SYNTHESIS OF 4-TRIFLUOROMETHYLATED 2-ALKYL AND 2,3-DIALKYLAZETIDINES

Jinlong Jiang,* Hemal Shah and Robert J. DeVita

Department of Medicinal Chemistry, Merck Research Laboratory, P.O. Box 2000, Rahway, NJ 07065

Supporting Information

Experimental

***N*-(*tert*-Butoxycarbonyl)-4-trifluoromethyl lactam 2.** 4-Trifluoromethyl-β-actam was prepared from commercially available carboxylic acid **1**(10 g, 64 mmol) following the literature procedure in 45% yield (3.95 g, 28.4 mmol) as a crude product. The lactam thus obtained was stirred with di-*tert*-butyl bicarbonate (9.2 g, 42.6 mmol) and 4-*N,N*-dimethylpyridine (0.34 g, 2.84 mmol) in CH_2Cl_2 at r.t. for 2 h. The solvent was removed and the crude material was purified by column chromatograph (7:1 hexane: ethyl acetate) to give *N*-*tert*-butoxycarbonyl lactam **2** (3.85 g, 25.2 % from acid). ^{1}H NMR ($CDCl_3$) δ 4.44-4.40 (1 H, m), 3.28 (1 H, dd, J_1 = 16.3 Hz, J_2 = 6.7 Hz), 3.09 (1 H, dd, J_1 = 16.3 Hz, J_2 = 2.3 Hz), 1.50 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 167.1, 146.8, 123.9 (q, J = 278 Hz), 84.9, 50.4 (q, J = 35.9), 38.9, 28.1. Anal. Calcd for $C_9H_{12}F_3NO_3$: C, 45.19; H, 5.06; N, 5.86. Found: C, 45.38; H, 4.90; N, 5.79.

Representative procedure for preparation of Wittig adducts 3: *N*-(*tert*-butoxycarbonyl)-2-(methoxycarbonymethylene)-4-trifluoromethylazetidine (3a). *N*-(*tert*-Butoxycarbonyl)-4-trifluoromethyl lactam (**2**, 0.25 g, 1.05 mmol) and (methoxycarbonylmethylene)triphenylphosphorane (0.46 g, 1.36 mmol) were heated

under nitrogen at reflux in dry toluene (50 ml) for 16 h. The toluene was removed *in vacuo* and the crude material was purified by column chromatography (9:1 hexane: ethyl acetate) to give *N*-(*tert*-butoxycarbonyl)-2-(methoxycarbonylmethylene)-4-trifluoromethylazetidine (**3a**) as an oil (0.26 g, 85% yield). ^{1}H NMR ($CDCl_3$) δ 5.83 (1 H, br s), 4.70-4.60 (1 H, m), 3.69 (3 H, s), 3.42 (1 H, dd, J_1 = 16.9 Hz, J_2 = 6.9 Hz), 3.19 (1 H, dd, J_1 = 16.9 Hz, J_2 = 3.7 Hz), 1.52 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 168.1, 156.3, 150.3, 123.8 (q, J = 279.3), 46.1, 81.6, 59.2 (q, J = 37.9), 51.2, 29.6, 28.2. Anal. Calcd for $C_{12}H_{16}F_3NO_4$: C, 48.81; H, 5.46; N, 4.74. Found: C, 48.62; H, 5.28; N, 4.76.

***N*-(*tert*-Butoxycarbonyl)-2-(cyanomethylene)-4-trifluoromethylazetidine (3b)** was obtained in 82% yield by refluxing in dry toluene for 24 h and was purified by column chromatography (9:1 hexane:ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 5.42 (1 H, br s), 4.73-4.68 (1 H, m), 3.29 (1 H, dd, J = 10.0 Hz, J_2 = 5.7 Hz), 3.28 (1 H, dd, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 1.53 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 157.7, 149.5, 123.1 (q, J = 279.3 Hz), 116.4, 84.3, 74.7, 58.2 (q, J = 38.3 Hz), 28.2, 27.7. Anal. Calcd for $C_{11}H_{13}F_3N_2O_2$: C, 50.38; H, 5.00; N, 10.68. Found: C, 50.46; H, 5.02; N, 10.62.

***N*-(*tert*-Butoxycarbonyl)-2-(1-ethoxycarbonylethylene)-4-trifluoromethylazetidine (3c)** was obtained in 78% yield by refluxing in dry toluene for 48 h and was purified by column chromatography (9:1 hexane:ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 4.60-4.55 (1 H, m), 4.18 (2 H, q, J = 7.1 Hz), 3.50 (1 H, dd, J_1 = 16.8 Hz, J_2 = 1.5 Hz), 3.11 (1 H, dd, J_1 = 16.8 Hz, J_2 = 2.1 Hz), 2.06 (3 H, s), 1.52 (9 H, s), 1.30 (3 H, t, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 168.7, 151.0, 150.7, 124.4 (q, J = 279.3 Hz), 106.9, 83.4, 60.5, 59.7 (q, J = 34.6 Hz), 31.7, 28.2, 14.6, 14.1. Anal. Calcd for $C_{14}H_{20}F_3NO_4$: C, 52.01; H, 6.24; N, 4.33. Found: C, 51.72; H, 6.24; N, 4.24.

Representative procedure for preparation of azetidines 4: *N*-(*tert*-Butoxycarbonyl)-2-(methoxycarbonylmethylene)-4-trifluoromethylazetidine (**3a**) was hydrogenated (45 psi H_2) over Pd on carbon (10% mol) for 12 h. The catalyst was filtered off and the filtrate was concentrated. The crude material was purified by column chromatography (9:1 hexane: ethyl acetate) to give *N*-(*tert*-butoxycarbonyl)-2-(methoxycarbonylmethyl)-4-trifluoromethylazetidine (**4a**) in 92% yield. ^{1}H NMR ($CDCl_3$) δ 4.48-4.40 (2 H, m), 3.70 (3 H, s), 3.00 (1 H, dd, J_1 = 6.2 Hz, J_2 = 4.1 Hz), 2.72-2.65 (1 H, m), 2.09-2.03 (1 H, m), 1.47 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 170.9, 156.3, 124.1 (q, J = 278.3 Hz), 81.5, 58.1 (q, J = 37.4 Hz), 56.3, 52.0, 40.1, 28.4, 23.7. The *cis* relationship between 2-alkyl substituent and the 4- CF_3 group was confirmed by noediff ^{1}H NMR of 2-vinyl compound **7** in which the 2-H and 4-H signals do not overlapped each other. Irradiation of one of 3-protons of olefin **7** resulted in positive noe signals of both 2-H and 4-H. Anal. Calcd for $C_{12}H_{18}F_3NO_4$: C, 49.48; H, 6.10; N, 4.71. Found: C, 49.28; H, 6.27; N, 4.70.

***N*-(*tert*-Butoxycarbonyl)-2-(1-ethoxycarbonylethyl)-4-trifluoromethylazetidine (4b)** was obtained in 78% yield. ^{1}H NMR ($CDCl_3$) δ 4.45-4.37 (2 H, m), 4.18-4.10 (2 H, m), 3.0-2.93 (1 H, m), 2.47-2.40 (1 H, m), 2.21-2.15 (1 H, m), 1.46 (9 H, s), 1.26 (3 H, t, J = 7.1 Hz), 1.22 (3 H, d, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 173.9, 157.0, 124.4 (q, J = 279.3 Hz), 81.4, 60.8, 57.7 (q, J = 34.5 Hz), 43.0, 28.6, 20.0, 14.4, 11.0. Anal. Calcd for $C_{14}H_{22}F_3NO_4$: C, 51.69; H, 6.82; N, 4.31. Found: C, 51.95; H, 6.82; N, 4.35.

Representative procedure for preparation of azetidines 5: *N*-(*tert*-Butoxycarbonyl)-2-(methoxycarbonylmethylene)-4-trifluoromethyl lactam (**3a**, 0.20 g,

0.68 mmol) was stirred with lithium bis(trimethylsilyl)amide (0.60 mL, 0.90 mmol, 1.5 M in toluene) under nitrogen at -78 °C for 10 min. Iodomethane (0.11 mL, 1.8 mmol) was added by injection. The resultant solution was stirred for 2 h at -78 °C. The reaction mixture was quenched with water at -78 °C, allowed to warm up to r.t. and diluted with ethyl acetate. The organic layer was separated and the aqueous was extracted with ethyl acetate. The combined extract was dried ($MgSO_4$) and concentrated. The crude material was purified by column chromatography (5:1 hexane : ethyl acetate) to give *N*-(*tert*-butoxycarbonyl)-2-(methoxycarbonylmethylene)-3-methyl-4-trifluoromethylazetidine (**5a**, 0.16 g, 75% yield). ^{1}H NMR ($CDCl_3$) δ 6.00-5.80 (1 H, br s), 4.24-4.19 (1 H, m), 3.70 (3 H, s), 3.55-3.48 (1 H, m), 1.55 (3 H, d, J = 7.0 Hz), 1.53 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 167.5, 161.0, 150.2, 123.9 (q, J = 279.7 Hz), 95.5, 83.9, 66.0 (q, J = 33.5 Hz), 51.2, 38.0, 28.1, 16.0. The positive noe ^{1}H NMR signal of the 3-CH_3 group resulted from irradiation of 4-H suggests the *trans* relationship between the 4-CF_3 group and the 3-methyl group. Anal. Calcd for $C_{13}H_{18}F_3NO_4$: C, 50.48; H, 5.87; N, 4.53. Found: C, 50.68; H, 5.89; N, 4.41.

***N*-(*tert*-Butoxycarbonyl)-2-(methoxycarbonylmethylene)-3-(2,4-difluorobenzyl)-4-trifluoromethylazetidine** (**5b**) was obtained from 2,4-difluorobenzyl bromide and compound **3a** in 68% yield. ^{1}H NMR ($CDCl_3$) δ 6.80 (2 H, d, J = 6.6 Hz), 6.73 (1 H, t, J = 8.9 Hz), 5.85 (1 H, br s), 4.25-4.22 (1 H, m), 3.75 (3 H, s), 3.71 (1 H, dd, J_1 = 7.8 Hz, J_2 = 2.5 Hz), 3.63 (1 H, dd, J_1 = 4.2 Hz, J_2 = 2.1 Hz), 2.92 (1 H, dd, J_1 = 14.3 Hz, J_2 = 9.5 Hz), 1.51 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 167.7, 163.4 (d, J = 242.1 Hz), 163.3 (d, J = 242.1 Hz), 149.8, 141.0 (t, J = 9.3 Hz), 123.4 (q, J = 279.7 Hz), 112.1 (dd, J_1 = 18.0 Hz, J_2 = 6.3 Hz), 102.9 (t, J = 25.7 Hz), 96.3, 84.2, 63.4 (q, J = 22.6 Hz), 51.5,

43.5, 35.3, 28.2. Anal. Calcd for $C_{19}H_{20}F_3NO_4$: C, 54.16; H, 4.78; N, 3.32. Found: C, 54.29; H, 4.74; N, 3.07.

***N*-(*tert*-Butoxycarbonyl)-2-(methoxycarbonylmethylene)-3-(α-hydroxybenzyl)-4-trifluoromethylazetidine (5c)** was obtained from benzaldehyde and compound **3a** in 71% yield. ^{1}H NMR ($CDCl_3$) δ 7.47–7.30 (5 H, m), 6.10-6.00 (1 H, br s), 5.53-5.42 (1 H, br s), 5.17 (2 H, d, J = 8.2 Hz), 4.22-4.18 (1 H, m), 3.80 (1 H, dd, J_1 = 15.8 Hz, J_2 = 8.4 Hz), 3.78 (3 H, s), 1.47 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 169.7, 158.1, 139.9, 128.9, 128.8, 125.5, 123.5 (q, J = 281.2 Hz), 97.0, 84.4, 74.2, 61.5 (q, J = 35.4 Hz), 52.1, 49.9, 28.1. Anal. Calcd for $C_{19}H_{22}F_3NO_5$: C, 56.86; H, 5.52; N, 3.49. Found: C, 57.07; H, 5.42; N, 3.28.

Representative procedure for preparation of 3-substituted azetidine 6: *N*-(*tert*-Butoxycarbonyl)-2-(methoxycarbonylmethylene)-4-trifluoromethyl lactam (**5a**, 0.10 g, 0.32 mmol) was hydrogenated (45 psi H_2) over Pd on carbon (10% mol) for 12 h. The catalyst was filtered off and the filtrate was concentrated. The crude material was purified by column chromatography (9:1 hexane : ethyl acetate) to give *N*-(*tert*-butoxycarbonyl)-2-(methoxycarbonylmethyl)-3-methyl-4-trifluoromethylazetidine (**6a**, 0.091 g, 90% yield). ^{1}H NMR ($CDCl_3$) δ 4.01-3.94 (2 H, m). 3.68 (3 H, s), 2.98 (1 H, dd, J_1 = 16.4 Hz, J_2 = 4.3 Hz), 2.65 (1 H, dd, J_1 = 16.4 Hz, J_2 = 9.9 Hz), 2.41-2.35 (1 H, m), 1.44 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 171.0, 156.4, 124.3 (q, J = 278.1 Hz), 81.3, 64.7 (q, J = 34.3 Hz), 51.8, 39.6, 33.4, 28.4, 18.3. Positive noe signals of 3-H resulted from irradiation of 2-CH_2 protons indicate that the 3-CH_3 group and 2-CH_2CO_2Me group have the *trans* relationship. Anal. Calcd for $C_{13}H_{20}F_3NO_4$: C, 50.16; H, 6.48; N, 4.50. Found: C, 49.89; H, 6.35; N, 4.55.

***N*-(*tert*-Butoxycarbonyl)-2-(methoxycarbonylmethyl)-3-(2,4-difluorobenzyl)-4-trifluoromethylazetidine (6b)** was obtained in 93% yield. ^{1}H NMR ($CDCl_3$) δ 6.78-6.70 (3 H, m), 4.18-4.11 (2 H, m), 3.68 (3 H, s), 3.15 (1 H, dd, J_1 = 15.8 Hz, J_2 = 5.9 Hz), 2.98 (1 H, dd, J_1 = 16.1 Hz, J_2 = 4.2 Hz), 2.87 (1 H, dd, J_1 = 13.9 Hz, J_2 = 8.9 Hz), 2.69 (1 H, dd, J_1 = 16.2 Hz, J_2 = 9.8 Hz), 1.46 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 170.9, 163.2 (dd, J_1 = 249.5, J_2 = 13.4), 156.2, 141.3 (t, J = 8.6), 123.9 (q, J = 279.3 Hz), 112.1 (dd, J_1 = 19.2, J_2 = 5.7 Hz), 102.7 (t, J = 25.9 Hz), 81.75, 62.7 (q, J = 34.5 Hz), 61.4, 52.0, 39.5, 39.1, 38.5, 28.4. Anal. Calcd for $C_{19}H_{22}F_5NO_4$: C, 53.91; H, 5.24; N, 3.31. Found: C, 54.06; H, 5.30; N, 3.18.

***N*-(*tert*-Butoxycarbonyl)-2-(methoxycarbonylmethyl)-3-(α-hydroxybenzyl)-4-trifluoromethylazetidine (6c)** was obtained in 87% yield. ^{1}H NMR ($CDCl_3$) δ 7.30-7.21 (5 H, m), 4.86 (1 H, d, J = 8.2 Hz), 4.44-4.42 (1 H, m), 4.43-4.08 (1 H, m), 3.90 (1 H, br s), 3.70 (3 H, s), 3.00 (1 H, dd, J_1 = 7.1 Hz, J_2 = 3.7 Hz), 2.75 (1 H, dd, J_1 = 16.7 Hz, J_2 = 10.0 Hz), 2.68-2.60 (1 H, m), 1.47 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 172.6, 156.2, 140.1, 128.9, 126.8, 125.7, 123.8 (q, J = 279.3 Hz), 60.2 (q, J = 35.3 Hz), 52.5, 45.1, 39.0, 28.4. Anal. Calcd for $C_{19}H_{24}F_3NO_5$: C, 56.57; H, 6.00; N, 3.47. Found: C, 56.79; H, 6.22; N, 3.47.

