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Selective deprotection of tethered glycoderivatives with unsaturated spacer

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Abstract

A double regioselective deprotection of symmetrical tethered isopropylidenated monosaccharides has been elaborated. This mild and simple methodology involving iodine and acetonitrile, allows breaking of dioxolane and dioxane moieties and affords new chiral structures in good yields. Spectroscopic characterization of these molecules includes FTIR, ESI-MS, ^{1}H and ^{13}C NMR, and also 2D-COSY, HMQC and HMBC measurements.

Keywords: acetonide; deprotection; iodine; isopropylidene; monosaccharide; tether.

Introduction

We recently reported the synthesis and spectroscopic characterization of five monosaccharide based tethered derivatives with unsaturated spacer (**1**–**5**, Figure 1 step II, and Figure 2). The study was aimed towards obtaining chiral building blocks for the synthesis of bolaform and gemini type surfactants with enhanced biodegradability and biocompatibility (Pascariu et al., 2011). In this work, we present the regioselective removal of two out of the four isopropylidene protecting groups characteristic to these structures. This is an expansion of a procedure elaborated for simple monosaccharides (Yadav et al., 2005) to include symmetrical tethered glycoderivatives.

This method permits the selective hydrolysis of terminal acetonide groups using iodine (Vaino et al., 2001; Banerjee et al., 2006) in acetonitrile. This high yield simple reaction of catalytic nature which involves non-toxic, inexpensive and readily available reagents, complements well other similar synthetic methodologies (Szarek et al., 1986; Park et al., 1994; Gouéth et al., 1995; Ravikumar and Farquhar, 2002; Agarwal and Vankar, 2005; Catelani et al., 2006; Rajput et al., 2006; Procopio et al., 2007; Wuts and Greene, 2007; Bhaskar et al., 2008; Procopio et al., 2008; Xavier et al., 2009).

The induced breaking of 1,3-dioxolane or 1,3-dioxane ring structures exposes one pair of vicinal hydroxyl groups or a 1,3-diol per carbohydrate moiety (Figure 1 step III, and Figure 3) which can be further derivatized with hydrocarbon chains or various functional groups for constructing specific targets.

Results and discussion

Reactions were carried out using 10, 20 or 60 mol% molecular iodine and a 10:1 water excess, at room temperature. Before column separation, a thorough extraction with ethyl acetate (EtOAc) was necessary, because of the good water solubility of the compounds.

Deprotection of compounds **1**–**3** was readily indicated by TLC and FTIR. In each case, TLC analysis (EtOAc) showed the formation of several compounds with increased polarity. These were assigned to structures which lost one, two or more isopropylidene groups, with increasing polarity following this order (due to increasing number of OH groups). After isolation, FTIR analysis of the major products (compounds **1′**–**3′**) clearly showed the O-H stretching band, as indicated in Table 1, which was previously nonexistent in the starting materials spectra.

ESI-MS confirmed the molecular mass for structures **1′**–**3′**, which were detected in both positive ionization mode as proton ($[M+1]^{+}$), ammonium ($[M+18]^{+}$), sodium ($[M+23]^{+}$) and potassium ($[M+39]^{+}$) adducts, and negative ionization mode as chlorine adduct ($[M+35]^{-}$, $[M+37]^{-}$) or with one proton loss ($[M-H]^{-}$). Positive MS/MS of the sodium adducts indicated the loss of two fragments with 58 mass units (as acetone) corresponding to both remaining isopropylidene protecting groups (Figure 4).

NMR analysis (Tables 2 and 3) confirmed the structure of these compounds. The disappearance of signals for the terminal isopropylidene group in both ^{1}H and ^{13}C (Rusu et al., 2002; Şişu et al., 2002; Pascariu et al., 2011) was in agreement with the stated purpose. Also, the signals for the hydroxyl protons appeared (with areas corresponding to one proton each, or less, due to the isotopic exchange with the solvent). The carbon atoms bearing these groups shifted about 3 ppm to the right for **1′** and **2′** when compared with the corresponding positions in the starting materials, which also suggested a dealkylation process (Pascariu et al., 2011).

