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The iodosulfonamidation of peracetylated glycals revisited: access to 1,2-di-nitrogenated sugars

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ABSTRACT

Iodosulfonamidation of peracetylated glycals was investigated using either a combination of *N*-iodosuccinimide/iodine or iodine chloride as a source of iodonium ion. 1,2-*trans*- and 1,2-*cis*-2-deoxy-2-iodo-1-sulfonamido hexoses were, respectively, obtained depending on the reagent system used. Both series of isomers were successfully converted to 1,2-di-nitrogenated compounds, for example, 1-azido-1,2-dideoxy-2-sulfonamido sugars, which are useful intermediates for the synthesis of N-linked glycoproteins or glycoconjugates.

1. Introduction

The 1,2-dideoxy-1,2-di-nitrogenated hexoses are important subunits of *N*-glycoproteins or *N*-glycopeptides as well as many glycoconjugates. For instance, *N*-glycans in *N*-glycoproteins are linked to the proteins at asparagine residues almost exclusively via a β-*N*-acetylglucosamine.[1] Among the few other types of *N*-glycan linkages, *N*-acetylgalactosamine and 2,4-diacetamido-2,4,6-trideoxy-D-glucopyranose (bacillosamine) have also been reported in Archaea and Bacteria.[2,3] Hence access to these *N*-(aspartoyl)-2-*N*-acetamido-glycosylamines or analogues thereof is essential to study the structures and functions of natural and artificial *N*-glycoproteins or glycopeptides. In addition, the presence of a nitrogen-based functional group at the anomeric centre of 2-amino-2-deoxy sugars provides a unique opportunity to modify proteins, peptides or drugs to improve their activity or their bioavailability. Properties like aqueous solubility, oral uptake or diversion from liver biliary clearance may be affected.[4] This modification can equally be used for the preparation of immunogens, amphiphiles, lectin ligands as well as enzyme inhibitors or substrates.[5] Anomeric azides are particularly well-suited for these purposes: they are easily prepared from glycosyl halide or hydrazide precursors,[6] are more stable than anomeric amines and readily react in Cu^{I}-catalysed Huisgen azide-alkyne 1,3-dipolar cycloadditions.[7–9] When the parent 2-amino-2-deoxy sugar is accessible, anomeric amines/amides can also be prepared from glycosyl azides,[10] α-hydroxy nitriles,[11] isonitriles,[12] or by simple straightforward amination.[13] Otherwise, 1,2-di-nitrogenated compounds can be accessed either through a combination of one among the above mentioned strategies and one method of preparation of 2-aminosugars[14] or through specific approaches. For example, a clever approach but limited to the preparation of 2-azido mannosylamine makes use of Burgess's reagent.[15] Alternatively, glycals have emerged as versatile intermediates for the introduction of nitrogen substituents at C-1 and C-2 of sugars. This can be achieved by 1,2-addition of azide on 2-nitroglycals.[16] Metal-catalysed nitrogen transfer[17] or dipolar cycloaddition/photoisomerisation[18] processes have also been reported. However, true generalisation or application to electron-rich alkenes remains hitherto to be developed, respectively. Gratifyingly, introduction of an amide at C-2 and an azide at the anomeric centre are concomitantly accomplished following the Gin's C-2-amidoglycosylation procedure. However, Ferrier rearrangement is observed when an acetyl group is present next to the unsaturation.[19] Kumar and Ramesh have recently described the interesting iodine-catalysed 1,2-bis-sulfonamidation of glycals. While differentiation of both sulfonamides is easily operated later during the synthesis, their deprotection requires very large excess of the reducing reagent.[20] Therefore, in search for a general and straightforward entry to 2-amino-1-azido sugars, we have turned our attention to the Danishefsky's azido-iodosulfonamidation:[21] this two-steps procedure first involves the iodosulfonamidation of a glycal, followed by azidolysis (Scheme 1).[22]

The overall process is based on the intramolecular displacement of the iodide to form an unstable aziridine which, in turn, is opened by the incoming azide. Marked advantages of the procedure are obviously its initial high stereoselectivity and its compatibility

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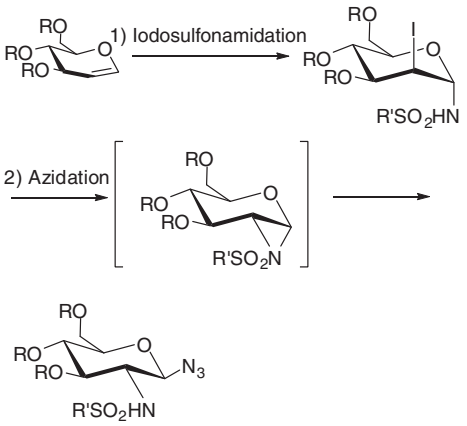


Scheme 1. Danishefsky's azido-sulfonamidation procedure.

with a broad range of sugars as well as protecting groups, such as silyl and benzyl ethers, carbonates, esters and acetals as witnessed by the numerous reported synthetic applications.[23] However, it was shown that the initially formed *trans*-1,2-iodosulfonamides could rapidly and extensively isomerised into their corresponding *cis*-1,2-iodosulfonamides which are claimed to be inert towards aziridination.[24] This side reaction, which considerably reduces the scope of the iodosulfonamidation, seems to strongly depend on the reaction temperature and duration. For example, 1-benzenesulfonamido-2-deoxy-2-iodo-4,6-*O*-isopropylidene-3-*O*-triethylsilyl-D-mannoside was obtained in a 10:1 or 2:5 *trans*:*cis* ratio for reaction times of 25 min or 2.5 h, respectively. Iodosulfonamidation of 3,4,6-tri-*O*-benzyl-D-glucal (1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enitol) using *p*-nitrobenzenesulfonamide gave rise to a 5:2 *trans*:*cis* isomeric ratio at 0 °C but only the *cis* isomer when conducted at rt (Chart 1).[24]

While glycals are easily obtained as peresterified derivatives,[25] such reactants proved particularly sensitive to anomerisation, maybe because the effective transformation of these electron-poor derivatives usually requires higher temperature and longer reaction times. We report herein our efforts to define new experimental conditions which would limit isomerisation of peracetylated substrates thereby avoiding laborious protecting group exchange and restoring the full utility of the iodosulfonamidation/azidolysis procedure.

2. Results and discussion

We elected to study the addition of 2-(trimethylsilyl)ethanesulfonamide on hexa-*O*-acetyl-D-lactal (1,5-anhydro-3,6-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-β-D-galactopyranosyl)-2-deoxy-D-*arabino*-hex-1-enitol) **1** (Scheme 2).[26] This sulfonamide is expensive, but it is deprotected in conditions (fluoride) milder and more selective than arylsulfonamides.[27,20] Besides, access to lactosamine, a motif recognised by galectins, is essential to understand structure–function relationships of these lectins and design effective antagonists.[28]

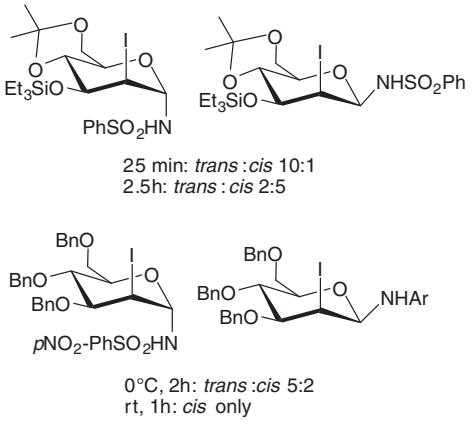
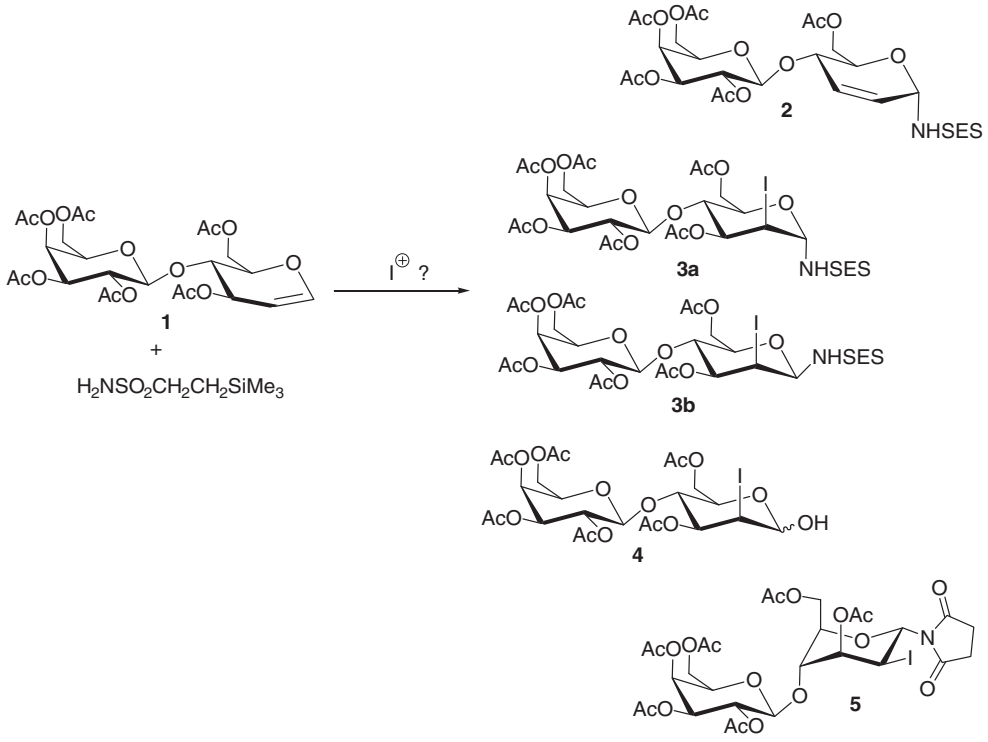


Chart 1. Examples of temperature and reaction times dependence of iodosulfonamide anomerisation.

