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Convenient synthesis and evaluation of glycosidase inhibitory activity of α- and β-galactose-type valienamines, and some *N*-alkyl derivatives

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Abstract—Valienamine analogues having α- and β-galactose-type structures were synthesized by racemic modification from (1*SR*,2*RS*,3*SR*)-6-methylenecyclohex-4-ene-1,2,3-triol. Four *N*-alkyl derivatives of the β-anomer were readily prepared selectively by treatment of key intermediate 2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-5a-carba-α- and β-L-*arabino*-hex-5(5a)-enopyranosyl bromides with alkyl amines. All compounds were assayed for inhibitory activity against six glycosidases, and the *N*-dodecyl derivative was shown to be a very strong inhibitor of β-galactosidase (IC_{50} 0.01 μM, bovine liver).

1. Introduction

Mutant forms of enzyme proteins have been shown to be labile and rapidly degraded in somatic cells from patients with lysosomal storage diseases.[1] However, they can be stabilized and transported to the lysosomes by competitive inhibitors of low molecular weight (chemical chaperones) for therapeutic purposes. This phenomenon was confirmed for the mutant enzyme causing Fabry disease (α-galactosidase deficiency),[2] and very recently this strategy has been extended to two other diseases involving β-galactosidase deficiency in the central nervous system: GM1-gangliosidosis and Morquio B disease. Some unsaturated carbaglycosylamine derivatives have recently been found with remarkable effects: galactose-type[3] [*N*-octyl-β-D-5aCGal(5,5a)enamine,† GalX **1**] and glucose-type *N*-octyl-β-valienamine[4,5] [*N*-octyl-β-D-5aCGlc(5,5a)enamine, GlcX **2**] for β-galactosidase and β-glucosidase, respectively (Fig. 1). Compound **1** was actually demonstrated[3] to be a very potent inhibitor of human β-galactosidase ($IC_{50} = 0.3$ μM), and has been extensively studied as a candidate novel therapeutic agent for treatment of several human genetic diseases. Thus, such unsaturated 5a-carba-sugars are now regarded as important lead compounds.

2. Results and discussion

We report here a sequence worked out by modification of the route[6] for 5a-carba-α-fucopyranosylamines[7] with nucleophilic substitution of the primary bromo group of 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-5a-carba-α- and β-DL-*arabino*-hex-5(5a)-enopyranosyl bromides‡ (**5α,β**), derived from the alkadiene[8] **4** (Scheme 1). Selective preparation of **4** was also here achieved in a 72% yield

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† For convenience, we herewith propose abbreviations for naming the carba sugar and unsaturated carba sugars as follows: 5a-Carba-α-D-glucopyranose: α-D-5aCGlc; 2-Acetamido-2-deoxy-5a-carba-α-D-glucopyranose: α-D-5aCGlcNAc; 5a-Carba-α-D-glucopyranosylamine (validamine): α-D-5aCGlcamine; 5a-Carba-α-D-*xylo*-hex-(5,5a)-enopyranosylamine (valienamine): α-D-5aCGlc(5,5a)enamine not β-L-5aCIdo(5,5a)enamine. As exemplified above, the (5,5a)-unsaturated 5a-carba-sugar is a named derivative of the parent D-hexopyranose.

‡ In the text use of carba-sugar nomenclature following the IUPAC-IUBMB Nomenclature of Carbohydrates (Recommendation 1996: *Carbohydr. Res.*, **1997**, *297*, 1-92) is discussed. However, in the experimental section, IUPAC nomenclature for bi- and tri-cyclic compounds was used throughout for the sake of general understanding.

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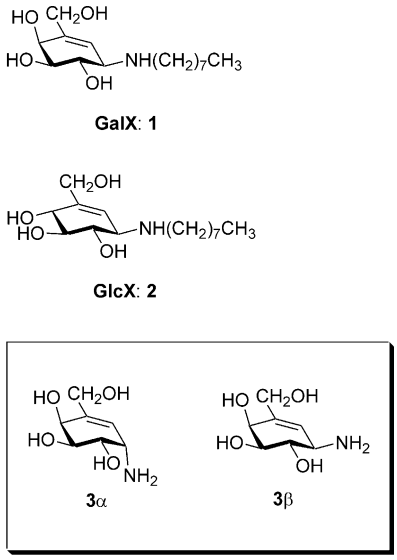
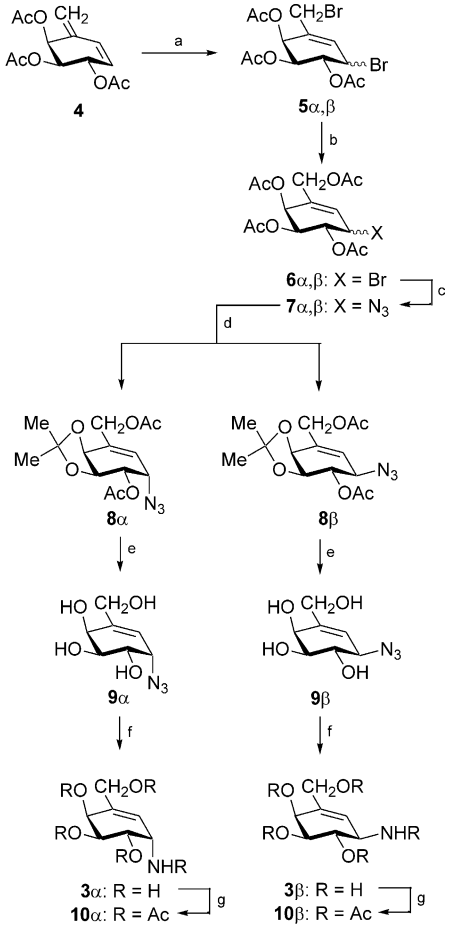


Figure 1.



Scheme 1. Reagents and conditions: (a) Br_2 (molar equiv), CCl_4, 1 h, rt; (b) NaOAc (molar equiv), DMF, 20 h, rt; (c) NaN_3, DMF, r.t.; (d) 1M NaOMe-MeOH, 1 h, rt; $(MeO)_2CMe_2$;, DMF, TsOH hydrate, 1 day, rt; Ac_2O, pyridine; (e) 4 M HCl:THF (1:1), 1 h, reflux; f) Ph_3P (3 molar equiv), 50% aq THF, 1 day, rt; Dowex 50 W×2 (H^+) resin, 1% aq NH_3; g) Ac_2O, pyridine.

by treatment of (1*SR*,2*SR*,3*RS*,4*SR*,6*RS*)-1,2,3-triacetoxy-4-bromo-6-(bromomethyl)cyclohexane[8] with sodium acetate in HMPA at 120 °C.

