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Synthesis and characterization of a new methacrylic glycomonomer

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The carbohydrate containing monomer 3-O-(2′-hydroxy-3′-methacryloyloxypropyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose was easily prepared from D-glucose and methacrylic acid in 4 steps. The structure of the new methacrylic monomer was confirmed using FTIR, NMR (including ^{1}H-NMR, ^{13}C-NMR, COSY, HMQC and HMBC), and HPLC-MS. This work is part of our group's effort to obtain new polymers based on renewable resources with enhanced biodegradability and biocompatibility.

Key Words: D-glucose, glycomonomer, biodegradability, methacrylic acid, epoxidation

Introduction

The field of biodegradable polymers represents one of the important industrial achievements of the 20th century, but the current rising consumption of petrochemical raw materials associated with polymer production has motivated many researchers to find alternative starting materials.[1,2] It is predicted that by 2040 ground biomass will be a cheaper raw material than petroleum hydrocarbons. The progressive transition of the chemical industry toward renewable feedstock is emerging as an inevitable necessity.[3] Therefore, carbohydrates are an excellent substitute for products of fossil origin for industrial development.[4–7] Polymers containing carbohydrate moieties

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have also proved to be biodegradable and biocompatible, and so this could be a viable alternative for developing environmental friendly products.

Synthetic carbohydrate polymers are being increasingly investigated as biodegradable, biocompatible, and biorenewable materials for use, among others, as water absorbents, chromatographic supports, and medical devices.[8,9] Moreover, polymers with pendant carbohydrate moieties have been useful in clinical diagnostic applications, and for targeted gene therapies. Applications of these polymers are essential in surgery, for prosthetic systems and in pharmacology.[10–14]

This paper presents the synthesis of a new D-glucose based glycomonomer, namely 3-O-(2′-hydroxy-3′-methacryloyloxypropyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**4**). Starting with D-glucose, this product can be easily prepared in 4 steps involving isopropylidenation, allylation, epoxidation, and acylation of the resulting "epoxy" diacetonated sugar (**3**) with methacrylic acid (Figure 1). (+)-D-glucose was submitted to di-isopropylidenation according to the literature.[15,16] The resulting 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**1**) was protected with allyl chloride in anhydrous DMF using NaH as catalyst.[17,18]

Epoxides can be prepared by reacting vinyl groups with peroxy acids. From the various methods used for this conversion, the one using meta-chloroperbenzoic acid (MCPBA) at low temperature seemed the most appropriate for the preparation of compound **3**.[19] The oxirane or epoxy ring can be further homopolymerized or reacted with active hydrogen containing compounds such as amines, phenols, or acids.[20] We chose methacrylic acid to construct a biocompatible vinylic monomer.[21] The structure of the monomer **4** thus obtained was proved using IR and NMR analyses while HPLC-MS confirmed its molecular weight.

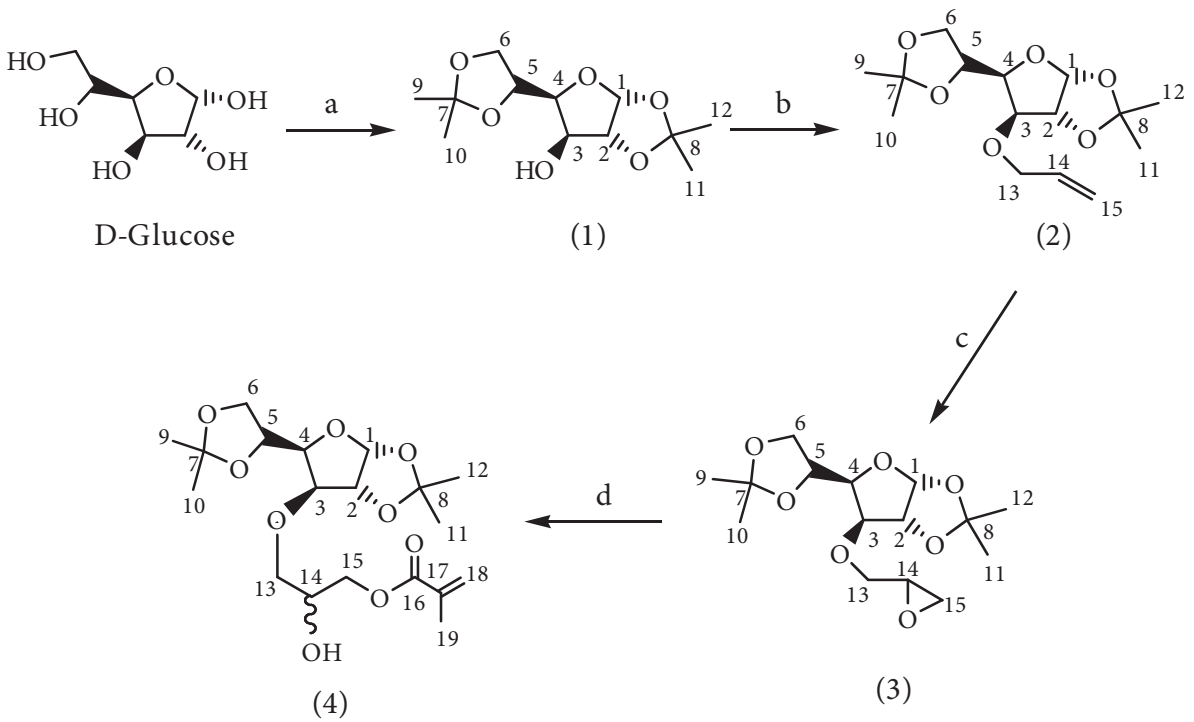

Figure 1. Preparation of D-glucose monomer: (a) acetone, H_2SO_4; (b) AllCl, NaH, DMF; (c) MCPBA, $CHCl_3$; (d) methacrylic acid, TEA.

