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Note

Synthesis of three different galactose-based methacrylate monomers for the production of sugar-based polymers

Jessica S. Desport [a, 1], Daniele Mantione [a, **, 1], Mónica Moreno [a], Haritz Sardón [a], María J. Barandiaran [a], David Mecerreyes [a, b, *]

[a] POLYMAT, University of the Basque Country UPV/EHU, Joxe Mari Korta Center, 20018, Donostia-San Sebastián, Spain
[b] Ikerbasque, Basque Foundation for Science, E-48011, Bilbao, Spain

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ABSTRACT

Glycopolymers, synthetic sugar-containing macromolecules, are attracting ever-increasing interest from the chemistry community. Glycidyl methacrylate (GMA) is an important building block for the synthesis of sugar based methacrylate monomers and polymers. Normally, glycidyl methacrylate shows some advantages such as reactivity against nucleophiles or milder synthetic conditions such as other reactive methacrylate monomers. However, condensation reactions of glycidyl methacrylate with for instance protected galactose monomer leads to a mixture of two products due to a strong competition between the two possible pathways: epoxide ring opening or transesterification. In this paper, we propose two alternative routes to synthesize regiospecific galactose-based methacrylate monomers using the epoxy-ring opening reaction. In the first alternative route, the protected galactose is first oxidized to the acid in order to make it more reactive against the epoxide of GMA. In the second route, the protected sugar was first treated with epichlorohydrin followed by the epoxy ring opening reaction with methacrylic acid, to create an identical analogue of the ring-opening product of GMA. These two monomers were polymerized using conventional radical polymerization and were compared to the previously known galactose-methacrylate one. The new polymers show similar thermal stability but lower glass transition temperature (Tg) with respect to the known galactose methacrylate polymer.

Glycopolymers, synthetic sugar-containing macromolecules, are attracting ever-increasing interest from the chemistry community due to their role as biomimetic analogues and their potential for commercial applications. Glycopolymers play an important role in many biological recognition events such as cell-cell adhesion, development of new tissues and infectious behavior of virus and bacteria. They have high potential in targeted drug delivery, tissue engineering and synthesis of biocompatible materials. On the other hand, there is a general trend to synthesize polymers using renewable raw materials istead of oil based ones [1]. Counting the fact that about 75% of biomass consists of carbohydrates [2], several sugar based polymers have been synthesized over the years [3–5], contributing to the developments and applications of bio-based plastic materials [6–8]. Among the different glycopolymers, galactose based ones have shown interesting performance as extracellular matrices for tissue engineering, as antimicrobial agents or as thermoresponsive materials [9].

In this work, a galactose based monosaccharide carrying acetonide protecting groups will be envisaged as valuable precursor: 1,2:3,4-Di-O-isopropylidene-D-galactopyranose (DAGA). In order to make this protected galactose polymerizable we coupled it with bio-based methacrylate monomers such as glycidyl methacrylate or methacrylic acid reagent [10]. From this precursor three different methacrylic monomers are synthesized. The incorporation of a polymerizable methacrylic group will be achieved through the use of two different functional agents: glycidyl methacrylate (GMA) on the one hand and epichlorohydrin plus methacrylic acid on the other hand. Noteworthy that the first two are both coming from the biggest biodiesel production side product: glycerol [1,11]. Exploring the literature, a variety of different mechanisms are reported for the

* Corresponding author. POLYMAT, University of the Basque Country UPV/EHU, Joxe Mari Korta Center, 20018, Donostia-San Sebastián, Spain.
** Corresponding author. POLYMAT, University of the Basque Country UPV/EHU, Joxe Mari Korta Center, 20018, Donostia-San Sebastián, Spain.
E-mail addresses: daniele.mantione@ehu.es, david.mecerreyes@ehu.es (D. Mecerreyes).
[1] These authors contributed equally.

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reaction between an alcohol and GMA [12–19]. We can note that in aqueous media, the reaction of GMA with alcohol groups is strongly pH dependent and could lead to both products: the one resulting from the epoxide ring opening and, the other, from the transesterification of the methacrylic ester [16,18–21]. In organic solvents, even if there are some exceptions in recent literature [13,22], the predominant mechanism appear to be the unexpected transesterification [16,17,20]. These different pathways result in product formed by a mixture of two chemical compounds with a predominance of the esterification one. The two products are methacrylic monomers showing the presence or not of a spacer between the sugar ring and the methacrylate group as shown in Fig. 1. It is worth remarking that if the target product would be the one obtained by transesterification, other routes with higher yield and higher atom economy may be used instead of the glycidyl methacrylate one, such as esterification using methacryloyl chloride or methacrylic anhydride [8,23].

