SUPPORTING INFORMATION

Solvent-free reactions at work towards densely functionalized targets: synthesis of 3-amino(azido)-3-deoxy-D-galactose, a key structural motif of galectin ligands

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Experimental section

General information

Reactions were primarily monitored by TLC analysis; after elution, detection of compounds was performed by soaking the plates in 5% H_2SO_4 in ethanol and following heating at 230 °C. Eventual detection of UV-visible compounds under UV lamp preceded the acid treatment. NMR spectra were recorded in a Bruker 400 MHz in $CDCl_3$ or D_2O at 298 K.

p-Methoxyphenyl 6-O-trityl-β-D-galactopyranoside (**9**). Synthesis of tritylated compound **9** was accomplished by adapting a recently described solvent-free tritylation procedure.[11] To a round-bottom flask containing galactoside **8** (1.388 g, 4.85 mmol) and trityl chloride (1.487 g, 5.33 mmol), pyridine was added (0.98 mL, 12.1 mmol). The flask was immersed in an oil bath a 100 °C keeping the mixture under stirring, and after 20 minutes DIPEA (1.69 mL, 9.7 mmol) and further trityl chloride (1.351 g, 4.85 mmol) were added. After 40 min from the start, TLC analysis (eluent: ethyl acetate) evidenced the large prevalence of a tritylated compound (featuring a yellow charring spot in the plate). The crude mixture was directly subjected to silica-gel flash-chromatography (eluent from hexane/ethyl acetate 6:4 v/v to 0:1, always with three drops of pyridine for 100 mL of eluent), to isolate pure compound **9** as a foam (1.891 g, yield 74%). Compound **9**: $[\alpha]_D^{19}$: -10.0 (c 1.3, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-6.70 (aromatic protons, 19 H), 4.68 (d, J = 7.6 Hz, 1H, H-1), 3.96 (m, 1H, H-2), 3.81 (d, J = 2.8 Hz, 1H, H-4), 3.70 (s, 3H, -OCH_3), 3.60 (dd, J = 2.8 and 9.6 Hz, 1H, H-3), 3.55-3.45 (m, 2H, 6-CH_2), 3.26 (m, 1H, H-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 151.2, 143.8, 128.8, 127.8, 127.1, 118.7, 114.5, 102.5, 86.9, 74.2, 73.6, 71.3, 69.4, 63.2, 55.6. HRMS (MALDI): m/z $[M+Na]^+$ calcd for $[C_{32}H_{32}O_7+Na]^+$: 551.2046; found: 551.2038; Anal. Calcd for $C_{32}H_{32}O_7$: C, 72.71; H, 6.10; found C, 72.60; H, 6.20.

p-Methoxyphenyl 3-O-toluensulfonyl-6-O-trityl-β-D-galactopyranoside (**10**). Synthesis of tosylated compound **10** was accomplished by applying a recently described solvent-free tosylation procedure.[9] To a round-bottom flask containing galactoside **9** (1.447 g, 2.74 mmol), dibutyltin oxide (68 mg, 0.27 mmol), and tetrabutylammonium bromide (TBAB) (265 mg, 0.82 mmol), were sequentially added DIPEA (1.91 mL, 10.9 mmol) and tosyl chloride (783 mg, 4.11 mmol). The mixture was suspended with

dichloromethane (0.5 mL) and the flask was immersed in an oil bath at 75 °C keeping the mixture under stirring and allowing the solvent to distill off. After 45 min from the start, TLC analysis (eluent: hexane/ethyl acetate 3:2) evidenced the conversion of **9** to less polar **10**. The crude mixture was directly subjected to silica-gel flash-chromatography (eluent: hexane/ethyl acetate from 3:2 to 0:1 v/v, always with three drops of pyridine for 100 mL of eluent), to isolate pure compound **10** as a foam (1.601 g, yield 85%). Compound **10**: $[\alpha]_D^{19}$: +27.3 (c 1.1, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-6.80 (aromatic protons, 23 H), 4.74 (d, J = 7.6 Hz, 1H, H-1), 4.50 (dd, J = 3.2 and 10.0 Hz, 1H, H-3), 4.15-4.08 (overlapped signals, 2H, H-2 e H-4), 3.77 (s, 3H, -OCH_3), 3.60-3.50 (overlapped signals, 2H, H-5 and H-6a), 3.37 (dd, J = 4.0 and 9.2 Hz, 1H, H-6b), 2.42 (s, 3H, tosyl -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 151.1, 145.2, 143.5, 129.9-127.1, 118.7, 114.5, 102.3, 86.9, 82.6, 73.3, 68.9, 68.5, 62.9, 55.6, 21.7. HRMS (MALDI): m/z $[M+Na]^+$ calcd for $[C_{39}H_{38}O_9S+Na]^+$: 705.2134; found: 705.2145; Anal. calcd for $C_{39}H_{38}O_9S$: C, 68.60; H, 5.61; found: C, 68.45; H, 5.60.

p-Methoxyphenyl 2,3-Anhydro-6-O-trityl-β-D-gulopyranoside (**11**) and *p-Methoxyphenyl 3,4-Anhydro-6-O-trityl-β-D-galactopyranoside* (**12**). To a round-bottom flask containing galactoside **10** (1.314 g, 1.92 mmol) was added a concentrated solution of DBU (586 mg, 3.8 mmol) in DCM (0.5 mL). The flask was immersed in an oil bath at 80 °C keeping the mixture under stirring and allowing dichloromethane to distill off. After 2 hours from the start, TLC analysis (eluent: hexane/ethyl acetate 3:2) evidenced the prevalent conversion of **10** to a less polar compound **11**. The crude mixture was diluted with dichloromethane and the organic phase washed with water. The aqueous phase was re-extracted with fresh dichloromethane, and collected organic phases were dried with dry sodium sulfate, filtered and concentrated *in vacuo*. The resulting crude was directly subjected to silica-gel flash-chromatography (eluent: hexane/ethyl acetate from 2.5:1 to 0:1 v/v, always with three drops of pyridine for 100 mL of eluent), to afford pure compound **11** as a foam (477 mg, yield 48%). Elution also provided a mixture of residual amounts of recovered **10** and rearranged epoxide **12** (129 mg, 13%). Compound **11**: $[\alpha]_D^{19}$: -61.9 (c 0.85, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-6.83 (aromatic protons, 19 H), 5.48 (s, 1H, H-1), 4.10 (bs, 1H, H-4), 3.85 (dd, 1H, J = 5.2 and 6.4 Hz, H-5), 3.77 (s, 3H, -OCH_3), 3.47 (bs, 2H,

overlapped, H-2 and H-3), 3.43 (dd, 1H, *J* = 6.4 and 9.6 Hz, H-6a), 3.30 (dd, 1H, *J* = 5.2 and 9.6 Hz, H-6b), 2.61 (bs, 1H, OH-4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 150.7, 143.8, 128.8-127.0, 117.8, 114.5, 96.2 (C-1), 86.9, 69.9 (C-5), 64.9 (C-4), 63.2 (C-6), 55.7 (-OCH_3), 53.5, 52.5 (C-2, C-3). HRMS (MALDI): m/z $[M+Na]^+$ calcd for $[C_{32}H_{30}O_6+Na]^+$: 533.1940; found: 533.1935; Anal. calcd for $C_{32}H_{30}O_6$: C, 75.28; H, 5.92; found: C, 75.45; H, 5.80. Compound **12** $[\alpha]_D^{19}$: - 57.8 (c 1.0, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-6.83 (aromatic protons, 19 H), 4.64 (d, 1H, *J* = 7.2 Hz, H-1), 4.09 (dd, 1H, *J* = 6.0 and 7.2 Hz, H-5), 3.96 (d, 1H, *J* = 7.2 Hz, H-2), 3.80 (s, 3H, -OCH_3), 3.52 (dd, 1H, *J* = 7.2 and 9.6 Hz, H-6a), 3.38 (dd, 1H, *J* = 6.0 and 9.6 Hz, H-6b), 3.33 (bd, 1H, *J*= 4.0 Hz, H-4), 3.27 (bd, 1H, *J* = 4.0 Hz, H-3), 2.51 (bs, 1H, OH-2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 150.8, 143.7, 128.7, 127.8, 127.1, 118.4, 114.5, 102.0 (C-1), 87.0, 72.3 (C-5), 66.6 (C-2), 63.5 (C-6), 55.6 (-OCH_3), 54.2, 50.4 (C-3, C-4). HRMS (MALDI): m/z $[M+Na]^+$ calcd for $[C_{32}H_{30}O_6+Na]^+$: 533.1940; found: 533.1955. Anal. calcd for $C_{32}H_{30}O_6$: C, 75.28; H, 5.92; found: C, 75.15; H, 6.00.

p-Methoxyphenyl 3-deoxy-3-amino-3-N-4-O-trichloroethylidene-6-O-trityl-β-D-galactopyranoside (**14**). To a solution of epoxide **11** (447 mg, 0.876 mmol) in dry dichloromethane (4 mL) were sequentially added trichloroacetonitrile (220 μL, 2.19 mmol), and a solution of DBU (40 mg, 0.26 mmol) in dichloromethane (1 mL). After 1h TLC analysis (eluent: hexane/ethyl acetate 3:1) evidenced the conversion of **11** into the less polar compound **13** (as ascertained by NMR). Flash-chromatography silica gel (2.5 g) was added and the volatiles were distilled off under vacuum at roto-evaporator. The resulting powder was kept in a bath at 50 °C under vacuum at roto-evaporator for 30 minutes. The powder was then loaded onto a short glass column and washed with an 85:10:5 DCM/MeOH/acetonitrile mixture in order to desorb crude compound **14** which was recovered upon removal *in vacuo* of the solvents, and directly submitted to the following step after concentration under vacuum.

Compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (s, 1H, -C=NH), 7.50-6.80 (aromatic protons, 19 H), 5.43 (bs, 1H, H-4), 5.41 (s, 1H, H-1), 3.94 (bt, 1H, *J* = 5.2 Hz, H-5), 3.77 (s, 3H, -OCH_3), 3.63 (bs, 1H, H-3), 3.55-3.45 (m, 2H, overlapped, H-2 and H-6a), 3.27 (dd, 1H, *J* = 5.2 and 9.6 Hz, H-6b). ^{13}C NMR

(100 MHz, $CDCl_3$): δ 162.2, 155.2, 150.7, 143.7, 128.7, 127.7, 127.1, 117.8, 114.5, 96.4, 86.9, 69.8, 69.1, 62.5, 55.6, 54.1, 49.8.

