Solid-Phase Oligosaccharide Synthesis (SOS): Preparation of Complex Structures Using A Novel Linker and Different Glycosylating Agents

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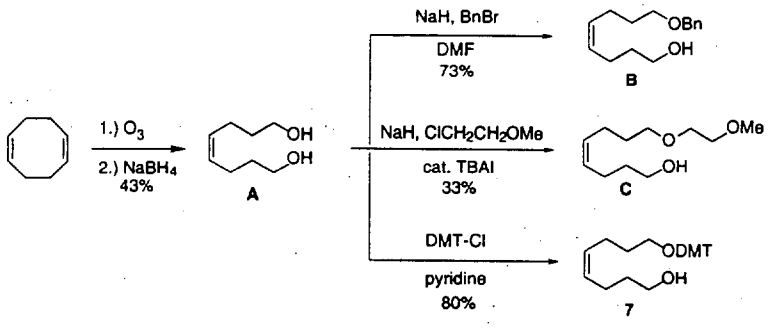
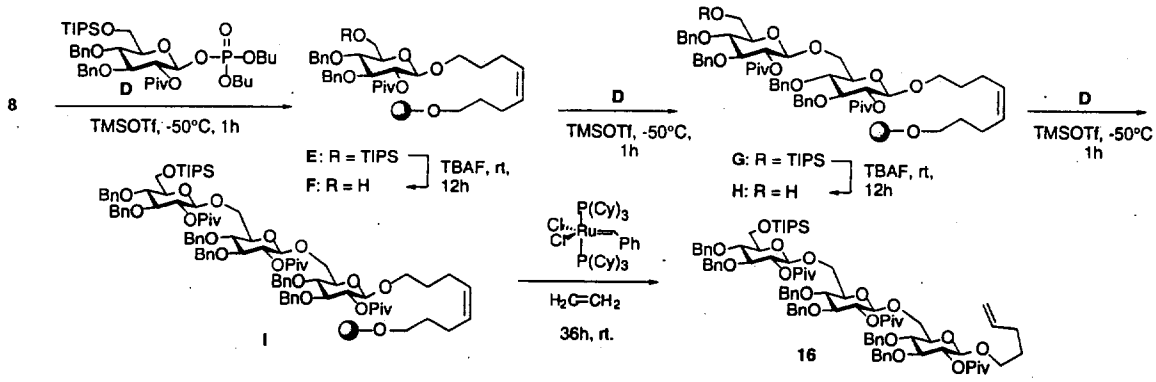
Supplementary Material



Scheme A. Synthesis of linker **7** and model systems.



Scheme B. Synthesis of trisaccharide **16** using glycosyl phosphate donor **D**.

Experimental Section

General Methods. All chemicals used were reagent grade and used as supplied except where noted. Dichloromethane (CH_2Cl_2) was distilled from

calcium hydride under N_2. Tetrahydrofuran (THF) was distilled from Na/benzophenone under N_2. Methanol was obtained from Aldrich in Sure-Seal containers and used without further purification. Glycosyl donors **17**[1] and **D**[2] were prepared following published procedures. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized by dipping the plates in a cerium sulfate-ammonium molybdate solution followed by heating. Liquid column chromatography was performed using forced flow of the indicated solvent on Sigma H-type silica (10-40 μm). ^{1}H NMR spectra were obtained on a Varian VXR-300 (300 MHz) or Varian VXR-500 (500 MHz) and are reported in parts per million (δ) relative to $CHCl_3$ (7.24 ppm). Coupling constants (*J*) are reported in Hertz. ^{13}C NMR spectra were obtained on a VXR-300 (75 MHz) or VXR-500 (125 MHz) and are reported in δ relative to $CDCl_3$ (77.0 ppm) as an internal reference. ^{31}P NMR spectra were obtained on a VXR-500 (200 MHz) and are reported in δ relative to H_3PO_4 (0.0 ppm) as an external reference. Polymer bound compounds were analyzed by HR-MAS NMR using the following conditions: All spectra were obtained on a Bruker DRX600 spectrometer, operating at 600 MHz (^{1}H) equipped with a 4 mm Bruker CCA HR-MAS probe. Samples (10 mg at 0.45-0.55 mmol g^{-1}) were loaded into a ceramic rotor, suspended in 30 μL $CDCl_3$ and spun at the magic angle at 3.0 KHz. ^{1}H NMR spectra were obtained with a Carr-Purcell-Meiboom-Gill pulse sequence[3]; 128 transients (64 s acquisition time, 0.5 s relaxation delay) were accumulated. MALDI-TOF mass spectrometry was performed as follows. A 1 μl aliquot of matrix solution [10 mg/mL 2,5-dihydroxybenzoic acid (DHB) in THF] was spotted on the sample holder and allowed to dry. Addition of a 1 μl aliquot of

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[1] Mayer, T. G.; Kratzer, B.; Schmidt, R. R. *Angew. Chem. Int. Ed.* **1994**, *33*, 2177.
[2] Plante, O. J.; Andrade, R. B.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 211.
[3] Carr, H. Y.; Parcell, E. M. *Phys. Rev.* **1954**, *94*, 630; Meiboom, S.; Gill, D. *Rev. Sci. Instr.* **1958**, *29*, 688.

oligosaccharide solution (5 mg/mL EtOAc) was co-spotted on the matrix, dried, and analyzed in the positive ion mode.

Synthesis of (*Z*)-Oct-4-ene-1,8-diol[4] A. Ozone was bubbled through a stirred solution of 1,5-cyclooctadiene (88.2 g, 0.815 mol, 1.0 equiv) in CH_2Cl_2/MeOH (3:2, 500 mL) at -78°C for 4 h at a rate of 3.3 mmol ozone/min. This solution was then added batchwise to a stirred solution of $NaBH_4$ (30 g, 0.815 mol, 1.0 equiv) in MeOH (2 L) at 0°C. The reaction mixture was warmed to room temperature over the course of 4-5 h and stirred an additional 12 h. The reaction was quenched with 100 mL of 10:1 (H_2O/glacial AcOH), filtered through a plug of silica gel, and concentrated under vacuum. The aqueous phase was extracted several times with hexanes, and the organic fractions were discarded. The aqueous phase was then extracted several times with diethyl ether. The combined organic phases were dried over Na_2SO_4 and co-evaporated with toluene to afford 50.2 g of **A** (43% yield).

Synthesis of 8-*O*-Benzyl-4-(*Z*)-octenol B. To a solution of (*Z*)-oct-4-ene-1,8-diol **A** (2.44 g, 16.9 mmol, 1.0 equiv) in DMF (40 mL) at 0°C was added sodium hydride (60% dispersion in mineral oil, 744 mg, 18.6 mmol, 1.1 equiv). The reaction mixture was stirred for 1 h at 0°C followed by the addition of benzyl bromide (2.2 mL, 18.6 mmol, 1.1 equiv). The reaction mixture was allowed to reach room temperature over 1 h and stirred for an additional 2 h. The reaction was quenched with 100 mL of water followed by extraction with diethyl ether (2 x 75 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Purification by flash silica column chromatography (15%→30% EtOAc/hexanes) afforded 2.89 g of **B** (73% yield). IR (thin film) 3387, 2933, 2861, 1107, 1073 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.37-7.23 (m, 10H), 5.39 (dd, *J* = 4.6, 5.1 Hz, 1H), 4.51 (s, 2H), 3.58 (t, *J* = 11.0 Hz, 2H), 3.49 (t, *J* = 6.4, 2H), 2.20-2.05 (m, 4H), 1.75-1.56 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ

[4] The protocol was modified from: Tolstikov, G. A.; Odinokov, V. N.; Galevva, P. J.; Bekevva, R. S. *Tetrahedron Lett.* **1978**, *21*, 1857.

138.4, 129.8, 129.7, 128.4, 127.7, 127.6, 72.9, 69.8, 62.2, 32.6, 29.7, 23.9, 23.6; FAB MS *m/z* (M^+) calcd 235.1698, obsd 235.1700.

Synthesis of 8-*O*-(2-Methoxyethyl)-4-(*Z*)-octenol C. To a solution of (*Z*)-oct-4-ene-1,8-diol **A** (2.15 g, 14.9 mmol, 1.0 equiv) in DMF (40 mL) at 0°C was added sodium hydride (60% dispersion in mineral oil, 656 mg, 16.4 mmol, 1.1 equiv). The reaction mixture was stirred for 1 h at 0°C followed by the addition of 2-chloroethyl methyl ether (1.5 mL, 16.40 mmol, 1.1 equiv) and tetrabutylammonium iodide (55 mg, 0.15 mmol, 0.01 equiv). The reaction mixture was allowed to reach room temperature over 1 h and stirred for an additional 12 h. The reaction was quenched with 100 mL of water followed by extraction with diethyl ether (2 x 75 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Purification by flash silica column chromatography (30%→50% EtOAc/hexanes) afforded 1.45 g of **C** (33% yield). IR (thin film) 3416, 2930, 2868, 1654, 1453, 1360, 1111 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.31 (m, 2H), 3.54 (t, *J* = 6.6 Hz, 2H), 3.48 (m, 4H), 3.89 (t, *J* = 6.6 Hz, 2H), 3.31 (s, 3H), 2.35 (s, 1H), 2.05 (m, 4H), 1.56 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 129.8, 129.7, 72.0, 70.6, 69.9, 62.1, 59.1, 32.6, 29.4, 23.6, 23.5; FAB MS m/z (M^+) calcd 202.1569, obsd 202.1580.

Synthesis of 8-*O*-Benzyl-4-(*Z*)-octenyl-2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside 1. 3,4,6-tri-*O*-benzyl-2-*O*-acetyl-α-D-trichloroacetimidate **17** (814 mg, 1.28 mmol, 1 equiv) and 8-*O*-benzyl-4-(*Z*)-octenol **B** (350 mg, 1.92 mmol, 1.5 equiv) were azeotropically dried by co-evaporation with toluene, dissolved in CH_2Cl_2 (10 mL) and cooled to 0°C. TMSOTf (23 µl, 0.128 mmol, .1 equiv) was added dropwise. After stirring for 20 minutes, triethylamine (23 µl) was added. The reaction mixture was partitioned between diethyl ether and water. The aqueous phase was extracted again with diethyl ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification by flash silica column chromatography (15% EtOAc/hexanes) afforded 660 mg of **1** (71% yield). $[\alpha]^{24}_D$: +14.0° (c 1.28,

CH_2Cl_2); IR (thin film) 3029, 2933, 2863, 1744, 1496 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.42-7.08 (m, 20H), 5.31 (m, 3H), 4.80 (d, *J* = 10.5 Hz, 1H), 4.78 (s, 1H), 4.65 (d, *J* = 8.5 Hz, 1H), 4.61 (d, *J* = 8.9 Hz, 1 H), 4.48 (d, *J* = 7.4 Hz, 1 H), 4.44 (d, *J* = 7.6 Hz, 1 H), 4.43 (s, 2H), 4.40 (d, *J* = 13.4 Hz, 1H), 3.95-3.34 (m, 9H), 2.17-1.92 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 170.6, 138.7, 138.5, 138.3, 138.0, 130.0, 129.4, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 97.8, 78.4, 75.3, 74.4, 73.6, 73.0, 71.9, 71.4, 69.9, 68.9, 67.4, 29.8, 29.5, 23.9, 23.8, 21.3; FAB MS *m/z* (M^+) calcd 709.3740, obsd 709.3727.

Synthesis of 8-*O*-(2-Methoxyethyl)-4-(*Z*)-octenyl-2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside 2. 3,4,6-tri-*O*-benzyl-2-*O*-acetyl-α-D-trichloroacetimidate **17** (502 mg, 0.788 mmol, 1 equiv) and 8-*O*-(2-methoxyethyl)-4-(*Z*)-octenol **C** (239 mg, 1.18 mmol, 1.5 equiv) were azeotropically dried by co-evaporation with toluene, dissolved in CH_2Cl_2 (10 mL) and cooled to 0°C. TMSOTf (22 µl, 0.118 mmol, 0.15 equiv) was added dropwise. After stirring for 20 minutes, triethylamine (22 µl) was added. The reaction mixture was partitioned between diethyl ether and water. The aqueous phase was extracted again with diethyl ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification by flash silica column chromatography (15% EtOAc/hexanes) afforded 435 mg of **2** (82% yield). $[\alpha]^{24}_D$: +7.5° (c 0.93, CH_2Cl_2); IR (thin film) 3283, 2867, 1740, 1496, 1453 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.45-7.00 (m, 15H), 5.39 (m, 2H), 4.90 (d, *J* = 2.1 Hz, 1H), 4.86 (s, 2H) 4.72 (dt, *J* = 1.8, 8.9 Hz, 2H), 4.57 (d, *J* = 10.5 Hz, 1H), 4.50 (d, *J* = 10.5 Hz, 1H), 4.16-3.30 (m, 14 H), 3.41 (s, 3H), 2.18 (s, 3H), 2.16-1.9 (m, 4H), 1.78-1.52 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 170.6, 138.7, 138.2, 137.9, 129.9, 129.3, 129.9, 129.3, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 97.8, 78.3, 78.4, 74.4, 73.5, 72.0, 71.9, 71.4, 70.9, 70.1, 68.8, 67.4, 59.2, 29.6, 29.5, 23.8, 21.3; FAB MS m/z (M^+) calcd 676.3611, obsd 676.3619.

Synthesis of 4-Pentenyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-

mannopyranoside 3.[5] 8-*O*-benzyl-4-(*Z*)-octenyl-2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-α-mannopyranoside **1** (47 mg, 0.065 mmol, 1.0 equiv) was azeotropically dried by co-evaporation with toluene and dissolved in 1.5 mL CH_2Cl_2. Grubbs' catalyst (10 mg, 0.013 mmol, 0.10 equiv) was added, and the reaction mixture was purged with ethylene and stirred at room temperature for 18 h. Another 0.10 equiv of the catalyst was added, and the solution was stirred for an additional 18 h. The mixture was diluted with CH_2Cl_2 and passed through a plug of Celite. Purification by flash silica column chromatography afforded 36 mg of **3** (100% yield).

Synthesis of 4-Butanal-2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside 4. Ozone was bubbled through a stirred solution of 8-*O*-benzyl-4-(*Z*)-octenyl-2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-α-mannopyranoside **1** (293 mg, 0.404 mmol, 1 equiv) in CH_2Cl_2 (8 mL) at -78°C until a blue color persisted. Triphenylphosphine (159 mg, 0.606 mmol, 1.5 equiv) was added, and the cooling bath was removed. After stirring 2 h at room temperature, the solution was partitioned between diethyl ether and water. The aqueous phase was extracted again with diethyl ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification by flash silica column chromatography (30% EtOAc/hexanes) afforded 200 mg of **4** (88% yield). $[\alpha]^{24}_D$: +9.5° (c 1.26, CH_2Cl_2); IR (thin film) 3029, 2918, 1743, 1728, 1496 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.76 (s, 1H), 7.27-7.08 (m, 15H), 5.27 (d, *J* = 1.3 Hz, 1H), 4.79 (d, *J* = 10.9 Hz, 1H), 4.76 (s, 1H), 4.65 (d, *J* = 10.8 Hz, 1H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 10.6 Hz, 1H), 4.41 (d, *J* = 10.5 Hz, 1H), 3.90-3.62 (m, 6H), 3.40-3.33 (m, 1H), 2.42 (t, *J* = 6.9 Hz, 2H), 2.08 (s, 3H), 1.82 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 201.6, 170.5, 138.3, 138.2, 137.9, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 97.8, 78.1, 75.2, 74.3, 73.5, 71.8, 71.6, 68.8, 68.7, 66.8, 40.7, 22.1, 21.1; FAB MS *m/z* (M^+) calcd 563.2645, obsd 563.2652.

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[5]J. R. Merritt, E. Naisang, B. Fraser-Reid, *J. Org. Chem.* **1994**, 59, 4443.

Benzyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside 5[6]. 8-*O*-(2-methoxyethyl)-4-(*Z*)-octenyl-2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopy-ranoside **2** (96 mg, 0.142 mmol, 1 equiv) was azeotropically dried by co-evaporation with toluene. Benzyl alcohol (74 μL, 0.710 mmol, 5 equiv) was added, and the reaction mixture was diluted with 4 mL CH_2Cl_2. *N*-Iodosuccinimide (48 mg, 0.213 mmol, 1.5 equiv) was added followed by triethylsilyl triflate (12 μL, 0.053 mmol, 0.375 equiv). The reaction mixture was stirred for 15 min at ambient temperature. The reaction was quenched with 10% $Na_2S_2O_4$ and diluted with ether. The aqueous layer was extracted again with diethyl ether, and the combined organic phases were washed with brine. Drying over Na_2SO_4 and purification by flash silica column chromatography (15→30% EtOAc/hexanes) afforded 11 mg of **5** (13% yield).

Synthesis of 8-(4,4'-Dimethoxytrityl)-4-(*Z*)-octenol 7. To a solution of (*Z*)-oct-4-ene-1,8-diol **A** (3.12 g, 21.6 mmol, 3.0 equiv) in pyridine (50 mL) at 0°C was added 4,4'-dimethoxytrityl chloride (2.44 g, 7.20 mmol, 1.0 equiv). The reaction mixture was gradually warmed to room temperature over 3 h and stirred for an addional 12 h. Ethyl acetate (150 mL) was added and the organic phase was washed with water (100 mL), saturated aqueous $NaHCO_3$ (100 mL), saturated aqueous NaCl (100 mL), and water (100 mL). Drying over Na_2SO_4 and purification by flash silica column chromatography (20%→50% EtOAc/hexanes, 1% triethylamine) afforded 2.51 g of **7** (80% yield). IR (thin film) 3390, 2934, 1607, 1508, 1250 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.39-7.31 (m, 2H), 7.28-7.06 (m, 7H), 6.73 (tt, *J* = 1.2, 9.0 Hz, 4H), 5.36-5.19 (m, 2H), 3.71 (s, 3H), 3.68 (s, 3H), 3.55 (td, *J* = 6.1, 13.2 Hz, 2H), 2.97 (dd, *J* = 6.6, 13.4 Hz, 2H), 2.17-1.95 (m, 4H), 1.66-1.45 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 158.5, 145.6, 136.8, 131.3, 130.2, 128.4, 128.0, 127.9, 126.8, 113.1, 85.9, 63.1, 55.4, 33.6, 32.8, 30.4, 25.8, 24.3; FAB MS *m/z* (M^+) calcd 469.2354, obsd 469.2346.

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[6] Itoh, Y.; Tejima, S. *Chem. Pharm. Bull.* **1984**, *32*, 957.

Synthesis of Functionalized Resin 8. 8-(4,4' dimethoxytrityl)-4-(*Z*)-octenol **7** (1.487 g, 3.17 mmol, 3.3 equiv) was dissolved in DMF (10 mL) and transferred to a solid-phase flask. Upon cooling to 0°C, NaH (60% dispersion in mineral oil, 0.127 g, 3.17 mmol, 3.3 equiv) was added and the solution was stirred for 1 h. Merrifield's resin (1% crosslinked: 0.800 g, 0.960 mmol, 1.0 equiv) was added along with tetrabutylammonium iodide (35.5 mg, 0.096 mmol, 0.1 equiv). After shaking for 1 h at 0°C, the reaction mixture was warmed to room temperature and shaken for 12 h. Capping of unreacted sites was accomplished by reaction with methanol (0.10 mL) and NaH (60% dispersion in mineral oil, 0.10 g) for 4 h. Methanol (5 mL) was added and the resin was washed with 10 mL each: 1:1 MeOH:DMF, DMF, 3 x THF and 3 x CH_2Cl_2. Drying under vacuum over P_2O_5 afforded 1.077 g resin. Analysis of a small sample of resin (10 mg) via a standard dimethoxytrityl cation assay revealed the loading to be 0.55 mmol/g.[7] Deprotection of the DMT functionalized resin was accomplished by washing the resin with 3 x 20 mL of 3% dichloroacetic acid/CH_2Cl_2. Further washing with 3 x 20 mL of CH_2Cl_2, 1% TEA/CH_2Cl_2, CH_2Cl_2 and drying under vacuum afforded 0.945 g resin **8** (0.62 mmol/g).

Correction for Loading Changes. Significant weight changes during repetitive glycosylations and deprotections were corrected for as follows: *Initial Loading x (Starting Mass Resin/Final Mass Resin) = Final Loading.* This calculation assumes complete conversion as is the case for all deprotections and most glycosylations. Example: Reaction of 0.171 g resin **8** (0.50 mmol/g) with 3.0 equiv donor **17** in the presence of 0.15 equiv TMSOTf afforded 0.217 g resin **18.** The loading of **18** was determined as follows: (0.50 mmol/g) x (0.171 g/0.217 g) = 0.39 mmol/g for **18.**

Synthesis of Dibutyl 4-*O*-*tert*-butyldimethylsilyl-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside phosphate 9. 4-*O*-*tert*-butyldimethylsilyl-3,6-di-*O*-benzyl-D-*arabino*-hex-1-enitol (1.05 g, 2.39 mmol, 1

[7] Pon, R. T. in: *Methods in Molecular Biology 20: Protocols for Oligonucleotides and Analogs* (Ed.: S. Agrawal), Humana Press, Totowa, **1993**, p. 467.

equiv) was azeotropically dried by co-evaporation with toluene, dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C. A 0.08 M solution of dimethyldioxirane in acetone (40 mL, 2.87 mmol, 1.2 equiv) was added and the reaction mixture was stirred for 15 min. After the solvent was removed under vacuum and the remaining residue dried *in vacuo* for 15 min at 0°C, CH_2Cl_2 (15 mL) was added. The solution was cooled to -78°C for 15 min. A solution of dibutylphosphate (0.50 mL, 2.51 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL) was added dropwise over 5 min. After warming to 0°C, DMAP (1.168 g, 9.56 mmol, 4.0 equiv) and pivaloyl chloride (0.59 mL, 4.78 mmol, 2.0 equiv) were added. The solution was warmed to room temperature over 1 h. A solution of 30% EtOAc/hexanes (50 mL) was added, and the white precipitate formed was filtered off through a silica plug (20 mL silica). The eluent was concentrated under vacuum and the residue was purified by flash silica column chromatography (25% EtOAc/hexanes) to afford **9** (1.48 g, 86% yield). $[\alpha]^{24}_D$: +18.6° (c 1.66, CH_2Cl_2); IR (thin film) 2959, 2858, 1741, 1455, 1362 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.35-7.22 (m, 10H), 5.73 (dd, *J* = 7.0, 7.3 Hz, 1H), 5.19 (dd, *J* = 7.9, 8.8 Hz, 1H), 4.73-4.61 (m, 2H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.49 (d, *J* = 12.2 Hz, 1H), 4.07-3.97 (m, 4H), 3.79 (t, *J* = 8.8 Hz, 1H), 3.74-3.71 (m, 1H), 3.67-3.63 (m, 1H), 3.61-3.52 (m, 2H), 1.63-1.55 (m, 4H), 1.40-1.32 (m, 4H), 1.13 (s, 9H), 0.92-0.81 (m, 15H), -0.02 (s, 3H), -0.09 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 177.0, 138.2, 138.0, 128.3, 128.2, 128.0, 127.7, 127.4, 126.9, 96.7, 83.2, 77.0, 74.6, 73.5, 73.4, 70.4, 68.9, 68.2, 68.1, 68.0, 67.9, 39.0, 32.3, 32.2, 27.3, 27.2, 26.2, 26.0, 18.8, 18.7, 18.1, 13.8, 13.7, 3.8, -4.8; ^{31}P-NMR ($CDCl_3$) δ -2.45; FAB MS *m/z* (M^++H) calcd 751.4006, obsd 751.3996.

General Procedure A: Solid-Phase Glycosylations Using Glycosyl Phosphates. Acceptor bound resin (50-200 mg, 0.45-0.55 mmol/g) was swollen in CH_2Cl_2 (3 mL) and shaken for 15 min. Following addition of 3 equiv donor (azeotropically dried by co-evaporation with toluene) in CH_2Cl_2 (2

mL/100 mg resin), the flask was shaken for 15 min and cooled to -78°C. A solution of 3.0 equiv TMSOTf in CH_2Cl_2 (0.5 mL) was added and shaking continued for 1 h. Upon warming to room temperature, 10 mL of methanol were added and the resin was washed with 3 x 5 mL MeOH, 5 mL 1:1 MeOH:THF, 3 x 5 mL each: THF and CH_2Cl_2. The resin was dried under vacuum for 8-12 h prior to deprotection or cleavage.

General Procedure B: Removal of Silyl Protecting Groups on the Solid-Phase. Silyl protected carbohydrate bound resin (50-200 mg) was swollen in THF (2 mL/100 mg resin) and shaken for 15 min. Following addition of 10 equiv TBAF (1.0 M in THF), the reaction mixture was shaken for 12 h at room temperature. The resin was washed with 3 x 5 mL MeOH, 5 mL 1:1 MeOH:THF, 3 x 5 mL THF, 3 x 5 mL CH_2Cl_2, and dried under vacuum over P_2O_5 for 8-12 h prior to glycosylation.

General Procedure C: Cleavage from the Solid Support by Olefin Cross-metathesis with Ethylene. Carbohydrate bound resin (5-100 mg, 0.45-0.55 mmol/g) was swollen in CH_2Cl_2 (1.5 mL). Grubbs' catalyst (0.1 equiv) was added, and the reaction mixture was purged with ethylene and was stirred at room temperature for 18 h. Another 0.1 equiv of the catalyst was added, and the solution was stirred for an additional 18 h. The mixture was diluted with CH_2Cl_2 and passed through a plug of Celite. Subsequent purification by flash silica column chromatography afforded the *n*-pentenyl glycoside.

4-Pentenyl 4-*O*-*tert*-butyldimethylsilyl-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside 15. Glycosylation of **8** with donor **9** according to General Procedure A at -50°C provided functionalized resin **10** (Scheme 3). Subsequent deprotection following General Procedure B and double glycosylation with General Procedure A at -50°C afforded disaccharide functionalized resin **12**. A second deprotection with General Procedure B and

double glycosylation with General Procedure A at -50°C gave trisaccharide functionalized resin **14**. Cleavage of resin **14** (72.5 mg, 0.31 mmol/g) with General Procedure C afforded 17.7 mg of **15** (53% yield) after flash silica column chromatography (5%→10% EtOAc/Hexanes). $[\alpha]^{24}_{D}$: -17.1° (c 1.65, CH_2Cl_2); IR (thin film) 2957, 1740, 1454, 1364, 1276 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.37-7.11 (m, 30H), 5.84-5.75 (m, 1H), 5.12-4.94 (m, 8H), 4.78 (d, *J* = 12.2 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.60-4.48 (m, 4H), 4.44-4.29 (m, 8H), 4.07-4.00 (m, 5H), 3.86-3.76 (m, 2H), 3.68-3.66 (m, 1H), 3.62-3.56 (m, 2H), 3.53-3.49 (m, 2H), 3.46-3.41 (m, 1H), 3.32-3.26 (m, 2H), 3.24-3.16 (m, 3H), 3.13-3.08 (m, 1H), 2.12-2.07 (m, 2H), 1.70-1.62 (m, 2H), 1.10 (s, 9H), 1.08 (s, 9H), 1.06 (s, 9H), 0.83 (s, 9H), -0.09 (s, 3H), -0.13 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 177.5, 177.4, 177.2, 140.0, 139.8, 139.4, 138.8, 138.7, 138.3, 129.4, 129.2, 129.1, 128.9, 128.8, 128.4, 128.1, 127.8, 127.7, 127.6, 127.5, 127.2, 115.5, 102.0, 100.4, 99.9, 83.8, 82.0, 81.6, 76.2, 75.9, 75.7, 75.6, 75.2, 75.0, 74.5, 74.1, 74.0, 73.2, 72.9, 71.9, 69.8, 69.6, 68.4, 39.5, 39.4, 30.8, 29.5, 27.9, 27.8, 26.6, 18.6, -3.2, -4.1; FAB MS *m/z* (M^+) calcd 1478.7724, obsd 1478.7699.

General Procedure D: Solid-Phase Glycosylations Using Trichloroacetimidates and TMSOTf. Acceptor bound resin (50-200 mg, 0.45-0.55 mmol/g) was swollen in a solution of 3.0 equiv donor (azeotropically dried by co-evaporation with toluene) in CH_2Cl_2 (2 mL/100 mg resin) and shaken for 15 min. A solution of 0.5 M TMSOTf in CH_2Cl_2 (0.15 or 0.30 equiv relative to acceptor) was added and the reaction mixture was shaken for 1 h at ambient temperature. The resin was then washed with 3 x 5 mL 20% MeOH/CH_2Cl_2, 1 x 5 mL MeOH, 3 x 5 mL each: 20% MeOH/THF, THF and CH_2Cl_2. The resin was dried under vacuum for 8-12 h prior to deprotection, cleavage or a second glycosylation. Double glycosylations were performed for all couplings described in Scheme 4.

General Procedure E: Solid-Phase Glycosylations Using Trichloroacetimidates and TESOTf. Acceptor bound resin (50-200 mg, 0.45-0.55 mmol/g) was swollen in a solution of 3.0 equiv donor (azeotropically

dried by co-evaporation with toluene) in CH_2Cl_2 (2 mL/100 mg resin) and shaken for 15 min. The resin was cooled to 0°C and shaken for 20 min. TESOTf (1.8 equiv) was added and shaking was continued for 4 h at 0°C. The resin was then washed with 3 x 5 mL CH_2Cl_2, 3 x 5 mL MeOH/CH_2Cl_2 (1:1), 1 x 5 mL MeOH, 3 x 5 mL THF, 3 x 5 mL CH_2Cl_2. The resin was dried under vacuum for 8-12 h prior to deprotection or cleavage.

General Procedure F: Removal of Acetate Protecting Groups on the Solid Support. Acetate protected carbohydrate bound resin (50-200 mg) was swollen in CH_2Cl_2 (10 x volume NaOMe/MeOH used) and shaken for 15 min. A solution of NaOMe (6 equiv, 0.5 M in MeOH) was added and shaking continued for 2 h. The resin was then washed with 3 x 5 mL 20% MeOH/CH_2Cl_2, 1 x 5 mL MeOH, 3 x 5 mL each: 20% MeOH/THF, THF and CH_2Cl_2. Drying under vacuum for 8-12 h provided resin of constant weight for glycosylation or cleavage.