To minimise the anomerisation, we tried to find out experimental conditions which could promote iodosulfonamidation at lower temperature than those reported in the literature.[24] I(sym-collidine)$_2$ClO$_4$ (IDCP) or NIS are the usual iodine sources employed in the iodosulfonamidation process. However, neither of them was effective at promoting the reaction at −10 °C. Indeed, less than 30% conversion of starting lactal was observed after one day at this temperature in CH_2Cl_2 (Table 1, entries 1 and 2). The reaction was tentatively carried out in CH_3CN, a more polar solvent commonly used for electrophilic addition.[20,29] Compound **1** reacted rapidly under these conditions to afford the corresponding Ferrier's rearranged product **2** in 82% yield. Switching back to CH_2Cl_2 as solvent, the reaction was attempted with molecular iodine, a more powerful electrophile. Again, rearranged compound **2** was isolated as the sole product (Table 1, entries 3 and 4). At this stage, we reasoned that the electrophilic character of the reagent should ideally be comprised between those of NIS and iodine. Along this line interhalogen compounds have been largely used to promote glycosylation reactions.[30] When peracetyl-D-lactal **1** was treated with iodine chloride, whose possible implication in the *bis*-sulfonamidation of glycals was previously suggested by Kumar and Ramesh,[20b] the clean and rapid formation of the unwanted *cis*-1,2-iodosulfonamide **3b** was observed at −10 °C (Table 1, entry 5). Its structure was proposed based on the resonances of H-1 in the ^{1}H NMR and C-2 in the ^{13}C NMR observed at 4.1 and 38.9 ppm, respectively, in accordance with the previously reported data.[24] Pursuing our quest, we tried to define another system. It is well known that the reactivity of NIS is generally enhanced in the presence of a catalytic amount of acid. This property has been extensively exploited in glycosylations[31] and also in iodination of aromatic compounds.[32] While NIS/acid systems were not tested in this study since acids are known to promote the Ferrier rearrangement,[33] we were encouraged to test a combination of reagents. Gratifyingly, treatment of a mixture of compound **1** and 2-(trimethylsilyl)ethanesulfonamide with NIS followed by the addition of molecular iodine afforded the expected *trans*-1,2-iodosulfonamide **3a** in acceptable yield (Table 1, entry 6). Notably, no isomerisation occurred in the reaction vessel, even after prolonged reaction time, or during the flash-chromatography purification. Compared with the *cis* isomer **3b**, the chemical shifts of C-2 and H-1 were observed at 26.0 ppm and at 5.40 ppm, respectively. Noteworthy, the $^1C_4$ chair conformation seems to be substantially present as suggested by the rather large $J_{1,2}$ (7.5 Hz) as well as the small $J_{3,4}$ and $J_{4,5}$ (4.8 Hz) coupling constants. 4-*O*-(Tetra-2,3,4,6-*O*-acetyl-β-D-galactopyranosyl)-2-deoxy-2-iodo-D-mannose **4** and known mannosylsuccinimide **5**[34] arising from adventitious water and competitive addition of released succinimide were also isolated from the reaction mixture in variable amounts depending on the experiments.

The exact nature of the electrophile has not been determined but stoichiometric amount of iodine seems to be required since diminishing the ratio to 0.2 or 0.5 equiv leads to a reaction profile similar to the one observed for NIS alone.

To further confirm the observed selectivity, both reagent systems were tested on tri-*O*-acetyl-D-glucal **6** and tri-*O*-acetyl-D-galactal (3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol) **7** (Table 2). NIS/I_2 treatment afforded the corresponding *trans*-diaxial-1,2-iodosulfonamides **8a** and **9a** in shorter reaction times and higher isolated yields, an issue being ascribed to their lower number of electron-withdrawing substituents (Table 2,



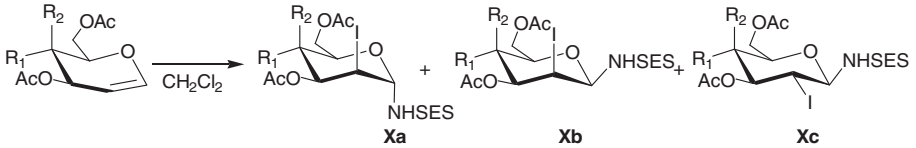
Scheme 2. Disaccharides obtained from iodosulfonamidation of per-acetyl-D-glycal **1** with $SESNH_2$.

Table 1
Products and yields (%) formed upon iodosulfonamidation of peracetyl-D-lactal **1** with $SESNH_2$[a]

Entry	Conditions	2	3a	3b	4	5
1	NIS (1 equiv)		30 (+ starting material)[b]			
2	IDCP (1 equiv)			25		
3	NIS (1 equiv), CH_3CN	82				
4	I_2 (1 equiv)	85				
5	ICl (2 equiv)[c]			40–60	20–30	
6	NIS (1 equiv)/I_2 (1 equiv)		45–30		30–40	0–15[d]

[a] Unless otherwise mentioned, all reactions were performed at −10 °C using 1 equiv of $SESNH_2$ in CH_2Cl_2.
[b] Estimated yield from mass spectroscopy, the ratio of isomer *cis*:*trans* was not determined.
[c] In the presence of 4 Å MS, from −10 °C to rt.
[d] Only detectable in its $^1C_4$ conformation.[34,35]

Table 2
Iodosulfonamidation of representative glycals[a]



Entry	Compounds	Electrophile	Products (isolated yield in %)		
1	**6** R_1 = OAc; R_2 = H	NIS/I_2 (1 + 1 equiv)[a]	**8a** (65)[c]		
2	**6** R_1 = OAc; R_2 = H	ICl (2 equiv)[b]		**8b** (45)[c]	
3	**7** R_1 = H; R_2 = OAc	NIS/I_2 (1 + 1 equiv)[a]	**9a** (61)[c]		
4	**7** R_1 = H ; R_2 = OAc	ICl (2 equiv)[b]	**9a** (16)	**9b** (19)	**9c** (6)

[a] 4 Å MS, from −10 °C to 0 °C over 1 h then 0 °C, 1 h.
[b] 4 Å MS, −10 °C to rt.
[c] Products of hydrolysis were not isolated.

entries 1 and 3). ICl-promoted iodosulfonamidation of glycal **6** was also stereoselective, affording the β-1,2-*trans* isomer **8b** in moderate yield (Table 2, entry 2). Under the same conditions, compound **7** was transformed into an inseparable mixture of α/β-*talo*- **9a**/**9b** and β-*galacto*-iodosulfonamides **9c** in a modest 41% overall yield (Table 2, entry 4). This last compound was identified from the ^1H NMR proton coupling constants ($J_{1,2}$ = 9.9 Hz, $J_{2,3}$ = 11.3 Hz, $J_{3,4}$ = 3.2 Hz and $J_{4,5}$ = 0.8 Hz) as well as from the downfield

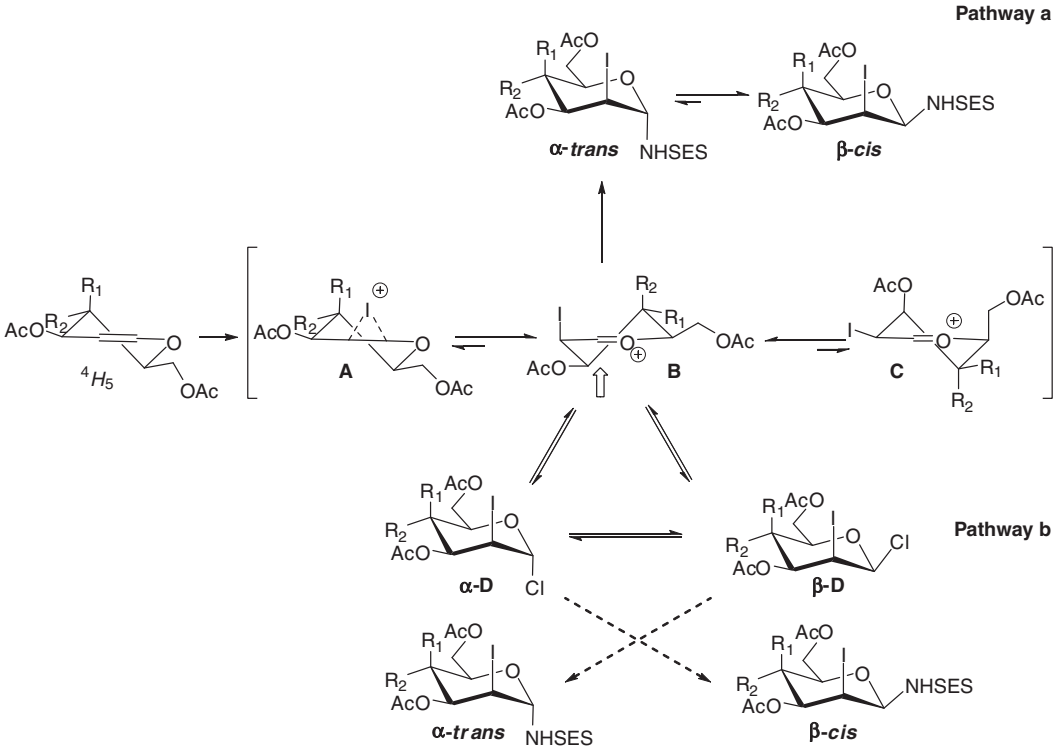
resonance of C-1 compared with the corresponding anomeric carbons of the *talo* isomers in the ^{13}C NMR spectra (85.7 vs 80.6 and 78.9 ppm, respectively). Taken together, these data are in full agreement with a galactopyranose derivative in a $^4C_1$ conformation. Proton NMR coupling constants of both *manno* and *talo* derivatives indicate some substantial deviation from the classical $^4C_1$ conformations, the $^1C_4$ conformation being predominant for compound **9a**, for which three substituents change from an axial to an equatorial orientation.

Stereoselectivity of the iodonium-promoted electrophile addition upon glycals is controlled, among others, by the preferred initial attack on the glycal, the ionic character of the reactive intermediates and the stability of the products, notably in acidic medium.

