Synthesis and Biological Evaluation of α-L-Fucosidase Inhibitors: 5a-Carba-α-L-fucopyranosylamine and Related Compounds[‡]

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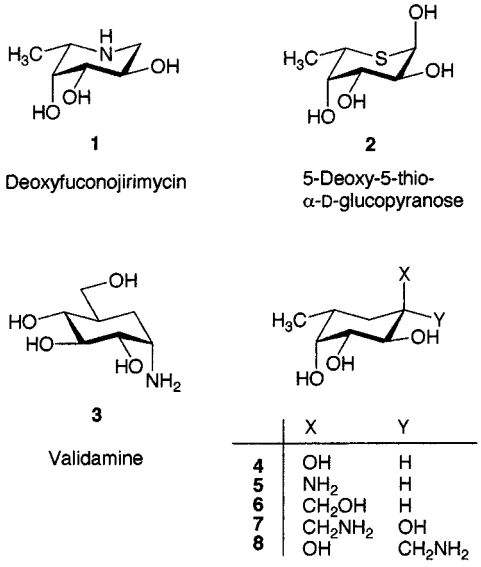
5a-Carba-α-L-fucopyranosylamine (**5**), an α-glucosidase inhibitor validamine analog possessing an α-L-fucose-type structure, and four related compounds (**4** and **6**–**8**) were synthesized and their glycosidase inhibitory potential determined. Carbafucosylamine has already been shown to possess a specific and very strong inhibitory activity against α-L-fucosidase ($K_i = 1.2 \times 10^{-8}$ M, bovine kidney). Judging from the activity of the other analogs prepared, this amine might be expected to be a lead compound for development of a new type of α-L-fucosidase inhibitor.

Introduction

Our interest has been focused on the development of new types of inhibitors of α-L-fucosidase, which plays important roles in the turnover of glycoproteins by lysosomal degradation[2] and in fertilization in some organisms by triggering acrosome reactions.[3] α-Fucosidase inhibitors are potential research tools for these fucosidase-relevant events and even as potential drugs for cancer and HIV, through inhibition of the contribution of turnover processes and/or invasion of the extracellular matrix secreted fucosidases.[4]

1-Deoxyfuconojirimycin[5] (**1**, Scheme 1) is the most powerful inhibitor of α-L-fucosidase known to date, and is therefore an important biological tool in glycobiology. Recently, many pseudo-sugars, aza-sugar-type compounds[6] mimicking **1**, and thia-sugars − including 5-thio-5-deoxy-α-L-fucopyranose[7] (**2**) − have been designed and synthesized as prospective, effective α-L-fucosidase inhibitors.

Some 5a-carbahexopyranosylamines and their analogs − validamine (**3**), valienamine, and valiolamine − first isolated by degradation of validamycins,[8] are important classes of α-glucosidase inhibitors, and their syntheses and chemical modifications have been extensively examined, and biochemical studies[9] made. In fact, acarbose,[10] the pseudo-tetrasaccharide composed of the imino-linked valienamine, and voglibose,[11] *N*-(1,3-dihydroxyprop-2-yl)valiolamine, have been widely used clinically for treatment of diabetes. Experience gained indicates that 5a-carba-sugar derivatives have comparatively low toxicities, commensurate with further clinical uses in mammals. Therefore, several validamine analogs possessing α-*galacto*,[12] β-*gluco*,[13] and α-*manno*-type[13] structures were synthesized and their glycosidase inhibitory activity tested. These analogs, however, were found to be only rather weak or moderate glycosidase inhibitors, in comparison with the potential exhibited by the α-*gluco*-type validamine.



	X	Y
4	OH	H
5	NH_2	H
6	CH_2OH	H
7	CH_2NH_2	OH
8	OH	CH_2NH_2

Scheme 1. α-D-Fucosidase inhibitors deoxyfuconojirimycin (**1**), 5-deoxy-5-thio-α-D-glucopyranose (**2**), and some validamine-type α-D-fucosidase inhibitors synthesized in this study

In a preceding paper,[1] the first synthesis of 5a-carba-α-DL-fucopyranosylamine was described, and its specific and very strong α-L-fucosidase inhibition demonstrated. As a next step, it is important both to determine the activity of the pure L-antipode, corresponding to the L-fucopyranose residue contained in cell surface oligosaccharide chains, and to estimate its scope for structural modification. We here report[14] details of the synthesis and evaluation of fucosidase inhibitory activity of 5a-carba-α-L-fucopyranosylamine,

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along with two carbafucopyranose derivatives possessing branched aminomethyl functions at their C-1 positions.

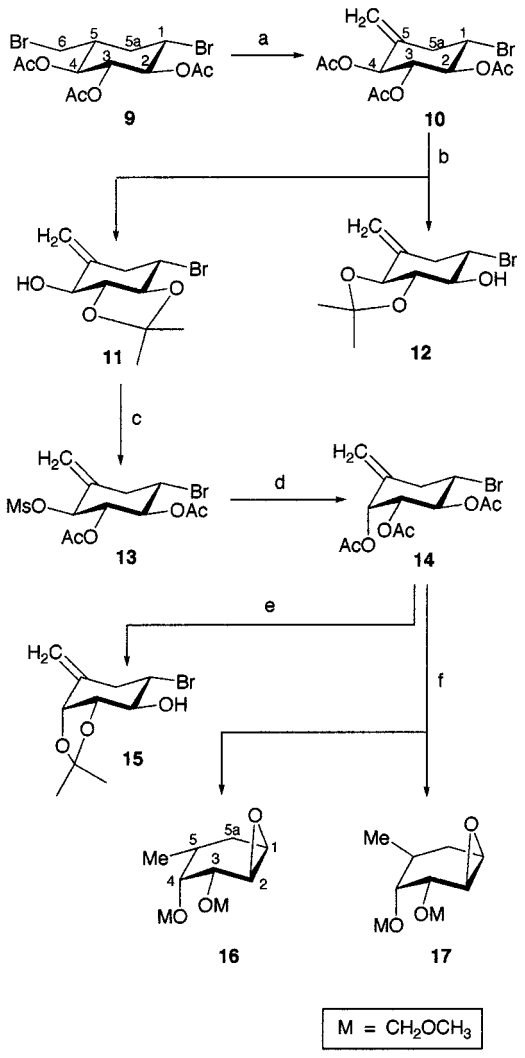
Results and Discussion

As a starting compound for the preparation of 5a-carba-L-fucopyranose derivatives, we chose 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-5a-carba-β-L-glucopyranosyl bromide[15] (**9**), obtained from the optically resolved *endo* adduct[16] of furan and acrylic acid.

