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N–O Bond as a Glycosidic-Bond Surrogate: Synthetic Studies Toward Polyhydroxylated *N*-Alkoxypiperidines

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Abstract: A series of novel polyhydroxylated *N*-alkoxypiperidines has been synthesized by ring-closing double reductive amination (DRA) of highly functionalized 1,5-dialdehydes with various hydroxylamines. The required saccharide-based dialdehydes were prepared efficiently from sodium cyclopentadienylide in seven steps. A two-step protocol has been developed for the DRA; it led, after deprotection, to isofagomine, 3-deoxyisofagomine, and numerous other *N*-alkoxy analogues. The barrier to inversion in these polyhydroxylated *N*-alkoxypiperidine derivatives was found by variable-temperature NMR methods to be approximately 15 kcal mol^{-1}. With the exception of *N*-hydroxyisofagomine itself, none of the compounds prepared showed significant inhibitory activity against sweet almond β-glucosidase.

Keywords: carbohydrates · glycosidases · iminosugars · nitrogen heterocycles · reductive amination

Introduction

Oligosaccharides display a wide range of biological activities, some of which may potentially be exploited for medicinal purposes.[1] In particular, the glycans present a wide range of biological activities[2] and have long been considered as biological-response modifiers,[3] capable of boosting a biological response, for example, by eliciting natural defenses through the production of reactive oxygen species and phytoallexins or by the stimulation of macrophages, although they do not display cytotoxicity individually. Notably, it has been shown that glycans are immunostimulating agents against infectious diseases[2b,c] and cancer,[4] the activities of which are mediated by various pattern-recognition receptors, such as complement receptor 3,[4b] lactosyl ceramide,[5] scavenger receptors, and dectin-1,[6] a protein of the lectin class. Although several syntheses of high-molecular-weight glycans have been achieved,[6a,7] the critical reaction in such syntheses, that is, efficient stereocontrolled glycosidic-bond formation, is far from being a perfected art and represents a major hurdle to future progress.[8] Indeed, more than a century after the pioneering work of Koenigs and Knorr,[9] the development of new and improved glycosylation reactions remains an active field of research.[8b,10] Most problems in the area are associated with a combination of inadequate yields for the synthesis of complex oligomeric species and imperfect anomeric selectivities, which arise from stereochemical mismatching of donor/acceptor pairs in some cases;[11] the products frequently require tedious time-consuming separations with the associated decrease in yield and difficulties in scale up. Recognizing that glycosylation reactions are unlikely to be fully perfected in the near future, we have initiated a program[12] to explore avenues for the ideally iterative synthesis of novel oligosaccharide mimetics,[13] with a focus on the development of systems that mimic the glycosidic bond as closely as possible but that lack the issue of stereoselectivity that plagues actual glycosylation reactions.

From the various possibilities considered, we selected oligomers based on iminosugars linked through a hydroxylamine N–O bond, illustrated for a β-1,3-glucan mimetic in Figure 1 (X: CH_2). In particular, we were attracted to the hydroxylamine moiety because it is reported that the barrier to inversion at the nitrogen atom in trialkyl hydroxylamines is higher than that in simple amines but, at approximately 15 kcal mol^{-1}, is not sufficient to prevent rapid inversion at room temperature.[14] This is in contrast with the closer mimics of the glycosidic bond based on dialkoxyamines (Figure 1, X: O), in which the barrier to inversion is predicted to be approximately 29 kcal mol^{-1}, based on studies with

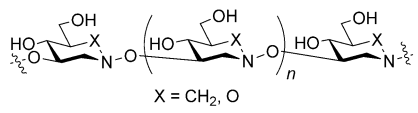

Figure 1. Representative hydroxylamine-based oligosaccharide mimetics.

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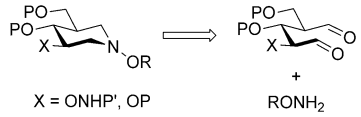
model compounds,[15] and in which the nitrogen atom therefore constitutes an undesirable stereogenic center at room temperature. With the low barrier to inversion, it is anticipated that any oligosaccharide based on the hydroxylamine motif (Figure 1, X: CH_2) would sample the full extent of conformational space available to it at room temperature and so would adapt for binding to lectins that are specific for either axially or equatorially linked oligosaccharides.

Hydroxylamines are considerably less basic than amines, which is considered to be the reason why an endocyclic hydroxylamine analogue of an iminosugar was found to have only low potency for the inhibition of a glycosidase enzyme, relative to that of the corresponding amine.[16] As our ultimate goal is the synthesis of oligosaccharide mimetics rather than glycosidase inhibitors, we viewed this lack of basicity as an advantage, rather than as a disadvantage. Nevertheless, there is considerable current interest in 1-*N*-iminosugars, which have emerged as potent carbohydrate mimics and in which the anomeric carbon atom has been replaced by a nitrogen atom and the ring oxygen atom has been replaced by a methylene group, as glycosidase and other enzyme inhibitors. For example, isofagomine, a non-natural azasugar[17] from this class and an analogue of the natural product fagomine isolated from buckwheat seeds,[18] has emerged as one of the more potent inhibitors of β-glucosidase[19] and hepatic glycogen phosphorylase.[20]

We have embarked on a program of engineering robust synthetic methods for the formation of hydroxylamine-linked iminosugars (Figure 1, X: CH_2) with the ultimate goal of developing oligosaccharide mimetics. Herein, we describe in full our exploratory chemistry[12a] toward this end, along with the glycosidase activities of the various simple *N*-alkoxyiminosugars prepared in these endeavors. We also report on the determination of the barrier to inversion of conformation/configuration in a number of simple *N*-alkoxyiminosugars, which previous to our work were only sparsely mentioned in the literature[21] but which, subsequent to our preliminary communication,[12a] were also reported by Fernández-Bolaños and co-workers.[22]

Results and Discussion

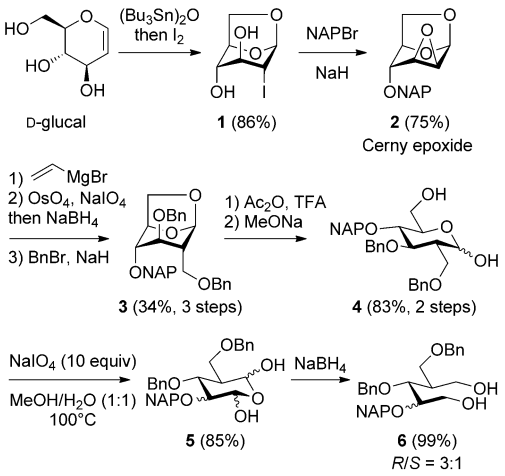
The ideal route to the hydroxylamine-linked imino saccharide mimetics (Figure 1, X: CH_2) involves N−O bond formation; however, there are very few examples of the formation of trialkyl hydroxylamines by displacement of a leaving group from a nitrogen atom by an alcohol(ate) in the literature[23] and even fewer of the formation of such substances by displacement of a leaving group from an oxygen atom by an amine or amide. Furthermore, exploratory work along these lines was not promising and, thus, we turned to more classic approaches for the synthesis of *N*-substituted piperidines, of which there are numerous examples in the literature.[24] We were inclined toward the use of a ring-closing double reductive amination of a 1,5-dialdehyde, such as that employed by the groups of Bols and Cardona,[25] but with the employment of an O-substituted hydroxylamine as the nitrogen source rather than ammonia (Scheme 1). Interestingly though, and heightening our interest in this approach,



Scheme 1. Retrosynthetic analysis based on the ring-closing double reductive amination. P: permanent protection; P′: semipermanent protection.

the reductive amination of hydroxylamines with dialdehydes was unknown, with the exception of a single example employing hydroxylamine itself that had been reported by Du and Hindsgaul.[26] Ultimately, this approach requires a dialdehyde in which any hydroxyl groups carry permanent protection (P), ideally in the form of benzyl ethers, and a hydroxylamine group with semipermanent protection (P′), perhaps in the form of a 9-fluorenylmethoxycarbonyl group (Scheme 1, X: ONHP′). However, for the purpose of the developmental work that we report here, we have worked simply with protected polyhydric dialdehydes (Scheme 1, X: OP).

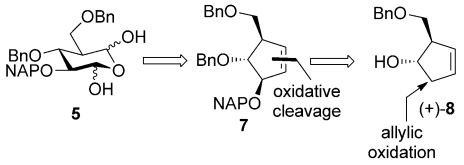
Dialdehyde synthesis starting from Cerny's epoxide: Very few approaches to saccharide-based dialdehyde scaffolds exist in the literature beyond that first employed by Bols and co-workers for the synthesis of isofagomine in 1994,[25a] which started with Cerny's epoxide (1,6:2,3-dianhydro-4-*O*-benzyl-β-D-mannopyranose).[27] Although first reported in the 1970s, synthetic applications of Cerny's epoxide derivatives have been limited, possibly due to the tendency of these compounds to undergo isomerization under alkaline conditions and by the lengthy methods needed for their preparation.[27,28] Bols and co-workers prepared Cerny's epoxide from levoglucosan (1,6-anhydro-β-D-glucopyranose) in a four-step sequence that suffered from low yields. The preparation of Cerny's epoxide derivatives was recently simplified by Xue and Guo, who proposed a three-step sequence from readily available D-glucal.[29] By adopting this protocol, we generated iodide **1** through the one-step oxidative 1,6-iodocyclization of D-glucal in 86% yield (Scheme 2).[28e,30] Exposure of **1** to NaH and an alkylating agent directly produced epoxide **2** with the desired regiochemistry, as described by Arndt and Hsieh-Wilson.[31] We envisaged the use of an O4 protecting group orthogonal to those intended for the remaining hydroxyl functions in the ultimate dialdehyde, in order to obtain piperidines that could be selectively deprotected at that position. We selected the naphthylmethyl ether for this purpose and obtained **2** in 75% yield. In accordance with the conditions of Noort and co-workers for the synthesis of a perbenzylated analogue of **4**,[32] a hydroxymethyl group was introduced at the C2 position by epoxide opening with vinyl magnesium bromide[33] in tetrahydrofuran (THF) under reflux conditions, followed by



Scheme 2. Preparation of highly functionalized 1,5-dialdehydes via Cerny's epoxide. NAP: naphthylmethyl; Bn: benzyl; TFA: trifluoroacetic acid.

