Synthesis of the Glycopeptidolipid of *Mycobacterium avium* Serovar 4: First Example of a Fully Synthetic C-Mycoside GPL

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Supporting Information

Content:

General Methods. Chemicals were purchased from Sigma, Aldrich, Fluka and Senn Chemicals and were of high purity. For amino acids and sugars grades of >98%ee min were used, while only technical quality behenic acid was purchased. Solvents were dried according to common laboratory procedures. Chloroform and dichloromethane were purified, if required, by washing with sulfuric acid and water and finally distilled from phosphorus pentoxide and calcium hydride respectively. Thin-layer chromatography was performed on 0.25 mm silica plates ($60F_{254}$). The determination of spots was conducted by inspection under UV light (254 nm), as well as by spraying the developed plates with a solution of ammonium phosphomolybdate (H_2SO_4 = 100 mL/ H_3PO_4 =100 mL/ H_2O = 3.8 L/ $(NH_4)_6Mo_7O_{24}$ = 100 g) and charring on a hot plate or spraying with ninhydrin (0.2 % in ethanol) and moderate heating. Chromatography was performed by the flash procedure using hexanes and ethyl acetate on silica gel 60 (230-400 mesh).

Melting points are uncorrected. Optical rotations were measured at room temperature (21 ± 4° C) for solutions in 0.1 and 1 dm cells. NMR spectra were recorded at 360 and 250 MHz, respectively (90 and 63 MHz for ^{13}C), in $CDCl_3$ and at room temperature, unless otherwise noted. HRMS spectra have been processed at the Nebraska Center for Mass Spectrometry, University of Nebraska-Lincoln in the FAB mode. LRMS spectra have been taken at ICOA, Université d'Orléans, using ion spray, heated-nebulizer or MALDI-TOF mode. Combustion analysis have been performed by the Service Central d'Analyse Elementaire of CNRS, Vernaison, France.

3,4-Di-*O*-acetyl-1,2-*O*-(S-1-benzyloxyethylidene)-β-L-rhamnopyranose (3a). Acetobromorhamnose (**2**[1], crude product from 10.0 g rhamnose monohydrate, 54.9 mmol) was dissolved in absol. $CHCl_3$ (100 mL) and treated with BnOH (11.5 mL, 111 mmol) followed by sym-collidine (18 mL, 136 mmol). The solution was kept overnight at rt, then diluted with $CHCl_3$(200 mL) and washed with water, 2 N aq HCl and sat aq $NaHCO_3$. Drying over $MgSO_4$ was followed by coevaporation with toluene and $CHCl_3$.

Final chromatography using Hex/EtOAc 5:1 led to **3a** (16.0 g, 77 %) as a crystallizing syrup: mp 62°C; $[\alpha]_D^{21}$ + 9 (*c* 2.0, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) 7.37–7.25 (m, 5 H), 5.44 (d, 1 H, *J* 2.4 Hz), 5.12–5.02 (m, 2 H), 4.61–4.52 (m, 3 H), 3.55 (dq, 1 H, *J* 11, 3 x 6.2 Hz), 2.09, 2.06 (2s, 2×3 H), 1.85 (s, 3 H), 1.24 (d, 3 H, *J* 6.2 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) 170.4, 169.7, 137.7, 128.3, 127.6, 127.5, 124.3, 97.3, 76.7, 70.7, 70.4, 69.3, 64.6, 25.0, 24.9, 20.8, 17.6.

1,2-*O*-(*S*-1-Benzyloxyethylidene)-3,4-di-*O*-methyl-β-L-rhamnopyranose (3b). A solution of **3a** (6.7 g, 18 mmol) in 1,4-dioxane (150 mL) was treated with fresh powdered NaOH (7.0 g, 180 mmol) and the mixture was stirred for about 30 min at rt. MeI (5.5 mL, 88 mmol) was added and the suspension was stirred overnight. The excess methylating reagent was destroyed by addition of MeOH (about 10 mL). After 2 h the solvent was removed under vacuum and the residue was taken up in CH_2Cl_2 and water. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic layers were washed with water and 10% aq $Na_2S_2O_3$. The organic phase was dried with $MgSO_4$ and the solvent was evaporated, thus leading to **3b** (5.0 g, 88 %) as a yellow crystallizing syrup that could be recrystallized from ether or ether/hexanes (colorless plates) : mp_1 80–81°C, mp_2 87–88°C; $[\alpha]_D^{21}$ +5 (*c* 2.0, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) 7.4–7.2 (m, 5 H), 5.38 (d, 1 H, $J_{1,2}$ 2.4 Hz), 4.64, 4.61 (2 d, 2 H, *J* 11.5 Hz), 4.57 (dd, 1 H, *J* 2.4, 4.5 Hz), 3.59, 3.48 (2s, 2×3 H), 3.38 (dd, 1 H, *J* 4.5, 9.4 Hz), 3.28 (dq, 1 H, *J* 9, 3 x 6.0 Hz), 3.13 (t, 1 H, *J* 9.2 Hz), 1.83 (s, 3 H), 1.34 (d, 3 H, *J* 6.0 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) 137, 128.3, 127.5, 123.8, 97.5, 81.3, 81.2, 76.3, 70.4, 65.0, 58.0, 57.7, 24.9, 17.8.

2-*O*-Acetyl-1,5-anhydro-3,4-di-*O*-methyl-L-rhamnitol (5). Crystalline **3b** (200 mg) was dissolved in EtOAc (50 mL) and treated with HOAc (5 drops) and $Pd(OH)_2$/C (20 %, 100 mg).The mixture was hydrogenolyzed at 400 psi for some hours; the catalyst was then removed by filtration through celite and the solution concentrated. The crude product contained predominantly **5**: ^{1}H NMR (360 MHz,

$CDCl_3$) 5.10 (ddd, 1 H, *J* 2.0, 0.6, 3.6 Hz), 3.94 (dd, 1 H, *J* 2.0, 13.1 Hz), 3.57, 3.42 (2s, 2×3 H), 3.48 (dd, 1 H, *J* 0.6, 13 Hz), 3.26 (dd, 1 H, *J* 3.6, 9.2 Hz), 3.20 (dq, 1 H, *J* 9.2, 3 x 6.1 Hz), 3.05 (t, 1 H, *J* 9.2 Hz), 2.15 (s, 3 H), 1.34 (d, 3 H, *J* 6.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) 170.5, 82.7, 81.9, 77.4, 67.7, 67.6, 60.8, 57.1, 20.9, 17.9.

2-*O*-Acetyl-3,4-di-*O*-methyl-α-L-rhamnopyranosyl trichloroacetimidate (6). Compound **3b** (700 mg, 2.15 mmol) was dissolved in aqueous 1,4-dioxane (50 mL, 90 %) and treated with HOAc (2 drops) and $Pd(OH)_2$/C (20 %, 100 mg). The mixture was hydrogenated at 200 psi overnight. The catalyst was removed by membrane filtration and the residue concentrated to afford a clear syrup. Compound **4**[2] was not purified but dried under vacuum and directly converted into the trichloroacetimidate. Compound **4**: ^{13}C NMR (90 MHz, $CDCl_3$) 170.6, 92.2, 82.0, 79.1, 69.2, 67.7, 60.9, 57.6, 21.1, 17.9; $C_{10}H_{18}O_6$. Crude **4** (2.15 mmol) was dissolved in anhydr CH_2Cl_2 (10 mL) and treated with trichloroacetonitrile (2.1 mL, 21 mmol). DBU (20 µL, 130 µmol) was added and the solution was stirred for 1 h at rt. The solvent was removed and the residue purified by chromatography using CH_2Cl_2/acetone 100:1. Compound **6**[2] was isolated as a yellow partially crystallizing syrup (660 mg, 82 %). It was immediately used for glycosylation. (A second batch led to 600 mg, 74 %). Compound **5**: ^{1}H NMR (360 MHz, $CDCl_3$) 8.67 (s, 1 H, NH), 6.16 (d, 1 H, *J* 1.9 Hz), 5.43 (dd, 1 H, *J* 1.9, 3.4 Hz), 3.84 (dq, 1 H, *J* 9.6, 3 x 6.2 Hz), 3.62 (dd, 1 H, *J* 3.4, 9.4 Hz), 3.57, 3.44 (2s, 2×3 H), 3.15 (t, 1 H, *J* 9.5 Hz), 2.16 (s, 3 H), 1.35 (d, 3 H, *J* 6.2 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) 170.0, 160.1, 95.1, 91, 81.3, 79.4, 70.6, 67.1, 61.1, 57.8, 20.9, 17.9.

***N*-Benzyloxycarbonyl-D-alaninyl-L-alanine methyl ester (8).** To a solution of L-Ala-OMe×HCl (3.5 g, 25 mmol) and NEt_3 (3.5 mL, 25 mmol) in CH_2Cl_2 (50 mL) was added a solution of Z-D-Ala (5.0 g, 22 mmol) and EEDQ (6.5 g, 26 mmol) in CH_2Cl_2 (75 mL). The reaction was stirred overnight, the

mixture was washed with aq $NaHCO_3$, dried over $MgSO_4$ and concentrated. The crude product was crystallized from toluene giving **8** (6.1 g, 88 %): mp 136–137°C; $[\alpha]_D^{21}$ +17 (*c* 2.0 $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) 7.36–7.31 (m, 5 H), 6.66 (bs, 1 H, NH), 5.34 (bs, 1 H, NH), 5.12 (m_c, 2 H), 4.56 (quint, 1 H, *J* 7.0 Hz), 4.23 (m_c, 1 H, *J* 7.0 Hz), 3.73 (s, 3 H), 1.39 (2 d, *J* 7.0 Hz, 2×3 H); ^{13}C NMR (90 MHz, $CDCl_3$) 128.5, 128.2, 128.1, 67.1, 52.5, 48.1, 18.5, 18.2.

Alternative synthesis for 9: L-Alaninol (50 µL, 65µmol) was added to a solution of Z-D-Ala (120 mg, 54 µmol) and EEDQ (170 mg, 69 µmol) in CH_2Cl_2 (5 mL). The reaction was stirred at rt overnight. After removal of the solvents by evaporation, the product was crystallized from toluene giving **8b** (125 mg, 83 %): mp 143–144°C; $[\alpha]_D^{21}$ -2 (*c* 2.0, $CHCl_3$)

Alternative synthesis of 10

Trichloroacetimidate glycosylation: Compounds **6** (650 mg, 1.7 mmol) and **9** (520 mg, 1.9 mmol) were dissolved in anhydr CH_2Cl_2 (50 mL) and treated with activated powdered 4Å molecular sieves (1.0 g) under an inert atmosphere. The suspension was cooled in an acetone/dry ice bath, TMS triflate (30 µL, 150 µmol) was added and the mixture was stirred overnight allowing to warm up slowly to rt inside the cooling bath. NEt_3 (100µL) was added, the molecular sieves were removed by filtration and the filtrate was concentrated. Chromatography of the residue gave compound **10** (617 mg, 72 %).

(2*S*)-2-(*N*-benzyloxycarbonyl-D-alaninylamino)propyl 3,4-di-*O*-methyl-α-L-rhamnopyranoside (deacetylated **10**)**:** mp 44–48°C; $[\alpha]_D^{23}$ -51 (*c* 0.7, $CHCl_3$), $[\alpha]_D^{22}$ -45 (*c* 0.6 MeOH); ^{1}H NMR (360 MHz, $CDCl_3$) 7.31–7.08 (m, 5 H), 6.09 (d, 1 H, *J* 8.2 Hz, NH), 5.36 (bs, 1 H, NH), 5.08, 5.04 (2d, 2×1 H, *J* 12.2 Hz), 4.71 (d, 1 H, *J* 1.8 Hz), 4.18–4.04 (m, 2 H), 3.92 (dd, 1 H, *J* 1.8, 3.4 Hz), 3.55 (dd, 1 H, *J* 4.7, 10.0 Hz), 3.49–3.27 (m, 3 H), 3.46, 3.36 (2s, 2×3 H), 2.99 (t, 1 H, *J* 9.2 Hz), 1.30 (d, 3 H, *J*

7.1 Hz), 1.21 (d, 3 H, *J* 6.2 Hz), 1.11 (d, 3 H, *J* 6.3 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) 171.5, 136.2, 128.5, 128.2, 128.0, 99.3, 81.8, 81.2, 70.1, 67.6, 67.4, 67.1, 60.8, 57.3, 50.6, 44.9, 18.3, 17.8, 17.6.

Alternative synthesis of 13: A solution of DMSO (1.45 mL, 21 mmol) in anhydr CH_2Cl_2 (5 mL) was added dropwise to a solution of oxalyl chloride (850 µL, 10 mmol) in the same solvent (25 mL) at -60°C under argon. Afterwards a solution of **12** (crude product from 1.5 g, 8.2 mmol, L-rhamnose monohydrate) in anhydr CH_2Cl_2 (20 mL) was added, keeping the temperature below -60°C all the time. The mixture was stirred for 30 min before the addition of NEt_3 (5.2 mL, 37 mmol). After 1.5 h the reaction was allowed to warm to rt and water (20 mL) was added. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were then washed with 2 N aq HCl and sat aq $NaHCO_3$ and dried over $MgSO_4$. Concentration and coevaporation with EtOH led to NMR pure **13**. (For yield see preparation of **19**).

4-Pentenyl 2,4-di-*O*-benzyl-6-deoxy-α-L-talopyranoside (17b): $[\alpha]_D^{18}$ -42 (*c* 1.0, $CDCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) 7.44–7.23 (m, 10 H), 5.80 (m_c, 1 H), 5.07–4.92 (m, 2 H), 4.90 (d, 1 H, *J* 1.0 Hz), 4.82, 4.79, 4.63, 4.50 (4 d, 4 H, *J* 11.9 Hz), 3.88 (dq, 1 H, *J* 1.6, 3 x 6.6 Hz), 3.84 (dt, 1 H, *J* 2 x 4.2, 11.3 Hz), 3.51 (dd, 1 H, *J* 1.0, 4.2 Hz), 3.47 (dd, 1 H, *J* 4.2, 1.6 Hz), 3.64, 3.39 (2 m_c, 2 H), 2.79 (d, 1 H, *J* 11.3 Hz, OH), 2.09, 1.64 (2 m_c, 2×2 H), 1.29 (d, 3 H, *J* 6.6 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) 138.6, 138.0, 128.4, 128.3, 127.9, 127.8, 127.7, 127.5, 114.9, 97.7, 79.3, 76.6, 76.0, 73.5, 66.9, 66.7, 65.9, 30.3, 28.6, 16.8.

Alternative synthesis of 20 (rearrangement of 14): 2,2-Dimethoxypropane (1 mL) and $TsOH \times H_2O$ (5 mg, 26 µmol) were added to a solution of **14** (700 mg, 2.6 mmol) in anhydr CH_2Cl_2 (10 mL). The solution was stirred at rt overnight and then concentrated. The residue was taken up in CH_2Cl_2, the

solution was washed with $NaHCO_3$ and dried over $MgSO_4$. The crude mixture was submitted to chromatography using Hex/EtOAc 4:1. Beside unchanged **14** (220 mg, 31 %), syrupy **20** (310 mg, 44 %) was isolated.

***N*-2,2,2-Trichloroethoxycarbonyl-D-phenylalanine (24).** A solution of D-phenylalanine (3.3 g, 20 mmol) in NaOH aq (30 mL, 1 N) was cooled with an ice bath. 2,2,2-Trichloroethylchloroformate (3.5 mL, 25 mmol) and aq NaOH (20 mL, 1 N) were added dropwise alternately (4 times) under nitrogen. Stirring was continued overnight at rt and the mixture was acidified with aq HCl. The product was extracted with ether, the organic phase was washed with 2 N aq HCl and dried over $MgSO_4$. After concentration the product was crystallized from hexane/ether giving **24** (6.0 g, 88 %): mp 131–132°C (Lit.[3] 129-130°C); $[\alpha]_D^{25}$ - 44 (c 2.3, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) 7.35–7.10 (m, 5 H), 5.40 (d, 1 H, *J* 7.9 Hz, NH), 4.87–4.60 (m, 3 H), 3.25 (dd, 1H, *J* 5.2, 14.0 Hz), 3.13 (dd, 1 H, *J* 6.3, 14.0 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) 175.9, 154.0, 135.1, 129.3, 128.8, 127.4, 74.7, 54.8, 37.8.

(4-Iodo-5-succinimidylpentyl) 3,4-di-*O*-benzyl-2-*O*-chloroacetyl-α-L-talopyranoside (30). ^{1}H NMR (250 MHz, $CDCl_3$) 7.48–7.20 (m, 10 H), 5.33 (m_c, 1 H), 4.92–4.49 (m, 4 H), 4.84 (bs, H-1), 4.42 (m_c, 1 H), 4.16–3.89 (m, 3 H), 3.86 (bq, 1 H, *J* 3 x 6.4 Hz), 3.80 (m_c, 1 H), 3.72–3.37 (m, 2 H), 3.57 (m_c, 1 H), 3.50–3.37 (m, 1 H), 2.74/2.72 (s, 4 H), 1.95–1.60 (m, 4 H), 1.27 (d, 3 H, *J* 6.4 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) 176.6 (C), 167.3 (C), 138.6/137.8 (C), 128.3–127.4 (m), 98.00/97.95 (CH), 75.7 (CH), 74.86/74.78 (CH), 74.3 (CH_2), 71.0 (CH_2), 68.7 (CH), 66.9 (CH), 66.64/66.46 (CH_2), 46.4 (CH_2), 41.0 (CH_2), 34.1/33.8 (CH_2), 30.27/30.22 (CH), 29.16/29.03 (CH_2), 28.0 (CH_2), 16.7 (CH_3);. LRMS (IS): 752/754 (M+K), 736/734 (M+Na), 714/716 (M+H).

