Supporting Information

Synthesis of Pachastrissamine from Phytosphingosine: A Comparison of Cyclic Sulfate vs Epoxide Intermediate in Cyclization

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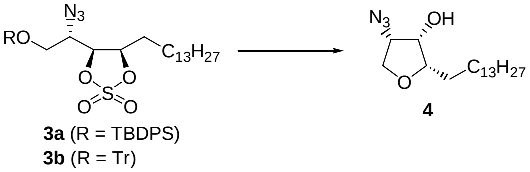
Contents

General. All chemicals were reagent grade and used as purchased. All reactions were performed under an inert atmosphere of dry argon or nitrogen using distilled dry solvents. Reactions were monitored by TLC analysis using silica gel 60 F-254 TLC plates. Melting points are uncorrected. Flash column chromatography was carried out on silica gel (230-400 mesh). Optical rotations were measured using sodium light (D line 589.3 nm). ^{1}H NMR and ^{13}C NMR spectra were recorded in δ units relative to deuterated solvent as internal reference at 300 and 75 MHz, respectively. IR spectra were measured on a Fourier Transform Infrared spectrometer. High resolution mass spectra (HRMS) were recorded using fast atom bombardment (FAB) or chemical ionization (CI).

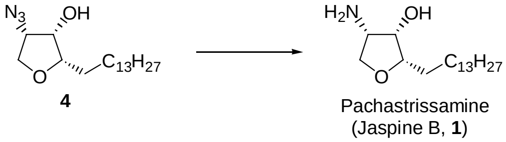
(2*S*,3*S*,4*S*)-4-Azido-2-tetradecyl-tetrahydrofuran-3-ol (4)



From **3a**: To a solution of cyclic sulfate **3a**[5] (258 mg, 0.400 mmol) in THF (8 mL) was added TBAF (0.44 mL, 0.440 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 1 h at room temperature, and to it were added concentrated H_2SO_4 (34 μL), H_2O (42 μL) and THF (524 μL). The mixture was stirred for 1 h at room temperature and then diluted with EtOAc. It was washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography (hexane/EtOAc, 5:1) to give **4** (112 mg, 86%) as a white solid.

From **3b**: To a solution of cyclic sulfate **3b**[5] (136 mg, 0.210 mmol) in CH_3CN (3 mL) was added H_2O (0.20 mL, 11.1 mmol, 50 equvi) at room temperature. The reaction mixture was heated to reflux for 6 h, and then concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 5:1) to give **4** (50 mg, 74%) as a white solid: mp 99.4-100.1 ^{o}C; $[\alpha]^{24}_{D}$ +16.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.25-1.43 (m, 24H), 1.63 (m, 2H), 2.10 (br s. 1H), 3.76 (ddd, *J* = 3.6, 6.9, 6.9 Hz, 1H), 3.85 (dd, *J* = 6.6, 9.0 Hz, 1H), 3.97 (dd, *J* = 7.2, 9.0 Hz, 1H), 4.11 (ddd, *J* = 4.8, 6.9, 6.9 Hz, 1H), 4.20 (dd, *J* = 3.9, 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 14.1, 22.7, 26.0, 28.8, 29.3, 29.51, 29.55, 29.65, 31.9, 63.7, 68.4, 72.5, 82.1; IR (CH_3Cl) υ_{max} 3329, 2917, 2849, 2105, 1468 (cm^{-1}); HRMS (CI) calcd for $C_{18}H_{36}O_2N_3$ ($[M + H]^+$) 326.2808, found 326.2805.

(2*S*,3*S*,4*S*)-4-Amino-2-tetradecyl-tetrahydrofuran-3-ol (pachastrissamine, 1)

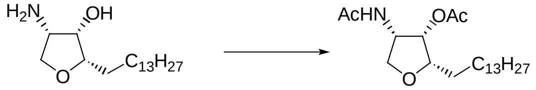


4

Pachastrissamine (Jaspine B, **1**)

A solution of **4** (88 mg, 0.27 mmol) in MeOH (4 mL) and CH_2Cl_2 (2 mL) was charged with 10% Pd/C (45 mg, 50 wt%). The mixture was stirred for 3 h under a balloon filled with H_2 at room temperature. It was diluted with CH_2Cl_2/MeOH and filtered through a pad of Celite. The solvent was removed, and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1, 1% NH_4OH) to give pachastrissamine (**1**) (74 mg, 93%) as a white solid: mp 96.6-97.2 ^{o}C (lit.[3c] mp 70-72 ^{o}C, lit.[3e] mp 89-91 ^{o}C); $[\alpha]^{24}_{D}$ +76.0 (*c* 0.2, $CHCl_3$), $[\alpha]^{23}_{D}$ +19.7 (*c* 0.5, MeOH), (lit.[1] $[\alpha]_{D}$ +18 (*c* 0.1, EtOH), lit.[2] $[\alpha]^{20}_{D}$ +7 (*c* 0.1, $CHCl_3$), lit.[3a] $[\alpha]_{D}$ +9 (*c* 1.5, $CHCl_3$), lit.[3b] $[\alpha]^{25}_{D}$ +7 (*c* 0.2, $CHCl_3$), lit.[3c] $[\alpha]^{25}_{D}$ +7.0 (*c* 0.1, $CHCl_3$), lit.[3e] $[\alpha]^{22}_{D}$ +4.8 (*c* 1.0, MeOH)); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.24-1.43 (m, 24H), 1.65 (m, 2H), 2.09 (br s, 3H), 3.50 (dd *J* = 6.9, 8.1 Hz, 1H), 3.64 (dt, *J* = 5.1, 6.9 Hz, 1H), 3.73 (app. dt, *J* = 3.3, 6.9 Hz, 1H), 3.86 (dd, *J* = 3.6, 4.8 Hz, 1H), 3.92 (dd, *J* = 7.2, 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 26.3, 29.3, 29.4, 29.57, 29.59, 29.7, 29.8, 31.9, 54.3, 71.8, 72.3, 83.2; IR (CH_3Cl) υ_{max} 3351, 3056, 2907, 2851, 1477 (cm^{-1}); HRMS (FAB) calcd for $C_{18}H_{38}O_2N$ ($[M + H]^+$) 300.2903, found 300.2898.

(2*S*,3*S*,4*S*)-4-Acetamido-2-tetradecyl-tetrahydrofuran-3-yl acetate(pachastrissamine diacetate)

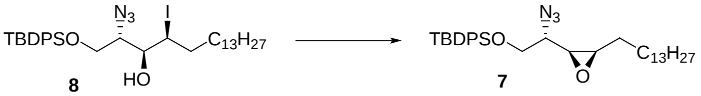


Pachastrissamine (Jaspine B, **1**)

pachastrissamine diacetate

To a solution of pachastrissamine (**1**) (33 mg, 0.11 mmol) in CH_2Cl_2 (4 mL) were added acetic anhydride (50 μL, 0.53 mmol) and triethylamine (80 μL, 0.57 mmol) at 0 ^{o}C. After 6 h, this reaction mixture was poured into water and extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 2:1) to give pachastrissamine diacetate (39 mg, 91%) as a white solid; mp 109.7-110.4 ^{o}C (lit.[3e] mp 95-98 ^{o}C); $[\alpha]^{24}_{D}$ -18.5 (*c* 0.7, $CHCl_3$) (lit.[3a] $[\alpha]_D$ -28.4 (*c* 1, $CHCl_3$), lit.[3e] $[\alpha]^{22}_{D}$ -22.6 (*c* 1.0, $CDCl_3$)); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.25-1.47 (m, 26H), 1.98 (s, 3H), 2.16 (s, 3H), 3.59 (t, *J* = 8.1 Hz, 1H), 3.90 (m, 1H), 4.07 (t, *J* = 8.4 Hz, 1H), 4.81 (dddd, *J* = 5.4, 8.1, 8.1, 8.1 Hz, 1H), 5.38 (dd, *J* = 3.3, 5.4 Hz, 1H), 5.60 (br d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 20.7, 22.7, 23.1, 26.0, 29.27, 29.32, 29.4, 29.51, 29.55, 29.62, 29.65, 31.9, 51.3, 69.9, 73.5, 81.2, 169.8, 169.9; IR ($CHCl_3$) υ_{max} 2919, 2853, 1739, 1643 (cm^{-1}); HRMS (FAB) calcd for $C_{22}H_{42}O_4N$ ($[M + H]^+$) 384.3114, found 384.3107.

