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Direct Asymmetric α -Fluorination of Aldehydes [**]

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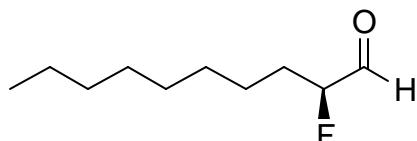
[**] This study was supported in part by the NIH (CA27489) and by the Skaggs Institute for Chemical Biology.

General. Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdc acid in ethanol followed by heating. Flash column chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm). ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on Bucker AMX-400 and Brucker DRX-500 instruments. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants J are given in Hz. The spectra were recorded in CDCl_3 (unless otherwise stated) as solvent at RT, TMS served as internal standard ($\delta = 0$ ppm) for ^1H NMR, and CDCl_3 was used as internal standard ($\delta = 77.0$) for ^{13}C NMR. External hexafluorobenzene ($\delta = -163$ ppm) served as an internal standard for ^{19}F NMR. High-resolution mass spectra were recorded on an Ion Spec Fourier Transform Mass Spectrometer using dihydrobenzoic acid (DHB) as the matrix. Reversed phase HPLC was carried out using an Agilent series 1100 system using . All HRMS run with hydrazone derivative of corresponding aldehyde made with benzoic hydrazide. All chiral GLC were recorded on an Agilent 6980 FID with Helium carrier gas using a (30 m x 0.25

mm) Bodman γ -TA capillary column.

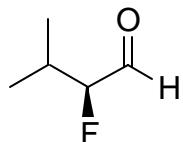
General procedure for the direct fluorination of linear aldehydes, Method A:

To a flask containing a stir bar, 200 μ L of DMF was added, followed by 1 equivalent (0.25 mmol) of imidazolidinone **14b** and 1.0 equivalent of linear aldehyde. To this solution 300 μ L of a fresh 1M solution of NFSi in DMF (1.2 eq., 0.3 mmol) was added. The resulting solution was stirred at room temperature until complete. The reaction was then diluted with 2 mL of pentane. The pentane was then extracted two times with 1 mL of saturated NH₄CL, dried over MgSO₄ and filtered. The organic layer was evaporated carefully and analyzed directly. The enantioselectivity was determined by chiral GLC analysis. Column chromatography with hexane/ethyl acetate resulted in very low yields. Direct derivatization of the aldehyde with benzoic hydrazine proceeds rapidly in methanol to form a stable hydrazone. The resulting α -fluoro hydrazone can then be separated by column chromatography or isolated via recrystallization and is readily ionized on HRMS while the aldehyde is not. Racemic standards were synthesized using same procedure, but substituting pyrrolidine or D+L-proline for chiral catalyst.

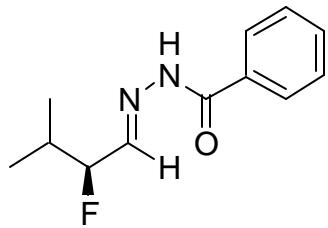


(S)-2-Fluoro-decanal (Table 4, entry 2): Prepared according to general procedure, method A, from decyl aldehyde (47.1 μ L, 0.25 mmol) catalyzed by imidazolidinone **14b** (54.5 mg, 0.25 mmol) for 3 h to provide as a colorless oil (90% yield by crude ¹H NMR, 88%ee). ¹H NMR (400 MHz) **d** : 0.86 (t, 3H, -CH₃), 1.26 (m, 10H), 1.45 (m, 2H), 1.73 (m, 2H), 4.67 (dd, *J* = 49.5 Hz, 1H), 9.75 (dd, *J* = 6.2 Hz, 1H); ¹³C NMR (125 MHz) **d** = 14.1, 22.6, 24.19 (d, *J* = 3.9 Hz), 29.13, 29.18, 29.26, 30.27 (d, *J* = 20.9 Hz), 31.8, 94.1 (d, *J* = 178.7 Hz), 200.2 (d, *J* = 34.9; ¹⁹F NMR (CDCl₃) **d** = -199.3 ppm; HRMS (ESI) exact mass calculated for (C₁₀H₁₉FO) requires [M-H]⁻ 173.1347, found [M-H]⁻ 173.1347. $[\alpha]_D$ = -10.55 (c = 1.4, CHCl₃). The enantiomeric ratio was determined by GLC using a Bodman ChiralDEX γ -TA (30 m x 0.25 mm) column (90 °C isotherm) isomer (*R*) *t*_r = 13.48 min and isomer (*S*)*t*_r = 13.98

min. Structure was confirmed by comparison to literature values.

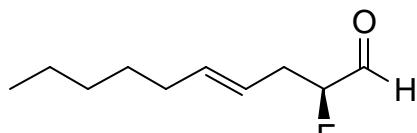


(S)-(-)-2-Fluoro-isovaleraldehyde (Table 4, entry 1): Prepared according to general procedure, method A, from isovaleraldehyde (69 μ L, 0.25 mmol) catalyzed by imidazolidinone **14b** (54.5 mg, 0.25 mmol) for 2 h. Initial samples were lost upon evaporation of pentane, so 1 equivalent (34 mg, 0.25 mmol) benzoic hydrazine was added directly to pentane with 2 mL of MeOH. (74% yield by crude HPLC of hydrazone derivative, 96%ee). 1 H NMR of crude reaction in CD₃CN, (400 MHz, CD₃CN) δ : 0.98 (d, J = 6.9 Hz, 3H), 1.032 (d, J = 6.9 Hz, 3H), 1.99 (m, 1H), 4.63-4.77 (dd, J = 48.7 Hz, 1H), 9.75-9.74(d, J = 9.3 Hz, 1H); 19 F NMR (CD₃CN) δ = -203.2 ppm. $[\alpha]_D$ = -22.1 (c = 2.2, pentane) unpurified.



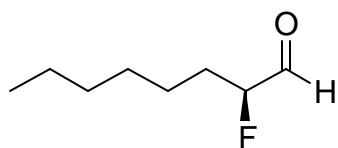
Benzoic acid, [(S)-2-fluoro-3-methylbutylidene]hydrazide :

Prepared according to general procedure, method A. HRMS (ESI) exact mass calculated for (C₁₂H₁₅FN₂O) requires MH⁺ 223.1241, found MH⁺ 223.1246. 1 H NMR (400 MHz) δ : 0.97 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 2.03 (m, 1H), 4.77-4.89 (d, J = 48.6 Hz, 1H), 7.43 (m, 2H), 7.53 (m, 1H), 7.82 (m, 2H), 9.66 (bs, 1H); 13 C NMR (125 MHz) δ = 17.42(d, J = 5.2 Hz), 18.04(d, J = 4.9 Hz), 32.24(d, J = 21.2 Hz), 95.6(d, J = 169.9 Hz), 127.80, 129.1, 129.89 (d, J = 43.3 Hz), 132.67, 133.00, 164.7; 19 F NMR (CDCl₃) δ = -188.4 ppm. $[\alpha]_D$ = -3.20 (c = 0.5, CHCl₃). The enantiomeric ratio was determined by reverse phase HPLC using a Diacel Chiracel OD-R column (45% acetonitrile/water isocratic) isomer (S) t_r = 11.94 min and isomer (R) t_r = 12.83 min.

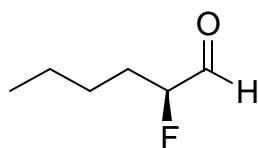


(S)-(-)-2-Fluoro-4-trans-decenal (Table 4, entry 3): Prepared according to general procedure, method A, from 4-trans-decenal (45.8 μ L, 0.25 mmol) catalyzed

by imidazolidinone **14b** (54.5 mg, 0.25 mmol) for 3 h to provide as a colorless oil (59% yield by crude ^1H NMR, 93%ee). ^1H NMR (400 MHz) δ : 0.86 (t, 3H, -CH₃), 1.26 (m, 8H), 2.46 (m, 2H), 4.68 (dd, J = 49.0 Hz, 1H), 5.41 (m, 1H), 5.58(m, 1H), 9.74 (dd, J = 6.6 Hz, 1H); ^{13}C NMR (125 MHz) δ = 14.05, 22.34, 28.08, 31.30, 33.75 (d, J = 20.2 Hz), 34.12, 93.53(d, J = 183.4 Hz), 121.48 (d, J = 3.9 Hz), 32.11, 200.92 (d, J = 33.9); ^{19}F NMR (CDCl₃) δ = -198.7 ppm; HRMS (ESI) exact mass calculated for hydrazone (C₁₇H₂₃FN₂O) requires MH⁺ 291.1867, found MH⁺ 291.1868. $[\alpha]_D$ = -14.10 (c= 1.0, CHCl₃). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex γ -TA (30 m x 0.25 mm) column (80 °C isotherm) isomer (*R*) t_r = 18.96 min and isomer (*S*) t_r = 19.69 min.

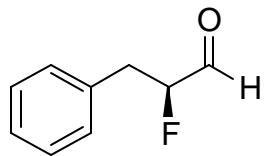


(*S*)-(-)-2-Fluoro octyl aldehyde (Table 4, entry 4): Prepared according to general procedure, method A, from octyl aldehyde (39.0 μL , 0.25 mmol) catalyzed by imidazolidinone **14b** (54.5 mg, 0.25 mmol) for 3 h to provide as a colorless oil (94% yield by crude ^1H NMR, 86%ee). ^1H NMR (400 MHz) δ : 0.86 (t, 3H, -CH₃), 1.27 (m, 6H), 1.45 (m, 2H), 1.75 (m, 2H), 4.67-4.825 (dd, J = 49.5 Hz, 1H), 9.75 (dd, J = 6.3 Hz, 1H); ^{13}C NMR (125 MHz) δ = 14.45, 22.89, 24.59 (d, J = 3.0 Hz), 29.25, 30.71 (d, J = 20.4 Hz), 31.89, 94.76(d, J = 178.9 Hz), 200.92 (d, J = 34.8); ^{19}F NMR (CDCl₃) δ = -199.3 ppm; HRMS (ESI) exact mass calculated for hydrazone (C₁₅H₂₁FN₂O) requires MH⁺ 265.1711, found MH⁺ 265.1707. $[\alpha]_D$ = -12.52 (c= 1.2, CHCl₃). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex γ -TA (30 m x 0.25 mm) column (60 °C isotherm) isomer (*R*) t_r = 16.35 min and isomer (*S*) t_r = 17.7 min. 2-fluoro octyl aldehyde was diluted with MeOH (1.0 mL) and NaBH₄ (50mg, 1.3 mmol) at 0 °C and stirred for 2 h. The corresponding (*S*)-2-fluoro-1-octanol was diluted in 2 mL ether, extracted with water and dried over MgSO₄. The absolute configuration was determined by optical rotation and compared with literature values.



(*S*)-(-)-2-Fluoro-hexanal (Table 4, entry 5): Prepared according to general

procedure, method A, from hexanal (30.0 μ L, 0.25 mmol) catalyzed by imidazolidinone **14b** (54.5 mg, 0.25 mmol) for 3 h to provide as a colorless oil (40% yield by crude HPLC of hydrazone derivative, 92%ee). 1 H NMR (400 MHz) **d** : 0.86 (t, 3H, -CH₃), 1.23-1.83(m, 6H), 4.64 (dd, *J* = 49.4 Hz, 1H), 9.74 (dd, *J* = 6.2 Hz, 1H); 19 F NMR (CDCl₃) **d** = -199.3 ppm, . [α]_D = -26.9 (c = 2.1, pentane) unpurified; HRMS (ESI) exact mass calculated for hydrazone (C₁₃H₁₇FN₂O) requires MH⁺ 237.1398, found MH⁺ 237.1403. The enantiomeric ratio was determined by reverse phase HPLC using a Diacel Chiracel OD-R column (45% acetonitrile/water isocratic) isomer (*S*) *t*_r = 20.95 min and isomer (*R*) *t*_r = 21.89 min.

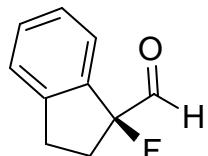


(S)-(-)-2-Fluoro-3-phenylpropionaldehyde (Table 4, entry 6): Prepared according to general procedure, method A, from 3-phenylpropionaldehyde aldehyde (33.0 μ L, 0.25 mmol) catalyzed by imidazolidinone **14b** (54.5 mg, 0.25 mmol) for 2 h to provide as a colorless oil (97% yield by crude 1 H NMR, 88%ee). 1 H NMR (400 MHz) **d** : 2.66-2.73 (m, 2H), 4.67-5.03 (dd, *J* = 48.9 Hz, 1H), 7.21-7.32 (m, 5H), 9.77 (dd, *J* = 5.4 Hz, 1H); 13 C NMR (125 MHz) **d** = 37.13 (d, *J* = 20.3 Hz), 94.74(d, *J* = 182.2 Hz), 127.68, 127.94, 129.13, 130.99, 131.06, 200.15 (d, *J* = 37.4); 19 F NMR (CDCl₃) **d** = -199.3 ppm; HRMS (ESI) exact mass calculated for hydrazone (C₁₆H₁₅FN₂O) requires MH⁺ 271.1241, found MH⁺ 271.1244. [α]_D = -15.4 (c = 0.5, CHCl₃). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex γ -TA (30 m x 0.25 mm) column (90 °C isotherm) isomer (*R*) *t*_r = 16.14 min and isomer (*S*) *t*_r = 18.05 min.

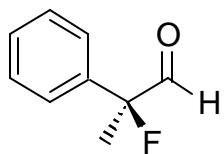
General procedure for the direct fluorination of branched aldehydes, Method B:

To a flask containing a stir bar, 200 μ L of THF was added, followed by 0.3 equivalents (0.075 mmol) of catalyst and 1.0 equivalent of branched aldehyde. To this solution 300 μ L of a fresh 1M solution of NFSi in THF (1.2 eq., 0.3 mmol) was added. The resulting solution was stirred at

room temperature until complete. The reaction was then diluted with 2 mL of Et₂O from which a white precipitate formed. The Et₂O was decanted from the solid and extracted one time with 1 mL of saturated NH₄Cl, one time with 1 mL of NaHCO₃, dried over MgSO₄ and filtered. The organic layer was evaporated carefully and analyzed directly. The enantioselectivity was determined by chiral GLC analysis. Column chromatography with hexane/ethyl acetate resulted in very low yield. Derivatization of the aldehyde with benzoic hydrazine proceeds rapidly in methanol to form a stable hydrazone. The resulting α -fluoro hydrazone can then be separated by column chromatography or isolated via recrystallization. Racemic standards were synthesized using same procedure, but substituting pyrrolidine or D+L-proline for chiral catalyst.



