



HAL
open science

Scalable synthesis of versatile rare deoxyamino sugar building blocks from d-glucosamine

Debashis Dhara, Marion Bouchet, Laurence Mulard

► **To cite this version:**

Debashis Dhara, Marion Bouchet, Laurence Mulard. Scalable synthesis of versatile rare deoxyamino sugar building blocks from d-glucosamine. *Journal of Organic Chemistry*, 2023, 88 (11), pp.6645-63. 10.1021/acs.joc.2c03016 . pasteur-04638985

HAL Id: pasteur-04638985

<https://pasteur.hal.science/pasteur-04638985v1>

Submitted on 8 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Scalable Synthesis of Versatile Rare Deoxyamino Sugar Building Blocks from D-Glucosamine

Debashis Dhara, Marion Bouchet, and Laurence A. Mulard*



Cite This: *J. Org. Chem.* 2023, 88, 6645–6663



Read Online

ACCESS |



Metrics & More

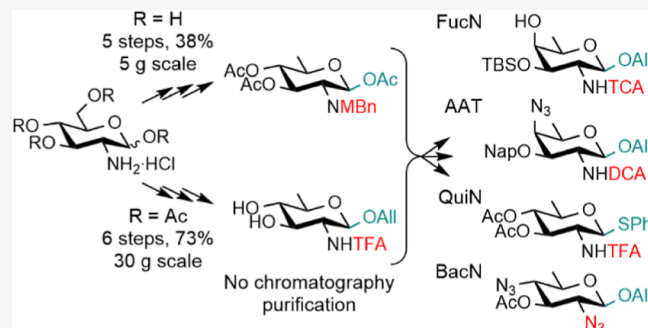


Article Recommendations



Supporting Information

ABSTRACT: We report the syntheses of 1,3,4-tri-*O*-acetyl-2-amino-2,6-dideoxy- β -D-glucopyranose and allyl 2-amino-2,6-dideoxy- β -D-glucopyranoside from D-glucosamine hydrochloride. The potential of these two versatile scaffolds as key intermediates to a diversity of orthogonally protected rare deoxyamino hexopyranosides is exemplified in the context of fucosamine, quinovosamine, and bacillosamine. The critical C-6 deoxygenation step to 2,6-dideoxy aminosugars is performed at an early stage on a precursor featuring an imine moiety or a trifluoroacetamide moiety in place of the 2-amino group, respectively. Robustness and scalability are demonstrated for a combination of protecting groups and incremental chemical modifications that sheds light on the promise of the yet unreported allyl 2,6-dideoxy-2-*N*-trifluoroacetyl- β -D-glucopyranoside when addressing the feasibility of synthetic zwitterionic oligosaccharides. In particular, allyl 3-*O*-acetyl-4-azido-2,4,6-trideoxy-2-trifluoroacetamido- β -D-galactopyranoside, an advanced 2-acetamido-4-amino-2,4,6-trideoxy-D-galactopyranose building block, was achieved on the 30 g scale from 1,3,4,6-tetra-*O*-acetyl- β -D-glucosamine hydrochloride in 50% yield and nine steps, albeit only two chromatography purifications.



INTRODUCTION

Carbohydrates are ubiquitous cell surface components. They play major roles in a myriad of complex biological processes governed by cell–cell or cell–environment interactions including host–pathogen recognition. Going far beyond the structural diversity seen within the human glycome, the prokaryote glycome is highly varied.^{1,2} Diversity stems for a large part from the large number of unique monosaccharides composing its alphabet. It expands as novel monosaccharides are revealed paralleling the structural analysis of natural glycans of increasing complexity.³ Among distinct monosaccharides not found in mammalian glycans are several rare deoxyamino sugars often present in glycans from pathogenic bacteria but essentially absent from the human microbiota.^{4,5} Whether as components of zwitterionic polysaccharides (ZPSs),^{6,7} substrates for selective metabolic labeling,⁴ key biosynthetic intermediates, and potential targets for novel antibiotics⁸ or in the context of epitope mapping and vaccine design,^{7,9} 2-amino-2,6-dideoxyhexoses (ADDH) and 2,4-diamino-2,4,6-trideoxyhexoses (DATDH) are the subject of wide interest.¹⁰

Mostly identified in ZPSs, AAT (D-FucpNAc4N) is among the most studied DATDH. Being α -linked in glycans from the well-established immunomodulators *Streptococcus pneumoniae* 1 (Sp1)¹¹ and *Bacteroides fragilis* (PS A1),¹² in the enterobacterial common antigen¹³ and in several other ZPSs, it is β -linked in the surface polysaccharides from *Shigella sonnei*,¹⁴ *Plesiomonas shigelloides*,¹⁵ and other bacteria.^{16–19} Otherwise, it is occasionally found in both forms within the same glycans such as in the *S.*

pneumoniae lipoteichoic acid (Sp LTA).²⁰ AAT also occurs in various 4-acylamino forms.²¹ It may even be present as both 4-amino and 4-acetylamino residues within selected strains.²² Obviously, the different *N*-substitutions at C-2 and C-4 increase the synthetic complexity.

Going beyond the original paths to 2-acetamido^{14,23–27} and 2,4-diacetamido glycosides,^{27–29} or post-glycosylation functionalization routes,^{30–32} a large variety of advanced AAT intermediates featuring 2,4-orthogonal protecting groups were designed (Figure 1).¹⁰ Most focus was on precursors to α -linked AAT for use in the synthesis of PS A1,^{33–35} Sp1,^{11,24,30,36–40} and Sp LTA.^{41,42} Except for a precursor bearing a 2-imino group³⁹ and stereotunable 2-*N*,3-*O*-oxazolidinone donors,^{32,39} intermediates set up for use as glycosylating agents basically feature a 2-azido moiety.⁴³ Otherwise, interest in β -linked AAT led to donors equipped for anchimeric assistance at position 2 including *N*-phthaloyl,¹⁴ *N*-2,2,2-trichloroethoxycarbonyl,⁴² and *N*-trichloroacetyl^{14,44–48} derivatives. Besides routes based on an azidonitration step³⁵ (Figure 1A) and original concepts such as a de novo path from L-threonine³⁴ (Figure 1B) or a 4-

Received: December 16, 2022

Published: May 4, 2023



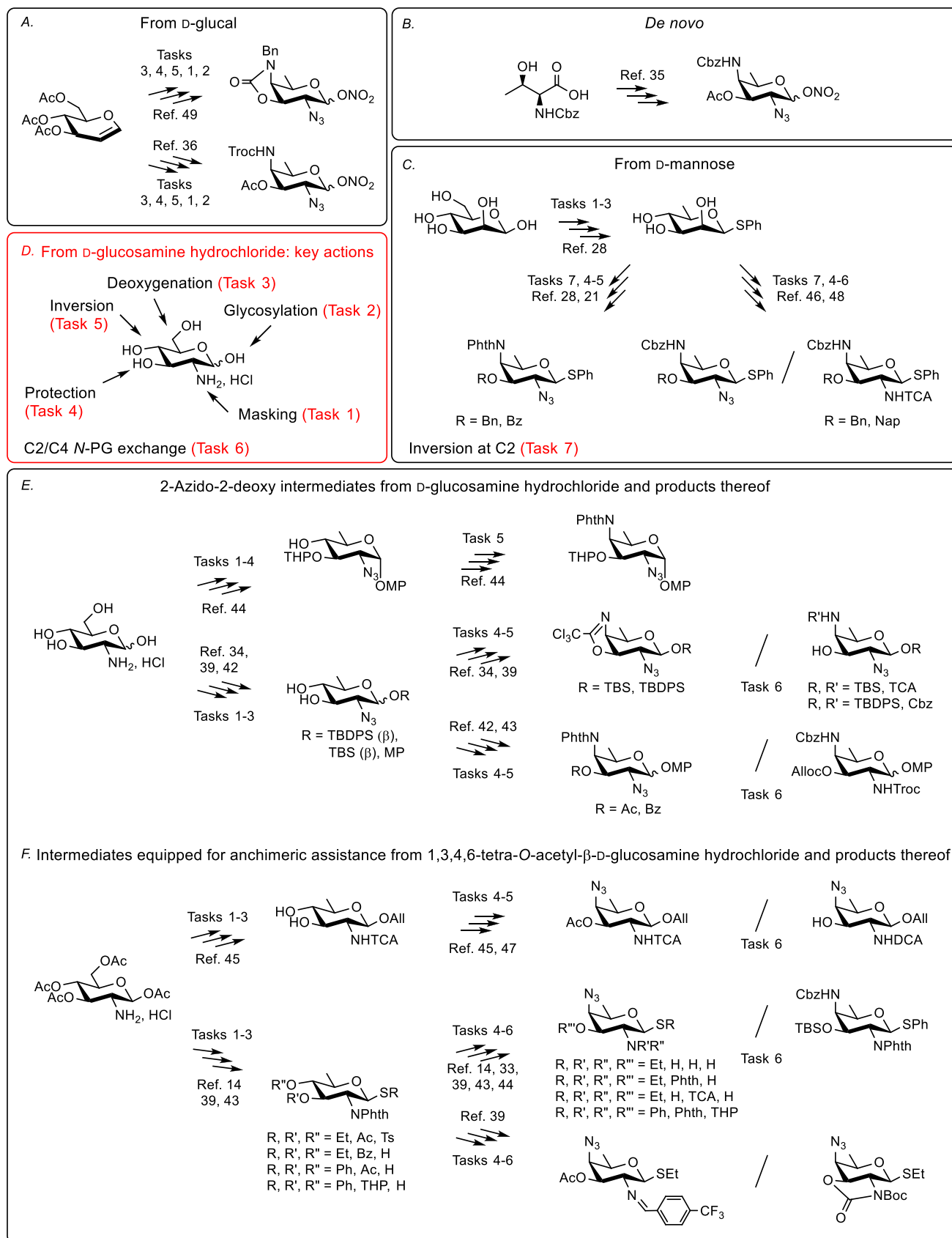


Figure 1. Main representative strategies to 2-*N*,4-*N*-protected AAT building blocks (panels A–C,E,F) and key actions when starting from D-glucosamine hydrochloride (panel D). All: allyl, Alloc: allyloxycarbonyl, Boc: *tert*-butoxycarbonyl, Cbz: benzyloxycarbonyl, DCA: dichloroacetyl, MP: 4-methoxyphenyl, PG: protecting group; Phth: phthalimidoyl, TBS: *tert*-butyldimethylsilyl, TBDPS: *tert*-butyldiphenylsilyl, TCA: trichloroacetyl, THP: tetrahydropyranyl, Troc: 2,2,2-trichloroethoxycarbonyl, Ts: tosyl.

amino group introduction by means of an intramolecular displacement^{38,49} (Figure 1A,E), most syntheses start from *D*-glucosamine^{14,25,33,38,42,43,45} (Figure 1E,F) or involve an elegant one-pot sequential inversion of 2,4-bistriflate *D*-thiorhamnoside intermediates (Figure 1C).^{11,21,27,43,50} They comprise 10–15 steps in average with the orthogonal masking/unmasking of the amino/acetamido groups being common concerns owing to the harsh conditions employed for the C-6 deoxygenation step. Briefly, five interdependent key actions can be identified to build 2-amino-2,6-dideoxy-hexoses and 2,4-diamino-2,4,6-trideoxy-hexoses from *D*-glucosamine hydrochloride: 2-NH₂ masking, aglycon insertion, C-6 deoxygenation, 3-OH protection, and C-4 inversion, possibly complemented by protecting group exchange at positions 2 and/or 4 (Figure 1D). These five actions can be organized in multiple ways, several of which were already explored (Figure 1E,F).

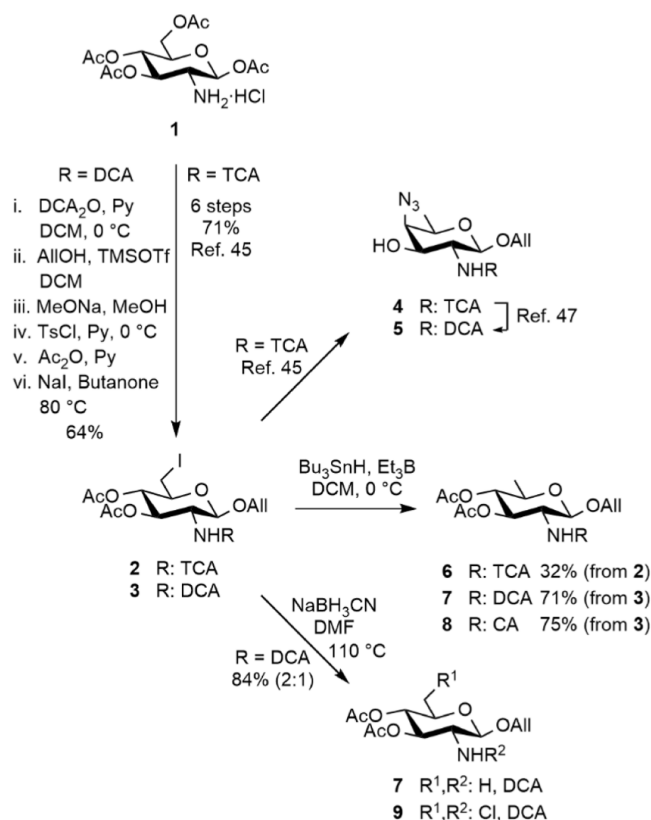
The growing interest in large homogeneous segments of ZPSs^{6,11,47} has underlined the importance of robust and scalable versatile strategies to orthogonally protected ADDH. Herein, going beyond the existing paths, we propose two handy 2-amino-2,6-dideoxy scaffolds easily achievable in high yield on a large scale from the naturally abundant *D*-glucosamine hydrochloride. We exemplify versatility through their conversion into diverse protected ADDH and DATDH. Moreover, we demonstrate robustness for the 30 g scale synthesis of a key orthogonally protected AAT brick used in the assembly of *S. sonnei* glycans of interest for vaccine development.⁴⁷

RESULTS AND DISCUSSION

Starting from *D*-glucosamine hydrochloride, the limiting C-6 deoxygenation step is commonly performed on a 2-azido or a 2-phthalimido intermediate (Figure 1E,F).³⁸ Instead, we have reported the 2-trichloroacetamide **2**, easily obtained from 1,3,4,6-tetra-*O*-acetyl- β -*D*-glucosamine hydrochloride **1** (Scheme S1), as a precursor to the AAT building block **4** (Scheme 1).⁴⁵

In this work, the C-6 reduction step of the 6-iodo precursor **2** into trichloroacetamide **6** met with issues. Variations around the initial conditions did not fulfill the efficiency criteria either (Scheme S2). In particular, the use of NaBH₃CN/CuX (X = Cl, Br, or I) was found less effective.⁵¹ Radical-mediated reduction by means of (TMS)₃SiH/AIBN,⁵² Bu₃SnH/Et₃B,⁵³ or (TMS)₃SiH/Et₃B did not overcome limitations.⁵⁴ Concomitant hydrodechlorination yielding dichloroacetamide **7** could not be avoided, and chloroacetamide **8** was also observed under certain conditions. Similar observations stemmed from the Seeberger group⁵⁵ and the Codée group,⁵⁶ which reported that the thiol- and phosphine-mediated azide reduction of unrelated 2-trichloroacetamido derivatives had generated the corresponding 2-dichloroacetamido side products, respectively. We have previously achieved dichloroacetamide **5** from trichloroacetamide **4** (Scheme 1).⁴⁷ Herein, the more straightforward synthesis of the AAT acceptor **5** from precursor **3** also met with limitations. In particular, chloroacetamide **8** and the 6-chloro derivative **9** were observed repeatedly upon radical^{51,53} or hydride-mediated reduction,⁴⁵ respectively (Schemes 1 and S3). Having reconsidered the interdependence between the five key actions identified to build ADDH and DATDH from *D*-glucosamine (Figure 1D), we now propose two original alternatives to the existing paths. The critical C-6 deoxygenation step is performed on a precursor featuring either an imine moiety at position 2 in place of the starting 2-amino group

Scheme 1. Initial Route to the 2-*N*-Trichloroacetyl and 2-*N*-Dichloroacetyl AAT (4** and **5**) and Quinvosamine (QuiN, **6** and **7**) Building Blocks^a**



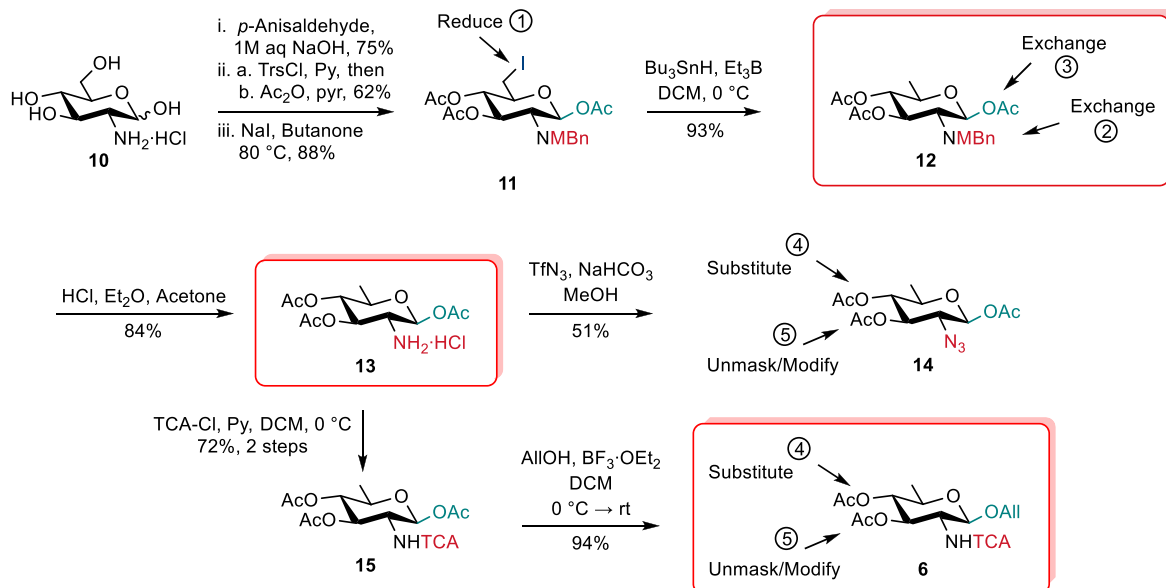
^aCA: chloroacetyl, Py: pyridine.

(generic route 1) or a 2-trifluoroacetamide moiety to mask that same amino group (generic route 2).

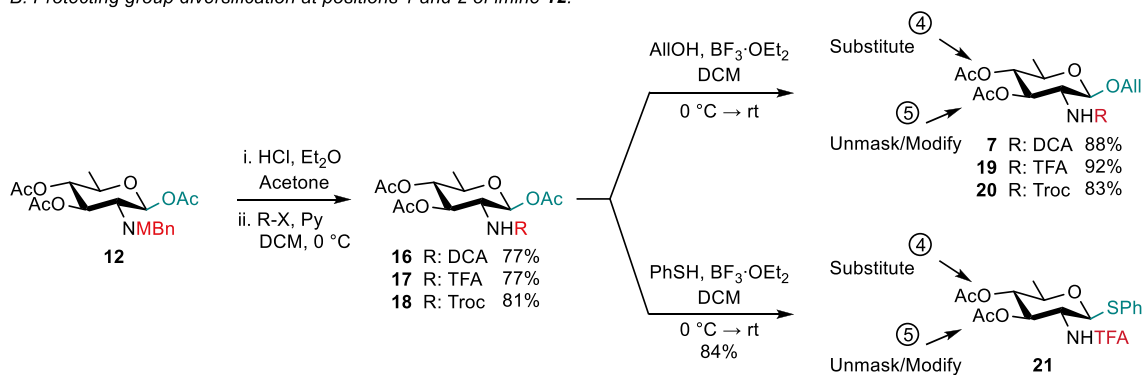
Generic Route 1. Aiming to achieve **4** while avoiding interference of the TCA moiety during C-6 deoxygenation, we set to investigate a route featuring a late-stage suitable *N*-protection step. We reasoned that a route encompassing an early deoxygenation step would offer a faster and more versatile access to intermediates bearing any protecting group combination. Satisfactorily, treatment of the upstream 6-iodo imine **11** with Bu₃SnH/Et₃B provided the 6-deoxy analogue **12** in high yield (Scheme 2). Varying the tosylation conditions had little influence (Scheme S4). In contrast, changing the tosyl group for the bulkier triisopropylbenzenesulfonyl moiety was beneficial. Acidic hydrolysis of the C-2 imine gave the versatile 1,3,4-tri-*O*-acetyl- β -*D*-quinvosamine (QuiN) **13** from *D*-glucosamine hydrochloride in five steps and 32% yield on a 5 g scale. Conversion of triacetate **13** into the 2-azido analogue **14** paved the way to a panel of AAT and QuiN donors ready for 1,2-*cis* glycosylation. Otherwise, starting from imine **12**, *N*-unmasking and subsequent trichloroacetylation of intermediate **13** furnished triacetate **15**, in turn converted into allyl glycoside **6**, a well-established AAT precursor.⁴⁵ This efficient three-step protocol provides an access to the known **6** in eight steps from *D*-glucosamine hydrochloride (Scheme 2A). The process was adapted to give the *N*-dichloroacetyl (**7**), *N*-trifluoroacetyl (**19**), and *N*-Troc (**20**) analogues with excellent anomeric control (Scheme 2B). Likewise, the thiophenyl QuiN **21** was easily achieved from imine **12** by means of trifluoroacetamide **17**, demonstrating that aglycon diversification post-*N*-protection is

Scheme 2. From D-Glucosamine Hydrochloride to Orthogonally Protected ADDH and DATDH Precursors via the QuiN Imine **12**^a

A. Main path to scaffolds **14** and **6**.



B. Protecting group diversification at positions 1 and 2 of imine **12**.



X = Cl (R: Troc), X = OC(O)CHCl₂ (R: DCA) and X = OC(O)CF₃ (R: TFA).

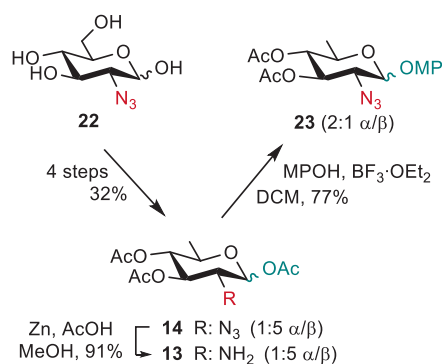
^aMBn: *para*-methoxybenzylidene, Tf: trifluoromethanesulfonyl, TFA: trifluoroacetyl, Trs: triisopropylbenzenesulfonyl.

straightforward. Subjected to improving the path to iodide **11**, imine **12** represents a highly versatile precursor to ADDH and DATDH.

With the azido moiety fulfilling all orthogonality criteria, the more stable 2-azido-2,6-dideoxy derivative **14**, easily obtained as a 1:5 α/β mixture from the commercially available 2-azido-2-deoxy-β-D-glucose⁵⁷ **22** (Scheme S5), was envisioned as a possible alternative to imine **12**. Similarly to the original route whereby glycosylation preceded deoxygenation,⁴² conventional glycosylation of triacetate **14** with *para*-methoxyphenol gave the known AAT precursor **23** as a 2:1 α/β mixture (Scheme 3). Otherwise, reduction of the azido moiety in **14** was high yielding, providing an expedite access to scaffold **13**. Of note, this route delivered triacetate **13** as a 1:5 α/β mixture.

