Synthetic Studies on Norissolide; Enantioselective Synthesis of the Norrisane Side Chain

Charles Kim, Richard Hoang and Emmanuel A. Theodorakis*

Department of Chemistry and Biochemistry,
University of California, San Diego, 9500 Gilman Drive,
La Jolla, California 92093-0358

Supporting Information

General techniques. Organic solutions were concentrated by rotary evaporation below 45 °C at about 20 mmHg. All nonaqueous reactions were carried out using flame-dried glassware, under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. THF and Et_2O were distilled from sodium/benzophenone; CH_2Cl_2 and toluene from calcium hydride; and benzene from potassium. Pyridine, triethylamine and boron trifluoride etherate were distilled from calcium hydride prior to use. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on a Varian 400 MHz instrument and calibrated using residual undeuterated solvent as an internal reference. IR spectra were recorded on a Perkin-Elmer Model 781 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High resolution mass

spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. Melting points (mp) are uncorrected, and were recorded on a Thomas Hoover Unimelt capillary melting point apparatus.

Procedures

To a suspension of D-mannose (**8**) (50 g, 0.28 mol) in 2.5 L of acetone was added iodine (14.21 g, 0.056 mol) and the mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched at 0 °C with sodium thiosulfate and sodium bicarbonate and the organic residues extracted with chloroform. After three washings with sodium bicarbonate (ca. 300 ml), the organic layer was dried over $MgSO_4$, concentrated and crystallized from an acetone/hexane mixture to produce **9** (60 g, 0.24 mol, 85%). **9**: colorless solid; R_f = 0.33 (silica, 50% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (1H, d, *J*= 2.4Hz), 4.81 (1H, dd, *J*= 3.6, 6 Hz), 4.62 (1H, d, *J*= 6.0 Hz), 4.40 (1H, m), 4.18 (1H, dd, *J*= 3.6, 7.2 Hz), 4.06 (2H, m), 2.57 (1H, bs), 1.46 (3H, s), 1.45 (3H, s), 1.38 (3H, s), 1.32 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.4, 108.9, 100.9, 85.3, 79.9, 79.5, 73.2, 66.3, 26.7, 25.8, 25.1, 24.4.

A solution of compound **9** (20 g, 0.077 mol) in dry methylene chloride was treated sequentially with DMAP (5.64 g, 0.046 mol), tosyl chloride (16.32 g, 0.092 mol) and triethylamine (10.7 ml, 0.077 mol). The reaction mixture was stirred at 25 °C until TLC showed completion of reaction (approx. 2 h) at which time the solution was washed with aqueous copper sulfate, sodium bicarbonate and extracted with ethyl ether. The organic layer was extracted with sodium chloride (3 X 200 ml), dried over $MgSO_4$, concentrated and chromatographed (silica, 10-50% ether in

hexanes) to afford **10** (13.5 g, 46.2 mmol, 60%). **10:** viscous, amber-colored oil; R_f = 0.80 (50% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (1H, s), 4.96 (1H, d, *J*= 5.6Hz), 4.89 (1H, m), 4.44 (1H, m), 4.21 (1H, dd, *J*= 3.6, 11.2 Hz), 4.10 (1H, dd, *J*= 6.0, 8.8 Hz), 4.02 (1H, dd, *J*= 4.4, 8.8 Hz), 1.47 (3H, s), 1.46 (3H, s), 1.39 (3H, s), 1.33 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.2, 109.4, 97.5, 89.1, 82.3, 78.5, 72.3, 66.7, 27.0, 25.9, 25.2, 24.7.

A solution of glycal **11** (2.0 g, 10 mmol) in THF (5 ml) at 0 ℃ was treated under argon with sodium hydride (283 mg, 12 mmol), benzyl bromide (2.02 g, 12 mmol), and tetrabutyl ammonium iodide (0.198 g, 0.54 mmol). The reaction mixture was allowed to warm up to 25 °C and stirred for 2 h at which time the TLC showed disappearance of the starting material. The reaction was quenched with brine and extracted with ether. The organic layer was washed with brine (3 X 50 ml), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, 5-30% ether in hexanes) to produce compound **7** (2.5 g, 9 mmol, 90%). **7:** viscous, bright-yellow oil; $[\alpha]^{25}_D$: -103.4 (c=1.0, CH_2Cl_2); R_f = 0.65 (30% ether in hexanes); IR (film) ν_{max} 2978, 2925, 1606, 1064; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 6.62 (1H, d, *J*= 2.4 Hz), 5.29 (1H, t, *J*= 2.8 Hz), 4.66 (1H, m), 4.55 (3H, m), 4.44 (1H, dd, *J*= 4.4, 5.2 Hz), 4.12 (1H, m), 3.99 (1H, m), 1.47 (3H, s), 1.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 138.2, 128.1, 127.4, 127.3, 108.5, 101.7, 83.9, 79.1, 73.0, 70.9, 65.9, 26.6, 25.3.

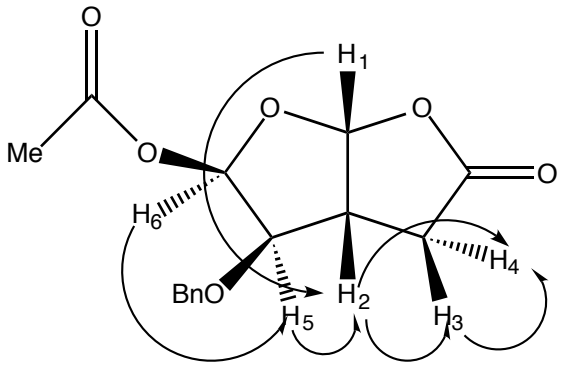
Benzyl ether **7** (7.75 g, 0.028 mol) was dissolved in CH_2Cl_2 (30 ml) and a catalytic amount of rhodium acetate (0.023 g, 0.01 equiv.) was added to give a blue-green colored solution. As the solution

was being stirred, ethyl diazoacetate (3.52 g, 0.031 mol), dissolved in 40 ml of CH_2Cl_2 was added via syringe pump over a period of 14 h. The reaction was carried out at 25 ℃ and open to the atmosphere. After the completion of addition, the mixture was allowed to stir for another 3 h and then concentrated to reveal a blue, viscous oil. After silica gel separation the two isomeric cyclopropyl esters (4:1 ratio at the C13 center) were isolated together and were taken forward to the remaining steps. **6** (3.7 g, 0.013 mmol, 45%). **6:** (major isomer): R_f = 0.75 (50% ether in hexanes); $[\alpha]^{25}_D$: - 4.95 (c= 0.93, CH_2Cl_2); IR (film) ν_{max} 2984, 2935, 1715, 1268, 1187, 1097; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (5H, m), 4.71 (1H, d, *J*= 11.6 Hz), 4.59 (1H, d, *J*= 12 Hz), 4.35 (2H, m), 4.18 (1H, d, *J*= 4.8 Hz), 4.07 (3H, m), 3.95 (1H, dd, *J*= 6.0, 8.4 Hz), 3.68 (1H, m), 2.34 (1H, t, *J*= 4.4, 4.8 Hz), 1.89 (1H, d, *J*= 2.8 Hz) 1.40 (3H, s), 1.36 (3H, s), 1.24 (3H, t, *J*= 6.8, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 137.5, 128.2, 127.6, 127.5, 108.6, 81.9, 78.8, 72.7, 72.1, 66.5, 64.9, 60.7, 28.5, 26.7, 25.4, 21.4, 14.3; HRMS, calcd for $C_{20}H_{26}O_6$ (M+Na^+): 385.1627, found: 385.1623.

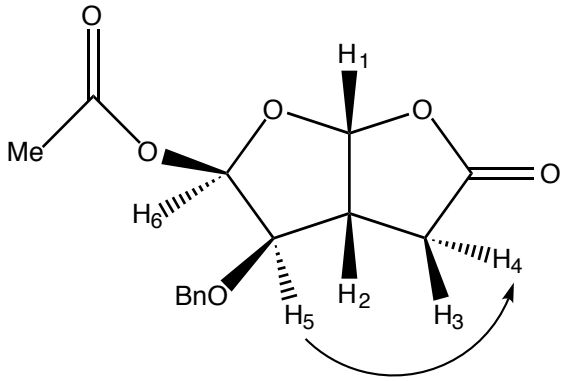
A solution of ester **14** (0.929 g, 2.64 mmol) in dry CH_2Cl_2 (90 ml) was cooled to -20 °C and treated under argon with methanesulfonic acid (1 mL, 6 equiv) added dropwise via syringe. The temperature of the reaction mixture was allowed to rise to -5 ℃ where it was stirred for 6 h. During this time the reaction mixture changed from a light yellow to a dark brown color. At the end of 6 h, the dry-ice bath was exchanged for an ice-water bath and allowed to stir for another 6 h. Upon completion of the reaction (TLC test, the cyclized product is distinctly more polar than the starting material) the reaction was quenched with a mixture of triethylamine and sodium bicarbonate and extracted with ethyl ether. The organic layer was washed with sodium bicarbonate (3 X 50 ml), dried over $MgSO_4$ and concentrated. The resulting crude solid was chromatographed (silica, 30-80% ether in hexanes) to afford lactone **5** (0.491 g, 1.76

mmol, 67%). **5:** yellowish solid; R_f = 0.40 (80% ether in hexanes); $[\alpha]^{25}_D$: -53.56 (c= 0.85, CH_2Cl_2); IR (film) ν_{max} 3634, 3528, 2918, 2861, 1780, 1731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (3H, t, *J*= 7.2, 10 Hz), 7.23 (2H, d, *J*= 6.4 Hz), 6.33 (1H, d, *J*= 5.6 Hz), 4.54 (2H, m), 4.46 (1H, d, *J*= 11.6 Hz), 4.15 (1H, d, *J*= 4 Hz), 3.23 (1H, q, *J*= 5.6, 6.0 Hz), 2.84 (1H, dd, *J*= 19.2, 11.6 Hz), 2.33 (1H, dd, *J*= 5.2, 18.8 Hz), 2.27 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 173.5, 136.2, 128.5, 128.2, 127.6, 107.4, 85.4, 85.1, 72.2, 44.3, 31.1, 28.4; HRMS, calcd for $C_{15}H_{16}O_5$ ($M+Cs^+$): 409.0049, found: 409.0055.

