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Synthesis and biological evaluation of *RON*-neoglycosides as tumor cytotoxins

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ABSTRACT

Cardenolides such as digitoxin have been shown to inhibit cancer cell growth, to reduce cancer metastasis, and to induce apoptosis in tumor cells. Among the most potent digitoxin-based cytotoxins identified to date are *MeON*-neoglycosides generated via oxyamine neoglycosylation. Here, we report our studies of oxyamine neoglycosylation aimed at facilitating the elucidation of linkage-diversified digitoxin neoglycoside structure–activity relationships. We identified conditions suitable for the convenient synthesis of digitoxin neoglycosides and found that sugar structure, rather than *RON*-glycosidic linkage, exerts the strongest influence on neoglycoside yield and stereochemistry. We synthesized a library of digitoxin neoglycosides and assessed their cytotoxicity against eight human cancer cell lines. Consistent with previous findings, our data show that the structure of *RON*-neoglycosidic linkages influences both the potency and selectivity of digitoxin neoglycosides.

1. Introduction

Cardiac glycosides have been used for several centuries as drugs to treat congestive heart failure and arrhythmias.[1] However, more recently, cardenolides such as digitoxin (**1**, Fig. 1) have been shown to inhibit cancer cell growth, to reduce cancer metastasis, and to induce apoptosis in tumor cells.[2–10] Thus, the receptor of cardiac glycosides, Na^+/K^+-ATPase,[11] is receiving increasing attention as a novel target for cancer chemotherapy.[12] The primary role of Na^+/K^+-ATPase is to maintain an electrochemical gradient across the plasma membrane of eukaryotes by transporting sodium ions out of cells and potassium ions into cells. The resulting Na^+ gradient plays a role in osmotic regulation and drives secondary transport processes ranging from nutrient intake to Na^+/Ca^{2+} exchange. However, a growing body of evidence suggests that a subset of Na^+/K^+-ATPase, likely localized within plasma membrane caveolae, plays a role in cell signaling instead of ion transport.[13] Inhibition of this population by cardiac glycosides activates the non-receptor tyrosine kinase Src,[14] leading to a number of downstream effects that can influence the development and progression of cancers. These effects include the transactivation of EGRF and activation of the Ras/MAPK signaling cascade,[14b,15] an increase of reactive oxygen species in mitochondria,[16] the regulation of caveolin-1 trafficking,[17] the modulation of the structure of cell–cell tight junctions,[18] and apoptosis.[2–9,10a–c]

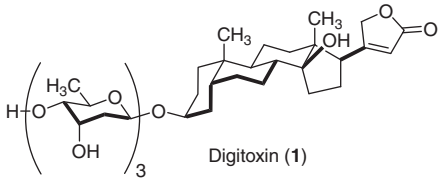

Figure 1. Digitoxin, a cardiac glycoside, is receiving increasing attention for its activity against human cancer cells.

As researchers work to elucidate the complex mechanisms of action associated with the anticancer activities of cardiac glycosides, structure–activity relationship (SAR) studies have identified several structural features of digitoxin derivatives that are critical to Na^+/K^+-ATPase inhibition and cytotoxicity.[9,10,19] The presence of the carbohydrate moiety is critical; cardiac glycosides are invariably better Na^+/K^+-ATPase inhibitors than the corresponding aglycons.[9c,19] The cytotoxicity of both *O*-glycosidic and *MeON*-neoglycosidic analogs of digitoxin is dependent on carbohydrate stereochemistry[10a] and on saccharide chain length,[9a,10b] with monosaccharide derivatives displaying the most potent activities.

Among the most potent digitoxin-based cytotoxins identified to date are L-riboside and L-xyloside *MeON*-neoglycosides[9c] generated via oxyamine neoglycosylation (Fig. 2), a chemoselective glycosylation methodology that employs unprotected, unactivated

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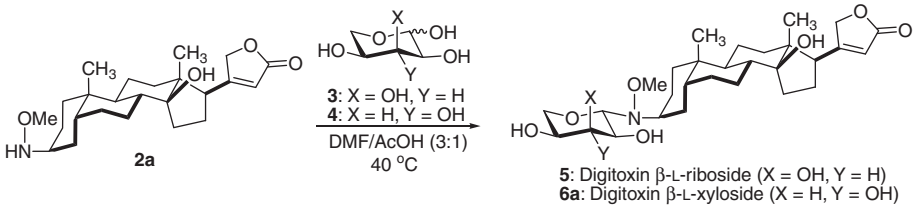


Figure 2. L-Riboside and L-xyloside *MeON*-neoglycosides generated via oxyamine neoglycosylation.

reducing sugars to form the corresponding closed ring neoglycosides in good yields.[9,20–23] The fact that these molecules are active, despite containing non-natural *MeON*-neoglycosidic linkages, led us to realize that glycosidic linkages could represent a third point of diversity to optimize cardiac glycosides, complementing the modification of aglycons and sugars. Although this additional site of diversification has received little attention, we recently showed that oxyamine linkages can be modified to identify structural variants with enhanced tumor selectivities.[9b]

Here, we report our studies of oxyamine neoglycosylation aimed at facilitating the further elucidation of digitoxin neoglycoside structure–activity relationships. First, we explored new oxyamine neoglycosylation reaction conditions, as well as the influence different oxyamine structures have on *RON*-neoglycoside yield, stereochemistry, and stability. Finally, we synthesized and evaluated an expanded library of digitoxin cytotoxins bearing *RON*-neoglycosidic linkages.

2. Results and discussion

2.1. Oxyamine neoglycosylation optimization

Many conditions for oxyamine neoglycosylation have been published;[9,20–23] most take place in either aqueous acidic buffers or organic solvents containing acetic acid. Previous efforts to generate digitoxin analogs via oxyamine neoglycosylation successfully employed DMF/AcOH (3:1),[9c,20,21] but we have found that the difficulties associated with evaporating DMF from crude reaction mixtures significantly diminish our ability to generate neoglycoside libraries efficiently. Thus, we set out to determine the compatibility of lower boiling solvent mixtures with oxyamine neoglycosylation. We conducted this study using a simple, achiral secondary oxyamine (**7a**) that we generated from inexpensive starting materials (Fig. 3).

Methoxyamine **7a** was treated with D-glucose (1.1 equiv) for two days in 10 different solvent mixtures that contained either a molar equivalent of AcOH or AcOH as a cosolvent; percent conversions were estimated using LC–MS (Table 1). We were gratified to find that all conditions we examined provided good to excellent percent conversions to neoglucoside **8a**. Although conditions employing AcOH as a cosolvent generally provided the highest yields, it was simpler to evaporate solvents from reaction mixtures containing only a single molar equivalent of AcOH. Because digitoxin oxyamines **2** were sparingly soluble in alcoholic solvents, somewhat soluble in MeOH/$CHCl_3$ (4:1), and readily soluble in MeOH/$CHCl_3$ (9:1), we chose the latter conditions for our subsequent studies.

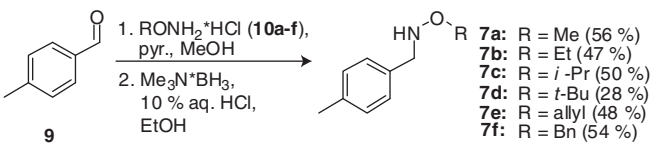
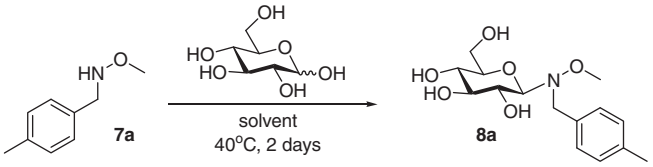


Figure 3. Synthesis of model aglycons.

Table 1
Effect of reaction conditions on percent conversion of neoglycosylation



Entry	Solvent	Conversion[a] (%)
1	DMF/AcOH (3:1)	94
2	Pyridine/AcOH (3:1)	97
3	Acetone/AcOH (3:1)	93
4	THF/AcOH (3:1)	95
5	AcOH	94
6	MeOH[b]	87
7	EtOH[b]	84
8	*i*PrOH[b]	81
9	MeOH/$CHCl_3$ (9:1)[b]	87
10	MeOH/$CHCl_3$ (4:1)[b]	92
11	MeOH/$CHCl_3$ (1:1)[b]	72

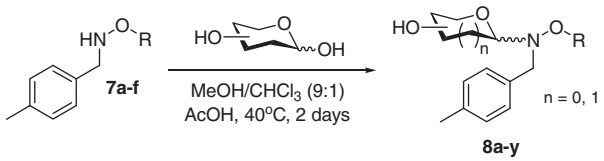
[a] As estimated by LC–MS.
[b] With 1 eq AcOH.

2.2. *RON*-neoglycoside yield and stereochemistry

Because of the expense associated with generating digitoxin oxyamines, we decided to employ model aglycons to study systematically the influence of oxyamine structure on *RON*-neoglycoside yield, stereochemistry, and stability. Model secondary oxyamine aglycons **7a**–**f** were synthesized from *p*-tolualdehyde (**9**) by a simple reductive oxyamination strategy as shown in Figure 3. These oxyamines were reacted with D-glucose, D-galactose, D-mannose, *N*-acetylglucosamine, and *N*-acetylgalactosamine under the optimized conditions discussed above to form *RON*-neoglycosides **8a**–**y** (Table 2).

For a given sugar, oxyamine structure appeared not to significantly influence yield until a steric threshold was reached; nearly all of the tested oxyamine neoglycosylations proceeded with good to excellent yields, the chief exception being those involving sterically bulky oxyamine **7d** (R = *t*-Bu). Interestingly, among the glycosylated *O*-*tert*-butylhydroxylamines, the mannoside provided a significantly higher yield (46%) than the other glycosides (17–19%). It is possible that the axial O-2 group of the mannoside does not interact as strongly with the *tert*-butyl group as does the equatorial O-2 of the other derivatives. In accord with previously published work,[20] isomer ratios varied dramatically as a function of the sugar, with glucose derivatives affording β-pyranose products, galactose derivatives affording β-pyranose/β-furanose mixtures, and D-mannose affording β-pyranose/α-pyranose/α-furanose mixtures. Attempts to resolve neoglycoside product mixtures are known to fail due to rapid equilibration between product isomers.[9c]

Table 2
Effect of aglycon and sugar on percent yield and glycoside stereochemistry



Entry	Substrate	R	Sugar	Neoglycoside	Yield (%)	β-Pyr/α-pyr/β-fur/α-fur[a]
1	**7a**	Me	Glc	**8a**	71	100:0:0:0
2	**7b**	Et	Glc	**8b**	82	100:0:0:0
3	**7c**	*i*-Pr	Glc	**8c**	73	100:0:0:0
4	**7d**	*t*-Bu	Glc	**8d**	19	n.d.[b]
5	**7e**	Allyl	Glc	**8e**	54	100:0:0:0
6	**7f**	Bn	Glc	**8f**	67	100:0:0:0
7[c]	**7a**	Me	GlcNAc	**8g**	47	100:0:0:0
8	**7a**	Me	Gal	**8h**	82	96:0:4:0
9	**7b**	Et	Gal	**8i**	88	71:0:29:0
10	**7c**	*i*-Pr	Gal	**8j**	76	63:0:37:0
11	**7d**	*t*-Bu	Gal	**8k**	19	n.d.[b]
12	**7e**	Allyl	Gal	**8l**	47	89:0:11:0
13	**7f**	Bn	Gal	**8m**	56	59:0:41:0
14	**7a**	Me	GalNAc	**8n**	78	41:0:59:0
15	**7b**	Et	GalNAc	**8o**	77	59:0:41:0
16	**7c**	*i*-Pr	GalNAc	**8p**	64	61:0:39:0
17	**7d**	*t*-Bu	GalNAc	**8q**	17	n.d.[b]
18	**7e**	Allyl	GalNAc	**8r**	69	64:0:36:0
19	**7f**	Bn	GalNAc	**8s**	61	49:0:51:0
20	**7a**	Me	Man	**8t**	91	37:41:0:21
21	**7b**	Et	Man	**8u**	88	39:39:0:22
22	**7c**	*i*-Pr	Man	**8v**	80	39:40:0:21
23	**7d**	*t*-Bu	Man	**8w**	46	n.d.[b]
24	**7e**	Allyl	Man	**8x**	85	40:39:0:21
25	**7f**	Bn	Man	**8y**	88	39:40:0:21

[a] Estimated by ^{1}H NMR in CD_3OD.
[b] Not determined due to signal overlap.
[c] Performed in 2%M aq NH_4OAc (pH 4.5) since GlcNAc was not soluble in MeOH/$CHCl_3$.