Generic Route 2. Aiming at improving robustness, we identified the more advanced allyl 2,6-dideoxy-2-trifluoroacetamido-β-D-glucopyranoside **28** as a promising alternative to imine **12** and azide **14** (Scheme 4). The trifluoroacetyl moiety was envisioned as an easy-to-introduce participating *N*-protecting group stable under harsh reductive conditions, albeit

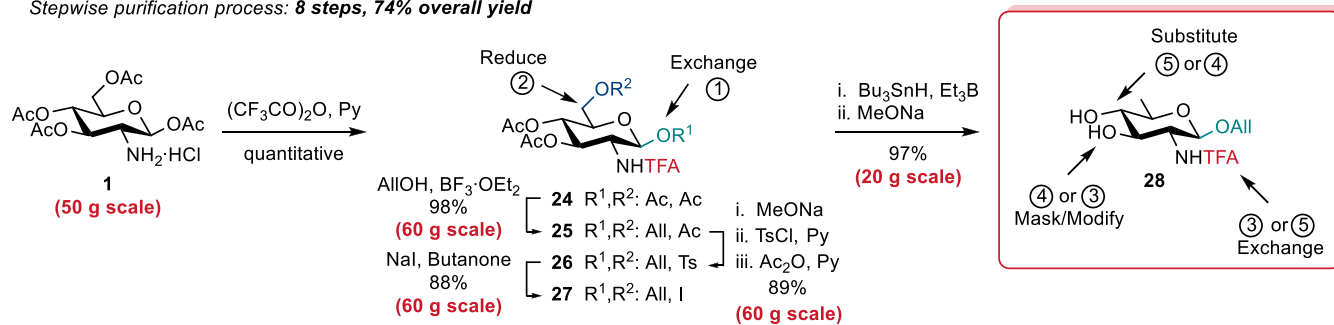
Scheme 3. 2-Azido QuiN **14** as a Scaffold



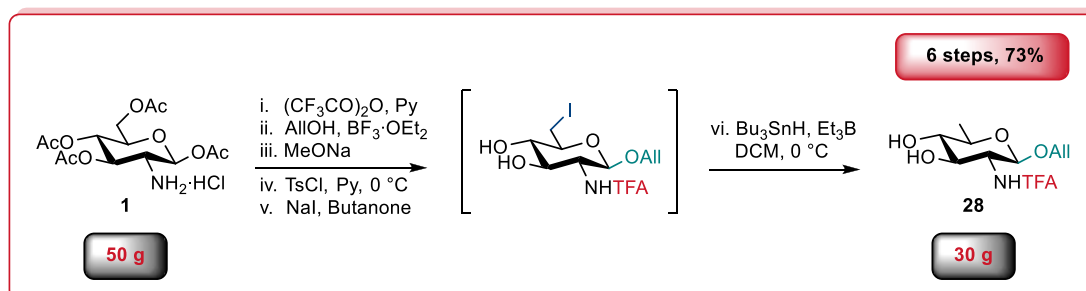
seemingly cleavable under relatively mild basic conditions.⁵⁸ The synthesis of diol **28** from **1** by means of **24**⁵⁸ followed that reported for the trichloroacetamide analogue (Scheme 1).⁴⁵ The conversion of tetra-acetate **1** into the 6-iodo **27** went smoothly to deliver the latter intermediate in 77% yield over six steps (Scheme 4A). It is noteworthy that the key reduction step

Scheme 4. From 1,3,4,6-Tetra-*O*-acetyl- β -D-glucosamine Hydrochloride **1** to Trifluoroacetamide QuiN **28**

A. The 3,4-di-*O*-acetyl-6-iodo **27** as the deoxygenation precursor
Stepwise purification process: **8 steps, 74% overall yield**



B. The 6-iodo diol as the deoxygenation precursor
No chromatography purification of intermediates



furnished diacetate **19** in excellent yield (96%, 40 g scale) when using an optimized $\text{Bu}_3\text{SnH}/\text{Et}_3\text{B}$ combination (Scheme S6). Robustness was confirmed as reduction at C-6 of **27** and subsequent transesterification gave diol **28** in a 90–97% yield on a 20 g scale (Scheme S7). Moreover, investigation toward scale-up demonstrated that re-*O*-acetylation post-tosylation was not mandatory. This step and the related transesterification of diacetate **19** into diol **28** were removed from the process. As a reward, scaffold **28**, serving as a versatile intermediate to protected ADDH and DATDH, was obtained in six steps and 78% overall yield from the commercially available **1** on a 150 mmol scale (Schemes 4B and S8). Modification at positions 2, 3, and 4 of diol **28** can follow multiple paths (Scheme 4A), in part exemplified below.

From the *N*-Trifluoroacetyl QuiN **28 to AAT and D-FucNAc Building Blocks: 3-*O*-Protection and C-4 Inversion.** Applying the diisopropylethylamine (DIPEA)-triggered self-catalyzed regioselective acetylation conditions⁵⁹ to diol **28** provided acetate **29** together with its regioisomer (Scheme 5, entries 1 and 2). Aiming at avoiding formation of the latter, diol **28** was treated with acetyl chloride under conditions previously established for the trichloroacetamide analogue.⁴⁵ This more demanding protocol delivered the expected **29** with an improved regioselectivity (entry 3). This option was adopted on a multigram scale. Otherwise, the 3-*O*-benzoyl **30** was achieved smoothly (77%) in the presence of Me_2SnCl_2 (entry 4).⁶⁰ In contrast, *tert*-butyldimethylsilylation required attention to furnish the expected **31**. The 4-*O*-*tert*-butyldimethylsilyl isomer was always present (entries 5 and 6). Moreover, the 4-*O*-benzyl **32** was formed preferentially while the reaction was stopped before completion to avoid extensive *N*-benzylation in the presence of sodium hydride (entry 7). To our knowledge, the observed regioselectivity was not reported previously for *N*-protected QuiN derivatives. Further attempts at achieving a

Scheme 5. Regioselective *O*-Protection of the QuiN Diol **28**^a

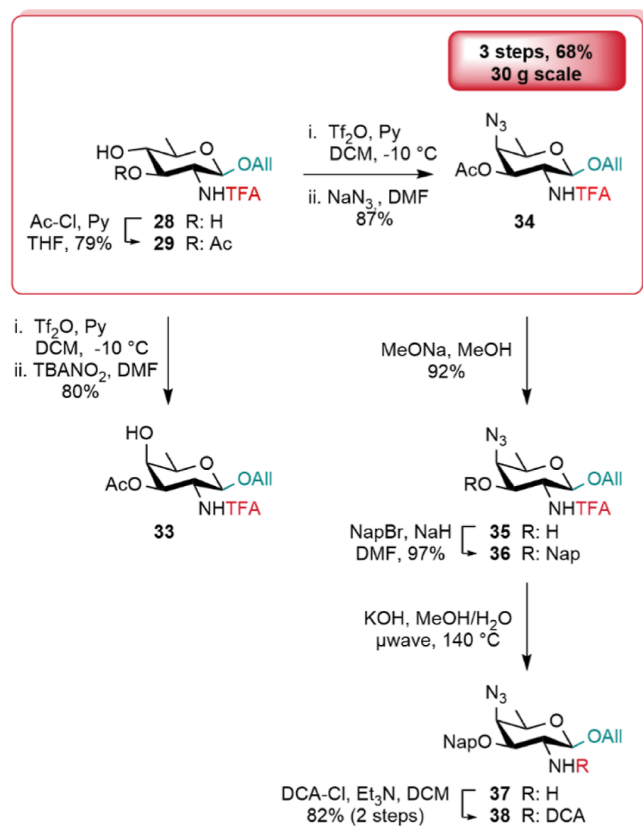
Entry	Conditions	Product Yield, $\text{R}^1:\text{R}^2$
1	Ac_2O , DIPEA, MeCN 40 °C, 24 h	29 76%, 9:1
2	Ac_2O , DIPEA, MeCN 100 °C, 3 h	29 84%, 5:1
3	AcCl , Py, THF -78 °C \rightarrow rt, 24 h	29 86%, 20:1
4	BzCl , Me_2SnCl_2 , Py, THF 0 °C \rightarrow rt, 16 h	30 77%, 1:0
5	TBSOTf, 2,6-lutidine, THF -80 °C \rightarrow 0 °C, 6 h	31 92%, 1:1
6	TBSCl, Imidazole, Taylor catalyst, DMF, 0 °C \rightarrow rt, 16 h	31 82%, 4:3
7 ^b	BnBr, NaH, DMF 0 °C, 3 h	32 42%, 0:1

^aIsolated yields. ^bCorrected yield: 79%. DIPEA: *N,N*-diisopropylethylamine.

better regioselectivity by use of a diaryl boronic acid catalyst⁶¹ or an iron catalyst⁶² were unsuccessful.

Alcohol **29** was next elaborated into D-FucNAc **33** in high yield via triflate-mediated inversion using the nitrite-mediated Lattrell-Dax method.⁶³ Alternatively, azide-mediated substitution of the intermediate triflate readily generated upon reaction of **29** with triflic anhydride in the presence of pyridine delivered the fully protected AAT **34** in excellent yield (Scheme 6). Moreover, scale-up toward a robust synthesis of AAT was in agreement with expectations. In particular, the key intermediate **34** was achieved in 68% yield from diol **28** on the 30 g scale by means of the 3-*O*-acetyl QuiN **29**, readily obtained as a >15:1 mix with its 4-*O*-acetyl regioisomer (Scheme 6).

Scheme 6. From the *N*-Trifluoroacetyl QuiN **28 to D-FucNAc (**33**) and AAT (**34–38**) Building Blocks^a**



^aTBANO₂: tetrabutylammonium nitrite.

Selective unmasking of 3-OH in **34** provided acceptor **35** on the way to diversely 3-*O*-protected analogues. Going beyond the unsuccessful 3-*O*-benzylation of the QuiN diol **28**, the 3-*O*-Nap **36** was easily achieved from the 4-azido AAT precursor **35**. As exemplified by the conversion of AAT **36** into its dichloroacetamide counterpart **38** by way of amine **37** (Scheme 6), AAT derivatives bearing a 3-*O*-ether protecting group are achievable in high yield from their fully protected trifluoroacetamide equivalents. Nevertheless, in contrast to 3-*O*-ester-equipped analogues, the cleavage of the trifluoroacetamide moiety in these substrates requires rather harsh conditions.

From the *N*-Trifluoroacetyl QuiN **28 and AAT **34** to Diversely 2-*N*-Protected AAT Building Blocks.** The next step ensuring a versatile strategy consisted in establishing that trifluoroacetamide **34** was a suitable intermediate to a large variety of AAT bricks differing by the 2-acetamido masking, which may find interest in the synthesis of glycans obeying

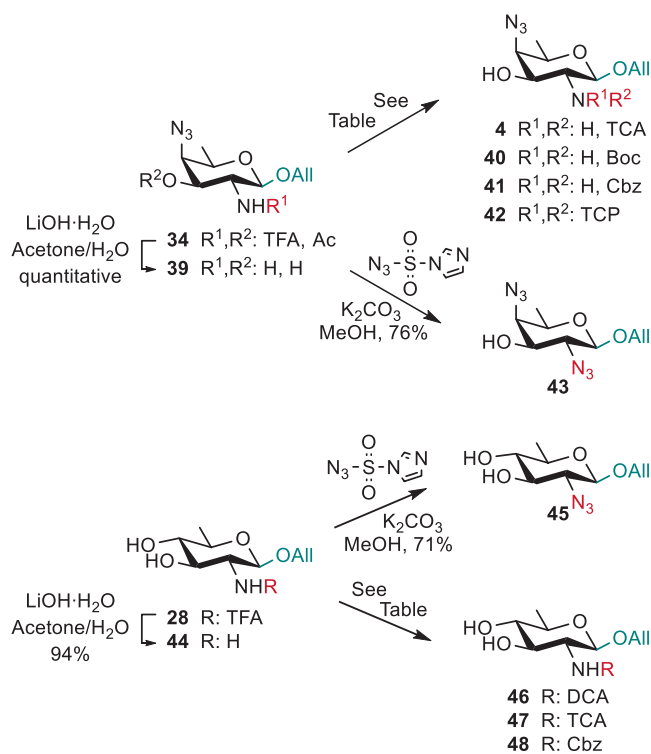
stringent orthogonality criteria. Thus, AAT **34** was subjected to a smooth *N*-trifluoroacetyl cleavage upon treatment with lithium hydroxide (Scheme 7). Subsequent selective *N*-protection of amino alcohol **39** delivered the known trichloroacetamide acceptor **4**⁴⁵ (entry 1) and carbamates **40** and **41** (entries 2 and 3), all in high yield in contrast to the tetrachlorophthalimide **42** (entry 4). Trichloroacetamide **4**, a well-established AAT acceptor in the synthesis of *S. sonnei* oligosaccharides, was achieved in 13 g amounts from 1,3,4,6-tetra-*O*-acetyl- β -D-glucosamine hydrochloride **1** in 11 steps, three chromatography purifications, and 45% overall yield. Otherwise, starting from the QuiN diol **28**, *N*-trifluoroacetyl cleavage delivered amine **44**, facilitating selective *N*-masking, as required. Accordingly, trichloroacetamide **47**⁴⁵ (entry 6), the novel dichloroacetamide **46** (entry 5), and carbamate **48** (entry 7) QuiN derivatives, C-2-equipped for anchimeric assistance, are easily accessible from diol **28**. Similarly, analogues **43** and **45** bearing a C-2 azide were achieved by an azido transfer reaction from amines **39** and **44**, respectively (Scheme 7).

Alike the *N*-trifluoroacetyl diol **28**, the *N*-protected QuiN **45**⁴⁵–**47** provided an additional set of orthogonally protected D-FucNAc and AAT derivatives when subjected to regioselective protection at OH-3, triflation, and subsequent nucleophilic substitution at C-4 (Scheme 8). This is exemplified for QuiN **49**, **50**,⁴⁵ and **51** and next converted in good to excellent yields into the corresponding AAT (**52** and **53**⁴⁵) and FucNAc (**54** and **55**) bricks, respectively. Overall, the trifluoroacetyl protecting group was found superior. However, as for the trifluoroacetamide QuiN **28**, attempted 3-*O*-silylation of diol **47** met with issues. Alternatively, the 3-*O*-silylated FucNAc **57** was easily obtained from acetate **54**. Illustrating further the broad scope of building block **28**, the FucNAc intermediate **55** was converted to the 2,4-diazido bacillosamine **56** (Scheme 8).

CONCLUSIONS

The proof of concept is established for two versatile strategies to rare D-deoxyamino sugars from the naturally abundant D-glucosamine hydrochloride and its more advanced commercially available 1,3,4,6-tetra-acetate equivalent. Key features include a temporary 2-*N*-protection in the form of an imine or a trifluoroacetamide, enabling a high yielding early stage C-6 deoxygenation step. The tosylation–iodination–reduction at the primary hydroxyl was achieved in high yield on the 3,4,6-triol substrate. Subsequent diversity-oriented chemical manipulation provided orthogonally protected QuiN, FucNAc, and AAT intermediates equipped for 1,2-*cis* and/or 1,2-*trans* glycosylation. Versatility is illustrated in terms of protecting group selection and sequential introduction to deliver multiple ADDH and DATDH bricks. Some examples are closely related to known compounds as the disclosed routes may be envisioned as alternatives to published syntheses. The novel 6-deoxy-D-glucosamine derivatives, diacetate **19** and its diol equivalent **28**, both of which feature a 2-trifluoroacetamide moiety, were shown to be easily achievable on the multidecagram scale. While these allyl glycosides are the main model scaffolds in this study, the proposed strategies are easily applicable to other substrates, especially thioglycosides, thus enabling greener C-6 reduction conditions. Beyond novelty, this study adds to previous demonstrations of the potential of fine-tuned generic scaffolds for the synthesis of rare deoxyamino sugars, the interest for which is manifest. Synthesis robustness and scalability are demonstrated for the pivotal QuiN diol **28** (30 g, six steps, 73%, no chromatography purification) and the more advanced AAT

Scheme 7. *N*-Protecting Group Manipulation from the *N*-Trifluoroacetyl AAT and QuIN Precursors, **34** and **28**, Respectively^a



Entry	Conditions	Product (Yield)
1 ^{a,45}	TCA-Cl, Et ₃ N, DCM, then H ₂ O	4 (86%)
2 ^a	Boc ₂ O, DMAP, THF	40 (83%)
3 ^a	Cbz-Cl, aq. NaHCO ₃ , DCM	41 (86%)
4 ^a	TCPO, Et ₃ N, DCE, then TCPO, Py	42 (25%)
5 ^b	(DCA) ₂ O, Et ₃ N, EtOAc, then H ₂ O	46 (81%)
6 ^b	TCA-Cl, Et ₃ N, DCM, then H ₂ O	47 (85%)
7 ^b	Cbz-Cl, aq. NaHCO ₃ , EtOAc	48 (81%)

^aFrom **39**. ^bFrom **44**. TCPO: tetrachlorophthalic anhydride, (DCA)₂O: dichloroacetic anhydride.

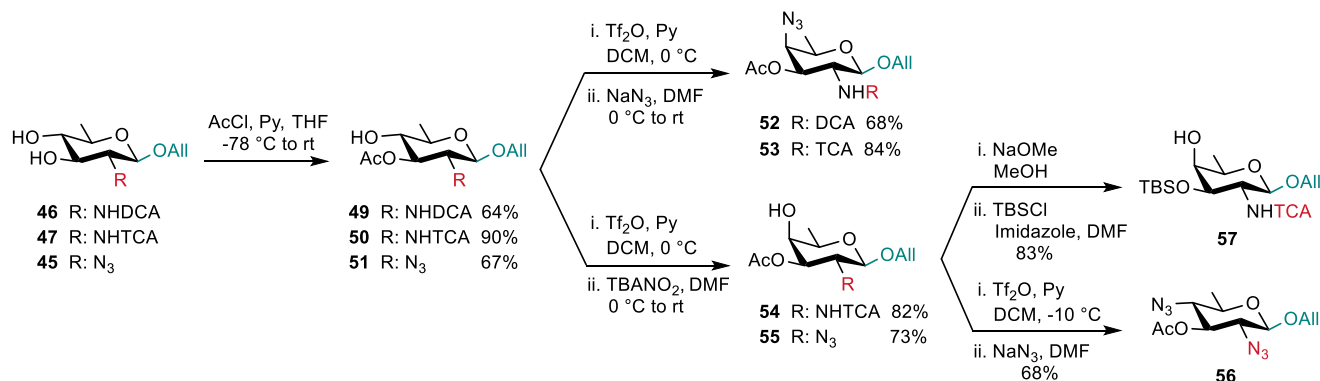
34 (30 g, nine steps, 53%, two chromatography purifications) proposed for use in the synthesis of zwitterionic glycans of relevance in adjuvant and vaccine development.

EXPERIMENTAL SECTION

General Procedures. Anhydrous (Anhyd.) solvents—including DCM, 1,2-dichloroethane (DCE), tetrahydrofuran (THF), *N,N*-dimethylformamide (DMF), MeOH, MeCN, Py, and toluene (Tol)—were delivered over molecular sieves (MS) and used as received. Reactions requiring anhyd. conditions were run under an argon (Ar) atmosphere using dried glassware. Freshly activated 4 Å MS were prepared before use by heating under high vacuum. Reactions were performed at a concentration of 100–200 mmol/L with respect to the limiting starting material unless indicated otherwise. The amount of added reagents with respect to the limiting starting material is according to specific indications in the experimental procedures. Reactions run under microwave conditions used a Biotage Initiator+ Fourth Generation Microwave Synthesizer and high-precision 20 mL microwave vials. Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F254, 0.25 mm pre-coated TLC aluminum foil plates. Compounds were visualized using UV ($\lambda = 254$ nm) and/or orcinol (1 mg·mL⁻¹) in 10% aq H₂SO₄ with charring. Flash column chromatographies were carried out using silica gel (25 or 40–63 μ m particle size). Reactions that required heating were run in flasks equipped with an air flux condenser using a heat-on block equipped with an external temperature probe and filled in with sand whenever necessary to ensure proper heat transfer. NMR spectra were recorded at 303 K on a Bruker AVANCE spectrometer equipped with a BBO probe at 400 MHz (¹H) and 100 MHz (¹³C). Spectra were recorded in CDCl₃, CD₃CN, CD₃OD, and DMSO-*d*₆. Chemical shifts are reported in ppm (δ) relative to residual solvent peaks at 7.28/77.0 ppm for CDCl₃, 1.39/1.32 ppm for CD₃CN, 3.33/49.0 ppm for CD₃OD, and 2.50/39.5 ppm for DMSO-*d*₆ for the ¹H and ¹³C spectra, respectively. Coupling constants are reported in hertz (Hz). Elucidation of chemical structures is based on ¹H, COSY, DEPT-135, HSQC, decoupled HSQC, ¹³C, decoupled ¹³C, and HMBC spectra. Signals are reported as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), q (quartet), dt (doublet of triplet), dq (doublet of quartet), ddd (doublet of doublet of doublet), m (multiplet), and broad (prefix br). Of the two magnetically non-equivalent geminal protons at C-6, the one resonating at a lower field is denoted as H-6a, and the one at a higher field is denoted as H-6b. HRMS spectra were recorded in the positive-ion electrospray ionization (ESI⁺) mode on a WATERS QTOF Micromass instrument or on a Q exactive mass spectrometer (Thermo Fisher Scientific) equipped with a H-ESI II Probe source. Solutions were prepared using 1:1 MeCN/H₂O containing 0.1% formic acid. In the case of sensitive compounds, solutions were prepared using 1:1 MeOH/H₂O to which was added 10 mM ammonium acetate.

Allyl 3,4-Di-O-acetyl-2-deoxy-2-dichloroacetamido-6-iodo- β -D-glucopyranoside (3). Allyl 3,4-di-O-acetyl-2-deoxy-2-dichloroacetamido-6-O-toluenesulfonyl- β -D-glucopyranoside (9.8 g, 17.2 mmol, 1.0

Scheme 8. From *N*-Protected QuIN **45**–**47** to ADDH and DATDH Bricks



equiv) was dissolved in butanone (122 mL), and sodium iodide (6.8 g, 45.3 mmol, 2.5 equiv) was added. After stirring at 80 °C for 6 h, TLC monitoring (Tol/EtOAc 4:1) showed the complete consumption of the starting material (R_f 0.25) and the presence of a less polar material (R_f 0.4). Volatiles were evaporated, and the residue was diluted with dichloromethane (300 mL). The organic phase was washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. Flash chromatography of the residue (Tol/EtOAc 86:14 → 80:20) gave the 6-iodo derivative **3** as a white solid (7.6 g, 14.1 mmol, 82%). The desired **3** had R_f 0.3 (Tol/EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3): δ 6.53 (d, 1H, $J_{\text{NH},2} = 8.8$ Hz, NH), 5.95–5.85 (m, 1H, CH_{All}), 5.89 (s, 1H, CHCl_2), 5.39–5.32 (m, 2H, H-3, $\text{CH}_{2\text{All}}$), 5.27–5.23 (m, 1H, $\text{CH}_{2\text{All}}$), 4.92 (dd, 1H, $J_{4,3} = 9.2$ Hz, $J_{4,5} = 9.6$ Hz, H-4), 4.77 (d, 1H, $J_{1,2} = 8.0$ Hz, H-1), 4.44–4.39 (m, 1H, $\text{CH}_{2\text{All}}$), 4.23–4.17 (m, 1H, $\text{CH}_{2\text{All}}$), 3.95 (dt, 1H, $J_{2,3} = 10.8$ Hz, H-2), 3.59 (ddd, 1H, H-5), 3.33 (dd, 1H, $J_{5,6a} = 2.7$ Hz, $J_{6a,6b} = 10.9$ Hz, H-6a), 3.19 (dd, 1H, $J_{5,6b} = 8.8$ Hz, H-6b), 2.09, 2.04 (2s, 6H, $\text{CH}_{3\text{Ac}}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 170.74, 169.45 (2C, CO_{Ac}), 164.44 (CO_{NH}), 133.18 (CH_{All}), 118.43 ($\text{CH}_{2\text{All}}$), 99.88 (C-1), 73.87 (C-5), 72.36 (C-4), 71.19 (C-3), 70.15 ($\text{CH}_{2\text{All}}$), 66.19 (CHCl_2), 55.33 (C-2), 20.76, 20.55 (2C, C_{Ac}), 2.91 (C-6). HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{20}\text{Cl}_2\text{INO}_7\text{Na}$, 545.9559; found, 545.9572.

Allyl 3,4-Di-O-acetyl-2,6-dideoxy-2-trichloroacetamido- β -D-glucopyranoside (6).⁴⁵ A solution of triacetate **15** (200 mg, 462 μmol , 1.0 equiv) in anhyd. DCM (5 mL) containing allyl alcohol (94 μL , 1.38 mmol, 3.0 equiv) was stirred with 4 Å MS (300 mg) under an Ar atmosphere at rt for 1 h before being cooled to 0 °C. $\text{BF}_3 \cdot \text{OEt}_2$ (116 μL , 924 μmol , 2.0 equiv) was slowly added dropwise. After stirring for 1 h at 0 °C, the reaction mixture was allowed to reach rt slowly and was stirred for 8 h at this temperature. A TLC analysis (Tol/EtOAc 3:1) showed the consumption of the starting material (R_f 0.55) and the presence of a new spot (R_f 0.65). The suspension was filtered and washed with DCM (2 \times 5 mL). The filtrate was washed with water (20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography (Tol/EtOAc 70:30 → 65:35) to give the known allyl glycoside **6** as a white solid (188 mg, 436 μmol , 94%). The 6-deoxy derivative **6** had R_f 0.45 (Tol/EtOAc 4:1). HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_7\text{Cl}_3\text{Na}$, 454.0203; found, 454.0222. Other analytical data were as published.⁴⁵

Allyl 3,4-Di-O-acetyl-2-dichloroacetamido-2,6-dideoxy- β -D-glucopyranoside (7). Route a: Bu_3SnH (48 μL , 210 μmol , 1.1 equiv) followed by Et_3B (1.0 M in hexane, 19 μL , 19 μmol , 0.1 equiv) was added to a solution of the starting material **3** (100 mg, 191 μmol , 1.0 equiv) in anhyd. DCM at 0 °C. After stirring for 1 h at this temperature, a TLC analysis (Tol/EtOAc, 7:3) showed the consumption of the starting material and the presence of two more polar spots. MeOH was added, and after stirring for another 10 min, volatiles were evaporated. Flash chromatography purification (Tol/EtOAc 85:15 → 60:40) gave by order of elution the desired product **7** (54 mg, 71%) and the chloroacetamide derivative **8** (8 mg, 11%), both isolated as white solids.

