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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; Witzack & Culhane, 2005). The best-documented stable glycomimetics 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 F_{254} (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 $MgSO_4$, and concentrated in vacuum. The ^{1}H NMR (360 MHz and 400 MHz) and ^{13}C 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 ℃ (Germany). Chemical shifts are referenced to Me_4Si or DSS as parts per million (0.00 ppm for ^{1}H) and to the solvent signals ($CDCl_3$: 77.00 ppm for ^{13}C). The ^{1}H and ^{13}C 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 CH_2Cl_2–MeOH (φ_r = 85 : 15), R_f = 0.38, to give *IVa* (113 mg, 88 %) as a colorless syrup. $[\alpha]_D$(c = 0.16, $CHCl_3$) = 21.6°. For $C_{40}H_{37}NO_{12}S$ (M_r = 755.79) w_i/mass %: calculated: C, 63.57; H, 4.93; S, 4.24, found: C, 63.41; H, 4.90; S, 4.25. ^{1}H NMR (360 MHz, $(CD_3)_2SO$), 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). ^{13}C NMR (90 MHz, $(CD_3)_2SO$), δ: 172.8, 169.0, 165.3, 165.1, 164.8, 164.7 (6 × CO), 133.7–128.5 (24 × 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, CH_2), 22.4 (CH_3).

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 CH_2Cl_2–MeOH (φ_r = 9 : 1), R_f = 0.44, to give *IVb* (123 mg, 90 %) as a colorless syrup. $[\alpha]_D$(c = 0.02, $CHCl_3$) = –44.3°. For $C_{44}H_{43}NO_{12}S$ (M_r = 809.88) w_i/mass %: calculated: C, 65.25; H, 5.35; S, 3.96, found: C, 65.08; H, 5.33; S, 3.94. ^{1}H NMR (360 MHz, CD_3OD), 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). ^{13}C NMR (90 MHz, CD_3OD), δ: 176.1, 175.9, 167.5, 167.2, 166.8, 166.8 (6 × 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 (CHCH$_3$), 48.4, 37.7, 34.8, 30.2, 25.6 (C-1, 4 x CH_2), 17.3 (CH_3).

Compound IVc

Compound *I* (100 mg, 0.169 mmol) and glutathione *IIIc* (104 mg, 0.338 mmol) were reacted in DMF–H_2O 2 : 1 vol. (12 mL) according to the general method. The crude product was purified by silica gel chromatography in CH_2Cl_2–MeOH–H_2O (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, MeOH) = +91.7°. For $C_{45}H_{45}N_3O_{15}S$ (M_r = 899.91) w_i/mass %: calculated: C, 60.06; H, 5.04; S, 3.56, found: C, 59.98; H, 5.02; S, 3.54. ^{1}H NMR (360 MHz, CD_3OD), δ: 7.98–7.37 (m, 22H_{arom}, 2 × 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). ^{13}C NMR (90 MHz, CD_3OD), δ: 172.6, 172.5, 169.8, 165.6, 165.3, 165.0, 164.9 (8 × 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 × CH_2).

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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 CH_2Cl_2–MeOH (φ_r = 85 : 15), R_f = 0.67, to give *IVd* (138 mg, 90 %) as a colorless syrup. For $C_{37}H_{33}NaO_{12}S_2$ (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. ^{1}H NMR (360 MHz, $(CD_3)_2SO$), 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). ^{13}C NMR (90 MHz, $(CD_3)_2SO$): 165.4, 165.2, 164.9, 164.8 (4 × 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 (NaO_3SCH_2), 33.1 (C-1), 28.1 (CH_2S).

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, $CHCl_3$) = 24.5°. For $C_{42}H_{40}O_{13}S$ (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. ^{1}H NMR (360 MHz, $CDCl_3$), 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 × s, 6H). ^{13}C NMR (90 MHz, $CDCl_3$), δ: 170.4, 170.1, 166.0, 165.8, 165.2, 165.1 (6 × 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, CHOAc), 63.7, 62.9 (C-7, CH_2OAc), 33.6, 33.5, 33.4, 33.3 (C-1, CH_2S), 20.8, 20.6 (2 × CH_3).

