

## Supporting Information for:

# Strategy for the Enantioselective Synthesis of trans-2,4-Disubstituted Piperidines: Application to the CCR3 Antagonist IS811

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**General.** NMR spectra were obtained at 25 °C in CDCl<sub>3</sub> unless otherwise indicated at a field strength for <sup>1</sup>H spectra of 400.1 (compounds **2-6a**) or 300 MHz and for <sup>13</sup>C spectra of 100.6 (compounds **2-6a**) or 75 MHz. Coupling constants (*J*) are given in Hertz. Flash chromatography was performed on 220-400 mesh silica (E. Merck) following the standard procedure.<sup>1</sup> (*R*)-Epichlorohydrin (**1**) was purchased in kilogram quantities from Rhodia-Chirex and used as received. Anhydrous tetrahydrofuran and acetonitrile were used as received. Glassware was oven-dried overnight and flushed with dry nitrogen while still hot. Melting points were determined by differential scanning calorimetry (dsc).

### **Synthetic Details**

**(*R*)-1,2-Epoxy-4-cyanobutane, 2.** A flask was charged with (*R*)-epichlorohydrin (36 mL, 460 mmol), 120 mL of acetonitrile and 330 mL of tetrahydrofuran under nitrogen. The solution was cooled to -78 °C and 2.5M n-butyllithium (184 mL, 460 mmol) was added dropwise over 90 min during which time the solution remained homogeneous. The mixture was allowed to warm to room temperature overnight and was then re-cooled to 0 °C. Saturated aqueous ammonium chloride (50 mL) was added over 1 min followed by sufficient water to redissolve any undissolved material. The organic phase was separated, concentrated at reduced pressure, and filtered through a plug of silica gel using 1:1 ethyl acetate/heptane. Removal of solvent at reduced pressure afforded 40.42 g of substantially pure **2**. However, we elected to distill this material (40-45 °C, 0.5 torr). This process was accompanied by some decomposition but afforded pure **2** (28 g, 63%) as a pale yellow

oil.  $^1\text{H}$  NMR:  $\delta$  1.79 (m, 1H), 2.04 (m, 1H), 2.53 (m, 2H), 2.60 (m, 1H), 2.82 (m, 1H), 3.02 (m, 1H).  $^{13}\text{C}$  NMR:  $\delta$  14.0, 28.5, 47.0, 50.4, 119.3. Anal. Calcd for  $\text{C}_5\text{H}_7\text{NO}$ : C, 61.83; H, 7.27; N, 14.42. Found: C, 61.70; H, 7.13; N, 14.11. The enantiomeric excess of the product was shown to be 99% by chiral capillary column gas chromatography by comparison with a sample of authentic racemate prepared by the literature procedure.<sup>2</sup>

**(R)-5-Hydroxy-7-cyanohept-2-ynoic acid ethyl ester, 3.** A solution of 1-hexyne (4.1 g, 50 mmol) in dry THF (50 mL) was cooled to 0 °C and a 1.6 M solution of n-butyllithium in hexanes (31 mL, 50 mmol) was added dropwise. The mixture was cooled to -78 °C whereupon a solution of ethyl propiolate (4.9 g, 50 mmol) in dry THF (10 mL) was added dropwise. The solution was stirred an additional 15 min at -78 °C after which a solution of epoxynitrile **2** (4.9 g, 50 mmol) in dry THF (10 mL) was added. Finally boron trifluoride diethyl etherate (6.3 mL, 50 mmol) was slowly added and the solution was stirred for a further 2 h at -78 °C. The reaction was quenched with half-saturated aqueous ammonium chloride (50 mL) and was allowed to warm to room temperature. The organic phase was separated and washed with water (50 mL). The solvent was removed at reduced pressure and the residue was dried overnight *in vacuo* to remove a small amount of unreacted starting material. This afforded **3** (8.51 g, 87%) as a straw-colored oil of sufficient purity for the subsequent transformation.  $^1\text{H}$  NMR:  $\delta$  1.32 (t, J = 7, 3H), 1.83 (m, 1H), 1.94 (m, 1H), 2.57 (superimposed m, 4H), 3.29 (s, 1H), 4.00 (m, 1H), 4.24 (m, 2H).  $^{13}\text{C}$  NMR:  $\delta$  13.9, 14.2, 27.8, 31.7, 62.4, 69.6, 75.5, 85.1, 119.7, 153.9. Anal. Calcd for  $\text{C}_{10}\text{H}_{13}\text{NO}_3$ : C, 61.53; H, 6.71; N, 7.18. Found: 61.23; H, 6.85; N, 7.34.

**Preparation of 4-Fluorobenzylmagnesium Chloride Solution.** The competing formation of 4,4'-difluorobibenzyl apparently proceeds via a (second order)  $S_N2$  type mechanism. For this reason an excess of activated magnesium was used, and the final concentration of the Grignard reagent was kept  $< 1.0M$ . p-Fluorobenzyl chloride gave a higher yield of Grignard reagent compared with the p-fluorobenzyl bromide. A convenient method to assay the Grignard solution is to add a few drops of benzene- $d_6$  as a deuterium lock and run the  $^{19}F$  NMR of the solution. Chemical shifts are  $\delta$  118.9 (for the bibenzyl), 119.9 (for p-fluorotoluene resulting from trace hydrolysis), and 132.2 (for the Grignard reagent.) Using this technique it was shown that, under otherwise identical conditions, bibenzyl formation was inversely proportional to the excess of magnesium turnings employed. The following procedure reproducibly afforded the Grignard with  $<10\%$  bibenzyl formation. A flask was charged with magnesium turnings (58 g, 2.4 mol) which were activated by dry stirring as recommended by Brown and co-workers.<sup>3</sup> Anhydrous tetrahydrofuran (475 mL) was added after which 4-fluorobenzyl chloride (57.83 g, 400.0 mmol) was added dropwise over 70 minutes. Cooling was applied as needed to keep the temperature at or below 30 °C. Following the addition, the mixture was held at room temperature for 1 h.

**(R)-5,6-dihydro-6-(2-cyanoethyl)-4-(4-fluorobenzyl)-2H-pyran-2-one, 4.** A flask was charged with copper (I) cyanide (35.9 g, 401 mmol) and lithium chloride (34.0 g, 802 mmol). Anhydrous tetrahydrofuran (225 mL) was added dropwise at such a rate that the temperature does not exceed 40 °C. The mixture was stirred for 1 h at room temperature. The thin slurry was then cooled to -30 °C at which point some additional solids separated from solution. The p-fluorobenzylmagnesium chloride solution generated as above was

transferred to a septum-covered addition funnel and was added dropwise over 1 h while maintaining the temperature between -30 and -20 °C. The Grignard vessel was rinsed with 15 mL additional THF which was then added via the addition funnel. After 10 min, ynol **3** (26.1 g, 133 mmol) was added dropwise via syringe. The flask was slowly warmed to -5 °C and maintained at that temperature overnight. At that point TLC (1:1 ethyl acetate/heptane) indicated complete consumption of starting material. Methanol (5.0 mL) was added all at once and the reaction was stirred for 1 h at 0 °C then warmed to room temperature. After stirring an additional 2 h, 120 mL of 2N HCl was added. The organic layer was separated and washed with 75 mL of brine. Removal of solvent at reduced pressure affords a thick oil which was subjected to flash chromatography (1:1 ethyl acetate/heptane). The product containing cuts were crystallized from hot isopropanol to afford **4** (24.2 g, 70%) as large off-white needles, m.p. 67.4 °C,  $[\alpha]_D^{25}$  -66.2 ( $c$  = 0.98, chloroform). A sample of the racemic lactone melted at 57.2 °C.  $^1\text{H}$  NMR:  $\delta$  1.99 (m, 2H), 2.22 (m, 2H), 2.60 (m, 2H), 3.52 (s, 2H), 4.43 (m, 2H), 5.79 (s, 1H), 7.01 (m, 2H), 7.12 (m, 2H).  $^{13}\text{C}$  NMR:  $\delta$  13.4, 30.7, 32.7, 42.2, 75.1, 116.1 (d,  $J$  = 21), 117.0, 119.0, 130.8, 131.4, 159.0, 162.2 (d,  $J$  = 245), 164.2. Anal. Calcd for  $\text{C}_{15}\text{H}_{14}\text{FNO}_2$ : C, 69.49; H, 5.44; N, 5.40. Found: C, 69.36; H, 5.49; N, 5.55. The enantiomeric excess was determined to be >99% by supercritical fluid chromatography by comparison with a sample of the authentic racemate prepared analogously.

**(4*S*,6*R*)-tetrahydro-6-(2-cyanoethyl)-4-(4-fluorobenzyl)-2*H*-pyran-2-one, 5.** A 500 mL Fisher-Porter tube was charged with dehydrolactone **4** (9.58 g, 36.9 mmol), 5% platinum on alumina catalyst (7.5 g, -325 mesh, Aldrich #311324), and tetrahydrofuran (100 mL). The tube was flushed with hydrogen and the mixture was stirred under 50 psi

H<sub>2</sub> for 24 h at room temperature. The reaction mixture was filtered through a short bed of Sorbamol 420FF and the solvent was removed at reduced pressure. Crystallization of the crude product from hot isopropanol afforded **5** (7.87 g, 82%) as large off-white needles. m.p. 75.6 °C,  $[\alpha]_D^{25}$  -44.4 (c = 1.01, chloroform). <sup>1</sup>H NMR:  $\delta$  1.29 (m, 1H), 1.91 (m, 3H), 2.11-2.33 (superimposed m, 2H), 2.52-2.71 (superimposed m, 5H), 4.36 (m, 1H), 7.01 (m, 2H), 7.14 (m, 2H). <sup>13</sup>C NMR:  $\delta$  13.4, 32.1, 33.9, 34.6, 36.3, 41.8, 78.0, 115.9 (d, *J* = 21), 119.3, 130.8, 134.0, 162.1 (d, *J* = 245), 170.4. Anal. Calcd for C<sub>15</sub>H<sub>16</sub>FNO<sub>2</sub>: C, 68.95; H, 6.17; N, 7.27. Found: C, 69.01; H, 6.32; N, 7.10. The diastereomer ratio for the product was shown to be >99:1 by HPLC analysis.