Route b: A solution of triacetate **16** (150 mg, 376 μmol , 1.0 equiv) in anhyd. DCE (5.0 mL) containing allyl alcohol (76 μL , 1.12 mmol, 3.0 equiv) was stirred with 4 Å MS (200 mg) under an Ar atmosphere at rt for 1 h before being cooled to 0 °C. $\text{BF}_3 \cdot \text{OEt}_2$ (92 μL , 752 μmol , 2.0 equiv) was added dropwise over 5 min. The suspension was stirred overnight at this temperature, at which time a TLC follow-up (Tol/EtOAc, 3:1) indicated completion. The suspension was filtered and rinsed with DCM (10 mL). The combined filtrates were washed with water (10 mL) and brine (15 mL), dried over Na_2SO_4 , and concentrated. Flash chromatography (Tol/EtOAc 70:30 → 55:45) gave allyl glycoside **7** as a white solid (132 mg, 286 μmol , 88%). Dichloroacetamide **7** had R_f 0.4 (Tol/EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3): δ 6.69 (d, 1H, $J_{\text{NH},2} = 8.8$ Hz, NH), 5.91 (s, 1H, CHCl_2), 5.89–5.81 (m, 1H, CH_{All}), 5.34–5.25 (m, 2H, H-3, $\text{CH}_{2\text{All}}$), 5.21–5.17 (m, 1H, $\text{CH}_{2\text{All}}$), 4.85 (t, 1H, $J_{3,4} = J_{4,5} = 9.6$ Hz, H-4), 4.67 (d, 1H, $J_{1,2} = 8.0$ Hz, H-1), 4.37–4.31 (m, 1H, $\text{CH}_{2\text{All}}$), 4.12–4.06 (m, 1H, $\text{CH}_{2\text{All}}$), 3.97 (dt, 1H, $J_{2,3} = 8.4$ Hz, H-2), 3.60 (dq, 1H, H-5), 2.05, 2.03 (2s, 6H, $\text{CH}_{3\text{Ac}}$), 1.27 (d, 3H, $J_{5,6} = 6.0$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 170.90, 169.55 (2C, CO_{Ac}), 164.43 (CO_{NH}), 133.48 (CH_{All}), 117.81 ($\text{CH}_{2\text{All}}$), 99.21 (C-1), 73.52 (C-4), 71.78 (C-3), 70.12

(C-5), 69.96 ($\text{CH}_{2\text{All}}$), 66.26 (CHCl_2), 55.28 (C-2), 20.66, 20.58 (2C, C_{Ac}), 17.41 (C-6). HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{21}\text{Cl}_2\text{NO}_7\text{Na}$, 420.0593; found, 420.0593.

Allyl 3,4-Di-O-acetyl-2-chloroacetamido-2,6-dideoxy- β -D-glucopyranoside (8). The 6-iodo derivative **3** (75 mg, 143 μmol , 1.0 equiv) in DCM (3 mL) was cooled to 0 °C. Bu_3SnH (165 μL , 717 μmol , 5.0 equiv) was added, followed by Et_3B (1 M in hexane, 29 μL , 29 μmol , 0.2 equiv). After stirring for 1 h at 0 °C, a TLC analysis (Tol/EtOAc 6:4) showed the absence of **3** (R_f 0.7) and appearance of a single more polar spot (R_f 0.5). MeOH was added, and volatiles were eliminated under reduced pressure. Flash chromatography (Tol/EtOAc 60:40 → 50:50) of the residue gave chloroacetamide **8** (39 mg, 107 μmol , 75%) as a white solid. Chloroacetamide **8** had R_f 0.55 (Tol/EtOAc 3:2). ^1H NMR (400 MHz, CDCl_3): δ 6.58 (d, 1H, $J_{2,\text{NH}} = 8.8$ Hz, NH), 5.92–5.82 (m, 1H, CH_{All}), 5.33–5.25 (m, 2H, H-3, $\text{CH}_{2\text{All}}$), 5.22–5.19 (m, 1H, $\text{CH}_{2\text{All}}$), 4.85 (t, 1H, $J_{3,4} = J_{4,5} = 9.4$ Hz, H-4), 4.72 (d, 1H, $J_{1,2} = 8.1$ Hz, H-1), 4.38–4.32 (m, 1H, $\text{CH}_{2\text{All}}$), 4.12–4.06 (m, 1H, $\text{CH}_{2\text{All}}$), 4.04 (d, 1H, $J = 15.1$ Hz, $\text{CH}_{2\text{CA}}$), 3.99 (d, 1H, $\text{CH}_{2\text{CA}}$), 3.90 (ddd, 1H, H-2), 3.59 (dq, 1H, H-5), 2.05, 2.04 (2s, 6H, $\text{CH}_{3\text{Ac}}$), 1.27 (d, 3H, $J_{5,6} = 6.0$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 170.75, 169.62 (CO_{Ac}), 166.23 (CO_{NH}), 133.58 (CH_{All}), 117.75 ($\text{CH}_{2\text{All}}$), 99.18 (C-1), 73.58 (C-4), 71.96 (C-3), 70.07 (C-5), 69.88 ($\text{CH}_{2\text{All}}$), 55.39 (C-2), 42.46 ($\text{CH}_{2\text{CA}}$), 20.67, 20.61 (2C, $\text{CH}_{3\text{Ac}}$), 17.45 (C-6). HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{22}\text{ClNO}_7\text{Na}$, 386.0982; found, 386.0984.

Allyl 3,4-Di-O-acetyl-6-chloro-2,6-dideoxy-2-dichloroacetamido- β -D-glucopyranoside (9). Sodium cyanoborohydride (180 mg, 28.6 mmol, 3.0 equiv) was added to a solution of the dichloroacetamide **3** (500 mg, 9.56 mmol, 1.0 equiv) in anhyd. DMF (9.6 mL) under an Ar atmosphere. After heating at 110 °C for 24 h, the reaction mixture was left to return to rt and diluted with water. The aq phase was extracted with DCM (3 \times 30 mL), and the combined organic phases were dried over Na_2SO_4 , filtered, and concentrated. Flash chromatography of the crude (Tol/EtOAc 85:15 → 80:20) gave a 1:2 mixture of the 6-chloro derivative **9** and the targeted 6-deoxy analogue **7** as a white solid (330 mg, 84%). An analytical sample of the 6-chlorinated side product **9** had R_f 0.4 (Tol/EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3): δ 6.76 (d, 1H, $J_{2,\text{NH}} = 8.8$ Hz, NH), 5.92 (s, 1H, CHCl_2), 5.90–5.82 (m, 1H, CH_{All}), 5.40 (dd, 1H, $J_{2,3} = 10.3$ Hz, $J_{3,4} = 9.2$ Hz, H-3), 5.33–5.28 (m, 1H, $\text{CH}_{2\text{All}}$), 5.24–5.21 (m, 1H, $\text{CH}_{2\text{All}}$), 5.04 (t, 1H, $J_{4,5} = 9.4$ Hz, H-4), 4.77 (d, 1H, $J_{1,2} = 8.0$ Hz, H-1), 4.40–4.35 (m, 1H, $\text{CH}_{2\text{All}}$), 4.17–4.12 (m, 1H, $\text{CH}_{2\text{All}}$), 3.99 (ddd, 1H, H-2), 3.77 (ddd, 1H, H-5), 3.67–3.58 (m, 2H, H-6a, H-6b), 2.07, 2.05 (2s, 6H, $\text{CH}_{3\text{Ac}}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 170.82, 169.42 (CO_{Ac}), 164.51 (CO_{NH}), 133.20 (CH_{All}), 118.26 ($\text{CH}_{2\text{All}}$), 99.05 (C-1), 73.88 (C-5), 71.46 (C-3), 70.38 (C-4), 70.14 ($\text{CH}_{2\text{All}}$), 66.20 (CHCl_2), 55.02 (C-2), 43.30 (C-6), 20.66, 20.57 (2C, $\text{CH}_{3\text{Ac}}$). HRMS (ESI^+) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{15}\text{H}_{24}\text{Cl}_3\text{N}_2\text{O}_7$, 449.0644; found, 449.0639.

1,3,4-Tri-O-acetyl-2,6-dideoxy-2-(4-methoxybenzylidene)amino-6-iodo- β -D-glucopyranose (11). Route a: 1,3,4-Tri-O-acetyl-2-deoxy-2-N-(4-methoxybenzylidene)-6-O-toluenesulfonyl- β -D-glucopyranose (8.0 g, 13.8 mmol, 1.0 equiv) was dissolved in butanone (69 mL), and sodium iodide (6.2 g, 41.5 mmol, 3.0 equiv) was added. After stirring at 80 °C until complete disappearance of the starting material (R_f 0.25) as monitored by TLC (Tol/EtOAc, 4:1), the reaction mixture was cooled to rt and concentrated to one-third (~20 mL) under reduced pressure. DCM (200 mL) and water (300 mL) were added. The organic layer was separated, dried over Na_2SO_4 , and concentrated in vacuo. Flash chromatography (Tol/EtOAc 90:10 → 80:20) of the residue gave iodide **11** as a white solid (6.6 g, 12.3 mmol, 89%).

Route b: Sodium iodide (1.0 g, 7.25 mmol, 2.5 equiv) was added to a solution of 1,3,4-tri-O-acetyl-2-deoxy-2-N-(4-methoxybenzylidene)-6-O-(2,4,6-triisopropylbenzenesulfonyl)- β -D-glucopyranose (2.0 g, 2.90 mmol, 1.0 equiv) in butanone (20 mL). The reaction was stirred at 80 °C for 16 h at which time TLC (Tol/EtOAc 7:3) showed reaction completion. The reaction mixture was allowed to reach rt and concentrated to dryness under reduced pressure. DCM (50 mL) and water (50 mL) were added. The DCM layer was separated, dried over Na_2SO_4 , and concentrated. The crude was purified (Tol/EtOAc 85:15 → 80:20) to give iodide **11** (1.37 g, 2.57 mmol, 88%). The desired **11**

had R_f 0.5 (Tol/EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3): δ 8.17 (s, 1H, CH=N), 7.68–7.66 (m, 2H, H_{Ar}), 6.94–6.92 (m, 2H, H_{Ar}), 5.99 (d, 1H, $J_{1,2} = 8.4$ Hz, H-1), 5.45 (t, 1H, $J_{4,3} = J_{2,3} = 9.6$ Hz, H-3), 5.03 (t, 1H, $J_{4,5} = 9.6$ Hz, H-4), 3.85 (s, 3H, OCH_3), 3.68 (ddd, H-5), 3.46 (dd, 1H, H-2), 3.40 (dd, 1H, $J_{5,6a} = 2.8$ Hz, $J_{6a,6b} = 11.2$ Hz, H-6a), 3.24 (dd, 1H, $J_{5,6b} = 6.1$ Hz, H-6b), 2.08, 2.05, 1.90 (3s, 9H, $\text{CH}_{3\text{Ac}}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 169.73, 169.54, 168.69 (3C, CO_{Ac}), 164.28 (CH=N), 162.33 ($\text{C}_{\text{q,Ar}}$), 130.24 (C_{Ar}), 128.38 ($\text{C}_{\text{q,Ar}}$), 114.08 (C_{Ar}), 92.92 (C-1, $^1J_{\text{C,H}} = 167$ Hz), 73.28 (C-5), 73.02 (C-3), 72.99 (C-2), 72.47 (C-4), 55.40 (OCH_3), 20.76, 20.48 (3C, C_{Ac}), 3.38 (C-6). HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{INO}_8$, 534.0625; found, 534.0628.

1,3,4-Tri-O-acetyl-2,6-dideoxy-2-(4-methoxybenzylidene)amino- β -D-glucopyranose (12). A solution of the 6-iodo derivative **11** (6.4 g, 12.0 mmol, 1.0 equiv) in anhyd. DCM (100 mL) was cooled to 0 °C. Tributyltin hydride (3.04 mL, 13.2 mmol, 1.1 equiv) was added, followed by the addition of Et_3B (1 M in hexane, 1.2 mL, 1.2 mmol, 1.0 equiv). After stirring for 1 h at 0 °C, a TLC monitoring (DCM/EtOAc 9:1) showed the absence of the starting material (R_f 0.65) and the presence of a new spot (R_f 0.6). MeOH (2 mL) was added, and after 15 min, volatiles were evaporated. Flash chromatography of the crude residue (Tol/EtOAc 81:18 \rightarrow 80:20) gave the 6-deoxy derivative **12** as a white solid (4.55 g, 11.1 mmol, 93%). Triacetate **12** had R_f 0.5 (Tol/EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3): δ 8.17 (s, 1H, CH=N), 7.69–7.66 (m, 2H, H_{Ar}), 6.95–6.91 (m, 2H, H_{Ar}), 5.95 (d, 1H, $J_{1,2} = 8.4$ Hz, H-1), 5.41 (t, 1H, $J_{3,4} = J_{2,3} = 9.6$ Hz, H-3), 4.89 (t, 1H, $J_{4,5} = 9.6$ Hz, H-4), 3.89–3.85 (m, 4H, H-5, OCH_3), 3.42 (dd, 1H, H-2), 2.07, 2.03, 1.89 (3s, 9H, $\text{CH}_{3\text{Ac}}$), 1.30 (d, 3H, $J_{5,6} = 6.2$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 170.11, 169.53, 168.84 (3C, CO_{Ac}), 163.92 (CH=N), 162.25 ($\text{C}_{\text{q,Ar}}$), 130.19 (C_{Ar}), 128.50 ($\text{C}_{\text{q,Ar}}$), 114.06 (C_{Ar}), 93.11 (C-1, $^1J_{\text{C,H}} = 168$ Hz), 73.46 (C-4), 73.40 (C-3), 73.30 (C-2), 70.92 (C-5), 55.39 (OCH_3), 20.79, 20.76, 20.52 (3C, C_{Ac}), 17.47 (C-6). HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_8$, 408.1658; found, 408.1654.

1,3,4-Tri-O-acetyl-2-amino-2,6-dideoxy- β -D-glucopyranose (13). Route a: Zn (108 mg, 1.65 mmol, 8.0 equiv) and AcOH (94 μL , 1.65 mmol, 8.0 equiv) were added to a solution of azide **14** (65 mg, 206 μmol , 1.0 equiv) in anhyd. THF (4 mL). The reaction mixture was stirred for 6 h at rt. The suspension was filtered over a bed of Celite and washed with THF (2 \times 5 mL). The combined filtrate was concentrated to give the crude amine **13** as a 1:5 α/β mixture (54 mg, 189 μmol , 91%). The target **13** had HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_7\text{Na}$, 312.1054; found, 312.1051.

Route b: Imine **12** (6.0 g, 14.7 mmol, 1.0 equiv) was dissolved in acetone (60 mL), and commercially available 2 N HCl in Et_2O (8.1 mL, 16.2 mmol, 1.1 equiv) was added. The reaction mixture was heated for 30 min at 60 °C and a precipitate appeared. After precipitation completion at 0 °C, the precipitate was filtered and washed thoroughly with Et_2O . The target **13** was isolated as a white solid (4.04 g, 12.4 mmol, 84%). Amine **13**, isolated in the form of the hydrochloride salt, had R_f 0.1 (EtOAc/MeOH 4:1). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.77 (brs, 3H, NH_3^+), 5.85 (d, 1H, $J_{1,2} = 8.4$ Hz, H-1), 5.29 (dd, 1H, $J_{4,3} = 9.2$ Hz, $J_{2,3} = 10.0$ Hz, H-3), 4.69 (t, 1H, H-4), 3.83–3.76 (m, 1H, H-5), 3.53 (dd, 1H, H-2), 2.16, 2.03, 2.01 (3s, 9H, $\text{CH}_{3\text{Ac}}$), 1.12 (d, 3H, $J_{5,6} = 6.1$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{DMSO}-d_6$): δ 170.22, 169.99, 169.17 (3C, CO_{Ac}), 90.53 (C-1), 73.24 (C-4), 70.79 (C-3), 70.46 (C-5), 52.87 (C-2), 21.41, 21.31, 20.87 (3C, C_{Ac}), 17.44 (C-6). HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{20}\text{NO}_7$, 290.1240; found, 290.1250.

1,3,4-Tri-O-acetyl-2-azido-2-deoxy- α/β -D-glucopyranose (14). Route a: Bu_3SnH (230 μL , 998 μmol , 1.1 equiv) and Et_3B (1 M in Hexane, 91 μL , 91 μmol , 0.1 equiv) were successively added to a solution of 1,3,4-tri-O-acetyl-2-azido-2,6-dideoxy-6-iodo- α/β -D-glucopyranose (400 mg, 907 μmol , 1.0 equiv) in anhyd. DCM (5 mL) cooled to 0 °C. After 30 min at this temperature and following a TLC analysis, more Bu_3SnH (42 μL , 181 μmol , 0.2 equiv) was added. The reaction was left for another 30 min at 0 °C, at which point a TLC follow-up (Tol/EtOAc 4:1) revealed completion. MeOH was added, and after 10 min, volatiles were evaporated. Flash chromatography (Tol/EtOAc 90:10 \rightarrow 88:12) gave the 6-deoxy derivative **14** as a 1:5 α/β mixture

(250 mg, 793 μmol , 87%). HRMS (ESI^+) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{19}\text{H}_{27}\text{N}_4\text{O}_{10}\text{S}$, 333.1407; found, 333.1405.

Route b: Sodium azide (144 mg, 2.21 mmol, 8.0 equiv) was dissolved in water (3 mL). DCM (6 mL) was added, and the biphasic mixture was cooled to 0 °C. Trifluoromethane-sulfonic anhydride (69 μL , 415 μmol , 1.5 equiv) was added dropwise. After stirring the reaction mixture for 2 h at 0 °C, the organic phase was separated and washed with satd aq NaHCO_3 . Amine hydrochloride **13** (90 mg, 277 μmol , 1.0 equiv) was dissolved in MeOH, and NaHCO_3 (23 mg, 277 μmol , 1.0 equiv) was added. The reaction mixture was cooled to 0 °C, and the DCM extract was immediately added to the solution. The reaction mixture was allowed to reach rt and stirred overnight at this temperature. Following a TLC analysis (Tol/EtOAc 1:1), the mixture was concentrated in vacuo. Flash chromatography (Tol/EtOAc 90:10 \rightarrow 88:12) of the crude gave **14** as a colorless oil (45 mg, 143 μmol , 51%).

The β isomer had R_f 0.6 (Tol/EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3): δ 5.55 (d, 1H, $J_{1,2} = 8.4$ Hz, H-1), 5.06 (dd, 1H, $J_{2,3} = 10.0$ Hz, $J_{3,4} = 9.6$ Hz, H-3), 4.78 (t, 1H, $J_{4,5} = 9.6$ Hz, H-4), 3.69 (dq, 1H, H-5), 3.64 (dd, 1H, H-2), 2.20, 2.10, 2.06 (3s, 9H, $\text{CH}_{3\text{Ac}}$), 1.24 (d, 3H, $J_{5,6} = 6.2$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 169.81, 169.77, 168.64 (3C, CO_{Ac}), 92.50 (C-1, $^1J_{\text{C,H}} = 168$ Hz), 73.09 (C-4), 72.68 (C-3), 70.96 (C-5), 62.94 (C-2), 20.84, 20.60 (3C, C_{Ac}), 17.22 (C-6).

1,3,4-Tri-O-acetyl-2,6-dideoxy-2-trichloroacetamido- β -D-glucopyranose (15). The 6-deoxy derivative **12** (300 mg, 737 μmol , 1.0 equiv) was dissolved in acetone (6 mL), and 1 N HCl in Et_2O (0.81 mL, 810 μmol , 1.1 equiv) was added. The reaction mixture was heated to reflux for 10 min, at which time a precipitate appeared. The system was cooled to 0 °C to allow complete precipitation. The precipitate was filtered and washed with Et_2O (2 \times 5 mL). Pyridine (297 μL , 3.68 mmol, 5.0 equiv) and then trichloroacetyl chloride (164 μL , 1.47 mmol, 2.0 equiv) were added to a suspension of the precipitate in DCM (6 mL) at 0 °C. After 30 min, the suspension had turned into a clear solution. At completion, MeOH (1 mL) was added. Volatiles were evaporated and coevaporated with toluene (3 \times 5 mL). Flash chromatography (Tol/EtOAc 85:15 \rightarrow 80:20) gave the triacetate **15** as a white solid (230 mg, 531 μmol , 72%). Trichloroacetamide **15** had R_f 0.5 (Tol/EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3): δ 7.03 (d, 1H, $J_{2,\text{NH}} = 9.6$ Hz, NH), 5.80 (d, 1H, $J_{1,2} = 10.0$ Hz, H-1), 5.30 (dd, 1H, $J_{4,3} = 9.6$ Hz, $J_{2,3} = 10.8$ Hz, H-3), 4.95 (t, 1H, $J_{4,5} = 9.6$ Hz, H-4), 4.28 (ddd, 1H, H-2), 3.76 (dq, 1H, H-5), 2.13, 2.10, 2.07 (3s, 9H, $\text{CH}_{3\text{Ac}}$), 1.30 (d, 3H, $J_{5,6} = 6.2$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 171.32, 169.44, 169.39 (3C, CO_{Ac}), 162.18 (CO_{NH}), 92.18 (C_{Cl_3}), 92.12 (C-1), 72.74 (C-4), 71.86 (C-3), 71.45 (C-5), 55.03 (C-2), 20.70, 20.60, 20.52 (3C, C_{Ac}), 17.30 (C-6). HRMS (ESI^+) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{14}\text{H}_{22}\text{Cl}_3\text{N}_2\text{O}_8$, 451.0442; found, 451.0444.

1,3,4-Tri-O-acetyl-2,6-dideoxy-2-dichloroacetamido- β -D-glucopyranose (16). Imine **12** (330 mg, 810 μmol , 1.0 equiv) was dissolved in acetone (9 mL), and HCl (1 N in Et_2O , 0.89 mL, 892 μmol , 1.1 equiv) was added. The reaction mixture was stirred at 60 °C for 30 min while becoming turbid over time. The system was cooled to 0 °C to allow complete precipitation. The precipitate was filtered and washed thoroughly with Et_2O (2 \times 5 mL). Anhyd. pyridine (327 μL , 4.05 mmol, 5.0 equiv) was added to a suspension of the crude amine **13** in DCM (10 mL). The suspension was cooled to 0 °C, and dichloroacetic anhydride (117 μL , 1.21 mmol, 1.5 equiv) was added slowly. After stirring for 1 h at this temperature, a TLC follow-up (Tol/EtOAc 4:1) revealed reaction completion. MeOH (1.0 mL) was added, and stirring was pursued at rt for an additional 5 min. After dilution with DCM (10 mL), the organic layer was washed with 1 N aq HCl (20 mL), satd aq NaHCO_3 (20 mL), and brine (20 mL). The organic phase was dried over Na_2SO_4 , filtered, and concentrated to dryness. Flash chromatography (Tol/EtOAc 80:20 \rightarrow 75:25) gave the desired **16** as a white solid (250 mg, 626 μmol , 77%). The dichloroacetamide **16** had R_f 0.4 (Tol/EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3): δ 6.92 (d, 1H, $J_{2,\text{NH}} = 9.6$ Hz, NH), 5.88 (s, 1H, CHCl_2), 5.80 (d, 1H, $J_{1,2} = 8.8$ Hz, H-1), 5.31 (dd, 1H, $J_{4,3} = 9.2$ Hz, $J_{2,3} = 10.8$ Hz, H-3), 4.90 (t, 1H, $J_{4,5} = 9.6$ Hz, H-4), 4.27 (ddd, 1H, H-2), 3.76 (dq, 1H, H-5), 2.12, 2.09, 2.06 (3s, 9H, $\text{CH}_{3\text{Ac}}$), 1.29 (d, 3H, $J_{5,6} = 6.2$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 171.24, 169.53, 169.42 (3C, CO_{Ac}), 164.70 (CO_{NH}), 92.10 (C-1, $^1J_{\text{C,H}} = 165.8$ Hz), 72.96 (C-4), 71.90 (C-3), 71.33 (C-5), 66.10

(CHCl₃), 53.80 (C-2), 20.72, 20.61, 20.55 (3C, C_{Ac}), 17.31 (C-6). HRMS (ESI⁺) *m/z*: [M + NH₄]⁺ calcd for C₁₄H₂₃Cl₂N₂O₈, 417.0832; found, 417.0835.

1,3,4-Tri-O-acetyl-2,6-dideoxy-2-trifluoroacetamido-β-D-glucopyranose (17). To a solution of triacetate **12** (400 mg, 982 μmol, 1.0 equiv) in acetone (12 mL) was added 1 N HCl in Et₂O (2.94 mL, 2.94 mmol, 3.0 equiv). The solution was stirred at 80 °C for 2 h and a white precipitate appeared. The suspension was allowed to reach rt, and anhyd. DCM (10 mL) was added. The solution was cooled to 0 °C, and pyridine (396 μL, 4.91 mmol, 5.0 equiv) was added, followed by trifluoroacetic anhydride (273 μL, 1.96 mmol, 2.0 equiv). After stirring at 0 °C for 1 h, MeOH (1 mL) was added to the obtained yellowish solution. After another 20 min while the temperature reached rt, volatiles were removed. The residue was diluted with DCM (30 mL), and the organic phase was washed with water, dried over Na₂SO₄, and concentrated. Flash chromatography (Tol/MeCN 88:12 → 86:14) gave the desired **17** as a white solid (290 mg, 629 μmol, 77%). Trifluoroacetamide **17** had *R_f* 0.35 (Tol/MeCN 6:1). ¹H NMR (400 MHz, CDCl₃): δ 7.42 (d, 1H, *J*_{2,NH} = 9.7 Hz, NH), 5.74 (d, 1H, *J*_{1,2} = 8.8 Hz, H-1), 5.31 (dd, 1H, *J*_{4,3} = 9.5 Hz, *J*_{2,3} = 10.7 Hz, H-3), 4.88 (t, 1H, *J*_{4,5} = 9.6 Hz, H-4), 4.38–4.31 (m, 1H, H-2), 3.76 (dq, 1H, H-5), 2.12, 2.08, 2.06 (3s, 9H, CH_{3Ac}), 1.28 (d, 3H, *J*_{5,6} = 6.2 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 171.80, 169.64, 169.61 (3C, CO_{Ac}), 157.50 (CO_{NH}, *J*_{C,F} = 37.4 Hz), 115.62 (CF₃, *J*_{C,F} = 286.1 Hz), 91.79 (C-1, ¹*J*_{C,H} = 166.0 Hz), 73.05 (C-4), 72.24 (C-3), 71.18 (C-5), 53.38 (C-2), 20.59, 20.52, 20.31 (3C, C_{Ac}), 17.22 (C-6). HRMS (ESI⁺) *m/z*: [M + NH₄]⁺ calcd for C₁₄H₂₂F₃N₂O₈, 403.1322; found, 403.1323.