Compound **14**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-6.77 (aromatic protons, 19 H), 4.95 (d, 1H, J = 6.0 Hz, H-1), 4.94 (dd, 1H, J = 2.4 and 8.8 Hz, H-4), 4.47 (dd, 1H, J = 6.0 and 8.8 Hz, H-3), 4.05 (td, 1H, J = 2.4 and 6.8 Hz, H-5), 3.82 (t, 1H, J = 6.0 Hz, H-2), 3.75 (s, 3H, -OCH_3), 3.58 (dd, 1H, J = 6.8 and 9.6 Hz, H-6a), 3.48 (dd, 1H, J = 6.8 and 9.6 Hz, H-6b). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 155.3, 150.9, 143.6, 128.8-127.0, 118.5, 114.5, 101.4, 86.9, 81.9, 71.9, 71.7, 69.1, 62.3, 55.6.

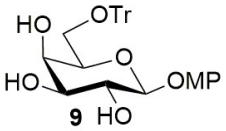
p-Methoxyphenyl 3-deoxy-3-amino-β-D-galactopyranoside chlorohydrate (**15**). To a solution of crude cyclic imidate **14** (estimated amount, 0.876 mmol) in THF (5.35 mL) was added a HCl aq solution (1M, 0.34 mL) in an ice bath. The mixture was stirred allowing the temperature to gradually raise, and after 40 minutes TLC analysis (eluent: ethyl acetate) evidenced generation of a polar not migrating compound. Solvent was removed with iterated co-evaporations with toluene. The resulting crude was treated with ethyl acetate (1 mL) in order to remove most of the trityl side products in the supernatant. The solid residue was directly used in the following step. ^{1}H NMR (400 MHz, D_2O): δ 7.27-6.77 (2 x d, J = 6.0 Hz, aromatic protons), 4.92 (d, 1H, J = 7.6 Hz, H-1), 4.09 (d, 1H, J = 3.8 Hz, H-4), 3.86-3.80 (overlapped signals, 2H, H-5 and H-6a), 3.71 (s, 3H, -OCH_3), 3.67 (m, 1H, H-6b), 3.44 (dd, 1H, J = 3.2 and 10.8 Hz, H-3). ^{13}C NMR (100 MHz, D_2O): δ 154.8, 150.9, 118.2, 115.0, 101.8, 75.8, 67.2, 64.9, 60.2, 55.8, 55.0.

p-Methoxyphenyl 2,4,6-tri-O-acetyl-3-deoxy-3-azido-β-D-galactopyranoside (**17**). Diazotransfer agent **16**[15] (307 mg, 1.1 mmol) was added to a suspension of compound **17** (estimated amount, 0.876 mmol), K_2CO_3 (363 mg, 2.6 mmol), $CuSO_4 \cdot 7H_2O$ (7 mg, 0.028 mmol) in MeOH (4 mL). The mixture was kept 3 hours under stirring, when TLC analysis (eluent: ethyl acetate) evidenced the largely prevalent generation of a mobile product. Solvent was removed under vacuum immersing the reaction flask in a bath not exceeding 40 °C. The residue was treated with pyridine (3 mL) and acetic anhydride (1.5 mL). After 4 hours the reaction was quenched by addition of MeOH (2 mL) and the mixture was diluted with dichloromethane, and the organic phase washed with water. The aqueous phase was re-extracted with fresh dichloromethane, and collected organic phases were dried with dry sodium sulfate, filtered and

concentrated *in vacuo*. The resulting crude was directly subjected to silica-gel flash-chromatography (eluent: hexane/ethyl acetate from 3:1 to 0:1 v/v) to afford pure compound **17** (302 mg, yield 79% over five steps) as an oil.

$[\alpha]_D^{19}$: + 13.8 (c 0.5, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 6.97 and 6.83 (AB, J = 9.2 Hz, 4H, aromatic protons), 5.49 (d, 1H, *J* = 3.2 Hz, H-4), 5.43 (dd, 1H, *J* = 8.0 and 10.4 Hz, H-2), 4.91 (d, 1H, *J* = 8.0 Hz, H-1), 4.18 (d, 2H, *J* = 6.4 Hz, H_2-6), 3.99 (t, 1H, *J* = 6.4 Hz, H-5), 3.80 (s, 3H, -OCH_3), 3.67 (dd, 1H, *J* = 3.2 and 10.4 Hz, H-3), 2.22, 2.19, 2.09 (3 x s, 9H, 3 x –$COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 170.0, 169.3, 155.8, 150.9, 118.7, 114.6, 100.9 (C-1), 71.9 (C-5), 69.5 (C-2), 67.6 (C-4), 61.6 (C-3), 61.5 (C-6), 55.6 (-OCH_3), 20.7, 20.6. HRMS (MALDI): m/z $[M+Na]^+$ calcd for $[C_{19}H_{23}N_3O_9+Na]^+$: 460.1332; found: 460.1320. Anal. calcd for $C_{19}H_{23}N_3O_9$: C, 52.17; H, 5.30; found: C, 52.26; H, 5.20.

1,2,4,6-tri-O-acetyl-3-deoxy-3-azido-a/β-D-galactopyranose (**18**). Compound **17** (205 mg, 0.47 mmol) was dissolved with a mixture of acetic anhydride/acetic acid/conc H_2SO_4 10:4:1 v:v:v (6 mL) keeping the vessel immersed in an ice bath. The mixture was kept under stirring, and the ice bath was removed after 30 minutes. After 5.5 hours, the mixture was diluted with dichloromethane, and the organic phase washed with water. The aqueous phase was re-extracted with fresh dichloromethane, and collected organic phases were dried with dry sodium sulfate, filtered and concentrated *in vacuo*. The residue was submitted to silica-gel flash-chromatography (eluent: hexane/ethyl acetate from 3:1 to 0:1 v/v) to afford compound **18** as an oil (α/β 6.5:1, 130 mg, yield 74%). ^1H NMR (400 MHz, $CDCl_3$): signals of prevalent anomer α at δ 6.38 (d, 1H, *J* = 3.6 Hz, H-1), 5.51 (d, 1H, *J* = 3.2 Hz, H-4), 5.27 (dd, 1H, *J* = 3.6 and 10.4 Hz, H-2), 4.30 (t, 1H, *J* = 6.4 Hz, H-5), 4.12 (dd, 1H, *J* = 6.8 and 10.6 Hz, H-6_a), 4.06-4.00 (m, 2H, H-3 and H-6_b), 2.18 (x2), 2.10, 2.07 (3 x s, 12H, 4 x –$COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 169.8, 169.7, 168.8, 89.2 (C-1), 69.0 (C-5), 68.0 (C-2), 67.6 (C-4), 61.4 (C-6), 57.6 (C-3), 20.9, 20.7, 20.6, 20.5. HRMS (MALDI): m/z $[M+Na]^+$ calcd for $[C_{14}H_{19}N_3O_9+Na]^+$: 396.1019; found: 396.1025. Anal. calcd for $C_{14}H_{19}N_3O_9$: C, 45.04; H, 5.13. Found C, 45.15; H, 5.00.



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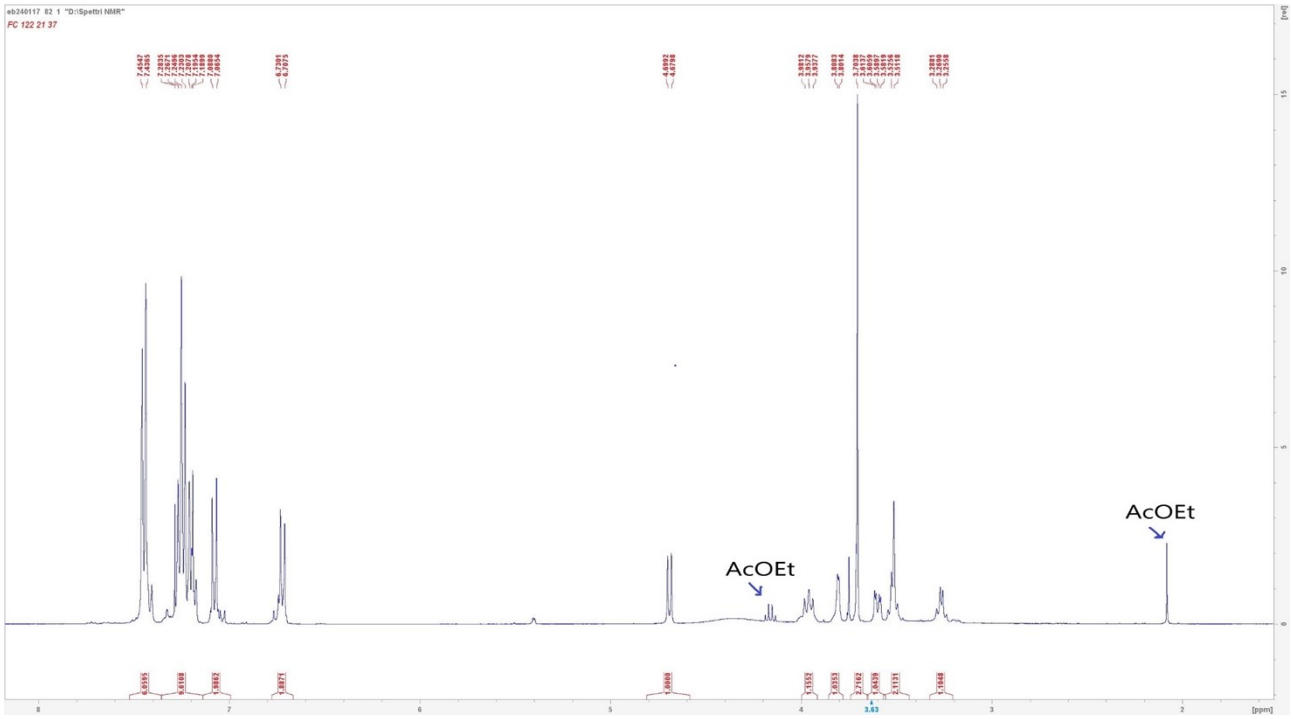