In order to confirm previous studies in organic solvent and to exploit all the possible products, the reaction between DAGA and GMA has been performed in bulk in the presence of trimethylamine at 60 °C (Fig. 1, route in the right). The resulted mixture of products was analyzed by UPLC-QTOF and subsequently separated by flash chromatographic column, confirming that the major product was **1** (Fig. 2a). It is interesting to note that the molecule resulting from ring-opening mechanism was also detected in ratio 90/10: transesterification product **1**/ring opening product **5**. It is worthwhile to note that the only product detected is the one resulting from the α attached to the epoxide leading to a secondary alcohol.

In this paper, we propose two alternative routes to synthesize galactose-based methacrylate monomers using the epoxy-ring opening reaction (Fig. 1, routes in the left). In the first alternative route (Fig. 1 route in the left upper side), 1,2:3,4-Di-O-isopropylidene-D-galactopyranose is first oxidized with $KMnO_4$ in order to make it more reactive against the epoxide of GMA [24]. Consequently, the oxidized sugar **2** has been reacted with GMA in the presence of a catalytic amount of an industrial catalyst called AMC-2. Specifically designed to promote reactions of epoxides, AMC-2 has shown efficiency in promoting the regiospecific ring-opening reaction of GMA with carboxylic acid groups [25]. The resulting product (**3**) was isolated by flash column chromatography and characterized (Fig. 2b).

In the second route (Fig. 1 route in the left down side), the GMA was split in two synthons, epichlorohydrin and methacrylic acid, to create an identical analogue of the ring opening product of GMA. Since the opening of epoxy-ring in the presence of AMC-2 catalyst was successful for the reaction of carboxylic acid, a second strategy where the epoxy function was grafted to DAGA [26] using epichlorohydrin was tested, and made react with methacrylic acid in the presence of AMC-2, leading to product **5** (Fig. 2c). It is worthy to point out that in the two last examples of ring-opening no mixture of isomers was observed, indicating that the use of AMC-2 catalyst allowed stereospecific opening of the epoxide. This was deeply demonstrated by ^{1}H and ^{13}C NMR spectroscopy, using HSQC, HMBC, DEPT at different temperatures, due to the high similarity of the two possible regioisomers (Supporting information).

Therefore, using different synthetic routes, we were able to synthesize three different methacrylate galactose monomers, whose difference is found in the spacer between the methacrylate and galactose groups. In order to compare the different properties that the spacer could give to the final polymers, the monomers were polymerized at 70 °C using conventional radical polymerization in benzene with Azobisisobutyronitrile (AIBN) as thermal initiator. After purification we were able to isolate and characterize three polymers from monomers **1**, **3** and **5**, called HOMO-1, HOMO-

