NJC

Accepted Manuscript

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ROYAL SOCIETY OF CHEMISTRY

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View Article Online
DOI: 10.1039/C7NJ03069J

New synthesis of *C*-β-D-glycopyranosylmethyl sulfides by metal-free coupling of anhydro-aldose tosylhydrazones with thiols

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Abstract

Cross couplings of *O*-peracylated 2,6-anhydro-aldose tosylhydrazones with aliphatic, (hetero)aromatic and sugar derived thiols were studied under thermic conditions in the presence of K_3PO_4. The reactions with aliphatic thiols gave the corresponding *C*-β-D-glycopyranosylmethyl sulfides in 20-50 % yields, while 50-80 % yields were achieved with thiophenols. Sugar thiols failed to give the expected compounds with acceptable selectivity. The transformations represent a new access to these types of glycomimetic compounds. The method is complementary with the thiol-ene additions of *exo*-glycals (also obtained from the above tosylhydrazones) providing good yields of aliphatic and sugar derived *C*-glycosylmethyl sulfides. Thus, anhydro-aldose tosylhydrazones represent a common starting material toward any kind of the target compounds either in a direct coupling or via *exo*-glycals.

Keywords: Cross coupling; Anhydro-aldose tosylhydrazones; Carbenes; *C*-β-D-Glycopyranosylmethyl sulfides.

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DOI: 10.1039/C7NJ03069J

Introduction

Carbohydrates play important roles in various biological processes such as metastasis, immune response, inflammation, bacterial and viral infections, thus their pharmaceutical potential offers great opportunities. However, the low hydrolytic stability of the natural *O*-glycosidic bonds reduces the applicability of carbohydrate-type molecules as drug candidates.[1] The replacement of the glycosidic oxygen with other atoms, most frequently by S, N, and C, may result in hydrolytically stable moieties which open several ways to the syntheses of glycomimetic compounds.[2] In several glycomimetics there are two or even more atoms linking the glycon and the aglycon part of the molecules.[3]

C-Glycosylmethyl sulfide derivatives (compounds **G** in Scheme 1) with a hydrolitically highly stable CH_2–S moiety represent an important class of glycomimetics. In the literature only a few methods can be found for the preparation of such compounds most of which use *O*-protected *exo*-glycals[4] **A** as starting materials. Thus, hydroboration-oxidation of *O*-perbenzylated *exo*-glucal **A** to give *C*-β-D-glucosylmethanol **B** followed by iodine replacement gave **D** (X = I) which was reacted with thiols to give **G** (R = aliphatic amino acid precursor, glycosyl).[5, 6] Mesylation of *C*-β-D-glucopyranosylmethanol **B** to give **D** (X = OMs) followed by reaction with AcSK yielded **G** (R = Ac).[7] *O*-Peracetylated β-D-galactopyranosylmethyl iodide (**D**, X = I), prepared from methyl 2,6-anhydro-D-*glycero*-L-*manno*-heptonate (**C**) in several steps via **B**,[8] was converted to the corresponding **G** (R = Bz) by BzSNa.[9] An *O*-benzyl protected *C*-allyl α-D-mannopyranosyl derivative **E** was converted by an isomerization–ozonolysis–reduction sequence to **B** which on mesylation and subsequent bromine substitution gave **D** (X = Br) to be reacted with a heteroaromatic thiol toward the α-D-configured **G** (R = 2-thiazolyl).[10] Acetal-protected *C*-β-D-mannopyranosylmethyl

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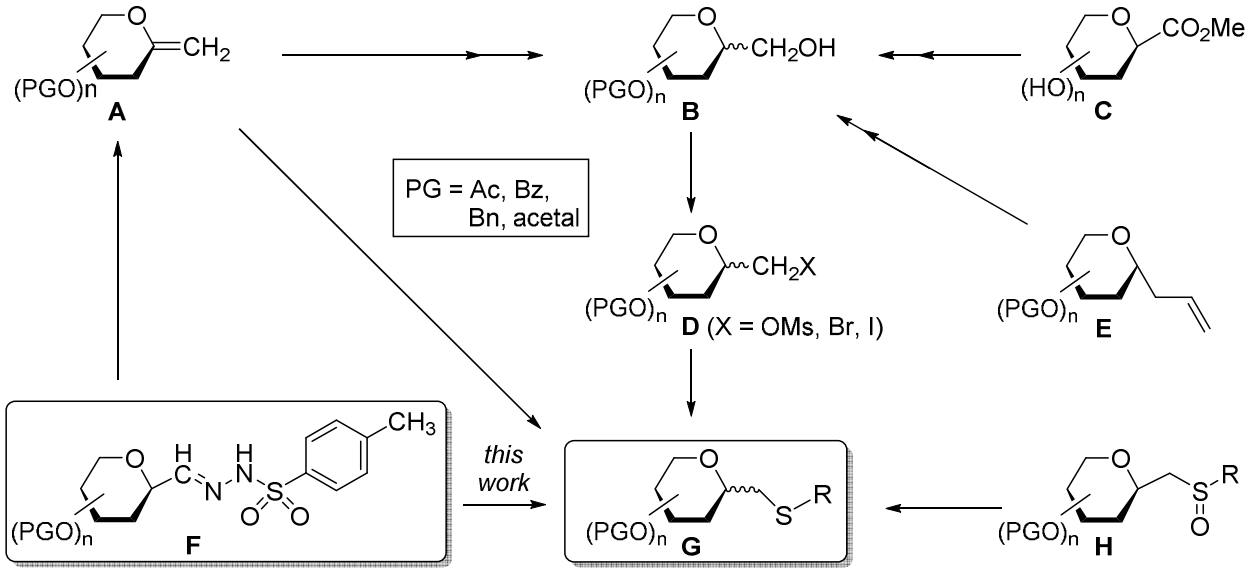
sulfoxides **H**, obtained by ring-closure of a mannose-derived vinyl sulfoxide, also gave **G** (R = TBDMS-O-CH_2) in a Pummerer-type rearrangement with *O*-methyl-*O*-TBDMS ketene acetal.[11]

Direct conversions of *exo*-glycals **A** to compounds of type **G** with β-D-configuration by radical-mediated thiol-ene additions are also known. Thus, addition of AcSH to *O*-perbenzylated *exo*-glucals **A** in the presence of AIBN gave **G** (R = Ac).[12] More recently photoinitiated addition of a wide range of thiols including sugar derived ones to a series of *O*-peracylated *exo*-glycals **A** were reported to result in compounds **G** (R = aliphatic, aromatic, glycosyl and other sugar-derived groups).[13-15]



Scheme 1. Synthetic routes toward *C*-glycosylmethyl sulfides **G** (for details see text).

As a part of a program to evaluate the synthetic potential of cross-coupling reactions of anhydro-aldose tosylhydrazones **F**, we have recently reported a novel route to *C*-β-D-glycopyranosylmethyl ethers and esters from the aforesaid hydrazones and hydroxy

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compounds as well as carboxylic acids.[16] These transformations represent the first application of tosylhydrazone couplings[17-19] in carbohydrate chemistry.

Given the above interest in *C*-glycopyranosylmethyl sulfides **G** and based on the long known intra-[20, 21]and intermolecular[22-24] insertion of carbenes/carbenoids[25] into SH-bonds as well as on some recent literature reports on reactions of simple aldehyde or ketone tosylhydrazones with thiols[26-29] we envisaged that cross couplings of anhydro-aldose tosylhydrazones **F** with sulfanyl derivatives may directly result in glycomimetics of type **G**. In addition, a simplification of the synthetic route was also expected, since *O*-acylated *exo*-glycals **A** are best prepared from the same tosylhydrazones **F**.[30-32] Herein we reveal our studies in this field which provide a new, alternative, and shorter synthetic pathway to certain types of the target sulfides **G**.

Results and discussion

In our previous work, for the coupling of anhydro-aldose tosylhydrazones with hydroxy compounds and carboxylic acids, the best results, in terms of yields and by-product formation, were achieved by using K_3PO_4 in dry 1,4-dioxane at reflux temperature.[16] Thus, it seemed to be evident to use the same reaction conditions in the present couplings with thiols, as well. To find the optimal reagent ratios tosylhydrazone **1**[30-32] was reacted in the presence of different amounts of thiophenol and K_3PO_4 in dry 1,4-dioxane at reflux temperature (Table 1). Using 20-fold excess of thiophenol and 10-fold excess of base gave the corresponding *C*-β-D-glucopyranosylmethyl sulfide **2h** in good yield, accompanied by a small amount of *exo*-glucal **3** (Table 1, entry 1). The formation of **3** can be explained by an intramolecular carbene insertion reaction into the C-2–H bond.[31, 33, 34] Reducing the amount of thiophenol (entries 2, 3) resulted in lower yields of **2h** with increasing amounts of **3**. Keeping the ratio of **1** : PhSH

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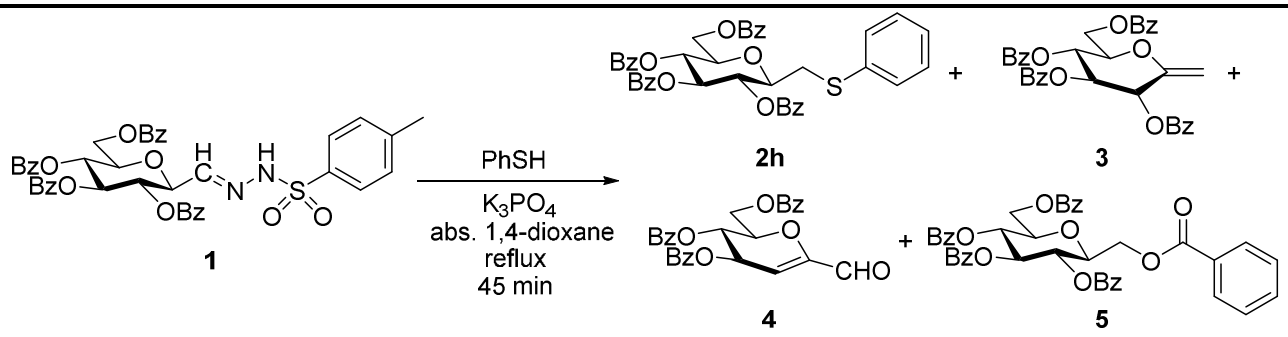
at 4-5 and diminishing the amount of the base to 2-5 equivalents relative to **1** (entries 4-6) gave acceptable yields of **2h**, however, further by-products could be observed in the reaction mixtures. The formation of **4** and **5** was attributed to traces of water in the reaction mixtures as explained in our previous paper.[16] A further decrease of the PhSH excess (entry 7) proved only slightly detrimental for the yield (compare to entry 5), however, with 1 equivalent of the reagent the yield was much less (entry 8), and in each case the by-products could be detected. Based on these observations, in the following transformations 5-20-fold excess of thiol and 2-10-fold excess of K_3PO_4 were employed.