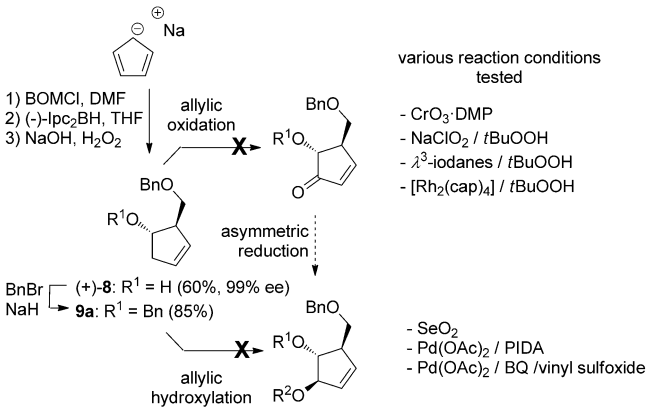
oxidative cleavage of the vinyl group with sodium periodate in the presence of osmium tetroxide. The corresponding aldehyde was directly converted into the hydroxymethyl derivative by reduction with sodium borohydride (35% over 2 steps; Scheme 2), and this was followed by dibenzylation to give **3** in high yield. Cleavage of the 1,6-anhydro bond was realized by a two-step procedure with trifluoroacetic acid in acetic anhydride to afford the diacetate as a mixture of anomers ($\alpha/\beta = 2.6:1$) and then a Zemplén deacetylation, to give **4** with an overall yield of 83% ($\alpha/\beta = 1:0.9$). Modification of the conditions of Bols and co-workers for the subsequent lactol cleavage, by increasing the temperature to 100°C and adding a large excess of $NaIO_4$ (10 equiv), gave the pentodialdose **5** in 85% yield,[34] which consists of a mixture of the dialdehyde and the diastereomeric forms of the hydrate dihemiacetal. A sample was reduced to diol **6** with sodium borohydride to check the efficiency of the oxidative cleavage.[25a] Surprisingly, diol **6**, which was obtained quasi-quantitatively, was a mixture of two epimers at the C3 position (3:1 *arabino*/*ribo*). The site of epimerization, and its stereochemical composition, was identified subsequently after the synthesis of diols (3*R*)-**6** and (3*S*)-**6** by another strategy (see below).[35] As the two epimers of the corresponding piperidine could be observed after a ring-closing double reductive amination assay,[36] the loss of stereochemical integrity was confirmed to occur during the oxidation step. The use of periodic acid (HIO_4), a stronger oxidant, allowed the reaction temperature to be lowered to 45°C and the excess of reagent to be five equivalents, while still giving the pentodialdose in 71% yield.[37] Nevertheless, this still resulted in epimerization (2:1 *arabino*/*ribo*), as confirmed by reduction of the product to the diol. Various other oxidants, including lead tetraacetate and iodobenzene diacetate, were investigated but were not satisfactory.

Dialdehyde synthesis starting from a cyclopentene precursor: The length and the complications inherent in the Cerny's epoxide route prompted the design of a second strategy for dialdehyde synthesis involving oxidative cleavage of a suitably functionalized cyclopentene **7** (Scheme 3),



Scheme 3. Proposed 1,5-dialdehyde synthesis from a cyclopentene intermediate.

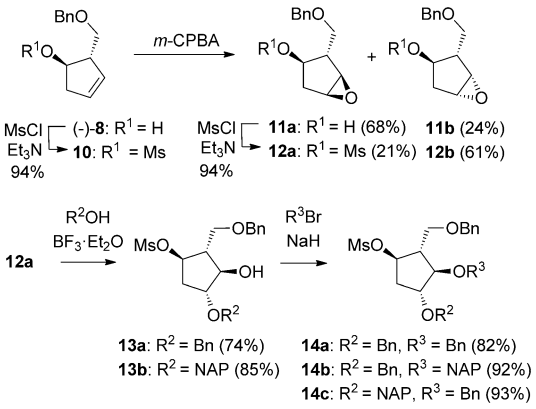
as first proposed by Mehta and Mohal in 2000.[38] However, instead of accessing the cyclopentene by fragmentation of a complex norbornyl derivative,[39] we opted for an approach based on allylic hydroxylation of the known optically pure cyclopentene (+)-**8**, a frequent intermediate in the synthesis of carbosugars and carbocyclic nucleosides.[40] From among the literature approaches to (+)-**8**,[36] we focused on the modification of Gellman and co-workers[40h] involving the alkylation of sodium cyclopentadienylide with benzyloxymethylchloride (BOMCl) in *N*,*N*-dimethylformamide (DMF), rather than the previously preferred THF, because it avoids isomerization of the sensitive initial adduct. Immediate desymmetrization by reaction of the adduct with (−)-diisopinocampheylborane ((−)-Ipc_2BH),[41] followed by oxidative workup, afforded the cyclopentene (+)-**8** with a satisfactory 60% yield[40k] and 99% enantiomeric purity on a 40 mmol scale (Scheme 4). After benzylation of (+)-**8**, the cyclopen-



Scheme 4. Synthesis of optically pure alcohol (+)-**8** and attempted allylic oxidation of **9a**. DMP: Dess–Martin periodinane; cap: caprolactamate; PIDA: phenyliodine diacetate; BQ: benzoquinone.

tene product **9a** was submitted to various allylic oxidation conditions,[42] none of which gave the desired product in useful quantities.

The problematic allylic oxidation step was circumvented by the adaptation of recent work from the Meier laboratory[40l] with (−)-**8**. Thus, (−)-**8** was accessed in the same manner as its enantiomer, but with (+)-Ipc_2BH employed

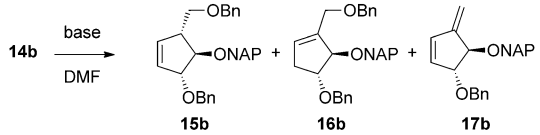


Scheme 5. Preparation of highly functionalized cyclopentanes. Ms: methane sulfonyl; *m*-CPBA: *meta*-chloroperoxybenzoic acid.

for the hydroboration step. In accordance with Jessel and Meier,[40l] alcohol (−)-**8** was mesylated to give **10** in excellent yield (Scheme 5), which was subjected to *m*CPBA-mediated epoxidation, to afford the epoxide **12** as a separable mixture of diastereomers **12a** and **12b** in a 1:3 ratio favoring the undesired isomer **12b**. Fortunately, if the *m*CPBA epoxidation was conducted directly on cyclopentene (−)-**8**, the reaction occurred preferentially syn to the directing hydroxy group and gave the two diastereomeric epoxides **11a** and **11b** in a ratio of 3:1 in favor of the desired epoxide. With $Mo(CO)_6$ as the catalyst for this directed epoxidation and *tert*-butyl hydroperoxide as the oxidant,[40g,i] the yield of desired epoxide **11a** could not be increased to 64%. After mesylation, epoxide **12a** was opened regioselectively with benzyl or naphthylmethyl alcohols in the presence of catalytic $BF_3{\cdot}OEt_2$ to afford alcohols **13a** and **13b** as single diastereoisomers in 74% and 85% yields, respectively (Scheme 5). The resulting alcohols were then protected with benzyl bromide or naphthylmethyl bromide in the presence of NaH to provide the cyclitols **14a–c** in 82%, 92%, and 93% yields, respectively.

For the elimination of the mesylate group in a series of closely related compounds, Jessel and Meier[40l] identified *t*BuOK in an aprotic polar solvent at 100 °C as suitable conditions to afford the desired Hofmann product, based on the low nucleophilicity and steric hindrance of the base. Consequently, we evaluated the action of various alkoxides on mesylate **14b** (Table 1). Depending on the base, three products were obtained in various ratios, namely the Hofmann and Saytzeff products **15b** and **16b**, respectively, and a product, **17b**, resulting from elimination of the benzyloxy group. The ratios of products were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. The use of 1,8-bis(dimethylamino)naphthalene (proton sponge), a strong organic base, led only to recovered starting material with no observable elimination product (Table 1, entry 1). With the phosphazene superbase (PhP_4), conversion was complete after 40 min, but an unsatisfactory ratio of the various elimination products was formed (Table 1, entry 2). The use of potassium alkoxides was next investigated. The Meier conditions

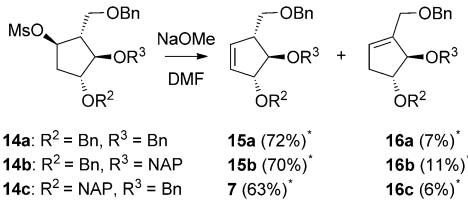
Table 1. Base-assisted elimination of the mesylate **14b**.