4-Pentenyl 3-*O*-acetyl-2-*O*-methyl-β-L-fucopyranoside (32a). A solution of **31**[4] (568 mg, 2.3 mmol) in toluene (25 mL) was treated with bis(tributyltin)oxide (900 μL, 1.8 mmol) and the solution was heated under reflux. After 1 h, water was continously removed by azeotropic distillation while the reaction was refluxed for 3 additional hours. The mixture was cooled to rt and AcCl (190 μL, 2.7 mmol) was added. After stirring at rt for 2 h, MeOH (1 mL) was added and the solution was concentrated after having been stirred for 1 more hour. The residue was taken up in MeCN (50 mL) and washed three times with hexane (50 mL each). After concentration the crude product was purified by chromatography using Hex/EtOAc 3:1 to give **32a** (420 mg, 63 %) as a crystallising yellow syrup. In addition, a smaller amount of the regioisomeric 4-acetate **32b** (175 mg, 26 %) was obtained. Compound **32a**: $[\alpha]_D^{20}$ -18 (*c* 1.0, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) 5.82, 5.03, 4.98 (3 m_c, 3 H), 4.79 (dd, 1 H, *J* 10.1, 3.2 Hz), 4.30 (d, 1 H, *J* 7.7 Hz), 3.94 (m_c, 1 H), 3.80 (≈d, 1 H, *J* 3.2 Hz), 3.69 (≈q, 1 H, *J* 3 x 6.5 Hz), 3.54 (m_c, 1 H), 3.54 (s, 3 H), 3.32 (dd, 1 H, *J* 7.7, 10.1 Hz), 2.16 (s, 3 H), 2.15, 1.74 (2 m_c, 2×2 H), 1.30 (d, 3 H, *J* 6.5 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) 138.0, 114.9, 103.7, 78.3, 75.5, 70.3, 70.0, 69.3, 60.8, 30.1, 28.9, 21.1, 16.1.

4-Pentenyl 4-*O*-acetyl-2-*O*-methyl-β-L-fucopyranoside (32b): ^{1}H NMR (360 MHz, $CDCl_3$) 5.83, 5.04, 4.99 (3 m_c, 3 H), 5.18 (≈d, 1 H, *J* 3.5 Hz), 4.27 (d, 1 H, *J* 7.7 Hz), 3.96 (m_c, 1 H), 3.73-3.66 (m, 2 H), 3.63 (s, 3 H), 3.55-3.44 (m, 1 H), 3.21 (dd, 1 H, *J* 7.7, 9.6 Hz), 2.18 (s, 3 H), 2.16, 1.76 (2 m_c, 2×2 H), 1.21 (d, 3 H, *J* 6.4 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) 138.0, 114.9, 103.6, 80.9, 72.2, 69.4, 69.2, 60.9, 30.2, 28.9, 16.3.

4-Pentenyl 3-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-4-*O*-methyl-α-L-rhamnopyranosyl)-2-*O*-methyl-α-L-fucopyranoside (35). Activated powdered 4Å MS (1 g) was added to a solution of **32a** (350 mg, 1.2 mmol) in anhydr CH_2Cl_2 (35 mL) under nitrogen. Compound **34** (550 mg, 1.4 mmol) was added

and the solution was then cooled to -78°C. TMSOTf (15 µL) was added and the reaction was allowed to warm up slowly to rt overnight. After addition of NEt_3, the solids were removed by filtration and the solution was concentrated. Chromatography of the residue using CH_2Cl_2/acetone 25:1 gave **35** (517 mg, 80 %): mp 99–104°C; $[\alpha]_D^{25}$ -63 (*c* 1.0, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) 5.81 (m_c, 1 H), 5.32 (dd, 1 H, *J* 3.5, 9.6 Hz), 5.28 (dd, 1 H, *J* 1.5, 3.5 Hz), 5.02, 4.96 (2 m_c, 2 H), 4.77 (dd, 1 H, *J* 10.4, 3.3 Hz), 4.70 (d, 1 H, *J* 1.5 Hz), 4.24 (d, 1 H, *J* 7.6 Hz), 4.08, 3.91 (2 m_c, 2 H), 3.83 (≈d, 1 H, *J* 3.3 Hz), 3.61-3.44 (m, 2 H), 3.52, 3.48 (2 s, 2×3 H), 3.31 (dd, 1 H, *J* 7.6, 10.4 Hz), 3.20 (≈t, 1 H, *J* 9.5 Hz), 2.13 (m_c, 2 H), 2.12, 2.11, 2.07 (3 s, 3×3 H), 1.73 (m_c, 2 H), 1.31, 1.28 (2 d, 2 x 3 H, *J* 6.2 Hz and 6.6 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) 138.2, 114.8 (CH_2), 103.7 (J_{CH} 157 Hz, Fuc-1), 99.1 (J_{CH} 173 Hz, Rha-1), 80.7, 78.0, 77.6, 74.1, 70.8, 70.7, 70.1, 69.2 (CH_2), 68.7, 60.7, 60.6, 30.2 (CH_2), 28.9 (CH_2), 21.2, 21.0, 18.1, 16.8.

Benzyl 2,4-di-*O*-acetyl-α-L-rhamnopyranoside (36). A solution of benzyl α-L-rhamnopyranoside[5] (1.35 g, 5.3 mmol), $TsOH.H_2O$ (50 mg) and trimethyl orthoacetate (1.5 mL, 12 mmol) in anhydr DMF (25 mL) was heated to 50°C for 2 h. NEt_3 (3 mL) was added and the solvent was evaporated under vaccum. The residue was taken in pyridine (10 mL, 0.12 mol) and Ac_2O (5 mL, 50 mmol) was added. After stirring at rt overnight, the excess acetylating reagent was quenched with MeOH (5 mL). The mixture was poured onto aq HCl and the product was extracted with CH_2Cl_2. The organic layer was washed with aq $NaHCO_3$ and dried over $MgSO_4$. Chromatography of the residue using Hex/EtOAc 3:1 afforded **36** (1.42 g, 79 %): mp 102°C; $[\alpha]_D^{25}$ -64 (*c* 2.0, $CDCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) 7.40–7.25 (m, 5 H), 5.11 (dd, 1 H, *J* 1.5, 3.6 Hz), 4.89 (d, 1 H, *J* 1.5 Hz), 4.86 (dd, 1 H, *J* 10.0, 9.7 Hz), 4.69, 4.52 (2 d, 2 H, *J* 12.0 Hz), 4.08 (dd, 1 H, *J* 3.6, 10 Hz), 3.84 (dq, 1 H, *J* 9.7, 3 x 6.2 Hz), 2.15, 2.12 (2 s, 2×3 H), 1.19 (d, 3 H, *J* 6.2 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) 128.5, 128.0, 127.8, 96.7, 74.7, 72.8, 69.7, 68.6, 66.2, 21.0, 17.4.

Benzyl 2,4-di-*O*-acetyl-3-*O*-[3-*O*-acetyl-4-(2,3-di-*O*-acetyl-4-*O*-methyl-α-L-rhamnopyranosyl)-2-*O*-methyl-α-L-fucopyranosyl]-α-L-rhamnopyranoside (37).

A mixture of **35** (400 mg, 0.75 mmol) and **36** (320 mg, 0.95 mmol) was dried by coevaporation with toluene followed by treatment at 50°C under vacuum for 1 h. The mixture was then dissolved in anhydr CH_2Cl_2/Et_2O (12 mL, 1:5) and placed under nitrogen. NIS (200 mg, 0.89 mmol) was added followed by TMSOTf (150 μL). The mixture was stirred at rt for 4 h, then diluted with CH_2Cl_2 and washed successively with aq $Na_2S_2O_3$, aq $NaHCO_3$ and brine. The organic phase was dried with $MgSO_4$ and concentrated. Final chromatography using Hex/EtOAc 1:1 afforded **37** (250 mg, 42 %). ^{1}H NMR (360 MHz, $CDCl_3$) 7.40–7.25 (m, 5 H), 5.28 (dd, 1 H, *J* 3.3, 9.5 Hz), 5.23 (dd, 1 H, *J* 1.5, 3.3 Hz), 5.20 (dd, 1 H, *J* 1.5, 3.5 Hz), 5.09 (dd≈t, 1 H, *J* 10.0, 9.7 Hz), 5.03 (d, 1 H, *J* 3.6 Hz), 5.02 (dd, 1 H, *J* 10.9, 3.0 Hz), 4.82 (bs, 1 H), 4.67 (d, 1 H, *J* 11.9 Hz), 4.66 (bs, 1 H), 4.52 (d, 1 H, *J* 11.9 Hz), 4.20 (≈t, 1 H, *J* 9.5 Hz), 4.10 (dd, 1 H, *J* 3.5, 10 Hz), 4.01 (m_c, H-5'), 4.01, 3.97 (2 dq, 2 x 1 H), 3.91 (≈bd, 1 H, *J* 3.0 Hz), 3.56 (dd, 1 H, *J* 3.6, 10.9 Hz), 3.48, 3.38 (2 s, 2×3 H), 2.13, 2.12, 2.07, 2.06, 2.04 (5 s, 5×3 H), 1.31, 1.16 (2 d, 3 H + 6 H, all *J* 6.2 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) 169.8, 128.5, 127.9, 99.2, 99.1, 96.9, 80.5, 78.9, 75.3, 74.6, 72.7, 71.7, 71.5, 71.0, 70.5, 69.7, 68.2, 66.8, 66.5, 60.7, 59.0, 21.3, 21.0, 21.0, 20.9, 20.85, 18.1, 17.4, 16.5.

2,4-Di-*O*-acetyl-3-*O*-[3-*O*-acetyl-4-(2,3-di-*O*-acetyl-4-*O*-methyl-α-L-rhamnopyranosyl)-2-*O*-methyl-α-L-fucopyranosyl]-α-L-rhamnopyranose (38). Compound **37** (230 mg, 0.29 mmol) was hydrogenolysed in methanol (70 mL) in the presence of $Pd(OH)_2/C$ (50 mg) and HOAc (5 drops) under atmospheric pressure for 2 d. The catalyst was removed by filtration and the solution was concentrated. Purification of the product by chromatography using Hex/EtOAc 1:1 removed impurities that had been

present in the starting material. Yield of **38**: 95 mg, 47 %: $[\alpha]_D^{19}$ -101 (*c* 0.5 $CHCl_3$); ^{13}C NMR (63 MHz, $CDCl_3$) 170.7, 170.2, 170.0, 169.4, 99.0 (2×), 91.8, 80.4, 78.8, 77.8, 75.1, 74.1, 72.7, 72.1, 71.4, 70.9, 70.3, 68.1, 66.4, 60.6, 58.9, 21.2, 21.0, 20.9, 20.85, 20.8, 18.0, 17.4, 16.3.

(*R*)-3-Hydroxytetracosanoic acid (49). A solution of **48** (2.5 g, 6.3 mmol) in hot EtOH (100 mL) was treated with 4N aq NaOH (5 mL). The immediately precipitating gel was redissolved by heating to reflux and the reaction mixture was then stirred for about 1 h at rt. The mixture was cooled in the refrigerator and the precipitate was collected and washed with cold EtOH. The solid was dissolved in hot water and the solution was then acidified with aq HCl. The precipitating **49** (1.9 g, 79 %) was collected, washed with water and dried under vacuum over $CaSO_4$: mp 98°C; $[\alpha]_D^{50}$ -10 (*c* 2.0, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$, 330 K) 4.03 (m_c, 1 H, H-3), 2.57 (dd, 1 H, *J* 3.5, 6.3 Hz), 2.47 (dd, 1 H, *J* 6.3, 16.3 Hz), 1.60-1.40 (m, 2 H), 1.28 (m_c, 38 H), 0.89 (t, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$, 330 K) 175.6, 68.2, 41.0, 36.8, 32.0, 29.7–29.3, 25.5, 22.7, 14.0. Anal. Calcd for $C_{24}H_{48}O_3$: C 74.94, H 12.58. Found: C 74.61/74.52, H 12.17/12.28.

Cyclic carbonate of 49 (53). To a solution of **49** (390 mg, 1.0 mmol) in warm anhydr dioxane (15 mL) was added charcoal (6 mg) and the mixture was heated to 60°C. Diphosgene (700 µL, 7 mmol) was added and the reaction was kept at 60°C under inert atmosphere for 2 d. The charcoal was removed by filtration through a membrane and the residue was evaporated to dryness. After codistillation with toluene and chloroform, the product was dried under vacuum and compound **53** (410 mg, 99%) was obtained as a solidifying syrup: mp 51-54°C; ^1H NMR (250 MHz, $CDCl_3$) 5.26 (m_c, 1 H, H-3), 2.78 (dd, 1 H, *J* 16.6, 7.8 Hz), 2.67 (dd, 1 H, *J* 16.6, 5.0 Hz), 1.72 (m_c, 2 H, H-4), 1.25 (m_c, 38 H), 0.88 (t, 3 H); ^{13}C NMR (63 MHz, $CDCl_3$) 174.7, 79.4, 38.5, 34.0, 32.3, 30.1–29.6 (m), 25.5, 23.1, 14.5.

[1] Fischer, E.; Bergmann, M.; Rabe, A. *Ber.* **1920**, *53*, 2362–2388.
[2] Gurjar, M.K.; Saha, U.K. *Tetrahedron* **1992**, *48*, 4039–4044.
[3] Carson, J.F. *Synthesis* **1981**, 268–270. (L-analog)
[4] a) Jain, R.K.; Locke, R.D.; Matta, K.L. *Carbohydr. Res.* **1991**, *212*, C1–C3; b) Debenham, J.S.; Rodebough, R.; Fraser-Reid, B. *J. Org. Chem.* **1997**, *62*, 4591–4600.
[5] Brimacombe, B.S.; Cook, M.C.; Tucker, L.C.N. *J. Chem. Soc.* **1965**, 2292–2294.