Compound **9** was selectively dehydrobrominated by treatment with 2 mol-equiv. of silver fluoride[17] in pyridine, converting it into the crystalline *exo*-methylene derivative **10** in 83% yield. Inversion of the configuration at C-4 was then attempted by means of an intramolecular nucleophilic substitution reaction of the 4-sulfonate of **10**, assisted by neighboring participation of the 3-acetoxy group (Scheme 2). Thus, compound **10** was de-*O*-acetylated with 4 M hydrochloric acid in aqueous THF, and the resulting triol was treated with 2,2-dimethoxypropane (10 mol-equiv.) in DMF in the presence of TsOH, giving the 2,3- and 3,4-*O*-isopropylidene derivatives **11** and **12** in 73 and 23% yield, respectively, after chromatography on silica gel. Compound **11** was successively treated with mesyl chloride in pyridine, de-*O*-isopropylidenated with 60% aqueous acetic acid, and acetylated with acetic anhydride in pyridine to give the crystalline mesylate **13** in an overall yield of 73%. Compound **13** smoothly underwent direct displacement in 60% aqueous acetic acid through an intermediate acetoxonium ion to give, after conventional acetylation, the 4-epimer **14** of **10** in 98% yield. Compound **14** was readily converted into the 3,4-*O*-isopropylidene derivative **15** (85%) by conventional means.

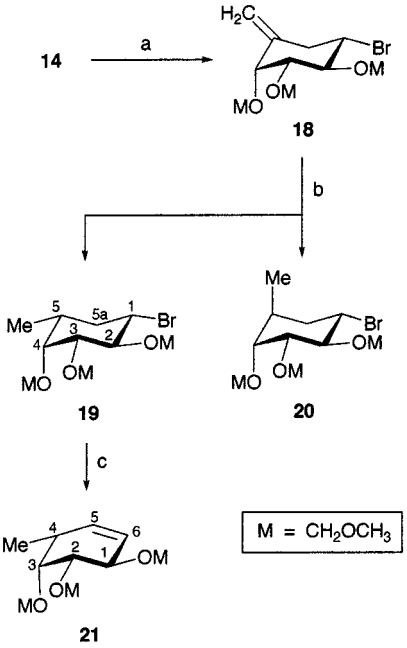
Furthermore, de-*O*-acetylation with 4 M hydrochloric acid, followed by treatment with *N*,*N*-diisopropylethylamine, gave the epoxide, which was hydrogenated without being isolated in the presence of Wilkinson catalyst, affording the α-L-fucose-type epoxide **16** (58%) and its 5-epimer **17** (14%). The former is a versatile intermediate[18] for the preparation of carbafucopyranose derivatives.

To provide compound **14** (Scheme 3) with protecting groups stable to basic conditions, methoxymethyl groups were introduced in place of the acetyl functions in the usual manner, with conversion into the tris(methoxymethyl) ether **18** (84%). Catalytic hydrogenation of **18** with Pt/C or Pd/C catalyst gave an approximately 3−4:1 ratio of the carbafucosyl and -altrosyl bromides **19** and **20**. However, hydrogenation in benzene with use of Wilkinson catalyst was shown to improve the selectivity, to afford **19** reproducibly in 80% yield, together with a trace of **20** (ca. 10%). In the presence of DBU in toluene, compound **19** produced the expected alkene **21**, together with an appreciable amount of isomerized alkenes. However, it was subsequently found that treatment of **19** with sodium hydride in the presence of a trace of methanol in DMF[19] selectively gave **21** in 91% yield. Compound **21** may be utilized for synthesis of carbafucopyranose derivatives.

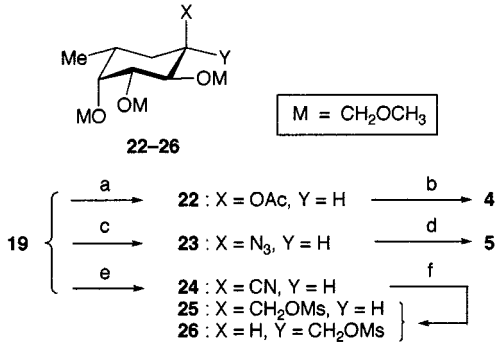


Scheme 2. Preparation of intermediates **14** and **16** for the synthesis of 5a-carbafucopyranose derivatives; reagents and conditions: (a) AgF (2 equiv.), pyridine, 5 h, room temp; (b) 4 M HCl/THF, 3 d, 60 °C; 2,2-dimethoxypropane (10 equiv.), TsOH (0.2 equiv.), DMF, 7 h, 60 °C; (c) MsCl/pyridine, 0 °C; 60% aq. AcOH, room temp; Ac_2O/pyridine, overnight, room temp; (d) 60% aq. AcOH, 3 h, 60 °C; Ac_2O/pyridine; (e) 4 M HCl/THF; 2,2-dimethoxypropane (4 equiv.), TsOH, DMF, 4 h, room temp; (f) 4 M HCl/THF; *N*,*N*-diisopropylethylamine (6 equiv.), CH_2Cl_2, overnight, 40 °C; H_2, Wilkinson catalyst (0.1 equiv.), benzene, 1 drop of MeOH, 12 h, room temp.

