Supplementary Information

Enantioselective synthesis of tetrafluorinated ribose and fructose

Bruno Linclau, *[a] A. James Boydell,[a] Roxana S. Timofte,[a] Kylie J. Brown,[a] Victoria Vinader,[b] and Alexander C. Weymouth-Wilson

Table of contents:

1) Determination of the enantioselectivity of the SAD reaction

a) Conversion to **(*2R*)-1,2-dibenzoyloxy-4-bromo-3,3,4,4-tetrafluoro-butane-1,2-diol**

To a solution of **9** (0.30 g, 1.25 mmol, 1 equiv) in pyridine (3.00 mL), BzCl (0.58 mL, 4.98 mmol, 4 equiv) was added. The reaction was stirred at RT for 2.5 h. To the reaction was added water (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 8 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), 1N aqueous HCl (2 x 10 mL), brine (2 x 10 mL) and dried over $MgSO_4$, filtered, concentrated *in vacuo* to give the crude as a transparent gel. Column chromatography (Petroleum ether/EtOAc: 90/10) gave the product the title compound as a transparent gel (0.4772 g, 1.06 mmol, 85% yield). $\mathbf{R_f}$ 0.36 (Petroleum ether/ EtOAc: 90/10). **IR** (Neat): 1728 (s), 1602 (m), 1452 (m), 1274 (s), 1244 (s) cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.08–7.98 (4H, m), 7.63–7.54 (2H, m), 7.49–7.40 (4H, m), 6.21 (1H, dtd, *J*=16.3, 6.8, 3.5 Hz), 4.91 (1H, ddd, *J*=12.2, 3.4, 1.5 Hz), 4.69 (1H, dd, *J*=12.3, 7.0 Hz) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 165.91 (C), 164.50 (C), 134.09(C), 133.53 (C) 130.24 (2 x C, CH), 129.91 (2 x C), 129.25 (CH), 128.76 (2 x C, CH), 128.60 (2 x C, CH), 128.39 (CH), 116.69 (tt, *J*=310.6, 38.6 Hz), 113.63 (ddt, *J*=262.7, 255.0, 31.9Hz), 67.43 (dd, *J*=30.5, 22.7 Hz, CH), 60.94 (CH_2) ppm. **^{19}F NMR** ($CDCl_3$, 282 MHz): δ -119.64 (1F, app dd, *J*=174.7, 16.0 Hz), -113.47 (1F, d, *J*=174.7 Hz), -64.29 (2F, s) ppm. **LR MS** (ES^+) m/*z* (%): 471 and 473 ($(M + Na)^+$, 1:1 ratio, 100). **HR MS** (ES^+): for $C_{18}H_{13}{}^{79}Br_1F_4O_4Na_1$ $(M + Na)^+$: calcd: 470.9826, found 470.9824.

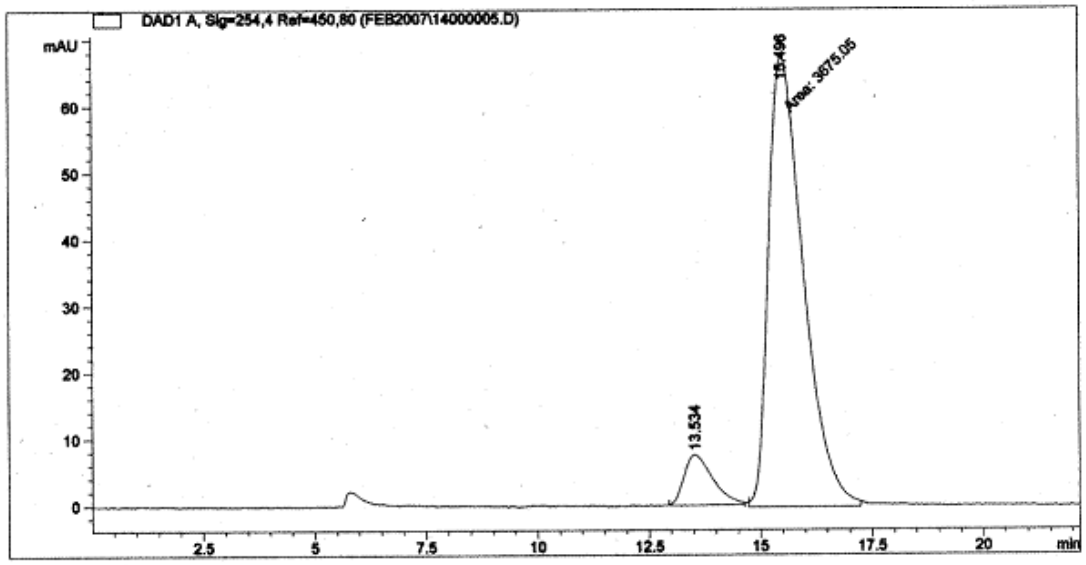
b) Conversion to **(*2R*)-1,2-diacetoxy-4-bromo-3,3,4,4-tetrafluoro-butane-1,2-diol**

9 (0.1 g, 0.41mmol) was dissolved in CH_2Cl_2 (3 mL) and Et_3N (0.14 mL, 1.0 mmol) and DMAP (0.005g, 0.04 mmol) were added. Acetyl chloride (0.071 mL, 1.0 mmol) was added dropwise and the reaction stirred at RT for 2 h. The reaction was quenched by the addition of HCl (0.5M, aq, 10 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 5 mL), the organic phases were combined, dried over $MgSO_4$, filtered and

concentrated *in vacuo*. Column chromatography (pentane / Et_2O, 80:20) gave the title compound as a colourless oil (0.111 g, 83%).

IR (neat): 1752 (s), 1372 (m), 1203 (s), 1143 (s), 1085 (s). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.77 (1H, dtd, *J* = 16.4, 7.1, 3.3 Hz, C**H**OAc), 4.60 (1H, ddd, *J* = 12.3, 3.3, 1.7 Hz, C**H**HCH), 4.24 (1H, dd, *J* = 12.2, 7.4 Hz, CH**H**CH), 2.15 (3H, s, C**H$_3$**), 2.07 (3H, s, C**H$_3$**) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.2 (**CO**), 168.7 (**CO**), 66.70 (1C, dd, *J* = 30.1, 22.4 Hz, **C**HCF$_2$), 60.1 (**CH$_2$**), 20.5 (**CH$_3$**), 20.3 (**CH$_3$**) ppm. The CF_2CF_2 carbons were not observed. **^{19}F NMR** (282 MHz, $CDCl_3$): δ -64.70 (2F, s, CF_2Br), -114.25 (1F, d, *J* = 272.9 Hz, CH**C**F**F**), -120.21 (1F, ddt, *J* = 272.9, 17.2, 4.3 Hz, CH**C**F**F**) ppm. **CIMS**: m/z (%):344 and 342 $(M+NH_4^+)^+$ (6, 1:1 ratio) **HRMS (ES$^+$)** for $C_8H_9{}^{79}BrF_4O_4Na_1$ $(M + Na)^+$: calcd: 346.9613, found; 346.9513.

Analysis of **(*2S*)-1,2-dibenzoyloxy-4-bromo-3,3,4,4-tetrafluoro-butane-1,2-diol** by reverse HPLC (OJ column, IPA/hexane eluent) showed a 83% *ee* when $(DHQD)_2PYR$ was used in the AD of **8** (Figure 1).



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 A, Sig=254,4 Ref=450,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.534	BB	0.5656	334.54205	7.54005	8.3435
2	15.496	MM	0.9053	3675.04858	67.65485	91.6565

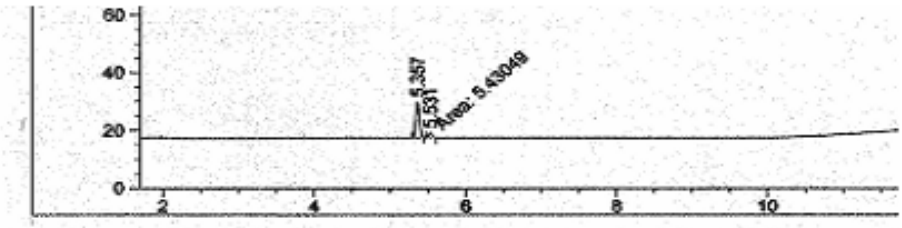
Totals : 4009.59064 75.19490

Results obtained with enhanced integrator!

*** End of Report ***

Figure 1

Analysis of the (***2R*)-1,2-diacetoxy-4-bromo-3,3,4,4-tetrafluoro-butane-1,2-diol** by chiral GC (Chiradex G9511-16 column,) showed a 78% *ee* when $(DHQ)_2PYR$ was used in the AD (Figure 2).



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	5.357	BB	0.0503	41.14046	12.39569	88.33933
2	5.531	MM	0.0557	5.43049	1.62436	11.66067

Totals : 46.57094 14.02004

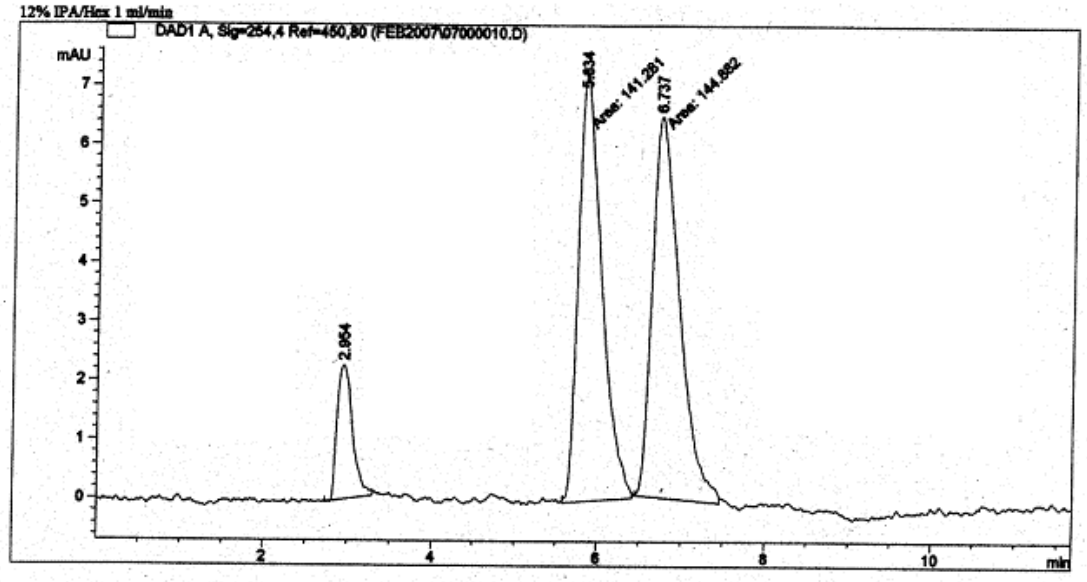
= 78% ee

Figure 2

2) Confirmation of the *ee* of **11** and **20**

i) Alkylation under basic conditions.

The *ee* values of **11** were obtained on chiral HPLC with an OJ column. The eluent used for the resolution of **11** was 12% IPA in hexane and the concentration of the samples was 2 mg/ mL. The injection volume was 10 µL and the flow 1 mL/min. The retention times were 5.8 min for (*S*)-**11** and 6.7 min for (*R*)-**11** (Figure 3).



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 A, Sig=254,4 Ref=450,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.954	PB	0.1979	28.59394	2.27449	9.0845
2	5.834	MM	0.3239	141.28108	7.27030	44.8858
3	6.737	MM	0.3738	144.88182	6.46055	46.0298
Totals :				314.75685	16.00534	

Figure 3: Chiral HPLC trace (OJ column) of racemic **11**.

Chiral HPLC chromatogram of a sample of **11** synthesised by treatment of **9** with Na_2CO_3 and BnBr. When compared to the 83% ee observed by a similar method in section 1 the sample shows no evidence of epimerisation (Figure 4).

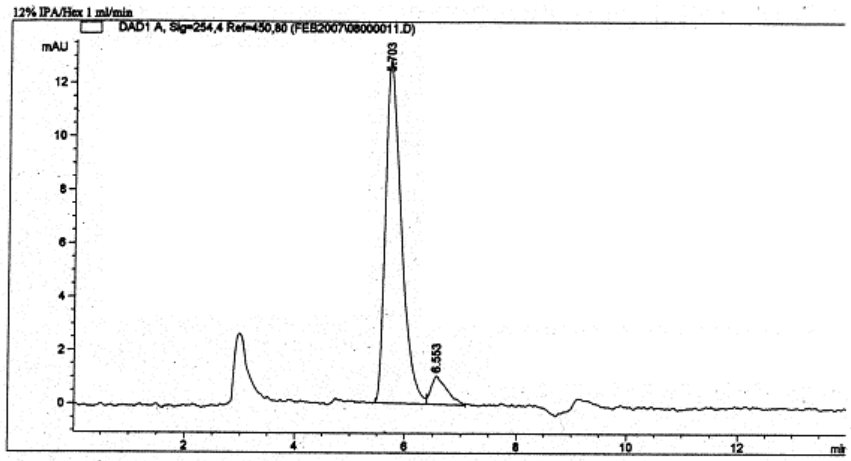


Figure 4

ii) Alkylation *via* the stannylene acetal methodology.

NMR analysis of the Mosher's ester of **20** showed an *ee* of 77% i.e. no reduction in *ee* after alkylation *via* a stannylene acetal (Figure 5).

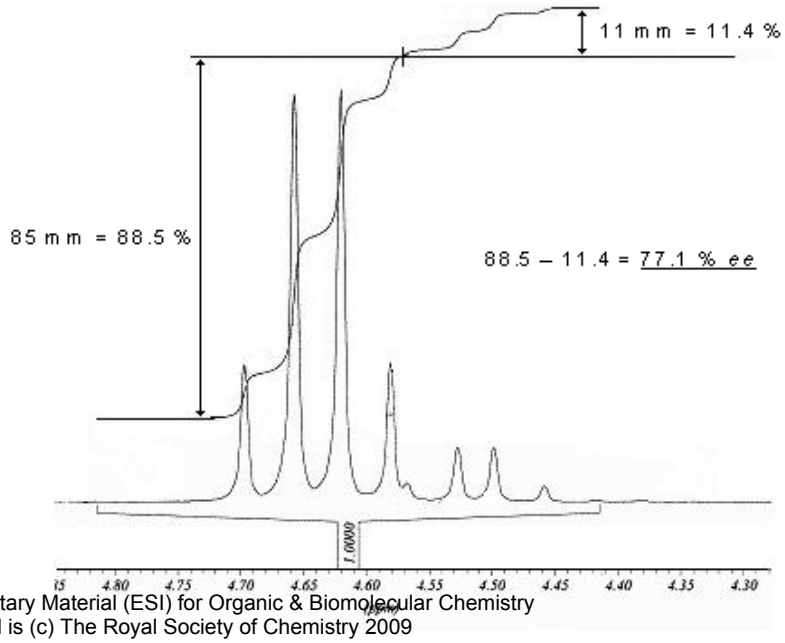
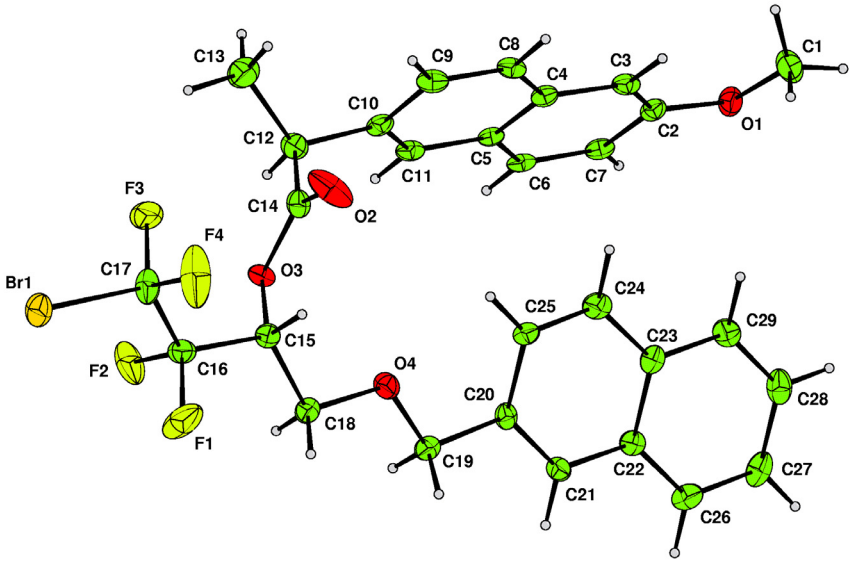


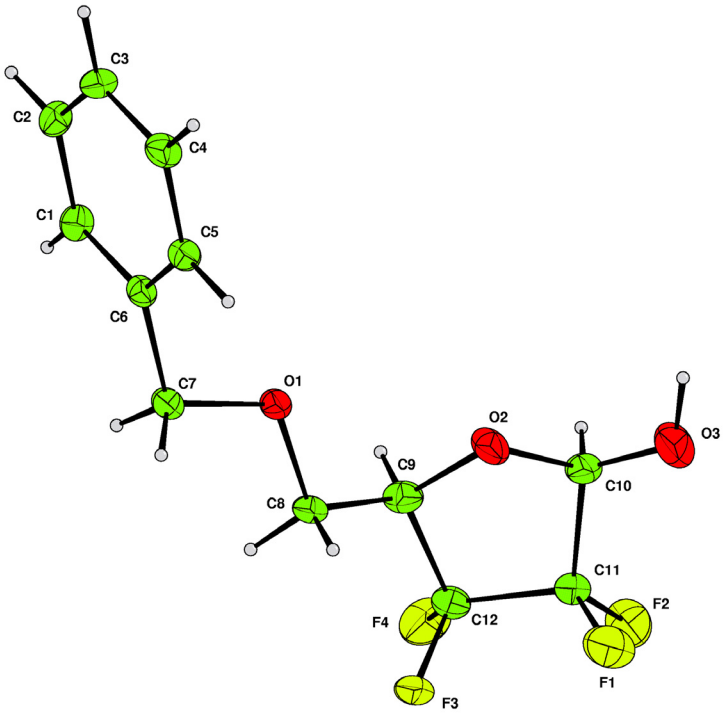
Figure 5

3) Crystal structure of **22**



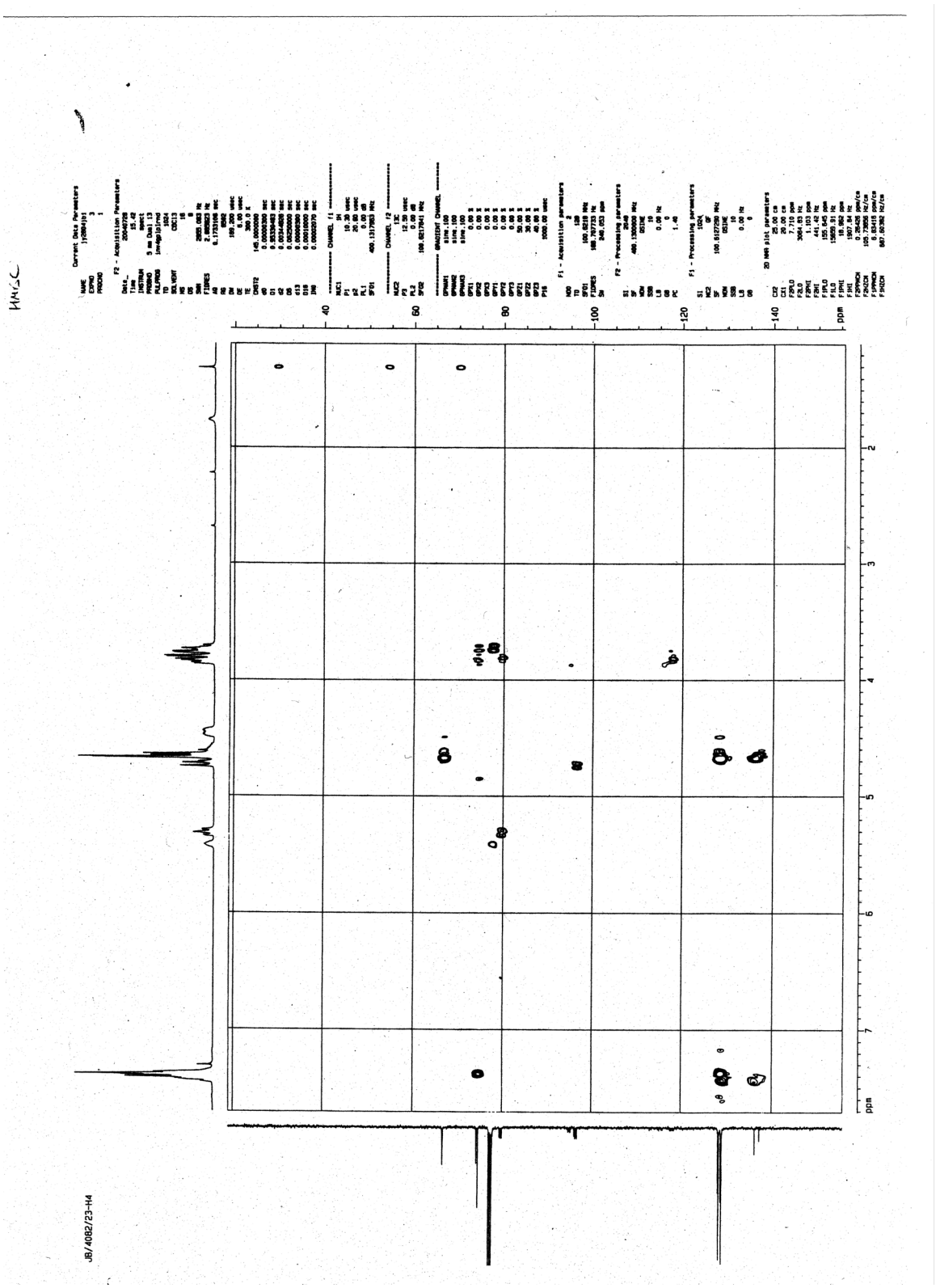
Thermal ellipsoids drawn at the 50% probability level

4) Crystal structure of **2**

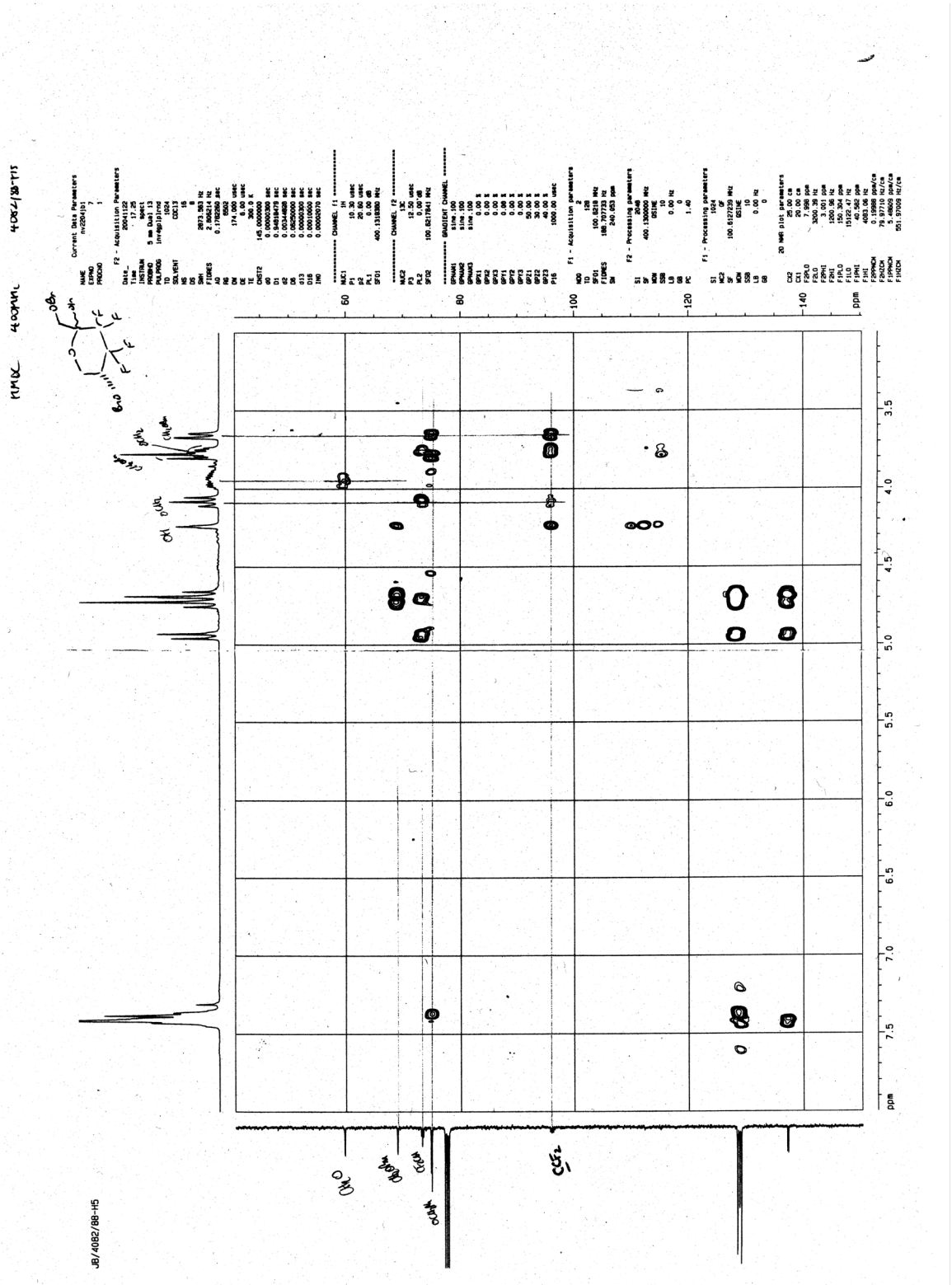


Thermal ellipsoids drawn at the 35% probability level

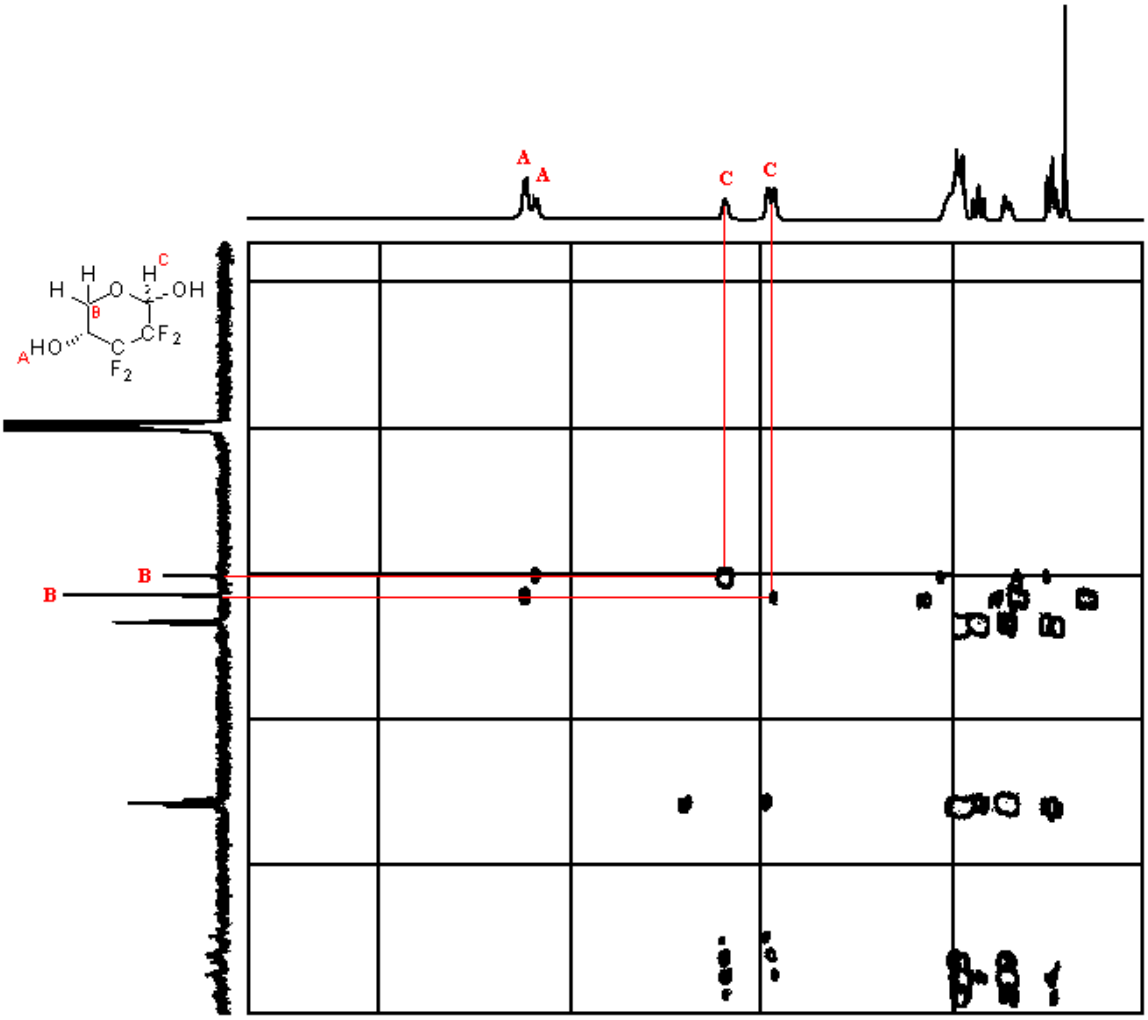
5) HMBC spectra of **2**, **5**, **6** and **7**



