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Synthesis of anomeric sulfonamides and their behaviour under radical-mediated bromination conditions

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ABSTRACT

Q-Peracetylated methyl 3-(D-glycopyranosylthio)propanoates of β-D-gluco, and α- and β-D-galacto configurations were oxidized to the corresponding S,S-dioxides (sulfoxes) by Oxone® or MCPBA. Oxidation of the β-D-gluco derivative with H₂O₂/Na₂WO₄ gave the corresponding S-oxide (sulfoxide). DBU-induced elimination of methyl acrylate from the β-D-gluco and β-D-galacto configured S,S-dioxides (sulfoxes) gave Q-peracetylated β-D-glycopyranosyl-1-C-sulfinates which, on treatment with H₂NOSO₃H, furnished the corresponding β-D-glycopyranosyl-1-C-sulfonamides. Radical-mediated bromination of the protected methyl 3-(β-D-glycopyranosylthio)propanoate S,S-dioxides gave mixtures of 1-C- and 5-C-bromoglycosyl compounds. Similar brominations of the Q-peracetylated β-D-glycopyranosyl-1-C-sulfonamides resulted in the formation of α-D-glycopyranosyl bromides and 1-C- and 5-C-bromoglycosyl sulfonamides. A rationale for these observations was proposed. Methyl 3-(β-D-glycopyranosylthio)propanoate, its S,S-dioxide, and β-D-glycopyranosyl-1-C-sulfonamide proved inefficient when tested as inhibitors of rabbit muscle glycogen phosphorylase b.

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1. Introduction

As part of an ongoing project to design and synthesize glycoenzyme inhibitors, we have prepared several compounds^{1–4} with glycogen phosphorylase (GP) inhibitory activity^{5,6} from (3,4,5,7-tetra-O-acyl-α-D-glyco-hept-2-ulopyranosyl bromide)onamides (A, Chart 1). Among them, compound C was shown to have moderate inhibition against rabbit muscle GPb (RMGPb).⁴ Since GP is a validated target for the treatment of type 2 diabetes mellitus many efforts

are devoted to finding new inhibitors (GPIs).^{7,8} To this end, among others, computational chemistry is in the forefront of GPI design.⁸ By using 4D-QSAR methods, it was predicted that compound D, a sulfonyl analogue of C, might be a very efficient GPI with an inhibition constant in the nanomolar range.⁹ Therefore, we envisaged to prepare D from B in a way analogous to the chemistry² applied to obtain A and its further transformations to C.

To the best of our knowledge, the necessary starting materials to get A, that is, N-unsubstituted anomeric sulfonamides, have not yet been described. The only analogous compound is the N,N-diethylsulfonamide in the α-anomeric position of N-acetyl-D-glucosamine obtained by substituting Et₂NH in the corresponding glycosylsulfenyl chloride or bromide and subsequent oxidation.¹⁰

In this paper we disclose our experiences in the preparation of glycopyranosyl sulfonamides and their reactivity under radical-mediated bromination conditions.

2. Results and discussion

A generally used method for the preparation of sulfonamides is the ammonolysis of the corresponding sulfonylchlorides. At the commencement of our work, glycosyl sulfonyl chlorides (e.g., 9) were not known, therefore chlorination of sugar sulfonate salt 4 was envisaged. Several sulfonic acids and their salts attached to a sugar skeleton were described.^{11–13,†} The general method for

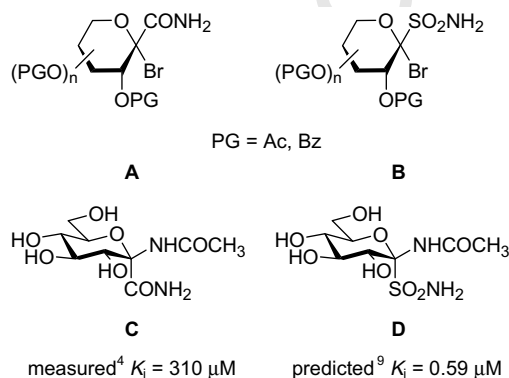
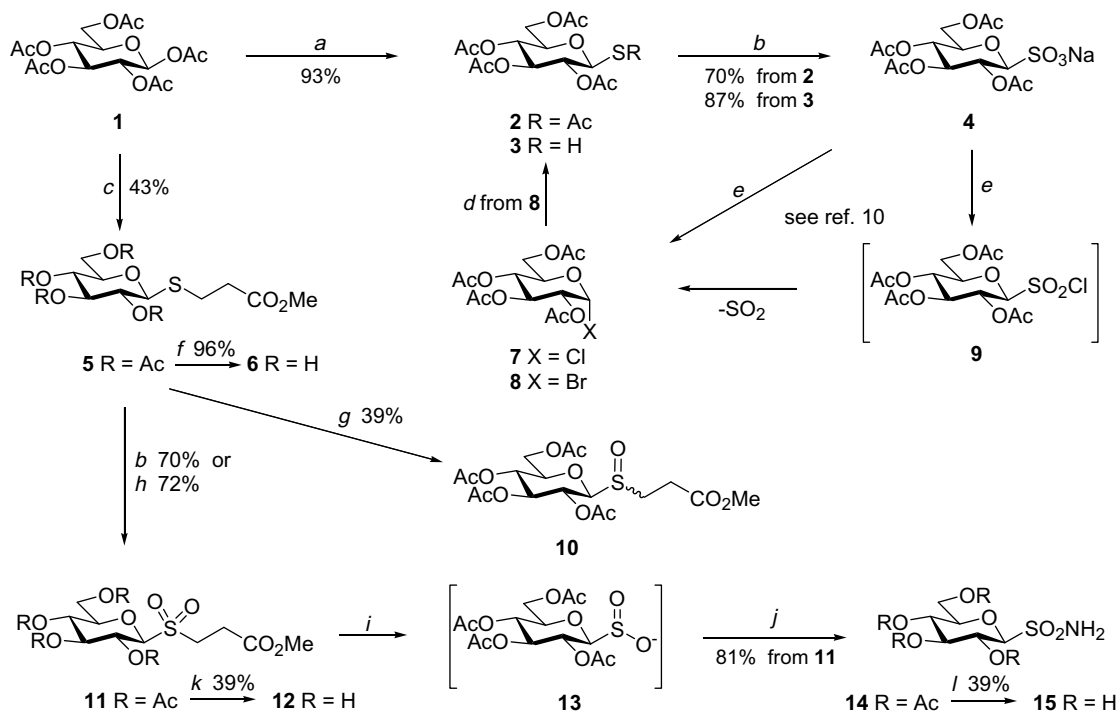


Chart 1.

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† For a more detailed list of citations see Ref. 23 in a paper by Knapp et al.¹⁰



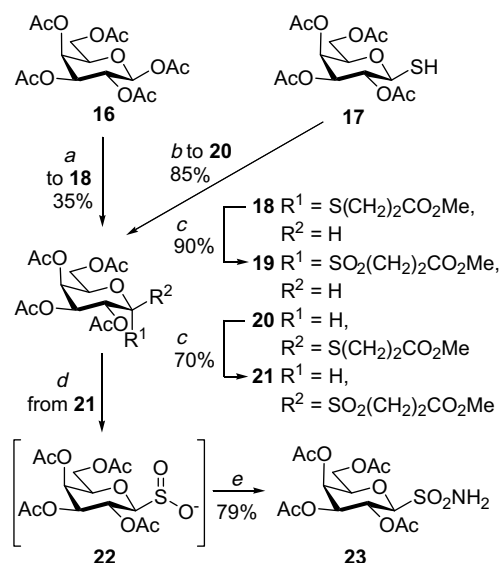
Scheme 1. Reagents and conditions: (a) AcSH, $\text{BF}_3 \cdot \text{OEt}_2$, dry CH_2Cl_2 , 0–20 °C; (b) Oxone[®], NaOAc, AcOH, rt; (c) $\text{HSCH}_2\text{CH}_2\text{CO}_2\text{Me}$, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , 0–20 °C; (d) (1) H_2NCSNH_2 , dry acetone, reflux; (2) NaHSO_3 , CHCl_3 – H_2O , reflux; (e) SOCl_2 , or PCl_5 , dry THF or dry Et_2O , reflux; (f) NaOMe , dry MeOH, rt; (g) Na_2WO_4 , H_2O_2 , MeOH, rt; (h) *m*CPBA, NaHCO_3 , CH_2Cl_2 , 0–20 °C; (i) DBU, CHCl_3 , rt; (j) $\text{H}_2\text{NOSO}_3\text{H}$, water, rt; (k) AcCl , dry MeOH rt; (l) NH_4OH , MeOH, rt.

obtaining such compounds was a nucleophilic displacement by AcSK in the corresponding sugar derivative followed by oxidation,¹³ and it was also extended to the anomeric position.¹⁴ Thus, to get sodium sulfonate **4** (Scheme 1), either *O*-peracetylated 1-*S*-acetyl-1-thio- β -*D*-glucopyranose¹⁵ (**2**) prepared from 1,2,3,4,6-penta-*O*-acetyl- β -*D*-glucopyranose (**1**) and thioacetic acid¹⁶ or *O*-peracetylated 1-thio- β -*D*-glucopyranose (**3**) obtained by the conventional literature method^{17,18} from **8** was oxidized by Oxone[®].¹⁴ The corresponding triethylammonium salt¹⁰ was made from **2** by DMDO oxidation followed by chromatography in the presence of Et_3N . Reactions of **4** under usual chlorination conditions (neat SOCl_2 , reflux; THF, SOCl_2 ; $\text{THF} \cdot \text{Et}_2\text{O}$, PCl_5) gave several compounds which were not separated. Experiments to add nucleophiles to the crude chlorination mixtures with the hope of trapping any sulfonyl chloride formed were **unsuccessful**. Knapp *et al.* isolated the corresponding glycosyl chloride **7** (70%) from the chlorination mixture of their triethylammonium sulfonate,¹⁰ and accounted for the formation of **7** by SO_2 extrusion from the unstable intermediate sulfonyl chloride **9**. For these reasons other possibilities were sought for the preparation of the target sulfonamides.