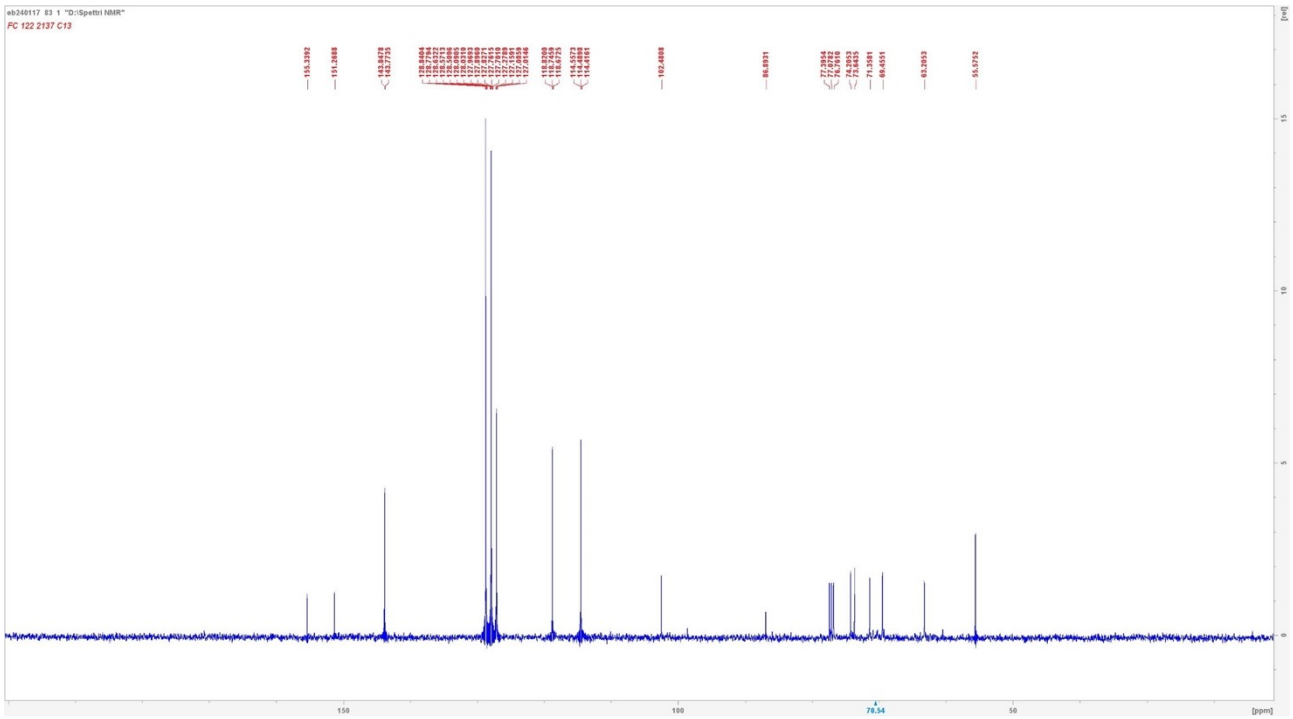

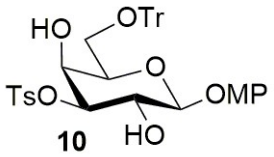

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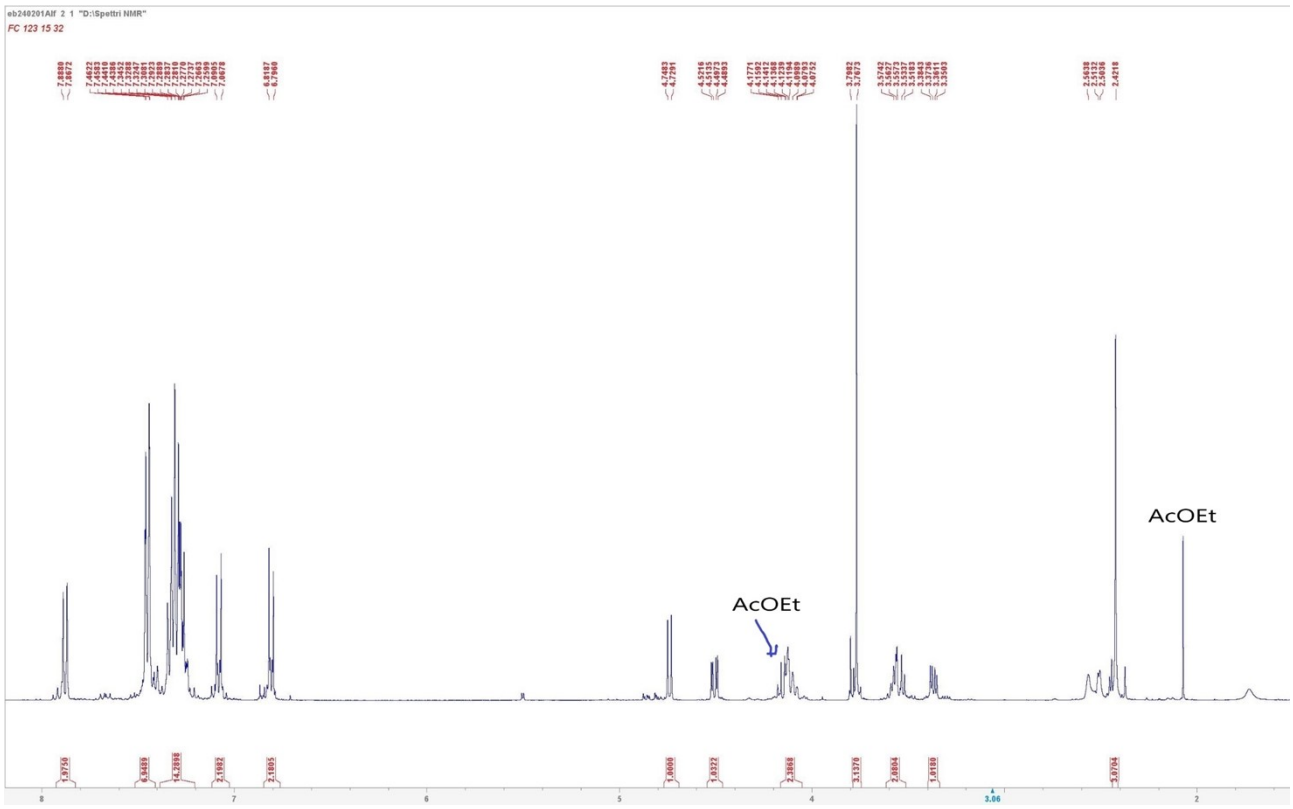

