Electronic Supplementary Information

Syntheses of Sugar Poly(orthoesters) through Reverse Anomeric Effect

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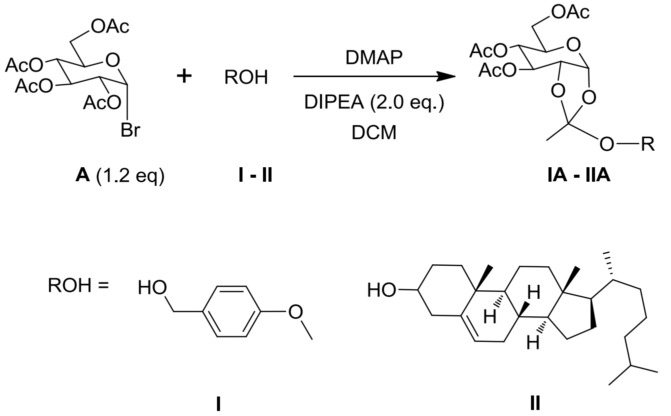
I. General Information

All chemicals and solvents were purchased from Sigma-Aldrich unless otherwise noted. Anhydrous dichloromethane (DCM) (99.8%) was purchased in capped Sureseal™ bottles, used without further purification, and stored under argon. Other solvents and reagents were used directly, unless otherwise noted. All glassware utilized was flame-dried before use. Glass-backed TLC plates (Silica Gel 60 with a 254 nm fluorescent indicator) were used without further manipulation and stored over desiccant. Silica gel column chromatography was performed using flash silica gel (32-63 μm) and employed a solvent or solvent mixture with their polarities correlated with TLC mobility.

IR spectra were obtained on a Thermo Scientific Nicolet™ iS™50 Fourier-Transform Infrared (FT-IR) spectrometer using NaCl plates, with the sample being deposited from CH_2Cl_2. ^1H NMR spectra were recorded at 500 MHz on a Varian Inova 500 spectrometer, with tetramethylsilane (TMS) protons signal as a reference. ^{13}C NMR spectra were recorded at 126 MHz on a Varian Inova 500 spectrometer, with TMS carbons signal as a reference. Mass spectrometry was measured with a Waters LCT Premier™ XE unit. The optical rotation values were measured on a DigiPol-DP1A11 polarimeter (Rudolph Instruments).

Gel permeation chromatography (GPC) analyses were conducted using a Viscotek GPC system equipped with a TDA270 dual-detector and a column system comprised of one PAS102 and one PAS103 column (Polyanalytik Inc.). The system was equilibrated at 35 °C in THF, which served as a solvent and an eluent with a flow rate of 1.0 mL min^{-1}. Polymer solutions were prepared at a known concentration (*ca.* 3 mg mL^{-1}). Data collections and analyses were performed by using OmniSEC software (Malvern Inc.). The GPC system was calibrated using polystyrene standards with molecular weights of 1.25, 3.25, 9.24, 28.5 and 66.0 kDa and PDI of 1.05-1.07 (Showa Denko K. K. Japan).

II. Small molecule studies



Scheme 1S. The syntheses of sugar orthoesters using 4-(dimethylamino)pyridine (DMAP) as an RAE-enabled promoter, and diisopropylethyl amine (DIPEA) as an acid scavenger.