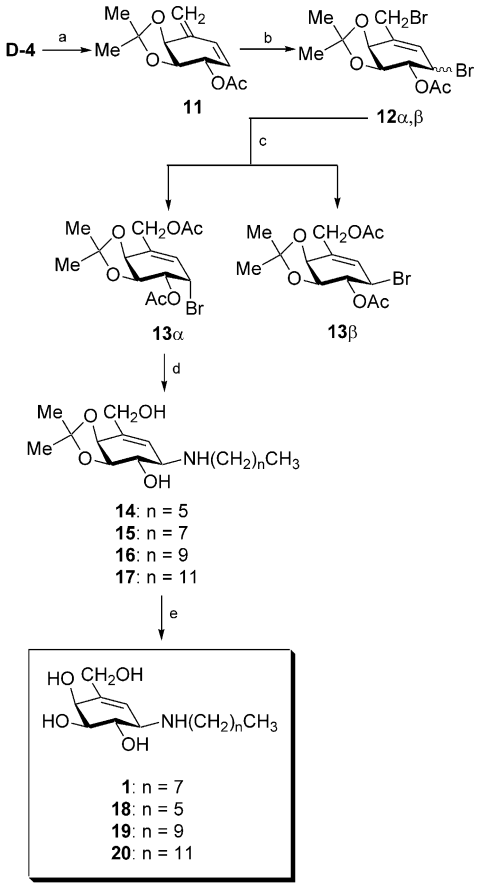
Treatment of **4** with a slight excess of bromine in carbon tetrachloride gave a 90% yield of approximately 1:1 mixture of the 1,4-addition products. The mixture was separable by silica gel chromatography to afford the dibromides[8] **5α** and **5β**. Compound **5α** was treated with sodium acetate to give a mixture of 2,3,4,6-tetra-*O*-acetyl-5a-carba-DL-*arabino*-hex-5(5a)-enopyranosyl bromides (**6α,β**). These results suggest that, although the allylic secondary bromo group remains unchanged, epimerization at C-1 occurs through nucleophilic attack by bromide ions generated in situ. Therefore, the mixture of **5α,β** was directly converted into the bromides **6α,β**, which was without purification treated with sodium azide in DMF at room temperature to give an inseparable 1:1 mixture of the azides[8] **7α,β** in 85% yield. In this case, neighboring group participation by the 2-acetoxyl group at C-1 was first anticipated to give rise to the β-azide **7β** selectively through formation of an intermediate 1,2-acetoxonium ion. However, the allylic carbon atom seems sufficiently active to suffer rear-side attack by an azide anion. Therefore, the mixture of **6α,β** was treated with sodium azide for conversion into a mixture of **7α,β** (85%), which was subsequently subjected to reduction with triphenylphosphine to generate free bases. The free bases were then converted into the *N*-acetyl and penta-*N*,*O*-acetyl derivatives in the usual manner. However, none of the above anomeric pairs could be separated by conventional silica gel chromatography.

O-Deacetylation of **7α,β** under Zemplén conditions gave the tetrols **9α,β**, which were treated with 2,2-dimethoxypropane-TsOH in DMF to afford, after acetylation, a mixture of the 2,3-*O*-isopropylidene derivatives **8α,β** selectively. These compounds were found to be separable on a silica gel column with 1:6 EtOAc/hexane as an eluent, giving **8α** (40%) and **8β** (42%), the ^{1}H NMR spectra of which showed a doublet of doublets (δ 4.25, $J = 3.8$ and 4.1 Hz) and a broad doublet (δ 3.97, $J = 8.9$ Hz) due to the pseudo-equatorial and axial protons on carbon atoms attached to the azido functions, respectively, supporting the proposed structures. Removal of the acetyl and isopropylidene groups of **8α** and **8β** was effected by treatment with 4 M hydrochloric acid at reflux temperature to give the respective azides **9α** (80%) and **9β** (74%). Reduction of the azido group of **9α** and **9β** with triphenylphosphine in 70% aqueous THF afforded, after purification over a column of Dowex 50 W×2 (H^+) resin with 5% aqueous NH_3 as eluent, the free amines[9] **3α** and **3β** in 86 and 86% yields, respectively. Their structures were further verified with ^{13}C and ^{1}H NMR spectra of the respective penta-*N*,*O*-acetyl derivatives[10] **10α** and **10β** obtained by conventional acetylation.

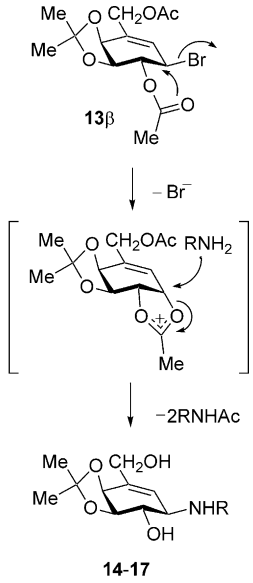
Incorporation of an alkylamino function at C-1 of the allyl bromides **6α,β** was attempted by treatment with an excess of *n*-octylamine. However, a complex mixture of products was formed. Then, the two *cis*-hydroxyl

groups of **6α,β** were protected, with the aim of restricting conformational flexibility and avoiding a possible participation of the 4-hydroxyl (Scheme 2). Thus, the optically pure diene[8,11] **D-4** was first converted into the 3,4-*O*-isopropylidene derivative **11**, which was subsequently treated with bromine to afford the 1,4-addition products, ca. 1.7:1 mixture (76%) of **12α** and **12β**. Treatment of **12α,β** with sodium acetate gave selectively a mixture of the bromides **13α,β**, which was separable by silica gel chromatography, affording **13α** (48%) and **13β** (23%). The ^{1}H NMR signals due to C-1 appeared as a doublet of doublets (δ 4.83, J = 3.9 and 7.7 Hz) and a broad doublet (δ 4.50, J 8.3 Hz), respectively. Reaction of the α-bromide **13α** with 4 molar equiv of octylamine proceeded smoothly in an S_N2 fashion to give the protected *N*-octyl derivative as a single β-amine **15** (68%), which was then treated with aqueous acetic acid and subsequently purified on a column of Dowex 50W×2 (H^+) resin with aqueous ammonia, affording **1**[3] (56%). Similar treatment with hexyl-, decyl- and dodecyl-amines produced the corresponding *N*-alkyl derivatives[12] **14**, **16**, and **17**, which were deprotected to provide the β-amines **18**, **19**, and **20** in 30–65% total yields.

It is interesting to note that, on treatment with alkyl amines, the β-bromide **13β** also gave the β-amines as sole products, conceivably through neighboring group participation with the 2-acetoxyl or hydroxyl group (Scheme 3). Therefore, synthesis of **1** and its analogues would be much improved by use of an intact mixture of **13α,β** as the starting material.



Scheme 2. Reagents and conditions: (a) 1 M NaOMe-MeOH, 1 h, rt; $(MeO)_2Me_2$, DMF, TsOH hydrate, 1 day, rt; Ac_2O, pyridine; (b) Br_2 (molar equiv), CCl_4; rt; (c) NaOAc (1.4 molar equiv), 2 days, rt; (d) for example; decylamine (6 molar equiv), 2-propanol, 3 days, rt; 80% aq AcOH, 8 h, 80 °C, 8 h; Dowex 50 W×2 (H^+) resin, 1% NH_3-MeOH.



