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

Katalin Czifrák, László Somsák *

Department of Organic Chemistry, University of Debrecen, PO Box 20, H-4010 Debrecen, Hungary

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ABSTRACT

O-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 (sulfones) by Oxone® or MCPBA. Oxidation of the β-D-*gluco* derivative with H_2O_2/Na_2WO_4 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 (sulfones) gave O-peracetylated β-D-glycopyranosyl-1-*C*-sulfinates which, on treatment with H_2NOSO_3H, 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 O-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-glucopyranosylthio)propanoate, its *S,S*-dioxide, and β-D-glucopyranosyl-1-*C*-sulfonamide proved inefficient when tested as inhibitors of rabbit muscle glycogen phosphorylase *b*.

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-glycohept-2-ulopyranosyl bromide)onamides (**A**, Chart 1). Among them, compound **C** was shown to have moderate inhibition against rabbit muscle GP*b* (RMGP*b*).[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 chemistry[2] applied to obtain **A** and its further transformations to **C**.

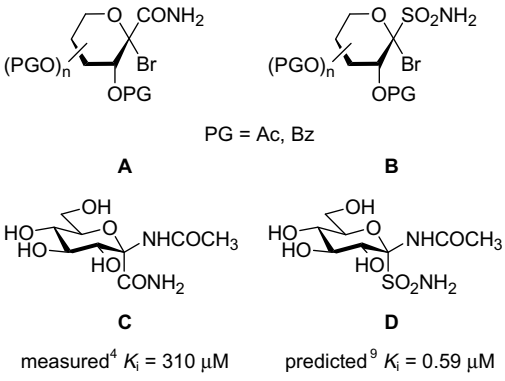

Chart 1.

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 Et_2NH 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 obtaining such compounds was a nucleophilic displacement

* Corresponding author. Tel.: +36 52 512 900/22348; fax: +36 52 453 836.
E-mail address: somsak@tigris.unideb.hu (L. Somsák).

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

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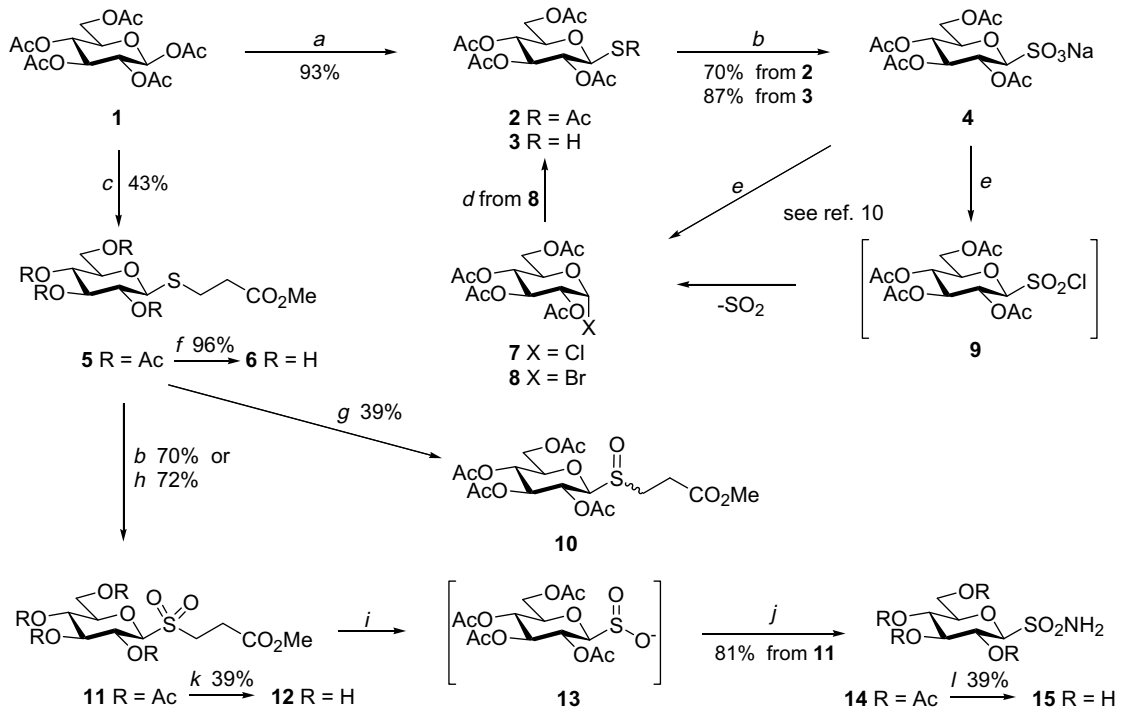
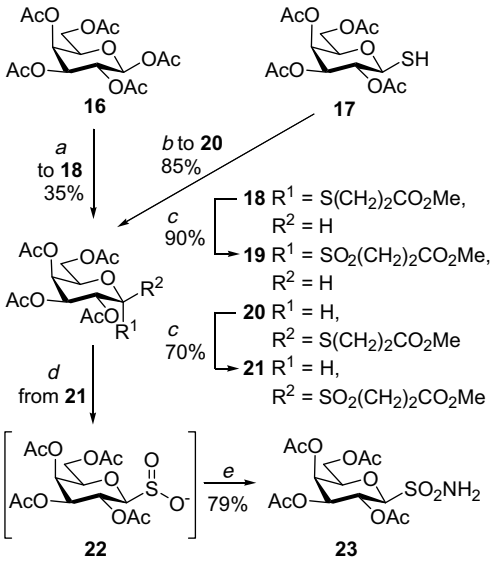


