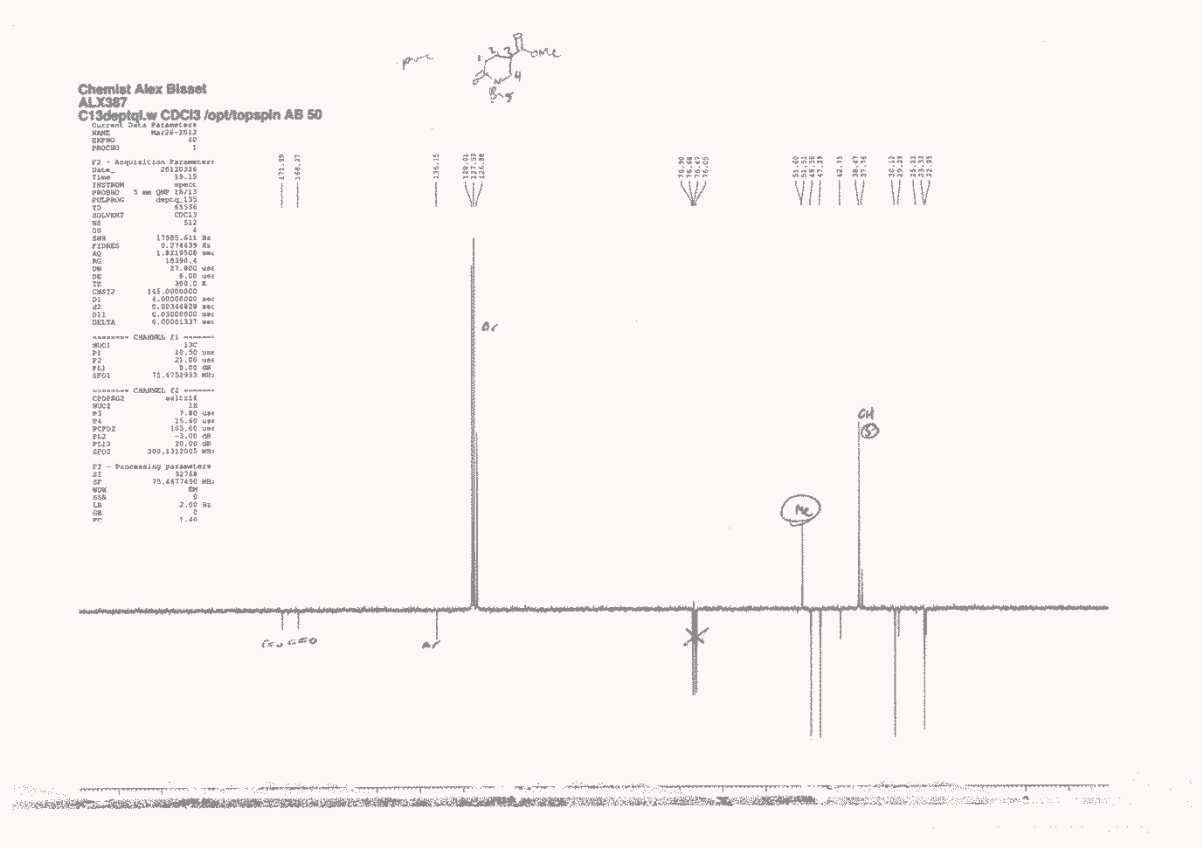
1-Benzyl-6-oxopiperidine-3-carboxylic acid, (±)-**4a.**





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





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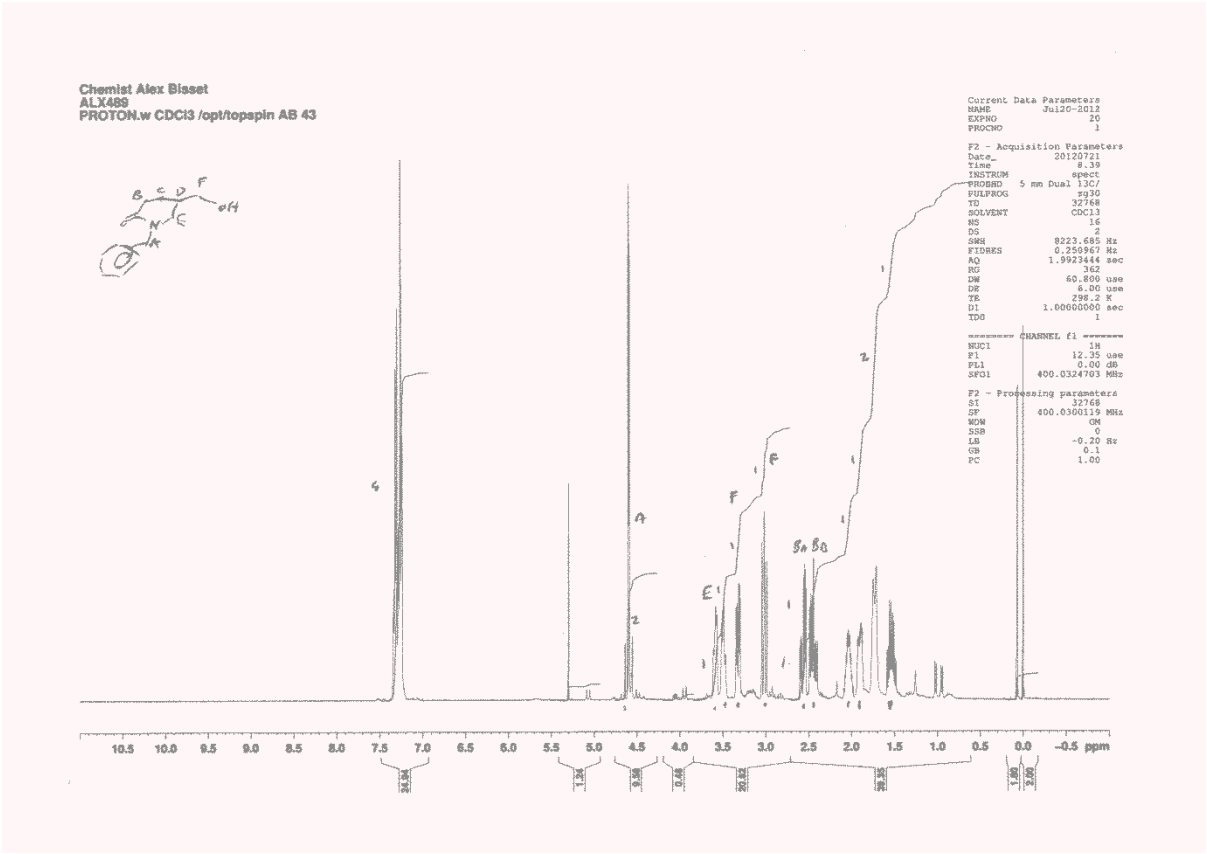
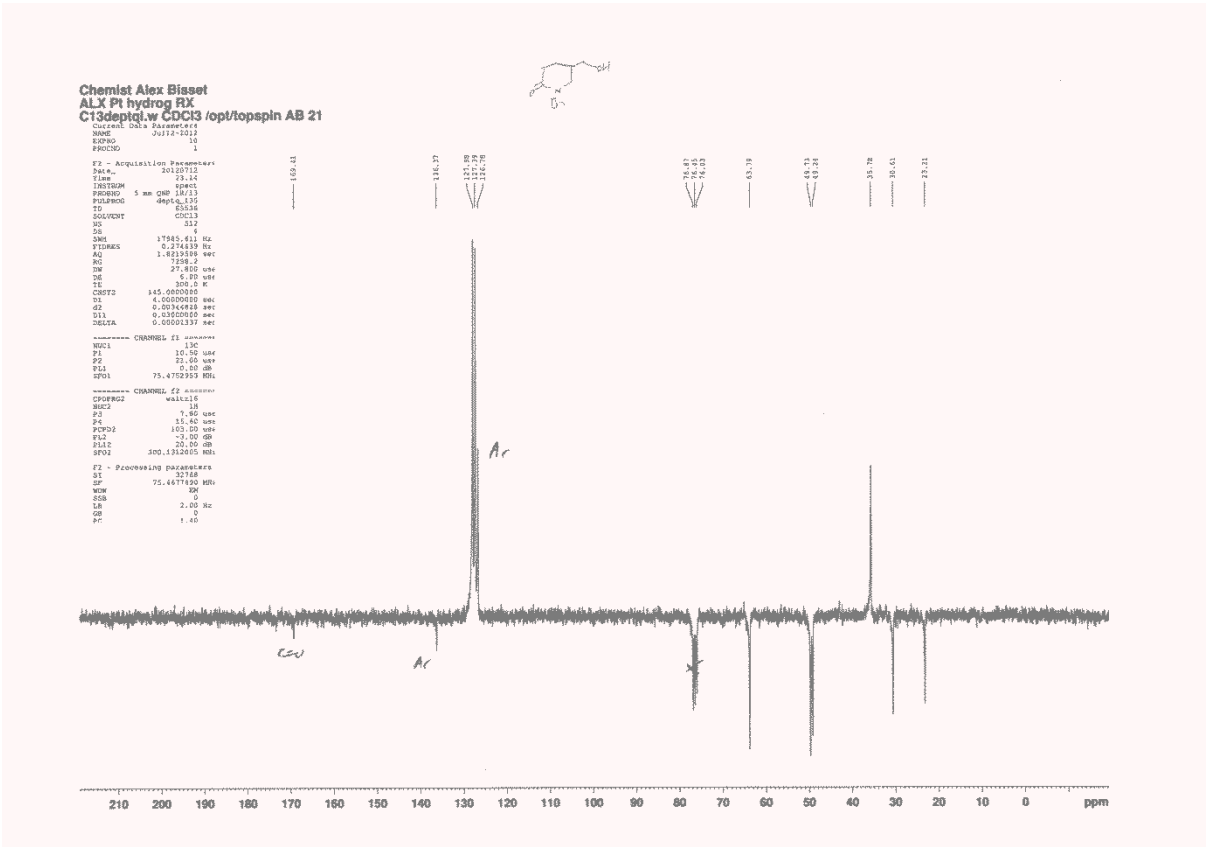
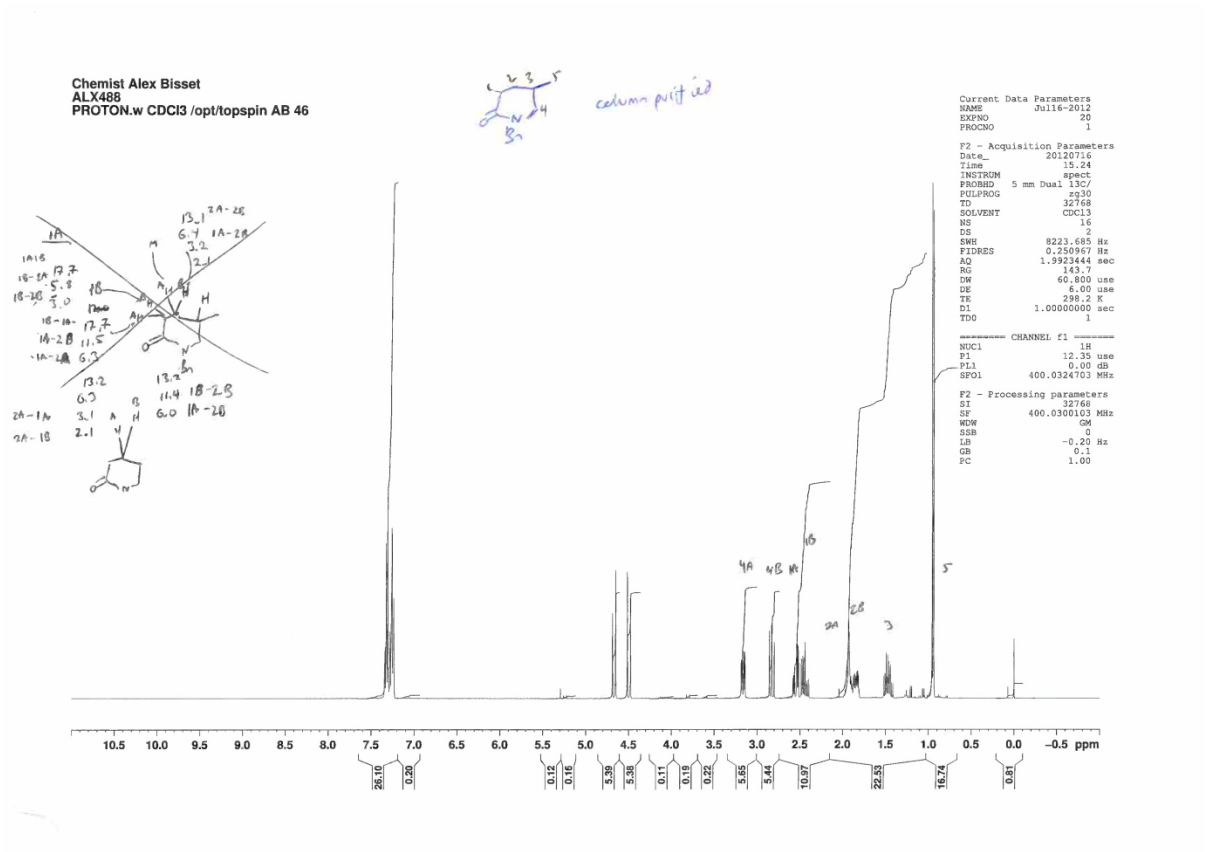
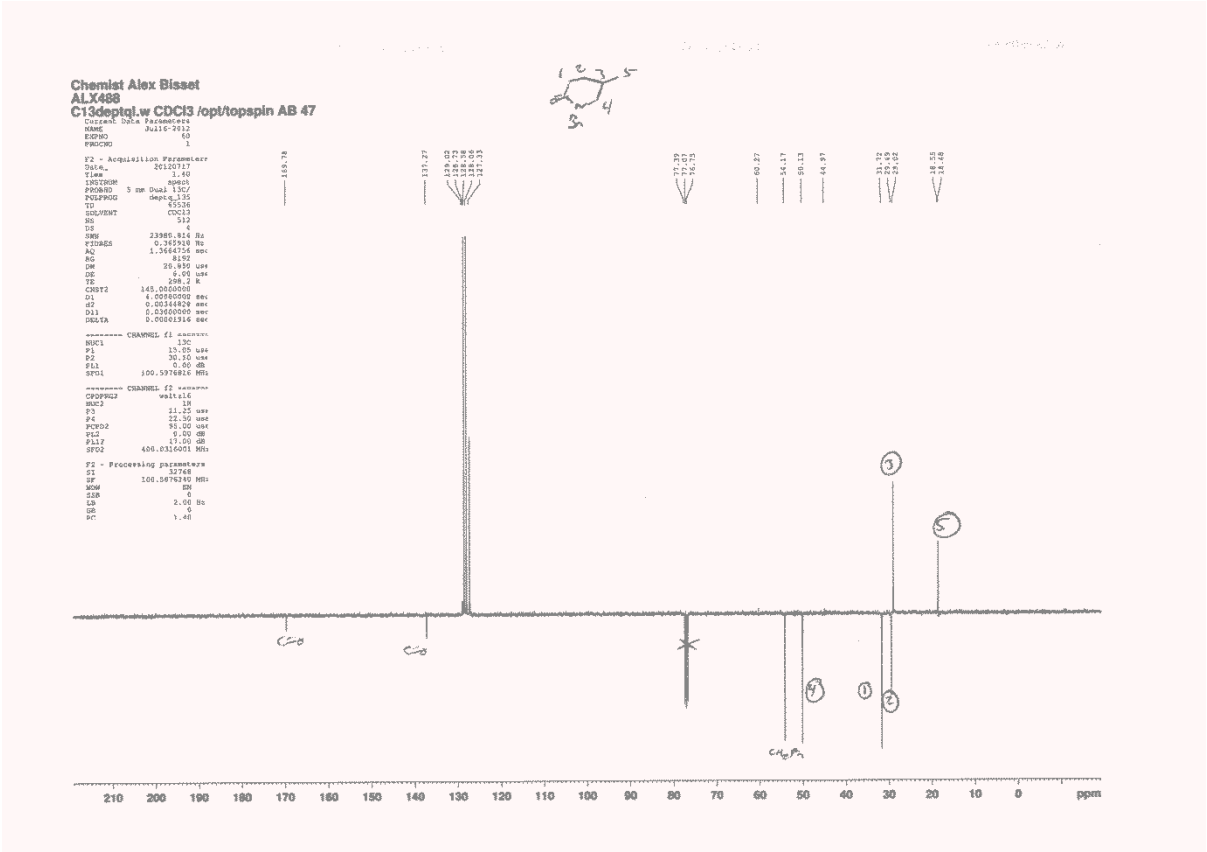




1-Benzyl-5-methylpiperidin-2-one, (±)**-21.**





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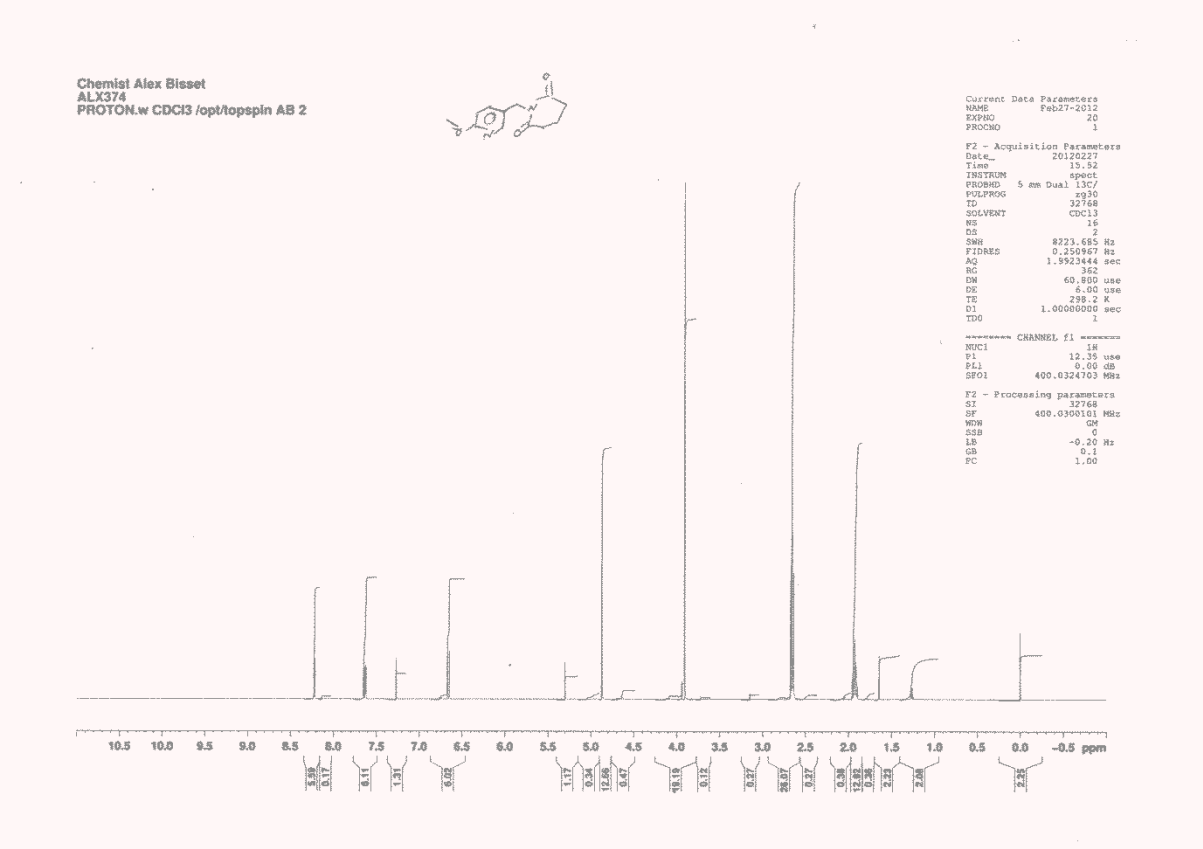
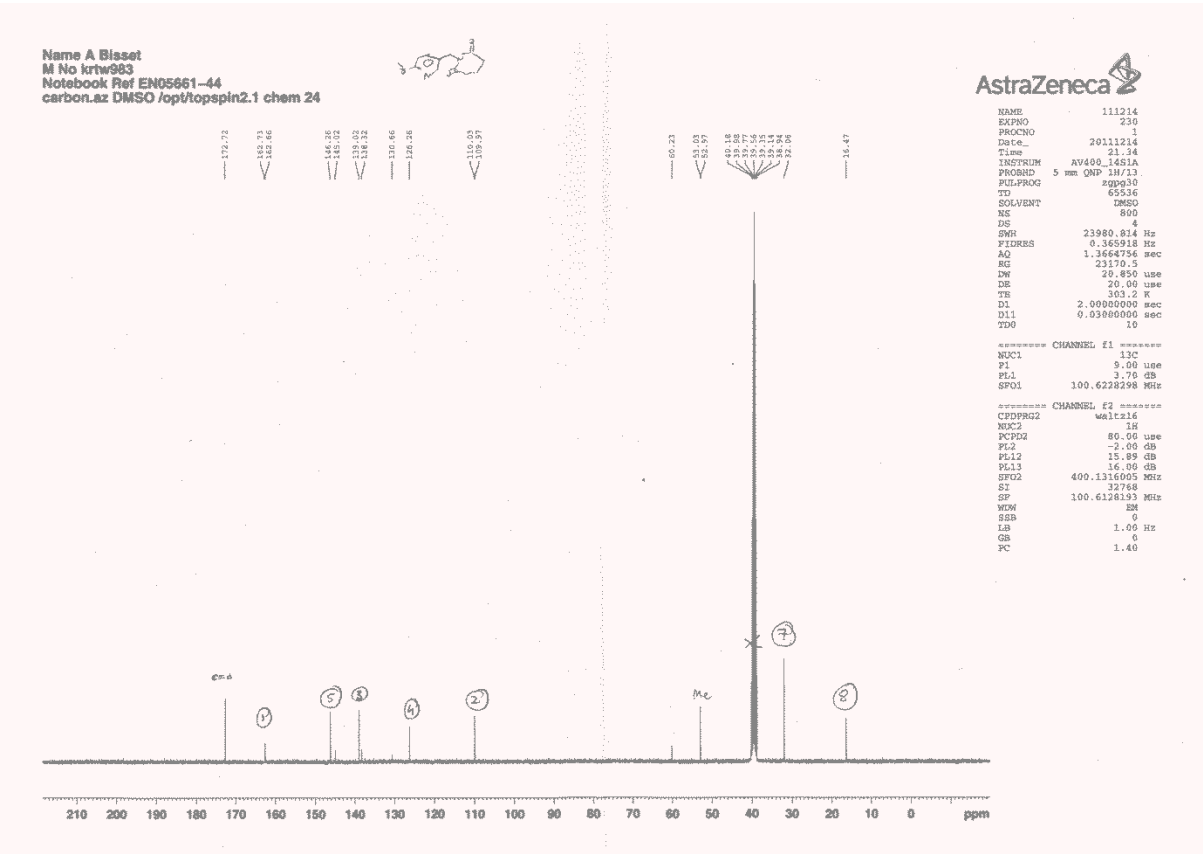
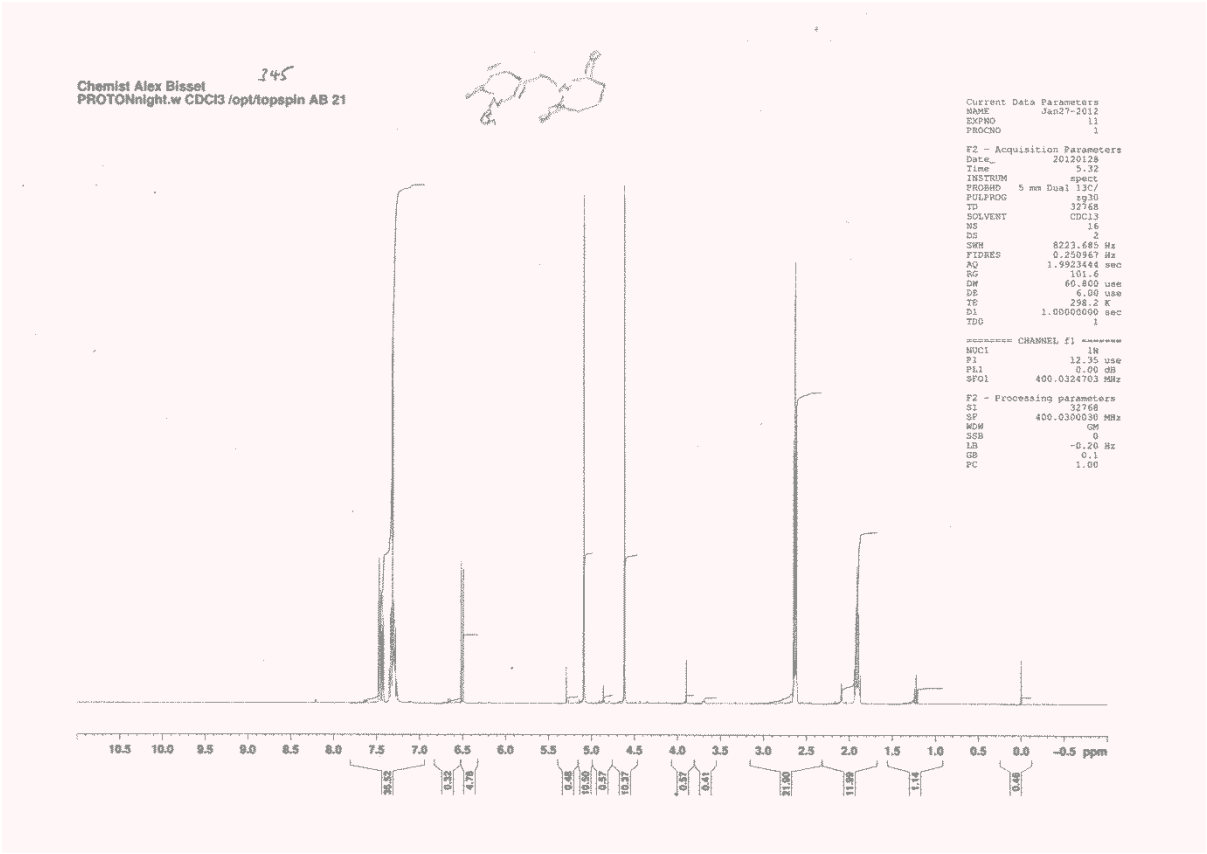




1-[(1-Benzyl-6-oxo-1,6-dihydropyridin-3-yl)methyl]piperidine-2,6-dione **3d.**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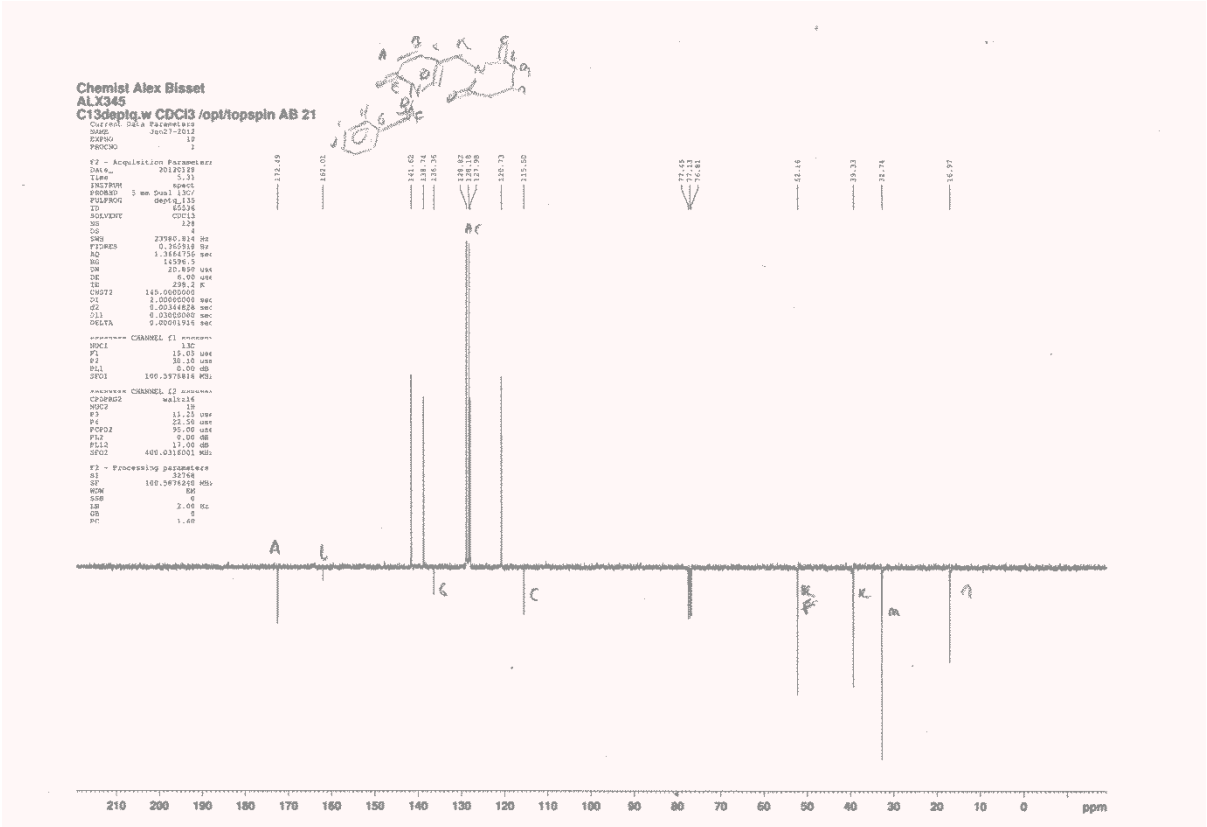
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PL12 17.00 dB
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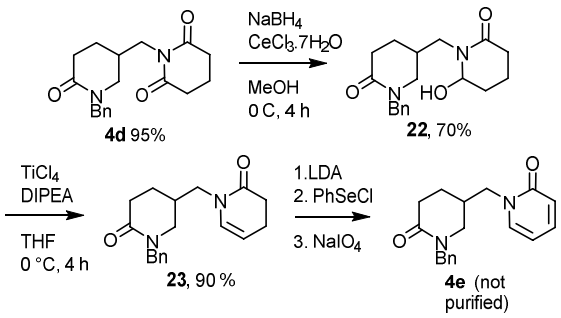
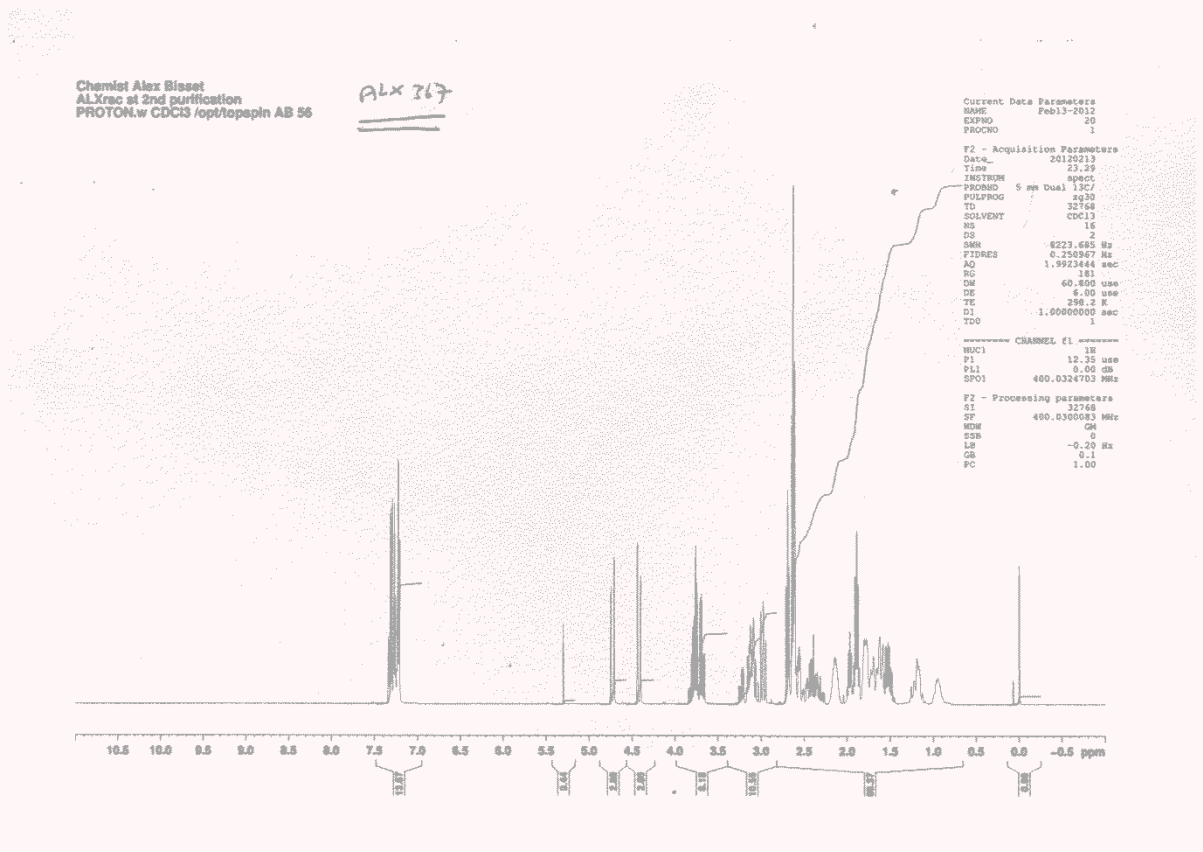
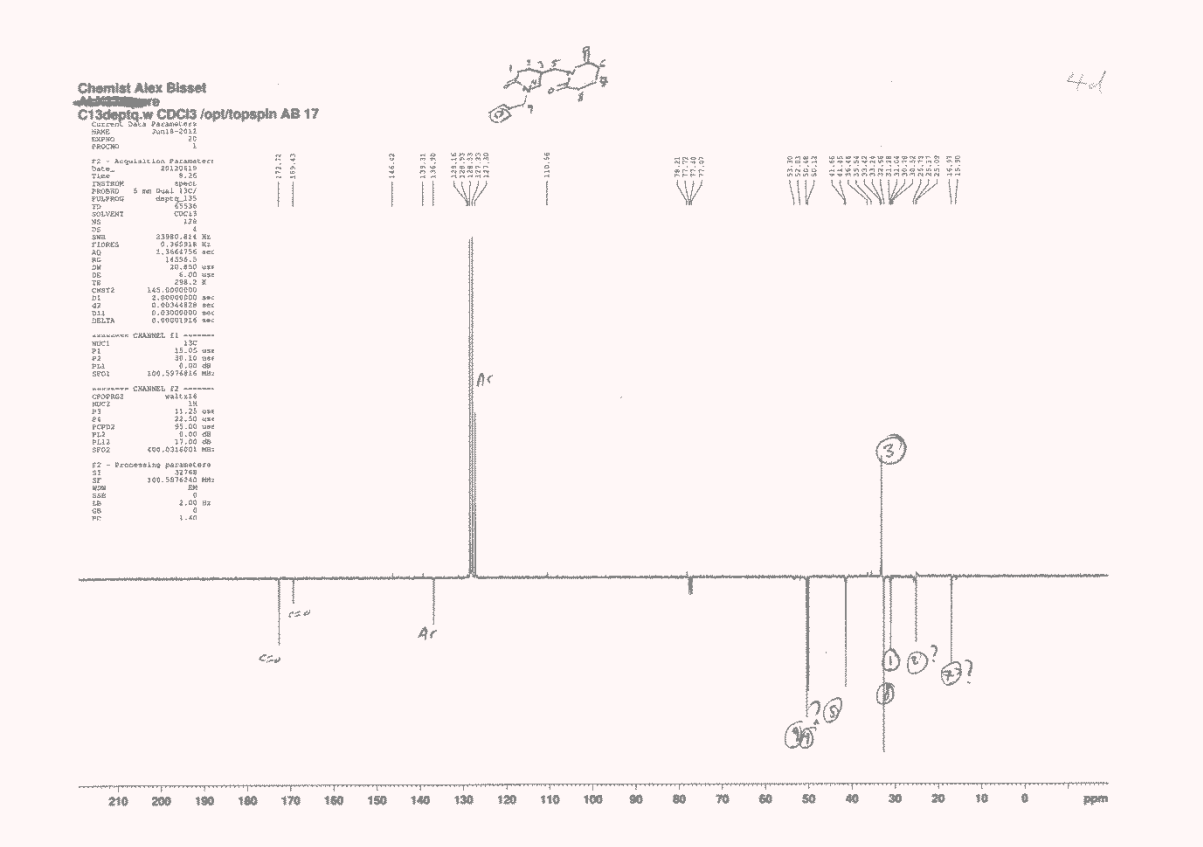
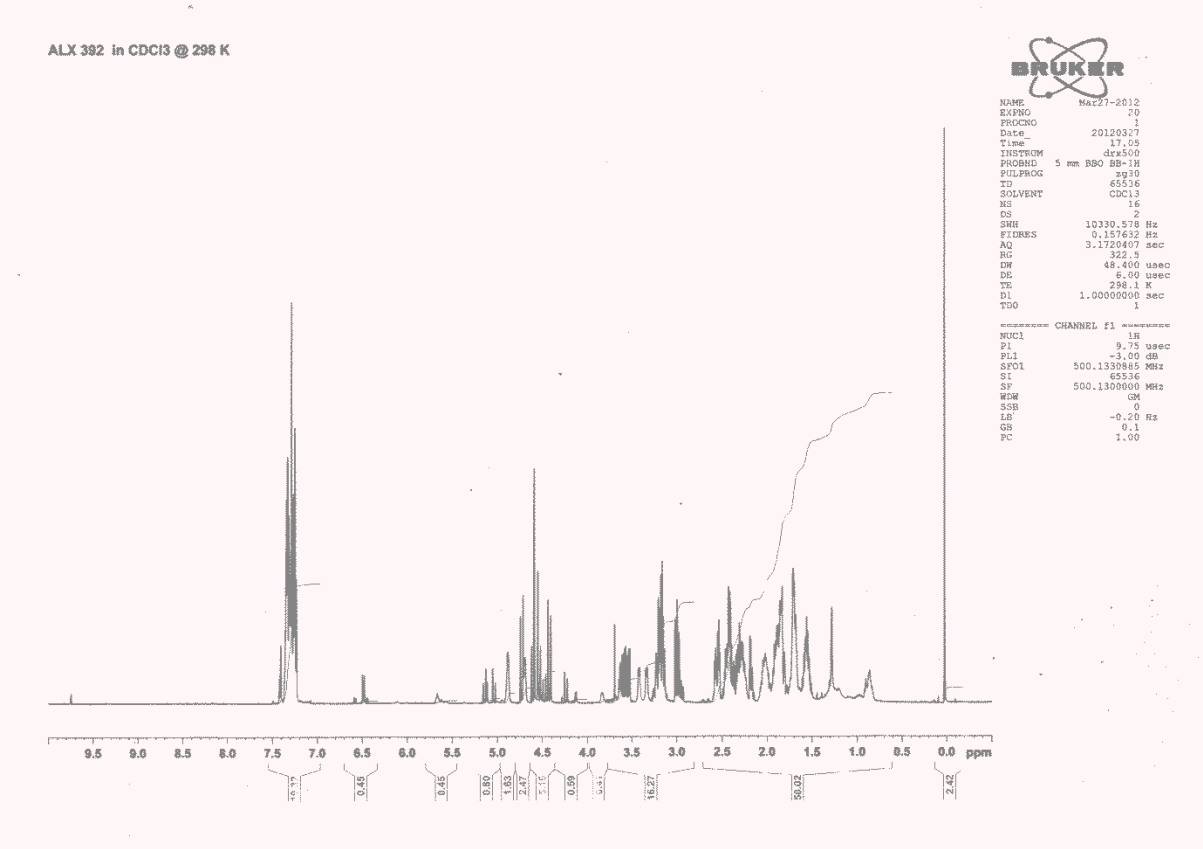