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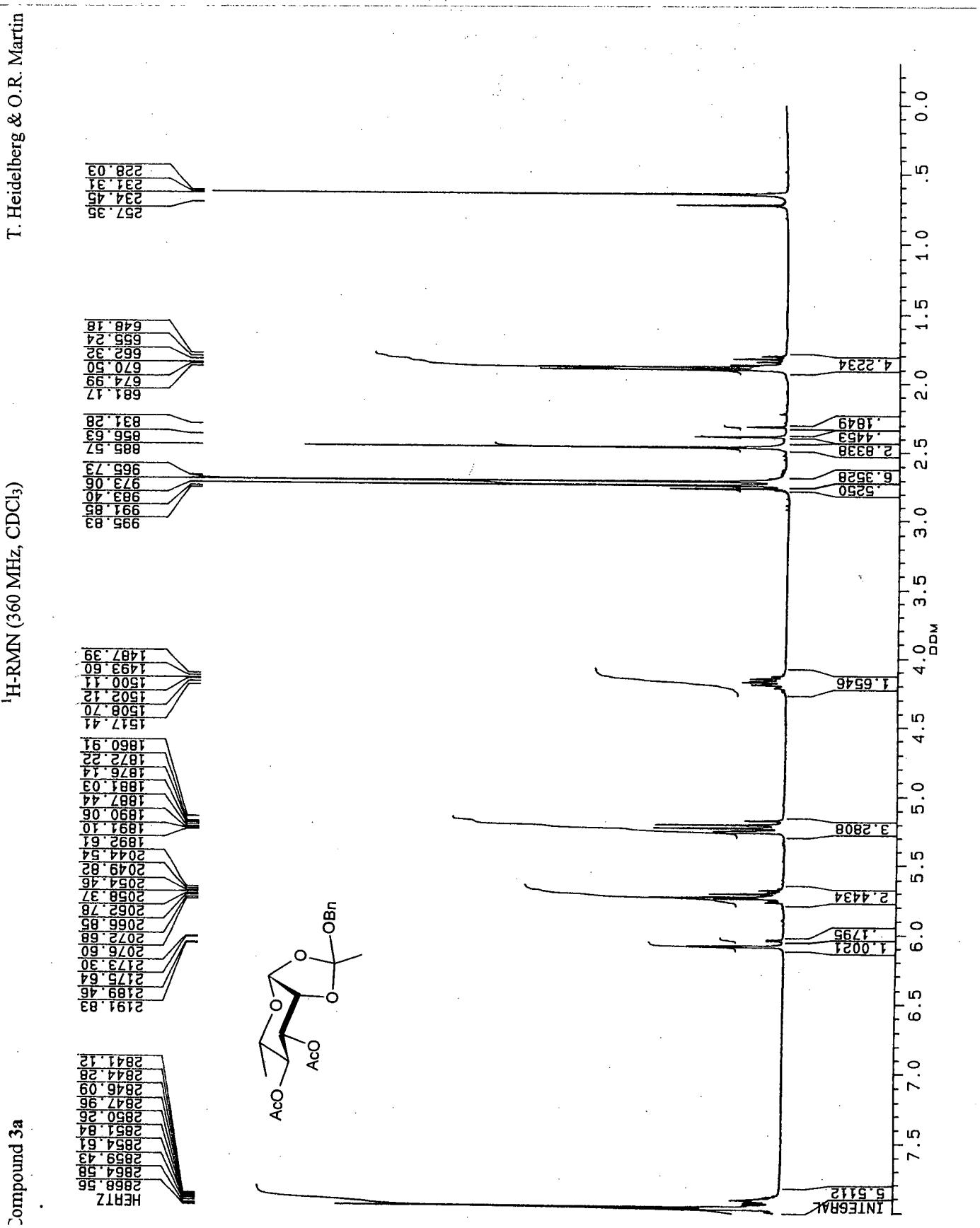
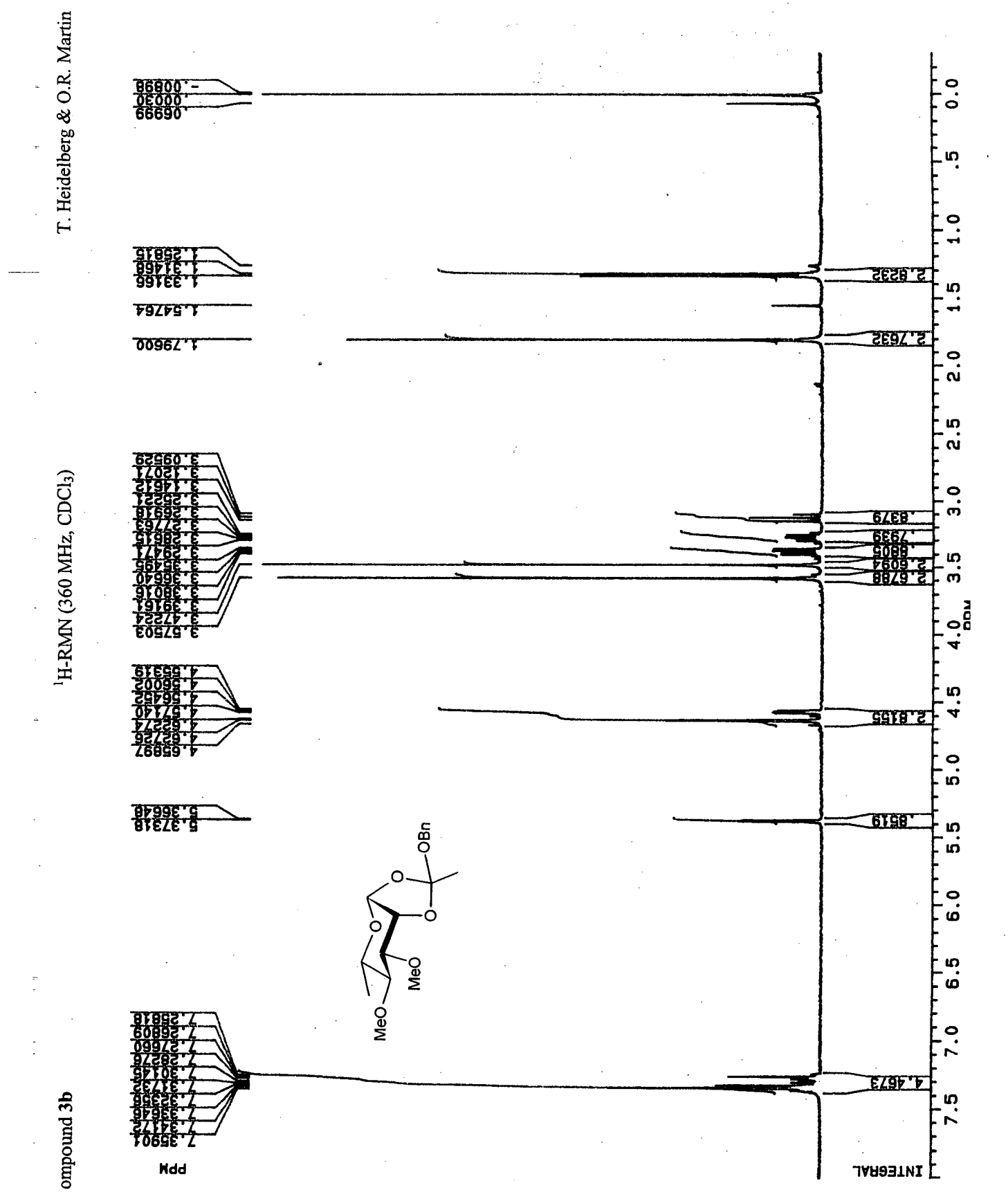
^{1}H-RMN (360 MHz, $CDCl_3$)



Compound 3a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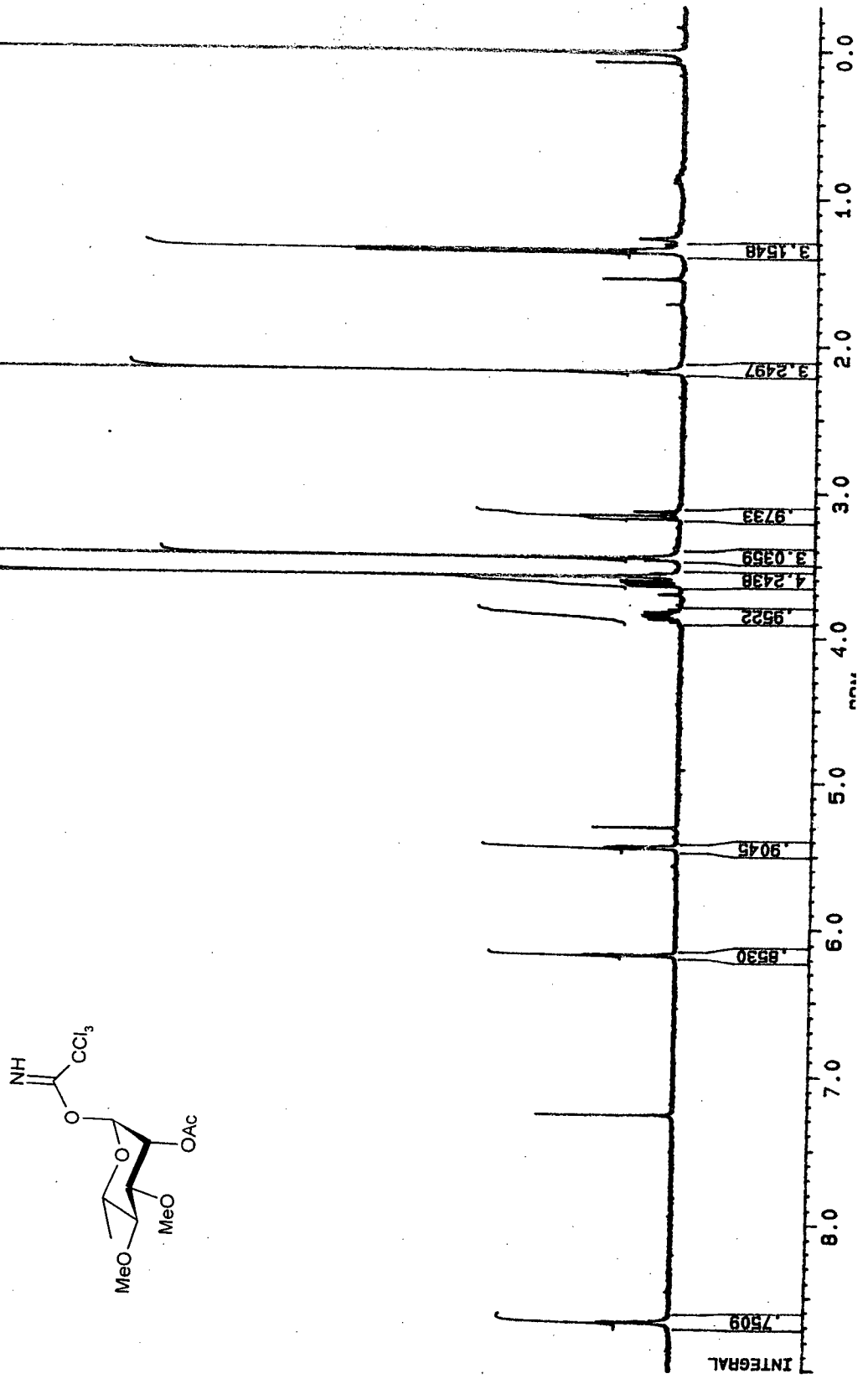
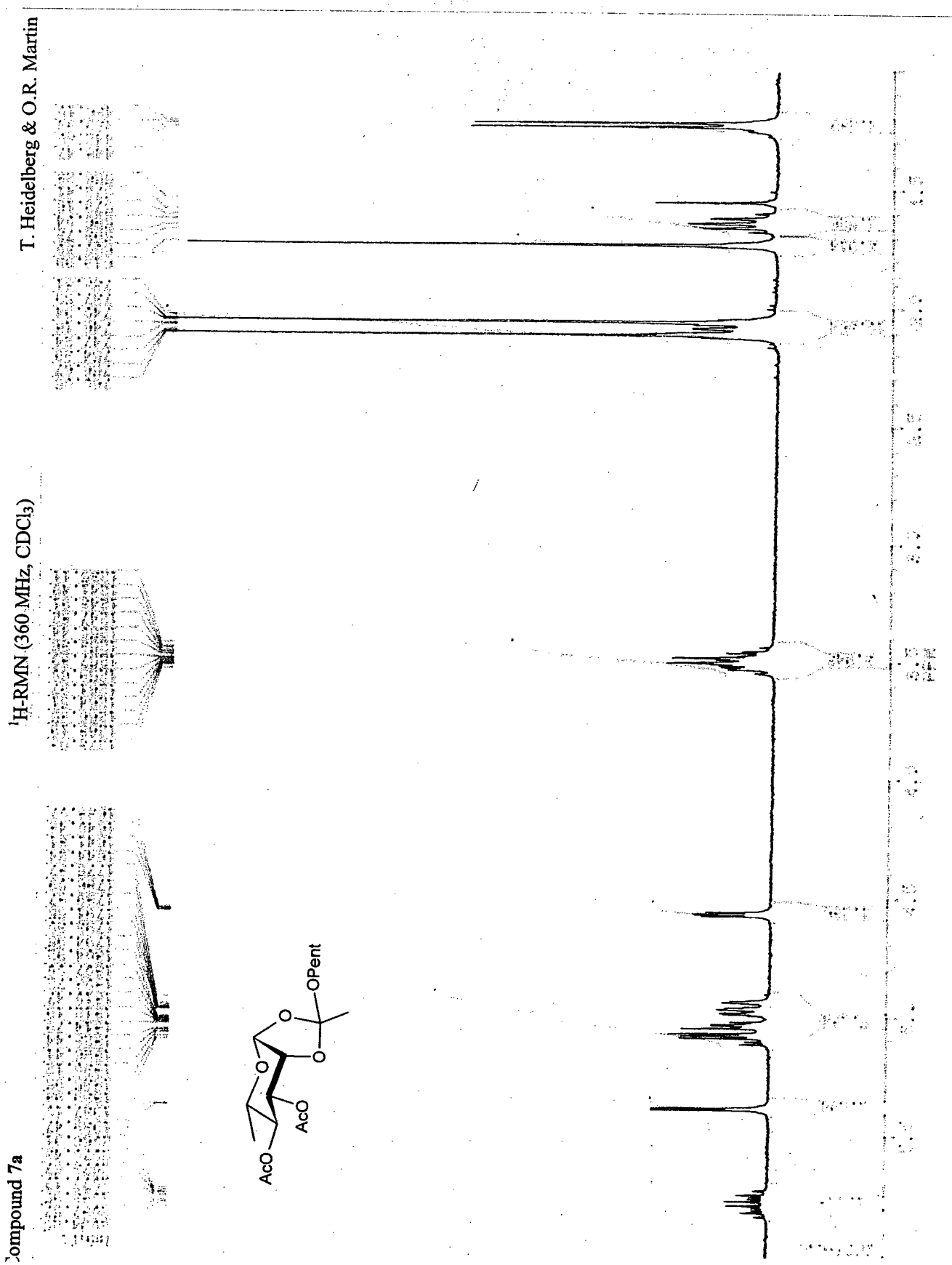
^{1}H-RMN (360 MHz, $CDCl_3$)
ompound **3b**
OBn
MeO
MeO
PPM
INTEGRAL

T. Heidelberg & O.R. Martin

^{1}H-RMN (360 MHz, $CDCl_3$)

Compound **6**





Compound **7b**

^{1}H-RMN (360 MHz, $CDCl_3$)