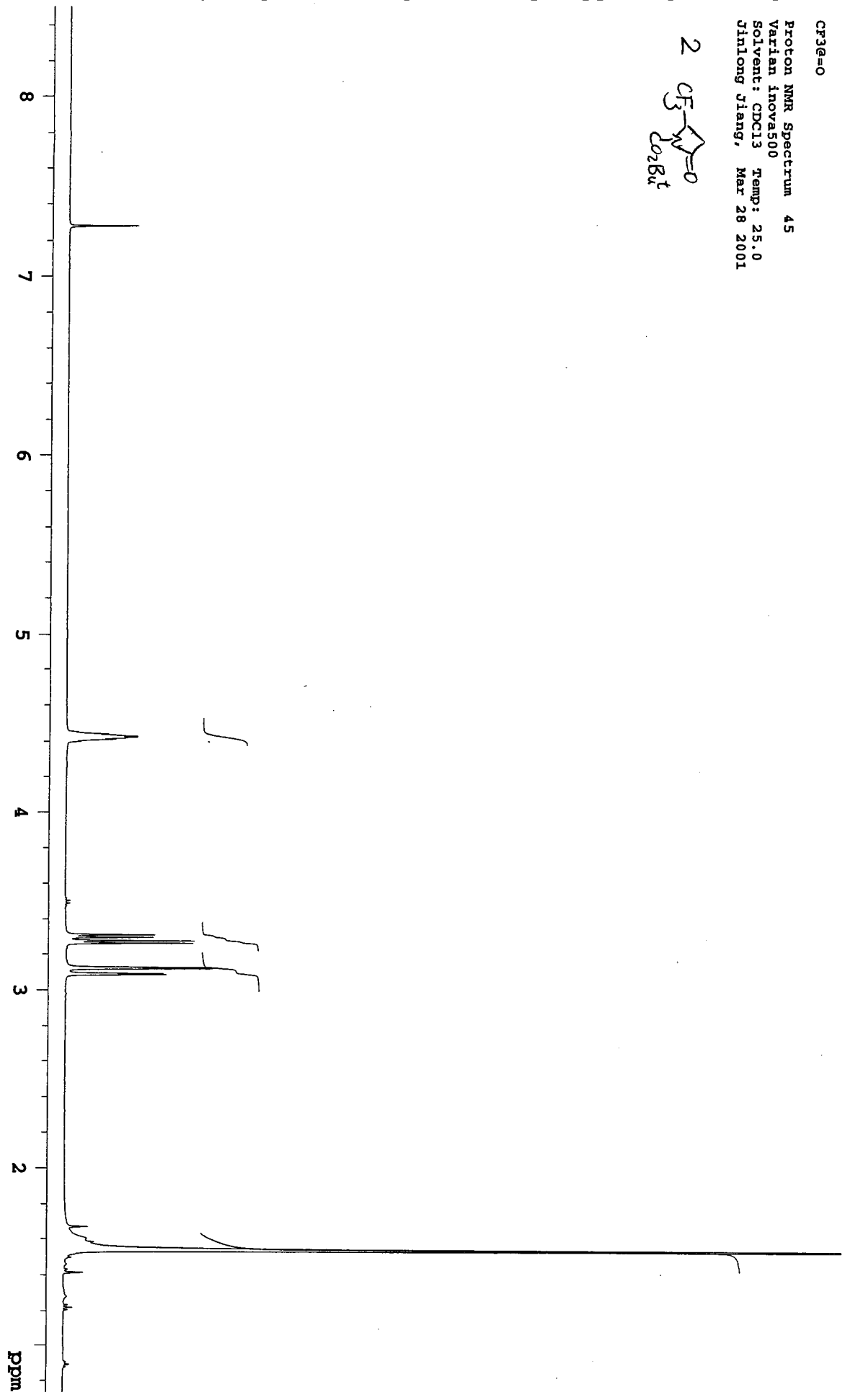
Preparation of *N*-(*tert*-butoxycarbonyl)-2-vinyl-4-trifluoromethylazetidine (7): *N*-(*tert*-Butoxycarbonyl)-2-(methoxycarbonylmethyl)-4-trifluoromethylazetidine (**4a**, 1.5 g, 5.1 mmol) was stirred in a mixture of methanol (20 mL) and aqueous solution of NaOH (20 mL, 2 *N*) for 4 h. The methanol was removed and the aqueous was acidified with saturated $KHSO_4$ aqueous solution to pH = 3-4 and was extracted with ethyl acetate (20 mL x 3). The combined organic extract was washed with brine and dried

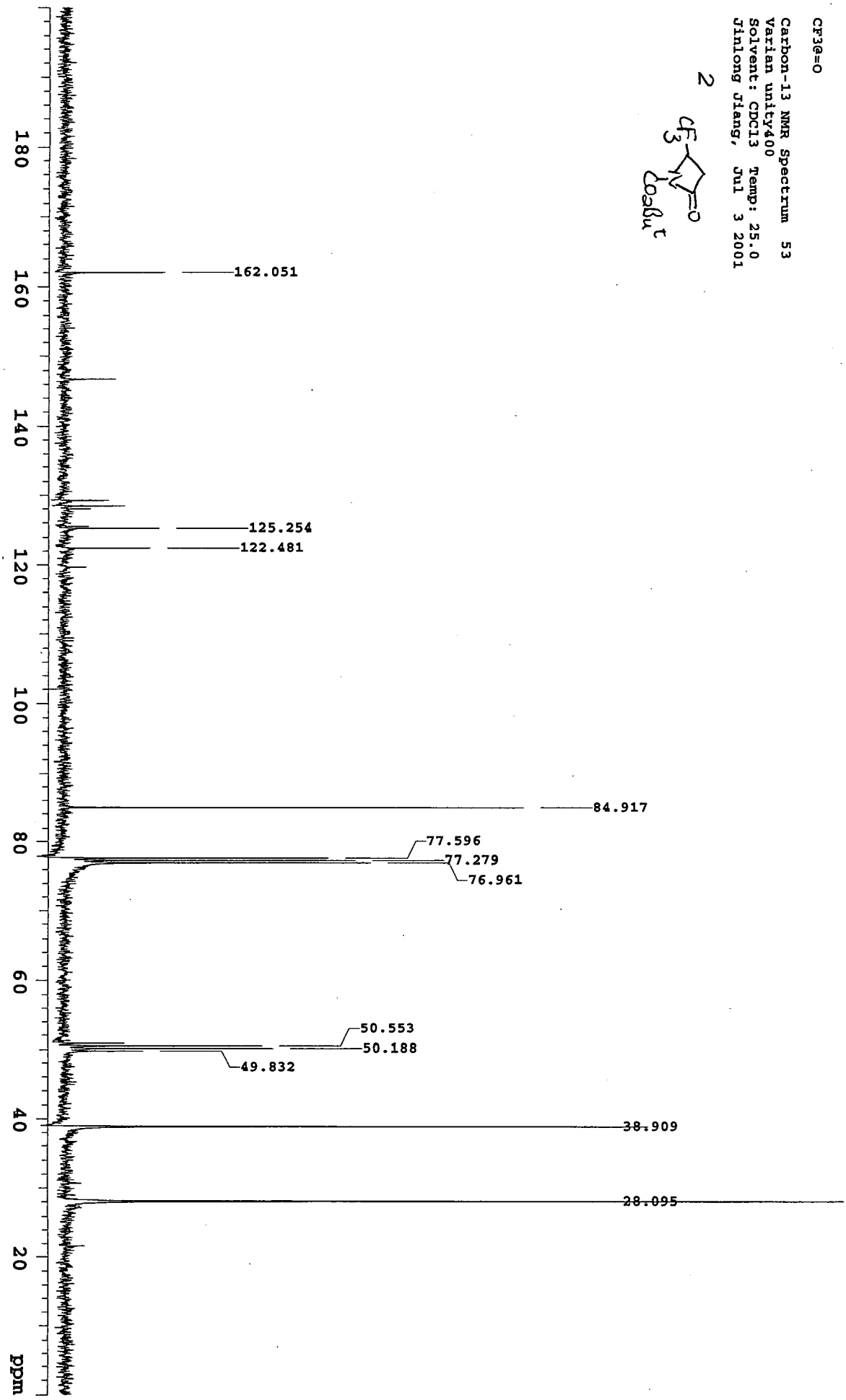
($MgSO_4$). The crude material thus obtained was treated with isobutyl chloroformate (0.85 g, 6.2 mmol) and trimethyl amine (1 mL, 7.2 mmol) in THF (20 mL) at -10 °C for 0.5 h then at r.t. for 2 h. The white solid was filtered off and the filtrate was reacted at r.t. with aqueous suspension of $NaBH_4$ (obtained by adding 0.75 g of $NaBH_4$ to 10 mL of water) for 16 h. The reaction mixture was diluted with ether and the organic layer was separated. The aqueous was extracted with ether (25 mL x 3) and the combined organic extract was washed with brine. The solvent was removed to give crude *N*-(*tert*-butoxycarbonyl)-2-(2-hydroxyethyl)-4-trifluoromethylazetidine that was directly used for the next step.

To a solution of the alcohol obtained above and *o*-nitrophenyl selenocyanate (3.4 g, 15.1 mmol) in THF (25 mL) was added tri-*n*-butylphosphine (3.1 g, 15.4 mmol) at 0 °C in 3 min. The mixture was stirred at 20 °C for 1 h and 30% aqueous hydrogen peroxide (20 mL) was added at 0 °C. The resultant mixture was stirred at 20 °C for 3 h, diluted with ether and quenched with saturated sodium bicarbonate. The aqueous was extracted with ether. The combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (9:1 hexane : ethyl acetate) to give compound **7** as an oil (0.53 g, 43% overall yield). ^1H NMR ($CDCl_3$) δ 6.04-5.97 (1 H, dd, J_1 = 17. 1 Hz, J_2 = 10.3 Hz), 5.31 (1 H, J = 17.1 Hz), 5.22 (1 H, d, J = 10.3 Hz), 4.60-4.50 (1 H, m), 4.48-4.40 (1 H, m), 2.69-2.60 (1 H, m), 2.13-1.57 (1 H, m), 1.46 (9 H, s). Irradiation of one of 3-protones resulted in positive noe signals of both 2-H and 4-H. This confirmed that the 4-CF_3 group and the 2-substituent have a cis relationship. ^{13}C NMR ($CDCl_3$) δ 156.6, 137.3, 124.2 (q, J = 278.3), 117.1,

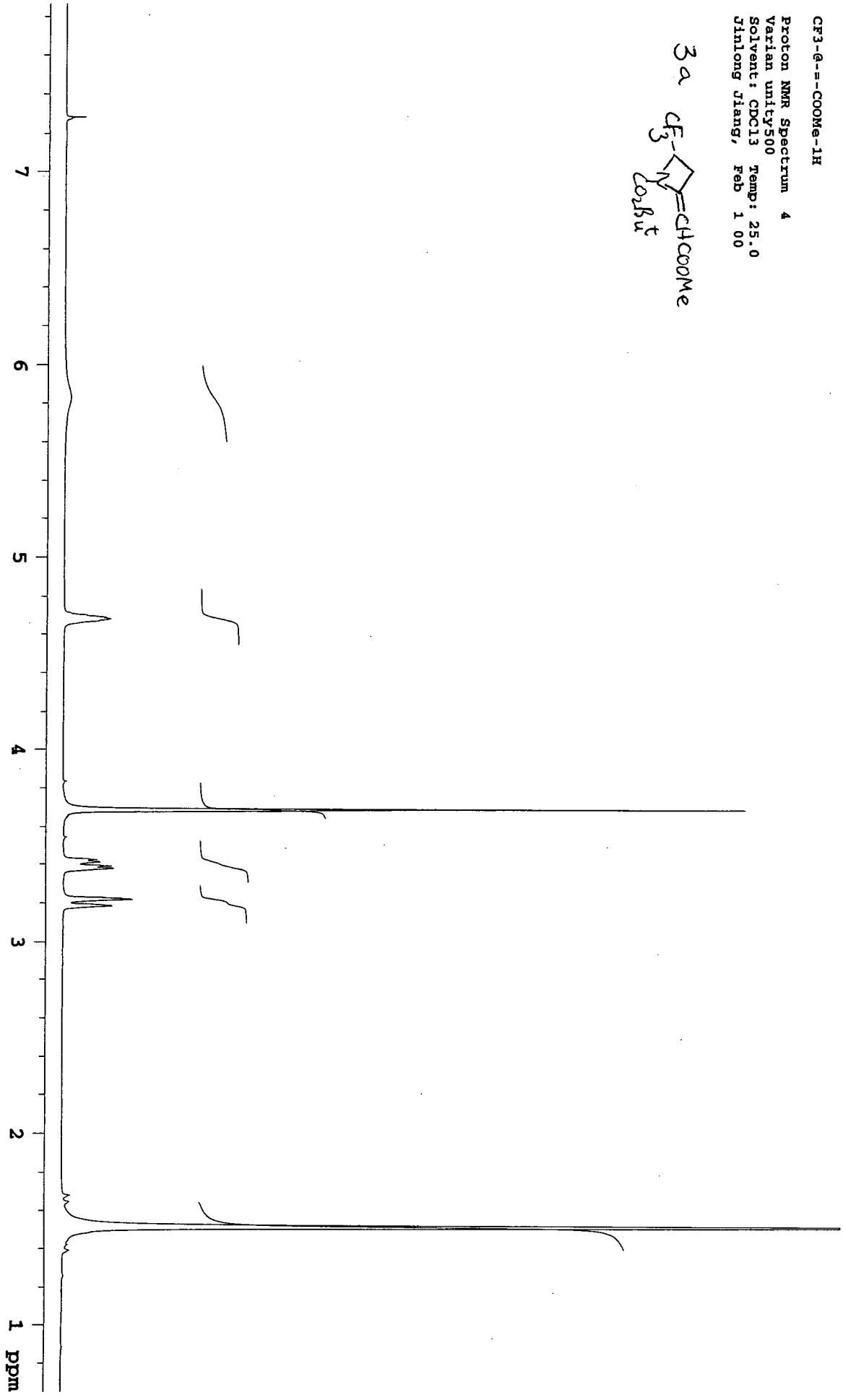
81.2, 61.3, 57.5 (q, J = 32.4), 28.4, 23.9. Anal. Calcd for $C_{11}H_{16}F_3NO_2$: C, 52.59; H, 6.42; N, 5.57. Found: C, 52.68; H, 6.32; N, 5.98.

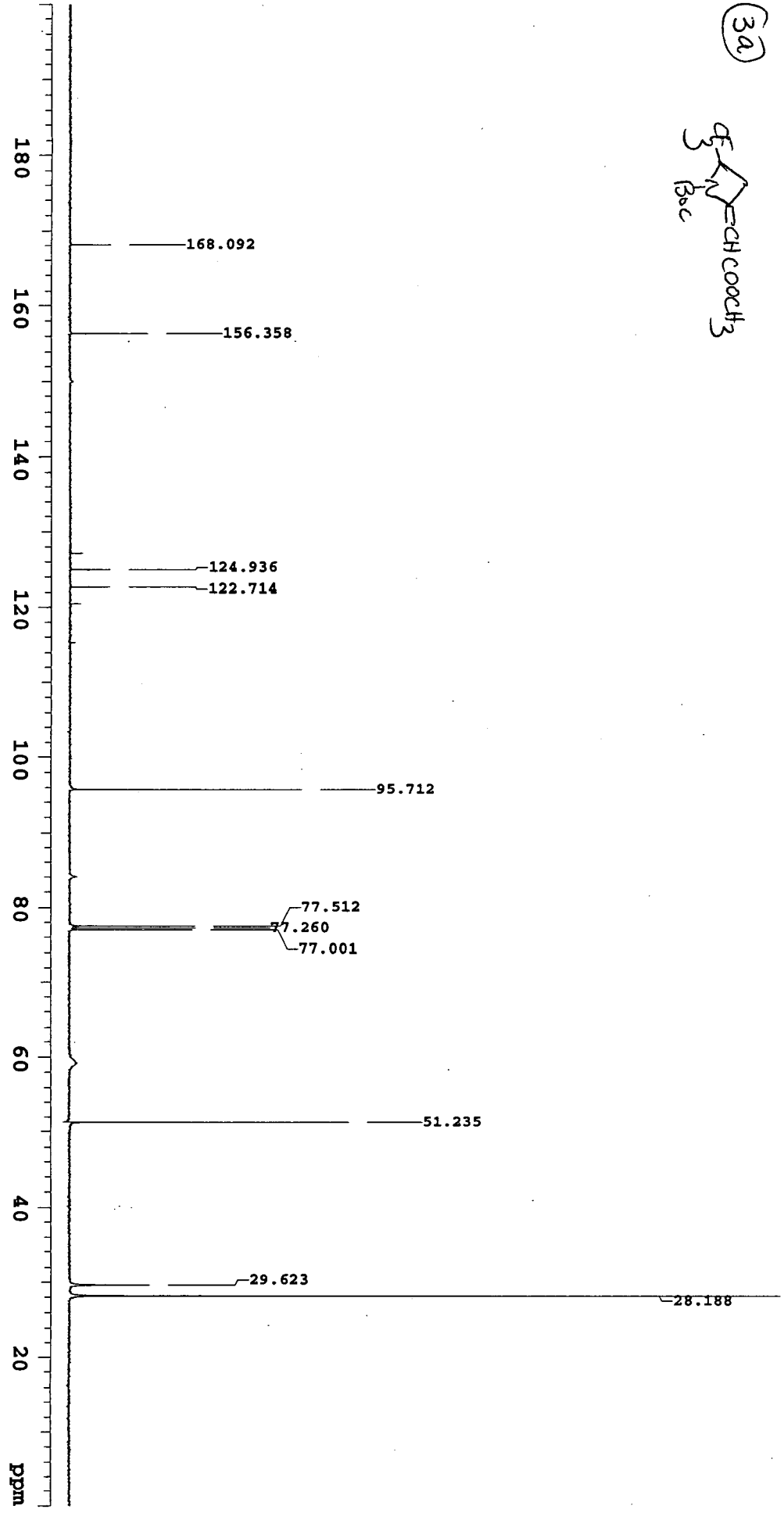
Preparation of *N*-(*tert*-butoxycarbonyl)-2-hydroxycarbonyl-4-trifluoromethylazetidine (8). $NaIO_4$ (0.70 g, 3.32 mmol) and $RuCl_3.H_2O$ (4.3 mg, 0,017 mmol) were added to a vigorously stirred solution of *N*-(*tert*-butoxycarbonyl)-2-vinyl-4-trifluoromethyl azetidine **7**, 0.20 mg, 0.80 mmol) in CH_2Cl_2-CH_3CN-H_2O (2:2:3, 1.2 mL). After 2 h, an additional $NaIO_4$ (0.70 mg, 3.32 mmol) was added, and the stirring was continued for 2 h. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$ and was concentrated. The residue was subjected to flash chromatography (5% acetic acid in 1:1 hexane:ethyl acetate) to give acid **8** (0.17, 80% yield): ^{1}H NMR ($CDCl_3$) δ 4.72-4.68 (1 H, t, J = 7.8 Hz), 4.57-4.51 (1 H, m), 2.86-2.60 (2 H, m), 1.51 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 164.0, 123.6 (q, J = 279.3 Hz), 84.5, 58.6, 58.0 (q, J = 38.3 Hz), 28.3, 21.0. Anal. Calcd for $C_{11}H_{14}F_3NO_4$: C, 44,61; H, 5.24; N, 5.20. Found: C, 44.35; H, 5.14; N, 5.11.