It is well accepted that iodine-based electrophiles preferentially react from the top-face of glycals in their half-chair $^4H_5$ conformation (Scheme 3). This results in the formation of the often postulated, bridged iodonium intermediate A,[23,29b,36,37] whose further trapping by nucleophiles can easily account for the regiospecificity and the high *trans* stereoselectivity observed, or more likely to the oxoniums **B** or **C**.[38,39] Indeed, a computational study performed on model compounds has shown that the open forms predominate.[38] This result should still be true for the present study although the presence of electron-withdrawing substituents (acetyl groups) might slightly shift the equilibrium towards the **A** form. Among the two open conformers, the axial iodine conformer **B** should be preferred due to stabilising hyperconjugative interactions between the σC-I and the π*C–O of the oxonium.[39] Thus, addition of the nucleophile is considered to mostly proceed on the iodocarbonium **B**, driven by a stereoelectronic α-anomeric effect,[37] leading preferentially to the formation of the α-*trans* isomer. The NIS/I_2-promoted reaction probably follows this pathway (Scheme 3, pathway a). The same mechanism might be invoked when using ICl. However, in this case, the *trans* diaxial-1,2-iodosulfonamides which are initially formed, further anomerise to furnish the more stable *cis* isomers as previously suggested.[24] Alternatively, the β-*cis*-isomer could arise from the competitive formation of 2-iodo-α-glycosyl chloride **α-D** and 2-iodo-β-glycosyl chloride **β-D** which, in turn, could give the iodosulfonamides via the above mentioned iodocarbonium **B**,[40] thereby suggesting an in situ isomerisation towards the β-*cis* isomer, or direct S_N2 substitution by the sulfonamide although anomeric halide nucleophilic substitution is rather observed in basic medium, under Phase Transfer Catalysis (Scheme 3, pathway b, dotted arrows).[41]

Fast and complete isomerisation of purified iodosulfonamide **3a** is observed by ^{13}C NMR in the presence of iodine chloride at 0 °C in CD_2Cl_2 as witnessed by the disappearance of the peak at 25.8 ppm and concomitant appearance of a peak at 38.8 ppm, corresponding to the C-2 resonance of the α and β isomers, respectively (Fig. 1). In contrast, β-isomer **3b** remains stable under these conditions while neither compound isomerises in the presence of NIS/I_2 (not shown). These observations are fully consistent with the proposed reactive pathway a. However, pathway b can not be totally ruled out. Indeed, ESI-MS monitoring of the reaction reveals the presence of isotopic profiles characteristic of chloro-derivatives, whose mass unit could be assigned to iodo-chloro sugars. Formation of these intermediates was further evidenced upon monitoring the ICl-promoted sulfonamidation of **6** by ^{13}C NMR (Fig. 2). Glucal **6** (Fig. 2a) is consumed soon after the addition of ICl to a mixture of the former compound and $SESNH_2$ in $CDCl_3$ (Fig. 2b), to give a mixture of at least three different compounds which were identified on the basis of their respective C-1 and C-2 chemical shifts.

In particular, chemical shifts at 79.8 and 37.4 ppm were assigned to the C-1 and C-2 signals of the 2-iodo-1-sulfonamido-β-*manno* derivative **8b**. These attributions were further ascertained by comparison with the ^{13}C NMR spectra of pure **8b** (Fig. 2c) and pure **8c** (Fig. 2d). Chemical shifts at 93.9 and 92.1 as well as 26.5 and 31.4 ppm were assigned to the resonances of C-1 and C-2 of the corresponding α-1-chloro (**α-D** form) and β-1-chloro (**β-D** form), respectively (Fig. 2b). The attribution was deduced from



Scheme 3. Tentative mechanism of formation of iodosulfonamide.

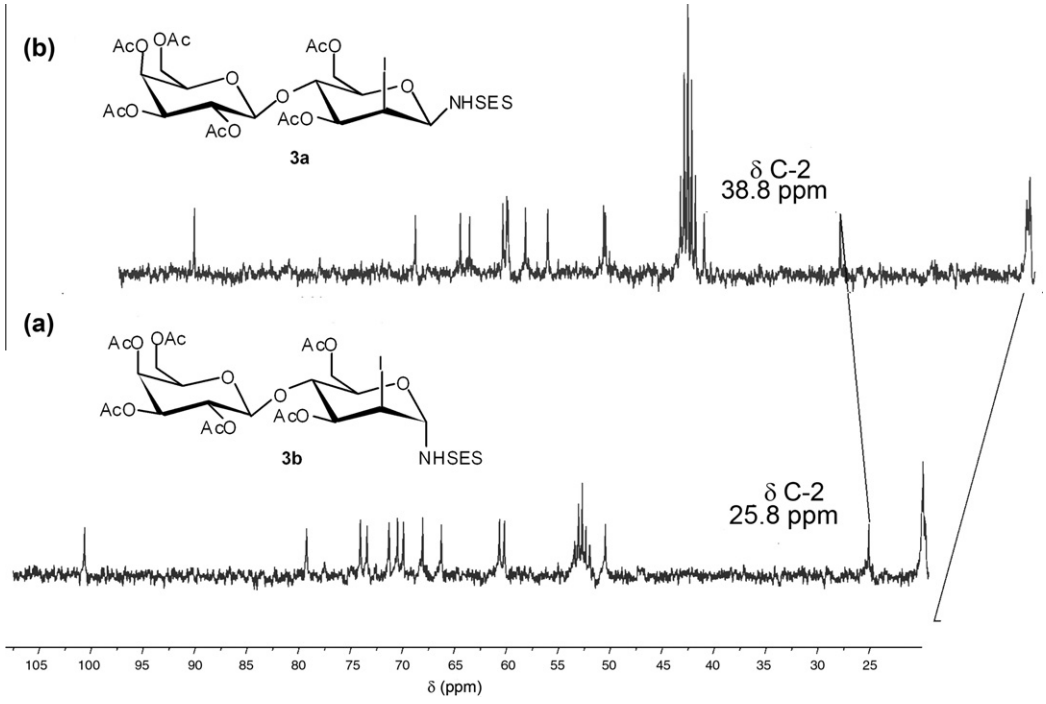


Figure 1. Facile isomerisation of **3a** into **3b**: ^{13}C NMR (75.5 MHz) spectra of compound **3a** in CD_2Cl_2 at 0 °C (a) in the absence or (b) after 5 min in the contact of 2 equiv ICl.

the crude ^{13}C NMR spectra of ICl addition onto **6** in the absence of the sulfonamide (Fig. 2e) since neither the α-**D** nor the β-**D** form was isolated by flash-chromatography purification. The H-1 resonances, at 6.48 and 6.28 ppm, strongly support the presence of a chlorine at the anomeric center. Moreover, these chemical shifts significantly differ from those reported for the known 3,4,6-tri-*O*-acetyl-2-iodo-D-mannopyranose[42] or for 1-iodo-glycopyranosides, usually observed near 7 ppm.[30] Remarkably, formation of compound **8b** is observed even if the sulfonamide is not initially present in the NMR tube but added after the formation of the

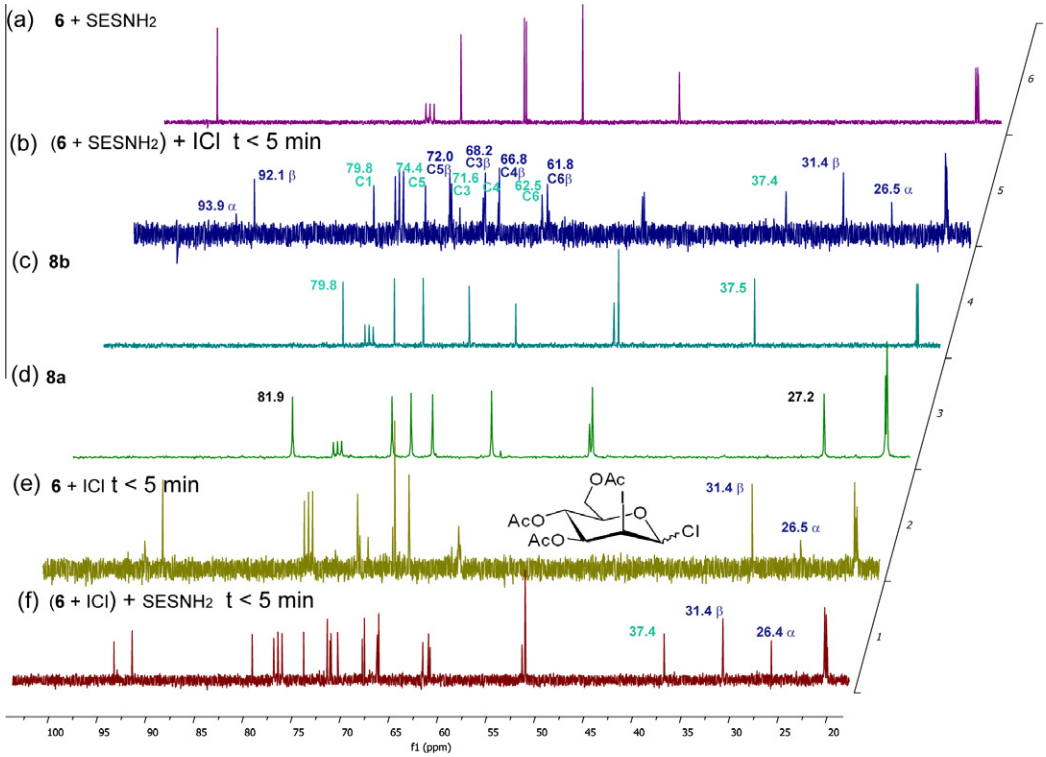


Figure 2. ^{13}C NMR monitoring of the ICl-promoted iodosulfonamidation of a 2 mM solution of tri-2,3,4-*O*-acetyl-D-glucal **6** in $CDCl_3$ at 0 °C: (a) spectrum of glycal **6**; (b) crude spectrum of a mixture of **6** and $SESNH_2$ (1 equiv), followed by addition of ICl (2 equiv); (c) spectrum of pure iodosulfonamide **8b**; (d) spectrum of pure iodosulfonamide **8a**; (e) crude spectrum of **6** in the presence of ICl (2 equiv); (f) crude spectrum of a mixture of **6** and ICl (2 equiv), followed by addition of $SESNH_2$ (1 equiv).

iodo-glycosyl chloride mixture, probing the labile character of the C–Cl bond at the anomeric centre and beyond, possible progression of the reaction through pathway b under these experimental conditions (Fig. 2f). Compound **8a** was not detected in any of these experiments which is in agreement with the propensity of the α isomer to isomerise rapidly (see above). The iodooxonium **B**, invoked as a plausible intermediate, was not detected either certainly as a consequence of its very high reactivity. A peak which could be assigned to this intermediate was observed during the monitoring of the iodosulfonamidation of compound **6** but its presence might simply reflect the commonly observed fragmentation of fragile anomeric bonds.