Treatment of **19** with potassium acetate (10 mol-equiv.) in DMF at 100 °C gave[20] the substitution product **22** (Scheme 4, 50%) and the elimination product **21** (46%), demonstrating that **19** is a poor substrate for moderate nucleophiles. Deprotection of **22** with 4 M hydrochloric acid in aqueous THF gave free 5a-carba-α-L-fucopyranose[21,22] **4** (65%). Azidolysis of **19** with sodium azide (5 mol-equiv.), however, proceeded very smoothly in DMF at 90 °C to afford the azide **23** selectively, in 86% yield. Deprotection of **23** with 4 M hydrochloric acid at room temperature and subsequent reduction of the azido group with triphenylphosphane in THF gave, after chromatography on Dowex 50 W × 2 (H^+) resin with 1% aqueous ammonia, the free carbafucopyranosylamine **5** in 66% yield. Treatment of **19** with a large excess of sodium cyanide (15 mol-equiv.) in dry DMF



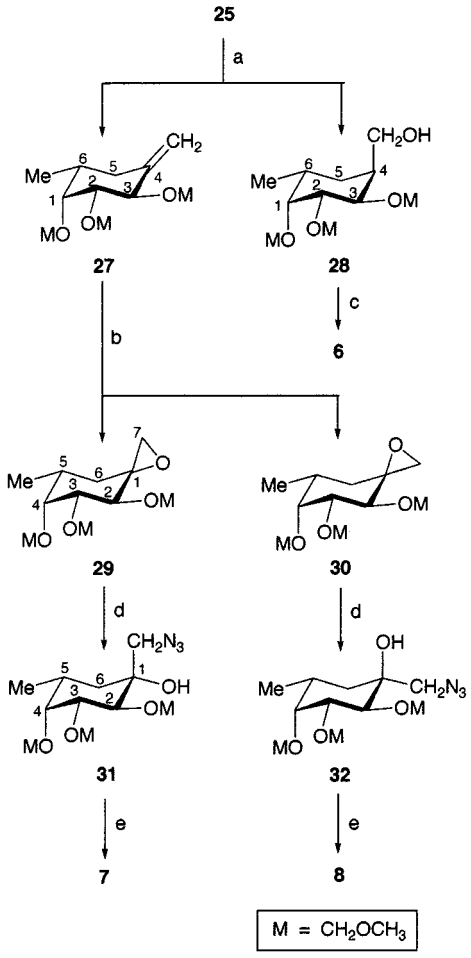
Scheme 3. Preparation of intermediates **19** and **21** for synthesis of 5a-carbafucopyranose derivatives; reagents and conditions: (a) 4 M HCl/THF; chloromethoxymethane (6 equiv.), diisopropylethylamine (6 equiv.), 14 h, 40 °C; (b) H_2, Wilkinson catalyst (0.2 equiv.), benzene/1 drop of MeOH, 16 h, room temp; (c) NaH (6 equiv.), DMF, 6 h, 60 °C



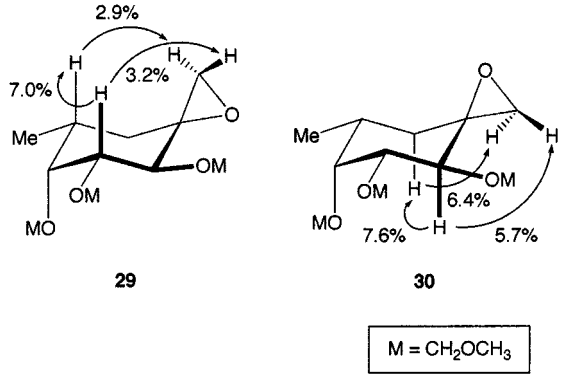
Scheme 4. Synthesis of 5a-carba-α-L-fucopyranose (**4**) and -fucopyranosylamine (**5**), and nitrile **24**; reagents and conditions: (a) AcOK (10 equiv.), 20 h, 100 °C; (b) 4 M HCl/THF, 3 h, 50 °C; (c) NaN_3 (5 equiv.), DMF, 9 h, 90 °C; (d) Ph_3P, 5% aq THF, 3 d, 60 °C; (e) NaCN (15 equiv.), DMF, 20 h, 100 °C; (f) 1 M DIBAL (2 equiv.)/toluene, 4 h, −78 → −60 °C; $NaBH_4$ (1 equiv.), MeOH; MsCl, Et_3N

at 100 °C afforded the nitrile **24** (90%), along with a trace of the alkene **21** (5%). Reduction of **24** with 1 M DIBAL (2 mol-equiv.) in toluene at −60 °C gave an approximately 2:1 mixture of epimeric aldehydes, which was treated (without separation) with sodium borohydride in methanol. The resulting alcohols were isolated as the mesylates **25** (47%) and **26** (38%).

Compound **25** was treated with DBU in toluene at 80 °C to give the *exo*-methylene compound **27** (Scheme 5, 85%) and the alcohol **28** (18%). Oxidation of **27** with *m*CPBA in CH_2Cl_2 at room temperature afforded epimeric spiro epoxides **29** and **30** in 77 and 21% yield (Scheme 6), respectively; their structures were established by NOE experiments. Rear-side attack of the peracid away from the methoxymethyloxy group at C-3 appeared to be preferable. Azidolysis of **29** and **30** in DMF at 80 °C afforded the azides **31** and **32** in 94 and 88% yield, respectively. Compounds **31** and **32** were transformed quantitatively into the respective amines **7** and **8** by hydrolysis with 4 M hydrochloric acid and successive



Scheme 5. Synthesis of spiro epoxides **29** and **30**, and their conversion into 1-aminomethyl derivatives **7** and **8** of 5a-carbafucopyranose; reagents and conditions: (a) DBU (6 equiv.), toluene, 80 °C, 4 h; (b) *m*CPBA (1.5 equiv.), CH_2Cl_2, 5.5 h, room temp; (c) 4 M HCl/THF; (d) NaN_3 (3 equiv.), DMF, 15-crown-5 ether, 20 h, 80 °C; (e) 4 M HCl/THF, 10 h, room temp; H_2, 5%Pd/C, EtOH, 3 d, 60 °C



Scheme 6. NOE experiments on compounds **29** and **30**

hydro-genation with Pd/C in ethanol. The amines **7** and **8** were purified on silica gel and subjected directly to biological assays.

Biological Assay

Compounds **4**−**8** were assayed[1] for inhibitory activity against α-L-fucosidase (bovine kidney), and their K_i values are listed in Table 1. Compound **4** ($K_i = 4.3 \times 10^{-5}$ M) showed moderate inhibitory activity comparable to that of 5-thiofucopyranose[7] **2** ($K_i = 8.4 \times 10^{-5}$ M). These results appeared to be due simply to hydrophobic interaction between the ring methylene group and the enzymes, as has been proposed for the cases of the sulfur atoms of 5-thioglucose[23] and 5-thiofucose.[7]

Table 1. Inhibitory activity of compounds **2** and **4**−**8** against α-L-fucosidase (α-L-fucosidase, bovine kidney, and *p*-nitrophenyl α-L-fucopyranoside were purchased from Sigma)

Compound	Inhibitory activity (K_i, M)[a]
2	8.4×10^{-5}
4	4.3×10^{-5}
5	1.2×10^{-8}
6	NI[b]
7	2.8×10^{-6}
8	3.0×10^{-7}

[a] 0.54−1.37 μM, *p*-nitrophenyl α-L-fucopyranoside, 17 μM citrate buffer, pH = 6.0, ref.[1] − [b] NI: No inhibitory activity ($<10^{-4}$).

