A Second-Chance Rearrangement Route to Novel 5(6)-*syn,anti*-Difunctional 2-Azabicyclo[2.1.1]hexanes.

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Supporting Information Available:

All experimental procedures, spectroscopic data, as well as copies of ^{1}H NMR and ^{13}C NMR for compounds **10a-g**.

Experimental Section

General Procedures. Thin layer chromatography was performed on precoated plates of silica gel GF 250 microns (Analtec, Inc.). Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh) purchased from Aldrich Chemical Co. *N*-(benzyloxycarbonyl)-6-*exo*-bromo-5-*endo*-hydroxy-2-azabicyclo[2.2.0]hexane (**7a**), *N*-(benzyloxycarbonyl)-5-*endo*-hydroxy-6-*exo*-iodo-2-azabicyclo[2.2.0]-hexane (**7b**), and *N*-(benzyloxycarbonyl)-5-*endo*-fluoro-6-*exo*-iodo-2-azabicyclo[2.2.0]hexane (**7c**) have been prepared previously.[6] Reagent chemicals were obtained from commercial suppliers and chemical grade solvents were used without further purification. ^{1}H NMR spectra were recorded at 300 or 400 MHz and ^{13}C NMR spectra were recorded at 75 or 100 MHz in $CDCl_3$, unless otherwise noted. The NMR spectra are often complicated by the presence of carbamate rotamers and pairs of ^{13}C NMR lines due to a single carbon, identified using proton-carbon correlation experiments, have been presented as pairs. Chemical shifts are expressed in parts per million related to internal TMS. High resolution mass spectra were performed at Drexel University. For purposes of nomenclature 5(6)-*syn* orientation on a 2-azabicyclo[2.1.1]hexane refers to the 5-substituent oriented toward the bridge containing the nitrogen atom.

General Procedure for reactions of 6-*exo*-bromides 7a and 6-*exo*-iodides 7b-c with silver halides and mercury halides. To a stirred solution of bromohydrin **7a** (100 mg, 0.32 mmol), iodohydrin **7b** (100 mg, 0.28 mmol), or iodofluoride **7c** (100 mg, 0.28 mmol) in $MeNO_2$ (10 mL) was added silver fluoride (2.5 eq), mercuric chloride (2.5 eq), or mercuric fluoride (2.5 eq). The solution was heated at 60 °C for 24 h unless otherwise noted. The mixture was diluted with brine (5 mL) and extracted with ether (4 x 15 mL). The ether extract was washed with H_2O, brine, dried over $MgSO_4$, evaporated under reduced pressure and chromatographed to give products **10a**, **10c-e**, and **10g**. For reactions with silver acetate, acetic acid (10 mL) was used as solvent. Acetic acid either was removed *in vacuo* prior to workup and chromatography to give product **10b** or the reaction was worked up as with nitromethane to give **10f**.

***N*-(Benzyloxycarbonyl)-5-*anti*-fluoro-6-*syn*-hydroxy-2-azabicyclo[2.1.1]hexane (10a).** (a) From *N*-(benzyloxycarbonyl)-6-*exo*-bromo-5-*endo*-hydroxyl-2-azabicyclo[2.2.0]hexane (**7a**) (100.0 mg, 0.32

mmol) in $MeNO_2$ (10 mL) and silver fluoride (101.6 mg, 0.80 mmol) at 85°C after 24h was obtained 18 mg (22%) of fluorohydrin **10a**, R_f = 0.29 (1:3 hexane/ether); H^1 NMR (400 Hz) δ 7.28 (s, 5H), 5.07 (s, 2H), 4.59 (br, 1H), 4.55 (d, J = 59.1 Hz, 1H), 4.39 (d, J = 6.80 Hz, 1H), 3.50 (d, J = 9.0 Hz, 1H), 3.24 (d, J = 9.0 Hz, 1H), 2.88 (b, 1H), 2.88~2.50 (b, 1H); ^{13}C NMR (100 Hz) δ 157.5, 136.8, 129.0, 128.6, 128.3, 91.0 (J= 212.0 Hz), 69.3, 67.6, 65.5, 48.2, 43.9; HRMS *m/z* 274.0853, calcd. for $C_{13}H_{14}NO_3FNa$ (M+Na) 274.0855. (b) From *N*-(benzyloxycarbonyl)-5-*endo*-hydroxy-6-*exo*-iodo-2-azabicyclo[2.2.0]hexane (**7b**) (180 mg, 0.50 mmol) in $MeNO_2$ (10 mL) and silver fluoride (159 mg, 1.25 mmol) at 60°C after 24 h was obtained 73 mg (58%) of fluorohydrin **10a**. (c) From iodohydrin **7b** (100 mg, 0.28 mmol) in $MeNO_2$ (10 mL) and mercury difluoride (167 mg, 0.70 mmol) at 60°C after 24 h was obtained 46 mg (65%) of fluorohydrin **10a**.

***N*-(Benzyloxycarbonyl)-5-*anti*-acetoxy-6-*syn*-hydroxy-2-azabicyclo[2.1.1]hexane (10b).** From *N*-(benzyloxycarbonyl)-5-*endo*-hydroxy-6-*exo*-iodo-2-azabicyclo[2.2.0]hexane (**7b**) (100 mg, 0.28 mmol) and AgOAc (116 mg, 0.70 mmol) in HOAc (10 mL) at 60-65 °C after 36 h was obtained 46mg (60%) of acetoxyalcohol **10b**, R_f = 0.25 (3:1 ether/hexane); ^{1}HNMR (300MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.16 (s, 2H), 4.53 (br, 1H), 4.47 (arm of d, 0.5H), 4.45 (s, 1.5H), 3.57 (d, J = 9.0 Hz, 1H), 3.42 (d, J = 9.0 Hz, 1H), 2.92 (m, $J_{1,4}$ = 6.9 Hz, by irradiation at δ 4.53, 1H), 2.50~2.30 (b, 1H), 2.08 (s, 3H); ^{13}CNMR (100MHz, $CDCl_3$) δ 170.9, 157.5, 136.9, 128.9, 128.5, 128.3, 73.6, 69.2, 67.5, 65.5, 47.5, 44.5, 30.7; HRMS *m/z* 314.1004, calcd for $C_{15}H_{17}NO_5Na$ (M+Na) 314.1004.

***N*-(Benzyloxycarbonyl)-5-*anti*-chloro-6-*syn*-hydroxy-2-azabicyclo[2.1.1]hexane (10c).** From *N*-(benzyloxycarbonyl)-5-*endo*-hydroxy-6-*exo*-iodo-2-azabicyclo[2.2.0]hexane (**7b**) (100 mg, 0.28 mmol) and mercury chloride (190 mg, 0.70 mmol) in $MeNO_2$ (10 mL) at 60°C after 24 h was obtained 56 mg (74%) of chloroalcohol **10c**, R_f = 0.17 (1:1 hexane/ether); ^{1}HNMR (400MHz, $CDCl_3$) δ 7.27 (m, 5H), 5.08 (s, 2H), 4.70 (b, 1H), 4.38 (dd, J = 6.8, 1.6 Hz, 1H), 3.59 (s, 1H), 3.50 (d, J = 8.9 Hz, 1H), 3.10 (d, J = 8.9 Hz, 1H), 2.86 (b, 1H); ^{13}CNMR (100MHz, $CDCl_3$) δ 158.2, 135.1, 127.5, 127.2, 127.0, 70.0, 67.7, 67.6, 55.0, 50.3, 45.6; HRMS *m/z* 290.0558, calcd for $C_{13}H_{14}NO_3{}^{35}ClNa$ (M+Na) 290.0559.

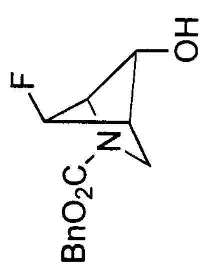
***N*-(Benzyloxycarbonyl)-5-*anti*-6-*syn*-difluoro-2-azabicyclo[2.1.1]hexane (10d).** (a) From *N*-(benzyloxycarbonyl)-5-*endo*-fluoro-6-*exo*-iodo-2-azabicyclo[2.2.0]hexane (**7c**) (100 mg, 0.28 mmol) and silver fluoride (89.0 mg, 0.70 mmol) in $MeNO_2$ (10 mL) at 60°C after 24 h was obtained 47 mg (67%) of difluoride **10d**, R_f = 0.61 (1:1 hexane/ether); ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.21~5.07 (br, 3H,), 4.75~4.53 (br, 2H), 3.54 (br,1H), 3.33 (br,1H), 3.11 (br,1H); ^{1}HNMR (400 MHz, DMSO-$d_{6,}$ 70 °C) 7.40 (s, 5H), 5.40 (d, *J* = 61.5Hz, 1H), 5.14(br, 2H), 4.95 (dd, *J* = 58.1, 22.8 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 3.43 (s, 2H), 3.1 (br, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 157.0, 136.7, 128.9, 128.6, 128.3, 89.5 (*J* = 210 Hz), 85.4 (*J* = 237 Hz), 67.8, (64.9, 64.69, 64.49, 64.19, 1C), 48.0, 43.6; HRMS *m/z* 276.0820, calcd for $C_{13}H_{13}NO_2$ F_2Na (M+Na) 276.0812. (b) From iodofluoride **7c** and mercury difluoride (167 mg, 0.70 mmol) at 60°C after 24h was obtained 38 mg (54%) of difluoride **10d**.

