Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting Information

Facile and robust methods for the regioselective acylation of N-acetylneuraminic acid

Melanie Shadrick, Charlene Yu, Scott Geringer, Sean Ritter, Alexanndra Behm , Abby Cox, Matt Lohman, and Cristina De Meo *

Department of Chemistry
Southern Illinois University Edwardsville
Science Building West, Box-1652,, Edwardsville, IL 62025, USA
Email: cdemeo@siue.edu

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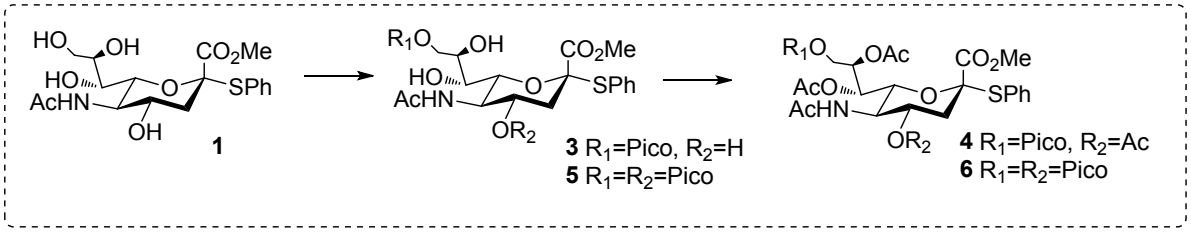
General Experimental

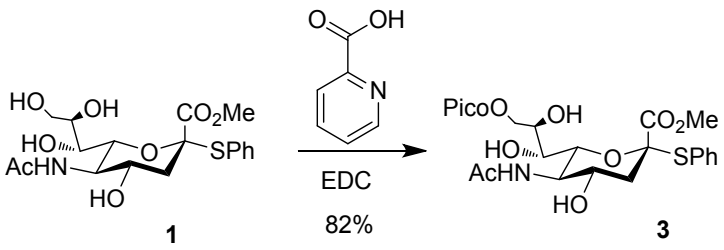
The reactions were performed using commercial reagents (Aldrich, Acros, Carbosynth) and solvents purified according to standard procedures. Column chromatography was performed on silica gel 60 (Silicycle, 70-230 mesh) or Sephadex LH-20 (GE Healthcare); reactions were monitored by TLC on TLC Silica Gel 60 F254S (Millipore). The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. CH_2Cl_2 and CH_3CN were purified by MBraun solvent purification system (MB-SPS-800). Molecular sieves (3Å), used for reactions, were crushed and activated *in vacuo* at 390 °C during 8 h in the first instance and then for 2-3 h at 390 °C directly prior to application. Optical rotations were measured at '*J*asco P-1020' polarimeter. ^{1}H NMR spectra were recorded using a Bruker Ascend 400 MHz NMR Spectrometer and ^{13}C NMR spectra were recorded at 75 MHz. The ^{1}H NMR chemical shifts are referenced to the signal of the residual $CHCl_3$ (δ_H = 7.27 ppm) for solutions in $CDCl_3$ and CD_3OD (δ_H = 3.31 ppm (q) and 4.87 ppm (s)). The ^{13}C NMR chemical shifts are referenced to the central signal of $CDCl_3$ (δ_C = 77.23 ppm) for solutions in $CDCl_3$. HRMS determinations were made with the use of *J*EOL MStation (*J*MS-700) Mass Spectrometer.

Synthesis of thiosialosides 3-6 from Polyol 1



Synthesis of 9-Picoloyl 4

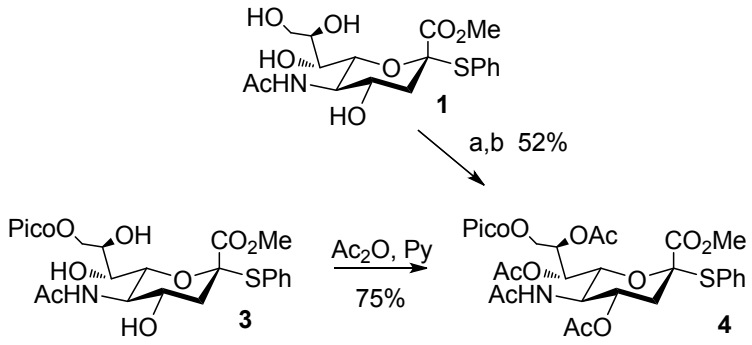
Methyl (2-thiophenyl 5-acetamido-3,5-dideoxy-4,7,8-tri-O-hydroxyl-9-O-picoloyl-D-glycero-β-D-galacto-2-nonulopyranosid)onate (3)



To a solution of **1** (100 mg, 0.24 mmol) in dry pyridine (4 mL), picolinic acid (177.3 mg, 1.44 mmol, 6.0 equiv) was added followed by EDC (149.0 mg, 0.96 mmol, 4.0 equiv). The reaction was allowed to stir for 1 h under argon at rt. The reaction was then co-evaporated with toluene (5 mL). The residue was purified by column chromatography on silica gel (ethanol/dichloromethane, 5% gradient) to afford **3** (103 mg, 0.198 mml, 82%).

Analytical Data: R_f = 0.49 (ethanol/dichloromethane, 1/5 v/v); $[\alpha]^{23}_D$ = +16.86 (*c* = 1, MeOH) ^{1}H NMR (CD_3OD) δ 8.72 (dq, *J* = 4.8 Hz, 1H, aromatic), 8.22 (bd, *J* = 7.8 Hz, 1H, aromatic), 8.06 (td, *J* = 7.8, *J* = 1.6 Hz, 1H, aromatic), 7.68 (ddd, *J* = 4.8, *J* = 1.2 Hz, 1H, aromatic), 7.59-7.55 (m, 2H, aromatic), 7.34-7.30 (m, 3H, aromatic), 4.70 (dd, $J_{8,9a}$ = 2.4 Hz, $J_{9a,\ 9b}$ = 11.4 Hz, 1H, H-9a), 4.39 (dd, $J_{8,9b}$ = 6.9 Hz, 1H, H-9b), 4.13 (m, $J_{7,8}$ = 9.1 Hz, 1H, H-8), 3.84 (bq, $J_{4,5}$ = 10.2 Hz, 1H, H-5), 3.65 (m, $J_{3eq,4}$ = 4.7 Hz, $J_{3ax,4}$ = 11.4 Hz 1H, H-4), 3.60 (s, 3H, COOCH3), 3.55 (dd, $J_{7,6}$ = 1.6 Hz, 1H, H-7), 3.47 (dd, $J_{5,6}$ = 10.6 Hz, 1H, H-6), 2.85 (dd, $J_{3ax,3eq}$ = 12.7, 1H, H-3eq), 1.98 (s, 3H, NHCOCH3), 1.86 (dd, 1H, H-3ax). ^{13}C NMR δ 173.62, 169.5, 164.5, 149.1, 147.4, 137.9, 136.6, 129.6, 128.9, 128.4, 127.4, 125.2, 86.4, 75.5, 69.2, 68.8, 67.7, 67.5, 52.1, 51.7, 40.3, 31.3, 21.2, 13.0. HR-FAB MS $[M+Na]^+$calcd for $C_{24}H_{28}N_2O_9SNa$ 543.1413, found 543.1409.

Methyl (2-thiophenyl 4,7,8-tri-acetyl-5-acetamido-3,5-dideoxy-9-O-picoloyl-D-glycero-β-D-galacto-2-nonulopyranosid)onate (4)



a: Picolinic acid, EDC, py, 45 min; b: Ac_2O, py, 16h

From **3**: To a solution of **3** (96 mg, 0.184 mmol) in dry pyridine (1.4 mL). Ac_2O (0.70 mL) was added dropwise. The reaction was allowed to stir for 16 h under argon at RT. The reaction was quenched with MeOH until no heat was detected, MeOH removed *in vacuo*. The crude mixture was diluted with CH_2Cl_2 and washed with brine (10mL), sat. aq. sodium bicarbonate (10mL), and brine (10mL). The organic phase was dried over MgSO4, filtered, concentrated *in vacuo*. The compound was then purified by column chromatography on silica gel (acetone/toluene, 10%) to afford **4** (88mg, 0.136 mmol, 75%).

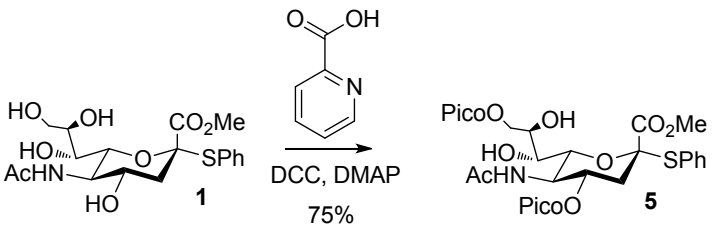
From **1**: To a solution of **1** (100 mg, 0.24 mmol) in dry pyridine (4 mL), picolinic acid (177.3 mg, 1.44 mmol, 6.0 equiv) was added followed by EDC (149.0 mg, 0.96 mmol, 4.0 equiv). The reaction was allowed to stir for 1 h under argon at rt. When starting material was fully consumed Ac_2O (0.91 mL, 9.6 mmol) was added dropwise and allowed to stir overnight. The reaction was quenched with MeOH until no heat was detected, MeOH removed *in vacuo*. The crude mixture was diluted with CH_2Cl_2 and washed with brine (10mL), sat. aq. sodium bicarbonate (10mL), and brine (10mL). The organic phase was dried over MgSO4, filtered, concentrated *in vacuo*. The compound was then purified by column chromatography on silica gel (acetone/dichloromethane, 10%) to afford **4** (81 mg, 0.13 mmol, 52%).

Analytical Data R_f = 0.62 (acetone/dichloromethane), 3/5 v/v); $[\alpha]^{23}_D$ = +22.67 (*c* = 1, $CHCl_3$); ^{1}H NMR ($CHCl_3$) δ 8.84 (bd, *J* = 4.4 Hz, 1H, aromatic), 8.17 (bd, *J* = 7.8 Hz, 1H, aromatic), 7.92 (bt, *J* = 6.7 Hz, 1H, aromatic), 7.58 – 7.51 (m, 3H, aromatic), 7.36 – 7.28 (m, 3H, aromatic), 5.82 (bs, 1H, NH), 5.49-5.41 (m, 2H, H-7, H-8), 4.88 (ddd, 1H, $J_{3eq,4}$ = 4.8 Hz, $J_{4,5}$ = 10.1 Hz, H-4), 4.81 (dd, 1H, $J_{8,9a}$ = 2.8 Hz, $J_{9a,9b}$ =

12.5 Hz H-9a), 4.46 (dd, $J_{8,\ 9b}$ = 5.0 Hz, 1H, H-9b), 4.07-3.98 (m, 2H, H-5, H-6), 3.54 (s, 3H, $COCH_3$), 2.79 (dd, $J_{3eq,4}$ = 4.7 Hz, $J_{3ax,3eq}$= 12.9 Hz, 1H, H-3eq), 2.16, 2.04, 2.03, 2.00, 1.84 (4s, 13H, $COOCH_3$, H-3ax). ^{13}C NMR δ170.8, 170.3, 170.2, 170.1, 149.5, 137.7, 136.5, 129.8, 128.8, 128.5, 127.2, 125.5, 87.4, 77.2, 74.5, 69.8, 69.7, 68.3, 63.7, 52.6, 49.3, 38.0, 31.5, 30.9, 23.1, 22.6, 20.9, 20.8, 14.1. HR-FAB MS $[M+Na]^+$calcd for $C_{30}H_{34}N_2O_{12}SNa$ 669.1722, found 669.1714.

Synthesis of C-4,9 di Picoloyl 6

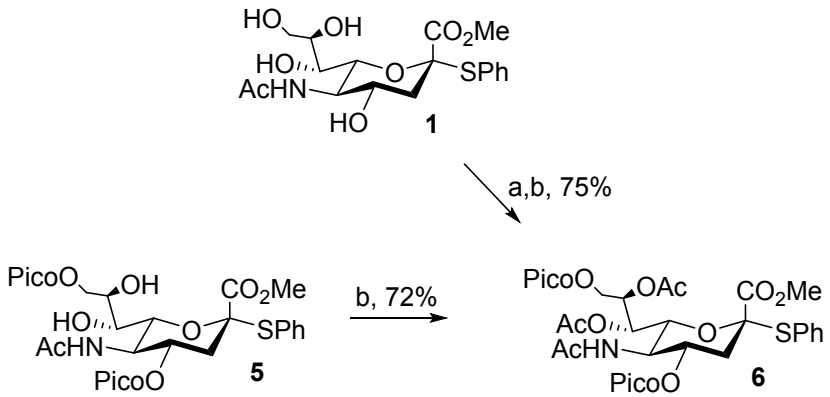
Methyl (2-thiophenyl 5-acetamido-3,5-dideoxy-7,8-di-O-hydroxyl-4,9-O-di-picoloyl -D-glycero-β-D-galacto-2-nonulopyranosid)onate (5)



To a solution of **1** (100 mg, 0.24 mmol) was dissolved in dry pyridine (4 mL). Picolinic acid (177.3 mg, 1.44 mmol, 6 equiv) was added, followed by DCC (198.8 mg, 0.96 mmol, 4 equiv) and DMAP (14.8 mg, 0.12 mmol, 0.5 equiv). The reaction was allowed to stir for 2.5 h under argon at rt. After 2.5 h, the reaction was co-evaporated with toluene (5 mL). The excess of reagent was crystallized with dichloromethane (5 mL) in the freezer for 1 h. The mixture was then filtered with cold dichloromethane and evaporated. The residue was purified by column chromatography on silica gel (acetone/dichloromethane, 10%, followed by methanol 100%) The residue was then further purified by column chromatography on silica gel (ethanol/dichloromethane, 5%) to afford **5** (113 mg, 0.18 mmol, 75%).

Analytical Data for **5** : R_f = 0.82 (ethanol/dichloromethane, 1/5, v/v); $[\alpha]^{23}_D$ = +22.56 (*c* = MeOH *)* ^{1}H NMR (CD_3OD) δ 8.74-8.69 (m, J = Hz, 2H, aromatic), 8.24 (dt, J = 7.9 Hz, 1H, aromatic), 8.15 (dt, J = 7.8 Hz, 1H, aromatic), 8.07 (dt, J = 7.9 Hz, 1H, aromatic), 8.02 (dd, J = 7.8 Hz, 1H, aromatic), 7.71-7.64 (m, 2H, aromatic), 7.62-7.59 (m, 2H, aromatic) 7.37-7.31 9m, 3H, aromatic), 5.27 (ddd, $J_{4,3eq}$ = 5.1 Hz, $J_{4,5}$ = 10.6 Hz, 1H, H-4), 4.73 (dd, $J_{9a,8}$ = 2.4 Hz, $J_{9a,9b}$ = 11.5 Hz, 1H, H-9_a), 4.40 (dd, $J_{8,9b}$ = 6.8 Hz, $J_{9a,9b}$ = 11.4 Hz, 1H, H-9_b), 4.37 (bt, 1H, H-5), 4.16 (ddd, $J_{8,9a}$ = 2.3 Hz, $J_{8,9b}$ = 6.5 Hz, $J_{8,7}$ = 8.9 Hz, 1H, H-8), 3.83 (dd, $J_{6,7}$ = 1.4 Hz, $J_{6,5}$ = 10.7 Hz, 1H, H-6), 3.67 (s, 3H, $COOCH_3$), 3.62 (dd, $J_{7,6}$ = 1.42 Hz, $J_{7,8}$ = 9.2 Hz, 1H, H-7), 3.08 (dd, $J_{3ax,3eq,}$ = 12.7 Hz, 1H, H-3eq), 2.18 (br t, 1H, H-3ax), 1.83 (s, 3H, $NHCOCH_3$,). ^{13}C NMR δ 174.2, 170.5, 166.1, 165.3, 150.9, 150.7, 148.9, 148.3, 139.4, 139.4, 138.2, 131.3, 130.2, 130.0, 129.1, 129.0, 126.9, 126.8, 87.9, 76.6, 73.1, 70.5, ,70.3, 69.1, 56.1, 53.4, 50.6, 38.6, 32.2, 29.6, 22.8. HR-FAB MS $[M+Na]^+$calcd for $C_{30}H_{31}N_3O_{10}SNa$ 648.1620, found 648.1684.

Methyl (2-thiophenyl 7,8-di-O-acetyl-5-acetamido-3,5-dideoxy-9,4-di-O-picoloyl-d-glycero-β-d-galacto-2-nonulopyranosid)onate (6)



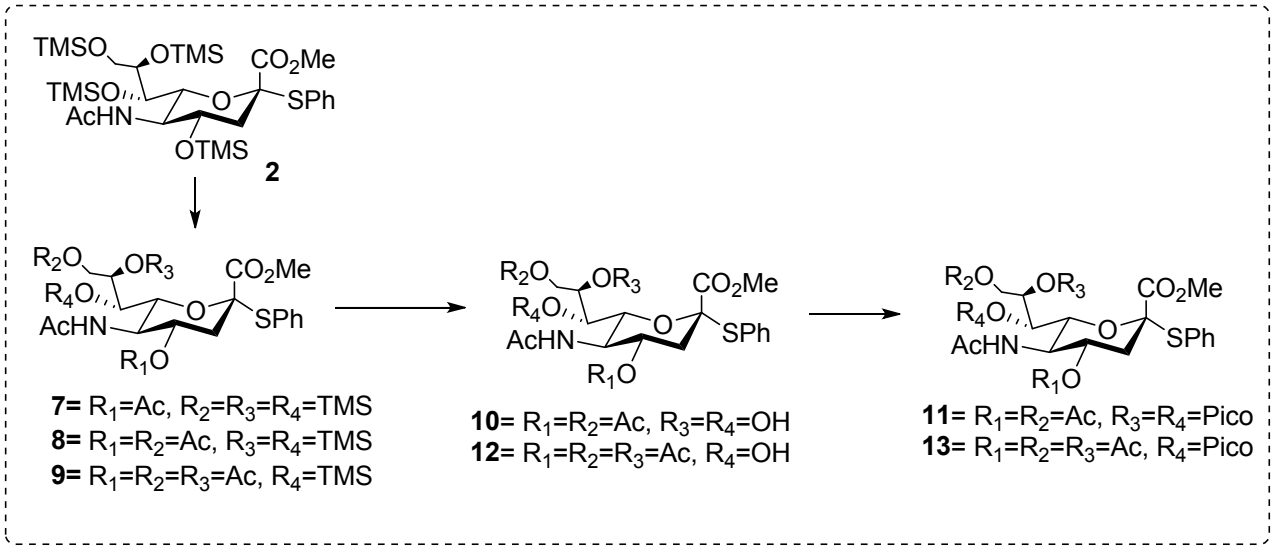
a: Picolinic acid, DDC, DMAP, py, 2.5 h; b: Ac_2O, py, 16h

From **5**: To a solution of **5** (111 mg, 0.177 mmol) in dry pyridine (1.34 mL). Ac_2O (0.67 mL) was added dropwise. DMAP (4.33 mg, 0.35 mmol, 0.2 equiv) was added. The reaction was allowed to stir for 16 h under argon at RT. The reaction was quenched with MeOH until no heat was detected, the residue was concentrated *vacuo* while co-evaporating with toluene. The compound was then purified by column chromatography on silica gel (acetone/dichloromethane, 10%) to afford **6** (90 mg, 0.13 mmol, 72%).

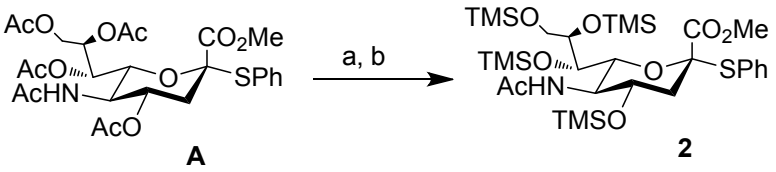
From **1:** To a solution of **1** (100 mg, 0.24 mmol) in dry pyridine (4 mL), picolinic acid (177.3 mg, 1.44 mmol, 6 equiv) was added, followed by DCC (198.8 mg, 0.96 mmol, 4 equiv) and DMAP (14.8 mg, 0.12 mmol, 0.5 equiv). The reaction was allowed to stir for 2.5 h under argon at rt. MeOH (0.4 mL) was added dropwise to quench any picolinic anhydride. Ac_2O (1.5 mL, 15.87 mmol) was added dropwise and allowed to stir overnight. The reaction was quenched with MeOH until no heat was detected, MeOH removed *in vacuo*. The crude mixture was diluted with CH_2Cl_2 and washed with brine (10mL), sat. aq. sodium bicarbonate (10mL), and brine (10mL). The organic phase was dried over MgSO4, filtered, concentrated *in vacuo*. The compound was then purified by column chromatography on silica gel (acetone/dichloromethane, 10%) to afford **6** (129 mg, 0.182 mmol, 75%).

Analytical Data R_f = 0.41 (acetone/dichloromethane, 3/5 v/v); $[\alpha]^{23}_D$ = +31.29 (*c* = 1, $CHCl_3$); ^{1}H NMR ($CHCl_3$) δ 8.85 (bdq, J = 0.8 Hz, J= 1.7 Hz, J= 4.8 Hz, 1H, aromatic), 8.80 (bdq, J = 0.8 Hz, J= 1.7 Hz, J= 4.8 Hz, 1H, aromatic), 8.14 (dt, J = 7.8 Hz, 1H, aromatic), 8.06 (dt, J = 7.8 Hz, 1H, aromatic), 7.89-7.80 (m, 2H, aromatic), 7.57-7.46 (m, 4H, aromatic), 7.38-7.29 (m, 3H, aromatic), 7.20-7.14 (m, 2H, aromatic), 6.25 (dd, $J_{NH,5}$ = 8.8 Hz, 1H, NH), 5.53-5.44 (m, 2H, H-7, H-8), 5.34-5.24 (m, 1H, H-4), 4.84 (dd, $J_{9a,8}$ = 2.4 Hz, $J_{9a,9b}$ = 12.1 Hz, 1H, H-9_a), 4.48 (dd, $J_{8,9b}$ = 4.8 Hz, 1H, H-9_b), 4.26-4.16 (m, 2H, H-5, H6), 3.54 (s, 3H, $COOCH_3$), 2.99 (dd, $J_{3eq,4}$ = 4.4 Hz, $J_{3ax,3eq,}$ = 12.4 Hz, 1H, H-3eq), 2.18, 2.19, 2.03, 1.74 (3s, 10H, $COOCH_3$, NHCOCH3 H-3ax). ^{13}C NMR δ 170.3, 170.3, 170.1, 167.9, 164.5, 150.2, 149.9, 147.1, 137.4, 137.3, 136.5, 129.8, 128.8, 128.5, 127.2, 125.6, 125.4, 87.4, 77.3, 74.3, 71.2, 69.7, 68.0, 63.6, 52.6, 49.4, 38.2, 23.1, 20.9. HR-FAB MS $[M+Na]^+$calcd for $C_{34}H_{35}N_3O_{12}SNa$ 732.1831, found 732.1826.