Scheme 3.

3. Biological assay

Results of biological assays[13] for inhibitory activity toward several glycohydrolases are listed in Table 1. None of the compounds showed any inhibitory activity against α-fucosidase (bovine kidney), α-glucosidase (Baker's yeast), or α-mannosidase (Jack beans). Although, for synthetic reasons,[3] only the *N*-octyl derivative **1** of **3β** has so far received attention as a β-galactosidase inhibitor, the present work provides the first description of inhibitory activity against glycohydrolases obtained by a series of N-substituted derivatives of **3β**. As expected,[4,6] *N*-alkylation dramatically improved the inhibitory activity against α- and β-galactosidases. It is worthy of note that the β-galactose-type valienamines **1** and **18**–**20** have both been shown to be very strong inhibitors of β-galactosidase and β-glucosidase, with no specificity regarding the 4-epimeric structures of the substrates. This characteristic is in good accordance with the cases of isofagomine[14] and calystegins.[15] Very recently, compound **1** has extensively been studied[16] as an important candidate for generation of novel therapeutic agents for treatment of GM_1-gangliosidosis and β-galactosidosis. Development of such enzyme-inhibitors might advantageously be accelerated by provision of various N-substituted derivatives, including **19** and **20**, readily prepared by use of the versatile precursors **13α,β**.

The present work describes a convenient synthetic route for the β-galactose-type valienamine **3β** and some *N*-alkyl derivatives thereof, demonstrating that enzyme-inhibitory activity can be significantly increased by a suitable N-substitution.

Table 1. Inhibitory activity (IC_{50}, μM) of compounds **1**, **3α**,**β**, and **18**–**20** against four glycosidases[a]

Compd	IC_{50} (μM)			
	α-Galactosidase (Green coffee beans)	β-Galactosidase (Bovine liver)	β-Glucosidase (Almonds)	α-Mannosidase (Jack beans)
1	3.1	0.87	3.1	NI
3α	56	NI	NI	370
3β	12	NI	NI	190
18	2.7	2.3	1.2	NI
19	1.9	0.13	2.5	NI
20	4.4	0.01	0.87	NI
DMJ	NT	NT	NT	150

[a] Compounds **3α** and **3β** are racemic; DMJ: deoxymannonojirimycin; NI: $IC_{50} > 0.1$ mg/mL; NT: Not tested.

4. Experimental

4.1. General methods

Optical rotations were measured with a JASCO DIP-370 polarimeter, and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^1H NMR spectra were recorded for solutions in deuteriochloroform and deuteriomethanol with internal tetramethylsilane (TMS) as a reference with a JEOL JNM LAMDA-300 (300 MHz) instrument. ^{13}C NMR spectra were recorded with the same instrument (75 MHz). IR spectra were recorded with a JASCO IR-810 or HITACHI Bio-Rad Digital Lab FTS-65 spectrometer. Mass spectra were determined with HITACHI M-8000 ion trap mass spectrometer using electrospray ionization (ESI). TLC was performed on silica gel 60 F-254 (E. Merck, Darmstadt). The silica gel used for a column chromatography was Wakogel C-300 (Wako Junyaku Kogyo Co., Osaka, 200–300 mesh) or silica gel 60 KO (Katayama Kagaku Kogyo Co., Osaka, 70–230 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated at $>45\,^\circ C$ under diminished pressure.

4.1.1. (1*SR*,2*RS*,3*SR*)-1,2,3-Triacetoxy-4-methylenecyclohex-5-ene (4). A mixture of (1*RS*,2*RS*,3*RS*,4*RS*,6*RS*)-1,2,3-triacetoxy-4-bromo-6-(bromomethyl)cyclohexane[8] (1.64 g, 3.81 mmol) and anhydrous sodium acetate (1.25 g, 15.2 mmol) in HMPA (65 mL) was stirred for 2 h at 120 °C. After cooling, the mixture was diluted with ethyl acetate (210 mL), and the solution was washed thoroughly with water, dried, and evaporated. The residue was chromatographed on a silica gel column (90 g, 1:8 acetone/hexane) to give the conjugated diene **4** (0.73 g, 72%) as a syrup, TLC: R_f 0.45 (1:3 acetone/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 6.25 (br d, 1H, $J = 10.0$ Hz, H-6), 5.79 (d, 1H, $J = 2.8$ Hz, H-3), 5.70 (br d, 1H, $J = 10.0$ Hz, H-5), 5.64 (br d, 1H, $J = 7.6$ Hz, H-1), 5.33 and 5.28 (2 s, each 1H, CH_2), 5.17 (dd, 1H, $J = 2.8$ and 7.6 Hz, H-2), 2.10 and 2.10 (3 s, each 3H, 3 Ac). This compound was identified with an authentic sample[8] on comparison with spectral data.

4.1.2. (1*RS*,2*RS*,3*SR*,6*SR*)- and (1*RS*,2*RS*,3*SR*,6*RS*)-1,2,3-Triacetoxy-6-bromo-4-(bromomethyl)cyclohex-4-ene [2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-5a-carba-α and β-DL-*arabino*-hex-5(5a)-enopyranosyl bromide] (5α and 5β). To a solution of the diene **4** (1.96 g, 7.34 mmol) in carbon tetrachloride (40 mL) was added dropwise bromine (1.2 g, 7.6 mmol) for 1 h at room temperature. The mixture was then diluted with chloroform (400 mL) and the solution was washed thoroughly with saturated aqueous sodium thiosulfate, aqueous sodium hydrogen carbonate, and water, dried, and evaporated. The residue was chromatographed on a silica gel column (280 g, 6:1 ethyl acetate/hexane) to give about 1:1 mixture of the dibromides **5α** and **5β** (2.82 g, 90%) as colorless crystals.

The mixture of the products obtained from **4** (320 mg) was carefully fractionated by chromatography on silica gel (10:1 EtOAc/hexane) to give pure **5α** (120 mg) and **5β** (43 mg), together with **5α**,**β** (220 mg): ^1H NMR (300 MHz, $CDCl_3$) **5α**: δ 6.22 (d, 1H, $J = 4.6$ Hz, H-5), 5.94 (d, 1H, $J = 4.1$ Hz, H-3), 5.48 (dd, 1H, $J = 4.1$ and 10.3 Hz, H-2), 5.10 (dd, 1H, $J = 3.7$ and 10.3 Hz, H-1), 5.08 (dd, 1H, $J = 3.7$ and 4.6 Hz, H-6), 3.93 (s, 2H, CH_2Br); **5β**: δ 6.18 (d, 1H, $J = 2.7$ Hz, H-5), 5.88 (d, 1H, $J = 3.6$ Hz, H-3), 5.69 (dd, 1H, $J = 7.6$ and 10.5 Hz, H-1), 5.10 (dd, 1H, $J = 3.6$ and 10.5 Hz, H-2), 4.61 (dd, 1H, $J = 2.7$ and 7.6 Hz, H-6), 3.91 (s, 2H, CH_2Br).