***N*-(Benzyloxycarbonyl)-5-*syn*-fluoro-6-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane (10e).** From *N*-(benzyloxycarbonyl)-5-*endo*-fluoro-6-*exo*-iodo-2-azabicyclo[2.2.0]hexane (**7c**) (100 mg, 0.28 mmol) and moist mercury difluoride (167.0 mg, 0.70 mmol) in $MeNO_2$ (10 mL) at 60°C after 24 h was obtained 46 mg (65%) of fluorohydrin **10e**, R_f = 0.36 (1:3 hexane/ether); ^{1}HNMR (400MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.14 (d, *J* = 67.2 Hz, 0.5H for one arm of the d), 5.07 (br, 2.5H), 4.38 (b, 1H), 3.87 (d, *J* = 23.1 Hz, 1H), 3.45 (d, *J* = 9.0 Hz, 1H), 3.25 (d, *J* = 9.0 Hz, 1H), 2.89 (br,1H), 2.83 and 2.47 (br, 1H, OH); ^{13}CNMR (100MHz, $CDCl_3$) δ 157.2, 136.9, 128.9, 128.5, 128.3, 86.5 (*J* = 233 Hz), 72.0, 71.8, 67.5, (66.0, 65.8, 65.5, 65.4, 1C), 48.5, 44.6; HRMS *m/z* 274.0847, calcd for $C_{13}H_{14}NO_3FNa$ (M + Na) 274.0855.

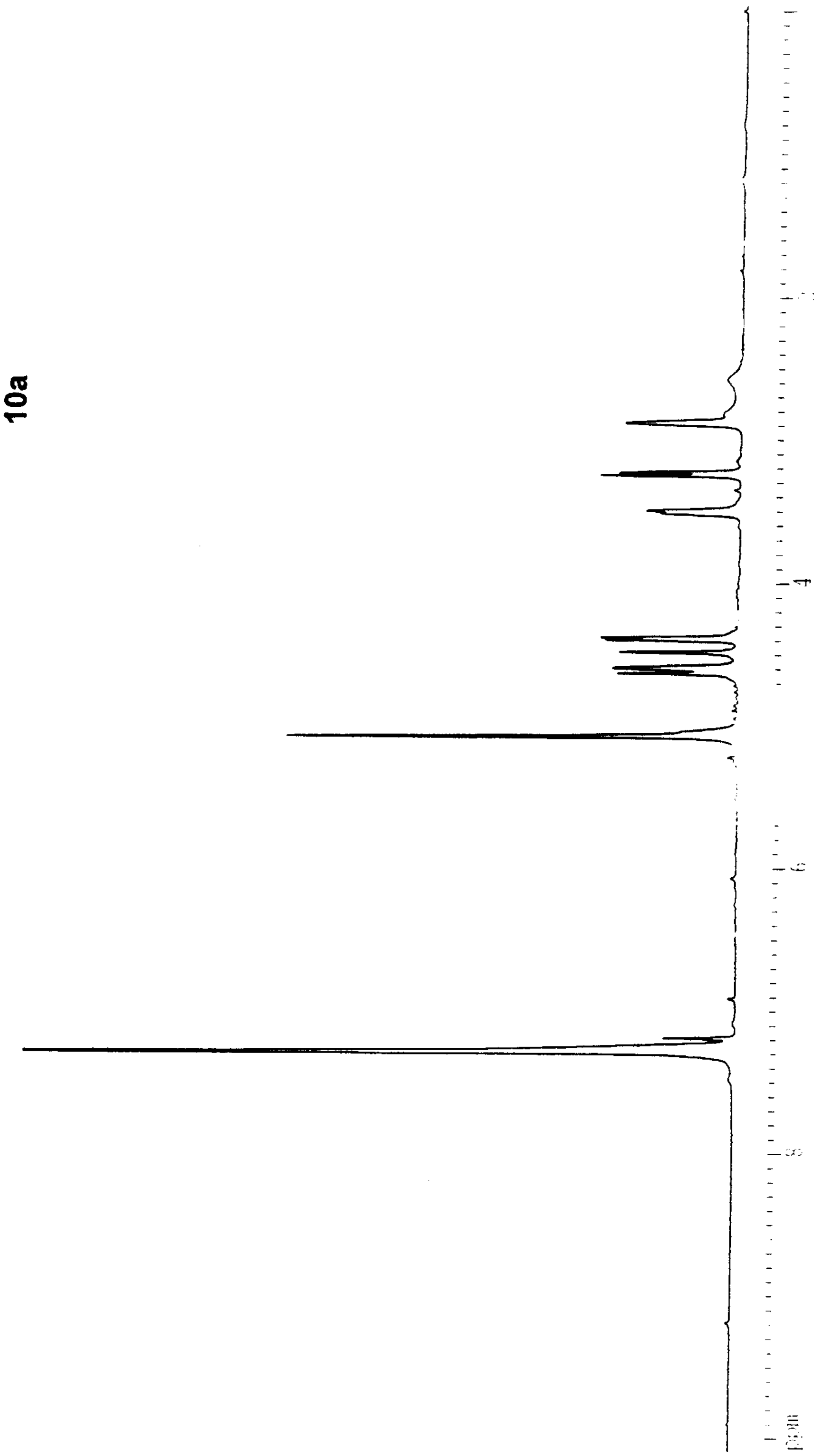
***N*-(Benzyloxycarbonyl)-6-*anti*-acetoxy-5-*syn*-fluoro-2-azabicyclo[2.1.1]hexane (10f).** From *N*-(benzyloxycarbonyl)-5-*endo*-fluoro-6-*exo*-iodo-2-azabicyclo[2.2.0]hexane (**7c**) (100 mg, 0.28 mmol) and mercuric diacetate (201 mg, 0.70mmol, moist) in HOAc (10 mL) at 60°C after 24 h was obtained 57 mg (73%) of acetoxyfluoride **10f**, R_f = 0.33 (1:1 hexane/ether); ^{1}HNMR (400MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.07 (br, 2.5H, arm of doublet), 4.92 (d, *J* = 67.2 Hz, 0.5H), 4.58 (br, 1H), 4.47 (d, *J* = 21.5 Hz, 1H), 3.54 (d, J= 8.8 Hz, 1H), 3.37 (d, *J* = 8.8 Hz, 1H), 3.04 (br, 1H), 1.99 (s, 3H); ^{13}CNMR (100MHz, $CDCl_3$) δ

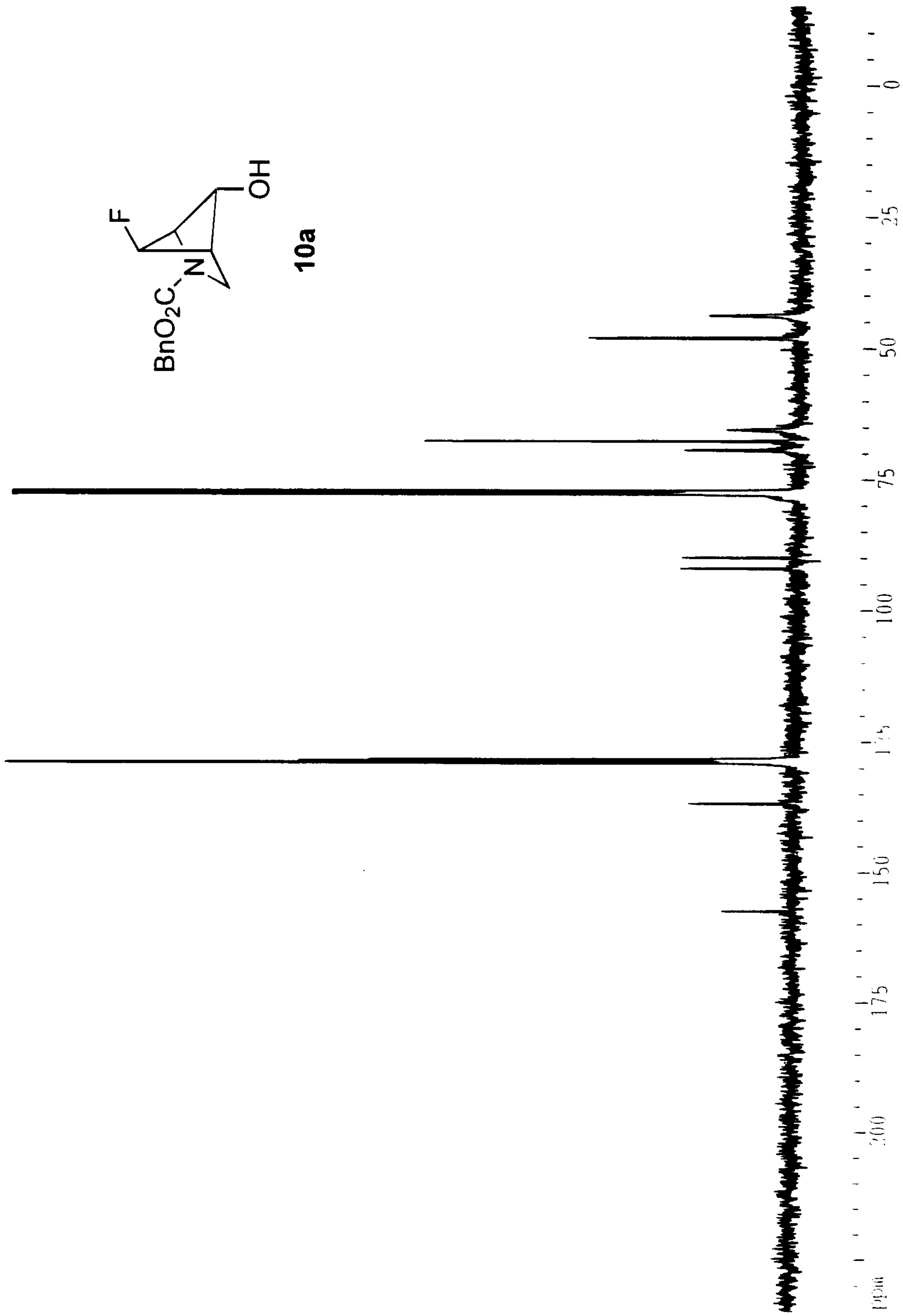
170.5, 157.2, 136.8, 128.9, 128.6, 128.3, 85.16 (J = 206.0 Hz), 72.3, 67.6, 63.3, 47.4, 44.4, 21.2; HRMS *m/z* 316.0962, calcd for $C_{15}H_{16}NO_4FNa$ (M+Na) 316.0961.

