Access to pyrrolidine imino sugars *via* tin(II)-mediated aldol reactions of bislactim ethers: synthesis of 2,5-dideoxy-2,5-imino-D-glucitol

Olga Blanco, Cristina Pato, María Ruiz and Vicente Ojea**

Departamento de Química Fundamental, Facultade de Ciencias, Universidade da Coruña, Campus da Zapateira s/n, 15071 A Coruña, Spain. Fax: +34 981167065; Tel: +34 981167000; E-mail: ojea@udc.es

Electronic Supplementary Information

Table of Contents

1. General methods.

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Reagents and solvents were purchased and used without further purification unless otherwise stated. THF was distilled from sodium/benzophenone, CH_2Cl_2 was distilled from calcium hydride and Et_3N was distilled from sodium. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (60F-254) using UV light as visualizing agent and cerium sulfate/ammonium molybdate in 10% sulfuric acid or ninhydrin in a 3% HOAc/*n*-BuOH solution as developing agents. E. Merck Silica gel and RP-18 (both 230-400 mesh) were used for liquid chromatography separations and Dowex 50W-X8 resin (H^+ form, 100-200 mesh) was used for ion-exchange chromatography. Melting points, determined with Bibby SM3P apparatus, are uncorrected. IR spectra were recorded on a Bruker Vector 22 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE spectrometers (300 MHz or 500 MHz). Coupling constants were measured in Hz. Chemical shifts were given in δ(ppm) relative to internal $CDCl_3$ (δ 7.27) or to HOD in D_2O (δ 4.79) for ^{1}H, relative to internal $CDCl_3$ (δ 77.0) for ^{13}C. ^{1}H or ^{13}C assignments were made on the basis of NOESY, COSY, HSQC and HMBC experiments. FABMS spectra were recorded on a Thermo Finnigan MAT95XP spectrometer using thioglycerol as a matrix. Optical rotations were taken at the Na_D-line using a Jasco DIP-1000 polarimeter. $[a]_D$ Values are given in units 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed at Servizos Xerais de Apoio á Investigación of Universidade da Coruña.

2. Experimental procedures and characterization data for new compounds.

3-[3-*tert*-Butyldiphenylsilyloxy-1-hydroxy-2,4-ethylidenedioxybutyl]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine (**7a and 8**): A solution of *n*-BuLi (2.5 M in hexane, 0.81 mL, 2.02 mmol) was added to a stirred solution of Schöllkopf´s bislactim ether **5** (344 mg, 1.86 mmol) in THF (15 mL) at −78 °C and the mixture was stirred for 1 h. Then, a 0.5 M solution of $SnCl_2$ (441 mg, 2.32 mmol) in THF was added dropwise. The mixture was stirred for 1 h, and a solution of freshly distilled aldehyde **6** (597 mg, 1.55 mmol) in THF (4 mL) was added dropwise. After being stirred at −78 °C for 4 h, the reaction was quenched with aqueous saturated $NaHCO_3$ solution. The crude reaction mixture was warmed to rt. The solids were removed by filtration and the filtrate was concentrated in *vacuo*. The resulting material was diluted with water and extracted with ether. The combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes 1:19) to yield adduct **7a** (652 mg, 74%) and adduct **8** (52 mg, 6%).

(3*S*,6*R*,1´*R*,2´S,3´*R*)-3-[3-*tert*-Butyldiphenylsilyloxy-1-hydroxy-2,4-ethylidenedioxybutyl]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine (**7a**): Colorless oil; *Rf* = 0.33 (EtOAc/hexanes 1:19); $[\alpha]^{23}_{D}$ −2.4 (*c* 1.0 in CH_2Cl_2); (Found: C, 65.71; H, 7.62; N, 4.86. Calc. for $C_{31}H_{44}N_2O_6Si$: C, 65.46; H, 7.80; N, 4.93%); ν_{max}/cm^{-1} 2959, 1701, 1241 and 1114; δ_H (300 MHz, $CDCl_3$) 0.70 (3H, d, *J* = 6.8), 1.06 (9H, s), 1.09 (3H, d, *J* = 6.8), 1.15 (3H, d, *J* = 5.0), 2.30 (1H, dsp, *J* = 6.8 and 3.4), 3.16 (1H, d, *J* = 10.4), 3.25 (1H, t, *J* = 10.4), 3.47 (1H, d, *J* = 9.0), 3.62-3.70 (1H, m), 3.70 (3H, s), 3.78 (3H, s), 3.86 (1H, t, *J* = 3.4), 3.96-4.05 (1H, m), 4.26-4.32 (1H, m), 4.37-4.40 (1H, m), 4.54 (1H, q, *J* = 5.0), 7.37-7.43 (6H, m), 7.63-7.70 (4H, m); δ_C (75 MHz, $CDCl_3$) 16.4 (CH_3), 19.1 (CH_3), 19.4 (C), 20.3 (CH_3), 26.9 (CH_3), 31.3 (CH), 52.4 (CH_3), 52.5 (CH_3), 58.4 (CH), 60.9 (CH), 62.5 (CH), 67.9 (CH), 71.1 (CH_2), 81.0 (CH), 98.4 (CH), 127.6 (CH), 127.7 (CH), 129.8 (CH), 129.9 (CH), 133.1 (C), 134.1 (C), 135.7 (CH), 135.8 (CH), 162.0 (C), 163.6 (C); FABMS (thioglycerol) *m/z* 569 (MH^+, 100%), 141 (66); HRMS 569.3067. $C_{31}H_{45}N_2O_6Si$ requires 569.3047.

(3*R*,6*R*)-3-[3-*tert*-Butyldiphenylsilyloxy-1-hydroxy-2,4-ethylidenedioxybutyl]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine (**8**): Colorless oil; *Rf* = 0.23 (EtOAc/hexanes 1:19); δ_H (300 MHz, $CDCl_3$) 0.73 (3H, d, *J* = 6.8), 1.06 (9H, s), 1.10 (3H, d, *J* = 6.8), 1.22 (3H, d, *J* = 5.0), 2.33 (1H, dsp, *J* = 6.8 and 3.8), 3.24-3.31 (2H, m), 3.61-3.78 (2H, m), 3.69 (3H, s), 3.74 (3H, s), 3.95 (1H, dd, *J* = 5.5 and 3.8), 4.07 (1H, ddd, *J* = 14.4, 10.1 and 5.3), 4.25-4.33 (2H, m), 4.55 (1H, q, *J* = 5.0), 7.34-7.47 (6H, m), 7.65-7.69 (4H, m).

(3*S*,6*R*,1´*R*,2´*S*,3´*R*)-3-[2,4-Ethylidenedioxybutyl-1-hydroxy-3-methanesulfonyloxy]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine (7c): Hydrated Bu_4NF (973 mg, 3.09 mmol) was added to a solution of adduct **7a** (585 mg, 1.03 mmol) in THF (14 mL) at 0 ºC, and the mixture was stirred at room temperature for 2 h. The solvent was evaporated and the resulting material was diluted with dichloromethane and washed with water. The organic layer was dried (Na_2SO_4) and evaporated to dryness, and the residue was used in the next step without further purification. A solution of the crude diol **7b**, Et_3N (0.28 mL, 2.02 mmol) and DMAP (21 mg, 0.17 mmol) in CH_2Cl_2 (15 mL) at 0 ºC was treated with MsCl (0.12 mL, 1.55 mmol). The mixture was stirred for 2 h at room temperature. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes 2:3) to give mesylate **7c** (327 mg, 78%) as a colorless oil; *Rf* = 0.5 (silica gel, EtOAc/hexanes 1:1); $[\alpha]^{23}_D$ –22.5 (*c* 1.0 in CH_2Cl_2); (Found: C, 47.15; H, 7.03; N, 6.58; S, 7.71. Calc. for $C_{16}H_{28}N_2O_8S$: C, 47.05; H, 6.91; N, 6.86; S, 7.85%); ν_{max}/cm^{-1} 2952, 2873, 1697, 1382, 1245, 1180 and 995; δ_H (300 MHz, $CDCl_3$) 0.71 (3H, d, *J* = 6.7), 1.07 (3H, d, *J* = 6.7), 1.25 (3H, d, *J* = 5.0), 2.27 (1H, dsp, *J* = 6.7 and 3.5), 3.15 (3H, s), 3.56-3.78 (2H, m), 3.70 (3H, s), 3.76 (3H, s), 3.89 (1H, t, *J* = 3.5), 3.95-4.01 (1H, m), 4.33-4.43 (2H, m), 4.58 (1H, q, *J* = 5.0), 4.74 (1H, ddd, *J* = 14.6, 9.8 and 5.3); δ_C (75 MHz, $CDCl_3$) 16.6 (CH_3), 19.1 (CH_3), 20.2 (CH_3), 31.6 (CH), 37.4 (CH_3), 52.6 (CH_3), 52.7 (CH_3), 56.3 (CH), 61.3 (CH), 67.6 (CH), 68.5 (CH_2), 68.9 (CH), 78.1 (CH), 99.0 (CH), 161.1 (C), 164.0 (C). FABMS (thioglycerol) *m/z* 409 (MH^+, 100%). HRMS 409.1652. $C_{16}H_{29}N_2O_8S$ requires 409.1645.

(3*S*,6*R*,1´*R*,2´*S*,3´*R*)-3-[1-Benzyloxy-2,4-ethylidenedioxybutyl-3-methanesulfonyloxy]-3,6-dihydro-6-isopropyl-2,5-dimetoxypyrazine (9): A solution of mesylate **7c** (340 mg, 0.83 mmol) in THF (2 mL) was added to a stirred suspension of NaH (60% dispersion in mineral oil, 40 mg, 1.0 mmol) in THF (10 mL) at 0 °C. After 1 h, NBu_4I (129 mg, 0.35 mmol) and BnBr (0.12 mL, 1.0 mmol) were added, and the resulting solution was stirred at rt for 3 h. The reaction mixture was cooled to 0 °C and quenched by the addition of CH_3OH (2.5 mL). The solvents were removed in *vacuo* and the resulting material was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes 1:3) to give compound **9** (291 mg, 70%) as a colorless oil; *Rf* = 0.4 (silica gel, EtOAc/hexanes 1:2); $[\alpha]^{22}_D$ +13.7 (*c* 1.0 in CH_2Cl_2); (Found: C, 55.48; H, 6.69; N, 5.73; S, 6.52. Calc. for $C_{23}H_{34}N_2O_8S$: C, 55.41; H, 6.87; N, 5.62; S, 6.43%); ν_{max}/cm^{-1} 1691, 1357, 1237, 1176 and 1098; δ_H (300 MHz, $CDCl_3$) 0.69 (3H, d, *J* = 6.8), 1.08 (3H, d, *J* = 6.8), 1.31 (3H, d, *J* = 5.0), 2.35 (1H, dsp, *J* = 6.8 and 3.2), 2.89 (3H, s), 3.59 (1H, t, *J* = 10.5), 3.71 (3H, s), 3.72 (3H, s), 3.85-3.96 (3H, m), 4.41 (1H, dd, *J* =10.8 and 5.4), 4.55 (1H, dd, *J* = 5.7 and 3.6), 4.64 (1H, q, *J* = 5.0), 4.66 (1H, AB system, *J* = 11.0), 4.73 (1H, AB system, *J* = 11.0), 4.95 (1H, ddd, *J* = 14.8, 9.6 and 5.4), 7.26-7.42 (5H, m); δ_C (75 MHz, $CDCl_3$) 16.4 (CH_3), 19.2 (CH_3), 20.3 (CH_3), 30.9 (CH), 38.3 (CH_3), 52.6 (CH_3), 52.7 (CH_3), 55.9 (CH), 60.4 (CH), 68.3 (CH_2), 69.2 (CH), 72.8 (CH_2), 77.4 (CH), 77.5 (CH), 99.4 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 137.9 (C), 161.9 (C), 165.0 (C). FABMS (thioglycerol) *m/z* 499 (MH^+, 16%), 242 (100). HRMS 499.2094. $C_{23}H_{35}N_2O_8S$ requires 499.2114.