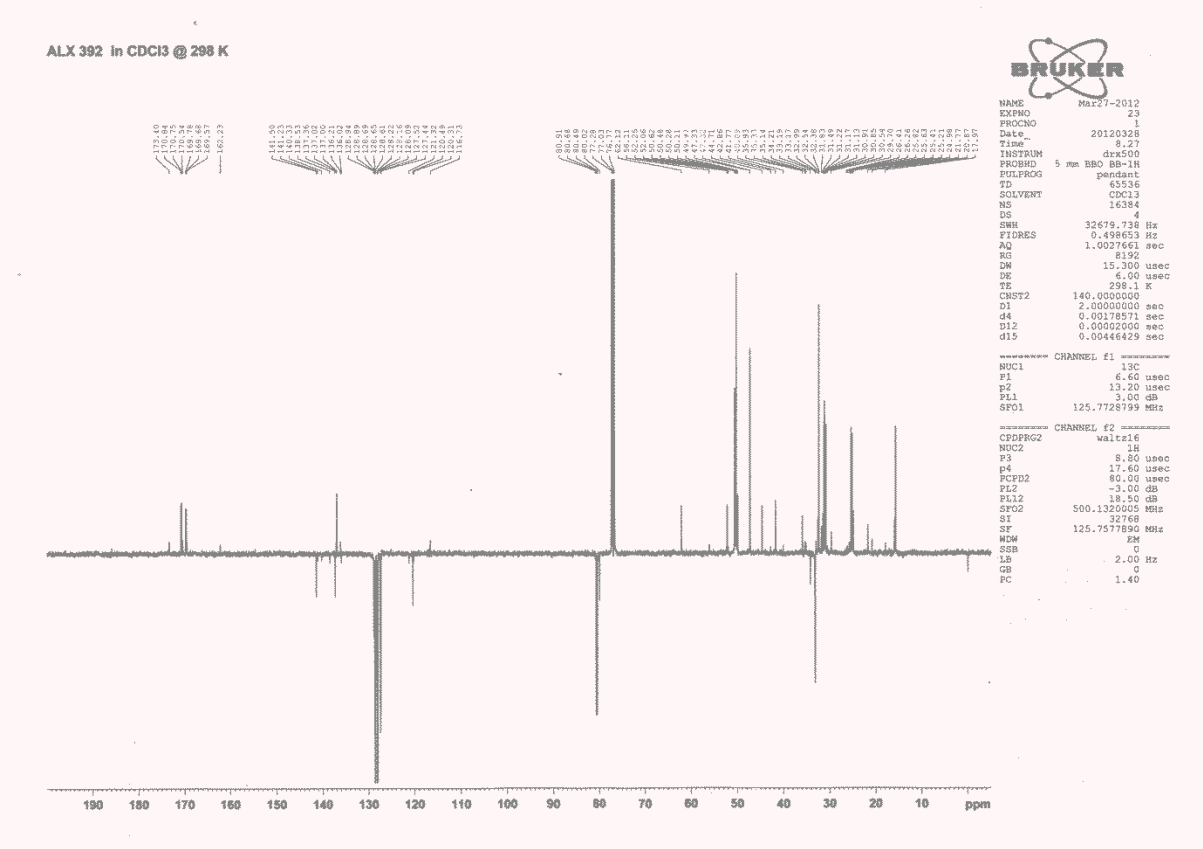
1-[(1-Benzyl-6-oxopiperidin-3-yl)methyl]piperidine-2,6-dione, (±)-**4d.**



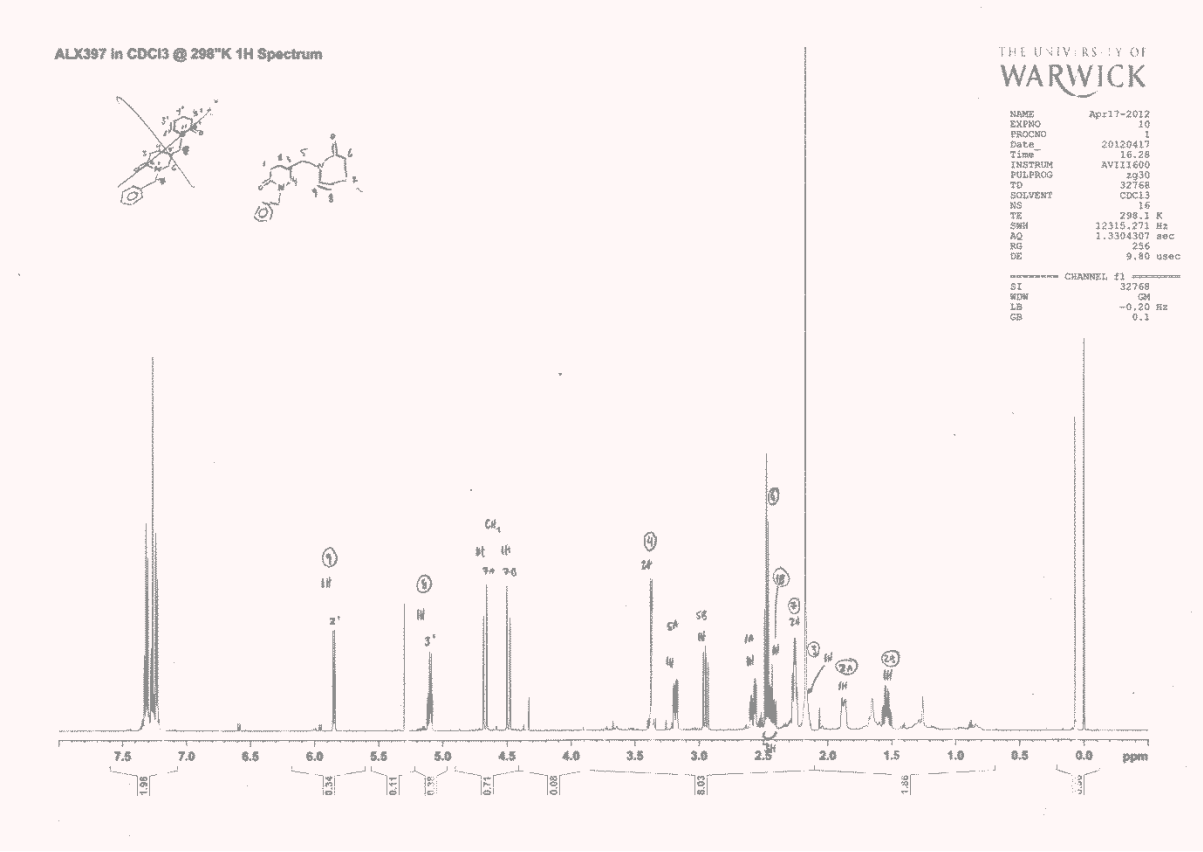


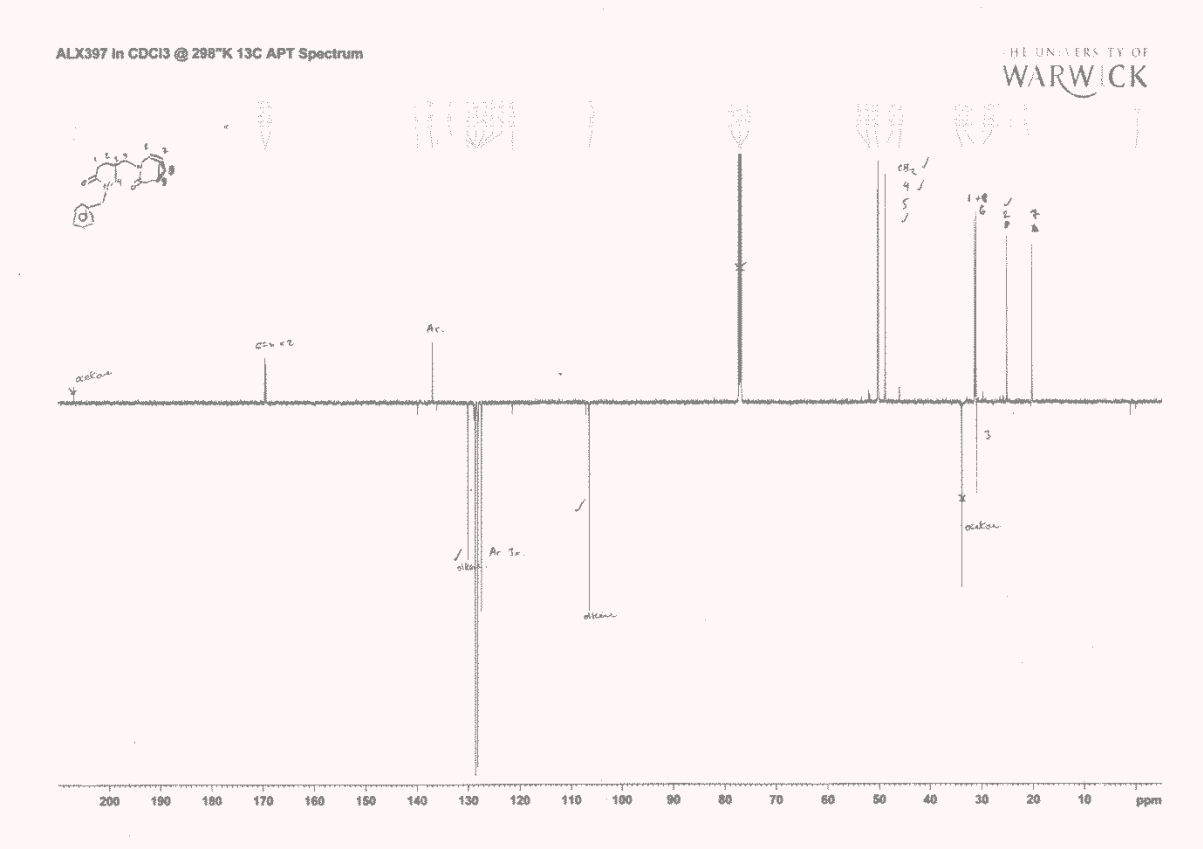
1-Benzyl-5-[(2-hydroxy-6-oxopiperidin-1-yl)methyl]piperidin-2-one, (±)-**22.**





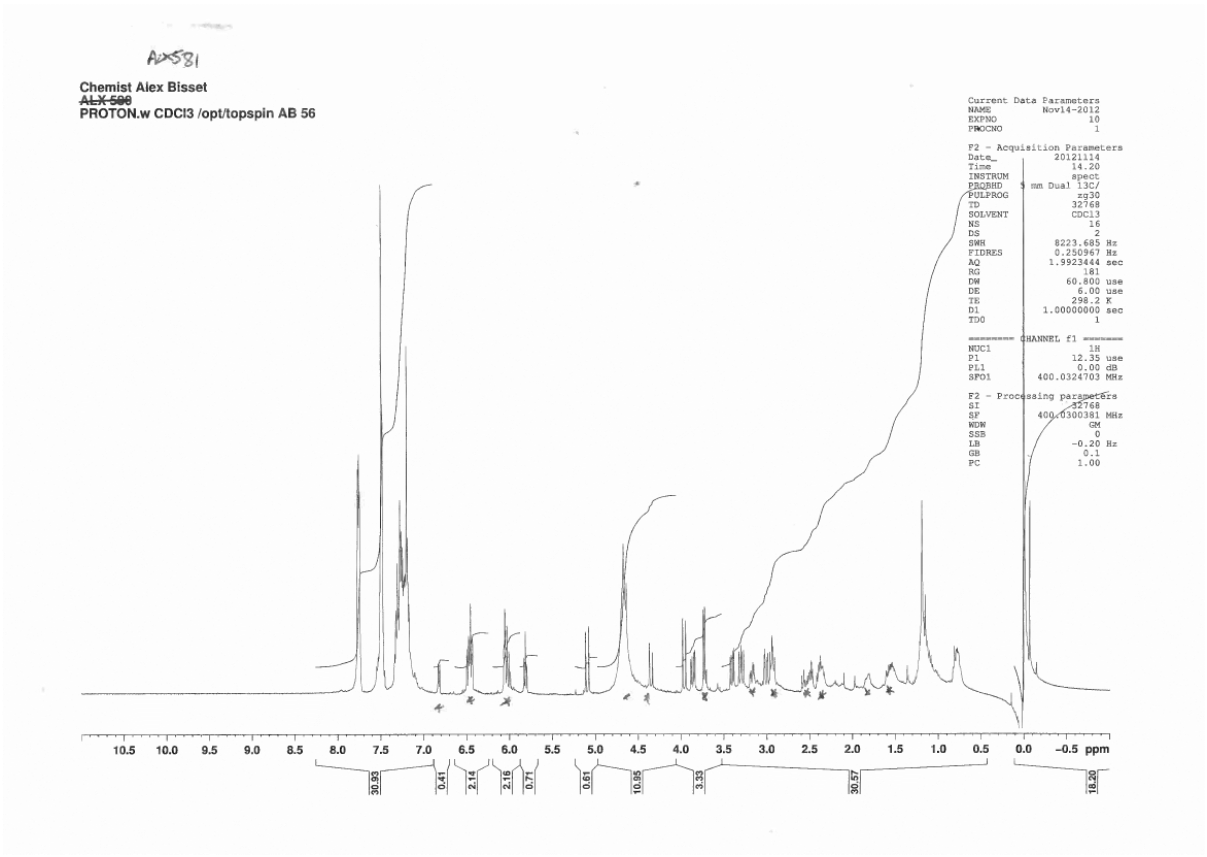
1-[(1-Benzyl-6-oxopiperidin-3-yl)methyl]-3,4-dihydropyridin-2(1H)-one, (±)-**23.**



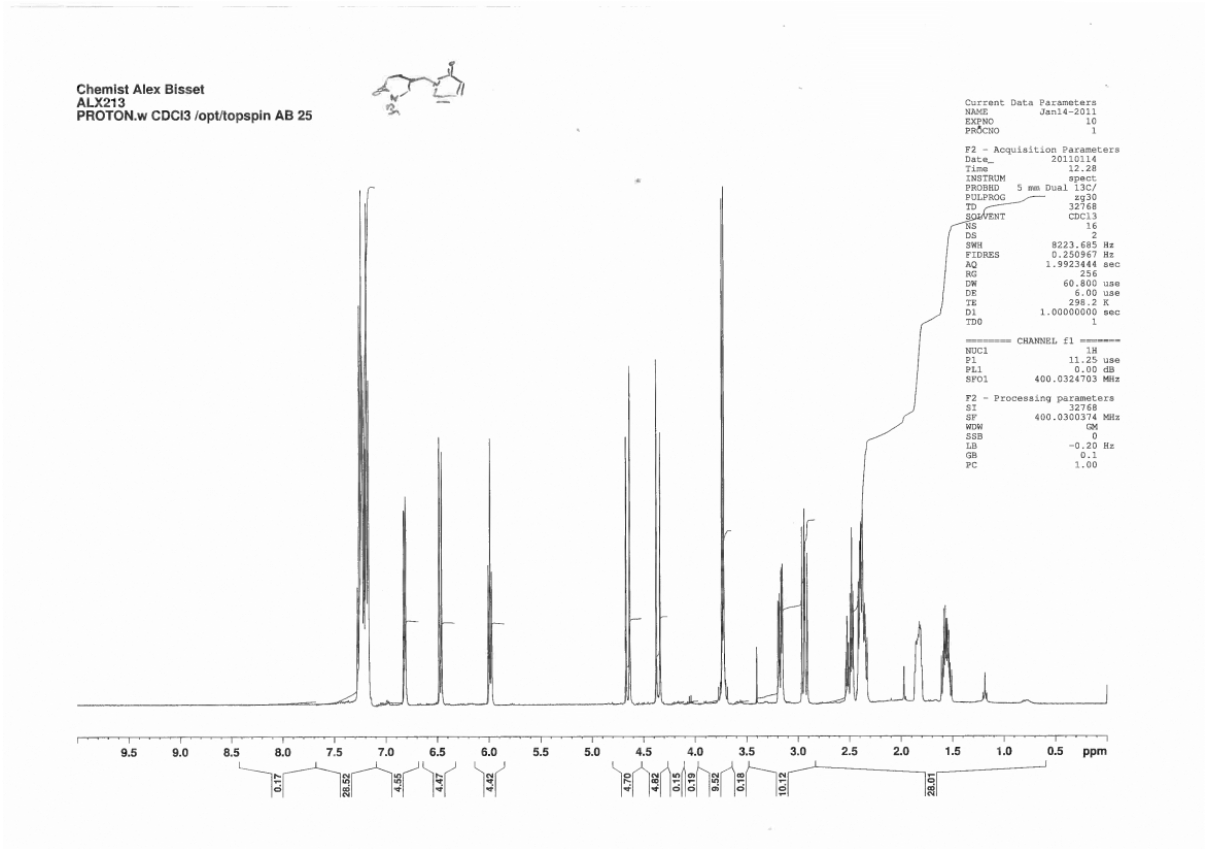


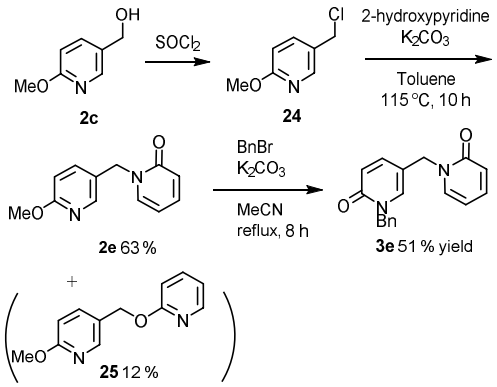
*The selenoxide oxidation – elimination of enamide (±)-**23**, yielding (±)-1-((1-benzyl-6-oxopiperidin-3-yl)methyl)pyridin-2(1H)-one, (±)-**4e.***

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

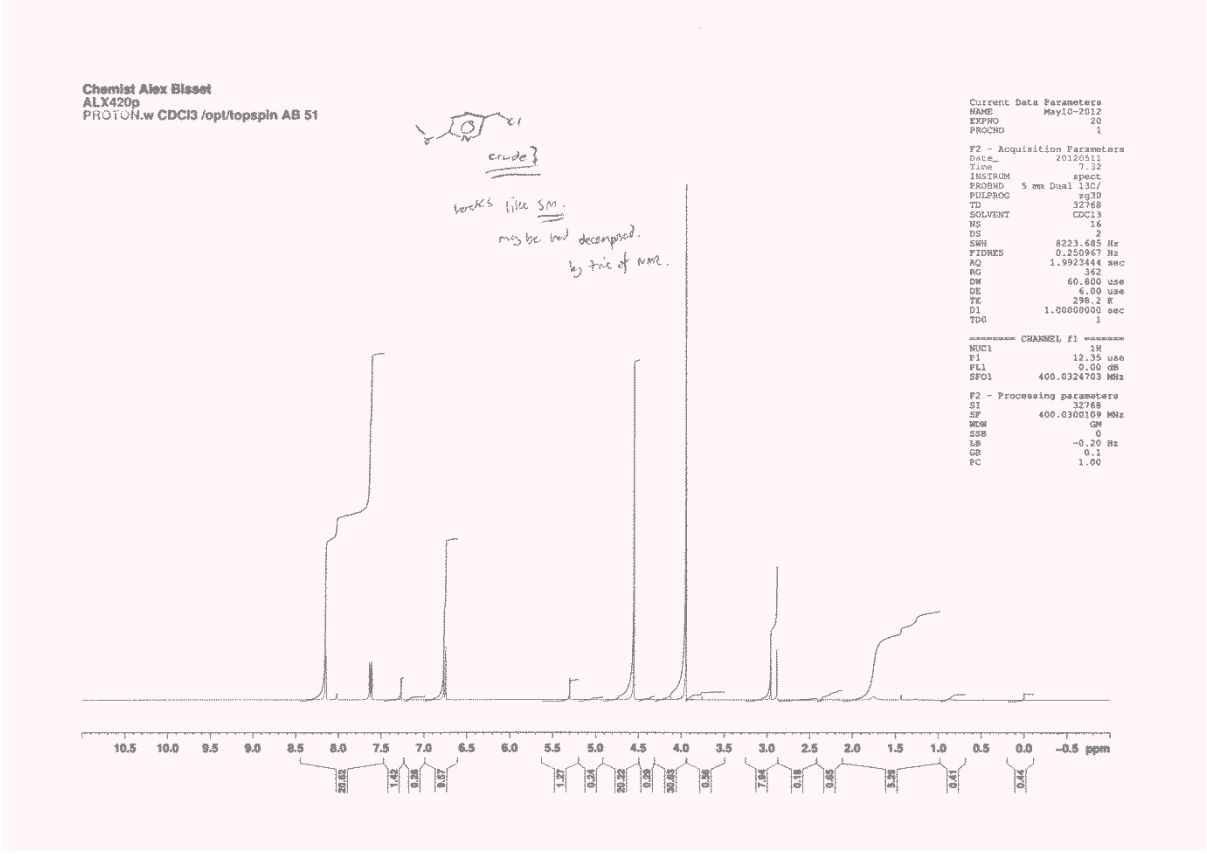


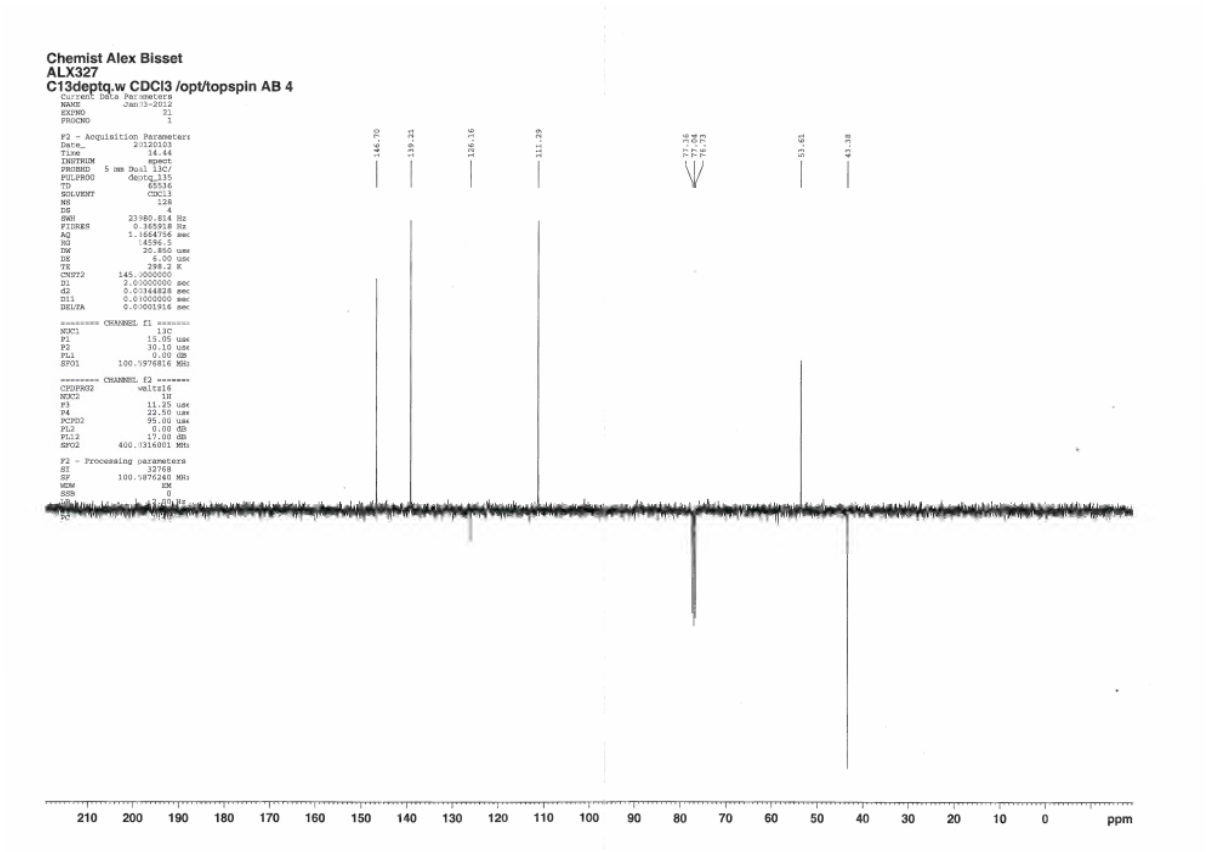
For comparison, a sample of authentic **4e** is shown below:



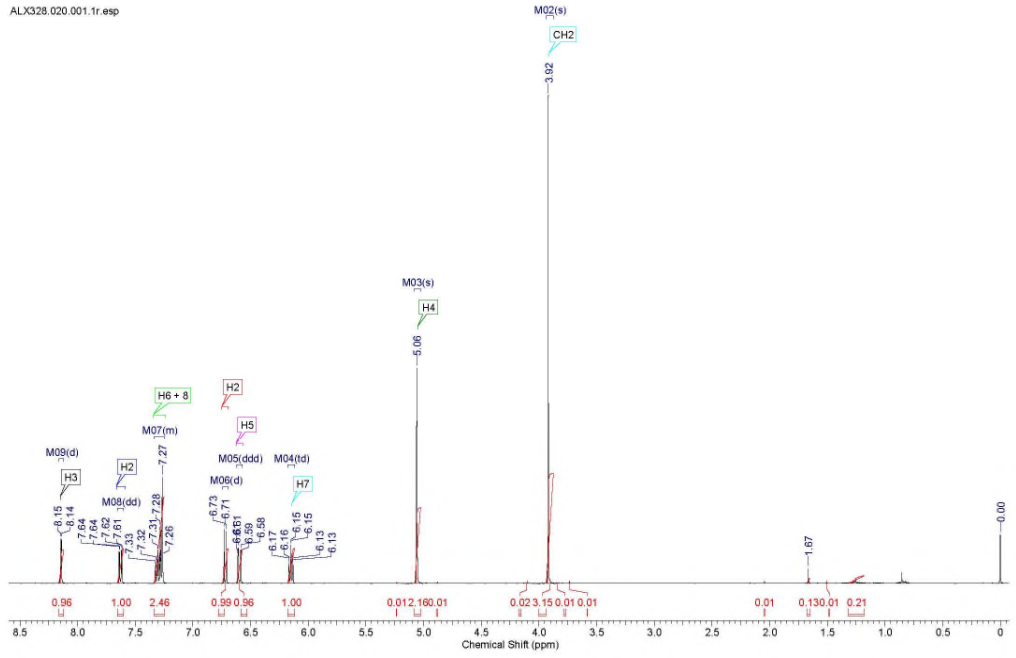


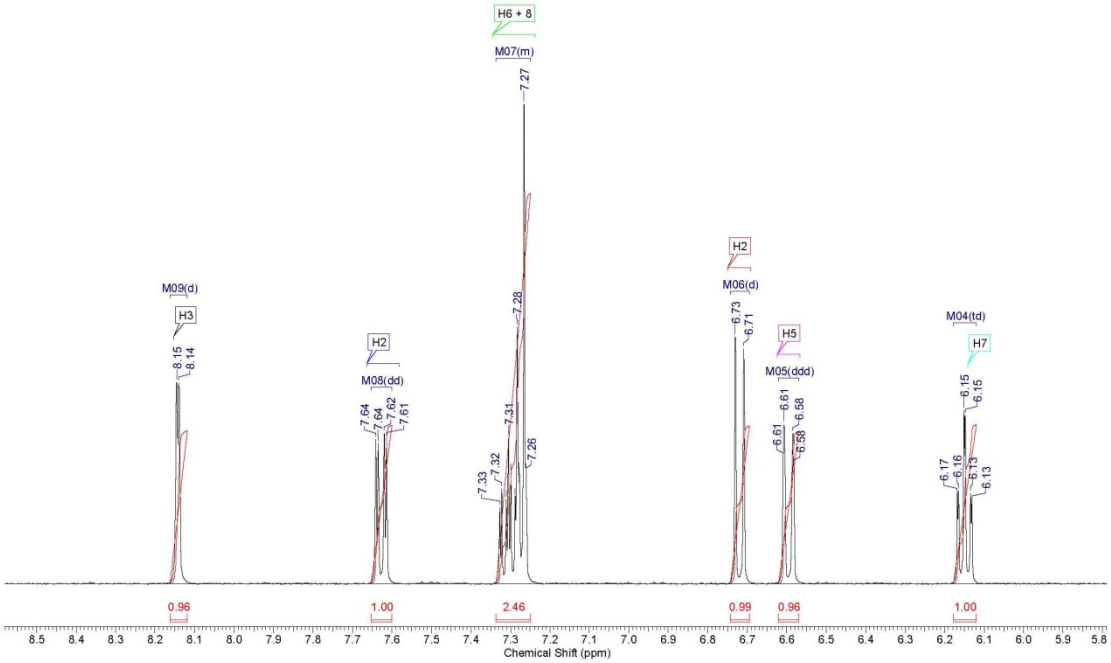
5-Chloromethyl-2-methoxypyridine, ***24.***

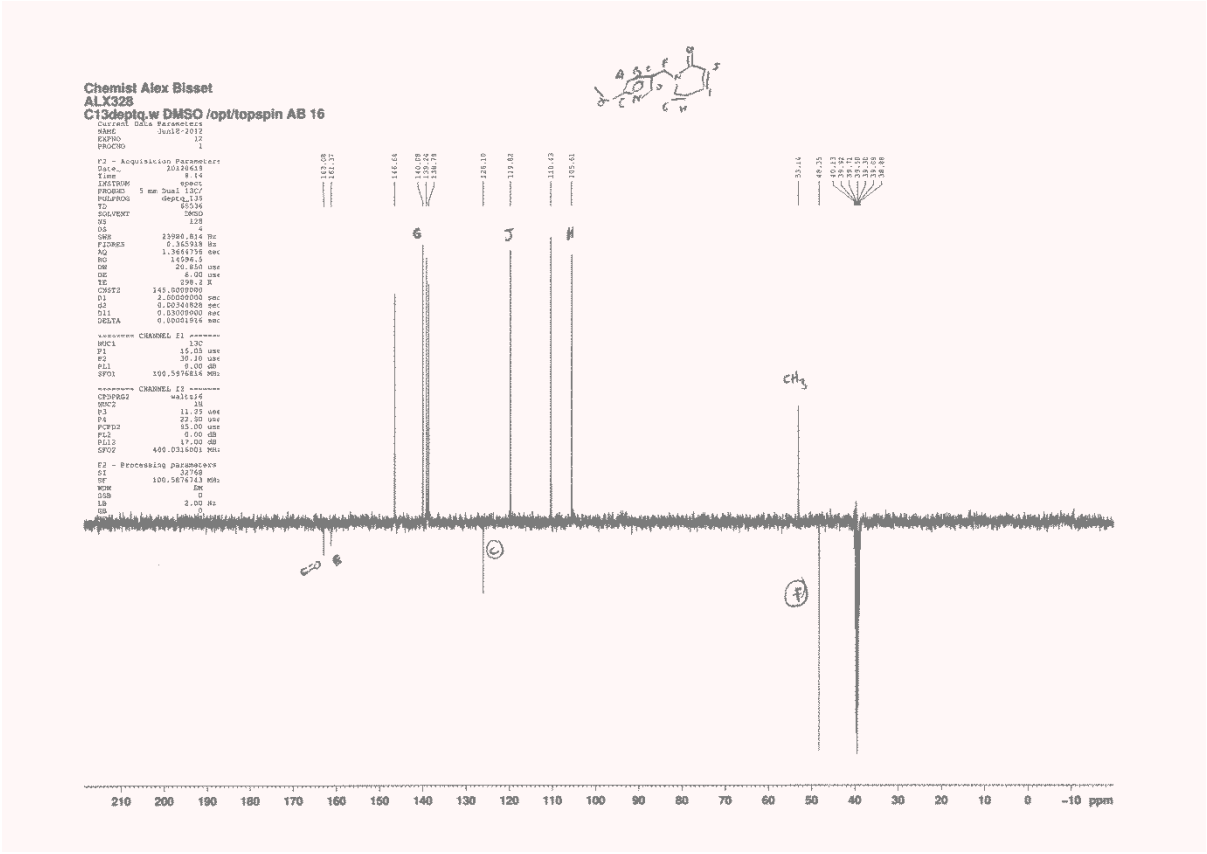




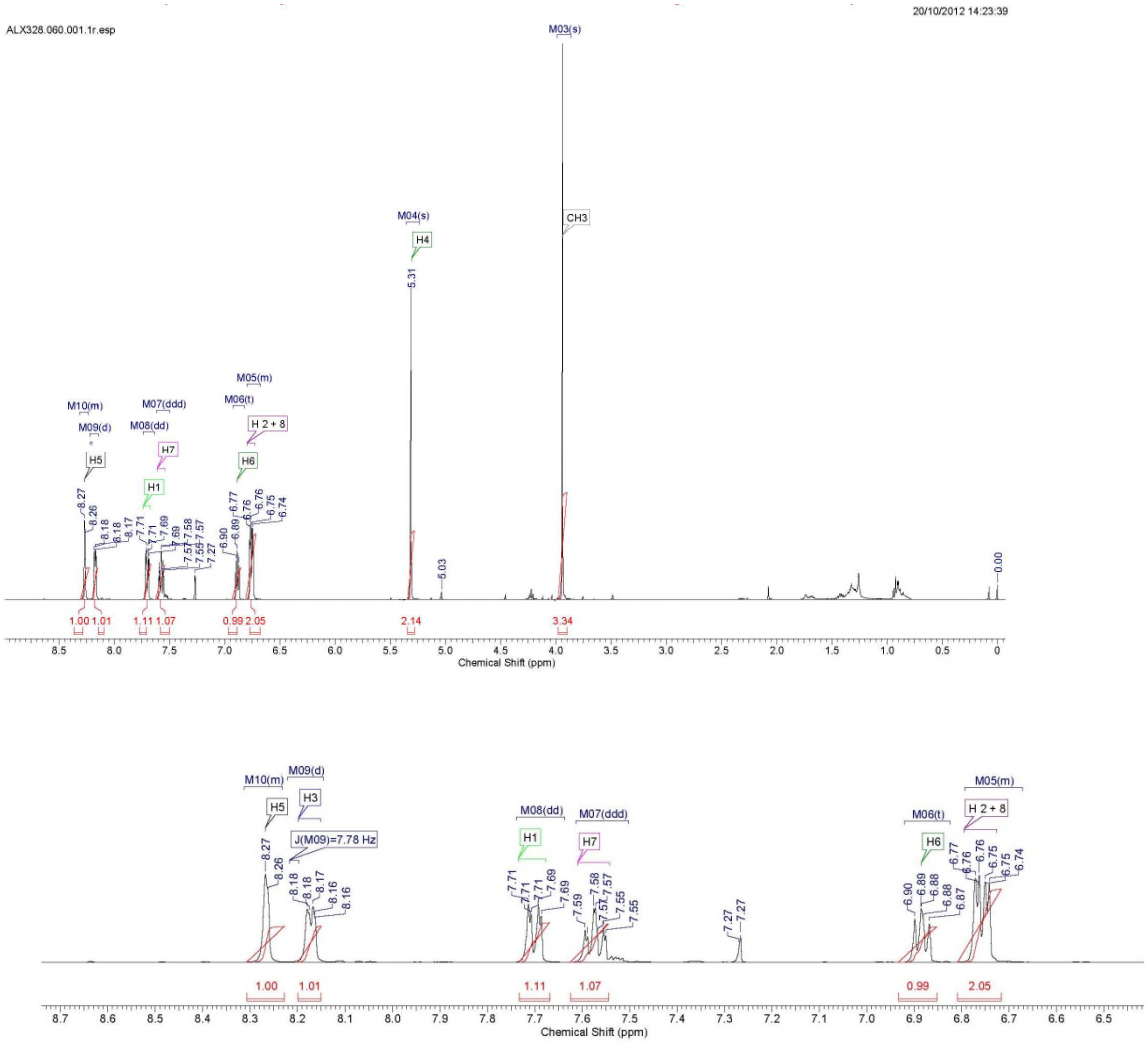
1-((6-methoxypyridin-3-yl)methyl)pyridin-2(1H)-one ***2e.***







