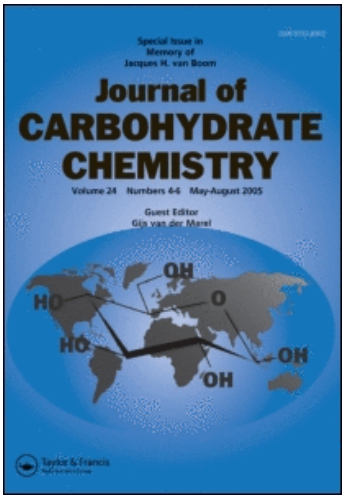

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Selective TEMPO-Catalyzed Chemicals vs. Electrochemical Oxidation of Carbohydrate Derivatives

Maximilien Barbier[a]; Tony Breton[b]; Karine Servat[b]; Eric Grand[a]; Boniface Kokoh[b]; José Kovensky[a]
[a] Laboratoire des Glucides, CNRS UMR 6219, Faculté des Sciences, Université de Picardie "Jules Verne", Amiens, France [b] Laboratoire de Catalyse en Chimie Organique, CNRS UMR 6503, Université de Poitiers, Poitiers Cedex, France

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Selective TEMPO-Catalyzed Chemicals vs. Electrochemical Oxidation of Carbohydrate Derivatives

Maximilien Barbier

Laboratoire des Glucides, CNRS UMR 6219, Faculté des Sciences, Université de Picardie "Jules Verne", Amiens, France

Tony Breton and Karine Servat

Laboratoire de Catalyse en Chimie Organique, CNRS UMR 6503, Université de Poitiers, Poitiers Cedex, France

Eric Grand

Laboratoire des Glucides, CNRS UMR 6219, Faculté des Sciences, Université de Picardie "Jules Verne", Amiens, France

Boniface Kokoh

Laboratoire de Catalyse en Chimie Organique, CNRS UMR 6503, Université de Poitiers, Poitiers Cedex, France

José Kovensky

Laboratoire des Glucides, CNRS UMR 6219, Faculté des Sciences, Université de Picardie "Jules Verne", Amiens, France

TEMPO-catalyzed electrochemical oxidation of carbohydrate derivatives was performed and compared with chemical oxidation, which requires the use of co-oxidants. Allyl-protected derivatives could be readily oxidized by both methods. Electrochemical selective

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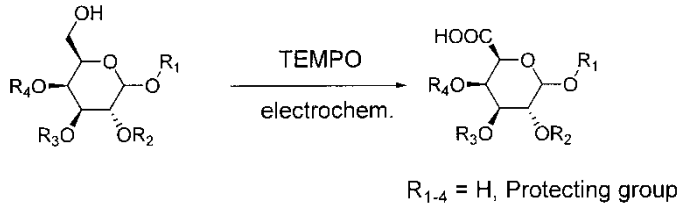
Address correspondence to José Kovensky, Laboratoire des Glucides, CNRS UMR 6219, Faculté des Sciences, Université de Picardie "Jules Verne", 33 rue Saint-Leu, 80039, Amiens, France. E-mail: jose.kovensky@u-picardie.fr

oxidation of primary positions has been adapted to unprotected mono- and oligosaccharides.



Keywords TEMPO, Selective oxidation, Allyl-protected carbohydrates

INTRODUCTION

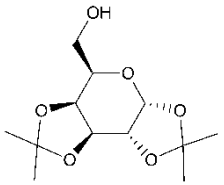
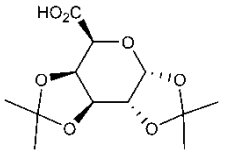
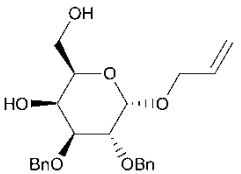
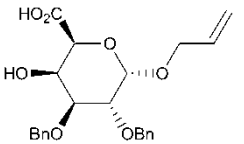
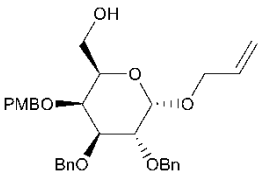
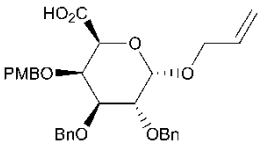
In the last decade, the use of organic nitroxyl radicals has been introduced in carbohydrate chemistry for the selective oxidation of primary alcohols. Successful oxidations of primary alcohol groups of monosaccharides, oligosaccharides, and polysaccharides to the corresponding carboxyl functionalities have been reported.[1–13] The stable nitroxyl radical—2,2,6,6-tetramethyl-1-piperidinyl-oxy (TEMPO)—is oxidized through a one-electron transfer reaction to the corresponding nitrosonium salt, which is the active oxidant in the primary alcohol oxidation.[14,15] Nitroxyl radicals can be used in catalytic amounts; the presence of a regenerating oxidant system is required. Typical procedures using homogeneous (aq NaClO-KBr or NaBr) or biphasic systems (water-CH_3CN-NaClO-$NaClO_2$) have been adapted to organic and water soluble substrates, respectively.

