

Supporting information

Preparation of Amphiphilic Sorbitan Monoethers through Hydrogenolysis of Sorbitan Acetals and Evaluation as Bio-Based Surfactants

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1. General information

All reagents and solvents used for synthesis were commercial and used without further purification. They were supplied by Aldrich and Acros. Sorbitol **1** (> 98% purity) was purchased from Sigma-Aldrich. Valeraldehyde, hexanal, octanal, decanal and dodecanal were supplied by Sigma-Aldrich or Alfa-Aesar. Amberlyst 15 dry and Amberlyst 36 were bought from Rohm and Haas. Pd/C (5 or 10 %, Pd on activated wood carbon, reduced and dry, Escat 1431) was purchased from Strem Chemicals. Information concerning this catalyst could be found online: http://www.strem.com/catalog/v/46-1902/palladium_7440-05-3. According to Strem Chemicals, the type of carbon is amorphous with the specifications of “activated charcoal, European pharmacopeia”. All new compounds were characterized by spectroscopic data. Reactions were monitored by TLC using aluminium silica gel (60F₂₅₄) and flash chromatography separations were performed using silica gel 60H (40-63µ). Nuclear magnetic resonance spectra were recorded either on a Brüker DRX 300 (¹H: 300 MHz, ¹³C: 75 MHz) or 400 (¹H: 400 MHz, ¹³C: 100 MHz) or Brüker ALS 300 or Brüker DRX 500 (¹H: 500 MHz, ¹³C: 125 MHz). Chemical shifts are given with reference to residual *d*₆-DMSO or CDCl₃ central peaks: 2.50 and 7.26 ppm for proton, 39.5 and 77.0 ppm for carbon, respectively. *J* values are given in Hertz (Hz). Abbreviations are defined as follow: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quadruplet, m = multiplet, br = broad. Electrospray ionization (ESI) mass spectra (MS) and High-Resolution Mass Spectra (HRMS) were recorded in positive-ion mode on a hybrid quadrupole time-of-flight mass spectrometer (MicroTOFQ-II, Bruker Daltonics, Bremen) with an Electrospray Ionization (ESI) ion source. The flow of spray gas was at 0.6 bar and the capillary voltage was 4.5 kV. The solutions were injected at 180 µL/h in a mixture of solvents (methanol/dichloromethane/water 45/40/15). The mass range of the analysis was 50-1000 m/z and the calibration was done with sodium formate. Infra-red (IR) spectra were recorded in a SMART iTR-Nicolet iS10 spectrometer using Attenuated Total Reflectance (ATR) and the wave numbers (*V*) are expressed in cm⁻¹. Melting points were measured using a BUCHI Melting point (SMPIO) and noted in °C. A first estimate of the melting point of some of our solids was performed on a Köfler bench.

2. Preparation of 1,4-D-sorbitan

2.1. HPLC method

HPLC analyses for the dehydration reaction of sorbitol were performed using a NH₂ bound column (Nucleosil NH₂, 5µm I.D., 250mm × 20mm) using a 80:20 mixture of CH₃CN/H₂O as eluent (flow rate = 1mL/min) with refraction index detection (RI-512, temperature = 40°C). Each compound has been separately injected (8 mg/mL, V_{inj} = 20 µL) and the HPLC chromatograms have been superimposed (Figure 1).

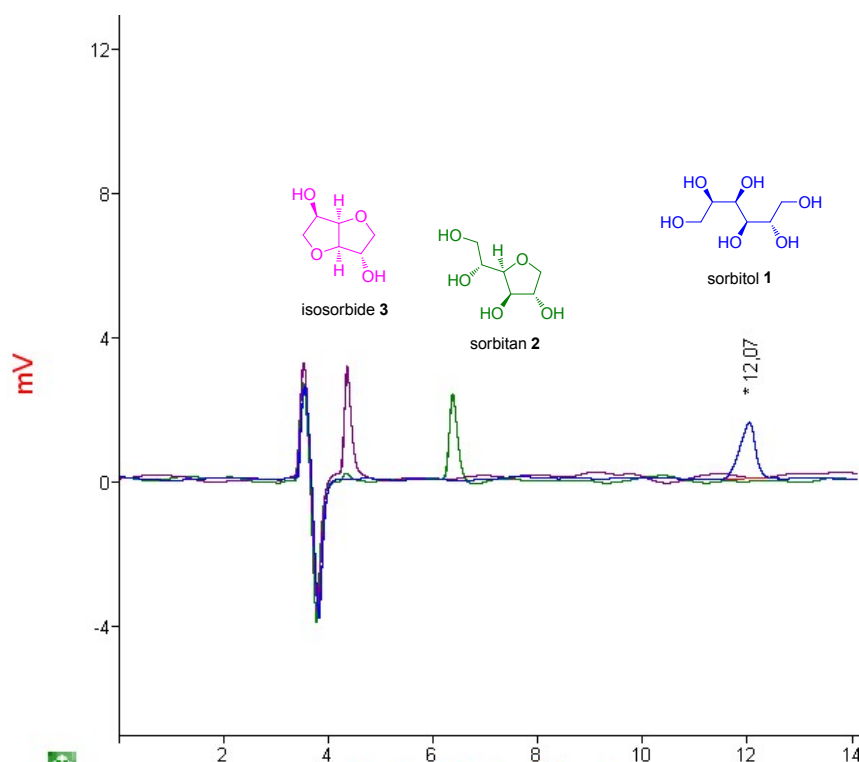


Figure 1. Superimposed HPLC chromatograms of sorbitol **1** (12.07 min, blue), 1,4-D-sorbitan **2** (6.42 min, green) and isosorbide **3** (4.37 min, purple).

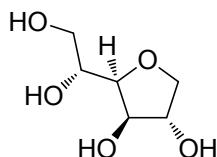
2.2. Preparation of sorbitan by dehydration of sorbitol under hydrogen pressure

1,4-D-Sorbitan **2** was synthesized according to the previously reported method of Holladay *et al.*¹ High purity (≥98%) sorbitol **1** (Ref. S1876; Aldrich) was utilized and the reaction was carried out under solvent-free conditions. D-Sorbitol **1** (20 g, 110 mmol), 0.1 mol% of camphorsulfonic acid (CSA) was added in a 150-mL stainless steel autoclave. The reactor was tightly closed, purged three times with hydrogen and hydrogen pressure was introduced (50 bar). The system was heated at 140°C and mechanically stirred for 15 hours. After cooling to room temperature, hydrogen pressure was released and the white foam was diluted in EtOH (200 mL) to obtain a homogeneous yellow mixture. The solvent was evaporated under reduced pressure and the residue was crystallized from cold

¹ J. E. Holladay, J. Hu, Y. Wang and T.A. Werpy, patent US20070173651, **2007**.

MeOH and filtered under vacuum. The product was washed with cold MeOH to give 1,4-D-sorbitan **2** (5.88 g, 33%) as a white solid (the purity was analyzed by HPLC >98%).

2.3. Preparation of sorbitan by dehydration of sorbitol under ambient pressure



1,4-D-Sorbitan 2: Following a modified literature procedure,² in a 3-L glass reactor (Figure 2), D-sorbitol **1** (1 kg, 5.49 mol) was dissolved in water (140 mL) and H₂SO₄ (12.4 mL). The mixture was magnetically stirred at 104°C. After 20 hours, 6.2 mL of H₂SO₄ was added. After a further 22 hours, 6.2 mL of H₂SO₄ was introduced. After a further 32 h, the mixture was cooled down to room temperature, then neutralized carefully with solid Na₂CO₃ and magnetically stirred during 30 min. *i*-PrOH (1 L) was added, followed by anhydrous Na₂SO₄ (1 kg). The residue was filtered and the solid was washed with *i*-PrOH (1.5 L) and EtOH (750 mL). The filtrate was treated with activated charcoal (25 g), filtered through Celite®, washed with *i*-PrOH and EtOH (300 mL each), and concentrated under reduced pressure. Toluene (1.5 L) was added to the residue, and concentrated *in vacuo* with heating to azeotropically remove water. The solid was dissolved with EtOH (2.5 L) with heating. The mixture was concentrated then cooled down to room temperature to give a suspension. The solid was filtered and washed with cold EtOH (1 L) and dried. A recrystallization of the crude solid was realized from hot EtOH, the solid obtained was filtered, washed with cold EtOH and dried to give 1,4-D-sorbitan **2** (388 g, 43%) as a white solid (m.p. = 113–114°C, lit.^{2a} 112–112.5°C); $[\alpha]_D^{20} - 20.7$ (c 5.4, H₂O), lit.^{2a} – 22.4 (c 5.4, H₂O); ¹H NMR (300 MHz, *d*₆-DMSO) δ_H 3.27–3.39 (1H, m), 3.43 (1H, d, *J* = 8.9), 3.50–3.59 (1H, m), 3.60–3.72 (2H, m), 3.80–4.01 (3H, m), 4.36 (1H, t, *J* = 5.7, OH), 4.49 (1H, d, *J* = 2.6, OH), 4.80 (1H, d, *J* = 4.2, OH), 4.99 (1H, d, *J* = 3.0, OH); ¹³C NMR (75 MHz, *d*₆-DMSO) δ_C 64.29 (CH₂), 69.35 (CH), 73.48 (CH₂), 75.96 (CH), 76.55 (CH), 80.48 (CH); MS (ESI⁺): 187.1 [M+Na]⁺; HPLC (isocratic 20:80 H₂O/CH₃CN + 0.1% H₃PO₄): R_t = 6.42 min.

² a) K. Bock, C. Pedersen and H. Thøgersen, *Acta. Chem. Scand. B*, 1981, **35**, 441-449. b) P. Delgado, R. E. Conrow, W. D. Dean and M. S. Gaines, Patent US6441196, **2002**.



Figure 2: 3-L glass reactor for the preparation of 1,4-D-sorbitan **2** on the large scale.

3. Preparation of sorbitan acetals

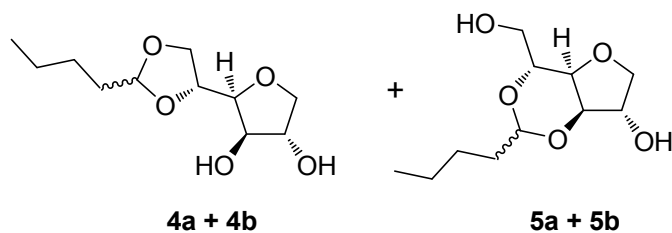
3.1. General procedure for the preparation of sorbitan acetals

In a round bottom flask equipped with a condenser fitted with a CaCl_2 guard, under an argon atmosphere, sorbitan **2** (5.00 g, 30.5 mmol, 3 equiv) was dissolved in dry EtOH (15 mL). The aldehyde (10.2 mmol, 1 equiv) was added dropwise, followed by camphorsulfonic acid (CSA, 10 wt%/aldehyde). Then, the mixture was magnetically stirred (750 rpm) at 80°C for 15 hours. The mixture was cooled down to room temperature and the solvent was evaporated under reduced pressure. The residue was triturated in EtOAc and the excess of sorbitan was filtered off and washed with cold EtOAc. This operation was repeated in order to remove any traces of sorbitan. The residue was concentrated and purified by flash chromatography to give the desired sorbitan acetals. The mixture of 5,6-*O*-alkylidene- and 3,5-*O*-alkylidene-1,4-D-sorbitan regioisomers was determined by HPLC analysis. Each regioisomers was obtained as a mixture of diastereoisomers.

3.2. HPLC conditions for sorbitan acetals

HPLC analyses for the acetalisation or transacetalisation of sorbitan were performed using a C18 column (Spherisorb C18, 5 μm I.D., 250 mm \times 20 mm) using a mixture of $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ + 0,1 %v/v H_3PO_4 as eluent (flow rate = 1 mL/min) with refraction index detection (RI-512, temperature = 40°C). The injected volume was 20 μL .

3.3. Characterization data of sorbitan acetals



5,6-*O*-Pentylidene-1,4-D-sorbitan 4a and 4b and **3,5-*O*-pentylidene-1,4-D-sorbitan 5a and 5b**: The title compounds were prepared according to the above general procedure from sorbitan **2** (0.49 g, 3 mmol) and valeraldehyde (0.107 mL, 1 mmol). The residue was purified by flash chromatography (EtOAc/cyclohexane 80:20 → 100:0) to give a 43:57 mixture of 5,6-*O*-regioisomers **4** and 3,5-*O*-regioisomers **5** (0.189 g, 81%) as a colorless oil. The product was obtained as a mixture of 5,6-*O*- and 3,5-*O*-regioisomers, each regioisomer being a pair of diastereoisomers (26:17:47:10) as determined by HPLC (Figure 3). ^1H NMR (300 MHz, d_6 -DMSO) δ_{H} for all isomers: 0.85 (3H, t, $J = 7.2$), 1.16–1.35 (4H, m), 1.35–1.60 (2H, m), 3.30–4.30 (8H, sorbitan protons), 4.67–5.33 (3H, 3m, 1H acetal and 2 OH); ^{13}C NMR (75 MHz, d_6 -DMSO) δ_{C} for 5,6-*O*-isomers **4a** and **4b**: 13.90 (CH_3), 22.06 (CH_2), 25.68 and 25.81 (CH_2), 33.16 (CH_2), 66.59 and 66.93 (CH_2), 72.79 and 73.19 (CH), 73.43 (CH_2), 75.46 and 75.68 (CH), 76.55 and 76.61 (CH), 80.74 and 81.01 (CH), 103.29 and 103.37 (CH); δ_{C} for 3,5-*O*-isomers **5a** and **5b**: 13.92 and 13.93 (CH_3), 21.95 and 22.00 (CH_2), 25.53 and 25.75 (CH_2), 33.73 and 34.13 (CH_2), 60.78 and 61.92 (CH_2), 72.37 and 73.55 (CH_2), 72.58 and 72.99 (CH), 73.19 and 73.96 (CH), 74.87 and 76.45 (CH), 78.38 and 79.08 (CH), 93.83 and 96.06 (CH); IR ν_{max} : 3386 (OH), 2954, 2873, 1716, 1412, 1145, 1461, 1061, 1029, 967; HRMS (ESI $^+$) calculated for $\text{C}_{11}\text{H}_{20}\text{NaO}_5$: 255.1208 $[\text{M}+\text{Na}]^+$; found: 255.1203 (+1.8 ppm); HPLC (isocratic 80:20 $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ + 0.1% H_3PO_4): R_{t} for 3,5-isomers = 9.70 min (**5a**, 47%) and 11.25 min (**5b**, 10%); R_{t} for 5,6-isomers = 12.50 min (**4a**, 26%) and 14.49 min (**4b**, 17%). The assignment of each peak was attributed after ^1H , ^{13}C NMR and HPLC-MS analyses, see paragraph 4.

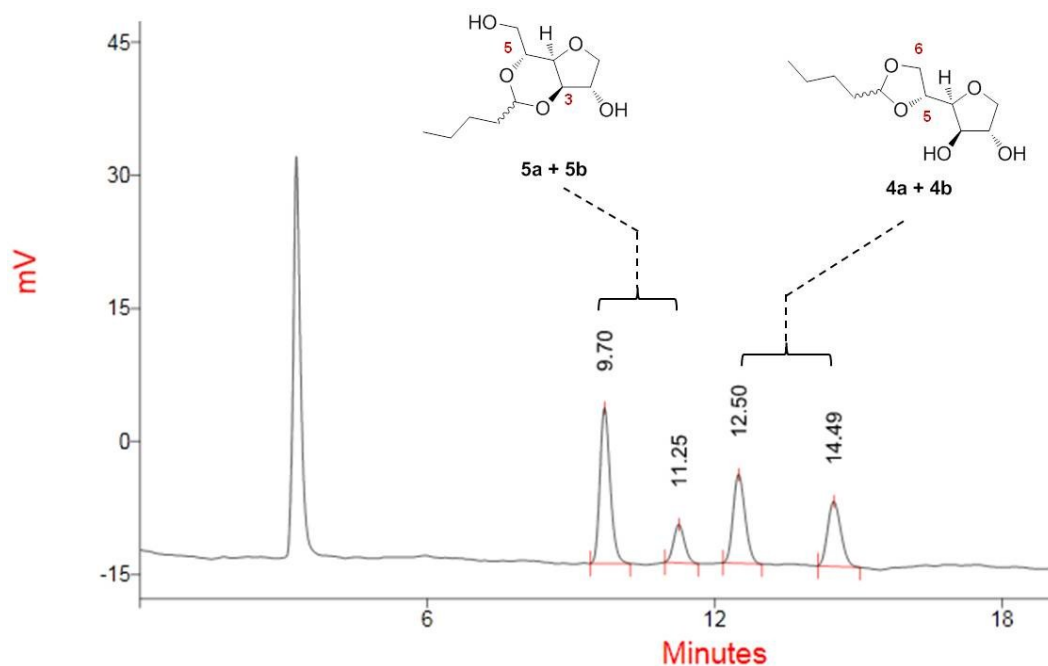
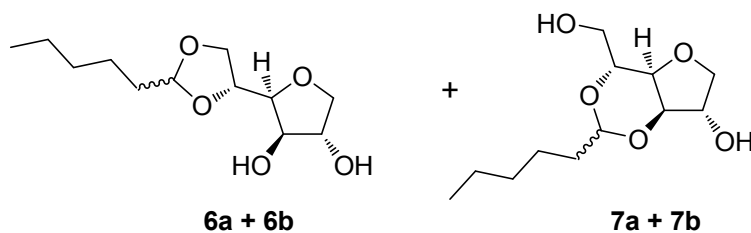


Figure 3. HPLC chromatogram of the mixture of sorbitan acetals **4a** and **4b** and **5a** and **5b**



5,6-*O*-Hexylidene-1,4-D-sorbitan 6a and 6b and 3,5-*O*-hexylidene-1,4-D-sorbitan 7a and 7b: The title compounds were prepared according to the above general procedure from sorbitan **2** (0.49 g, 3 mmol) and hexanal (0.124 mL, 1 mmol). The residue was purified by flash chromatography (EtOAc/cyclohexane 80:20 → 100:0) to give a 57:43 mixture of 5,6-*O*-regioisomers **6** and 3,5-*O*-regioisomers **7** (0.144 g, 58%) as a yellow oil. The product was obtained as a mixture of 5,6-*O*- and 3,5-*O*-regioisomers, each regioisomer being a pair of diastereoisomers (32:25:31:12) as determined by HPLC (Figure 4). ^1H NMR (300 MHz, d_6 -DMSO) δ_{H} for all isomers: 0.85 (3H, t, $J = 6.5$), 1.12–1.40 (6H, m), 1.45–1.58 (2H, m), 3.30–4.30 (8H, m, sorbitan protons), 4.72–4.90 (1H, m, acetal proton), 5.07–5.28 (2H, 2m, OH); ^{13}C NMR (75 MHz, d_6 -DMSO) δ_{C} for 5,6-*O*-isomers **6a** and **6b**: 13.91 (CH₃), 22.12 (CH₂), 23.24 and 23.38 (CH₂), 31.24 (CH₂), 33.50 (CH₂), 66.64 and 66.98 (CH₂), 72.86 and 73.24 (CH), 73.48 (CH₂), 75.50 and 75.73 (CH), 76.60 and 76.66 (CH), 80.78 and 81.06 (CH), 103.34 and 103.42 (CH); δ_{C} for 3,5-*O*-isomers **7a** and **7b**: 13.93 (CH₃), 22.12 (CH₂), 23.09 and 23.31 (CH₂), 31.17 (CH₂), 34.06 and 34.48 (CH₂), 60.85 and 61.97 (CH₂), 72.42 and 73.61 (CH₂), 72.64 and 72.86 (CH), 73.08 and 74.01 (CH), 74.94 and 76.48 (CH), 78.40 and 79.13 (CH), 93.90 and 96.13 (CH); IR ν max: 3386 (OH), 2929 (CH₃), 2871 (CH₂), 2360, 2341, 1465, 1407, 1143, 1034; HRMS (ESI⁺): [M+Na]⁺ C₁₂H₂₂NaO₅ requires 269.1359, found 269.1360 (-0.4 ppm); HPLC (isocratic 80:20 H₂O/CH₃CN + 0.1% H₃PO₄): R_{t} for 3,5-isomers = 20.77 min (**7a**, 31%) and 24.65 min (**7b**, 12%); R_{t} for 5,6-isomers = 28.28 min (**6a**, 32%) and 33.90 (**6b**, 25%). The assignment of each peak was attributed by analogy with those of pentylidene-sorbitans.

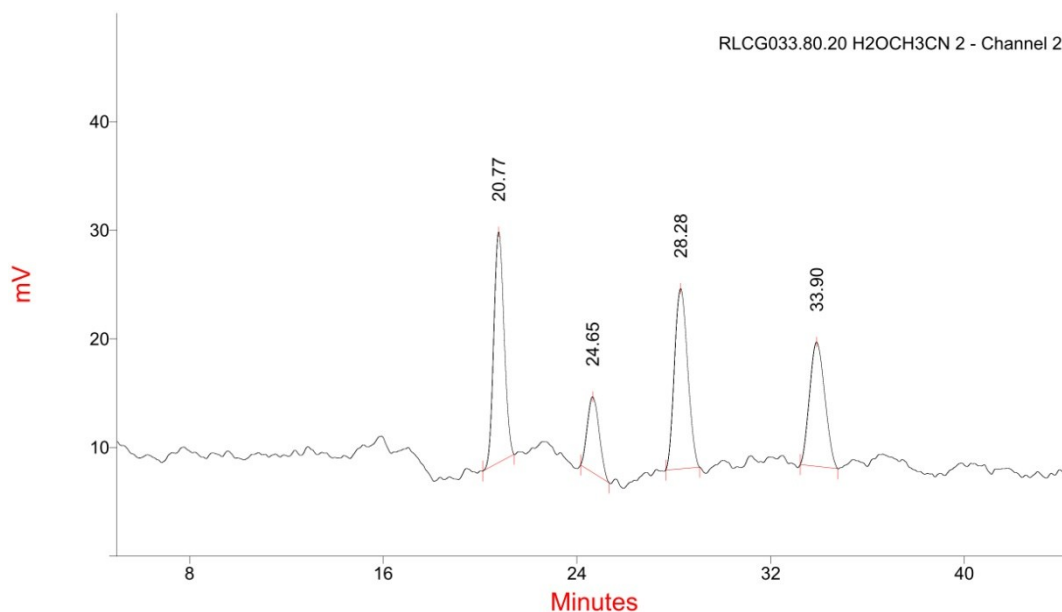
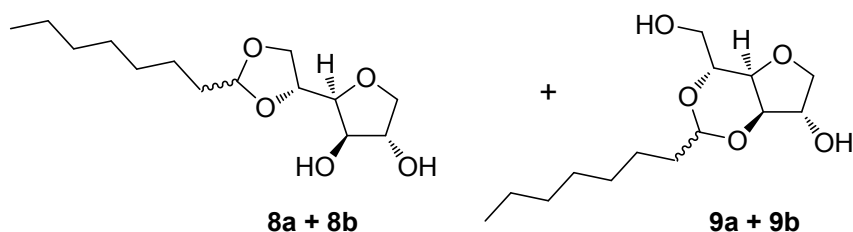


Figure 4. HPLC chromatogram of the mixture of sorbitan acetals **6a** and **6b** and **7a** and **7b**



5,6-*O*-Octylidene-1,4-D-sorbitan 8a and 8b and 3,5-*O*-octylidene-1,4-D-sorbitan 9a and 9b: The title compounds were prepared according to the above general procedure from sorbitan **2** (1.00 g, 6 mmol) and octanal (0.317 mL, 2 mmol). The residue was purified by flash chromatography (EtOAc/cyclohexane 60:40 → 100:0) to give a 61:39 mixture of 5,6-*O*-regioisomers **8** and 3,5-*O*-regioisomers **9** (0.102 g, 37%) as a white paste. The product was obtained as a mixture of 5,6-*O*- and 3,5-*O*-regioisomers, each regioisomer being a pair of diastereoisomers (32:29:28:11) as determined by HPLC (Figure 5). ^1H NMR (300 MHz, d_6 -DMSO) δ_{H} for all isomers: 0.86 (3H, t, $J = 8.7$), 1.10–1.42 (10H, m), 1.43–1.62 (2H, m), 3.38–4.31 (8H, m, sorbitan protons), 4.70–4.90 (1H, m, acetal proton), 5.02–5.28 (2H, 2m, OH); ^{13}C NMR (75 MHz, d_6 -DMSO) δ_{C} for 5,6-*O*-isomers **8a** and **8b**: 13.96 (CH₃), 22.13 (CH₂), 23.40 and 23.58 (CH₂), 28.72 (2 CH₂), 31.26 (CH₂), 33.54 (CH₂), 66.22 and 66.96 (CH₂), 72.85 and 73.24 (CH), 73.47 (CH₂), 75.49 and 75.72 (CH), 76.59 and 76.64 (CH), 80.77 and 81.05 (CH), 103.31 and 103.40 (CH); δ_{C} for 3,5-*O*-isomers **9a** and **9b**: 13.96 (CH₃), 22.13 (CH₂), 23.62 and 23.70 (CH₂), 28.92 and 28.99 (2 CH₂), 31.26 (CH₂), 34.09 and 34.51 (CH₂), 60.85 and 61.95 (CH₂), 72.42 and 73.60 (CH₂), 72.62 and 72.90 (CH), 73.10 and 73.99 (CH), 74.93 and 76.46 (CH), 78.36 and 79.10 (CH), 93.88 and 96.09 (CH); IR ν max: 3425 (OH), 2953 (CH₃), 2920 (CH₂), 2855, 1467, 1414, 1257, 1047; HRMS (ESI⁺): $[\text{M}+\text{Na}]^+$ C₁₄H₂₆NaO₅ requires 297.1672, found 297.1670 (+1.0 ppm); HPLC (isocratic 60:40 H₂O/CH₃CN + 0.1% H₃PO₄): R_{t} for 3,5-isomers = 11.50 min (**9a**, 28%) and 12.93 min (**9b**, 11%); R_{t} for 5,6-isomers = 14.83 min (**8a**, 32%) and 16.56 (**8b**, 29%). The assignment of each peak was attributed by analogy with those of pentylidene-sorbitans.

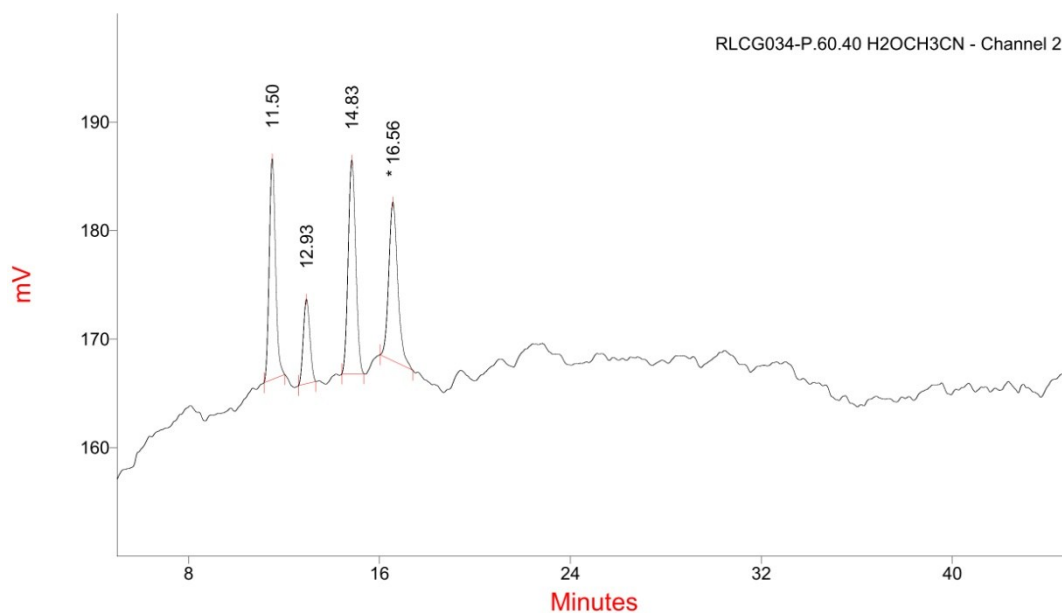
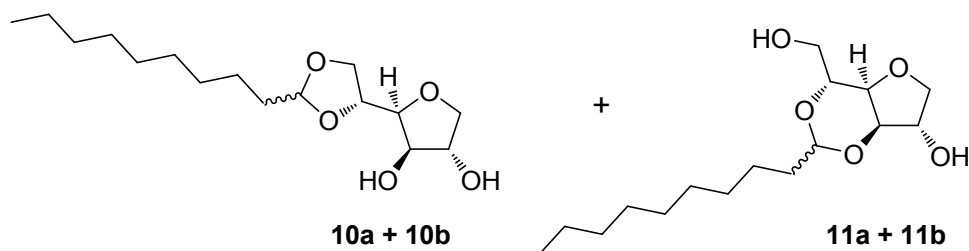


Figure 5. HPLC chromatogram of the mixture of sorbitan acetals **8a** and **8b** and **9a** and **9b**



5,6-*O*-Decylidene-1,4-*D*-sorbitan **10a and **10b** and 3,5-*O*-decylidene-1,4-*D*-sorbitan **11a** and **11b**:** The title compounds were prepared according to the above general procedure from sorbitan **2** (1.00 g, 6 mmol) and decanal (0.382 mL, 2 mmol). The residue was purified by flash chromatography (EtOAc/cyclohexane 50:50 → 80:20) to give a 64:36 mixture of 5,6-*O*-regioisomers **10** and 3,5-*O*-regioisomers **11** (0.098 g, 32%) as a white solid (m.p. = 72°C). The product was obtained as a mixture of 5,6-*O*- and 3,5-*O*-regioisomers, each regioisomer being a pair of diastereoisomers (35:29:25:11) as determined by HPLC (Figure 6). ^1H NMR (300 MHz, CDCl_3) δ_{H} for all isomers: 0.85 (3H, t, J = 6.9), 1.10–1.45 (14H, m), 1.47–1.70 (2H, m), 3.45 (2H, *br s*, OH protons), 3.60–4.39 (8H, m, sorbitan protons), 4.75 (t, 29%H acetal, J = 5.1), 4.83 (t, 11%H acetal, J = 4.8), 4.85 (t, 35%H acetal, J = 5.3), 4.97 (t, 26%H acetal, J = 4.8); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} for 5,6-*O*-isomers **10a** and **10b**: 14.19 (CH_3), 22.76 (CH_2), 24.12 and 24.17 (CH_2), 29.40 (CH_2), 29.63 (3 CH_2), 31.97 (CH_2), 33.98 and 34.12 (CH_2), 68.17 and 68.57 (CH_2), 73.57 and 73.66 (CH), 73.77 and 74.13 (CH_2), 75.51 and 75.91 (CH), 77.30 and 77.56 (CH), 79.64 and 81.15 (CH), 104.99 and 105.14 (CH); δ_{C} for 3,5-*O*-isomers **11a** and **11b**: 14.19 (CH_3), 22.76 (CH_2), 23.84 and 24.12 (CH_2), 29.40 (CH_2), 29.63 (3 CH_2), 31.97 (CH_2), 34.19 and 34.83 (CH_2), 61.76 and 63.41 (CH_2), 72.80 and 73.14 (CH), 73.81 (CH_2), 75.15 and 75.34 (CH), 77.25 and 77.90 (CH), 81.37 (CH), 95.73 and 97.92 (CH); IR ν max: 3433 (OH), 2918 (CH_3), 2851 (CH_2), 1739, 1123, 1080, 1048; HRMS (ESI^+): $[\text{M}+\text{Na}]^+$ $\text{C}_{16}\text{H}_{30}\text{NaO}_5$ requires 325.1985, found 325.1991 (–1.7 ppm); HPLC (isocratic 50:50 $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ + 0.1% H_3PO_4): R_{t} for 3,5-isomers = 11.97 min (**11a**, 25%) and 13.27 min (**11b**, 11%); R_{t} for 5,6-isomers = 15.21 min (**10a**, 35%) and 16.60 (**10b**, 29%). The assignment of each peak was attributed by analogy with those of pentylidene-sorbitans.