Table 1. Formation of phenyl *C*-glucopyranosylmethyl sulfide **2h**: effects of the reagent ratios **1** : PhSH : K_3PO_4



Entry	Reaction conditions		Yield (%)[a]			
	PhSH (equiv.)	K_3PO_4 (equiv.)	**2h**	**3**	**4**	**5**
1	20	10	70	3	-	-
2	10	10	40	23	-	-
3	2	10	33	18	-	-
4	5	5	44	13	+	-
5	5	2	76	+	+	+
6	4	2	53	12	-	+
7	2	2	72	-	+	-
8	1	1.5	59	-	+	-

[a] Isolated yields from a complex mixture which do not reflect the actual product ratios.

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Next, analogous reactions with other thiols were performed (Table 2). Tosylhydrazone **1**, when reacted with ethanethiol, gave the corresponding sulfide **2a** in moderate yield beside some aldehyde **4** (entry 1). A similar reaction with 1-propanethiol resulted in a low yield of **2b**, and formation of the side-product **4** was also observed (entry 2). Performing the reaction in a sealed tube to prevent loss of the thiol reagent allowed **2b** to be isolated in pure state (entry 3). Using 20 or 5-fold excess of 1-propanethiol beside 2-fold excess of K_3PO_4 gave mixtures of **2b** and **3** (entries 4-6) wherein the ratio of **2b** did not increase. Coupling reactions with 2-methylundecane-2-thiol, cyclohexanethiol, phenylmethanethiol, and methyl 3-mercaptopropanoate gave **2c-f**, respectively, in moderate and low yields (entries 7-10). In the case of propane-1,3-dithiol only the corresponding monosulfide **2g** (entry 11) was achieved. 2-Mercaptoethanol and 2-mercaptopropionic acid, reagents with OH-functionality, gave complex reaction mixtures from which no discrete products could be isolated. Coupling reactions with thiophenol and substituted thiophenols gave compounds **2h** and **2i-m**, respectively, in acceptable to good yields (entries 12-22). The presence of a free amino group (entry 19) proved disadvantageous, and the expected **2k** could be isolated in a yield of 23 % only (containing traces of an inseparable impurity), while the *N*-acetyl-protected counterpart gave 65 % of the coupled product **2l** (entry 20). A free phenolic hydroxy group allowed the isolation of **2m** in good yields (entries 21, 22). With 2-mercaptobenzoic acid a complex mixture was formed again. Reaction with 2-mercapto-benzothiazole gave the corresponding *C*-β-D-glucopyranosylmethyl sulfide **2n-I** in 70 % yield (entry 23) and the *N*-coupled product **2n-II** was also isolated in 10 % yield indicating the competition of the tautomers of the reagent in the coupling reaction. An attempted coupling with 2-mercapto-benzimidazole resulted in a complex reaction mixture, from which only *exo*-glucal **3** could be isolated (14 %). Under the same reaction conditions sugar derived thiols (2,3,4,6-tetra-*O*-acetyl-1-thio-β-

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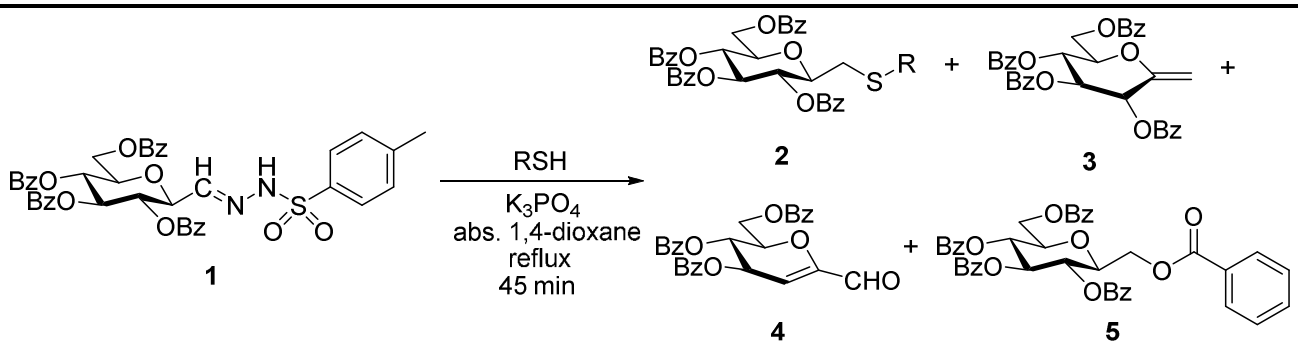
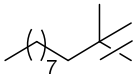
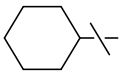
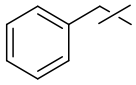
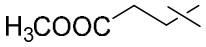
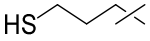
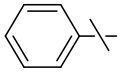
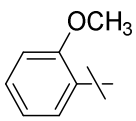
D-gluco- and galactopyranose, 1,2;3,4-di-*O*-isopropylidene-6-thio-α-D-galactopyranose) led to complex reaction mixtures.

Table 2. Reactions of tosylhydrazone **1** with thiols



Entry		R	RSH (equiv.)	K_3PO_4 (equiv.)	Yield (%)[a]	
					2	**3**
1	**a**[13]	CH_3CH_2-	20	10	51	-[b]
2	**b**	$CH_3CH_2CH_2$-	20	10	29	-[b]
3			20	10	21[d]	-
4			20	2	29[c,d]	14[c]
5			5	2	22[c]	20[c]
6			5	2	30[c,d]	36[c]
7	**c**		20	10	17	+[b,e]
8	**d**		20	10	39	-
9	**e**		20	10	44	+[e]
10	**f**		20	10	23	+
11	**g**		20	10	37	+[b,e]
12	**h**[13]		20	10	70	+[b,e]
13			5	2	76	+[b,e]
14	**i**		20	10	69	+
15			5	2	64	+[b]

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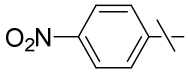
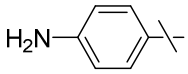
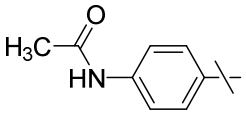
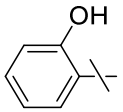
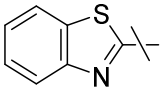
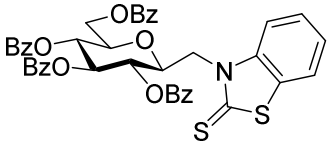
16			2	2	55	-
17	**j**		5	4	44	-
18			5	6	54	-
19	**k**		20	10	23[f]	-
20	**l**		5	2	65[g]	-
21	**m**		20	10	68	-
22			5	2	64	-
23	**n-I**		5	2	70[h]	-

[a] Isolated yields which do not reflect the actual product ratios.
[b] Compound **4** was detected in the mixture.
[c] Yields calculated on the basis of the proton NMR spectra of the worked-up reaction mixture.
[d] Performed in a sealed tube.
[e] Compound **5** was detected in the mixture.
[f] Containing some inseparable impurity.
[g] Performed under an argon atmosphere.
[h] Compound **2n-II** was also isolated in 10 % yield.



2n-II

The examinations were extended to the D-*galacto* configured tosylhydrazone **6** (Table 3). Sulfides **7a-e** derived from aliphatic thiols were isolated in low to moderate yields beside some side-product **8** (entries 1-5). Coupling with thiophenol (entries 6 and 7) or substituted thiophenols (entries 8, 9) gave the corresponding sulfides in good yields with some detectable *exo*-galactal **8**. Reactions with *O*-peracetylated 1-thio-β-D-glycopyranoses gave complex reaction mixtures.