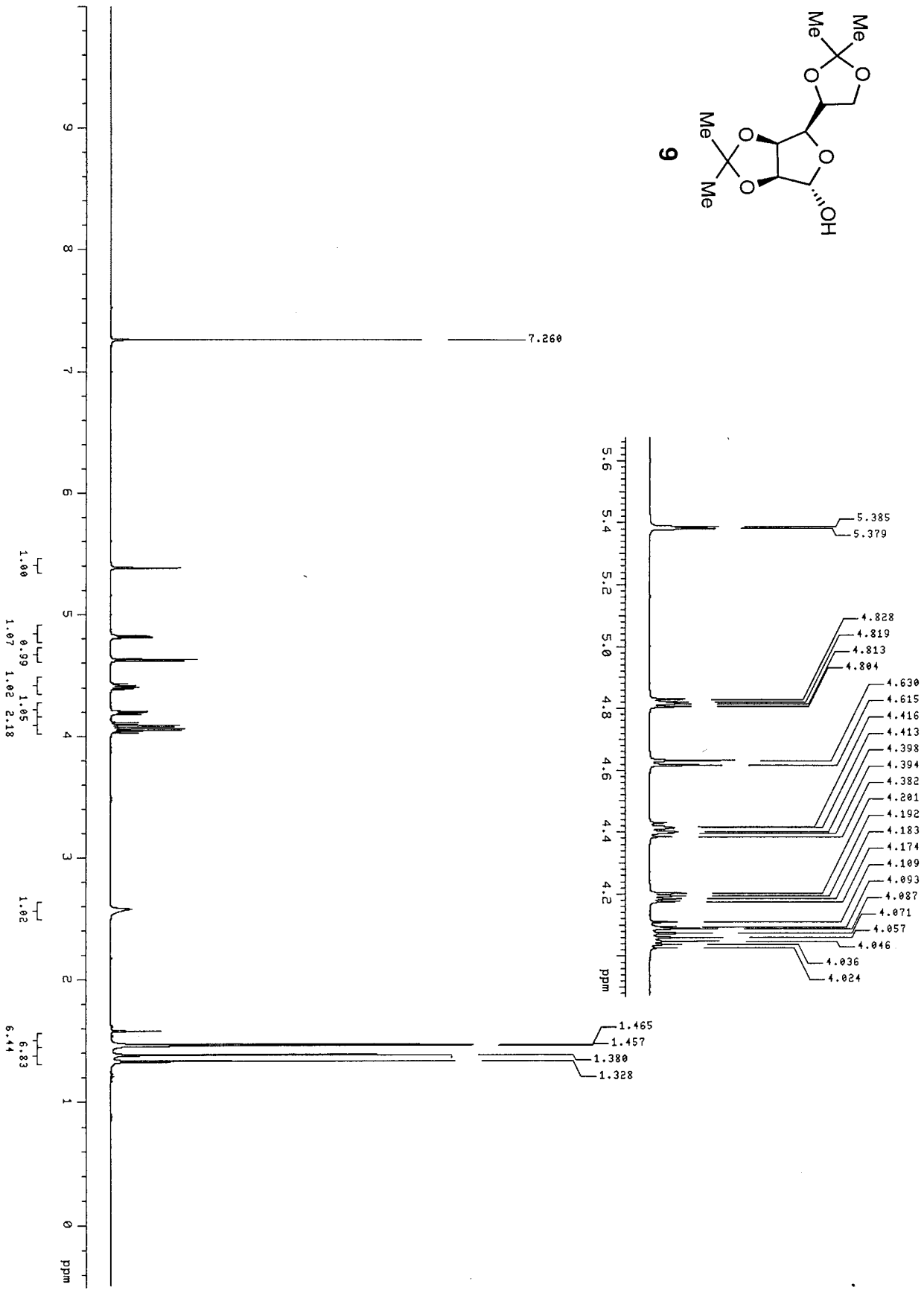
A suspension of Urea-hydrogen peroxide (0.447 g, 4.75 mmol) in dry CH_2Cl_2 (20 ml) was cooled to 0 °C and treated with trifluoroacetic anhydride (0.336 mL, 2.38 mmol) added dropwise over a 5 minute period. The reaction mixture was brought up to 25 °C and allowed to stir for 30 min and added via cannula to a solution of ketone **5** (0.164 g, 0.594 mmol) in dry CH_2Cl_2 (5 ml). After stirring at 25 °C for 2h (completion by TLC), the reaction was quenched with sodium thiosulfate and sodium bicarbonate at 0 °C and stirred for 0.5 h. The organic layer was diluted with ether and washed with sodium bicarbonate (3 X 20 ml). The organic layer was collected, dried over $MgSO_4$, concentrated and purified (silica, 20-60% ether in hexanes) to afford compound **4** (0.12g, 69% yield). **4:** white powdery solid; R_f = 0.30 (70% ether in hexanes); $[\alpha]^{25}_D$: +68.06 (c= 0.7, CH_2Cl_2); IR (film) ν_{max} 2919, 2854, 1788, 1745, 1374, 1235, 1138; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (3H, t, *J*= 7.2, 9.2 Hz), 7.30 (2H, d, *J*= 7.6 Hz), 6.45 (1H, d, *J*= 4.0 Hz), 6.04 (1H, d, *J*= 6.0 Hz), 4.63 (1H, d, *J*= 11.6 Hz), 4.487 (1H, d, *J*= 11.6 Hz), 3.88 (1H, qr, *J*= 4 Hz), 3.10 (1H, m), 2.79 (1H, dd, *J*= 9.2, 18.8 Hz), 2.48 (1H, dd, =2, *J*= 1.6, 18.8 Hz), 2.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 169.2, 136.5, 128.6, 128.4, 127.8, 105.3, 95.1, 81.9, 73.5, 41.7, 33.2, 21.1; HRMS, calcd for $C_{15}H_{16}O_6$ ($M+Na^+$): 315.0845, found: 315.0859.

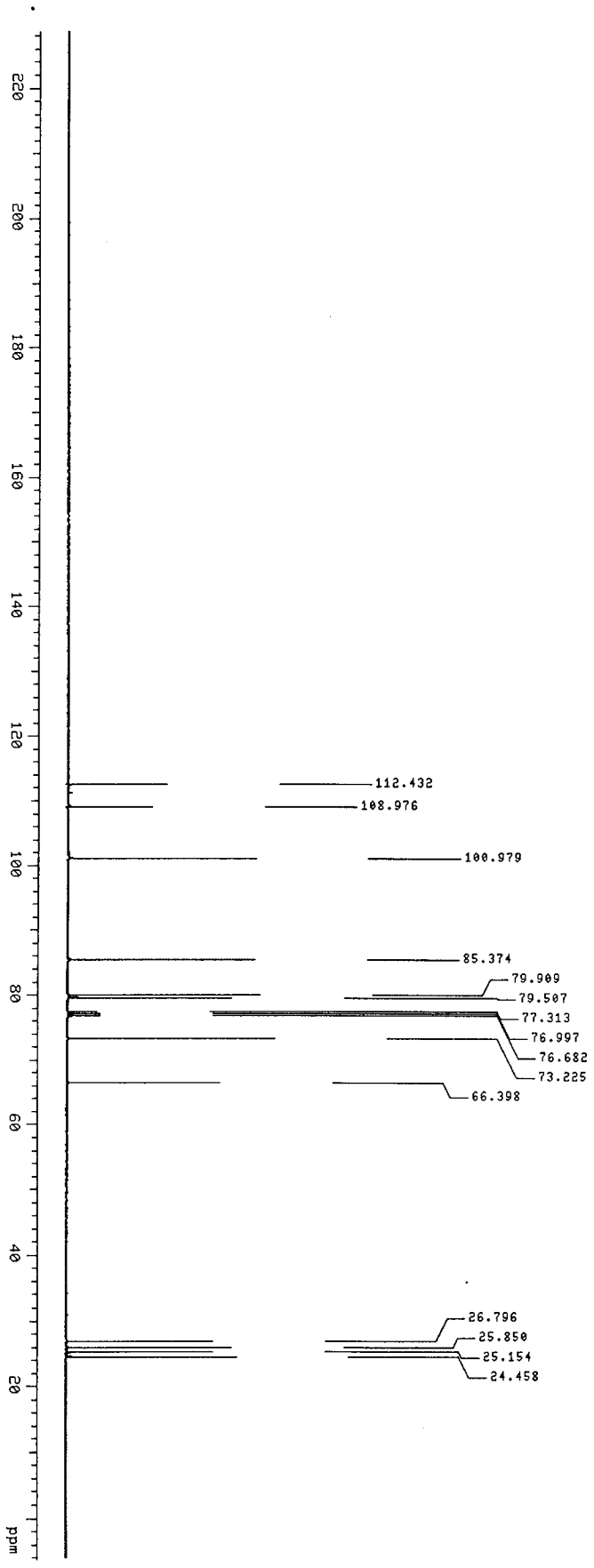


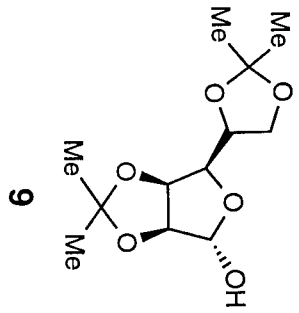
COSY for compound **4**: (H_1, H_2), (H_2, H_3, H_4, H_5), (H_5, H_6)