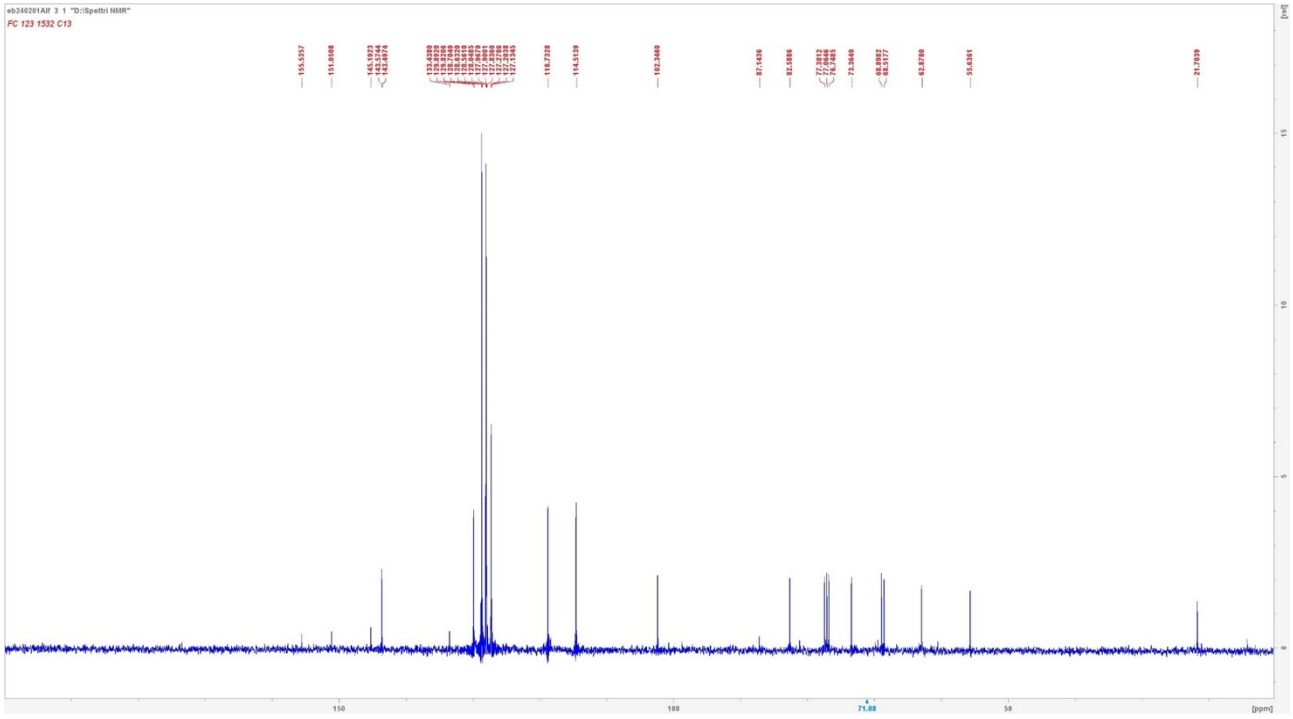

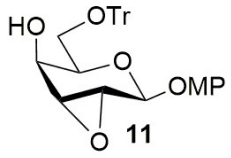
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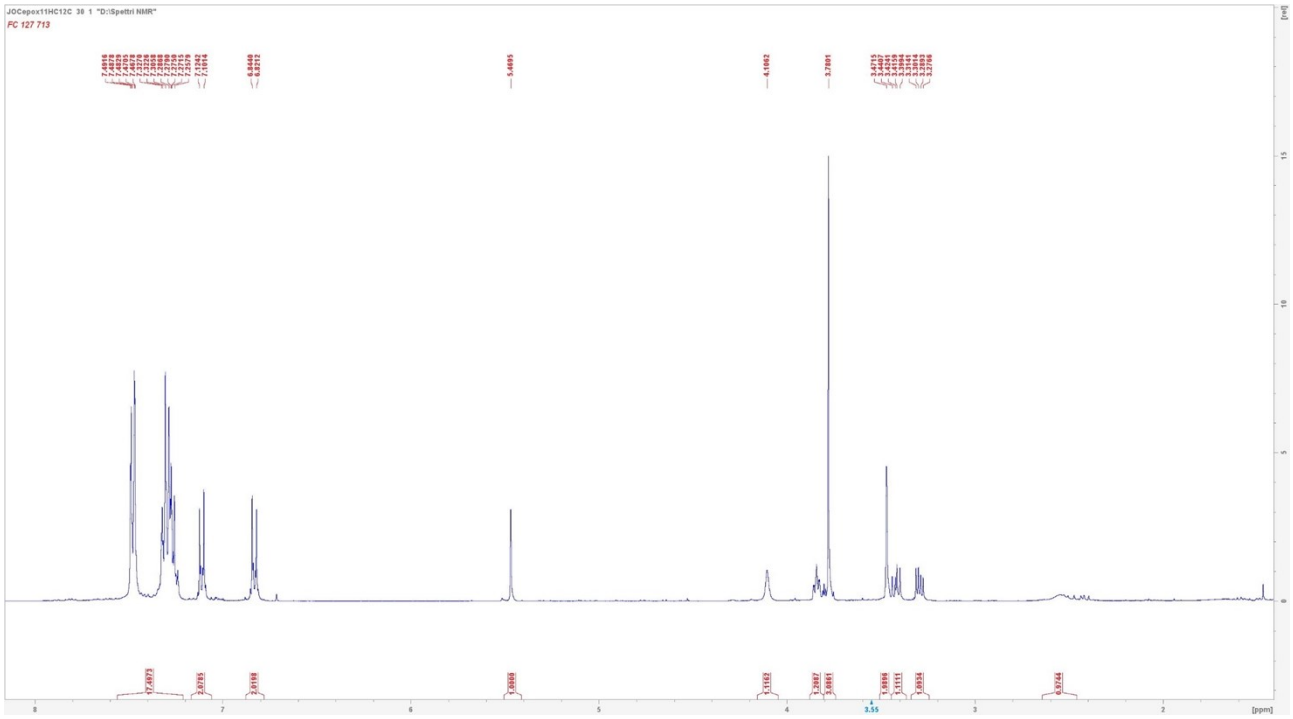
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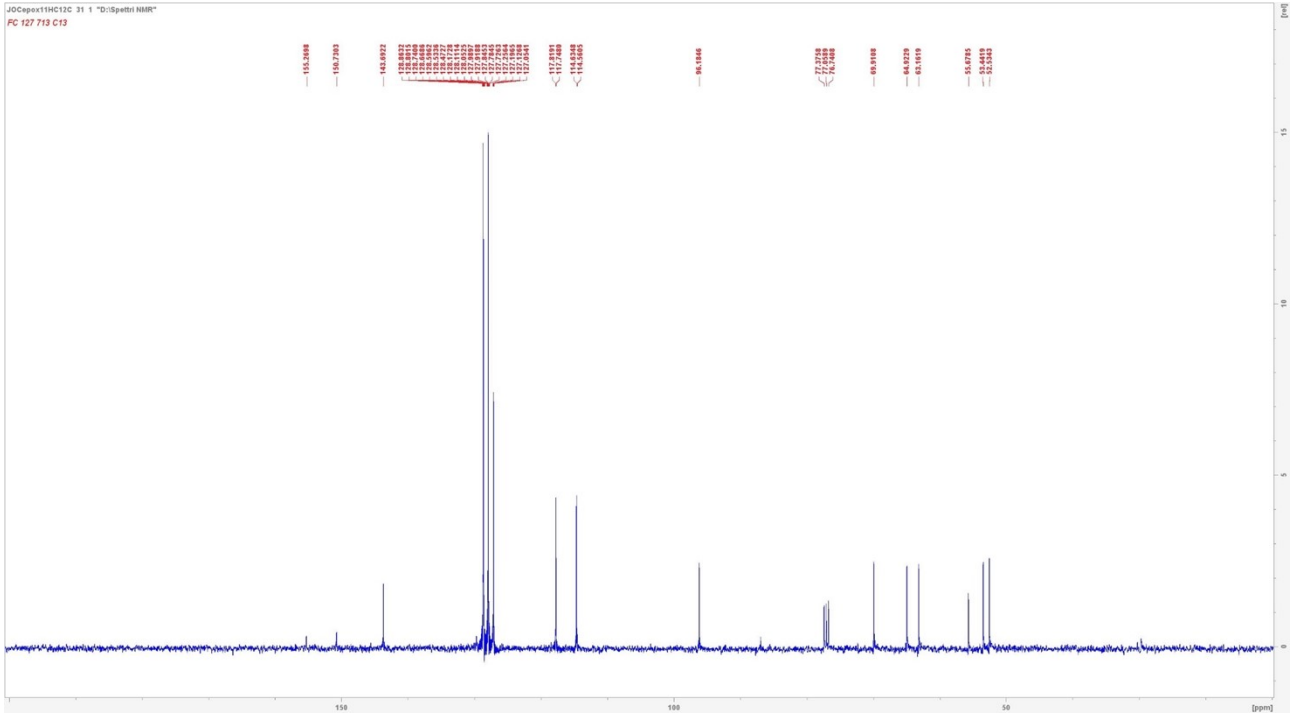
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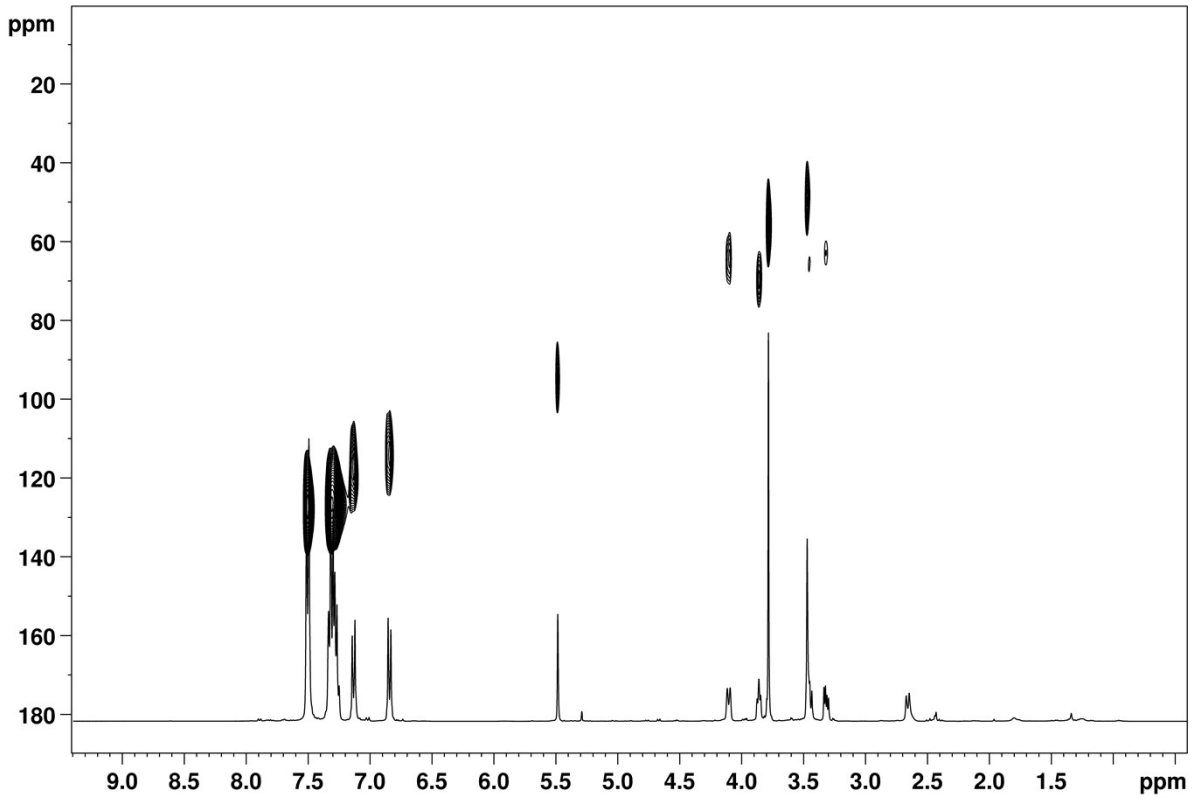