After 24 h at 0 °C, **8b** (major) and the β-**D** form are the two main sugars detected in the reaction mixture. The latter was not isolated during chromatography purification but might account for the presence of hydrolysed products. For comparison, activation of thioglycosides with iodine chloride also gives rise to kinetic β-glycosyl chlorides, which slowly isomerise to the thermodynamic α-linked products when the reaction mixture is warmed to rt. Iodine bromine leads exclusively to the thermodynamically favoured α-glycosyl bromides.[30] Though not tested, this latter reagent would certainly give rise to the *trans* α-2-iodo-1-bromide derivatives, ultimately leading to the formation of the β-*cis* products.

To further explore the scope of the NIS/I_2 procedure, the reaction was also applied to an acid-sensitive 6-deoxy sugar, the 3,4-di-*O*-acetyl-D-rhamnal **10**, and a strongly deactivated, perbenzoylated glycal, the 3,4,6-tri-*O*-benzoyl-D-glucal **11** (Scheme 4).

To our delight, their corresponding α-iodosulfonamides **12** and **14** were isolated in 65% and 46% (together with 30% starting material for the latter reaction) yield, respectively. Synthesis of **12** was accompanied by the formation of the *N*-(3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-α-L-mannopyranosyl) succinimide (**13**) (15%) as a by-product, but no trace of the β-isomer was detected in either of the two crude mixtures.

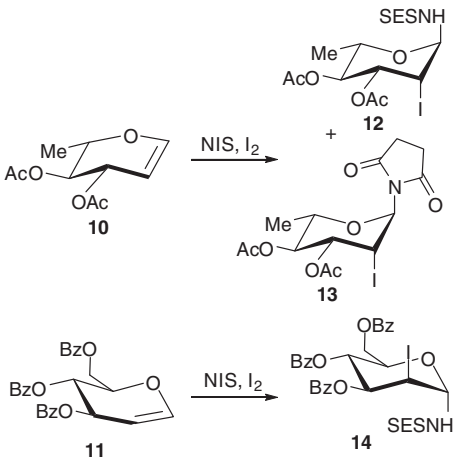
With this series of representative iodosulfonamides in hands, we next envisaged the azidolysis reaction. As expected, all α-*trans*-iodosulfonamides were converted to the corresponding β-*trans*-1-azido-1,2-dideoxy-2-sulfonamides in high yields upon treatment with sodium azide in DMF at rt (Table 3) whereas the β-*cis*-iodosulfonamides were totally unreactive under the same experimental conditions.

However, surprisingly, simple heating of the reaction mixtures at 40 °C afforded the β-*trans*-1-azido-1,2-dideoxy-2-sulfonamides in about 50% isolated yields (Table 3, entries 2 and 4). These results suggest the possible formation of an iminium/α-iodo-stabilised carbocation intermediate,[38,39] with concomitant endocyclic C–O bond cleavage,[43] rotation around the N–C_1 bond and cyclisation to provide the *trans*-diaxial-isomer which is required to promote the formation of the postulated aziridine intermediate. Finally, derivatives **12** and **14** were also transformed into their corresponding azides **17** and **18** in 88% and 82% yields, respectively.

Interestingly, the transformation was not limited to azide as a source of nucleophilic nitrogen but was also efficiently carried out using potassium phthalimide (54% yield). Even the β-*cis*-isomer **8b** was able to give the expected 1-phthalimido derivative **19**, showing that the epimerisation could occur in various conditions (Table 3, entries 7 and 8). Finally, treatment of iodosulfonamide **8a** with the 5-*tert*-butyl-2-methylthiophenol under Danishefsky's conditions[22] gave the 2-sulfonamido thioglycoside **20** in 77% yield. Such derivatives are key intermediates for the synthesis of complex oligosaccharides from glycals.[23,44]

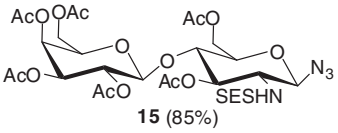
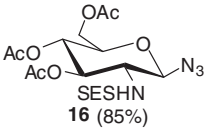
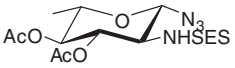
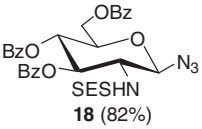
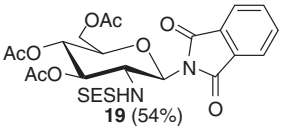
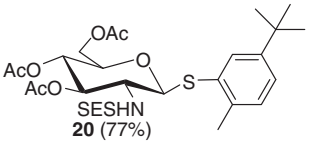
3. Conclusions

In conclusion, we have developed two reagent systems for the preparation of 2-iodo-1-sulfonamido sugars from peresterified glycals. In particular, the use of a combination of NIS/I_2 prevents the anomerisation of the products which is usually associated with the iodosulfonamidation reaction, thus increasing the scope of this methodology. Moreover, we have shown that even the hitherto unreactive β-*cis*-iodosulfonamides could be transformed into



Scheme 4. Extension of the NIS/I_2-promoted iodosulfonamidation.

Table 3
Iodine displacement using various nucleophiles[a]

Entry	Glycal	Conditions[a]	Product (yield)
1	**3a**	NaN_3[b]	 **15** (85%)
2	**3b**	NaN_3[c]	**15** (45%)
3	**8a**	NaN_3[b]	 **16** (85%)
4	**8b**	NaN_3[c]	**16** (48%)
5	**12**	NaN_3[b]	 **17** (88%)
6	**14**	NaN_3[b]	 **18** (82%)
7	**8a**	KPhthal.[d]	 **19** (54%)
8	**8b**	KPhthal.[c]	**19** (27%)
9	**8a**	ArSH[e]	 **20** (77%)

[a] All reactions were carried out in DMF.
[b] 2 equiv, rt, 2 h.
[c] 2 equiv, 40 °C, 2 h.
[d] 2 equiv, −30 °C to rt, 2 h.
[e] 1.4 equiv, LHMDS (1.2 equiv), −30 to −20 °C, 30 min.

valuable intermediates when treated with sodium azide. Finally, we have established a novel access to 1,2-*bis*-nitrogenated sugars.

4. Experimental methods

4.1. General methods

All reactions were monitored by TLC on Kieselgel 60 F254 (E. Merck). Detection was achieved by charring with vanillin. Silica gel (E. Merck, 240–400 mesh) was used for chromatography. Optical rotations were measured with a JASCO DIP-370 digital polarimeter, using a sodium lamp (λ = 589 nm) at 20 °C. All NMR experiments were performed at 300.13 MHz using a Bruker DMX300 spectrometer equipped with a *Z*-gradient unit for pulsed-field gradient spectroscopy. Assignments were performed by stepwise identification using COSY and HSQC experiments using standard pulse programmes from the Bruker library. Chemical shifts are given relative to external TMS with calibration involving the residual solvent signals.

Low-resolution ESI mass spectra were obtained on a hybrid quadrupole/time-of-flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass). High-resolution mass spectra were recorded in positive mode on a ZabSpec TOF (Micromass, UK) tandem hybrid mass spectrometer with EBETOF geometry. The compounds were individually dissolved in MeOH at a concentration of 10 μg mL^{-1} and then infused into the electrospray ion source at a flow rate of 10 μL min^{-1} at 60 °C. The mass spectrometer was operated at 4 kV whilst scanning the magnet at a typical range of 4000–100 Da. The mass spectra were collected as continuum profile data. Accurate mass measurement was achieved using polyethylene glycol as an internal reference with a resolving power set to a minimum of 10,000 (10% valley).

4.2. 6-*O*-Acetyl-1,2,3-tri-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-[2-(trimethylsilyl)ethanesulfonamido]-α-D-erythro-hex-2-enopyranose (2)

To a suspension of hexa-*O*-acetyl-D-lactal (1 g, 1.8 mmol), 2-(trimethylsilyl)ethanesulfonamide (333 mg, 1.8 mmol) and 4 Å molecular sieves in dry CH_3CN (5 mL) was added solid NIS (403 mg, 1.8 mmol) at −10 °C and the mixture was stirred at this temperature for 30 min. The crude reaction mixture was then filtered and diluted with CH_2Cl_2. The filtrate was washed with satd aq $Na_2S_2O_3$, and brine, dried ($Na_2S_2O_4$), filtered and concentrated under reduced pressure. Flash-chromatography purification (eluent: ethyl acetate/cyclohexane 4:6) of the resulting residue provided the Ferrier's rearranged product **2** (760 mg, 82%).