Electrochemical oxidation of the hydroxylamine formed to regenerate TEMPO is an interesting alternative to chemical co-oxidants.[16,17] We report here our results for the electrochemical TEMPO oxidation of primary positions of different carbohydrate derivatives compared with chemical oxidation.

RESULTS AND DISCUSSION

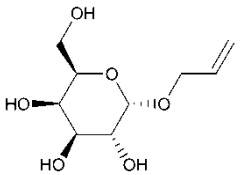
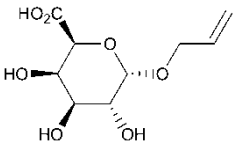
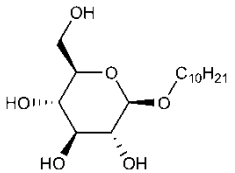
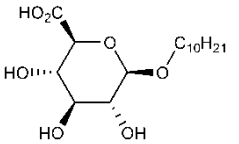
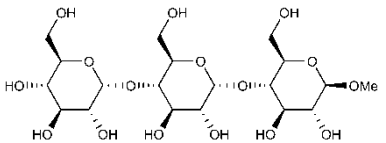
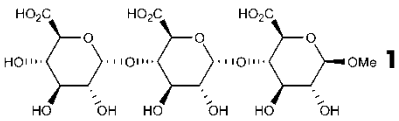
The results of chemical and electrochemical oxidation of a series of carbohydrate compounds are summarized in Table 1. A typical voltammogram, demonstrating the action of oxoammonium ions on protected carbohydrates, is presented in Figure 1. The shape of the voltammogram in the presence of allyl 2,3-di-O-benzyl-4-*O*-*p*-methoxybenzyl-α-D-galactopyranoside shows that the oxidation begins at ca. 0.25 V ($Ag/AgNO_3$) (i.e., after the formation of oxoammonium ions). The plateau observed on the j-E profile suggests that the oxidation mechanism is a controlled diffusion process.

Table 1: Carbohydrate derivatives used as starting materials and their oxidation products.

Starting material		Product		Time for total conversion/yield		
				H_5IO_6/CrO_3	TEMPO chemical	TEMPO electrochem.
	**1**		**7**	15 min 97%	4 days method A 91%	21 h method C 56%
	**2**		**8**	—	4 days method A 58%	24 h method C 57%
	**3**		**9**	Degradation	4 days method A 95%	24 h method C 50%

(*continued*)

Table 1: Continued.

Starting material		Product		Time for total conversion/yield		
				H_5IO_6/CrO_3	TEMPO chemical	TEMPO electrochem.
	**4**		**10**	—	14 days method A[#] 65%	29 h method D 70%
	**5**		**11**	—	4 days method A[§] 90%	23 h method D* 97%
	**6**		**12**	—	no reaction method B 8 days method A 74%	48 h method D 86%

Chemical oxidation. Method A: Acetonitrile - phosphate buffer pH 6.7 - $NaClO_2$ - NaClO. Method B: NaClO - KBr.
Electrochemical oxidation. Method C: CH_3CN - 5% of 0.2 M $NaClO_4$. Method D: Carbonate buffer (0.5 M, pH 10).
[#] After 14 days, the reaction was stopped at 80% conversion. Oxidation of **4** by method B gave mucic acid in 2 days.
[§] Oxidation of **5** by method B is slower, and complete disparition of starting material was not observed.
*5% CH_3CN was added to prevent foaming of the tensioactive compound **5** during stirring.

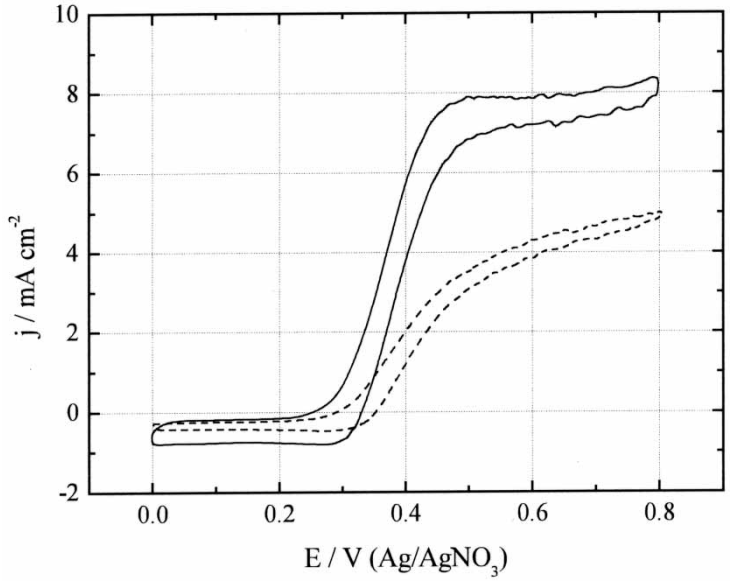


Figure 1: Cyclic voltammetry of 9.6 mg (0.3 equiv.) of TEMPO recorded at 50 mV s^{-1} in CH_3CN/H_2O (95/5), 0.2 M $NaClO_4$, under stirred conditions on a vitreous carbon anode with 8 equiv. of 2,6-lutidine (·····), and in presence of 0.20 mmole of allyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-α-D-galactopyranoside (—).