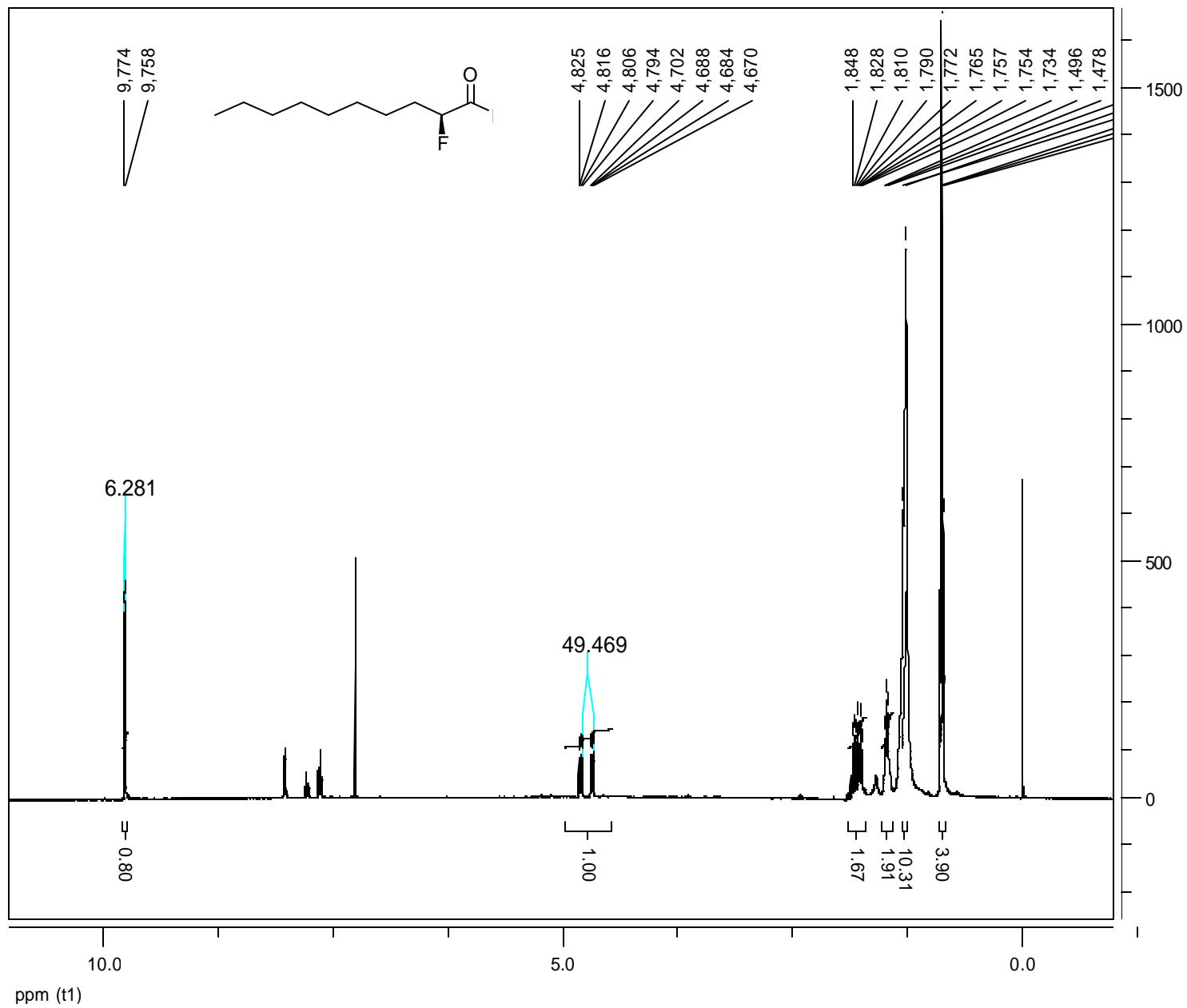
(S)-(-)-2-Fluoro-indane aldehyde (Table 4, entry 7): Prepared according to general procedure from indane aldehyde (32.1 μ L, 0.25 mmol) catalyzed by TIPS prolinol **9c** (19.3 mg, 0.075 mmol) for 6 h to provide as a colorless oil (40.2 mg, 98% yield, 66 %ee). Material was difficult to monitor by TLC, so yield varied from 75-98 %. ¹H NMR (400 MHz) **d** : 2.46 (m, 2H), 3.06 (m, 2H), 7.59-8.03 (m, 4H), 9.93 (d, *J* = 5.2 Hz, 1H); ¹³C NMR (100 MHz) **d** = 30.20, 33.36(d, *J* = 22.4 Hz), 106.56(d, *J* = 128.16 Hz), 127.59, 129.69, 130.05, 131.10 (d, *J* = 3.33), 134.81 (d, *J* = 4.74), 136.09, 197.43 (d, *J* = 41.70); ¹⁹F NMR (CDCl₃) **d** = -147.4 ppm; $[\alpha]_D$ = -7.1 (c = 1.2, CHCl₃); HRMS (ESI) exact mass calculated for hydrazone (C₁₇H₁₅FN₂O) requires MH⁺ 283.1247, found MH⁺ 283.1249. The enantiomeric ratio was determined by GLC using a Bodman Chiraldex γ -TA (30 m x 0.25 mm) column (110 °C isotherm) isomer t_r = 14.17 min and isomer t_r = 15.07 min.

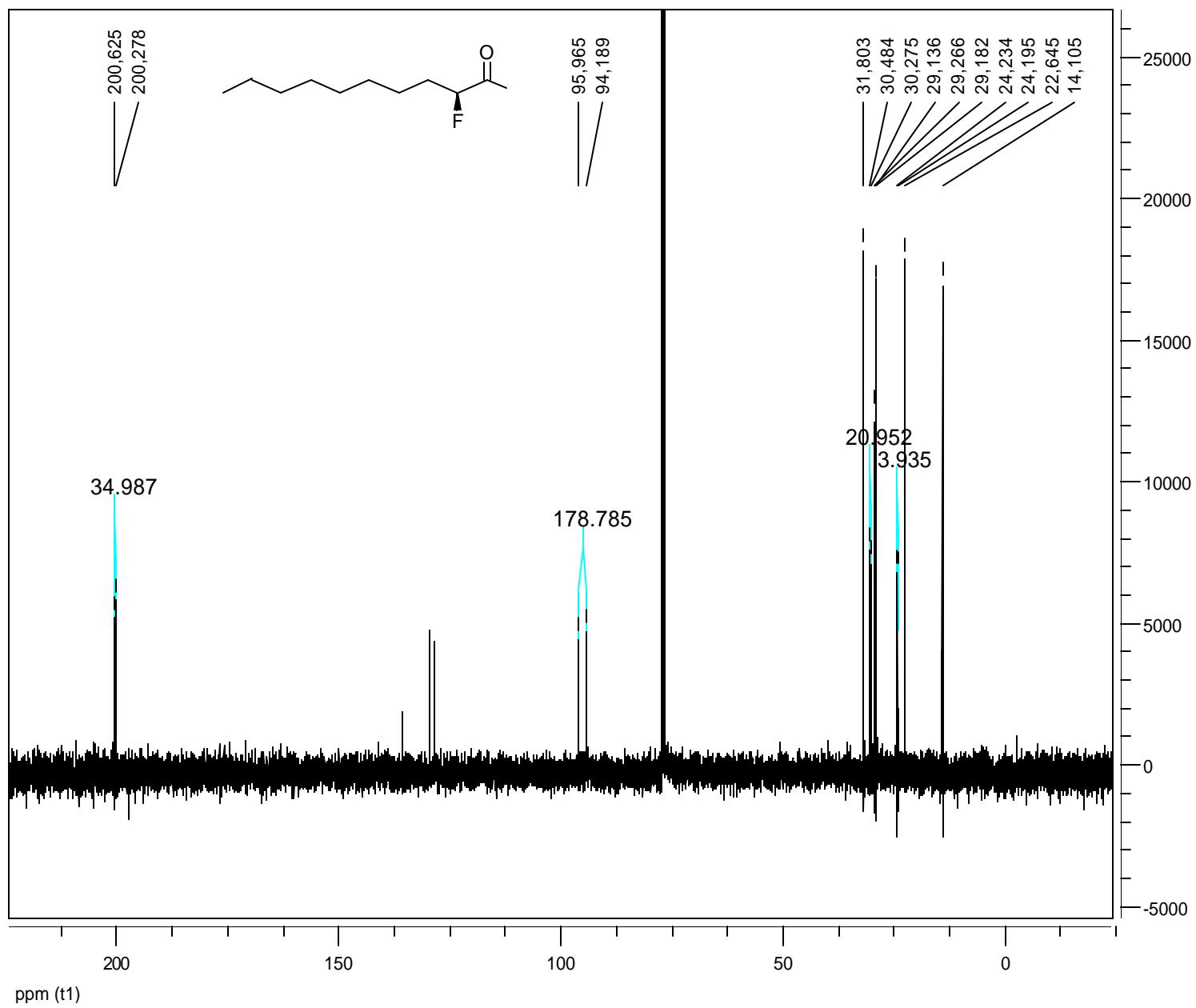


(S)-(-)-2-Fluoro-2-phenylpropionaldehyde (Table 4, entry 8): Prepared according to general procedure from 2-phenylpropionaldehyde **1a** (33.2 μ L, 0.25 mmol)

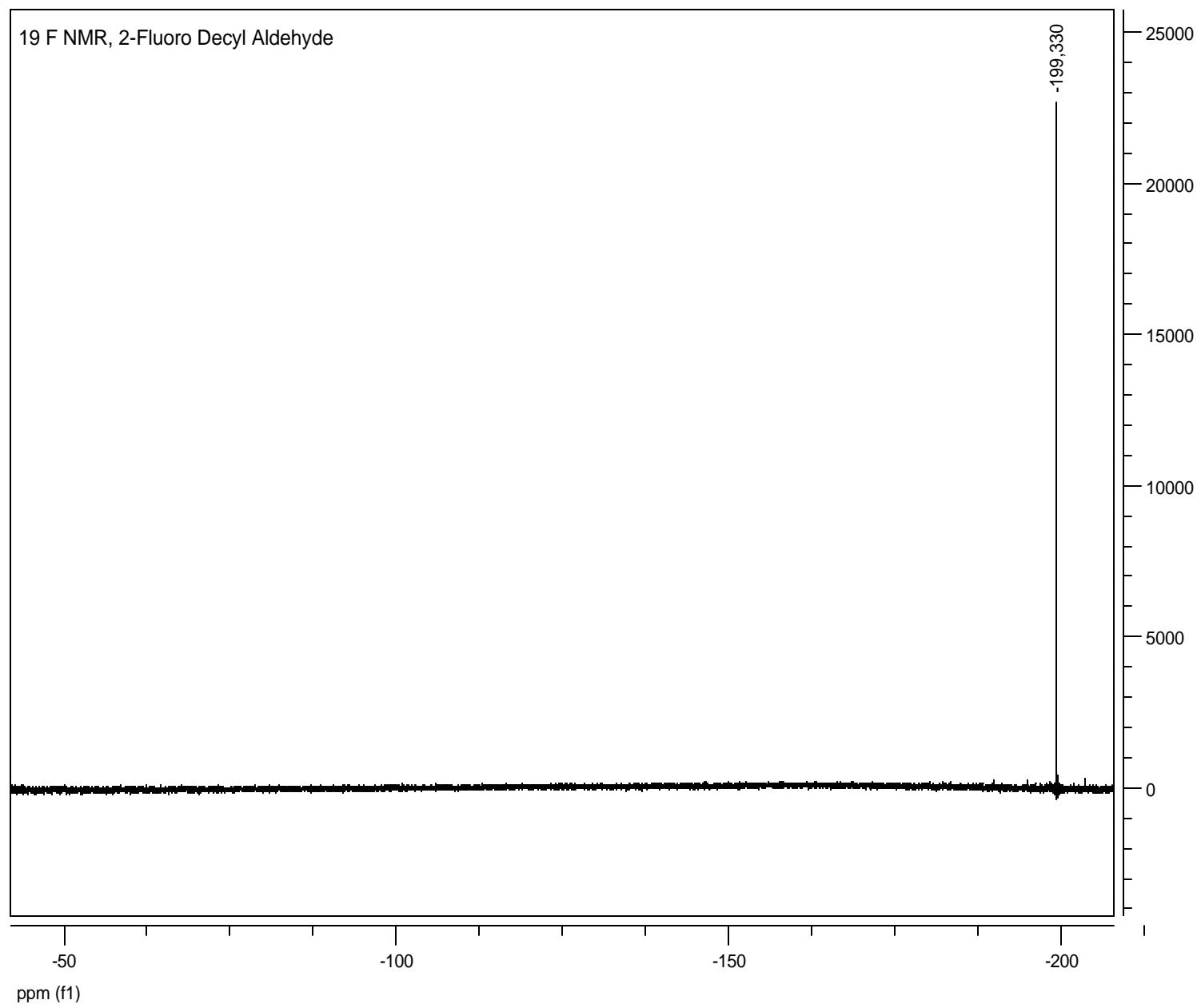
catalyzed by TIPS prolinol **9c** (19.3 mg, 0.075 mmol) for 6 h to provide as a colorless oil (35.0 mg, 90% yield, 40%ee). ^1H NMR (400 MHz) **d** : 1.76-1.82 (d, J = 22.7 Hz, 3H, -CH₃), 7.40 (m, 5H), 9.69-9.70 (d, J = 4.9 Hz, 1H); ^{19}F NMR (CDCl₃) **d** = -160.8 ppm; $[\alpha]_D$ = -8.2 (c = 5.6, CHCl₃); HRMS (ESI) exact mass calculated for hydrazone (C₁₆H₁₅FN₂O) requires MH⁺ 271.1241, found MH⁺ 271.1237. The enantiomeric ratio was determined by GLC using a Bodman Chiraldex γ -TA (30 m x 0.25 mm) column (90 °C isotherm) isomer t_r = 9.45 min and isomer t_r = 11.88 min.

(S)-(+)-2-Fluoro-2-phenylpropionic acid To a solution of (S)-(-)-2-Fluoro-2-phenylpropionaldehyde (112 mg, 0.4 mmol) in tBuOH-H₂O (5:1, 3 mL) at room temperature, NaClO₂ (143 mg, 1.6 mmol), NaH₂PO₄ (95 mg, 0.8 mmol) and 2-methyl-2-butene (1.6 mL of 2M THF solution, 3.2 mmol) was added and stirred for 1 h. The reaction mixture was then extracted with ethyl acetate and washed with brine and water. The organic layer was dried to a white solid. $[\alpha]_D$ = +2.6 (c = 0.4, MeOH); HRMS (ESI) exact mass calculated for (C₉H₉FO₂) requires [M-H]⁻ 167.0514, found [M-H]⁻ 167.0514.