Alternatively, to a suspension of hexa-*O*-acetyl-D-lactal (1 g, 1.8 mmol), 2-(trimethylsilyl)ethanesulfonamide (333 g, 1.8 mmol) and 4 Å molecular sieves in dry CH_2Cl_2 (5 mL) was added I_2 (450 mg, 1.8 mmol) at −10 °C and the mixture was stirred at this temperature for 30 min. Compound **2** (788 mg, 85%) was obtained following work-up carried as described above; TLC: R_f 0.56 (ethyl acetate/cyclohexane 1:1); $[\alpha]_D$ + 51 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 6.20 (br d, 1H, $J_{2,3}$ = 10.2 Hz, H-3), 5.82 (br d, 1H, $J_{NH,1}$ = 9.1 Hz, NH), 5.77 (ddd, 1H, *J* = 2.7 Hz, *J* = 1.9 Hz, H-2), 5.53–5.45 (m, 1H, H-1), 5.39 (dd, 1H, $J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 0.5 Hz, H-4′), 5.18 (dd, 1H, $J_{1',2'}$ = 7.8 Hz, $J_{2',3'}$ = 10.4 Hz, H-2′), 5.03 (dd, 1H, H-3′), 4.59 (d, 1H, H-1′), 4.26 (dd, 1H, $J_{5,6}$ = 3.8 Hz, $J_{6,6}$ 12 Hz, H-6), 4.20–3.81 (m, 5H, H-2, H-5, H-6, H-6′, H-6′), 3.96 (br t, 1H, $J_{5,6}$ = 6.5 Hz, H-5′), 3.85–3.80 (m, 1H, H-4), 3.16–2.96 (m, 2H, CH_2), 2.16 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.16–0.95 (m, 2H, CH_2), 0.07 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ_C 171.6 (CO), 170.5 (CO), 170.2 (CO), 170.1(CO), 169.6 (CO), 132.5 (C-3), 126.0 (C-2), 102.4 (C-1′), 76.9 (C-1), 72.3 (C-5), 70.8 and 70.7 (C-3′ and C-5′), 68.9 (C-2′), 68.0 (C-4), 66.9 (C-4′), 62.5 and 61.3 (C-6 and C-6′), 51.3 (CH_2), 20.9, 20.7 ($2CH_3$), 20.5, 10.1 (CH_2), −1.91 ($3CH_3$); HR-ESIMS *m/z* calcd for $[C_{27}H_{43}NO_{15}SSi]Na^+$ 704.2020, found 704.2000.

4.3. 3,6-Di-*O*-acetyl-1,2-dideoxy-2-iodo-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-[2-(trimethylsilyl) ethanesulfonamido]-α-D-mannopyranose (3a)

To a −10 °C stirred suspension of hexa-*O*-acetyl-D-lactal (6 g, 10.7 mmol), 2-(trimethylsilyl)ethanesulfonamide (2 g, 10.7 mmol) and 4 Å molecular sieves in dry CH_2Cl_2 (30 mL) was added solid NIS (2.42 g, 10.7 mmol) followed by I_2 (2.70 g, 10.7 mmol) 2 h later. The reaction mixture was allowed to warm to 5 °C overnight. The mixture was then filtered and diluted with CH_2Cl_2. The filtrate was washed with satd aq $Na_2S_2O_3$, and brine, dried ($Na_2S_2O_4$), filtered and concentrated under reduced pressure. Iodosulfonamide **3a** (6.20 g, 65%) was obtained following flash-chromatography purification (eluent: ethyl acetate/cyclohexane 4:6); TLC: R_f 0.68 (ethyl acetate/cyclohexane 6:4); $[\alpha]_D$ +6.3 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 6.10 (d, 1H, $J_{NH,1}$ = 9.6 Hz, NH), 5.40 (br d, 1H, $J_{3',4'}$ = 2.6 Hz, H-4′), 5.31 (dd, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 5.22 (br t, 1H, $J_{3,4}$ = 4.8 Hz, H-3), 5.17 (dd, 1H, $J_{1',2'}$ = 7.8 Hz, $J_{2',3'}$ = 10.5 Hz, H-2′), 5.03 (dd, $J_{3',4'}$ = 3.4 Hz, H-3′), 4.58 (d, 1H, H-1′), 4.49 (dd, 1H, $J_{2,3}$ = 1.3 Hz, H-2), 4.32–4.30 (m, 2H, H-6, H-6), 4.20–4.06 (m, 3H, H-6′, H6′, H-5), 3.91 (br t, 1H, *J* = 6.9 Hz, H-5′), 3.81 (t, 1H, $J_{4,5}$ = 4.8 Hz, H-4), 3.12–3.03 (m, 2H, CH_2), 2.19 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.07 (s, 6H, $2CH_3$), 2.00 (s, 3H, CH_3), 1.14–1.03 (m, 2H, CH_2), 0.07 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ_C (75 MHz, $CDCl_3$) 170.6 (CO), 170.5 (CO), 170.2(CO), 170.1 (CO), 169.7(CO), 169.4(CO), 101.2 (C-1′), 80.7 (C-1), 75.0 (C-4), 73.1 (C-5), 71.7 (C-3), 71.1 (C-5′), 70.6 (C-3′), 68.9 (C-2′), 66.9 (C-4′), 61.2 (C-6 and C-6′), 51.2 (CH_2), 26.0 (C-2), 20.9 (CH_3), 20.8 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 20.5 (CH_3), 10.3 (CH_2), −1.92 ($3CH_3$); HR-ESIMS *m/z* calcd for $[C_{29}H_{46}INO_{17}SSi]Na^+$ 890.1198, found 890.1211.

4.4. 3,6-Di-*O*-acetyl-1,2-dideoxy-2-iodo-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-[2-(trimethylsilyl) ethanesulfonamido]-β-D-mannopyranose (3b)

Hexa-*O*-acetyl-D-lactal (1 mmol, 560 mg), 2-trimethylsilylethanesulfonamide (1 mmol, 182 mg), 4 Å MS (1 g) and CH_2Cl_2 (5 mL) were introduced into a 50 cm^3 2-necked flask and cooled down to −10 °C. Iodine chloride (2 mmol, 100 μL) was dissolved in CH_2Cl_2 and added to the mixture. The mixture was stirred for 2.5 h at −10 °C, warmed up to rt, diluted in CH_2Cl_2 (50 mL) and washed with satd aq $Na_2S_2O_3$ (50 mL), satd aq $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was dried (Na_2SO_4) and evaporated. Flash chromatography of the crude material (ethyl acetate/cyclohexane 1:1) afforded the compound **3b** (435 mg, 50%) as a white powder; TLC: R_f 0.50 (ethyl acetate/cyclohexane 1:1); $[\alpha]_D$ −9.2 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 5.42 (d, 1H, $J_{NH,1}$ = 10.3 Hz, NH), 5.37 (dd, 1H, $J_{3',4'}$ = 3.3 Hz, $J_{4',5'}$ = 0.7 Hz, H-4′), 5.13 (dd, 1H, $J_{1',2'}$ = 7.9 Hz, $J_{2',3'}$ = 10.5 Hz, H-2′), 5.02 (dd, 1H, H-3′), 4.76 (dd, 1H, $J_{1,2}$ = 1.3 Hz, $J_{2,3}$ = 4.2 Hz, H-2), 4.61–4.56 (m, 2H, H-1′, H-6′), 4.47 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 4.21–3.91 (m, 6H, H-1, H-4, H-6, H-6, H-5′, H-6′), 3.67 (m, 1H, H-5), 3.11–3.06 (m, 2H, CH_2), 2.16 (s, 6H, $2CH_3$), 2.12 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.07–1.02 (m, 2H, CH_2), 0.08 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ_C (75 MHz, $CDCl_3$) 170.5 (CO), 170.2 (CO), 170.1 (CO), 170.0 (CO), 169.3 (CO), 169.2 (CO), 101.1 (C-1′), 79.6 (C-1), 75.3 (C-5), 74.5 (C-5′), 71.6 (C-3), 70.9 (C-3′), 70.7 (C-4), 69.2 (C-2′), 66.8 (C-4′), 61.5 (C-6′), 61.2 (C-6), 51.9 (CH_2), 38.8 (C-2), 20.9 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.6 ($2CH_3$), 10.2 (CH_2),

−2.0 (3CH_3). HR-ESIMS *m/z* calcd for $[C_{29}H_{46}INO_{17}SSi]Na^+$ 890.1198, found 890.1174.

4.5. 3,6-Di-*O*-acetyl-2-deoxy-2-iodo-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-D-mannose (4)

Selected data for the major β-isomer: TLC: R_f 0.24 (ethyl acetate/cyclohexane 1:1; ^1H NMR ($CDCl_3$): δ_H 5.52 (br s, 1H, H-1′), 5.36 (dd, 1H, $J_{3',4'}$ = 3.3 Hz, $J_{4',5'}$ = 0.8 Hz, H-4′), 5.13 (dd, 1H, $J_{1',2'}$ = 7.8 Hz, $J_{2',3'}$ = 10.5 Hz, H-2′), 5.01 (dd, 1H, H-3′), 4.79 (dd, 1H, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 8.3 Hz, H-3), 4.62 (d, 1H, H-1′), 4.55 (dd, 1H, $J_{1,2}$ = 2.0 Hz, H-2), 4.52–4.44 (m, 1H, H-6eq), 4.21–3.92 (m, 6H, H-4, H-5, H-5′, H-6′, H-6, H-6′), 2.17 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 1.98 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ_C 170.7 (CO), 170.5 (CO), 170.3 (CO), 170.1 (CO), 169.6 (CO), 169.4 (CO), 101.3 (C-1′), 95.5 (C-1), 75.8 (C-4), 71.0 (C-3′), 70.7 (C-5′), 69.7 (C-5), 69.5 (C-3), 69.2 (C-2′), 66.9 (C-4′), 62.1 and 61.2 (C-6 and C-6′), 31.1 (C-2), 21.1 (CH_3), 21.0 (CH_3), 20.7 (CH_3), 20.6 (2CH_3), 20.5; HR-ESIMS *m/z* calcd for $[C_{24}H_{33}NIO_{16}]Na^+$ 727.0711, found 727.0737.