Entry	Base	*T*	Conv.[a] [%]	Ratio[a] **15b**/**16b**/**17b**		
1	proton sponge	100 °C	0[b]	–		
2	phosphazene PhP_4[c]	100 °C	100	1	0.5	0.16
3	*t*BuOK	100 °C	100	1	0.19	0.05
4	*t*BuOK	RT	100	1	0.11	0.02
5	$Et(Me)_2COK$[d]	RT	100	1	1.9	1.75
6	$Et(Me)_2COK$[d]	100 °C	100	1	8.9	9.2
7	$(Et)_3COK$[e]	RT	100	1	0.85	0.86
8	MeONa	RT	100	1	0.13	–[f]

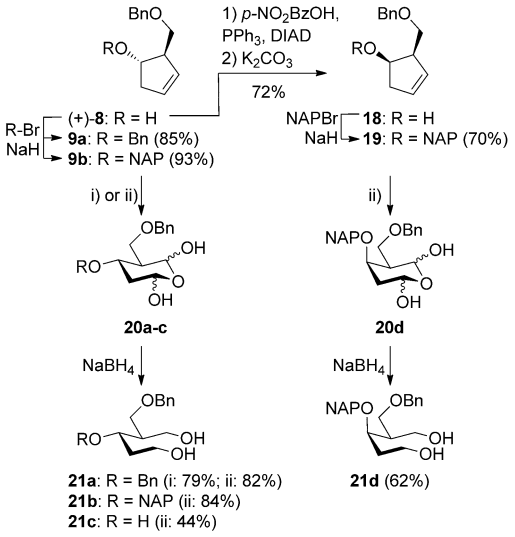
[a] Conversions (conv.) and ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] No reaction. [c] Used as a 1 M solution in hexanes. [d] Used as a 2 M solution in THF. [e] Used as a 2 M solution in $(Et)_3COH$. [f] **17b** was not observed under these conditions.

(*t*BuOK, DMF, 100 °C) led to a mixture of the three products in a 1:0.19:0.05 ratio (Table 1, entry 3). A decrease in the temperature to room temperature improved this ratio in favor of the Hofmann product **15b** (Table 1, entry 4). Interestingly, the use of more sterically hindered potassium alkoxides reversed the tendancy or led to almost identical amounts of the three products (Table 1, entries 5–7). Surprisingly enough, the best results were obtained with less basic, less hindered sodium methoxide at room temperature, in which case the formation of the over-elimination product **17b** could be avoided and the amount of Saytzeff product **16b** was limited (Table 1, entry 8). These practical conditions were selected and applied to mesylates **14a–c** to afford cyclopentenes **15a**, **15b**, and **7**, after removal of the minor products by preparative HPLC, in 72%, 70%, and 63% yields, respectively (Scheme 6).



Scheme 6. Synthesis of orthogonally protected cyclopentenes. Yields of isolated products are given in parentheses.

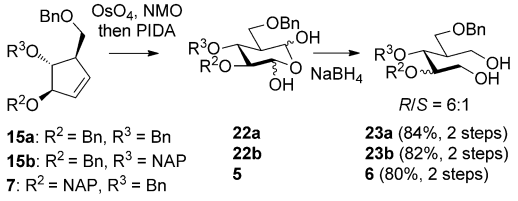
The key oxidative cleavage of the double bond was first evaluated on model cyclopentene **9a** (Scheme 7). Classical conditions with sodium periodate and osmium tetroxide in a mixture of dioxane and water furnished, after flash chromatography on silica gel, the expected dialdehyde **20a** as a mixture of dialdehyde and hemiacetal diastereoisomers. Reduction under the aforementioned conditions furnished diol **21a** as a single diastereoisomer in 79% yield (two steps), which validates the clean formation of the required dialde-



Scheme 7. Preparation of the model dialdehydes **20a–d**. Bz: benzoyl; DIAD: diisopropylazodicarboxylate.

hyde for the reductive double amination protocol. Nevertheless, we preferred the use of the more convenient conditions of Nicolaou et al.,[43] in which osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) are used first, followed by treatment with PIDA, to give diol **21a** in 82% yield after sodium borohydride mediated reduction. Application of these conditions to the naphthylmethyl-protected cyclopentene **9b**, obtained analogously to **9a** in 93% yield by alkylation with bromomethylnaphthalene (Scheme 7), led to diol **21b** in a comparable 84% yield over two steps. With the conditions for the oxidative ring opening established, analogous dialdehyde scaffolds also derived from (+)-**8** were synthesized in order to evaluate the double reductive amination on a galactose-type model (that is, **20d**) or on a free hydroxy-containing substrate (namely, **20c**). Thus, the latter conditions were applied directly to alcohol (+)-**8**, and, after reduction, diol **21c** was obtained in a modest 44% yield (two steps). The synthesis of the pentodialdose **20d** began with Mitsunobu inversion of the hydroxy group in (+)-**8** in 72% yield. After protection as a naphthylmethyl ether, cyclopentene **19** was cleaved oxidatively and then reduced to diol **21d** in 62% yield.

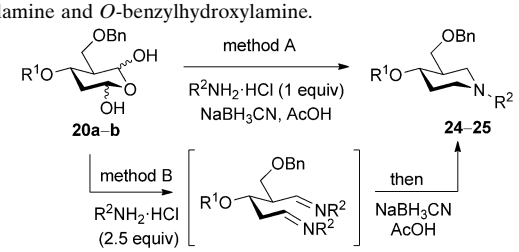
The protected trihydroxydialdehydes **22a**, **22b**, and **5** were obtained in high yield by NMO/OsO_4/PIDA oxidation of alkenes **15a**, **15b**, and **7** (Scheme 8), and the products



Scheme 8. Preparation of the dialdehydes **22a**, **22b**, and **5**.

were characterized after sodium borohydride mediated reduction. Interestingly, diols **23a**, **23b**, and **6** were obtained as 6:1 mixtures of two epimers (see the Supporting Information), but, as revealed by the subsequent epimerization-free ring-closing cyclizations (see below), the loss of stereochemical integrity occurred during the reduction step. As this phenomenon did not occur with the 4,6-hydroxylated substrates **20a–d**, we assume that the stereochemical integrity of the C3 position must have been compromised (see above; assignment of **6**, Scheme 2).

Table 2. Ring-closing double reductive amination of **20a** and **20b** with benzylamine and *O*-benzylhydroxylamine.



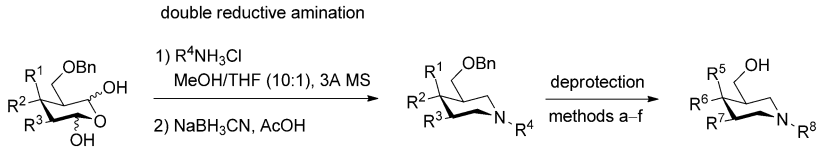
Entry	Method[a]	R^1	R^2	$RCHO/R^2NH_2$	Product	Yield[b] [%]
1	Ref. [46]	Bn	Bn	1.2:1	**24a**	71
2	Ref. [46]	NAP	Bn	1.2:1	**24b**	71
3	A	Bn	OBn	1.1:1	**25a**	46
4	A	Bn	OBn	1.5:1	**25a**	54
5	A	NAP	OBn	1.5:1	**25b**	51
6	A	Bn	OBn	2:1	**25a**	57
7	A	NAP	OBn	2:1	**25b**	59
8	A	Bn	OBn	2.5:1	**25a**	52[c]
9	B	Bn	OBn	1:2.5	**25a**	81
10	B	NAP	OBn	1:2.5	**25b**	85
11	B	NAP	OBn	1:2.5	**25b**	0[c]

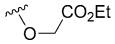
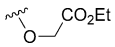
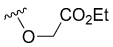
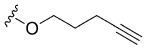
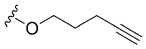
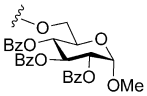
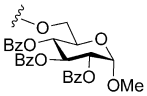
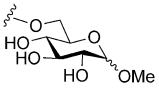
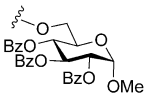
[a] Method A: R^2NH_2·HCl (1 equiv), $NaBH_3CN$ (5 equiv), AcOH (20 equiv), 3 Å molecular sieves, MeOH (0.04 M). Method B: R^2NH_2·HCl (2.5 equiv), $NaBH_3CN$ (5 equiv), AcOH (10 equiv), 3 Å molecular sieves, MeOH/THF (0.25 M, 10:1). [b] Yields of isolated products. [c] Reaction performed without molecular sieves.