Methyl 4-benzyloxy-1,3-ethylidenedioxy-2,5-dideoxy-2,5-imino-D-glucuronate (10): A solution of compound **9** (265 mg, 0.53 mmol) in MeOH (13 mL) and 0.25 N HCl (4.25 mL, 1.06 mmol) was stirred at rt for 9 h. Then, the solution was diluted with water (10 mL) and concentrated to one-third its initial volume. The aqueous solution was made basic (pH~10) by the addition of $NaHCO_3$ followed by concentrated ammonia. The aqueous layer was extracted with CH_2Cl_2 (7 x 12 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated. The crude was purified by flash chromatography

(silica gel, EtOAc) to give glucuronate **10** (134 mg, 82%) as a colorless oil; *Rf* = 0.35 (silica gel, EtOAc); $[\alpha]^{19}_{D}$ +22.6 (*c* 0.8 in CH_2Cl_2); (Found: C, 62.71; H, 6.75; N, 4.60. Calc. for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56%); ν_{max}/cm^{-1} 2910, 1739 and 1109; δ_H (500 MHz, $CDCl_3$) 1.25 (3H, d, *J* = 5.0, CHC*H*$_3$), 2.60 (1H, br s, NH), 3.11 (1H, m, 2-H), 3.78 (3H, s, OCH_3), 3.89 (1H, d, *J* = 2.1, 5-H), 3.98 (1H, dd, *J* = 12.5 and 2.4, 1-H), 4.04 (1H, d, *J* = 2.1, 4-H), 4.08 (1H, d, *J* = 2.1, 3-H), 4.18 (1H, d, *J* = 12.5, 1'-H), 4.59 (1H, AB system, *J* = 11.9, C*H*$_2$Ph), 4.64 (1H, q, *J* = 5.0, CH_3C*H*), 4.68 (1H, AB system, *J* = 11.9, C*H*$_2$Ph), 7.28-7.38 (5H, m, Ph); δ_C (75 MHz, $CDCl_3$) 21.0 (*C*H_3CH), 52.4 (OCH_3), 55.4 (C-2), 65.5 (C-1), 66.7 (C-5), 71.7 (*C*H_2Ph), 79.4 (C-3), 87.9 (C-4), 97.6 (*C*HCH_3), 127.7 (CH), 127.8 (CH), 128.4 (CH), 137.4 (C), 172.0 (C=O). FABMS (thioglycerol) *m/z* 308 (MH^+, 77%), 154 (100). HRMS 308.1500. $C_{16}H_{22}NO_5$ requires 308.1498.

4-Benzyloxy-1,3-ethylidenedioxy-2,5-dideoxy-2,5-imino-D-glucitol (11): $LiEt_3BH$ (1 M in THF, 1.5 mL, 1.5 mmol) was dropwise added to a solution of glucuronate **10** (150 mg, 0.49 mmol) in THF (9 mL) at 0 °C and the reaction mixture was stirred at this temperature for 1 h. The reaction mixture was quenched by the addition of aqueous saturated NH_4Cl solution, the solvents were removed in *vacuo* and the residue was diluted with water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated, and the crude was purified by flash chromatography (silica gel, MeOH/CH_2Cl_2 1:20), to give pyrrolidine **11** (123 mg, 90%) as a colorless oil; *Rf* = 0.30 (silica gel, MeOH/CH_2Cl_2 1:20), $[\alpha]^{22}_{D}$ + 35.1 (*c* 0.8 in CH_2Cl_2); (Found: C, 64.39; H, 7.57; N, 5.11. Calc. for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01%); ν_{max}/cm^{-1} 3277, 2990, 2862 and 1069; δ_H (500 MHz, $CDCl_3$) 1.32 (3H, d, *J* = 5.0, CHC*H*$_3$), 2.71 (1H, br s, NH), 3.11 (1H, br s, 2-H), 3.35-3.37 (1H, m, 5-H), 3.73 (1H, d, *J* = 2.7, 4-H), 3.74-3.80 (2H, m, 6-H and 6'-H), 4.00 (1H, dd, *J* = 12.5 and 2.5, 1-H), 4.15 (1H, d, *J* = 12.5, 1'-H), 4.17 (1H, d, *J* = 2.7, 3-H), 4.57 (1H, AB system, *J* = 11.8, C*H*$_2$Ph), 4.61 (1H, AB system, *J* = 11.8, C*H*$_2$Ph), 4.69 (1H, q, *J* = 5.0, CH_3C*H*), 7.28-7.37 (5H, m); δ_C (75 MHz, $CDCl_3$) 21.0 (*C*H_3CH), 55.1 (C-2), 63.3 (C-6), 66.4 (C-1), 66.9 (C-5), 72.0 (*C*H_2Ph), 80.1 (C-3), 86.8 (C-4), 97.9

(*C*HCH$_3$), 127.6 (CH), 127.8 (CH), 128.5 (CH), 137.8 (C). FABMS (thioglycerol) *m/z* 280 (MH$^+$, 88%), 154 (78), 147 (89), 136 (100). HRMS 280.1546. $C_{15}H_{22}NO_4$ requires 280.1549.

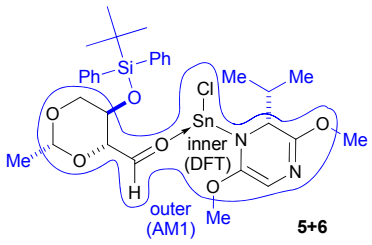
2,5-Dideoxy-2,5-imino-D-glucitol: A solution of pyrrolidine **11** (86 mg, 0.31 mmol) in THF (5 mL) and 0.25 N HCl (3 mL, 0.75 mmol) was stirred with 10% Pd/C (9 mg) under H_2 (1 atm) for 12 h at rt. The catalyst was removed by filtration through a short pad of Celite and the filtrate was concentrated in *vacuo*. The residue was dissolved in HCl 1 N (3 mL) and the mixture was heated to 100 ºC for 1 h. The reaction mixture was concentrated in *vacuo* and the residue was diluted with 1% aqueous NH_3 solution and was evaporated again. The residue was purified by ion-exchange chromatography (Dowex 50W−X8, H^+ form, eluting with 2% aqueous NH_3 solution) followed by reversed-phase flash chromatography (RP-18, using H_2O as eluent) to give DGDP (48 mg, 96%) as a white solid; m.p. 136-138 °C (from H_2O), (lit.,[1] m.p. 138-140 °C); *Rf* = 0.20 (silica gel, BuOH/AcOH/H_2O 12:3:5), $[\alpha]^{22}_D$ + 24.2 (*c* 0.7 in H_2O), (lit.,[1] $[\alpha]_D$ + 25.1 (*c* 1.5 in H_2O)); (Found: C, 44.34; H, 8.12; N, 8.43. Calc. for $C_6H_{13}NO_4$: C, 44.16; H, 8.03; N, 8.58%); ν_{max}/cm^{-1} 3274, 3272, 3198, 2905, 1318 and 1033; δ_H (300 MHz, $CDCl_3$) 3.14 (1H, app q, *J* = 5.3), 3.44 (1H, app q, *J* = 6.0), 3.69-3.91 (4H, m), 3.93 (1H, dd, *J* = 5.0 and 2.8), 4.17 (1H, dd, *J* = 5.0 and 2.8); δ_C (75 MHz, $CDCl_3$) 62.8 (CH_2), 64.1 (CH), 64.9 (CH_2), 68.1 (CH), 80.1 (CH), 81.8 (CH). FABMS (thioglycerol) *m/z* 164 (MH$^+$, 100%). HRMS 164.0920. $C_6H_{14}NO_4$ requires 164.0923.

3. Computational methods.

To shed light on the structural reasons for the unexpected *anti,syn*-selectivity in the reaction between azaenolate $SnCl^{+}$**5**$^{-}$ and D-erythrose derivative **6**, we have performed a computational study of the aldol process. Electronic structure calculations were performed using the Kohn-Sham formulation of the density functional theory (DFT) with the hybrid exchange functional of Becke [2] and the Lee, Yang, and Parr correlation functional [3] (B3LYP) and the cc-pVDZ basis set [4] with a small-core relativistic pseudopotential for Sn [5] (referred as B3LYP/cc-pVDZ-PP level). All reactants and products have positive defined Hessian matrices. Transition structures showed only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to motion along the reaction coordinate. All the energies reported are free energies and thus contain zero-point energy corrections (using frequencies scaled by 0.97) [6] and thermal and entropy effects at reaction temperature (195 K) and 1 atm pressure calculated at B3LYP/cc-pVDZ-PP level. Finally, single point energy calculations considering solvent effects were computed at B3LYP(SCRF)/cc-pVTZ-PP level for the gas-phase stationary points using the self-consistent reaction field method [7] based on the polarizable continuum model of Tomasi´s group [8] with a permittivity of 7.52 for THF. All optimizations and frequency calculations reported in this article were performed using Gaussian03 program package.[9] cc-pVDZ-PP and cc-pVTZ-PP basis sets and ECP parameters for Sn were obtained from Basis Set Exchange (BSE) software and the EMSL Basis Set Library (https://bse.pnl.gov/bse/portal).[10]

The conformational space accessible to the models was analyzed first by using hybrid methods, considering a two-layer scheme (DFT:semiempirical) and the ONIOM method for the partition of the system.[11] The DFT description (B3LYP method, using LANL2DZ basis set [12]) was limited to an "inner layer" including the critical parts of the reacting system: the atoms directly involved in the breaking and forming bonds and other areas sensitive to electronic effects. For the low-level treatment of the entire system, we employed the semiempirical AM1 method [13] (see Figure S1). Thus, the conformational space accessible to the azaenolate moiety was sampled by considering three different rotamers for the isopropyl group (those with the tertiary carbon atom pointing to the metal atom, to the nucleophilic carbon atom or to the imidate moiety) and two rotamers for each of the methoxy groups (directed to or opposite to the imidate nitrogen). In addition, for the erythrose moiety, three different rotamers for *tert*-butyldiphenylsilyloxy group were studied and labeled as I, II and III. Significative structures located with these conformational analyses were fully reoptimized at B3LYP/cc-pVDZ-PP level.

Figure S1. High-level (B3LYP/LANL2DZ) and low-level (AM1) layers for the ONIOM calculations.



Models for the addition of tin(II) azaenolate $SnCl^{+}\mathbf{5}^{-}$ to 2,4-ethylidene-D-erythrose derivative 6. The aldol reaction between $SnCl^{+}\mathbf{5}^{-}$ and **6** proceeds first by the endothermic formation of the intermediate complex **5**+**6** (see Figure S1). The possible pathways for the reorganization of this intermediate were analyzed next. Pericyclic transition structures (TSs) connecting intermediate **5**+**6** to the corresponding aldolates with either 3,6-*cis*-3,1′-*anti*-1′,2′-*anti*, 3,6-*cis*-3,1′-*syn*-1′,2′-*syn*, 3,6-*trans*-3,1′-*anti*-1′,2′-*syn*, or 3,6-*trans*-3,1′-*syn*-1′,2′-*anti* configuration were grouped into four diastereomeric pathways, that were designated as ***caa***, ***css***, ***tas*** and ***tsa***, respectively. In each diastereomeric pathway, different starting geometries were subjected to optimization considering the following main structural features: (1) boat-like and chair-like conformations for the pericyclic ring [14] (denoted "B" and "C", respectively), (2) Felkin-Anh,[15] Cornforth [16] and non-Anh [17] conformations (denoted "F", "M" and "N", respectively) for the erythrose moiety (see Figure S2) and (3) *R* and *S* configurations for the tetrahedral tin(II) cation were constructed for all the selected geometries.

Figure S2. Felkin-Anh, modified-Cornforth and non-Anh models for azaenolate addition to 2,4-ethylidene-D-erythrose derivative.