Various sulfonamides were prepared by reactions of sulfinate salts with electrophilic nitrogen sources such as hydroxylamine-*O*-sulfonic acid^{19,20} or bis(2,2,2-trichloroethyl)azodicarboxylate.²¹ The preparation of the required anomeric sulfinate **13** was effected by **base-induced** β -elimination from sulfon **11** which was obtained by oxidation of thioglycoside **5**^{22,23} by either Oxone[®] or *m*CPBA. Application of $\text{H}_2\text{O}_2/\text{Na}_2\text{WO}_4$ ^{20,21} to oxidize **5** gave sulfoxides **10** (two TLC spots of very similar mobility) from which one isomer could be isolated in pure state in moderate yield. As an alternative route to **sulfinates**, the reductive cleavage of benzothiazolyl sulfones was **proposed**;²¹ however, practically no change could be observed in the reaction of *O*-peracetylated β -*D*-glucopyranosyl benzothiazol-2-yl sulfone²⁴ with NaBH_4 in THF/MeOH for ~one week even at elevated temperature. Sulfinate **13**, without being

purified, was treated with $\text{H}_2\text{NOSO}_3\text{H}$ in water to give the desired sulfonamide **14** after chromatographic purification in **81%** yield for the two steps.

For the preparation of the *D*-galacto configured derivative **23** (Scheme 2), the corresponding thioglycoside had to be prepared first. BF_3 catalyzed reaction of 1,2,3,4,6-penta-*O*-acetyl- β -*D*-galactopyranose (**16**) with methyl 3-sulfanylpropanoate gave the α -thiogalactoside **17** in moderate yield. To get the β -anomer, 2,3,4,6-tetra-*O*-acetyl-1-thio- β -*D*-galactopyranose^{25,26} (**17**) was



Scheme 2. Reagents and conditions: (a) $\text{HSCH}_2\text{CH}_2\text{CO}_2\text{Me}$, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , 0–20 °C; (b) $\text{BrCH}_2\text{CH}_2\text{CO}_2\text{Me}$, Et_3N , CH_2Cl_2 , rt; (c) Oxone[®], NaOAc, AcOH, rt; (d) DBU, CHCl_3 , rt; (e) $\text{H}_2\text{NOSO}_3\text{H}$, water, rt.

Table 1
Radical-mediated bromination of sulfonyl derivatives

	R ¹	R ²		Isolated yields (product ratios) (%)		
11	OAc	H	a ¹	24 21	25 30	—
21	H	OAc	a ²	26 43	27 27	—
14	OAc	H	b ³	28 11 (22)	29 12 (17)	8 24 (26)
			b ⁴	(45)	(36)	(6)
			c ⁵	28 12	29 11	8 19
23	H	OAc	b ⁶	30 (12)	31 (6)	32 (59)

Bromination conditions:

(a) Br₂, CCl₄, K₂CO₃, hv, reflux.²⁷

(b) Br₂, CHCl₃, K₂CO₃, hv, reflux.²

(c) Br₂, PhCF₃, K₂CO₃, hv, reflux.³⁰

¹ Reaction time 3 h.

² Reaction time 2 h.

³ Conversion 65% after 8 h with 0.6 g starting material.

⁴ Conversion 87% after 4 h with 0.1 g starting material. Product ratio calculated from the ¹H NMR spectrum of the crude mixture.

⁵ Conversion 81% after 4 h.

⁶ Conversion 77% after 4 h. Product ratio calculated from the ¹H NMR spectrum of the crude mixture.

reacted with methyl 3-bromopropanoate in the presence of Et₃N, and the required compound **20** was obtained in good yield. The anomeric configuration of these derivatives was clearly indicated by the vicinal coupling constants: ³J_{1,2} = 5.3 Hz for **18** and ³J_{1,2} = 9.2 Hz for **20**. Oxidation of thiogalactosides **18** and **20** by Oxone[®] afforded the corresponding sulfones **19** and **21**, respectively, in good yields (³J_{1,2} = 2.6 Hz for **19** and ³J_{1,2} = 9.2 Hz for **21**). Treatment of the β-anomeric sulfone **21** with DBU followed by reaction of the non-isolated sulfinate **22** with H₂NOSO₃H gave the expected sulfonamide **23** in 79% overall yield for the two steps. Similar base-induced reaction of the α-anomer **19** resulted in a mixture from which no discrete product could be isolated.

Radical-mediated bromination of various carbohydrate derivatives proved a useful tool to produce versatile compounds for further functionalization.²⁷ Several pyranoid monosaccharide substrates showed excellent regio- and stereoselectivities under the bromination conditions to give either 1-C-bromo- or 5-C-bromo derivatives of pyranoid rings with the bromine substituents in axial positions. On the other hand, a study on bromination of phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl sulfone demonstrated similar reactivities for the 1- and 5-positions (C-1 bromide 48%, C-5 bromide 38%).²⁸

With these preliminaries in mind, it was to be expected that bromination (Table 1) of the *gluco* (**11**) and *galacto* (**21**) sulfones would give isomeric axial bromides **24** and **25**, as well as **26** and **27**, respectively. Bromination of sulfonamides **14** and **23** under different conditions gave varying proportions of the corresponding α-D-glucopyranosyl bromides **8** and **32**, respectively, the ratio also being dependent on the scale of the reaction. The ring brominated derivatives **28** and **29**, as well as **30** and **31**, respectively, were formed as minor products when the reaction was performed on a larger scale. Compounds **28** and **29** were isolated by chromatography; however, the very similar chromatographic behaviour of **30** and **31** did not allow these derivatives to be prepared in pure state. The position of the bromine substitution in the sugar ring followed clearly from the coupling pattern of the ¹H NMR spectra of these compounds.

[‡] In the literature there are some examples with a similar outcome to the present one: the corresponding α-D-glycosyl bromides were formed on radical mediated bromination of O-peracetylated phenyl β-D-glucopyranosyl sulfoxide,²⁸ celllobiosyl piperidine²⁹ and β-D-glucopyranosyl isothiocyanate.²⁹

These observations can be correlated with the relative radical stabilization (RRS) factors of substituents (Table 2) as in earlier explanations for the regioselectivity of radical-mediated bromination of sugar derivatives.²⁷ As shown in Figure 1a, the radical stabilization is highest in position 1 of the sugar ring (RRS = 8.3; for positions 2–4 the OAc substituent is characterized by an RRS value of 0.9³¹). Although the radical in position next to the CO₂Me group seems to be better stabilized than C-5 (RRS 7.9 vs 6.5), the observed higher reactivity of position 5 might be attributed to its tertiary character (as compared to the secondary carbon in the aglycon) which is not taken into consideration in the calculation of the RRS value. However, bromination in the methylene groups of the aglycon cannot be excluded, as very minor bromine-containing spots were observed by TLC in the reaction mixtures. Compounds with a carbon substituent at position one (for the present particular comparison a carboxamido group, but also other anhydro-aldehydic acid derivatives) showed an exclusive selectivity for that position^{2,32,33} as it can be concluded from the RRS values²⁷ (Fig. 1b). In the bromination of sulfonamides the relative reactivity of positions 1 and 5 was similar to those of the sulfones (Fig. 1a). However, the formation of glycosyl bromides needs further considerations. We propose that in the bromination of sulfonamides (Fig. 1c) the bromine radical may also abstract a hydrogen from the SO₂NH₂ moiety as illustrated in I. Further β-fragmentation of the intermediate sulfonamidyl radical II might give glycosyl radical³⁴ III which, on bromine abstraction from the reagent, could give the glycosyl bromide IV with high stereoselectivity. The preponderance of this pathway may be attributed to the relatively free

Table 2

Selected relative radical stabilization factors³¹ of substituents (RRS_X) and their combined values (RRS_{O,X}) at positions 1 and 5 of the pyranoid ring

X	RRS _X	RRS _{O,X}
CH ₃ (= CH ₂ OAc)	2.3	6.5
OMe (= O-ring)	4.5	
SO ₂ Ph	4.5	8.3
COOMe	7.9	11.3
CN	8.6	11.9
COMe	10.2	13.2

X represents the substituent in position 1 or 5 of the pyranoid ring while O stands for the ring oxygen (its numerical value equated with that of OMe). The combined effects were calculated by using the expression:³¹ 0.03 × RRS_{O,X} = 1 - (1 - 0.03 × RRS_{O,Me})(1 - 0.03 × RRS_X).