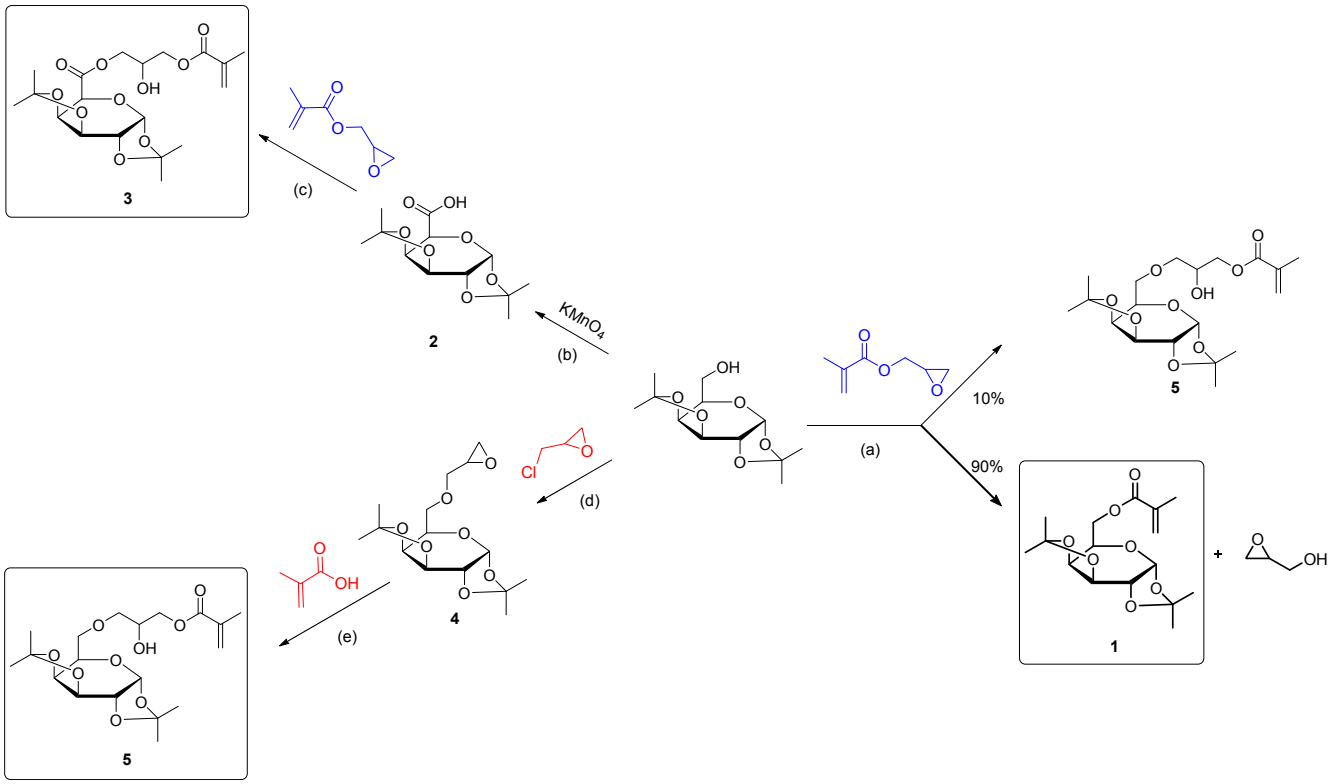

Fig. 1. Synthesis strategies to produce methacrylate galactose-based monomers from transesterification and epoxy-ring opening mechanisms. Reagents and conditions: (a) NEt_3, 60 °C, 5 h; (b) NaOH, $KMnO_4$, 45 °C, 12 h; (c) GMA, AMC-2, DCE, 70 °C, 3 h; (d) EPC, DCM, 80 °C, 12 h; (e) MA, AMC-2, DCE, 70 °C, 3 h.