However, compound **5** was demonstrated to be a specific and very strong inhibitor ($K_i = 1.2 \times 10^{-8}$ M). Replacement of the 1-hydroxy group of **4** by an amino function surprisingly resulted in a more than 3000-fold increase in its activity. Also, with regard to binding to enzymes, fucopyranosylamine is apparently overwhelmed by **4**, indicating the importance of its hydrophobic 5a-ring methylene portion. This compound has been shown to possess an inhibitory potency approaching that of the potent 1-deoxyfuconojirimycin[5] (**1**), which has promise as a therapeutic agent for cancer and AIDS.

The fact that both the epimers **7** and **8**, possessing aminomethyl branching groups at C-1, were shown to possess strong activity (K_i = 2.8 and 0.3×10^{-6} M, respectively) suggests that carbafucosylamine **4** is a potential lead compound, with possible improvement in potency achievable by chemical modification around the anomeric positions. Furthermore, 5a-carbafucopyranosyl residues could easily be introduced into the oligosaccharide chains by way of imino linkages, as shown[14] by the attempted preparation of imino-linked 5a-carba-L-fucopyranosyl-α-(1→4)-2-acetamido-2-deoxy-D-glucopyranose derivatives designed for fucosyltransferase inhibition. Since the enantiomeric 5a-carba-α-D-fucopyranosylamine[14] presumably has preserved activity to some extent, the structure−activity relationship of inhibitors of this kind seems to be rather flexible and not rigidly determined.

Experimental Section

General: Melting points: Mel-Temp capillary melting-point apparatus, uncorrected values. − Specific rotations: Jasco DIP-370 polarimeter, 1-dm cells. − IR spectra: Jasco A-202 or FT-IR-200. ^{1}H NMR spectra: Jeol JNM GSX-270 f.t. (270 MHz) and Jeol Lambda-300 (300 MHz); solvent $CDCl_3$, internal standard tetramethylsilane (TMS), CD_3OD external acetone. − Mass spectra: positive ion electrospray ionization with a Jasco GC-Mass GC-Mate, and Perseptive Biosystems Mariner LC Mass. − TLC: 60 GF silica gel (E. Merck, Darmstadt); detection by charring with concd. H_2SO_4. − Column chromatography: 60 K070 silica gel (Katayama Chemicals, Osaka) and Wakogel C-300 (silica gel, 300 mesh, Wako Chemical, Osaka). − Organic solutions, after drying with anhydrous Na_2SO_4, were concentrated at < 50 °C and reduced pressure.

2,3,4-Tri-*O*-acetyl-6-bromo-6-deoxy-5a-carba-β-L-glucopyranosyl Bromide (9): (1*R*)-2-*exo*,3-*endo*-Diacetoxy-5-*endo*-acetoxymethyl-7-oxabicyclo[2.2.1]heptane (3 g), prepared conventionally from (2*S*)-7-*endo*-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid,[16] was heated with 20% hydrobromic acid/acetic acid in a sealed tube for 22 h at 80 °C. The reaction mixture obtained from fourteen sealed tubes (total amount of the triacetate used: 42.0 g, 0.147 mol) was poured onto cold ethyl acetate (1.2 L), and the solution was washed with brine (400 mL × 3) and saturated aqueous sodium hydrogen carbonate (400 mL × 2), dried, and concentrated. The residual product (ca. 70 g) was eluted from a silica gel column (400 g) with ethyl acetate/hexane (1:3 → 1:1) to give **9** (ca. 44 g, 77%) as a colorless syrup; $[\alpha]_D^{20} = +2.8$ (c = 1.4, $CHCl_3$) [ref.[16] D-bromide, crystals, m.p. 99−100 °C, $[\alpha]_D^{16} = -3.6$ (c = 1.1, $CHCl_3$)]. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98−2.08 [m, 2 H, 4-H, 5a(ax)-H], 2.00, 2.05, and 2.08 (3 s, each 3 H, 3 × Ac), 2.61 [ddd, $J_{1,5a(eq)}$ = 4.4, $J_{5,5a(eq)}$ = 1.7, J_{5agem} = 13.4 Hz, 1 H, 5a(eq)-H], 3.26 (dd, $J_{5,6a}$ = 6.6, J_{6gem} = 10.7 Hz, 1 H, 6a-H), 3.40 (dd, $J_{5,6b}$ = 3.1 Hz, 1 H, 6b-H), 3.96 [ddd, $J_{1,2}$ = 10.2, $J_{1,5a(ax)}$ = 12.2 Hz, 1 H, 1-H], 5.02 (dd, $J_{3,4}$ = 9.8, $J_{4,5}$ = 9.9 Hz, 1 H, 4-H), 5.03 (dd, $J_{2,3}$ = 9.8 Hz, 1 H, 3-H), 5.21 (dd, 1 H, 2-H). − $C_{13}H_{18}Br_2O_6$ (430.1): calcd. C 36.30, H 4.22; found C 36.48, H 4.39.

2,3,4-Tri-*O*-acetyl-5a-carba-β-L-*xylo*-hex-5-enopyranosyl Bromide (10): Compound **9** (7.81 g, 18 mmol) in dry pyridine (50 mL) was stirred with silver fluoride (2 mol-equiv.) for 5 h at room temperature. The mixture was diluted with ethyl acetate (300 mL), and insoluble material was removed by filtration. The organic solution was washed with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, dried, and concentrated. Crystallization from ethanol gave **10** (5.26 g, 83.0%) as needles; m.p. 121−124 °C (from EtOH), $[\alpha]_D^{26} = +14$ (c = 0.40, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01, 2.11, and 2.17 (3 s, each 3 H, 3 × Ac), 2.97 [dd, $J_{1,5a(ax)}$ = 11.6, J_{5agem} = 13.9 Hz, 1 H, 5a(ax)-H], 3.01 [dd, $J_{1,5a(eq)}$ = 4.7 Hz, 1 H, 5a(eq)-H], 3.83 (ddd, $J_{1,2}$ = 9.6 Hz, 1 H, 1-H), 4.96 (dd, $J_{2,3}$ = 9.6, $J_{3,4}$ = 9.8 Hz, 1 H, 3-H), 5.02 and 5.09 (2 br. s, each 1 H, =CH_2), 5.32 (dd, 1 H, 2-H), 5.43 (d, 1 H, 4-H). − $C_{13}H_{17}BrO_6$ (349.2): calcd. C 44.72, H 4.91; found C 44.64, H 4.89.