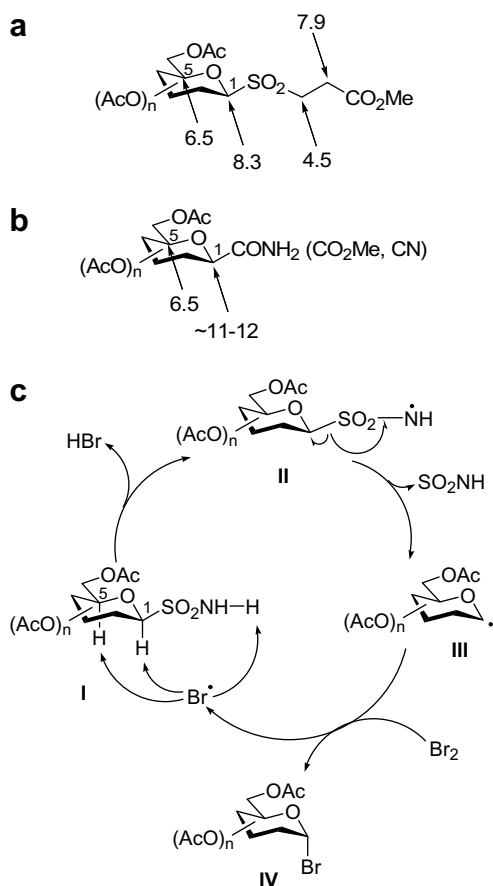


Figure 1. (a) Relative radical stabilization factors taken from Table 2 for glucopyranosyl sulfones and (b) anhydro-aldonic acid derivatives; (c) proposed reactivity pattern for the radical-mediated bromination of anomeric sulfonamides.

access to the NH_2 as compared to the ring positions, but radical stabilization factors may also play a role.

In 1-bromoglucopyranosyl sulfonamide **28** as well as sulfone **24** some nucleophilic substitutions, reactions analogous to those carried out easily^{1–3,35,36} with *O*-peracyl derivatives of (*D*-glyco-hept-2-ulopyranosyl bromide)onamides (Chart 1, **A**) were attempted. Contrary to these transformations, reactions either with azide or thiocyanate ions failed: either no change (**28** and AgSCN or NH_4SCN , CH_3NO_2 , 80 °C, Ar atm; **28** and NaN_3 , DMF, rt; **24** and NaN_3 , acetone, LiN_3 , DMF, or acetone, each at rt) or decomposition (**24** and NaN_3 , DMF, rt; AgOTf , TMSN_3 , CH_2Cl_2 , rt) of the starting material could be observed.

The prepared 1-thioglycoside **5** and glucosyl sulfonyl derivatives **11** and **14** were deprotected as shown in Scheme 1 to give compounds **6**, **12** and **15**, respectively. These compounds were tested as inhibitors of RMGPb (Table 3) in the way described earlier.³ While 1-thio- β -*D*-glucopyranose (entry 1) is a moderate inhibitor, its glycosides are either non-inhibitory (entries 2 and 3) or only slightly more efficient (entry 4). The latter effect may be due to interactions of the bulky aglycon in the so called β -channel of the enzyme.^{7,8} Sulfon **12** (entry 5) and sulfonamide **15** (entry 6) were inactive. Comparing the latter result to the effect of the 2,6-anhydro-aldonamide in entry 7 shows that introduction of the tetrahedral sulfonyl moiety in the β -anomeric position of *D*-glucose is not a useful modification with respect to inhibition of RMGPb.

In conclusion, a synthetic sequence has been elaborated for the preparation of *N*-unsubstituted β -*D*-glucopyranosyl-1-*C*-sulfonamides, which circumvents the unavailability of anomeric sulfonyl

Table 3
Inhibition of RMGPb by selected 1-thio derivatives of *D*-glucose

Entry	Compound	K_i (mM)
1		1 ³⁷
2		n.i.
3		n.i. ³⁷
4		0.65 ³⁷
5		n.i.
6		n.i.
7		0.44 ³⁷

chlorides. Further functionalization at C-1 of these sulfonamides by radical-mediated bromination, although possible, has proven limited because of formation of the corresponding glycosyl bromides and 5-*C*-bromides as accompanying products. 1-Bromoglycosyl sulfones and sulfonamides seem to be unreactive in nucleophilic substitutions. Appending the tetrahedral sulfonyl moiety to the anomeric centre of *D*-glucose results in a loss of activity against RMGPb.

3. Experimental

3.1. General methods

Melting points were measured in open capillary tubes or on a Kofler hot-stage and are uncorrected. Optical rotations were determined on a Perkin–Elmer 241 polarimeter at room temperature. NMR spectra were recorded with Bruker WP 360 SY (360/90 MHz for $^1\text{H}/^{13}\text{C}$) and Varian UNITYINOVA 400 WB (400/100 MHz for $^1\text{H}/^{13}\text{C}$) spectrometers. Chemical shifts are referenced to Me_4Si as the internal reference (1H) or to the residual solvent signal (^{13}C). ESIMS were recorded with a Bruker micrOTOF-Q instrument. Thin-layer chromatography (TLC) was carried out on aluminium sheets coated with Silica Gel 60 F₂₅₄ (Merck). TLC plates were inspected by UV light ($\lambda = 254$ nm) and after gentle heating. Brominated compounds were visualized on TLC plates by spraying first a 0.1% w/v fluorescein soln in absolute MeOH, then a 1:1 mixture of H_2O_2 (30% in water) and AcOH. Upon gentle heating, bromo-compounds gave pink-coloured spots. Silica gel column chromatography was performed with Silica Gel Si 60 (40–63 μm) purchased from Merck (Darmstadt, Germany). Organic solutions were dried over anhydrous MgSO_4 , and concentrated at diminished pressure at 40–50 °C (water bath).

3.2. 2,3,4,6-Tetra-O-acetyl-1-S-acetyl-1-thio-β-D-glucopyranose (adapted from¹⁴) (2)

1,2,3,4,6-Penta-O-acetyl-β-D-glucopyranose (**1**, 1.00 g, 2.56 mmol) was dissolved in dry CH₂Cl₂ (10 mL). To the soln, thioacetic acid (0.28 mL, 3.84 mmol) and BF₃·OEt₂ (0.54 mL, 5.12 mmol) were added at 0 °C. The mixture was then stirred at rt for 1 d, and after completion of the reaction (TLC, 95:5 CH₂Cl₂-acetone) it was diluted with CH₂Cl₂ (10 mL), washed with satd NaHCO₃ (2 × 10 mL) and water (1 × 10 mL). After drying the solvent was removed under diminished pressure. The crude product was crystallized from EtOH to give 0.97 g (93%) of **2** as a white crystalline product. Mp: 119–120 °C, lit.¹⁵ mp: 118 °C; [α]_D²⁰ +29 (c 0.38, CHCl₃), (lit.¹⁵ [α]_D²⁰ +11 (c 1.49, CHCl₃)); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 5.27, 5.12, 5.10 (pseudo t, 3H, J ~ 9.2 Hz in each, H-2, H-3, H-4), 5.26 (d, 1H, J_{1,2} 9.2 Hz, H-1), 4.24 (dd, 1H, J_{6,6'} 11.9, J_{5,6} 4.0 Hz, H-6), 4.10 (dd, 1H, J_{6,6'} 11.9, J_{5,6'} 2.6 Hz, H-6'), 3.86 (ddd, 1H, J_{4,5} 9.2, J_{5,6} 4.0, J_{5,6'} 2.6 Hz, H-5), 2.39 (s, 3H, SCOCH₃), 2.08, 2.03, 2.02, 2.01 (12H, 4s, 4 × OCOCH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 191.8 (SCOCH₃), 170.5, 169.2, 169.3 (2) (CO), 80.1 (C-1), 76.3, 73.8, 68.9, 67.8 (C-2 to C-5), 61.6 (C-6), 30.7 (SCOCH₃) 20.6, 20.5 (3) (CH₃).