***N*-(Benzyloxycarbonyl)-6-*anti*-chloro-5-*syn*-fluoro-2-azabicyclo[2.1.1]hexane (10g).** From *N*-(benzyloxycarbonyl)-5-*endo*-fluoro-6-*exo*-iodo-2-azabicyclo[2.2.0]hexane (**7c**) (100 mg, 0.28 mmol) and mercury dichloride (190 mg, 0.70 mmol) in $MeNO_2$ (10 mL) at 60°C after 24h was obtained 48 mg (63%) of chlorofluoride **10g**, R_f = 0.17 (1:1 hexane/ether); ^{1}HNMR (400MHz, $CDCl_3$) δ 7.27 (m, 5H), 5.22 (d, J = 54.9 Hz, 1H), 5.09 (s, 1H), 3.65 and 3.55 (two d, J = 21.3 Hz, 1H), 3.50 (br, 1H), 3.37 (two d, apparent t, J = 8.8 Hz, 1H), 3.08 (br, 1H); ^{13}CNMR (100MHz, $CDCl_3$) δ 155.3, 135.8, 128.9, 128.6, 128.3, 84.4 (J = 234 Hz), 65.7, 63.5, 51.5, 48.6, 44.2 and 44.0; HRMS *m/z* 292.0509, calcd for $C_{13}H_{14}NO_2{}^{35}ClFNa$ (M+Na) 292.0517.



10a





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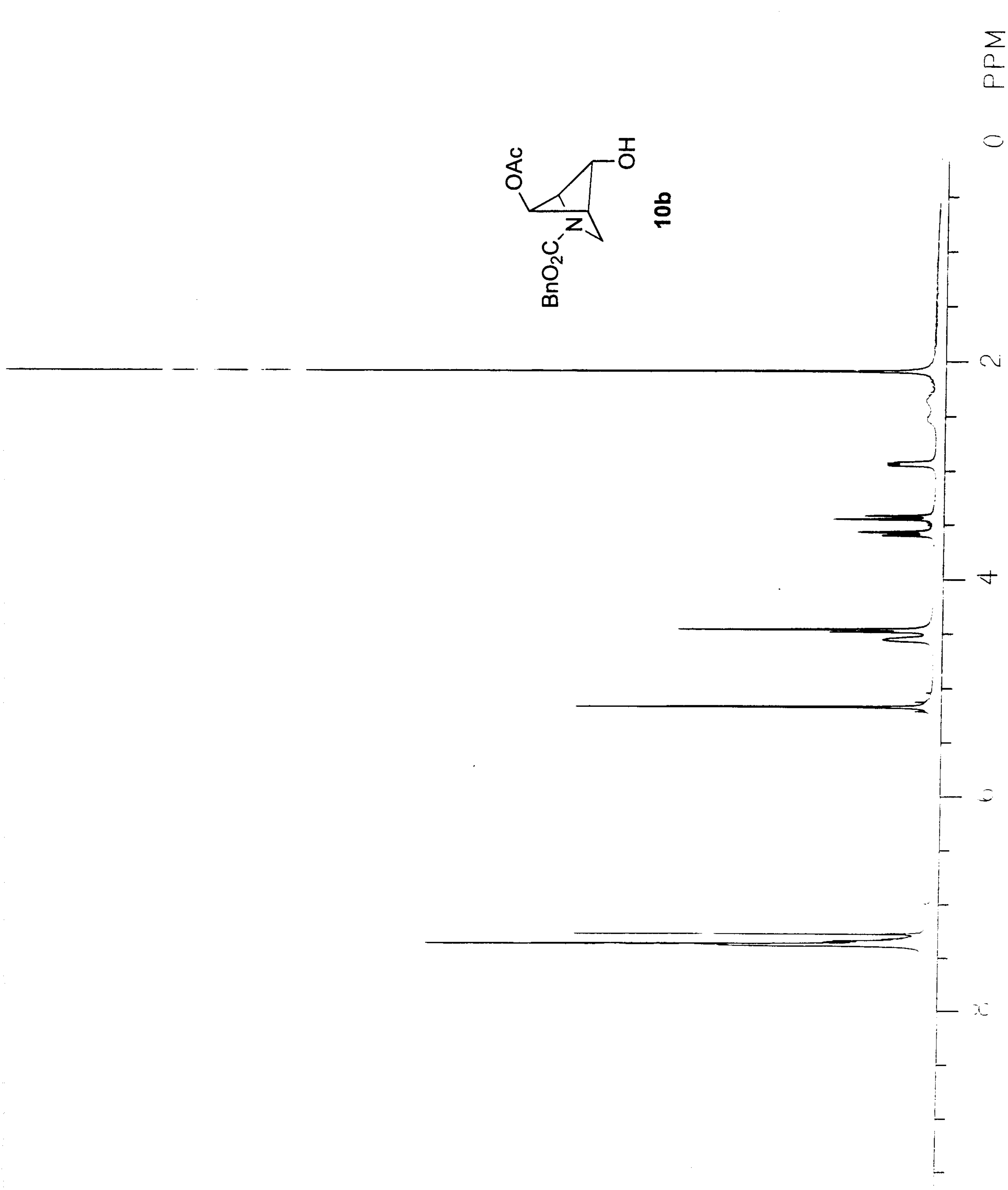
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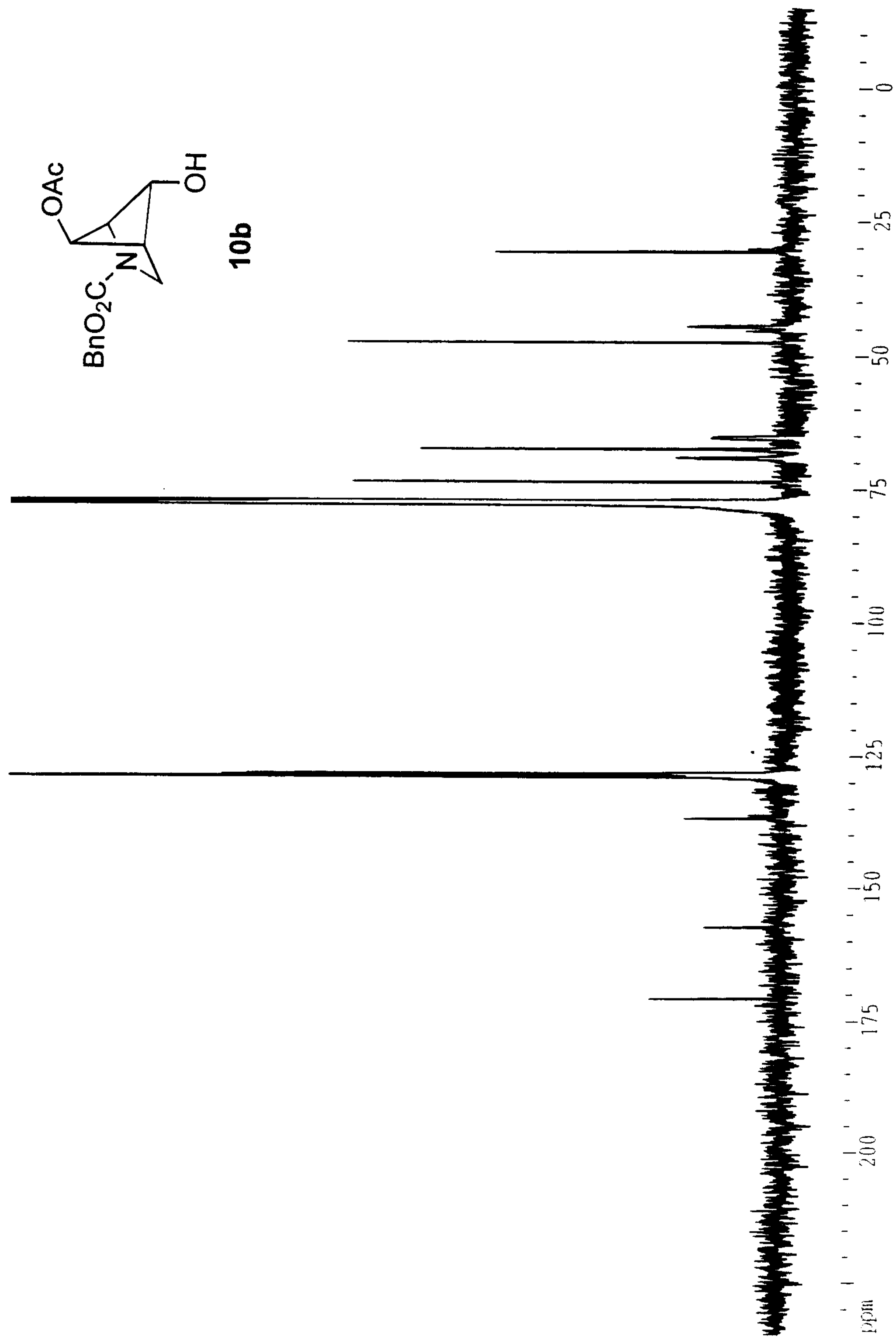