**(4*R*,6*R*)-6-(4-Fluorobenzyl)-4,8-dihydroxyoctanenitrile, 6a.** A flask was charged with lactone **5** (5.0 g, 15.3 mmol) and 40 mL of *tert*-butyl alcohol and 10 mL of methanol. To this stirred slurry was added sodium borohydride (1.00 g, 26.4 mmol) and the mixture was gradually warmed to 30 °C. The reaction was complete in 3 h by HPLC and was then quenched with 1N HCl (with cooling until foaming subsided). The mixture was extracted twice with 35 mL of ethyl acetate and the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>. The solution was concentrated and the residue was triturated with 1:1 ether/ethyl acetate and filtered through a short pad of Celite. Drying overnight at 0.1 torr afforded (4*R*,6*R*)-6-(4-Fluorobenzyl)-4,8-dihydroxyoctanenitrile (4.39 g, 86%) as a clear, colorless oil.  $[\alpha]_D^{25}$  + 1.98 (c = 0.00987, EtOAc). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.13-1.45 (m, 4H), 1.63 (m, 1H), 1.83 (m, 1H), 2.36-2.48 (m, 4H), 2.62 (dd, *J* = 5.8 and 13.5 Hz, 1H), 3.36-3.42 (m, 2H), 3.55 (m, 1H), 4.28 (t, *J* = 5.1 Hz, 1H), 4.67 (d, *J* = 5.9 Hz, 1H), 7.07 (t, *J* = 8.2 Hz, 2H), 7.18 (dd, *J* = 5.1 and 8.2 Hz, 2H). <sup>13</sup>C NMR:  $\delta$  13.8, 33.5, 33.6, 36.6, 40.6, 41.0, 60.0, 68.5, 115.2 (d, *J* = 21 Hz), 120.4, 130.8 (d, *J* = 7.4 Hz),

136.2 (d,  $J = 3.1$  Hz), 161.5 (d,  $J = 243.8$  Hz).  $^{19}\text{F}$  NMR ( $\text{CHCl}_3$ ):  $\delta$  -117.6. HRMS-ESI-LCT  $m/z$  266.1556 [ $\text{M}+\text{H}^+$ ; calcd. for  $\text{C}_{15}\text{H}_{21}\text{FNO}_2$ : 266.1566].

**(4*R*,6*R*)-6-(4-Fluorobenzyl)-4,8-bis(methanesulfonyloxy)octanenitrile, 6b.** A flask was charged with (4*R*,6*R*)-6-(4-fluorobenzyl)-4,8-dihydroxyoctanenitrile (4.36 g, 16.4 mmol) and 45 mL of dichloromethane. The mixture was cooled to -20 °C and triethylamine (5.80 mL, 41.5 mmol) was added. Methanesulfonyl chloride (4.22 g, 36.8 mmol) was added dropwise over 1 h maintaining the temperature at < -15 °C. The mixture was warmed to 0 °C over the course of 30 min and was then added to 50 mL of ice cooled 1N HCl. The organic layer was separated and the aqueous layer was further extracted with 2 x 25 mL of dichloromethane. The combined organic layers were washed with 50 mL of saturated sodium hydrogen carbonate, dried ( $\text{MgSO}_4$ ), filtered and concentrated to afford **6** (6.79 g, 98%) as a light amber oil.  $[\alpha]_{\text{D}}^{25} + 1.55$  ( $c = 0.0102$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.46-2.06 (m, 6H), 2.42-2.59 (m, 4H), 2.73 (dd,  $J = 5.4$  and 13.4 Hz, 1H), 3.22 (s, 3H), 3.30 (s, 3H), 4.19 (m, 3H), 4.79 (m, 1H), 7.09 (t,  $J = 9.0$  Hz, 2H), 7.23 (dd,  $J = 5.8$  and 8.4 Hz, 2H).  $^{13}\text{C}$  NMR:  $\delta$  13.5, 30.8, 33.0, 33.1, 37.6, 38.7, 38.8, 39.7, 67.8, 77.9, 115.7 (d,  $J = 21$  Hz), 119.2, 130.8 (d,  $J = 7.9$  Hz), 135.0 (d,  $J = 3.3$  Hz), 161.8 (d,  $J = 244.7$  Hz).  $^{19}\text{F}$  NMR:  $\delta$  -116.8. HRMS-ESI-LCT  $m/z$  439.1381 [ $\text{M}+\text{NH}_4^+$ ; calcd. for  $\text{C}_{17}\text{H}_{28}\text{FN}_2\text{O}_6\text{S}_2$ : 439.1373].

**(2*R*,4*R*)-1-propyl-2-(2-cyanoethyl)-4-(4-fluorobenzyl)piperidine, 7a.** A flask containing bis(mesylate) **6b** (6.79 g, 16.1 mmol) was cooled to 0 °C and 20 mL of propylamine was added. The mixture was stirred overnight and was then concentrated at reduced pressure. The residue was taken up in acetonitrile and was filtered to remove the propylammonium methanesulfonate co-product. The filtrate was then concentrated to

afford (2*R*,4*R*)-1-propyl-2-(2-cyanoethyl)-4-(4-fluorobenzyl)piperidine ( 4.064 g, 100%) as a clear orange oil.  $[\alpha]_{\text{D}}^{25}$  -1.16 ( $c = 0.00694$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  0.81 (t,  $J = 7.3$  Hz, 3H), 1.12-1.38 (m, 5H), 1.53 (m, 1H), 1.71-1.83 (m, 2H), 2.33-2.48 (m, 9H), 2.71 (m, 1H), 7.05 (t,  $J = 9.0$  Hz, 2H), 7.16 (dd,  $J = 6.0$  and 8.7 Hz, 2H).  $^{13}\text{C}$  NMR:  $\delta$  12.0, 14.7, 21.7, 23.9, 28.9, 32.1, 33.4, 42.7, 45.9, 55.9, 56.0, 115.6 (d,  $J = 21$  Hz), 120.4, 130.5 (d,  $J = 7.9$  Hz), 136.0 (d,  $J = 3.1$  Hz), 161.5 (d,  $J = 243.5$  Hz).  $^{19}\text{F}$  NMR:  $\delta$  -118.0. HRMS-ESI-LTQFT  $m/z$  289.2067  $[\text{M}+\text{H}^+]$ ; calcd. for  $\text{C}_{18}\text{H}_{26}\text{FN}_2$ : 289.2074].

**(2*R*,4*R*)-1-propyl-2-(3-aminopropyl)-4-(4-fluorobenzyl)piperidine, 7b.** A flask was charged with (2*R*,4*R*)-1-propyl-2-(2-cyanoethyl)-4-(4-fluorobenzyl)piperidine (0.61 g, 2.12 mmol) and 15 mL of anhydrous tetrahydrofuran. The solution was cooled to 0 °C after which 1.0M lithium aluminum hydride in tetrahydrofuran (2.5 mL, 2.5 mmol) was added dropwise over 5 min. The mixture was allowed to slowly warm to room temperature over 12 h. When HPLC indicated complete consumption of starting material, the flask was re-cooled to 0 °C after which the following additions were made via syringe in order: 100  $\mu\text{L}$  water, 100  $\mu\text{L}$  15% sodium hydroxide, and 300  $\mu\text{L}$  water. The resultant slurry was filtered through Celite and the flask and Celite were further washed with 2 x 15 mL THF. The product was extracted into 1N HCl and then released by increasing the pH to 13 and extracted into 2 x 25 mL of toluene. Removal of the solvent afforded **7b** (0.58 g, 94%) as clear pale yellow oil.  $[\alpha]_{\text{D}}^{25}$  +7.12 ( $c = 0.00534$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  0.80 (t,  $J = 7.2$  Hz, 3H), 1.04-1.42 (m, 7H), 1.70 (m, 1H), 2.00-2.48 (m, 11H), 2.61 (m, 1H), 3.26 (bs, 2H), 7.06 (t,  $J = 9.0$  Hz, 2H), 7.15 (dd,  $J = 6.0$  and 8.4 Hz, 2H).  $^{13}\text{C}$  NMR:  $\delta$  12.4, 21.4, 30.5, 30.9, 31.6, 32.7, 33.9, 42.5,



42.7, 46.6, 56.5, 56.9, 115.0 (d,  $J = 21$  Hz), 130.6 (d,  $J = 7.9$  Hz), 136.5 (d,  $J = 3.3$  Hz), 161.5 (d,  $J = 243.3$  Hz).  $^{19}\text{F}$  NMR:  $\delta$  -118.0. HRMS-ESI-LTQFT  $m/z$  293.2387

[ $\text{M}+\text{H}^+$ ; calcd. for  $\text{M} = \text{C}_{18}\text{H}_{30}\text{FN}_2$ : 293.2388].

**N-(3-acetylphenyl)-N'-[3-(2*R*,4*S*)-4-(4-fluorophenyl)methyl]-1-propyl-2-**

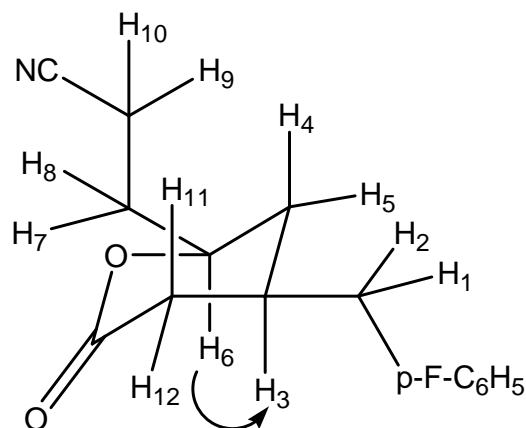
**piperidinyl]propyl urea, IS811.** Diamine **7b** (256 mg, 1.00 mmol) was dissolved in 10 mL of dichloromethane. A solution of 3-acetylphenyl isocyanate (161 mg, 1.00 mmol) in 5 mL of dichloromethane was added at such a rate that the temperature does not exceed 28 °C. (The reaction was run as a titration with careful HPLC monitoring of the endpoint as indicated by complete disappearance of **7b**.) Removal of the solvent and drying overnight at 0.1 torr afforded substantially pure **8** (448 mg, 96 % yield) as a white foam.

An analytical sample was further purified by flash chromatography (0-3%

methanol/ $\text{CH}_2\text{Cl}_2/\text{NH}_4\text{OH}$ , lower layer).  $[\alpha]_{\text{D}}^{25} + 7.44$  ( $c = 0.0146$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.79 (t,  $J = 7.1$  Hz, 3H), 1.09-1.42 (m, 7H), 1.71 (m, 1H), 2.31-2.51 (m, 9H), 2.66 (m, 1H), 3.02 (m, 2H), 6.13 (t,  $J = 5.5$  Hz, 1H), 7.02 (t,  $J = 9.0$  Hz, 2H), 7.15 (dd,  $J = 5.9$  and 8.5 Hz, 2H), 7.34 (t,  $J = 7.8$  Hz, 1H), 7.47 (d,  $J = 7.8$  Hz, 1H), 7.59 (t,  $J = 8.1$  Hz, 1H), 8.00 (s, 1H), 8.60 (s, 1H).  $^{13}\text{C}$  NMR:  $\delta$  12.2, 21.2, 23.5, 27.0, 27.9, 30.0, 32.7, 33.4, 40.6, 42.3, 46.4, 56.2, 57.0, 115.1 (d,  $J = 21.1$  Hz), 118.5, 122.8, 124.3, 129.5, 130.5 (d,  $J = 7.9$  Hz), 136.4, 137.7, 140.3, 156.2, 161.4 (d,  $J = 243.3$  Hz), 199.1.

$^{19}\text{F}$  NMR:  $\delta$  -118.1. HRMS-ESI-LTQFT  $m/z$  454.2857 [ $\text{M}+\text{H}^+$ ; calcd for  $\text{C}_{27}\text{H}_{37}\text{FN}_3\text{O}_2$ : 454.2864]. The purity of the product was shown to be >98 area% by supercritical fluid chromatography under conditions where all four potential product stereoisomers were well separated.