Scheme 1. Reagents and conditions: (a) AcSH, $BF_3{\cdot}OEt_2$, dry CH_2Cl_2, 0–20 °C; (b) Oxone®, NaOAc, AcOH, rt; (c) $HSCH_2CH_2CO_2Me$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0–20 °C; (d) (1) H_2NCSNH_2, dry acetone, reflux; (2) $NaHSO_3$, $CHCl_3$–H_2O, reflux; (e) $SOCl_2$, or PCl_5, dry THF or dry Et_2O, 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) H_2NOSO_3H, water, rt; (k) AcCl, dry MeOH rt; (l) NH_4OH, MeOH, rt.

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-glucopyranose[15] (**2**) prepared from 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**1**) and thiolacetic acid[16] 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 salt[10] 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, $SOCl_2$; THF–Et_2O, 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.

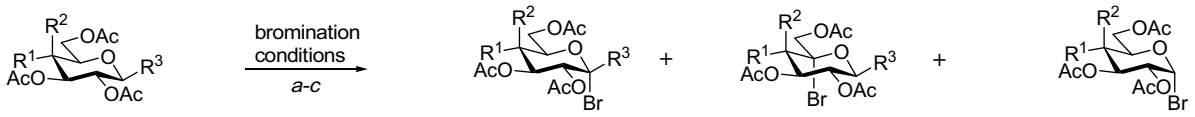
Various sulfonamides were prepared by reaction of sulfinate salts with electrophilic nitrogen sources such as hydroxylamine-*O*-sulfonic acid[19,20] or bis(2,2,2-trichloroethyl)azodicarboxylate.[21] The preparation of the required anomeric sulfinate **13** was effected by base-induced β-elimination from sulfone **11** which was obtained by oxidation of thioglucoside **5**[22,23] by either Oxone® or *m*CPBA. Application of H_2O_2/Na_2WO_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 sulfone[24] with $NaBH_4$ in THF/MeOH for ~one week even at elevated temperature. Sulfinate **13**, without being purified, was treated with H_2NOSO_3H 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* configurated 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 **18** in moderate yield. To get the β-anomer, 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranose[25,26] (**17**) was reacted



Scheme 2. Reagents and conditions: (a) $HSCH_2CH_2CO_2Me$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0–20 °C; (b) $BrCH_2CH_2CO_2Me$, Et_3N, CH_2Cl_2, rt; (c) Oxone®, NaOAc, AcOH, rt; (d) DBU, $CHCl_3$, rt; (e) H_2NSO_3H, water, rt.

Table 1
Radical-mediated bromination of sulfonyl derivatives



		R^1	R^2		Isolated yields (product ratios) (%)		
11	$R^3 = SO_2(CH_2)_2CO_2Me$	OAc	H	a^1	**24** 21	**25** 30	—
21		H	OAc	a^2	**26** 43	**27** 27	—
14	$R^3 = SO_2NH_2$	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*) Br_2, CCl_4, K_2CO_3, *hv*, reflux.[27]
(*b*) Br_2, $CHCl_3$, K_2CO_3, *hv*, reflux.[2]
(*c*) Br_2, $PhCF_3$, K_2CO_3, *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 ^{1}H NMR spectrum of the crude mixture.
[5] Conversion 81% after 4 h.
[6] Conversion 77% after 4 h. Product ratio calculated from the ^{1}H NMR spectrum of the crude mixture.

with methyl 3-bromopropanoate in the presence of Et_3N, 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 H_2NOSO_3H 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-glycopyranosyl 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 ^{1}H NMR spectra of these compounds.