4.6. *N*-[3,6-Di-*O*-acetyl-2-deoxy-2-iodo-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-mannopyranosyl] succinimide (5)

TLC: R_f 0.11 (ethyl acetate/cyclohexane 1:1); $[\alpha]_D$ +7.8 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 5.80 (d, 1H, $J_{1,2}$ = 10.5 Hz, H-1), 5.69 (m, 1H, H-3), 5.62 (dd, 1H, $J_{2,3}$ = 2.6 Hz, H-2), 5.40 (dd, 1H, $J_{3',4'}$ = 3.4 Hz, $J_{4',5'}$ = 0.9 Hz, H-4′), 5.22 (dd, 1H, $J_{1',2'}$ = 7.9 Hz, $J_{2',3'}$ = 10.3 Hz, H-2′), 5.02 (dd, 1H, H-3′), 4.69 (d, 1H, H-1′), 4.52–4.42 (m, 1H, H-6), 4.24 (dd, 1H, $J_{5',6'}$ = 3.5, $J_{6',6'}$ = 12.2 Hz, H-6′), 4.21–4.09 (m, 3H, H-5, H-6, H-6′), 4.02 (dt, $J_{5',6'}$ = 6.9 Hz, H-5′), 3.75 (dd, 1H, $J_{3,4}$ = 1.5 Hz, $J_{4,5}$ = 6.4 Hz, H-4), 2.77 (br s, 4H, 2CH_2), 2.20 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.04 (s, 6H, 2CH_3), 1.98 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ_C 176.2 (2CO), 170.6 (CO), 170.5 (CO), 170.3 (CO), 170.1 (CO), 169.6 (CO), 169.3 (CO), 101.6 (C-1′), 77.5 (C-1), 77.1 (C-4), 74.0 (C-3), 73.3 (C-5), 71.2 and 70.8 (C-5 and C-3′), 68.7 (C-2′), 67.3 (C-4′), 62.0 (C-6′), 61.3 (C-6), 28.0 (2CH_2), 20.9, 20.7 (2CH_3), 20.6, 20.5 (2CH_3), 18.6 (C-2); HR-ESIMS *m/z* calcd for $[C_{28}H_{36}NIO_{17}]Na^+$ 808.0926, found 808.0907.

4.7. 3,4,6-Tri-*O*-acetyl-1,2-dideoxy-2-iodo-1-[2-(trimethylsilyl) ethanesulfonamido]-α-D-mannopyranose (8a)

To a stirred suspension of tri-*O*-acetyl-D-glucal (1 g, 3.7 mmol), 2-(trimethylsilyl)ethanesulfonamide (731 mg, 4.04 mmol) and 4 Å molecular sieves in dry CH_2Cl_2 (5 mL) was added solid NIS (826 g, 3.7 mmol) followed by I_2 (922 g, 3.7 mmol) 2 h later. The reaction mixture was kept under stirring at −10 °C overnight. The mixture was then filtered and diluted with CH_2Cl_2. The filtrate was washed with satd aq $Na_2S_2O_3$, and brine, dried ($Na_2S_2O_4$), filtered and concentrated under reduced pressure. Iodosulfonamide **8a** (1.38 g, 65%) was obtained following flash-chromatography purification (eluent: ethyl acetate/cyclohexane 3:7); TLC: R_f 0.5 (ethyl acetate/cyclohexane 4:6); $[\alpha]_D$ −1 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 6.68 (d, 1H, $J_{N,H1}$ = 8.9 Hz, NH), 5.28 (dd, 1H, $J_{1,2}$ = 4.8 Hz, H-1), 5.01 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 6.7 Hz, H-4), 4.69 (dd, 1H, $J_{2,3}$ = 3.7 Hz, H-3), 4.40 (dd, 1H, H-2), 4.22 (dd, 1H, $J_{5,6}$ = 6.6 Hz, $J_{6,6}$ = 13.1 Hz, H-6), 4.05–3.93 (m, 2H, H-5 and H-6′), 2.95–2.88 (m, 2H, CH_2), 1.98 (s, 3H, CH_3), 1.94 (s, 6H, 2CH_3), 0.96–0.85 (m, 2H, CH_2), −0.10 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$): δ_C 170.6 (CO), 169.7 (CO), 169.5 (CO), 81.9 (C-1), 71.6, 69.7 and 67.5 (C-3, C-4 and C-5), 61.4 (C-6), 51.0 (CH_2), 27.2 (C-2), 20.9 (CH_3), 20.7 (2CH_3), 10.1 (CH_2), −1.93 (3CH_3); HR-ESIMS *m/z* calcd for $[C_{17}H_{30}INO_9SSi]Na^+$ 602.0353, found 602.0326.

4.8. 3,4,6-Tri-*O*-acetyl-1,2-dideoxy-2-iodo-1-[2-(trimethylsilyl) ethanesulfonamido]-β-D-mannopyranose (8b)

3,4,6-Tri-*O*-acetyl-D-glucal (545 mg, 2 mmol), 2-trimethylsilylethanesulfonamide (380 mg, 2 mmol) and 4 Å MS (1 g) were dried under vacuum for 1 h and dissolved in dry CH_2Cl_2 (5 mL). The mixture was cooled down to −10 °C, iodine monochloride was added, the mixture was stirred for 2 h at −10 °C, warmed up to rt and stirred overnight. The mixture was diluted with CH_2Cl_2 (100 mL), washed with satd aq sodium thiosulfate (30 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4) and concentrated under vacuum. Compound **8b** (526 mg, 45%). was isolated following flash chromatography purification (eluent: ethyl acetate/cyclohexane 3:7) as a thick oil; TLC R_f 0.59 (ethyl acetate/cyclohexane 1:1); $[\alpha]_D$ −3.1 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 5.55 (d, 1H, $J_{NH,1}$ = 10.5 Hz, NH), 5.31 (t, 1H, $J_{3,4}$ = $J_{4,5}$ 9.5 Hz, H-4), 4.77 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 4.2 Hz, H-2), 4.49 (dd, 1H, H-3), 4.25–4.19 (m, 2H, H-1 and H-6), 4.09 (dd, 1H, $J_{5,6}$ = 4.9 Hz, $J_{6,6'}$ 12.4 Hz, H-6′), 3.66–3.71 (m, 1H, H-5), 3.15–3.02 (m, 2H, CH_2), 2.11 (s, 3 H, CH_3), 2.09 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.11–1.03 (m, 2H, CH_2), −0.07 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$): δ_C 171.7, 170.7, 169.2, 79.8 (C-1), 74.5 (C-5), 71.6 (C-3), 66.8 (C-4), 62.0 (C-6), 51.9 (CH_2), 37.5 (C-2), 20.9, 20.8, 20.7, 10.3 (CH_2), −2.0 (3CH_3); HR-ESIMS *m/z* calcd for $[C_{17}H_{30}INO_9SSi]Na^+$ 602.0353, found 602.0361.

4.9. 1,2-Dideoxy-2-iodo-3,4,6-tri-*O*-acetyl-1-[2-(trimethylsilyl) ethanesulfonamido]-α-D-talopyranose (9a)

Compound **9a** (715 mg, 61%) was prepared as described for compound **8a**. TLC: R_f 0.53 (ethyl acetate/cyclohexane 4:6); $[\alpha]_D$ −6.7 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 6.38 (d, 1H, $J_{N,H1}$ = 10.0 Hz, NH), 5.50 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 3.2 Hz, H-3), 5.30 (dd, 1H, $J_{4,5}$ = 5.9 Hz, H-4), 5.23 (br t, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 4.57 (dd, 1H, $J_{5,6}$ = 9.1 Hz, $J_{6,6'}$ = 12.2 Hz, H-6), 4.41–4.26 (m, 3H, H-2, H-5 and H-6′), 3.14–3.05 (m, 2H, CH_2), 2.20 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.10–1.02 (m, 2H, CH_2), 0.06 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$): δ_C 170.7 (CO), 169.7 (CO), 169.5 (CO), 78.9 (C-1), 72.1 (C-5), 69.9 (C-3), 66.2 (C-4), 60.1 (C-6), 51.0 (CH_2), 24.7 (C-2), 21.0 (CH_3), 20.9 (CH_3), 20.7 (CH_3), 10.3 (CH_2), −1.94 (3CH_3); HR-ESIMS *m/z* calcd for $[C_{17}H_{30}INO_9SSi]Na^+$ 602.0353, found 602.0323.

4.10. 3,4,6-Tri-*O*-acetyl-1,2-dideoxy-2-iodo-1-[2-(trimethylsilyl) ethanesulfonamido]-β-D-talopyranose (9b) and 3,4,6-tri-*O*-acetyl-1,2-dideoxy-2-iodo-1-[2-(trimethylsilyl) ethanesulfonamido]-β-D-glucopyranose (9c)

Compounds **9b** and **9c** have been obtained as a mixture together with compound **9a** (see Supplementary data). Chemical shift attribution has been carried out from the NMR spectra of the mixture and comparison with the spectra of pure **9a** (see Section 4.9).

Compound **9b**: ^1H NMR ($CDCl_3$): δ_H 5.67 (d, 1H, $J_{N,H1}$ = 10.5 Hz, NH), 5.35 (br d, 1H, $J_{3,4}$ = 3.7 Hz, H-4), 4.85 (dd, 1H, $J_{2,3}$ = 4.1 Hz, H-3), 4.55 (br dd, $J_{1,2}$ = 2.0 Hz, H-2), 4.36–4.29 (m, H-6eq), 4.27–4.22 (m, H-6ax), 4.22 (dd, 1H, H-1), 4.10–3.98 (m, 1H, H-5), 3.16–3.03 (m, 2H, CH_2), 2.22 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 1.13–1.04 (m, 2H, CH_2), 0.09 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$): δ_C 170.7, 169.5, 169.3, 80.6 (C-1), 73.7 (C-5), 68.0 (C-3), 64.2 (C-4), 61.7 (C-6), 52.1 (CH_2), 29.7 (C-2), 21.0, 20.9, 20.7, 10.3 (CH_2), −1.94 (3CH_3);

Compound **9c**: ^1H NMR ($CDCl_3$): δ_H 5.75 (d, 1H, d, 1H, $J_{N,H1}$ = 9.9 Hz, NH), 5.25 (dd, 1H, $J_{3,4}$ = 3.2 Hz, $J_{4,5}$ = 0.8 Hz, H-4), 5.19 (dd, 1H, $J_{2,3}$ = 11.3 Hz, H-3), 4.99 (t, 1H, $J_{1,2}$ = 9.9 Hz, H-1), 4.18 (dd, 1H, $J_{5,6}$ = 4.7 Hz, $J_{6,6}$ = 9.3 Hz, H-6), 4.09–4.01 (m, 3H, H-2, H-5 and H-6), 3.16–3.09 (m, 2H, CH_2), 2.16 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 1.13–1.09 (m, 2H, CH_2), 0.07 (s,

9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ_C (75 MHz, $CDCl_3$) 170.4 (CO), 169.9 (CO), 169.3 (CO), 85.7 (C-1), 74.4 (C-3), 72.7 (C-5), 67.0 (C-4), 61.4 (C-6), 51.7 (CH_2), 26.3 (C-2), 20.7 (CH_3), 20.6 ($2CH_3$), 10.4 (CH_2), −1.9 ($3CH_3$); ESI-MS *m/z* $[C_{17}H_{30}INO_9SSi]Na^+$ 602.