Protected Carbohydrate Derivatives (No Free Secondary Alcohols)

Compounds **1** and **3** are galactose derivatives possessing their primary hydroxyls as the unique unprotected function. Conventional chemical methods should work well enough to obtain the oxidized products in good yields. H_5IO_6-CrO_3oxidation[18] of 1,2 : 3,4-di-*O*-isopropylidene-α-D-galactopyranose **1** allowed to obtain, as expected, the galacturonic acid **7**[19] in 15 min. In this case, TEMPO-catalyzed oxidation, either chemical or electrochemical, did not improve the yield, the reaction times being longer.

On the other hand, when allyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-α-D-galactopyranoside (**3**) was submitted to the same H_5IO_6-CrO_3 reaction conditions, the degradation of starting material was observed, probably due to the undesired deprotection of the acid-sensitive *p*-methoxybenzyl group at HO-4, leading to further oxidation. Compound **3** was smoothly converted to the corresponding acid **9** by TEMPO ($NaClO_2$-NaOCl in acetonitrile-phosphate buffer) in 4 days in very good yield. Electrochemical oxidation of **3**, performed in aqueous acetonitrile in the presence of 2,6-lutidine, was disappointing: Degradation of the starting material was observed, and the desired product **9** could be isolated in 30% yield. This result is probably due to the radical cleavage of the *p*-methoxybenzyl

group. Oxidation of benzyl groups by oxoammonium salts has been previously reported,[20] and the presence of the *p*-methoxy susbtituent would make the group easier to oxidize. However, in the chemical oxidation this cleavage was not detected. A possible explanation is that the biphasic medium used for the $NaClO_2$ system prevents the formation of radical species or their attack to the sensitive protecting group.

Partially Protected Carbohydrate Derivatives (One Free Secondary Hydroxyl)

The TEMPO-NaClO system is useful for the selective oxidation of primary positions in the presence of unprotected secondary hydroxyls, while no other chemical oxidation (i.e., chromium-based reactives) can be employed. The dibenzyl derivative **2**[21] could be readily oxidized to **8**, although in 58% yield and after several days. Electrochemical oxidation allowed to reach similar yield, but in shorter reaction times (24 h).

Unprotected Carbohydrate Derivatives (Several Free Hydroxyls)

The transformation of carbohydrates by electrochemical oxidation is carried out under mild conditions, avoiding the formation of side products and the use of co-oxidants. The main interest is to analyze the behavior of unprotected sugar derivatives in comparison to the chemical oxidation in a homogeneous system. For water-soluble starting materials, the electrochemical reaction was performed in aqueous carbonate buffer. Allyl α-D-galactopyranoside **4**[22] and *n*-decyl β-D-glucopyranoside **5** were submitted to chemical oxidation with TEMPO to give galacturonic acid **10** (see below) and glucuronic acid **11**, respectively. Both conditions A and B were tested for compound 5, due to its amphiphilic character. When KBr conditions were used, the reaction did not reach completion and was slower. On the other hand, the method A resulted more appropriately to prevent foaming, end the oxidized product **11** was obtained in 4 days. Electrochemical oxidation of both **4** and **5** proceeded in 29 h and 23 h, respectively, leading to **10** and **11** in very good yields.

Compatibility with Allyl Protecting Groups

The interesting results observed on chemical TEMPO oxidation of allyl-containing compounds such as **2**, **3**, and **4** merit some comment. It has been claimed that TEMPO-mediated oxidation with sodium hypochlorite was incompatible with allyl ether-protected carbohydrates,[23] and that the application of nitroxyl radicals in the presence of an allyl group would be impossible

as the double bond of this group is sensitive to radicals.[24] Actually, when we performed the oxidation of allyl galactoside **4** by the method B (aq NaOCl, KBr), the product obtained was mucic acid, thus indicating that the anomeric allyl-protecting group was lost and both primary positions oxidized to the dicarboxylic acid. On the other hand, compounds **2** and **3** were readily oxidized to **8** and **9**, respectively, in the standard conditions normally used for organic soluble starting materials (method A: $NaClO_2$ - NaOCl in water acetonitrile), without cleavage of the allyl group. When we applied these conditions to **4**, the oxidation proceeded slowly but smoothly to give compound **10**. Therefore, we can conclude that the allyl group is not incompatible with TEMPO oxidation. To prevent allyl cleavage, it is necessary to perform the oxidation without the use of NaBr (or KBr) in the reaction mixture. This effect is probably due to the known effect of enhancement of radical reactivity produced by these salts. A drawback of this NaBr-free system is the longer reaction times observed for oxidations (several days). Electrochemical TEMPO oxidation of different allyl-containing derivatives avoids this problem and afforded the expected carboxylic acids in good to excellent yields; these reactions proceed in the absence of NaBr or KBr salts.