Reaction yields were affected by both incomplete and advanced deprotection (we confirmed this deduction by ESI-MS analysis). Shorter reaction times favored compounds which had only one isopropylidene group removed. Increasing the catalyst concentration (from 20 mol% to 60 mol%) and decreasing the reaction time to half (from 12 to 6 h) decreased the reaction yields, which would indicate that the second

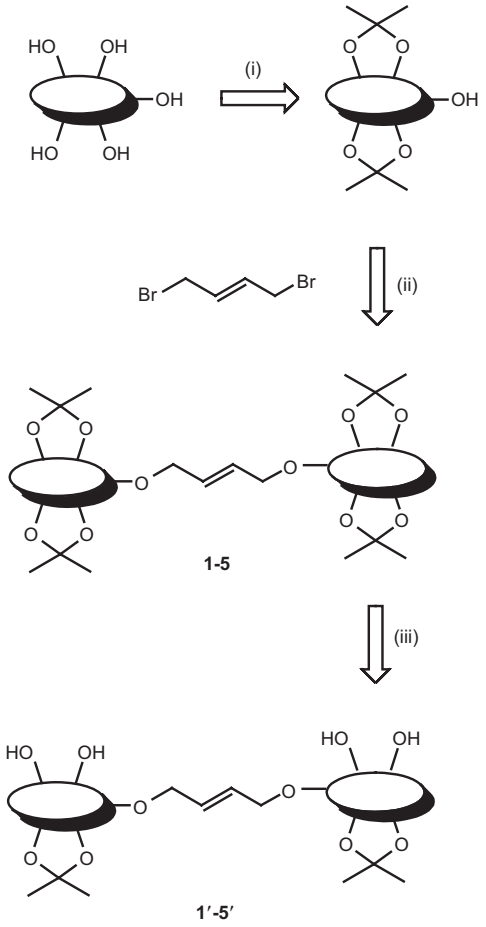


Figure 1 General synthetic steps: (i) acetone/acid; (ii) trans-1,4-dibromo-2-butene/base; (iii) $H_2O/I_2/CH_3CN$.

reaction parameter is prevalent. We found the best choice to be 10 mol% I_2 and 12 h reaction time.

The faster cleavage rate for the *cis*-fused 1,3-dioxane ring over the 1,3-dioxolanes is evident from the reaction yields (Chung and Moon, 1992). After 12 h and with 10 mol% I_2, TLC still showed traces of compounds which lost only one isopropylidene group for glucose and mannose derivatives, but not in the case of sorbose.

We also tested this procedure on the other two tethered glycoderivatives, compounds **4** and **5**. These structures are characterized by a *cis-cis* condensation geometry of two 1,3-dioxolane rings on the tetrahydropyran central unit, and do not exhibit the same feature of a terminal isopropylidene group as the other three compounds. Even at 60 mol% and after prolonged reaction times, the NMR analysis of some low yielding products (indicated by TLC, expected structures in Figure 5) showed mixtures in which the isopropylidene units were randomly cleaved in pairs. It would appear that the difference in the hydrolytic rates under these conditions was too small to allow chemoselectivity, even if the anomeric site is known to be somewhat more resilient towards ketal removal (Capon, 1969).

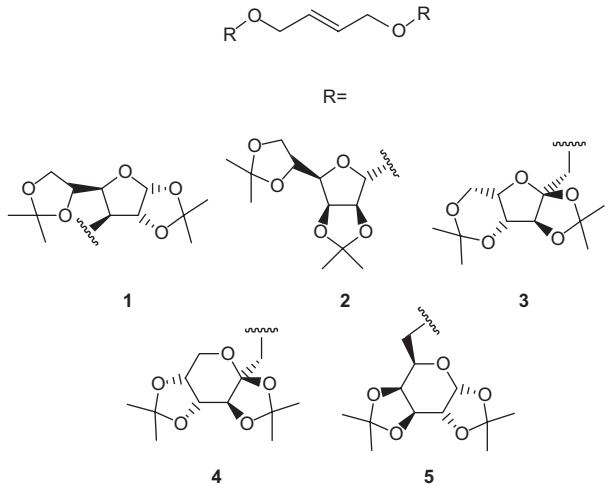


Figure 2 Structure of compounds **1**–**5**.

Experimental

Materials

Starting materials **1**–**5** were prepared as previously described (Pascariu et al., 2011). Acetonitrile was refluxed for several hours over CaH_2 and distilled. Water was distilled twice. All other chemicals were obtained from commercial sources. Analytical TLC was carried out on Merck silica gel 60 F_{254} aluminum sheets, while column chromatography was done with Merck silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM).