4.11. 3,4-Di-*O*-acetyl-2-iodo-1,2,6-tri-deoxy-1-[2-(trimethylsilyl) ethanesulfonamido]-α-L-mannopyranose (12) and *N*-[3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-α-L-mannopyranosyl] succinimide (13)

To a stirred suspension of di-*O*-acetyl-L-glucal (300 mg, 1.40 mmol), 2-(trimethylsilyl)ethanesulfonamide (254 mg, 1.40 mmol) and 4 Å molecular sieves in dry CH_2Cl_2 (6 mL) was added solid NIS (312 mg, 0.66 mmol) followed by I_2 (355 mg, 1.40 mmol) 1 h later. The reaction mixture was stirred at −10 °C for 2 h. The mixture was then filtered and diluted with CH_2Cl_2. The filtrate was washed with satd aq $Na_2S_2O_3$, and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified by flash-chromatography (eluent: ethyl acetate/cyclohexane 2.5:7.5) to give the iodosulfonamide **12** (475 mg, 65%) and then the succinimidyl adduct **13** (92 mg, 15%);

Compound **12**: TLC: R_f 0.38 (ethyl acetate/cyclohexane 3:7); $[\alpha]_D$ +0.6 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 6.54 (d, 1H, $J_{N,H1}$ = 9.0 Hz, NH), 5.45 (dd, 1H, $J_{1,2}$ = 4.4 Hz, H-1), 5.01 (t, 1H, $J_{3,4} = J_{4,5}$ = 7.3 Hz, H-4), 4.72 (dd, 1H, $J_{2,3}$ = 4.4 Hz, H-3), 4.53 (t, 1H, H-2), 4.06 (dt, 1H, $J_{5,6}$ = 6.6 Hz, H-5), 3.16–2.98 (m, 2H, CH_2), 2.15 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 1.34 (d, 3H, H-6), 1.15–0.98 (m, 2H, CH_2), 0.07 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ_C (75 MHz, $CDCl_3$) 169.9 (CO), 169.7 (CO), 81.9 (C-1), 71.8 (C-4), 70.0 (C-3), 69.6 (C-5), 62.1 (C-6), 51.2 (CH_2), 27.9 (C-2), 21.0 (CH_3), 20.9 (CH_3), 17.0 (C-6), 10.1 (CH_2), −1.93 ($3CH_3$); HR-ESI-MS calcd for $C_{15}H_{28}INO_7SSi$ $(M+Na)^+$ 544.0298, found 544.0281.

Compound **13**: TLC: R_f 0.20 (ethyl acetate/cyclohexane 3:7); $[\alpha]_D$ +2 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H (300 MHz, $CDCl_3$) 5.75 (d, 1H, $J_{1,2}$ = 10.5 Hz, H-1), 5.64 (dd, 1H, $J_{2,3}$ = 3.1 Hz, H-2), 5.31 (br t, 1H, H-3), 4.65 (t, 1H, $J_{3,4} = J_{4,5}$ = 2.6 Hz H-4), 4.28 (dt, 1H, $J_{5,6}$ = 8.2 Hz, H-5), 2.67 (br s, 4H, $2CH_2$), 2.18 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 1.42 (d, 3H, H-6); ^{13}C NMR ($CDCl_3$): δ_C 176.2 (2CO), 169.6 (CO), 168.9 (CO), 74.4 (C-1), 73.2 (C-5), 72.1 (C-3), 71.0 (C-4), 27.9 ($2CH_2$), 22.0 (C-2), 21.0 (CH_3), 20.9 (CH_3), 15.8 (C-6); HR-ESIMS *m/z* calcd for $[C_{14}H_{18}INO_7]Na^+$ 462.0026, found 462.0027.

4.12. 3,4,6-Tri-*O*-benzoyl-1,2-dideoxy-2-iodo-1-[2-(trimethylsilyl)ethanesulfonamido]-α-D-mannopyranose (14)

To a stirred suspension of tri-*O*-benzoyl-D-glucal (300 mg, 0.66 mmol), 2-(trimethylsilyl)ethanesulfonamide (118 mg, 0.66 mmol) and 4 Å molecular sieves in dry CH_2Cl_2 (6 mL) was added solid NIS (147 mg, 0.66 mmol) followed by I_2 (167 mg, 0.66 mmol) 2 h later. The reaction mixture was warmed to 0 °C over 2 h. The mixture was then filtered and diluted with CH_2Cl_2. The filtrate was washed with satd aq $Na_2S_2O_3$, and brine, dried ($Na_2S_2O_4$), filtered and concentrated under reduced pressure. The crude residue was purified by flash-chromatography (eluent: ethyl acetate/cyclohexane 2.5:7.5) to give unreacted glucal (91 mg, 30%) and then iodosulfonamide **14** (230 mg, 46%); TLC: R_f 0.5 (ethyl acetate/cyclohexane 3:7); $[\alpha]_D$ +21.2 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 8.09–7.95, 7.62–7.52 and 7.47–7.35 (m, 15H, H arom), 6.35 (d, 1H, $J_{N,H1}$ = 8.1 Hz, NH), 5.90 (t, 1H, $J_{3,4} = J_{4,5}$ = 7.5 Hz, H-4), 5.74 (dd, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 5.20 (dd, 1H, $J_{2,3}$ = 4.0 Hz, H-3), 4.82 (t, 1H, H-2), 4.75–4.68 (m, 1H, H-6), 4.62–4.52 (m, 2H, H-5 and H-6), 3.19–3.11 (m, 2H, CH_2), 1.15–1.08 (m, 2H, CH_2), 0.05 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ_C 166.1 (CO), 165.4 (CO), 165.1 (CO), 133.9, 133.7, 133.2, 129.9 (4C), 128.7 (2C), 128.5 (2C), 128.4 (2C), 82.7 (C-1), 71.5 (C-5), 70.3 (C-3), 68.3 (C-4), 62.1 (C-6), 51.5 (CH_2), 27.2 (C-2), 10.3 (CH_2), −1.99 ($3CH_3$); HR-ESIMS *m/z* calcd for $[C_{32}H_{36}INO_9SSi]Na^+$ 788.0822, found 788.0790.

4.13. General procedure for the azidolysis

Method A: To a solution of the α-iodosulfonamide in dry DMF (3 mL/mmol), cooled at 0 °C, was added NaN_3 (2 equiv) as a solid. The mixture was allowed to warm at rt and stirred for 3 h. The reaction mixture was diluted in CH_2Cl_2, washed with 5% aq $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure.

Method B: To a solution of the β-iodosulfonamide in dry DMF (3 mL/mmol), cooled at 0 °C, was added NaN_3 (2 equiv) as a solid. The mixture was heated at 40 °C and stirred for 3 h. The reaction mixture was then diluted in CH_2Cl_2, washed with 5% aq $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure.

4.13.1. 3,6-Di-*O*-acetyl-1-azido-1,2-dideoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-[2-(trimethylsilyl) ethanesulfonamido]-β-D-glucopyranose (15)

Compound **3a** (6 g, 6.92 mmol) was reacted with NaN_3 following general method A. Flash-chromatography purification (eluent: ethyl acetate/cyclohexane 4:6) of the crude residue provided the azide **15** (5.14 g, 95%); TLC R_f 0.40 (ethyl acetate/cyclohexane 1:1); $[\alpha]_D$ −18.4 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 5.37 (br d, 1H, $J_{3',4'}$ = 2.5 Hz, H-4′), 5.33 (d, 1H, $J_{NH,2}$ = 9.4 Hz, NH), 5.12–5.04 (m, 2H, H-2′ and H-3), 4.98 (dd, 1H, $J_{2',3'}$ = 10.4 Hz, H-3′), 4.75 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 4.54–4.50 (m, 2H, H-1′ and H-6′), 4.20–4.08 (m, 3H, H-6, H-6, H-6′), 3.94–3.79 (m, 3H, H-4, H-5, H-5′), 3.38 (q, 1H, $J_{2,3}$ 9.3 Hz), 3.16–2.96 (m, 2H, CH_2), 2.18 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.13–0.97 (m, 2H, CH_2), 0.06 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ_C 171.4, 170.3 (2CO), 170.0 (2CO), 169.5 (CO), 101.0 (C-1′), 88.9 (C-1), 75.6 and 74.3 (C-4 and C-5′), 73.0 (C-3), 70.8 (C-3′ and C-5), 69.0 (C-2′), 66.7 (C-4′), 61.8 (C-6′), 60.8 (C-6), 57.6 (C-2), 50.9 (CH_2), 21.1 (CH_3), 20.8 (CH_3), 20.6 ($3CH_3$), 20.5, 10.3 (CH_2), −2.05 ($3CH_3$); HR-ESIMS *m/z* calcd for $[C_{29}H_{46}N_4O_{17}SSi]Na^+$ 805.2248, found 805.2246.

Compound **15** was also obtained via general method B in 45% yield.