These compounds were identified with authentic samples[8] on comparison with spectral data.

4.1.3. (1*RS*,2*RS*,3*SR*,6*SR*)- and (1*RS*,2*RS*,3*SR*,6*RS*)-1,2,3-Triacetoxy-4-(acetoxymethyl)-6-bromocyclohex-4-ene [2,3,4,6-tetra-*O*-acetyl-5a-carba-α and β-DL-*arabino*-hex-5(5a)-enopyranosyl bromide] (6α and 6β). A ca. 1:1 mixture (912 mg, 2.13 mmol) of the dibromides **5α** and **5β**, anhydrous sodium acetate (175 mg, 2.13 mmol) in DMF (14 mL) was stirred for 20 h at room temperature. The mixture was then diluted with ethyl acetate (180 mL), and the solution was washed with saline (3×60 mL), dried, and evaporated. The residue was chromatographed on a silica gel column (80 g, 1:3 ethyl acetate/hexane) to give a 1:1 inseparable mixture (743 mg, 86%) of the bromides **6α** and **6β** as colorless crystals, TLC: R_f 0.35 (1:2 EtOAc/hexane). This mixture of the compounds was identified with an authentic sample[8] on comparison with spectral data.

Compound **5α** (45 mg) was similarly treated with sodium acetate (8.6 mg) in DMF (1 mL) to give products, which were shown to be a mixture of **6α**,**β** by ^1H NMR spectrum.

4.1.4. (1*RS*,2*RS*,3*SR*,6*SR*)- and (1*RS*,2*RS*,3*SR*,6*RS*)-1,2,3-Triacetoxy-4-(acetoxymethyl)-6-azidocyclohex-4-ene [2,3,4,6-tetra-*O*-acetyl-5a-carba-α and β-DL-*arabino*-hex-5(5a)-enopyranosyl azide] (7α and 7β). A ca. 1:1 mixture (676 mg, 1.58 mmol) of the bromides **5α** and **5β**, anhydrous sodium acetate (130 mg, 1.58 mmol) in DMF (10 mL) was stirred for 15 h at room temperature. When TLC demonstrated almost disappearance of **5α** and **5β**, sodium azide (205 mg, 3.15 mmol) was added to the mixture and it was stirred for further 24 h at room temperature. The mixture was diluted with ethyl acetate (120 mL), and a solution was washed with saline (3×40 mL), dried, and evaporated. The residue was chromatographed on a silica gel column (50 g, 1:4 ethyl acetate/hexane) to give about 1:1 inseparable mixture (456 mg, 78%) of the azides **7α** and **7β** as a colorless syrup, TLC: R_f 0.51 (1:1 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) (inter alia) δ 5.94 (d, 0.5H, J = 4.9 Hz, H-5 of **7α**), 5.88 (d, 0.5H, J = 1.2 Hz, H-5 of **7β**), 5.73 (br d, 0.5H, J = 2.1 Hz, H-3 of **7α**), 5.70 (d, 0.5H, J = 3.5 Hz, H-3 of **7β**), 5.48 (dd, 0.5H, J = 8.1 and 11.0 Hz, H-1 of **7β**). This mixture was identified with an authentic sample[8] on comparison with spectral data.

4.1.5. (1*SR*,4*SR*,5*SR*,6*SR*)- and (1*SR*,4*RS*,5*SR*,6*SR*)-5-Acetoxy-2-(acetoxymethyl)-4-azido-8,8-dimethyl-7,9-dioxabicyclo[4.3.0]non-2-ene [2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-5a-carba-α and β-DL-*arabino*-hex-5(5a)-enopyranosyl azide] (8α and 8β). A solution of the azides **7α,β** (113 mg, 0.305 mmol) in methanol (1.1 mL) was treated with 1 M methanolic sodium methoxide (0.57 mL) for 1 h at room temperature. After neutralization by treatment with Amberlite IR-120 (H^+) resin, the solution was evaporated and the residue was dissolved in dry DMF (0.87 mL), to which 2,2-dimethoxypropane (0.132 mL, 1.07 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate were added. The mixture was stirred for 24 h at room temperature, neutralized with triethyl amine, and then co-evaporated with *n*-butanol and toluene to dryness. The residue was treated with acetic anhydride (0.5 mL) and pyridine (1.0 mL) overnight at room temperature. After quenched by addition of methanol (1 mL), the mixture was evaporated to dryness. The residue was chromatographed on a silica gel column (8.3 g, 1:8 ethyl acetate/hexane) to give **8α** (44 mg, 44%) and **8β** (42 mg, 42%) as a colorless syrup.

For **8α**: TLC: R_f 0.53 (1:2 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (d, 1H, J = 4.1 Hz, H-3), 5.21 (dd, 1H, J = 3.8 and 7.4 Hz, H-2), 4.75 and 4.67 (2 d, each 1H, J = 14.9 Hz, CH_2OAc), 4.63 (d, 1H, J = 6.2 Hz, H-1), 4.46 (dd, 1H, J = 6.2 and 7.4 Hz, H-6), 4.25 (dd, 1H, J = 3.8 and 4.1 Hz, H-4), 2.13 and 2.17 (2 s, each 3H, 2 Ac), 1.38 and 1.42 (2 s, each 3H, CMe_2); ITMS-ESI (positive mode): m/z 349 $[M+Na]^+$, 365 $[M+K]^+$.

For **8β**: TLC: R_f 0.40 (1:2 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.77 (d, 1H, J = 1.5 Hz, H-3), 5.15 (dd, 1H, J = 8.9 and 8.9 Hz, H-5), 4.66 and 4.74 (2 d, each 1H, J = 13.7 Hz, CH_2OAc), 4.59 (d, 1H, J = 6.0 Hz, H-1), 4.22 (dd, 1H, J = 6.0 and 8.9 Hz, H-6), 3.97 (br d, 1H, J = 8.9 Hz, H-4), 2.12 and 2.17 (2 s, each 3H, 2 Ac), 1.38 and 1.51 (2 s, each 3H, CMe_2); ITMS-ESI (positive mode): m/z 349 $[M+Na]^+$, 364 $[M+K]^+$.