Experimental

Materials and methods

All reagents were used as purchased. The syntheses were monitored using thin-layer chromatography performed on silica gel plates, Merck silica gel 60 F_{254} aluminum sheets.

The FTIR spectra were recorded on a Jasco FT/IR-410 spectrometer. The FTIR analyses were done using KBr plates for liquid samples (530-4000 cm^{-1}) and KBr pellets for solids (400-4000 cm^{-1}). NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer using TMS as reference and $CDCl_3$ as solvent. Chemical shifts are given in ppm; coupling constants (J) are in Hz. Atom numbering is given in Figure 1. Mass spectrometry experiments were performed using a quadrupole time-of-flight mass spectrometer, equipped with an electrospray ion source (Agilent 6520 Accurate Mass Q-ToF LC/MS). The samples were dissolved in a chloroform/methanol mixture (6:4). The solutions were introduced into the ESI source via a syringe pump at a flow rate of 0.2 mL/min. The electrospray interface was set in positive ionization mode with the capillary voltage at 4000 V and the heat source at 325 °C, in full scan spectra (m/z 100-1000). Nitrogen was used as a drying and nebulizing gas (7 L/min, 35 psi). Data were collected and processed using MassHunter Workstation software.

Synthesis of compounds 1-4

1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (1)

This compound was synthesized according to the literature.[15] White crystals; mp 105-107 °C; R_f (hexane/ethyl acetate 2:1) 0.28; **IR** (cm^{-1}): 3429, 2985, 2952, 2903, 2872, 1457, 1376, 1318, 1249, 1222, 1162, 1069, 1030, 847, 784; data are consistent with the values reported in the literature.[22]

3-O-allyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (2)

This compound was synthesized according to the literature.[17,18] Colorless syrup; R_f (hexane/ethyl acetate 6:1) 0.3; **IR** (cm^{-1}): 3082, 2990, 2935, 2894, 1737, 1649, 1649, 1457, 1428, 1373, 1255, 1214, 1166, 1078, 1023; ^{1}**H-NMR** and ^{13}**C-NMR** are according to the literature.[23]

3-O-(2′,3′-epoxypropyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (3)

3-O-allyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **(2)** (1.00 g, 3.33 mmol) in 5 mL $CHCl_3$ was cooled to 0 °C. MCPBA (2.29 g, 13.27 mmol, 4 equiv.) was added. The reaction mass was stirred for 24 h. The mixture was diluted with $CHCl_3$ and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The product was purified by recrystallization from cyclohexane. White crystals; 0.895 g (85% yield); R_f (hexane/ethyl acetate 2:1) 0.40; **IR** (cm^{-1}): 3055, 2987, 2934, 2892, 1734, 1457, 1374, 1255, 1214, 1166, 1079, 1020, 849, 759, 637, 537; ^{1}**H-NMR** (δ, ppm): 1.32 (s, 3H, H-12, H-12′), 1.35 (s, 3H, H-10, H-10′), 1.43 (s, 3H, H-9, H-9′), 1.50 (s, 3H, H-11, H-11'), 2.62 (dd, J=4.8, 2.8, H-15b'), 2.65 (dd, J=5.0, 2.6, H-15b), 2.80 (t, J=4.6, H-15a), 2.82 (t, J=4.6, H-15a'), 3.15 (H-14, H-14′), 3.48 (dd, J=11.6, 6.4, 0.37H, H-13b'), 3.64

(dd, J=11.8, 5.0, 0.61H, H-13b), 3.89 (H-13a), 3.95 (H-13a'), 4.00 (H-6b, H-6b', H-3, H-3′), 4.11 (H-4, H-4′, H-6a, H-6a'), 4.31 (H-5, H-5′), 4.55 (d, J=3.6, H-2), 4.60 (d, J=3.6, H-2′), 5.88 (d, J=3.6, H-1), 5.89 (d, J=3.6, H-1'); ^{13}**C-NMR** (δ, ppm): 25.4 (C-10, C-10′), 26.2 (C-12, C-12′), 26.8 and 26.9 (C-9, C-9′, C-11, C-11'), 44.1 (C-15), 44.4 (C-15′), 50.5 (C-14), 50.7 (C-14′), 67.4 (C-6, C-6′), 70.6 (C-13), 72.1 (C-13′), 72.4 (C-5), 72.4 (C-5′), 81.1 (C-4, C-4′), 82.5 (C-2′), 82.6 (C-2), 82.9 (C-3), 82.9 (C-3′); 105.2 and 105.2 (C-1, C-1'), 109.1 (C-7, C-7′), 111.8 (C-8, C-8′); **ESI-MS:** calcd. for $[C_{15}H_{24}O_7Na]^+ m/z$ = 339.15, found: m/z = 339.10 $[M+Na]^+$ (95%); calcd. for $[C_{15}H_{24}O_7K]^+$ 355.10, found 355.07 $[M+K]^+$ (5%).