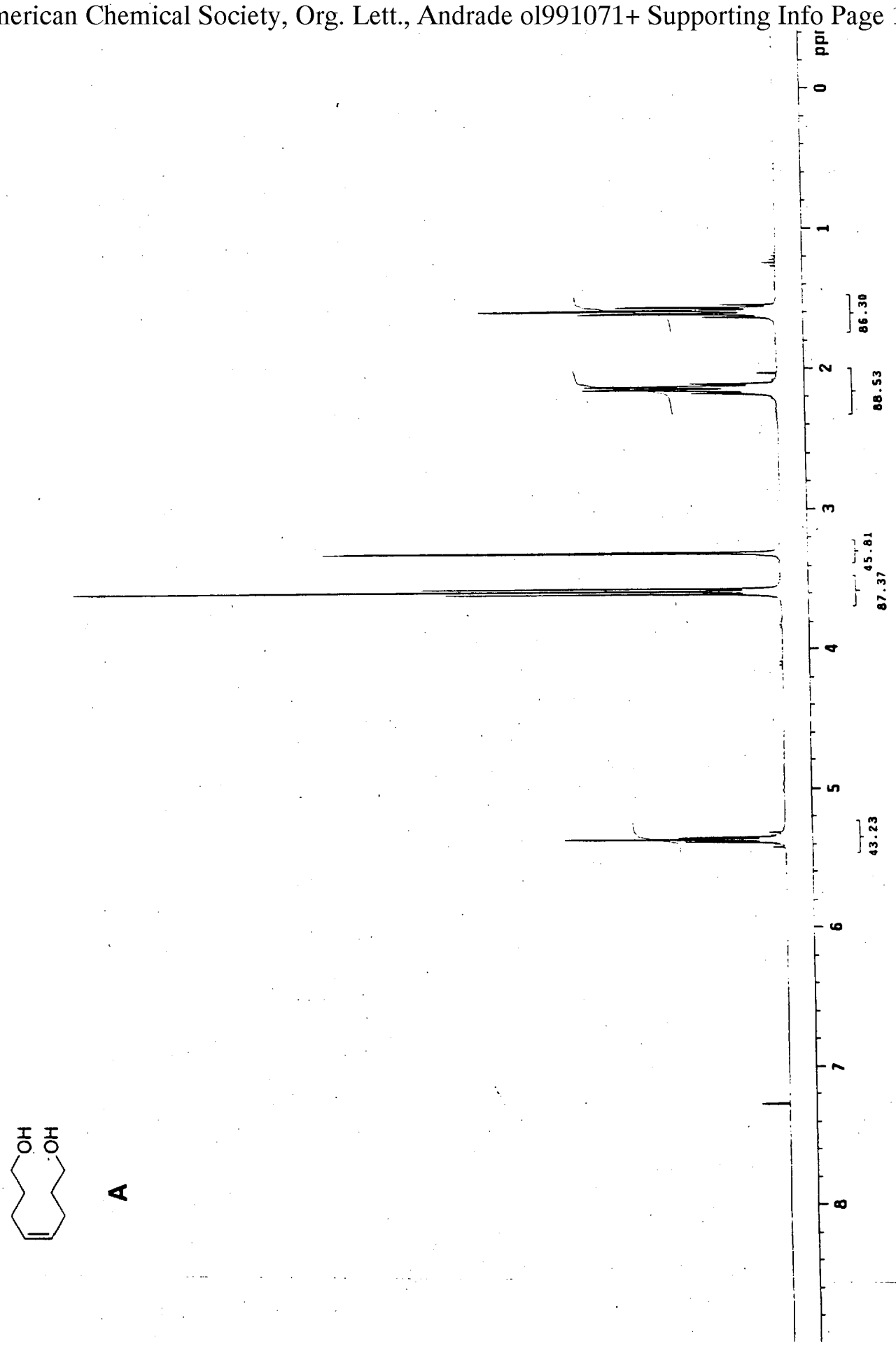
4-Pentenyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-*O*-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-*O*-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside 23[5]. Glycosylation of **8** with donor **17** according to General Procedure D provided functionalized resin **18** (Scheme 4). Subsequent deprotection following General Procedure F and glycosylation with General Procedure D afforded disaccharide functionalized resin **20**. A second deprotection with General Procedure F and glycosylation with General Procedure D gave trisaccharide functionalized resin **22**. When 0.30 equiv TMSOTf were used, cleavage of resin **22** (75.3 mg, 0.290 mmol/g) with General Procedure C afforded 22.8 mg of **23** (73% yield). When 0.15 equiv TMSOTf were used, cleavage of resin **22** (75.9 mg, 0.270 mmol/g) with General Procedure C afforded 19.8 mg of **23** (68% yield). When glycosylations were carried out with General Procedure E, cleavage of resin **22** (103 mg, 0.45 mmol/g) with General Procedure C afforded 50.1 mg of **23** (76% yield) after flash silica column chromatography (20% EtOAc/Hexanes). $[\alpha]^{24}_D$: +24.6° (c 1.50, CH_2Cl_2); IR (thin film) 3029, 2916, 2863, 2364, 2251, 1744, 1453; ^{1}H-NMR

($CDCl_3$) δ 7.45-7.15 (m, 45H), 5.77 (m, 1H), 5.55 (m, 1H), 5.19 (d, *J* = 1.5 Hz, 1H), 5.09 (d, *J* = 1.8 Hz, 1H), 5.06 (d, *J* = 1.8 Hz, 1H), 5.01-4.29 (m, 18H), 4.17-3.51 (m, 18H), 3.27 (m, 1H), 2.14 (s, 3H), 2.10-1.96 (m, 2H), 1.70-1.50 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 170.4, 138.8, 138.7, 138.6, 138.5, 138.4, 138.2, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 115.0, 100.8, 99.7, 99.6, 98.9, 79.9, 79.7, 78.3, 77.6, 77.4, 77.2, 76.8, 75.3, 75.0, 74.9, 74.8, 74.5, 74.4, 73.6, 73.5, 72.3, 72.2, 72.0, 69.7, 69.5, 68.9, 67.1, 30.5, 28.8, 21.3; FAB MS *m/z* (M^+) calcd 1438.6804, obsd 1438.6832.

4-Pentenyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-*O*-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-*O*-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-*O*-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-*O*-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside 28. Deprotection of trisaccharide functionalized resin **22** according to General Procedure F gave **24**. Glycosylation of **24** with donor **17** according to General Procedure D provided functionalized resin **25** (Scheme 4). Subsequent deprotection following General Procedure F and glycosylation with General Procedure D afforded pentasaccharide functionalized resin **27**. When 0.30 equiv TMSOTf were used, cleavage of resin **27** (46.5 mg, 0.24 mmol/g) with General Procedure C afforded 10.5 mg of **28** (41% yield). When 0.15 equiv TMSOTf were used, cleavage of resin **27** (47.5 mg, 0.23 mmol/g) with General Procedure C afforded 9.6 mg of **28** (38% yield) after flash silica column chromatography (15%→20% EtOAc/Hexanes). ^{1}H-NMR ($CDCl_3$) δ 7.43-7.02 (m, 75H), 5.81-5.72 (m, 1H), 5.59-5.57 (m, 1H), 5.28-5.17 (m, 3H), 5.06-4.32 (m, 34H), 4.22-4.05 (m, 6H), 4.02-3.42 (m, 30H), 3.26-3.21 (m, 2H), 2.15 (s, 3H), 2.12-2.01 (m, 2H), 1.66-1.57 (m, 2H); Calcd: $M^+(C_{142}H_{152}O_{27})$ = 2289.1 *m/z* ; Found: MALDI-TOF-MS (DHB, THF) = 2290.

4-Pentenyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopy-

ranosyl-(1→2)-*O*-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-*O*-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-*O*-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→2)-*O*-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-*O*-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-*O*-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside 33. Deprotection of pentasaccharide functionalized resin **27** according to General Procedure F gave **29**. Glycosylation of **29** with donor **17** according to General Procedure D provided functionalized resin **30** (Scheme 4). Subsequent deprotection following General Procedure F and glycosylation with General Procedure D afforded heptasaccharide functionalized resin **32**. When 0.30 equiv TMSOTf were used, cleavage of resin **32** (50.0 mg, 0.22 mmol/g) with General Procedure C afforded 2.8 mg of **33** (8% yield). When 0.15 equiv TMSOTf were used, cleavage of resin **32** (57.1 mg, 0.21 mmol/g) with General Procedure C afforded 3.1 mg of **33** (9% yield) after flash silica column chromatography (15%→20%→25% EtOAc/Hexanes). ^{1}H-NMR ($CDCl_3$) δ 7.40-6.95 (m, 105H), 5.81-5.74 (m, 1H), 5.56-5.54 (m, 1H), 5.31-5.24 (m, 4H), 5.17 (app s, 1H), 5.05 (app s, 1H), 5.00-4.33 (m, 50H), 4.29-4.20 (m, 4H), 4.17-4.09 (m, 11H), 4.03-3.42 (m, 49H), 2.11 (s, 3H), 2.05-1.99 (m, 2H), 1.66-1.57 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 170.3, 138.8, 138.7 (2 lines), 138.6, 138.5, 138.3, 138.2, 128.6, 128.5 (2 lines), 128.4 (3 lines), 128.3 (3 lines), 128.2 (2 lines), 128.1 (2 lines), 128.0 (2 lines), 127.9 (2 lines), 127.8, 127.7, 127.6 (3 lines), 127.5 (2 lines), 115.0, 101.7, 101.6, 107.4, 100.9, 99.6, 98.9 (2 lines), 79.8, 79.5, 78.4, 77.4, 76.8, 75.4, 75.3, 75.1, 74.9, 74.4, 73.5, 73.4, 72.5, 72.3, 72.2, 69.6, 68.8, 67.2, 30.5, 28.9, 21.4; Calcd: $M^+(C_{196}H_{208}O_{37})$ = 3153.4 *m/z*; Found: MALDI-TOF-MS (DHB, THF) = 3154.



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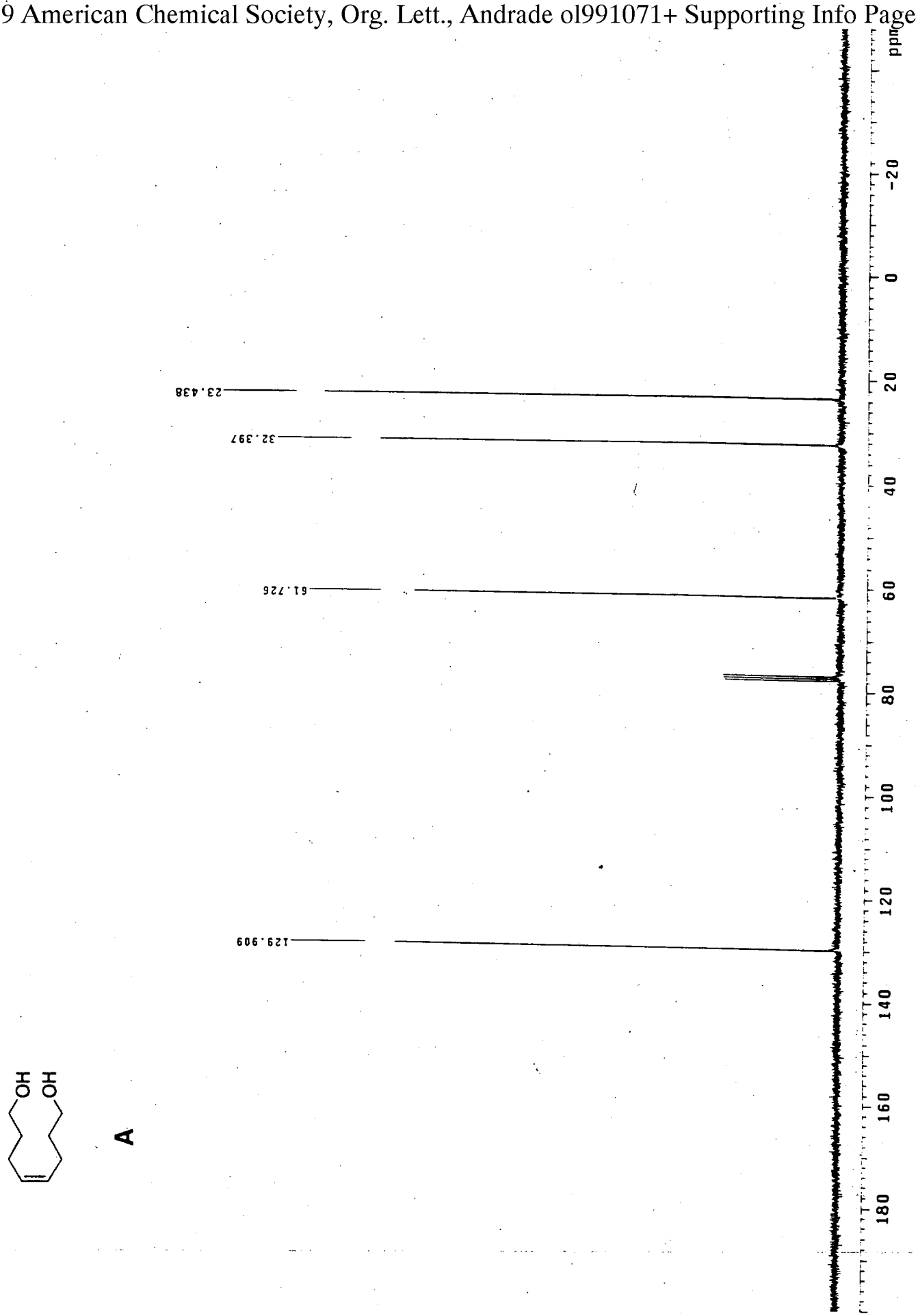