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 0.9[31]). Although the radical in position next to the CO_2Me 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-aldonic acid derivatives) showed an exclusive selectivity for that position[2,32,33] as it can be concluded from the RRS values[27] (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 SO_2NH_2 moiety as illustrated in **I**. Further β-fragmentation of the intermediate sulfonamidyl radical **II** might give glycosyl radical[34] **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 ac-

Table 2
Selected relative radical stabilization factors[31] 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_2OAc)	2.3	6.5
OMe (= O-ring)	4.5	
SO_2Ph	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] $0.03 \times RRS_{O,X} = 1 - (1 - 0.03 \times RRS_{OMe})(1 - 0.03 \times RRS_X)$.

[‡] 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] cellobiosyl pyperidine[29] and β-D-glucopyranosyl isothiocyanate.[29]

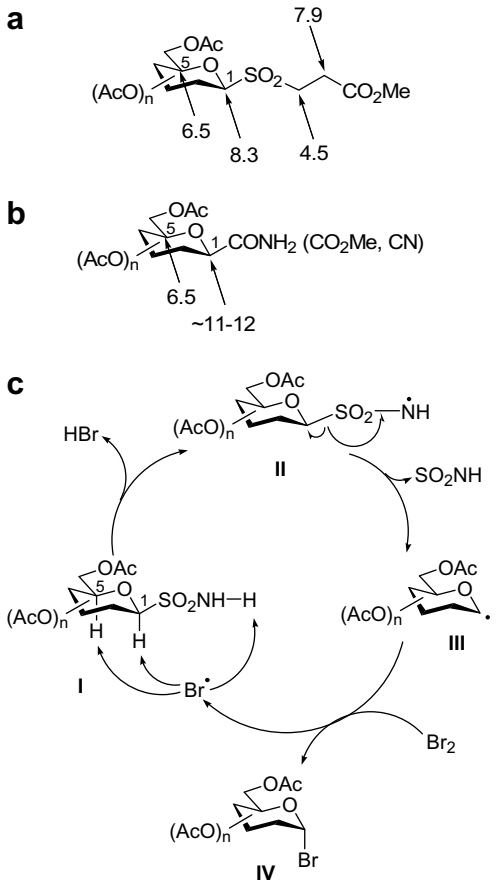


Figure 1. (a) Relative radical stabilization factors taken from Table 2 for glucopyranosyl sulfones and (b) anhydro-aldonic acid derivatives; (c) proposed reactivity pattern for the radical-mediated bromination of anomeric sulfonamides.

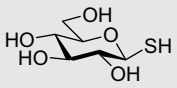
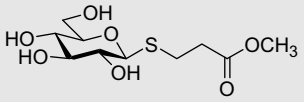
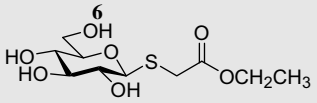
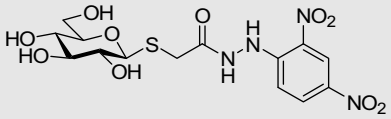
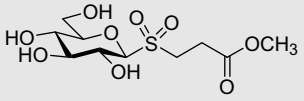
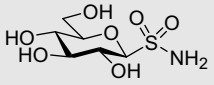
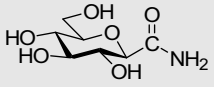
cess to the NH_2 as compared to the ring positions, but radical stabilization factors may also play a role.

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-thioglucoside **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 RMGP*b* (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] Sulfone **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 RMGP*b*.