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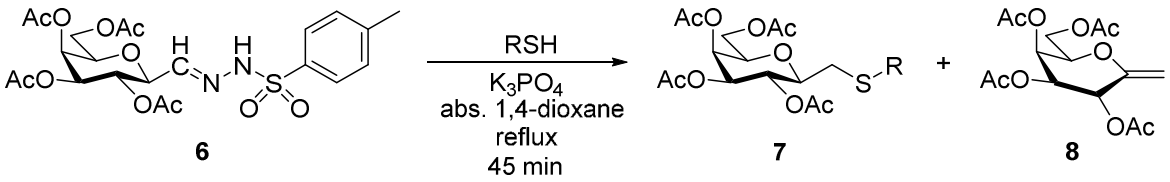
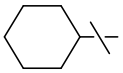
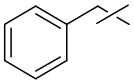
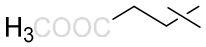
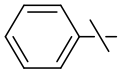
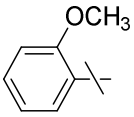
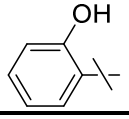
Table 3. Coupling of tosylhydrazone **6** with thiols



6 **7** **8**

Entry		R	RSH (equiv.)	K_3PO_4 (equiv.)	Yield (%)[a]	
					7	**8**
1	**a**	CH_3CH_2-	20	10	16	25
2	**b**[15]	$CH_3CH_2CH_2$-	20	10	30	+
3	**c**		5	2	36	+
4	**d**[15]		20	10	27	-
5	**e**		20	10	39	+
6	**f**[15]		20	10	62	+
7			5	2	77	+
8	**g**		20	10	60	+
9	**h**		20	10	51	-

[a] Isolated yields from a complex mixture which do not reflect the actual product ratios.

In both series of experiments either with **1** or **6** the corresponding sulfides **2** or **7**, respectively, were isolated in significantly lower yields when aliphatic thiols were applied in comparison to the aromatic ones. This observation prompted us to correlate the acidities of the thiol reagents to the yields of the transformations (similar correlation was found with the couplings of tosylhydrazones **1** or **6** with hydroxy compounds and carboxylic acids[16]). Acidities, characterized by the pK_a values for most of the applied thiols, together with the yields are collected in Table 4 to show that thiols with a pK_a ~ 9 or higher (entries 1-7) furnished the coupled products in ~20-50 % yields, while the more acidic aromatic thiols (pK_a < 7, entries

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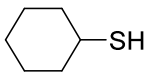
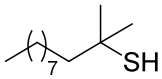
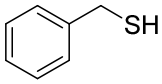
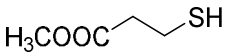
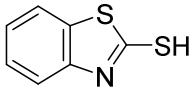
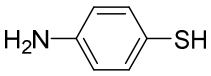
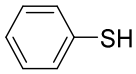
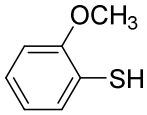
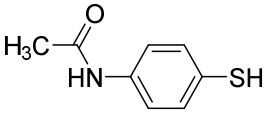
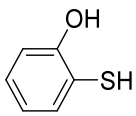
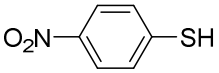
8-14) yielded the corresponding sulfides in the 50-80 % range (except entry 9 where the presence of the NH_2 group may be detrimental for the yield).

Table 4. Comparison of the acidity (pK_a) of the investigated thiols and its influence on the yields

Entry	Reagent	Reagent equiv.	Yield of the coupled product	pK_a	Ref.
1		20 (with **1**) 5 (with **6**)	39 (**2d**) 36 (**7c**)	10.69	35
2	CH_3CH_2SH	20 (with **1**) 20 (with **6**)	51 (**2a**) 16 (**7a**)	10.50	36
3	$CH_3CH_2CH_2SH$	20 (with **1**) 20 (with **6**)	29 (**2b**) 30 (**7b**)	10.20	37
4		20 (with **1**)	17 (**2c**)	9.99	37
5		20 (with **1**)	37 (**2g**)	9.89 and 10.51	37
6		20 (with **1**) 20 (with **6**)	44 (**2e**) 27 (**7d**)	9.43	36
7		20 (with **1**) 20 (with **6**)	23 (**2f**) 39 (**7e**)	9.33	38
8		5 (with **1**)	70 (**2n**)	6.93	39
9		20 (with **1**)	23 (**2k**)	6.86	37
10		5 (with **1**) 5 (with **6**)	76 (**2h**) 77 (**7f**)	6.62	36
11		5 (with **1**) 20 (with **6**)	64 (**2i**) 60 (**7g**)	6.11	37
12		5 (with **1**)	65 (**2l**)	6.08	38
13		20 (with **1**) 20 (with **6**)	68 (**2m**) 51 (**7h**)	6.01	37
14		5 (with **1**)	54 (**2j**)	4.72	36

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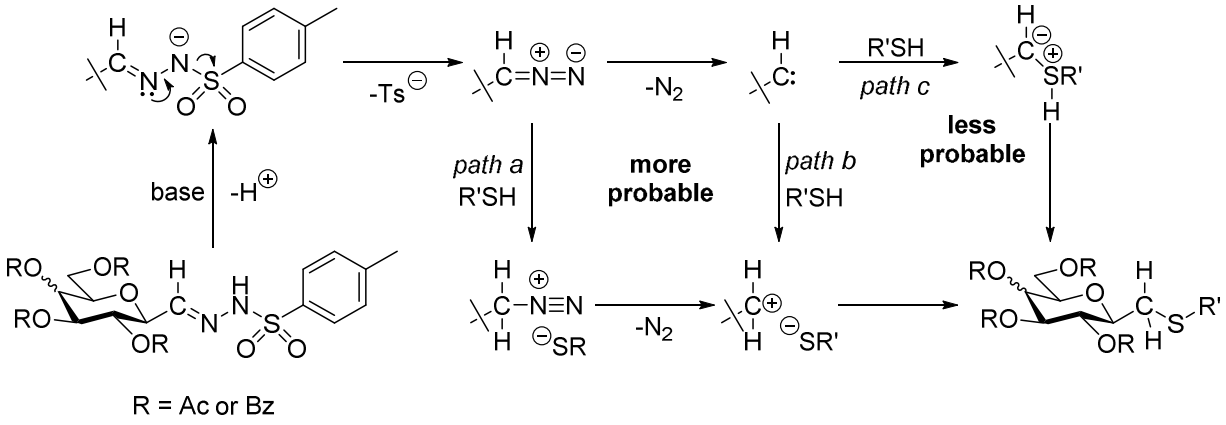
Based on the above correlation it is suggested that among the possible mechanistic pathways (Scheme 2) protonation of the intermediate azo compound (*path a*) or that of the carbene (*path b*) followed by attack of the thiolate versus direct insertion of the carbene into the S-H bond (*path c*) the first two seem more probable.



Scheme 2. Mechanistic possibilities for the coupling reactions.

C-glycosylmethyl sulfides have recently been prepared by phototinitiated thiol-ene additions of *exo*-glycals,[13-15] therefore, a comparison of the efficiency of the two synthetic methods seems appropriate. To this end Table 5 shows the relevant data for those compounds that were obtained by both *routes A* (tosylhydrazone coupling with thiols) and *B* (transformation of the tosylhydrazone to an *exo*-glycal followed by thiol-ene addition). The data clearly illustrate that the two methods are complementary. While the sulfides derived from aliphatic thiols (entries 1, 3, and 4) can be obtained in higher overall yields by the two-step *route B*, the aromatic ones (entries 2 and 5) are best prepared in the one step coupling of *route A*. Although sugar derived thiols failed to give the expected *C*-glycosylmethyl glycosyl sulfides in *route A* in the present study, they were obtained earlier[14, 15] in excellent yields in *route B*.

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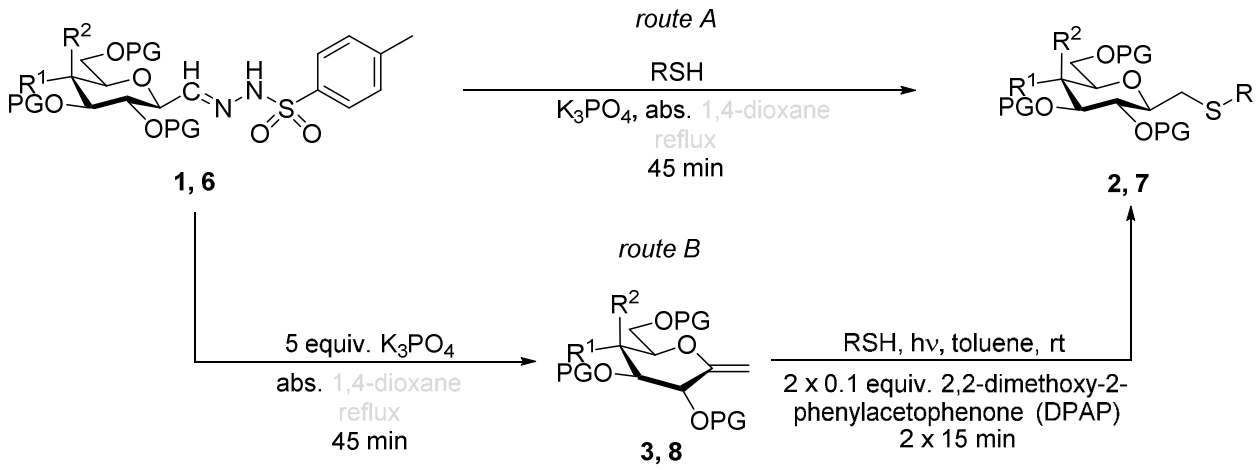
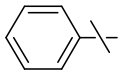
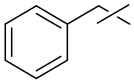
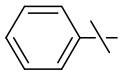
Table 5. Comparison of two synthetic routes resulting in *C*-glycosylmethyl sulfides



Entry	Starting compound	PG	R^1	R^2	R	RSH (equiv.) *routes*		Product	Yield (%) *routes*	
						A	*B*		*A*	*B* (for 2 steps)
1	**1**	Bz	OBz	H	CH_3CH_2-	20	5	**2a**	51	67
2		Bz	OBz	H		5	2	**2h**	76[a]	54
3	**6**	Ac	H	OAc	$CH_3CH_2CH_2$-	20	10	**7b**	30[b]	38
4		Ac	H	OAc		20	10	**7d**	27	48
5		Ac	H	OAc		5	10	**7f**	77[b]	40

[a] Compound **3** was detected in the mixture.
[b] Compound **8** was detected in the mixture.