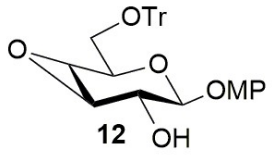
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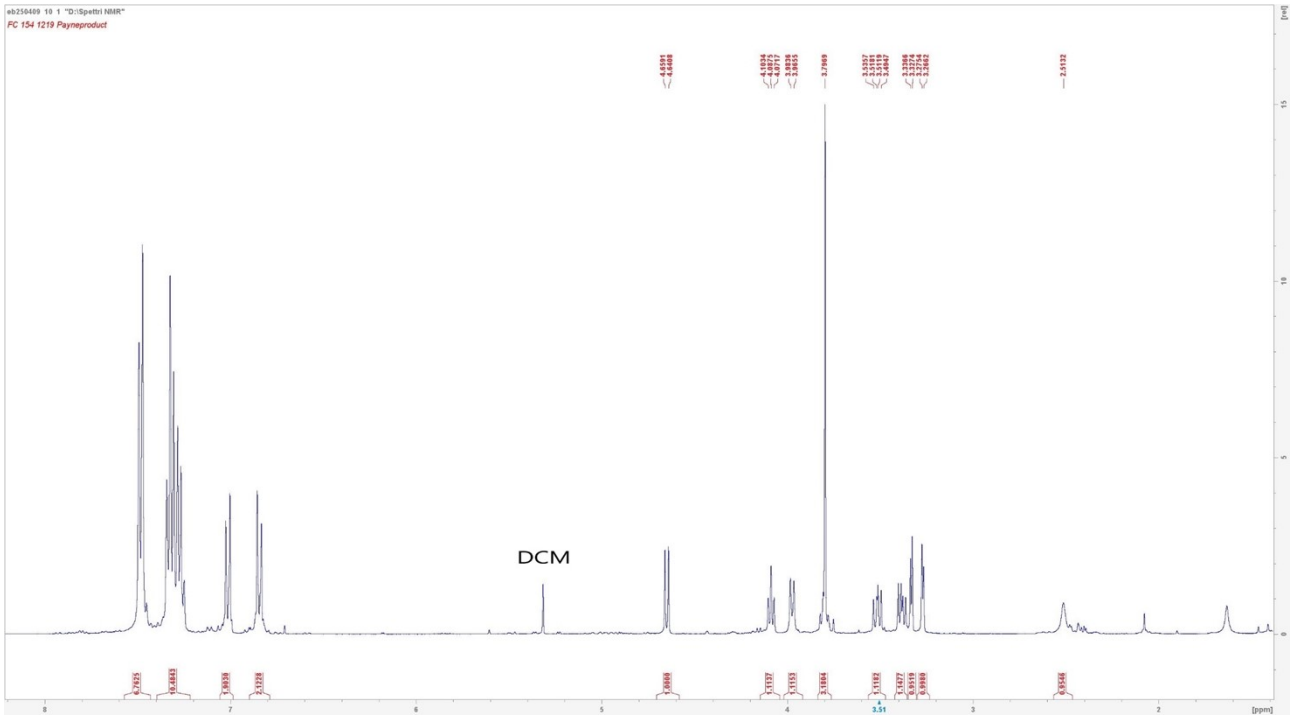
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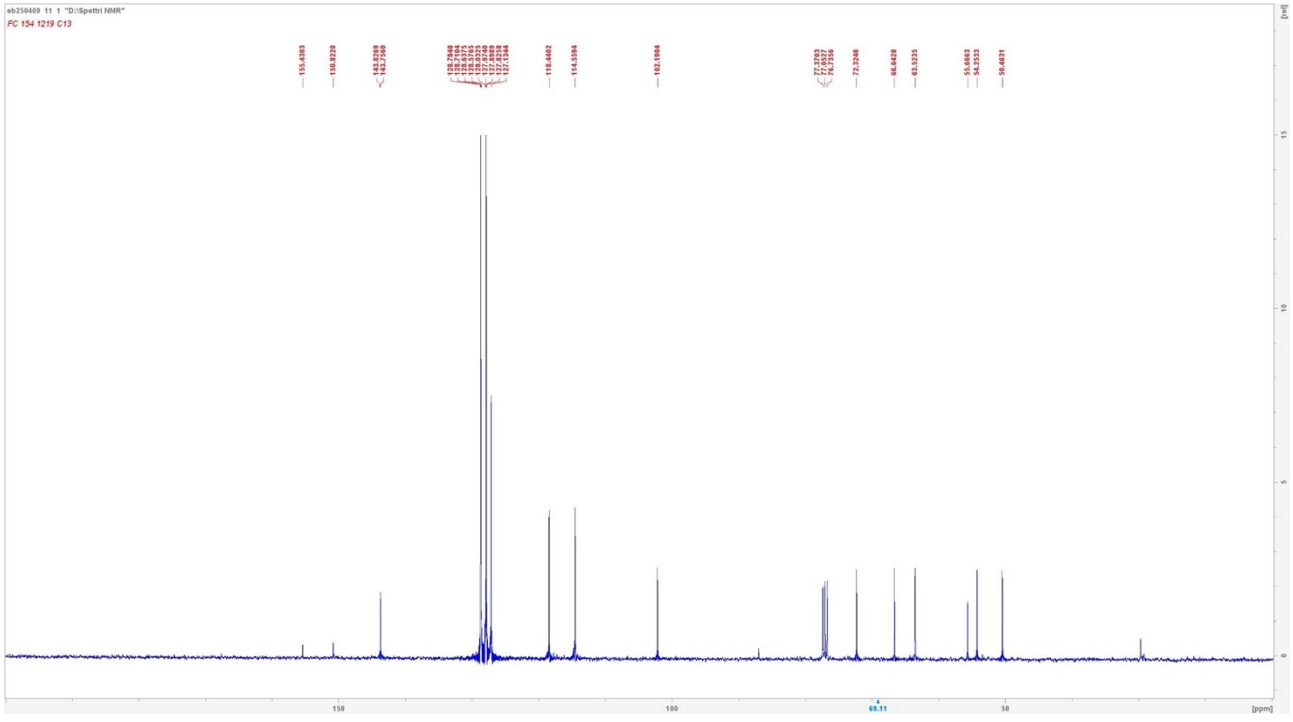
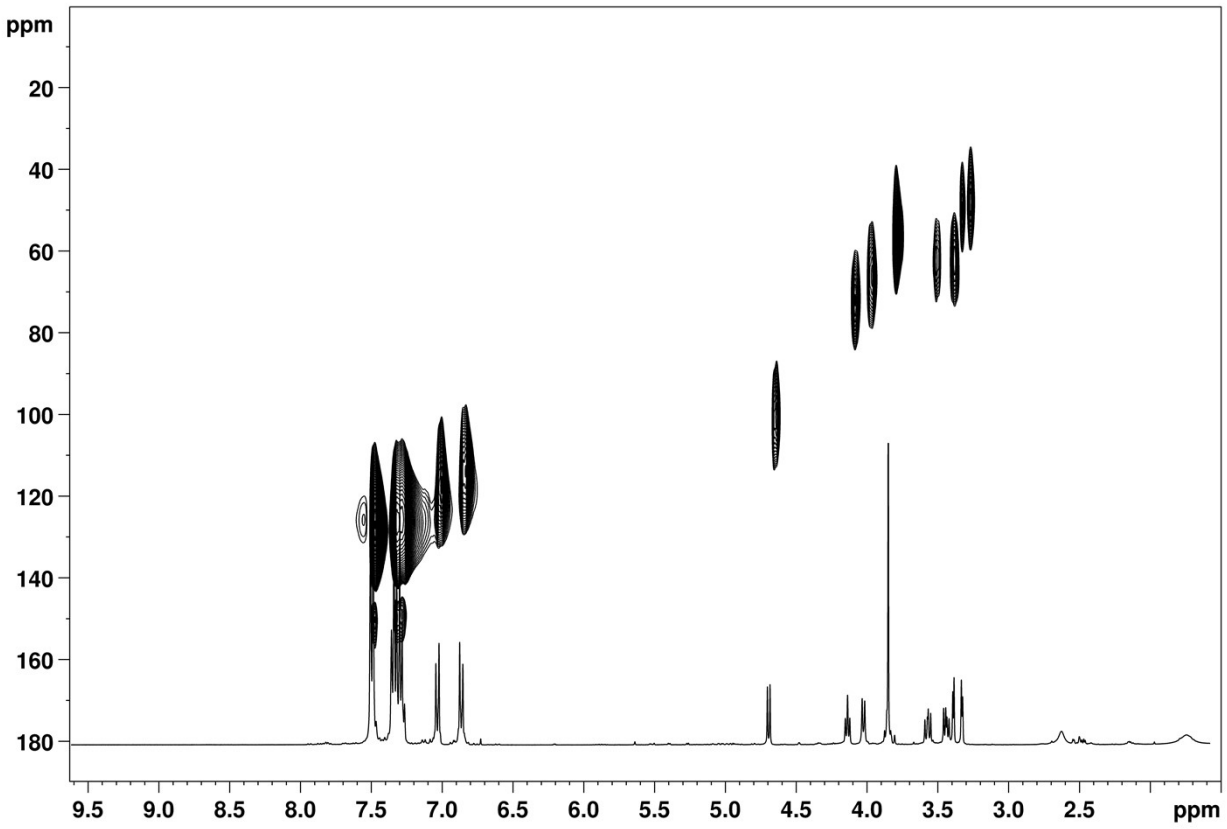
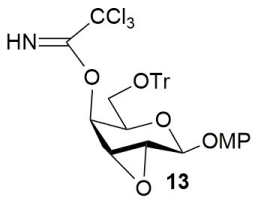


