Fucofullerenes are tight ligands of RSL and LecB, two bacterial lectins

Kevin Buffet, Emilie Gillon, Michel Holler, Jean-François Nierengarten*, Anne Imberty*, Stéphane P. Vincent*

Electronic Supplementary Information

I. Synthesis

General. Compounds **2**[1], **3**[1], **12**[2], **13**[3], **14**[4], **16**[5], **17**[6], **18**[2], **24**[7], **25**[8], **C_{60}(A)$_{12}$**[1] were prepared according to previously reported procedures. All reactions were carried out in standard glassware under an argon atmosphere. Yields refer to chromatographically and spectroscopically homogeneous materials. Reagents and chemicals were purchased from Sigma-Aldrich and Acros at ACS grade and were used without purification. All reactions were performed using purified and dried solvents: tetrahydrofuran (THF) was refluxed over sodium-benzophenone, dichloromethane (CH_2Cl_2), triethylamine (NEt_3), and pyridine were refluxed over calcium hydride (CaH_2). All reactions were monitored by thin-layer chromatography (TLC) carried out on Merck aluminum roll silica gel 60-F254 using UV light and a molybdate-sufuric acid solution as revelator. Merck silica gel (60, particle size 0.040–0.063 mm) was employed for flash column chromatography using technically solvent distilled prior to use as eluting solvents. IR spectra (cm^{-1}) were recorded on a Perkin–Elmer Spectrum 65 spectrophotometer. UV/Vis spectra (λ_{max} in nm (ε)) were recorded on a SPECORD 205 spectrophotometer. NMR spectra were recorded on a JEOL ECX 400 with solvent peaks as reference. All compounds were characterized by ^1H and ^{13}C NMR as well as by ^1H-^1H and ^1H-^{13}C correlation experiment when necessary. The following abbreviations are used to describe the multiplicities: s= singlet, d= doublet, t= triplet, m= multiplet, br= broad, br s= broad singlet. The numbering of the protons and carbons is analogous to the proton numbers resulting from the name of the compound. Aromatic, acetyl and methyl (carbons and protons) are respectively labeled with "Arom", "Ac" and "Me", quaternary carbons are indicated with a "q" subscript. Chemical shifts (δ) are reported in ppm and referenced indirectly to TMS *via* the solvent (or residual solvent) signals. MALDI-MS mass spectra were recorded in University of Mons (UMH, Mass Spectrometry Research Group - CISMa) using a Waters QToF Premier mass spectrometer.

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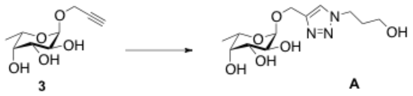
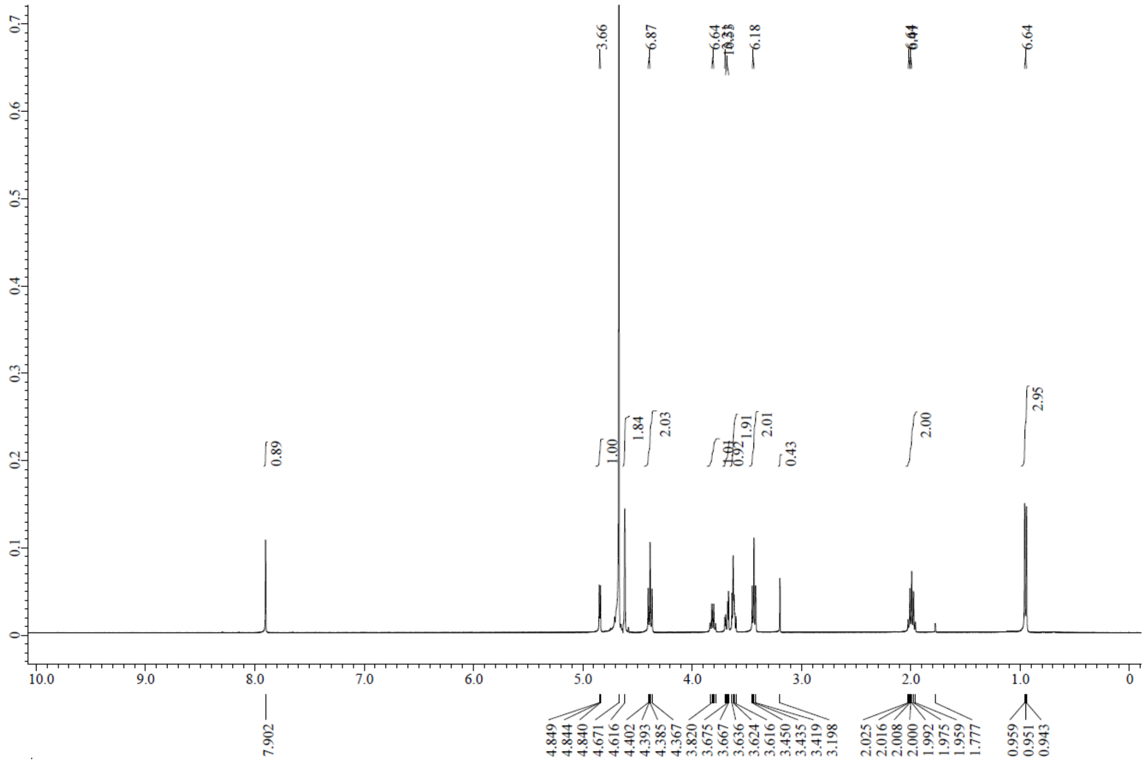
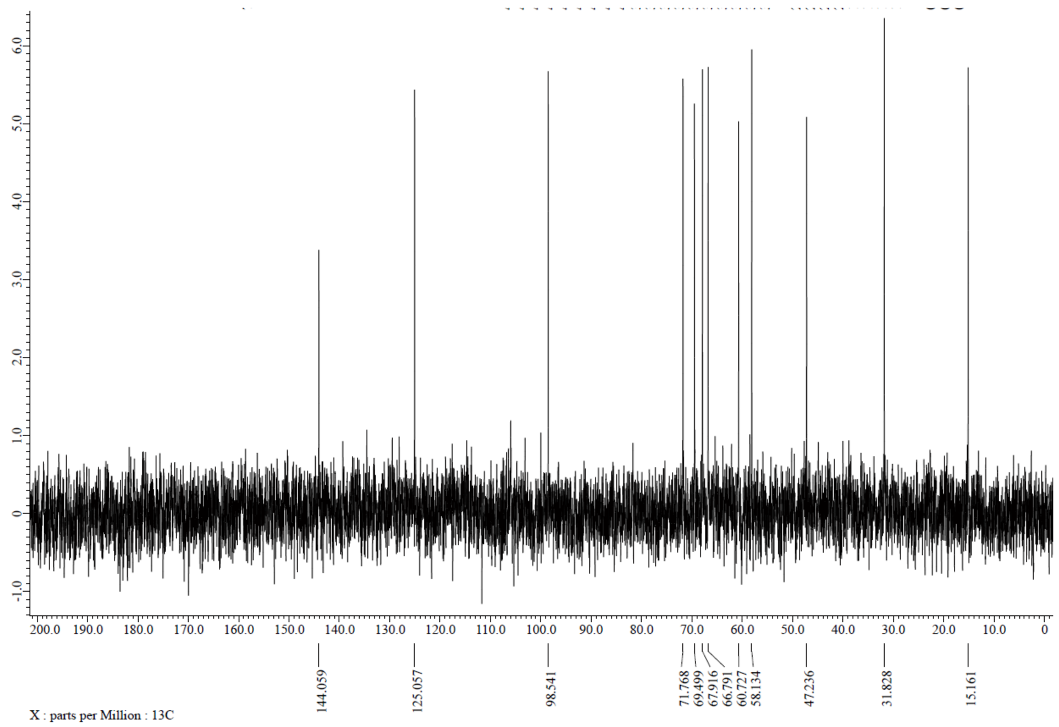
Synthesis of compound A

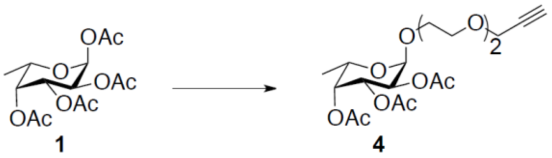


To a solution of **3** (0.100 g, 0.49 mmol, 1 eq) in *t*-BuOH/H_2O 1:1 (3 mL) was added **25** (0.060 g, 0.59 mmol, 1.2 eq), sodium ascorbate (0.020 g, 0.10 mmol, 0.2 eq) and copper (II) sulfate (0.008 g, 0.05 mmol, 0.1 eq) under argon atmosphere. The solution was stirred during three hours at room temperature. Afterwards the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc to EtOAc/MeOH 9:1) to afford **A** (0.100 g, 67%) as a colorless oil. **^{1}H NMR** (400 MHz, D_2O) δ = 7.90 (s, 1H, H_{arom}), 4.84 (d, J = 3.7Hz, 1H, H-1), 4.62 (s, 2H, O$\mathit{CH_2}$C=C), 4.39 (t, J = 3.9 Hz, 2H, N$\mathit{CH_2}$$CH_2CH_2$OH), 3.81 (q, J = 6.6Hz, 1H, H-5), 3.68 (dd, J = 3.2Hz, J = 10.5Hz, H-2, 1H), 3.64-3.60 (m, 2H, H-3, H-4), 3.44 (t, J = 6.2 Hz, 2H, N$CH_2CH_2$$\mathit{CH_2}$OH), 1.99 (tt, J = 6.4Hz, J = 6.6Hz, 2H, N$CH_2$$\mathit{CH_2}$$CH_2$OH), 0.95 (d, J = 6.6 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, D_2O) δ = 144.06 (C_{arom}) 125.06 (C_{arom}), 98.54 (C-1), 71.77, 69.50 (C-2), 67.92, 66.79 (C-5), 60.73 ($\mathit{CH_2}$C=C), 58.13 (N$CH_2CH_2$$\mathit{CH_2}$OH), 47.24 (N$\mathit{CH_2}$$CH_2CH_2$OH), 31.83 (N$CH_2$$\mathit{CH_2}$$CH_2$OH), 15.16 (C-6). **[α]$_d$** (MeOH, c=0.5, 20°C) = -126.4 **Mass** (TOF-MS-ESI$^+$): m/z: 326.13 (100%) [M+Na]$^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{19}H_{28}O_{10}Na^+$: 326.1323; found: 326.1312.

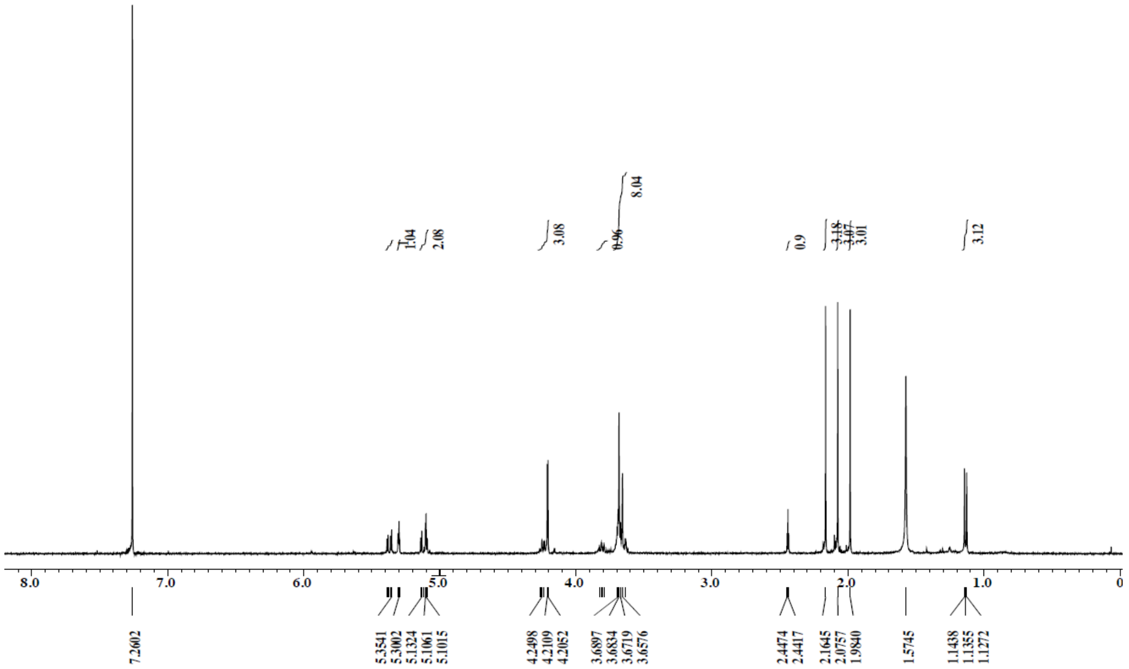




Synthesis of compound 4.



To a solution of **1** (3.00 g, 9.03 mmol, 1 eq) in dry CH_2Cl_2 (60.0 mL) was added **12** (5.20 g, 36.11 mmol, 4 eq) and boron trifluoride diethyl etherate (4.58 mL, 36.11 mmol, 4 eq) at 0°C under argon atmosphere and the solution was stirred during 7 days at room temperature. The reaction mixture was then washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and water (50 mL), extracted with CH_2Cl_2 (3x50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Cy/EtOAc 8:2 to Cy/EtOAc 5:5) to afford **4** (0.88 g, 23%) as a yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.36 (dd, J = 3.2 Hz, J = 10.0 Hz, 1H, H-2), 5.30 (d, J = 1.8 Hz, 1H, H-3), 5.14-5.09 (m, 2H, H-1, H-4), 4.23 (q, J = 6.4 Hz, 1H, H-5), 4.20 (d, J = 2.3 Hz, 2H, CH_2O), 3.82-3.76 (m, 1H, CH_2O), 3.68-3.62 (m, 7H, 4CH_2O), 2.43 (t, J = 2.3 Hz, 1H, $OCH_2C\mathit{CH}$), 2.15, 2.06, 1.97 (3s, 9H, 3CH_3), 1.12 (d, $J_{5,6}$ = 6.6 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 170.76, 170.58, 170.16 (3C, 3C=O), 96.34 (C-1), 79.68, 74.69, 71.32, 70.64, 70.22, 69.20, 68.25, 68.14, 67.60, 64.41 (10C, C-2, C-3, C-4, C-5, 4CH_2O, $OCH_2\mathit{C}CH$, $OCH_2C\mathit{CH}$), 58.52 ($O\mathit{CH_2}CCH$), 20.94, 20.82, 20.77 (3C, 3CH_3), 15.96 (C-6). **$[\alpha]_d$** ($CHCl_3$, c=1, 20°C) = -145.8 **Mass** (TOF-MS-ESI$^+$): m/z: 439.1584 (100%) $[M+Na]^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{19}H_{28}O_{10}Na^+$: 439.1575; found: 439.1584.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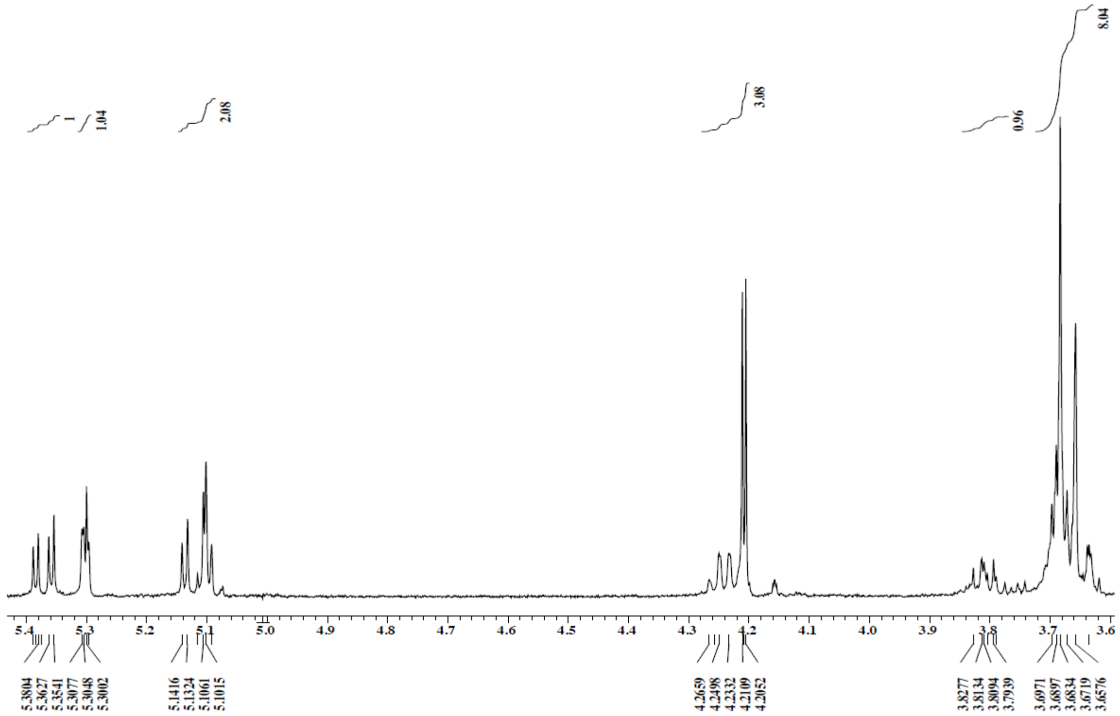
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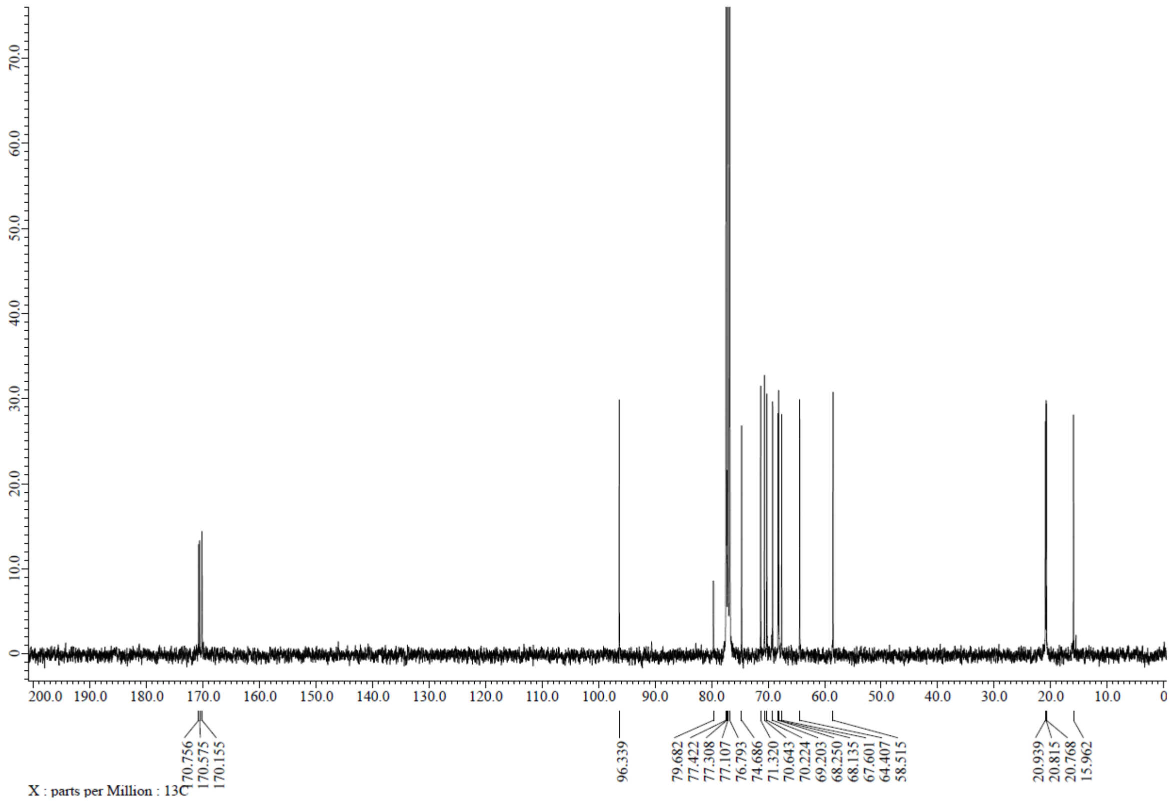
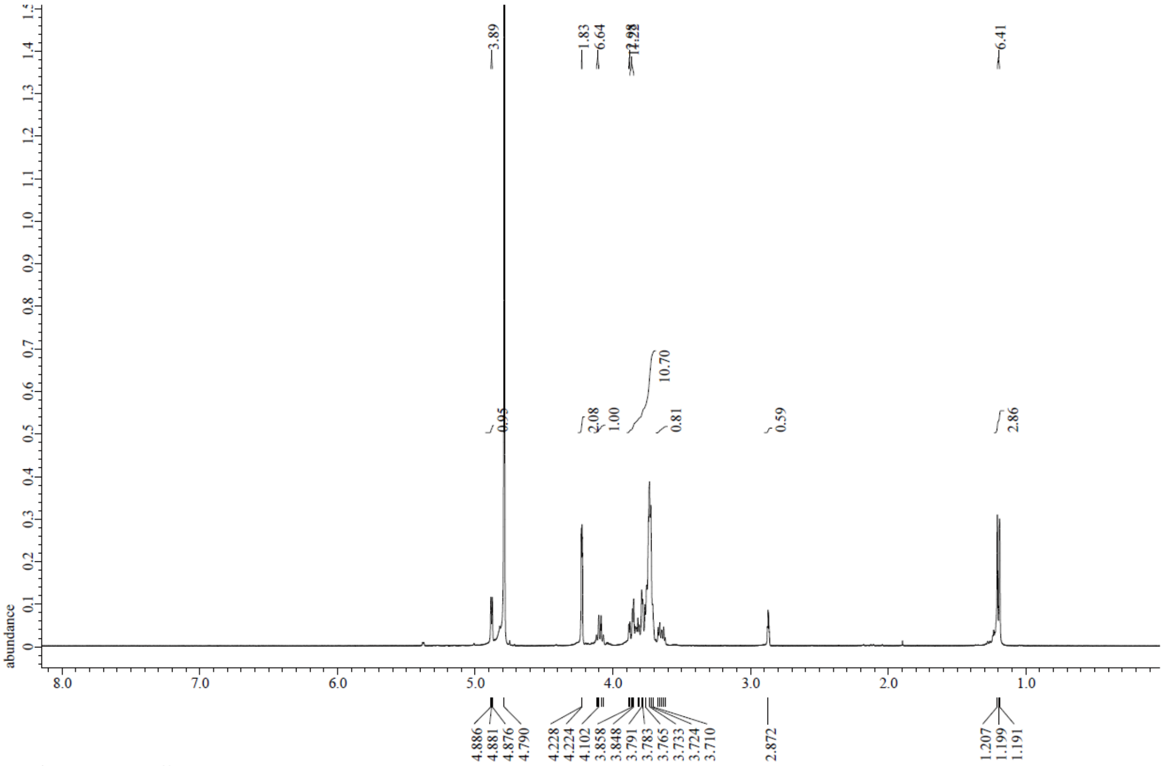


Synthesis of compound 5.

To a solution of **4** (0.40 g, 0.96 mmol, 1 eq) in methanol (5 mL) was added sodium methoxide (0.05 g, 0.96 mmol, 1 eq) at 0°C. The solution was stirred during two hours at room temperature then filtered over a short column of Dowex™ 50WX8-200 (H^+ resin form). The resin was washed with methanol (15 mL) and water (15 mL). Finally, the solvents were evaporated under reduced pressure to afford the desired product **5** as a yellowish oil (0.28 g, 99%). **^{1}H NMR** (400 MHz, D_2O) δ = 4.76 (d, J = 3.9 Hz, 1H, H-1), 4.10 (d, J = 1.6 Hz, 2H, OCH_2CCH), 3.97 (q, J = 6.6 Hz, 1H, H-5), 3.76-3.58 (m, 10H, H-2, H-3, H-4, 4CH_2O), 3.54-3.50 (m, 1H, CH_2O), 2.74 (s, 1H, $OCH_2CC\mathit{H}$), 1.07 (d, J = 6.6 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, D_2O) δ = 98.61 (C-1), 79.31 (OCH_2CCH), 75.96, 71.85, 69.75, 69.59, 69.48, 68.64, 68.13, 66.82, (8C, C-2, C-3, C-4, 4CH_2O, $OCH_2\mathit{CCH}$), 66.68 (C-5), 57.94 (OCH_2CCH), 15.32 (C-6). **[α]$_d$** (H_2O, c=1, 20°C) = -116.9 **Mass** (TOF-MS-ESI$^+$): m/z: 313.1253 (100%) $[M+Na]^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{13}H_{22}O_7Na^+$: 313.1258; found: 313.1253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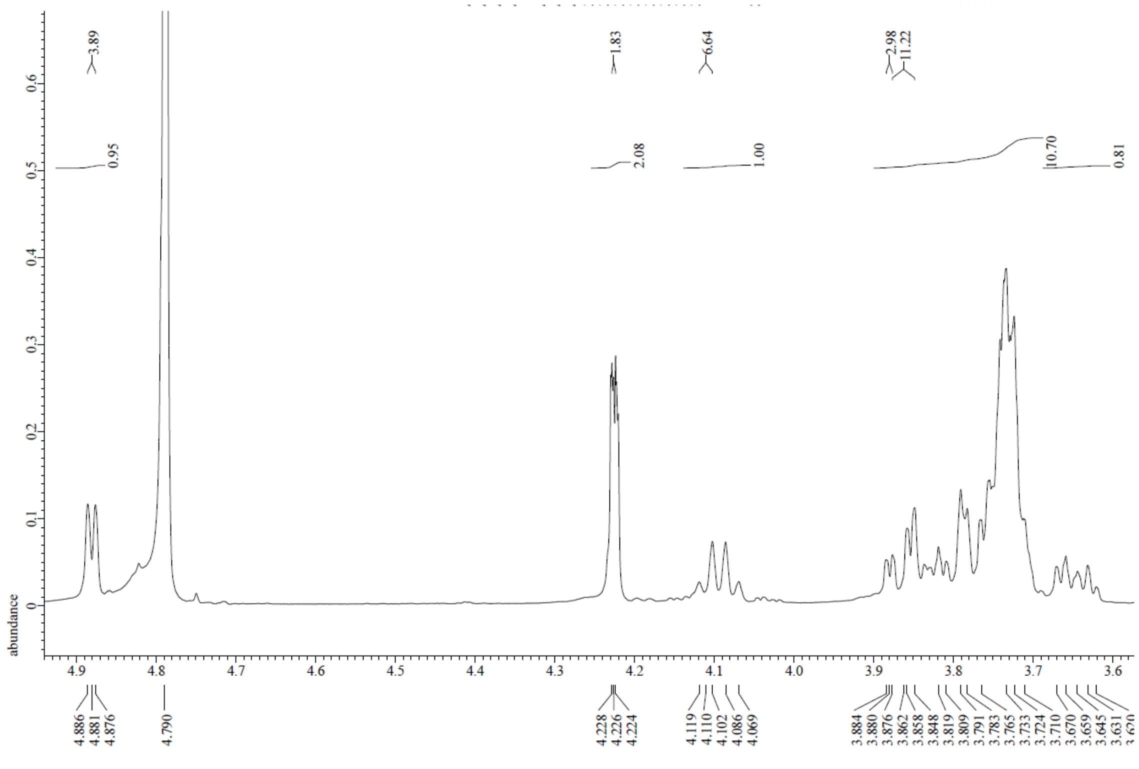
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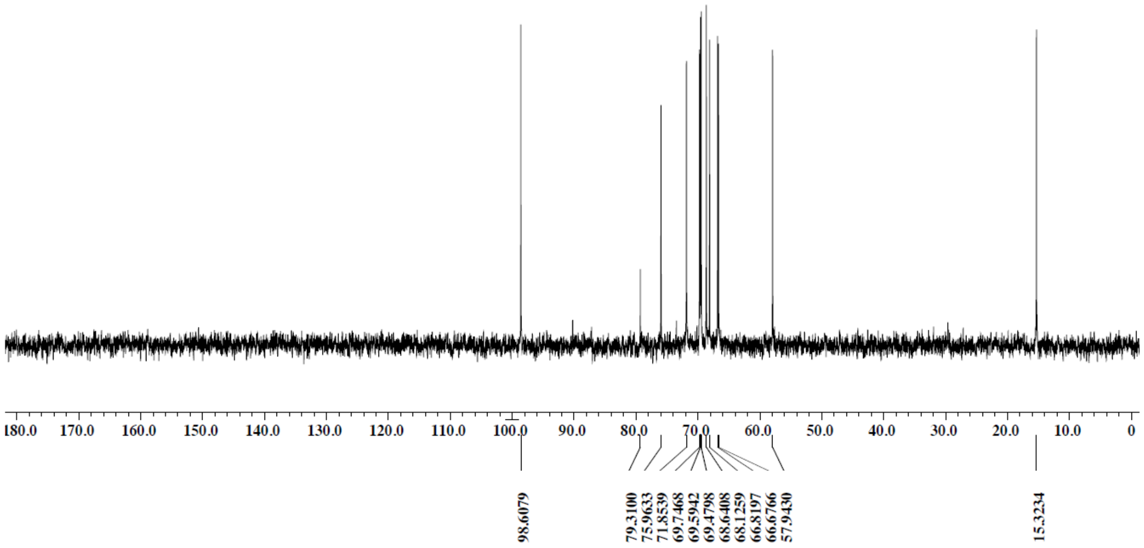
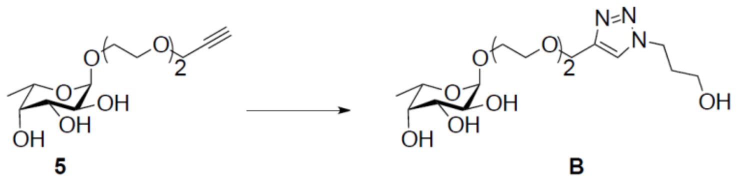
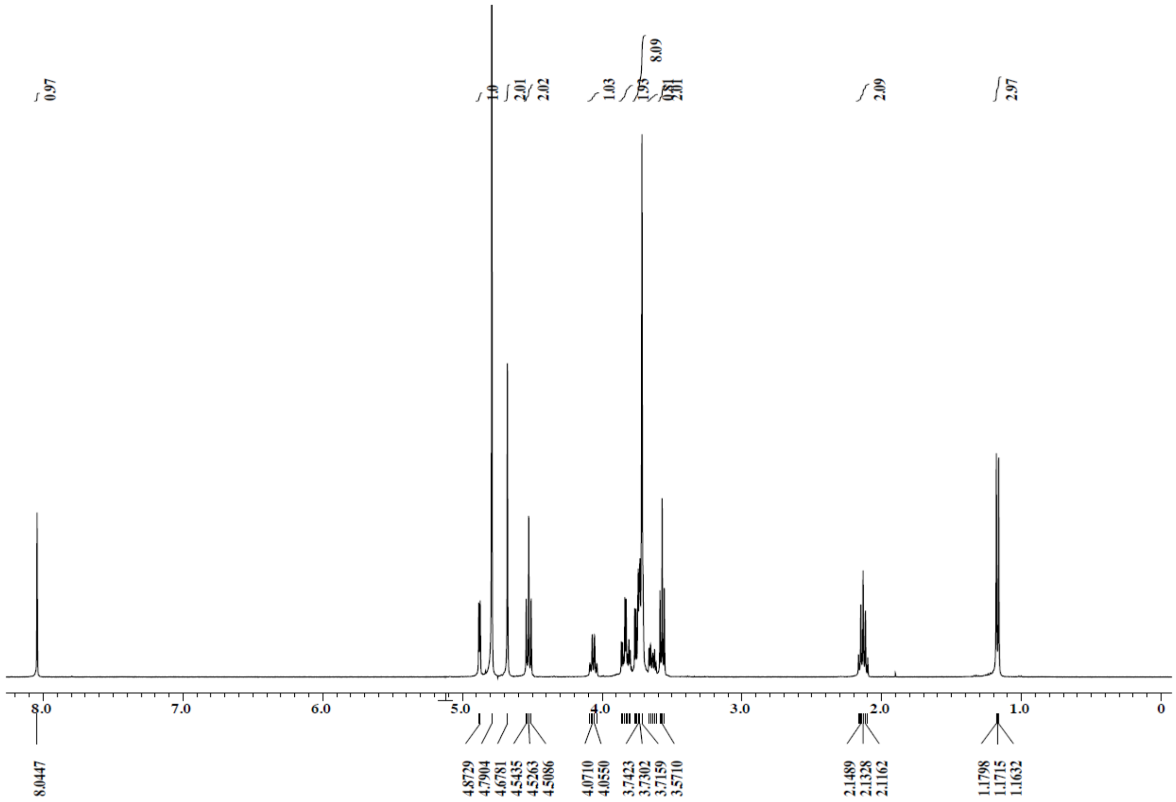