Conclusion

This study on the coupling reactions of 2,6-anhydro-aldose tosylhydrazones with SH-compounds revealed that thiophenols gave acceptable to good yields of the expected *C*-glycopyranosylmethyl sulfides, while aliphatic thiols resulted in low to moderate yields of the target compounds. Functional group tolerance of the coupling reaction was extended to esters, amino, acetamido, and phenolic hydroxy groups, however, the presence of alcoholic OH and COOH moieties was not tolerated. The method also did not work with sugar derived thiols.

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This coupling reaction is complementary with the thiol-ene additions of *exo*-glycals which represent a high yielding route toward aliphatic and sugar derived *C*-glycosylmethyl thioethers. Thus, anhydro-aldose tosylhydrazones, easily convertible to *exo*-glycals, provide a common platform for the synthesis of any types of *C*-glycosylmethyl sulfides.

Experimental

General methods

Optical rotations were determined with a Perkin–Elmer 241 polarimeter at room temperature. NMR spectra were recorded with Bruker AM Avance 360 (360/90 MHz for $^{1}H/^{13}C$) or Bruker 400 DRX (400/100 MHz for $^{1}H/^{13}C$) spectrometers. Chemical shifts are referenced to TMS as the internal reference (^{1}H), or to the residual solvent signals (^{13}C). The assignments of the ^{1}H and ^{13}C NMR signals of compounds **2**, **7** were performed by their COSY (**2c**, **2g**, **2m**, **2n-I**, **2n-II**, **7c**, **7e**, **7g**), HSQC (**2b**, **2d**, **2e**, **2g**, **2m**, **2n-I**, **7b**, **7c**, **7e**, **7g**), HMBC (**7e**) spectra. Mass spectra were recorded with Thermo LTQ XL (Thermo Electron Corp., San Jose, CA, USA) mass spectrometers operated in a full scan positive or negative ion ESI mode. TLC was performed on DCAlurolle Kieselgel 60 F254 (Merck). TLC plates were visualized under UV light, and by gentle heating (generally no spray reagent was used but, if more intense charring was necessary, the plate was sprayed with the following solution: abs. EtOH (95 mL), cc. H_2SO_4 (5 mL), anisaldehyde (1 mL)). For column chromatography Kieselgel 60 (Merck, particle size (0.063–0.200 mm) was applied. 1,4-Dioxane was distilled from sodium benzophenone ketyl and stored over sodium wires.

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General procedure for the synthesis of *C*-β-D-glycopyranosylmethyl sulfides

A thiol and K_3PO_4 (in a ratio relative to **1** or **6** indicated in Tables 2 and 3, respectively) were added to dry 1,4-dioxane (2 mL). The suspension was stirred and heated to reflux, and then a solution of a tosylhydrazone (**1**, 0.1 g, 0.13 mmol or **6**, 0.1 g, 0.19 mmol) in dry 1,4-dioxane (2 mL) was added dropwise in 10 minutes. When TLC (1:2 EtOAc–hexane for **1**, 1:1 EtOAc–hexane for **6**) indicated complete consumption of the starting compound (~ 35 min), the mixture was cooled and the insoluble material filtered off. The solvent was removed under reduced pressure, and the residue was purified by column chromatography with eluents indicated for the particular compounds to give *C*-β-D-glycopyranosylmethyl sulfides.

Characterization of the *C*-β-D-glycopyranosylmethyl sulfides

2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-ethyl-1-thio-D-*glycero*-D-*gulo*-heptitol (2a)

Prepared from tosylhydrazone **1** (0.1 g, 0.13 mmol), ethanethiol (0.19 mL, 0.16 g, 2.57 mmol), and K_3PO_4 (0.27 g, 1.29 mmol) according to the General procedure. Purified by column chromatography (1:5 acetone–hexane) to yield 43 mg (51 %) of **2a** as a white amorphous product. $[\alpha]_D$ +18 (c 0.88 in $CHCl_3$), lit.[13] $[\alpha]_D$ +23.5 (c 0.47 in $CHCl_3$); R_f: 0.37 (1:2 EtOAc–hexane). ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=677.18, found: $[M+Na]^+$=677.58, $C_{37}H_{34}O_9S$ (654.19). NMR spectra are identical with those reported.[13]

2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-(1-propyl)-1-thio-D-*glycero*-D-*gulo*-heptitol (2b)

Prepared from tosylhydrazone **1** (0.1 g, 0.13 mmol), 1-propanethiol (0.23 mL, 0.20 g, 2.57 mmol), and K_3PO_4 (0.27 g, 1.29 mmol) according to the General procedure. Purified by column chromatography (1:10 acetone–hexane) to yield 25 mg (29 %) of **2b** as a yellow amorphous product. $[\alpha]_D$ +24 (c 0.88 in $CHCl_3$); R_f: 0.39 (1:2 EtOAc–hexane). ^{1}H NMR (400

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MHz, $CDCl_3$) δ 8.14–7.76 (8H, m, aromatics), 7.64–7.21 (12H, m, aromatics), 5.90 (1H, pseudo t, $J_{4,5}$ 9.8 Hz, H-4), 5.66 (1H, pseudo t, $J_{5,6}$ 9.6 Hz, H-5), 5.55 (1H, pseudo t, $J_{3,4}$ 9.5 Hz, H-3), 4.64 (1H, dd, $J_{7a,7b}$ 12.2 Hz, H-7_a), 4.45 (1H, dd, H-7_b), 4.14 (1H, ddd, $J_{6,7a}$ 2.9, $J_{6,7b}$ 5.3 Hz, H-6), 4.00 (1H, ddd, $J_{1a,2}$ 2.7, $J_{1b,2}$ 5.3, $J_{2,3}$ 10.1 Hz, H-2), 2.79 (1H, dd, $J_{1a,1b}$ 14.3 Hz, H-1_a), 2.74 (1H, dd, H-1_b), 2.66–2.50 (2H, m, S–CH_2), 1.58–1.44 (2H, m, CH_2), 0.86 (3H, t, *J* 7.4 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 166.1, 165.5, 165.4 (4×CO), 133.8–128.2 (aromatics), 80.1 (C-2), 76.3 (C-6), 74.5 (C-4), 72.1 (C-3), 69.9 (C-5), 63.4 (C-7), 35.7 (S–CH_2), 33.4 (C-1), 22.9 (CH_2), 13.4 (CH_3). ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=691.20, found: $[M+Na]^+$=691.92, $C_{38}H_{36}O_9S$ (668.21).

2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-[(1,1-dimethyl)decyl]-1-thio-D-*glycero*-D-*gulo*-heptitol (2c)

Prepared from tosylhydrazone **1** (0.1 g, 0.13 mmol), 2-methylundecane-2-thiol (0.61 mL, 0.52 g, 2.57 mmol), and K_3PO_4 (0.27 g, 1.29 mmol) according to the General procedure. Purified by column chromatography (1:10 acetone–hexane) to yield 18 mg (17 %) of **2c** as a pale yellow amorphous product. $[\alpha]_D$ –1 (c 0.59 in $CHCl_3$); R_f: 0.47 (1:2 EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–7.74 (8H, m, aromatics), 7.65–7.17 (12H, m, aromatics), 5.87 (1H, pseudo t, $J_{4,5}$ 9.6 Hz, H-4), 5.65 (1H, pseudo t, $J_{5,6}$ 9.5 Hz, H-5), 5.48 (1H, pseudo t, $J_{2,3}$ 9.9, $J_{3,4}$ 9.0, Hz, H-3), 4.61 (1H, dd, $J_{6,7a}$ 2.1, $J_{7a,7b}$ 12.1 Hz, H-7_a), 4.45 (1H, dd, $J_{6,7b}$ 5.4 Hz, H-7_b), 4.19–4.06 (1H, m, H-6), 3.99–3.83 (1H, m, H-2), 2.83–2.61 (2H, m, H-1_a, H-1_b), 1.84–0.50 (25H, m, aliphatic, dodecyl CH_2, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 166.1, 165.6, 165.4 (4×CO), 134.4–128.1 (aromatics), 79.2 (C-2), 76.3 (C-6), 74.5 (C-4), 72.7 (C-3), 70.0 (C-5), 63.5 (C-7), 60.0–10.0 (C-1, quat. C, 8×CH_2, 3×CH_3). ESI-MS positive mode (m/z): calc. for $[M+K]^+$=833.31, found: $[M+K]^+$=833.83, $C_{47}H_{54}O_9S$ (794.35).