Compound IVf

Compound *I* (100 mg, 0.169 mmol) and 2,2′-(ethylenedioxy)diethanethiol *IIIf* (14 μL, 0.085 mmol) 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 (φ_r = 65 : 35), R_f = 0.20, to give *IVf* (70 mg, 61 %) as a colorless syrup. $[\alpha]_D$(c = 0.20, $CHCl_3$) = +18.8°. For $C_{76}H_{70}NO_{20}S_2$ (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. ^{1}H NMR (360 MHz, $CDCl_3$), 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). ^{13}C NMR (90 MHz, $CDCl_3$), δ: 166.0, 165.8, 165.3, 165.1 (8 × CO), 133.4–128.2 (48 C_{arom}), 79.7, 76.1, 74.2, 71.8, 69.6 [2 × (C-2, C-3, C-4, C-5, C-6)], 70.7, 70.0 [2 × (CH_2O, OCH_2)], 63.2 (2 × C-7), 33.7, 32.6 [2 × (C-1, SCH_2)].

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, $CHCl_3$) = 48.7°. For $C_{49}H_{48}O_{18}S$ (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. ^{1}H NMR (360 MHz, $CDCl_3$), 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, SCH_2), 1.98, 2.01, 2.05, 2.11 (4 × s, 12H, $CH_{3,ac}$).^{13}C NMR (90 MHz, $CDCl_3$), 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 (CH_2S), 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, $CHCl_3$) = 52.0°. For $C_{23}H_{39}NO_9S$ (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. ^{1}H NMR (400 MHz, $CDCl_3$), 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, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$), 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—CH_2), 53.39, 49.8 (C-3 and CH—NH), 35.4, 28.0 (2 × S—CH_2), 28.2, 26.7, 26.6, 26.3, 25.1, 14.1 (CH_3).

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 CH_2Cl_2–MeOH ($\varphi_r = 8 : 2$), R_f = 0.44, to give *Vb* (387 mg, 92 %) as a white solid. $[\alpha]_D$ (c = 0.33, $CHCl_3$) = 52.4°. For $C_{15}H_{25}NaO_8S_2$ (M_r = 420.47) w_i/mass %: calculated: C, 42.85; H, 5.99; S, 15.25, found: C, 42.73; H, 5.97; S, 15.21. ^{1}H NMR (360 MHz, CD_3OD), 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). ^{13}C NMR (90 MHz, CD_3OD), 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 (NaO_3SCH_2), 50.2 (C-3), 27.8, 27.8 (SCH_2, CH_2S), 27.1, 26.9, 26.6, 25.5 (4 × CH_3).

Compound Vc

Compound *II* (128 mg, 0.50 mmol) and 2,2′-(ethylenedioxy)diethanethiol *IIIf* (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, $CHCl_3$) = 73.4°. For $C_{32}H_{54}O_{12}S_2$ (M_r = 694.89) w_i/mass %: calculated: C, 55.31; H, 7.83; S, 9.23, found C, 55.22; H, 7.80; S, 9.15. ^{1}H NMR (360 MHz, $CDCl_3$), 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). ^{13}C NMR (90 MHz, $CDCl_3$), 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 × (CH_2O, OCH_2)], 67.5 (2 × C-6), 49.6 (2 × C-3), 32.0, 27.6 [2 × (CH_2S, SCH_2)], 26.7, 26.6, 26.4, 25.1 (8 × CH_3).

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 CH_2Cl_2–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, $CHCl_3$) = 114.1°. For $C_{27}H_{40}O_{14}S$ (M_r = 620.66) w_i/mass %: calculated: C, 52.25; H, 6.50; S, 5.17, found C, 52.11; H, 6.48; S, 5.15. ^{1}H NMR (360 MHz, $CDCl_3$), 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, SCH_2), 2.71–2.89 (m, 1H, SCH_2), 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, $CH_{3,ip}$).^{13}C NMR (91 MHz, $CDCl_3$), 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 (SCH_2), 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 λ_{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 *IIIf*, 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