Synthesis of IA

To a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**A**, 160 mg, 0.39 mmol) and 4-(dimethylamino)pyridine (DMAP, 4.7 mg, 0.039 mmol) in anhydrous dichloromethane (1.0 mL) was added 4-methoxybenzyl alcohol (**I**, 46 mg, 0.33 mmol) and N,N-diisopropylethylamine (DIPEA, 0.13 mL, 0.8 mmol). The reaction mixture was stirred for 2 h under refluxing. The solvent was removed under reduced pressure and the product was purified by silica gel column chromatography (hexanes/EtOAc = 7/3, v/v, R_f = 0.7) to afford the product as a clear wax (**IA**, 141 mg, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.31 – 7.15 (m, 2H), 6.87 (d, 2H), 5.68 (d, *J* = 5.2 Hz, 1H, α-H1), 5.21 (t, 1H), 4.91 (ddd, 1H), 4.49 (s, 2H), 4.31 (ddd, 1H), 4.22 – 4.19 (m, 1H), 4.00 – 3.92 (m, 1H), 3.80 (s, 3H), 2.10 (m, 9H), 1.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.95 (C=O), 169.91 (C=O), 169.38 (C=O), 159.49, 129.74, 129.70, 129.50, 121.61 (orthoester C), 114.11, 114.01, 97.18 (α-C1), 73.31, 70.28, 68.43, 67.17, 65.87, 63.30, 55.51, 21.20, 21.07 (-OAc), 21.04 (-OAc), 21.03 (-OAc). ESI-MS calc for $C_{22}H_{28}NaO_{11}$ $[M + Na]^+$ = 491.44, found: 491.26.