Oxyamine neoglycosylation is thought to proceed by a mechanism analogous to Fischer glycosidation, involving an intermediate oxyimminium ion.[20] The isomer ratios observed in Fisher glycosidations reflect a balance between the steric influence of monosaccharide substituents and electronic influences including the anomeric effect; the outcomes of oxyamine neoglycosylations can be understood using the same considerations. For instance, in glucose derivatives the exclusive formation of pyranosides with β-anomeric stereochemistry is easily rationalized. Both possible glucofuranoside anomers experience unfavorable steric interactions between the O-3 and C-5 groups (Fig. 4). In contrast, β-glucopyranosides contain no axial substituents and therefore little strain; the α-glucopyranoside anomer contains a single axial substituent and evidently oxyamines **7** do not impose a significant

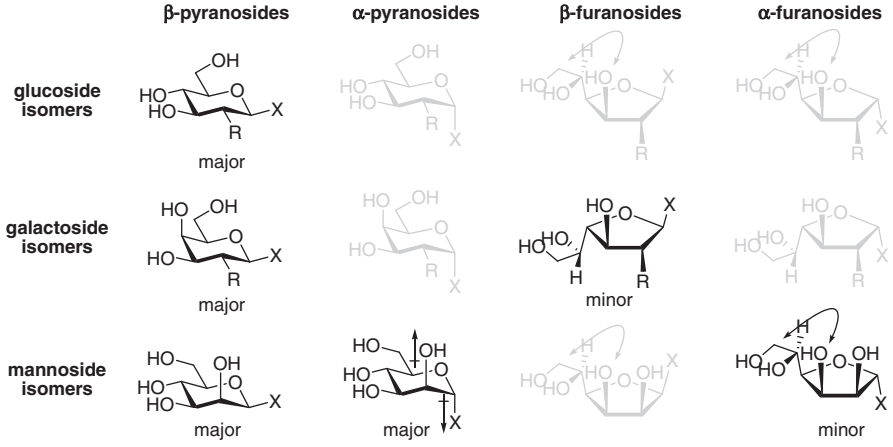


Figure 4. The possible isomers arising from oxyamine neoglycosylation. Those observed are shown in black; those not detected are shown in gray. Double headed arrows illustrate unfavorable steric interactions between the O-3 and C-5 groups. The favorably opposed C-1–C-2 dipole in α-mannopyranosides is also illustrated.

enough anomeric effect to offset the strain this arrangement would introduce. β-Galactopyranoside isomers were predominant in galactoside product mixtures. However, because of the 3,4-erythro configuration of galactose, β-galactofuranosides do not experience the unfavorable steric interactions between the O-3 and C-5 groups experienced by glucoside derivatives. Thus, furanosides make a significant contribution to the equilibrium mixture; 1,2-*trans* β-anomer is favored relative to 1,2-*cis* α-anomer, presumably for steric reasons and consistent with an insignificant oxyamine anomeric effect. While the mixture of three isomers observed in mannosides is more challenging to rationalize, the mixture of α and β pyranoside anomers in mannosides is consistent with a balance between steric and electronic factors where additional 1,3-diaxial interactions and gauche interactions suffered by the α-mannopyranoside anomer are offset by a favorably opposed C-1–C-2 dipole and possibly a modest anomeric effect. α-Mannofuranoside also makes a contribution to the equilibrium, despite unfavorable steric interactions between the O-3 and C-5 groups.

Unlike sugar structure, oxyamine structure did not appear to influence the isomeric outcome of oxyamine neoglycosylations significantly in most cases. However, oxyamine structure did appear to exert a subtle influence on the pyranose/furanose equilibrium in galactosides. *Methoxy*-, *ethoxy*, and *isopropoxy*-amine derived galactosides provided 4%, 29%, and 37% of β-furanose, respectively.

2.3. *RON*-neoglycoside hydrolytic stability

Few groups have investigated the stability of glycosylated oxyamines in aqueous solution,[9c,24] and rates of hydrolysis as a function of *RON*-neoglycoside structure have not been studied. Thus, we measured the rates of hydrolysis of neoglycosides **8a**–**f** at pH 3.0 and 7.0 (Fig. 5, Table 3). Pseudo-first order rate constants and half-lives for hydrolysis were calculated from semi-logarithmic plots of the hydrolysis traces. Consistent with previous results[9c,24] and an acid-catalyzed hydrolysis mechanism, we found that **8a**–**f** were completely stable under neutral conditions (data not shown) and that they hydrolyzed with half-lives ranging from 9 to 32 h at pH 3.0. While half-lives for neoglycosides **8e** and **8f** were approximately twice as long as those for neoglycosides **8a**–**d** we observed no systematic variation in hydrolysis rate as a function of oxyamine structure.

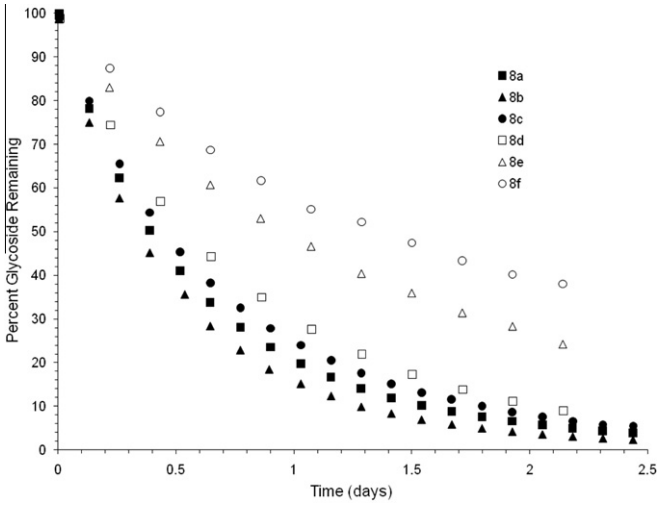


Figure 5. Hydrolysis of neoglycosides **8a**–**f** in 20 mM NaH_2PO_4 (pH 3.0) with 2% DMSO at 25 °C. Peak areas at 220 nM were used to estimate the neoglycoside/aglycon ratio, which is reported as percent neoglycoside remaining [$A_{neoglycoside}/(A_{neoglycoside} + A_{aglycon})$].

Table 3
Pseudo-first order hydrolysis rates and half-lives for **8a**–**f** at pH 3.0[a]

Entry	Neoglycoside	R	k_{obs} (s^{-1})	$t_{1/2}$ (h)
1	**8a**	Me	1.3×10^6	10.7
2	**8b**	Et	1.6×10^6	9.1
3	**8c**	*i*-Pr	1.2×10^6	11.6
4	**8d**	*t*-Bu	1.1×10^6	13.6
5	**8e**	Allyl	0.6×10^6	25.5
6	**8f**	Bn	0.5×10^6	31.8

[a] A sample of each neoglycoside (2 mM) in 20 mM NaH_2PO_4 (pH 3.0) with 2% DMSO at 25 °C was analyzed by HPLC approximately every 3 h for 2.5 days.

2.4. Library synthesis and biological evaluation

Having optimized reaction conditions and improved our understanding of oxyamine glycosylation outcomes as a function of aglycon structure, we set out to further elucidate digitoxin neoglycoside structure–activity relationships by modifying glycosidic linkages. Our previous work suggested that *i-PrON*-neoglycosides displayed enhanced cancer cell line selectivity relative to *MeON*-neoglycosides; however, our prior study probed cytotoxicity toward only four cell lines.[9b] Thus, we synthesized an expanded library of digitoxin neoglycosides that included three *i-PrON*-neoglycoside derivatives (*sec-Bu*-, *c-Pent*-, *c-HexON*-neoglycosides) and assessed their cytotoxicity against eight human cancer cell lines.

Digitoxin (**1**) was simultaneously hydrolyzed and oxidized under acidic conditions to provide digitoxigenone (Fig. 6). Subsequent treatment with alkoxyamines **10b**–**h** provided oxime ethers that were reduced with *tert*-butylamine-borane to provide separable ~1:1 mixtures of the desired C-3 β stereoisomers (**2b**–**h**) and undesired C-3 α stereoisomers. The C-3 β aglycons were then reacted with L-xylose under our optimized conditions (Table 2). In contrast to the good yields observed in our model studies (Table 2), neoglycosides **6b**–**f** were produced in low yields. Steric environment differences are a likely explanation for these results. The oxyamine nitrogen in model aglycons **7a**–**f** is attached to a primary carbon; in contrast, the oxyamine nitrogen in aglycons **2a**–**h** is attached to a secondary carbon. Despite low yields, excellent stereoselectivities (100% β-pyranoside) were observed, and sufficient quantities of **6b**–**f** were obtained to evaluate biological activity (see Fig. 7).

We assessed the activity of neoglycosides **6a**–**h** in cytotoxicity assays on eight human cancer cell lines representing a range of tumor types including basal epithelial, prostate, liver, colon, breast, brain, and ovarian cancers. Consistent with previous findings,[9b] our data show that the structure of *RON*-neoglycosidic linkages influences both the potency and selectivity of digitoxin neoglycosides. Digitoxin displayed potent cytotoxicity toward five of the eight cell lines tested (IC_{50} = 10–60 nM). Like digitoxin (**1**), *MeON*-neoglycoside **6a** was relatively potent and non-selective. Neoglycosides **6b**–**h** were significantly less potent cytotoxins than *MeON*-neoglycoside **6a**. However, *i-PrON*-neoglycoside **6c** and *i-PrON*-neoglycoside analogs **6f**–**h** appeared to display modestly enhanced selectivity relative to digitoxin (**1**) and other neoglycoside derivatives. For example, *i-PrON*-neoglycoside **6c** was two times more potent against NCI/ADR-RES cells (IC_{50} = 120 ± 10 nM) than any other cell line tested.[9b] To the best of our knowledge, we are the first group to observe such cell line selectivity resulting from a simple structural modifications to a glycosidic linkage. This finding is intriguing since NCI/ADR-RES cells have high levels of P-glycoprotein expression that confer multi-drug resistance.[25] Since many cardiac glycosides are substrates for P-glycoprotein, a possible explanation for such tumor specificity is that **6c** may no longer be a P-glycoprotein substrate.[26] Interestingly, *i-PrON*-neoglycoside derivatives **6f**–**h** also displayed significant cell line selectivity, but

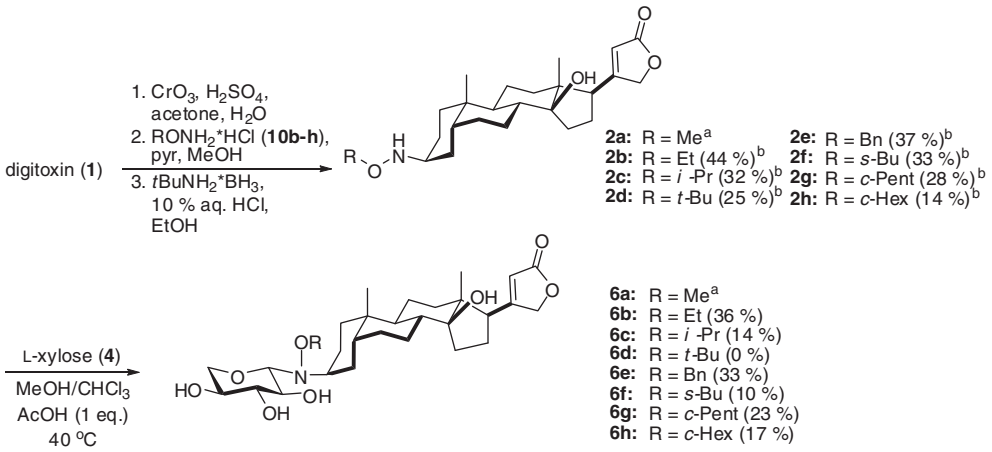


Figure 6. Synthesis of digitoxin neoglycosides. [a]Synthesized as previously described.[9c] [b]Isolated yield for the desired C-3 β-isomer.

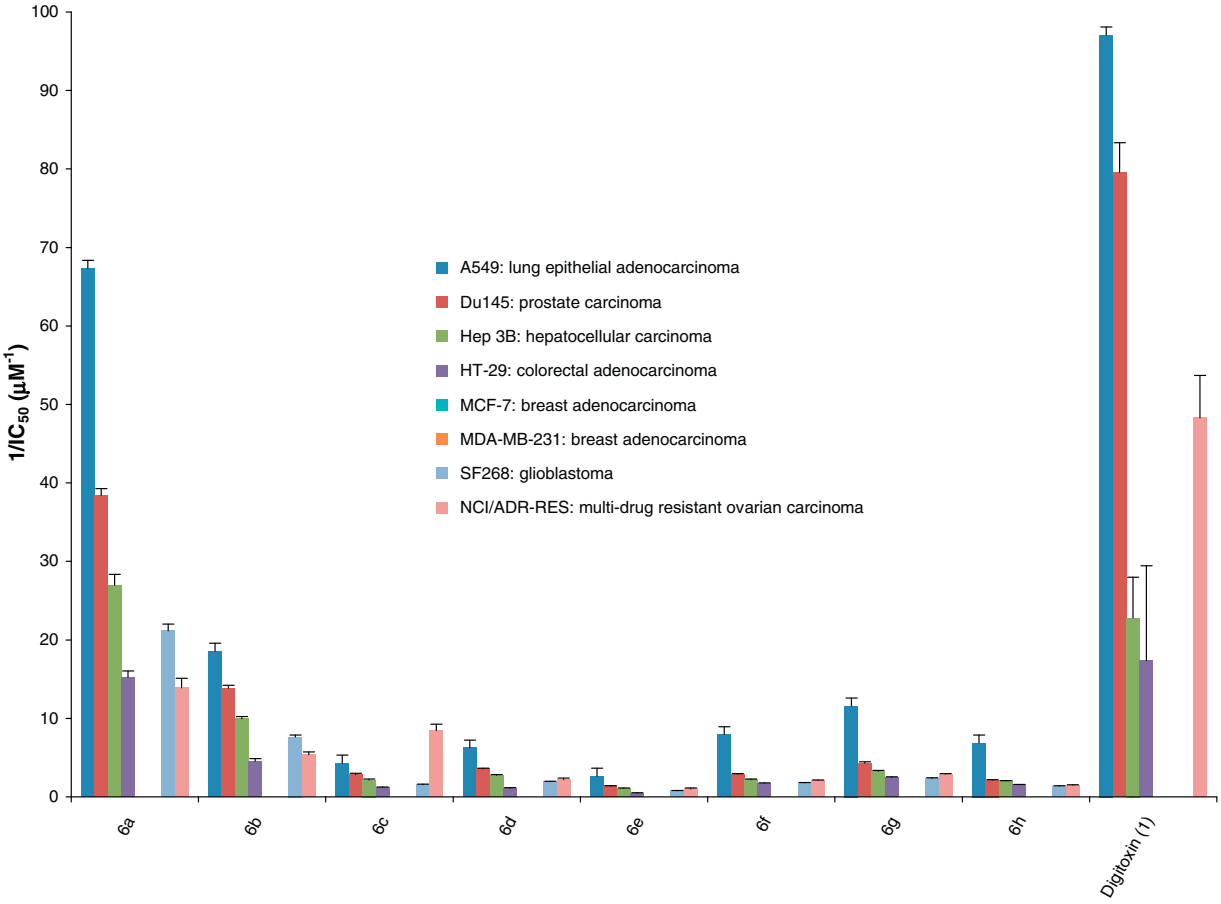


Figure 7. Summary of IC_{50} data from cytotoxicity assays. Reciprocal IC_{50} values are displayed for clarity; standard errors are depicted with error bars. The IC_{50} values of **6a–h** against MCF-7 and MDA-MB-231 cells was >10 μM. The IC_{50} of **1** against MCF-7, MDA-MB-231, and SF268 cells was >0.5 μM.

against A549 cells rather than against NCI/ADR-RES cells. For example, *c-Hex*-neoglycoside **6h** was approximately three times more potent against A549 cells than the other seven cell lines (IC_{50} = 145 ± 3 nM). Since A549 cells express a relatively high level of the α1 subunit of Na^+/K^+-ATPase,[27] it is possible that neoglycosides **6f–h** display a degree of selectivity toward this isoform. Because Na+/K+-ATPase isoforms are expressed in a tissue specific manner and since isoform expression differences have been noted between normal tissues and cancerous tissues,[27] cardenolides that display isoform specificity could be considered as targeted therapeutics.