Synthesis of compound B



To a solution of **5** (0.057 g, 0.19 mmol, 1 eq) in *t*-BuOH/H_2O 1:1 (1.5 mL) was added **25** (0.029 g, 0.24 mmol, 1.2 eq), sodium ascorbate (0.0077 g, 0.039 mmol, 0.2 eq) and copper (II) sulfate (3.0 mg, 0.019 mmol, 0.1 eq) under argon atmosphere. The solution was stirred during six hours. Afterwards the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc to EtOAc/MeOH 9:1) to afford **B** (0.038 g, 50%) as a colorless oil. **^{1}H NMR** (400 MHz, D_2O) δ = 8.04 (s, 1H, H_{arom}), 4.88 (d, J = 3.9 Hz, 1H, H-1), 4.68 (s, 2H, O*CH_2*C=C), 4.53 (t, J = 6.9 Hz, 2H, N*CH_2*CH_2CH_2OH), 4.06 (q, J = 6.9 Hz, 1H, H-5), 3.83 (dd, J = 3.4 Hz, J = 10.3 Hz, 1H, H-2), 3.85-3.80 (m, 1H), 3.77-3.72 (m, 8H, H-3, H-4, 3CH_2O), 3.66-3.61 (m, 1H, CH_2O), 3.57 (t, J = 6.2 Hz, 2H, NCH_2CH_2*CH_2*OH), 2.13 (tt, J = 6.4 Hz, J = 6.9 Hz, 2H, NCH_2*CH_2*CH_2OH), 1.17 (d, J = 6.6 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, D_2O) δ = 143.83 (C_{arom}), 125.19 (C_{arom}), 98.60 (C-1), 71.83, 69.72, 69.55, 68.89, 68.10, 66.82 (7C, C-2, C-3, C-4, 4CH_2O), 66.62 (C-5), 63.06 (O*CH_2*C=C), 58.12 (NCH_2CH_2*CH_2*OH), 47.25 (N*CH_2*CH_2CH_2OH), 31.81 (NCH_2CH_2*CH_2*OH), 15.39 (C-6). **$[\alpha]_d$** (MeOH, c=0.25, 20°C) = -70.8 **Mass** (TOF-MS-ESI$^-$): m/z: 414.18 (100%) $[M+Na]^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{18}H_{33}N_3O_9Na^+$: 414.1847 $[M+H]^+$, found: 414.1832.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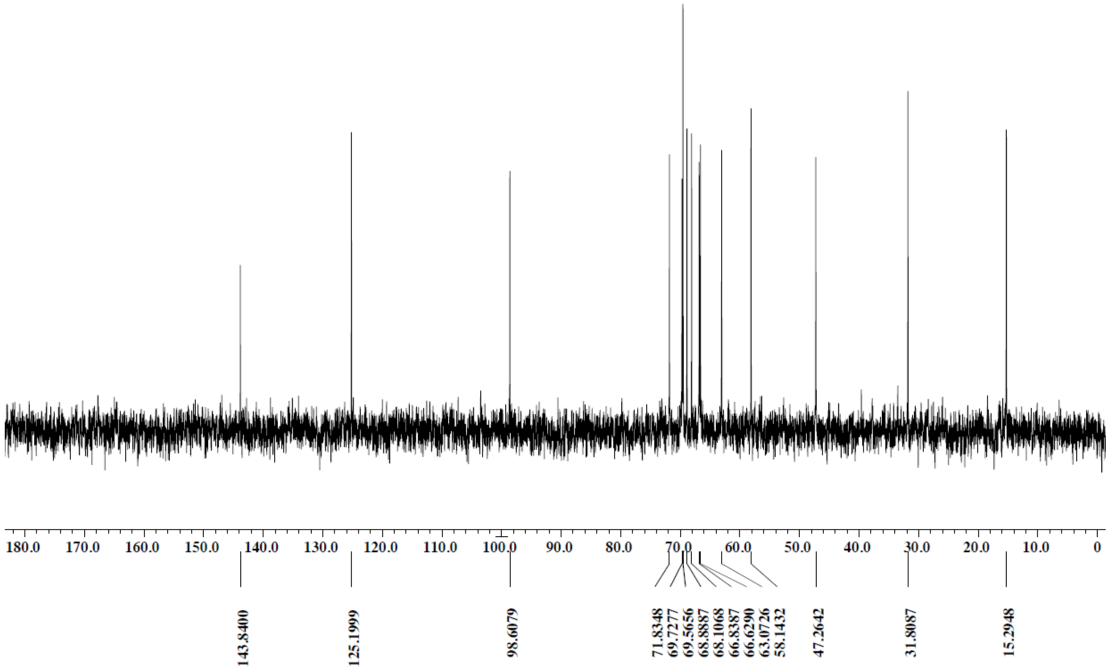
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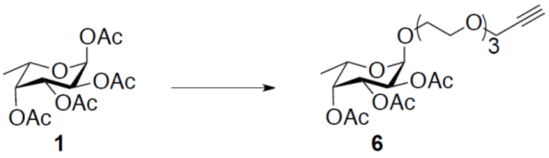
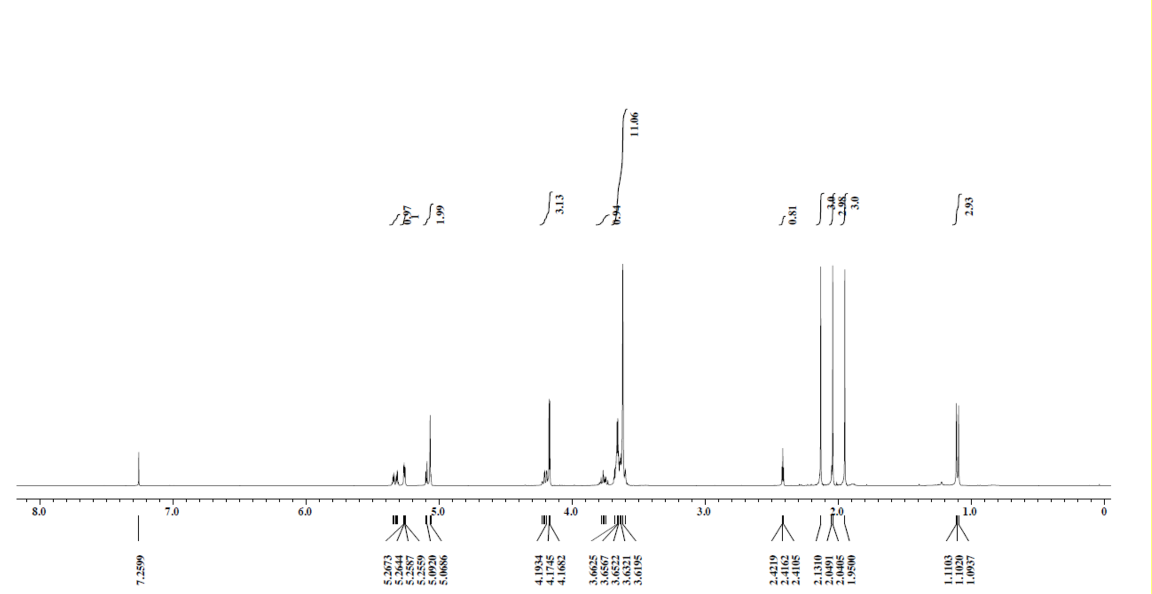
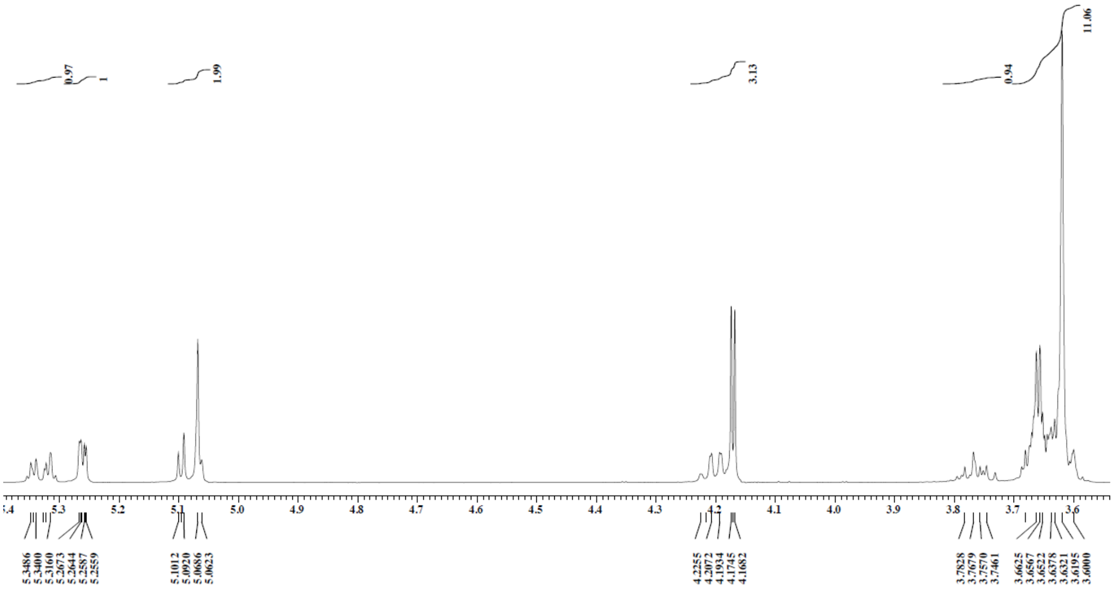
Synthesis of compound 6



To a solution of **1**(2.80 g, 8.40 mmol, 1 eq) in dry CH_2Cl_2 (60.0 mL) was added **13** (6.80 g, 33.7 mmol, 4 eq) and boron trifluoride diethyl etherate (4.27 mL, 33.7 mmol, 4 eq) at 0°C under argon atmosphere and the solution was stirred during three days at room temperature. The reaction mixture was washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and water (50 mL), extracted with CH_2Cl_2 (3x 50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Cy/EtOAc 8:2 to Cy/EtOAc 5:5) to afford **6** (0.93 g, 24%) as a yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.33 (dd, J = 3.4 Hz, J = 9.6 Hz, 1H, H-2), 5.26 (dd, J = 1.1 Hz, J = 3.4 Hz, 1H, H-4), 5.10 (d, J = 3.7 Hz, 1H, H-3), 5.07 (s, 1H, H-1), 4.25-4.21 (q, J = 7.3 Hz, 1H, H-5), 4.17 (d, J = 2.5 Hz, 2H, O*CH₂*CCH), 3.78-3.75 (m, 1H, CH_2O), 3.68-3.60 (m, 11H, $6CH_2O$), 2.42 (t, J = 2.3 Hz, 1H, OCH_2C*CH*), 2.13, 2.04, 1.95 (3s, 9H, $3CH_3$), 1.10 (d, J = 6.6 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 170.71, 170.53, 170.10 (3C, 3C=O), 96.32 (C-1), 79.73 (OCH_2*C*CH), 74.64 (OCH_2C*CH*), 71.28 (C-4), 70.78, 70.73, 70.52, 70.20, 69.17 (5C, $5CH_2O$), 68.22 (C-3), 68.10 (C-2), 67.58 (CH_2O), 64.37 (C-5), 58.44 (O*CH₂*CCH) 20.91, 20.79, 20.74 (3C, $3CH_3$), 15.94 (C-6). **[α]$_d$** ($CHCl_3$, c=1, 20°C) = -87.6 **Mass** (TOF-MS-ESI$^+$) : m/z : 483.1831 (100%) $[M+Na]^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{21}H_{32}O_{11}Na^+$: 483.1842; found: 483.1831.

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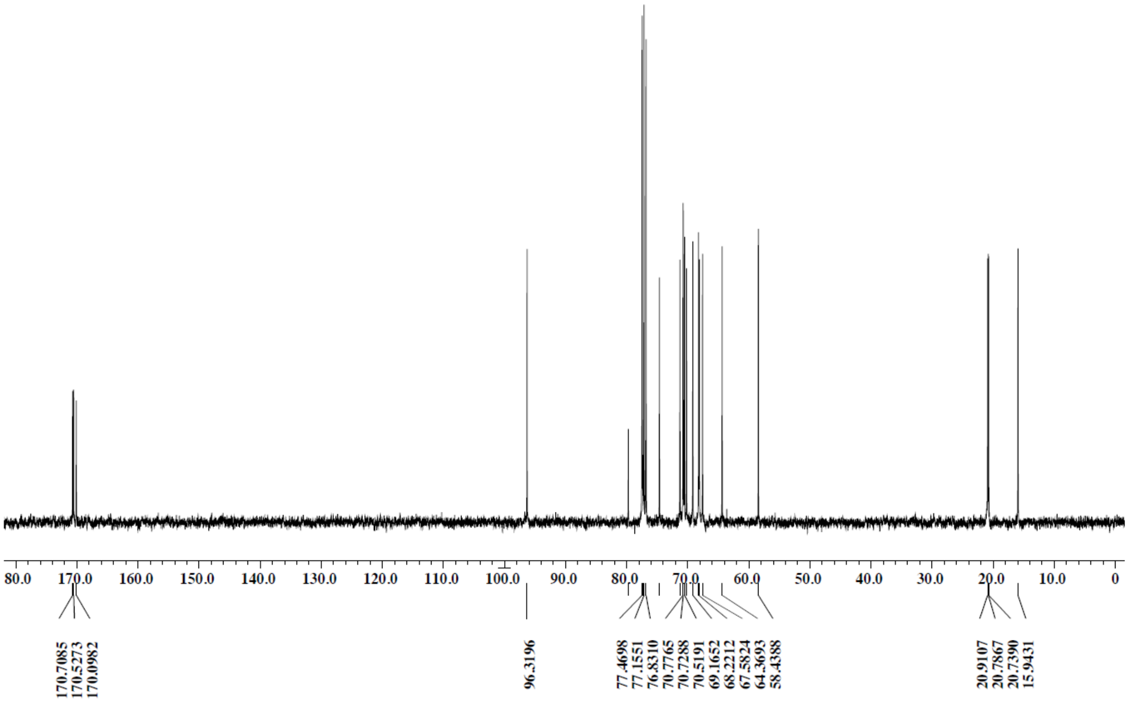
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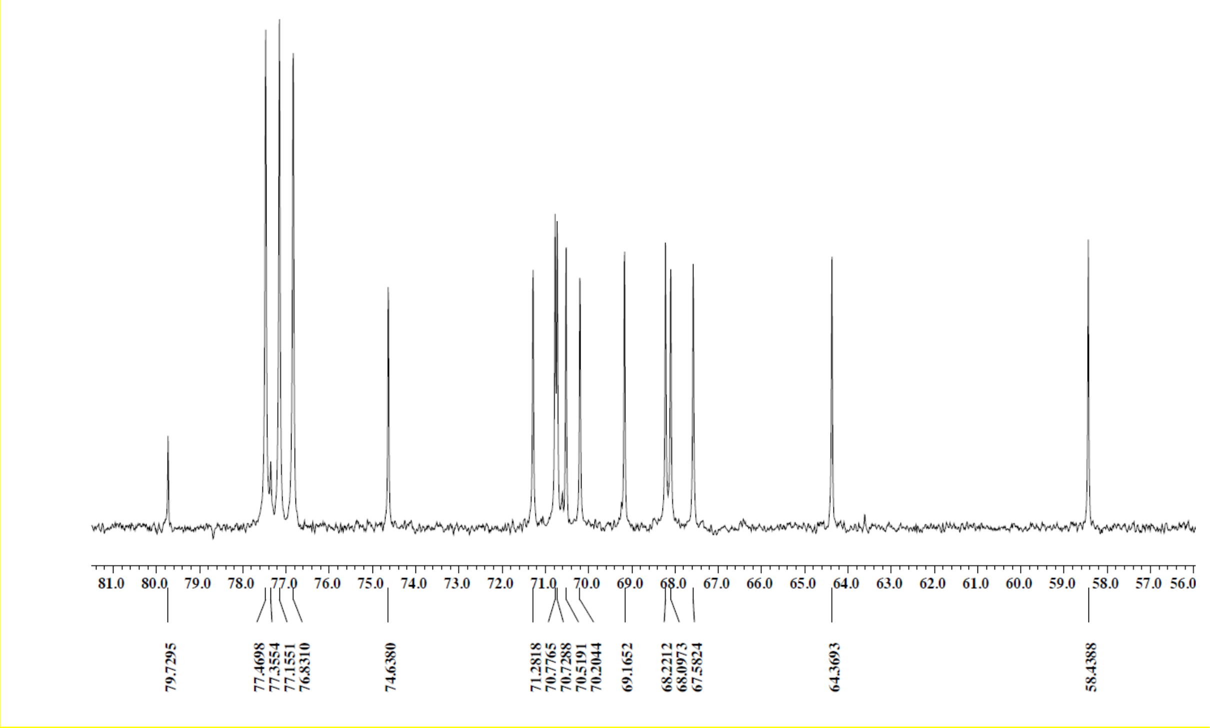
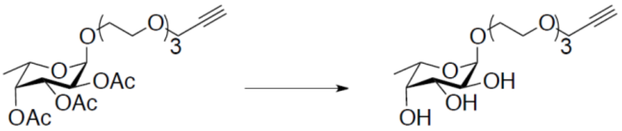
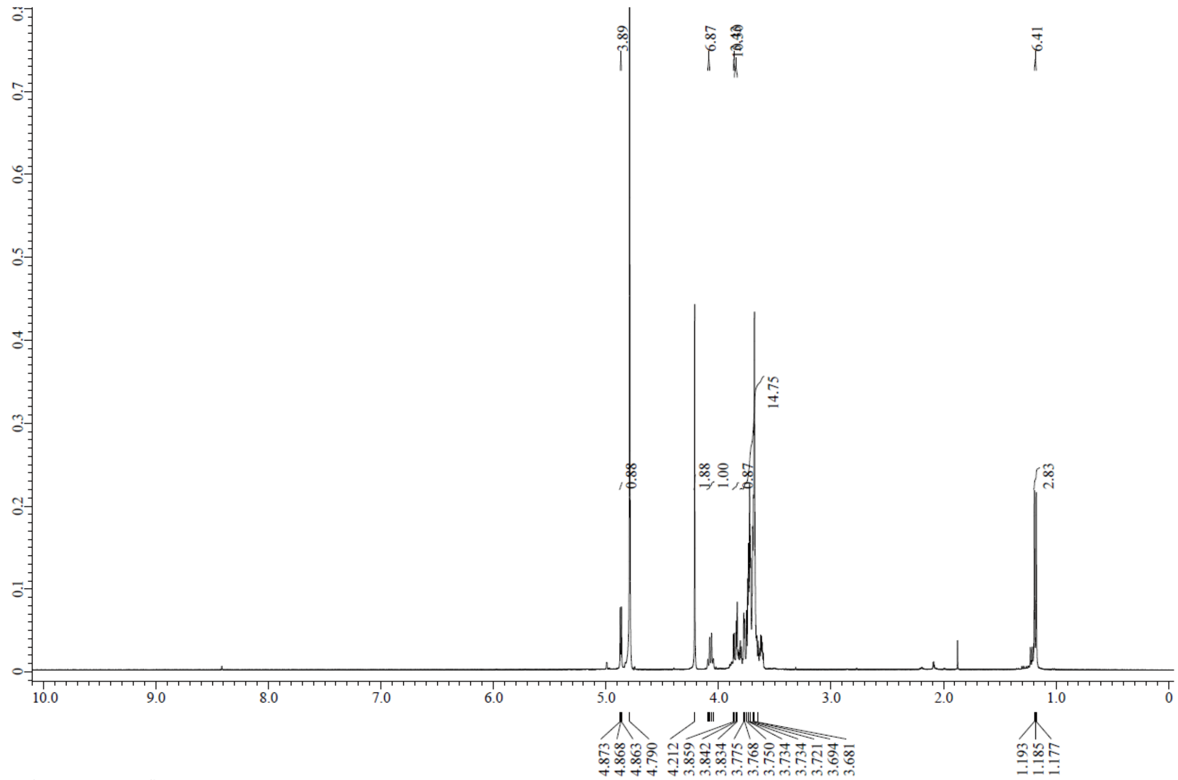


Synthesis of compound 7



6 **7**

To a solution of **6** (0.83 g, 1.81 mmol, 1 eq) in MeOH (10 mL) was added sodium methoxide (0.10 g, 1.81 mmol, 1 eq) at 0°C. The solution was stirred during two hours at room temperature then filtered over a short column of Dowex™ 50WX8-200 (H^+ resin form). The resin was washed with methanol (15 mL) and water (15 mL). Finally, the solvents were evaporated under reduced pressure to afford the desired product **7** as a yellowish oil (0.59 g, 97%). **^{1}H NMR** (400 MHz, D_2O) δ = 4.87 (d, J = 3.9 Hz, 1H, H-1), 4.21 (s, 2H, O*CH₂*CCH), 4.07 (q, J = 6.9 Hz, 1H, H-5), 3.85 (dd, J = 3.4 Hz, J = 10.3 Hz, 1H, H-3), 3.78-3.65 (m, 14H, H-2, H-4, 6CH_2O), 1.19 (d, J = 6.6 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, D_2O) δ = 98.64 (C-1), 71.84, 69.78, 69.61, 69.57, 69.46, 68.67, 68.12, 66.86, 66.66 (12C, C-2, C-3, C-4, C-5, 6CH_2O, OCH_2*C*CH, OCH_2C*CH*), 57.91 (O*CH₂*CCH), 15.30 (C-6). **[α]d** ($CHCl_3$, c=1, 20°C) = -65.7 **Mass** (TOF-MS-ESI$^+$): m/z: 357.1517 (100%) $[M+Na]^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{15}H_{26}O_8Na^+$: 357.1525; found: 357.1517.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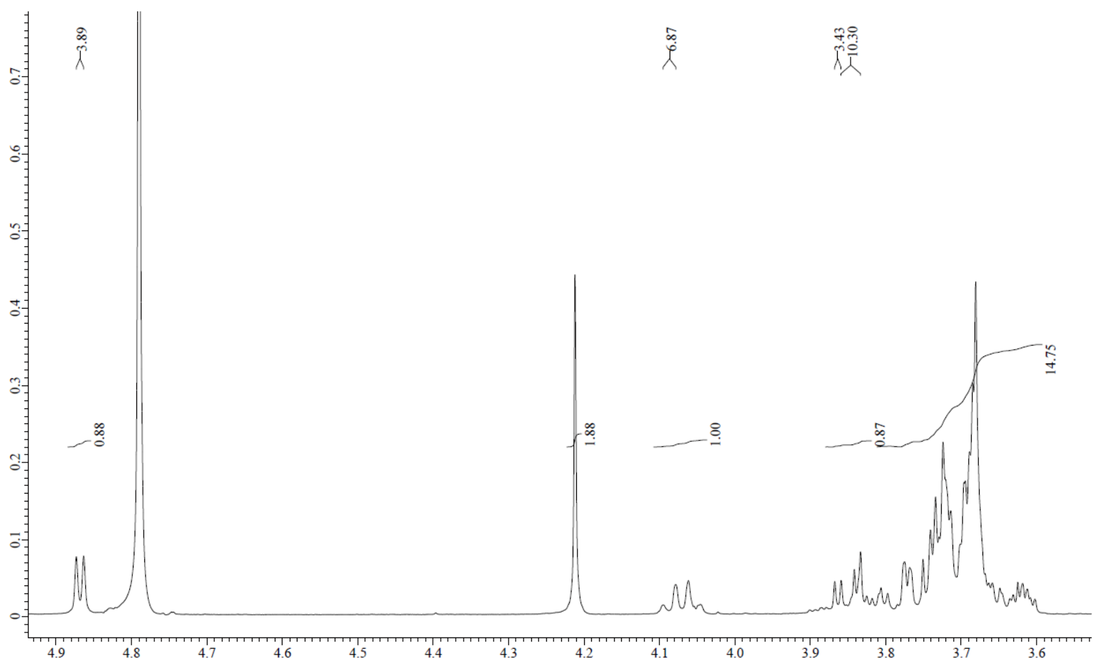
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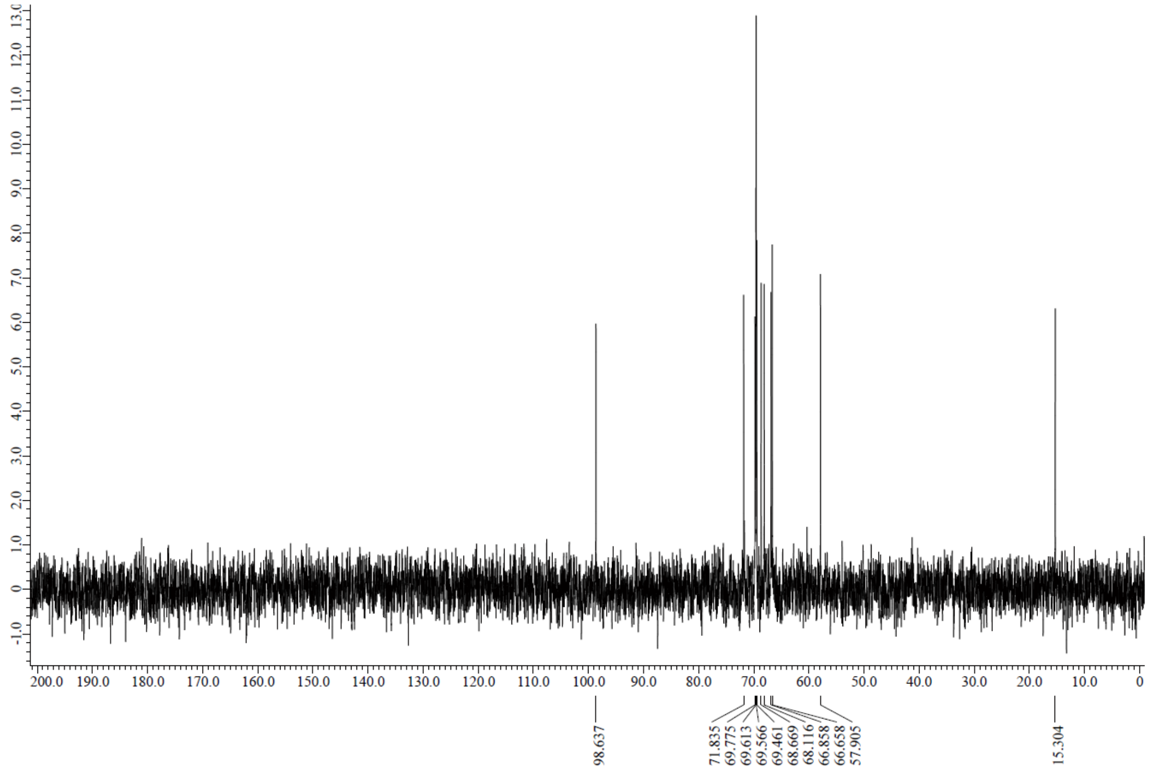

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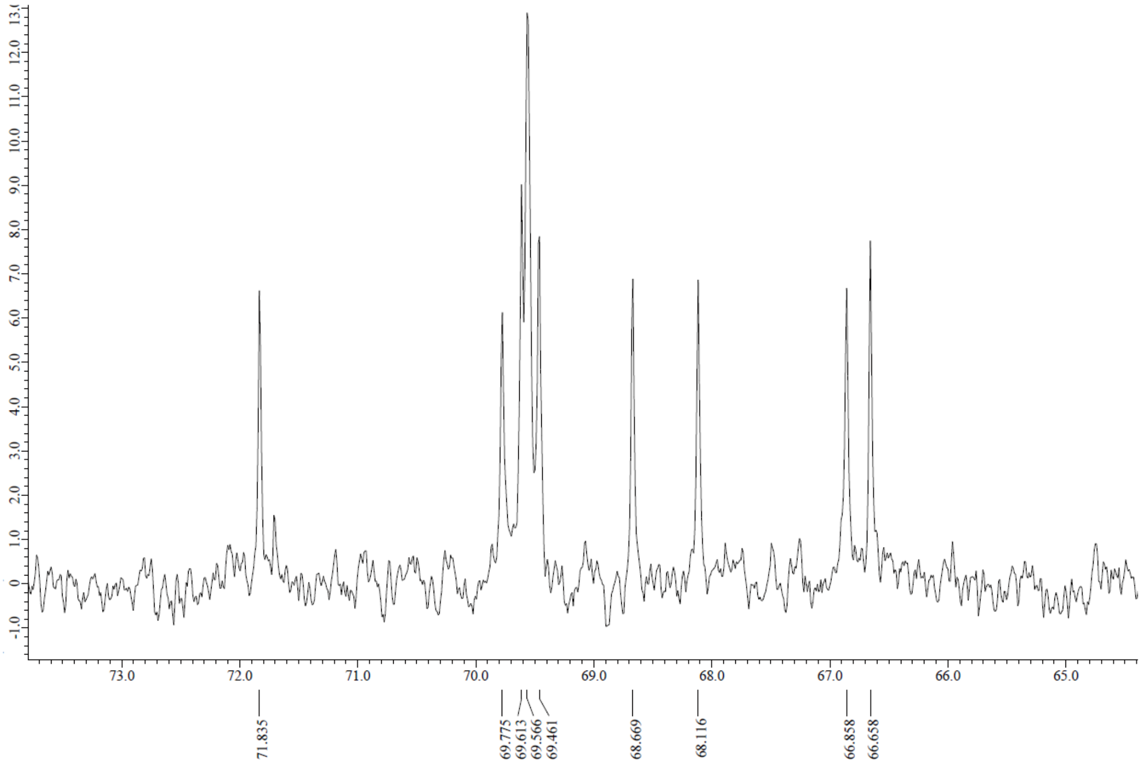

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-1.0
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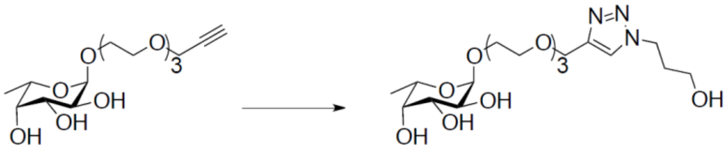
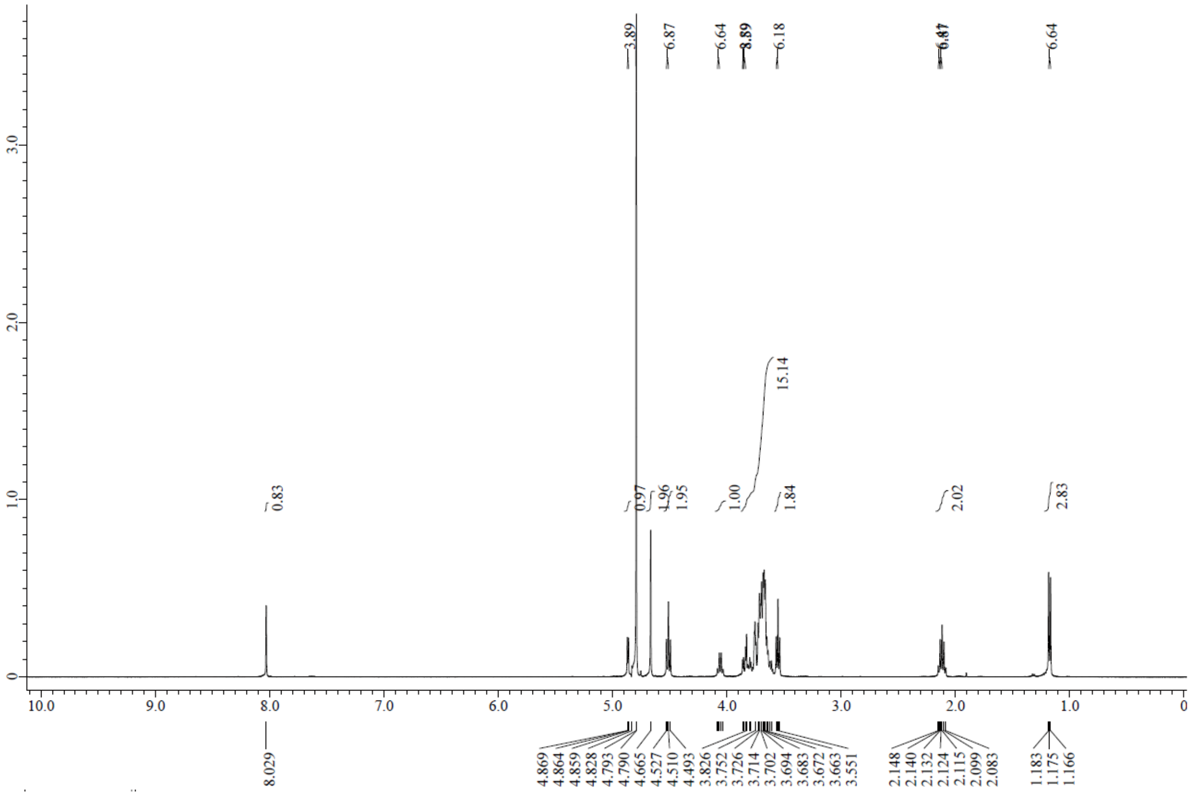
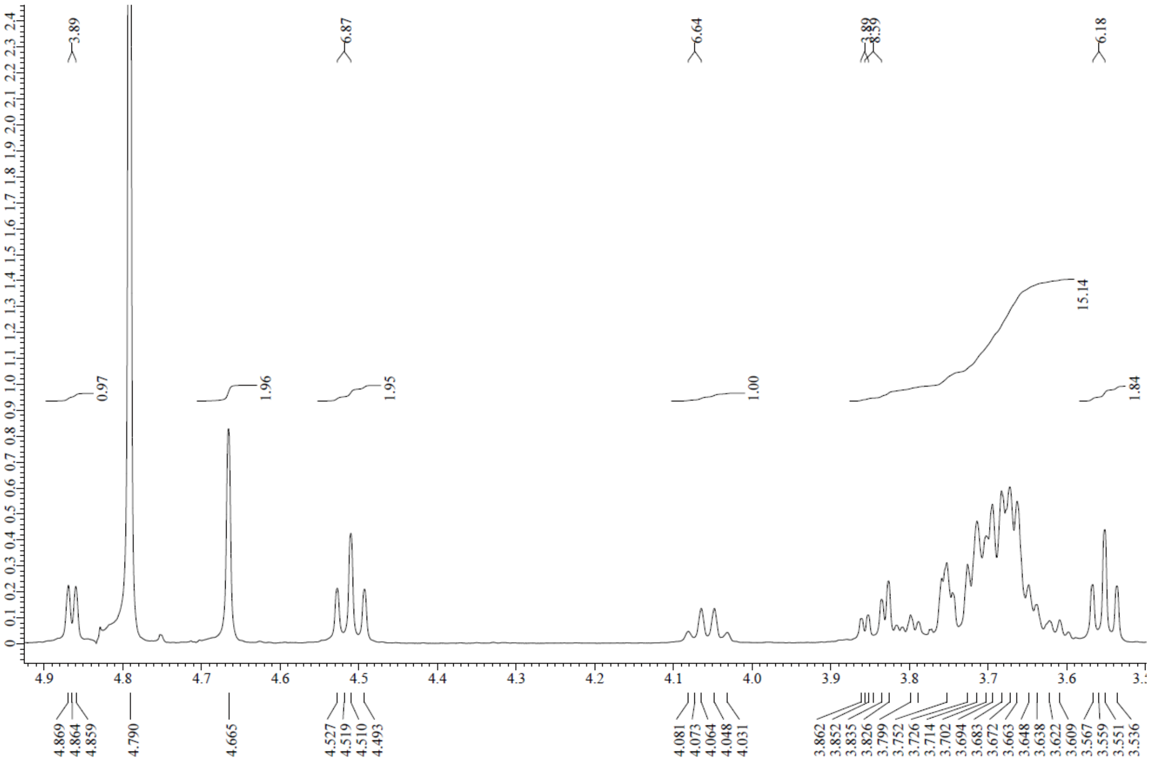
66.658

Synthesis of compound C



To a solution of **7** (0.054 g, 0.16 mmol, 1 eq) in *t*-BuOH/H_2O 1:1 (1.5 mL) was added **25** (0.020 g, 0.19 mmol, 1.2 eq), sodium ascorbate (0.0064 g, 0.032 mmol, 0.2 eq) and copper (II) sulfate (0.0025 g, 0.016 mmol, 0.1 eq) under argon atmosphere. The solution was stirred during 15 hours. Afterwards the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc to EtOAc/MeOH 9:1) to afford **C** (0.021 g, 30%) as a colorless oil. **^{1}H NMR** (400 MHz, D_2O) δ = 8.03 (s, 1H, H_{arom}), 4.86 (d, J = 3.9Hz, 1H, H-1), 4.67 (s, 2H, O*CH₂*C=C), 4.51 (t, J = 6.9Hz, 2H, N*CH₂*CH_2CH_2OH), 4.05 (q, J = 6.6Hz, 1H, H-5), 3.86-3.61 (m, 15H, H-2, H-3, H-4, 6CH_2O), 3.55 (t, J = 6.2Hz, 2H, NCH_2CH_2*CH₂*OH), 2.12 (tt, J = 6.1Hz, J = 6.9Hz, 2H, NCH_2*CH₂*CH_2OH), 1.18 (d, J = 6.6 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, D_2O) δ = 143.82 (C_{arom}), 125.21 (C_{arom}), 98.64 (C-1), 71.84, 69.78, 69.62, 69.58, 68.93, 68.13, 66.84, 66.65 (10C, C-2, C-3, C-4, C-5, 6CH_2O), 63.06 (O*CH₂*C=C), 58.13 (NCH_2CH_2*CH₂*OH), 47.26 (N*CH₂*CH_2CH_2OH), 31.81 (NCH_2*CH₂*CH_2OH) 15.41 (C-6). **[α]d** (MeOH, c=0.25, 20°C) = -64.0 **Mass** (TOF-MS-ESI$^+$): m/z: 458.21 (100%) [M+Na]$^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{19}H_{28}O_{10}Na^+$: 458.2109; found: 458.2105.