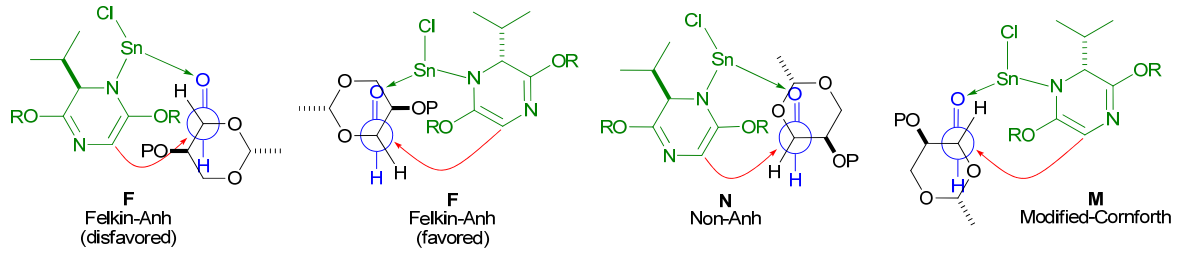


Table S1. Absolute (hartrees) and relative energies for the intermediate and TSs located in the gas phase (at ONIOM[B3LYP/LANL2DZ:AM1] level) in the reaction of **5** and **6**

	ONIOM[B3LYP/LANL2DZ:AM1]		B3LYP/cc-pVDZ-PP	
model (*config*)[a]	*Extrapolated E*	N_{imag}	E_{SCF}	G_{rel}
5+6	-854.749871215343	0		
caa-CM-I (*S*)	-854.687885374559	1	-2732.2362817	
caa-CM-II (*S*)	-854.688391724314	1	-2732.2318444	
caa-CM-III (*S*)	-854.687374756694	1	-2732.2385861	+16.5
css-CM-I (*S*)	-854.686361893126	1	-2732.2363112	+17.8
css-CM-II (*S*)	-854.684516189146	1	-2732.2312243	
css-CM-III (*S*)	-854.684529366818	1	-2732.2339494	
tas-BF-I (*S*)	-854.688528147326	1	-2732.2445315	
tas-BF-II (*S*)	-854.688778001830	1	-2732.2436110	
tas-BF-III (*S*)	-854.688400356620	1	-2732.2426655	
tas-BN-III (*R*)	-854.688627020292	1	-2732.2529568	
tas-BN-III (*R*)	-854.688627020292	1	-2732.2529568	
tas-BN-II (*S*)	-854.700479876065	1	-2732.2521243	
tas-BN-III (*S*)	-854.704228270728	1	-2732.2647003	**0.0**
tas-CF-I (*R*)	-854.692329984668	1	-2732.2411936	
tas-CN-I (*S*)	-854.700285873423	1	-2732.2594541	
tsa-CF-I (*S*)	-854.701432852654	1	-2732.2565139	
tsa-CM-I (*R*)	-854.700100125665	1	-2732.2616571	
tsa-CM-I (*R*)	-854.697779498367	1	-2732.2590093	
tsa-CM-I (*S*)	-854.702893403567	1	-2732.2620120	+1.97
tsa-CM-II (*S*)	-854.701591370682	1	-2732.2612969	
tsa-CM-III (*S*)	-854.703001626298	1	-2732.2593350	

[a] Legend: **caa**–cis,anti,anti; **css**–cis,syn,syn; **tas**–trans,anti,syn; **tsa**–trans,syn,anti; B–boat-like; C–chair-like; F–Felkin-Anh; M–Cornforth; N–non-Anh; I, II, III–rotamers of *tert*-butyldiphenilsilyloxi group; R,S–configuration at tin.

Table S2. Absolute energies (hartrees) and relative free energies (kcal/mol) calculated for most significative intermediate and TSs in the reaction of **5** and **6**.

	B3LYP/cc-pVDZ-PP			B3LYP(SCRF)/cc-pVTZ-PP	
model (*config*)[a]	E_{SCF}	N_{imag}	E_{cor}[b]	*G*	G_{rel}[c]
5+6	-2732.31374985	0	0.630336	-2732.865527	–3.2
caa-CM-III (*S*)	-2732.28971979	1	0.629974	-2732.841087	+11.9
css-CF-I (*S*)	-2732.28898016	1	0.632138	-2732.845374	+10,6
tas-BN-III (*S*)	-2732.31190623	1	0.632261	-2732.862376	**0.0**
tsa-CM-I (*S*)	-2732.31217719	1	0.631972	-2732.860255	+1.15

[a] Legend: **caa**–cis,anti,anti; **css**–cis,syn,syn; **tas**–trans,anti,syn; **tsa**–trans,syn,anti; B–boat-like; C–chair-like; F–Felkin-Anh; M–Cornforth; N–non-Anh; I, II, III–rotamers of *tert*-butyldiphenilsilyloxi group; *R*,*S*–configuration at tin.

[b] Zero-point energy corrections with thermal and entropy effects at 195.15 K and 1.0 atm, scaled by 0.97.

[c] With zero-point energy corrections and thermal and entropy effects (calculated at B3LYP/cc-pVDZ-PP level).

4. Cartesian coordinates of reported structures.

tas-BN

```
 ---------------------------------------------------------------------
 E(RB+HF-LYP) =  -2732.31190623
 ---------------------------------------------------------------------
 Zero-point correction=                           0.675296 (Hartree/Particle)
 Thermal correction to Energy=                    0.697580
 Thermal correction to Enthalpy=                  0.698198
 Thermal correction to Gibbs Free Energy=         0.632261
 Sum of electronic and zero-point Energies=          -2731.636611
 Sum of electronic and thermal Energies=             -2731.614326
 Sum of electronic and thermal Enthalpies=           -2731.613708
 Sum of electronic and thermal Free Energies=        -2731.679645
-----------------------------------------------------------------------
 Variational PCM results
 ======================
 <psi(f)|   H    |psi(f)>                    (a.u.) =   -2732.896547
 <psi(f)|H+V(f)/2|psi(f)>                    (a.u.) =   -2732.914031
 Total free energy in solution:
  with all non electrostatic terms           (a.u.) =   -2732.862376
 ---------------------------------------------------------------------
 (Polarized solute)-Solvent              (kcal/mol) =     -10.97
 ---------------------------------------------------------------------
 Cavitation energy                       (kcal/mol) =      65.96
 Dispersion energy                       (kcal/mol) =     -35.32
 Repulsion energy                        (kcal/mol) =       1.77
 Total non electrostatic                 (kcal/mol) =      32.41
-----------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          6             0        2.677734    1.466043   -1.550159
    2          6             0        0.834634    0.991729   -0.087966
    3          8             0        1.166152    1.001827    1.137844
    4         50             0        2.848223   -0.263263    2.037571
    5          7             0        3.726746   -0.103299   -0.051055
    6          6             0        3.446723    1.155608   -0.426680
    7          7             0        2.406469    0.476412   -2.513175
    8          6             0        2.863040   -0.700708   -2.284521
    9          8             0        2.611611   -1.728878   -3.120790
   10          6             0        3.717225   -1.134217   -1.103523
   11          8             0        3.774719    2.040864    0.544560
   12          6             0       -0.164231    2.008758   -0.603022
   13          8             0        0.159529    3.296927   -0.085323
   14          6             0       -0.756290    4.305294   -0.492604
   15          8             0       -2.055335    4.026864   -0.029395
   16          6             0       -2.536352    2.796608   -0.554312
   17          6             0       -1.608541    1.633919   -0.176941
   18         17             0        1.884360   -2.518683    1.530656
   19          6             0        1.822883   -1.436318   -4.279683
   20          6             0        3.414263    3.422600    0.398316
   21          6             0        5.154928   -1.544105   -1.545736
   22          6             0        5.943858   -0.381721   -2.159455
   23          6             0        5.917423   -2.182443   -0.379481
   24          6             0       -0.307833    5.620744    0.102007
   25          8             0       -1.993239    0.451511   -0.858872
   26         14             0       -3.007319   -0.804771   -0.266893
   27          6             0       -2.481285   -2.347853   -1.301019
   28          6             0       -4.818194   -0.375263   -0.664194
   29          6             0       -5.141378    0.550890   -1.675395
   30          6             0       -5.886549   -1.031129   -0.018472
   31          6             0       -6.469236    0.819259   -2.021808
   32          6             0       -7.216520   -0.770164   -0.362505
   33          6             0       -7.511271    0.158619   -1.364823
   34          6             0       -2.801380   -0.930786    1.616460
   35          6             0       -3.695026   -0.263721    2.481457
   36          6             0       -1.729144   -1.631522    2.206372
   37          6             0       -3.532052   -0.302571    3.869485
   38          6             0       -1.564366   -1.676361    3.593665
   39          6             0       -2.467408   -1.013893    4.429719
   40          6             0       -0.951169   -2.533215   -1.323255
   41          6             0       -2.959066   -2.142317   -2.756013
   42          6             0       -3.152864   -3.610484   -0.722547
   43          1             0       -2.903957   -4.490029   -1.343913
   44          1             0       -0.768034    4.336780   -1.606148
```

45	1	0	0.695847	5.884177	-0.261450
46	1	0	2.533605	2.494443	-1.877836
47	1	0	3.804593	3.918260	1.296141
48	1	0	3.900686	3.849657	-0.493917
49	1	0	2.323517	3.540749	0.339218
50	1	0	5.006413	-2.313619	-2.323592
51	1	0	1.758465	-2.378897	-4.837677
52	1	0	2.300029	-0.653510	-4.889040
53	1	0	0.818932	-1.089116	-3.990902
54	1	0	6.917009	-0.733045	-2.539462
55	1	0	6.143939	0.402049	-1.410148
56	1	0	5.405206	0.082693	-3.001722
57	1	0	6.903865	-2.546033	-0.710043
58	1	0	5.364985	-3.036666	0.044509
59	1	0	6.083968	-1.450774	0.428162
60	1	0	3.243994	-2.039493	-0.689560
61	1	0	0.886994	0.057695	-0.668717
62	1	0	-0.127984	2.002492	-1.709532
63	1	0	-2.613085	2.847399	-1.659983
64	1	0	-3.543686	2.643697	-0.143332
65	1	0	-0.286503	5.536798	1.198578
66	1	0	-1.012672	6.414970	-0.182046
67	1	0	-1.615614	1.503145	0.918778
68	1	0	-4.338725	1.067566	-2.206496
69	1	0	-5.681016	-1.755836	0.774001
70	1	0	-6.690810	1.544906	-2.808490
71	1	0	-8.024827	-1.291865	0.155984
72	1	0	-8.549882	0.366327	-1.633429
73	1	0	-4.536724	0.296830	2.067774
74	1	0	-0.991394	-2.144012	1.588367
75	1	0	-4.239854	0.224511	4.514154
76	1	0	-0.721441	-2.229421	4.014266
77	1	0	-2.340194	-1.048432	5.514591
78	1	0	-0.689349	-3.400028	-1.957420
79	1	0	-0.446919	-1.650194	-1.745381
80	1	0	-0.518105	-2.722044	-0.330024
81	1	0	-2.646692	-3.003172	-3.375048
82	1	0	-4.054306	-2.059170	-2.829568
83	1	0	-2.519575	-1.235703	-3.204288
84	1	0	-2.816527	-3.825069	0.304421
85	1	0	-4.252302	-3.523831	-0.707756

tsa-CM

E(RB+HF-LYP) = -2732.31217719

Zero-point correction=	0.674876 (Hartree/Particle)
Thermal correction to Energy=	0.697202
Thermal correction to Enthalpy=	0.697820
Thermal correction to Gibbs Free Energy=	0.631972
Sum of electronic and zero-point Energies=	-2731.637302
Sum of electronic and thermal Energies=	-2731.614975
Sum of electronic and thermal Enthalpies=	-2731.614357
Sum of electronic and thermal Free Energies=	-2731.680205

Variational PCM results

<psi(f)| H |psi(f)>	(a.u.) =	-2732.896741
<psi(f)|H+V(f)/2|psi(f)>	(a.u.) =	-2732.912827
Total free energy in solution: with all non electrostatic terms	(a.u.) =	-2732.860255
(Polarized solute)-Solvent	(kcal/mol) =	-10.09
Cavitation energy	(kcal/mol) =	66.20
Dispersion energy	(kcal/mol) =	-34.95
Repulsion energy	(kcal/mol) =	1.74
Total non electrostatic	(kcal/mol) =	32.99