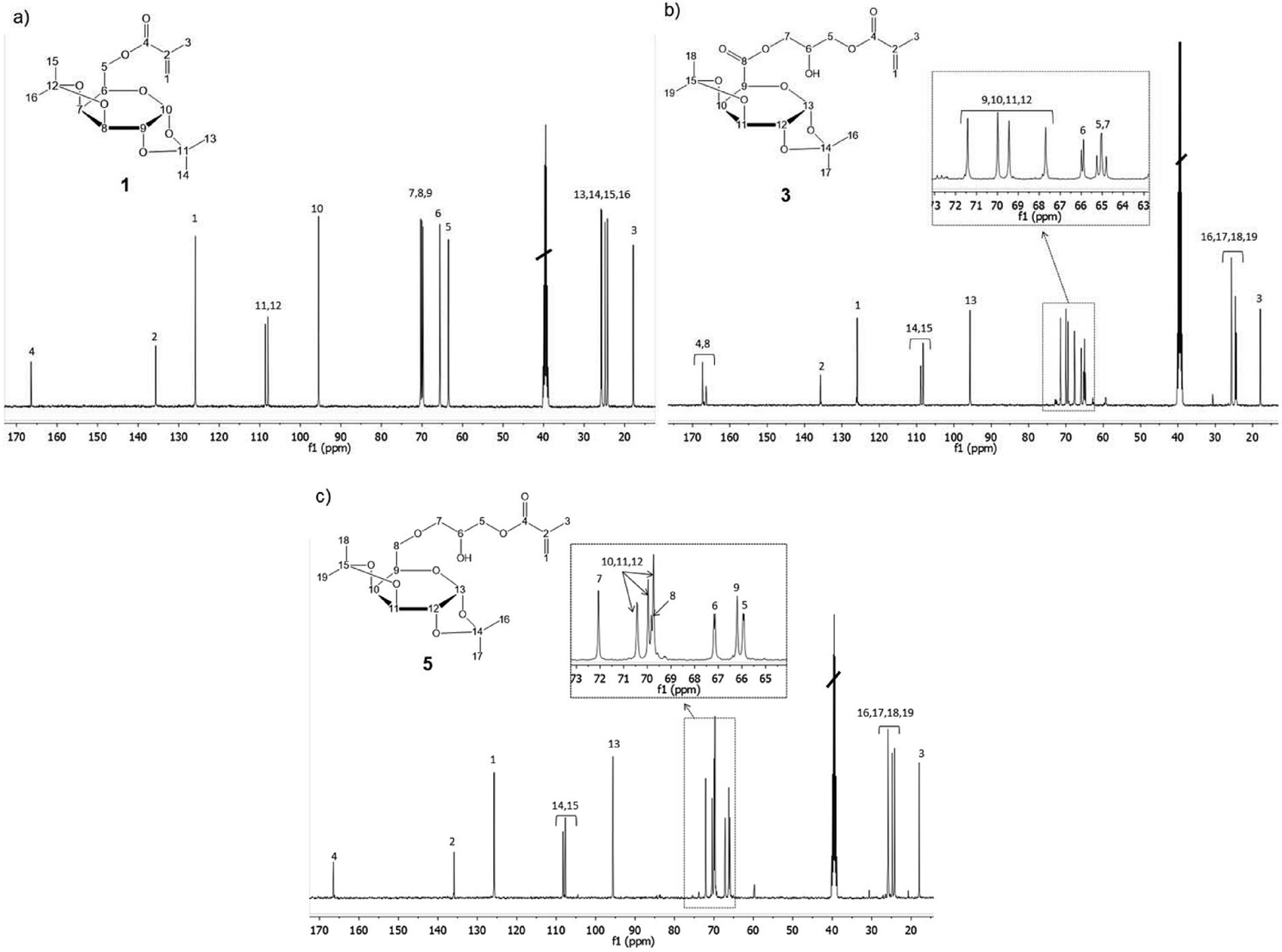

Fig. 2. ^{13}C NMR of methacrylate galactose-based monomers: a) monomer **1**; b) monomer **3**; c) monomer **5** in DMSO-d_6.

3 and HOMO-5 respectively. First, we measured the molecular weight by gel permeation chromatography (GPC) and secondly we compared their thermal stability by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). In the three cases we were able to obtain high molecular weight linear polymers with valued of 55 kDa, 54 kDa and 39 kDa for HOMO-1, HOMO-2 and HOMO-3 respectively [27,28]. In all the cases the dispersity (Đ) values were between 1.5 and 1.7 which is the expected ones for a radical polymerization mechanism. To conclude, as expected these 3 methacrylate monomers were polymerized by conventional radical polymerization.

As shown in Fig. 3a all three polymers exhibit good stability until 200 °C. However, at higher temperatures, the new polymers, HOMO-3 and HOMO-5, showed better thermal stability than the previously known HOMO-1. Indeed, at 300 °C, HOMO-1 has already lost 53 wt% while HOMO-3 lost 25 wt% and HOMO-5 only 18 wt%. These values demonstrate a higher stability of the new polymers and a beneficial character of the introduced alcoholic spatial moieties. These new polymers show a similar degradation profile of most methacrylic polymers such as PMMA that exhibit a degradation temperature range between 300 and 400 °C [29].

Furthermore, the three homopolymers were characterized by DSC in order to evaluate their glass transition temperatures. It is interesting to note the significant effect of the spacer between the methacrylate group and the sugar on glass transition temperature ranges. Indeed, we can observe a decrease in glass transition temperature when the monomers were produced by ring opening, as can be seen in Fig. 3b. Because of its cyclic nature, the protected pendant sugar scaffold provides stiffness to the chains and as it can be seen HOMO-1 exhibits a very high Tg around 113 °C. However, the presence of a short chain separating the methacrylate from the sugar helps improving significantly the mobility of the polymer chains and justifies the lower Tg of HOMO-3 and HOMO-5 around 65 °C and 36 °C respectively. We also believe that the planarity of the extra carbonyl group in HOMO-3 can explain its higher Tg compared to HOMO-5 [30].