2-methoxy-5-((pyridin-2-yloxy)methyl)pyridine, ***25****.*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H 2 + 8
H5
H7
H6
H1
8.27
8.26
8.18
8.17
7.71
7.69
7.58
7.57
6.90
6.77
6.76
6.75
6.74
5.03
0.00
1.00 1.01 1.11 1.07 0.99 2.05 2.14 3.34
Chemical Shift (ppm)
M10(m)
M09(d)
H5
H3
J(M09)=7.78 Hz
M08(dd)
M07(ddd)
H1
H7
8.16
7.59
7.55
7.27
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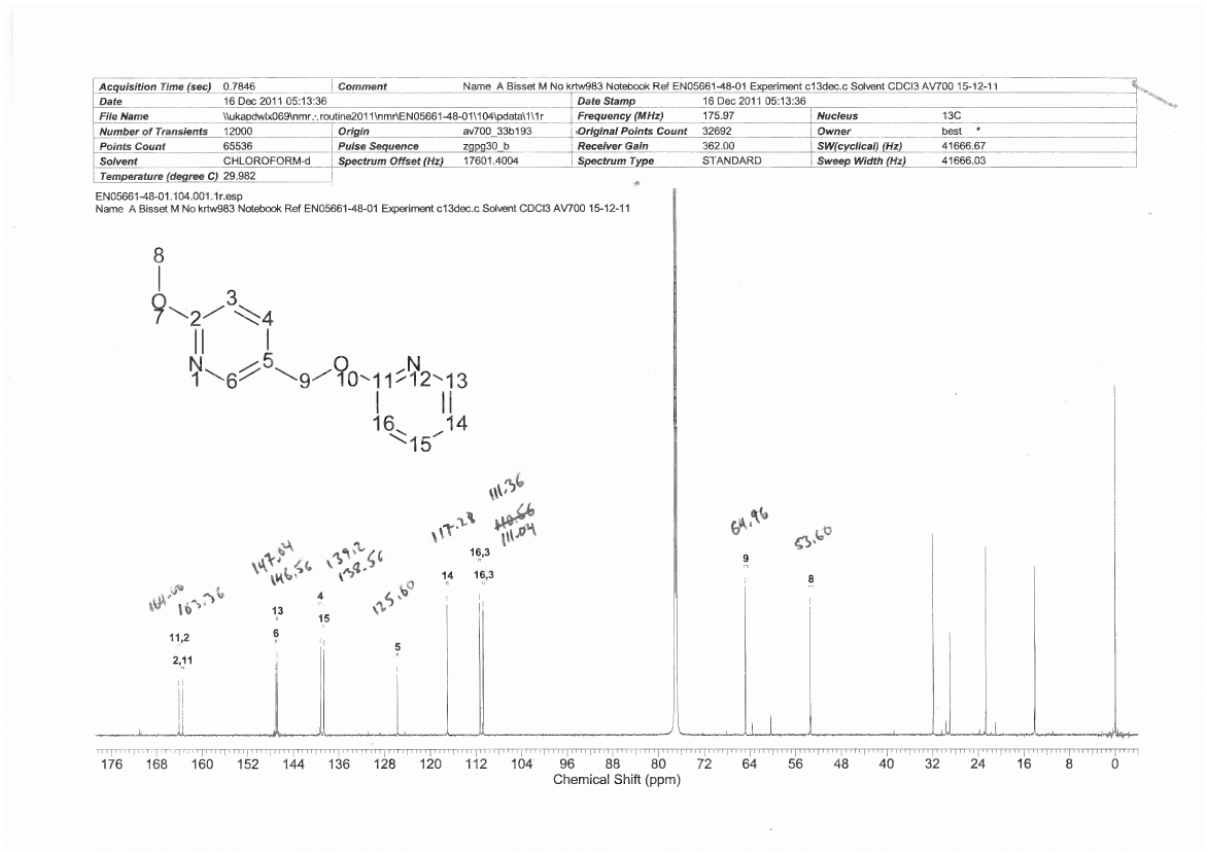
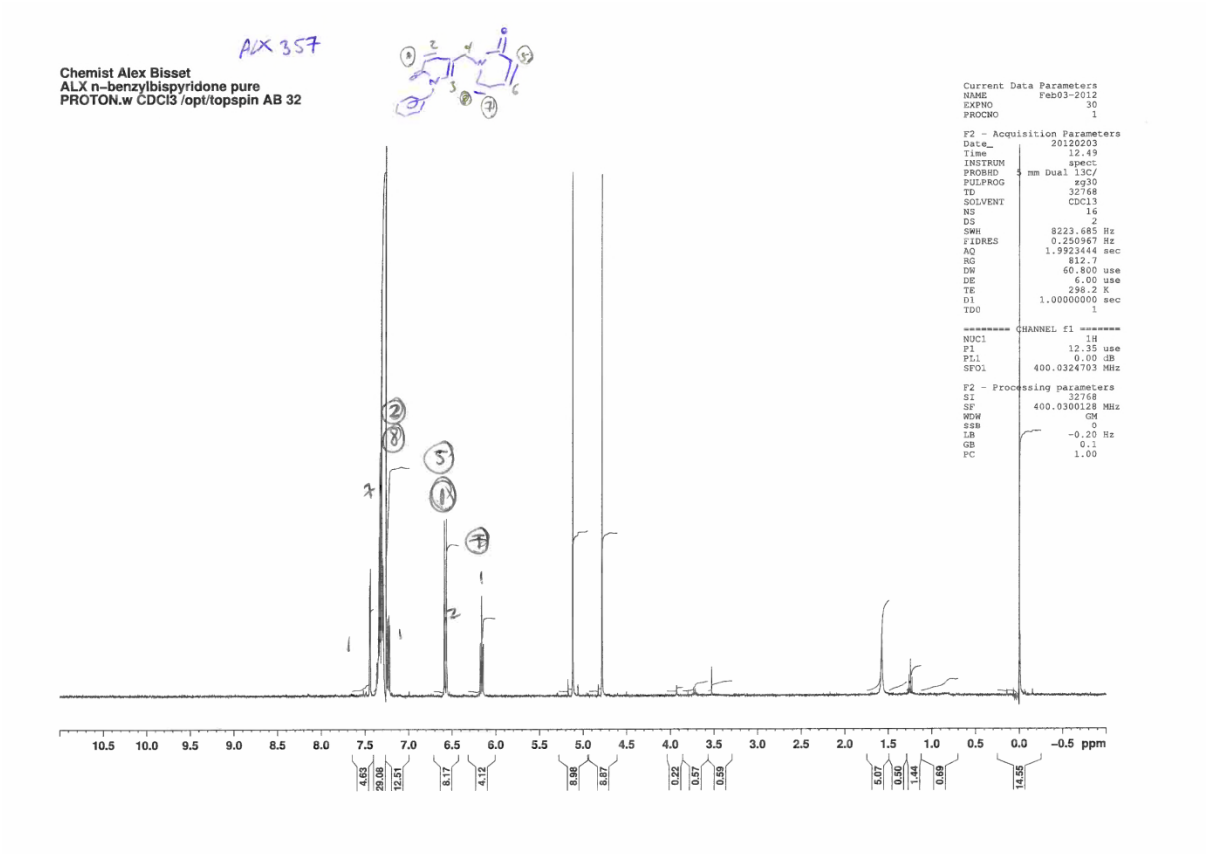
Chemical Shift (ppm)



1-Benzyl-5-[(2-oxopyridin-1(2H)-yl)methyl]pyridin-2(1H)-one, **3e.**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Chemist Alex Bisset
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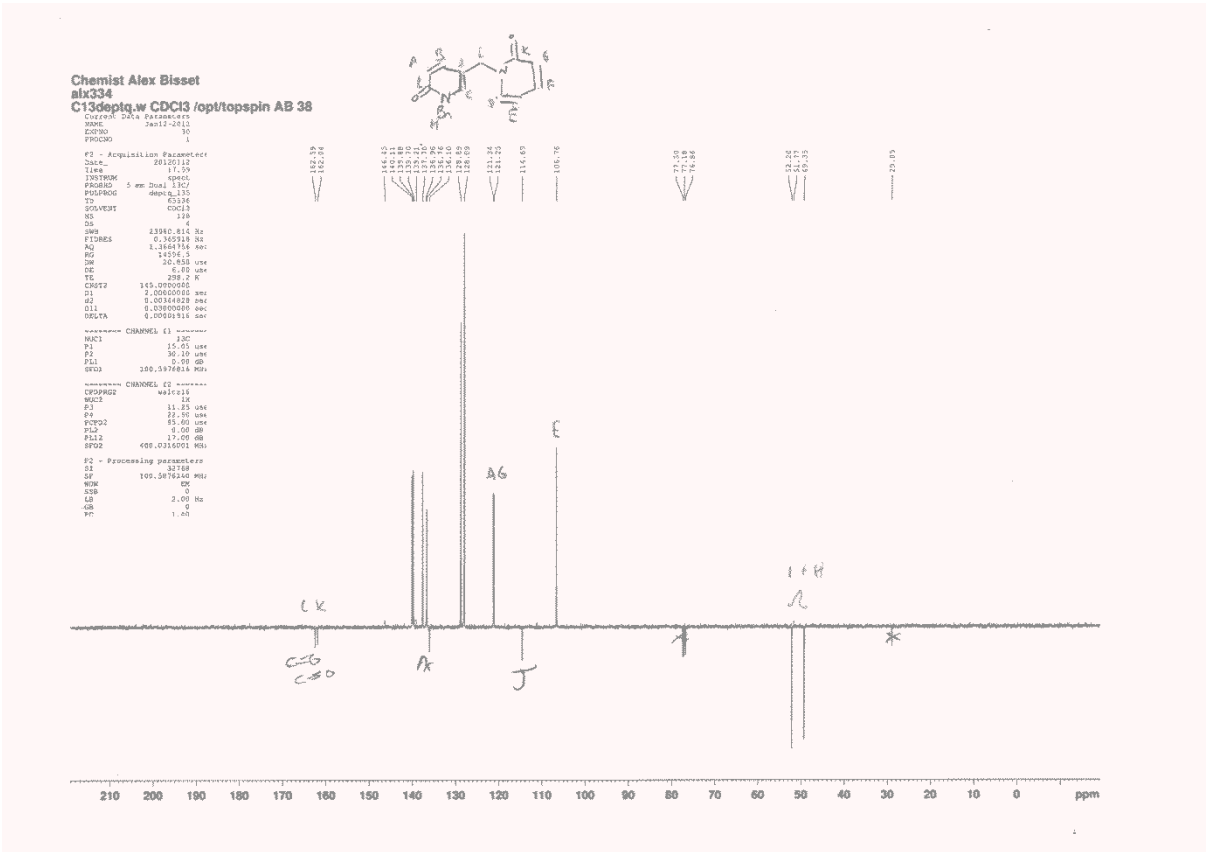
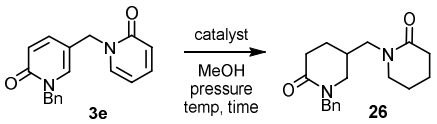
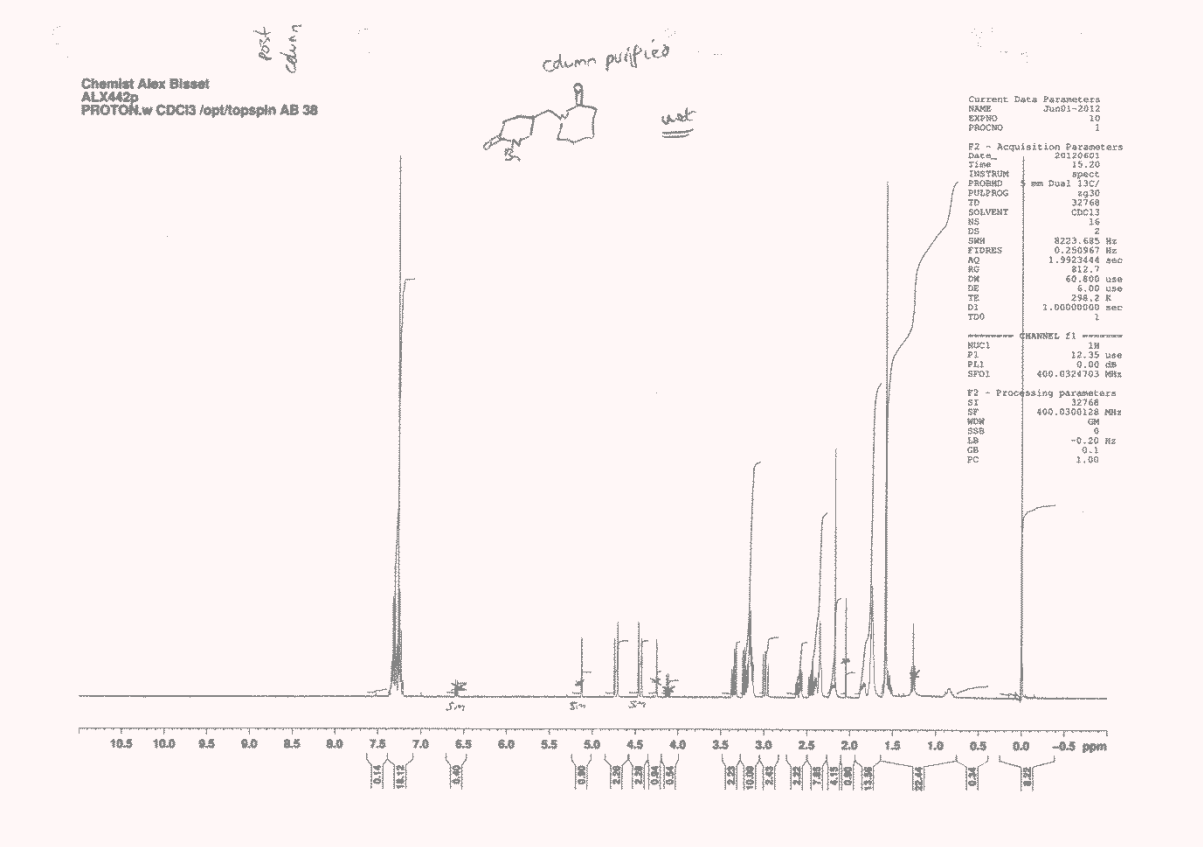
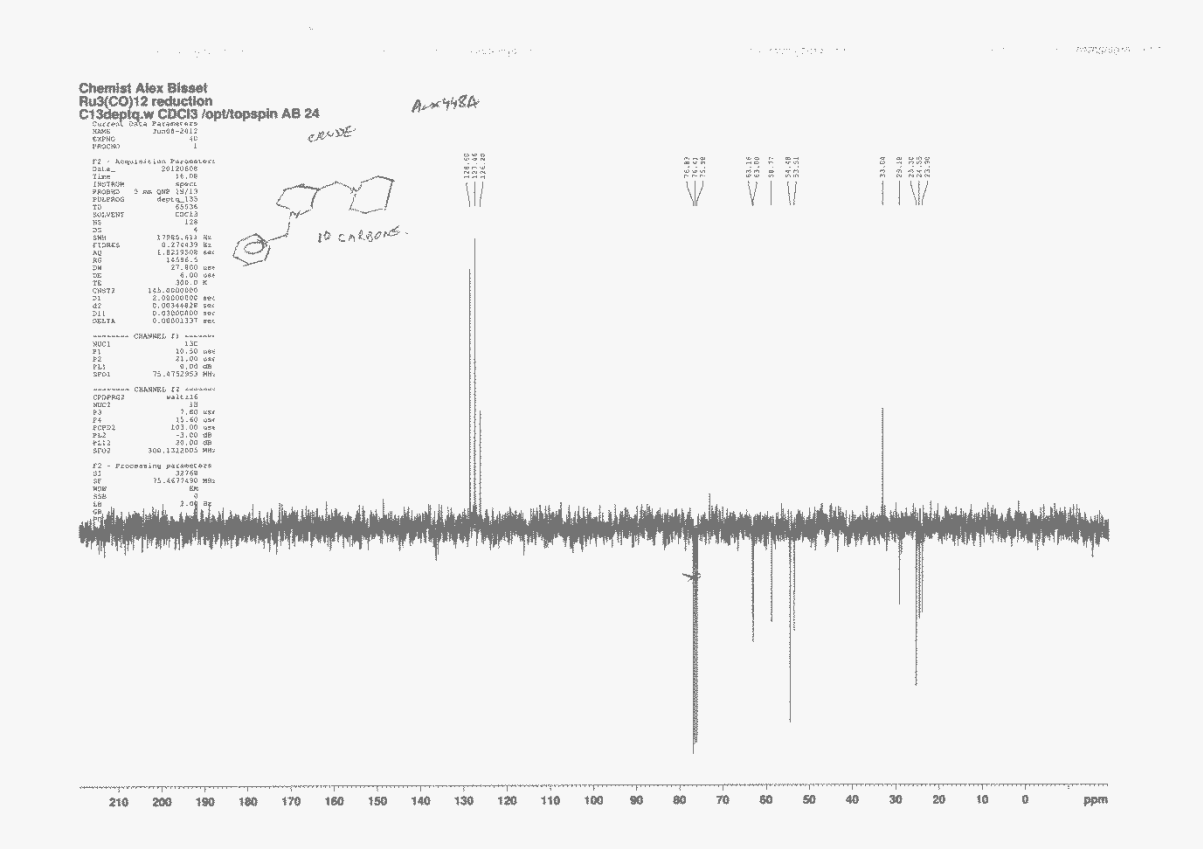
AQ 1.9923444 sec
RG 812.7
DW 60.800 use
DE 6.00 use
TE 298.2 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 12.35 use
PL1 0.00 dB
SFO1 400.0324703 MHz
F2 - Processing parameters
SI 32768
SF 400.0300128 MHz
WDW GM
SSB 0
LB -0.20 Hz
GB 0.1
PC 1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
4.63 29.08 12.51 8.17 4.12 8.98 8.87 0.22 0.57 0.59 5.67 0.90 1.44 0.69 14.55


Chemist Alex Bisset
alx334
C13deptq.w CDCl3 /opt/topspin AB 38
AG
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

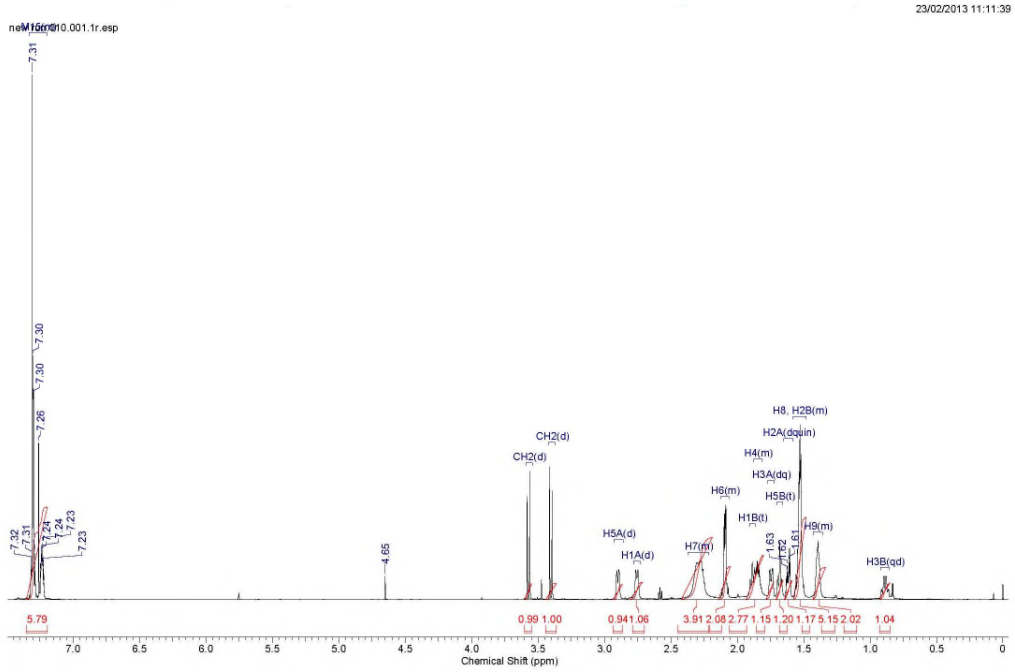


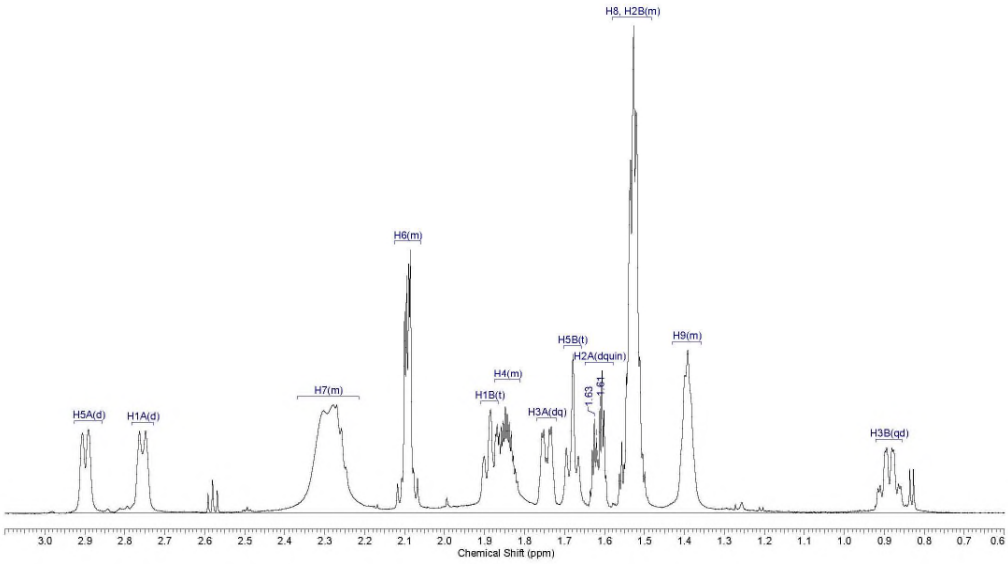
1-((1-Benzyl-6-oxopiperidin-3-yl)methyl)piperidin-2-one, (±)**-26.**

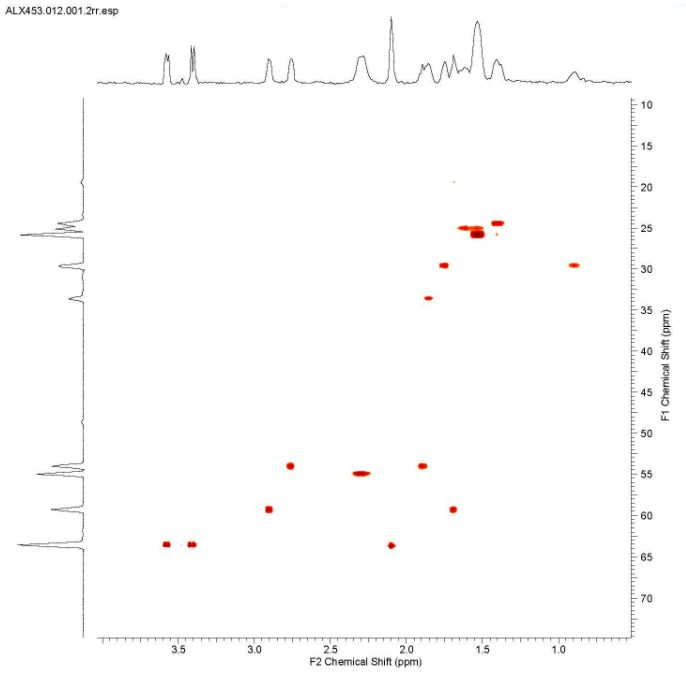




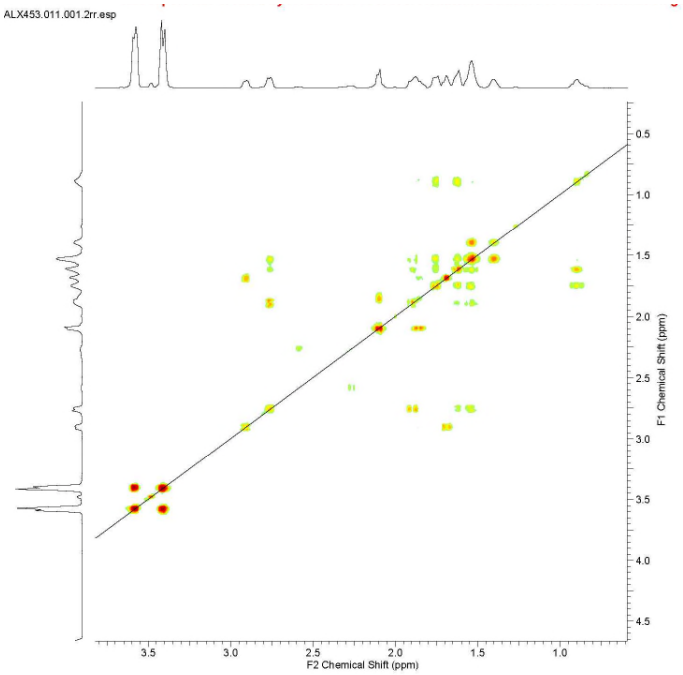
1-Benzyl-3-(piperidin-1-ylmethyl)piperidine, (±)-***1*** *(R=Bn).*





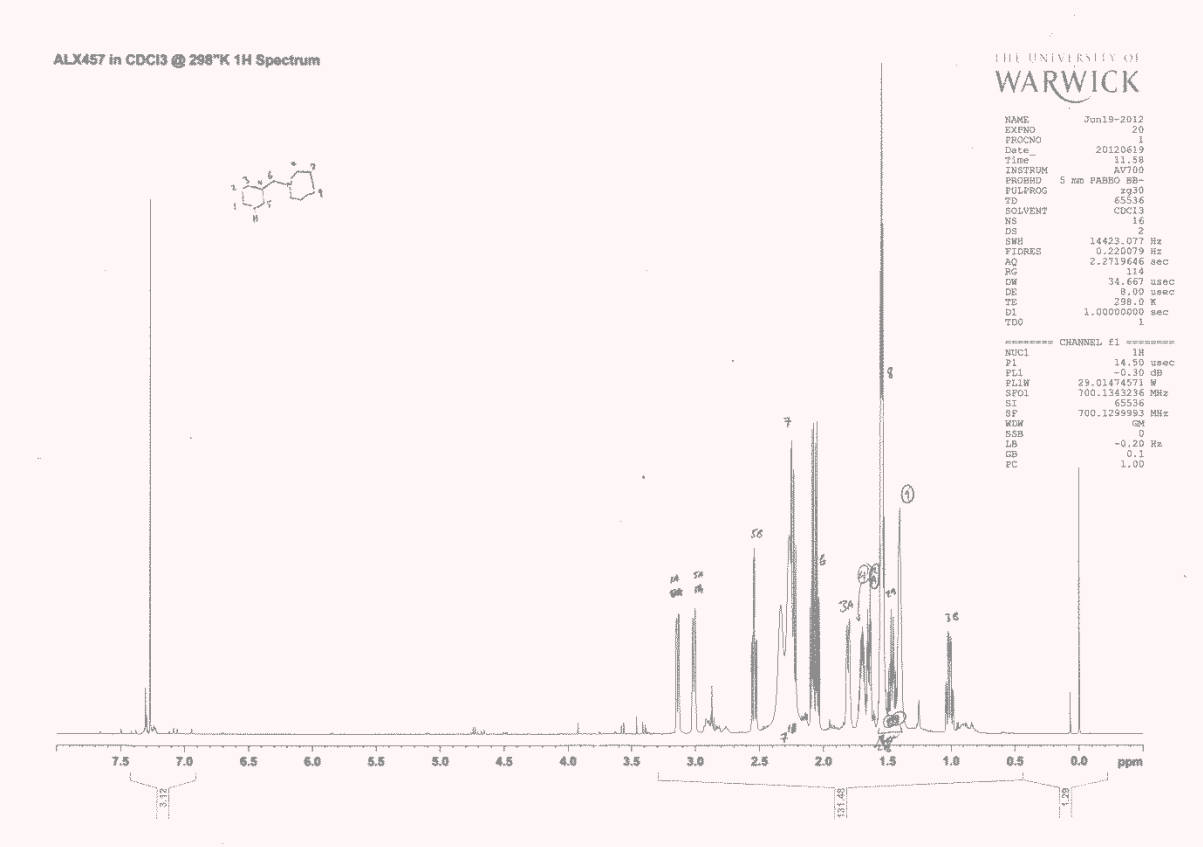


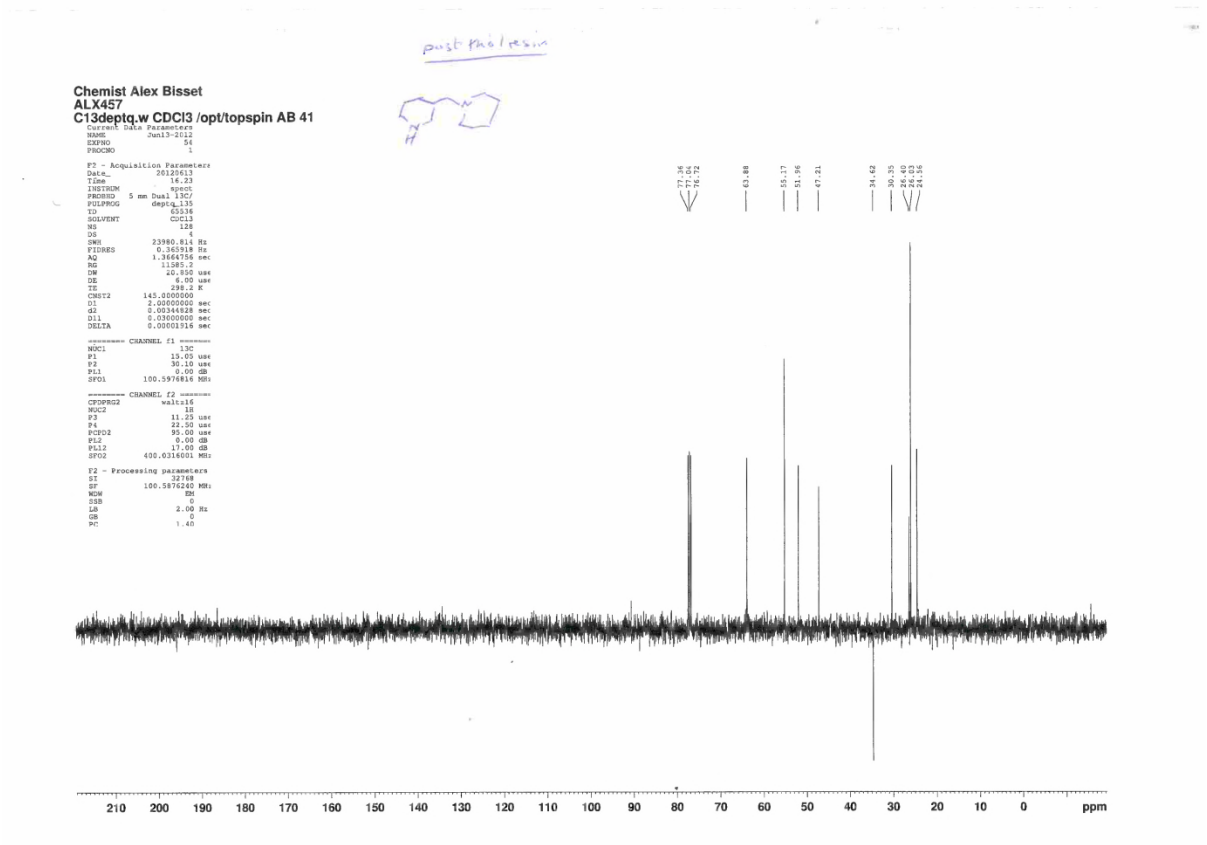
HMQC spectra of **1** (R=Bn), 700 MHz (^{1}H), 176 MHz (^{13}C) $CDCl_3$.

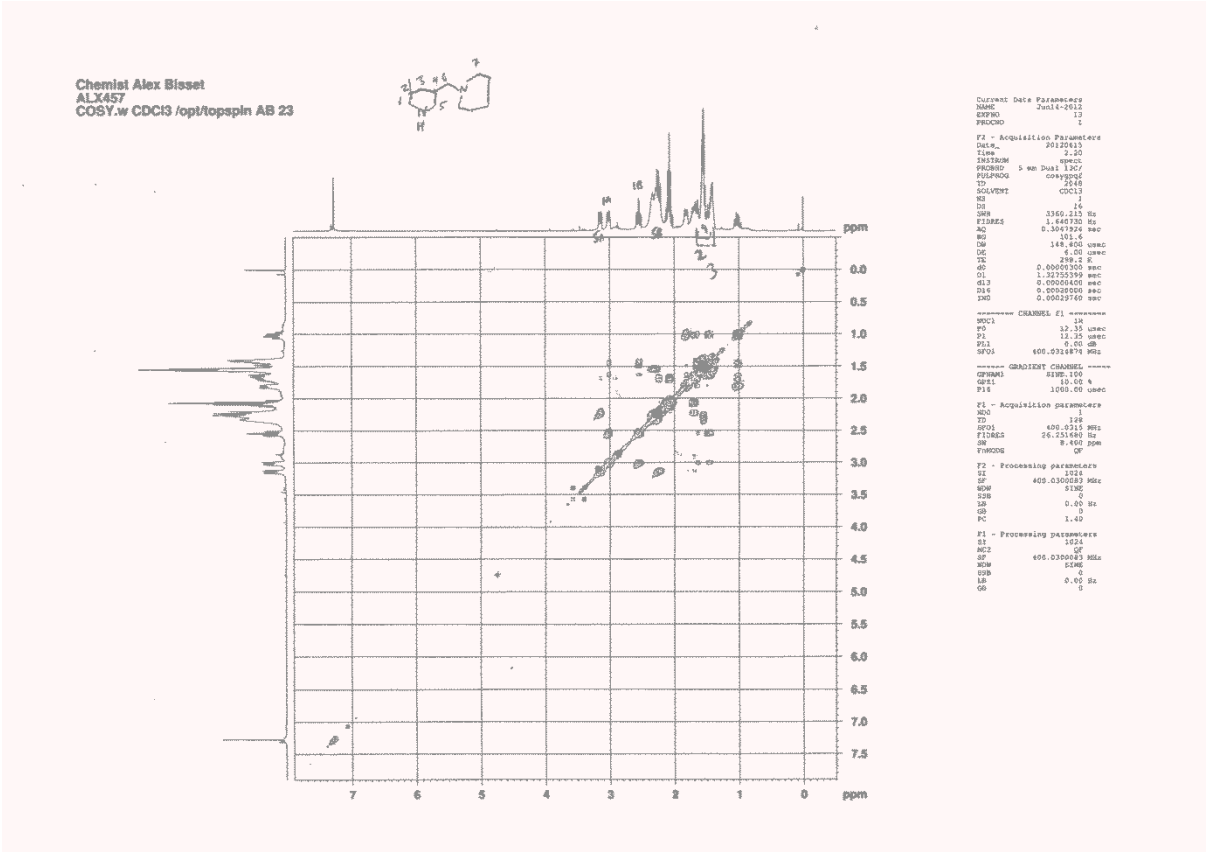


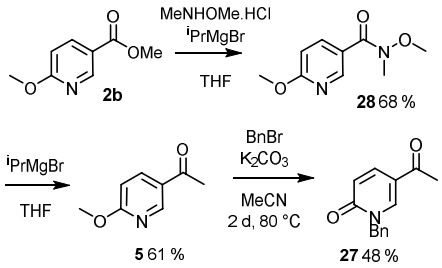
COSY **1** (R=Bn), 700 MHz ($^1H_1$,$^1H_2$), $CDCl_3$.

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

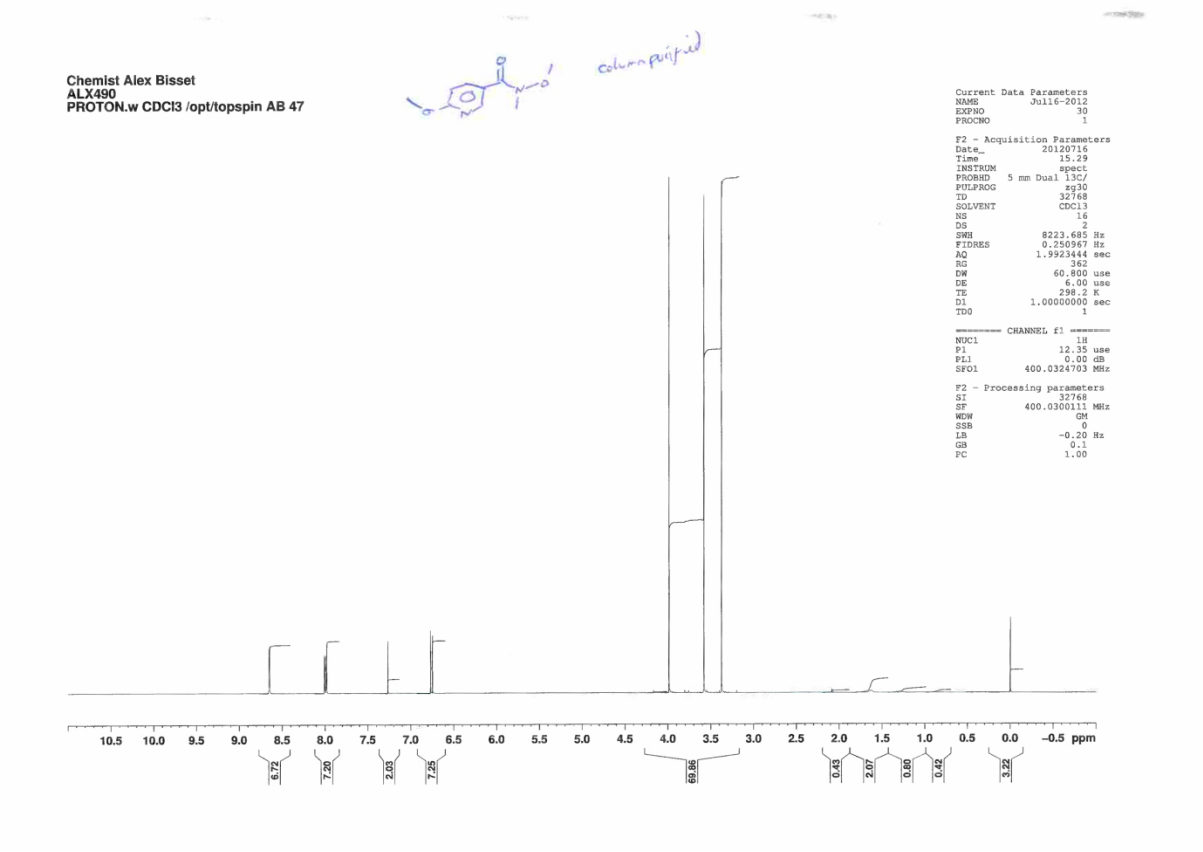


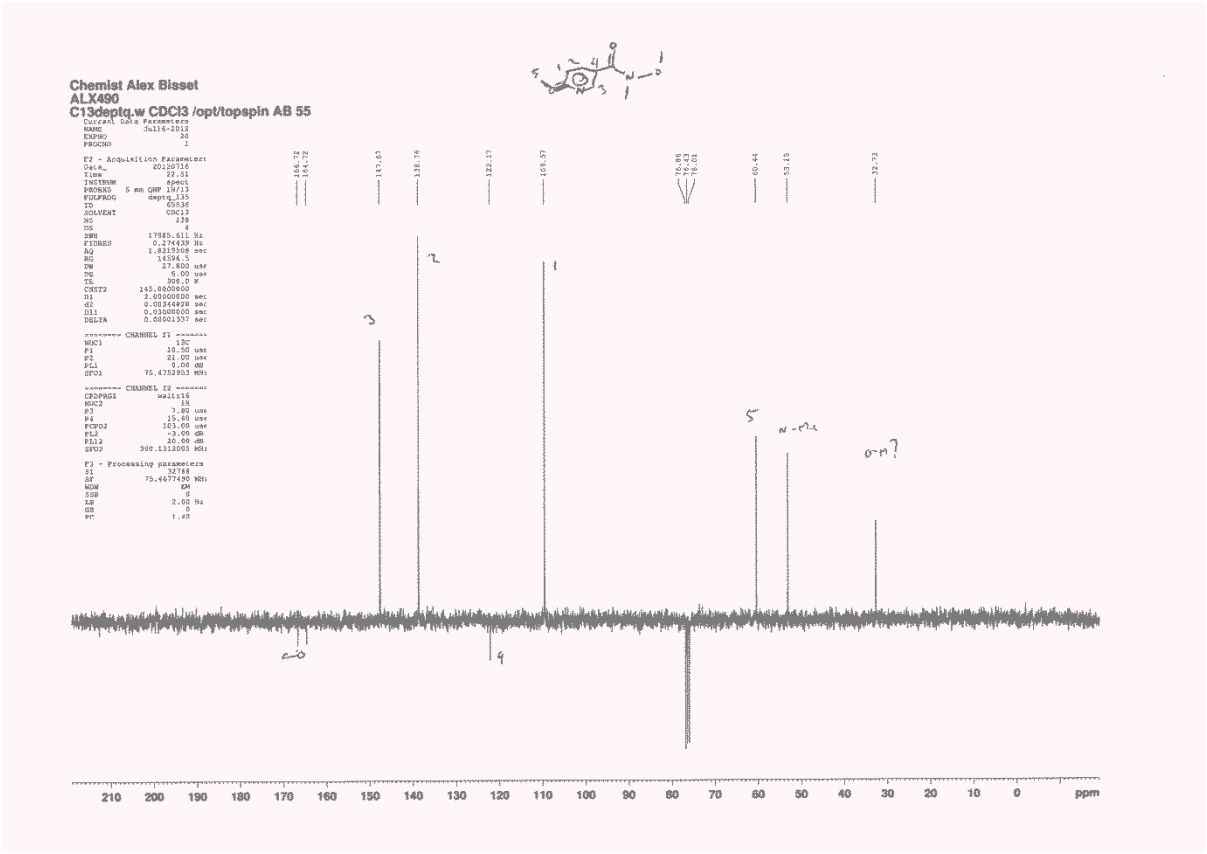

Chemist Alex Bisset
ALX457
C13deptq.w CDCl3 /opt/topspin AB 41
77.36
77.04
76.72
63.88
53.17
51.96
47.21
34.62
30.35
26.63
26.36
24.56
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