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.814476	2.047888	0.004689
2	6	0	-0.749822	1.029399	-0.870670
3	8	0	-0.774084	-0.134803	-0.382192

4	50	0	-2.285567	-1.634682	-1.302973
5	7	0	-3.613031	-0.215571	-0.166565
6	6	0	-3.420309	1.009797	-0.696921
7	7	0	-2.508232	1.908618	1.365447
8	6	0	-2.889276	0.823888	1.937016
9	8	0	-2.585508	0.552346	3.220674
10	6	0	-3.726523	-0.268447	1.302959
11	8	0	-3.655832	1.034644	-2.043231
12	6	0	0.125479	2.125595	-0.312185
13	8	0	-0.158975	3.268006	-1.127173
14	6	0	0.634472	4.401878	-0.818222
15	8	0	2.000551	4.126250	-1.020307
16	6	0	2.439239	3.079102	-0.167025
17	6	0	1.639631	1.783289	-0.388199
18	17	0	-2.112627	-3.287986	0.531120
19	6	0	-1.796386	1.522130	3.917563
20	6	0	-3.532581	2.284130	-2.726359
21	6	0	-5.203240	-0.243226	1.803208
22	6	0	-5.951490	1.047252	1.448380
23	6	0	-5.958616	-1.479976	1.303092
24	6	0	0.229928	5.528332	-1.741440
25	8	0	1.960325	0.867424	0.636977
26	14	0	2.873825	-0.581298	0.560486
27	6	0	2.457712	-1.447872	2.229497
28	6	0	3.167362	-2.815834	2.303991
29	6	0	2.983204	-0.551310	3.373503
30	6	0	0.937914	-1.626841	2.419685
31	6	0	2.470258	-1.533275	-1.035690
32	6	0	3.052838	-1.123592	-2.254217
33	6	0	1.584041	-2.628422	-1.079843
34	6	0	2.760224	-1.769432	-3.459767
35	6	0	1.298060	-3.287403	-2.280150
36	6	0	1.882704	-2.856792	-3.475057
37	6	0	4.725803	-0.137348	0.504213
38	6	0	5.671295	-1.019511	-0.057320
39	6	0	5.214204	1.047215	1.092055
40	6	0	7.039737	-0.731739	-0.037373
41	6	0	6.580430	1.343785	1.110781
42	6	0	7.497695	0.453400	0.544777
43	1	0	6.930143	2.271495	1.570714
44	1	0	8.566077	0.682329	0.558364
45	1	0	0.472043	4.664718	0.251143
46	1	0	-0.831176	5.777524	-1.598323
47	1	0	-2.741219	3.056605	-0.394427
48	1	0	-3.769193	2.073494	-3.777023
49	1	0	-4.252805	3.016803	-2.325540
50	1	0	-2.513994	2.698125	-2.648020
51	1	0	-5.127083	-0.305400	2.903981
52	1	0	-1.712895	1.149857	4.946404
53	1	0	-2.281097	2.510080	3.897372
54	1	0	-0.798270	1.610127	3.460402
55	1	0	-6.949234	1.052270	1.917145
56	1	0	-6.098678	1.136638	0.359454
57	1	0	-5.414333	1.944461	1.795304
58	1	0	-6.981214	-1.505467	1.713382
59	1	0	-5.448236	-2.410869	1.597508
60	1	0	-6.034552	-1.470982	0.203689
61	1	0	-3.303915	-1.227116	1.638119
62	1	0	-1.055300	1.202649	-1.919777
63	1	0	-0.131591	2.308038	0.747837
64	1	0	2.334349	3.370746	0.898075
65	1	0	3.503823	2.916563	-0.380981
66	1	0	0.392937	5.221037	-2.785238
67	1	0	0.840702	6.418106	-1.532627
68	1	0	1.863999	1.386886	-1.394852
69	1	0	4.260034	-2.720755	2.189316
70	1	0	2.980449	-3.284686	3.287242
71	1	0	2.807607	-3.517356	1.534326
72	1	0	4.075460	-0.416311	3.333655
73	1	0	2.513483	0.445432	3.355284
74	1	0	2.741422	-1.015034	4.347186
75	1	0	0.398818	-0.672457	2.326023
76	1	0	0.487256	-2.322667	1.697988
77	1	0	0.736177	-2.034275	3.427413
78	1	0	3.760529	-0.290175	-2.265839
79	1	0	1.098620	-2.980555	-0.169128

80	1	0	3.225449	-1.426266	-4.387223
81	1	0	0.615755	-4.140936	-2.276902
82	1	0	1.658904	-3.370121	-4.413416
83	1	0	5.335781	-1.948949	-0.525004
84	1	0	4.514673	1.750241	1.550483
85	1	0	7.749727	-1.434456	-0.480706

5. References.

(1) A. Dondoni, P. P. Giovannini and D. Perrone, *J. Org. Chem.*, 2002, **67**, 7203–7214.

(2) (a) A. D. Becke, *J. Chem. Phys,.* 1993, **98**, 5648–5652; (b) A. D. Becke, *Phys. Rev.*, 1988, **38**, 5648–5652.

(3) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785–789.

(4) (a) E. R. Davidson, *Chem. Phys. Lett.*, 1996, **220**, 514–518; (b) D. E. Woon and T. H. Dunning Jr., *J. Chem. Phys.*, 1993, **98**, 1358–1371; (c) T. H. Dunning Jr., *J. Chem. Phys.*, 1989, **90**, 1007–1023.

(5) K. A. Peterson *J. Chem. Phys.*, 2003, **119**, 11099–11112.

(6) P. Sinha, E. B. Scott, C. Gu, R. A. Wheeler and A. K. Wilson, *J. Phys. Chem.*, 2004, **108**, 9213–9217.

(7) J. Tomasi and M. Persico, *Chem. Rev.*, 1994, **94**, 2027–2094.

(8) (a) M. Cossi, G. Scalmani, N. Rega and V. Barone, *J. Chem. Phys.*, 2002, **117**, 43–54. (b) B. Mennucci and J. Tomasi, *J. Chem. Phys.*, 1997, **106**, 5151–5158.

(9) Gaussian 03, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. K. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

(10) (a) D. Feller, *J. Comp. Chem.*, 1996, **17**, 1571–1586; (b) K. L. Schuchardt, B. T. Didier, T. Elsethagen, L. Sun, V. Gurumoorthi, J. Chase, J. Li, and T. L. Windus, *J. Chem. Inf. Model.,* 2007, **47**, 1045–1052.

(11) M. Svensson, S. Humbel, R. D. J. Froese, T. Matsubara, S. Sieber and K. Morokuma, *J. Phys. Chem.*, 1996, **100**, 19357–19363.

(12) (a) T. H. Dunning Jr. and P. J. Hay, in *Methods of Electronic Structure Theory, Vol. 2*, H. F. Schaefer III, ed., Plenum Press, 1977; (b) P. J. Hay and W. R. Wadt, *J. Chem. Phys.,* 1982, **82**, 270, 284 and 299.

(13) (a) M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902–3909; (b) M. J. S. Dewar and E. G. Zoebisch, *Teochem.*, 1988, **49**, 1–21; (c) M. J. S. Dewar and C. Jie, *Organometallics*, 1987, **6**, 1486–1490; (d) M. J. S. Dewar, E. F. Healy, D. R. Kuhn and A. J. Holder, *Organometallics*, 1991, **10**, 431–435.

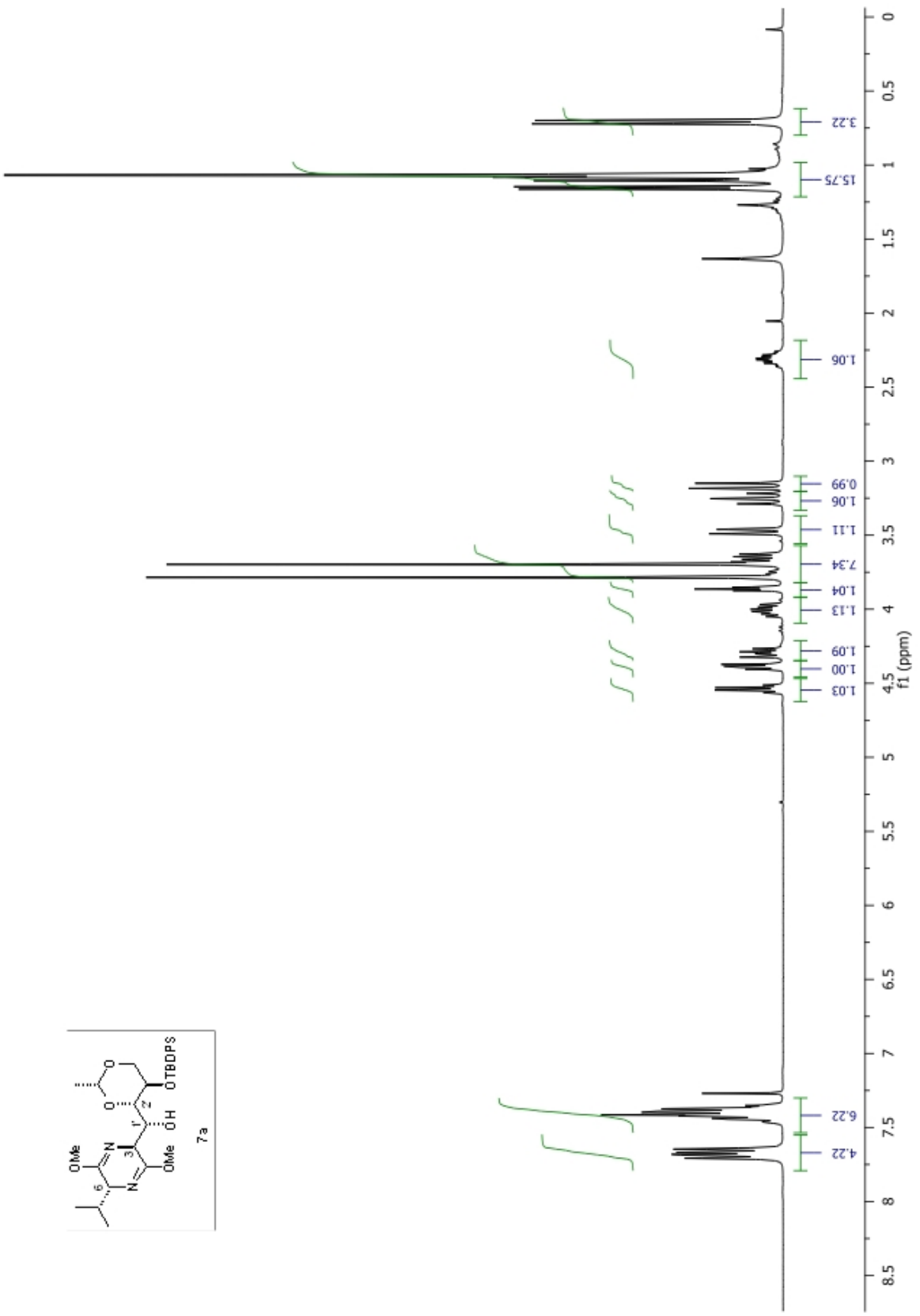
(14) (a) D. A. Evans, J. V. Nelson and T. R. Taber *Top. Stereochem.,* 1982, **13**, 1–115; (b) H. E. Zimmerman and M. D. Traxler *J. Am. Chem. Soc.,* 1957, **79**, 1920–1923.

