

ORIGINAL PAPER

Thio-click approach to the synthesis of stable glycomimetics[‡]

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Carbon-sulfur-bridged glycomimetics were prepared by free radical hydrothiolation of the exocyclic double bond of unsaturated sugars. Reaction between benzoyl-substituted pyranoid-exoglycal and a range of thiols including peptide, 1-thioglycerol and 1-thiosugar derivatives gave β -D-configured carbon-sulfur-linked glycoconjugates with full stereoselectivity. Addition of a panel of thiols to a 3-exomethylene-glucofuranose derivative also proceeded in a stereoselective manner and afforded a series of D-*allo*-configured 3-deoxy-3-*C-S*-bridged glycoconjugates.

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Introduction

Carbohydrates play an important role in diverse biological processes, including inflammation, immune response, cancer metastasis, as well as viral and bacterial infection and, in principle, offer immense opportunities for therapeutic drug development. However, the instability of glycosides toward chemical and enzymatic degradation due to the readily hydrolysable native glycosidic bond hampers the *in vivo* applications of carbohydrate-based molecules. Therefore, there has been a long-standing interest in the synthesis of hydrolytically stable carbohydrate mimetics that can be used as leads for new therapeutic agents and probes in biological studies (Ernst & Magnani, 2009).

Thiosugars containing a sulfur atom instead of an oxygen atom in the ring are stable monosaccharide mimics and have gained importance in glycobiology and as potential drugs (Robina et al., 2001; Witczak & Culhane, 2005). The best-documented stable gly-

comimetics are the *C*- and *S*-glycosides, in which the glycosidic oxygen is replaced by a methylene group or a sulfur atom (Liu et al., 2001; Szilágyi & Varela, 2006; Witczak et al., 2007). Research efforts have also been directed toward the incorporation of a novel, stable linker comprising two or three bridging atoms in place of a native *O*-glycosidic bond. Hence, among others, disulfide- (Szilágyi et al., 2001; Illyés et al., 2011), seleno-sulfide-, (Chakka et al., 2005), sulfonamide- (Lopez et al., 2011) or urea-bridged glycosides (Prosperi et al., 2004) have been prepared as novel carbohydrate derivatives with potential bioactive properties.

Over the last few years, photoinduced free-radical addition of thiols to alkenes, termed thiol-ene coupling or thiol-ene click reactions, has emerged in the field of carbohydrate chemistry as a robust ligation tool providing an easy access to *S*-linked glycoconjugates (Dondoni & Marra, 2012; Witczak & Bielski, 2013). Interestingly, there are very few examples of the incorporation of unsaturated carbohydrates bearing an

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exo- or endocyclic double bond within the thiol–ene coupling strategy (Fiore et al., 2009; Lázár et al., 2012, 2013; Staderini et al., 2012), and the inherent potential of this mild and efficient synthetic methodology of a sugar unit incorporation into another bioactive compound through a carbon–sulfur linker has remained unexploited until now.

Here, we demonstrate the benefits of free-radical hydrothiolation of alkenyl sugars bearing an exocyclic double bond providing stable carbon–sulfur-bridged glycomimetics.

Experimental

Optical rotation was measured at ambient temperature with a Perkin–Elmer 241 automatic polarimeter. TLC was performed on a Kieselgel 60 F₂₅₄ (Merck, USA) with detection using a 5 vol. % ethanolic sulfuric acid solution and heating. Column chromatography was performed on Silica gel 60 (Merck, Germany, 0.063–0.200 mm). Organic solutions were dried over MgSO₄, and concentrated in vacuum. The ¹H NMR (360 MHz and 400 MHz) and ¹³C NMR (90.54 MHz and 100.28 MHz) spectra were recorded with a Bruker Avance DRX-360 and a DRX-400 spectrometer, respectively, at 25 °C (Germany). Chemical shifts are referenced to Me₄Si or DSS as parts per million (0.00 ppm for ¹H) and to the solvent signals (CDCl₃: 77.00 ppm for ¹³C). The ¹H and ¹³C NMR assignments were established from 1D NMR spectra. Elemental analyses (C, H, S) were performed using an Elementar Vario MicroCube instrument (Germany).

General method for photoinduced addition of thiols (IIIa–IIIh) to glycals I and II

To a solution of the starting unsaturated monosaccharide (1.00 mmol) in the specified solvent (7 mL), thiol (2.0 eq.) and 2,2-dimethoxy-2-phenylacetophenone (DPAP, 25 mg, 0.10 mmol) were added. The solution was irradiated at ambient temperature for 15 min. Then, it was concentrated and the residue was purified using column chromatography.

