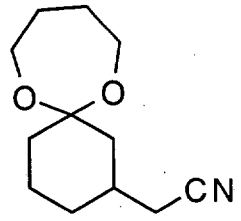
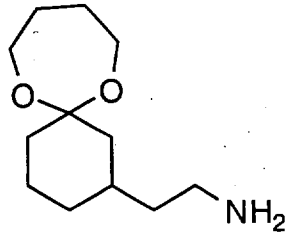
SUPPORTING INFORMATION



8

[7,12]-Dioxa-*spiro*[5,6]dodec-2-yl]-acetonitrile (8):

3-Acetonitrilecyclohexanone (4.33 g, 31.6 mmol), prepared according to a literature procedure,[5] was dissolved in benzene (40 mL), 1,4-butandiol (5.7 g, 63.2 mmol) was added. The mixture was treated with PTSA•H_2O (0.3 g, 1.6 mmol) and then refluxed for 20 h with a Dean-Stark apparatus. It was then cooled to rt and diluted with EtOAc (100 mL), washed with sat. $NaHCO_3$ (40 mL). The aqueous layer was extracted with EtOAc (50 mL), and the combined organic layers were dried with $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography, eluted with 20% EtOAc/hexane to give nitrile **8** (6.08 g, 29.1 mmol, 92%) as a pale yellow oil. Rf: 0.35 (EtOAc:Hexane = 20:80); ^1H NMR ($CDCl_3$, 270 MHz), 1.00-1.34 (m, 3H), 1.42-1.74 (m, 6H), 1.78-1.84 (m, 1H), 1.89-2.09 (m, 3H), 2.29 (d, J = 6.4 Hz, 2H), 3.63-3.67 (m, 2H), 3.69-3.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 67.9 MHz), 118.5, 100.7, 61.8, 61.6, 39.6, 32.9, 31.7, 31.3, 29.7, 29.5, 24.0, 21.6. IR (neat), 2236, 1733, 1462, 1287, 1246 cm^{-1}. HRMS calcd for $C_{12}H_{19}NO_2$ MH^+ 210.1494, found 210.1485.

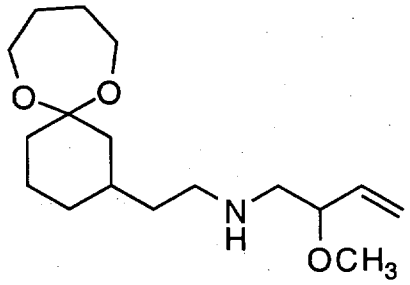


9

2-[7,12]-Dioxa-*spiro*[5,6]dodec-2-yl]-ethylamine (9):

A suspension of LAH (2.84 g, 74.8 mmol) in THF (40 mL) in a 250 mL flask was cooled to 0 °C in an ice bath. Then a solution of **8** (6.25 g, 29.9 mmol) in THF (20 mL) was added dropwise over a period of 5-10 min. The reaction was stirred at 0 °C for 10 min, then heated to reflux in an oil-bath and maintained at reflux overnight (10 h). The reaction was cooled to 0 °C, quenched with H_2O (2.9 mL) slowly, followed by the

addition of 15% NaOH (2.9 mL). During the process, the reaction was diluted with THF (50 mL) periodically to help reach a nice stir. Finally, more water was added (8.5 mL). The resulting mixture was stirred at 0 °C for 5 min then at rt for 15 min. The mixture was filtered through celite then the filter-cake was washed thoroughly with CH_3OH and EtOAc. The filtrate was concentrated and the crude product was purified by chromatography. The silica gel was deactivated by first eluting with 100 mL of 1% Et_3N in hexane. The faster moving impurities were eluted from the column with EtOAc, then the desired product was eluted with 1% Et_3N in CH_3OH to afford a yellow oil in 80% yield (5.10 g, 23.9 mmol). R_f 0.07 (1% $NH_3 \cdot H_2O$ in CH_3OH); ^1H NMR ($CDCl_3$, 270 MHz), 0.77-1.04 (m, 2H), 1.11-1.78 (m, 13H), 1.91-2.00 (m, 2H), 2.74 (bs, 2H), 3.63-3.74 (m, 4H). ^{13}C NMR ($CDCl_3$, 67.9 MHz), 101.3, 61.6, 61.3, 41.1, 40.8, 39.7, 33.7, 32.3, 32.1, 29.8, 29.6, 22.5. IR (neat), 3364 (b), 1574, 1456, 1348, 1307, 1287 cm^{-1}. HRMS calcd for $C_{12}H_{23}NO_2$ MH^+ 214.1807, found 214.1811.



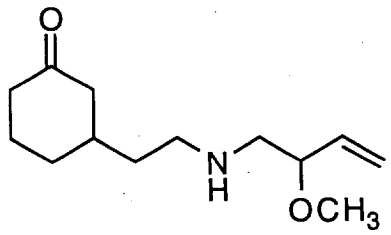
11

[2-[7,12-Dioxa-*spiro*[5,6]dodec-2-yl]-ethyl]-[2-methoxy-but-3-enyl]-amine (11):

Direct amine alkyaltion method: A solution of amine **9** (1.80 g, 8.44 mmol) and 4-bromo-3-methoxy-1-butene (1.13 g , 6.90 mmol) was stirred in an oil bath at 65-70 °C for 3 h. The reaction mixture was taken up with $CHCl_3$ (20 mL), washed with $NaHCO_3$ (10 mL). The aqueous layer was extracted with $CHCl_3$ (3 x 15 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel chromatography, eluting with 75% EtOAc/hexanes to remove the faster moving impurities, then the product **11** (0.563 g, 1.88 mmol, 22%) was eluted with 10%CH_3OH/EtOAc, and finally starting material **9** (1.26 g, 70%) was recovered by eluting with 1%Et_3N in CH_3OH.

The three-componet couping reaction method: To a 10 mL round-bottom flask was added amine **9** (0.170 g, 0.799 mmol), which was then dissolved in EtOH (2 mL), H_2O (1.0 mL) and paraformaldehyde (24 mg, 0.799 mmol) were then added, followed by the addition of allylboronate **10** (650 mg, 3.29 mmol), which was prepared (*Z*/*E*: 6/1) according to the literature. The reaction was stirred at rt overnight (14 h). The reaction

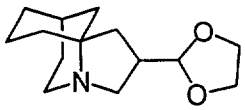
was concentrated to remove the organic solvent, it was then diluted with H_2O (5 mL), extracted with $CHCl_3$ (3 x 15 mL), dried with Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel chromatography, eluting first with 50% EtOAc/hexanes to remove the excess reagent **10**, then eluting with 20% CH_3OH/EtOAc afforded compound **11** (0.137, g, 0.46 mmol) in a 58% yield. R_f 0.28 (CH_3OH); ^1H NMR ($CDCl_3$, 270 MHz), 0.79-1.04 (m, 2H), 1.17-1.28 (m, 1H), 1.35-1.72 (m, 10H), 1.89-2.00 (m, 2H), 2.60-2.75 (m, 4H), 3.31 (s, 3H), 3.63-3.66 (m, 2H), 3.69-3.77 (m, 3H), 5.23-5.32 (m, 2H), 5.69 (ddd, J = 17.5, 10.2, 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 67.9 MHz), 136.9, 118.1, 101.3, 82.0, 61.6, 61.3, 56.4, 54.3, 47.5, 47.4, 40.8, 40.7, 37.3, 33.7, 32.7, 32.6, 32.4, 32.3, 29.8, 29.6, 22.5; IR (neat), 3323 (b), 3067, 1677, 1641, 1456, 1345, 127 cm^{-1}. HRMS calcd for $C_{17}H_{31}NO_3$ MH^+ 298.2382, found 298.2378.



7

3-[2-[2-Methoxy-but-3-enylamino]-ethyl]-cyclohexanone (7):