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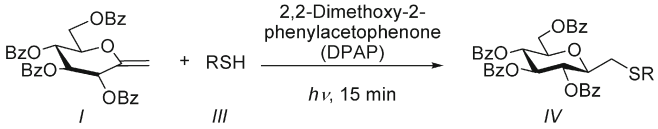
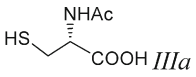
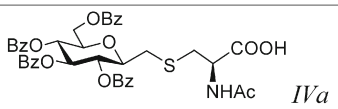
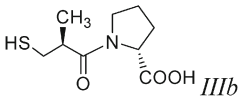
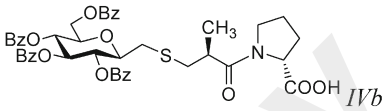
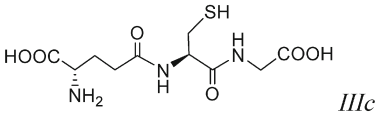
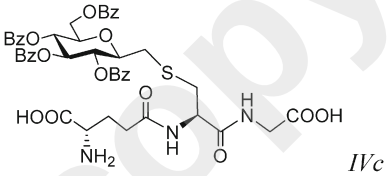
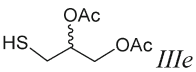
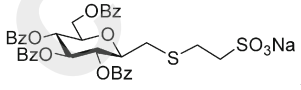
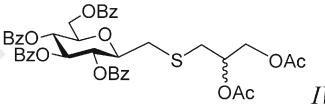
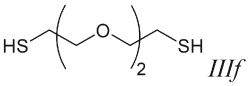
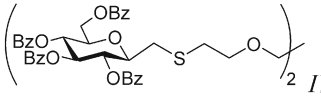
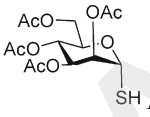
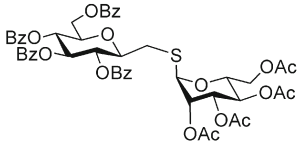
Table 1. Photoinduced addition of thiols to exoglycal *I*



RSH	Solvent	Product	Yield/%
 *IIIa*	Toluene–methanol	 *IVa*	88[a]
 *IIIb*	Toluene–methanol	 *IVb*	90[a]
 *IIIc*	DMF–water	 *IVc*	89[a]
 *IIId*	DMF–methanol	 *IVd*	90[a]
IIIe	Toluene	 *IVe*	86[a]
 *IIIf*	Toluene–methanol	 *IVf*	61[b]
 *IIIg*	Toluene	 *IVg*	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 *IIIf*. 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. Stereolectivity 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 *IIIf* with a 2 : 1 alkene : thiol mole ratio gave, upon 3 × 15 min irradiation, the desired pseudodisaccharide mimetic *Vc* in a 46 % yield.

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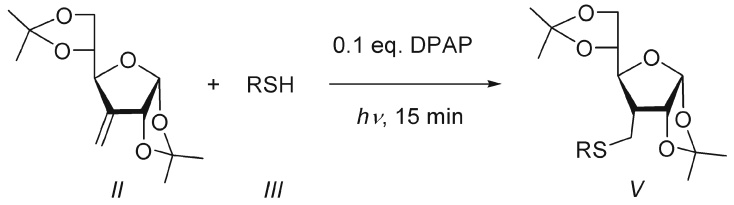
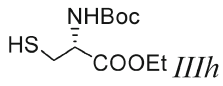
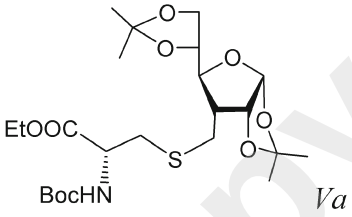
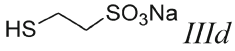
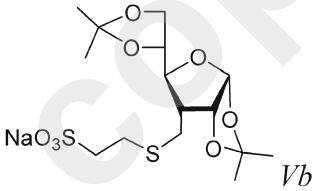
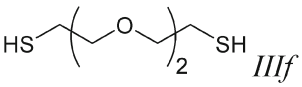
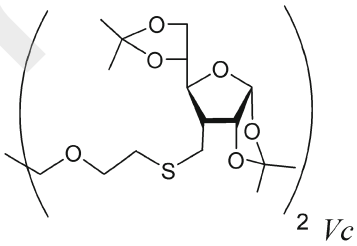
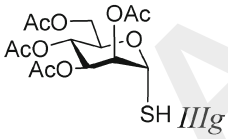
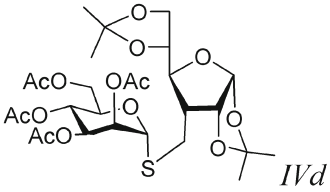
Table 2. Photoinduced addition of thiols to 3-exomethylene derivative *II*