Using IIIf as the thiol, an 1 : 2 thiol/alkene ratio was applied and the DPAP addition and irradiation were repeated twice more.

Compound IVa

Compound I (100 mg, 0.169 mmol) and *N*-acetylcysteine IIIa (55 mg, 0.338 mmol) were reacted in toluene–MeOH 1 : 1 vol. (6 mL) according to the general method. The crude product was purified by silica gel chromatography in CH₂Cl₂–MeOH (φ_r = 85 : 15), R_f = 0.38, to give IVa (113 mg, 88 %) as a colorless syrup. $[\alpha]_D(c = 0.16, \text{CHCl}_3) = 21.6^\circ$. For C₄₀H₃₇NO₁₂S (M_r = 755.79) $w_i/\text{mass } \%$: calculated: C, 63.57; H, 4.93; S, 4.24, found: C, 63.41; H, 4.90;

S, 4.25. ¹H NMR (360 MHz, (CD₃)₂SO), δ : 8.08–7.38 (m, 21H_{arom}, NH), 6.03 (t, 1H, J = 9.4 Hz), 5.62 (t, 1H, J = 9.3 Hz), 5.53 (t, 1H, J = 9.5 Hz), 4.52–4.49 (m, 3H), 4.42–4.34 (m, 2H), 3.12 (dd, 1H, J = 4.1 Hz, J = 13.4 Hz), 2.95–2.77 (m, 3H), 2.54 (s, 1H), 1.82 (s, 3H). ¹³C NMR (90 MHz, (CD₃)₂SO), δ : 172.8, 169.0, 165.3, 165.1, 164.8, 164.7 (6 \times CO), 133.7–128.5 (24 \times C_{arom}), 76.9, 74.4, 74.4, 71.6, 69.3 (C-2, C-3, C-4, C-5, C-6), 62.8 (C-7), 52.8 (CHCOOH), 34.8, 33.4 (C-1, CH₂), 22.4 (CH₃).

Compound IVb

Compound I (100 mg, 0.169 mmol) and captopril IIIb (73 mg, 0.338 mmol) were reacted in toluene–MeOH 1 : 1 vol. (6 mL) according to the general method. The crude product was purified by silica gel chromatography in CH₂Cl₂–MeOH (φ_r = 9 : 1), R_f = 0.44, to give IVb (123 mg, 90 %) as a colorless syrup. $[\alpha]_D(c = 0.02, \text{CHCl}_3) = -44.3^\circ$. For C₄₄H₄₃NO₁₂S (M_r = 809.88) $w_i/\text{mass } \%$: calculated: C, 65.25; H, 5.35; S, 3.96, found: C, 65.08; H, 5.33; S, 3.94. ¹H NMR (360 MHz, CD₃OD), δ : 8.03–7.75 (m, 8H_{arom}), 7.56–7.18 (m, 12H_{arom}), 6.04 (t, 1H, J = 9.5 Hz), 5.72 (t, 1H, J = 9.7 Hz), 5.63 (t, 1H, J = 9.6 Hz), 4.61 (dd, 1H, J = 2.9 Hz, J = 12.3 Hz), 4.50 (dd, 1H, J = 5.0 Hz, J = 12.2 Hz), 4.38–4.33 (m, 2H), 4.24–4.19 (m, 1H), 3.54–3.51 (m, 2H), 2.94–2.77 (m, 4H), 2.64–2.60 (m, 1H), 2.10–2.00 (m, 1H), 1.93–1.78 (m, 3H), 1.06 (d, 3H, J = 6.4 Hz). ¹³C NMR (90 MHz, CD₃OD), δ : 176.1, 175.9, 167.5, 167.2, 166.8, 166.8 (6 \times CO), 134.7–129.4 (24 C_{arom}), 80.1, 77.0, 76.0, 73.3, 71.3 (C-2, C-3, C-4, C-5, C-6), 64.6 (C-7), 60.4 (CHCOOH), 39.6 (CHCH₃), 48.4, 37.7, 34.8, 30.2, 25.6 (C-1, 4 \times CH₂), 17.3 (CH₃).