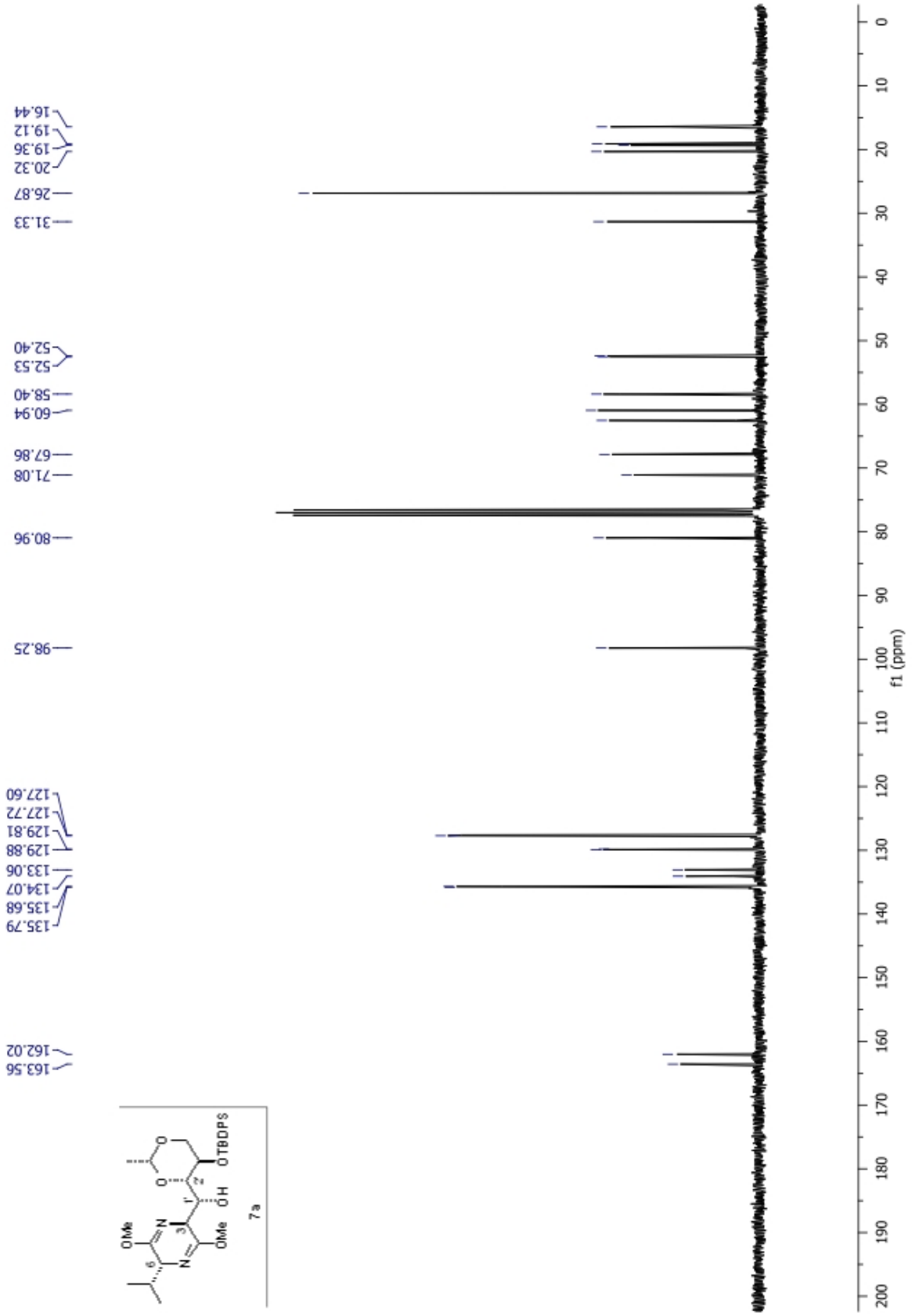
(15) (a) N. T. Anh *Top. Curr. Chem.,* 1980, **88**, 145−162; (b) N. T. Anh and O. Eisenstein, *Nouv. J. Chim.,* 1977, **1**, 61−70; (c) M. Chérest, H. Felkin and N. Prudent *Tetrahedron Lett.*, 1968, 2199-2204.

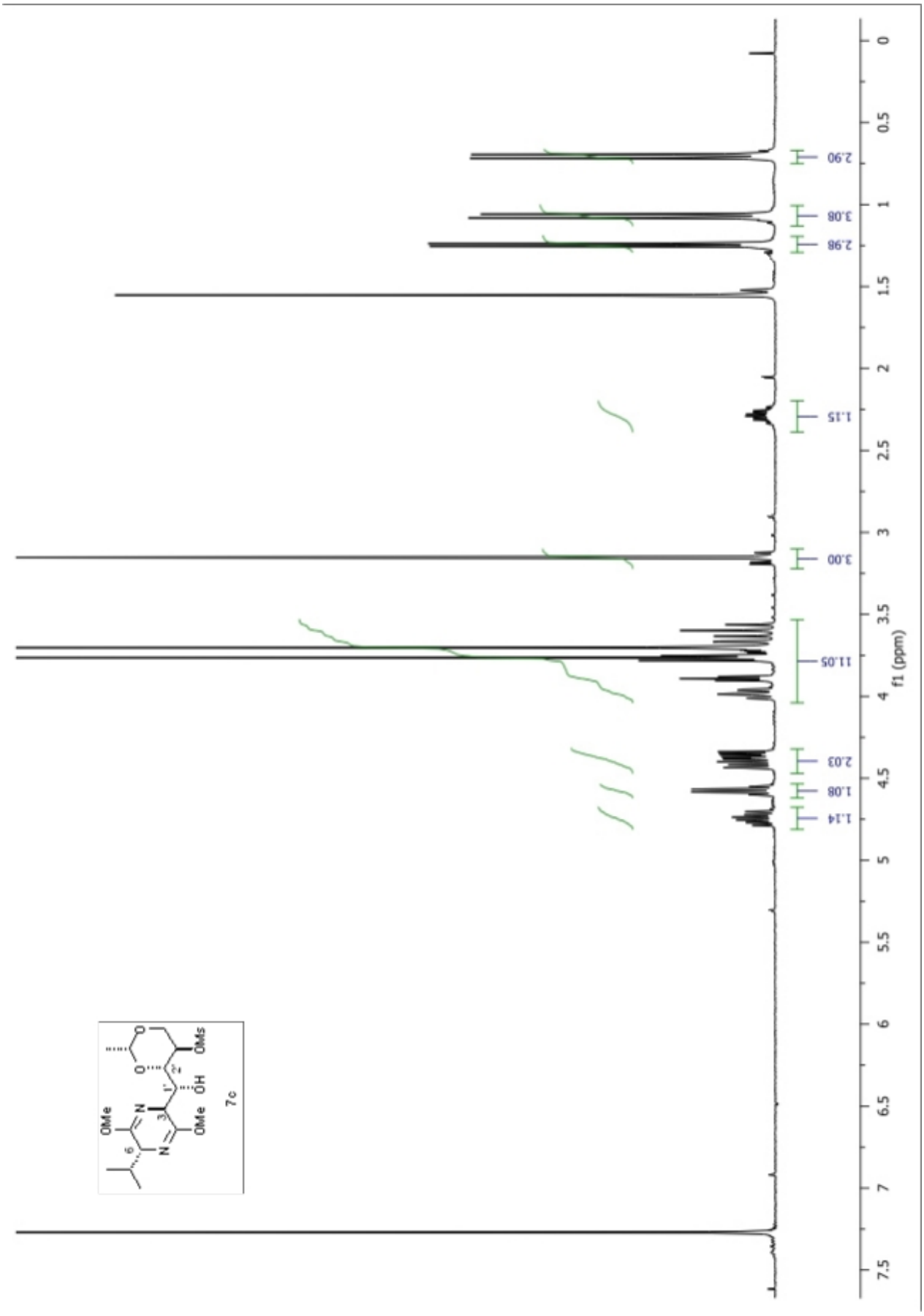
(16) D. A. Evans, V. J. Cee and S. J. Siska, *J. Am. Chem. Soc.,* 2006, **128**, 9433–9441, and references cited therein.

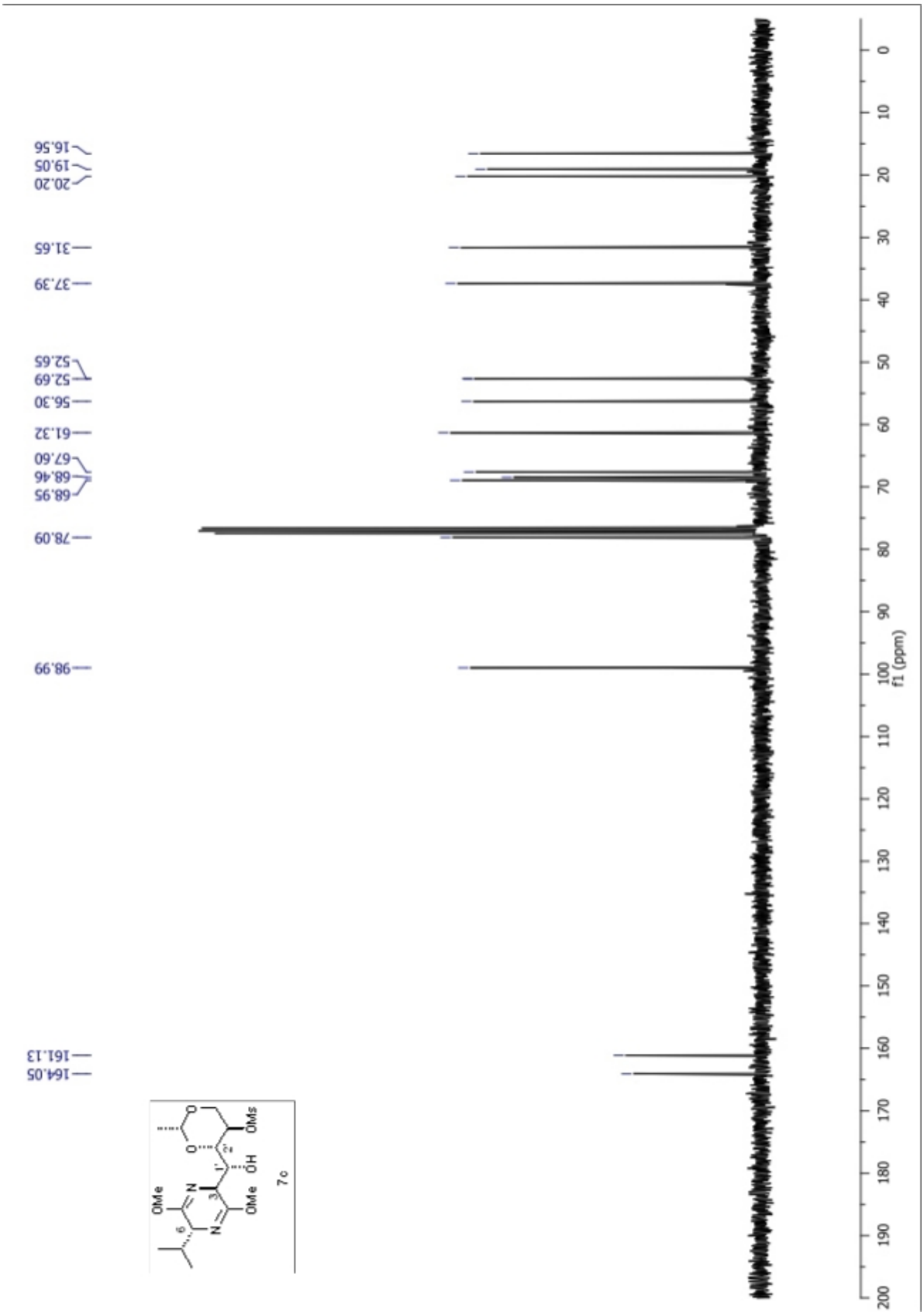
(17) E. P. Lodge and C. H. Heathcock, *J. Am. Chem. Soc.,* 1987, **109**, 3353–3361.