3.3. Sodium 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl-1-C-sulfonate (adapted from¹⁴) (4)

(a) Compound **2** (0.50 g, 1.23 mmol) was suspended in glacial acetic acid (10 mL), and Oxone[®] (1.89 g, 3.07 mmol) and NaOAc (1.34 g, 12.3 mmol) were added. The mixture was stirred at rt until TLC (4:1 CH₂Cl₂-MeOH) showed complete transformation of the starting material. After filtration the solvent was removed under diminished pressure. The obtained crude product was purified by column chromatography (eluent, 4:1 CHCl₃-MeOH) to give 0.42 g (70%) of **4** as a white crystalline product. Mp: 218–220 °C; [α]_D²⁰ -59 (c 0.23, H₂O); ¹H NMR (D₂O, 360 MHz): δ (ppm) 5.43, 5.37, 5.17 (pseudo t, 3H, J ~ 9.4 Hz in each, H-2, H-3, H-4), 4.57 (d, 1H, J_{1,2} 9.4 Hz, H-1), 4.43 (dd, 1H, J_{6,6'} 11.7, J_{5,6} 2.1 Hz, H-6), 4.27 (dd, 1H, J_{6,6'} 11.7, J_{5,6'} 1.0 Hz, H-6'), 4.14 (ddd, 1H, J_{4,5} 9.4, J_{5,6} 2.1, J_{5,6'} 1.0 Hz, H-5), 2.15, 2.12, 2.11, 2.09 (12H, 4s, 4 × OCOCH₃); ¹³C NMR (D₂O, 90 MHz): δ (ppm) 174.2, 173.6, 173.2, 172.8 (CO), 85.5 (C-1), 75.7, 74.7, 69.5, 68.5 (C-2 to C-5), 62.5 (C-6), 21.9, 20.8, 20.7, 20.6 (CH₃); ESI MS calcd for C₁₄H₁₉O₁₂SN_a 434.354, found 457.018 (M+Na).

(b) Also prepared from 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranose¹⁷ (**3**, 0.50 g, 1.31 mmol) by using the same procedure. Yield: 0.52 g (87%).

3.4. Methyl 3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylthio)propanoate (5)

Compound **1** (5.00 g, 12.8 mmol) was dissolved in dry CH₂Cl₂ (30 mL), then methyl 3-sulfanylpropanoate (2.1 mL, 19.2 mmol) and BF₃·OEt₂ (2.7 mL, 25.6 mmol) were added at 0 °C. The soln was stirred overnight (~16 h) at rt, (TLC, 1:2 EtOAc-hexane). After complete transformation of the starting material, the mixture was diluted with CH₂Cl₂ and washed with satd NaHCO₃ (2 × 15 mL) and water (1 × 15 mL), and then dried. The solvent was removed under diminished pressure and the crude product crystallized from EtOH to give 2.50 g (43%) of **5** as white needles. Mp: 86–87 °C (lit.²² mp: 88–89 °C); [α]_D²⁰ -64 (c 0.26, CHCl₃ (lit.²² [α]_D²⁰ -32 (c 1.00, CHCl₃)); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 5.23, 5.03, 5.01 (pseudo t, 3H, J ~ 9.2 Hz in each, H-2, H-3, H-4), 4.56 (d, 1H, J_{1,2} 10.6 Hz, H-1), 4.23 (dd, 1H, J_{6,6'} 11.9, J_{5,6} 5.3 Hz, H-6), 4.14 (dd, 1H, J_{6,6'} 11.9, J_{5,6'} 2.6 Hz, H-6'), 3.74 (ddd, 1H, J_{4,5} 9.2, J_{5,6} 5.3, J_{5,6'} 2.6 Hz, H-5), 3.69 (s, 3H, OCH₃), 2.99 (dt, 1H, J 7.9, J 6.6 Hz, CH₂), 2.88 (dt, 1H, J 7.9, J 6.6 Hz, CH₂), 2.69 (t, 2H, J 7.9, J 6.6 Hz, CH₂), 2.09, 2.06,

2.03, 2.01 (12H, 4s, 4 × OCOCH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 171.9 (COOCH₃), 170.5, 169.9, 169.2 (2) (CO), 83.7 (C-1), 75.7, 73.6, 69.5, 68.1 (C-2 to C-5), 61.9 (C-6), 51.6 (OCH₃), 35.1, 25.2 (CH₂), 20.5, 20.4 (2), 20.3 (CH₃). Anal. Calcd for C₁₈H₂₆O₁₁S₁ (450.47): C, 47.99; H, 5.82. Found: C, 47.86; H, 5.66.

3.5. Methyl 3-(β-D-glucopyranosylthio)propanoate (6)

Thioglycoside **5** (0.18 g, 0.41 mmol) was dissolved in dry MeOH (5 mL), and NaOMe (~1 M in MeOH) was added. The reaction mixture was kept at rt until completion of the transformation (TLC, 1:1 CHCl₃-MeOH). Amberlyst 15 (H⁺ form) was then added to remove sodium ions, the resin was filtered off, and the solvent was evaporated to give 0.11 g (96%) of **6** as a colourless oil. R_f = 0.73 (1:1 CHCl₃-MeOH); [α]_D²⁰ -74 (c 0.19, H₂O); ¹H NMR (D₂O, 360 MHz): δ (ppm) 4.51 (dd, 1H, J_{6,6'} 13.2, J_{5,6} 4.0 Hz, H-6), 3.85 (dd, 1H, J_{6,6'} 13.2, J_{5,6'} 1.2 Hz, H-6'), 3.68 (s, 3H, OCH₃), 3.64 (d, 1H, J_{1,2} 9.2 Hz, H-1), 3.44–3.23 (m, 3H, H-2, H-3, H-4), 3.26 (ddd, 1H, J_{4,5} 9.2, J_{5,6} 4.0, J_{5,6'} 1.2 Hz, H-5), 2.99 (quintet, 1H, J 7.9, J 6.6 Hz, CH₂), 2.93 (quintet, 1H, J 7.9, J 6.6 Hz, CH₂), 2.76–2.74 (m, 2H, CH₂); ¹³C NMR (D₂O, 90 MHz): δ (ppm) 175.7 (COOCH₃), 86.5 (C-1), 80.4, 77.4, 72.7, 70.0 (C-2 to C-5), 61.5 (C-6), 53.5 (OCH₃), 35.5, 25.7 (CH₂). Anal. Calcd for C₁₀H₁₈O₇S₁ (282.31): C, 42.55; H, 6.43. Found: C, 42.50; H, 6.48.

3.6. Methyl 3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylthio)propanoate S-oxide (10)

Thioglycoside **5** (0.1 g, 0.22 mmol) was dissolved in MeOH (3 mL). To this soln Na₂WO₄ (6.5 mg, 0.02 mmol) and H₂O₂ (0.1 mL, 3.30 mmol) were added in small portions. The mixture was stirred at rt until completion of the transformation (TLC, 1:1 EtOAc-hexane). After filtration the solvent was removed under diminished pressure. The obtained oil was purified by column chromatography (2:1 EtOAc-hexane) to give 0.04 g (39%) of **10** as a white powder. Mp: 115–117 °C; [α]_D²⁰ -128 (c 0.22, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 5.34, 5.26, 5.11 (pseudo t, 3H, J ~ 9.2 Hz in each, H-2, H-3, H-4), 4.37 (d, 1H, J_{1,2} 9.2 Hz, H-1), 4.29 (dd, 1H, J_{6,6'} 13.2, J_{5,6} 5.3 Hz, H-6), 4.21 (dd, 1H, J_{6,6'} 13.2, J_{5,6'} 2.6 Hz, H-6'), 3.82 (ddd, 1H, J_{4,5} 9.2, J_{5,6} 5.3, J_{5,6'} 2.6 Hz, H-5), 3.73 (s, 3H, OCH₃), 3.22–3.20 (m, 2H, CH₂), 2.85 (m, 2H, CH₂), 2.09, 2.07, 2.05, 2.03 (12H, 4s, 4 × OCOCH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 171.5 (COOCH₃), 170.4, 169.9, 169.5, 169.2 (CO), 90.1 (C-1), 76.8, 73.0, 68.3, 67.5 (C-2 to C-5), 61.3 (C-6), 52.2 (OCH₃), 42.0, 26.1 (CH₂), 20.5 (2), 20.4 (2) (CH₃). Anal. Calcd for C₁₈H₂₆O₁₂S₁ (466.46): C, 46.35; H, 5.62. Found: C, 46.15; H, 5.55.

3.7. Methyl 3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylthio)propanoate S,S-dioxide (11)

(a) Thioglycoside **5** (0.1 g, 0.22 mmol) was dissolved in glacial acetic acid (3 mL). To this soln, Oxone[®] (0.19 g, 0.33 mmol) and NaOAc (0.14 g, 2.20 mmol) were added. The mixture was stirred at rt until complete transformation of the starting material (TLC, 1:1 EtOAc-hexane). After filtration it was diluted with water (10 mL) and washed with CH₂Cl₂ (3 × 5 mL). The organic phase was washed with satd NaHCO₃ (2 × 5 mL) and water (1 × 5 mL), dried, and the solvent removed under diminished pressure. The crude product was recrystallized from Et₂O to give 0.07 g (70%) of **11**.