Compound IVc

Compound I (100 mg, 0.169 mmol) and glutathione IIIc (104 mg, 0.338 mmol) were reacted in DMF–H₂O 2 : 1 vol. (12 mL) according to the general method. The crude product was purified by silica gel chromatography in CH₂Cl₂–MeOH–H₂O (φ_r = 8 : 5 : 0.4), R_f = 0.43, to give IVc (135 mg, 89 %) as a white solid. $[\alpha]_D(c = 0.10, \text{MeOH}) = +91.7^\circ$. For C₄₅H₄₅N₃O₁₅S (M_r = 899.91) $w_i/\text{mass } \%$: calculated: C, 60.06; H, 5.04; S, 3.56, found: C, 59.98; H, 5.02; S, 3.54. ¹H NMR (360 MHz, CD₃OD), δ : 7.98–7.37 (m, 22H_{arom}, 2 \times NH), 5.98 (t, 1H, J = 9.1 Hz), 5.61 (t, 1H, J = 9.2 Hz), 5.54 (t, 1H, J = 9.4 Hz), 4.52–4.33 (m, 5H), 3.72–3.55 (m, 4H), 3.49–3.34 (m, 2H), 3.24–3.10 (m, 1H), 3.01–2.89 (m, 1H), 2.84–2.68 (m, 2H), 2.56 (s, 2H), 2.34–2.22 (m, 1H), 2.14–2.03 (m, 1H), 1.95–1.81 (m, 1H). ¹³C NMR (90 MHz, CD₃OD), δ : 172.6, 172.5, 169.8, 165.6, 165.3, 165.0, 164.9 (8 \times CO), 133.8–128.6 (24 C, arom), 77.1, 74.7, 74.7, 71.7, 69.5 (C-2, C-3, C-4, C-5, C-6), 62.9 (C-7), 53.0 (2 C, NCHCO), 43.4, 34.4, 29.1 (C-1, 4 \times CH₂).

Compound IVd

Compound *I* (120 mg, 0.203 mmol) and sodium 2-sulfanylethanesulfonate *IIId* (67 mg, 0.406 mmol) were reacted in MeOH–DMF 1 : 1 vol. (6 mL) according to the general method. The crude product was purified by silica gel chromatography in CH₂Cl₂–MeOH (φ_r = 85 : 15), R_f = 0.67, to give *IVd* (138 mg, 90 %) as a colorless syrup. For C₃₇H₃₃NaO₁₂S₂ (M_r = 756.77) w_i /mass %: calculated: C, 58.72; H, 4.40; S, 8.47, found: C, 58.61; H, 4.41; S, 8.45. ¹H NMR (360 MHz, (CD₃)₂SO), δ : 8.05–7.38 (m, 20H_{arom}), 6.06 (t, 1H, J = 9.4 Hz), 5.62 (t, 1H, J = 9.3 Hz), 5.53 (t, 1H, J = 9.3 Hz), 4.55 (br s, 3H), 4.39 (m, 1H), 2.94–2.76 (m, 6H). ¹³C NMR (90 MHz, (CD₃)₂SO): 165.4, 165.2, 164.9, 164.8 (4 \times CO), 133.7–128.5 (24 C_{arom}), 76.7, 74.4, 74.4, 71.9, 69.4 (C-2, C-3, C-4, C-5, C-6), 62.9 (C-7), 51.7 (NaO₃SCH₂), 33.1 (C-1), 28.1 (CH₂S).

Compound IVe

Compound *I* (100 mg, 0.169 mmol) and 2,3-di-*O*-acetyl-1-thioglycerol *IIIe* (65 mg, 0.338 mmol) were reacted in toluene (5 mL) according to the general method. The crude product was purified by silica gel chromatography in hexane–acetone (φ_r = 2 : 1), R_f = 0.50, to give *IVe* (114 mg, 86 %) as a colorless syrup. $[\alpha]_D(c = 0.03, \text{CHCl}_3) = 24.5^\circ$. For C₄₂H₄₀O₁₃S (M_r = 784.82) w_i /mass %: calculated: C, 64.28; H, 5.14; S, 4.09, found: C, 64.13; H, 5.12; S, 4.08. ¹H NMR (360 MHz, CDCl₃), δ : 8.07–7.80 (m, 8H_{arom}), 7.58–7.23 (m, 12H_{arom}), 5.92 (t, 1H, J = 9.5 Hz), 5.69 (t, 1H, J = 9.7 Hz), 5.62–5.55 (m, 1H), 5.21–5.12 (m, 1H), 4.71–4.66 (m, 1H), 4.48–4.41 (m, 1H), 4.31–4.26 (m, 1H), 4.20–4.02 (m, 3H), 2.92–2.78 (m, 4H), 2.01, 2.00, 1.99 (3 \times s, 6H). ¹³C NMR (90 MHz, CDCl₃), δ : 170.4, 170.1, 166.0, 165.8, 165.2, 165.1 (6 \times CO), 133.4–128.2 (24 C_{arom}), 79.7, 79.7, 76.1, 74.1, 71.6, 71.5, 70.5, 70.3, 69.4 (C-2, C-3, C-4, C-5, C-6, CH₂OAc), 63.7, 62.9 (C-7, CH₂OAc), 33.6, 33.5, 33.4, 33.3 (C-1, CH₂S), 20.8, 20.6 (2 \times CH₃).