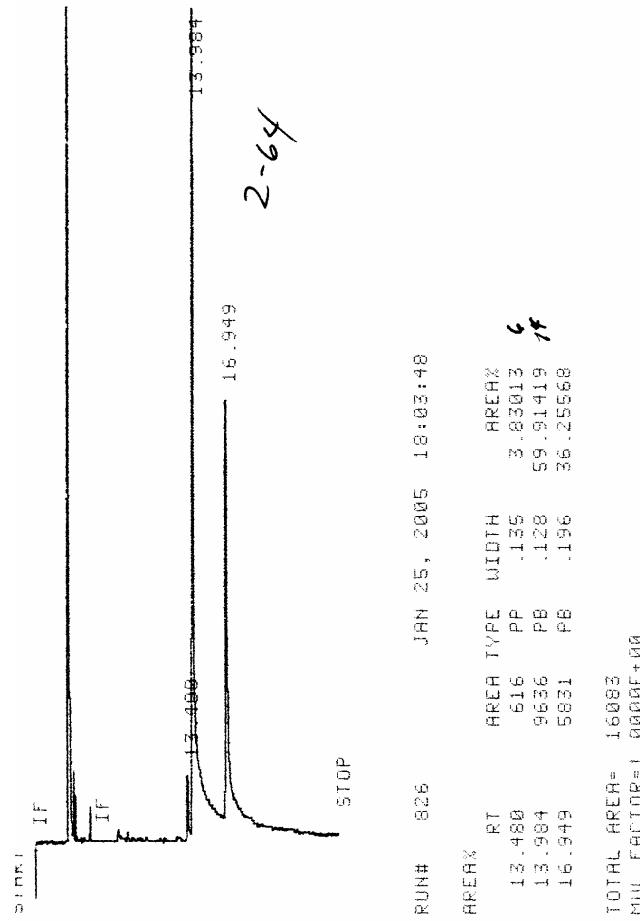


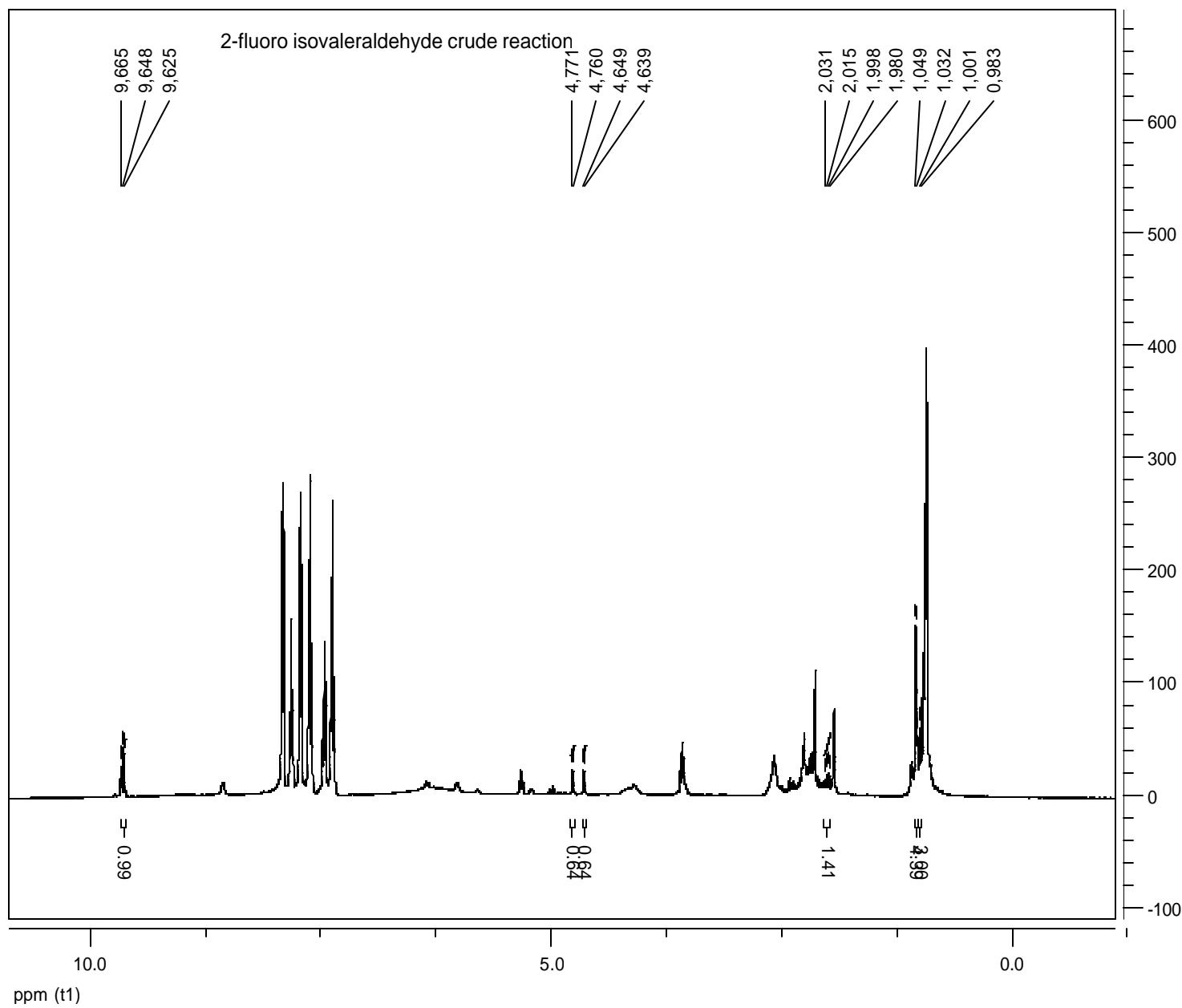


¹⁹ F NMR, 2-Fluoro Decyl Aldehyde

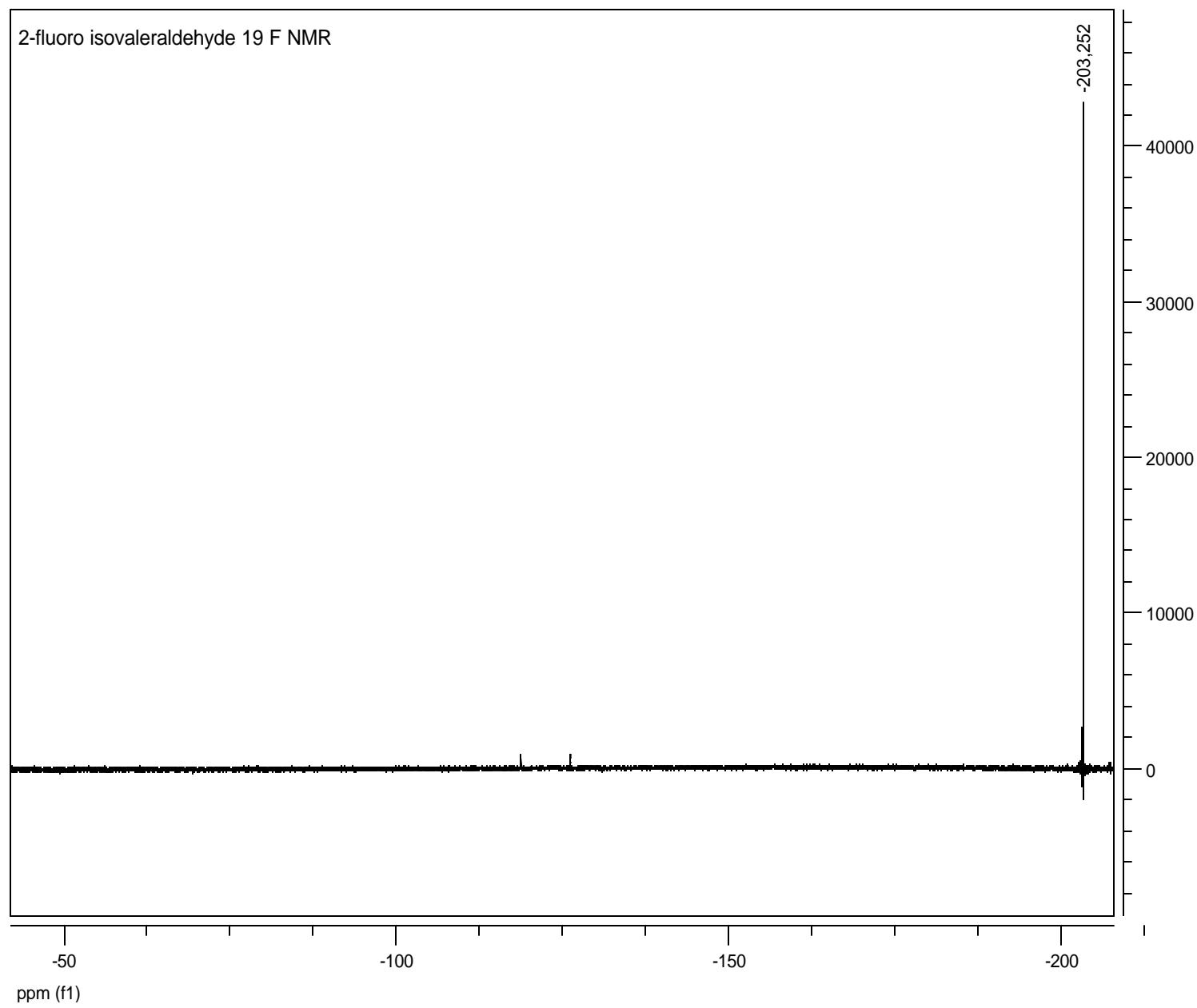


2-fluoro-decyl aldehyde: GLC using a Bodman Chiraldex γ -TA (30 m x 0.25 mm) column (90 °C isotherm) isomer (R) t_r = 13.48 min and isomer (S) t_r = 13.98, starting aldehyde t_r = 16.94