Oxidation of Methyl β-D-Maltotrioside

Finally, we tried the oxidation of maltotrioside **6**[25] to the corresponding glucuronic acid trisaccharide **12**. Unlike the monomers, a difference was observed in the uptake of charge. In fact, after 48 h, the reaction seemed to be stopped as no evolution in charge transfer was observed. For a calculated Q of 223C, the effective charge transferred was 176C. This fact can simply be due to a slow diffusion of oxidized species from the electrode, but it could indicate that one of the primary alcohol functions is particularly resistant to oxidation (i.e., the central C-6, or simply the last one to be oxidized). Analytical high-pressure anion exchange chromatography (HPAEC-PAD) of the reaction mixture before completion showed the presence of two products, but we were not able to characterize the partial oxidized trisaccharide. The oxidized trisaccharide was purified through Biogel P-2 and obtained as the trisodium salt. Attempts to perform chemical oxidation of **6** by method B were unsuccessful, and no change was observed even after a week. Surprisingly, oxidation could be accomplished by method A, where a biphasic system is used, and the reaction time was 8 days. Electrochemical oxidation is therefore a good alternative to obtain fully oxidized oligosaccharides.

CONCLUSIONS

The transformation of carbohydrates by electrochemical oxidation is carried out under mild conditions, which avoid the production of side products,

except in the presence of *p*-methoxybenzyl-protecting groups. The complete oxidation can be controlled by the quantity of electricity corresponding to the regeneration of oxoammonium ions. This electrochemical process allows shorter reaction times in comparison to a homogeneous system. We could also determine that in the absence of bromide salts, the TEMPO oxidation is compatible with allyl-protecting groups. On the other hand, electrochemical oxidation could be useful to perform extensive modifications of oligosaccharides. Although tested on a 100 mg scale, the method described can be easily adapted to multigram quantities for applying to synthesis of added value products.

EXPERIMENTAL

Chemical Oxidation

Method A (organic-soluble compounds). To a solution of the carbohydrate substrate and TEMPO (0.07 equiv.) in a 55 : 45 mixture of acetonitrile and 0.67 M phosphate buffer (pH 6.7), $NaClO_2$ (20% aq solution, 2.0 equiv.) and NaClO (15% aq solution, 0.06 equiv.) were added. After stirring for 4 days, ether and $Na_2S_2O_3$ (0.5 M aq solution) were added. The mixture was acidified to pH 2 with conc aq HCl, and the aqueous phase was extracted with ether. The organic layers were assembled, dried (anhydrous Na_2SO_4), filtered, and evaporated to give the crude acid, which was purified by silica gel chromatography.

Method B (water-soluble compounds). To a solution of the carbohydrate substrate, TEMPO (0.1 equiv.) and NaBr (0.3 equiv.) in water (30 mL) were added. NaClO (15% aq solution, 3.0 equiv.) were slowly added to the solution previously brought to pH 10 by adding 4 M HCl. The pH was automatically maintained at 10 by adding 0.5 M NaOH with a pH-stat. After stirring for 24 h, additional NaClO (15% aq solution, 3.0 equiv.) was added and the mixture stirred another 24 h. After solvent evaporation or lyophilization, the crude acid was purified and characterized.

Electrochemical Oxidation

Method C (organic-soluble compounds). To a solution of the starting carbohydrate derivative (100 mg) and TEMPO (0.3 equiv.) in 95 : 5 acetonitrile - 0.2 M aqueous $NaClO_4$ (40 mL), lutidine (8 equiv.) was added. The potential was applied until a total charge of 4 Faraday per mole was consumed. After solvent evaporation, ethyl acetate and 10% aq HCl were added. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and evaporated to give the crude acid. Flash chromatography using the indicated eluant gave pure products.

Method D (water-soluble compounds). A solution of the starting carbohydrate derivative (100 mg) and TEMPO (0.3 equiv.) in 0.5 M aqueous sodium carbonate buffer (40 mL, pH 10) was used. The potential was applied until a total charge of 4 Faraday per mole was consumed. The mixture was treated with Amberlite 200 (H^+), filtered, and concentrated.