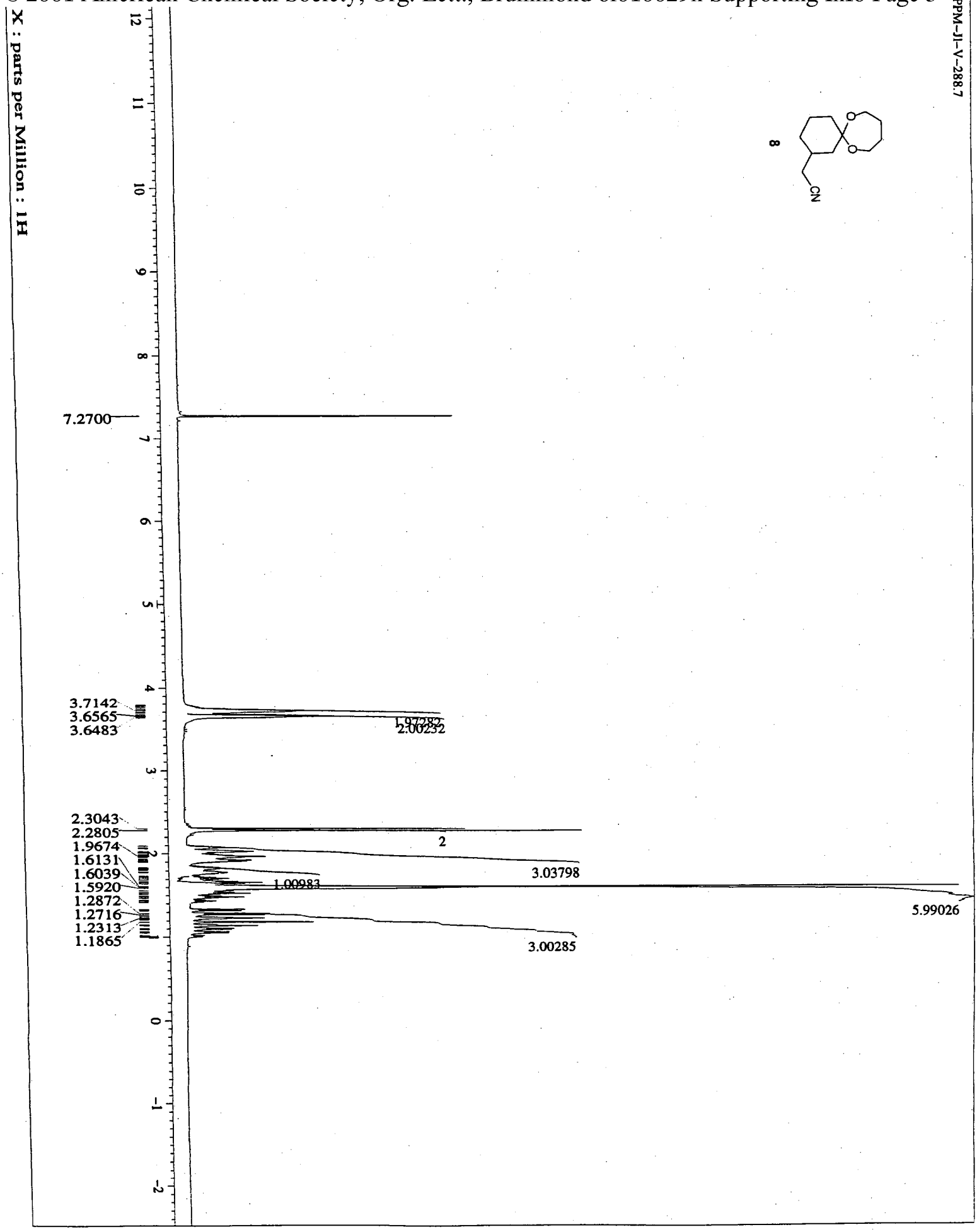
A solution of ketal **11** (55.0 mg, 0.185 mmol) in acetone (2 mL) was treated with 1 M HCl (1.0 mL) and the resulting solution was stirred at rt for 3 h. The organic solvent was evaporated, the pH of the solution was adjusted to *ca.* 8 using sat'd. $NaHCO_3$, then extracted with $CHCl_3$ (3 x 10 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography using silica gel, the faster moving impurities were eluted off the column using EtOAc, then the product with 10% CH_3OH/EtOAc to afford a yellow oil in 95% yield (39.6 mg, 0.176 mmol). R_f 0.28 (1% Et_3N in CH_3OH); ^1H NMR ($CDCl_3$, 270 MHz), 1.25-1.74 (m, 4H), 1.78-2.10 (m, 4H), 2.19-2.46 (m, 3H), 2.59-2.71 (m, 4H), 2.74 (bs, 1H), 3.30 (s, 3H), 3.72 (dt, J = 7.4, 4.5 Hz, 1H), 5.24-5.32 (m, 2H), 5.68 (ddd, J = 17.5, 10.2, 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 67.9 MHz), 211.5, 136.6, 118.3, 81.8, 56.4, 56.3, 54.1, 48.0, 47.1, 47.0, 41.4, 37.0, 36.9, 36.8, 36.7, 31.3, 25.1; IR (neat), 3323 (b), 3077, 1713, 1446, 1421, 1344, 1308, 1221 cm^{-1}. HRMS calcd for $C_{13}H_{23}NO_2$ MH^+ 226.1807, found 226.1801.



12

3-[1,3]-Dioxolan-2-yl-5-*aza*-tricyclo[6.3.1.0^{1,5}]dodecane (12):

The amino ketone **7** (74.0 mg, 0.33 mmol) was dissolved in benzene (5 mL) then treated with PTSA•H_2O (65 mg, 0.34 mmol). The resulting solution was refluxed in an oil bath with a Dean-Stark apparatus for 18 h. The reaction was cooled to rt and concentrated using rotary evaporation. The resulting residue was treated with dilute $NaHCO_3$ (5 mL) and extracted with $CHCl_3$ (4 x 10 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated. The diastereoselectivity of the tandem reaction was 2/1 according to the ^1H NMR integration of the formyl peaks. The crude product was dissolved in benzene (5 mL), treated with PTSA•H_2O (65 mg, 0.34 mmol) and ethylene glycol (36 μL, 0.65 mmol) and refluxed with a Dean-Stark apparatus for 3 h. The reaction was cooled to rt, the solvent was concentrated and the residue was treated with dilute $NaHCO_3$ (5 mL), extracted with $CHCl_3$ (4 x 10 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated. The diastereomeric ratio of the resulting ketal **12** (55.2 mg,) was 1/1 according to the ^1H NMR integration. The two diastereomers were separated by HPLC. Chromatographic conditions: semi-preparative column, MICROSORB™, Si 80-199-C5; solvent: Et_3N (1%) in CH_3OH; flow rate: 2.0 mL/min; t_R: 10.0 and 12.1 min, respectively. R_f: 0.1 (1% Et_3N, CH_3OH). HRMS calcd for $C_{14}H_{23}NO_2$ MH^+ 238.1807, found 238.1803. First diastereomer (t_R 10.0 min): ^1H NMR ($CDCl_3$, 270 MHz), 0.80-2.11 (m, 13H), 2.31-2.43 (m, 1H), 2.64-2.75 (m, 2H), 2.99-3.08 (m, 2H), 3.85-3.97 (m, 4H), 4.77 (d, J = 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 67.9 MHz), 106.9, 64.9, 55.1, 47.6, 41.9, 38.8, 37.2, 35.1, 31.6, 28.2, 27.0, 20.3; Second diastereomer (t_R 12.1 min): ^1H NMR ($CDCl_3$, 270 MHz) 0.84-2.14 (m, 13H), 2.32-2.48 (m, 1H), 2.72-2.92 (m, 2H), 3.03-3.31 (m, 2H), 3.84-3.98 (m, 4H), 4.81 (d, J = 6.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 67.9 MHz), 106.9, 65.0, 64.9, 53.5, 46.6, 41.9, 38.9, 36.5, 34.5, 30.7, 29.7, 27.7, 27.3, 21.8.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2.3043
2.2805
1.9674
1.6131
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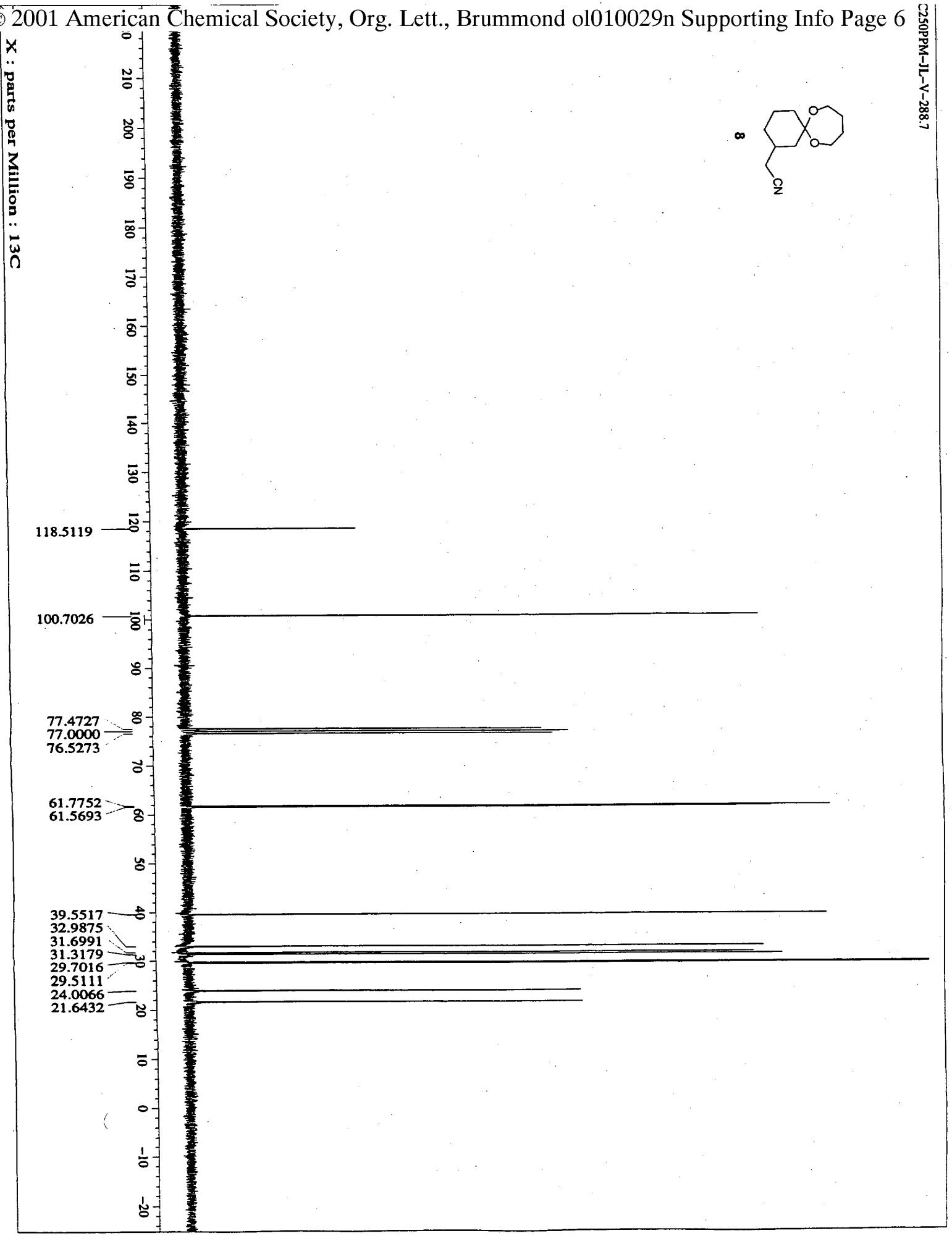