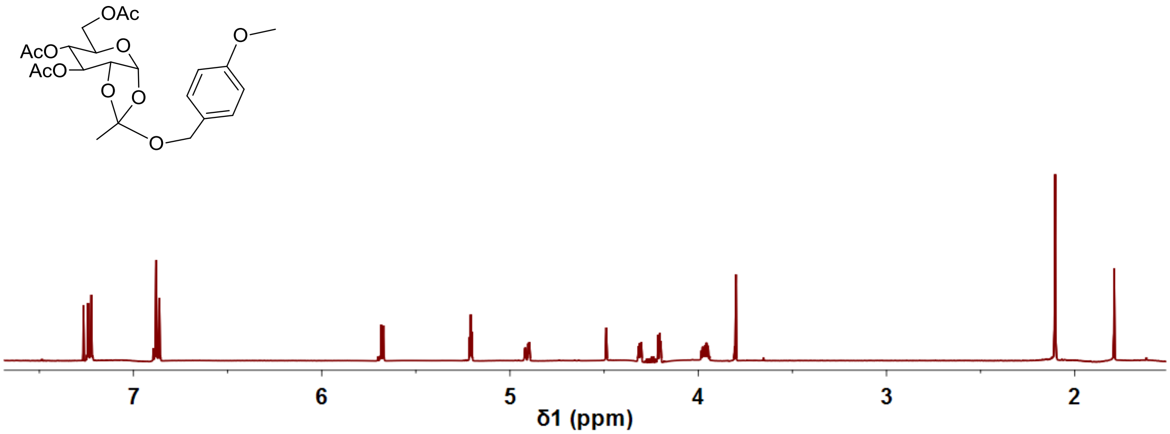


Figure 1S. ^{1}H NMR spectrum of **IA.**

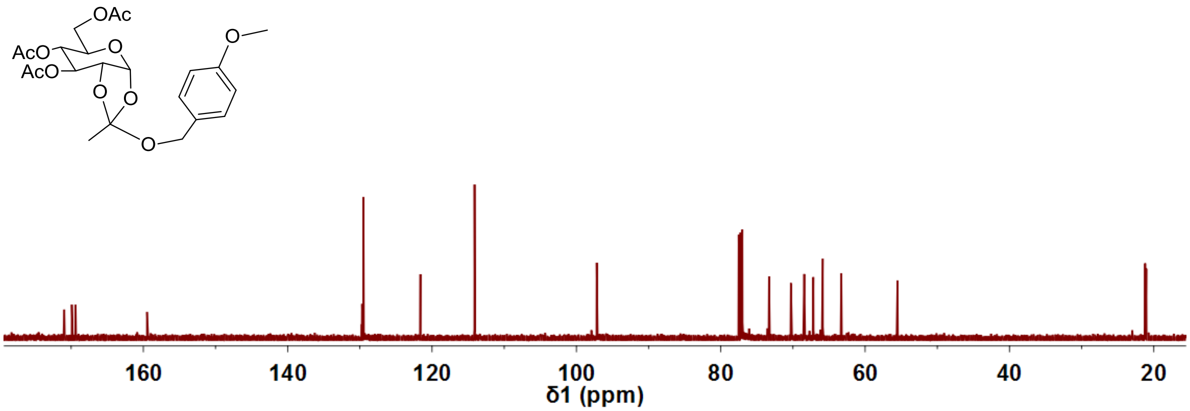


Figure 2S. ^{13}C NMR spectrum of **IA.**

Synthesis of IIA

The synthesis of **IIA** was conducted in a similar way to that of **IA**. The product was obtained as a clear wax (484 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.69 (d, J = 5.2 Hz, 1H, α-H1), 5.35 (d, 1H), 5.18 (t, 1H), 4.90 (dd, 1H), 4.35 (dd, 1H), 4.19 (t, 2H), 3.94 (dd, 1H), 3.48 (m, 1H), 2.43 – 2.19 (m), 2.11 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.02 – 1.95 (m), 1.85 – 1.79 (m), 1.73 (s), 1.61 – 1.21 (m), 1.18 – 1.01 (m), 0.97 (s), 0.92 – 0.90 (d), 0.87 – 0.85 (dd), 0.67 (s). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.92 (C=O), 169.87 (C=O), 169.39 (C=O), 140.98, 140.74, 122.26, 121.60 (orthoester C), 97.11 (α-C1), 73.99, 73.22, 72.01, 70.39, 68.47, 67.18, 63.33, 56.99, 56.37, 50.39, 42.54, 40.58, 40.01, 39.74, 37.53, 37.48, 36.74, 36.41, 36.01, 32.13, 32.08, 31.89, 30.06, 28.45, 28.24, 24.52, 24.05, 23.04, 22.78, 21.88, 21.31 (-OAc), 21.26 (-OAc), 21.04 (-OAc), 19.62, 18.94, 12.09. ESI-MS calc for $C_{41}H_{64}NaO_{10}$ [M + Na]$^+$ = 739.44, found: 739.46.