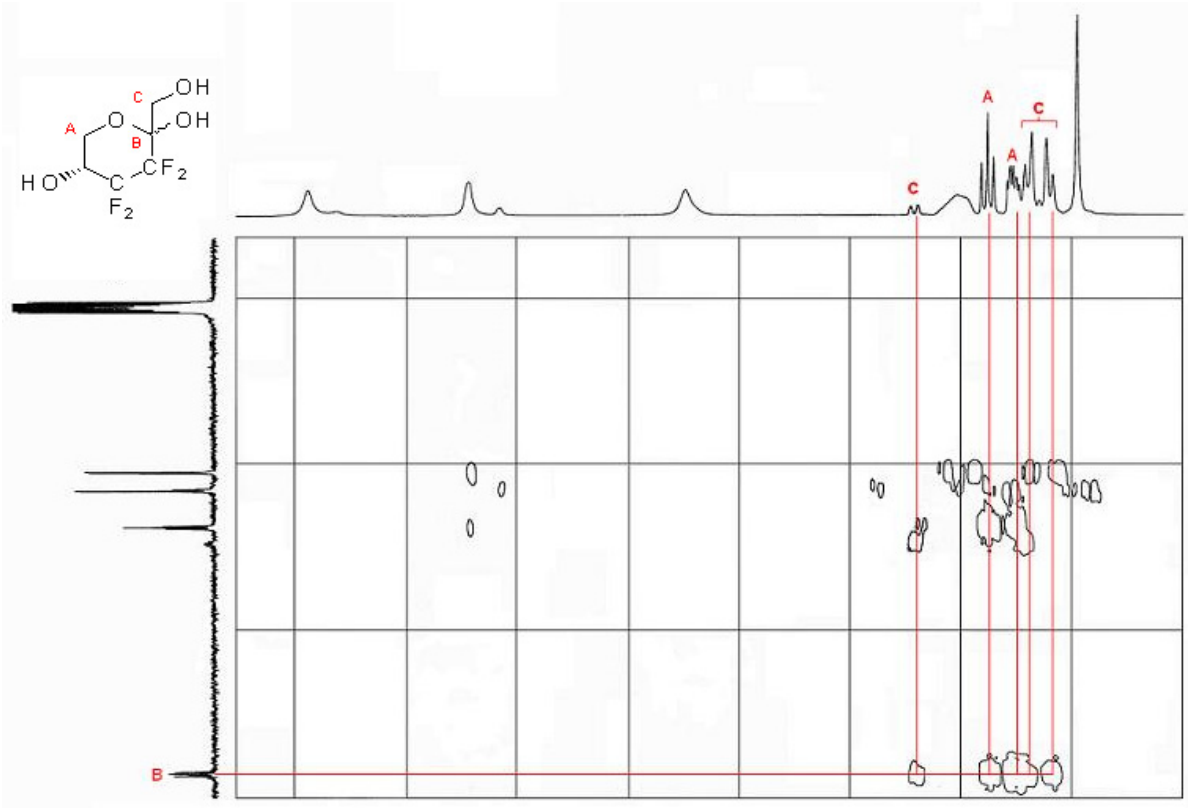
HMBC spectra of **2**



HMBC of **5**

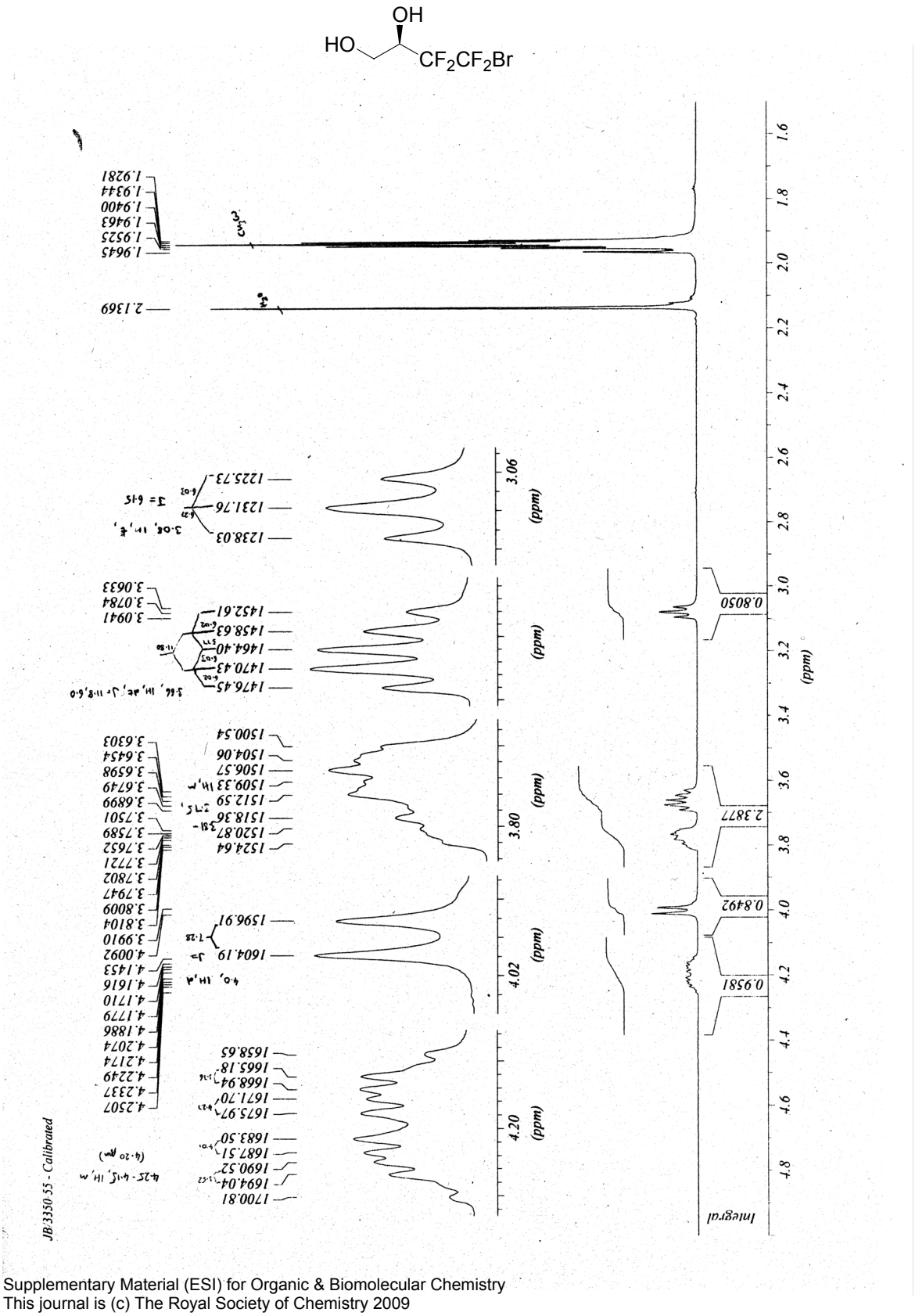


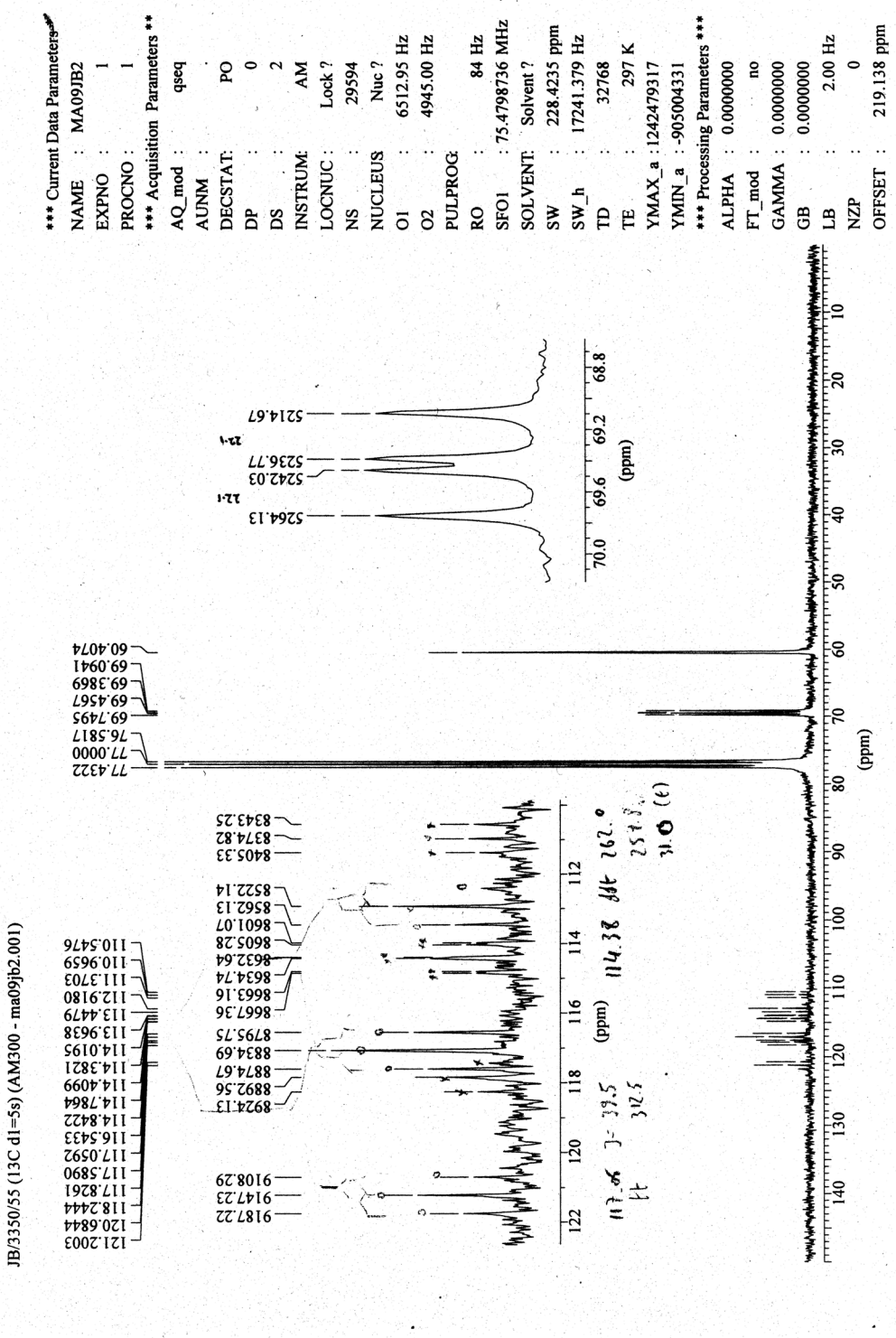
HMBC of **6**

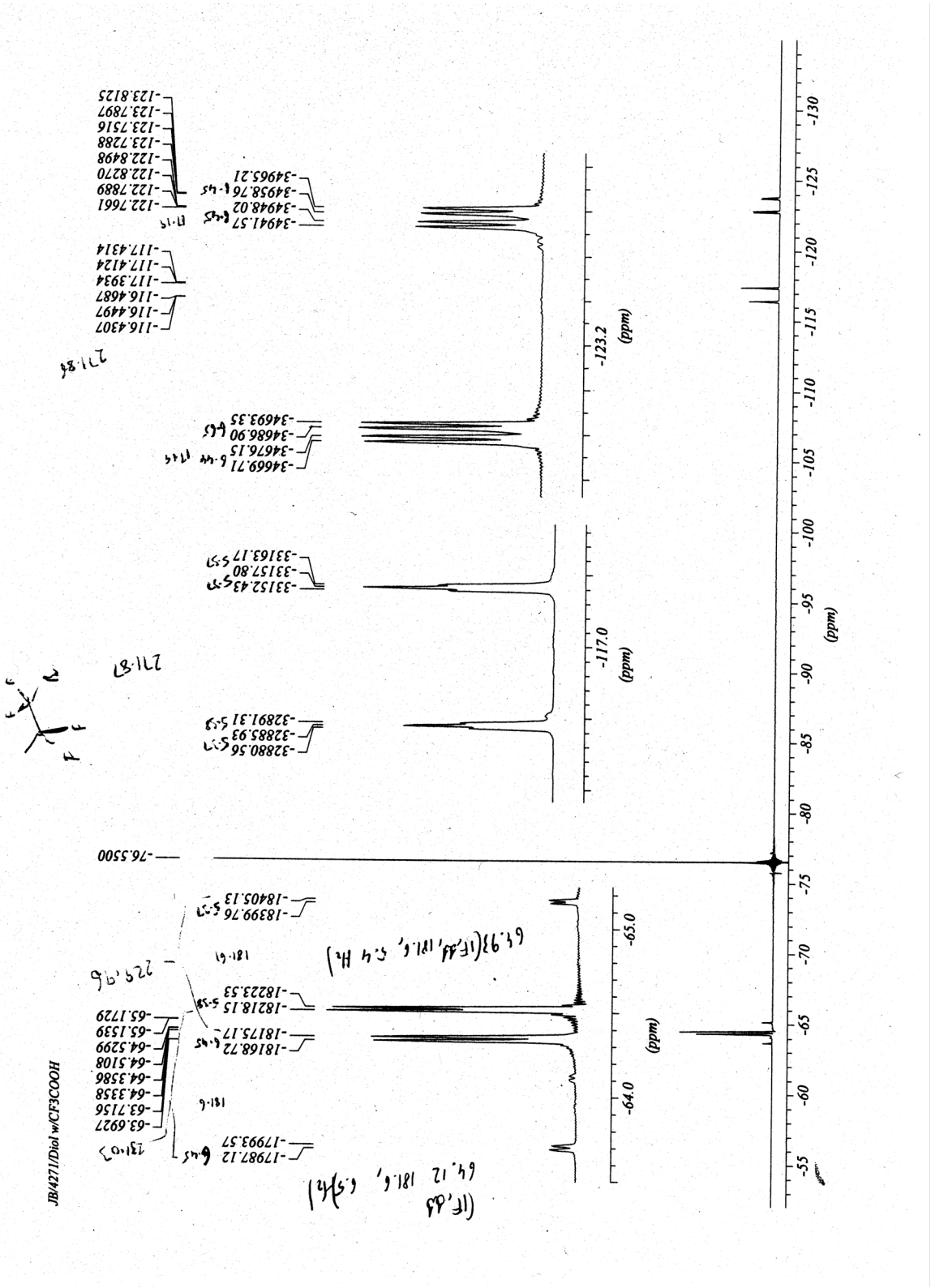


HMBC of **7**

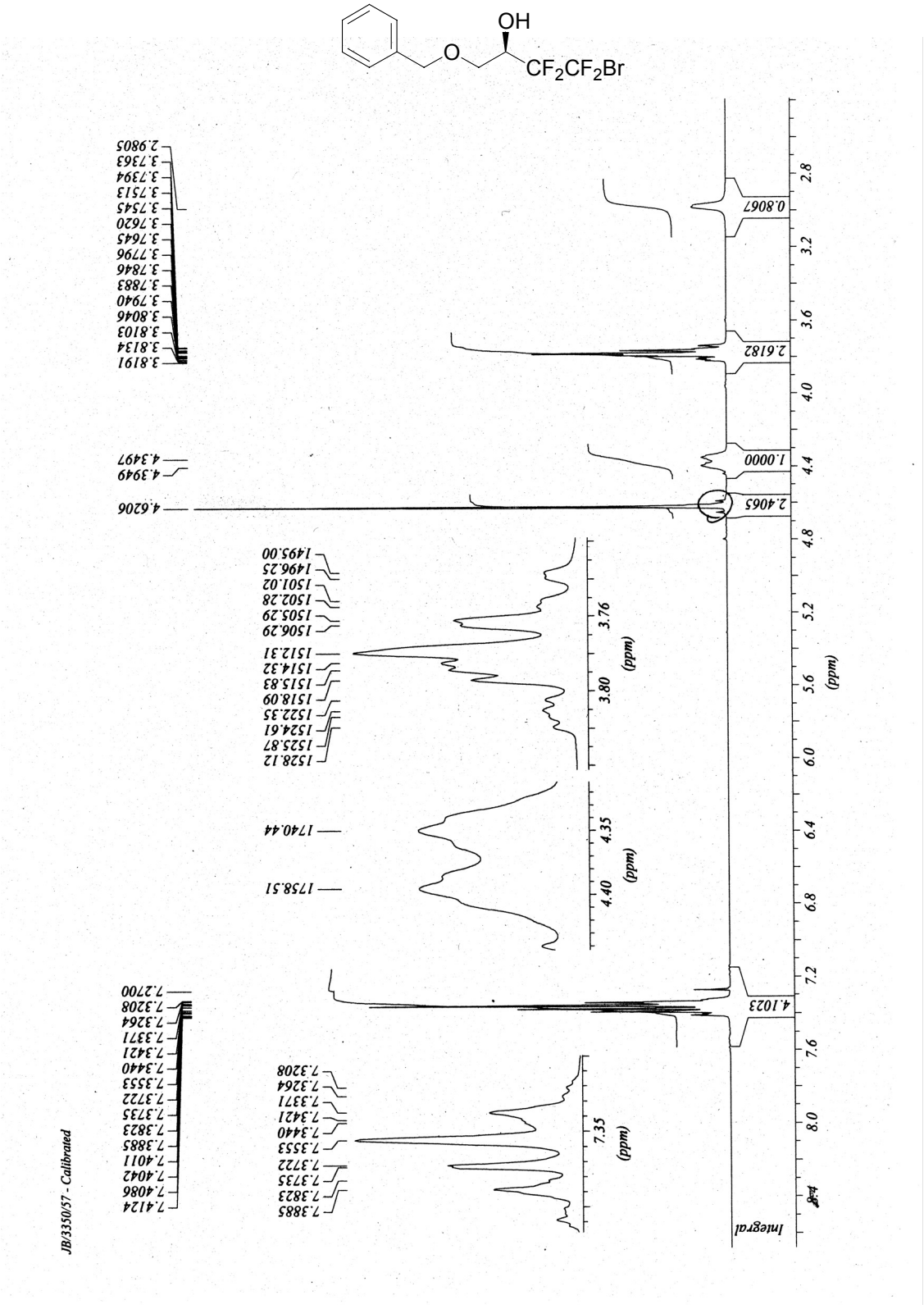
(2R)-4-bromo-3,3,4,4-tetrafluorobutane-1,2-diol (9)

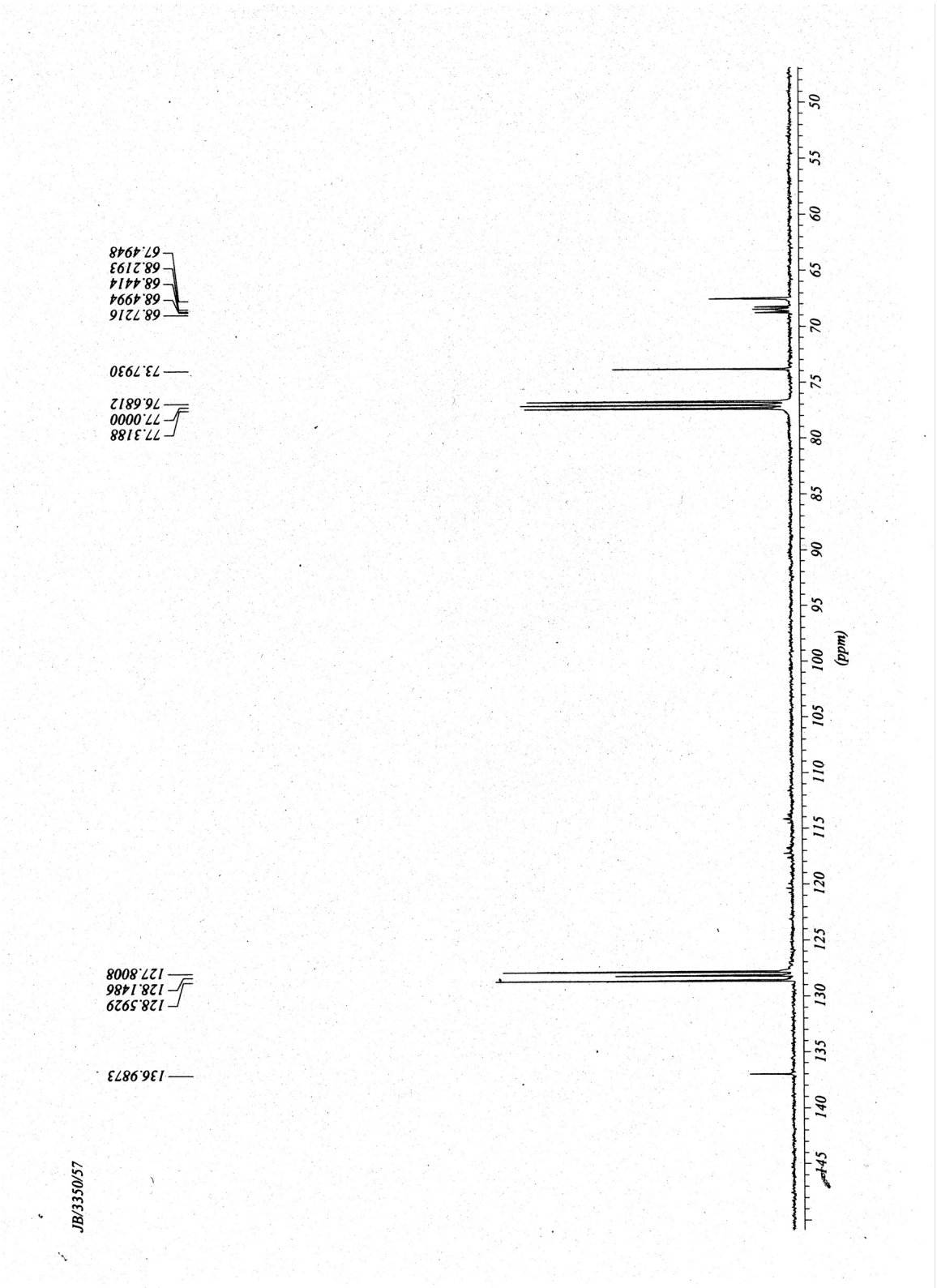


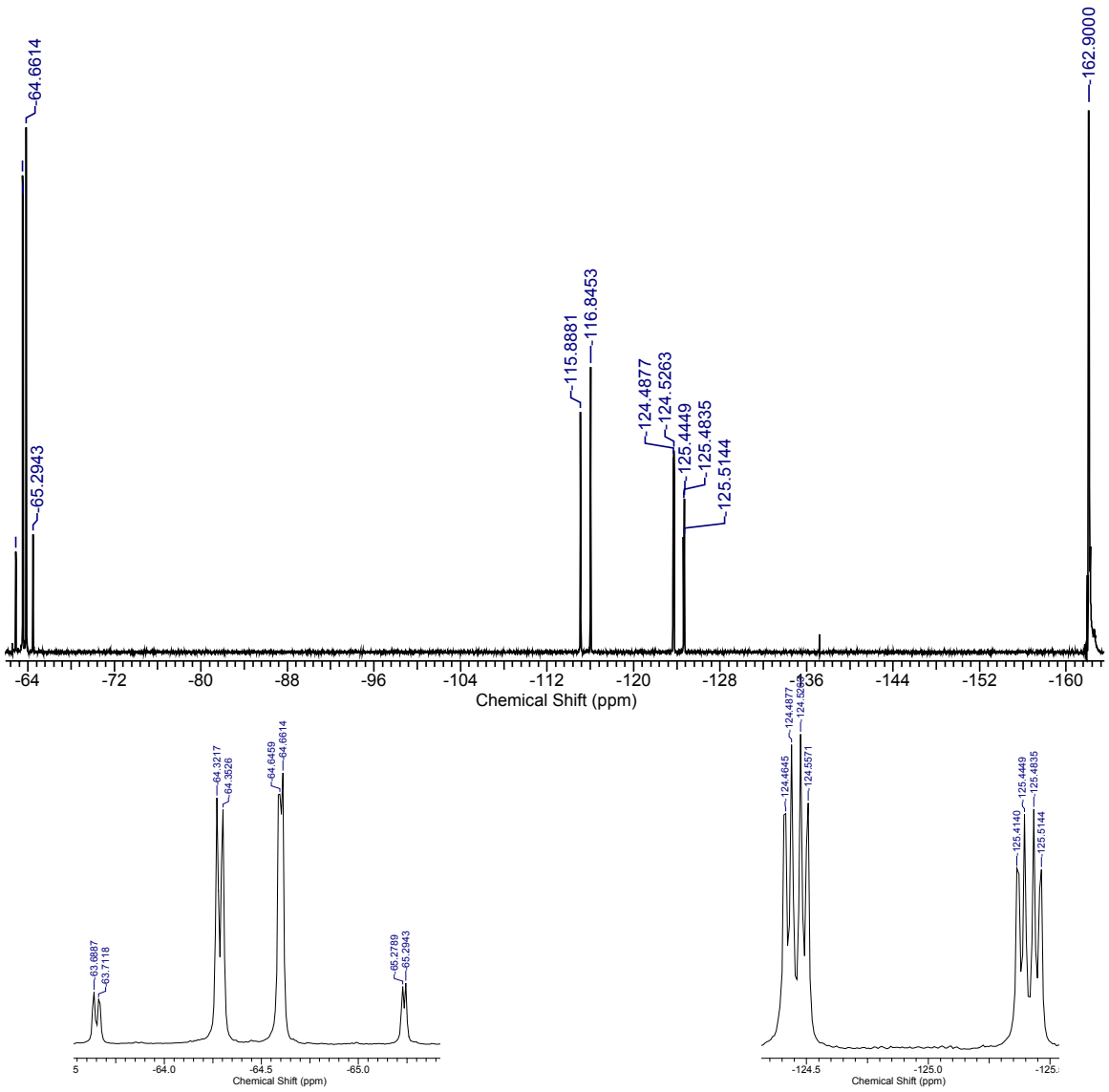




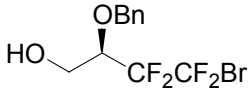
(2*R*)-1-Benzyloxy-4-bromo-3,3,4,4-tetrafluorobutan-1-ol (10)

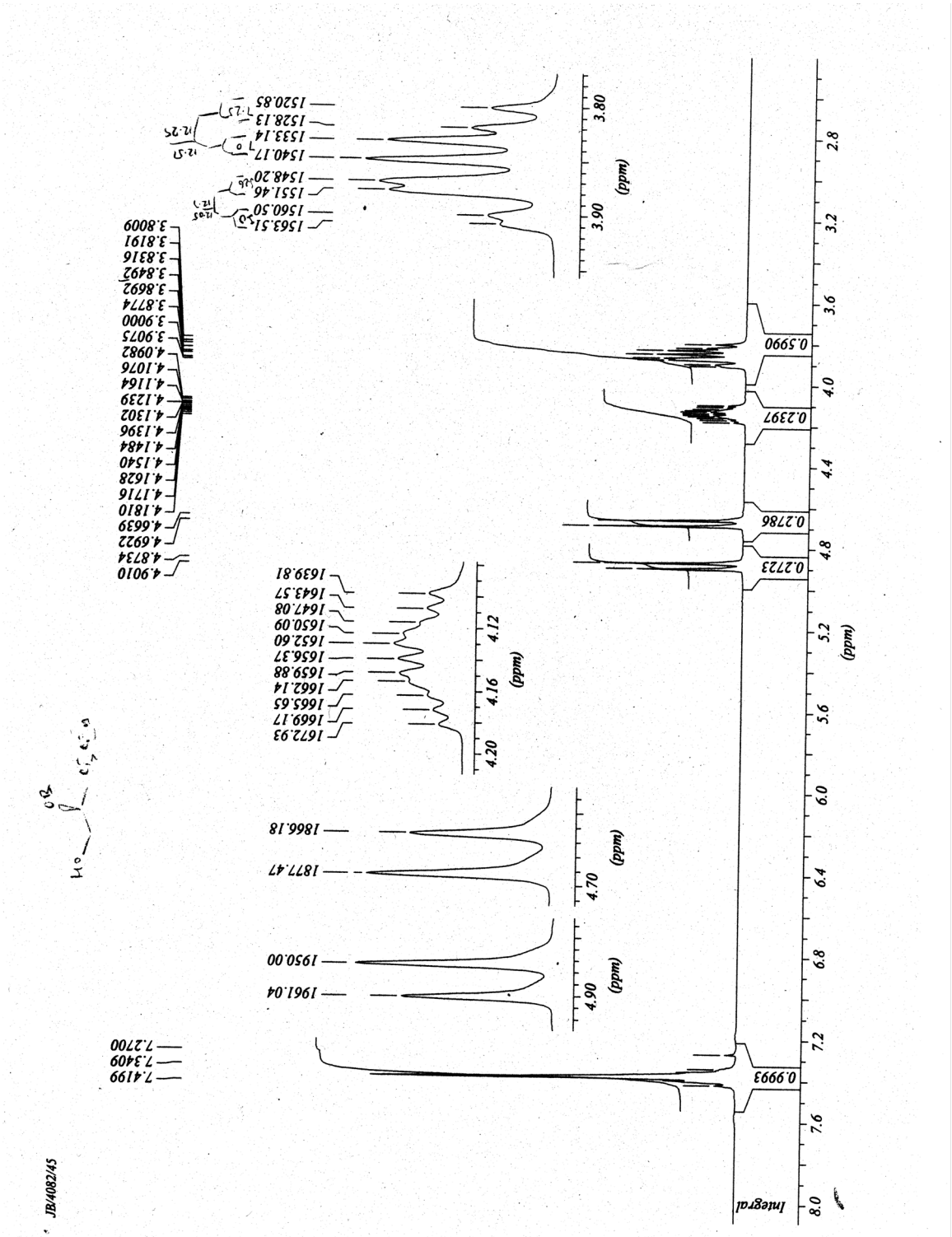


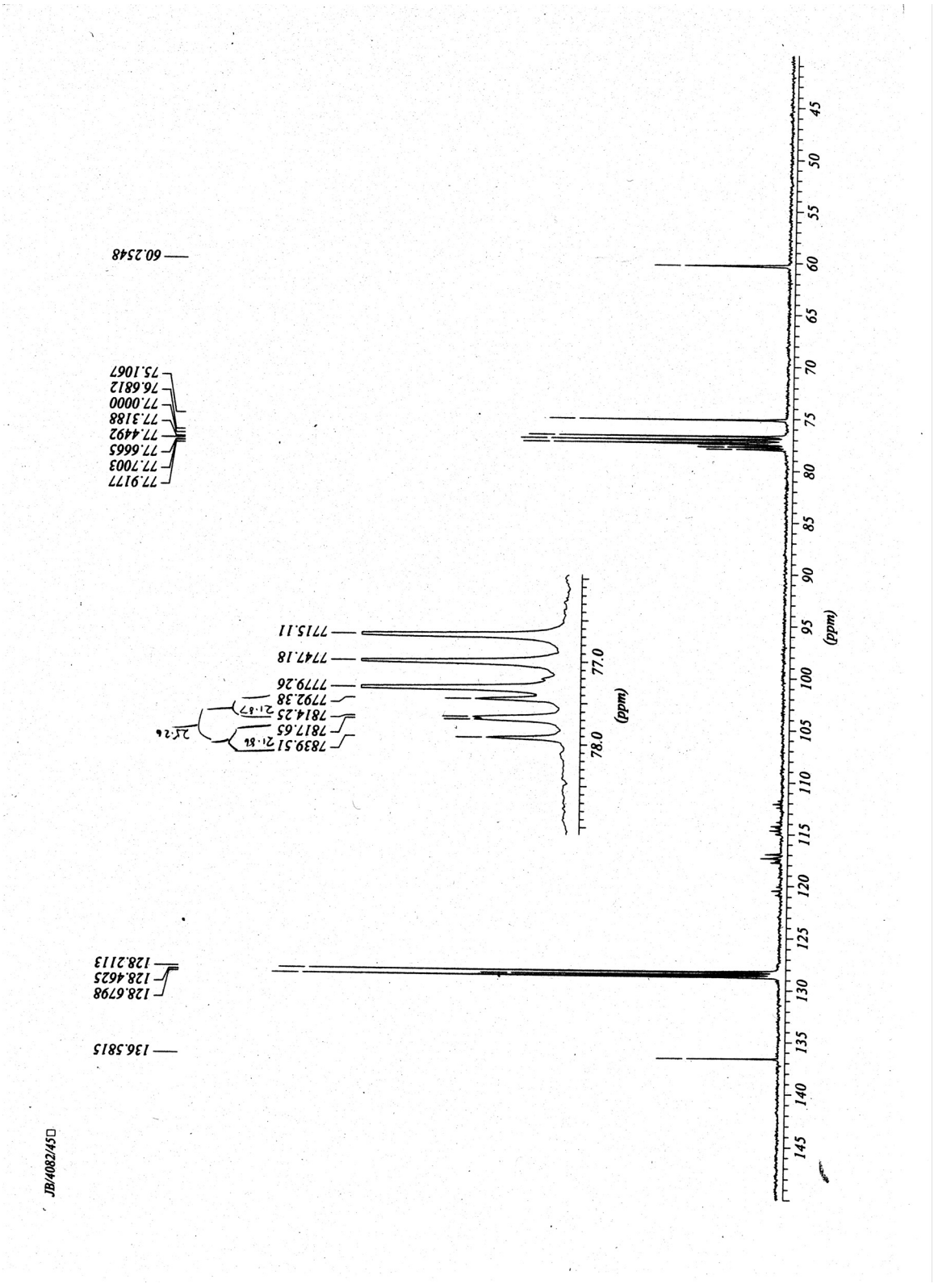


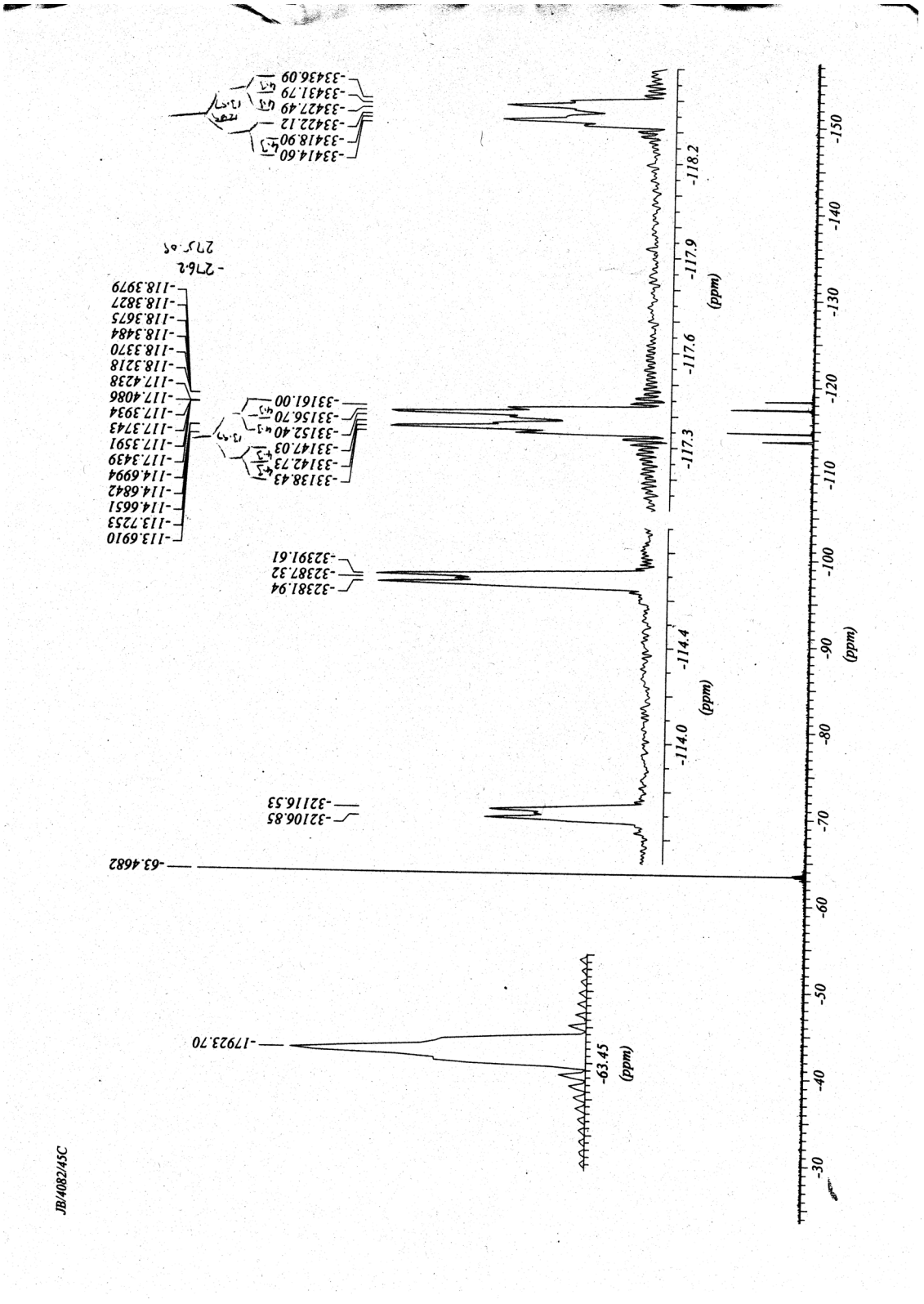


(2*R*)-2-Benzyloxy-4-bromo-3,3,4,4-tetrafluorobutan-1-ol (11)