RSH	Solvent	Product	Yield/%
 *IIIh*	Methanol	 *Va*	94
 *IIId*	Methanol	 *Vb*	92
 *IIIf*	Toluene–methanol	 *Vc*	46[a]
 *IIIg*	Methanol	 *IVd*	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-subsituted 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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References

Acton, E. M., Goerner, R. N., Uh, H. S., Ryan, K. J., Henry, D. W., Cass, C. E., & LePage, G. A. (1979). Improved antitumor effects in 3′-branched homologs of 2′-deoxythioguanine. Synthesis and evaluation of thioguanine nucleosides of 2,3-

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dideoxy-3-(hydroxymethyl)-D-erythro-pentofuranose. *Journal of Medicinal Chemistry*, *22*, 518–525. DOI: 10.1021/jm00191a012.

Chakka, N., Johnston, B. D., & Pinto, B. M. (2005). Synthesis and conformational analysis of disaccharide analogues containing disulfide and selenosulfide functionalities in the interglycosidic linkages. *Canadian Journal of Chemistry*, *83*, 929–936. DOI: 10.1139/v05-107.

Dénès, F., Pichowicz, M., Povie, G., & Renaud, P. (2014). Thiyl radicals in organic synthesis. *Chemical Reviews*, *114*, 2587–2693. DOI: 10.1021/cr400441m.

Dondoni, A., & Marra, A. (2012). Recent applications of thiol–ene coupling as a click process for glycoconjugation. *Chemical Society Reviews*, *41*, 573–586. DOI: 10.1039/c1cs15157f.

Ernst, B., & Magnani, J. L. (2009). From carbohydrate leads to glycomimetic drugs. *Nature Reviews Drug Discovery*, *8*, 661–677. DOI: 10.1038/nrd2852.

Fiore, M., Marra, A., & Dondoni, A. (2009). Photoinduced thiol–ene coupling as a click ligation tool for thiodisaccharide synthesis. *Journal of Organic Chemistry*, *74*, 4422–4425. DOI: 10.1021/jo900514w.

Illyés, T. Z., Szabó, T., & Szilágyi, L. (2011). Glycosylation via mixed disulfide formation using glycosylthiophthalimides and -succinimides as glycosylsulfenyl-transfer reagents. *Carbohydrate Research*, *346*, 1622–1627. DOI: 10.1016/j.carres.2011.04.020.

Lázár, L., Csávás, M., Herczeg, M., Herczegh, P., & Borbás, A. (2012). Synthesis of *S*-linked glycoconjugates and *S*-disaccharides by thiol–ene coupling reaction of enoses. *Organic Letters*, *14*, 4650–4653. DOI: 10.1021/ol302098u.

Lázár, L., Csávás, M., Hadházi, Á., Herczeg, M., Tóth, M., Somsák, L., Barna, T., Herczegh, P., & Borbás, A. (2013). Systematic study on free radical hydrothiolation of unsaturated monosaccharide derivatives with exo- and endocyclic double bonds. *Organic & Biomolecular Chemistry*, *11*, 5339–5350. DOI: 10.1039/c3ob40547h.

Liu, L., McKee, M., & Postema, M. H. D. (2001). Synthesis of *C*-saccharides and higher congeners. *Current Organic Chemistry*, *5*, 1133–1167. DOI: 10.2174/1385272013374699.

Lopez, M., Bornaghi, L. F., Driguez, H., & Poulsen, S. A. (2011). Synthesis of sulfonamide-bridged glycomimetics. *The Journal of Organic Chemistry*, *76*, 2965–2975. DOI: 10.1021/jo2001269.

Matta, K. L., Girotra, R. N., & Barlow, J. J. (1975). Synthesis of *p*-nitrobenzyl and *p*-nitrophenyl 1-thioglycopyranosides. *Carbohydrate Research*, *43*, 101–109. DOI: 10.1016/s0008-6215(00)83976-2.