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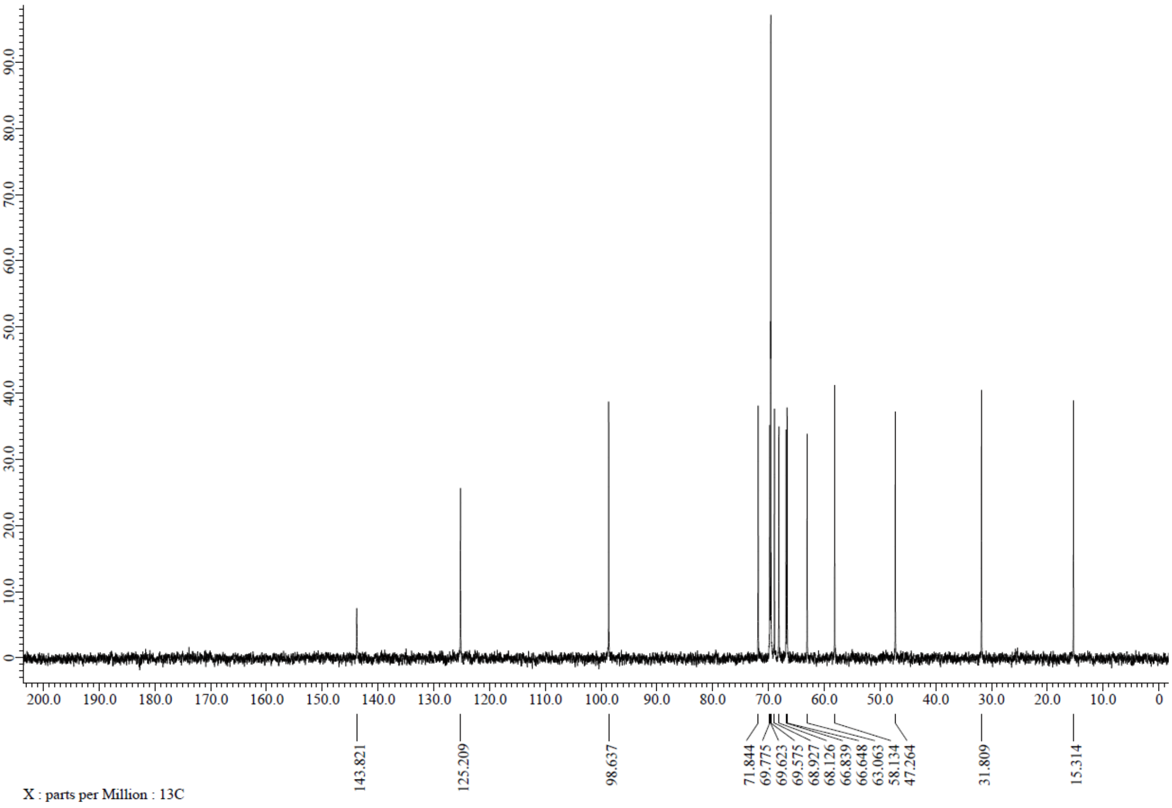
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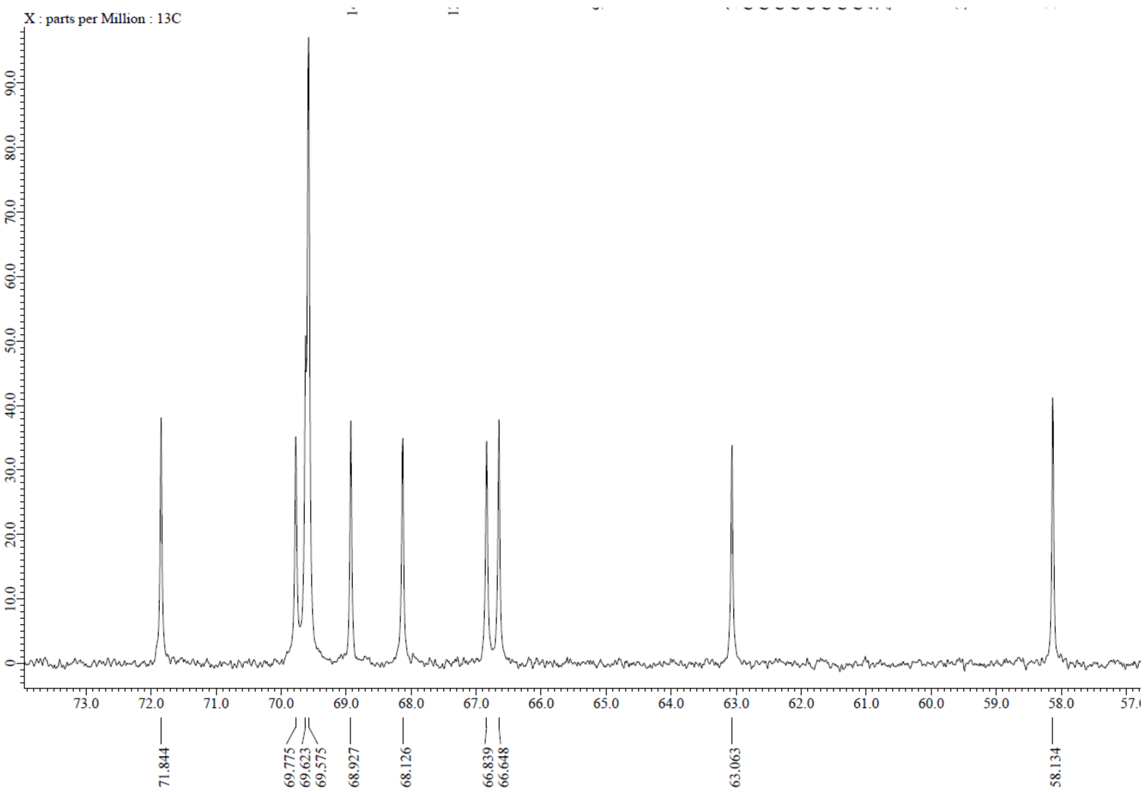
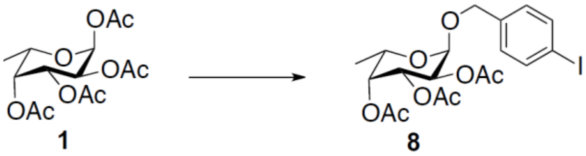
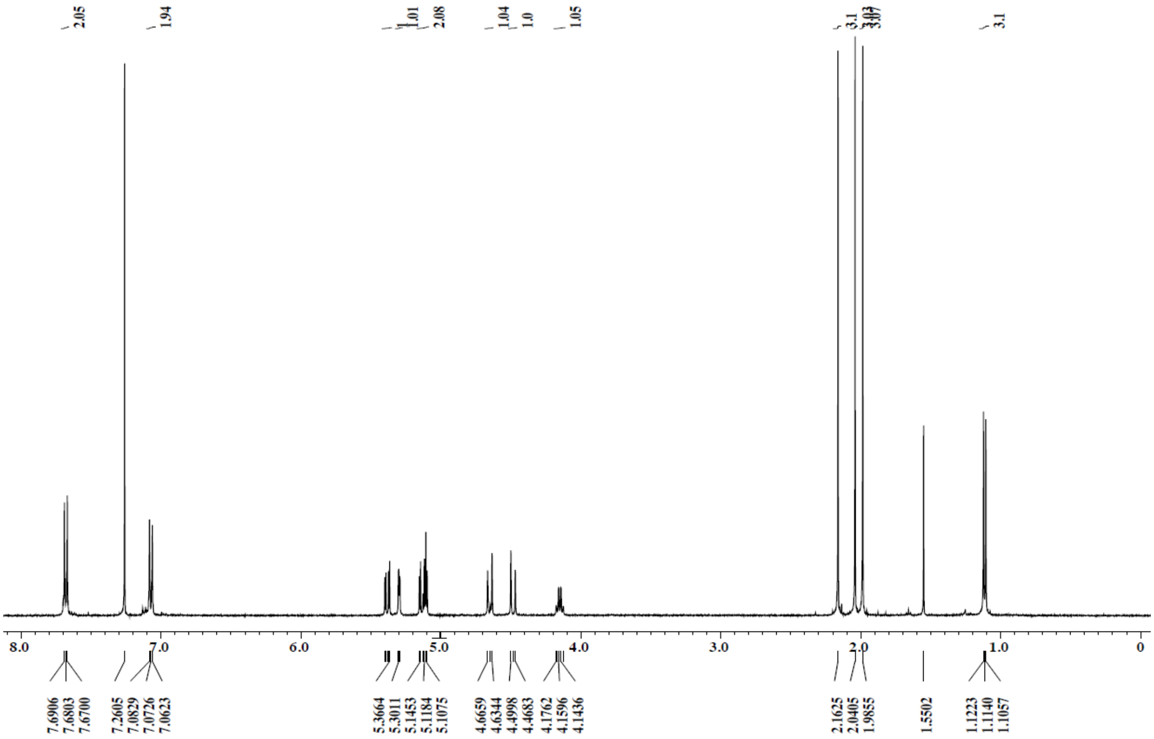


Synthesis of compound 8



To a solution of **1** (2.0 g, 6.02 mmol, 1 eq) in dry CH_2Cl_2 (50 mL) was added *p*-iodobenzyl alcohol (2.48 mL, 10.23 mmol, 1.7 eq) and boron trifluoride diethyl etherate (3.10 mL, 20.09 mmol, 5 eq) at 0°C under argon atmosphere and the solution was stirred overnight. The reaction mixture was then washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and water (50 mL), extracted with CH_2Cl_2 (3x50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Cy to Cy/EtOAc 8:2) to afford **8** (0.796 g, 26%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.67 (d, J = 8.2 Hz, 2H, H_{arom}), 7.06 (d, J = 8.2 Hz, 2H, H_{arom}), 5.37 (dd, $J_{3,4}$ = 3.4Hz, $J_{2,3}$ = 10.5Hz, 1H, H-2), 5.29 (d, $J_{1,2}$ = 3.0 Hz, 1H, H-3), 5.15-5.09 (m, 2H, H-1, H-4), 4.64 (AB, J = 12.6 Hz, 1H, O*CH₂*Ph), 4.48 (AB, J = 12.6 Hz, 1H, O*CH₂*Ph), 4.14 (q, $J_{5,6}$ = 6.6 Hz, 1H, H-5), 2.16, 2.03, 1.98 (3s, $3CH_3$, 3Ac), 1.11 (d, $J_{5,6}$ = 6.6 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 170.72, 170.45, 170.20 (3C, 3 C=O), 137.64, 136.92, 129.63 ($5C_{arom}$), 95.76 (C-1), 93.56 (C_{arom}), 71.17 (C-3), 69.25 (O*CH₂*Ph), 68.14, 68.07 (2C, C-2, C-4), 64.80 (C-5), 20.91, 20.83, 20.79 (3C, $3CH_3$), 15.94 (C-6). **$[\alpha]_d$** ($CHCl_3$, c=0.5, 20°C) = -112.8 **Mass** (TOF-MS-ESI$^+$): m/z: 529.03 (100%), 524.08 (100%) $[M+Na]^+$. **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{19}H_{23}O_8INa^+$: 529.0330; found: 529.0314.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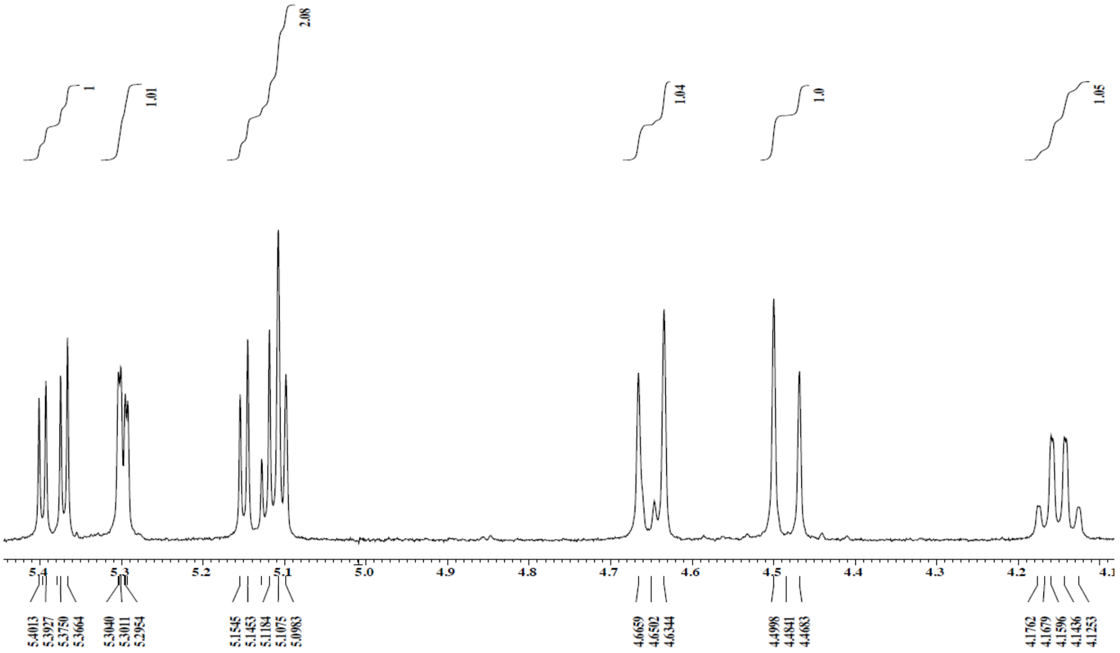
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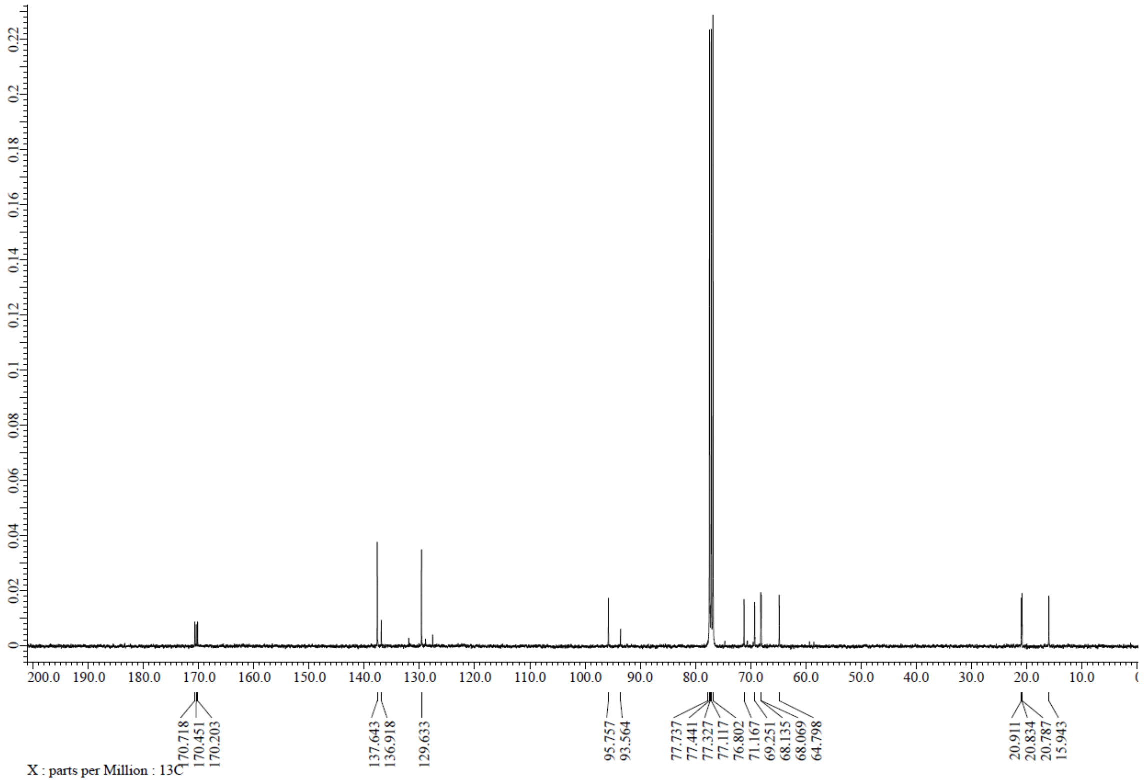
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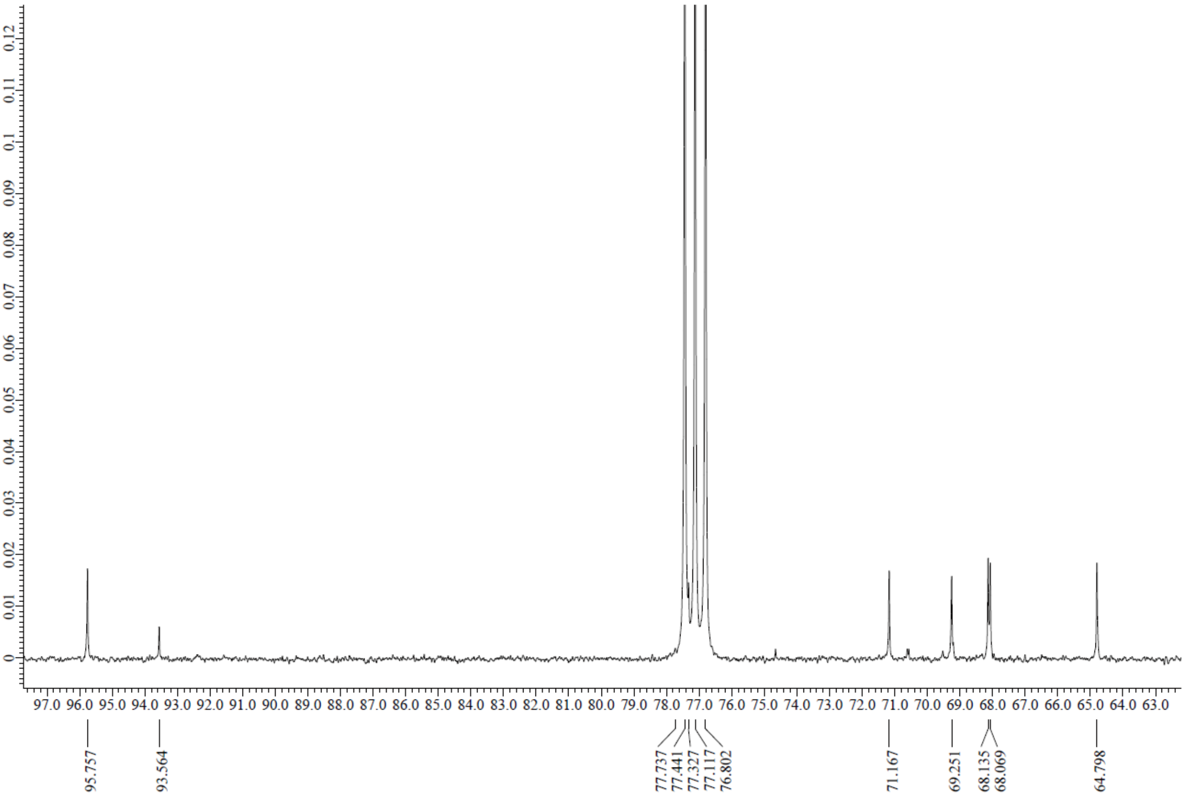
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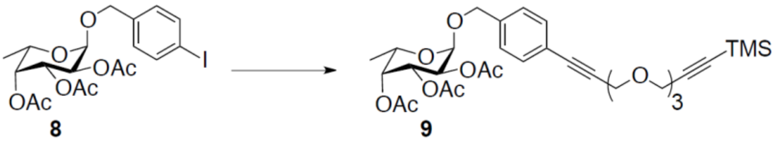
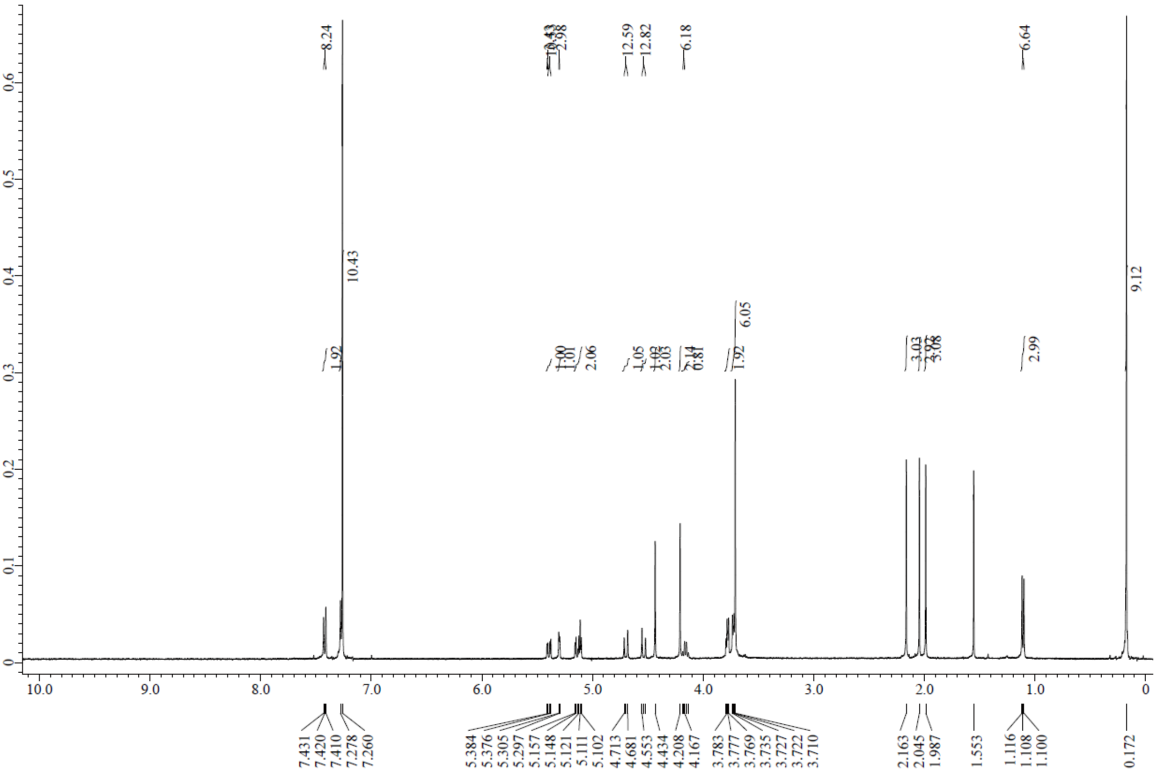
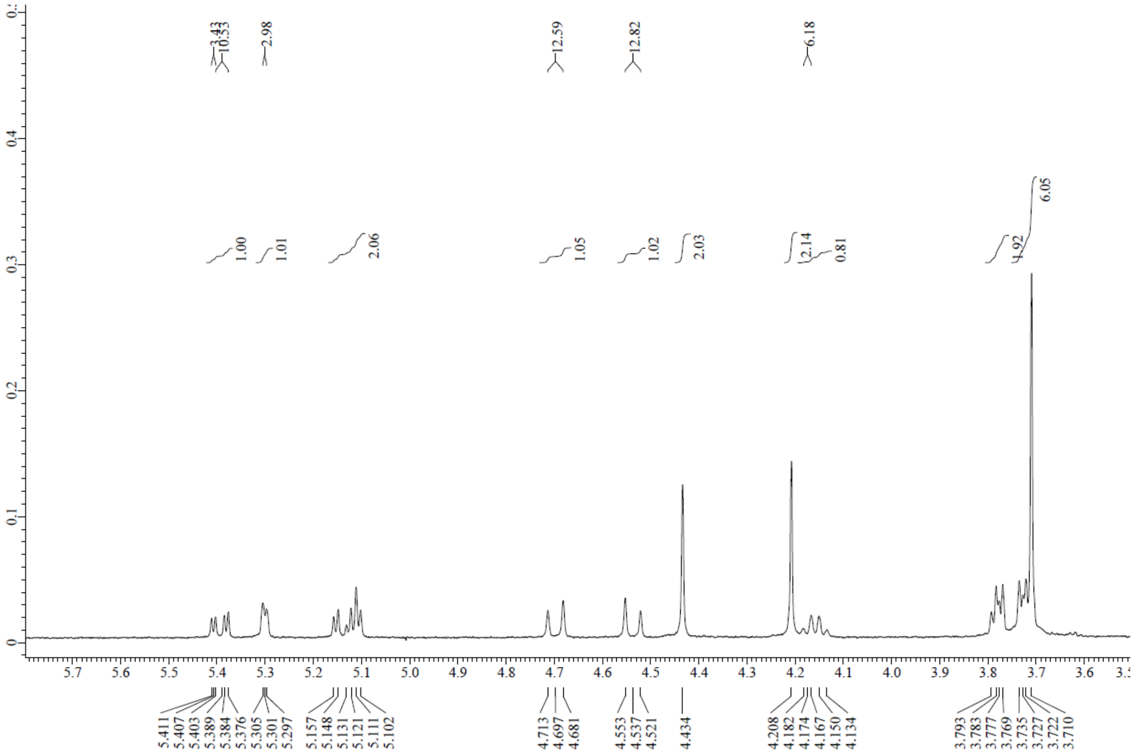
Synthesis of compound 9.



A solution of **8** (0.896 g, 1.77 mmol, 1 eq) in 9 mL of degazed DMF was added **15** (0.900 g, 3.54 mmol, 2 eq), degazed triethylamine (0.492 mL, 3.54 mmol, 2 eq), bistriphenylphosphine palladium chloride (0.124 g, 0.177 mmol, 0.1 eq) and copper iodide (0.067 g, 0.354 mmol, 0.2 eq) under argon atmosphere. The solution was stirred during 7 min at 80°C under microwave irradiation. Afterwards the mixture was diluted with EtOAc (100 mL), washed with brine (4x70 mL) and the aqueous phase was extracted with EtOAc (3x100 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Cy to Cy/EtOAc 85:15) to afford **9** (0.93 g, 83%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.42 (d, J = 8.2 Hz, 2H, H_{arom}), 7.27 (d, J = 8.2 Hz, 2H, H_{arom}), 5.39 (dd, J = 3.4 Hz, J = 10.5 Hz, 1H, H-2), 5.30 (d, J = 3.0 Hz, 1H, H-3), 5.16-5.10 (m, 2H, H-1, H-4), 4.70 (AB, J = 12.6 Hz, 1H, O*CH₂*Ph), 4.54 (AB, J = 12.8 Hz, 1H, O*CH₂*Ph), 4.43 (s, 2H, CH_2, O*CH₂*CC), 4.21 (s, 2H, CH_2, O*CH₂*CC), 4.16 (q, J = 6.2 Hz, 1H, H-5), 3.79-3.77 (m, 2H, CH_2O), 3.74-3.71 (m, 6H, $3CH_2O$), 2.16, 2.05, 1.99 (3s, $3CH_3$), 1.11 (d, J = 6.6 Hz, 3H, H-6), 0.17 (s, 9H, TMS). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 170.71, 170.44, 170.18 (3C, 3C=O), 137.63, 131.93, 127.59, 122.34 ($6C_{arom}$), 101.50 (C_q), 95.81 (C-1), 91.54, 86.07, 85.44 ($3C_q$), 71.22, 70.59, 69.54, 69.30, 69.14, 68.16, 68.12 (8C, C-2, C-3, C-4, $5CH_2O$), 64.78 (C-5), 59.32 (2C, 2 O*CH₂*CC), 20.89, 20.82, 20.76 (3C, $3CH_3$), 15.92 (C-6), -0.08 (3C, TMS). **[α]$_d$** ($CHCl_3$, c=0.5, 20°C) = -101.4 **Mass** (TOF-MS-ESI$^+$): m/z: 655.25 (100%) $[M+Na]^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{32}H_{44}O_{11}SiNa^+$: 655.2545; found: 655.2537.