Ring-closing double reductive amination (DRA): In order to validate the strategy, we first investigated the DRA on the disubstituted dialdehydes **20a** and **20b** with benzylamine (Table 2, entries 1 and 2). These reactions proceeded smoothly under classical Borch conditions[44] to afford the protected piperidines **24a** and **24b** in 71% yields. We next turned to the DRA of model dialdehydes **20a** and **20b** with hydroxylamines, an unknown process except for a single example with hydroxylamine.[26] With freshly prepared dialdehyde **20a**, *O*-benzylhydroxylamine (Table 2, entry 3) gave the corresponding cyclic hydroxylamine in 46% yield. When the amount of dialdehyde was increased from 1.1 to 1.5 equivalents (Table 2, entries 4 and 5), the hydroxylamines **25a** and **25b** could be obtained in 54% and 51% yields, respectively. Increasing the amount of dialdehyde to 2 equivalents slightly increased the yields to approximately 60% (Table 2, entries 6 and 7), but such one-pot conditions did not enable us to cross the 60% yield barrier. We consequently changed to a two-step process that first employed 2.5 equivalents of hydroxylamine, followed by in situ cyano-

borohydride-mediated reduction of the intermediate double oxime (Table 2, method B). In these reactions, the formation of the double oxime was monitored by LC-MS analysis, and the sodium cyanoborohydride was added once the formation of the double oxime was complete (approximately 2.5 h). This resulted in the clean formation of the target hydroxylamines **25a** and **25b** in 81% and 85% yields, respectively (Table 2, entries 9 and 10). Unlike method A, the presence of molecular sieves was necessary in method B for the efficient generation of the double oxime (Table 2, entries 8 and 11). Having established conditions for the DRA of hydroxylamines, we evaluated the scope of the reaction by varying the nature of both the hydroxylamine and the dialdehyde (Table 3). The use of *O*-benzylhydroxylamine afforded the

Table 3. Scope of the double reductive amination (DRA).[a]

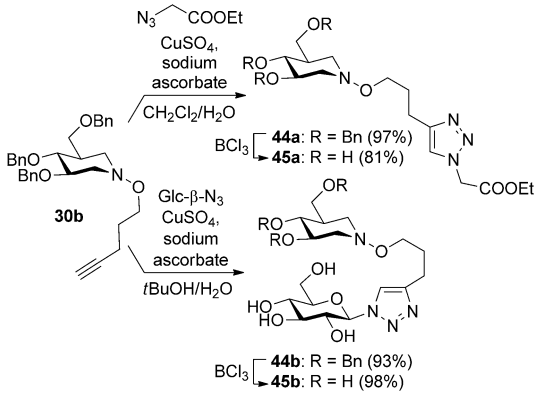


Entry	Double reductive-amination product						Deprotection conditions[c]	Deprotection product					
	R^1	R^2	R^3	R^4	Product	Yield[b] [%]		R^5	R^6	R^7	R^8	Product	Yield[b] [%]
1	H	OBn	H	Bn	**24a**	71	–[d]	–	–	–	–	–	–
2	H	ONAP	H	Bn	**24b**	71	A	H	OH	H	H	**32**	82
3	H	OBn	OBn	Bn	**24c**	18	–[e]	–	–	–	–	–	–
4	H	OBn	H	OBn	**25a**	81	B	H	OH	H	H	**32**	85
5							C	H	OH	H	OBn	**33**	93
6	H	ONAP	H	OBn	**25b**	85	C	H	OH	H	OBn	**33**	67
7	H	OH	H	OBn	**25c**	77	–	–	–	–	–	–	–
8	ONAP	H	H	OBn	**25d**	84	–	–	–	–	–	–	–
9	H	OBn	OBn	OBn	**25e**	87	B	H	OH	OH	H	**34**	72
10							C	H	OH	OH	OBn	**35**	90
11	H	ONAP	OBn	OBn	**25f**	85	C	H	OH	OH	OBn	**35**	63
12							E	H	OH	OBn	OBn	**36**	60
13	H	ONAP	H	OAll	**26a**	80	C	H	OH	H	OAll	**37**	66
14	H	OH	H	OAll	**26b**	81	C	H	OH	H	OAll	**37**	79
15	ONAP	H	H	OAll	**26c**	78	–	–	–	–	–	–	–
16	H	OBn	OBn	OAll	**26d**	89	C	H	OH	OH	OAll	**38**	88
17	H	ONAP	OBn	OAll	**26e**	87	C	H	OH	OH	OAll	**38**	52
18	H	ONAP	H	OPMB	**27a**	81	C	H	OH	H	OH	**39**	49
19	H	OBn	OBn	OPMB	**27b**	90	C	H	OH	OH	OH	**40a**	96
20							D	H	OBn	OBn	OH	**40b**	74
21	H	ONAP	OBn	OPMB	**27c**	90	E	H	OH	OBn	OPMB	**41a**	53
22	H	OBn	ONAP	OPMB	**27d**	58	E	H	OBn	OH	OPMB	**41b**	44
23	H	ONAP	H	OMe	**28**	75	–	–	–	–	–	–	–
24	H	ONAP	H		**29a**	69	–	–	–	–	–	–	–
25	H	OBn	OBn		**29b**	76	C	H	OH	OH		**42**	46[f]
26	H	ONAP	H		**30a**	75	–[g]	–	–	–	–	–	–
27	H	OBn	OBn		**30b**	72	–[g]	–	–	–	–	–	–
28	H	ONAP	H		**31a**	72	–	–	–	–	–	–	–
29	H	OBn	OBn		**31b**	70	F, C	H	OH	OH		**43**	61[h]
30	H	ONAP	OBn		**31c**	63	–	–	–	–	–	–	–

[a] PMB: *para*-methoxybenzyl; All: allyl; TFA: trifluoroacetic acid; DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. [b] Yields of isolated products. [c] Method A: H_2, $Pd(OH)_2$, MeOH, AcOH; method B: BBr_3, CH_2Cl_2; method C: BCl_3, CH_2Cl_2; method D: TFA, CH_2Cl_2; method E: DDQ, CH_2Cl_2/H_2O (20:1); method F: NaOMe, MeOH. [d] 3-Deoxyisofagomine (**32a**) was obtained from **24b** (entry 2). [e] Isofagomine (**34**) was obtained from **25e** (entry 10). [f] Obtained as a 1.9:1 mixture of ethyl and methyl esters, respectively (see the Supporting Information). [g] The presence of the alkyne is not compatible with BCl_3 deprotection. [h] Obtained as a 1:1 mixture of the two anomers.

piperidines **25a–f** in high yields (77–87%) with various di- or trisubstituted dialdehydes (Table 3, entries 4–11). In particular, we showed that the presence of an unprotected alcohol did not affect the DRA process (Table 3, entry 7). Curiously, the DRA with the tribenzyloxydialdehyde **22a** and benzylamine resulted in the formation of the protected isofagomine **24c** in a significantly lower 18% yield (Table 3, entry 3), which did not depend on the equivalents of dialdehyde employed, than the 87% yield obtained with *O*-benzylhydroxylamine (Table 3, entry 9). The use of *O*-allyl hydroxylamine afforded the *N*-allyloxy piperidines **26a–e** in excellent yield with the same set of dialdehydes (Table 3, entries 13–17). Likewise, *O*-(*para*-methoxybenzyl)hydroxylamine (Table 3, entries 18–22), and *O*-methylhydroxylamine (Table 3, entry 23) also provided the corresponding piperidines in good yields. Finally, we turned our attention to more functionalized hydroxylamines, such as a glucose-derived hydroxylamine and ester- or alkyne-bearing hydroxylamines.[46] The DRA of ester- and alkyne-bearing hydroxylamines furnished piperidines **29** and **30** in 69–76% yield (Table 3, entries 24–27). Pseudo-disaccharides **31a–c** were obtained with similarly good yields (Table 3, entries 28–30). Overall, it is clear that this protocol accommodates the presence of various functionalities on the hydroxylamine, as well as various types of saccharide-based dialdehydes. The majority of these derivatives were deprotected to give the target *N*-alkoxy piperidines, all of which are analogues of isofagomine characterized by the presence of an N–O bond linked to various functional groups (Table 3). Owing to the relative instability of the *N*-alkoxy[45] or *N*-hydroxy bond[46] under palladium-catalyzed hydrogenation conditions, we selected BCl_3, known for its compatibility with the hydroxylamine function,[47] as the reagent of choice for benzyl- and naphthylmethyl-group removal (Table 3, method C). Thus, for example, pseudo-disaccharide **43** could be obtained in 61% yield, by removal of the benzoyl groups by Zemplén deacylation followed by treatment with BCl_3 (Table 3, method F, entry 29). This isomaltose mimic differs simply by the presence of one oxygen atom linked to the nitrogen atom from a pseudo-disaccharide synthesized by Bols and co-workers in 1996, which was reported to be a potent glycosidase inhibitor.[48] The simple *N*-hydroxyisofagomine, **40a**, which is closely related to the *N*-hydroxy-1-deoxymannojirimicin and *N*-hydroxy polyoxygenated pyrrolidines previously described by Py and co-workers,[47a,b] could be obtained from the PMB-protected piperidine **27b** by treatment with BCl_3 under the aforementioned conditions (Table 3, entry 19). As an alternative to BCl_3, the PMB group can be orthogonally removed by the action of TFA in CH_2Cl_2 to give benzylated compound **40b** in 74% yield (Table 3, method D, entry 20). The naphthylmethyl groups can be removed in the presence of benzyl ethers and *N*-OPMB groups by treatment with DDQ, as shown for compounds **27c** and **27d** (Table 3, method E, entries 21 and 22). Finally, simple piperidines were obtained in high yields by the action of BBr_3 (Table 3, method B), which cleaved the hydroxylamine N–O bond in addition to removing benzyl ethers, in sharp contrast to BCl_3. Hydrogenolysis of **24b** was accomplished by using Pearlman's catalyst in a slightly acidic medium (Table 3, entry 2) and provided 3-deoxyisofagomine (**32**),[20,49] a known inhibitor of β-glucosidase[49b] and hepatic glycogen phosphorylase,[20] albeit a poor one compared to isofagomine itself. The BBr_3 conditions also furnished compound **32**[20,49] from **25a** (Table 3, entry 4) in a comparable yield to that from the hydrogenolysis (Table 3, method A, entry 2), whereas isofagomine (**34**) could be isolated in 72% yield after purification if liberated in this manner (Table 3, entry 9).