2,3-*O*-Isopropylidene-5a-carba-β-L-*xylo*-hex-5-enopyranosyl Bromide (11) and 3,4-*O*-Isopropylidene-5a-carba-β-L-*xylo*-hex-5-enopyranosyl Bromide (12): Compound **10** (13.3 g, 38.0 mmol) was dissolved in a mixture of 4 M hydrochloric acid (25 mL) and THF (75 mL), and heated for 3 d at 60 °C. The mixture was concentrated to dryness and the residue was crystallized from ethanol. The crystalline triol (ca. 7.8 g) was treated with 2,2-dimethoxypropane

(46 mL, 10 mol-equiv.) in DMF (150 mL) in the presence of TsOH hydrate (1.5 g, 0.20 mol-equiv.) for 7 h at 60 °C. After neutralization with triethylamine, the mixture was diluted with ethyl acetate (600 mL), and the solution was washed with water and saturated aqueous sodium hydrogen carbonate, dried, and concentrated. The residual syrup was chromatographed on a silica gel column (300 g) with ethyl acetate/toluene (1:13) as the eluent to give crystalline **11** (7.29 g, 72.2%) and syrupy **12** (2.31 g, 23.0%).

Compound 11: M.p. 96−98 °C (from EtOH), $[\alpha]_D^{28} = +64$ ($c = 0.10$, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 and 1.51 (2 s, each 3 H, CMe_2), 2.57 [dd, $J_{1,5a(a)} = 1.1$, $J_{5agem} = 14.4$ Hz, 1 H, 5a(a)-H], 3.02 [dd, $J_{1,5a(b)} = 4.8$ Hz, 1 H, 5a(b)-H], 3.28 (dd, $J_{2,3} = 9.1$, $J_{3,4} = 9.8$ Hz, 1 H, 3-H), 3.70 (dd, $J_{1,2} = 10.5$, Hz, 1 H, 2-H), 3.88 (ddd, 1 H, 1-H), 4.30 (d, 1 H, 4-H), 5.13 and 5.35 (2 br. s, each 1 H, $=CH_2$). − $C_{10}H_{15}BrO_3$ (265.1): calcd. C 45.65, H 5.75; found C 45.87, H 6.12.

Compound 12: $[\alpha]_D^{26} = +84$ ($c = 0.12$, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 and 1.50 (2 s, each 3 H, CMe_2), 2.65 [dd, $J_{1,5a(a)} = 1.3$, $J_{5agem} = 14.4$ Hz, 1 H, 5a(a)-H], 2.92 [dd, $J_{1,5a(b)} = 5.4$, Hz, 1 H, 5a(b)-H], 3.30 (dd, $J_{2,3} = 9.3$, $J_{3,4} = 9.5$ Hz, 1 H, 3-H), 3.80 (ddd, $J_{1,2} = 9.3$ Hz, 1 H, 1-H), 3.98 (dd, 1 H, 2-H), 3.99 (d, 1 H, 4-H), 4.96 and 5.10 (2 br. s, each 1 H, $=CH_2$). − $C_{10}H_{15}BrO_3$ (265.1): calcd. C 45.65, H 5.75; found C 46.04, H 6.09.

2,3-Di-*O*-acetyl-4-*O*-mesyl-5a-carba-β-L-*xylo*-hex-5-enopyranosyl Bromide (13): To a solution of **11** (3.8 g, 14.5 mmol) in pyridine (30 mL) was added mesyl chloride (2.2 mL, 2 mol-equiv.) at 0 °C, and the mixture was stirred for 2 h at the same temperature. After addition of a small amount of methanol, the mixture was diluted with ethyl acetate (200 mL) and the solution was washed with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, dried, and concentrated. The crystalline residue was treated with 60% aqueous acetic acid (100 mL) for 4 h at room temperature, concentrated to dryness, and acetylated overnight at room temperature with acetic anhydride (8 mL) and pyridine (20 mL). The mixture was diluted with ethyl acetate (200 mL), and the solution was washed with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, dried, and concentrated. Crystallization from ethanol gave **13** (4.0 g, 73%) as needles: m.p. 119−121 °C (from EtOH), $[\alpha]_D^{21} = +71$ ($c = 0.10$, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.07 and 2.09 (2 s, each 3 H, 2 × Ac), 2.64 [dd, $J_{1,5a(ax)} = 12.8$, $J_{5agem} = 14.3$ Hz, 1 H, 5a(ax)-H], 3.04 [dd, $J_{1,5a(eq)} = 4.8$ Hz, 1 H, 5a(eq)-H], 3.06 (s, 3 H, Ms), 3.82 (ddd, $J_{1,2} = 10.6$ Hz, 1 H, 1-H), 4.98 (dd, $J_{2,3} = 9.5$, $J_{3,4} = 9.9$ Hz, 1 H, 3-H), 5.14 (d, 1 H, 4-H), 5.29 (dd, 1 H, 2-H), 5.34 and 5.22 (2 br. s, each 1 H, $=CH_2$). − $C_{12}H_{17}BrO_7S$ (385.2): calcd. C 37.41, H 4.45; found C 37.60, H 4.63.

2,3,4-Tri-*O*-acetyl-5a-carba-β-L-*arabino*-hex-5-enopyranosyl Bromide (14): Compound **13** (3.9 g, 10.1 mmol) was mixed with 60% aqueous acetic acid (100 mL), maintained for 3 h at 60 °C, and then concentrated to dryness. The residual product was acetylated in the usual manner to give **14** (3.5 g, 98%) as crystals; m.p. 137−138 °C (from EtOH), $[\alpha]_D^{26} = +14$ ($c = 0.34$, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01, 2.10, and 2.14 (3 s, each 3 H, 3 × Ac). 2.81−2.97 [m, 2 H, 5a(ax)-H, 5a(eq)-H], 3.85 [ddd, $J_{1,2} = 10.3$, $J_{1,5a(ax)} = 9.6$, $J_{1,5a(eq)} = 1.7$ Hz, 1 H, 1-H], 4.83 (dd, $J_{2,3} = 10.2$, $J_{3,4} = 3.2$ Hz, 1 H, 3-H), 5.58 (dd, 1 H, 2-H), 5.68 (d, 1 H, 4-H). − $C_{13}H_{17}BrO_6$ (349.2): calcd. C 44.72, H 4.91; found C 44.80, H 5.07.