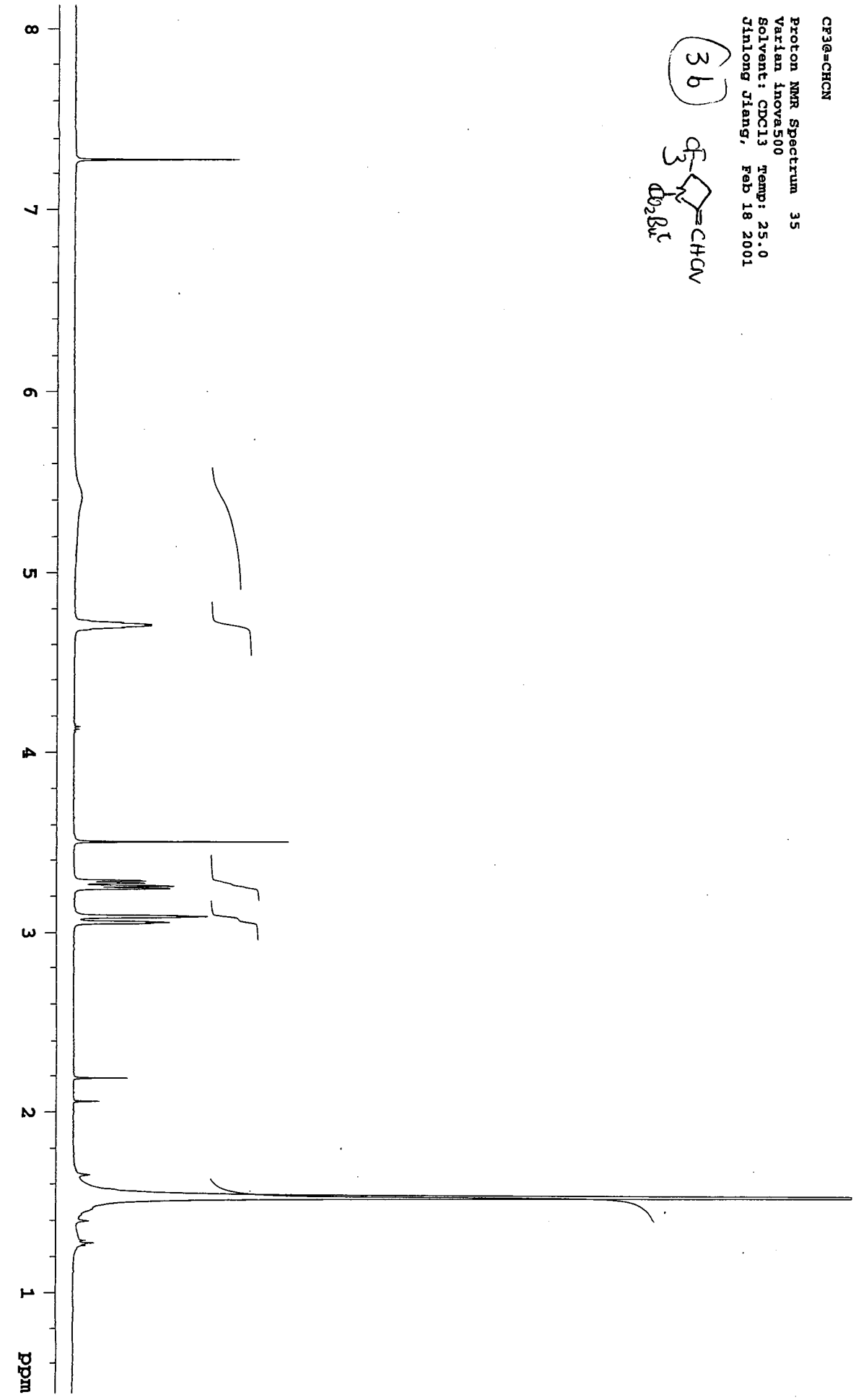

CF3@=O
Proton NMR Spectrum 45
Varian inova500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Mar 28 2001
2
CF3
CO2But
8
7
6
5
4
3
2
ppm

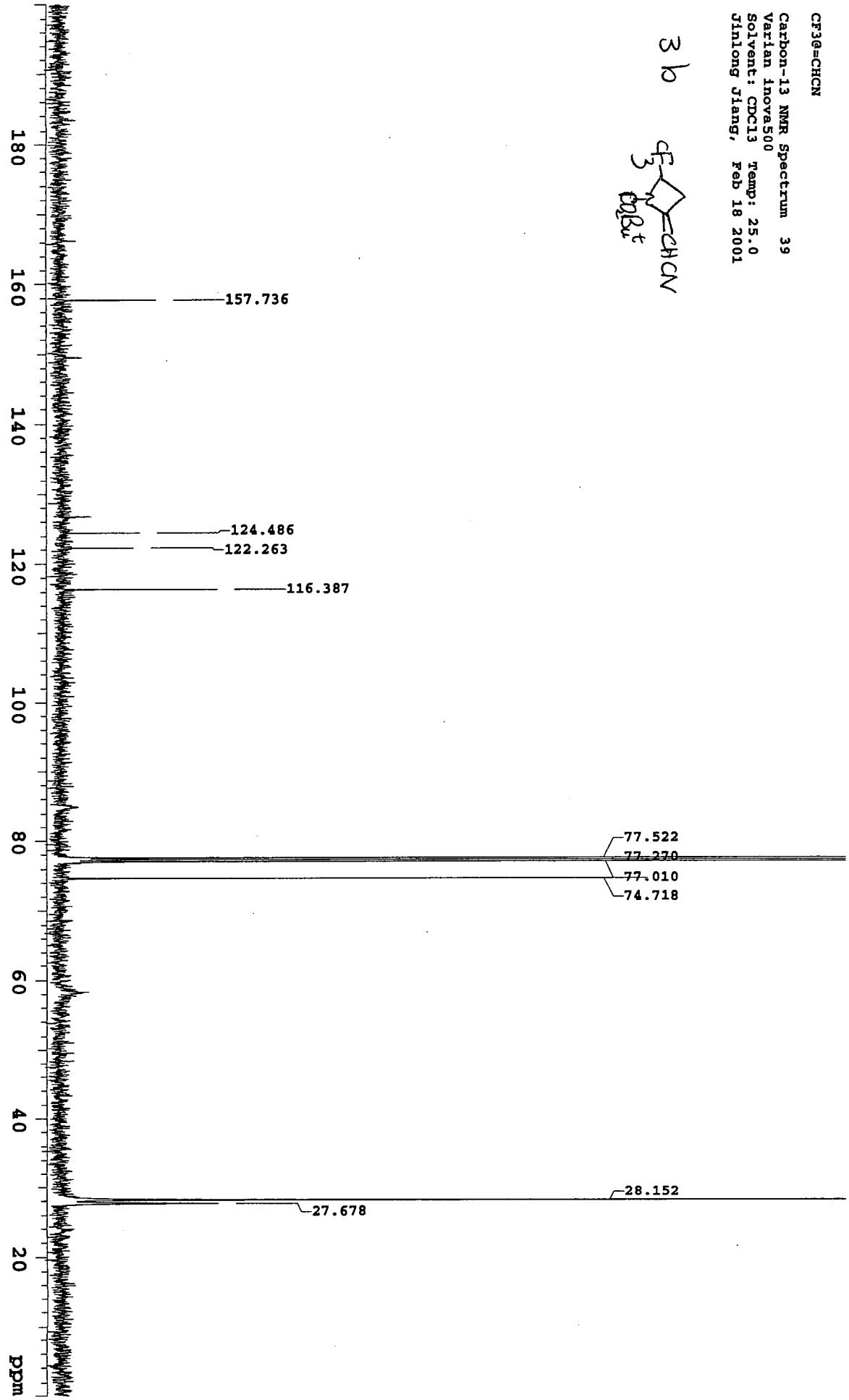

CF3C=O
Carbon-13 NMR Spectrum 53
Varian unity400
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Jul 3 2001
2
162.051
125.254
122.481
84.917
77.596
77.279
76.961
50.553
50.188
49.832
38.909
28.095
ppm

S10

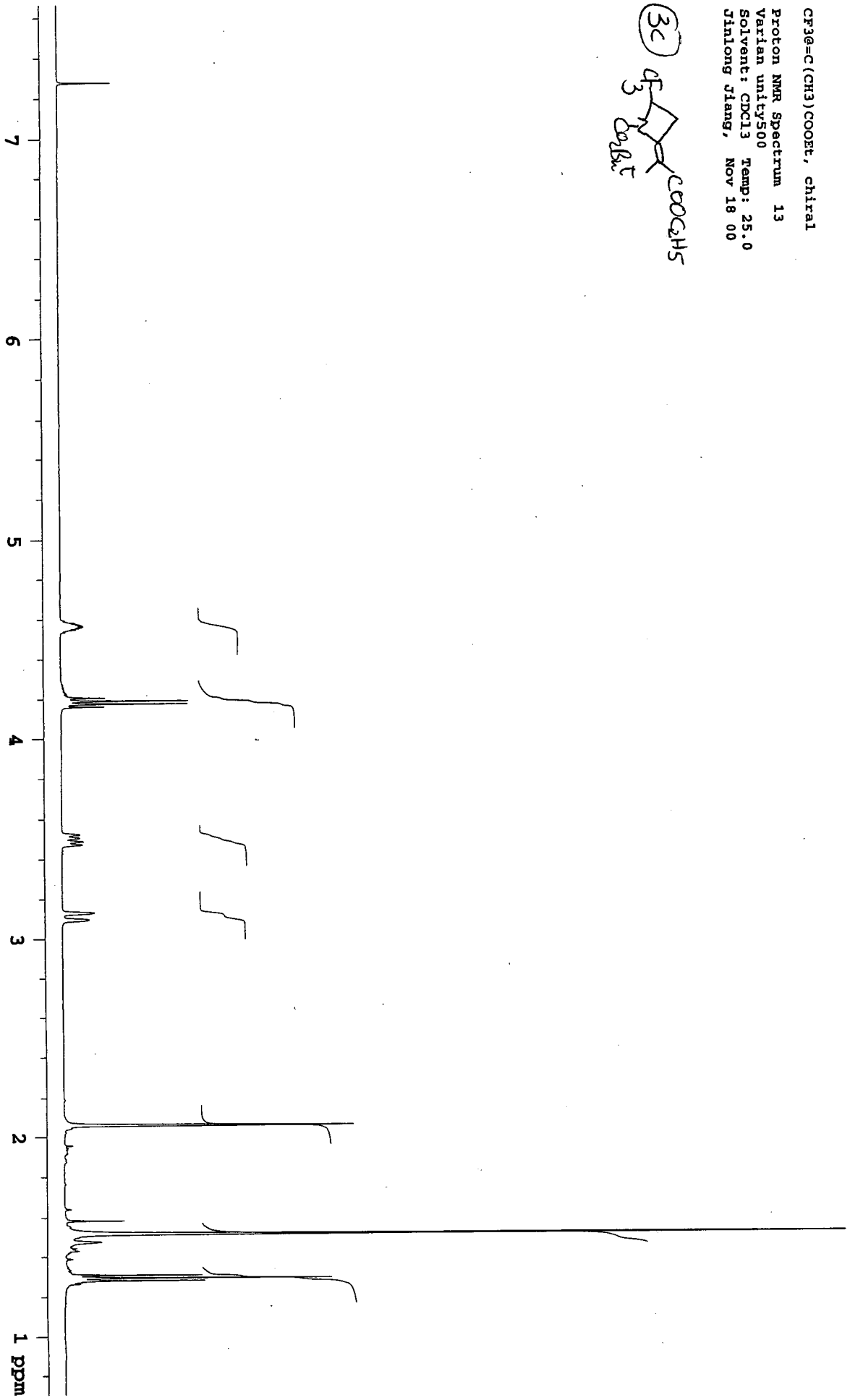

CF3-@-=-COOMe-1H
Proton NMR Spectrum 4
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Feb 1 00
3a
CF3
CO2But
CHCOOMe
7
6
5
4
3
2
1 ppm

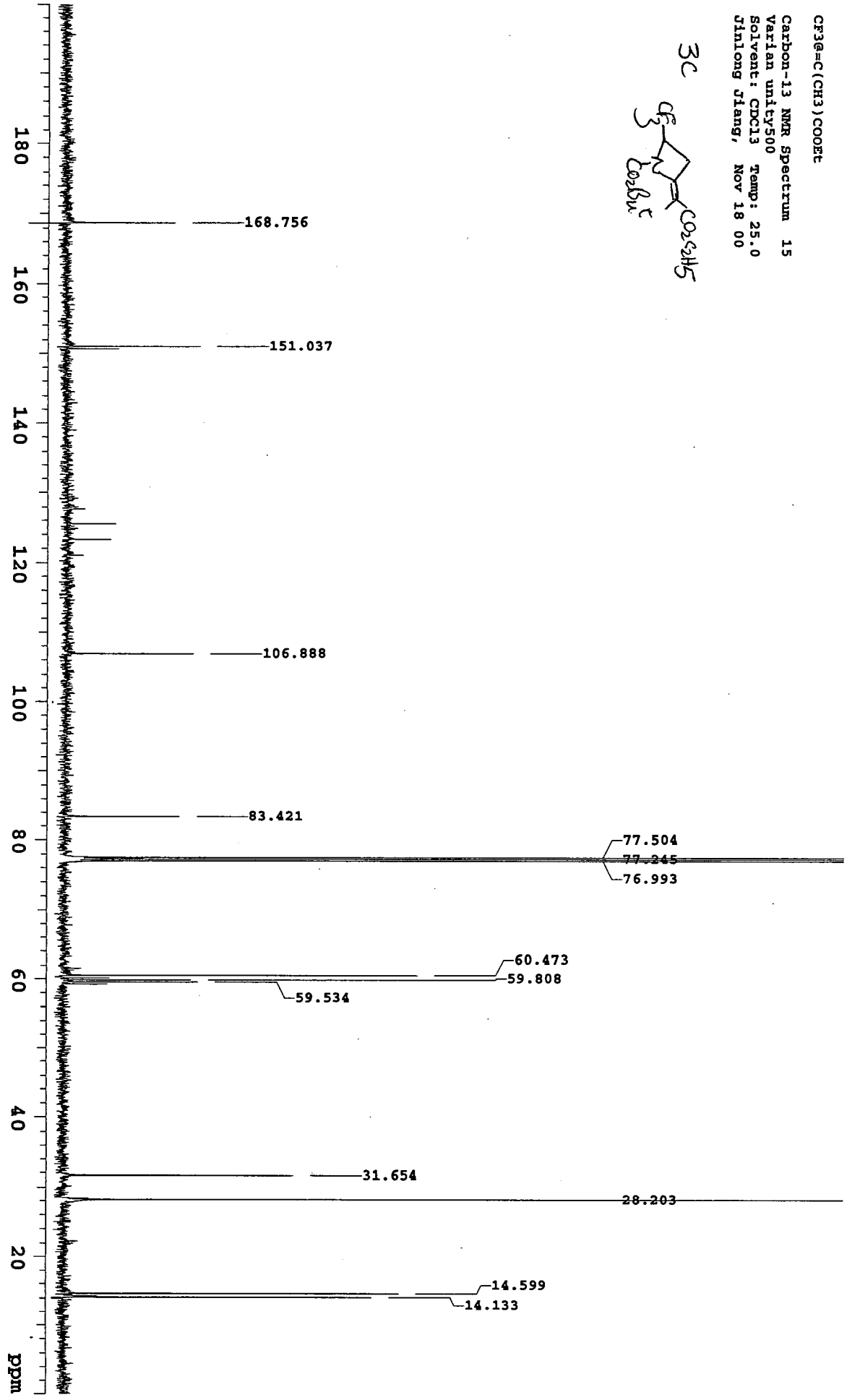

CF3(BOC)-=-COOMe
Carbon-13 NMR Spectrum 6
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Feb 5 00
3a
CF3
N
Boc
CH
COOCH3
168.092
156.358
124.936
122.714
95.712
77.512
77.260
77.001
51.235
29.623
28.188
180
160
140
120
100
80
60
40
20
ppm