3. Conclusions

Traditional chemical glycosylation strategies are often undermined by elaborate protecting and activating group schemes. Oxyamine neoglycosylation has emerged as powerful tool that addresses this shortcoming.[20] We became interested in determining

if modified *RON*-neoglycosidic linkages produced by oxyamine neoglycosylation could influence the biological activities of analogs of digitoxin.[9b] As a preliminary step toward this goal, we initiated a model study to optimize oxyamine neoglycosylation reaction conditions and then set out to assess the influence a simple steric series of oxyamine structures has on *RON*-neoglycoside yield, stereochemistry, and stability. We identified conditions suitable for the convenient synthesis of digitoxin neoglycosides and found that sugar structure, rather than *RON*-glycosidic linkage, exerts the strongest influence on neoglycoside yield and stereochemistry. To further elucidate digitoxin neoglycoside structure–activity relationships, we synthesized an expanded library of digitoxin neoglycosides that included three *i-PrON*-neoglycoside derivatives (*sec-Bu-*, *c-Pent-*, *c-HexON*-neoglycosides) and we assessed their cytotoxicity against eight human cancer cell lines. Consistent with previous findings,[9b] our data show that the structure of *RON*-neoglycosidic linkages influences both the potency and selectivity of digitoxin neoglycosides.

4. Experimental

4.1. General methods

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in deuterated solvents on a Bruker Avance III 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (0.00) for *d*-chloroform, or the residual protic solvent peak for other solvents. ^{1}H NMR splitting patterns with observed first order coupling are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker Avance III 400 MHz spectrometer. Mass spectra (MS) were obtained using electrospray ionization (ESI). Commercially available reagents and solvents were used without further purification. Analytical thin layer chromatography (TLC) was carried out on TLC plates pre-coated with Silica Gel 60 (250 μm layer thickness). Visualization was accomplished using either a UV lamp or potassium permanganate stain (2 g $KMnO_4$, 13.3 g K_2CO_3, 2 mL 2 M NaOH, 200 mL H_2O). Flash column chromatography was performed on 40–60 μm silica gel (230–400 mesh). Solvent mixtures used for TLC and flash column chromatography are reported in v/v ratios.

4.2. Percent conversion estimates

LCMS percent conversion estimates used reverse phase HPLC on a Zorbax Eclipse XDB-C8 column (4.6 × 150 mm; Agilent Technologies) with a flow rate of 0.8 mL/min and a linear gradient of 45% CH_3OH/H_2O to 85% CH_3OH/H_2O over 20 min and ESI. Percent conversion was estimated by dividing the sum of the peak areas at 220 nm of peaks corresponding to the desired product mass by the total area of all peaks eluting between 5 and 22 min.

4.3. Neoglycoside hydrolysis

The hydrolytic degradation of neoglycosides **8** was monitored by reverse phase HPLC on a Zorbax Eclipse XDB-C8 column (4.6 × 150 mm; Agilent Technologies) with a flow rate of 0.8 mL/min and a linear gradient of 4.5% CH_3OH/H_2O to 95.5% CH_3OH/H_2O over 60 min. At $t = 0$, a solution of neoglycoside (2 mM) in 20 mM NaH_2PO_4 buffer (pH 3) with 2% DMSO or a solution of neoglycoside (2 mM) in 20 mM K_2HPO_4 buffer (pH 7) with 2% DMSO was immediately injected onto the HPLC column at 25 °C. Peak areas at 220 nM were used to estimate the neoglycoside/aglycon ratio, which is reported as percent neoglycoside remaining $[A_{neoglycoside}/(A_{neoglycoside} + A_{aglycon})]$. Pseudo-first order rate constants and half-lives for hydrolysis were calculated from semi-logarithmic plots of the hydrolysis traces.

4.4. Cytotoxicity assays

The product solutions were concentrated, weighed, and dissolved in DMSO to make 30 mM stock solutions. All cell lines were maintained as previously reported.[1] Cells were harvested by trypsinization using 0.25% trypsin and 0.1% EDTA and then counted in a Cellometer Auto T4 cell counter (Nexcelom, Inc.), before dilution for assay plating. Cell plating, compound handling and assay set up were performed as previously reported[1] except the cells were plated in 50 μL volumes in 384-well clear bottom, tissue culture plates (Corning-Costar, Inc.). Compounds were added from the 384-well compound stock plates at a 1:100 dilution using a Biomek FX liquid handler equipped with a 384 channel head (Beckman Coulter, Inc.). Cell titer-glo reagent (15 μL) (Promega Corporation, Inc.) was added and incubated for 10 min at room temperature with gentle agitation to lyse the cells. Each plate was read for luminescence. The IC_{50} value for each compound represents at least four replicates of dose–response experiments conducted over six concentrations at two-fold dilutions. Within each experiment, percent inhibition values at each concentration were expressed as a percentage of the maximum luminescence signal observed for a 0 nM control. IC_{50} values were determined using XLFit 4.0 as previously reported (see Supplementary data for IC_{50} values).[9c]

4.5. Synthesis

4.5.1. O-Methyl-*N*-(4-methylbenzyl)hydroxylamine (7a)

p-Tolualdehyde (4.6 mL, 38.9 mmol), methoxyamine hydrochloride (4.55 g, 54.5 mmol), and pyridine (6.9 mL, 85.6 mmol) were dissolved in CH_2Cl_2 (60 mL) and the resulting solution was stirred overnight. The reaction mixture was washed with 1 M HCl, brine, dried over $MgSO_4$, filtered, and then concentrated. The mixture of oxime diastereomers was suspended in ethanol (19 mL) and cooled to 0 °C. Borane pyridine complex (19.5 mL, 155.6 mmol) was added, followed by the dropwise addition 20% aq HCl (39 mL). The reaction mixture was stirred overnight at room temperature. Na_2CO_3 was added until gas evolution ceased, and the mixture was concentrated. The resulting residue was dissolved in CH_2Cl_2, washed with water, satd aq $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 1:7 EtOAc/hexane to provide **7a** (TLC $R_f = 0.42$ in 1:4 EtOAc/hexane) as a volatile oil (3.29 g, 56% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25–7.13 (m, 4H), 5.67 (s, 1H), 4.01 (s, 2H), 3.51 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.6, 140.0, 129.4, 126.9, 61.9, 21.5; ESI-MS *m/z* (M+H) calculated for $C_9H_{14}NO$ 152.1, observed 152.1.

4.5.2. *O*-Ethyl-*N*-(4-methylbenzyl)hydroxylamine (7b)

p-Tolualdehyde (1.0 mL, 8.2 mmol), ethoxyamine hydrochloride (1.15 mg, 11.8 mmol), and pyridine (1.5 mL, 18.0 mmol) were dissolved in CH_2Cl_2 (18 mL) and the resulting solution was stirred for 1 h. The reaction mixture was washed with 1 M HCl, 1 M $CuSO_4$, and brine, then dried over $MgSO_4$, filtered, and concentrated. The mixture of oxime diastereomers was suspended in ethanol (18 mL) and cooled to 0 °C. Borane trimethylamine complex (1.64 g, 22.5 mmol) was added, followed by the dropwise addition 10% aq HCl (18 mL). The reaction mixture was stirred 3 h at room temperature then diluted in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with

1:4 EtOAc/hexane to provide **7b** (TLC R_f = 0.45 in 1:9 EtOAc/hexane) as an oil (632.0 mg, 47% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24–7.12 (m, 4H), 5.54 (s, 1H), 4.00 (s, 2H), 3.70 (t, 2H, J = 7.0), 2.33 (s, 3H), 1.14 (t, 3H, J = 7.0); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.1, 134.4, 129.1, 128.9, 69.2, 56.3, 21.1, 14.2; ESI-MS m/z (M+H) calculated for $C_{10}H_{16}NO$ 166.1, observed 166.1.

4.5.3. *N*-(4-Methylbenzyl)-*O*-*iso*-propylhydroxylamine (7c)

p-Tolualdehyde (0.77 mL, 6.4 mmol), *iso*-propoxyamine hydrochloride (1.0 g, 8.96 mmol), and pyridine (1.2 mL, 14.1 mmol) were dissolved in CH_2Cl_2 (14 mL) and the resulting solution was stirred 90 min. The reaction mixture was washed with 1 M HCl, 1 M $CuSO_4$, and brine, then dried over $MgSO_4$, filtered, and concentrated. The mixture of oxime diastereomers was suspended in ethanol (16.3 mL) and cooled to 0 °C. Borane trimethyl complex (1.45 g, 19.8 mmol) was added, followed by the dropwise addition of 10% aq HCl (16.3 mL). The reaction mixture was stirred overnight at room temperature then diluted in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 1:4 EtOAc/hexane to provide **7c** (TLC R_f = 0.61 in 1:4 EtOAc/hexane) as an oil (572.0 mg, 50% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25–7.12 (m, 4H), 5.37 (s, 1H), 3.98 (s, 2H), 3.81 (sept, 1H, J = 6.2), 2.33 (s, 3H), 1.12 (t, 6H, J = 6.2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.2, 134.7, 129.2, 74.9, 56.9, 21.5, 21.3; ESI-MS m/z (M+H) calculated for $C_{11}H_{18}NO$ 180.1, observed 180.1.

4.5.4. *O*-*tert*-Butyl-*N*-(4-methylbenzyl)hydroxylamine (7d)

p-Tolualdehyde (1.5 mL, 12.3 mmol), *tert*-butoxyamine hydrochloride (2.23 g, 17.8 mmol), and pyridine (2.25 mL, 27.9 mmol) were dissolved in CH_2Cl_2 (28 mL) and the resulting solution was stirred 90 min. The reaction mixture was washed with 1 M HCl, 1 M $CuSO_4$, and brine, then dried over $MgSO_4$, filtered, and concentrated. The crude oxime was suspended in ethanol (22 mL) and cooled to 0 °C. Borane trimethyl complex (2.30 g, 26.4 mmol) was added, followed by the dropwise addition 10% aq HCl (22 mL). The reaction mixture was stirred 6 h at room temperature then diluted in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 99:1 toluene/EtOAc to provide **7d** (TLC R_f = 0.34 in 99:1 toluene/EtOAc) as an oil (428.0 mg, 28% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.12 (m, 4H), 4.94 (s, 1H), 3.94 (s, 2H), 2.33 (s, 3H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.1, 133.3, 128.2, 128.0, 76.1, 56.5, 25.8, 20.2; ESI-MS m/z (M+H) calculated for $C_{12}H_{20}NO$ 194.2, observed 194.2.

4.5.5. *O*-Allyl-*N*-(4-methylbenzyl)hydroxylamine (7e)

p-Tolualdehyde (0.5 mL, 4.2 mmol), *O*-allylhydroxylamine hydrochloride (67.5 mg, 5.9 mmol), and pyridine (0.75 mL, 9.3 mmol) were dissolved in CH_2Cl_2 (10 mL) and the resulting solution was stirred 30 min. The reaction mixture was washed with 1 M HCl, 1 M $CuSO_4$ (2×), and brine, then dried over $MgSO_4$, filtered, and concentrated. The mixture of oxime diastereomers was suspended in ethanol (8 mL) and cooled to 0 °C. Borane trimethyl complex (68.3 mg, 9.4 mmol) was added, followed by the dropwise addition of 10% aq HCl (8 mL). The reaction mixture was stirred 2.5 h at room temperature then Na_2CO_3 was added until gas evolution ceased. The mixture was diluted in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 9:1 hexanes/EtOAc to provide **7e** (TLC R_f = 0.32 in 4:1 hexanes/EtOAc) as an oil (503.0 mg, 48% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.13 (m, 4H), 5.91 (ddt, 1H, J = 17.3, 10.4, 5.8), 5.69 (s, 1H), 5.25 (m, 1H), 5.17 (m, 1H), 4.16 (m, 2H), 4.02 (s, 2H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.1, 134.6, 134.5, 129.1, 129.0, 117.6, 75.1, 56.3, 21.2, ESI-MS m/z (M+H) calculated for $C_{11}H_{16}NO$ 177.1, observed 177.1.