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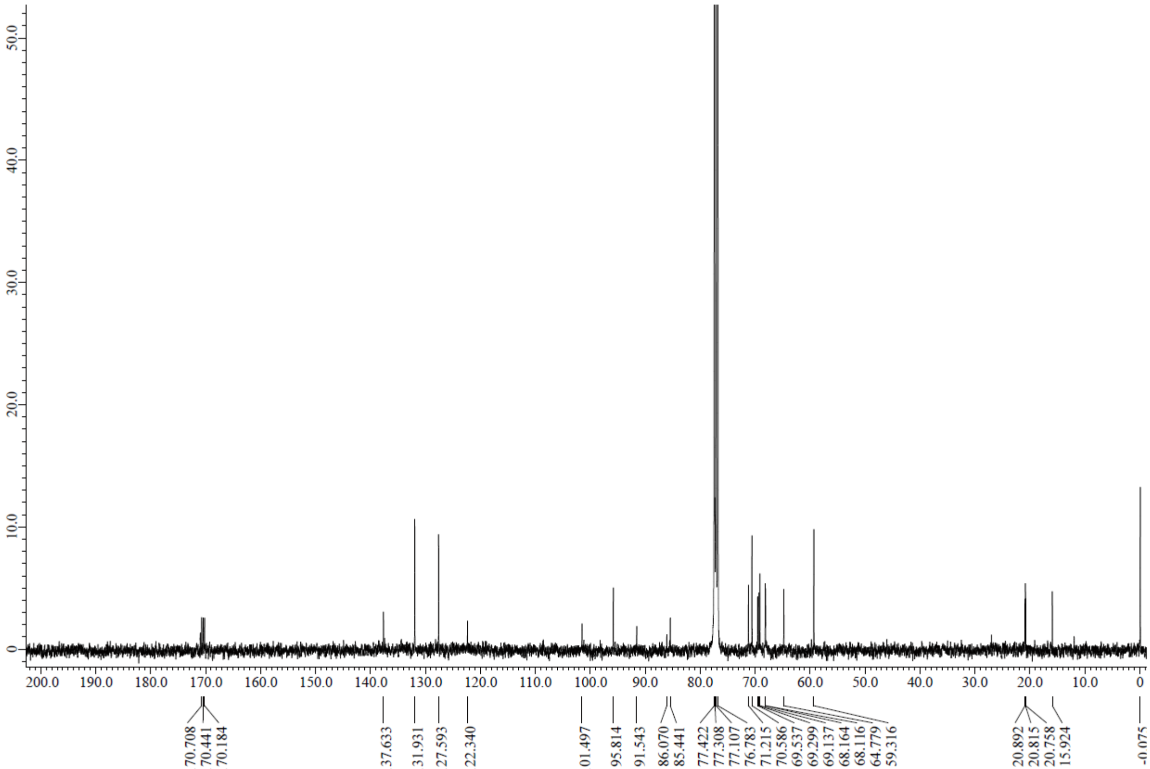
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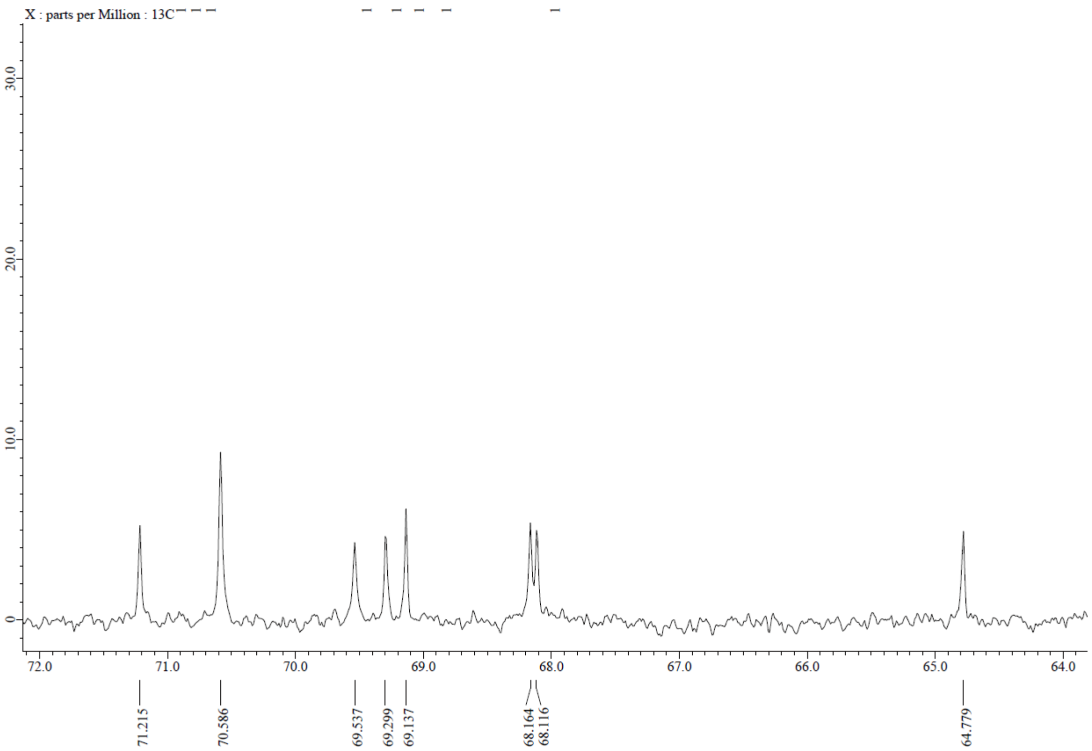
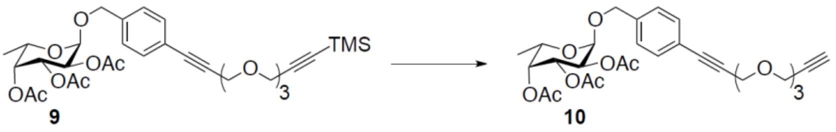
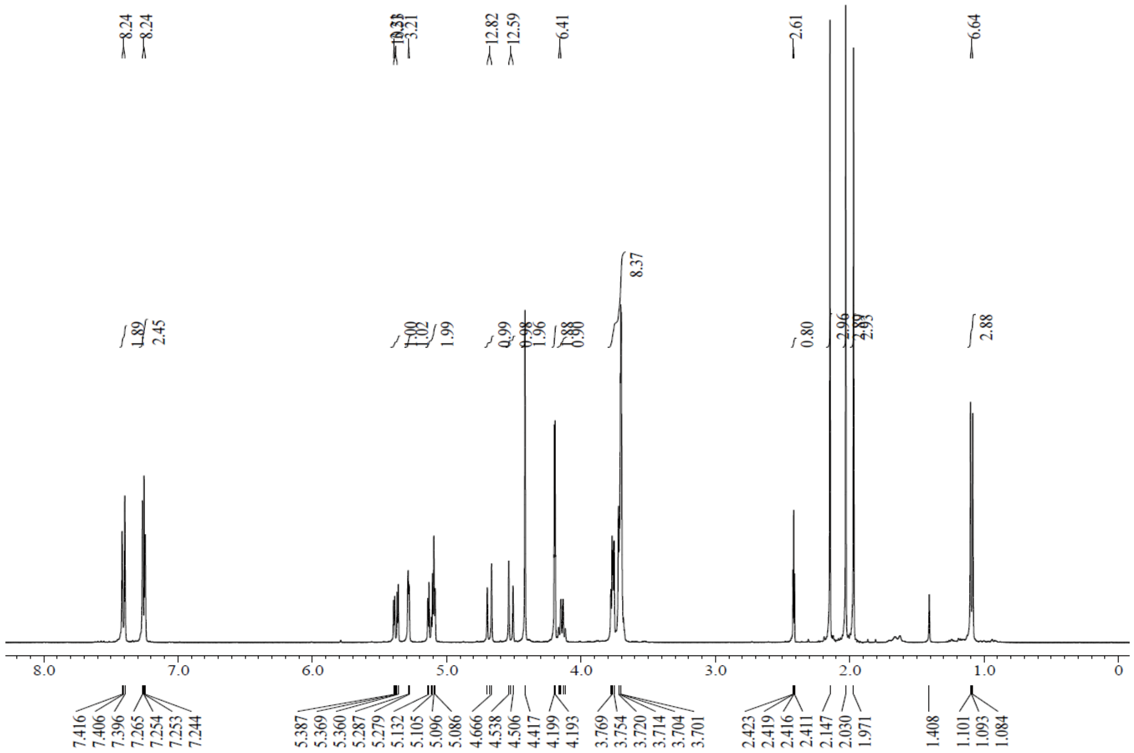
X : parts per Million : 13C

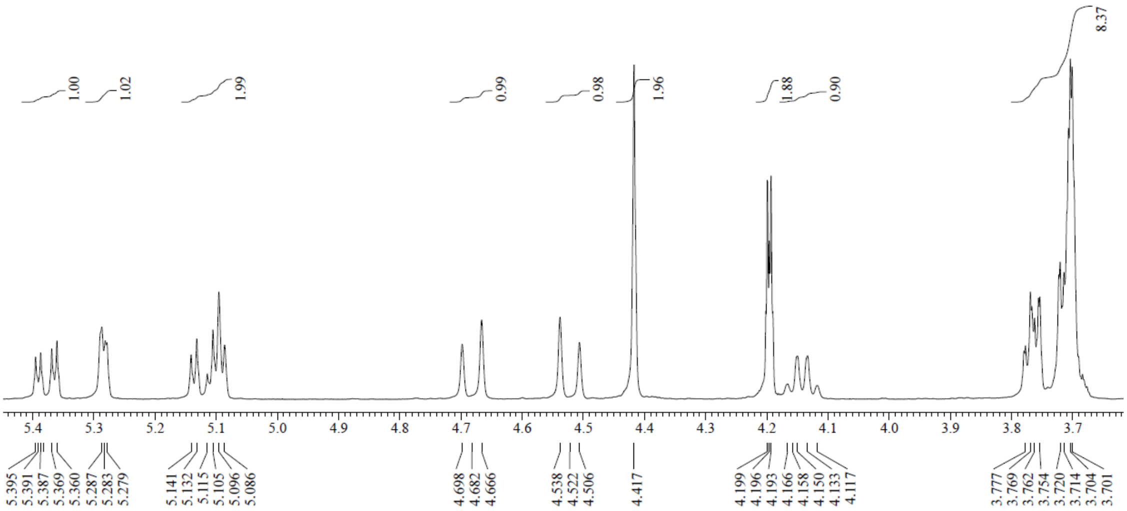


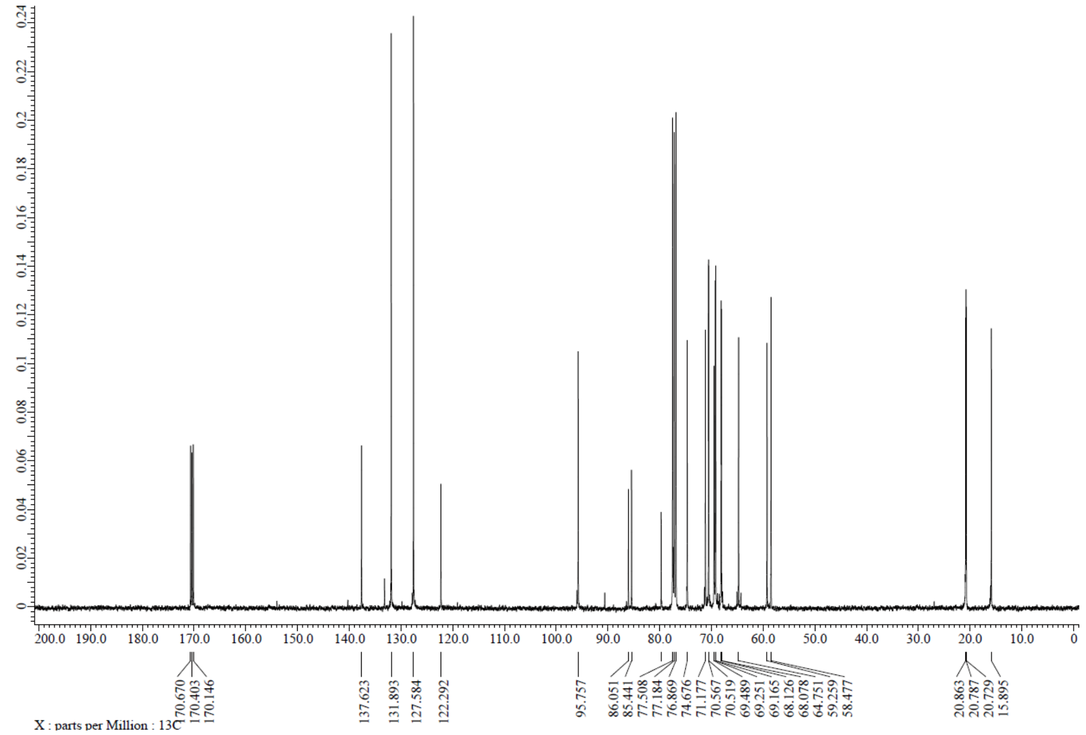
Synthesis of compound 10.



Tetrabutylammonium fluoride (0.416 g, 1.59 mmol, 1.2 eq) was added to a solution of **9** (0.840 g, 1.33 mmol, 1 eq) in 20 mL of distilled THF and the mixture was stirred during 5 minutes at room temperature. The solution was washed with a saturated aqueous solution of NH_4Cl (50 mL) and the aqueous phase was extracted with CH_2Cl_2 (3x 50 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Cy to Cy/EtOAc 7:3) to afford **10** (0.550 g, 73%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.41 (d, J = 8.2 Hz, 2H, H_{arom}), 7.25 (d, J = 8.2 Hz, 2H, H_{arom}), 5.38 (dd, J = 3.2 Hz, J = 10.5 Hz, 1H), 5.28 (d, J = 3.1 Hz, 1H), 5.14-5.09 (m, 2H, H-1), 4.68 (AB, J = 12.8 Hz, 1H, O*CH₂*Ph), 4.52 (AB, J = 12.6 Hz, 1H, O*CH₂*Ph), 4.42 (s, 2H, O*CH₂*CC), 4.20 (m, 2H, O*CH₂*CC), 4.14 (q, J = 6.6 Hz, 1H, H-5), 3.78-3.70 (m, 8H, $4CH_2O$), 2.42 (t, J = 2.6 Hz, 1H, OCH_2C*CH*), 2.15, 2.03, 1.97 (3s, $3CH_3$), 1.11 (d, J = 6.6 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 170.67, 170.40, 170.15 (3C, 3C=O), 137.62, 131.89, 127.58, 122.29 ($6C_{arom}$), 95.76 (C-1), 86.05, 85.44, 79.72 ($3C_q$), 74.68 (OCH_2C*CH*), 71.18, 70.57, 70.52, 69.49, 69.25, 69.17, 68.13, 68.08 (8C, C-2, C-3, C-4, $4CH_2O$, CH_2), 64.75 (C-5), 59.29, 58.48 (2C, 2O*CH*$_2$CC), 20.86, 20.79, 20.73 (3C, 3CH$_3$), 15.90 (C-6). **[α]$_d$** (CHCl$_3$, c=0.5, 20°C) = -48.2 **Mass** (TOF-MS-ESI$^+$): m/z: 583.21 (100%) [M+Na]$^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{29}H_{36}O_{11}Na^+$: 583.2150; found: 583.2148.



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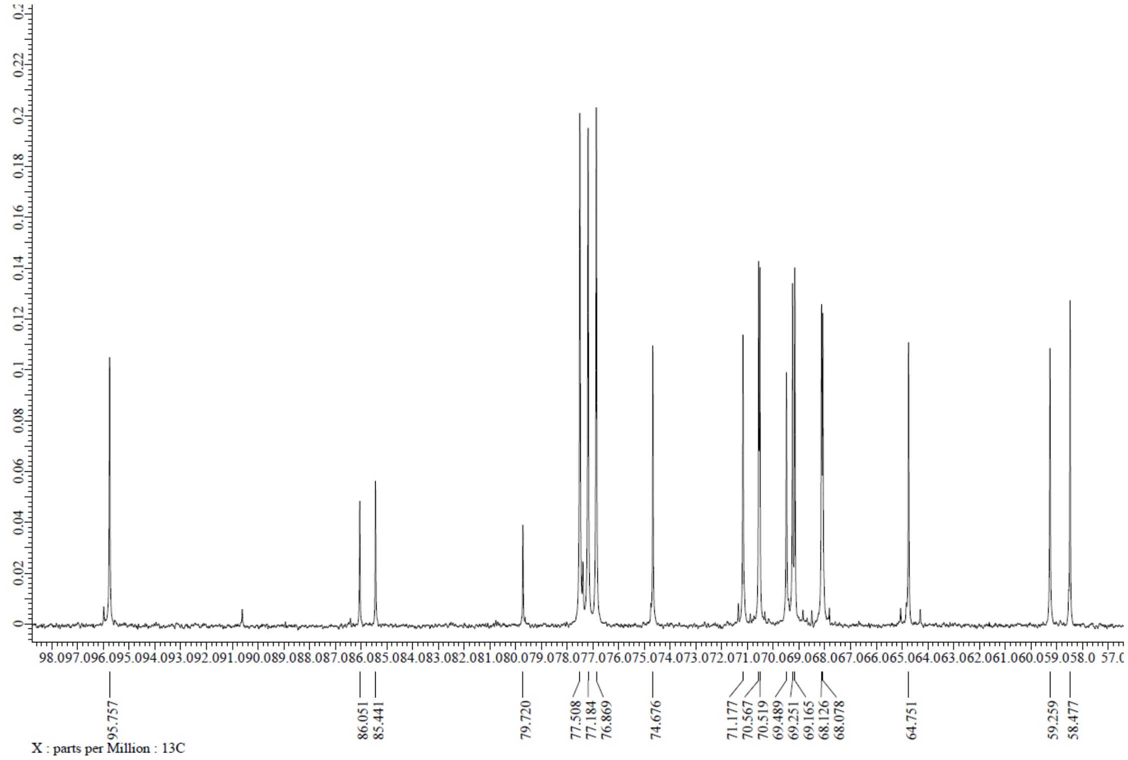
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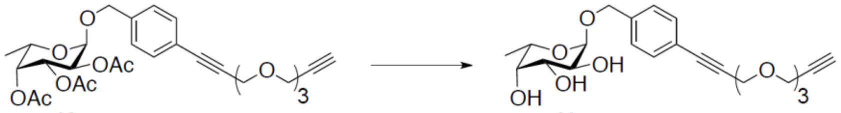
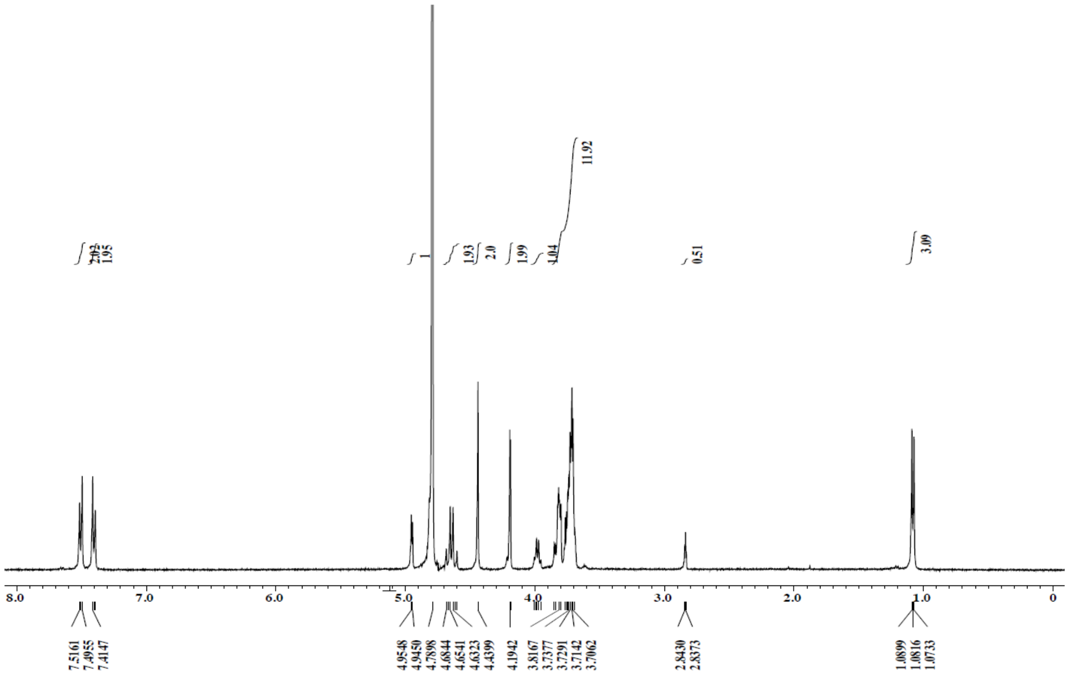
X : parts per Million : 13C

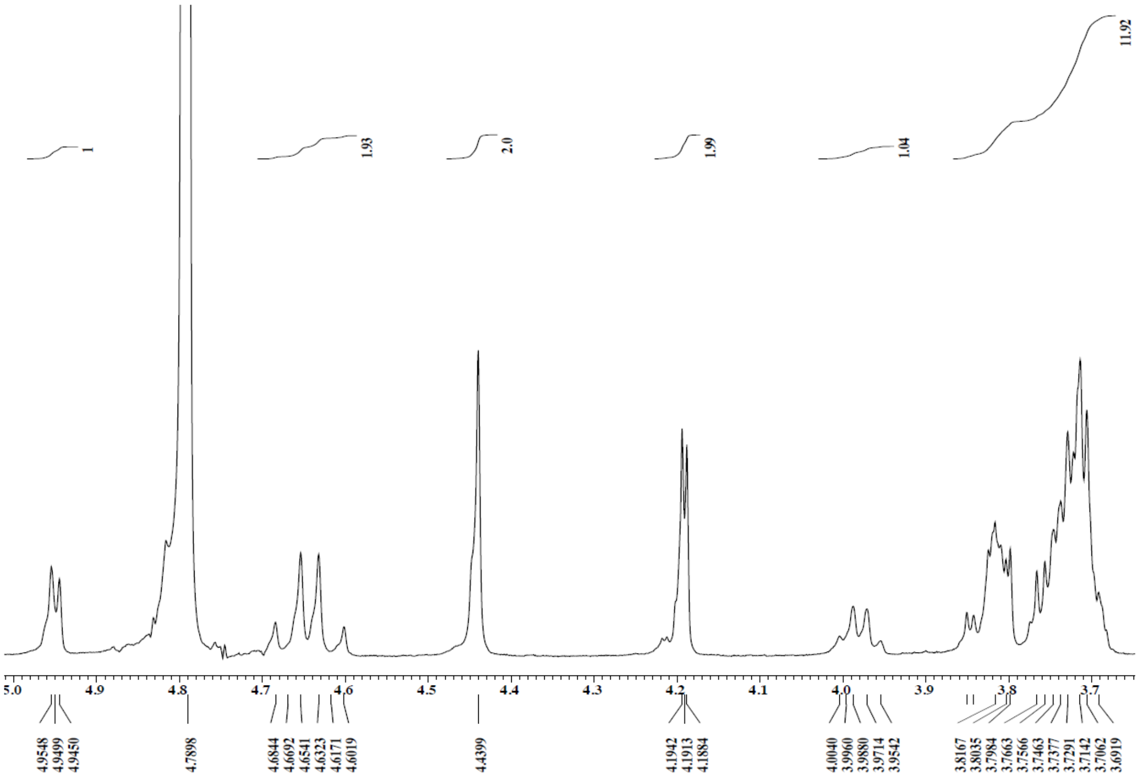
Synthesis of compound 11



10 **11**

Sodium methoxide (0.008 g, 0.16 mmol, 1 eq) was added to a solution of **10** (0.087 g, 0.16 mmol, 1 eq) in 2 mL of MeOH at 0°C and the mixture was stirred during two hours at room temperature. The solution was filtered over a short column of Dowex™ 50WX8-200 (H^+ resin form). The resin was washed with methanol (15 mL) and water (15 mL). Finally, the solvents were evaporated under reduced pressure to afford the product **11** (0.066 g, 98%) as a colorless oil. **^{1}H NMR** (400 MHz, D_2O) δ = 7.51 (d, J = 8.2 Hz, 2H, H_{arom}), 7.40 (d, J = 8.2 Hz, 2H, H_{arom}), 4.95 (d, J = 3.9 Hz, 1H, H-1), 4.67 (AB, J = 12.1 Hz, 1H, O*CH₂*Ph), 4.62 (AB, J = 12.1 Hz, 1H, O*CH₂*Ph), 4.44 (s, 2H, O*CH₂*CC), 4.19 (d, J = 2.3 Hz, 2H, O*CH₂*CC), 3.98 (q, J = 6.4 Hz, 1H, H-5), 3.85-3.69 (m, 11H, H-2, H-3, H-4, $4CH_2O$), 2.84 (t, J = 2.3 Hz, 1H, OCH_2C*CH*), 1.08 (d, J = 6.6 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, D_2O) δ = 138.22, 131.85, 128.39, 121.37 ($6C_{arom}$), 98.28 (C-1), 86.50, 85.00, 79.28 ($3C_q$), 75.97 (OCH_2C*CH*), 71.81, 69.61, 69.57, 69.50, 69.40, 68.67, 68.00 (8C, C-2, C-3, C-4, $5CH_2O$), 66.83 (C-5), 58.55, 57.90 (2C, 2 O*CH₂*CC), 15.18 (C-6). **[α]d** (MeOH, c=0.5, 20°C) = -88.6 **Mass** (TOF-MS-ESI$^+$): m/z: 457.18 (100%) [M+Na]$^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{23}H_{30}O_8Na^+$: 457.1833; found: 457.1846.

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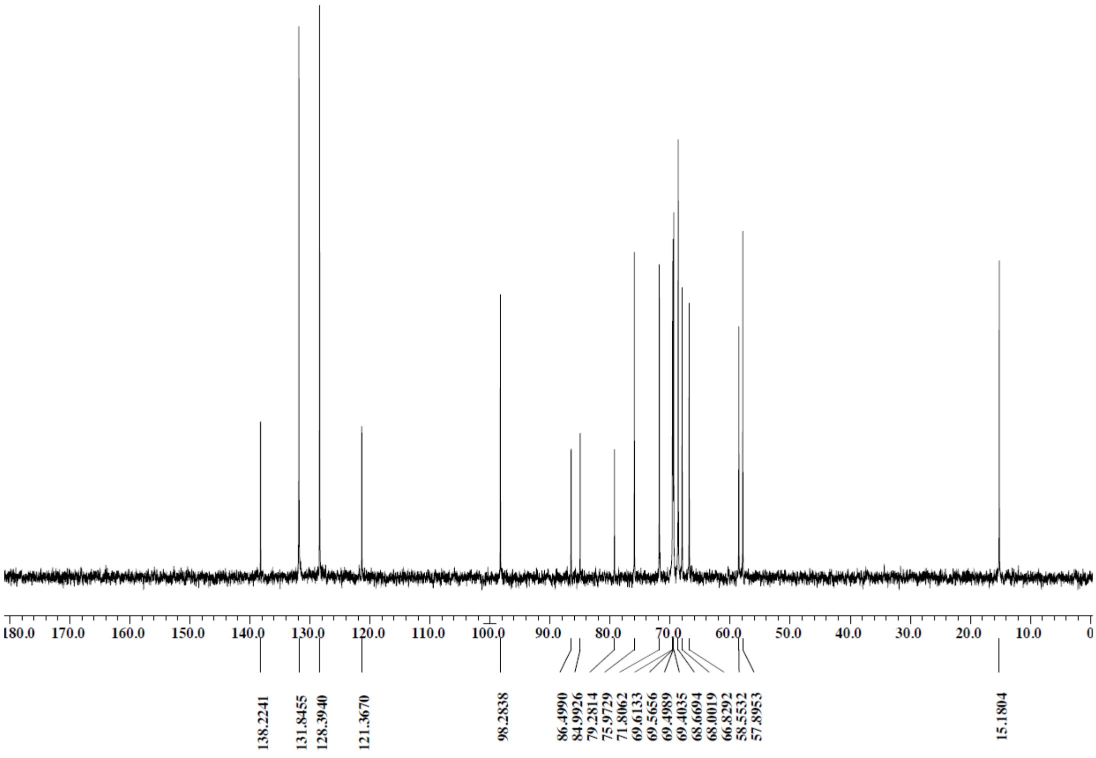
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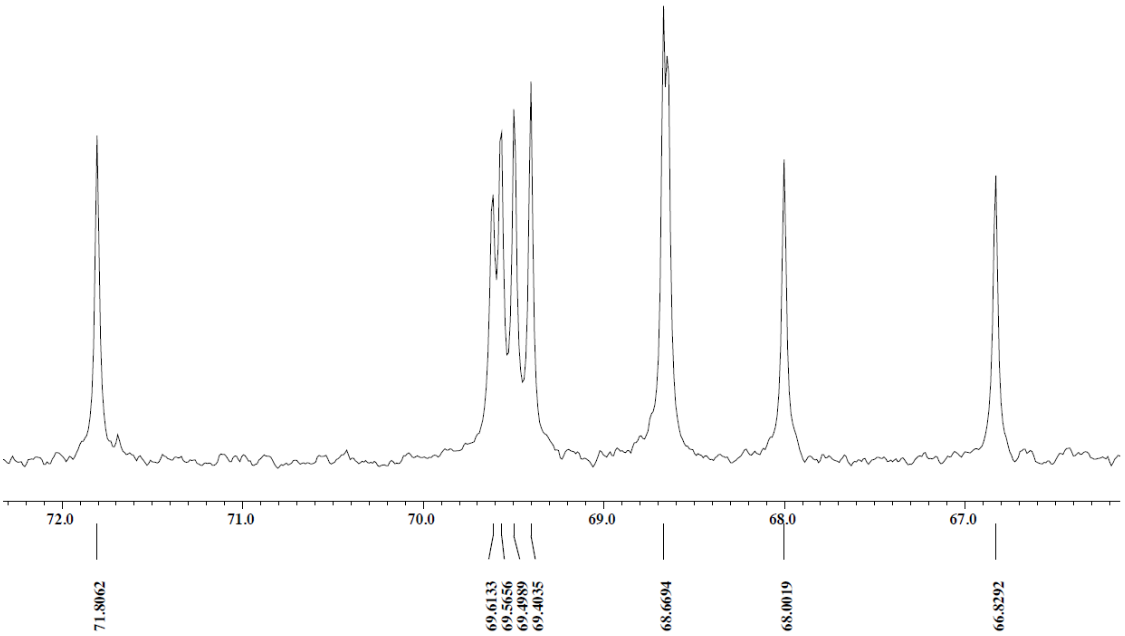
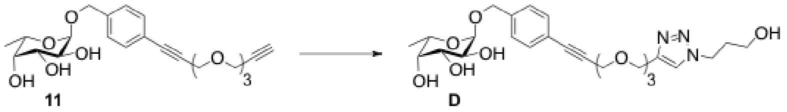
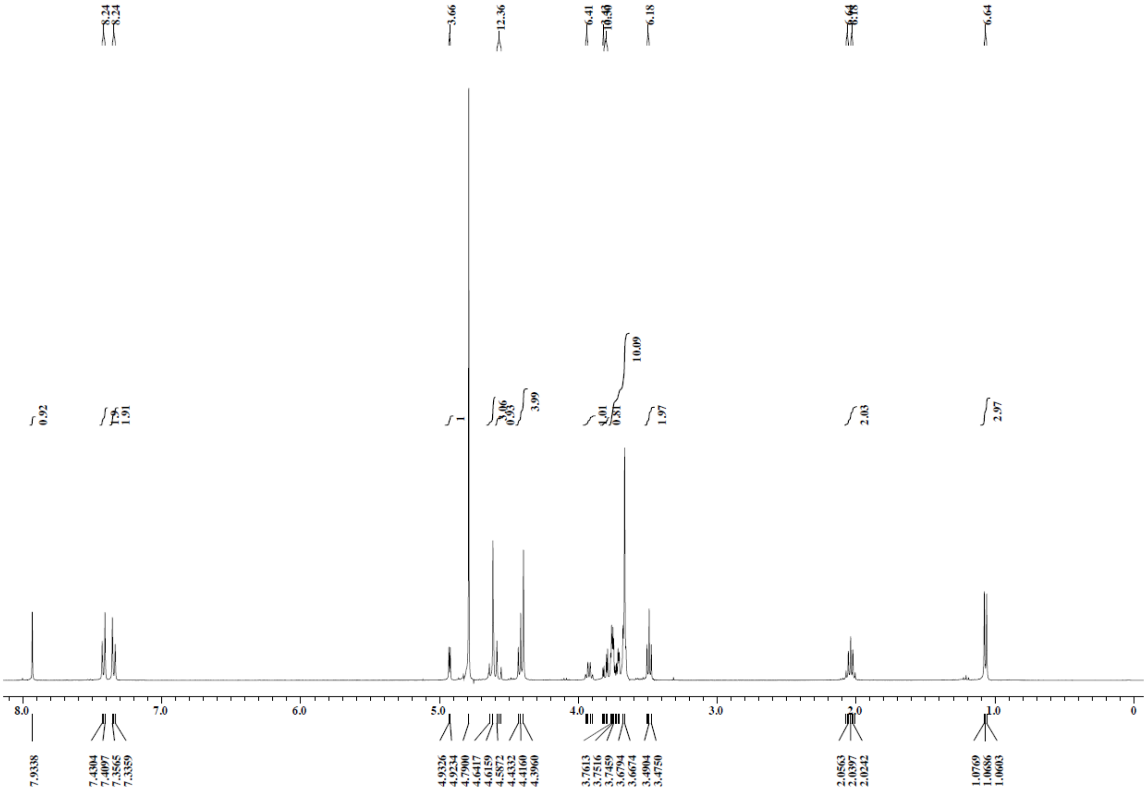


Synthesis of compound D.