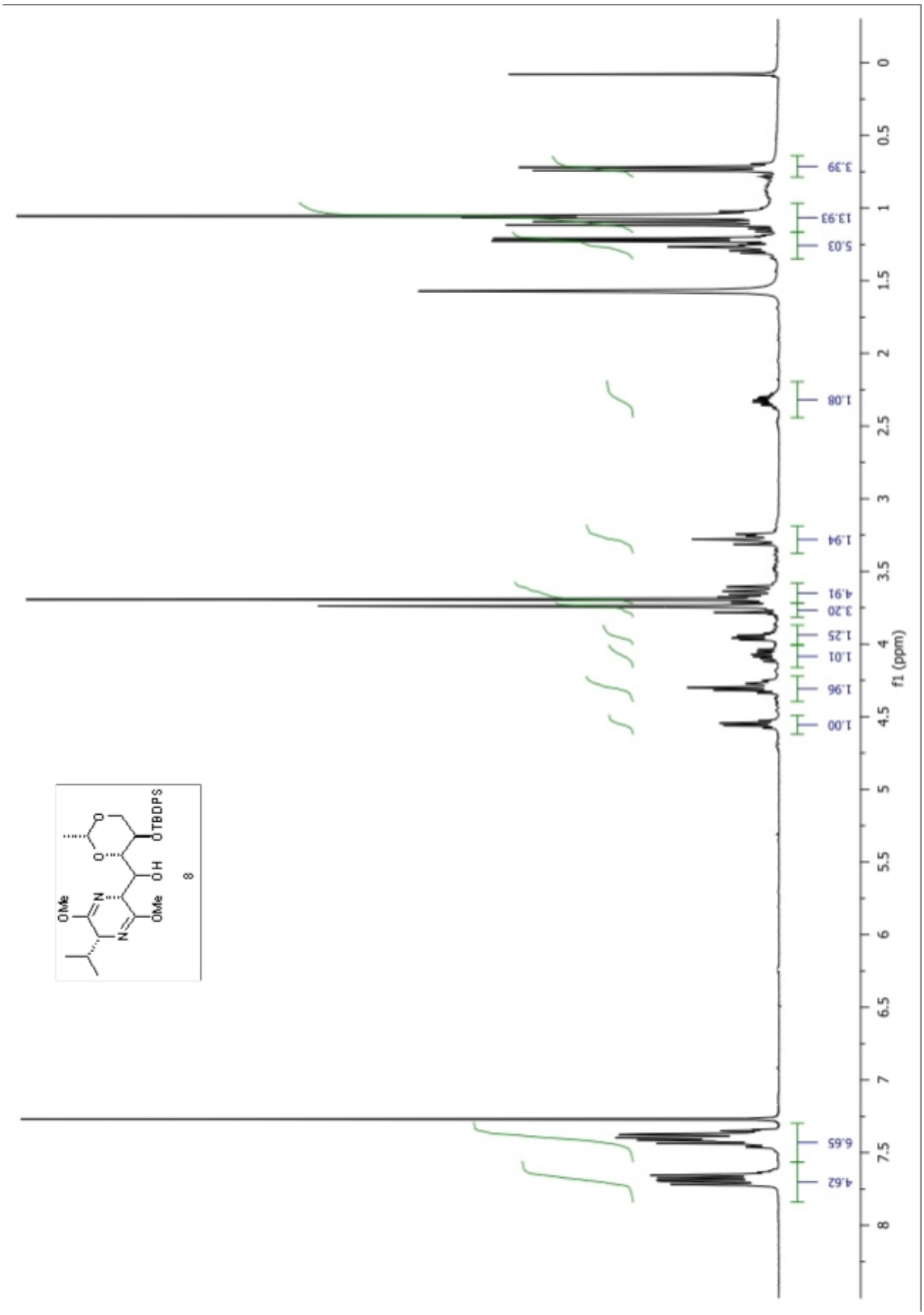
6. NMR spectra.

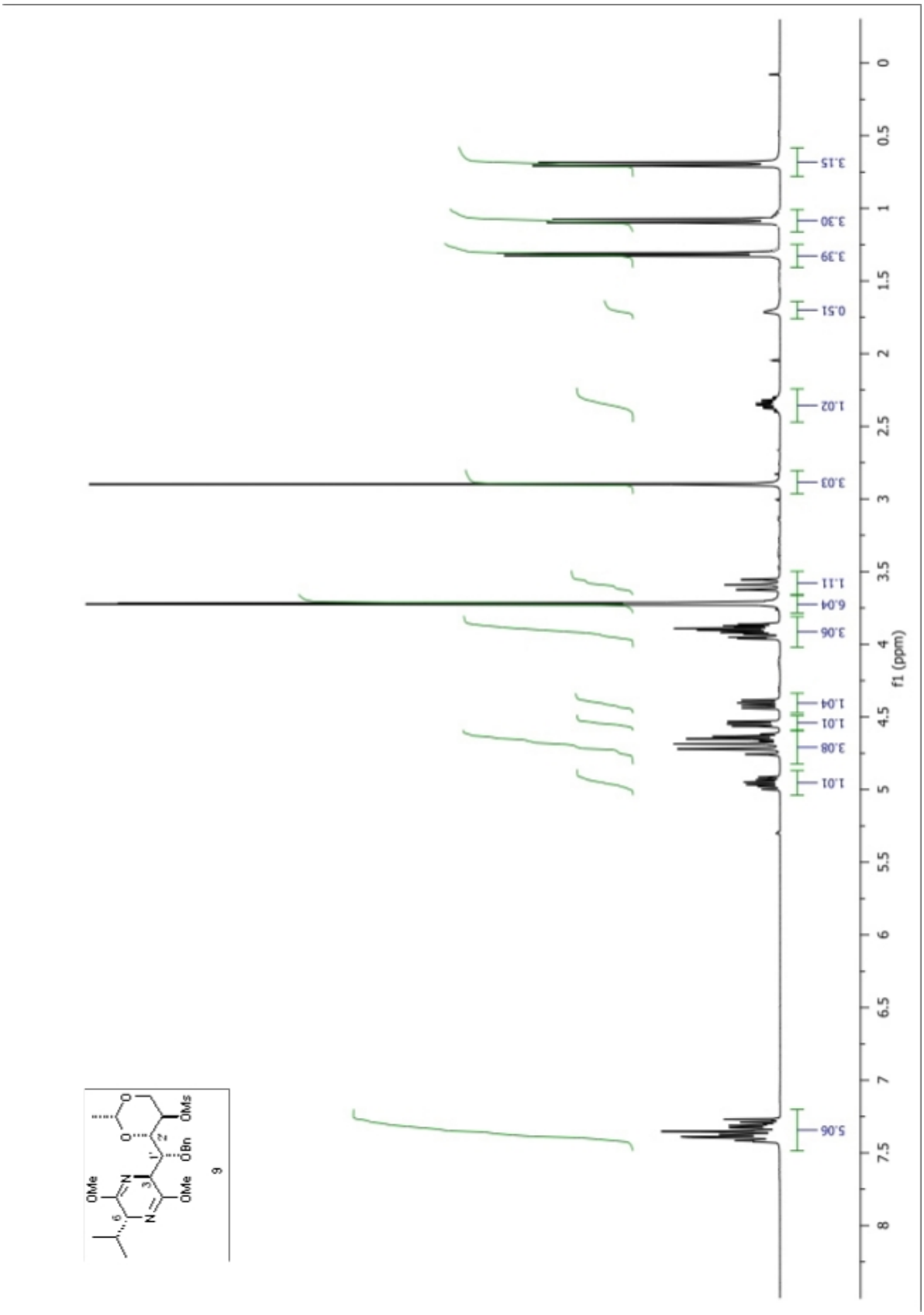


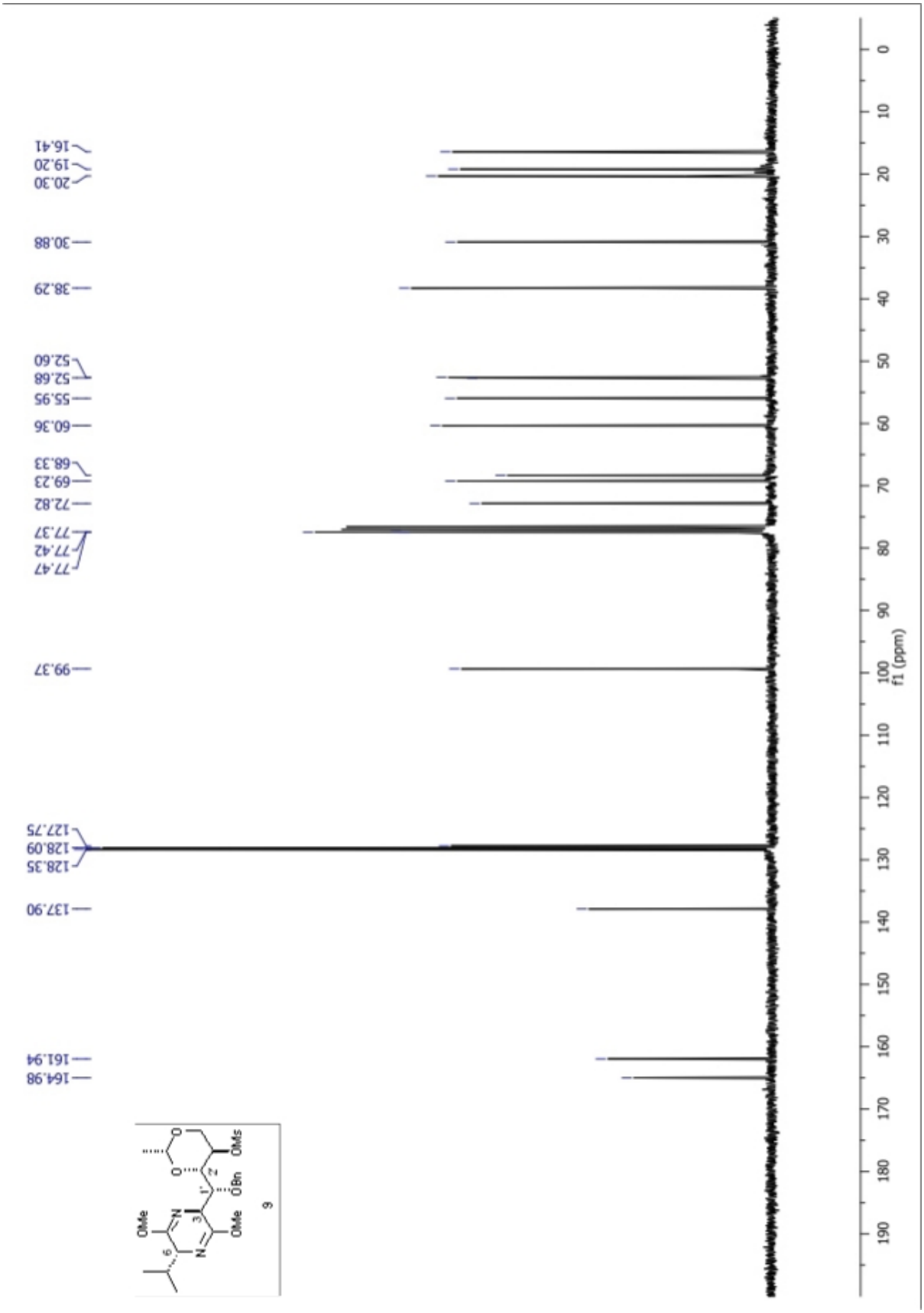

16.44
19.12
19.36
20.32
26.87
31.33
52.40
52.53
58.40
60.94
67.86
71.08
80.96
98.25
127.60
127.72
129.81
129.88
133.06
134.07
135.68
135.79
162.02
163.56
OTBDPS
OH
OMe
OMe
7a
f1 (ppm)