4.5.6. *O*-Benzyl-*N*-(4-methylbenzyl)hydroxylamine (7f)

p-Tolualdehyde (0.5 mL, 4.2 mmol), *O*-benzylhydroxylamine hydrochloride (94.5 mg, 5.9 mmol), and pyridine (0.75 mL, 9.3 mmol) were dissolved in CH_2Cl_2 (10 mL) and the resulting solution was stirred 24 h. The reaction mixture was washed with 1 M HCl, 1 M $CuSO_4$ (2×), and brine, then dried over $MgSO_4$, filtered, and concentrated. The mixture of oxime diastereomers was suspended in ethanol (12 mL) and cooled to 0 °C. Borane trimethyl complex (1.02 mg, 13.9 mmol) was added, followed by the dropwise addition 10% aq HCl (11.4 mL). The reaction mixture was stirred 2.5 h at room temperature then Na_2CO_3 was added until gas evolution ceased. The mixture was diluted in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product mixture was purified by SiO_2 column chromatography eluting with 12:1 hexanes/EtOAc to provide **7f** (TLC R_f = 0.33 in 12:1 hexanes/EtOAc) as an oil (584.5 mg, 54% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.25 (m, 5H), 7.25–7.13 (m, 4H), 5.69 (s, 1H), 4.66 (s, 2H), 4.01 (s, 2H), 2.33 (s, 3H); ESI-MS m/z (M+H) calculated for $C_{15}H_{18}NO$ 227.1, observed 227.1.

4.5.7. General procedure for the synthesis of glycosylated oxyamines 8

Aglycon **7** (1 equiv) and sugar (1.1 equiv) were added to a glass vial equipped with a stirring flea and then were dissolved in 9:1 MeOH/$CHCl_3$ (0.1 mL/mmol). AcOH was added (1 equiv) and the reaction mixture was stirred at 40 °C for 2 days. Silica gel (125 mg) was added and the crude reaction mixture was concentrated then purified via SiO_2 column chromatography. NMR spectra were assigned via gCOSY experiments and comparison to published chemical shift values and coupling constants.[20]

4.5.7.1. *O*-Methyl-*N*-(4-methylbenzyl)-*N*-(β-D-glucopyranosyl)hydroxylamine (8a). Via the general procedure, **7a** (28.6 mg, 0.189 mmol), D-glucose (37.5 mg, 0.208 mmol), and AcOH (10.8 μL, 0.189 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8a** (TLC R_f = 0.26 in 10:1 CH_2Cl_2/MeOH) as a white powder (39.8 mg, 71% yield). ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.30 (A of AB, 2H, J = 8.2), 7.11 (B of AB, 2H, J = 7.7), 4.12 (A of AB, 1H, J = 12.4), 3.99 (B of AB, 1H, J = 12.3), 3.89 (d, 1H, J = 8.7, H-1), 3.87 (A of ABX, 1H, J = 12.0, 3.9, H-6), 3.67 (B of ABX, 1H, J = 12.0, 15.2, H-6'), 3.50 (m, 1H, H-2), 3.40 (s, 3H), 3.29 (m, 2H, H-3, H-4), 3.13 (m, 1H, H-5), 2.30 (s, 3H). ^{13}C NMR (MeOD-d_4, 100 MHz): δ 136.7, 133.8, 129.5, 128.3, 91.5, 78.1, 78.0, 70.0, 69.7, 61.3, 61.0, 55.7, 19.7. HRMS m/z (M+H) calculated for $C_{15}H_{24}NO_6$ 314.16014, observed 314.15932.

4.5.7.2. *O*-Ethyl-*N*-(4-methylbenzyl)-*N*-(β-D-glucopyranosyl)hydroxylamine (8b). Via the general procedure, **7b** (23.6 mg, 0.138 mmol), D-glucose (27.3 mg, 0.151 mmol), and AcOH (7.9 μL, 0.138 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8b** (TLC R_f = 0.33 in 10:1 CH_2Cl_2/MeOH) as a white powder (37.0 mg, 82% yield). ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.31 (A of AB, 2H, J = 7.9), 7.13 (B of AB, 2H, J = 7.9), 4.12 (A of AB, 1H, J = 12.4), 4.02 (B of AB, 1H, J = 12.4), 3.91 (d, 1H, J = 8.9, H-1), 3.89 (A of ABX, 1H, J = 12.0, 2.2, H-6), 3.72 (B of ABX, 1H, J = 12.0, 5.4, H-6'), 3.70 (A of ABX_3, 1H, J = 7.2, 3.8), 3.58 (B of ABX_3, 1H, J = 7.2, 3.8), 3.50 (m, 1H, H-2), 3.30 (m, 2H, H-3, H-4), 3.14 (m, 1H, H-5), 2.32 (s, 3H), 1.01 (t, 3H, J = 7.0). ^{13}C NMR (MeOD-d_4, 100 MHz): δ 138.8, 138.2, 135.4, 131.1, 129.9, 93.2, 79.6, 71.6, 71.2, 70.8, 62.8, 57.7,

21.2, 14.1. ESI-MS *m*/*z* (M+H) calculated for $C_{16}H_{26}NO_6$ 328.2, observed 328.2.

4.5.7.3. *N*-(4-Methylbenzyl)-*N*-(β-D-glucopyranosyl)-*O*-*iso*-propylhydroxylamine (8c). Via the general procedure, **7c** (35.0 mg, 0.195 mmol), D-glucose (38.7 mg, 0.215 mmol), and AcOH (11.0 μL, 0.195 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8c** (TLC R_f = 0.37 in 10:1 CH_2Cl_2/MeOH) as a white powder (48.6 mg, 73% yield). ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.28 (A of AB, 2H, J = 7.6), 7.11 (B of AB, 2H, J = 7.7), 4.07 (q, 2H, J = 12.6), 3.89 (d, 1H, J = 9.4, H-1), 3.88 (m, 1H, H-6), 3.88 (m, 1H), 3.70 (m, 1H, H-6'), 3.46 (t, 1H, J = 8.7, H-2), 3.29 (m, 2H, H-3, H-4), 3.09 (m, 1H, H-5), 2.30 (s, 3H), 1.15 (d, 3H, J = 5.9), 1.01 (d, 3H, J = 5.6). ^{13}C NMR (MeOD-d_4, 100 MHz): δ 136.6, 133.7, 129.6, 129.4, 128.3, 91.5, 78.0, 75.0, 70.1, 69.6, 61.3, 56.0, 20.3, 20.0, 19.7. ESI-MS *m*/*z* (M+H) calculated for $C_{17}H_{28}NO_6$ 342.2, observed 342.2.

4.5.7.4. *O*-*tert*-Butyl-*N*-(4-methylbenzyl)-*N*-(D-glucosyl)-hydroxylamine (8d). Via the general procedure, **7d** (22.5 mg, 0.116 mmol), D-glucose (23.1 mg, 0.128 mmol), and AcOH (6.6 μL, 0.116 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8d** (TLC R_f = 0.23 in 10:1 CH_2Cl_2/MeOH) as a white powder (8.0 mg, 19% yield). ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.29 (m, 2H), 7.12 (m, 2H), 4.45–2.87 (m, 5H), 4.15 (m, 1H), 3.89 (m, 1H), 2.32 (s, 3H), 1.49–0.85 (m, 9H). ESI-MS *m*/*z* (M+H) calculated for $C_{18}H_{30}NO_6$ 356.2, observed 356.2.

4.5.7.5. *O*-Allyl-*N*-(4-methylbenzyl)-*N*-(β-D-glucopyranosyl)-hydroxylamine (8e). Via the general procedure, **7e** (28.8 mg, 0.162 mmol), D-glucose (32.2 mg, 0.179 mmol), and AcOH (9.3 μL, 0.162 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8e** (TLC R_f = 0.47 in 10:1 CH_2Cl_2/MeOH) as a white powder (29.5 mg, 54% yield). ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.31 (A of AB, 2H, J = 8.1), 7.14 (B of AB, 2H, J = 7.8), 5.79 (ddt, 1H, J = 17.4, 10.3, 6.1), 5.16 (ddt, 1H, J = 17.4, 1.6, 1.6), 5.10 (m, 1H), 4.16 (A of AB, 1H, J = 12.4), 4.16 (m, 1H), 4.04 (B of AB, 1H, J = 12.4), 4.02 (ddd, 1H, J = 11.5, 6.4, 1.1), 3.93 (d, 1H, J = 12.3, H-1), 3.89 (A of ABX, 1H, J = 12.2, 2.2, H-6), 3.72 (B of ABX, 1H, J = 12.2, 5.3, H-6'), 3.53 (m, 1H, H-2), 3.31 (m, 2H, H-3, H-4), 3.15 (m, 1H, H-5), 2.34 (s, 3H). ^{13}C NMR (MeOD-d_4, 100 MHz): δ 138.3, 135.3, 134.8, 131.2, 129.9, 119.0, 93.2, 79.7, 79.5, 77.1, 71.6, 71.2, 62.8, 57.8, 21.2. ESI-MS *m*/*z* (M+H) calculated for $C_{17}H_{26}NO_6$ 340.2, observed 340.2.

4.5.7.6. *O*-Benzyl-*N*-(4-methylbenzyl)-*N*-(β-D-glucopyranosyl)-hydroxylamine (8f). Via the general procedure, **7f** (23.4 mg, 0.103 mmol), D-glucose (20.4 mg, 0.113 mmol), and AcOH (6.0 μL, 0.103 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8f** (TLC R_f = 0.42 in 10:1 CH_2Cl_2/MeOH) as a white powder (26.7 mg, 67% yield). ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.34 (m, 1H), 7.29 (m, 3H), 7.18 (m, 4H), 4.65 (A of AB, 1H, J = 9.7), 4.46 (B of AB, 1H, J = 9.7), 4.16 (A of AB, 1H, J = 12.4), 4.05 (B of AB, 1H, J = 12.4), 4.00 (d, 1H, J = 9.0, H-1), 3.86 (A of ABX, 1H, J = 12.1, 2.2, H-6), 3.70 (B of ABX, 1H, J = 12.1, 5.1, H-6'), 3.65 (m, 1H, H-2), 3.31 (m, 2H, H-3, H-4), 3.15 (m, 1H, H-5), 2.35 (s, 3H). ^{13}C NMR (MeOD-d_4, 100 MHz): δ 138.4, 137.7, 135.4, 131.3, 130.7, 129.9, 129.4, 129.3, 93.3, 79.63, 79.58, 78.1, 71.6, 71.1, 62.7, 57.8, 21.3. ESI-MS *m*/*z* (M+H) calculated for $C_{21}H_{28}NO_6$ 390.2, observed 390.2.

4.5.7.7. *O*-Methyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-glucosyl)hydroxylamine (8g). Aglycon **7a** (21.0 mg, 0.139 mmol) and 2-aminoacetyl-2-deoxy-D-glucose (29.8 mg, 0.135 mmol) were dissolved in 0.18 mL of 2 M aq ammonium acetate buffer (pH 4.5) and stirred at 40 °C for 72 h. The mixture was concentrated and 1 mL of toluene was added. After concentrating again, the crude reaction mixture was purified by SiO_2 column chromatography eluting with 8:1:1 EtOAc/MeOH/H_2O to afford **8g** (TLC R_f = 0.32 in 8:1:1 EtOAc/MeOH/H_2O) as a white powder (22.3 mg, 47% yield). ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.25 (m, 2H), 7.12 (m, 2H), 4.15 (d, 1H, J = 9.9, H-1), 4.13–3.97 (m, 2H), 3.98 (m, 1H, H-2), 3.91 (m, 1H, H-6), 3.73 (m, 1H, H-6'), 3.39–3.30 (m, 2H, H-3, H-4), 3.26 (s, 3H), 3.18 (m, 1H, H-5), 2.31 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (MeOD-d_4, 100 MHz): δ 176.5, 141.3, 138.9, 134.2, 133.1, 95.0, 83.1, 80.9, 75.0, 66.2, 65.2, 59.3, 57.1, 26.3, 24.4. ESI-MS *m*/*z* (M+H) calculated for $C_{17}H_{27}N_2O_6$ 355.2, observed 355.2.