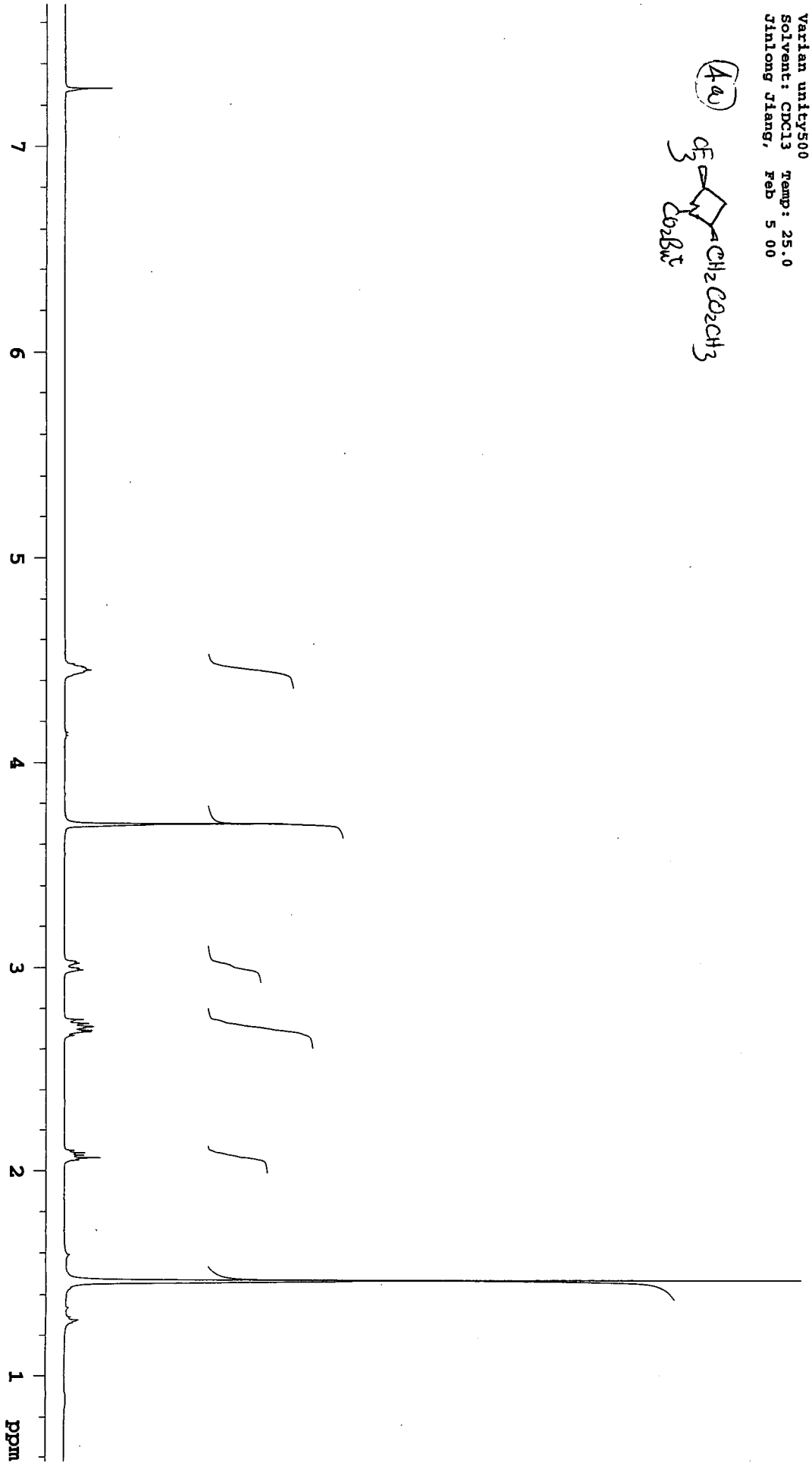

CF3@=CHCN
Proton NMR Spectrum 35
Varian inova500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Feb 18 2001
3b
CF3
CO2Bu-t
=CHCN
8
7
6
5
4
3
2
1
ppm

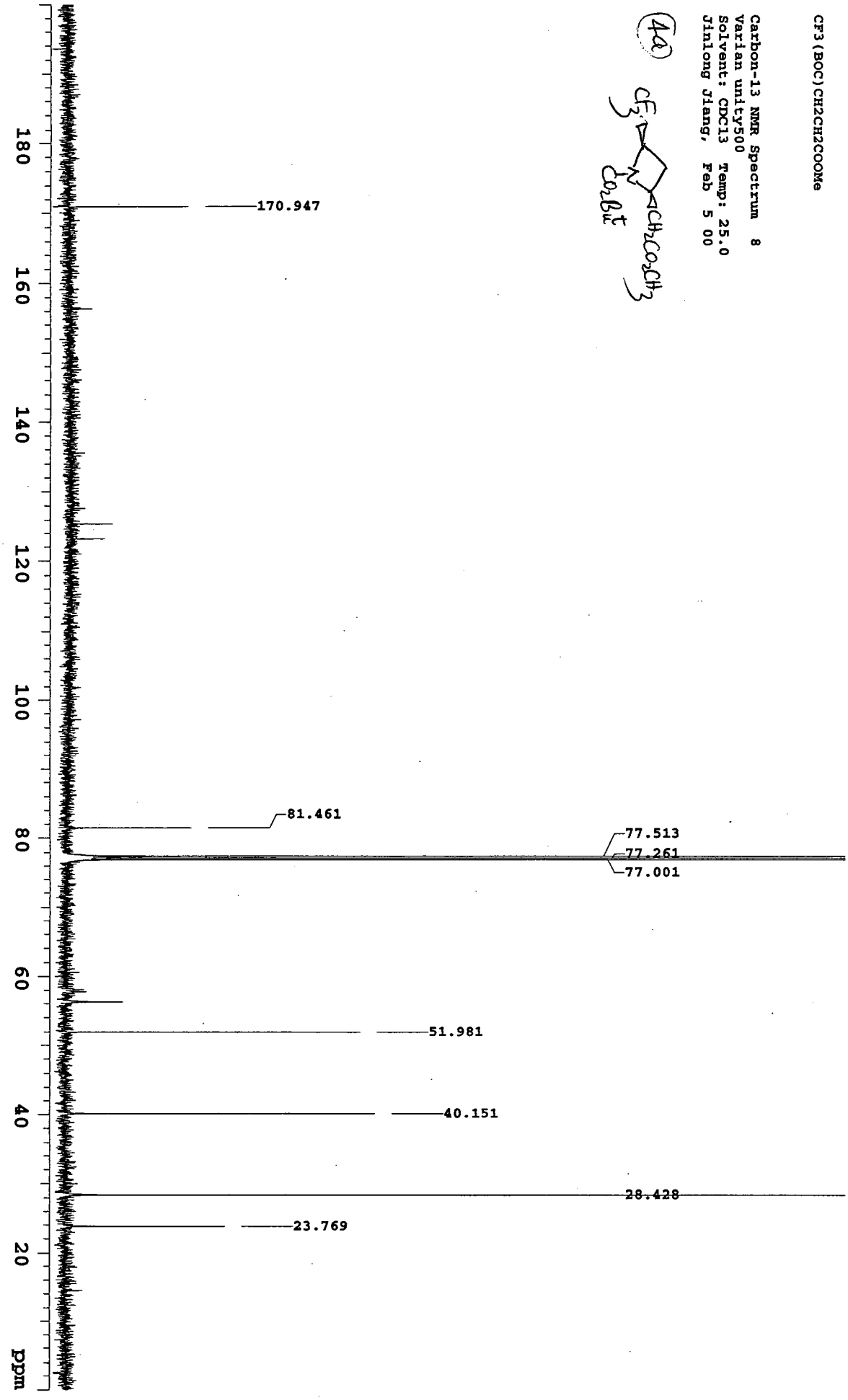

CF3C≡CHCN
Carbon-13 NMR Spectrum 39
Varian inova500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Feb 18 2001
3b
CF3
CHCN
tBu
157.736
124.486
122.263
116.387
77.522
77.270
77.010
74.718
28.152
27.678
180
160
140
120
100
80
60
40
20
ppm

S114

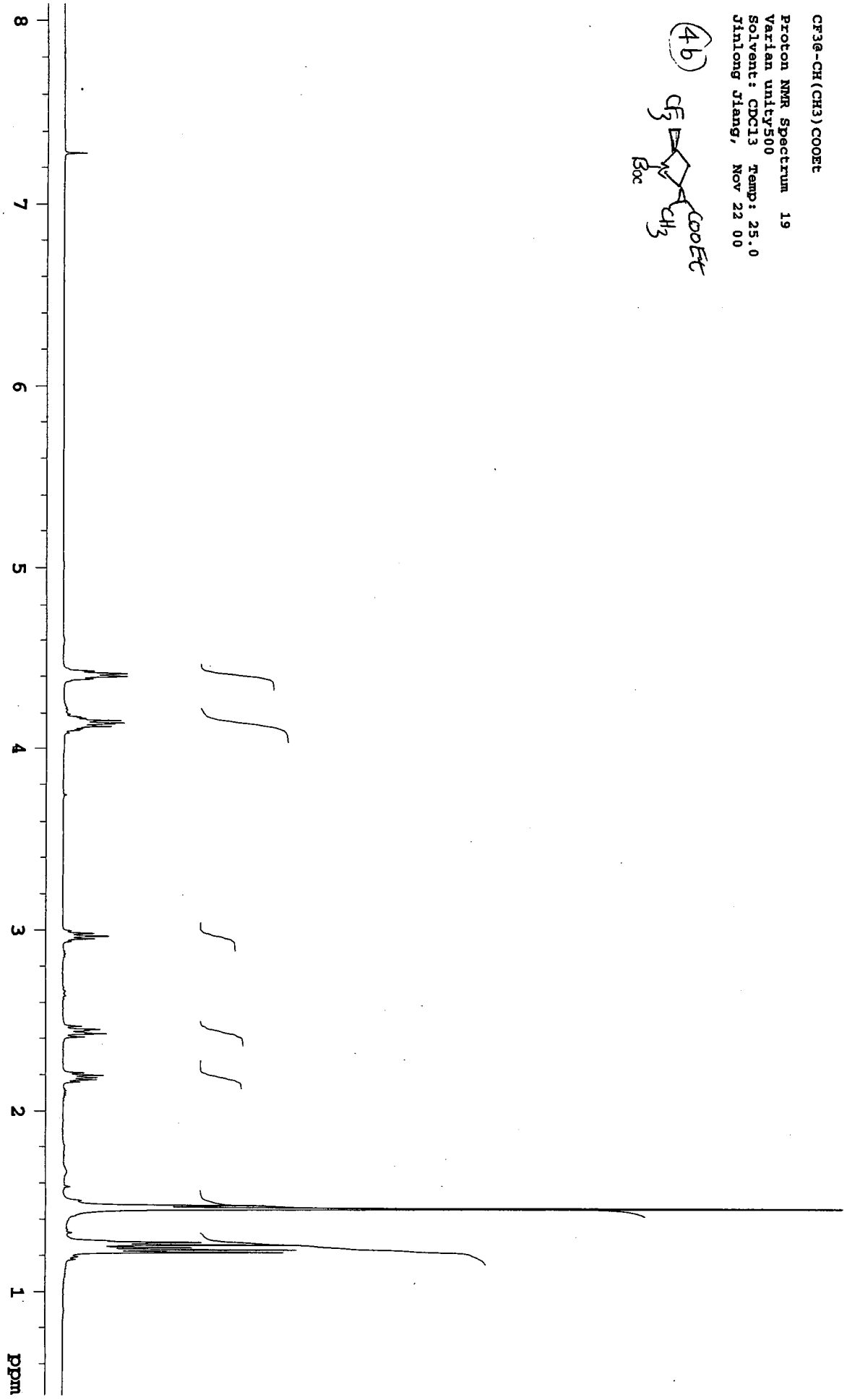

CF3C=C(CH3)COOEt, chiral
Proton NMR Spectrum 13
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Nov 18 00
(3c)
CF3
COOC2H5
7
6
5
4
3
2
1 ppm


CF3@=C(CH3)COOEt
Carbon-13 NMR Spectrum 15
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Nov 18 00
3c
CF3
CO2tBu
CO2C2H5
168.756
151.037
106.888
83.421
77.504
77.245
76.993
60.473
59.808
59.534
31.654
28.203
14.599
14.133
180
160
140
120
100
80
60
40
20
ppm

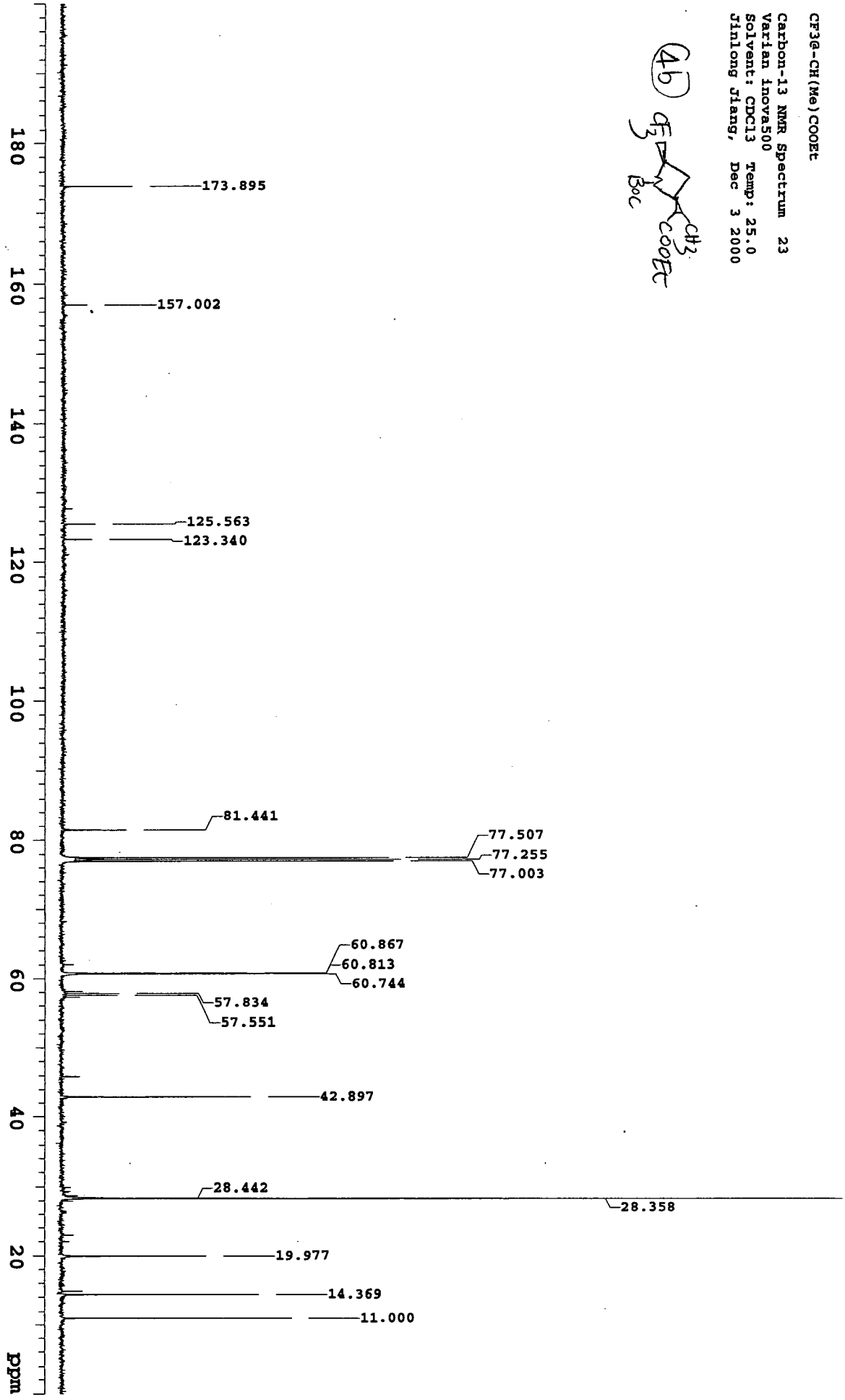

CF3(BOC)CH2CH2COOMe
Proton NMR Spectrum 7
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Feb 5 00
(4a)
CF3
CO2But
CH2CO2CH3
7
6
5
4
3
2
1
ppm