A


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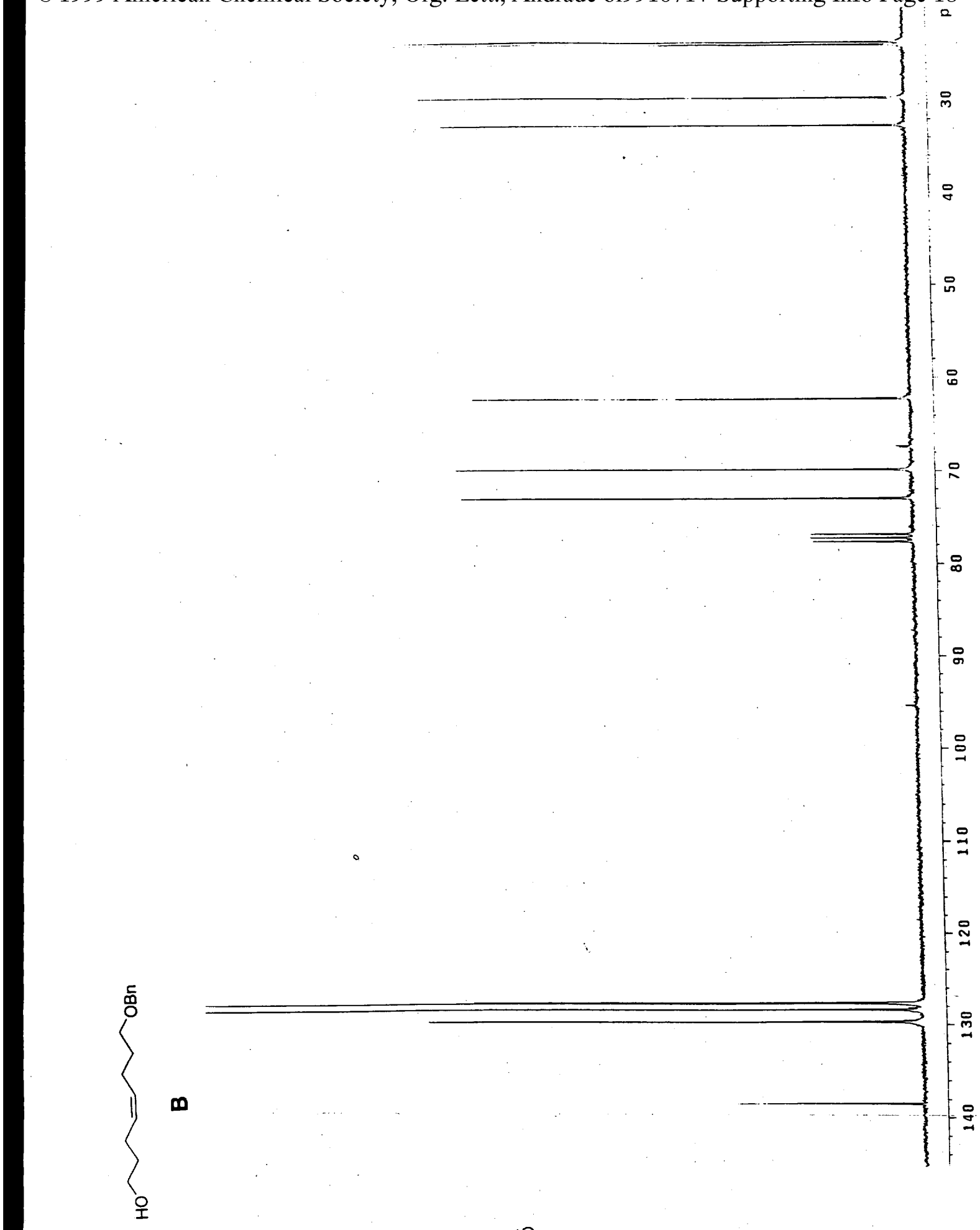
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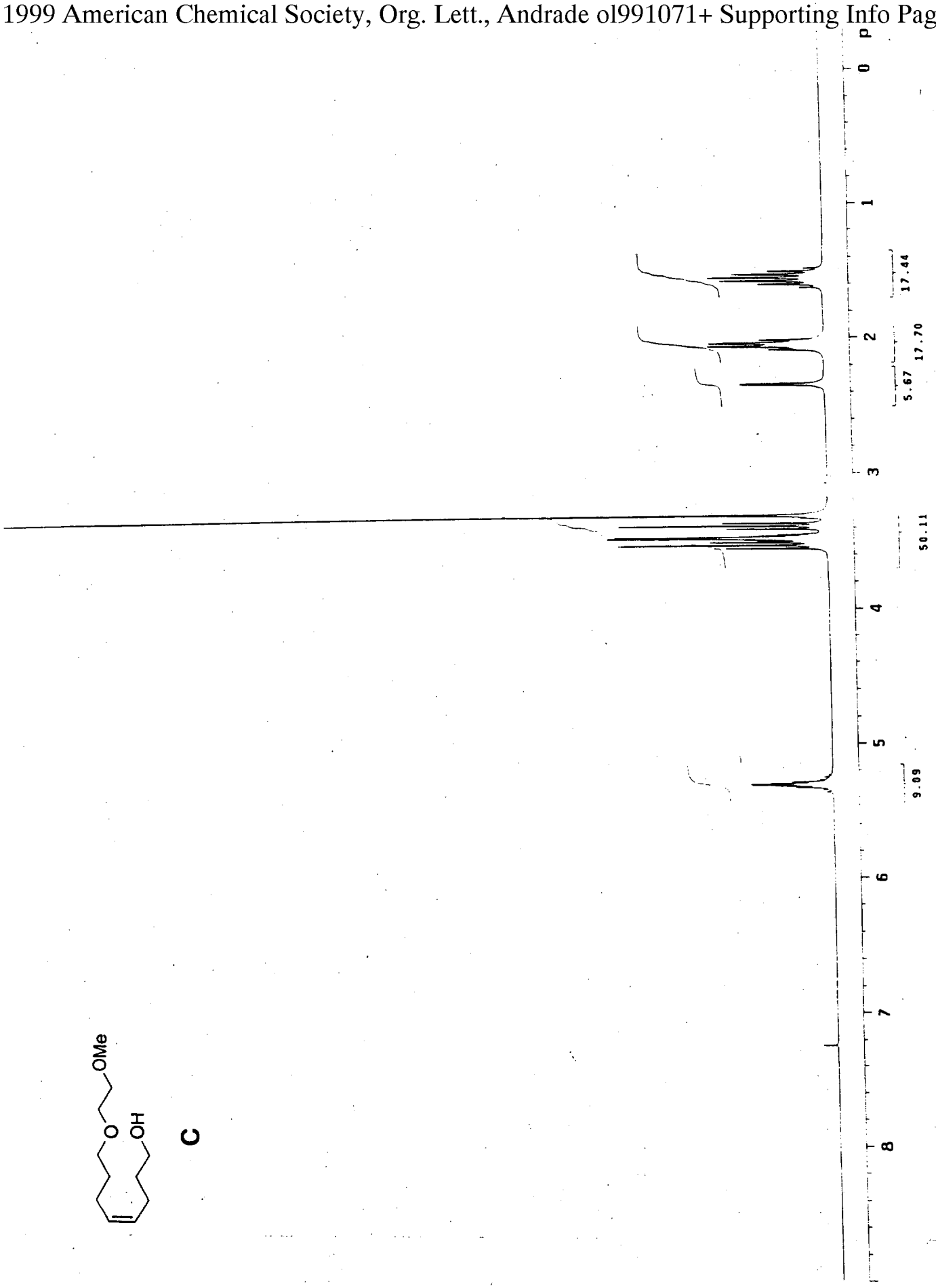

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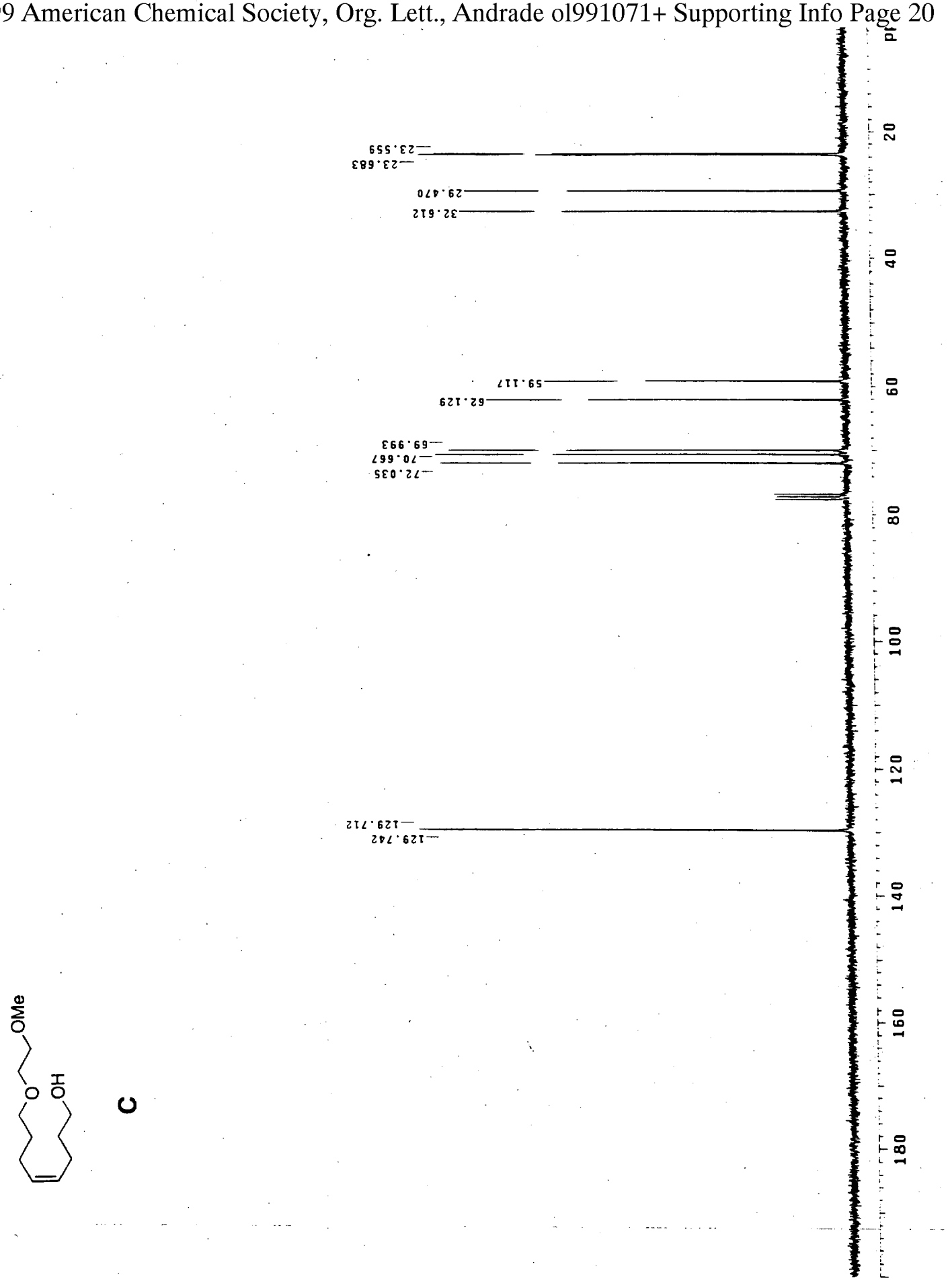

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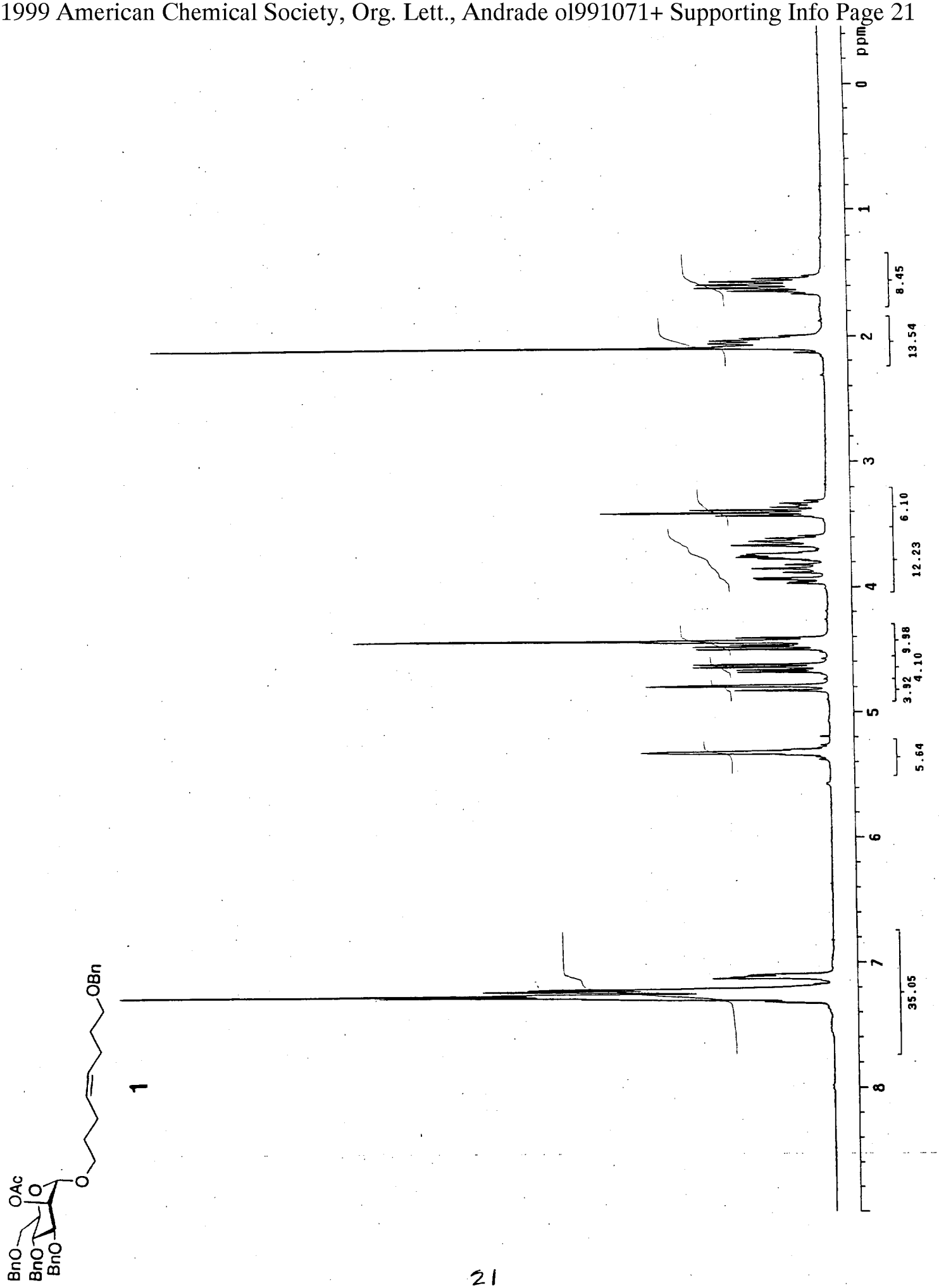

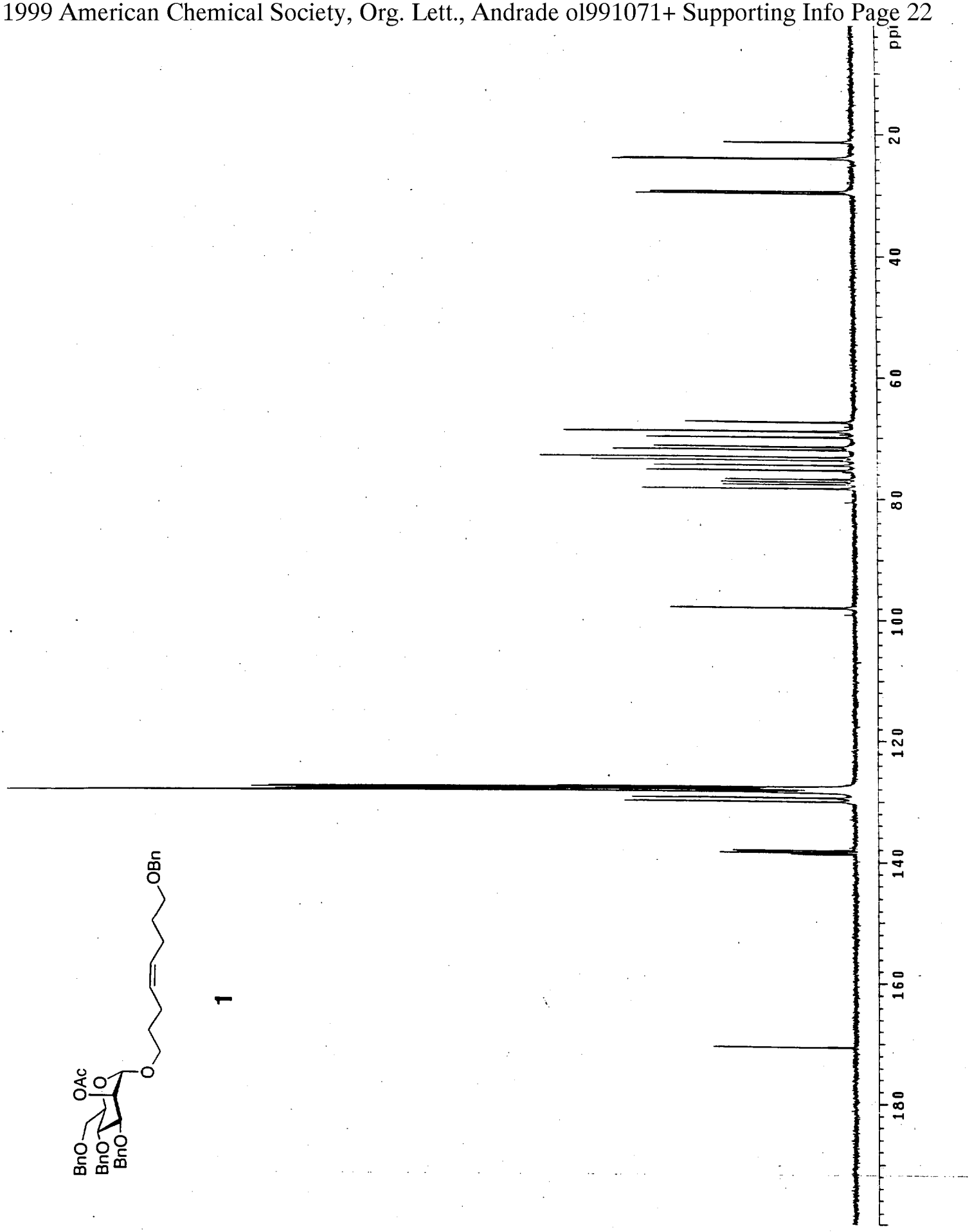
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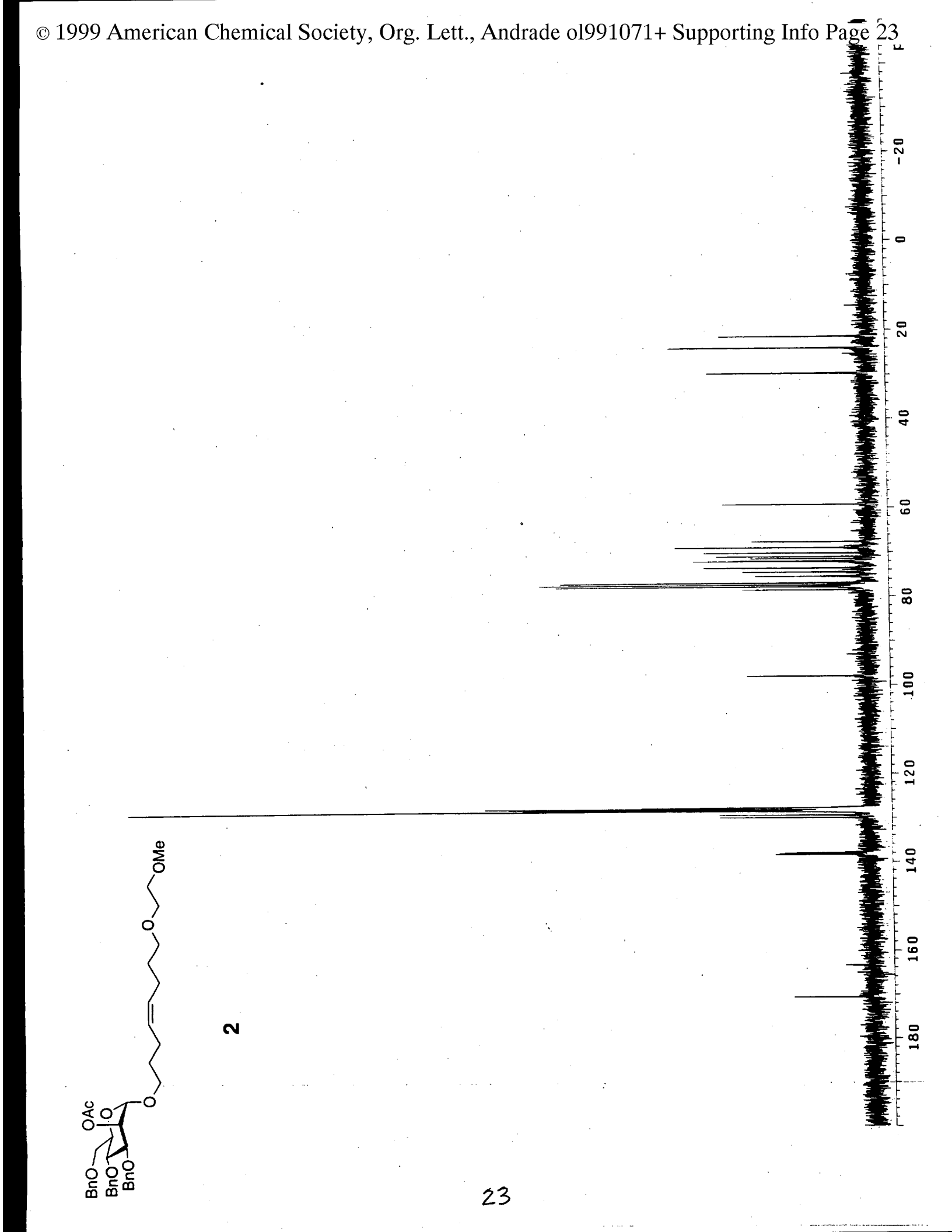