Compound IVf

Compound *I* (100 mg, 0.169 mmol) and 2,2'-(ethylenedioxy)diethanethiol *IIIf* (14 μ L, 0.085 mmol) were reacted in toluene–MeOH 1 : 1 vol. (4 mL) according to the general method, using 3 \times 0.1 eq. of DPAP (3 \times 5 mg) and irradiation for 3 \times 15 min. The crude product was purified by silica gel chromatography in hexane–acetone (φ_r = 65 : 35), R_f = 0.20, to give *IVf* (70 mg, 61 %) as a colorless syrup. $[\alpha]_D(c = 0.20, \text{CHCl}_3) = +18.8^\circ$. For C₇₆H₇₀NO₂₀S₂ (M_r = 1367.49) w_i /mass %: calculated: C, 66.75; H, 5.16; S, 4.69, found: C, 66.61; H, 5.14; S, 4.67. ¹H NMR (360 MHz, CDCl₃), δ : 8.05–8.03 (m, 4H_{arom}), 7.94–7.89 (m, 8H_{arom}), 7.82–7.79 (m, 4H_{arom}), 7.56–7.46

(m, 6H_{arom}), 7.43–7.31 (m, 14H_{arom}), 7.27–7.23 (m, 4H_{arom}), 5.90 (t, 2H, J = 9.6 Hz), 5.66 (t, 2H, J = 9.8 Hz), 5.54 (t, 2H, J = 9.6 Hz), 4.63 (dd, 2H, J = 2.9 Hz, J = 12.2 Hz), 4.44 (dd, 2H, J = 5.3 Hz, J = 12.2 Hz), 4.17–4.12 (m, 2H), 4.03–3.97 (m, 2H), 3.52 (t, 4H, J = 6.7 Hz), 3.40 (s, 4H), 2.87–2.72 (m, 8H). ¹³C NMR (90 MHz, CDCl₃), δ : 166.0, 165.8, 165.3, 165.1 (8 \times CO), 133.4–128.2 (48 C_{arom}), 79.7, 76.1, 74.2, 71.8, 69.6 [2 \times (C-2, C-3, C-4, C-5, C-6)], 70.7, 70.0 [2 \times (CH₂O, OCH₂)], 63.2 (2 \times C-7), 33.7, 32.6 [2 \times (C-1, SCH₂)].

Compound IVg

Compound *I* (50 mg, 0.09 mmol) and 2,3,4,6-tetra-*O*-acetyl-1-thiomannopyranose *IIIg* (44 mg, 0.14 mmol) were reacted according to the general method. The crude product was purified by silica gel chromatography in hexane–EtOAc (φ_r = 6 : 4), R_f = 0.28, to provide compound *IVg* (59 mg, 74 %) as a colorless syrup. $[\alpha]_D(c = 0.03, \text{CHCl}_3) = 48.7^\circ$. For C₄₉H₄₈O₁₈S (M_r = 1367.49) w_i /mass %: calculated: C, 61.50; H, 5.06; S, 3.35, found: C, 61.65; H, 5.04; S, 3.34. ¹H NMR (360 MHz, CDCl₃), δ : 8.00–8.10 (m, 2H_{arom}), 7.85–7.97 (m, 4H_{arom}), 7.72–7.84 (m, 2H_{arom}), 7.19–7.61 (m, 20 H_{arom}), 5.89 (t, 1H, J = 9.6 Hz), 5.70 (t, 1H, J = 9.8 Hz), 5.54 (s, 1H, H-1), 5.45 (t, 1H, J = 9.6 Hz), 5.39 (dd, 1H, J = 3.2, J = 1.4 Hz), 5.29 (t, 1H, J = 9.8 Hz), 5.21 (dd, 1H, J = 10.0 Hz, J = 3.3 Hz), 4.70 (dd, 1H, J = 12.3, J = 2.7 Hz), 4.20–4.44 (m, 3H), 3.9–4.18 (m, 3H), 2.96 (dd, 1H, J = 14.6, J = 9.0 Hz), 2.81 (dd, 1H, J = 14.6, J = 2.5 Hz, SCH₂), 1.98, 2.01, 2.05, 2.11 (4 \times s, 12H, CH_{3,ac}). ¹³C NMR (90 MHz, CDCl₃), δ : 169.9, 169.6, 165.8, 165.1 (CO), 133.6, 133.4, 133.1, 129.7, 129.6, 128.8, 128.4, 128.4, 128.2 (C_{arom}), 83.1 (C-1'), 79.6, 76.3, 74.1, 72.3, 70.1, 69.2, 69.1, 66.3, 62.7, 62.5 (C-6, C-6'), 31.9 (CH₂S), 20.7 (CH_{3,ac}).