(b) Thioglycoside **5** (0.1 g, 0.22 mmol) was suspended in CH₂Cl₂ (3 mL), and NaHCO₃ (0.19 g, 2.20 mmol) and mCPBA (0.22 g, 15.8 mmol, ~70%) were added in five portions at 0 °C. The mixture was stirred at rt until complete transformation of the starting material (TLC, 1:1 EtOAc-hexane). After filtration it was diluted

with water (10 mL) and washed with CH₂Cl₂ (2 × 5 mL). The organic phase was washed with NaCl (1 × 5 mL), satd NaHCO₃ (2 × 5 mL) and water (1 × 5 mL), dried, and the solvent removed under diminished pressure. The crude product was recrystallized from Et₂O to yield 0.08 g (72%) of **11** as white crystalline product. Mp: 146–147 °C; $[\alpha]_D^{20}$ -36 (c 0.22, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 5.52, 5.33, 5.14 (pseudo t, 3H, J ~ 9.3 Hz in each, H-2, H-3, H-4), 4.56 (d, 1H, J_{1,2} 9.2 Hz, H-1), 4.28 (dd, 1H, J_{6,6'} 11.9, J_{5,6'} 5.3 Hz, H-6), 4.21 (dd, 1H, J_{6,6'} 11.9, J_{5,6'} 2.6 Hz, H-6'), 3.88 (ddd, 1H, J_{4,5} 9.3, J_{5,6} 5.3, J_{5,6'} 2.6 Hz, H-5), 3.75 (s, 3H, OCH₃), 3.60 (dt, 1H, J 7.9, 6.6 Hz, CH₂), 3.41 (dt, 1H, J 7.9, 6.6 Hz, CH₂), 2.89 (m, 2H, CH₂), 2.10, 2.05 (2), 2.03 (12H, 4s, 4 × OCOCH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 170.5 (COOCH₃), 170.3, 169.9, 169.2, 169.1 (CO), 87.9 (C-1), 76.6, 72.9, 67.2, 66.2 (C-2 to C-5), 61.2 (C-6), 52.3 (OCH₃), 45.3, 26.2 (CH₂), 20.4 (2), 20.3 (2) (CH₃). Anal. Calcd for C₁₈H₂₆O₁₃S₁ (482.46): C, 44.81; H, 5.43. Found: C, 44.78; H, 5.40.

3.8. Methyl 3-(β-D-glucopyranosylthio)propanoate S,S-dioxide (12)

Sulfone **11** (0.1 g, 0.21 mmol) was suspended in a mixture of dry MeOH (3 mL) and dry CHCl₃ (2 mL). To this soln two drops of AcCl were added. The mixture was kept at rt until completion of the transformation (~one week, TLC, 4:1 CHCl₃-MeOH). It was then neutralized with solid NaHCO₃ and the solvent evaporated after filtration. The crude oil was purified by column chromatography (4:1 CHCl₃-MeOH) to give 0.05 g (75%) of **12** as a colourless oil. R_f = 0.37 (4:1 CHCl₃-MeOH); $[\alpha]_D^{20}$ -53 (c 0.26, H₂O); ¹H NMR (D₂O, 360 MHz): δ (ppm) 4.68 (d, 1H, J_{1,2} 9.2 Hz, H-1), 3.90 (dd, 1H, J_{6,6'} 13.2, J_{5,6} 5.3 Hz, H-6), 3.85 (s, 3H, OCH₃), 3.83 (dd, 1H, J_{6,6'} 13.2, J_{5,6'} 2.6 Hz, H-6'), 3.78–3.36 (m, 6H, H-2, H-3, H-4, H-5, CH₂), 2.98–2.92 (m, 2H, CH₂); ¹³C NMR (D₂O, 90 MHz): δ (ppm) 173.8 (COOCH₃), 90.0 (C-1), 81.3, 77.2, 69.2, 69.1, (C-2 to C-5), 61.0 (C-6), 53.4 (OCH₃), 47.1, 27.1 (CH₂). Anal. Calcd for C₁₀H₁₈O₉S₁ (314.31): C, 38.21; H, 5.77. Found: C, 38.25; H, 5.80.

3.9. Mixed salt of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl-1-C-sulfonic acid (13)

Sulfone **11** (0.1 g, 0.21 mmol) was dissolved in freshly distilled dry CHCl₃ (10 mL), and DBU (30 μL, 0.21 mmol) was added. The mixture was stirred at rt until complete transformation of the starting material (TLC, 7:3 CHCl₃-MeOH). The solvent was evaporated and the crude oil was purified by column chromatography (7:3 CHCl₃-MeOH) to give 0.06 g of **13** as a white crystalline product. ¹H NMR (D₂O, 360 MHz): δ (ppm) 5.36, 5.29, 5.08 (pseudo t, 3H, J ~ 9.2 Hz in each, H-2, H-3, H-4), 4.38 (dd, 1H, J_{6,6'} 11.9, J_{5,6} 2.6 Hz, H-6), 4.27 (dd, 1H, J_{6,6'} 11.9, J_{5,6'} 1.0 Hz, H-6'), 4.00 (ddd, 1H, J_{4,5} 9.2, J_{5,6} 2.6, J_{5,6'} 1.0 Hz, H-5), 3.66 (d, 1H, J_{1,2} 9.2 Hz, H-1), 2.10, 2.05, 2.04 (2) (12H, 3s, 4 × OCOCH₃); ¹³C NMR (D₂O, 90 MHz): δ (ppm) 174.3, 173.9, 173.3 (2) (CO), 92.8 (C-1), 75.8, 75.2, 68.7, 68.5 (C-2 to C-5), 62.5 (C-6), 20.9, 20.7, 20.6 (2) (CH₃); Ms: [M+Na]⁺ 419.059, [M+K]⁺ 435.035. Repeated from 1.5 g sulfone. Yield: 1.35 g (~100%). For further preparative purposes, the crude product obtained after solvent removal was used without purification.

3.10. 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl-1-C-sulfonamide (14)

Sulfinate **13** (0.1 g) was suspended in water (5 mL). To this soln, H₂NOSO₃H (0.08 g, 0.71 mmol) and NaOAc (0.06 g, 0.73 mmol) were added and the mixture was stirred at rt for 2 h. After extraction with EtOAc, (5 × 5 mL) the organic phase was washed with satd NaHCO₃ (2 × 5 mL) and water (5 mL), dried and evaporated.

It was crystallized slowly to give 0.07 g (81%, from the sulfone, 0.1 g) of **14** as a white crystalline product. Mp: 201–204 °C; $[\alpha]_D^{20}$ -20 (c 0.2, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 5.39, 5.31, 5.14 (pseudo t, 3H, J ~ 9.3 Hz in each, H-2, H-3, H-4), 4.56 (d, 1H, J_{1,2} 9.2 Hz, H-1), 4.36 (dd, 1H, J_{6,6'} 13.2, J_{5,6} 5.3 Hz, H-6), 4.46 (dd, 1H, J_{6,6'} 13.2, J_{5,6'} 1.0 Hz, H-6'), 3.93–3.86 (m, 3H, H-5, NH₂), 2.11, 2.08, 2.06, 2.04 (12H, 4s, 4 × OCOCH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 170.9, 170.4, 170.1, 169.5 (CO), 87.0 (C-1), 75.9, 72.9, 67.8, 67.5 (C-2 to C-5), 61.3 (C-6), 20.2 (2), 20.1 (2) (CH₃). Anal. Calcd for C₁₄H₂₁O₁₁NS (411.39): C, 40.88; H, 5.15. Found: C, 40.82; H, 5.05. Ms: [M+Na]⁺ 434.081. Repeated from 1.5 sulfone. Yield: 1.03 g (81%).

3.11. β-D-Glucopyranosyl-1-C-sulfonamide (15)

Sulfonamide **14** (0.1 g, 0.24 mmol) was suspended in dry MeOH (3 mL). A few drops of NH₄OH were added and the mixture was kept at rt until completion of the transformation (TLC, 4:1 CHCl₃-MeOH). Amberlyst 15 (H⁺ form) was then added to remove sodium ions, the resin was filtered off and the solvent removed under diminished pressure. The crude oil was purified by column chromatography (4:1 CHCl₃-MeOH) to give 0.05 g (85%) of **15** as a colourless oil. R_f = 0.59 (1:1 CHCl₃-MeOH); $[\alpha]_D^{20}$ -34 (c 0.24, H₂O); ¹H NMR (D₂O, 360 MHz): δ (ppm) 4.46 (d, 1H, J_{1,2} 9.2 Hz, H-1), 3.91 (dd, 1H, J_{6,6'} 11.9, J_{5,6} 5.3 Hz, H-6), 3.74–3.54 (m, 4H, H-2, H-3 or H-4, H-5, H-6'), 3.43 (t, 1H, J 9.2, J 9.2 Hz, H-4 or H-3); ¹³C NMR (D₂O, 90 MHz): δ (ppm) 90.5 (C-1), 80.9, 77.1, 70.8, 69.5, (C-2 to C-5), 61.2 (C-6); Anal. Calcd for C₆H₁₃O₇S₁ (243.24): C, 29.60; H, 5.39. Found: C, 29.65; H, 5.36.