**Structure Assignment of 5 via nOe.** Based on the interpretation of the COSY spectra, the following critical  $^1\text{H}$  chemical shifts can be established:



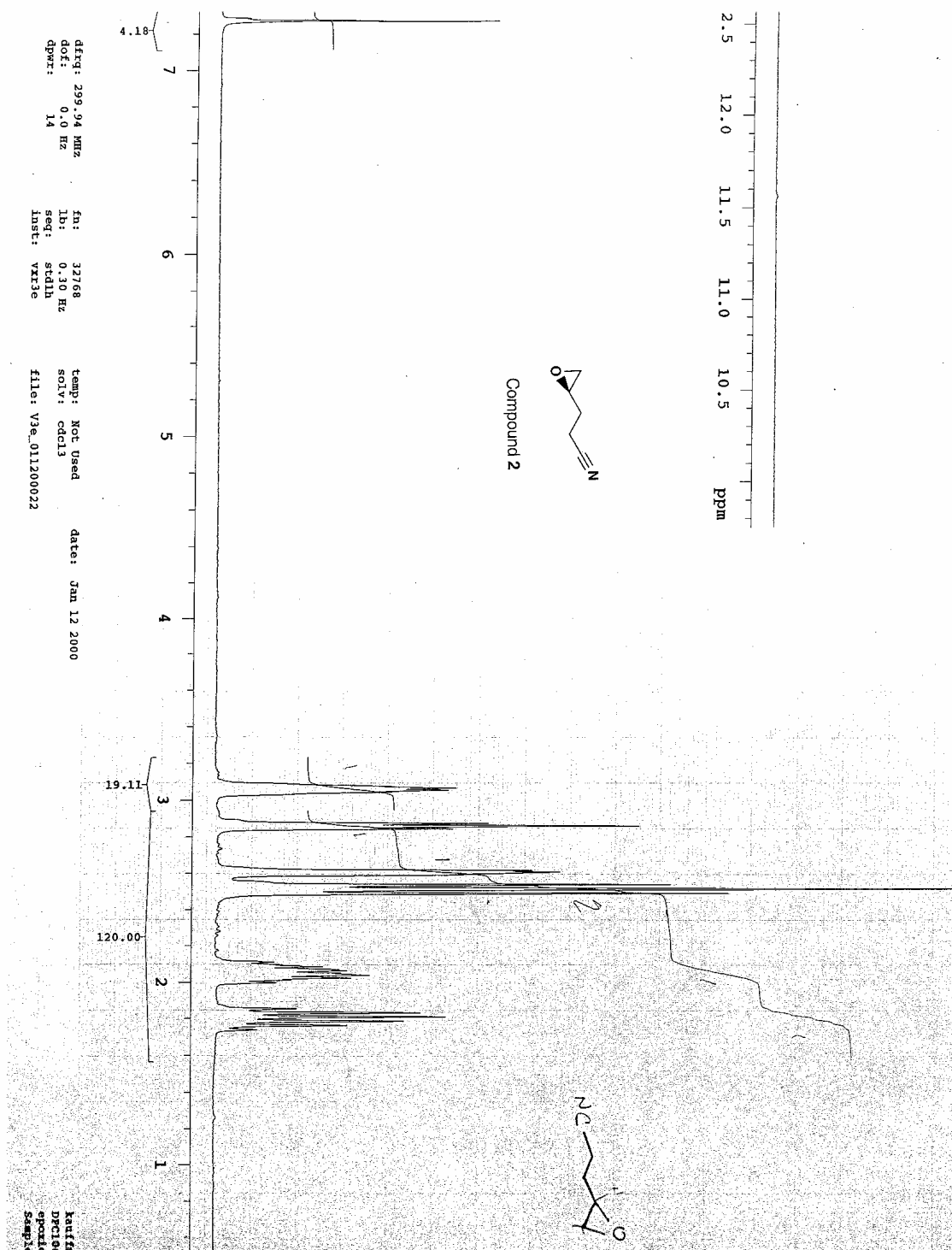
$\delta$  4.36 (m,  $\text{H}_6$ ) coupled to  $\delta$  1.91 (m,  $\text{H}_7$ ,  $\text{H}_8$  and either  $\text{H}_4$  or  $\text{H}_5$ )  
 $\delta$  4.36 (m,  $\text{H}_6$ ) coupled to  $\delta$  1.29 (m, 1H, either  $\text{H}_4$  or  $\text{H}_5$ )  
 $\delta$  2.23 (m,  $\text{H}_3$ ) coupled to  $\delta$  2.52-2.71 (m,  $\text{H}_1$ ,  $\text{H}_2$ )  
 $\delta$  2.23 (m,  $\text{H}_3$ ) coupled to  $\delta$  1.91 (either  $\text{H}_4$  or  $\text{H}_5$ )  
 $\delta$  2.23 (m,  $\text{H}_3$ ) coupled to  $\delta$  1.29 (either  $\text{H}_4$  or  $\text{H}_5$ )  
 $\delta$  2.23 (m,  $\text{H}_3$ ) coupled to  $\delta$  2.21 (m, either  $\text{H}_{11}$  or  $\text{H}_{12}$ )  
 $\delta$  2.23 (m,  $\text{H}_3$ ) coupled to  $\delta$  2.52-2.71 (either  $\text{H}_{11}$  or  $\text{H}_{12}$ )  
 $\delta$  2.21 (m,  $\text{H}_{11}$  or  $\text{H}_{12}$ ) coupled to  $\delta$  1.29 (m, 1H, either  $\text{H}_4$  or  $\text{H}_5$ )

Irradiation of  $\delta$  4.36 establishes a nOe effect between:

$\delta$  4.36 ( $\text{H}_6$ ) and  $\delta$  2.5 (assigned as  $\text{H}_{12}$ )  
 $\delta$  4.36 ( $\text{H}_6$ ) and  $\delta$  2.23 (assigned as  $\text{H}_3$ )  
 $\delta$  4.36 ( $\text{H}_6$ ) and  $\delta$  1.91 (assigned as  $\text{H}_5$  and/or  $\text{H}_7/\text{H}_8$ )

### **References and Notes.**

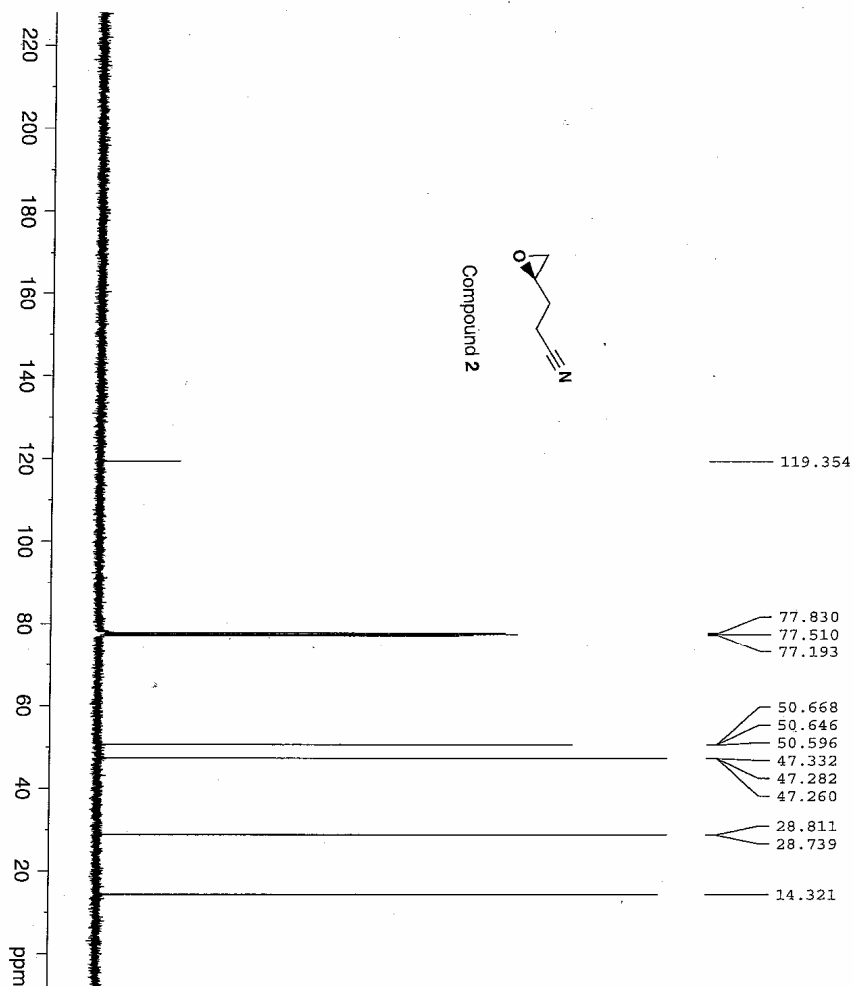
1. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
2. Hughes, S.; Griffiths, G.; Stirling, C. J. M. *J. Chem. Soc. Perkin Trans. 2* **1987**, 1253.
3. Baker, K. V.; Brown, J. M.; Hughes, N.; Skarnulis, A. J.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698.



## 4,5-epoxypentanitrile



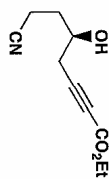
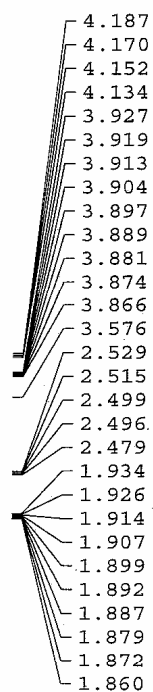
Compound 2



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SWH 34246.574 Hz  
FIDRES 1.045123 Hz  
AQ 0.4784774 sec  
RG 2048  
DW 14.600 usec  
DE 6.00 usec  
TE 295.2 K  
D1 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.50000000 sec  
MCREST 0.00000000 sec  
MCWPRK 0.01500000 sec

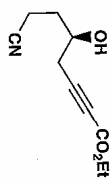
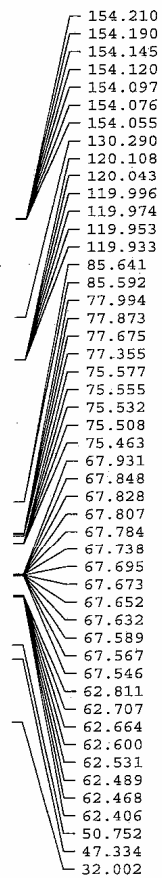
## Crude Ynoate