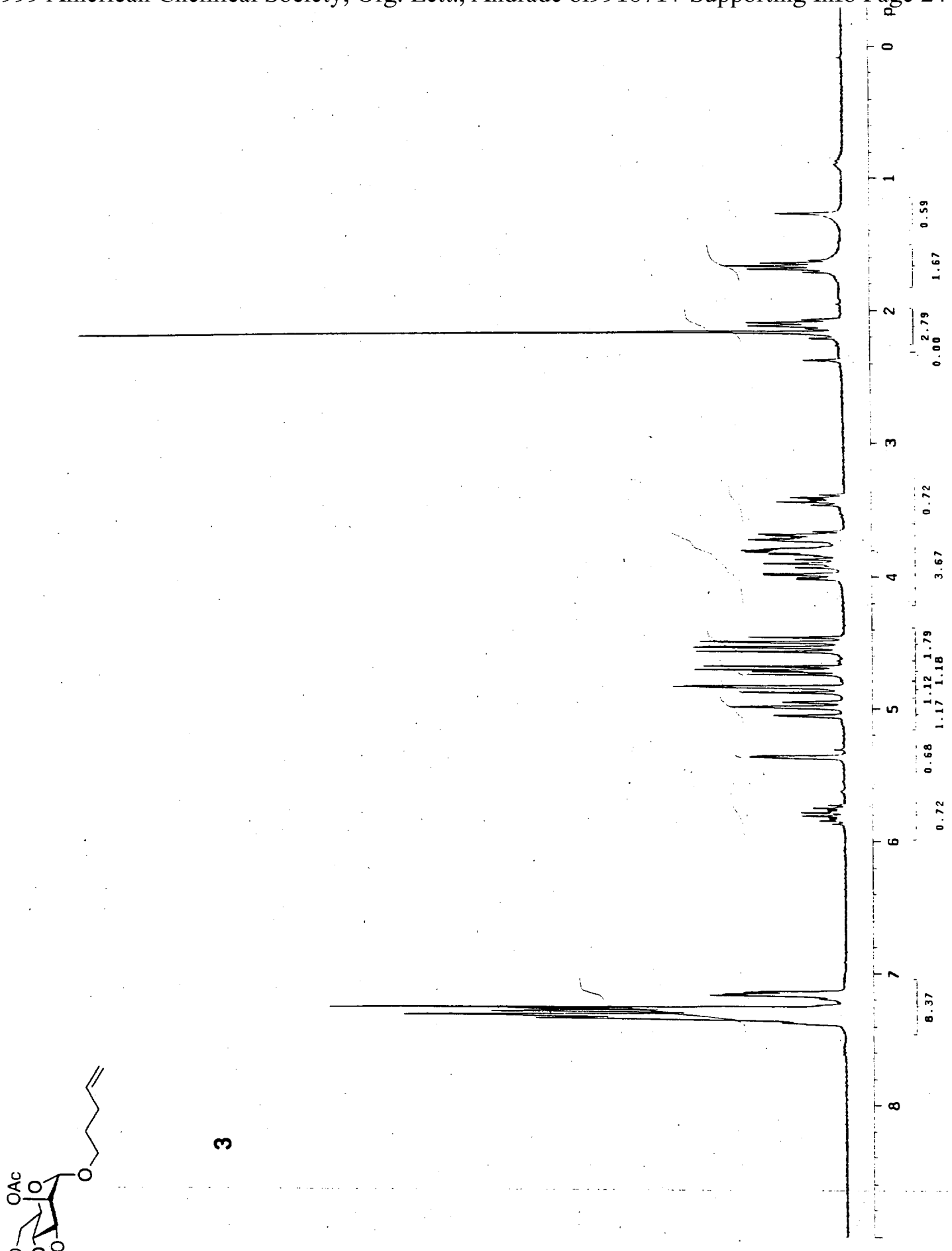

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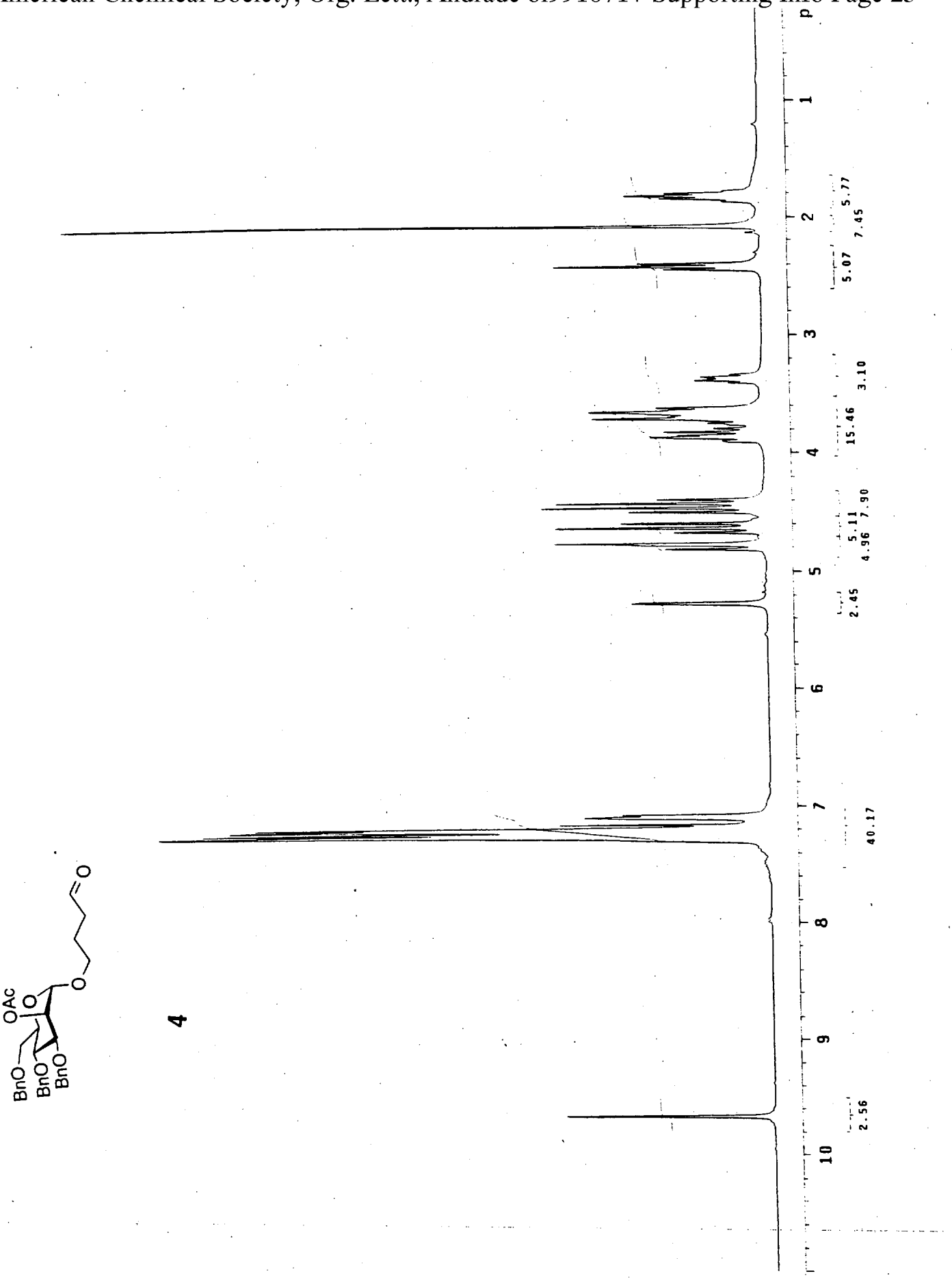

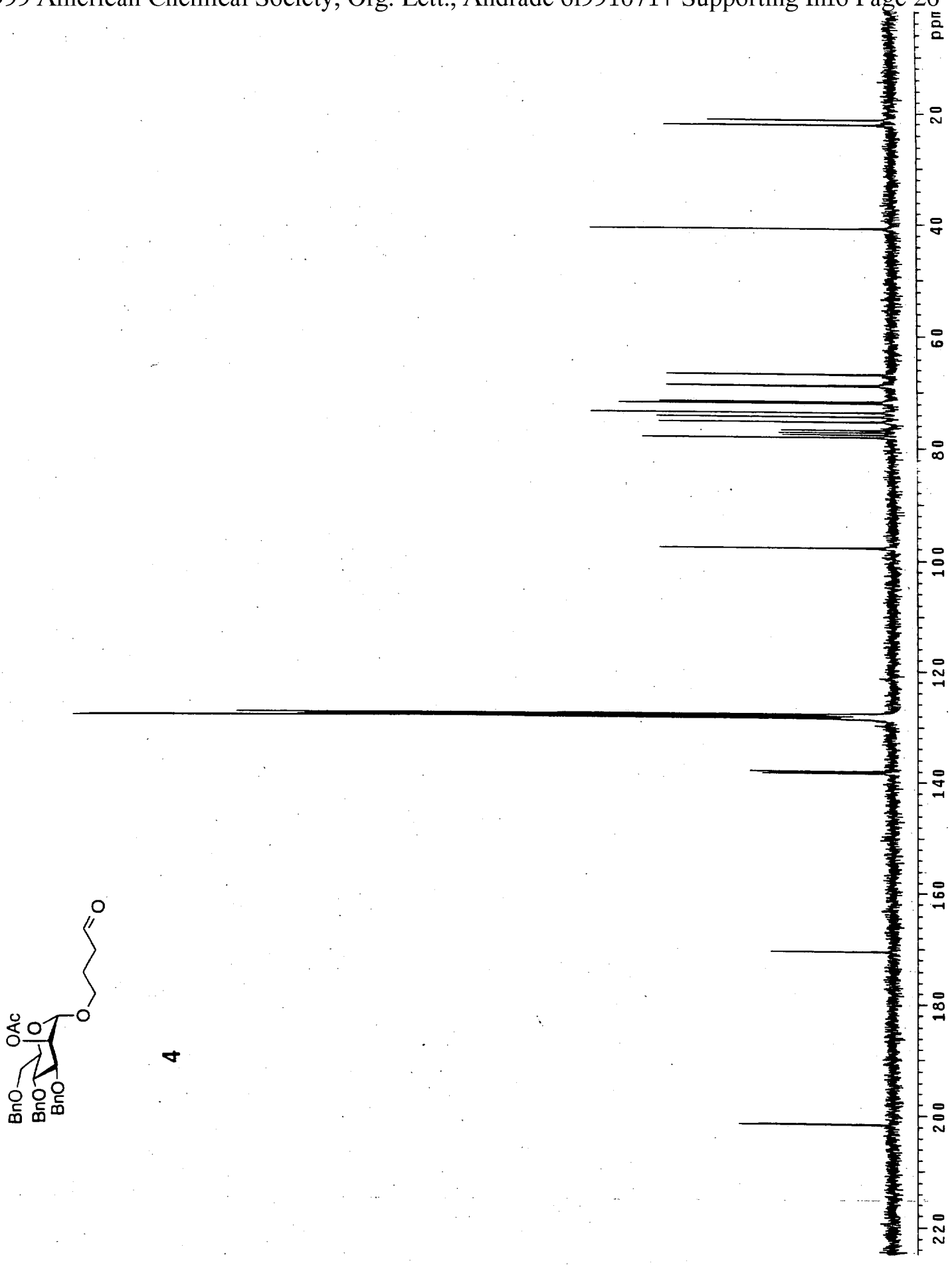

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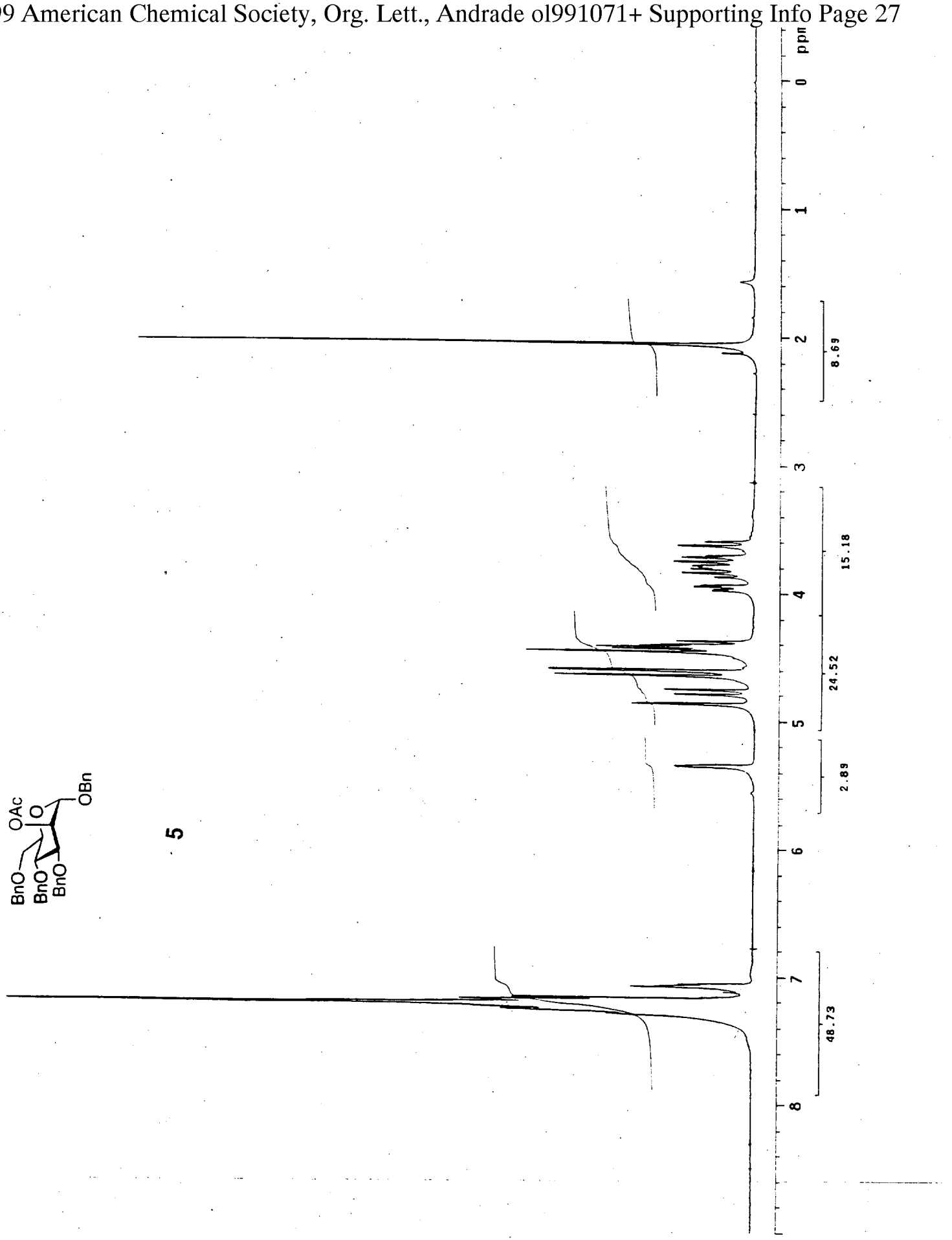