To a solution of **11** (0.022 g, 0.051 mmol, 1 eq) in *t*-BuOH/H_2O 1:1 (0.6 mL) was added azide **25** (0.006 g, 0.061 mmol, 1.2 eq), sodium ascorbate (0.002 g, 0.010 mmol, 0.2 eq) and copper (II) sulfate (0.001 g, 0.0051 mmol, 0.1 eq) under argon atmosphere. The solution was stirred during 15 hours. Afterwards the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc to EtOAc/MeOH 9:1) to afford **D** (0.016 g, 60%) as a colorless oil. **^{1}H NMR** (400 MHz, D_2O) δ = 7.93 (s, 1H, H_{arom}), 7.42 (d, J = 8.2 Hz, 2H, H_{arom}), 7.35 (d, J = 8.2 Hz, 2H, H_{arom}), 4.93 (d, J = 3.7 Hz, 1H, H-1), 4.64-4.62 (m, 3H, OCH_2Ph, CH_2O), 4.57 (AB, J = 12.4 Hz, 1H, OCH_2Ph), 4.43-4.40 (m, 4H, $N\mathit{CH_2}CH_2CH_2OH$, CH_2O), 3.92 (q, J = 6.4 Hz, 1H, H-5), 3.81 (dd, J = 3.4 Hz, J = 10.3 Hz, 1H), 3.77-3.67 (m, 10H, $4CH_2$), 3.49 (t, J = 6.2 Hz, 2H, $NCH_2CH_2\mathit{CH_2}OH$) 2.04 (tt, J = 6.2 Hz, J = 6.6 Hz, $NCH_2\mathit{CH_2}CH_2OH$), 1.07 (d, J = 6.6 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, D_2O) δ = 143.88, 138.22, 131.78, 128.34, ($6C_{arom}$), 125.04 (C_{arom}), 121.31 (C_{arom}), 98.29 (C-1), 86.42, 85.04 ($2C_q$), 71.82, 69.58, 69.53, 68.93, 68.68, 68.02, (8C, C-2, C-3, C-4, $5CH_2O$), 66.83 (C-5), 63.12 (CH_2O), 58.54, 58.08 (2C, $NCH_2CH_2\mathit{CH_2}OH$, CH_2O), 47.21 ($N\mathit{CH_2}CH_2CH_2OH$), 31.81 ($NCH_2\mathit{CH_2}CH_2OH$), 15.19 (C-6). **$[\alpha]_d$** (MeOH, c=0.45, 20°C) = -74.0 **Mass** (TOF-MS-ESI$^+$): m/z: 536.26 (100%) $[M+H]^+$, 558.24 (90%) $[M+Na]^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{26}H_{37}N_3O_9H^+$: 536.2603; found: 536.2609.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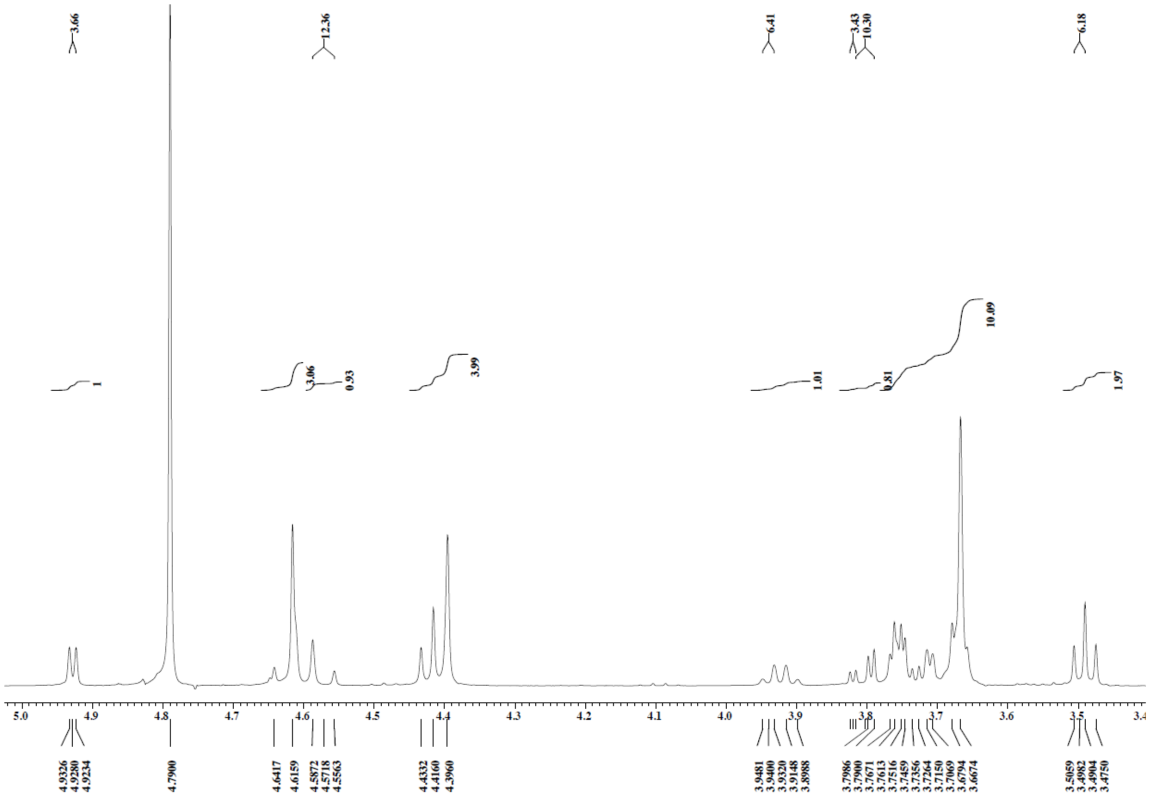
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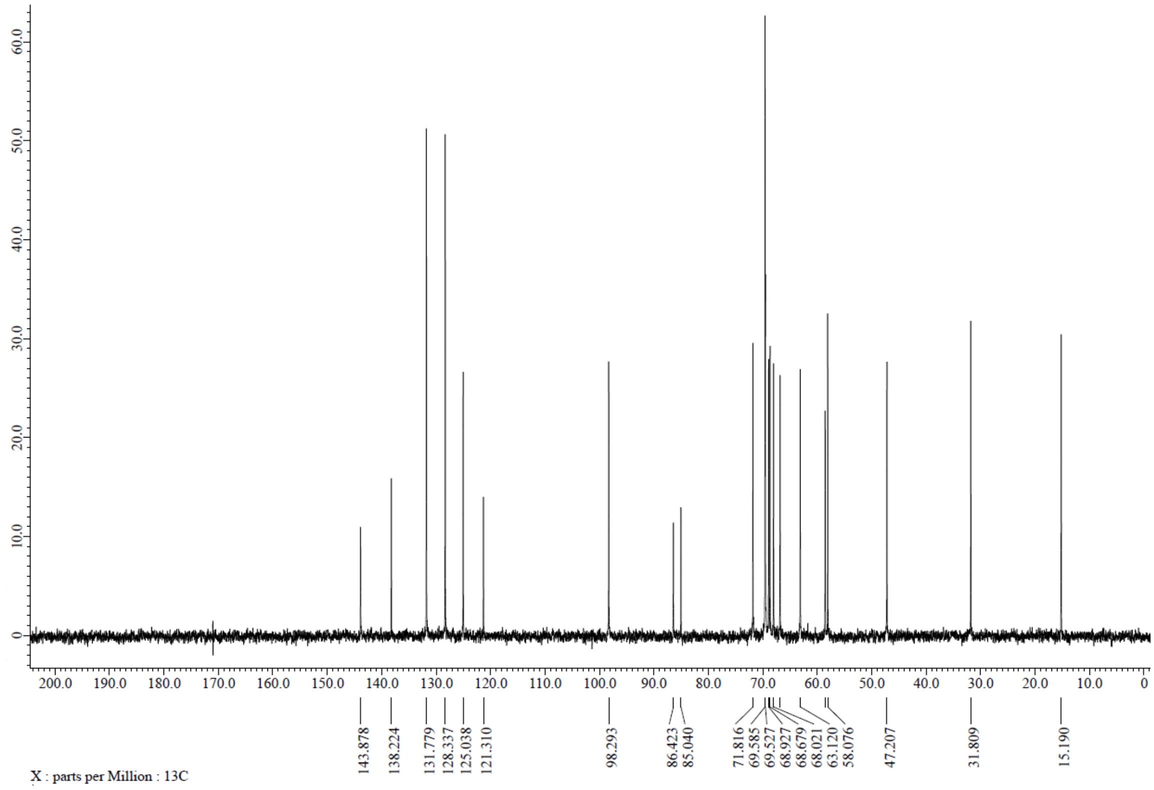
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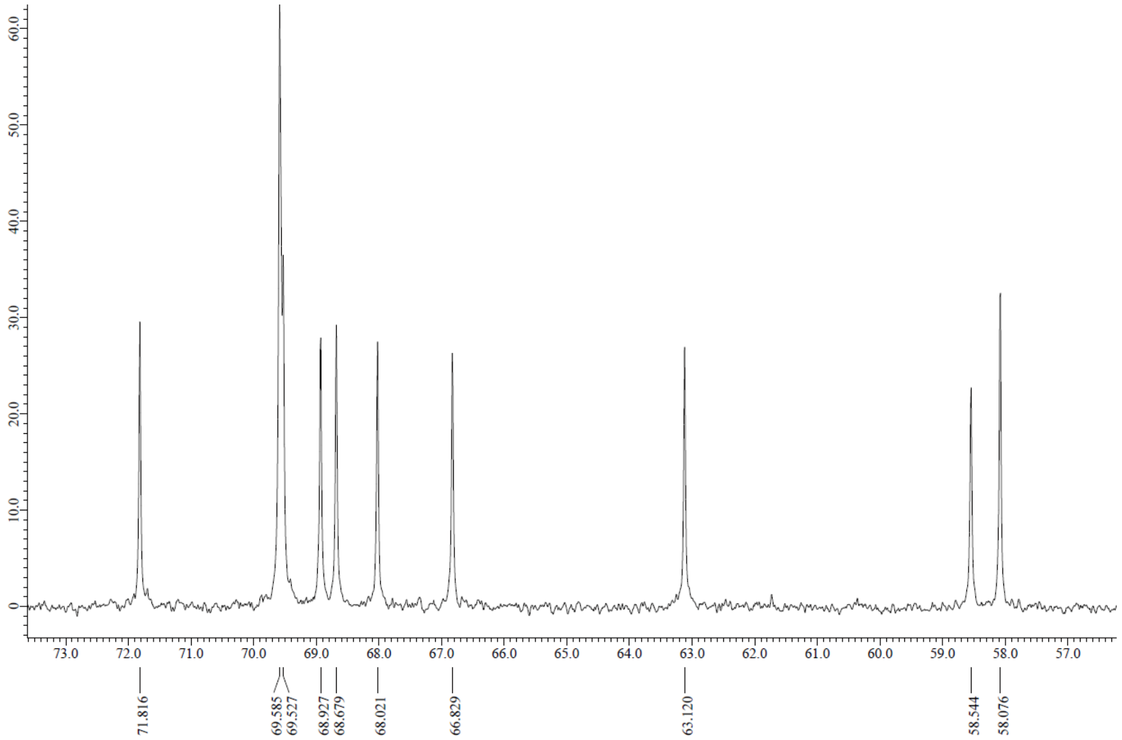
X : parts per Million : 13C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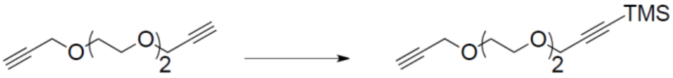
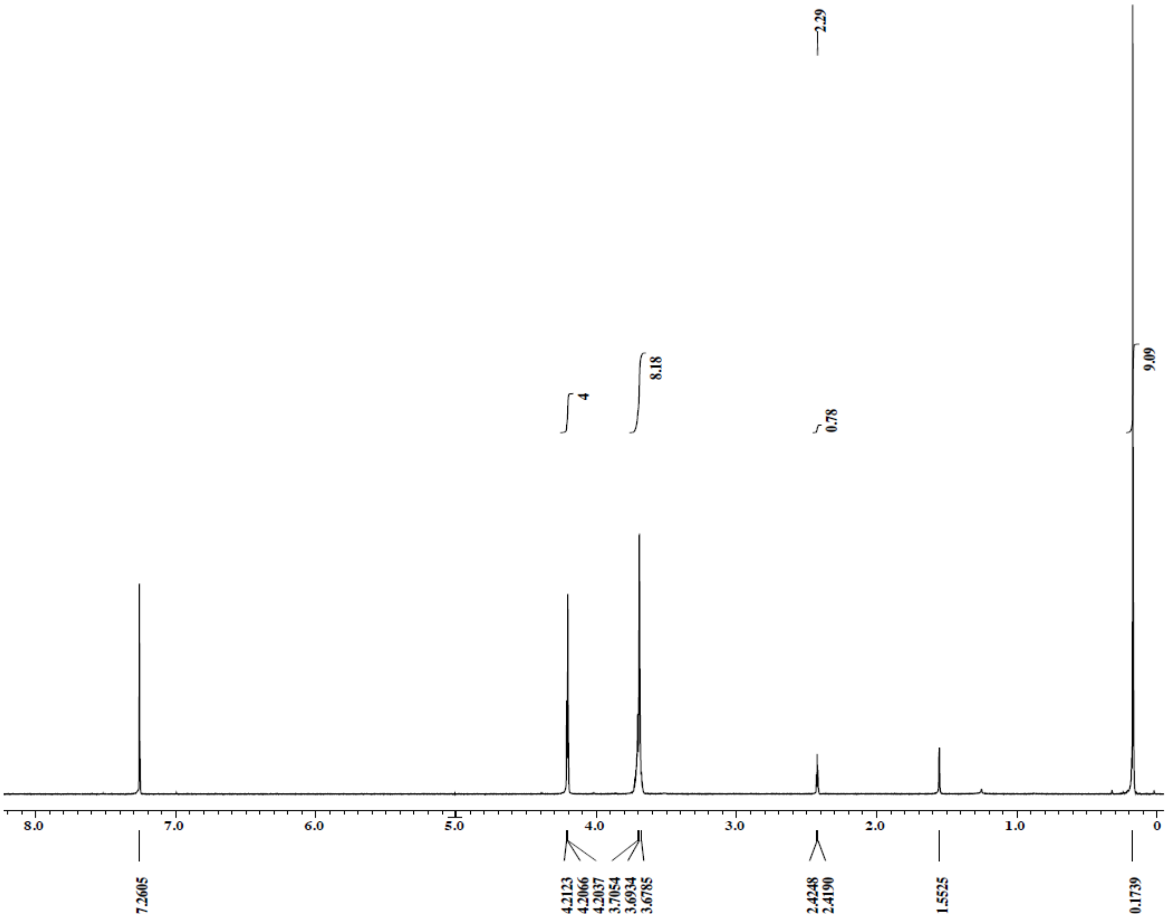
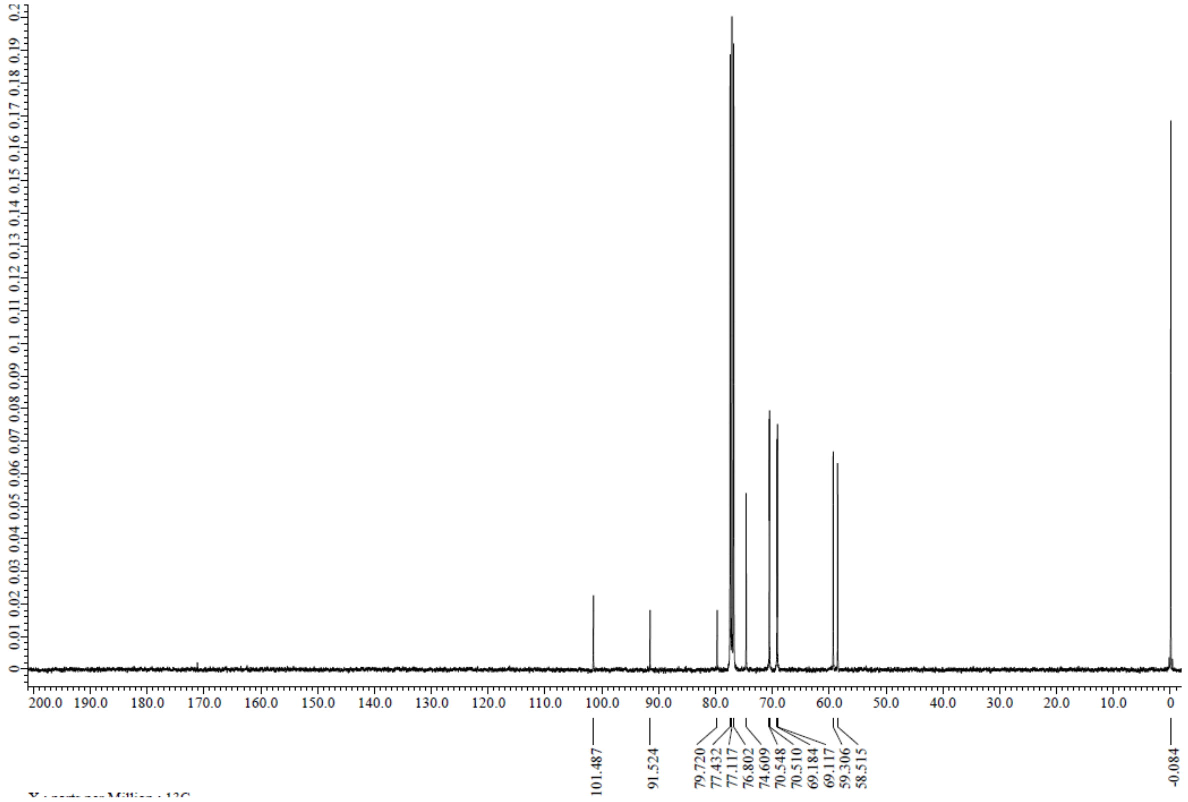
Synthesis of compound 15

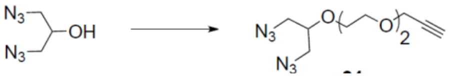


To a solution of **14** (5.00 g, 27.44 mmol, 1 eq) in dry THF (100 mL) was added dropwise *n*-butyl lithium 2.3 M (17.89 mL, 41.15 mmol, 1.5 eq) at -78°C. The solution was stirred during 60 minutes at -78°C afterwards trimethylsilyl chloride (3.85 mL, 30.18 mmol, 1.1 eq) was added to the mixture and stirred during 15h at room temperature. The THF was evaporated under reduced pressure and the product was solubilized in CH_2Cl_2 (100 mL). Water (100 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3x 10 mL) and the organic phase was dried over $MgSO_4$, filtered and solvents were evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Cy to Cy/EtOAc 9:1) to afford **15** (2.12 g, 30%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.21-4.20 (m, 4H, $2CH_2$), 3.71-3.67 (m, 8H, $4CH_2O$), 2.43 (t, *J* = 2.3 Hz, 1H, OCH_2C*CH*), 0.17 (s, 9H, TMS). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 101.49, 91.52, 79.72 ($3C_q$), 74.61 (OCH_2C*CH*), 70.55, 70.51, 69.18, 69.12, 59.31, 58.52 ($6CH_2O$), -0.08 ($3CH_3$, TMS). **Mass** (TOF-MS-ESI$^+$): m/z: 277.1228 (100%) $[M+Na]^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{13}H_{22}O_3SiNa^+$: 277.1230; found: 277.1228.

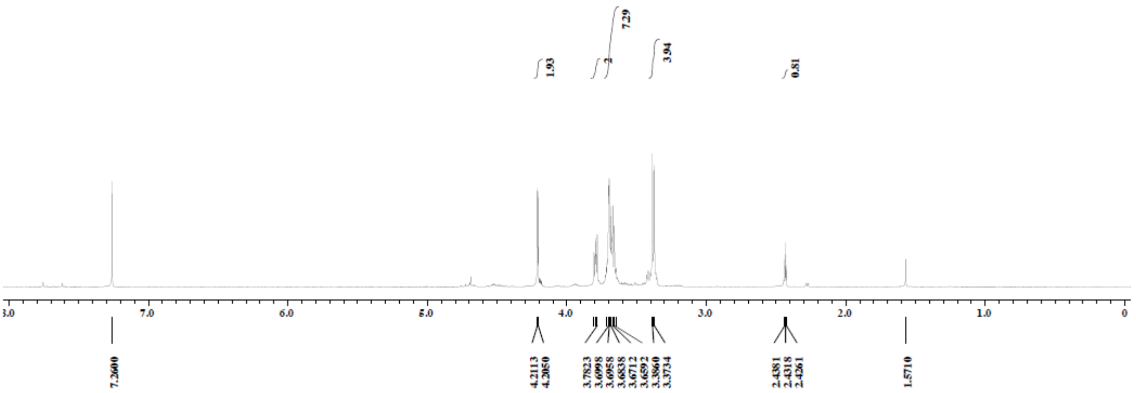


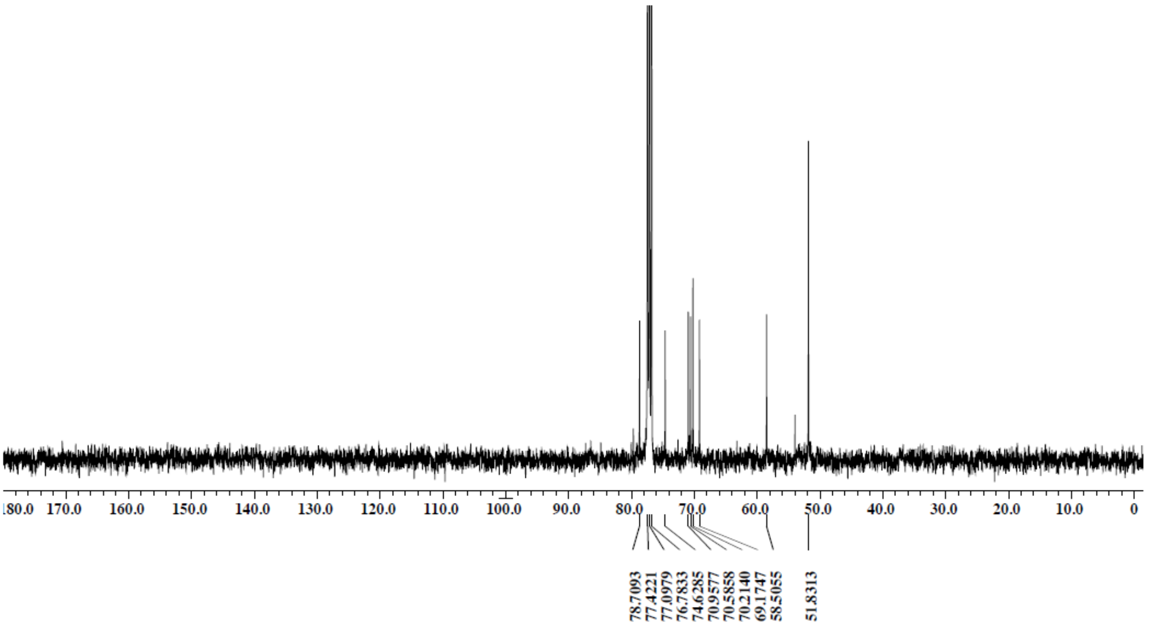


Synthesis of compound 19.

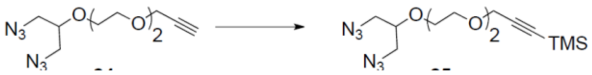


To a solution of **17** (0.500 g, 2.78 mmol, 1 eq) in DMF (7 mL) at 0°C was added sodium hydride (60% w/w in mineral oil, 0.120 g, 3.05 mmol, 1.1 eq). The solution was stirred for 30 minutes. Afterwards **18** (0.910 g, 3.05 mmol, 1.1 eq) diluted in DMF (3 mL) was added. After overnight reaction, the solution was diluted with EtOAc (50 mL), washed with brine (3x 25 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Cy to Cy/EtOAc 85:15) to afford **19** (0.687 g, 92%) as colorless oil. *N.B. It was not possible to obtain the compound totally pure by chromatography, however the impurities were removed after the following step.* **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.21 (d, J = 2.5 Hz, 2H, *CH_2*CCH), 3.81-3.78 (m, 2H, CH_2O), 3.72-3.65 (m, 7H, CH_2O*C(H)*$(CH_2N)_2$, $3CH_2O$), 3.38 (d, J = 5.0 Hz, 4H, $2CH_2N$), 2.43 (t, J = 2.5 Hz, 1H, CH_2C*CH*). **^{13}C NMR** (100 MHz, D_2O) δ = 78.71, 74.63 ($2C_q$), 70.96, 70.59, 70.21, 69.17, 58.51 (6C, $5CH_2O$, C(H)O, 51.83 (2C, $2CH_2N_3$). **Mass** (TOF-MS-ESI$^-$): m/z: 269.1368 (100%) $[M+H]^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{10}H_{17}N_6O_3^+$: 269.1357; found: 269.1368.

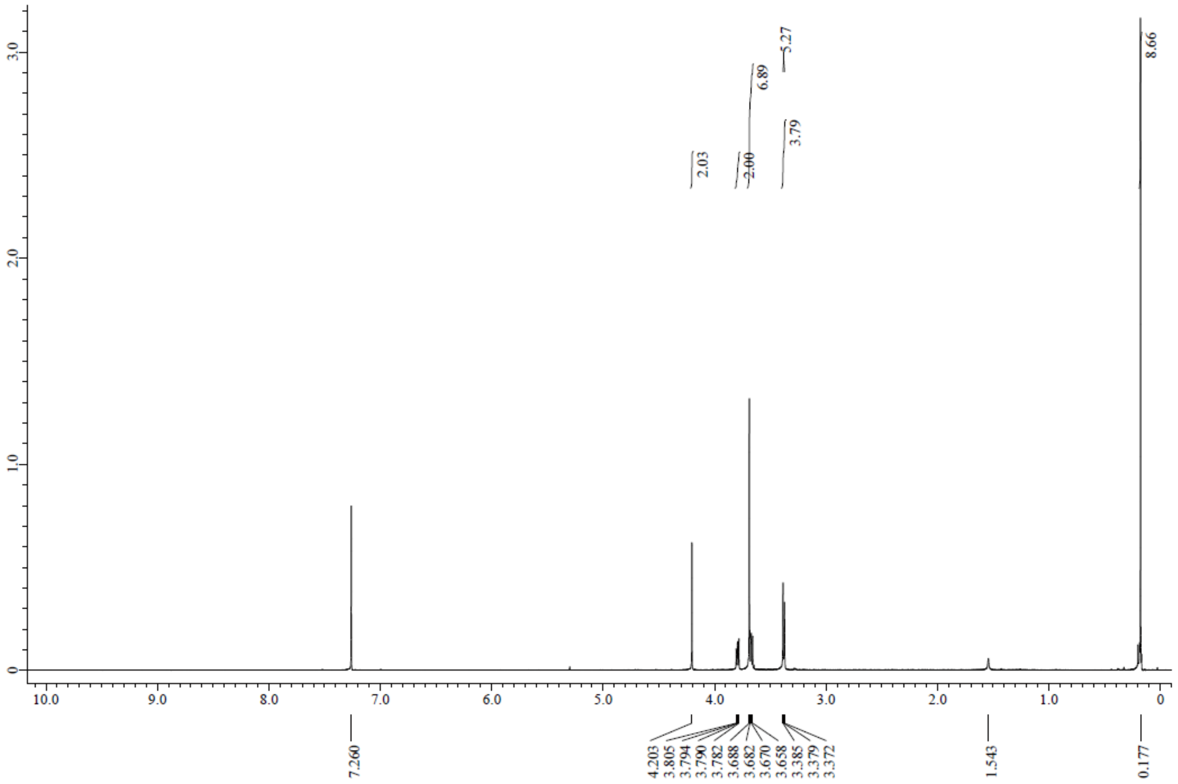




Synthesis of compound 20.



To a solution of **19** (2.015 g, 7.51 mmol, 1 eq) in THF (40 mL) at -84°C was added dropwise *n*-BuLi (2.0 M in hexanes, 4.50 mL, 9.01 mmol, 1.2 eq). The solution was stirred for 15 minutes afterwards trimethylsilyl chloride (1.91 mL, 15.02 mmol, 2.0 eq) was added. After 30 minutes, the solution was diluted with Et_2O (50 mL) and washed with water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3x 10 mL) and the organic phase was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Cy to Cy/EtOAc 9:1) to afford **20** (0.998 g, 39%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.20 (s, 2H, OCH_2CC-TMS), 3.81-3.78 (m, 2H, CH_2O), 3.69-3.66 (m, 7H, $3CH_2O$, $(N_3CH_2)_2C(H)OCH_2$), 3.38 (d, J = 5.3 Hz, 4H, $2CH_2N_3$), 0.18 (s, 9H, TMS). **^{13}C NMR** (100 MHz, D_2O) δ = 101.46, 91.57 (2C, $2C_q$), 78.70 (CH), 70.93, 70.61, 70.20, 69.11(4C, $4CH_2O$), 59.29 (OCH_2CC-TMS) , 51.86 (2C, $2CH_2N_3$), -0.10 (3C, TMS). **Mass** (TOF-MS-ESI$^-$): m/z: 341.1756 (100%) $[M+H]^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{13}H_{25}N_6O_3^+$: 341.1752; found: 341.1756.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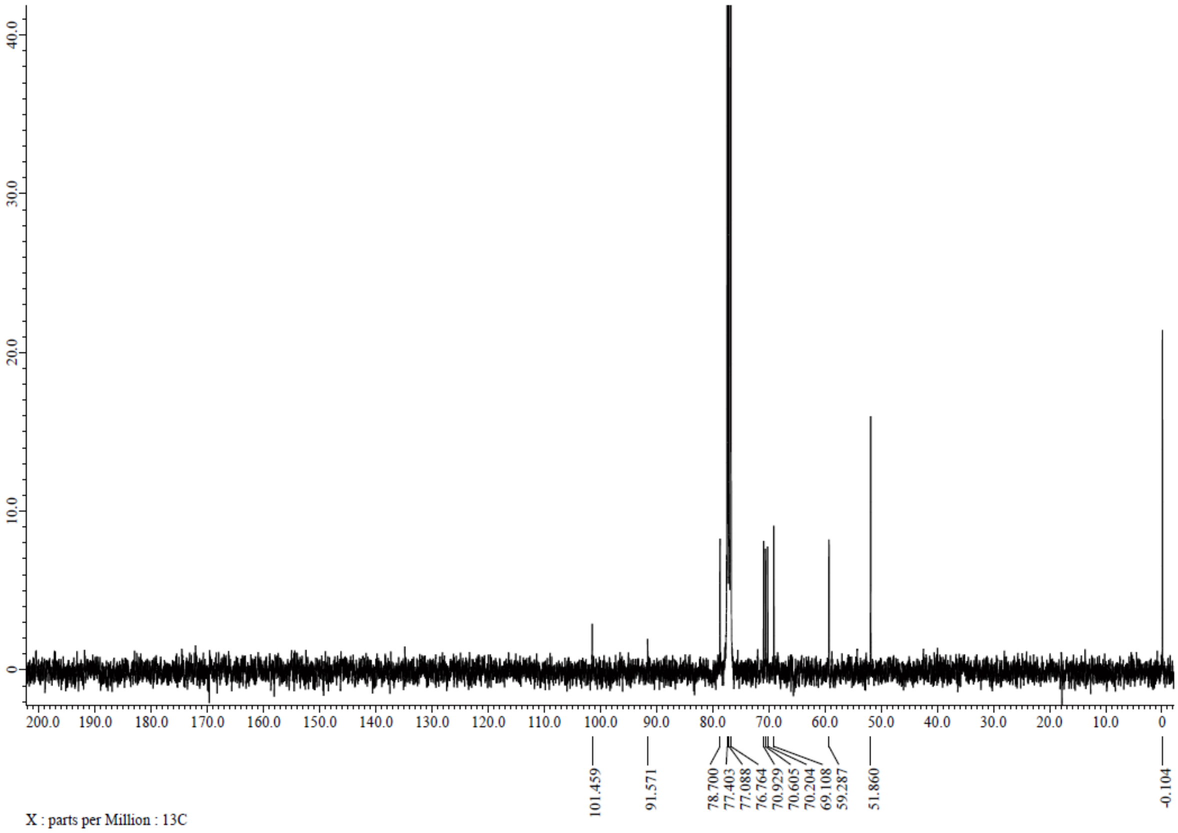
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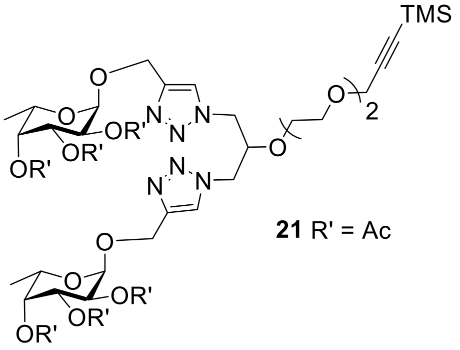
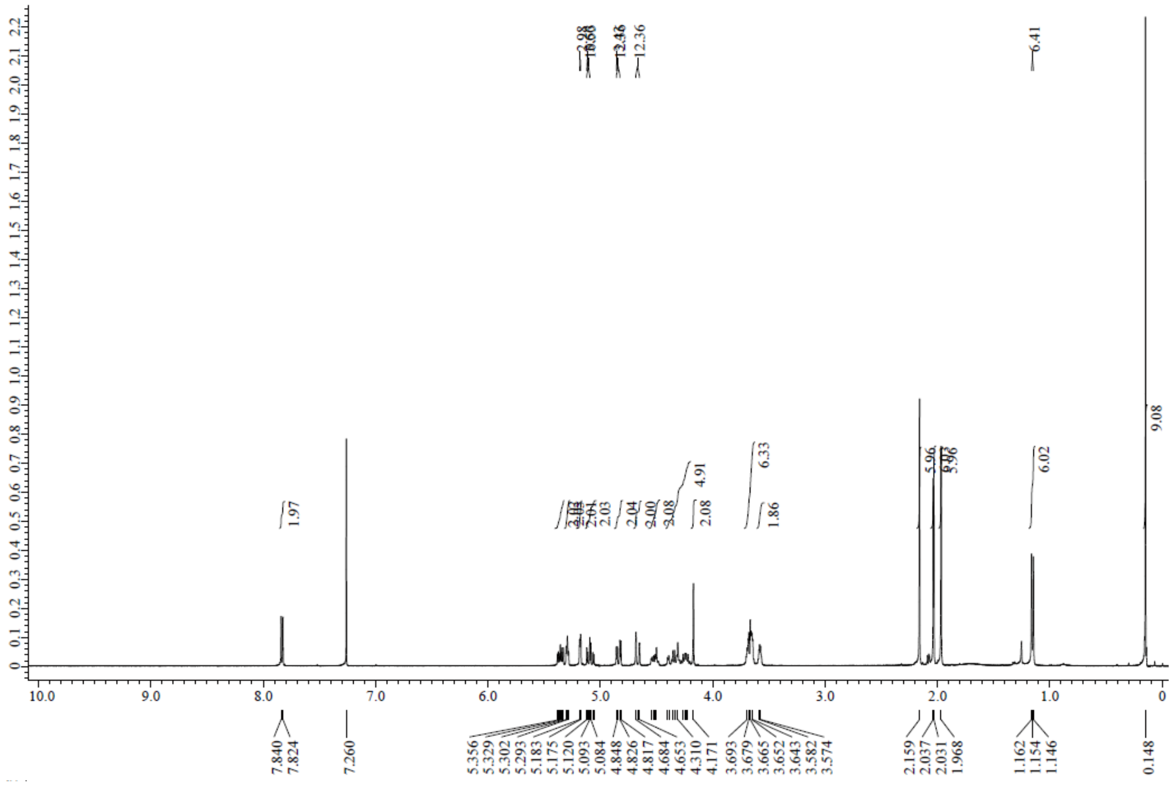
X : parts per Million : 13C

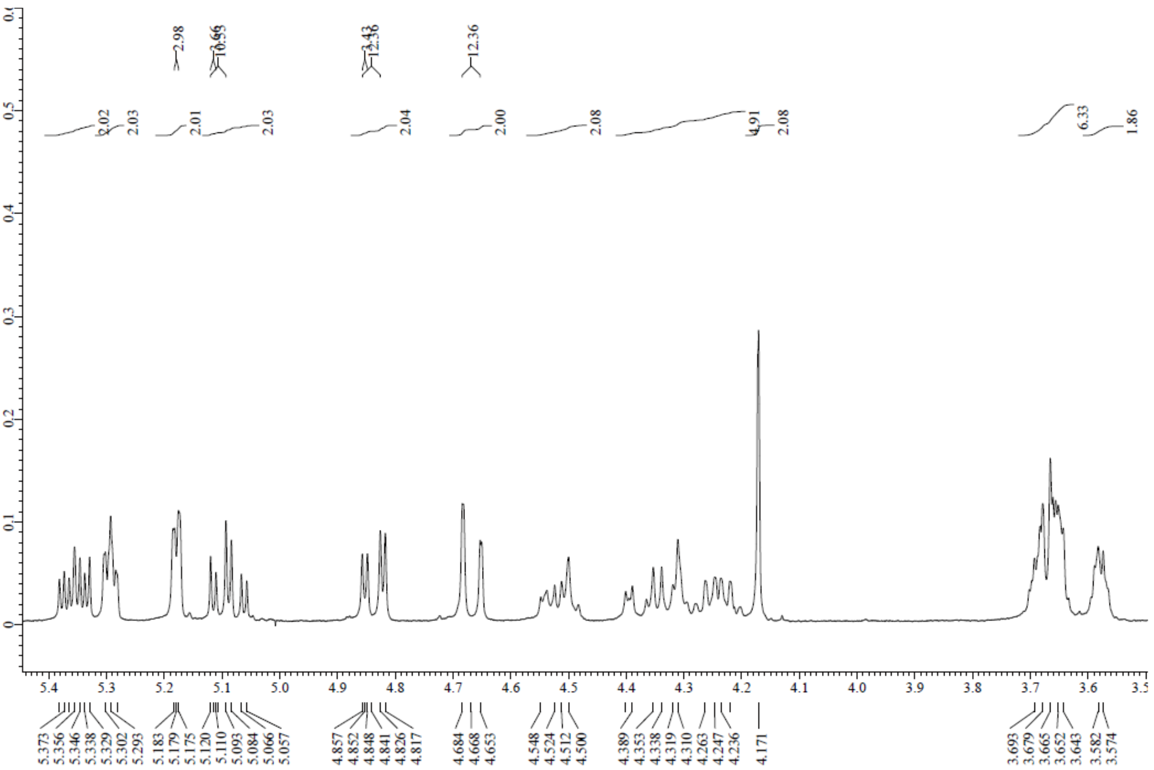
Synthesis of compound 21.