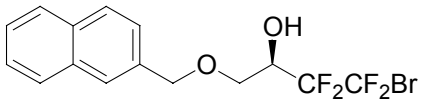


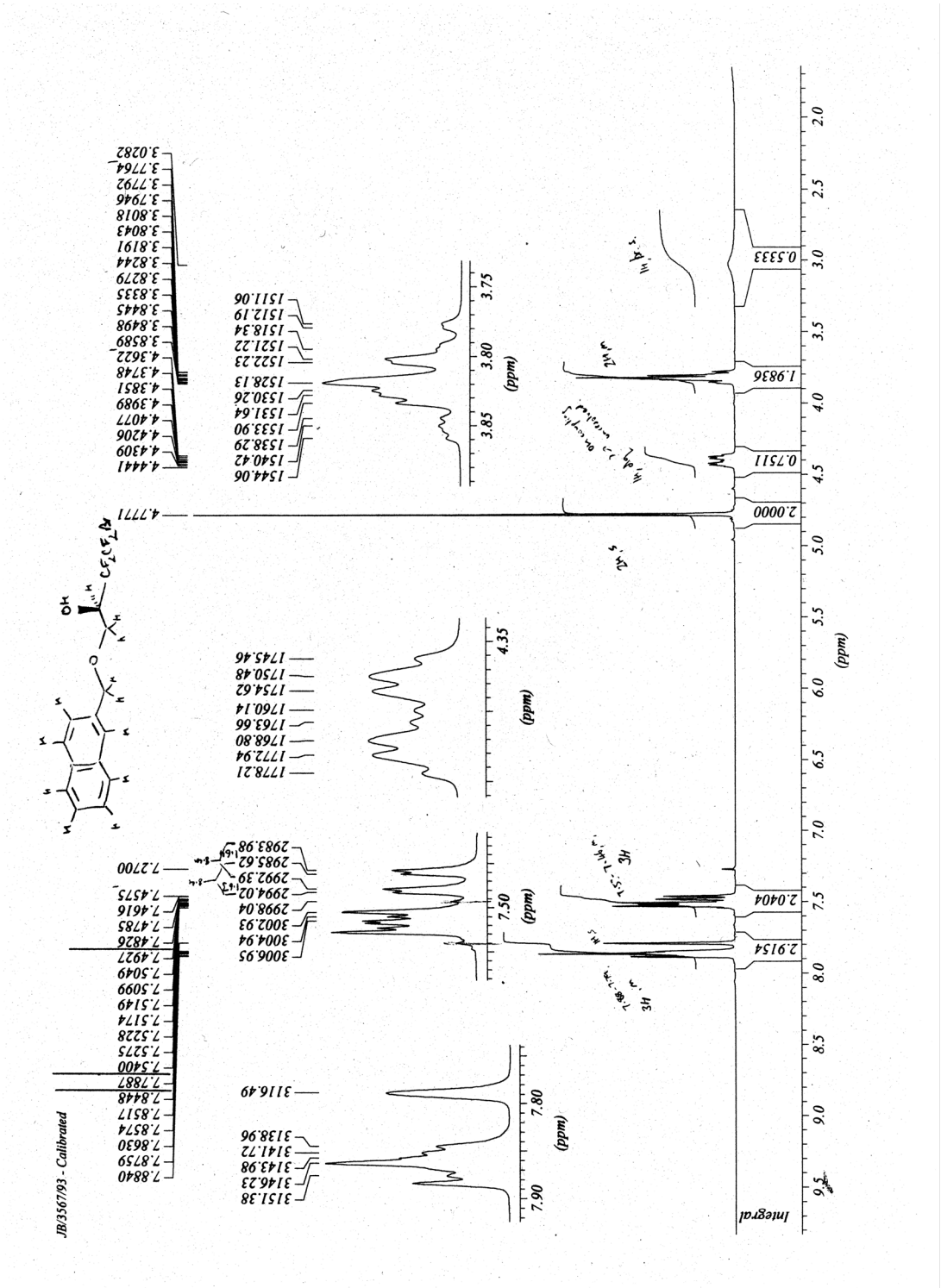


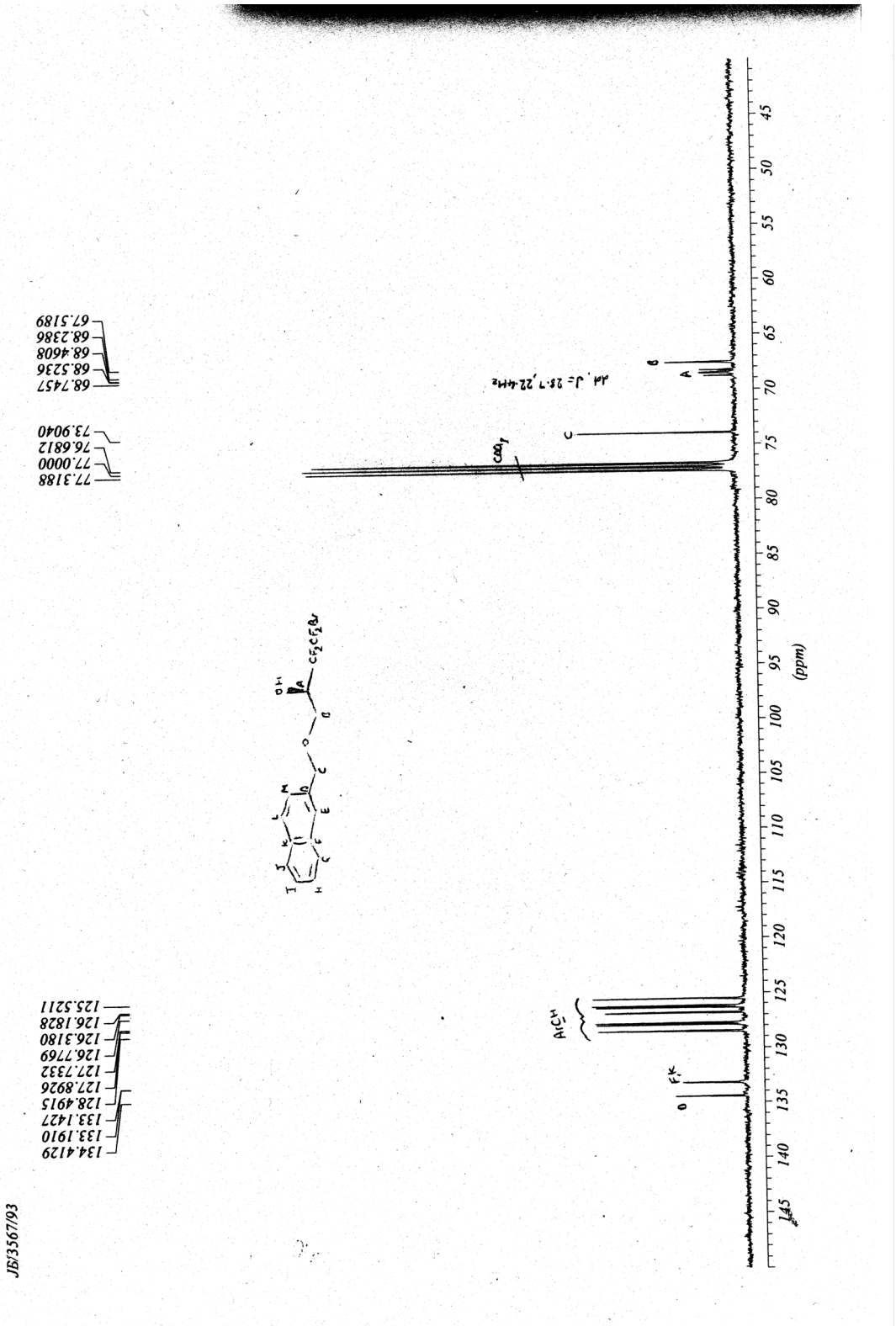


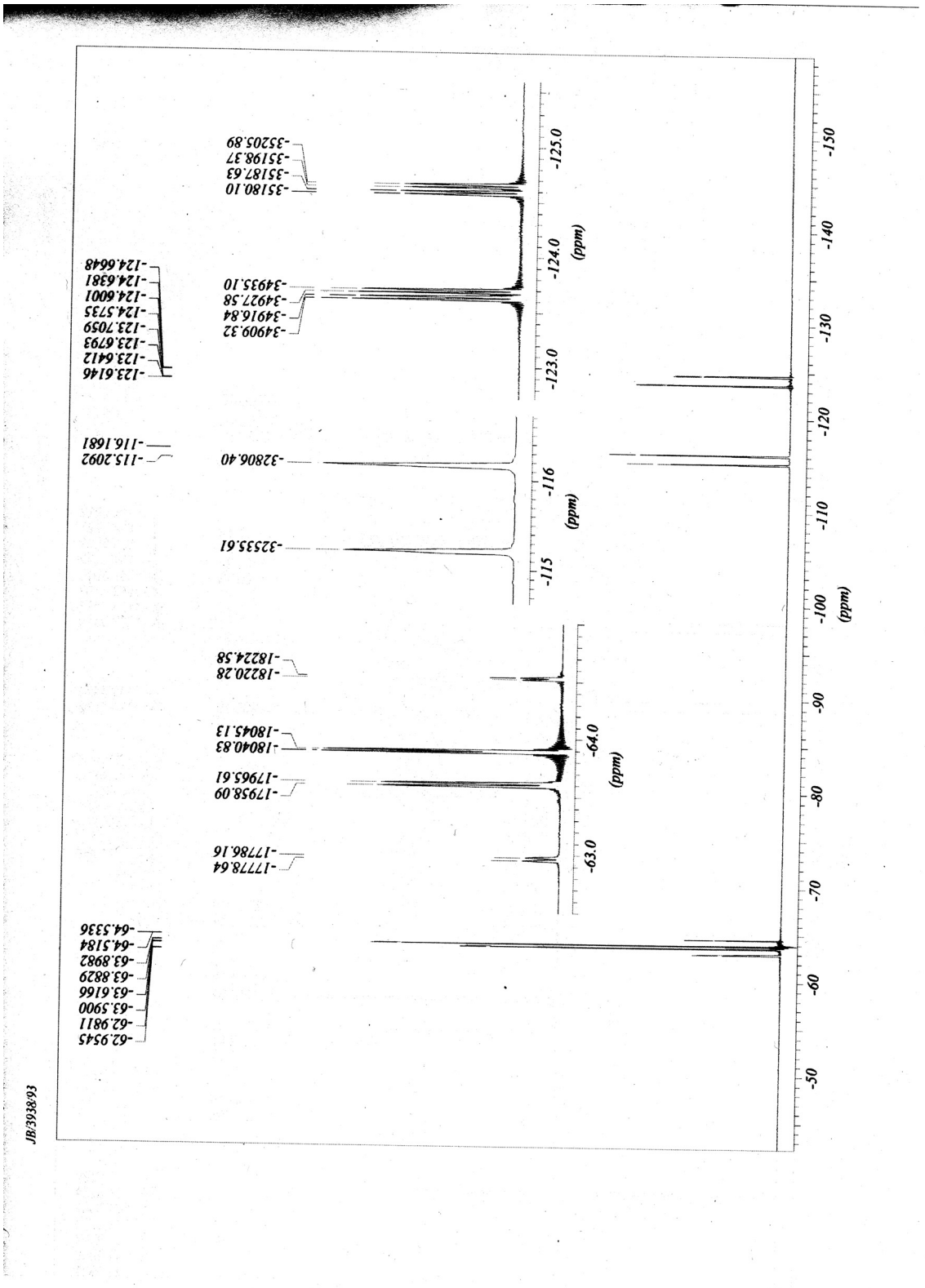


(2*R*)-4-bromo-1-(naphth-2-ylmethyloxy)-3,3,4,4-tetrafluorobutan-1-ol (20)

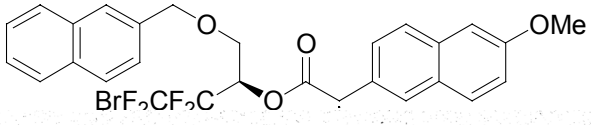


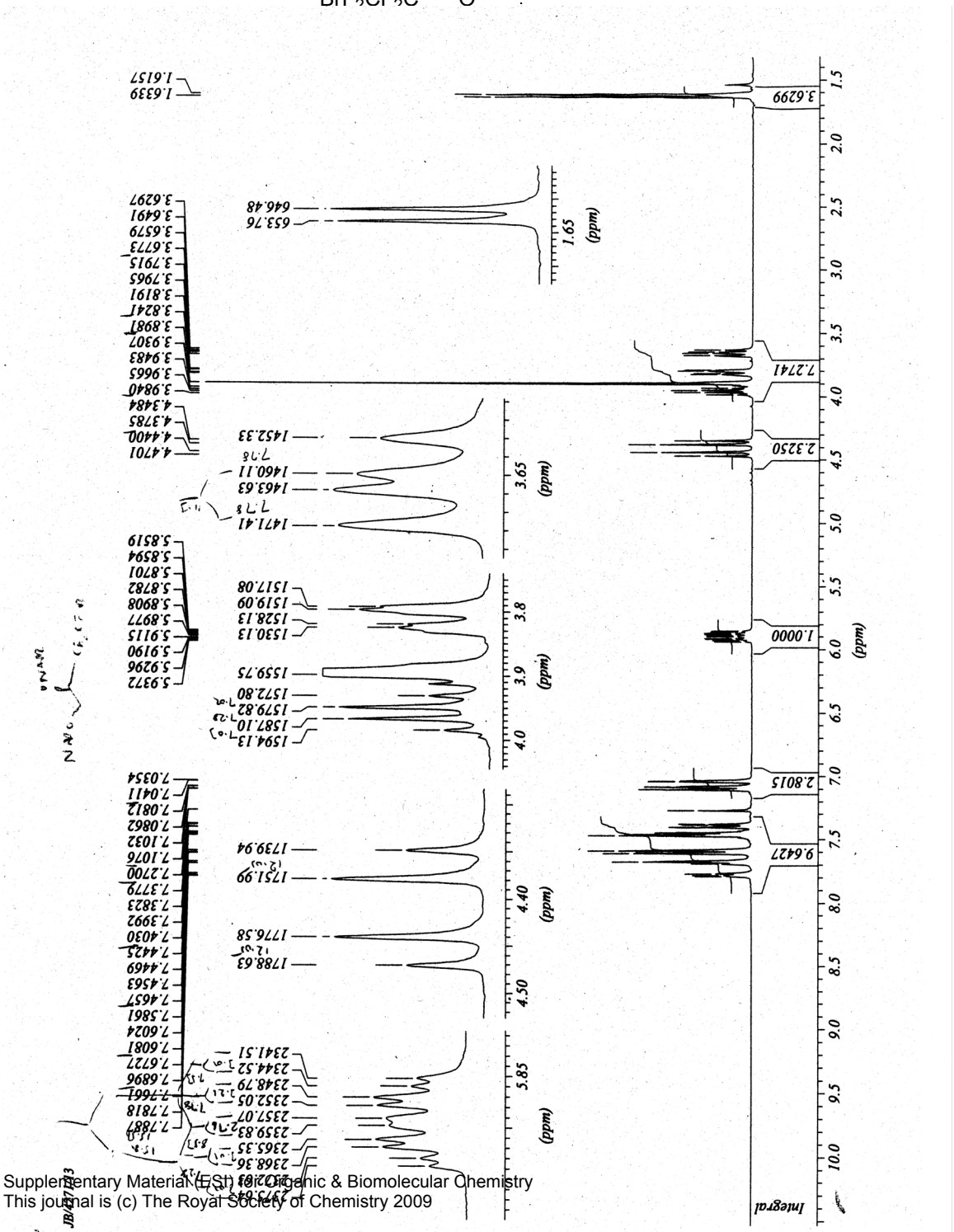


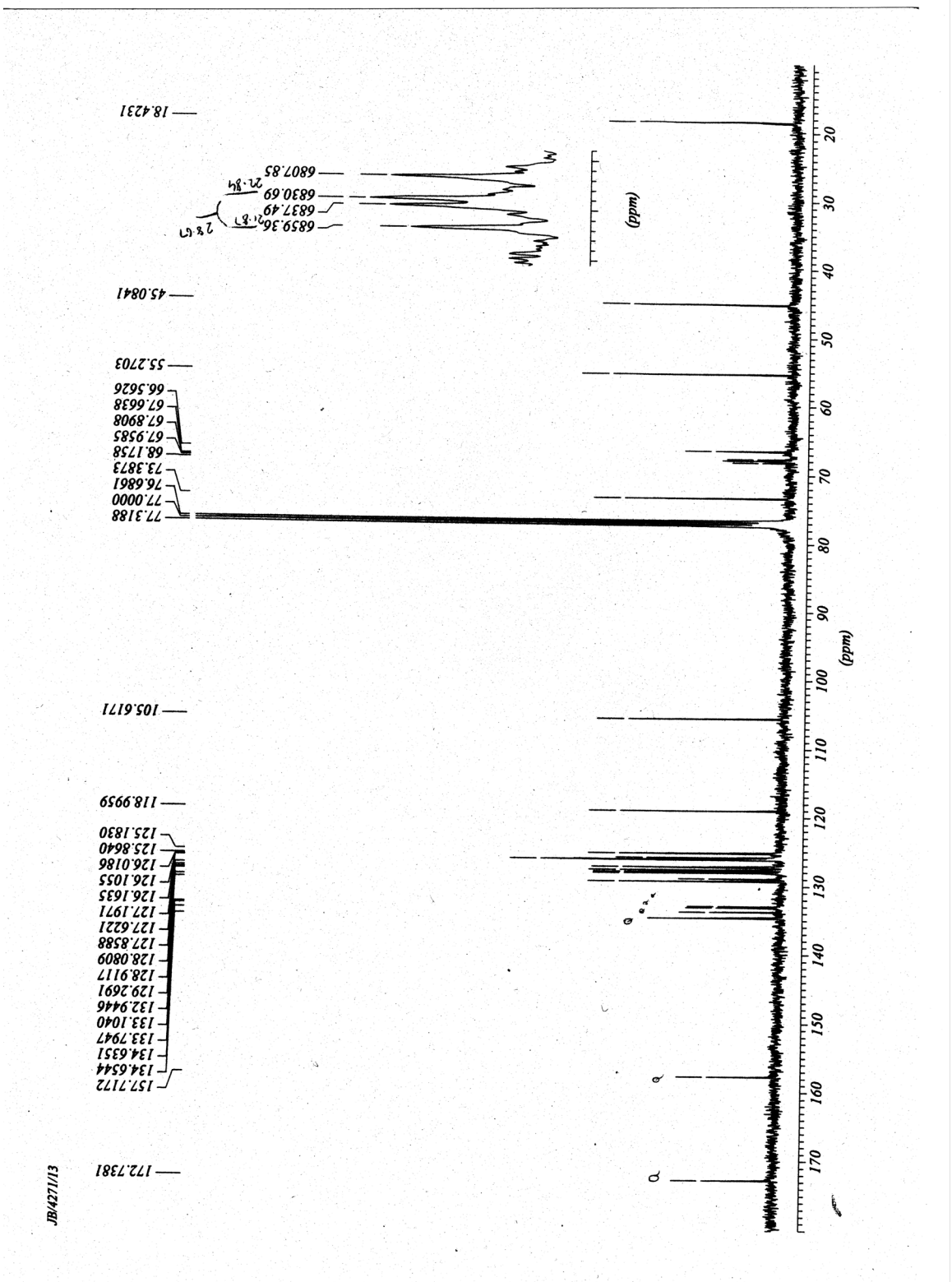


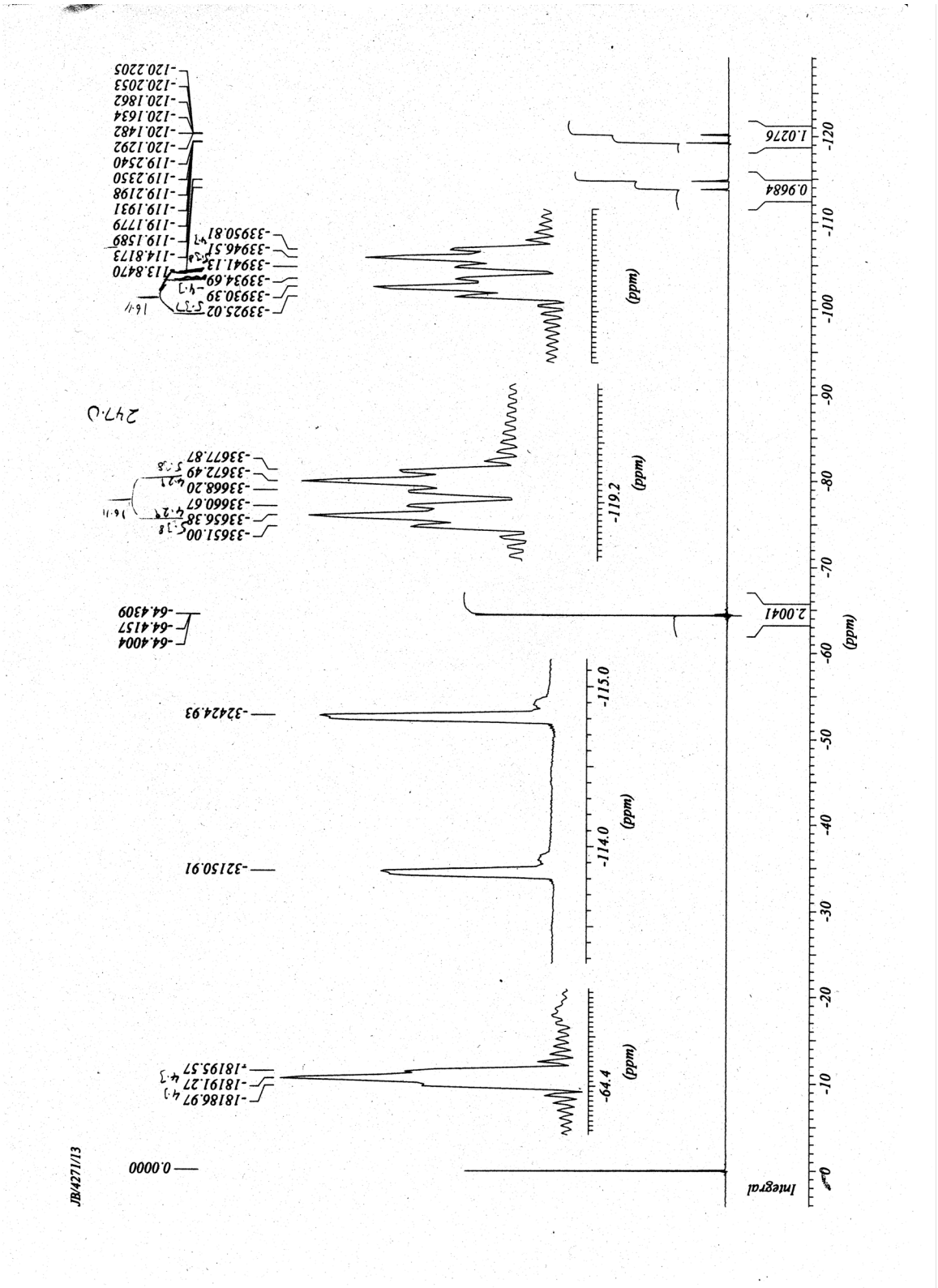


(2*S*)-[(2*R*)-4-bromo-1-(2-naphthylmethyl)-3,3,4,4-tetrafluorobut-2-yl]-2-(6-methoxy-2-naphthyl) propanoate (21)

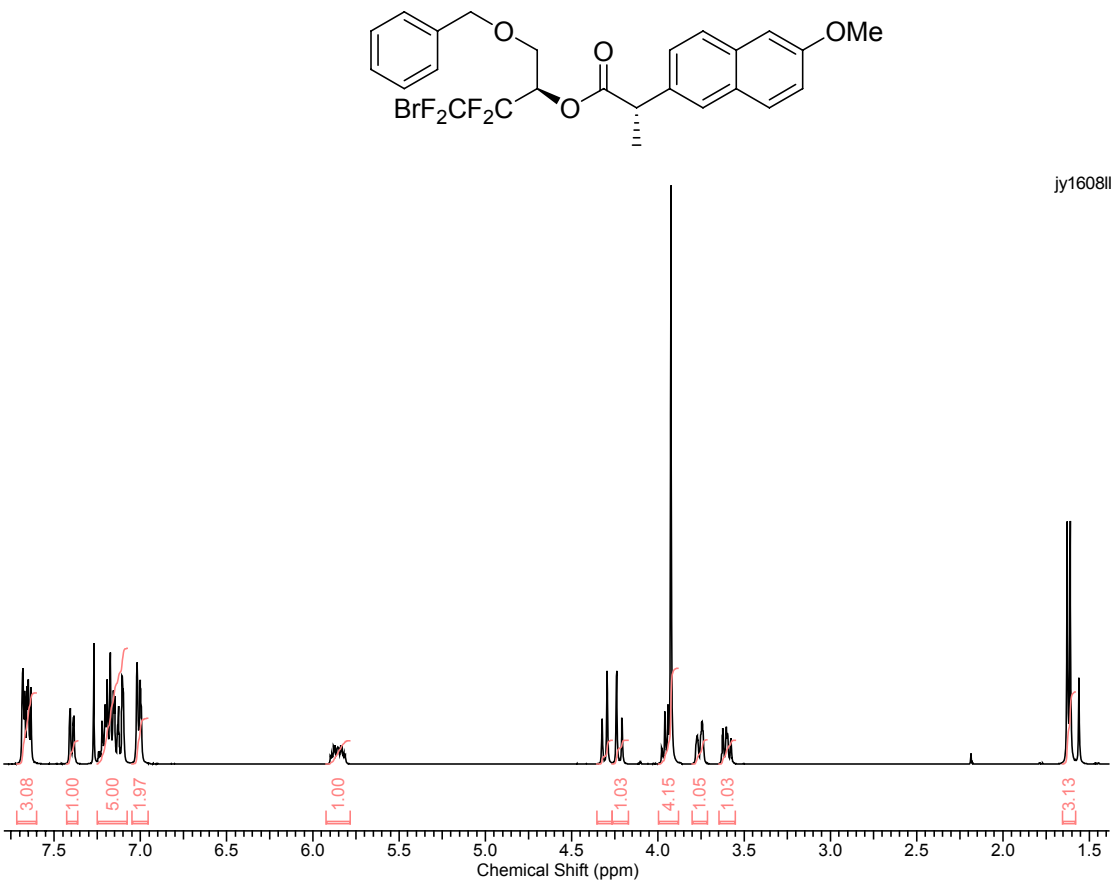


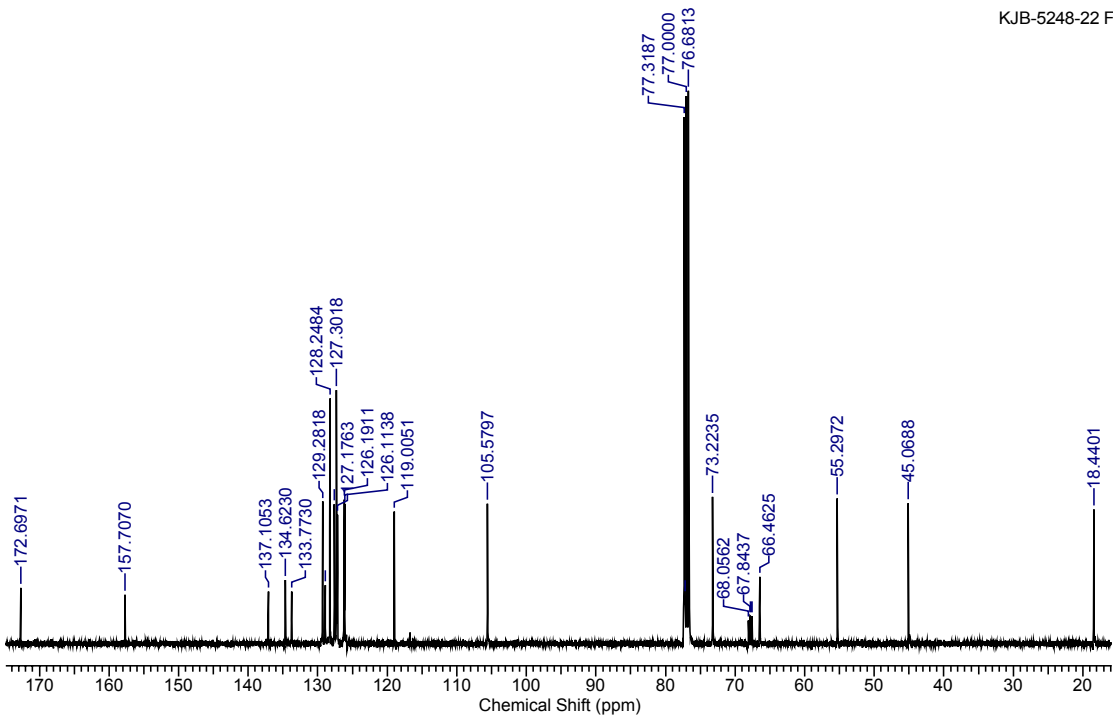


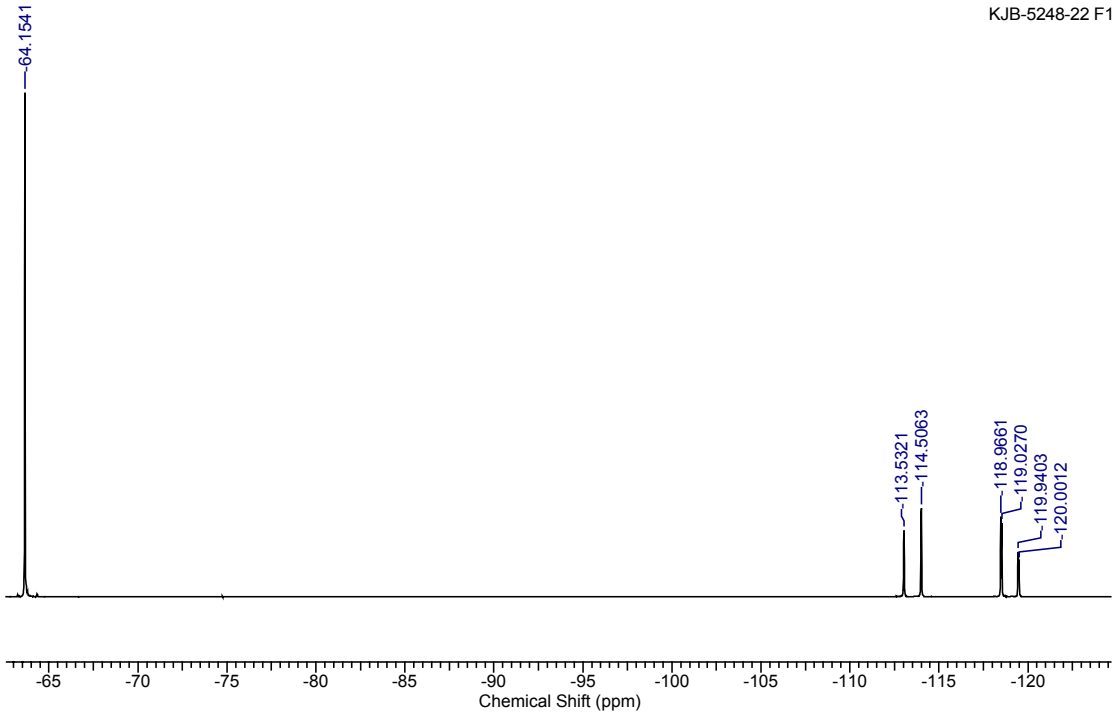




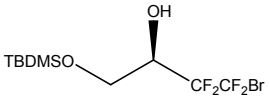
(2*S*)-[(2*R*)-4-bromo-1-(2-benzyl)-3,3,4,4-tetrafluorobut-2-yl]-2-(6-methoxy-2-naphthyl) propanoate (22)