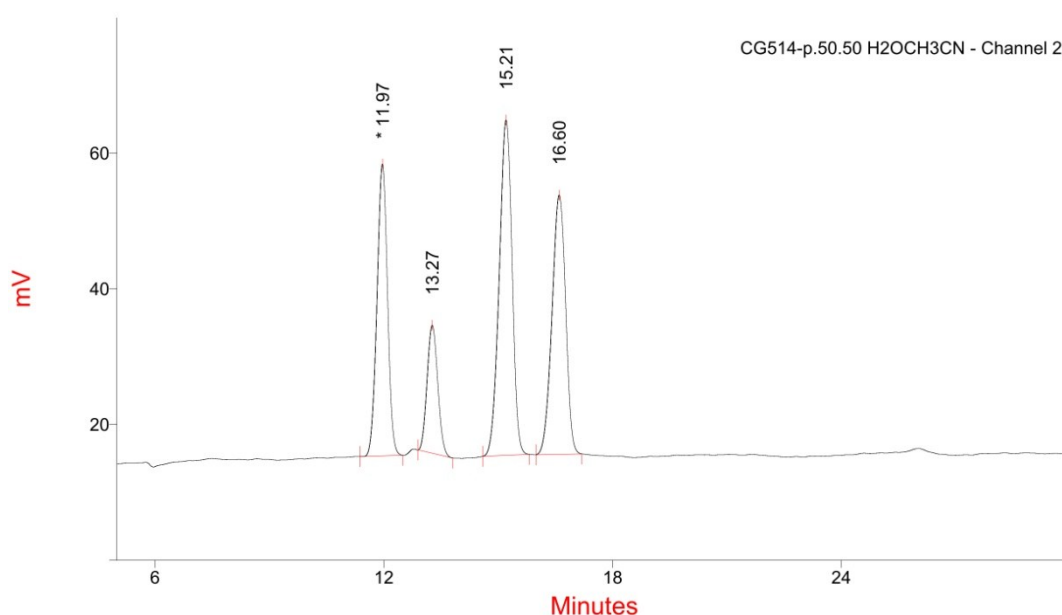
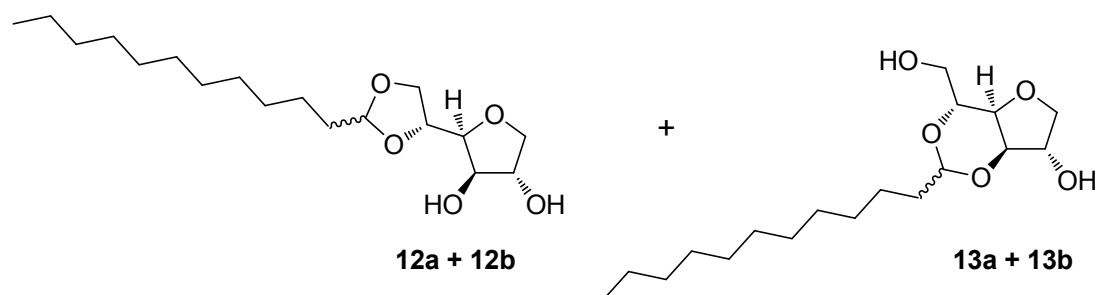


Figure 6. HPLC chromatogram of the mixture of sorbitan acetals **10a** and **10b** and **11a** and **11b**



5,6-*O*-Dodecylidene-1,4-D-sorbitan 12a and 12b and 3,5-*O*-dodecylidene-1,4-D-sorbitan 13a and 13b: The title compounds were prepared according to the above general procedure from sorbitan **2** (1.00 g, 6 mmol) and dodecanal (0.450 mL, 2 mmol). The residue was purified by flash chromatography (EtOAc/cyclohexane 50:50 → 70:30) to give a 48:52 mixture of 5,6-*O*-regioisomers **12** and 3,5-*O*-regioisomers **13** (0.095 g, 29%) as a white solid (m.p. = 82°C). The product was obtained as a mixture of 5,6-*O*- and 3,5-*O*-regioisomers, each regioisomer being a pair of diastereoisomers (25:23:40:12) as determined by HPLC (Figure 7). ¹H NMR (300 MHz, *d*₆-DMSO) δ_H for all isomers: 0.85 (3H, t, *J* = 6.9), 1.12–1.42 (18H, m), 1.43–1.59 (2H, m), 3.41–4.30 (8H, m, sorbitan protons), 4.72–4.89 (1H, m, acetal proton), 5.00–5.12 and 5.17–5.33 (2H, 2m, OH protons); ¹³C NMR (75 MHz, *d*₆-DMSO) δ_C for 5,6-*O*-isomers **12a** and **12b**: 13.95 (CH₃), 22.15 (CH₂), 23.60 and 23.69 (CH₂), 28.79 (CH₂), 28.93 (CH₂), 29.05 (CH₂), 29.07 (CH₂), 29.08 (CH₂), 29.10 (CH₂), 31.37 (CH₂), 33.54 (CH₂), 66.59 and 66.93 (CH₂), 72.87 and 73.26 (CH), 73.46 (CH₂), 75.49 and 75.72 (CH), 76.58 and 76.63 (CH), 80.75 and 81.04 (CH), 103.29 and 103.38 (CH); δ_C for 3,5-*O*-isomers **13a** and **13b**: 13.95 (CH₃), 22.15 (CH₂), 23.38 and 23.60 (CH₂), 28.79 (CH₂), 28.93 (CH₂), 29.05 (CH₂), 29.07 (CH₂), 29.08 (CH₂), 29.10 (CH₂), 31.37 (CH₂), 34.10 and 34.51 (CH₂), 60.84 and 61.94 (CH₂), 72.60 and 72.95 (CH), 72.43 and 73.59 (CH₂), 73.17 and 73.98 (CH), 74.92 and 76.43 (CH), 78.31 and 79.07 (CH), 93.87 and 96.06 (CH); IR ν max: 3412 (OH), 2917 (CH₃), 2849 (CH₂), 1468, 1418, 1256, 1082, 1050; HRMS (ESI⁺): [M+Na]⁺ C₁₈H₃₄NaO₅ requires 353.2298, found 353.2300 (-0.3 ppm); HPLC (isocratic 50:50 H₂O/CH₃CN + 0.1% H₃PO₄): R_t for 3,5-isomers = 31.89 min (**13a**, 40%) and 35.77 min (**13b**, 12%); R_t for 5,6-isomers = 41.72 min (**12a**, 25%) and 46.18 min (**12b**, 23%). The assignment of each peak was attributed by analogy with those of pentylidene-sorbitans.

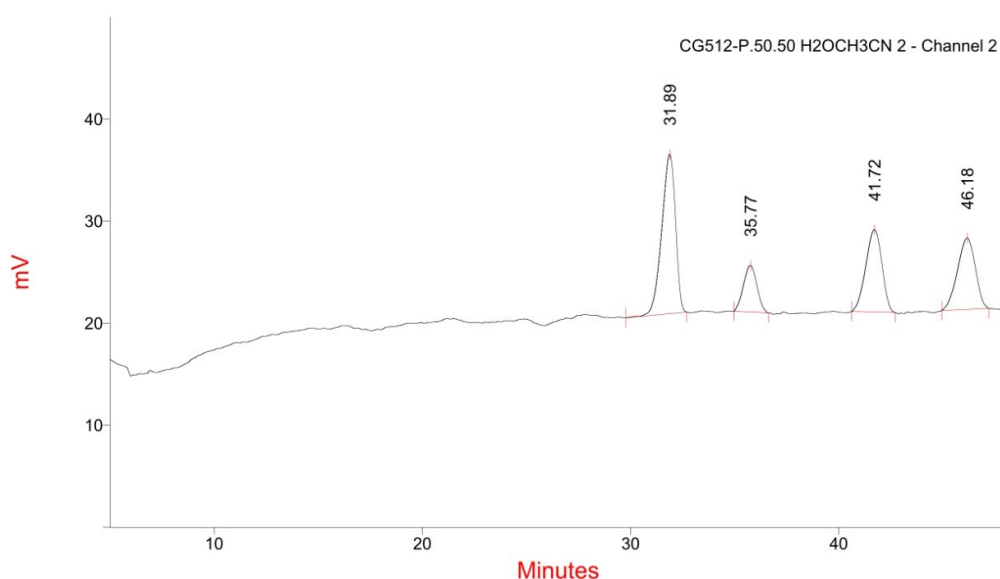


Figure 7. HPLC chromatogram of the mixture of sorbitan acetals **12a** and **12b** and **13a** and **13b**

4. Assignments of the mixture of sorbitan acetals (for C5 alkyl chain)

^1H and ^{13}C NMR spectra and HRMS analysis confirmed the formation of pentylidene-1,4-D-sorbitan. HPLC analysis of the isolated mixture of pentylidene-sorbitan acetals revealed the formation of four products (Figure 3). Further analysis by HPLC-MS permitted to assign the two first peaks as a pair of diastereoisomers of the six-membered 3,5-*O*-acetal (Figure 8) and the two last peaks as another pair of diastereoisomers of the five-membered 5,6-*O*-acetal (Figure 8).

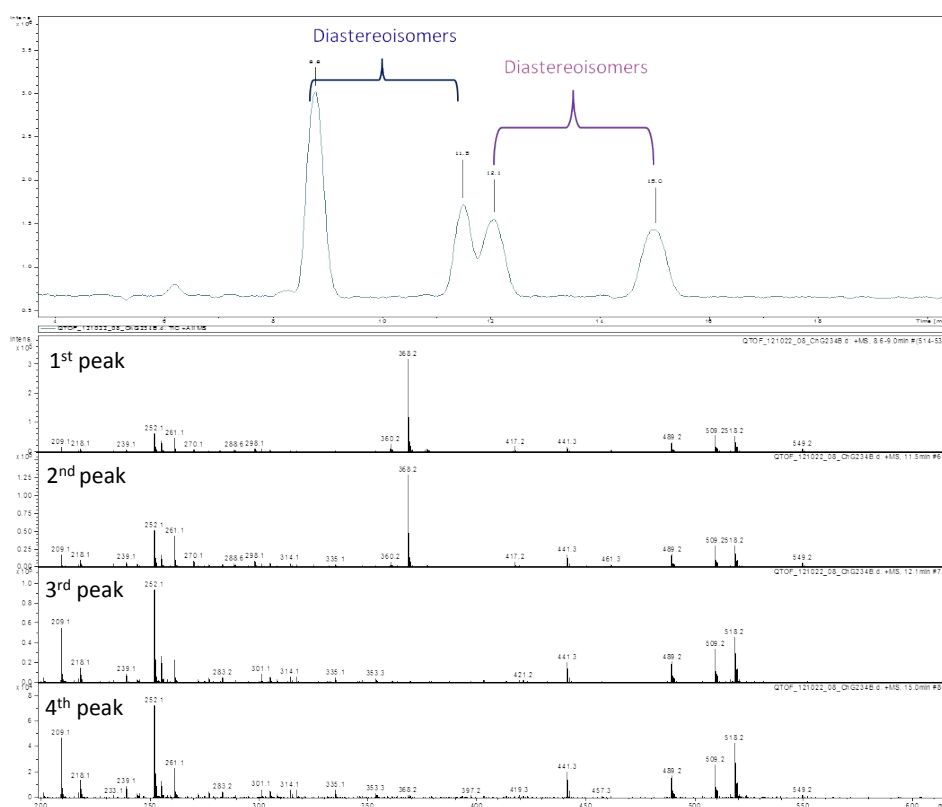


Figure 8. HPLC-MS chromatogram and MS spectra of mixture of pentylidene-1,4-D-sorbitans.

After careful purification by column chromatography (EtOAc/cyclohexane 80:20 \rightarrow 100:0), 2 fractions could be obtained: F1 (R_f = 0.40 in EtOAc) containing 3 products (purple peaks at 11.25, 12.50 and 14.49 min in Figure 9) and F2 (R_f = 0.34 in EtOAc) containing only one product (blue peak at 9.70 min in Figure 9).

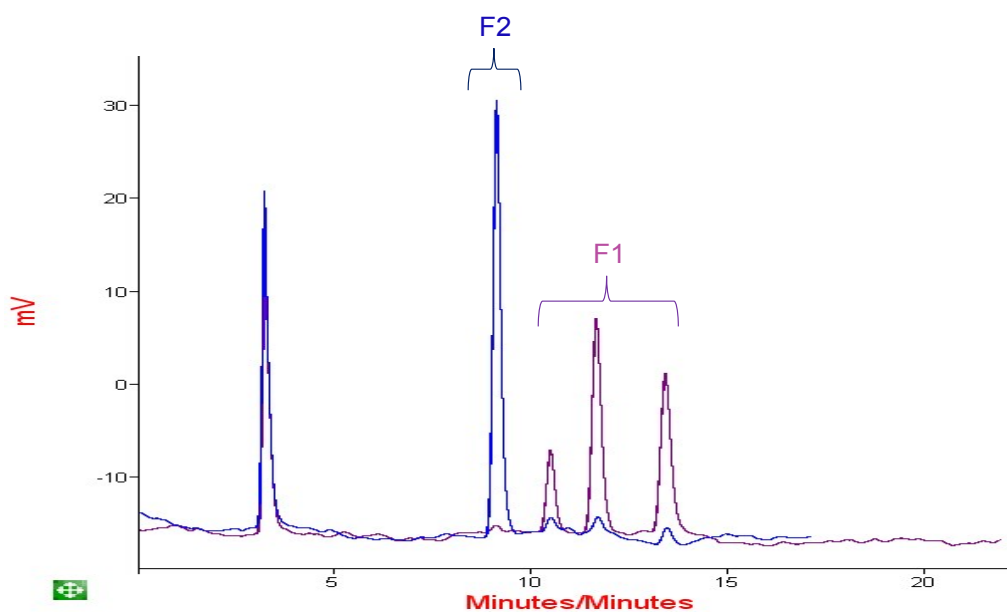


Figure 9. Superimposed HPLC chromatograms of fractions F1 and F2.

Fractions F1 and F2 have been analyzed by ^1H and ^{13}C NMR (including COSY and HMQC 2D experiments). ^{13}C NMR shifts were found the most useful information to assign the pair of regioisomers (Figure 10).

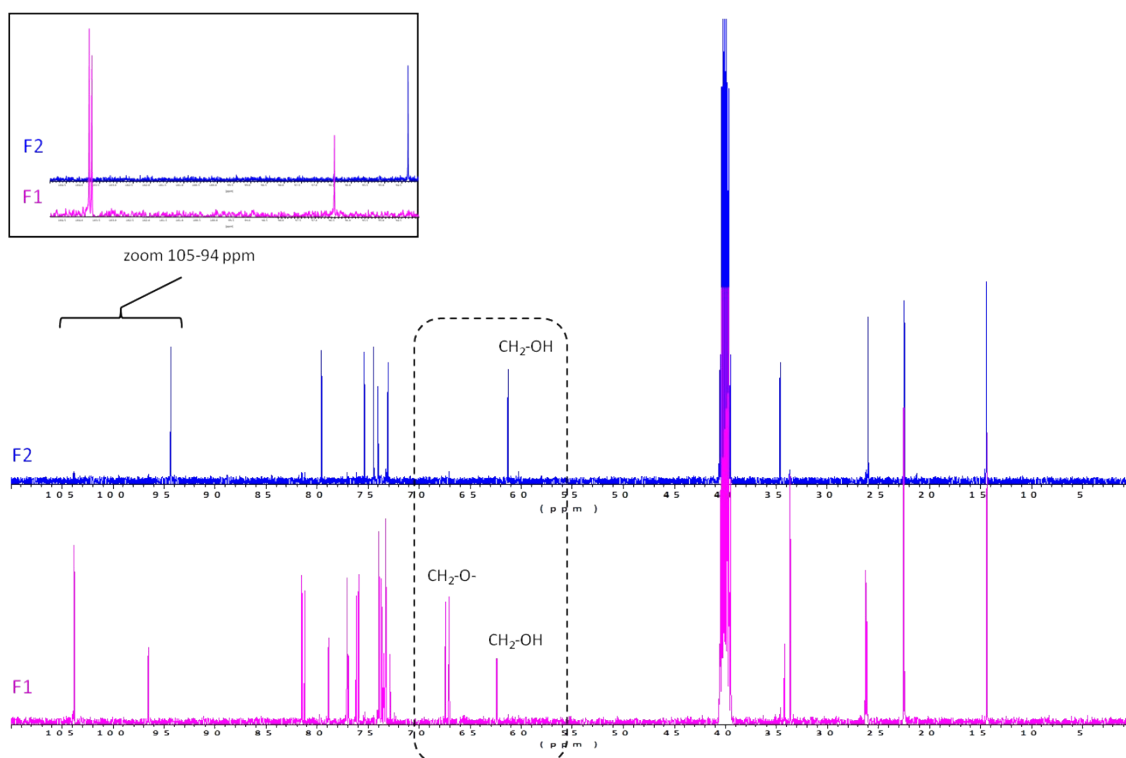


Figure 10. ^{13}C NMR (125 MHz, d_6 -DMSO) spectra of F1 and F2 after purification by column chromatography

The product of F2 has a ^{13}C NMR shift at 60.78 ppm, characteristic of a $\text{CH}_2\text{-OH}$ group, indicating that this product is one of the 3,5-regioisomers (Figure 10, blue spectrum). One of the products of F1 has

a similar ^{13}C NMR shift at 61.92 ppm, characteristic of a $\text{CH}_2\text{-OH}$ group, indicating that this product is the other diastereoisomer of the 3,5-regioisomers (Figure 10, pink spectrum). The 2 other products of F1 have ^{13}C NMR shifts at 66.59 and 66.93 ppm, characteristic of a $\text{CH}_2\text{-O-}$ group, indicating that these two products are the two diastereoisomers of the 5,6-regioisomers. Great differences are also observed for the acetal protons. The characteristic ^{13}C NMR shifts of all acetals are gathered in the table 1.

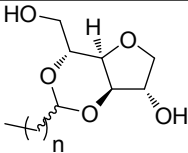
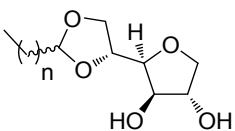
								
Alkyl chain	^{13}C NMR shifts (ppm in $d_6\text{-DMSO}$)				^{13}C NMR shifts (ppm in $d_6\text{-DMSO}$)			
	CH_2^6		$\text{CH}^{\text{acetal}}$		CH_2^6		$\text{CH}^{\text{acetal}}$	
n = 3	60.78	61.92	93.83	96.06	66.59	66.93	103.29	103.37
n = 4	60.85	61.97	93.90	96.13	66.64	66.98	104.34	103.42
n = 6	60.85	61.95	93.88	96.09	66.62	66.96	103.31	103.40
n = 8*	61.76	63.41	95.73	97.92	68.17	68.57	104.99	105.11
n = 10	60.84	61.94	93.87	96.06	66.59	66.93	103.29	103.38

Table 1. Characteristic ^{13}C NMR shifts of sorbitan acetals. * ^{13}C NMR shifts in CDCl_3 .

5. Preparation of sorbitan ethers

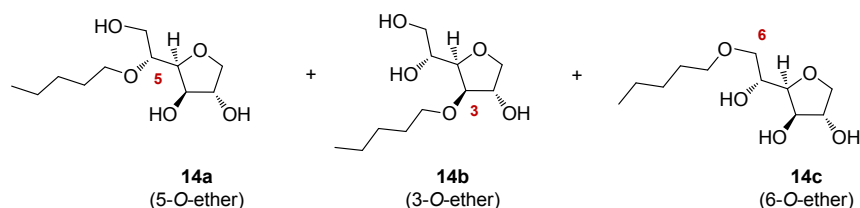
5.1. General procedure for the preparation of sorbitan ethers

The mixture of 1,4-D-sorbitan acetals (20 mmol) was diluted in dry CPME (200 mL) and 5%-Pd/C (1.00 g, 5 mol% in Pd) was added in a 300-mL stainless steel autoclave. The reactor was tightly closed, purged three times with hydrogen and hydrogen pressure was introduced (30 bar). The system was heated at 120°C and mechanically stirred for 15 hours. After cooling to room temperature, hydrogen pressure was released and the reaction mixture was then dissolved in absolute EtOH (100 mL) and filtered (Millipore Durapore filter 0.01 μm). The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography to give sorbitan ethers as mixtures of 3 regioisomers.

5.2. HPLC method for sorbitan ethers

HPLC analyses for the hydrogenolysis of sorbitan acetals to ethers were performed using a C18 column (Spherisorb C18, 5 μm I.D., 250 mm \times 20 mm) using a mixture of $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ + 0,1 %v/v H_3PO_4 as eluent (flow rate = 1 mL/min) with refraction index detection (RI-512, temperature = 40°C). The injected volume was 20 μL .

5.3. Characterization data of sorbitan ethers



Pentyl-1,4-D-sorbitan 14a-c: The title compound was prepared from a 43:57 mixture of 5,6-*O*-pentylidene-1,4-D-sorbitan **4a-4b** and 3,5-*O*-pentylidene-1,4-D-sorbitan **5a-5b** (0.98 g, 4.22 mmol) according to the above general procedure. After reaction, the residue was purified by flash chromatography (EtOAc/cyclohexane 90:10 to 100:0 then EtOH/EtOAc 10:90) to give sorbitan ethers **14a-c** (0.686 g, 69%) as a white paste. The product was obtained as a 26:33:41 mixture of 5-*O*-pentyl-**14a**, 3-*O*-pentyl- **14b** and 6-*O*-pentyl-1,4-D-sorbitan **14c** regioisomers as determined by HPLC (Figure 11). ^1H NMR (300 MHz, d_6 -DMSO) δ_{H} for all regioisomers: 0.86 (3H, t, J = 6.9), 1.19–1.35 (4H, m), 1.39–1.56 (2H, m), 3.22–3.99 and 4.05–4.11 (10H, m, sorbitan protons + OCH_2 ethers), δ_{H} for isomer **14a**: 4.31 (1H, t, J = 5.8, OH^6), 4.84 (1H, d, J = 4.3, OH^3), 5.00 (1H, d, J = 2.9, OH^2), δ_{H} for isomer **14b**: 4.31 (1H, t, J = 5.2, OH^6), 4.37 (1H, d, J = 5.4, OH^5), 5.06 (1H, d, J = 3.3, OH^2), δ_{H} for isomer **14c**: 4.55 (1H, d, J = 5.8, OH^5), 4.82 (1H, d, J = 4.3, OH^3), 4.99 (1H, d, J = 2.8, OH^2); ^{13}C NMR (75 MHz, d_6 -DMSO) δ_{C} for the minor (26%) isomer **14a**: 14.03 (CH_3), 22.06 (CH_2), 27.88 (CH_2), 29.55 (CH_2), 62.02 (CH_2), 69.79 (CH_2), 73.15 (CH_2), 75.53 (CH), 76.46 (CH), 77.38 (CH), 79.29 (CH); δ_{C} for the intermediary (33%) isomer **14b**: 13.99 (CH_3), 22.03 (CH_2), 27.91 (CH_2), 29.22 (CH_2), 64.20 (CH_2), 68.72 (CH), 69.52 (CH_2), 73.23 (CH), 73.61 (CH_2), 80.10 (CH), 83.96 (CH); δ_{C} for major (41%) isomer **14c**: 13.99 (CH_3), 22.02 (CH_2), 27.87 (CH_2), 28.99 (CH_2), 67.50 (CH), 70.60 (CH_2), 73.36 (CH_2), 73.49 (CH_2), 75.66 (CH), 76.38 (CH), 80.34 (CH); HRMS (ESI $^+$): $[\text{M}+\text{Na}]^+$ $\text{C}_{11}\text{H}_{22}\text{NaO}_5$ requires 257.1359, found 257.1363 (-1.4 ppm); HPLC (C18 column, isocratic 80:20 $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ + 0.1% H_3PO_4): R_{t} 7.20 min (**14a**, 26%), 9.25 min (**14b**, 33%) and 10.79 min (**14c**, 41%). The assignment of each peak was attributed after ^1H , ^{13}C NMR and HPLC analyses, see paragraph 6.

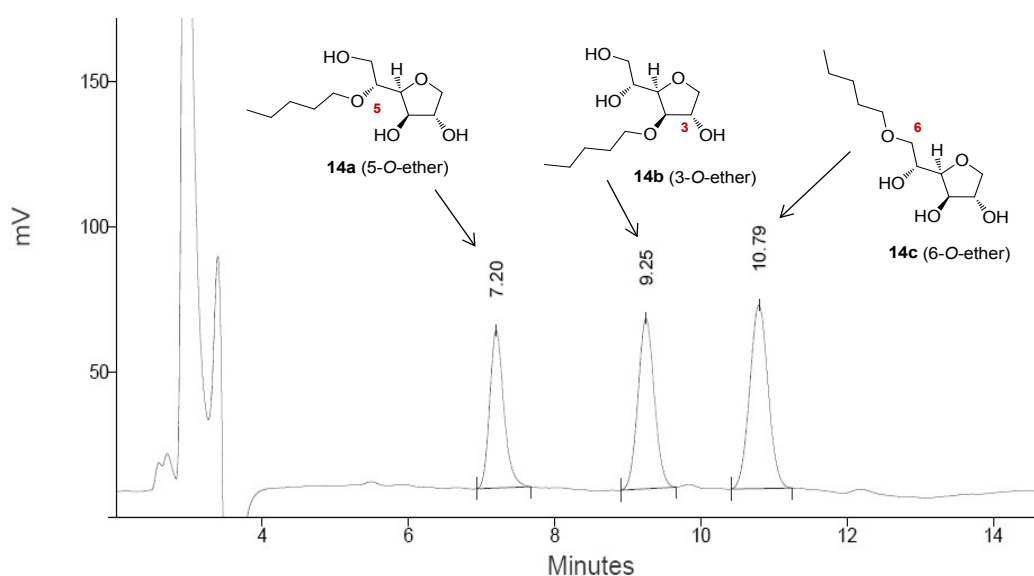
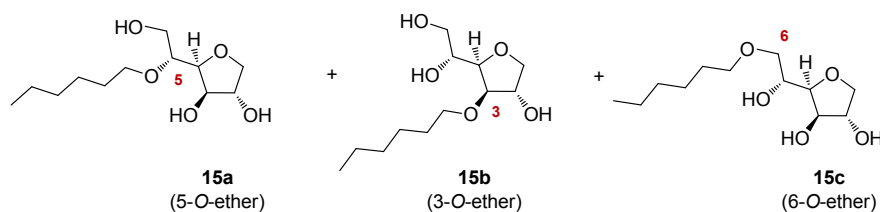


Figure 11. HPLC chromatogram of sorbitan ethers **14a-c**.