4.1.6. (1*SR*,2*SR*,3*SR*,6*SR*)-6-Azido-4-(hydroxymethyl)-cyclohex-4-ene-1,2,3-triol [5a-carba-α-DL-*arabino*-hex-5(5a)-enopyranosyl azide] (9α). A solution of **8α** (37 mg, 0.113 mmol) in a mixture of 4 M hydrochloric acid (0.5 mL) and THF (0.5 mL) for 1 h at reflux temperature. The mixture was evaporated and the residue was chromatographed on silica gel (1.1 g, 1:10 MeOH/$CHCl_3$) to give **9α** (18 mg, 80%) as a colorless syrup; TLC: R_f 0.40 (1:4 MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, $CHCl_3$): δ 5.70 (d, 1H, J = 4.2 Hz, H-5), 4.17 (dd, 1H, J = 4.2 and 4.5 Hz, H-6), 4.10 (d, 1H, J = 3.9 Hz, H-3), 4.01 (s, 2H, CH_2OH), 3.93 (dd, 1H, J = 4.5 and 10.0 Hz, H-1), 3.68 (dd, 1H, J = 3.9 and 10.0 Hz, H-2).

4.1.7. (1*SR*,2*RS*,3*SR*,6*RS*)-6-Azido-4-(hydroxymethyl)-cyclohex-4-ene-1,2,3-triol [5a-carba-β-DL-*arabino*-hex-5(5a)-enopyranosyl azide] (9β). Compound **8β** (31 mg, 0.094 mmol) was hydrolyzed as described in the preparation of **9α** to give **9β** (14 mg, 74%) as a colorless syrup; TLC: R_f 0.40 (1:4 MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, $CHCl_3$): δ 5.57 (d, 1H, J = 1.3 Hz, H-5), 4.07 (d, 1H, J = 4.2 Hz, H-3), 4.00 (s, 2H, CH_2OH), 3.83 (dd, 1H, J = 1.3 and 8.3 Hz, H-6), 3.62 (dd, 1H, J = 8.3 and 10.7 Hz, H-1), 3.47 (dd, 1H, J = 4.2 and 10.7 Hz, H-2).

4.1.8. (1*SR*,2*RS*,3*SR*,6*SR*)-6-Amino-4-(hydroxymethyl)-cyclohex-4-ene-1,2,3-triol [5a-carba-α-DL-*arabino*-hex-5(5a)-enopyranosylamine] (3α). A solution of **9α** (19 mg, 92 μmol) in 50% aqueous THF (2.5 mL) containing triphenylphosphine (73 mg, 0.28 mmol) was stirred for 24 h at room temperature. The mixture was then passed through a column of Dowex 50W×2 (H^+) resin (1 mL) with 1% aqueous ammonia as eluent to give **3α** (14 mg, 86%) as a white powder; TLC: R_f 0.35 (1:1:2 H_2O/AcOH/*n*-BuOH); ^{1}H NMR (300 MHz, D_2O): δ 5.61 (d, 1H, J = 3.9 Hz, H-5), 4.11 (d, 1H, J = 3.9 Hz, H-3), 4.00 and 3.95 (ABq, J = 15.1 Hz, CH_2OH), 3.81 (dd, 1H, J = 9.5 and 9.5 Hz, H-1), 3.72 (dd, 1H, J = 3.9 and 9.5 Hz, H-2), 3.47 (br d, 1H, H-6); ^{13}C NMR (75 MHz, D_2O): δ 139.16 (C-4), 126.96 (C-5), 69.79 (C-3 or 1), 69.44 (C-1 or 3), 67.40 (C-2), 63.15 (C-7), 49.48 (C-6); ITMS-ESI (positive mode): m/z 177 $[M+H]^+$, 198 $[M+Na]^+$.

4.1.9. (1*SR*,2*RS*,3*SR*,6*RS*)-6-Amino-4-(hydroxymethyl)-cyclohex-4-ene-1,2,3-triol [5a-carba-β-DL-*arabino*-hex-5(5a)-enopyranosylamine] (3β). Compound **9β** (20 mg, 0.10 mmol) was treated with triphenylphosphine (53 mg, 0.20 mmol) in 50% aqueous THF (3.5 mL) and a crude product was purified, as in the preparation of **3α**, to give **3β** (15 mg, 86%) as a white powder; TLC: R_f 0.36 (1:1:2 H_2O/AcOH/*n*-BuOH); ^{1}H NMR (300 MHz, D_2O): δ 5.54 (d, 1H, J = 1.7 Hz, H-5), 4.10 (d, 1H, J = 3.9 Hz, H-3), 4.01 (s, 2H, CH_2OH), 3.57 (dd, 1H, J = 3.9 and 10.3 Hz, H-2), 3.53 (dd, 1H, J = 8.3 and 10.3 Hz, H-1); ^{13}C NMR (75 MHz, D_2O): δ 139.46 (C-4), 127.49 (C-5), 73.34 (C-3 or 1), 72.34 (C-1 or 3), 67.40 (C-2), 62.84 (C-7), 54.41 (C-6); ITMS-ESI (positive mode): m/z 176.43 $[M+H]^+$, 198 $[M+Na]^+$.

4.1.10. (1*SR*,2*RS*,3*SR*,6*SR*)-6-Acetamido-1,2,3-triacetoxy-4-(acetoxymethyl)cyclohex-4-ene (10α). Compound **3α** was treated with acetic anhydride and pyridine in the usual manner to give the penta-*N*,*O*-acetyl derivative **10α**, as a syrup, quantitatively; TLC: R_f 0.42 (1:1 acetone/toluene); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86 (d, 1H, J = 4.4 Hz, H-5), 5.70 (d, 1H, J = 2.9 Hz, H-3), 5.57 (d, 1H, J = 11.3 Hz, NH), 5.35 (dd, 1H, J = 4.2 and 9.6 Hz, H-1), 5.32 (dd, J = 2.9 and 9.6 Hz, 1H, H-2), 5.10 (ddd, 1H, J = 4.2, 4.4, and 11.3 Hz, H-6), 4.59 and 4.46 (ABq, each 1H, J = 13.4 Hz, CH_2OAc), 2.09, 2.08, 2.06, 2.05 and 2.02 (5 s, each 3H, 5 Ac); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.38, 170.25, 170.09, 169.84 (2) (5 *C*H_3CO), 133.00 (C-4), 127.77 (C-5), 67.21 (C-3 or 1), 66.65 (C-1 or 3), 65.36 (C-2), 63.42 (C-7), 45.29 (C-6), 23.26, 21.59, 20.82, 20.69, 20.65 (5 H_3*C*O); ITMS-ESI (positive mode): m/z 387 $[M+H]^+$, 408 $[M+Na]^+$.