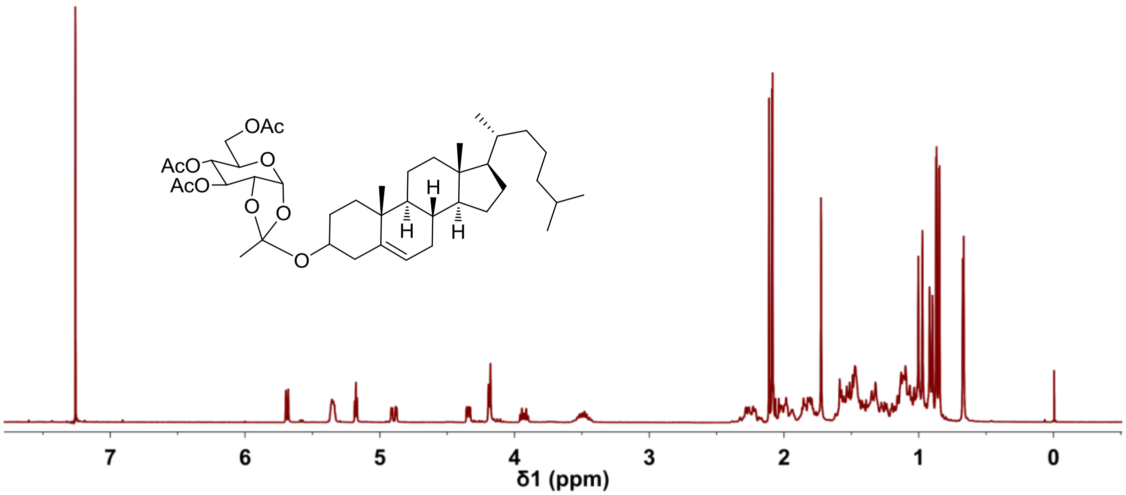


Figure 3S. ^{1}H NMR spectrum of **IIA.**

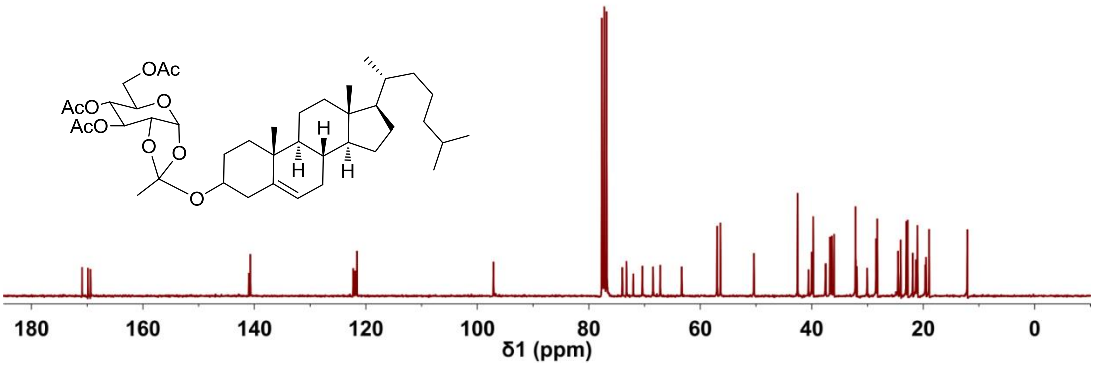
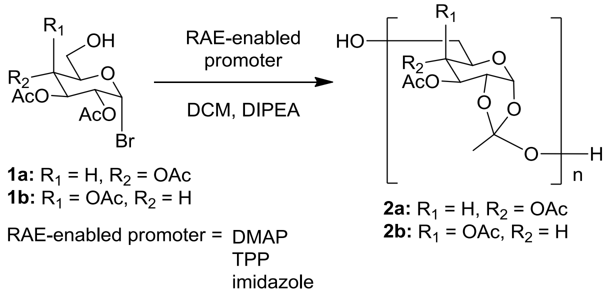


Figure 4S. ^{13}C NMR spectrum of **IIA.**

III. Syntheses of sugar poly(orthoesters)



Scheme 2S. RAE-mediated syntheses of sugar poly(orthoesters) **2a** and **2b**.

A. Synthesis of glucose poly(orthoester) (2a)

Monomer **1a** was synthesized according to the procedures reported previously.[1] To a 5 mL Schlenk flask was added monomer **1a**, (0.10 g, 0.27 mmol), anhydrous CH_2Cl_2 (1.0 mL), 4-(dimethylamino)pyridine (DMAP) (3.5 mg, 0.027 mmol) and N,N-diisopropylethylamine (DIPEA, 0.09 mL, 0.54 mmol). The reaction mixture was stirred under argon for 18 h. The solvent was removed by reduced pressure. The polymer was precipitated three times using a mixture solvent of water/methanol (9/1, v/v) at rt to afford the product as a slightly brown powder (57 mg, 72%). $[\alpha]_D^{25} = +98.8$ ($c = 1$ in $CHCl_3$). The NMR data are in good agreement with those reported previously.[2] ^1H NMR (500 MHz, $CDCl_3$) δ = 5.72 (d, J = 5.0, 1H, H-1), 5.20 – 5.08 (m, 1H, H-3), 4.92 (t, 1H, H-4), 4.39 – 4.20 (m, 1H, H-2), 3.90 – 3.71 (m, 1H, H-5), 3.65 – 3.51 (m, 2H, H-6,6'), 2.15 – 1.68 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 169.99 (C=O), 169.96 (C=O), 169.48 (C=O), 121.31 (orthoester C), 97.27 (C-1), 72.78 (C-2), 70.06 (C-3), 68.32 (C-4), 67.78 (C-5), 63.22 (C-6), 21.09 (-OAc), 20.65 (-OAc), 20.56 (-OAc). IR: 3333 (-OH), 2961 (C-H), 2874 (C-H), 1744 (C=O) cm^{-1}.