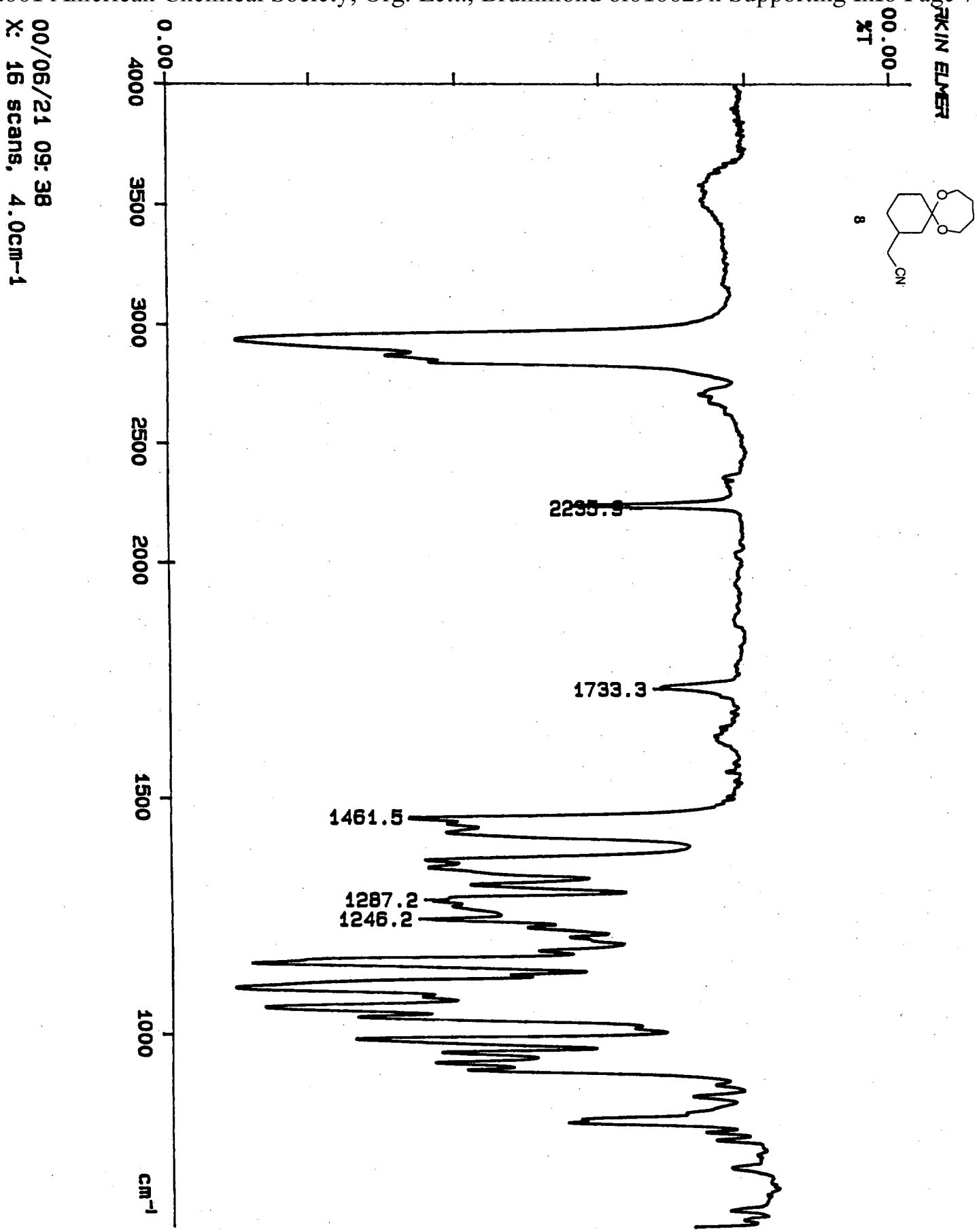

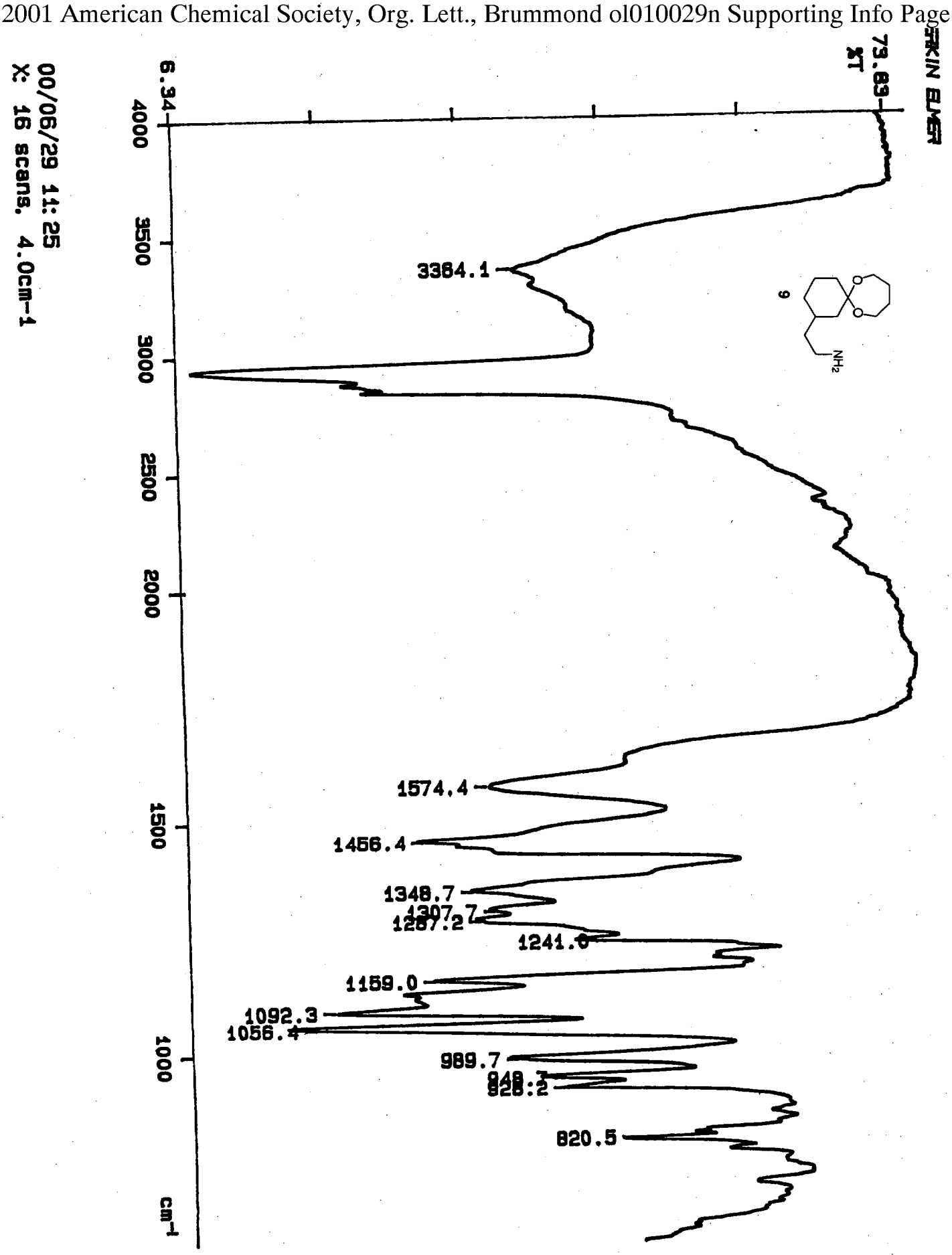

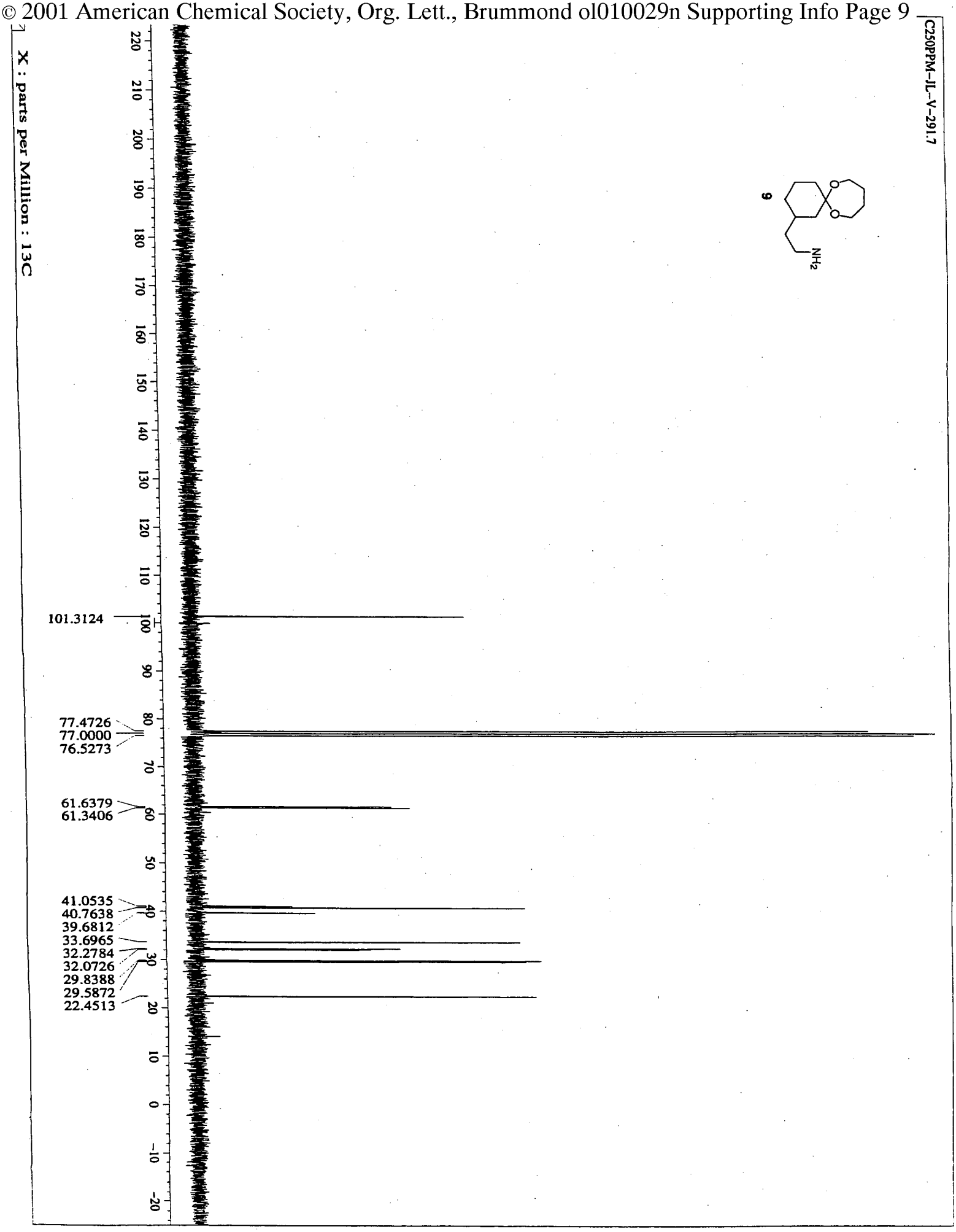
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32.0726
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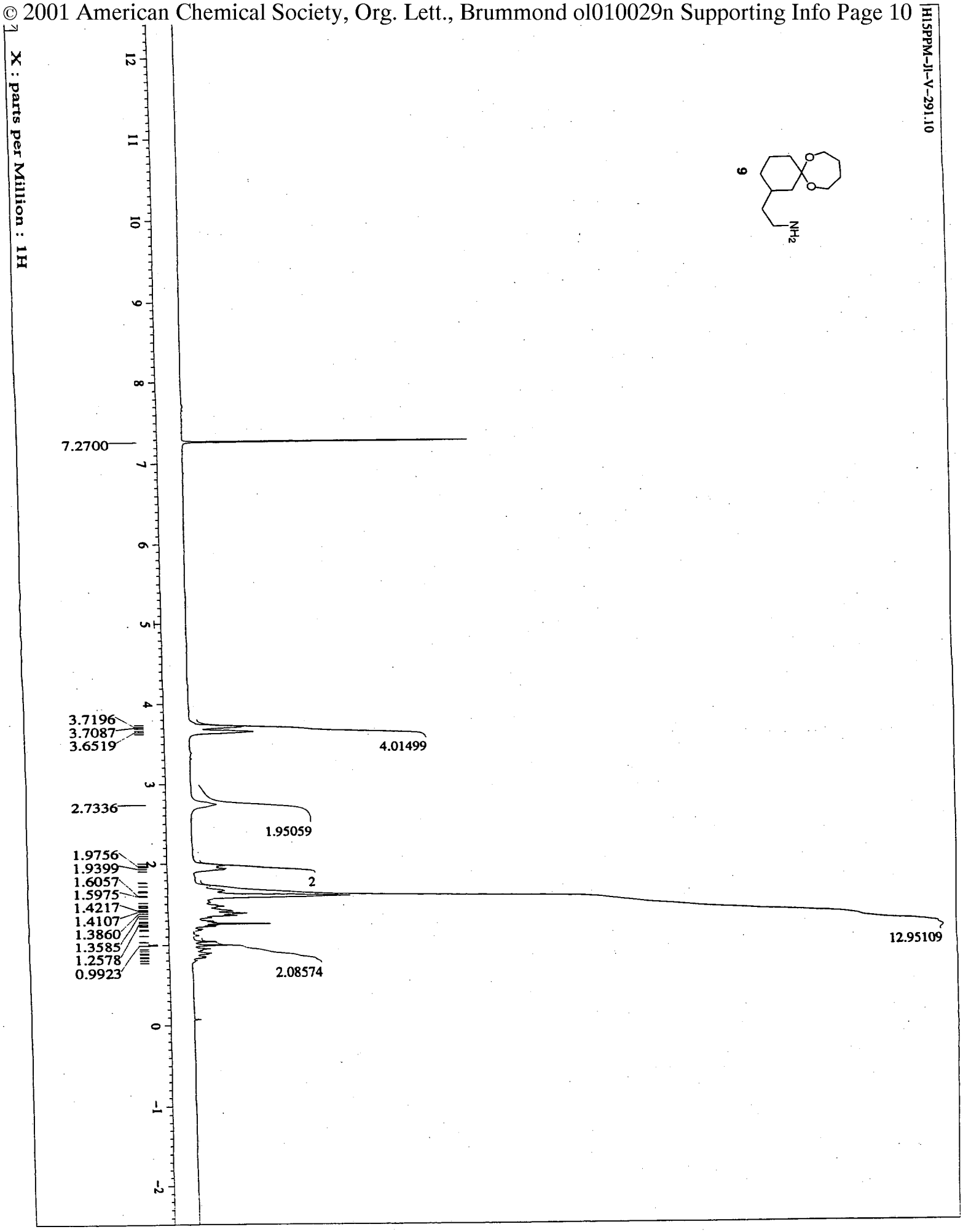
29.5872
22.4513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1.9399