1,3,4-Tri-O-acetyl-2,6-dideoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranose (18). 2 N HCl in Et₂O (1.62 mL, 3.24 mmol, 1.1 equiv) was added to a solution of imine **12** (1.2 g, 2.94 mmol, 1.0 equiv) in acetone, and the reaction mixture was refluxed for 1 h. A white precipitate was formed, which was filtered off and washed thoroughly with Et₂O. Pyridine (476 μL, 5.89 mmol, 2.0 equiv) and 2,2,2-trichloroethoxycarbonyl chloride (609 μL, 4.42 mmol, 1.5 equiv) were added to a suspension of the crude amine in DCM (20 mL) at 0 °C. After stirring for 1 h while allowing the reaction to reach rt, a TLC (Tol/EtOAc 4:1) follow-up revealed reaction completion. MeOH (1.0 mL) was added, and after stirring for another 10 min, volatiles were evaporated. Flash chromatography (Tol/EtOAc 85:15 → 80:20) gave triacetate **18** as a white solid (1.1 g, 2.37 mmol, 81%). Triacetate **18** had *R_f* 0.45 (Tol/EtOAc, 4:1). ¹H NMR (400 MHz, CDCl₃): δ 5.72 (d, 1H, *J*_{1,2} = 8.7 Hz, H-1), 5.47 (d, 1H, *J*_{2,NH} = 9.5 Hz, NH), 5.21 (dd, 1H, *J*_{4,3} = 9.6 Hz, *J*_{2,3} = 10.3 Hz, H-3), 4.86 (t, 1H, *J*_{4,5} = 9.6 Hz, H-4), 4.77–4.71 (m, 2H, CH_{2Troc}), 4.00–3.93 (m, 1H, H-2), 3.74 (dq, 1H, H-5), 2.11, 2.07, 2.05 (3s, 9H, CH_{3Ac}), 1.26 (d, 3H, *J*_{5,6} = 6.2 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 171.94, 169.66, 169.38 (3C, CO_{Ac}), 154.23 (CO_{NH}), 95.48 (CCl₃), 92.34 (C-1), 74.48 (CH_{2Troc}), 73.23 (C-4), 72.24 (C-3), 71.01 (C-5), 55.39 (C-2), 20.82, 20.64, 20.61 (3C, C_{Ac}), 17.31 (C-6). HRMS (ESI⁺) *m/z*: [M + NH₄]⁺ calcd for C₁₅H₂₄Cl₃N₂O₉, 481.0542; found, 481.0544.

Allyl 3,4-Di-O-acetyl-2,6-dideoxy-2-trifluoroacetamido-β-D-glucopyranoside (19). Route a: Et₃B (1 M in hexane, 8.5 mL, 8.5 mmol, 0.1 equiv) was added dropwise to a solution of the 6-iodo precursor **27** (43.4 g, 85.2 mmol, 1.0 equiv) and Bu₃SnH (21.5 mL, 93.7 mmol, 1.1 equiv) in anhyd. DCM (600 mL) at 0 °C. The solution was stirred for 1 h at 0 °C, at which time a follow-up by TLC (Tol/EtOAc 7:3) indicated the absence of the starting material (*R_f* 0.5) and the presence of a less polar product (*R_f* 0.4). Volatiles were evaporated, and the crude was purified by flash chromatography (Tol/EtOAc 5:1 → 3:1). The desired **19** (31.4 g, 81.9 mmol, 96%) was obtained as a white solid. Analytical data of **19** were as described below.

Route b: Allyl alcohol (52 μL, 779 μmol, 3.0 equiv) was added to triacetate **17** (100 mg, 260 μmol, 1.0 equiv) in anhyd. DCM (3 mL). The mixture was stirred with activated 4 Å MS (200 mg) under Ar for 1 h at rt and cooled to 0 °C. BF₃·OEt₂ (70 μL, 571 mmol, 2.2 equiv) was added. The suspension was stirred for 12 h while slowly reaching rt. Following a TLC control (DCM/EtOAc, 9:1), the suspension was filtered and thoroughly washed with DCM. The combined filtrates were washed with water (10 mL) and brine (10 mL). Flash chromatography (Tol/EtOAc 80:20 → 75:25) of the crude gave the desired **19** as a white

solid (92 mg, 240 μmol, 92%). Allyl glycoside **19** had *R_f* 0.4 (Tol/EtOAc 7:3). ¹H NMR (400 MHz, CDCl₃): δ 6.82 (d, 1H, *J*_{NH,2} = 9.0 Hz, NH), 5.89–5.79 (m, 1H, CH_{All}), 5.30–5.23 (m, 2H, H-3, CH_{2All}), 5.22–5.18 (m, 1H, CH_{2All}), 4.86 (t, 1H, *J*_{4,3} = *J*_{4,5} = 9.5 Hz, H-4), 4.63 (d, 1H, *J*_{1,2} = 8.3 Hz, H-1), 4.37–4.32 (m, 1H, CH_{2All}), 4.11–4.03 (m, 2H, H-2, CH_{2All}), 3.61 (dq, 1H, H-5), 2.05, 2.04 (2s, 6H, CH_{3Ac}), 1.28 (d, 3H, *J*_{5,6} = 6.2 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 171.30, 169.52 (2C, CO_{Ac}), 157.35 (CO_{NH}, *J*_{C,F} = 37.3 Hz), 133.25 (CH_{All}), 117.81 (CH_{2All}), 115.55 (CF₃, *J*_{C,F} = 286.1 Hz), 98.99 (C-1, ¹*J*_{C,H} = 161.0 Hz), 73.42 (C-4), 72.02 (C-3), 70.11 (C-5), 69.87 (CH_{2All}), 54.99 (C-2), 20.61, 20.39 (2C, CH_{3Ac}), 17.36 (C-6). HRMS (ESI⁺) *m/z*: [M + NH₄]⁺ calcd for C₁₅H₂₄F₃N₂O₇, 401.1536; found, 401.1530.

Allyl 3,4-Di-O-acetyl-2,6-dideoxy-2-(2,2,2-trichloroethoxyacetamido)-β-D-glucopyranoside (20). A solution of triacetate **18** (1.0 g, 2.16 mmol, 1.0 equiv) in anhyd. DCM (10 mL) containing allyl alcohol (440 μL, 6.47 mmol, 3.0 equiv) was stirred with 4 Å MS (500 mg) in an Ar atmosphere at rt for 1 h before being cooled to 0 °C. BF₃·OEt₂ (533 μL, 4.31 mmol, 2.0 equiv) was added dropwise, and the reaction mixture was allowed to reach rt. After 36 h, a TLC (Tol/EtOAc, 3:1) follow-up indicated complete conversion. The suspension was filtered and rinsed with DCM (10 mL). The combined filtrates were washed with water (20 mL) and 50% aq NaHCO₃ (20 mL), dried over Na₂SO₄, and concentrated to dryness. Flash chromatography (Tol/EtOAc 90:10 → 88:12) gave the desired **20** as a white solid (800 mg, 1.80 mmol, 83%). The allyl glycoside **20** had *R_f* 0.15 (Tol/EtOAc, 9:1). ¹H NMR (400 MHz, CDCl₃): δ 5.91–5.83 (m, 1H, CH_{All}), 5.32–5.27 (m, 1H, CH_{2All}), 5.24–5.20 (m, 2H, CH_{2All}, H-3), 5.13 (d, 1H, *J*_{NH,2} = 8.4 Hz, NH), 4.84 (t, 1H, *J*_{4,3} = *J*_{4,5} = 9.6 Hz, H-4), 4.79 (d, 1H, CH_{2Troc}), 4.70 (d, 1H, *J* = 11.9 Hz, CH_{2Troc}), 4.61 (d, 1H, *J*_{1,2} = 8.4 Hz, H-1), 4.40–4.35 (m, 1H, CH_{2All}), 4.12–4.07 (m, 1H, CH_{2All}), 3.71–3.64 (m, 1H, H-2), 3.57 (dq, 1H, H-5), 2.06, 2.05 (2s, 6H, CH_{3Ac}), 1.25 (d, 3H, *J*_{5,6} = 6.2 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 170.72, 169.69 (2C, CO_{Ac}), 154.10 (CO_{NH}), 133.57 (CH_{All}), 117.68 (CH_{2All}), 99.63 (C-1, *J*_{C,H} = 162.4 Hz), 95.50 (CCl₃), 74.44 (CH_{2Troc}), 73.74 (C-4), 72.04 (C-3), 70.00 (CH_{2All}), 69.94 (C-5), 56.51 (C-2), 20.68, 20.65 (2C, C_{Ac}), 17.41 (C-6). HRMS (ESI⁺) *m/z*: [M + NH₄]⁺ calcd for C₁₆H₂₆Cl₃N₂O₈, 479.0749; found, 479.0740.

Phenyl 3,4-Di-O-acetyl-2,6-dideoxy-2-trifluoroacetamido-1-thio-β-D-glucopyranoside (21). A solution of triacetate **17** (200 mg, 519 μmol, 1.0 equiv) and thiophenol (158 μL, 1.55 mmol, 3.0 equiv) in anhyd. DCM (6 mL) was stirred with activated 4 Å MS (300 mg) for 1 h and cooled to –10 °C. BF₃·OEt₂ (128 μL, 1.03 mmol, 2.0 equiv) was added, and after reaching rt slowly, the reaction mixture was stirred overnight. The suspension was filtered and washed thoroughly with DCM (15 mL). The organic phase was washed with water (10 mL), satd aq NaHCO₃ (10 mL), and brine (10 mL); dried over Na₂SO₄; and concentrated to dryness. Flash chromatography (Tol/EtOAc 90:10 → 86:14) gave the desired **21** as a white solid (190 mg, 436 μmol, 84%). The phenyl thioglycoside **21** had *R_f* 0.5 (Tol/EtOAc 4:1). ¹H NMR (400 MHz, CDCl₃): δ 7.52–7.48 (m, 2H, H_{Ar}), 7.35–7.30 (m, 3H, H_{Ar}), 7.07 (d, 1H, *J*_{2,NH} = 9.6 Hz, NH), 5.27 (dd, 1H, *J*_{4,3} = 9.8 Hz, *J*_{2,3} = 10.0 Hz, H-3), 4.82 (t, 1H, *J*_{4,5} = 9.6 Hz, H-4), 4.75 (d, 1H, *J*_{1,2} = 10.4 Hz, H-1), 4.14–4.06 (m, 1H, H-2), 3.64 (dq, 1H, H-5), 2.01, 1.93 (2s, 6H, CH_{3Ac}), 1.29 (d, 3H, *J*_{5,6} = 6.2 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 171.64, 169.39 (2C, CO_{Ac}), 157.15 (CO_{NH}, *J*_{C,F} = 37.4 Hz), 133.42 (C_{Ar}), 131.43 (C_{qAr}), 129.06, 128.65 (C_{Ar}), 115.64 (CF₃, *J*_{C,F} = 286.1 Hz), 85.98 (C-1, ¹*J*_{C,H} = 156 Hz), 74.47 (C-5), 73.61 (C-3), 73.15 (C-4), 53.47 (C-2), 20.46, 20.36 (2C, C_{Ac}), 17.64 (C-6). HRMS (ESI⁺) *m/z*: [M + NH₄]⁺ calcd for C₁₈H₂₄F₃N₂O₆S, 453.1301; found, 453.1289.

4-Methoxyphenyl 3,4-Di-O-acetyl-2-azido-2-deoxy-α/β-D-glucopyranoside (23). A solution of triacetate **14** (120 mg, 312 μmol, 1.0 equiv) and 4-methoxyphenol (116 mg, 935 μmol, 3.0 equiv) in anhyd. DCM (5 mL) was stirred with activated MS 4 Å (250 mg) for 1 h. The suspension was cooled to 0 °C, and BF₃·OEt₂ (115 μL, 935 μmol, 3.0 equiv) was added. After warming up to rt, the reaction mixture was heated at 40 °C for 24 h. A TLC analysis (Tol/EtOAc 4:1) showed the presence of a new spot (*R_f* 0.65) migrating closely to the starting material (*R_f* 0.6). After reaching rt, the reaction mixture was filtered and

washed with DCM (2 × 5 mL). The organic phase was washed with water, satd aq NaHCO₃, and brine; dried over Na₂SO₄; filtered; and concentrated to dryness. Flash chromatography (Tol/EtOAc 90:10) gave the target glycoside **23** as a 2:1 α/β mixture (105 mg, 273 μ mol, 77%). The obtained white solid had R_f 0.7 (Tol/Acetone 4:1). The α anomer had ¹H NMR (400 MHz, CDCl₃): δ 7.08–7.05 (m, 2H, H_{Ar}), 6.89–6.85 (m, 2H, H_{Ar}), 5.66 (dd, 1H, $J_{3,4}$ = 9.6 Hz, H-3), 5.46 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.88 (t, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 4.11 (dq, 1H, H-5), 3.80 (s, 3H, OCH₃), 3.41 (dd, 1H, $J_{2,3}$ = 10.8 Hz, H-2), 2.14, 2.08 (2s, 6H, CH_{3Ac}), 1.21 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6). ¹³C{¹H} NMR (CDCl₃): δ 170.10, 169.98 (2C, CO_{Ac}), 155.51, 150.32, 118.73, 117.84, 114.84, 114.68 (C_{Ar}), 97.41 (C-1, $J_{C,H}$ = 174.4 Hz), 73.80 (C-4), 70.25 (C-3), 66.16 (C-5), 61.16 (C-2), 55.67 (OCH₃), 20.71, 20.67 (CH_{3Ac}), 17.28 (C-6). HRMS (ESI⁺) m/z : [M + NH₄]⁺ calcd for C₁₇H₂₅N₄O₇, 397.1718; found, 397.1711.

The β anomer had ¹H NMR (400 MHz, CDCl₃): δ 7.08–7.05 (m, 2H, H_{Ar}), 6.89–6.85 (m, 2H, H_{Ar}), 5.03 (dd, 1H, $J_{3,4}$ = 9.6 Hz, $J_{2,3}$ = 10.4 Hz, H-3), 4.91–4.82 (m, 2H, H-4, H-1), 3.78 (s, 3H, OCH₃), 3.75 (dd, 1H, $J_{1,2}$ = 8.1 Hz, H-2), 3.65 (dq, 1H, $J_{4,5}$ = 9.6 Hz, H-5), 2.12, 2.06 (2s, 6H, CH_{3Ac}), 1.30 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6). ¹³C{¹H} NMR (CDCl₃): δ 169.94, 169.82 (2C, CO_{Ac}), 155.90, 150.86, 118.73, 117.85, 116.02, 114.84, 114.77, 114.68 (C_{Ar}), 101.41 (C-1, $J_{C,H}$ = 162.0 Hz), 73.31 (C-4), 72.41 (C-3), 70.17 (C-5), 63.92 (C-2), 55.77 (OCH₃), 20.71, 20.67 (CH_{3Ac}), 17.42 (C-6).

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-trifluoroacetamido- β -D-glucopyranose (24).⁵⁸ Anhyd. pyridine (42.1 mL, 521 mmol, 4.0 equiv) was added to a suspension of commercially available tetraacetate **1** (50.0 g, 130 mmol, 1.0 equiv) in anhyd. DCM (370 mL). The suspension was cooled to 0 °C. Trifluoroacetic anhydride (36.7 mL, 260 mmol, 2.0 equiv) was added slowly, and the mixture was stirred for 1 h while the bath temperature was allowed to reach rt. A follow-up by TLC (Tol/EtOAc 7:3) indicated the absence of **1** and the presence of a less polar product (R_f 0.25). MeOH (30 mL) was added, and after an additional 30 min at rt, DCM (200 mL) was added. The organic layer was washed with 1 N aq HCl (800 mL) and satd aq NaHCO₃ (600 mL), dried over Na₂SO₄, filtered, and concentrated to dryness. The crude **24** (57.7 g, quant.) was obtained as a pale yellow solid. An analytical sample of the trifluoroacetamide target had R_f 0.35 (Tol/MeCN 4:1). ¹H NMR (400 MHz, CDCl₃): δ 7.15 (d, 1H, $J_{NH,2}$ = 9.6 Hz, NH), 5.77 (d, 1H, $J_{1,2}$ = 8.7 Hz, H-1), 5.34 (dd, 1H, $J_{3,2}$ = 10.6 Hz, $J_{3,4}$ = 9.4 Hz, H-3), 5.15 (t, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 4.41–4.33 (m, 1H, H-2), 4.30 (dd, 1H, $J_{6a,5}$ = 4.8 Hz, H-6a), 4.18 (dd, 1H, $J_{6b,5}$ = 2.3 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6b), 3.91 (ddd, 1H, H-5), 2.14, 2.12, 2.08, 2.07 (4s, 12H, CH_{3Ac}). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 171.63, 170.59, 169.37, 169.30 (4C, CO_{Ac}), 157.50 (CO_{NH}, $J_{C,F}$ = 37.6 Hz), 115.65 (CF₃, $J_{C,F}$ = 286.1 Hz), 91.86 (C-1, $J_{C,H}$ = 166.2 Hz), 73.04 (C-5), 72.08 (C-3), 67.91 (C-4), 61.62 (C-6), 53.26 (C-2), 20.61, 20.46, 20.33 (4C, C_{Ac}). HRMS (ESI⁺) m/z : [M + Na]⁺ calcd for C₁₆H₂₀F₃N₂O₁₀Na, 466.0937; found, 466.0931.

Allyl 3,4,6-Tri-O-acetyl-2-deoxy-2-trifluoroacetamido- β -D-glucopyranoside (25). A solution of the crude trifluoroacetamide **24** (57.7 g, 130 mmol, 1.0 equiv) and allyl alcohol (26.4 mL, 387 mmol, 3.0 equiv) in anhyd. DCM (120 mL) was stirred with freshly activated MS 4 Å (17 g) for 30 min under an Ar atmosphere. The suspension was cooled to 0 °C, and BF₃·OEt₂ (35 mL, 284 mmol, 2.2 equiv) was added dropwise. The bath was allowed to reach rt, and the reaction mixture was stirred for 48 h at this temperature. A TLC (DCM/EtOAc 9:1) follow-up indicated the conversion of the starting material (R_f 0.25) into a less polar compound (R_f 0.35). The suspension was passed through a fitted funnel, and solids were rinsed with DCM (2 × 50 mL). The organic layer was washed with water and satd aq NaHCO₃, dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (DCM/EtOAc 98:2 → 90:10) of the residue gave the desired allyl glycoside **25** as a white solid (56.3 g, 127 mmol, 98%) and had R_f 0.6 (Tol/EtOAc 2:1). ¹H NMR (400 MHz, CDCl₃): δ 6.63 (bs, 1H, NH), 5.90–5.80 (m, 1H, CH_{2All}), 5.35–5.30 (t, 1H, $J_{2,3}$ = 10.2 Hz, H-3), 5.26–5.22 (m, 2H, CH_{2All}), 5.12 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.7 Hz, H-4), 4.70 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1), 4.39–4.34 (m, 1H, CH_{2All}), 4.30 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, $J_{6a,5}$ = 4.9 Hz, H-6a), 4.18 (dd, 1H, $J_{6b,5}$ = 2.5 Hz, H-6b), 4.12–4.01 (m, 2H, CH_{2All}, H-2), 3.75 (ddd, 1H, H-5), 2.11 (s, 3H, CH_{3Ac}), 2.05 (s, 6H, CH_{3Ac}). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 171.07, 170.65, 169.27

(CO_{Ac}), 157.33 (CO_{NH}, $J_{C,F}$ = 37.4 Hz), 133.02 (CH_{2All}), 118.16 (CH_{2All}), 115.57 (CF₃, $J_{C,F}$ = 286.5 Hz), 99.06 (C-1, $J_{C,H}$ = 160.5 Hz), 71.98 (C-5), 71.76 (C-3), 70.12 (CH_{2All}), 68.48 (C-4), 62.02 (C-6), 54.88 (C-2), 20.67, 20.53, 20.37 (3C, CH_{3Ac}). HRMS (ESI⁺) m/z : [M + NH₄]⁺ calcd for C₁₇H₂₆F₃N₂O₉, 459.1590; found, 459.1586.

Allyl 3,4-Di-O-acetyl-2-deoxy-6-O-toluenesulfonyl-2-trifluoroacetamido- β -D-glucopyranoside (26). NaOMe (25% in MeOH, 8.15 mL, 37.7 mmol, 0.3 equiv) was added to a solution of triacetate **25** (57.4 g, 130 mmol, 1.0 equiv) in MeOH (600 mL), and the mixture was stirred at rt for 1 h at which time a TLC follow-up (Tol/EtOAc 7:3) indicated reaction completion. A minimal amount of Dowex-H⁺ resin was added portionwise to reach neutral pH. The suspension was filtered, and the resin was thoroughly washed with MeOH. Volatiles were evaporated, and the crude material was dried under high vacuum before being dissolved in anhyd. pyridine (800 mL). Tosyl chloride (59.9 g, 314.5 mmol, 2.5 equiv) was added to the resulting solution at 0 °C. After 2.5 h at this temperature, acetic anhydride (59.4 mL, 629 mmol, 5.0 equiv) was added, and the reaction mixture was stirred for another 1 h at 0 °C and then for 2 h at rt. A follow-up by TLC (Tol/EtOAc 7:3) indicated the presence of a major product (R_f 0.5). MeOH (40 mL) was added, and after 30 min, volatiles were evaporated. The crude was dissolved in DCM (500 mL), and the organic layer was washed with 1 N aq HCl and satd aq NaHCO₃, dried over Na₂SO₄, filtered, and concentrated. Flash chromatography (Tol/EtOAc 80:20 → 75:25) gave the desired **26** (64.0 g, 89% over three steps). The tosylate **26** had R_f 0.35 (Tol/EtOAc 4:1). ¹H NMR (400 MHz, CDCl₃): δ 7.80–7.78 (m, 2H, H_{Ar}), 7.38–7.36 (m, 2H, H_{Ar}), 7.04 (d, 1H, $J_{NH,2}$ = 9.1 Hz, NH), 5.86–5.76 (m, 1H, CH_{2All}), 5.34 (dd, 1H, $J_{2,3}$ = 10.6 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 5.27–5.22 (m, 1H, CH_{2All}), 5.21–5.18 (m, 1H, CH_{2All}), 4.96 (t, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 4.66 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1), 4.30–4.24 (m, 1H, CH_{2All}), 4.17 (dd, 1H, $J_{5,6a}$ = 3.2 Hz, $J_{6a,6b}$ = 11.2 Hz, H-6a), 4.12 (dd, 1H, $J_{5,6b}$ = 5.8 Hz, H-6b), 4.06–3.99 (m, 2H, H-2, CH_{2All}), 3.85 (ddd, 1H, H-5), 2.48 (s, 3H, CH_{3Ts}), 2.03 (s, 6H, CH_{3Ac}). ¹³C{¹H} NMR (CDCl₃): δ 171.20, 169.47 (2C, CO_{Ac}), 157.42 (CO_{NH}, $J_{C,F}$ = 37.4 Hz), 145.29 (C_{Ar}), 132.98 (CH_{2All}), 132.44, 129.95, 128.00 (C_{Ar}), 118.00 (CH_{2All}), 115.60 (CF₃, $J_{C,F}$ = 286.0 Hz), 98.91 (C-1, $J_{C,H}$ = 161.5 Hz), 71.76 (2C, C-5, C-3), 69.96 (CH_{2All}), 68.91 (C-4), 68.01 (C-6), 54.48 (C-2), 21.62 (CH_{3Ts}), 20.51, 20.33 (2C, CH_{3Ac}). HRMS (ESI⁺) m/z : [M + NH₄]⁺ calcd for C₂₂H₃₀F₃N₂O₁₀S, 571.1573; found, 571.1570.