4.5.7.8. *O*-Methyl-*N*-(4-methylbenzyl)-*N*-(β-D-galactosyl)hydroxylamine (8h). Via the general procedure, **7a** (28.4 mg, 0.188 mmol), D-galactose (37.2 mg, 0.207 mmol), and AcOH (10.7 μL, 0.188 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8h** (TLC R_f = 0.27 in 10:1 CH_2Cl_2/MeOH) as a white powder (48.2 mg, 82% yield). The product comprised an inseparable mixture of β-pyranoside (96%) and β-furanoside (4%) isomers. ESI-MS *m*/*z* (M+H) calculated for $C_{15}H_{24}NO_6$ 314.2, observed 314.2. *O*-Methyl-*N*-(4-methylbenzyl)-*N*-(β-D-galactopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.32 (A of AB, 2H, J = 8.2), 7.12 (B of AB, 2H, J = 7.8), 4.13 (A of AB, 1H, J = 12.7), 4.01 (B of AB, 1H, J = 12.7), 3.90 (d, 1H, J = 9.0, H-1), 3.85–3.71 (m, 4H, H-2, H-4, H-6, H-6'), 3.44–3.33 (m, 2H, H-3, H-5), 3.40 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (MeOD-d_4, 100 MHz): δ 138.1, 135.6, 131.1, 129.9, 93.8, 78.5, 76.5, 70.6, 69.0, 62.7, 62.4, 56.9, 21.2. *O*-Methyl-*N*-(4-methylbenzyl)-*N*-(β-D-galactofuranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.28 (A of AB, 2H, J = 8.2), 7.12 (B of AB, 2H, J = 7.8), 4.45 (d, 1H, J = 5.3, H-1), 4.26 (dd, 1H, J = 7.9, 5.3, H-2), 4.13 (A of AB, 1H, J = 12.7), 4.01 (B of AB, 1H, J = 12.7), 4.09 (dd, 1H, J = 8.4, 6.8, H-3), 4.05–3.55 (m, 4H, H-4, H-5, H-6, H-6'), 3.40 (s, 3H), 2.33 (s, 3H).

4.5.7.9. *O*-Ethyl-*N*-(4-methylbenzyl)-*N*-(β-D-galactosyl)hydroxylamine (8i). Via the general procedure, **7b** (14.1 mg, 0.085 mmol), D-galactose (16.9 mg, 0.094 mmol), and AcOH (5.0 μL, 0.085 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8i** (TLC R_f = 0.30 in 10:1 CH_2Cl_2/MeOH) as a white powder (24.8 mg, 88% yield). The product comprised an inseparable mixture of β-pyranoside (71%) and β-furanoside (29%) isomers. ESI-MS *m*/*z* (M+H) calculated for $C_{16}H_{26}NO_6$ 328.2, observed 328.2. *O*-Ethyl-*N*-(4-methylbenzyl)-*N*-(β-D-galactopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.31 (A of AB, 2H, J = 8.0), 7.12 (B of AB, 2H, J = 7.8), 4.12 (A of AB, 1H, J = 12.3), 4.01 (B of AB, 1H, J = 12.6), 3.91 (d, 1H, J = 9.0, H-1), 3.87–3.70 (m, 4H, H-2, H-4, H-6, H-6'), 3.70–3.40 (m, 2H), 3.45–3.34 (m, 2H, H-3, H-5), 2.32 (s, 3H), 1.00 (t, 3H, J = 7.0). ^{13}C NMR (MeOD-d_4, 100 MHz): δ 138.1, 135.9, 131.1, 129.8, 94.1, 83.1, 78.5, 76.5, 70.7, 69.1, 62.8, 57.2, 21.2, 14.1. *O*-Ethyl-*N*-(4-methylbenzyl)-*N*-(β-D-galactofuranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.27 (A of AB, 2H, J = 8.0), 7.12 (B of AB, 2H, J = 7.8), 4.46 (d, 1H, J = 5.7, H-1), 4.25 (dd, 1H, J = 6.9, 5.8, H-2), 4.15–3.99 (m, 2H), 4.08 (m, 1H, H-3), 3.95–3.34 (m, 6H), 2.32 (s, 3H), 0.97 (t, 3H, J = 7.0). ^{13}C NMR (MeOD-d_4, 100 MHz): δ 138.1, 135.9, 131.0, 129.8, 98.7, 83.1, 78.8, 77.4, 73.0, 71.0, 64.6, 58.3, 21.2, 14.1.

4.5.7.10. *N*-(4-Methylbenzyl)-*N*-(β-D-galactosyl)-*O*-*iso*-propylhydroxylamine (8j). Via the general procedure, **7c** (47.3 mg, 0.264 mmol), D-galactose (52.3 mg, 0.290 mmol), and AcOH (15 μL, 0.264 mmol) were reacted. The crude product mixture

was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8j** (TLC R_f = 0.33 in 10:1 CH_2Cl_2/MeOH) as a white powder (74.9 mg, 87% yield). The product comprised an inseparable mixture of β-pyranoside (63%) and β-furanoside (37%) isomers. ESI-MS *m*/*z* (M+H) calculated for $C_{17}H_{28}NO_6$ 342.2, observed 342.2. *N*-(4-Methylbenzyl)-*N*-(β-D-galactopyranosyl)-*O*-*iso*-propylhydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.31 (A of AB, 2H, *J* = 7.2), 7.12 (B of AB, 2H, *J* = 5.8), 4.13–3.34 (m, 10H, H-1–6), 2.31 (s, 3H), 1.16 (d, 3H, *J* = 5.8), 0.96 (d, 3H, *J* = 4.5). ^{13}C NMR (MeOD-d_4, 100 MHz): δ 138.1, 135.7, 131.3, 129.9, 94.6, 83.0, 78.5, 76.5, 70.6, 62.9, 58.9, 54.9, 21.9, 21.6, 21.3. *N*-(4-Methylbenzyl)-*N*-(β-D-galactofuranosyl)-*O*-*iso*-propylhydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.27 (A of AB, 2H, *J* = 7.4), 7.12 (B of AB, 2H, *J* = 5.8), 4.47 (d, 1H, *J* = 5.6, H-1), 4.30 (dd, 1H, *J* = 6.6, 6.6, H-2), 4.13–3.34 (m, 8H, H-3–6), 2.31 (s, 3H), 1.08 (d, 3H, *J* = 6.0), 1.05 (d, 3H, *J* = 5.7). ^{13}C NMR (MeOD-d_4, 100 MHz): δ 138.1, 135.7, 131.0, 129.8, 98.2, 83.0, 78.5, 77.4, 76.1, 72.2, 64.7, 58.1, 21.9, 21.8, 21.3.

4.5.7.11. *O*-*tert*-Butyl-*N*-(4-methylbenzyl)-*N*-(D-galactosyl)-hydroxylamine (8k). Via the general procedure, **7d** (51.2 mg, 0.265 mmol), D-galactose (52.5 mg, 0.291 mmol), and AcOH (15.2 μL, 0.285 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8k** (TLC R_f = 0.35 in 10:1 CH_2Cl_2/MeOH) as a white powder (18.3 mg, 19% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.18 (m, 4H), 4.69–2.89 (m, 9H), 2.33 (s, 3H), 1.48–0.99 (m, 9H). ESI-MS *m*/*z* (M+H) calculated for $C_{18}H_{30}NO_6$ 356.2, observed 356.2.

4.5.7.12. *O*-Allyl-*N*-(4-methylbenzyl)-*N*-(β-D-galactosyl)hydroxylamine (8l). Via the general procedure, **7e** (23.7 mg, 0.134 mmol), D-galactose (26.5 mg, 0.147 mmol), and AcOH (7.7 μL, 0.134 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 5:1 CH_2Cl_2/MeOH to afford **8l** (TLC R_f = 0.75 in 5:1 CH_2Cl_2/MeOH) as a white powder (21.5 mg, 47% yield). The product comprised an inseparable mixture of β-pyranoside (89%) and β-furanoside (11%) isomers. ESI-MS *m*/*z* (M+H) calculated for $C_{17}H_{26}NO_6$ 340.2, observed 340.2. *O*-Allyl-*N*-(4-methylbenzyl)-*N*-(β-D-galactopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.31 (A of AB, 2H, *J* = 7.8), 7.12 (B of AB, 2H, *J* = 8.0), 5.79 (ddt, 1H, *J* = 17.2, 10.4, 6.4), 5.15 (ddd, 1H, *J* = 17.3, 3.0, 1.3), 5.08 (m, 1H), 4.15 (A of AB, 1H, *J* = 12.8), 4.04 (B of AB, 1H, *J* = 12.8), 4.07 (m, 2H), 3.95–3.39 (m, 7H, H-1–6), 2.32 (s, 3H). ^{13}C NMR (MeOD-d_4, 100 MHz): δ 138.2, 135.6, 135.0, 131.1, 129.9, 118.6, 94.1, 78.6, 76.9, 76.5, 70.6, 69.1, 62.8, 57.2, 21.2. *O*-Allyl-*N*-(4-methylbenzyl)-*N*-(β-D-galactofuranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.28 (A of AB, 2H, *J* = 8.2), 7.23 (B of AB, 2H, *J* = 7.9), 5.87 (ddt, 1H, *J* = 17.3, 10.4, 5.8), 5.21 (ddd, 1H, *J* = 17.2, 3.4, 1.6), 5.12–5.02 (m, 1H), 4.47 (d, 1H, *J* = 5.7, H-1), 4.28 (dd, 1H, *J* = 6.9, 5.3, H-2), 4.08 (m, 1H, H-3), 4.16–3.39 (m, 8H), 2.32 (s, 3H). ^{13}C NMR (MeOD-d_4, 100 MHz): δ 138.1, 135.7, 134.9, 131.0, 130.2, 117.6, 94.2, 79.5, 77.4, 77.1, 70.6, 69.1, 62.8, 56.7, 21.2.

4.5.7.13. *O*-Benzyl-*N*-(4-methylbenzyl)-*N*-(β-D-galactosyl)-hydroxylamine (8m). Via the general procedure, **7f** (26.0 mg, 0.114 mmol), D-galactose (22.6 mg, 0.125 mmol), and AcOH (6.5 μL, 0.114 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8m** (TLC R_f = 0.55 in 10:1 CH_2Cl_2/MeOH) as a white powder (26.2 mg, 59% yield). The product comprised an inseparable mixture of β-pyranoside (59%) and β-furanoside (41%) isomers. ESI-MS *m*/*z* (M+H) calculated for $C_{21}H_{28}NO_6$ 390.2, observed 390.2. *O*-Benzyl-*N*-(4-methylbenzyl)-*N*-(β-D-galactopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.35–7.15 (m, 9H), 4.60 (A of AB, 1H, *J* =9.6), 4.51 (B of AB, 1H, *J* = 9.6), 4.15 (A of AB, 1H, *J* = 12.1), 4.07 (A of AB, 1H, *J* = 12.1), 3.99 (d, 1H, *J* = 8.9, H-1), 3.91 (m, 1H, H-2), 3.81 (m, 2H, H-4, H-6), 3.70 (m, 1H, H-6'), 3.43 (m, 2H, H-3, H-5), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.2, 138.0, 135.6, 131.3, 130.5, 129.9, 129.3, 94.1, 78.6, 77.8, 76.5, 70.8, 69.1, 62.8, 57.2, 21.2. *O*-Benzyl-*N*-(4-methylbenzyl)-*N*-(β-D-galactofuranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.35–7.15 (m, 9H), 4.56 (m, 2H), 4.53 (m, 1H, H-1), 4.38 (m, 1H, H-2), 4.13 (m, 1H, H-3), 4.11 (m, 2H), 3.91 (m, 1H, H-4), 3.86–3.37 (m, 3H, H-5, H-6, H-6'), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.2, 138.0, 135.8, 131.2, 130.3, 129.9, 129.2, 98.9, 83.0, 78.7, 78.3, 77.3, 72.0, 69.1, 64.5, 58.5, 21.2.

4.5.7.14. *O*-Methyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactosyl)hydroxylamine (8n). Via the general procedure, **7a** (23.0 mg, 0.152 mmol), 2-aminoacetyl-2-deoxy-D-galactose (37.0 mg, 0.167 mmol), and AcOH (8.7 μL, 0.152 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8n** (TLC R_f = 0.32 in 10:1 CH_2Cl_2/MeOH) as a white powder (42.1 mg, 78% yield). The product comprised an inseparable mixture of β-furanoside (59%) and β-pyranoside (41%) isomers. ESI-MS *m*/*z* (M+H) calculated for $C_{17}H_{27}N_2O_6$ 355.2, observed 355.2. *O*-Methyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactofuranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.26 (m, 2H), 7.11 (m, 2H), 4.69 (dd, 1H, *J* = 8.2, 6.9, H-2), 4.43 (d, 1H, *J* = 6.9, H-1), 4.16–3.82 (m, 7H, H-3–6), 3.36 (s, 3H), 2.31 (s, 3H), 1.98 (s, 3H). *O*-Methyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.26 (m, 2H), 7.11 (m, 2H), 4.26–3.81 (m, 2H), 4.23 (m, 1H, H-2), 4.14 (d, 1H, *J* = 9.8, H-1), 3.84 (m, 1H, H-6), 3.83 (m, 1H, H-4), 3.74 (m, 1H, H-6'), 3.50 (dd, 1H, *J* = 10.1, 3.2, H-3), 3.43 (m, 1H, H-5), 3.23 (s, 3H), 2.31 (s, 3H), 2.01 (s, 3H).

4.5.7.15. *O*-Ethyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactosyl)hydroxylamine (8o). Via the general procedure, **7b** (14.7 mg, 0.089 mmol), 2-aminoacetyl-2-deoxy-D-galactose (21.6 mg, 0.098 mmol), and AcOH (5.0 μL, 0.089 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8o** (TLC R_f = 0.22 in 10:1 CH_2Cl_2/MeOH) as a white powder (25.1 mg, 77% yield). The product comprised an inseparable mixture of β-pyranoside (59%) and β-furanoside (41%) isomers. ESI-MS *m*/*z* (M+H) calculated for $C_{18}H_{29}N2O_6$ 369.2, observed 369.2. *O*-Ethyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.25 (m, 2H), 7.11 (m, 2H), 4.26–3.40 (m, 11H, H-1–6), 2.31 (s, 3H, 2.01 (s, 3H), 0.89 (t, 3H, *J* = 7.1). *O*-Ethyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactofuranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.25 (m, 2H), 7.11 (m, 2H), 4.67 (dd, 1H, *J* = 8.2, 6.9, H-2), 4.46 (d, 1H, *J* = 6.9, H-1), 4.26–3.40 (m, 9H), 2.31 (s, 3H), 1.98 (s, 3H), 0.98 (t, 3H, *J* = 7.1).