Working electrode: graphite
Counter electrode: Pt separated from the electrolyte with a proton exchange membrane
Reference electrode: $Ag/AgNO_3$ (0.1 M)

Allyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-*α*-D-galactopyranoside (3). Allyl *α*-D-galactopyranoside **4**[22] was first converted to its 4,6-*O*-*p*-methoxybenzylidene derivative (*p*-methoxybenzaldehyde dimethyl acetal, *p*-toluenesulfonic acid, DMF), followed by benzylation (NaH, BnBr, DMF) and finally reductive opening of the *p*-methoxybenzylidene acetal ($LiAlH_4$, $AlCl_3$, dichloromethane-ether) to give **3** (59% overall yield), as syrup: $[\alpha]_D + 10$ (*c* 0.23, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.32 (m, 10H, H_{Ar}-Bn), 7.29 (d, 2H, J_o 8.3 Hz, PMB), 6.90 (d, 2H, J_o 8.3 Hz, PMB), 5.98 (dddd, 1H, $J_{2',3'trans}$ 17.2 Hz, $J_{2',3'cis}$ 10.3 Hz, $J_{1'a,2'}$ 5.5 Hz, $J_{1'b,2'}$ 6.4 Hz, H-2′), 5.35 (broad d, 1H, $J_{2',3'trans}$ 17.2 Hz, H-3′a), 5.24 (broad d, 1H, $J_{2',3'cis}$ 10.3 Hz, H-3′b), 4.97 (d, 1H, $J_{1,2}$ 3.2 Hz, H-1), 4.94 (d, 2H, J_{gem} 11.4 Hz, C<u>H</u>Ph), 4.87 (d, 1H, J_{gem} 11.8 Hz, C<u>H</u>Ph), 4.80 (d, 1H, J_{gem} 11.4 Hz, C<u>H</u>Ph), 4.73 (d, 1H, J_{gem} 11.8 Hz, C<u>H</u>Ph), 4.63 (d, 1H, J_{gem} 11.4 Hz, C<u>H</u>Ph), 4.19 (broad dd, 1H, J_{gem} 13.2 Hz, $J_{1'a,2'}$ 5.5 Hz, H-1′a), 4.11 (dd, 1H, $J_{1,2}$ 3.2 Hz, $J_{2,3}$ 9.9 Hz, H-2), 4.08–4.05 (m, 1H, $J_{1'b,2'}$ 6.4 Hz, H-1′b), 4.02 (dd, 1H, $J_{2,3}$ 9.9 Hz, $J_{3,4}$ 2.8 Hz, H-3), 3.93 (broad d, 1H, $J_{3,4}$ 2.8 Hz, H-4), 3.85–3.78 (m, 4H, H-5, OMe), 3.73 (dd, 1H, J_{gem} 11.1 Hz, $J_{5,6a}$ 6.2 Hz, H-6a), 3.53 (m, 1H, J_{gem} 11.1 Hz, H-6b), 2.04 (s large, 1H, OH). ^{13}C NMR (75,5 MHz, $CDCl_3$): 159.2 (<u>C</u>$_i$-OMe), 138.7, 138.4 (<u>C</u>$_i$-Ph), 133.8 (C-2′), 130.1 (<u>C</u>$_i$-PMB), 130.0 (PMB), 128.2–127.3 (Ph), 117.8 (C-3'), 113.7 (PMB), 96.2 (C-1), 79.0 (C-3), 76.4 (C-2), 74.5 (C-4), 73.8, 73.4, 73.2 (<u>C</u>H_2Ph), 70.3 (C-5), 68.2 (C-1′), 62.2 (C-6), 55.1 (OMe).

ES-HRMS (+Na): Calcd. for $C_{31}H_{36}O_7Na$: m/z 543.2359. Found: 543.2371.

1,2:3,4-di-*O*-isopropylidene-*α*-D-galactopyranosiduronic acid (7). TEMPO-chemical oxidation: Method A (91% yield). TEMPO-electrochemical oxidation: Method C (56% yield). E = +0.55 V ($Ag/AgNO_3$). Q = 215 C (theor. 154 C). Chromium-chemical oxidation: To a solution of 1,2:3,4-Di-*O*-isopropylidene-*α*-D-galactopyranose (**1**, 105 mg, 0.403 mmol) in acetonitrile (2.0 mL) and water (15 μL), a solution of H_5IO_6/CrO_3 (2.45 mL, 4.84 mmol/1.2 mol % in 0.75% H_2O/CH_3CN) was added at 0°C. After 15 min, $Na_2S_2O_3$ (10 mL of a 14% aq solution) was added and the aqueous solution was washed with