Allyl 3,4-Di-O-acetyl-2-deoxy-6-iodo-2-trifluoroacetamido- β -D-glucopyranoside (27). To a solution of tosylate **26** (64.0 g, 115.6 mmol, 1.0 equiv) in butanone (770 mL) was added sodium iodide (43.3 g, 289.2 mmol, 2.5 equiv). The reaction mixture was heated to reflux for 4 h. A TLC (Tol/EtOAc 7:3) follow-up indicated reaction completion with conversion of the starting material (R_f 0.5) into a less polar compound (R_f 0.6). The suspension was filtered over a pad of Celite and washed with Et₂O, and the filtrate was concentrated to dryness. Flash chromatography (Tol/EtOAc 6:1 → 4:1) gave the desired **27** (52.0 g, 88%) as a white solid. The 6-iodo derivative had R_f 0.75 (Tol/EtOAc 1:1). ¹H NMR (400 MHz, CDCl₃): δ 6.61 (bd, 1H, $J_{NH,2}$ = 7.0 Hz, NH), 5.93–5.83 (m, 1H, CH_{2All}), 5.36–5.30 (m, 2H, H-3, CH_{2All}), 5.28–5.24 (m, 1H, CH_{2All}), 4.93 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.4 Hz, H-4), 4.72 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1), 4.44–4.39 (m, 1H, CH_{2All}), 4.21–4.16 (m, 1H, CH_{2All}), 4.09–4.02 (m, 1H, H-2), 3.63–3.57 (ddd, 1H, H-5), 3.33 (dd, 1H, $J_{5,6a}$ = 2.7 Hz, H-6a), 3.20 (dd, 1H, $J_{5,6b}$ = 8.8 Hz, $J_{6a,6b}$ = 10.9 Hz, H-6b), 2.10, 2.06 (2s, 6H, CH_{3Ac}). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 171.08, 169.39 (2C, CO_{Ac}), 157.42 (CO_{NH}, $J_{C,F}$ = 37.3 Hz), 132.94 (CH_{2All}), 118.55 (CH_{2All}), 115.55 (CF₃, $J_{C,F}$ = 285.9 Hz), 98.64 (C-1, $J_{C,H}$ = 162.5 Hz), 73.88 (C-5), 72.22 (C-4), 71.39 (C-3), 70.08 (CH_{2All}), 55.10 (C-2), 20.72, 20.37 (2C, CH_{3Ac}), 2.64 (C-6). HRMS (ESI⁺) m/z : [M + NH₄]⁺ calcd for C₁₅H₂₃F₃I₂N₂O₇, 527.0502; found, 527.0510.

Allyl 2,6-Dideoxy-2-trifluoroacetamido- β -D-glucopyranoside (28). Route a: Sodium methoxide (25% NaOMe in MeOH, 340 μ L, 1.56 mmol, 0.2 equiv) was added to a solution of diacetate **19** (3.0 g, 7.83 mmol, 1.0 equiv) in MeOH (70 mL). The solution was stirred for 2 h at rt. More sodium methoxide (25% NaOMe in MeOH, 170 μ L, 0.78 mmol, 0.1 equiv) was added, and after another 2 h, a TLC analysis (Tol/EtOAc 3:1) indicated reaction completion. Dowex-H⁺ resin was

added portionwise under gentle stirring until neutral pH was reached. The suspension was filtered and washed with MeOH (3 × 10 mL), and the filtrate was concentrated in vacuo. The crude was purified by flash chromatography (cHex/EtOAc 40:60 → 10:90) to get the desired diol **28** (2.2 g, 7.35 mmol, 94%) as a white solid. Trifluoroacetamide **28** had R_f 0.25 (Tol/EtOAc 1:1). ^1H NMR (400 MHz, CD_3OD): δ 5.92–5.83 (m, 1H, CH_{All}), 5.29–5.23 (m, 1H, $\text{CH}_{2\text{All}}$), 5.16–5.13 (m, 1H, $\text{CH}_{2\text{All}}$), 4.51 (d, 1H, $J_{1,2} = 8.4$ Hz, H-1), 4.32–4.27 (m, 1H, $\text{CH}_{2\text{All}}$), 4.07–4.02 (m, 1H, $\text{CH}_{2\text{All}}$), 3.73 (dd, 1H, $J_{2,3} = 10.4$ Hz, H-2), 3.51 (dd, 1H, $J_{3,4} = 8.8$ Hz, H-3), 3.37–3.30 (m, 1H, H-5), 3.07 (t, 1H, $J_{4,5} = 8.8$ Hz, H-4), 1.32 (d, 3H, $J_{5,6} = 6.1$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CD_3OD): δ 158.00 (CO_{NH} , q , $J_{\text{C,F}} = 36.5$ Hz), 133.89 (CH_{All}), 116.65 (CF_3 , q , $J_{\text{C,F}} = 284.9$ Hz), 114.79 ($\text{CH}_{2\text{All}}$), 99.70 (C-1, $^1J_{\text{C,H}} = 160.8$ Hz), 76.13 (C-4), 73.44 (C-3), 72.00 (C-5), 69.43 ($\text{CH}_{2\text{All}}$), 56.61 (C-2), 16.61 (C-6). HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{11}\text{H}_{16}\text{F}_3\text{NO}_5\text{Na}$, 322.0878; found, 322.0874.

Route b: Et_3B (1 M in hexane, 7.8 mL, 7.8 mmol, 0.2 equiv) was added dropwise to a solution of iodide **27** (20 g, 39.3 mmol, 1.0 equiv) and Bu_3SnH (10.7 mL, 47.1 mmol, 1.2 equiv) in anhyd. DCM (390 mL) cooled to 0 °C. The solution was stirred for 1 h at 0 °C, at which time a follow-up by TLC (Tol/EtOAc 7:3) indicated the total consumption of the starting material (R_f 0.5) and the presence of a more polar product (R_f 0.4). The mixture was concentrated in vacuo. The crude was taken in MeOH (200 mL) and treated with sodium methoxide (25% in MeOH, 13.4 mL, 58.9 mmol, 1.5 equiv) to reach pH 9. After stirring at rt for 4 h, a TLC follow-up (Tol/EtOAc 7:3) indicated the presence of a single more polar product. A minimal amount of Dowex- H^+ resin was added portionwise until neutral pH was reached. The suspension was filtered, and the resin was washed thoroughly with MeOH. Solvents were evaporated. Flash chromatography of the crude material (Tol/EtOAc, 55:45 → 20:80) gave the desired diol **28** (11.5 g, 97%) as a white solid.

Route c: The crude allyl 2,6-dideoxy-6-iodo-2-trifluoroacetamido- β -D-glucopyranoside (50 g, 117 mmol, 1.0 equiv, see the Supporting Information, Scheme S8) was dissolved in anhyd. THF (590 mL) and cooled to 0 °C. Bu_3SnH (29.7 mL, 129 mmol, 1.1 equiv) was added, followed by the addition of Et_3B (1.0 M in hexane, 11.7 mL, 11.7 mmol, 0.1 equiv). A careful follow-up by TLC (Tol/EtOAc 2:3) showed completion after stirring for 1 h at this temperature. MeOH (10 mL) was added, and after another 15 min, volatiles were evaporated, and the residue was dissolved in DCM (400 mL). The precipitate was filtered and washed with DCM (2 × 50 mL) to give the expected QuiN derivative **28** (31.0 g, 103 mmol, 88%). The filtrate was concentrated, and the residue was purified by chromatography eluting with (cHex/EtOAc 40:60 → 20:80) to give an additional amount (2.5 g, 8.3 mmol) of **28** as a white solid to reach an isolated yield of 95%. Analytical data for **28** were as described above.

Allyl 3-O-Acetyl-2,6-dideoxy-2-trifluoroacetamido- β -D-glucopyranoside (**29**). Route a: A solution of diol **28** (11.5 g, 38.4 mmol, 1.0 equiv) in anhyd. THF (350 mL) was cooled to -78 °C. Anhyd. pyridine (6.2 mL, 76.9 mmol, 2.0 equiv) was added, followed by acetyl chloride (3.0 mL, 42.3 mmol, 1.1 equiv). The reaction mixture was allowed to reach rt over 8 h and stirred for another 16 h. A follow-up by TLC (Tol/EtOAc 7:3) indicated the conversion of the starting material into a less polar product (R_f 0.25). MeOH (3.0 mL) was added, and after stirring at rt for 30 min, solvents were evaporated. Flash chromatography (Tol/EtOAc 65:35 → 55:45) gave by order of elution diacetate **19** (600 mg, 1.56 mmol, 4.0%) as a white solid and the 3-O-acetyl derivative **29** (11.3 g, 32.2 mmol, 86%) as a white solid, albeit as a 20:1 mix with the 4-O-acetyl isomer.

Scale-Up: A solution of diol **28** (33.5 g, 112 mmol, 1.0 equiv) in anhyd. THF (560 mL) was cooled to -78 °C. Anhyd. pyridine (18.1 mL, 224 mmol, 2.0 equiv) was added, followed by the addition of acetyl chloride (8.7 mL, 123 mmol, 1.1 equiv). The reaction mixture was allowed to reach rt over 8 h and stirred overnight at this temperature. A follow-up by TLC (Tol/EtOAc 1:1) indicated conversion of the starting **28** into a less polar product (R_f 0.35). MeOH (15 mL) was added, and after stirring at rt for another 30 min, volatiles were evaporated. Flash chromatography using Tol/EtOAc (65:35 → 55:45) gave first the undesired diacetate **19** (3.6 g, 9.39 mmol, 8.3%) and then a

non-separable >15:1 mix of the desired **29** and its regioisomer (30 g, 87.9 mol, 79%), both as a white solid. The target **29** had R_f 0.5 (Tol/EtOAc 1:1). ^1H NMR (400 MHz, CDCl_3): δ 6.93 (d, 1H, $J_{\text{NH}_2} = 9.0$ Hz, NH), 5.88–5.80 (m, 1H, CH_{All}), 5.29–5.24 (m, 1H, $\text{CH}_{2\text{All}}$), 5.22–5.16 (m, 2H, $\text{CH}_{2\text{All}}$, H-3), 4.60 (d, 1H, $J_{1,2} = 8.4$ Hz, H-1), 4.37–4.32 (m, 1H, $\text{CH}_{2\text{All}}$), 4.10–4.04 (m, 1H, $\text{CH}_{2\text{All}}$), 4.02–3.95 (m, 1H, $J_{2,3} = 10.5$ Hz, H-2), 3.48–3.38 (m, 2H, H-4, H-5), 2.72 (d, 1H, $J_{4,\text{OH}} = 6.0$ Hz, OH-4), 2.11 (s, 3H, CH_3Ac), 1.38 (d, 3H, $J_{5,6} = 5.8$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 172.43 (CO_{Ac}), 157.49 (CO_{NH} , q , $J_{\text{C,F}} = 37.3$ Hz), 133.31 (CH_{All}), 117.79 ($\text{CH}_{2\text{All}}$), 115.68 (CF_3 , q , $J_{\text{C,F}} = 286.1$ Hz), 98.94 (C-1, $^1J_{\text{C,H}} = 160.5$ Hz), 75.13 (C-3), 74.21 (C-4), 72.02 (C-5), 69.95 ($\text{CH}_{2\text{All}}$), 55.08 (C-2), 20.75 (C, CH_3Ac), 17.51 (C-6). HRMS (ESI^+) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{18}\text{F}_3\text{NO}_6\text{Na}$, 364.0978; found, 364.0974.

Route b: DIPEA (20 μL , 114 μmol , 0.2 equiv) and acetic anhydride (54 μL , 574 μmol , 1.01 equiv) were added to diol **28** (170 mg, 568 μmol , 1.0 equiv) dissolved in dry MeCN (6.0 mL) and stirred vigorously for 3 h at 100 °C under an Ar atmosphere. The resulting mixture was allowed to reach rt, and volatiles were evaporated. Flash chromatography of the crude gave the 3-O-acetyl derivative **29** and its regioisomer as a non-separable 5:1 mixture (164 mg, 480 μmol , 84%). Analytical data were as described above.

Allyl 3-O-Benzoyl-2,6-dideoxy-2-trifluoroacetamido- β -D-glucopyranoside (**30**). Dimethyltin dichloride (38 mg, 174 μmol , 0.2 equiv) was added to a solution of diol **28** (260 mg, 869 μmol , 1.0 equiv) in anhyd. THF containing pyridine (140 μL , 1.73 mmol, 2.0 equiv) at 0 °C. Benzoyl chloride (111 μL , 956 μmol , 1.1 equiv) was added dropwise, and the reaction mixture was stirred overnight while it slowly reached rt. At completion, MeOH was added, and after stirring for another 15 min, volatiles were removed under reduced pressure. Flash chromatography (Tol/EtOAc 75:25 → 70:30) gave the 3-O-benzoylated product **30** as a white solid (270 mg, 669 μmol , 77%). Compound **30** had R_f 0.4 (Tol/EtOAc 7:3). ^1H NMR (400 MHz, CDCl_3): δ 8.01–7.99 (m, 2H, H_{Ar}), 7.63–7.60 (m, 1H, H_{Ar}), 7.51–7.44 (m, 2H, H_{Ar}), 7.14 (d, 1H, $J_{\text{NH}_2} = 9.2$ Hz, NH), 5.90–5.82 (m, 1H, CH_{All}), 5.53 (dd, 1H, $J_{3,4} = 8.4$ Hz, $J_{2,3} = 10.2$ Hz, H-3), 5.30–5.25 (m, 1H, $\text{CH}_{2\text{All}}$), 5.20–5.17 (m, 1H, $\text{CH}_{2\text{All}}$), 4.69 (d, 1H, $J_{1,2} = 8.5$ Hz, H-1), 4.39–4.34 (m, 1H, $\text{CH}_{2\text{All}}$), 4.24–4.17 (m, 1H, H-2), 4.11–4.06 (m, 1H, $\text{CH}_{2\text{All}}$), 3.60–3.55 (m, 2H, H-4, H-5), 1.42 (d, 3H, $J_{5,6} = 5.4$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 167.98 (CO_{Bz}), 157.57 (CO_{NH} , q , $J_{\text{C,F}} = 37.3$ Hz), 133.92 (C_{Ar}), 133.35 (CH_{All}), 129.90, 128.61 (4C, C_{Ar}), 117.75 ($\text{CH}_{2\text{All}}$), 115.63 (CF_3 , q , $J_{\text{C,F}} = 286.4$ Hz), 99.11 (C-1, $^1J_{\text{C,H}} = 160.5$ Hz), 75.98 (C-3), 74.58 (C-4), 72.10 (C-5), 70.00 ($\text{CH}_{2\text{All}}$), 55.09 (C-2), 17.54 (C-6). HRMS (ESI^+) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{18}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_6$, 421.1581; found, 421.1572.

Allyl 3-O-tert-Butyldimethylsilyl-2,6-dideoxy-2-trifluoroacetamido- β -D-glucopyranoside (**31**). 2,6-Lutidine (138 μL , 1.44 mmol, 1.2 equiv) and TBSOTf (304 μL , 1.32 mmol, 1.1 equiv) were added to a solution of diol **28** (360 mg, 669 μmol , 1.0 equiv) in anhyd. THF (12 mL) at -78 °C. The reaction was allowed to attain rt slowly over 6 h. MeOH was added, and volatiles were evaporated. Flash chromatography (Tol/EtOAc 90:10 → 80:20) gave by order of elution the 4-O-silylated analogue (220 mg, 532 μmol , 44%) and the desired **30**, both as a white solid (240 mg, 580 μmol , 48%). The 3-O-silyl ether **31** had R_f 0.3 (Tol/EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3): δ 6.39 (d, 1H, $J_{2,\text{NH}} = 8.2$ Hz, NH), 5.89–5.79 (m, 1H, CH_{All}), 5.28–5.23 (m, 1H, $\text{CH}_{2\text{All}}$), 5.21–5.18 (m, 1H, $\text{CH}_{2\text{All}}$), 4.75 (d, 1H, $J_{1,2} = 8.4$ Hz, H-1), 4.36–4.31 (m, 1H, $\text{CH}_{2\text{All}}$), 4.07–4.02 (m, 1H, $\text{CH}_{2\text{All}}$), 3.92 (dd, 1H, $J_{3,4} = 8.3$ Hz, $J_{2,3} = 10.0$ Hz, H-3), 3.56–3.49 (m, 1H, H-2), 3.41 (dq, 1H, $J_{4,5} = 9.4$ Hz, H-5), 3.23–3.18 (m, 1H, H-4), 2.04 (d, 1H, $J_{4,\text{OH}} = 3.4$ Hz, OH), 1.36 (d, 3H, $J_{5,6} = 6.2$ Hz, H-6), 0.89 (s, 9H, $\text{C}(\text{CH}_3)_3\text{TBS}$), 0.14 (s, 3H, CH_3TBS), 0.06 (s, 3H, CH_3TBS). ^{13}C NMR (100 MHz, CDCl_3): δ 157.27 (CO_{NH} , q , $J_{\text{C,F}} = 36.8$ Hz), 133.50 ($\text{CH}_{2\text{All}}$), 117.75 ($\text{CH}_{2\text{All}}$), 115.65 (CF_3 , q , $J_{\text{C,F}} = 287.0$ Hz), 98.22 (C-1, $^1J_{\text{C,H}} = 161$ Hz), 77.29 (C-4), 74.37 (C-3), 71.38 (C-5), 70.02 ($\text{CH}_{2\text{All}}$), 58.78 (C-2), 25.66 (CH_3TBS), 18.04 (C_{qTBS}), 17.66 (C-6), -4.03, -4.84 (2C, CH_3TBS). HRMS (ESI^+) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{30}\text{F}_3\text{NO}_5\text{Si}$, 414.1924; found, 414.1934.

Allyl 4-O-Benzyl-2,6-dideoxy-2-trifluoroacetamido- β -D-glucopyranoside (**32**). NaH (60% in mineral oil, 32 mg, 669 μmol , 1.0 equiv)

was added portionwise to a solution of diol **28** (200 mg, 0.67 mmol, 1.0 equiv) and benzyl bromide (87 μ L, 0.74 mmol, 1.1 equiv) in anhyd. DMF (5.0 mL) under vigorous stirring at 0 °C. After 3 h at 0 °C, 0.5 M aq NH_4Cl (10 mL) was added, and the aqueous phase was extracted with EtOAc (20 mL). The organic phases were pooled and washed with brine, dried over Na_2SO_4 , and concentrated. Flash chromatography (Tol/EtOAc 65:35 \rightarrow 40:60) gave by order of elution the *N,N*-dibenzylated side product (12 mg, 31 μ mol, 4.6%), the 4-*O*-benzyl ether **32** (110 mg, 282 μ mol, 42%) as a white solid, and the unreacted **28** (95 mg, 317 μ mol, 47%). The target **32** had R_f 0.55 (Tol/EtOAc 1:1). ^1H NMR (400 MHz, CDCl_3): δ 7.39–7.30 (m, 5H, H_{Ar}), 6.75 (d, 1H, $J_{\text{NH},2} = 7.2$ Hz, NH), 5.92–5.82 (m, 1H, CH_{All}), 5.30–5.26 (m, 1H, $\text{CH}_{2\text{All}}$), 5.24–5.21 (m, 1H, $\text{CH}_{2\text{All}}$), 4.81 (d, 1H, $J = 11.6$ Hz, $\text{CH}_{2\text{Bn}}$), 4.74 (d, 1H, $\text{CH}_{2\text{Bn}}$), 4.64 (d, 1H, $J_{1,2} = 8.1$ Hz, H-1), 4.37–4.32 (m, 1H, $\text{CH}_{2\text{All}}$), 4.09–3.98 (m, 2H, $\text{CH}_{2\text{All}}$ -H-3), 3.62–3.56 (m, 1H, H-2), 3.52–3.46 (dq, 1H, $J_{4,5} = 9.0$ Hz, H-5), 3.15–3.13 (m, 2H, H-4, OH), 1.37 (d, 3H, $J_{5,6} = 6.2$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 157.76 (CO_{NH} , q, $J_{\text{C,F}} = 36.9$ Hz), 138.01 ($\text{C}_{\text{q,Ar}}$), 133.34 (CH_{All}), 128.57, 128.04, 127.98 (C_{Ar}), 118.06 ($\text{CH}_{2\text{All}}$), 115.73 (CF_3 , q, $J_{\text{C,F}} = 286.6$ Hz), 98.43 (C-1, $^1J_{\text{C,H}} = 161.4$ Hz), 84.01 (C-4), 75.08 ($\text{CH}_{2\text{Bn}}$), 73.13 (C-3), 71.45 (C-5), 69.96 ($\text{CH}_{2\text{All}}$), 58.24 (C-2), 18.08 (C-6). HRMS (ESI⁺) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{18}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_5$, 407.1788; found, 407.1778.

Allyl 3-*O*-Acetyl-2,6-dideoxy-2-trifluoroacetamido- β -*D*-galactopyranoside (33). Pyridine (71 μ L, 880 μ mol, 1.5 equiv) and triflic anhydride (118 μ L, 704 μ mol, 1.2 equiv) were added to a solution of allyl glycoside **29** (200 mg, 586 μ mol, 1.0 equiv) in anhyd. DCM (6 mL) at –10 °C. After stirring for 1 h at this temperature, DCM (10 mL) was added, and the solution was washed with 1 N aq HCl (10 mL), 0.5 M aq NaHCO_3 (10 mL), and 50% aq NaCl (10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, and the crude was extensively dried under high vacuum. TBANO₂ (253 mg, 880 μ mol, 1.5 equiv) was added to a solution of the crude material in anhyd. DMF (3.0 mL) at rt. After stirring overnight, a TLC analysis (Tol/EtOAc 7:3) indicated the absence of the triflate intermediate (R_f 0.8) and the presence of a polar spot (R_f 0.15). DCM (10 mL) was added, followed by water (40 mL). The DCM layer was separated, and the aqueous phase was extracted with DCM (2 \times 10 mL). The organic layers were combined, washed with 50% aq NaCl (50 mL), separated, dried over Na_2SO_4 , and concentrated under vacuum. Flash chromatography of the crude eluting with Tol/EtOAc (70:30 \rightarrow 60:40) gave the expected **33** as a white solid (160 mg, 469 μ mol, 80%). Alcohol **33** had R_f 0.25 (Tol/EtOAc 7:3). ^1H NMR (400 MHz, CDCl_3): δ 6.51 (d, 1H, $J_{\text{NH},2} = 8.7$ Hz, NH), 5.89–5.81 (m, 1H, CH_{All}), 5.30–5.25 (m, 1H, $\text{CH}_{2\text{All}}$), 5.23–5.20 (m, 1H, $\text{CH}_{2\text{All}}$), 5.16 (dd, 1H, $J_{3,4} = 3.1$ Hz, $J_{2,3} = 11.2$ Hz, H-3), 4.62 (d, 1H, $J_{1,2} = 8.4$ Hz, H-1), 4.40–4.34 (m, 1H, $\text{CH}_{2\text{All}}$), 4.24–4.17 (m, 1H, H-2), 4.12–4.06 (m, 1H, $\text{CH}_{2\text{All}}$), 3.86 (brs, 1H, H-4), 3.74 (dq, 1H, $J_{4,5} = 0.8$ Hz, H-5), 2.31 (d, 1H, $J_{4,\text{OH}} = 5.1$ Hz, OH), 2.12 (s, 3H, $\text{CH}_{3\text{Ac}}$), 1.37 (d, 3H, $J_{5,6} = 6.5$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 170.95 (C_{Ac}), 157.51 (CO_{NH}), 133.33 (CH_{All}), 117.89 ($\text{CH}_{2\text{All}}$), 114.22 (CF_3), 99.38 (C-1, $^1J_{\text{C,H}} = 161$ Hz), 72.54 (C-3), 70.60 (C-5), 69.94 ($\text{CH}_{2\text{All}}$), 69.60 (C-4), 51.71 (C-2), 20.66 ($\text{CH}_{3\text{Ac}}$), 16.17 (C-6). HRMS (ESI⁺) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{13}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_6$, 359.1424; found, 359.1417.

Allyl 3-*O*-Acetyl-4-azido-2,4,6-trideoxy-2-trifluoroacetamido- β -*D*-galactopyranoside (34). Alcohol **29** (10.3 g, 30.1 mmol, 1.0 equiv), containing traces of the 4-*O*-acetyl isomer, was dissolved in anhyd. DCM (280 mL) under an Ar atmosphere. The solution was cooled to –10 °C. Triflic anhydride (6.5 mL, 39 mmol, 1.3 equiv) was added, followed by the addition of anhyd. pyridine (4.84 mL, 60 mmol, 2.0 equiv). The solution was stirred for 1 h at –10 °C. A follow-up by TLC (Tol/EtOAc 2:1) indicated the absence of the starting material (R_f 0.25) and the presence of a less polar product (R_f 0.8). The reaction mixture was diluted with DCM (100 mL). The organic layer was washed with 1 N aq HCl (200 mL) and 0.5 M aq NaHCO_3 (200 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude was dried under high vacuum for 2 h.

The residue was dissolved in anhyd. DMF (100 mL), and sodium azide (9.8 g, 150 mmol, 5.0 equiv) was added. After stirring at rt overnight, TLC (Tol/EtOAc 4:1) showed the total conversion of the

intermediate triflate (R_f 0.45) and the presence of a more polar product (R_f 0.35). The reaction mixture was diluted with DCM (200 mL) and washed with H₂O (300 mL) and brine (300 mL). The organic phase was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Flash chromatography (Tol/EtOAc 80:20 \rightarrow 75:25) gave by order of elution the unwanted 3-azido allopiperanoside (100 mg, 273 μ mol, 1%) and the azido derivative **34** (9.1 g, 82%), both as a white solid.