CF3(BOC)CH2CH2COOMe
Carbon-13 NMR Spectrum 8
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Feb 5 00
(4a)
CF3
CO2Bt
CH2CO2CH3
170.947
81.461
77.513
77.261
77.001
51.981
40.151
28.428
23.769
180
160
140
120
100
80
60
40
20
ppm

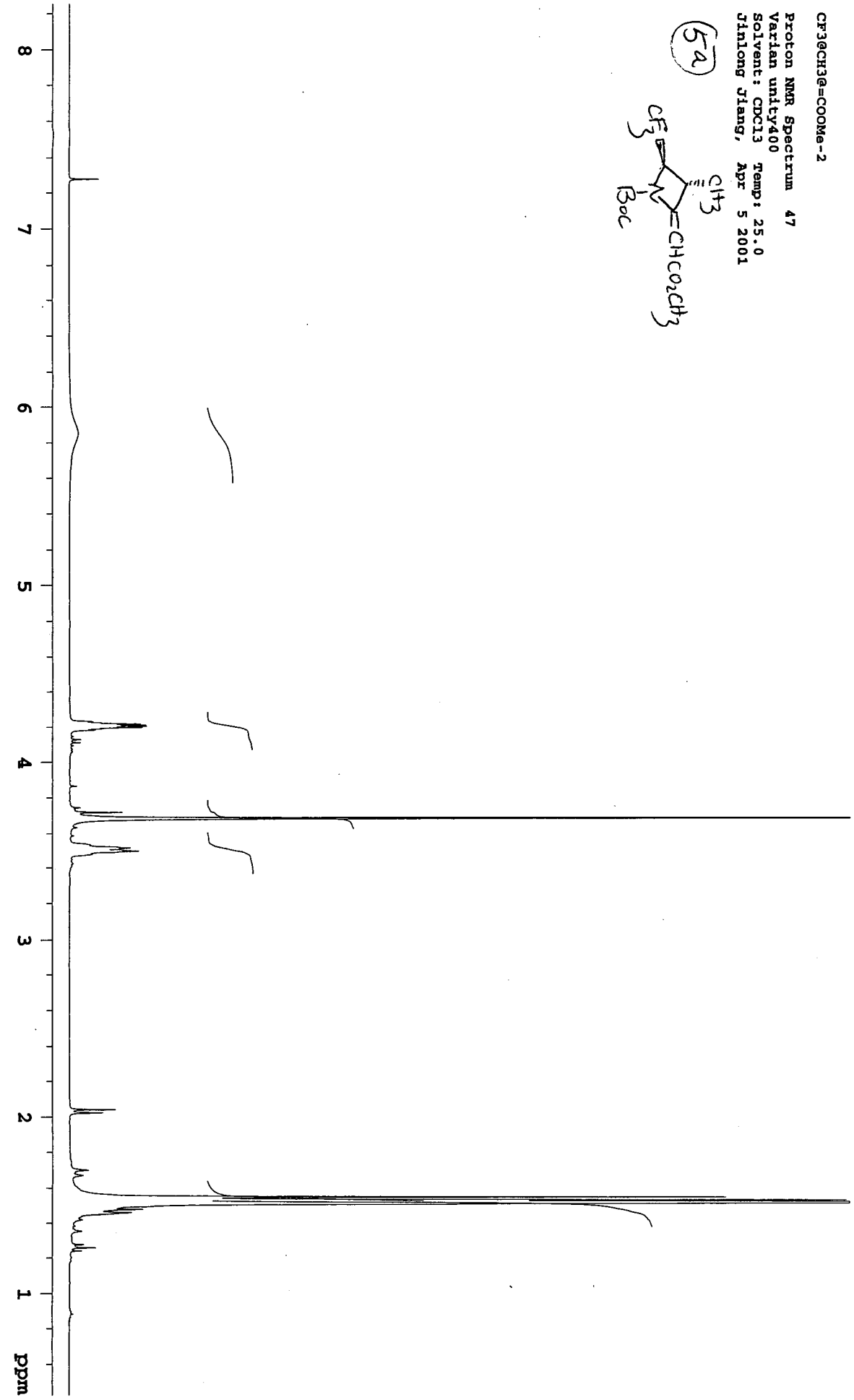
S18

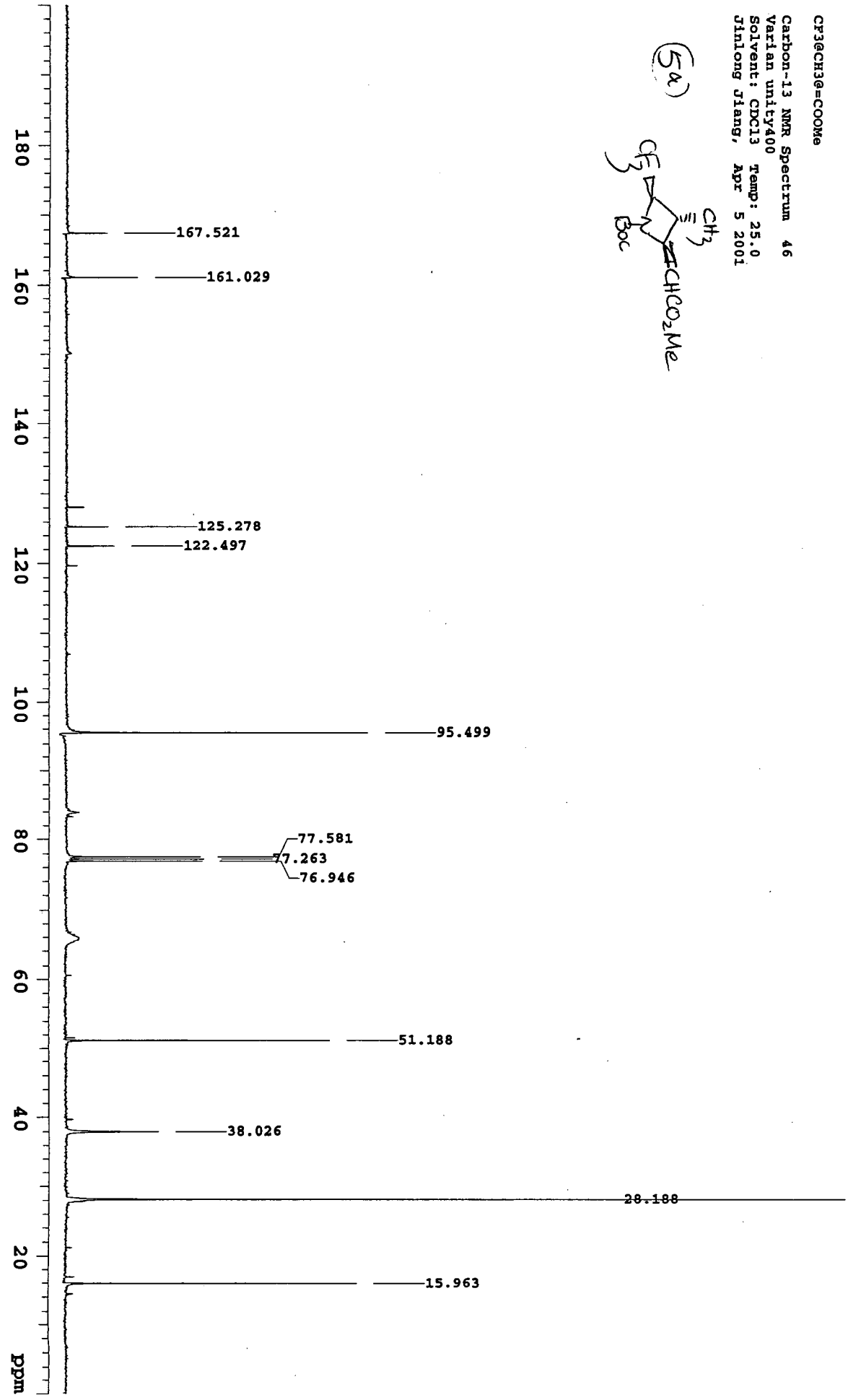

CF3@-CH(CH3)COOEt
Proton NMR Spectrum 19
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Nov 22 00
(4b)
CF3
Boc
CH3
COOEt
8
7
6
5
4
3
2
1
ppm

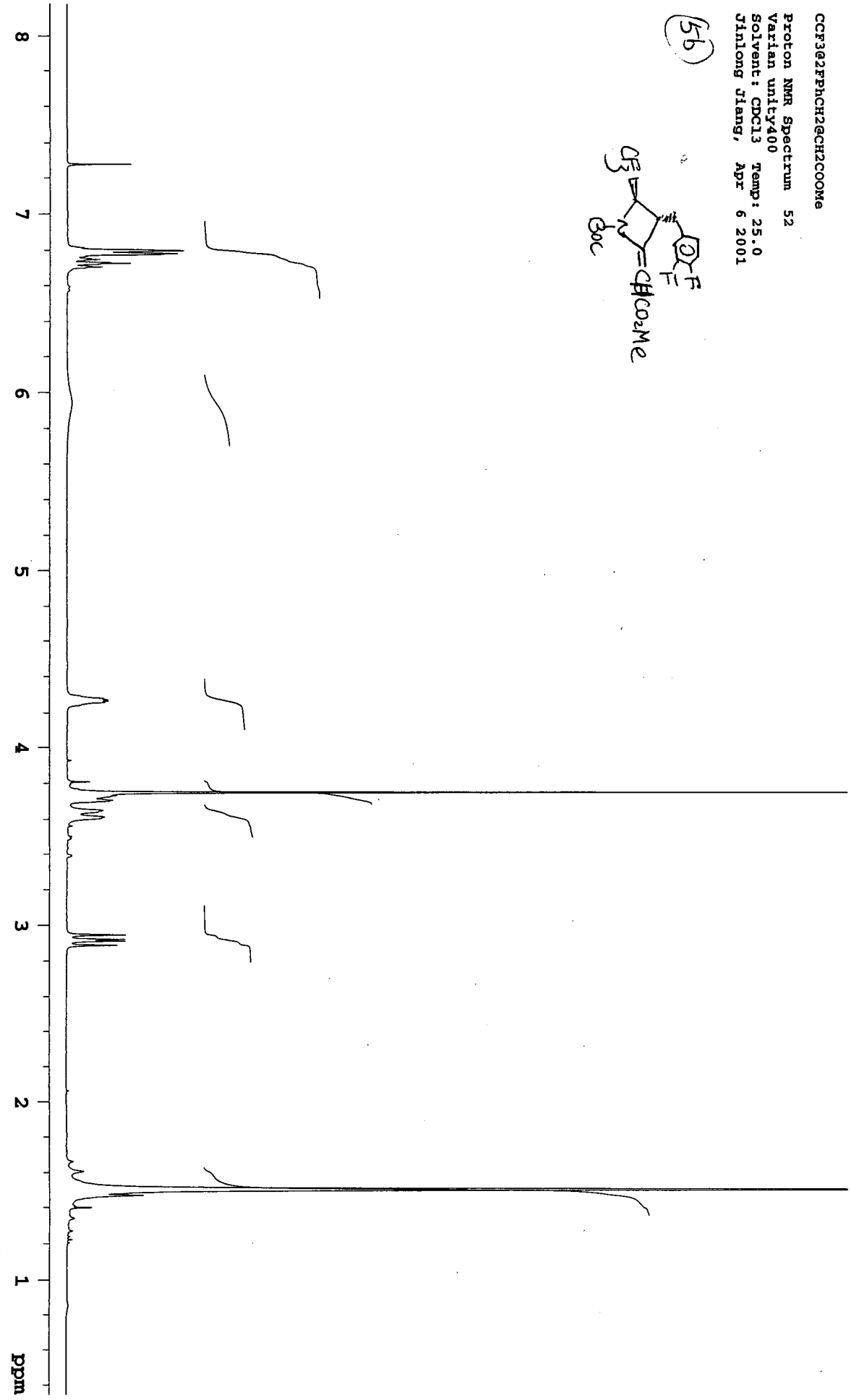
S19

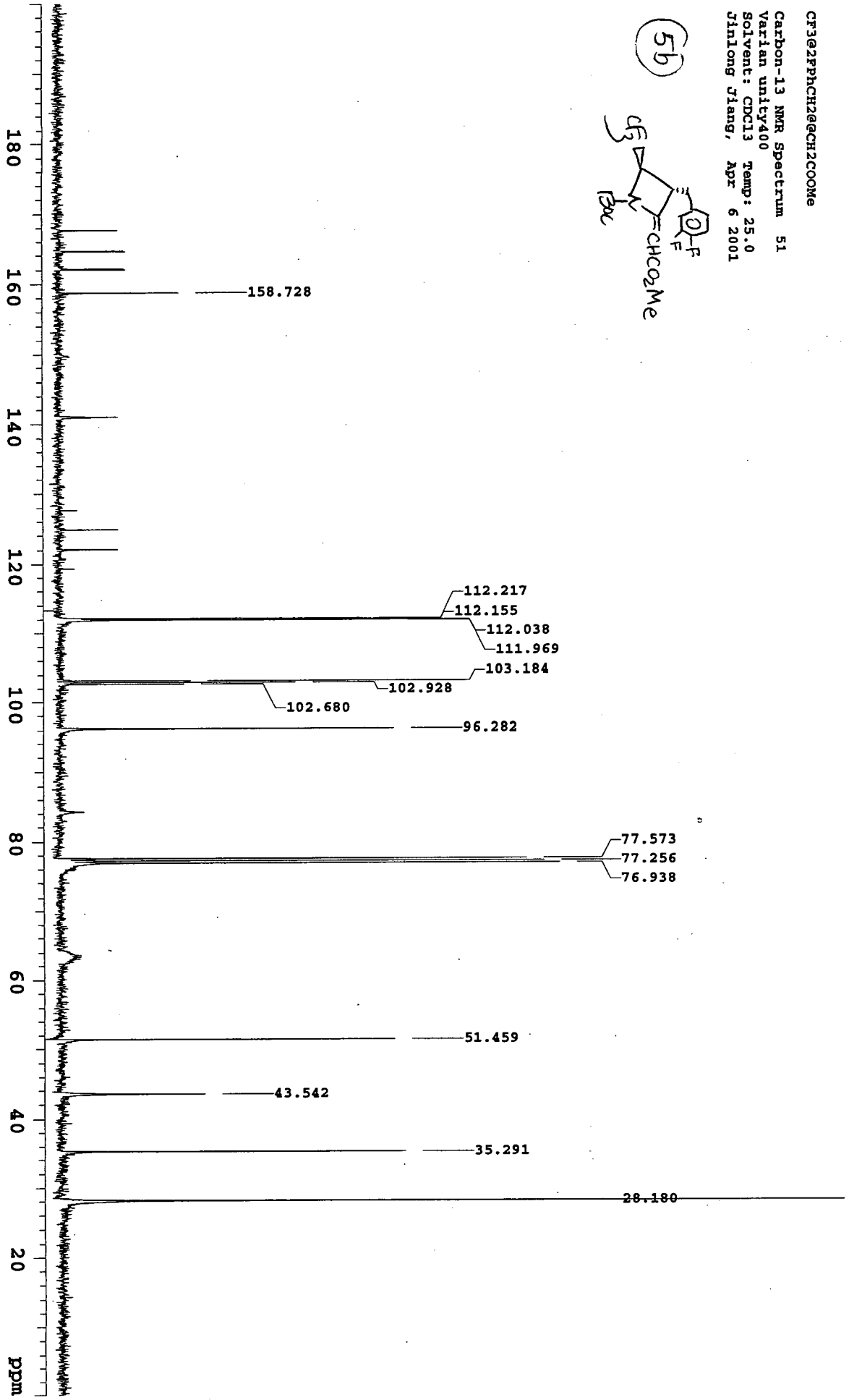

CF3@-CH(Me)COOEt
Carbon-13 NMR Spectrum 23
Varian inova500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Dec 3 2000
(4b)
CF3
1
Boc
CH2
COOEt
173.895
157.002
125.563
123.340
81.441
77.507
77.255
77.003
60.867
60.813
60.744
57.834
57.551
42.897
28.442
28.358
19.977
14.369
11.000
180
160
140
120
100
80
60
40
20
ppm