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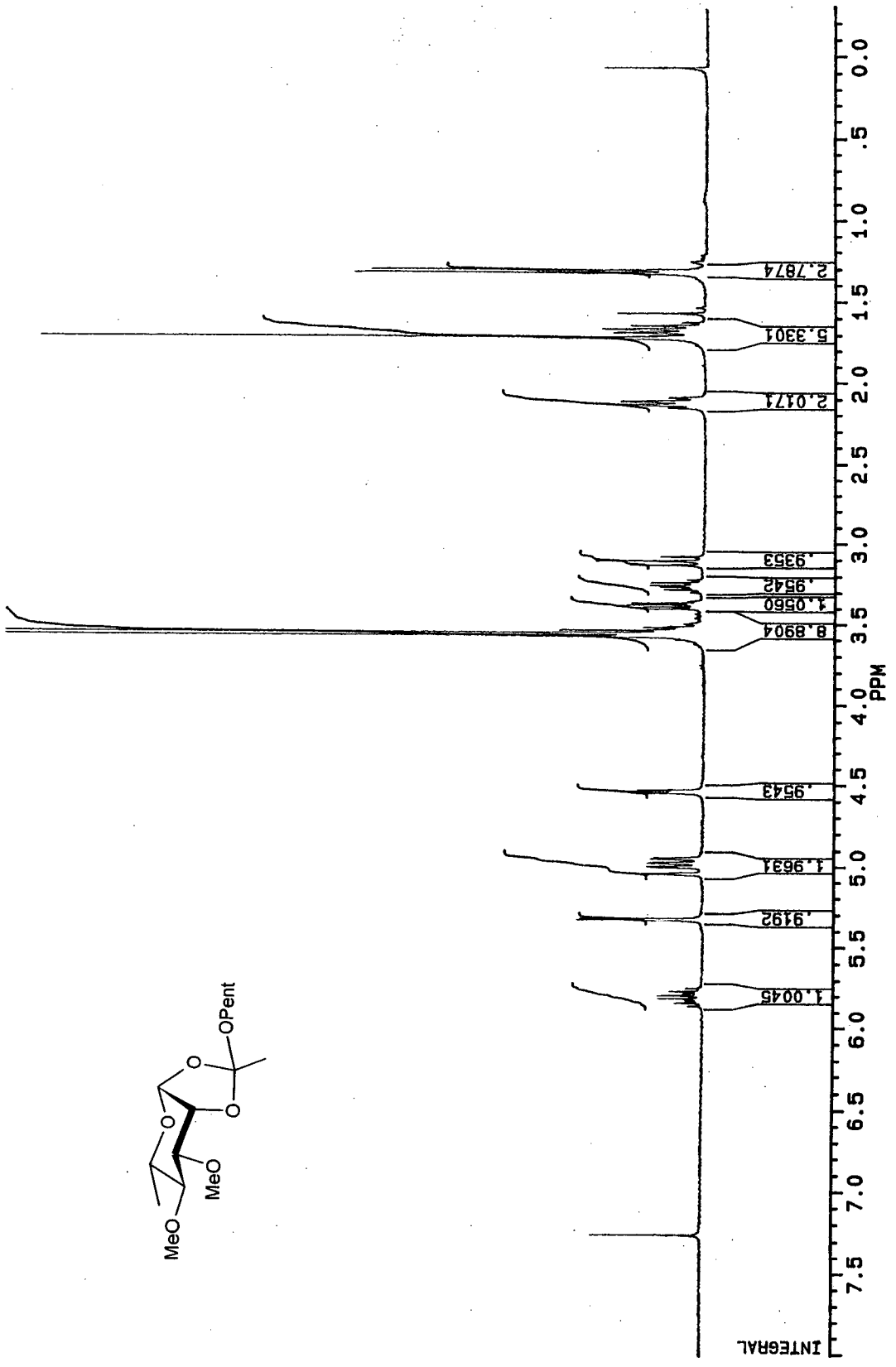
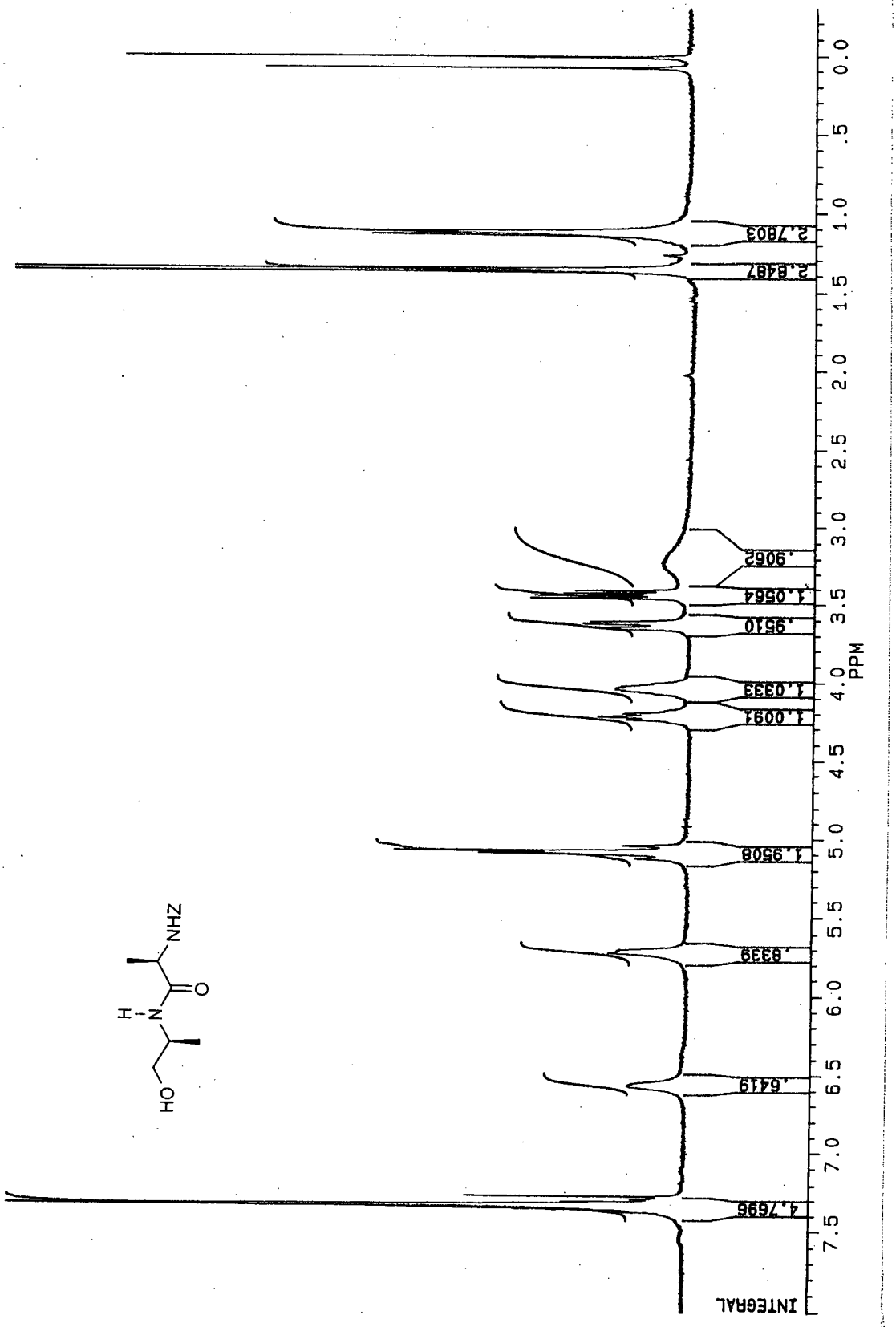
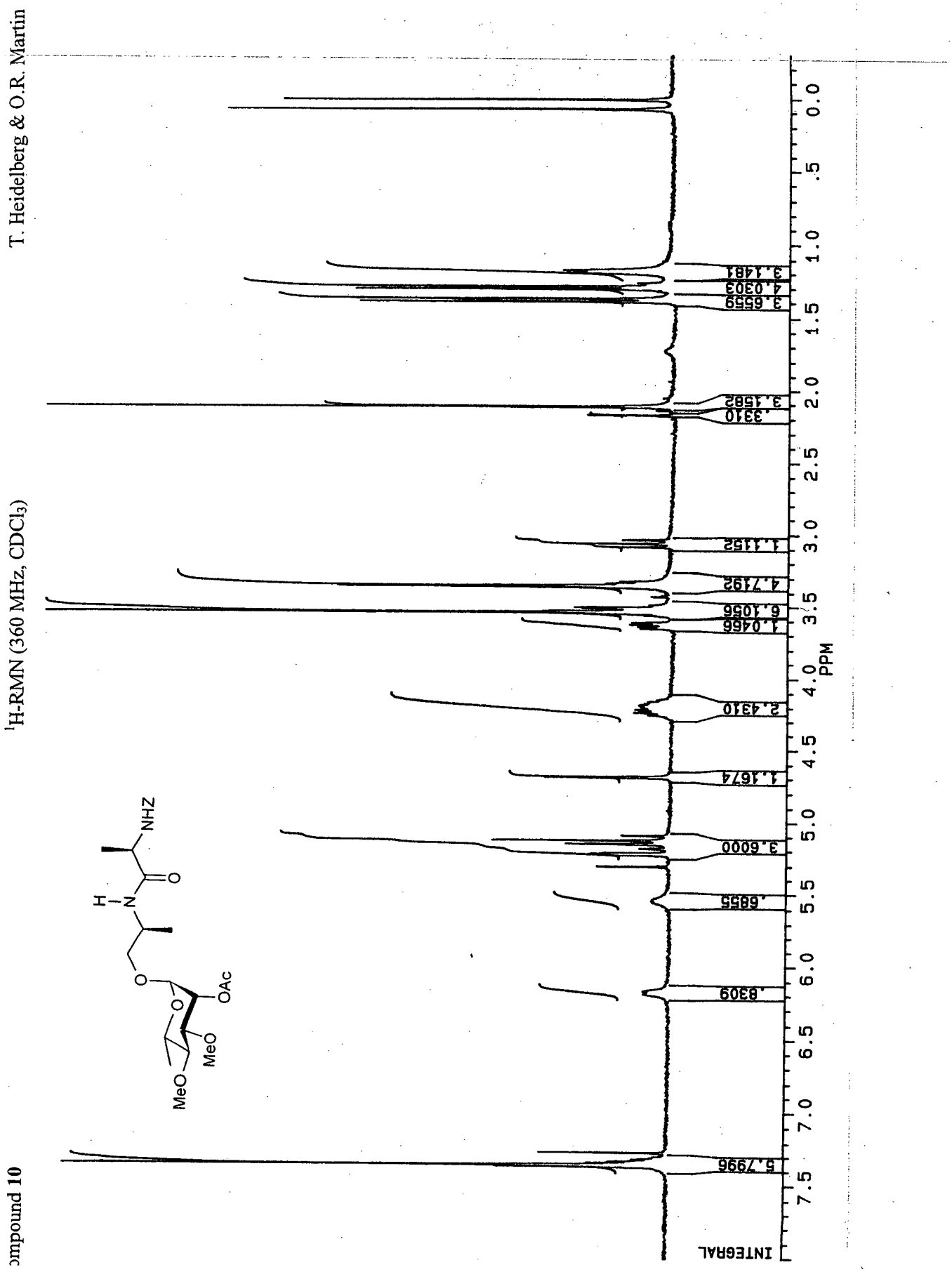


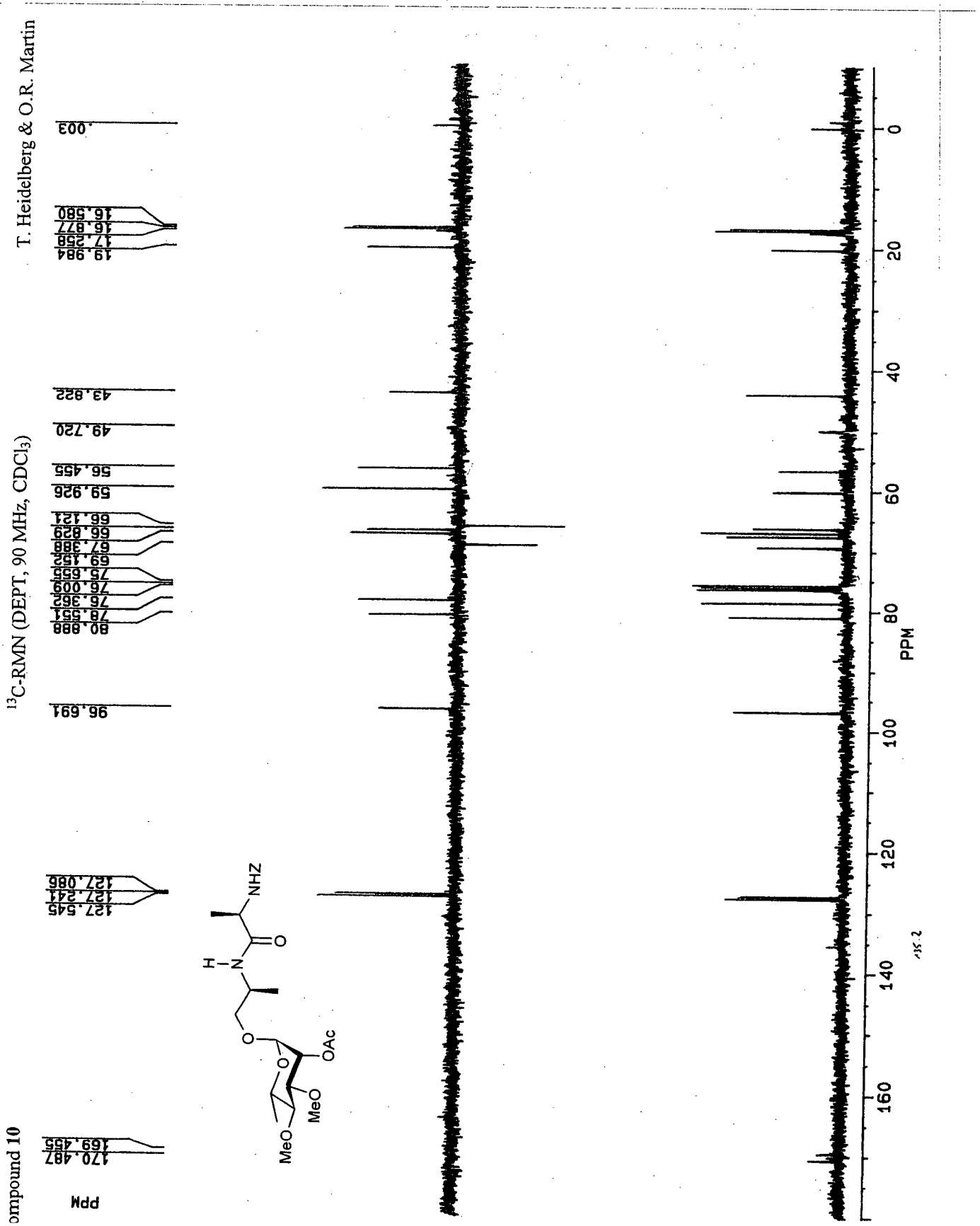
ompound **9**

^{1}H-RMN (360 MHz, $CDCl_3$)

T. Heidelberg & O.R. Martin



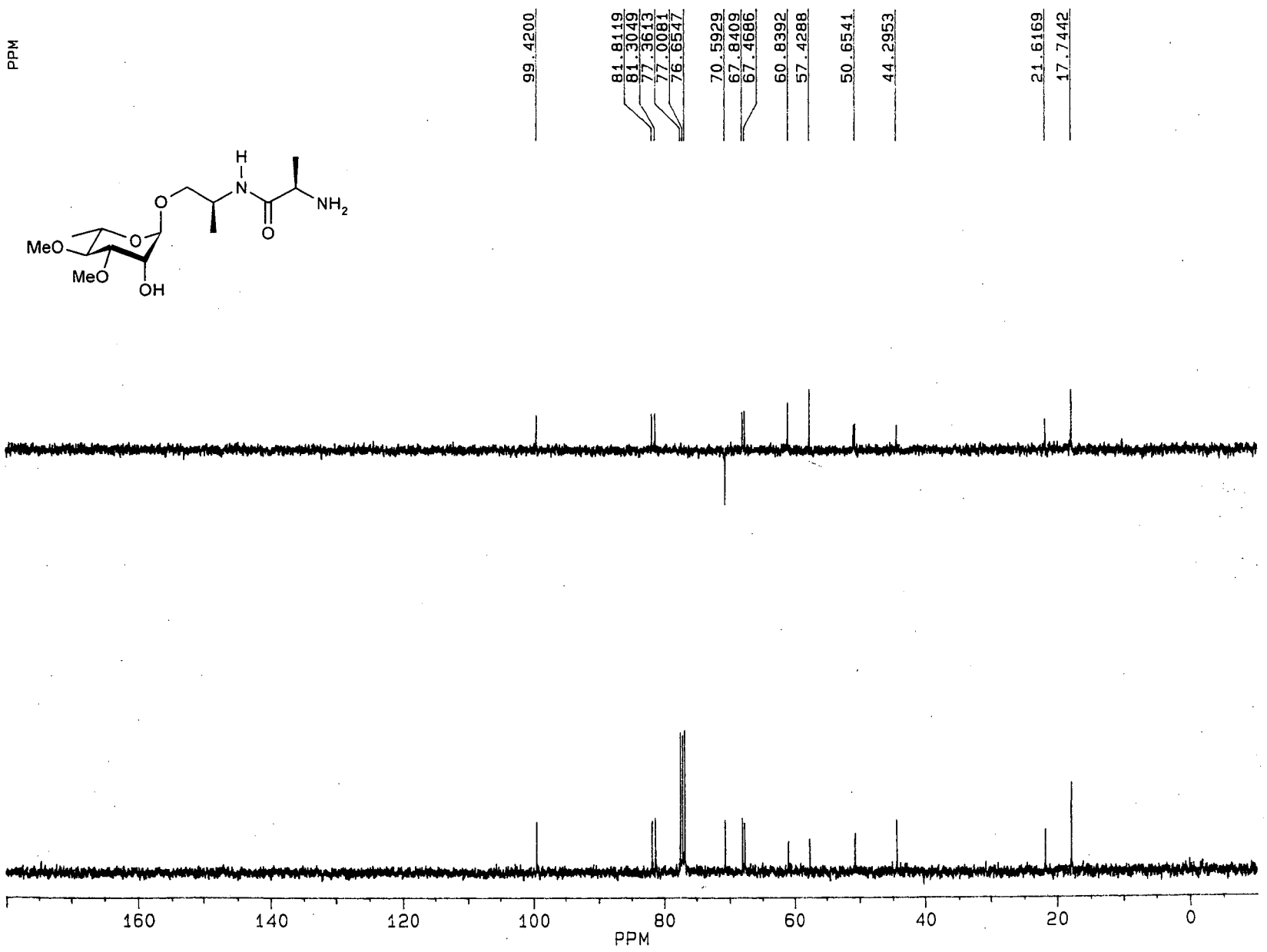

T. Heidelberg & O.R. Martin
^{1}H-RMN (360 MHz, CDCl$_3$)
ompound **10**
NHZ
H–N
O
OAc
MeO
MeO
5.7996
.8309
.6855
3.6000
1.1674
2.4310
1.0466
6.1056
4.7192
1.1152
.3310
3.1582
3.6559
4.0303
3.1481
INTEGRAL
PPM
0.0
.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5

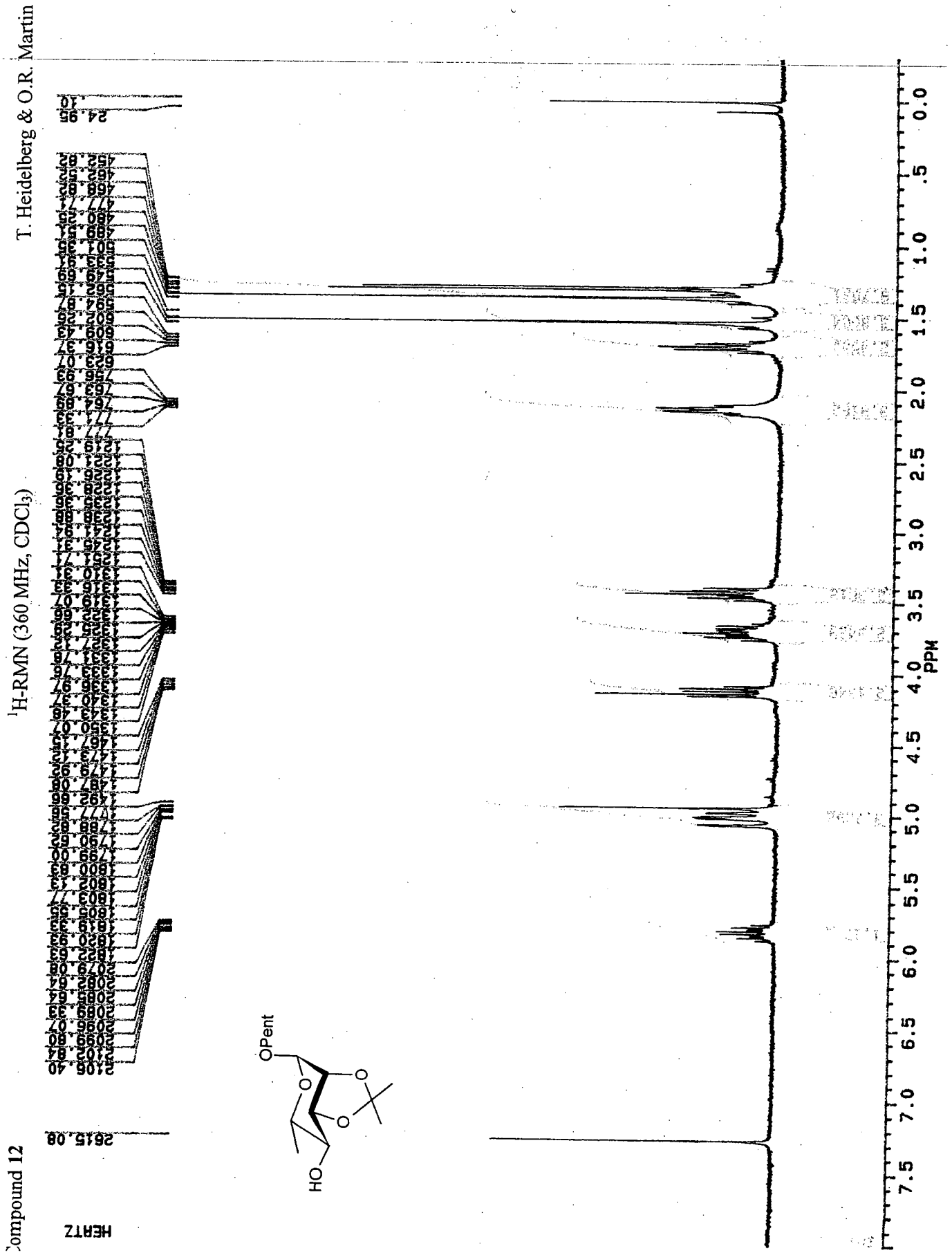


ɔmpound **11**

^{13}C-RMN (DEPT, 90 MHz, $CDCl_3$)