4.13.2. 3,4,6-Tri-*O*-acetyl-1-azido-1,2-dideoxy-2-[2-(trimethylsilyl)ethanesulfonamido]-β-D-glucopyranose (16)

Compound **8b** (100 mg, 0.17 mmol) was reacted with NaN_3 following general method B. Compound **15** was isolated by flash chromatography (ethyl acetate/cyclohexane 3:7) and obtained as a white fluffy solid (40 mg, 48%); R_f 0.47 (ethyl acetate/cyclohexane 1:1); $[\alpha]_D$ −38.2 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 5.19–5.11 (m, 2H, H-3, H-4), 4.77 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 4.31 (dd, 1H, $J_{5,6eq}$ = 4.8 Hz, $J_{6,6}$ = 12.4 Hz, H-6), 4.18 (dd, 1H, $J_{5,6}$ = 2.1 Hz, H-6), 3.83 (br s, 1H, H-5), 3.52–3.42 (m, 1H, H-2), 3.01–3.12 (m, 2H, CH_2), 2.15 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 1.09–0.88 (m, 2H, CH_2), 0.08 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ_C 171.7 (CO), 170.7 (CO), 169.2 (CO), 89.0 (C-1), 73.8 (C-5), 72.9 (C-3), 67.9 (C-4), 61.7 (C-6), 57.7 (C-2), 50.9 (CH_2), 21.0 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 10.5 (CH_2), −2.0 ($3CH_3$); HR-ESIMS *m/z* calcd for $[C_{17}H_{30}N_4O_9SSi]Na^+$ 517.1400, found 517.1393.

Compound **16** was also obtained via general method A in 85% yield.

4.13.3. 3,4-Di-*O*-acetyl-1-azido-1,2,6-trideoxy-2-[2-(trimethylsilyl)ethanesulfonamido]-β-L-glucopyranose (17)

Compound **12** (100 mg, 0.19 mmol) was reacted with NaN_3 following general method A. Flash-chromatography purification (eluent: ethyl acetate/cyclohexane 3:7) of the crude residue provided

the azide **17** (74 mg, 88%); TLC R_f 0.67 (ethyl acetate/cyclohexane 4:6); $[\alpha]_D$ +22.3 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 5.11–5.03 (m, 2H, NH and H-3), 4.86 (t, 1H, $J_{3,4} = J_{4,5} = 9.7$ Hz, H-4), 4.68 (d, 1H, $J_{1,2} = 9.2$ Hz, H-1), 3.74–3.62 (m, 1H, H-5), 3.44 (q, 1H, $J_{NH,2} = J_{2,3} = 9.2$ Hz, H-2), 3.17–2.98 (m, 2H, CH_2), 2.14 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.13–0.98 (m, 2H, CH_2), 0.07 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ_C 171.7 (CO), 169.5 (CO), 88.9 (C-1), 72.9 (C-3 and C-4), 72.3 (C-5), 58.0 (C-2), 50.9 (CH_2), 20.9 (CH_3), 20.7 (CH_3), 17.4 (C-6), 10.4 (CH_2), −2.0 ($3CH_3$); HR-ESIMS *m/z* calcd for $[C_{15}H_{28}N_4O_7SSi]Na^+$ 459.1346, found 459.1342.

4.13.4. 1-Azido-3,4,6-tri-*O*-benzoyl-1,2-dideoxy-2-[2-(trimethylsilyl)ethanesulfonamido]-β-D-glucopyranose (18)

Compound **14** (100 mg, 0.13 mmol) was reacted with NaN_3 following general method A. Flash-chromatography purification (eluent: ethyl acetate/cyclohexane 2:8) of the crude residue provided the azide **18** (75 mg, 82%); TLC R_f 0.35 (ethyl acetate/cyclohexane 3:7); $[\alpha]_D$ −30.9 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 8.08–7.90 and 7.63–7.32 (m, 15H, H arom), 5.70 (br t, 1H, $J_{3,4} = J_{4,5} = 9.8$ Hz, H-4), 5.56 (br t, 1H, $J_{3,2} = 9.8$ Hz, H-3), 5.12–5.04 (m, 2H, H-2′ and H-3), 5.00–4.96 (m, 1H, NH), 4.82 (d, 1H, $J_{1,2} = 9.2$ Hz, H-1), 4.68 (dd, 1H, $J_{5,6} = 3.0$ Hz, $J_{6,6} = 12.2$ Hz, H-6), 4.52 (dd, 1H, $J_{5,6} = 5.0$ Hz, H-6), 4.24–4.19 (m, 1H, H-5), 3.08–2.93 (m, 2H, CH_2), 1.13–0.97 (m, 2H, CH_2), 0.06 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ_C 167.2 (CO), 166.0 (CO), 165.0 (CO), 133.9 (C arom), 133.6 (C arom), 133.3 (C arom), 130.1 (2C arom), 129.8 (4C arom), 128.6 (2C arom), 128.5 (4C arom), 89.7 (C-1), 74.2 (C-5), 73.3 (C-3), 69.0 (C-4), 62.7 (C-6), 58.0 (C-2), 51.2 (CH_2), 10.3 (CH_2), −2.21 ($3CH_3$); HR-ESIMS *m/z* calcd for $[C_{32}H_{36}N_4O_9SSi]Na^+$ 703.1870, found 703.1898.

4.14. 3,4,6-Tri-*O*-acetyl-1,2-dideoxy-1-phthalimido-2-[2-(trimethylsilyl)ethanesulfonamido]-β-D-glucopyranose (19)

Compound **8b** (100 mg, 0.17 mmol) and potassium phthalimide (22 mg, 0.34 mmol) were dissolved in DMF (5 mL). The mixture was heated to 40 °C under argon for 3 h, cooled down to rt, diluted in CH_2Cl_2 (50 mL), washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Compound **19** was isolated following flash chromatography purification (eluent: ethyl acetate/cyclohexane 3:7) as a white solid (29 mg, 27%). R_f 0.38 (ethyl acetate/cyclohexane 1:1); $[\alpha]_D$ −14.1 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 8.04–7.91 (m, 2H, H arom), 7.83–7.77 (m, 2H, H arom), 5.57 (d, 1H, $J_{1,2}$ 9.7 Hz, H-1), 5.42 (t, 1H, $J_{2,3} = J_{3,4} = 9.7$ Hz, H-3), 5.30 (t, 1H, $J_{4,5} = 9.7$ Hz, H-4), 5.26 (d, 1H, $J_{NH,2} = 9.7$ Hz, NH), 4.73 (q, 1H, $J_{1,2} = 9.7$ Hz, H-2), 4.26–4.24 (m, 2H, H-6, H-6), 3.99 (ddd, 1H, $J_{5,6} = 1.1$ Hz, $J_{5,6} = 2.9$ Hz, H-5), 2.77–2.72 (m, 2H, CH_2), 2.16 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 0.86–0.80 (m, 2H, CH_2), −0.12 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ_C 176.0 (2C), 171.1 (CO), 170.8 (CO), 169.5 (CO), 134.8–134.4 (C arom), 124.1–123.9 (C arom), 79.5 (C-1), 74.4 (C-5), 73.7 (C-3), 68.5 (C-4), 61.9 (C-6), 53.6 (C-2), 50.7 (CH_2), 20.9 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 10.1 (CH_2), −2.2 ($3CH_3$); HR-ESIMS *m/z* calcd for $[C_{25}H_{34}N_2O_{11}SSi]Na^+$ 621.1550, found 621.1569.

4.15. (5-*tert*-Butyl-2-methyl)phenyl 3,4,6-tri-*O*-acetyl-1,2-dideoxy-1-thio-2-[2-(trimethylsilyl)ethanesulfonamido]-β-D-glucopyranoside (20)

To a solution of 5-*tert*-Butyl-2-methyl-phenyl sulfide (93.65 mg, 0.52 mmol) in DMF (1 mL) was added LiHMDS (1 M in THF, 445 μL, 0.46 mmol) dropwise under Ag at −30 °C. The suspension was then transferred to a solution of compound **8a** (215 mg, 0.38 mmol) in DMF (1 mL) at −30 °C. The reaction mixture was allowed to warm at −20 °C over 30 min. The reaction mixture was diluted in CH_2Cl_2 and quenched by addition of satd aq NH_4Cl. The organic layer was washed with 5% aq $Na_2S_2O_3$ and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash-chromatography (eluent: ethyl acetate/cyclohexane 1:9) of the resulting residue provided compound **20** (180 mg, 77%); TLC R_f 0.77 (ethyl acetate/cyclohexane 1:1); $[\alpha]_D$ −4.8 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ_H 7.60 (d, 1H, *J* = 1.9 Hz, H arom), 7.27 (dd, 1H, *J* = 8.0 Hz, H arom), 7.16 (dd, 1H, H arom), 5.38 (d, 1H, $J_{N,H2} = 9.6$ Hz, NH), 5.21 (t, 1H, $J_{2,3} = J_{3,4} = 9.4$ Hz, H-3), 5.12 (t, 1H, $J_{4,5} = 9.4$ Hz, H-4), 4.76 (d, 1H, $J_{1,2} = 10.5$ Hz, H-1), 4.24 (dd, 1H, $J_{5,6} = 4.7$ Hz, $J_{6,6} = 12.4$ Hz, H-6), 4.08 (dd, 1H, $J_{5,6} = 2.1$ Hz, H-6), 3.76 (q, 1H, H-2), 3.74–3.66 (m, 1H,), 3.23–3.15 (m, 2H, CH_2), 2.43 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.33 (s, 9H, *t*Bu), 1.20–1.12 (m, 2H, CH_2), 0.05 (s, 9H, $3CH_3$); ^{13}C NMR ($CDCl_3$): δ_C 171.8 (CO), 170.8 (CO), 169.3 (CO), 149.7 (C arom), 137.3 (C arom), 131.6 (C arom), 130.5 (C arom), 130.1 (C arom), 125.5 (C arom), 87.8 (C-1), 78.4 and 74.8 (C-3 and C-5), 68.4 (C-4), 62.3 (C-6), 57.2 (C-2), 51.4 (CH_2), 34.5 (*C*tBu), 31.3 (*t*Bu), 21.0 (CH_3), 20.8 (CH_3), 20.6 (CH_3), 20.5 (CH_3), 10.3 (CH_2), −1.94 ($3CH_3$); HR-ESIMS *m/z* calcd for $[C_{28}H_{45}NO_9S_2Si]Na^+$ 654.2203, found 654.2207.

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Supplementary data

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