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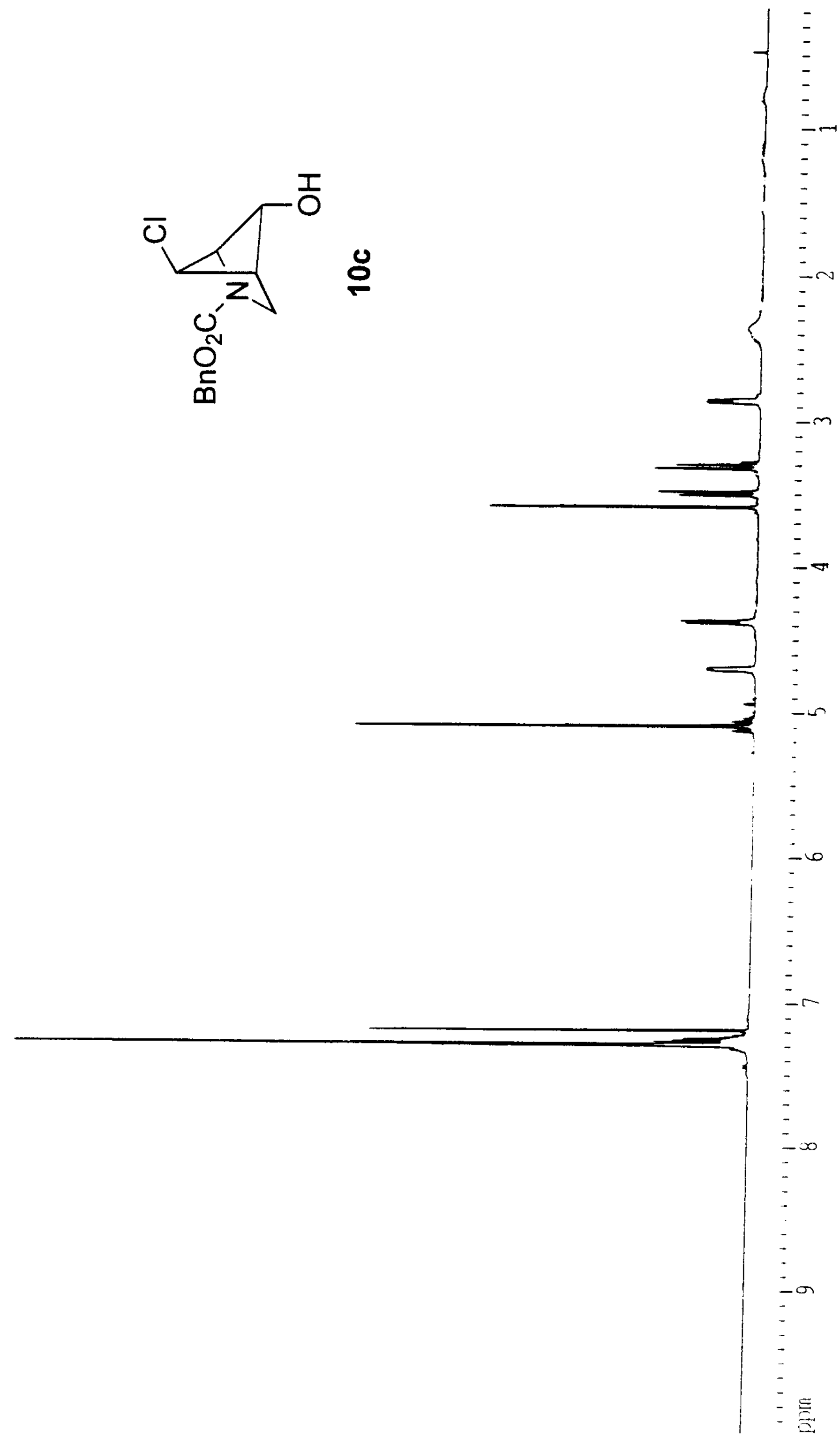
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