{(*S*)-2-Azido-2-[(2*S*,3*R*)-3-tetradecyloxiran-2-yl]ethoxy}-*tert*-butyldiphenylsilane (7)

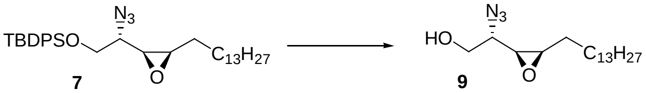


8

7

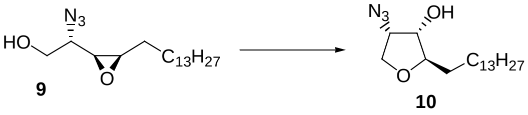
To a solution of **8**[5] (102 mg, 0.147 mmol) in MeOH (4 mL) was added K_2CO_3 (41 mg, 0.30 mmol). This reaction mixture was stirred at room temperature for 2 h, and then diluted with CH_2Cl_2. It was washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash silica gel column chromatography (hexane/EtOAc, 15:1) to give epoxide **7** (83 mg, 99%) as a colorless oil: $[\alpha]^{24}_{D}$ +7.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, *J* = 6.6 Hz, 3H), 1.10 (s, 9H), 1.28-1.60 (m, 26H), 2.99-3.03 (m, 2H), 3.19 (ddd, *J* = 3.0, 6.3, 8.7 Hz, 1H), 3.89 (dd, *J* = 6.3, 11.1 Hz, 1H), 3.98 (dd, *J* = 3.0, 10.5 Hz, 1H), 7.38-7.48 (m, 6H), 7.70-7.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 19.1, 22.7, 26.4, 26.7, 27.9, 29.3, 29.41, 29.47, 29.51, 29.7, 31.9, 54.1, 57.0, 60.9, 65.3, 127.8, 129.8, 132.7, 132.9, 135.57, 135.59; IR (CH_3Cl) υ_{max} 2924, 2841, 2106, 1425 (cm^{-1}); HRMS (CI) calcd for $C_{34}H_{54}O_2N_3Si$ ($[M + H]^+$) 564.3985, found 564.3981.

(*S*)-2-Azido-2-[(2*S*,3*R*)-3-tetradecyloxiran-2-yl]ethanol (9)



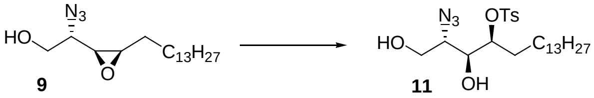
To a solution of epoxide **7** (123 mg, 0.218 mmol) in THF (5 mL) was added TBAF (0.3 mL, 0.30 mmol, 1.0 M solution in THF) at room temperature. After being stirred for 2 h at room temperature, the reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 5:1) to give epoxy alcohol **9** (70 mg, 99%) as a white solid: mp 67.1-67.4 °C; $[\alpha]^{24}_{D}$ +34 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.26-1.68 (m, 26H), 1.91 (br s, 1H), 3.02 (dd, *J* = 3.9, 8.7 Hz, 1H), 3.08 (ddd, *J* = 3.9, 4.2, 6.3 Hz, 1H), 3.25 (ddd, *J* = 3.9, 6.3, 8.7 Hz, 1H), 3.79 (dd, *J* = 6.3, 11.4 Hz, 1H), 3.93 (dd, *J* = 3.9, 11.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.6, 26.4, 28.0, 29.3, 29.40, 29.44, 29.5, 29.57, 29.61, 29.63, 29.64, 31.9, 54.7, 57.2, 60.9, 63.6; IR (CH_3Cl) υ_{max} 3285, 3177, 2917, 2851, 2141, 2095, 1472 (cm^{-1}); HRMS (CI) calcd for $C_{18}H_{36}O_2N_3$ ($[M + H]^+$) 326.2808, found 326.2806.

(2*R*,3*S*,4*S*)-4-Azido-2-tetradecyl-tetrahydrofuran-3-ol (10)



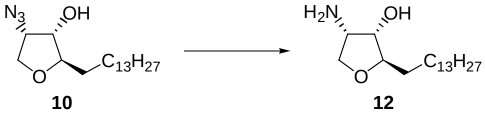
To a solution of epoxy alcohol **9** (43 mg, 0.132 mmol) in toluene (4 mL) was added TsOH (2 mg, 10 μmol, 0.1 equiv). The reaction mixture was heated to reflux for 12 h and cooled to room temperature. It was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 5:1) to give **10** (34 mg, 79%) as a white solid: mp 64.7-65.8 °C; $[\alpha]^{24}_D$ +29.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.25-1.69 (m, 26H), 2.24 (br d, *J* = 7.2 Hz, 1H), 3.58-3.65 (m, 1H), 3.80 (dd, *J* = 4.5, 9.3 Hz, 1H), 3.89 (br app. q, *J* = 6.3 Hz, 1H), 4.03 (ddd, *J* = 4.8, 5.4, 6.0 Hz, 1H), 4.13 (dd, *J* = 5.7, 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 25.7, 29.3, 29.50, 29.55, 29.58, 29.6, 29.7, 31.9, 33.2, 63.3, 69.3, 76.2, 82.9; IR (CH_3Cl) υ_{max} 3293, 2920, 2849, 2108, 1468 (cm^{-1}); HRMS (CI) calcd for $C_{18}H_{36}O_2N_3$ ($[M + H]^+$) 326.2808, found 326.2806.

(2*S*,3*S*,4*S*)-2-Azido-1,3-dihydroxyoctadecan-4-yl 4-methylbenzenesulfonate (11)



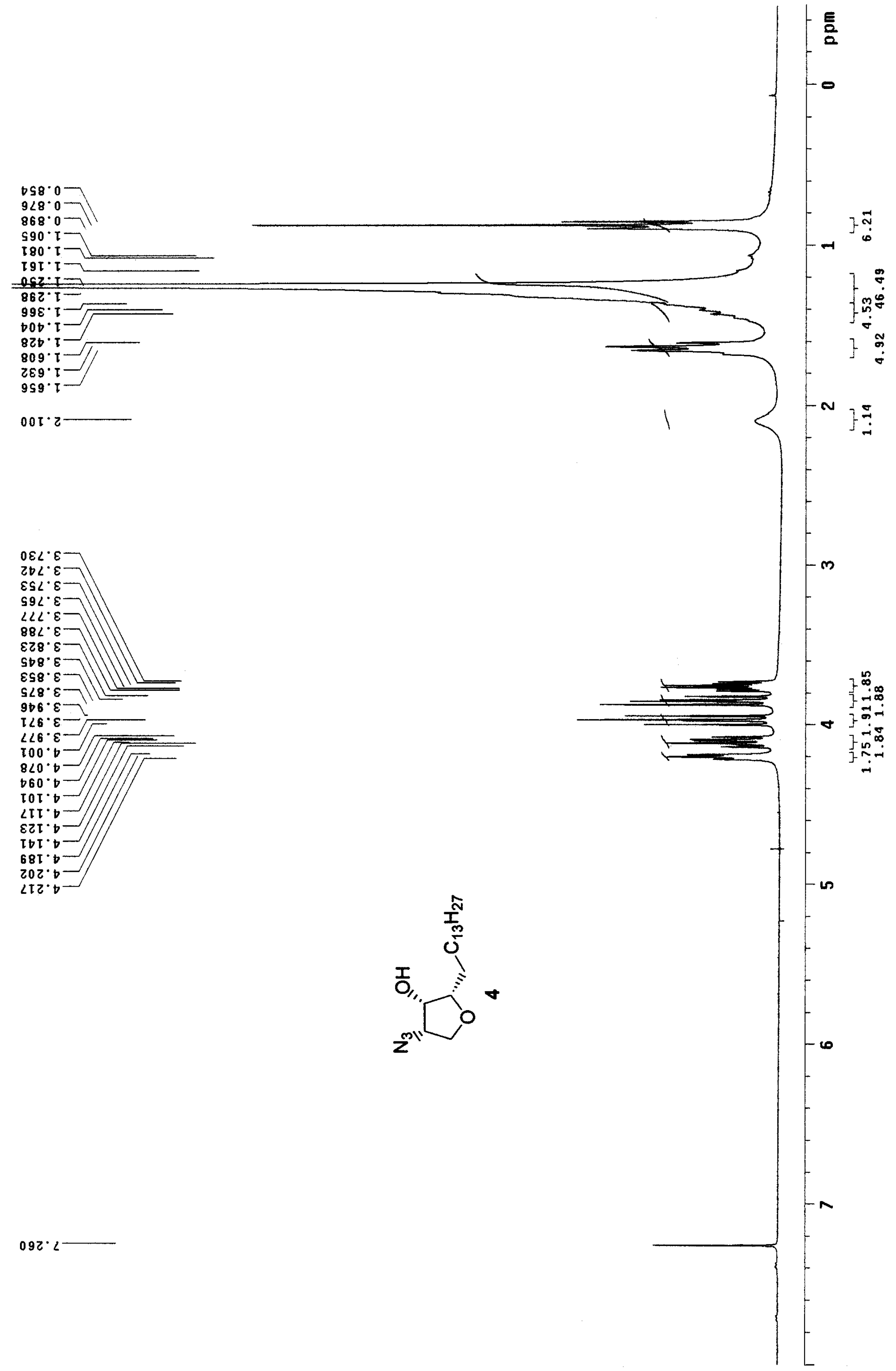
To a solution of epoxy alcohol **9** (42 mg, 0.129 mmol) in CH_2Cl_2 (4 mL) was added TsOH (30 mg, 0.158 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 8 h, and then diluted with CH_2Cl_2. It was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 5:1) to give **10** (20 mg, 48%) and the unstable hydroxyl tosylate **11** (21 mg, 32%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.26-1.78 (m, 26H), 2.45 (s, 3H), 3.46-3.56 (m, 2H), 3.92 (dd, *J* = 4.2, 11.7 Hz, 1H), 4.00 (dd, *J* = 3.6, 11.7 Hz, 1H), 4.82 (t, *J* = 6.6 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.83 (dt, *J* = 1.5, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 21.6, 22.7, 25.0, 25.7, 29.1, 29.3, 29.4, 29.7, 31.1, 31.9, 62.5, 62.9, 71.1, 82.3, 127.8, 129.9, 133.7, 145.2.