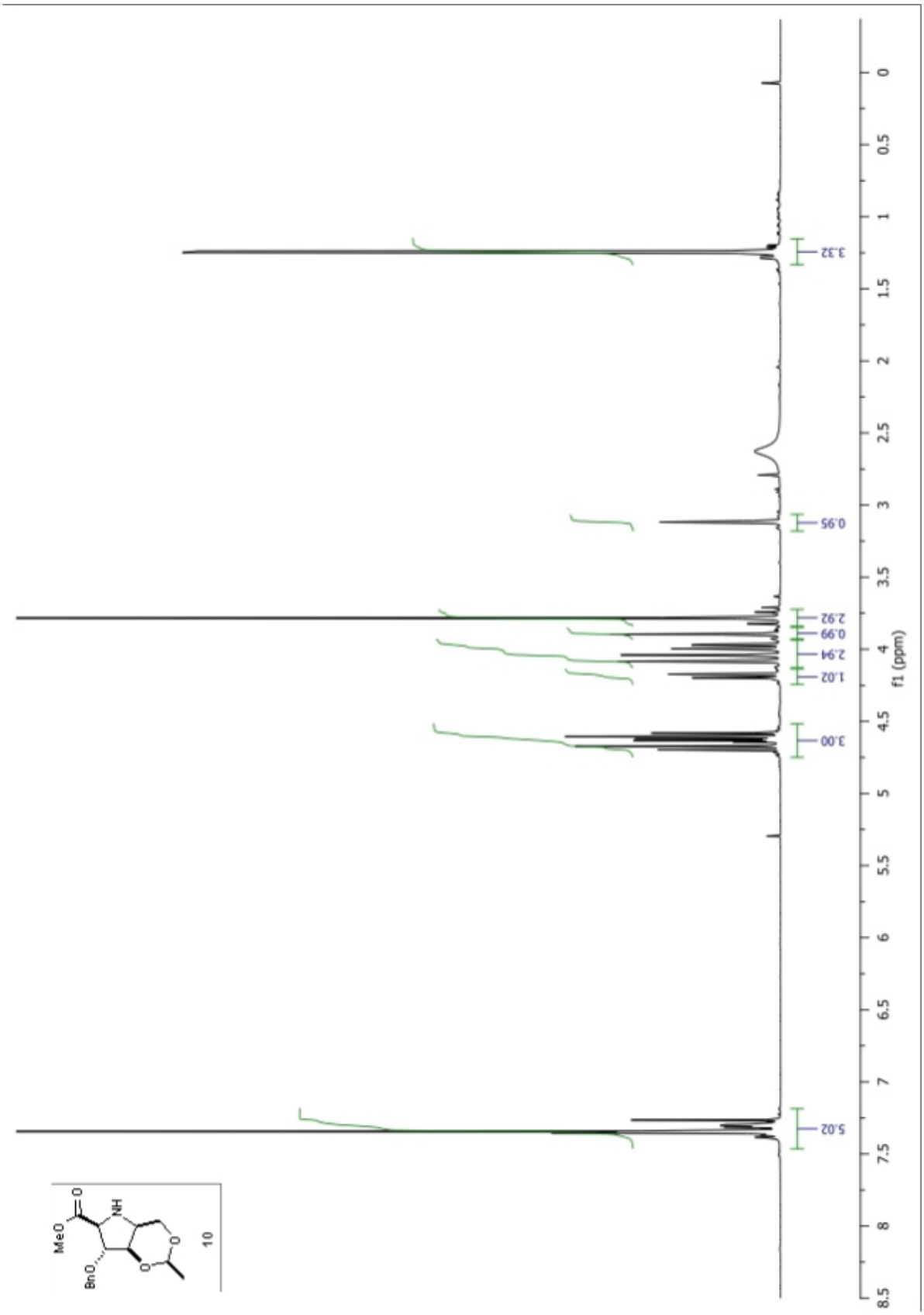

2.90
3.08
2.98
1.15
3.00
11.05
2.03
1.08
1.14
f1 (ppm)
OMe
OMe
OH
OMs
7c

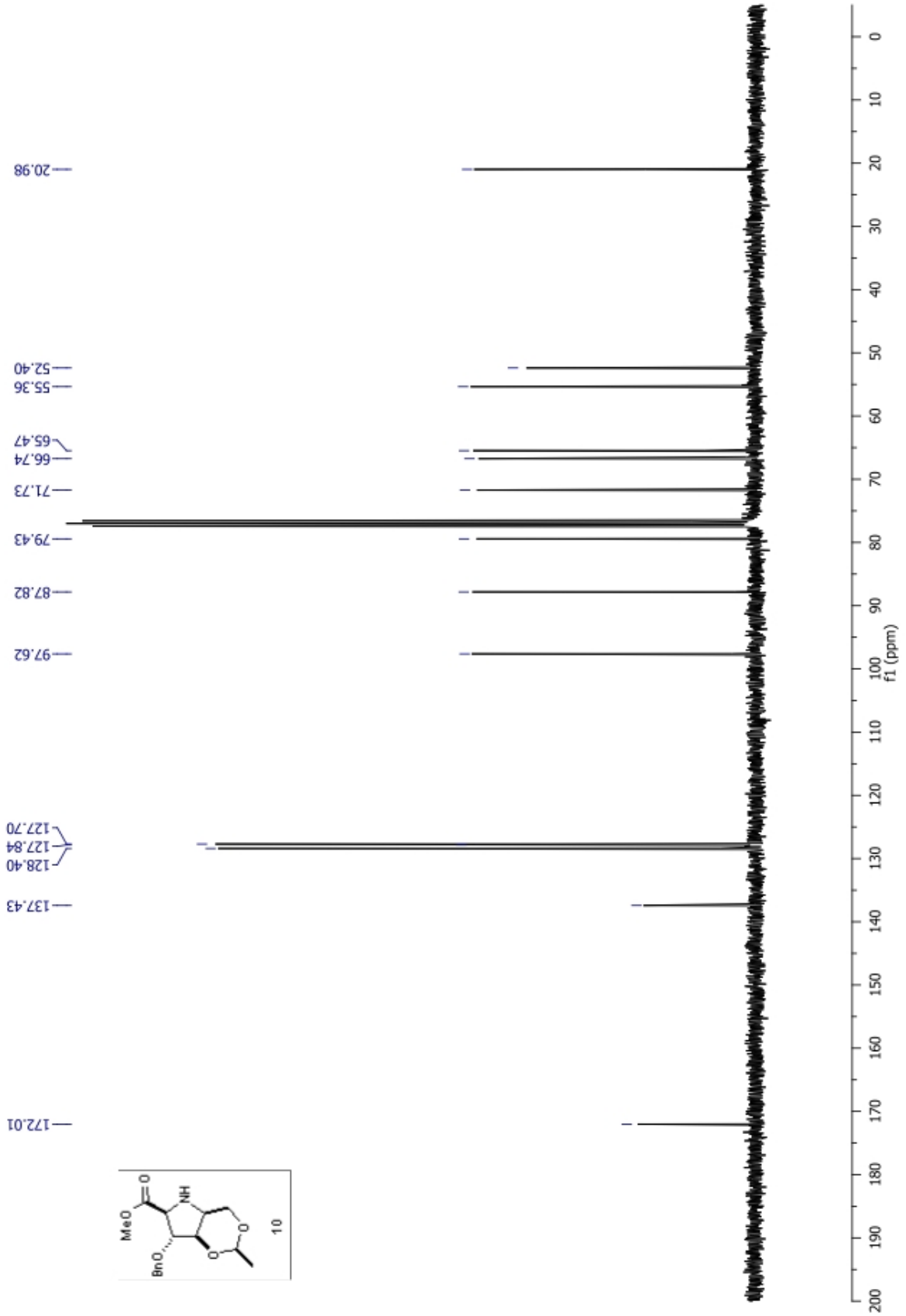

16.56
19.05
20.20
31.65
37.39
52.65
52.69
56.30
61.32
67.60
68.46
68.95
78.09
98.99
161.13
164.05
f1 (ppm)
OMe
OMe
OH
OMs
7c

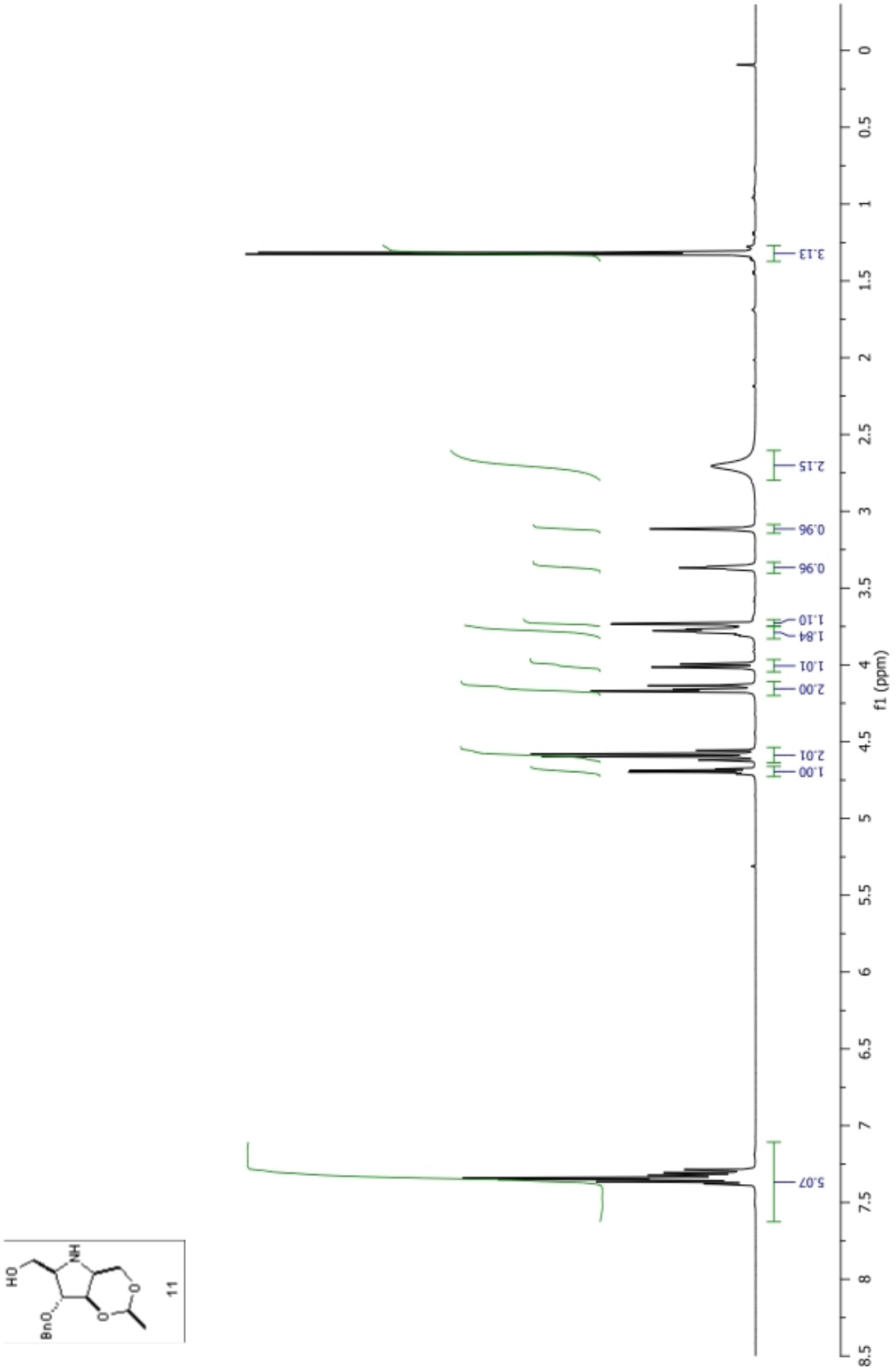

3.39
13.93
5.03
1.08
1.94
4.91
3.20
1.25
1.01
1.96
1.00
6.65
4.62
f1 (ppm)
OMe
N
N
OMe
OH
OTBDPS
O
O
8

