Syntheses of Optically Active Monomers and Copolymers Derived from Protected 6’-O-Acryloyl Sucroses

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Abstract: Selectively 6’-O-monoacrylated monomers of fully protected sucrose moieties were synthesized by a multistep route. Chiral copolymers were prepared from these monomers with styrene or methyl methacrylate using radical initialization with azobisisobutyronitrile (AIBN). The quantitative incorporation of substoichiometric components was verified. Copolymers composition and purity were reliably analyzed by ‘H NMR and SEC.

Key words: carbohydrates, monoacrylates, regioselectivity, free radical polymerization, polymers

Vinyl sugars can be easily copolymerized with various comonomers and constitute polymers of a special structural type. They have potential for modifying and improving several properties of conventional polymer structures namely the introduction of chirality, superior biodegradability and biocompatibility.1,2 Extensive studies on the syntheses of vinyl monomers and polymers of saccharides have been reported.3–7

The most common approach to these compounds, in order to attain the monomer susceptible to polymerization, is by the attachment of an unsaturated component to the sugar. This linkage is usually in the form of an ether, ester or amido group.4

In the context of the use of sucrose as a chemical raw material8,9 there is an increasing interest in this chemistry field10,11 and several studies in this area can be found during the last decade.8,12,13

The hydroxyl positions where the vinyl group has been regioselectively introduced in the sucrose molecule have traditionally been the primary hydroxyl or the 4-OH on the glucose moiety,12,13 or the 1’-OH of the fructose moiety.9,14 A high degree of regioselectivity can be achieved by the enzymatic approach9,14 although some disadvantages and limitations can be found in the use of enzymes (low stability of the enzymes in organic solvents or the correct choice of agents for introducing the unsaturation).11 To our knowledge, ester sucrose monomers have never been prepared chemically at the 6’-O position for building vinyl polymers.

Several strategies have been employed to obtain sucrose with the 6’-OH free for functionalization.15–20 We have developed21 a multistep procedure22 that allowed us to obtain selectively the unprotected 6’-hydroxyl and we have prepared vinyl sucrose derivatives from this intermediate. Using this strategy, we were able to control the regioselective monofunctionalization of the sugar in order to form a monomer which could be converted into pure linear polymers, avoiding the presence of mixtures of mono- and (or) multi-substituted modified sucrose molecules that results in cross-linked polymerization.2,11

The properties of these polymers are dependent on the diverse substituents on the sugar,1 and we have prepared several sucrose monomers protected with different groups. These sugar monomers, containing a unique polymerizable double bond, were subjected to free-radical polymerization using azobisisobutyronitrile (AIBN) affording optically active copolymers.

Here we report the selective preparation of three new 6’-O-methacryloyl esters of protected sucroses and the synthesis of new crotonyl derivatives monomers of sucrose. The study of the copolymerization of one monomer with styrene or methyl methacrylate as well as the characterization of the corresponding sucrose polymers is also described.

The first step to our targets consisted in a regioselective silylation of the 6’-hydroxyl group (Scheme 1) of the sucrose using tert-butylidiphenylchlorosilane (TBDPSCI) according to the methods described earlier,22 followed by an acylation or alklylation of the remaining hydroxyl groups.

The monosilylated sucrose 122 was reacted with three different agents, namely methyl iodide (MeI), benzoyl chloride (BzCl) and 3,4,5-tri-O-methylgalloyl chloride, leading respectively to the compounds 2,3,22 and 4. Because of a slight instability of the TBDPS protecting group under strongly basic conditions (KOH, DMSO), required for the alkylation,23 we have always obtained the expected octamethylsuccrose as a byproduct during the preparation of 2. Good yields have been obtained in the acylation step for the synthesis of 3 in the presence of 4-dimethylaminopyridine (4-DMAP), or in the presence of tetramethylethlenediamine (TMEDA) for the synthesis of 4.21,24 To prepare this latter product, it has been necessary to heat at reflux temperature in order to protect all the hydroxyl groups, otherwise the hexaacylated sugar was isolated, being unprotected at the 2-OH.