dichloromethane (2 × 10 mL) and ethyl acetate (15 mL). The mixture was acidified to pH 2 with conc aq HCl, and the aqueous phase was extracted with dichloromethane (3 × 15 mL) and ethyl acetate (3 × 15 mL). The organic layers were assembled, dried (anhydrous Na_2SO_4), filtered, and evaporated to give the crude acid, which was purified by silica gel chromatography (ethyl acetate, then 1 : 1 ethyl acetate – methanol), leading to **7** (108 mg, 97% yield) as a white solid, which was recrystallized from diisopropylether-cyclohexane: m.p. 159.5–160°C (lit.[19] 157°C); $[\alpha]_D - 49$ (*c* 0.1, CH_3OH) (lit.[19] −84, $CHCl_3$). (Sell, 1938); ^{1}H NMR (300 MHz, CD_3OD) δ 5.59 (d, 1H, $J_{1,2}$ 4.9 Hz, H-1), 4.72 (dd, 1H, $J_{2,3}$ 2.6 Hz, $J_{3,4}$ 7.7 Hz, H-3), 4.58 (dd, 1H, $J_{3,4}$ 7.7 Hz, $J_{4,5}$ 2.2 Hz, H-4), 4.44 (dd, 1H, $J_{1,2}$ 4.9 Hz, $J_{2,3}$ 2.6 Hz, H-2), 4.38 (d, 1H, $J_{4,5}$ 2.2 Hz, H-5), 1.50 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.33 (s, 3H, CH_3). ^{13}C NMR (75,5 MHz, CD_3OD) δ 171.6 (C-6), 110.8 ($\underline{C}Me_2$), 110.2 ($\underline{C}Me_2$), 97.7 (C-1), 73.2 (C-4), 72.0 (C-3), 71.6 (C-2), 69.1 (C-5), 26.2 ($2CH_3$), 25.0 (CH_3), 24.7 (CH_3).

ES-HRMS (+Na): Calcd. for $C_{12}H_{17}O_7Na_2$ (sodium salt): m/z 319.0770. Found: 319.0776.

Allyl 2,3-di-*O*-benzyl-α-D-galactopyranosiduronic acid (8). TEMPO-chemical oxidation: Method A (58% yield). TEMPO-electrochemical oxidation: Method C (57% yield). E = + 0.55 V ($Ag/AgNO_3$). $Q = 113$ C (theor. 102 C). Allyl 2,3-di-*O*-benzyl-α-D-galactopyranoside **2**[21] was oxidized by and purified by silica gel chromatography (9 : 1 to 1 : 1 ethyl acetate – methanol), leading to **8** as a white solid, m.p. 215.5–216.5°C; $[\alpha]_D + 64$ (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 7.30–7.20 (m, 10H, Ph), 5.89 (ddt, 1H, $J_{2',3'trans}$ 17.4 Hz, $J_{2',3'cis}$ 11.2 Hz, $J_{1',2'}$ 5.3 Hz, H-2′), 5.37 (broad s, 1H, H-1), 5.32 (broad d, 1H, $J_{2',3'trans}$ 17.4 Hz, H-3′a), 5.13 (d, 1H, $J_{2',3'cis}$ 11.2 Hz, H-3′b), 4.76 (d, 1H, J_{gem} 10.5 Hz, C$\underline{H}$Ph), 4.71 (d, 1H, J_{gem} 11.4 Hz, C$\underline{H}$Ph), 4.67 (d, 1H, J_{gem} 11.4 Hz, C$\underline{H}$Ph), 4.64 (d, 1H, J_{gem} 10.5 Hz, C$\underline{H}$Ph), 4.52 (broad s, 1 H, H-4), 4.35 (broad s, 1H, H-5), 4.20 (dd, 1H, J_{gem} 13.3 Hz, $J_{1'a,2'}$ 4.7 Hz, H-1′a), 4.09–4.06 (m, 2H, H-2, H-1′b), 3.90 (dd, 1H, $J_{2,3}$ 10.0 Hz, $J_{3,4}$ 2.8 Hz, H-3). ^{13}C NMR (75,5 MHz, CD_3OD) δ 176.9 (C-6), 139.8, 139.7 ($\underline{C}_i$-Ph), 135.3 (C-2′), 129.3–128.7 (Ph), 117.6 (C-3′), 98.4 (C-1), 78.3 (C-3), 76.9 (C-2), 74.0 ($\underline{C}H_2Ph$), 73.9 (C-5), 73.0 ($\underline{C}H_2Ph$), 70.2 (C-1′), 70.0 (C-4).

ES-HRMS (+Na): Calcd. for $C_{23}H_{26}O_7Na$: m/z 437.1576. Found: 437.1580.

Allyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-α-D-galactopyranosiduronic acid (9). TEMPO-chemical oxidation: Method A (95% yield). TEMPO-electrochemical oxidation: Method C (50 % yield). E = + 0.55 V ($Ag/AgNO_3$). $Q = 237$ C (theor. 79 C). Allyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-α-D--galactopyranoside (**3**) was oxidized by and purified by silica gel chromatography (9 : 1 ethyl acetate – methanol), leading to **9** as a white solid, m.p. 101.5–102°C; $[\alpha]_D + 83$ (*c* 0.21, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$-D_2O) δ 7.40–7.20 (m, 12H, Ph), 6.75 (d, 2H, J_o 8.4 Hz, PMB), 5.79 (ddt, 1H, $J_{2',3'trans}$