(2*R*,3*S*,4*S*)-4-Amino-2-tetradecyl-tetrahydrofuran-3-ol (*epi*-pachastrissamine, 12)



A solution of **10** (52 mg, 0.16 mmol) in MeOH (4 mL) and CH_2Cl_2 (2 mL) was charged with 10% Pd/C (26 mg, 50 wt%). The mixture was stirred for 3 h under a balloon filled with H_2 at room temperature. It was diluted with CH_2Cl_2/MeOH and filtered through a pad of Celite. The solvent was removed, and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 9:1, 1% NH_4OH) to give *epi*-pachastrissamine (**12**) (45 mg, 94%) as a white solid: solid: mp 103.9-104.9 ^{o}C (lit.[3e] mp 85-87 ^{o}C, lit.[16] mp 103.5-104.2 ^{o}C); $[\alpha]^{23}_D$ +23.2 (*c* 1.0, MeOH) (lit.[3e] $[\alpha]^{22}_D$ +15.0 (*c* 1.0, MeOH), lit.[16] $[\alpha]^{23}_D$ +14.8 (*c* 0.2, EtOH)); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.24-1.60 (m, 26H), 2.13 (br s, 3H), 3.39 (dd, *J* = 6.9, 8.4 Hz, 1H), 3.45

(m, 1H), 3.60 (dd, *J* = 5.1, 10.8 Hz, 1H), 3.62 (m, 1H), 4.11 (dd, *J* = 6.0, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 25.9, 29.4, 29.5, 29.6, 29.7, 31.9, 33.7, 52.7, 73.1, 74.8, 85.2; IR (CH_3Cl) υ_{max} 3420, 2917, 2851, 1474 (cm^{-1}); HRMS (FAB) calcd for $C_{18}H_{38}O_2N$ ($[M + H]^+$) 300.2903, found 300.2903.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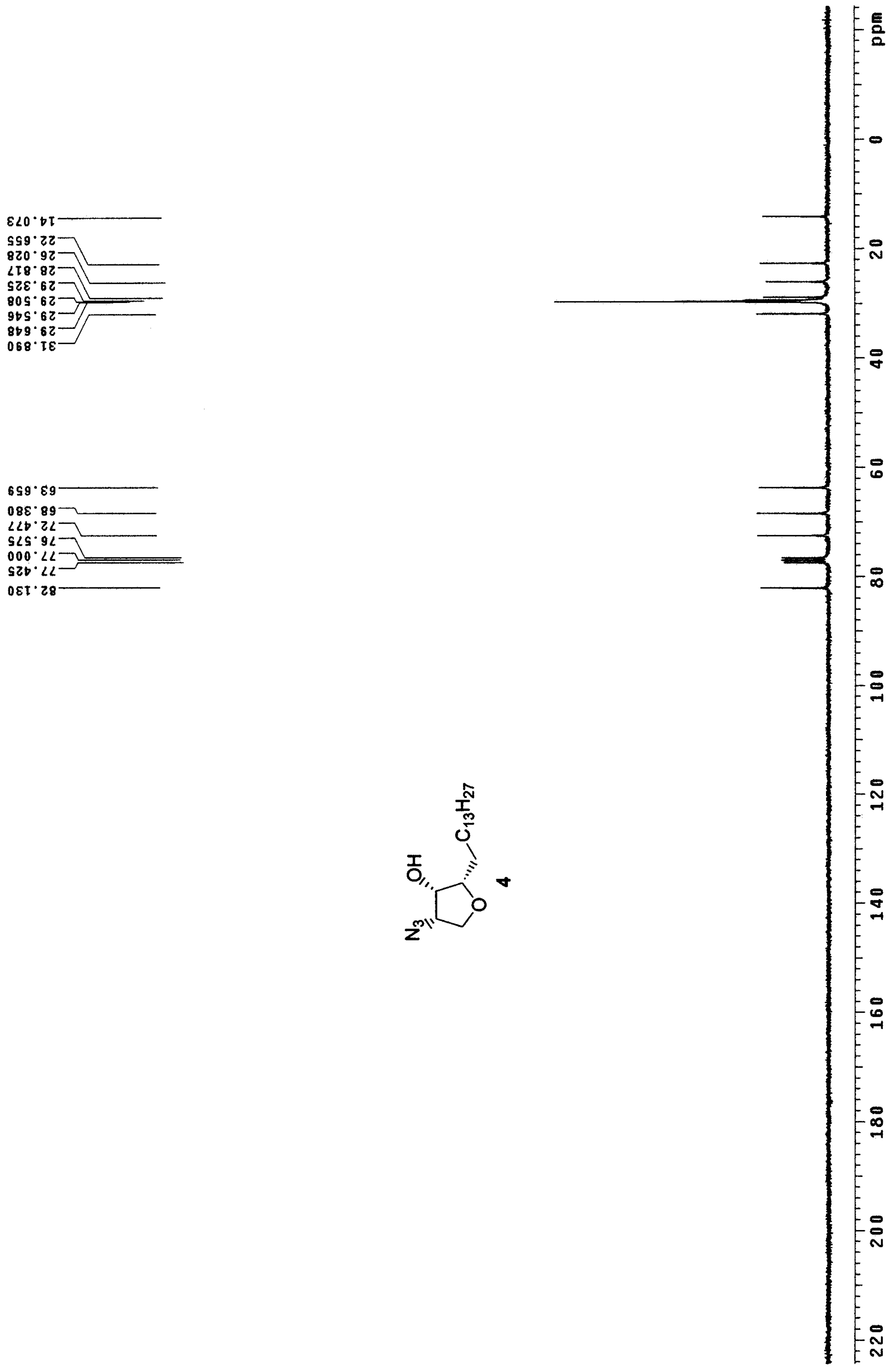
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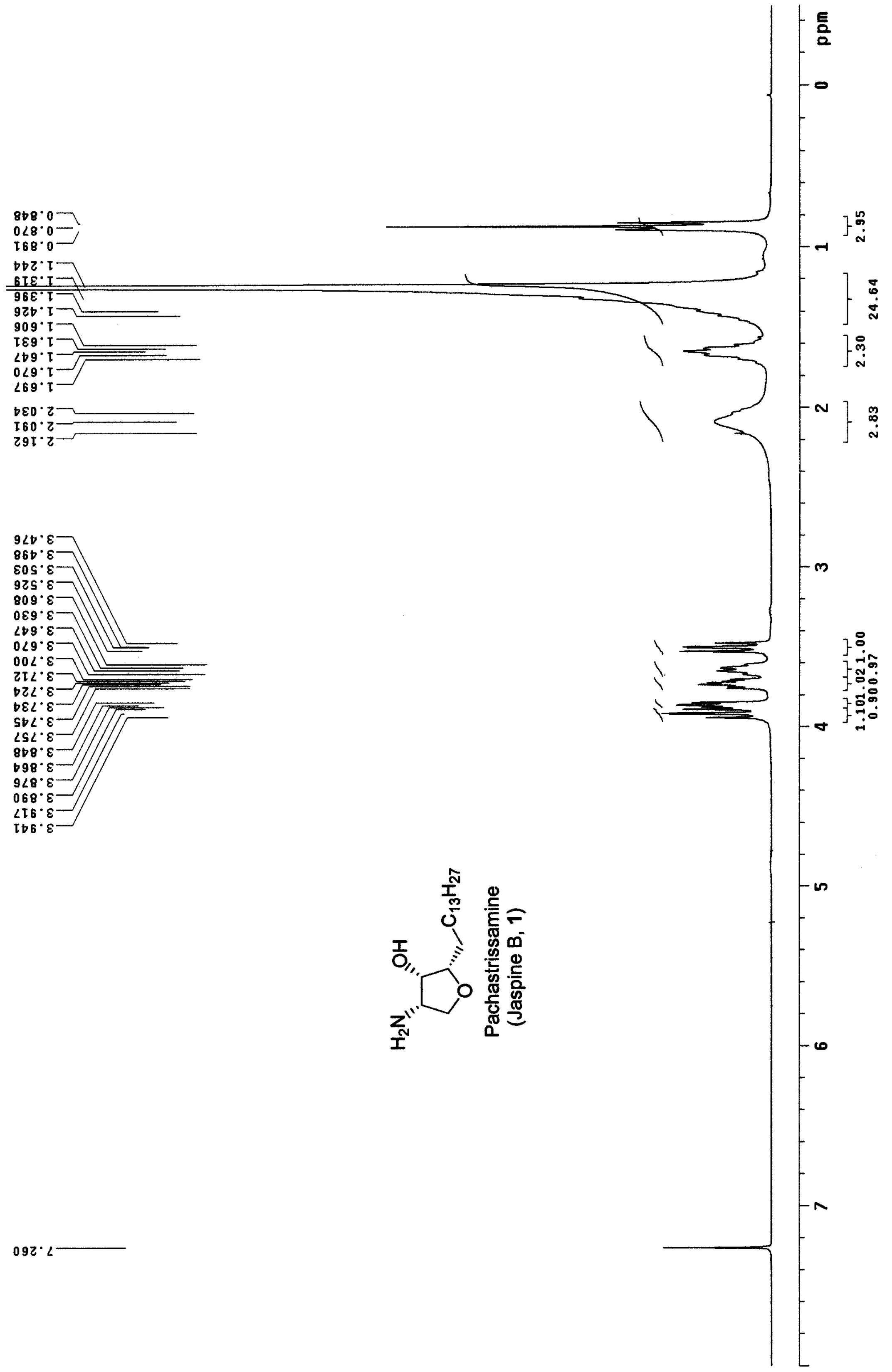
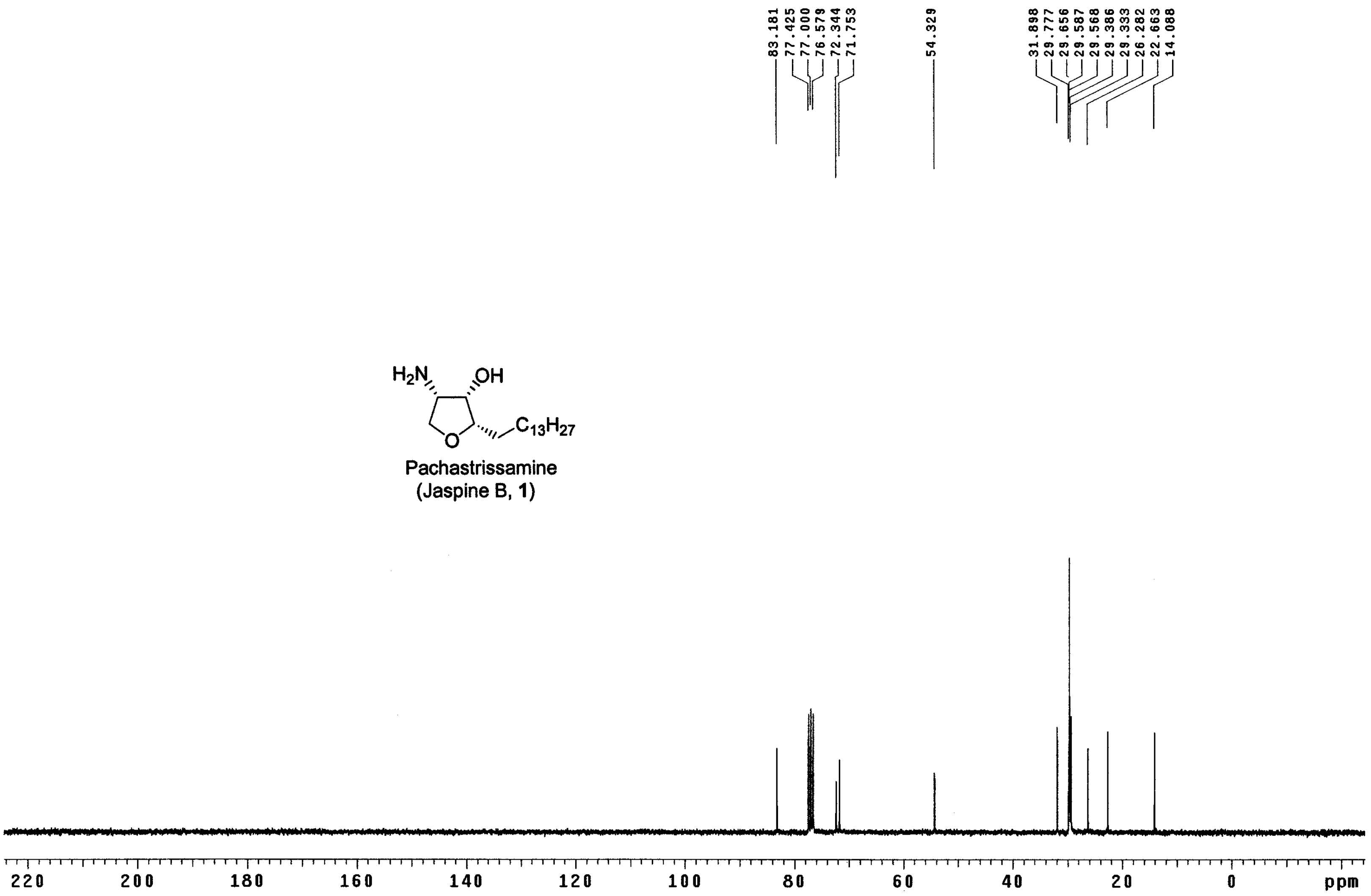
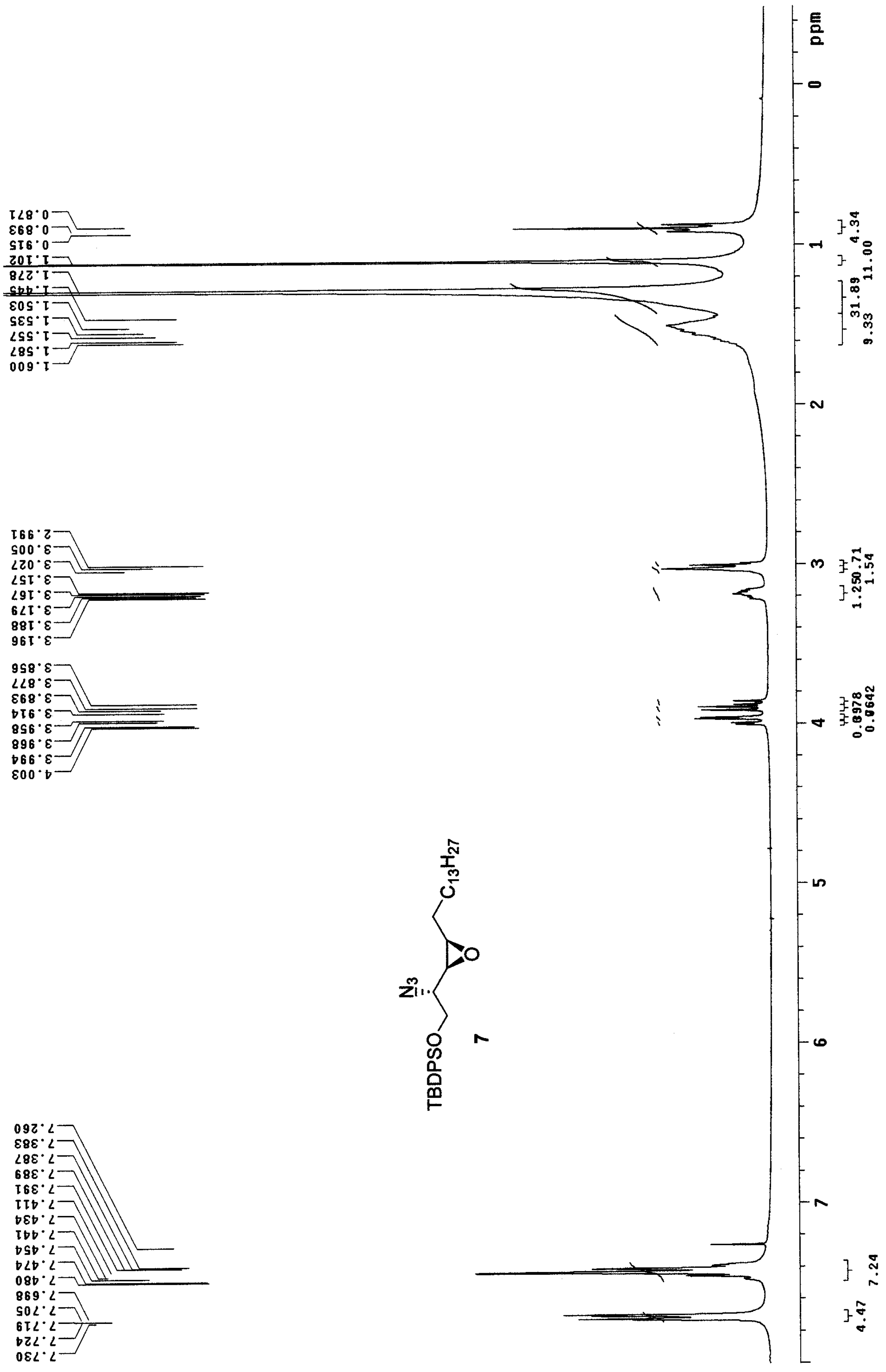


Pachastrissamine (Jaspine B, 1)