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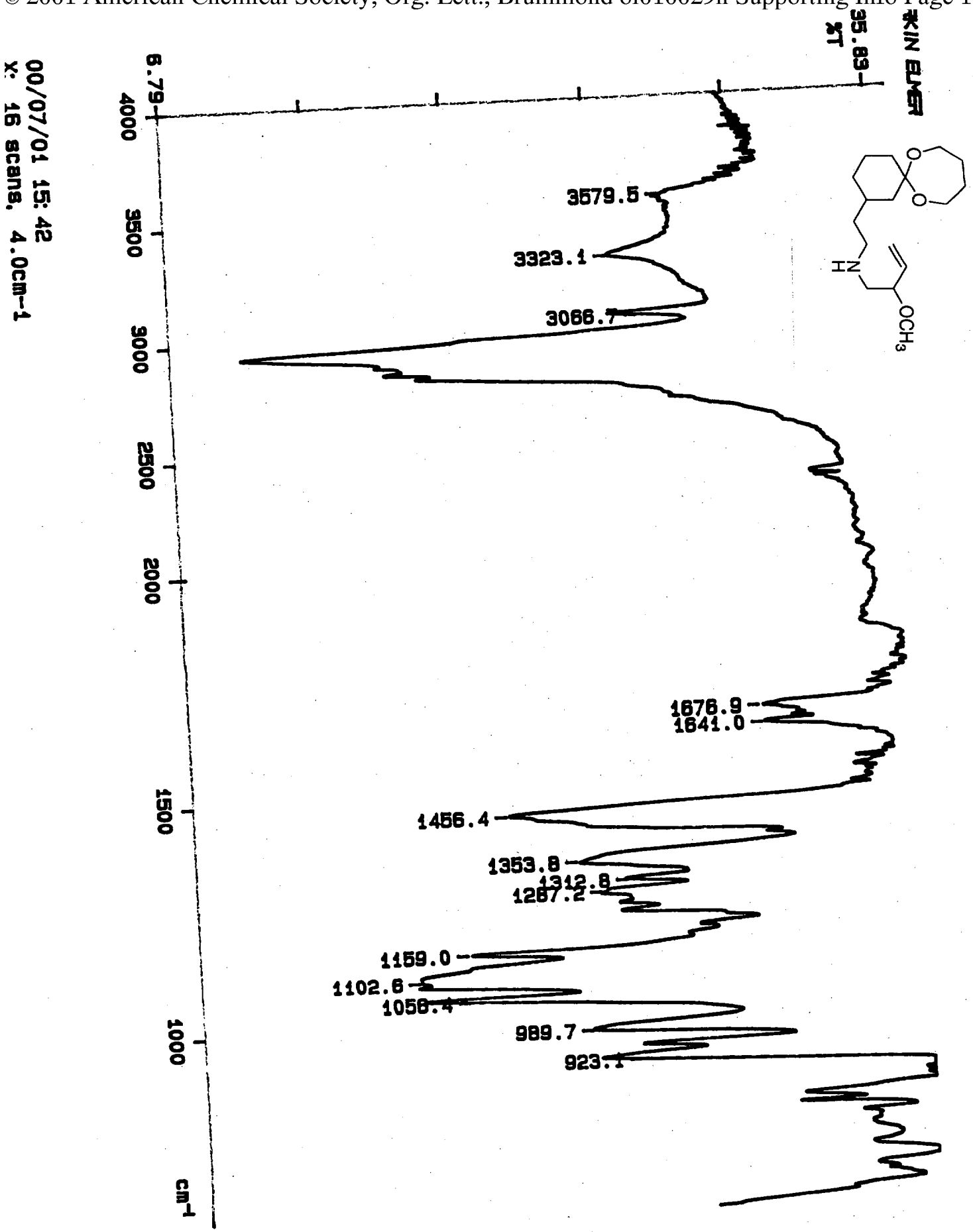
12.95109
2.08574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3000
2500
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1500
1000
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3066.7
1676.9
1641.0
1456.4
1353.8
1312.8
1287.2
1159.0
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00/07/01 15:42