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2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-cyclohexyl-1-thio-D-*glycero*-D-*gulo*-heptitol (2d)

Prepared from tosylhydrazone **1** (0.1 g, 0.13 mmol), cyclohexanethiol (0.31 mL, 0.30 g, 2.57 mmol), and K_3PO_4 (0.27 g, 1.29 mmol) according to the General procedure. Purified by column chromatography (1:10 acetone–hexane) to yield 35 mg (39 %) of **2d** as a white amorphous product. $[\alpha]_D$ +14 (c 0.91 in $CHCl_3$); R_f: 0.39 (1:2 EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–7.76 (8H, m, aromatics), 7.62–7.20 (12H, m, aromatics), 5.90 (1H, pseudo t, $J_{4,5}$ 9.7 Hz, H-4), 5.67 (1H, pseudo t, $J_{5,6}$ 9.8 Hz, H-5), 5.55 (1H, pseudo t, $J_{3,4}$ 9.6 Hz, H-3), 4.63 (1H, dd, $J_{7a,7b}$ 12.2 Hz, H-7_a), 4.44 (1H, dd, H-7_b), 4.14 (1H, ddd, $J_{6,7a}$ 2.9, $J_{6,7b}$ 5.3 Hz, H-6), 3.98 (1H, ddd, $J_{1b,2}$ 5.3, $J_{2,3}$ 10.0 Hz, H-2), 2.85–2.74 (3H, m, H-1_a, H-1_b, S–CH) 2.00–1.83 (2H, m, aliphatic, cyclohexyl), 1.71–1.43 (3H, m, aliphatic, cyclohexyl), 1.29–1.04 (5H, m, aliphatic, cyclohexyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 166.1, 165.5, 165.3 (4×CO), 133.8–128.2 (aromatics), 80.0 (C-2), 76.3 (C-6), 74.5 (C-4), 72.2 (C-3), 69.8 (C-5), 63.4 (C-7), 44.4 (CH), 33.6, 33.5 (*CH_2*–CH–*CH_2*), 31.4 (C-1), 26.0, 25.9 (3×CH_2). ESI-MS positive mode (m/z): calc. for $[M+H]^+$=709.25, found: $[M+H]^+$=709.83, $C_{41}H_{40}O_9S$ (708.24).

2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-benzyl-1-thio-D-*glycero*-D-*gulo*-heptitol (2e)

Prepared from tosylhydrazone **1** (0.1 g, 0.13 mmol), phenylmethanethiol (0.30 mL, 0.32 g, 2.57 mmol), and K_3PO_4 (0.27 g, 1.29 mmol) according to the General procedure. Purified by column chromatography (1:5 acetone–hexane) to yield 42 mg (44 %) of **2e** as a yellow amorphous product. $[\alpha]_D$ +22 (c 0.89 in $CHCl_3$); R_f: 0.34 (1:2 EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–7.74 (8H, m, aromatics), 7.61–7.07 (17H, m, aromatics), 5.88 (1H, pseudo t, $J_{4,5}$ 9.8 Hz, H-4), 5.68 (1H, pseudo t, $J_{5,6}$ 9.7 Hz, H-5), 5.53 (1H, pseudo t, $J_{3,4}$ 9.6 Hz, H-3), 4.70 (1H, dd, $J_{7a,7b}$ 12.2 Hz, H-7_a), 4.47 (1H, dd, H-7_b), 4.14 (1H, ddd, $J_{6,7a}$ 2.7, $J_{6,7b}$ 5.3 Hz, H-6), 3.97 (1H, ddd, $J_{1a,2}$ 3.6, $J_{1b,2}$ 6.7, $J_{2,3}$ 10.1 Hz, H-2), 3.84 (1H, d, $J_{CH2a,CH2b}$ 13.4

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Hz, CH_{2a}), 3.76 (1H, d, CH_{2b}), 2.64 (1H, dd, $J_{1a,1b}$ 14.8 Hz, H-1_a), 2.59 (1H, dd, H-1_b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 166.0, 165.4, 165.4 (4×CO), 140.1–126.8 (aromatics), 80.3 (C-2), 76.4 (C-6), 74.4 (C-4), 72.0 (C-3), 69.8 (C-5), 63.4 (C-7), 37.2 (CH_2), 31.7 (C-1). ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=739.20, found: $[M+Na]^+$=739.83, $C_{42}H_{36}O_9S$ (716.21).

2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-(3-methoxycarbonylpropyl)-1-thio-D-*glycero*-D-*gulo*-heptitol (2f)

Prepared from tosylhydrazone **1** (0.1 g, 0.13 mmol), methyl 3-mercaptopropanoate (0.29 mL, 0.31 g, 2.57 mmol), and K_3PO_4 (0.27 g, 1.29 mmol) according to the General procedure. Purified by column chromatography (1:5 acetone–hexane) to yield 22 mg (23 %) of **2f** as a pale yellow amorphous product. $[\alpha]_D$ +18 (c 0.20 in $CHCl_3$); R_f: 0.26 (1:2 EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–7.77 (8H, m, aromatics), 7.64–7.22 (12H, m, aromatics), 5.90 (1H, pseudo t, $J_{4,5}$ 9.9 Hz, H-4), 5.66 (1H, pseudo t, $J_{5,6}$ 9.8 Hz, H-5), 5.55 (1H, pseudo t, $J_{3,4}$ 9.3 Hz, H-3), 4.64 (1H, dd, $J_{7a,7b}$ 12.2 Hz, H-7_a), 4.44 (1H, dd, H-7_b), 4.15 (1H, ddd, $J_{6,7a}$ 2.9, $J_{6,7b}$ 5.3 Hz, H-6), 4.02 (1H, ddd, $J_{1a,2}$ 3.9, $J_{1b,2}$ 6.4, $J_{2,3}$ 10.0 Hz, H-2), 3.60 (3H, s, O–CH_3), 2.98–2.84 (2H, m, S–CH_2), 2.81 (1H, dd, $J_{1a,1b}$ 14.9 Hz, H-1_a), 2.78 (1H, dd, H-1_b), 2.55 (2H, dd, *J* 4.1, 10.1 Hz, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 166.2, 166.0, 165.5, 165.4 (5×CO), 133.9–128.3 (aromatics), 80.1 (C-2), 76.4 (C-6), 74.4 (C-4), 72.0 (C-3), 69.8 (C-5), 63.4 (C-7), 51.8 (O–CH_3), 34.6 (CH_2), 33.5 (C-1), 28.5 (S–CH_2). ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=735.19, found: $[M+Na]^+$=735.83, $C_{39}H_{36}O_{11}S$ (712.19).

2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-(3-mercaptopropyl)-1-thio-D-*glycero*-D-*gulo*-heptitol (2g)

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Prepared from tosylhydrazone **1** (0.1 g, 0.13 mmol), propane-1,3-dithiol (0.26 mL, 0.28 g, 2.57 mmol), and K_3PO_4 (0.27 g, 1.29 mmol) according to the General procedure. Purified by column chromatography (1:5 acetone–hexane) to yield 33 mg (37 %) of **2g** as a white amorphous product. $[\alpha]_D$ +16 (c 0.84 in $CHCl_3$); R_f: 0.34 (1:2 EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–7.76 (8H, m, aromatics), 7.63–7.21 (12H, m, aromatics), 5.90 (1H, pseudo t, $J_{4,5}$ 9.7 Hz, H-4), 5.67 (1H, pseudo t, $J_{5,6}$ 9.8 Hz, H-5), 5.56 (1H, pseudo t, $J_{3,4}$ 9.7 Hz, H-3), 4.66 (1H, dd, $J_{7a,7b}$ 12.2 Hz, H-7_a), 4.45 (1H, dd, H-7_b), 4.15 (1H, ddd, $J_{6,7a}$ 2.9, $J_{6,7b}$ 5.3 Hz, H-6), 4.01 (1H, ddd, $J_{1a,2}$ 3.4, $J_{1b,2}$ 6.8, $J_{2,3}$ 9.9 Hz, H-2), 2.79 (1H, dd, $J_{1a,1b}$ 14.5 Hz, H-1_a), 2.76 (1H, dd, H-1_b), 2.73–2.66 (2H, m, S–CH_2), 2.49 (2H, dd, *J* 7.1, 15.0 Hz, CH_2–SH), 1.78 (2H, p, *J* 7.1 Hz, CH_2), 1.25 (1H, t, *J* 8.1 Hz, SH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 166.1, 165.5, 165.4 (4×CO), 133.8–128.1 (aromatics), 80.1 (C-2), 76.3 (C-6), 74.4 (C-4), 72.0 (C-3), 69.8 (C-5), 63.3 (C-7), 33.4, 33.3 (C-1, CH_2), 31.9 (S–CH_2), 23.4 (CH_2–SH). ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=723.17, found: $[M+Na]^+$=723.83, $C_{38}H_{36}O_9S_2$ (700.18).

2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-phenyl-1-thio-D-*glycero*-D-*gulo*-heptitol (2h)

Prepared from tosylhydrazone **1** (0.3 g, 0.39 mmol), benzenethiol (0.20 mL, 0.21 g, 1.93 mmol), and K_3PO_4 (0.16 g, 0.77 mmol) according to the General procedure. Purified by column chromatography (1:10 acetone–hexane) to yield 207 mg (76 %) of **2h** as a white amorphous product. $[\alpha]_D$ +6 (c 0.77 in $CHCl_3$); lit.[13] $[\alpha]_D$ +4.0 (c 0.50 in $CHCl_3$); R_f: 0.42 (1:2 EtOAc–hexane). ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=725.18, found: $[M+Na]^+$=725.42, $C_{41}H_{34}O_9S$ (702.19). NMR spectra are identical with those reported.[13]

2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-(2-methoxyphenyl)-1-thio-D-*glycero*-D-*gulo*-heptitol (2i)