Compound Va

Compound *II* (256 mg, 1.0 mmol) and *N*-t-butoxycarbonyl-L-cysteine ethyl ester *IIIh* (443 mg, 2.0 mmol) were reacted according to the general method. The crude product was purified by silica gel chromatography in hexane–EtOAc (φ_r = 7 : 3), R_f = 0.46, to provide compound *Va* (475 mg, 94 %) as a yellow syrup. $[\alpha]_D(c = 0.50, \text{CHCl}_3) = 52.0^\circ$. For C₂₃H₃₉NO₉S (M_r = 505.62) w_i /mass %: calculated: C, 54.63; H, 7.77; S, 6.34, found: C, 54.51; H, 7.76; S, 6.32. ¹H NMR (400 MHz, CDCl₃), δ : 7.29 (d, 1H, J = 3.9 Hz, NH), 5.76 (d, 1H, J = 3.6 Hz, H-1), 5.40 (d, 1H, J = 7.6 Hz), 4.78 (t, 1H, J = 4.1 Hz), 4.52 (m, 1H), 4.22 (m, 2H), 4.10 (m, 1H), 3.99 (m, 1H), 3.90 (m, 1H), 3.69 (m, 1H), 3.03 (m, 4H), 2.74 (t, J = 8.4 Hz, 1H), 2.09 (m, 1H), 1.52–1.28 (m, 24H, CH₃). ¹³C NMR (101 MHz, CDCl₃), δ : 171.0 (CO), 112.0, 109.6 (2C_q), 104.7 (C-1), 81.1, 80.8, 77.6 (C-2, C-3

and C-4), 67.5 (C-6), 61.6 (O—CH₂), 53.39, 49.8 (C-3 and CH—NH), 35.4, 28.0 (2 × S—CH₂), 28.2, 26.7, 26.6, 26.3, 25.1, 14.1 (CH₃).

Compound Vb

Compound *II* (256 mg, 1.00 mmol) and sodium 2-sulfanylethanesulfonate *IIId* (328 mg, 2.00 mmol) were reacted in MeOH (8 mL) according to the general method. The crude product was purified by silica gel chromatography in CH₂Cl₂–MeOH ($\varphi_r = 8 : 2$), $R_f = 0.44$, to give *Vb* (387 mg, 92 %) as a white solid. $[\alpha]_D (c = 0.33, \text{CHCl}_3) = 52.4^\circ$. For C₁₅H₂₅NaO₈S₂ ($M_r = 420.47$) $w_i/\text{mass } \%$: calculated: C, 42.85; H, 5.99; S, 15.25, found: C, 42.73; H, 5.97; S, 15.21. ¹H NMR (360 MHz, CD₃OD), δ : 5.76 (d, 1H, $J_{1,2} = 3.3$ Hz, H-1), 4.81 (d, 1H, $J = 3.7$ Hz), 4.10–4.04 (m, 2H), 3.85 (dd, 1H, $J = 8.3$ Hz, $J = 10.7$ Hz), 3.72 (dd, 1H, $J = 6.2$ Hz, $J = 9.4$ Hz), 3.12–2.92 (m, 5H), 2.73 (t, 1H, $J = 12.1$ Hz), 2.18–2.13 (m, 1H, H-3), 1.48, 1.39, 1.33, 1.33 (4 × s, 12H). ¹³C NMR (90 MHz, CD₃OD), δ : 113.0, 110.7 (2C_q), 106.3 (C-1), 82.5, 82.2 (C-2, C-4), 78.9 (C-5), 68.1 (C-6), 52.8 (NaO₃SCH₂), 50.2 (C-3), 27.8, 27.8 (SCH₂, CH₂S), 27.1, 26.9, 26.6, 25.5 (4 × CH₃).