Selective deprotection of the silyl group, with TBAF at room temperature or with Br₂/MeOH at reflux, furnished, compounds 5, 6, 7 (73% yield, 22% of the starting material was recovered), respectively, from 2, 3 and 4, after column chromatography. In the case of 6 or 7 migrations of the acyl groups were avoided by the use of bromine (Br₂) in methanol (MeOH) at reflux, a recently developed methodology.25

Esterification reactions of the 6′-hydroxyl free sucrose were carried out by treating the sugars 5–7, in dichloromethane in the presence of triethylamine at room temperature with the appropriate anhydride as reagent, to give the expected compounds 8–13 (Scheme 2) in good yields. Some problems were encountered in the purification of the monomers, particularly in the case of 13, where traces of impurities were difficult to separate from the required compound.

In the ¹H NMR spectra of all these compounds two signals have been attributed to the double bond: singlet at 6.14 ppm and triplet at 5.55 ppm for the compounds with the methacrylic moiety (8, 9 and 10), and for those compounds with the crotonic moiety (11, 12 and 13) a double quadruplet or multiplet at 6.93 ppm and a doublet at 5.80 ppm. We could also assign the allylic methyl groups of the molecules at 1.90 ppm (s for 8–10) and 1.75 ppm (d for 11–13). The presence of a signal at about 18 ppm in each of the homodecoupled ¹³C NMR spectra of these six compounds, confirmed the presence of the new methyl group. The polymerizability (homo- and copolymerization) of monomer 9 has been examined in the presence of AIBN as free-radical initiator in toluene at 70 °C. Unfortunately, homopolymerization of compound 9 failed to give polymers of high molar mass as did the copolymerization with acrylonitrile. We found that copolymerization of compound 9 (Table) with styrene or methyl methacrylate afforded the expected poly(sucrose 6′-acrylate) after 24 hours of reaction and precipitation with ethanol (0 °C). A study of the effect of varying the stoichiometry of the comonomers on the sugar incorporation in the final copolymers has been carried out. As a result, we obtained several copolymers with diverse degrees of protected sucrose appended. This resulted in different physical properties such as optical rotations. As expected this lowered progressively with the larger participation of the non-optically active comonomer.

Poly(sucrosyl) composition has been determined from the ¹H NMR spectra of the copolymers. The structures have been verified by comparing the peak areas of both the methylene and methyl protons of the polymer chain (0.8–2.2 ppm), as well as the methoxy protons, when the comonomer is methyl methacrylate, with the 14 protons area of the sucrose units. We have noticed in the ¹³C NMR spectrum of the copolymer with methyl methacrylate, the presence of two different groups of carbonyl signals, one from the sugar ester moiety and the other from the carbonyls of the comonomer.

Data obtained by Size Exclusion Chromatography (SEC) analysis, revealed monomodal distributions. Copolymer molecular weights (Mw), estimated by the same method, were in a similar range of values to those of similar copolymers.8,12 Polydispersity values (Mw/Mn) revealed a certain degree of heterogeneity under the adopted conditions of work. Copolymers were soluble in classical organic solvents and insoluble in water as would be expected for a fully capped sugar.

In summary, some 6′-hydroxyl free (otherwise protected) sucrose derivatives have been prepared. Selective incorporation of unsaturated ester groups for the preparation of sucrose monomers was accomplished through its reaction with the corresponding symmetrical anhydrides in the presence of DMAP as catalyst. As a final point, new chiral copolymers containing sucrose were synthesized by radical polymerization and some of their physical properties were determined.
Reagents and solvents were purified before use. All reactions were run under a positive pressure of dry argon except for the preparation of 2,6 and 7. Flash chromatography was performed on silica gel (Merck–Nagel Kieselgel 60). Preparative TLC was performed on glass plates coated with 1 mm of silica gel (Merck–Nagel, Kieselgel DGF35L). Analytical TLC: Aluminum-backed silica gel Kieselgel DGF 254. Optical rotations were measured at 20 °C on an AA-1000 polarimeter (0.5 dm cell). NMR spectra were recorded on a Bruker AMX-400 spectrometer (1H at 400 MHz and 13C at 100 MHz) in CDCl₃ with chemical shift values (δ) in ppm downfield from TMS. Some compound signals were assigned by performing additional 1H–1H COSY and HMBC measurements on the same TEMS. SEC analyses were performed on a Knauer apparatus. The remaining solid yielded 4 (1.10 g, 82%) as a white powder. [α]D +23.3 (c = 1.2, CHCl₃).