B. Synthesis of galactose poly(orthoester) (2b)

Monomer **1b** was synthesized in a similar manner as that reported previously.[1] The synthesis of polymer **2b** was conducted in a similar way to that of **2a**, affording the polymer as a slightly brown powder (370 mg, 71%). $[\alpha]_D^{25}$ = +113.8 (*c* = 1 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.70 (d, *J* = 5.0, 1H, H-1), 5.43 (s, 1H, H-4), 5.04 – 4.91 (m, 1H, H-3), 4.36 – 4.25 (m, 1H, H-2), 4.23 – 4.09 (m, 1H, H-5), 3.60 – 3.51(m, 2H, H-6,6’), 2.12 (s, 3H), 2.06 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.02 (C=O), 169.92 (C=O), 120.98 (orthoester C), 97.62 (C-1), 74.21 (C-2), 71.76 (C-3), 69.89 (C-5), 65.94 (C-4), 60.24 (C-6), 23.55 (-CH_3), 20.75 (-OAc), 20.61 (-OAc). IR: 3410 (-OH), 2960 (C-H), 2856 (C-H), 1736 (C=O) cm^{-1}.

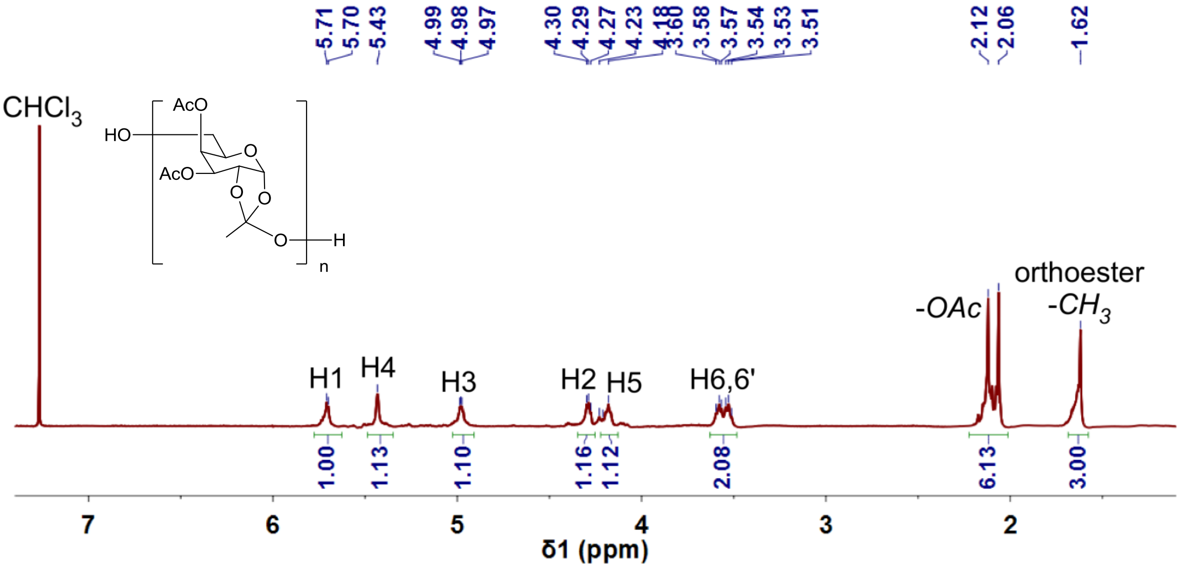


Figure 5S. ^{1}H NMR spectrum of **2b.**

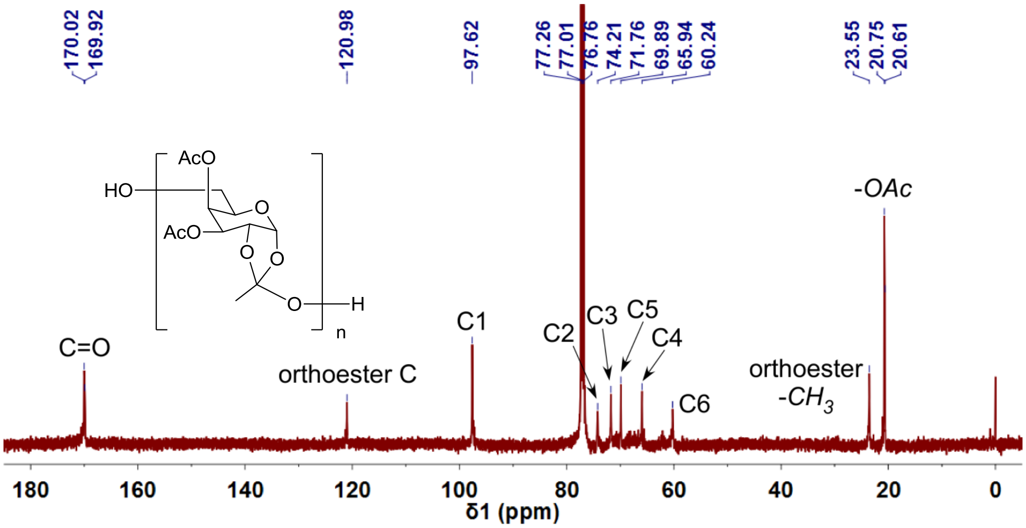