Characterization

The IR spectra were recorded by dissolving the sample in $CHCl_3$ and evaporating the solvent on KBr plates on a Jasco FT/IR-430 spectrometer (spectral range 4000–530 cm^{-1}). The major bands are reported in Table 1. Each spectrum was an average of 16 spectra measured at a resolution of 4 cm^{-1}. Wave numbers are given in cm^{-1}.

^1H and ^{13}C NMR data were recorded on a Bruker Avance DRX-400 spectrometer (400 MHz ^1H, 100 MHz ^{13}C) in deuterochloroform or deuterated water, referenced to TMS as internal standard. Chemical shifts are given in ppm, while coupling constants are in Hz. The ^1H and ^{13}C results are given in Tables 2 and 3, respectively.

Mass spectrometry was conducted on a Bruker Daltonics spectrometer. A fully automated nanoESI chip (NanoMate robot incorporating ESI 400, Advion Bioscience) in conjunction with a high capacity ion trap (HCT Ultra PTM Discovery) was used. Electrospray ionization was conducted in positive and negative ion modes (1.0–1.7 kV; capillary exit: 20 V) using N_2 as the nebulizer (dry gas temperature: 100°C). MS/MS was carried out by collision induced dissociation (CID) using He as collision gas.

TLC and column chromatography were carried out using EtOAc as eluent and vanillin/H_2SO_4 (2.5 g vanillin, 2.5 ml H_2SO_4, 45 ml ethanol) for spot visualization.

General procedure for the synthesis of compounds 1′–3′

Iodine (10 mol%) was added to a solution of tetraacetonide in acetonitrile and after adding water the reaction was stirred at room temperature for 12 h. The reaction mixture was diluted with a small

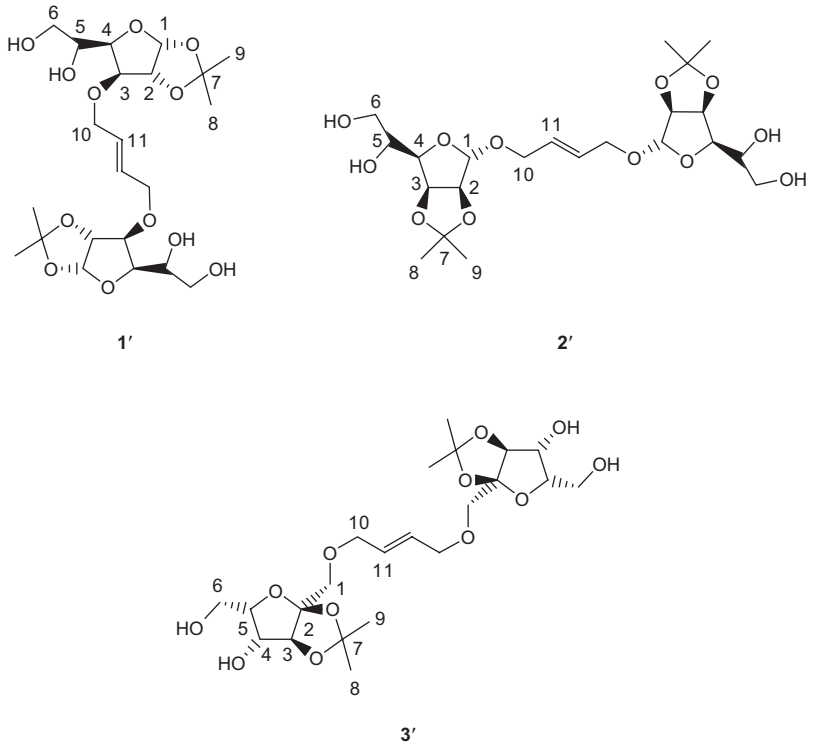


Figure 3 Structure of products **1′**–**3′**.

amount of aqueous $Na_2S_2O_3$ (10 ml) and extracted five times with EtOAc (50 ml). The organic layers were dried over anhydrous Na_2CO_3. The resulting tetrol was purified through silica gel column chromatography using EtOAc and kept under vacuum for several hours.