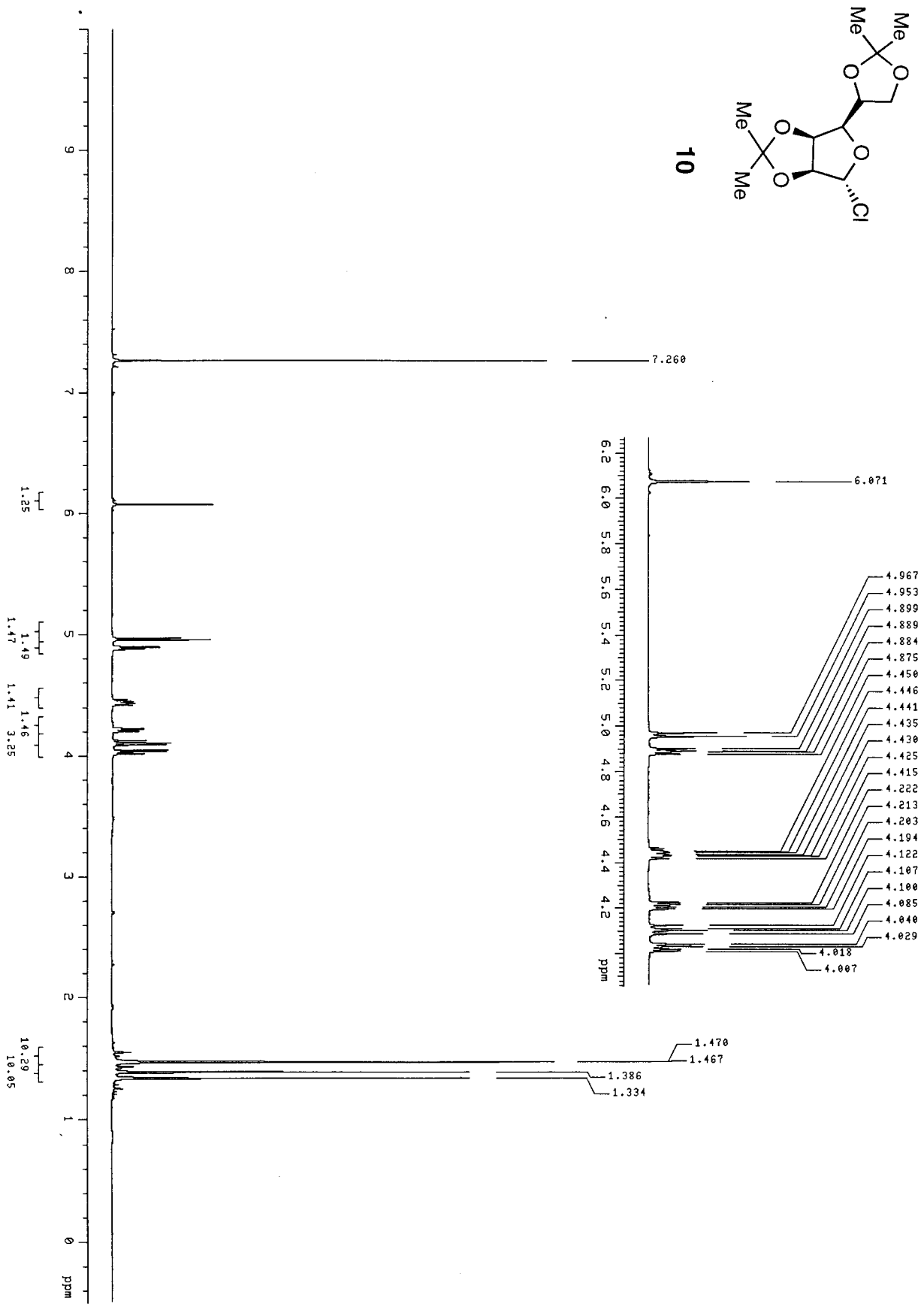
1D NOE for compound **4**: (H_4, H_5)

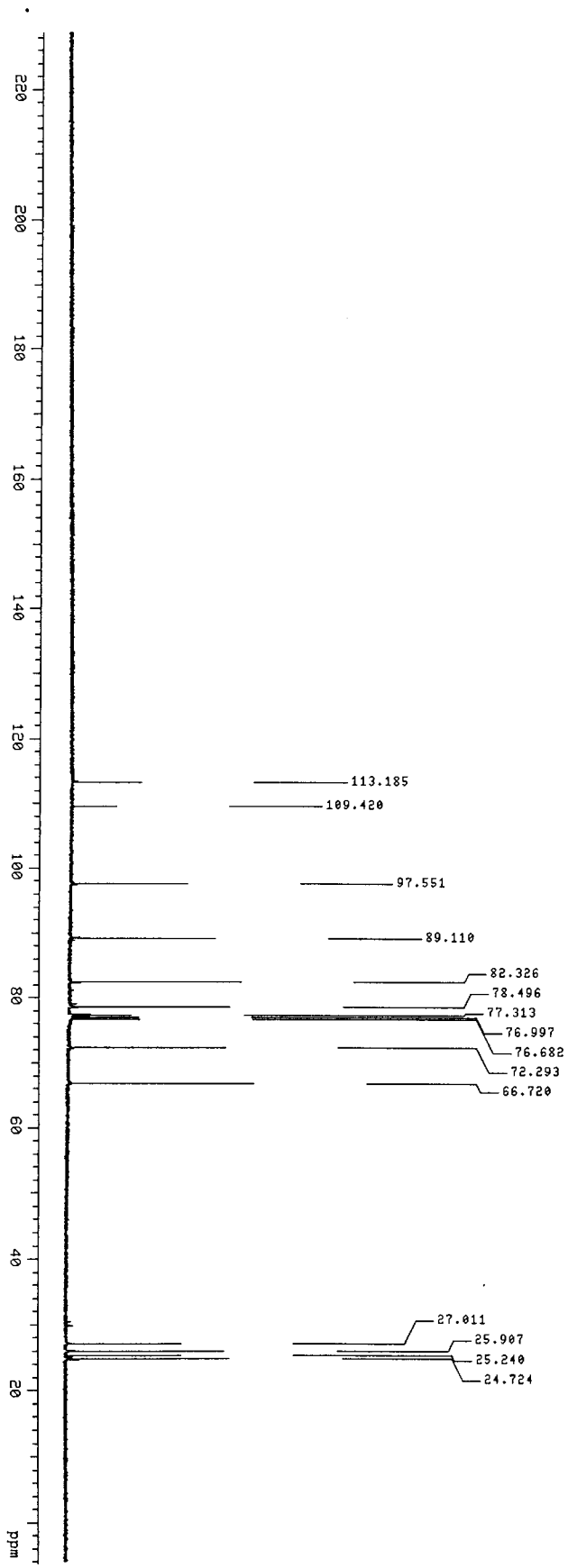

Me
Me
O
O
O
O
Me
Me
O
O
OH
9
7.260
5.385
5.379
4.828
4.819
4.813
4.804
4.630
4.615
4.416
4.413
4.398
4.394
4.382
4.201
4.192
4.183
4.174
4.109
4.093
4.087
4.071
4.057
4.046
4.036
4.024
1.465
1.457
1.380
1.328
1.00
0.99
1.05
1.07
1.02
2.18
1.02
6.83
6.44
ppm

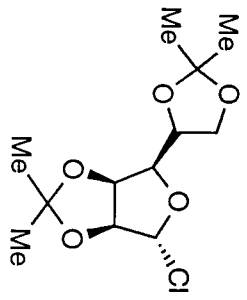

220
200
180
160
140
120
100
80
60
40
20
ppm
112.432
108.976
100.979
85.374
79.909
79.507
77.313
76.997
76.682
73.225
66.398
26.796
25.850
25.154
24.458