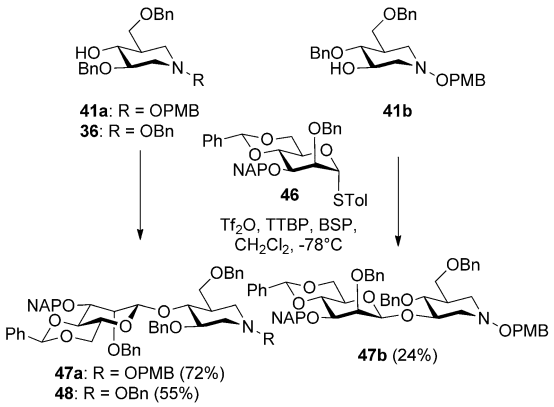
Synthesis of novel glycoconjugates: Carbohydrates are usually found in nature in the form of a variety of glycoconjugates, so we undertook a brief study of the compatibility of the *N*-alkoxy piperidines with click chemistry conditions. Accordingly, we realized a Cu^I-catalyzed azide alkyne cycloaddition with two functionalized azides, that is, ester- and glucose-bearing azides under the conditions of Vauzeilles and co-workers[50] (Scheme 9). Glycoconjugates **44a** and **44b**



Scheme 9. Novel glycoconjugates obtained by click chemistry.

were obtained in excellent yields and were successfully deprotected by the standard BCl_3 conditions to afford **45a** and **45b** in 81% and 98% yields, respectively.

We also evaluated the effect of the N–OR functionality of **41a** and **41b** on the glycosylation reaction and screened various glycosyl donors, in the gluco and manno series. Unfortunately, standard trichloroacetimidate conditions and more conventional methods such as the Koenigs Knorr glycosylation proved unsuitable for application to **25c** (see the Supporting Information). However, thioglycosides and, in particular, methods relying on the preactivation of the donor before addition of the acceptor were found to be compatible with the hydroxylamine functionality. Thus, β-mannosyl donor **46** was activated with 2-(phenylsulfinyl)piperidine (BSP) and triflic anhydride at −78°C in dichloromethane before addition of the acceptors **41a** and **41b**, which led to isolation of the pseudo-disaccharides **47a** and **47b**. Interestingly given the known low reactivity of the 4-OH group in pyranosyl acceptors toward glycosylation, compound **47a** was obtained in an acceptable 72% yield, where-



Scheme 10. Diastereoselective glycosylations at positions 3 or 4 of *N*-alkoxy piperidines. PMB: *para*-methoxybenzyl; Tol: tolyl; Tf: trifluoromethanesulfonyl; TTBP: tri-*tert*-butylpyrimidine; BSP: 1-benzenesulfinyl piperidine.

as the glycosyl acceptor containing a hydroxy function at the 3 position furnished compound **47b** in only 24% yield (Scheme 10). Encouraged by the positive result in the glycosylation of the 4-OH acceptor, the *N*-benzyloxypiperidine **36** was also subjected to glycosylation under the same conditions and provided glycoside **48** in 55% yield.

Dynamic NMR study of nitrogen inversion in *N*-alkoxy piperidines: As discussed in the introduction, we anticipated the *N*-alkoxy piperidines prepared in the course of this study to have a barrier for inversion at the nitrogen atom of approximately 15 kcal mol^{-1}. In the event, the ^{1}H NMR spectra of the *N*-alkoxy piperidines synthesized present structureless and broadened resonances at room temperature, which suggests a slow conformational interconversion on the NMR timescale. When the samples were heated to around 100 °C in DMF,[51] clean sharp spectra representing an average conformation could be obtained, and all such compounds were characterized under these conditions (see the Supporting Information). When the temperature at which the spectra were recorded was reduced to 263 K, relatively well-resolved ^{1}H and ^{13}C NMR spectra showing distinct signals for two conformational/configurational isomers could be obtained, in a 1:2.9 ratio for **26a**, most likely in favor of the equatorial isomer. The free energy of activation ($\Delta G^{\neq}$) for the dynamic process was determined for compound **26a** by variable-temperature (VT) NMR spectroscopy. To this end, the ^{1}H and ^{13}C NMR spectra of **26a** were recorded over a temperature range of −10 °C to 95 °C. In the ^{1}H NMR spectrum, the most pronounced effect[52] was observed for the allylic CH_2 group linked to the N–O bond. These two diastereotopic protons form a doublet at 95 °C and become two doublets at low temperature (−10 °C; Figure 2). The coalescence point for the two sets of signals is observed at approximately 40 °C. The free energy of activation, $\Delta G_c^{\neq}$ (kcal mol^{-1}), for the observed dynamic process at the coalescence temperature (T_c in K) was then estimated by measuring the maximum frequency difference between

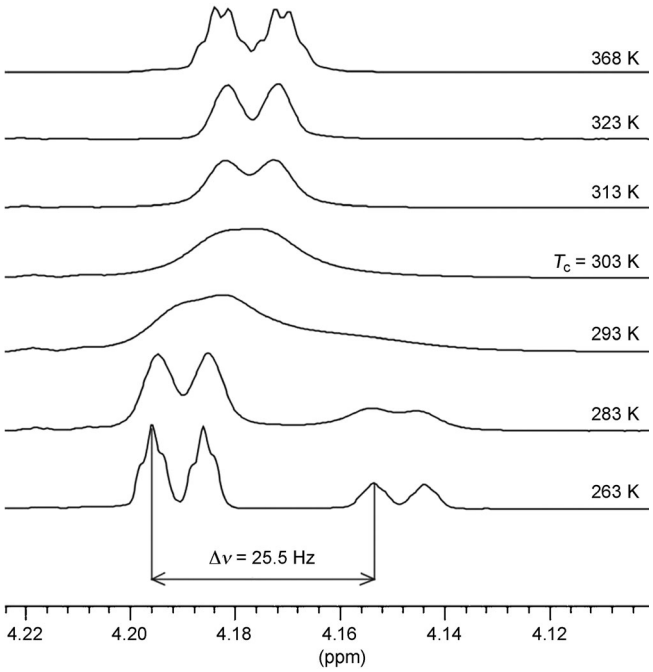


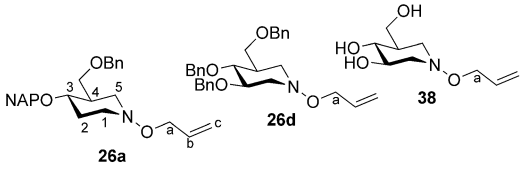
Figure 2. Selected region of the ^{1}H NMR spectra ([D$_7$]DMF, 600 MHz) of **26a** recorded at different temperatures ranging from −10 °C to 95 °C (δ = 4.12–4.22 ppm; allylic protons H_a).

the signals of the two exchanging species at low temperature ($\Delta\nu$ in Hz) and by application of Equation (1).[53]

$$\Delta G_C^{\neq} = 4.575 \times 10^{-3} T_C [9.972 + \log(T_C/\Delta\nu)] \quad (1)$$

As the estimated barrier $\Delta G_c^{\neq}$ for the inversion process is independent of the temperature, we also calculated the rate constant and deduced the half-life time of the process at 293 K in the standard manner for first-order processes, which led to the values given in Table 4. The barrier to inversion obtained in this manner for **26a** was 15.3 kcal mol^{-1}, which is in agreement with literature values for endocyclic six-membered-ring hydroxylamines[14a] and which corresponds to a half-life for inversion of 28.4 ms at 293 K. The

Table 4. Barriers to exchange and half-life times for various *N*-allyloxy piperidines determined by VT-NMR spectroscopy.



Entry	Compound	^{1}H/^{13}C signal observed	T_c [K]	$\Delta\nu$ [Hz]	ΔG_c [kcal mol^{-1}]	$t_{1/2}^{293K}$ [ms]
1	**26a**	H_a	303	25.5	15.3	
2	**26a**	C1	333	404.0	15.1	
3	**26a**	C5	343	505.7	15.4	
4	**26a**	C4	343	592.9	15.3	
5	**26a** (average values)				15.28	28.4
6	**26d**	H_a	293	35.0	14.6	8.8
7	**38**	H_a	288	25.1	14.5	7.4

^{13}C NMR spectrum of **26a** also shows temperature dependence but is relatively well resolved into two sets of signals at room temperature. The coalescence temperature was determined to be approximately 70 °C (see the Supporting Information). For reasons of resolution, the barrier to inversion was calculated based on the frequency difference of the methylene signals in the α position to the inverting nitrogen site (that is, the C1 and C5 atoms; see Table 4) and was found to be 15.1 and 15.4 kcal mol^{-1}, respectively, values that are consistent with that obtained by ^{1}H NMR spectroscopy. The same series of VT-NMR experiments were realized on the tri(benzyloxy) compound **26d** and on the triol **38**, with both compounds showing a slightly lower inversion barrier of 14.5 kcal mol^{-1} and correspondingly shorter half-lives for inversion. At 263 K, the tribenzyl-protected compound **26d** presumably exists as a 1:2.5 mixture of isomers, whereas the trihydroxy analogue **38** exhibits a 1:5.2 ratio of isomers at the same temperature; we presume that the major isomer in each case is the chair conformer with the equatorial allyloxy substituent. The low-millisecond half-lives for inversion at room temperature determined for compounds **26a**, **26d**, and **38** are in agreement with literature values for the conformation inversion of piperidines[54] and are much higher than standard values for the inversion of pyramidal nitrogen atoms in amines, which is consistent with the well-known increase in nitrogen-inversion barriers upon introduction of electronegative substituents.[17a] Although VT-NMR studies have not been previously conducted on *N*-alkoxy piperidines to the best of our knowledge, studies have been conducted on *N*-alkoxy pyrrolidines,[55] on acyclic hydroxylamines,[14b,15b] and on endocyclic six-membered-ring hydroxylamines,[14a] and similar values were obtained. Overall, the measured inversion barriers for **26a**, **26d**, and **38**, which we take as representative of the series as a whole, are consistent with our initial hypothesis that oligosaccharide mimetics based on the hydroxylamine linkage will adapt for binding to lectins that have evolved to accommodate either axial or equatorial glycosides.