2,3,4-Tri-*O*-(methoxymethyl)-5a-carba-β-L-*arabino*-hex-5-enopyranosyl Bromide (18): A solution of compound **14** (3.71 g) in a mixture of 4 M hydrochloric acid (25 mL) and THF (75 mL) was stirred for 20 h at 60 °C, and then concentrated to dryness. The residue was treated with chloromethoxymethane (4.8 mL, 6 mol-equiv.) in the presence of diisopropylethylamine (11 mL, 6 mol-equiv.) for 14 h at 40 °C. The mixture was then diluted with chloroform (300 mL), and the solution was washed thoroughly with water, dried, and concentrated. The residue was eluted from a column of silica gel (200 g) with ethyl acetate/hexane (1:5 → 1:3) to give **18** (3.2 g, 84%) as a syrup; $[\alpha]_D^{26} = +59$ ($c = 1.00$, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.72 [dd, 1 H, $J_{1,5a(eq)} = 5.4$, $J_{5agem} = 13.1$ Hz, 5a(eq)-H], 2.86 [dd, $J_{1,5a(ax)} = 12.5$ Hz, 1 H, 5a(ax)-H], 3.38 (m, 1 H, 2-H), 3.40, 3.44, and 3.52 (3 s, each 3 H, 3 × OMe), 3.76 [ddd, $J_{1,2} = 9.7$ Hz, 1 H, 1-H], 4.08 (dd, $J_{2,3} = 9.5$ Hz, 1 H, 2-H), 4.35 (d, $J_{3,4} = 3.0$ Hz, 1 H, 4-H), 4.60 and 4.66 (ABq, $J_{gem} = 6.6$ Hz), 4.78 (s, 2 H), and 4.84 and 4.97 (ABq, $J_{gem} = 6.1$ Hz) (3 × CH_2OMe), 5.09 and 5.11 (2 br. s, each 1 H, $=CH_2$). − $C_{13}H_{23}BrO_6$ (355.2): calcd. C 43.96, H 6.53; found C 44.11, H 6.60.

3,4-*O*-Isopropylidene-5a-carba-β-L-*arabino*-hex-5-enopyranosyl Bromide (15): A solution of the triacetate **14** (0.32 g, 0.90 mmol) in a mixture of 4 M hydrochloric acid (7 mL) and THF (21 mL) was maintained for 20 h at 60 °C, and then concentrated. Crude triol obtained was dissolved in dry DMF (6 mL) and the solution was treated with 2,2-dimethoxypropane (0.45 mL, 4 mol-equiv.) and TsOH hydrate (34 mg) for 4 h at room temperature. After neutralization with triethylamine, the mixture was concentrated and the residue was chromatographed on a silica gel column (18 g) with ethyl acetate/hexane (1:6) to give **15** (0.20 g, 85%) as a syrup; $[\alpha]_D^{24} = -30$ ($c = 0.55$, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 and 1.57 (2 s, each 3 H, CMe_2), 2.82−2.95 (m, 2 H, 5a,5a-H), 3.78 [ddd, $J_{1,2} = 10.5$, $J_{1,5a(a)} = 5.1$, $J_{1,5a(b)} = 4.8$ Hz, 1 H, 1-H], 3.83 (dd, $J_{2,3} = 7.0$ Hz, 1 H, 2-H), 4.00 (dd, $J_{3,4} = 5.3$ Hz, 1 H, 3-H), 4.56 (d, 1 H, 4-H), 5.27 and 5.33 (2 s, each 1 H, $=CH_2$). − $C_{10}H_{15}BrO_3$ (263.1): calcd. C 45.65, H 5.75; found C 45.43, H 5.96.

1,2-Anhydro-3,4-di-*O*-(methoxymethyl)-5a-carba-α-L-fucopyranose (16) and 1,2-Anhydro-6-deoxy-3,4-di-*O*-(methoxymethyl)-5a-carba-β-D-altropyranose (17): Compound **14** (0.44 g, 1.26 mmol) was de-*O*-acetylated as in the preparation of **10** to give the crude triol, which, without purification, was treated with *N*,*N*-diisopropylethylamine (1.3 mL, 6 mol-equiv.) in CH_2Cl_2 (6 mL) and maintained overnight at 40 °C. The mixture was diluted with chloroform (200 mL) and the solution was washed thoroughly with water, dried, and concentrated. The residue was eluted from a column of silica gel (15 g) with ethyl acetate/hexane (1:4), to give a major fraction as a homogeneous syrup. The product was hydrogenated in benzene (4 mL) containing 1 drop of methanol in the presence of Wilkinson catalyst (120 mg, ca. 0.1 mol-equiv.) for 12 h at room temperature. The products were chromatographed on a silica gel column (15 g) with ethyl acetate/toluene (1:8) to give syrupy **16** (0.17 g, 58%) and **17** (0.04 g, 14%).

Compound 16: $[\alpha]_D^{22} = +82$ ($c = 1.10$, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, $J_{5,Me} = 6.8$ Hz, 3 H, CMe), 1.53 [br. ddd, $J_{5,5a(a)} = 11.5$, $J_{5,5a(b)} = 5.5$ Hz, 1 H, 5-H], 1.76 [ddd, $J_{1,5a(a)} = 2.1$, $J_{5agem} = 14.7$ Hz, 1 H, 5a(a)-H], 1.92 [ddd, $J_{1,5a(b)} = 11.5$, Hz, 1 H, 5a(b)-H], 3.09 (dd, $J_{2,3} = 2.2$, $J_{3,4} = 3.6$ Hz, 1 H, 3-H), 3.31 (br. ddd, $J_{1,2} = 1.7$, Hz, 1 H, 1-H), 3.42 and 3.43 (2 s, each 3 H, 2 × OMe), 3.63 (dd, 1 H, 2-H), 3.74 (d, 1 H, 4-H), 4.67 and 4.76, and 4.80 and 4.86 (2 ABq, $J_{gem} = 6.8$ Hz, 2 × OCH_2-OMe). − HRMS [$C_{10}H_{17}O_4$, $M^+ - OCH_3$]: calcd. 201.1127; found 201.1140.