D-glucose monomer (4)

To a solution of **3** (2 g, 6.32 mmol) in 10 mL of DMF were added methacrylic acid (4.29 mL, 4.36 g, 50.6 mmol) and triethylamine (0.7 mL, 0.51 g, 5.06 mmol) dropwise. The mixture was stirred vigorously while being heated to 65 °C. After 24 h, the mixture was cooled by adding distilled water. The resulting product was extracted into CH_2Cl_2, then washed with water, and dried over Na_2SO_4. The product was purified by silica gel column chromatography (hexane/ethyl acetate 1:1). Brownish viscous syrup; 1.65 g (65% yield); R_f (hexane/ethyl acetate) (1:1) 0.38; **IR** (cm^{-1}): 3482, 2987, 2934, 2896, 1719, 1637, 1459, 1375, 1216, 1167, 1076, 1020, 946, 848, 637, 540; ^{1}**H-NMR** (δ, ppm): 1.32 (s, 3H, H-12), 1.37 (s, 3H, H-10), 1.44 (s, 3H, H-9), 1.50 (s, 3H, H-11), 1.95 (s, 3H, H-19), 2.90 and 2.97 (OH, OH'), 3.46 (H-13b), 3.62 (H-13b'), 3.81 (H-13a'), 3.90 (H-13a), 4.02 (H-6b), 4.03 (H-14), 4.06 (H-3), 4.11 (H-4), 4.16 (H-6a), 4.21 (H-15), 4.330 (H-5); 4.38 (H-15′), 4.57 (H-2), 5.60 (t, 0.78 H, H-18b), 5.66 (t, 0.24 H, H-18b'), 5.90 (H-1), 6.14 (s, 0.77 H, H-18a), 6.22 (s, 0.22 H, H-18a'); ^{13}**C-NMR** (δ, ppm): 18.0 (C-19′), 18.3 (C-19), 25.1 (C-10′), 25.1 (C-10), 26.2 (C-12, C-12′), 26.8, 26.8 and 26.9 (C-9, C-9′, C-11, C-11'); 65.0 (C-15), 65.1 (C-15′); 67.9 and 67.9 (C-6, C-6′), 69.5 (C-14, C-14′), 71.0 (C-13′), 72.9 (C-13), 72.9 (C-5, C-5′), 81.3 (C-4, C-4′), 82.6 (C-2, C-2′), 83.1 (C-3′), 84.5 (C-3), 105.6 (C-1), 105.7 (C-1'), 109.5 (C-7′), 109.5 (C-7), 112.1 and 112.1 (C-8, C-8′), 126.1 (C-18), 127.3 (C-18′), 135.9 (C-17), 136.0 (C-17′), 167.3 (C-16), 171.2 (C16′); **ESI-MS:** calcd. for $[C_{19}H_{30}O_9Na]^+$ m/z = 425.19, found: m/z = 425.09 $[M+Na]^+$ (100%).

Results and discussion

FT-IR study

Allylation of **1** was readily proven from the FTIR spectra. The intense O-H bond stretching absorption band at 3429 cm^{-1} disappeared in the product **2** spectrum. The medium intensity ν_{as} C=CH_2 appeared at 3082 cm^{-1} while ν C=C revealed itself at 1645 cm^{-1}, both belonging to the allylic residue from the third OH of the furanosic ring. Both signals disappeared in the compound **3** spectrum as the epoxidic structure was formed; this and the epoxidic ν O-CH from 3055 cm^{-1} confirmed the oxidation of the double bond.

The FTIR spectrum of **4** confirms the structure of the D-glucose monomer. While the C=O from the esteric group shows a strong absorption band at 1719 cm^{-1}, the signal corresponding to ν_{as} C-O esteric bond overlaps with the acetal bands that appear around 1160 cm^{-1} in all mentioned compounds. The broad peak from 3482 cm^{-1} confirms the generated OH, while the signal at 1637 cm^{-1} is characteristic of the C=C bond from the methacrylic moiety.

NMR study

The NMR spectroscopy also confirmed the D-glucose derivatives structure. From ^{1}H-NMR spectroscopy we could observe that the singlet at 3.024 ppm corresponding to the free hydroxyl proton from **1** had disappeared (Figure 2). This confirms that O-allylation was achieved. Figure 3 displays the ^{1}H-NMR spectrum of allylated product. The synthesized compound **2** shows a shift value increase of 7-8 ppm at the alkylated carbon, typical for the conversion of a hydroxyl group into an alkoxyl.[24] The attached proton suffers a displacement in the opposite direction (from 4.305 to 3.947 ppm)

The ^{1}H-NMR spectrum of the epoxidated product **3** indicated the formation of both *cis-* and *trans-*epoxides ($\sim$ 3:2 ratio using protons 15b/15b') (Figure 4). The presence of the 2 diastereomers increased the complexity of this NMR spectrum (and also in the case of **4**) by doubling the ^{13}C and ^{1}H signals. As expected, the signals corresponding to the double bond protons of compound **2** (5.893 ppm and 5.254 ppm) are replaced by those of the epoxy group in compound **3** (2.708 ppm and 3.154 ppm, in this particular order). The allylic protons also suffer a similar shift to the right, and also an increase in the difference of magnetic vicinity. An increase in the magnetic shielding could be observed for carbons 14 (from 134.16 to 50.71/50.51) and 15 (from 117.32 to 44.43/44.07) of compound **3** when compared to compound **2**.