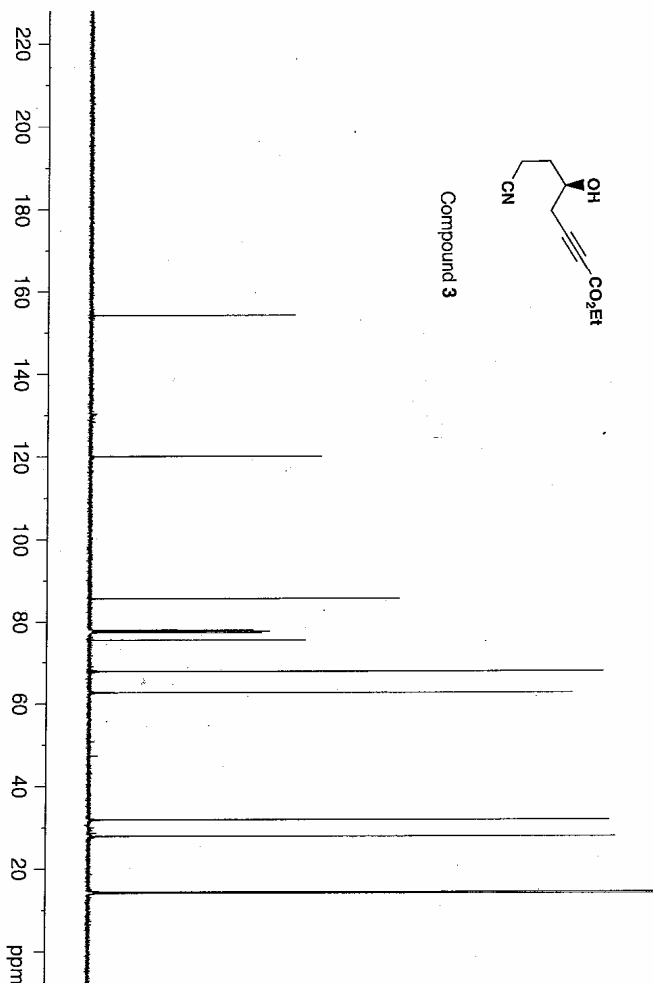
Compound 3



## Crude Ynoate

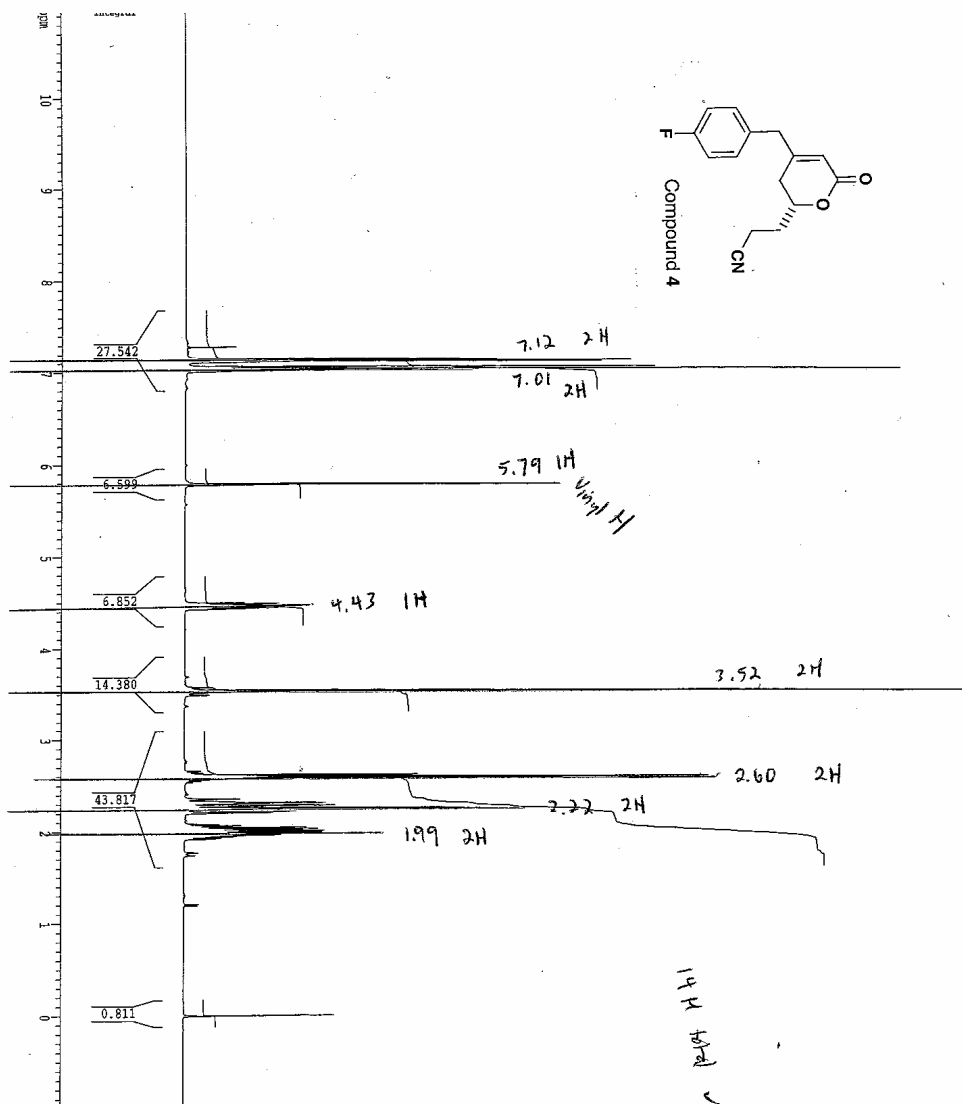
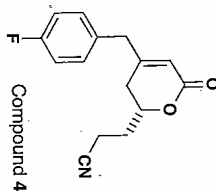


Compound 3



Current Data Parameters  
 NAME 62479-181  
 EXPNO 21  
 PROCNO 1  
 F2 - Acquisition Parameters  
 Date\_ 20060704  
 Time 7.23  
 INSTRUM spect  
 PROBHD 5 mm QNP 1H/13  
 PULPROG zgpg30  
 TD 32768  
 SOLVENT CDCl3  
 NS 256  
 DS 0  
 SWH 34246.574 Hz  
 FIDRES 1.045123 Hz  
 AQ 0.474774 sec  
 RG 1625.5  
 DW 14.600 usec  
 DE 6.00 usec  
 TE 294.2 K  
 D1 2.00000000 sec  
 d11 0.03000000 sec  
 DELTA 1.89999998 sec  
 MCWREST 0.00000000 se  
 MCWPRK 0.01500000 se  
 ===== CHANNEL f1 =====  
 NUC1 13C  
 P1 8.75 usec  
 PL1 -3.00 dB  
 SFO1 100.626268 MHz  
 ===== CHANNEL f2 =====  
 CPDPRG2 waltz16  
 NUC2 1H  
 PCPD2 100.00 usec  
 PL2 -2.25 dB  
 PL12 16.92 dB  
 PL13 18.00 dB  
 SFO2 400.1316005 MHz

Notebook/Page No.: 12195-107-1  
 Title: unsat'd lactone  
 PROTONLP CDCl3 u kauffings 13



Current Data Parameters  
 NAME 09262001-kauff  
 EXPNO 10  
 PROCNO 1

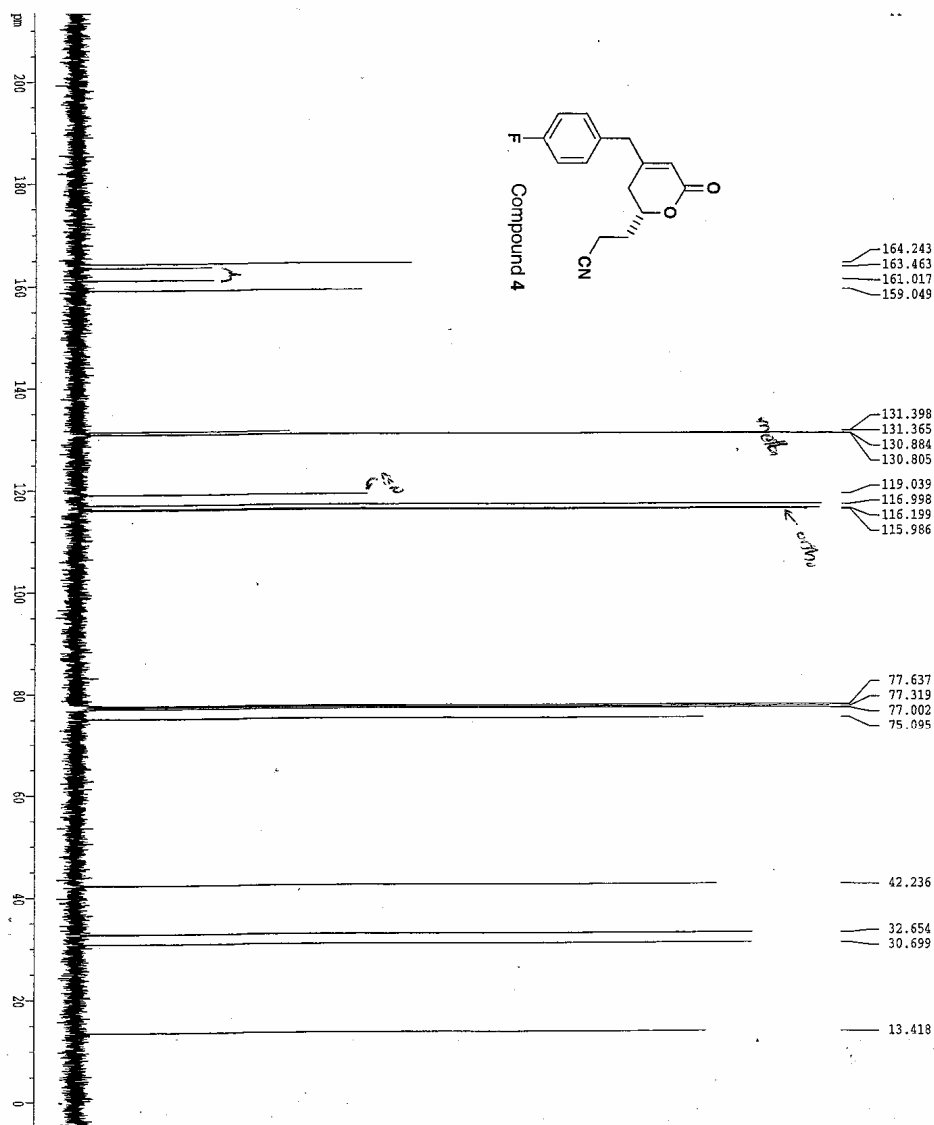
F2 - Acquisition Parameters  
 Date\_ 20010926  
 Time 14.02  
 INSTRUM spect  
 PROBHD 5 mm QNP 1H  
 PULPROG zgpg30  
 TD 32768  
 SOLVENT CDCl3  
 NS 16  
 DS 2  
 SWH 8278.146 Hz  
 FIDRES 0.252629 Hz  
 AQ 1.9792372 sec  
 RG 80.6  
 DN 60.400 usec  
 DE 6.00 usec  
 TE 300.0 K  
 D1 1.00000000 sec

===== CHANNEL f1 =====  
 NUC1 1H  
 P1 6.50 usec  
 PL1 -5.00 dB  
 SFO1 400.1224710 MHz

F2 - Processing parameters  
 SI 16384  
 SF 400.1259991 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.00

ID NMR Plot Parameters  
 CX 30.00 cm  
 FLIP 11.000 ppm  
 F1 4401.43 Hz  
 F2 -1.000 ppm  
 F2 -400.13 Hz  
 PPMCM 0.40000 ppm/cm  
 HZCM 160.05220 Hz/cm