Chemist Alex Bisset
ALX457
COSY.w CDCl3 /opt/topspin AB 23
ppm
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5
7 6 5 4 3 2 1 0 ppm

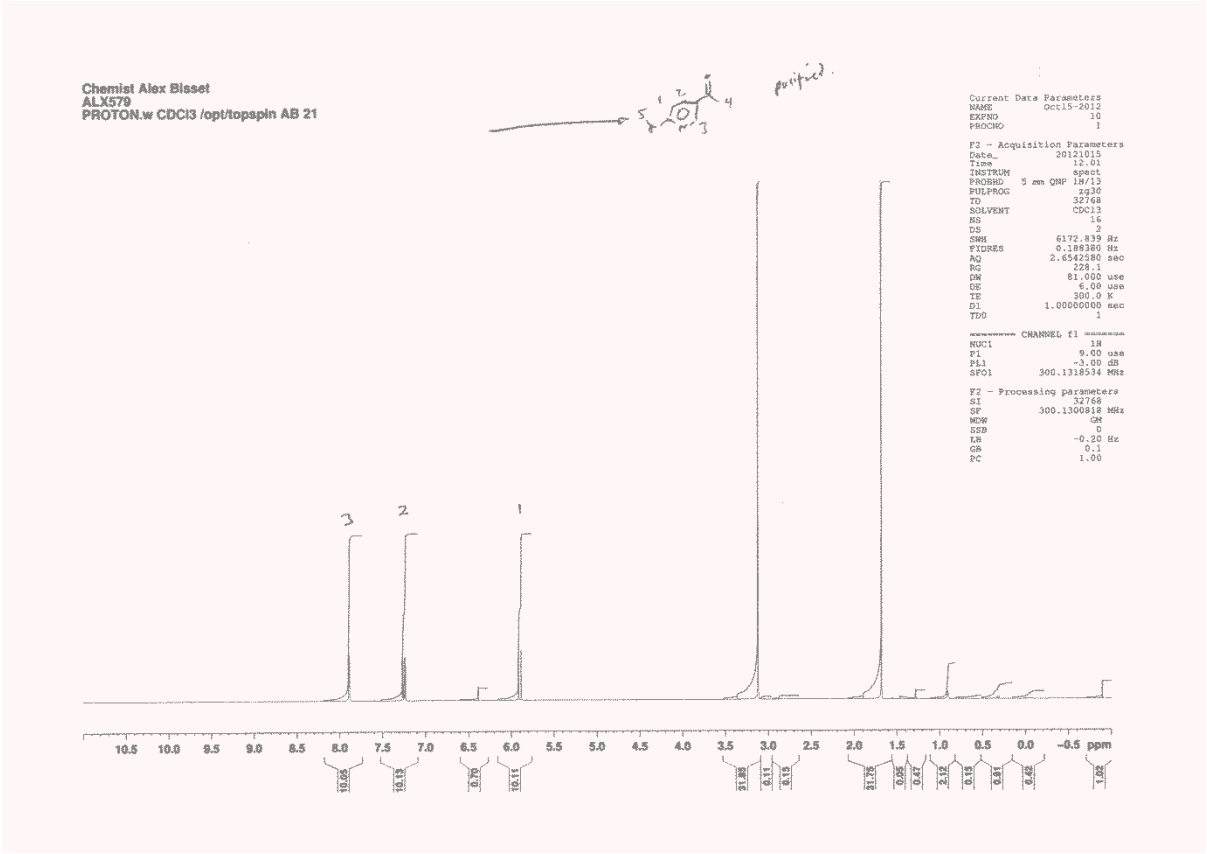


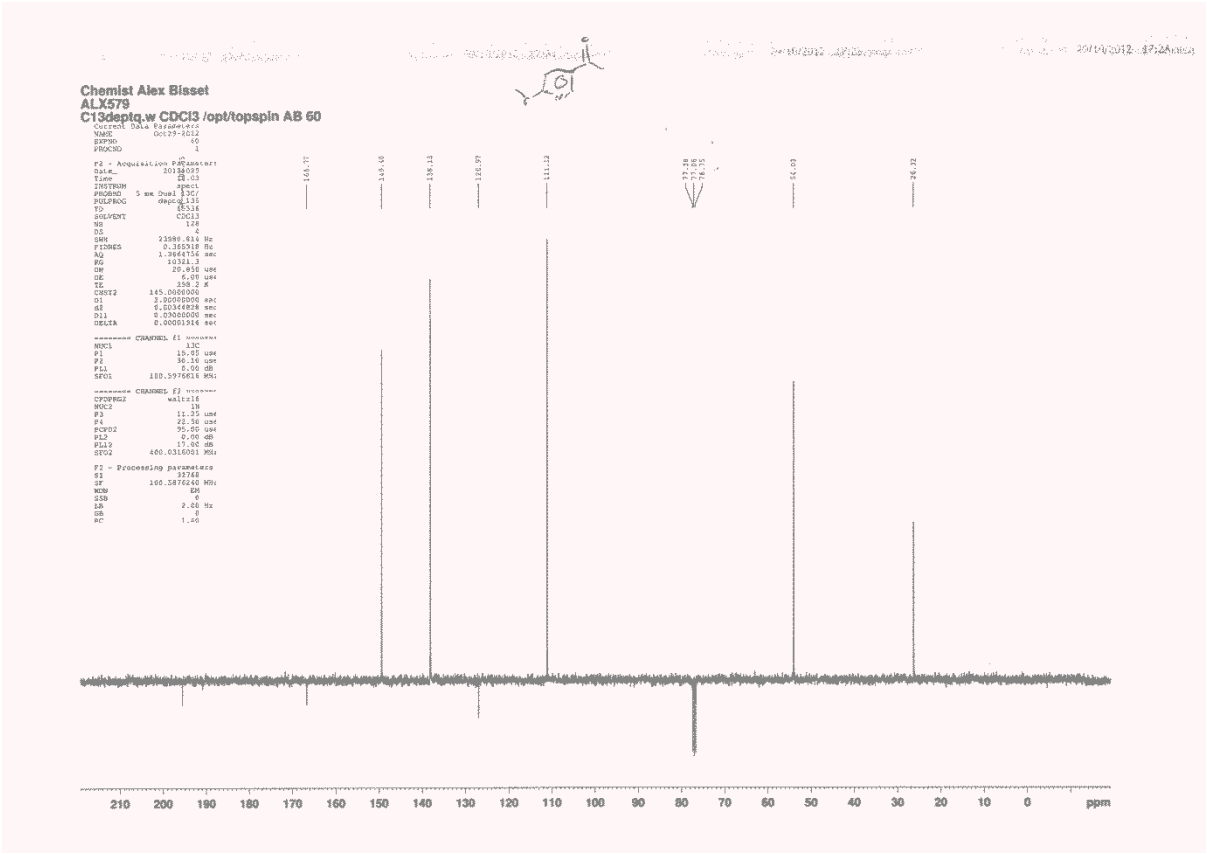
N,6-Dimethoxy-N-methylpyridine-3-carboxamide, ***28.***



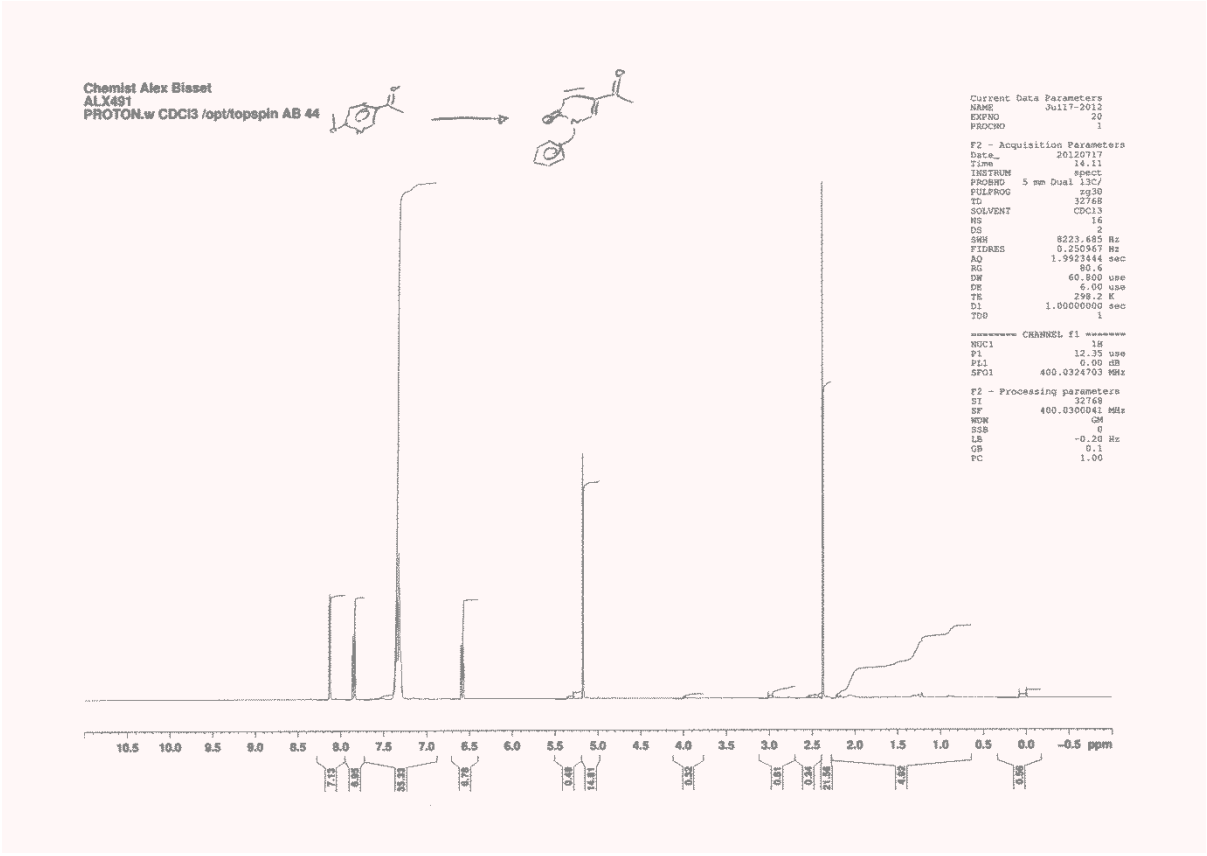


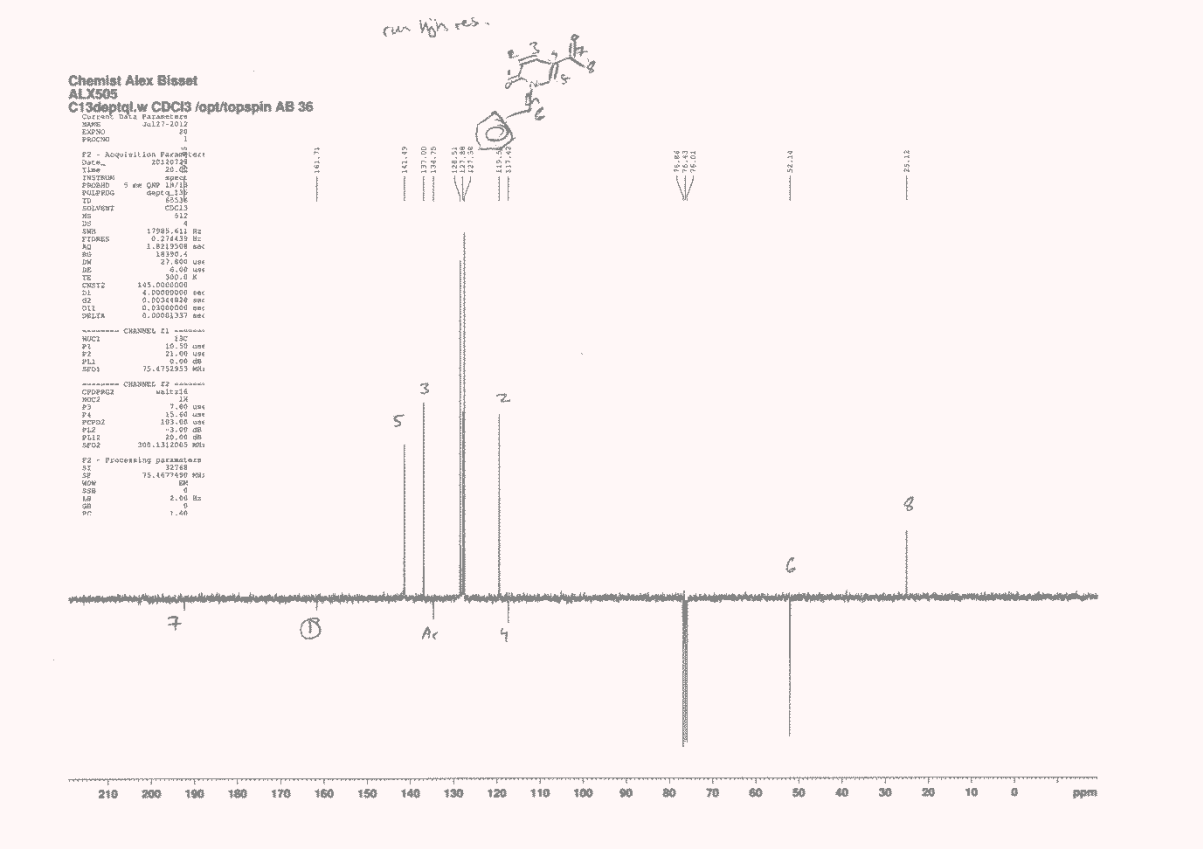
1-(6-Methoxypyridin-3-yl)ethanone, ***5***.

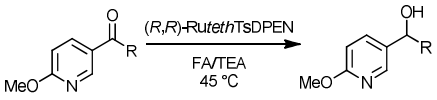




5-Acetyl-1-benzylpyridin-2(1H)-one, **27**.

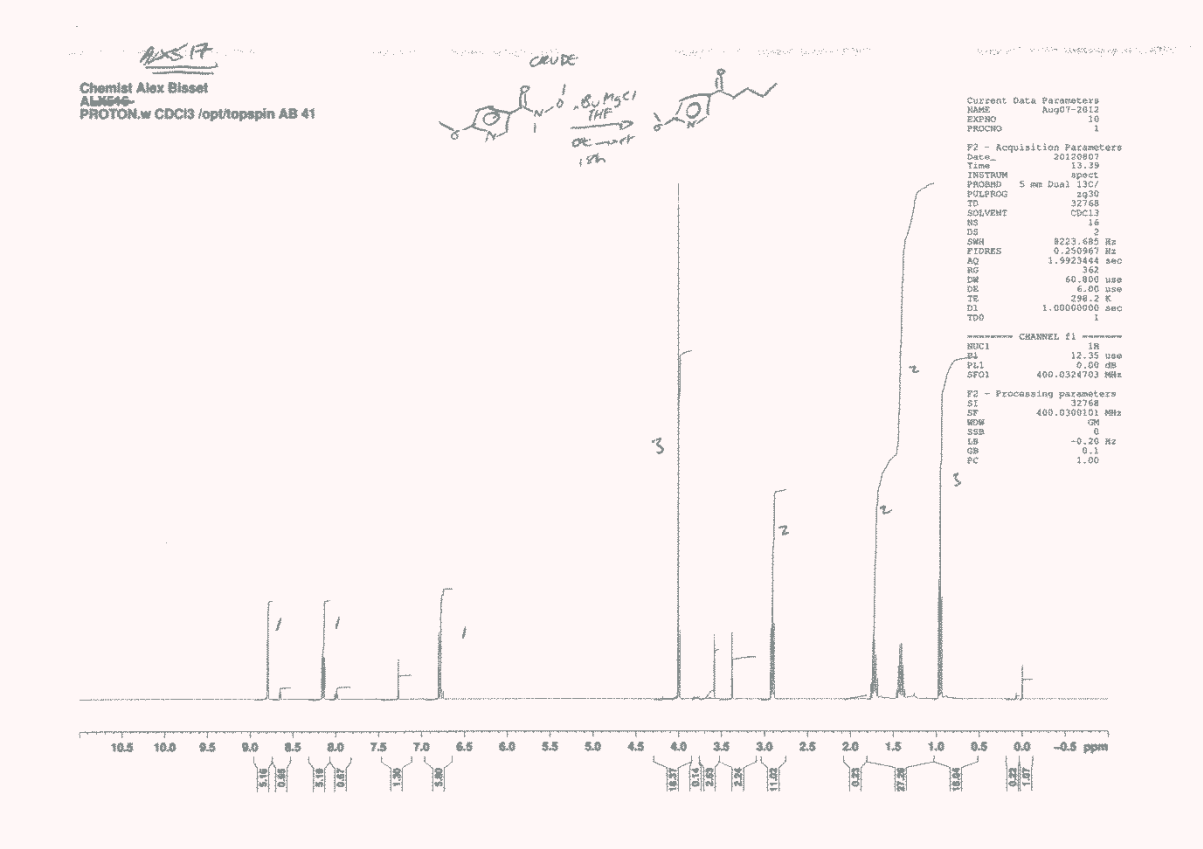


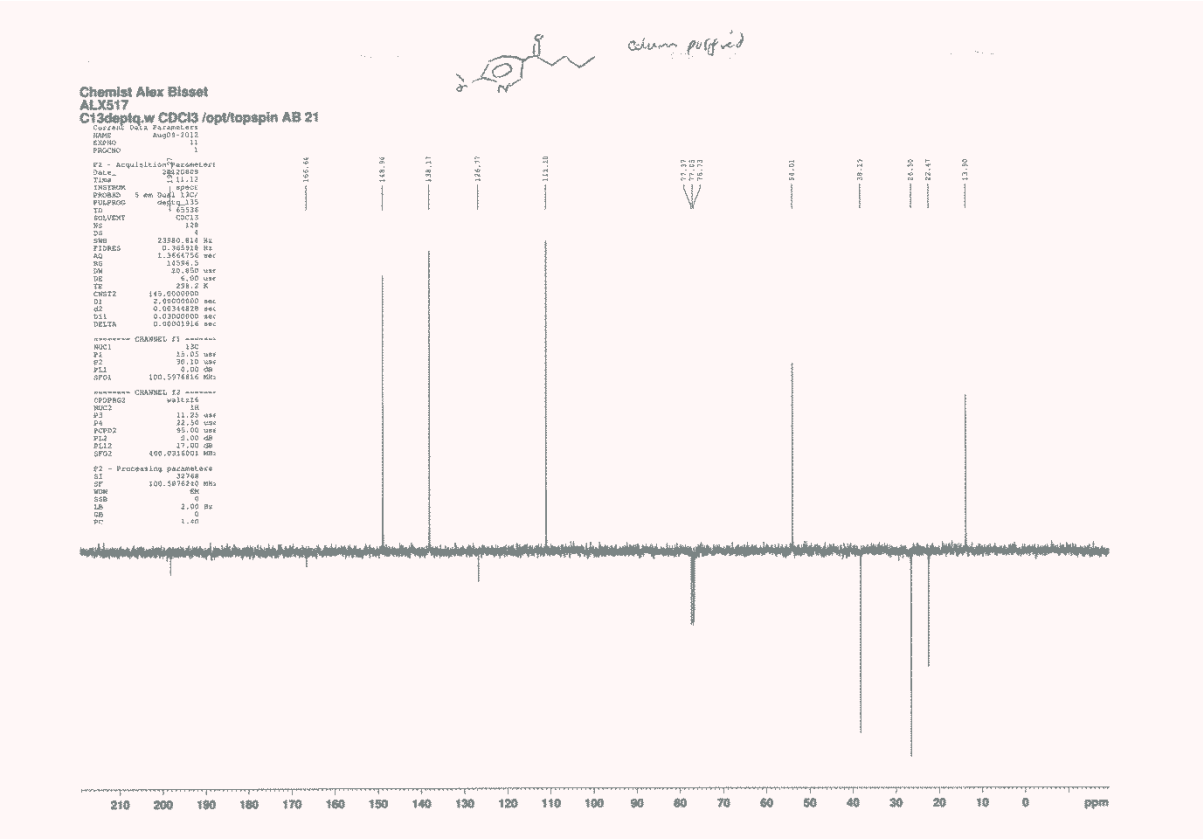




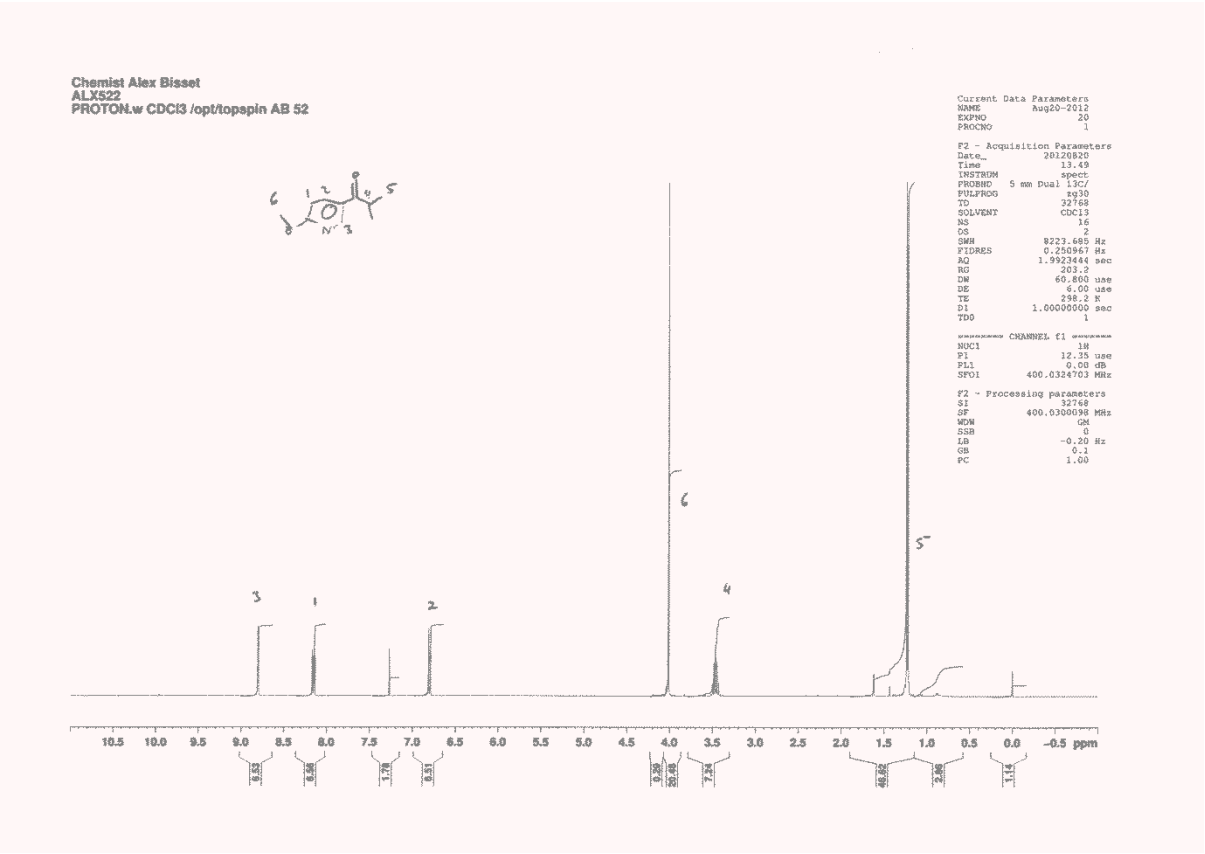
Entry	ketone[a]	R	t / h [g]	Prod.	Ee / %
1	**5**[b]	Methyl	21	(*R*)- **10**[h]	83[d]
2	**6**	*n*-butyl	20	(*R*)-**11**[i]	76[d]
3	**7**	*i*-propyl	22	(*R*)-**12**[i]	53[c]
4	**8**	Cyclohexyl	24	(*R*)-**13**[i]	35[f]
5	**9**	Phenyl	24	(-)-**14**	48[e]

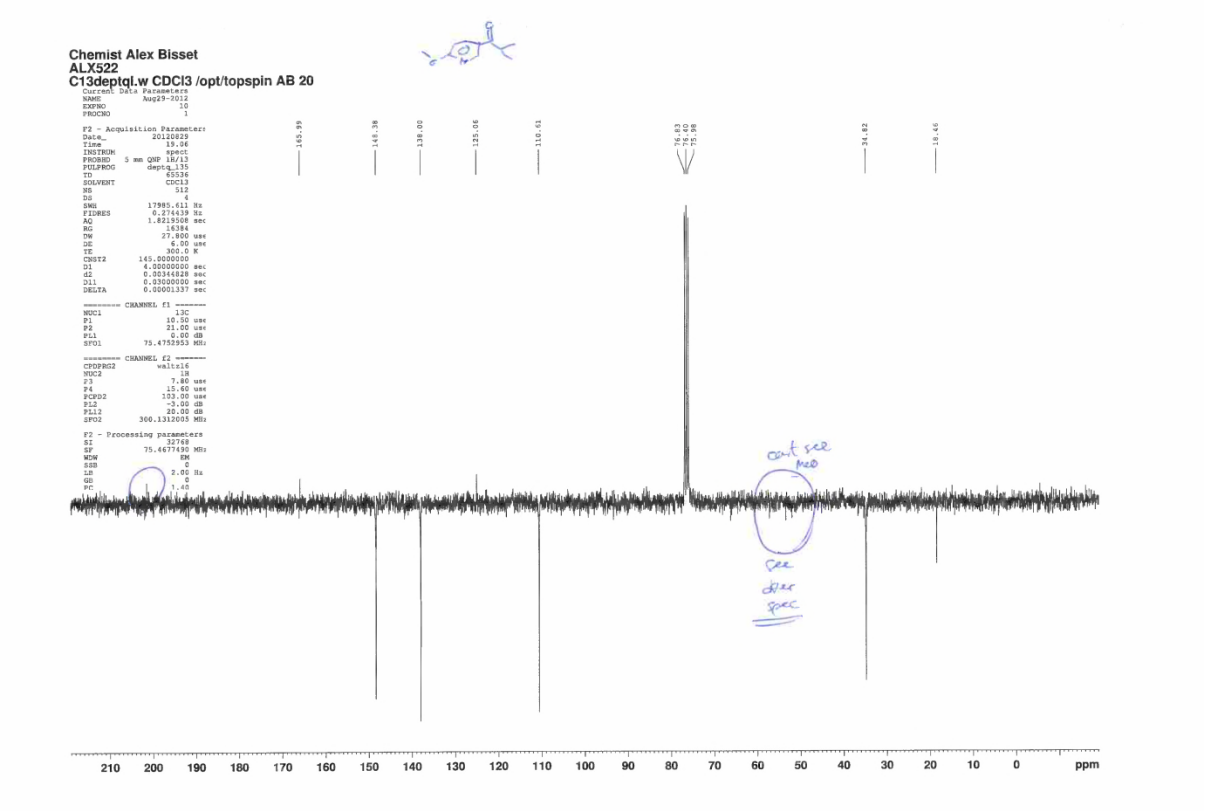
1-(4-Methoxyphenyl)pentan-1-one, **6.**



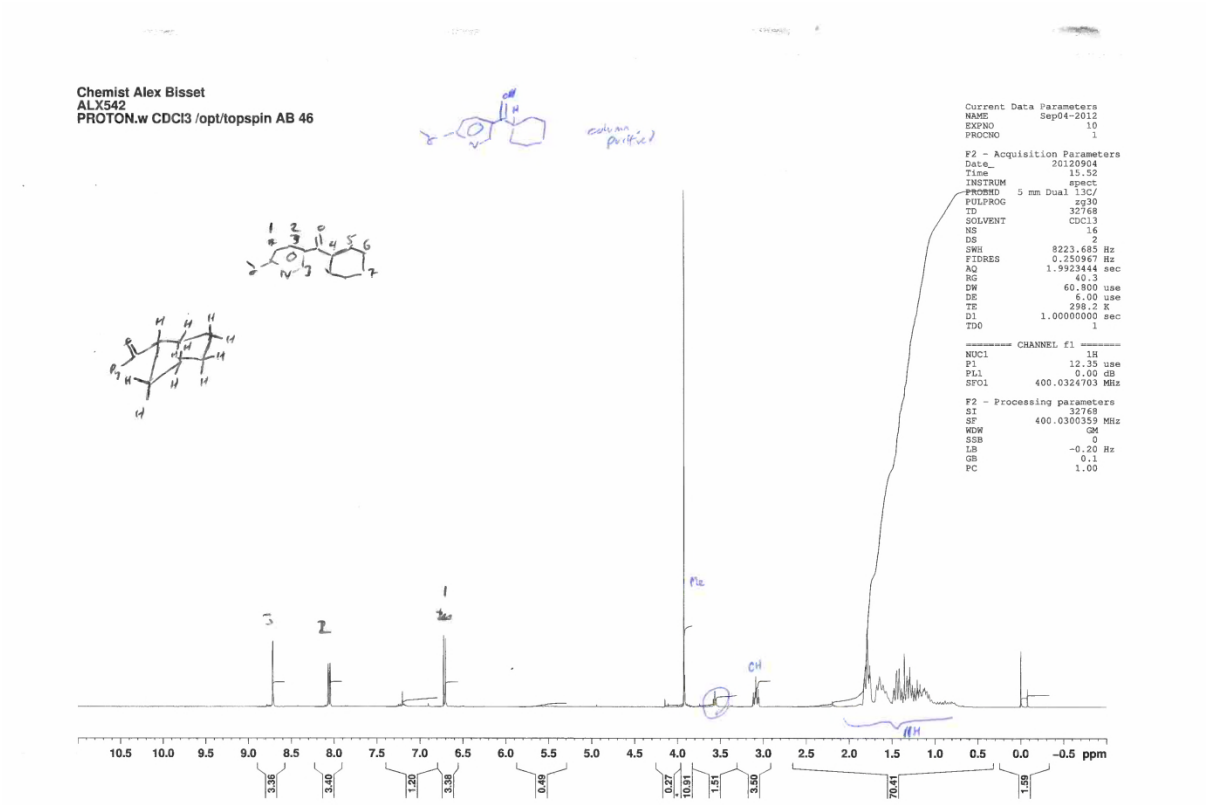


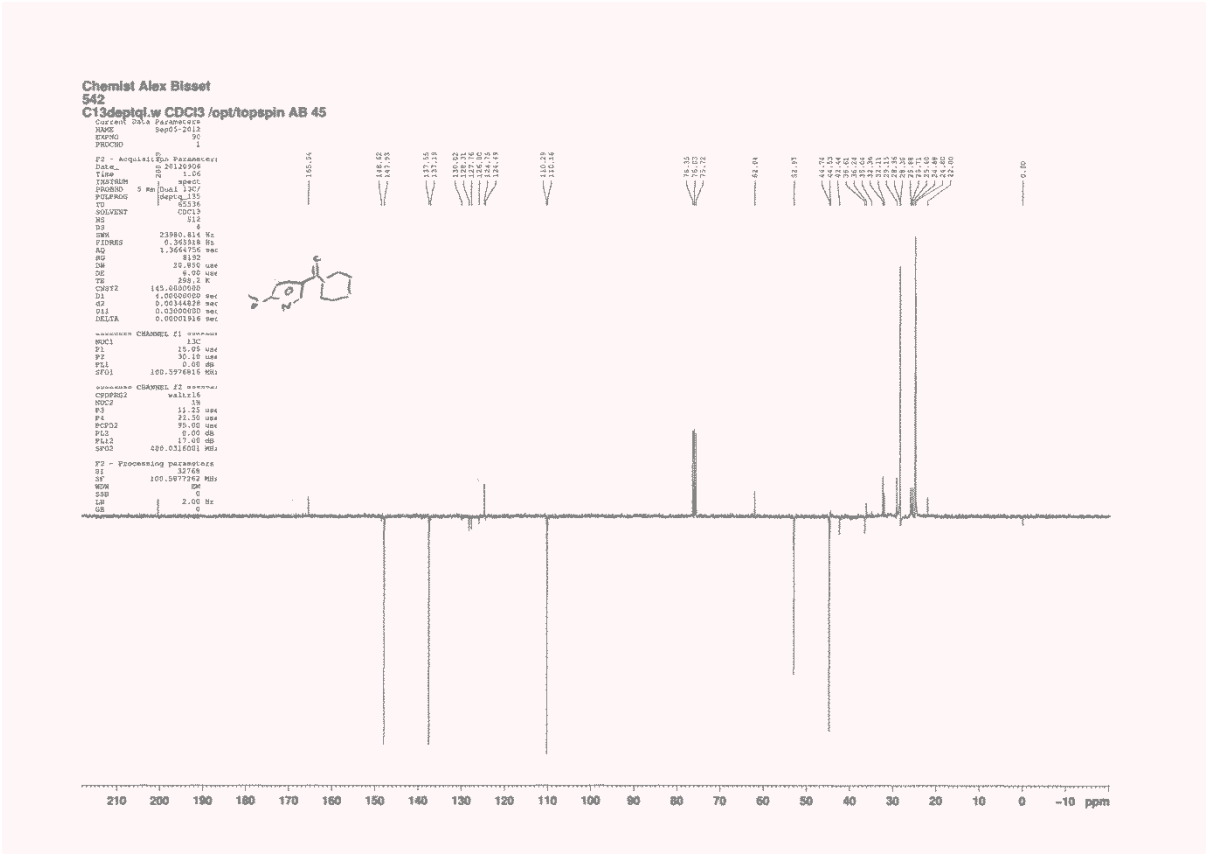
1-(6-Methoxypyridin-3-yl)-2-methylpropan-1-one, **7.**



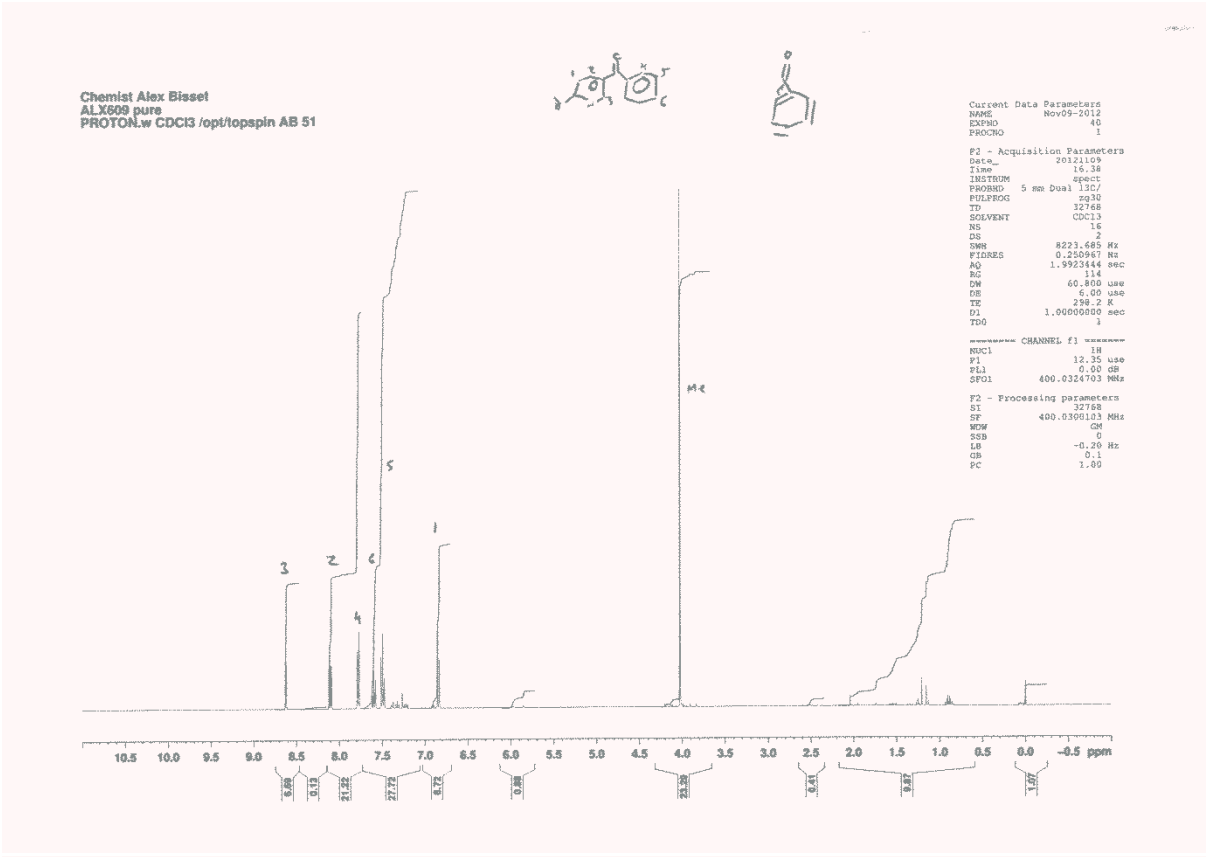


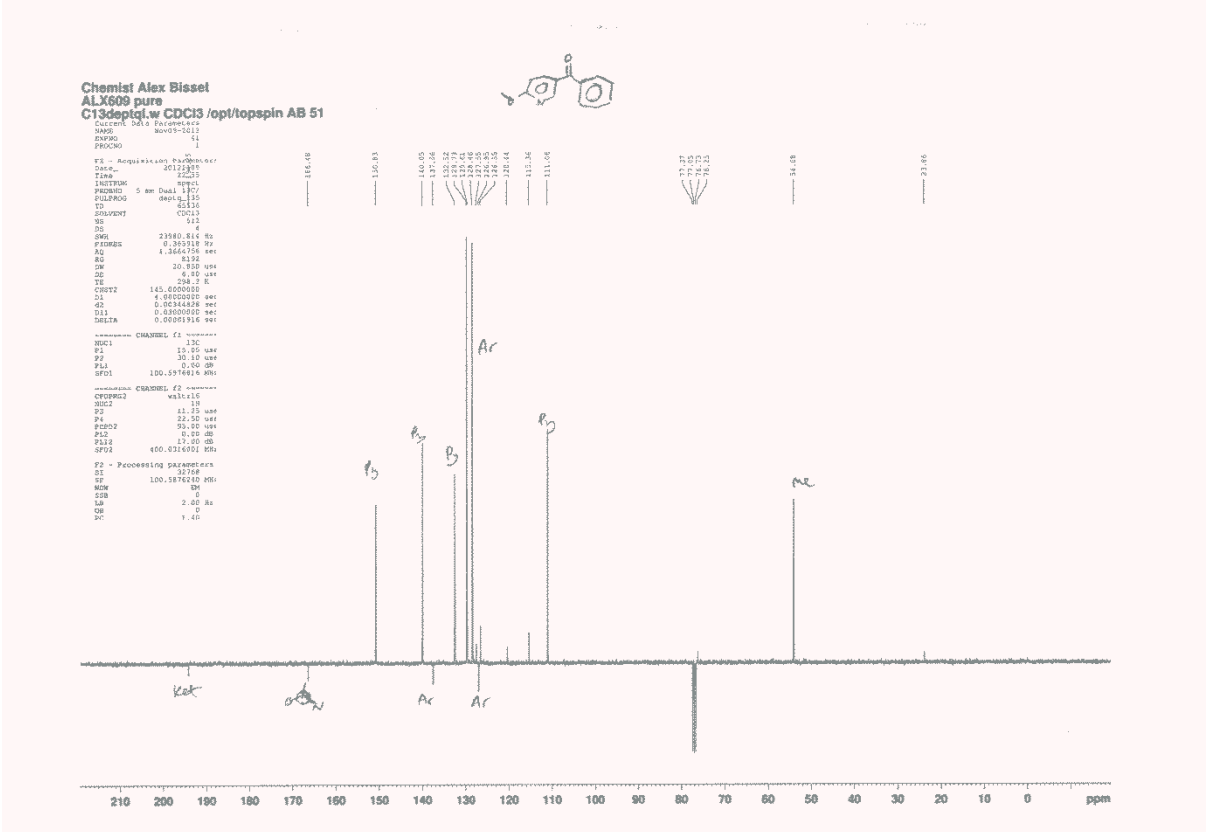
Cyclohexyl(6-methoxypyridin-3-yl)methanone, ***8.***