4.5.7.16. *N*-(4-Methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactosyl)-*O*-*iso*-propylhydroxylamine (8p). Via the general procedure, **7c** (26.1 mg, 0.146 mmol), 2-aminoacetyl-2-deoxy-D-galactose (35.4 mg, 0.160 mmol), and AcOH (8.3 μL, 0.146 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8p** (TLC R_f = 0.32 and 0.22 in 10:1 CH_2Cl_2/MeOH) as a white powder (35.7 mg, 64% yield). The product comprised an inseparable mixture of β-pyranoside (61%) and β-furanoside (39%) isomers. ESI-MS *m*/*z* (M+H) calculated for $C_{19}H_{31}N_2O_6$ 383.2, observed 383.2.

O-*N*-(4-Methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactopyranosyl)-*O*-*iso*-propylhydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.26 (m, 2H), 7.10 (m, 2H), 4.25–4.10 (m, 2H, H-1, H-2), 4.10–3.69 (m, 2H), 3.88 (m, 1H, H-6), 3.85 (m, 1H, H-4), 3.71 (m, 1H, H-6'), 3.55 (dd, 1H, J = 9.6, 3.0, H-3), 3.47 (dd, 1H, J = 7.0, 5.0, H-5), 3.28 (m, 1H), 2.31 (s, 3H), 2.03 (s, 3H), 1.01 (d, 3H, J = 5.8), 0.68 (d, 3H, J = 6.0). *N*-(4-Methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactofuranosyl)-*O*-*iso*-propylhydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.26 (m, 2H), 7.10 (m, 2H), 4.67 (dd, 1H, J = 8.0, 7.1, H-2), 4.49 (d, 1H, J = 7.1, H-1), 4.05 (m, 1H, H-3), 4.25–3.58 (m, 6H), 3.78 (m, 1H), 2.30 (s, 3H), 1.97 (s, 3H), 1.07 (d, 3H, J = 6.0), 1.03 (d, 3H, J = 6.2).

4.5.7.17. *O*-*tert*-Butyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactosyl)-hydroxylamine (8q). Via the general procedure, **7d** (49.8 mg, 0.258 mmol), 2-aminoacetyl-2-deoxy-D-galactose (62.7 mg, 0.283 mmol), and AcOH (14.8 μL, 0.258 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8q** (TLC R_f = 0.27 in 10:1 CH_2Cl_2/MeOH) as a white powder (17.7 mg, 17% yield). ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.16 (m, 2H), 6.98 (m, 2H), 4.65–3.39 (m, 9H), 2.20 (s, 3H), 1.26–0.69 (m, 9H). ESI-MS m/z (M+H) calculated for $C_{20}H_{33}N_2O_6$ 397.2, observed 397.2.

4.5.7.18. *O*-Allyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactosyl)hydroxylamine (8r). Via the general procedure, **7e** (21.8 mg, 0.123 mmol), 2-aminoacetyl-2-deoxy-D-galactose (29.9 mg, 0.135 mmol), and AcOH (7.0 μL, 0.123 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8r** (TLC R_f = 0.27 and 0.17 in 10:1 CH_2Cl_2/MeOH) as a white powder (32.4 mg, 69% yield). The product comprised an inseparable mixture of β-pyranoside (64%) and β-furanoside (36%) isomers. ESI-MS m/z (M+H) calculated for $C_{19}H_{29}N_2O_6$ 381.2, observed 381.2. *O*-Allyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.26 (m, 2H), 7.11 (m, 2H), 5.67 (ddt, 1H, J = 17.0, 10.2, 6.5), 5.19–5.01 (m, 2H), 4.27–4.14 (m, 2H, H-1, H-2), 4.14–3.63 (m, 4H), 3.86 (m, 1H, H-6), 3.85 (m, 1H, H-4), 3.73 (dd, 1H, J = 11.4, 5.0, H-6'), 3.51 (dd, 1H, J = 9.7, 3.2, H-3), 3.44 (m, 1H, H-5), 2.32 (s, 3H), 2.01 (s, 3H). *O*-Allyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactofuranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.26 (m, 2H), 7.11 (m, 2H), 5.77 (ddt, 1H, J = 17.3, 10.5, 6.2), 5.19–5.01 (m, 2H), 4.70 (dd, 1H, J = 8.2, 7.0, H-2), 4.46 (d, 1H, J = 6.9, H-1), 4.09 (m, 1H, H-3), 4.27–3.63 (m, 8H), 2.32 (s, 3H), 1.97 (s, 3H).

4.5.7.19. *O*-Benzyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactosyl)hydroxylamine (8s). Via the general procedure, **7f** (23.2 mg, 0.102 mmol), 2-aminoacetyl-2-deoxy-D-galactose (24.8 mg, 0.112 mmol), and AcOH (5.8 μL, 0.102 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8s** (TLC R_f = 0.36 in 10:1 CH_2Cl_2/MeOH) as a white powder (26.9 mg, 61% yield). The product comprised an inseparable mixture of β-pyranoside (49%) and β-furanoside (51%) isomers. ESI-MS m/z (M+H) calculated for $C_{23}H_{31}N_2O_6$ 431.2, observed 431.2. *O*-Benzyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.32–7.10 (m, 9H), 4.66 (d, 1H, J = 9.3, H-1), 4.30 (m, 1H, H-2), 4.40–3.59 (m, 4H), 3.84 (m, 2H, H-4, H-6), 3.71 (m, 1H, H-6'), 3.51 (dd, 1H, J = 10.1, 3.1, H-3), 3.44 (m, 1H, H-5), 2.34 (s, 3H), 2.06 (s, 3H). *O*-Benzyl-*N*-(4-methylbenzyl)-*N*-(2-aminoacetyl-2-deoxy-β-D-galactofuranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.32–7.10 (m, 9H), 4.84 (dd, 1H, J = 8.4, 7.2, H-2), 4.50 (d, 1H, J = 7.1, H-1), 4.11 (m, 1H, H-3), 4.39–3.60 (m, 8H), 2.34 (s, 3H), 2.00 (s, 3H).

4.5.7.20. *O*-Methyl-*N*-(4-methylbenzyl)-*N*-(D-mannosyl)hydroxylamine (8t). Via the general procedure, **7a** (22.0 mg, 0.146 mmol), D-mannose (29.0 mg, 0.160 mmol), and AcOH (8.3 μL, 0.146 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8t** (TLC R_f = 0.48 in 10:1 CH_2Cl_2/MeOH) as a white powder (41.6 mg, 91% yield). The product comprised an inseparable mixture of α-pyranoside (41%), β-pyranoside (37%), and α-furanoside (21%) isomers. ESI-MS m/z (M+H) calculated for $C_{15}H_{24}NO_6$ 314.2, observed 314.1. *O*-Methyl-*N*-(4-methylbenzyl)-*N*-(α-D-mannopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.20 (m, 4H), 4.04 (d, 1H, J = 3.0, H-1), 3.61 (m, 1H, H-3), 3.41 (dd, 1H, J = 9.3, 3.0, H-2), 4.31–3.19 (m, 6H), 3.23 (s, 3H), 3.22 (m, 1H), 2.32 (s, 3H). *O*-Methyl-*N*-(4-methylbenzyl)-*N*-(β-D-mannopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.20 (m, 4H), 4.27 (d, 1H, J = 12.8, H-1), 3.88 (m, 1H, H-2), 4.41–3.52 (m, 7H), 3.33 (s, 3H), 2.32 (s, 3H). *O*-Methyl-*N*-(4-methylbenzyl)-*N*-(α-D-mannofuranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.20 (m, 4H), 4.54 (d, 1H, J = 6.6, H-1), 4.35 (dd, 1H, J = 6.6, 4.6, H-2), 4.24–3.53 (m, 7H), 3.34 (s, 3H), 2.32 (s, 3H).

4.5.7.21. *O*-Ethyl-*N*-(4-methylbenzyl)-*N*-(D-mannosyl)hydroxylamine (8u). Via the general procedure, **7b** (15.2 mg, 0.092 mmol), D-mannose (18.2 mg, 0.101 mmol), and AcOH (5.0 μL, 0.092 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8u** (TLC R_f = 0.27 in 10:1 CH_2Cl_2/MeOH) as a white powder (26.3 mg, 88% yield). The product comprised an inseparable mixture of α-pyranoside (39%), β-pyranoside (39%), and α-furanoside (22%) isomers. ESI-MS m/z (M+H) calculated for $C_{16}H_{26}NO_6$ 328.2, observed 328.2. *O*-Ethyl-*N*-(4-methylbenzyl)-*N*-(α-D-mannopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.27 (m, 2H), 7.12 (m, 2H), 4.29–3.28 (m, 4H), 4.04 (d, 1H, J = 3.0, H-1), 3.75 (m, 1H, H-6), 3.62 (m, 3H, H-3, H-4, H-6'), 3.39 (dd, 1H, J = 9.4, 3.1, H-2), 3.21 (ddd, 1H, J = 8.2, 5.9, 2.3, H-5), 2.32 (s, 3H), 0.99–0.90 (m, 3H). *O*-Ethyl-*N*-(4-methylbenzyl)-*N*-(β-D-mannopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.27 (m, 2H), 7.12 (m, 2H), 4.27 (d, 1H, J = 13.1), 4.24–3.28 (m, 10H), 2.32 (s, 3H), 0.99–0.90 (m, 3H). *O*-Ethyl-*N*-(4-methylbenzyl)-*N*-(α-D-mannofuranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.27 (m, 2H), 7.12 (m, 2H), 4.54 (d, 1H, J = 6.4, H-1), 4.34 (dd, 1H, J = 6.3, 4.6, H-2), 4.24–3.28 (m, 9H), 2.32 (s, 3H), 0.99–0.90 (m, 3H).

4.5.7.22. *N*-(4-Methylbenzyl)-*N*-(D-mannosyl)-*O*-*iso*-propylhydroxylamine (8v). Via the general procedure, **7c** (15.2 mg, 0.092 mmol), D-mannose (18.2 mg, 0.101 mmol), and AcOH (5.0 μL, 0.092 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8v** (TLC R_f = 0.30 in 10:1 CH_2Cl_2/MeOH) as a white powder (26.3 mg, 88% yield). The product comprised an inseparable mixture of α-pyranoside (39%), β-pyranoside (39%), and α-furanoside (22%) isomers. ESI-MS m/z (M+H) calculated for $C_{17}H_{28}NO_6$ 342.2, observed 342.2. *N*-(4-Methylbenzyl)-*N*-(α-D-mannopyranosyl)-*O*-*iso*-propylhydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.27 (m, 2H), 7.11 (m, 2H), 4.14–3.57 (m, 3H), 4.03 (d, 1H, J = 3.1, H-1), 3.75 (m, 1H, H-6), 3.59 (m, 3H, H-3, H-4, H-6'), 3.34 (dd, 1H, J = 9.4, 3.1, H-2), 3.15 (ddd, 1H, J = 9.5, 6.1, 2.2, H-5), 2.31 (s, 3H), 1.11–0.95 (m, 6H). *N*-(4-Methylbenzyl)-*N*-(β-D-mannopyranosyl)-*O*-*iso*-propylhydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.27 (m, 2H), 7.11 (m, 2H), 4.28 (d,

1H, *J* = 13.6, H-1), 4.04 (m, 1H, H-2), 4.14–3.57 (m, 8H), 2.31 (s, 3H), 1.11–0.95 (m, 6H). *N*-(4-Methylbenzyl)-*N*-(α-D-mannofuranosyl)-*O*-*iso*-propylhydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 4.52 (d, 1H, *J* = 6.8, H-1), 4.37 (dd, 1H, *J* = 6.5, 4.6, H-2), 4.20 (dd, 1H, *J* = 4.6, 2.4, H-3), 4.14–3.57 (m, 7H), 2.31 (s, 3H), 1.11–0.95 (m, 6H).

4.5.7.23. *O*-*tert*-Butyl-*N*-(4-methylbenzyl)-*N*-(D-mannosyl)-hydroxylamine (8w). Via the general procedure, **7d** (21.7 mg, 0.112 mmol), D-mannose (22.2 mg, 0.123 mmol), and AcOH (6.4 μL, 0.112 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8w** (TLC R_f = 0.47 in 10:1 CH_2Cl_2/MeOH) as a white powder (18.4 mg, 46% yield). ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.28–6.95 (m, 4H), 3.52–2.80 (m, 9H), 2.21 (s, 3H), 1.36–0.74 (m, 9H). ESI-MS *m*/*z* (M+H) calculated for $C_{18}H_{30}NO_6$ 356.2, observed 356.2.