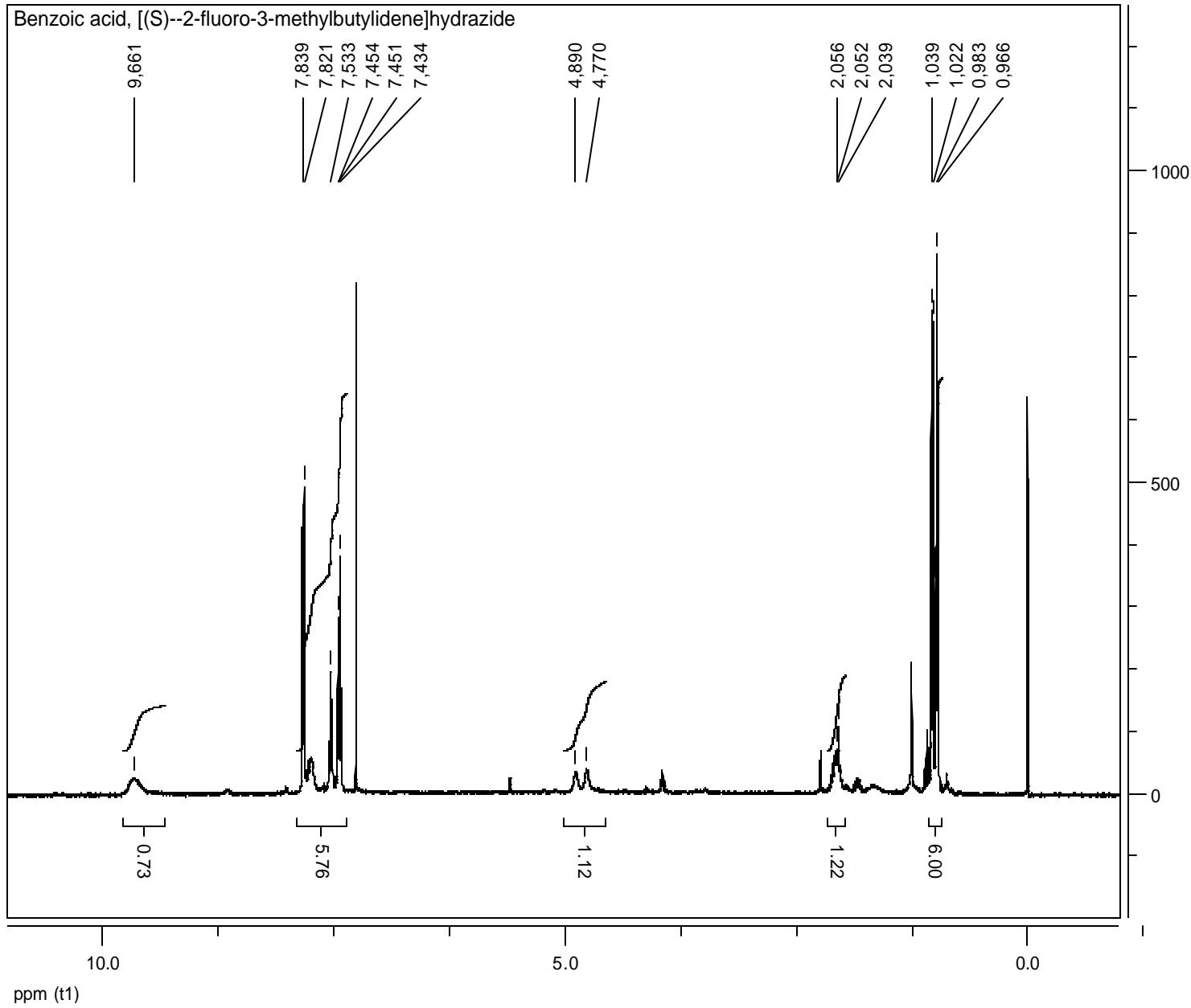


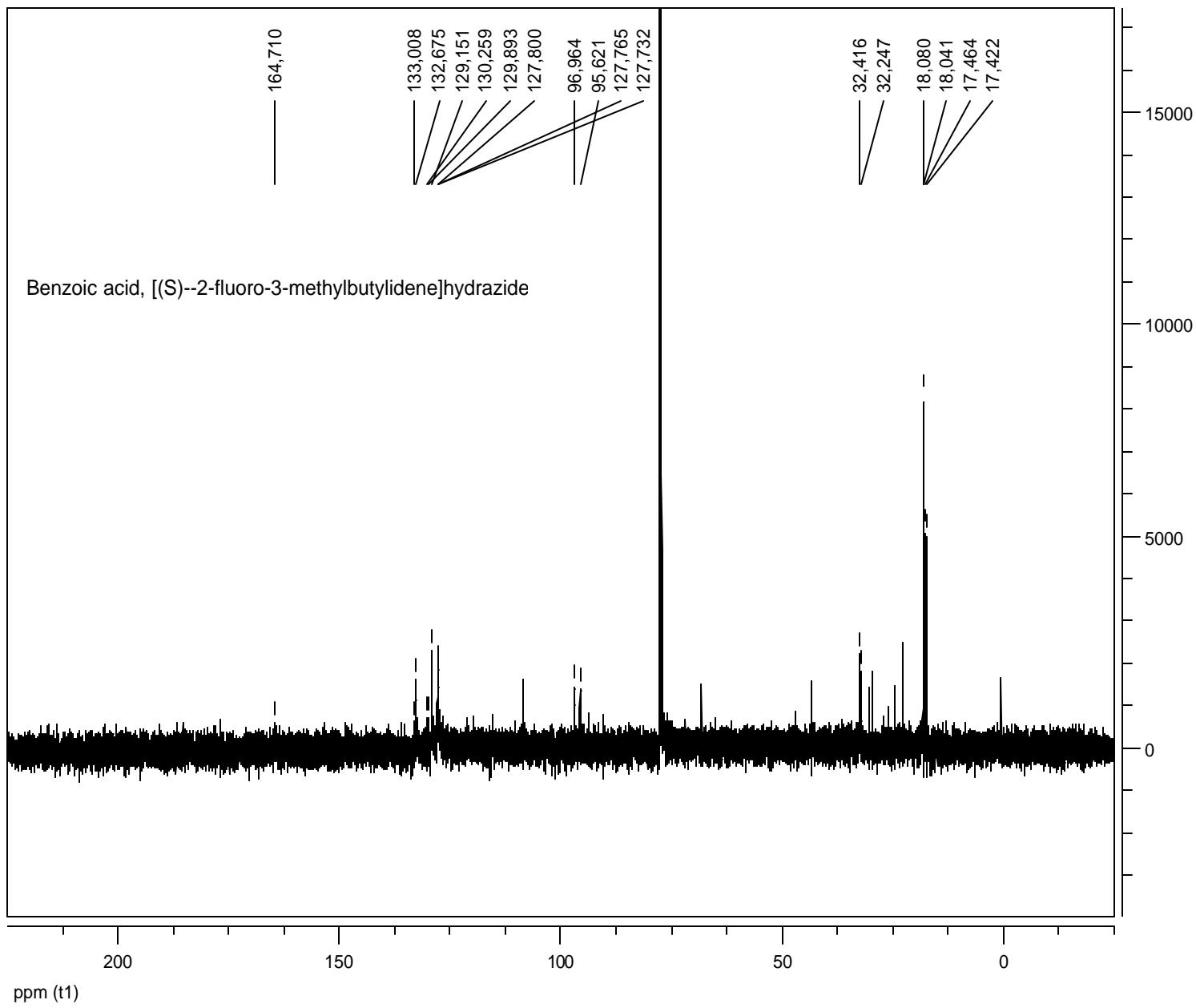


2-fluoro isovaleraldehyde ^{19}F NMR

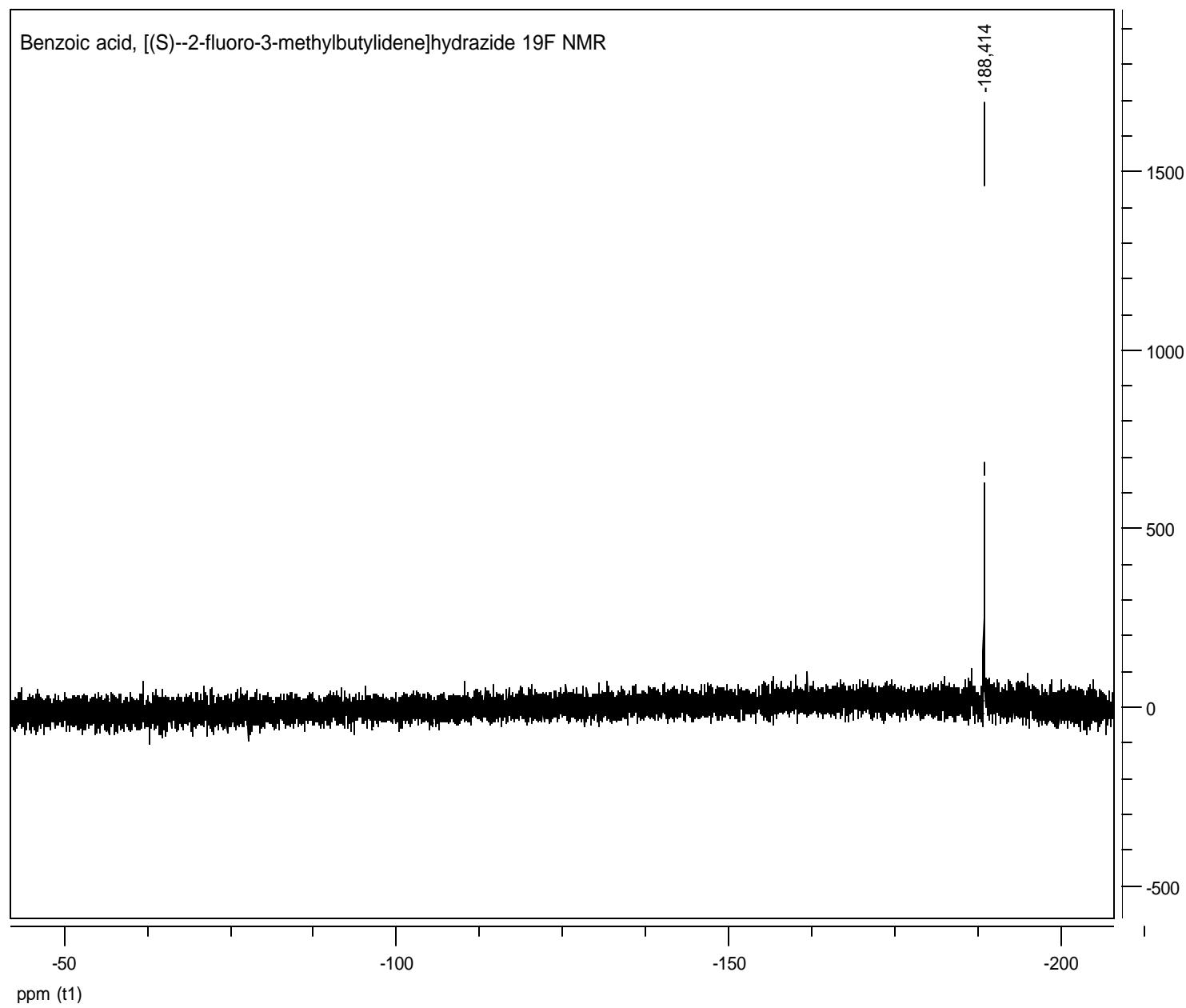


Benzoic acid, [(S)--2-fluoro-3-methylbutylidene]hydrazide





Benzoic acid, [(S)-2-fluoro-3-methylbutylidene]hydrazide 19F NMR



Benzoic acid, [(S)--2-fluoro-3-methylbutylidene]hydrazide: phase HPLC using a Diacel Chiracel OD-R column (45% acetonitrile/water isocratic) isomer (S) $t_r = 11.94$ min and isomer (R) $t_r = 12.83$ min.

Figure 1: racemic sample

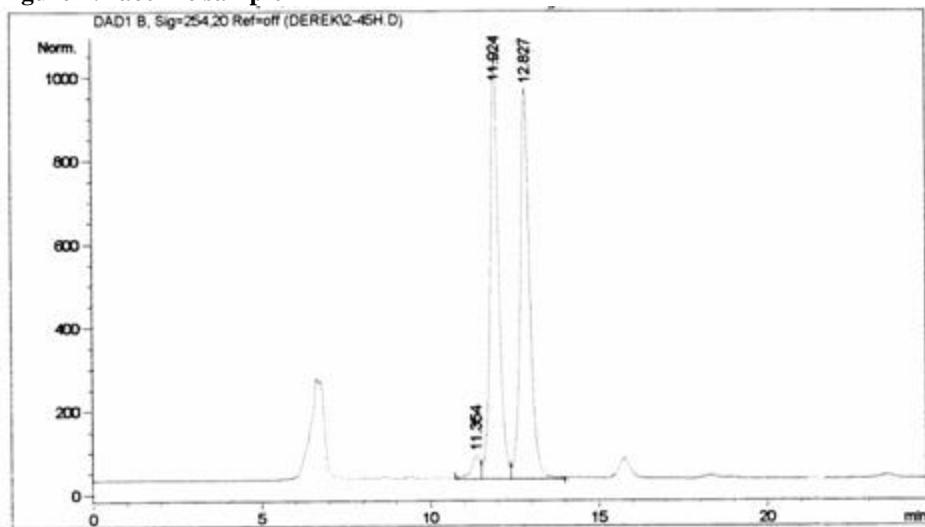
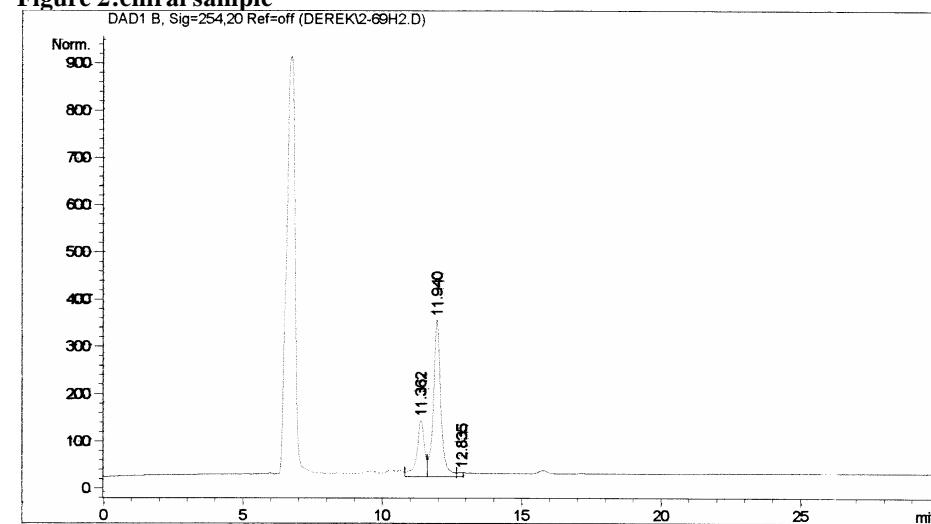
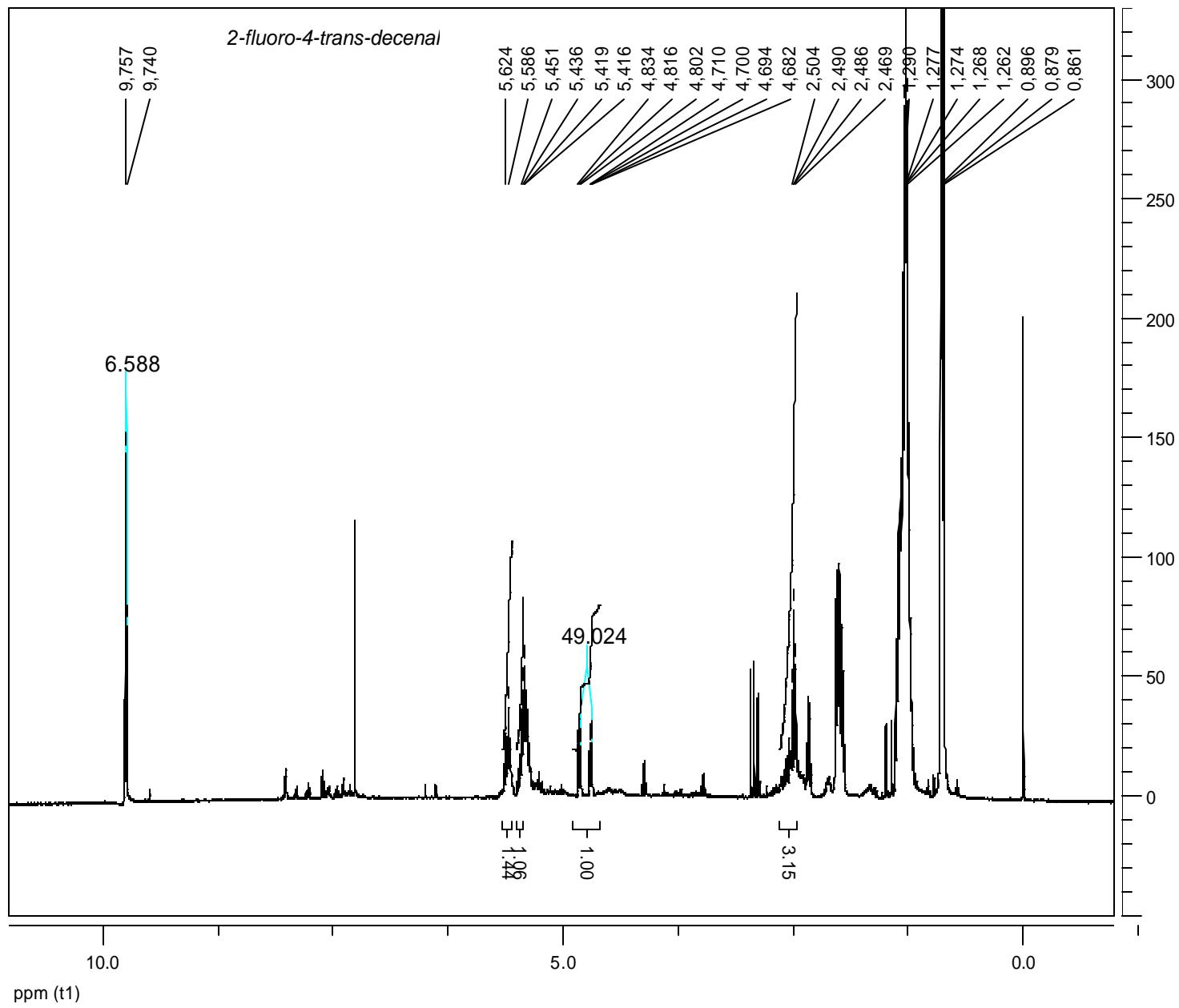
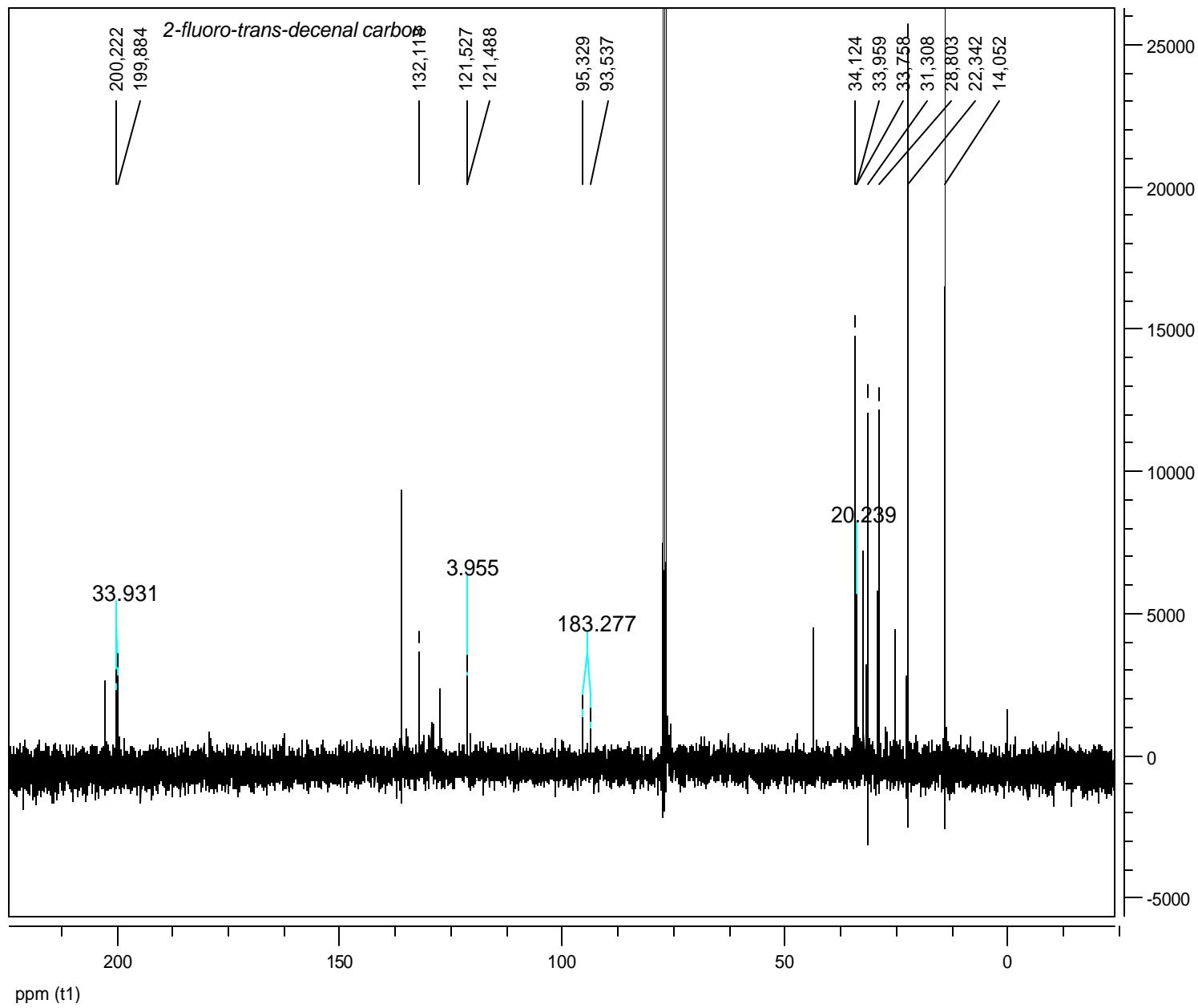