T. Heidelberg & O.R. Martin

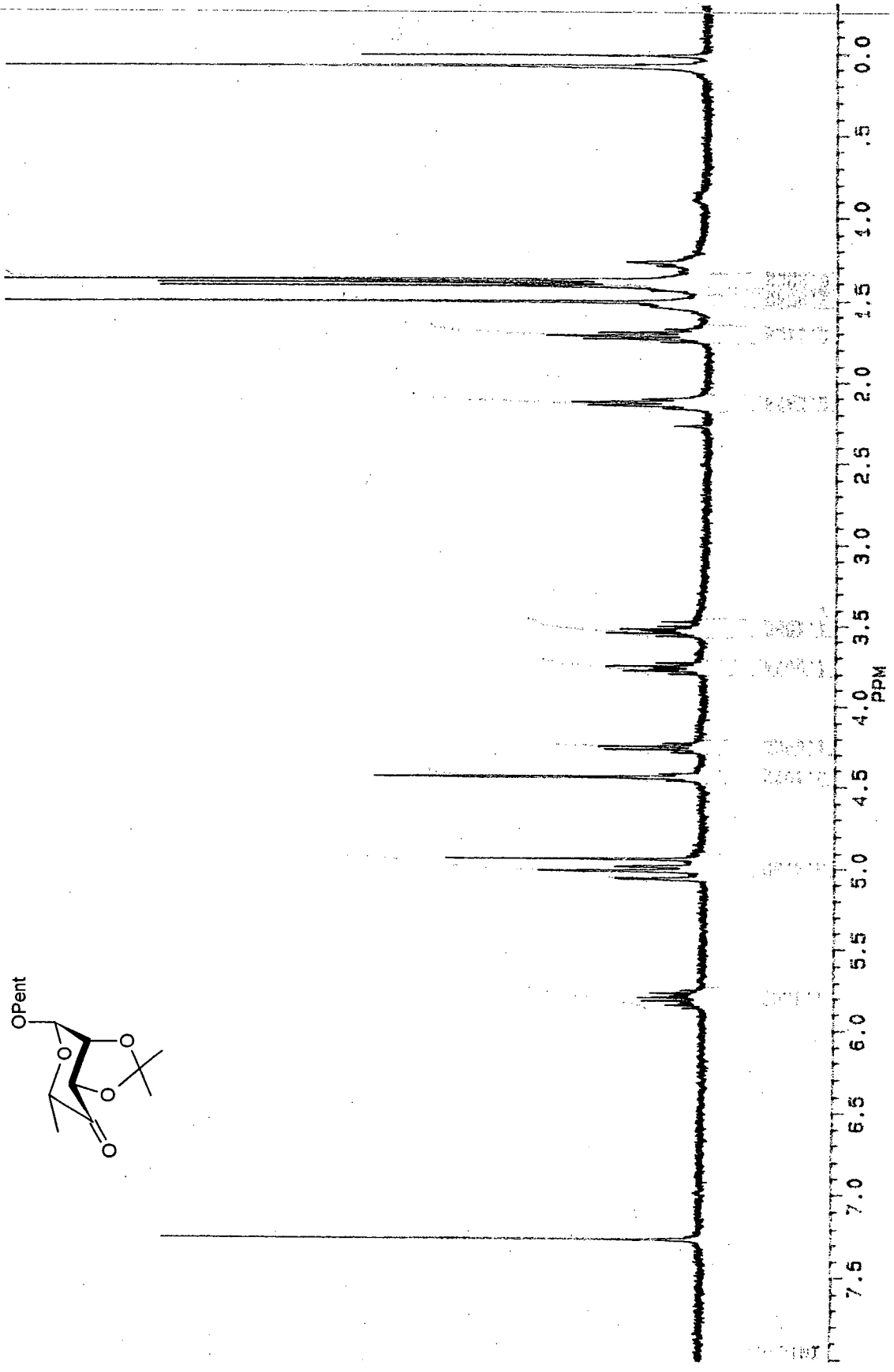


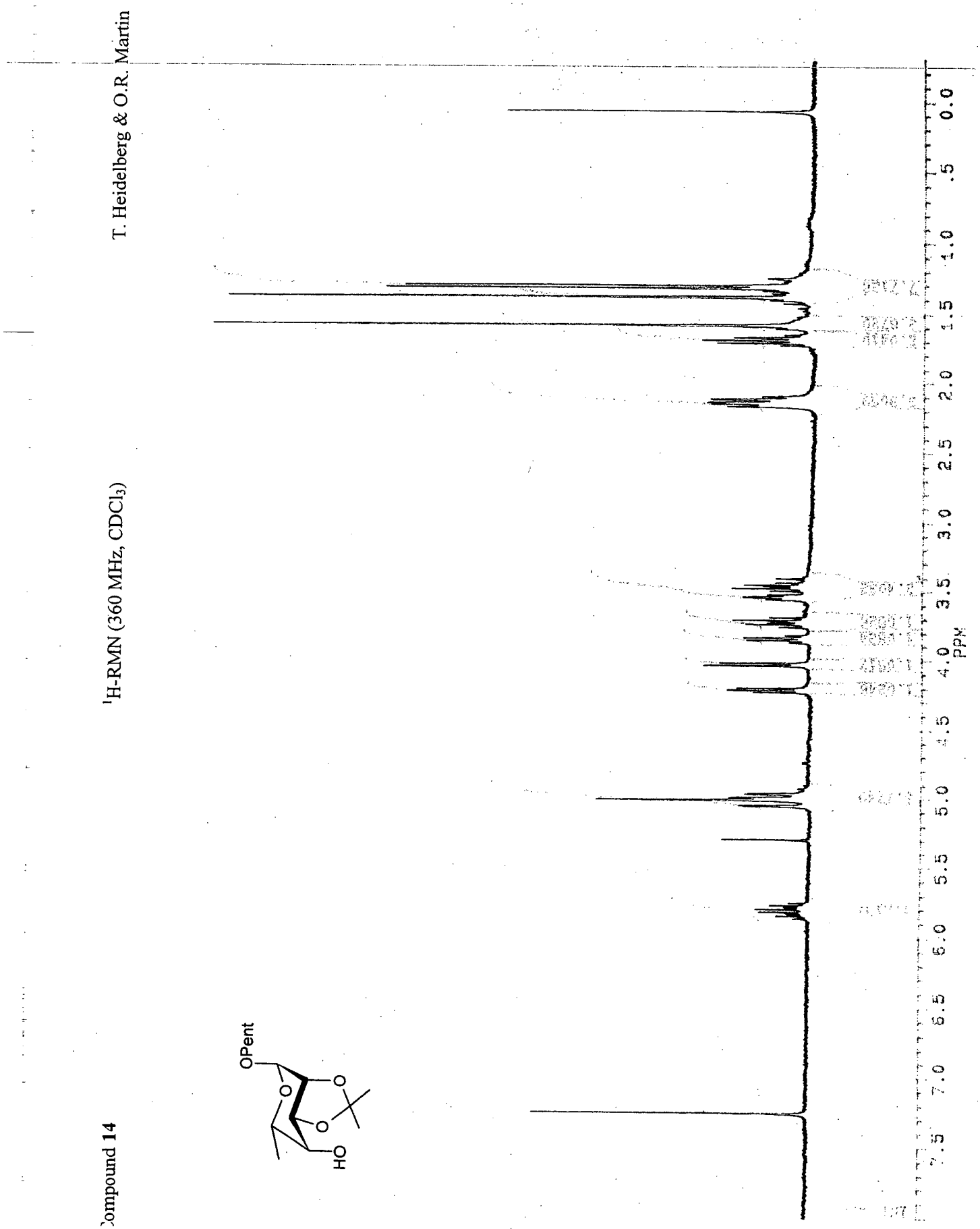


Compound **13**

^{1}H-RMN (360 MHz, $CDCl_3$)