Hexyl-1,4-D-sorbitan 15a-c: The title compound was prepared from a 57:43 mixture of 5,6-*O*-hexylidene-1,4-D-sorbitan **6a-6b** and 3,5-*O*-hexylidene-1,4-D-sorbitan **7a-7b** (4.92 g, 20.0 mmol) according to the above general procedure. After reaction, the residue was purified by flash chromatography (EtOAc/cyclohexane 80:20 to 100:0 then EtOH/EtOAc 10:90) to give sorbitan ethers **15a-c** (3.25 g, 65%) as a white paste. The product was obtained as a 33:16:51 mixture of 5-*O*-hexyl-**15a**, 3-*O*-hexyl- **15b** and 6-*O*-hexyl-1,4-D-sorbitan **15c** regioisomers as determined by HPLC (Figure 12). ^1H NMR (300 MHz, d_6 -DMSO) δ_{H} for all regioisomers: 0.86 (3H, t, $J = 6.9$), 1.16–1.36 (6H, m), 1.38–1.56 (2H, m), 3.25–4.00 and 4.05–4.11 (10H, m, sorbitan protons + OCH_2 ethers), δ_{H} for isomer **15a**: 4.31 (1H, t, $J = 5.5$, OH^6), 4.83 (1H, d, $J = 4.4$, OH^3), 4.99 (1H, d, $J = 2.9$, OH^2), δ_{H} for isomer **15b**: 4.31 (1H, t, $J = 5.5$, OH^6), 4.36 (1H, d, $J = 5.4$, OH^5), 5.06 (1H, d, $J = 3.3$, OH^2), δ_{H} for isomer **15c**: 4.54 (1H, d, $J = 5.8$, OH^5), 4.81 (1H, d, $J = 4.3$, OH^3), 4.99 (1H, d, $J = 2.9$, OH^2); ^{13}C NMR (75 MHz, d_6 -DMSO) δ_{C} for isomer **15a** (33%): 14.00 (CH_3), 22.14 (CH_2), 25.36 (CH_2), 29.87 (CH_2), 31.27 (CH_2), 62.03 (CH_2), 69.84 (CH_2), 73.17 (CH_2), 75.57 (CH), 76.49 (CH), 77.40 (CH), 79.31 (CH); δ_{C} for isomer **15b** (16%): 13.97 (CH_3), 22.17 (CH_2), 25.34 (CH_2), 29.52 (CH_2), 31.19 (CH_2), 64.21 (CH_2), 68.74 (CH), 69.56 (CH_2), 73.27 (CH), 73.62 (CH_2), 80.11 (CH), 83.98 (CH); δ_{C} for isomer **15c** (51%): 13.97 (CH_3), 22.17 (CH_2), 25.40 (CH_2), 29.31 (CH_2), 31.23 (CH_2), 67.54 (CH), 70.65 (CH_2), 73.38 (CH_2), 73.50 (CH_2), 75.70 (CH), 76.40 (CH), 80.35 (CH); HRMS (ESI $^+$): $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{24}\text{NaO}_5$ requires 271.1516, found 271.1521 (-1.7 ppm); HPLC (C18 column, isocratic 80:20 $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ + 0.1% H_3PO_4): R_{t} 17.49 min (**15a**, 33%), 24.45 min (**15b**, 16%) and 29.58 min (**15c**, 51%). The assignment of each peak was attributed by analogy with those of pentyl-sorbitans.

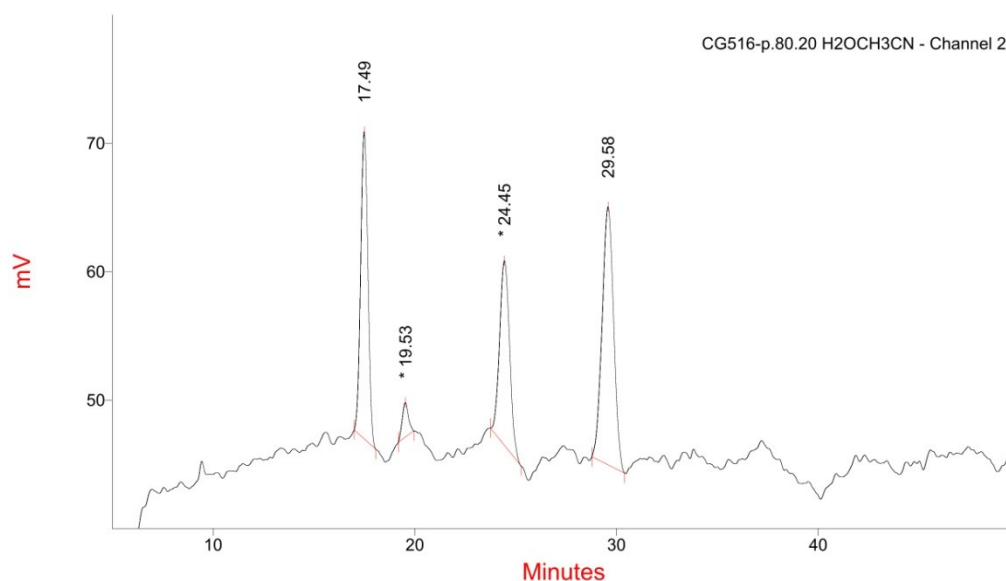
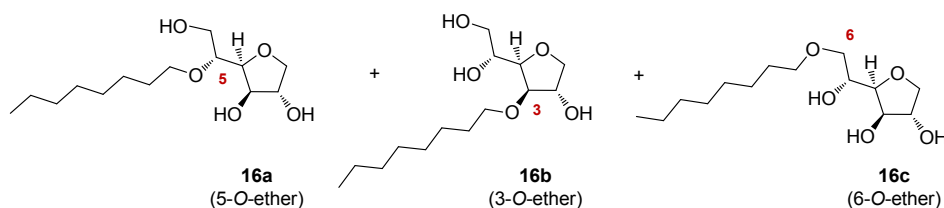


Figure 12. HPLC chromatogram of sorbitan ethers **15a-c**.



Octyl-1,4-D-sorbitan 16a-c: The title compound was prepared from a 61:39 mixture of 5,6-O-octylidene-1,4-D-sorbitan **8a-8b** and 3,5-O-octylidene-1,4-D-sorbitan **9a-9b** (5.61 g, 20.4 mmol) according to the above general procedure. After reaction, the residue was purified by flash chromatography (EtOAc/cyclohexane 80:20 to 100:0 then EtOH/EtOAc 10:90) to give sorbitan ethers **16a-c** (4.79 g, 85%) as a white solid. The product was obtained as a 33:22:45 mixture of 5-O-octyl-**16a**, 3-O-octyl- **16b** and 6-O-octyl-1,4-D-sorbitan **16c** regioisomers as determined by HPLC (Figure 13). ^1H NMR (300 MHz, d_6 -DMSO) δ_{H} for all regioisomers: 0.86 (3H, t, $J = 6.8$), 1.13–1.35 (10H, m), 1.36–1.55 (2H, m), 3.27–3.99 and 4.05–4.11 (10H, m, sorbitan protons + OCH_2 ethers), δ_{H} for isomer **16a**: 4.31 (1H, t, $J = 5.8$, OH^6), 4.84 (1H, d, $J = 4.5$, OH^3), 5.00 (1H, d, $J = 2.8$, OH^2), δ_{H} for isomer **16b**: 4.31 (1H, t, $J = 5.2$, OH^6), 4.37 (1H, d, $J = 5.4$, OH^5), 5.06 (1H, d, $J = 3.3$, OH^2), δ_{H} for isomer **16c**: 4.54 (1H, d, $J = 5.8$, OH^5), 4.81 (1H, d, $J = 4.3$, OH^3), 4.99 (1H, d, $J = 2.8$, OH^2); ^{13}C NMR (75 MHz, d_6 -DMSO): δ_{C} for isomer **16a** (33%): 13.98 (CH_3), 22.13 (CH_2), 25.66 (CH_2), 28.78 (CH_2), 28.99 (CH_2), 29.89 (CH_2), 31.32 (CH_2), 62.01 (CH_2), 69.83 (CH_2), 73.15 (CH_2), 75.53 (CH), 76.45 (CH), 77.38 (CH), 79.29 (CH); δ_{C} for isomer **16b** (22%): 13.98 (CH_3), 22.13 (CH_2), 25.70 (CH_2), 28.75 (CH_2), 28.90 (CH_2), 29.53 (CH_2), 31.30 (CH_2), 64.18 (CH_2), 68.71 (CH), 69.52 (CH_2), 73.23 (CH), 73.60 (CH_2), 80.08 (CH), 83.95 (CH); δ_{C} for isomer **16c** (45%): 13.98 (CH_3), 22.13 (CH_2), 25.70 (CH_2), 28.75 (CH_2), 28.93 (CH_2), 29.32 (CH_2), 31.30 (CH_2), 67.49 (CH), 70.61 (CH_2), 73.36 (CH_2), 73.49 (CH_2), 75.66 (CH), 76.37 (CH), 80.34 (CH); HRMS (ESI $^+$): $[\text{M}+\text{Na}]^+$ $\text{C}_{14}\text{H}_{28}\text{NaO}_5$ requires 299.1829, found 299.1832 (-1.2 ppm); HPLC (C18 column, isocratic 60:40 $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ + 0.1% H_3PO_4): R_{t} 8.79 min (**16a**, 33%), 9.80 min (**16b**, 22%) and 11.77 min (**16c**, 45%). The assignment of each peak was attributed by analogy with those of pentyl-sorbitans.

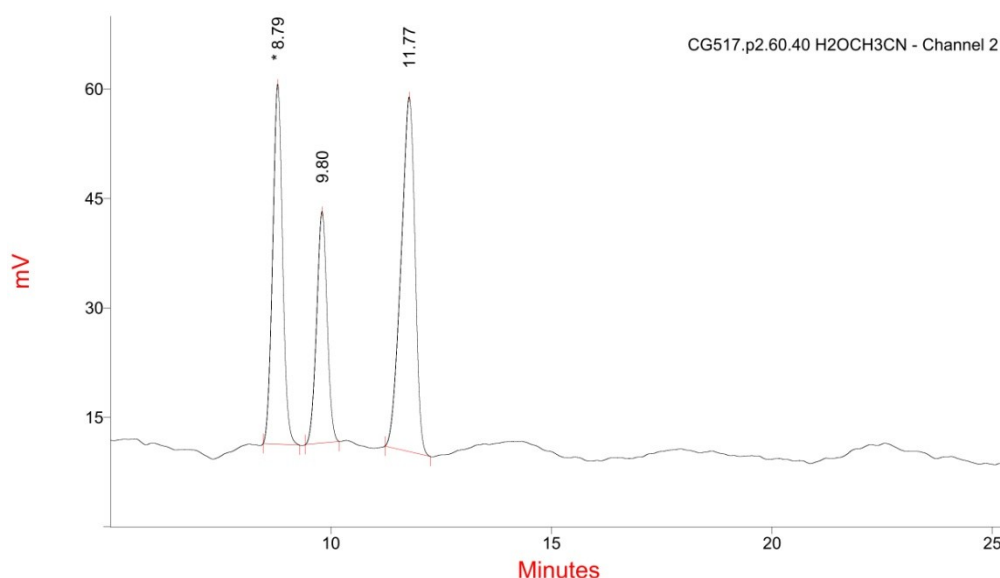
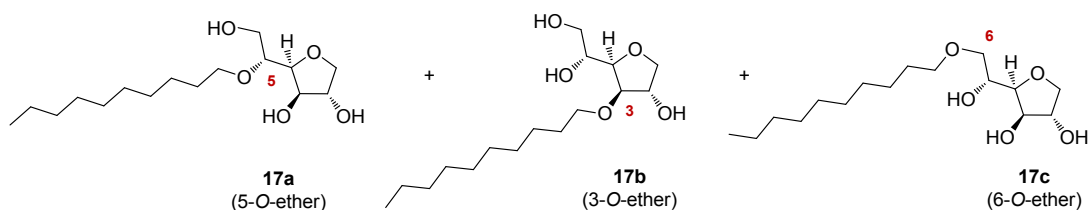


Figure 13. HPLC chromatogram of sorbitan ethers **16a-c**.



Decyl-1,4-D-sorbitan 17a-c: The title compound was prepared from a 64:36 mixture of 5,6-*O*-decylidene-1,4-D-sorbitan **10a-10b** and 3,5-*O*-decylidene-1,4-D-sorbitan **11a-11b** (6.12 g, 20.2 mmol) according to the above general procedure. After reaction, the residue was purified by flash chromatography (EtOAc/cyclohexane 70:30 to 100:0 then EtOH/EtOAc 10:90) to give sorbitan ethers **17a-c** (3.66 g, 59%) as a white solid. The product was obtained as a 32:16:52 mixture of 5-*O*-decyl-**17a**, 3-*O*-decyl- **17b** and 6-*O*-decyl-1,4-D-sorbitan **17c** regioisomers as determined by HPLC (Figure 14). ^1H NMR (300 MHz, d_6 -DMSO) δ_{H} for all regioisomers: 0.85 (3H, t, $J = 6.9$), 1.14–1.35 (14H, m), 1.37–1.55 (2H, m), 3.25–3.98 and 4.05–4.11 (10H, m, sorbitan protons + OCH_2 ethers), δ_{H} for isomer **17a**: 4.31 (1H, t, $J = 5.4$, OH^6), 4.82 (1H, d, $J = 4.3$, OH^3), 4.99 (1H, d, $J = 2.9$, OH^2), δ_{H} for isomer **17b**: 4.31 (1H, t, $J = 5.4$, OH^6), 4.35 (1H, d, $J = 5.5$, OH^5), 5.06 (1H, d, $J = 3.3$, OH^2), δ_{H} for isomer **17c**: 4.53 (1H, d, $J = 5.8$, OH^5), 4.80 (1H, d, $J = 4.3$, OH^3), 4.98 (1H, d, $J = 1.9$, OH^2); ^{13}C NMR (75 MHz, d_6 -DMSO) δ_{C} for isomer **17a** (32%): 13.98 (CH_3), 22.16 (CH_2), 25.69 (CH_2), 28.79 (CH_2), 29.07 (CH_2), 29.10 (CH_2), 29.17 (CH_2), 29.92 (CH_2), 31.37 (CH_2), 62.01 (CH_2), 69.84 (CH_2), 73.16 (CH_2), 75.56 (CH), 76.48 (CH), 77.41 (CH), 79.30 (CH); δ_{C} for isomer **17b** (16%): 13.98 (CH_3), 22.16 (CH_2), 25.72 (CH_2), 28.79 (CH_2), 28.98 (CH_2), 29.07 (CH_2), 29.12 (CH_2), 29.57 (CH_2), 31.37 (CH_2), 64.18 (CH_2), 68.72 (CH), 69.55 (CH_2), 73.27 (CH), 73.60 (CH_2), 80.08 (CH), 83.96 (CH); δ_{C} for isomer **17c** (52%): 13.98 (CH_3), 22.16 (CH_2), 25.72 (CH_2), 28.79 (CH_2), 29.01 (CH_2), 29.07 (CH_2), 29.14 (CH_2), 29.35 (CH_2), 31.37 (CH_2), 67.53 (CH), 70.64 (CH_2), 73.37 (CH_2), 73.50 (CH_2), 75.69 (CH), 76.40 (CH), 80.35 (CH); HRMS (ESI^+): $[\text{M}+\text{Na}]^+$ $\text{C}_{16}\text{H}_{32}\text{NaO}_5$ requires 327.2142, found 327.2135 (+2.1 ppm); HPLC (C18 column, isocratic 50:50 $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ + 0.1% H_3PO_4): R_{t} 9.03 min (**17a**, 32%), 9.67 min (**17b**, 16%) and 11.61 min (**17c**, 52%). The assignment of each peak was attributed by analogy with those of pentyl-sorbitans.

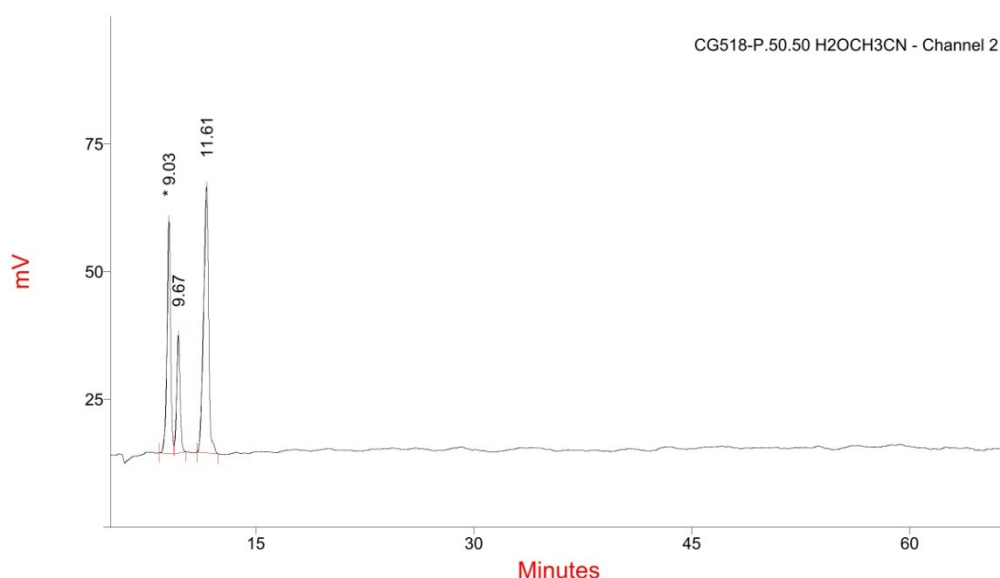
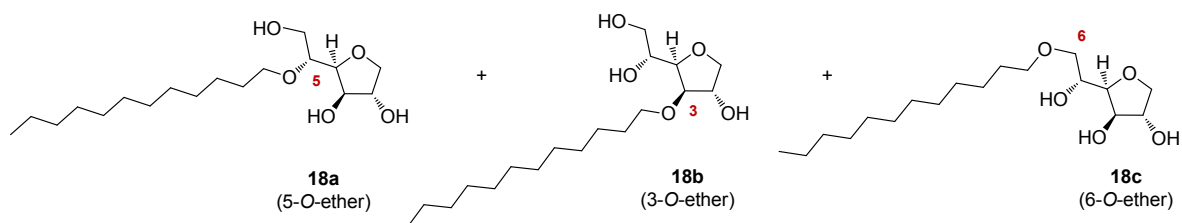


Figure 14. HPLC chromatogram of sorbitan ethers **17a-c**.



Dodecyl-1,4-D-sorbitan 18a-c: The title compound was prepared from a 48:52 mixture of 5,6-*O*-dodecylidene-1,4-D-sorbitan **12a-12b** and 3,5-*O*-dodecylidene-1,4-D-sorbitan **13a-13b** (1.29 g, 3.92 mmol) according to the above general procedure. After reaction, the residue was purified by flash chromatography (EtOAc/cyclohexane 70:30 to 100:0 then EtOH/EtOAc 10:90) to give sorbitan ethers **18a-c** (0.72 g, 55%) as a colorless oil. The product was obtained as a 27:33:40 mixture of 5-*O*-dodecyl-**18a**, 3-*O*-dodecyl-**18b** and 6-*O*-dodecyl-1,4-D-sorbitan **18c** regioisomers as determined by HPLC (Figure 15). ^1H NMR (300 MHz, d_6 -DMSO) δ_{H} for all regioisomers: 0.85 (3H, t, $J = 6.9$), 1.16–1.34 (18H, m), 1.38–1.54 (2H, m), 3.26–3.98 and 4.05–4.11 (10H, m, sorbitan protons + OCH_2 ethers), δ_{H} for isomer **18a**: 4.32 (1H, t, $J = 5.5$, OH^6), 4.84 (1H, d, $J = 3.7$, OH^3), 5.00 (1H, d, $J = 2.8$, OH^2), δ_{H} for isomer **18b**: 4.32 (1H, t, $J = 5.5$, OH^6), 4.37 (1H, d, $J = 5.4$, OH^5), 5.06 (1H, d, $J = 3.3$, OH^2), δ_{H} for isomer **18c**: 4.55 (1H, d, $J = 5.8$, OH^5), 4.82 (1H, d, $J = 4.1$, OH^3), 4.99 (1H, d, $J = 2.1$, OH^2); ^{13}C NMR (75 MHz, d_6 -DMSO) δ_{C} for isomer **18a** (27%): 13.97 (CH_3), 22.11 (CH_2), 25.64 (CH_2), 28.74 (CH_2), 29.05 (3 CH_2), 29.08 (2 CH_2), 29.88 (CH_2), 31.32 (CH_2), 62.00 (CH_2), 69.81 (CH_2), 73.14 (CH_2), 75.52 (CH), 76.44 (CH), 77.38 (CH), 79.27 (CH); δ_{C} for isomer **18b** (33%): 13.97 (CH_3), 22.11 (CH_2), 25.68 (CH_2), 28.74 (CH_2), 29.05 (3 CH_2), 29.08 (2 CH_2), 29.52 (CH_2), 31.32 (CH_2), 64.16 (CH_2), 68.69 (CH), 69.51 (CH_2), 73.22 (CH), 73.58 (CH_2), 80.06 (CH), 83.93 (CH); δ_{C} for isomer **18c** (40%): 13.97 (CH_3), 22.11 (CH_2), 25.68 (CH_2), 28.74 (CH_2), 28.92 (CH_2), 28.96 (CH_2), 29.05 (2 CH_2), 29.08 (CH_2), 29.31 (CH_2), 31.32 (CH_2), 67.47 (CH), 70.59 (CH_2), 73.35 (CH_2), 73.48 (CH_2), 75.63 (CH), 76.35 (CH), 80.34 (CH); HRMS (ESI $^+$): $[\text{M}+\text{Na}]^+$ $\text{C}_{18}\text{H}_{36}\text{NaO}_5$ requires 355.2455, found 355.2458 (-0.9 ppm); HPLC (C18 column, isocratic 50:50 $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ + 0.1% H_3PO_4): R_{t} 22.65 min (**18a**, 27%), 25.04 min (**18b**, 33%) and 30.81 min (**18c**, 40%). The assignment of each peak was attributed by analogy with those of pentyl-sorbitans.

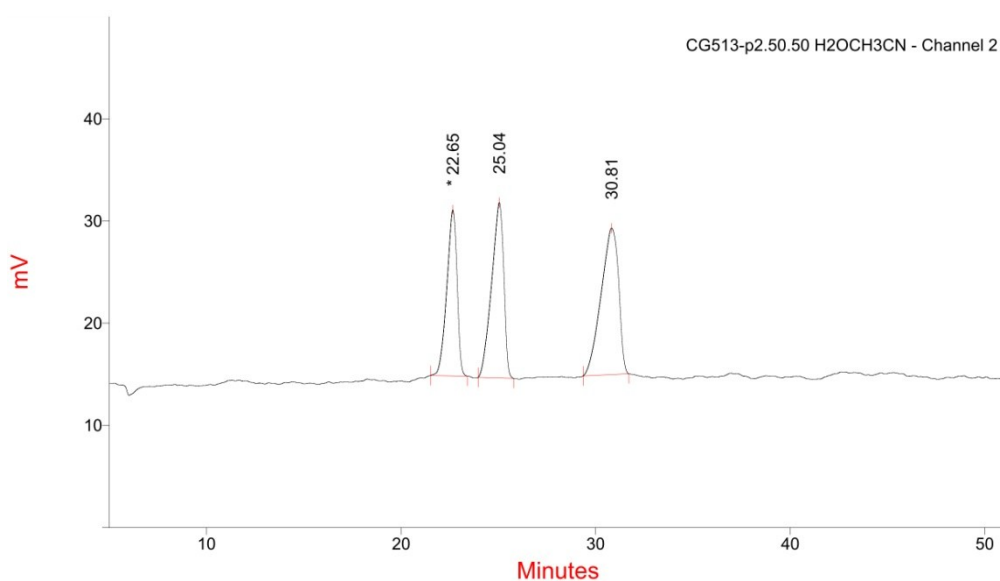
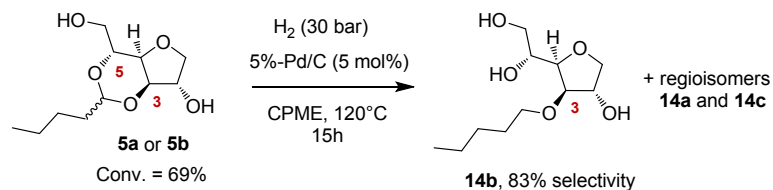


Figure 15. HPLC chromatogram of sorbitan ethers **18a-c**.

6. Mechanism experiment and assignments of regioisomers



A pure 3,5-*O*-pentylidene sorbitan **5a** or **5b** (Fraction acetals F2, 0.30 g, 1.29 mmol) was diluted in dry CPME (13 mL) and 5%-Pd/C (0.137 g, 0.0645 mmol in Pd, 5 mol% in Pd) was added in a 30-mL stainless steel autoclave. The reactor was tightly closed, purged three times with hydrogen and hydrogen pressure was introduced (30 bar). The system was heated at 120°C and magnetically stirred for 15 hours. After cooling to room temperature, hydrogen pressure was released and the reaction mixture was then dissolved in absolute EtOH (10 mL) and filtered (Millipore Durapore filter 0.01 μm). The filtrate was evaporated under reduced pressure. HPLC analysis revealed a 69% conversion of the acetal. The residue was purified by flash chromatography (EtOAc/cyclohexane 80:20 to 100:0 then EtOH/EtOAc 10:90) to give 3-*O*-pentyl-sorbitan **14b** as the major regioisomer (83%) as determined by HPLC (Figure 16).

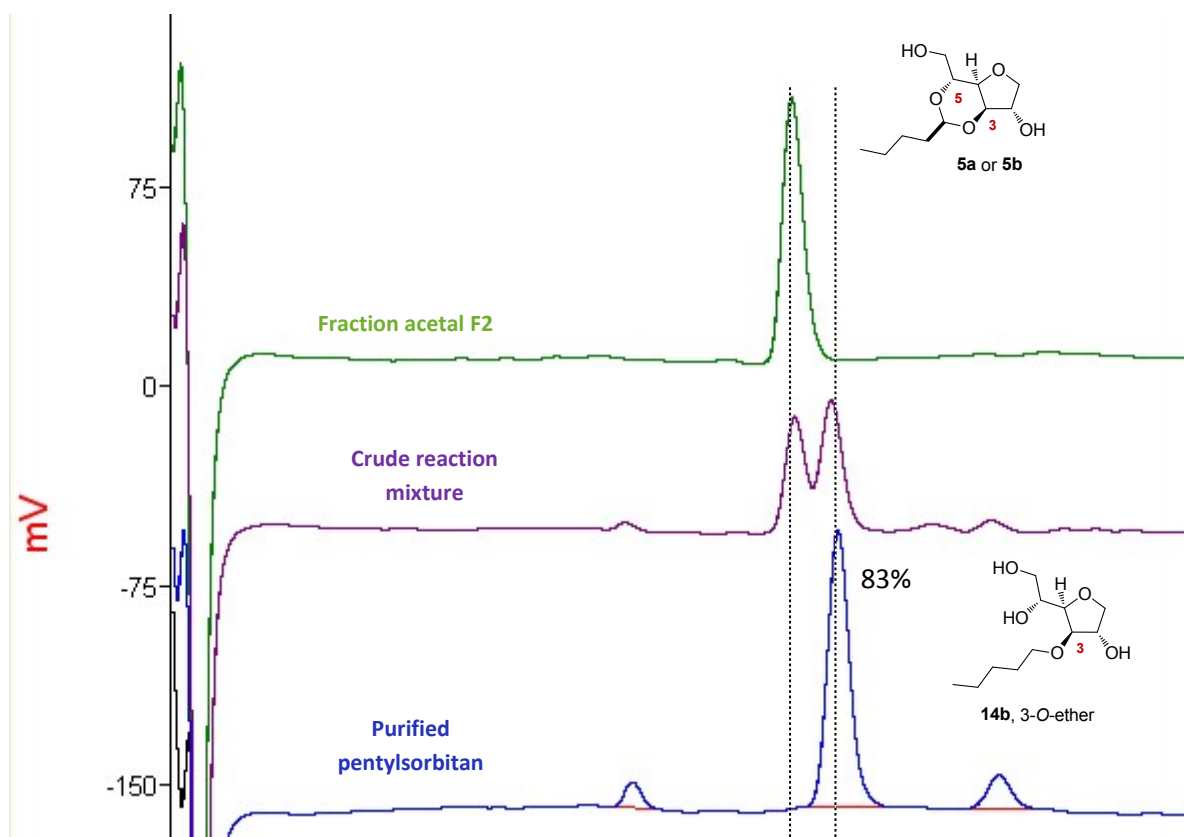


Figure 16. HPLC chromatogram (80:20 H₂O:CH₃CN + 0.1 % H₃PO₄) of pure 3,5-*O*-pentylidene sorbitan (top), crude reaction mixture (middle) and isolated 3-*O*-pentylsorbitan **14b** (bottom)

Assignment of the major regioisomer:

^1H NMR (400 MHz, d_6 -DMSO) δ_{H} : 0.86 (3H, t, $J = 6.9$), 1.15–1.35 (4H, m), 1.40–1.55 (2H, m), 3.28–3.72 (8H, m, 6H sorbitan moiety + 2H OCH_2 ether), 3.84 (1H, dd, $J = 9.2, 4.2$), 4.08 (1H, t, $J = 3.9$), 4.32 (1H, t, $J = 5.7$, OH^6), 4.37 (1H, d, $J = 5.6$, OH^5), 5.06 (1H, d, $J = 3.2$, OH^2); ^{13}C NMR (100 MHz, d_6 -DMSO) δ_{C} : 13.95 (CH_3), 21.97 (CH_2), 27.82 (CH_2), 29.18 (CH_2), 64.17 (CH_2), 68.69 (CH), 69.49 (CH_2), 73.21 (CH), 73.58 (CH_2), 80.08 (CH), 83.94 (CH).

From the structure of the starting material, the hydrogenolysis of a pure 3,5-*O*-pentylidene sorbitan **5a** or **5b**, could lead to either 5-*O*-pentylsorbitan or 3-*O*-pentylsorbitan as the major regioisomer. In order to determine either 5-*O*-pentylsorbitan **14a** or 3-*O*-pentylsorbitan **14b** was the major regioisomer, a HMBC analysis has been carried out (Figure 17).