S20

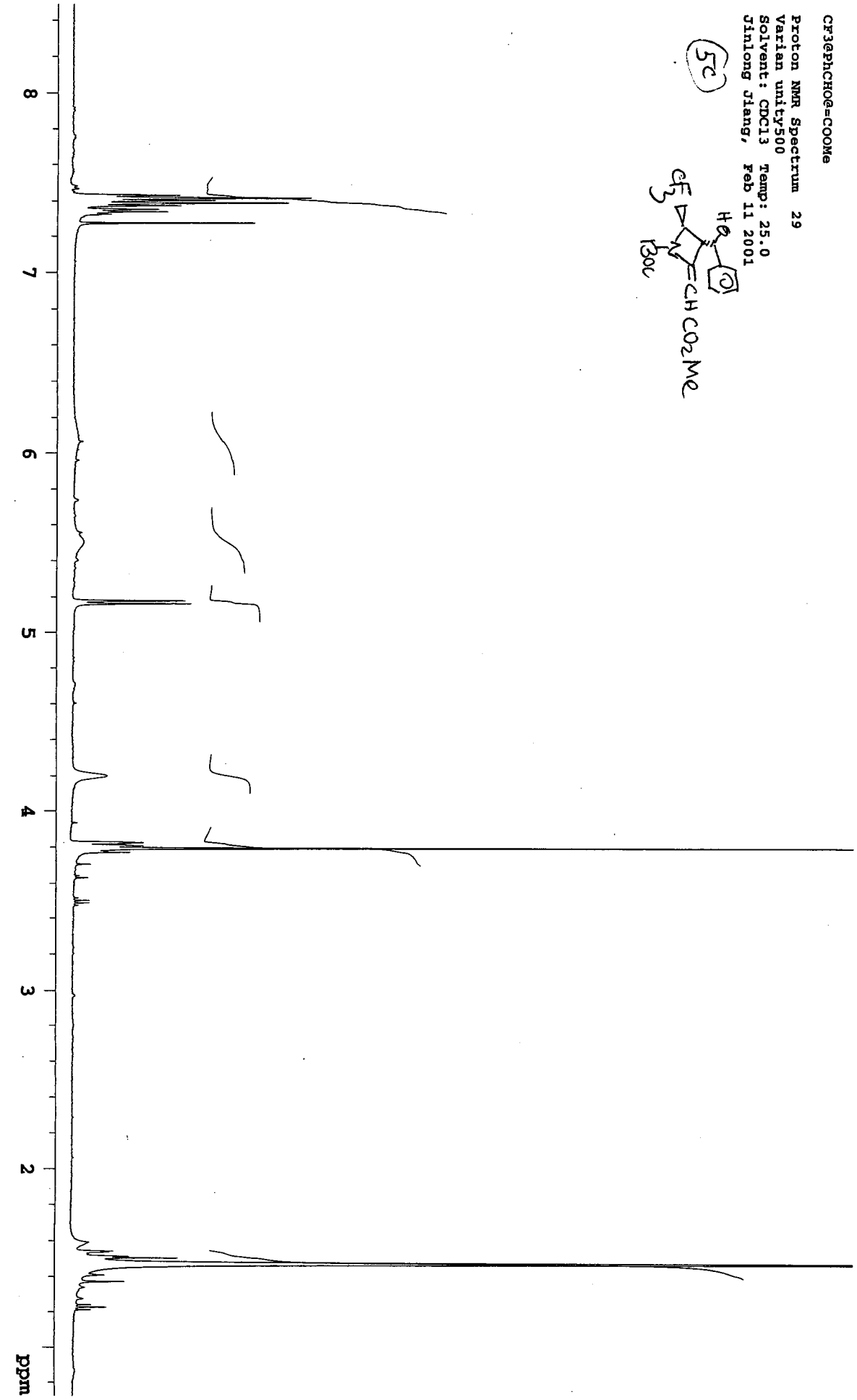

CF3@CH3@=COOMe-2
Proton NMR Spectrum 47
Varian unity400
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Apr 5 2001
(5a)
CF3
CH3
Boc
CHCO2CH3
8
7
6
5
4
3
2
1
ppm

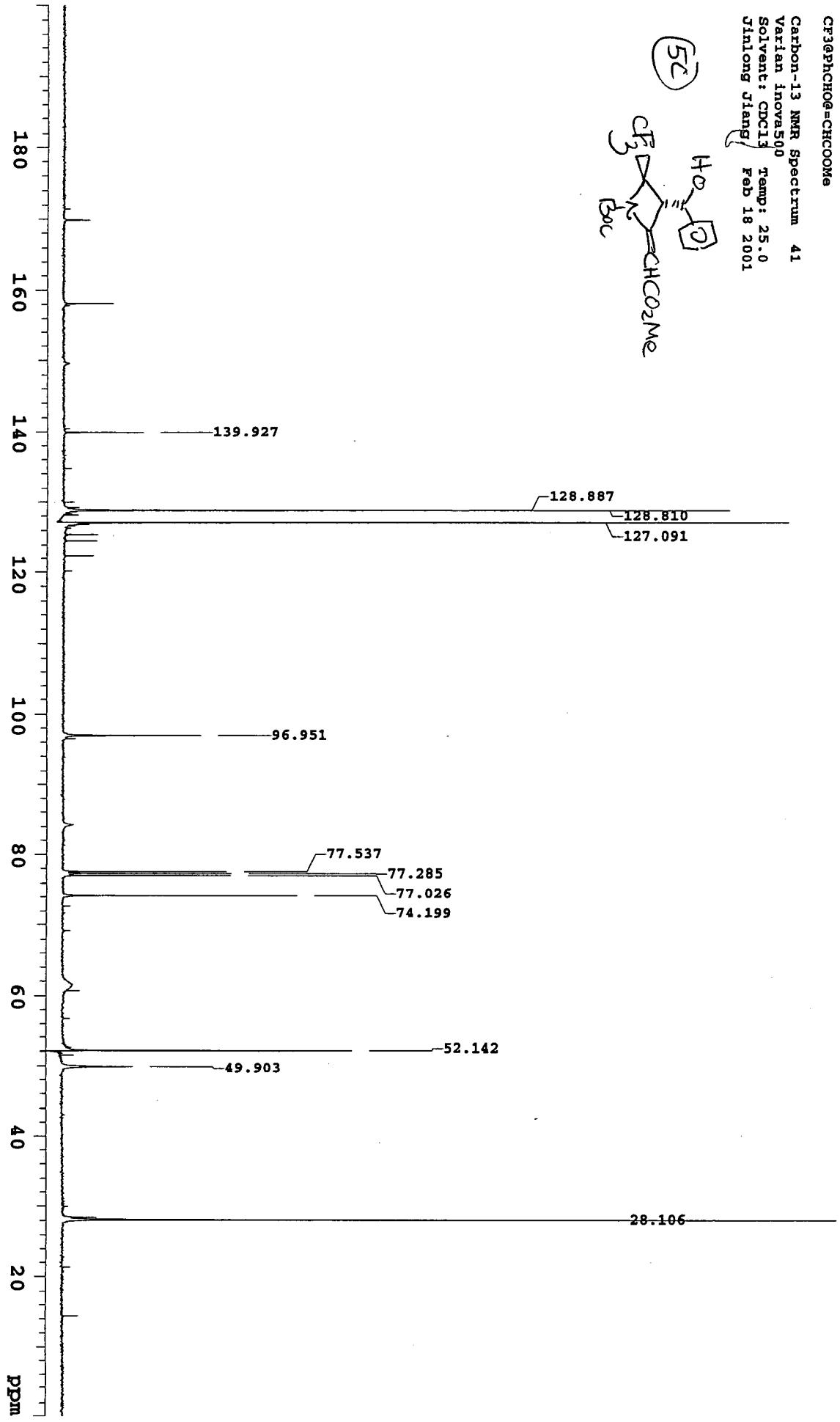

CF3@CH3@=COOMe
Carbon-13 NMR Spectrum 46
Varian unity400
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Apr 5 2001
(5a)
CF3
Boc
CH3
CHCO2Me
167.521
161.029
125.278
122.497
95.499
77.581
77.263
76.946
51.188
38.026
28.188
15.963
180
160
140
120
100
80
60
40
20
ppm



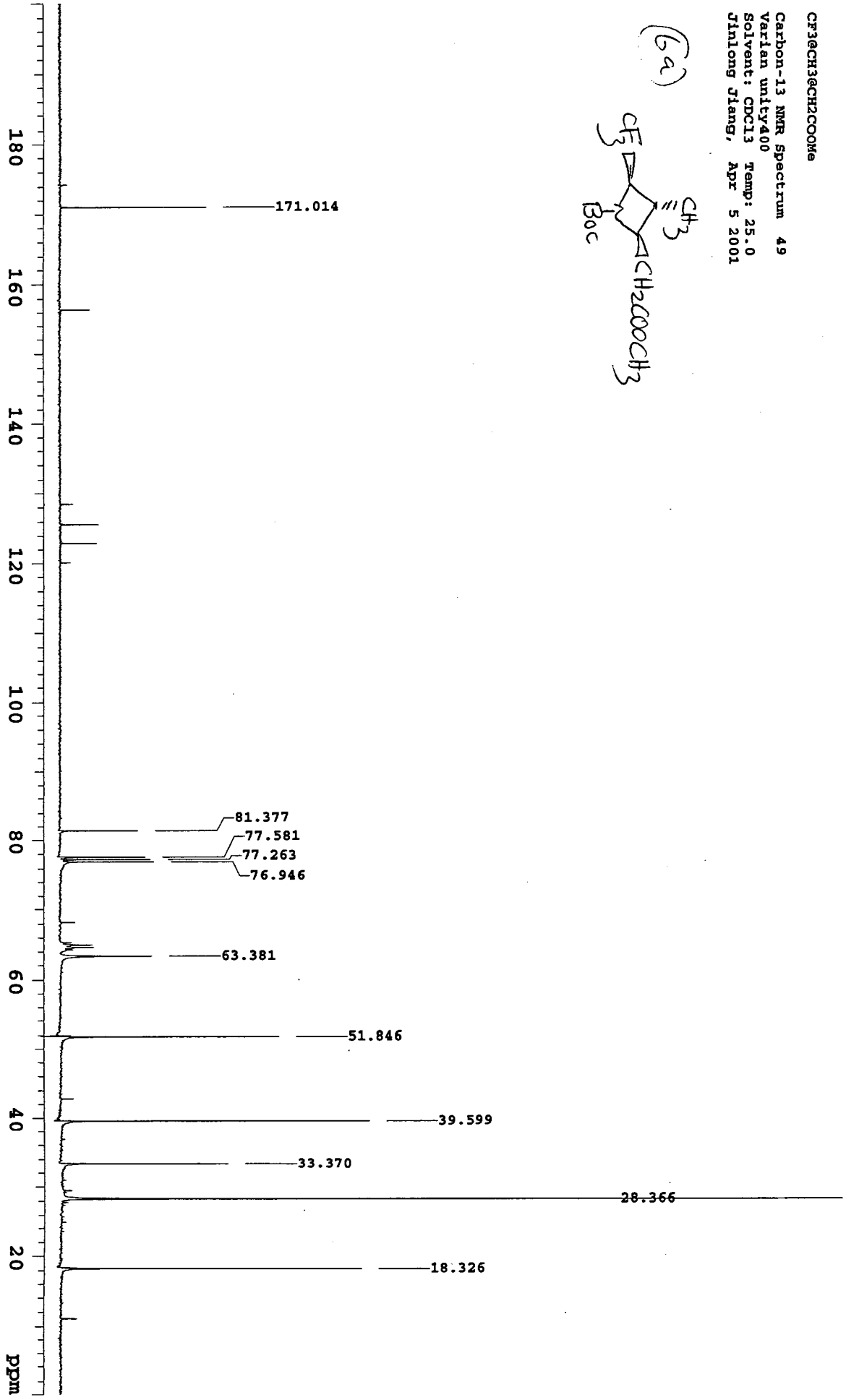

CF3@2FPhCH2@@CH2COOMe
Carbon-13 NMR Spectrum 51
Varian unity400
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Apr 6 2001
5b
158.728
112.217
112.155
112.038
111.969
103.184
102.928
102.680
96.282
77.573
77.256
76.938
51.459
43.542
35.291
28.180
ppm

S214

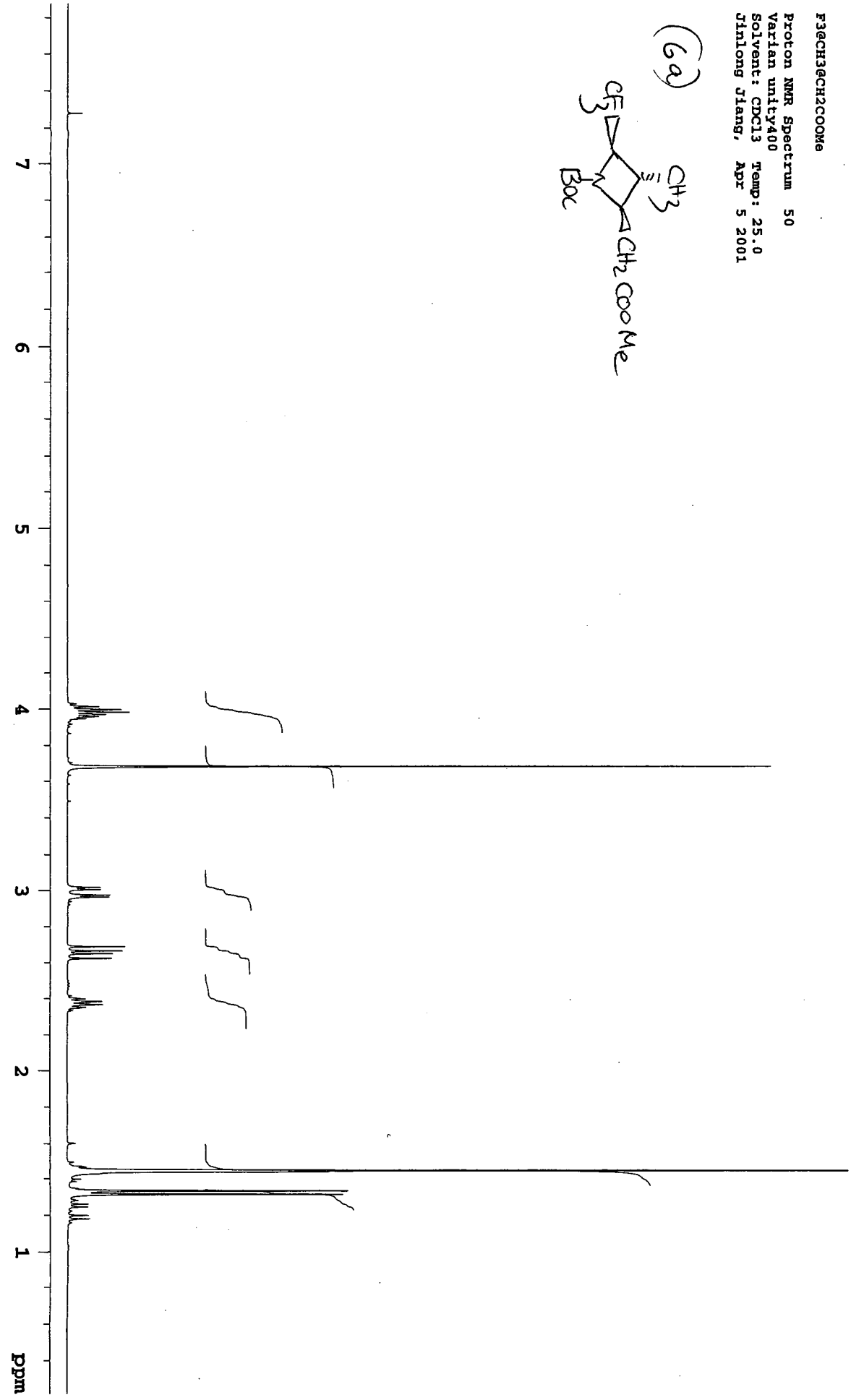

CF3@PhCHO@=COOMe
Proton NMR Spectrum 29
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Feb 11 2001
(5c)
CF3
Ha
Boc
CH CO2Me
8
7
6
5
4
3
2
ppm