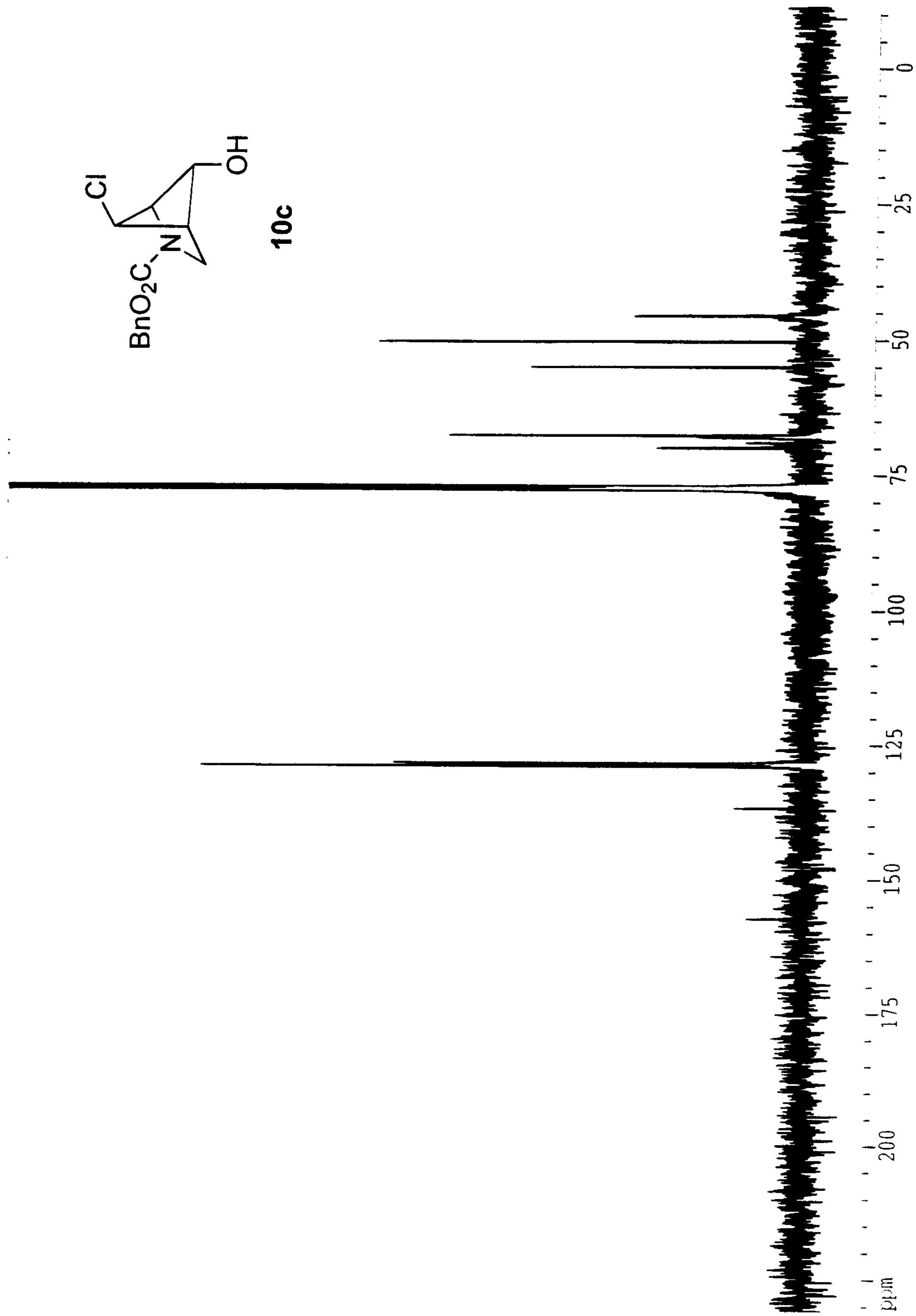
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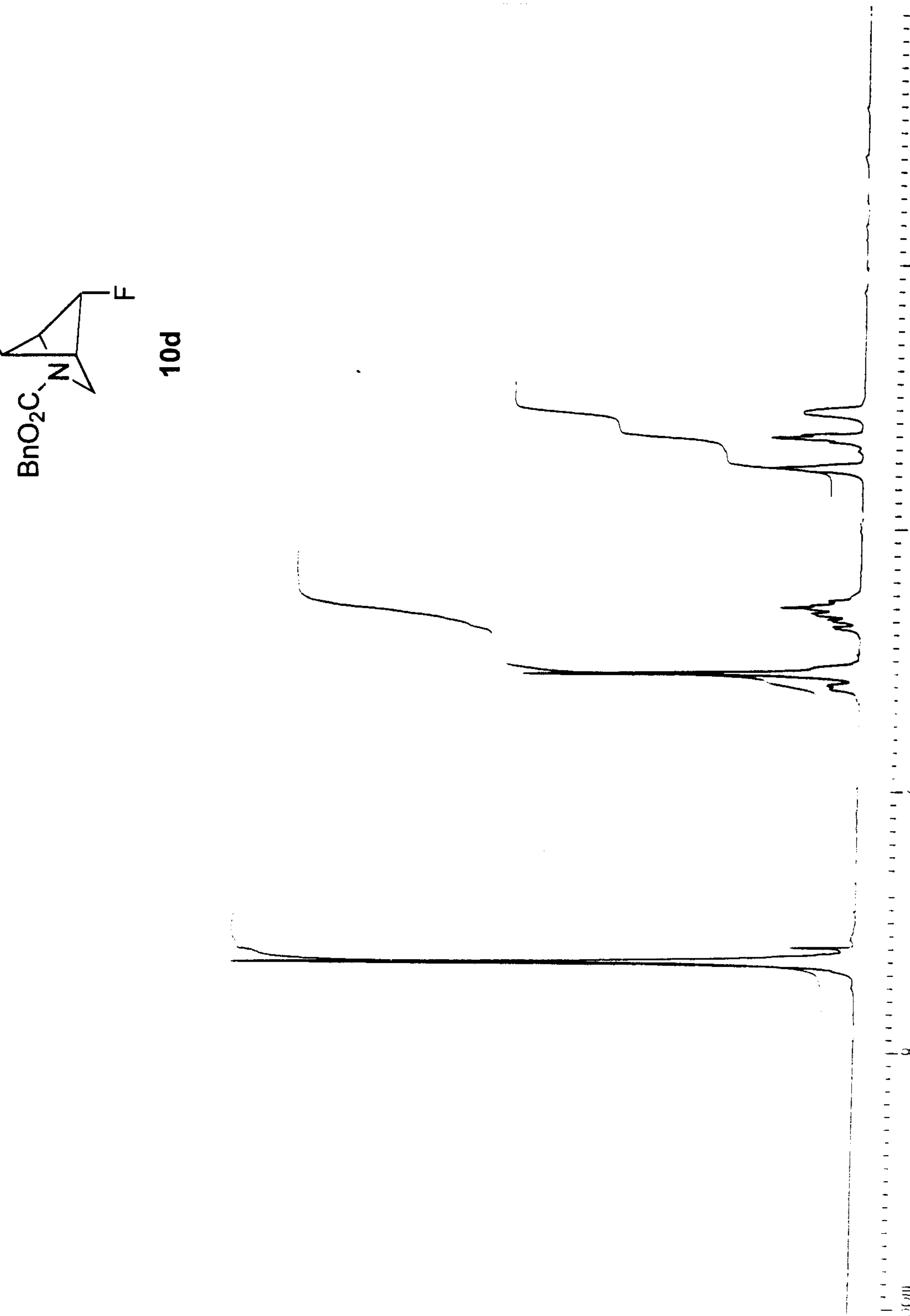
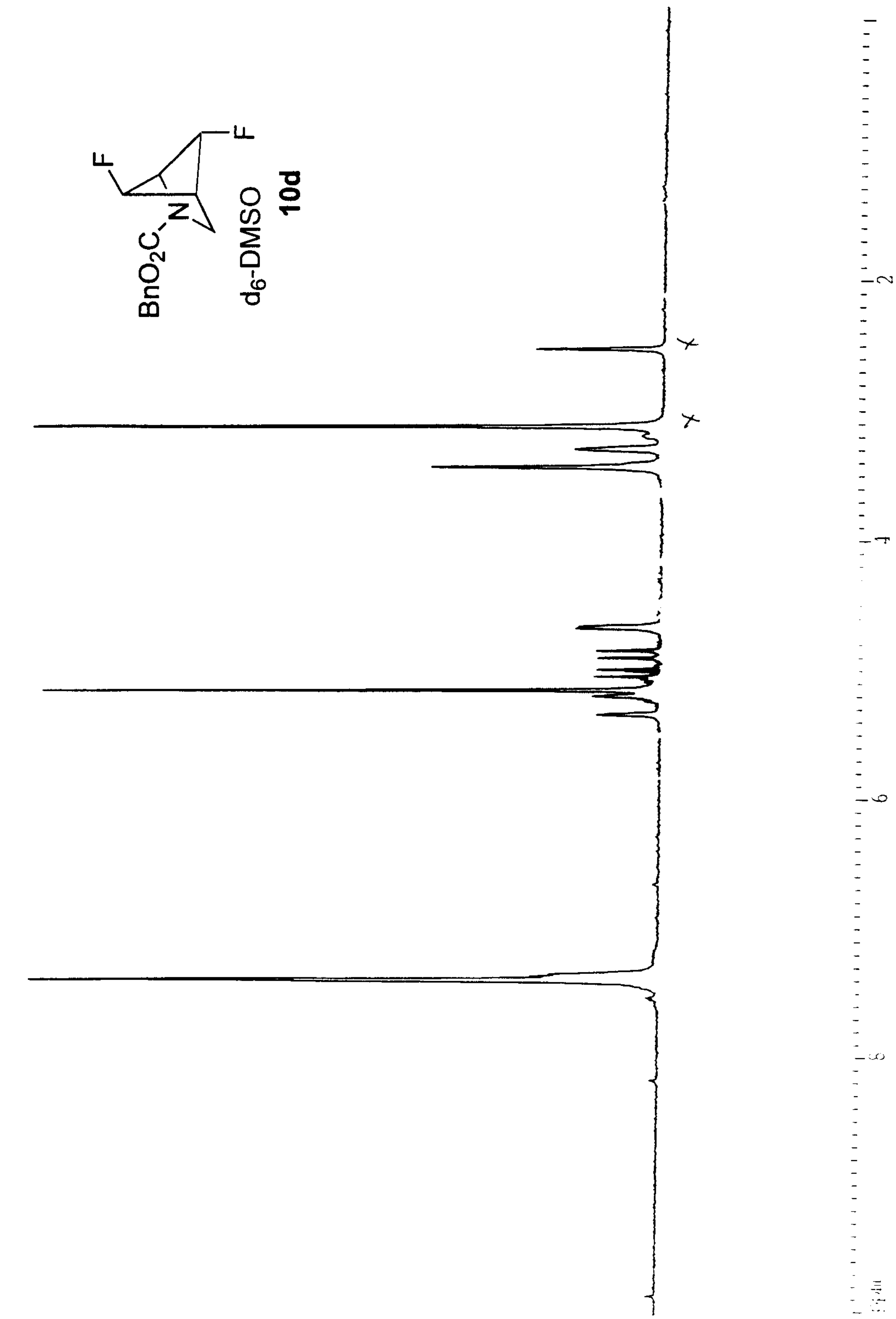