Me
Me
O
O
O
O
O
Me
Me
O
OH

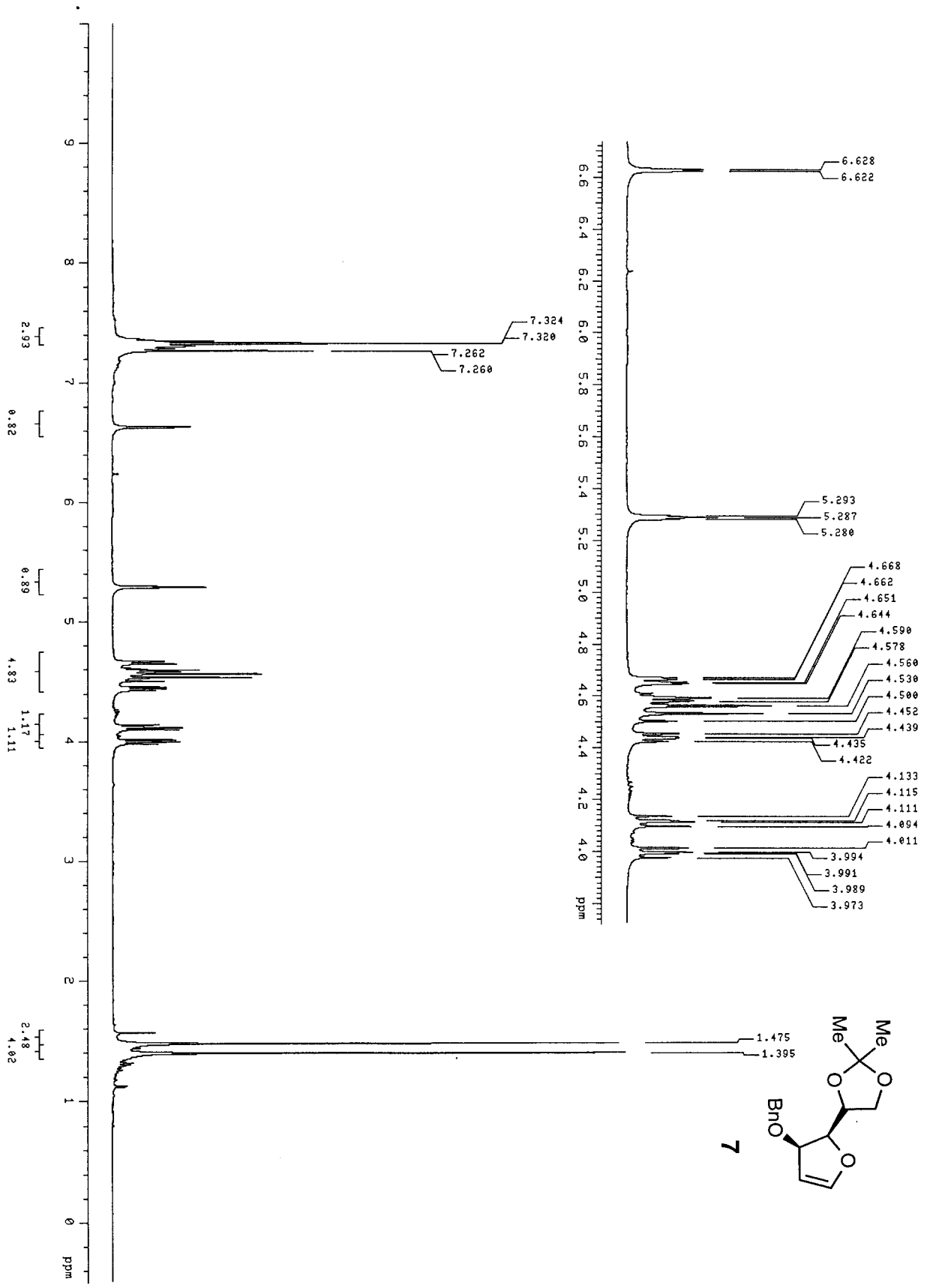
6

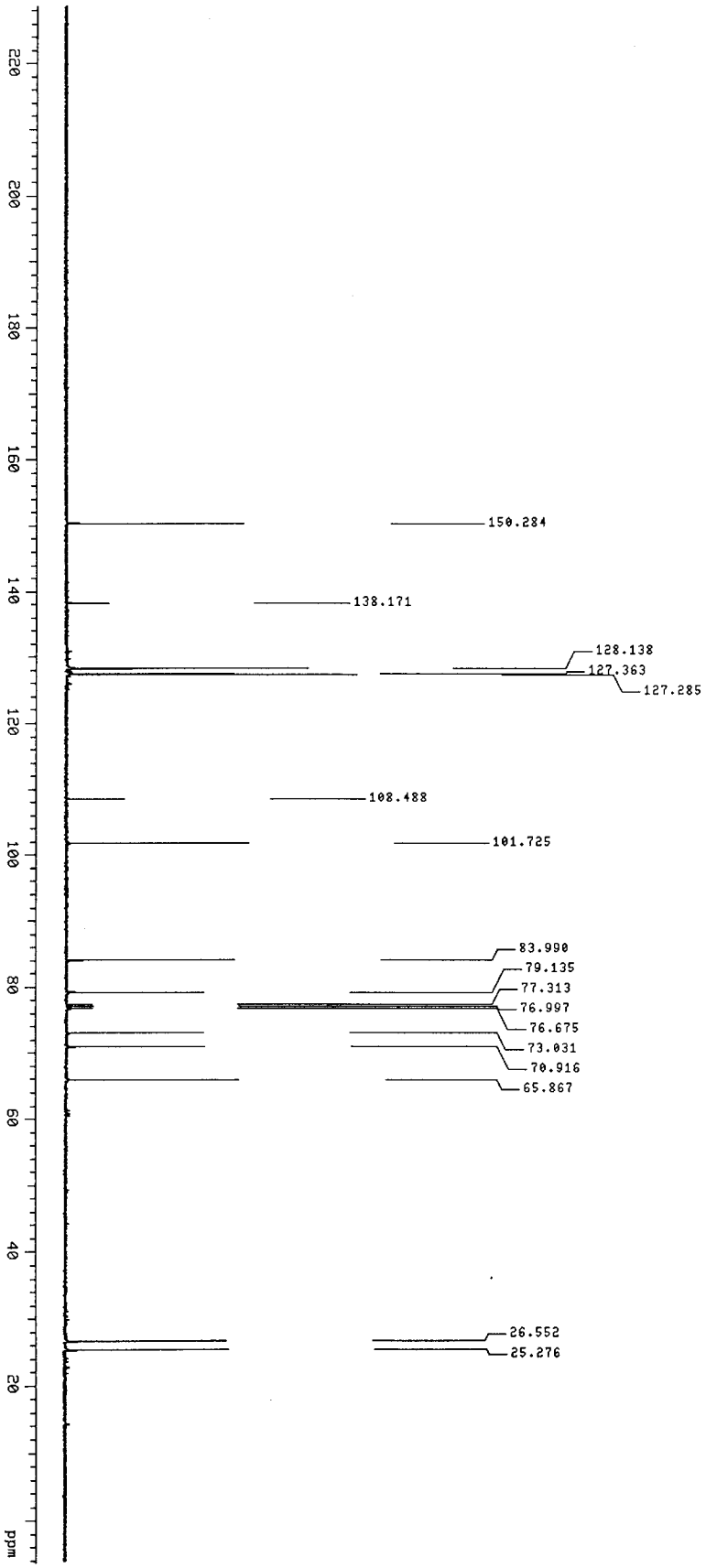

10
Me
Me
Me
Me
O
O
O
O
Cl
7.260
6.071
4.967
4.953
4.899
4.889
4.884
4.875
4.450
4.446
4.441
4.435
4.430
4.425
4.415
4.222
4.213
4.203
4.194
4.122
4.107
4.100
4.085
4.040
4.029
4.018
4.007
1.470
1.467
1.386
1.334
1.25
1.47
1.49
1.41
1.46
3.25
10.29
10.05
ppm

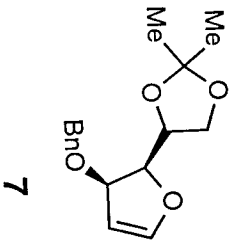

220
200
180
160
140
120
100
80
60
40
20
ppm
113.185
109.420
97.551
89.110
82.326
78.496
77.313
76.997
76.682
72.293
66.720
27.011
25.907
25.240
24.724