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

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

Entry	Compound	K_i (mM)
1		1[37]
2		n.i.
	6	
3		n.i.[37]
4		0.65[37]
5		n.i.
	12	
6		n.i.
	15	
7		0.44[37]

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 $^1H/^{13}C$) and Varian UNITYINOVA 400 WB (400/100 MHz for $^1H/^{13}C$) 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 F_{254} (Merck). TLC plates were inspected by UV light (λ = 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, bromocompounds 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 from[14]) (2)

1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose (**1**, 1.00 g, 2.56 mmol) was dissolved in dry CH_2Cl_2 (10 mL). To the soln, thioacetic acid (0.28 mL, 3.84 mmol) and $BF_3{\cdot}OEt_2$ (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 CH_2Cl_2–acetone) it was diluted with CH_2Cl_2 (10 mL), washed with satd $NaHCO_3$ (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); $[\alpha]_D$ +29 (*c* 0.38, $CHCl_3$), (lit.[15] $[\alpha]_D$ +11 (*c* 1.49, $CHCl_3$)); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 5.27, 5.12, 5.10 (pseudo t, 3H, $J \sim 9.2$ 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, $SCOCH_3$), 2.08, 2.03, 2.02, 2.01 (12H, 4s, 4 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 191.8 ($SCOCH_3$), 170.5, 169.2, 169.3 (2) (*C*O), 80.1 (C-1), 76.3, 73.8, 68.9, 67.8 (C-2 to C-5), 61.6 (C-6), 30.7 ($SCOCH_3$) 20.6, 20.5 (3) (CH_3).

3.3. Sodium 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-1-*C*-sulfonate (adapted from[14]) (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 CH_2Cl_2–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 $CHCl_3$–MeOH) to give 0.42 g (70%) of **4** as a white crystalline product. Mp: 218–220 °C; $[\alpha]_D$ −59 (*c* 0.23, H_2O) ; ^1H NMR (D_2O, 360 MHz): δ (ppm) 5.43, 5.37, 5.17 (pseudo t, 3H, $J \sim 9.4$ 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 × $OCOCH_3$); ^{13}C NMR (D_2O, 90 MHz): δ (ppm) 174.2, 173.6, 173.2, 172.8 (*C*O), 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 (CH_3); ESI MS calcd for $C_{14}H_{19}O_{12}SNa$ 434.354, found 457.018 (M+Na).

(b) Also prepared from 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose[17] (**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 CH_2Cl_2 (30 mL), then methyl 3-sulfanylpropanoate (2.1 mL, 19.2 mmol) and $BF_3{\cdot}OEt_2$ (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 CH_2Cl_2 and washed with satd $NaHCO_3$ (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); $[\alpha]_D$ −64 (*c* 0.26, $CHCl_3$ (lit.[22] $[\alpha]_D$ −32 (*c* 1.00, $CHCl_3$)); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 5.23, 5.03, 5.01 (pseudo t, 3H, $J \sim 9.2$ 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, OCH_3), 2. 99 (dt, 1H, *J* 7.9, *J* 6.6 Hz, CH_2), 2.88 (dt, 1H, *J* 7.9, *J* 6.6 Hz, CH_2), 2.69 (t, 2H, *J* 7.9, *J* 6.6 Hz, CH_2), 2.09, 2.06, 2.03, 2.01 (12H, 4s, 4 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 171.9 ($COOCH_3$), 170.5, 169.9, 169.2 (2) (*C*O), 83.7 (C-1), 75.7, 73.6, 69.5, 68.1 (C-2 to C-5), 61.9 (C-6), 51.6 (OCH_3), 35.1, 25.2 (CH_2), 20.5, 20.4 (2), 20.3 (CH_3). Anal. Calcd for $C_{18}H_{26}O_{11}S_1$ (450.47): C, 47.99; H, 5.82. Found: C, 47.86; H, 5.66.

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

Thioglucoside **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 $CHCl_3$–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 $CHCl_3$–MeOH); $[\alpha]_D$ −74 (*c* 0.19, H_2O); ^1H NMR (D_2O, 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, OCH_3), 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, CH_2), 2.93 (quintet, 1H, *J* 7.9, *J* 6.6 Hz, CH_2), 2.76–2.74 (m, 2H, CH_2); ^{13}C NMR (D_2O, 90 MHz). δ (ppm) 175.7 ($COOCH_3$), 86.5 (C-1), 80.4, 77.4, 72.7, 70.0, (C-2 to C-5), 61.5 (C-6), 53.5 (OCH_3), 35.5, 25.7 (CH_2). Anal. Calcd for $C_{10}H_{18}O_7S_1$ (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)