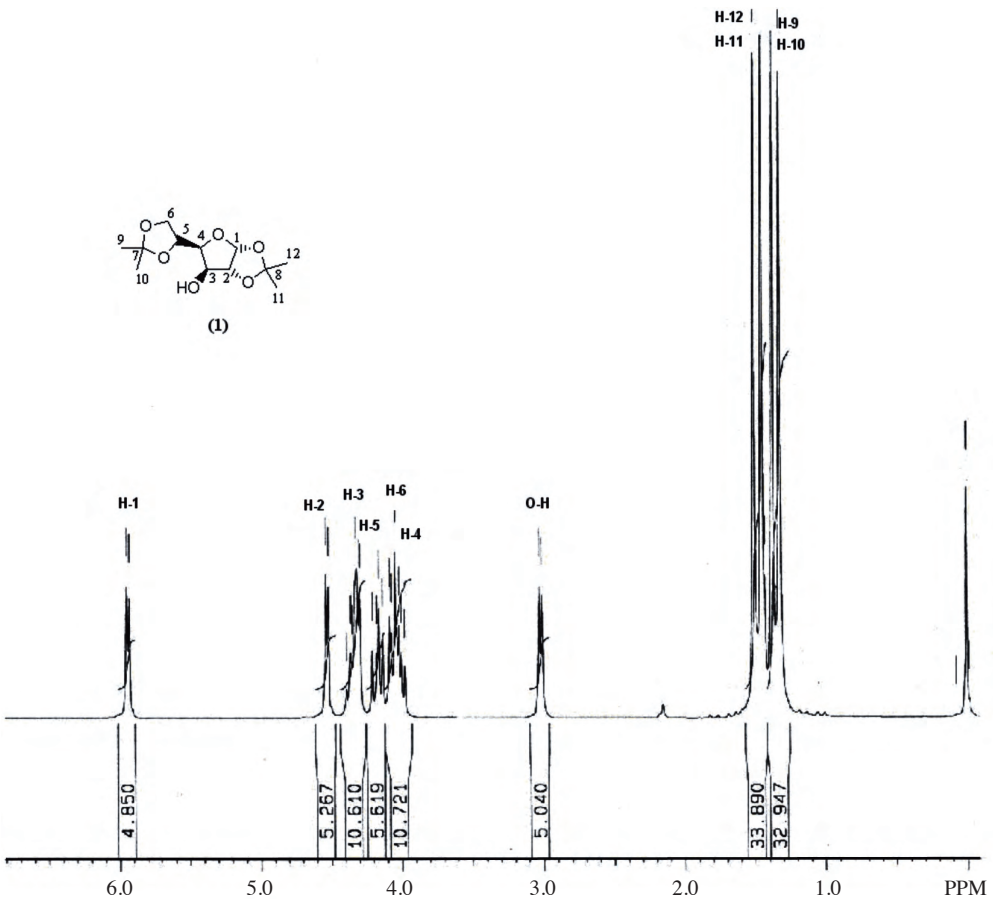

Figure 2. ^{1}H-NMR spectrum of **1**.

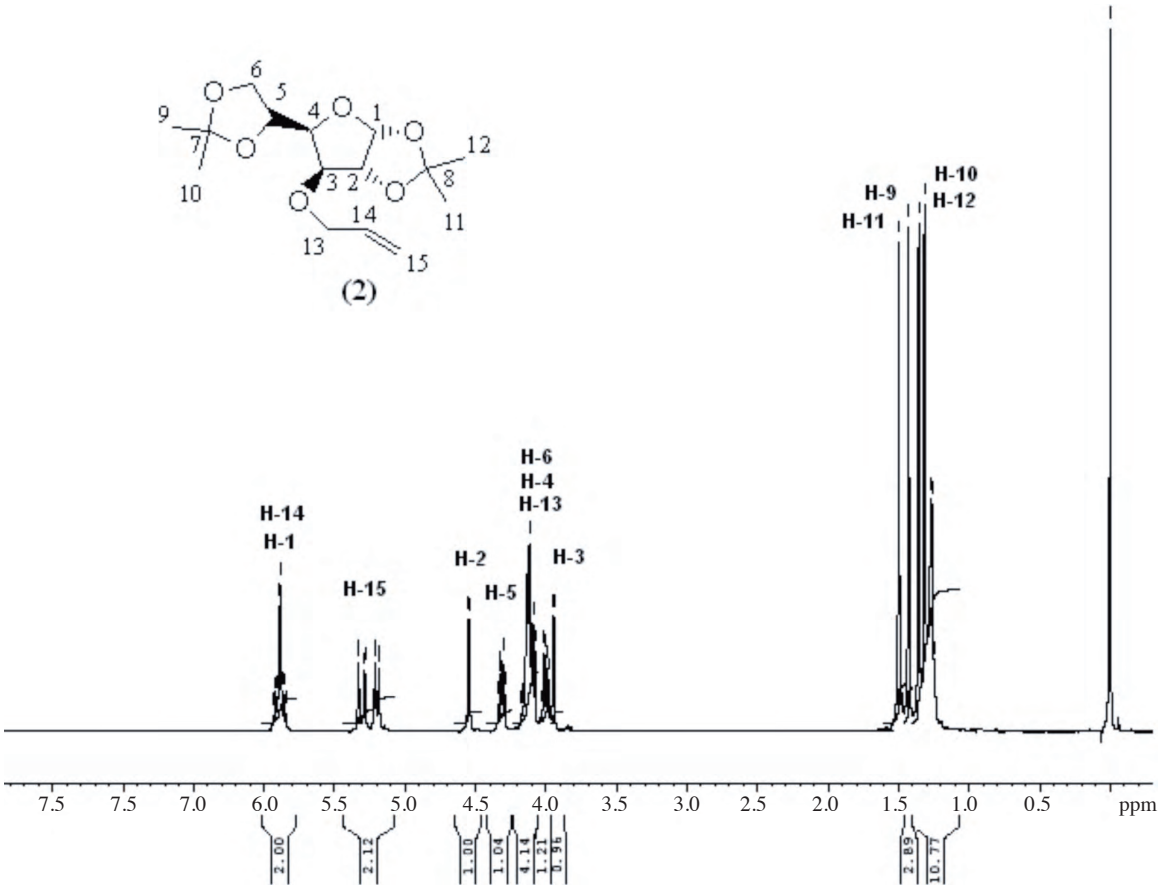

Figure 3. ^{1}H-NMR spectrum of **2**.