X: 16 scans, 4.0cm-1
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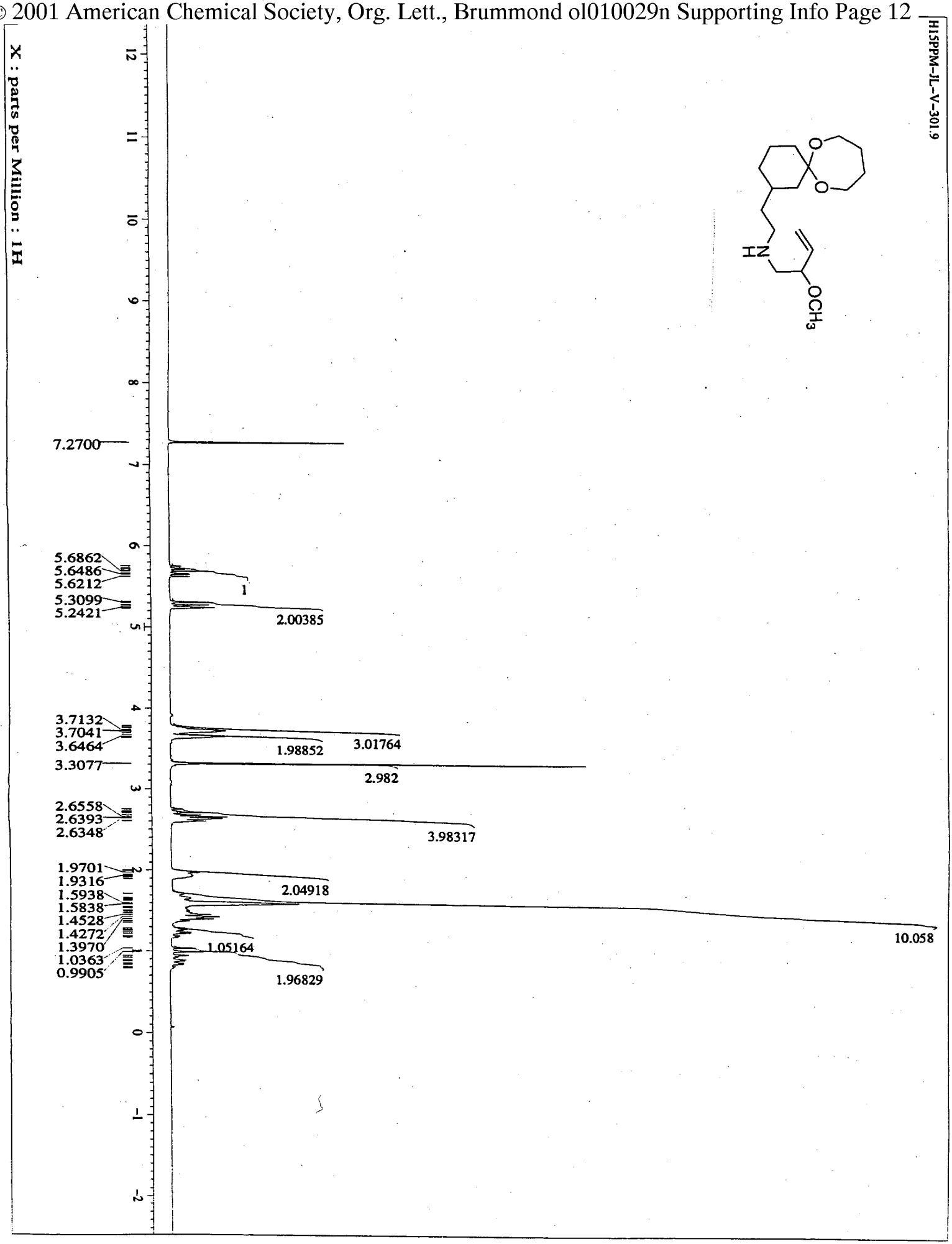
O
HN
OCH3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2.6393
2.6348
1.9701
1.9316
1.5938
1.5838
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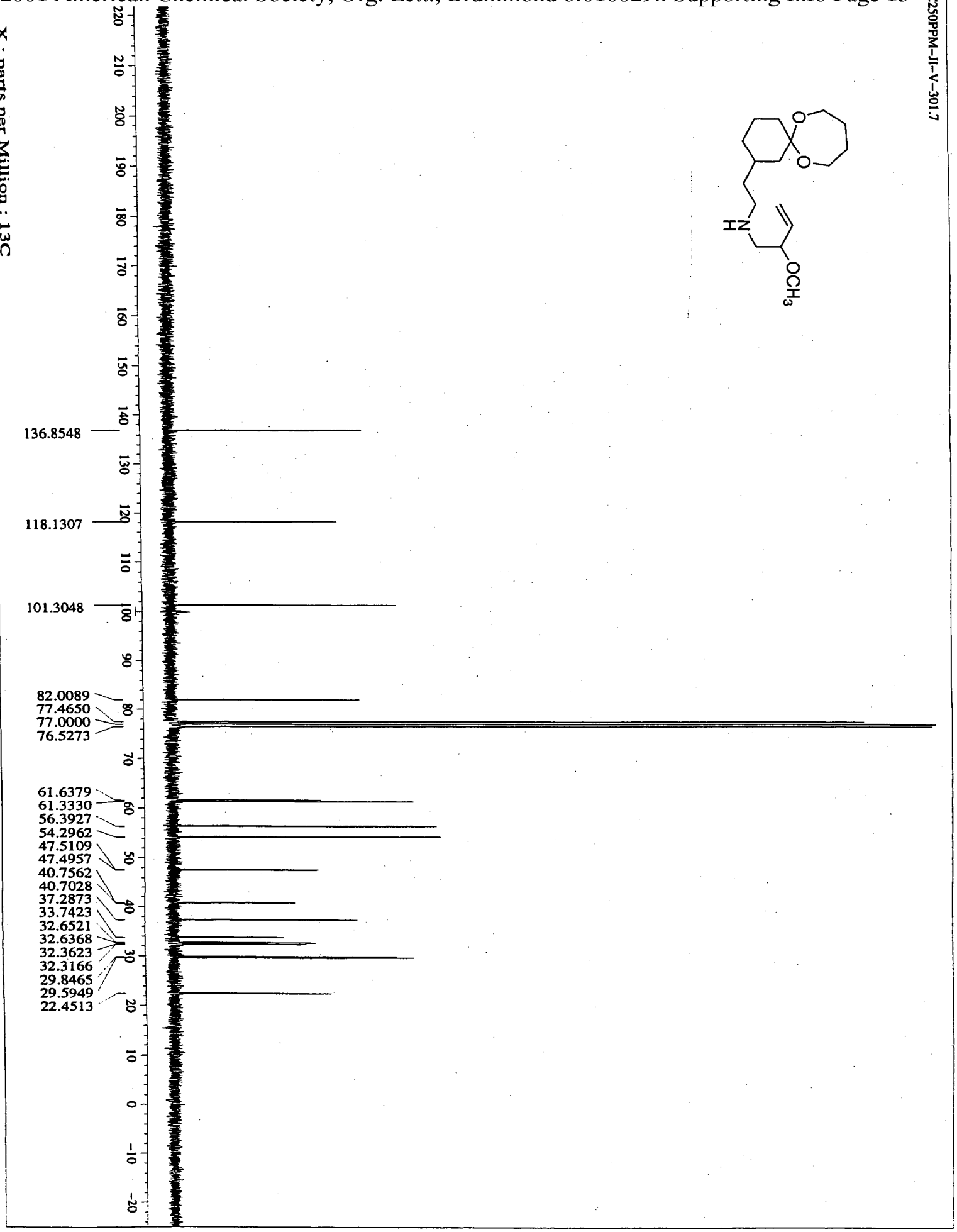
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54.2962
47.5109
47.4957