Synthesis of thiosialosides 7-14 by ReSEt modified technology



Methyl (2-thiophenyl 5-acetamido-3,5-dideoxy-4,7,8,9-tetra-O-trimethylsilyl-D-glycero-β-D-galacto-2-nonulopyranosid)onate (2)



a: MeoNa, MeOH; b:MSCl, HMDS, Pyridine, 69%

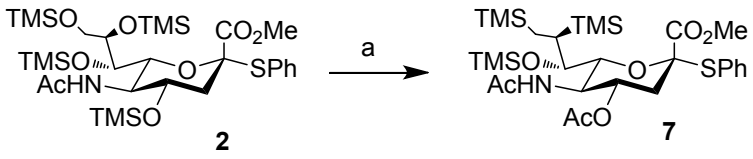
To a solution of methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-glycero α-D-galacto-non-2-ulopyranosid)onate (**A**,[1] 1.9 g, 3.2 mmol) in MeOH (167 mL), 1 M NaOMe (4.82 mL) was added dropwise. The resulting mixture was stirred for 1 h under argon and then neutralized with Dowex H^+. The resin was then filtered off, rinsed with MeOH, concentrated *in vacuo* and dried. Part of the residue (1.0 g, 2.4 mmol) was then dissolved in pyridine (10 mL), brought to 0 °C and hexamethyldisilazane (19.3 mmol, 4.2 mL, 8 equiv) was added drop wise followed by trimethylsilyl chloride (19.3 mmol, 2.4 mL, 8 equiv) and allowed to stir under argon for 16 h at rt. The reaction was then diluted with hexane, and washed with ice water (50 mL x 2), brine (50 mL x 2). The aqueous layer was washed with hexane (50 mL x2). The organic phase was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 10% gradient) to afford **2** (1.2 g, 1.6 mmol, amorphous, white, 69%).

Analytical Data R_f = 0.59 (ethyl acetate/hexane, 2/5 v/v); $[\alpha]^{23}_D$ = +11.13 (*c* = 1, $CHCl_3$); ^{1}H NMR ($CHCl_3$) δ 7.6-7.5 (m, 2H, aromatic), 7.44 – 7.29 (m, 3H, aromatic), 5.30 (d, $J_{5,NH}$ = 8.1 Hz, 1H, NH), 4.06 (dd, $J_{8,9a}$ = 2.8 Hz, $J_{9a,9b}$ = 10.6 Hz, 1H, H-9a), 3.95 (dd, $J_{5,6}$ = 10.5 Hz, $J_{6,7}$ = 2.2 Hz, 1H, H-6), 3.93-3.87 (m, $J_{3ax,4}$ = 11.4 Hz, $J_{H3eq,4}$ = 4.5 Hz 1H, H-4), 3,88-3.83 (m, $J_{7,8}$ = 2.9 Hz, $J_{8,9b}$ = 6.4 Hz, 1H, H-8), 3.78 (dd, 1H, H-7), 3.6 (s, 3H, COOCH_3), 3.5 (dd, 1H, H-9b), 3.41-3.32 (m, 1H, H-5), 2.63 (dd, $J_{3ax,3eq}$ = 12.9, 1H, H-3eq), 1.90 (s, 1H, N*H*COCH$_3$), 1.74 (dd, 1H, H-3ax), 0.16, 0.15, 0.11, 0.08 (s x4, 36H, Si(CH_3)$_3$). ^{13}C NMR δ

169.8, 169.1, 136.4, 129.7, 129.4, 128.6, 87.5, 77.2, 75.7, 74.7, 68.8, 64.2, 54.5, 52.4, 41.9, 23.9, 0.5, 0.5, 0.08. HR-FAB MS $[M+Na]^+$calcd for $C_{30}H_{57}NO_8SSi_4Na$ 726.2779, found 726.2759.

(1) Kirchner, E.; Thiem, F.; Dernick, R.; Heukeshoven, J.; Thiem, J. *J. Carbohydr. Chem.* **1988**, *7*, 453.

Methyl (2-thiophenyl 4-O-aceyl-5-acetamido-3,5-dideoxy-7,89-tri-O-trimethylsilyl -d-glycero-β-d-galacto-2-nonulopyranosid)onate (7)



a: Ac_2O. DMAP, py, 48%

A solution of **2** (200 mg, 0.28 mmol) in dry pyridine (3 mL). Ac_2O (2.8 mmol, 0.27 mL, 10 equiv) was added dropwise followed by DMAP (3.40 mg, 0.03 mmol, 0.1 equiv). The reaction was allowed to stir for 15 hours under argon. The reaction was quenched with MeOH until no heat was detected, and the solvent evaporated *in vacuo*. The crude mixture was diluted with CH_2Cl_2 and washed with brine (15mL), sat. aq. sodium bicarbonate (15mL), and brine (15mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (acetone/hexane, 10%) to afford **7** (90 mg, 0.133 mmol, 48%).

Analytical Data R_f = 0.59 (acetone/hexane, 2/5 v/v); $[\alpha]^{23}_D$ = +5.12 (*c* = 1.1, $CHCl_3$) ^{1}H NMR ($CHCl_3$) δ 7.62 – 7.56 (m, 2H, aromatic), 7.41 – 7.29 (m, 3H, aromatic), 5.13 (d, $J_{5,NH}$ = 10.0 Hz, 1H, NH), 4.84 (ddd, $J_{5,6}$ = 4.5 Hz, 1H, H-4), 4.02 – 3.95 (m, 2H, H5, H-9a), 3.87 – 3.82 (ddd, $J_{8,9a}$ = 2.6 Hz, $J_{7,8}$ = 5.5 Hz, $J_{8,9b}$ = 7.3 Hz, 1H, H-4), 3.72 (dd, $J_{6,7}$ = 1.7 Hz, 1H, H-8), 3.69 – 3.65 (dd, s, 4H, H-6, $COOCH_3$), 3.51 (dd, $J_{9a,9b}$ = 10.5 Hz, 1H, H-9b), 2.65 (dd, $J_{4,3eq.}$ = 4.63 Hz, $J_{3eq.,3ax.}$ = 12.7 Hz, 1H, H-3eq.), 2.01, 1.89 (s, 6H, NHCOCH_3, COCH_3), 1.90 (t, 1H, H-3ax), 0.17,0.15, 0.10 (3s, 27H, Si(CH_3)$_3$). ^{13}C NMR δ 171.0, 169.8, 169.5, 168.6, 145.0, 136.6, 129.6, 129.1, 128.8, 128.7, 107.6, 86.7, 77.2, 76.1, 74.7, 73.4, 72.8, 71.4, 70.9, 68.8, 64.2, 63.2, 52.7, 52.3, 50.0, 47.4, 37.5, 23.4, 21.1, 20.9, 0.5. HR-FAB MS $[M+Na]^+$calcd for $C_{29}H_{51}NO_9SSi_3Na$ 696.2482, found 696.2502

<u>Synthesis of C-7,8 di Picoloyl 11</u>

Methyl (2-thiophenyl 4,9-di-O-aceyl-5-acetamido-3,5-dideoxy-7,8-tri-O-trimethylsilyl-d-glycero-β-d-galacto-2-nonulopyranosid)onate (8)

To a solution of **2** (100 mg, 0.142 mmol) in dry pyridine (1.5 mL), Ac_2O (0.71, mmol, 0.07 mL, 5 equiv) was added followed by DMAP (3.47 mg, 0.028 mmol, 0.2 equiv). The reaction was allowed to stir for 20 h under argon at RT. The reaction was quenched with MeOH until no heat was detected, MeOH removed *in vacuo*. The crude mixture was diluted with CH_2Cl_2 and washed with brine (15mL), sat. aq. sodium bicarbonate (15mL), and brine (15mL The organic phase

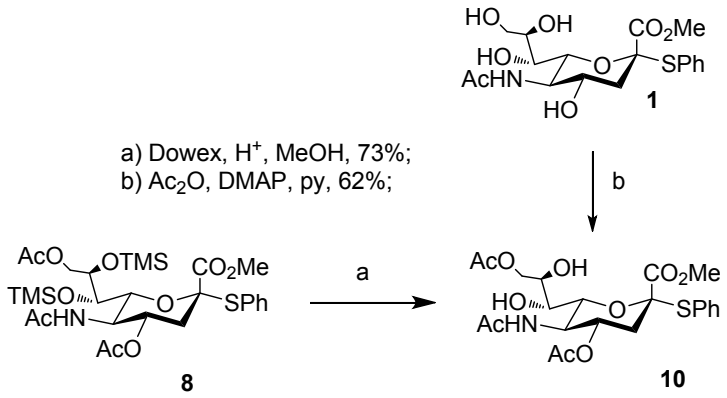
a: Ac_2O. DMAP, py, 57%

was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (acetone/hexane, 10%) to afford **8** (52 mg, 0.08 mmol, 57%).

Analytical Data R_f = 0.54 (acetone/hexane, 2/5 v/v); $[\alpha]^{23}_D$ = +8.73 (*c* = 1, $CHCl_3$); ^{1}H NMR ($CHCl_3$) δ 7.61-7.53 (m, 2H, aromatic), 7.42-7.13 (m, 3H, aromatic), 5.06 (d, $J_{NH,5}$ = 9.9 Hz, 1H, NH), 4.85 (ddd, $J_{4,3eq}$ = 4.6 Hz, $J_{4,5}$ = 10.1 Hz, 1H, H-4), 4.46 (dd, $J_{9a,8}$ = 2.6 Hz, $J_{9a,9b}$ = 12.1 Hz, 1H, H-9a), 4.09 (dd, $J_{9b,8}$ = 6.1 Hz, 1H, H-9b), 3.99 (bq, $J_{5,6}$ = 10.6 Hz, 1H, H-5), 3.95 (td, $J_{8,7}$ = 5.1 Hz, 1H, H-8), 3.77 (dd, $J_{7,6}$ = 1.2 Hz, 1H, H-7), 3.68 (s, 3H, COOCH_3), 3.60 (dd, 1H, H-6), 2.70 (dd, $J_{3eq,\ 3ax}$ = 12.8 Hz, 1H, H-3eq), 1.94 (bt, 1H, H-3ax), 2.09, 2.03, 1.89 (3s, 9H, NHCOCH_3, COCH_3), 0.17, 0.08 (2s, 18H, Si(CH_3)$_3$). ^{13}C NMR δ 171.1, 170.8, 168.6, 136.9, 128.7, 86.7, 73.0, 72.1, 70.7, 66.4, 52.8, 50.2, 37.6, 23.5, 21.2, 20.9. HR-FAB MS $[M+Na]^+$calcd for $C_{28}H_{45}NO_{10}SSi_2Na$ 666.2200, found 666.2161

Methyl (2-thiophenyl 4,9-di-O-acetyl 5-acetamido-3,5-dideoxy-7,8-di-O-hydroxyl-d-glycero-β-d-galacto-2-nonulopyranosid)onate (10)

From **8**: Dowex H^+ (176.8 mg) was added to a solution of **8** (172 mg, 0.76 mmol) in MeOH (15.2 mL). The residue was allowed to stir for 2.5 h under argon. It was then filtered, concentrated *in vacuo*, and purified by column chromatography on silica gel (acetone/hexane, 10%) to afford **10** (277 mg, 0.55 mmol, 73%)

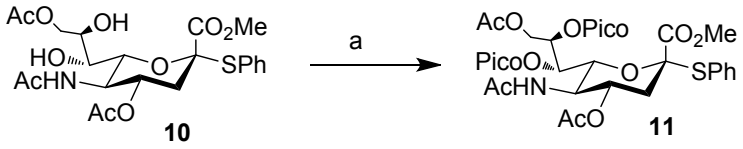


From **1**: to a solution of **1** (200 mg, 481 mmol) in dry pyridine (9.6 mL), Ac_2O (4.81mmol, 0.46 mL, 10 equiv) was added dropwise. The reaction was allowed to stir for 3.5 h under argon at RT. The reaction was quenched with MeOH until no heat was detected, and the crude mixture was concentrated *in vacuo*. The compound was then purified by column chromatography on silica gel (acetone/dichloromethane, 10%) to afford **10** (150 mg, 0.301 mmol, 62%).

Analytical Data R_f = 0.17 (acetone/hexane, 2/5 v/v); $[\alpha]^{23}_D$ = +23.75 (*c* = 1, $CHCl_3$); ^{1}H NMR ($CHCl_3$) δ 7.56-7.51 (2H, aromatic), 7.47-7.30 (3H, aromatic), 5.99 (bs, 1H, NH), 4.90 (ddd, $J_{4,3eq}$ = 4.9 Hz, $J_{4,5}$ = 10.7 Hz, 1H, H-4), 4.77 (d, $J_{7,OH}$ = 4.3 Hz, 1H, OH-7), 4.42 (bd, $J_{9a,9b}$ = 11.4 Hz, 1H, H-9a), 4.14 (dd, $J_{9b,8}$ = 6.7 Hz, 1H, H-9b), 4.05-3.96 (m, 2H, H-5, H-8), 3.67 (s, 3H, COOCH_3), 3.43 (bdd, $J_{7,6}$ = 1.4 Hz, $J_{7,8}$ = 9.4 Hz, 1H, H-7), 3.33 (dd, $J_{5,6}$ = 10.5 Hz, 1H, H-6), 3.27 (d, $J_{8,OH}$ = 4.0 Hz, 1H, OH-8), 2.85 (dd, $J_{3eq,\ 3ax}$ = 13.0 Hz, 1H, H-3eq), 2.15 (m, 1H, H-3ax), 2.11, 2.10, 1.96 (s, 9H, NHCOCH_3, COCH_3). ^{13}C NMR δ 172.8, 171.2, 169.2, 136.9, 130.5, 128.0, 85.9, 69.3, 69,3, 68.9, 66.1, 53.3, 51.3, 37.2, 30.9, 23.0, 21.0, 21.0. HR-FAB MS $[M+Na]^+$calcd for $C_{22}H_{29}NO_{10}SNa$ 522.1409, found 522.1411

Methyl (2-thiophenyl 4,9-di-O-aceyl-5-acetamido-3,5-dideoxy-7,8-di-O-picoloyl-d-glycero-β-d-galacto-2-nonulopyranosid)onate (11)

DCC (419.3 mg, 2.03 mmol, 8 equiv), DMAP (24.8 mg, 0.2 mmol, 0.8 equiv), and Picolinic acid (250.13 mg, 2.03 mmol, equiv) were added to a solution of **10** (127 mg, 0.254 mmol) in CH_2Cl_2 (3.81 mL). The mixture was stirred under argon for 3 h at rt. The resulting residue was then diluted with CH_2Cl_2 and washed with brine (15 mL), sat. aq. Sodium bicarbonate (15 mL), and brine (15 mL). The organic phase was dried over MgSO4, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography on silica gel (acetone/methylene chloride, 10% gradient) to afford **5b** (120 mg, 0.169 mmol, 67%).



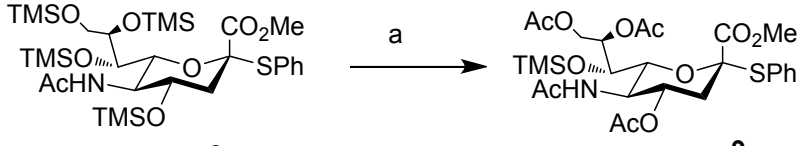
a) Picolinic acid, DCC, DMAP, 67%

Analytical Data R_f = 0.20 (acetone/dichloromethane, 2/5 v/v); $[\alpha]^{23}_D$ = +54.64 (*c* = 1, $CHCl_3$); ^{1}H NMR ($CHCl_3$) δ 8.81 (dt, J= 4.5 Hz, 1H, aromatic), 8.75 (dt, J= 4.4 Hz, 1H, aromatic), 8.12 (bdd, J= 3.3 Hz, J= 7.8 Hz, 2H, aromatic), 7.92-7.82 (m, 2H, aromatic), 7.62-7.57 (m, 2H, aromatic), 7.54-7.47 (m, 2H, aromatic), 7.45-7.33 (m, 3H, aromatic), 5.90 (dd, $J_{7,6}$ = 1.7 Hz, $J_{7,8}$ = 7.3 Hz, 1H, H-7), 5.85-5.77 (m, 2H, NH, H-8), 4.95 (ddd, $J_{4,3eq}$ = 4.7 Hz, $J_{4,5}$ = 10.8 Hz,1H, H-4), 4.66 (dd, $J_{9a,9b}$ = 12.6 Hz, $J_{9a,8}$ = 2.8 Hz, 1H, H-9a), 4.43 (dd, $J_{9b,8}$ = 5.7 Hz, 1H, H-9b), 4.17 (dd, $J_{5,6}$ = 10.8 Hz, 1H, H-6), 3.99 (bq, 1H, H-5), 2.83 (dd, $J_{3eq,\ 3ax}$ = 12.9 Hz, 1H, H-3eq), 1.99, 1.98, 1.96, 1.88 (s, 10H, H-3ax, NHCOCH_3, COCH_3). ^{13}C NMR δ 170.7, 170.7, 170.3, 168.1, 163.8, 163.7, 150.2, 149.7, 147.7, 147.4, 137.2, 137.1, 129.9, 128.7, 125.7, 125.6, 87.7, 74.7, 71.2, 69.6, 69.3, 62.1, 52.5, 49.8, 38.0, 30.9, 29.3, 23.2, 20.8. HR-FAB MS $[M+Na]^+$calcd for $C_{34}H_{35}N_3O_{12}SNa$ 732.1838, found 732.1836.

<u>Synthesis of C-7 Picoloyl 13</u>

Methyl (2-thiophenyl 4,8,9-tri-O-aceyl-5-acetamido-3,5-dideoxy-7-O-trimethylsilyl -d-glycero-β-d-galacto-2-nonulopyranosid)onate (9)

To a solution of **2** (100mg, 0.142 mmol) in dry pyridine (1.5 mL), Ac_2O (2.84 mmol, 0.27 mL, 20 equiv) was added followed by DMAP (3.42 mg, 0.028 mmol, 0.2 equiv). The reaction was brought to 40°C and allowed to stir for 20 h under argon. The reaction was then brought to RT and quenched with MeOH until no heat was detected, MeOH removed *in vacuo*. The crude mixture was diluted with CH_2Cl_2 and washed with brine (15mL), sat. aq. sodium bicarbonate (15mL), and brine (15mL). The organic phase was dried over MgSO4, filtered, concentrated *in vacuo*. The compound was then purified by column chromatography on silica gel (acetone/hexane, 10%) to afford **9** (55 mg, 0.089, 63%)



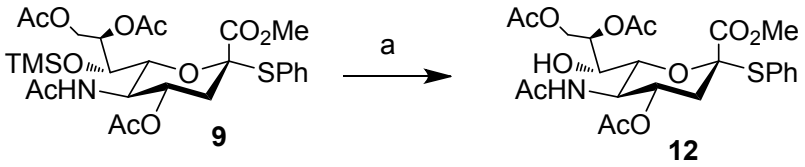
a) Ac_2O, DMAP, py, 63%

Analytical Data: R_f = 0.28 (acetone/hexane, 2/3 v/v); $[\alpha]^{23}_D$ = +10.26 (*c* = 1, $CHCl_3$); H NMR ($CHCl_3$) δ 7.59 – 7.51 (m, 2H, aromatic), 7.43 – 7.36 (m, 1H, aromatic), 7.36 – 7.30 (m, 2H, aromatic), 5.16 (d, $J_{NH,5}$ = 10.0 Hz, 1H, NH), 5.12 (ddd, $J_{7,8}$ = 7.1 Hz, $J_{8.9a}$ = 4.4 Hz, $J_{8,9b}$ = 2.4 Hz, 1H, H-8), 4.81 (ddd, $J_{4,5}$ = 11.9 Hz, 1H, H-4), 4.67 (dd, 1H, H-9b), 4.29 (dd, $J_{9a,9b}$ = 12.4 Hz, 1H, H-9a), 4.10 – 3.97 (m, 2H, H-5, H-7),

3.63 (s, 1H, OCH_3), 3.57 (dd, $J_{6,7}$ = 10.6 Hz, $J_{5,6}$ = 1.2 Hz, 1H, H-6), 2.71 (dd, J = 12.8 Hz, $J_{3eq,4}$ = 4.7 Hz, 1H, H-3eq), 2.08, 2.05, 2.03 (s x3, 9H, $N(COCH_3)_2$, $OCOCH_3$), 1.96 (t, $J_{3ax,4}$ = 10.2 Hz 1H, H-3ax), 1.89 (s, 3H, $OCOCH_3$), 0.18 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR δ 171.1, 170.6, 170.3, 170.1, 168.6, 136.6, 129.8, 128.8, 128.8, 87.4, 77.2, 76.5, 73.9, 70.7, 70.1, 62.7, 52.9, 49.8, 37.6, 23.4, 21.2, 20.9, 20.9. HR-FAB MS $[M+Na]^+$calcd for $C_{27}H_{39}NO_{11}SSiNa$ 636.1913, found 636.1890

Methyl (2-thiophenyl 4,8,9-tri-O-aceyl-5-acetamido-7-O-hydroxyl -3,5-dideoxy-D-glycero-β-D-galacto-2-nonulopyranosid)onate (12)

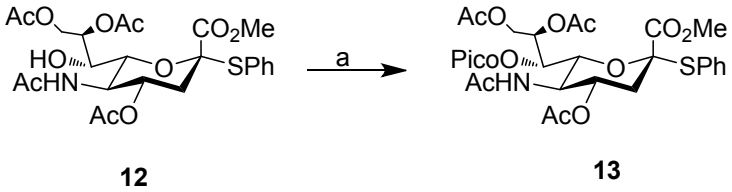
Dowex H^+(104.1mg) was added to a solution of **9** (289.1 mg, 0.47 mmol) in MeOH (9.42 mL). The residue was allowed to stir for 1 h under argon. It was then filtered, concentrated *in vacuo*, yielding **12** (209.2 mg, 0.39, 82%).



a) Dowex, H^+, MeOH, 82%;

Analytical Data: R_f = 0.49 (acetone/hexane, 1/1 v/v); $[\alpha]^{23}_D$ = -15.37 ; ^{1}H NMR ($CHCl_3$) δ 7.53-7.48 (m, 2H, aromatic), 7.44 – 7.29 (m, 3H, aromatic), 5.97 (d, $J_{5,NH}$ = 8.0 Hz, 1H, NH), 5.19 (ddd, $J_{7,8}$ = 9.1, $J_{8,9a}$ = 4.1, $J_{8,9b}$ = 2.4 Hz, 1H, H-8), 4.90 (td, $J_{3ax,4}$ = 11.7 Hz, 1H, H-4), 4.65 (dd, 1H, H-9b), 4.55 (d, $J_{OH,8}$ = 3.8 Hz, 1H, OH-8), 4.34 (dd, $J_{9a,9b}$ = 12.2 Hz, 1H, H-9a), 3.99 (td, $J_{5,6}$ = 10.5 Hz, 1H, H-5), 3.69 (d, $J_{6,7}$ = 8.9 Hz, 1H, H-7), 3.53 – 3.41 (m, 4H, OCH_3, H-6), 2.83 (dd, $J_{3ax,3eq}$ = 12.8 Hz, $J_{3eq,4}$ = 4.7 Hz, 1H, H-3eq), 2.10, 2.05, 1.99, 1.97 (s x4, 13H, $NCOCH_3$, $OCOCH_3$, H-3ax). ^{13}C NMR δ 172.6, 172.3, 170.8, 169.6, 167.8, 136.2, 129.7, 128.9, 128.7, 87.3, 75.7, 70.0, 69.2, 66.9, 62.9, 52.5, 51.7, 37.9, 29.3, 23.1, 21.0, 21.0, 20.9. HR-FAB MS [M+Na]+calcd for $C_{24}H_{31}NO_{11}SNa$ 564.1508, found 564.1514.