HSQC spectrum

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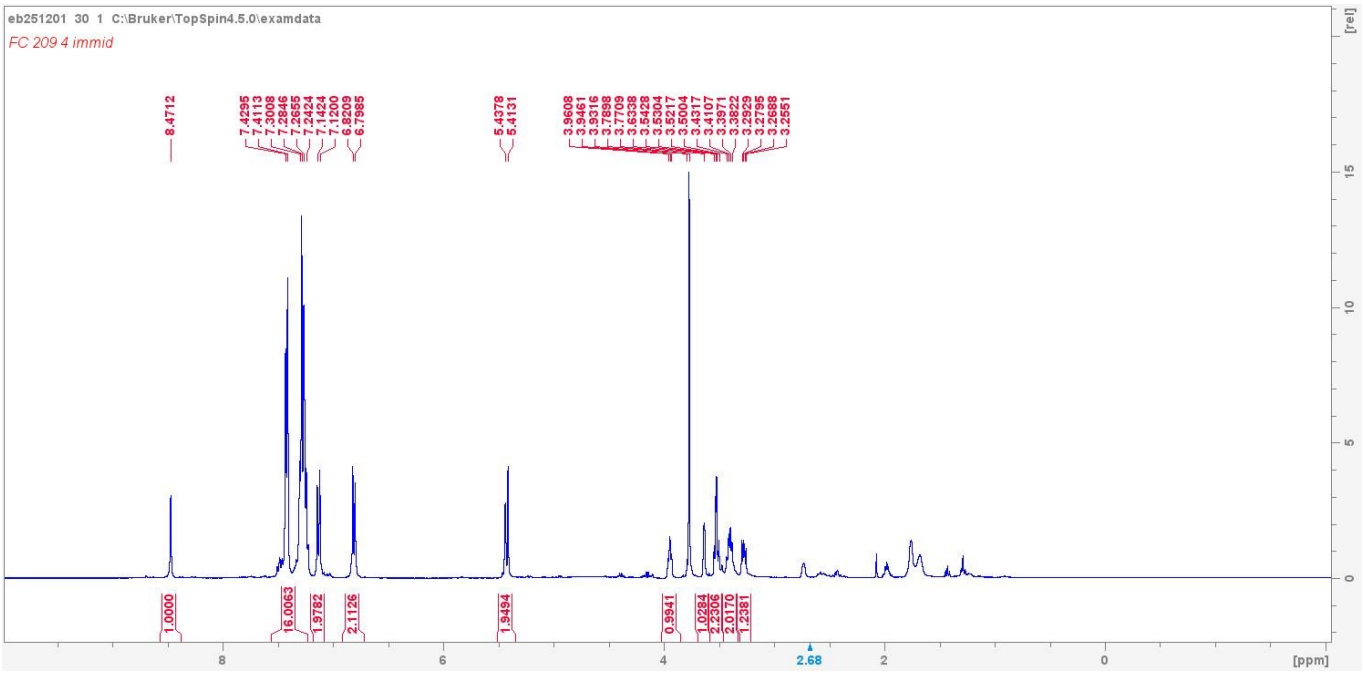
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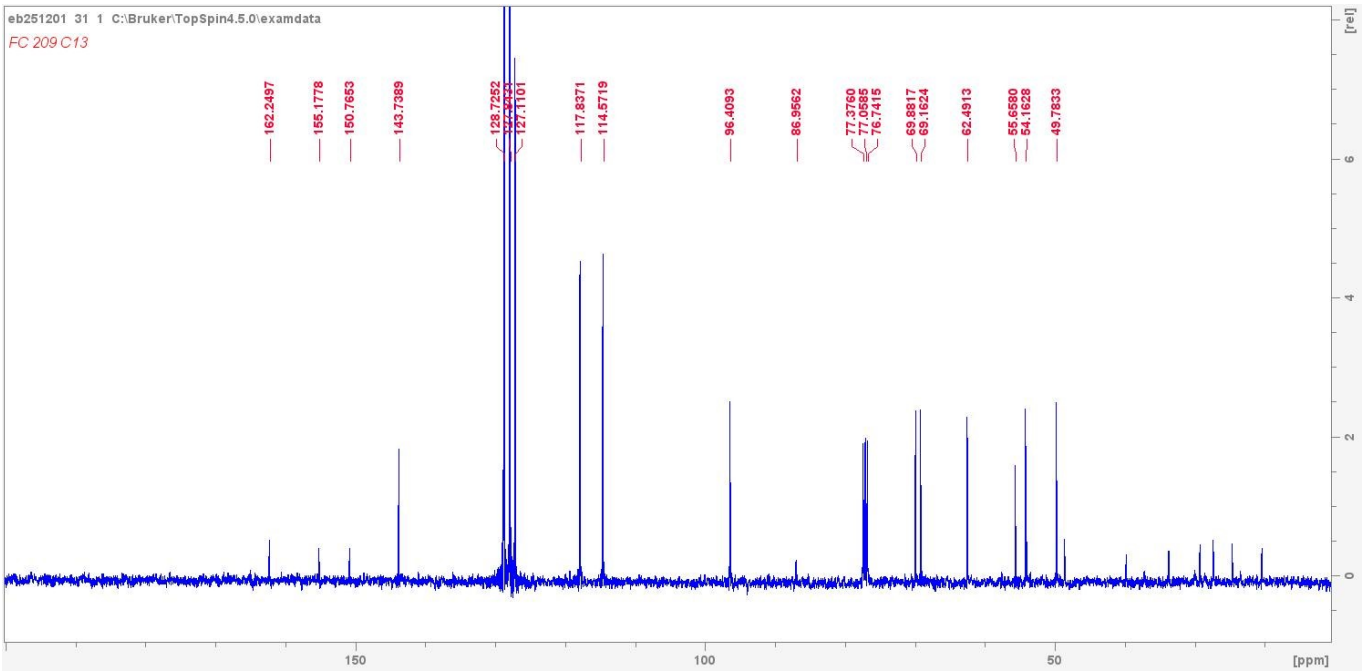
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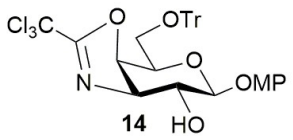
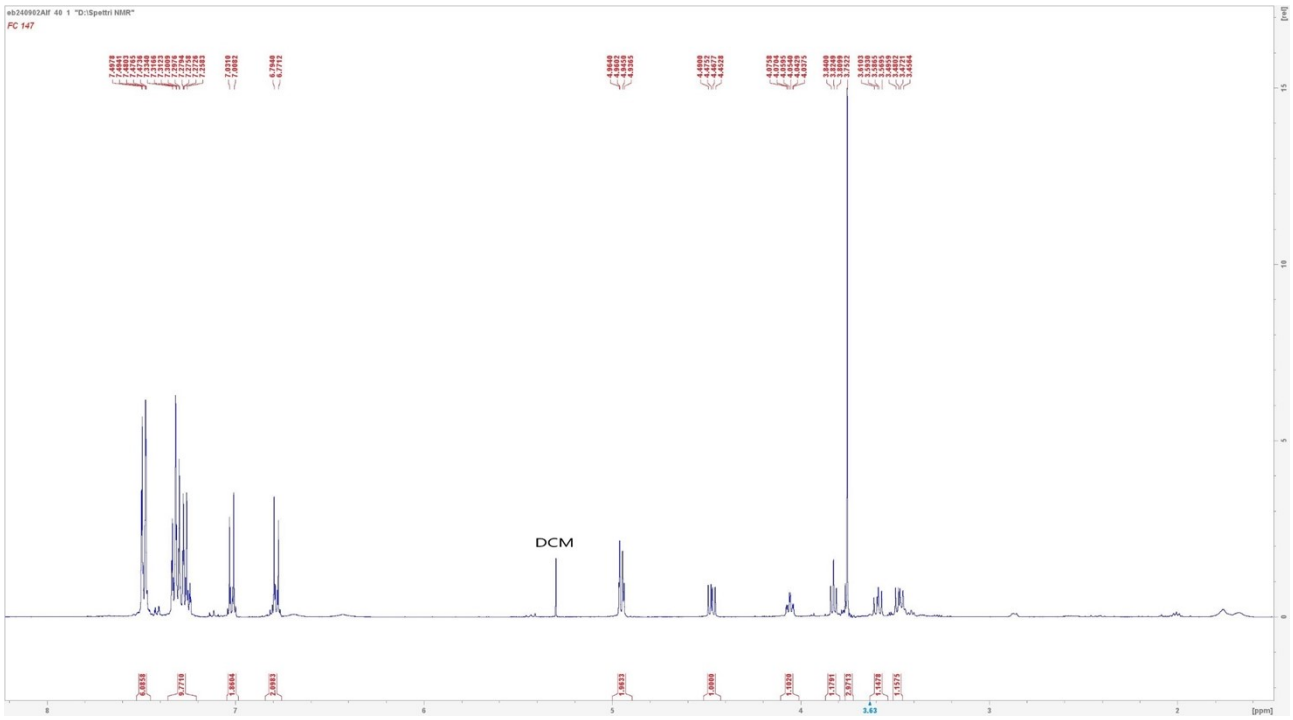
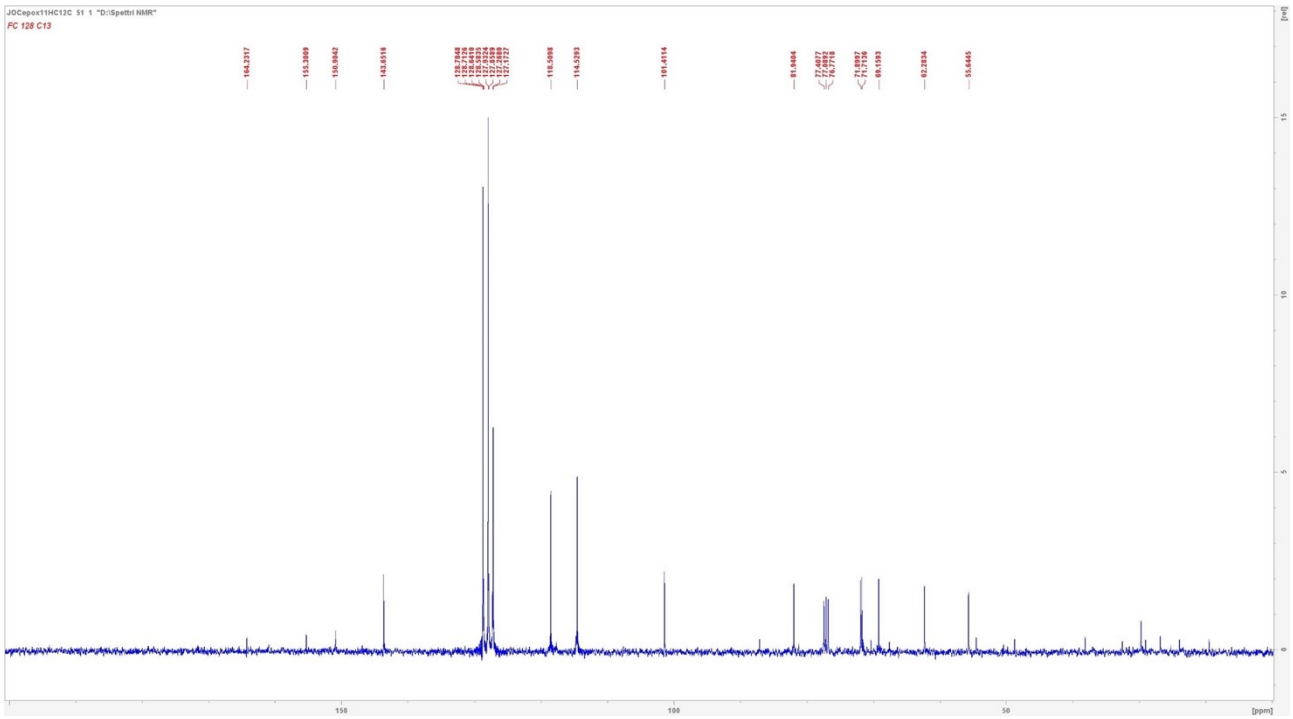
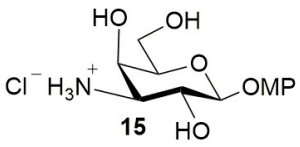