Compound Vc

Compound *II* (128 mg, 0.50 mmol) and 2,2'-(ethylenedioxy)diethanethiol *IIIIf* (51 μL , 0.25 mmol, 0.5 eq.) were reacted in toluene–MeOH 1 : 1 vol. (4 mL) according to the general method using 3 × 0.1 eq. of DPAP (3 × 5 mg) and irradiation for 3 × 15 min. The crude product was purified by silica gel chromatography in hexane–acetone ($\varphi_r = 8 : 2$), $R_f = 0.30$, to give compound *Vc* (80 mg, 46 %) as a colorless syrup. $[\alpha]_D (c = 0.38, \text{CHCl}_3) = 73.4^\circ$. For C₃₂H₅₄O₁₂S₂ ($M_r = 694.89$) $w_i/\text{mass } \%$: calculated: C, 55.31; H, 7.83; S, 9.23, found C, 55.22; H, 7.80; S, 9.15. ¹H NMR (360 MHz, CDCl₃), δ : 5.76 (d, 2H, $J_{1,2} = 3.6$ Hz, H-1), 4.79 (d, 2H, $J = 3.9$ Hz), 4.09 (dd, 2H, $J = 6.2$ Hz, $J = 8.3$ Hz), 4.03–3.97 (m, 2H), 3.91 (dd, 2H, $J = 5.2$ Hz, $J = 8.3$ Hz), 3.73–3.64 (m, 10H), 2.99 (dd, 2H, $J = 3.7$, $J = 12.9$ Hz), 2.81–2.73 (m, 6H), 2.15–2.07 (m, 2H), 1.51, 1.41, 1.34 (3 × s, 24H). ¹³C NMR (90 MHz, CDCl₃), δ : 111.9, 109.5 (4C_q), 104.7 (2 × C-1), 81.1, 80.8 [2 × (C-2, C-4)], 77.7 (2 × C-5), 70.7, 70.2 [2 × (CH₂O, OCH₂)], 67.5 (2 × C-6), 49.6 (2 × C-3), 32.0, 27.6 [2 × (CH₂S, SCH₂)], 26.7, 26.6, 26.4, 25.1 (8 × CH₃).

Compound Vd

Compound *II* (256 mg, 0.10 mmol) and 2,3,4,6-tetra-*O*-acetyl-1-thiomannopyranose *IIIg* (520 mg, 0.15 mmol) were reacted according to the general method. The crude product was purified by silica gel chromatography in CH₂Cl₂–acetone ($\varphi_r = 98 : 2$), to

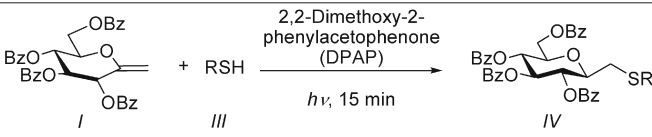
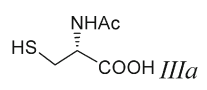
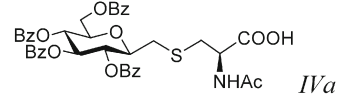
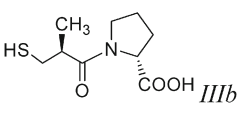
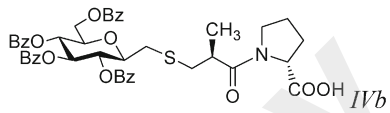
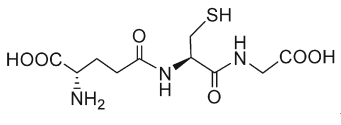
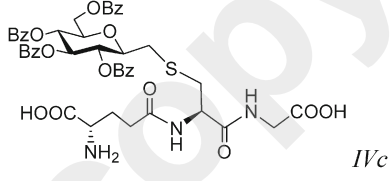
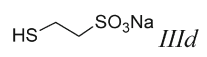
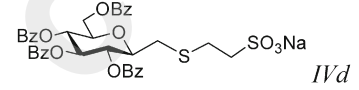
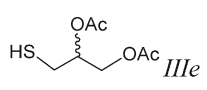
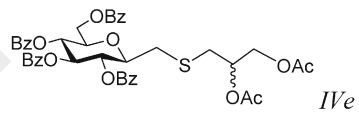
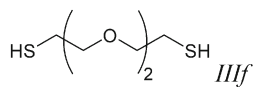
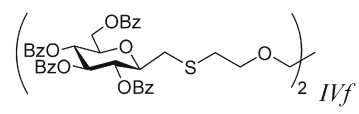
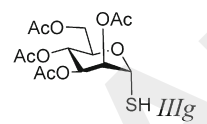
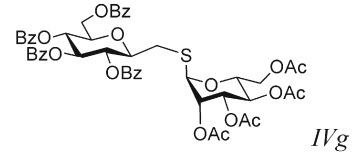
give compound *Vd* (412 mg, 95 %), $R_f = 0.32$, as a white solid. $[\alpha]_D (c = 0.34, \text{CHCl}_3) = 114.1^\circ$. For C₂₇H₄₀O₁₄S ($M_r = 620.66$) $w_i/\text{mass } \%$: calculated: C, 52.25; H, 6.50; S, 5.17, found C, 52.11; H, 6.48; S, 5.15. ¹H NMR (360 MHz, CDCl₃), δ : 5.78 (dd, 1H, $J = 12.5$, $J = 3.8$ Hz), 5.23–5.43 (m, 4H), 4.78 (dd, 1H, $J = 14.8$, $J = 10.8$ Hz), 4.30–4.46 (m, 2H), 4.03–4.16 (m, 2H), 3.85–4.04 (m, 2H), 3.69 (dd, $J = 9.5$, $J = 7.6$ Hz, 1H), 3.06 (dd, $J = 12.7$, $J = 3.6$ Hz, 1H, SCH₂), 2.71–2.89 (m, 1H, SCH₂), 2.00, 2.05, 2.11, 2.18 (4 × s, 12H, CH_{3,ac}), 1.33, 1.34, 1.39, 1.51 (4 × s, 12H, CH_{3,ip}). ¹³C NMR (91 MHz, CDCl₃), δ : 170.5, 169.9, 169.7, 169.5 (CO), 112.0, 109.6 (C_q), 104.7 (C-1), 81.8 (C-1'), 81.0, 80.9, 77.6, 71.0, 69.4, 68.9, 67.7, 66.0 (C-6), 62.1 (C-6'), 48.6 (C-3), 26.7, 26.5, 26.4, 25.0 (CH_{3,ip}), 25.7 (SCH₂), 20.8, 20.6 (CH_{3,ac}).