Methyl (2-thiophenyl 4,8,9-tri-O-aceyl-5-acetamido-3,5-dideoxy-7-O-picoloyl-D-glycero-β-D-galacto-2-nonulopyranosid)onate (13)



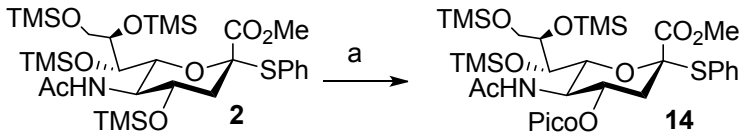
a) Picolinic acid, DCC, DMAP, 92%

DCC (159.2 mg, .77 mmol, 4 equiv), DMAP (9.4 mg, .077 mmol, 0.4 equiv), and Picolinic acid (95.03 mg, 0.77 mmol, 4 equiv) were added to a solution of **12** (209.2 mg, 0.39 mmol) in CH_2Cl_2 (6.27 mL). The mixture was stirred under argon for 2 h at rt. The resulting residue was then diluted with CH_2Cl_2 and washed with brine (15 mL), sat. aq. Sodium bicarbonate (15 mL), and brine (15 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, placed in the freezer overnight, and filtered in the morning and then purified by column chromatography on silica gel (acetone/hexane, 10% gradient) to afford **13** (229.3 mg, 0.35 mmol, 92%). Analytical Data for **13**: R_f = 0.5 (acetone/toluene, 3/2 v/v); $[\alpha]^{21}_D$ = + 29.68 (*c* = 1, $CHCl_3$) ^{1}H NMR ($CHCl_3$) δ 8.83 (bd, *J* = 4.6 Hz, 1H, aromatic), 8.10 (bd, *J* = 8.0 Hz, 1H, aromatic), 7.90 (td, *J* = 7.7 Hz, *J* = 1.6 Hz, 1H, aromatic), 7.60 – 7.50 (m, 3H, aromatic), 7.45 – 7.31 (m, 3H, aromatic), 5.65 (dd, $J_{7,8}$ = 6.9 Hz, 1H, H-7), 5.48-5.39 (m, 2H, NH, H-8), 5.01 (ddd, $J_{4,5}$ = 10.5 Heq, $J_{3ax,4}$ = 11.3 Hz, 1H, H-4), 4.52 (dd, $J_{8,9a}$ = 3.1 Hz, $J_{9a,9b}$ = 12.5 Hz, 1H, H-9a), 4.26 (dd, $J_{8,9b}$ = 5.4 Hz, 1H, H-9b), 4.16 (dd, $J_{5,6}$ = 10.9 Hz, $J_{6,7}$ = 1.8 Hz, 1H, H-6), 3.86 (dd, $J_{5,NH}$

= 9.8 Hz, 1H, H-5), 3.61 (s, 3H, OCH_3), 2.85 (dd, $J_{3ax,3eq}$ = 12.8 Hz, $J_{3eq,4}$ = 4.7 Hz, 1H, H-3eq), 2.08, 2.03, 2.00, 1.97, 1.89 (s x4, 13H, $NCOCH_3$, $OCOCH_3$, H-3ax). ^{13}C NMR δ 170.8, 170.6, 170.2, 170.2, 167.9, 163.6, 150.0, 147.1, 137.4, 136.6, 129.9, 128.9, 128.6, 127.2, 125.6, 87.5, 74.4, 69.8, 69.3, 69.2, 62.1, 52.9, 50.1, 38.2, 21.0, 20.8, 20.8. HR-FAB MS $[M+Na]^+$calcd for $C_{30}H_{34}N_2O_{12}SNa$ 669.1722, found 669.1749.

Synthesis of C-4 Picoloyl 14

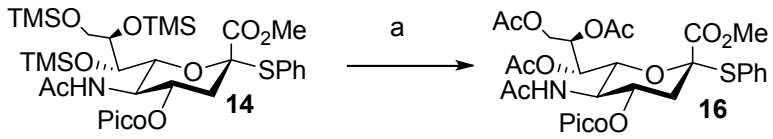
Methyl (2-thiophenyl 4-O-picoloyl 7,8,9-tri-O-trimethylsilyl 5-acetamido-3,5-dideoxy-d-glycero-β-d-galacto-2-nonulopyranosid)onate



To a solution of **2** (200mg, 0.284 mmol) in dry pyridine (6mL), Picolinic Acid (87.9 mg, 0.71 mmol, 2.5 eq), EDC (110 mg, 0.71 mmol, 2.5 equiv) and DMAP (8.7 mg, 0.07 mmol) were added and stirred at room temperature under argon. Every 1.5 hours an additional 2.5 equivalents of Picolinic acid and EDC were added to solution for a total of 4.5 hours. The resulting residue was then diluted with CH_2Cl_2 and washed with brine (15 mL), sat. aq. sodium bicarbonate (15 mL), and brine (15 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was then purified by column chromatography on silica gel (acetone/hexane, 10% gradient) to afford **14** (129 mg, 0.097 mmol, 62%).

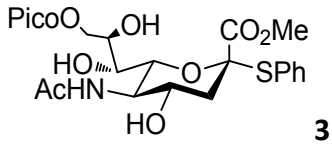
Analytical Data R_f=0.69 (acetone/hexane, 2/3 v/v); $[\alpha]^{23}_D$ = +19.616 (*c* = 1, $CHCl_3$); ^{1}H NMR ($CHCl_3$) δ 8.79-8.72 (m, 1H, aromatic), 8.07 (bd, 1H, aromatic), 7.85-7.80 (td, 1H aromatic), 7.63-7.59 (m, 2H, aromatic), 7.48-7.43 (m, 1H, aromatic) 7.41 – 7.29 (m, 3H, aromatic), 5.45-5.37 (bs, 1H, NH), 5.15 (ddd, $J_{5,6}$ = 4.3 Hz, 1H, H-4), 4.17 (dd, $J_{5,6}$ = 10.0 Hz, 1H, H5), 4.01(dd, $J_{8,9a}$ = 2.6 Hz, $J_{9a,9b}$ = 10.6 Hz 2H, H-9a), 3.92-3.84 (m, 2H, H-8, H-6), 3.78 (dd, $J_{6,7}$ = 1.9 Hz, 1H, H-7), 3.71 (s, 3H, $COOCH_3$), 3.54 (dd, , 1H, H-9b), 2.89 (dd, $J_{4,3eq.}$ = 4.3 Hz, $J_{3eq.,3ax.}$ = 12.6 Hz, 1H, H-3eq.), 1.79 (s, 3H, $NHCOCH_3$), 2.05 (t, 1H, H-3ax), 0.18,0.16, 0.12 (3s, 27H, $Si(CH_3)_3$). ^{13}C NMR δ 170.0, 168.7, 168.5, 164.4, 149.9, 148.3, 147.3, 136.8, 136.6, 129.6, 129.1, 128.8, 128.7, 127.0, 125.7, 86.8, 75.3, 74.7, 73.5, 73.1, 72.6, 72.0, 64.2, 63.1, 52.8, 49.9, 37.8, 37.6, 23.5, 23.3, 19.1, 14.1, 1.3, 0.6. HR-FAB MS $[M+Na]^+$calcd for $C_{33}H_{52}N_2O_9SSi_3Na$ 759.2591, found 759.2610.

Methyl (2-thiophenyl 4-O-picoloyl 7,8,9-tri-O-Acetyl 5-acetamido-3,5-dideoxy-d-glycero-β-d-galacto-2-nonulopyranosid)onate (16)



a) Ac_2O, DMAP, Pyridine

To a solution of **14** (170 mg, 0.23 mmol) in dry pyridine (2.5 mL), Ac_2O (1.3 mL) was added dropwise and DMAP (0.05 mmol, 5.6 mg, 0.2 equiv) was added. The reaction was allowed to stir for 16 h under argon at 40°C. The reaction was quenched with MeOH until no heat was detected, and the crude mixture was concentrated *in vacuo*. The compound was then purified by column chromatography on silica gel (acetone/dichloromethane, 10%) to afford **16** (110 mg, 0.17 mmol, 74%). The compound isolated matched previously published data.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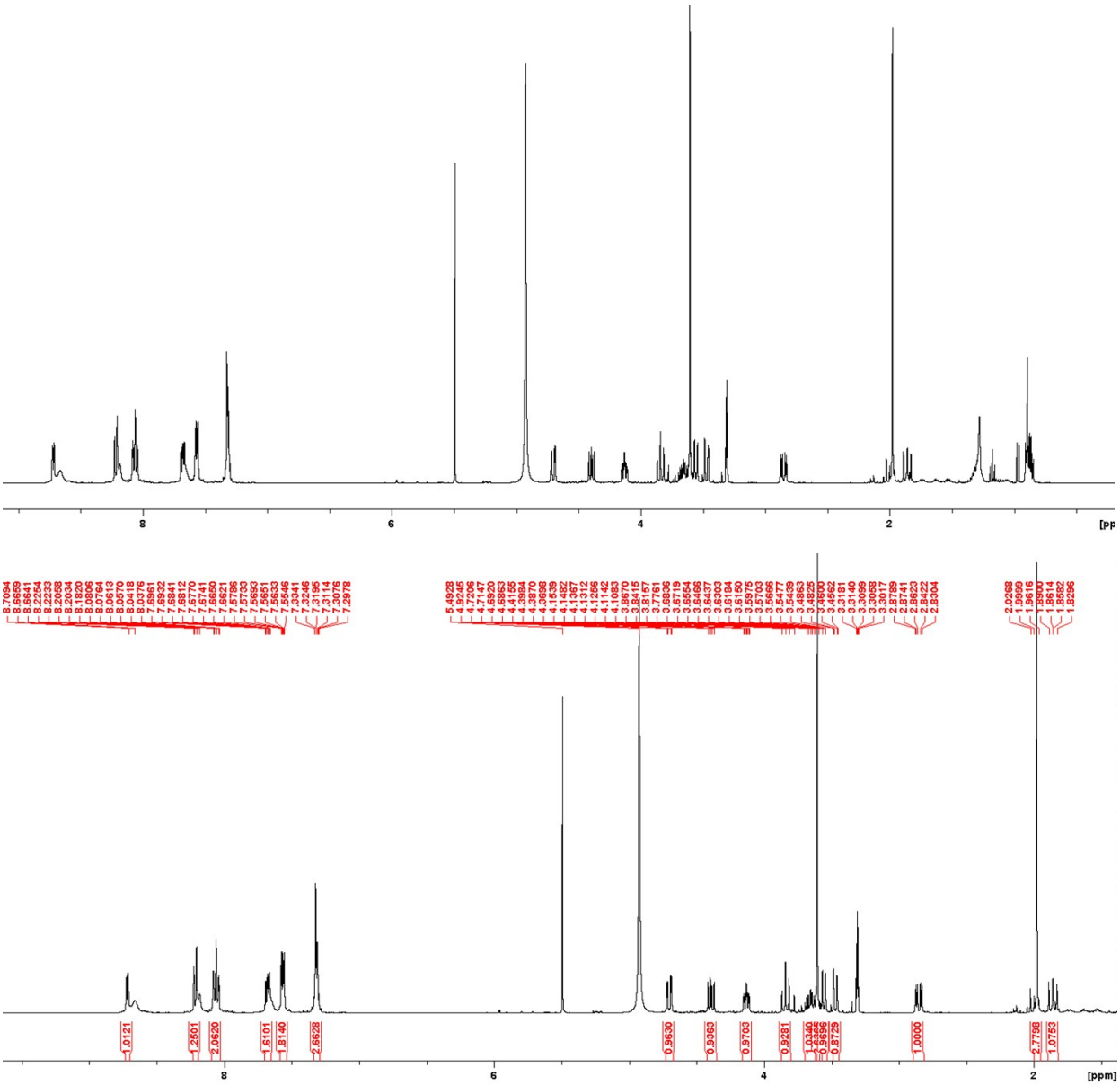
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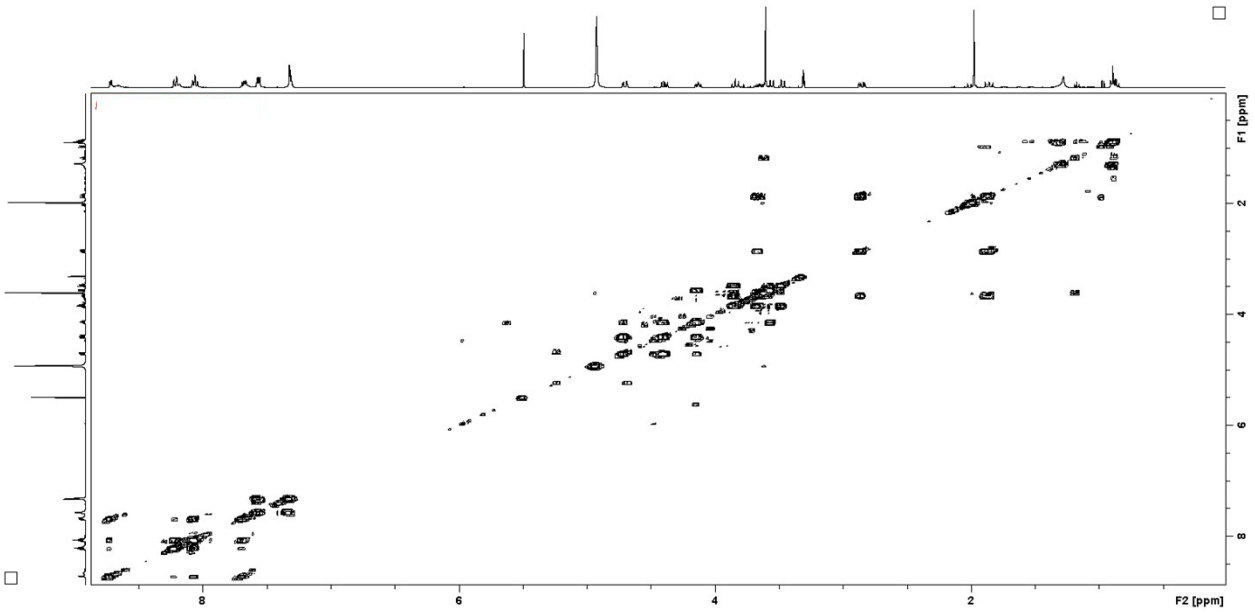
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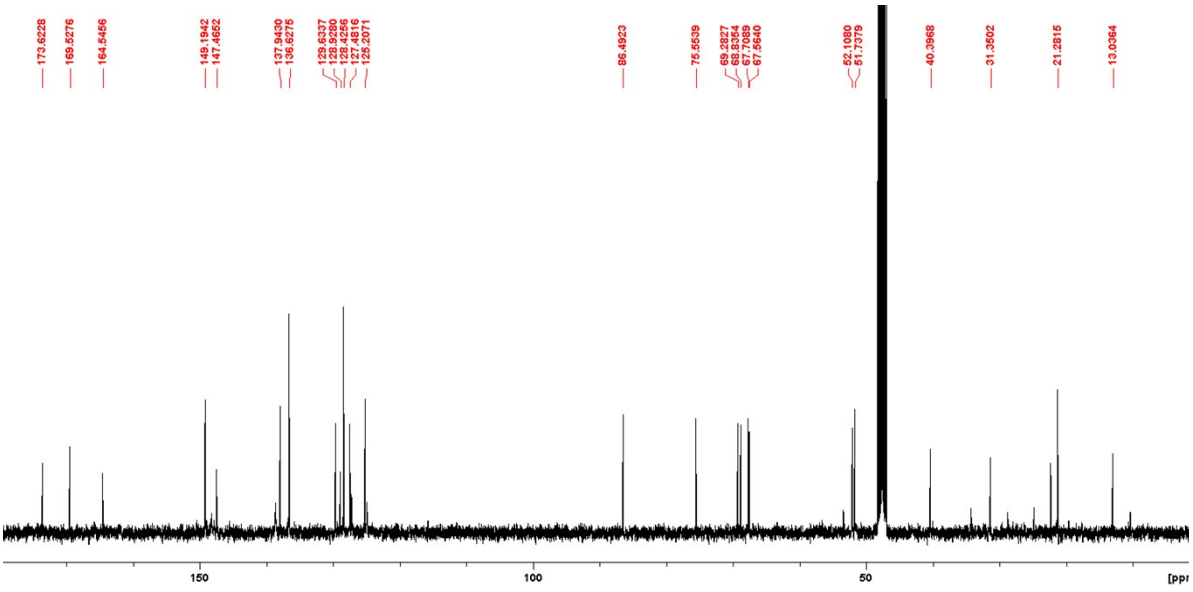
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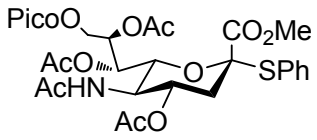
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CO2Me
AcO
O
SPh
AcHN
AcO