Compound 17: $[\alpha]_D^{21} = +49$ ($c = 0.48$, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, $J_{5,Me} = 6.6$ Hz, 3 H, CMe), 1.62

[br. dd, $J_{5,5a(a)}$ = 10.5, J_{5agem} = 14.7 Hz, 1 H, 5a(a)-H], 2.06 [dddd, $J_{5,5a(b)}$ = 7.3, Hz, 1 H, 5-H], 2.19 [ddd, $J_{1,5a(b)}$ = 4.2, 1 H, 5a(b)-H], 3.17 (br. dd, $J_{1,2}$ = 3.9 Hz, 1 H, 1-H), 3.35 (dd, $J_{2,3}$ = 2.9 Hz, 1 H, 2-H), 3.43 and 3.40 (2 s, each 3 H, 2 × OMe), 3.47 (dd, $J_{3,4}$ = 3.1, $J_{4,5}$ = 9.8 Hz, 1 H, 4-H), 4.28 (dd, 1 H, 3-H), 4.60 and 4.73, and 4.77 and 4.84 (2 ABq, J_{gem} = 6.7 Hz, 2 × OCH_2OMe). – HRMS [$C_{10}H_{17}O_4$, $M^+ - OCH_3$]: calcd. 201.1127; found 201.1140.

2,3,4-Tri-*O*-(methoxymethyl)-5a-carba-β-L-fucopyranosyl Bromide (19) and 6-Deoxy-2,3,4-tri-*O*-(methoxymethyl)-5a-carba-α-D-altropyranosyl Bromide (20): To a solution of **18** (0.82 g, 2.3 mmol) in dry benzene (6.0 mL) were added Wilkinson catalyst (430 mg, 0.2 mol-equiv.) and 2 drops of methanol. The mixture was vigorously stirred under hydrogen for 16 h at room temperature, and then concentrated to dryness. The residue was chromatographed on a silica gel column (60 g) with ethyl acetate/toluene (1:8 → 1:6) to give syrupy **19** (0.66 g, 80%) and **20** (0.12 g, 15%).

Compound 19: $[\alpha]_D^{21}$ = +104 (*c* = 0.90, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, $J_{5,Me}$ = 6.6 Hz, 3 H, CMe), 1.64 (dddd, $J_{4,5}$ = 2.0 Hz, 1 H, 5-H), 2.01 [ddd, $J_{1,5a(eq)}$ = 4.7, $J_{5,5a(eq)}$ = 5.0, J_{5agem} = 12.4 Hz, 1 H, 5a(eq)-H], 2.07 [ddd, $J_{1,5a(ax)}$ = 10.4, $J_{5,5a(ax)}$ = 9.0 Hz, 1 H, 5a(ax)-H], 3.44 (dd, $J_{3,4}$ = 2.2 Hz, 1 H, 3-H), 3.41, 3.42, and 3.51 (3 s, each 3 H, 3 × OMe), 3.83 (br. s, 1 H, 4-H), 3.86 (ddd, $J_{1,2}$ = 9.3 Hz, 1 H, 1-H), 3.93 (dd, $J_{2,3}$ = 9.1 Hz, 1 H, 2-H), 4.73 (s, 2 H), 4.65 and 4.90 (ABq, J_{gem} = 6.6 Hz), and 4.81 and 4.84 (ABq, J_{gem} = 6.4 Hz) (3 × CH_2OMe). – HRMS [$C_{13}H_{25}O_6Br$, $M^+ - OCH_3$]: 325.0650; found 325.0658.

Compound 20: $[\alpha]_D^{26}$ = +89 (*c* = 0.18, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, $J_{5,Me}$ = 6.5 Hz, 3 H, CMe), 2.01 [ddd, $J_{1,5a(eq)}$ = 5.4, $J_{5,5a(eq)}$ = 7.1, J_{5agem} = 13.0 Hz, 1 H, 5a(eq)-H], 2.18 [dddd, 1 H, 5-H], 2.39 [ddd, $J_{1,5a(ax)}$ = 12.5, $J_{5,5a(ax)}$ = 4.5 Hz, 1 H, 5a(ax)-H], 3.40, 3.42, and 3.49 (3 s, each 3 H, 3 × OMe), 3.71 (dd, $J_{2,3}$ = 8.6, $J_{3,4}$ = 3.0 Hz, 1 H, 3-H), 3.76 (ddd, $J_{1,2}$ = 8.8 Hz, 1 H, 1-H), 3.76 (dd, $J_{4,5}$ = 3.7 Hz, 1 H, 4-H), 3.96 (dd, 1 H, 2-H), 4.08 [ddd, $J_{1,5a(ax)}$ = 11.3, $J_{1,5a(eq)}$ = 4.9 Hz, 1 H, 1-H], 4.08 (dd, 1 H, 2-H), 4.35 (d, 1 H, 4-H), 4.70 and 4.72 (ABq, J_{gem} = 6.6 Hz), 4.72 and 4.76 (ABq, J_{gem} = 6.9 Hz), and 4.80 and 4.89 (ABq, J_{gem} = 6.4 Hz) (3 × CH_2OMe).

(1*S*,2*S*,3*R*,6*R*)-1,2,3-Tri-*O*-(methoxymethyl)-4-methylcyclohex-5-ene-1,2,3-triol (21): To a solution of **19** (110 mg, 3.10 mmol) in DMF (1 mL) were added sodium hydride (74 mg, 6 mol-equiv.) and 1 drop of methanol, and the mixture was stirred for 6 h at 60 °C. After neutralization with Dowex 50 W × 2 (H^+) resin, the mixture was concentrated and the residue was eluted from a column of silica gel (8 g) with ethyl acetate/toluene (1:9 → 1:6) to give **21** (78 mg, 91%) as a syrup; $[\alpha]_D^{28}$ = +12 (*c* = 1.2, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, 3 H, $J_{4,Me}$ = 7.3 Hz, CMe), 2.55 (dddd, $J_{3,4}$ = 1.7, $J_{4,6}$ = 1.9 Hz, 1 H, 4-H), 3.40, 3.41, and 3.42 (3 s, each 3 H, 3 × OMe), 3.80 (dd, $J_{1,2}$ = 7.9, $J_{2,3}$ = 2.0 Hz, 1 H, 2-H), 4.01 (br. dd, 1 H, 3-H), 4.39 (ddd, $J_{1,5}$ = 2.5, $J_{1,6}$ = 3.1 Hz, 1 H, 1-H), 4.67 and 4.73 (ABq, J_{gem} = 6.8 Hz), 4.75 and 4.79 (ABq, J_{gem} = 6.6 Hz), and 4.83 and 4.96 (ABq, J_{gem} = 6.6 Hz) (3 × OCH_2OMe), 5.47 (ddd, $J_{5,6}$ = 10.0 Hz, 1 H, 6-H), 5.68 (ddd, 1 H, 5-H). – HRMS [$C_{13}H_{24}O_6$, M^+]: calcd. 276.1573; found 276.1573.