In conclusion, in this work three different protected galactose monomers were synthesized by the condensation of glycidyl methacrylate and a protected galactose building block, 1,2:3,4-Di-O-isopropylidene-D-galactopyranose (DAGA). The three monomers presented similar methacrylic and protected galactose moiety and the main difference was the spacer in between. The monomers were polymerized and resulting galactose-polymethacrylates were compared. The new polymers showed better thermal stability and lower glass transition temperature (Tg) than the previously known galactose polymer. Incorporation of these bio-based materials could give added value to the resulting polymeric materials. Preparation of waterborne polymeric binders and additives from these monomers are under investigation.

1. Materials and methods

1.1. Materials

All reactants were used without prior purification. 1,2:3,4-Di-O-isopropylidene-D-galactopyranose was obtained from Carbosynth (UK). Glycidyl methacrylate, triethylamine, methacrylic acid, sodium hydroxide, azobisisobutyronitrile (AIBN) were coming from Sigma-Aldrich. AMC-2, which is a mixture of 50% trivalent organic chromium complexes and 50% phthalate esters, was purchased from AMPAC Fine Chemicals. Solvents were purchased from Acros-Organic and Sigma-Aldrich.

1.2. Instrumentation

^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature with a 400 MHz Bruker equipment whereas 2D-NMRs were recorded with a 500 MHz equipment. An extra amount of inhibitor (benzoquinone) was added in the tube when recording spectra at high temperatures to prevent polymerization. TLC were carried out on aluminium precoated plates (silica gel 40-60 Å 400 mesh, F_{254}, Aldrich) using hexane/ethyl acetate 7:3 (v:v) as eluent. The compounds were highlighted by spraying the TLC plates with EtOH/H_2SO_4 9:1 (v:v) stain and heat.

Polymers glass transition temperature (Tg) was measured by means of a differential scanning calorimeter, series DSC Q1000 (TA Instruments). The scanning cycles consisted of first cooling to -20 °C at 10 °C/min, then heating from −20 to 200 °C at 10 °C/min, cooling again from 200 to −20 °C at 10 °C/min, and then heating to 200 °C at a rate of 10 °C/min. The results from the second heating from −20 to 200 °C will be presented herein. Thermogravimetric analysis were carried out in a TGA Q500 (TA instruments) from 20 °C to 800 °C, using a heating rate of 10 °C/min under a nitrogen flow rate of 90 mL/min.

Polymers molecular weights were determined via gel permeation chromatography using an Agilent technologies GPC system, equipped with a mixed column (Shodex KD-806M), and a refractive index detector. The analysis was performed at 1.0 mL/min flow rate in dimethylformamide (DMF) at 40 °C. Relative Mw was determined thanks to a conventional calibration obtained with polystyrene narrow standards.

Fourier Transform Infrared Spectroscopy (FTIR) measurements were performed on a Brüker Alpha-p FTIR spectrometer. Spectra were collected from 4000 to 250 cm^{-1} with the following settings:

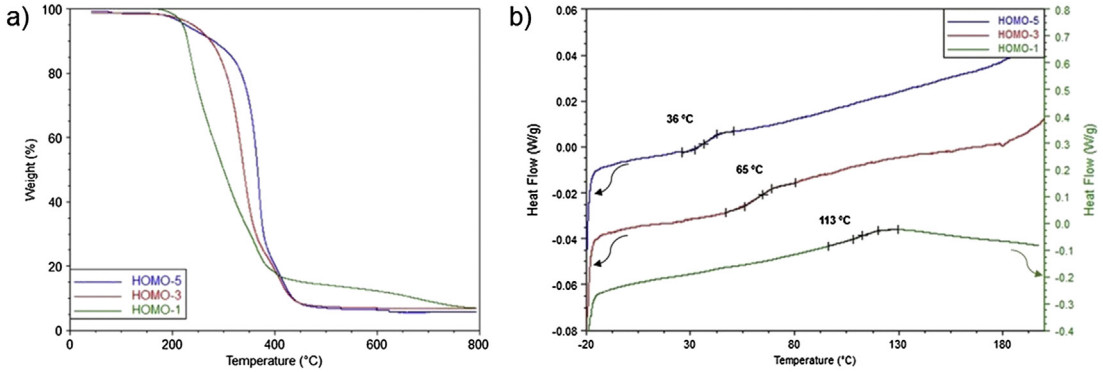

Fig. 3. a) Thermogravimetric analysis; b) Differential Scanning Calorimetry of HOMO-1, HOMO-3 and HOMO-5.

42 scans per sample and spectral resolution: 4 cm^{-1}.