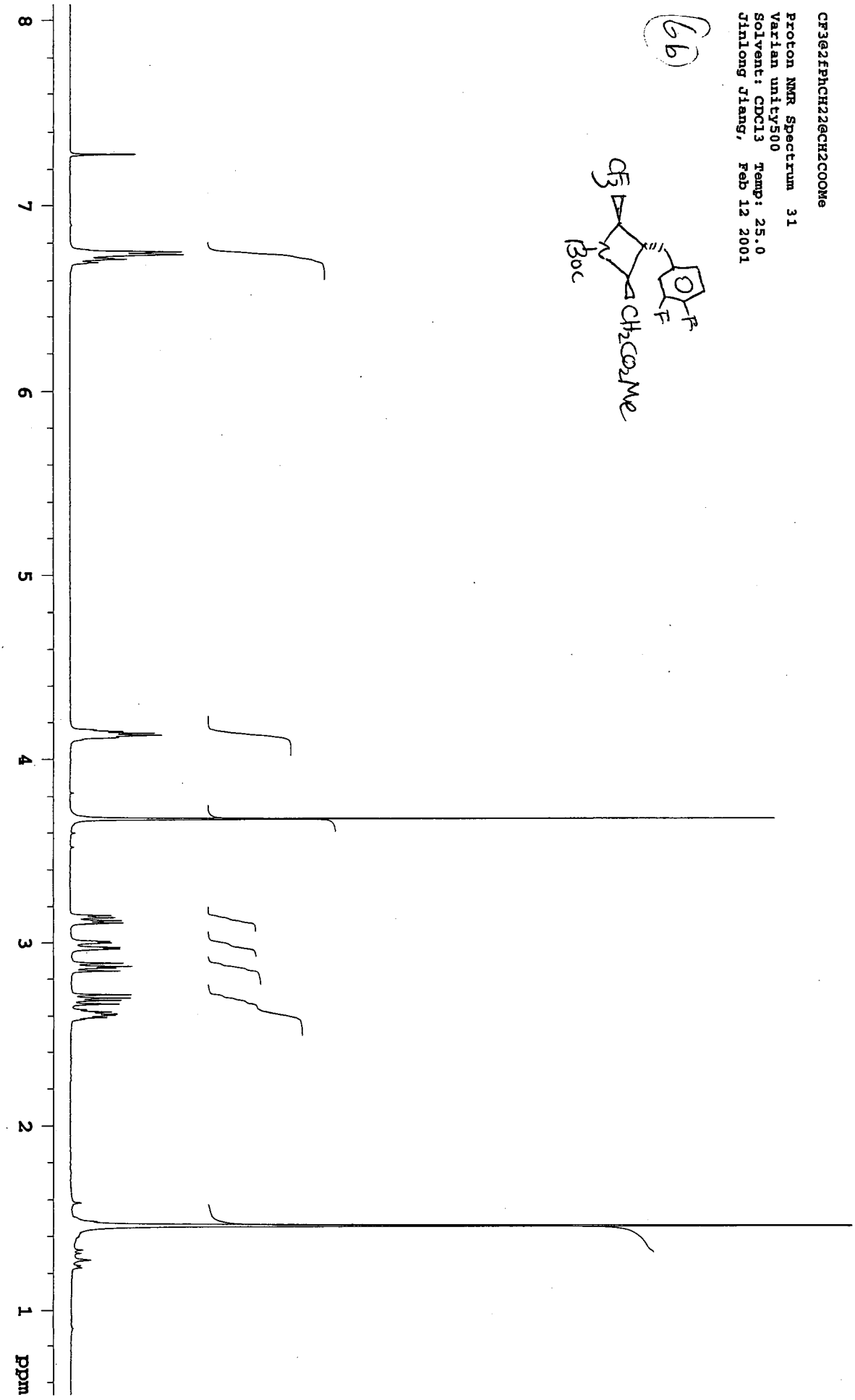

CF3@PhCHO@=CHCOOMe
Carbon-13 NMR Spectrum 41
Varian inova500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang Feb 18 2001
5C
CF3
HO
Boc
CHCO2Me
139.927
128.887
128.810
127.091
96.951
77.537
77.285
77.026
74.199
52.142
49.903
28.106
180
160
140
120
100
80
60
40
20
ppm

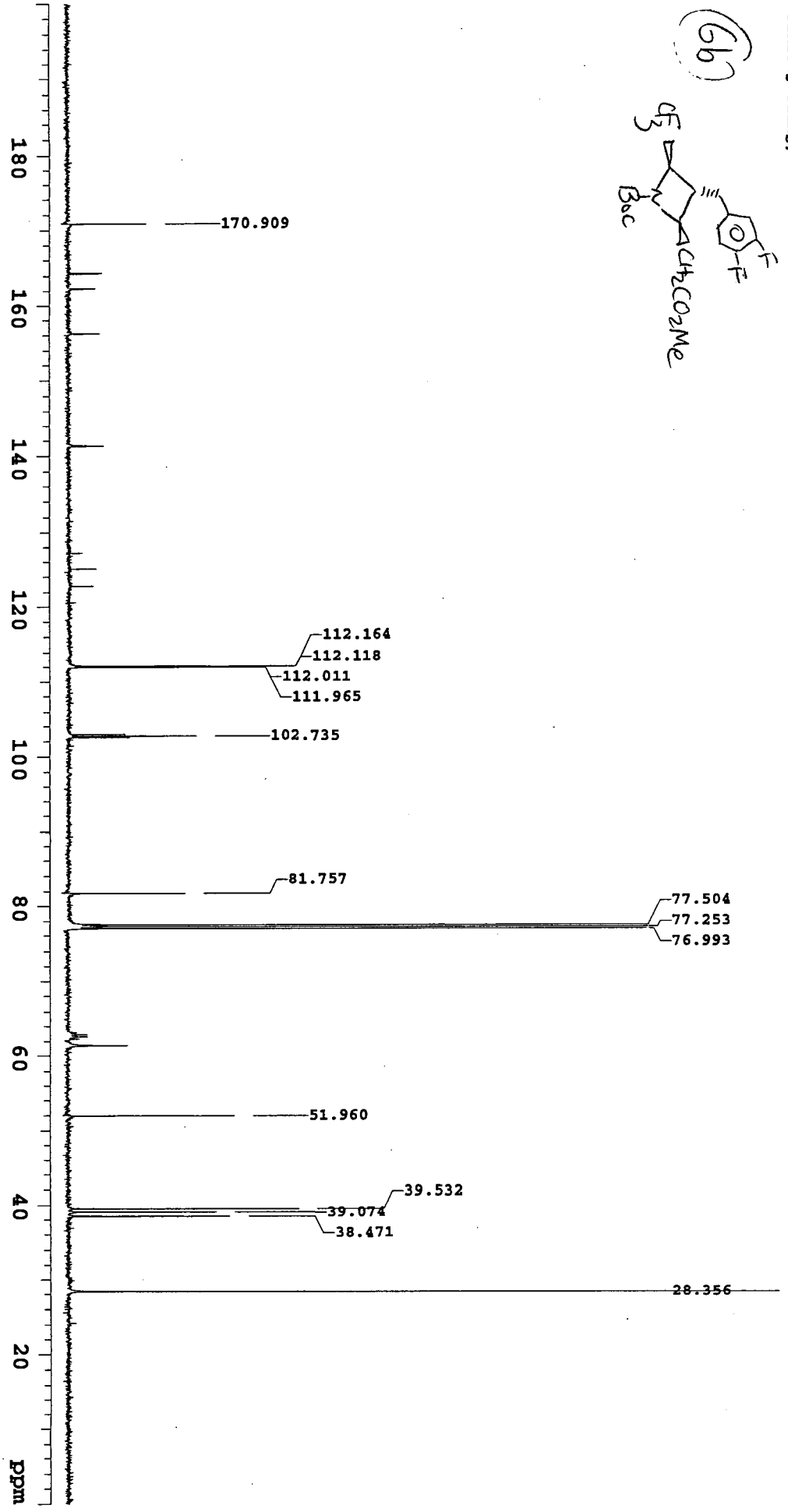
S.26

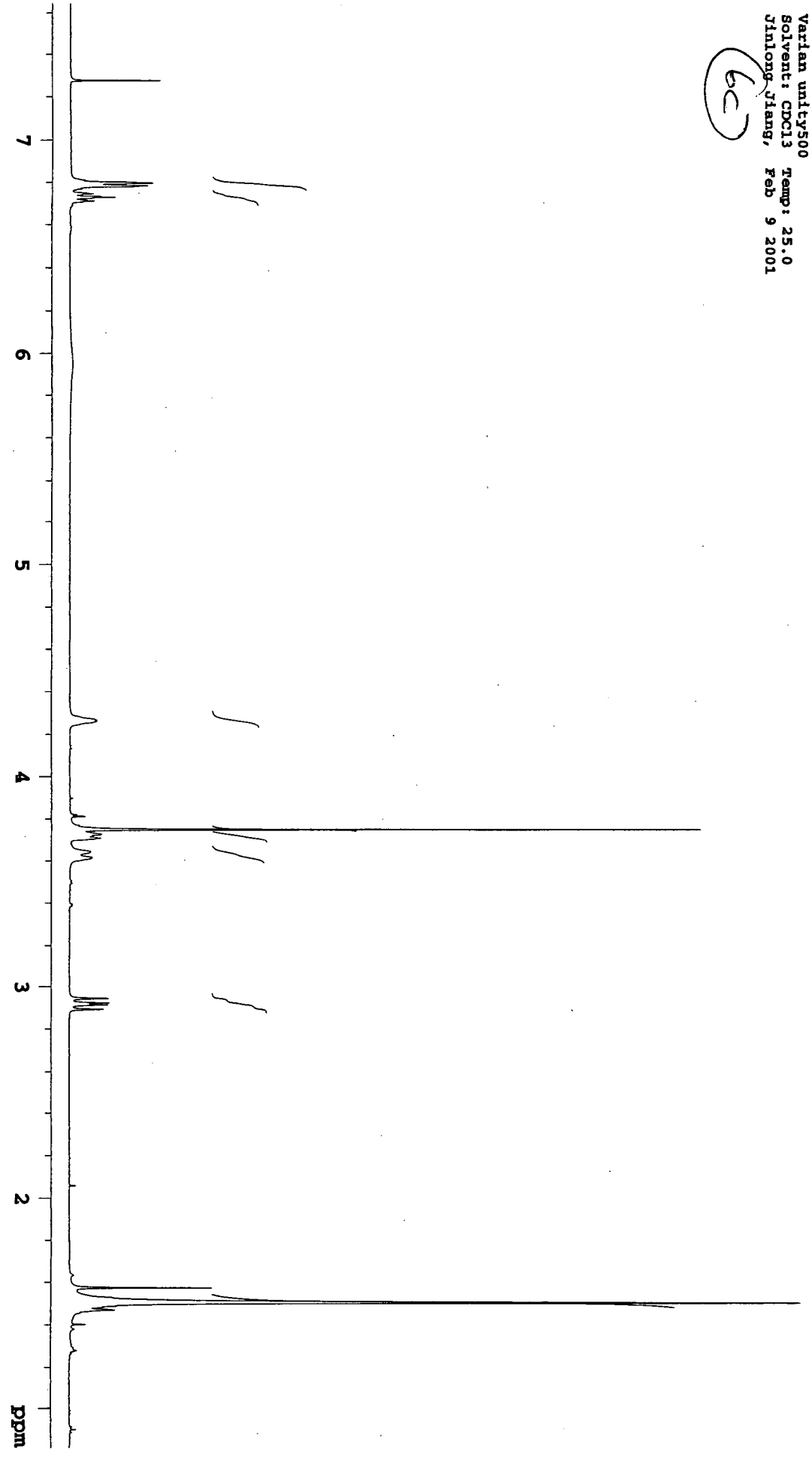

CF3@CH3@CH2COOMe
Carbon-13 NMR Spectrum 49
Varian unity400
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Apr 5 2001
(6a)
CF3
CH3
Boc
CH2COOCH3
171.014
81.377
77.581
77.263
76.946
63.381
51.846
39.599
33.370
28.366
18.326
180
160
140
120
100
80
60
40
20
ppm