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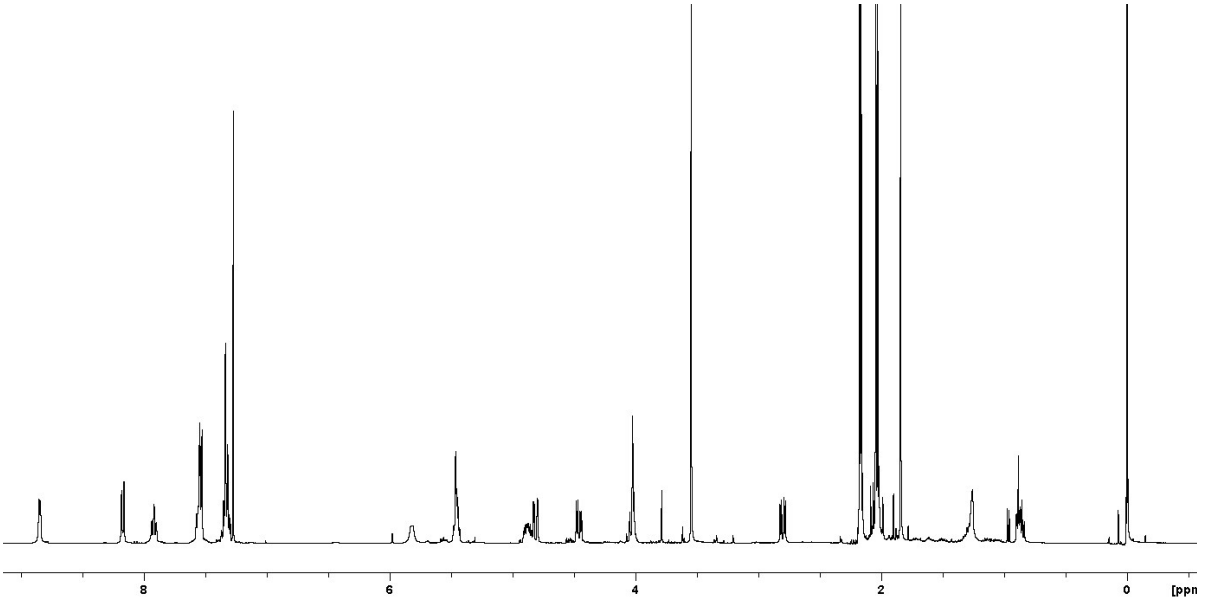
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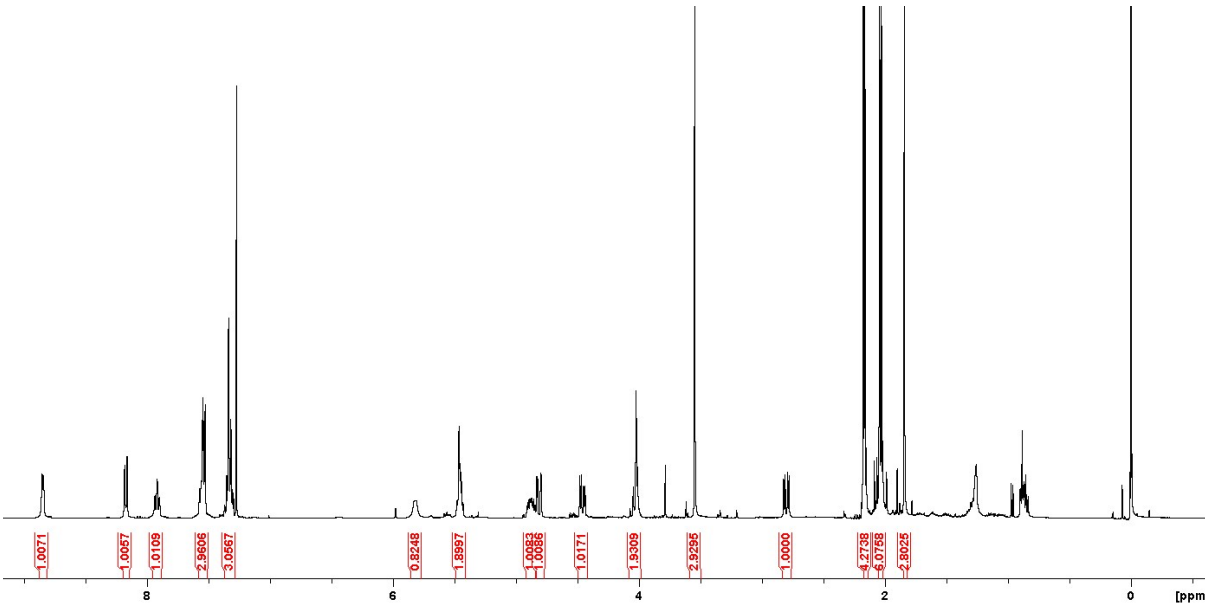
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6
4
2
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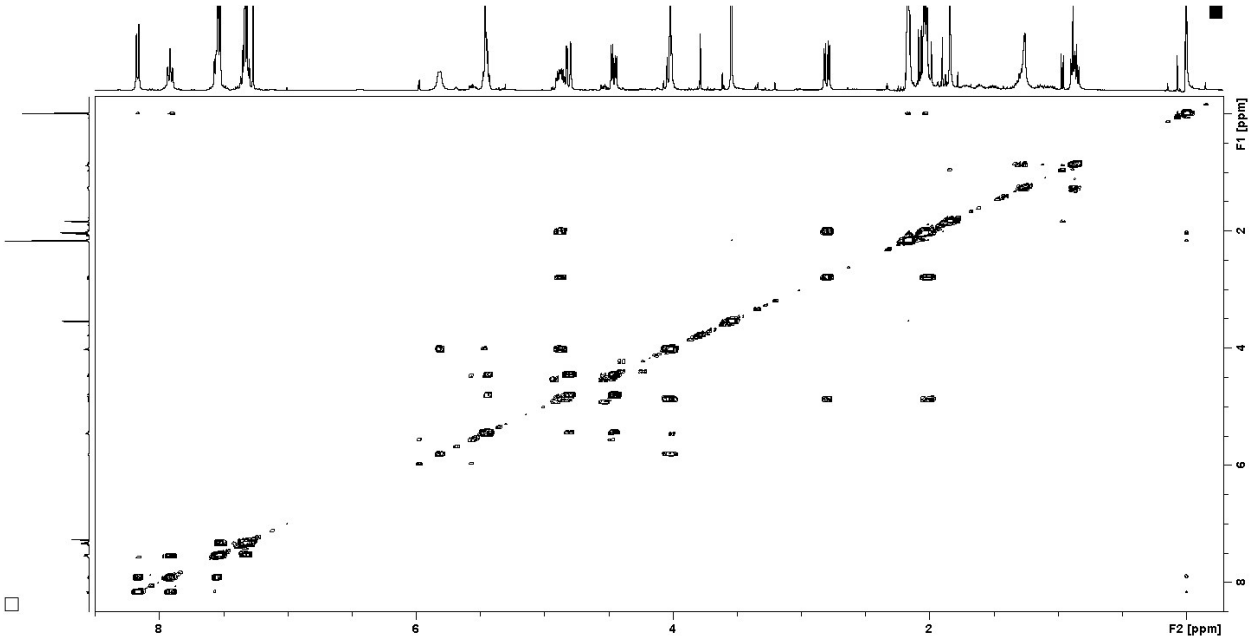
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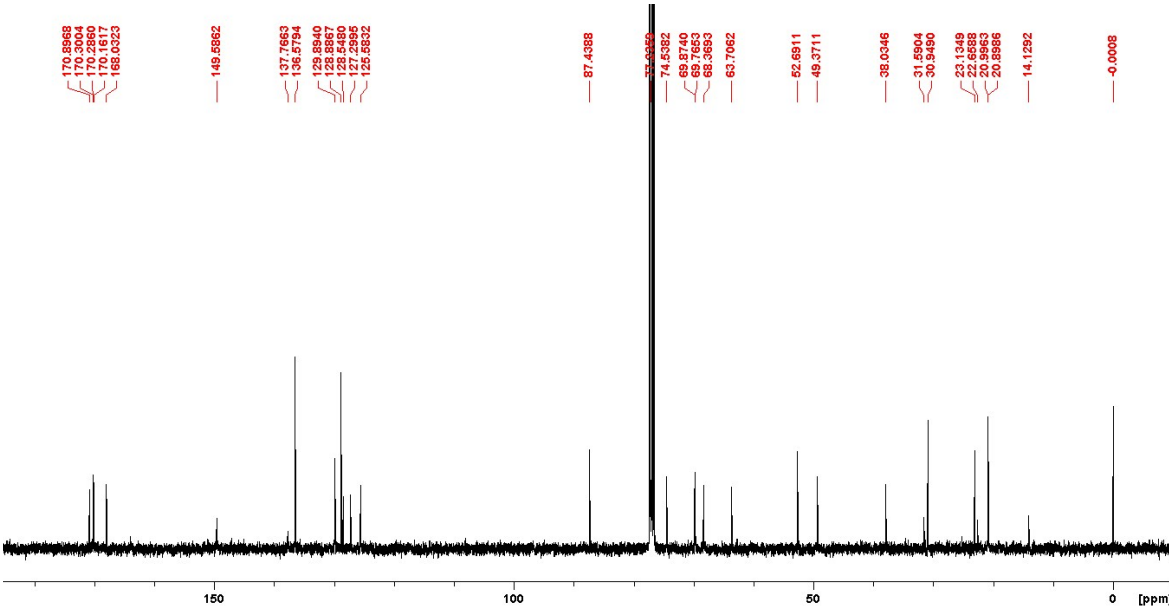
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68.3853
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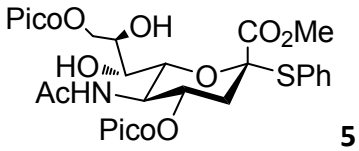

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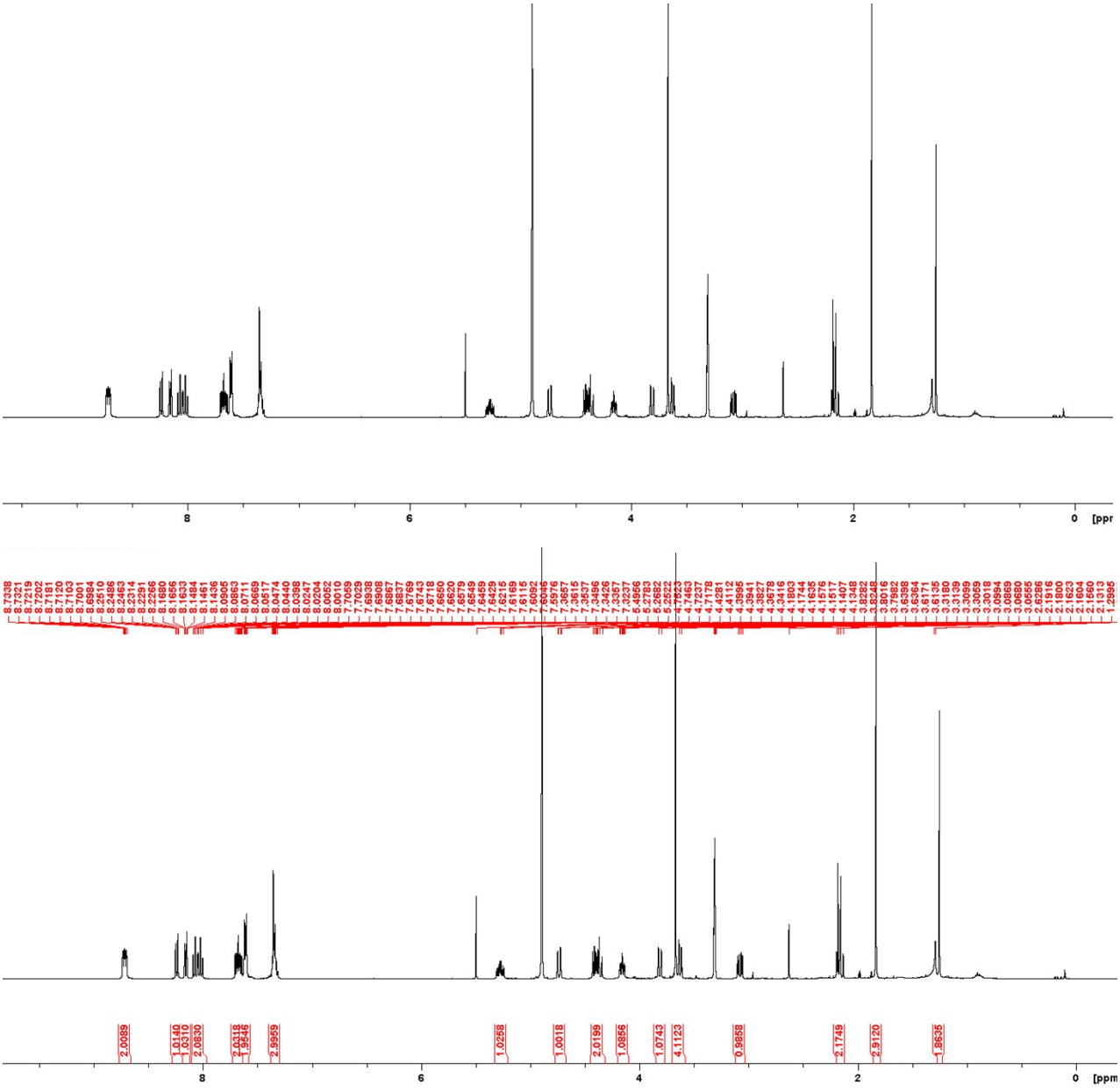

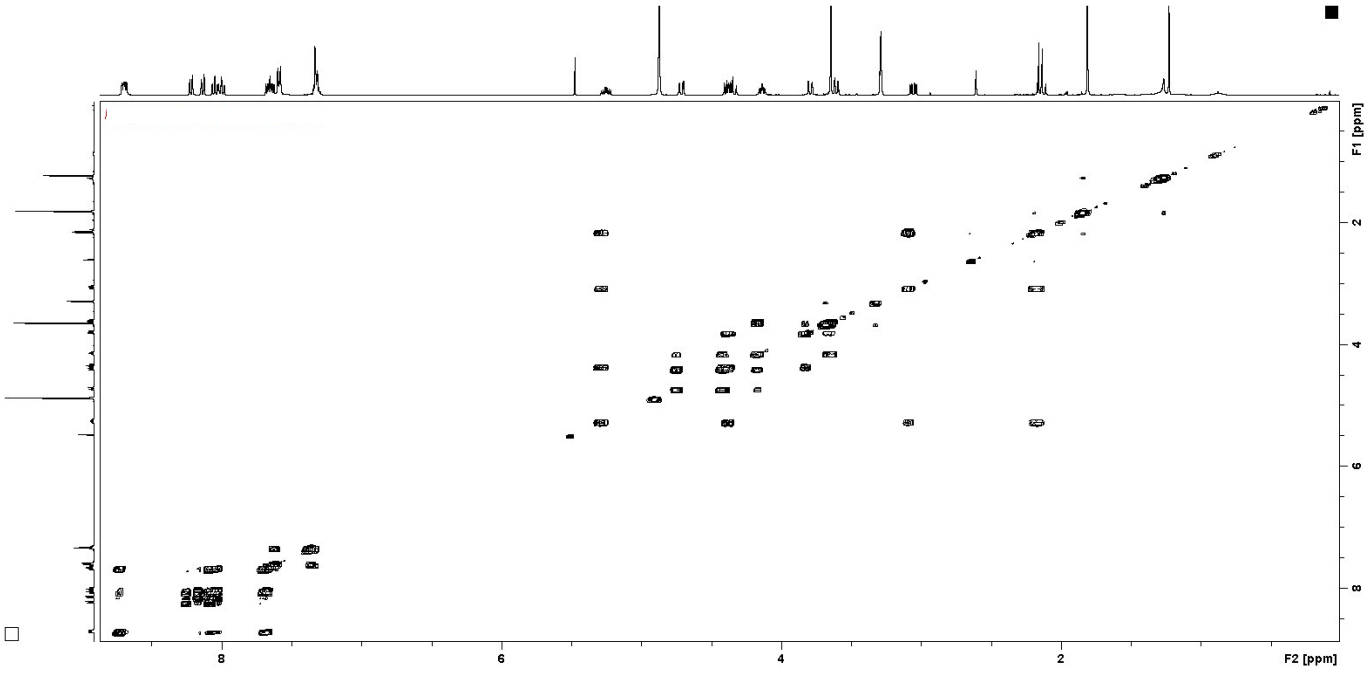
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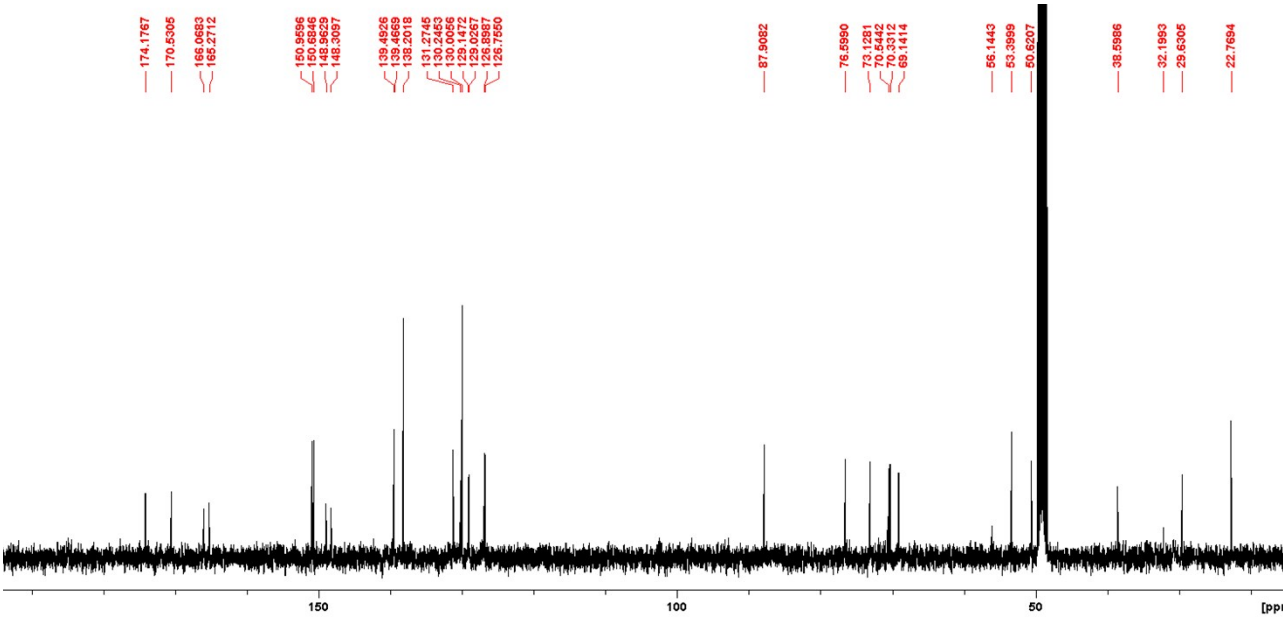
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130.0066
129.1472
129.0267
128.8987
128.7550
87.9082
76.5990
73.1281
70.5442
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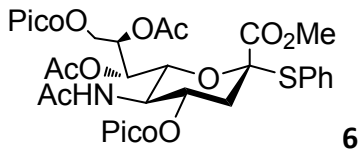

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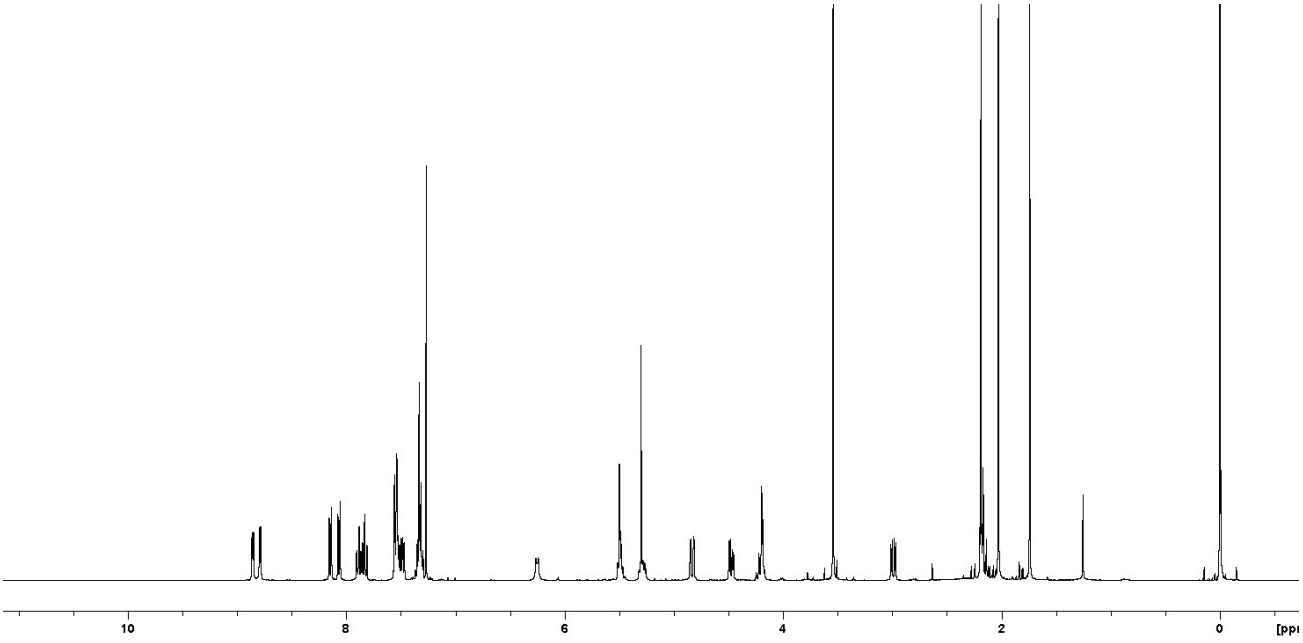