crude







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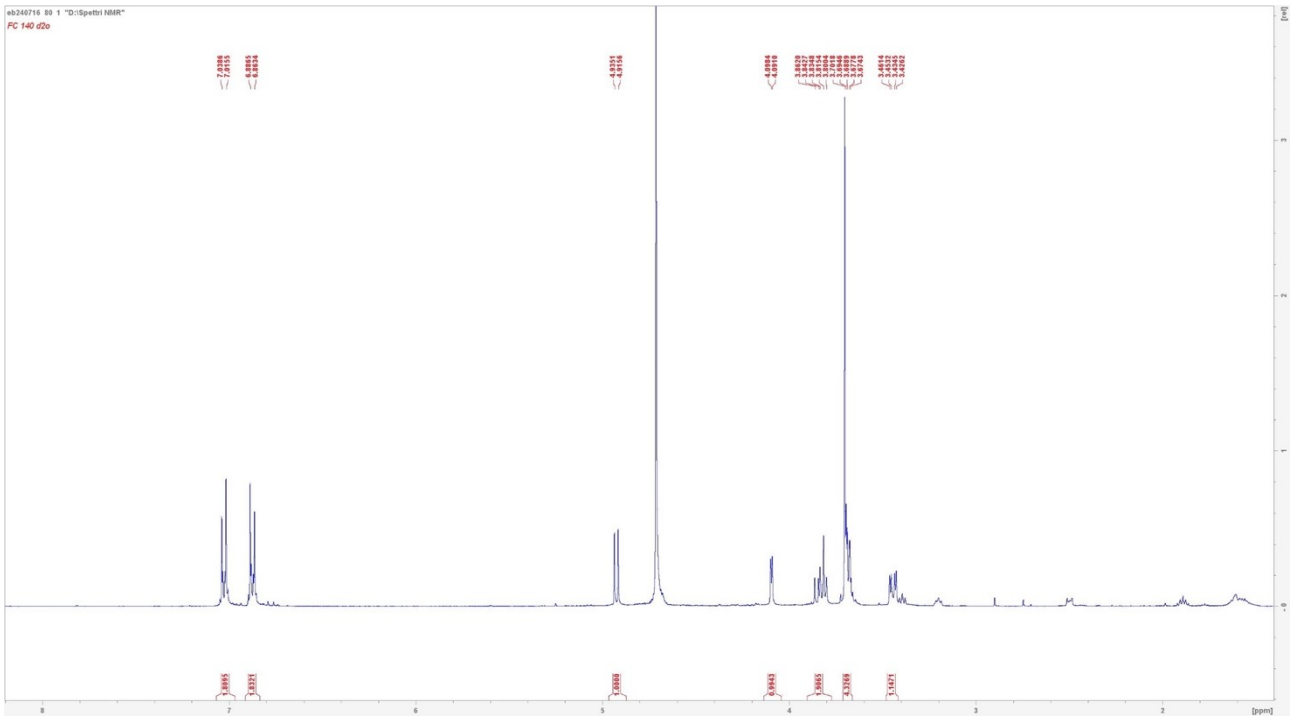
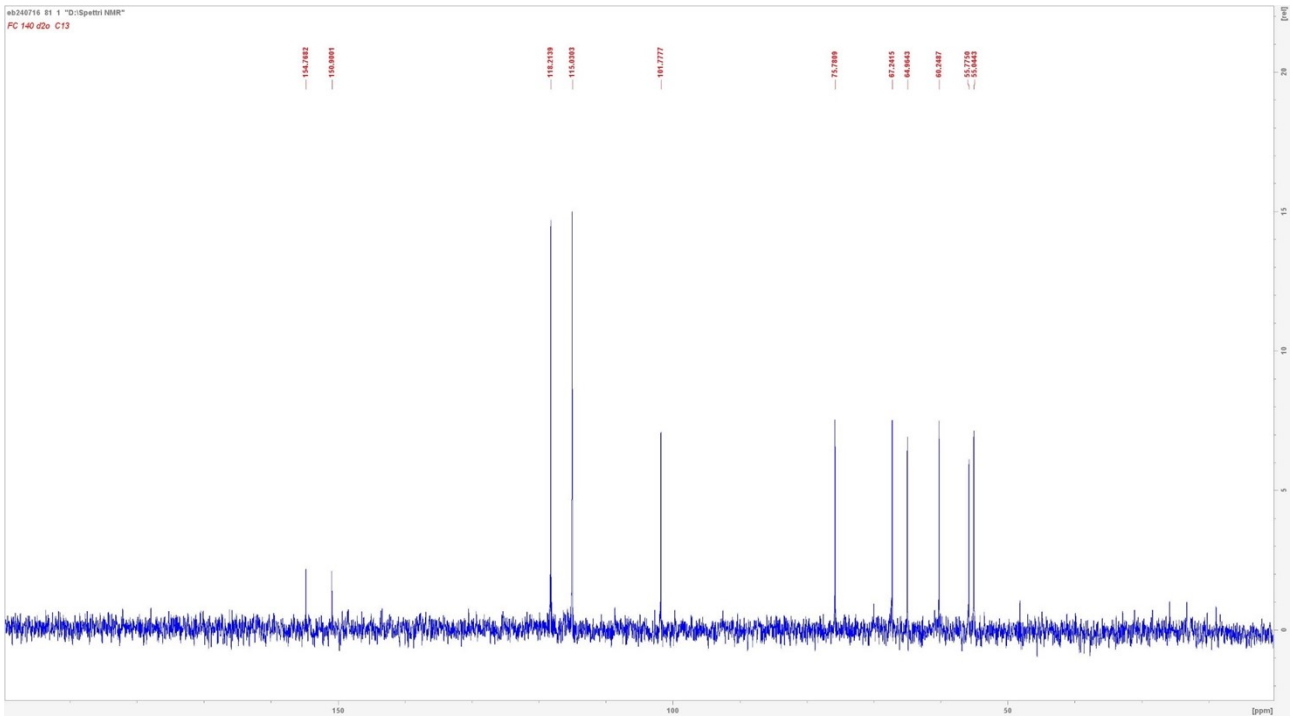
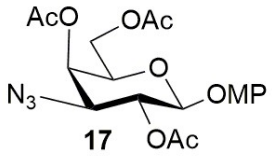
crude







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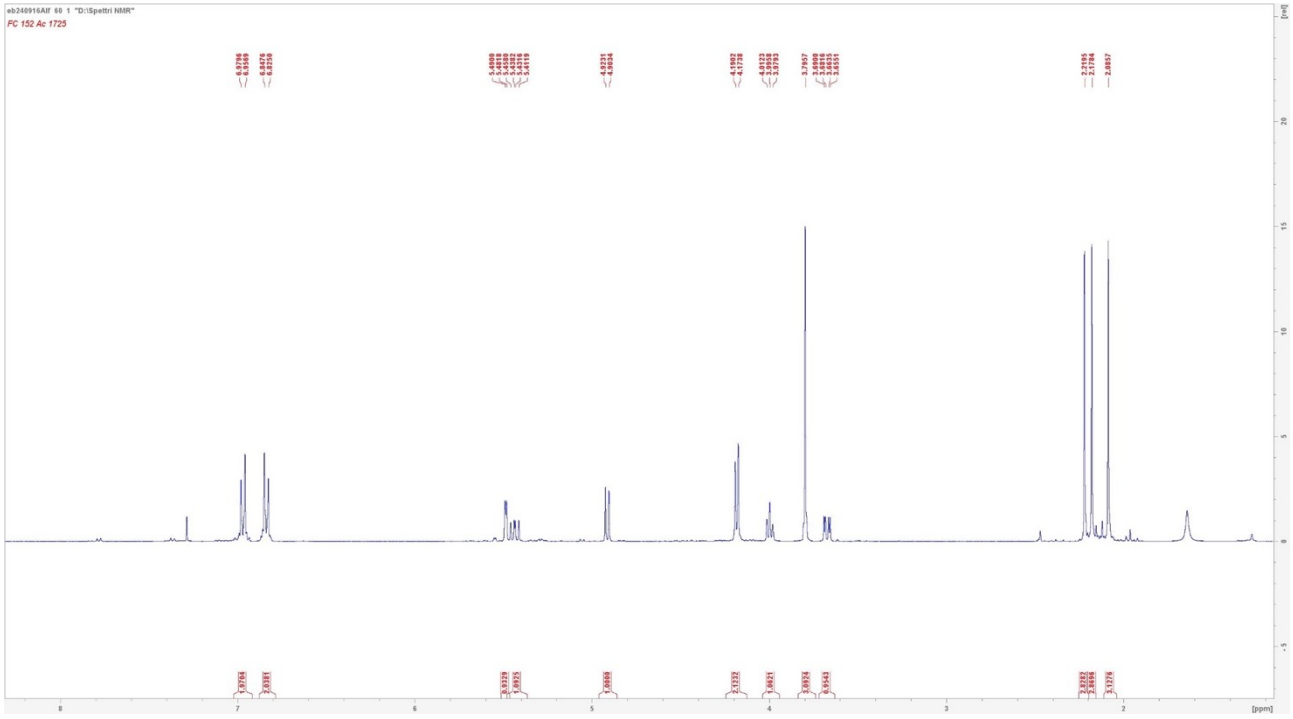
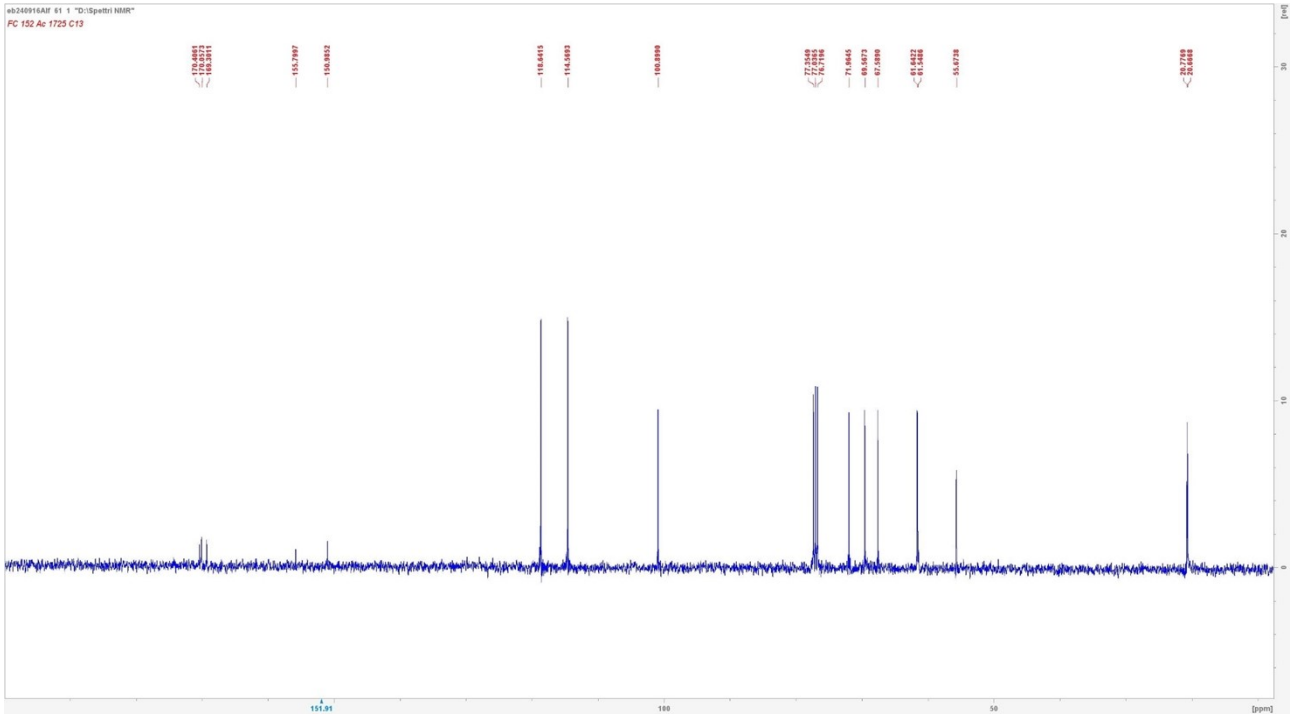
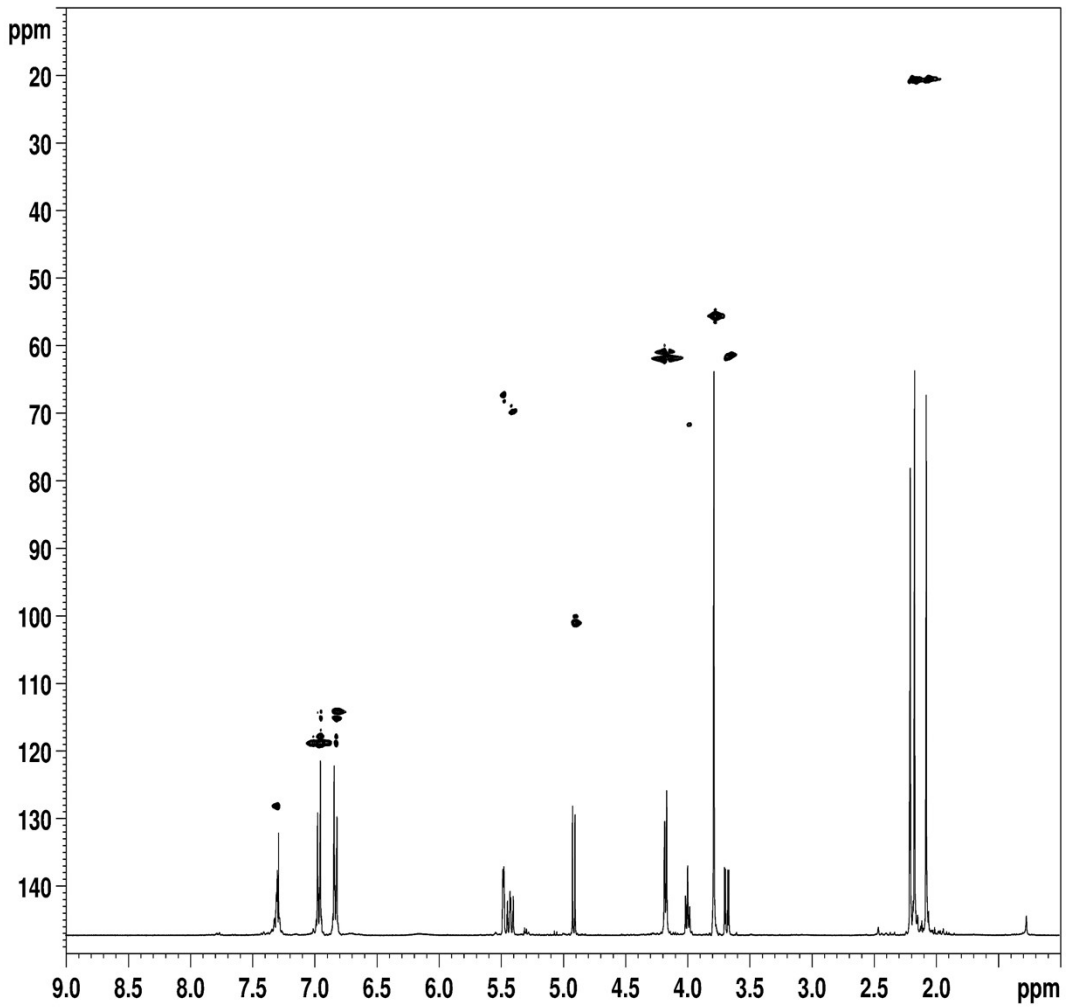
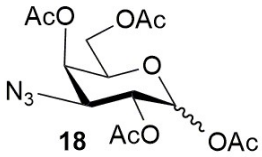