1H NMR (CDCl₃): δ = 7.69 (m, 4H, Ar), 7.32–6.98 (7 s, 14 H, Ar), 7.31 (m, 6H, Ar), 6.27 (t, 2H, H–1′, H–4′), 6.02 (t, 1H, J = 10.0 Hz, H–3′), 5.84 (d, 1H, J = 7.6 Hz, H–5′), 5.74 (t, 1H, J = 10.0 Hz, H–4′), 5.31 (dd, 1H, J = 10.2, 3.6 Hz, H–2′), 4.75 (d, 1H, J = 11.8 Hz, H–1′a), 4.57 (d, 1H, J = 10.0 Hz, H–5), 4.50 (d, 1H, J = 11.6 Hz, H–1′b), 4.32 (dd, 1H, J = 7.6, 4.4, 4.2 Hz, H–5′), 4.10 (m, 4H, H–2–6′ and 2–6′), 3.93–3.76 (11 s, 63 H, 21 CH₃O), 1.01 (s, 9H, t–C₃H₅).

13C NMR (CDCl₃): δ = 197.2 (CMe₂), 172.9 (C(CH₃)₃), 65.89–56.93 (CH₂OAr), 61.51 (CH₂OAr), 63.33, 63.76, 66.78 (C–6′ and C–6′), 69.54, 70.09, 71.53, 72.09 (C–2′, C–3′, C–4 and C–5′), 74.62, 78.60 (C–3′ and C–4′), 81.09 (C–3′), 90.30 (C–1′), 104.18 (C–2′), 107.75–153.68 (Ar). 165.52, 165.69, 165.86, 166.86, 166.03, 166.24 (7 CO).


6′-O-tert-Butyldiphenylsilyl-2,3,4,6,1′,3′,4′-hepta-O-(tri-O-methylgalloyl)sucrose (4)

To a suspension of KOH (2.70 g, 28.0 equiv, 482 mmol) in DMSO (4 mL) at r.t. was added, after 30 min, compound 1 (1.00 g, 1.7 mmol), immediately followed by MeI (1.50 mL, 14.0 equiv, 24.1 mmol). The mixture was stirred for an additional 10 min. Then, H₂O (10 mL) was added and several extractions with CH₂Cl₂ (5×15 mL) were performed. The combined organic layers were dried (Na₂SO₄), and the solvent was evaporated to afford a pale yellow oil that was purified by flash column chromatography (EtOAc–hexane, 1:1) to yield 0.85 g (73%) of 2; [α]D +41.5 (c = 1.5, CHCl₃).

1H NMR (CDCl₃): δ = 7.67 (m, 4H, Ar), 7.38 (m, 6H, Ar), 5.56 (d, 1H, J = 3.6 Hz, H–1), 4.04 (t, 1H, J = 7.2 Hz, H–3′), 3.90 (t, 1H, J = 7.2 Hz, H–4′), 3.89 (t, 1H, J = 7.2 Hz, H–5′), 3.88 (m, 2H, H–2′), 3.84 (m, 1H, H–5), 3.60 (t, 1H, H–1′a), 3.56, 3.51, 3.47, 3.44, 3.41, 3.39, 3.28 (7 s, 21H, 7CH₃O), 3.49 (m, 1H, H–6a), 3.38 (m, 1H, H–6), 3.18 (t, 1H, J = 9.6 Hz, H–4), 3.05 (dd, 1H, J = 9.6, 3.6 Hz, H–2), 1.05 (s, 9H, t–C₃H₅).