Me
Me
O
O
Me
Me
O
O
O
Cl

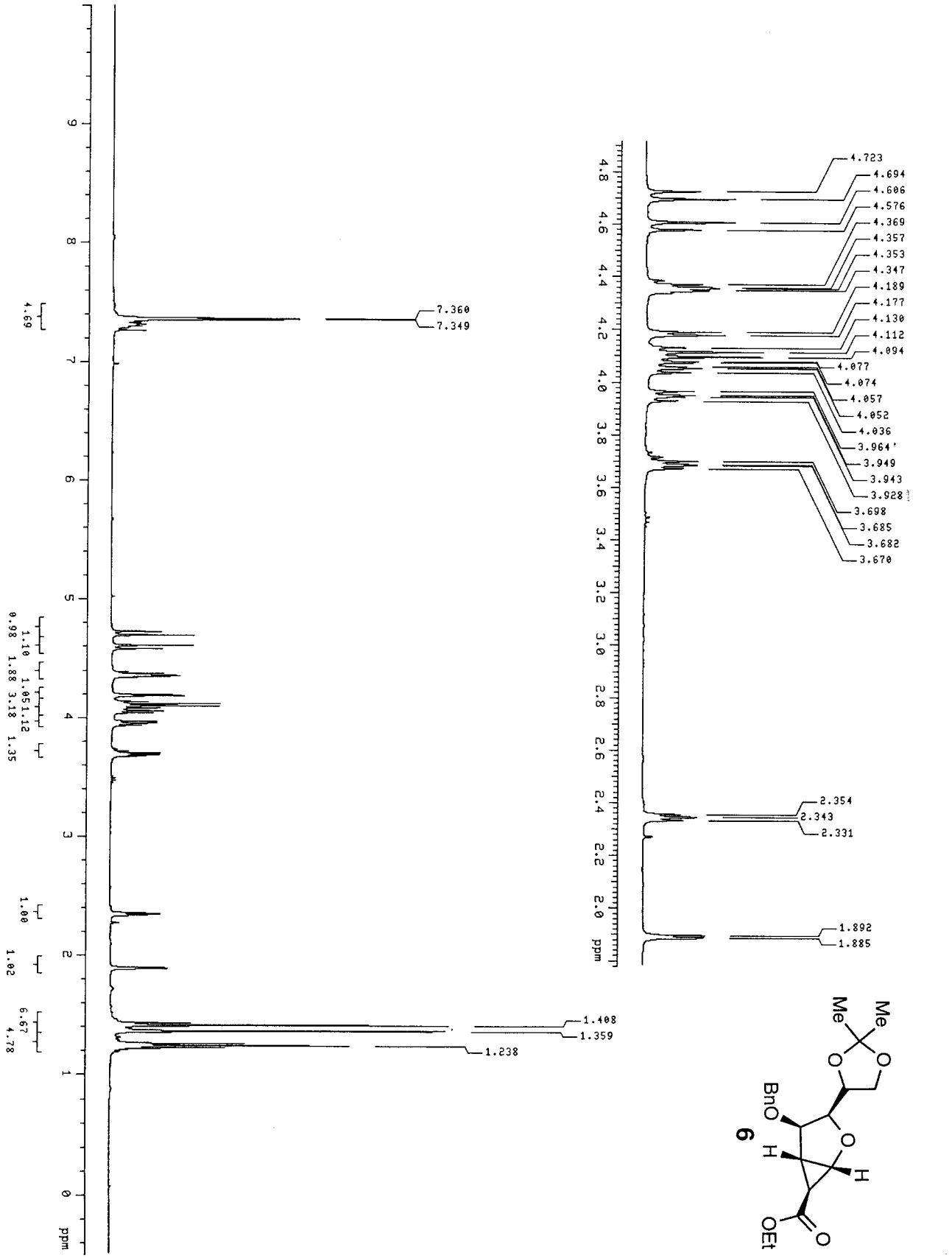
10

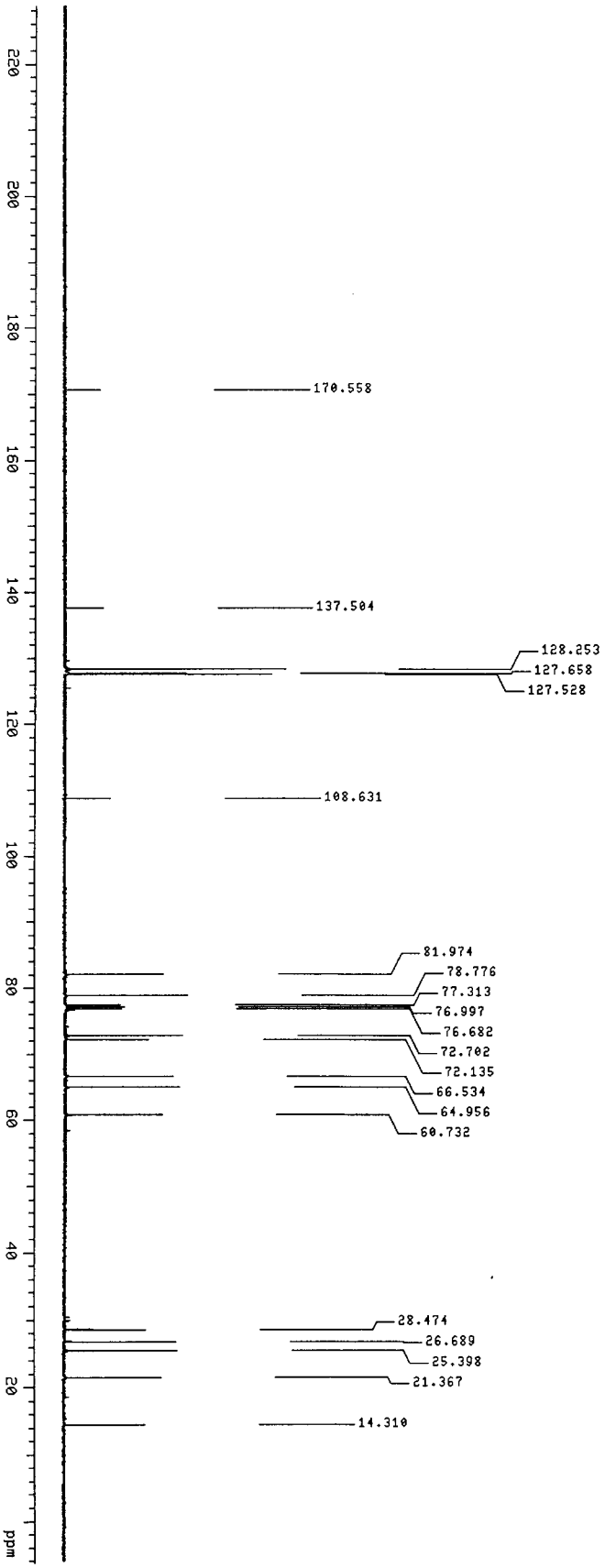

7.324
7.320
7.262
7.260
6.628
6.622
5.293
5.287
5.280
4.668
4.662
4.651
4.644
4.590
4.578
4.560
4.530
4.500
4.452
4.439
4.435
4.422
4.133
4.115
4.111
4.094
4.011
3.994
3.991
3.989
3.973
1.475
1.395
2.93
0.82
0.89
4.83
1.17
1.11
2.48
4.02
ppm
Me
Me
O
O
O
BnO
7

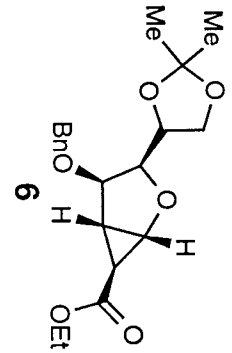

220
200
180
160
140
120
100
80
60
40
20
ppm
150.284
138.171
128.138
127.363
127.285
108.488
101.725
83.990
79.135
77.313
76.997
76.675
73.031
70.916
65.867
26.552
25.276