Conclusion

A practical seven-step asymmetric synthesis of densely functionalized dialdehydes was developed by starting from sodium cyclopentadienylide. This synthetic route compares favorably with other known procedures and presents a high degree of flexibility through the ability to introduce orthogonal protecting groups or to invert the stereochemistry of a given alcohol by a Mitsunobu sequence. Protocols for the double reductive amination of *O*-alkyl hydroxylamines with these dialdehydes were established and enabled rapid access to numerous polyhydroxylated *N*-alkoxy piperidines. The flexibility of this protocol was demonstrated by the use of various functionalized *O*-alkyl hydroxylamines, including a sugar-derived hydroxylamine. Deprotection of the compounds by sequential or one-pot methods furnished various di- and trihydroxylated *N*-alkoxy piperidines. Importantly, the N–O bond can also be precursor to an amino group, depending on the mode of deprotection, as illustrated by a de novo synthesis of isofagomine. A dynamic ^{1}H and ^{13}C NMR study on representative compounds revealed an inversion barrier of approximately 14.5 kcal mol^{-1} for trisubstituted *N*-alkoxy piperidines, which indicates a half-life for inversion of 8 ms at room temperature. Further work directed at the synthesis of hydroxylamine oligosaccharide mimetics and their biological applications is currently underway and will be reported in due course.

Experimental Section

Detailed descriptions of experimental procedures, ^{1}H and ^{13}C NMR spectra of all new compounds, and preliminary biological tests for glycosidase inhibition are given in the Supporting Information.

General procedure for the oxidative cleavage of cyclopentene derivatives: In accordance with the procedure described in the literature,[43] 4-methylmorpholine *N*-oxide (1.5 equiv) and osmium tetroxide (0.02 M in water, 0.02 equiv) were added to a solution of alkene (1 equiv) in a 10:1 mixture of acetone/H_2O (0.1 M), and the mixture was stirred at room temperature. After the starting material had been consumed (approximately 2.5 h), as monitored by TLC (4:1 CH_2Cl_2/methyl *tert*-butyl ether), $PhI(OAc)_2$ (1.5 equiv) was added to the reaction mixture. After being stirred for 1–3 h, the reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (15 mL mmol^{-1}). The mixture was extracted with EtOAc (3× 10 mL mmol^{-1}), and the extract was washed with a saturated aqueous solution of $CuSO_4$ (2×15 mL mmol^{-1}) and brine (2×15 mL mmol^{-1}), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1 then 1:1 heptane/EtOAc, unless otherwise stated) to give the expected 1,5-dialdehyde. *Representative example*: 3,4,6-tri-*O*-benzyl-2-deoxy-D-arabinohexodialdose monohydrate **22a** was prepared according to the general procedure by using **15a** (300 mg, 0.75 mmol), 4-methylmorpholine *N*-oxide (132 mg, 1.12 mmol), osmium tetroxide (0.75 mL, 0.015 mmol), and $PhI(OAc)_2$ (362 mg, 1.12 mmol) in a 10:1 mixture of acetone/H_2O (7.7 mL). The reaction mixture was worked up and purified as described to give dialdehyde **22a** (298 mg, 0.66 mmol, 88%) as a pale yellow oil that was directly engaged in the double reductive amination.

General procedure for the double reductive amination with *O*-alkyl hydroxylamines: Powdered and activated 3 Å molecular sieves (1 g mmol^{-1} of dialdehyde) were added to a stirred solution of dialdehyde (1 equiv) in anhydrous THF (2.5 M) and MeOH (0.25 M). *O*-Alkyl hydroxylamine hydrochloride (2.5 equiv) was added, and the mixture was stirred at room temperature for 2.5 h. The complete formation of dioxime was confirmed by LC-MS analysis. AcOH (10 equiv) and $NaBH_3CN$ (5 equiv) were then added, and the mixture was stirred at room temperature. The reduction was followed by LC-MS analysis, and if necessary (that is, if the reduction was not complete after 3 h), a second portion of AcOH (10 equiv) and $NaBH_3CN$ (5 equiv) were added and the mixture was stirred for the indicated time. The reaction was quenched by addition of an aqueous 1 M solution of NaOH (20 mL mmol^{-1} of dialdehyde) and brine (20 mL mmol^{-1} of dialdehyde). After extraction with EtOAc (3×30 mL mmol^{-1} of dialdehyde), the combined organic layers were washed with brine (2× 30 mL mmol^{-1} of dialdehyde), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography with the indicated eluent to yield the expected *N*-alkoxypiperidine derivative. *Representative example 1*: (3*R*,4*R*,5*R*)-1,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)piperidine (**25e**) was prepared according to the general procedure by using dialdehyde **22a** (155 mg, 0.344 mmol) and *O*-benzylhydroxylamine hydrochloride (137 mg, 0.86 mmol) in MeOH (1.5 mL) and THF (0.15 mL). After addition of AcOH (400 μL, 6.88 mmol, in two portions) and $NaBH_3CN$ (216 mg, 3.44 mmol, in two portions), the mixture was stirred for 20 h and worked up as described. The crude product was purified by column chromatography (95:5 heptane/EtOAc) to yield

25e (156 mg, 0.298 mmol, 87%) as a colorless oil: $R_f = 0.46$ (4:1 heptane/EtOAc); $[\alpha]_D^{22} = +20.4$ ($c = 0.96$ in $CHCl_3$); ^{1}H NMR (500 MHz, [D$_7$]DMF, 373 K): $\delta = 2.10$–2.14 (m, 1H; H5), 2.54 (t, $J = 10.6$ Hz, 1H; H2), 2.66 (t, $J = 11.2$ Hz, 1H; H7), 3.38–3.41 (m, 1H; H7), 3.46 (t, $J = 9.0$ Hz, 1H; H4), 3.58–3.61 (m, 1H; H2), 3.65–3.70 (m, 2H; H6), 3.76–3.80 (m, 1H; H3), 4.50 and 4.51 (AB, $J_{AB} = 12.3$ Hz, 2H; CH_2–Bn), 4.64 and 4.89 (AB, $J_{AB} = 11.5$ Hz, 2H; CH_2–Bn), 4.68 and 4.70 (AB, $J_{AB} = 11.8$ Hz, 2H; CH_2–Bn), 4.73 (s, 2H; NO–CH_2–Bn), 7.27–7.38 ppm (m, 20H; H–Ar); ^{13}C NMR (125 MHz, [D$_7$]DMF, 373 K): $\delta = 140.8$ (C_q–Bn), 140.5 (C_q–Bn), 140.3 (C_q–Bn), 139.9 (C_q–Bn), 129.5 (CH–Ar), 129.3 (CH–Ar), 129.3 (CH–Ar), 129.2 (CH–Ar), 128.8 (CH–Ar), 128.7 (CH–Ar), 128.6 (CH–Ar), 128.5 (CH–Ar), 128.5 (CH–Ar), 128.3 (CH–Ar), 81.5 (C4), 80.1 (C3), 75.1 (NO–CH_2–Bn), 75.0 (CH_2–Bn), 74.1 (CH_2–Bn), 73.0 (CH_2–Bn), 70.6 (C6), 59.0 (C2), 58.1 (C7), 40.9 ppm (C5); IR (neat): $\nu_{max} = 1454$, 1364, 1095, 1077, 1046, 1027, 733, 695 cm^{-1}; HRMS (ESI-TOF): calcd for $C_{34}H_{38}NO_4$ $[M+H]^+$: 524.2801; found: 524.2789.