17.4 Hz, $J_{2',3'cis}$ 10.5 Hz, $J_{1',2'}$ 6.0 Hz, H-2′), 5.34 (broad s, 1H, H-1), 5.28 (d, 1H, $J_{2',3'trans}$ 17.4 Hz, H-3′a), 5.09 (d, 1H, $J_{2',3'cis}$ 10.5 Hz, H-3′b), 4.80 (d, 2H, J_{gem} 10.5 Hz, C<u>H</u>Ph), 4.72 (d, 2H, J_{gem} 11.8 Hz, C<u>H</u>Ph), 4.67 (d, 2H, J_{gem} 12.1 Hz, C<u>H</u>Ph), 4.65–4.55 (m, 3H, C<u>H</u>Ph), 4.49 (broad s, 1 H, H-4), 4.34 (broad s, 1H, H-5), 4.11 (broad dd, 1H, J_{gem} 13.3 Hz, $J_{1',2'}$ 4.5 Hz, H-1′a), 4.05–4.00 (m, 1H, H-1′b), 4.00 (broad s, 2H, H-2, H-3), 3.67 (s, 3H, OMe). ^{13}C NMR (75,5 MHz, $CDCl_3$) δ 175.2 (C-6), 159.1 (<u>C</u>$_i$-OMe), 138.7, 138.4 (<u>C</u>$_i$-Ph), 133.9 (C-2′), 130.2 (<u>C</u>$_i$- PMB), 129.8 (C_{Ar}-PMB), 128.2–127.3 (Ph), 117.2 (C-3′), 113.5 (C_{Ar}-PMB), 96.8 (C-1), 78.0 (C-3), 76.9 (C-4), 76.1 (C-2), 74.8, 72.7 (<u>C</u>H_2Ph), 72.3 (C-5), 68.8 (C-1′), 54.9 (OMe).

ES-HRMS (+Na): Calcd. for $C_{31}H_{34}O_8Na$: m/z 557.2151. Found: 557.2148.

Allyl α-D-galactopyranosiduronic acid (10). TEMPO-chemical oxidation: Method A (65% yield). TEMPO-electrochemical oxidation: Method D (70% yield). E = +0.30 V (MSE). Q = 178 C (theor. 175 C). Allyl α-D-galactopyranoside **4**[22] was oxidized and the crude acid was peracetylated (pyridine - acetic acid) prior to purification by preparative HPLC (RP-C18 column, water-acetonitrile gradient) to give **allyl 2,3,4-tri-O-acetyl-α-D-galactopyranosiduronic acid** as a syrup; $[\alpha]_D$ −25 (*c* 0.13, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (dddd, 1H, $J_{2',3'trans}$ 17.2 Hz, $J_{2',3'cis}$ 10.6 Hz, $J_{1'a,2'}$ 5.0 Hz, $J_{1'b,2'}$ 6.1 Hz, H-2′), 5.46 (d, 1H, $J_{4,5}$ 2.6 Hz, H-5), 5.32 (dd, 1H, $J_{2',3'trans}$ 17.2 Hz, J_{gem} 1.4 Hz, H-3′a), 5.22 (dd, 1H, $J_{2',3'cis}$ 10.6 Hz, J_{gem} 1.4 Hz, H-3′b), 5.15 (broad s, 2H, H-1-2), 5.06 (dd, 1H, $J_{2,3}$ 0.8 Hz, $J_{3,4}$ 5.6 Hz, H-3), 4.59 (dd, 1H, $J_{3,4}$ 5.6 Hz, $J_{4,5}$ 2.6 Hz, H-4), 4.20 (dd, 1H, $J_{1'a,2'}$ 5.0 Hz, J_{gem} 13.1 Hz, H-1′a), 4.03 (dd, 1H, $J_{1'b,2'}$ 6.1 Hz, J_{gem} 13.1 Hz, H-1′b), 2.24 (s, 3H, OMe), 2.13 (s, 3H, OMe), 2.12 (s, 3H, OMe). ^{13}C NMR (75,5 MHz, $CDCl_3$) δ 171.9 (CO_2H), 170.5–169.8 (<u>C</u>O_2CH_3), 133.3 (C-2′), 117.8 (C-3′), 104.7 (C-1), 81.3 (C-2), 80.7 (C-4), 76.8 (C-3), 70.3 (C-5), 68.1 (C-1′), 20.8–20.6 (CO_2<u>C</u>H_3).

ES-HRMS (+Na): Calcd. for $C_{15}H_{20}O_{10}Na$: m/z 383.0954. Found: 383.0966.