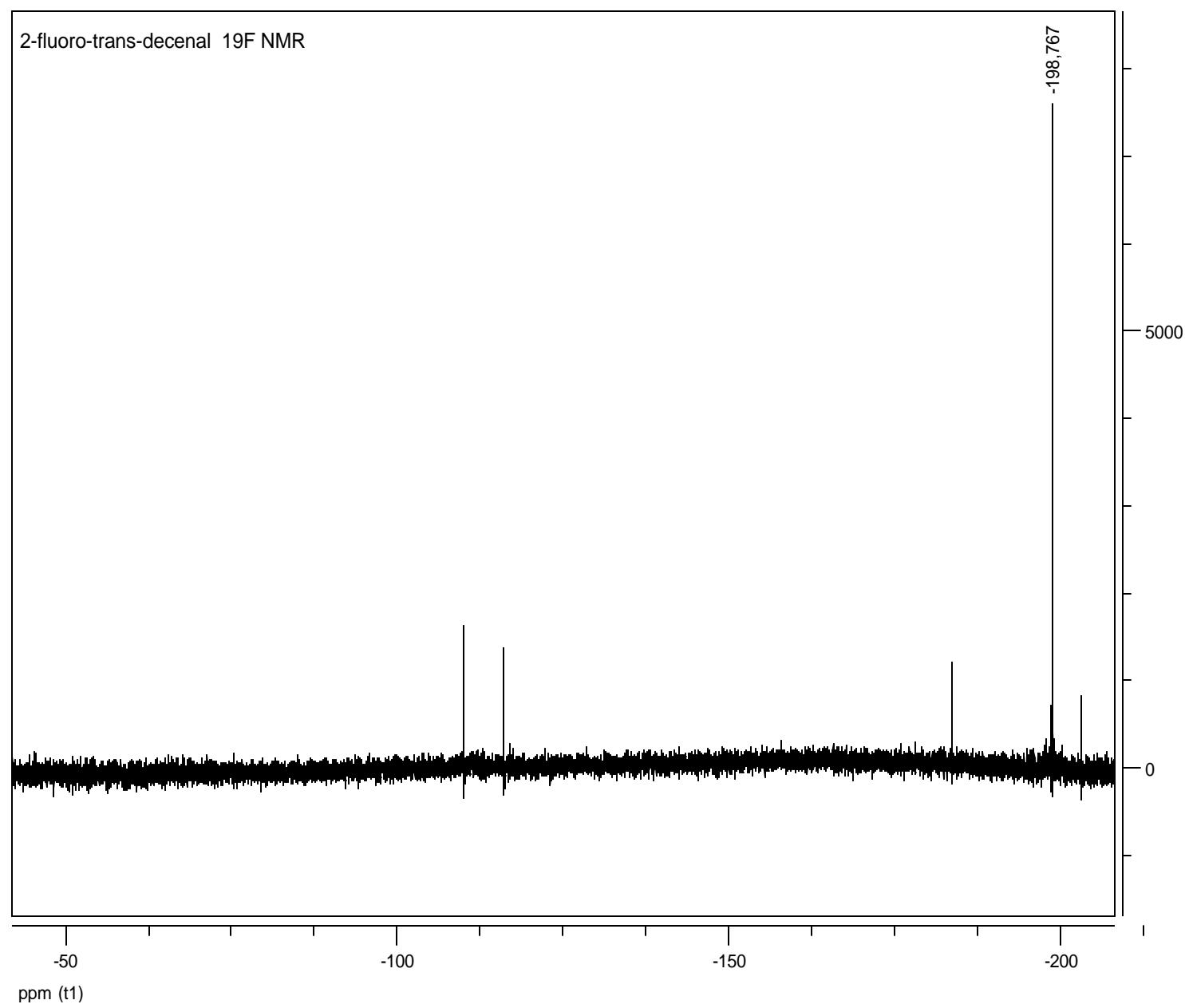
Figure 2:chiral sample



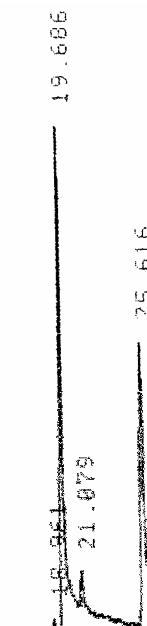
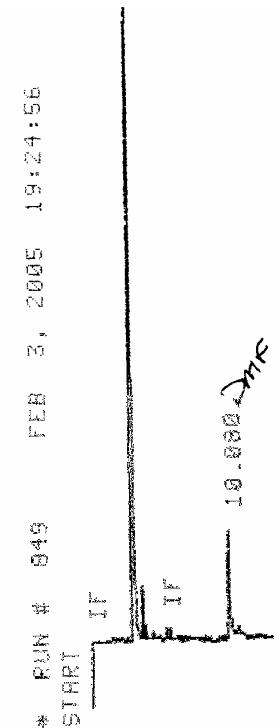
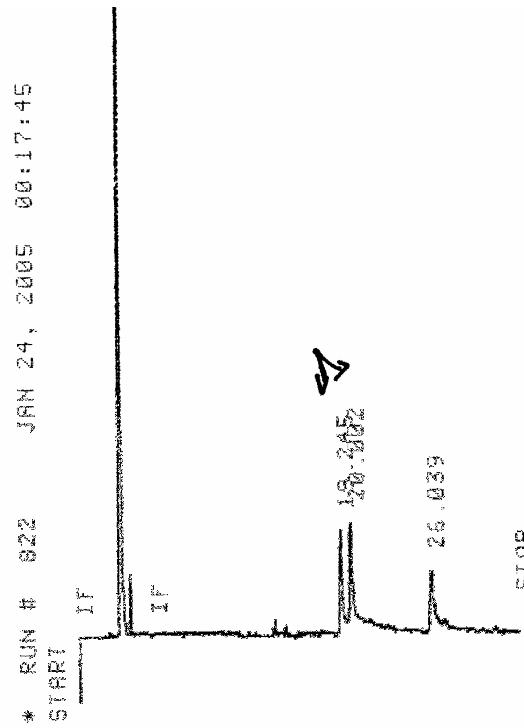




2-fluoro-trans-decenal 19F NMR

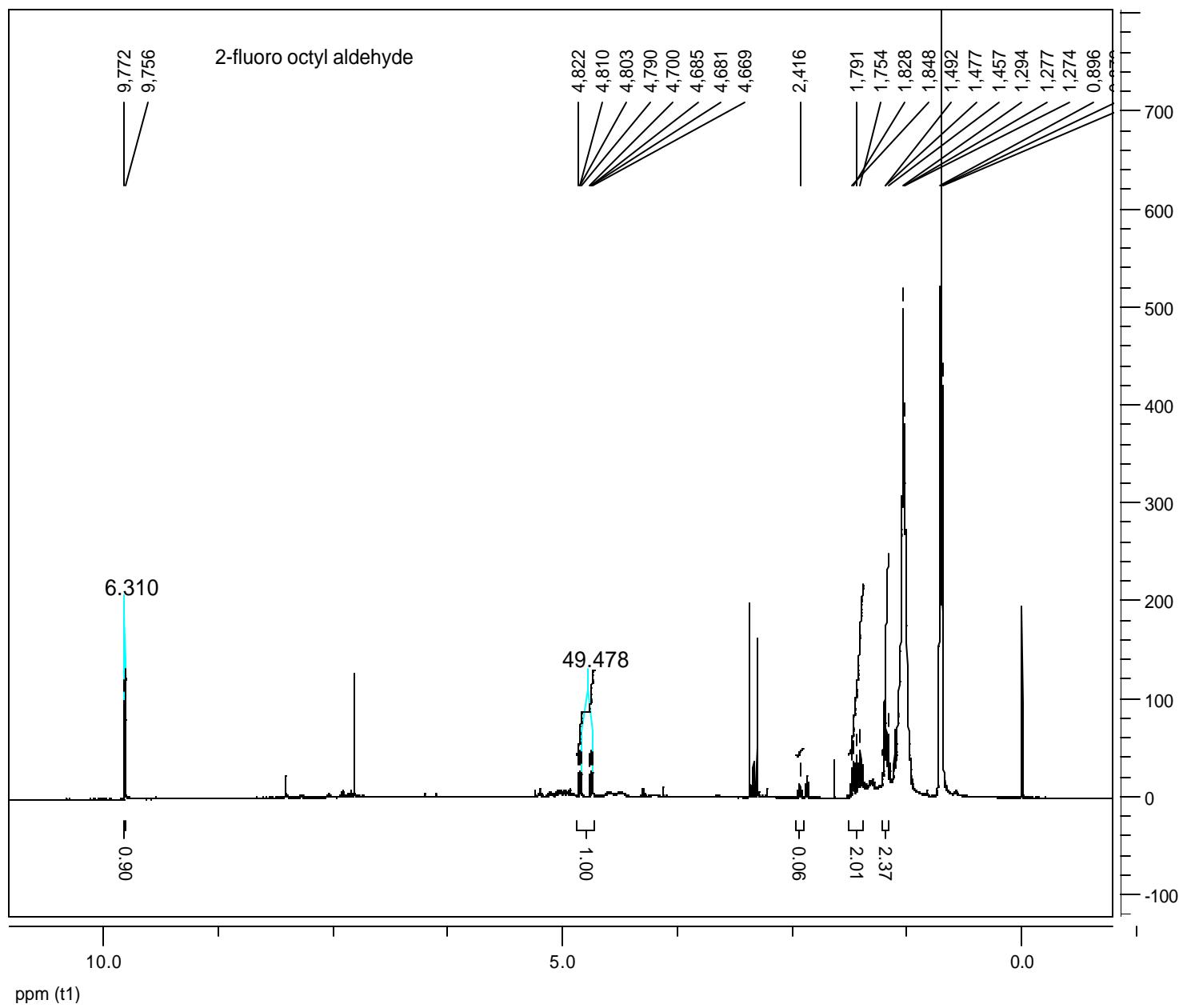


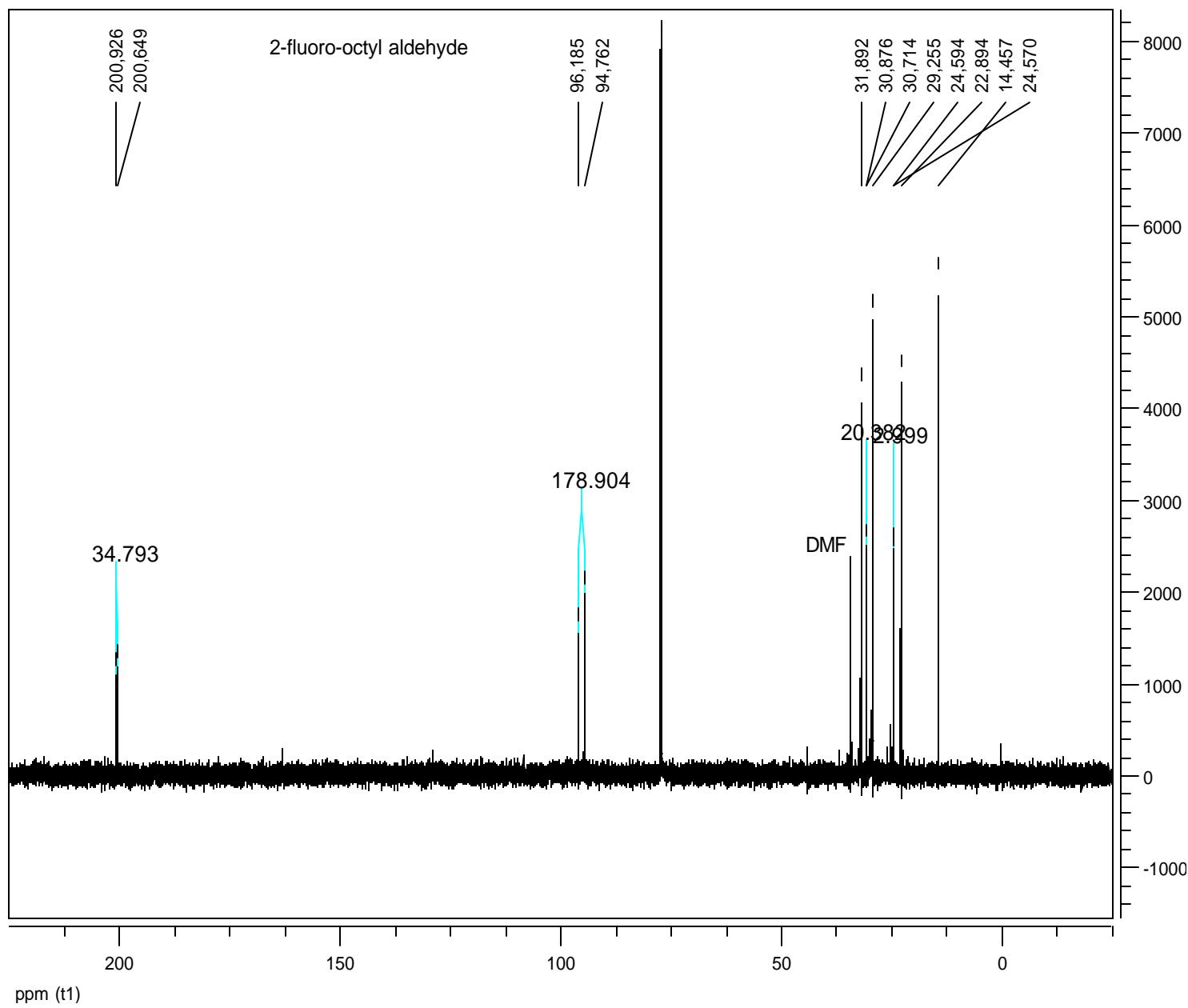
2-Fluoro-4-*trans*-decenal: Bodman ChiralDEX γ -TA (30 m x 0.25 mm) column (80 °C isotherm) isomer (*R*) $t_r = 18.96$ min and isomer (*S*) $t_r = 19.69$ min. 4-*trans*-decenal $t_r = 25.6$ min.