3.12. Methyl 3-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosylthio)propanoate (18)

1,2,3,4,6-Penta-O-acetyl-β-D-galactopyranose (**16**, 5.0 g, 12.8 mmol) was dissolved in dry CH₂Cl₂ (30 mL), and methyl 3-sulfanylpropanoate (2.1 mL, 19.2 mmol) and BF₃·OEt₂ (2.7 mL, 25.6 mmol) were added at 0 °C. The soln was stirred overnight (~16 h) at rt (TLC, 1:2 EtOAc-hexane). After complete transformation of the starting material the mixture was diluted with CH₂Cl₂ and washed with satd NaHCO₃ (2 × 15 mL) and water (1 × 15 mL), dried, and the solvent removed under diminished pressure. The crude product was purified by silica gel column chromatography (1:2 EtOAc-hexane) EtOH to give 2.00 g (35%) of **18** as a colourless oil. R_f = 0.16 (1:2 EtOAc-hexane), $[\alpha]_D^{20}$ +496 (c 0.34, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 5.76 (d, 1H, J_{1,2} 5.3 Hz, H-1), 5.45 (dd, 1H, J_{3,4} 2.6, J_{4,5} 1.0 Hz, H-4), 5.26 (dd, 1H, J_{2,3} 10.6, J_{1,2} 5.3 Hz, H-2), 5.18 (dd, 1H, J_{2,3} 10.6, J_{3,4} 2.6 Hz, H-3), 4.58 (t, 1H, J_{5,6} 6.6, J_{5,6'} 5.8 Hz, H-5), 4.15–4.09 (m, 2H, H-6, H-6'), 3.71 (s, 3H, OCH₃), 2.88 (dt, 1H, J 7.9, J 6.6 Hz, CH₂), 2.78 (dt, 1H, J 7.9, J 6.6 Hz, CH₂), 2.68–2.64 (m, 2H, CH₂), 2.15, 2.06 (2), 1.96 (12H, 3s, 4 × OCOCH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 171.8 (COOCH₃), 170.3, 170.1 (2), 169.7 (CO), 89.9 (C-1), 67.9, 67.8, 67.7, 66.6 (C-2 to C-5), 61.8 (C-6), 51.7 (OCH₃), 34.4, 25.1 (CH₂), 20.6, 20.5 (3) (CH₃); Anal. Calcd for C₁₈H₂₆O₁₁S₁ (450.47): C, 47.99; H, 5.82. Found: C, 47.89; H, 5.76.

3.13. Methyl 3-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosylthio)propanoate S,S-dioxide (19)

Thiogalactoside **18** (0.5 g, 1.10 mmol) was dissolved in glacial acetic acid (15 mL). To this soln, Oxone[®] (0.95 g, 1.65 mmol) and NaOAc (0.60 g, 11.0 mmol) were added. The mixture was stirred at rt until complete transformation of the starting material (TLC, 1:1 EtOAc-hexane). After filtration it was diluted with water (15 mL) and extracted with CH₂Cl₂ (3 × 15 mL). The organic phase was washed with satd NaHCO₃ (2 × 15 mL) and water (1 × 15 mL),

dried, and the solvent removed under diminished pressure. The crude product was purified by column chromatography (1:1 EtOAc–hexane) to give 0.48 g (90%) of **19** as a colourless oil. $R_f = 0.36$ (1:1 EtOAc–hexane), $[\alpha]_D^{+33}$ (c 0.25, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 5.79 (dd, 1H, $J_{2,3}$ 10.6, $J_{3,4}$ 2.6 Hz, H-3), 5.56 (dd, 1H, $J_{3,4}$ 2.6, $J_{4,5}$ 1.0 Hz, H-4), 5.47 (dd, 1H, $J_{2,3}$ 10.6, $J_{1,2}$ 2.6 Hz, H-2), 5.36 (d, 1H, $J_{1,2}$ 2.6 Hz, H-1), 4.81 (t, 1H, $J_{5,6}$ 6.6, $J_{6,6'}$ 5.8 Hz, H-5), 4.19–4.06 (m, 2H, H-6, H-6'), 3.62 (s, 3H, OCH₃), 3.49–3.44 (m, 2H, CH₂), 2.93–2.85 (m, 2H, CH₂), 2.16, 2.13, 2.09, 2.01 (12H, 4s, 4 × OCOCH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 170.6 (COOCH₃), 170.3, 170.0, 169.5, 169.2 (CO), 84.8 (C-1), 71.3, 66.9, 66.7, 65.7 (C-2 to C-5), 62.2 (C-6), 52.3 (OCH₃), 46.5, 25.8 (CH₂), 20.4, 20.2 (3) (CH₃); Anal. Calcd for C₁₈H₂₆O₁₃S₁ (482.46): C, 44.81; H, 5.43. Found: C, 44.86; H, 5.38.

3.14. Methyl 3-(2,3,4,6-tetra-O-acetyl- β -D-galactopyranosylthio)propanoate (**20**)

A 2,3,4,6-tetra-O-acetyl-1-thio- β -D-galactopyranose^{25,26} (**17**, 3.0 g, 7.86 mmol) was dissolved in dry CH₂Cl₂ (50 mL). To this soln methyl 3-bromopropanoate (1.11 mL, 9.43 mmol) and Et₃N (1.05 mL, 9.43 mmol) were added. The mixture was stirred at rt for 3 days (TLC, 1:2 EtOAc–hexane). It was then diluted with CH₂Cl₂ and washed with satd NaHCO₃ (2 × 50 mL) and water (1 × 50 mL), dried, and the solvent evaporated. The crude product was purified by column chromatography (1:2 EtOAc–hexane) to give 2.10 g (85%) of **20** (conversion is 65%) as a yellowish oil. $R_f = 0.18$ (1:2 EtOAc–hexane); $[\alpha]_D^{+169}$ (c 0.42, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 5.40 (dd, 1H, $J_{3,4}$ 2.6, $J_{4,5}$ 1.0 Hz, H-4) 5.23 (pseudo t, 1H, $J_{2,3}$ 10.6, $J_{1,2}$ 9.2 Hz, H-2), 5.05 (dd, 1H, $J_{2,3}$ 10.6, $J_{3,4}$ 2.6 Hz, H-3) 4.54 (d, 1H, $J_{1,2}$ 9.2 Hz, H-1), 4.16 (dd, 1H, $J_{6,6'}$ 11.9, $J_{5,6}$ 5.3 Hz, H-6), 4.12 (dd, 1H, $J_{6,6'}$ 11.9, $J_{5,6'}$ 2.6 Hz, H-6'), 3.95 (t, 1H, $J_{5,6}$ 6.6, $J_{5,6'}$ 5.8 Hz, H-5), 3.70 (s, 3H, OCH₃), 3.02 (dt, 1H, J 7.9, J 6.6 Hz, CH₂), 2.93 (dt, 1H, J 7.9, J 6.6 Hz, CH₂), 2.72–2.68 (m, 2H, CH₂), 2.16, 2.05 (2), 1.98 (12H, 3s, 4 OCOCH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 172.0 (COOCH₃), 170.3, 170.1, 169.9, 169.7 (CO), 84.5 (C-1), 74.4, 71.7, 67.1, 67.0 (C-2 to C-5), 61.4 (C-6), 51.7 (OCH₃), 35.1, 25.4 (CH₂), 20.6, 20.5 (2), 20.4 (CH₃); Anal. Calcd for C₁₈H₂₆O₁₁S₁ (450.47): C, 47.99; H, 5.82. Found: C, 47.85; H, 5.92.