4.5.7.24. *O*-Allyl-*N*-(4-methylbenzyl)-*N*-(D-mannosyl)hydroxylamine (8x). Via the general procedure, **7e** (29.9 mg, 0.169 mmol), D-mannose (33.4 mg, 0.185 mmol), and AcOH (9.7 μL, 0.169 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8x** (TLC R_f = 0.40 in 10:1 CH_2Cl_2/MeOH) as a white powder (48.5 mg, 85% yield). The product comprised an inseparable mixture of α-pyranoside (39%), β-pyranoside (40%), and α-furanoside (21%) isomers. ESI-MS *m*/*z* (M+H) calculated for $C_{17}H_{26}NO_6$ 340.2, observed 340.2. *O*-Allyl-*N*-(4-methylbenzyl)-*N*-(α-D-mannopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.29 (m, 2H), 7.12 (m, 2H), 5.80–5.62 (m, 1H), 5.14–5.03 (m, 2H), 4.06 (m, 1H, H-1), 3.76 (m, 1H, H-6), 3.62 (m, 3H, H-3, H-4, H-6'), 4.12–3.60 (m, 4H), 3.40 (dd, 1H, *J* = 9.1, 2.8, H-2), 3.22 (ddd, 1H, *J* = 9.6, 5.8, 2.2, H-5), 2.32 (s, 3H). *O*-Allyl-*N*-(4-methylbenzyl)-*N*-(β-D-mannopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.29 (m, 2H), 7.12 (m, 2H), 5.80–5.62 (m, 1H), 5.14–5.03 (m, 2H), 4.29 (d, 1H, *J* = 13.2, H-1), 3.92 (m, 1H, H-2), 4.25–3.60 (m, 9H), 2.32 (s, 3H). *O*-Allyl-*N*-(4-methylbenzyl)-*N*-(α-D-mannofuranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.29 (m, 2H), 7.12 (m, 2H), 5.80–5.62 (m, 1H), 5.14–5.03 (m, 2H), 4.56 (d, 1H, *J* = 6.6, H-1), 4.37 (dd, 1H, *J* = 6.4, 4.6, H-2), 4.25–3.60 (m, 9H), 2.32 (s, 3H).

4.5.7.25. *O*-Benzyl-*N*-(4-methylbenzyl)-*N*-(D-mannosyl)hydroxylamine (8y). Via the general procedure, **7f** (29.5 mg, 0.130 mmol), D-mannose (25.7 mg, 0.143 mmol), and AcOH (7.4 μL, 0.130 mmol) were reacted. The crude product mixture was purified by SiO_2 column chromatography eluting with 10:1 CH_2Cl_2/MeOH to afford **8y** (TLC R_f = 0.39 in 10:1 CH_2Cl_2/MeOH) as a white powder (44.4 mg, 88% yield). The product comprised an inseparable mixture of α-pyranoside (40%), β-pyranoside (39%), and α-furanoside (21%) isomers. ESI-MS *m*/*z* (M+H) calculated for $C_{21}H_{28}NO_6$ 390.2, observed 390.2. *O*-Benzyl-*N*-(4-methylbenzyl)-*N*-(α-D-mannopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.33 (m, 2H), 7.25 (m, 3H), 7.16 (m, 2H), 7.11 (m, 2H), 4.53–3.58 (m, 4H), 4.11 (d, 1H, *J* = 3.0, H-1), 3.76 (m, 1H, H-6), 3.63 (m, 3H, H-3, H-4, H-6'), 3.40 (dd, 1H, *J* = 9.4, 3.2, H-2), 3.23 (ddd, 1H, *J* = 9.6, 5.8, 2.2, H-5), 2.34 (s, 3H). *O*-Benzyl-*N*-(4-methylbenzyl)-*N*-(β-D-mannopyranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.33 (m, 2H), 7.25 (m, 3H), 7.16 (m, 2H), 7.11 (m, 2H), 4.53–3.58 (m, 9H), 4.31 (d, 1H, *J* = 13.6, H-1), 3.94 (m, 1H, H-2), 2.34 (s, 3H). *O*-Benzyl-*N*-(4-methylbenzyl)-*N*-(α-D-mannofuranosyl)hydroxylamine: ^{1}H NMR (MeOD-d_4, 400 MHz) δ 7.33 (m, 2H), 7.25 (m, 3H), 7.16 (m, 2H), 7.11 (m, 2H), 4.62 (d, 1H, *J* = 6.0, H-1), 4.45 (m, 1H, H-2), 4.53–3.58 (m, 9H), 2.34 (s, 3H).

4.5.8. General procedure for generation of aglycons 2

Digitoxigenone[9c] (9.48 g, 25.5 mmol) was dissolved in methanol (2.2 mL/mmol) and pyridine (2.2 equiv). Oxyamine hydrochloride (1.6 equiv) was added, and the solution was stirred for 2.5 h then concentrated. The resulting residue was dissolved in CH_2Cl_2 and washed with 1 M HCl, brine, dried over $MgSO_4$, filtered, and then concentrated. The mixture of oxime diastereomers (1 equiv) was suspended in ethanol (2.9 mL/mmol) and cooled to 0 °C. Borane *tert*-butylamine complex (3.3 equiv) was added, followed by the dropwise addition 10% aq HCl (2.7 mL/mmol). The reaction mixture was stirred at 0 °C for 2.5 h. After this time, Na_2CO_3 was added until gas evolution ceased, and the mixture was partitioned between water and $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting diastereomeric mixture was resolved via SiO_2 column chromatography.

4.5.8.1. 3β-Ethoxyaminodigitoxigenin 2b. Via the general procedure, digitoxigenone (200 mg, 0.537 mmol) was converted to a mixture of ethoxyamine diastereomers. The mixture was purified by SiO_2 column chromatography eluting with 1:1 EtOAc/hexane to elute **2b** (β-isomer) (TLC R_f = 0.24 in 1:1 EtOAc/hexane) and then with 3:2 EtOAc/hexane to elute the undesired α-isomer (TLC R_f = 0.07 in 1:1 EtOAc/hexane). Aglycon **2b** was obtained as a foam (76.5 mg, 44% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (m, 1H), 5.01 (A of ABX, 1H, *J* = 18.1, 1.2), 4.82 (B of ABX, 1H, *J* = 18.1, 1.7), 3.73 (q, 2H), 3.24 (br s, 1H), 2.79 (m, 1H), 2.15 (m, 2H), 1.85 (m, 3H), 1.73–1.22 (m, 17H), 1.17 (t, 3H), 0.94 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.9, 174.6, 117.5, 85.5, 73.5, 69.6, 55.0, 50.9, 49.6, 41.8, 40.0, 36.6, 35.6, 35.5, 33.1, 30.4, 28.7, 26.9, 26.6, 25.3, 23.7, 21.2, 21.0, 15.8, 14.3; ESI-MS *m*/*z* (M+H) calculated for $C_{25}H_{40}NO_4$ 418.3, observed 418.3. The undesired α-isomer was obtained as a foam (69.5 mg, 40% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (s, 1H), 5.00 (A of ABX, 1H, *J* = 18.1, 1.4), 4.82 (B of ABX, 1H, *J* = 18.1, 1.5), 3.74 (q, 2H), 2.91 (m, 1H), 2.77 (m, 1H), 2.16 (m, 2H), 1.85 (m, 3H), 1.74–1.22 (m, 17H), 1.18 (t, 3H), 0.94 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.9, 174.7, 117.7, 85.6, 77.4, 73.6, 70.1, 60.6, 51.1, 49.7, 42.1, 41.7, 40.1, 36.4, 35.6, 35.3, 33.4, 31.3, 27.3, 27.0, 25.6, 23.6, 21.7, 21.1,15.9, 14.4.

4.5.8.2. 3β-*iso*-Propoxyaminodigitoxigenin 2c. Via the general procedure, digitoxigenone (200 mg, 0.537 mmol) was converted to a mixture of *iso*-propoxyamine diastereomers. The mixture was purified by SiO_2 column chromatography eluting with 2:3 EtOAc/hexane to elute **2c** (β-isomer) (TLC R_f = 0.30 in 2:3 EtOAc/hexane) and then the undesired α-isomer (TLC R_f = 0.16 in 2:3 EtOAc/hexane). Aglycon **2c** was obtained as a foam (62.5 mg, 32% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (m, 1H), 5.01 (A of ABX, 1H, *J* = 18.0, 1.3), 4.91 (B of ABX, 1H, *J* = 18.0, 1.6), 3.81 (sept, 1H), 3.20 (br s, 1H), 2.77 (m, 1H), 2.16 (m, 2H), 1.86 (m, 3H), 1.73–1.22 (m, 17H), 1.14 (d, 6H), 0.93 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.0, 174.7, 117.7, 85.7, 77.4, 74.8, 73.6, 55.2, 51.1, 49.8, 42.0, 40.2, 36.8, 35.8, 35.6, 33.3, 30.6, 29.0, 27.0, 26.8, 23.9, 21.5, 21.3, 21.2, 15.9; ESI-MS *m*/*z* (M+H) calculated for $C_{26}H_{42}NO_4$ 432.3, observed 432.4. The undesired α-isomer was obtained as a foam (66.9 mg, 34% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (s, 1H), 5.00 (A of ABX, 1H, *J* = 18.1, 1.6), 4.81 (B of ABX, 1H, *J* = 18.1, 1.7), 3.82 (sept, 1H), 2.87 (m, 1H), 2.77 (m, 1H), 2.15 (m, 2H), 1.84 (m, 3H), 1.74–1.22 (m, 17H), 1.15 (d, 6H), 0.93 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.7, 174.6, 117.6, 85.5, 77.3, 75.2, 73.5, 60.5, 50.9, 49.6, 42.0, 41.6, 40.0, 36.3, 35.5, 35.3, 33.2, 31.3, 27.2, 26.9, 25.6, 23.5, 21.6, 21.4, 20.9, 15.8.

4.5.8.3. 3β-*tert*-Butoxyaminodigitoxigenin 2d. Via the general procedure, digitoxigenone (200 mg, 0.537 mmol) was converted to a mixture of *tert*-butoxyamine diastereomers. The mixture was purified by SiO_2 column chromatography eluting with

1:4 EtOAc/toluene to elute **2d** (β-isomer) (TLC R_f = 0.19 in 1:4 EtOAc/toluene) and then the undesired α-isomer (TLC R_f = 0.14 in 1:4 EtOAc/toluene). Aglycon **2d** was obtained as a white solid (37.2 mg, 25% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (br t, 1H), 5.00 (A of ABX, 1H, J = 17.9, 1.3), 4.81 (B of ABX, 1H, J = 17.9, 1.7), 3.12 (br s, 1H), 2.78 (m, 1H), 2.16 (m, 2H), 1.86 (m, 3H), 1.73–1.22 (m, 17H), 1.18 (s, 9H), 0.93 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.8, 174.7, 117.8, 85.8, 76.5, 73.6, 55.2, 51.1, 49.8, 42.1, 40.2, 36.9, 35.8, 35.6, 33.4, 30.8, 29.0, 27.2, 27.1, 26.8, 24.0, 23.1, 21.4, 21.3, 15.9; ESI-MS m/z (M+H) calculated for $C_{27}H_{44}NO_4$ 446.3, observed 446.4. The undesired α-isomer was obtained as a white solid (83.8 mg, 57% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (s, 1H), 5.00 (A of ABX, 1H, J = 18.0, 1.3), 4.81 (B of ABX, 1H, J = 18.0, 1.4), 4.71 (br s 1H), 2.77 (m, 2H), 2.15 (m, 2H), 1.92–1.22 (m, 20H), 1.17 (s, 9H), 0.93 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.9, 174.7, 117.7, 85.6, 77.4, 76.4, 73.6, 60.5, 51.1, 49.7, 42.1, 41.9, 40.1, 36.4, 35.6, 35.5, 31.7, 31.7, 27.3, 27.1, 26.0, 23.7, 21.7, 21.1, 15.9.

4.5.8.4. 3β-Benzyloxyaminodigitoxigenin 2e. Via the general procedure, digitoxigenone (200 mg, 0.537 mmol) was converted to a mixture of benzyloxyamine diastereomers. The mixture was purified by SiO_2 column chromatography eluting with 2:3 EtOAc/toluene to elute **2e** (β-isomer) (TLC R_f = 0.24 in 2:3 EtOAc/hexane) and then the undesired α-isomer (TLC R_f = 0.13 in 2:3 EtOAc/hexane). Aglycon **2e** was obtained as a foam (77.5 mg, 37% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (m, 5H), 5.86 (s, 1H), 5.43 (br s, 1H), 5.00 (A of ABX, 1H, J = 18.1, 1.4), 4.81 (B of ABX, 1H, J = 18.1, 1.8), 4.70 (s, 2H), 3.29 (s, 1H), 2.77 (m, 1H), 2.15 (m, 2H), 1.85 (m, 3H), 1.74–1.22 (m, 17H), 0.94 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.0, 174.7, 138.2, 128.6, 128.4, 127.9, 117.7, 85.6, 73.6, 55.1, 51.1, 49.8, 41.9, 40.1, 36.7, 35.8, 35.6, 33.3, 30.5, 28.8, 27.0, 26.7, 23.9, 23.0, 21.3, 21.2, 15.9; ESI-MS m/z (M+H) calculated for $C_{30}H_{42}NO_4$ 480.3, observed 480.4. The undesired α-isomer was obtained as a white powder (73.1 mg, 35% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (m, 5H), 5.87 (br t, 1H), 5.48 (br s, 1H), 4.99 (A of ABX, 1H, J = 18.1, 1.4), 4.81 (B of ABX, 1H, J = 18.1, 1.8), 4.73 (s, 2H), 2.96 (m, 1H), 2.77 (m, 1H), 2.15 (m, 2H), 1.84 (m, 3H), 1.86–1.00 (m, 17H), 0.93 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.8, 174.7, 138.0, 128.5, 128.4, 128.0, 117.7, 85.6, 77.1, 73.6, 60.6, 51.1, 49.7, 42.1, 41.7, 40.1, 36.4, 35.6, 35.4, 33.4, 31.2, 27.3, 27.0, 25.6, 23.6, 21.7, 21.1, 15.9.