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Prepared from tosylhydrazone **1** (0.1 g, 0.13 mmol), 2-methoxybenzenethiol (0.08 mL, 0.09 g, 0.64 mmol), and K_3PO_4 (0.05 g, 0.26 mmol) according to the General procedure. Purified by column chromatography (1:10 acetone–hexane) to yield 60 mg (64 %) of **2i** as a pale brown amorphous product. $[\alpha]_D$ –5 (c 1.64 in $CHCl_3$); R_f: 0.29 (1:2 EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–7.74 (8H, m, aromatics), 7.58–7.21 (13H, m, aromatics), 7.20–7.12 (1H, m, aromatic), 6.83–6.70 (2H, m, aromatics), 5.85 (1H, pseudo t, $J_{4,5}$ 9.7 Hz, H-4), 5.65 (1H, pseudo t, $J_{5,6}$ 9.6 Hz, H-5), 5.52 (1H, pseudo t, $J_{3,4}$ 9.6 Hz, H-3), 4.53 (1H, dd, $J_{7a,7b}$ 12.1 Hz, H-7_a), 4.39 (1H, dd, H-7_b), 4.05 (1H, ddd, $J_{6,7a}$ 3.0, $J_{6,7b}$ 5.2 Hz, H-6), 3.93 (1H, ddd, $J_{1a,2}$ 2.3, $J_{2,3}$ 9.3 Hz, H-2), 3.68 (3H, s, O–CH_3), 3.24 (1H, dd, $J_{1a,1b}$ 14.1 Hz, H-1_a), 3.08 (1H, dd, $J_{1b,2}$ 8.6 Hz, H-1_b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 166.0, 165.5, 165.3 (4×CO), 159.0–110.6 (aromatics), 78.3 (C-2), 76.2 (C-6), 74.5 (C-4), 72.4 (C-3), 69.9 (C-5), 63.4 (C-7), 55.6 (O–CH_3), 34.3 (C-1). ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=755.19, found: $[M+Na]^+$=755.75, $C_{42}H_{36}O_{10}S$ (732.20).

2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-(4-nitrophenyl)-1-thio-D-*glycero*-D-*gulo*-heptitol (2j)

Prepared from tosylhydrazone **1** (0.1 g, 0.13 mmol), 4-nitrobenzenethiol (0.10 g, 0.64 mmol), and K_3PO_4 (0.16 g, 0.77 mmol) according to the General procedure. Purified by column chromatography (1:5 acetone–hexane) to yield 52 mg (54 %) of **2j** as a yellow amorphous product. $[\alpha]_D$ –21 (c 1.07 in $CHCl_3$); R_f: 0.29 (1:2 EtOAc–hexane). ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.14–7.70 (10H, m, aromatics), 7.61–7.16 (14H, m, aromatics), 5.93 (1H, pseudo t, $J_{4,5}$ 9.8 Hz, H-4), 5.68 (1H, pseudo t, $J_{5,6}$ 9.4 Hz, H-5), 5.62 (1H, pseudo t, $J_{3,4}$ 9.6 Hz, H-3), 4.57 (1H, dd, $J_{7a,7b}$ 12.2 Hz, H-7_a), 4.39 (1H, dd, H-7_b), 4.15 (1H, ddd, $J_{6,7a}$ 2.6, $J_{6,7b}$ 5.2 Hz, H-6), 4.08 (1H, ddd, $J_{1a,2}$ 2.8, $J_{1b,2}$ 7.4, $J_{2,3}$ 9.8 Hz, H-2), 3.36 (1H, dd, $J_{1a,1b}$ 14.7 Hz, H-1_a), 3.26 (1H, dd, H-1_b). ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.1, 166.0, 165.6, 165.3 (4×CO), 146.9–

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123.2 (aromatics), 78.2 (C-2), 76.4 (C-6), 74.2 (C-4), 72.1 (C-3), 69.6 (C-5), 63.0 (C-7), 34.2 (C-1). ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=770.17, found: $[M+Na]^+$=770.42, $C_{41}H_{33}NO_{11}S$ (747.18).

2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-(4-aminophenyl)-1-thio-D-*glycero*-D-*gulo*-heptitol (2k)

Prepared from tosylhydrazone **1** (0.1 g, 0.13 mmol), 4-aminobenzenethiol (0.32 g, 2.57 mmol), and K_3PO_4 (0.27 g, 1.29 mmol) according to the General procedure. Purified by column chromatography (1:6 acetone–hexane) to yield 22 mg (23 %) of **2k** as a pale yellow amorphous product. $[\alpha]_D$ +3 (c 0.73 in $CHCl_3$); R_f: 0.29 (1:2 EtOAc–hexane). ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.14–7.69 (8H, m, aromatics), 7.68–7.21 (14H, m, aromatics), 6.77–6.52 (2H, m, aromatics), 5.82 (1H, pseudo t, $J_{4,5}$ 9.6 Hz, H-4), 5.64 (1H, pseudo t, $J_{5,6}$ 9.6 Hz, H-5), 5.46 (1H, pseudo t, $J_{3,4}$ 9.6 Hz, H-3), 4.77 (1H, s, NH_{2a}), 4.62 (1H, dd, $J_{7a,7b}$ 12.0 Hz, H-7_a), 4.45 (1H, dd, H-7_b), 4.36 (1H, s, NH_{2b}), 4.11 (1H, ddd, $J_{6,7a}$ 2.8, $J_{6,7b}$ 5.5 Hz, H-6), 3.82 (1H, ddd, $J_{1a,2}$ 2.7, $J_{1b,2}$ 8.5, $J_{2,3}$ 9.6 Hz, H-2), 3.06 (1H, dd, $J_{1a,1b}$ 14.0 Hz, H-1_a), 2.90 (1H, dd, H-1_b). ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.1, 166.0, 165.6, 165.4 (4×CO), 151.0–114.6 (aromatics), 77.2 (C-2), 76.3 (C-6), 74.5 (C-4), 72.2 (C-3), 70.1 (C-5), 63.6 (C-7), 36.9 (C-1). ESI-MS positive mode (m/z): calc. for $[M+H]^+$=718.21, found: $[M+H]^+$=718.42, $C_{41}H_{35}NO_9S$ (717.20).

1-*S*-(4-Acetamidophenyl)-2,6-anhydro-3,4,5,7-tetra-*O*-benzoyl-1-thio-D-*glycero*-D-*gulo*-heptitol (2l)

Prepared from tosylhydrazone **1** (0.1 g, 0.13 mmol), *N*-(4-mercaptophenyl)acetamide (0.11 g, 0.64 mmol), and K_3PO_4 (0.05 g, 0.26 mmol) under Ar atmosphere according to the General procedure. Purified by column chromatography (1:5 acetone–hexane) to yield 64 mg (65 %)

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of **2l** as a pale yellow amorphous product. $[\alpha]_D$ +2 (c 1.09 in $CHCl_3$); R_f: 0.19 (1:1 EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–7.71 (8H, m, aromatics), 7.66–7.13 (17H, m, NH, aromatics), 5.86 (1H, pseudo t, $J_{4,5}$ 9.8 Hz, H-4), 5.65 (1H, pseudo t, $J_{5,6}$ 9.8 Hz, H-5), 5.54 (1H, pseudo t, $J_{3,4}$ 9.8 Hz, H-3), 4.55 (1H, dd, $J_{7a,7b}$ 12.1 Hz, H-7_a), 4.39 (1H, dd, H-7_b), 4.08 (1H, ddd, $J_{6,7a}$ 2.6, $J_{6,7b}$ 5.2 Hz, H-6), 3.94 (1H, ddd, $J_{1a,2}$ 2.2, $J_{1b,2}$ 7.9, $J_{2,3}$ 10.0 Hz, H-2), 3.17 (1H, dd, $J_{1a,1b}$ 14.2 Hz, H-1_a), 3.09 (1H, dd, H-1_b), 2.12 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 166.3, 166.0, 165.6, 165.3 (5×CO), 137.4–119.6 (aromatics), 78.0 (C-2), 76.2 (C-6), 74.4 (C-4), 72.2 (C-3), 69.8 (C-5), 63.4 (C-7), 37.0 (C-1), 24.7 (CH_3). ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=782.20, found: $[M+Na]^+$=782.42, $C_{43}H_{37}NO_{10}S$ (759.21).

2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-(2-hydroxyphenyl)-1-thio-D-*glycero*-D-*gulo*-heptitol (2m)

Prepared from tosylhydrazone **1** (0.1 g, 0.13 mmol), 2-mercaptophenol (0.27 mL, 0.32 g, 2.57 mmol), and K_3PO_4 (0.27 g, 1.29 mmol) according to the General procedure. Purified by column chromatography (1:6 acetone–hexane) to yield 64 mg (68 %) of **2m** as a white amorphous product. $[\alpha]_D$ –6 (c 0.09 in $CHCl_3$); R_f: 0.34 (1:2 EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–7.74 (8H, m, aromatics), 7.59–7.18 (14H, m, aromatics), 7.08 (1H, bs, OH), 7.02–6.92 (1H, m, aromatic), 6.85–6.77 (1H, m, aromatic), 5.85 (1H, pseudo t, $J_{4,5}$ 9.7 Hz, H-4), 5.67 (1H, pseudo t, $J_{5,6}$ 9.6 Hz, H-5), 5.47 (1H, pseudo t, $J_{3,4}$ 9.6 Hz, H-3), 4.68 (1H, dd, $J_{7a,7b}$ 12.3 Hz, H-7_a), 4.49 (1H, dd, H-7_b), 4.17 (1H, ddd, $J_{6,7a}$ 2.8, $J_{6,7b}$ 5.5 Hz, H-6), 3.75 (1H, ddd, $J_{1a,2}$ 2.7, $J_{2,3}$ 9.2 Hz, H-2), 3.01 (1H, dd, $J_{1a,1b}$ 14.1 Hz, H-1_a), 2.89 (1H, dd, $J_{1b,2}$ 8.8 Hz, H-1_b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 166.0, 165.6, 165.3 (4×CO), 158.0–115.0 (aromatics), 76.4 (C-2, C-6), 74.2 (C-4), 72.1 (C-3), 69.7 (C-5), 63.3 (C-7), 38.6 (C-1).