1,4-Bis(1,2-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) but-*trans*-2-ene (1′)

Using the general procedure above, 1.96 g (3.42 mmol) of **1**, 35.3 ml acetonitrile, 0.087 g I_2 and 0.62 ml H_2O gave 1.07 g (64%) of **1′**. White foam; R_f 0.16 (EtOAc, red spot, then brown); MS: calculated for $C_{22}H_{36}O_{12}$: m/z: 492.2; ESI-MS positive found: m/z 493.2 $[M+H]^+$ (2%), 510.3 $[M+NH_4]^+$ (6%), 515.2 $[M+Na]^+$ (100%), 531.4 $[M+K]^+$ (19%); ESI-MS negative found 491.2 $[M-H]^-$ (31%), 527.2 and 529.2 $[M+Cl]^-$ (40%, 19%, respectively).

1,4-Bis(2,3-*O*-isopropylidene-α-D-mannofuranosyloxy) but-*trans*-2-ene (2′)

Compound **2** (1.72 g, 3.00 mmol), 30.9 ml acetonitrile, 0.076 g I_2 and 0.54 ml H_2O gave 0.81 g (55%) of **2′**. White foam; R_f 0.13 (EtOAc, red spot, then green); MS: calculated for $C_{22}H_{36}O_{12}$: m/z: 492.2; ESI-MS positive found: m/z 493.2 $[M+H]^+$, 510.3 $[M+NH_4]^+$, 515.2 $[M+Na]^+$, 531.4 $[M+K]^+$; ESI-MS negative found 491.2 $[M-H]^-$.

1,4-Bis(2,3-*O*-isopropylidene-α-L-sorbofuranos-1-*O*-yl) but-*trans*-2-ene (3′)

Compound **3** (0.67 g, 1.17 mmol), 12.1 ml acetonitrile, 0.03 g I_2 and 0.21 ml H_2O gave 0.46 g (80%) of **3′**. Colorless syrup; R_f 0.23 (EtOAc, violet spot, then dark green); MS: calculated for $C_{22}H_{36}O_{12}$: m/z: 492.2; ESI-MS positive found: m/z 515.2 $[M+Na]^+$; ESI-MS negative 491.2 $[M-H]^-$.

Deprotection of tethered glycoderivatives 4 and 5 with iodine in acetonitrile and water

Iodine (0.263 g, 60 mol%) was added to a solution of 1.00 g (1.75 mmol) tetraacetonide **4** or **5** in 18.2 ml acetonitrile and after adding 0.35 ml of water the reaction was stirred at room temperature for 24 h. The reaction mixture was diluted with a small amount of aqueous $Na_2S_2O_3$ (10 ml) and extracted five times with EtOAc

Table 1 FTIR absorption bands for compounds **1′**–**3′**.

Product	ν_{O-H} s, br	ν_{C-H} m-s	$\nu_{C=C}$ w	Fingerprint (ν_{C-C}, ν_{C-O}, δ_{C-H}, γ_{C-H}, δ_{O-H}, γ_{O-H}, sk)
1	3446	2988, 2937, 2881	1652	1457, 1376, 1349, 1296, 1255, 1217, 1165, 1118, 1080, 1019, 960, 888, 856, 666, 632, 540
2	3438	2987, 2938, 2874	1658	1458, 1375, 1269, 1211, 1164, 1089, 1017, 979, 921, 887, 857, 820, 585, 557
3	3417	2988, 2934, 2873	1644	1456, 1375, 1335, 1281, 1246, 1218, 1185, 1085, 1045, 989, 944, 889, 863, 832, 814, 788, 647, 616, 580, 565, 552

s, Strong; m, medium; w, weak; br, broad.