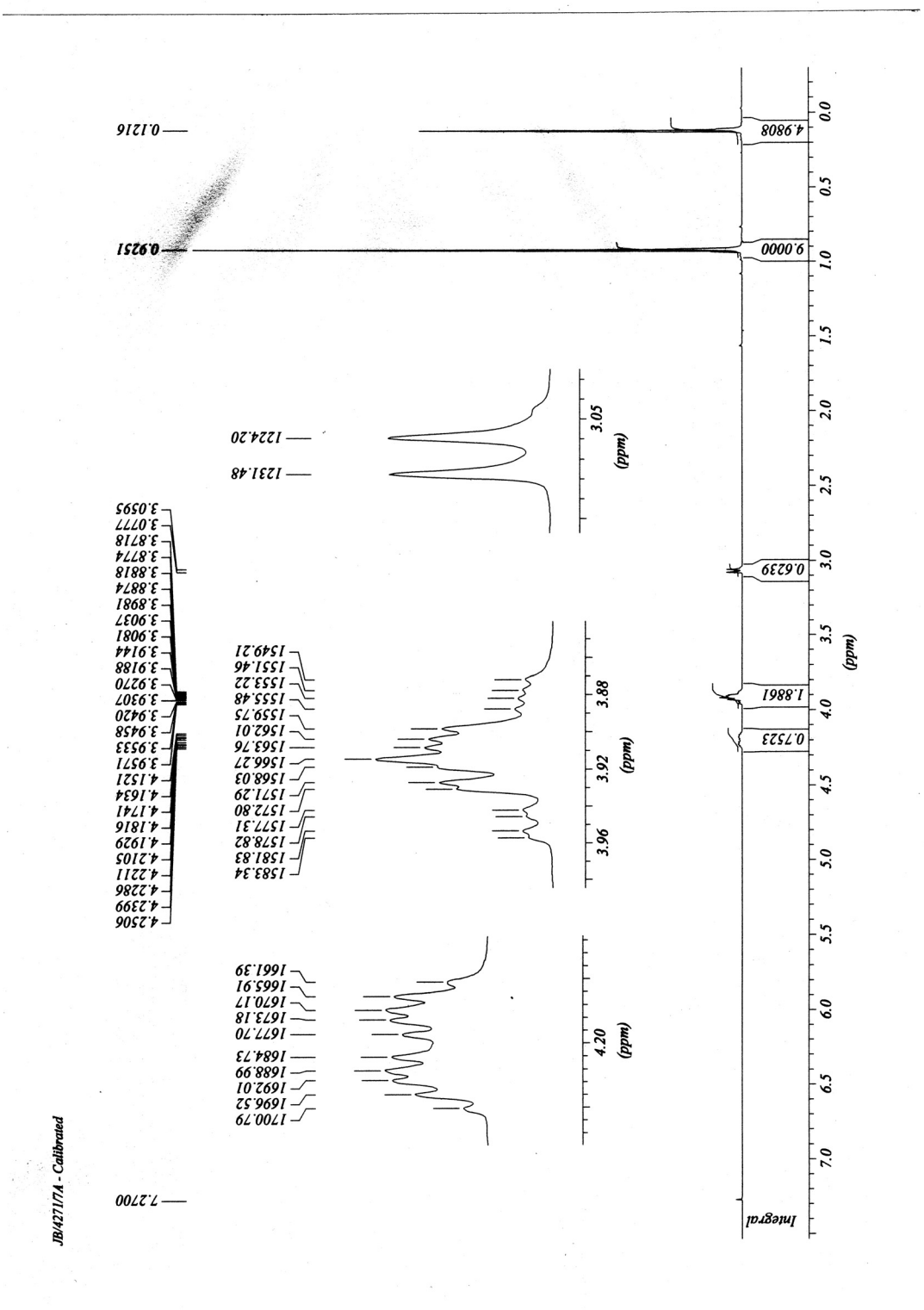


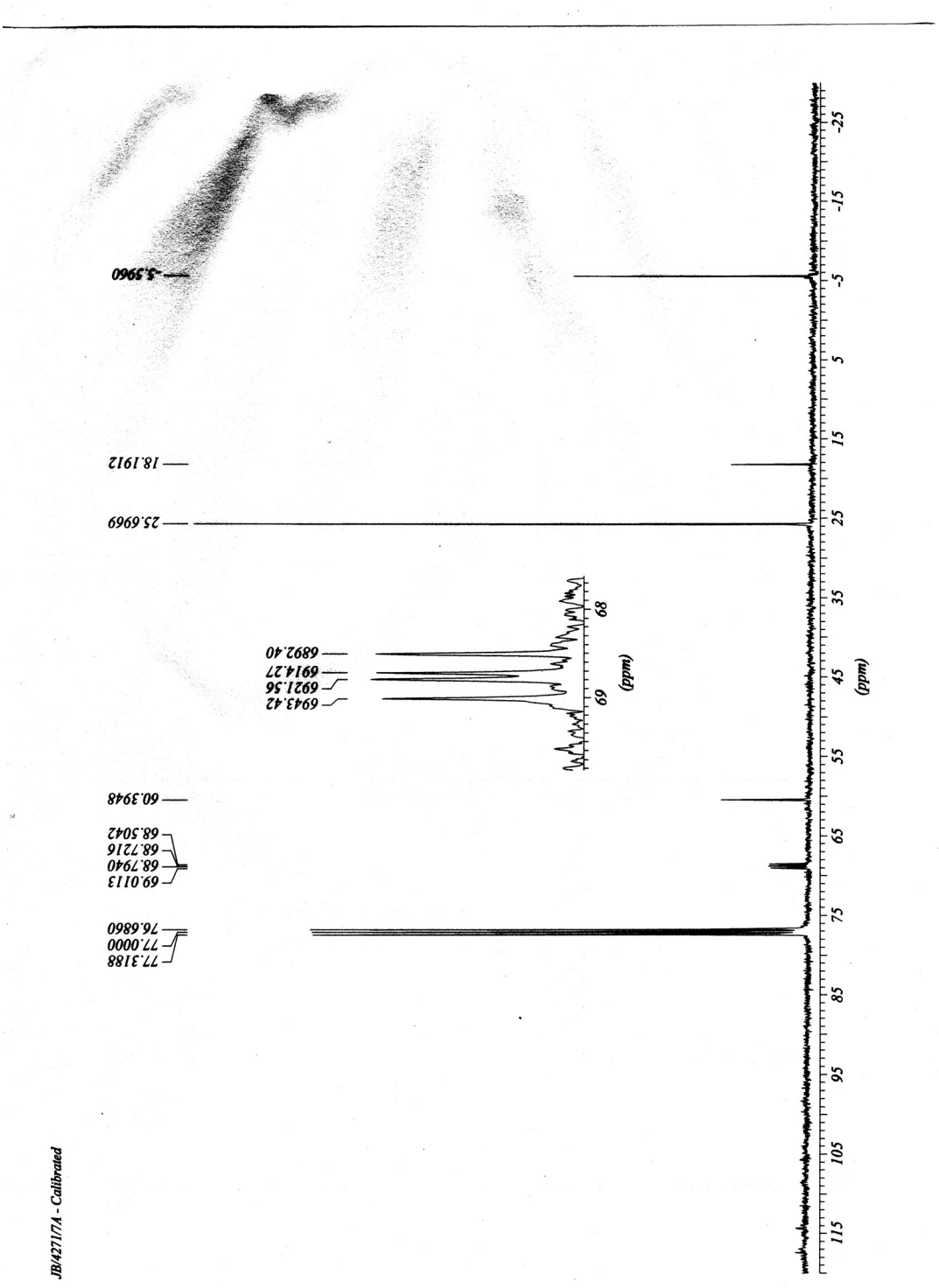


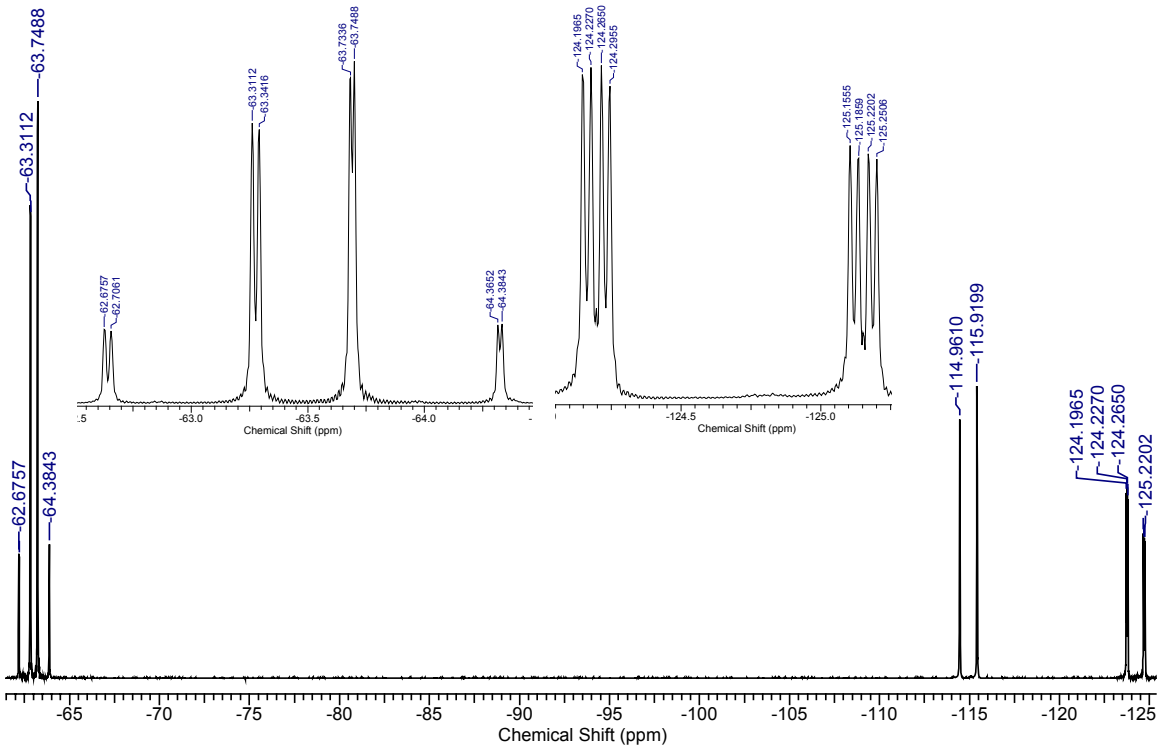


(2*R*)-1-*tert*-Butyldimethylsilyloxy-4-brmo-3,3,4,4-tetrafluorobutan-2-ol (24)

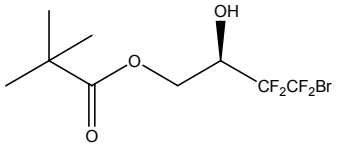


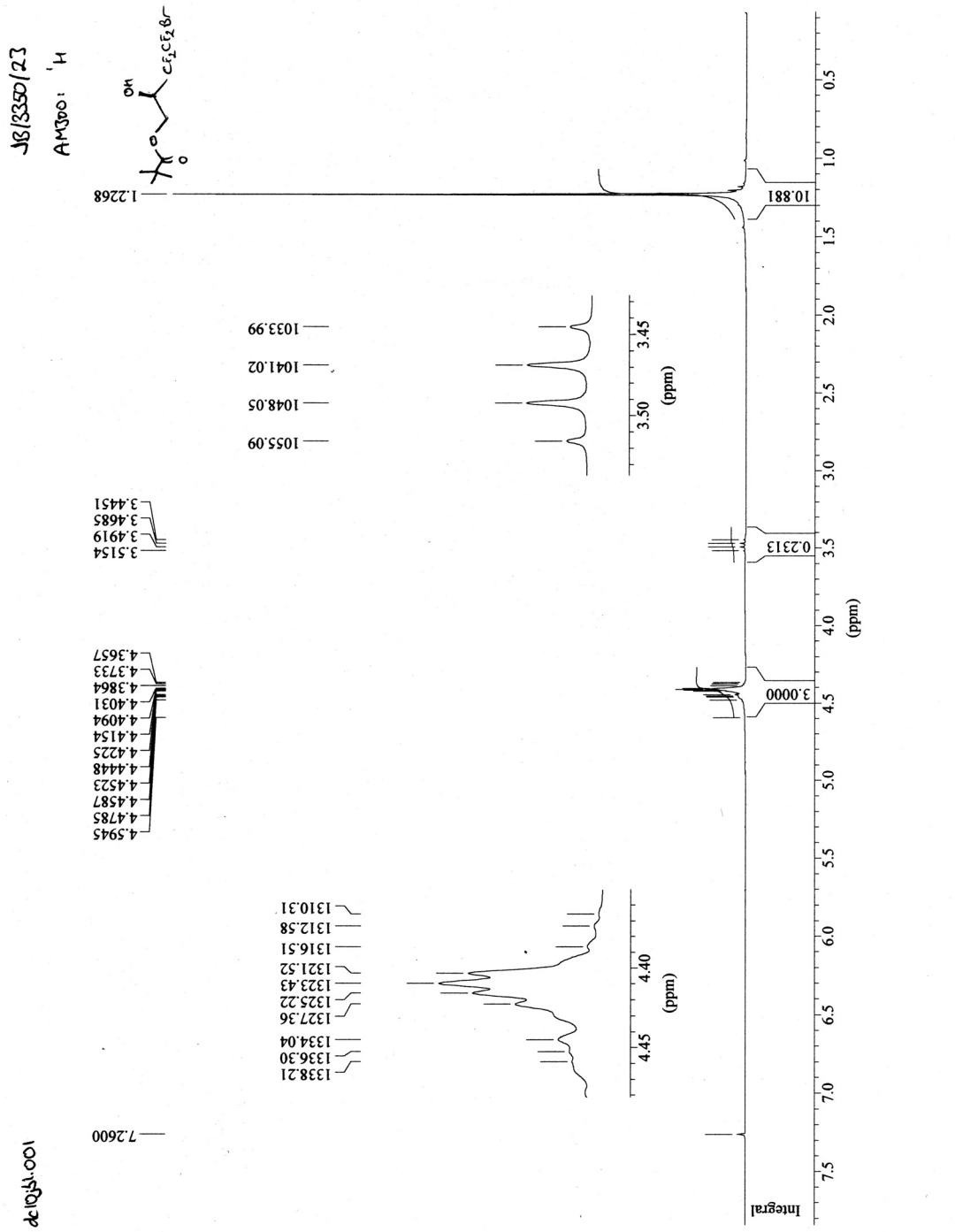


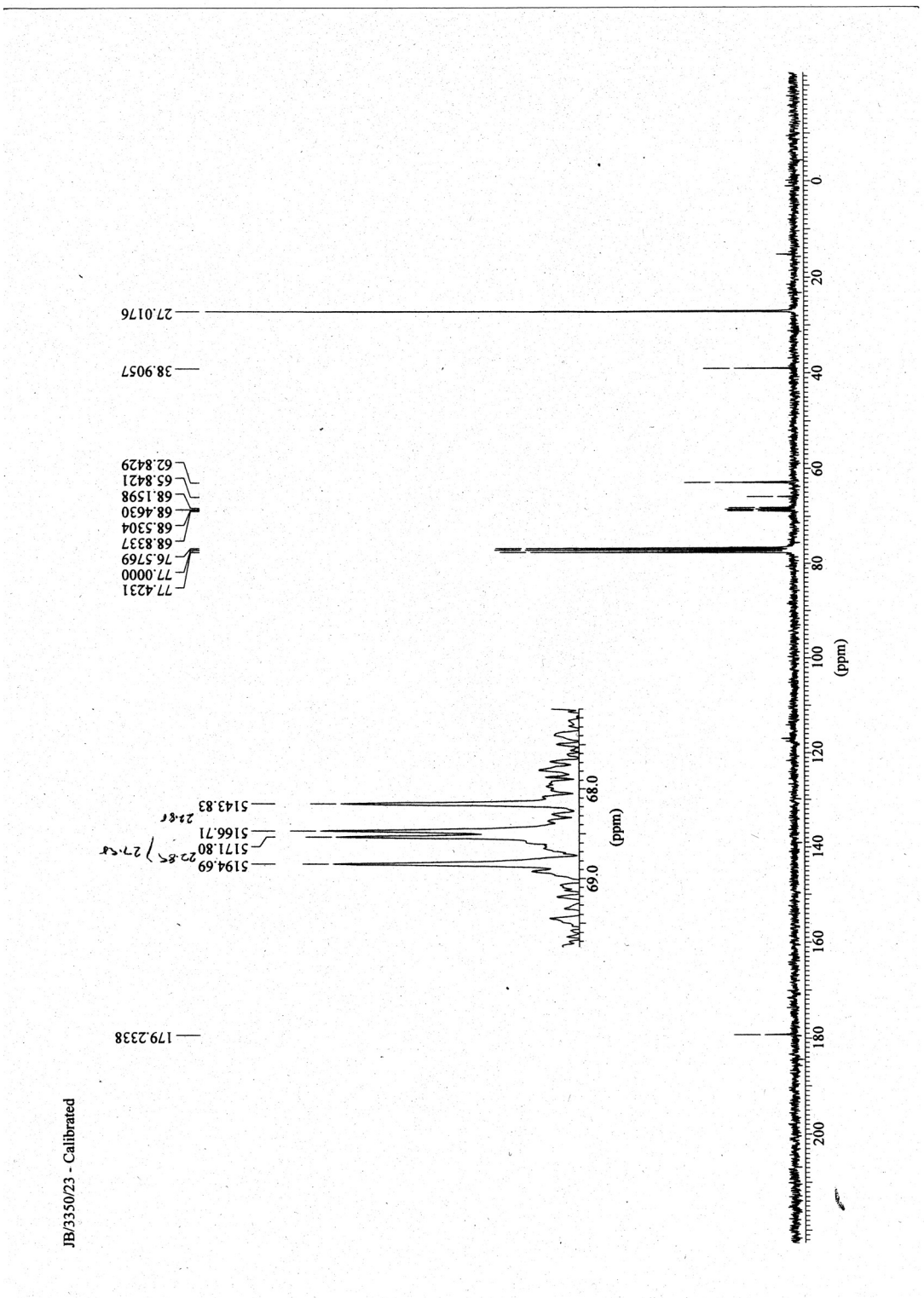

5.5960
18.1912
25.6969
6892.40
6914.27
6921.56
6943.42
60.3948
68.5042
68.7216
68.7940
69.0113
76.6860
77.0000
77.3188
JB/4271/7A - Calibrated
(ppm)
(ppm)

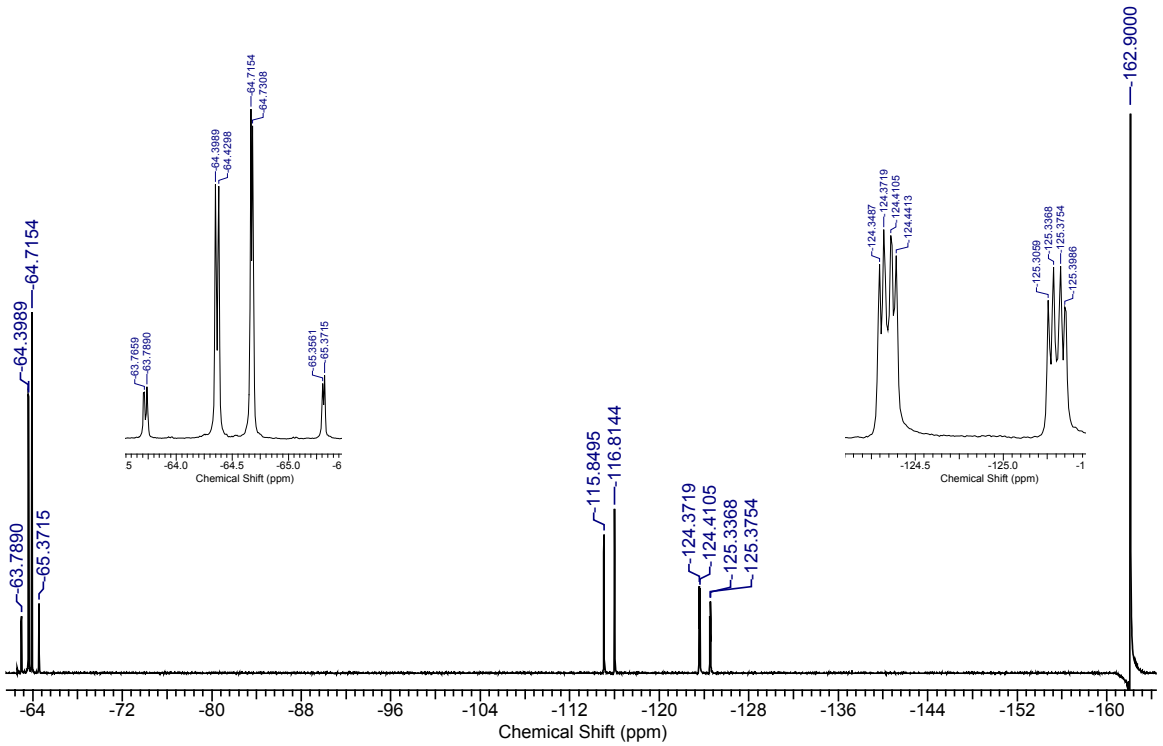

63.7488
63.3112
62.6757
64.3843
114.9610
115.9199
124.1965
124.2270
124.2650
125.2202
Chemical Shift (ppm)

(2R)-(4-bromo-2-hydroxy-3,3,4,4-tetrafluorobut-1-yl)-2,2-dimethyl propanoate (25)

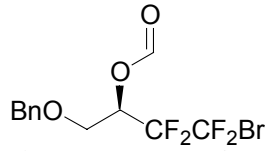


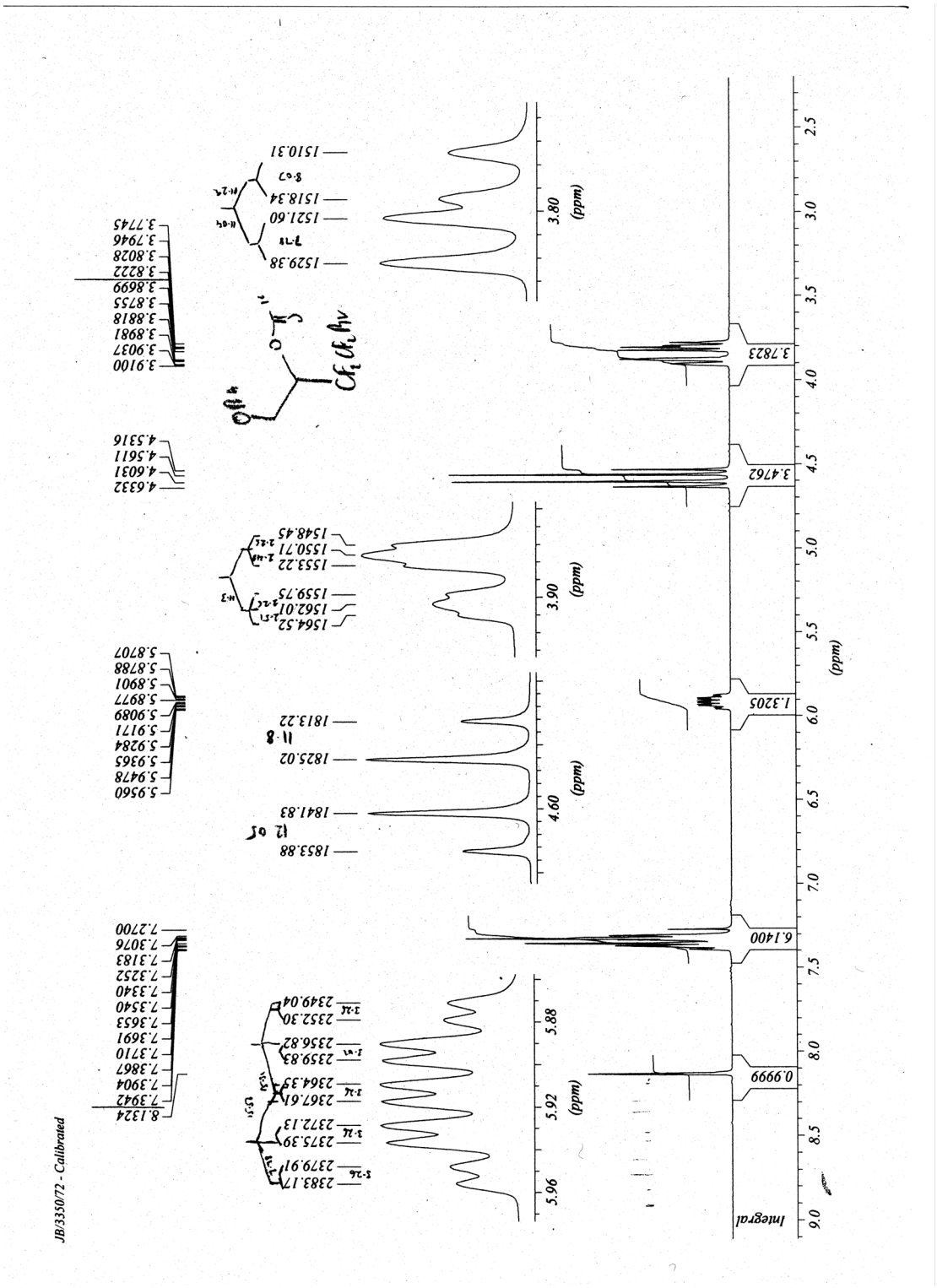


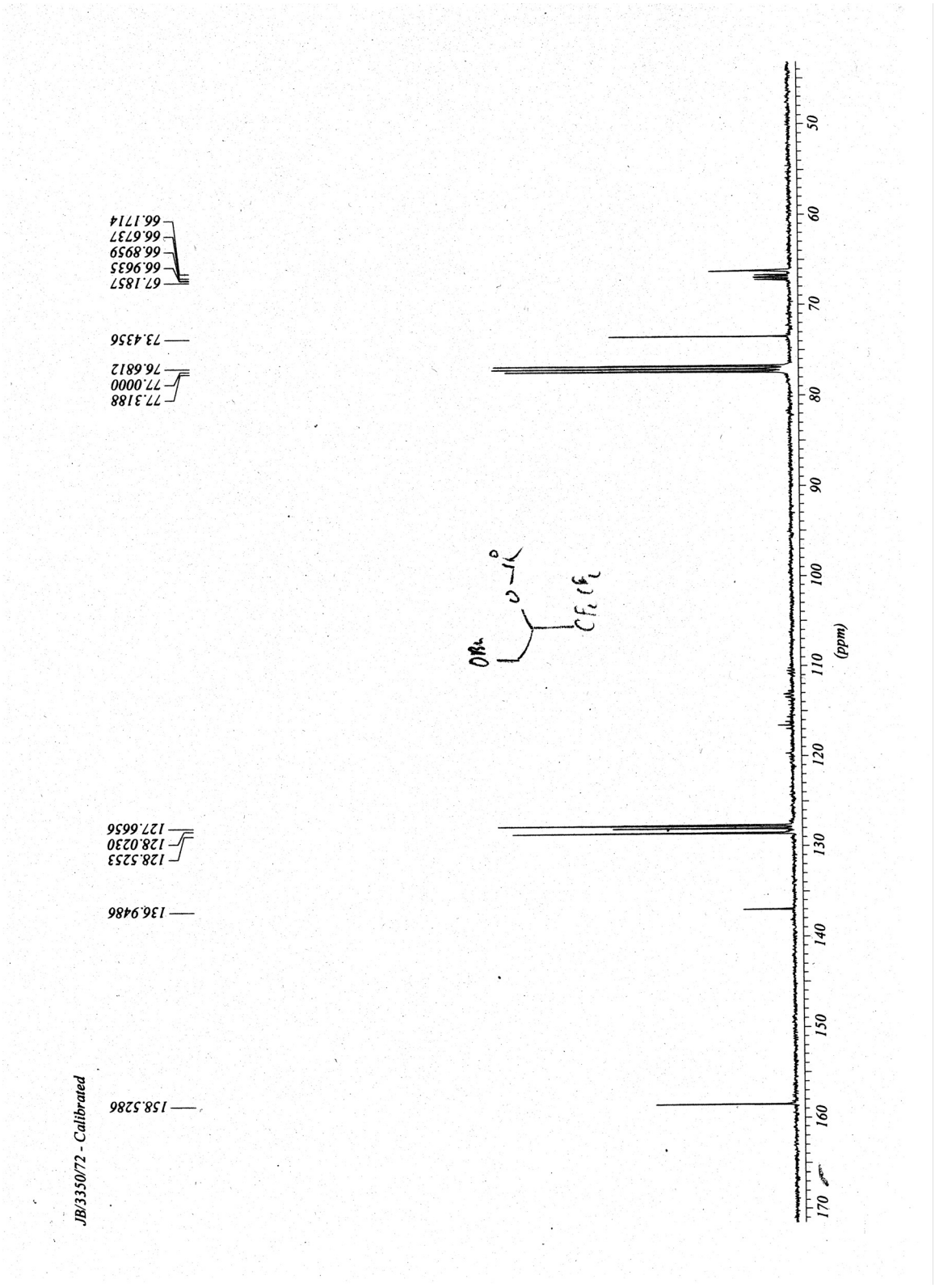

JB/3350/23 - Calibrated
179.2338
27.0176
38.9057
77.4231
77.0000
76.5769
68.8337
68.5304
68.4630
68.1598
65.8421
62.8429
51943.69
51711.80
51663.71
51438.83
(ppm)
(ppm)

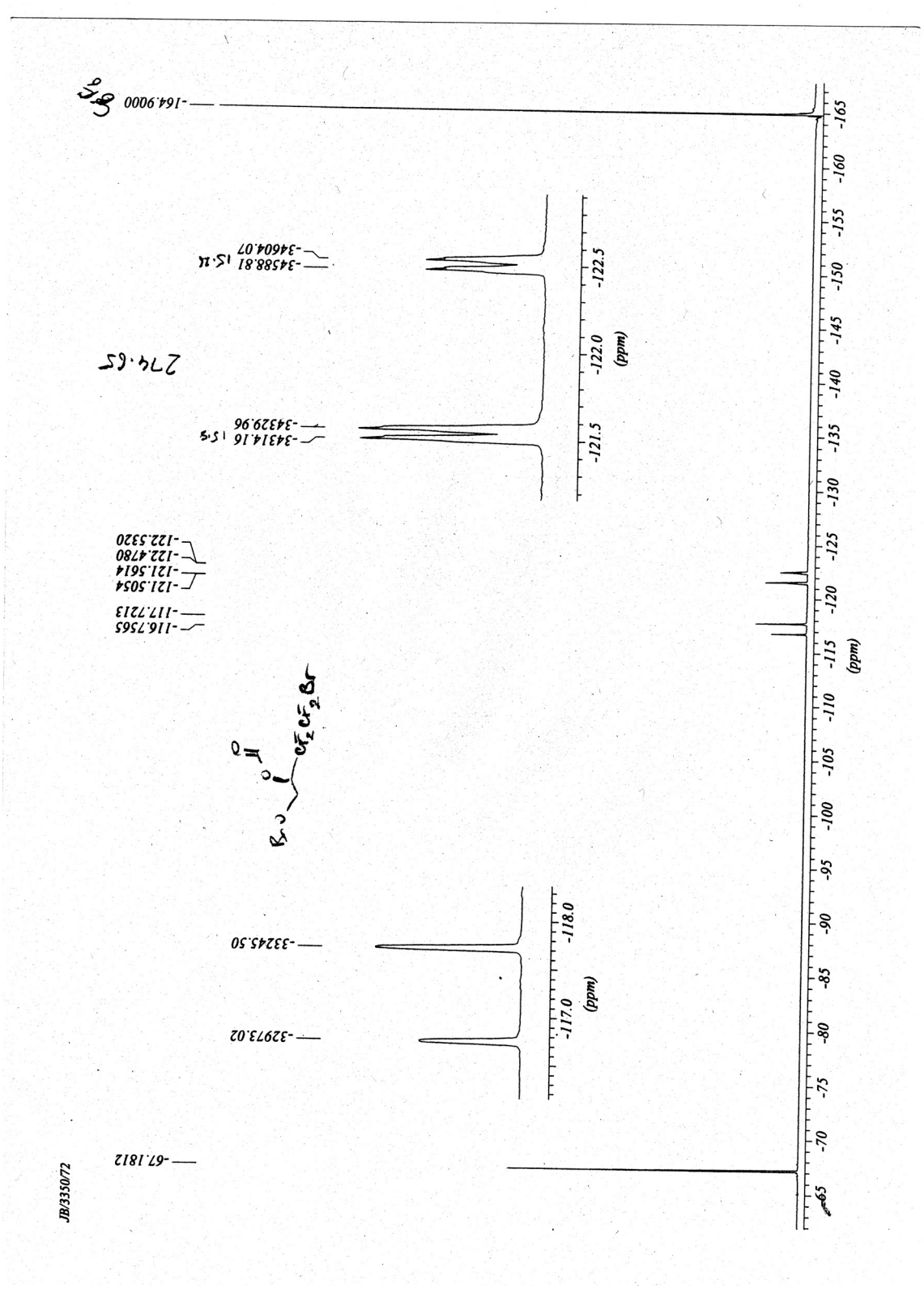

-63.7890
-64.3989
-64.7154
-65.3715
-115.8495
-116.8144
-124.3719
-124.4105
-125.3368
-125.3754
-162.9000
Chemical Shift (ppm)