40.7562
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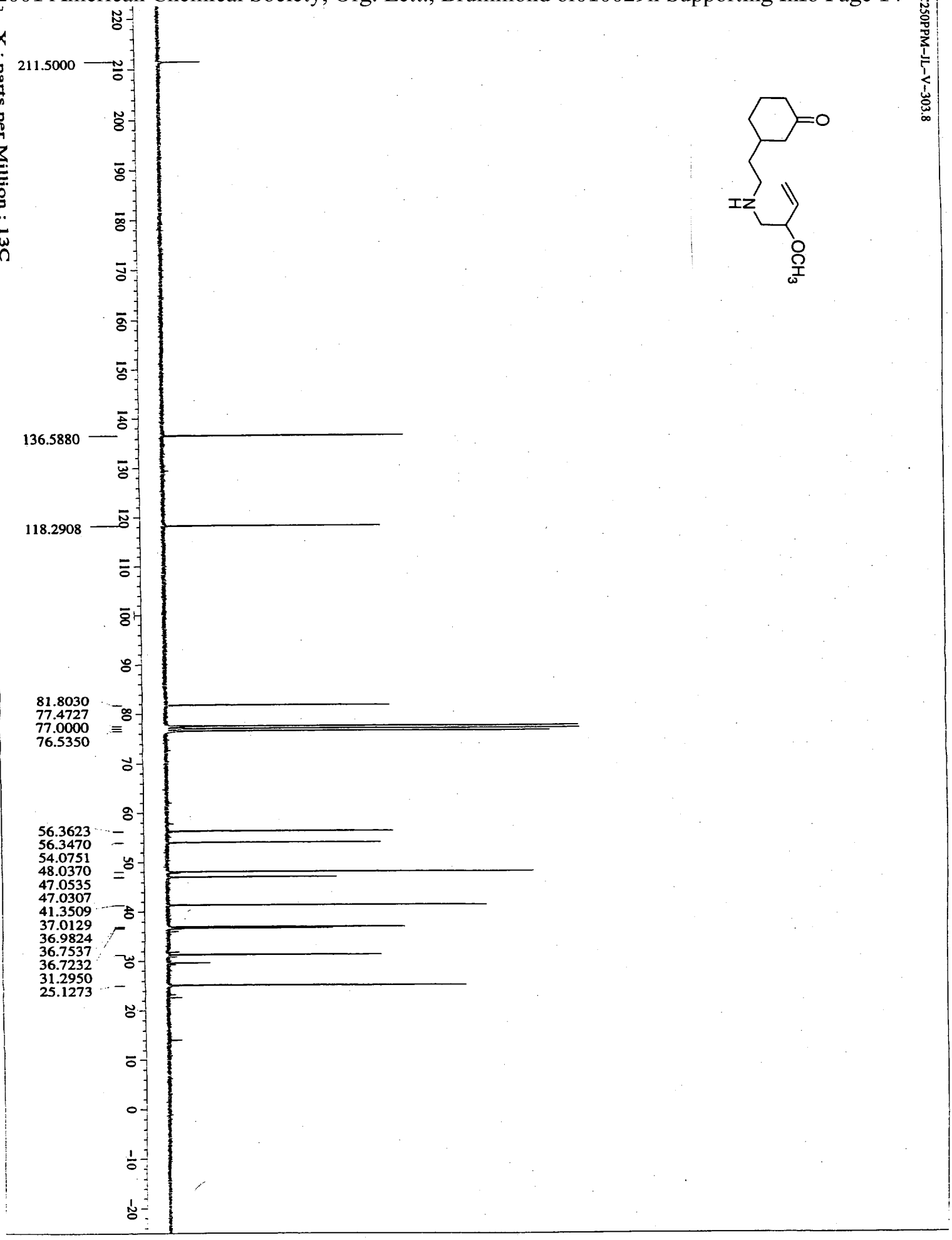
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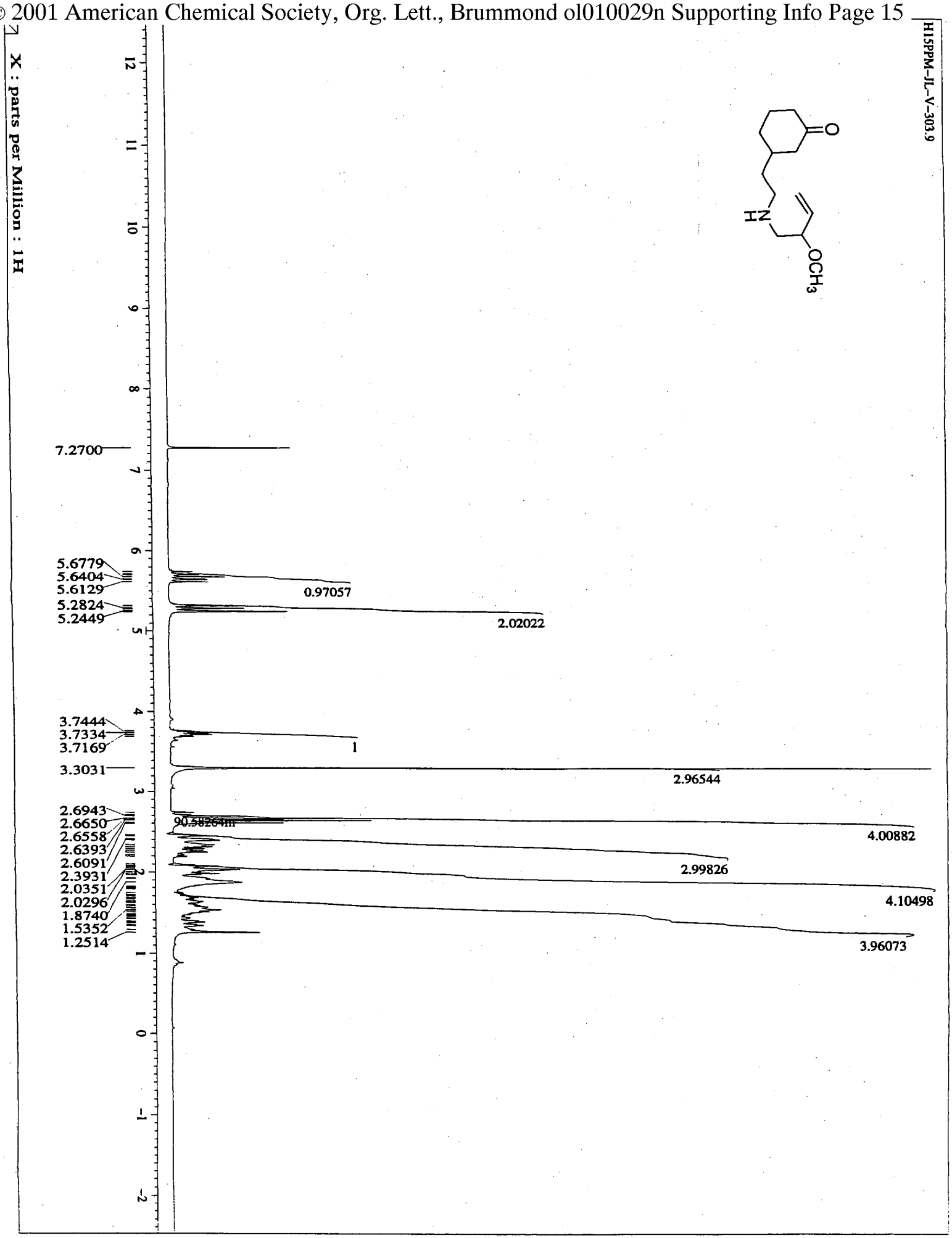
H
N
OCH3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2.6650
2.6558
2.6393
2.6091
2.3931
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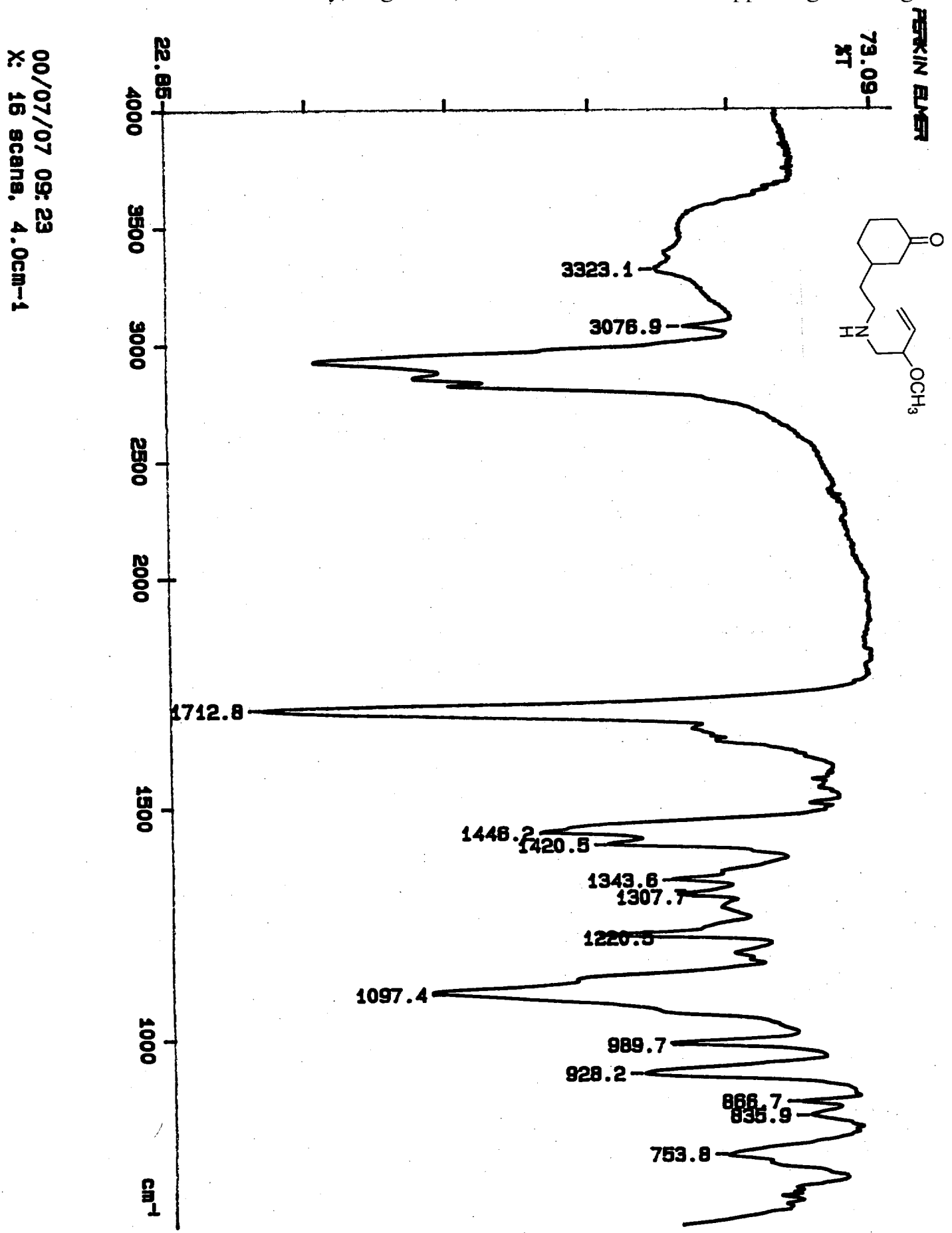