Scale-Up: Pyridine (14.1 mL, 175 mmol, 2.0 equiv) was added to the contaminated **29** (30.0 g, 87.9 mmol, 1.0 equiv) in anhyd. DCM (550 mL). The solution was cooled to 0 °C, and triflic anhydride (17.7 mL, 105 mmol, 1.2 equiv) was added. After 2 h at 0 °C, DCM (200 mL) was added. The organic phase was washed with 1 N aq HCl (600 mL), 0.5 M aq NaHCO_3 (600 mL), and brine (600 mL); then dried over Na_2SO_4 ; filtered; and concentrated. After extensive drying under high vacuum, the crude was dissolved in anhyd. DMF (250 mL). The solution was cooled to 0 °C, and sodium azide (28.5 g, 439 mmol, 5.0 equiv) was added. After stirring for 8 h while allowing the bath to reach rt, the mixture was concentrated, and the crude was diluted with DCM (700 mL) and water (700 mL). The organic layer was separated, dried over Na_2SO_4 , and concentrated under reduced pressure. Flash chromatography (Tol/EtOAc 80:20 \rightarrow 70:30) gave the desired AAT derivative **34** (28.2 g, 87.5%) obtained as a white solid. The targeted **34** had R_f 0.5 (Tol/EtOAc 7:3). ^1H NMR (400 MHz, CDCl_3): δ 6.41 (d, 1H, $J_{\text{NH},2} = 8.0$ Hz, NH), 5.89–5.79 (m, 1H, CH_{All}), 5.42 (dd, 1H, $J_{3,4} = 3.6$ Hz, $J_{2,3} = 11.2$ Hz, H-3), 5.29–5.23 (m, 1H, $\text{CH}_{2\text{All}}$), 5.22–5.19 (m, 1H, $\text{CH}_{2\text{All}}$), 4.68 (d, 1H, $J_{1,2} = 8.4$ Hz, H-1), 4.37–4.32 (m, 1H, $\text{CH}_{2\text{All}}$), 4.10–4.04 (m, 2H, H-2, $\text{CH}_{2\text{All}}$), 3.85 (dd, 1H, H-4), 3.62 (dq, 1H, $J_{4,5} = 1.0$ Hz, H-5), 2.14 (s, 3H, $\text{CH}_{3\text{Ac}}$), 1.39 (d, 3H, $J_{5,6} = 6.3$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 170.53 (C_{Ac}), 157.35 (CO_{NH} , q, $J_{\text{C,F}} = 37.3$ Hz), 133.24 (CH_{All}), 118.04 ($\text{CH}_{2\text{All}}$), 115.53 (CF_3 , q, $J_{\text{C,F}} = 286.6$ Hz), 98.70 (C-1, $^1J_{\text{C,H}} = 160.4$ Hz), 71.72 (C-3), 69.85 ($\text{CH}_{2\text{All}}$), 69.30 (C-5), 63.27 (C-4), 52.34 (C-2), 20.31 ($\text{CH}_{3\text{Ac}}$), 17.29 (C-6). HRMS (ESI⁺) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{13}\text{H}_{21}\text{F}_3\text{N}_3\text{O}_5$, 384.1489; found, 384.1481.

Allyl 4-Azido-2,4,6-trideoxy-2-trifluoroacetamido- β -*D*-galactopyranoside (35). NaOMe (25% in MeOH, 273 μ mol, 0.1 equiv) was added to a solution of azide **34** (1.0 g, 2.73 mmol, 1.0 equiv) in MeOH (25 mL). After stirring for 1 h at rt and a TLC follow-up (Tol/EtOAc 3:2), the reaction was quenched by adding Dowex-H⁺ resin under gentle stirring to reach pH \sim 7.0. The suspension was filtered and thoroughly washed with MeOH. The combined filtrate was concentrated in vacuo. Flash chromatography (Tol/EtOAc 70:30 \rightarrow 60:40) of the crude gave **35** as a white solid (810 mg, 2.49 mmol, 92%). Alcohol **35** had R_f 0.4 (Tol/EtOAc 3:2). ^1H NMR (400 MHz, DMSO-*d*₆): δ 9.17 (d, 1H, $J_{\text{NH},2} = 9.2$ Hz, NH), 5.84–5.75 (m, 2H, CH_{All} , OH), 5.22–5.16 (m, 1H, $\text{CH}_{2\text{All}}$), 5.12–5.08 (m, 1H, $\text{CH}_{2\text{All}}$), 4.38 (d, 1H, $J_{1,2} = 8.4$ Hz, H-1), 4.20–4.14 (m, 1H, $\text{CH}_{2\text{All}}$), 3.97–3.92 (m, 2H, $\text{CH}_{2\text{All}}$ -H-3), 3.79 (dd, 1H, $J_{3,4} = 3.6$ Hz, $J_{4,5} = 1.2$ Hz, H-4), 3.76–3.69 (m, 1H, H-2), 3.64 (dq, 1H, H-5), 1.21 (d, 3H, $J_{5,6} = 6.3$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-*d*₆): δ 157.02 (CO_{NH} , q, $J_{\text{C,F}} = 36.2$ Hz), 133.90 ($\text{CH}_{2\text{All}}$), 116.47 (CF_3 , q, $J_{\text{C,F}} = 286.8$ Hz), 116.45 ($\text{CH}_{2\text{All}}$), 100.16 (C-1, $^1J_{\text{C,H}} = 160.5$ Hz), 70.47 (C-3), 69.19 ($\text{CH}_{2\text{All}}$), 68.92 (C-5), 66.02 (C-4), 53.37 (C-2), 17.76 (C-6). HRMS (ESI⁺) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{11}\text{H}_{19}\text{F}_3\text{N}_3\text{O}_4$, 342.1384; found, 342.1382.

Allyl 4-Azido-3-*O*-(2-naphthylmethyl)-2,4,6-trideoxy-2-trifluoroacetamido- β -*D*-galactopyranoside (36). Route a: 2-Naphthylmethyl bromide (171 mg, 741 μ mol, 1.2 equiv) was added to a solution of alcohol **35** (200 mg, 617 μ mol, 1.0 equiv) in anhyd. DMF (6 mL) at 0 °C. NaH (60% in oil, 61 mg, 1.54 mmol, 2.5 equiv) was then added portionwise to the solution stirred vigorously at this temperature. The suspension was allowed to reach rt within 1 h and then heated at 40 °C for 2 h. At completion, 5% aq NH_4Cl (15 mL) was added. The aqueous phase was extracted with DCM (3 \times 10 mL). The combined DCM layers were washed with brine (20 mL), dried over Na_2SO_4 , and concentrated. Flash chromatography (cHex/EtOAc 80:20 \rightarrow 70:30) gave the desired **36** (280 mg, 603 μ mol, 97%).

Route b: A solution of acetate **34** (2.0 g, 5.46 mmol, 1.0 equiv) in MeOH (40 mL) containing NaOMe (25% in MeOH, 132 μ L, 617 μ mol, 0.1 equiv) was stirred at rt for 1 h. TLC (Tol/EtOAc 2:1)

indicated reaction completion, and Dowex-H⁺ resin was added under gentle stirring until neutral pH. The resin was filtered and washed thoroughly, and volatiles were evaporated and co-evaporated with toluene (2 × 10 mL). The crude product was dissolved in anhyd. DMF (20 mL) and cooled to 0 °C. 2-Naphthylmethyl bromide (1.51 g, 6.55 mmol, 1.2 equiv) was added, followed by the portionwise addition of NaH (60% in oil, 436 mg, 10.9 mmol, 2.0 equiv). After stirring for 3 h while the reaction mixture had reached rt, 5% aq NH₄Cl (60 mL) was added, and the organics were extracted with DCM (3 × 40 mL). The combined DCM layers were washed with brine (100 mL), dried over Na₂SO₄, and concentrated. Flash chromatography (Tol/EtOAc 90:10 → 88:12) gave by order of elution the 2-naphthylmethyl ether **36** (1.3 g, 2.80 mmol, 51%) obtained as a white solid and the intermediate alcohol **35** (600 mg, 1.63 mmol, 35%) as a white solid. The naphthylmethyl ether **36** had *R*_f 0.6 (Tol/EtOAc 9:1). ¹H NMR (400 MHz, CDCl₃): δ 7.88–7.78 (m, 4H, H_{Ar}), 7.54–7.51 (m, 2H, H_{Ar}), 7.48–7.45 (m, 1H, H_{Ar}), 6.48 (d, 1H, J_{NH,2} = 6.8 Hz, NH), 5.89–5.79 (m, 1H, CH_{All}), 5.27–5.22 (m, 1H, CH_{2All}), 5.21–5.18 (m, 1H, CH_{2All}), 4.89 (d, 1H, J_{1,2} = 8.4 Hz, H-1), 4.85 (d, 1H, J = 11.6 Hz, CH_{2Napp}), 4.73 (d, 1H, CH_{2Napp}), 4.49 (dd, 1H, J_{3,4} = 3.6 Hz, J_{2,3} = 10.8 Hz, H-3), 4.35–4.29 (m, 1H, CH_{2All}), 4.07–4.02 (m, 1H, CH_{2All}), 3.79 (dd, 1H, J_{4,5} = 1.0 Hz, H-4), 3.68–3.58 (m, 2H, H-2, H-5), 1.38 (d, 3H, J_{5,6} = 6.3 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 157.46 (CO_{NH}, q, J_{C,F} = 36.9 Hz), 134.16, 133.39, 133.28 (C_{q,Ar}), 133.20 (CH_{All}), 128.72, 127.96, 127.75, 127.43, 126.39, 126.36, 125.84 (C_{Ar}), 118.15 (CH_{2All}), 115.51 (CF₃, q, J_{C,F} = 286.7 Hz), 97.55 (C-1, ¹J_{C,H} = 164.0 Hz), 75.92 (C-3), 72.51 (CH_{2Bn}), 70.03 (CH_{2All}), 69.12 (C-5), 62.75 (C-4), 55.32 (C-2), 17.55 (C-6). HRMS (ESI⁺) *m/z*: [M + NH₄]⁺ calcd for C₂₂H₂₇F₃N₅O₄, 482.2010; found, 482.2010.

Allyl 2-Amino-4-azido-3-O-(2-naphthylmethyl)-2,4,6-trideoxy-β-D-galactopyranoside (37). KOH (241 mg, 4.30 mmol, 5.0 equiv) was added portionwise to a suspension of the 2-naphthylmethyl ether **36** (400 mg, 862 μmol, 1.0 equiv) in MeOH/H₂O (1:1, 18 mL), and the solution was set into a 20 mL microwave vial. The reaction was set up in a Biotage Initiator+ instrument. After heating to 140 °C for 3 h, during which time the pressure reached 10 bar, a TLC analysis (EtOAc/MeCN 4:1) indicated the absence of the starting material and the presence of a more polar spot (*R*_f 0.5). Volatiles were eliminated, and DCM (50 mL) followed by water (50 mL) was added. The organic phase was separated, dried over Na₂SO₄, and concentrated to give the crude amine following extensive drying. Amine **37** had ¹H NMR (400 MHz, CDCl₃): δ 7.89–7.84 (m, 4H, H_{Ar}), 7.56–7.49 (m, 3H, H_{Ar}), 5.97–5.90 (m, 1H, CH_{All}), 5.31–5.27 (m, 1H, CH_{2All}), 5.21–5.18 (m, 1H, CH_{2All}), 4.95 (d, 1H, J = 11.2 Hz, CH_{2Napp}), 4.76 (d, 1H, J = 11.8 Hz, CH_{2Napp}), 4.39–4.35 (m, 1H, CH_{2All}), 4.21 (d, 1H, J_{1,2} = 7.9 Hz, H-1), 4.10–4.05 (m, 1H, CH_{2All}), 3.72 (d, 1H, H-4), 3.62 (dd, 1H, J_{3,4} = 3.4 Hz, H-3), 3.59 (q, 1H, H-5), 3.21 (dd, 1H, J_{2,3} = 9.8 Hz, H-2), 2.39 (brs, 2H, NH₂), 1.25 (d, 3H, J_{5,6} = 6.3 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 134.62 (C_{q,Ar}), 133.99 (CH_{All}), 133.25, 133.22 (C_{q,Ar}), 128.61, 127.97, 127.75, 127.18, 126.31, 126.22, 125.88 (C_{Ar}), 117.66 (CH_{2All}), 102.84 (C-1), 82.14 (C-3), 72.25 (CH_{2Napp}), 69.95 (CH_{2All}), 69.30 (C-5), 61.40 (C-4), 52.59 (C-2), 17.69 (C-6). HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd for C₂₀H₂₄N₄O₃, 369.1927; found, 369.1927.

Allyl 4-Azido-2-dichloroacetamido-3-O-(2-naphthylmethyl)-2,4,6-trideoxy-β-D-galactopyranoside (38). The crude **37** was dissolved in anhyd. DCM (18 mL) containing pyridine (600 μL, 4.30 mmol, 5.0 equiv). Dichloroacetyl chloride (165 μL, 1.72 mmol, 2.0 equiv) was added to the solution stirred at 0 °C. After 2 h while the bath reached rt, a TLC (Tol/EtOAc 6:4) follow-up indicated reaction completion. MeOH (1.0 mL) was added, and after stirring for another 10 min, volatiles were evaporated. Flash chromatography of the crude eluting with Tol/EtOAc (90:10 → 85:15) gave dichloroacetamide **38** as a yellowish solid (340 mg, 711 μmol, 82%). Compound **38** had *R*_f 0.5 (Tol/EtOAc 4:1). ¹H NMR (400 MHz, CDCl₃): δ 7.87–7.81 (m, 4H, H_{Ar}), 7.53–7.49 (m, 3H, H_{Ar}), 6.72 (d, 1H, J_{NH,2} = 8.0 Hz, NH), 5.91–5.82 (m, 1H, CH_{All}), 5.81 (s, 1H, CHCl₂), 5.28–5.23 (m, 1H, CH_{2All}), 5.19–5.16 (m, 1H, CH_{2All}), 4.92 (d, 1H, J_{1,2} = 8.3 Hz, H-1), 4.85 (d, 1H, J = 11.8 Hz, CH_{2Napp}), 4.78 (d, 1H, J = 11.8 Hz, CH_{2Napp}), 4.54 (dd, 1H, J_{3,4} = 3.4 Hz, J_{2,3} = 10.6 Hz, H-3), 4.35–4.29 (m, 1H, CH_{2All}), 4.08–4.03 (m, 1H, CH_{2All}), 3.74 (dd, 1H, J_{4,5} = 1.2 Hz, H-4), 3.65 (dq,

1H, H-5), 3.61–3.54 (m, 1H, H-2), 1.34 (d, 3H, J_{5,6} = 6.4 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 164.47 (CO_{NH}), 134.53 (C_{q,Ar}), 133.70 (CH_{All}), 133.21 (C_{q,Ar}), 128.53, 127.96, 127.73, 127.36, 126.33, 126.27, 126.07 (C_{Ar}), 117.91 (CH_{2All}), 97.74 (C-1), 76.04 (C-3), 72.68 (CH_{2Napp}), 70.14 (CH_{2All}), 69.01 (C-5), 66.40 (CHCl₂), 63.16 (C-4), 55.64 (C-2), 17.59 (C-6). HRMS (ESI⁺) *m/z*: [M + NH₄]⁺ calcd for C₂₂H₂₈Cl₂N₅O₄, 496.1518; found, 496.1514.

Allyl 2-Amino-4-azido-2,4,6-trideoxy-β-D-galactopyranoside (39). LiOH·H₂O (6.87 g, 163 mmol, 3.0 equiv) was added to a solution of azide **34** (20.0 g, 54.6 mmol, 1.0 equiv) in acetone/water (2:1, 320 mL). After stirring for 2 h at rt, a follow-up by TLC (Tol/EtOAc 1:1) indicated the total conversion of the starting **34** (*R*_f 0.7). Volatiles were evaporated, and the crude was purified by flash chromatography eluting with DCM/MeOH (20:1 → 12:1). The expected amine **39** (13.9 g, quant.), isolated as a yellowish oil, had *R*_f 0.15 (EtOAc/MeOH 9:1). ¹H NMR (400 MHz, CDCl₃): δ 5.97–5.87 (m, 1H, CH_{All}), 5.32–5.28 (m, 1H, CH_{2All}), 5.25–5.22 (m, 1H, CH_{2All}), 4.61 (brs, 3H, OH, NH₂), 4.38–4.34 (m, 1H, CH_{2All}), 4.23 (d, 1H, J_{1,2} = 8.0 Hz, H-1), 4.09–4.04 (m, 1H, CH_{2All}), 3.84 (dd, 1H, J_{3,4} = 3.6 Hz, H-3), 3.67–3.64 (m, 2H, H-4, H-5), 2.95 (dd, 1H, J_{2,3} = 10.2 Hz, H-2), 1.36 (d, 3H, J_{5,6} = 6.4 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 133.42 (CH_{All}), 118.41 (CH_{2All}), 101.31 (C-1), 72.49 (C-3), 70.18 (CH_{2All}), 69.72 (C-5), 65.51 (C-4), 53.90 (C-2), 17.34 (C-6). HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd for C₂₀H₂₄N₄O₃, 369.1927; found, 369.1926.

Allyl 4-Azido-2-trichloroacetamido-2,4,6-trideoxy-β-D-galactopyranoside (4).⁴⁵ Amine **39** (13.9 g, 54.6 mmol, 1.0 equiv) in DCM (60 mL) was treated with triethylamine (22.8 mL, 163 mmol, 3.0 equiv) and trichloroacetyl chloride (12.1 mL, 109 mmol, 2.0 equiv) at rt. The reaction mixture was stirred for 30 min. A follow-up by TLC (Tol/EtOAc 7:3) indicated the presence of a major less polar product (*R*_f 0.45) and a minor one (*R*_f 0.7). DCM (50 mL) and water (50 mL) were added, and the biphasic mixture was stirred for another 1 h. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined DCM layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Flash chromatography (Tol/EtOAc 80:20 → 70:30) gave the known **4** (17.5 g, 86%) as a white solid. Analytical data were as reported.⁴⁵

Allyl 4-Azido-2-N-(tert-butyloxycarbonyl)-2,4,6-trideoxy-β-D-galactopyranoside (40). DMAP (10.7 mg, 88 μmol, 0.1 equiv) and *tert*-butyl dicarbonate (Boc₂O, 287 mg, 131 mmol, 1.5 equiv) were added to a solution of amine **39** (200 mg, 877 μmol, 1.0 equiv) in anhyd. THF (6.0 mL). After heating at 50 °C for 2 h, a follow-up by TLC (Tol/EtOAc 7:3) indicated completion. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by flash chromatography (cHex/EtOAc 70:30 → 60:40) to give by order of elution the 2-*N*,3-*O*-di-*tert*-butyloxycarbonyl side product (16 mg, 37 μmol, 4%) and the desired alcohol **40** (185 mg, 5.63 mmol, 83%), both as a white solid. Carbamate **40** had *R*_f 0.25 (Tol/EtOAc 7:3). ¹H NMR (400 MHz, CDCl₃): δ 5.98–5.88 (m, 1H, CH_{All}), 5.33–5.28 (m, 1H, CH_{2All}), 5.25–5.22 (m, 1H, CH_{2All}), 5.00 (brs, 1H, OH), 4.80 (brs, 1H, NH), 4.39–4.33 (m, 2H, CH_{2All}, H-1), 4.09–4.04 (m, 1H, CH_{2All}), 4.00 (bd, 1H, J_{2,3} = 8.4 Hz, H-3), 3.68 (brd, 1H, J_{3,4} = 3.4 Hz, H-4), 3.64 (q, 1H, H-5), 3.56–3.50 (m, 1H, H-2), 1.47 (brs, 9H, CH_{3tBu}), 1.37 (d, 3H, J_{5,6} = 6.2 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 157.77 (CO_{NH}), 133.62 (CH_{All}), 118.09 (CH_{2All}), 99.47 (C-1), 81.05 (C_{q,tBu}), 74.40 (C-3), 69.57 (CH_{2All}), 69.56 (C-5), 65.23 (C-4), 55.40 (C-2), 28.26 (CH_{3tBu}), 17.48 (C-6). HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd for C₁₄H₂₄N₄O₅Na, 351.1638; found, 351.1636.

Allyl 4-Azido-2-N-carboxybenzyl-2,4,6-trideoxy-β-D-galactopyranoside (41). Benzyl chloroformate (150 μL, 1.05 mmol, 1.2 equiv) was added to the DCM layer of a biphasic solution of amine **39** (200 mg, 877 μmol, 1.0 equiv) in DCM/satd aq NaHCO₃ (2:1, 15 mL) at 0 °C. After stirring at this temperature for 2 h, a TLC (Tol/EtOAc 1:1) follow-up indicated completion. DCM (10 mL) and water (10 mL) were added. The DCM layer was separated, dried over Na₂SO₄, and concentrated. Flash chromatography (cHex/EtOAc 65:35 → 60:40) of the residue gave the *N*-protected derivative **41** (275 mg, 759 μmol, 86%) as a white solid. Azide **41** had *R*_f 0.4 (Tol/EtOAc 1:1). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.36–7.29 (m, 5H, H_{Ar}), 7.11 (d, 1H, J_{2,NH} =

9.2 Hz, NH), 5.84–5.76 (m, 1H, CH_{2All}), 5.56 (d, 1H, J_{3,OH} = 4.4 Hz, OH), 5.25–5.19 (m, 1H, CH_{2All}), 5.10–4.98 (m, 3H, CH_{2Bn}, CH_{2All}), 4.25 (d, 1H, J_{1,2} = 8.6 Hz, H-1), 4.20–4.14 (m, 1H, CH_{2All}), 3.96–3.91 (m, 1H, CH_{2All}), 3.80–3.77 (m, 1H, J_{2,3} = 8.8 Hz, H-3), 3.74 (brd, 1H, J_{3,4} = 3.2 Hz, H-4), 3.60 (q, 1H, H-5), 3.45–3.40 (m, 1H, H-2), 1.18 (d, 3H, J_{5,6} = 6.3 Hz, H-6). ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 156.64 (CO), 137.81 (C_{qAr}), 135.14 (CH_{2All}), 128.72, 128.10, 128.04 (C_{Ar}), 116.40 (CH_{2All}), 101.26 (C-1), 71.27 (C-3), 69.08 (CH_{2All}), 68.72 (C-5), 66.34 (C-4), 65.51 (CH_{2Bn}), 54.37 (C-2), 17.86 (C-6). HRMS (ESI⁺) *m/z*: [M + NH₄]⁺ calcd for C₁₇H₂₆N₅O₅, 380.1928; found, 380.1924.

Allyl 4-Azido-2-tetrachlorophthalimido-2,4,6-trideoxy-β-D-galactopyranoside (42). Tetrachlorophthalic anhydride (TCPO, 150 mg, 525 μmol, 0.6 equiv) was added to a solution of amine 39 (200 mg, 877 μmol, 1.0 equiv) in anhyd. DCE (6.0 mL). After stirring for 30 min at rt under an Ar atmosphere, Et₃N (146 μL, 1.05 mmol, 1.2 equiv) was added, followed by more TCPO (150 mg, 525 μmol, 0.6 equiv). After 1 h, a TLC (EtOAc/MeOH 9:1) follow-up indicated the absence of the starting amine. Volatiles were evaporated, and the residue was dried under high vacuum. The crude was dissolved in anhyd. pyridine (60 mL), and more TCPO (50 mg, 175 μmol, 0.2 equiv) was added. After heating at 50 °C for 1 h, a TLC (cHex/EtOAc 3:2) follow-up indicated completion. Volatiles were evaporated and co-evaporated with toluene (2 × 5 mL). A solution of the crude in DCM (20 mL) was washed with water (30 mL) and brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Flash chromatography (cHex/EtOAc 75:25 → 70:30) of the residue gave the tetrachlorophthalimide 42 (110 mg, 223 μmol, 25%) as a white solid. The target 42 had *R*_f 0.65 (Tol/EtOAc 7:3). ¹H NMR (400 MHz, CDCl₃): δ 5.80–5.70 (m, 1H, CH_{2All}), 5.19–5.14 (m, 2H, CH_{2All}, H-1), 5.12–5.08 (m, 1H, CH_{2All}), 5.50 (brs, 1H, H-3), 4.31–4.26 (m, 1H, CH_{2All}), 4.23 (dd, 1H, J_{1,2} = 8.4 Hz, J_{2,3} = 11.0 Hz, H-2), 4.06–4.00 (m, 1H, CH_{2All}), 3.88 (dq, 1H, H-5), 3.80 (dd, 1H, J_{3,4} = 3.8 Hz, J_{4,5} = 0.9 Hz, H-4), 2.40 (d, 1H, J_{3,OH} = 8.0 Hz, OH), 1.48 (d, 3H, J_{5,6} = 6.4 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 163.47 (CO), 140.36 (C_{Ar}), 133.51 (CH_{2All}), 127.22 (C_{Ar}), 117.68 (CH_{2All}), 96.87 (C-1), 70.25 (C-5), 69.68 (CH_{2All}), 68.37 (C-3), 66.99 (C-4), 55.20 (C-2), 17.43 (C-6). HRMS (ESI⁺) *m/z*: [M + NH₄]⁺ calcd for C₁₇H₁₈Cl₄N₅O₅, 512.0062; found, 512.0071.

Allyl 2,4-Diazido-2,4,6-trideoxy-β-D-galactopyranoside (43). K₂CO₃ (242 mg, 1.75 mmol, 2.0 equiv) and *N*-diazimidazole-1-sulfonamide; sulfuric acid (356 mg, 1.31 mmol, 1.5 equiv) were added to a solution of the amine 39 (200 mg, 877 μmol, 1.0 equiv) in MeOH (10 mL). After stirring overnight at rt, a TLC (Tol/EtOAc 6:4) follow-up indicated reaction completion. Volatiles were evaporated, and the residue in DCM (20 mL) was washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered, and concentrated. Flash chromatography (Tol/EtOAc 75:25 → 70:30) of the residue gave the diazide 43 (155 mg, 610 μmol, 76%) as a white solid. The galactoside analogue 43 had *R*_f 0.65 (Tol/EtOAc 6:4). ¹H NMR (400 MHz, CDCl₃): δ 6.00–5.90 (m, 1H, CH_{2All}), 5.37–5.31 (m, 1H, CH_{2All}), 5.25–5.22 (m, 1H, CH_{2All}), 4.44–4.39 (m, 1H, CH_{2All}), 4.30 (d, 1H, J_{1,2} = 7.6 Hz, H-1), 4.15–4.10 (m, 1H, CH_{2All}), 3.68 (dd, 1H, J_{3,4} = 3.6 Hz, J_{4,5} = 1.0 Hz, H-4), 3.66–3.61 (m, 2H, H-3, H-5), 3.56 (dd, 1H, J_{2,3} = 10.0 Hz, H-2), 2.53 (d, 1H, J_{3,OH} = 4.4 Hz, OH-3), 1.38 (d, 3H, J_{5,6} = 6.4 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 133.39 (CH_{2All}), 117.72 (CH_{2All}), 101.06 (C-1), 72.65 (C-3), 70.17 (CH_{2All}), 69.67 (C-5), 64.76 (C-4), 63.97 (C-2), 17.36 (C-6). HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd for C₉H₁₃N₆O₃, 255.1200; found, 255.1199.