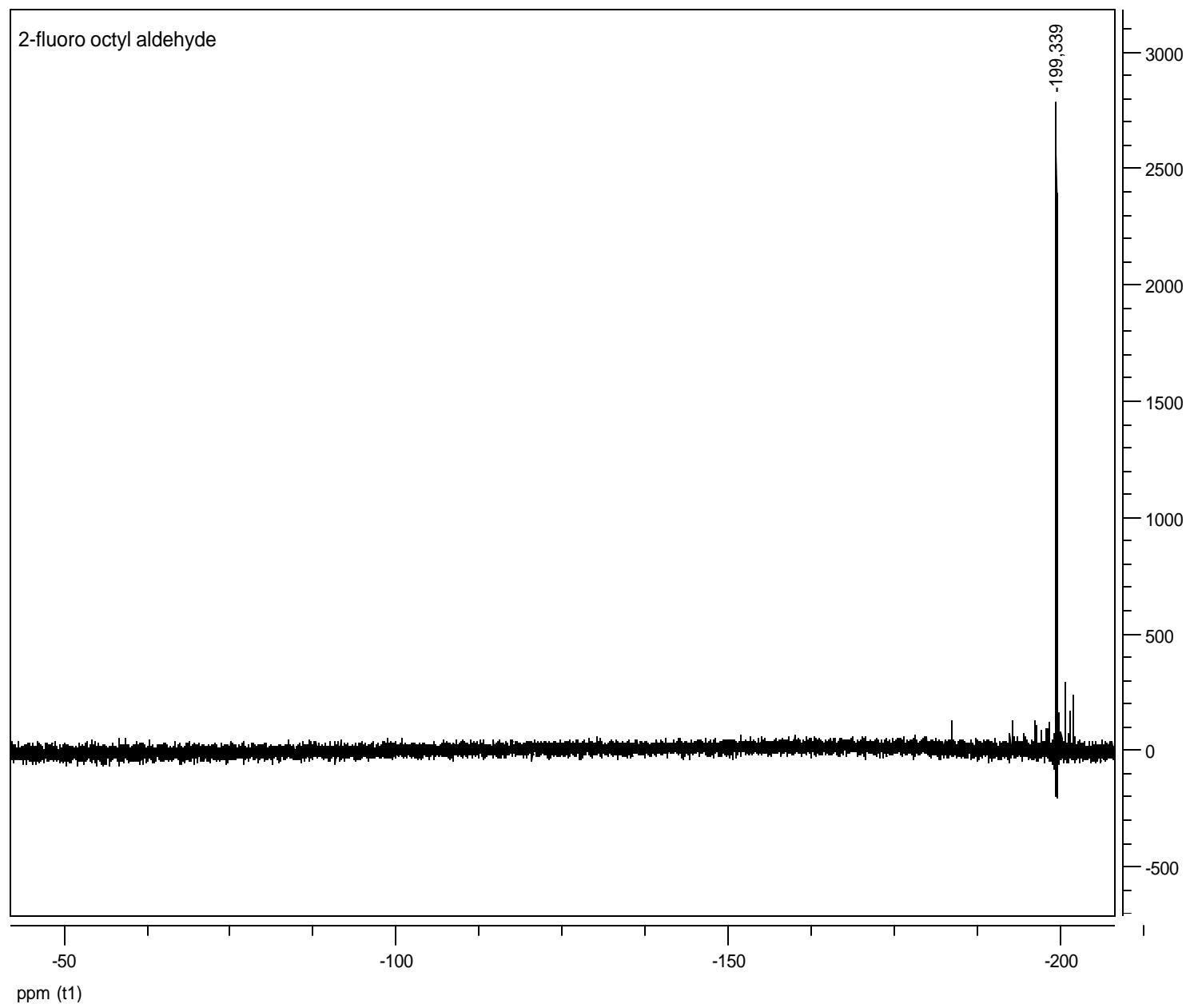
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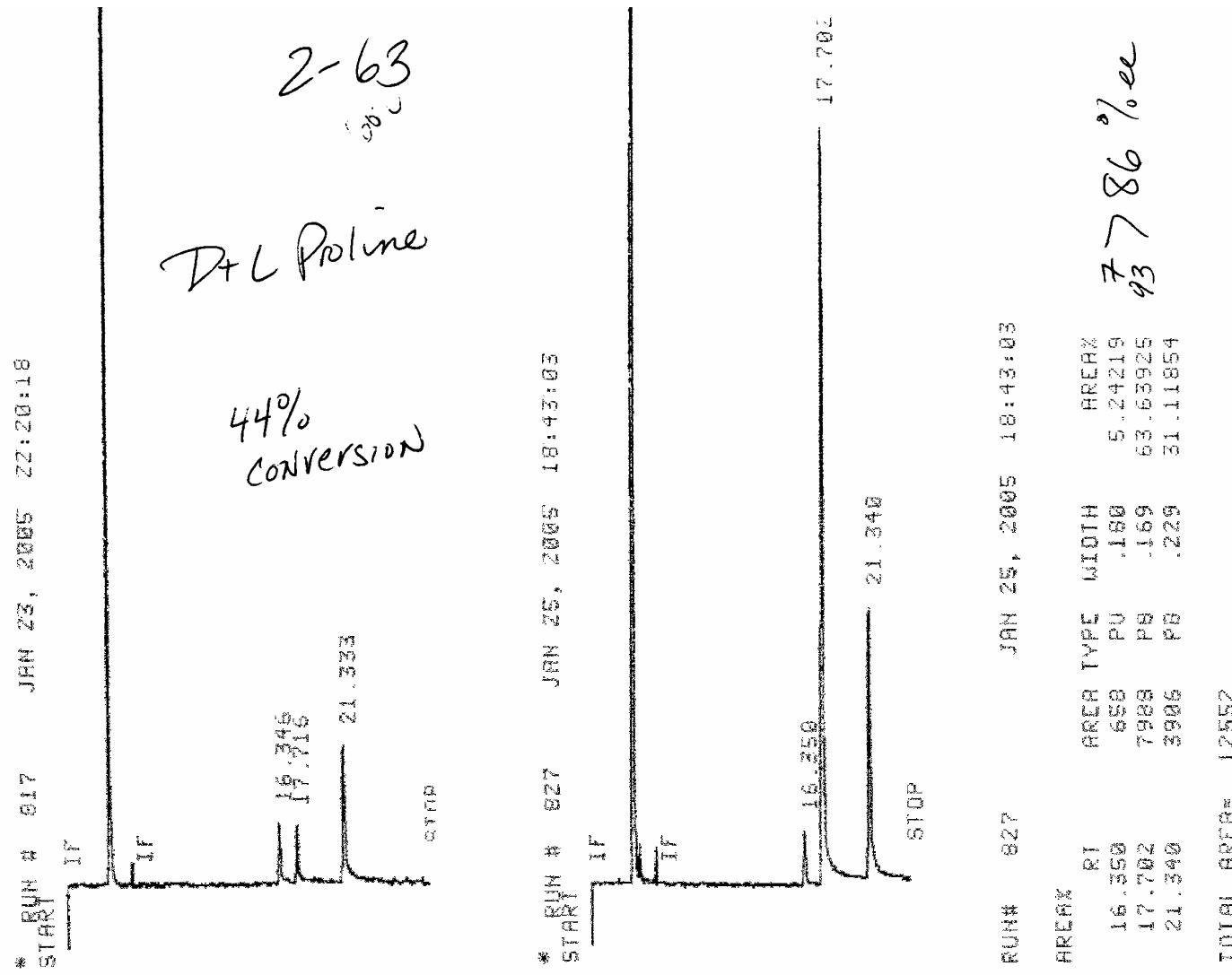


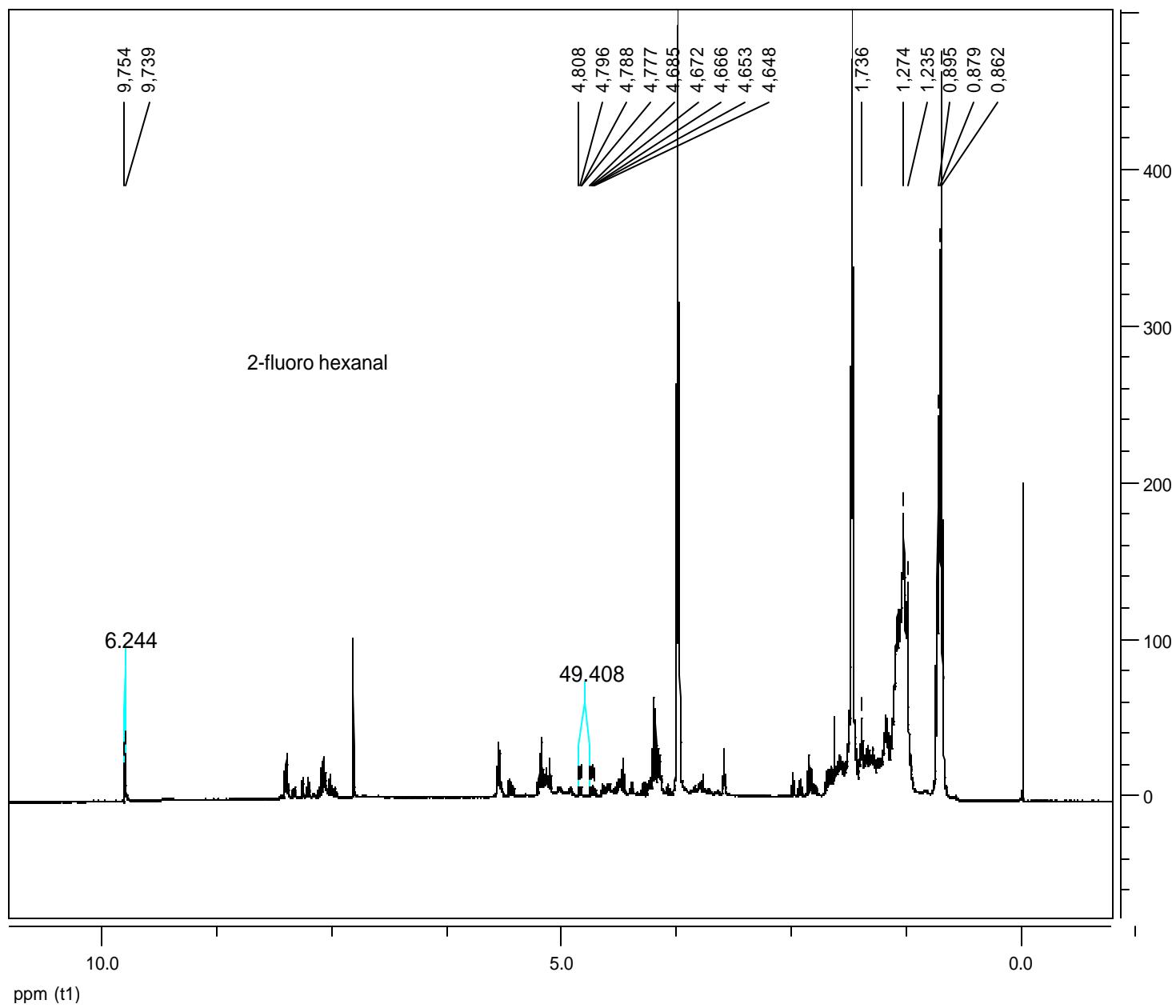


2-fluoro octyl aldehyde

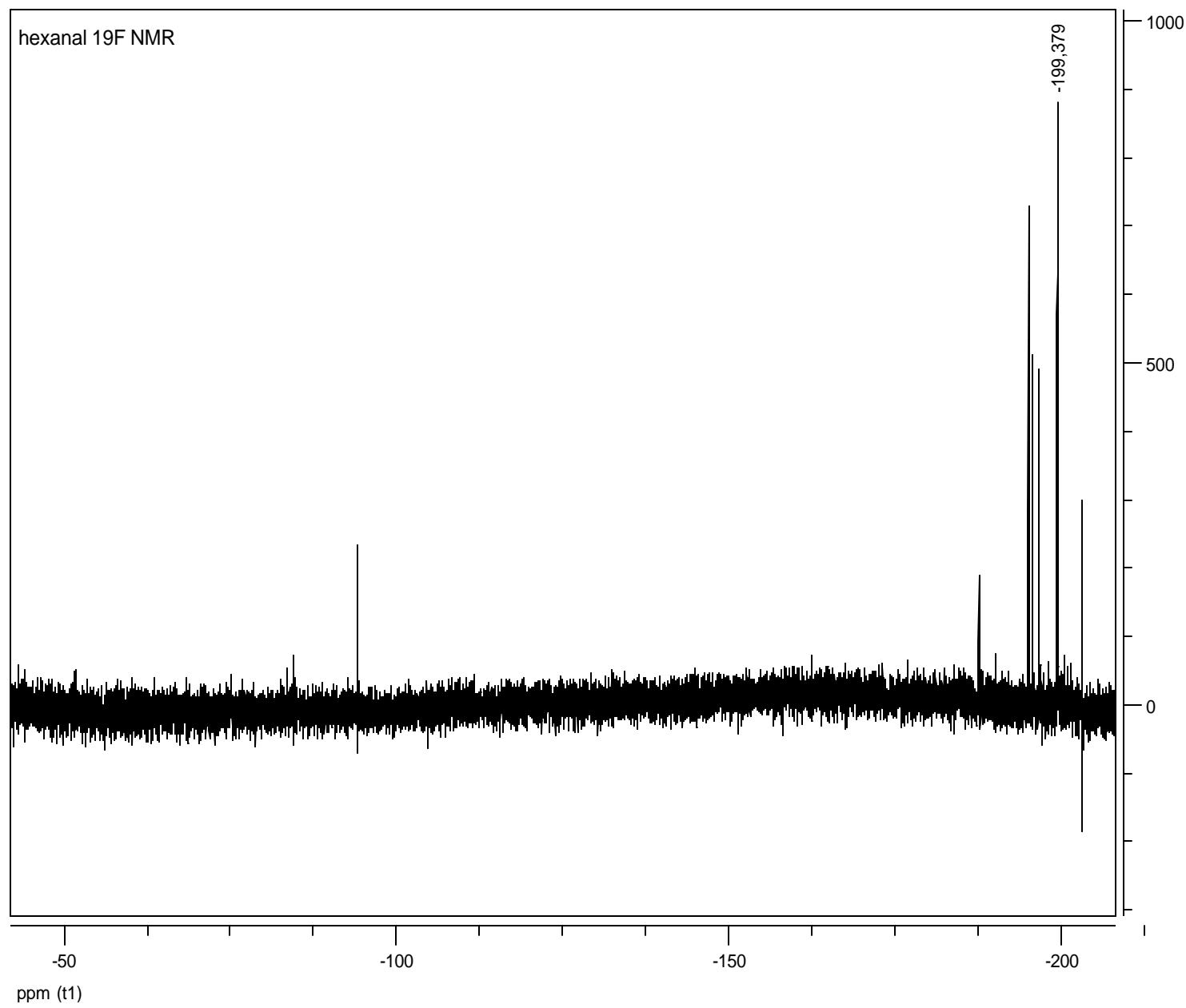


Bodman Chiraldex γ -TA (30 m x 0.25 mm) column (60 °C isotherm) isomer (R) $t_r = 16.35$ min and isomer (S) $t_r = 17.7$ min. Octyl aldehyde $t_r = 21.34$