HSQC spectrum





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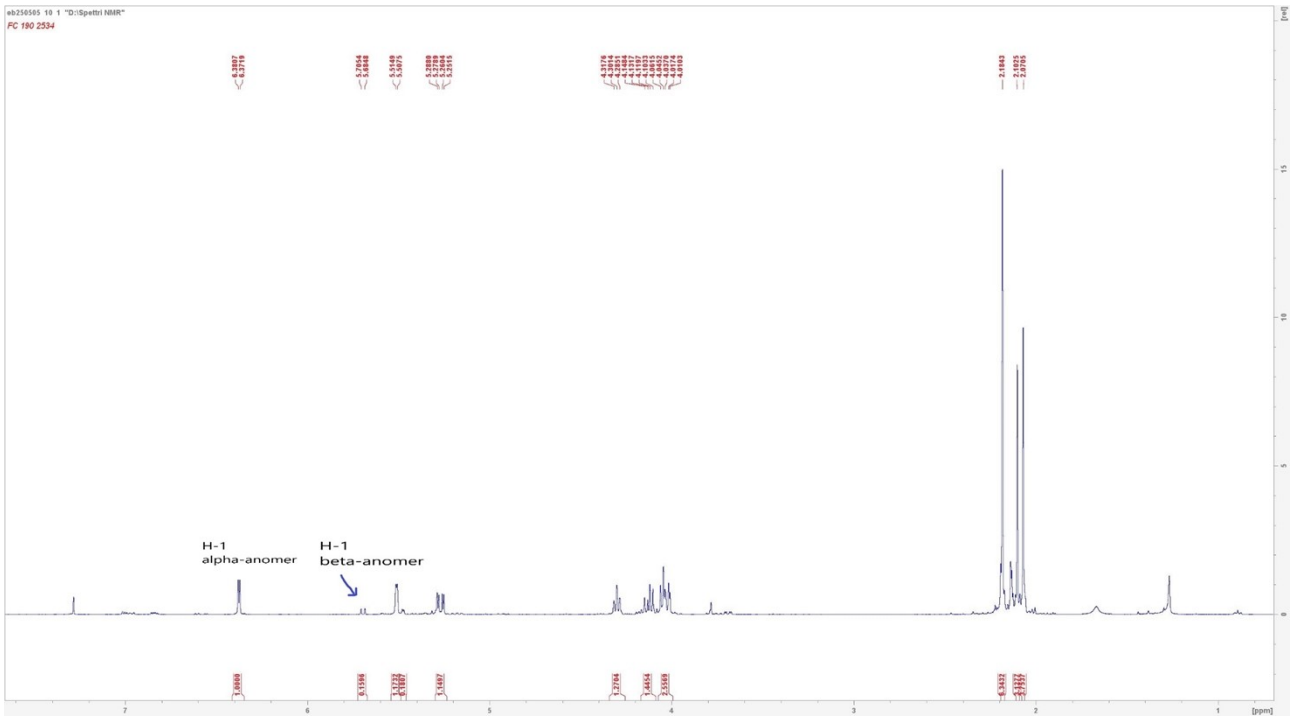
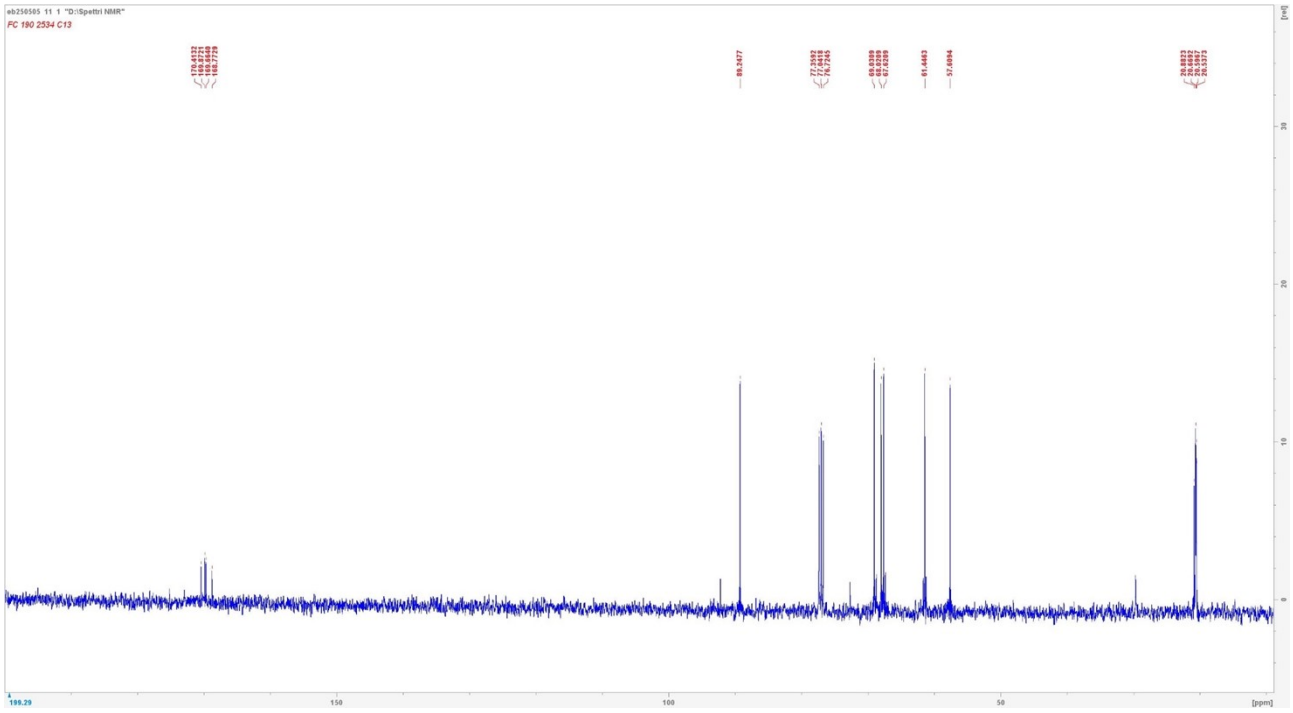
α/β 6.5:1





HSQC spectrum