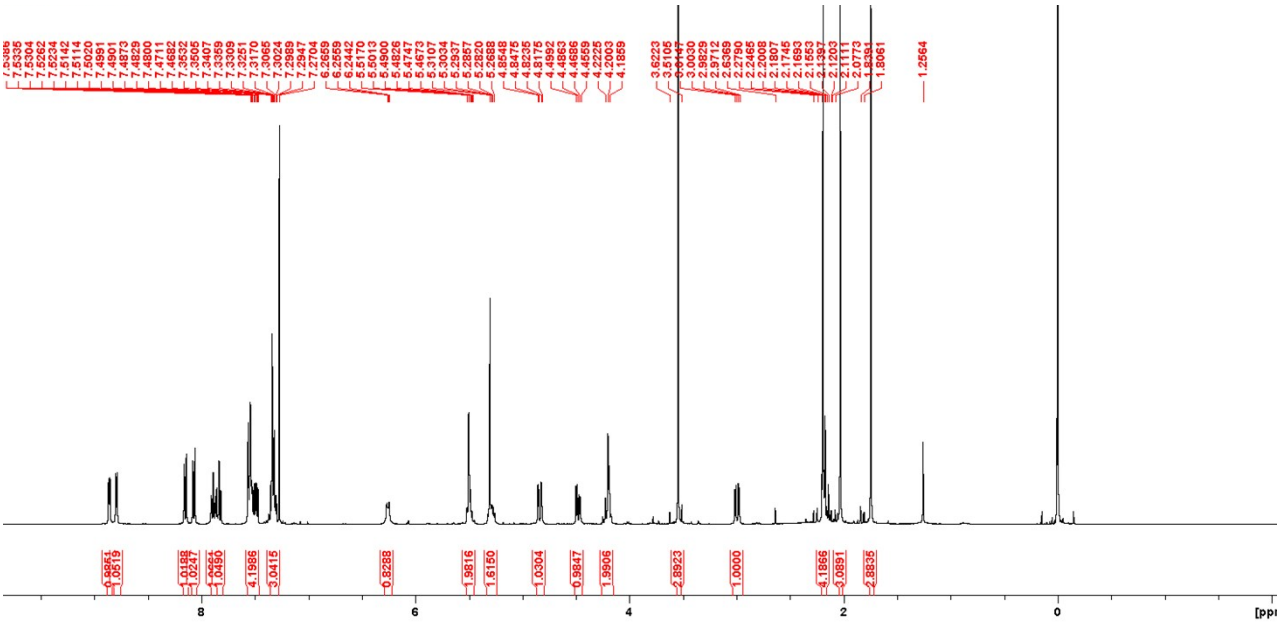

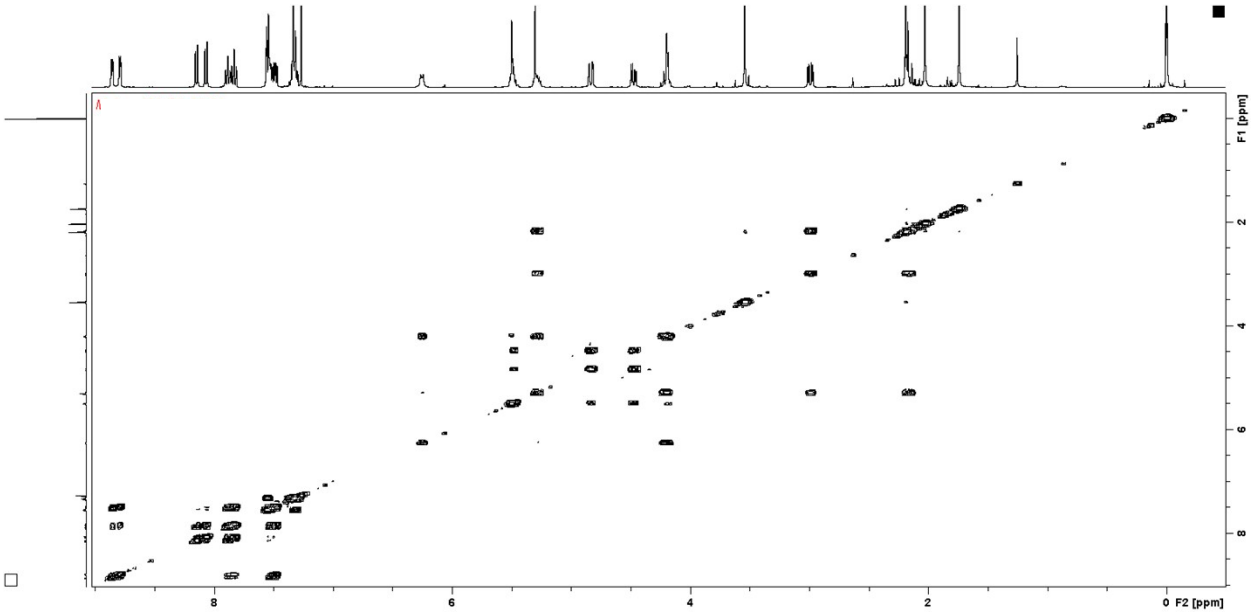
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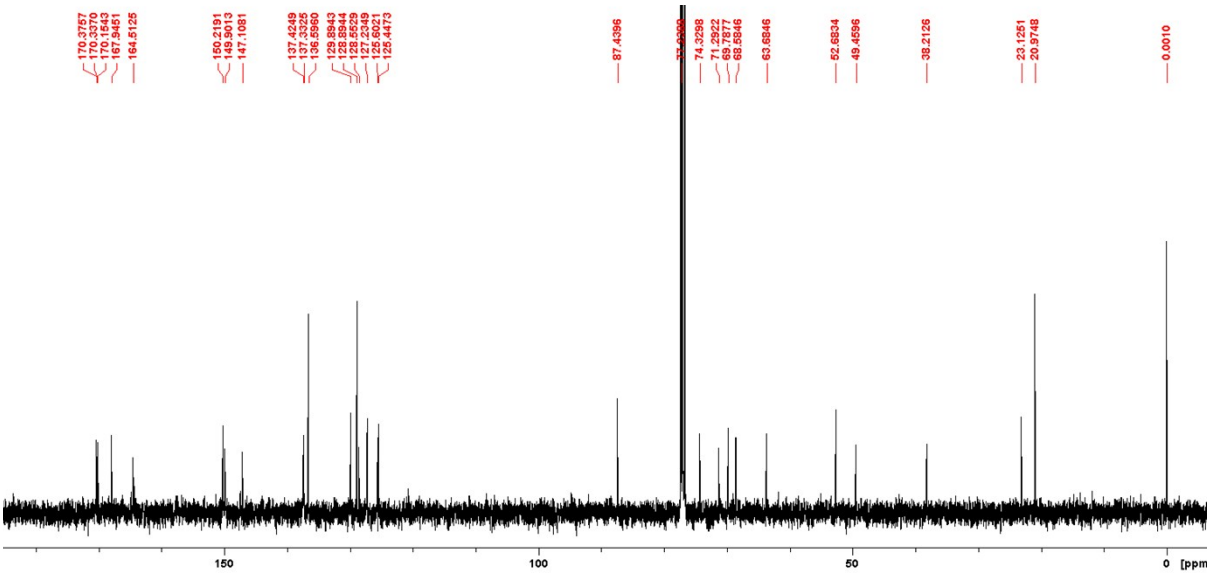
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127.2349
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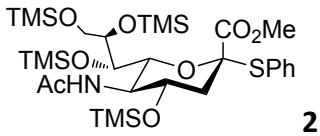

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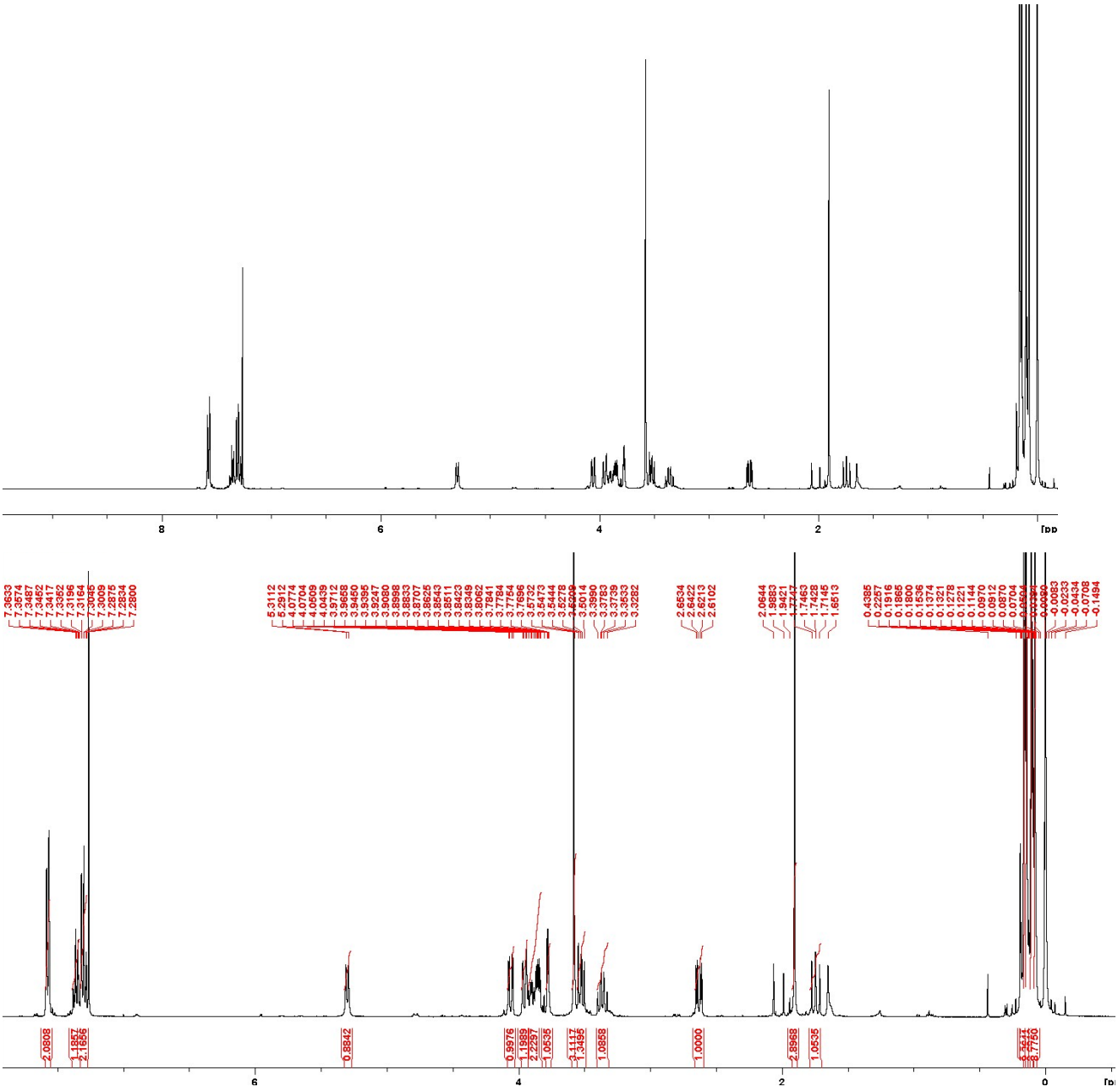

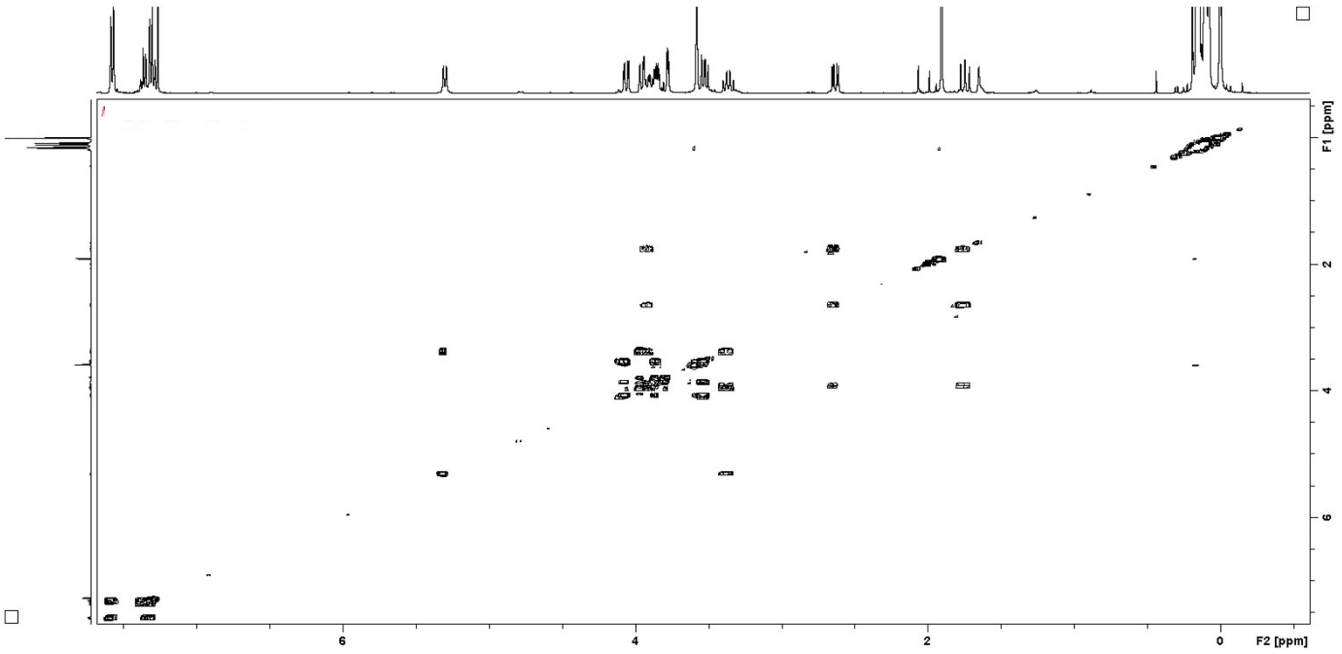
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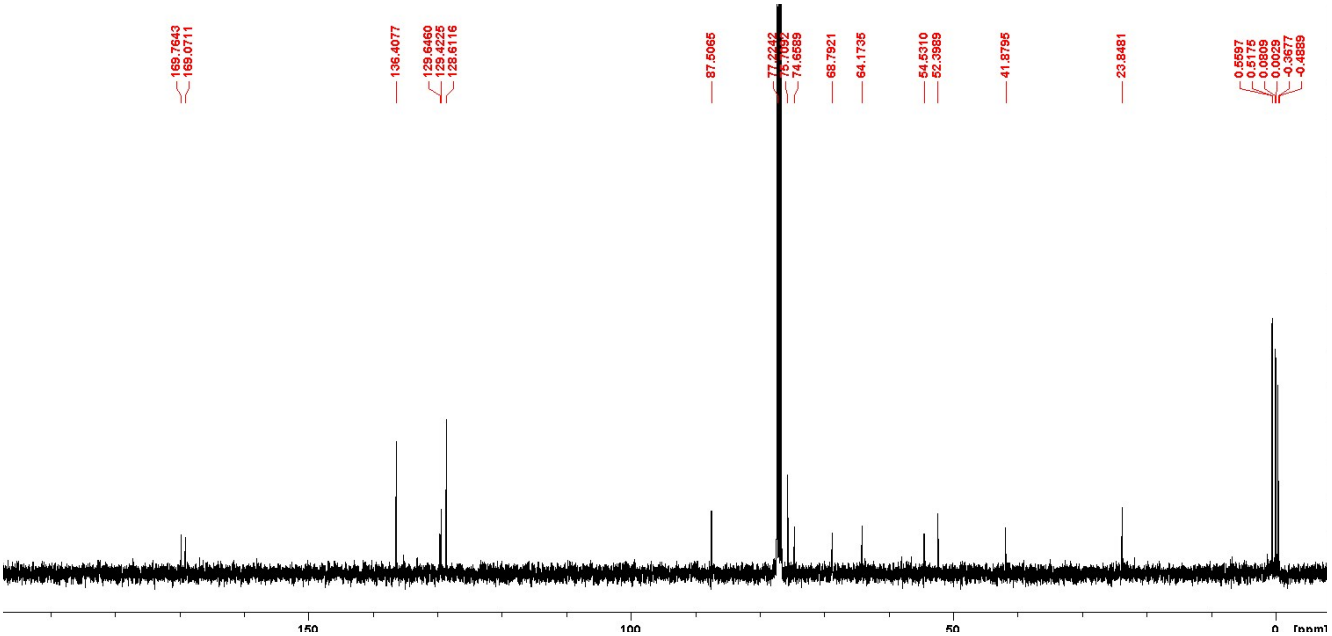
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68.7921
64.1735
54.5310
52.3989
41.8795
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100
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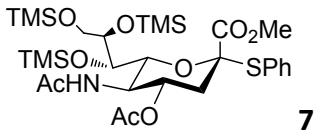
0 [ppm]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TMSO
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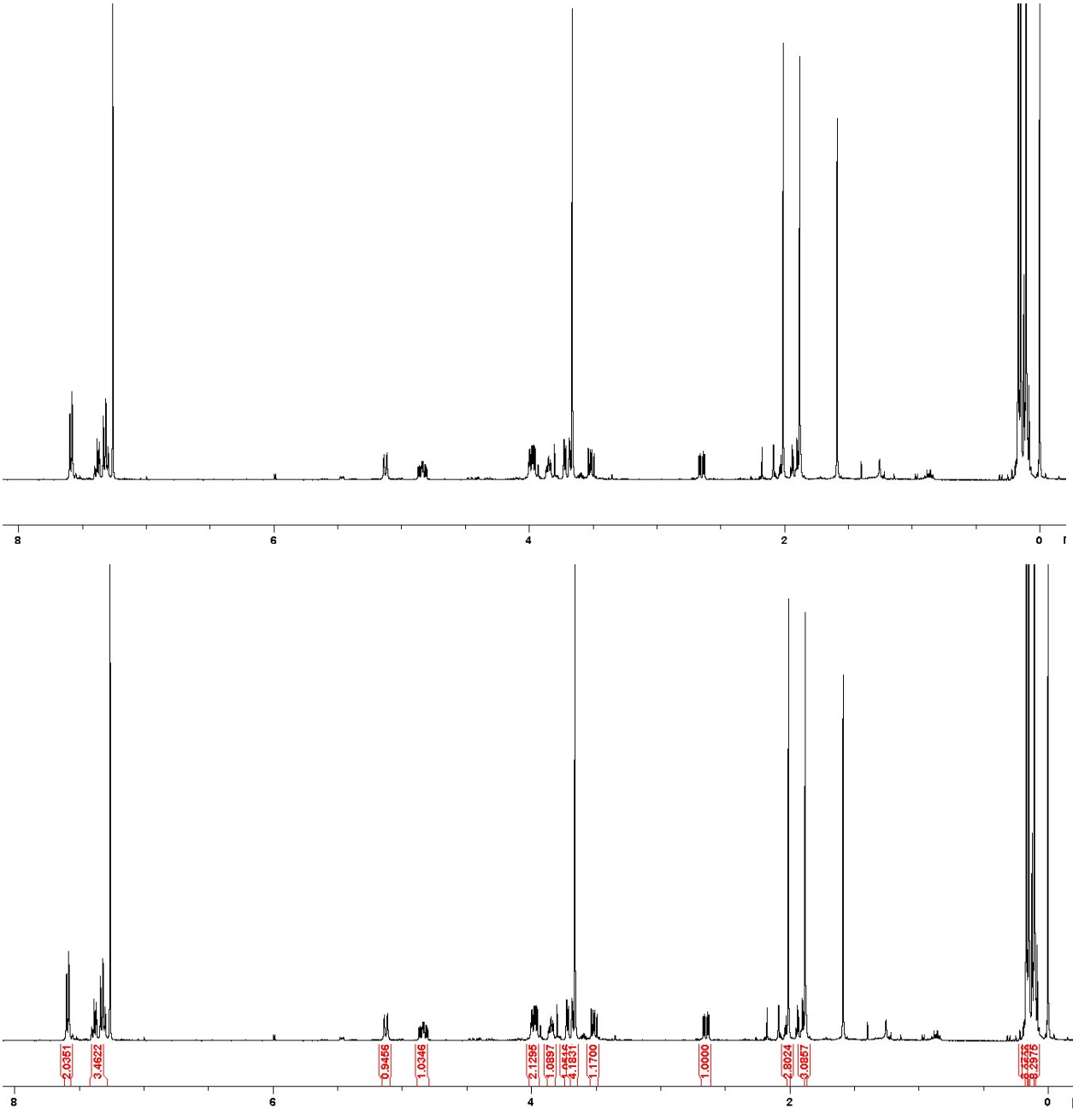
SPh
AcHN
AcO

7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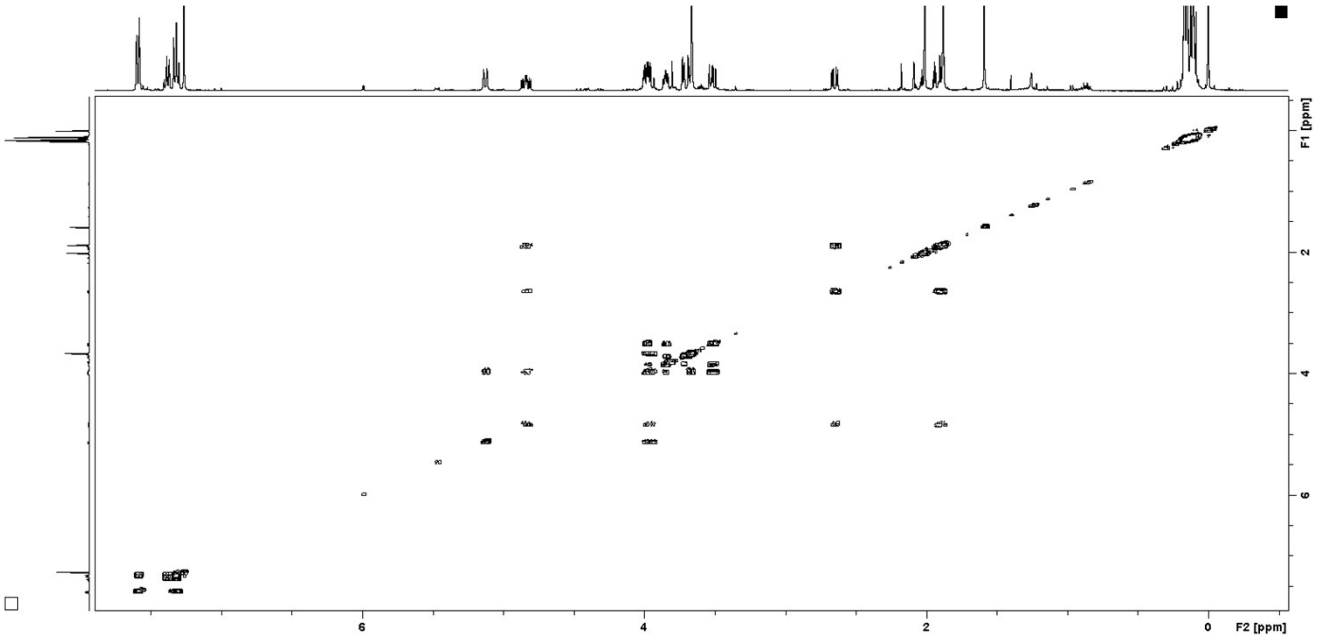
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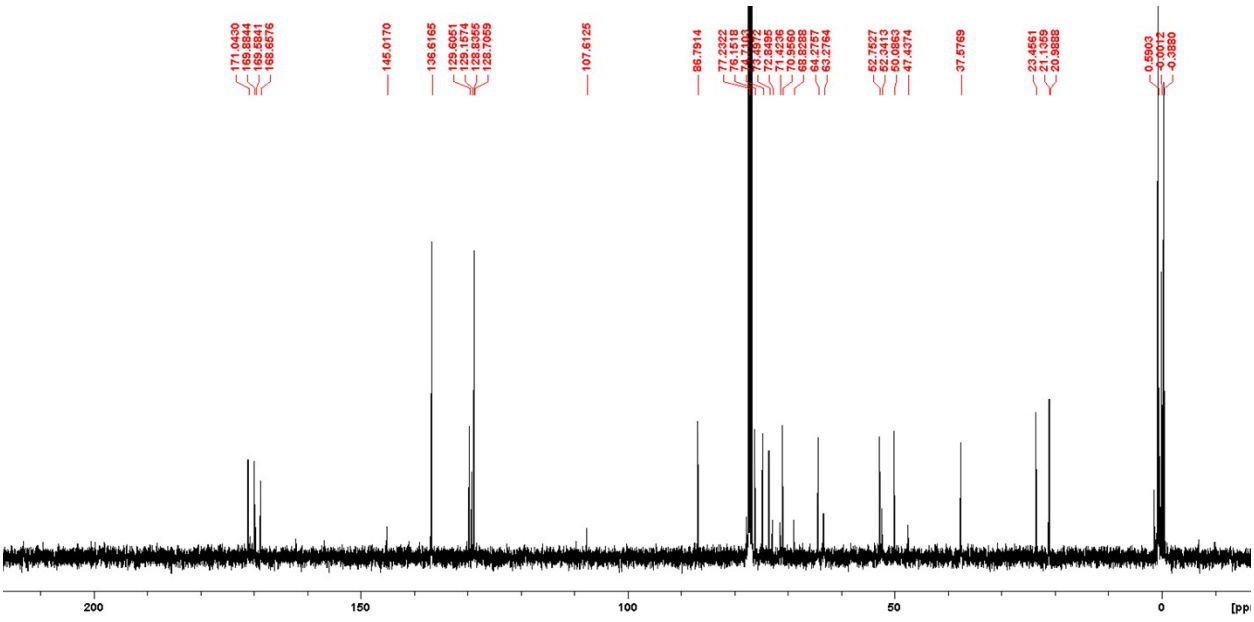
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63.2764
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50.0863
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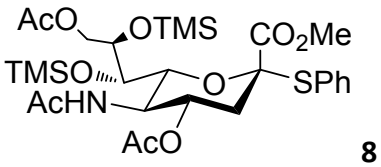