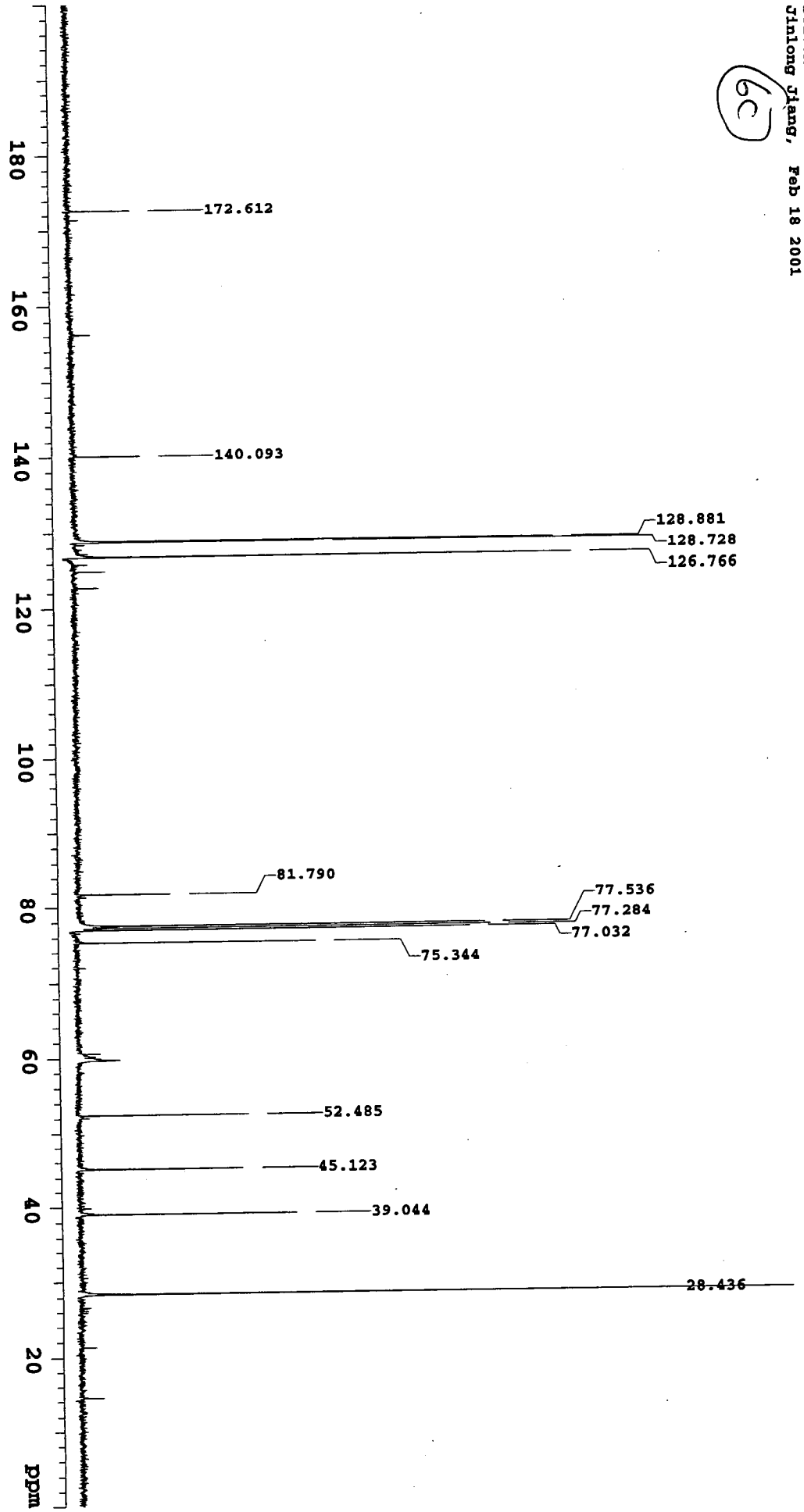
527

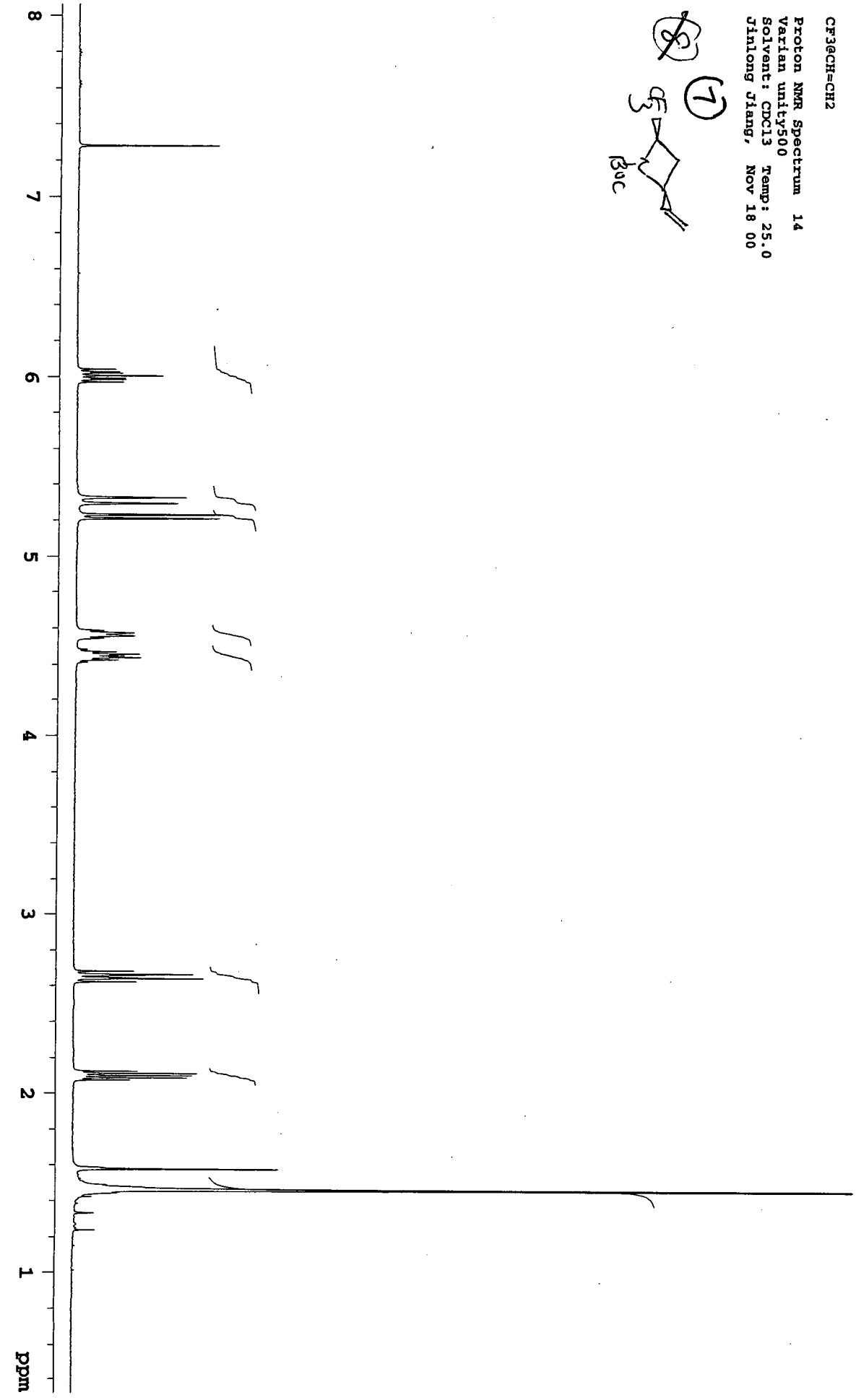

F3@CH3@CH2COOMe
Proton NMR Spectrum 50
Varian unity400
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Apr 5 2001
(6a)
CF3
CH3
Boc
CH2 COO Me
7
6
5
4
3
2
1
ppm

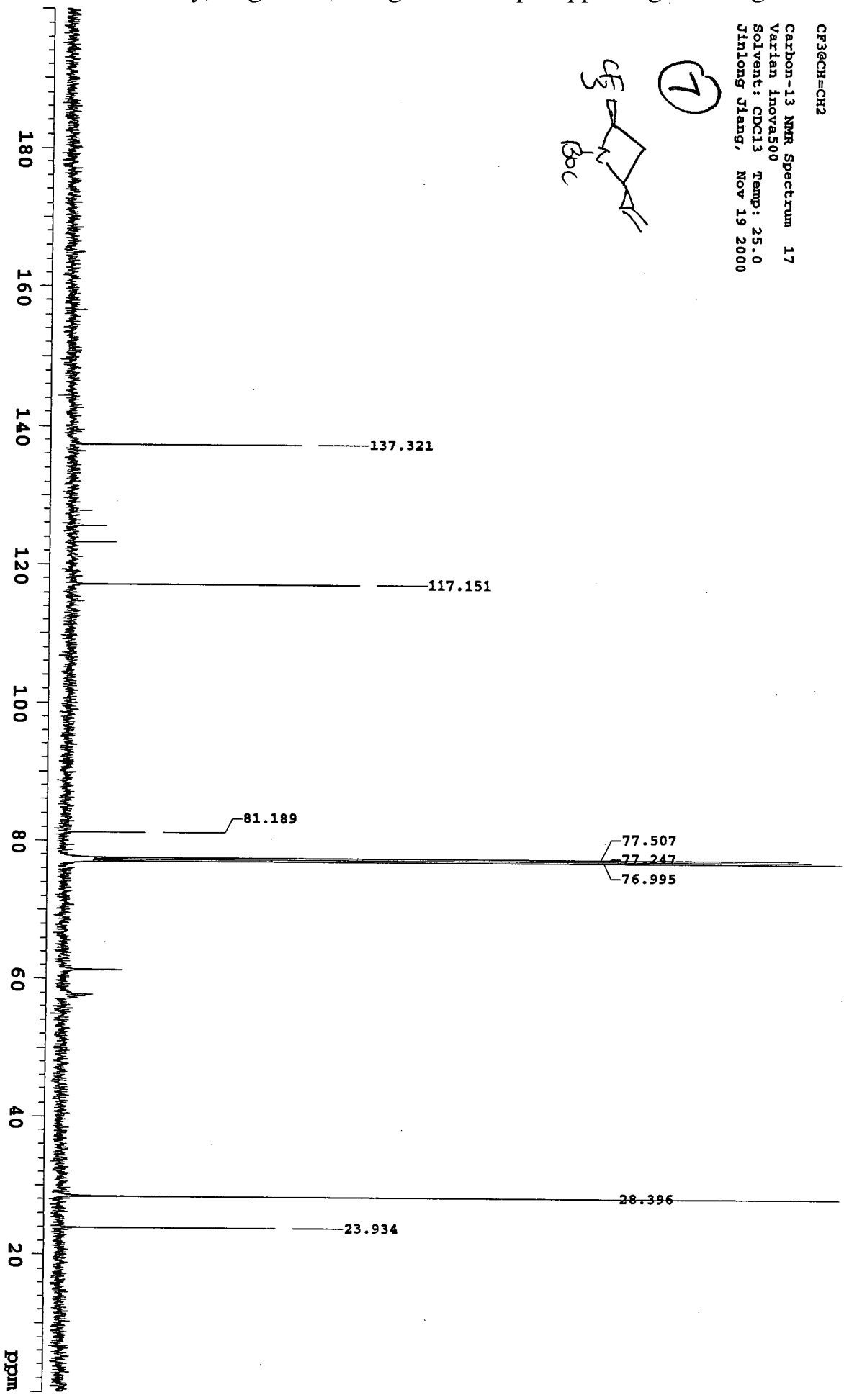

CF3@2FPhCH22@CH2COOMe
Proton NMR Spectrum 31
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Feb 12 2001
(6b)
CF3
Boc
CH2CO2Me
F
F
8
7
6
5
4
3
2
1
ppm


CF3@2fPhCH2@CH2COOMe
Carbon-13 NMR Spectrum 32
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Feb 17 2001
(6b)
CF3
Boc
CH2CO2Me
F
170.909
112.164
112.118
112.011
111.965
102.735
81.757
77.504
77.253
76.993
51.960
39.532
39.074
38.471
28.356
180
160
140
120
100
80
60
40
20
ppm

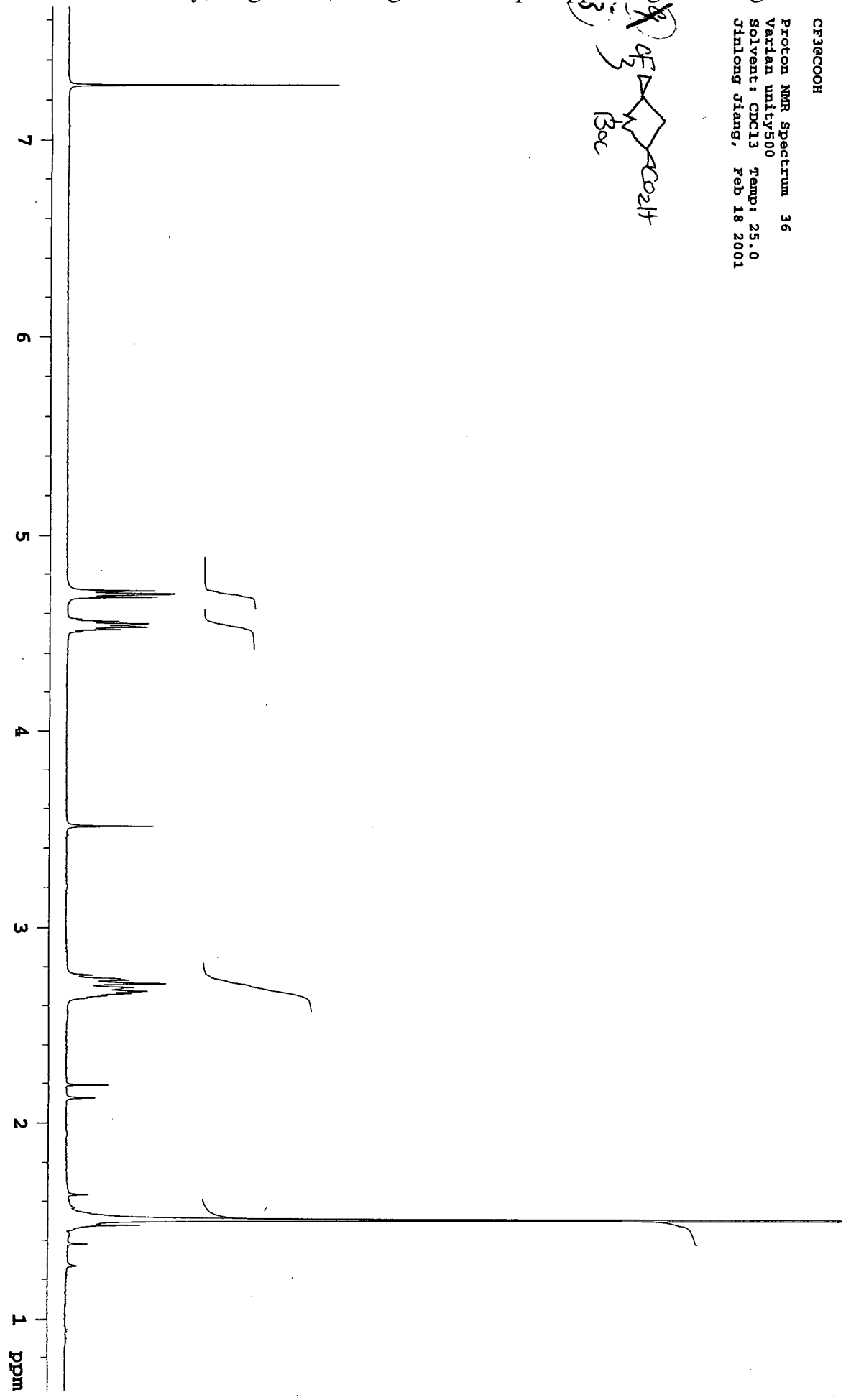

CF3CPhCHOCH2COOMe
Proton NMR Spectrum 54
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Feb 9 2001
6c
7
6
5
4
3
2
ppm

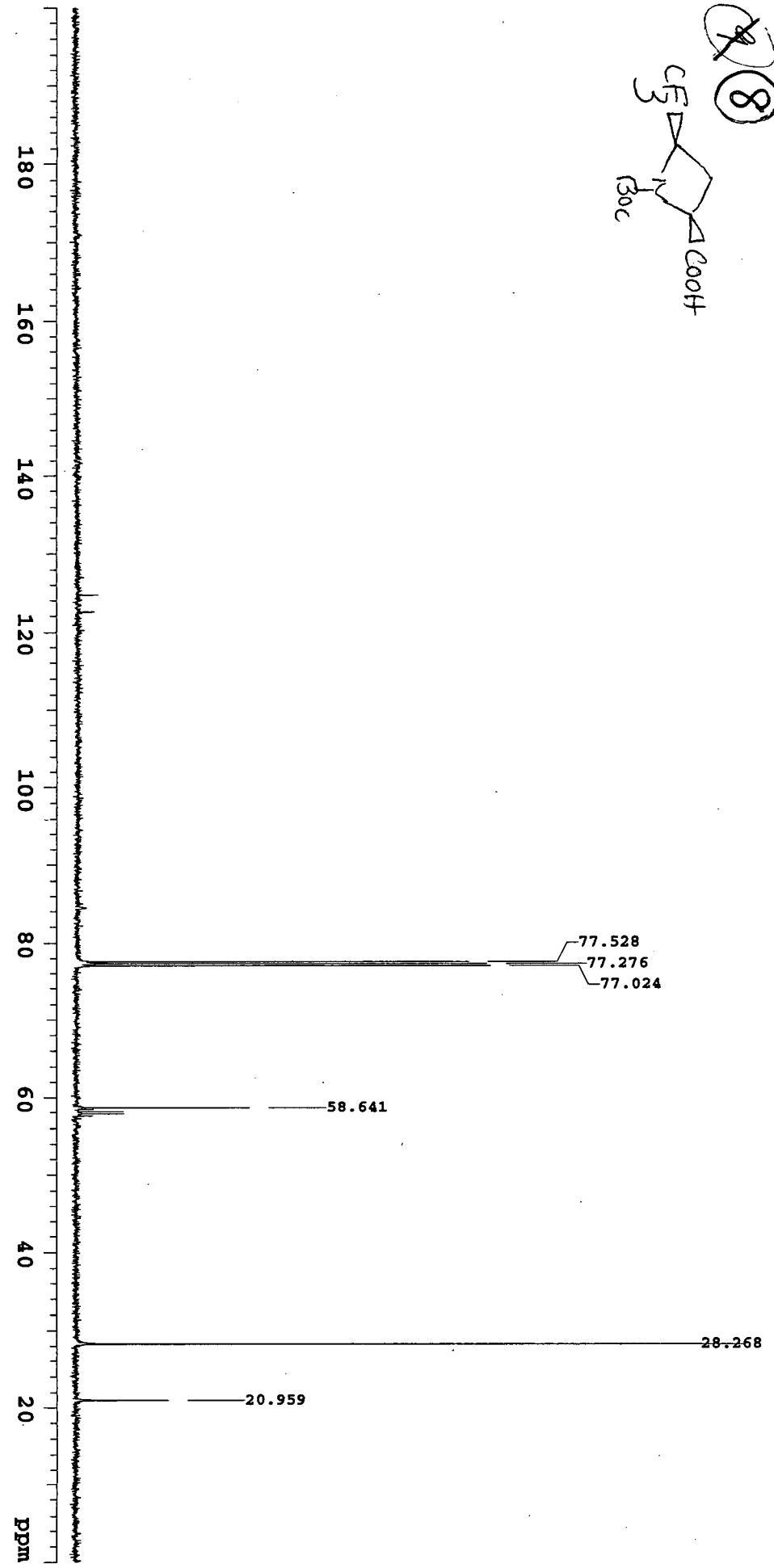

CF3@PhCHO@CH2COOMe
Carbon-13 NMR Spectrum 42
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Feb 18 2001
6C
172.612
140.093
128.881
128.728
126.766
81.790
77.536
77.284
77.032
75.344
52.485
45.123
39.044
28.436
180
160
140
120
100
80
60
40
20
ppm




CF3@CH=CH2
Carbon-13 NMR Spectrum 17
Varian inova500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Nov 19 2000
CF3
Boc
7
137.321
117.151
81.189
77.507
77.247
76.995
28.396
23.934
180
160
140
120
100
80
60
40
20
ppm

5:34


CF3@COOH
Proton NMR Spectrum 36
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Feb 18 2001
CF3
CO2H
Boc
7
6
5
4
3
2
1
ppm


CF3@COOH
Carbon-13 NMR Spectrum 37
Varian unity500
Solvent: CDCl3 Temp: 25.0
Jinlong Jiang, Feb 18 2001
CF3
N
Boc
COOH
180
160
140
120
100
80
60
40
20
ppm
77.528
77.276
77.024
58.641
28.268
20.959