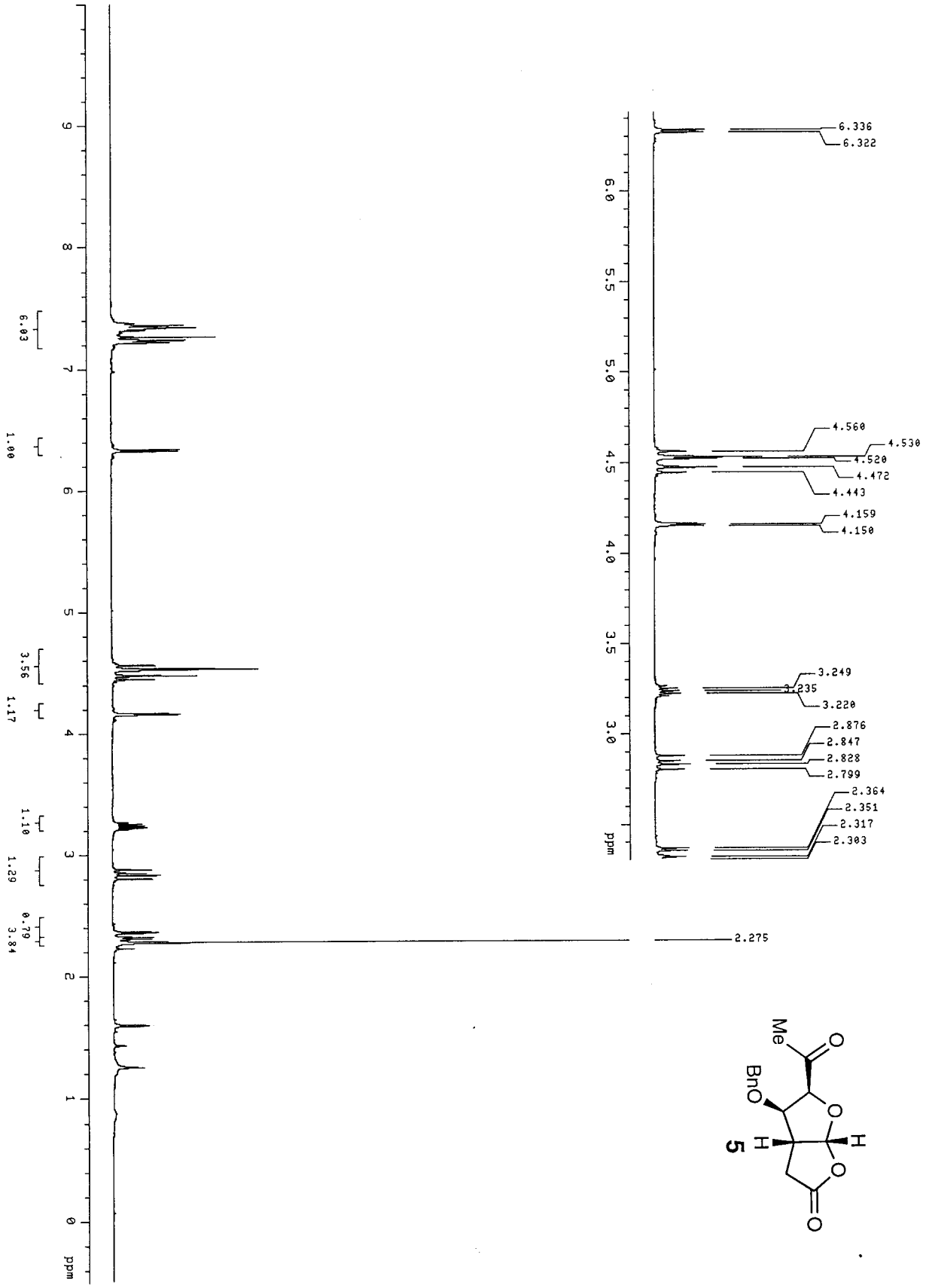

Me
Me
O
O
BnO
O

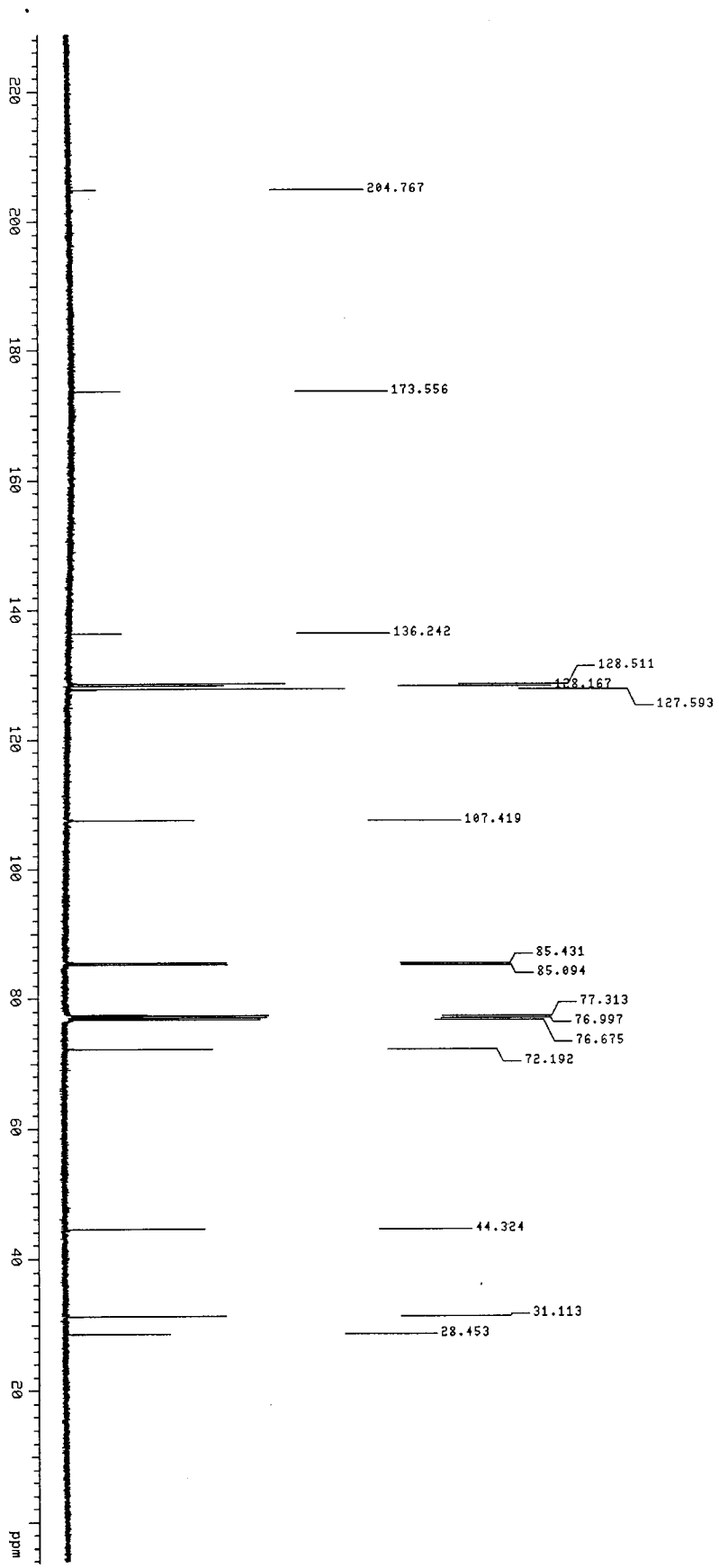
7

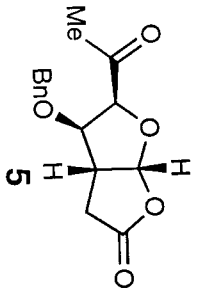

4.723
4.694
4.606
4.576
4.369
4.357
4.353
4.347
4.189
4.177
4.130
4.112
4.094
4.077
4.074
4.057
4.052
4.036
3.964
3.949
3.943
3.928
3.698
3.685
3.682
3.670
2.354
2.343
2.331
1.892
1.885
7.360
7.349
1.408
1.359
1.238
4.69
1.10
1.85
1.12
0.98
1.88
3.18
1.35
1.00
1.02
6.67
4.78
ppm
Me
Me
O
O
BnO
O
H
H
6
OEt
O

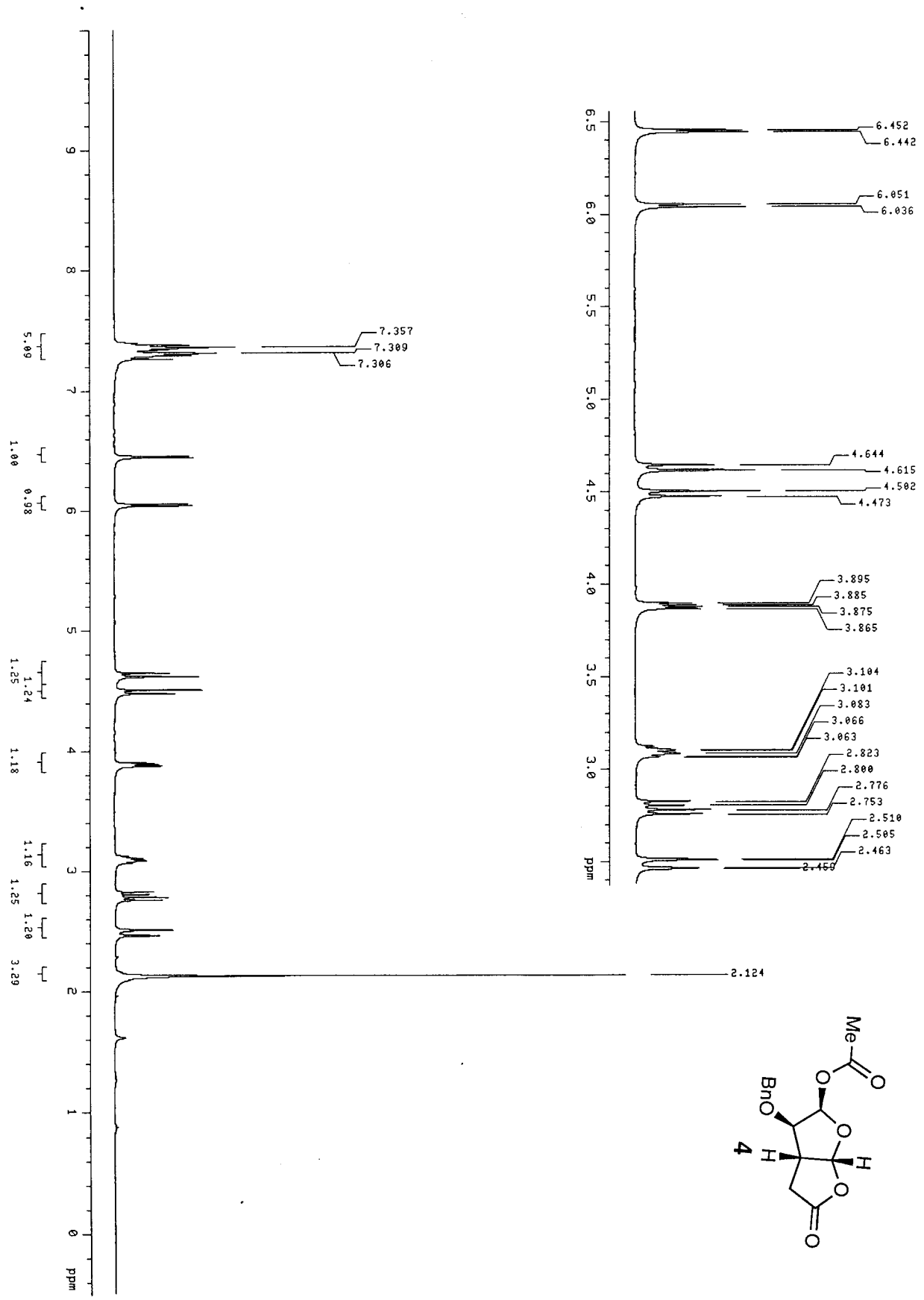

220
200
180
160
140
120
100
80
60
40
20
ppm
170.558
137.504
128.253
127.658
127.528
108.631
81.974
78.776
77.313
76.997
76.682
72.702
72.135
66.534
64.956
60.732
28.474
26.689
25.398
21.367
14.310