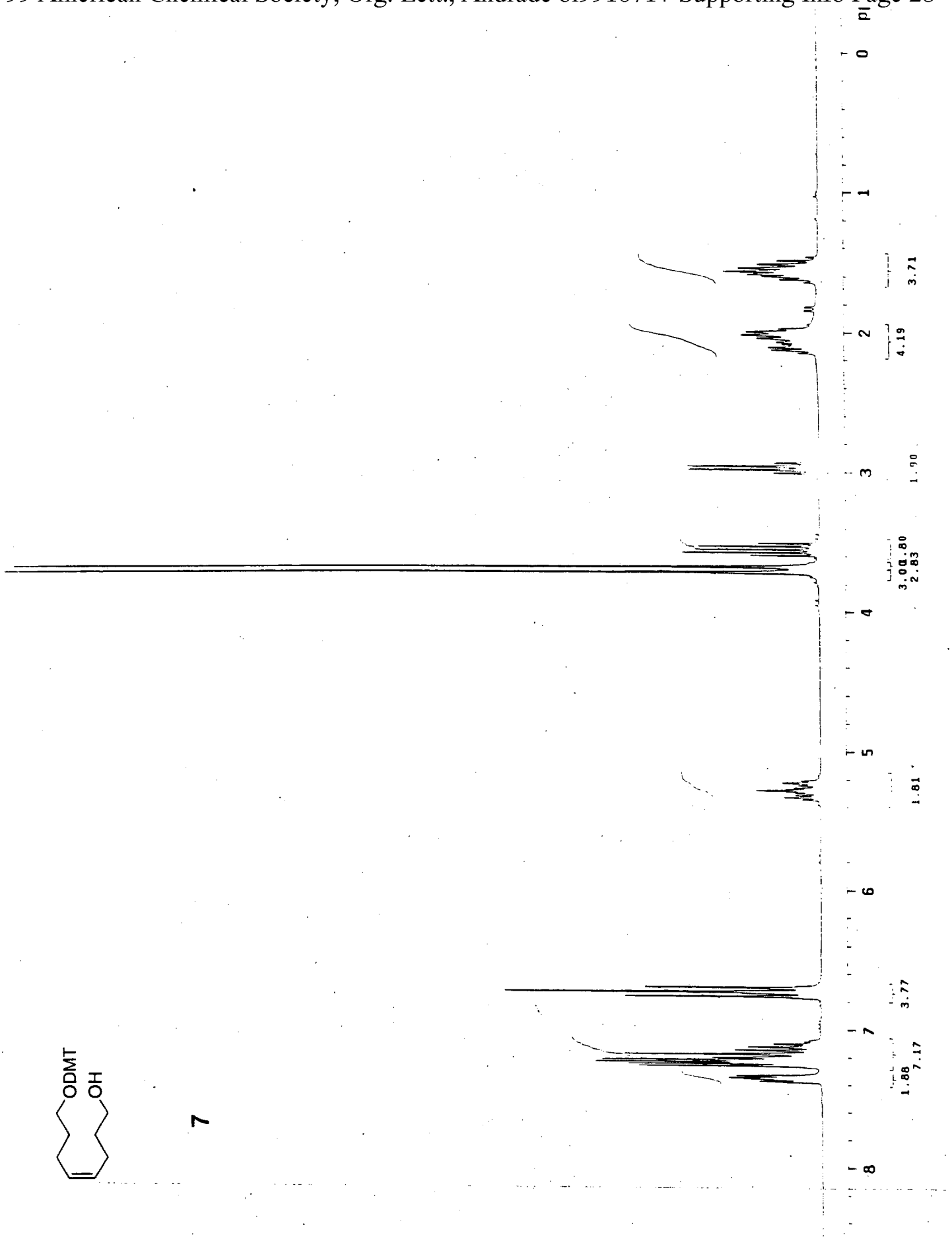

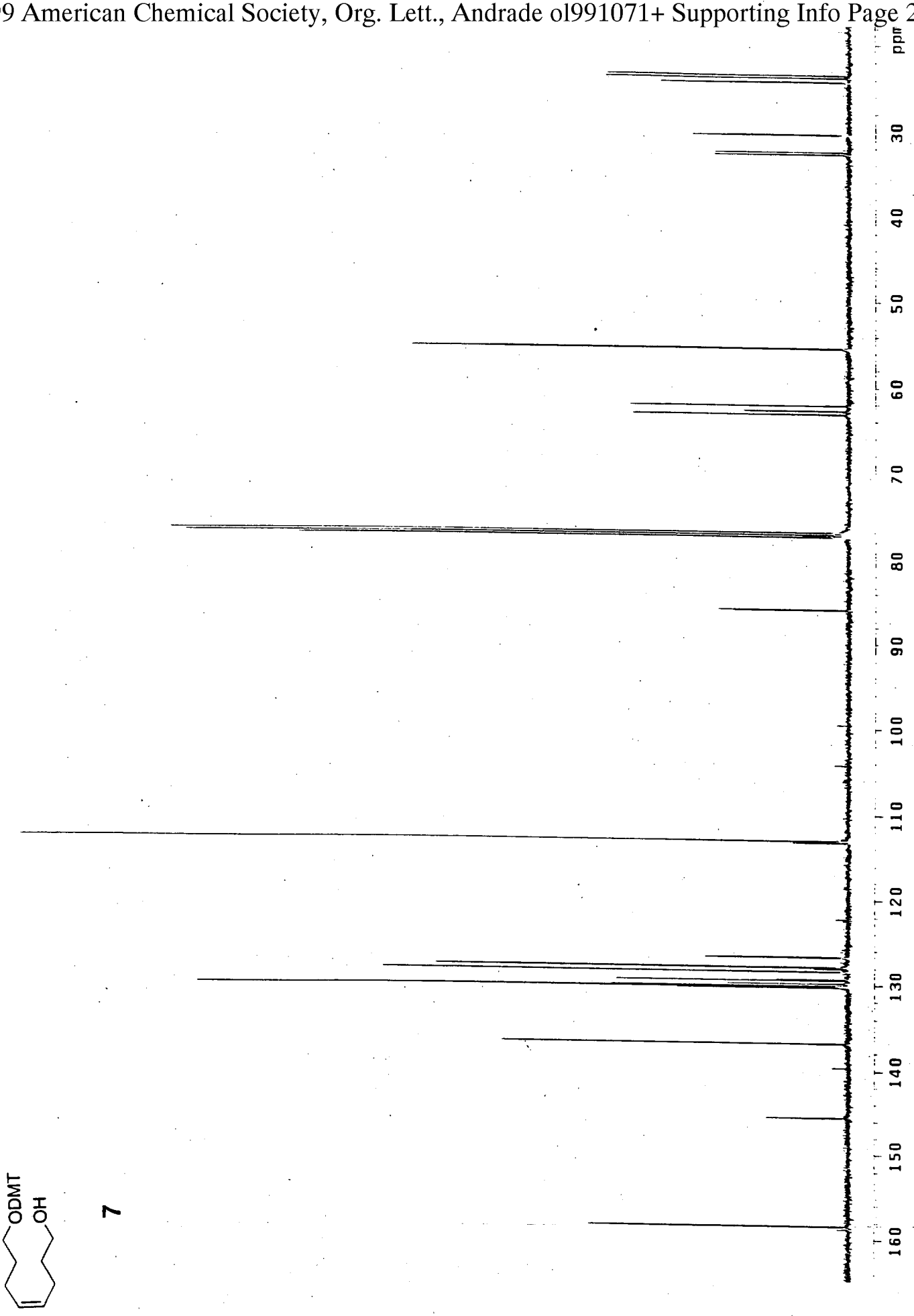

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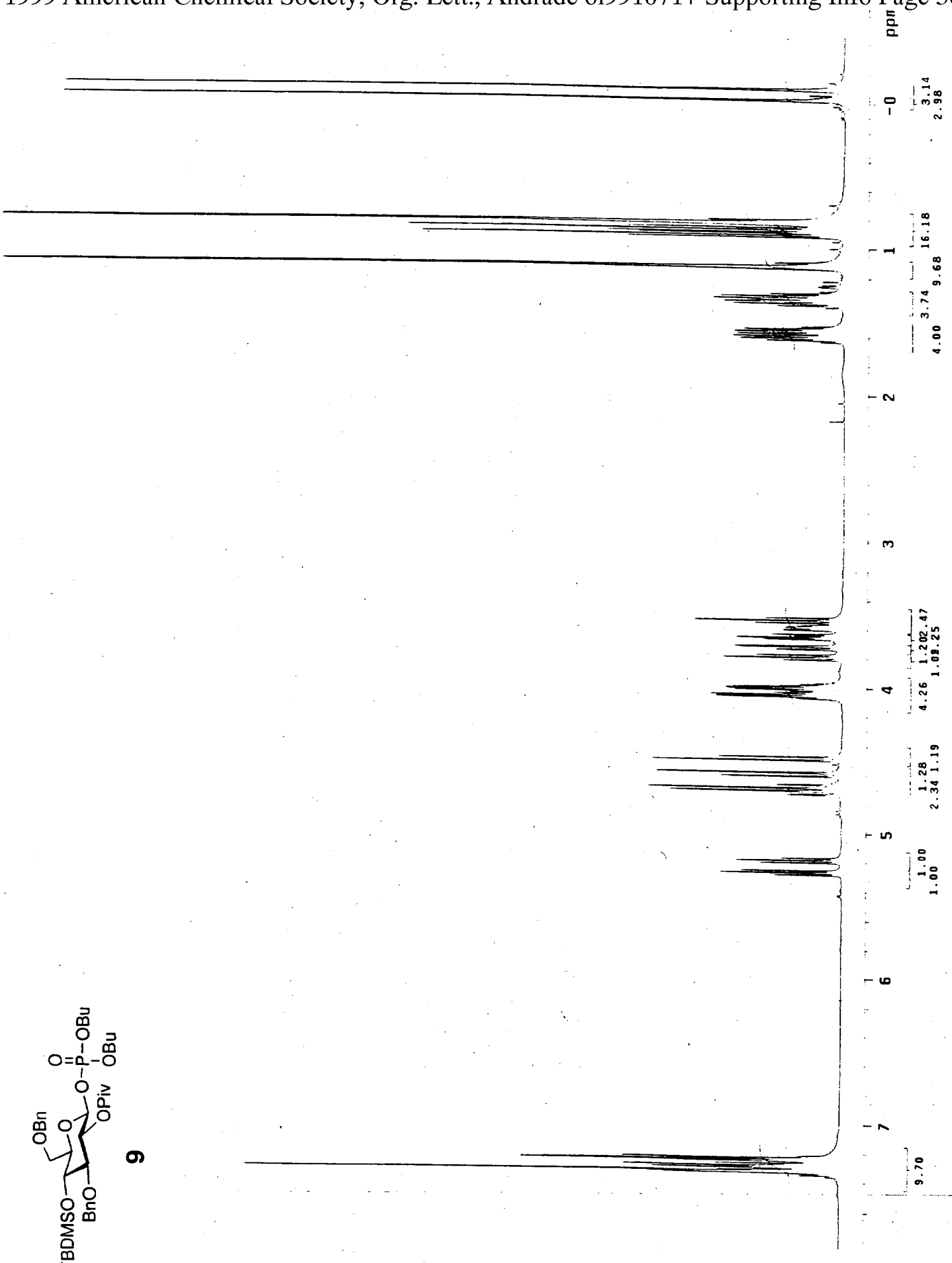