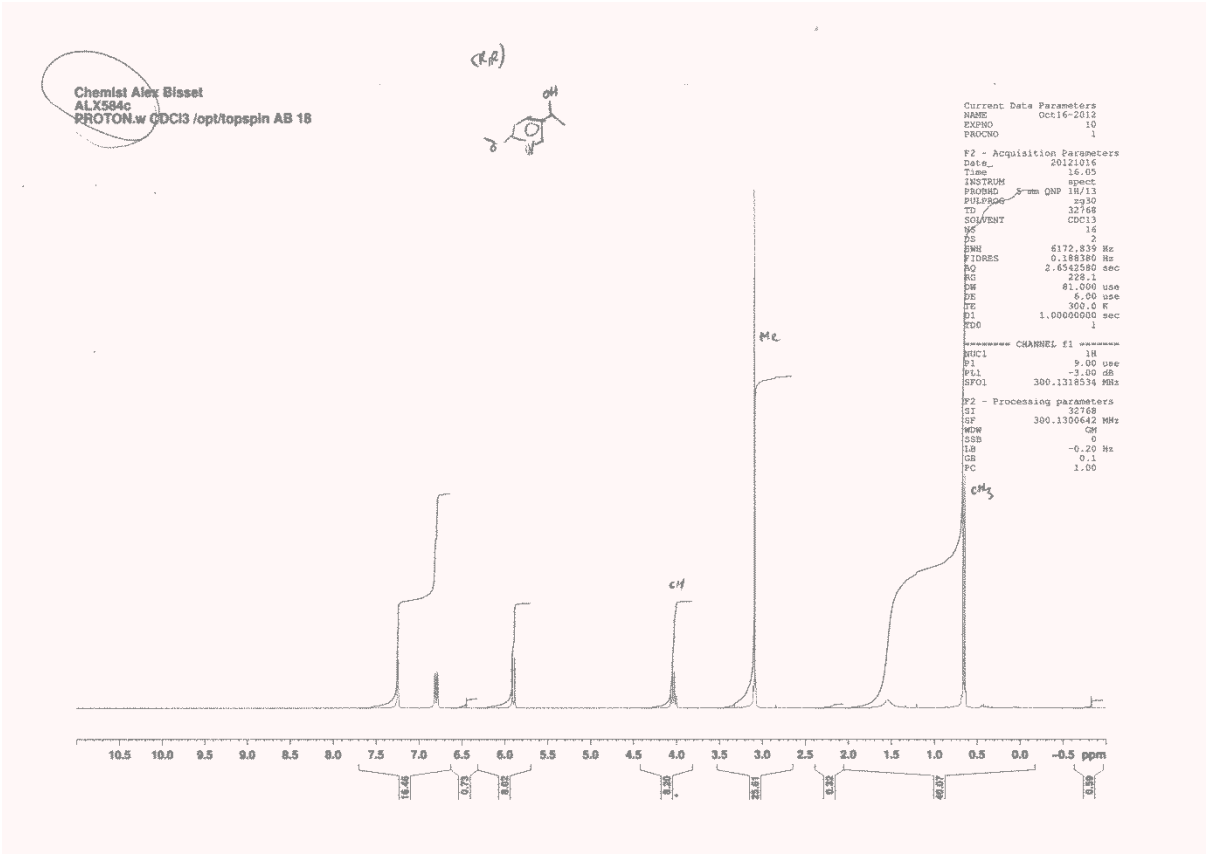


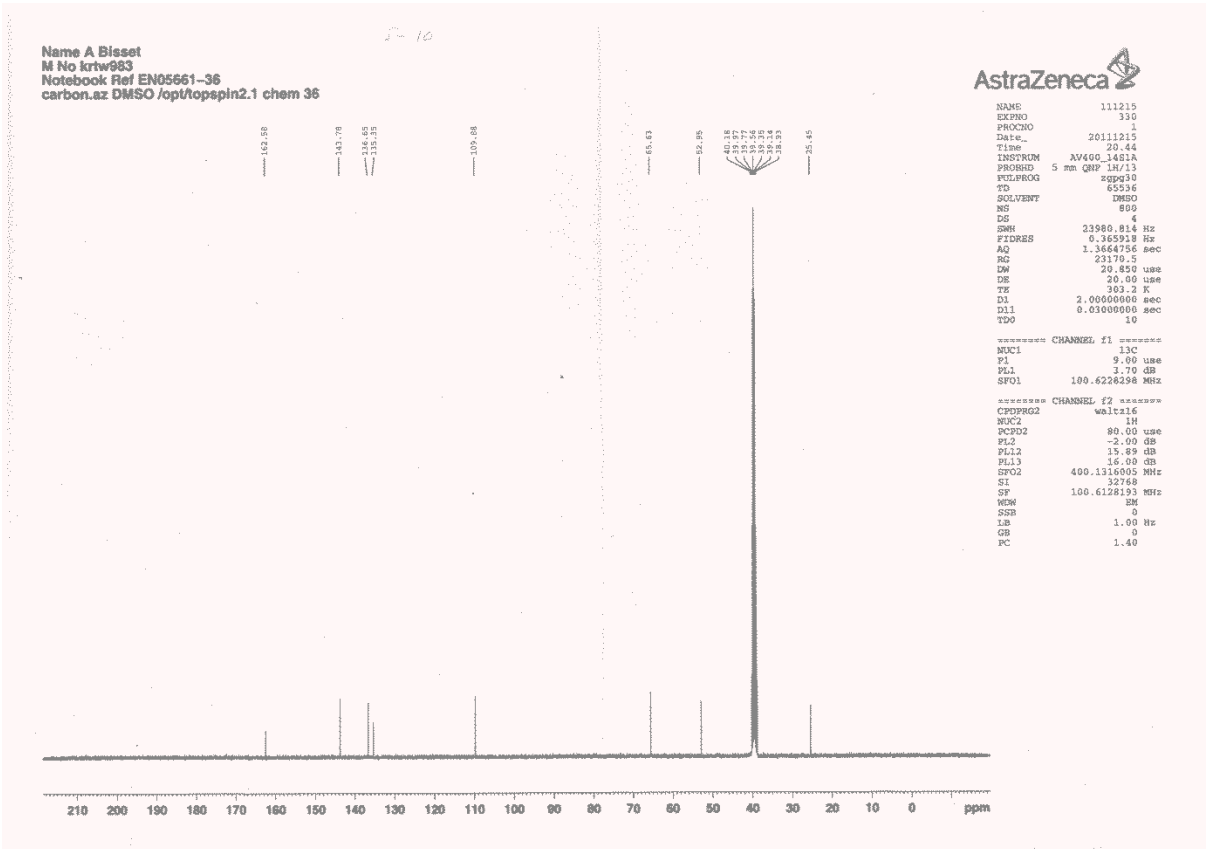
(6-Methoxypyridin-3-yl)(phenyl)methanone, ***9****.*

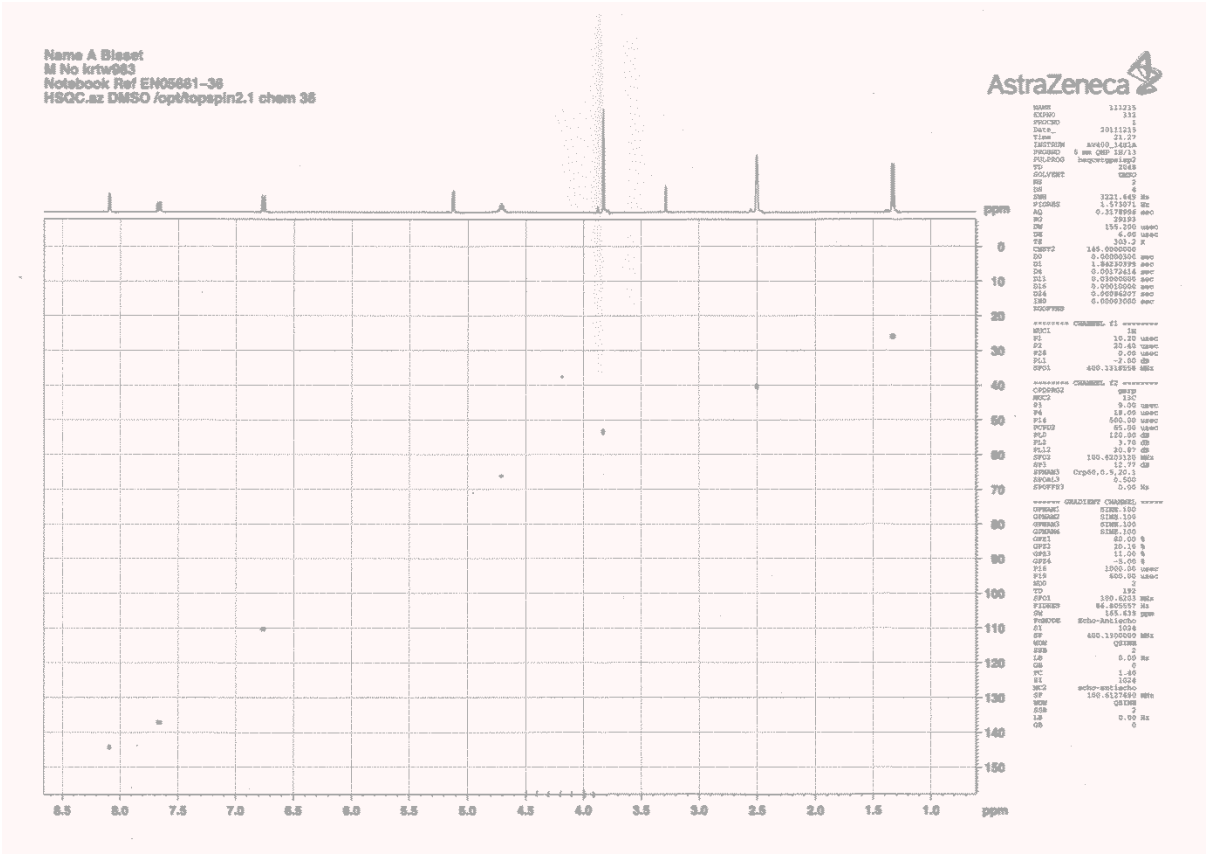




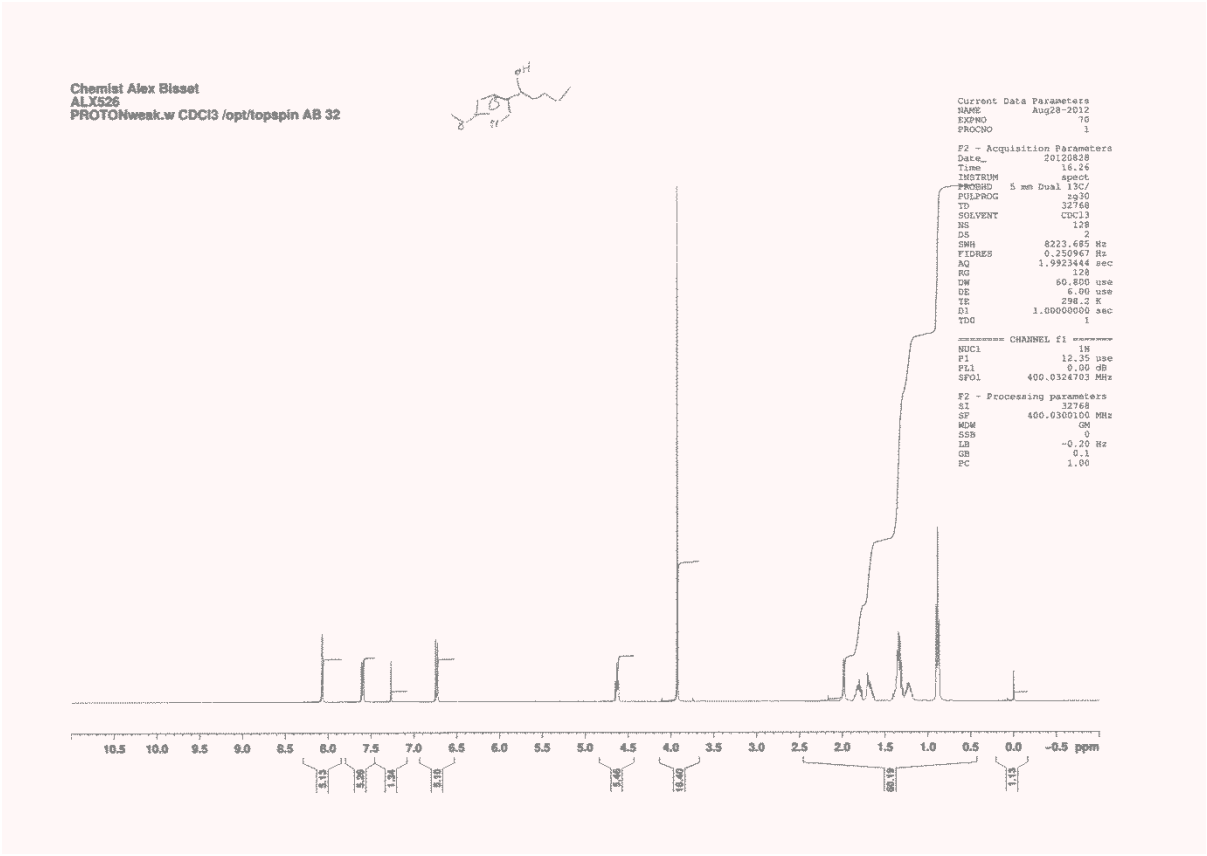
*(S)-1-(6-Methoxypyridin-3-yl)ethanol, (S)-***10**.

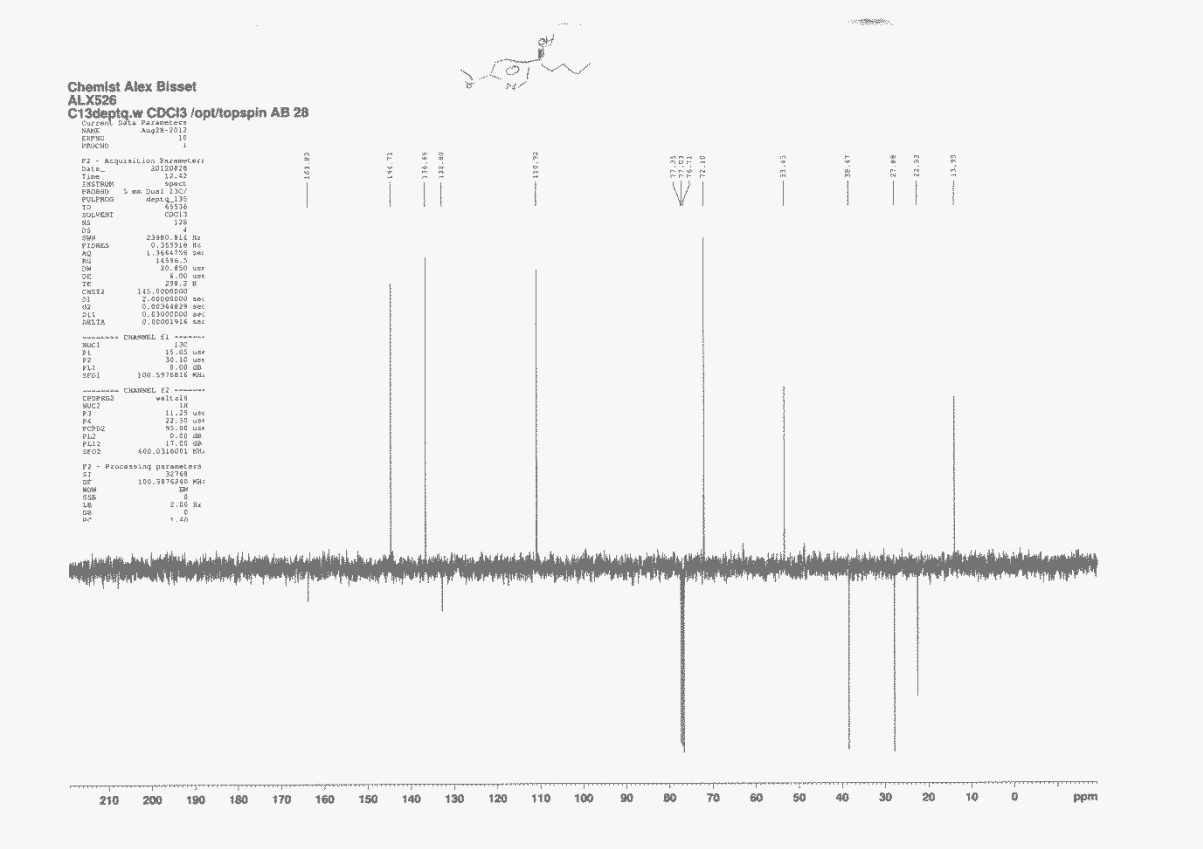

Chemist Alex Bisset
ALX584c
PROTON.w CDCl3 /opt/topspin AB 18
(R,R)
OH
Me
CH
CH3
Current Data Parameters
NAME Oct16-2012
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121016
Time 16.05
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 228.1
DW 81.000 use
DE 6.00 use
TE 300.0 K
D1 1.00000000 sec
TD0 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
WDW GM
SSB 0
LB -0.20 Hz
GB 0.1
PC 1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
16.46
0.73
8.62
8.30
25.61
0.32
40.37
0.59


Name A Bisset
M No krtw983
Notebook Ref EN05661-36
carbon.az DMSO /opt/topspin2.1 chem 36
AstraZeneca
162.58
143.78
136.65
135.35
109.88
65.63
52.95
40.18
39.77
39.56
39.35
39.14
38.93
25.45
NAME 111215
EXPNO 330
PROCNO 1
Date_ 20111215
Time 20.44
INSTRUM AV400_1481A
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 23170.5
DW 20.850 use
DE 20.00 use
TE 303.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 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
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

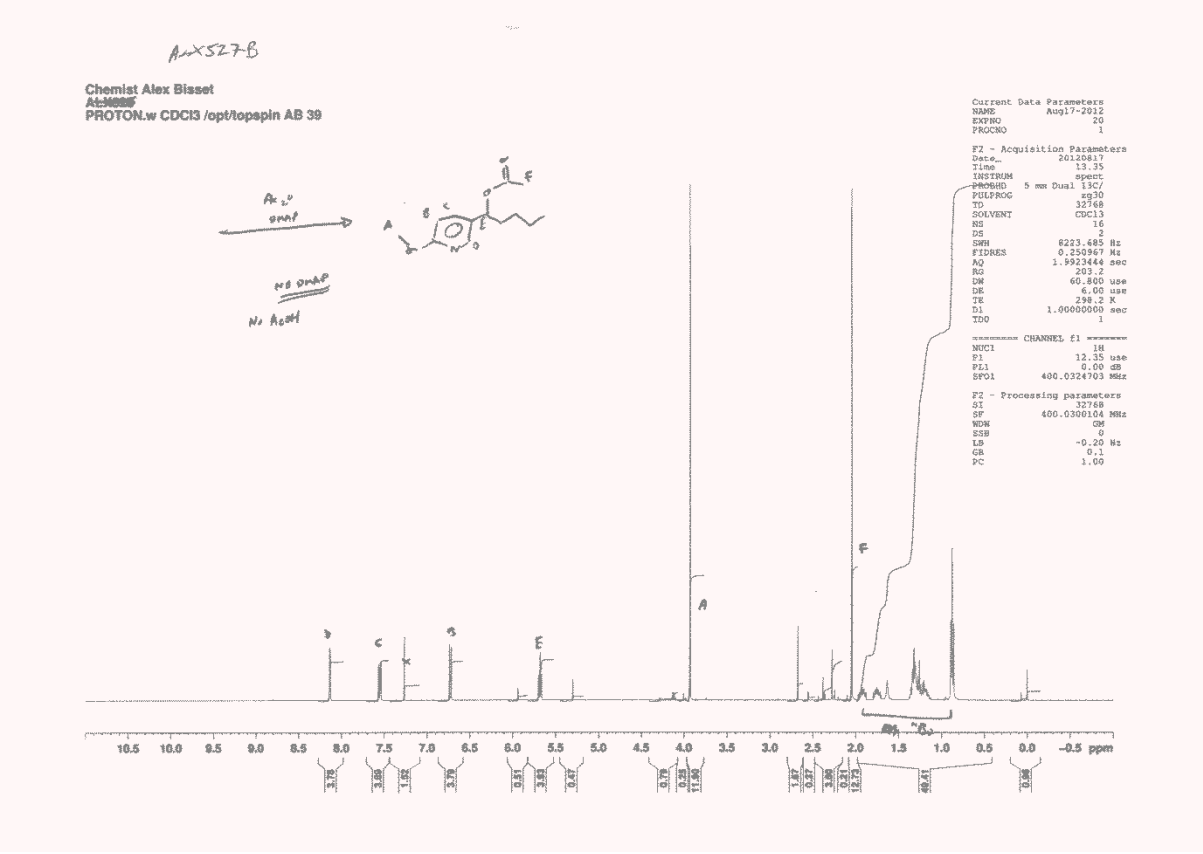


(R)-1-(6-Methoxypyridin-3-yl)pentan-1-ol, (*R*)**-11.**

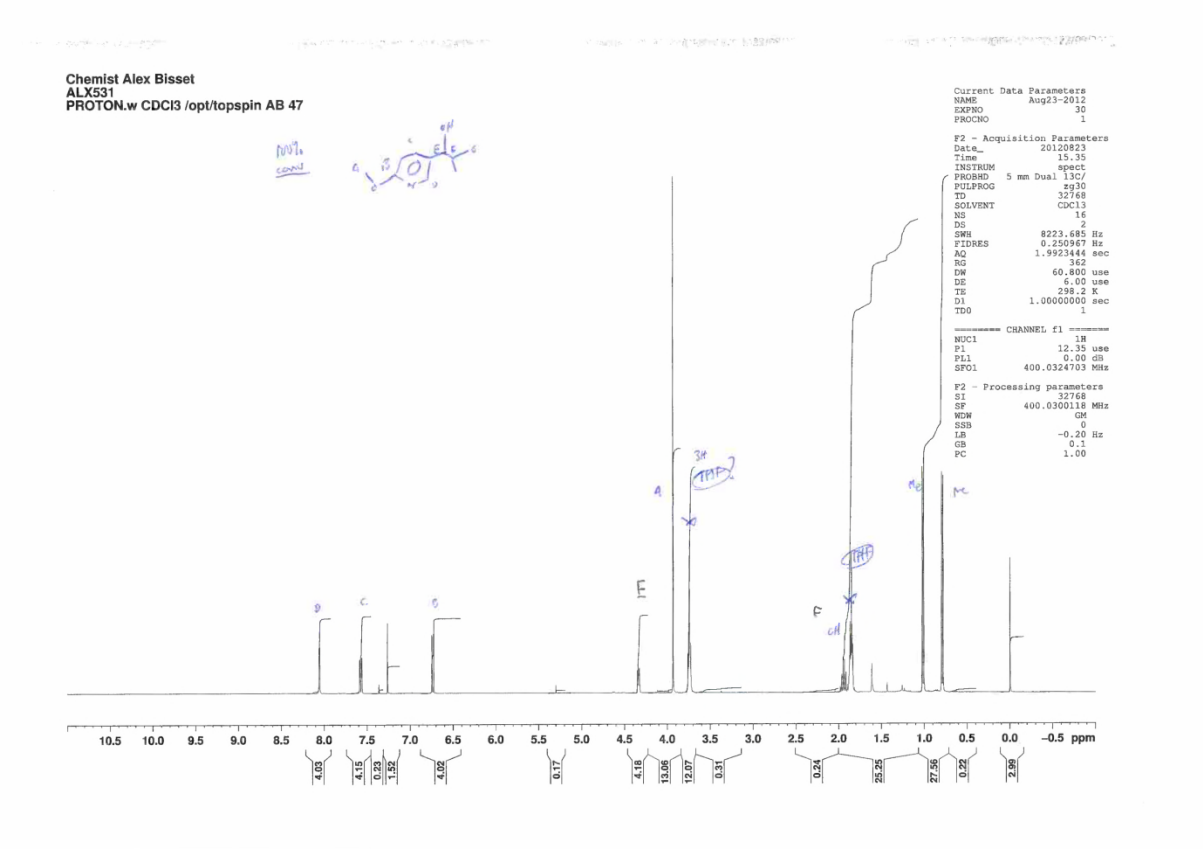


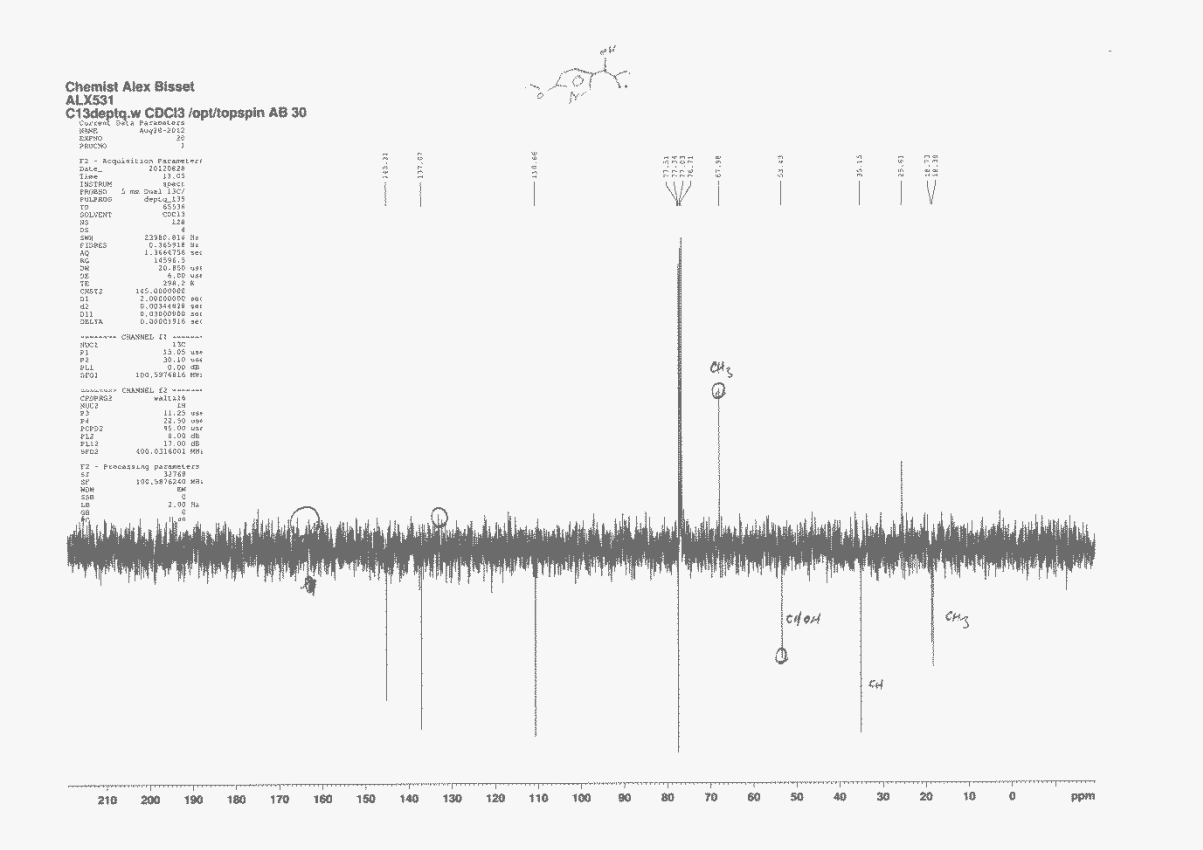


Acetate derivative for ee determination:

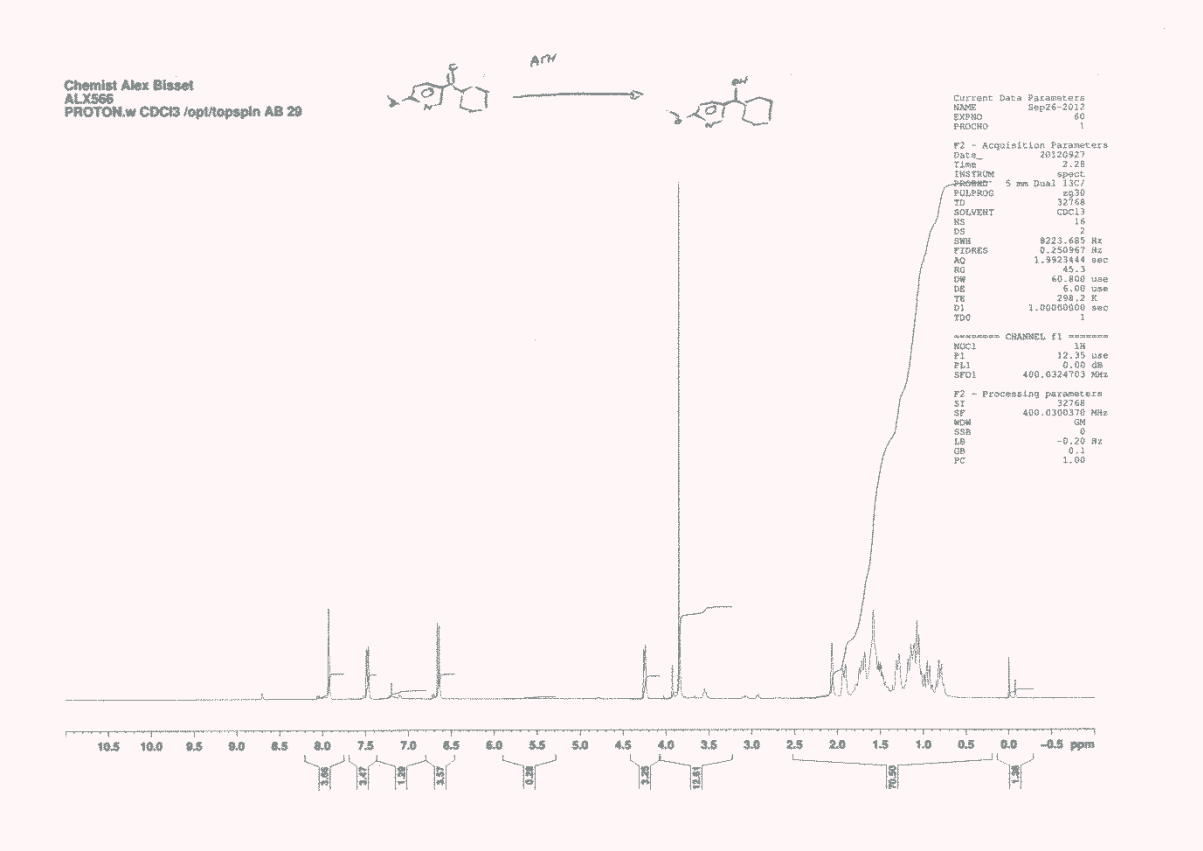


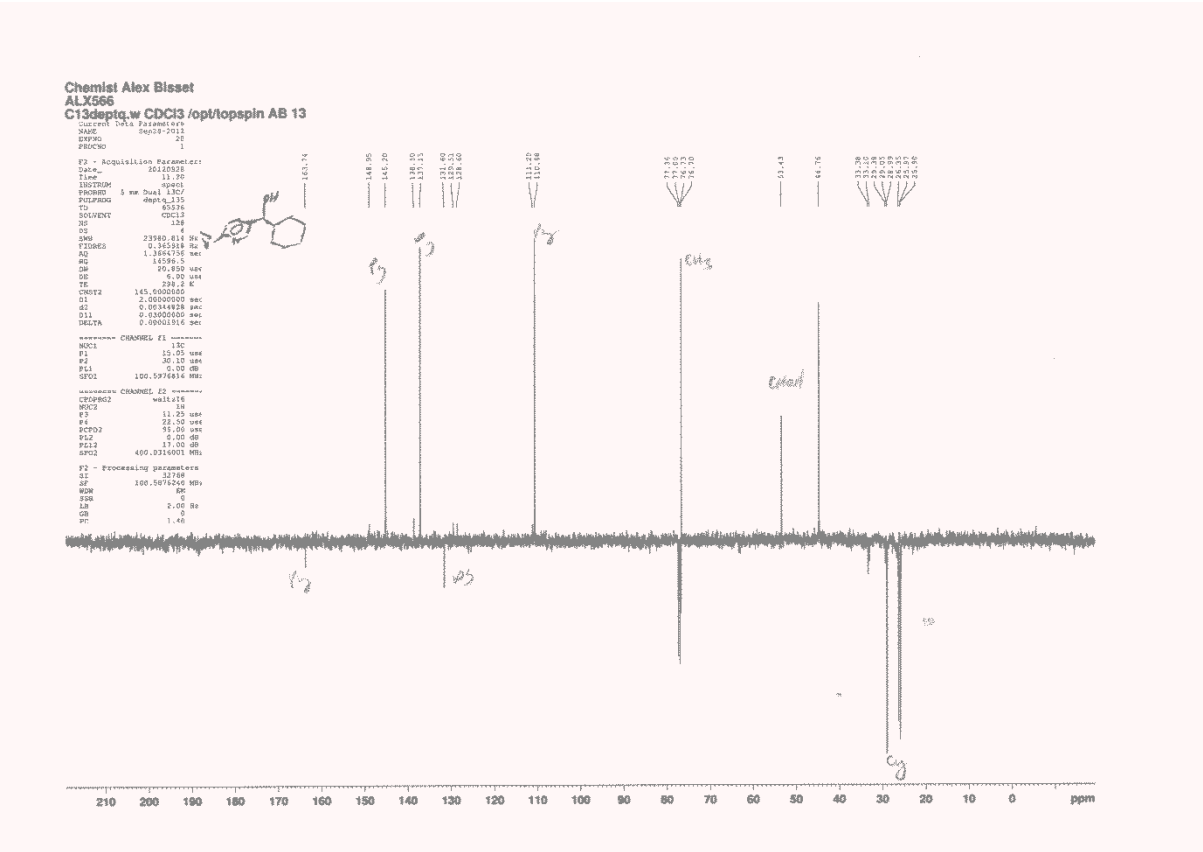
(R)-1-(6-Methoxypyridin-3-yl)-2-methylpropan-1-ol, (*R*)-**12.**



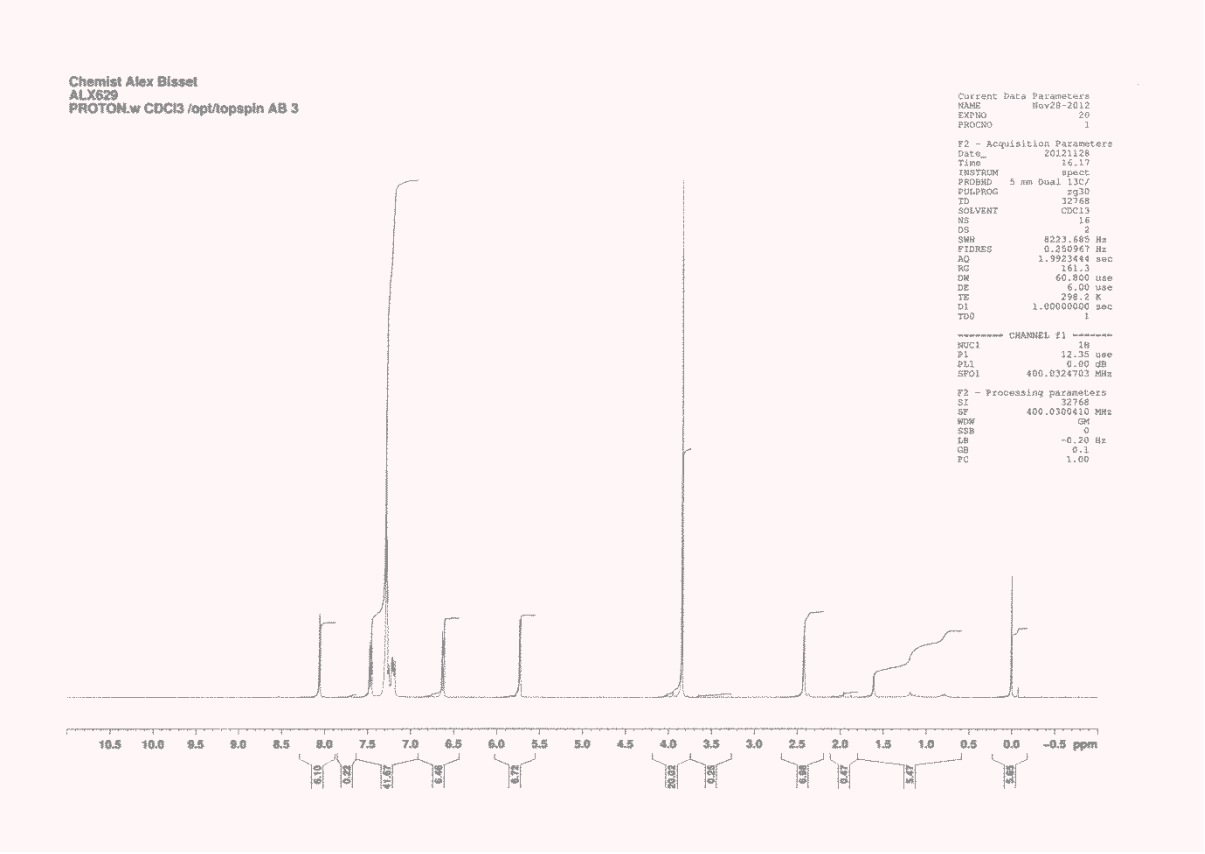


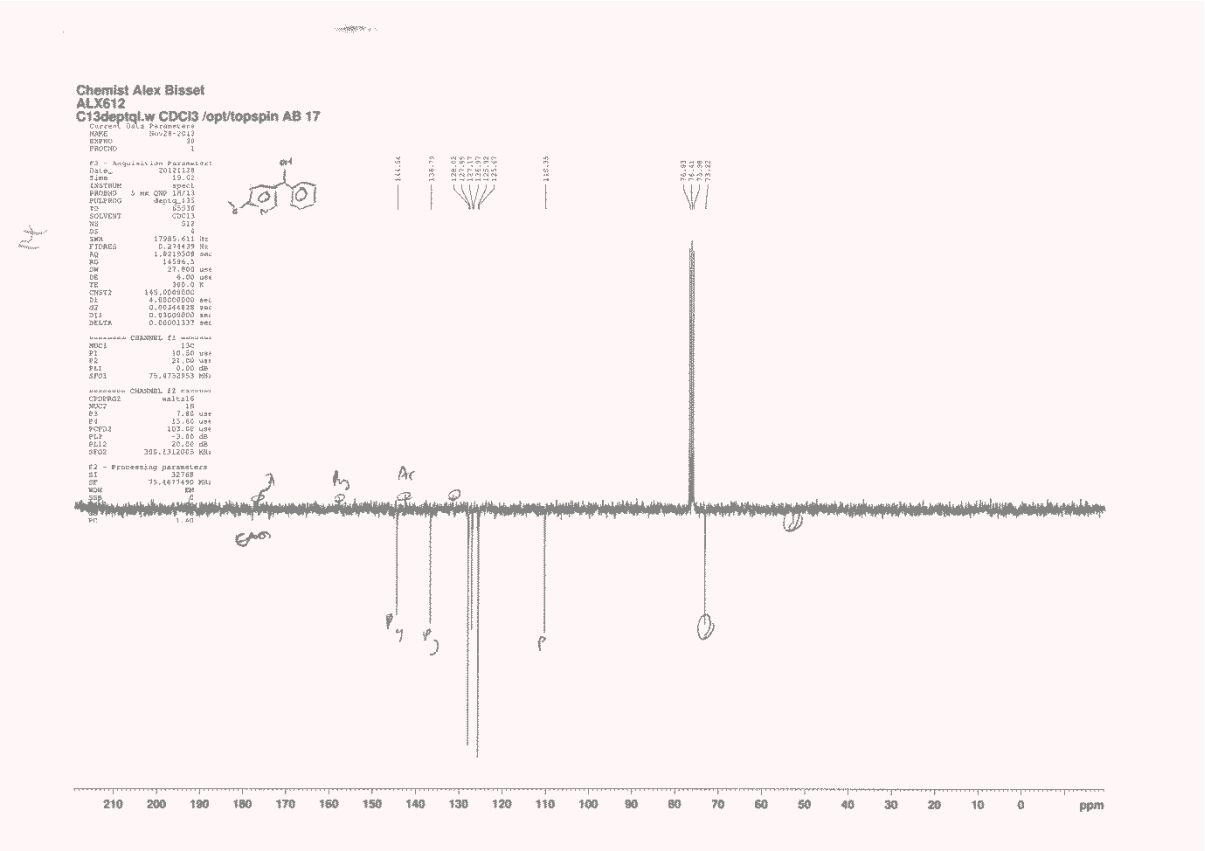
(R)-Cyclohexyl(6-methoxypyridin-3-yl)methanol, (*R*)-**13**.