Results and discussion

To produce carbon-sulfur-linked glycoconjugates by the proposed thio-click approach, 3,4,5,7-tetra-*O*-benzoyl-2,6-anhydro-1-deoxy-D-*gluco*-hept-1-enitol *I* (Tóth & Somsák, 2001; Tóth et al., 2003, 2011) and 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-methylene- α -D-*ribo*-hexofuranose *II* (Acton et al., 1979) were reacted with functionalized thiols (*IIIa–IIIh*). The reactions were carried out at ambient temperature with a 2 : 1 thiol : alkene molar ratio and irradiation at $\lambda_{\text{max}} = 365$ nm for 15 min in the presence of the cleavable photoinitiator 2,2-dimethoxy-2-phenylacetophenone (DPAP). In case of the bivalent thiol *IIIIf*, an 1 : 2 thiol : ene molar ratio was used. The choice of the solvent was governed by the solubility of the reactants.

As the ligation of sugars to peptides and proteins is a current frontier in glycobiology, reactions of *I* with amino acids (*IIIa* and *IIIb*) and tripeptide *IIIc* were studied first. Both *N*-acetyl-L-cysteine (*IIIa*) and captopril (*IIIb*), an angiotensin converting enzyme (ACE) inhibitor, reacted readily with the exocyclic double bond of *I* in toluene–MeOH and gave the corresponding *C*-glycosyl derivatives *IVa* and *IVb* in 88 % and 90 % yields, respectively (Table 1). The exclusive formation of the β -glycosides can be explained by the preferred axial attack on the glucopyranosyl radical (Praly, 2000; Dénès et al., 2014). Finding a suitable medium for hydrothiolation of *I* with glutathione *IIIc* turned out to be difficult because of their extremely different solubility. Fortunately, in the 2 : 1 vol. ratio of DMF and water, almost complete conversion of the exoglycal was observed, providing the *C*-*S*-bridged glycopeptide *IVc* in an 89 % yield. Sodium sulfonatoethyl mercaptane *IIId* (Mesna), used as a detoxifying adjuvant in cancer chemotherapy, and exoglycal *I* were reacted in a 1 : 1 vol. mixture of DMF and MeOH to afford the sulfide derivative *IVd* in good yield. Reaction between *I* and racemic 2,3-di-*O*-acetyl-1-thioglycerol *IIIe* (Mugunthan et al., 2011) in toluene resulted in the

Table 1. Photoinduced addition of thiols to exoglycal *I*

			
RSH	Solvent	Product	Yield/%
 <i>IIIa</i>	Toluene–methanol	 <i>IVa</i>	88 ^a
 <i>IIIb</i>	Toluene–methanol	 <i>IVb</i>	90 ^a
 <i>IIIc</i>	DMF–water	 <i>IVc</i>	89 ^a
 <i>IIId</i>	DMF–methanol	 <i>IVd</i>	90 ^a
 <i>IIIe</i>	Toluene	 <i>IVe</i>	86 ^a
 <i>IIIf</i>	Toluene–methanol	 <i>IVf</i>	61 ^b
 <i>IIIg</i>	Toluene	 <i>IVg</i>	74 ^a

a) Yield of isolated compounds with a 2 : 1 thiol : ene molar ratio using a 0.1 eq. of DPAP; b) 3 × 15 min irradiation, 0.5 eq. of thiol, 0.3 eq. of DPAP.