Thioglucoside **5** (0.1 g, 0.22 mmol) was dissolved in MeOH (3 mL). To this soln Na_2WO_4 (6.5 mg, 0.02 mmol) and H_2O_2 (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; $[\alpha]_D$ −128 (*c* 0.22, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 5.34, 5.26, 5.11 (pseudo t, 3H, $J \sim 9.2$ 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, OCH_3), 3.22–3.20 (m, 2H, CH_2), 2.85 (m, 2H, CH_2), 2.09, 2.07, 2.05, 2.03 (12H, 4s, 4 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 171.5 ($COOCH_3$), 170.4, 169.9, 169.5, 169.2 (*C*O), 90.1 (C-1), 76.8, 73.0, 68.3, 67.5 (C-2 to C-5), 61.3 (C-6), 52.2 (OCH_3), 42.0, 26.1 (CH_2), 20.5 (2), 20.4 (2) (CH_3). Anal. Calcd for $C_{18}H_{26}O_{12}S_1$ (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) Thioglucoside **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 CH_2Cl_2 (3 × 5 mL). The organic phase was washed with satd $NaHCO_3$ (2 × 5 mL) and water (1 × 5 mL), dried, and the solvent removed under diminished pressure. The crude product was recrystallized from Et_2O to give 0.07 g (70%) of **11**.

(b) Thioglucoside **5** (0.1 g, 0.22 mmol) was suspended in CH_2Cl_2 (3 mL), and $NaHCO_3$ (0.19 g, 2.20 mmol) and *m*CPBA (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 CH_2Cl_2 (2 × 5 mL). The

organic phase was washed with NaCl (1 × 5 mL), satd $NaHCO_3$ (2 × 5 mL) and water (1 × 5 mL), dried, and the solvent removed under diminished pressure. The crude product was recrystallized from Et_2O to yield 0.08 g (72%) of **11** as white crystalline product. Mp: 146–147 °C; $[\alpha]_D$ −36 (*c* 0.22, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 5.52, 5.33, 5.14 (pseudo t, 3H, $J \sim 9.3$ 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, OCH_3), 3.60 (dt, 1H, *J* 7.9, 6.6 Hz, CH_2), 3.41 (dt, 1H, *J* 7.9, 6.6 Hz, CH_2), 2.89 (m, 2H, CH_2), 2.10, 2.05 (2), 2.03 (12H, 4s, 4 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.5 (*C*$OOCH_3$), 170.3, 169.9, 169.2, 169.1 (*C*O), 87.9 (C-1), 76.6, 72.9, 67.2, 66.2 (C-2 to C-5), 61.2 (C-6), 52.3 (O*C*H_3), 45.3, 26.2 (*C*H_2), 20.4 (2), 20.3 (2) (*C*H_3). Anal. Calcd for $C_{18}H_{26}O_{13}S_1$ (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 $CHCl_3$ (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 $CHCl_3$–MeOH). It was then neutralized with solid $NaHCO_3$ and the solvent evaporated after filtration. The crude oil was purified by column chromatography (4:1 $CHCl_3$–MeOH) to give 0.05 g (75%) of **12** as a colourless oil. R_f = 0.37 (4:1 $CHCl_3$–MeOH); $[\alpha]_D$ −53 (*c* 0.26, H_2O); ^1H NMR (D_2O, 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, OCH_3), 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, CH_2), 2.98–2.92 (m, 2H, CH_2); ^{13}C NMR (D_2O, 90 MHz): δ (ppm) 173.8 (*C*$OOCH_3$), 90.0 (C-1), 81.3, 77.2, 69.2, 69.1, (C-2 to C-5), 61.0 (C-6), 53.4 (O*C*H_3), 47.1, 27.1 (*C*H_2). Anal. Calcd for $C_{10}H_{18}O_9S_1$ (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*-sulfinic acid (13)