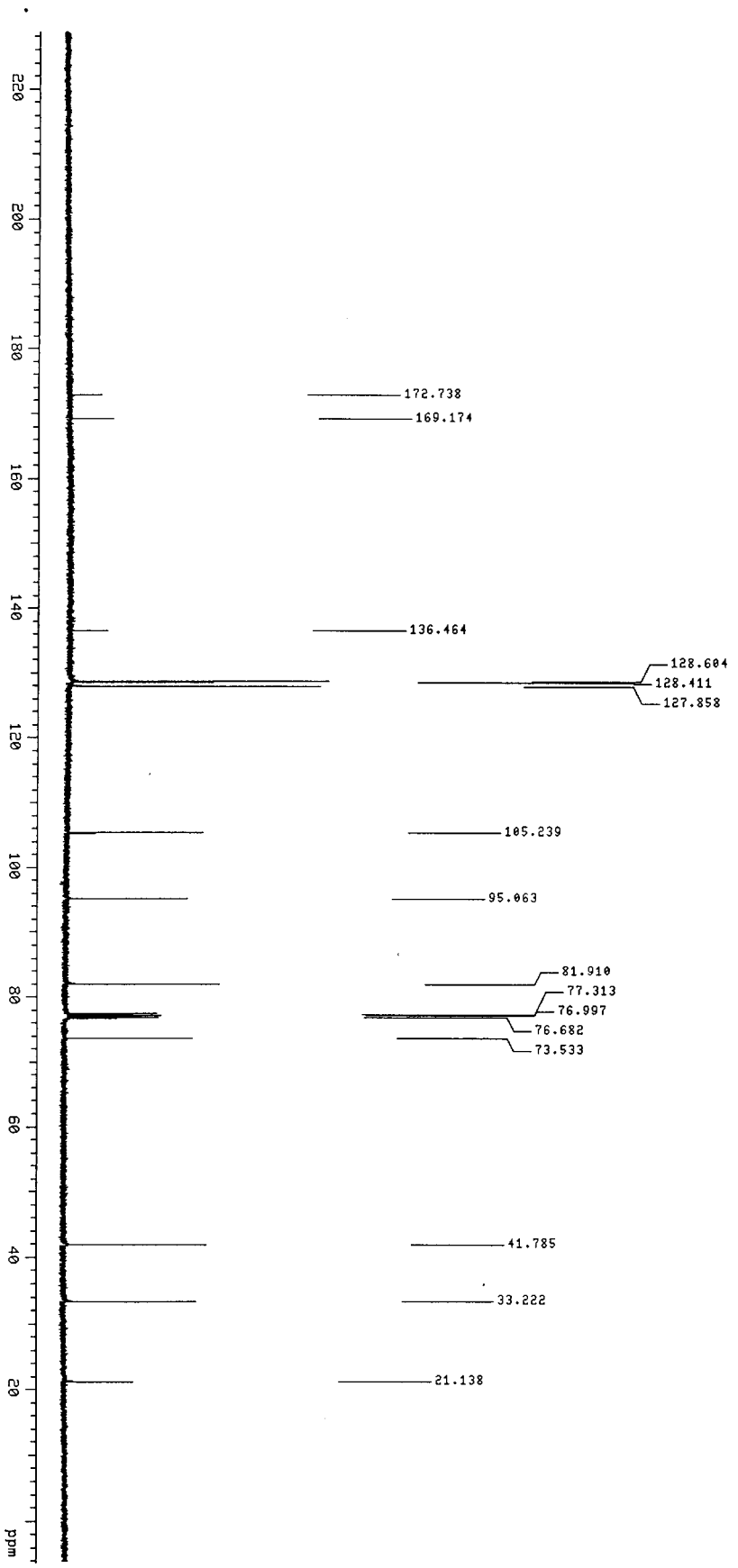

Me
Me
O
O
BnO
O
H
H
6
O
OEt

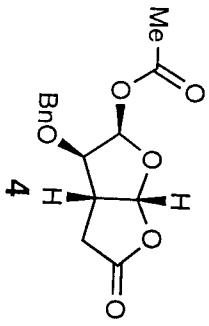

6.336
6.322
4.560
4.530
4.520
4.472
4.443
4.159
4.150
3.249
3.235
3.220
2.876
2.847
2.828
2.799
2.364
2.351
2.317
2.303
2.275
6.03
1.00
3.56
1.17
1.10
1.29
0.79
3.84
ppm
Me
BnO
H
H
O
O
O
O
5

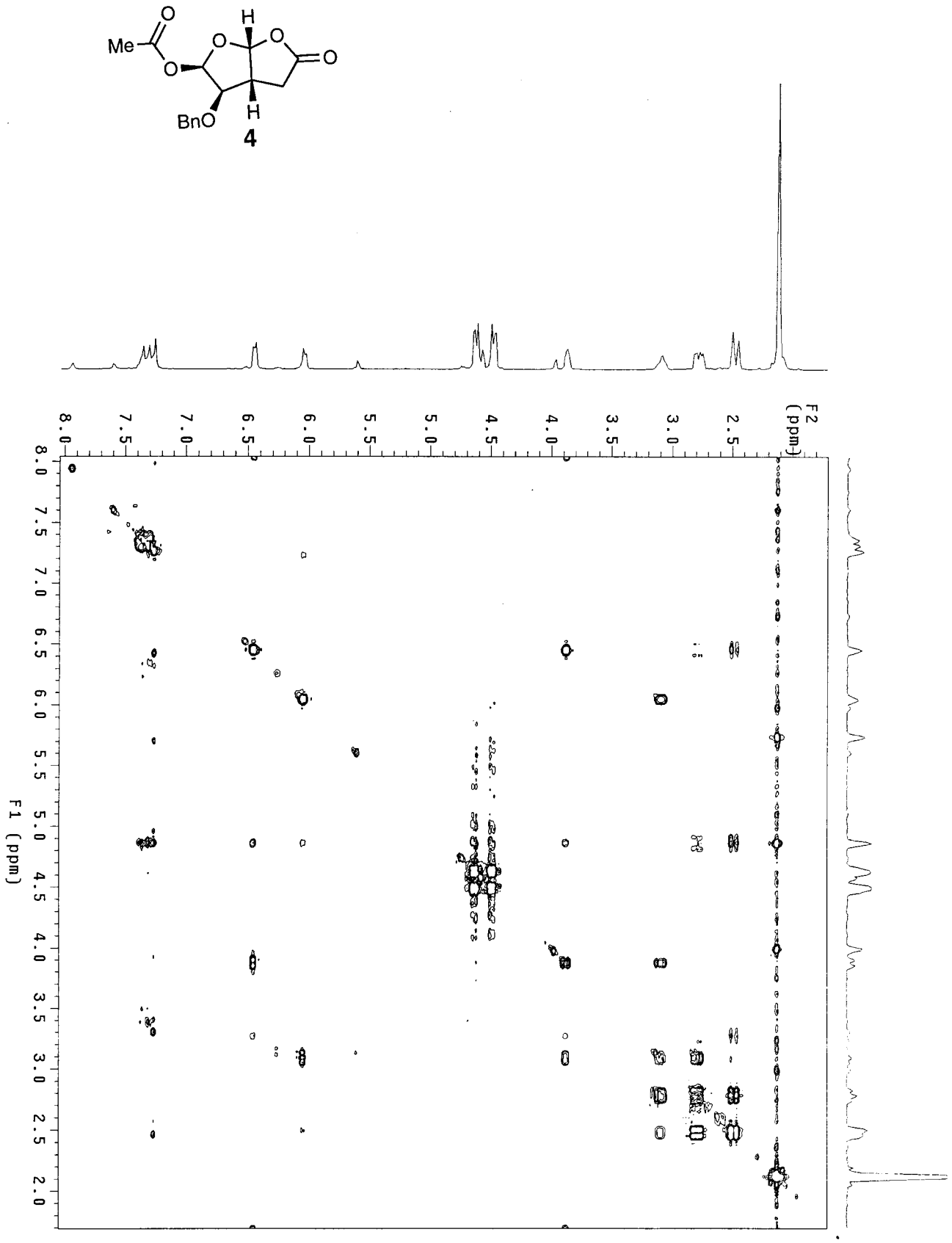

204.767
173.556
136.242
128.511
128.167
127.593
107.419
85.431
85.094
77.313
76.997
76.675
72.192
44.324
31.113
28.453
220
200
180
160
140
120
100
80
60
40
20
ppm