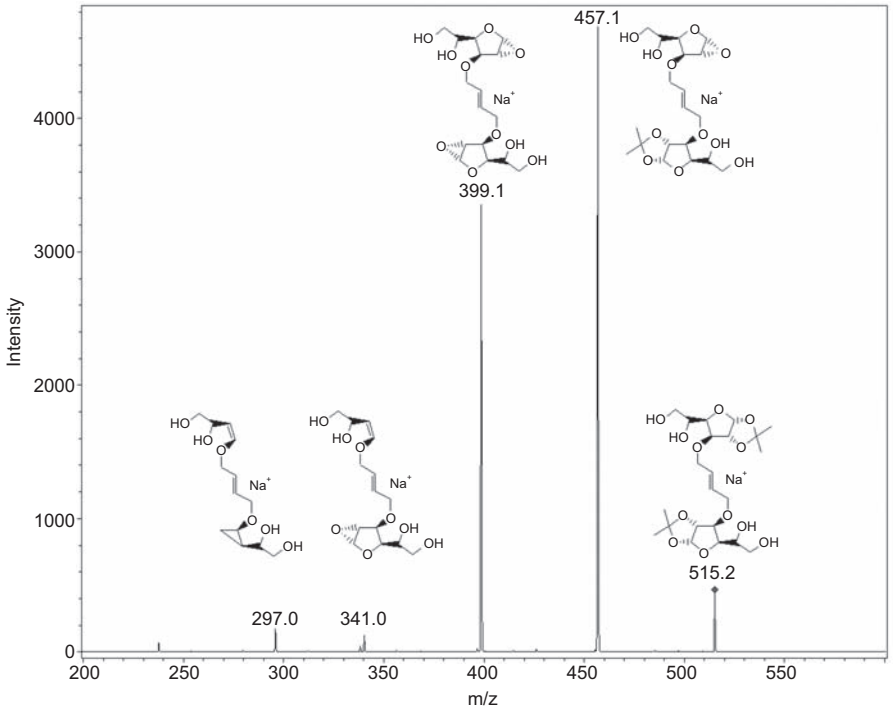


Figure 4 MS/MS and proposed fragmentation of the sodium adduct of product **1′**.

Table 2 Assignment of ^{1}H chemical shifts (in ppm) for compounds **1′–3′**[a].

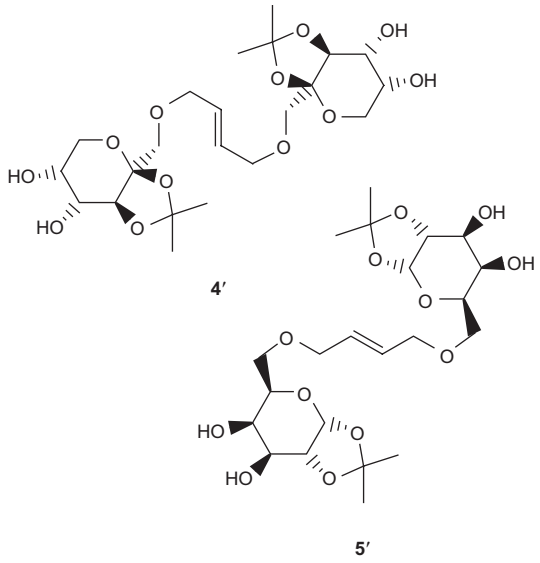
Product	H-1	H-2	H-3	H-4	H-5	H-6	H-8	H-9	H-10	H-11	OH
1	5.90 d (4.0)	4.55 d (3.6)	4.00 m	4.00 m	4.00 m	3.84 dd (10.6, 1.0) 3.64 dd (11.6, 6.4)	1.48 s	1.31 s	4.22 d (11.6) 4.00 m	5.87 s	3.84 3.64
2	5.04 s	4.61 d (5.6)	4.86 dd (5.8, 3.4)	3.98 m	3.98 m	3.84 dd (11.6, 2.8) 3.70 dd (11.6, 5.2)	1.47 s	1.33 s	4.10 dd (11.2, 1.6) 3.98 m	5.77 dd (3.0, 3.0)	3.58 bs 3.33 bs
3	3.79 d (12.8) 3.75 d (11.6)	–	4.57 s	4.32 d (2.4)	4.41 ddd (7.0, 4.4, 2.8)	3.88 dd (11.8, 4.6) 3.81 d (6.8)	1.56 s	1.44 s	4.21 m	5.92 dd (2.8, 2.8)	2.11 d (4.0)

Coupling constants (in Hz) are given in parentheses. [a]Atom numbering is given in Figure 3.

Table 3 Assignment of ^{13}C chemical shifts (in ppm) for compounds **1′–3′**[a].

Product	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
1	105.1	82.0	81.5	79.9	68.9	64.6	111.8	26.7	26.2	69.6	129.1
2	105.9	84.8	80.0	79.1	70.0	64.2	112.6	26.0	24.7	67.3	129.2
3	70.1	113.3	85.4	74.1	81.9	59.6	113.2	26.5	25.7	71.5	129.5

[a]Atom numbering is given in Figure 3.



4′ 5′

Figure 5 Proposed structure for products **4′** and **5′**.

(50 ml). The organic layers were dried over anhydrous Na_2CO_3. The resulting tetrol mixtures were passed through silica gel column using EtOAc followed by ethanol. After solvent removal, the syrups were kept under vacuum for several hours.

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