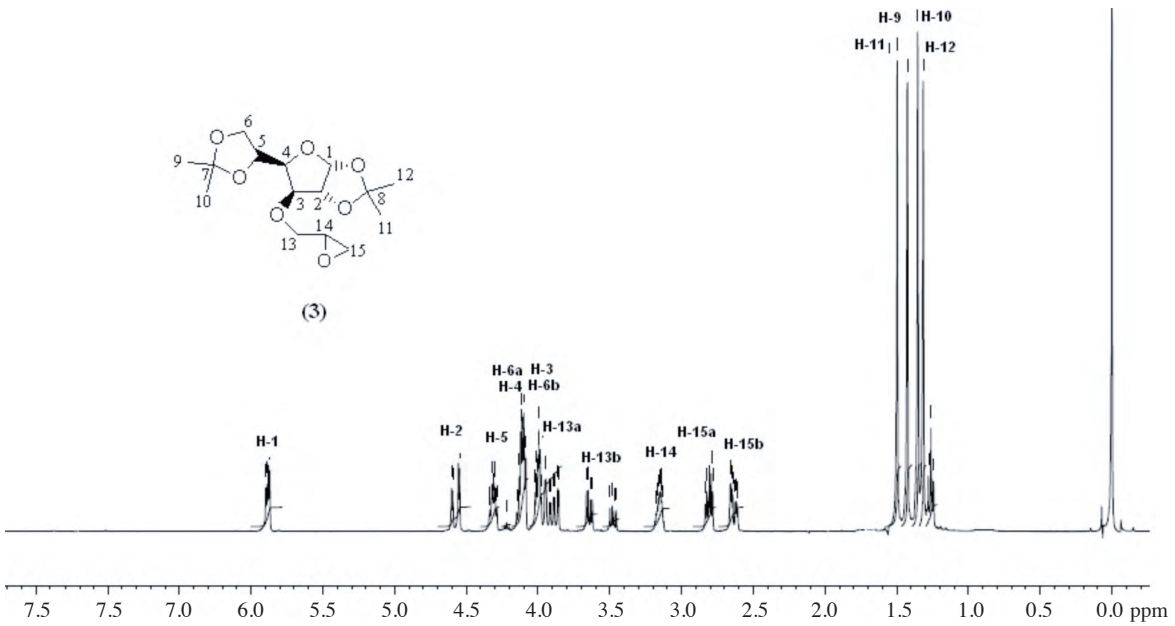

Figure 4. ^{1}H-NMR spectrum of **3**.

The ^{1}H spectrum of the D-glucose monomer (**4**) is presented in Figure 5 and shows the specific double bond protons in 2 groups (5.5-6.5 ppm) and the methyl (1.95 ppm) from the methacrylic moiety. From protons 18a/18a' and 18b/18b' we obtained a 3:1 ratio between the 2 diastereomers. The protons 14 and 15 move to higher values when compared with the same positions in compound **3**. Hydroxylic protons show faint signals at about 2.9 ppm. The esteric carbon atom gives a typical signal at about 170 ppm, while both double bond carbon atoms appear near 130 ppm in the ^{13}C spectrum of compound **4**. C-14 and C-15 move approximately 20 ppm to higher values when compared to compound **3**.