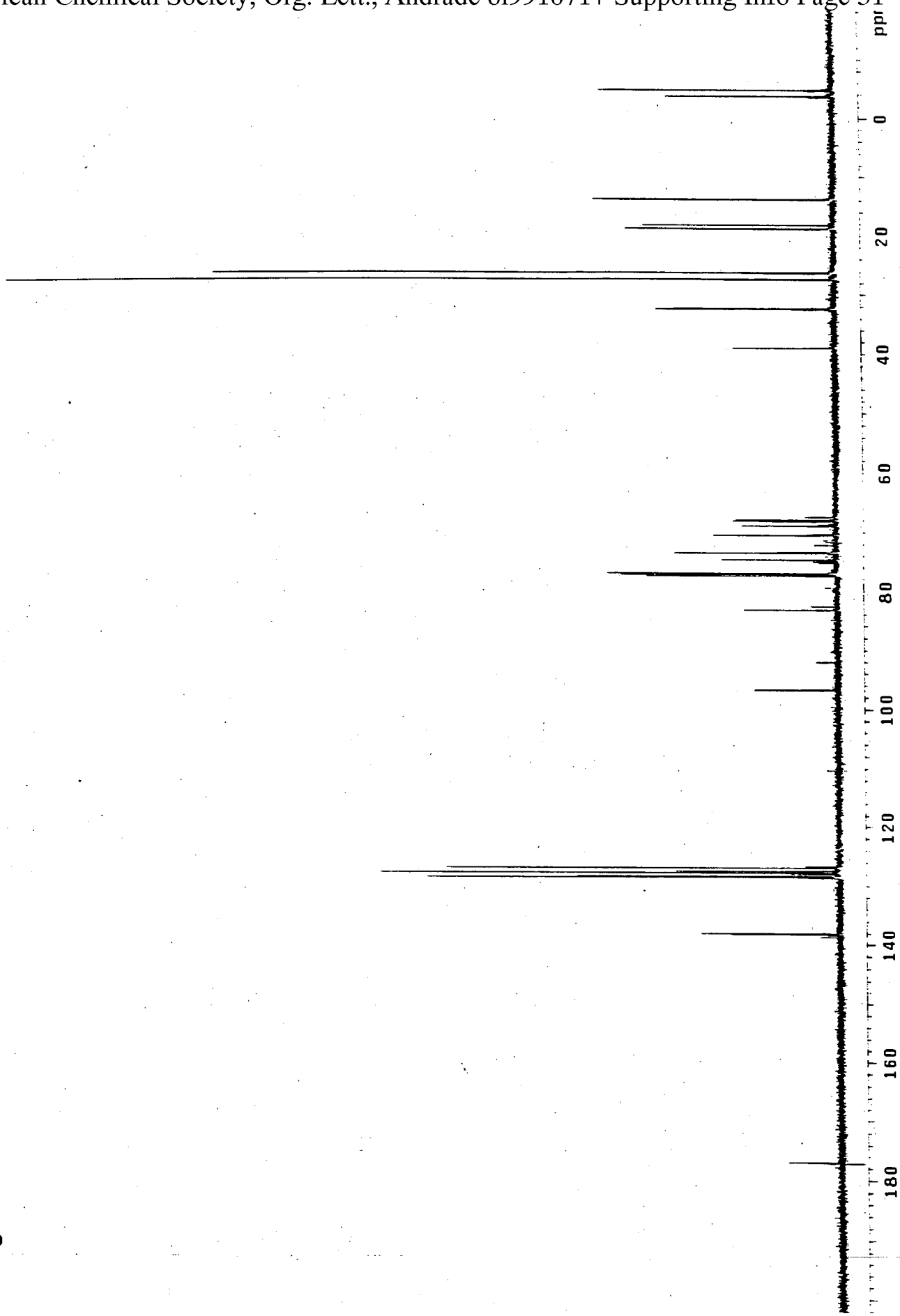
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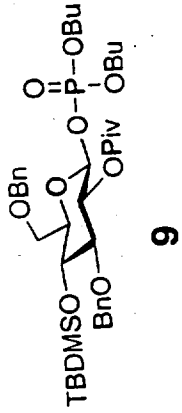
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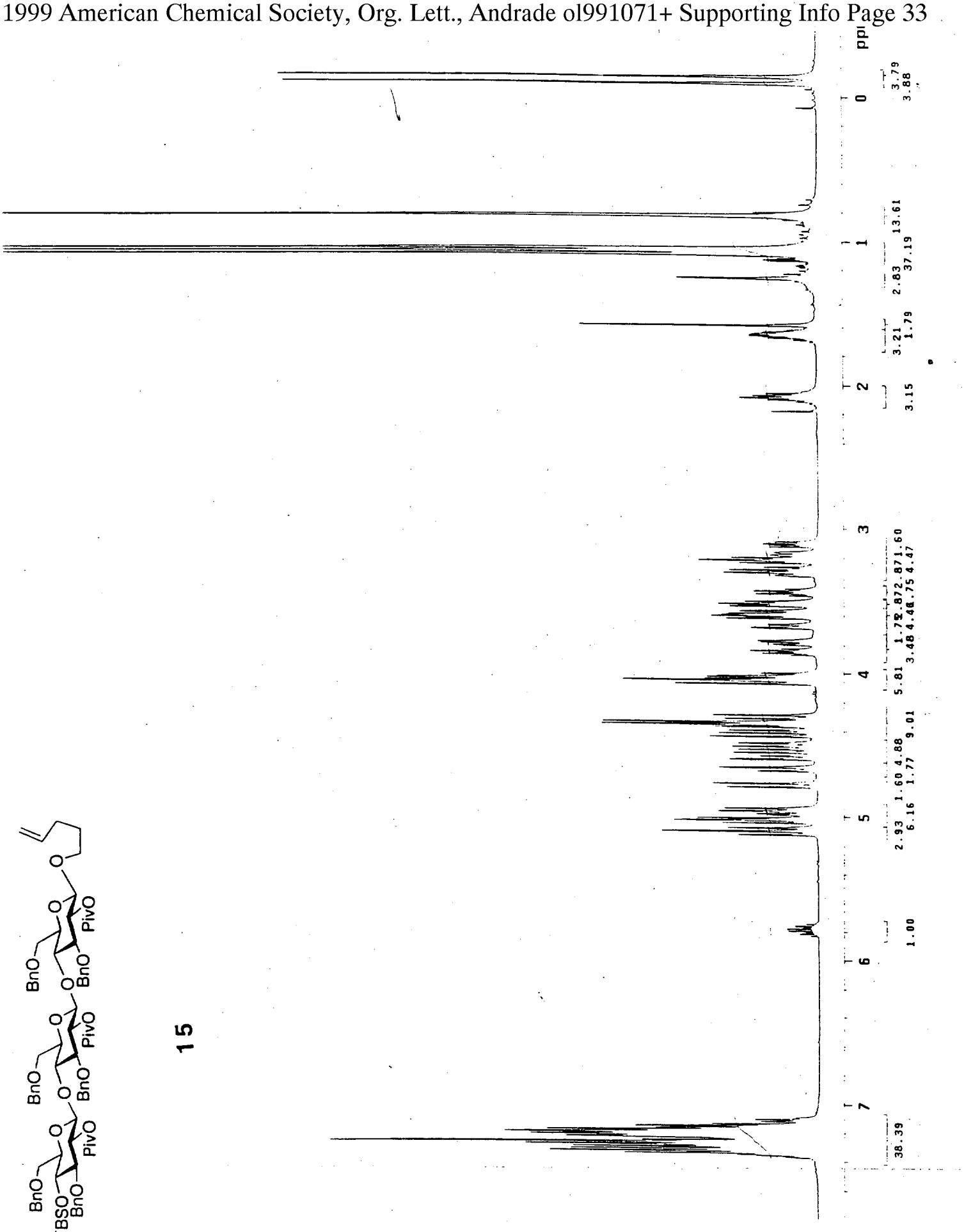

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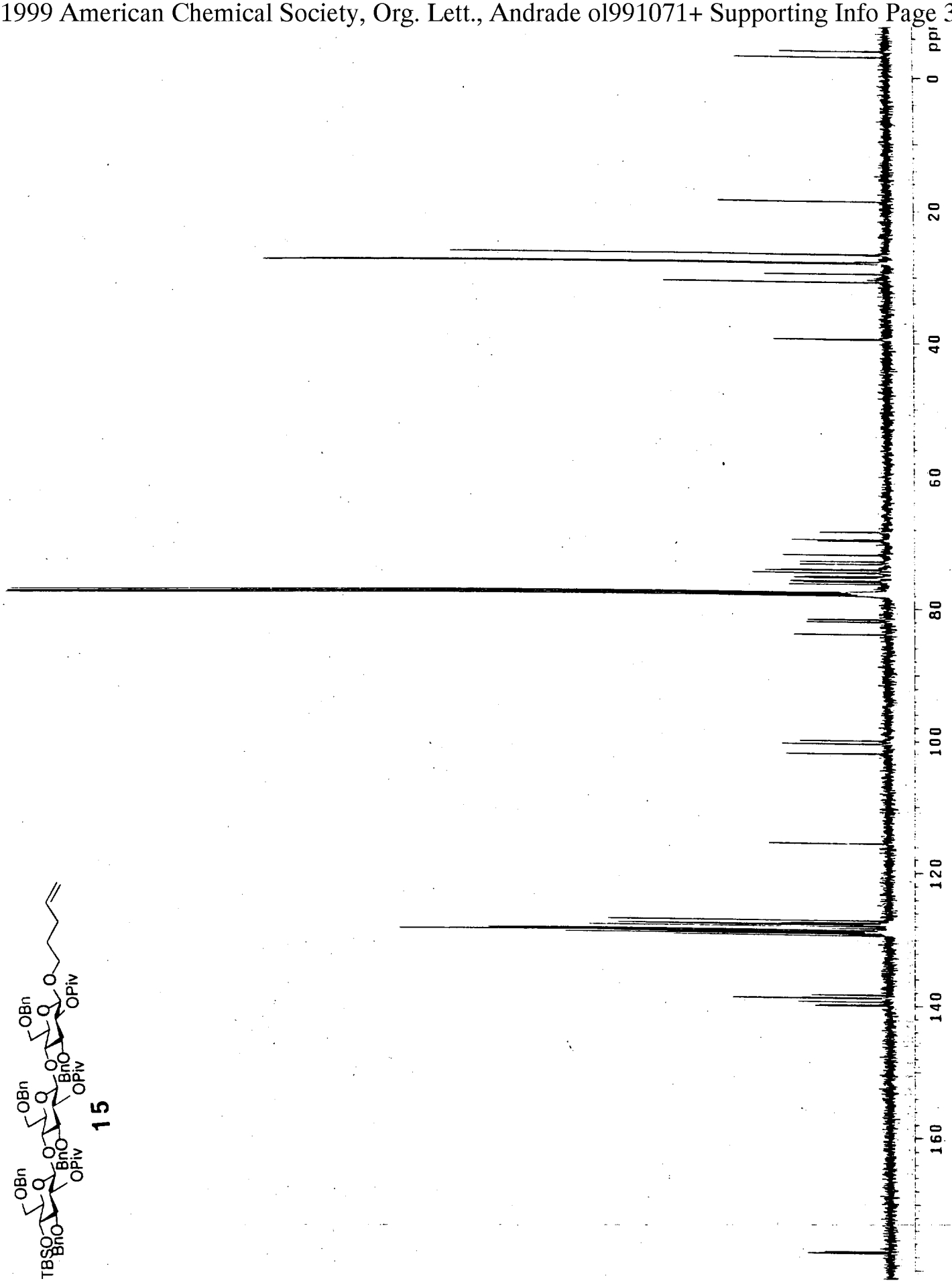