T. Heidelberg & O.R. Martin

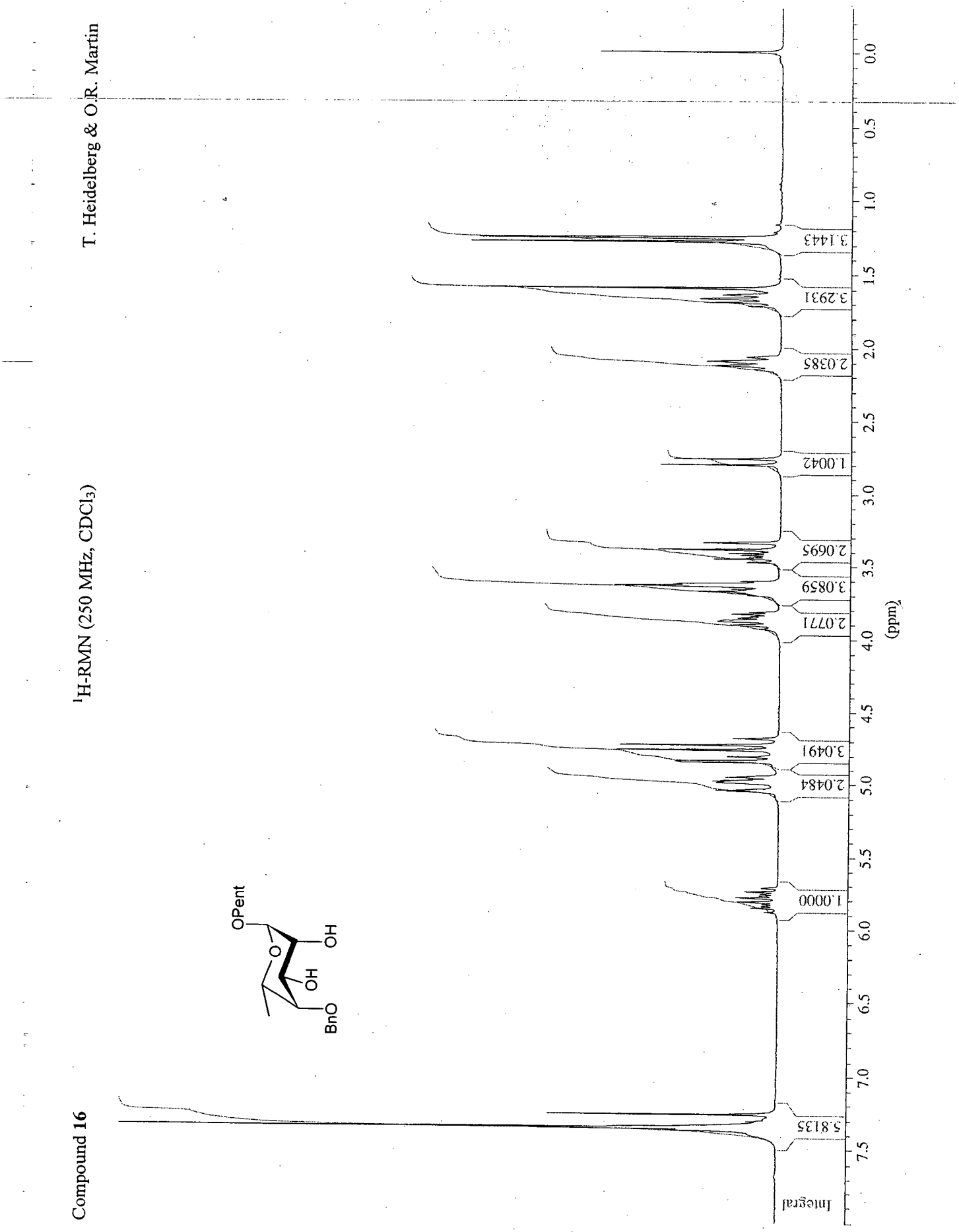


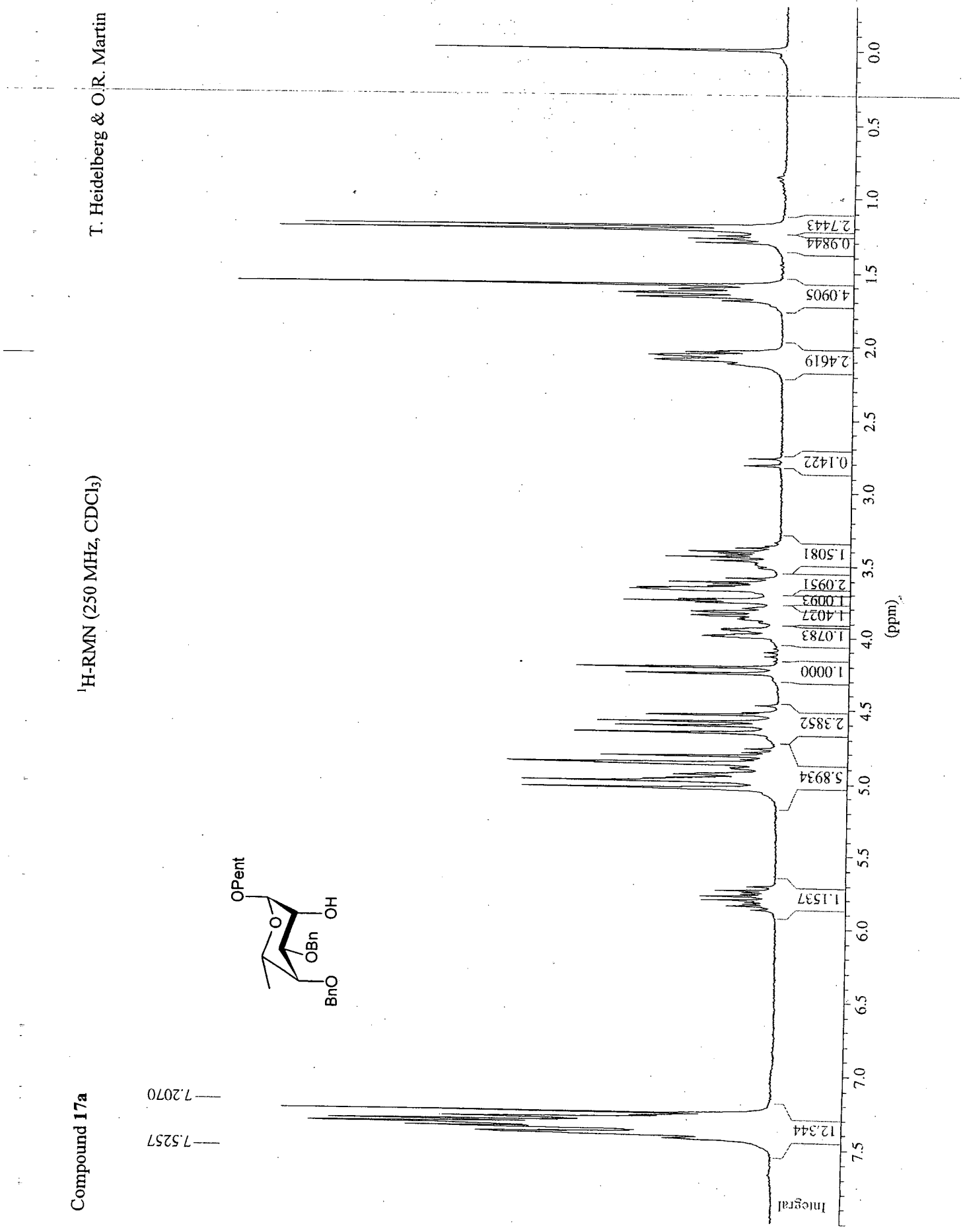


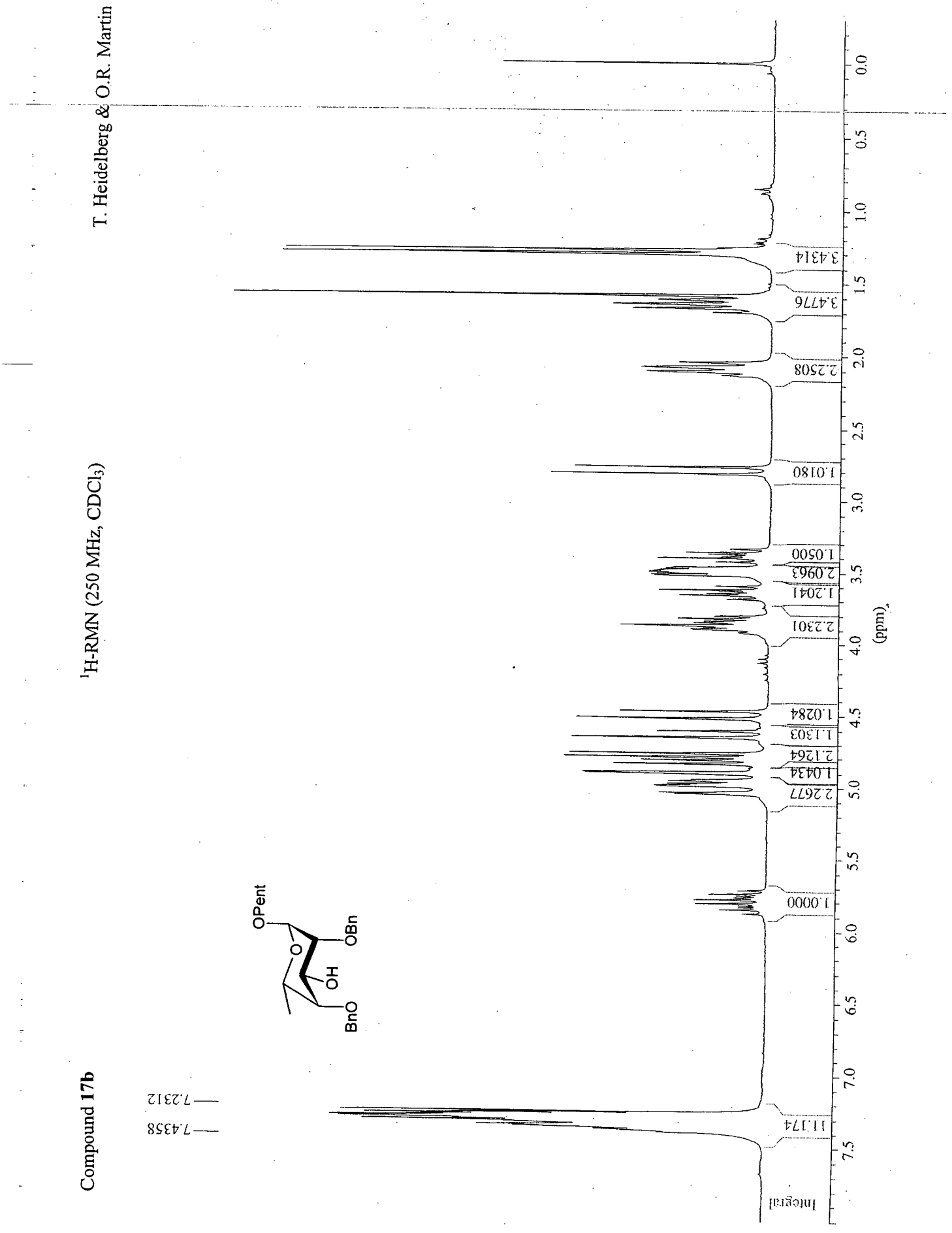
Compound **16**

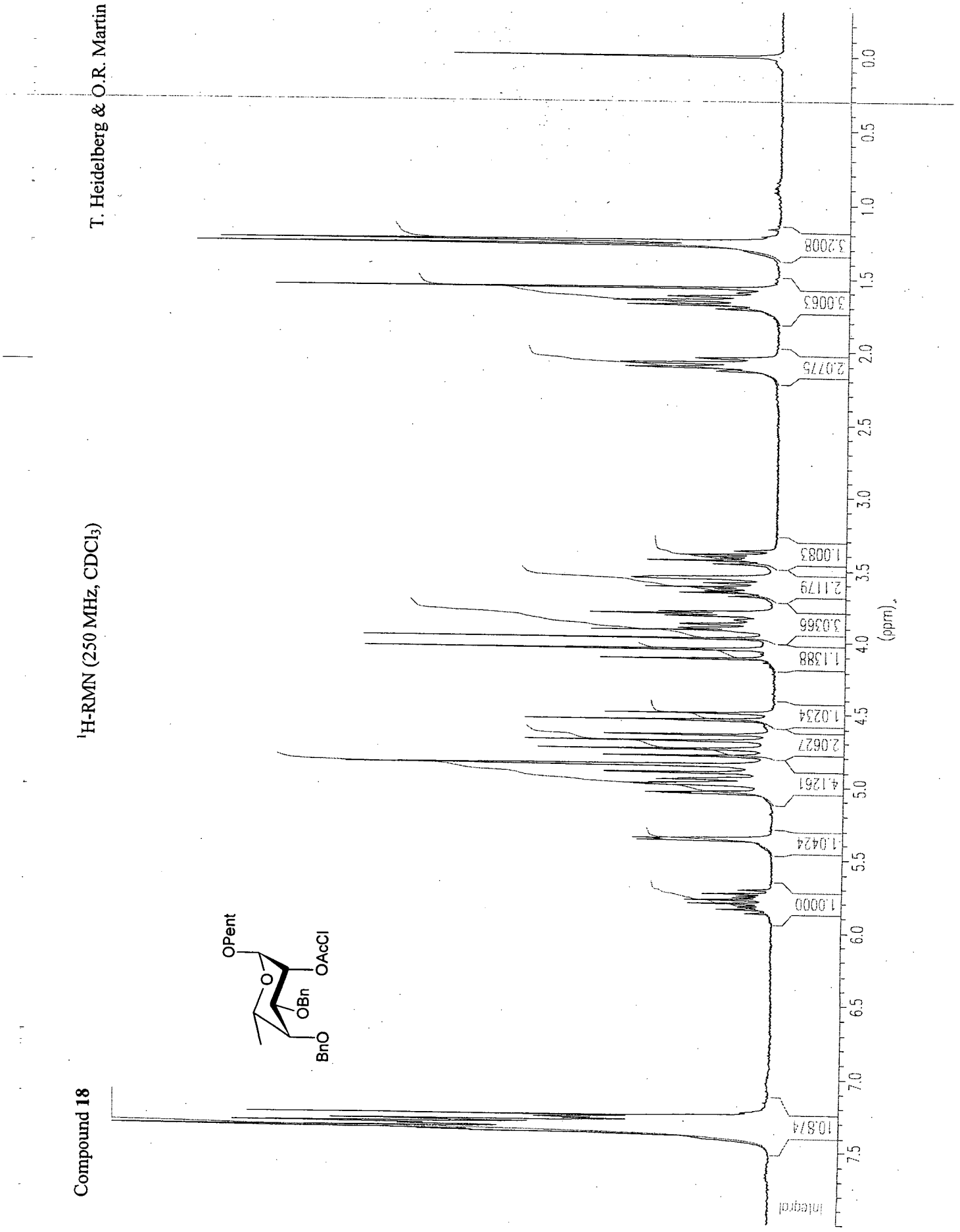
^{1}H-RMN (250 MHz, $CDCl_3$)

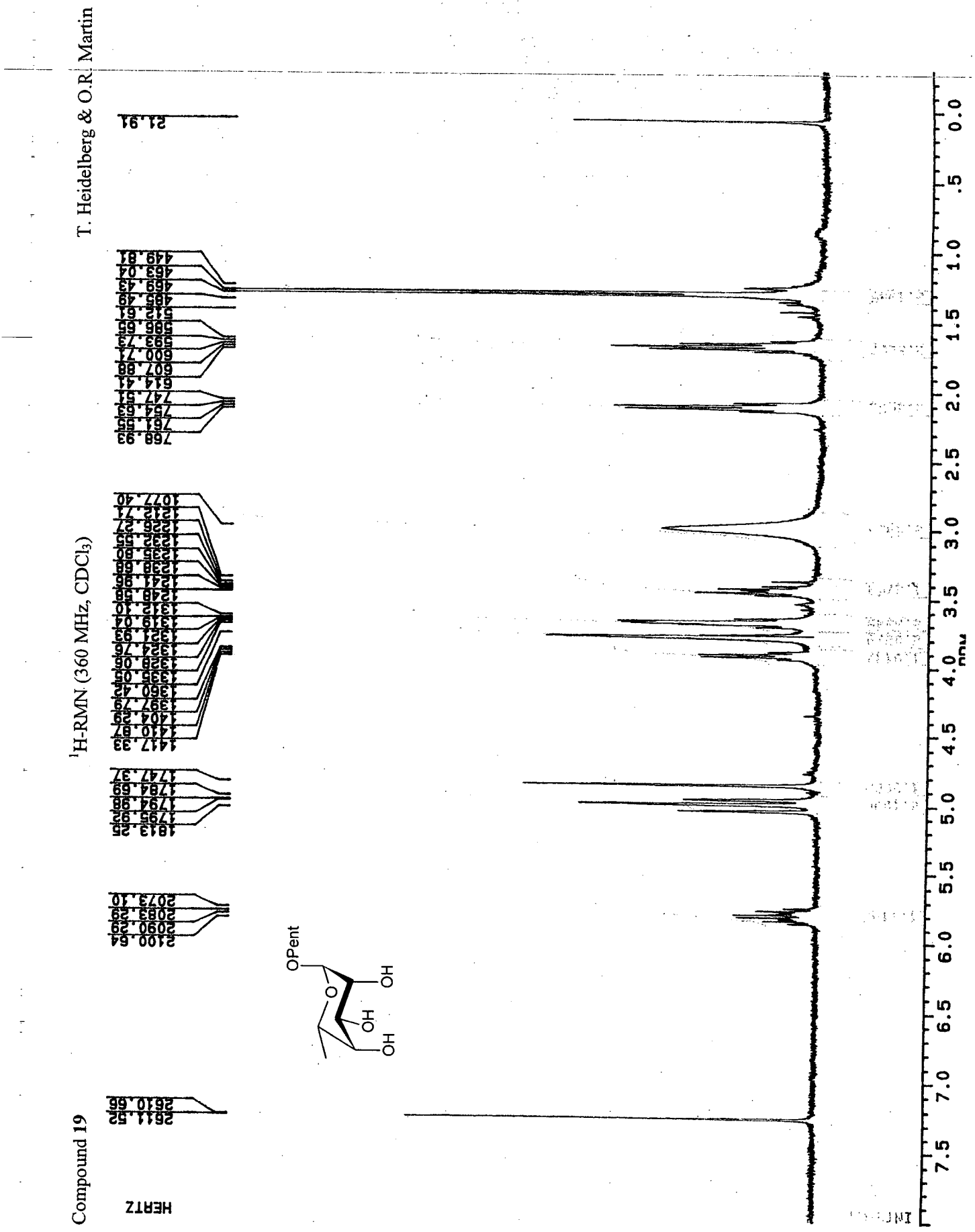
T. Heidelberg & O.R. Martin

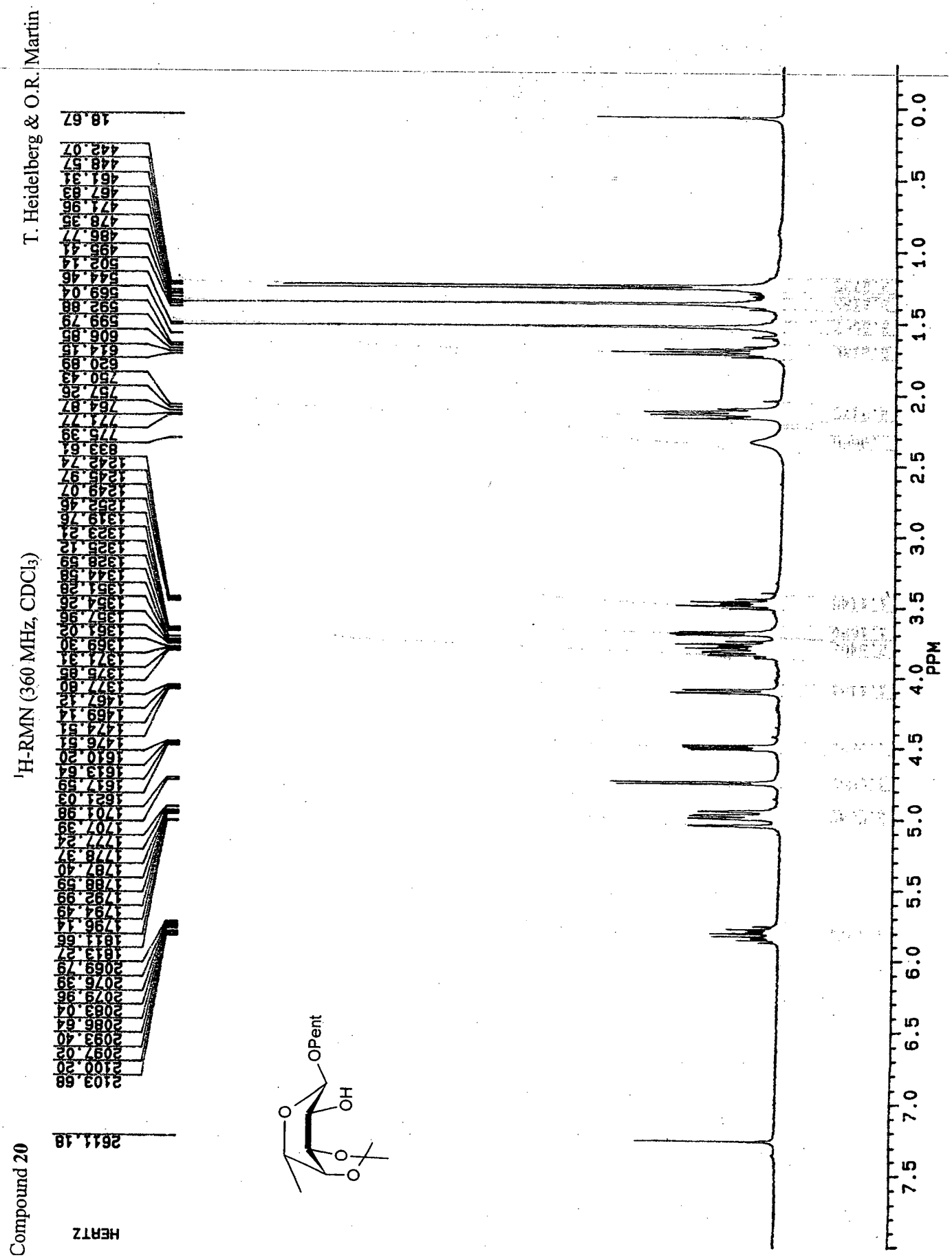


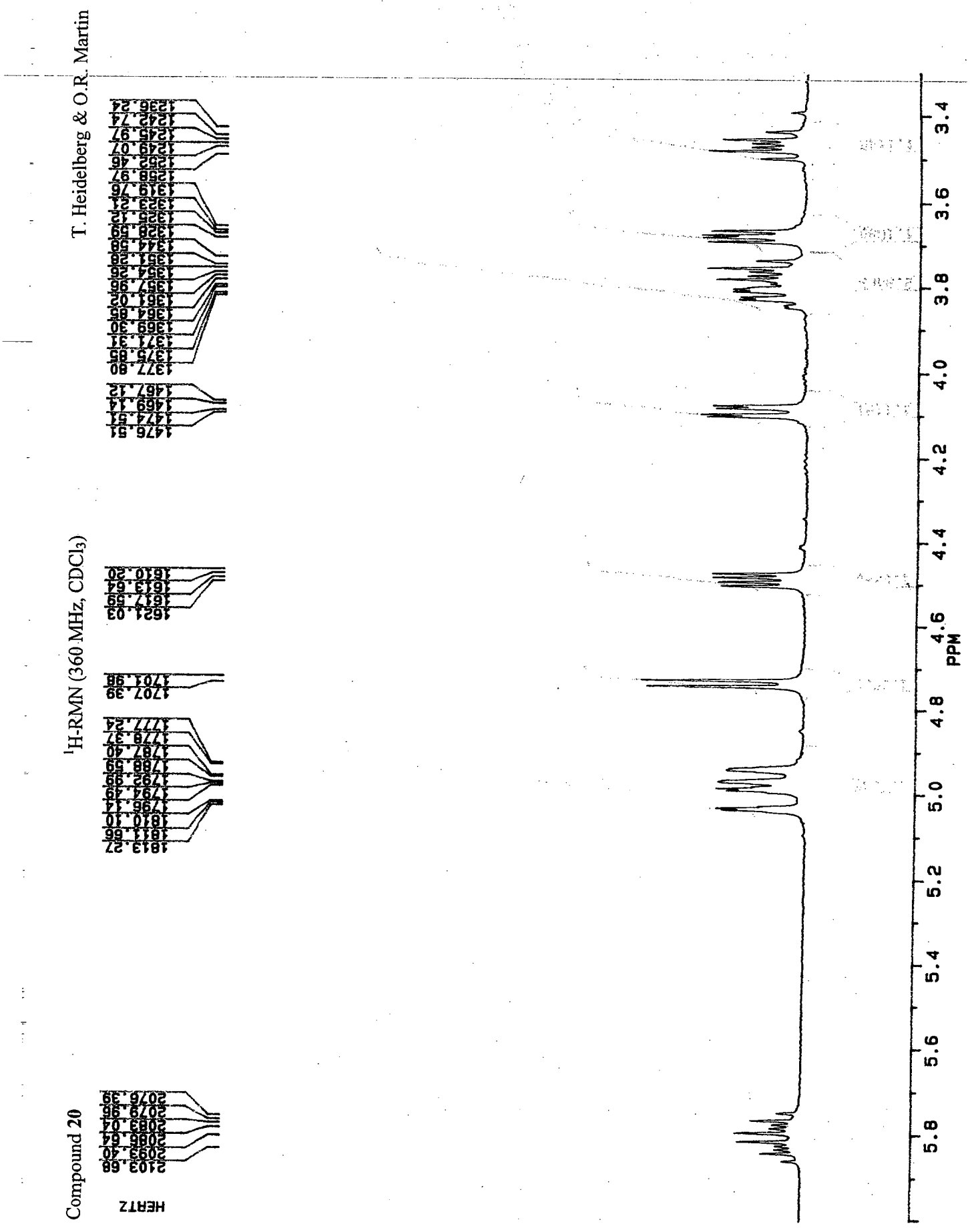







Compound 19
^{1}H-RMN (360 MHz, CDCl$_3$)
T. Heidelberg & O.R. Martin
HERTZ
PPM
OPent
HO
OH
OH
O