Figure 6S. ^{13}C NMR spectrum of **2b.**

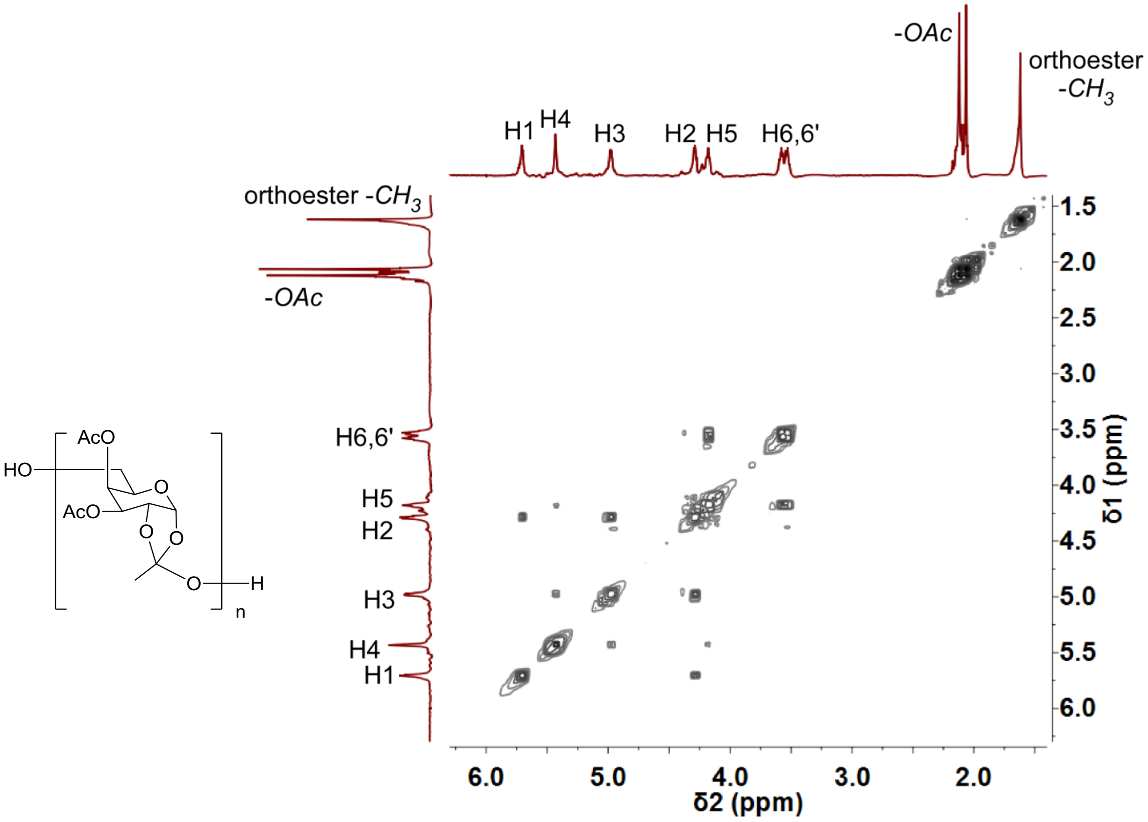


Figure 7S. 2D COSY NMR spectrum of **2b.**

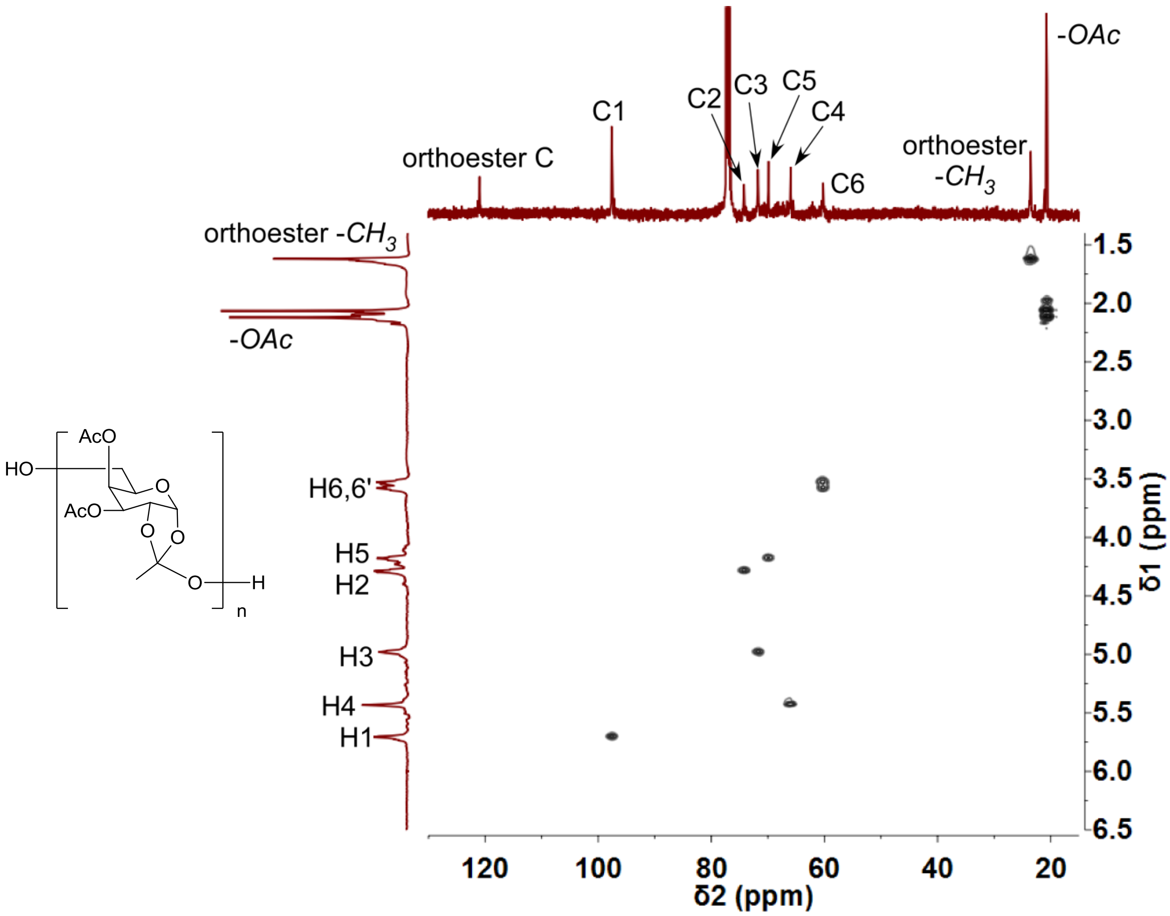


Figure 8S. 2D HMQC NMR spectrum of **2b.**

IV. Reference

1 L. Li, E. A. Franckowiak, Y. Xu, E. McClain, W. Du, *J. Polym. Sci. Part A: Polym. Chem.*, 2013, **51**, 3693-3699.

2 L. Li, Y. Xu, I. Milligan, L. Fu, E. A. Franckowiak, W. Du, *Angew. Chem. Int. Ed.* , 2013, **52**, 13699-13072.