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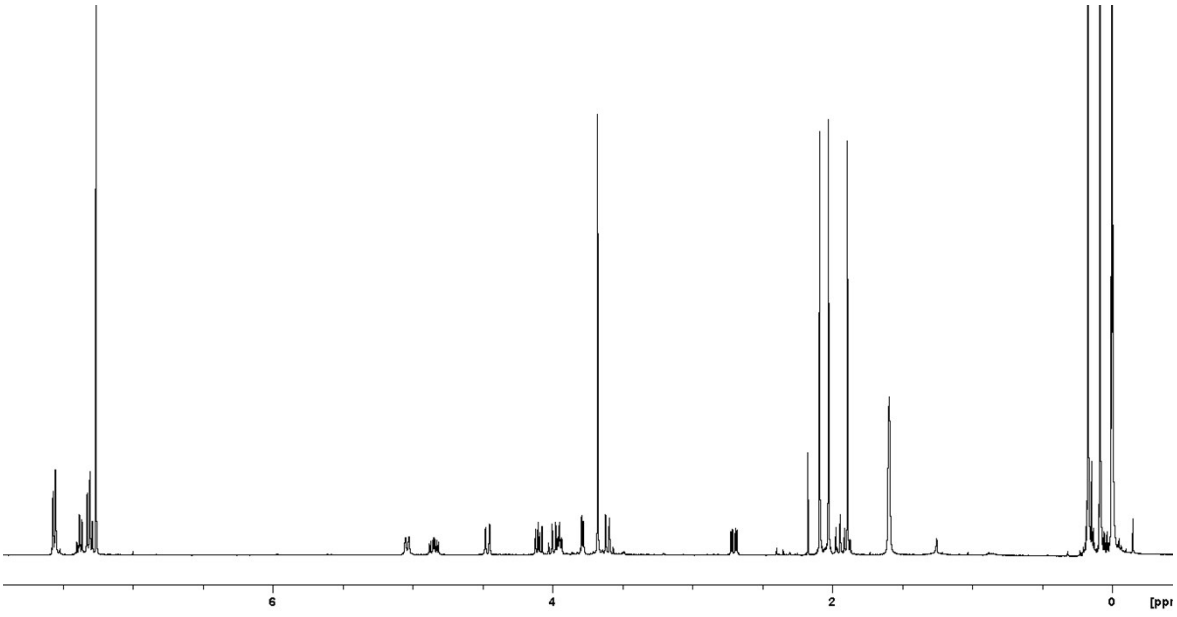

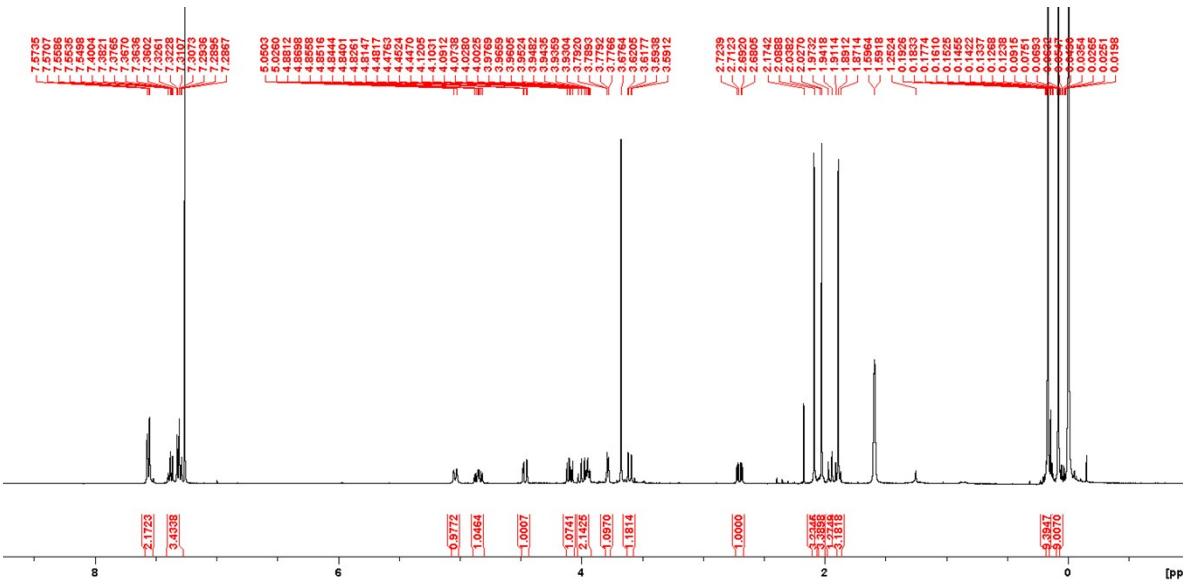

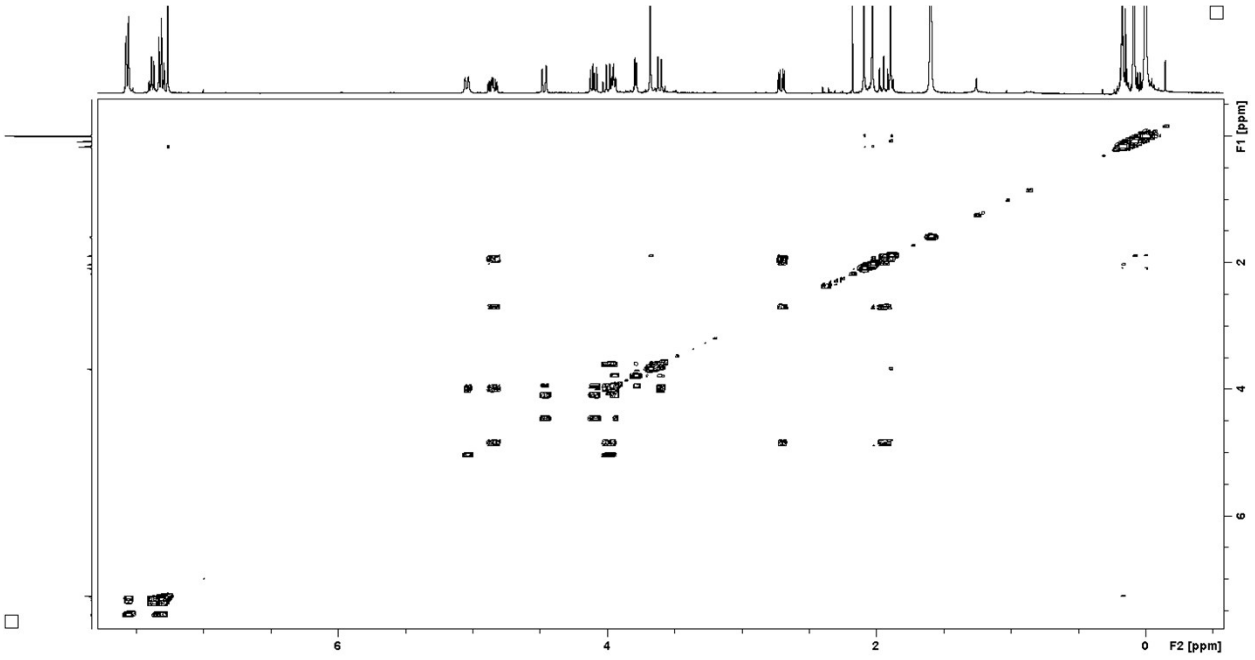
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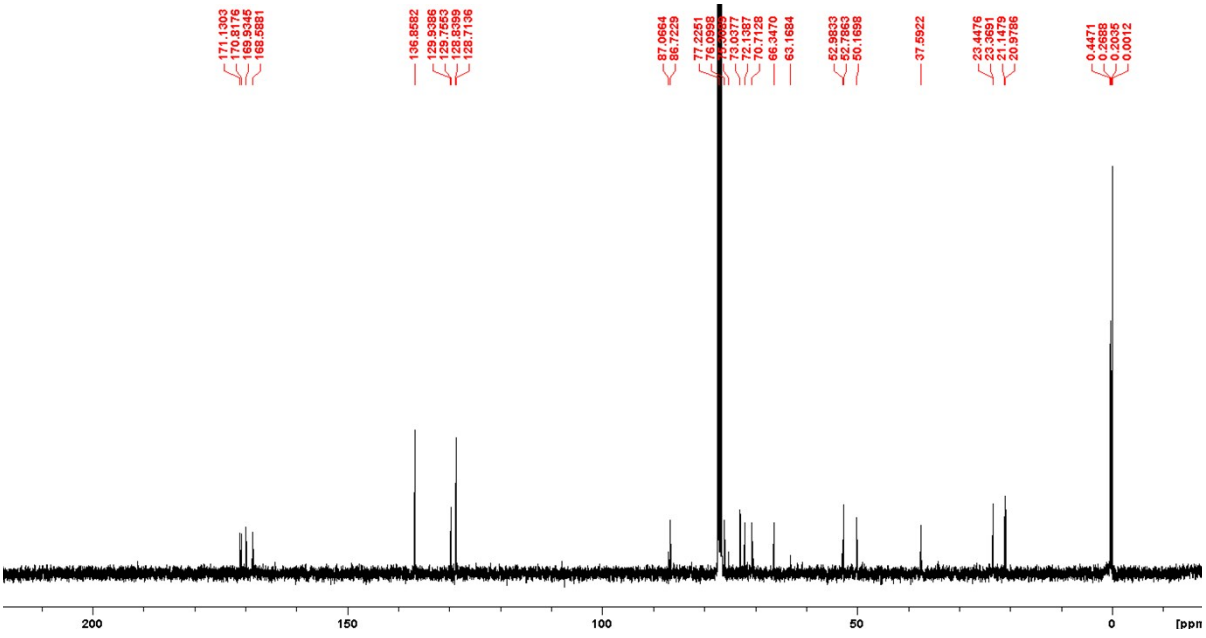
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23.4476
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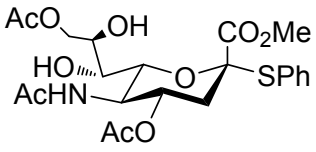

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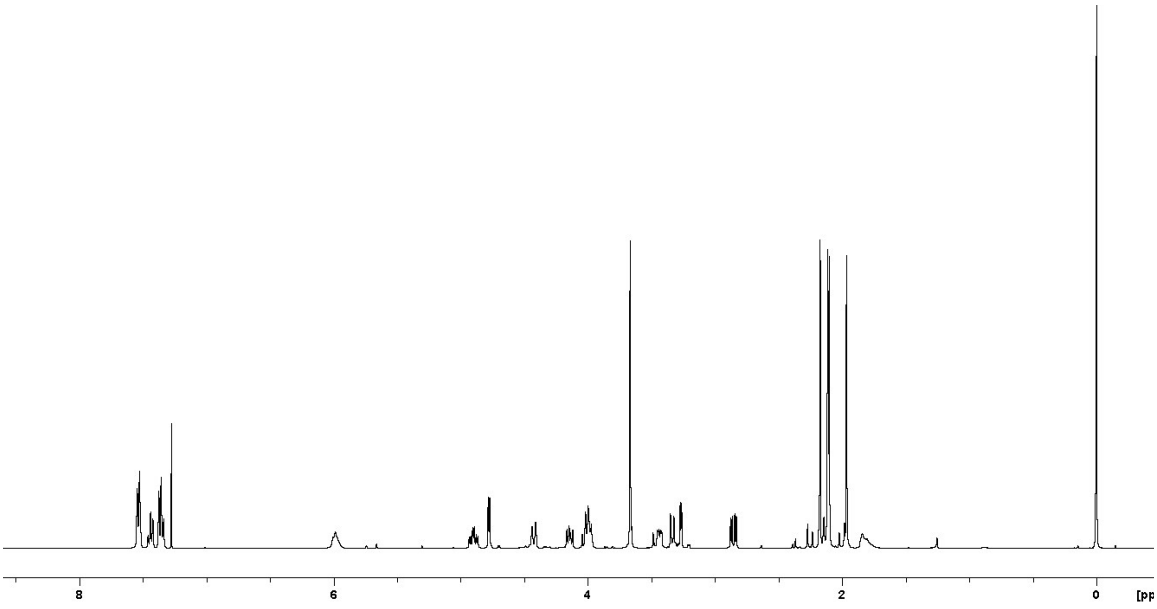