4.1.11. (1*SR*,2*RS*,3*SR*,6*RS*)-6-Acetamido-1,2,3-triacetoxy-4-(acetoxymethyl)cyclohex-4-ene (10β). Compound **3β** was acetylated in the usual manner to give the penta-*N*,*O*-acetyl derivative **10β**, as a syrup, quantitatively; TLC: R_f 0.42 (1:1 acetone/toluene); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.84 (d, 1H, $J_{1,5a}$ = 1.4 Hz, H-5), 5.79 (d, 1H, J = 3.9 Hz, H-3), 5.73 (d, 1H, J = 8.5 Hz, NH), 5.29 (dd, 1H, J = 8.5 and 10.0 Hz, H-1), 5.19 (dd, 1H, J = 3.9 and 10.0 Hz, H-2), 4.80 (ddd, 1H, J = 1.4, 8.5 and 8.5 Hz, H-6), 4.55 and 4.46 (ABq, each 1H, J = 13.4 Hz, CH_2OAc), 2.11, 2.05 and 1.98 (3 s, each 3H, 3 Ac), 2.08 (br s, 6H, 2 Ac); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.46, 170.37, 170.06, 169.97, 169.61 (5 *C*H_3CO), 131.08 (C-4), 130.49 (C-5), 69.39 (C-3 or 1), 68.92 (C-1 or 3), 65.76 (C-2), 63.64 (C-7), 51.07 (C-6), 23.23, 20.83, 20.77, 20.74, 20.54 (5 H_3*C*O); ITMS-ESI (positive mode): m/z 387 $[M+H]^+$, 408 $[M+Na]^+$.

4.1.12. (1*S*,2*S*,6*S*)-2-Acetoxy-8,8-dimethyl-5-methylene-7,9-dioxabicyclo[4.3.0]non-3-ene (11). A solution of the diene[8,11] **D**–**4** (1.36 g, 5.06 mmol) in methanol (21 mL) was treated with sodium methoxide (55 mg, 1.0 mmol) for 2 h at room temperature. After neutralization with Amberlite IR-120 (H^+) resin, the mixture was evaporated. The residue was treated with 2,2-dimethoxypropane (2.0 mL, 1.6 mmol) and *p*-toluenesulfonic acid monohydrate (0.21 g, 1.1 mmol) for 23 h at room temperature. After neutralization with triethylamine, the mixture was evaporated to dryness and the residual product was acetylated with acetic anhydride (5.5 mL) and pyridine (11 mL) overnight at room temperature in the usual manner. The product was chromatographed on a silica gel column (30 g, 1:11 EtOAc/hexane) as eluent to give **11** (807 mg, 71%) as a colorless syrup; TLC: R_f 0.52 (1:1 EtOAc/hexane), $[\alpha]_D^{23}$ +149° (*c* 0.89, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.30 (br d, 1H, J = 10.3 Hz, H-4), 5.67 (br d, 1H, H-3), 5.43 (d, 1H, J = 5.4 Hz, H-2), 5.42 and 5.44 (2 s, each 1H, CH_2), 4.71 (d, 1H, J = 5.5 Hz, H-6), 4.21 (dd, 1H, J = 5.4 and 5.5 Hz, H-1), 2.11 (s, 3H, Ac), 1.44 and 1.49 (2 s, each 3H, CMe_2); ITMS-ESI (positive mode): m/z 247 $[M+Na]^+$, 263 $[M+K]^+$.

4.1.13. (1*S*,4*S*,5*R*,6*S*)- and (1*S*,4*R*,5*R*,6*S*)-5-acetoxy-4-bromo-2-(bromomethyl)-8,8-dimethyl-7,9-dioxabicyclo-[4.3.0]non-2-ene [2-*O*-acetyl-6-bromo-6-deoxy-3,4-*O*-isopropylidene-5a-carba-α and β-L-*arabino*-hex-5(5a)-enopyranosyl bromide] (12α and 12β). To a solution of **11** (0.657 g, 2.93 mmol) in carbon tetrachloride (6.6 mL) was added dropwise bromine (0.15 mL, ca. 3 mmol) for 7 min at room temperature. After treatment with saturated aqueous sodium thiosulfate, the mixture was diluted with chloroform (300 mL), and the solution was thoroughly washed with saturated sodium hydrogen carbonate and water, dried, and evaporated. The residue was chromatographed on silica gel (20 g, 1:50 EtOAc/toluene) to give about 1.7:1 inseparable mixture (824 mg, 76%) of **12α** and **12β** as a colorless syrup.

For **12α**: ^{1}H NMR (300 MHz, $CDCl_3$) (inter alia): δ 6.17 (br d, 1H, J = 6.4 Hz, H-3), 4.99 (br d, 1H, J = 8.3 Hz, H-5), 4.81 (dd, 1H, J = 3.7 and 6.4 Hz, H-4), 4.76 (dd, 1H, J = 6.8 and 8.3 Hz, H-6), 4.02 and 4.20 (2 d, each 1H, J = 10.5 Hz, CH_2Br), 2.19 (s, 3H, Ac), 1.42 and 1.46 (2 s, each 3H, CMe_2).

For **12β**: ^{1}H NMR (300 MHz, $CDCl_3$) (inter alia): δ 6.17 (br s, 1H, H-3), 5.37 (dd, 1H, J = 8.3 and 8.3 Hz, H-5), 4.87 (d, 1H, J = 5.5 Hz, H-1), 4.49 (br d, 1H, H-4), 4.20 (s, 2H, CH_2Br), 2.15 (s, 3H, Ac), 1.41 and 1.51 (2 s, each 3H, CMe_2).

4.1.14. (1*S*,4*S*,5*R*,6*S*)- and (1*S*,4*R*,5*R*,6*S*)-5-Acetoxy-2-(acetoxymethyl)-4-bromo-8,8-dimethyl-7,9-dioxabicyclo-[4.3.0]non-2-ene [2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-5a-carba-α and β-L-*arabino*-hex-5(5a)-enopyranosyl bromide] (13α and 13β). A mixture (27 mg, 70 μmol) of **12α,β** and sodium acetate (6.3 mg, 0.10 mmol) in DMF (1 mL) was stirred for 2 days at room temperature. The mixture was then diluted with ethyl acetate (12 mL), the solution was thoroughly washed with saline and water, dried, and evaporated. The residual product (27 mg) was chromatographed on silica gel (4 g, 1:8 EtOAc/hexane) to give **13α** (12 mg, 48%) and **13β** (6 mg, 23%) as a colorless syrup.

For **13α:** TLC: R_f 0.36 (1:2 ethyl acetate/hexane); $[\alpha]_D^{20}$ +277° (*c* 1.13, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.09 (d, 1H, J = 7.7 Hz, H-3), 4.83 (dd, 1H, J = 3.9 and 7.7 Hz, H-4), 4.79 (dd, 1H, J = 3.9 and 8.5 Hz, H-5), 4.71 (d, 1H, J = 6.5 Hz, H-1), 4.67 and 4.74 (ABq, each 1H, J = 14.3 Hz, CH_2OAc), 4.55 (dd, 1H, J = 6.5 and 8.5 Hz, H-6), 2.13 and 2.19 (2 s, each 3H, 2 Ac), 1.40 and 1.46 (2 s, each 3H, CMe_2); ITMS-ESI (positive mode): m/z 283 $[M-^{79}Br]^+$, 305 $[M+Na-^{79}Br]^+$, 385 $[M+Na]^+$.