Allyl 2-Amino-2,6-dideoxy-β-D-glucopyranoside (44). LiOH·H₂O (1.32 g, 3.14 mmol, 2.0 equiv) was added to a solution of diacetate 19 (6.0 g, 1.57 mmol, 1.0 equiv) in acetone/water (2:1, 15 mL) at rt. After stirring for 3 h at rt, the mixture was concentrated under reduced pressure. The crude was passed through a short silica gel column eluting with DCM/MeOH (90:10 → 85:15) to give the expected amine 44 (3.0 g, 1.47 mmol, 94%) as a yellowish oil. The amine 44 had *R*_f 0.2 (DCM/MeOH 9:1). ¹H NMR (400 MHz, CDCl₃): δ 6.06 (brs, 4H, OH, NH₂), 5.97–5.87 (m, 1H, CH_{2All}), 5.32–5.28 (m, 1H, CH_{2All}), 5.25–5.22 (m, 1H, CH_{2All}), 4.44 (d, 1H, J_{1,2} = 8.0 Hz, H-1), 4.37–4.32 (m, 1H, CH_{2All}), 4.11–4.06 (m, 1H, CH_{2All}), 3.66–3.61 (m, 1H, H-3), 3.38–3.35 (m, 1H, H-5), 3.22–3.18 (m, 1H, H-4), 2.94–2.89 (m, 1H,

H-2), 1.32 (d, 3H, J_{5,6} = 6.4 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 133.19 (CH_{2All}), 118.84 (CH_{2All}), 99.11 (C-1), 75.69 (C-4), 73.56 (C-3), 72.24 (C-5), 70.39 (CH_{2All}), 56.86 (C-2), 17.33 (C-6). HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd for C₉H₁₈NO₄, 204.1230; found, 204.1226.

Allyl 2-Azido-2,6-dideoxy-β-D-glucopyranoside (45). K₂CO₃ (2.0 g, 14.7 mmol, 1.5 equiv) and imidazole-1-sulfonyl azide and sulfuric acid (2.4 g, 1.18 mmol, 1.2 equiv) were added to a solution of the amine 44 (2.0 g, 9.84 mmol, 1.0 equiv) in MeOH (30 mL) at 0 °C. The reaction was run overnight at rt. A TLC follow-up (Tol/EtOAc 6:4) revealed the presence of a major product (*R*_f 0.3). The reaction mixture was concentrated. The residue was dissolved in DCM (30 mL), and the organic phase was washed with water. The organic layer was separated, dried over Na₂SO₄, filtered, and concentrated. Flash chromatography (Tol/EtOAc 70:30 → 60:40) of the residue gave the expected azide 45 (1.6 g, 6.98 mmol, 71%) as a yellowish oil. Azide 45 had *R*_f 0.3 (Tol/EtOAc 1:1). ¹H NMR (400 MHz, CDCl₃): δ 6.01–5.92 (m, 1H, CH_{2All}), 5.38–5.34 (m, 1H, CH_{2All}), 5.26–5.24 (m, 1H, CH_{2All}), 4.44–4.37 (m, 2H, CH_{2All}, H-1), 4.18–4.13 (m, 1H, CH_{2All}), 3.49 (brs, 1H, OH), 3.37–3.30 (m, 3H, H-2, H-4, H-5), 3.25–3.23 (m, 2H, H-3, OH), 1.35 (d, 3H, J_{5,6} = 6.0 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 133.37 (CH_{2All}), 117.86 (CH_{2All}), 101.82 (C-1), 75.33 (C-3), 74.93 (C-5), 71.67 (C-4), 70.36 (CH_{2All}), 66.21 (C-2), 17.48 (C-6). HRMS (ESI⁺) *m/z*: [M + H]⁺ calcd for C₉H₁₆N₃O₄, 230.1136; found, 230.1136.

Allyl 2-Dichloroacetamido-2,6-dideoxy-β-D-glucopyranoside (46). Route a: 25% Methanolic NaOMe (0.76 μL, 0.35 mmol, 0.2 equiv) was added to a solution of diacetate 7 (700 mg, 1.76 mmol, 1.0 equiv) in MeOH (9 mL). After stirring at rt for 1 h, Dowex-H⁺ resin was added slowly until neutral pH is reached. The suspension was filtered and washed thoroughly with MeOH. Volatiles were evaporated, and the crude was purified by passing through a short pack of silica gel eluting with cHex/EtOAc (20:80 → 10:90). The desired diol 46 (500 mg, 1.25 mmol, 90%) was isolated as a white solid.

Route b: Triethylamine (1.3 mL, 9.84 mmol, 5.0 equiv) and dichloroacetic anhydride (0.9 mL, 5.90 mmol, 3.0 equiv) were added to a solution of amine 44 (400 mg, 1.96 mmol, 1.0 equiv) in EtOAc (10 mL) at 0 °C. The reaction mixture was stirred for 2 h while reaching rt. Following a TLC analysis (EtOAc/MeCN 4:1), water (5 mL) was added, and after another 3 h at rt, a TLC analysis (EtOAc) showed the presence of one major spot. Volatiles were evaporated, and the crude was purified by column chromatography (cHex/EtOAc, 10:90 → 0:100) to give the target 46 as a white solid (500 mg, 1.59 mmol, 81%). Dichloroacetamide 46 had *R*_f 0.4 (EtOAc/MeCN, 4:1). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.41 (d, 1H, J_{NH,2} = 8.8 Hz, NH), 6.37 (s, 1H, CHCl₂), 5.83–5.75 (m, 1H, CH_{2All}), 5.25–5.19 (m, 1H, CH_{2All}), 5.10–5.07 (m, 2H, CH_{2All}, OH-4), 5.00 (d, 1H, J_{OH,3} = 6.0 Hz, OH-3), 4.37 (d, 1H, J_{1,2} = 8.4 Hz, H-1), 4.19–4.14 (m, 1H, CH_{2All}), 3.97–3.92 (m, 1H, CH_{2All}), 4.08 (dt, 1H, H-2), 3.35–3.30 (ddd, 1H, J_{2,3} = 10.2 Hz, H-3), 3.21–3.17 (dq, 1H, J_{4,5} = 9.3 Hz, H-5), 2.85 (dt, 1H, J_{3,4} = 9.0 Hz, H-4), 1.18 (d, 3H, J_{5,6} = 6.2 Hz, H-6). ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 163.34 (CO_{NH}), 134.52 (CH_{2All}), 116.12 (CH_{2All}), 99.92 (C-1), 75.89 (C-4), 73.20 (C-3), 71.67 (C-5), 68.76 (CH_{2All}), 67.19 (CHCl₂), 56.38 (C-2), 17.83 (C-6). HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd for C₁₁H₁₇Cl₂NO₅Na, *m/z* 336.0381; found, 336.0388.

Allyl 2,6-Dideoxy-2-trichloroacetamido-β-D-glucopyranoside (47). The amine 44 (80 mg, 394 μmol, 1.0 equiv) was dissolved in DCM (5 mL). The solution was cooled to 0 °C, and Et₃N (326 μL, 2.36 μmol, 6.0 equiv) was added, followed by the dropwise addition of trichloroacetyl chloride (131 μL, 1.18 mmol, 3.0 equiv). After stirring for 2 h at 0 °C, a TLC analysis (Tol/EtOAc, 5:1) showed complete conversion. DCM (5 mL) and water (10 mL) were added at rt and stirring went on for 2 h. At this time, a TLC analysis (Tol/EtOAc, 1:4) revealed the presence of one major spot (*R*_f 0.6). The DCM layer was collected, and the aq layer was extracted with DCM (285 mL). The DCM parts were combined, dried over Na₂SO₄, and concentrated in vacuo. Flash chromatography (Tol/EtOAc, 40:60 → 20:80) of the crude gave 47 as a white solid (101 mg, 85%). Analytical data were as published.⁴⁵

Alllyl 2-*N*-Carboxybenzyl-2,6-dideoxy- β -*D*-glucopyranoside (48). NaHCO₃ (414 mg, 1.96 mmol, 2.0 equiv) in water (2 mL) was added to a solution of the amine **44** (200 mg, 985 μ mol, 1.0 equiv) in EtOAc (6.0 mL) at 0 °C. Benzyl chloroformate (154 μ L, 1.08 mmol, 1.1 equiv) was added dropwise. After stirring for 1 h at 0 °C, MeOH (200 μ L) was added. After stirring for another 5 min at rt, EtOAc (10 mL) was added, and the organic phase was washed with brine (20 mL), dried over Na₂SO₄, and concentrated. Flash chromatography (Tol/EtOAc 20:80 \rightarrow 10:90) gave the expected carbamate **48** (240 mg, 711 μ mol, 81%) as a white solid. The diol **48** had *R*_f 0.15 (Tol/EtOAc 1:4). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.38–7.29 (m, 5H, H_{Ar}), 7.14 (d, 1H, *J*_{2,NH} = 7.2 Hz, NH), 5.87–5.77 (m, 1H, CH_{2All}), 5.26–5.20 (m, 1H, CH_{2All}), 5.10–4.94 (m, 5H, CH_{2All}, CH_{2Cbz}, OH, OH-3), 4.28 (d, 1H, *J*_{1,2} = 7.2 Hz, H-1), 4.21–4.17 (m, 1H, CH_{2All}), 3.98–3.93 (m, 1H, CH_{2All}), 3.31–3.20 (m, 2H, H-2, H-3), 3.17–3.10 (dq, 1H, *J*_{4,5} = 9.3 Hz, H-5), 2.87–2.83 (m, 1H, H-4), 1.17 (d, 3H, *J*_{5,6} = 6.1 Hz, H-6). ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 156.55 (CO_{NH}), 137.87 (C_{qAr}), 135.22 (CH_{All}), 128.71, 128.02 (C_{Ar}), 116.35 (CH_{2All}), 101.16 (C-1), ¹*J*_{C,H} = 163.0 Hz, 76.44 (C-4), 74.18 (C-3), 72.08 (C-5), 69.11 (CH_{2All}), 65.43 (CH_{2Cbz}), 57.98 (C-2), 18.40 (C-6). HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd for C₁₇H₂₃NO₆Na, 360.1418; found, 360.1403.

Alllyl 3-*O*-Acetyl-2-dichloroacetamido-2,6-dideoxy- β -*D*-glucopyranoside (49). A solution of diol **46** (400 mg, 1.27 mmol, 1.0 equiv) in anhyd. THF (30 mL) was cooled to –78 °C. Anhyd. pyridine (206 μ L, 2.55 mmol, 2.0 equiv) was added, followed by the addition of acetyl chloride (95 μ L, 1.34 mmol, 1.05 equiv). The reaction mixture slowly reached rt over 8 h and was stirred overnight at this temperature. A follow-up by TLC (cHex/EtOAc 3:7) indicated the conversion of the starting **46** and the presence of less polar products. MeOH (0.1 mL) was added, and after stirring at rt for 10 min, solvents were evaporated. The crude was purified by flash chromatography using cHex/EtOAc (60:40 \rightarrow 50:50). The 3-*O*-acetyl derivative **49** (292 mg, 822 μ mol, 64%), isolated as a white solid, had *R*_f 0.4 (cHex/EtOAc 1:1). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.62 (d, 1H, *J*_{NH,2} = 9.2 Hz, NH), 6.36 (s, 1H, CHCl₂), 5.86–5.77 (m, 1H, CH_{All}), 5.40 (d, 1H, *J*_{OH,4} = 6.0 Hz, OH-4), 5.23–5.18 (m, 1H, CH_{2All}), 5.11–5.08 (m, 1H, CH_{2All}), 4.88 (dd, 1H, *J*_{3,4} = 9.0 Hz, *J*_{3,2} = 10.6 Hz, H-3), 4.56 (d, 1H, *J*_{1,2} = 8.4 Hz, H-1), 4.21–4.16 (m, 1H, CH_{2All}), 4.01–3.96 (m, 1H, CH_{2All}), 3.71–3.64 (m, 1H, H-2), 3.38–3.31 (dq, 1H, *J*_{4,5} = 9.3 Hz, H-5), 3.13–3.07 (m, 1H, H-4), 1.94 (s, 3H, CH_{3Ac}), 1.21 (d, 3H, *J*_{5,6} = 6.0 Hz, H-6). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 170.10 (CO_{Ac}), 164.13 (CO_{NH}), 134.84 (CH_{All}), 116.77 (CH_{2All}), 99.71 (C-1, ¹*J*_{C,H} = 162 Hz), 75.36 (C-3), 73.55 (C-4), 72.05 (C-5), 69.40 (CH_{2All}), 67.24 (CHCl₂), 54.66 (C-2), 21.19 (CH_{3Ac}), 18.11 (C-6). HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd for C₁₃H₁₉Cl₂NO₆Na, 378.0487; found, 378.0492.

Alllyl 3-*O*-Acetyl-2-azido-2,6-dideoxy- β -*D*-glucopyranoside (51). Acetyl chloride (102 μ L, 14.4 mmol, 1.1 equiv) was added dropwise to a solution of the diol **45** (300 mg, 1.30 mmol, 1.0 equiv) and pyridine (210 μ L, 26.1 mmol, 2.0 equiv) in anhyd. THF (15 mL) at –78 °C. The reaction mixture slowly reached rt. After 16 h, a TLC analysis (Tol/EtOAc 4:1) indicated reaction completion. MeOH (0.1 mL) was added, and after 10 min, volatiles were evaporated. Flash chromatography (Tol/EtOAc 84:16 \rightarrow 80:20) gave the 3-*O*-acetylated product **51** (240 mg, 0.88 mmol, 67%) along with the regioisomer (65 mg, 0.23 mmol, 18%). The target **51** had *R*_f 0.55 (Tol/EtOAc 4:1). ¹H NMR (400 MHz, CDCl₃): δ 5.99–5.91 (m, 1H, CH_{All}), 5.38–5.33 (m, 1H, CH_{2All}), 5.26–5.23 (m, 1H, CH_{2All}), 4.74 (dd, 1H, *J*_{3,4} = 9.2 Hz, H-3), 4.43–4.38 (m, 2H, CH_{2All}, H-1), 4.19–4.14 (m, 1H, CH_{2All}), 3.46 (dd, 1H, *J*_{1,2} = 8.1 Hz, *J*_{3,2} = 10.1 Hz, H-2), 3.41–3.35 (dq, 1H, *J*_{4,5} = 9.4 Hz, H-5), 3.34–3.26 (m, 1H, H-4), 2.62 (d, 1H, *J*_{4,OH} = 5.6 Hz, OH), 2.18 (s, 3H, CH_{3Ac}), 1.36 (d, 3H, *J*_{5,6} = 6.0 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 172.04 (CO_{Ac}), 133.29 (CH_{All}), 117.97 (CH_{2All}), 100.56 (C-1), 76.33 (C-3), 74.60 (C-4), 72.21 (C-5), 70.39 (CH_{2All}), 63.93 (C-2), 20.94 (CH_{3Ac}), 17.42 (C-6). HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd for C₁₁H₁₇N₃O₅Na, 294.1060; found, 294.1055.

Alllyl 3-*O*-Acetyl-4-azido-2-dichloroacetamido-2,4,6-trideoxy- β -*D*-galactopyranoside (52). Alcohol **49** (280 mg, 789 μ mol, 1.0 equiv) was dissolved in anhyd. DCM (7.0 mL) under an Ar atmosphere. The solution was cooled to –10 °C. Anhyd. pyridine (113 μ L, 1.41 mmol, 2.0 equiv) was added, followed by addition of triflic anhydride

(177 μ L, 105 mmol, 1.5 equiv). After stirring for 1 h at –10 °C, a follow-up by TLC (Tol/EtOAc 3:1) revealed the absence of the starting **49** (*R*_f 0.2) and the presence of a less polar product (*R*_f 0.8). The reaction mixture was diluted with DCM (10 mL). The organic layer was washed with 1 N aq HCl (20 mL) and NaHCO₃ (20 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude was dried under high vacuum for 2 h. The residue was dissolved in anhyd. DMF (7 mL), and sodium azide (229 mg, 3.52 mmol, 5.0 equiv) was added. After overnight stirring, TLC (Tol/EtOAc 2:1) revealed the absence of the intermediate triflate (*R*_f 0.85) and the presence of a less polar product (*R*_f 0.65). The reaction mixture was diluted with DCM (20 mL) and washed with water (70 mL) and brine (70 mL). The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Flash chromatography (Tol/EtOAc 80:20 \rightarrow 70:30) gave the azido derivative **52** (205 mg, 539 μ mol, 68%) as a white solid. The azide **52** had *R*_f 0.35 (Tol/EtOAc 4:1). ¹H NMR (400 MHz, CDCl₃): δ 6.51 (d, 1H, *J*_{NH,2} = 8.0 Hz, NH), 5.89 (s, 1H, CHCl₂), 5.91–5.81 (m, 1H, CH_{All}), 5.49 (dd, 1H, *J*_{3,4} = 4.0 Hz, *J*_{3,2} = 11.2 Hz, H-3), 5.30–5.24 (m, 1H, CH_{2All}), 5.21–5.17 (m, 1H, CH_{2All}), 4.72 (d, 1H, *J*_{1,2} = 8.4 Hz, H-1), 4.37–4.32 (m, 1H, CH_{2All}), 4.11–4.05 (m, 1H, CH_{2All}), 4.02 (dt, 1H, H-2), 3.85 (dd, 2H, *J*_{4,5} = 1.2 Hz, H-4), 3.80 (dq, 1H, H-5), 2.14 (s, 3H, CH_{3Ac}), 1.41 (d, 3H, *J*_{5,6} = 6.4 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 170.42 (CO_{Ac}), 164.47 (CO_{NH}), 133.52 (CH_{All}), 117.91 (CH_{2All}), 98.91 (C-1), 71.62 (C-3), 69.91 (CH_{2All}), 69.24 (C-5), 66.31 (CHCl₂), 63.44 (C-4), 52.45 (C-2), 20.44 (CH_{3Ac}), 17.34 (C-6). HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd for C₁₃H₁₈Cl₂N₄O₃Na, 403.0552; found, 403.0552.

Alllyl 3-*O*-Acetyl-2,6-dideoxy-2-trichloroacetamido- β -*D*-galactopyranoside (54). A solution of alcohol **50** (1.1 g, 2.82 mmol, 1.0 equiv) in anhyd. DCM (15 mL) was cooled to –10 °C. Pyridine (454 μ L, 5.65 mmol, 2.0 equiv) and triflic anhydride (569 μ L, 3.39 mmol, 1.2 equiv) were added. The mixture was stirred for 1 h at this temperature and then diluted with DCM (20 mL). The organic phase was washed with 1 N aq HCl (40 mL), satd aq NaHCO₃ (40 mL), and brine (40 mL); passed through a phase separator filter; and concentrated to dryness. The crude was dissolved in anhyd. DMF (8.0 mL) and cooled to 0 °C. TBANO₂ (2.0 g, 7.06 mmol, 2.5 equiv) was added, and the reaction mixture was stirred for 12 h after having reached rt slowly. A TLC analysis (Tol/EtOAc 7:3) showed the absence of the intermediate triflate (*R*_f 0.7) and the presence of a polar spot (*R*_f 0.1). The mixture was diluted with DCM (30 mL) and washed with water (100 mL) and brine (60 mL). The organic layer was separated, dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (Tol/EtOAc 70:30 \rightarrow 65:35) gave the fucosaminide derivative **54** (910 mg, 2.33 mmol, 82%) as a white solid. The latter had *R*_f 0.35 (Tol/EtOAc, 7:3). ¹H NMR (400 MHz, CDCl₃): δ 6.92 (d, 1H, *J*_{2,NH} = 8.8 Hz, NH), 5.89–5.81 (m, 1H, CH_{All}), 5.30–5.16 (m, 3H, H-3, CH_{2All}), 4.68 (d, 1H, *J*_{1,2} = 8.4 Hz, H-1), 4.40–4.34 (m, 1H, CH_{2All}), 4.25–4.18 (m, 1H, H-2), 4.12–4.06 (m, 1H, CH_{2All}), 3.84 (d, 1H, *J*_{3,4} = 2.9 Hz, H-4), 3.74 (q, 1H, H-5), 2.49 (brs, 1H, OH), 2.12 (s, 3H, CH_{3Ac}), 1.36 (d, 3H, *J*_{5,6} = 6.3 Hz, H-6). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 170.95 (CO_{Ac}), 162.16 (CO_{NH}), 133.57 (CH_{All}), 117.65 (CH_{2All}), 99.77 (C-1), 92.48 (CCl₃), 72.50 (C-3), 70.65 (C-5), 70.10 (CH_{2All}), 69.77 (C-4), 52.80 (C-2), 20.84 (CH_{3Ac}), 16.22 (C-6). HRMS (ESI⁺) *m/z*: [M + NH₄]⁺ calcd for C₁₃H₂₂Cl₃N₂O₆, 407.0538; found, 407.0530.

Alllyl 3-*O*-Acetyl-2-azido-2,6-dideoxy- β -*D*-galactopyranoside (55). Pyridine (236 μ L, 2.95 mmol, 2.0 equiv) and triflic anhydride (346 μ L, 2.06 mmol, 1.4 equiv) were added to alcohol **51** (400 mg, 1.47 mmol, 1.0 equiv) in anhyd. DCM (10 mL) at –10 °C. After stirring for 1 h at –10 °C, a TLC analysis (Tol/EtOAc 4:1) indicated the conversion of the starting **51** (*R*_f 0.35) to a less polar compound (*R*_f 0.95). DCM (10 mL) was added, and the reaction mixture was washed with 20% aq CuSO₄ (10 mL) and brine (10 mL). The organic layer was separated, dried over Na₂SO₄, concentrated, and extensively dried under high vacuum. The crude was dissolved in anhyd. DMF (8.0 mL), and TBANO₂ (851 mg, 2.95 mmol, 2.0 equiv) was added. After stirring overnight, DCM (50 mL) was added, and the reaction was washed with 50% aq NaCl (50 mL). The aq phase was extracted with DCM (2 \times 20 mL). The combined organic phases were dried over Na₂SO₄ and concentrated. Flash chromatography (cHex/EtOAc 65:35 \rightarrow 60:40) of

the crude gave the expected alcohol **55** (290 mg, 1.06 mmol, 73%) as a white solid. Compound **55** had R_f 0.2 (Tol/EtOAc 9:1). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.99–5.91 (m, 1H, CH_{All}), 5.38–5.33 (m, 1H, $\text{CH}_{2\text{All}}$), 5.26–5.23 (m, 1H, $\text{CH}_{2\text{All}}$), 4.70 (dd, 1H, $J_{3,4} = 3.0$ Hz, $J_{2,3} = 10.4$ Hz, H-3), 4.45–4.40 (m, 1H, $\text{CH}_{2\text{All}}$), 4.36 (d, 1H, $J_{1,2} = 8.0$ Hz, H-1), 4.19–4.14 (m, 1H, $\text{CH}_{2\text{All}}$), 3.81 (brs, 1H, H-4), 3.71 (dd, 1H, H-2), 3.65 (q, 1H, H-5), 2.18 (s, 3H, $\text{CH}_{3\text{Ac}}$), 2.11 (brs, 1H, OH), 1.33 (d, 3H, $J_{5,6} = 6.6$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 170.11 (CO_{Ac}), 133.35 (CH_{All}), 117.92 ($\text{CH}_{2\text{All}}$), 101.07 (C-1), 74.07 (C-3), 70.39 (C-5), 70.35 ($\text{CH}_{2\text{All}}$), 69.34 (C-4), 60.70 (C-2), 20.93 ($\text{CH}_{3\text{Ac}}$), 16.10 (C-6). HRMS (ESI^+) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{11}\text{H}_{21}\text{N}_4\text{O}_5$, 289.1506; found, 289.1494.