T. Heidelberg & O.R. Martin
^{1}H-RMN (360 MHz, CDCl$_3$)
Compound 20
HERTZ
PPM
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
5.4
5.6
5.8

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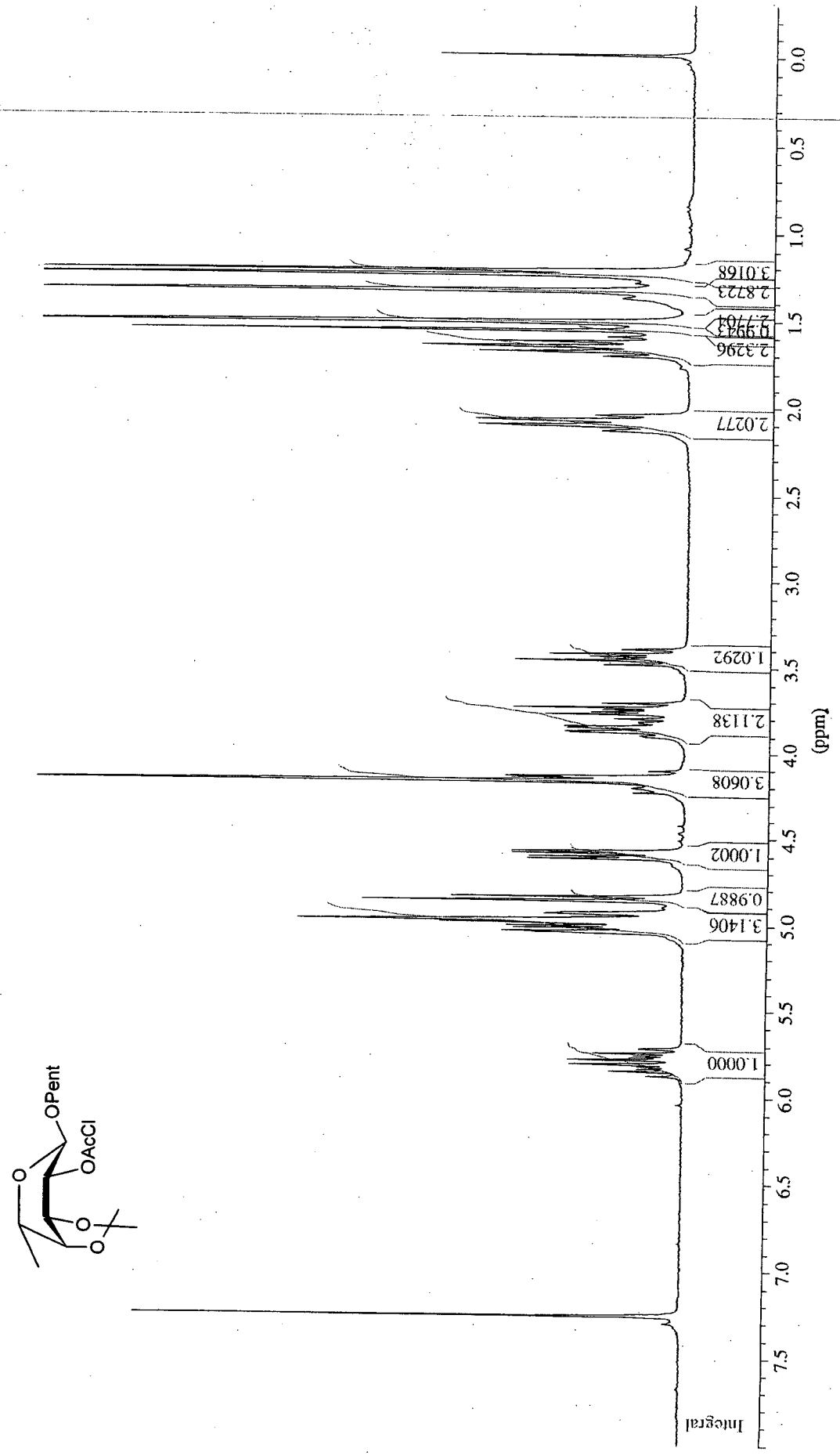
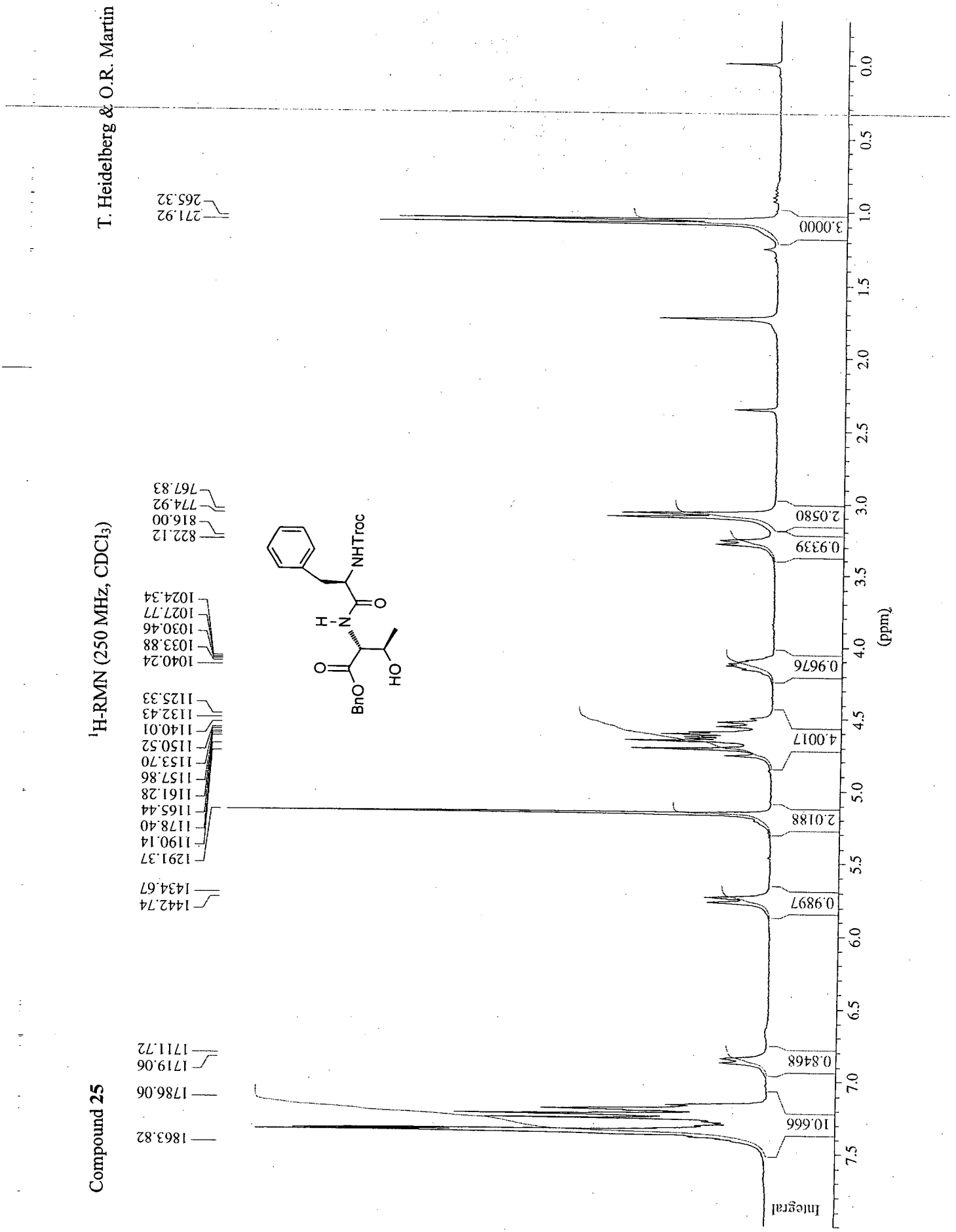
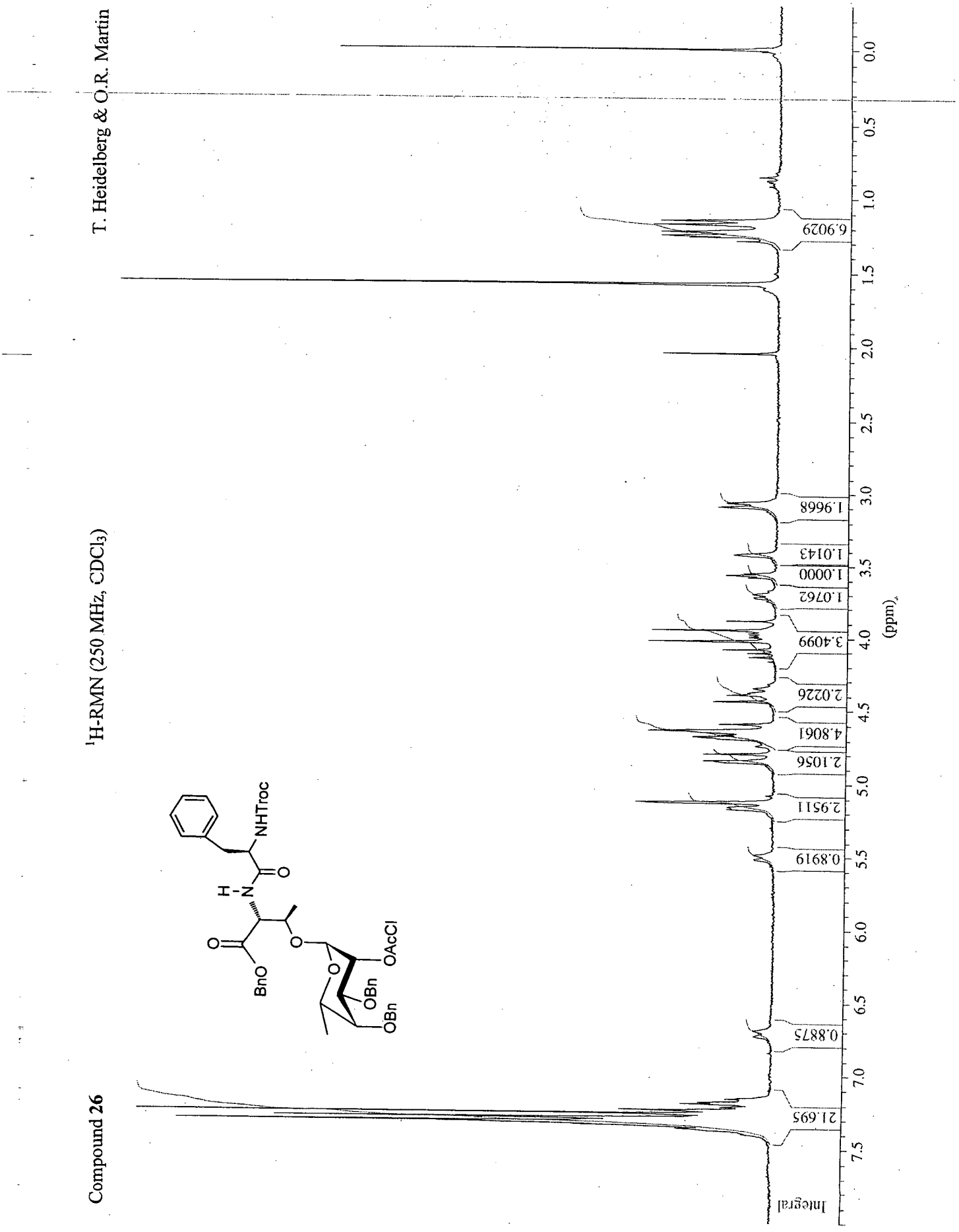
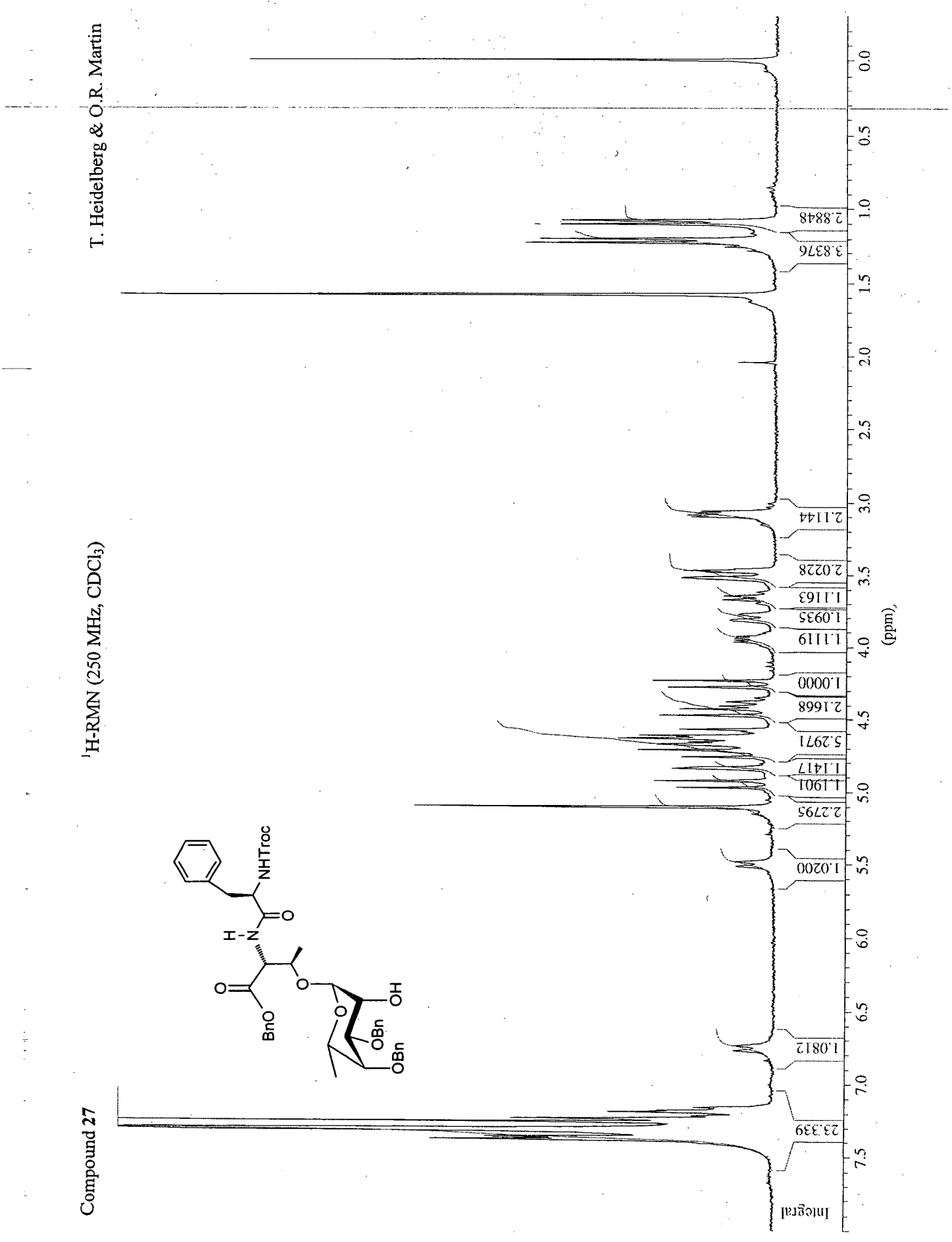
^{1}H-RMN (250 MHz, $CDCl_3$)