Pachastrissamine
(Jaspine B, **1**)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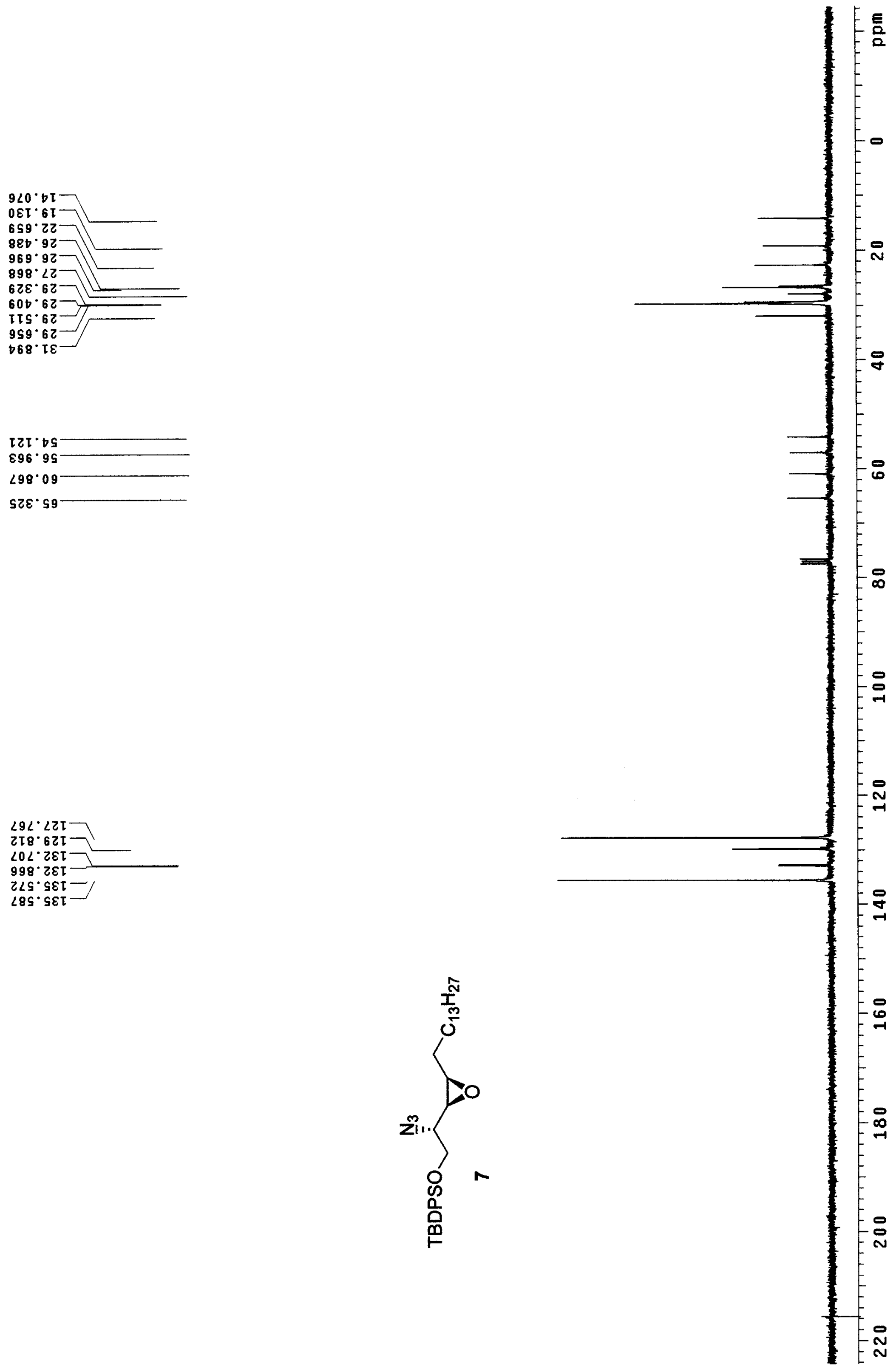
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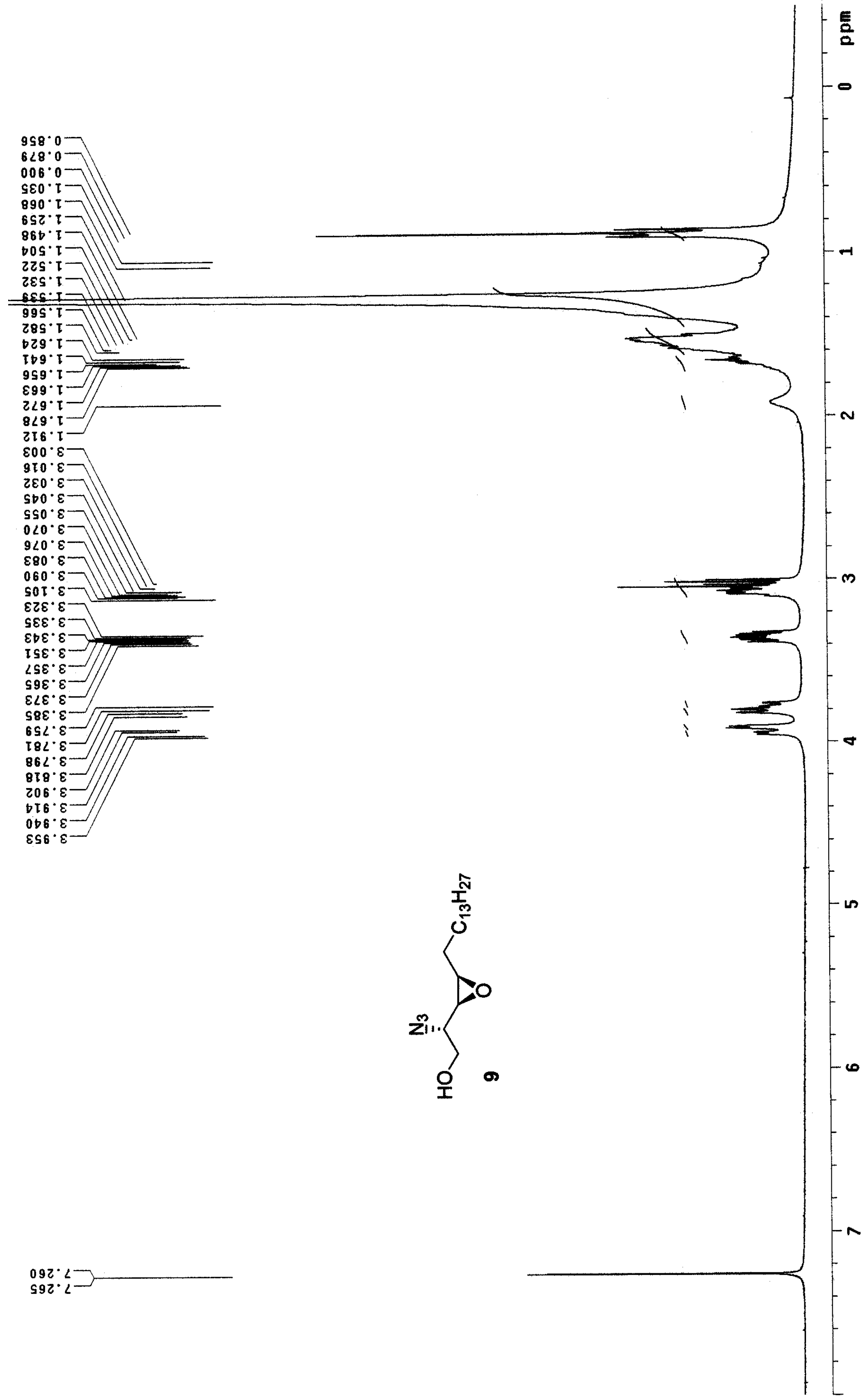
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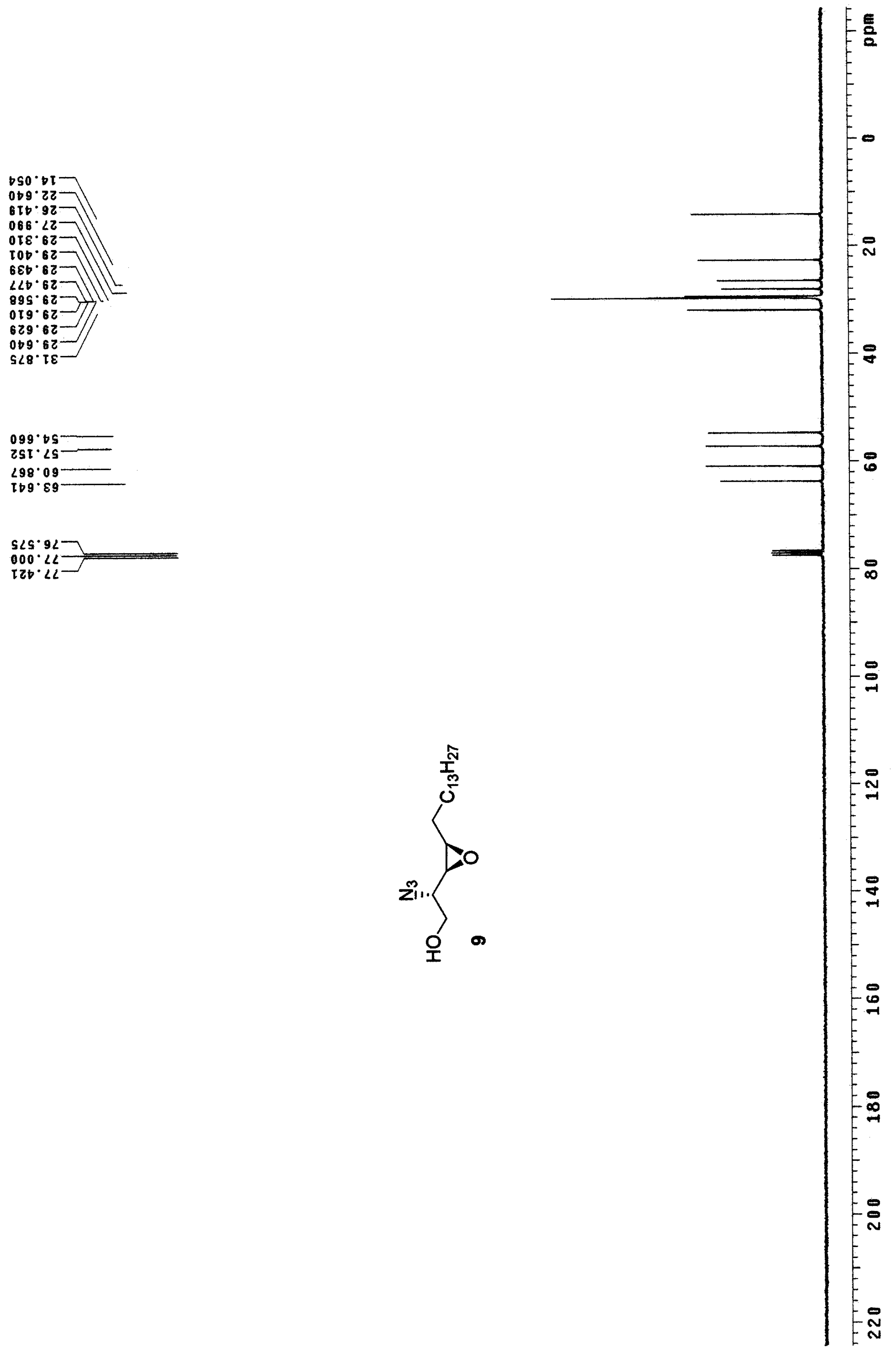
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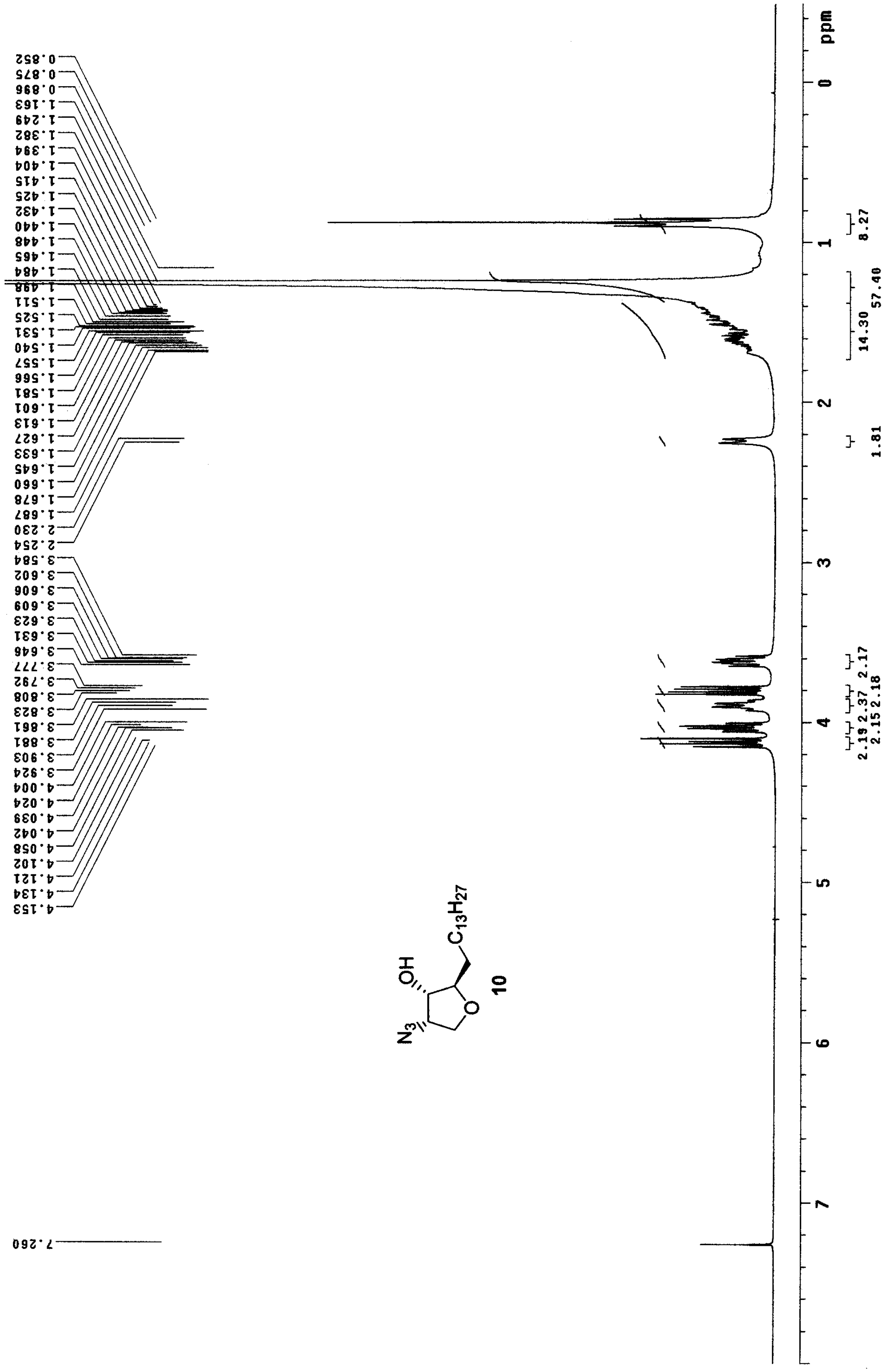
9
ppm
220
200
180
160
140
120
100
80
60
40
20