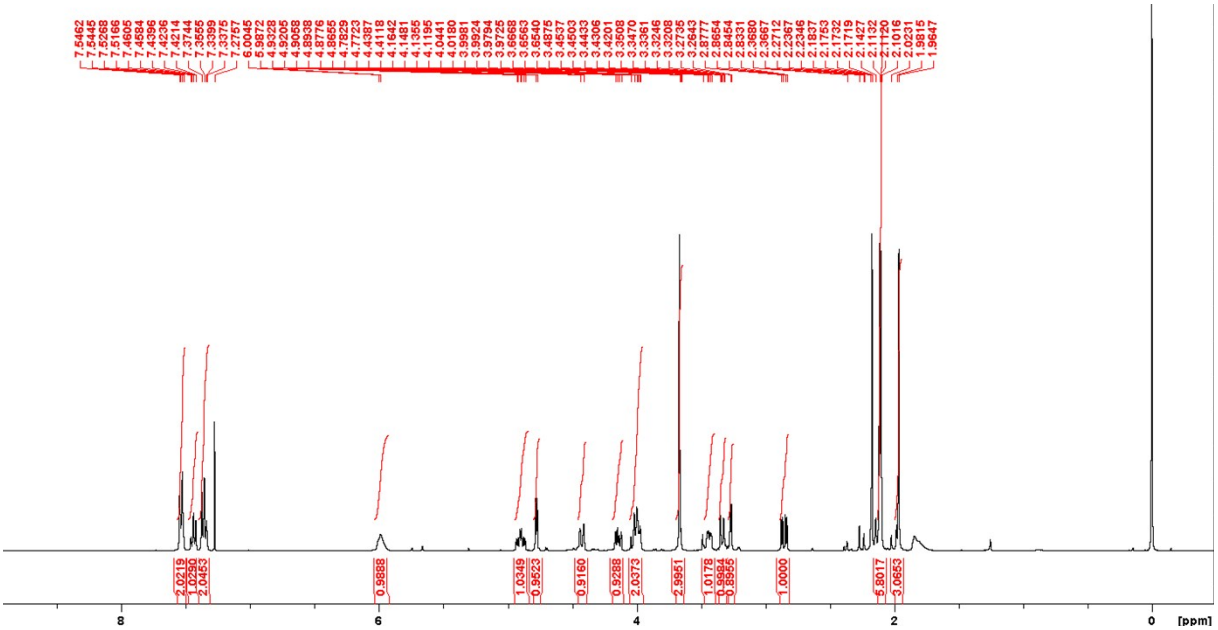

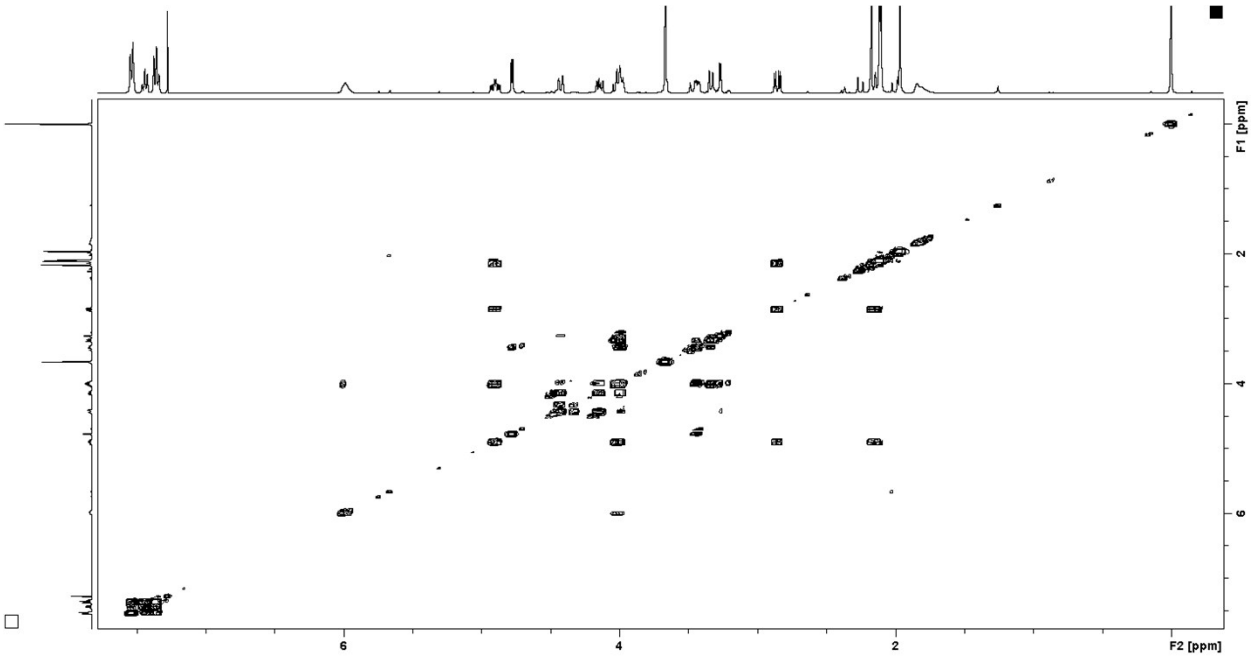
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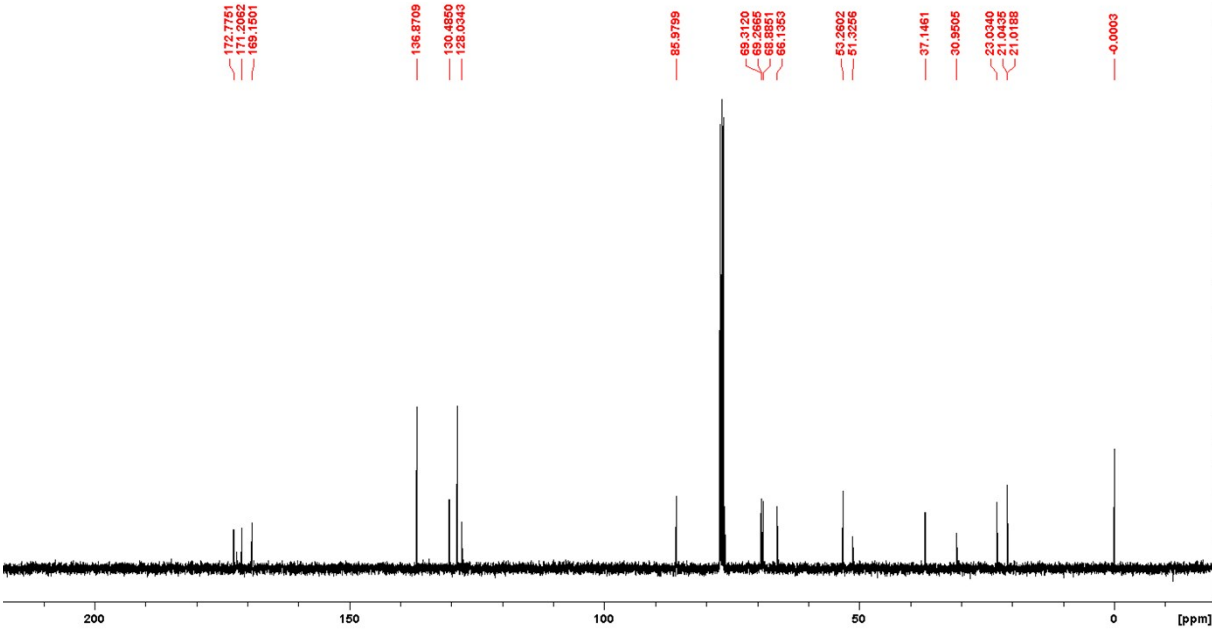
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21.0188
-0.0003
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50
0
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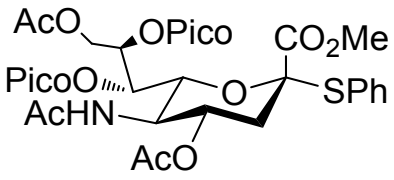
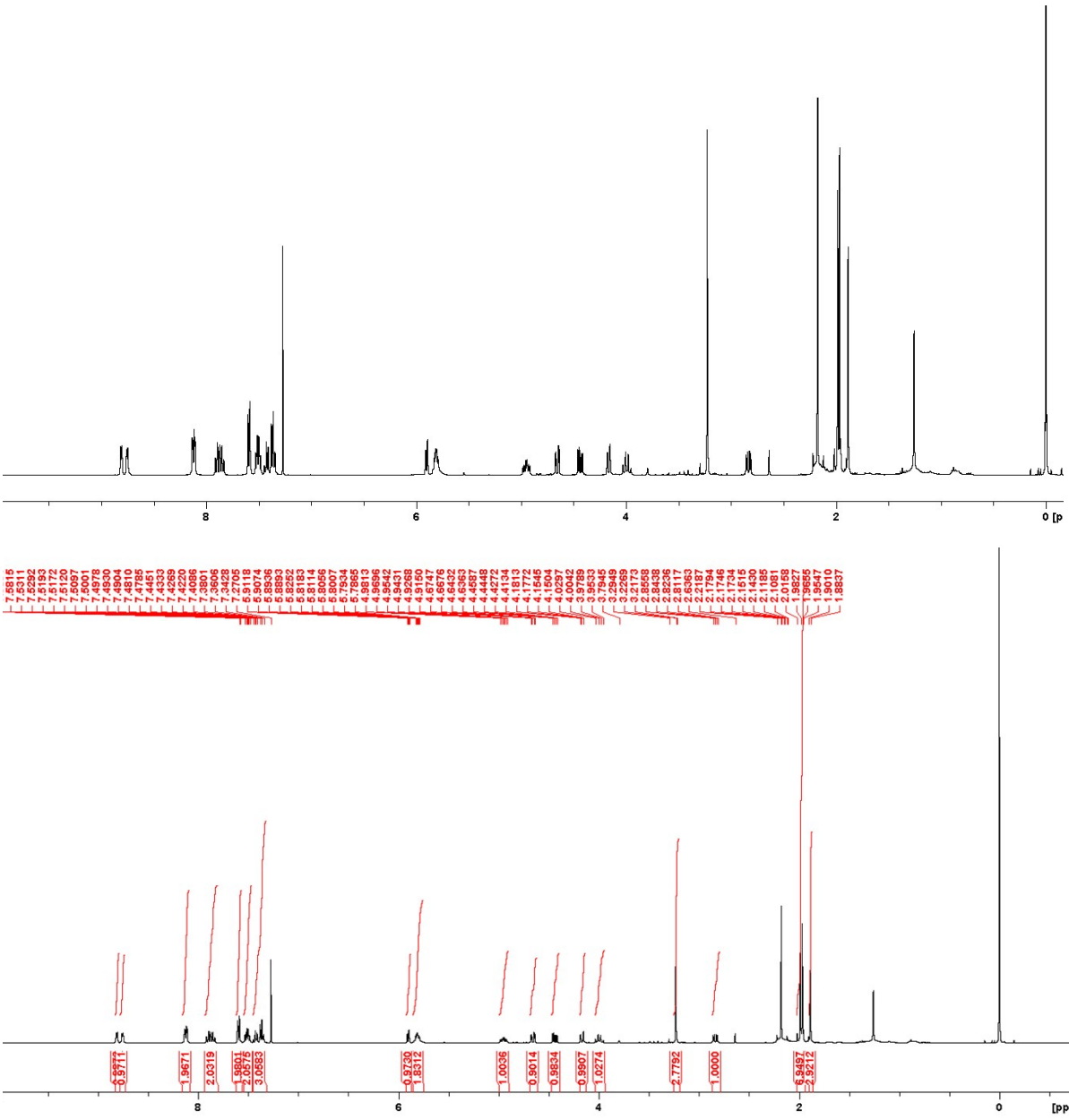
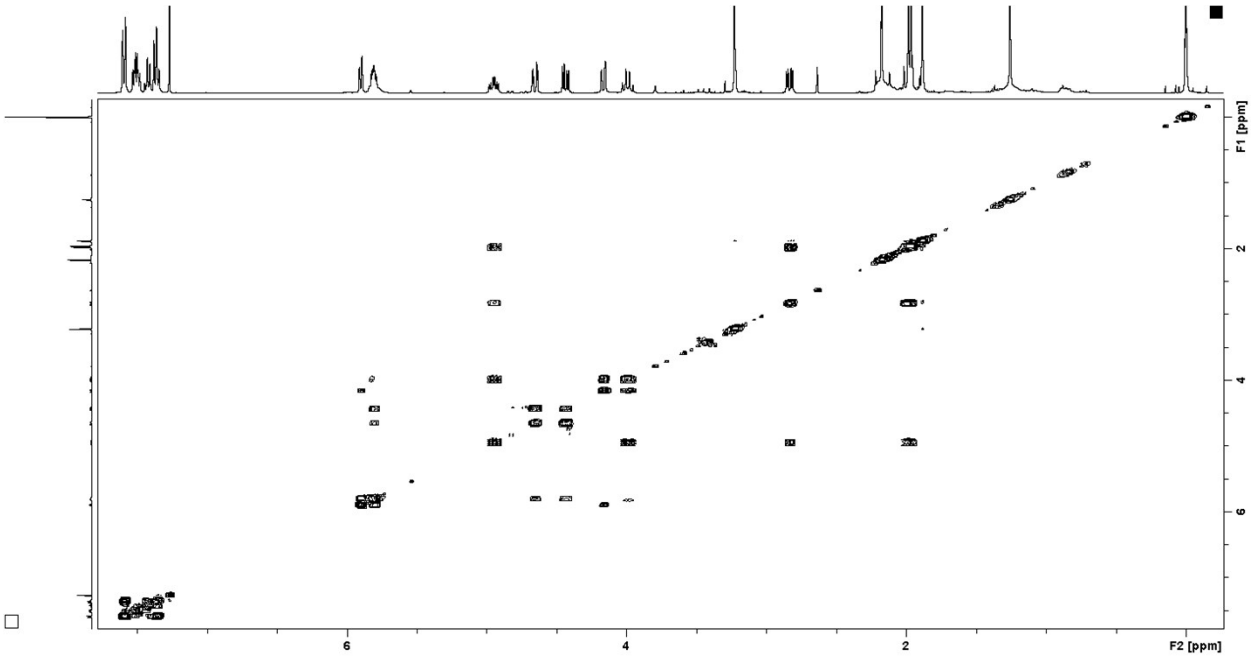


11

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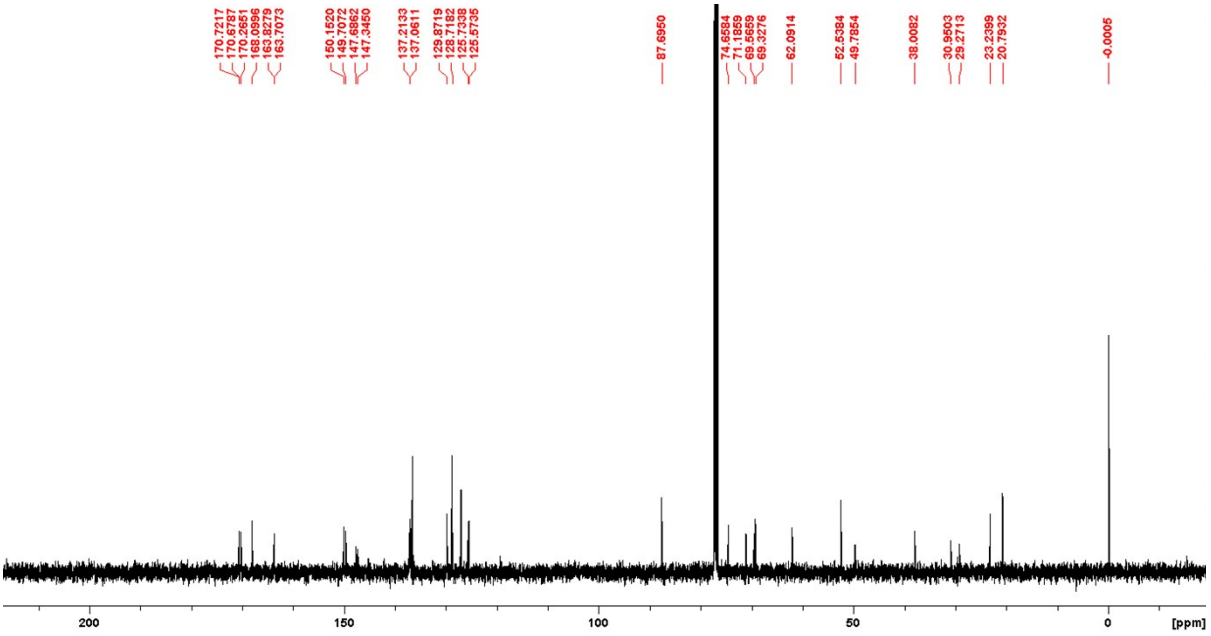
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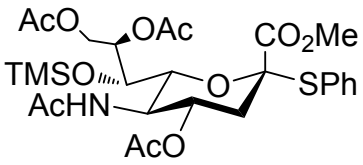
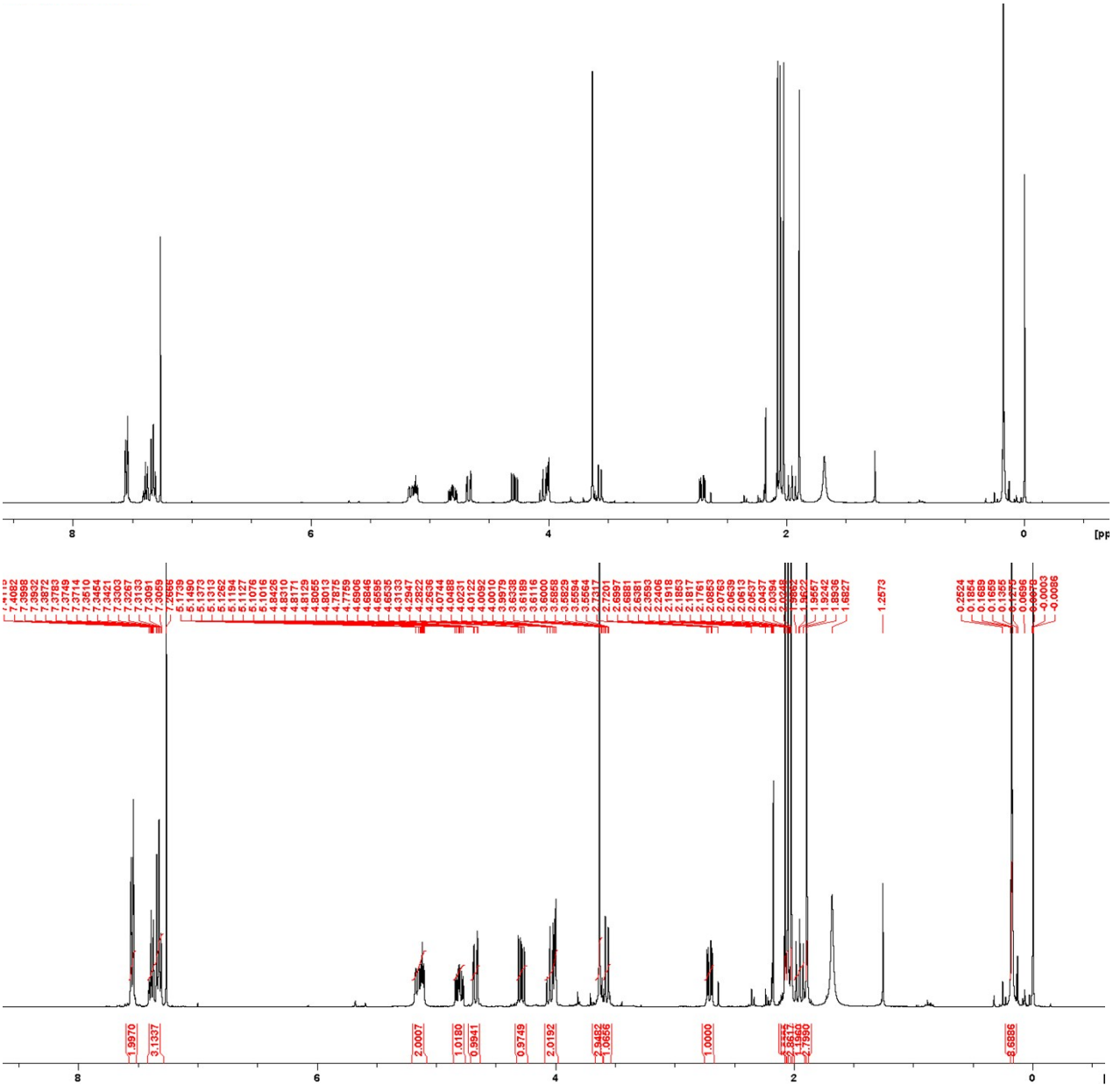
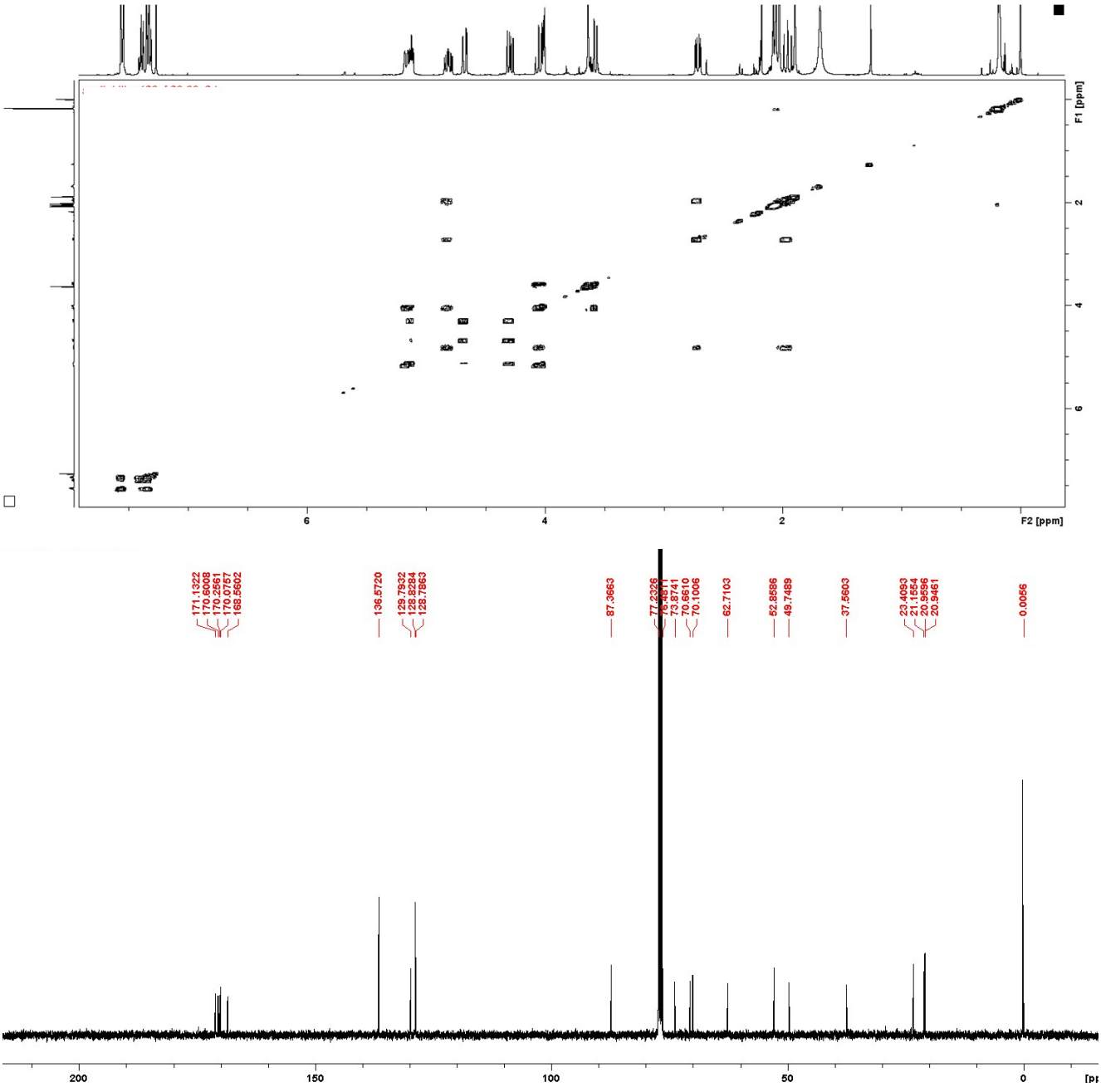


9

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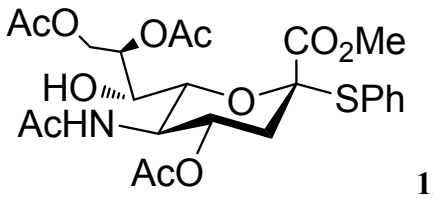
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HO
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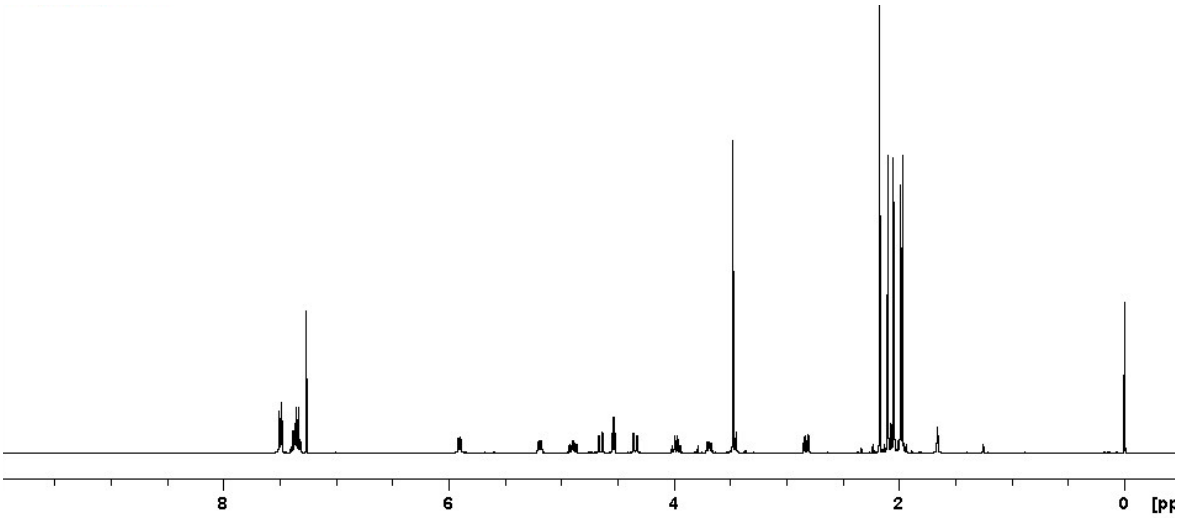
AcO