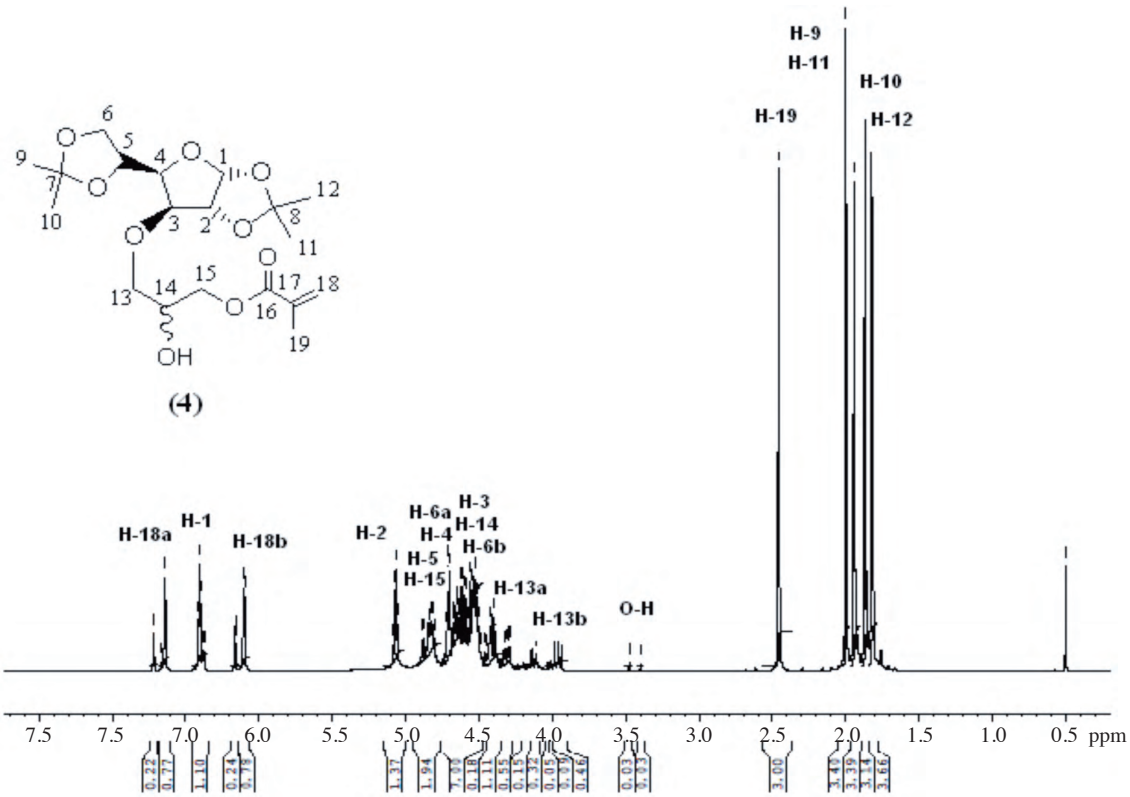

Figure 5. ^{1}H-NMR spectrum of **4**.

MS analysis

Soft ionization methods in mass spectrometry are now widely available for structure elucidation of natural products, particularly for glycoconjugates.[25–27] This is why we performed HPLC-ESI-MS analyses on our products. These were detected as Na or K adducts. The mass spectrum for compound **2** is presented in Figure 6. The peak observed at $m/z = 323.11$ is associated with the presence of the single-charge sodium adduct. The peak at $m/z = 623.25$ corresponds to the dimeric sodium adduct $[2M+Na]^+$. Furthermore, other ions of $m/z = 363.14$ (the base peak), 379.33, and 703.31 could be attributed to sodium adducts $[M+C_3H_4+Na)]^+$, $[M+C_3H_4O+Na)]^+$, and $[2(M+C_3H_4)+Na)]^+$.

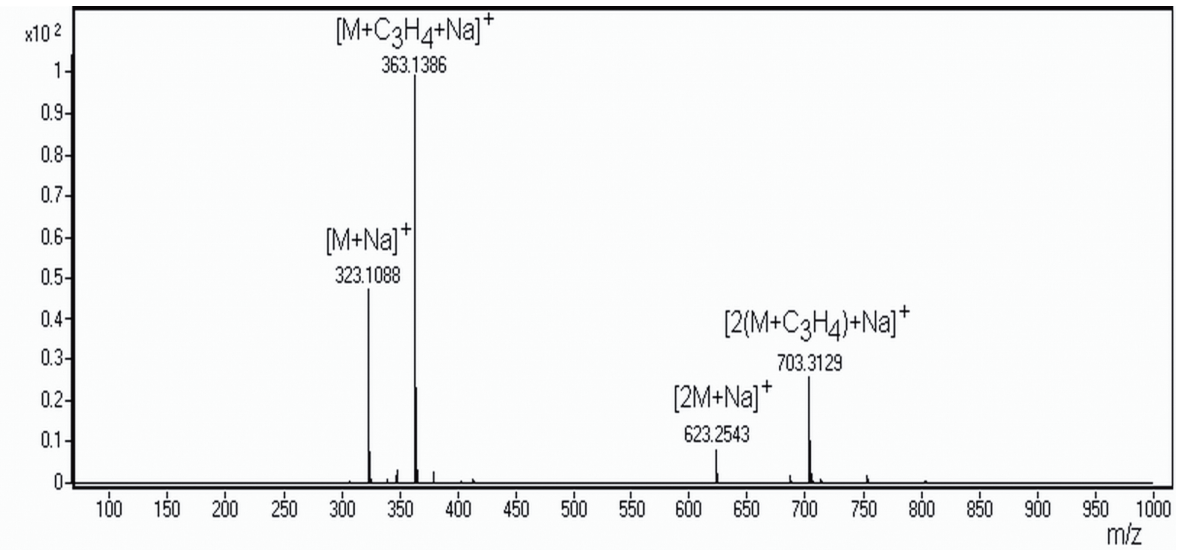

Figure 6. ESI mass spectrum of **2**.

Figure 7 displays the mass spectrum for **3**. The most abundant ion corresponds to single-charge sodium adduct at $m/z = 339.10$. The peaks observed at $m/z = 317.09$ and $m/z = 355.08$ are associated with $[M+H]^+$ and the presence of the potassium adduct $[M+K]^+$, respectively. The peaks accompanying the base peak are $[2M+C_3H_6O_2+Na]^+$ at $m/z = 729.36$ and $[2(M+C_3H_6O_2)+Na]^+$ at $m/z = 803.48$, corresponding to the dimeric adduct with sodium and $C_3H_6O_2$. Moreover, an additional peak can be observed at $m/z = 413.22$ and can be associated with $[M+C_3H_6O_2+Na]^+$. CID MS/MS of the sodium adduct at 339.10 displayed 2 M = 58 losses (at $m/z = 281.06$ and 223.02), assigned to the cleavage of the isopropylidene protecting groups. The epoxidic oxygen loss can be clearly seen at $m/z = 323.80$, while the peak at $m/z = 144.98$ indicates the leaving of both acetal groups and of the epoxidic 3 carbon atom chain (Figure 8).