0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0.896
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1.249
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1.432
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1.448
1.465
1.484
1.498
1.511
1.525
1.531
1.540
1.557
1.566
1.581
1.601
1.613
1.627
1.633
1.645
1.660
1.678
1.687
2.230
2.254
3.584
3.602
3.606
3.609
3.623
3.631
3.646
3.777
3.792
3.808
3.823
3.861
3.881
3.903
3.924
4.004
4.024
4.039
4.042
4.058
4.102
4.121
4.134
4.153
7.260
N3
OH
O
C13H27
10
8.27
57.40
14.30
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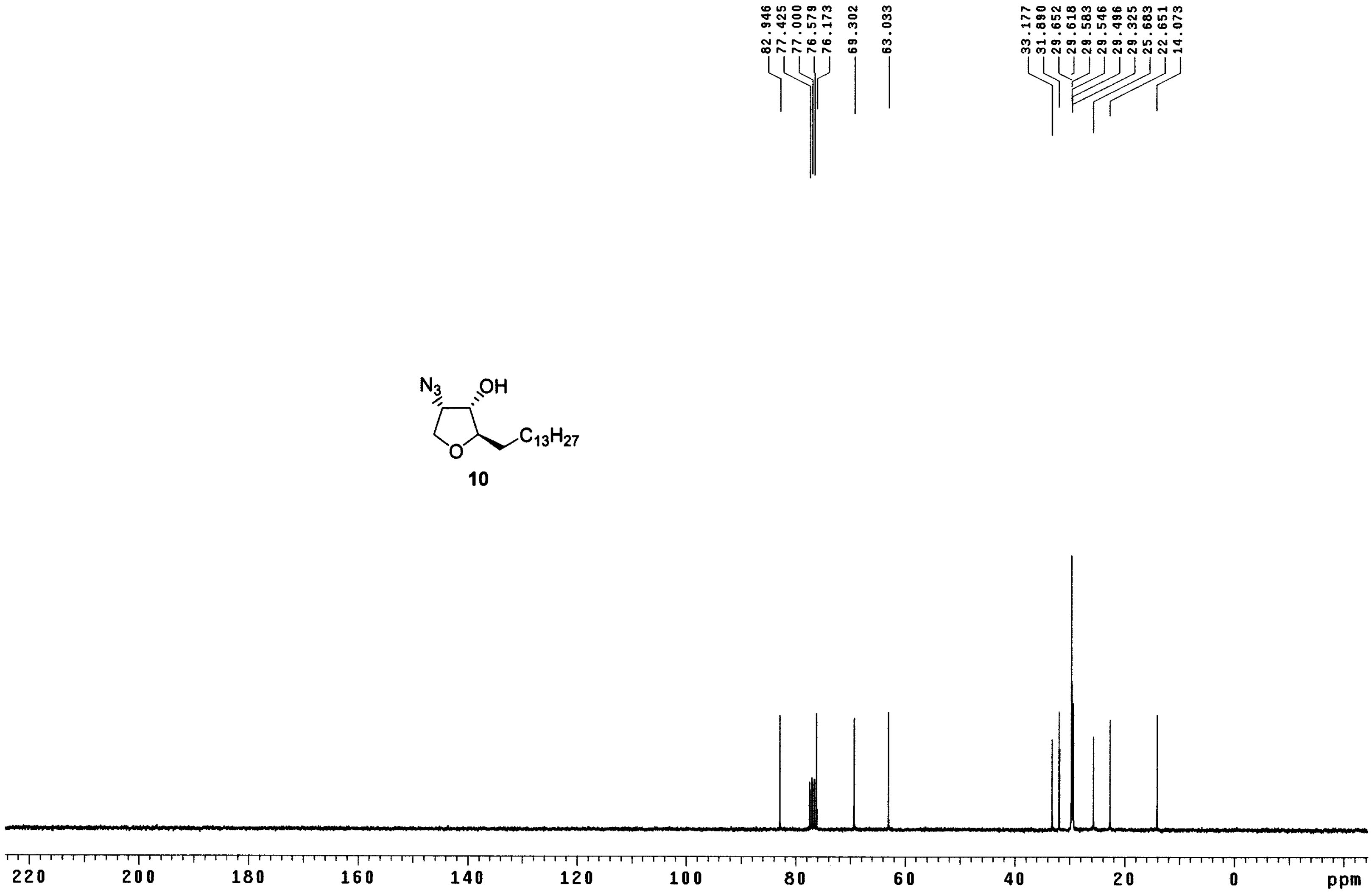
2.37
2.18
2.19
2.15
ppm
0
1
2
3
4
5
6
7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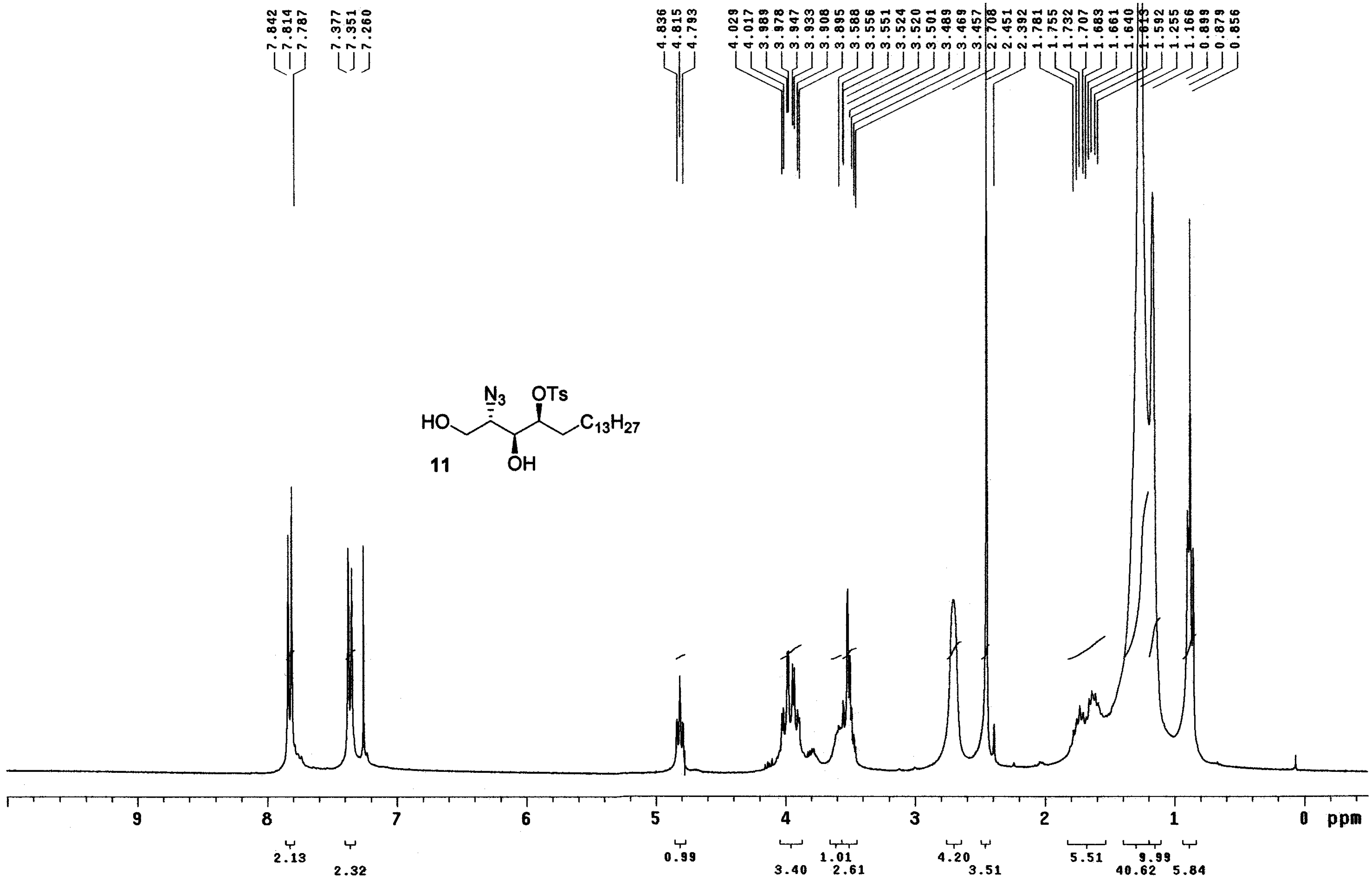
77.000
76.579
76.173
69.302
63.033
33.177
31.890
29.652
29.618
29.583
29.546
29.496
29.325
25.683
22.651
14.073
N3
OH
C13H27
10
220
200
180
160
140
120
100
80
60
40
20
0
ppm