Mugunthan, G., Sriram, D., Yogeeswari, P., & Kartha, K. P. R. (2011). Synthetic analogues of mycobacterial arabinogalactan linkage-disaccharide part II: Synthesis and preliminary screening of lipophilic *O*-alkyl glycosides. *Carbohydrate Research*, *346*, 2401–2405. DOI: 10.1016/j.carres.2011.08.027.

Praly, J. P. (2000). Structure of anomeric glycosyl radicals and their transformations under reductive conditions. *Advances in Carbohydrate Chemistry and Biochemistry*, *56*, 65–151. DOI: 10.1016/s0065-2318(01)56003-5.

Prosperi, D., Ronchi, S., Lay, L., Rencurosi, A., & Russo, G. (2004). Efficient synthesis of unsymmetrical ureido-linked disaccharides. *European Journal of Organic Chemistry*, *2004*, 395–405. DOI: 10.1002/ejoc.200300483.

Robina, I., Vogel, P., & Witczak, Z. (2001). Synthesis and biological properties of monothiosaccharides. *Current Organic Chemistry*, *5*, 1177–1214. DOI: 10.2174/1385272013374743.

Staderini, S., Chambery, A., Marra, A., & Dondoni, A. (2012). Free-radical hydrothiolation of glycals: A thiol–ene-based synthesis of *S*-disaccharides. *Tetrahedron Letters*, *53*, 702–704. DOI: 10.1016/j.tetlet.2011.11.140.

Stellenboom, N., Hunter, R., & Caira, M. R. (2010). One-pot synthesis of unsymmetrical disulfides using 1-chlorobenzotriazole as oxidant: Interception of the sulfenyl chloride intermediate. *Tetrahedron*, *66*, 3228–3241. DOI: 10.1016/j.tet.2010.02.077.

Szilágyi, L., Illyés, T. Z., & Herczegh, P. (2001). Elaboration of a novel type of interglycosidic linkage: Syntheses of disulfide disaccharides. *Tetrahedron Letters*, *42*, 3901–3903. DOI: 10.1016/s0040-4039(01)00578-0.

Szilágyi, L., & Varela, O. (2006). Non-conventional glycosidic linkages: Syntheses and structures of thiooligosaccharides and carbohydrates with three-bond glycosidic connections. *Current Organic Chemistry*, *10*, 1745–1770. DOI: 10.2174/138527206778249874.

Tóth, M., & Somsák, L. (2001). *exo*-Glycals from glycosyl cyanides. First generation of *C*-glycosylmethylene carbenes from 2,5- and 2,6-anhydroaldose tosylhydrazones. *Journal of the Chemical Society, Perkin Transactions 1*, 942–943. DOI: 10.1039/b102963k.

Tóth, M., Kövér, K. E., Bényei, A., & Somsák, L. (2003). *C*-Glycosylmethylene carbenes: Synthesis of anhydro-aldose tosylhydrazones as precursors; generation and a new synthetic route to *exo*-glycals. *Organic & Biomolecular Chemistry*, *1*, 4039–4046. DOI: 10.1039/b307378e.

Tóth, M., Kun, S., Somsák, L., & Goyard, D. (2011). Preparation of *exo*-glycals from 2,6-anhydro-aldose-tosylhydrazones. In P. Kovac (Ed.) *Carbohydrate chemistry: Proven synthetic methods* (pp. 365–373). Boca Raton, FL, USA: CRC Press.

Witczak, Z. J., & Culhane, J. M. (2005). Thiosugars: New perspectives regarding availability and potential biochemical and medicinal applications. *Applied Microbiology and Biotechnology*, *69*, 237–244. DOI: 10.1007/s00253-005-0156-x.

Witczak, Z. J., Lorchak, D., & Nguyen, N. (2007). A click chemistry approach to glycomimetics: Michael addition of 2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-D-glucopyranose to 4-deoxy-1,2-*O*-isopropylidene-L-glycero-pent-4-enopyranos-3-ulose – a convenient route to novel 4-deoxy-(1→5)-5-*C*-thiodisaccharides. *Carbohydrate Research*, *342*, 1929–1931. DOI: 10.1016/j.carres.2007.06.005.

Witczak, Z. J., & Bielski, R. (2013). *Click chemistry in glycoscience: New developments and strategies*. New York, NY, USA: Wiley.

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