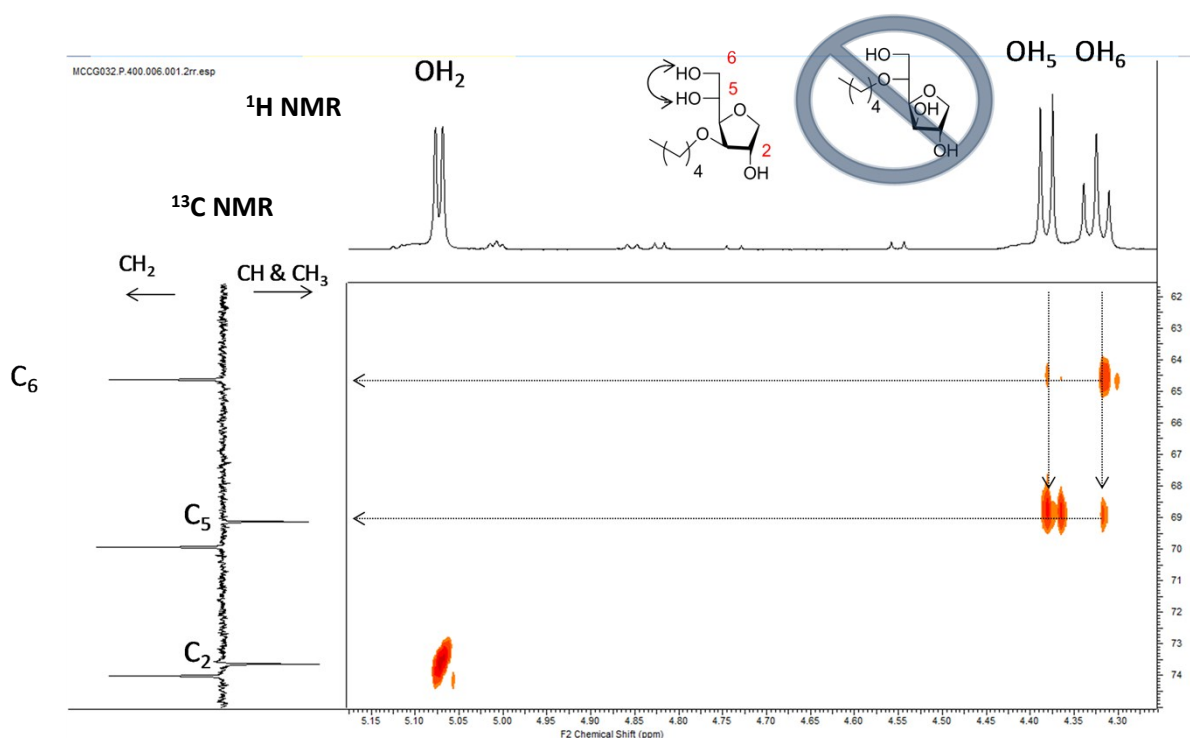


Figure 17. $^1\text{H}/^{13}\text{C}$ HMBC spectrum (in d_6 -DMSO) of the major regioisomer (zoom 4.25–5.15 ppm for ^1H and 61–76 ppm for ^{13}C).

First, the ^1H NMR spectra in d_6 -DMSO and D_2O permitted to assign the signals in the 4.25–5.15 ppm region as OH groups. Then, the OH group at 4.32 ppm is a triplet (Figure 17, ^1H NMR spectrum) and is coupling with carbon C^6 (Figure 17, ^{13}C NMR spectrum). This indicates that the OH^6 is a primary alcohol, so the major regioisomer could not be 6-*O*-pentylsorbitan **14c** but could be either 5-*O*-pentylsorbitan **14a** or 3-*O*-pentylsorbitan **14b**. Moreover, there is a 3J coupling between OH^6 and the carbon C^5 bearing the OH group at 4.38 ppm, indicating that this OH group is OH^5 . Similarly, there is a 3J coupling between OH^5 and the carbon C^6 . Finally, the OH group at 5.07 ppm has no long-range coupling with carbon C^5 or C^6 indicating that this OH group is OH^2 . Therefore, the major regioisomer

should have a secondary alcohol next to the primary alcohol and has been assigned to 3-*O*-pentylsorbitan **14b**.

Assignment of the other regioisomers:

The isolated fraction F1 of sorbitan acetals as a 77:23 mixture of 5,6-*O*-sorbitan acetals **4a** and **4b** and 3,5-*O*-sorbitan acetals **5a** or **5b** was also reacted under the same conditions. After reaction, HPLC analysis revealed a 23% conversion of the mixture of acetals. The residue was purified by flash chromatography (EtOAc/cyclohexane 80:20 to 100:0 then EtOH/EtOAc 10:90) to give a 41:59 mixture of 5-*O*-pentyl-sorbitan **14a** and 6-*O*-pentyl-sorbitan **14c** as determined by HPLC (Figure 18).

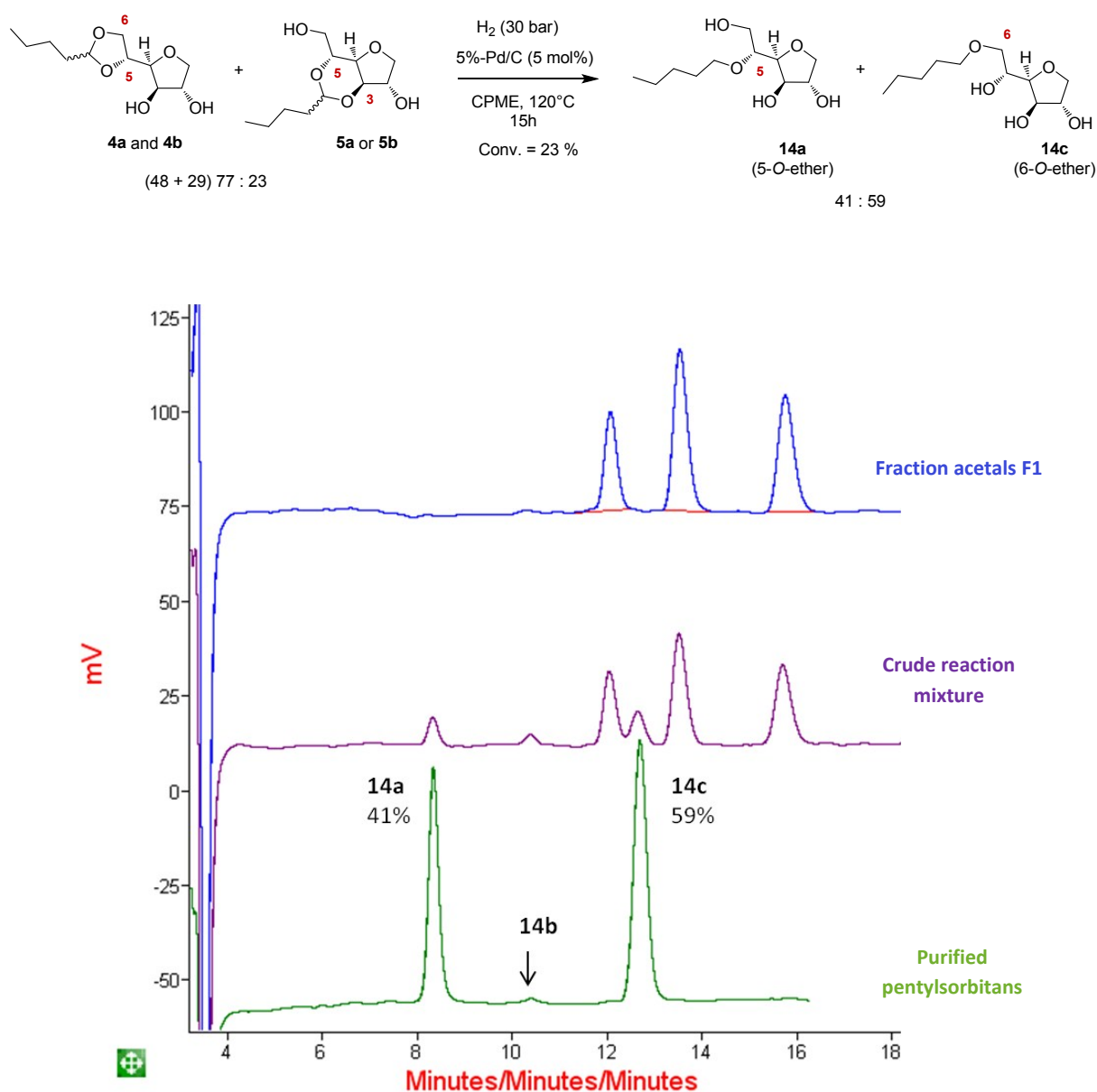


Figure 18. HPLC chromatograms (80:20 $H_2O:CH_3CN$ + 0,1 % H_3PO_4) of a mixture of pentylidene sorbitan (top), crude reaction mixture (middle) and isolated mixture of 5-*O*-pentylsorbitan **14a** and 6-*O*-pentylsorbitan **14c** (bottom).

Finally, ^{13}C NMR of the 41:59 mixture of purified pentyl-sorbitans was carried out (Figure 19). The minor isomer (41%) has a ^{13}C NMR shift at 61.42 ppm, characteristic of a $\text{CH}_2\text{-OH}$ group, indicating that this minor regioisomer is 5-*O*-pentyl-sorbitan **14a**. As a result, the major isomer (59%) is 6-*O*-pentyl-sorbitan **14c**.

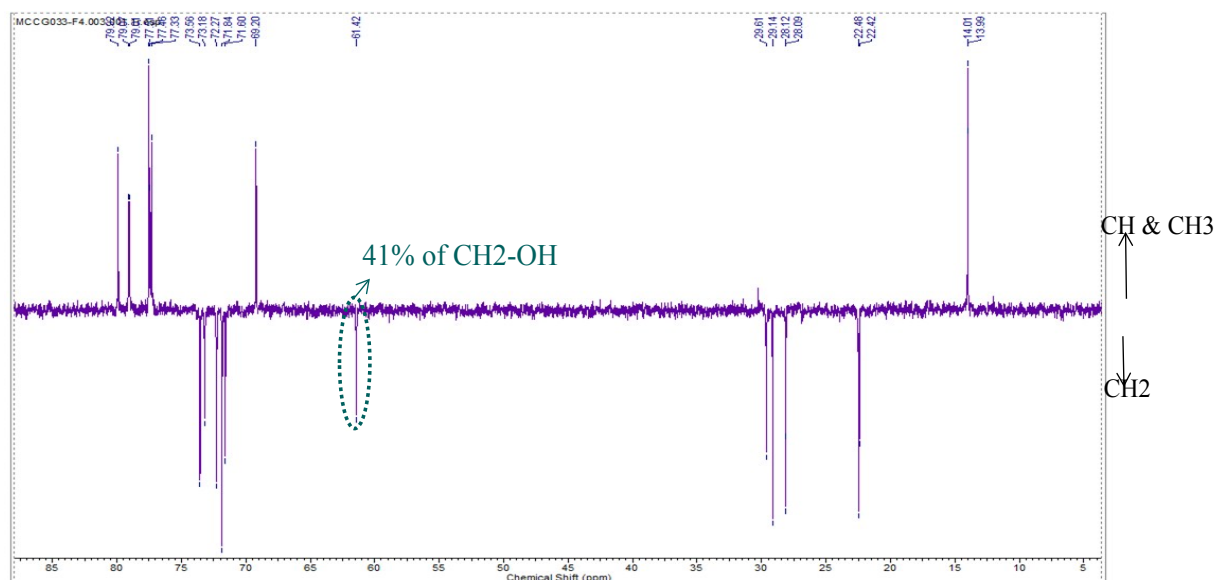


Figure 19. ^{13}C NMR spectrum of the 41:59 mixture of 5-*O*-pentylsorbitan **14a** and 6-*O*-pentylsorbitan **14c**.

7. Procedure for the acetalisation/hydrogenolysis sequence

(Table 8, Entry 1): In a 100-mL round bottom flask equipped with a condenser fitted with a CaCl_2 guard, under an argon atmosphere, sorbitan **2** (10.0 g, 60.9 mmol, 2 equiv) was dissolved in dry CPME (30 mL). After 10 minutes at room temperature, Na_2SO_4 (6.5 g, 45.8 mmol, 1.5 equiv) was added followed by valeraldehyde (2.63 g, 30.5 mmol, 1 equiv). After another 10 minutes at room temperature, Amberlyst A15 (0.53 g, 20 wt% / ald) was added and the reaction mixture was refluxed at 80°C for 15 hours. A sample was taken to determine the conversion of valeraldehyde by ^1H NMR (75% conv.). After cooling to room temperature, the reaction mixture was filtered on Celite®, washed with CPME (2 * 25mL) and the filtrate was transferred in a 500-mL stainless steel autoclave. The mixture was diluted in dry CPME (220 mL to reach a total of 300 mL) and 5%-Pd/C (3.25 g, 1.53 mmol in Pd, 5 mol% in Pd) was added. The reactor was tightly closed, purged three times with hydrogen and hydrogen pressure was introduced (30 bar). The system was heated at 120°C and mechanically stirred for 15 hours. After cooling to room temperature, hydrogen pressure was released and the reaction mixture was filtered (Millipore Durapore filter 0.01 μm). The filtrate was evaporated under reduced pressure. HPLC analysis revealed a complete conversion (> 98%) of the acetal. The residue

was purified by flash chromatography (EtOAc/cyclohexane 90:10 to 100:0 then EtOH/EtOAc 10:90) to give sorbitan ethers **14a-c** (3.97 g, 56%) as a white paste.

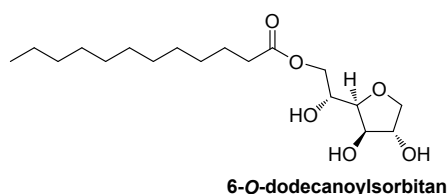
(Table 8, Entry 3): The same procedure was followed using decanal (4.77 g, 30.5 mmol, 1 equiv) as starting material. After reaction, the residue was purified by column chromatography (EtOAc/cyclohexane 70:30 to 100:0 then EtOH/EtOAc 10:90) to give sorbitan ethers **17a-c** (2.05 g, 22%) as a white solid.

8. Procedure for the acetalisation/transacetalisation cascade

In a 100-mL round bottom flask equipped with a condenser fitted with a CaCl₂ guard, under an argon atmosphere, sorbitan **2** (10.0 g, 60.9 mmol, 1 equiv) was dissolved in dry CPME (30 mL). After 10 minutes at room temperature, Na₂SO₄ (6.5 g, 45.8 mmol, 0.75 equiv) was added followed by valeraldehyde (2.63 g, 30.5 mmol, 0.5 equiv). After another 10 minutes at room temperature, Amberlyst A15 (0.53 g, 20 wt%) was added and the reaction mixture was refluxed at 80°C for 3 hours. A sample was taken to determine the conversion of valeraldehyde by ¹H NMR (76% conv.). Then, dodecanal (5.6 g, 30.5 mmol, 0.5 equiv) was added and the mixture was stirred for 15 hours at 80°C. A sample was taken to measure the conversion of dodecanal by ¹H NMR (76% conv.). After cooling to room temperature, the reaction mixture was filtered on Celite®, washed with CPME and the filtrate was concentrated under reduced pressure. The residue was triturated in EtOAc to precipitate excess sorbitan, filtered, washed with EtOAc and concentrated under reduced pressure. The residue was purified by column chromatography (cyclohexane/EtOAc 100:0 → 20:80) to give 9.35 g of a 46:54 mixture of pentyldene **4-5** and dodecyldene sorbitan **12-13** as determined by HPLC. The yield of sorbitan acetals **4-5** (3.50 g, 49%) and **12-13** (5.85 g, 58%) have been calculated based on the overall mass recovered and the HPLC ratio.

The same procedure was followed for the reaction under solvent-free conditions. After reaction, the residue was purified by column chromatography (cyclohexane/EtOAc 100:0 → 20:80) to give 11.82 g of a 38:62 mixture of pentyldene **4-5** and dodecyldene sorbitan **12-13** as determined by HPLC. The yield of sorbitan acetals **4-5** (3.56 g, 50%) and **12-13** (8.26 g, 82%) have been calculated based on the overall mass recovered and the HPLC ratio.

9. Preparation of C12 sorbitan ester



6-O-dodecanoylsorbitan. Following a literature procedure,³ in a two-necked round-bottom flask fitted with a soxlet apparatus containing oven-dried 3 Å molecular sieves in a cellulose cartridge and a condenser, sorbitan **2** (5.00 g, 30.5 mmol) and lauric acid (6.94 mL, 6.10 g, 30.5 mmol) were dissolved in a 22:78 mixture of *tert*-butanol/*n*-hexane (5 mL / 18 mL, 23 mL in total). The reaction mixture was heated at 64°C and the reflux system was stabilized with solvent condensing on the drying agent and returning to the reaction vessel. Once the system had come to steady state, the lipase was added (2.75 g of Novozyme 435 from *Candida Antartica*) and the reaction mixture was refluxed for 8 hours. After cooling to room temperature, MeOH was added (50 mL) and the lipase was removed by filtration using a millipore® filter. This operation was repeated twice with MeOH (2 * 50 mL). The filtrates were gathered and evaporated *in vacuo* to give a white viscous oil (9.82 g of crude product). GC/MS analysis revealed the formation of dodecanoylsorbitan mono- and di-esters. The residue was purified by column chromatography (CH₂Cl₂/MeOH 99:1 → 90:10) to give dodecanoylsorbitan diesters (1.85 g, 11%, R_f = 0.57 in CH₂Cl₂/MeOH 90:10) and dodecanoylsorbitan monoester (2.44 g, 23%, R_f = 0.23 in CH₂Cl₂/MeOH 90:10). ¹H NMR (300 MHz, *d*₆-DMSO) δ_H for the major regioisomer: 0.85 (3H, t, *J* = 6.7), 1.13–1.36 (16H, m), 1.41–1.60 (2H, m), 2.27 (2H, t, *J* = 7.4), 3.29–3.62 (2H, m), 3.67 (1H, dd, *J* = 8.6, 2.8), 3.80–4.02 (4H, m), 4.23 (1H, dd, *J* = 10.7, 1.7), 4.78 (1H, d, *J* = 5.7, OH), 4.87 (1H, d, *J* = 4.4, OH), 5.02 (1H, d, *J* = 3.0, OH); ¹³C NMR (75 MHz, *d*₆-DMSO) δ_C for the major regioisomer: 13.96 (CH₃), 22.21 (CH₂), 24.56 (CH₂), 28.62 (CH₂), 28.86 (CH₂), 28.89 (CH₂), 29.05 (CH₂), 29.15 (2 CH₂), 31.43 (CH₂), 33.62 (CH₂), 66.07 (CH), 66.95 (CH₂), 73.53 (CH₂), 75.50 (CH), 76.43 (CH), 80.48 (CH), 173.00 (Cq).

10. Physico-chemical properties

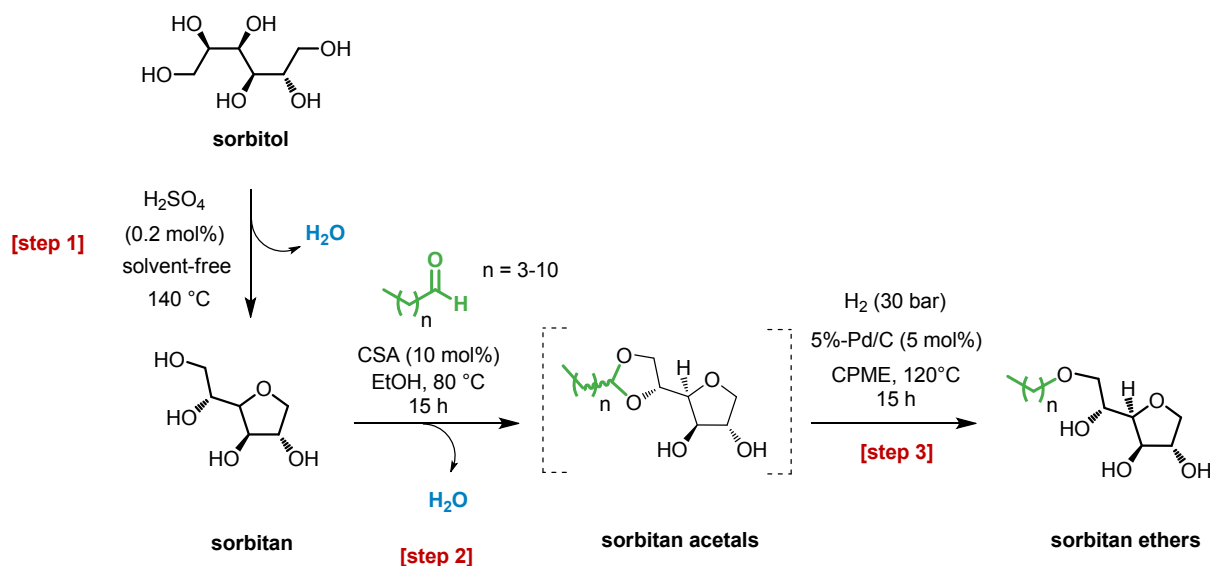
The surface tensions were measured at (25.0 ± 0.1)°C with a K100MK2 Krüss tensiometer using a platinum rod as the probe. A total of 2.5 mL of water was added in the vat. The solution was concentrated with surfactant solution (a manual dilution keeping volume constant was performed) till the surface tension was stable (standard deviation of the 5 final steps of 0,2 mN.m⁻¹).

11. Evaluation of economical and environmental impacts

The synthesis of sorbitan ethers has not been reported before (in terms of yields and selectivities), so the comparison with existing routes is not feasible. It is somewhat not simple to quantify the economical and environmental impacts of our route to sorbitan ethers but it is important to evaluate them at least qualitatively.

³ D. B. Sarney, M. J. Barnard, M. Virto and E. N. Vulfson, *Biotech. & Bioeng.*, 1997, **54**, 351-356.

The preparation of sorbitan ethers is using sorbitol as starting material which is a bio-based compound produced by catalytic hydrogenation of glucose. The worldwide production is estimated to 700 000 tons per year and its low price (about 0.7 euros/Kg) makes it an ideal renewable platform molecule. Sorbitan ethers were prepared following a 3-step sequence involving dehydration / acetalisation / hydrogenolysis.



Our reported synthesis of sorbitan ethers respects most of the 12 principles of Green Chemistry:

- Principle 1: waste prevention

Only 2 molecules of water are formed. Moreover, hydrogen was used as a clean reducing agent and does not lead to excessive wastes, contrary to the use of organic hydrides.

- Principle 2: atom economy

Theoretical atom-economy ranges from 87 to 90% depending on the alkyl chain length of the aldehydes.

- Principle 3: less hazardous synthesis

No toxic compounds or solvents, and more importantly, no CMR compounds have been used for the preparation of sorbitan ethers.

- Principle 5: benign solvents and auxiliaries

Solvent-free conditions have been used in step 1 and EtOH and CPME have been used as benign solvents in steps 2 and 3.

- Principle 7: use of renewable feedstocks

Sorbitol has been used as bio-based starting material.

- Principle 8: reduce derivatives

Protective groups have not been used during the synthesis.

- Principle 9: use of catalysts

Catalysts have been used for all the steps (H_2SO_4 in step 1, CSA in step 2 and Pd/C in step 3). Heterogeneous Pd/C could be easily recovered by filtration and could be recycled. Moreover, we have shown that H_2SO_4 and CSA could be advantageously substituted by acid resins (Amberlyst 15 for example) that could be recovered and reused.

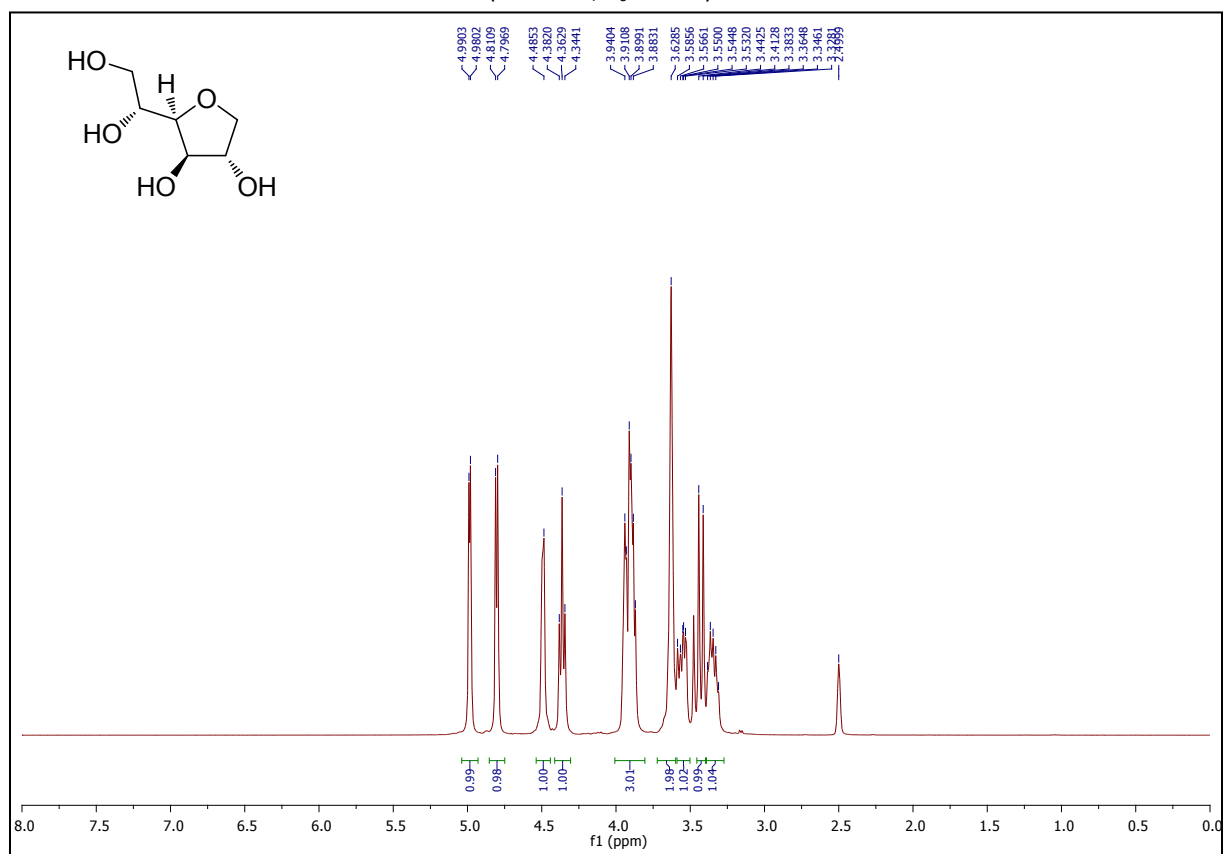
- Principle 10: design for degradation

Although more stable towards hydrolysis, sorbitan ethers share the same sorbitan moiety and alkyl linear chain than the corresponding Span and Tween derivatives (that are readily biodegradable and not expected to persist indefinitely in the environment).

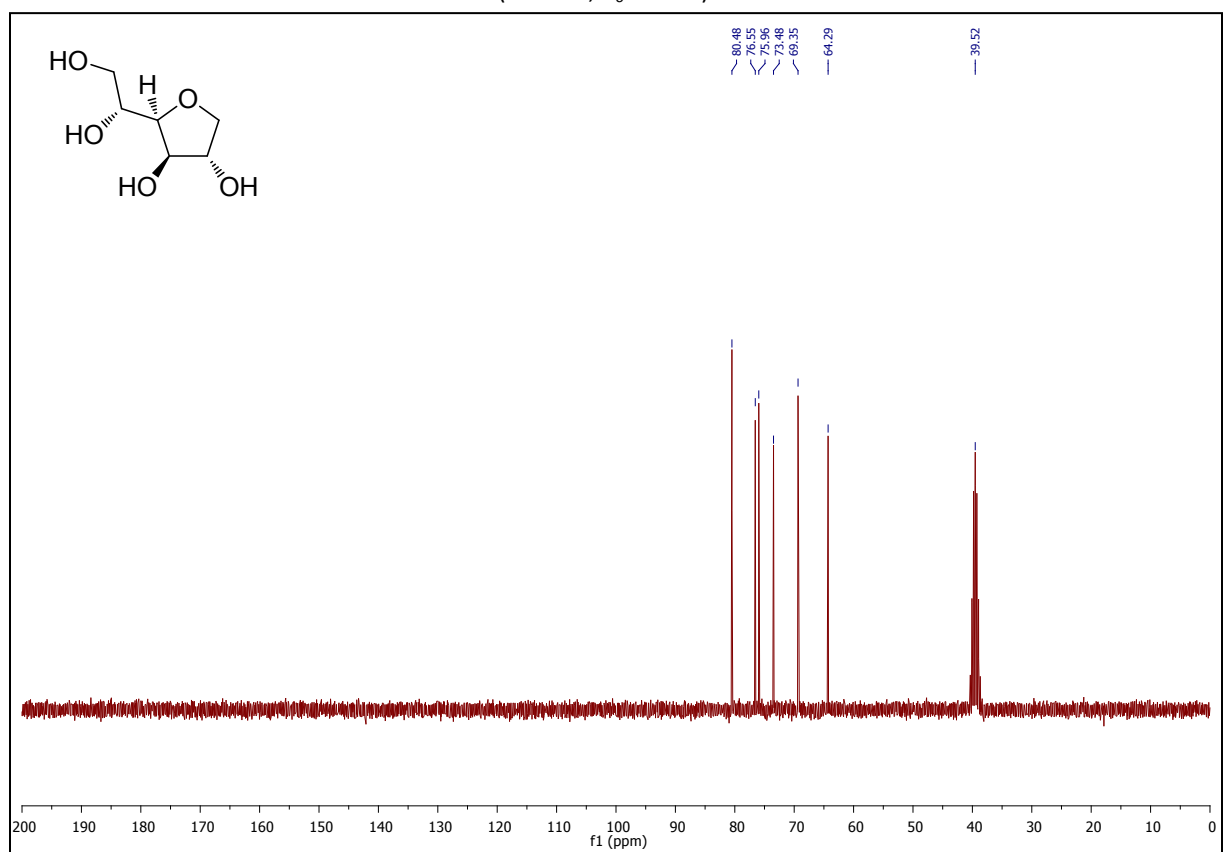
For all these reasons, our preparation of sorbitan ethers has been qualified as “cheap and environmentally-friendly” in the article.