Representative example 2: Methyl 2,3,4-tri-*O*-benzoyl-6-[(3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)-piperidinyl]-α-D-glucopyranoside

31b was prepared according to the general procedure by using dialdehyde **22a** (113 mg, 0.25 mmol) and methyl 2,3,4-tri-*O*-benzoyl-6-*O*-amino-α-D-glucopyranoside hydrochloride[12a] (349 mg, 0.63 mmol) in MeOH (1 mL) and THF (0.1 mL). After addition of AcOH (290 μL, 5 mmol, in two portions) and $NaBH_3CN$ (157 mg, 2.5 mmol, in two portions), the mixture was stirred for 18 h and worked up as described. The crude product was purified by column chromatography (9:1→7:3 heptane/EtOAc) to yield **31b** (162 mg, 0.176 mmol, 70%) as a colorless oil: $R_f = 0.63$ (3:2 heptane/EtOAc); $[\alpha]_D^{22} = +46.4$ ($c = 0.81$, $CHCl_3$); ^{1}H NMR (500 MHz, [D$_7$]DMF, 373 K): $\delta = 2.03$–2.10 (m, 1H; H5), 2.49 (t, $J = 10.4$ Hz, 1H; H2), 2.61 (t, $J = 11.3$ Hz, 1H; H7), 3.37–3.40 (m, 1H; H7), 3.43 (t, $J = 9.1$ Hz, 1H; H4), 3.57 (s, 3H; OMe), 3.60–3.64 (m, 3H; H2, H6), 3.75 (dt, $J = 4.1$, 8.8 Hz, 1H; H3), 3.98 and 4.01 (ABX, $J_{AB} = 11.9$ Hz, $J_{AX} = 3.2$ Hz, $J_{BX} = 5.0$ Hz, 2H; H6′), 4.38 (ddd, $J = 3.4$, 4.6, 10.1 Hz, 1H; H5′), 4.48 and 4.49 (AB, $J_{AB} = 12.3$ Hz, 2H; CH_2–Bn), 4.62 and 4.86 (AB, $J_{AB} = 11.5$ Hz, 2H; CH_2–Bn), 4.64 and 4.67 (AB, $J_{AB} = 11.8$ Hz, 2H; CH_2–Bn), 5.30 (d, $J = 3.8$ Hz, 1H; H1′), 5.40 (dd, $J = 3.8$, 10.1 Hz, 1H; H2′), 5.60 (t, $J = 9.8$ Hz, 1H; H4′), 6.09 (t, $J = 9.8$ Hz, 1H; H3′), 7.28–7.64 (m, 24H; H–Ar), 7.86–7.98 ppm (m, 6H; H–Ar); ^{13}C NMR (125 MHz, [D$_7$]DMF, 373 K): $\delta = 166.8$ (C=O), 166.6 (C=O), 166.3 (C=O), 140.6 (C_q–Bn), 140.3 (C_q–Bn), 140.2 (C_q–Bn), 134.5 (CH–Ar), 134.5 (CH–Ar), 134.3 (CH–Ar), 130.9 (2C_q–Bz), 130.5 (C_q–Bz), 130.3 (CH–Ar), 129.7 (CH–Ar), 129.7 (CH–Ar), 129.5 (CH–Ar), 129.3 (CH–Ar), 129.2 (CH–Ar), 129.1 (CH–Ar), 128.7 (CH–Ar), 128.7 (CH–Ar), 128.6 (CH–Ar), 128.4 (CH–Ar), 128.4 (CH–Ar), 98.5 (C1′), 81.3 (C4), 80.0 (C3), 74.8 (CH_2–Bn), 74.0 (CH_2–Bn), 73.3 (C2′), 72.9 (CH_2–Bn), 72.7 (C3′), 72.3 (C6′), 71.8 (C4′), 70.4 (C6), 69.4 (C5′), 58.7 (C2), 57.9 (C7), 56.4 (OMe), 40.7 ppm (C5); IR (neat): $\nu_{max} = 2922$, 2856, 1725, 1452, 1276, 1259, 1092, 1068, 1050, 1026, 706, 697 cm^{-1}; HRMS (ESI-TOF): calcd for $C_{55}H_{56}NO_{12}$ $[M+H]^+$: 922.3803; found: 922.3772.

Selected examples of deprotections:

*(3R,4R,5R)-1-(Hydroxy)-5-(hydroxymethyl)piperidine-3,4-diol hydrochloride (**40a**)*: BCl_3 (1M solution in hexanes, 870 μL, 0.867 mmol, 12 equiv) was added to a solution of **27b** (40 mg, 0.072 mmol) in CH_2Cl_2 (7 mL), and the mixture was stirred at room temperature for 4 h. After addition of MeOH (5 mL), the solution was stirred for 30 min and concentrated in vacuo. The crude residue was purified by flash column chromatography (95:4:1 *i*PrOH/H_2O/NH_4OH). The hydroxylamine was then protonated by addition of a 3M HCl solution in MeOH (1 mL) and concentrated in vacuo to give **40a** (13.8 mg, 0.069 mmol, 96%) as a white amorphous solid (1:1 mixture of anomers): $R_f = 0.35$ (95:4:1 *i*PrOH/H_2O/NH_4OH); $[\alpha]_D^{24} = +8.0$ ($c = 0.56$, EtOH, free base); ^{1}H NMR (300 MHz, D_2O, 300 K): $\delta = 1.89$–2.01 (m, 1H; H5β), 2.32–2.44 (m, 1H; H5α), 3.20–3.88 (m, 15H; H2, H3β, H4, H6, H7), 4.14 ppm (ddd, $J = 4.8$, 9.1, 10.5 Hz, 1H; H3α); ^{13}C NMR (75 MHz, D_2O, 300 K): $\delta = 70.6$, 70.4 (C4), 68.2 (C3β), 66.0 (C3α), 59.0, 58.7, 58.6, 57.7 (C2, C6), 56.4, 55.3 (C7), 39.8 (C5β), 37.4 ppm (C5α); IR (neat): $\nu_{max} = 3231$, 3031, 1433, 1173, 1094, 1044, 1016, 985 cm^{-1}; HRMS (ESI-TOF): calcd for $C_6H_{14}NO_4$ $[M-HCl+H]^+$: 164.0923; found: 164.0916.

*Methyl 6-[(3R,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)-piperidinyl]-α,β-D-glucopyranoside (**43**)*: A catalytic amount of NaOMe (25% solution in MeOH, 1 drop) was added to a stirred solution of **31b** (80 mg, 0.087 mmol) in dry MeOH (2 mL). TLC analysis indicated complete conversion of the starting material after 4 h. The solution was then concentrated in vacuo, and the crude material was purified by column chromatography (EtOAc) to give the intermediate triol (47 mg, 0.077 mmol, 89%) as a white foam: $R_f = 0.23$ (EtOAc); $[\alpha]_D^{24} = +59.7$ ($c = 1.5$, MeOH); ^{1}H NMR (500 MHz, [D$_7$]DMF, 363 K): $\delta = 2.08$–2.15 (m, 1H; H5), 2.50 (t, $J = 10.7$ Hz, 1H; H2), 2.63 (t, $J = 11.3$ Hz, 1H; H7), 3.23 (t, $J = 9.3$ Hz, 1H; H4′), 3.37–3.40 (m, 1H; H2′), 3.39 (s, 3H; Me), 3.43–3.47 (m, 2H; H4, H7), 3.63 (t, $J = 9.1$ Hz, 1H; H3′), 3.66–3.72 (m, 4H; H2, H5′, H6), 3.76–3.79 (m, 1H; H3), 3.81 (dd, $J = 6.6$, 11.3 Hz; 1H, H6′), 3.97 (brs, 1H; OH), 4.08 (dd, $J = 2.2$, 11.3 Hz, 1H; H6′), 4.33 (brs, 1H; OH), 4.50 (brs, 1H; OH), 4.51 and 4.52 (AB, $J_{AB} = 12.1$ Hz, 2H; CH_2–Bn), 4.63 and 4.89 (AB, $J_{AB} = 11.3$ Hz, 2H; CH_2–Bn), 4.64 (d, $J = 3.5$ Hz, 1H; H1′), 4.71 and 4.74 (AB, $J_{AB} = 11.8$ Hz, 2H; CH_2–Bn), 7.26–7.42 ppm (m, 15H; H–Ar); ^{13}C NMR (125 MHz, [D$_7$]DMF, 363 K): $\delta = 140.7$ (C_q–Bn), 140.5 (C_q–Bn), 140.3 (C_q–Bn), 129.4 (CH–Ar), 129.3 (CH–Ar), 129.2 (CH–Ar), 128.8 (CH–Ar), 128.7 (CH–Ar), 128.7 (CH–Ar), 128.5 (CH–Ar), 128.3 (CH–Ar), 101.7 (C1′), 81.6 (C4), 80.2 (C3), 75.6 (C3′), 75.0 (CH_2–Bn), 74.1 (C2′), 74.1 (CH_2–Bn), 73.6 (C6′), 73.0 (CH_2–Bn), 73.0 (C4′), 72.1 (C5′), 70.6 (C6), 58.9 (C2), 58.1 (C7), 55.9 (Me), 40.8 ppm (C5); IR (neat): $\nu_{max} = 3392$, 2925, 2856, 1454, 1364, 1102, 1073, 1049, 1030, 749, 736, 698 cm^{-1}; HRMS (ESI-TOF): calcd for $C_{34}H_{44}NO_9$ $[M+H]^+$: 610.3016; found: 610.3022. BCl_3 (1M solution in hexanes, 450 μL, 0.45 mmol, 9 equiv) was added to a solution of the triol (30 mg, 0.049 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at room temperature for 5 h. After addition of MeOH (5 mL), the solution was stirred for 30 min and concentrated in vacuo. The crude residue was purified by flash column chromatography (90:5:5→80:15:5 *i*PrOH/H_2O/NH_4OH) to give **43** as a colorless oil that contained a 1:1 mixture of α and β anomers (11.5 mg, 0.034 mmol, 69%), which were separated by preparative HPLC (SunFire prep C18 OBD column, Waters, 150×19 mm, isocratic 99:1:0.1 H_2O/MeOH/HCOOH, 17 mL min^{-1}, ELS detection) and characterized separately: $R_f = 0.51$ (70:20:10 *i*PrOH/H_2O/NH_4OH); α-**43**: $t_R = 9.6$ min (SunFire C18 5 μm column, Waters, 150×4.6 mm, isocratic 99:1:0.1 H_2O/MeOH/HCOOH, 1 mL min^{-1}, ELS detection); $[\alpha]_D^{24} = +62.2$ ($c = 0.32$, H_2O); ^{1}H NMR (500 MHz, [D$_7$]DMF, 363 K): $\delta = 1.77$–1.84 (m, 1H; H5), 2.32 (t, $J = 10.6$ Hz, 1H; H2), 2.37 (t, $J = 11.3$ Hz, 1H; H7), 3.19 (t, $J = 9.1$ Hz, 1H; H4), 3.21 (t, $J = 9.1$ Hz, 1H; H5′), 3.38 (dd, $J = 3.8$, 9.8 Hz, 1H; H2′), 3.40 (s, 3H, Me), 3.42–3.46 (m, 1H; H7), 3.47–3.50 (m, 1H; H2), 3.55–3.64 (m, 3H; H3, H6, H3′), 3.67–3.71 (m, 1H; H4′), 3.76–3.80 (m, 2H; H6, H6′), 4.06 (dd, $J = 1.9$, 11.3 Hz, 1H; H6′), 4.63 ppm (d, $J = 3.5$ Hz, 1H; H1′); ^{13}C NMR (125 MHz, [D$_7$]DMF, 363 K): $\delta = 101.7$ (C1′), 76.5 (C4), 75.6 (C3′), 74.1 (C2′), 73.4 (C6′), 73.0 (C5′), 72.3 (C3), 72.1 (C4′), 63.1 (C6), 61.7 (C2), 58.4 (C7), 55.8 (Me), 43.2 ppm (C5); IR (neat): $\nu_{max} = 3368$, 2922, 1044 cm^{-1}; HRMS (ESI-TOF): calcd for $C_{13}H_{25}NNaO_9$ $[M+Na]^+$: 362.1427; found: 362.1430; β-**43**: $t_R = 8.5$ min (SunFire C18 5 μm column, Waters, 150×4.6 mm, isocratic 99:1:0.1 H_2O/MeOH/HCOOH, 1 mL min^{-1}, ELS detection); $[\alpha]_D^{24} = +6.6$ ($c = 0.32$, H_2O); ^{1}H NMR (500 MHz, [D$_7$]DMF, 363 K): $\delta = 1.78$–1.85 (m, 1H; H5), 2.34 (t, $J = 10.7$ Hz, 1H; H2), 2.37 (t, $J = 11.3$ Hz, 1H; H7), 3.16–3.24 (m, 3H; H2′, H4, H5′), 3.38 (t, $J = 8.8$ Hz, 1H; H3′), 3.41–3.50 (m, 3H; H2, H4′, H7), 3.48 (s, 3H; Me), 3.56–3.61 (m, 2H; H3, H6), 3.76 (dd, $J = 6.9$, 11.5 Hz, 1H; H6′), 3.79 (dd, $J = 4.4$, 10.7 Hz, 1H; H6), 4.10 (dd, $J = 1.9$, 11.3 Hz, 1H; H6′), 4.18 ppm (d, $J = 7.9$ Hz, 1H; H1′); ^{13}C NMR (125 MHz, [D$_7$]DMF, 363 K): $\delta = 105.6$ (C1′), 79.0 (C3′), 76.5, 76.1, 75.4 (C4, C4′, C5′), 73.5 (C6′), 72.8 (C2′), 72.3 (C3), 63.1 (C6), 61.8 (C2), 58.5 (C7), 56.8 (Me), 43.2 ppm (C5).