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ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=741.18, found: $[M+Na]^+$=741.75, $C_{41}H_{34}O_{10}S$ (718.19).

2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-(benzothiazol-2-yl)-1-thio-D-*glycero*-D-*gulo*-heptitol (2n-I)

Prepared from tosylhydrazone **1** (0.2 g, 0.26 mmol), benzothiazole-2-thiol (0.22 g, 1.29 mmol), and K_3PO_4 (0.11 g, 0.51 mmol) according to the General procedure. Purified by column chromatography (1:14 acetone–hexane) to yield 136 mg (70 %) of **2n-I** as a white amorphous product. $[\alpha]_D$ +10 (c 0.88 in $CHCl_3$); R_f: 0.32 (1:2 EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–7.74 (8H, m, aromatics), 7.69–7.19 (16H, m, aromatics), 5.95 (1H, pseudo t, $J_{4,5}$ 9.7 Hz, H-4), 5.71 (1H, pseudo t, $J_{5,6}$ 9.7 Hz, H-5), 5.61 (1H, pseudo t, $J_{3,4}$ 10.0 Hz, H-3), 4.60 (1H, dd, $J_{7a,7b}$ 12.2 Hz, H-7_a), 4.45 (1H, dd, H-7_b), 4.25 (1H, ddd, $J_{1a,2}$ 2.5, $J_{1b,2}$ 8.0, $J_{2,3}$ 10.0 Hz, H-2), 4.16 (1H, ddd, $J_{6,7a}$ 2.9, $J_{6,7b}$ 5.2 Hz, H-6), 3.99 (1H, dd, $J_{1a,1b}$ 14.3 Hz, H-1_a), 3.51 (1H, dd, H-1_b). ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.3, 166.2, 166.1, 165.7, 165.3 (4×CO, S–C), 153.5–116.6 (aromatics), 77.8 (C-2), 76.4 (C-6), 74.4 (C-4), 72.0 (C-3), 69.9 (C-5), 63.3 (C-7), 34.9 (C-1). ESI-MS positive mode (m/z): calc. for $[M+H]^+$=760.17, found: $[M+H]^+$=760.17, $C_{42}H_{33}NO_9S$ (759.16).

2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-*S*-(2-thioxobenzothiazol-3-yl)-1-thio-D-*glycero*-D-*gulo*-heptitol (2n-II)

Isolated as a by-product beside **2n-I** from the previous reaction mixture by column chromatography (1:14 acetone–hexane) to yield 20 mg (10%) of **2n-II** as a white amorphous product. $[\alpha]_D$ –9 (c 0.31 in $CHCl_3$); R_f: 0.32 (1:2 EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17–7.62 (8H, m, aromatics), 7.59–7.14 (15H, m, aromatics), 7.11–6.99 (1H, m, aromatic), 5.96 (1H, pseudo t, $J_{4,5}$ 9.4 Hz, H-4), 5.65 (1H, pseudo t, $J_{5,6}$ 9.4 Hz, H-5), 5.61

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(1H, pseudo t, $J_{3,4}$ 9.7 Hz, H-3), 5.12 (1H, dd, $J_{1a,1b}$ 14.3 Hz, H-1_a), 4.52 (1H, ddd, $J_{1a,2}$ 1.5, $J_{1b,2}$ 8.1, $J_{2,3}$ 9.6 Hz, H-2), 4.39 (1H, dd, $J_{7a,7b}$ 12.1 Hz, H-7_a), 4.31 (1H, dd, H-7_b), 4.25 (1H, dd, H-1_b), 4.00 (1H, ddd, $J_{6,7a}$ 2.6, $J_{6,7b}$ 6.3 Hz, H-6). ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.2, 165.8, 165.4, 164.9 (4×CO), 143.2–99.0 (aromatics), 76.4 (C-2), 76.2 (C-6), 74.0 (C-4), 71.0 (C-3), 69.7 (C-5), 63.1 (C-7), 48.3 (C-1). ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=782.15, found: $[M+Na]^+$=782.33, $C_{42}H_{33}NO_9S$ (759.16).

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DOI: 10.1039/C7NJ03069J

3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-*S*-ethyl-1-thio-D-*glycero*-L-*manno*-heptitol (7a)

Prepared from tosylhydrazone **6** (0.1 g, 0.19 mmol), ethanethiol (0.27 mL, 0.24 g, 3.78 mmol), and K_3PO_4 (0.40 g, 1.89 mmol) according to the General procedure. Purified by column chromatography (1:5 acetone–hexane) to yield 14 mg (16 %) of **7a** as a white amorphous product. $[\alpha]_D$ +25 (c 0.48 in $CHCl_3$); R_f: 0.38 (1:1 EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (1H, dd, $J_{5,6}$ 0.7 Hz, H-5), 5.18 (1H, pseudo t, $J_{3,4}$ 9.9 Hz, H-3), 5.03 (1H, dd, $J_{4,5}$ 3.4 Hz, H-4), 4.14 (1H, dd, $J_{7a,7b}$ 11.3 Hz, H-7_a), 4.07 (1H, dd, H-7_b), 3.91 (1H, ddd, $J_{6,7a}$ 6.6, $J_{6,7b}$ 6.4 Hz, H-6), 3.61 (1H, ddd, $J_{1a,2}$ 3.5, $J_{1b,2}$ 7.4, $J_{2,3}$ 9.8 Hz, H-2), 2.75–2.58 (4H, m, H-1_a, H-1_b CH_2), 2.15, 2.06, 2.05, 1.98 (12H, 4s, 4×CH_3), 1.24 (3H, t, J 7.1 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.4, 170.3, 170.0 (4×CO), 80.0 (C-2), 74.3 (C-6), 72.2 (C-4), 69.2 (C-3), 67.8 (C-5), 61.7 (C-7), 33.2 (C-1), 27.4 (CH_2), 21.0, 20.8 (4×CH_3), 14.8 (CH_3). ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=429.12, found: $[M+Na]^+$=429.25, $C_{17}H_{26}O_9S$ (406.13).

3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-*S*-propyl-1-thio-D-*glycero*-L-*manno*-heptitol (7b)

Prepared from tosylhydrazone **6** (0.1 g, 0.19 mmol), propanethiol (0.34 mL, 0.29 g, 3.78 mmol), and K_3PO_4 (0.40 g, 1.89 mmol) according to the General procedure. Purified by column chromatography (1:3 acetone–hexane) to yield 24 mg (30 %) of **7b** as a white amorphous product. $[\alpha]_D$ +12 (c 0.65 in $CHCl_3$); lit.[15] $[\alpha]_D$ +5 (c 0.52 in $CHCl_3$); R_f: 0.41 (1:1 EtOAc–hexane). NMR and MS spectra are identical with those reported.[15]

3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-*S*-cyclohexyl-1-thio-D-*glycero*-L-*manno*-heptitol (7c)

Prepared from tosylhydrazone **6** (0.1 g, 0.19 mmol), cyclohexanethiol (0.12 mL, 0.11 g, 0.95 mmol), and K_3PO_4 (0.08 g, 0.38 mmol) according to the General procedure. Purified by

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column chromatography (1:5 acetone–hexane) to yield 32 mg (36 %) of **7c** as a white amorphous product. $[\alpha]_D$ +5 (c 0.52 in $CHCl_3$); R_f: 0.44 (1:1 EtOAc–hexane). ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.42 (1H, dd, $J_{5,6}$ 0.7 Hz, H-5), 5.18 (1H, pseudo t, $J_{3,4}$ 10.1 Hz, H-3), 5.02 (1H, dd, $J_{4,5}$ 3.4 Hz, H-4), 4.13 (1H, dd, $J_{7a,7b}$ 11.2 Hz, H-7_a), 4.08 (1H, dd, H-7_b), 3.90 (1H, ddd, $J_{6,7a}$ 6.8, $J_{6,7b}$ 6.4 Hz, H-6), 3.59 (1H, ddd, $J_{1a,2}$ 3.3, $J_{1b,2}$ 7.6, $J_{2,3}$ 9.8 Hz, H-2), 2.82–2.74 (1H, m, S–CH) 2.73 (1H, dd, $J_{1a,1b}$ 14.1 Hz, H-1_a), 2.65 (1H, dd, H-1_b) 2.15, 2.06, 2.05, 1.98 (12H, 4s, 4×CH_3) 1.97–1.89 (2H, m, aliphatic, cyclohexyl), 1.85–1.70 (2H, m, aliphatic, cyclohexyl), 1.65–1.54 (1H, m, aliphatic, cyclohexyl), 1.37–1.15 (5H, m, aliphatic, cyclohexyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.4, 170.3, 169.9 (4×CO), 79.8 (C-2), 74.3 (C-6), 72.1 (C-4), 69.2 (C-3), 67.8 (C-5), 61.7 (C-7), 44.5 (CH), 33.7, 33.6 (CH_2–CH–CH_2), 31.8 (C-1), 26.2, 26.1, 25.9 (3×CH_2) 21.0, 20.8, 20.7 (4×CH_3). ESI-MS positive mode (m/z): calc. for $[M+K]^+$=499.14, found: $[M+K]^+$=499.33, $C_{21}H_{32}O_9S$ (460.18).