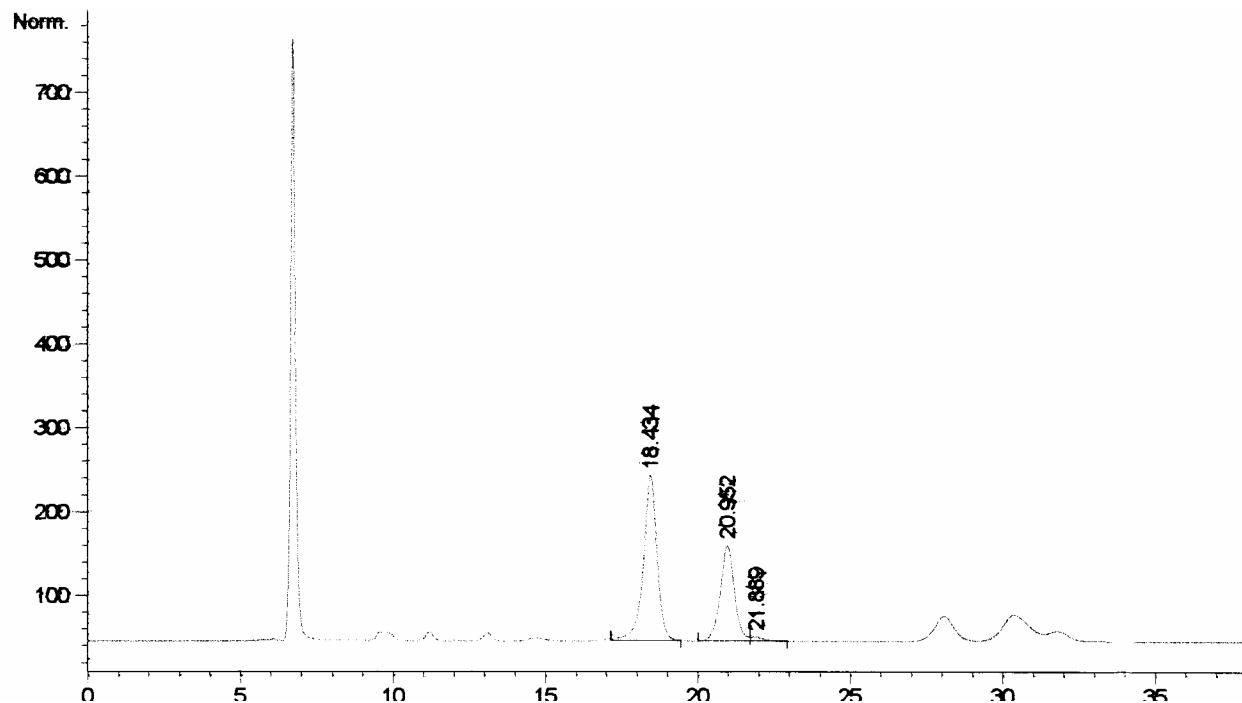


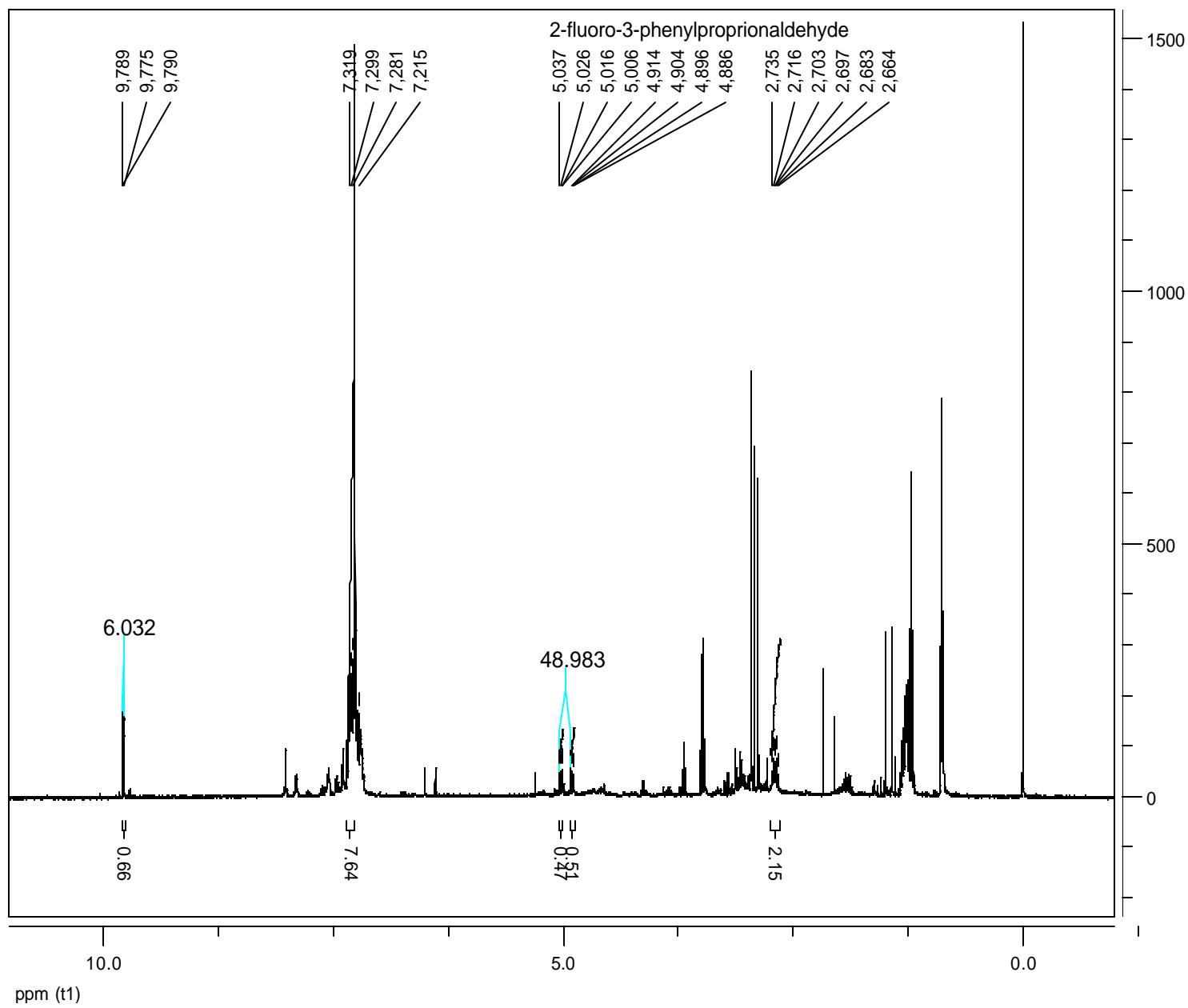


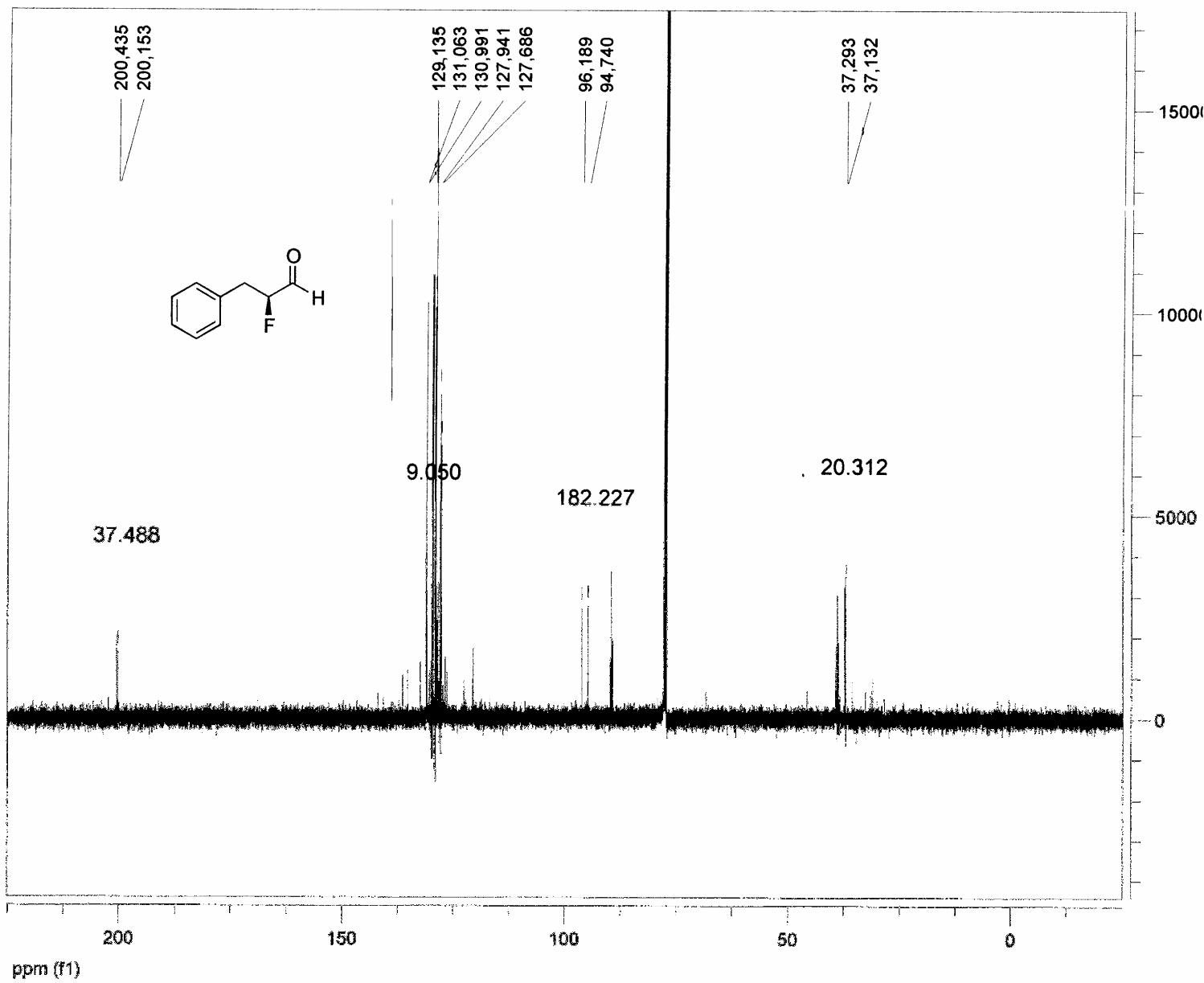
hexanal 19F NMR

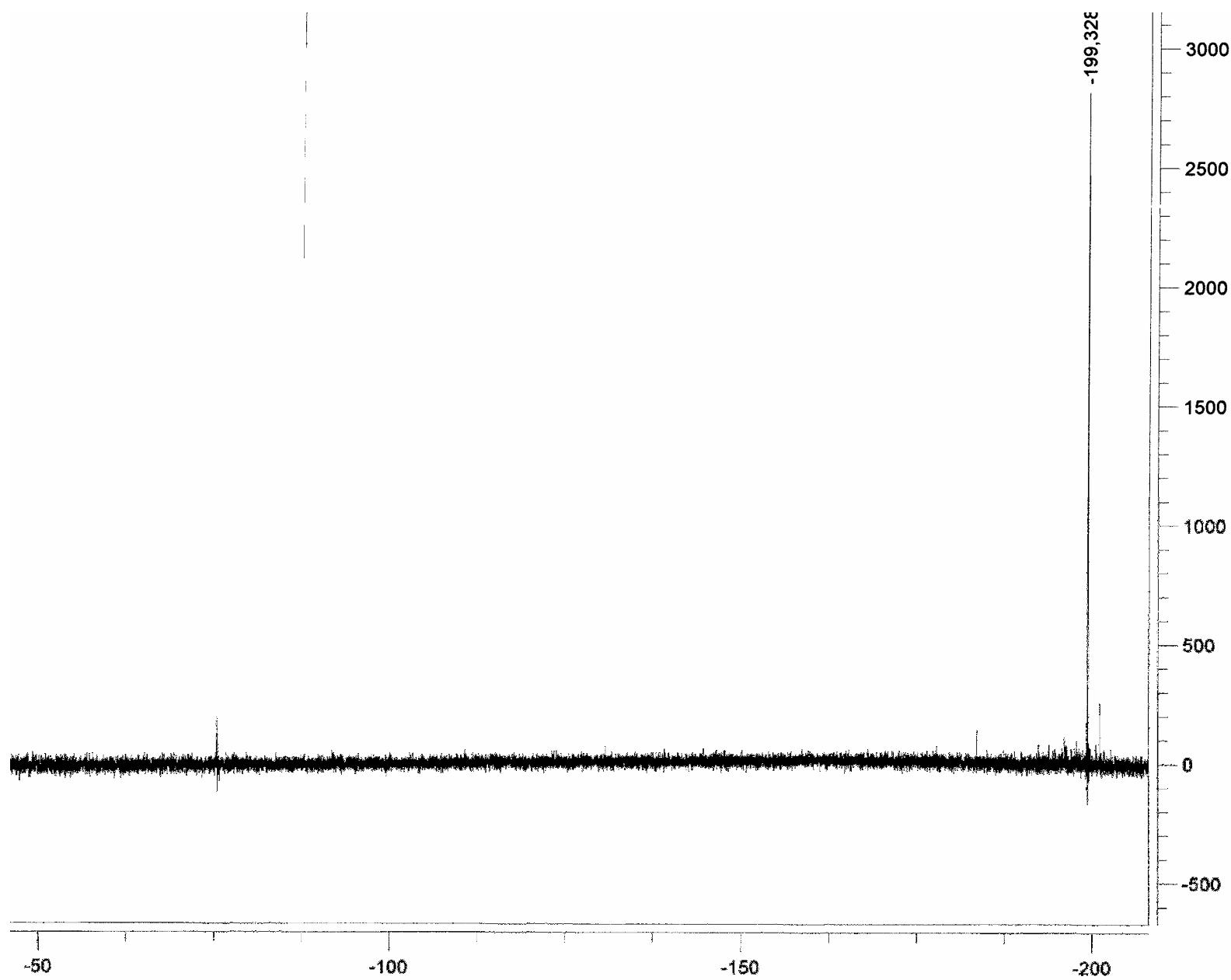


Diacel Chiracel OD-R column (45% acetonitrile/water isocratic) hydrazone of isomer (S) $t_r = 20.95$ min and isomer (R) $t_r = 21.89$ min.
hexanal hydrazone $t_r = 18.43$ min