Notebook/Page No.: 12195-107-1  
 Title: unsat'd Lactone  
 C13CPD128 CDCl3 u kaufings 13



```

Current Data Parameters
NAME      09262001-1enf
EXPNO     11
PROCNO    1

F2 - Acquisition Parameters
Date_     20010926
Time      14.10
INSTRUM   spect
PROBHD    5 mm QNP 1H
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         128
DS         2
SWH        25125.629 Hz
FIDRES     0.383387 Hz
AQ         1.3042164 sec
RG          16384
DW         19.900 usec
DE         6.00 usec
TE         300.0 K
D1         2.00000000 sec
d11        0.03000000 sec
d12        0.00002000 sec

===== CHANNEL f1 =====
NUC1       13C
P1         6.50 usec
PL         -6.00 dB
SFO1       100.627959 MHz

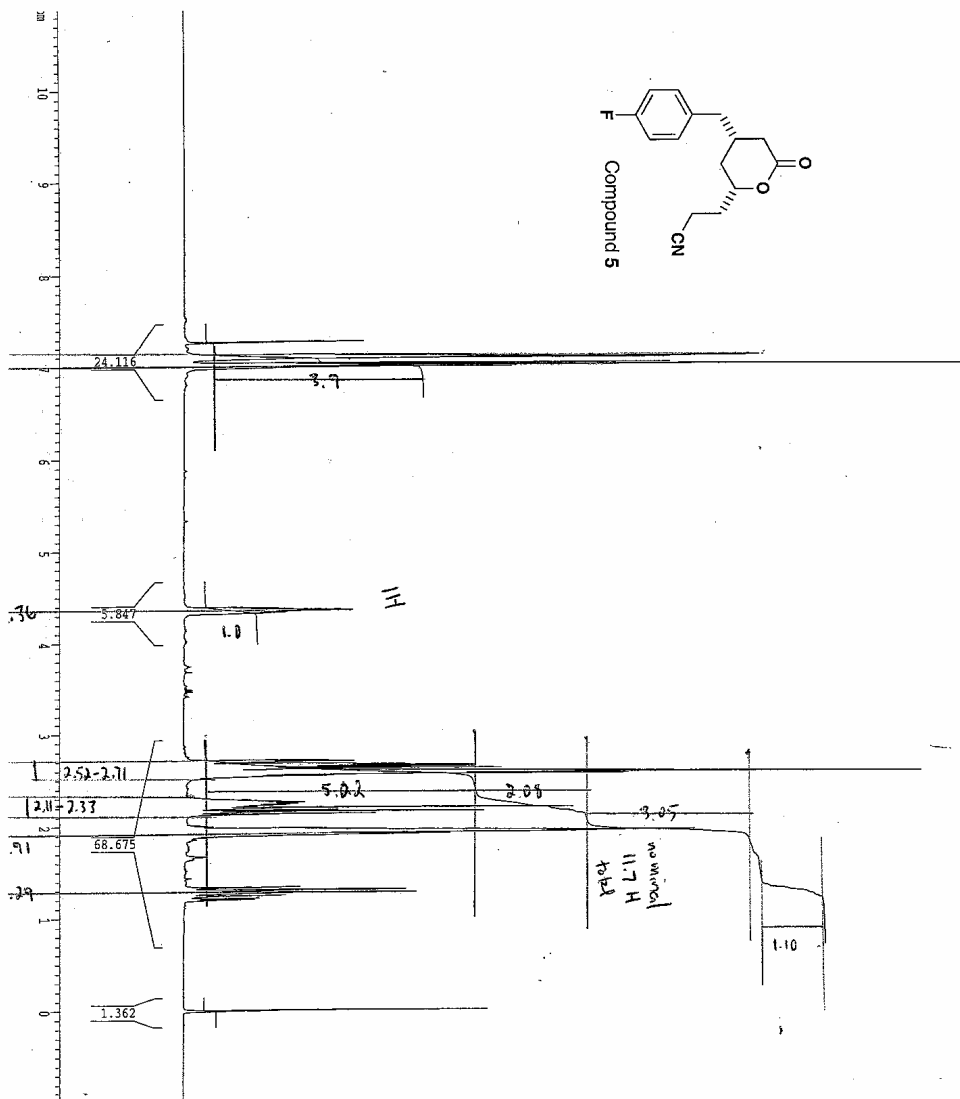
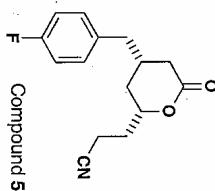
===== CHANNEL f2 =====
CPDPRG2    waltz16
NUC2       1H
PCPD2      100.00 usec
PL2        -5.00 dB
PL12       19.00 dB
PL13       19.00 dB
SFO2       400.1316005 MHz

F2 - Processing parameters
SI          32768
SF          100.6127491 MHz
WDW         RM
SSB         0
LB          1.00 Hz
GB          0
PC          1.40

1D NMR plot parameters
CX          30.00 cm
F1P         215.000 ppm
F1          21631.74 Hz
F2P         -5.000 ppm
F2          -503.06 Hz
PWCW        7.33333 ppm/cm
HZCW        737.82878 Hz/cm
  
```



Notebook/Page No.: 12972-73a  
 Title: lactone sat'd  
 PROTONMF CDC13 u kaufings 15



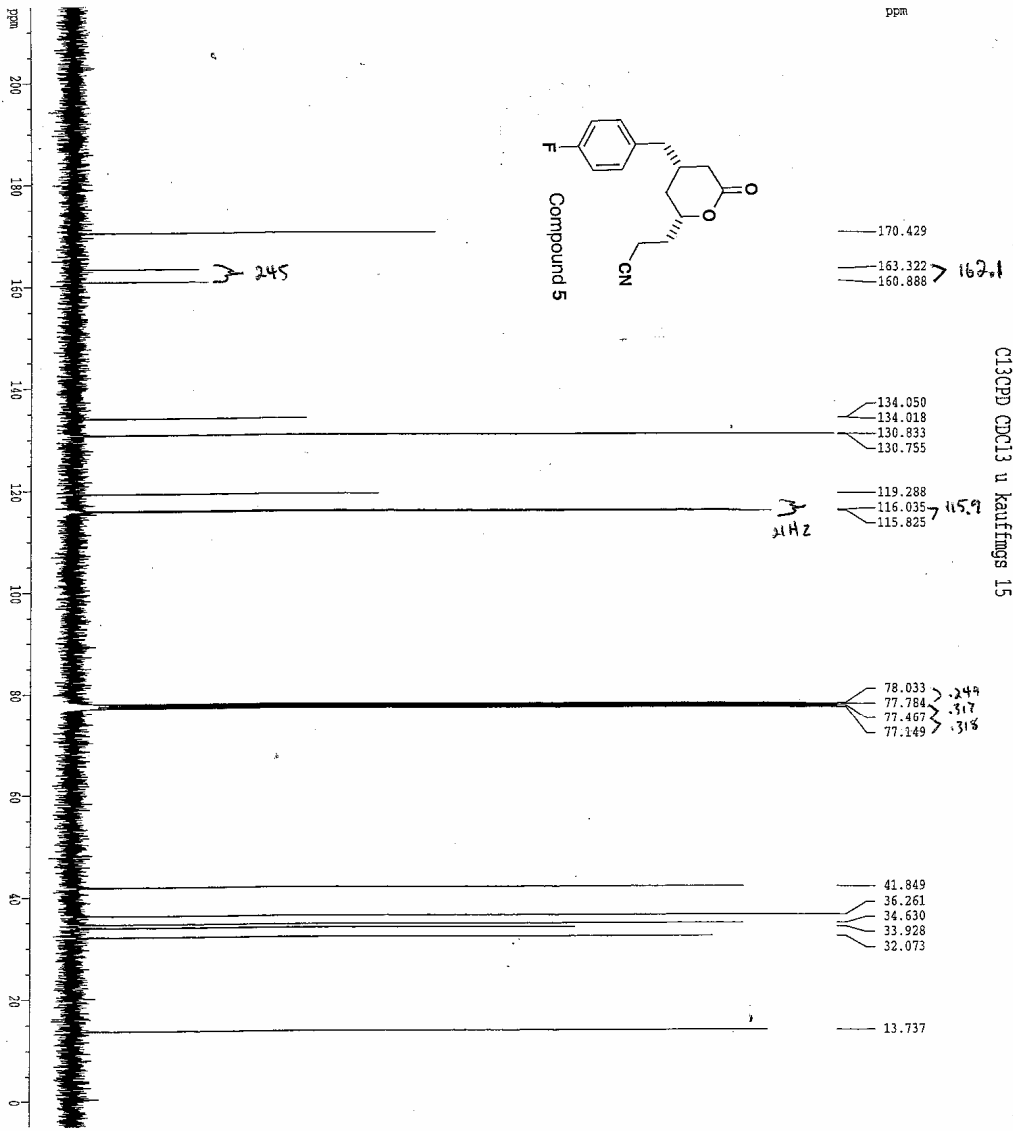
Current Data Parameters  
 NAME 1020200-kauf  
 EXPNO 10  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20010220  
 Time 12.59  
 INSTRUM spect  
 PROBP0 5 mm QNP 1H  
 PULPROG zgpg30  
 TD 32768  
 SOLVENT CDCl3  
 NS 16  
 DS 2  
 SWH 8278.146 Hz  
 FIDRES 0.255632 Hz  
 AQ 1.9792372 sec  
 RG 143.7  
 RW 60.400 usec  
 DE 6.00 usec  
 TE 300.0 K  
 D1 1.00000000 sec

===== CHANNEL f1 =====  
 NUC1 1H  
 P1 6.50 usec  
 PL1 -5.00 dB  
 SFO1 400.1324710 MHz

F2 - Processing parameters  
 SI 16384  
 SF 400.130048 MHz  
 WDR 2M  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.00

F2 - NMR plot parameters  
 CA 30.09 cm  
 V1P 11.000 ppm  
 V1 4401.43 Hz  
 F2P -1.000 ppm  
 F2 -400.13 Hz  
 PPMCK 0.40000 ppm/cm  
 HZCM 160.05200 Hz/cm



Notebook/Page No.: 12972-73C  
Title: lactone sat'd  
C13CPD CDCl3 u kaufmings 15

Current Data Parameters  
NAME 10202000-kaufi  
EXPNO 12  
PROCNO 1  
F2 - Acquisition Parameters  
Date\_ 20001020  
Time 20.01  
INSTRUM spect  
PROBHD 5 mm QNP 1H  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 1024  
DS 4  
SWH 25125.629 Hz  
FIDRES 0.38187 Hz  
AQ 1.3042164 sec  
RG 16384  
TB 19.900 usec  
TE 300.0 K  
D1 2.0000000 sec  
d11 0.0300000 sec  
d12 0.0002000 sec