21 R' = Ac

To a solution of **20** (0.940 g, 2.761 mmol, 1 eq) in *t*-BuOH/H_2O 3:1 (25 mL) was added **2** (1.99 g, 6.074 mmol, 2.2 eq), sodium ascorbate (0.109 g, 0.552 mmol, 0.2 eq) and copper (II) sulfate (0.044 g, 0.2761 mmol, 0.1 eq). The solution was stirred overnight at 60°C. Afterwards the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Cy to EtOAc) to afford **21** (1.927 g, 72%) as a white powder. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.84, 7.82 (2s, 2H, $2H_{arom}$), 5.38-5.33 (m, 2H, 2H-3), 5.30-5.28 (m, 2H, 2H-4), 5.18 (d, J = 3.0 Hz, 2H, 2H-1), 5.09 (td, J = 3.7 Hz, J = 10.3 Hz, 2H, 2H-2), 4.84 (AB, J = 3.4 Hz, J = 12.4 Hz, 2H, CH_2O), 4.67 (d, J = 12.4 Hz, 2H, CH_2O), 4.55-4.50 (m, 2H, CH_2N), 4.40-4.22 (m, 5H, 2H-5, CH_2N, $(CH_2)C$*(H)*OCH_2), 4.17 (s, 2H, CH_2), 3.69-3.64 (m, 6H, $3CH_2O$), 3.58-3.57 (m, 2H, CH_2O), 2.16, 2.04, 2.03, 1.97 (4s, 18H, $6CH_3$), 1.15 (d, J = 6.4 Hz, 6H, 2H-6), 0.15 (s, 9H, TMS). **^{13}C NMR** (100 MHz, D_2O) δ = 170.66, 170.61, 170.55, 170.05 (6C, 6C=O), 143.72 (2C, $2C_{arom}$), 125.28 (2C, $2C_{arom}$), 101.21 (2C, $2C_q$), 95.33 (C-1), 95.19 (C-1), 91.88 (2C, $2C_q$), 71.24, 70.63, 70.36, 69.00, 68.22, 68.16, 68.02 (10C, $4CH_2O$, 2C-2, 2C-3, 2C-4), 64.82 (2C, 2C-5), 60.91 (2C, $2CH_2O$), 59.14 (*CH_2*CC-TMS), 50.58 (CH_2N), 50.49 (CH_2N), 20.94, 20.91, 20.77, 20.73 (6C, $6CH_3$), 16.00 (2C, 2C-6), -0.13 (3C, TMS). **$[\alpha]_d$** ($CHCl_3$, c=0.5, 20°C) = -72.0 **Mass** (TOF-MS-ESI$^-$): m/z: 1019.3924 (100%) $[M+Na]^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{43}H_{64}N_6O_{19}SiNa^+$: 1019.3888; found: 1019.3924.

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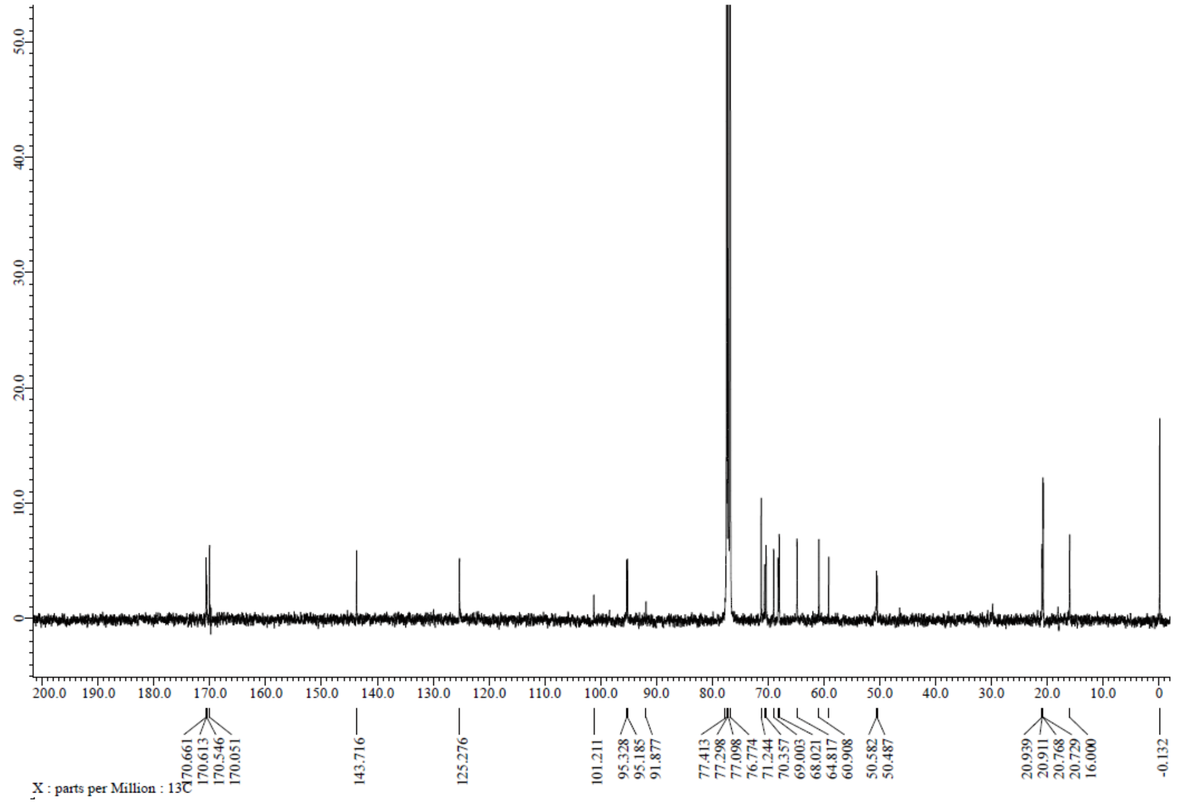
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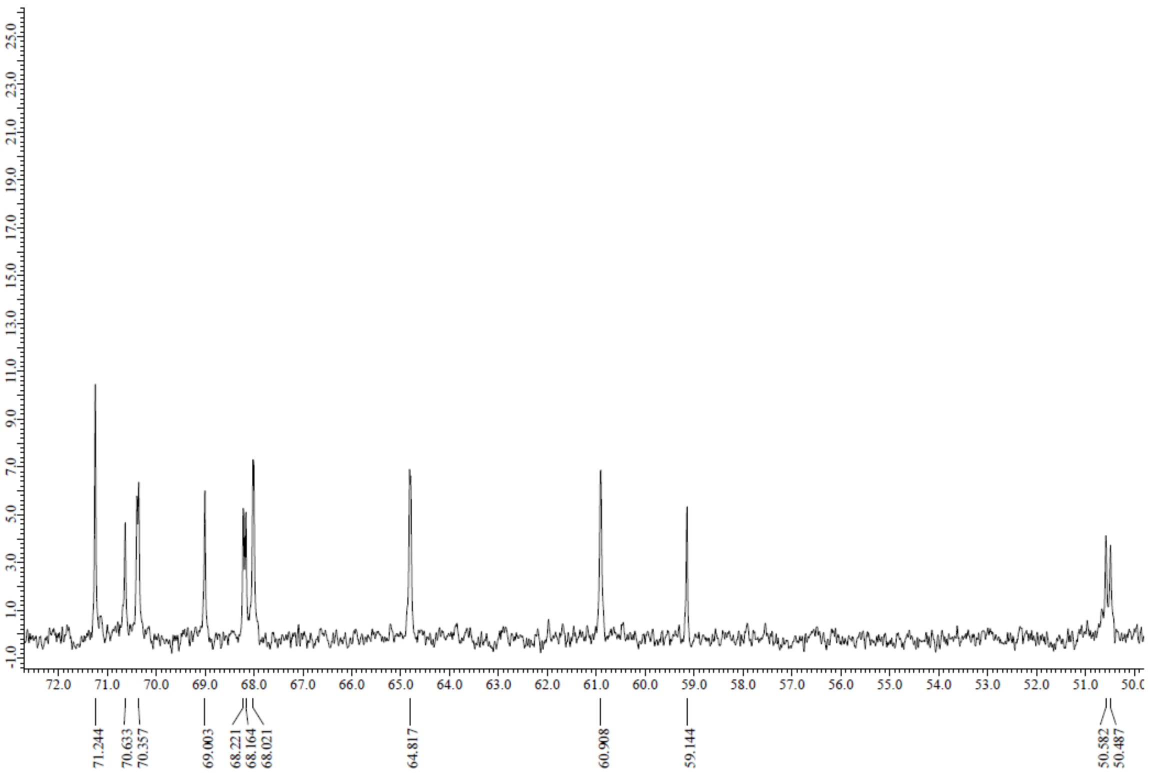
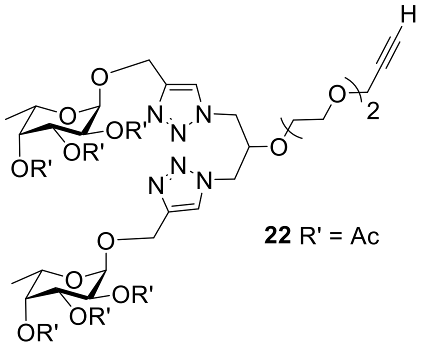
X : parts per Million : 13C



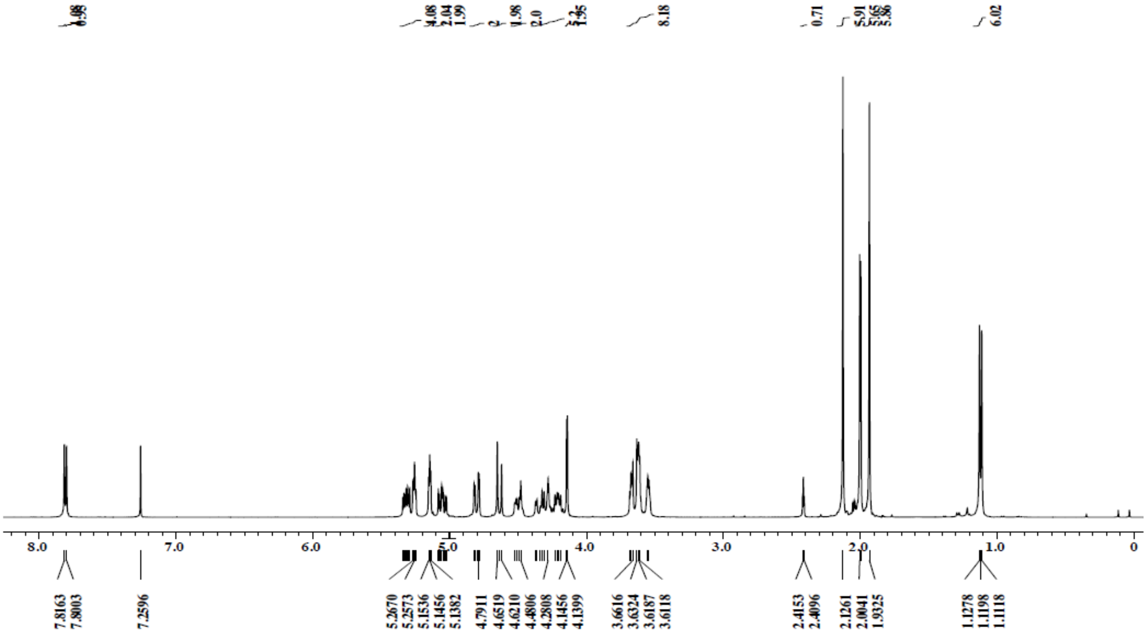
Synthesis of compound 22.

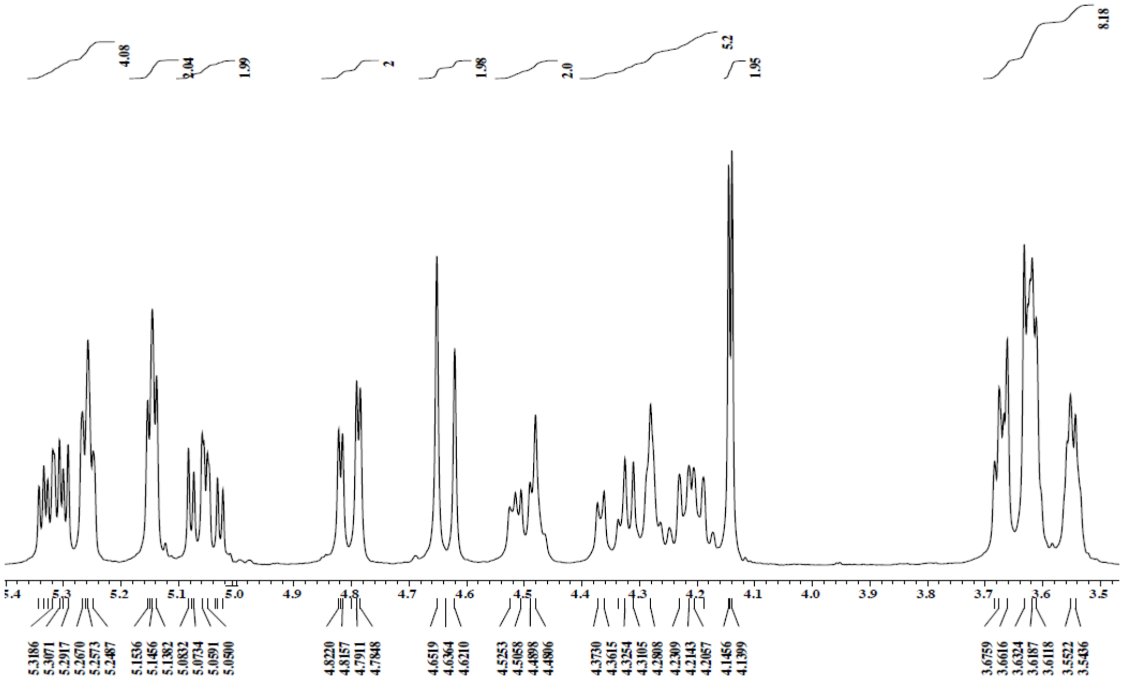


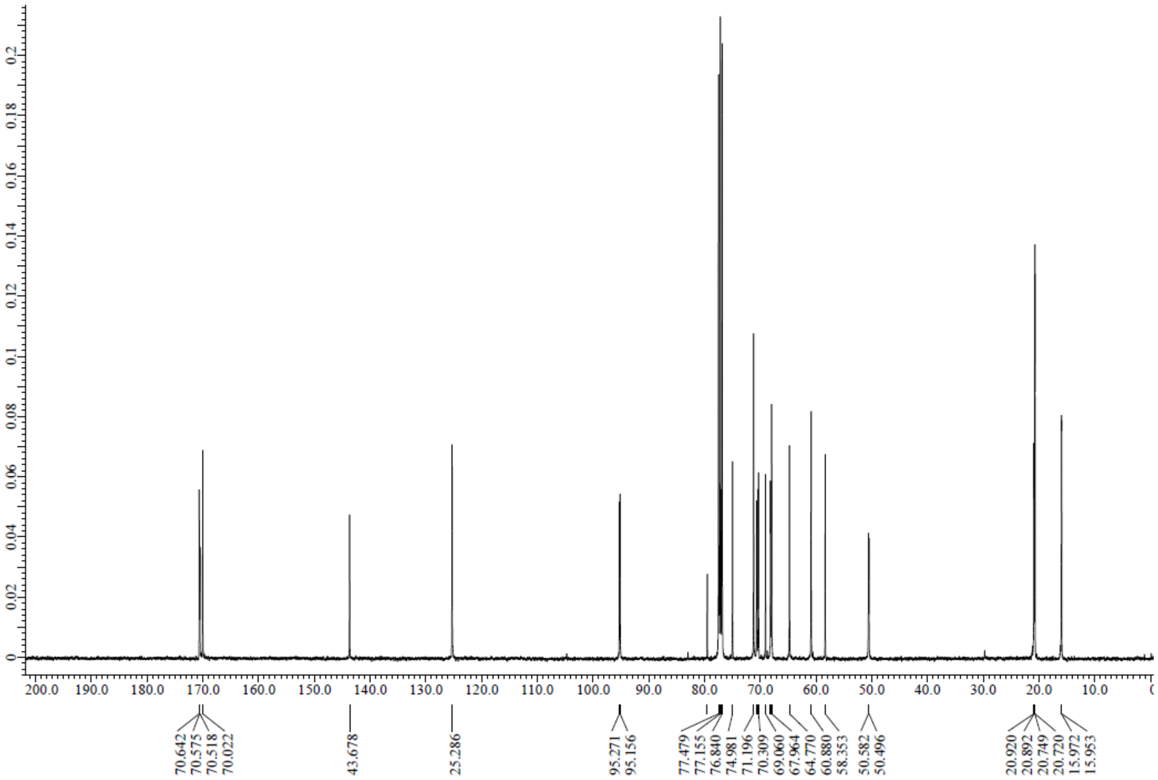
22 R' = Ac

To a solution of **21** (1.927 g, 1.933 mmol, 1 eq) in THF (50 mL) at 0°C was added TBAF•3H_2O (0.606 mg, 2.319 mmol, 1.2 eq). The solution was stirred for three minutes afterwards the solvents were evaporated, the residue dissolved in CH_2Cl_2 (100 ml) and washed with a saturated solution of NH_4Cl (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3x 50 mL) and the organic phase was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Cy to EtOAc) to afford **22** (1.59 g, 86%) as a white powder. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ = 7.82 (s, 1H, H_{arom}), 7.80 (s, 1H, H_{arom}), 5.35-5.29 (m, 2H, 2H-3), 5.26 (t, J = 3.9 Hz, 2H), 5.15 (t, J = 3.2 Hz, 2H, 2H-1), 5.06 (td, J = 3.9 Hz, J = 10.8 Hz, 2H, 2H-2), 4.80 (dd, J = 2.5 Hz, J = 12.4 Hz, 2H), 4.64 (d, J = 12.4 Hz, 2H), 4.53-4.48 (m, 2H), 4.37-4.19 (m, 5H, H-5), 4.14 (d, J = 2.3 Hz, 2H, OCH_2CCH), 3.68-3.54 (m, 8H, 4CH_2O), 2.43 (t, J = 2.4 Hz, 1H, OCH_2C*CH*), 2.13, 2.00, 2.00, 1.93 (4s, 18H, 6CH_3), 1.12 (d, J = 6.4 Hz, 6H, 2H-6). ^{13}**C NMR** (100 MHz, $CDCl_3$) δ = 170.64, 170.58, 170.52, 170.02 (6C, 6 C=O), 143.68 (2C, 2C_{arom}), 125.29 (2C, 2C_{arom}), 95.27, 95.16 (2C, 2C-1), 79.51 (OCH_2*C*CH), 74.98 (OCH_2C*CH*), 71.20, 70.65, 70.40, 70.31, 69.06 (8C, 2C-4, 5*CH_2*O), 68.17, 68.14, 67.96 (4C, 2C-2, 2C-3), 64.77 (2C, 2C-5), 60.88 (2C), 58.35 (O*CH_2*CCH), 50.58, 50.50 (2C, 2*CH_2*N), 20.92, 20.89, 20.75, 20.72 (6C, 6CH_3), 15.97, 15.95 (2C, 2C-6). **[α]d** ($CHCl_3$, c=0.5, 20°C) =

-116.6 **Mass** (TOF-MS-ESI$^-$): m/z: 947.3513 (100%) [M+Na]$^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{40}H_{56}N_6O_{19}Na^+$: 947.3492; found: 947.3513.



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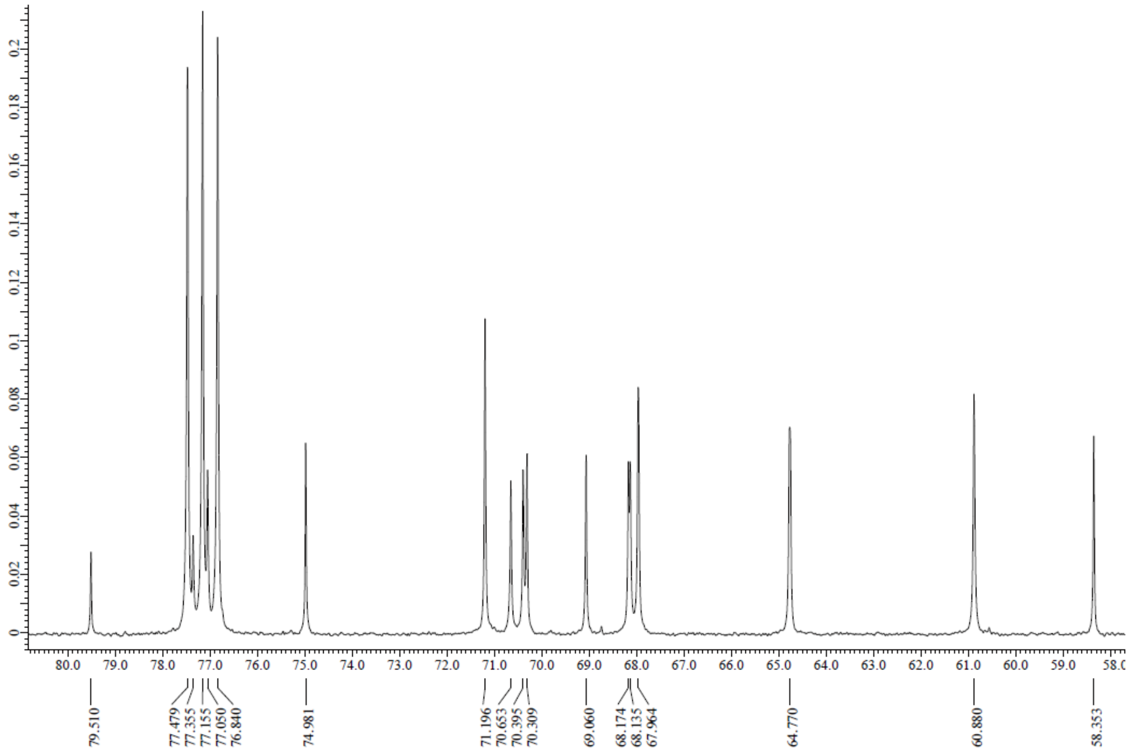
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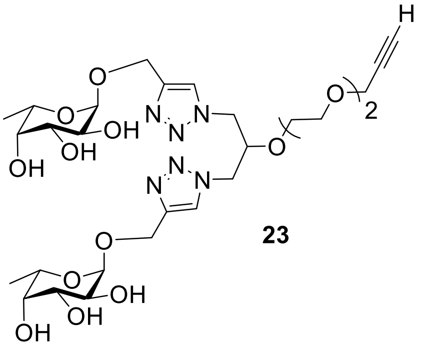
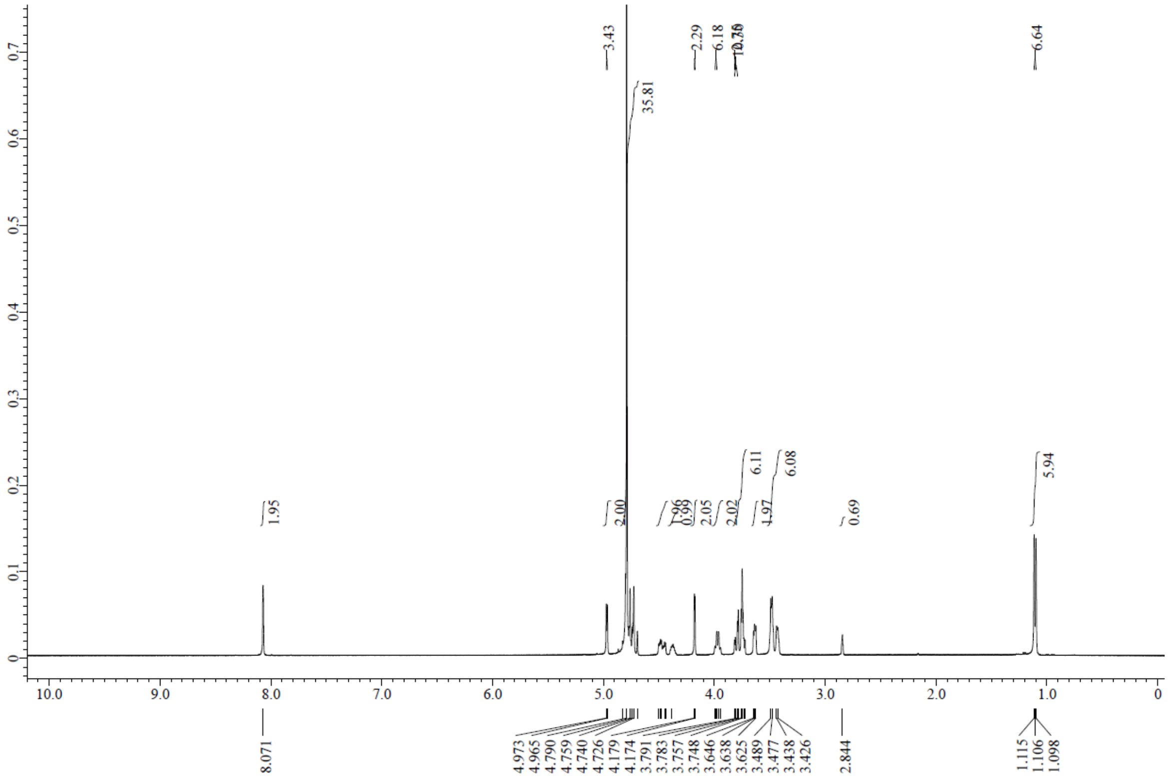
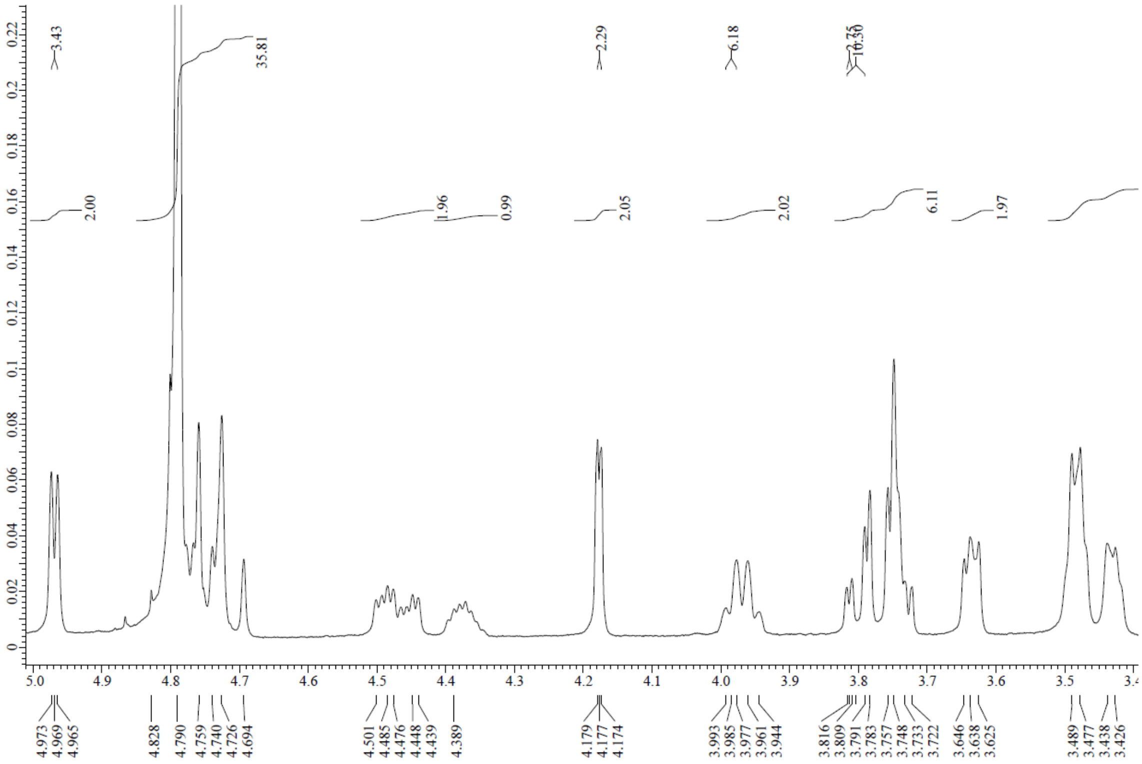
Synthesis of compound 23.



23

To a solution of **22** (1.44 g, 1.556 mmol, 1 eq) in MeOH (25 mL) was added sodium methoxide (0.168 g, 3.114 mmol, 2 eq) at 0°C. The solution was stirred during two hours at room temperature and the solution was filtered over a short column of Dowex™ 50WX8-200 (H^+ resin form). The resin was washed with MeOH (15 mL) and water (15 mL). Finally, the solvents were evaporated under reduced pressure to afford the desired product **23** as a colorless oil (1.036 g, 99%). **^{1}H NMR** (400 MHz, D_2O) δ = 8.07 (s, 2H, 2H$_{arom}$), 4.97 (d, J = 3.4 Hz, 2H, 2H-1), 4.82-4.69 (m), 4.50-4.44 (m, 2H, CH_2), 4.39 (m, 1H, CH_2O*C(H)*(CH_2N)$_2$), 4.18 (d, J = 2.3 Hz, 2H, O*CH$_2$*CCH), 3.97 (q, J = 6.2 Hz, 2H, 2H-5), 3.80 (dd, J = 2.8 Hz, J = 10.3 Hz, 2H, 2H-2), 3.76-3.72 (m, 4H), 3.65-3.63 (m, 2H), 3.49-3.48 (m, 4H), 3.44-3.43 (m, 2H), 2.84 (s, 1H, OCH_2C*CH*), 1.11 (d, J = 6.6 Hz, 6H, 2H-6). **^{13}C NMR** (100 MHz, D_2O) δ = 144.12 (2C, 2C$_{arom}$), 126.15 (2C, 2C$_{arom}$), 98.45 (2C, 2C-1), 79.43 (C$_q$), 76.75 (CH_2O*C(H)*(CH_2N)$_2$), 76.09 (OCH_2C*CH*), 71.79, 69.69, 69.57, 69.49, 69.34, 68.67, 67.95 (10C, 2C-2, 2C-3, 2C-4, 4CH_2O), 66.82 (2C, 2C-5), 60.50 (2C, 2CH_2O), 57.91 (O*CH$_2$*CCH), 51.05 (2C, 2*CH$_2$*N), 15.34 (2C, 2C-6). **[α]$_d$** (MeOH, c=0.5, 20°C) = -108.0 **Mass** (TOF-MS-ESI$^-$): m/z: 695.2889 (100%) [M+Na]$^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{28}H_{44}N_6O_{13}Na^+$: 695.2859; found: 695.2889.

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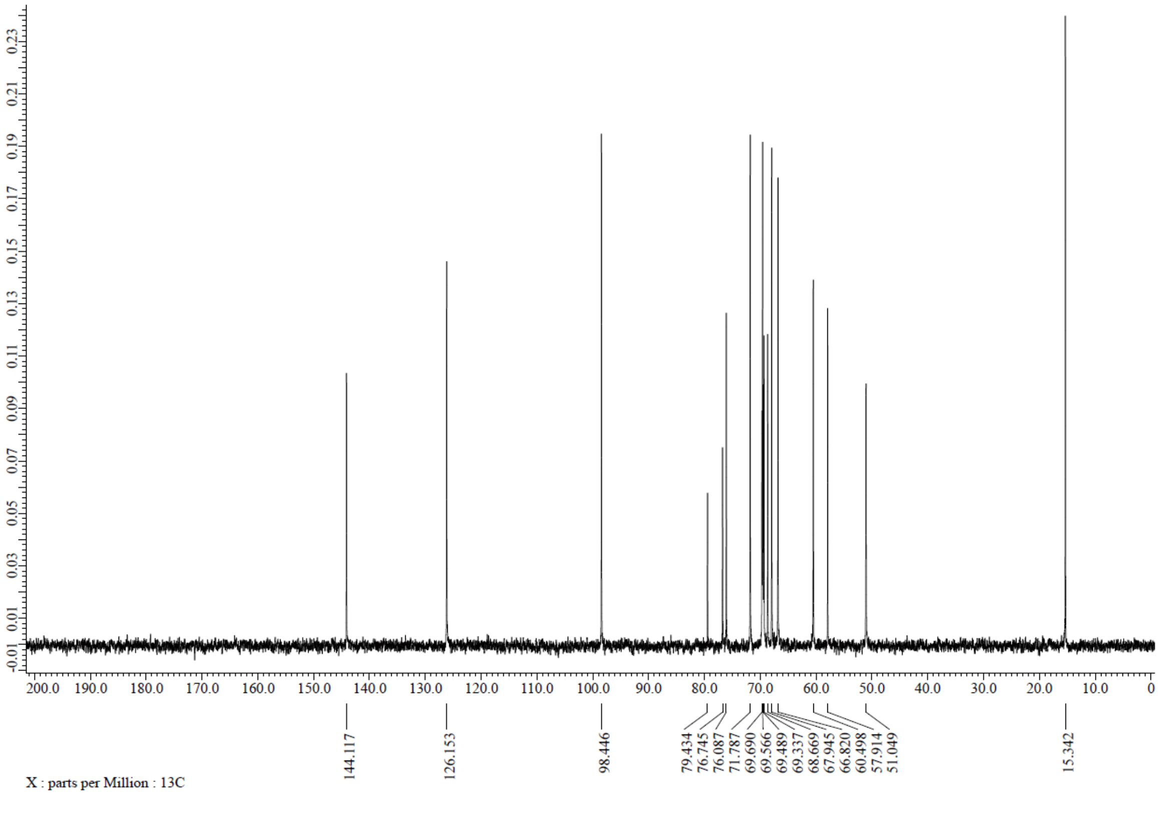
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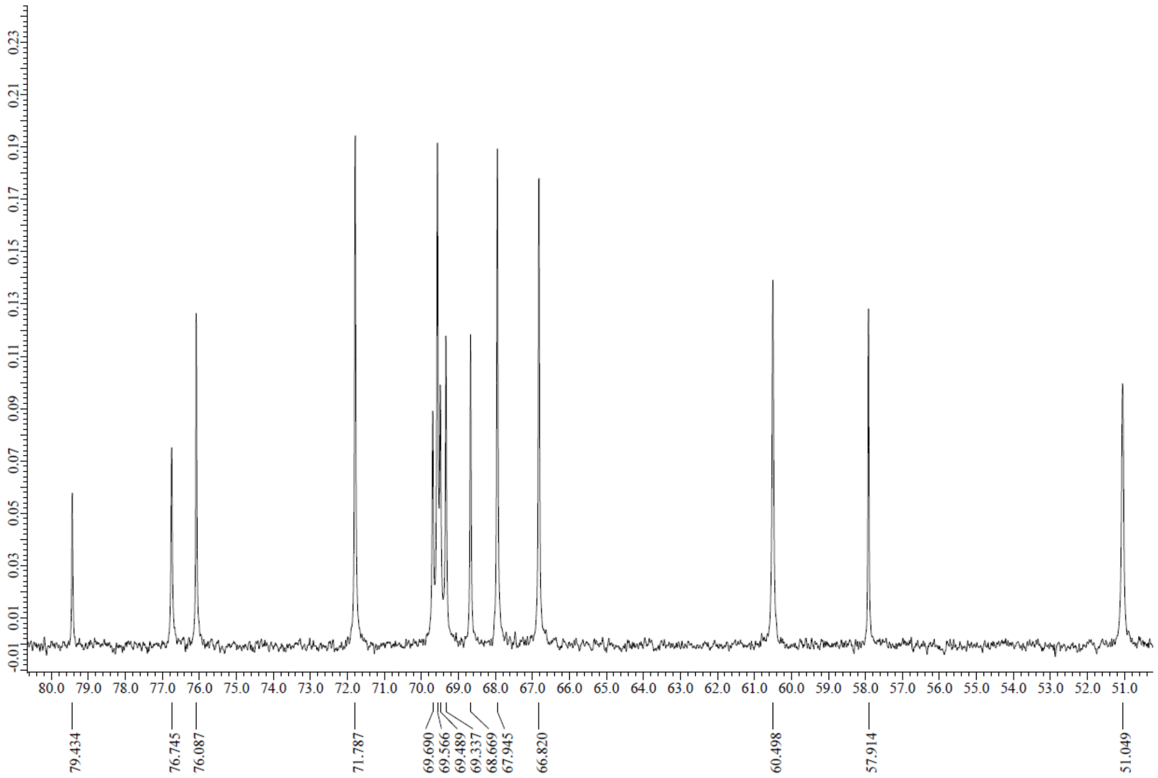
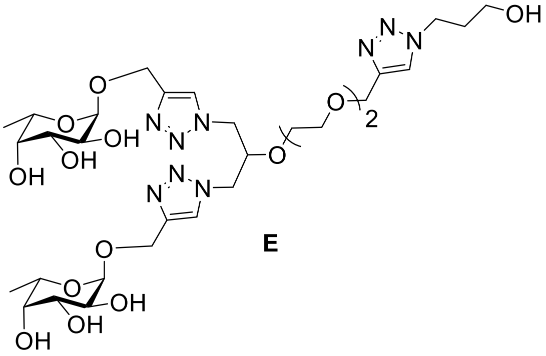
X : parts per Million : 13C

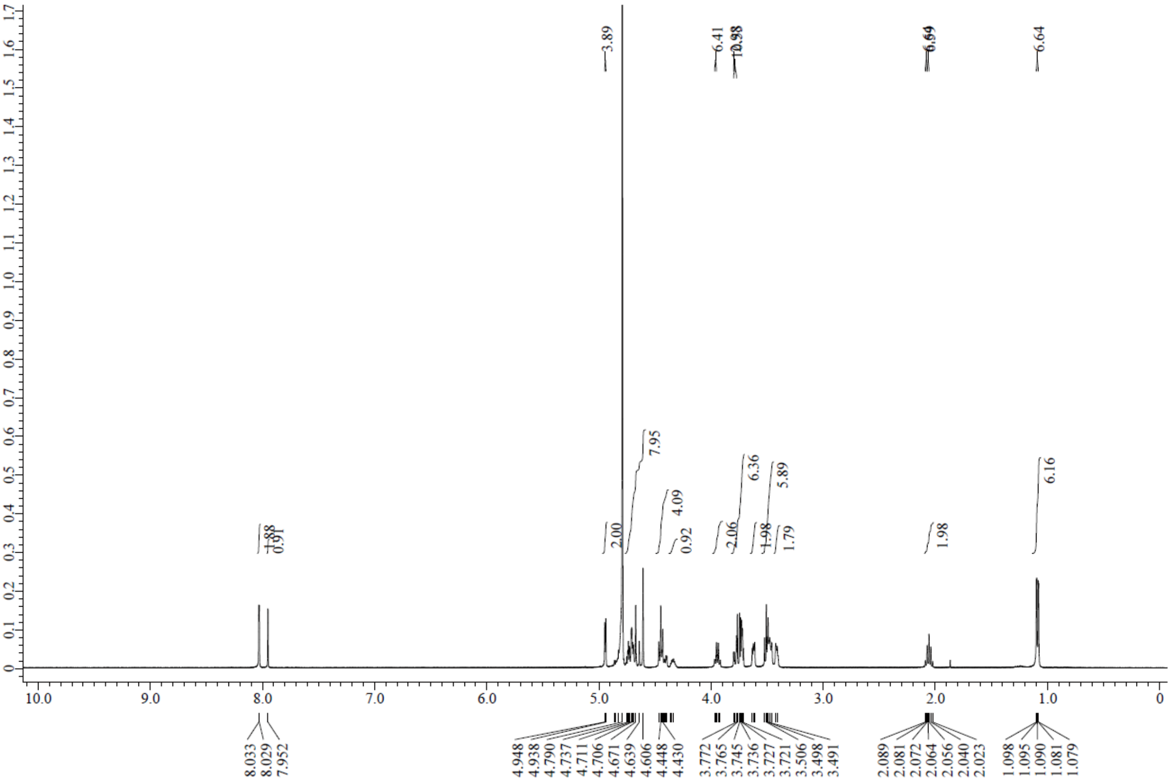


Synthesis of compound E.