Sulfone **11** (0.1 g, 0.21 mmol) was dissolved in freshly distilled dry $CHCl_3$ (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 $CHCl_3$–MeOH). The solvent was evaporated and the crude oil was purified by column chromatography (7:3 $CHCl_3$–MeOH) to give 0.06 g of **13** as a white crystalline product. ^1H NMR (D_2O, 360 MHz): δ (ppm) 5.36, 5.29, 5.08 (pseudo t, 3H, $J \sim 9.2$ 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 × $OCOCH_3$); ^{13}C NMR (D_2O, 90 MHz): δ (ppm) 174.3, 173.9, 173.3 (2) (*C*O), 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) (*C*H_3); 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, H_2NOSO_3H (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 $NaHCO_3$ (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 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 5.39, 5.31, 5.14 (pseudo t, 3H, $J \sim 9.3$ 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, NH_2), 2.11, 2.08, 2.06, 2.04 (12H, 4s, 4 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.9, 170.4, 170.1, 169.5 (*C*O), 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) (*C*H_3). Anal. Calcd for $C_{14}H_{21}O_{11}NS$ (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 NH_4OH were added and the mixture was kept at rt until completion of the transformation (TLC, 4:1 $CHCl_3$–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 $CHCl_3$–MeOH) to give 0.05 g (85%) of **15** as a colourless oil. R_f = 0.59 (1:1 $CHCl_3$–MeOH); $[\alpha]_D$ −34 (*c* 0.24, H_2O); ^1H NMR (D_2O, 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); ^{13}C NMR (D_2O, 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 $C_6H_{13}O_7S_1$ (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 CH_2Cl_2 (30 mL), and methyl 3-sulfanylpropanoate (2.1 mL, 19.2 mmol) and $BF_3{\cdot}OEt_2$ (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 CH_2Cl_2 and washed with satd $NaHCO_3$ (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), $[\alpha]_D$ +496 (*c* 0.34, $CHCl_3$); ^1H NMR ($CDCl_3$, 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, OCH_3), 2.88 (dt, 1H, *J* 7.9, *J* 6.6 Hz, CH_2), 2.78 (dt, 1H, *J* 7.9, *J* 6.6 Hz, CH_2), 2.68–2.64 (m, 2H, CH_2), 2.15, 2.06 (2), 1.96 (12H, 3s, 4 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 171.8 (*C*$OOCH_3$), 170.3, 170.1 (2), 169.7 (*C*O), 89.9 (C-1), 67.9, 67.8, 67.7, 66.6 (C-2 to C-5), 61.8 (C-6), 51.7 (OCH_3), 34.4, 25.1 (*C*H_2), 20.6, 20.5 (3) (*C*H_3); Anal. Calcd for $C_{18}H_{26}O_{11}S_1$ (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 CH_2Cl_2 (3 × 15 mL). The organic phase was washed with satd $NaHCO_3$ (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, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 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, $J_{5,6'}$ 5.8 Hz, H-5), 4.19–4.06 (m, 2H, H-6, H-6′), 3.62 (s, 3H, OCH_3), 3.49–3.44 (m, 2H, CH_2), 2.93–2.85 (m, 2H, CH_2), 2.16, 2.13, 2.09, 2.01 (12H, 4s, 4 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.6 ($COOCH_3$), 170.3, 170.0, 169.5, 169.2 (*C*O), 84.8 (C-1), 71.3, 66.9, 66.7, 65.7 (C-2 to C-5), 62.2 (C-6), 52.3 (OCH_3), 46.5, 25.8 (CH_2), 20.4, 20.2 (3) (CH_3); Anal. Calcd for $C_{18}H_{26}O_{13}S_1$ (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)