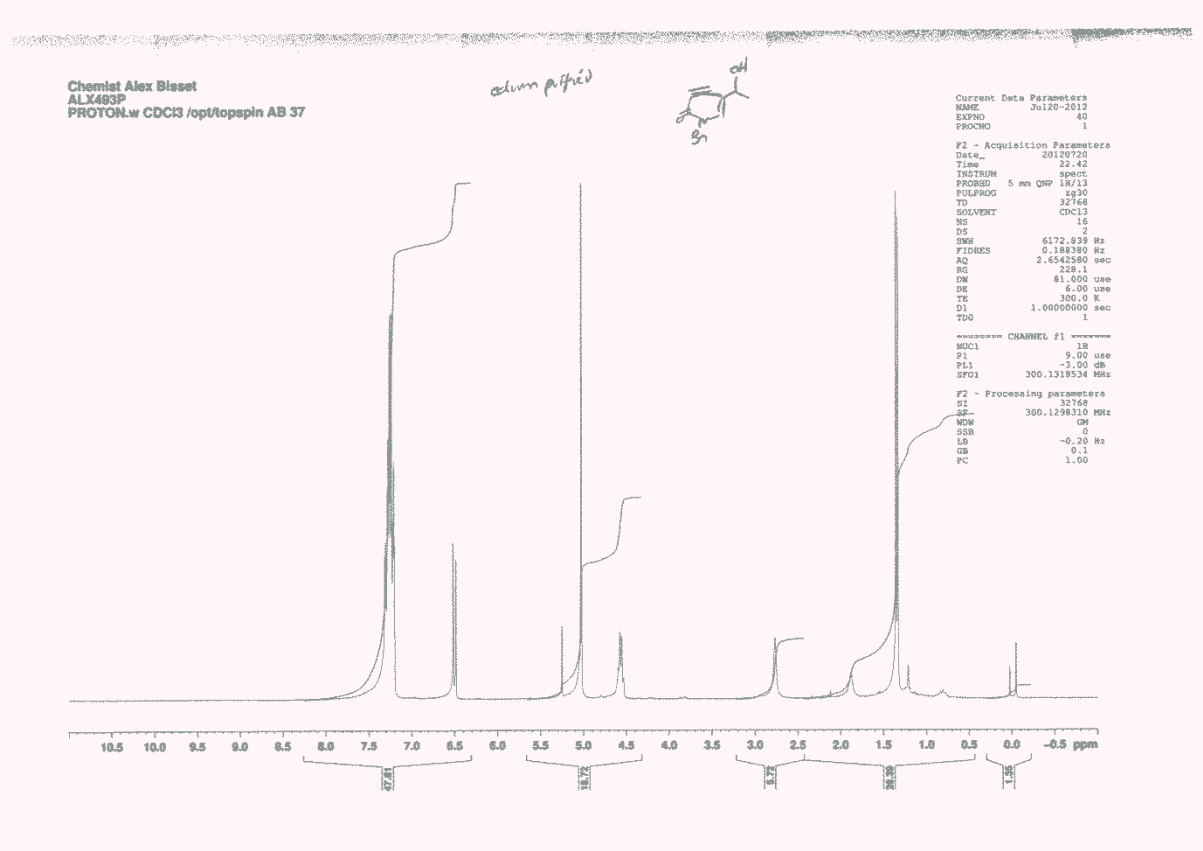


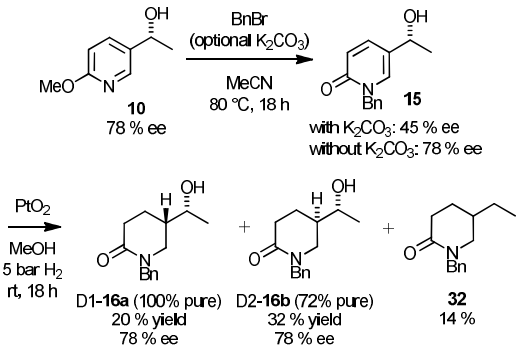
(6-Methoxypyridin-3-yl)(phenyl)methanol, (**-**)**-14.**



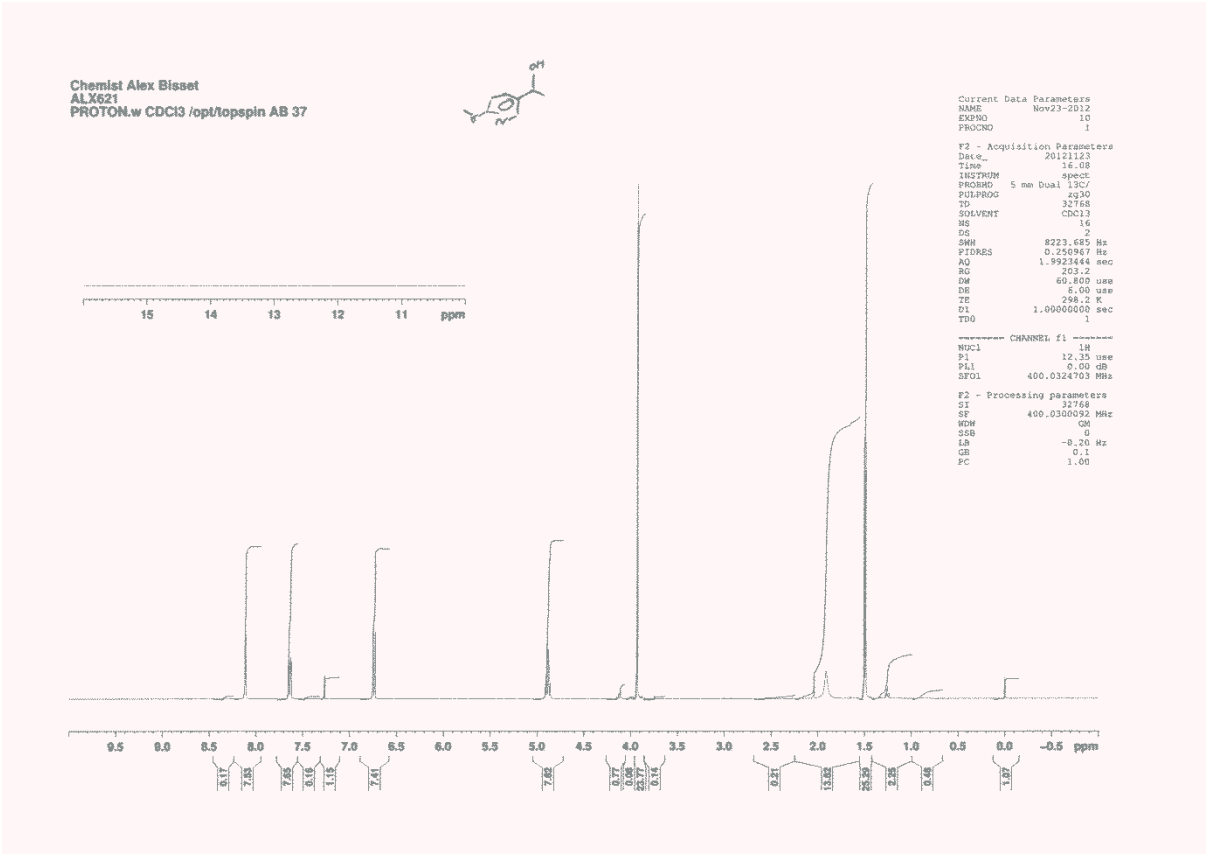


1-Benzyl-5-(1-hydroxyethyl)piperidin-2-one, (*R*)-**15** sample from reduction of **27** in 42% ee.



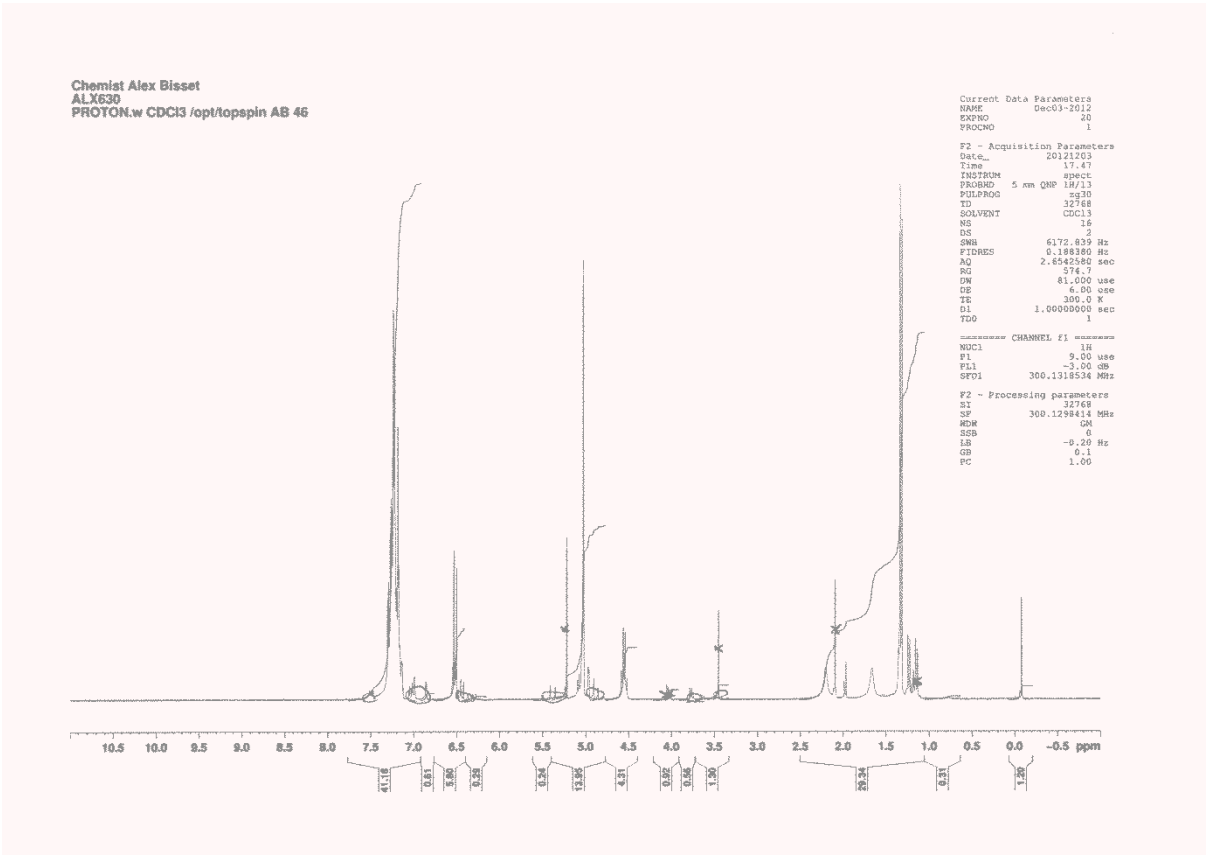


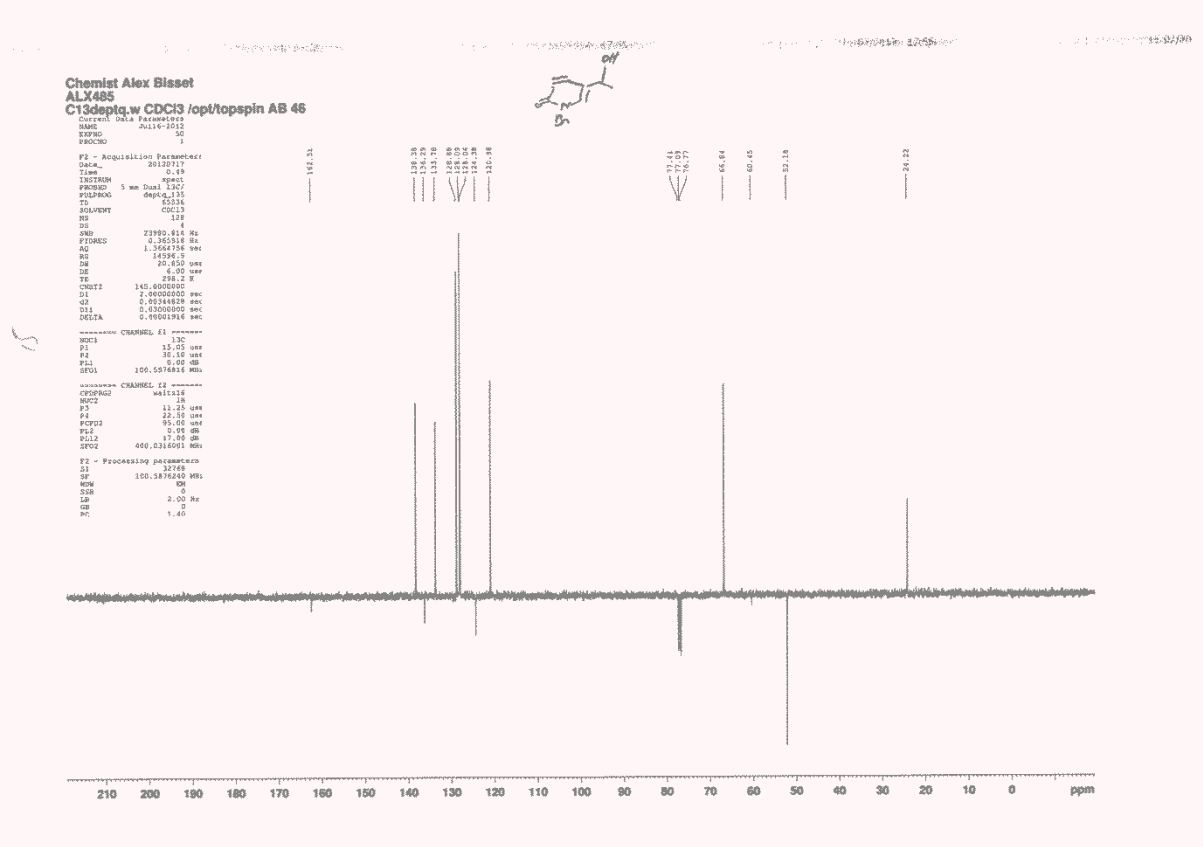
*(R)-1-(6-Methoxypyridin-3-yl)ethanol, (R)-***10** (larger scale preparation).



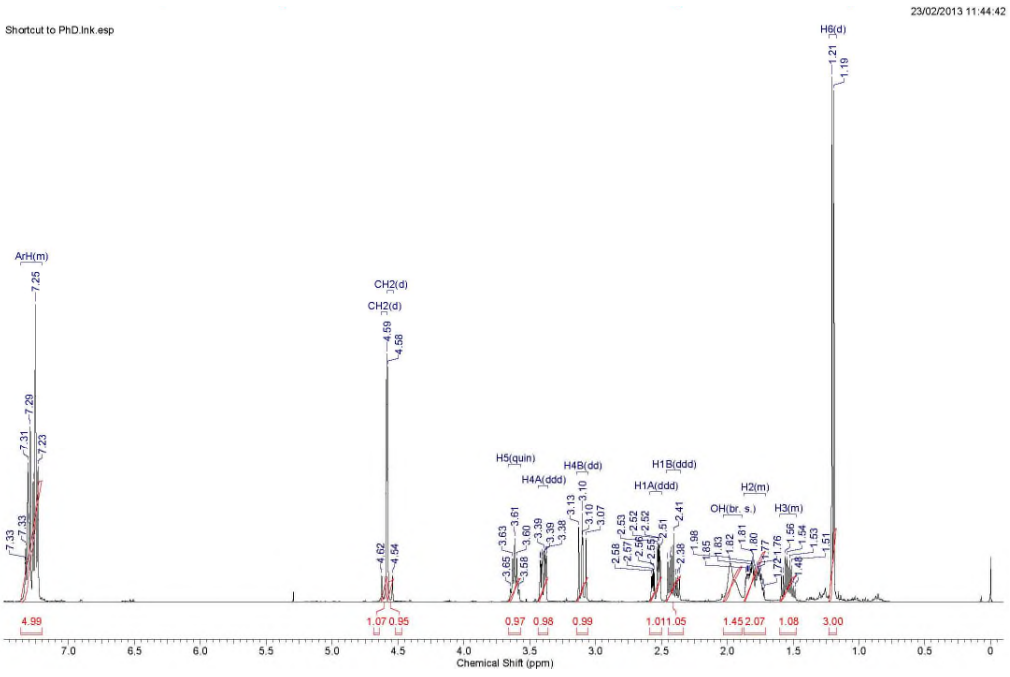
1-Benzyl-5-(1-hydroxyethyl)pyridin-2(1H)-one,(R)- **15** made from the pyridine **10.**

Crude product:

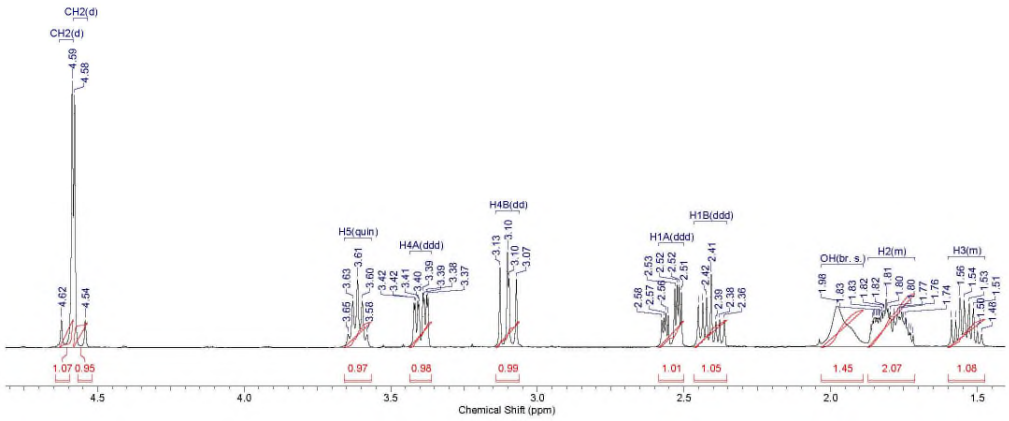




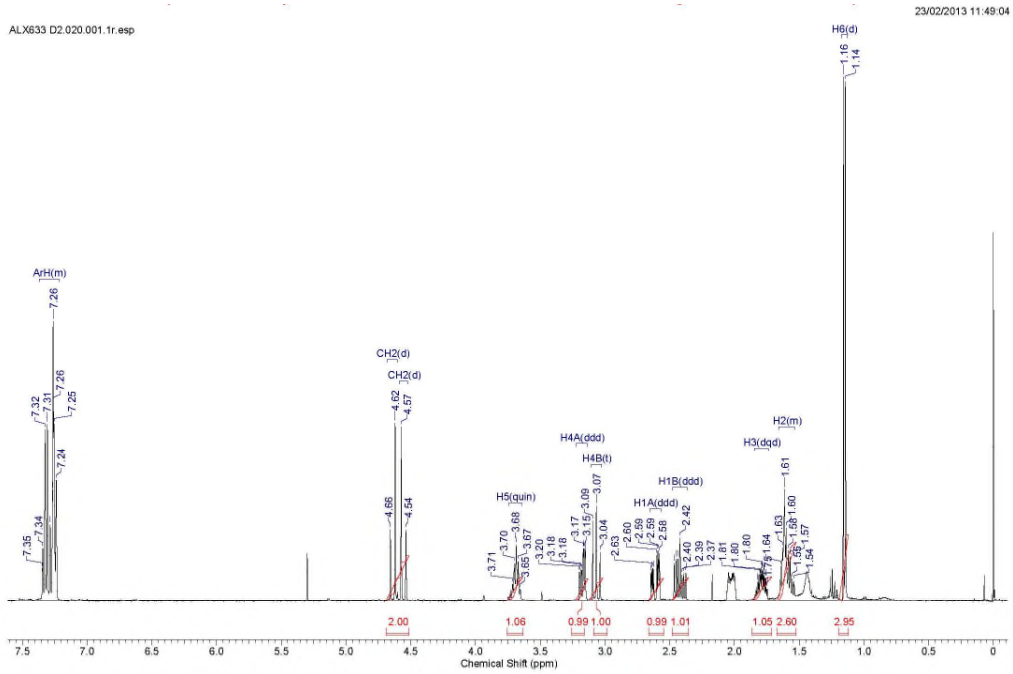
1-benzyl-5-(1-hydroxyethyl)piperidin-2-one, D1- **16a**.

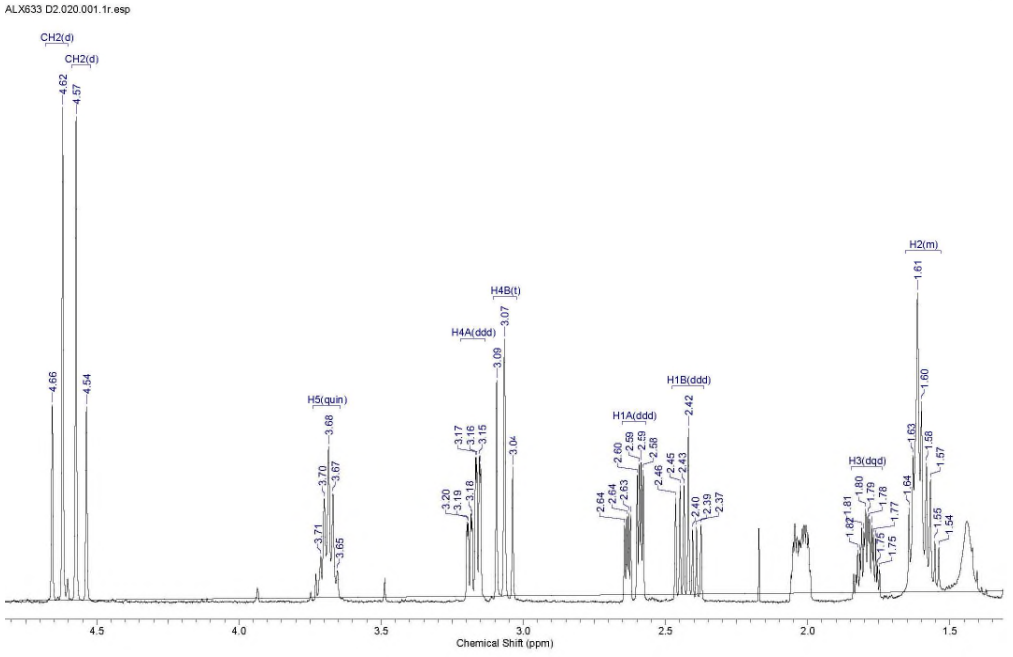


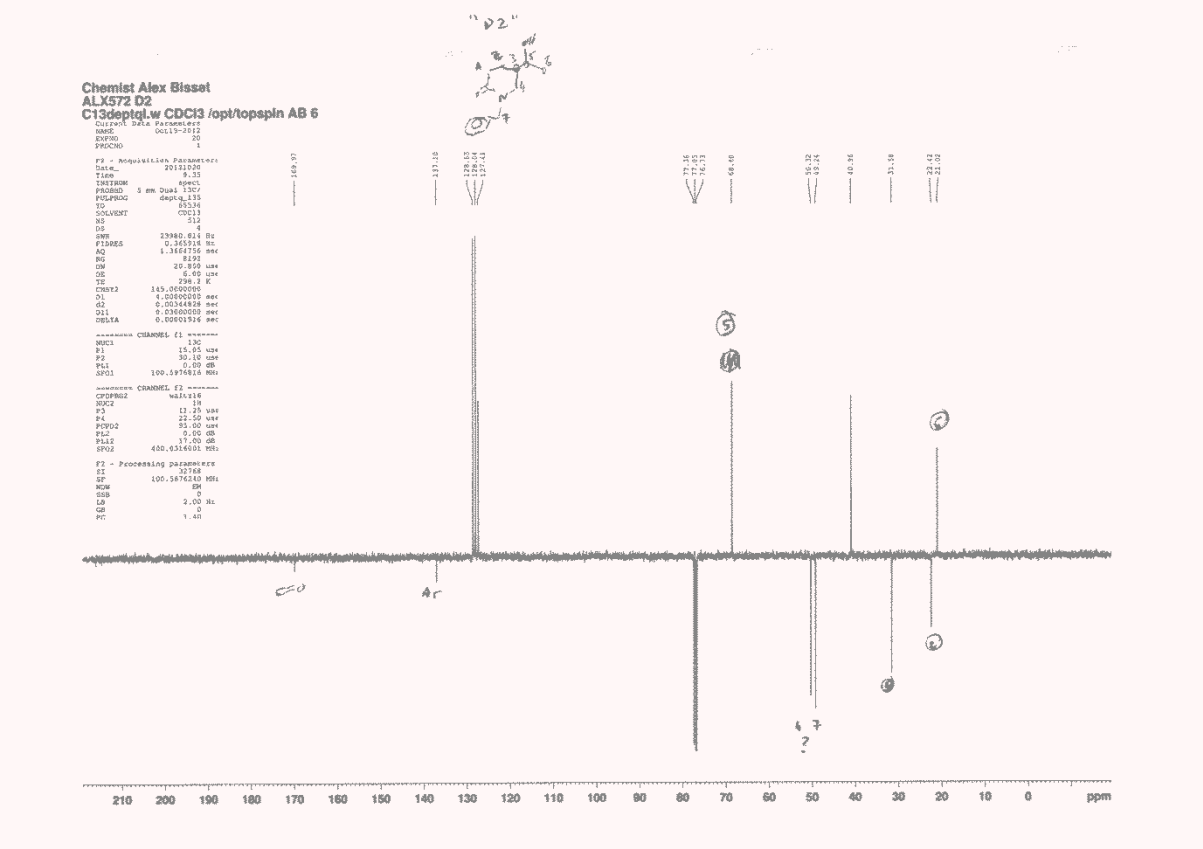
Shortcut to PhD.lnk.esp



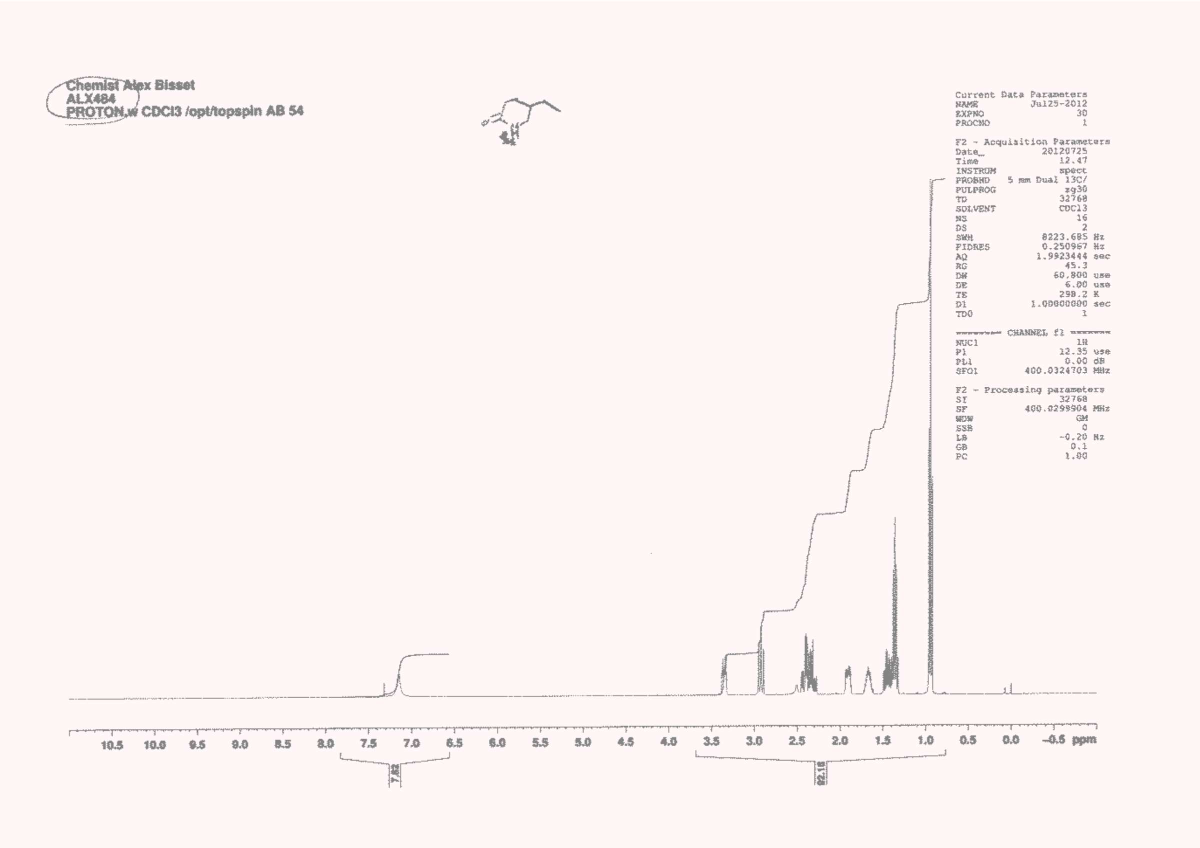
1-benzyl-5-(1-hydroxyethyl)piperidin-2-one, D2-**16b**.

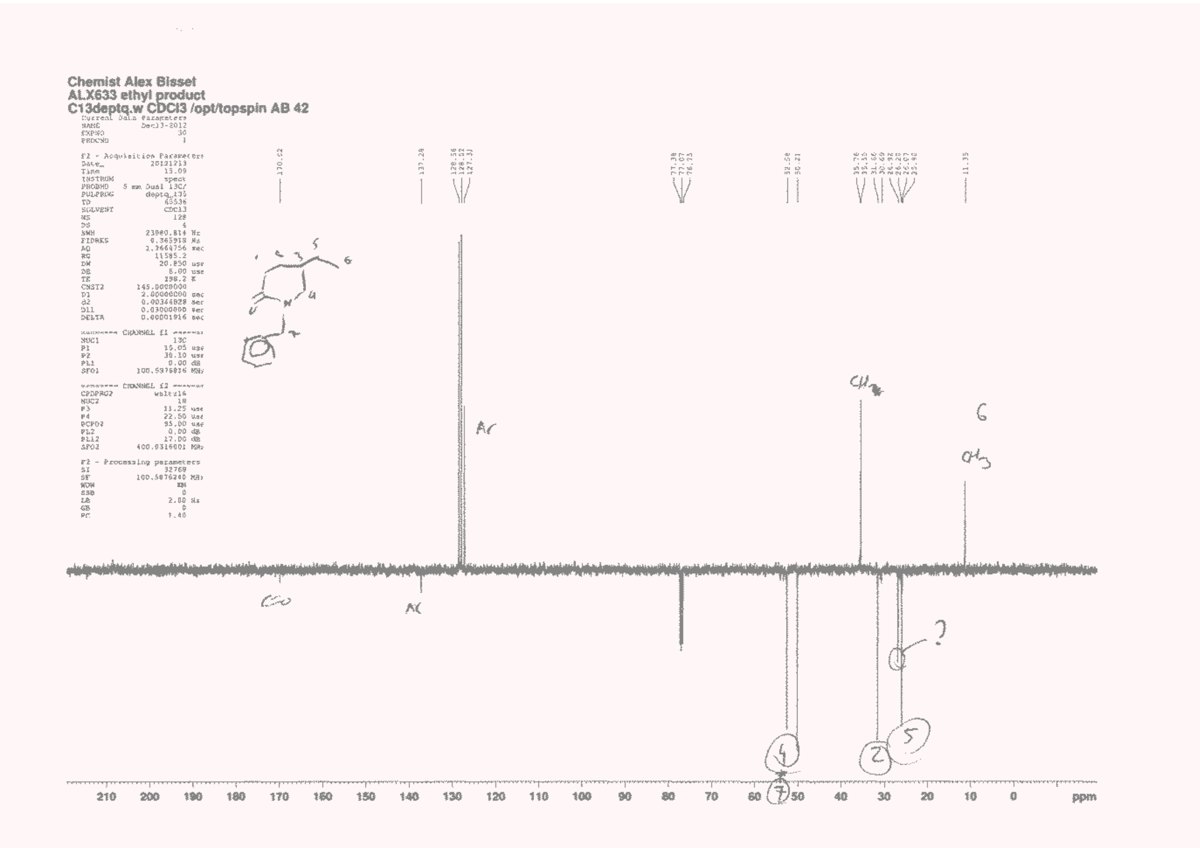

ALX633 D2.020.001.1r.esp
23/02/2013 11:49:04
H6(d)
ArH(m)
CH2(d)
CH2(d)
H4A(ddd)
H4B(t)
H5(quin)
H1A(ddd)
H1B(ddd)
H3(dqd)
H2(m)
2.00
1.06
0.99
1.00
0.99
1.01
1.05
2.60
2.95
Chemical Shift (ppm)


ALX633 D2.020.001.1r.esp
CH2(d)
CH2(d)
H5(quin)
H4A(ddd)
H4B(t)
H1A(ddd)
H1B(ddd)
H3(dqd)
H2(m)
Chemical Shift (ppm)

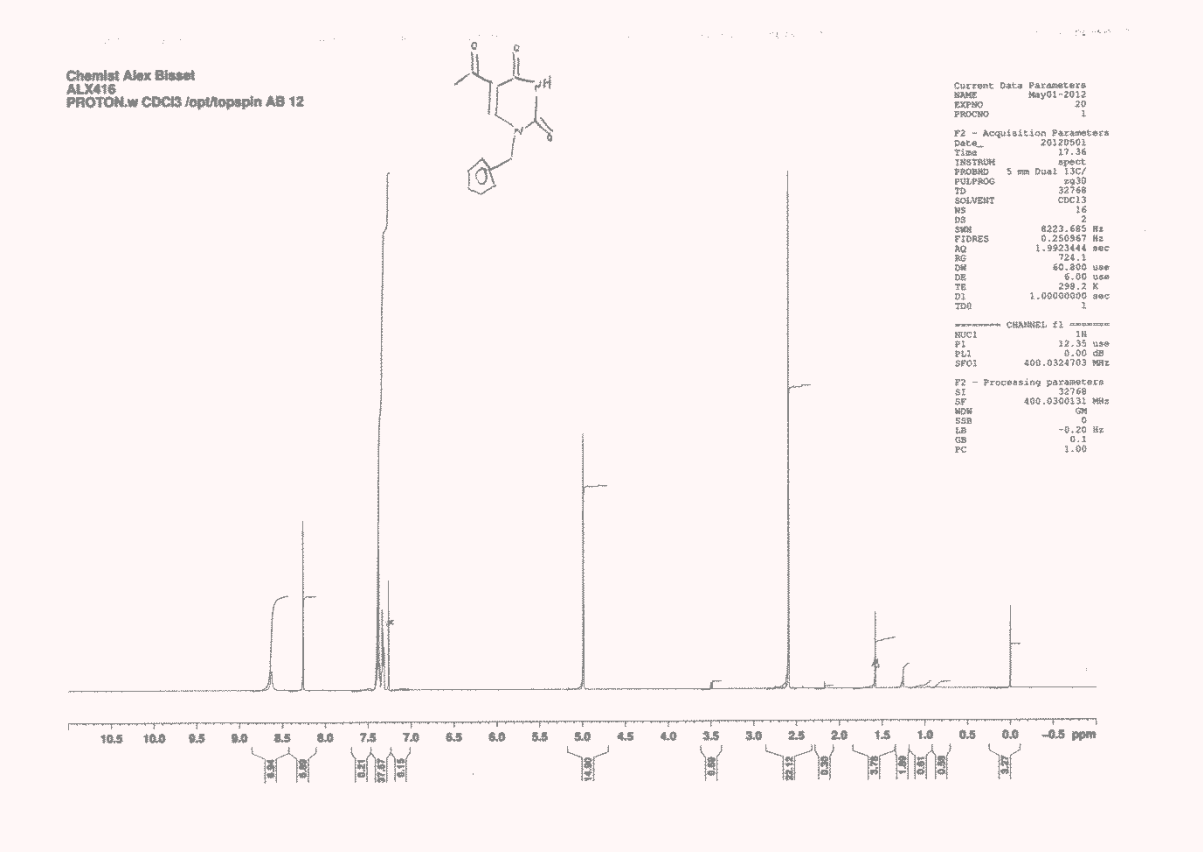


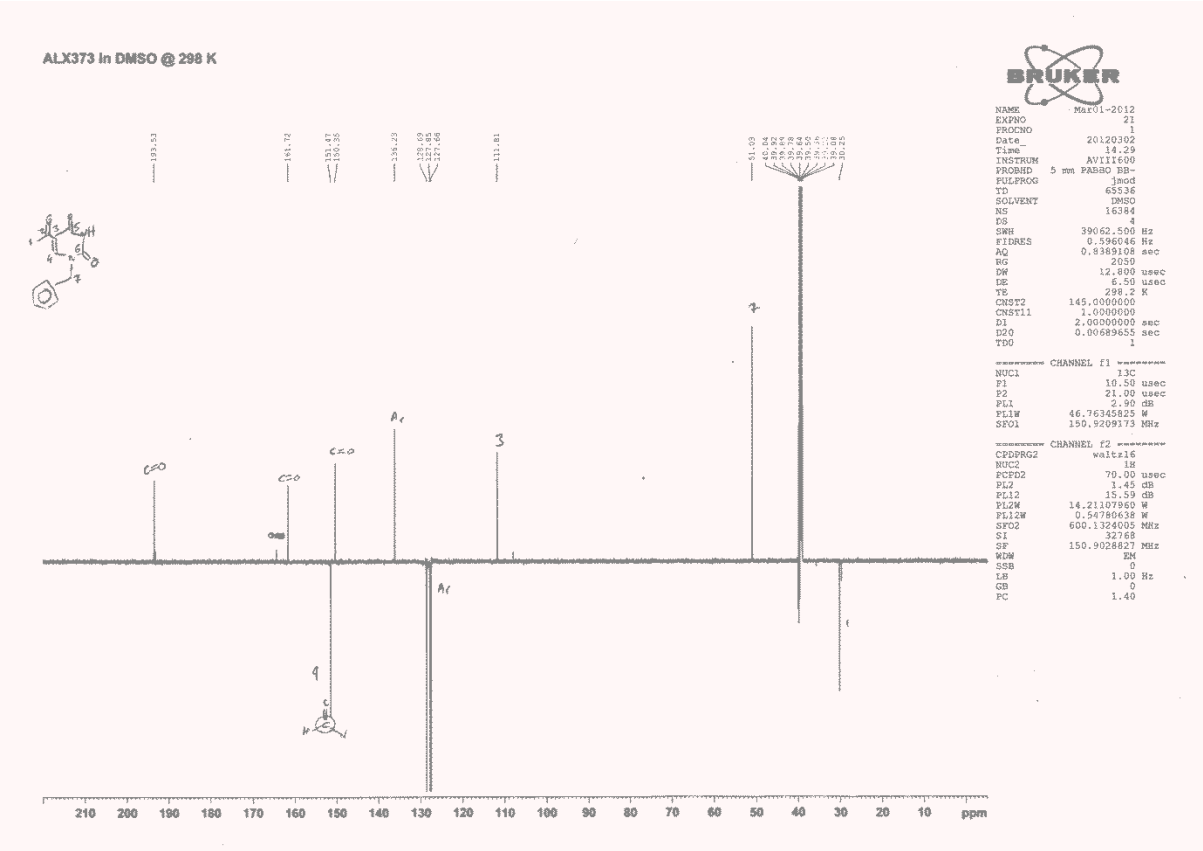
The hydrogenolysis product 1-benzyl-5-ethylpiperidin-2-one, **32**.