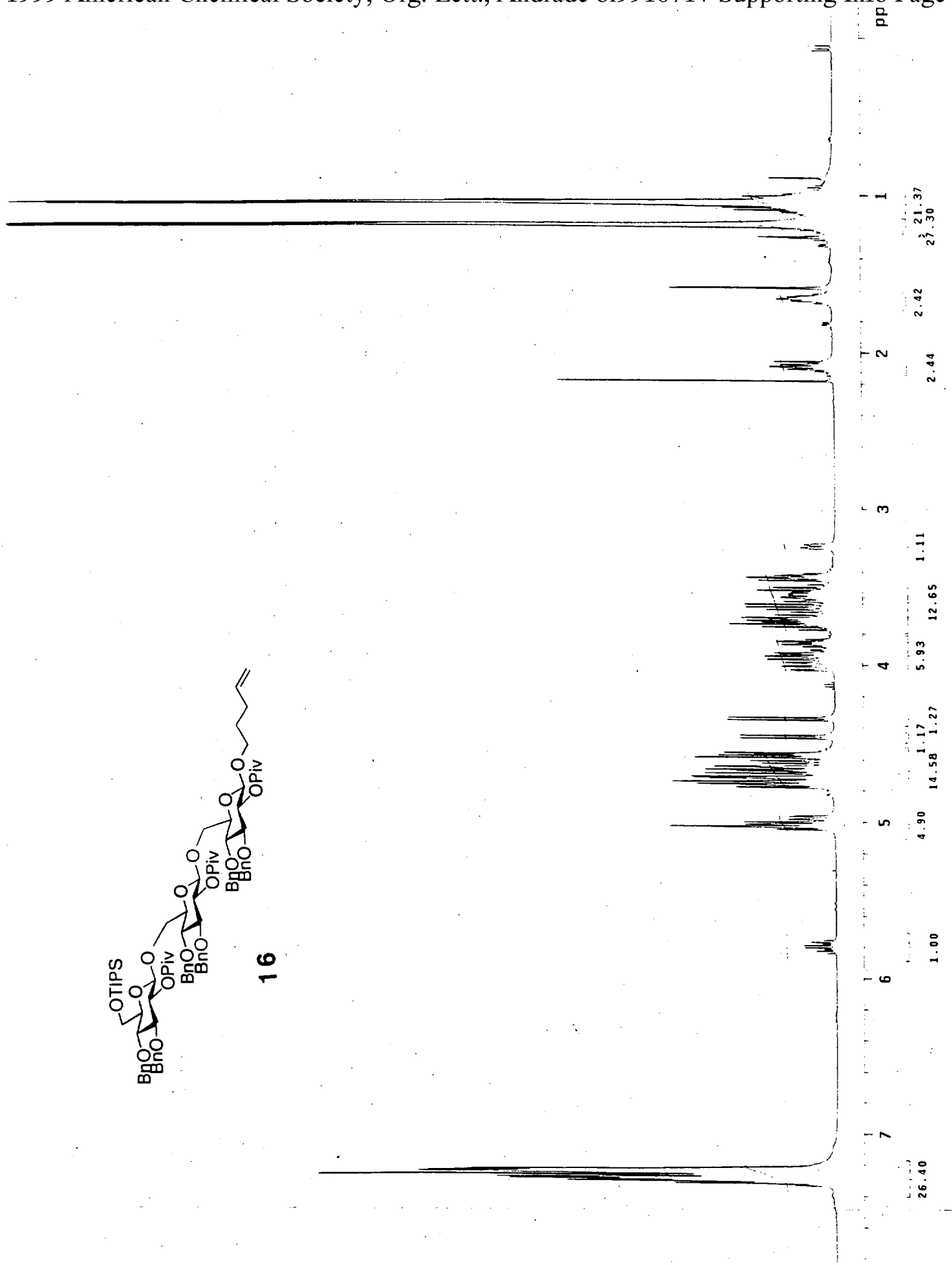
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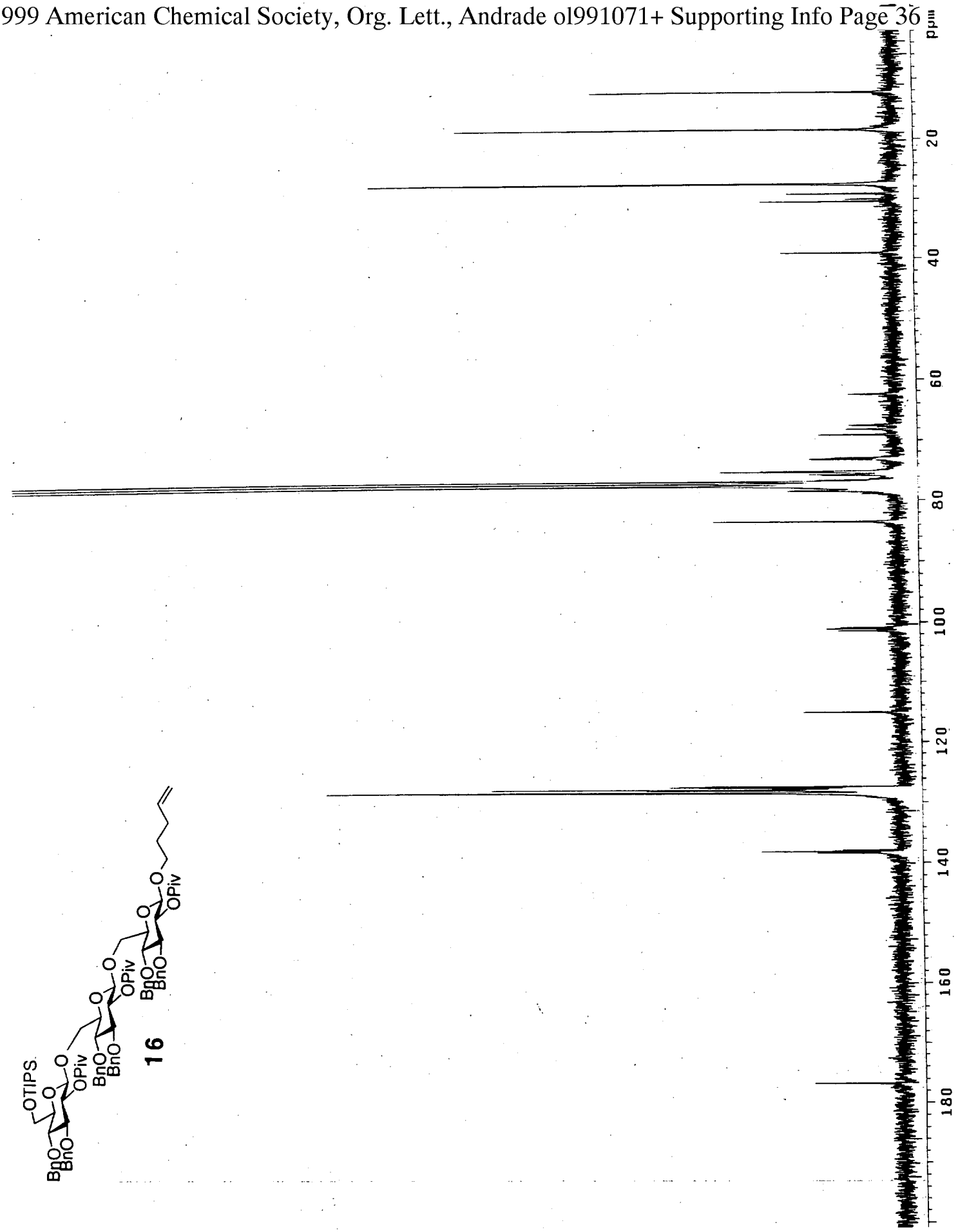
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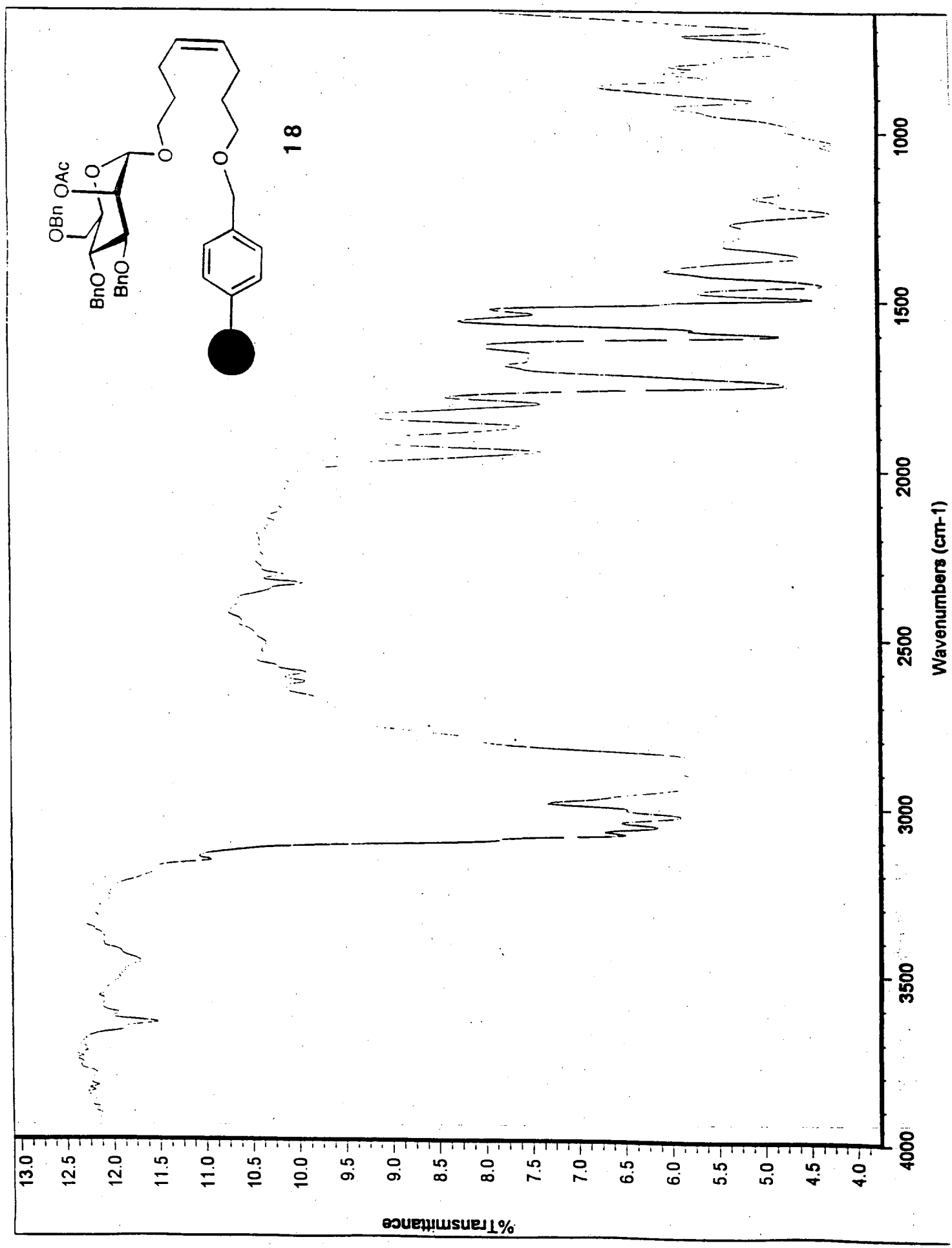
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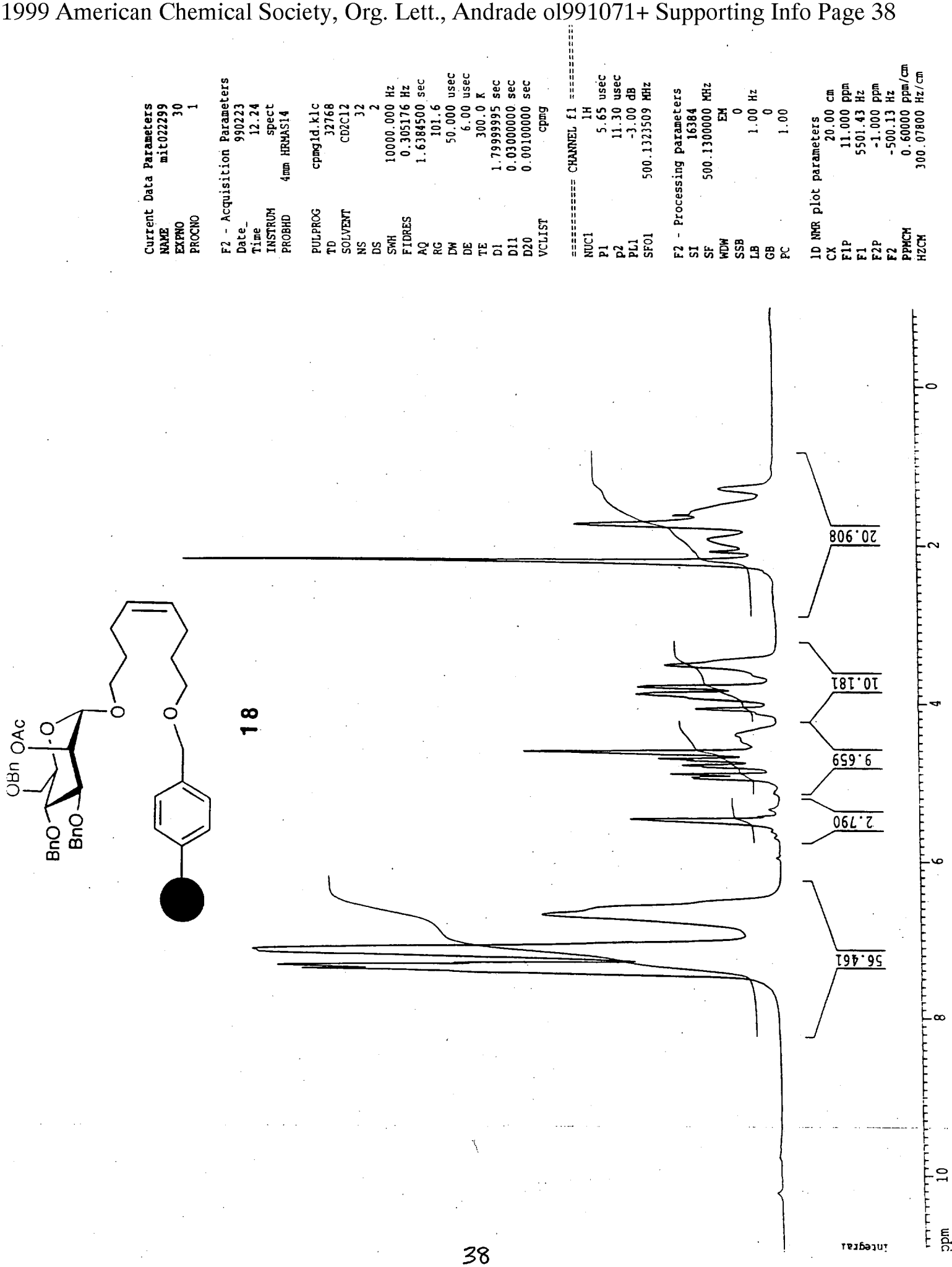

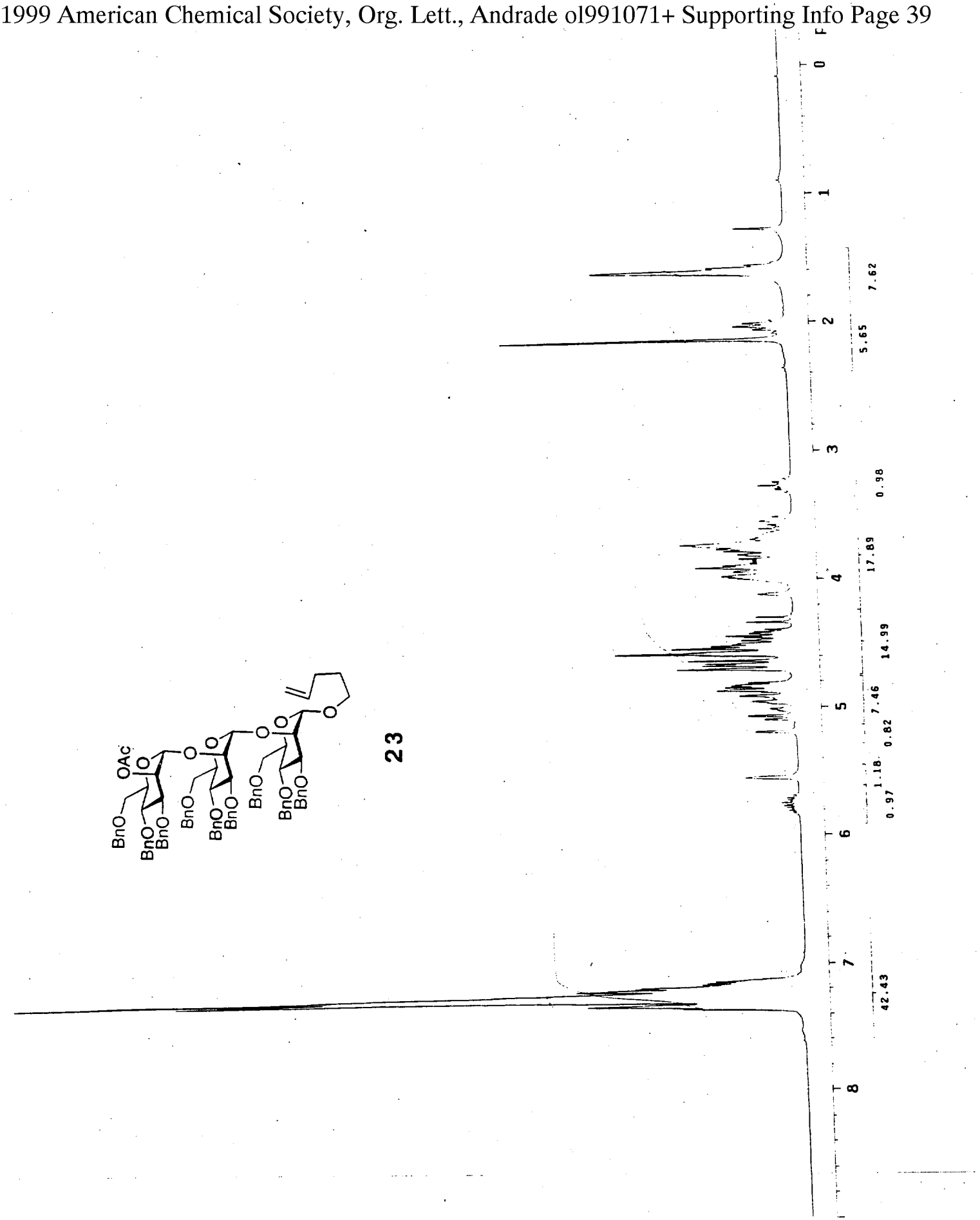

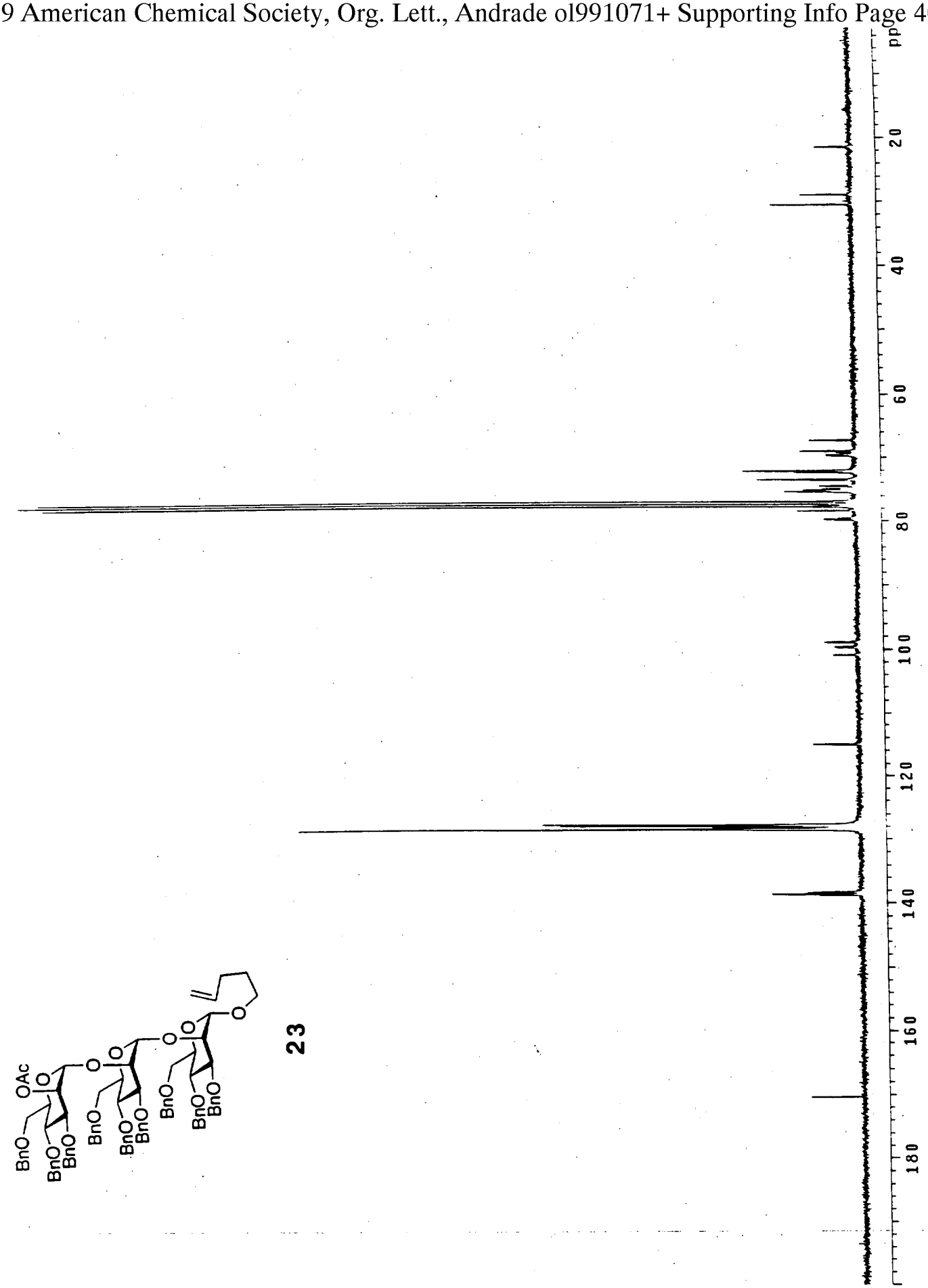

23