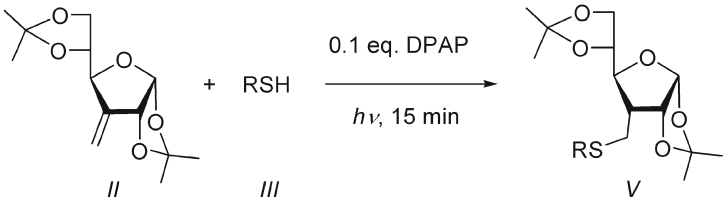
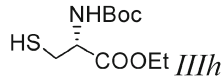
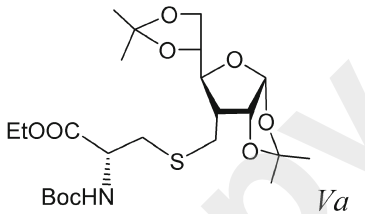
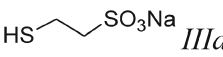
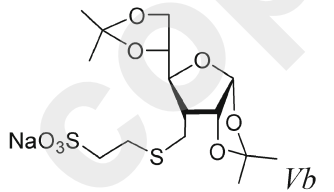
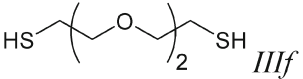
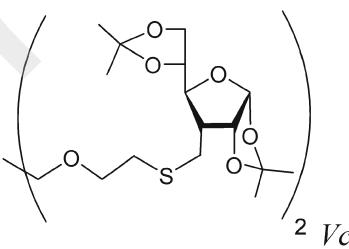
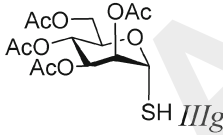
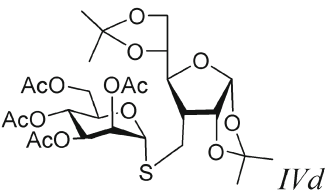
glycerol glycoside derivative *IVe* as a 1 : 1 diastereoisomeric mixture. To couple two *C*-glycosyl units, compound *I* was reacted with a 0.5 equivalent of the bivalent thiol *IIIg*. In this case, the reaction showed low conversion after 15 min; therefore, the DPAP addition and the irradiation were repeated twice more. Thus, after three cycles of irradiation, compound *IVf* was isolated in a 61 % yield. Finally, the synthesis of a *C*-*S*-bridged disaccharide was achieved by hydrothiolation of *I* with 2,3,4,6-tetra-*O*-acetyl-1-thiomannopyranose *IIIg* (Matta et al., 1975) producing the disaccharide mimetic *IVg* in a 74 % yield.

Then, the free-radical hydrothiolation reactions of the 3-exomethylene-derivative *II* bearing the exocyclic double bond anchored to a furanose ring were studied. We were pleased to find that an addition of *N*-

t-butoxycarbonyl-L-cysteine ethyl ester *IIIh* (Stellenboom et al., 2010) across the double bond of *II* resulted into completion within 15 min, providing the *D*-*allo*-configured sugar–amino acid conjugate *Va* exclusively, in a 94 % yield. Stereoselectivity of the reaction can be explained by the preferential β -side hydrogen abstraction from the thiol by the carbon-centered radical. Hydrothiolation of *II* with both the sulfonic acid salt *IIId* and the 1-thiomannose *IIIg* showed high efficacy and full stereoselectivity, affording *Vb* and *Vd* in 92 % and 95 % yields, respectively.

Reaction between *II* and dithiol *IIIg* with a 2 : 1 alkene : thiol mole ratio gave, upon 3 × 15 min irradiation, the desired pseudodisaccharide mimetic *Vc* in a 46 % yield.

Table 2. Photoinduced addition of thiols to 3-exomethylene derivative *II*

			
RSH	Solvent	Product	Yield/%
 <i>IIIh</i>	Methanol	 <i>Va</i>	94
 <i>IIIc</i>	Methanol	 <i>Vb</i>	92
 <i>IIIf</i>	Toluene–methanol	 <i>Vc</i>	46 ^a
 <i>IIIg</i>	Methanol	 <i>IVd</i>	95

a) 3×15 min irradiation, 0.5 eq. of thiol, 0.3 eq. of DPAP.

Conclusions

In conclusion, it has been demonstrated that photoinduced addition of thiols to exocyclic double bonds of furanose or pyranose ring sugars proceeds with total selectivity offering an easy access to carbon-sulfur bridged glycomimetics. Addition of a range of thiols to the benzoyl-substituted pyranoid-exoglycal *I* provided exclusively the β -carbon-sulfur-linked glycoconjugates in high yields. Reactions between thiols and the 3-exomethylene-glucofuranose derivative *II* also proceeded with both high efficacy and full stereoselectivity and afforded a series of D-*allo*-configured 3-deoxy-3-*C-S*-bridged glycoconjugates.

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