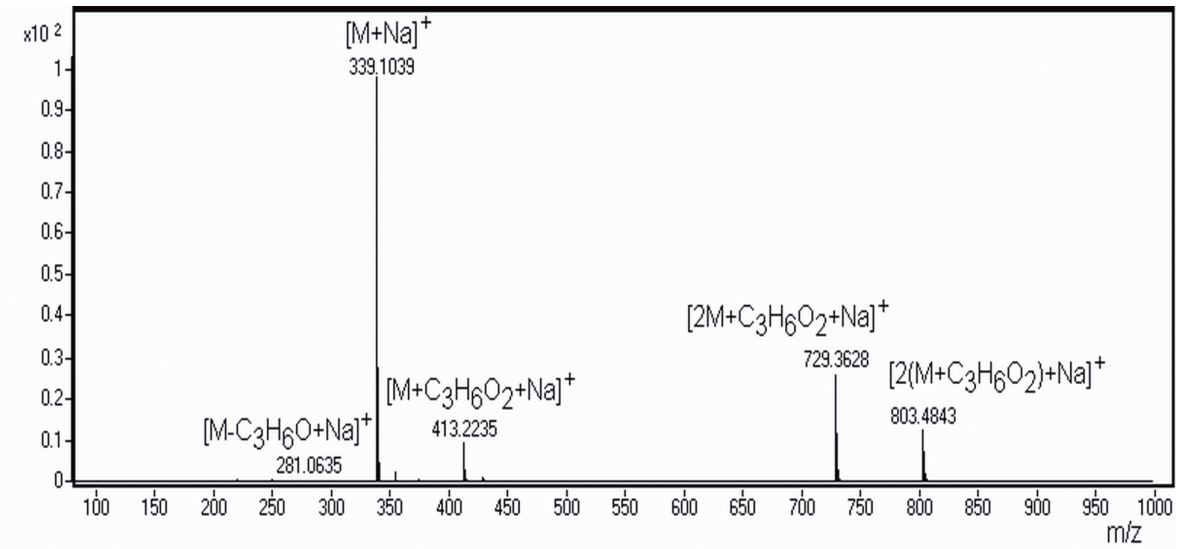

Figure 7. ESI mass spectrum of **3**.

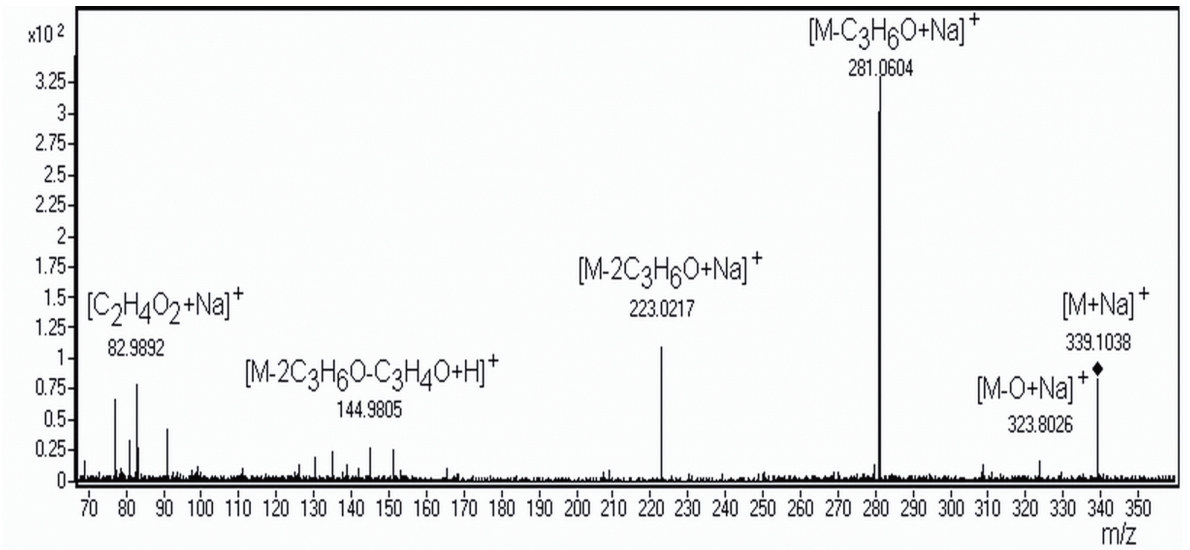

Figure 8. MS/MS spectrum of **3**.

Figure 9 displays the mass spectrum for **4**. The base peak is observed at $m/z = 425.09$ and is associated with the presence of the single-charge sodium adduct. Another ion of $m/z = 464.02$ is also detectable and can be attributed to the sodium adduct $[M+C_3H_3+Na)]^+$. The peaks at $m/z = 287.04$ and $m/z = 345.08$ indicate the loss of the 2 isopropylidene units, while the peak at $m/z = 143.03$ was associated with the cleavage of the glycosidic moiety at C-13.