(2*R*)-(1-benzyloxy-4-bromo-3,3,4,4-tetrafluoro)but-2-yl formate (27)

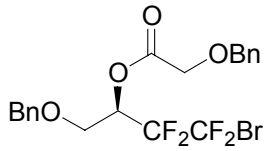


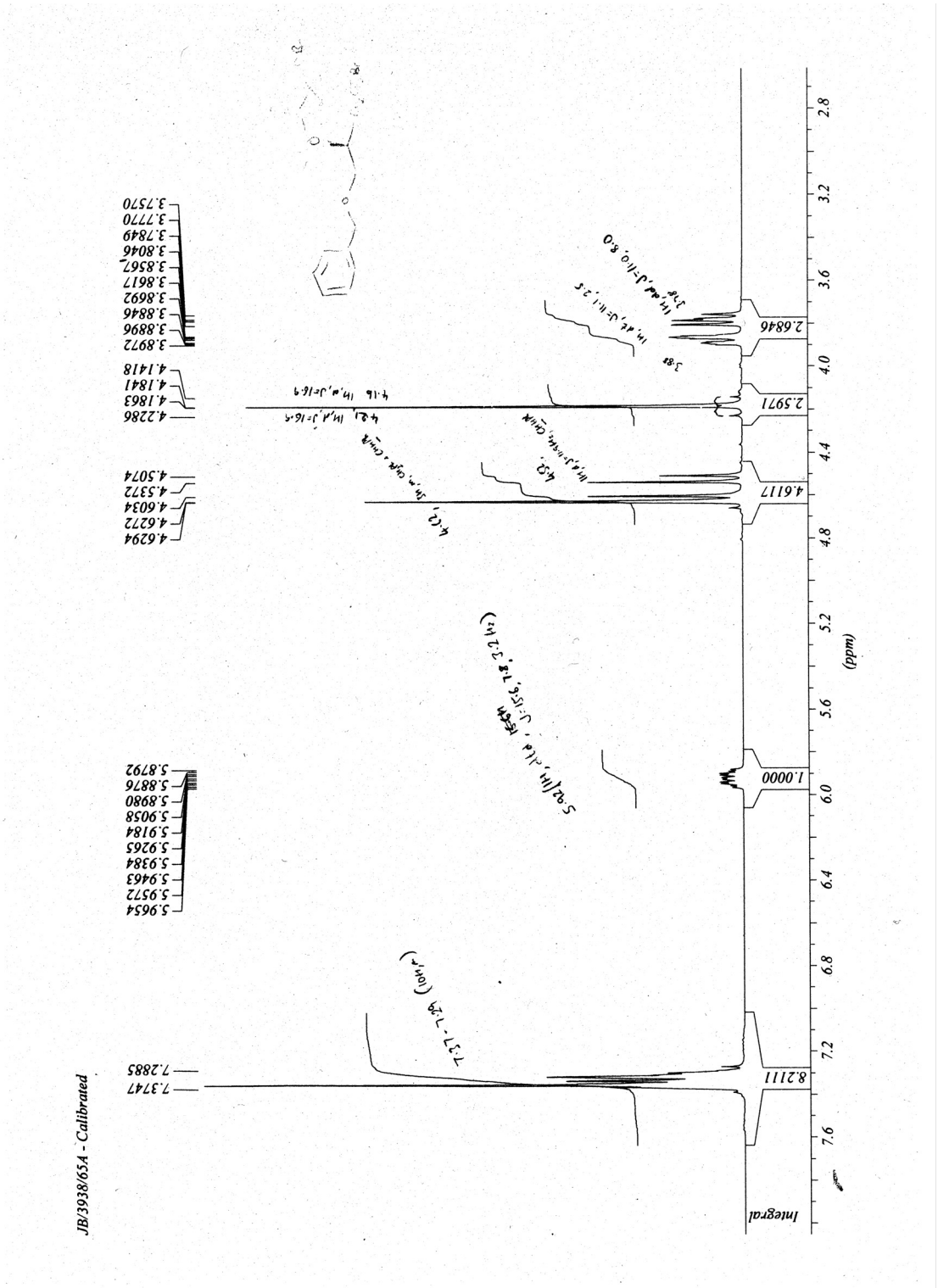


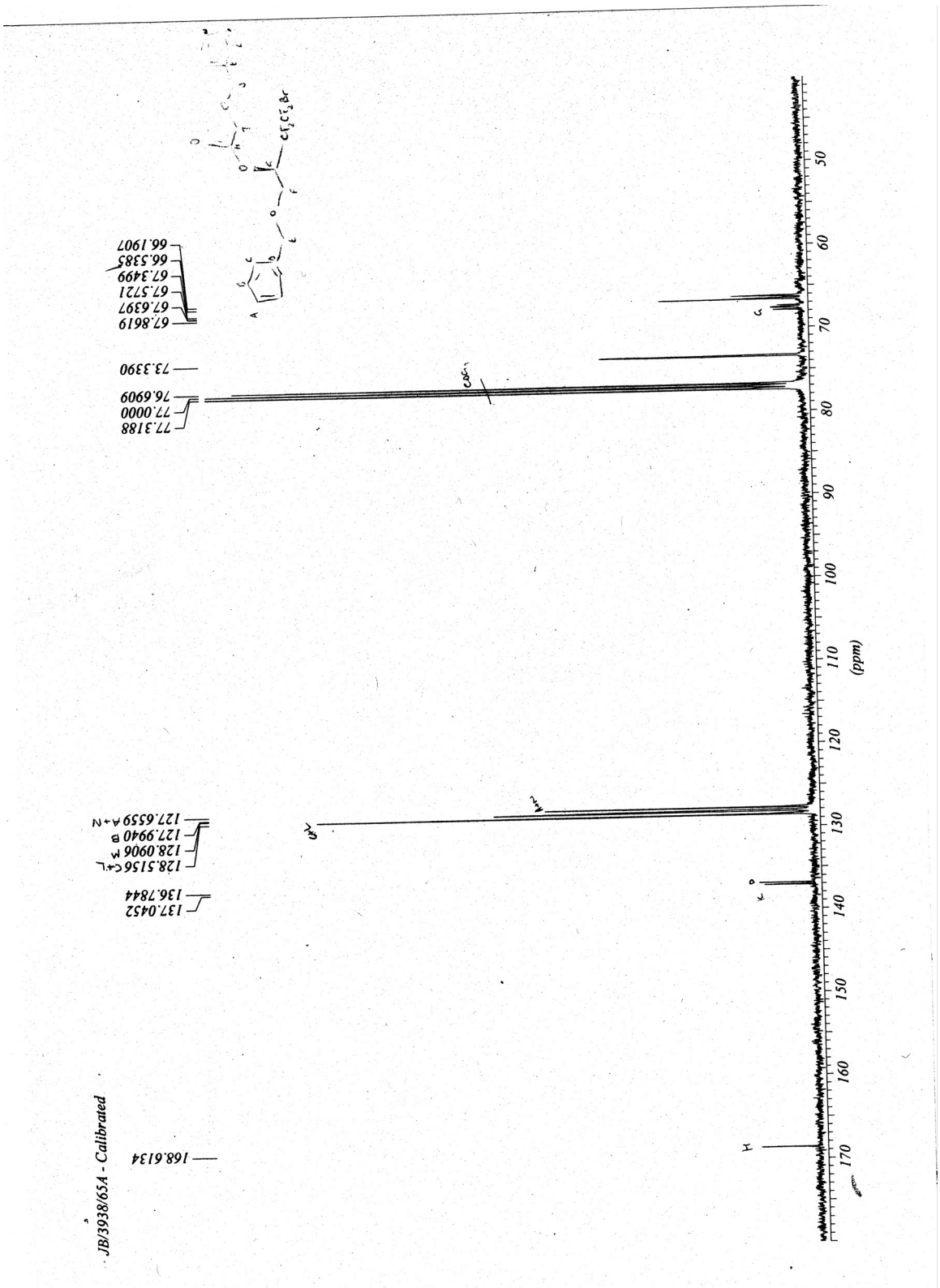

JB/3350/72 - Calibrated
158.5286
136.9486
128.5253
128.0230
127.6656
77.3188
77.0000
76.6812
73.4356
67.1857
66.9635
66.8959
66.6737
66.1714
(ppm)

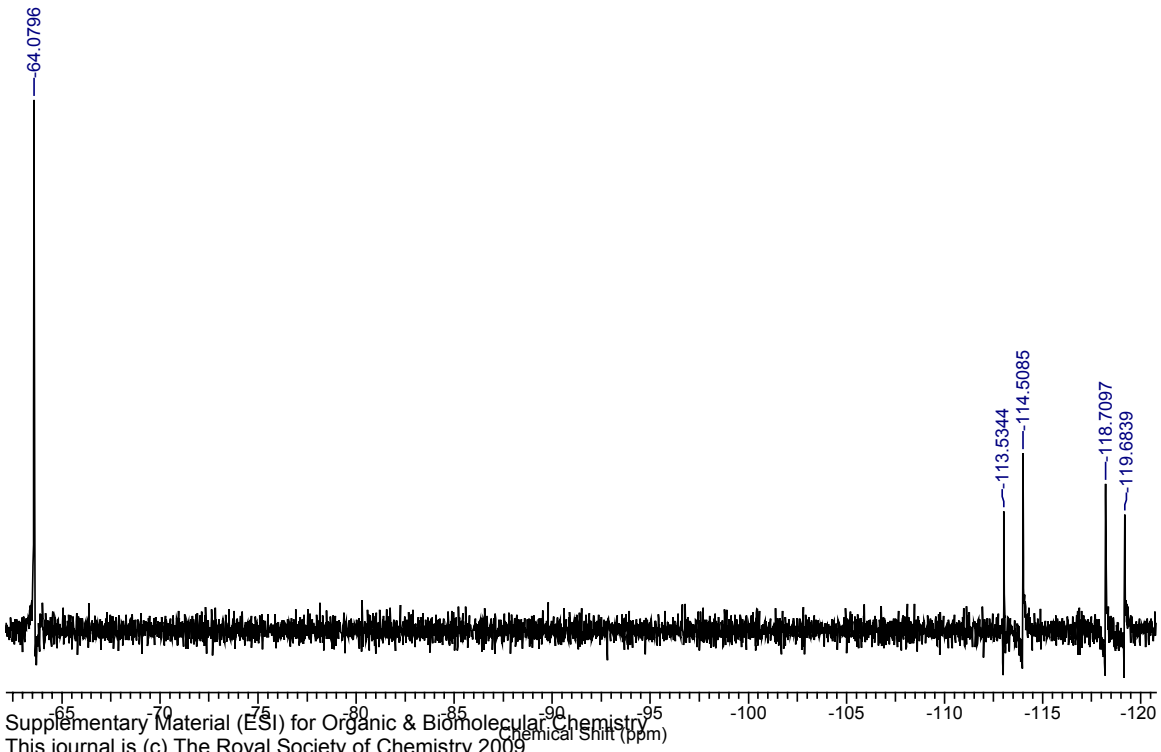

JB/335072
-67.1812
-164.9000
-332.45.50
-329.73.02
-118.0
-117.0
(ppm)
-116.7565
-117.7213
-121.5054
-121.5614
-122.4780
-122.5320
-343.14.16
-343.29.96
-345.88.81
-346.04.07
-121.5
-122.0
-122.5
(ppm)
(ppm)

(2*R*)-(1-benzyloxy-4-bromo-3,3,4,4-tetrafluoro)but-2-yl benzyloxyethanoate (32)

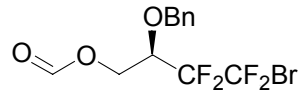


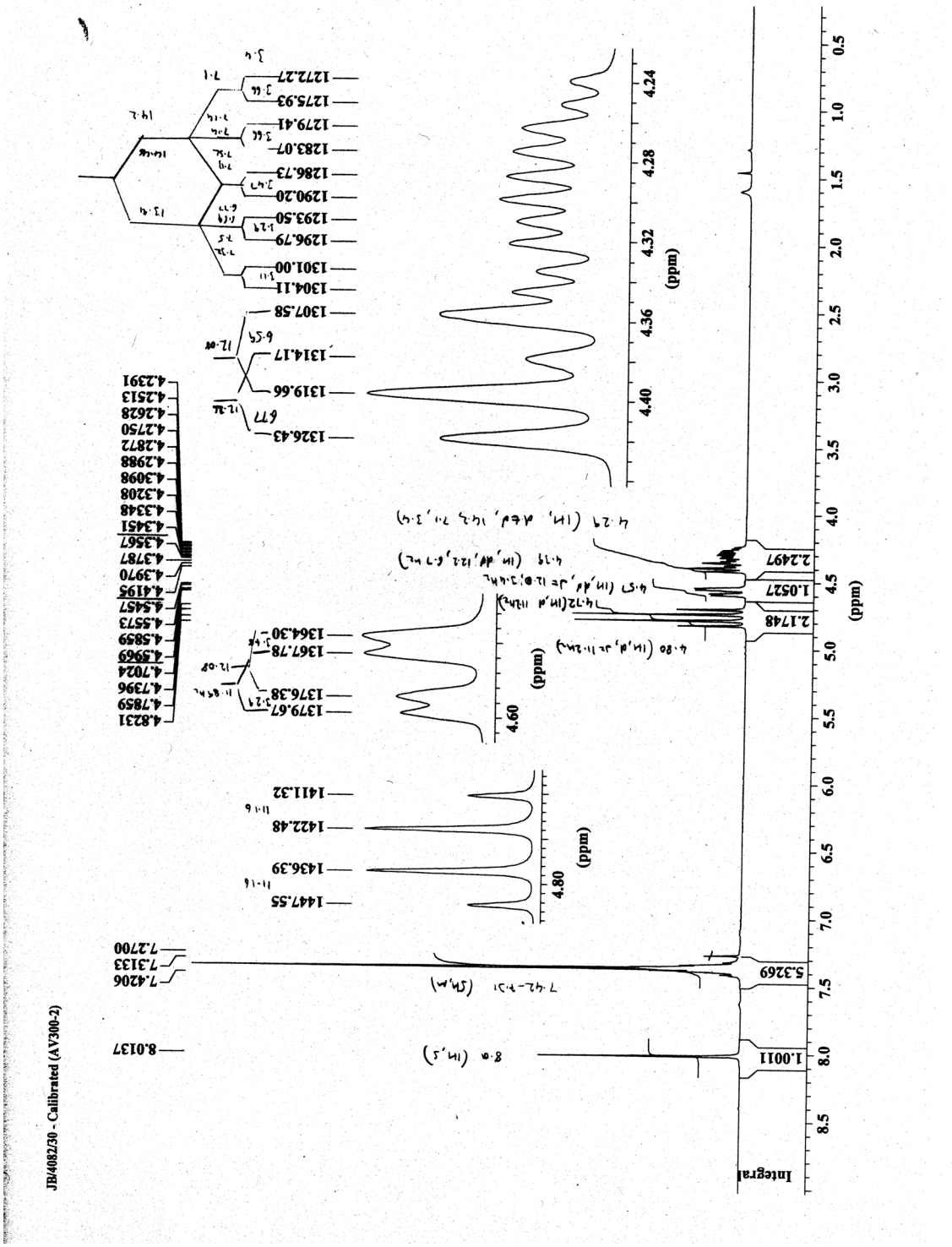


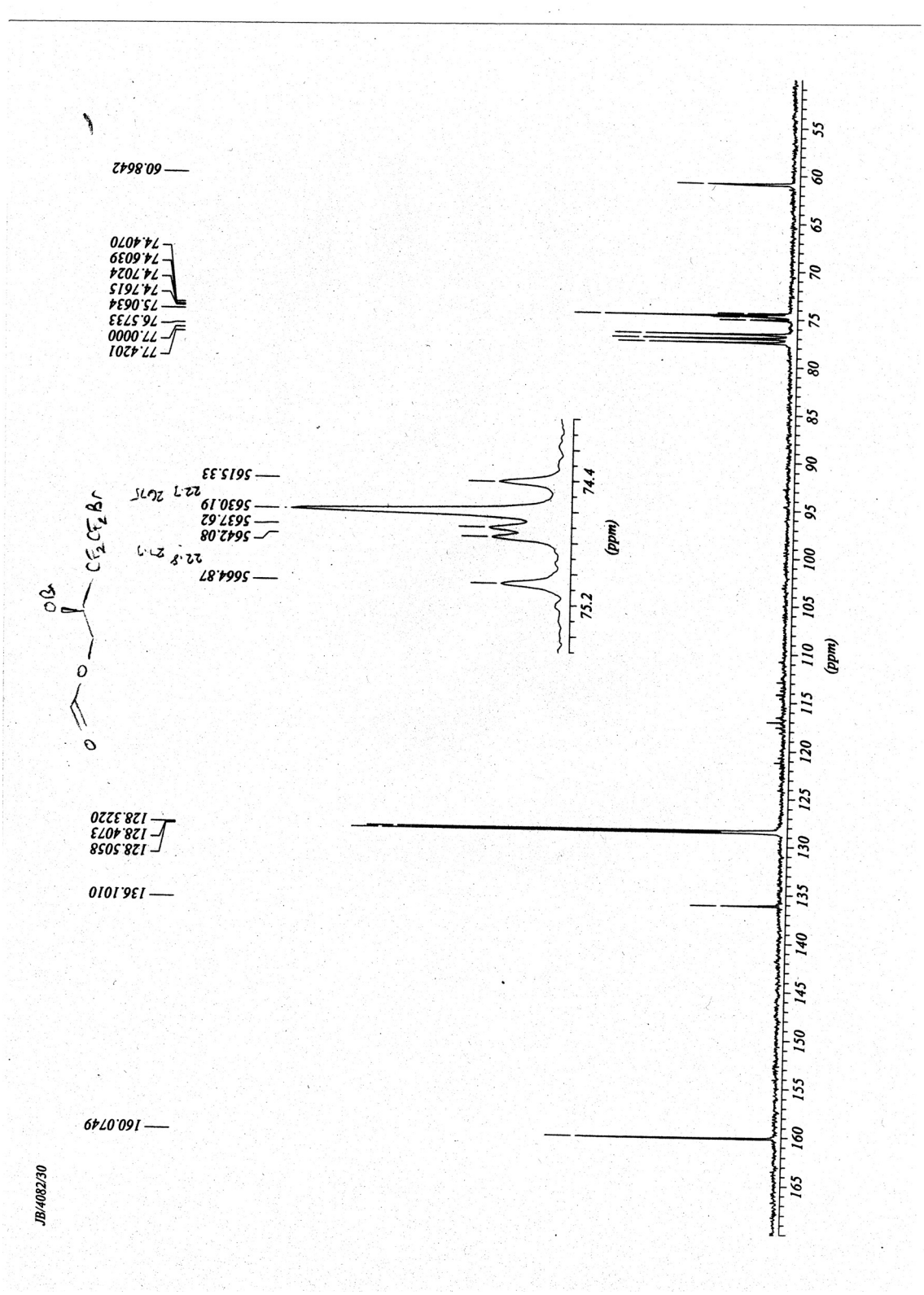

JB/3938/65A - Calibrated
168.6134
137.0452
136.7844
128.5156
128.0906
127.9940
127.6559
77.3188
77.0000
76.6909
73.3390
67.8619
67.6397
67.5721
67.3499
66.5385
66.1907
(ppm)

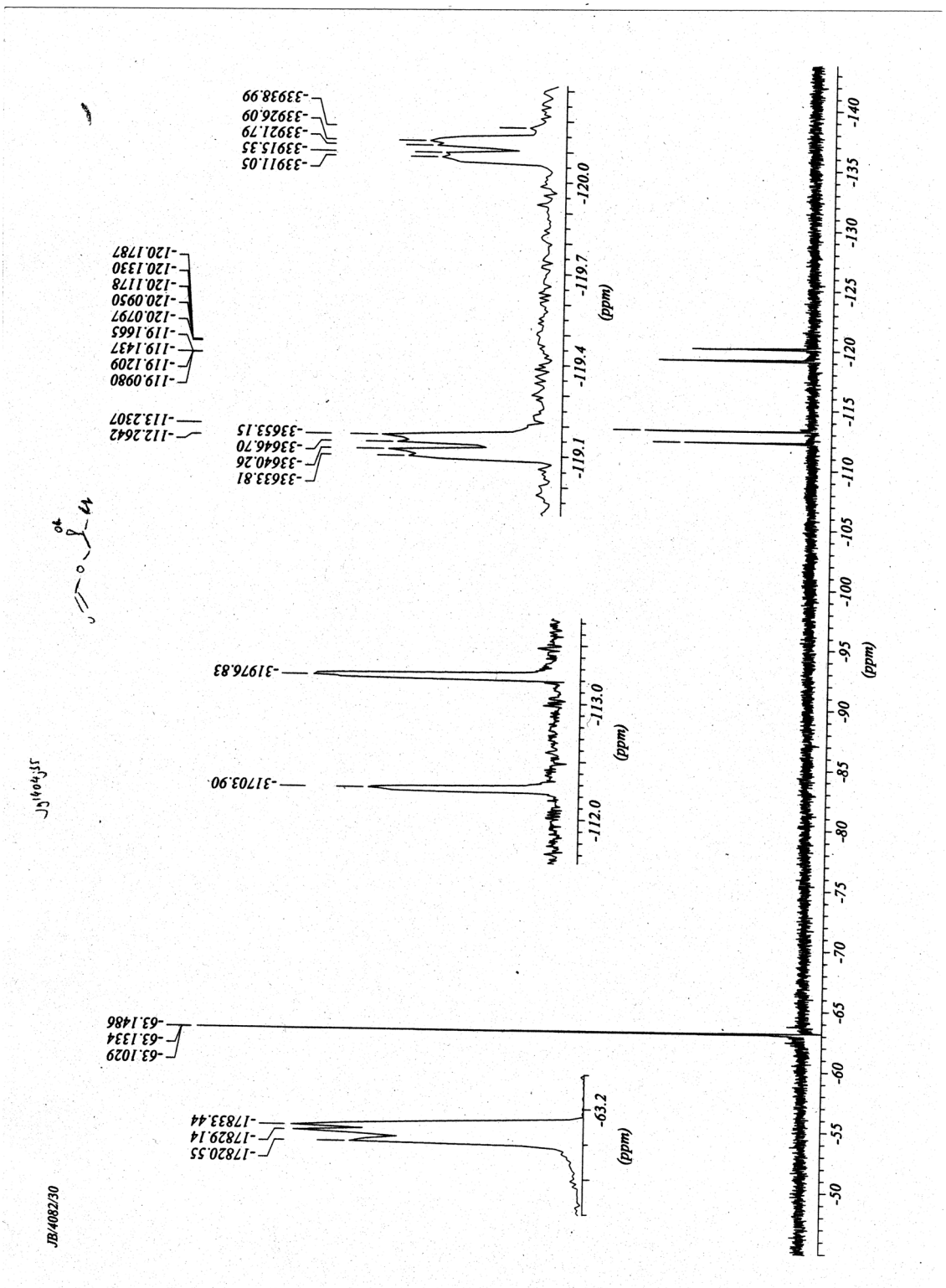


(2*R*)-(2-benzyloxy-4-bromo-3,3,4,4-tetrafluoro)but-1-yl formate (33)

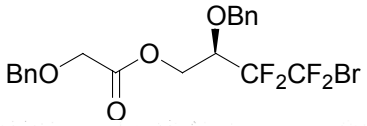


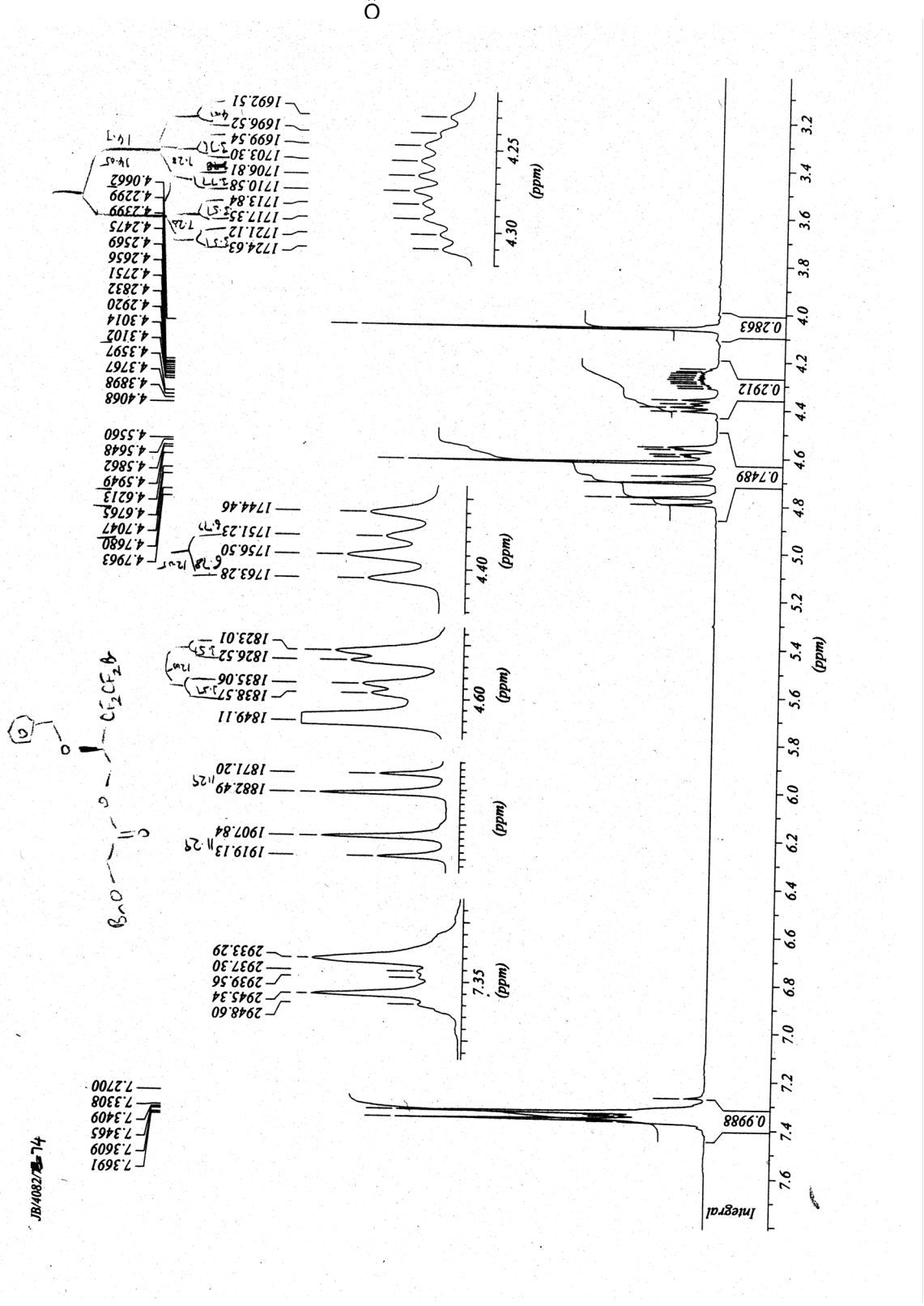


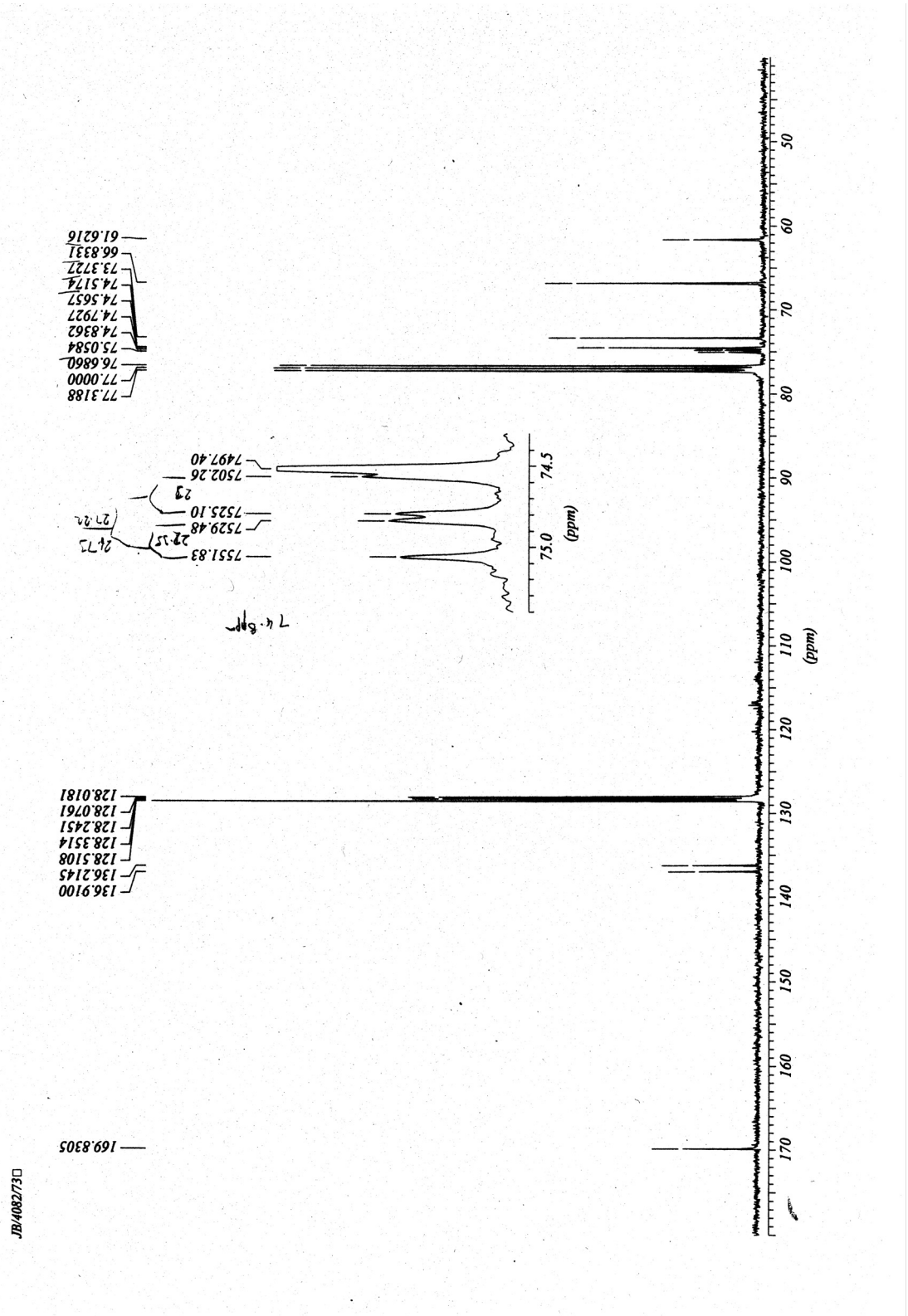

JB/4082/30
160.0749
136.1010
128.5058
128.4073
128.3220
77.4201
77.0000
76.5733
75.0634
74.7615
74.7024
74.6039
74.4070
60.8642
5664.87
5642.08
5637.62
5630.19
5615.33
74.4
75.2
(ppm)
(ppm)