E

To a solution of **23** (0.050 g, 0.0743 mmol, 1 eq) in *t*-BuOH/H_2O 1:1 (1 mL) was added **25** (0.009 g, 0.0892 mmol, 1.2 eq), sodium ascorbate (0.003 g, 0.0148 mmol, 0.2 eq) and copper (II) sulfate (0.0012 g, 0.00743 mmol, 0.1 eq). The solution was stirred three hours at room temperature afterwards the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc to EtOAc/EtOH 1:1) to afford **E** (0.044 g, 76%) as a white powder. **^{1}H NMR** (400 MHz, D_2O) δ = 8.03 (2s, 2H, 2H$_{arom}$), 7.95 (s, 1H, H$_{arom}$), 4.94 (d, J = 3.9 Hz, 2H, 2H-1), 4.75-4.61 (m, 8H), 4.47-4.39 (m, 4H, CH_2, N*CH₂*CH_2CH_2OH), 4.36-4.33 (m, 1H, CH_2O*C(H)*(CH_2N)$_2$), 3.94 (q, J = 6.4 Hz, 2H, 2H-5), 3.78 (dd, J = 3.0 Hz, J = 10.5 Hz, 2H, 2H-2), 3.75-3.71 (m, 4H), 3.63-3.61 (m, 2H), 3.52-3.46 (m, 6H, NCH_2CH_2*CH₂*OH), 3.42-3.41 (m, 2H), 2.06 (tt, J = 6.6 Hz Hz, J = 6.6 Hz Hz, 2H, NCH_2*CH₂*CH_2OH), 1.09 (2d, J = 6.6 Hz, J = 6.6 Hz, 6H, 2H-6). **^{13}C NMR** (100 MHz, D_2O) δ = 144.02, 143.82 (3C, 3C$_{arom}$), 126.12, 125.05 (3C, 3C$_{arom}$), 98.38 (2C, 2C-1), 76.75, 71.75, 69.62, 69.51, 69.39, 68.93, 67.90, 66.80, 66.82, 63.03, 60.41, 58.08 (17C, 2C-2, 2C-3, 2C-4, 2C-5, 9CH_2), 51.00 (2C, 2*CH₂*N), 47.21 (CH_2), 31.79 (NCH_2*CH₂*CH_2OH), 15.23 (2C, 2C-6). **$[\alpha]_d$** (MeOH, c=1.15, 20°C) = -64.7 **Mass** (TOF-MS-ESI$^-$): m/z: 796.3474 (100%) [M+Na]$^+$ **HRMS** (TOF-MS-ESI$^+$, m/z): calculated for $C_{31}H_{51}N_9O_{14}Na^+$: 796.3448; found: 796.3474.



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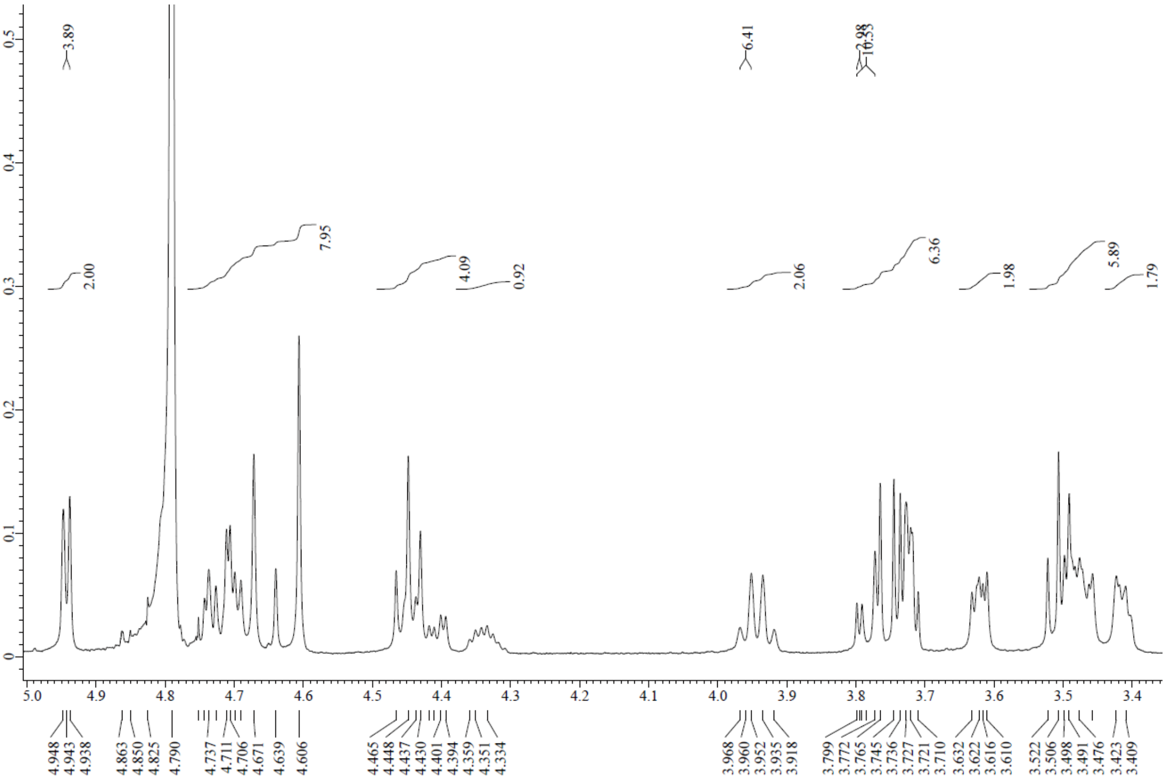

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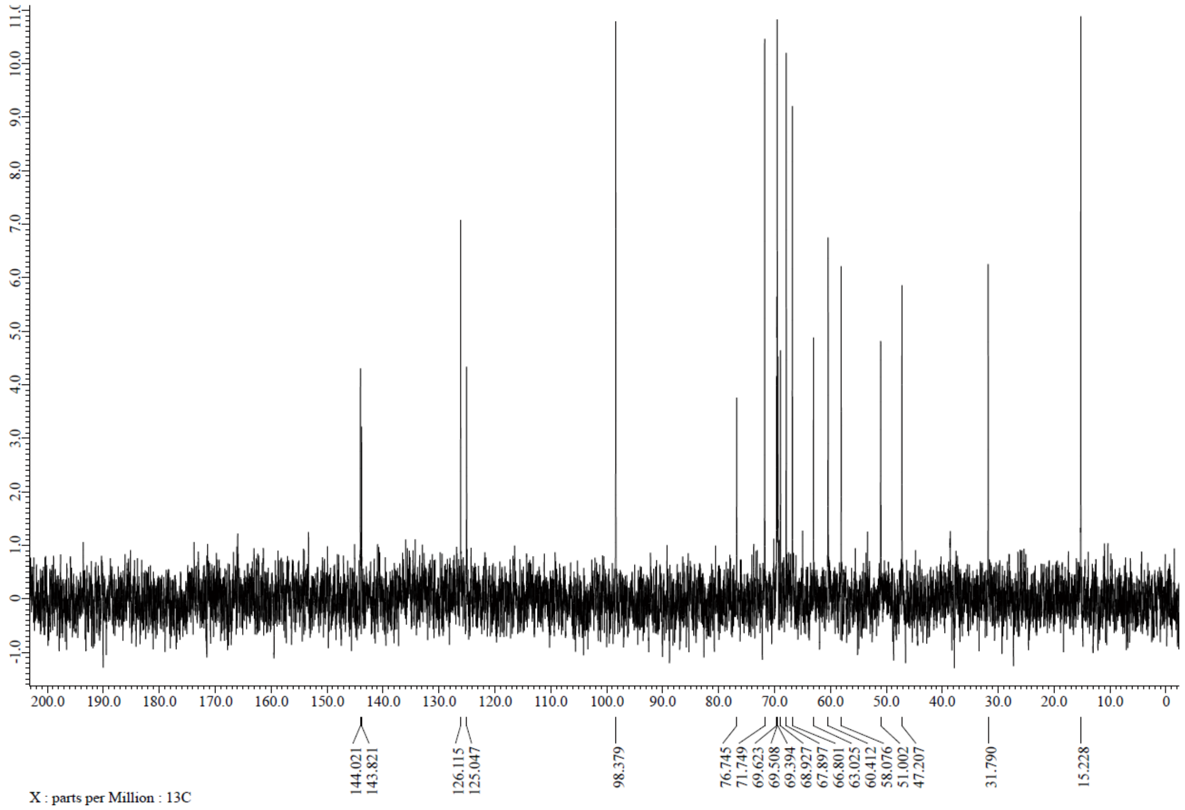
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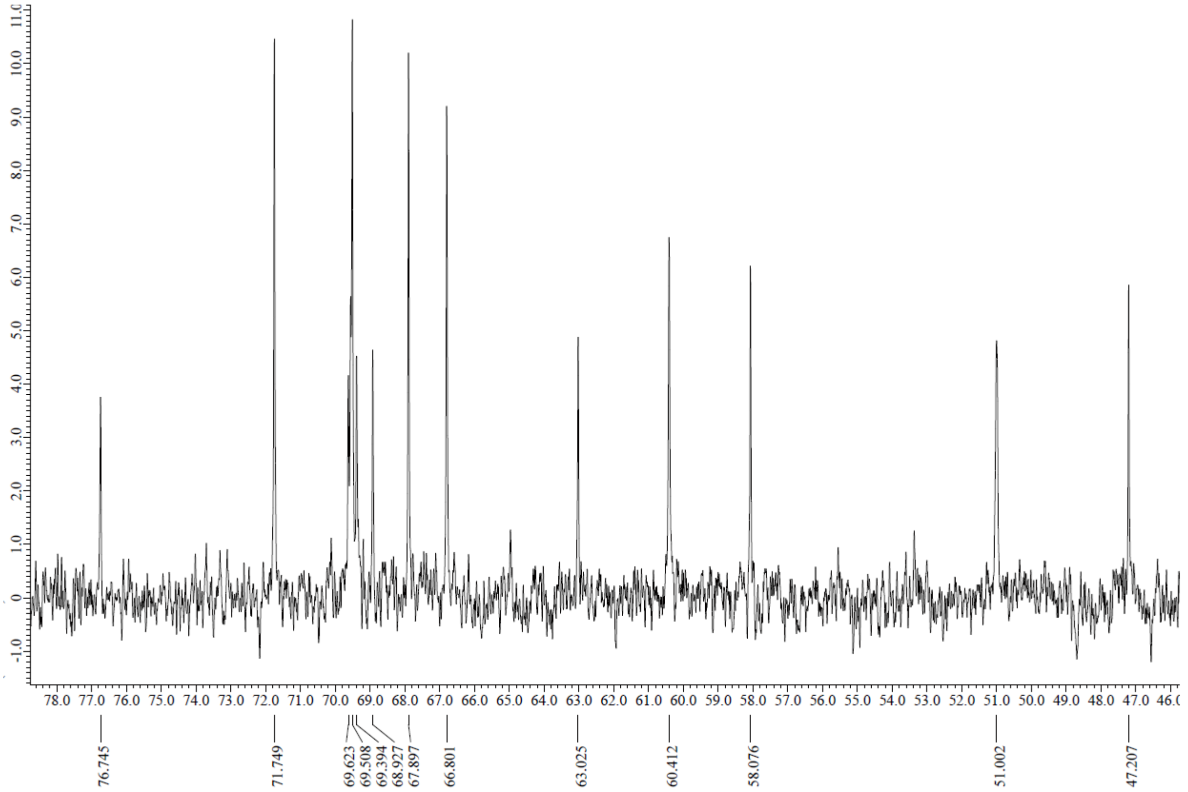
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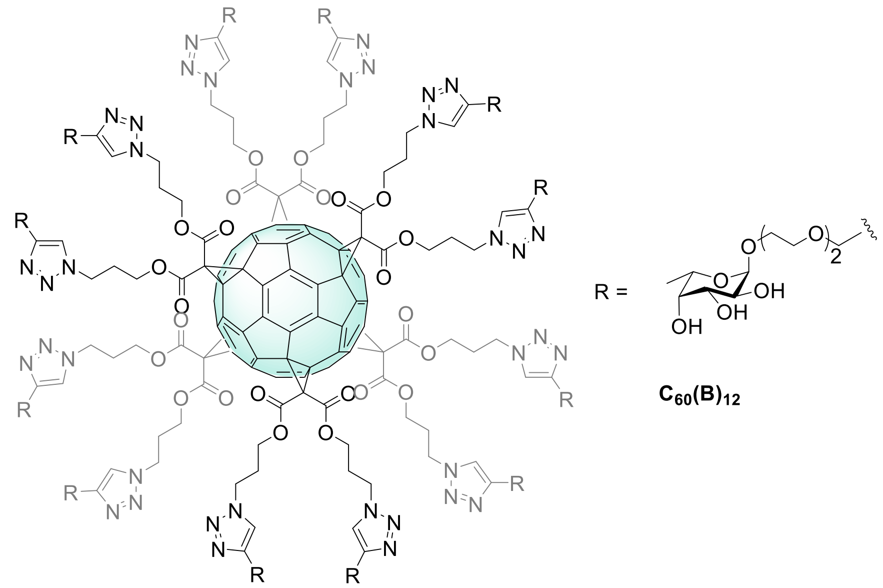
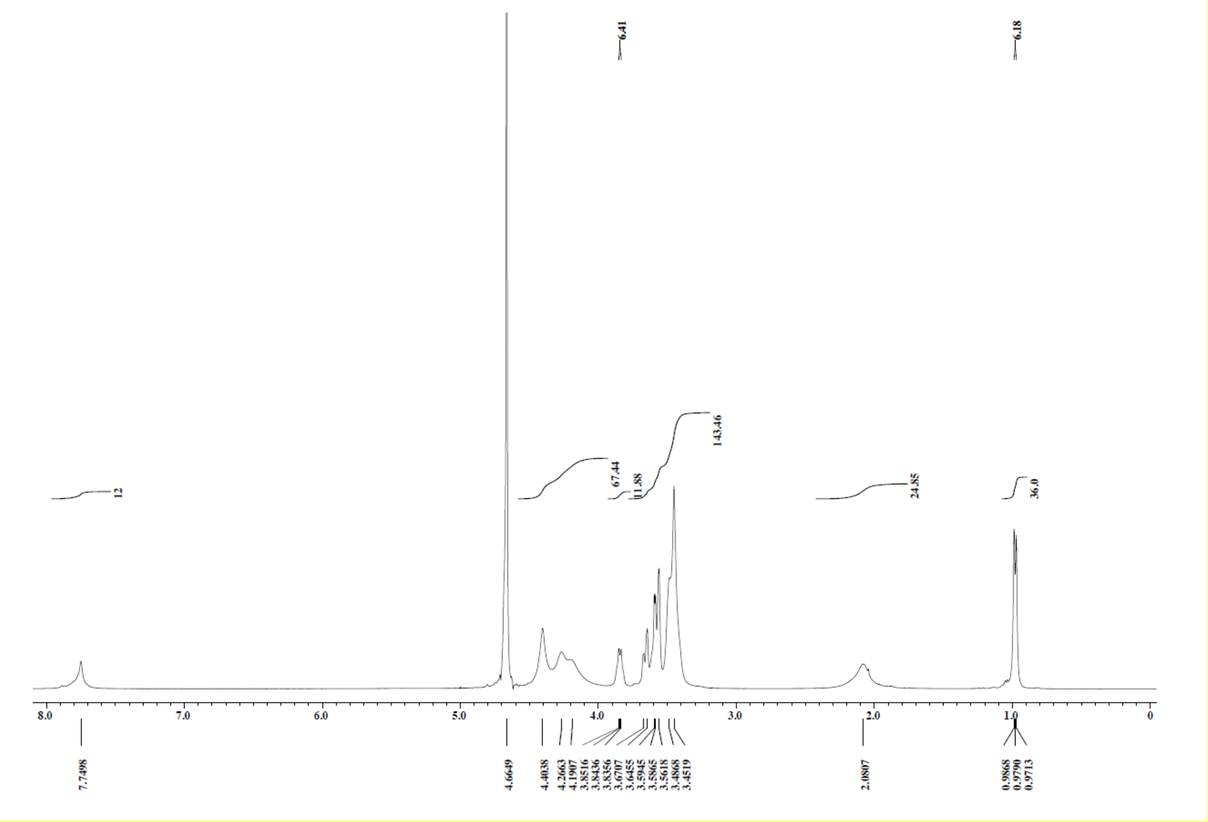
Synthesis of compound $C_{60}(B)_{12}$



$C_{60}(B)_{12}$

To a solution of **24** (75 mg, 3.22 10^{-2} mmol, 1 eq) in THF (3 mL) was added **5** (121 mg, 41.9 10^{-2} mmol, 13 eq) dissolved in 1 mL of DMSO. Afterwards sodium ascorbate (1.9 mg, 0.97 10^{-2} mmol, 0.3 eq) and copper (II) sulfate (0.5 mg, 0.32 10^{-2} mmol, 0.1 eq) dissolved in 1 mL of water were added. Microwave irradiation during two hours afforded the desired product, which was then precipitated with acetone (3 mL), washed with acetone (10 mL) and methanol (5mL) and purified on Sephadex™ G-25. Evaporation of the solvent afforded **$C_{60}(B)_{12}$** (127 mg, 68%) as a red solid. **IR**: 3391 (O-H), 1743 (C=O). **UV/Vis** (H_2O): 246 (sh, 72700), 276 (63400), 319 (sh, 34700), 337 (sh, 28400). **^{1}H NMR** (400 MHz, D_2O) δ = 7.75 (s, 12H), 4.40-4.19 (m, 72H), 3.84 (d, J = 6.4 Hz, 12H), 3.67-3.45 (m, 144H), 2.08 (s, 24H), 0.98 (d, J = 6.2 Hz, 36H, H-6). **^{13}C NMR** (100 MHz, D_2O) δ = 163.71 (C=O), 145.73, 144.21, 141.10, 124.74 (4C, $4C_{arom}$), 98.76 (C-1), 71.93, 69.89, 69.73, 69.20, 69.01, 68.23, 66.85, 66.66 (C-2, C-3, C-4, C-5, $4CH_2O$), 64.62, 63.28 ($2CH_2O$), 47.26 (CH_2N), 45.46 (C_q), 28.76 (CH_2), 15.58 (C-6). **Mass** (TOF-MS-LD$^+$): m/z: 5838.2 $[M+Na]^+$, 5420.0 $[M-C_{17}H_{28}N_3O_9+Na]^+$, 5989.8 $[M-C_{35}H_{56}N_6O_{18}+Na]^+$, 4570.6 $[M-C_{52}H_{84}N_9O_{27}+Na]^+$, 4141.4 $[M-C_{70}H_{112}N_{12}O_{36}+Na]^+$, 3723.2 $[M-C_{87}H_{140}N_{15}O_{45}+Na]^+$, 3293.0 $[M-C_{105}H_{168}N_{18}O_{54}+Na]^+$, 2874.9 $[M-C_{122}H_{196}N_{21}O_{63}+Na]^+$, 2443.7 $[M-C_{140}H_{224}N_{24}O_{72}+Na]^+$, 2025.5 $[M-C_{157}H_{252}N_{27}O_{81}+Na]^+$.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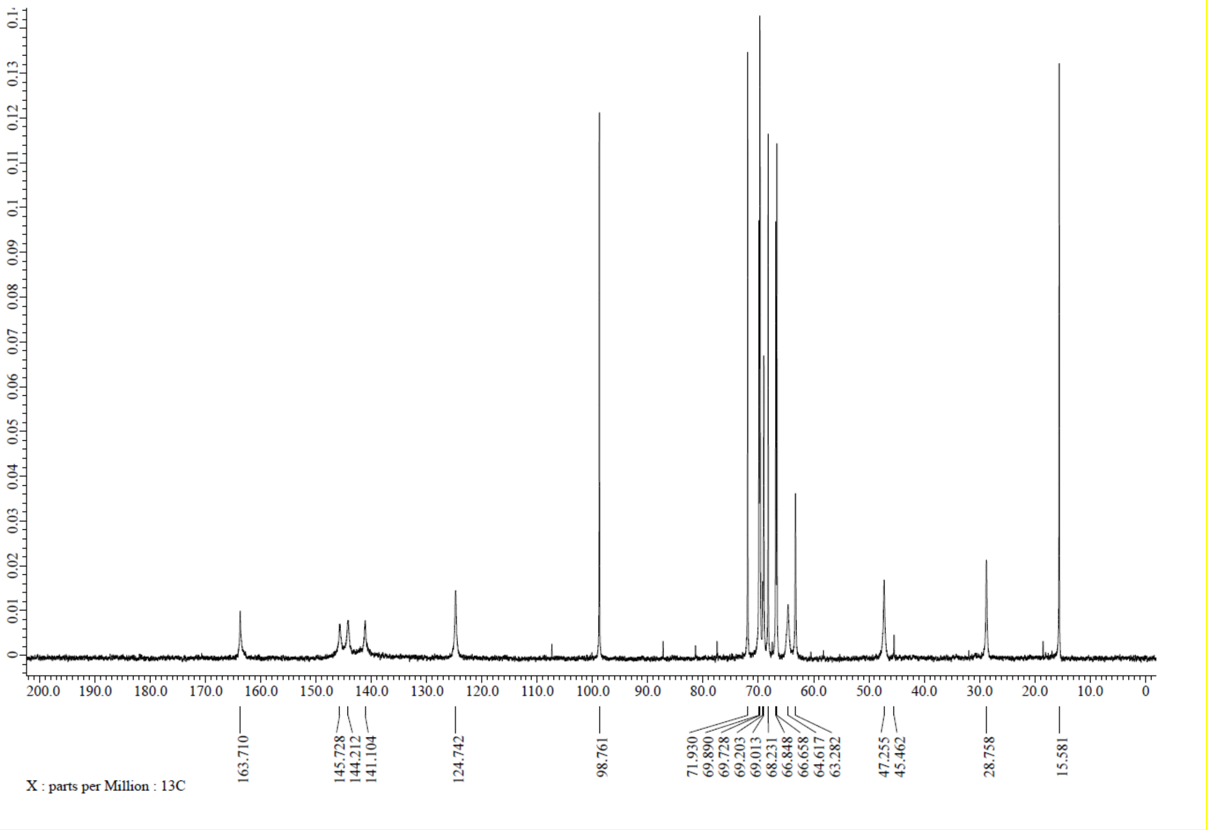
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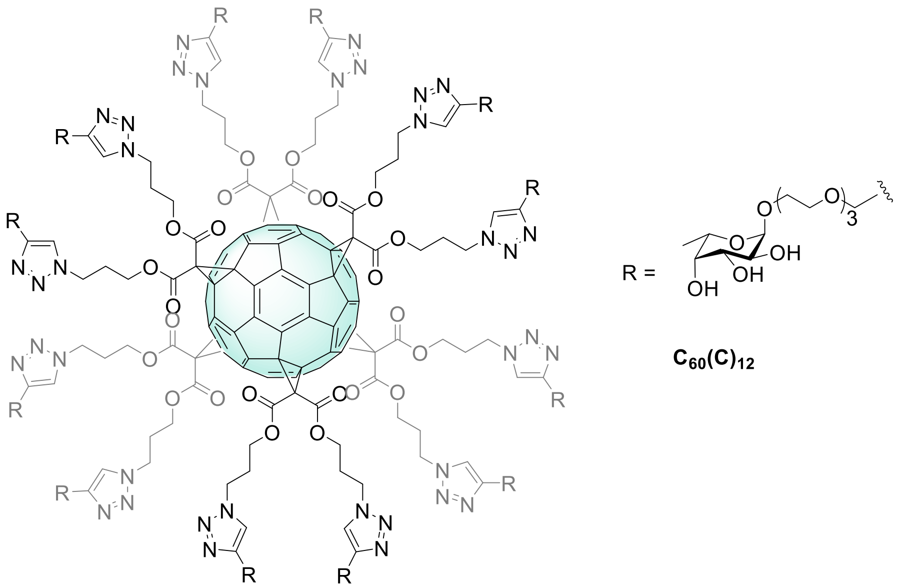
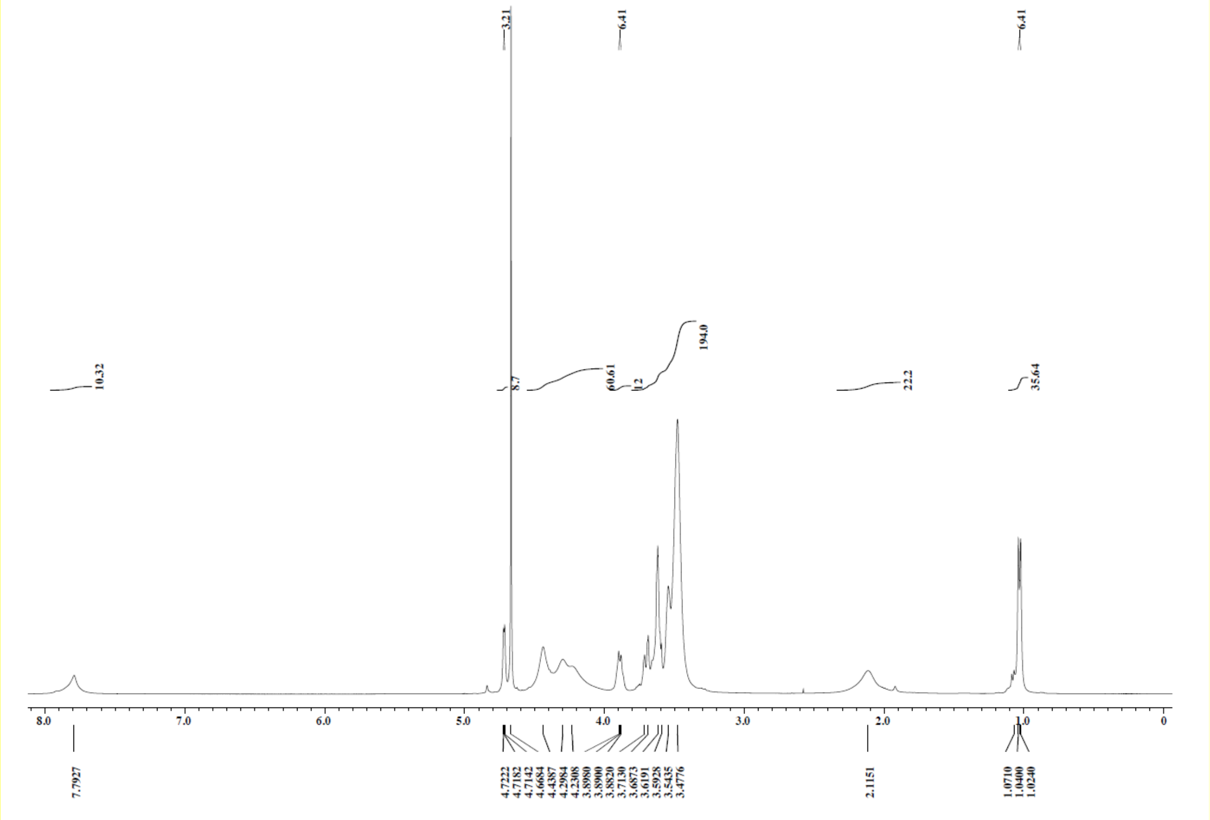
Synthesis of compound $C_{60}(C)_{12}$