10d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F
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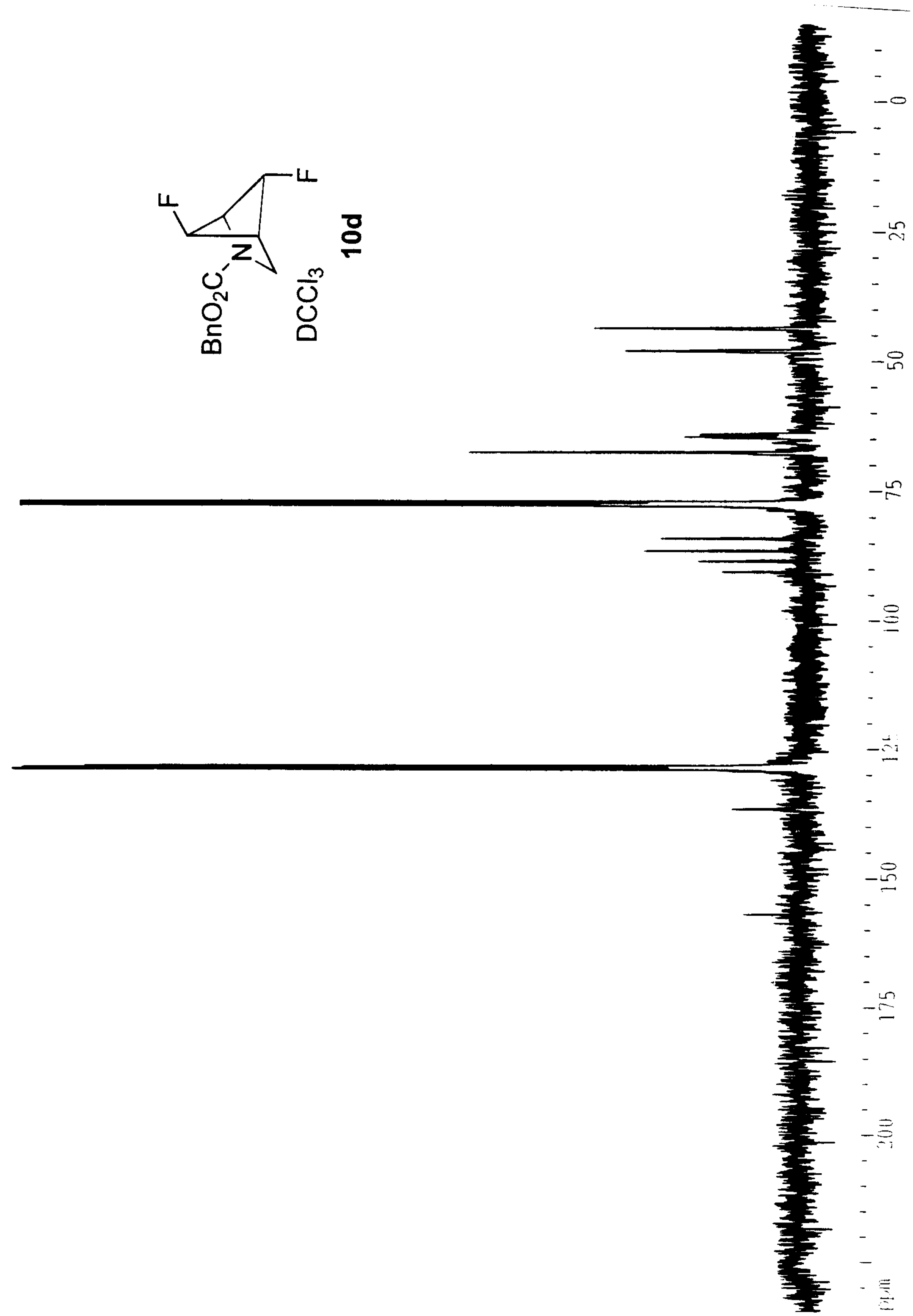
d6-DMSO
10d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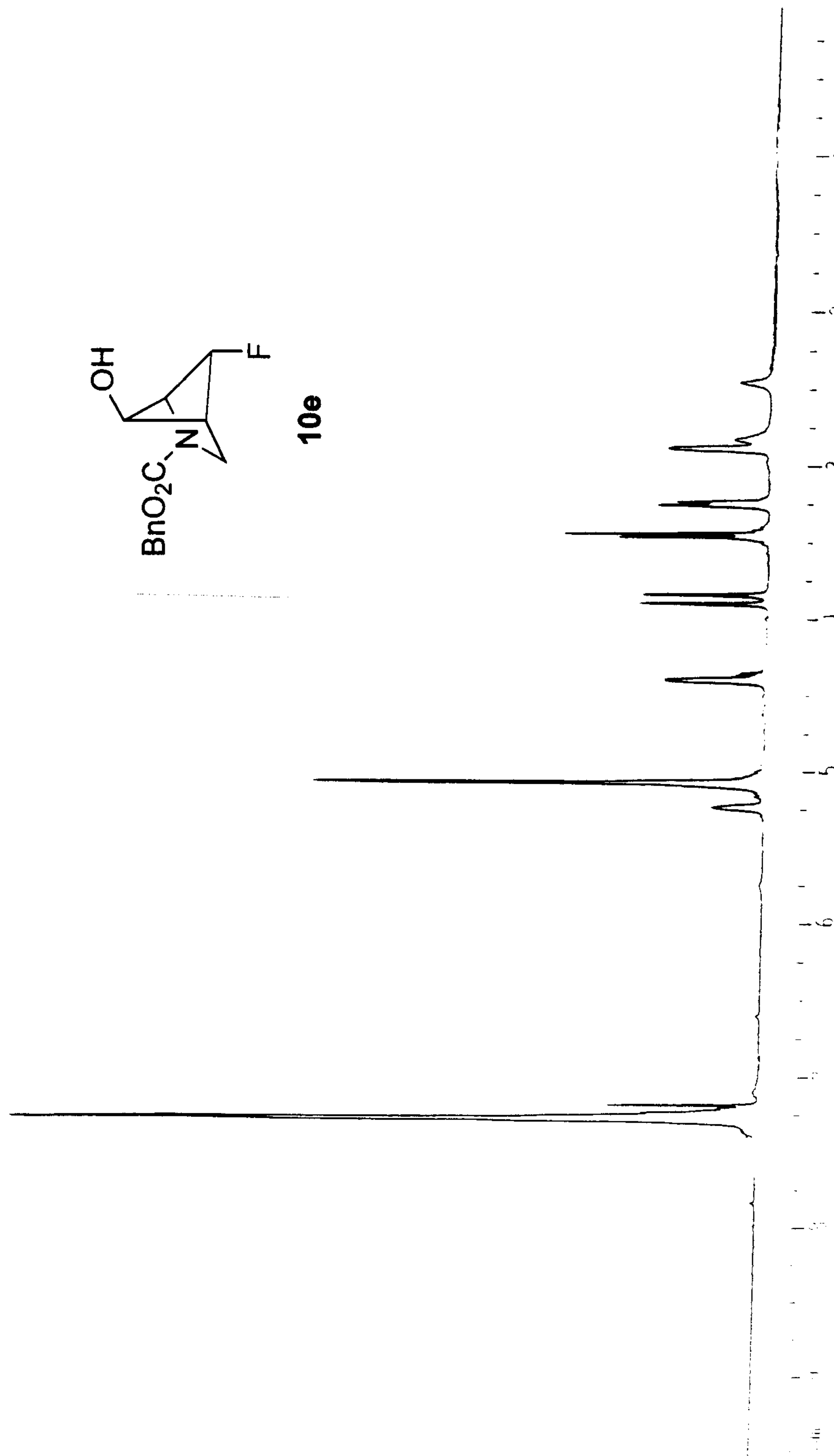
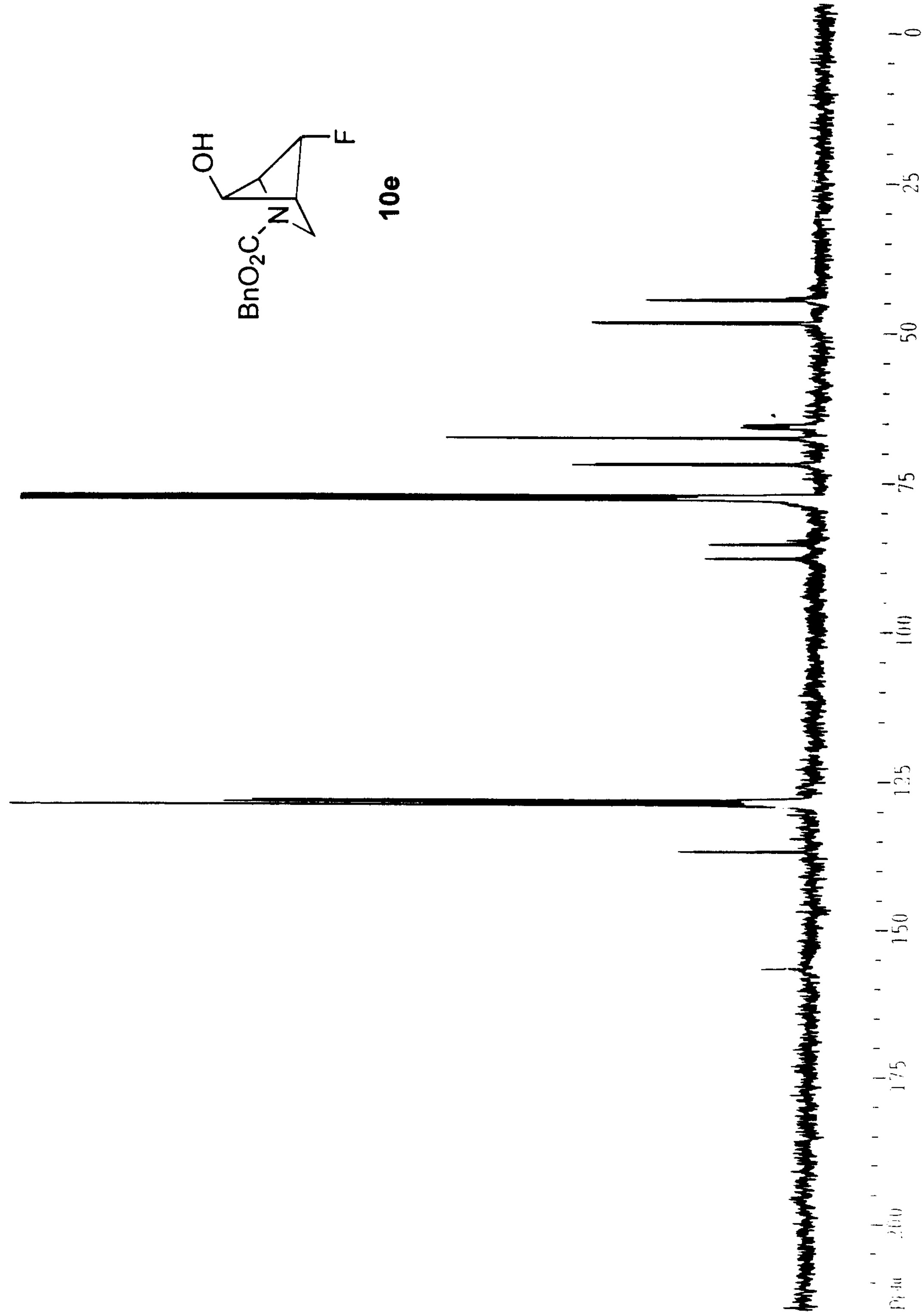