12. ^1H and ^{13}C NMR spectra

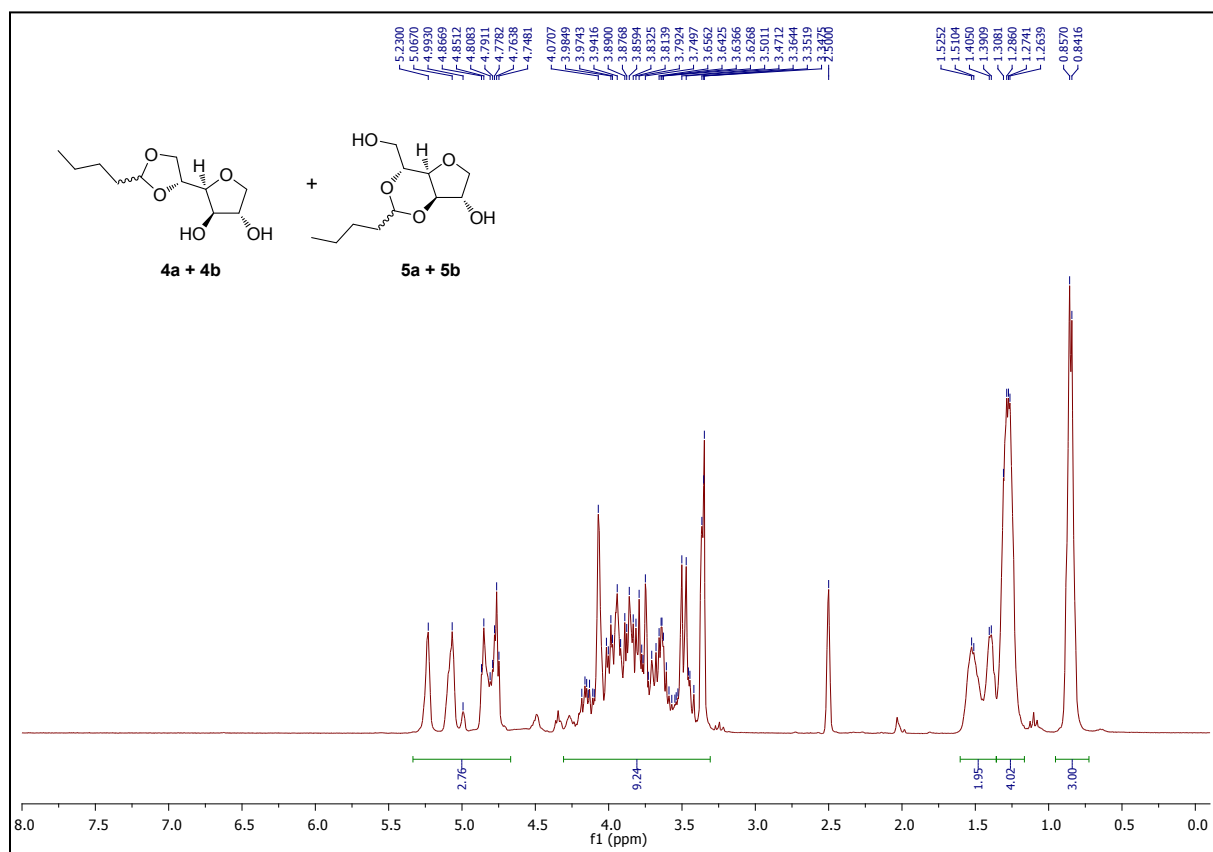
¹H NMR (300 MHz, d₆-DMSO) sorbitan **2**



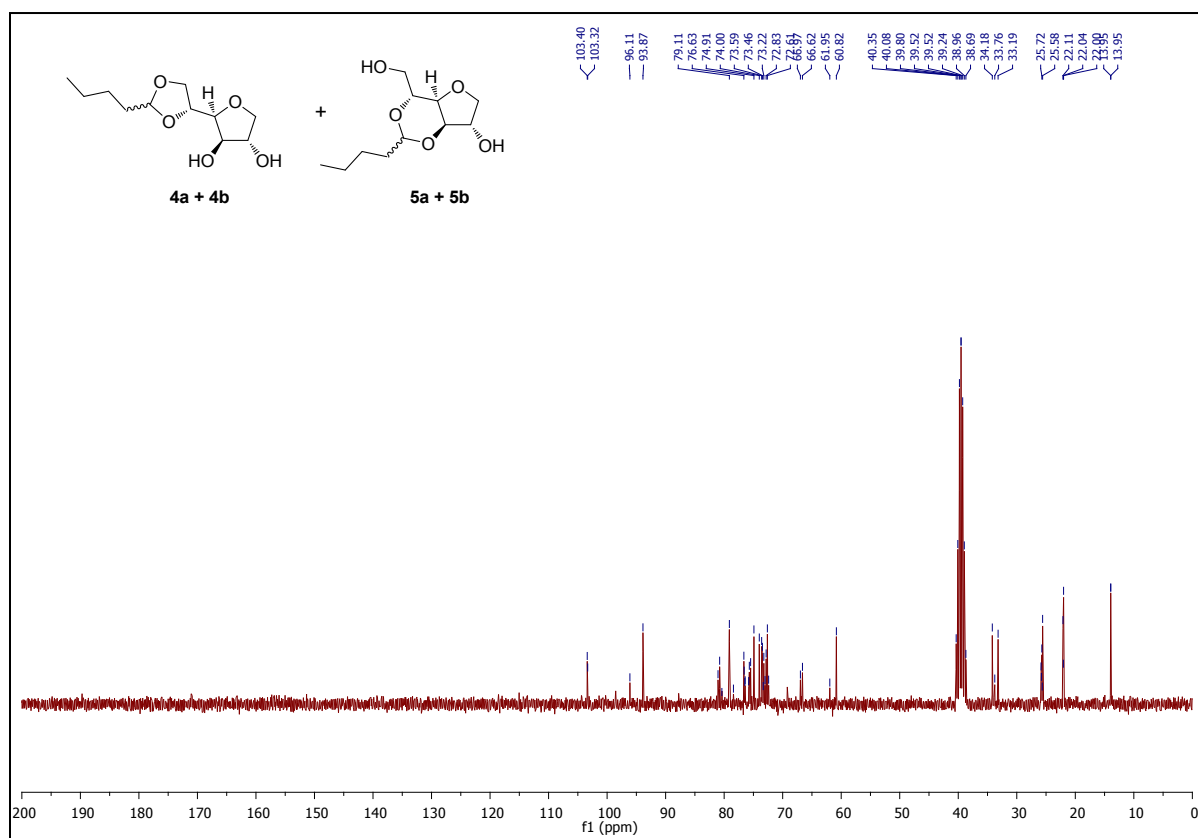
¹³C NMR (75 MHz, d₆-DMSO) sorbitan **2**



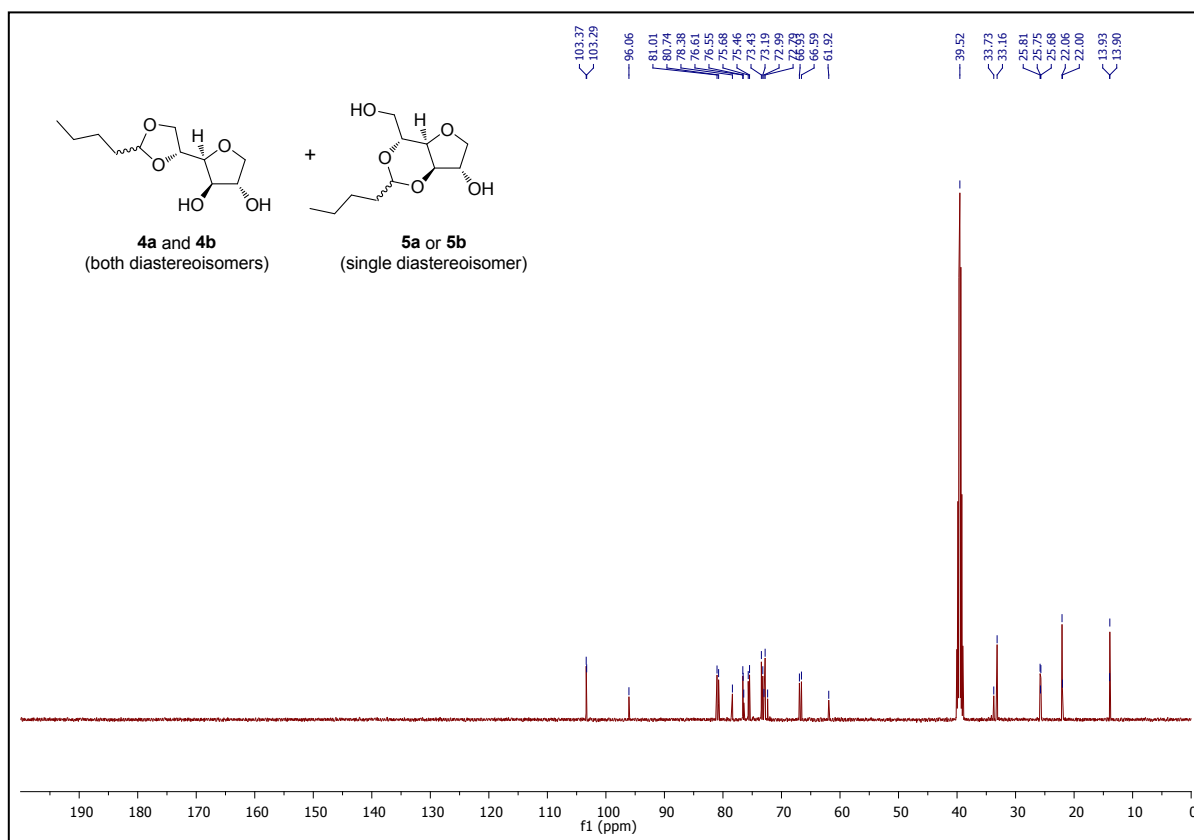
¹H NMR (300 MHz, *d*₆-DMSO) **5,6-*O*-Pentylidene-1,4-D-sorbitan 4a** and **4b** and **3,5-*O*-pentylidene-1,4-D-sorbitan 5a** and **5b**



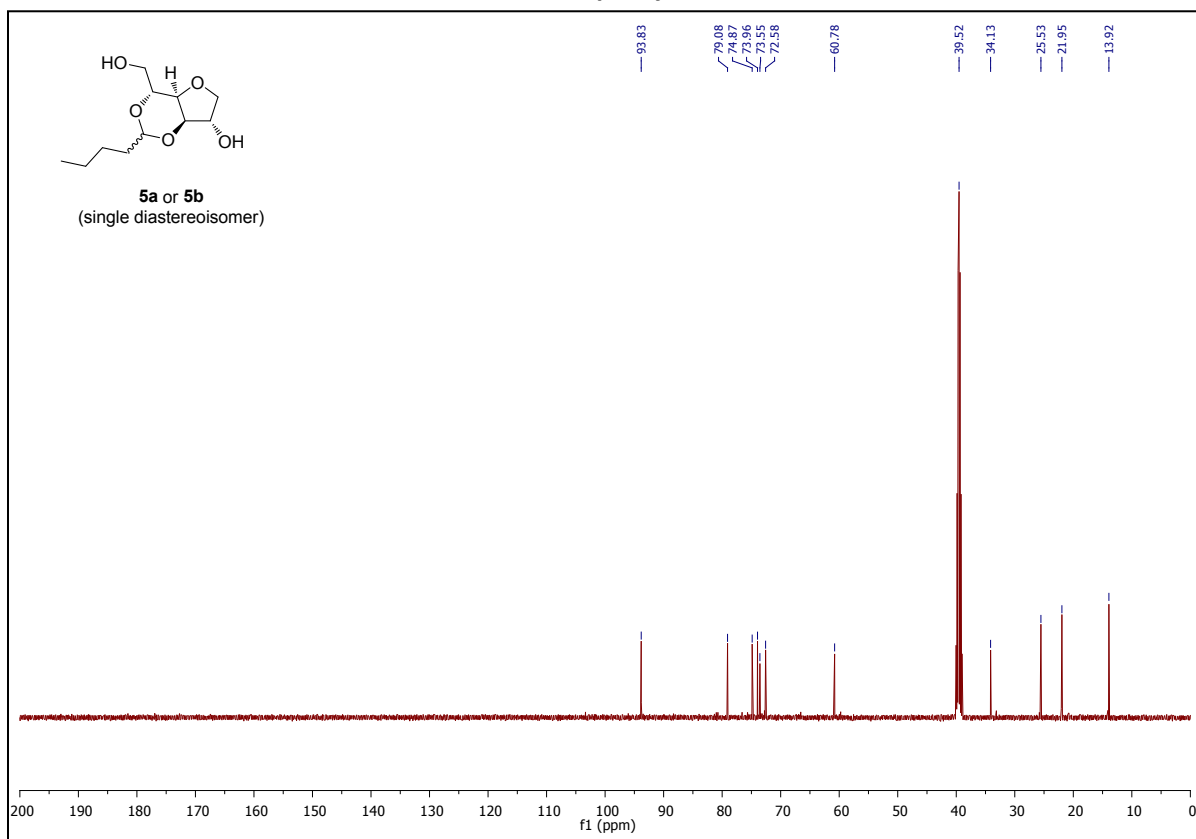
¹³C NMR (75 MHz, *d*₆-DMSO) **5,6-*O*-Pentylidene-1,4-D-sorbitan 4a** and **4b** and **3,5-*O*-pentylidene-1,4-D-sorbitan 5a** and **5b**



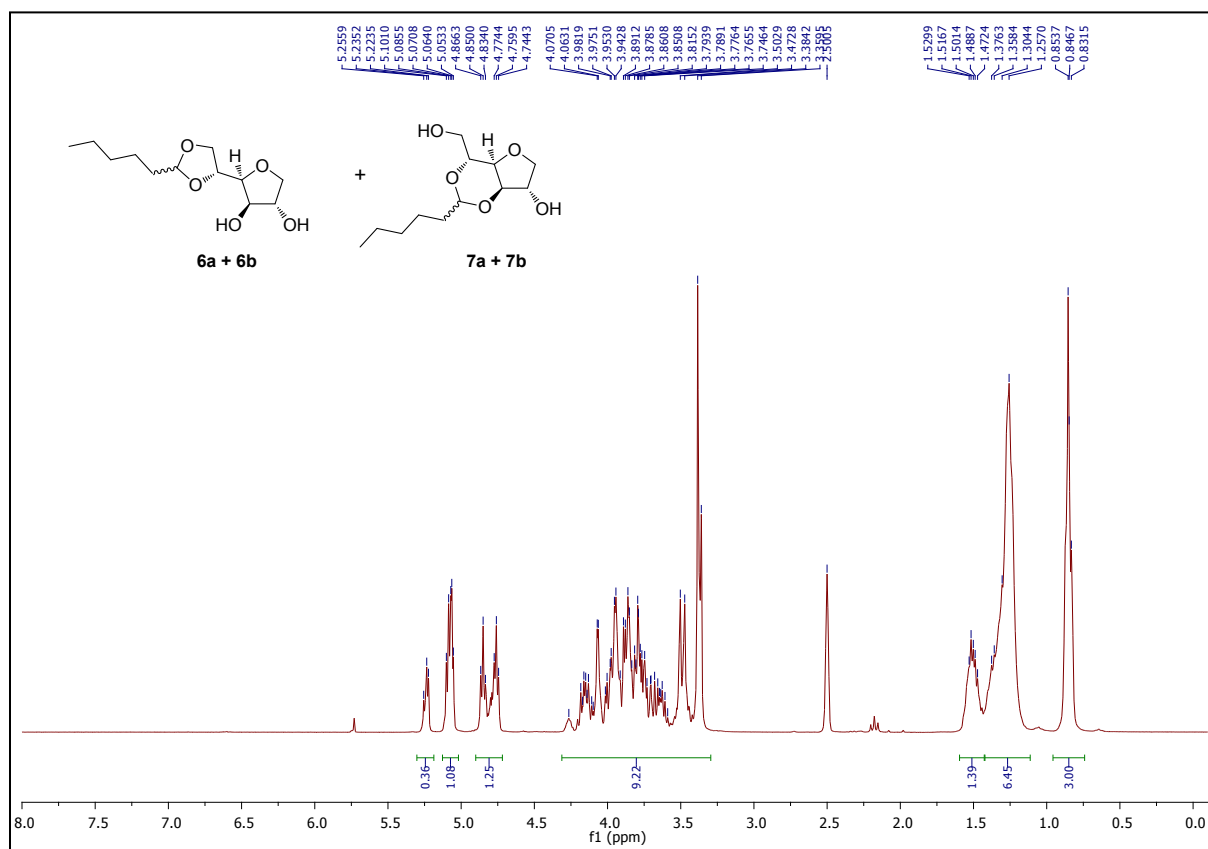
^{13}C NMR (125 MHz, d_6 -DMSO) **5,6-*O*-Pentylidene-1,4-D-sorbitan 4a and 4b** and **3,5-*O*-pentylidene-1,4-D-sorbitan 5a or 5b**



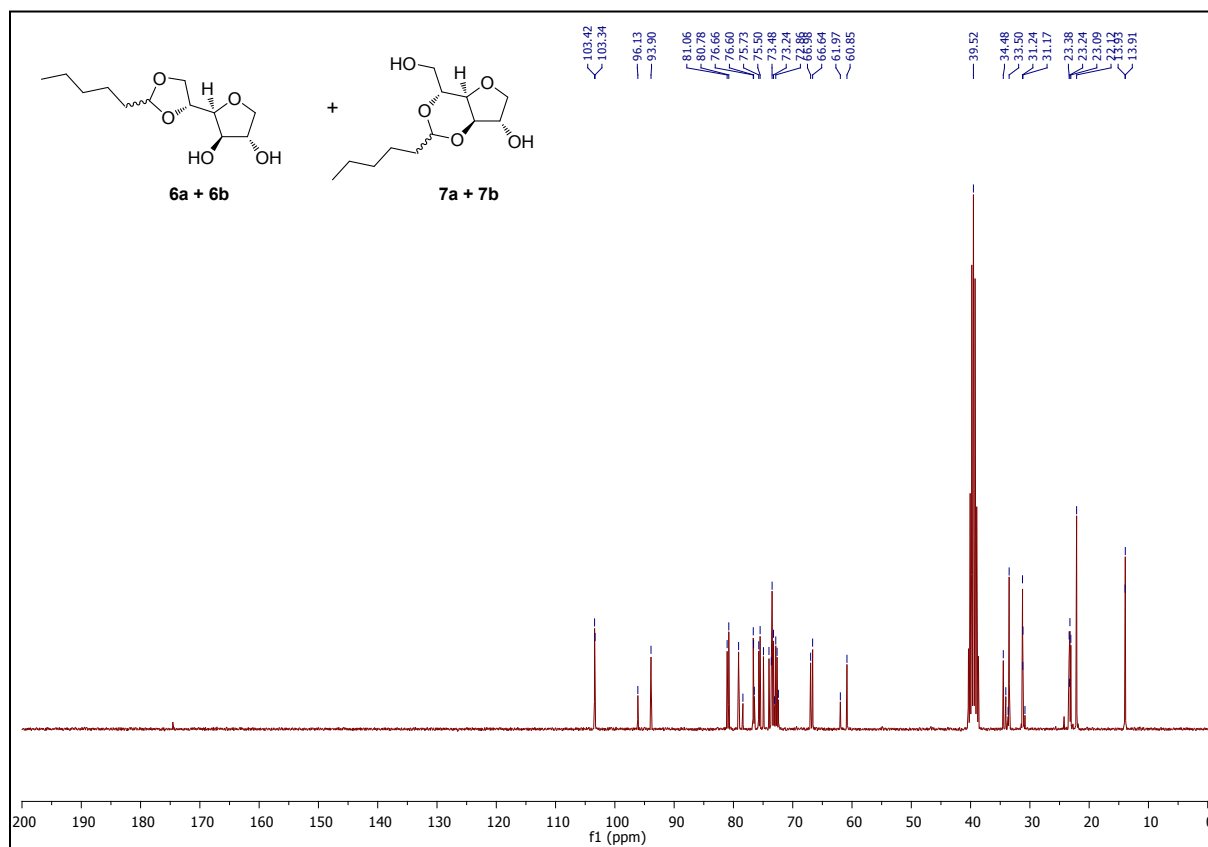
^{13}C NMR (125 MHz, d_6 -DMSO) **3,5-*O*-pentylidene-1,4-D-sorbitan 5a or 5b**



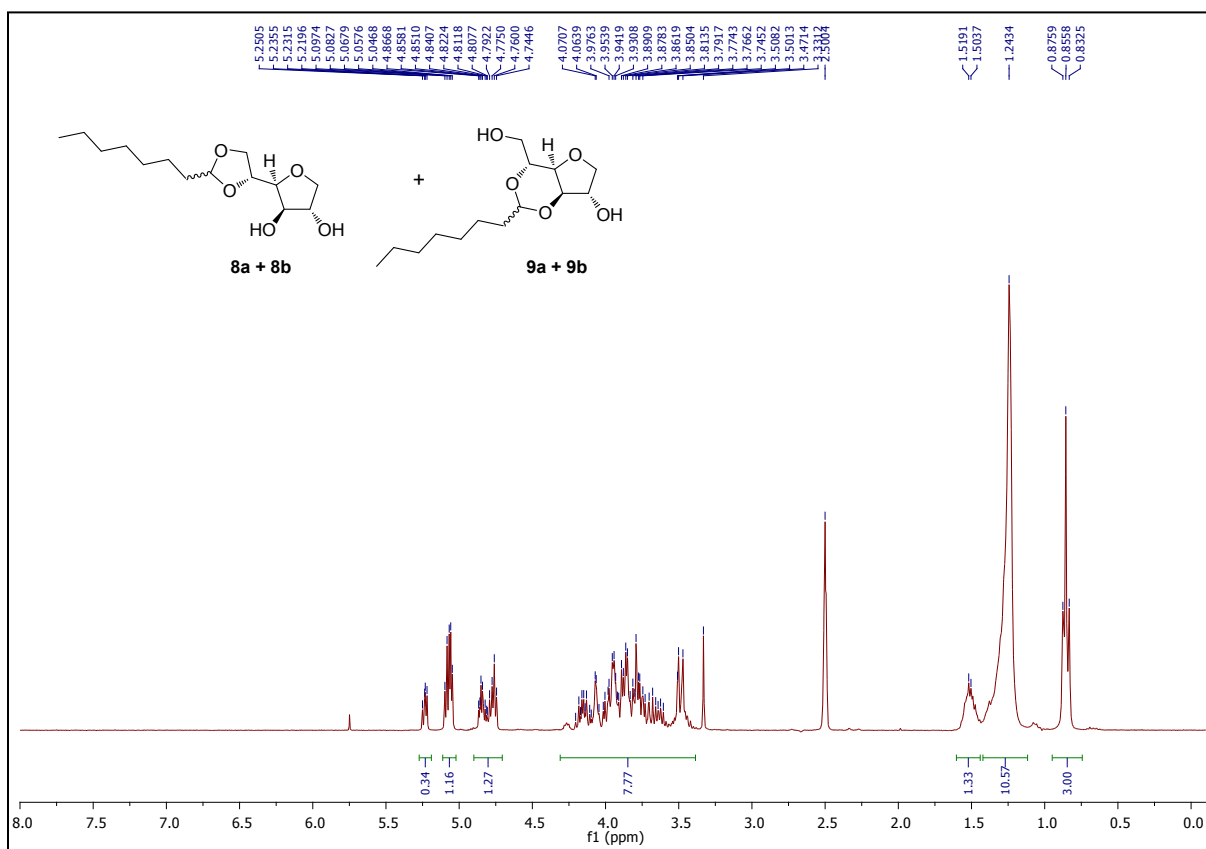
¹H NMR (300 MHz, *d*₆-DMSO) **5,6-*O*-Hexylidene-1,4-D-sorbitan 6a and 6b** and **3,5-*O*-hexylidene-1,4-D-sorbitan 7a and 7b**



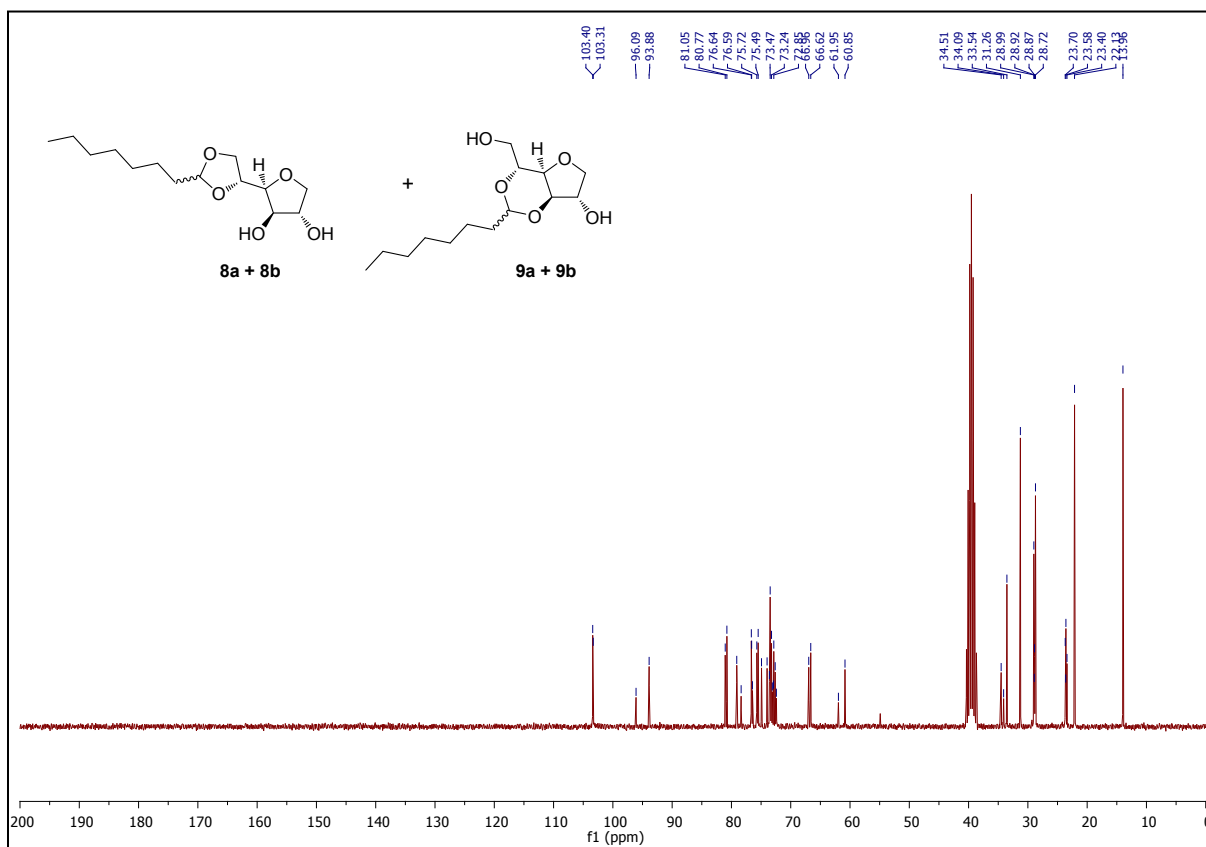
¹³C NMR (75 MHz, *d*₆-DMSO) **5,6-*O*-Hexylidene-1,4-D-sorbitan 6a and 6b** and **3,5-*O*-hexylidene-1,4-D-sorbitan 7a and 7b**