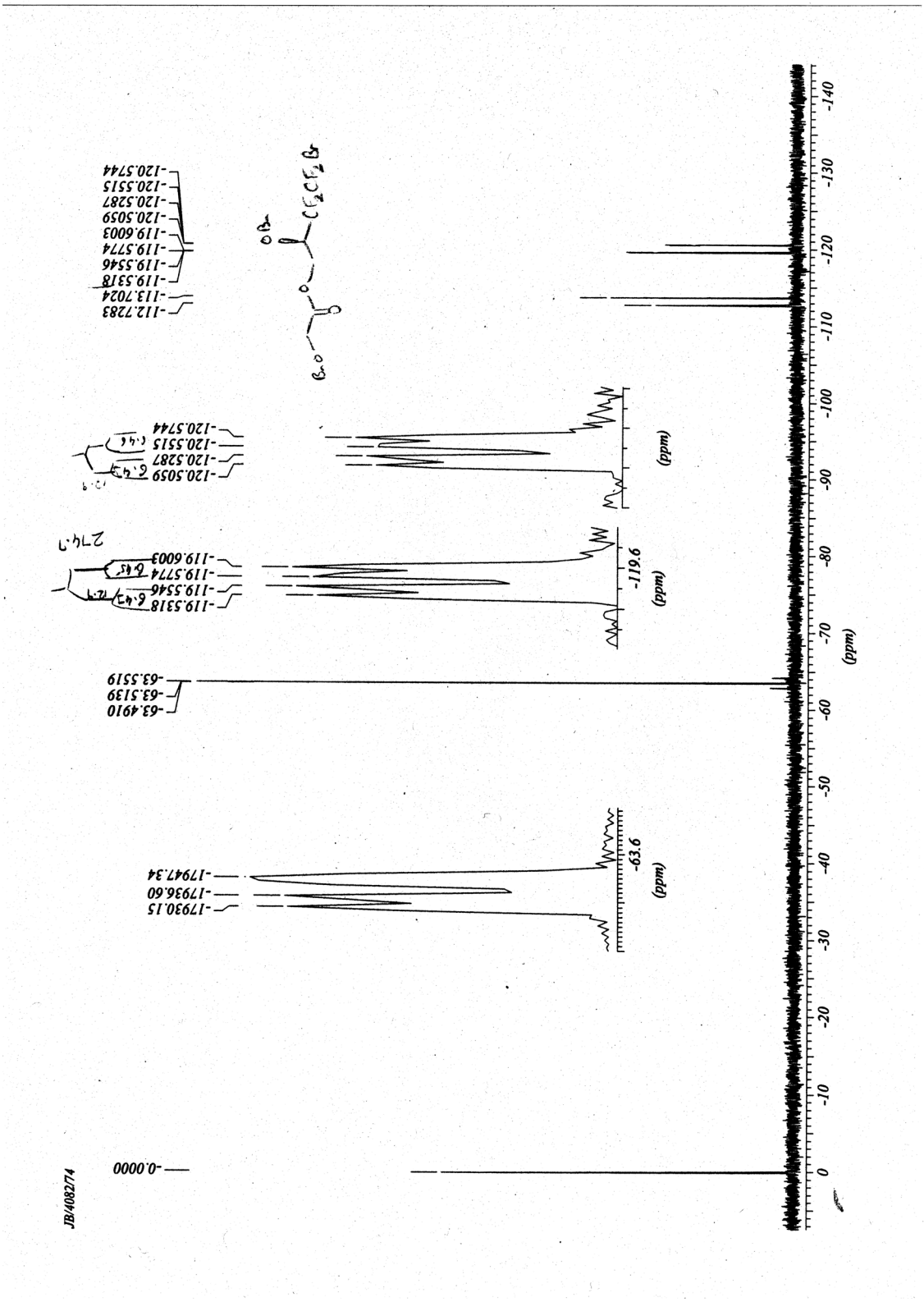

JB/4082/30
-63.1486
-63.1334
-63.1029
-17833.44
-17829.14
-17820.55
-63.2
(ppm)
-31703.90
-31976.83
-113.0
-112.0
(ppm)
-33938.99
-33926.09
-33921.79
-33915.35
-33911.05
-33633.81
-33640.26
-33646.70
-33653.15
-119.1
-119.4
-119.7
-120.0
(ppm)
-112.2642
-113.2307
-119.0980
-119.1209
-119.1437
-119.1665
-120.0797
-120.0950
-120.1178
-120.1330
-120.1787
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
(ppm)

(2*R*)-(2-benzyloxy-4-bromo-3,3,4,4-tetrafluoro)but-1-yl benzyloxyethanoate 34

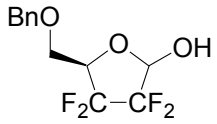


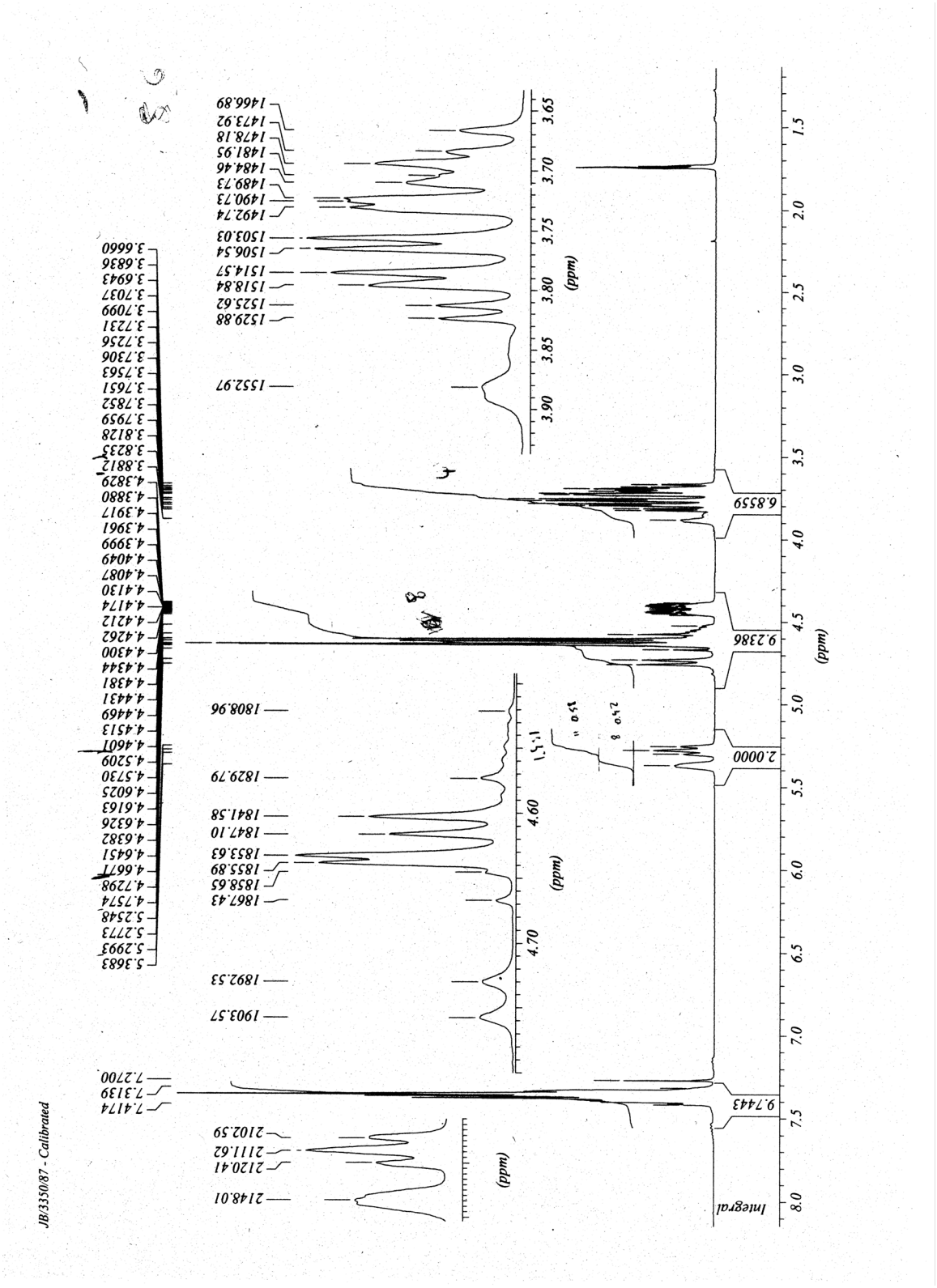


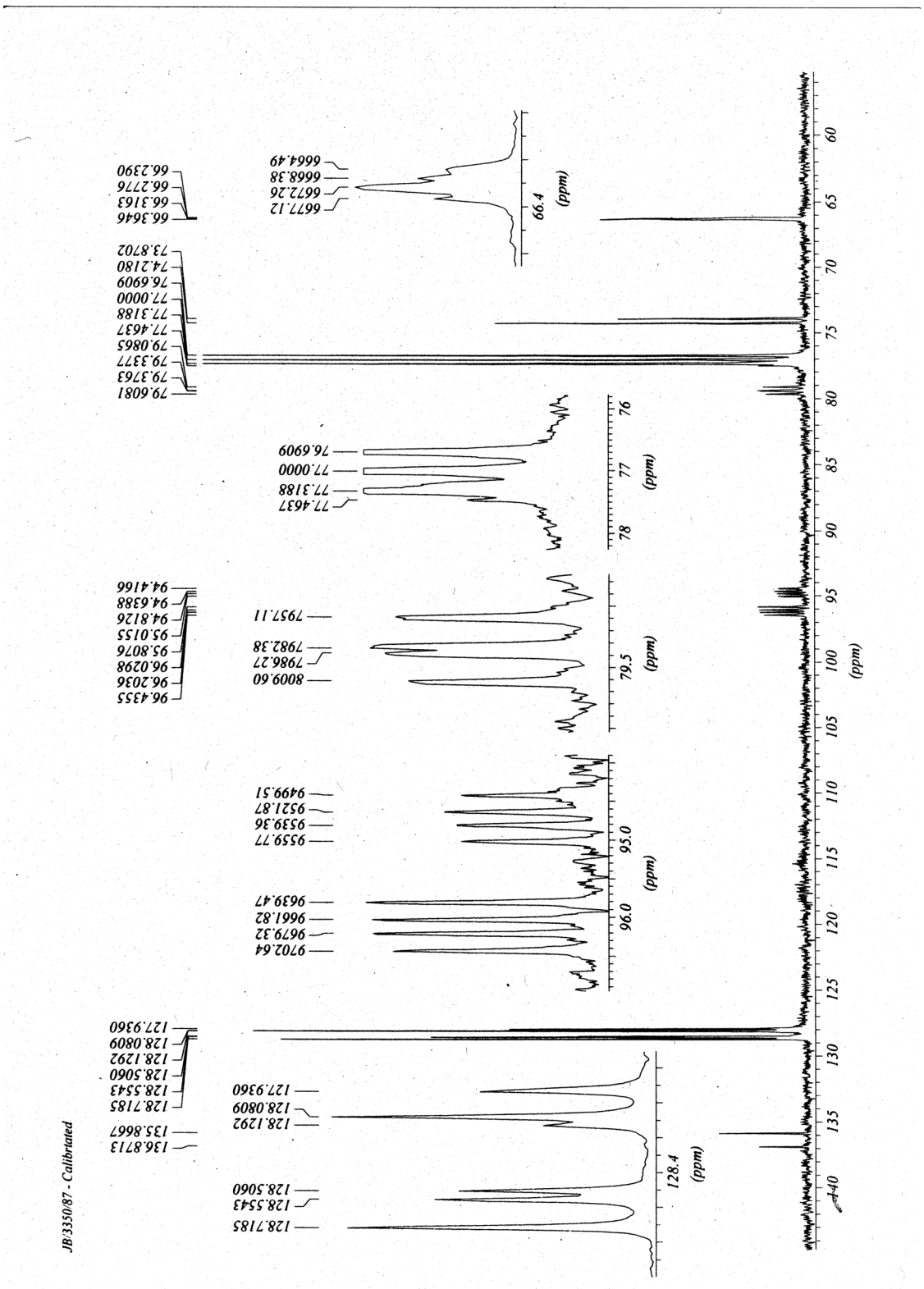

169.8305
136.9100
136.2145
128.5108
128.3514
128.2451
128.0761
128.0181
77.3188
77.0000
76.6860
75.0584
74.8362
74.7927
74.5657
74.5174
73.3727
66.8331
61.6216
7551.83
7529.48
7525.10
7502.26
7497.40
(ppm)
JB/4082/73

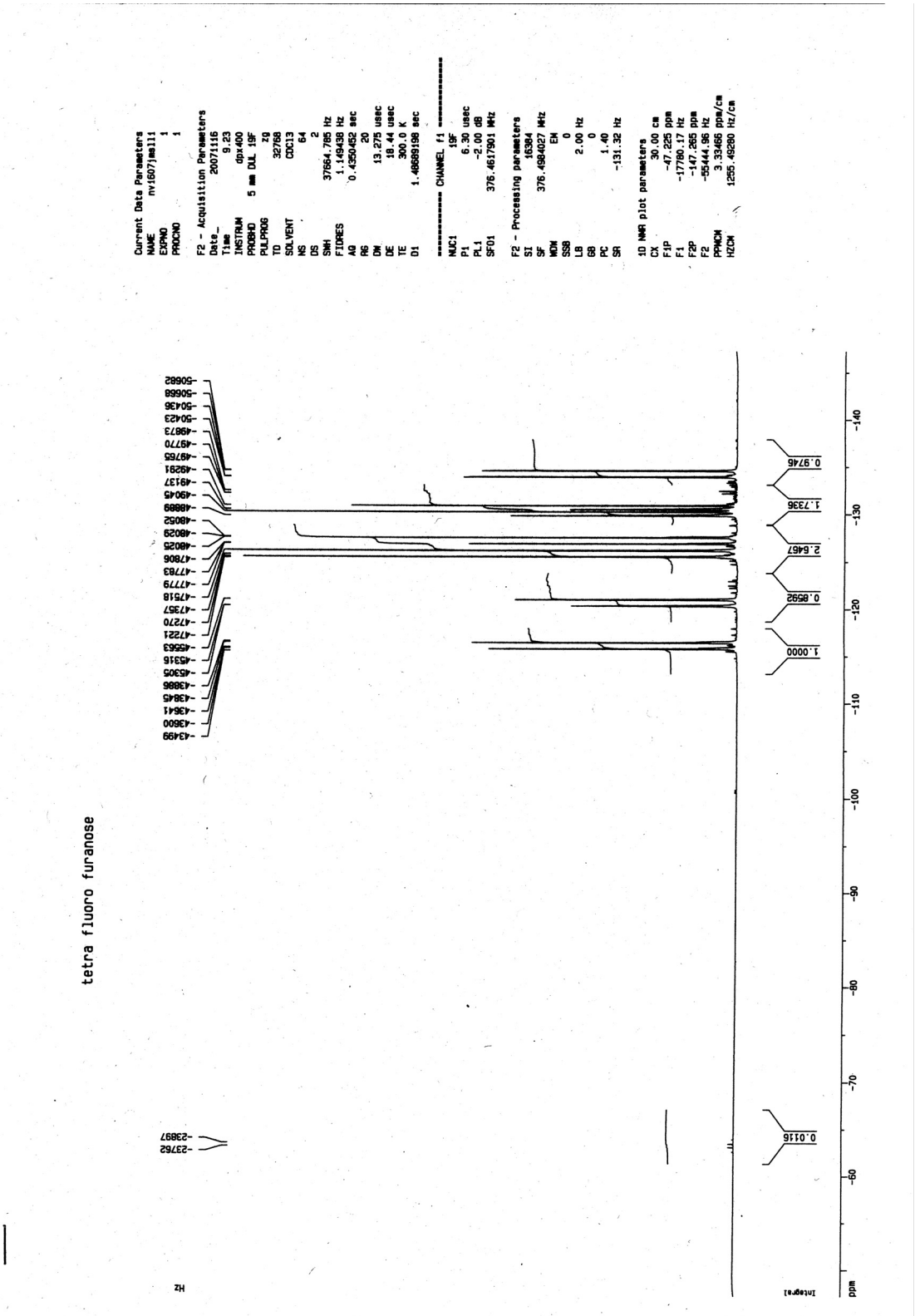


(5*R*)-5-Benzyloxymethyl-3,3,4,4-tetrafluoro-tetrahydrofuran-2-ol 2

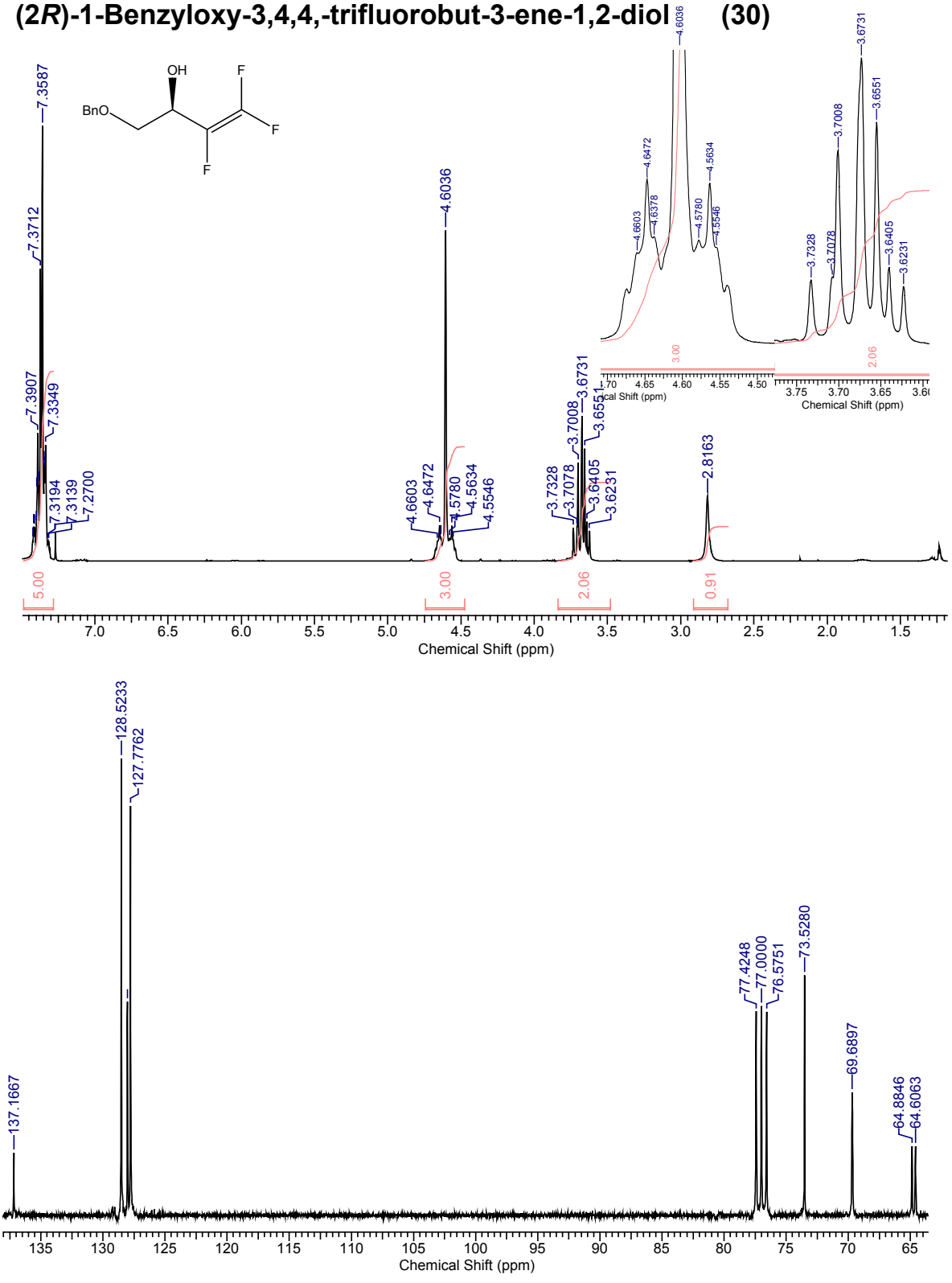


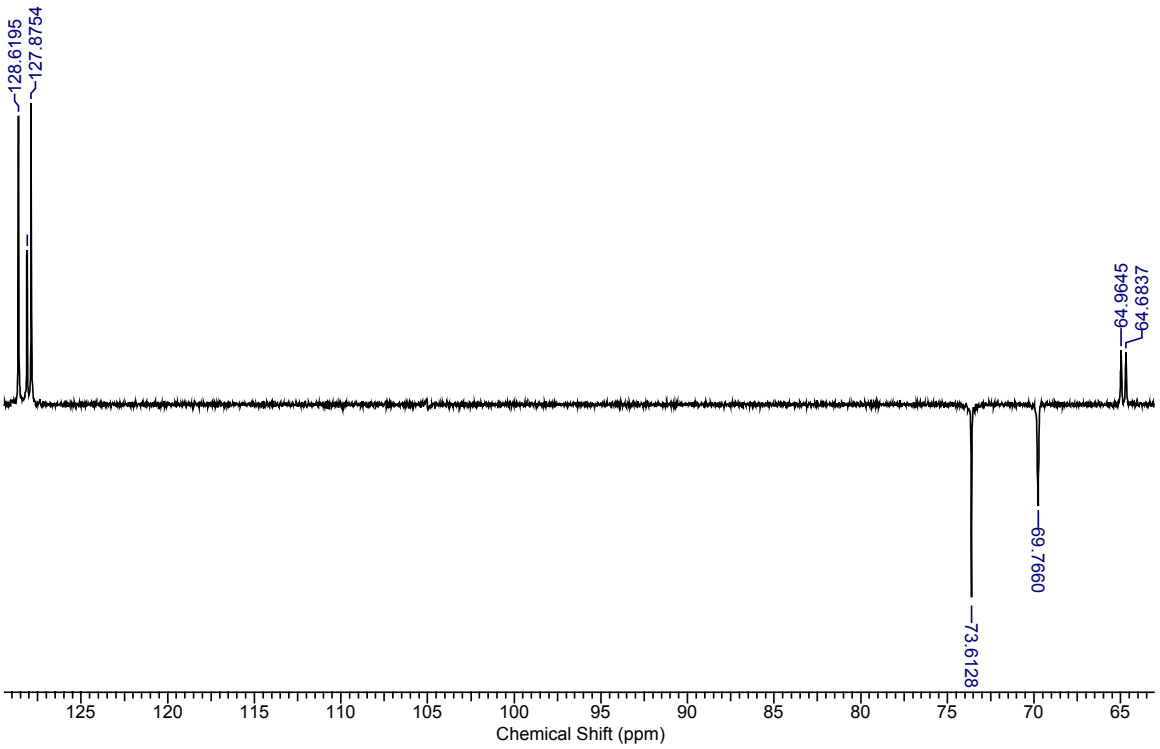


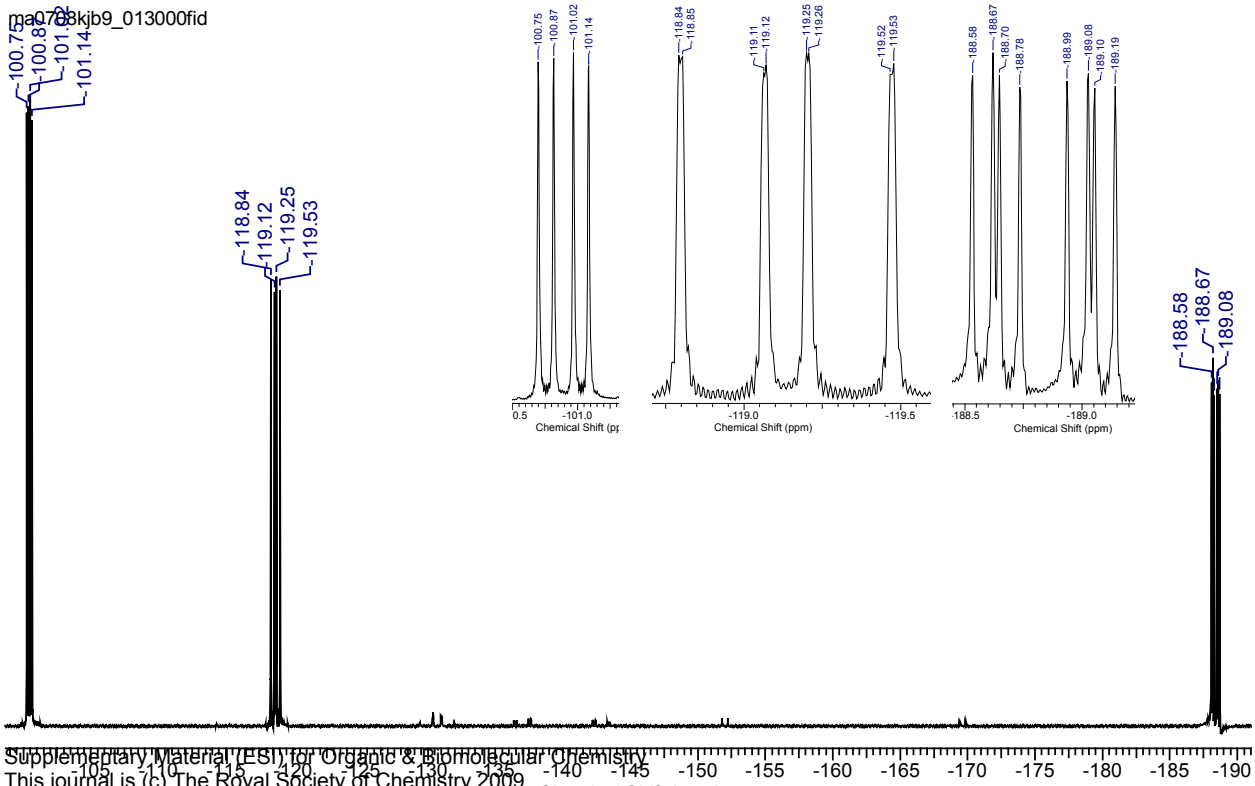

JB:3350/87 - Calibrated
(ppm)
128.4
66.4
79.5
95.0
96.0
78
77
76


Current Data Parameters
NAME nv16071ms111
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071116
Time 9.23
INSTRUM dpx400
PROBHD 5 mm DUL 19F
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 64
DS 2
SWH 37664.785 Hz
FIDRES 1.149438 Hz
AQ 0.4350452 sec
RG 20
DW 13.275 usec
DE 18.44 usec
TE 300.0 K
D1 1.48689198 sec
========== CHANNEL f1 ==========
NUC1 19F
P1 6.30 usec
PL1 -2.00 dB
SFO1 376.4617901 MHz
F2 - Processing parameters
SI 16384
SF 376.4984027 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40
SR -131.32 Hz
1D NMR plot parameters
CX 30.00 cm
F1P -47.225 ppm
F1 -17780.17 Hz
F2P -147.265 ppm
F2 -55444.96 Hz
PPMCM 3.33466 ppm/cm
HZCM 1255.49280 Hz/cm
tetra fluoro furanose
0.9746
1.7336
2.6467
0.8592
1.0000
0.0116
Integral
ppm
Hz

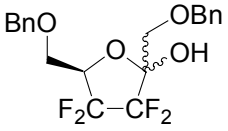
(2*R*)-1-Benzyloxy-3,4,4,-trifluorobut-3-ene-1,2-diol (30)

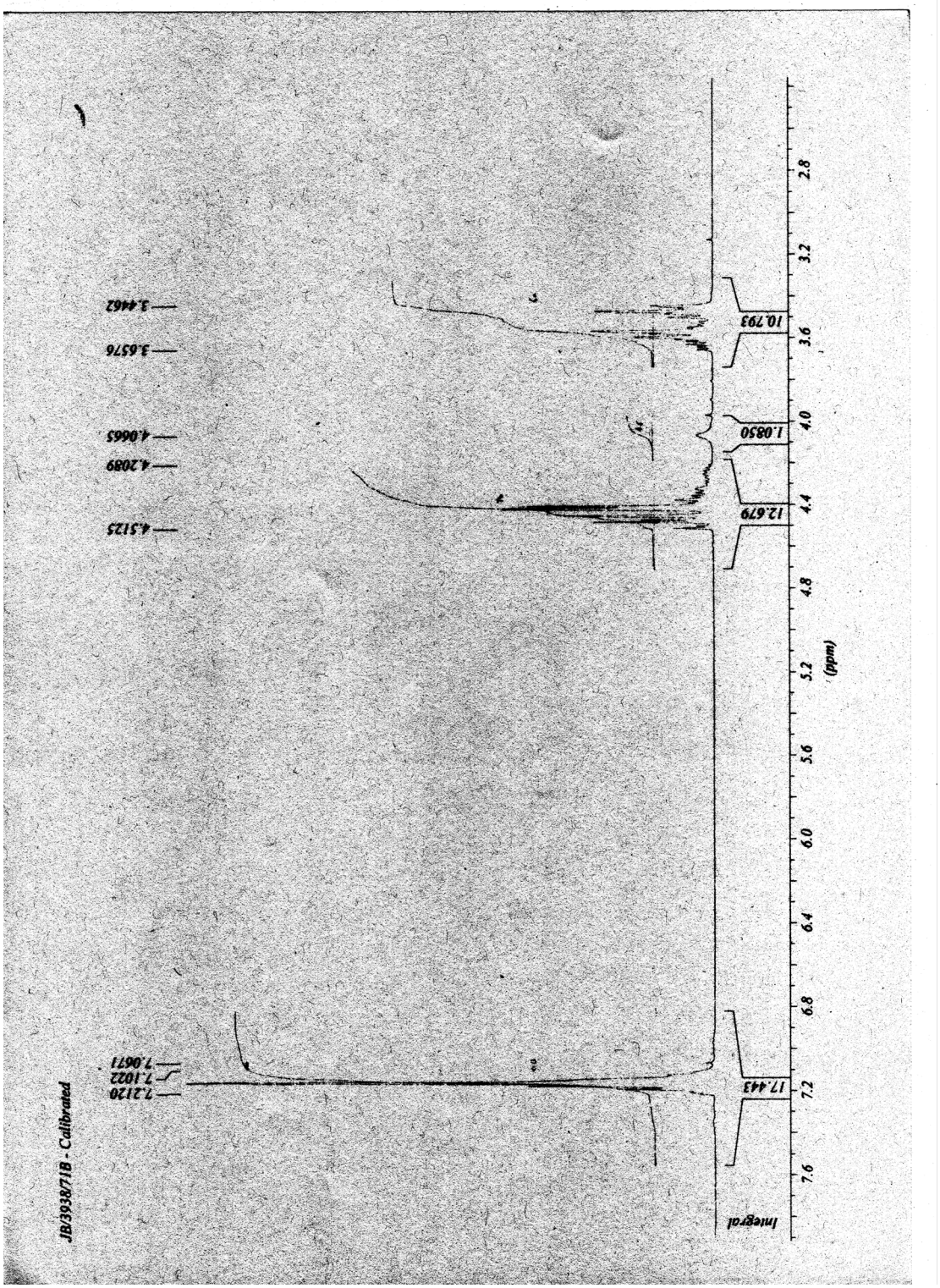


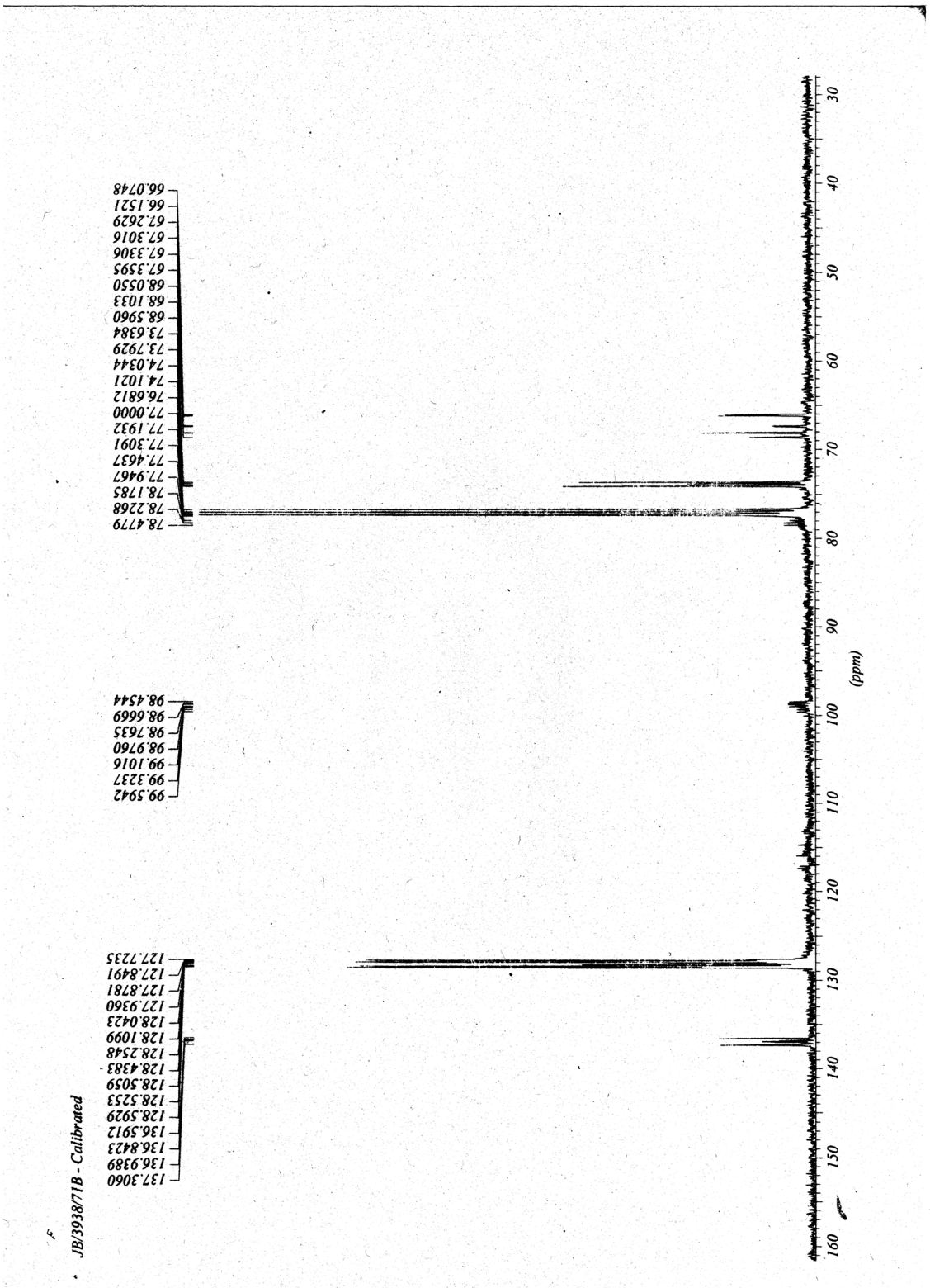

128.6195
127.8754
64.9645
64.6837
69.7660
73.6128
125
120
115
110
105
100
95
90
85
80
75
70
65
Chemical Shift (ppm)