10e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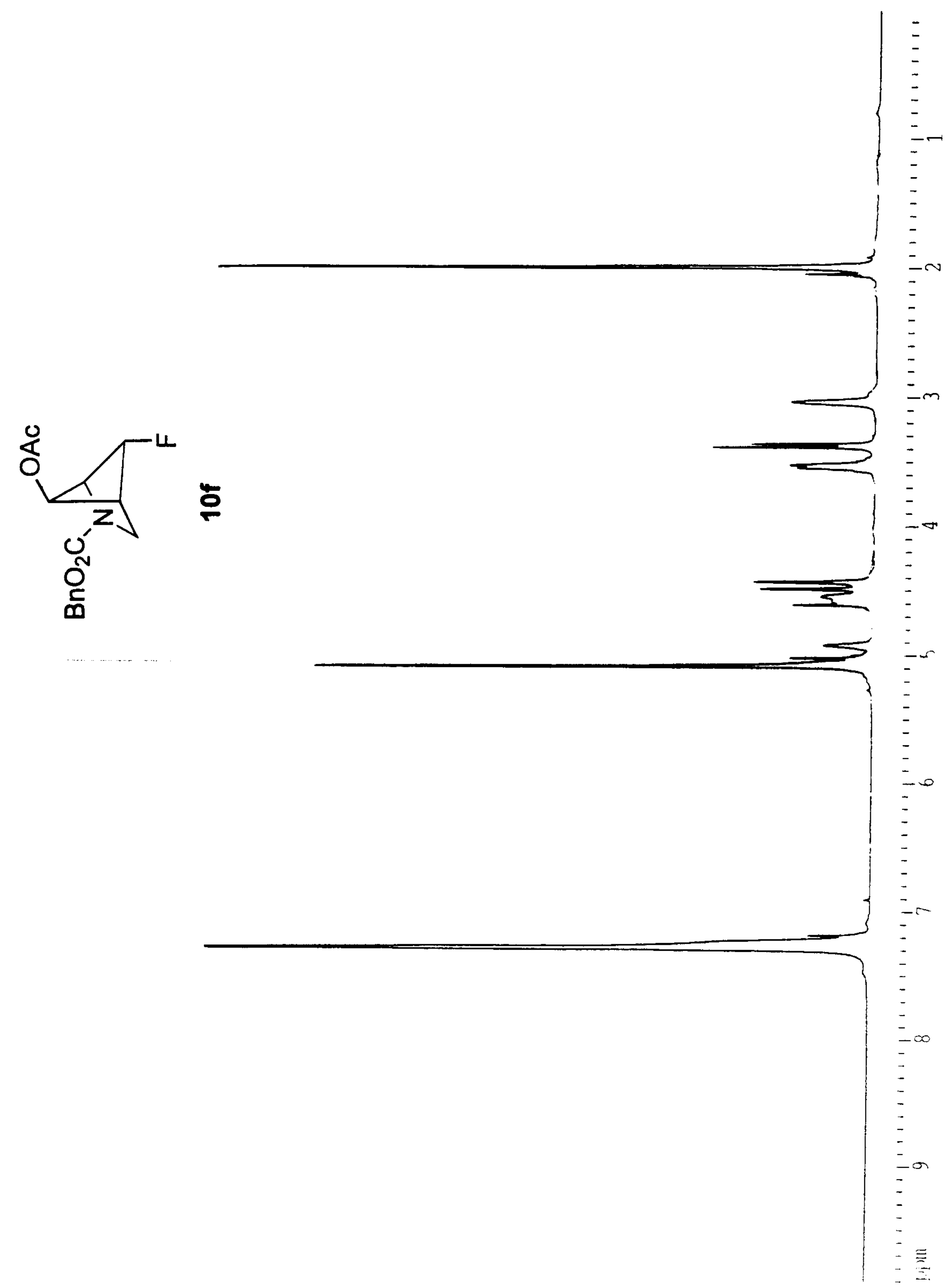
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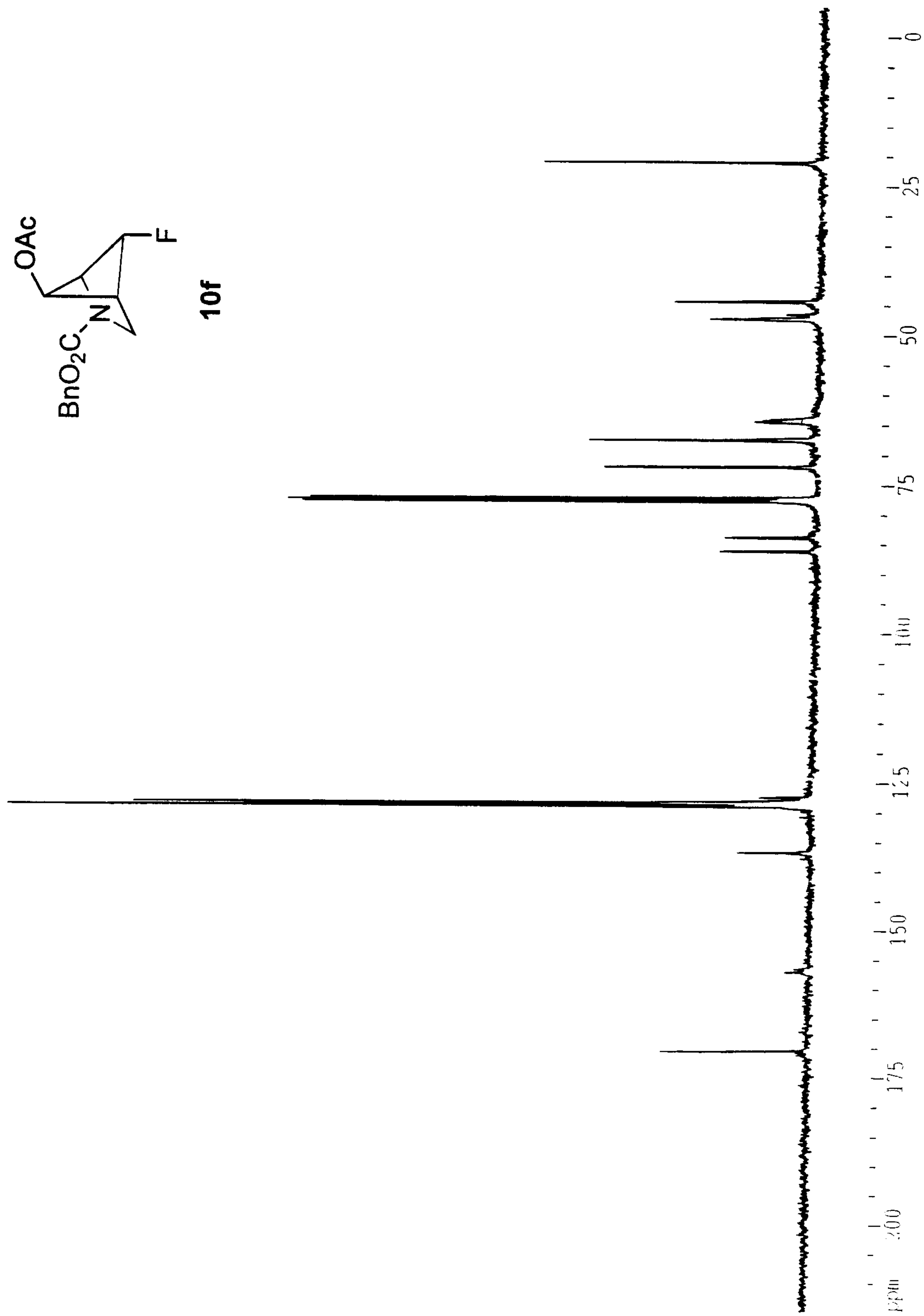