***n*-Decyl β-D-glucopyranosiduronic acid (11).** TEMPO-chemical oxidation: Method A (90% yield). TEMPO-electrochemical oxidation: Method D (97% yield). E = +0.40 V (MSE). Q = 159 C (theor. 122 C). *n*-Decyl β-D-glucopyranoside **5** was oxidized and the crude acid was purified by preparative HPLC (RP-C18 column, water-acetonitrile gradient) to give **11**[26] as a white solid, m.p. 166.5–167°C; $[\alpha]_D$ −34 (*c* 0.11, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 4.23 (d, 1H, $J_{1,2}$ 7.7 Hz, H-1), 3.98 (dt, 1H, J_{gem} 9.4 Hz, $J_{1'a,2'}$ 6.8 Hz, H-1′a), 3.61 (d, 1H, $J_{4,5}$ 8.9 Hz, H-5), 3.54 (dt, 1H, J_{gem} 9.4 Hz, $J_{1'b,2'}$ 6.8 Hz, H-1′b), 3.47 (t, 1H, $J_{3,4}$ 9.4 Hz, H-4), 3.41 (t, 1H, $J_{3,4}$ 9.4 Hz, H-3), 3.23 (t, 1H, $J_{1,2}$ 7.7 Hz, H-2), 1.64 (quint, 2H, $J_{1,2}$ 6.8 Hz, $J_{2',3'}$ 6.8 Hz, H-2′), 1.44–1.22 (m, 14 H, H3′-9′), 0.92 (t, 3H, $J_{9',10'}$ 6.7 Hz, H-10′). ^{13}C NMR (75,5 MHz, CD_3OD) δ 176.9 (C-6), 104.4 (C-1), 77.9 (C-3), 74.9 (C-2), 73.7 (C-4), 71.0 (C-1′), 33.1-23.7 (C-2′-9′), 14.4 (C-10′).

ES-HRMS (+Na): Calcd. for $C_{16}H_{30}O_7Na$: m/z 357.1889. Found: 357.1884.

Methyl α-D-glucopyranosiduronate-(1 → 4)-α-D-glucopyranosiduronate-(1 → 4)-β-D-glucopyranosiduronate, trisodium salt (12). TEMPO-chemical oxidation: Method B. After 4 days, no oxidized product was detected. Method A (74% yield). TEMPO-electrochemical oxidation: Method D (86% yield). E = +0.40 V (MSE). Q = 176 C (theor. 223 C). Methyl β-D-maltotrioside **6**[25] was oxidized and the crude mixture was purified through Biogel P-2 (170 × 6 mm column, 50 mM $NaHCO_3$). Fractions corresponding to the product were collected and stirred 10 min with IR 120 plus (H+) resin. After filtration, the solution was stirred 10 min with IR 120 plus (Na+). After filtration, the solvent was evaporated at 30°C under diminished pressure to give **12** as a white solid, m.p. 273.2°C (dec.); $[\alpha]_D$ + 109 (*c* 0.12, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 5.44 (d, 1H, $J_{1b,2b}$ 3.8 Hz, H-1b), 5.41 (d, 1H, $J_{1c,2c}$ 3.8 Hz, H-1c), 4.26 (d, 1H, $J_{1a,2a}$ 8.0 Hz, H-1a), 3.94 (d, 1H, $J_{4c,5c}$ 10.0 Hz, H-5c), 3.85 (d, 1H, $J_{4b,5b}$ 10.2 Hz, H-5b), 3.83 (dd, 1H, $J_{2c,3c}$ 9.9 Hz, $J_{3c,4c}$ 8.9 Hz, H-3c), 3.66 (m, 3H, H-3a, H-4a, H-5a), 3.60 (dd, 1H, $J_{2b,3b}$ 10.0 Hz, $J_{3b,4b}$ 9.1 Hz, H-3b), 3.57 (dd, 1H, $J_{3c,4c}$ 8.9 Hz, $J_{4c,5c}$ 10.0 Hz, H-4c), 3.44 (dd, 1H, $J_{1c,2c}$ 3.8 Hz, $J_{2c,3c}$ 9.9 Hz, H-2c), 3.41 (s, 3H, OMe), 3.38 (dd, 1H, $J_{1b,2b}$ 3.8 Hz, $J_{2b,3b}$ 10.0 Hz, H-2b), 3.27 (dd, 1H, $J_{3b,4b}$ 9.1 Hz, $J_{4b,5b}$ 10.2 Hz, H-4b), 3.19 (dd, 1H, $J_{1a,2a}$ 8.0 Hz, $J_{2a,3a}$ 9.3 Hz, H-2a). ^{13}C NMR (75,5 MHz, D_2O) δ 177.1, 176.1, 175.2 (C-6a, C-6b, C-6c), 103.4 (C-1a), 98.0 (C-1c), 97.5 (C-1b), 76.6, 76.5 (C-3a, C-4a, C-5a), 76.1 (C-4c), 73.3 (C-2a), 73.2 (C-3c), 72.7 (C-3b), 72.3 (C-4b, C-5b, C-5c), 71.9, 71.8 (C-2b, C-2c), 57.5 (OMe). a, b, c indicate the three sugar rings starting form right to left.

ES-HRMS (+Na): Calcd. for $C_{19}H_{25}O_{19}Na_4$: m/z 649.0581. Found: 649.0573.

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