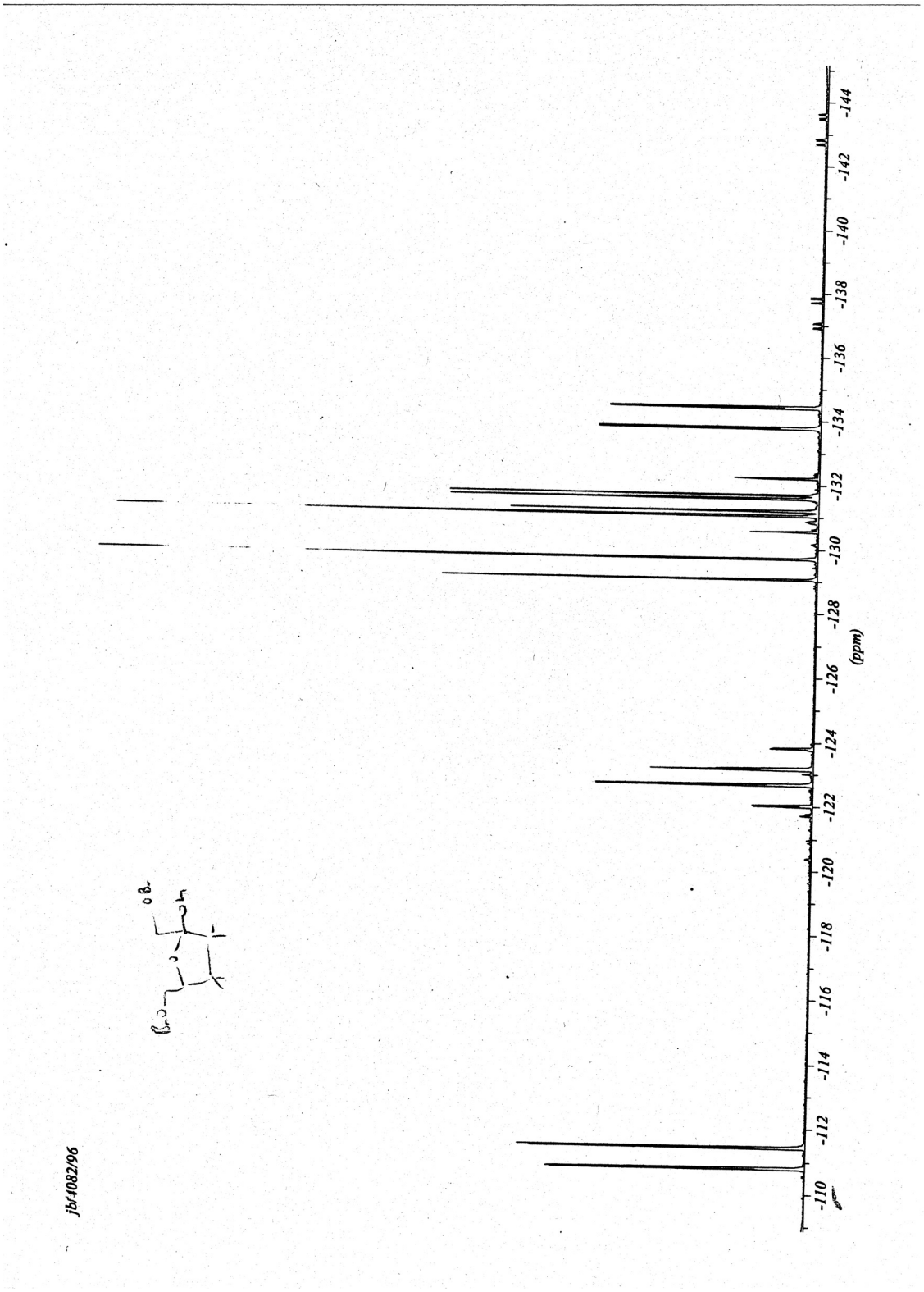

ma0708kjb9_013000fid
100.75
100.87
101.02
101.14
118.84
119.12
119.25
119.53
188.58
188.67
189.08
Chemical Shift (ppm)

(5*R*)-2,5-Bisbenzyloxymethyl-3,3,4,4-tetrafluoro-tetrahydrofuran-2-ol (3)

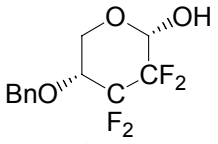


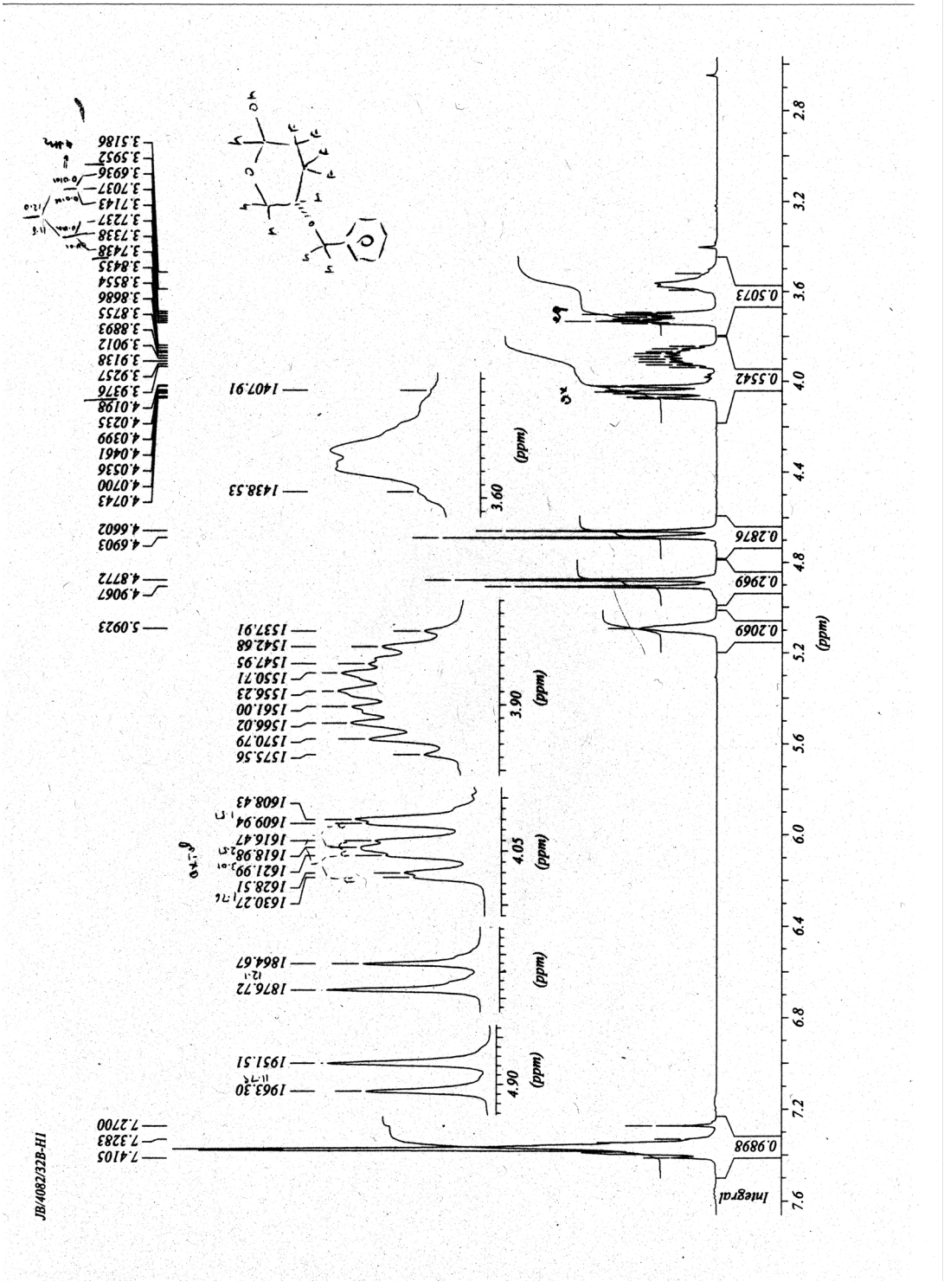


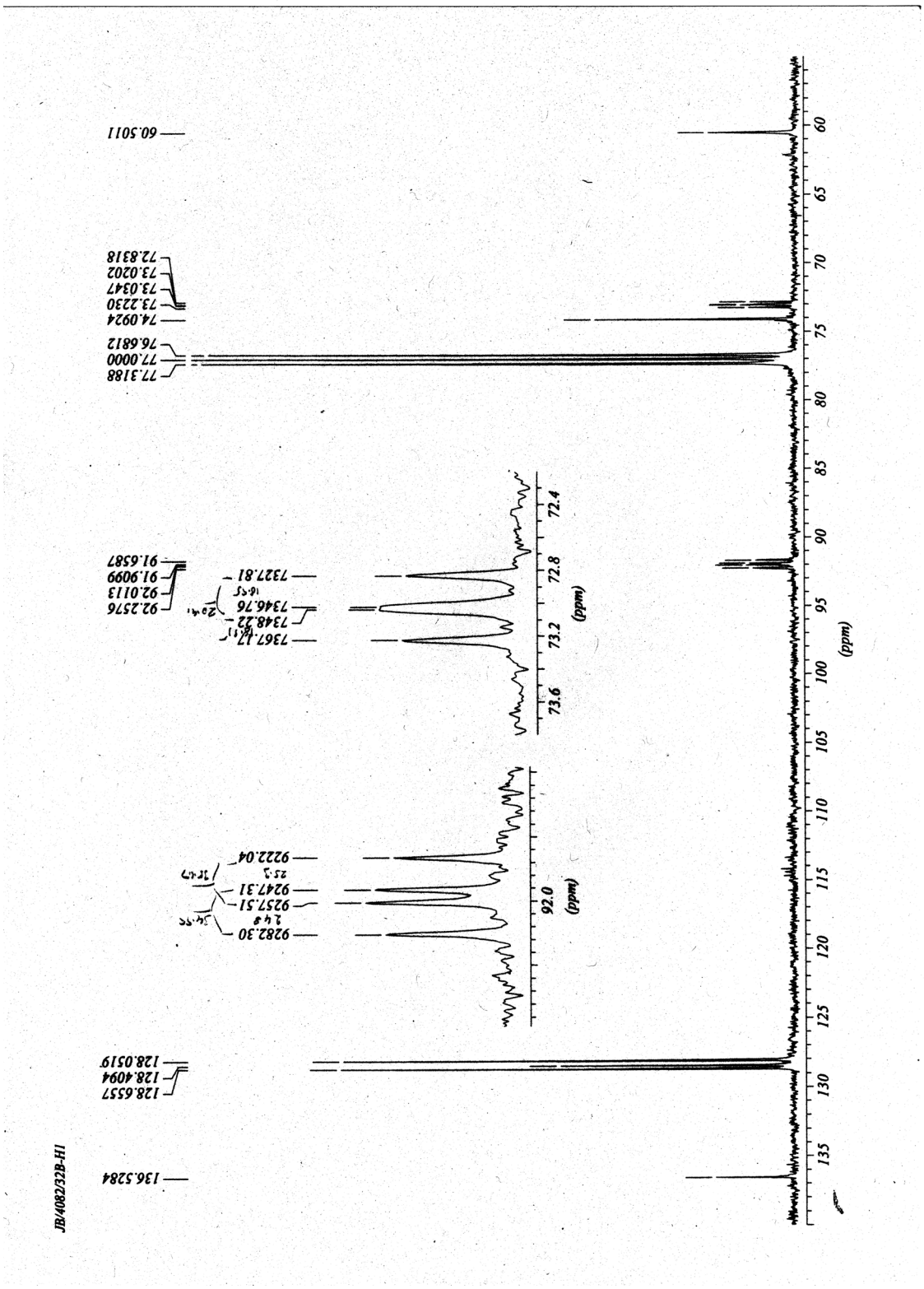


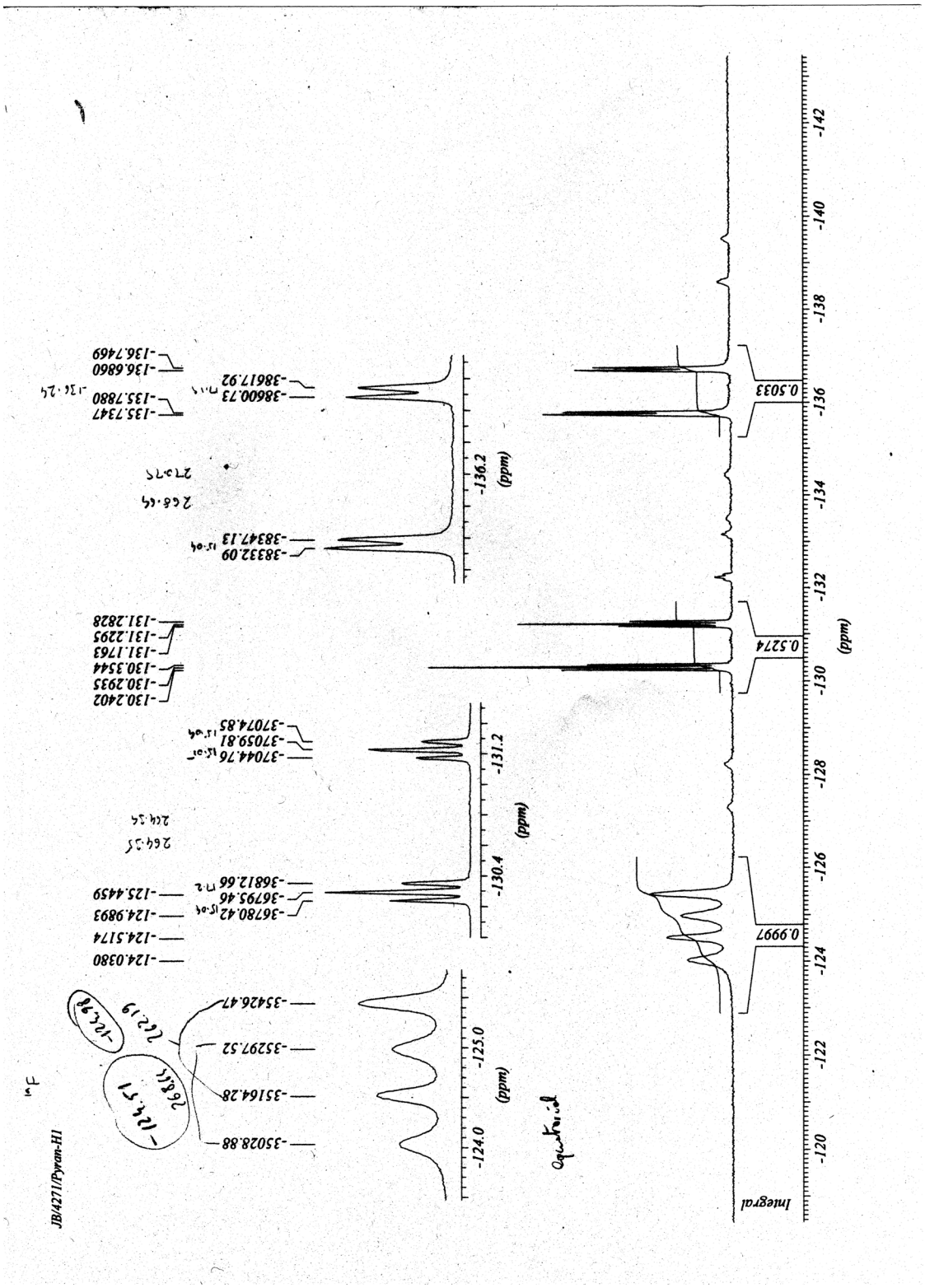

jb/4082/96
-110
-112
-114
-116
-118
-120
-122
-124
-126
-128
-130
-132
-134
-136
-138
-140
-142
-144
(ppm)

(2*S*,5*R*)-5-Benzyloxy-3,3,4,4-tetrafluoro tetrahydropyran-2-ol (4) (α anomer)

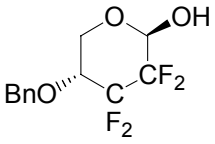


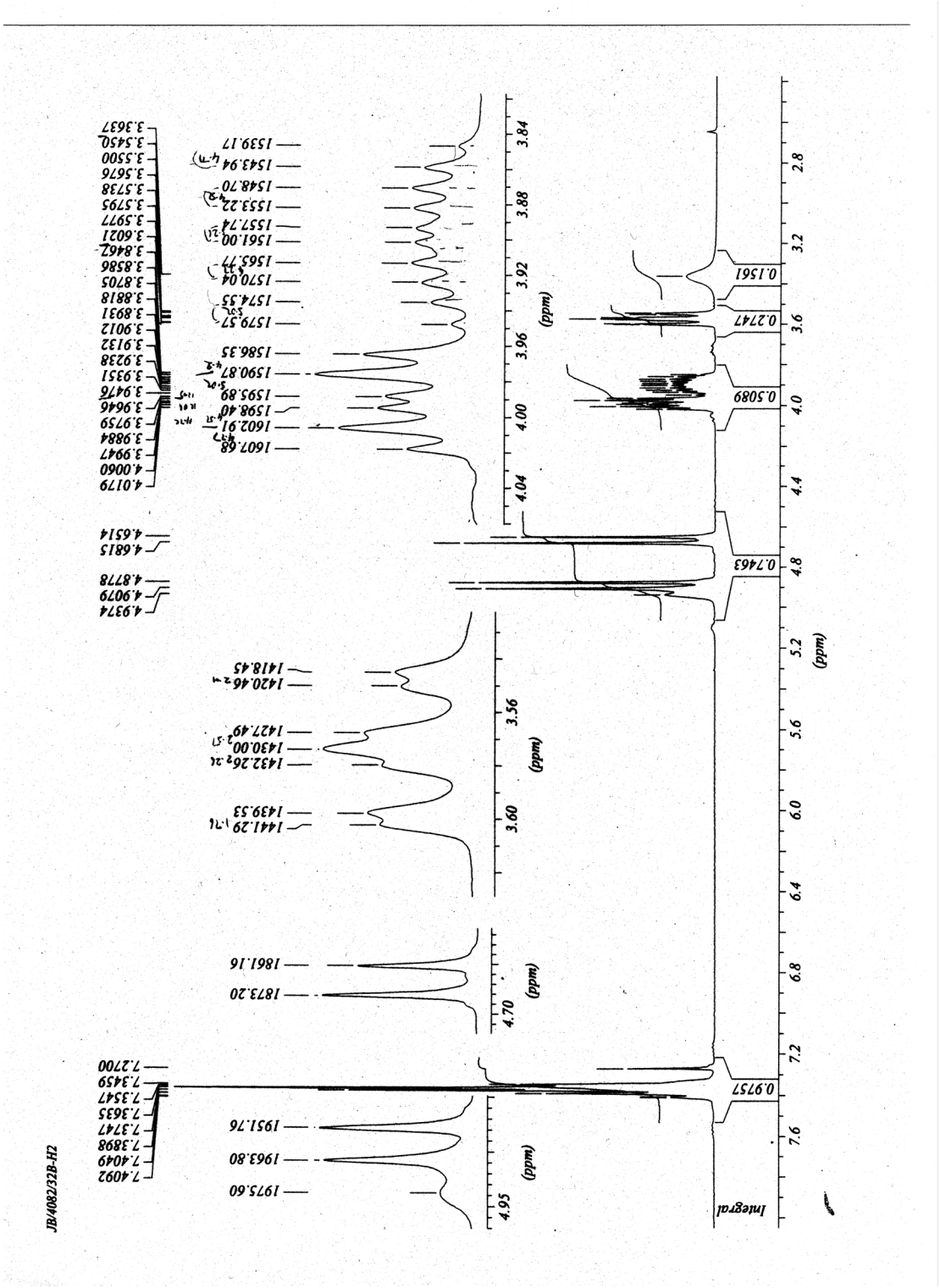


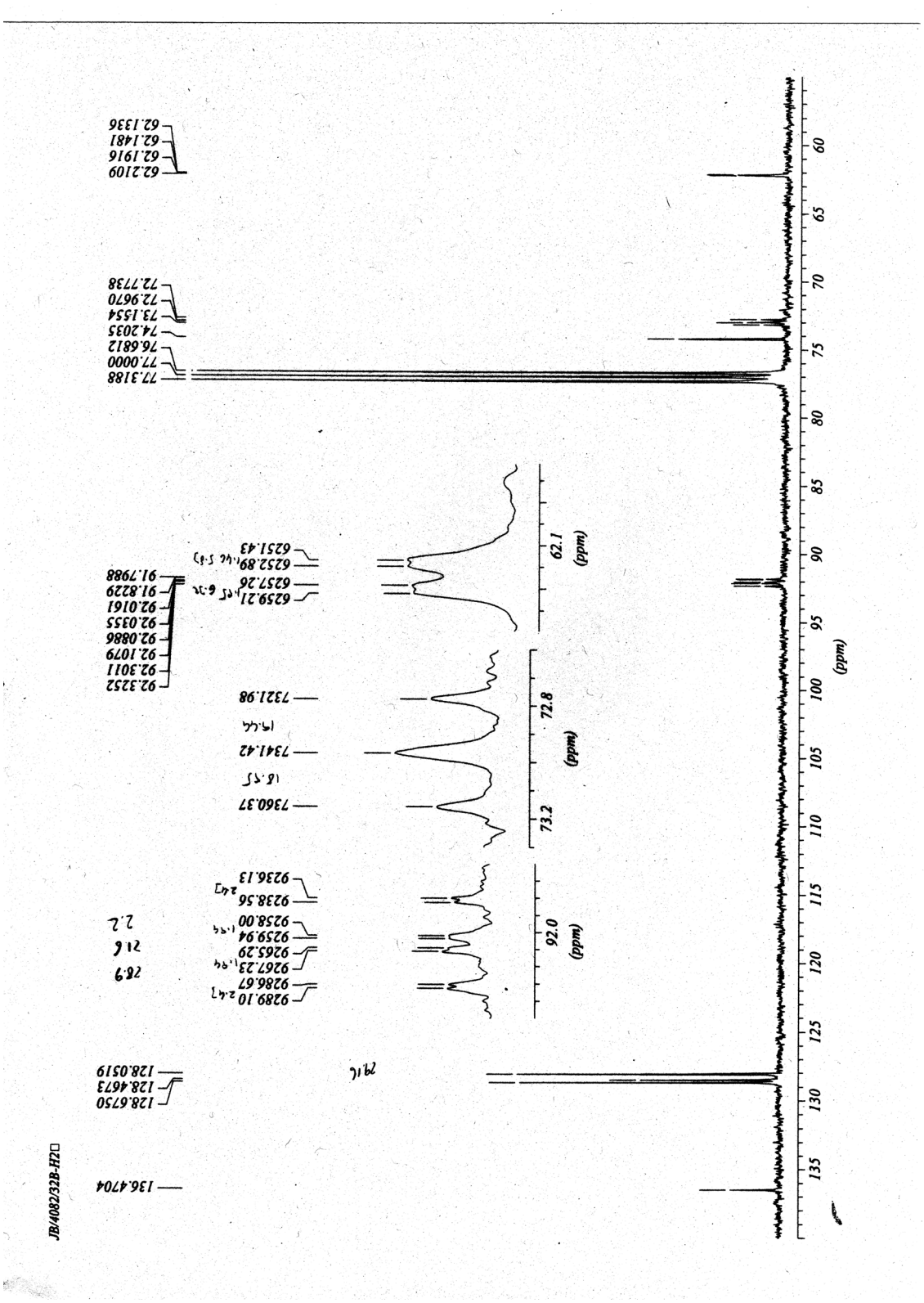

JB/4082/32B-H1
136.5284
128.6557
128.4094
128.0519
92.2576
92.0113
91.9099
91.6587
77.3188
77.0000
76.6812
74.0924
73.2230
73.0347
73.0202
72.8318
60.5011
7367.17
7348.22
7346.76
7327.81
9282.30
9257.51
9247.31
9222.04
(ppm)

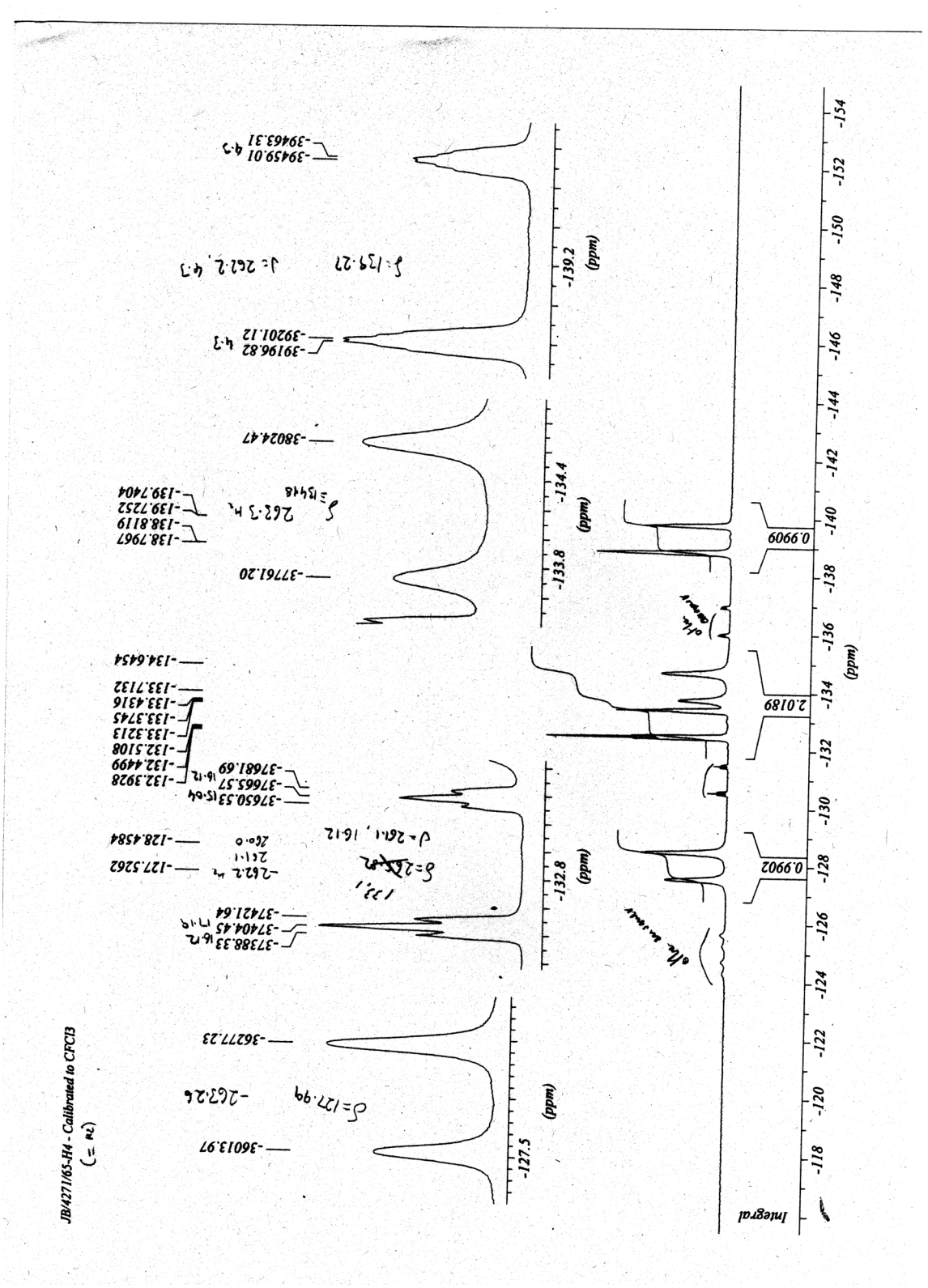

JB/4271/Pyran-H1
Integral
0.9997
0.5274
0.5033
(ppm)
-124.0
-125.0
-130.4
-131.2
-136.2
-120
-122
-124
-126
-128
-130
-132
-134
-136
-138
-140
-142

(2*R*,5*R*)-5-Benzyloxy-3,3,4,4-tetrafluoro tetrahydropyran-2-ol (4)(β anomer)