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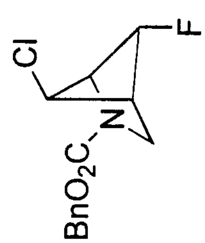

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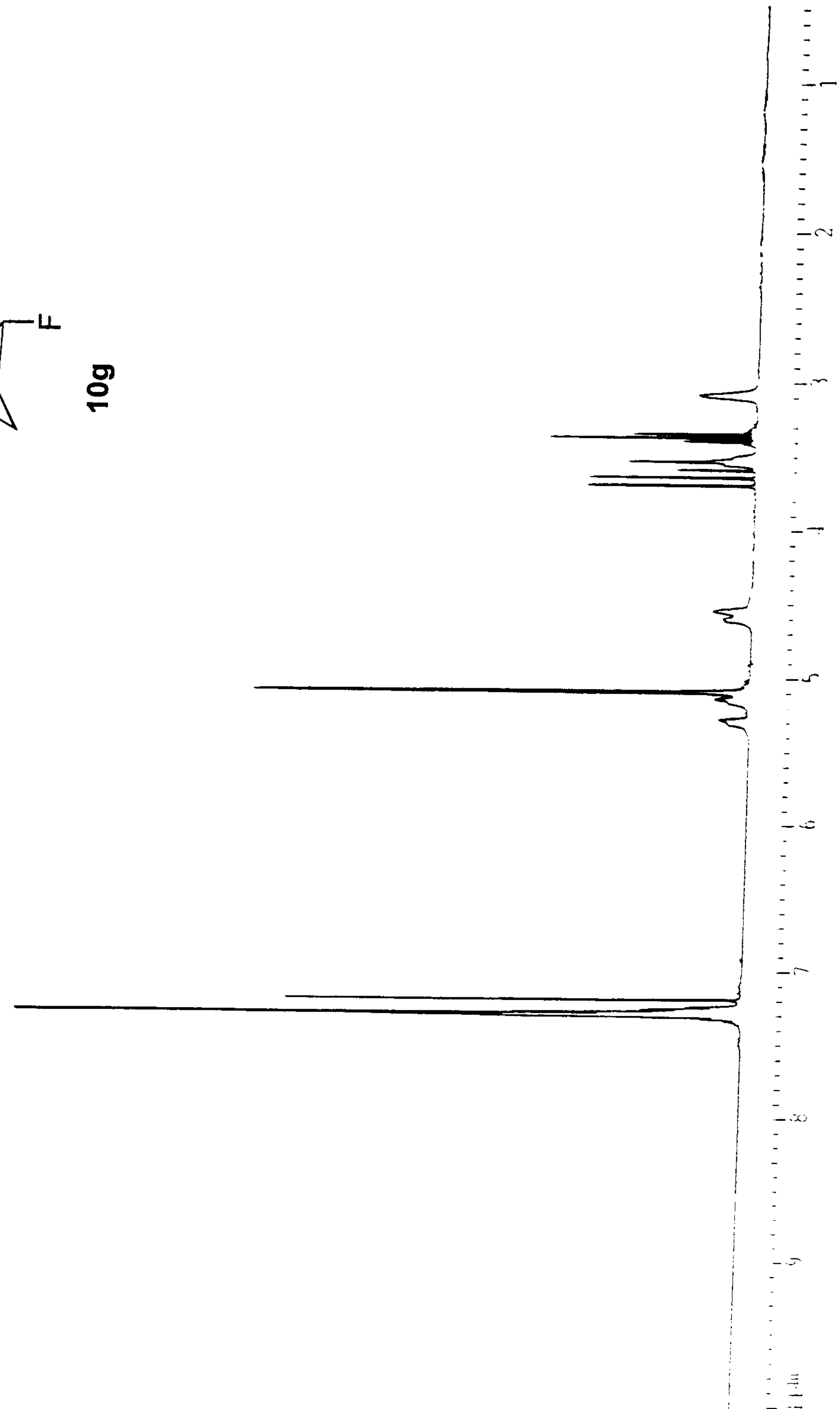

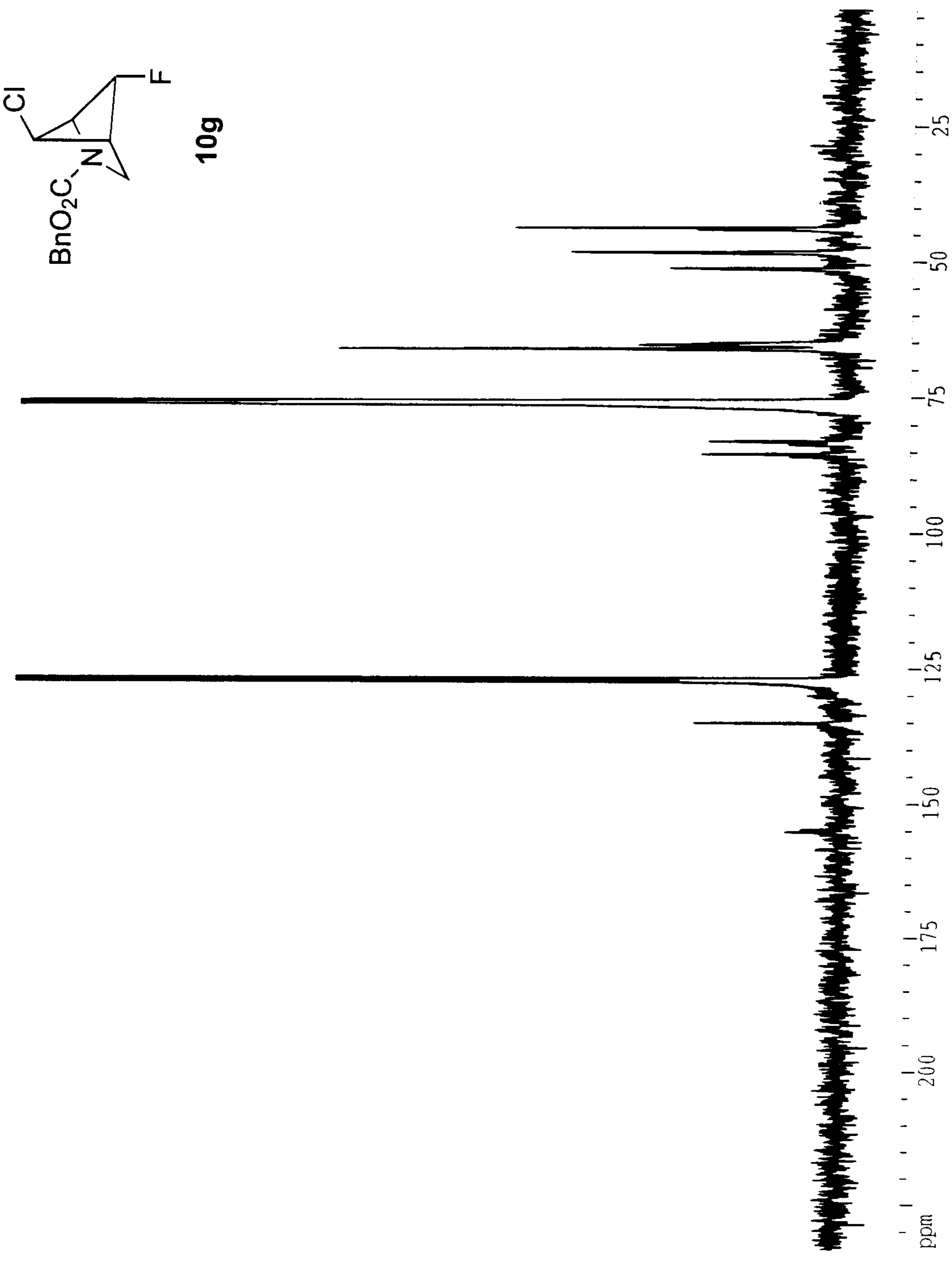

BnO_2C
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Cl
F
10g
ppm
200
175
150
125
100
75
50
25

Computational Data for reference 7

The structures were optimized at the restricted Hartree Fock (RHF) level using the 6-31G* basis set with the Gaussian 98 suite of computational software.

Gaussian 98, Revision ;M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi,
V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari,
J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham,
C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.

Energies

Compound	Energy[a]	ZPE[b]	ZPE(corr)[c]	Energy(corr)	Relative Energy[d]
i	-549.618650	0.185388	0.169352	-549.449298	0.0
ii	-549.563159	0.185326	0.169295	-549.393864	+34.8

[a]Energy in Hartrees; 1 Hartree = 627.51 kcal/mol; [b]Zero point energy; [c]ZPE scaled by 0.9135; [d]Kcal/mol.

Coordinates

Obtained from the logs of the optimized structures

i

C	0.159139	-0.338876	-2.335988
H	0.847636	-0.279949	-3.170010
C	0.976299	-0.476615	-1.057255
H	1.630842	-1.238600	-0.683681
C	1.030244	0.963982	-0.876345
H	1.772149	1.625368	-0.476056
C	-0.206819	1.077381	-1.825904
H	-0.418078	1.887893	-2.500509
C	-1.108628	0.790792	-0.623416
H	-1.382451	1.670389	-0.063146
H	-1.933000	0.109633	-0.747489
N	0.102363	0.184537	0.013472
C	0.355434	-0.106024	1.402719
O	1.436120	-0.404603	1.758328
O	-0.735812	0.029538	2.071620
C	-0.683866	-0.231480	3.494053
H	0.009707	0.452442	3.955446
H	-1.687530	-0.064730	3.841970

H	-0.378264	-1.252256	3.655794
O	-0.897403	-1.183900	-2.546234
H	-0.731614	-1.805188	-3.243521

ii

C	-0.188433	0.541769	-2.479871
H	-0.304794	1.144601	-3.360121
C	-1.129160	-0.268922	-1.720069
H	-2.170677	-0.489445	-1.850615
C	0.031827	-1.082054	-1.100406
H	-0.081671	-2.149696	-1.209217
C	1.023587	-0.210127	-1.910097
H	1.682543	-0.611782	-2.663272
C	1.604138	0.275191	-0.554621
H	2.618310	-0.052564	-0.383645
H	1.516177	1.328856	-0.333947
N	0.608778	-0.582329	0.108414
C	-0.116148	-0.386289	1.253752
O	-1.229574	-0.801916	1.363798
O	0.557957	0.296204	2.139602
C	-0.066064	0.519798	3.407589
H	-0.281809	-0.424790	3.881376
H	0.651014	1.080019	3.983129
H	-0.977045	1.083356	3.277891
O	-0.864257	1.142284	-1.254176
H	-1.584989	1.738979	-1.471933