$C_{60}(C)_{12}$

To a solution of **24** (75 mg, 3.22 10^{-2} mmol, 1 eq) in THF (3 mL) was added **7** (140 mg, 41.9 10^{-2} mmol, 13 eq) dissolved in 1 mL of DMSO. Afterwards sodium ascorbate (1.9 mg, 0.97 10^{-2} mmol, 0.3 eq) and copper (II) sulfate (0.5 mg, 0.32 10^{-2} mmol, 0.1 eq) dissolved in 1 mL of water was added. Microwave irradiation during two hours afforded the desired product, which was then precipitated with acetone (2 mL), washed with acetone (10 mL) and methanol (5 mL) and purified on Sephadex™ G-25. Evaporation of the solvent afforded **$C_{60}(C)_{12}$** (102 mg, 50%) as a red solid. **IR**: 3401 (O-H), 1742 (C=O). **UV/Vis** (H_2O): 246 (sh, 69600), 276 (59500), 320 (sh, 33900), 337 (sh, 27900). **^{1}H NMR** (400 MHz, D_2O) δ = 7.79 (s, 12H), 4.72 (d, J = 3.2 Hz, 12H) 4.44-4.23 (m, 60H), 3.89 (d, J = 6.4 Hz, 12H, H-5), 3.71-3.48 (m, 192H), 2.12 (s, 24H), 1.04 (d, J = 6.4 Hz, 36H, H-6). **^{13}C NMR** (75 MHz, D_2O) δ = 163.63 (C=O), 145.63, 144.09, 141.06, 124.65 (4C, $4C_{arom}$), 98.68 (C-1), 71.85, 69.80, 69.64, 68.98, 68.16, 66.77, 66.56, 64.58, 63.19 (12C, C-2, C-3, C-4, C-5, $8CH_2O$), 47.16 (CH_2N), 45.43 (C_q), 28.64 (CH_2), 15.48 (C-6). **Mass** (TOF-MS-LD$^+$): m/z: 6365.8 $[M+Na]^+$, 5902.7 $[M-C_{19}H_{32}N_3O_{10}+Na]^+$, 5428.6 $[M-C_{39}H_{64}N_6O_{20}+Na]^+$, 4965.4 $[M-C_{58}H_{96}N_9O_{30}+Na]^+$, 4492.2 $[M-C_{78}H_{128}N_{12}O_{40}+Na]^+$, 4028.0 $[M-C_{97}H_{160}N_{15}O_{50}+Na]^+$.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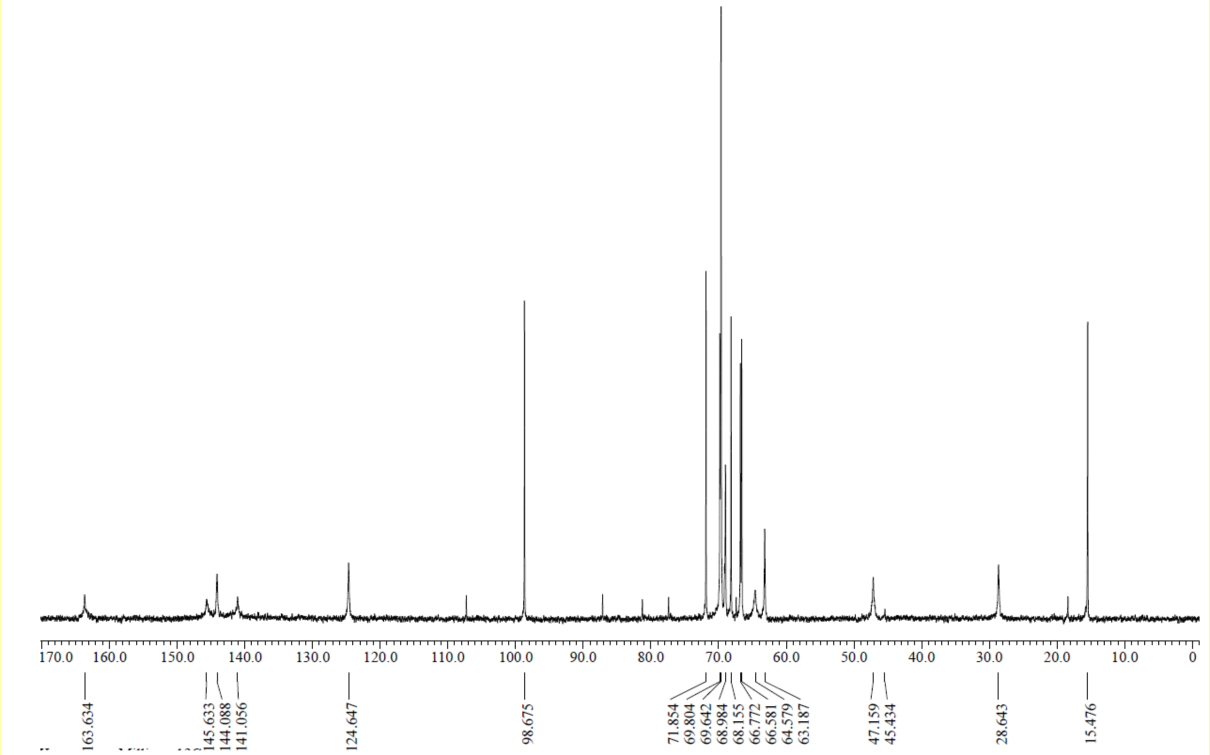
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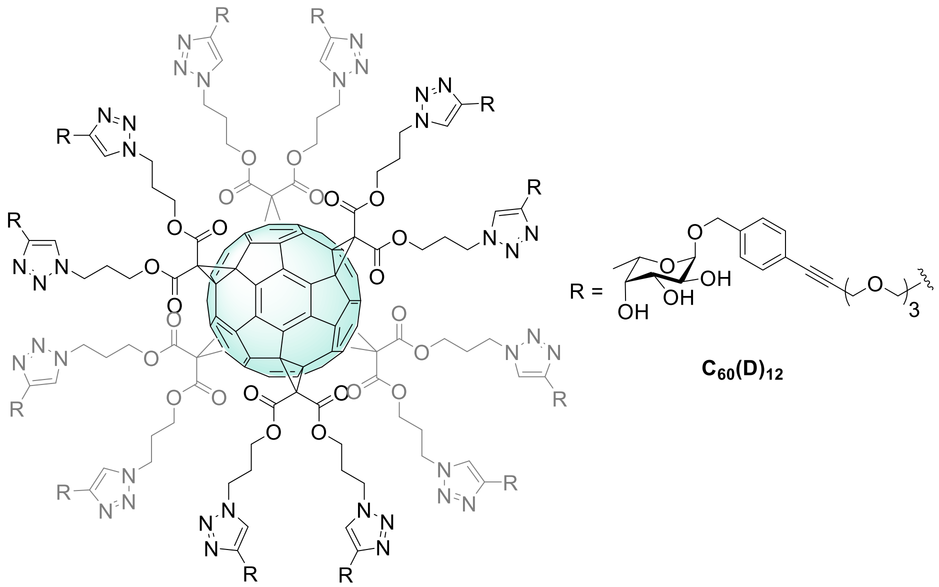
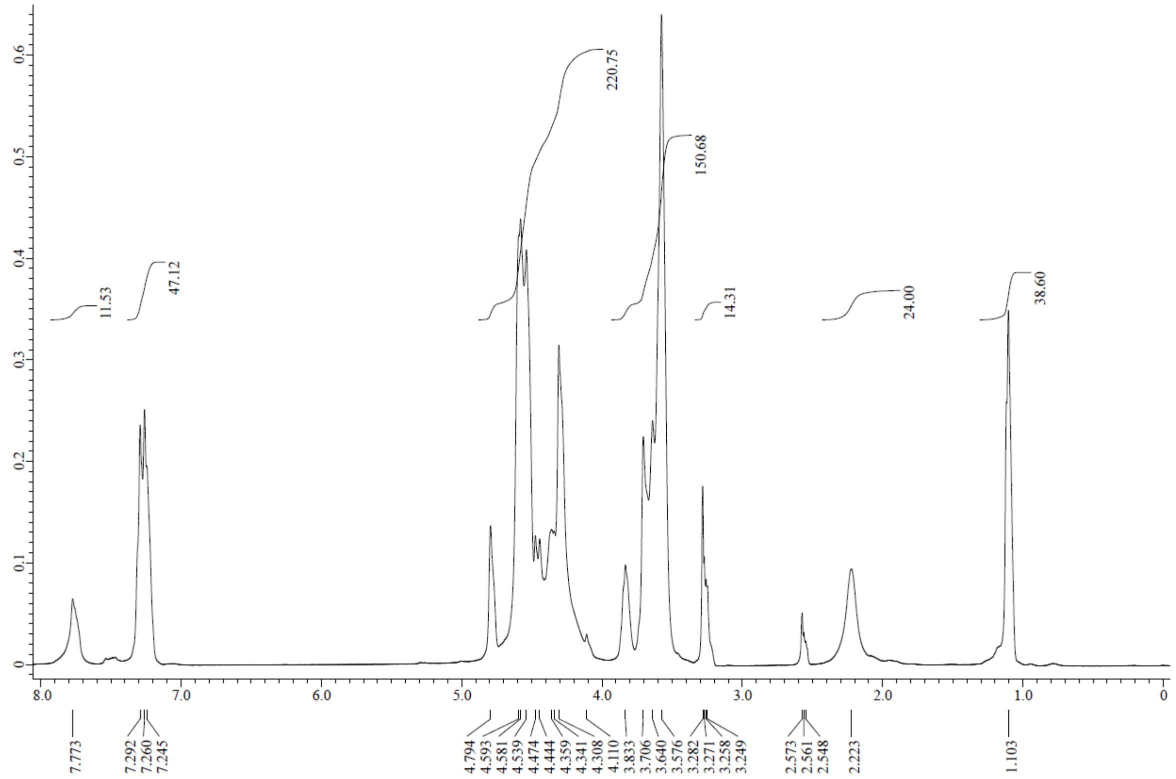
Synthesis of compound $C_{60}(D)_{12}$



$C_{60}(D)_{12}$

To a solution of **24** (50 mg, $2.14\ 10^{-2}$ mmol, 1 eq) in THF (1.5 mL) was added **11** (121 mg, $27.9\ 10^{-2}$ mmol, 13 eq) dissolved in 0.5 mL of DMSO. Afterwards sodium ascorbate (1.3 mg, $0.64\ 10^{-2}$ mmol, 0.3 eq) and copper (II) sulfate (0.3 mg, $0.21\ 10^{-2}$ mmol, 0.1 eq) dissolved in 0.5 mL of water were added. Microwave irradiation during two hours afforded the desired product, which was then precipitated with water (2 mL), washed with water (10 mL) and purified on Sephadex™ G-25. Evaporation of the solvent afforded **$C_{60}(D)_{12}$** (122 mg, 76%) as a red solid. **IR**: 3424 (O-H), 1743 (C=O). **UV/Vis** ($CHCl_3$/MeOH): 249 (178300), 258 (147300), 274 (sh, 43600), 282 (sh, 44400), 319 (sh, 24300), 339 (sh, 18100). **^{1}H NMR** (400 MHz, $CDCl_3$/MeOD 1:1) δ = 7.77 (s, 12H), 7.29-7.24 (m), 4.79-4.31 (m), 3.83-3.58 (m), 3.29-3.25 (m), 2.22 (s, 24H), 1.10 (s, 36H, H-6). **^{13}C NMR** (100 MHz, $CDCl_3$/MeOD 1:1) δ = 163.74 (C=O), 146.15, 145.18, 141.50, 138.75, 131.92, 128.14, 124.13, 122.10 (10C, $10C_{arom}$), 98.88 (C-1), 86.44 (C_q), 85.34 (C_q), 72.43, 70.71, 71.63, 71.55, 69.89, 69.38, 69.31, 69.03, 66.80 (11C, C-2, C-3, C-4, C-5, C_q, $6CH_2O$), 64.35 (CH_2O), 59.21 (CH_2O), 47.24 (CH_2N), 40.04 (C_q), 29.44 (CH_2), 16.15 (C-6). **Mass** (TOF-MS-LD$^+$): m/z: 7568.8 $[M+Na]^+$, 6430.5 $[M-C_{55}H_{72}N_6O_{20}+Na]^+$, 5868.2 $[M-C_{82}H_{108}N_9O_{30}+Na]^+$, 5297.0 $[M-C_{110}H_{144}N_{12}O_{40}+Na]^+$, 4732.7 $[M-C_{137}H_{180}N_{15}O_{50}+Na]^+$, 4156.4 $[M-C_{165}H_{210}N_{18}O_{60}+Na]^+$, 3593.2 $[M-C_{192}H_{252}N_{21}O_{70}+Na]^+$, 3018.9 $[M-C_{220}H_{288}N_{24}O_{80}+Na]^+$.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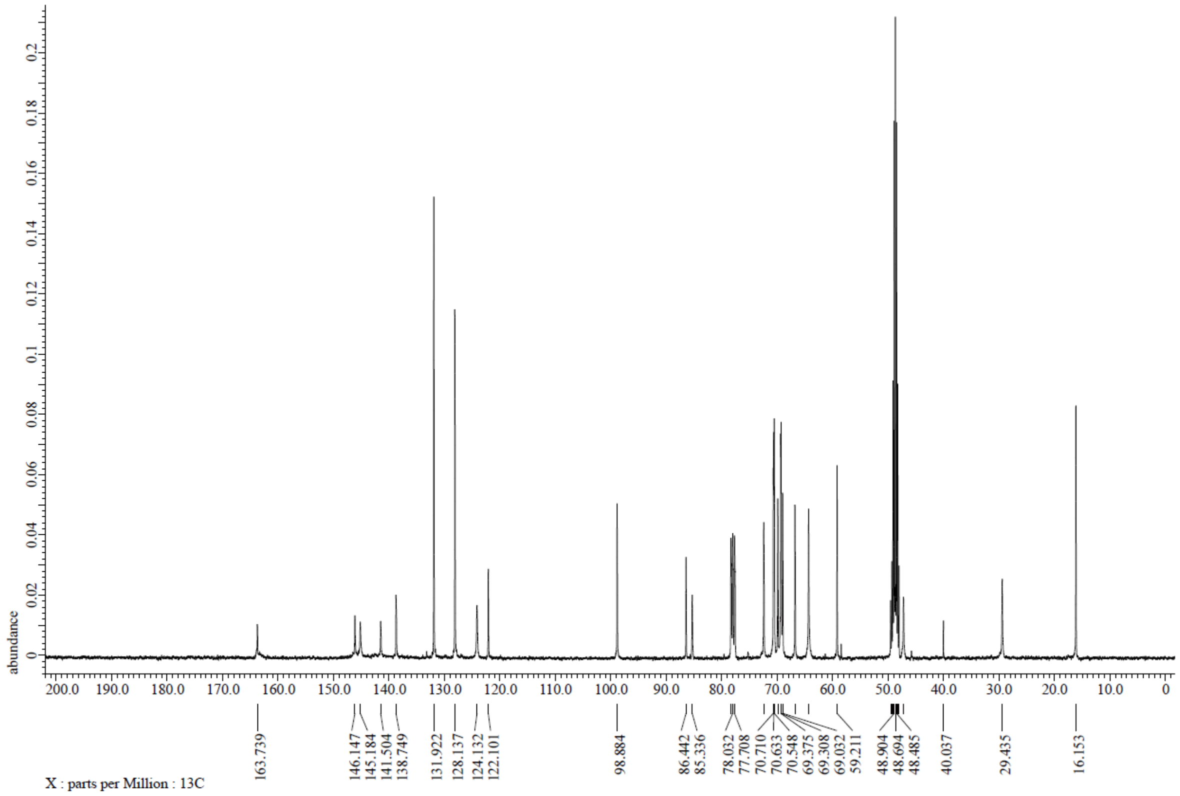
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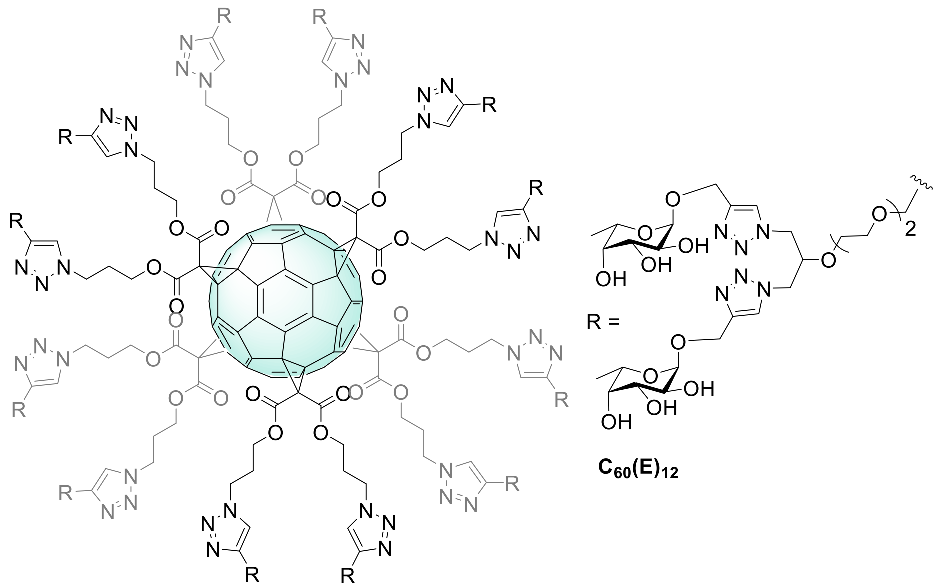
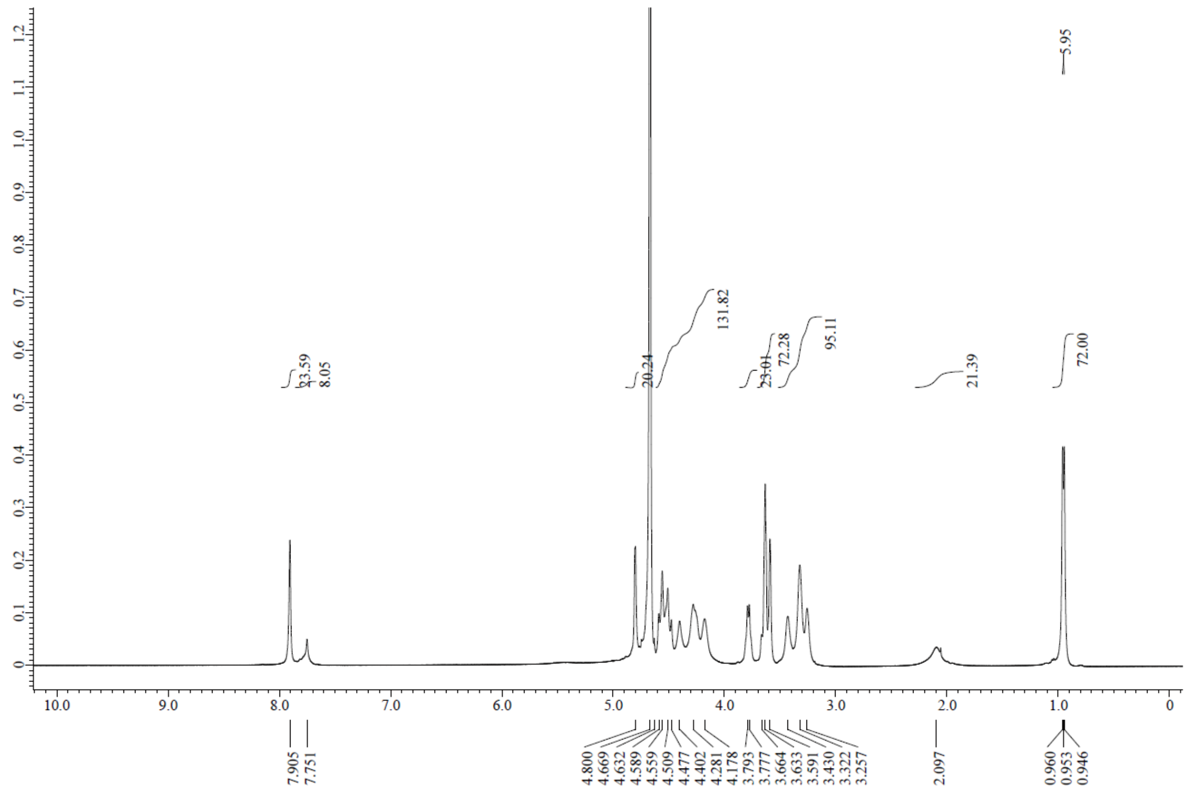
X : parts per Million : 13C

Synthesis of compound C_{60}(E)$_{12}$



C_{60}(E)$_{12}$

To a solution of **24** (50 mg, 2.146 10^{-2} mmol, 1 eq) in THF (1 mL) was added **23** (180 mg, 27.9 10^{-2} mmol, 13 eq) dissolved in 0.3 mL of DMSO. Afterwards sodium ascorbate (1.3 mg, 0.2146 10^{-2} mmol, 0.3 eq) and copper (II) sulfate (0.5 mg, 0.32 10^{-2} mmol, 0.1 eq) dissolved in 0.3 mL of water were added. Microwave irradiation during two hours afforded the desired product, which was then precipitated with acetone (2 mL), washed with acetone (10 mL) and methanol (5mL) and purified on Sephadex™ G-25. Evaporation of the solvent afforded **C_{60}(E)$_{12}$** (182 mg, 81%) as a red solid. **IR**: 3424 (O-H), 1744 (C=O). **UV/Vis** (H_2O): 248 (sh, 76900), 277 (67400), 321 (sh, 36500), 340 (sh, 29400). **^{1}H NMR** (400 MHz, D_2O) δ = 7.91 (s, 24H), 7.75 (s, 12H), 4.80 (m, 24H), 4.66-4.18 (m), 3.78 (d, J = 6.4 Hz, 24H), 3.66-3.59 (m, 72H), 3.43-3.26 (m, 96H), 2.10 (s, 24H), 0.95 (d, J = 6.0 Hz, 72H, H-6). **^{13}C NMR** (100 MHz, D_2O) δ = 163.70 (C=O), 145.56, 144.09, 141.08 (4C_{arom}), 126.04, 124.61 (2C_{arom}), 98.39 (C-1), 76.76, 71.79, 69.76, 69.61, 69.51, 69.00, 67.97, 66.75, 64.77, 63.18, 60.39 (C-2, C-3, C-4, C-5, 6CH_2, CH_2O*C(H)*$(CH_2N)_2$, C_q), 51.01($CH_2OC(H)$*$(CH_2N)_2$*), 47.14 (CH_2N), 45.57 (C_q), 28.56(OCH_2*CH_2*CH_2N), 15.46 (C-6). **Mass** (TOF-MS-LD$^+$): m/z: 10424.6 $[M+Na]^+$, 9627.9 $[M-C_{32}H_{46}N_9O_{15}+Na]^+$, 8818.1 $[M-C_{65}H_{92}N_{18}O_{30}+Na]^+$, 8014.9 $[M-C_{97}H_{138}N_{27}O_{45}+Na]^+$, 7213.4 $[M-C_{130}H_{184}N_{36}O_{60}+Na]^+$, 6400.1 $[M-C_{162}H_{230}N_{45}O_{75}+Na]^+$, 5600.5 $[M-C_{195}H_{276}N_{54}O_{90}+Na]^+$.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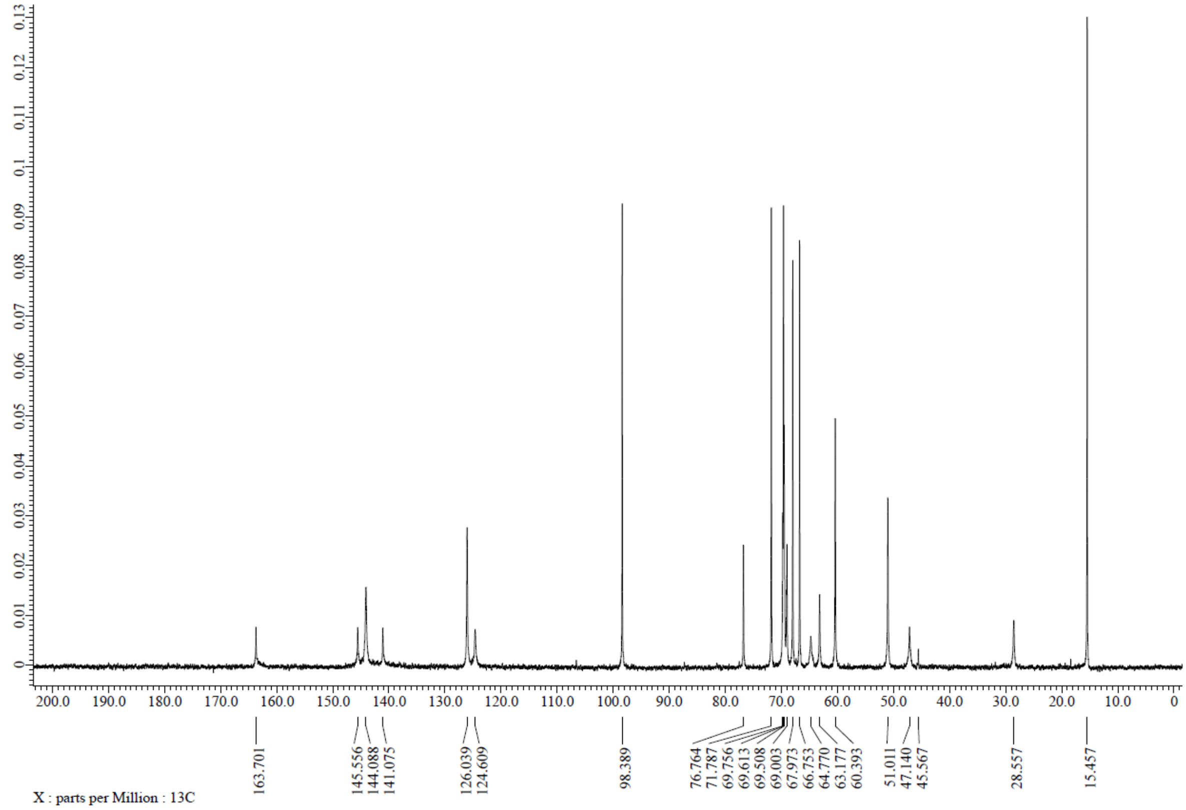
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69.508
69.003
67.973
66.753
64.770
63.177
60.393
51.011
47.140
45.567
28.557
15.457
X : parts per Million : 13C

II. Biochemical techniques.

Isothermal Titration Microcalorimetry (ITC).

LecB and RSL were produced in *Escherichia coli* and purified on affinity columns as previously described.(1,2) Lyophilized LecB and RSL were dissolved in buffer (20 mM Tris-HCl, 0.1 M NaCl pH 7.5 with 100 µM $CaCl_2$). Titration was performed using ITC200 microcalorimeter (Malvern Instruments, UK) with a 200 µl sample cell operating at 25°C. Titrations were performed with 20 injections of 2 µl every 120 s.

For direct titration of monovalent probes **A** to **D**, the glycocompounds (50mM water stock solution) were diluted to 1 mM in the same buffer as lectins, loaded in the injection syringe, and injected in solution of LecB (100 µM) or RSL (50 µM) in the microcalorimeter cell. For inverse titration of divalent compound **E**, the lectins LecB (200 µM) or RSL (100 µM) were injected in the cell containing the glycocompound (10 µM). The glycofullerenes were dissolved in the same buffer with the addition of 5% DMSO (in both fullerene and lectin solutions). They were loaded in the syringe at concentrations varying from 0.5 to 20 µM and injected in the cell containing either LecB (200 to 400 µM) or RSL (30 to 300 µM).

The experimental data were fitted to a theoretical titration curve using the supplied Origin software, with ΔH (enthalpy change), Ka (association constant) and n (number of binding sites per monomer) as adjustable parameters. Free energy change (ΔG) and entropy contributions (TΔS) were derived from the equation $\Delta G = \Delta H - T\Delta S = -RT \ln Ka$ (with T as the absolute temperature and $R = 8.314\ J\ mol^{-1}\ K^{-1}$). Two or three independent titrations were performed for each tested ligand.

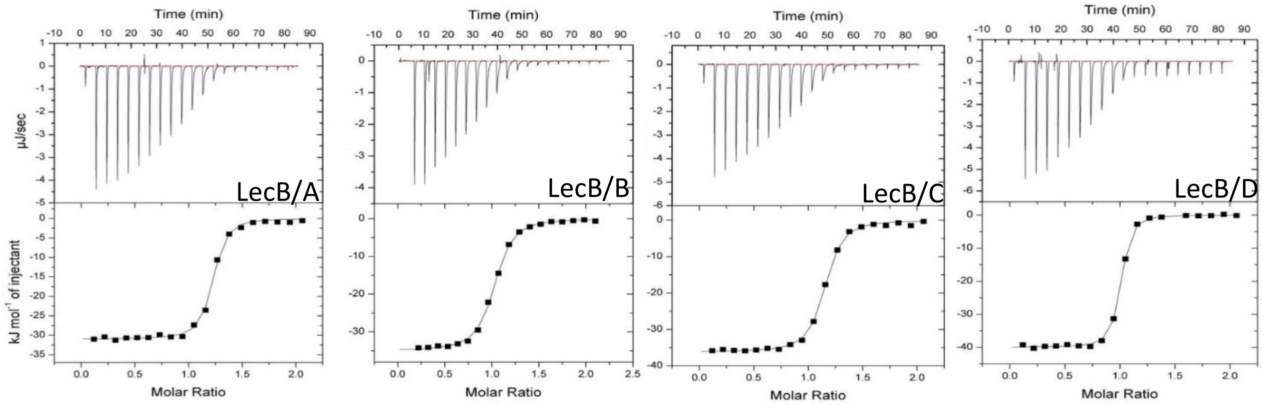

Figure S1: ITC data for direct titration of LecB by monovalent probes. Top: thermograms obtained by injection of compounds **A** to **D** (1 mM) in LecB solution (100 µM). Bottom: Corresponding integrated titration curve as a function of molar ratio compound/lecB.

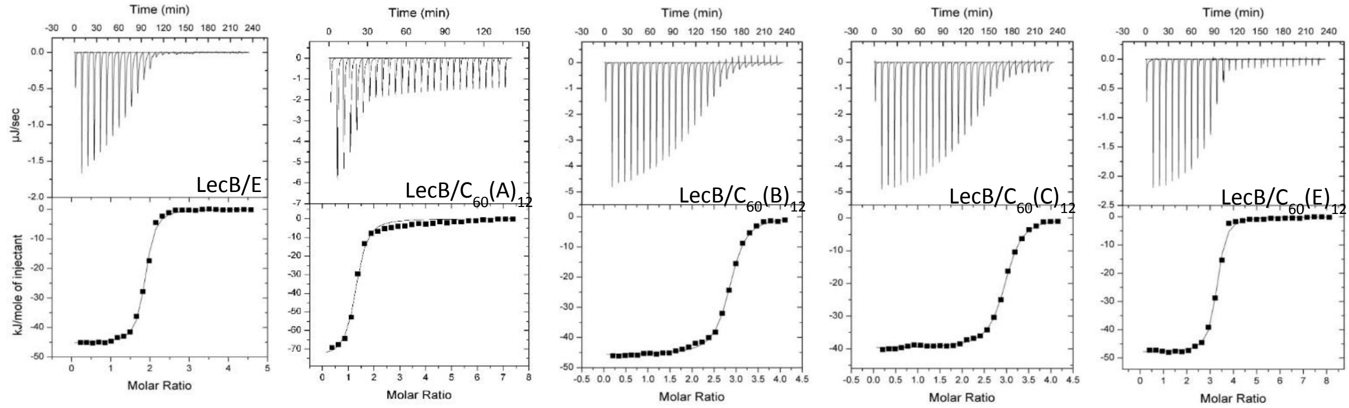

Figure S2 ITC data for reverse titration of LecB by divalent probe and glycosylated fullerenes. Top: thermograms obtained by injection of LecB (200 to 400 µM) in compound **E** solution (10 µM) or in glycofullerene solutions (10 to 20 µM). Bottom: Corresponding integrated titration curves as a function of molar ratio LecB/compound.

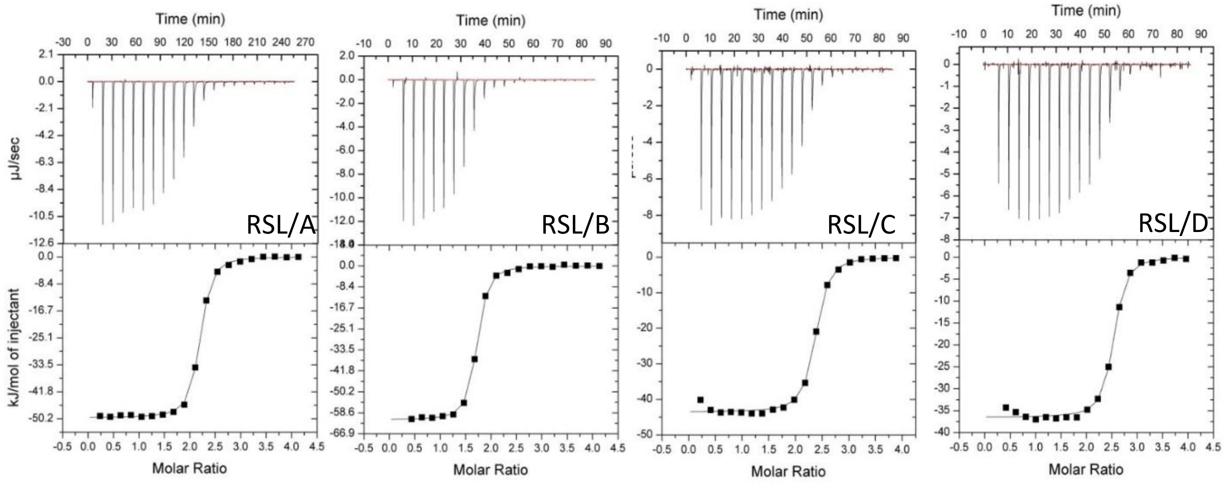

Figure S3: ITC data for direct titration of RSL by monovalent probes. Top: thermograms obtained by injection of compounds **A** to **D** (1 mM) in RSL solution (50 µM). Bottom: Corresponding integrated titration curve as a function of molar ratio compound/RSL.

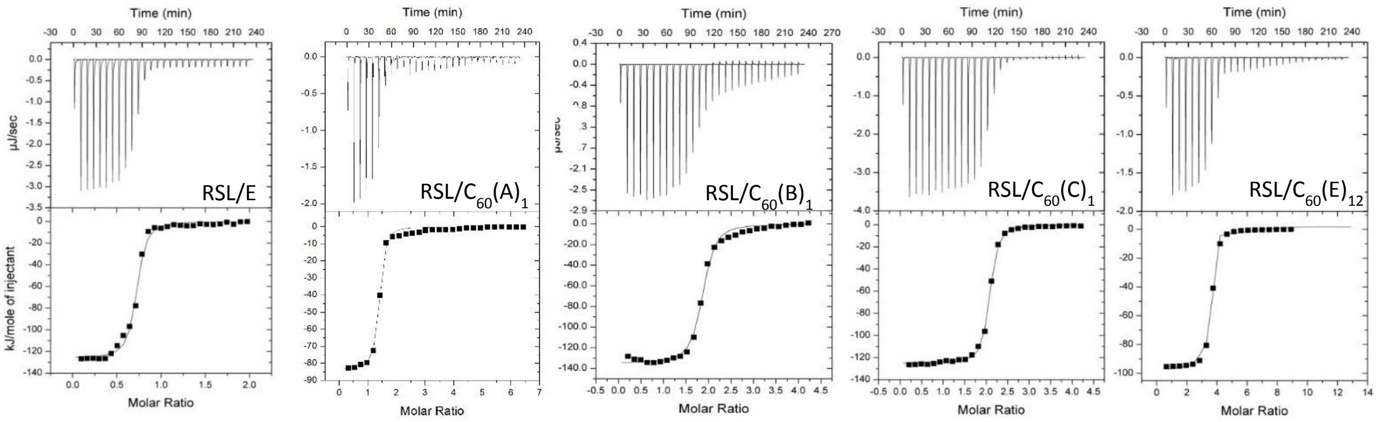

Figure S4: ITC data for reverse titration of RSL by divalent probe and glycosylated fullerenes. Top: thermograms obtained by injection of RSL (30 to 300 µM) in glycofullerene solution (10 µM) or in glycosylated fullerene solution (0.5 to 10 µM). Bottom: Corresponding integrated titration curve as a function of molar ratio RSL/compound.

Model Building

The C60 fullerene starting structure was generated using Nanotube Modeler Software (JCrystalSoft, jcrystal.com). The attached linkers decorated with fucose were built in their extended conformation using the molecular editor from the Sybyl-X suite (Certara, www.certara.com), and structures were optimized for removing any steric conflict with the Tripos force field.[2] Crystal structures of LecB/fucose (PDB code 1GZT)[4] and RSL/α-methyl-fucoside (PDB code 2BT9)[2] were used for building the complexes. Docking of glycosylated fullerenes in the proteins binding sites was performed by fitting the fucose residues from fucosylated fullerenes to the same sugar in the binding site of crystal structure with the use of the fitting procedure in Sybyl-X.

III. References

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[4] E. Mitchell, C. Houles, D. Sudakevitz, M. Wimmerova, C. Gautier, S. Pérez, A. M. Wu, N. Gilboa-Garber and A. Imberty, *Nature Struct. Biol.* **2002**, *9*, 918-921.