Ultra-Performance Liquid Chromatography (UPLC-Q-TOF) was performed using a chromatograph from Acquity, equipped with a diode array detector and coupled with a mass spectrometer (Waters, model SYNAPTTM G2 HDMSTM) with ESI ionization sources. Analyses were conducted in positive ionization mode.

1.3. Reaction of oxidize-DAGA (**2**) and GMA: synthesis of **3**

2 (3.60 g, 13 mmol) was mixed with glycidyl methacrylate (3 g, 21 mmol) in 150 mL of 1,2-dichloroethane (DCE) in the presence of 1,5 wt%, in respect of the sugar, of AMC-2. A few ppm of benzoquinone was added to the media. The mixture was heated up to 70 °C and stirred for 3 h. DCE (150 mL) was used to dilute the reaction and the resulting organic phase was washed with distilled water 3 × 50 mL. Solvent evaporation was performed after drying over Na_2SO_4. Purification was completed by flash column chromatography (Hexane/Ethyl Acetate (EtOAc) from 7/3 to 1/1) to obtain **3**. Yield = 2.45 g (45%) as a slightly yellow oil. Rf 0.42 (Hexane/EtOAc 6/4). FTIR ($\nu = cm^{-1}$) 3500; 2986; 1768; 1717; 1637. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.07 (s, 1H), 5.70 (s, 1H), 5.56 (d, 1H), 5.38 (s, 1H), 4.68 (d, 1H), 4.54 (d, 1H), 4.44 (s, 1H), 4.34 (s, 1H), 4.19–4.04 (m, 4H), 4.02–3.90 (m, 1H), 1.89 (s, 3H), 1.56–1.18 (m, 12H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.21, 166.24, 135.67, 126.01, 125.79, 108.84, 108.81, 108.16, 95.60, 71.34, 69.90, 69.36, 67.61, 65.91, 65.80, 65.17, 64.97, 64.94, 64.72, 40.09, 39.88, 25.60, 25.57, 24.55, 24.32, 24.28, 17.85. MS (ESI HRMS) for $C_{19}H_{30}O_9$ (+Na) 439.1580, found 439.1580 $[M+Na]^+$ SI Fig. 6.

1.4. Reaction of epoxy-DAGA (**4**) and MAA: synthesis of **5**

To a concentrated solution of **4** (2 g, 6.4 mmol) in dry DCE (50 mL) was added methacrylic acid (810 μL, 9.6 mmol) with 1.5 wt %, with respect to the sugar, of AMC-2 catalyst. A few ppm of benzoquinone was added to the media. The solution was let stirred at 70 °C for 3 h under nitrogen atmosphere. After the solution was diluted with DCE, washed with DI water 3 × 50 mL and dried with Na_2SO_4. The solvent then was removed under vacuum and the mixture purified via flash column chromatography (Hexane/EtOAc 8/2). Yield = 1.2 g (47%) as a yellowish oil. Rf 0.46 (Hexane/EtOAc 7/3). FTIR ($\nu = cm^{-1}$) 3488; 2986; 2934; 1716; 1637. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.07 (s, 1H), 5.69 (s, 1H), 5.45 (d, 1H), 5.09 (d, 1H), 4.58 (d, 1H), 4.34 (s, 1H), 4.21 (d, 1H), 4.16–3.94 (m, 2H), 3.93–3.75 (m, 2H), 3.69–3.53 (m, 1H), 3.53–3.38 (m, 3H), 1.89 (s, 3H), 1.56–1.15 (m, 12H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 135.87, 125.72, 108.22, 107.69, 95.61, 72.07, 70.45, 70.42, 69.97, 69.83, 69.74, 67.19, 67.13, 66.20, 65.96, 65.91, 25.88, 25.81, 24.79, 24.19, 17.97. MS (ESI HRMS) for $C_{19}H_{30}O_9$ (+Na) 425.1788, found 425.1794 $[M+Na]^+$ SI Fig. 7.

1.5. Homopolymerization procedure

0.5 g of monomer was dissolved in 10 mL of benzene. The reaction mixture was purged with nitrogen for 20 min and then heated up to 70 °C. AIBN 1 wt% with respect to the sugar, dissolved in benzene (ca. 0.1 mL) was added as a shot to initiate the polymerization. After 48 h of reaction, the polymer was precipitated in a large amount of heptane. The product was filtered under vacuum, then dissolved in THF and re-precipitated again in heptane. The resulting fine powder was suction filtrated and dried for one night under vacuum.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.carres.2016.06.008.

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