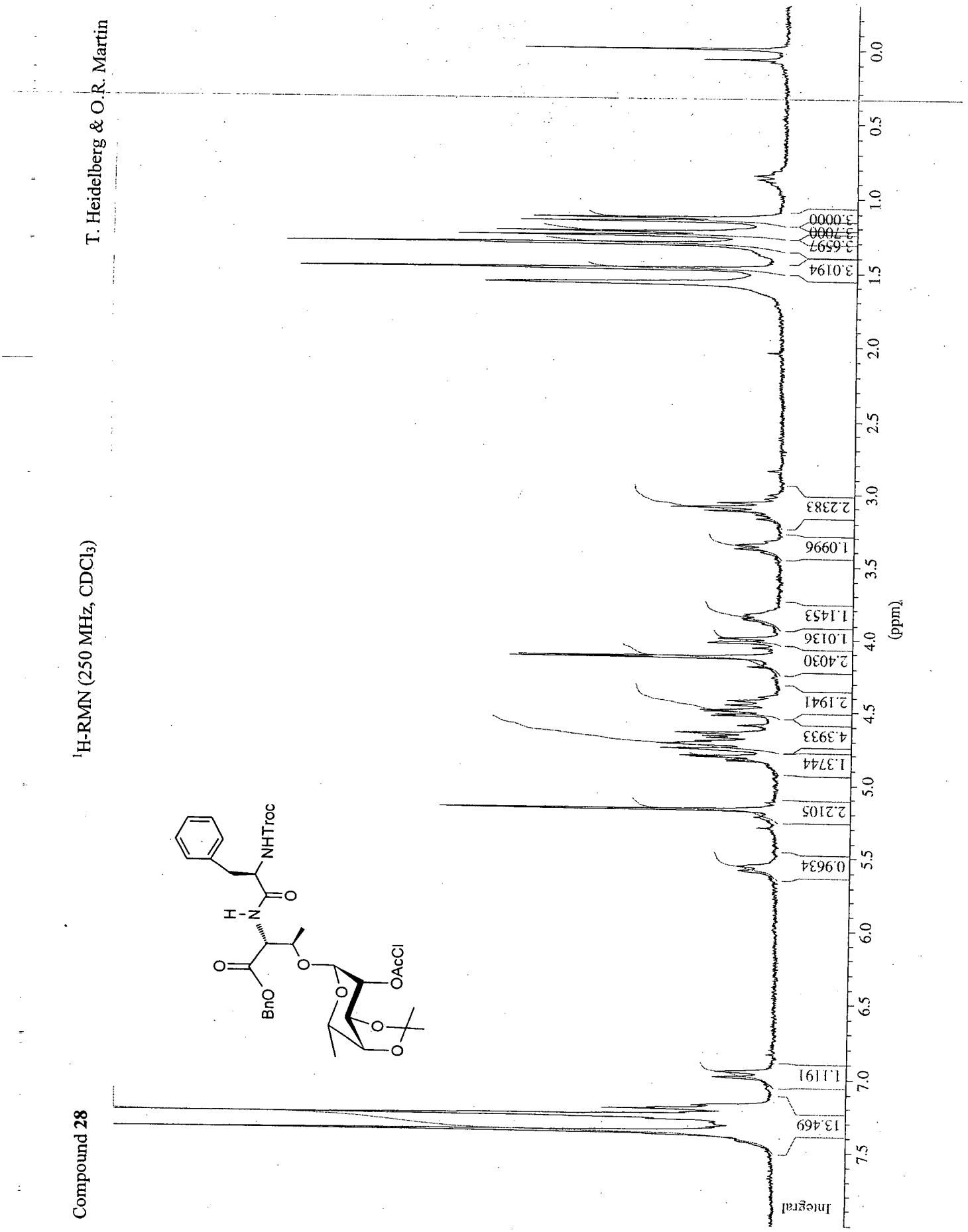
Compound **21**

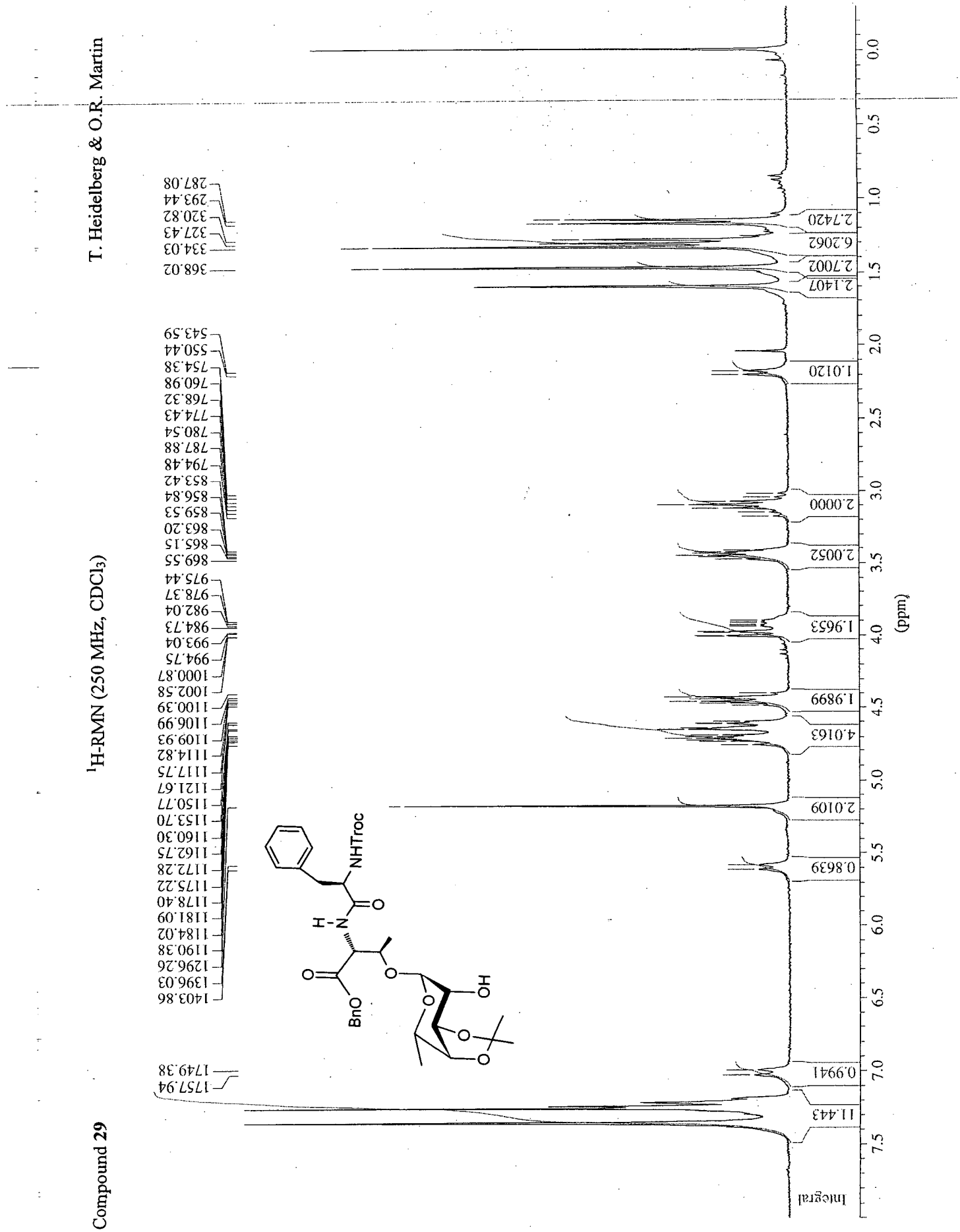


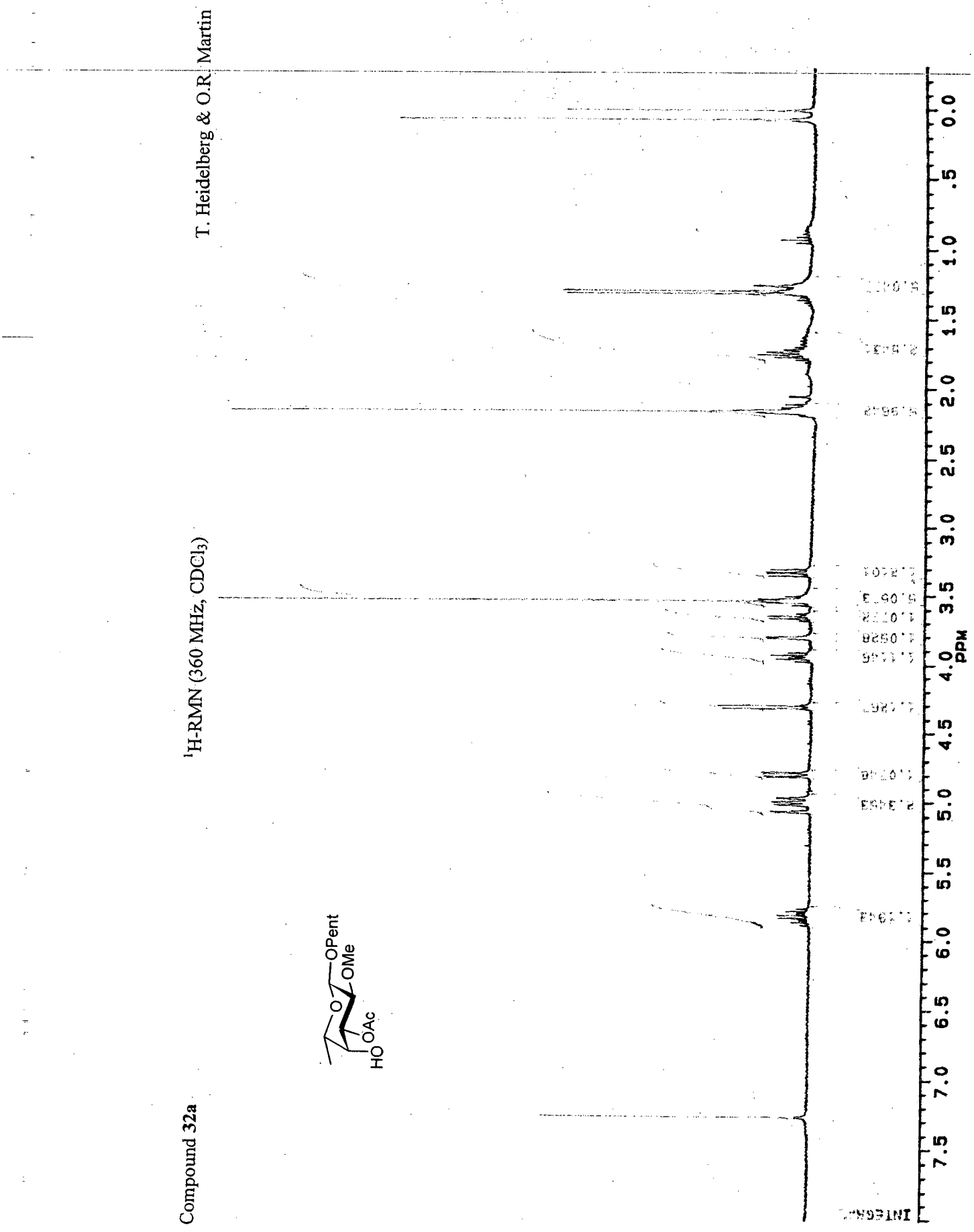


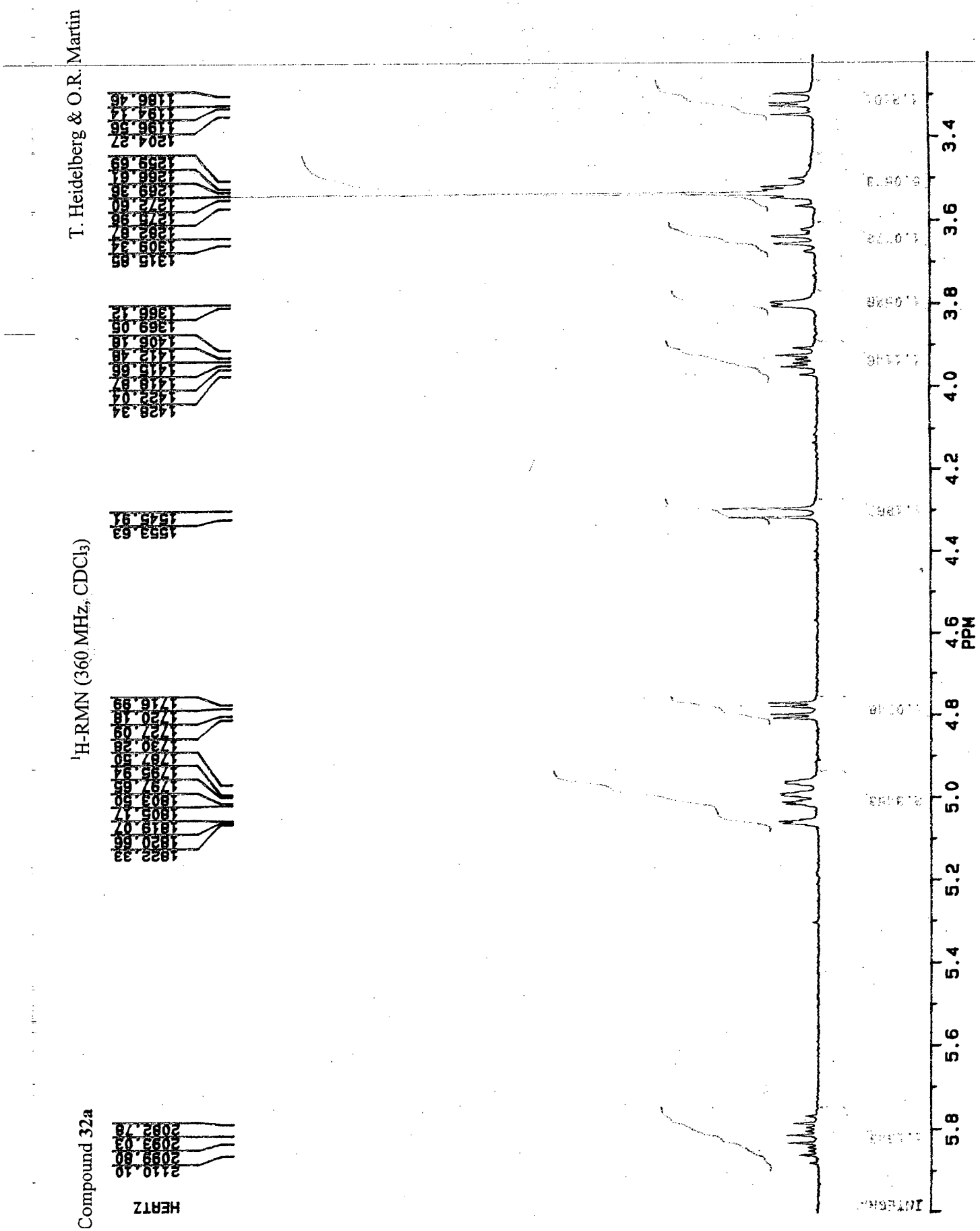


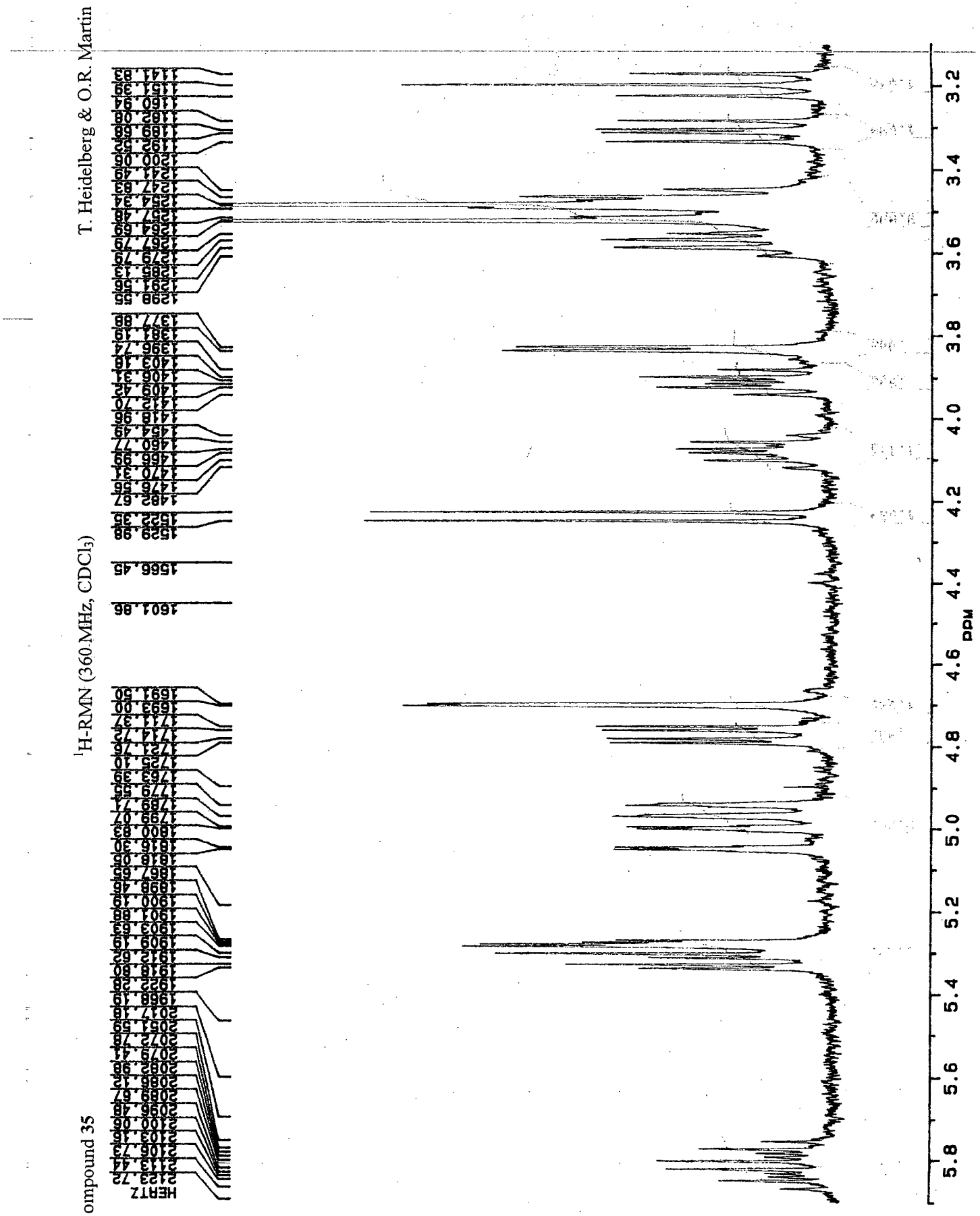











T. Heidelberg & O.R. Martin
^{1}H-RMN (360 MHz, CDCl$_3$)
ompound 35
PPM