Allyl 3-O-Acetyl-2,4-diazido-2,4,6-trideoxy- β -D-glucopyranoside (56). Pyridine (26 μL , 336 μmol , 1.3 equiv) and triflic anhydride (52 μL , 310 μmol , 1.2 equiv) were added to a solution of alcohol **55** (70 mg, 258 μL , 1.0 equiv) in anhyd. DCM (3.0 mL) cooled to -10 $^\circ\text{C}$. After stirring for 2 h at this temperature, DCM (5 mL) was added. The organic phase was washed with 20% aq CuSO_4 (10 mL), aq NaHCO_3 (10 mL), and brine (10 mL). The DCM part was separated, dried over Na_2SO_4 , concentrated, and dried under high vacuum. NaN_3 (149 mg, 516 μmol , 2.0 equiv) was added to the crude in anhyd. DMF (3.0 mL). After stirring for 6 h at rt, DCM was added, and the DCM layer was washed with water and brine. The organic layer was separated, dried, and concentrated. Flash chromatography (Tol/EtOAc 95:5 \rightarrow 90:10) of the crude gave the diazide **56** (52 mg, 175 μmol , 68%) as a white solid. Compound **56** had R_f 0.75 (Tol/EtOAc 9:1). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.98–5.90 (m, 1H, CH_{All}), 5.38–5.33 (m, 1H, $\text{CH}_{2\text{All}}$), 5.28–5.24 (m, 1H, $\text{CH}_{2\text{All}}$), 4.95 (dd, 1H, $J_{3,4} = J_{2,3} = 10.0$ Hz, H-3), 4.42–4.38 (m, 2H, $\text{CH}_{2\text{All}}$, H-1), 4.19–4.13 (m, 1H, $\text{CH}_{2\text{All}}$), 3.44 (dd, 1H, $J_{1,2} = 8.0$ Hz, H-2), 3.34 (dq, 1H, $J_{4,5} = 9.8$ Hz, H-5), 3.18 (t, 1H, $J_{3,4} = 10.0$ Hz, H-4), 2.19 (s, 3H, $\text{CH}_{3\text{Ac}}$), 1.40 (d, 3H, $J_{5,6} = 6.1$ Hz, H-6). $^{13}\text{C}\{^1\text{H}\}$ NMR (400 MHz, CDCl_3): δ 169.63 (CO_{Ac}), 133.11 (CH_{All}), 118.16 ($\text{CH}_{2\text{All}}$), 100.54 (C-1), 72.89 (C-3), 70.68 (C-5), 70.48 ($\text{CH}_{2\text{All}}$), 65.81 (C-4), 64.18 (C-2), 20.71 ($\text{CH}_{3\text{Ac}}$), 18.23 (C-6). HRMS (ESI^+): calcd for $\text{C}_{11}\text{H}_{17}\text{N}_6\text{O}_4$, $[\text{M} + \text{H}]^+$ m/z 297.1306; found, 297.1303.

Allyl 3-O-tert-Butyldimethylsilyl-2,6-dideoxy-2-trichloroacetamido- β -D-galactopyranoside (57). NaOMe (25% NaOMe in MeOH, 36 μL , 167 μmol , 0.1 equiv) was added to a solution of acetate **54** (650 mg, 1.67 mmol, 1.0 equiv) in MeOH (12 mL). After stirring for 1 h at rt, Dowex- H^+ resin was added to reach pH \sim 7.0. The suspension was filtered and washed thoroughly with MeOH, and the filtrate was concentrated to dryness. The crude diol was dissolved in anhyd. DMF (10 mL). TBSCl (277 mg, 1.83 mmol, 1.1 equiv) was added, followed by the addition of imidazole (170 mg, 2.50 mmol, 1.5 equiv). After stirring overnight at rt, a TLC analysis (Tol/EtOAc, 1:1) showed complete conversion of the starting material (R_f 0.2) into a less polar product (R_f 0.6). MeOH was added, and after an additional hour, volatiles were evaporated. Flash chromatography of the crude (Tol/EtOAc 15:85 \rightarrow 50:50) gave the silylated derivative **57** as a white solid (640 mg, 1.38 mmol, 83%). Alcohol **57** had R_f 0.5 (Tol/EtOAc 4:1). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.87 (d, 1H, $J_{2,\text{NH}} = 7.2$ Hz, NH), 5.93–5.83 (m, 1H, CH_{All}), 5.29–5.24 (m, 1H, $\text{CH}_{2\text{All}}$), 5.19–5.15 (m, 1H, $\text{CH}_{2\text{All}}$), 4.95 (d, 1H, $J_{1,2} = 8.4$ Hz, H-1), 4.42 (dd, 1H, $J_{2,3} = 10.2$ Hz, $J_{3,4} = 3.4$ Hz, H-3), 4.38–4.33 (m, 1H, $\text{CH}_{2\text{All}}$), 4.11–4.05 (m, 1H, $\text{CH}_{2\text{All}}$), 3.69 (dq, 1H, $J_{4,5} = 0.8$ Hz, H-5), 3.66 (d, 1H, $J_{3,4} = 3.4$ Hz, H-4), 3.54–3.48 (m, 1H, H-2), 2.45 (brs, 1H, OH), 1.41 (d, 3H, $J_{5,6} = 6.5$ Hz, H-6), 0.92 (s, 9H, $\text{CH}_{3\text{tBu}}$), 0.13, 0.12 (2s, 6H, $\text{CH}_{3\text{TBBS}}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 161.80 (CO_{NH}), 133.79 (CH_{All}), 117.80 ($\text{CH}_{2\text{All}}$), 97.45 (C-1), 92.49 (CCl_3), 71.68 (C-4), 70.45 (C-3), 70.11 ($\text{CH}_{2\text{All}}$), 69.92 (C-5), 57.12 (C-2), 25.67 ($\text{CH}_{3\text{tBu}}$), 17.87 (C_{qTBu}), 16.44 (C-6), –4.53, –4.73 (2C, $\text{CH}_{3\text{TBBS}}$). HRMS (ESI^+) m/z : $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{17}\text{H}_{34}\text{Cl}_3\text{N}_2\text{O}_5\text{Si}$, 479.1297; found, 479.1291.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

■ Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.2c03016>.

Abbreviations, experimental procedures, analytical data of the synthesized compounds, as well as ^1H and ^{13}C NMR spectra of novel compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Laurence A. Mulard – Institut Pasteur, Université Paris Cité, UMR CNRS3523, Chemistry of Biomolecules Laboratory, 75015 Paris, France; orcid.org/0000-0002-5622-1422; Email: laurence.mulard@pasteur.fr

Authors

Debashis Dhara – Institut Pasteur, Université Paris Cité, UMR CNRS3523, Chemistry of Biomolecules Laboratory, 75015 Paris, France

Marion Bouchet – Institut Pasteur, Université Paris Cité, UMR CNRS3523, Chemistry of Biomolecules Laboratory, 75015 Paris, France

Complete contact information is available at:

<https://pubs.acs.org/doi/10.1021/acs.joc.2c03016>

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work, including a PRC postdoctoral fellowship to D.D., was funded by the Institut Pasteur. The authors also gratefully acknowledge generous funding from the Bill & Melinda Gates Foundation (grant agreement Investment ID OPP1191130) and from the Bill & Melinda Gates Medical Research Institute (contract ID: Collaboration & License Agreement Institut Pasteur, Gates MRI, December 2019). Both funds included fellowships to D.D. and M.B. The authors thank F. Bonhomme (CNRS UMR3523) for the HRMS spectra and L. Hinry (Chemistry of Biomolecules Laboratory) for her contribution to the synthesis work.

■ REFERENCES

- (1) Herget, S.; Toukach, P. V.; Ranzinger, R.; Hull, W. E.; Knirel, Y. A.; von der Lieth, C.-W. Statistical analysis of the Bacterial Carbohydrate Structure Data Base (BCSDB): Characteristics and diversity of bacterial carbohydrates in comparison with mammalian glycans. *BMC Struct. Biol.* **2008**, *8*, 35.
- (2) Adibekian, A.; Stallforth, P.; Hecht, M.-L.; Werz, D. B.; Gagneux, P.; Seeberger, P. H. Comparative bioinformatics analysis of the mammalian and bacterial glycomes. *Chem. Sci.* **2011**, *2*, 337–344.
- (3) Marchetti, R.; Forgione, R. E.; Fabregat, F. N.; Di Carluccio, C.; Molinaro, A.; Silipo, A. Solving the structural puzzle of bacterial glycome. *Curr. Opin. Struct. Biol.* **2021**, *68*, 74–83.
- (4) Clark, E. L.; Emmadi, M.; Krupp, K. L.; Podilapu, A. R.; Helble, J. D.; Kulkarni, S. S.; Dube, D. H. Development of Rare Bacterial Monosaccharide Analogs for Metabolic Glycan Labeling in Pathogenic Bacteria. *ACS Chem. Biol.* **2016**, *11*, 3365–3373.
- (5) Morrison, M. J.; Imperiali, B. The Renaissance of Bacillosamine and Its Derivatives: Pathway Characterization and Implications in Pathogenicity. *Biochemistry* **2014**, *53*, 624–638.
- (6) Zhang, Q.; Overkleeft, H. S.; van der Mare, G. A.; Codée, J. D. Synthetic wittertonic polysaccharides. *Curr. Opin. Chem. Biol.* **2017**, *40*, 95–101.

- (7) Gattoji, V. K.; Valentin, G.; Geremia, M. L.; Andreana, P. R. Zwitterionic Polysaccharides in Immunity. In *Comprehensive Glycoscience*, 2nd ed.; Barchi, J. J., Ed.; Elsevier, 2021; pp 454–469.
- (8) Williams, D. A.; Pradhan, K.; Paul, A.; Olin, I. R.; Tuck, O. T.; Moulton, K. D.; Kulkarni, S. S.; Dube, D. H. Metabolic inhibitors of bacterial glycan biosynthesis. *Chem. Sci.* **2020**, *11*, 1761–1774.
- (9) Behera, A.; Kulkarni, S. S. Chemical Synthesis of Rare, Deoxy-Amino Sugars Containing Bacterial Glycoconjugates as Potential Vaccine Candidates. *Molecules* **2018**, *23*, 1997.
- (10) Emmadi, M.; Kulkarni, S. S. Recent advances in synthesis of bacterial rare sugar building blocks and their applications. *Nat. Prod. Rep.* **2014**, *31*, 870–879.
- (11) Zhang, Q.; Gimeno, A.; Santana, D.; Wang, Z.; Valdés-Balbin, Y.; Rodríguez-Noda, L. M.; Hansen, T.; Kong, L.; Shen, M.; Overkleeft, H. S.; et al. Synthetic, Zwitterionic Sp1 Oligosaccharides Adopt a Helical Structure Crucial for Antibody Interaction. *ACS Cent. Sci.* **2019**, *5*, 1407–1416.
- (12) Tzianabos, A. O.; Pantosti, A.; Baumann, H.; Brisson, J. R.; Jennings, H. J.; Kasper, D. L. The capsular polysaccharide of *Bacteroides fragilis* comprises two ionically linked polysaccharides. *J. Biol. Chem.* **1992**, *267*, 18230–18235.
- (13) Eade, C. R.; Wallen, T. W.; Gates, C. E.; Oliverio, C. L.; Scarbrough, B. A.; Reid, A. J.; Jorgenson, M. A.; Young, K. D.; Troutman, J. M. Making the Enterobacterial Common Antigen Glycan and Measuring Its Substrate Sequestration. *ACS Chem. Biol.* **2021**, *16*, 691–700.
- (14) Medgyes, A.; Farkas, E.; Lipták, A.; Pozsgay, V. Synthesis of the monosaccharide units of the O-specific polysaccharide of *Shigella sonnei*. *Tetrahedron* **1997**, *53*, 4159–4178.
- (15) Kubler-Kielb, J.; Schneerson, R.; Mocca, C.; Vinogradov, E. The elucidation of the structure of the core part of the LPS from *Plesiomonas shigelloides* serotype O17 expressing O-polysaccharide chain identical to the *Shigella sonnei* O-chain. *Carbohydr. Res.* **2008**, *343*, 3123–3127.
- (16) Ovchinnikova, O. G.; Kocharova, N. A.; Bialczak-Kokot, M.; Shashkov, A. S.; Rozalski, A.; Knirel, Y. A. Structure of the O-Polysaccharide of *Providencia alcalifaciens* O22 Containing D-Glyceramide 2-Phosphate. *Eur. J. Org. Chem.* **2012**, *2012*, 3500–3506.
- (17) Kondakova, A. N.; Kirsheva, N. A.; Arbatsky, N. P.; Shaikhutdinova, R. Z.; Shashkov, A. S.; Ivanov, S. A.; Anisimov, A. P.; Knirel, Y. A. Structure of a zwitterionic O-polysaccharide from *Photobacterium temperata* subsp. *cinerea* 3240. *Carbohydr. Res.* **2015**, *407*, 1–4.
- (18) Gisch, N.; Schwudke, D.; Thomsen, S.; Heß, N.; Hakenbeck, R.; Denapate, D. Lipoteichoic acid of *Streptococcus oralis* Uo5: a novel biochemical structure comprising an unusual phosphorylcholine substitution pattern compared to *Streptococcus pneumoniae*. *Sci. Rep.* **2015**, *5*, 16718.
- (19) Vinogradov, E.; St Michael, F.; Cox, A. D. Structure of the LPS O-chain from *Fusobacterium nucleatum* strain MJR 7757 B. *Carbohydr. Res.* **2018**, *463*, 37–39.
- (20) Fischer, W. Pneumococcal lipoteichoic and teichoic acid. *Microb. Drug Resist.* **1997**, *3*, 309–325.
- (21) Podilapu, A. R.; Kulkarni, S. S. First Synthesis of *Bacillus cereus* Ch HF-PS Cell Wall Trisaccharide Repeating Unit. *Org. Lett.* **2014**, *16*, 4336–4339.
- (22) Garcia-Vello, P.; Di Lorenzo, F.; Lamprinaki, D.; Notaro, A.; Speciale, I.; Molinaro, A.; Juge, N.; De Castro, C. Structure of the O-Antigen and the Lipid A from the Lipopolysaccharide of *Fusobacterium nucleatum* ATCC 51191. *ChemBioChem* **2021**, *22*, 1252–1260.
- (23) Liav, A.; Hildesheim, J.; Zehavi, U.; Sharon, N. Synthesis of 2-acetamido-2,6-dideoxy-D-glucose (N-acetyl-D-quinovosamine), 2-acetamido-2,6-dideoxy-D-galactose (N-acetyl-D-fucosamine), and 2,4-diacetamido-2,4,6-trideoxy-D-glucose from 2-acetamido-2-deoxy-D-glucose. *Carbohydr. Res.* **1974**, *33*, 217–227.
- (24) Lönn, H.; Lönngren, J. Synthesis of a disaccharide component of the capsular polysaccharide antigen of *Streptococcus pneumoniae* type 1. *Carbohydr. Res.* **1984**, *132*, 39–44.
- (25) Liang, H.; Grindley, T. B. An Efficient Synthesis of Derivatives of 2-Acetamido-4-amino-2,4,6-trideoxy-D-galactopyranose. *J. Carbohydr. Chem.* **2004**, *23*, 71–82.
- (26) Cai, Y.; Ling, C.-C.; Bundle, D. R. Concise and Efficient Synthesis of 2-Acetamido-2-deoxy- β -D-hexopyranosides of Diverse Aminosugars from 2-Acetamido-2-deoxy- β -D-glucose. *J. Org. Chem.* **2009**, *74*, 580–589.
- (27) Emmadi, M.; Kulkarni, S. S. Synthesis of orthogonally protected bacterial, rare-sugar and D-glycosamine building blocks. *Nat. Protoc.* **2013**, *8*, 1870–1889.
- (28) Hermans, J. P. G.; Elie, C. J. J.; van der Marel, G. A.; Van Boom, J. H. Benzyl-2,4-Diacetamido-2, 4,6-Tri-Deoxy- $\alpha(\beta)$ -D-Galactopyranoside. *J. Carbohydr. Chem.* **1987**, *6*, 451–462.
- (29) Schmöler, C.; Nowikow, C.; Kählig, H.; Schmid, W. Gram scale de novo synthesis of 2,4-diacetamido-2,4,6-trideoxy-D-galactose. *Carbohydr. Res.* **2013**, *367*, 1–4.
- (30) Wu, X. Y.; Cui, L. N.; Lipinski, T.; Bundle, D. R. Synthesis of Monomeric and Dimeric Repeating Units of the Zwitterionic Type 1 Capsular Polysaccharide from *Streptococcus pneumoniae*. *Chem.—Eur. J.* **2010**, *16*, 3476–3488.
- (31) Pfister, H. B.; Paoletti, J.; Poveda, A.; Jimenez-Barbero, J.; Mulard, L. A. Zwitterionic Polysaccharides of *Shigella sonnei*: Synthetic Study toward a Ready-for-Oligomerization Building Block Made of Two Rare Amino Sugars. *Synthesis* **2018**, *50*, 4270–4282.
- (32) Manabe, S.; Ito, Y. 1,2-cis-Selective Formation of a Unique Amino-Containing Amino Glycoside by Endocyclic Cleavage Strategy. *Heterocycles* **2019**, *99*, 1304–1314.
- (33) van den Bos, L. J.; Boltje, T. J.; Provoost, T.; Mazurek, J.; Overkleeft, H. S.; van der Marel, G. A. A synthetic study towards the PSA1 tetrasaccharide repeating unit. *Tetrahedron Lett.* **2007**, *48*, 2697–2700.
- (34) Pragani, R.; Seeberger, P. H. Total Synthesis of the *Bacteroides fragilis* Zwitterionic Polysaccharide A1 Repeating Unit. *J. Am. Chem. Soc.* **2011**, *133*, 102–107.
- (35) Eradi, P.; Ghosh, S.; Andreana, P. R. Total Synthesis of Zwitterionic Tetrasaccharide Repeating Unit from *Bacteroides fragilis* ATCC 25285/NCTC 9343 Capsular Polysaccharide PS A1 with Alternating Charges on Adjacent Monosaccharides. *Org. Lett.* **2018**, *20*, 4526–4530.
- (36) Smid, P.; Zwart, M. d.; Jörning, W. P. A.; Van Der Marel, G. A.; Van Boom, J. H. Stereoselective Synthesis of a Tetrameric Fragment of *Streptococcus pneumoniae* Type 1 Containing an α -Linked 2-Acetamido-4-amino-2,4,6-trideoxy-D-galactopyranose (SUGp) Unit. *J. Carbohydr. Chem.* **1993**, *12*, 1073–1090.
- (37) Christina, A. E.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. Galacturonic Acid Lactones in the Synthesis of All Trisaccharide Repeating Units of the Zwitterionic Polysaccharide Sp1. *J. Org. Chem.* **2011**, *76*, 1692–1706.
- (38) Christina, A. E.; Blas Ferrando, V. M.; de Bordes, F.; Spruit, W. A.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. Multigram-scale synthesis of an orthogonally protected 2-acetamido-4-amino-2,4,6-trideoxy-D-galactose (AAT) building block. *Carbohydr. Res.* **2012**, *356*, 282–287.
- (39) Cheallaigh, A. N.; Oscarson, S. Synthesis of building blocks for an iterative approach towards oligomers of the *Streptococcus pneumoniae* type 1 zwitterionic capsular polysaccharide repeating unit. *Can. J. Chem.* **2016**, *94*, 940–960.
- (40) Ghosh, A.; Kulkarni, S. S. Total Synthesis of the Repeating Unit of *Streptococcus pneumoniae* Zwitterionic Polysaccharide Sp1. *J. Org. Chem.* **2021**, *86*, 18292–18299.
- (41) Pedersen, C. M.; Figueroa-Perez, I.; Boruwa, J.; Lindner, B.; Ulmer, A. J.; Zähringer, U.; Schmidt, R. R. Synthesis of the Core Structure of the Lipoteichoic Acid of *Streptococcus pneumoniae*. *Chem.—Eur. J.* **2010**, *16*, 12627–12641.
- (42) Pedersen, C. M.; Figueroa-Perez, I.; Lindner, B.; Ulmer, A. J.; Zähringer, U.; Schmidt, R. R. Total Synthesis of Lipoteichoic Acid of *Streptococcus pneumoniae*. *Angew. Chem., Int. Ed.* **2010**, *49*, 2585–2590.

- (43) Chaudhury, A.; Ghosh, R. A target oriented expeditious approach towards synthesis of certain bacterial rare sugar derivatives. *Org. Biomol. Chem.* **2017**, *15*, 1444–1452.
- (44) Tóth, A.; Medgyes, A.; Bajza, B.; Lipták, A.; Batta, G.; Kontróhr, T.; Péterffy, K.; Pozsgay, P. Synthesis of the repeating unit of the O-specific polysaccharide of *Shigella sonnei* and quantitation of its serologic activity. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 19–21.
- (45) Pfister, H. B.; Mulard, L. A. Synthesis of the Zwitterionic Repeating Unit of the O-Antigen from *Shigella sonnei* and Chain Elongation at Both Ends. *Org. Lett.* **2014**, *16*, 4892–4895.
- (46) Ghotekar, B. K.; Podilapu, A. R.; Kulkarni, S. S. Total Synthesis of the Lipid-Anchor-Attached Core Trisaccharides of Lipoteichoic Acids of *Streptococcus pneumoniae* and *Streptococcus oralis* Uo5. *Org. Lett.* **2020**, *22*, 537–541.
- (47) Dhara, D.; Mulard, L. A. Exploratory N-Protecting Group Manipulation for the Total Synthesis of Zwitterionic *Shigella sonnei* Oligosaccharides. *Chem.—Eur. J.* **2021**, *27*, 5694–5711.
- (48) Podilapu, A. R.; Kulkarni, S. S. Total Synthesis of Repeating Unit of O-Polysaccharide of *Providencia alcalifaciens* O22 via One-Pot Glycosylation. *Org. Lett.* **2017**, *19*, 5466–5469.
- (49) Iynkkaran, I.; Bundle, D. R. A novel glycosyl donor for synthesis of 2-acetamido-4-amino-2,4,6-trideoxy- α -D-galactopyranosides. *Carbohydr. Res.* **2010**, *345*, 2323–2327.
- (50) Jörning, W. P. A.; van Duuren, A. M. G.; Boons, G. J. R. H.; van der Marel, G. A.; van Boom, J. H. Stereoselective Synthesis of a Dimer Containing an α -Linked 2-Acetamido-4-Amino-2,4,6-Trideoxy-D-Galactopyranose (Sugg) Unit. *J. Carbohydr. Chem.* **1992**, *11*, 849–865.
- (51) Guiard, J.; Rahali, Y.; Praly, J.-P. NaBH_3CN : A Janus Substitute for Tin-Free Radical-Based Reactions. *Eur. J. Org. Chem.* **2014**, *2014*, 4461–4466.
- (52) Lloyd, D.; Bennett, C. S. Gram-Scale Synthesis of an Armed Colitose Thioglycoside. *J. Org. Chem.* **2014**, *79*, 9826–9829.
- (53) Zhang, X.; Zhou, Y.; Zuo, J.; Yu, B. Total synthesis of periploside A, a unique pregnane hexasaccharide with potent immunosuppressive effects. *Nat. Commun.* **2015**, *6*, 5879.
- (54) Cheng, G.-J.; Drosos, N.; Morandi, B.; Thiel, W. Computational Study of $\text{B}(\text{C}_6\text{F}_5)_3$ -Catalyzed Selective Deoxygenation of 1,2-Diols: Cyclic and Noncyclic Pathways. *ACS Catal.* **2018**, *8*, 1697–1702.
- (55) Qin, C.; Schumann, B.; Zou, X.; Pereira, C. L.; Tian, G.; Hu, J.; Seeberger, P. H.; Yin, J. Total Synthesis of a Densely Functionalized *Plesiomonas shigelloides* Serotype 51 Aminoglycoside Trisaccharide Antigen. *J. Am. Chem. Soc.* **2018**, *140*, 3120–3127.
- (56) van Mechelen, J.; Voorneveld, J.; Overkleeft, H. S.; Filippov, D. V.; van der Marel, G. A.; Codée, J. D. C. Synthesis of orthogonally protected and functionalized bacillosamines. *Org. Biomol. Chem.* **2020**, *18*, 2834–2837.
- (57) Yan, R. B.; Yang, F.; Wu, Y. F.; Zhang, L. H.; Ye, X. S. An efficient and improved procedure for preparation of triflyl azide and application in catalytic diazotransfer reaction. *Tetrahedron Lett.* **2005**, *46*, 8993–8995.
- (58) Silva, D. J.; Wang, H.; Allanson, N. M.; Jain, R. K.; Sofia, M. J. Stereospecific Solution- and Solid-Phase Glycosylations. Synthesis of β -Linked Saccharides and Construction of Disaccharide Libraries Using Phenylsulfenyl 2-Deoxy-2-Trifluoroacetamido Glycopyranosides as Glycosyl Donors. *J. Org. Chem.* **1999**, *64*, 5926–5929.
- (59) Ren, B.; Gan, L.; Zhang, L.; Yan, N. N.; Dong, H. Diisopropylethylamine-triggered, highly efficient, self-catalyzed regioselective acylation of carbohydrates and diols. *Org. Biomol. Chem.* **2018**, *16*, 5591–5597.
- (60) Demizu, Y.; Kubo, Y.; Miyoshi, H.; Maki, T.; Matsumura, Y.; Moriyama, N.; Onomura, O. Regioselective Protection of Sugars Catalyzed by Dimethyltin Dichloride. *Org. Lett.* **2008**, *10*, 5075–5077.
- (61) Chan, L. N.; Taylor, M. S. Regioselective Alkylation of Carbohydrate Derivatives Catalyzed by a Diarylborinic Acid Derivative. *Org. Lett.* **2011**, *13*, 3090–3093.
- (62) Ren, B.; Ramström, O.; Zhang, Q.; Ge, J.; Dong, H. An Iron(III) Catalyst with Unusually Broad Substrate Scope in Regioselective Alkylation of Diols and Polyols. *Chem.—Eur. J.* **2016**, *22*, 2481–2486.
- (63) Dong, H.; Pei, Z.; Ramström, O. Stereospecific ester activation in nitrite-mediated carbohydrate epimerization. *J. Org. Chem.* **2006**, *71*, 3306–3309.