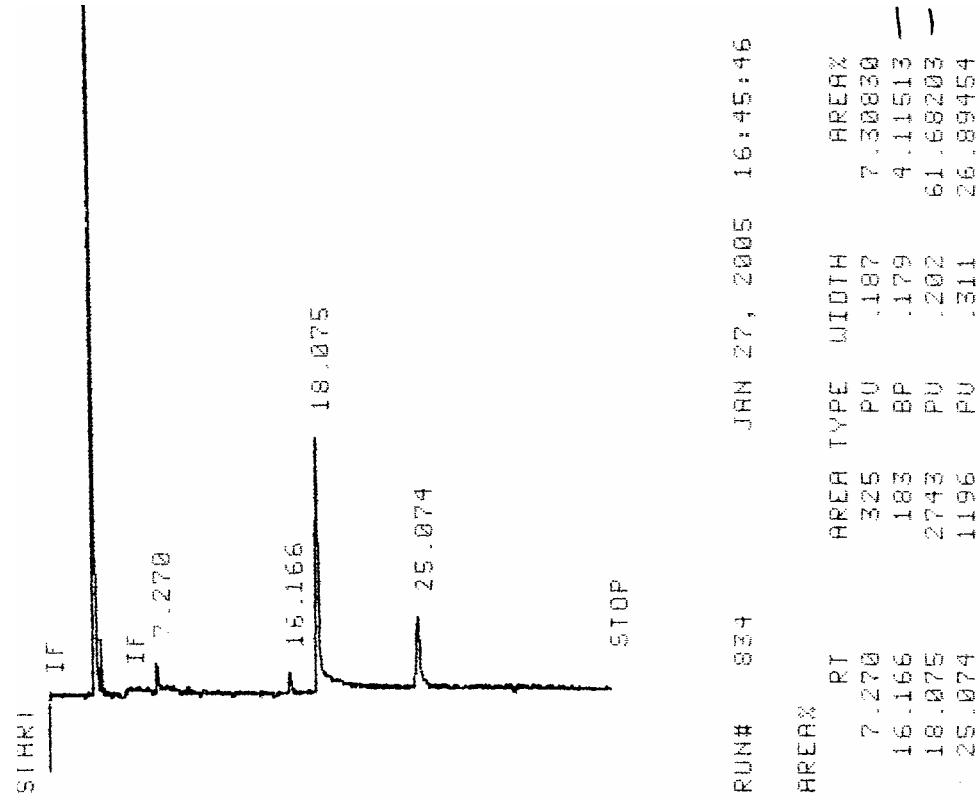


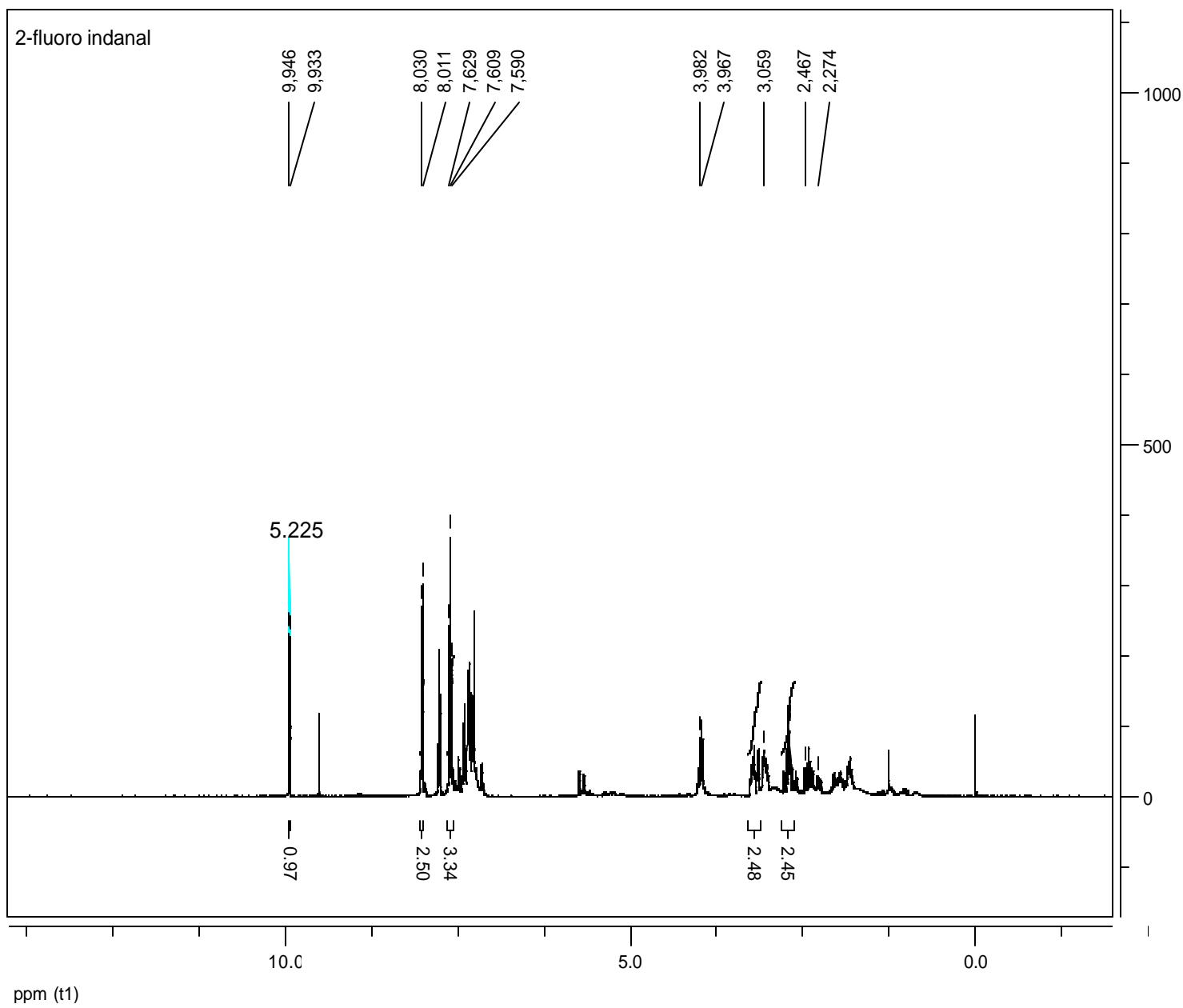


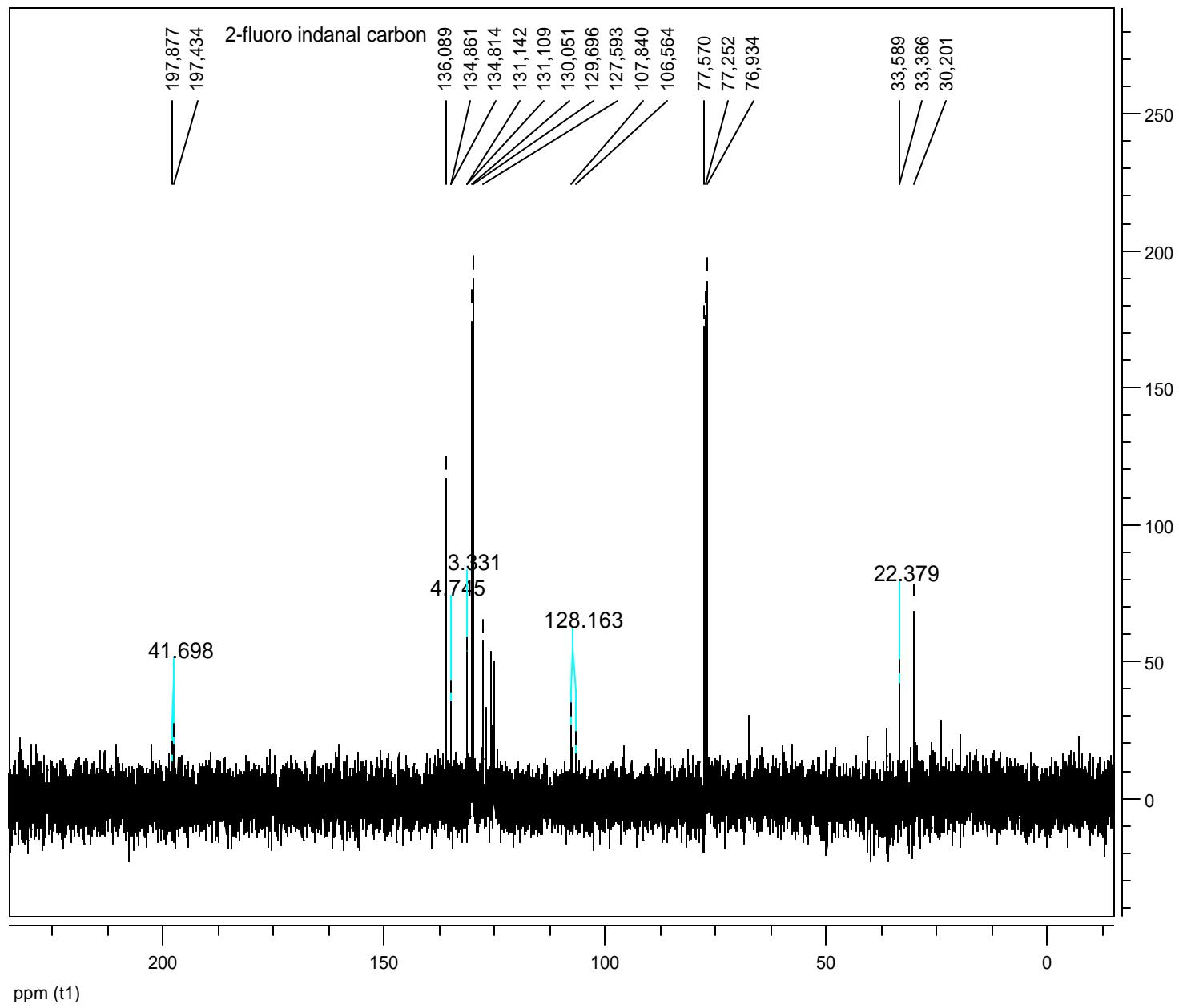




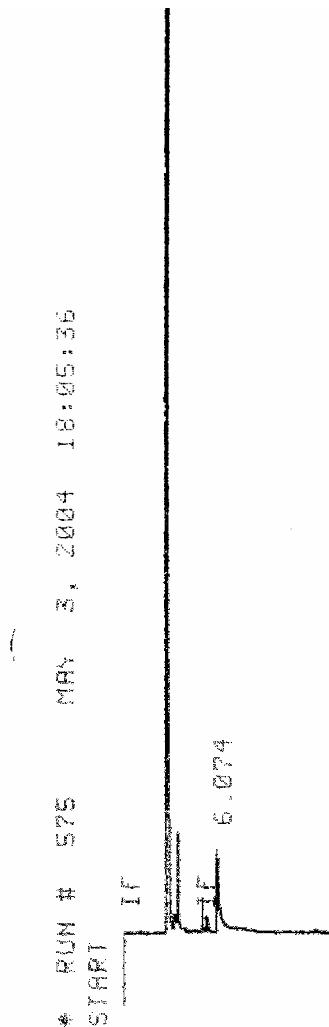
2-fluoro-phenylpropionaldehyde Bodman Chiraldex γ -TA (30 m x 0.25 mm) column (90 °C isotherm) isomer (R) t_r = 16.14 min and isomer (S) t_r = 18.05 min. 2-phenyl propionaldehyde t_r = 26.89 min







2-fluoro-indanaldehyde: Bodman Chiraldex γ -TA (30 m x 0.25 mm) column (110 °C isotherm) isomer t_r = 14.17 min and isomer t_r = 15.07 min. Indanal t_r = 18.32 min.

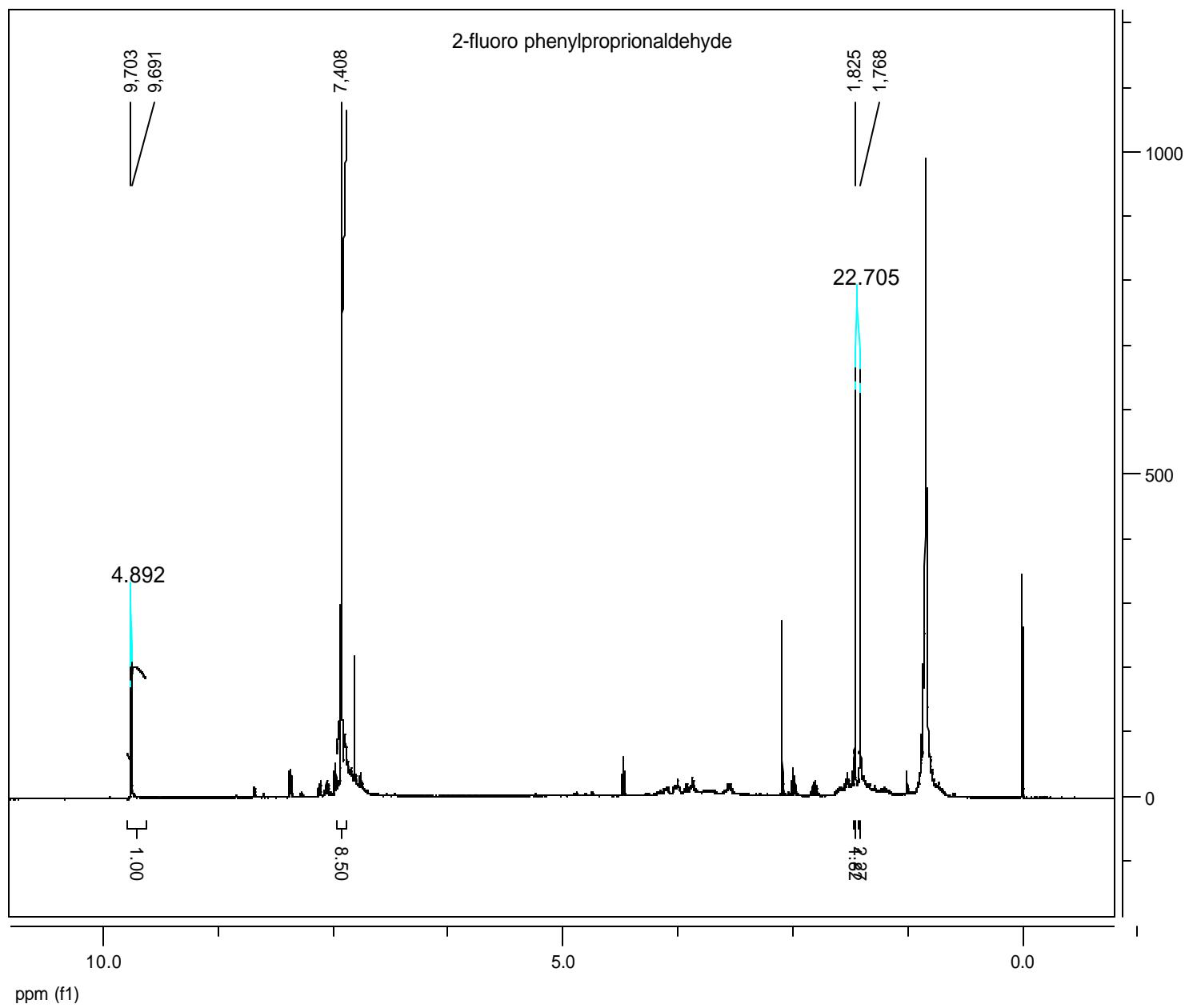


STOP

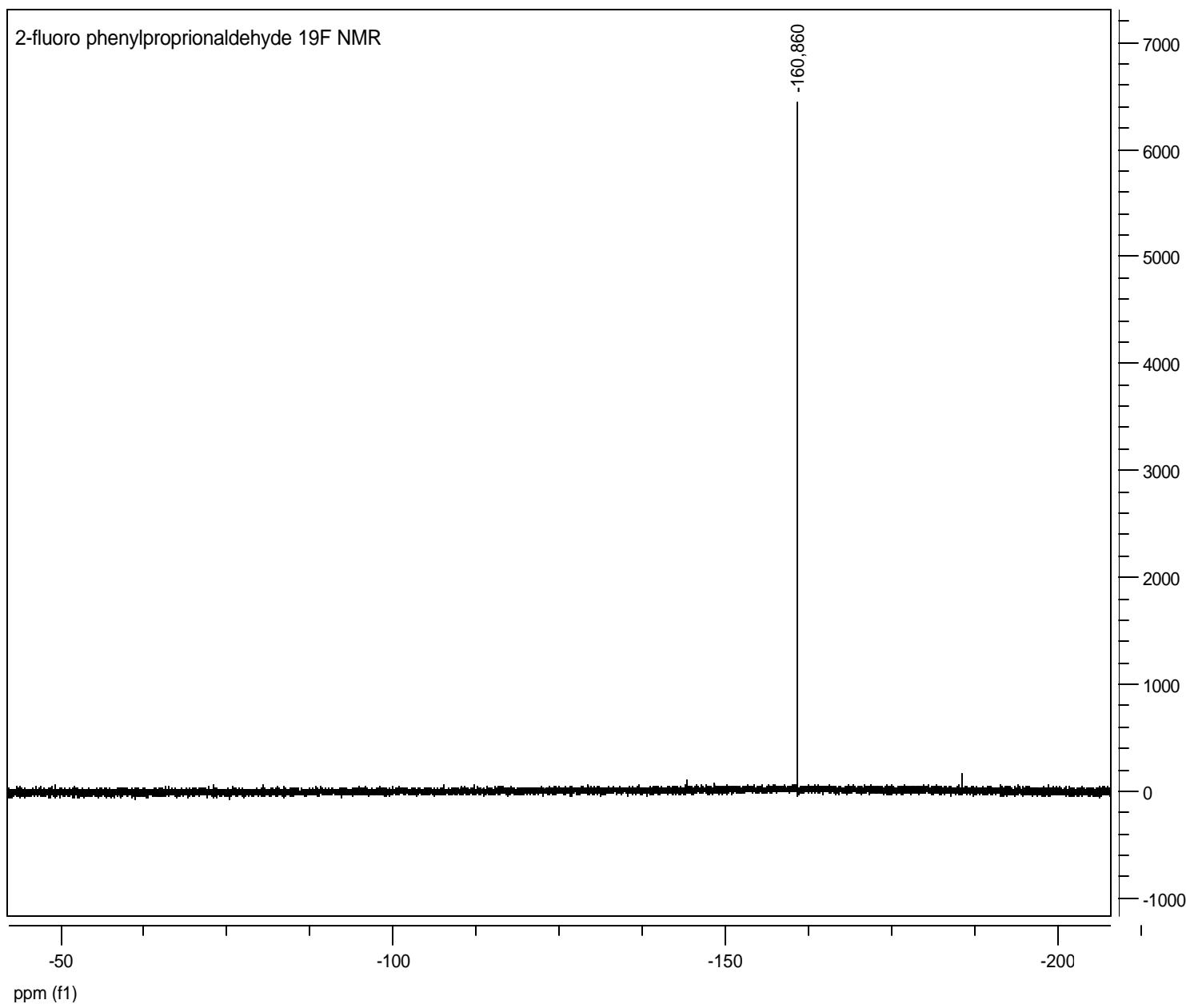
RUN# 575 MAY 3, 2004 18:05:36

AREAX	RT	AREATYPE	WIDOTH	AREAX
6.074	27.35	PG	.157	6.28111
14.176	49.17	PG	.138	14.88782
15.075	24.588	PG	.164	74.42394
18.322	7.95	BU	.182	2.40712

TOTAL AREAS= 33027
MULT. FACTOR=1.0000E+00



2-fluoro phenylpropionaldehyde ^{19}F NMR



2-fluoro-phenylpropionaldehyde: Bodman ChiralDEX γ -TA (30 m x 0.25 mm) column (90 °C isotherm) isomer $t_r = 9.45$ min and isomer $t_r = 11.88$ min.