11

7.842
7.814
7.787
7.377
7.351
7.260
4.836
4.815
4.793
4.029
4.017
3.989
3.978
3.947
3.933
3.908
3.895
3.588
3.556
3.551
3.524
3.520
3.501
3.489
3.469
3.457
2.708
2.451
2.392
1.781
1.755
1.732
1.707
1.683
1.661
1.640
1.615
1.592
1.255
1.166
0.899
0.879
0.856
HO
N3
OTs
C13H27
OH
9
8
7
6
5
4
3
2
1
0
ppm
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2.32
0.99
3.40
1.01
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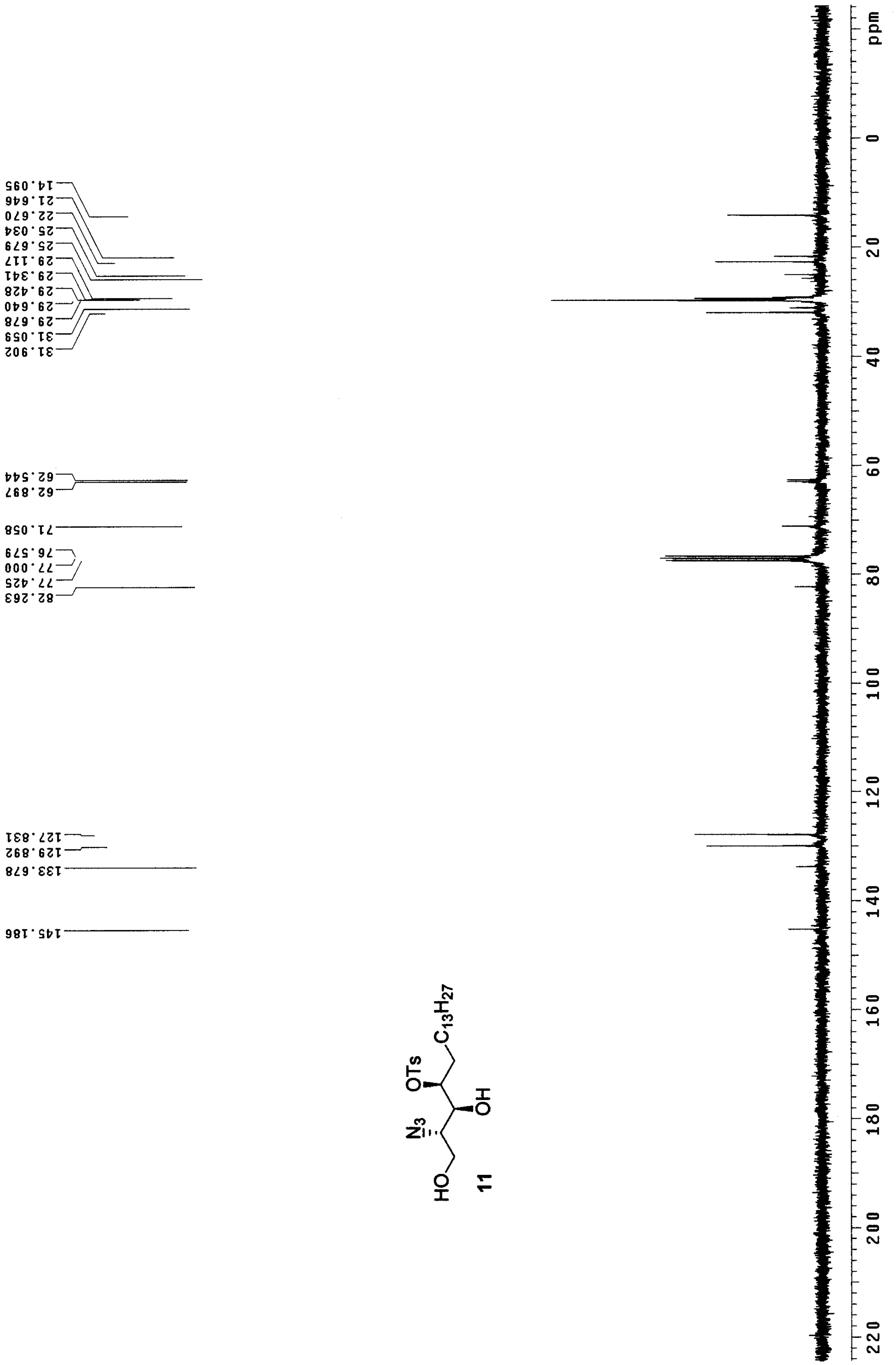
5.51
9.99
40.62
5.84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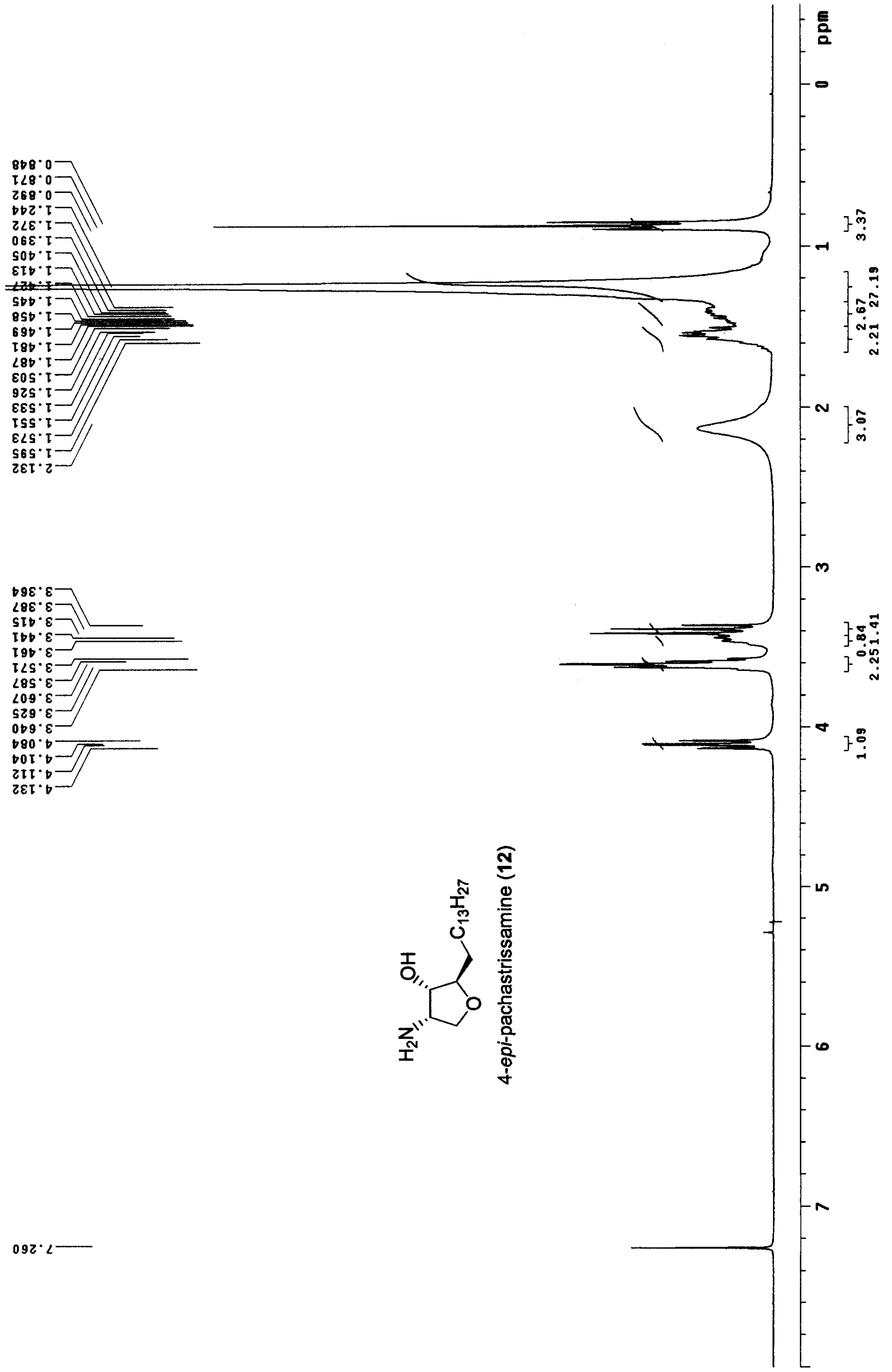
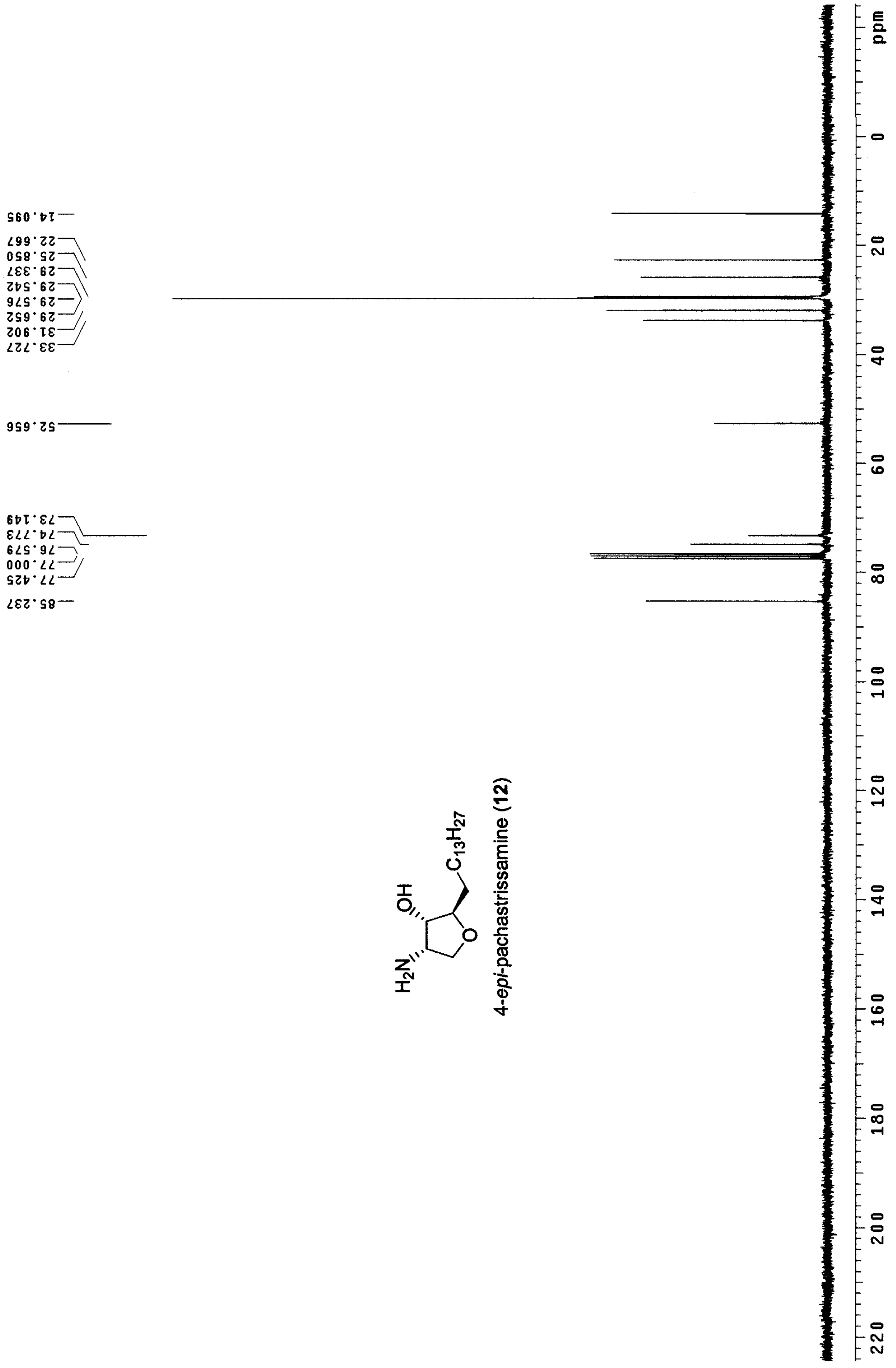
22.670
25.034
25.679
29.117
29.341
29.428
29.640
29.678
31.059
31.902
62.544
62.897
71.058
76.579
77.000
77.425
82.263
127.831
129.892
133.678
145.186
HO
N3
OTs
OH
C13H27
220
200
180
160
140
120
100
80
60
40
20
0
ppm

11



4-*epi*-pachastrissamine (**12**)



4-*epi*-pachastrissamine **(12)**