For **13β**: TLC: R_f 0.31 (1:2 EtOAc/hexane); $[\alpha]_D^{21}$ +33° (*c* 0.78, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.04 (br s, 1H, H-3), 5.39 (dd, 1H, J = 8.3 and 8.3 Hz, H-5), 4.67 and 4.75 (ABq, each 1H, J = 13.6 Hz, CH_2OAc), 4.58 (d, 1H, J = 5.9 Hz, H-1), 4.50 (br d, 1H, J = 8.3 Hz, H-4), 4.17 (dd, 1H, J = 5.9 and 8.3 Hz, H-6), 2.12 and 2.15 (2 s, each 3H, 2 Ac), 1.38 and 1.52 (2 s, each 3H, CMe_2); ITMS-ESI (negative mode): m/z 361 $[M-H]^-$.

4.1.15. (1*S*,4*R*,5*R*,6*S*)-4-Hexylamino-5-hydroxy-2-(hydroxymethyl)-8,8-dimethyl-7,9-dioxabicyclo[4.3.0]non-2-ene [*N*-hexyl-3,4-*O*-isopropylidene-5a-carba-α-L-*arabino*-hex-

5(5a)-enopyranosylamine] (14). A mixture of **13α** (39 mg, 0.11 mmol), *n*-hexylamine (143 μL, 1.1 mmol), and 2-propanol (0.4 mL) was stirred for a week at room temperature, and then evaporated to dryness. The residue was chromatographed on a silica gel column (4 g, 1:40 MeOH/$CHCl_3$) to give **14** (21 mg, 64%) as a white powder, TLC: R_f 0.46 (1:4 MeOH/$CHCl_3$); $[\alpha]_D^{20}$ −27 ° (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (br s, 1H, H-5), 4.63 (d 1H, *J* = 6.8 Hz, H-3), 4.18 and 4.26 (ABq, each 1H, *J* = 11.7 Hz, C*H*$_2$OH), 4.13 (dd, 1H, *J* = 6.8 and 8.5 Hz, H-2), 3.44 (dd, 1H, *J* = 8.5 and 9.2 Hz, H-1), 3.04 (d, 1H, *J* = 9.2 Hz, H-6), 2.81 and 2.43 (2 dt, each 1H, *J* = 7.3 and 11.2 Hz, NHC*H*$_2$), 2.58 (br s, 2H, OH), 1.49 and 1.40 (2 s, each 3H, CMe_2), 1.54–1.26 [m, 8H, $NHCH_2(CH_2)_4$], 0.89 (t, 3H, *J* = 6.7 Hz, CH_2CH_3).

4.1.16. (1*S*,2*R*,3*S*,6*R*)-6-Hexylamino-4-(hydroxymethyl)-cyclohex-4-ene-1,2,3-triol [*N*-hexyl-5a-carba-β-L-*arabino*-hex-5(5a)-enopyranosylamine] (18). A mixture of **14** (7.9 mg, 26 μmol) and 80% aqueous acetic acid (2 mL) was stirred for 30 h at 80 °C. The product was purified by a column of Dowex 50 W×2 (H^+) resin (0.7 g) with methanolic 1% ammonia as eluent to give **18** (7.5 mg, ∼100%) as a white powder, $[\alpha]_D^{20}$ −1.9° (*c* 0.34, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 5.71 (br s, 1H, H-5), 4.15 (d, 1H, *J* = 4.2 Hz, H-3), 4.12 (br s, 2H, C*H*$_2$OH), 3.70 (dd, 1H, *J* = 8.1 and 10.3 Hz, H-1), 3.43 (dd, 1H, *J* = 4.2 and 10.3 Hz, H-2), 3.10 (dd, 1H, *J* = 2.0 and 8.1 Hz, H-6), 2.56 and 2.74 (2 dt, each 1H, *J* = 7.3 and 11.4 Hz, NHC*H*$_2$), 1.52 (m, 2H, $NHCH_2CH_2$), 1.32 [m, 6H, $CH_2(CH_2)_3CH_3$], 0.91 (t, 3H, *J* = 6.7 Hz, CH_2CH_3); ITMS-ESI (positive mode): *m*/*z* 260 $[M+H]^+$.

4.1.17. (1*S*,4*R*,5*R*,6*S*)-5-Hydroxy-2-(hydroxymethyl)-8,8-dimethyl-4-octylamino-7,9-dioxabicyclo[4.3.0]non-2-ene [*N*-octyl-3,4-*O*-isopropylidene-5a-carba-α-L-*arabino*-hex-5(5a)-enopyranosylamine] (15). A mixture of **13α** (38 mg, 0.105 mmol), *n*-octylamine (174 μL, 1.1 mmol), and 2-propanol (0.4 mL) was stirred for a week at room temperature. The reaction mixture was processed as in the preparation of **14** to give, after chromatography on silica gel, **15** (24 mg, 68%) as a white powder, TLC: R_f 0.46 (1:4 MeOH/$CHCl_3$); $[\alpha]_D^{20}$ −20 ° (*c* 0.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (br s, 1H, H-5), 4.64 (d, 1H, *J* = 6.8 Hz, H-3), 4.18 and 4.27 (ABq, each 1H, *J* = 13.7 Hz, C*H*$_2$OH), 4.14 (dd, 1H, *J* = 6.8 and 8.7 Hz, H-2), 3.43 (dd, 1H, *J* = 8.7 and 9.0 Hz, H-1), 3.04 (d, 1H, *J* = 9.0 Hz, H-6), 2.81 and 2.55 (dt, each 1H, *J* = 7.3 and 11.3 Hz, H-6), 2.36 (br s, 2H, OH), 1.40 and 1.50 (2 s, each 3H, CMe_2), 1.27–1.53 [m, 12H, $NHCH_2(CH_2)_6$], 0.88 (t, 3H, *J* = 6.5 Hz, CH_2CH_3).

4.1.18. (1*S*,2*R*,3*S*,6*R*)-4-(Hydroxymethyl)-6-octylamino-cyclohex-4-ene-1,2,3-triol [*N*-octyl-5a-carba-α-L-*arabino*-hex-5(5a)-enopyranosylamine] (1). Compound **15** (4.7 mg, 14 μmol) was deprotected as in the preparation of **14** to give, after passage through a column of Dowex 50 W×2 with 1% methanolic ammonia, **1** (2.3 mg, 56%) as a white powder, TLC: R_f 0.38 (1:3:6 AcOH/MeOH/$CHCl_3$); $[\alpha]_D^{20}$ +6.3° (c 0.5, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 5.71 (br s, 1H, H-5), 4.15 (d, 1H, *J* = 4.2 Hz, H-3), 4.12 (br s, 2H, C*H*$_2$OH), 3.70 (dd, 1H, *J* = 8.1 and 10.3 Hz, H-1), 3.43 (dd, 1H, *J* = 4.2 and 10.3 Hz, H-2), 3.12 (d, 1H, *J* = 8.1 Hz, H-6), 2.56 and 2.75 (2 m, each 1H, NCH_2), 1.52 (m, 2H, $NHCH_2CH_2$), 1.31 [m, 10H, $CH_2(CH_2)_5CH_3$], 0.89 (t, 3H, *J* = 6.7 Hz, CH_2CH_3); ITMS-ESI (positive mode): *m*/*z* 288 $[M+H]^+$.

