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Note

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

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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

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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-

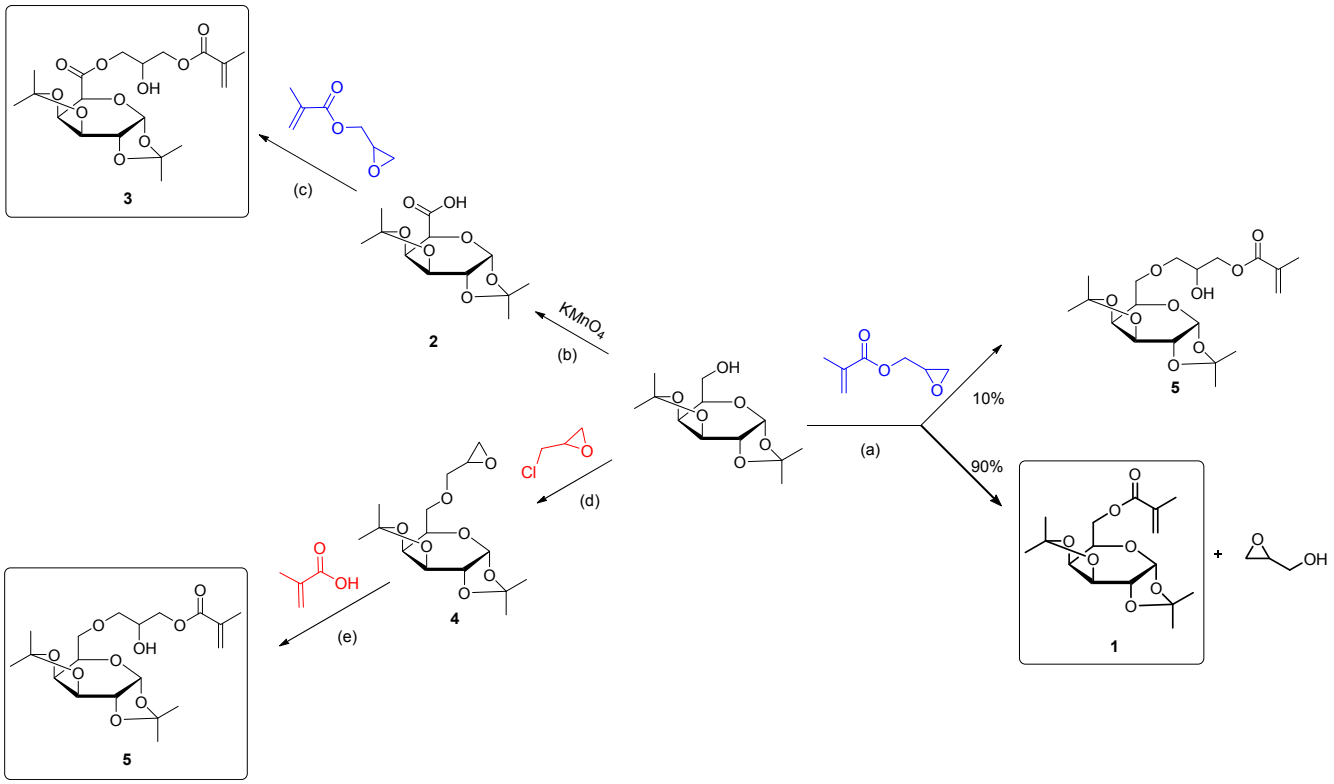

Fig. 1. Synthesis strategies to produce methacrylate galactose-based monomers from transesterification and epoxy-ring opening mechanisms. Reagents and conditions: (a) NEt_3, 60 °C, 5 h; (b) NaOH, $KMnO_4$, 45 °C, 12 h; (c) GMA, AMC-2, DCE, 70 °C, 3 h; (d) EPC, DCM, 80 °C, 12 h; (e) MA, AMC-2, DCE, 70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