4.5.8.5. 3β-(2-Butyloxyamino)digitoxigenin 2f. Via the general procedure, digitoxigenone (890 mg, 0.239 mmol) was converted to a mixture of 2-butyloxyamine diastereomers. The mixture was purified by SiO_2 column chromatography eluting with 2:3 EtOAc/hexane to elute **2f** (3β-isomer) (TLC R_f = 0.37 in 2:3 EtOAc/hexane) and then the undesired 3α-isomer (TLC R_f = 0.23 in 2:3 EtOAc/hexane). Aglycon **2f** was obtained as a foam (33.8 mg, 33% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.88 (m, 1H), 5.00 (A of ABX, 1H, J = 18.1, 1.6), 4.81 (B of ABX, 1H, J = 18.1, 1.7), 3.59 (dq, 1H, J = 12.6, 6.0), 3.22 (m, 1H), 2.79 (m, 1H), 2.15 (m, 2H), 1.77–1.16 (m, 18H), 1.13 (d, 3H, J = 6.4), 0.93 (s, 3H), 0.90 (t, 3H, J = 7.7), 0.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.6, 174.5, 117.7, 85.6, 80.0, 73.4, 55.0, 55.0, 50.9, 49.6, 41.9, 40.0, 36.6, 35.6, 35.5, 33.2, 30.5, 28.8, 28.7, 28.2, 28.1, 26.9, 26.6, 23.8, 23.0, 22.9, 21.2, 21.0, 18.8, 15.8, 9.98, 9.95. ESI-MS m/z (M+H) calculated for $C_{27}H_{44}NO_4$ 446.3, observed 446.3. The undesired 3α-isomer was obtained as a white powder (45.2 mg, 45% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.87 (m, 1H), 4.99 (A of ABX, 1H, J = 18.0, 1.5), 4.81 (B of ABX, 1H, J = 18.0, 1.7), 3.60 (dq, 1H, J = 12.3, 6.2), 2.88 (m, 1H), 2.77 (m, 1H), 2.15 (m, 2H), 1.84 (m, 3H), 1.86–1.00 (m, 17H), 1.13 (d, 3H, J = 5.5), 0.93 (s, 3H), 0.91 (m, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.6, 174.5, 117.6, 85.6, 80.44, 80.40, 73.4, 60.5, 50.9, 49.5, 42.0, 41.6, 39.9, 36.2, 35.4, 35.3, 35.2, 33.2, 31.2, 28.2, 27.1, 26.8, 25.61, 25.57, 23.5, 21.6, 20.9, 18.8, 15.7, 10.0, 9.9.

4.5.8.6. 3β-Cyclopentoxyaminodigitoxigenin 2g. Via the general procedure, digitoxigenone (92 mg, 0.247 mmol) was converted to a mixture of cyclopentoxyamine diastereomers. The mixture was purified by SiO_2 column chromatography eluting with 2:3 EtOAc/hexane to elute **2g** (β-isomer) (TLC R_f = 0.25 in 2:3 EtOAc/hexane) and then the undesired α-isomer (TLC R_f = 0.11 in 2:3 EtOAc/hexane). Aglycon **2g** was obtained as a foam (31.7 mg, 28% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.87 (m, 1H), 5.00 (A of ABX, 1H, J = 18.1, 1.7), 4.82 (B of ABX, 1H, J = 18.1, 1.8), 4.17 (m, 1H), 3.21 (s, 1H), 2.79 (m, 1H), 2.15 (m, 2H), 1.85 (m, 3H), 1.77–1.16 (m, 26H), 0.93 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.7, 174.6, 117.6, 85.6, 84.6, 73.5, 55.0, 50.9, 49.6, 41.8, 40.0, 36.6, 35.6, 35.5, 33.2, 31.7, 30.5, 29.7, 28.8, 26.9, 26.6, 23.8, 23.61, 23.58, 22.9, 21.2, 21.0, 15.8. ESI-MS m/z (M+H) calculated for $C_{28}H_{44}NO_4$ 458.3, observed 458.3. The undesired α-isomer was obtained as a white powder (31.2 mg, 28% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.87 (m, 1H), 4.99 (m, 1H), 4.81 (m, 2H), 4.20 (m, 1H), 2.88 (m, 1H), 2.78 (m, 1H), 2.15 (m, 2H), 1.92–1.00 (m, 29H), 0.93 (s, 3H), 0.87 (s, 3H).

4.5.8.7. 3β-Cyclohexoxyaminodigitoxigenin 2h. Via the general procedure, digitoxigenone (101.4 mg, 0.272 mmol) was converted to a mixture of cyclohexoxyamine diastereomers. The mixture was purified by SiO_2 column chromatography eluting with 2:3 EtOAc/hexane to elute **2h** (β-isomer) (TLC R_f = 0.27 in 2:3 EtOAc/hexane) and then the undesired α-isomer (TLC R_f = 0.16 in 2:3 EtOAc/hexane). Aglycon **2h** was obtained as a foam (17.6 mg, 14% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.88 (m, 1H), 5.00 (A of ABX, 1H, J = 18.2, 1.6), 4.82 (B of ABX, 1H, J = 18.2, 1.8), 3.49 (m, 1H), 3.21 (s, 1H), 2.79 (m, 1H), 2.17 (m, 2H), 1.98–1.16 (m, 31H), 0.93 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.63, 174.6, 117.7, 85.6, 80.6, 73.5, 55.1, 50.9, 49.6, 41.9, 40.0, 36.6, 35.6, 35.5, 33.2, 32.2, 31.7, 30.5, 28.8, 26.9, 26.6, 25.9, 24.21, 24.18, 23.8, 22.9, 21.2, 21.0, 15.8. ESI-MS m/z (M+H) calculated for $C_{29}H_{46}NO_4$ 472.3, observed 472.3. The undesired α-isomer was obtained as a white powder (14.2 mg, 12% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.02 (m, 1H), 5.91 (s, 1H), 4.93 (m, 2H), 4.10 (m, 1H), 2.73 (m, 2H), 2.03 (m, 2H), 1.85–1.01 (m, 31H), 0.86 (s, 3H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.4, 173.9, 116.2, 83.7, 79.5, 73.1, 59.9, 59.7, 50.2, 49.4, 41.3, 41.1, 35.4, 35.1, 32.2, 31.3, 30.5, 27.0, 26.3, 25.6, 25.0, 23.6, 23.4, 21.3, 20.8, 20.6, 15.7, 14.1.

4.5.9. General procedure for generation of neoglycosides 6

Aglycon **2** (1 equiv) and L-xylose (1.1 equiv) were added to a glass vial equipped with a stirring flea and then were dissolved in 9:1 MeOH/$CHCl_3$ (5.6 mL/mmol). AcOH was added (1 equiv) and the reaction mixture was stirred at 40 °C for 4 days. The crude reaction mixture was concentrated, then suspended in 2% MeOH in $CHCl_3$. The crude suspension was purified on a disposable SiO_2 solid-phase extraction column. Three treatments with 2 mL of 3% MeOH/CH_2Cl_2 eluted unreacted aglycon and five treatments with 2 mL of 5% MeOH/CH_2Cl_2 eluted product. After purification, only a single product spot was observed by TLC.

4.5.9.1. 3β-Ethoxyaminodigitoxigen-β-D-xylopyranoside (6b). Via the general procedure, **2b** (10.7 mg, 0.026 mmol), L-xylose (4.2 mg, 0.029 mmol), and AcOH (1.1 μL, 0.026 mmol) were reacted to provide **6b** as a white powder after purification (5.1 mg, 36%). (TLC R_f = 0.53 in 10% MeOH/CH_2Cl_2). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.91 (s, 1H), 4.99–4.87 (m, 4H), 4.48 (m, 1H), 4.10 (s, 1H), 3.91 (m, 1H), 3.87 (d, 1H, J = 7.8), 3.68 (dd, 1H, J = 11.1, 5.2), 3.59 (m, 1H), 3.48–3.09 (m, 5H), 2.92 (t, 1H, J = 10.9), 2.73 (m,

1H), 2.05 (m, 2H), 1.93–1.05 (m, 18H), 0.99 (t, 3H, J = 6.2), 0.88 (s, 3H), 0.76 (s, 3H); HRMS m/z (M+H) calculated for $C_{30}H_{48}NO_8$ 550.3380, observed 550.3371.

4.5.9.2. 3β-*iso*-Propoxyaminodigitoxigen-β-D-xylopyranoside (6c). Via the general procedure, **2c** (13.1 mg, 0.030 mmol), L-xylose (5.0 mg, 0.033 mmol), and AcOH (1.7 μL, 0.030 mmol) were reacted to provide **6c** as a white powder after purification (2.4 mg, 14%). (TLC R_f = 0.42 in 10% MeOH/CH_2Cl_2). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.91 (s, 1H), 4.99–4.87 (m, 4H), 4.48 (m, 1H), 4.09 (s, 1H), 3.98 (m, 1H), 3.89 (d, 1H, J = 8.5), 3.69 (m, 1H), 3.48–3.09 (m, 5H), 2.91 (t, 1H, J = 10.7), 2.73 (m, 1H), 2.05 (m, 2H), 1.86–1.05 (m, 18H), 1.07 (d, 6H, J = 6.2), 0.88 (s, 3H), 0.76 (s, 3H); HRMS m/z (M+H) calculated for $C_{31}H_{50}NO_8$ 564.35404, observed 564.35313.

4.5.9.3. 3β-Benzoxyaminodigitoxigen-β-D-xylopyranoside (6d). Via the general procedure, **2d** (8.9 mg, 0.018 mmol), L-xylose (3.1 mg, 0.020 mmol), and AcOH (1.1 μL, 0.018 mmol) were reacted to provide **6d** as a white powder after purification (3.7 mg, 33%). (TLC R_f = 0.49 in 10% MeOH/CH_2Cl_2). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.33 (m, 5H), 5.91 (s, 1H), 4.99–4.87 (m, 4H), 4.76 (m, 1H), 4.55 (d, 1H, J = 9.6), 4.10 (s, 1H), 3.96 (d, 1H, J = 8.4), 3.68 (dd, 1H, J = 10.7, 5.4), 3.48–3.09 (m, 5H), 2.94 (m, 1H), 2.73 (m, 1H), 2.04 (m, 3H), 1.86–1.05 (m, 18H), 0.91 (s, 3H), 0.77 (s, 3H); HRMS m/z (M+H) calculated for $C_{35}H_{50}NO_8$ 612.3537, observed 612.3534.

4.5.9.4. 3β-*sec*-Butoxyaminodigitoxigen-β-D-xylopyranoside (6e). Via the general procedure, **2e** (19.2 mg, 0.043 mmol), L-xylose (7.0 mg, 0.047 mmol), and AcOH (2.5 μL, 0.043 mmol) were reacted to provide **6e** as a white powder after purification (2.5 mg, 10%). (TLC R_f = 0.36 in 10% MeOH/CH_2Cl_2). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.90 (s, 1H), 4.94 (m, 4H), 4.45 (m, 1H), 4.10 (s, 1H), 3.92–3.08 (m, 6H), 2.91 (m, 1H), 2.72 (m, 1H), 2.04 (m, 2H), 1.86–1.05 (m, 25H), 0.88 (s, 3H), 0.80 (m, 3H), 0.76 (s, 3H); HRMS m/z (M+NH_4) calculated for $C_{32}H_{52}NO_8$ 578.36914, observed 578.36721.

4.5.9.5. 3β-Cyclopentoxyaminodigitoxigen-β-D-xylopyranoside (6f). Via the general procedure, **2f** (11.0 mg, 0.024 mmol), L-xylose (4.0 mg, 0.026 mmol), and AcOH (1.4 μL, 0.024 mmol) were reacted to provide **6f** as a white powder after purification (3.2 mg, 23%). (TLC R_f = 0.40 in 10% MeOH/CH_2Cl_2). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.91 (s, 1H), 4.94 (m, 4H), 4.46 (m, 1H), 4.35 (m, 1H), 4.11 (s, 1H), 3.87 (d, 1H, J = 9.0), 3.68 (dd, 1H, J = 11.0, 5.2), 3.52–3.08 (m, 4H), 2.91 (m, 1H), 2.73 (m, 1H), 2.04 (m, 2H), 1.86–1.05 (m, 27H), 0.88 (s, 3H), 0.76 (s, 3H); HRMS m/z (M+H) calculated for $C_{33}H_{52}NO_8$ 590.36906, observed 590.36964.

4.5.9.6. 3β-Cyclohexoxyaminodigitoxigen-β-D-xylopyranoside (6g). Via the general procedure, **2g** (15.2 mg, 0.032 mmol), L-xylose (5.3 mg, 0.035 mmol), and AcOH (1.8 μL, 0.032 mmol) were reacted to provide **6g** as a white powder after purification (3.3 mg, 17%). (TLC R_f = 0.47 in 10% MeOH/CH_2Cl_2). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.91 (s, 1H), 4.94 (m, 4H), 4.46 (m, 1H), 4.10 (s, 1H), 3.89 (d, 1H, J = 8.3), 3.69 (dd, 1H, J = 11.0, 5.3), 3.60 (m, 1H), 3.52–3.08 (m, 4H), 2.91 (m, 1H), 2.73 (m, 1H), 2.02 (m, 4H), 1.86–1.05 (m, 27H), 0.88 (s, 3H), 0.76 (s, 3H); HRMS m/z (M+H) calculated for $C_{34}H_{54}NO_8$ 604.38553, observed 604.38569.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.09.019.

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