Chemist Alex Bisset
ALX484
PROTON.w CDCl3 /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 zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 45.3
DW 60.800 use
DE 6.00 use
TE 298.2 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 12.35 use
PL1 0.00 dB
SFO1 400.0324703 MHz
F2 - Processing parameters
SI 32768
SF 400.0299904 MHz
WDW GM
SSB 0
LB -0.20 Hz
GB 0.1
PC 1.00
ppm
7.82
92.18

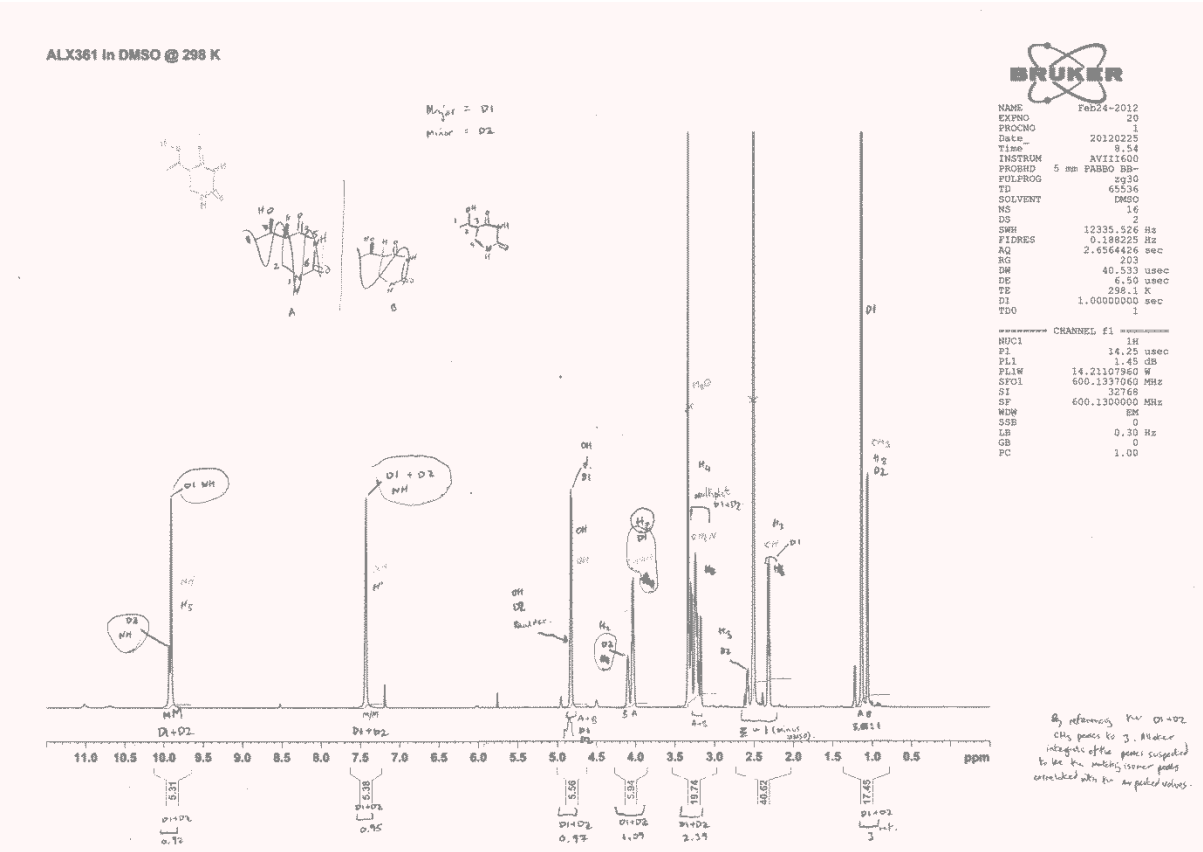

Chemist Alex Bisset
ALX633 ethyl product
C13deptq.w CDCl3 /opt/topspin AB 42
Ar
CH2
CH3
C=O
ppm

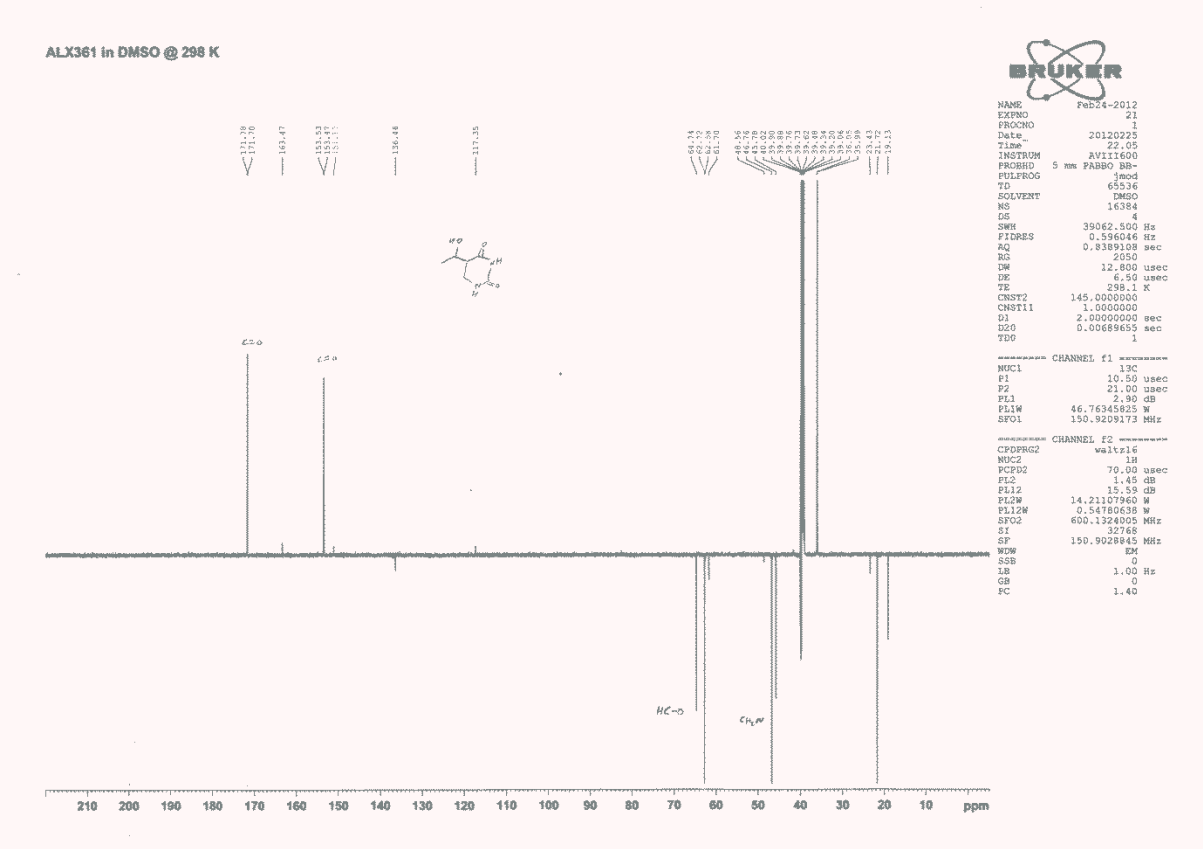
5-Acetyl-1-benzylpyrimidine-2,4(1H,3H)-dione, **34.**





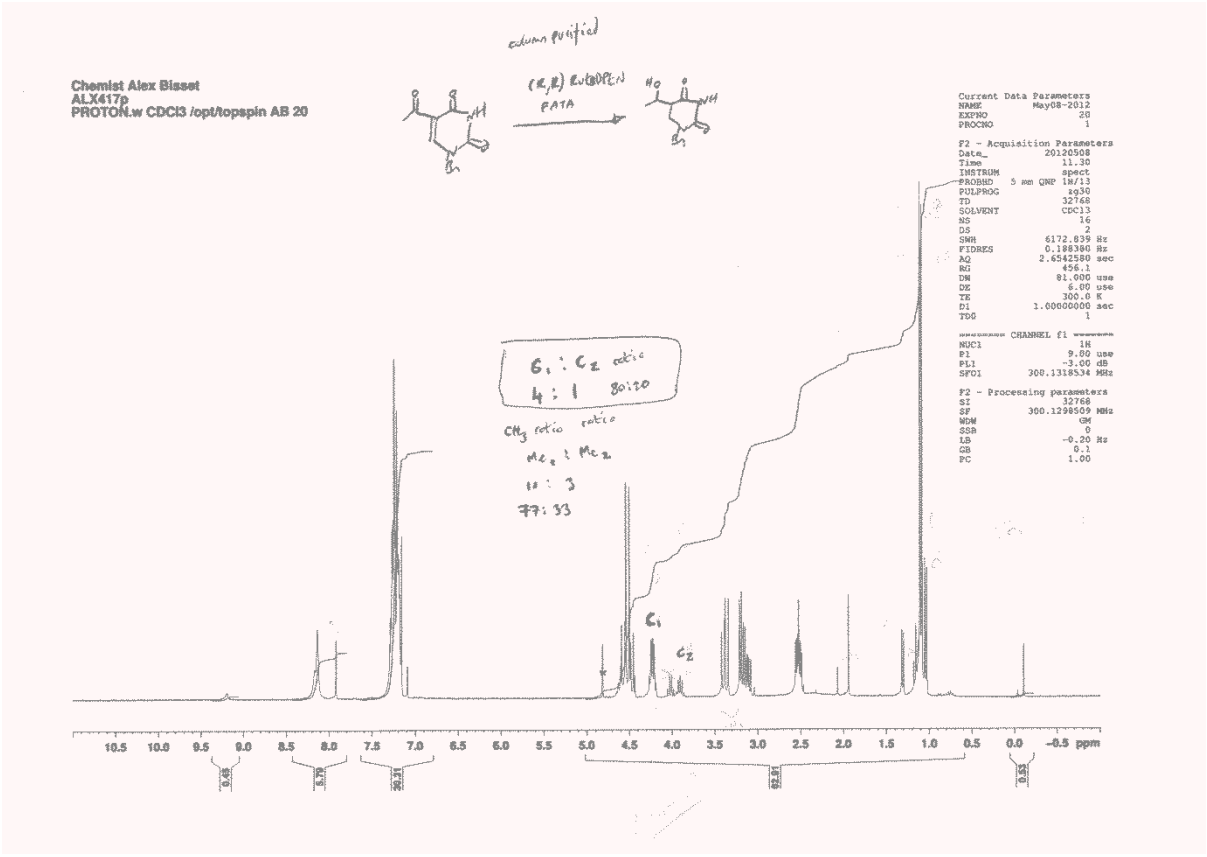
5-(1-hydroxyethyl)dihydropyrimidine-2,4(1H,3H)-dione, **35.**



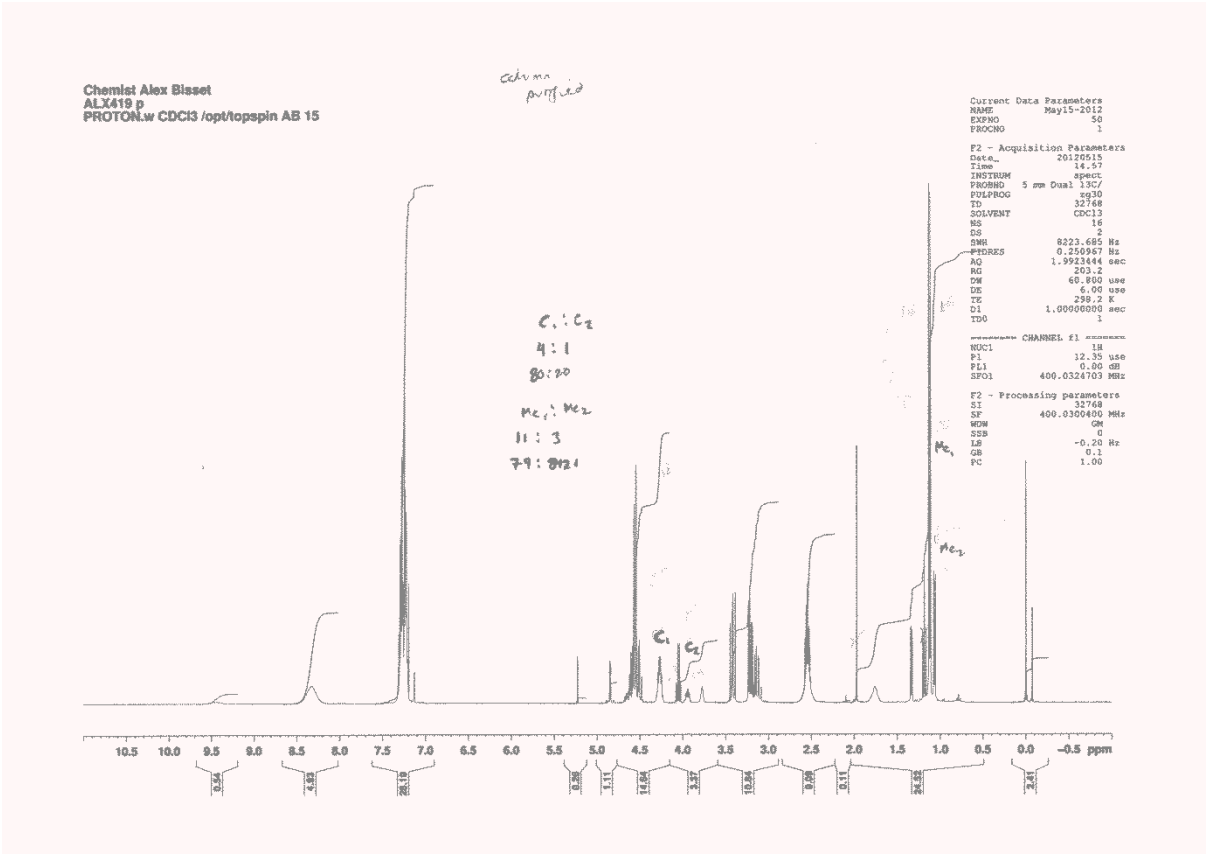


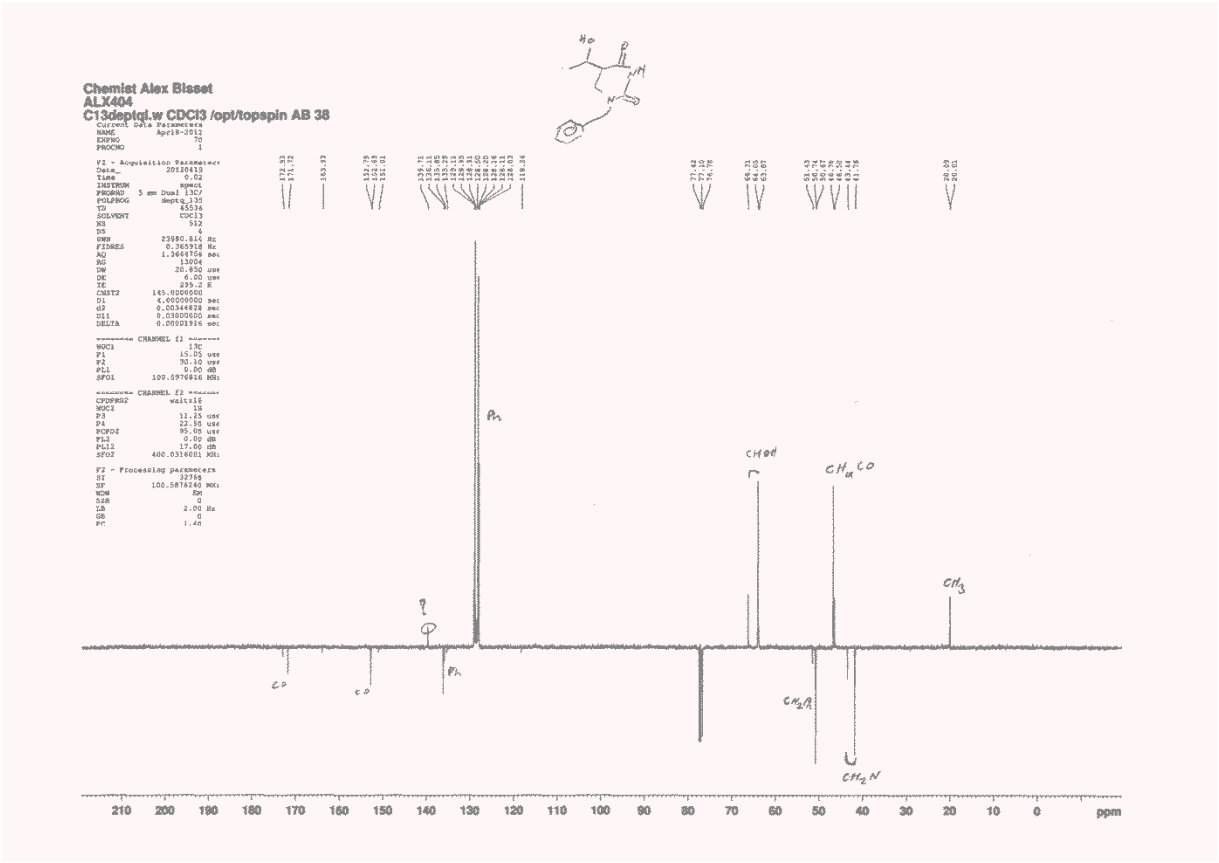
1-Benzyl-5-(1-hydroxyethyl)dihydropyrimidine-2,4(1H,3H)-dione, **37a and b.**

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



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

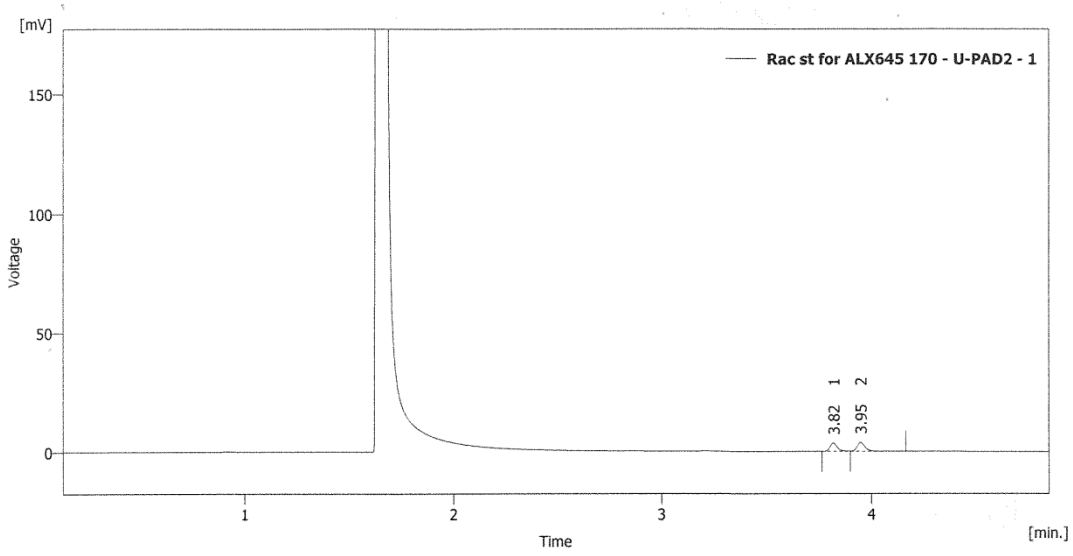



Chemist Alex Bisset
ALX404
C13deptq.w CDCl3 /opt/topspin AB 38
CHOH
CH2CO
CH3
CH2N
CH2/A
CO
CO
PA
PM
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

Chiral HPLC and GC Traces.

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

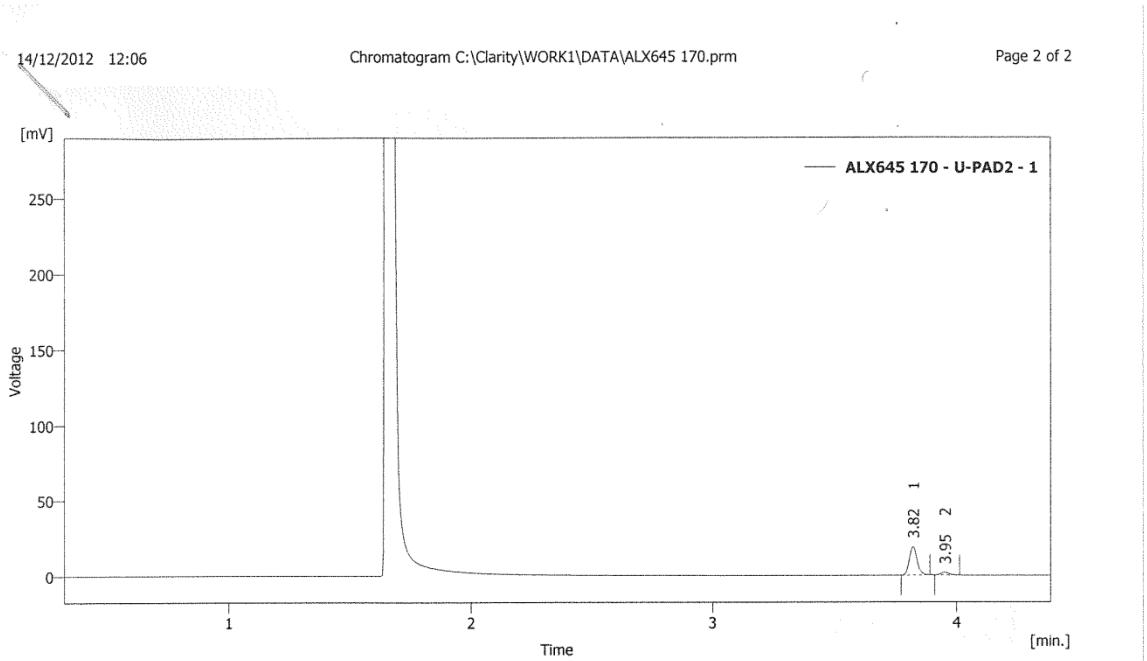
Racemic:



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):

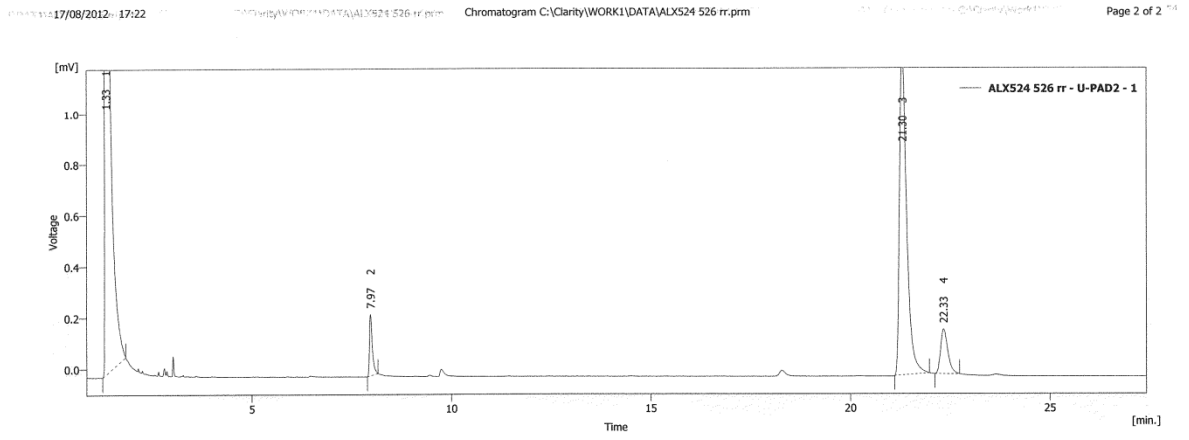


Result Table (Uncal - ALX645 170 - U-PAD2 - 1)

	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).

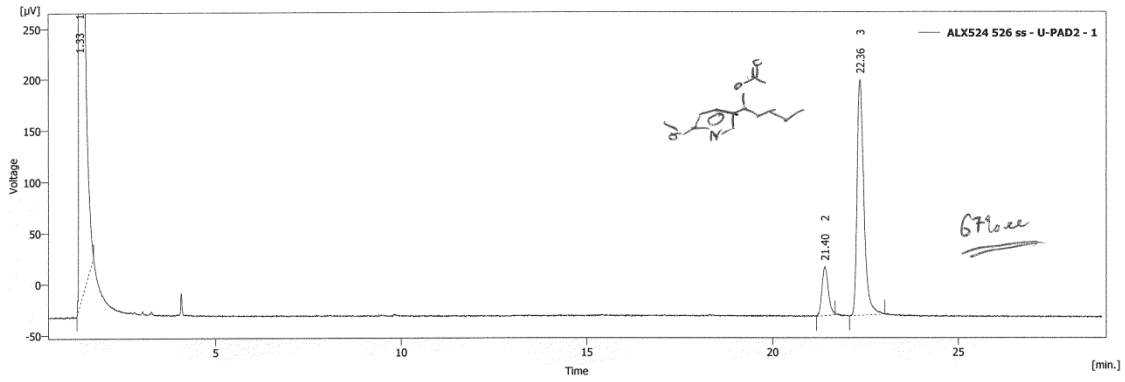
(R)-enantiomer 76% ee compound **11** (under condtions given in Table 5):



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:



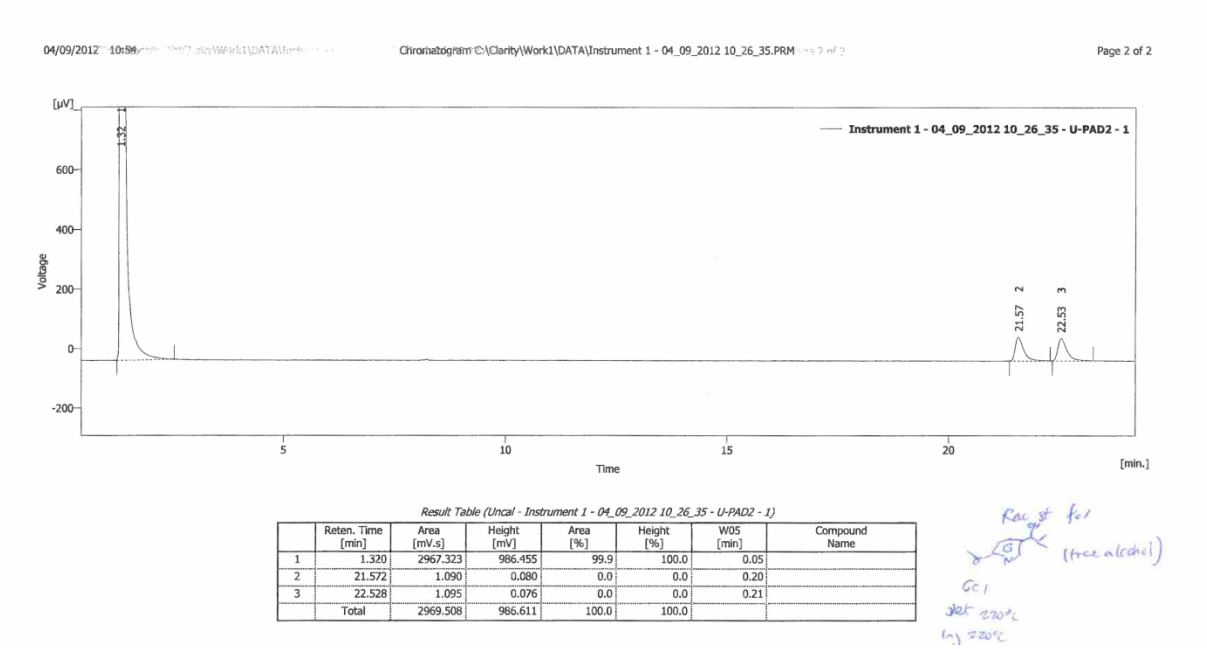
Result Table (Uncal - ALX524 526 ss - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	1.328	2902.984	986.394	99.9	100.0	0.05	
2	21.404	0.569	0.048	0.0	0.0	0.18	
3	22.360	2.943	0.230	0.1	0.0	0.19	
	Total	2906.496	986.673	100.0	100.0		

ALX 528 (ALX526)
140°C
He
18 psi

Compound 12:

Racemic:

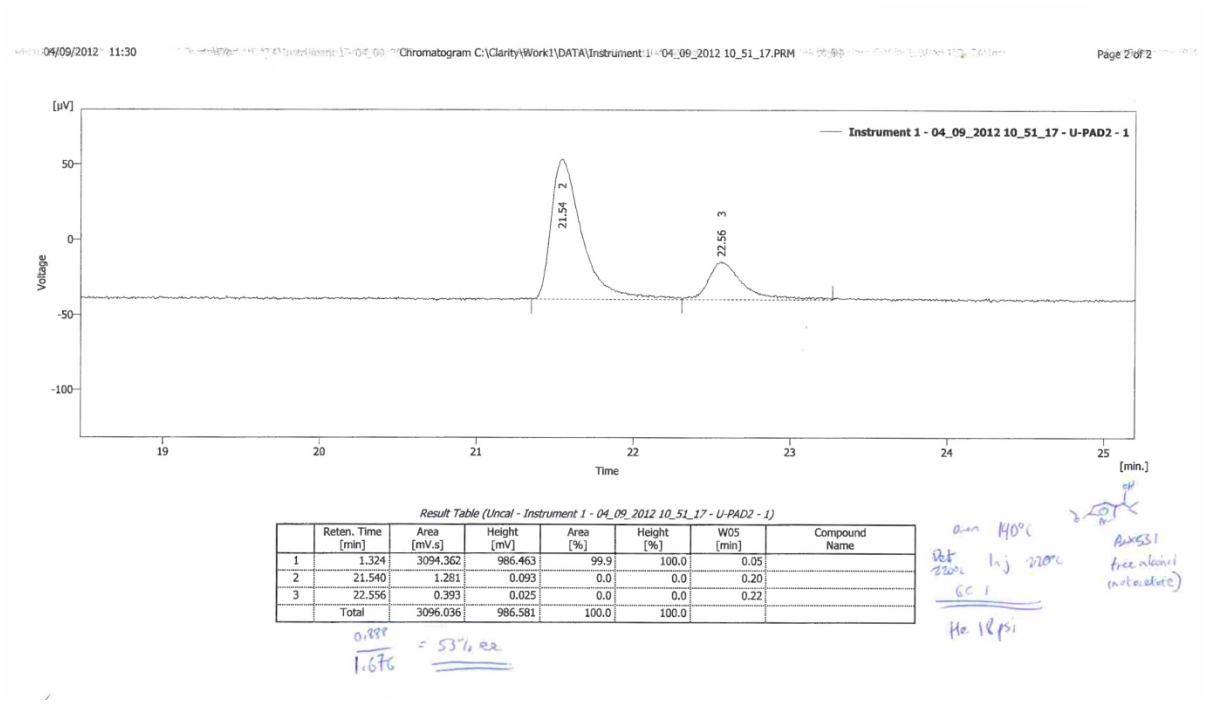


Result Table (Uncal - Instrument 1 - 04_09_2012 10_26_35 - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	1.320	2967.323	986.455	99.9	100.0	0.05	
2	21.572	1.090	0.080	0.0	0.0	0.20	
3	22.528	1.095	0.076	0.0	0.0	0.21	
	Total	2969.508	986.611	100.0	100.0		

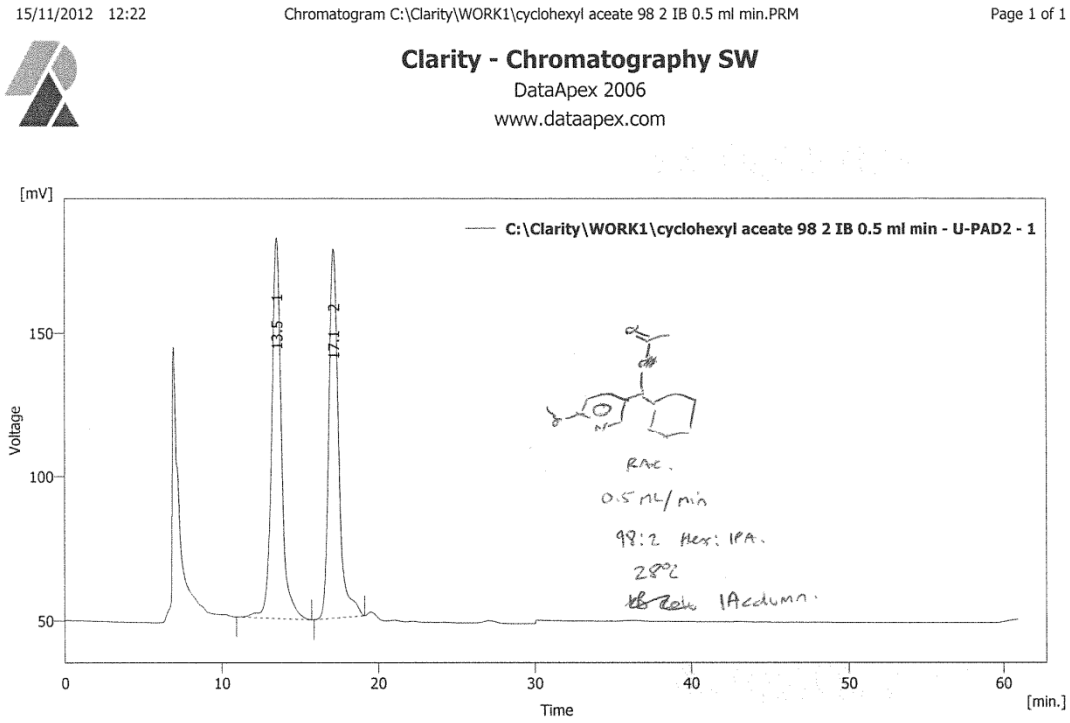
Rac st for (free alcohol)
GC1
start 220°C
inj 220°C

(R)-product, 53% ee



Compound 13

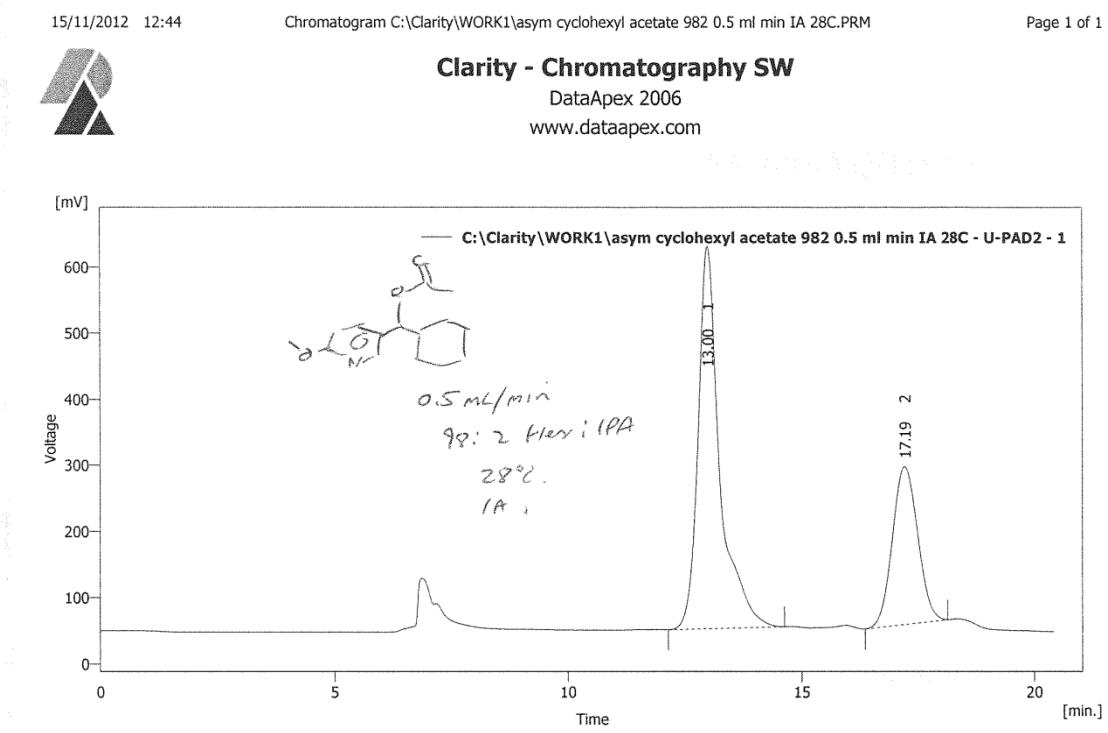
racemic:



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	13.516	5720.937	132.321	50.8	50.8	0.61	
2	17.144	5540.240	128.312	49.2	49.2	0.62	
	Total	11261.176	260.632	100.0	100.0		

(R)-product, 35 % ee:



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		

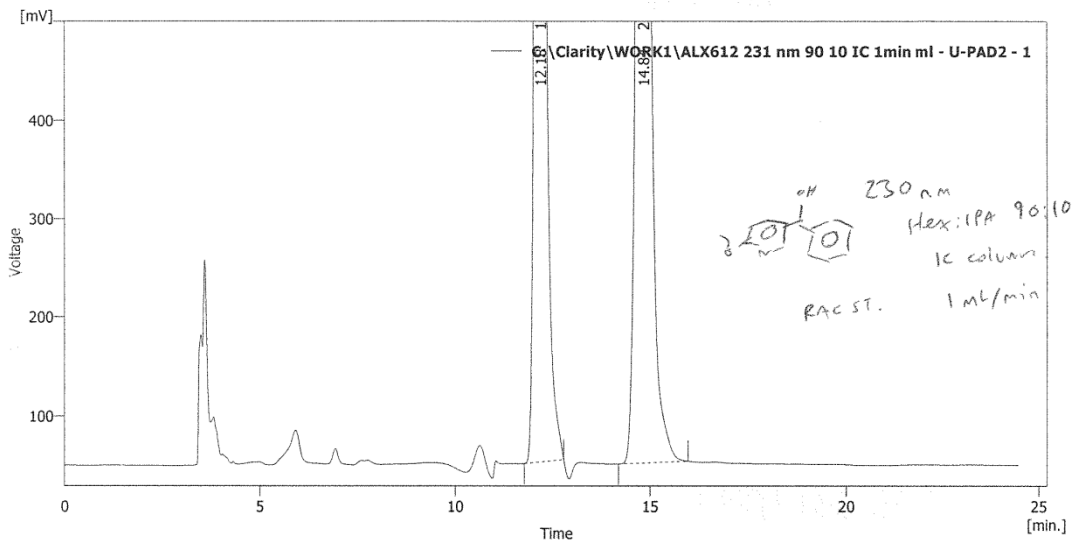
Compound 14

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)