3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-*S*-benzyl-1-thio-D-*glycero*-L-*manno*-heptitol (7d)

Prepared from tosylhydrazone **6** (0.1 g, 0.19 mmol), phenylmethanethiol (0.45 mL, 0.47 g, 3.78 mmol), and K_3PO_4 (0.40 g, 1.89 mmol) according to the General procedure. Purified by column chromatography (1:3 acetone–hexane) to yield 24 mg (27 %) of **7d** as a white amorphous product. $[\alpha]_D$ +9 (c 0.51 in $CHCl_3$); lit.[15] $[\alpha]_D$ +4 (c 1.10 in $CHCl_3$)*; R_f: 0.36 (1:1 EtOAc–hexane) NMR and MS spectra are identical with those reported.[15]

3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-*S*-(3-methoxycarbonylpropyl)-1-thio-D-*glycero*-L-*manno*-heptitol (7e)

Prepared from tosylhydrazone **6** (0.2 g, 0.38 mmol), methyl 3-mercaptopropanoate (0.84 mL, 0.91 g, 7.57 mmol), and K_3PO_4 (0.80 g, 3.78 mmol) according to the General procedure.

* A value of $[\alpha]_D$ −10 (c 0.56 in $CHCl_3$) was erroneously published in ref.15.

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Purified by column chromatography (1:4 acetone–hexane) to yield 68 mg (39 %) of **7e** as a pale yellow amorphous product. $[\alpha]_D$ –6 (c 0.08 in $CHCl_3$); R_f: 0.63 (1:1 EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 5.42 (1H, dd, $J_{5,6}$ 0.9 Hz, H-5), 5.20 (1H, pseudo t, $J_{3,4}$ 10.1 Hz, H-3), 5.03 (1H, dd, $J_{4,5}$ 3.3 Hz, H-4), 4.12 (1H, dd, $J_{7a,7b}$ 11.3 Hz, H-7_a), 4.08 (1H, dd, H-7_b), 3.92 (1H, ddd, $J_{6,7a}$ 6.8, $J_{6,7b}$ 6.4 Hz, H-6), 3.70 (3H, s, O–CH_3), 3.63 (1H, ddd, $J_{1a,2}$ 4.9, $J_{1b,2}$ 6.9, $J_{2,3}$ 10.2 Hz, H-2), 2.95–2.83 (2H, m, S–CH_2), 2.71 (1H, dd, $J_{1a,1b}$ 14.4 Hz, H-1_a), 2.68 (1H, dd, H-1_b) 2.67–2.56 (2H, m, CH_2), 2.16, 2.06, 2.05, 1.98 (12H, 4s, 4×CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 170.5, 170.3, 169.9 (5×CO), 79.9 (C-2), 74.4 (C-6), 72.1 (C-4), 68.9 (C-3), 67.8 (C-5), 61.8 (C-7), 51.9 (O–CH_3), 34.8 (CH_2), 33.6 (C-1), 28.3 (S–CH_2), 20.9, 20.8, 20.7 (4×CH_3). ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=487.13, found: $[M+Na]^+$=487.42, $C_{19}H_{28}O_{11}S$ (464.14).

3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-*S*-phenyl-1-thio-D-*glycero*-L-*manno*-heptitol (7f)

Prepared from tosylhydrazone **6** (0.1 g, 0.19 mmol), benzenethiol (0.10 mL, 0.10 g, 0.95 mmol), and K_3PO_4 (0.08 g, 0.38 mmol) according to the General procedure. Purified by column chromatography (1:5 acetone–hexane) to yield 66 mg (77 %) of **7f** as a pale yellow amorphous product. $[\alpha]_D$ –9 (*c* 0.85 in $CHCl_3$); lit.[15] $[\alpha]_D$ -15 (c 0.53 in $CHCl_3$); R_f: 0.36 (1:1 EtOAc–hexane). NMR and MS spectra are identical with those reported.[15]

3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-*S*-(2-methoxyphenyl)-1-thio-D-*glycero*-L-*manno*-heptitol (7g)

Prepared from tosylhydrazone **6** (0.1 g, 0.19 mmol), 2-methoxybenzenethiol (0.46 mL, 0.53 g, 3.78 mmol), and K_3PO_4 (0.40 g, 1.89 mmol) according to the General procedure. Purified by column chromatography (1:5 acetone–hexane) to yield 56 mg (60 %) of **7g** as a pale brown amorphous product. $[\alpha]_D$ –21 (c 0.86 in $CHCl_3$); R_f: 0.33 (1:1 EtOAc–hexane). ^1H NMR (400

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MHz, $CDCl_3$) δ 7.32 (1H, dd, *J* 1.6, 7.6 Hz, aromatic), 7.26–7.19 (1H, m, aromatic), 6.94–6.88 (1H, m, aromatic), 6.86 (1H, dd, *J* 0.7, 8.2 Hz, aromatic), 5.39 (1H, dd, $J_{5,6}$ 0.8 Hz, H-5), 5.19 (1H, pseudo t, $J_{3,4}$ 10.0 Hz, H-3), 5.01 (1H, dd, $J_{4,5}$ 3.4 Hz, H-4), 4.08 (1H, dd, $J_{7a,7b}$ 11.3 Hz, H-7_a), 4.03 (1H, dd, H-7_b), 3.89 (3H, s, O–CH_3), 3.84 (1H, ddd, $J_{6,7a}$ 6.7, $J_{6,7b}$ 6.8 Hz, H-6), 3.61 (1H, ddd, $J_{1a,2}$ 3.5, $J_{1b,2}$ 7.8, $J_{2,3}$ 9.7 Hz, H-2), 3.07 (1H, dd, $J_{1a,1b}$ 13.7 Hz, H-1_a), 3.01 (1H, dd, H-1_b), 2.15, 2.05, 2.04, 1.98 (12H, 4s, 4×CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.3, 170.2, 169.9 (4×CO), 158.8–109.1 (aromatics), 78.0 (C-2), 74.3 (C-6), 72.1 (C-4), 69.3 (C-3), 67.7 (C-5), 61.4 (C-7), 55.8 (O–CH_3), 34.5 (C-1), 20.9, 20.8, 20.7 (4×CH_3). ESI-MS positive mode (m/z): calc. for $[M+Na]^+$=507.13, found: $[M+Na]^+$=507.33, $C_{22}H_{28}O_{10}S$ (484.14).

3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-*S*-(2-hydroxyphenyl)-1-thio-D-*glycero*-L-*manno*-heptitol (7h)

Prepared from tosylhydrazone **6** (0.1 g, 0.19 mmol), 2-mercaptophenol (0.38 mL, 0.48 g, 3.78 mmol), and K_3PO_4 (0.40 g, 1.89 mmol) according to the General procedure. Purified by column chromatography (1:5 acetone–hexane) to yield 45 mg (51 %) of **7h** as a white amorphous product. $[\alpha]_D$ +4 (c 0.08 in $CHCl_3$); R_f: 0.49 (1:1 EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, dd, *J* 1.6, 7.7 Hz, aromatic), 7.31–7.25 (1H, m, aromatic), 7.04 (1H, s, OH), 7.02–6.94 (1H, m, aromatic), 6.87 (1H, dd, *J* 1.2, 7.5 Hz, aromatic), 5.43 (1H, dd, $J_{5,6}$ 0.7 Hz, H-5), 5.19 (1H, pseudo t, $J_{3,4}$ 10.1 Hz, H-3), 4.99 (1H, dd, $J_{4,5}$ 3.4 Hz, H-4), 4.17 (1H, dd, $J_{7a,7b}$ 11.4 Hz, H-7_a), 4.13 (1H, dd, H-7_b), 3.93 (1H, ddd, $J_{6,7a}$ 6.1, $J_{6,7b}$ 6.8 Hz, H-6), 3.39 (1H, ddd, $J_{1a,2}$ 2.9, $J_{1b,2}$ 8.7, $J_{2,3}$ 9.5 Hz, H-2), 2.89 (1H, dd, $J_{1a,1b}$ 14.1 Hz, H-1_a), 2.78 (1H, dd, H-1_b) 2.17, 2.09, 2.02, 1.97 (12H, 4s, 4×CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.3, 170.2, 170.0 (4×CO), 158.2–109.9 (aromatics), 76.1 (C-2), 74.6 (C-6), 71.9 (C-4), 68.8 (C-3),

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67.8 (C-5), 61.9 (C-7), 38.8 (C-1), 20.9, 20.8, 20.7 (4×CH_3). ESI-MS negative mode (m/z): calc. for $[M-H]^-$=469.13, found: $[M-H]^-$=469.50, $C_{21}H_{26}O_{10}S$ (470.13).

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

This work was supported by the Hungarian Scientific Research Fund (OTKA 109450), by the European Union and the State of Hungary, co-financed by the European Social Fund in the framework of TÁMOP-4.2.4.A/2-11/1-2012-0001 'National Excellence Program' (to MT) and by the University of Debrecen (5N5XBTDDTOMA320).

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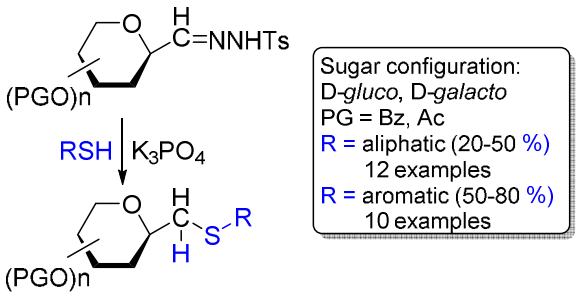

Sugar configuration:
D-*gluco*, D-*galacto*
PG = Bz, Ac
R = aliphatic (20-50 %)
12 examples
R = aromatic (50-80 %)
10 examples

Cross coupling of anhydro-aldose tosylhydrazones with thiols gave a new access to *C*-glycopyranosylmethyl sulfides