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 CH_2Cl_2 (50 mL). To this soln methyl 3-bromopropanoate (1.11 mL, 9.43 mmol) and Et_3N (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 CH_2Cl_2 and washed with satd $NaHCO_3$ (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, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 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, OCH_3), 3.02 (dt, 1H, *J* 7.9, *J* 6.6 Hz, CH_2), 2.93 (dt, 1H, *J* 7.9, *J* 6.6 Hz, CH_2), 2.72–2.68 (m, 2H, CH_2), 2.16, 2.05 (2), 1.98 (12H, 3s, 4 $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 172.0 ($COOCH_3$), 170.3, 170.1, 169.9, 169.7 (*C*O), 84.5 (C-1), 74.4, 71.7, 67.1, 67.0 (C-2 to C-5), 61.4 (C-6), 51.7 (OCH_3), 35.1, 25.4 (CH_2), 20.6, 20.5 (2), 20.4 (CH_3); Anal. Calcd for $C_{18}H_{26}O_{11}S_1$ (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, 22.0 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 (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was washed with satd $NaHCO_3$ (2 × 30 mL) and water (1 × 30 mL), dried, and the solvent was removed under diminished pressure. The crude product was recrystallized from Et_2O to give 0.74 g (70%) of **21** as a white crystalline product. Mp: 120–122 °C; $[\alpha]_D$ +6 (*c* 0.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 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, OCH_3), 3.55 (dt, 1H, *J* 7.9, *J* 6.6 Hz, CH_2), 3.42 (dt, 1H, *J* 7.9, *J* 6.6 Hz, CH_2), 2.92–2.87 (m, 2H, CH_2), 2.20, 2.07, 2.06, 1.98 (12H, 4s, 4 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.5 ($COOCH_3$), 170.2, 169.9, 169.8, 169.2 (*C*O), 88.6 (C-1), 75.4, 71.1, 66.6, 63.3 (C-2 to C-5), 61.0 (C-6), 52.3 (OCH_3), 45.1, 26.1 (CH_2), 20.6, 20.5, 20.4, 20.3 (CH_3); Anal. Calcd for $C_{18}H_{26}O_{13}S_1$ (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 $CHCl_3$ (15 mL) and DBU (150 μL, 1.05 mmol) was added. The mixture was stirred at rt until complete transformation of the starting material (TLC, 7:3 $CHCl_3$–MeOH). The solvent was evaporated and the crude oil was purified by column chromatography (7:3 $CHCl_3$–MeOH) to give 0.35 g of **22** as a yellowish oil. ^{1}H NMR (D_2O, 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 × $OCOCH_3$); ^{13}C NMR (D_2O, 90 MHz): δ (ppm) 173.6, 173.4, 173.0, 172.9 (*C*O), 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 (CH_3). 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). H_2NOSO_3H (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 $NaHCO_3$ (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, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz): δ (ppm) 5.51 (s, 1H, NH_2), 5.48 (1H, dd, $J_{3,4}$ 4.0, $J_{4,5}$ 1.0 Hz, H-4), 5.29 (s, 1H, NH_2), 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, NH_2), 2.17, 2.08, 2.05, 1.99 (12H, 4s, 4 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 171.1, 170.5, 170.0, 169.8 (*C*O), 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 (CH_3). Anal. Calcd for $C_{14}H_{21}O_{11}NS$ (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-glycopyranosylthio) propanoate *S*,*S*-dioxide (**11** or **21**, 0.1 g, 0.21 mmol) was dissolved in dry CCl_4 (10 mL), and bromine (30 μL, 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 ~2–3 cm, height of the soln 1–2 cm), and refluxed. It was monitored by (TLC, 1:1 EtOAc–hexane). After 3 h $CHCl_3$ (10 mL) was added, and the mixture 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 and the residue purified by column chromatography (1:1 EtOAc–hexane).

(b) A 2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosyl-1-*C*-sulfonamide (**14** or **23**, 0.1 g, 0.24 mmol) was dissolved in dry $CHCl_3$ (10 mL), and bromine (30 μL, 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 ~2–3 cm, height of the soln 1–2 cm), and refluxed. If the mixture decolourized, bromine (10 μL) was added again. It was monitored by (TLC, 1:1 EtOAc–hexane). After 8 h $CHCl_3$ (10 mL) was added, and the mixture 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 and the residue purified by column chromatography (1:1 EtOAc–hexane).

(c) 2,3,4,6-Tetra-*O*-acetyl-β-D-glycopyranosyl-1-*C*-sulfonamide (**14**, 0.1 g, 0.24 mmol) was dissolved in dry $PhCF_3$ (10 mL), and bro-

mine (30 μL, 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 ~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-glucopyranosylthio)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 °C; $[\alpha]_D$ +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 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.3 ($COOCH_3$), 170.2, 169.6, 168.9, 168.6 (*C*O), 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-glucopyranosylthio)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); $[\alpha]_D$ −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 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.1 ($COOCH_3$), 169.6, 169.5, 168.9, 168.7 (*C*O), 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); $[\alpha]_D$ +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 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$) δ (ppm): 170.2 ($COOCH_3$), 172.0, 170.1, 169.7, 169.6 (*C*O), 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); $[\alpha]_D$ −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 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.2 ($COOCH_3$), 169.5 (2), 169.0 (2) (*C*O), 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-glucopyranosyl-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 °C; $[\alpha]_D$ +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 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.9, 169.8, 169.7, 169.3 (*C*O), 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-glucopyranosyl-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); $[\alpha]_D$ −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 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.2 (2), 169.6, 169.0 (*C*O), 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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