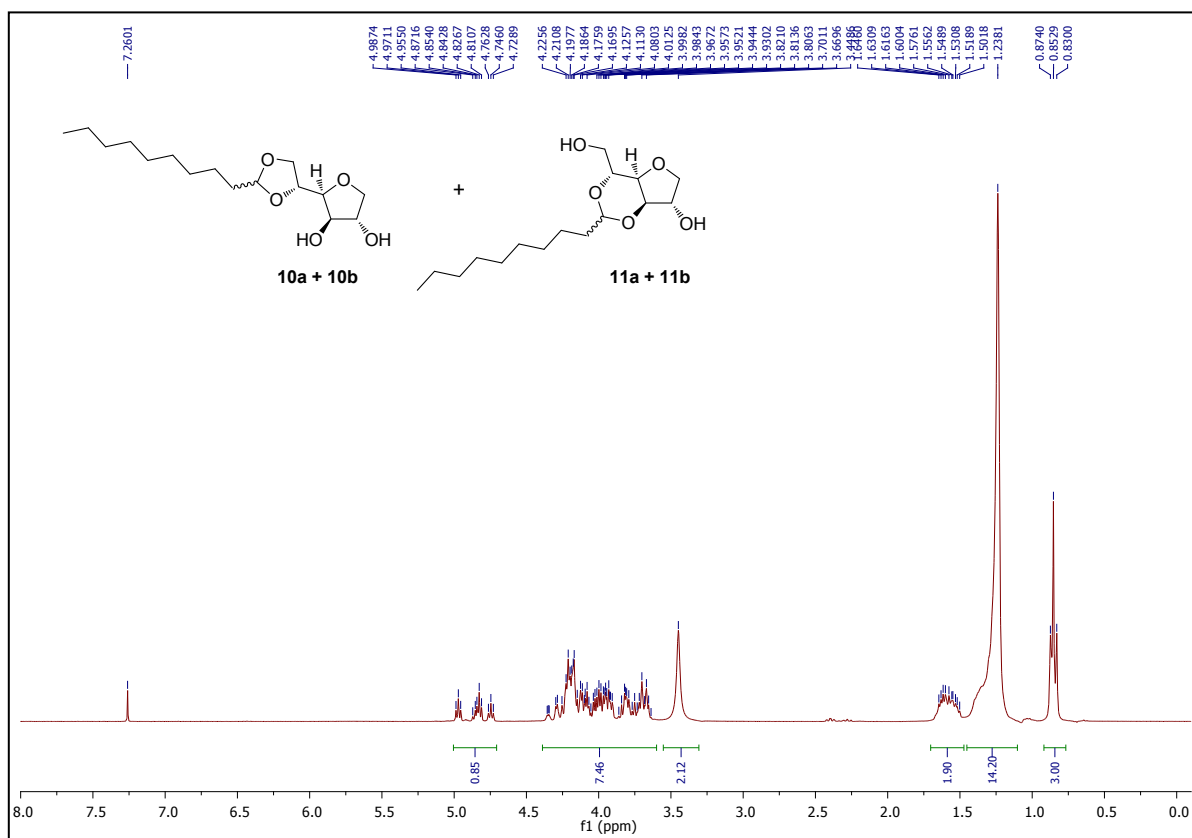
¹H NMR (300 MHz, *d*₆-DMSO) **5,6-*O*-Octylidene-1,4-D-sorbitan 8a and 8b** and **3,5-*O*-octylidene-1,4-D-sorbitan 9a and 9b**



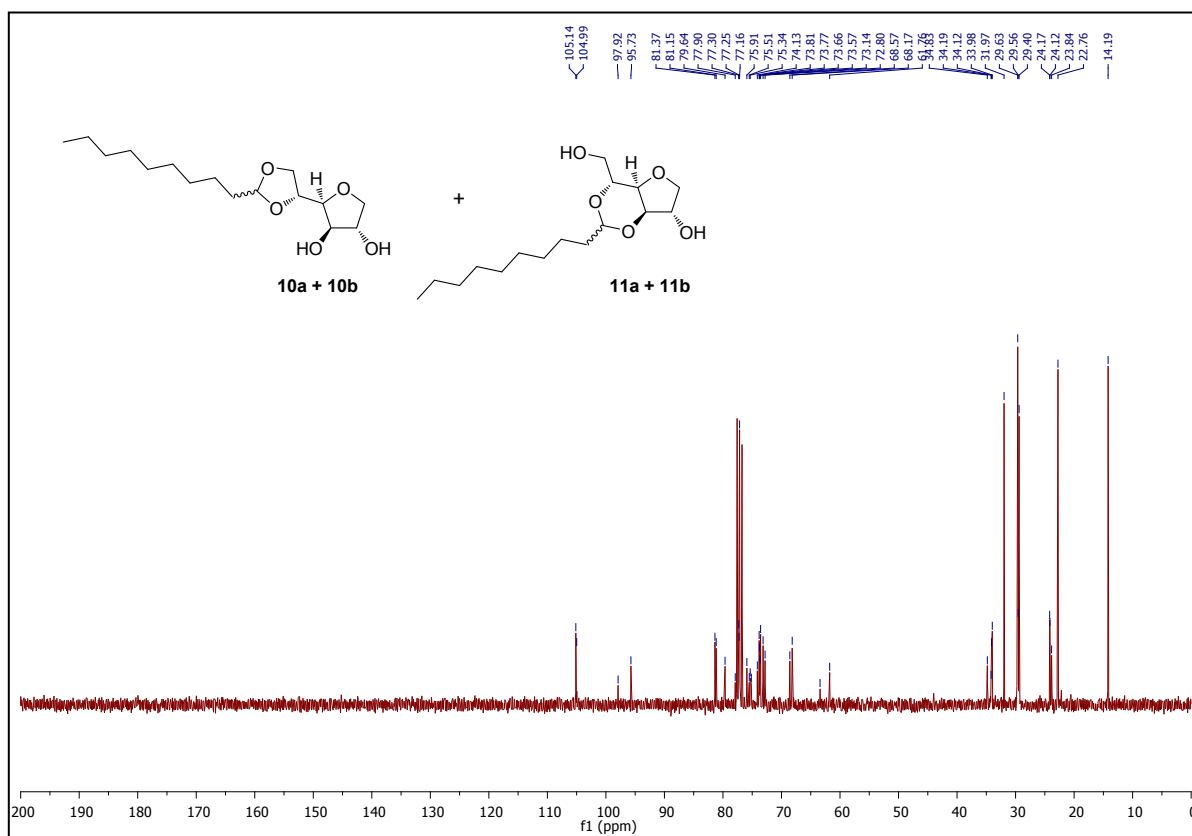
¹³C NMR (75 MHz, *d*₆-DMSO) **5,6-*O*-Octylidene-1,4-D-sorbitan 8a and 8b** and **3,5-*O*-octylidene-1,4-D-sorbitan 9a and 9b**



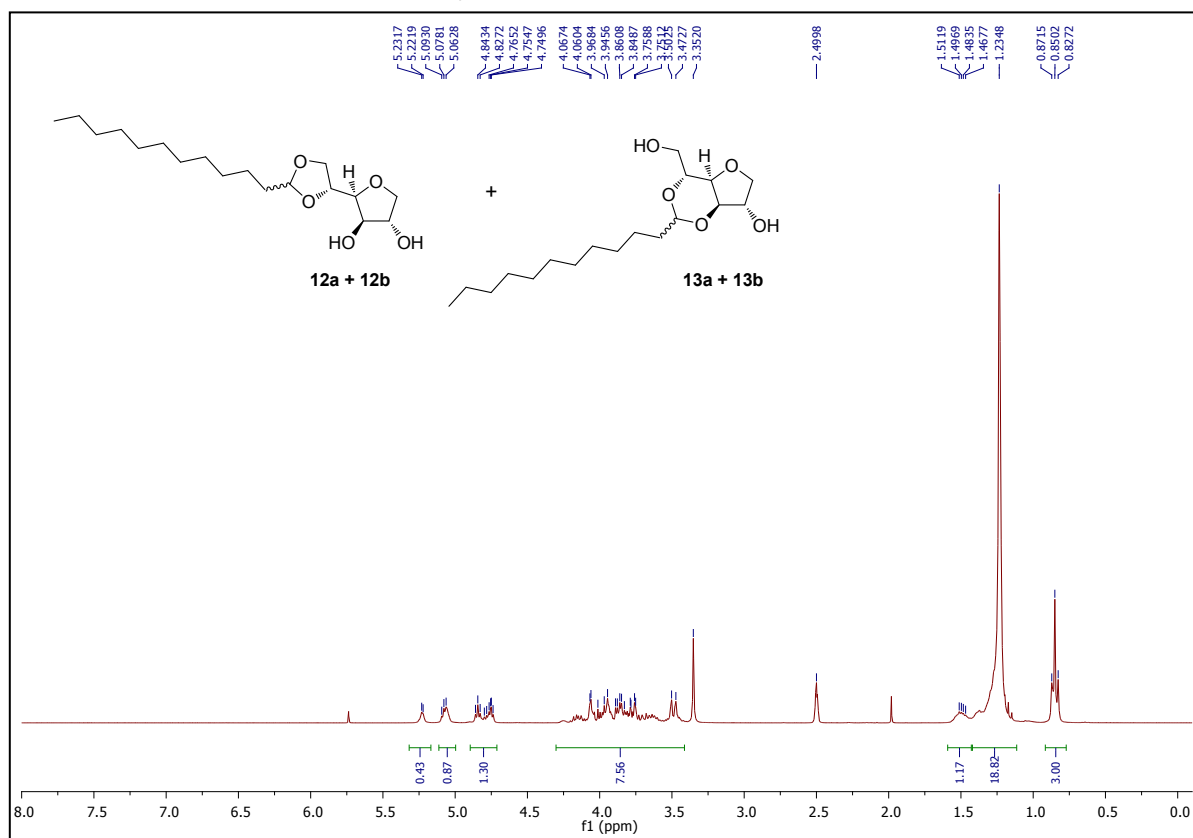
¹H NMR (300 MHz, CDCl₃) **5,6-*O*-Decylidene-1,4-d-sorbitan 10a and 10b** and **3,5-*O*-decylidene-1,4-d-sorbitan 11a and 11b**



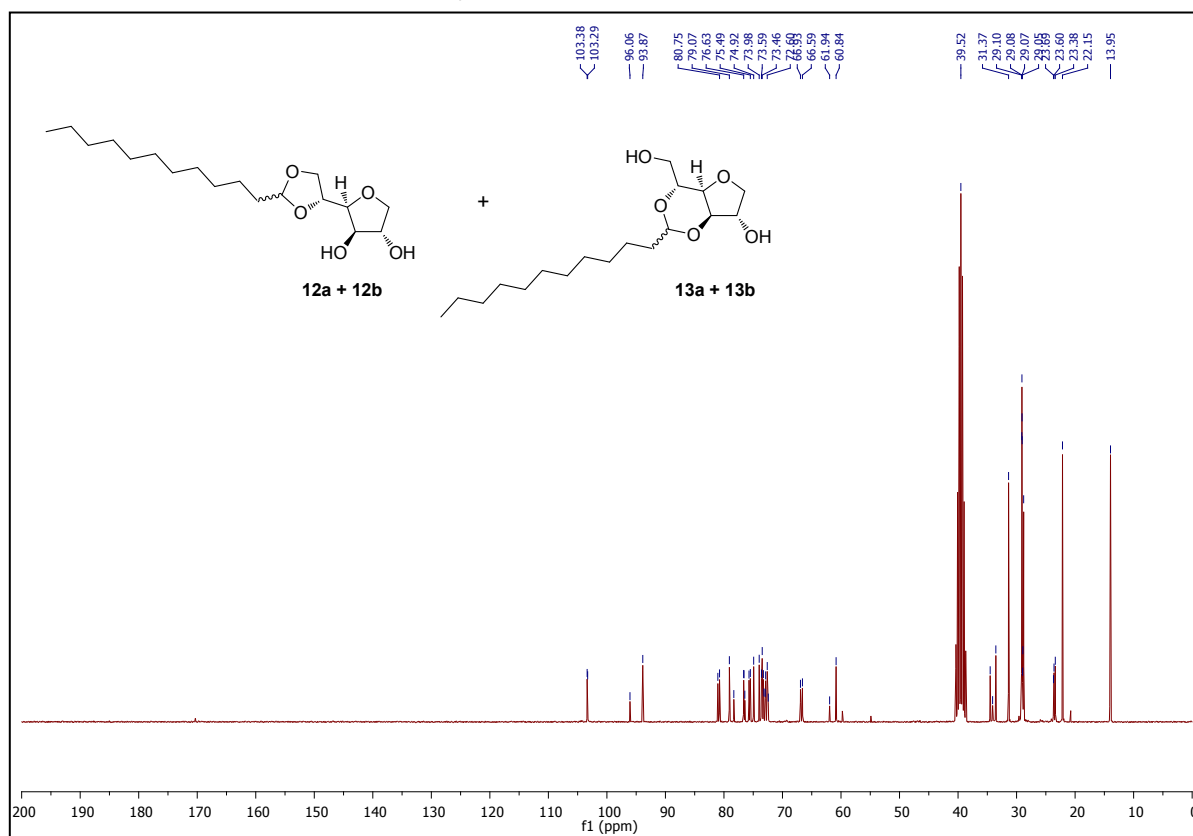
¹³C NMR (75 MHz, CDCl₃) **5,6-*O*-Decylidene-1,4-d-sorbitan 10a and 10b** and **3,5-*O*-decylidene-1,4-d-sorbitan 11a and 11b**



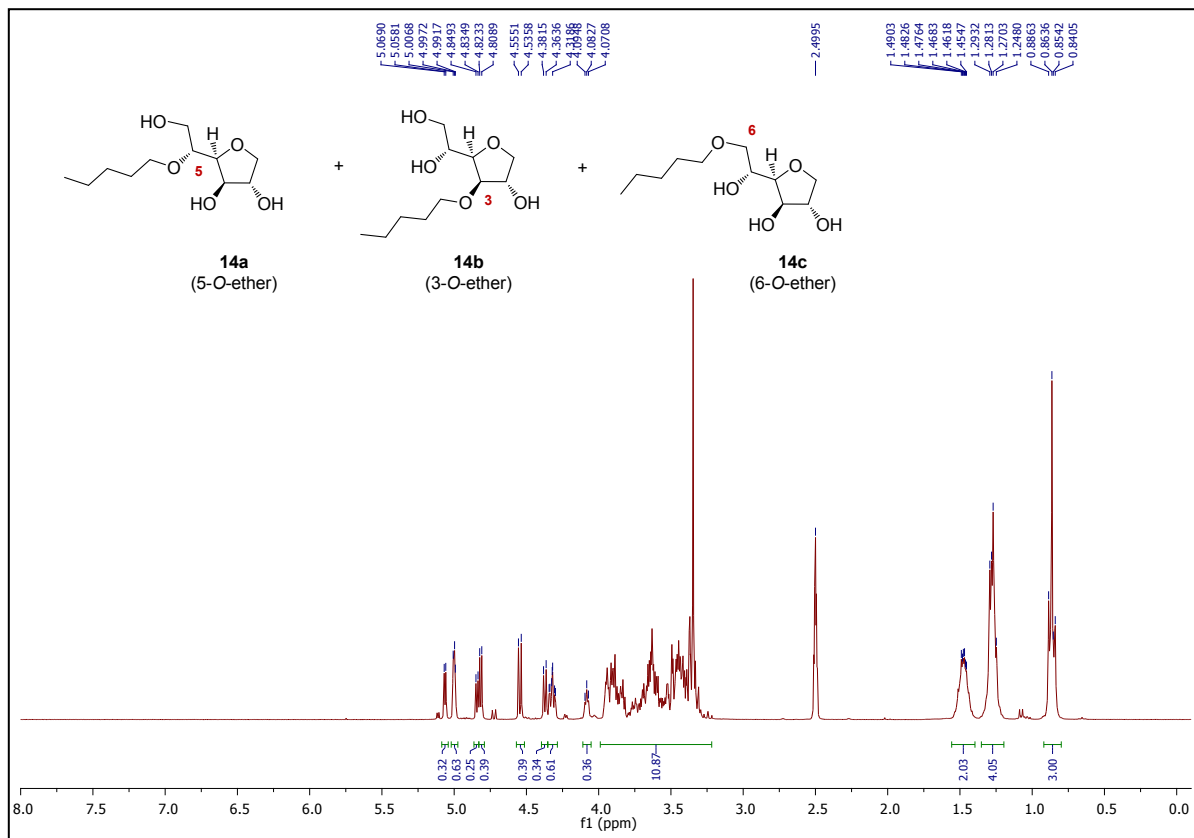
¹H NMR (300 MHz, *d*₆-DMSO) **5,6-*O*-Dodecylidene-1,4-D-sorbitan 12a and 12b** and **3,5-*O*-dodecylidene-1,4-D-sorbitan 13a and 13b**



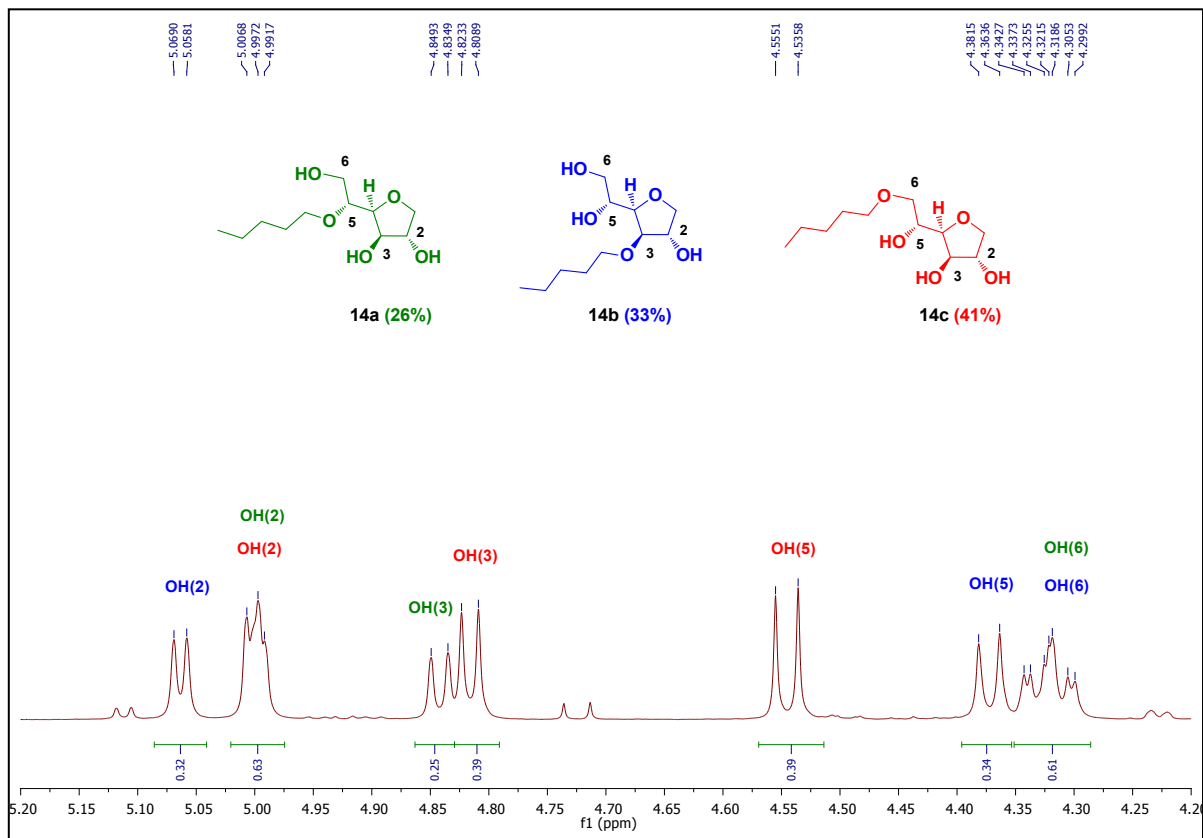
¹³C NMR (75 MHz, *d*₆-DMSO) **5,6-*O*-Dodecylidene-1,4-D-sorbitan 12a and 12b** and **3,5-*O*-dodecylidene-1,4-D-sorbitan 13a and 13b**



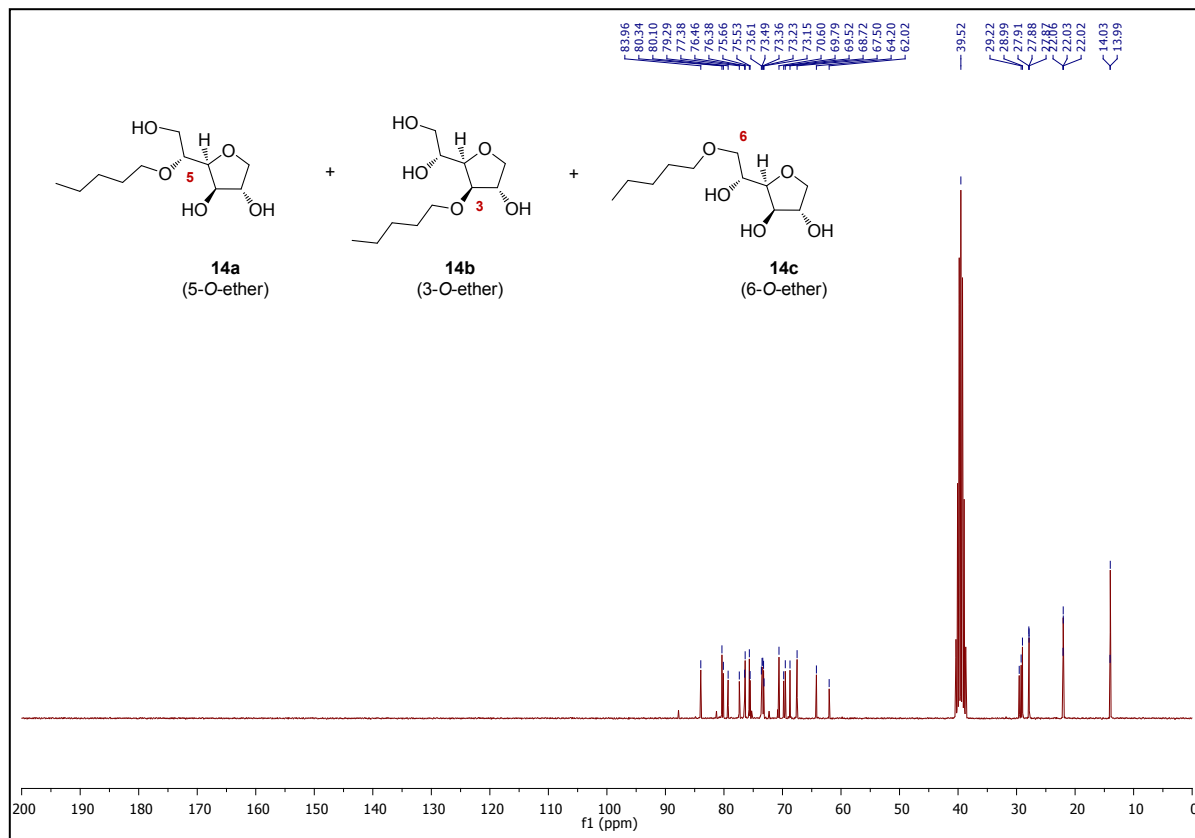
¹H NMR (300 MHz, d₆-DMSO) **Pentyl-1,4-D-sorbitan 14a-c**



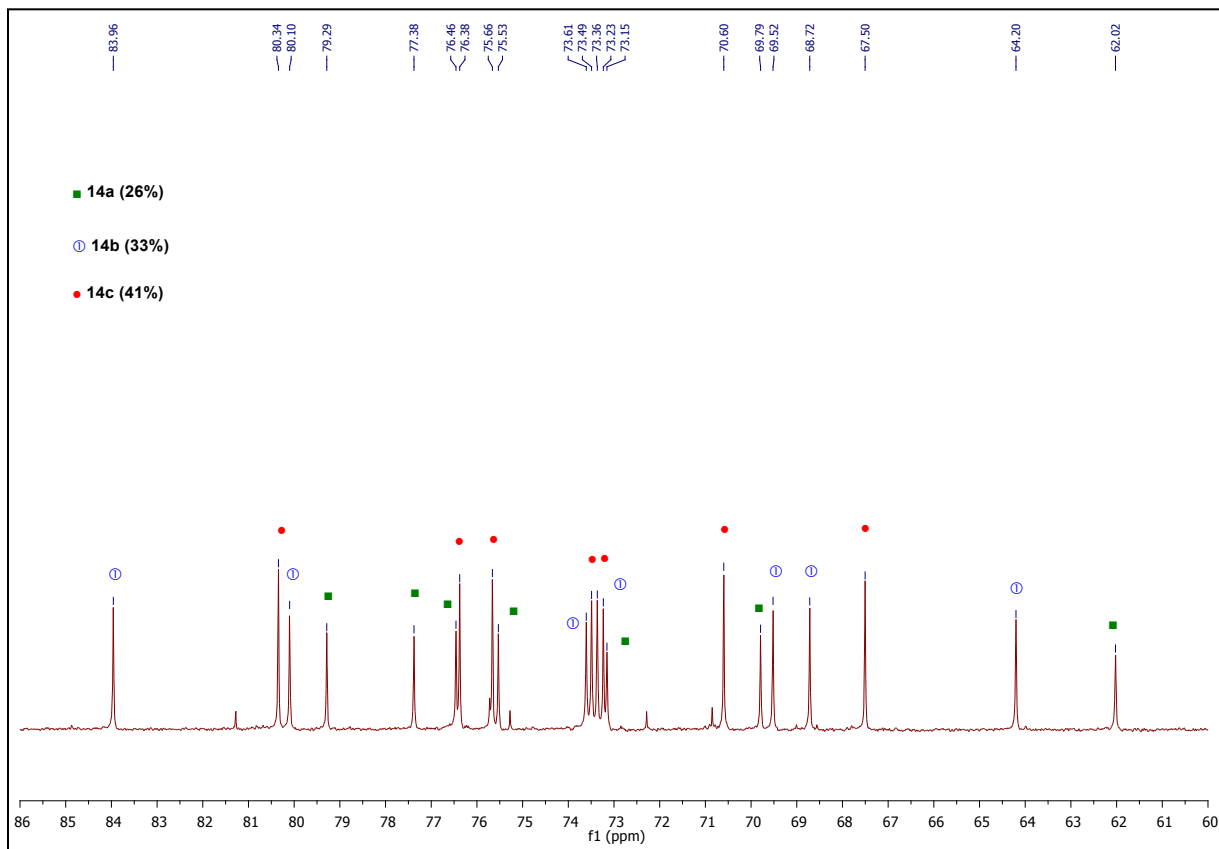
zoom 5.20-4.20 ppm



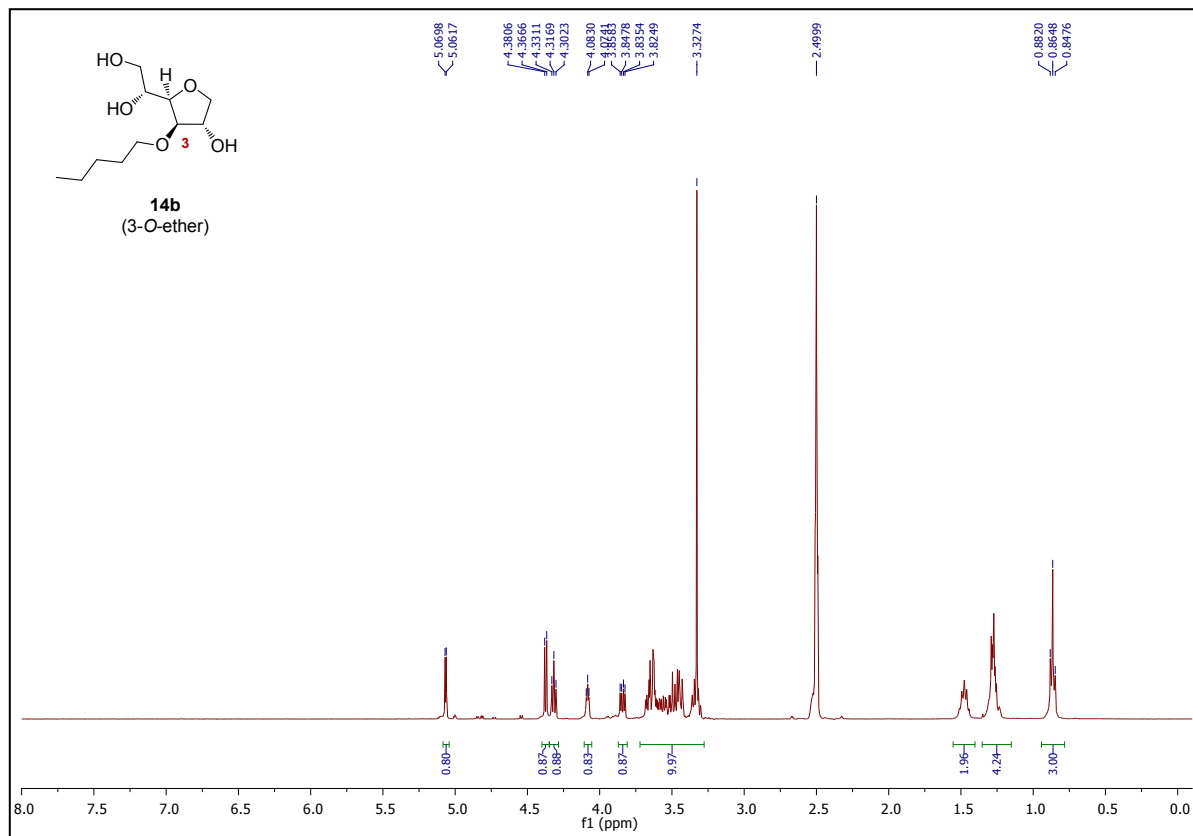
¹³C NMR (75 MHz, d₆-DMSO) **Pentyl-1,4-D-sorbitan 14a-c**