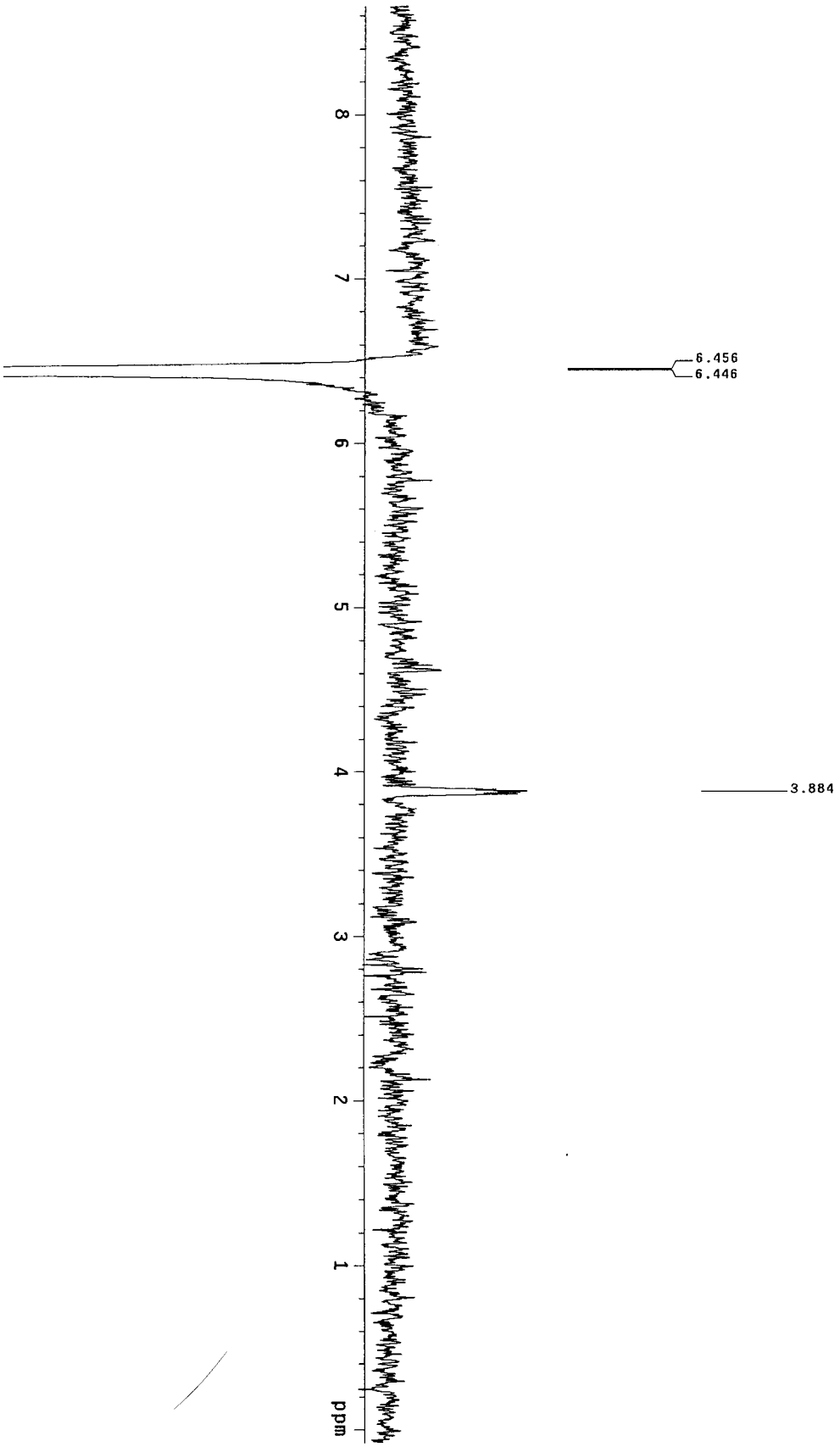

Me
O
BnO
O
H
H
O
O
5

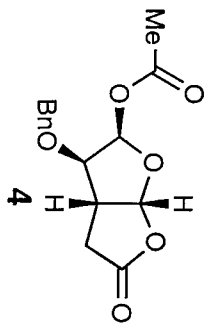

7.357
7.309
7.306
2.124
6.452
6.442
6.051
6.036
4.644
4.615
4.502
4.473
3.895
3.885
3.875
3.865
3.104
3.101
3.083
3.066
3.063
2.823
2.800
2.776
2.753
2.510
2.505
2.463
2.459
5.09
1.00
0.98
1.25
1.24
1.18
1.16
1.25
1.20
3.29
ppm
Me
O
BnO
H
4

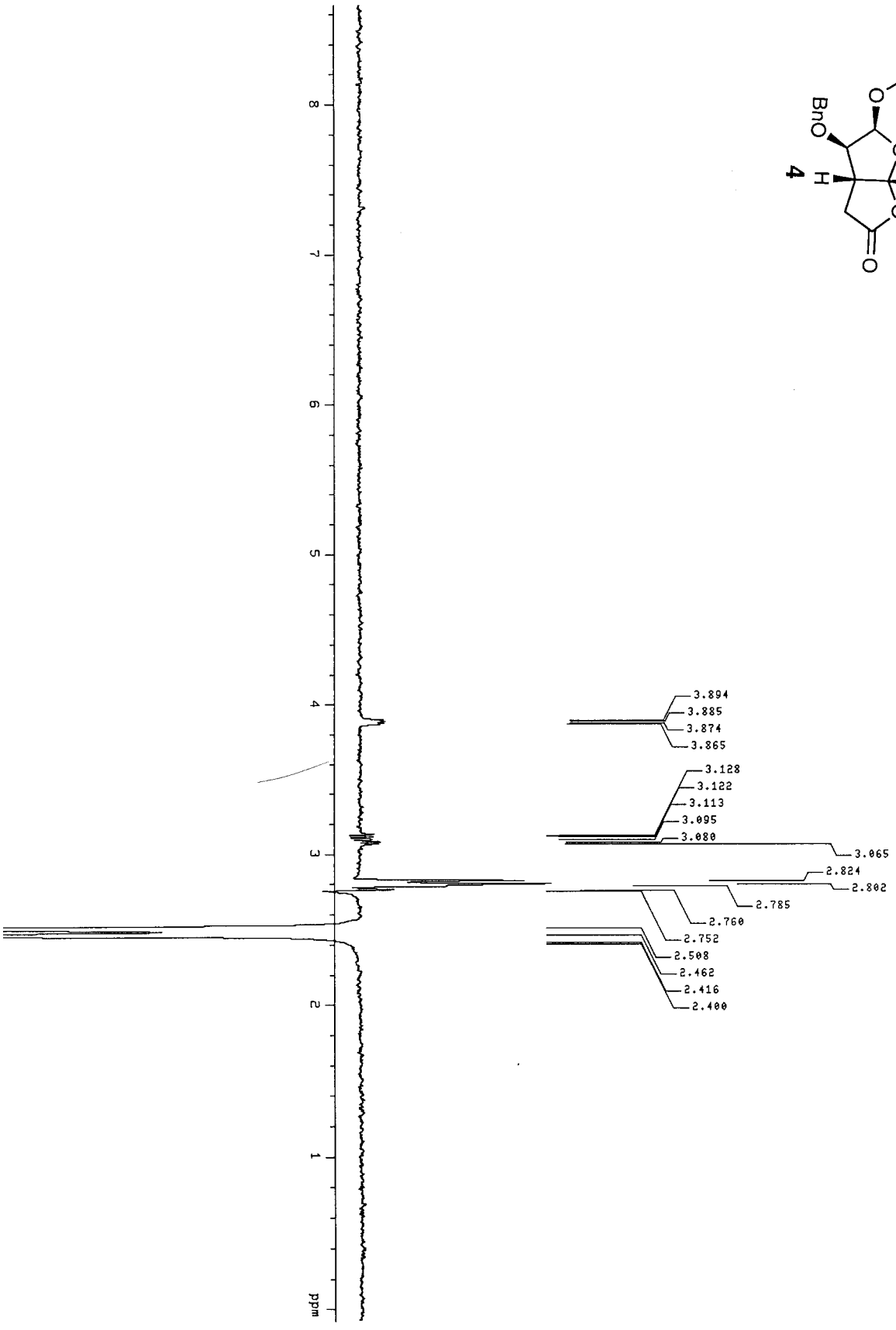

220
200
180
160
140
120
100
80
60
40
20
ppm
172.738
169.174
136.464
128.604
128.411
127.858
105.239
95.063
81.910
77.313
76.997
76.682
73.533
41.785
33.222
21.138


Me
O
O
BnO
O
H
4
H
O
O


Me
O
O
H
O
O
O
BnO
H
4
F2 (ppm)
F1 (ppm)


6.456
6.446
3.884
8
7
6
5
4
3
2
1
ppm


Me
O
O
BnO
O
H
4
H
O
O


Me
O
O
BnO
H
4
O
H
O
O
3.894
3.885
3.874
3.865
3.128
3.122
3.113
3.095
3.080
3.065
2.824
2.802
2.785
2.760
2.752
2.508
2.462
2.416
2.400
8
7
6
5
4
3
2
1
ppm