Selected example of glycoconjugation and deprotection:

*(2R,3R,4S,5S,6R)-2-(4-(3-(((3R,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)-piperidin-1-yl)oxy)propyl)-1H-1,2,3-triazol-1-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**45b**)*: In a schlenk flask, **30b** (75 mg, 0.150 mmol, 1 equiv) and β-D-glucopyranosyl azide (31 mg, 0.150 mmol, 1 equiv) were dissolved in a 1:1 mixture of *t*BuOH and H_2O (1.5 mL). A 375 mM aqueous solution of phenylene diamine (61 μL, 23 μmol, 0.15 equiv), a 250 mM aqueous solution of sodium ascorbate (61 μL, 15 μmol, 0.10 equiv), and a 125 mM aqueous solution of $CuSO_4$ (61 μL,

7.5 μmol, 0.05 equiv) were added. The reaction mixture was then purged with Ar, stirred for 4 h at room temperature, and concentrated in vacuo. Purification by column chromatography (1:0→10:1 EtOAc/MeOH) gave **44b** (99 mg, 0.140 mmol, 93%) as a yellow foam: R_f=0.12 (100:5 EtOAc/MeOH); $[\alpha]_D^{24}$=+10.7 (c=0.81, MeOH); ^{1}H NMR (500 MHz, [D$_7$]DMF, 363 K): δ=1.91–1.99 (m, 2H; CH$_2$), 2.06–2.15 (m, 1H; H5), 2.50 (t, J=10.7 Hz, 1H; H2), 2.63 (t, J=11.3 Hz, 1H; H7), 2.75–2.80 (m, 2H; CH$_2$), 3.36–3.41 (m, 1H; H5′), 3.46 (dd, J=8.5, 9.8 Hz, 1H; H4), 3.52 (t, J=9.1 Hz, 1H; H4′), 3.58–3.66 (m, 3H; H2, H3′, H7), 3.76–3.74 (m, 3H; H6, H6′), 3.76 (t, J=6.3 Hz, 2H; CH$_2$), 3.77–3.82 (m, 1H; H3), 3.85–3.91 (m, 1H; H6′), 3.96 (t, J=9.1 Hz, 1H; H2′), 4.11 (brs, 1H; OH), 4.51 and 4.53 (AB, J_{AB}=12.1 Hz, 2H; CH$_2$–Bn), 4.64 and 4.90 (AB, J_{AB}=11.5 Hz, 2H; CH$_2$–Bn), 4.68 (brs, 1H; OH), 4.71 and 4.75 (AB, J_{AB}=11.7 Hz, 2H; CH$_2$–Bn), 4.75 (brs, 1H; OH), 4.94 (brs, 1H; OH), 5.59 (d, J=9.1 Hz, 1H; H1′), 7.26–7.44 (m, 15H; H–Ar), 7.92 ppm (s, 1H; CH–triazole); ^{13}C NMR (125 MHz, [D$_7$]DMF, 373 K): δ=148.1 (C$_q$–triazole), 140.7 (C$_q$–Bn), 140.4 (C$_q$–Bn), 140.2 (C$_q$–Bn), 129.3 (CH–Ar), 129.3 (CH–Ar), 129.2 (CH–Ar), 128.8 (CH–Ar), 128.7 (CH–Ar), 128.5 (CH–Ar), 128.5 (CH–Ar), 128.3 (CH–Ar), 121.7 (CH–triazole), 89.5 (C1′), 81.5 (C4), 81.4 (C3′), 80.1 (C3), 79.2 (C5′), 75.0 (CH$_2$–Bn), 74.3 (C2′), 74.1 (CH$_2$–Bn), 73.0 (CH$_2$–Bn), 71.9 (C4′, CH$_2$), 70.5 (C6), 63.1 (C6′), 59.1 (C2), 58.2 (C7), 40.8 (C5), 29.8 (CH$_2$), 23.4 ppm (CH$_2$); IR (neat): ν_{max}=3348, 2921, 2856, 1631, 1454, 1364, 1092, 1042, 1027, 898, 734, 696 cm^{-1}; HRMS (ESI-TOF): calcd for $C_{38}H_{47}N_4O_9$ [M−H]$^-$: 703.3343; found: 703.3374. BCl_3 (1 M solution in hexanes, 380 μL, 0.38 mmol, 9 equiv) was added dropwise to a stirred solution of **44b** (30 mg, 0.043 mmol, 1 equiv) in anhydrous CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 5 h before being quenched by addition of MeOH (3 mL) and then concentrated in vacuo. The residue was dissolved in H_2O (5 mL) and the solution was neutralized with Amberlite IRA400 (OH$^-$ form). The mixture was further stirred for 30 min and filtered. The resin was washed profusely with H_2O, and the filtrate was lyophilized to afford **45b** (18.1 mg, 0.042 mmol, 98%) in pure form as a pale yellow amorphous solid: R_f=0.72 (3:2:1 EtOAc/*i*PrOH/H_2O); $[\alpha]_D^{24}$=+2.5 (c=1.5, MeOH); ^{1}H NMR (500 MHz, [D$_7$]DMF, 363 K): δ=1.74–1.87 (m, 1H; H5), 1.89–2.01 (m, 2H; CH$_2$), 2.27–2.42 (m, 2H; H2, H7), 2.74–2.82 (m, 2H; CH$_2$), 3.20 (t, J=9.1 Hz, 1H; H4), 3.32–3.91 (m, 16H; H2, H3, H7, H6, H3′, H4′, H5′, H6′, CH$_2$, 4OH), 3.96 (t, J=8.8 Hz, 1H; H2′), 5.59 (d, J=9.1 Hz, 1H; H1′), 7.94 ppm (s, 1H; CH–triazole); ^{13}C NMR (125 MHz, [D$_7$]DMF, 363 K): δ=148.0 (C$_q$–triazole), 121.6 (CH–triazole), 89.4 (C1′), 81.4 (C5′), 79.1 (C3′), 76.3 (C4), 74.2 (C2′), 72.2 (C3), 71.8 (C4′), 71.7 (CH$_2$), 62.9 (C6, C6′), 61.8 (C2), 58.3 (C7), 43.1 (C5), 29.7 (CH$_2$), 23.4 ppm (CH$_2$); IR (neat): ν_{max}=3285, 1372, 1036 cm^{-1}; HRMS (ESI-TOF): calcd for $C_{17}H_{31}N_4O_9$ [M+H]$^+$: 435.2091; found: 435.2090.

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