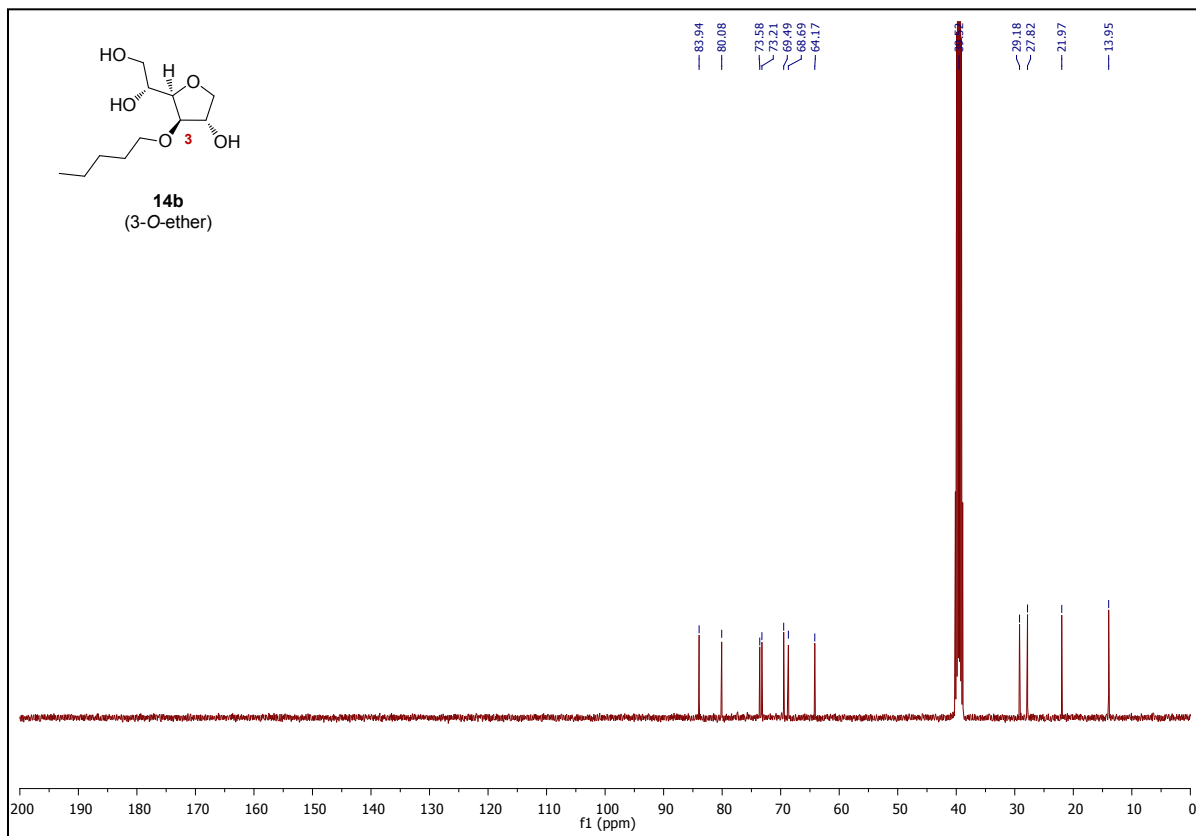
Zoom 86-60 ppm



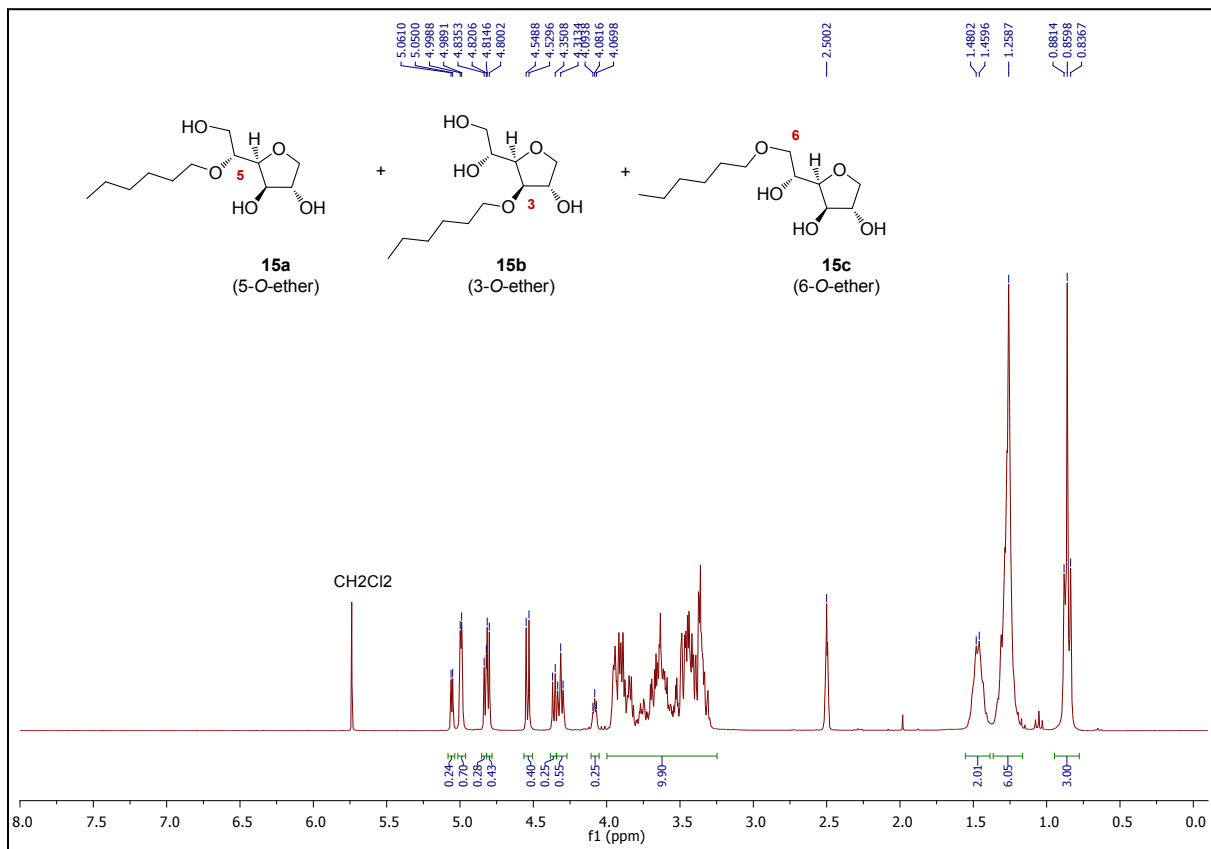
¹H NMR (400 MHz, d₆-DMSO) 3-O-Pentyl-1,4-D-sorbitan **14b**



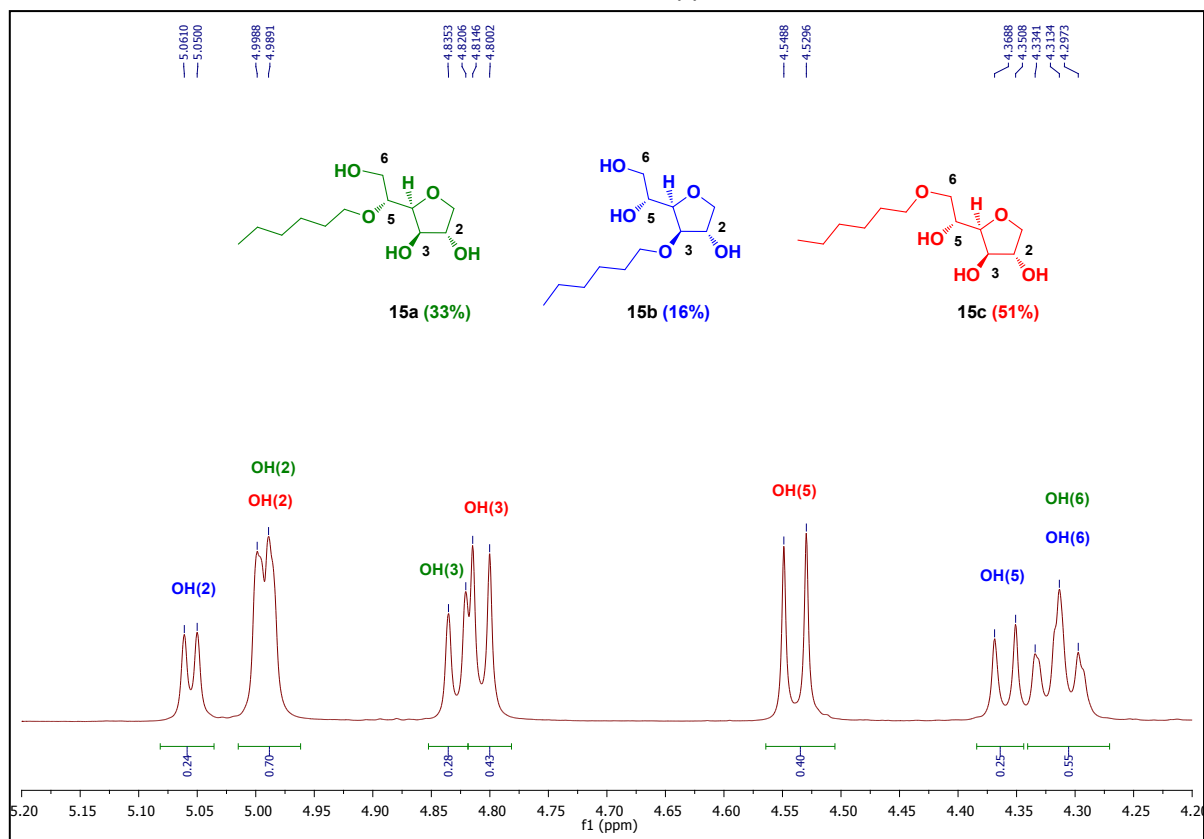
¹³C NMR (100 MHz, d₆-DMSO) 3-O-Pentyl-1,4-D-sorbitan **14b**



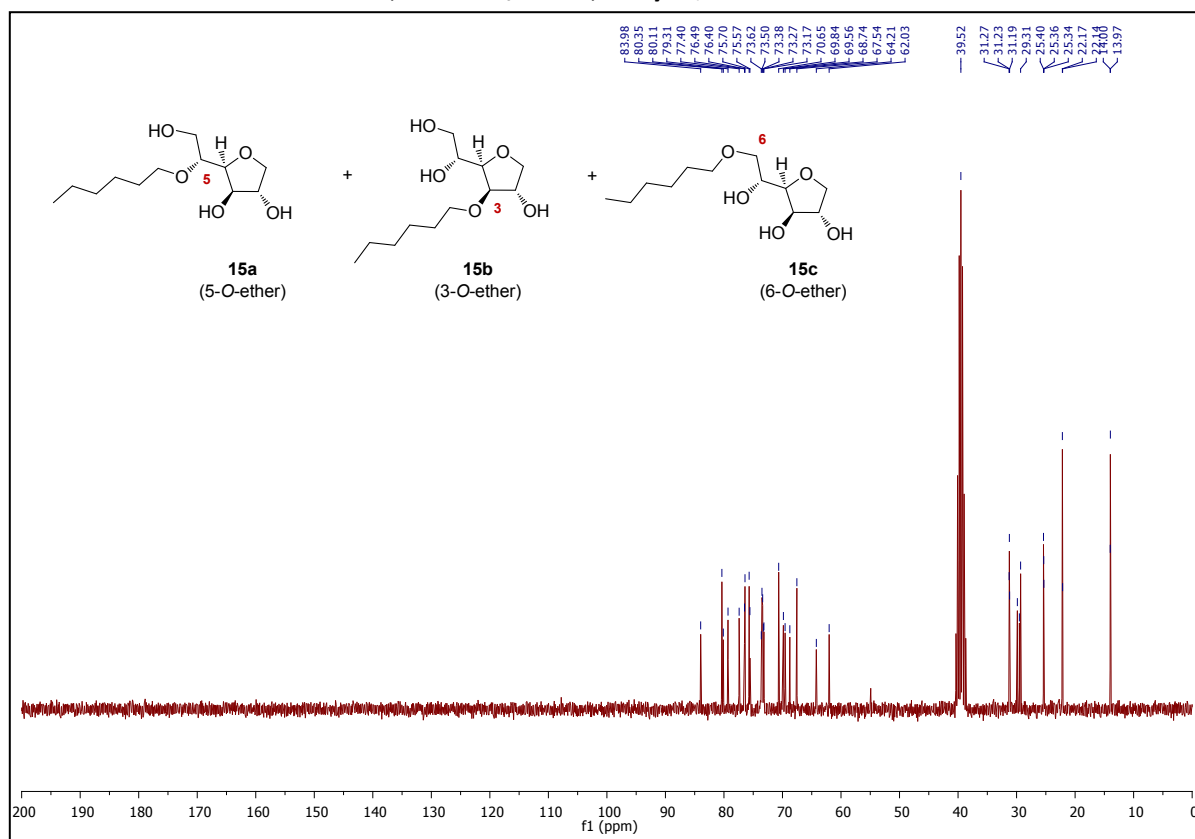
¹H NMR (300 MHz, d₆-DMSO) Hexyl-1,4-D-sorbitan 15a-c



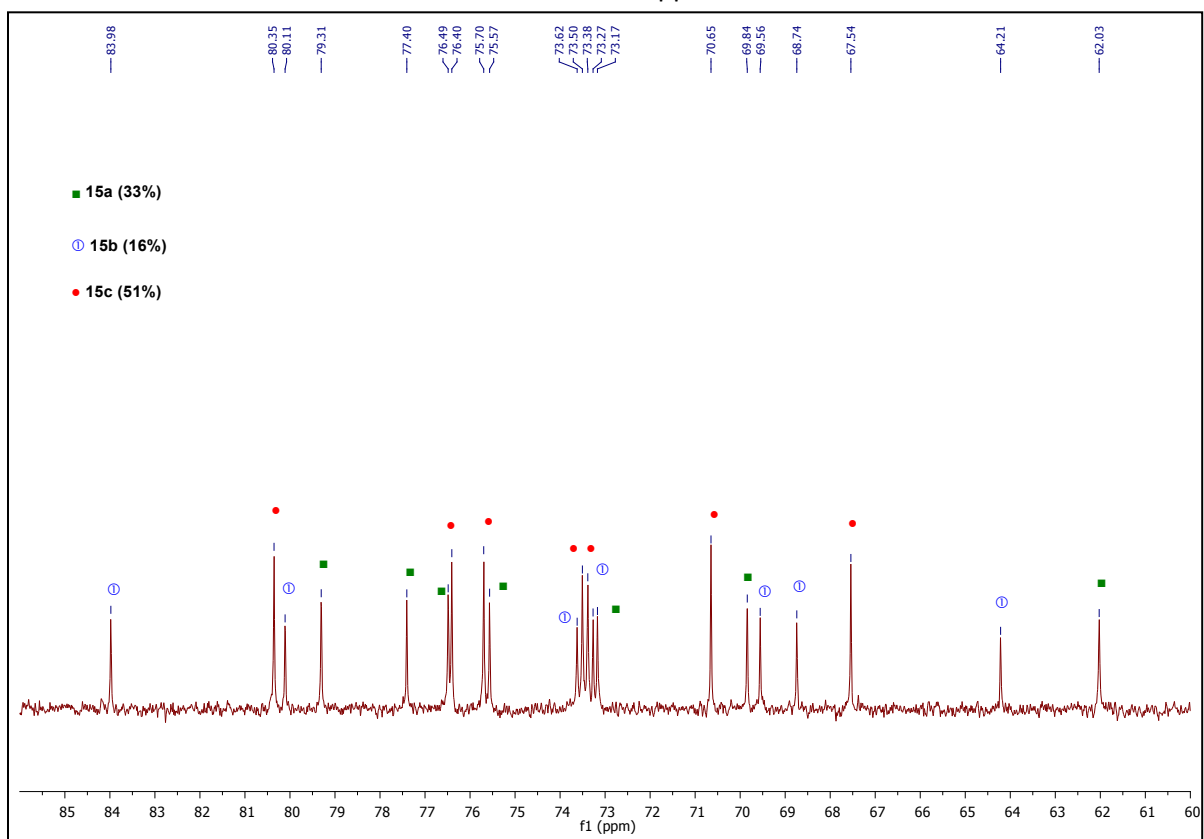
zoom 5.20-4.20 ppm



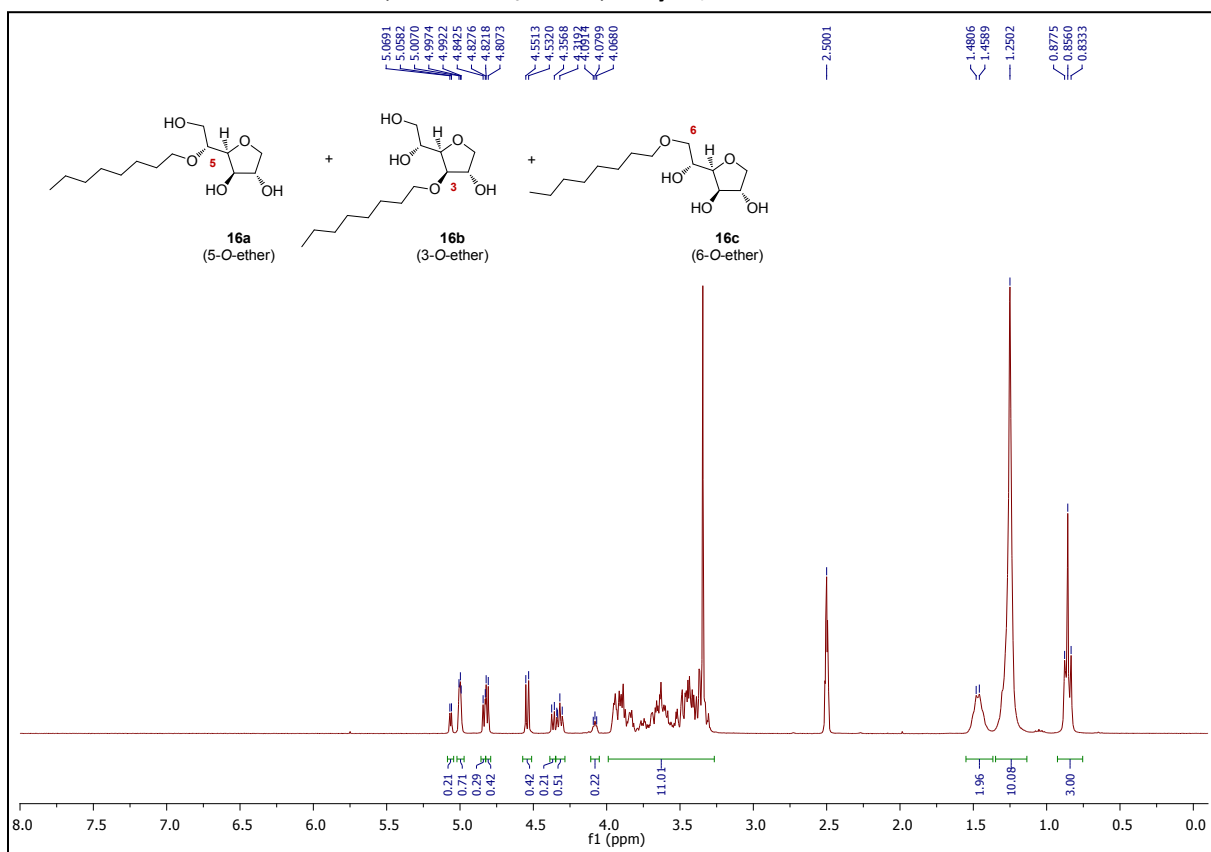
¹³C NMR (75 MHz, d₆-DMSO) Hexyl-1,4-D-sorbitan 15a-c



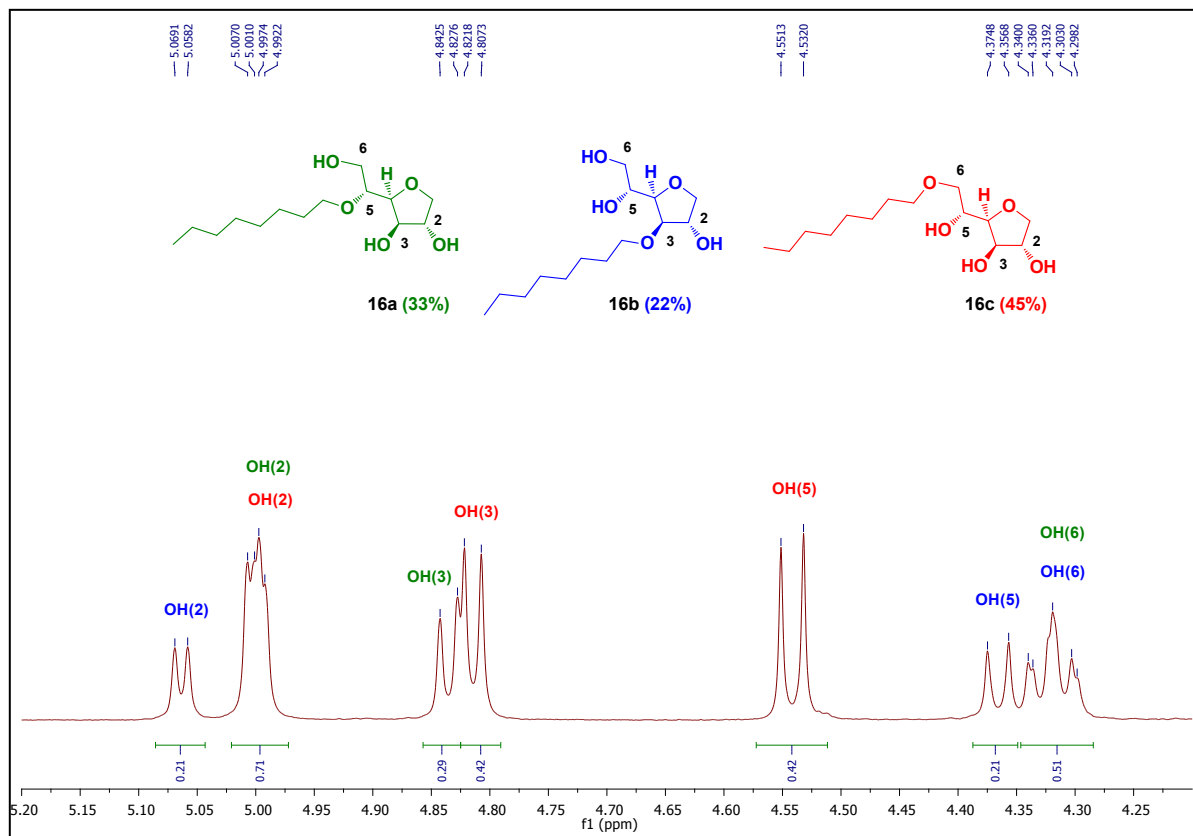
Zoom 86-60 ppm



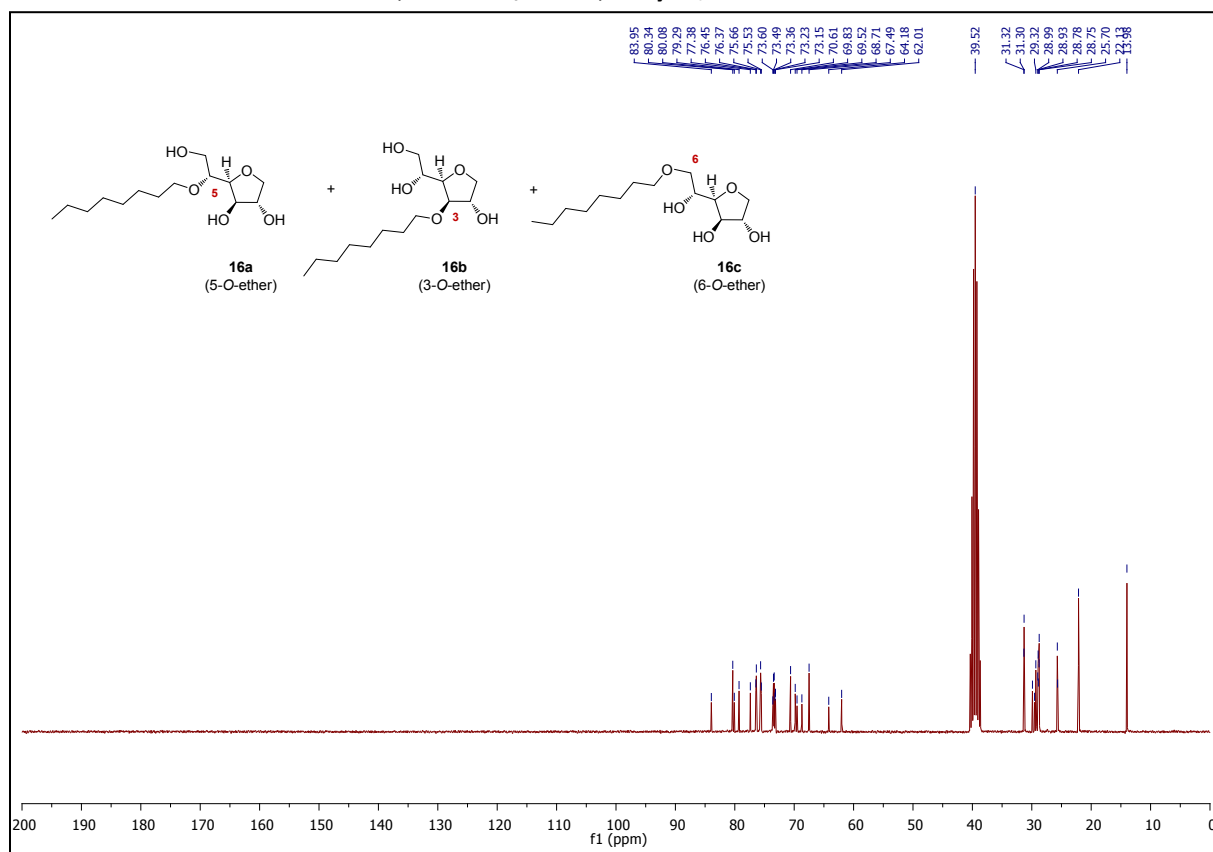
¹H NMR (300 MHz, d₆-DMSO) **Octyl-1,4-D-sorbitan 16a-c**



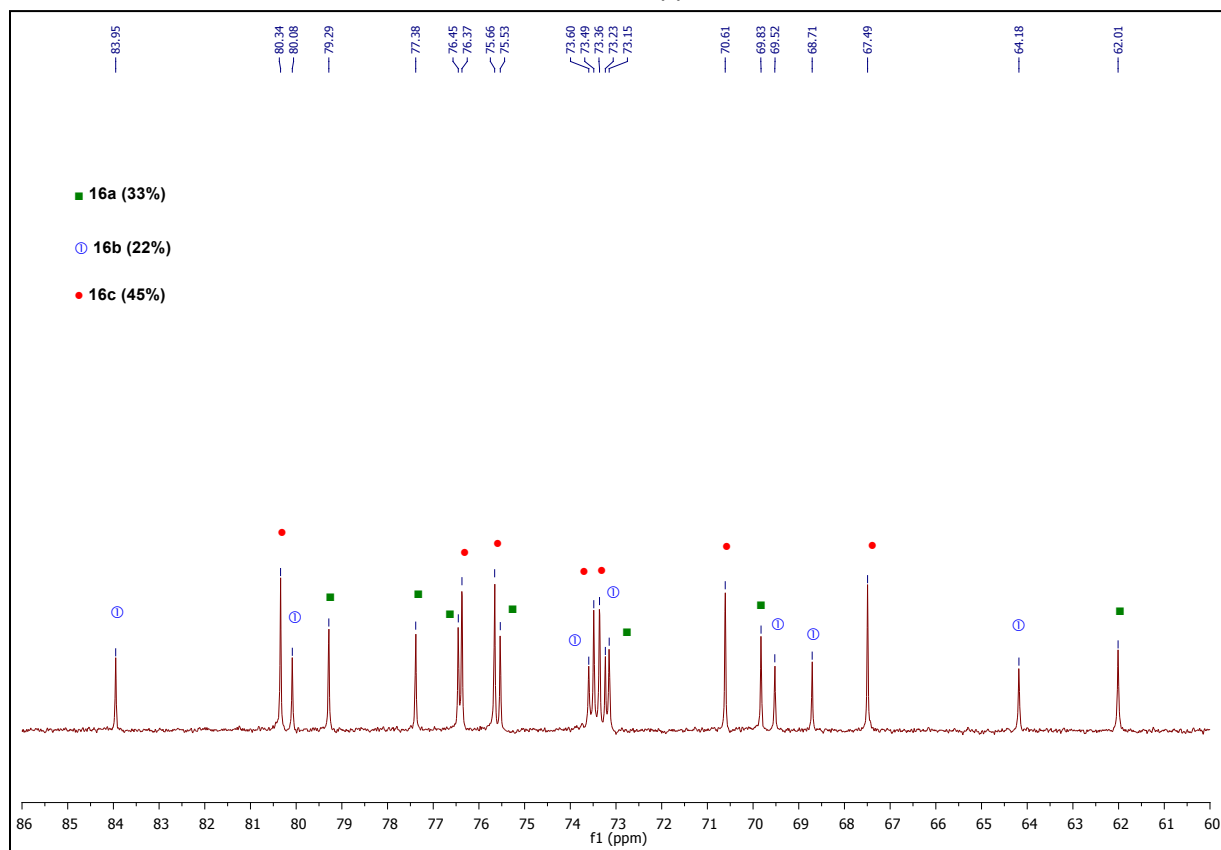
zoom 5.20-4.20 ppm



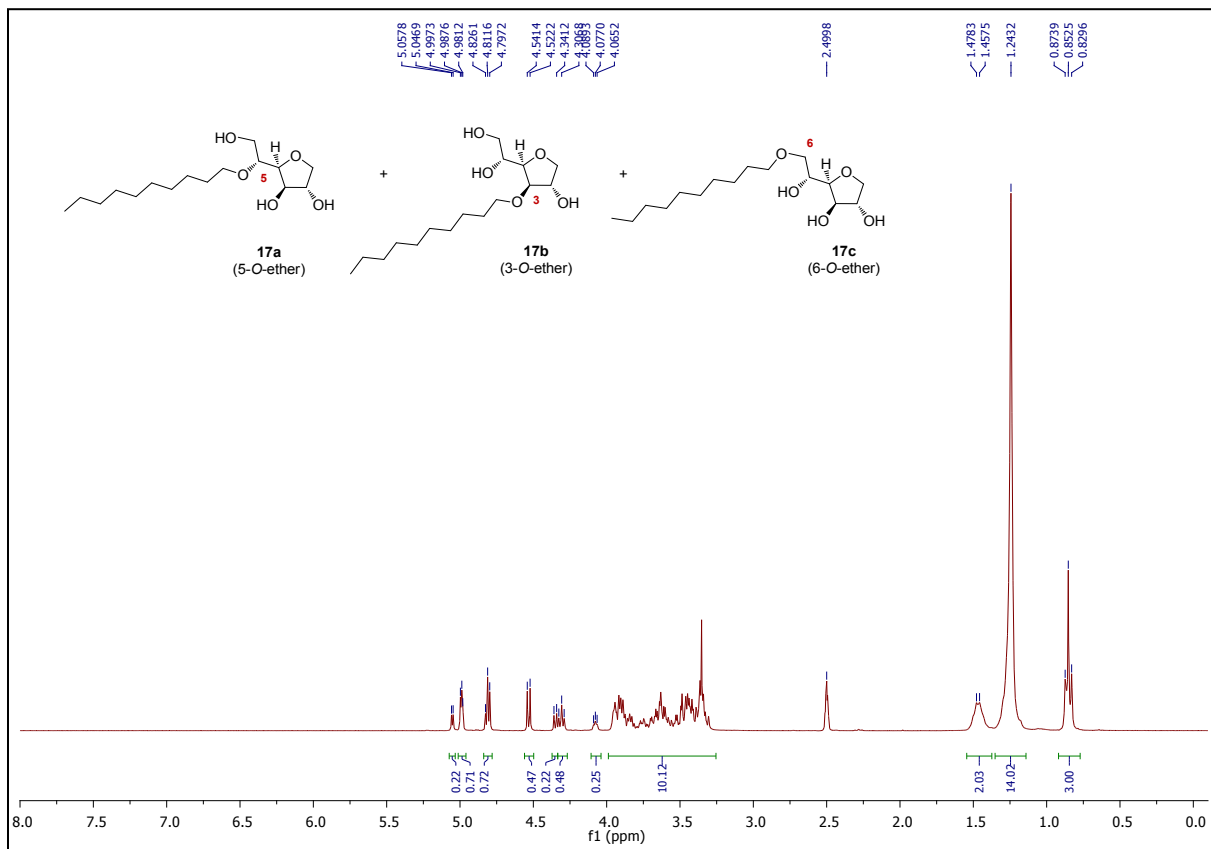
¹³C NMR (75 MHz, d₆-DMSO) **Octyl-1,4-D-sorbitan 16a-c**