3.15. Methyl 3-(2,3,4,6-tetra-O-acetyl- β -D-galactopyranosylthio)propanoate S,S-dioxide (**21**)

Thiogalactoside **20** (1.0 g, 2.20 mmol) was dissolved in glacial acetic acid (30 mL). To this soln, Oxone[®] (1.90 g, 3.30 mmol) and NaOAc (1.20 g, 2.20 mmol) were added. The mixture was stirred at rt until complete transformation of the starting material (TLC, 1:1 EtOAc–hexane). After filtration it was diluted with water (30 mL) and extracted with CH₂Cl₂ (3 × 30 mL). The organic phase was washed with satd NaHCO₃ (2 × 30 mL) and water (1 × 30 mL), dried, and the solvent was removed under diminished pressure. The crude product was recrystallized from Et₂O to give 0.74 g (70%) of **21** as a white crystalline product. Mp: 120–122 °C; $[\alpha]_D^{+6}$ (c 0.24, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 5.68 (1H, pseudo t, $J_{2,3}$ 10.6, $J_{1,2}$ 9.2 Hz, H-2), 5.47 (dd, 1H, $J_{3,4}$ 4.0, $J_{4,5}$ 2.6 Hz, H-4) 5.16 (dd, 1H, $J_{2,3}$ 10.6, $J_{3,4}$ 4.0 Hz, H-3), 4.52 (d, 1H, $J_{1,2}$ 9.2 Hz, H-1), 4.23–4.16 (m, 2H, H-5, H-6), 4.11 (dd, 1H, $J_{6,6'}$ 11.9, $J_{5,6}$ 5.3 Hz, H-6'), 3.74 (s, 3H, OCH₃), 3.55 (dt, 1H, J 7.9, J 6.6 Hz, CH₂), 3.42 (dt, 1H, J 7.9, J 6.6 Hz, CH₂), 2.92–2.87 (m, 2H, CH₂), 2.20, 2.07, 2.06, 1.98 (12H, 4s, 4 × OCOCH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 170.5 (COOCH₃), 170.2, 169.9, 169.8, 169.2 (CO), 88.6 (C-1), 75.4, 71.1, 66.6, 63.3 (C-2 to C-5), 61.0 (C-6), 52.3 (OCH₃), 45.1, 26.1 (CH₂), 20.6, 20.5, 20.4, 20.3 (CH₃); Anal. Calcd for C₁₈H₂₆O₁₃S₁ (482.46): C, 44.81; H, 5.43. Found: C, 44.74; H, 5.46.

3.16. Mixed salt of 2,3,4,6-tetra-O-acetyl- β -D-galactopyranosyl-1-C-sulfinic acid (**22**)

Sulfone **21** (0.5 g, 1.05 mmol) was dissolved in freshly distilled dry CHCl₃ (15 mL) and DBU (150 μ L, 1.05 mmol) was added. The mixture was stirred at rt until complete transformation of the starting material (TLC, 7:3 CHCl₃–MeOH). The solvent was evaporated and the crude oil was purified by column chromatography (7:3 CHCl₃–MeOH) to give 0.35 g of **22** as a yellowish oil. ¹H NMR (D₂O, 360 MHz): δ (ppm) 5.47 (dd, 1H, $J_{3,4}$ 4.0, $J_{4,5}$ 1.0 Hz, H-4), 5.43 (t, 1H, $J_{1,2}$ 10.6, $J_{2,3}$ 10.6 Hz, H-2), 5.26 (dd, 1H, $J_{2,3}$ 10.6, $J_{3,4}$ 4.0 Hz, H-3), 3.64 (d, 1H, $J_{1,2}$ 10.6 Hz, H-1), 3.55–3.45 (m, 2H, H-6, H-6'), 3.29 (pseudo t, 1H, $J_{5,6}$ 6.6, $J_{5,6'}$ 6.6 Hz, H-5), 2.21, 2.06 (2), 2.00 (12H, 3s, 4 × OCOCH₃); ¹³C NMR (D₂O, 90 MHz): δ (ppm) 173.6, 173.4, 173.0, 172.9 (CO), 92.8 (C-1), 74.4, 72.4, 68.3, 65.4 (C-2 to C-5), 62.1 (C-6), 20.4, 20.2, 20.1, 20.0 (CH₃). For further preparative purposes, the crude product obtained after solvent removal was used without purification.

3.17. 2,3,4,6-Tetra-O-acetyl- β -D-galactopyranosyl-1-C-sulfonamide (**23**)

Sulfinate salt **22** (~0.35 g) was suspended in water (5 mL). H₂NOSO₃H (0.28 g, 2.5 mmol) and NaOAc (0.24 g, 2.92 mmol) were added and the mixture was stirred at rt for 2 h. After extraction with EtOAc (5 × 10 mL), the organic phase was washed with satd NaHCO₃ (2 × 10 mL) and water (10 mL), dried, and the solvent evaporated to give 0.27 g (79%, from the sulfone, 0.4 g) of **23** as a yellowish oil. $R_f = 0.23$ (1:1 EtOAc–hexane); $[\alpha]_D^{+32}$ (c 0.22, CHCl₃); ¹H NMR (CDCl₃, 360 MHz): δ (ppm) 5.51 (s, 1H, NH₂), 5.48 (1H, dd, $J_{3,4}$ 4.0, $J_{4,5}$ 1.0 Hz, H-4), 5.29 (s, 1H, NH₂), 5.26 (t, 1H, $J_{1,2}$ 10.6, $J_{2,3}$ 10.6 Hz, H-2), 5.17 (dd, 1H, $J_{2,3}$ 10.6, $J_{3,4}$ 2.3 Hz, H-3), 4.41 (d, 1H, $J_{1,2}$ 10.6 Hz, H-1), 4.22 (t, 1H, $J_{5,6}$ 6.6, $J_{5,6'}$ 6.6 Hz, H-5), 4.16–4.11 (m, 2H, H-6, H-6'), 3.93–3.86 (m, 3H, H-5, NH₂), 2.17, 2.08, 2.05, 1.99 (12H, 4s, 4 × OCOCH₃); ¹³C NMR (CDCl₃, 90 MHz): δ (ppm) 171.1, 170.5, 170.0, 169.8 (CO), 87.8 (C-1), 75.2, 70.7, 66.9, 65.3 (C-2 to C-5), 60.9 (C-6), 20.8, 20.6 (2), 20.5 (CH₃). Anal. Calcd for C₁₄H₂₁O₁₁NS (411.39): C, 40.88; H, 5.15. Found: C, 40.80; H, 5.21.

3.18. Bromination methods

(a) A methyl 3-(2,3,4,6-tetra-O-acetyl- β -D-galactopyranosylthio)propanoate S,S-dioxide (**11** or **21**, 0.1 g, 0.21 mmol) was dissolved in dry CCl₄ (10 mL), and bromine (30 μ L, 0.73 mmol) and some K₂CO₃ were added. The mixture was placed in an Erlenmeyer flask above a heat lamp (375 W, distance from the lamp ~2–3 cm, height of the soln 1–2 cm), and refluxed. It was monitored by (TLC, 1:1 EtOAc–hexane). After 3 h CHCl₃ (10 mL) was added, and the mixture washed with 1 M aq Na₂S₂O₃ (10 mL), satd NaHCO₃ (2 × 10 mL) and water (10 mL). After drying, the solvent was removed and the residue purified by column chromatography (1:1 EtOAc–hexane).

(b) A 2,3,4,6-tetra-O-acetyl- β -D-galactopyranosyl-1-C-sulfonamide (**14** or **23**, 0.1 g, 0.24 mmol) was dissolved in dry CHCl₃ (10 mL), and bromine (30 μ L, 0.73 mmol) and some K₂CO₃ were added. The mixture was placed in an Erlenmeyer flask above a heat lamp (375 W, distance from the lamp ~2–3 cm, height of the soln 1–2 cm), and refluxed. If the mixture decolorized, bromine (10 μ L) was added again. It was monitored by (TLC, 1:1 EtOAc–hexane). After 8 h CHCl₃ (10 mL) was added, and the mixture washed with 1 M aq Na₂S₂O₃ (10 mL), satd NaHCO₃ (2 × 10 mL) and water (10 mL). After drying, the solvent was removed and the residue purified by column chromatography (1:1 EtOAc–hexane).

(c) 2,3,4,6-Tetra-O-acetyl- β -D-galactopyranosyl-1-C-sulfonamide (**14**, 0.1 g, 0.24 mmol) was dissolved in dry PhCF₃ (10 mL), and

bromine (30 μ L, 0.73 mmol) and some K_2CO_3 were added. The mixture was placed in an Erlenmeyer flask above a heat lamp (375 W, distance from the lamp \sim 2–3 cm, height of the **soln** 1–2 cm), and refluxed. It was monitored by (TLC, 1:1 EtOAc–hexane). After 4 h, the mixture was washed with 1 M aq $Na_2S_2O_3$ (10 mL), satd $NaHCO_3$ (2×10 mL) and water (10 mL). After drying, the solvent was removed under diminished pressure, and the residue purified by column chromatography (1:1 EtOAc–hexane).