12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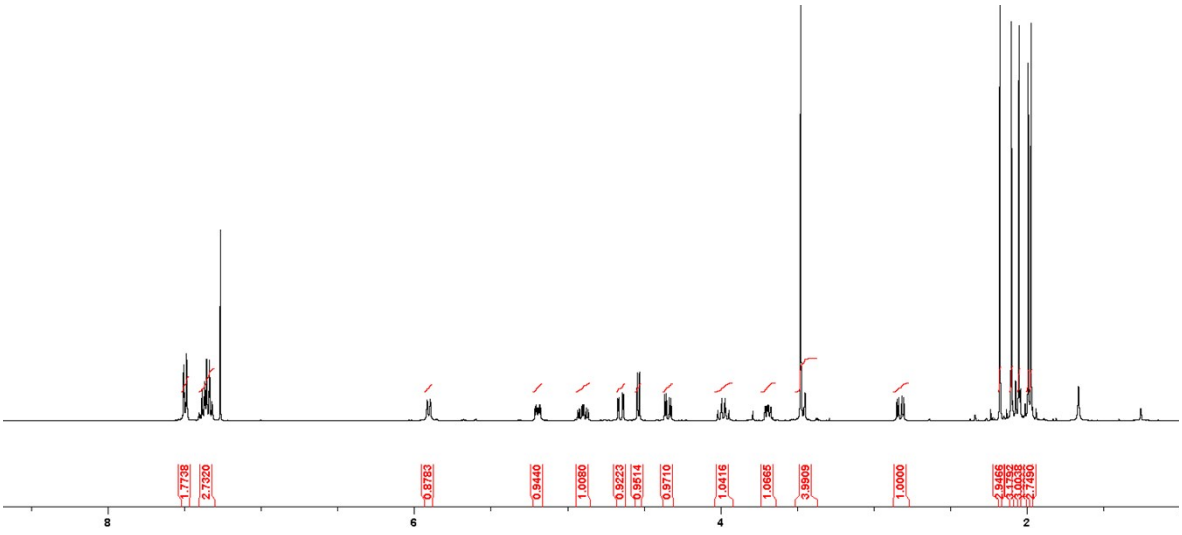
2
0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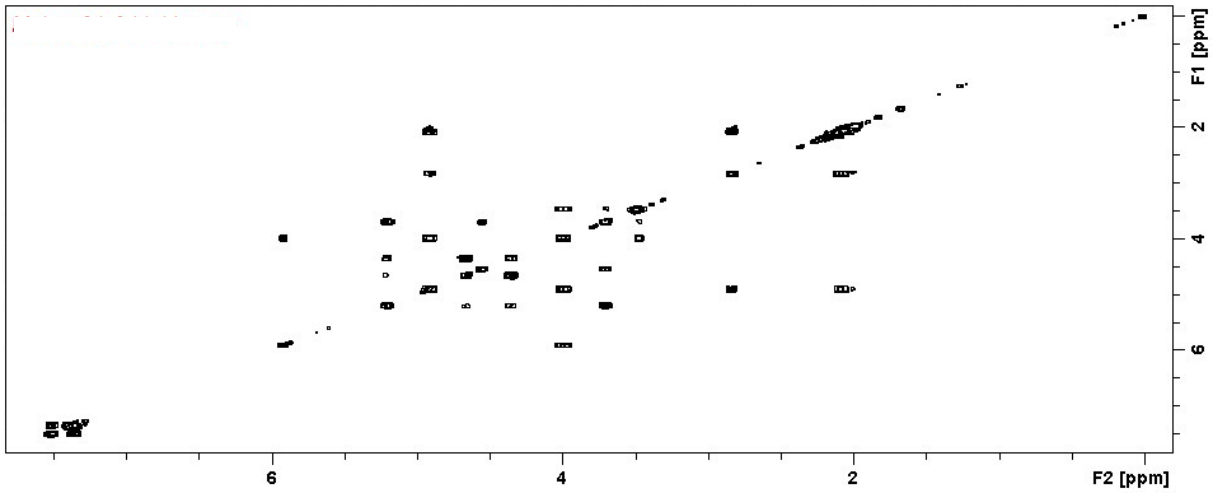
8
6
4
2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6
6
4
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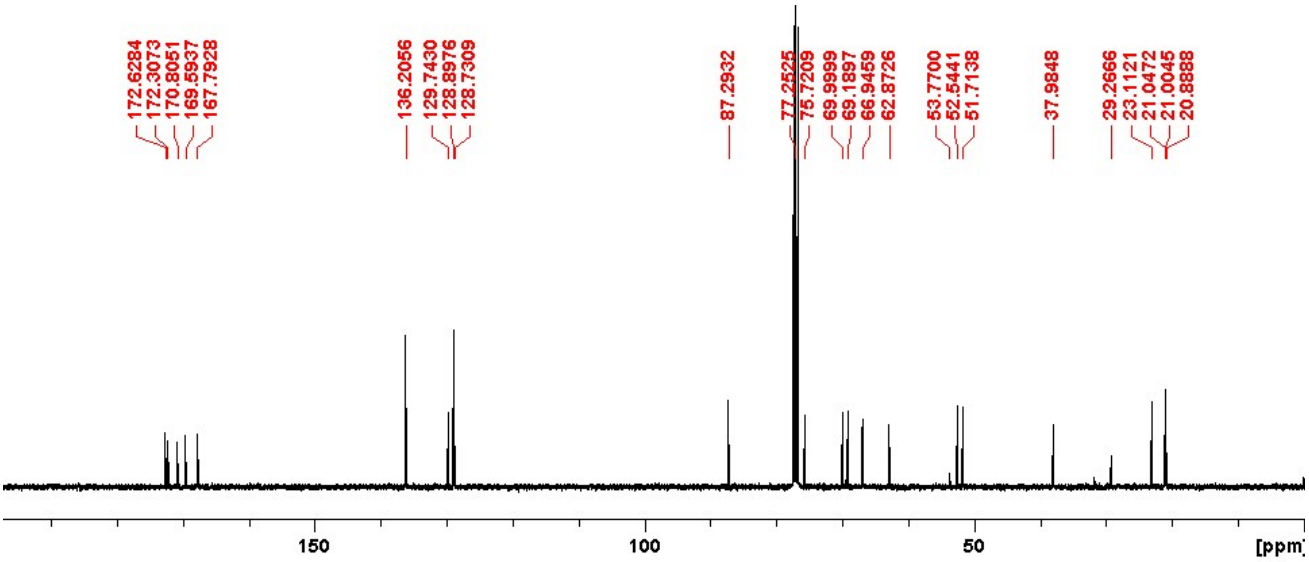
F2 [ppm]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75.7209
69.9999
69.1897
66.9459
62.8726
53.7700
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37.9848
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23.1121
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21.0045
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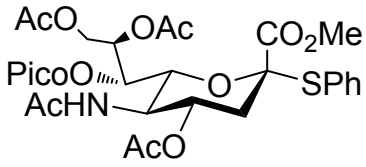
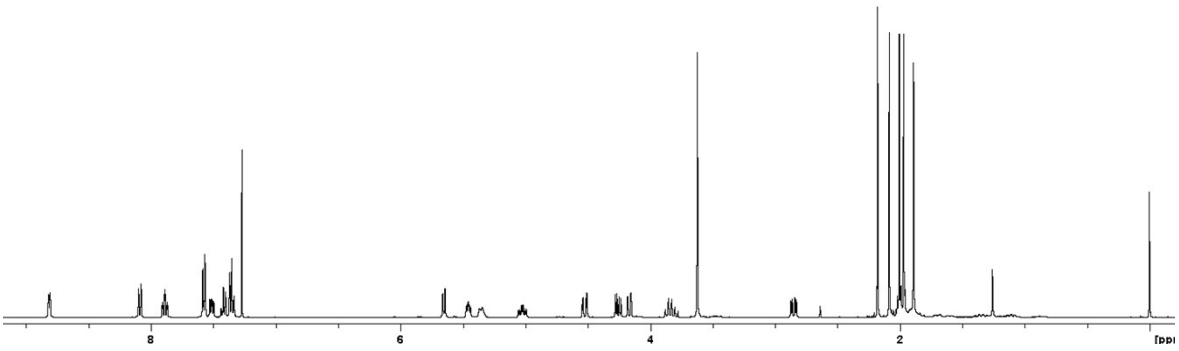
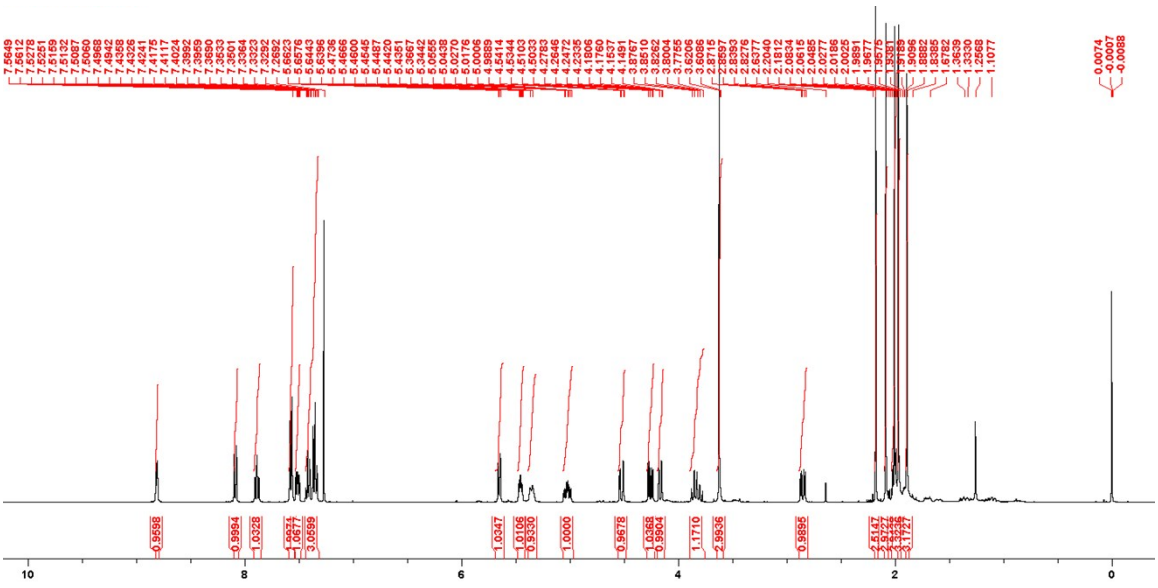
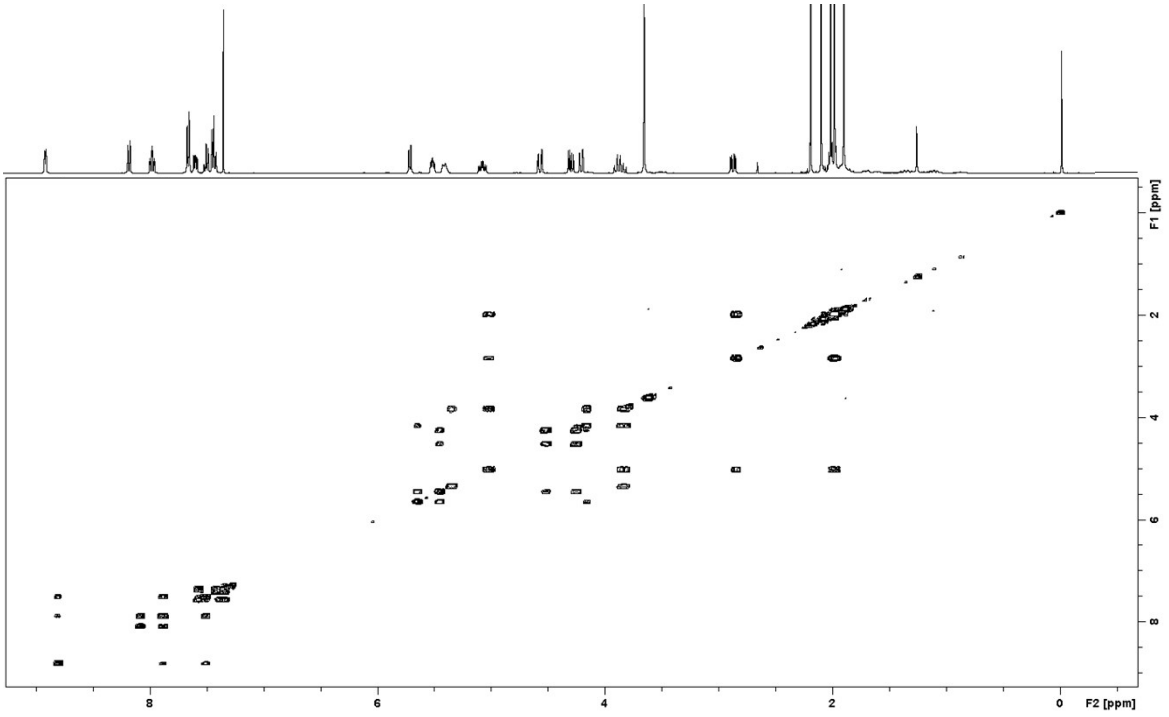
150
100
50
[ppm]

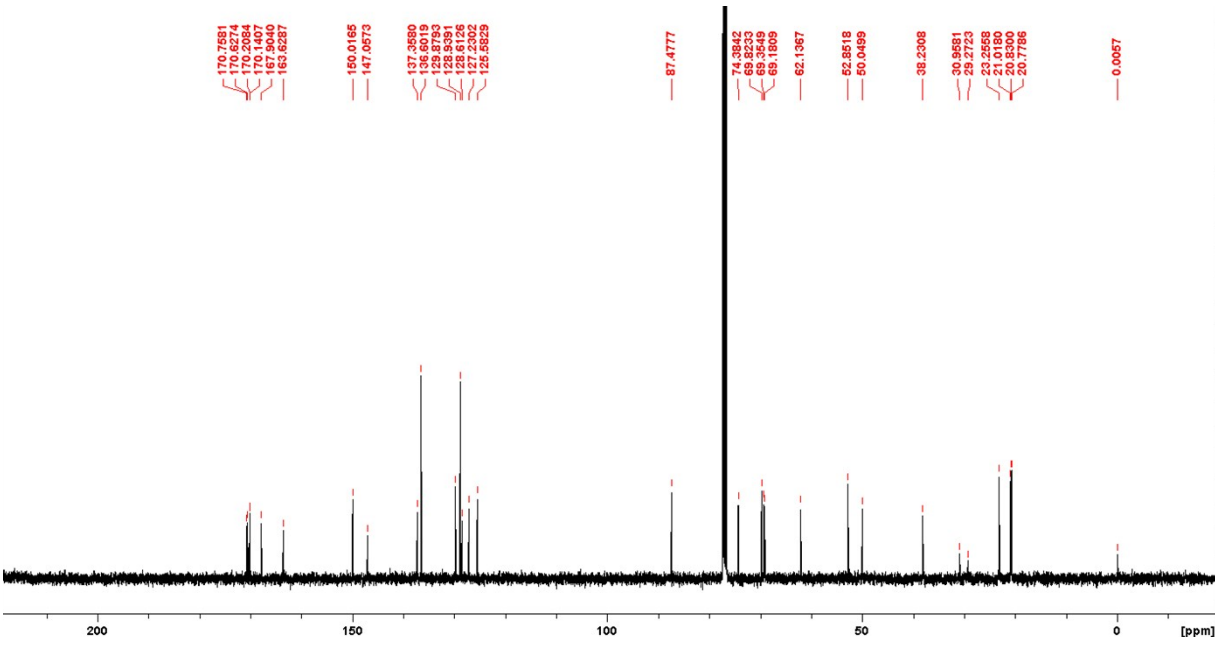


13






F1 [ppm]
F2 [ppm]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137.3580
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128.9391
128.6126
127.2302
125.5829
87.4777
74.3842
69.3223
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69.1809
62.1367
52.8518
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23.2558
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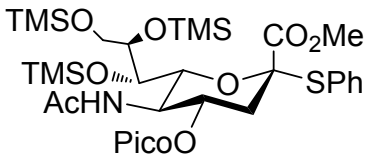
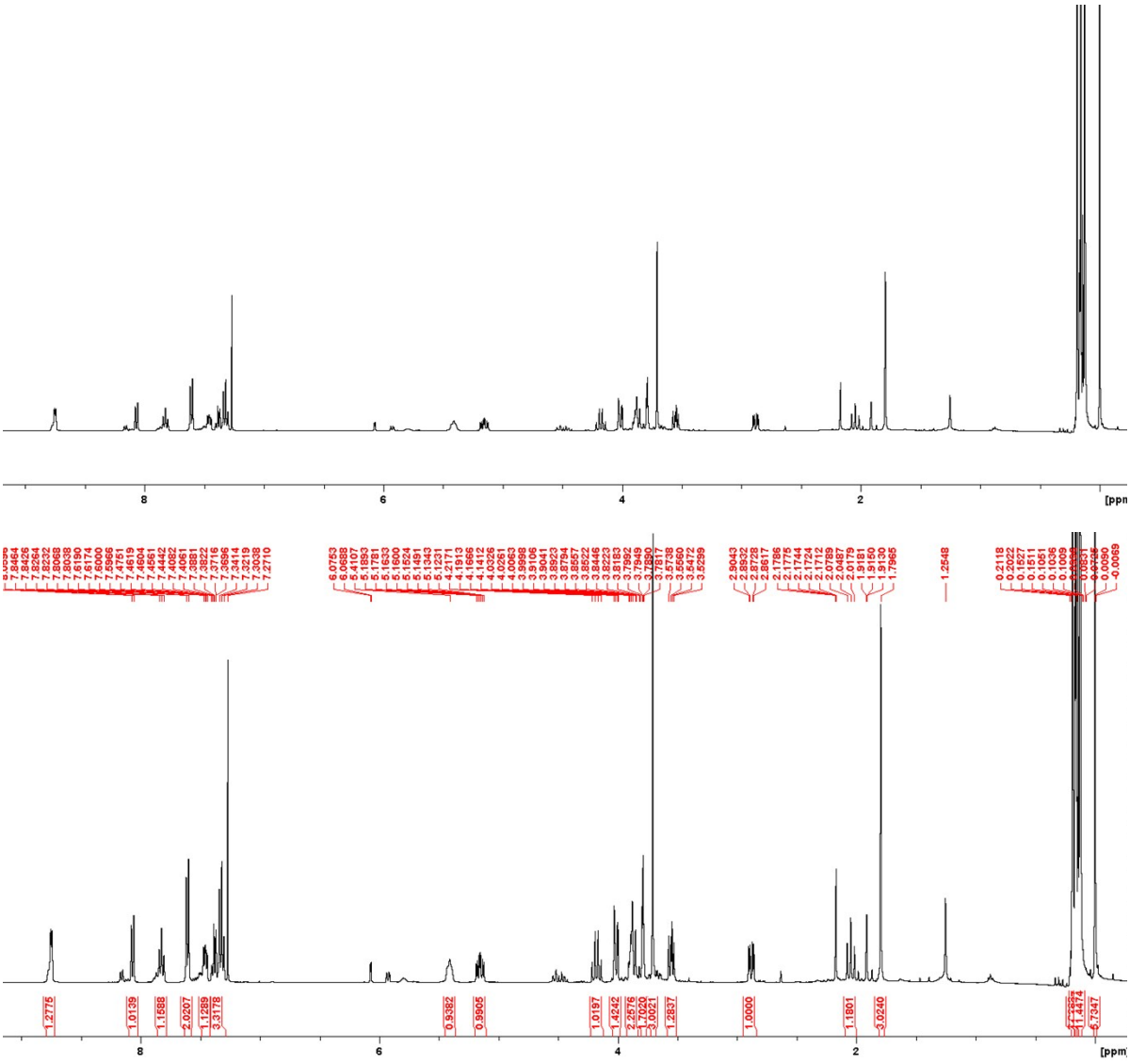
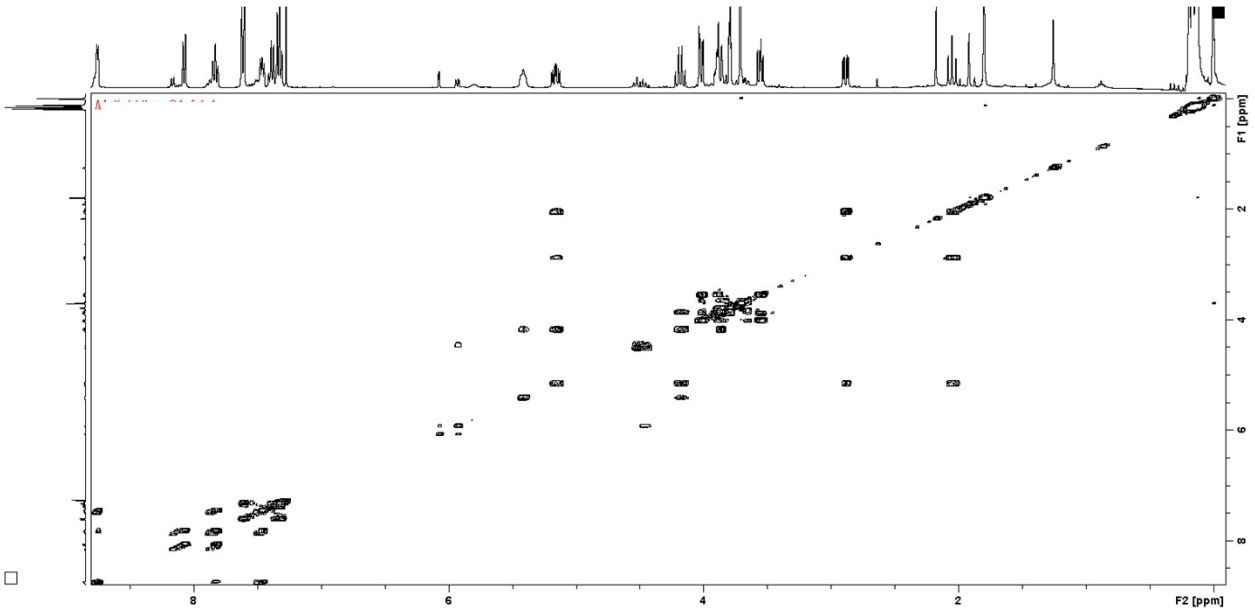


14

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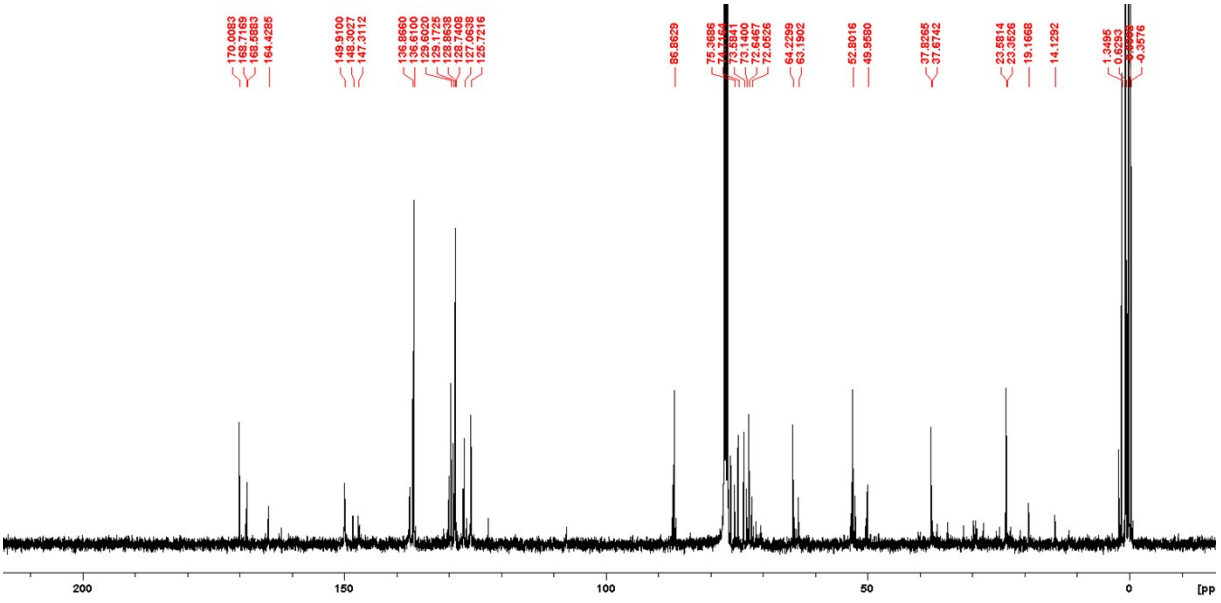
F2 [ppm]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127.7238
125.7216
86.8629
75.3686
74.3641
73.1400
72.6467
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150
100
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0
[pp