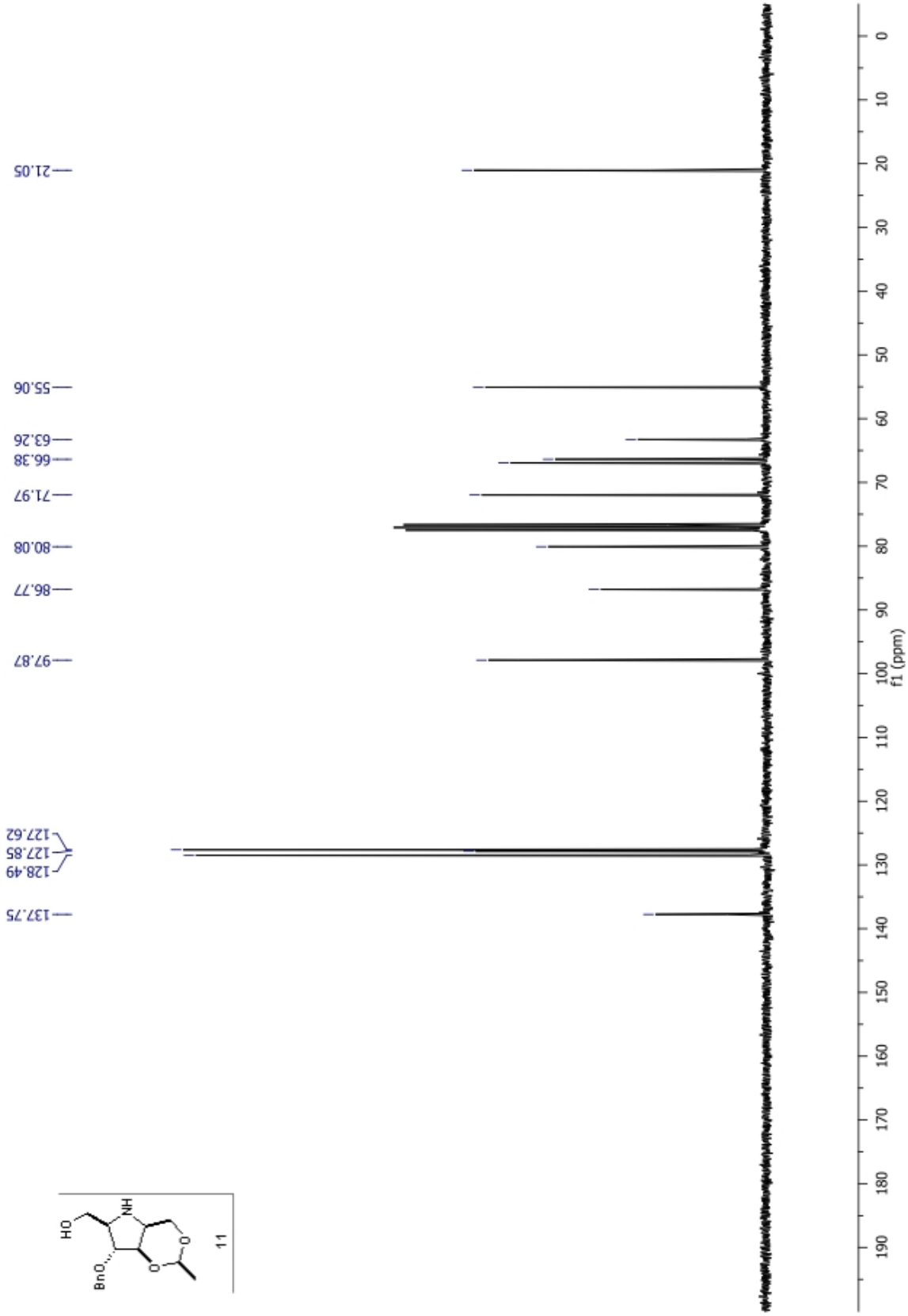

3.15
3.30
3.39
0.51
1.02
3.03
1.11
6.04
3.06
1.04
1.01
3.08
1.01
5.06
f1 (ppm)
OMe
OMe
OBn
OMs
9

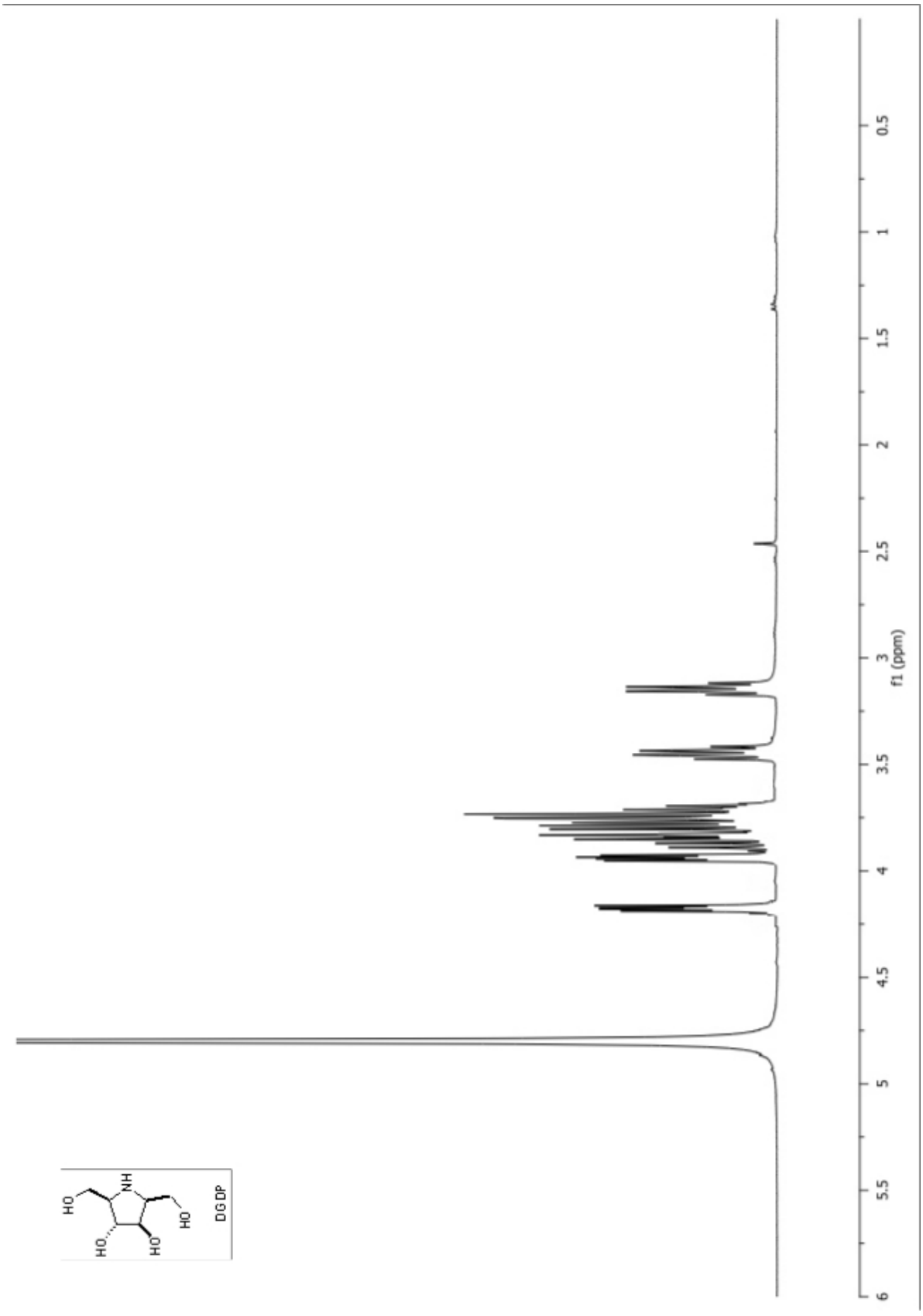

16.41
19.20
20.30
30.88
38.29
52.60
52.68
55.95
60.36
68.33
69.23
72.82
77.37
77.42
77.47
99.37
127.75
128.09
128.35
137.90
161.94
164.98
f1 (ppm)
OMe
OMe
OBn
OMs
9

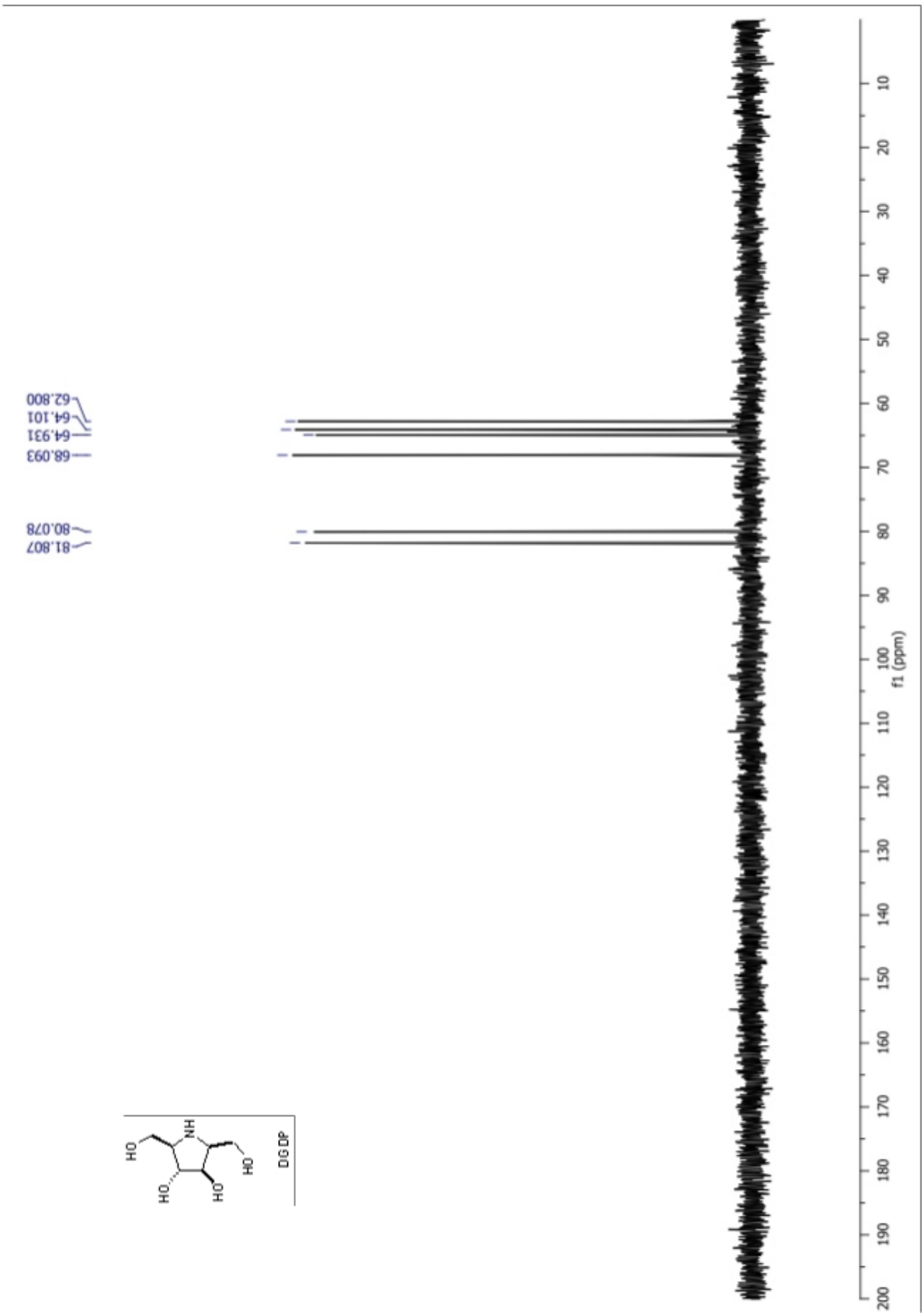

MeO
O
NH
BnO
O
O
10
3.32
0.95
2.92
0.99
2.94
1.02
3.00
5.02
f1 (ppm)


20.98
52.40
55.36
65.47
66.74
71.73
79.43
87.82
97.62
127.70
127.84
128.40
137.43
172.01
MeO
O
NH
BnO
O
O
10
f1 (ppm)


HO
NH
BnO
O
O
11
3.13
2.15
0.96
0.96
1.10
1.84
1.01
2.00
2.01
1.00
5.07
f1 (ppm)


21.05
55.06
63.26
66.38
71.97
80.08
86.77
97.87
127.62
127.85
128.49
137.75
f1 (ppm)
HO
NH
BnO
O
O
11


HO
NH
HO
HO
HO
DG DP
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
f1 (ppm)


62.800
64.101
64.931
68.093
80.078
81.807
DGDP
f1 (ppm)