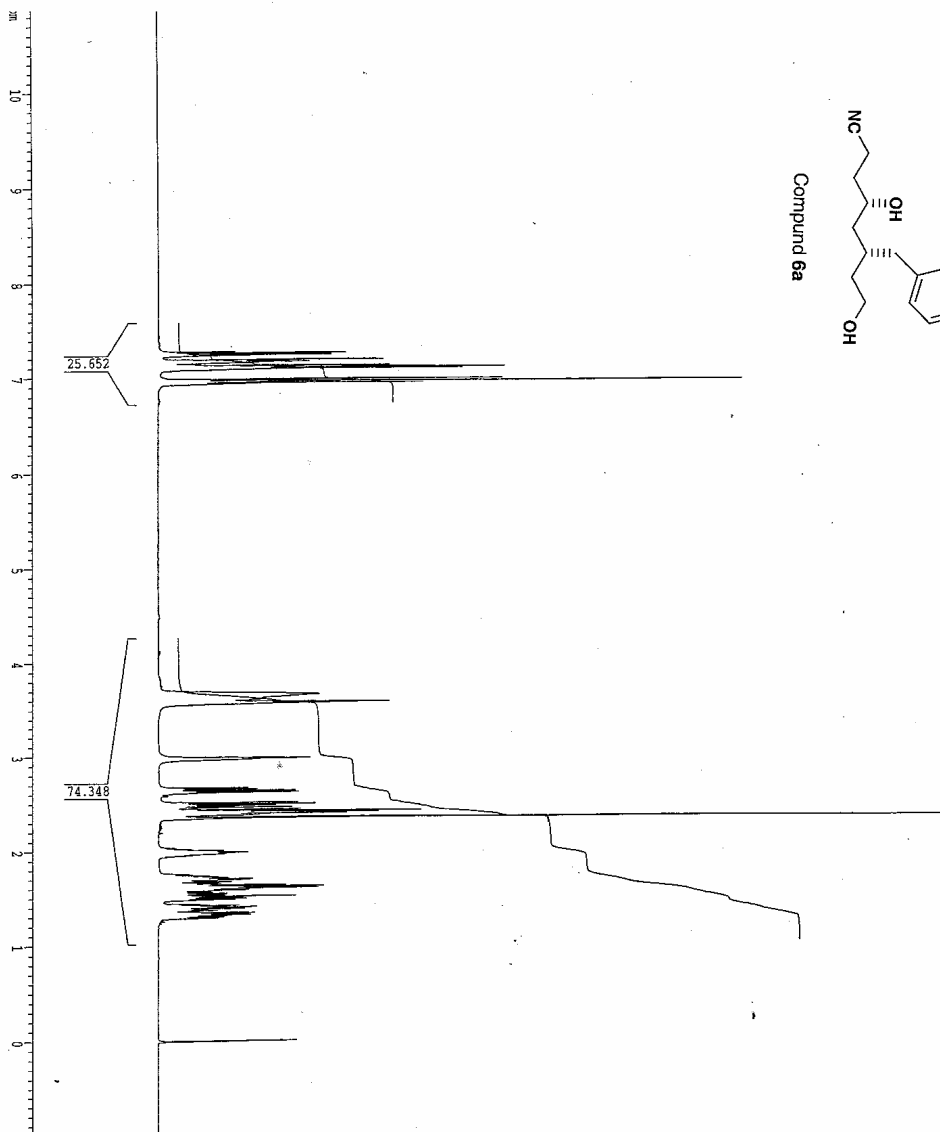
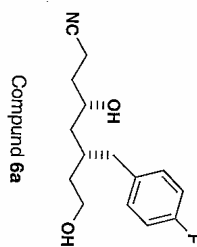
===== CHANNEL f1 =====  
NUC1 13C  
P1 6.50 usec  
PL1 -6.00 dB  
SFO1 100.627959 MHz

===== CHANNEL f2 =====  
CDEPRG2 waltz16  
NUC2 1H  
PCPD2 100.00 usec  
PL2 -5.00 dB  
PL12 19.00 dB  
PL13 19.00 dB  
SFO2 400.1316095 MHz

F2 - Processing Parameters  
SF 32768  
SF 100.6127290 MHz  
KMG BM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

1D NMR plot parameters  
CX 30.00 cm  
CTP 213.000 ppm  
F1P 21631.74 Hz  
F2P -5.000 ppm  
F2 503.06 Hz  
PNUC1 13C3333 ppm/cm  
HZCM 737.82672 Hz/cm

Notebook/Page No.: 10615-170-1

Title: diol  
PROTONEXP CDCl3 u kaufings 31

Current Data Parameters  
NAME 06192006-kauf  
EXPNO 10  
PROCNO 1

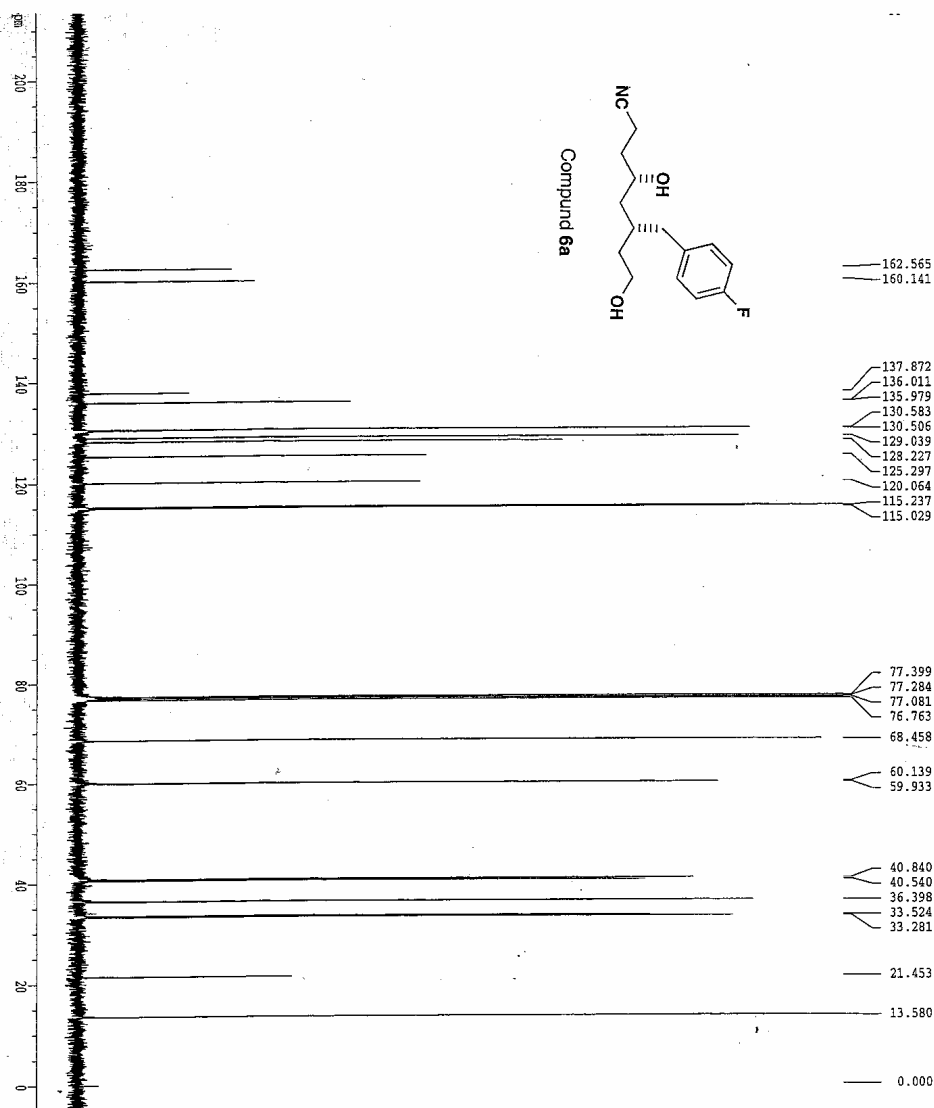
F2 - Acquisition Parameters  
Date\_ 20000619  
Time 16.08  
INSTRUM spect  
PROBHD 5 mm QNP 1H  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9584243 sec  
RG 64  
LW 60.400 usec  
DE 6.00 usec  
TE 300.0 K  
D1 1.00000000 sec

===== CHANNEL f1 =====  
NUC1 1H  
P1 6.50 usec  
PL1 -5.00 dB  
SFO1 400.134710 MHz

F2 - Processing parameters  
SI 32768  
SF 400.130015 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

1D NMR plot parameters  
CX 30.00 cm  
FLP 11.000 ppm  
F1 4401.43 Hz  
F2P -1.000 ppm  
F2 -400.13 Hz  
FREQM 0.40000 ppm/cm  
HZCM 160.05200 Hz/cm

Notebook/Page No.: 10615-170-1  
 Title: diol  
 C13CPD CDCl3 u Kaufmings 31



Current Data Parameters  
 NAME 06152000-kauff  
 EXEND 11  
 PROCNO 1

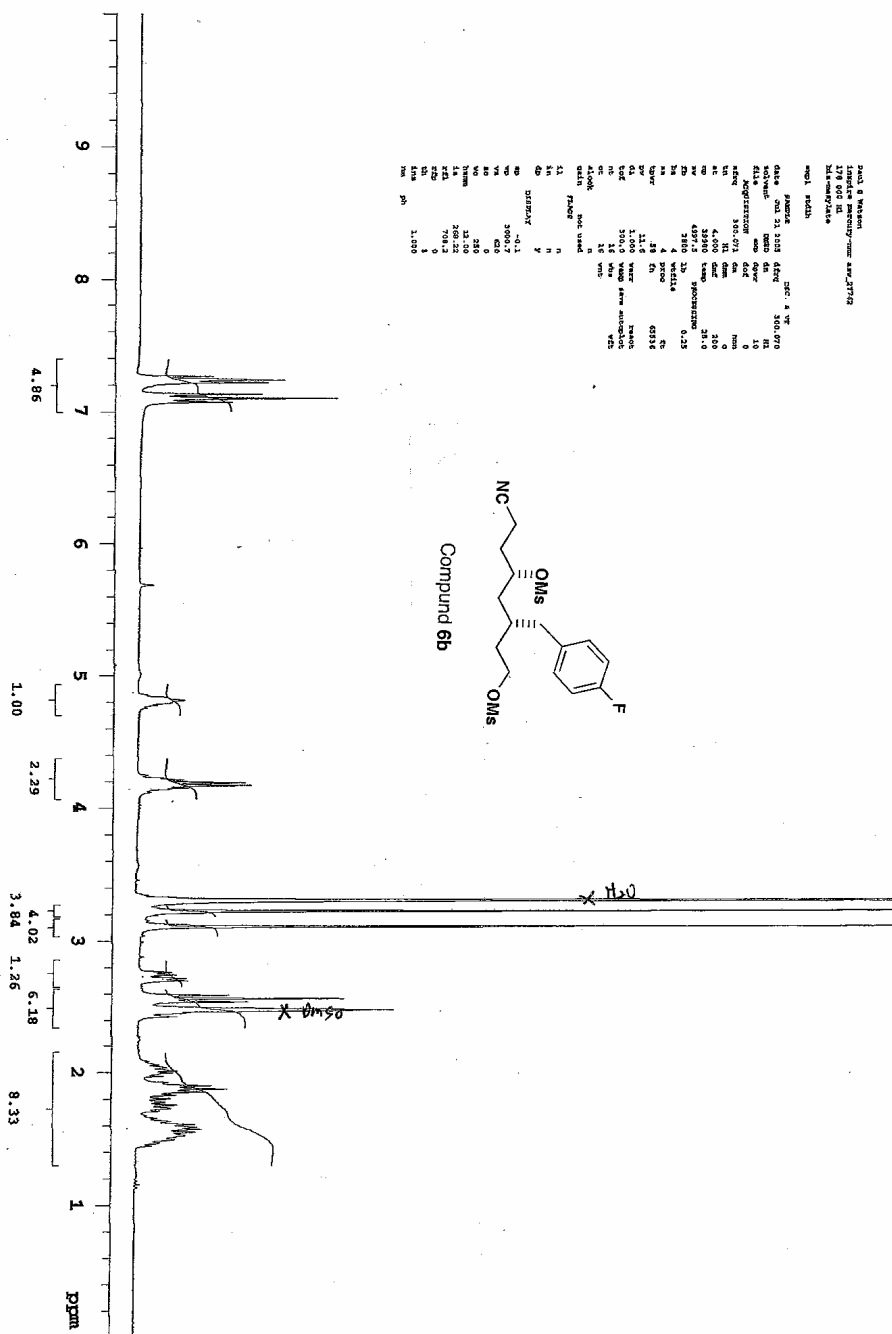
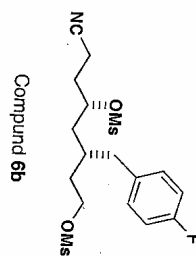
F2 - Acquisition Parameters  
 Date\_ 20000619  
 Time 23.11  
 INSTRUM spect  
 PROBRD 5 mm QNP 1H  
 PULPROG zgpg30  
 TD 65536  
 SFOFREQ 500.13  
 SOLVENT CDCl3  
 NS 1024  
 DS 4  
 SWH 25125.629 Hz  
 FIDRES 0.383387 Hz  
 AQ 1.3642164 sec  
 RG 16384  
 DW 19.900 usec  
 DE 6.00 usec  
 TE 300.0 K  
 D1 2.00000000 sec  
 d11 0.03000000 sec  
 d12 0.00020000 sec