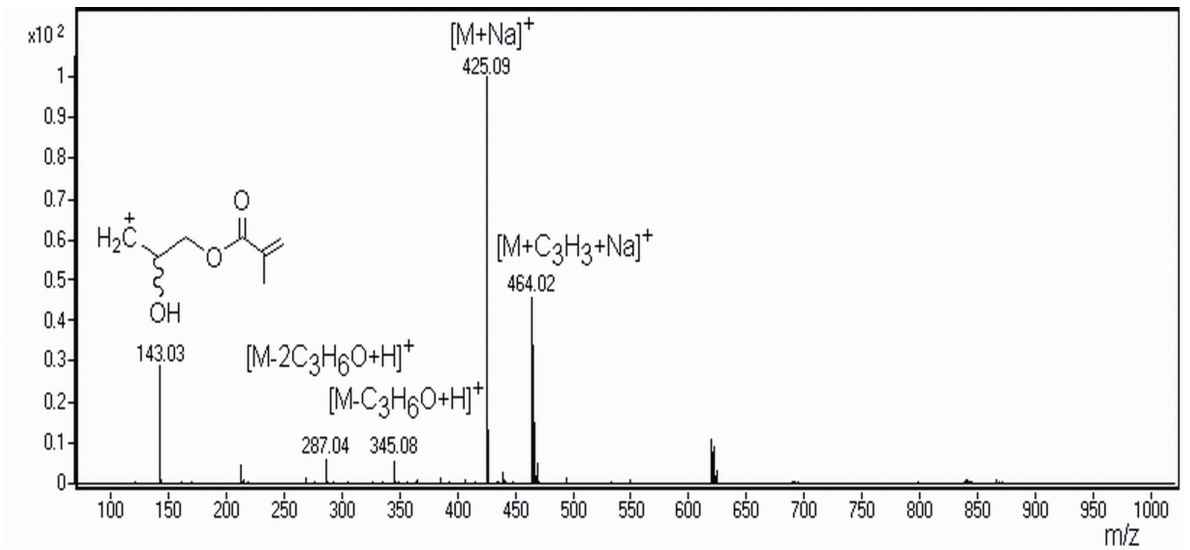

Figure 9. ESI mass spectrum of the D-glucose monomer **4**.

Acknowledgments

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References

1. Dontulwar, J. R.; Borikar, D. K.; Gogte, B. B. *Carbohyd. Polym.* **2006**, *63*, 375-378.
2. Saiah, R.; Sreekumar, P. A.; Leblanc, N.; Saiter, J. M. *Ind. Crop. Prod.* **2009**, *29*, 241-247.
3. Cuervo-Rodríguez, R.; Bordegé, V.; Fernández-García, M. *Carbohyd. Polym.* **2007**, *68*, 89–94.
4. Borges, M. R.; Dos Sandos, J. A.; Vieira, M.; Balaban, R. *Mat. Sci. Eng.: C.* **2009**, *29*, 519-523.
5. Pană, A. M.; Rusnac, L.; Bandur, G.; Şişu, E.; Badea, V. *Mater. Plast.* **2010**, *47*, 28-34.
6. Şişu, E.; Neanu, C.; Şişu, I.; Lascu A.; Căproiu, M.; Francisc, P.; Csunderlik, C.; Rusu, V. *Rev. Chim.* **2002**, *53*, 750-754.
7. Rusu, V.; Şişu, E.; Neanu, C.; Şişu, I.; Lascu, A.; Căproiu, M.; Francisc, P.; Csunderlik, C. *Rev. Chim.* **2002**, *53*, 815-818.
8. Bertini, V.; Pocci, M.; Alfei, S.; Idini, B.; Lucchesini, F. *Tetrahedron* **2007**, *63*, 11672-11680.
9. Sanchez-Chaves, M.; Ruiz, C.; Cerrada, M. L.; Fernandez-Garcia, M. *Polymer* **2008**, *49*, 2801-2807.
10. Lichtenthaler, F. W.; Peters, *S. C. R. Chimie* **2004**, *7*, 65-90.
11. Varma, A. J.; Kennedy, J. F.; Galgali, P. *Carbohyd. Polym.* **2004**, *56*, 429-445.
12. Sampath, C. A.; Edward, T. *Carbohyd. Polym.* **2007**, *70*, 32-37.
13. Stanek, L. G.; Heilmann S. M.; Gleason W. B. *Carbohyd. Polym.* **2006**, *65*, 552-556
14. Vert, M. *Progr. Polym. Sci.* **2007**, *32*, 755-761.
15. Hanessian, S. *Preparative Carbohydrate Chemistry*, CRC Press, Boca Raton, FL, 1997.
16. Rajput, V. K.; Mukhopadhyay, B. *Tetrahedron Lett,* **2006**, *47*, 5939-5941.
17. Osborn, H. M. I. *An Introduction to Carbohydrate Synthesis*, Academic Press, New York, 2002.
18. Pană, A. M.; Rusnac, L.; Bandur, G.; Deleanu C.; Bălan, M. *E-Polymers* **2011**, *004*, 1-14.
19. Srinivasan, R.; Chandrasekharam, M.; Vani, P. V. S. N.; Seema Chida, A.; Singhy, A. K. *Synthetic Commun.* **2002**, *32*, 1853-1858.
20. Evtushenko, Yu. M.; Ivanov, V. M.; Zaitsev, B. E. *J. Anal. Chem.* **2002**, *57*, 624-628.
21. Salagean, I. R.; Bandur, G.; Martin P.; Lequart, V.; Rusnac L. M. *Rev. Chim.* **2009**, *60*, 905-908.
22. Pană, A. M. *Oligomers Including Carbohydrates in the Main Chain and Derived Glycopolymers*, Politehnica, Timisoara, 2010.

23. Shing, T. K. M.; Leung, G. Y. C. *Tetrahedron* **2002**, *58*, 7545-7552.

24. Bertini, V.; Pocci, M.; Alfei, S.; Idini, B.; Lucchesini, F. *Tetrahedron* **2007**, *63*, 11672-11680.

25. Şişu, I.; Udrescu, V.; Flangea, C.; Dinca, N.; Tudor S.; Rusnac, L.; Zamfir, A. D.; Şişu, E. *Cent. Eur. J. Chem.* **2009**, *7*, 66-73.

26. Şişu, E.; Bosker, W. T. E.; Norde, W.; Slaghek, T. M.; Timmermans, J. W.; Katalinic, J. P.; Cohn-Stuart, M. A.; Zamfir, A. D. *Rapid Commun. Mass Sp.* **2006**, *20*, 209-218.

27. Perdivara, I.; Şişu, E.; Sisu, I.; Dinca, N.; Tomer, K. B.; Przybylski, M.; Zamfir, A. D. *Rapid Commun. Mass Sp.* **2008**, *22*, 773-782.