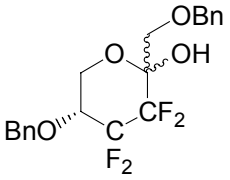


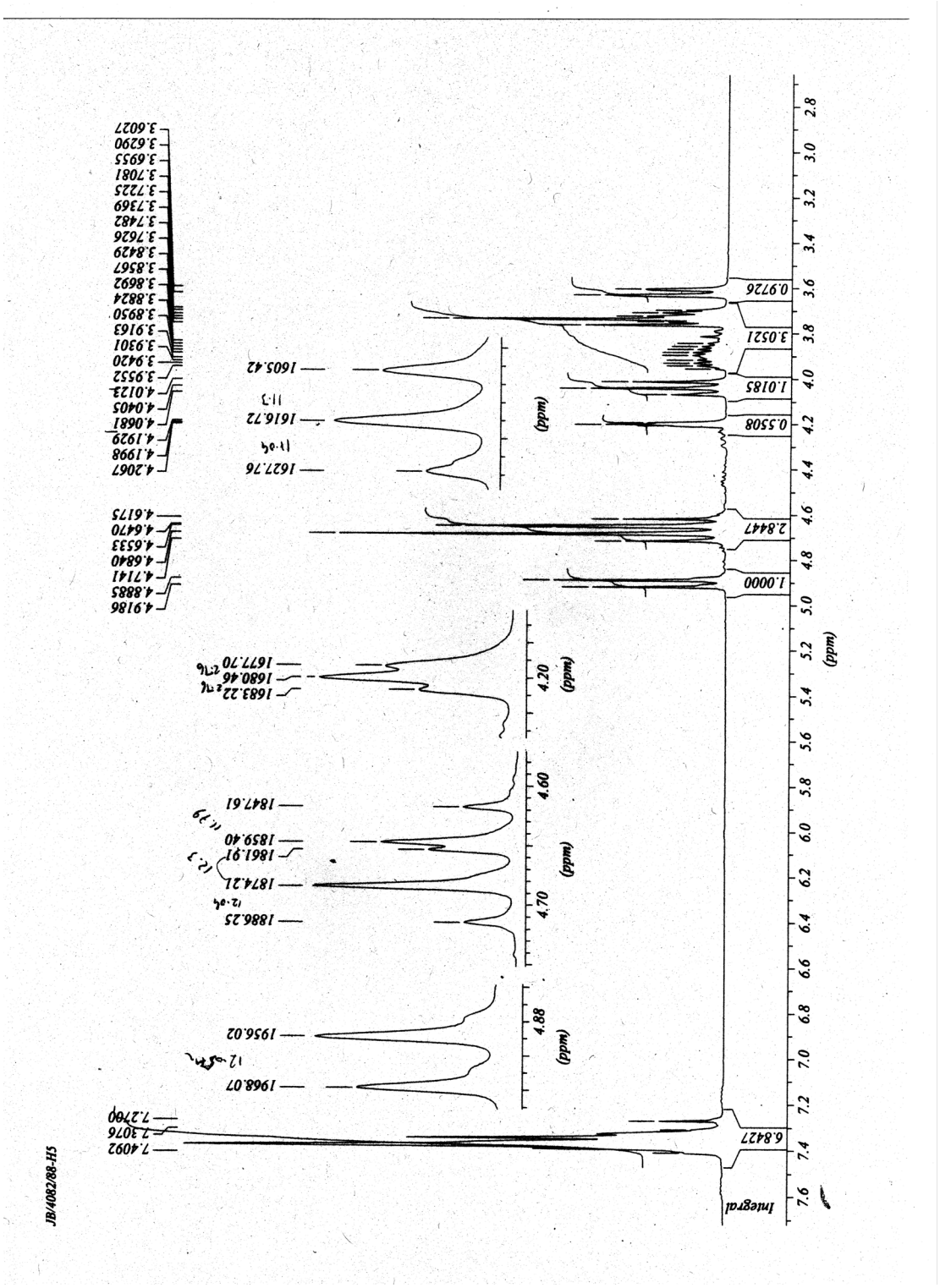


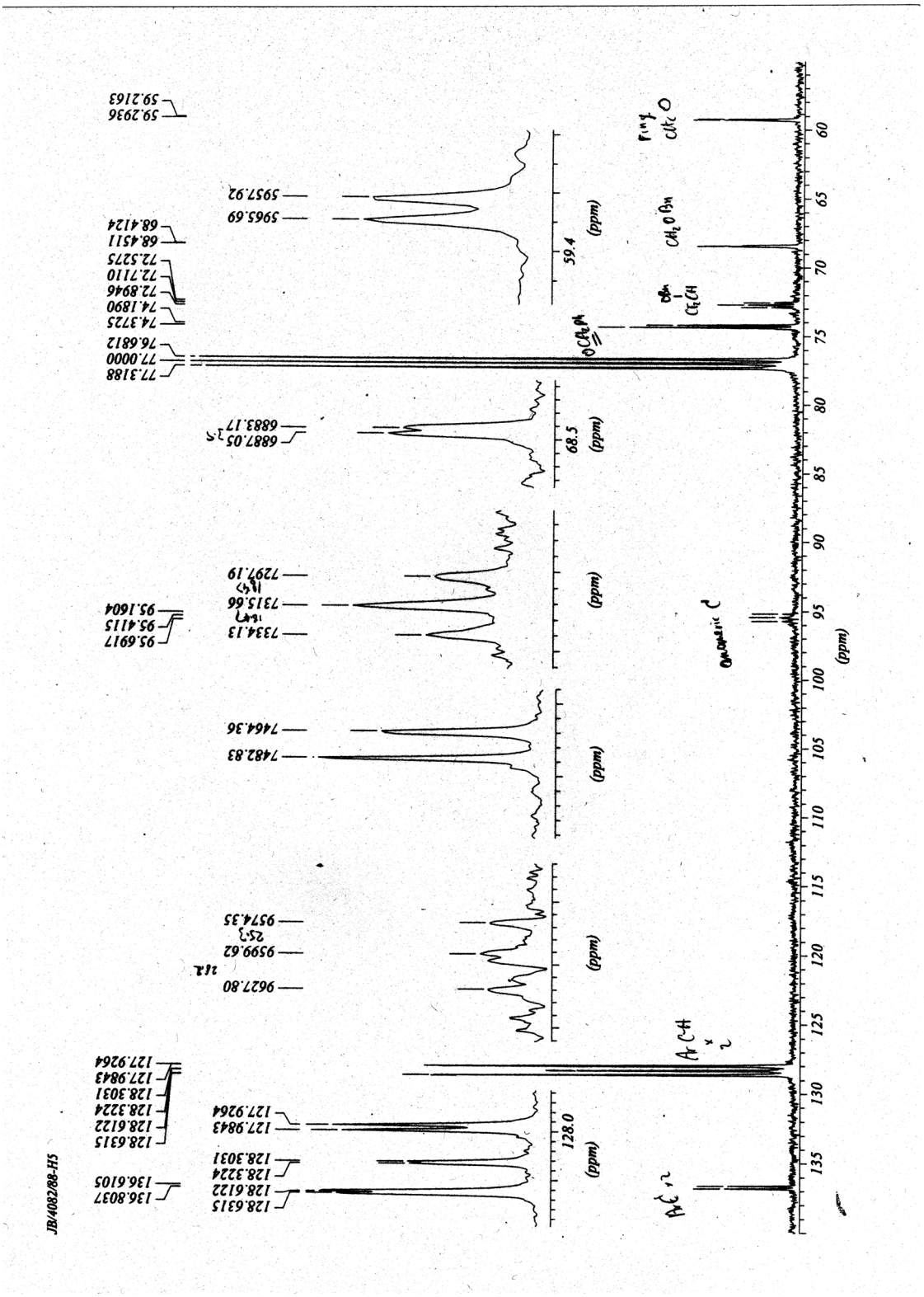


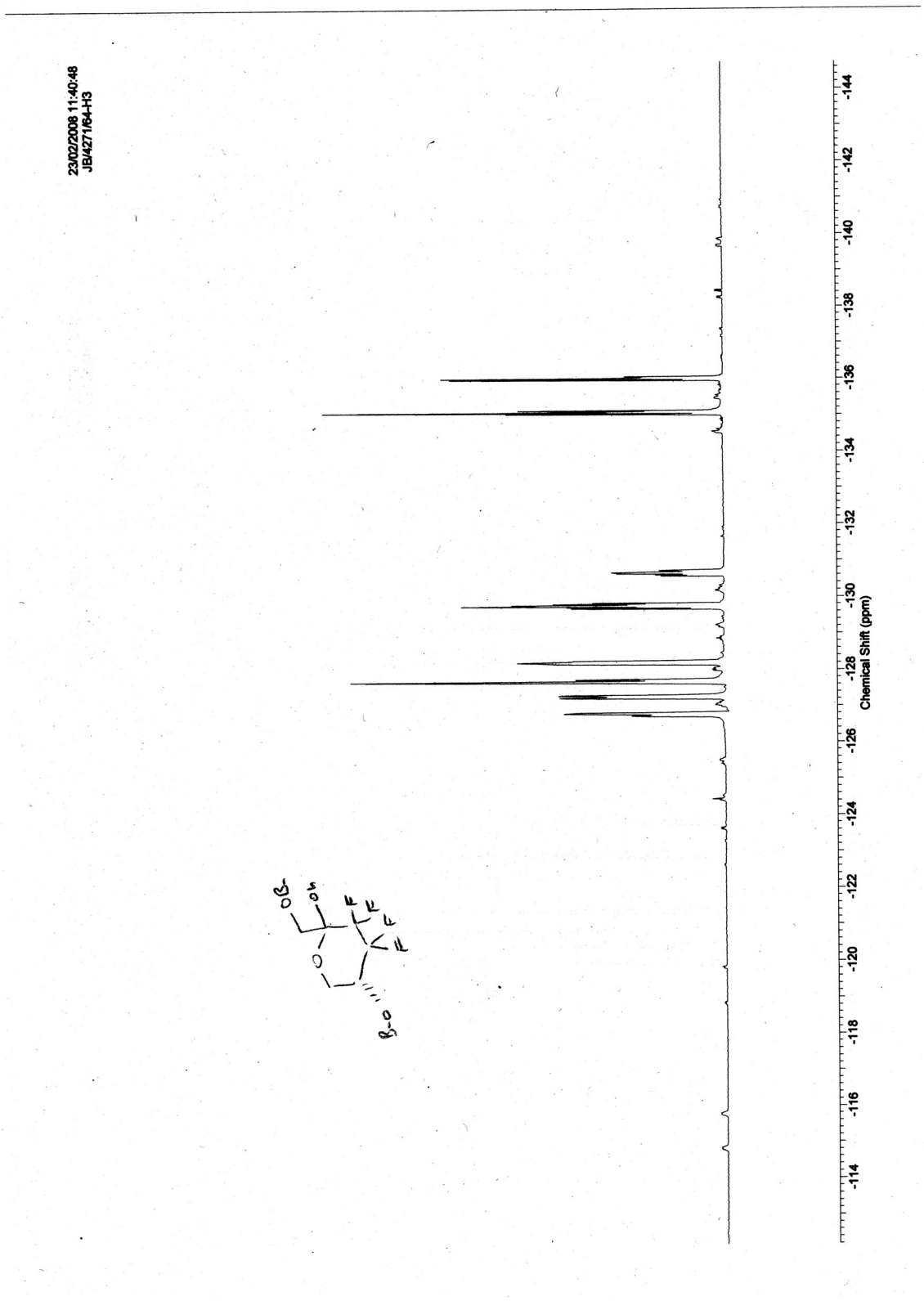


(5R)-2,5-Bisbenzyloxymethyl-3,3,4,4-tetrafluoro-tetrahydropyran-2-ol (5)

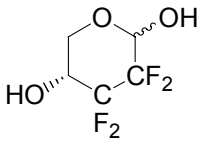


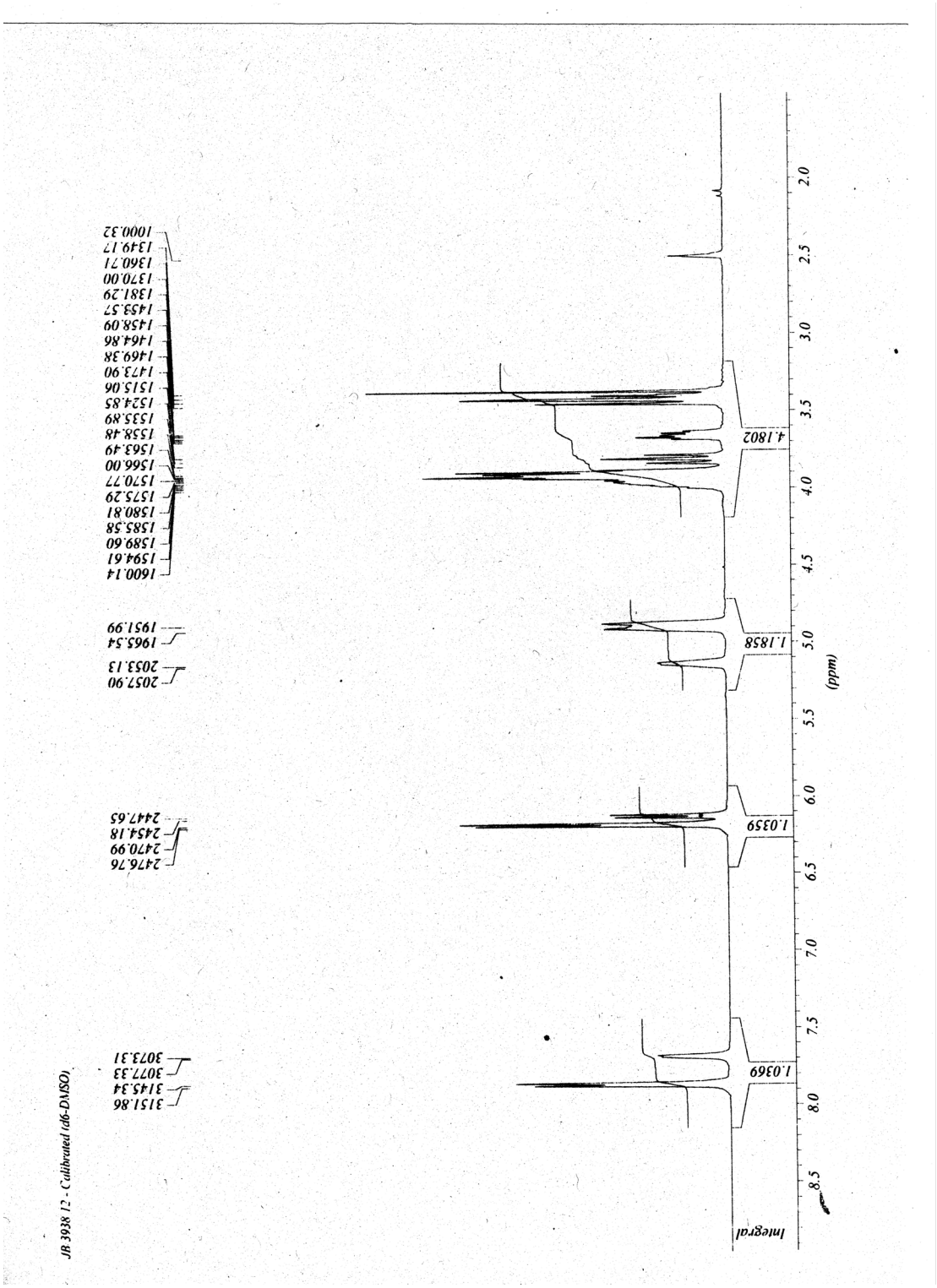


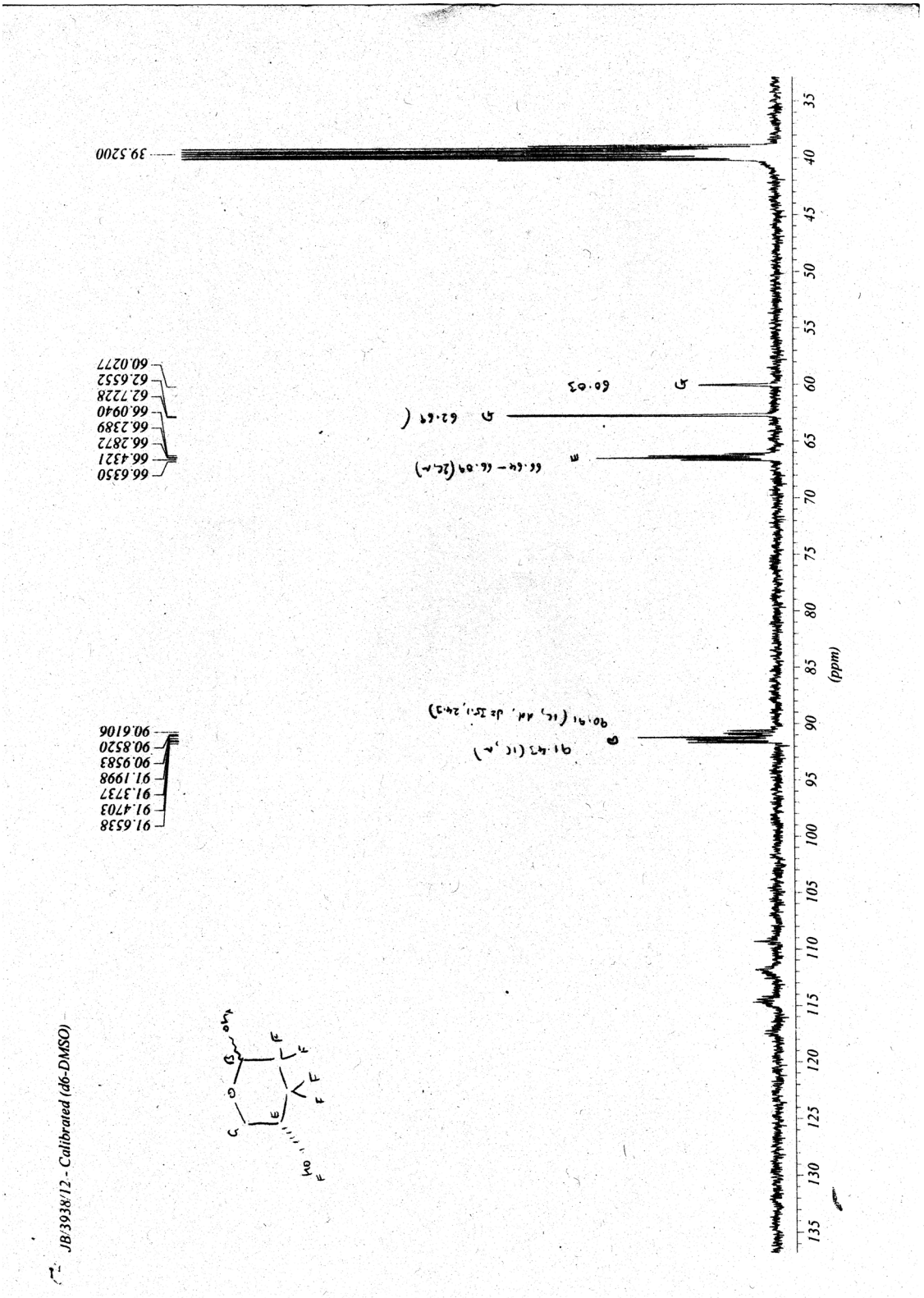


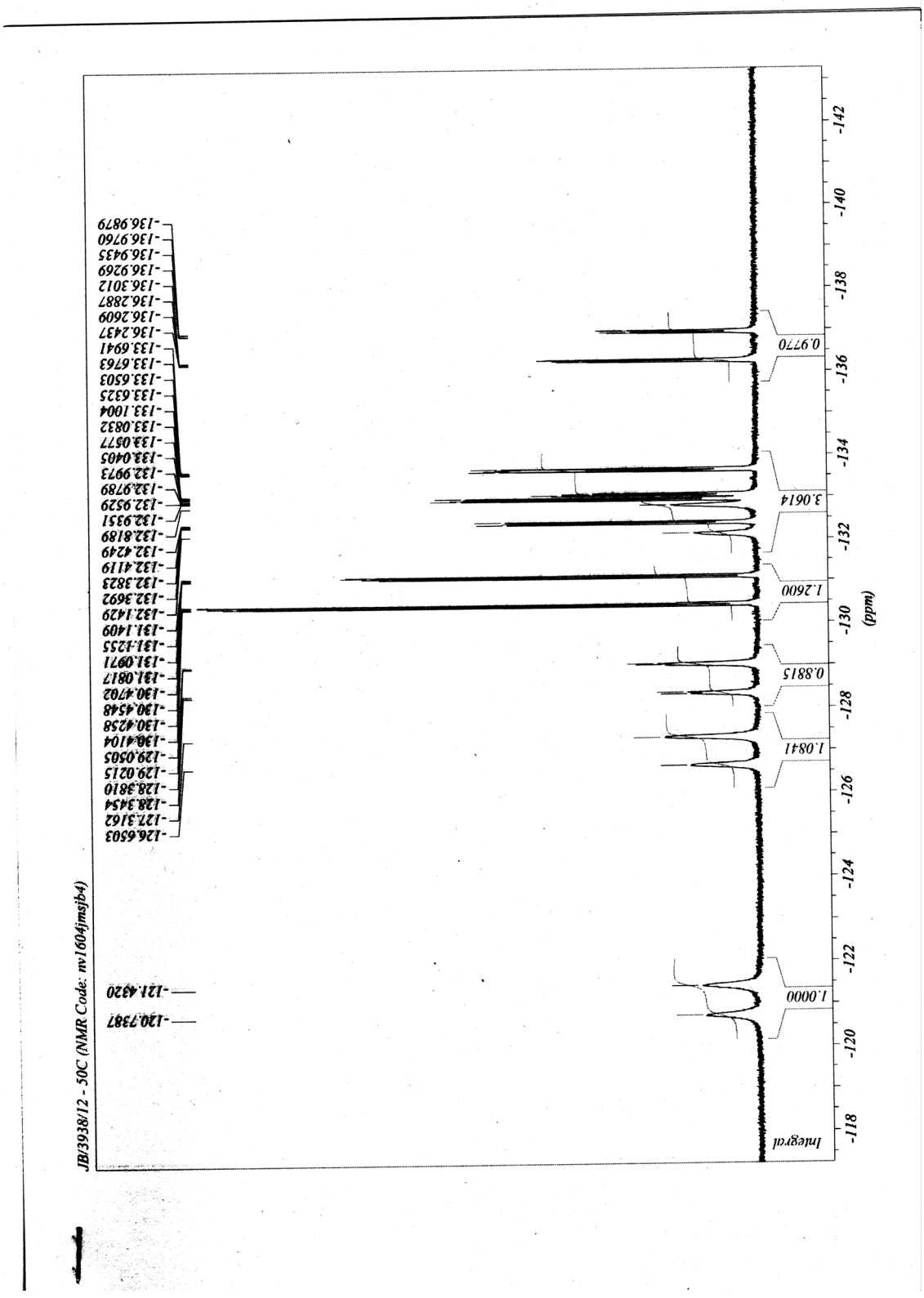

23/02/2008 11:40:48
JB/4271/64-H3
-114
-116
-118
-120
-122
-124
-126
-128
-130
-132
-134
-136
-138
-140
-142
-144
Chemical Shift (ppm)

(5*R*)-3,3,4,4-Tetrafluoro-tetrahydropyran2,5-diol (6)

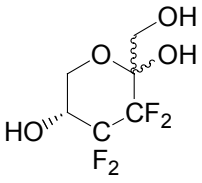


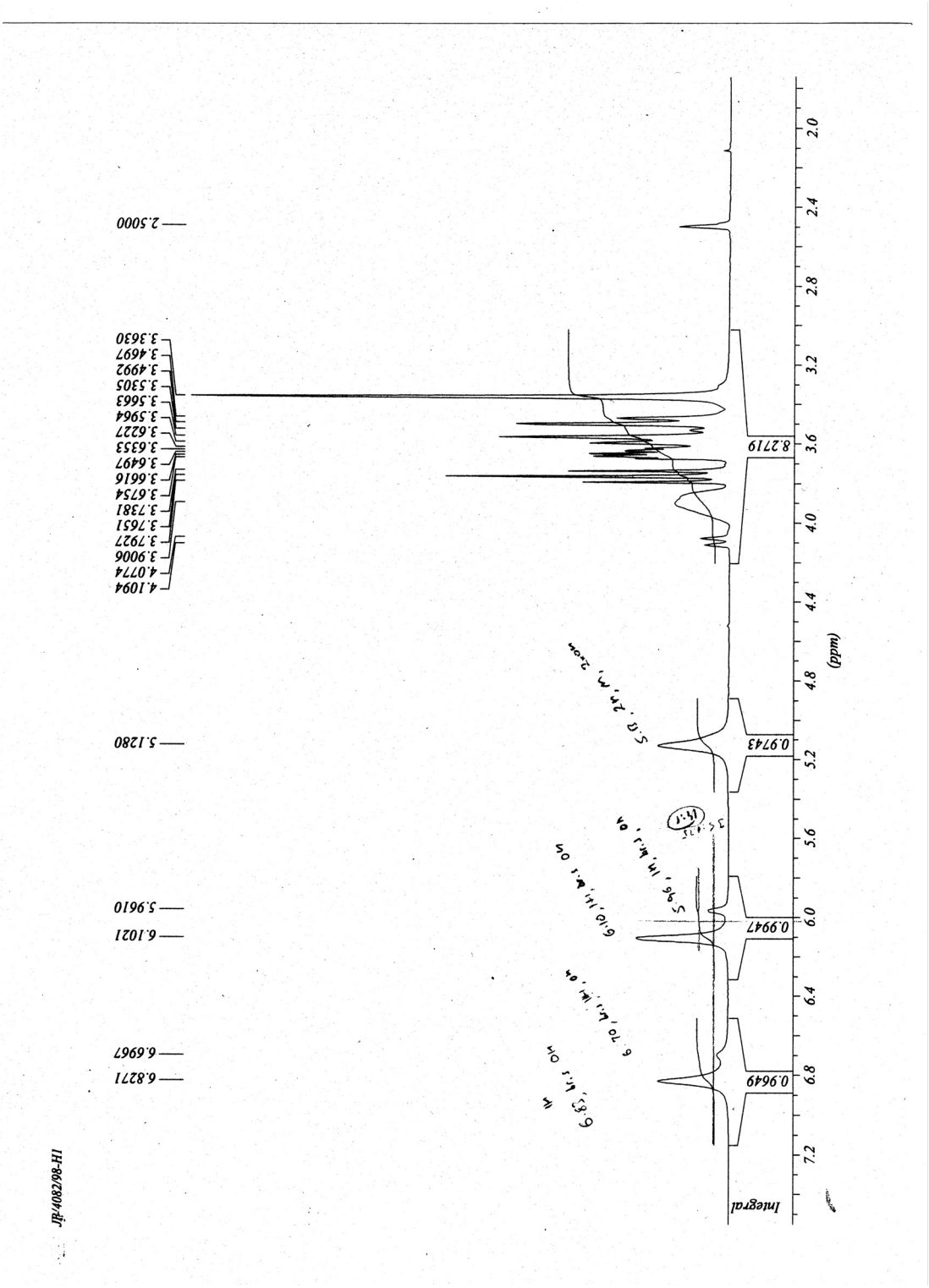


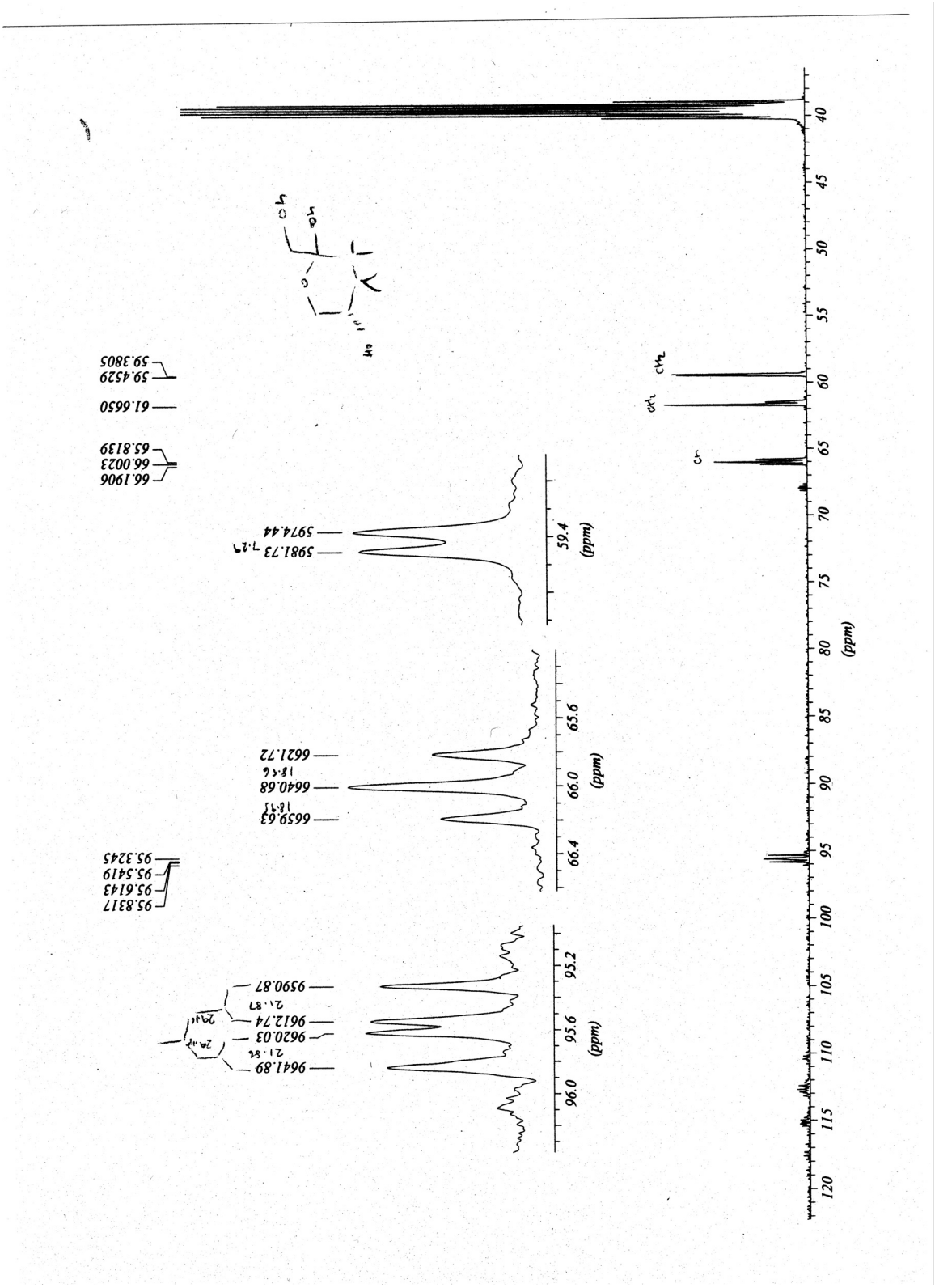

JB/3938/12 - Calibrated (d6-DMSO)
(ppm)
39.5200
60.0277
62.6552
62.7228
66.0940
66.2389
66.2872
66.4321
66.6350
90.6106
90.8520
90.9583
91.1998
91.3737
91.4703
91.6538

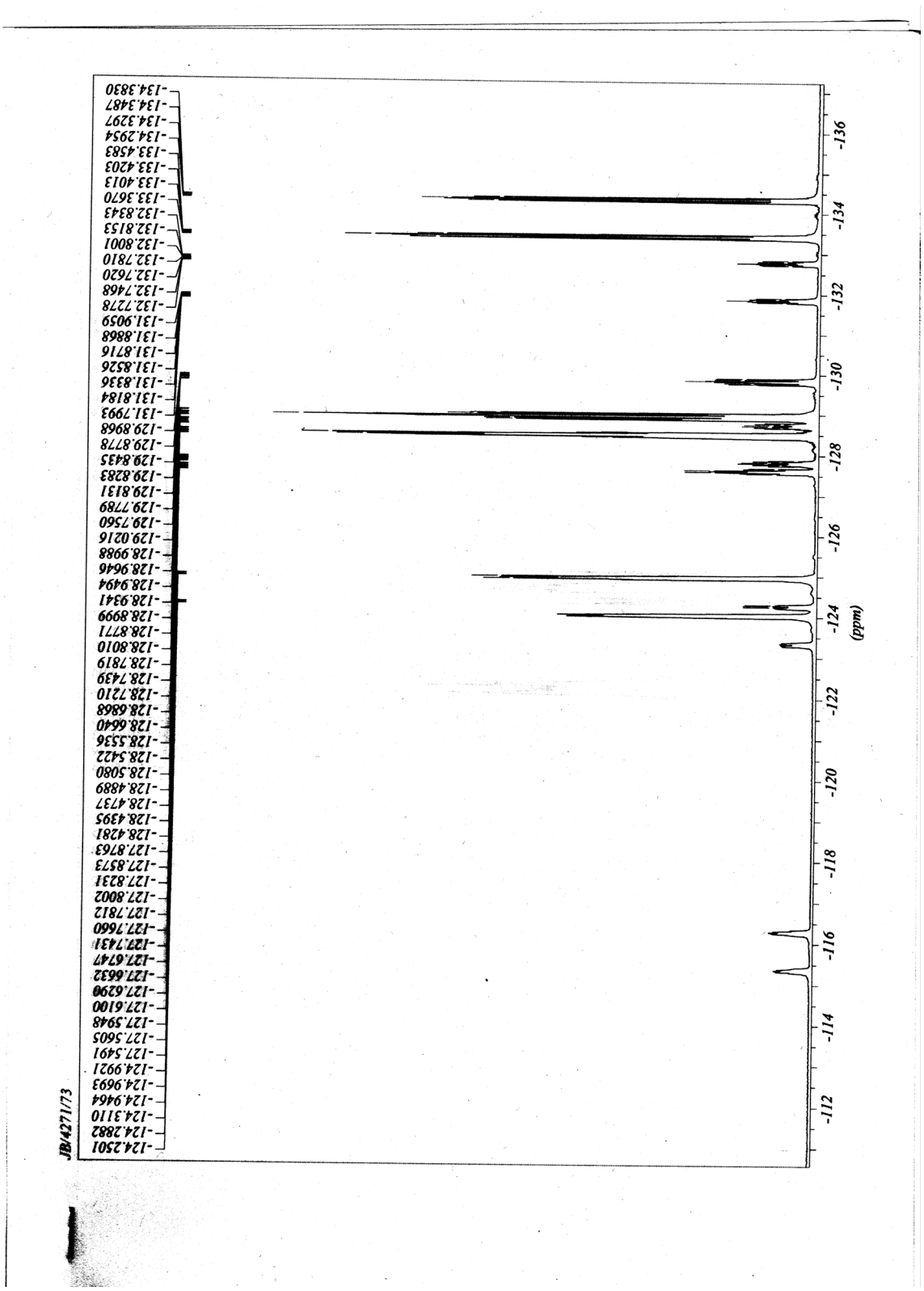

JB/3938/12 - 50C (NMR Code: nv1604jmsjb4)
Integral
0.9770
3.0614
1.2600
0.8815
1.0841
1.0000
(ppm)

(5*R*)-2,5-bishydroxymethyl-3,3,4,4-tetrafluoro-tetrahydropuran-2-ol (7)








JB/4271/73
-112
-114
-116
-118
-120
-122
-124
-126
-128
-130
-132
-134
-136
(ppm)