4.1.19. (1*S*,4*R*,5*R*,6*S*)-4-Decylamino-5-hydroxy-2-(hydroxymethyl)-8,8-dimethyl-7,9-dioxabicyclo[4.3.0]non-2-ene [*N*-decyl-3,4-*O*-isopropylidene-5a-carba-α-L-*arabino*-hex-5(5a)-enopyranosylamine] (16). A mixture of **13α** (36 mg, 99 μmol), *n*-decylamine (120 μL, 0.59 mmol) was stirred for 3 days at room temperature. The mixture was processed as in the preparation of **14** to give **16** (14 mg, 40%) as a white powder, TLC: R_f 0.44 (1:5 MeOH/$CHCl_3$); $[\alpha]_D^{20}$ −19° (*c* 0.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (br s, 1H, H-5), 4.63 (d, 1H, *J* = 6.6 Hz, H-3), 4.17 and 4.27 (ABq, each 1H, *J* = 13.7 Hz, C*H*$_2$OH), 4.14 (dd, 1H, *J* = 6.6 and 8.5 Hz, H-2), 3.44 (dd, 1H, *J* = 8.5 and 9.0 Hz, H-1), 3.06 (d, 1H, *J* = 9.0 Hz, H-6), 2.81 and 2.55 (2 dt, each 1H, *J* = 7.2 and 11.2 Hz, NHC*H*$_2$), 2.66 (br s, 2H, OH), 1.40 and 1.49 (2 s, each 3H, CMe_2), 1.26–1.54 [m, 16H, $(CH_2)_8CH_3$], 0.88 (t, 3H, *J* = 6.6 Hz, CH_2CH_3).

4.1.20. (1*S*,2*R*,3*S*,6*R*)-6-Decylamino-4-(hydroxymethyl)-cyclohex-4-ene-1,2,3-triol [*N*-decyl-5a-carba-α-L-*arabino*-hex-5(5a)-enopyranosylamine] (19). Compound **16** (10.4 mg, 29 μmol) was deprotected as in the preparation of **14** to give **19** (6.7 mg, 73%) as a white powder, TLC: R_f 0.48 (1:3:6 AcOH /MeOH/$CHCl_3$); $[\alpha]_D^{21}$ +12° (*c* 0.12, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 5.62 (d, 1H, *J* = 2.0 Hz, H-5), 4.06 (d, 1H, *J* = 4.2 Hz, H-3), 4.03 (br s, 2H, C*H*$_2$OH), 3.60 (dd, 1H, *J* = 7.6 and 10.3 Hz, H-1), 3.34 (dd, 1H, *J* = 4.2 and 10.3 Hz, H-2), 3.01 (d, 1H, *J* = 8.1 Hz, H-6), 2.46 and 2.65 (2 dt, each 1H, *J* = 7.4 and 11.3 Hz, NHC*H*$_2$), 1.43 (m, 2H, $NHCH_2CH_2$), 1.20 [m, 14H, $CH_2(CH_2)_7CH_3$], 0.80 (t, 3H, *J* = 6.7 Hz, CH_2CH_3); ITMS-ESI (positive mode): *m*/*z* 316 $[M+H]^+$.

4.1.21. (1*S*,4*R*,5*R*,6*S*)-4-Dodeylamino-5-hydroxy-2-(hydroxymethyl)-8,8-dimethyl-7,9-dioxabicyclo[4.3.0]non-2-ene [*N*-dodeyl-3,4-*O*-isopropylidene-5a-carba-α-L-*arabino*-hex-5(5a)-enopyranosylamine] (17). A mixture of **13α** (40 mg, 0.11 mmol), *n*-dodecylamine (203 mg, 1.1 mmol), and 2-propanol (0.4 mL) was stirred for a week at room temperature. The mixture was processed as in the preparation of **14** to give, after chromatography on silica gel to give **17** (14 mg, 40%) as a white powder, TLC: R_f 0.39 (1:5 MeOH/$CHCl_3$); $[\alpha]_D^{20}$ −11 ° (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90 (br s, 1H, H-5), 4.63 (d, 1H, *J* = 6.8 Hz, H-3), 4.18 and 4.27 (ABq, each 1H, *J* = 13.7 Hz, C*H*$_2$OH), 4.14 (dd, 1H, *J* = 6.8 and 8.7 Hz, H-2), 3.45 (dd, 1H, *J* = 8.7 and 9.1 Hz, H-1), 3.07 (d, 1H, *J* = 9.1 Hz, H-6), 2.56 and 2.82 (2 dt, each 1H, *J* = 7.2 and 11.3 Hz, NHC*H*$_2$), 2.69 (br s, 2H, OH), 1.40 and 1.50 (2 s, each 3H, CMe_2), 1.26–1.56 [m, 20H, $(CH_2)_{10}CH_3$], 0.88 (t, 3H, *J* = 6.6 Hz, CH_2CH_3).

4.1.22. (1*S*,2*R*,3*S*,6*R*)-6-Dodecylamino-4-(hydroxymethyl)-cyclohex-4-ene-1,2,3-triol [*N*-dodecyl-5a-carba-α-L-*arabino*-hex-5(5a)-enopyranosylamine] (20). Compound **17**

(7.0 mg, 18 μmol) was deprotected as in the preparation of **18** to give **20** (5.4 mg, 87%) as a white powder, TLC: R_f 0.41 (1:2:6 AcOH/MeOH/$CHCl_3$); $[\alpha]_D^{21}$ +0.7° (*c* 0.27, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 5.71 (br s, 1H, H-5), 4.15 (d, 1H, J = 4.1 Hz, H-3), 4.12 (br s, 2H, CH_2OH), 3.69 (dd, 1H, J = 8.1 and 9.6 Hz, H-1), 3.43 (dd, 1H, J = 4.1 and 9.6 Hz, H-2), 3.10 (d, 1H, J = 8.1 Hz, H-6), 2.56 and 2.74 (2 dt, each 1H, J = 7.1 and 11.5 Hz, $NHCH_2$), 1.52 (m, 2H, $NHCH_2CH_2$), 1.28 [m, 18H, $CH_2(CH_2)_9CH_3$], 0.89 (t, 3H, J = 6.6 Hz, CH_2CH_3); ITMS-ESI (positive mode): m/z 344 $[M+H]^+$.

4.2. Biological assay

Compounds were assayed[13] for enzyme inhibitory activity (IC_{50}) against six glycohydrolases: α-glucosidase (Baker's yeast), β-glucosidase (almonds), α-galactosidase (green coffee beans), β-galactosidase (bovine liver), α-mannosidase (Jack beans), and α-fucosidase (bovine kidney). All compounds did not exhibit any inhibitory activity toward α-glucosidase and α-fucosidase.

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