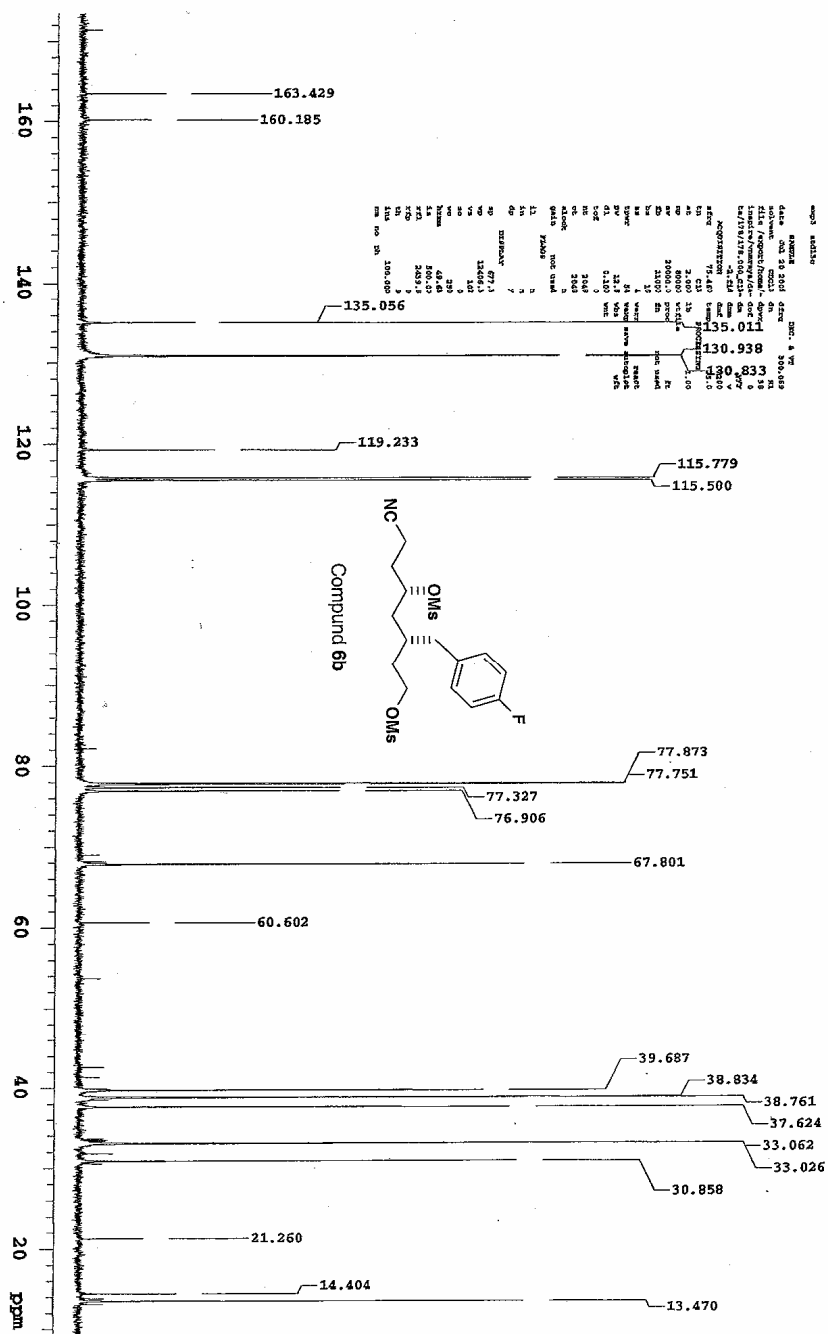
===== CHANNEL f1 =====  
 NUC1 13C  
 P1 6.50 usec  
 PL -5.00 dB  
 SFO1 100.621959 MHz

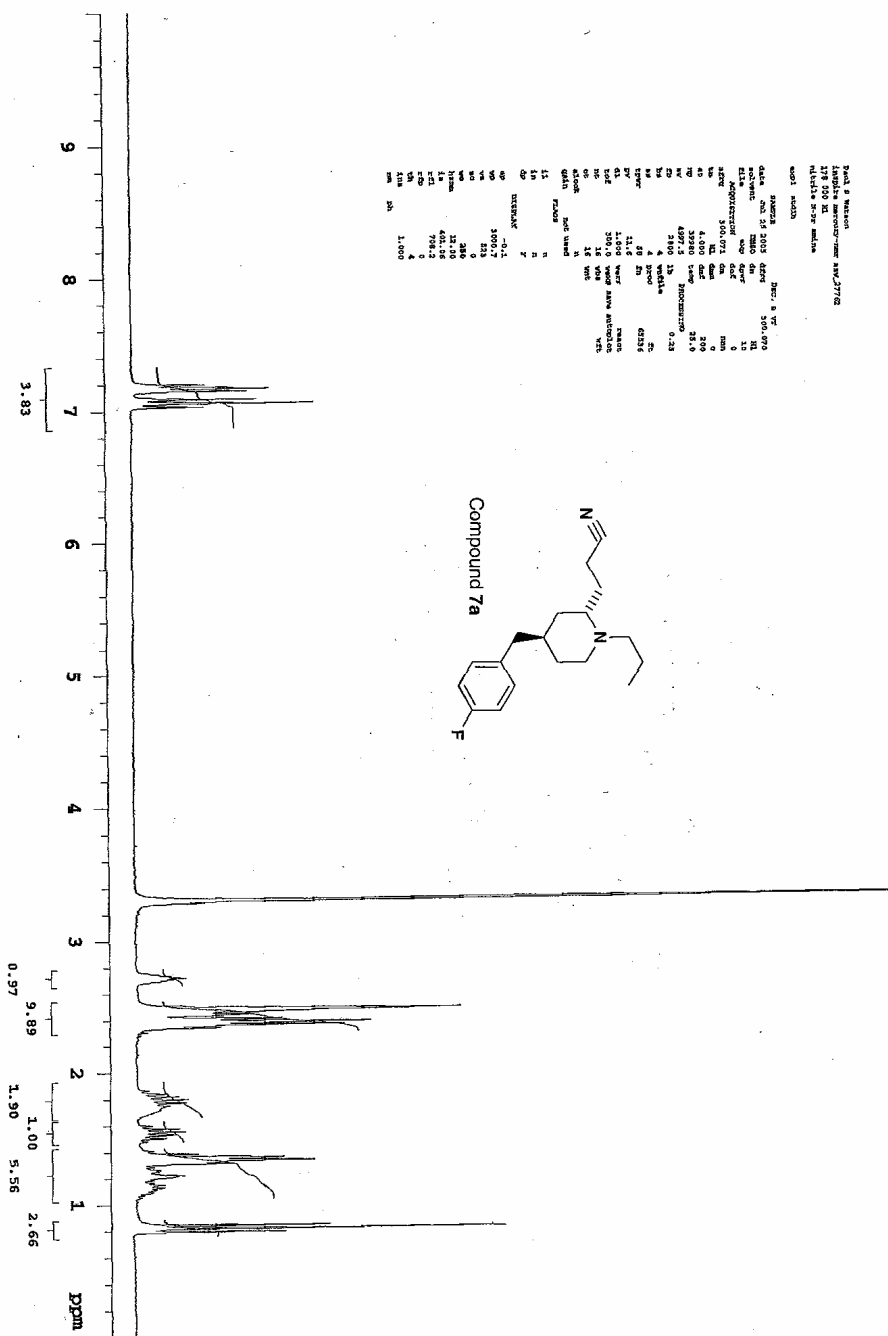
===== CHANNEL f2 =====  
 CPROG2 waltz16  
 NUC2 1H  
 PCPD2 100.00 usec  
 PL2 -5.00 dB  
 PL12 19.00 dB  
 PL13 19.00 dB  
 SFO2 400.1146065 MHz

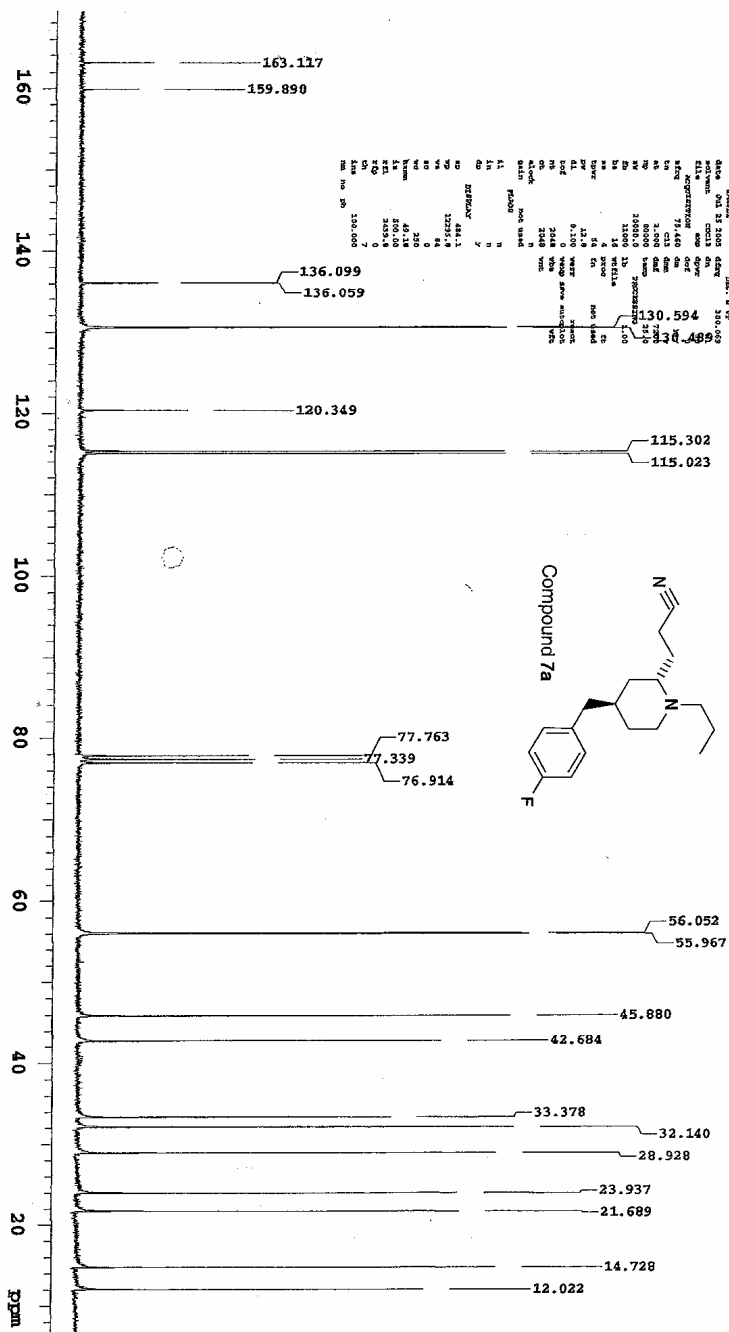
F2 - Processing parameters  
 SI 32768  
 SF 100.6127699 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40