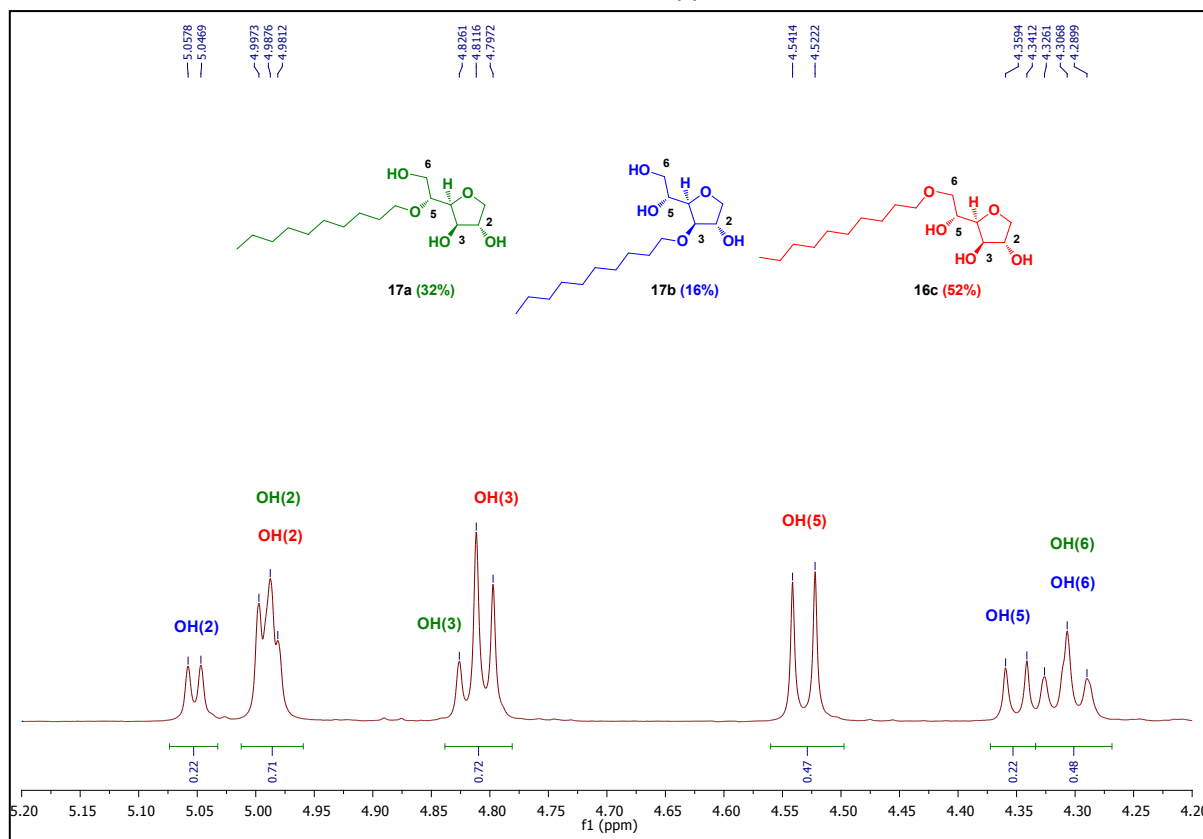
Zoom 86-60 ppm



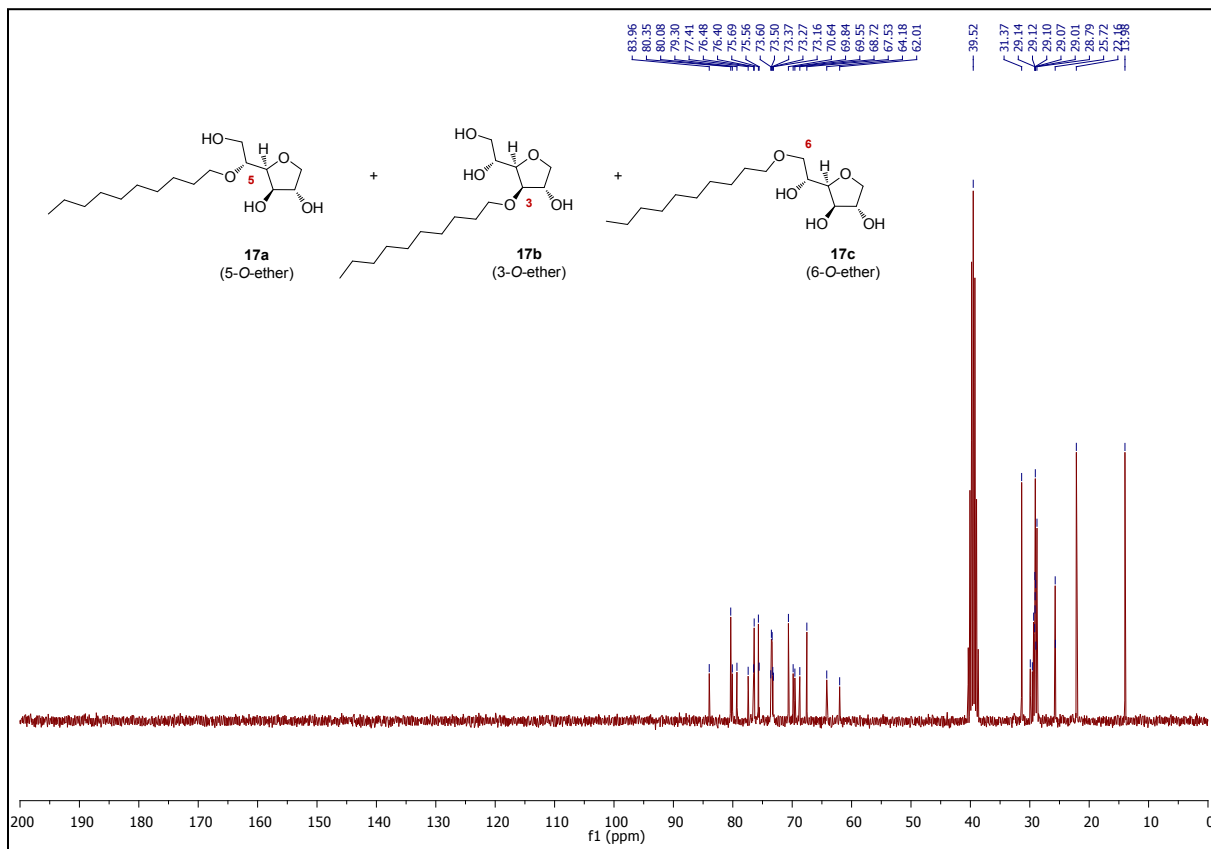
¹H NMR (300 MHz, d₆-DMSO) **Decyl-1,4-D-sorbitan 17a-c**



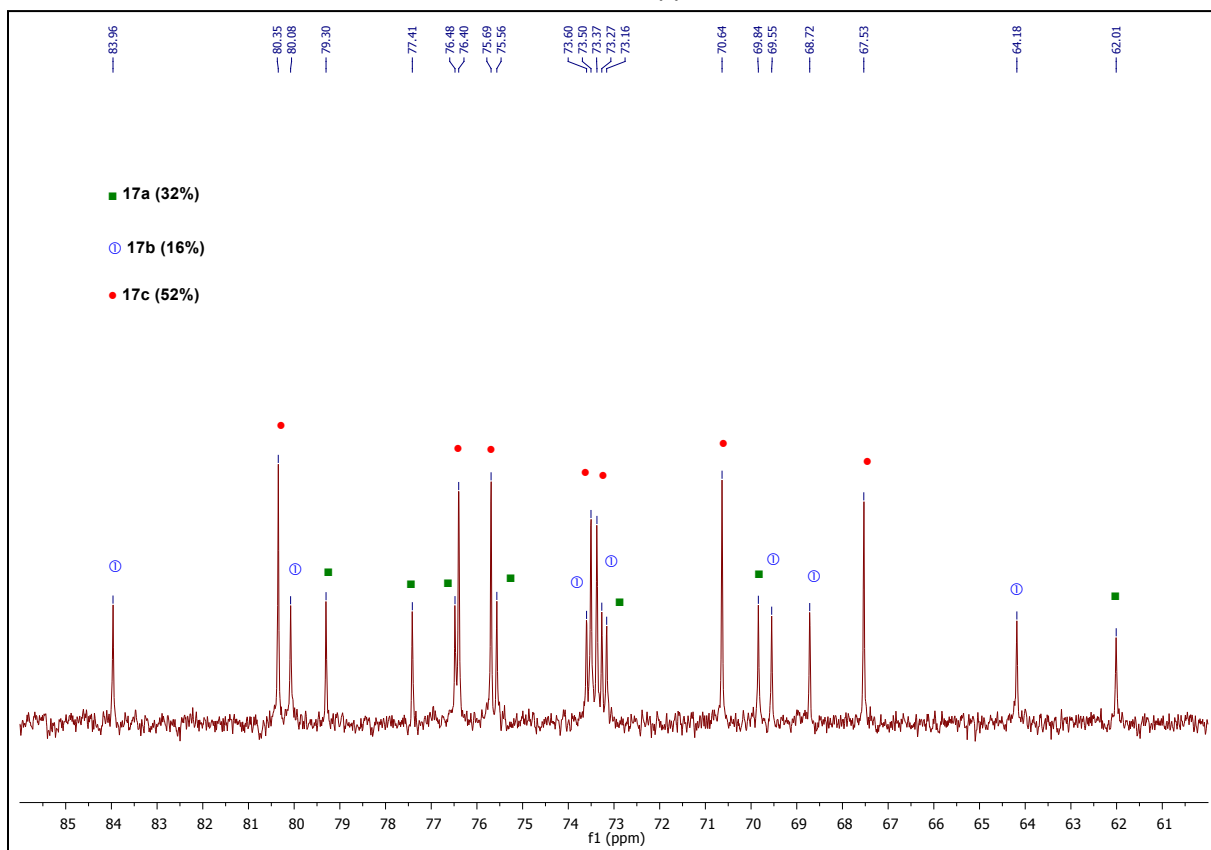
zoom 5.20-4.20 ppm



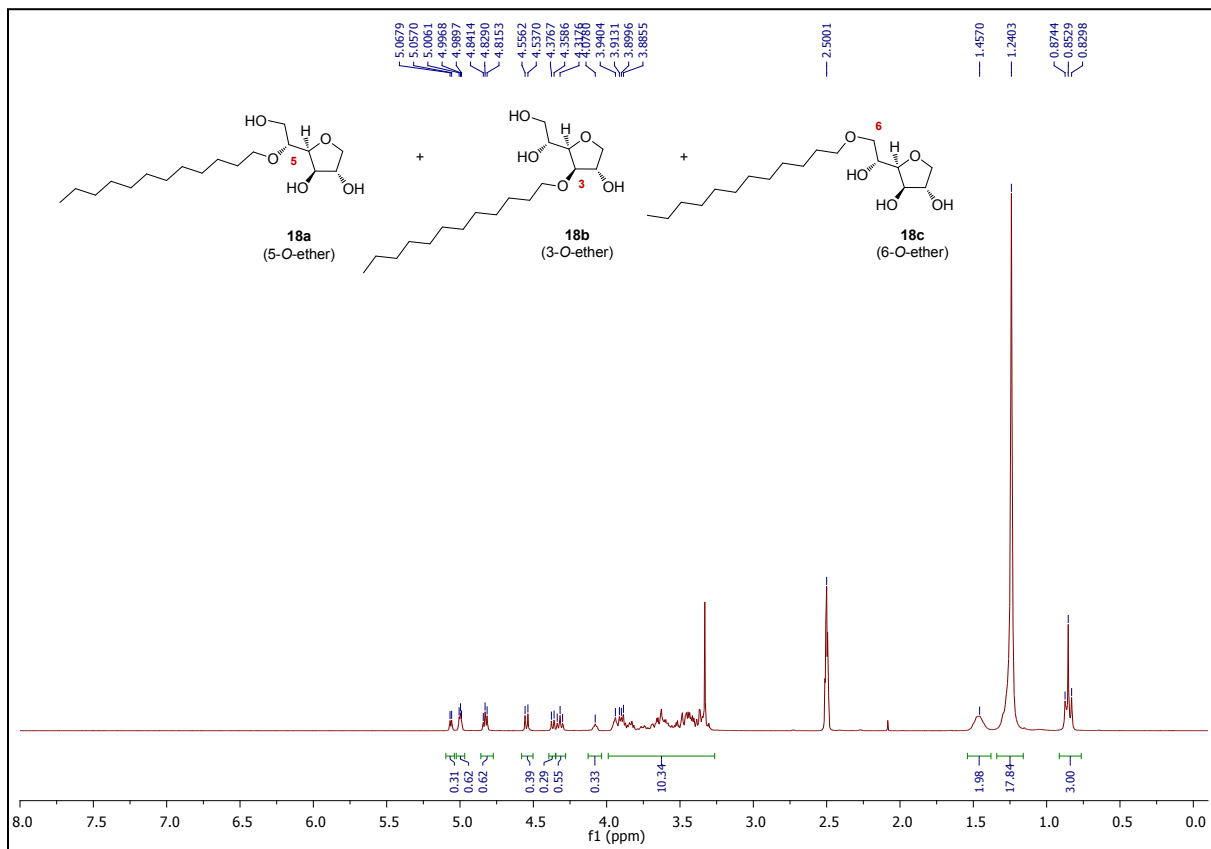
¹³C NMR (75 MHz, d₆-DMSO) Decyl-1,4-D-sorbitan 17a-c



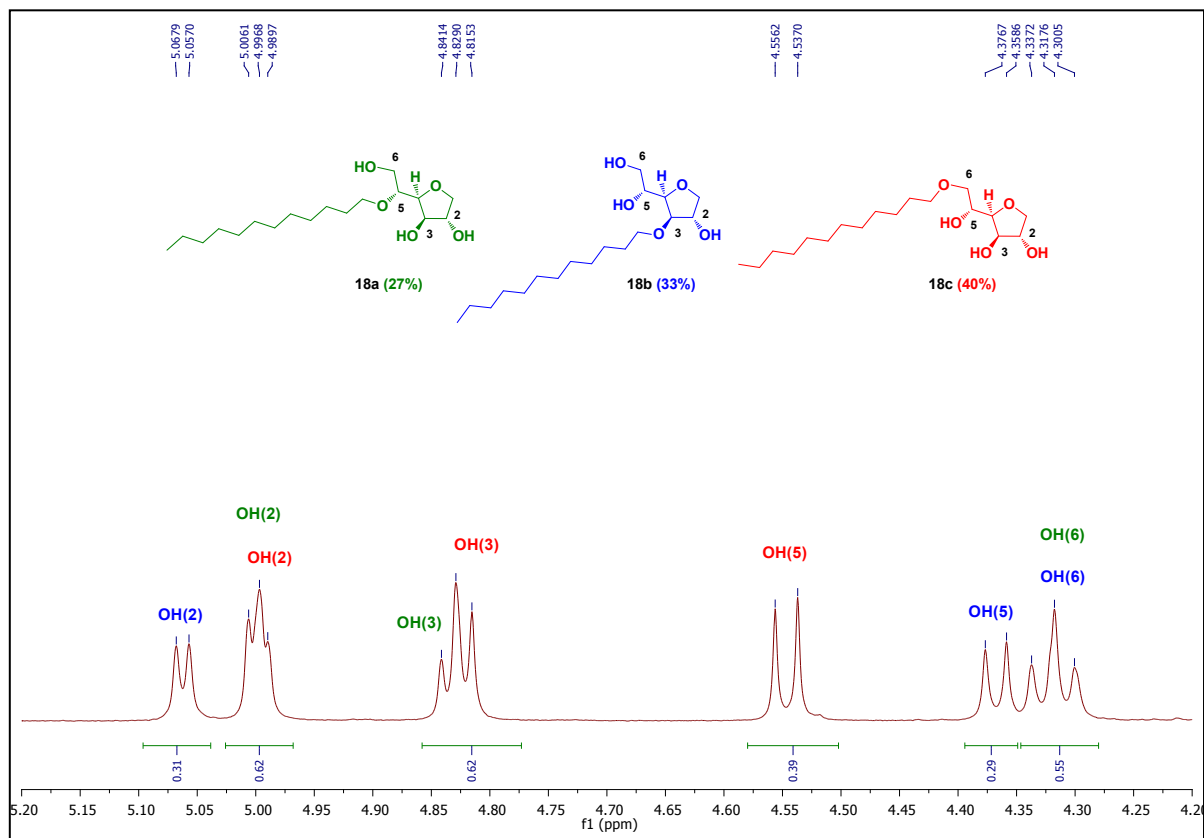
Zoom 86-60 ppm



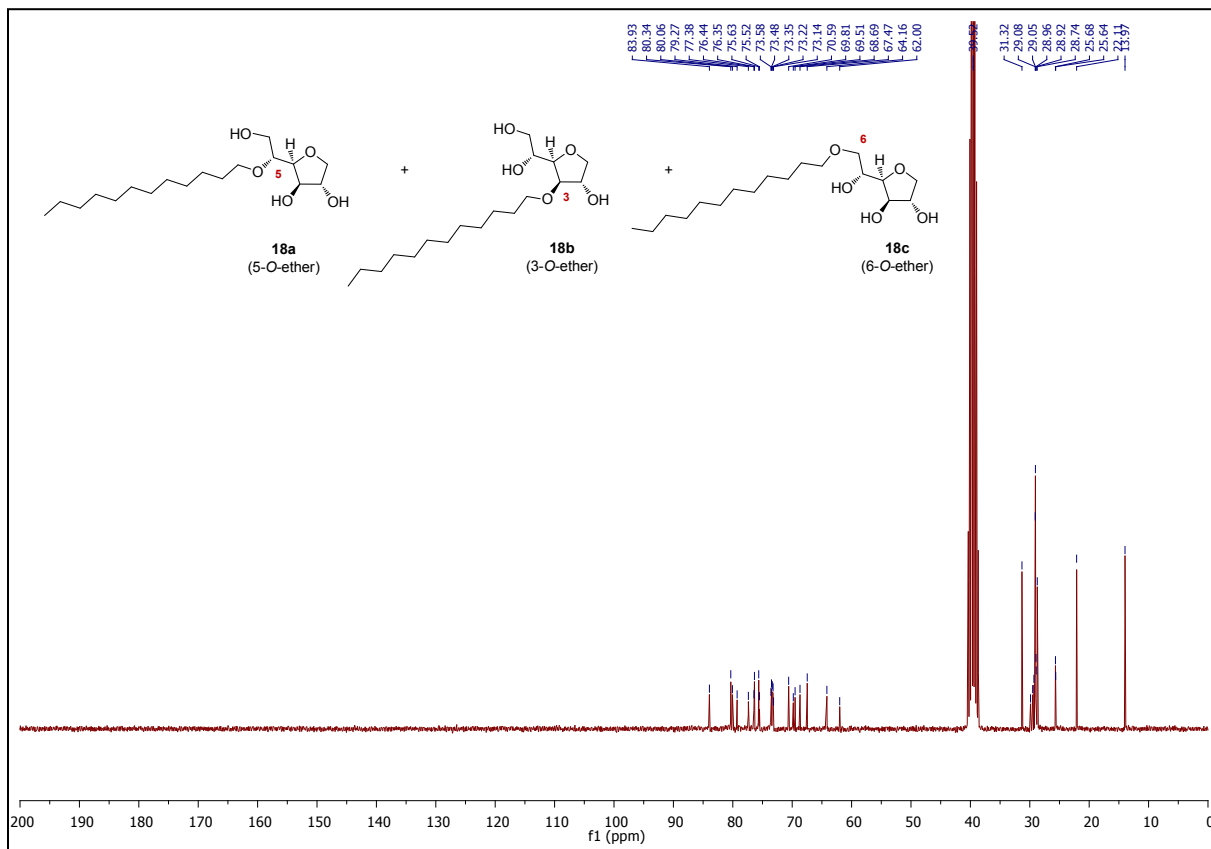
¹H NMR (300 MHz, d₆-DMSO) Dodecyl-1,4-D-sorbitan **18a-c**



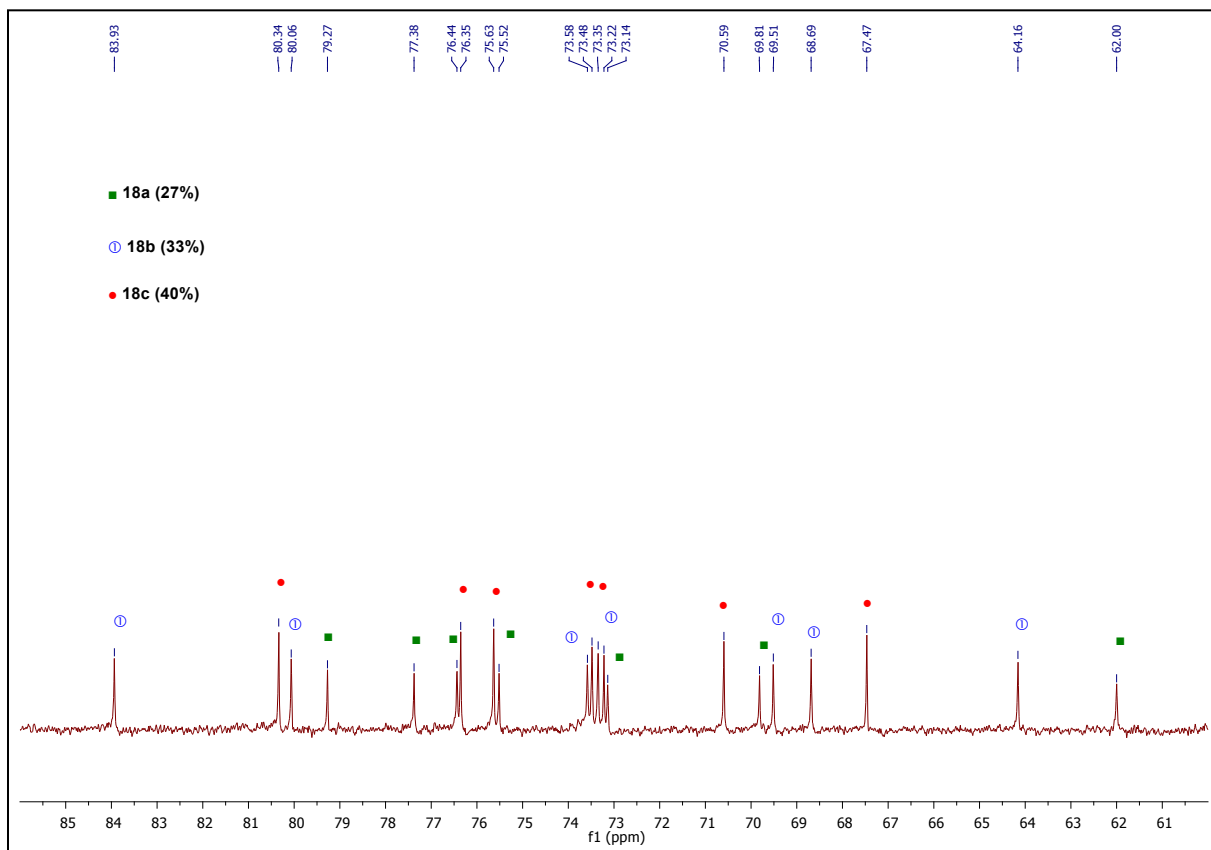
zoom 5.20-4.20 ppm



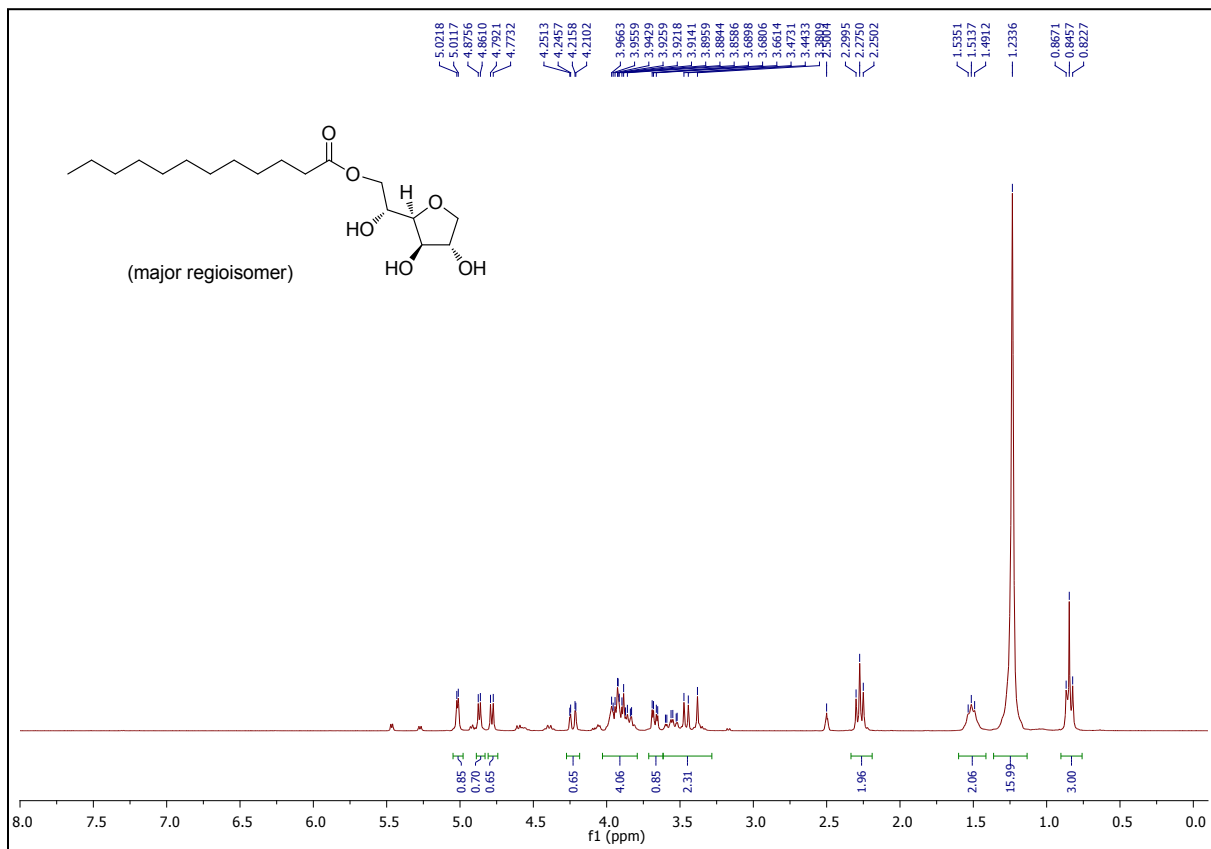
¹³C NMR (75 MHz, d₆-DMSO) Dodecyl-1,4-D-sorbitan 18a-c



Zoom 86-60 ppm



¹H NMR (300 MHz, *d*₆-DMSO) 6-*O*-Dodecanoyl-1,4-D-sorbitan



¹³C NMR (75 MHz, *d*₆-DMSO) 6-*O*-Dodecanoyl-1,4-D-sorbitan