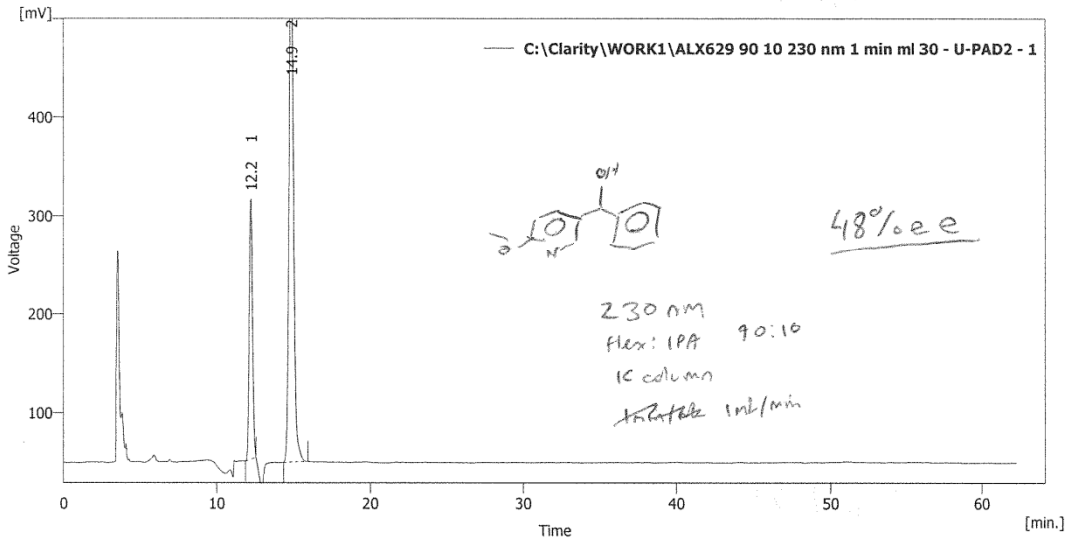
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	12.184	22901.444	1104.474	46.3	51.1	0.32	
2	14.836	26613.840	1055.027	53.7	48.9	0.40	
	Total	49515.284	2159.501	100.0	100.0		

Of 48% ee:

Clarity - Chromatography SW

DataApex 2006

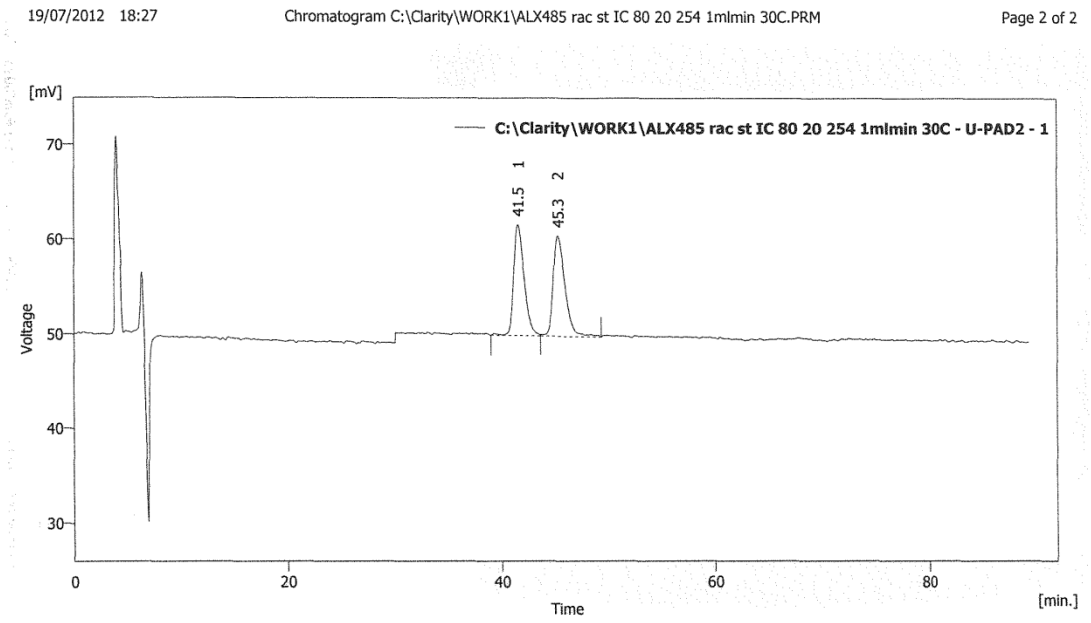
www.dataapex.com



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		

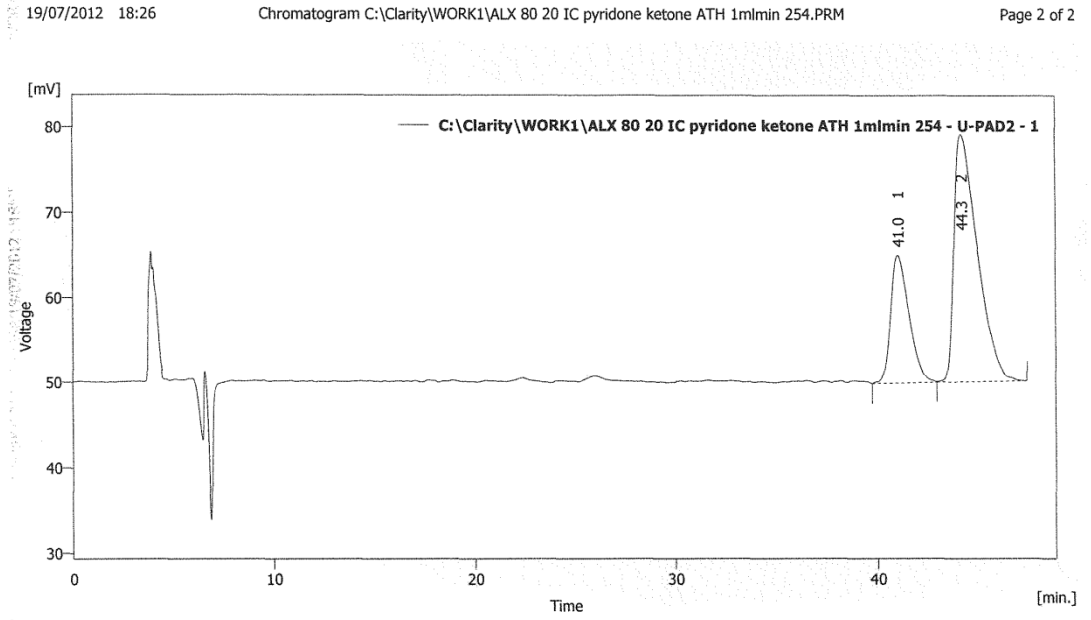
Compound 15 racemic



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**:

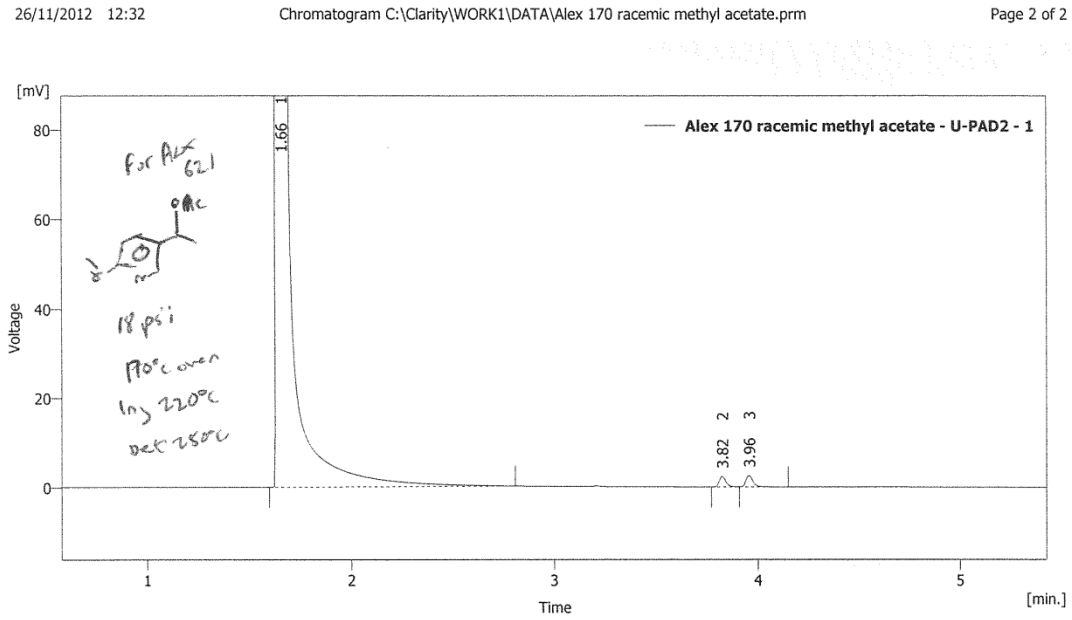


Result Table (Uncal - C:\Clarity\WORK1\ALX 80 20 IC pyridone ketone ATH 1mlmin 254 - U-PAD2 - 1)

	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):

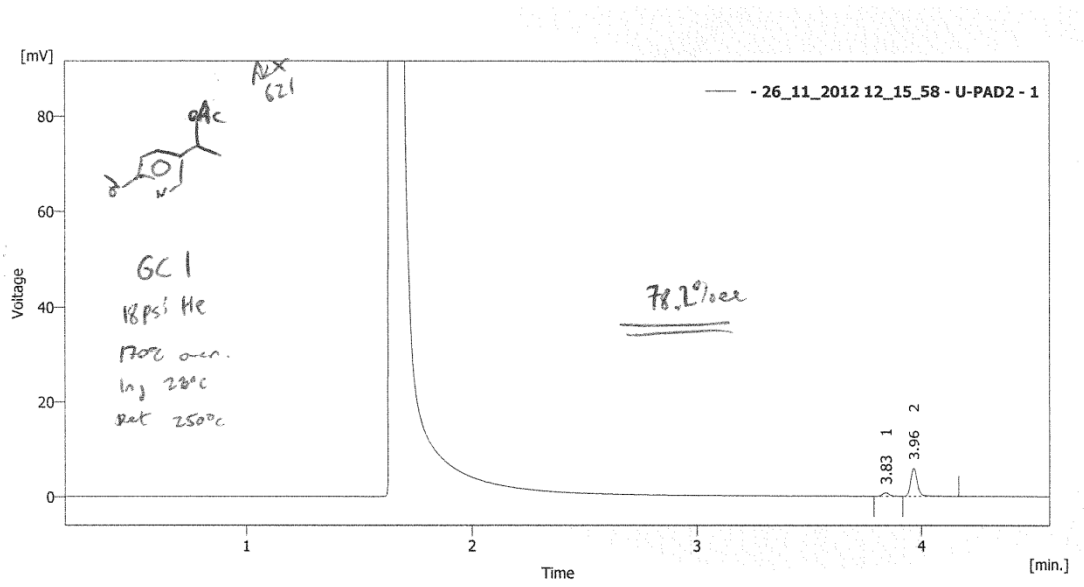
Racemic standard:



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**:

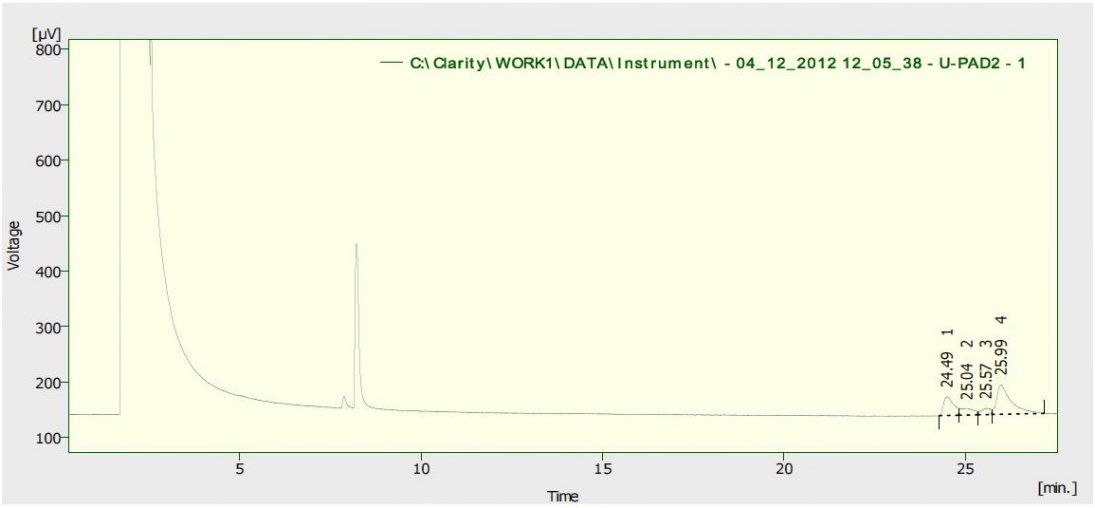


Result Table (Uncal - - 26_11_2012 12_15_58 - U-PAD2 - 1)

	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 PtO_2 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.

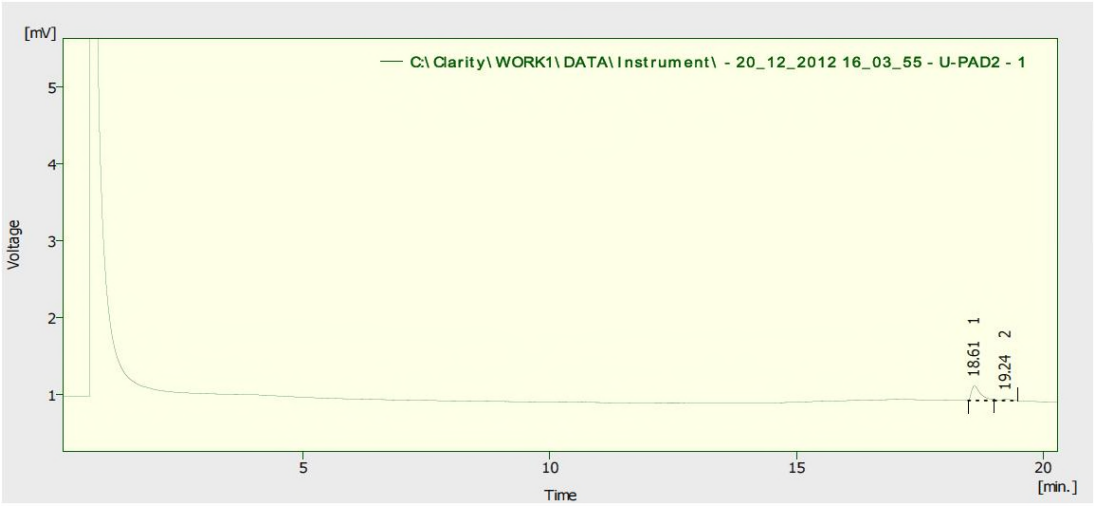


	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	24.492	0.652	0.034	24.6	30.8	0.34
2	25.044	0.310	0.012	11.7	10.6	0.52
3	25.572	0.213	0.012	8.0	10.5	0.33
4	25.988	1.479	0.053	55.7	48.1	0.37
	Total	2.654	0.111	100.0	100.0	

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

*D1-**16a**, 78 % ee.*

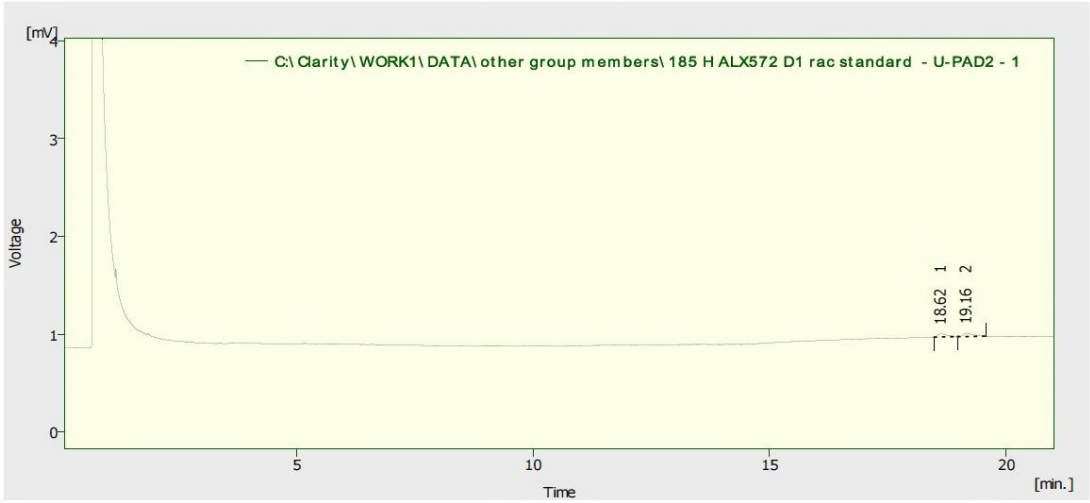
This GC trace was obtained from a chromatographically separated sample of D1-**16a**. Different GC conditions (to those in GC trace 1) were required for adequate separation. The racemic standard for this run is shown in GC trace 3. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 µm, 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	

*(±)-(D1)-**16a** (racemic standard).*

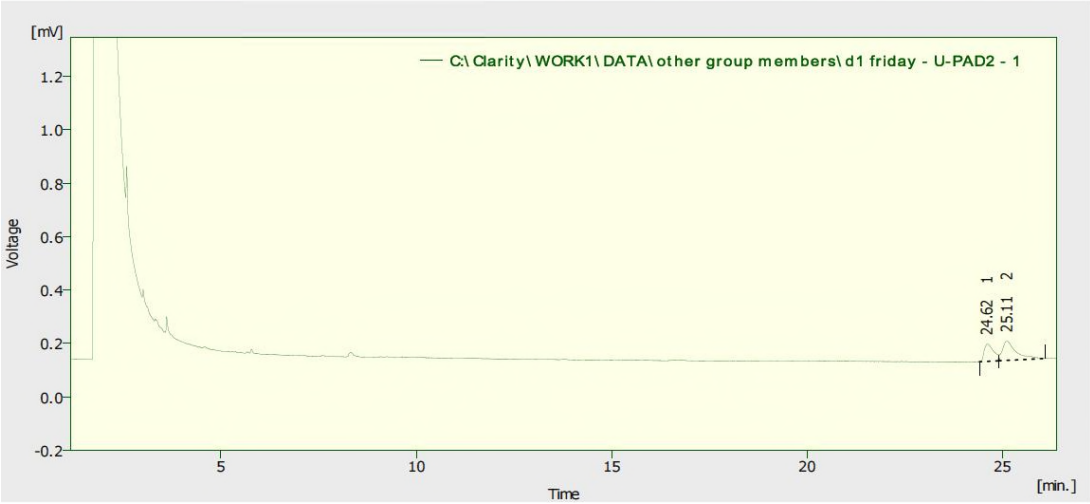
This GC trace of (D1)- **16a** was used as a racemic standard for GC trace 2: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 µm, gas: H, T = 185 °C, P = 18 psi H, det = 250 °C, inj = 220 °C, (*S*,*R*) isomer 18.64 min., (*R*,*S*) isomer 19.16 min.).



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	18.624	0.489	0.034	49.0	50.4	0.23
2	19.164	0.509	0.034	51.0	49.6	0.24
	Total	0.998	0.068	100.0	100.0	

*(±)-D1-**16a** (in reference to GC 1).*

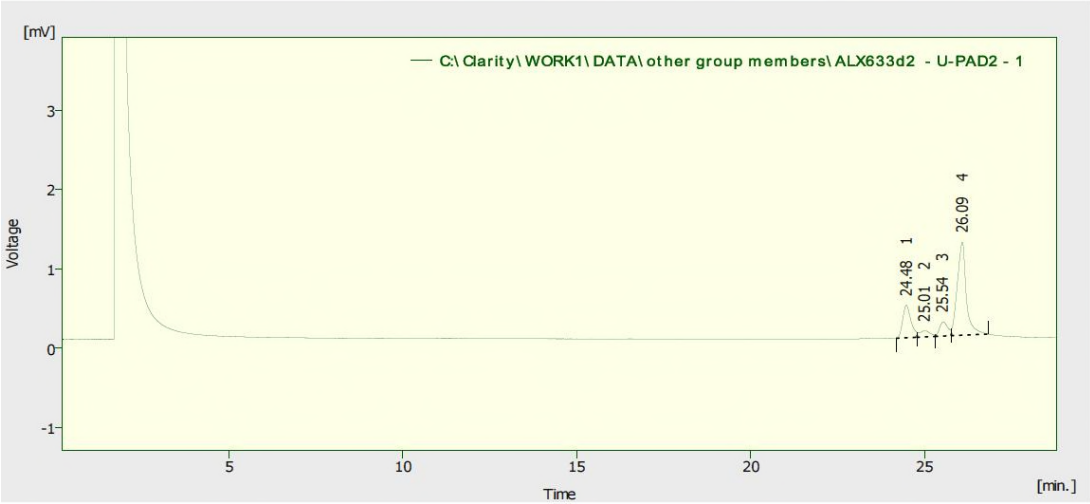
This GC trace of racemic (D1)-**16a** was run at the same conditions as GC trace 1 to enable comparison. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 µm, gas: He, T = 200 °C, P = 18 psi He, det = 250 °C, inj = 220 °C, (*S*,*R*) isomer 24.62 min., (*R*,*S*) isomer 25.11 min.).



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	24.616	1.089	0.065	37.9	47.0	0.30
2	25.112	1.784	0.073	62.1	53.0	0.33
	Total	2.874	0.138	100.0	100.0	

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

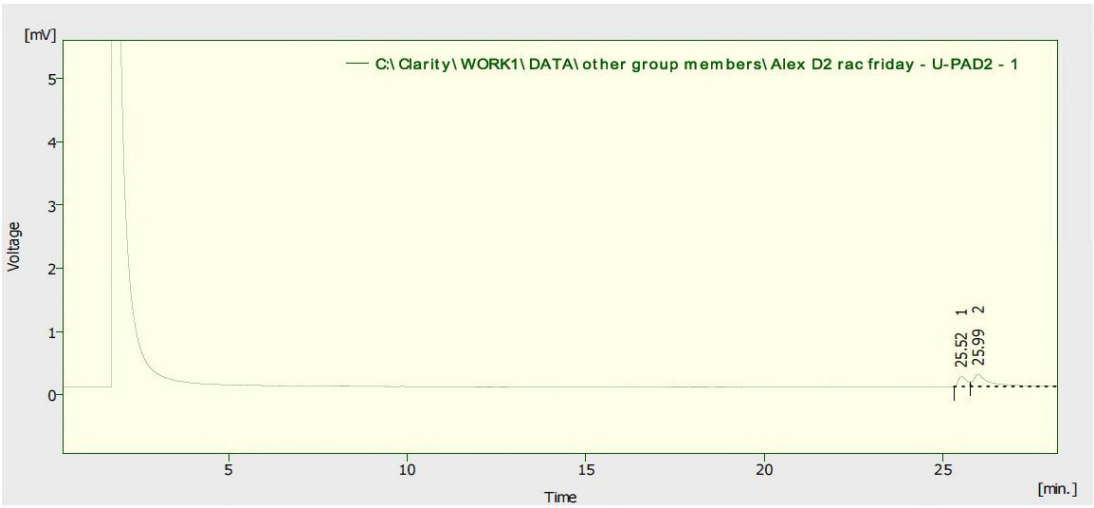
This GC trace was obtained from a chromatographically enriched sample of D2-**16b** (72 % D2). The racemic standard is shown in GC trace 6. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 µm, gas: H, T = 200 °C, P = 18 psi He, det = 250 °C, inj = 220 °C, (*S*,*R*) isomer 24.48 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: (±)-D2-**16b**.*

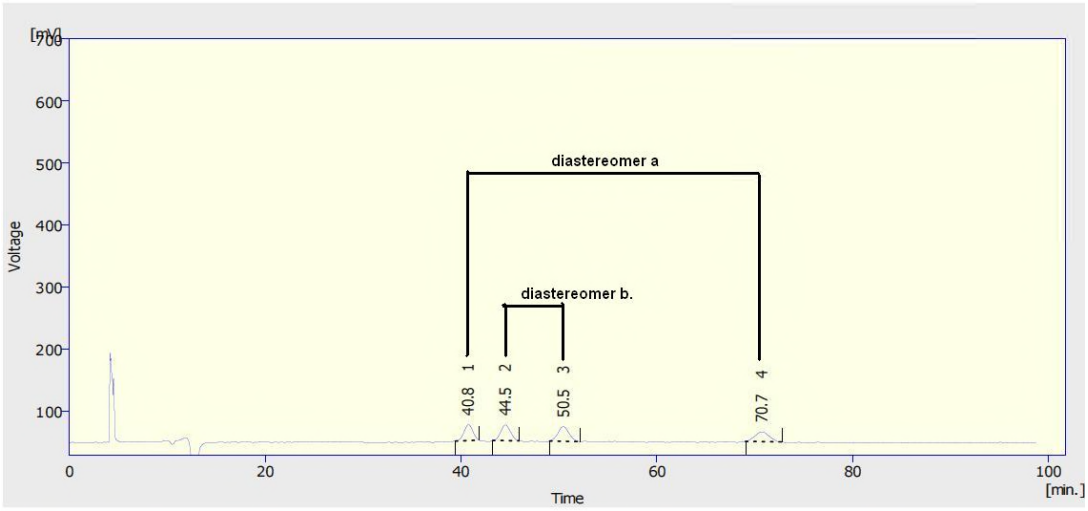
This GC trace of *(±)-D2-**16b*** was used as a racemic standard for GC trace 5. Chiral separation details: (CP – ChiraSil – DEX CB 25 m x 0.25 mm x 0.25 µm, gas: He, T = 200 °C, P = 18 psi He, det = 250 °C, inj = 220 °C, (*S*,*S*) isomer 25.52 min., (*R*,*R*) isomer 25.99 min.).



	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	

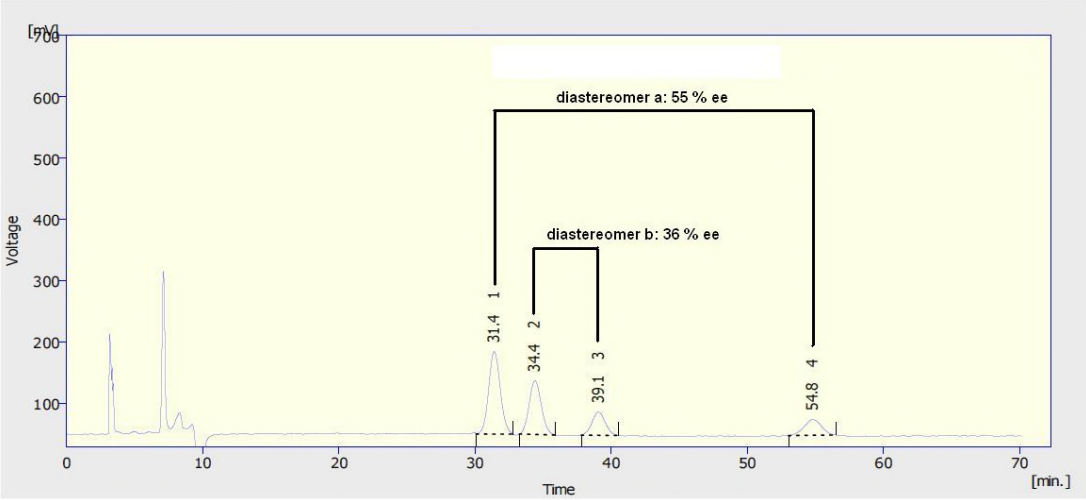
ATH of N-benzyl-5-acetyluracil **34***.*

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.



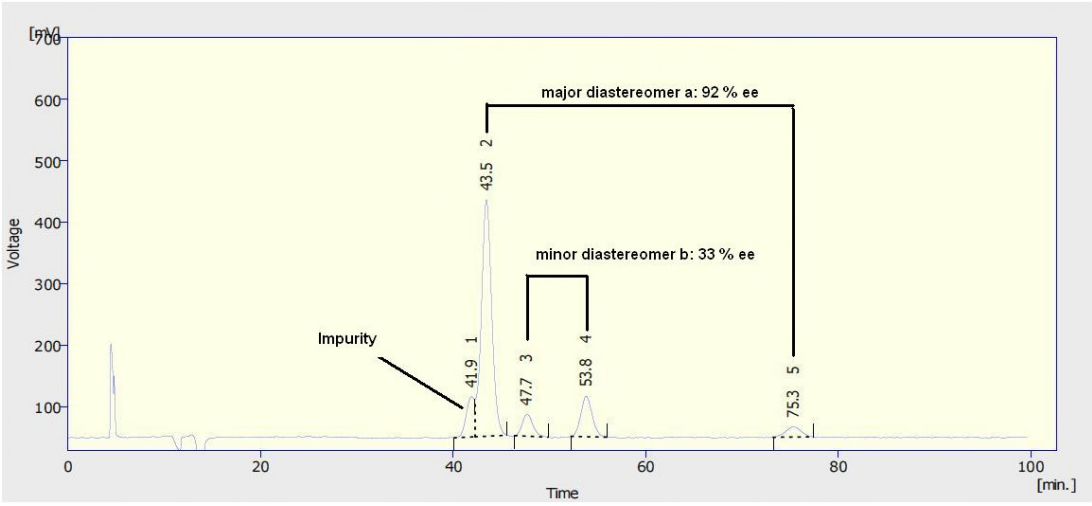
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	40.752	1615.491	25.718	23.6	28.3	1.00	diastereomer a; enantiomer a.
2	44.544	1758.386	25.366	25.7	28.0	1.12	diastereomer b; enantiomer a.
3	50.468	1889.580	23.823	27.6	26.3	1.22	diastereomer b; enantiomer b.
4	70.728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



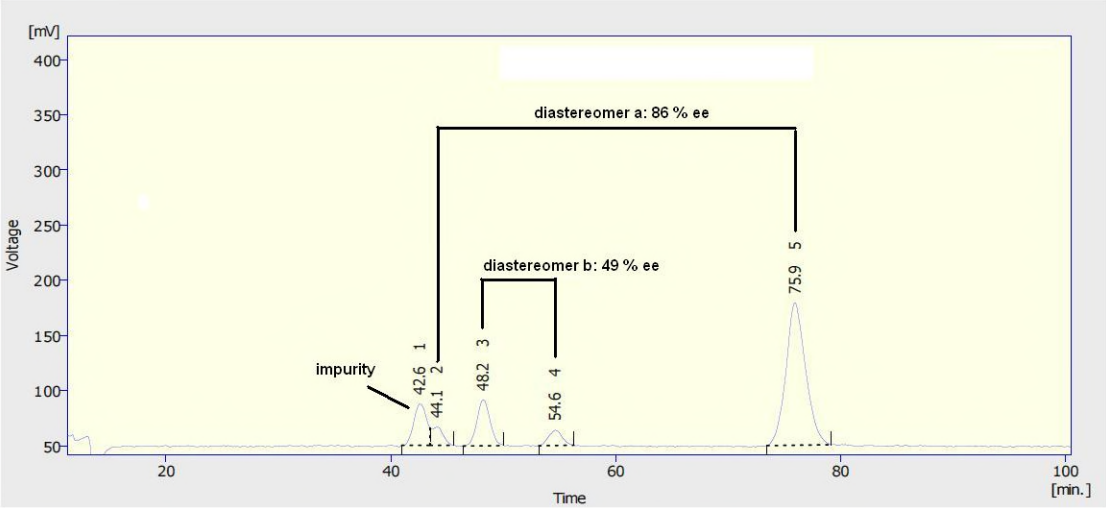
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	31.416	7997.752	134.399	43.6	46.9	0.92	diastereomer a; enantiomer a.
2	34.404	5467.036	87.831	29.8	30.7	0.97	diastereomer b; enantiomer a.
3	39.076	2577.286	37.902	14.1	13.2	1.06	diastereomer b; enantiomer b.
4	54.792	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*)-Ru*eth*TsDPEN, (*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		

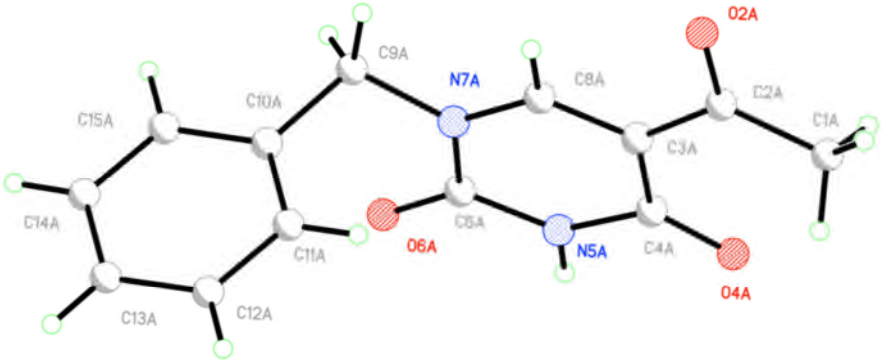
Reduction with (*S*,*S*)-Ru*eth*TsDPEN, (*S*,*S*)- **19**, (entry 5, Table 6); chiral separation details: (Chiralpak IA, 4.6 mm x 250 mm, hexane : IPA 90 : 10, 1 mL/min, T = 30 °C) **37a**: 86 % ee; **37b**: 49 % ee. **a** : **b** dr = 4:1.



	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		

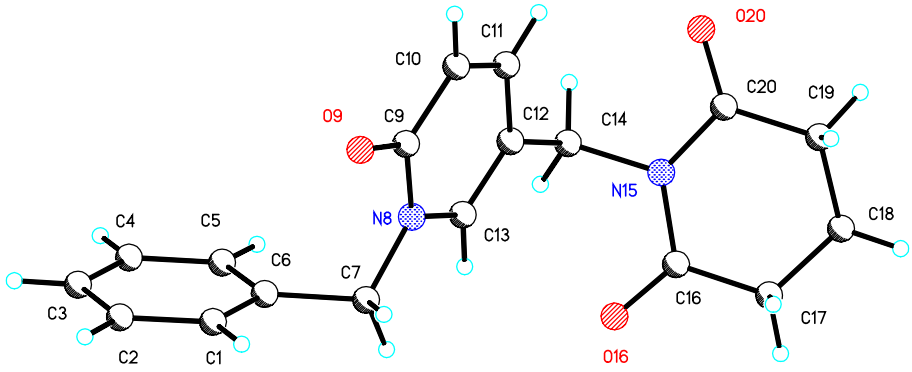
X-ray crystallographic structures.

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



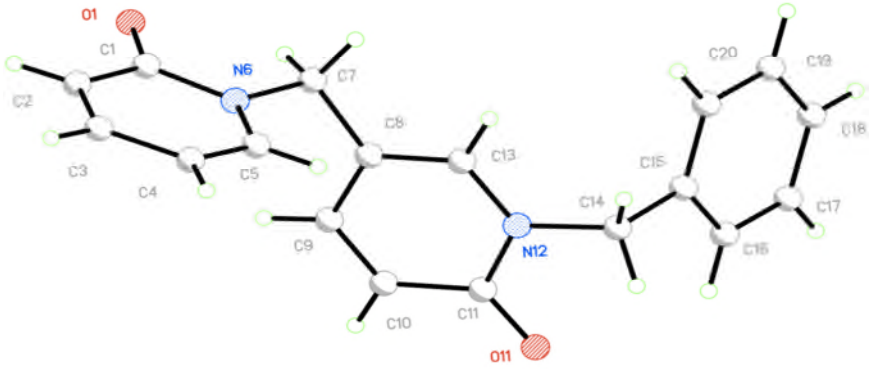
This structure was determined by the EPSRC Crystallographic Service. Crystallographic data for **34**: $C_{13}H_{12}N_2O_3$, M = 244.25, Monoclinic, space group P2(1)/n, a = 9.680(15), b = 23.71(3), c = 10.025(13) Å, alpha = 90 deg., beta = 97.78(3) deg., gamma = 90 deg., U = 2280(5) Å^3 (by least squares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

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



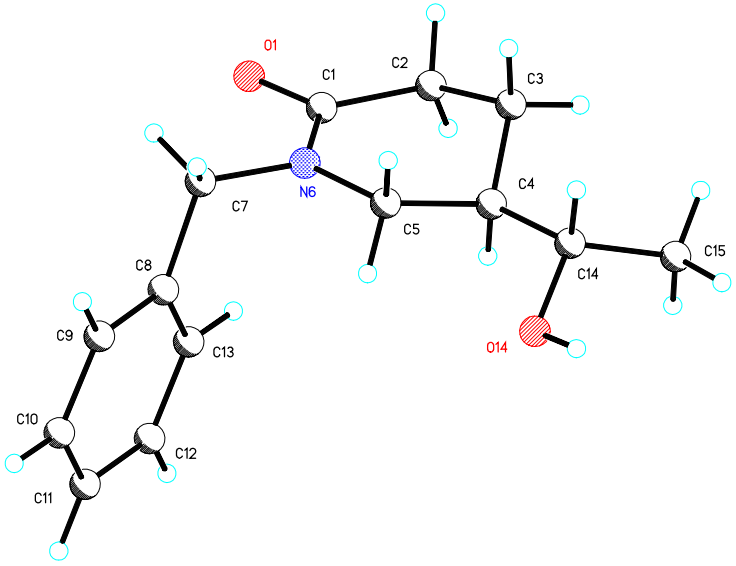
Crystallographic data for **3d**: $C_{18}H_{18}N_2O_3$, M = 310.34, Orthorhombic, space group Pbca, a = 8.60003(9), b = 17.41730(19), c = 20.1379(3)Å, α = 90 deg., β = 90 deg., γ = 90 deg., U = 3016.45(6) 3 Å (by least squares refinement on 9775 reflection positions), T =100(2)K, lambda = 1.54184 Å, Z = 8, D(cal) = 1.367 Mg/m^3, F(000) = 1312. mv(MoK-alpha) = 0.766 mm^{-1}. Crystal character: colourless block. Crystal dimensions 0.40 x 0.40 x 0.28 mm, 15826 reflections measured, 2892 unique [R(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) A^3 (by least squares refinement on 2682 reflection positions), T =150(2)K, lambda = 1.54184 Å, Z = 4, D(cal) = 1.342 Mg/m^3, F(000) = 616. mv (MoK-alpha) = 0.714 mm^{-1}. Crystal character:colourless plate. Crystal dimensions 0.20 x 0.20 x 0.01 mm. 5296 reflections measured, 2543 unique [R(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) $Å^3$ (by least squares refinement on 5741 reflection positions), T =150(2)K, lambda = 1.54184 Å, Z = 4, D(cal) = 1.205 Mg/m^3, F(000) = 504. Mv (MoK-alpha) = 0.638 mm^{-1}. Crystal character: colourless needle. Crystal dimensions 0.50 x 0.01 x 0.01 mm, 10079 reflections measured, 2146 unique [R(int) = 0.0250].