1D NMR plot parameters  
 CX 30.00 cm  
 P1P 215.000 ppm  
 F1 21631.75 Hz  
 F2P -5.000 ppm  
 F2 -503.06 Hz  
 PWDCK 7.33333 ppm/cm  
 HZCK 737.86697 Hz/cm







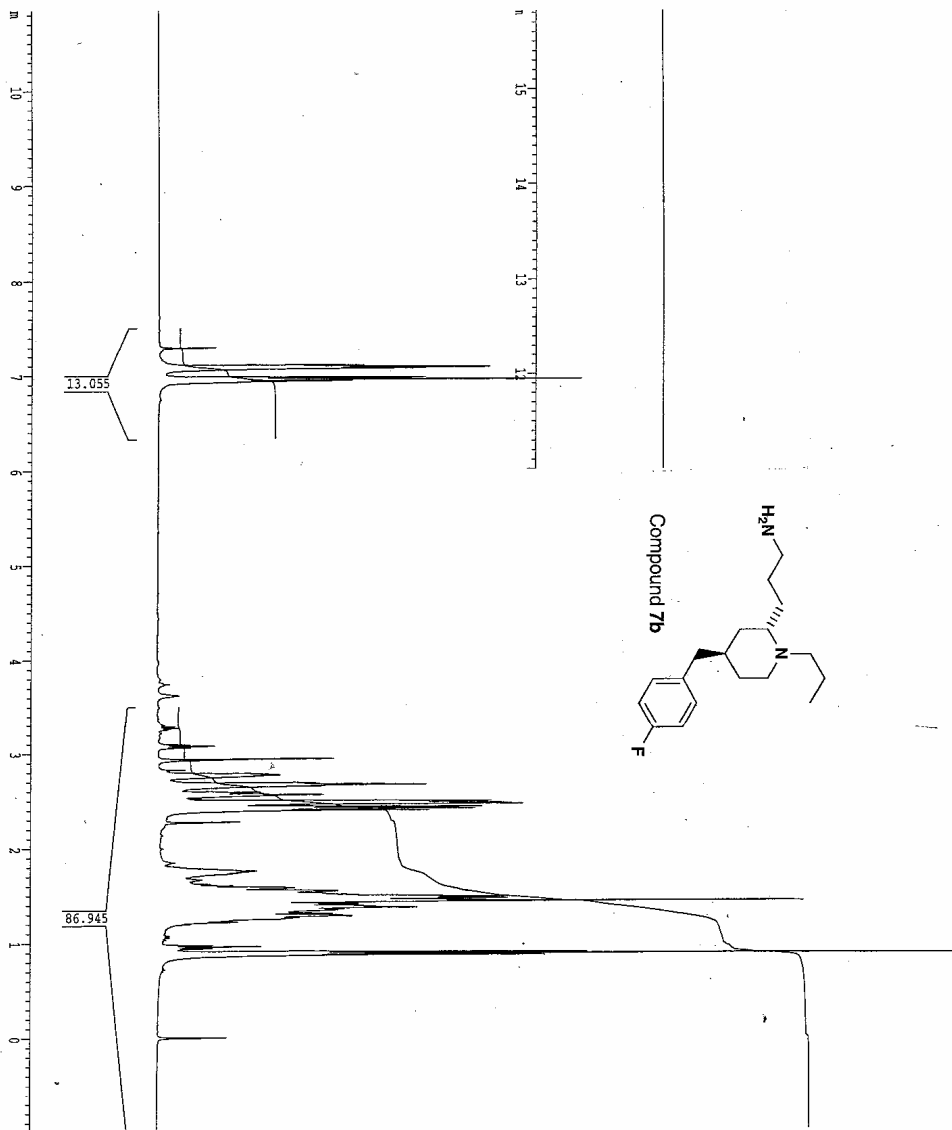
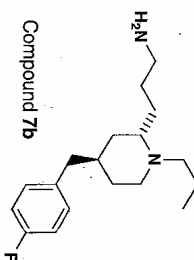




Notebook/Page No.: 12195-

Title: LAH Prod.

PROTON1F CDCl3 u kauffings 15



Current Data Parameters  
 NAME 09272001-kauf  
 EXPNO 30  
 PROCNO 1

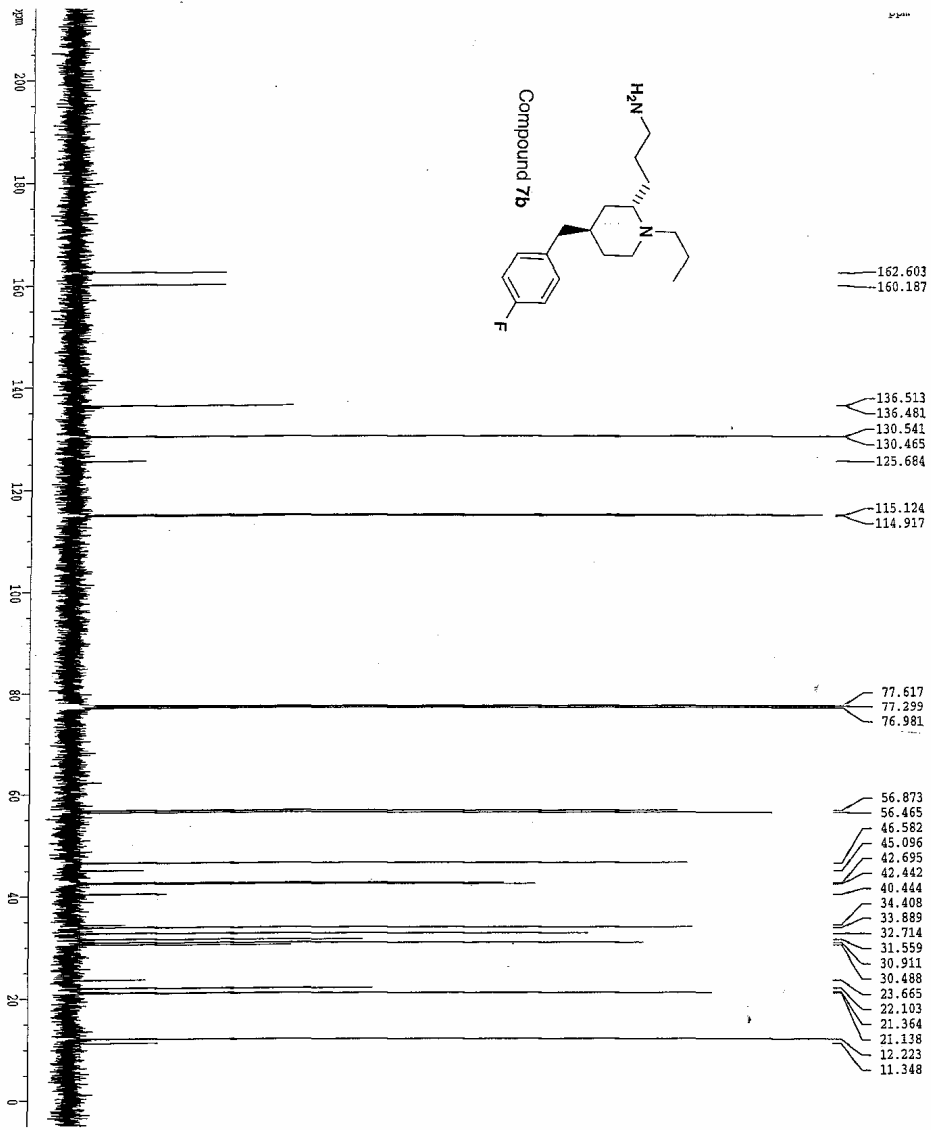
F2 - Acquisition Parameters  
 Date\_ 20010927  
 Time 14.40  
 INSTRUM spect  
 PROBRD 5 mm QNP 1H  
 PULPROG zg30  
 TD 32768  
 SFO100 32768  
 SOLVENT CDCl3  
 NS 16  
 DS 2  
 SWH 8278.146 Hz  
 FIDRES 0.252629 Hz  
 AQ 1.9792372 sec  
 RG 35.9  
 INE 60.400 usec  
 DE 6.00 usec  
 TE 300.0 K  
 D1 1.00000000 sec

===== CHANNEL f1 =====  
 NUCL 1H  
 P1 6.50 usec  
 PL1 -5.00 dB  
 SFO1 400.1324710 MHz

F2 - Processing parameters  
 SI 16384  
 SF 400.1299944 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.00

1D NMR plot parameters  
 CA 30.00 cm  
 P1P 11.000 ppm  
 F1 4401.43 Hz  
 F2P -1.000 ppm  
 F2 -400.13 Hz  
 PPMCM 0.40000 ppm/cm  
 HZCM 160.05200 Hz/cm

Notebook/Page No.: 12195-  
Title: LAH Prod.  
C13CPD128 CDCl3 u kauffmgs 15



Current Data Parameters  
NAME 09272001-kauff  
EXPNO 31  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20010927  
Time 14.48  
INSTRUM spect  
PROBHD 5 mm QNP 1H  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 128  
DS 2  
SWH 25125.628 Hz  
FIDRES 0.383387 Hz  
AQ 1.3042164 sec  
RG 16384  
BW 19.900 usec  
DE 6.00 usec  
TE 300.15 K  
D1 2.00000000 sec  
d11 0.03000000 sec  
d12 0.00020000 sec

===== CHANNEL f1 =====  
NUC1 13C  
P1 6.50 usec  
PL1 -6.00 dB  
SFO1 100.6279959 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 100.00 usec  
PL2 -5.00 dB  
PL12 19.00 dB  
PL13 19.00 dB  
SFO2 400.1316005 MHz

F2 - Processing parameters  
SI 32768  
SF 100.6127493 MHz  
WFOV 64  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

1D NMR Plot parameters  
CK 30.00 cm  
F1P 215.000 ppm  
F1 2161.74 Hz  
F2P -5.000 ppm  
F2 -505.06 Hz  
PROC4  
H2CM 737.82678 Hz/cm