13C NMR (CDCl₃): δ = 190.4 (CMe₂), 126.83 (C(CH₃)₃), 57.91, 58.25, 58.52, 58.99, 59.36, 60.06, 60.49 (7CH₂O), 64.96 (C–6′), 70.25 (C–5), 70.92 (C–6), 74.18 (C–1′), 79.20 (C–4′), 80.83 (C–5′), 81.41 (C–2′), 83.00 (C–3′), 84.15 (C–4′), 85.60 (C–3′) 89.01 (C–1), 104.07 (C–2′), 127.71–135.70 (Ar).
3.89 (t, 1 H, J = 11.2 Hz), 5.57 (t, 1 H, J = 7.5 Hz, H-3'), 5.43 (m, 1 H, J = 1.0 Hz, H-4'), 5.29 (dd, 1 H, J = 11.9 Hz, H-1'a), 4.70 (m, 1 H, 5'-H or 6'-H'), 4.60 (d, 1 H, H-1'b), 4.52 (s, 2 H, 2-H'), 4.47–4.45 (m, 2 H, 5'-H or 5'H-6'a), 4.35 (dd, 1 H, J = 12.5, 3.0 Hz, H-6'b), 1.89 (s, 3 H, CH 3(CH 2)CH 3).

C NMR (CDCl 3 ): δ = 85.67, 56.35 (CH 2 OAr), 62.13, 63.28, 65.31 (C-6, C-1' and C-6'), 69.53, 69.81, 71.81, 72.50 (C-2, C-3, C-4 and C-5), 75.09, 78.29 (C-3' and C-4'), 82.26 (C-5'), 94.17 (C-1), 103.71 (C-2'), 107.54–153.38 (Ar), 165.60, 165.79, 165.90, 166.00, 166.40, 166.51, 167.08 (C-6).

Synthesis of Monomers; General Procedure
To a 0.1 M solution of the 0'-OH free sugars 5–7 in anhyd CH 2 Cl 2 was added Et 3 N (2.5 equiv) and a catalytic amount of DMAP. The mixture was cooled to 0°C and then a 0.5 M solution of methacryloyl-(tri-methylsucrose (11) D +59.7 (c = 1.0, CHCl 3 ).

C NMR (CDCl 3 ): δ = 14.88 (16.6 Hz, H-2'), 4.58 (s, 2 H, 2-H'), 4.47–4.45 (m, 2 H, 5'-H or 5'H-6'a), 4.35 (dd, 1 H, J = 12.5, 3.0 Hz, H-6'b), 1.89 (s, 3 H, CH 3(CH 2)CH 3).

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The reaction of 6 (0.5 g, 0.5 mmol) with crotonic anhydride (83.5 μL, 0.6 mmol) was carried out according to the general procedure during 1.5 h. Chromatographic purification (silica gel, EtOAc–hexane, 1:2) afforded 0.43 g (80%) of 12; [α]D +33.0 (c = 1.0, CHCl3).

1H NMR (CDCl3): δ = 8.21–7.12 (m, 35 H, Ar), 6.95 (dq, 1 H, J = 156.6 Hz, H-J), 6.24 (t, 1 H, J = 5.0 Hz, H-3), 6.15 (d, 1 H, J = 3.2 Hz, H-1), 5.97 (d, 1 H, J = 5.6 Hz, H-4), 5.83 (d, 1 H, J = 15.6 Hz, H-α), 5.79 (t, 1 H, J = 9.4 Hz, H-4), 5.45 (dd, 1 H, J = 10.6, 3.4 Hz, H-2), 4.73 (m, 2 H, H-1’a and H-Sor H-5’), 4.61 (d, 1 H, J = 12.0 Hz, H-’b’), 4.50 (m, 3 H, H-6a, H-5’ or H-3 and 2 H-6’), 4.35 (dd, 1 H, J = 12.4, 3.2 Hz, H-6b), 1.72 (d, 3 H, J = 6.8 Hz, CH3CH=CHCO).

13C NMR (CDCl3): δ = 17.82 (CH2CH=CHCO), 62.28, 63.16, 64.78 (C-6, C-1’ and C-6’), 68.94, 69.12, 70.03, 71.25 (C-2, C-3, C-4 and C-5), 76.06, 77.38 (C-3’ and C-4’), 79.04 (C-5’), 90.80 (C-1), 104.58 (C-2’), 121.84, 128.21–133.55 (Ar and CH=CH), 164.99, 165.25, 165.42, 166.58, 166.76, 166.94 (8 CO).


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