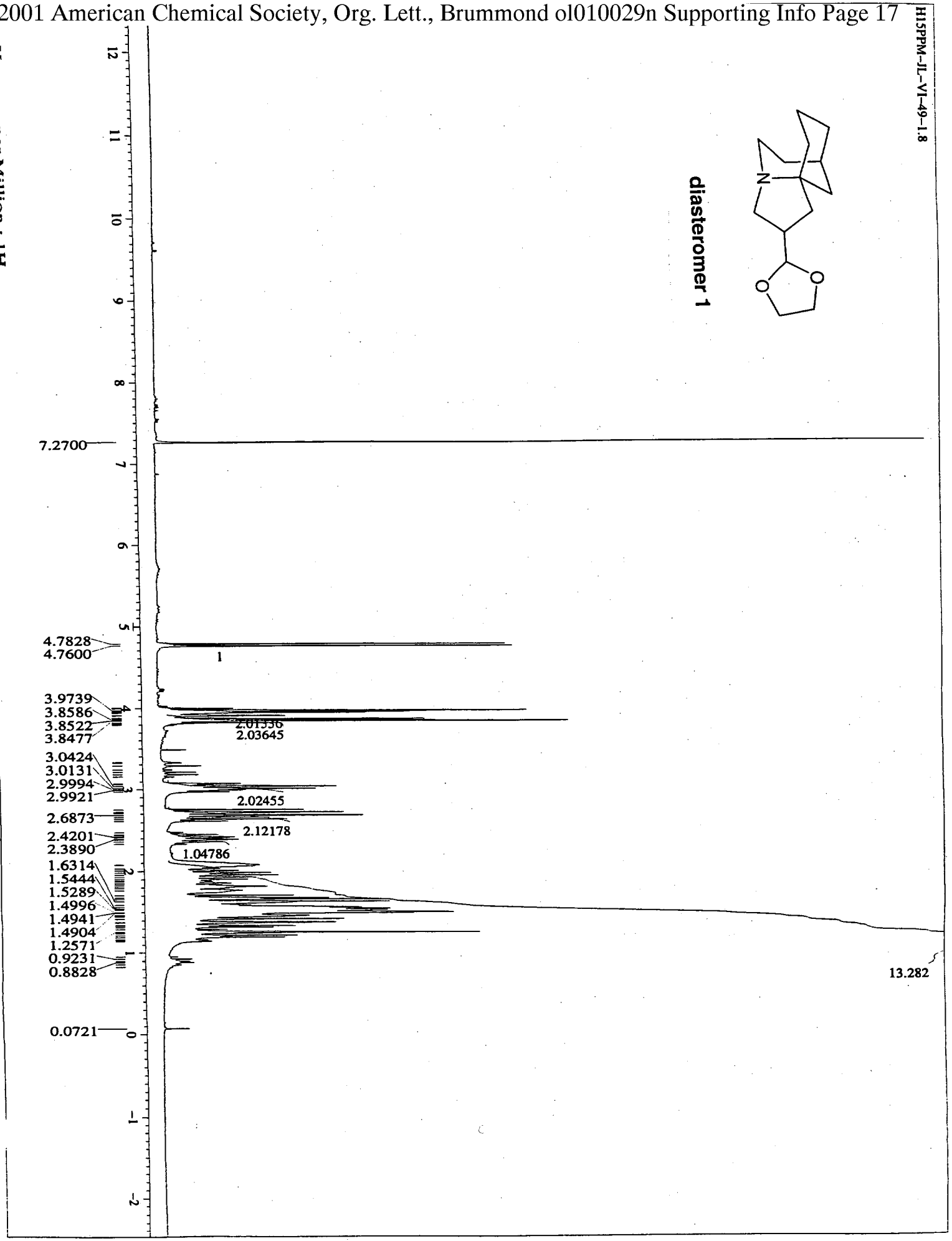

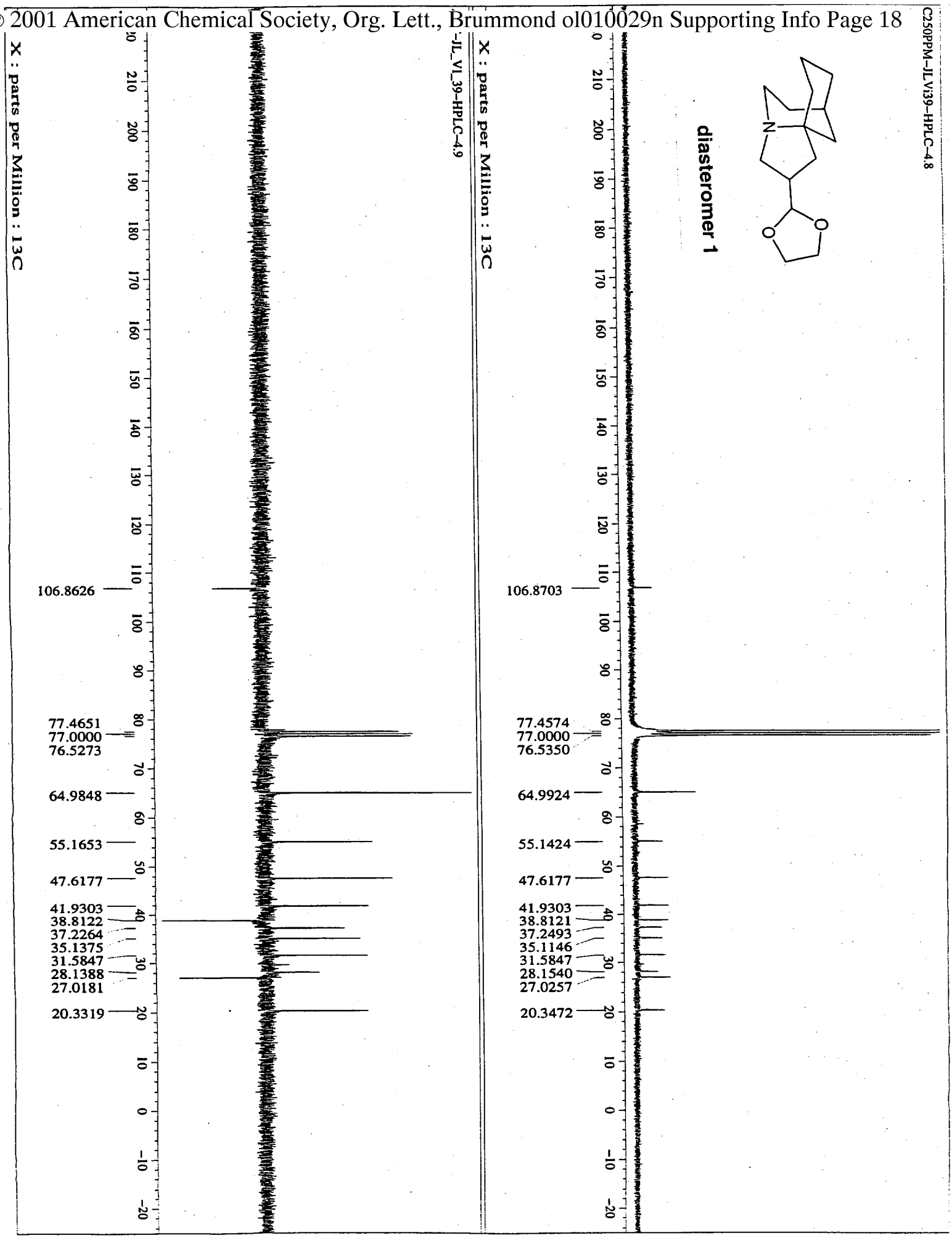

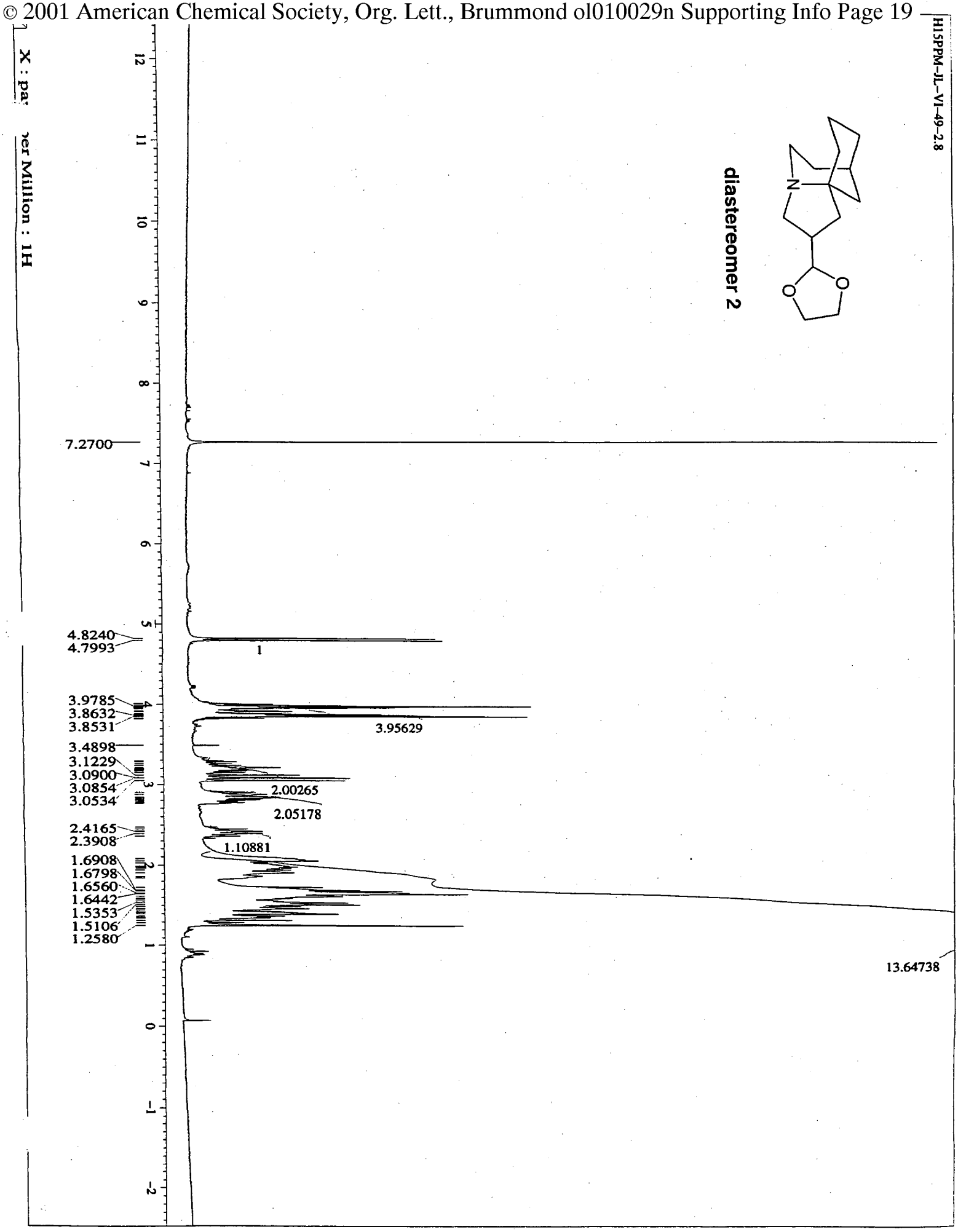
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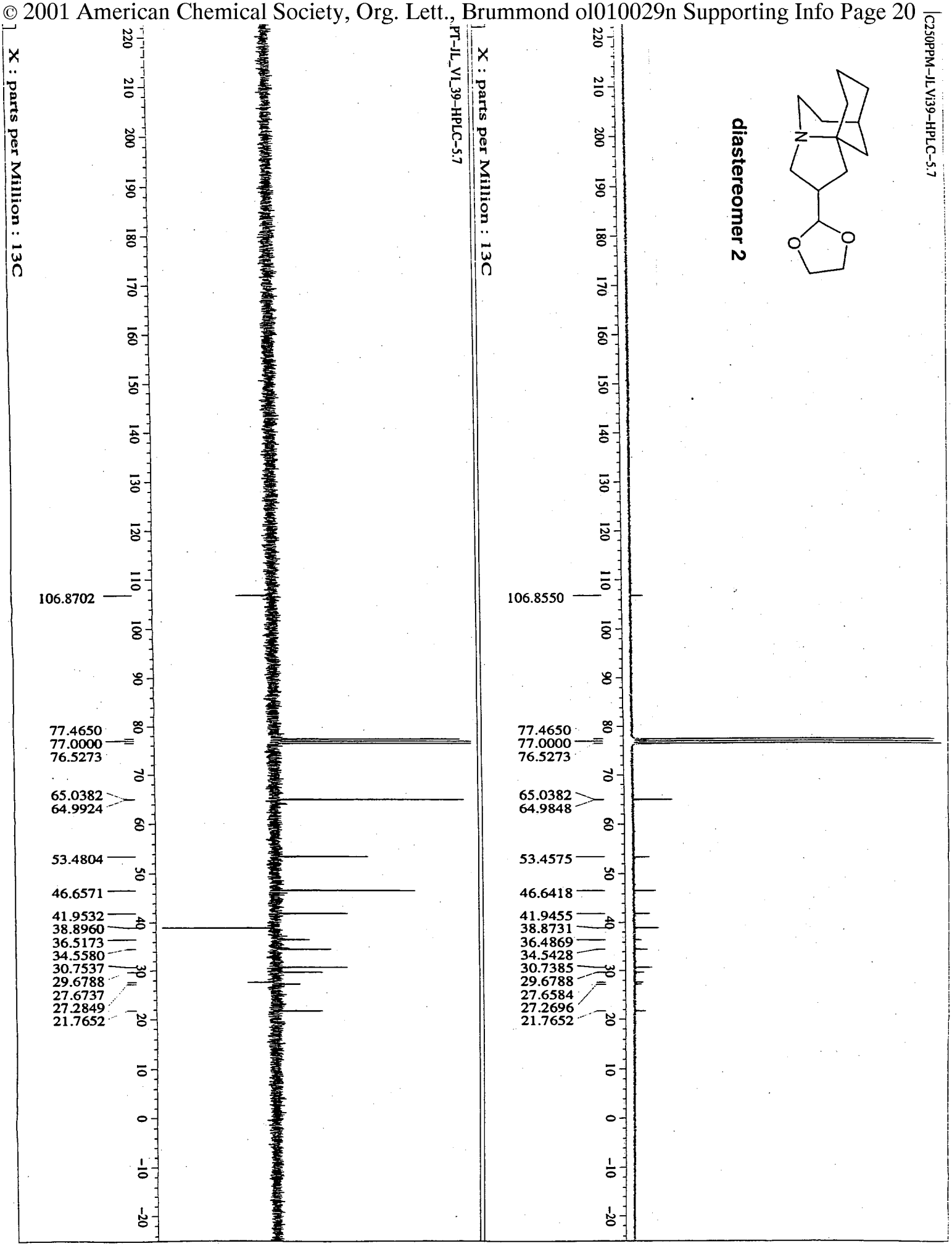
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30.7385
29.6788
27.6584
27.2696
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77.0000
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27.6737
27.2849
21.7652
X : parts per Million : 13C