3.19. Methyl (2,3,4,6-tetra-O-acetyl-1-C-bromo- β -D-glucofuranosylthio)propanoate S,S-dioxide (24)

Isolated from the bromination mixture of **11** (1.0 g, 2.07 mmol) obtained by method (a) as a white crystalline product (0.25 g, 21%) from hexane. Mp: 92–93 $^{\circ}C$; $[\alpha]_D^{25} +176$ (c 0.28, $CHCl_3$); 1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 5.66 (d, 1H, $J_{1,2}$ 9.2 Hz, H-2), 5.49, 5.25 (pseudo t, 2H, $J \sim 9.2$ Hz in each, H-3, H-4), 4.36–4.18 (m, 3H, H-5, H-6, H-6'), 3.75 (s, 3H, OCH_3), 3.72–3.63 (m, 2H, CH_2), 2.89–2.84 (m, 2H, CH_2), 2.12, 2.09, 2.06, 2.02 (12H, 4s, $4 \times OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.3 ($COOCH_3$), 170.2, 169.6, 168.9, 168.6 (CO), 106.8 (C-1), 75.4, 71.3, 66.9, 66.2 (C-2 to C-5), 60.2 (C-6), 52.4 (OCH_3), 43.1, 26.3 (CH_2), 20.4 (3) 20.3 (CH_3). Anal. Calcd for $C_{18}H_{25}O_{13}S_1$ (561.36): C, 38.50; H, 4.49; S, 5.71. Found: C, 38.55; H, 4.42; S, 5.77.

3.20. Methyl (2,3,4,6-tetra-O-acetyl-5-C-bromo- β -D-glucofuranosylthio)propanoate S,S-dioxide (25)

Isolated from the bromination mixture of **11** (1.0 g, 2.07 mmol) by method (a) as a colourless oil (0.35 g, 30%). $R_f = 0.66$ (1:1 EtOAc–hexane); $[\alpha]_D^{25} -252$ (c 0.20, $CHCl_3$); 1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 5.66, 5.58 (pseudo t, 2H, $J \sim 9.2$ Hz in each, H-2, H-3), 5.26 (d, 1H, $J_{1,2}$ 10.6 Hz, H-1), 4.96 (d, 1H, $J_{3,4}$ 9.2 Hz, H-4), 4.58 (d, 1H, $J_{6,6'}$ 11.9 Hz, H-6), 4.46 (d, 1H, $J_{6,6'}$ 11.9 Hz, H-6'), 3.76 (s, 3H, OCH_3), 3.82–3.54 (m, 2H, CH_2), 2.88–2.84 (m, 2H, CH_2), 2.13, 2.10, 2.07, 2.03 (12H, 4s, $4 \times OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.1 ($COOCH_3$), 169.6, 169.5, 168.9, 168.7 (CO), 98.3 (C-5), 85.5 (C-1), 71.2, 67.9, 66.9, (C-2 to C-4), 60.2 (C-6), 52.4 (OCH_3), 45.9, 26.1 (CH_2), 20.4 (2) 20.3 (2) (CH_3). Anal. Calcd for $C_{18}H_{25}O_{13}S_1$ (561.36): C, 38.50; H, 4.49. Found: C, 38.48; H, 4.45.

3.21. Methyl (2,3,4,6-tetra-O-acetyl-1-C-bromo- β -D-galactopyranosylthio)propanoate S,S-dioxide (26)

Isolated from the bromination mixture of **21** (0.20 g, 0.41 mmol) obtained by method (a) as a colourless oil (0.1 g, 43%). $R_f = 0.55$ (1:1 EtOAc–hexane); $[\alpha]_D^{25} +154$ (c 0.18, $CHCl_3$); 1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 5.82 (d, 1H, $J_{1,2}$ 10.6 Hz, H-2), 5.55 (dd, 1H, $J_{3,4}$ 2.6, $J_{4,5}$ 1.0 Hz, H-4), 5.32 (dd, 1H, $J_{2,3}$ 10.6, $J_{3,4}$ 2.6 Hz, H-3), 4.52 (t, 1H, $J_{5,6}$ 6.6, $J_{5,6'}$ 6.6 Hz, H-5), 4.26–4.22 (m, 2H, H-6, H-6'), 3.75 (s, 3H, OCH_3), 3.72–3.66 (m, 2H, CH_2), 2.96–2.92 (m, 2H, CH_2), 2.12, 2.07, 2.05, 2.00 (12H, 4s, $4 \times OCOCH_3$); ^{13}C NMR ($CDCl_3$) δ (ppm): 170.2 ($COOCH_3$), 172.0, 170.1, 169.7, 169.6 (CO), 108.1 (C-1), 74.8, 69.6, 66.1, 63.8 (C-2 to C-5), 60.3 (C-6), 52.4 (OCH_3), 43.0, 26.3 (CH_2), 20.9 20.4 (3) (CH_3). Anal. Calcd for $C_{18}H_{25}O_{13}S_1$ (561.36): C, 38.50; H, 4.49; S, 5.71. Found: C, 38.53; H, 4.41; S, 5.77.

3.22. Methyl (2,3,4,6-tetra-O-acetyl-5-C-bromo- β -D-galactopyranosylthio)propanoate S,S-dioxide (27)

Isolated from the bromination mixture of **21** (0.20 g, 0.41 mmol) obtained by method (a) as a colourless oil (0.06 g, 27%). $R_f = 0.50$ (1:1 EtOAc–hexane); $[\alpha]_D^{25} -131$ (c 0.18, $CHCl_3$); 1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 5.80–5.70 (m, 2H, H-2, H-3),

5.63 (dd, 1H, $J_{3,4}$ 2.6, $J_{4,5}$ 1.0 Hz, H-4), 4.92 (d, 1H, $J_{1,2}$ 9.2 Hz, H-1), 4.67 (d, 1H, $J_{6,6'}$ 11.9 Hz, H-6), 4.40 (d, 1H, $J_{6,6'}$ 11.9 Hz, H-6'), 3.73 (3H, s, OCH_3), 3.46–3.40 (2H, m, CH_2), 2.89–2.82 (2H, m, CH_2), 2.15, 2.06 (2), 1.97 (12H, 3s, $4 \times OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.2 ($COOCH_3$), 169.5 (2), 169.0 (2) (CO), 95.7 (C-5), 85.9 (C-1), 69.8, 68.5, 65.9, (C-2 to C-4), 60.3 (C-6), 52.5 (OCH_3), 45.8, 26.0 (CH_2), 20.9, 20.5, 20.4, 20.3 (CH_3). Anal. Calcd for $C_{18}H_{25}O_{13}S_1$ (561.36): C, 38.50; H, 4.49. Found: C, 38.59; H, 4.53.

3.23. 2,3,4,6-Tetra-O-acetyl-1-C-bromo- β -D-glucofuranosyl-1-C-sulfonamide (28)

Obtained by bromination of **14** (0.60 g, 1.45 mmol) by method (b) 0.05 g (11%) and method (c) 0.058 g (12%) as a white crystalline product from hexane. Mp: 185–187 $^{\circ}C$; $[\alpha]_D^{25} +235$ (c 0.26, $CHCl_3$); 1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 5.56–5.45 (m, 2H, H-2, H-3 or H-4), 5.38–5.34 (m, 2H, NH_2), 5.26 (t, 1H, J 9.2, J 9.2 Hz, H-4 or H-3), 4.33–4.26 (m, 3H, H-5, H-6, H-6'), 2.10 (2), 2.05, 2.01 (12H, 4s, $4 \times OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.9, 169.8, 169.7, 169.3 (CO), 105.4 (C-1), 75.2, 71.5, 68.7, 66.6 (C-2 to C-5), 60.4 (C-6), 20.7 (2), 20.5, 20.4 (CH_3). Anal. Calcd for $C_{14}H_{20}O_{11}BrNS$ (490.28): C, 34.30; H, 4.11. Found: C, 34.35; H, 4.01.

3.24. 2,3,4,6-Tetra-O-acetyl-5-C-bromo- β -D-glucofuranosyl-1-C-sulfonamide (29)

Obtained by bromination of **14** (0.60 g, 1.45 mmol) by method (b) 0.054 g (12%) and method (c) 0.056 g (12%) as a yellowish oil. $R_f = 0.59$ (1:1 EtOAc–hexane); $[\alpha]_D^{25} -284$ (c 0.24, $CHCl_3$); 1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 5.58, 5.51 (pseudo t, 2H, $J \sim 9.2$ Hz in each, H-2, H-3), 5.38–5.32 (m, 2H, NH_2), 5.23 (d, 1H, $J_{1,2}$ 9.2 Hz, H-1), 4.84 (d, 1H, $J_{3,4}$ 9.2 Hz, H-4), 4.90–4.56 (m, 2H, H-6, H-6'), 2.11, 2.08 (2), 2.01 (12H, 3s, $4 \times OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.2 (2), 169.6, 169.0 (CO), 98.4 (C-5), 85.6 (C-1), 71.1, 68.2, 67.0 (C-2 to C-4), 65.5 (C-6), 20.6 (2), 20.4 (2) (CH_3). Anal. Calcd for $C_{14}H_{20}O_{11}BrNS$ (490.28): C, 34.30; H, 4.11. Found: C, 34.28; H, 4.08.

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