2,3,4-Tri-*O*-(methoxymethyl)-5a-carba-α-L-fucopyranosyl Acetate (22): A mixture of **19** (45 mg, 0.13 mmol), potassium acetate (93 mg, 10 mol-equiv.), and DMF (1 mL) was stirred for 20 h at 100 °C. After cooling, the mixture was diluted with ethyl acetate (30 mL), and the solution was washed thoroughly with brine, dried, and concentrated. The products were chromatographed on a silica gel column (3 g) with ethyl acetate/toluene (1:8) to give syrupy **21** (17 mg, 46%) and **22** (22 mg, 50%); $[\alpha]_D^{26}$ = −1 (*c* = 0.6, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (d, $J_{5,Me}$ = 4.9 Hz, 3 H, CMe), 1.26–1.68 [m, 2 H, 5a(ax)-H, H-5a(eq)-H], 1.96 (m, 1 H, 5-H), 2.09 (s, 3 H, Ac), 3.36, 3.41, and 3.42 (3 s, each 3 H, 3 × OMe), 3.85 (br. s, 1 H, 4-H), 3.97 (dd, $J_{1,2}$ = 3.1, $J_{2,3}$ = 9.6 Hz, 1 H, 2-H), 4.68 and 4.72 (ABq, J_{gem} = 6.8 Hz), 4.73 and 4.77 (ABq, J_{gem} = 6.9 Hz), and 4.83 and 4.91 (ABq, J_{gem} = 6.6 Hz) (3 × OCH_2OMe), 5.34 [br. dd, $J_{1,5a(ax)} \approx 0$, $J_{1,5a(eq)}$ = 6.0 Hz, 1 H, 1-H]. – HRMS [$C_{13}H_{26}O_6$, M^+ − OAc + H]: calcd. 278.1729; found 278.1729.

5a-Carba-α-L-fucopyranose (4): Compound **22** (21 mg, 62 μmol) was treated with a mixture of 4 M hydrochloric acid (0.5 mL) and THF (0.5 mL) over 3 h at 50 °C. The product was eluted from a column of silica gel (1 g) with methanol/chloroform (1:3) to give **4** (6.4 mg, 65%) as a syrup; $[\alpha]_D^{28}$ = −9 (*c* = 0.10, MeOH). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (d, $J_{5,Me}$ = 7.0 Hz, 3 H, Me), 1.23 [ddd, $J_{1,5a(eq)}$ = 5.4, $J_{5,5a(eq)}$ = 2.5, $J_{5a\ gem}$ = 12.0 Hz, 1 H, 5a(eq)-H], 1.49–1.65 [m, 2 H, 5-H, 5a(ax)-H], 3.24–3.40 (m, 3 H, 1-H, 2-H, 3-H), 3.64 (br. s, 1 H, 4-H). – HRMS [$C_7H_{14}O_4$, M^+ + Na]: calcd. 162.1130; found 162.1130.

2,3,4-Tri-*O*-(methoxymethyl)-5a-carba-α-L-fucopyranosyl Azide (23): A mixture of **19** (45 mg, 0.13 mmol), sodium azide (40 mg, 5 mol-equiv.), and DMF (2.5 mL) was stirred for 9 h at 90 °C. The mixture was diluted with ethyl acetate (30 mL) and the solution was washed thoroughly with brine, dried, and concentrated. The residue was eluted from a column of silica gel (30 g) with ethyl acetate/toluene (1:8) to give **23** (34 mg, 86%) as a syrup; $[\alpha]_D^{23}$ = +12 (*c* = 0.90, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84 (br. s, 3 H, CMe), 3.38, 3.41, and 3.42 (3 s, each 3 H, 3 × OMe), 4.06 (dd, $J_{2,3}$ = 8.1, $J_{3,4}$ = 3.4 Hz, 1 H, 3-H), 4.12–4.13 (m, 1 H, 1-H), 4.17 (dd, $J_{1,2}$ = 4.1 Hz, 1 H, 2-H), 4.23 (br. d, 1 H, 4-H), 4.67 and 4.88, 4.70 and 4.78, and 4.74 and 4.77 (3 ABq, J_{gem} = 6.6 Hz, 3 × CH_2OMe). – HRMS [$C_{13}H_{26}O_6$, $M^+ - N_3$ + H]: calcd. 278.1729; found 278.1729.

5a-Carba-α-L-fucopyranosylamine (5): A mixture of **23** (20 mg, 63 μmol), 4 M hydrochloric acid (0.5 mL), and THF (0.5 mL) was stirred for 10 h at room temperature, and concentrated. The residue was treated with triphenylphosphane (0.1 mL) in 5% aqueous THF (1 mL) over 3 d at 60 °C. The mixture was concentrated and the residue was chromatographed on a Dowex 50 W × 2 (H^+) resin with 1% aqueous ammonia as eluent to give **5** (6.6 mg, 66%) as a syrup; $[\alpha]_D^{20}$ = −38 (*c* = 0.15, MeOH). – ^{1}H NMR (300 MHz, CD_3OD): δ = 1.43 [ddd, $J_{1,5a(eq)} = J_{5,5a(eq)} \approx 3$, J_{5agem} = 12.9 Hz, 1 H, 5a(eq)-H], 1.68 [ddd, $J_{1,5a(ax)}$ = 3.7, $J_{5,5a(ax)}$ = 12.9 Hz, 1 H, 5a(ax)-H], 1.72–1.97 (m, 1 H, 5-H), 3.15 (ddd, $J_{1,2}$ = 4.4 Hz, 1 H, 1-H), 3.59 (dd, $J_{2,3}$ = 9.5, $J_{3,4}$ = 2.9 Hz, 1 H, 3-H), 3.71 (dd, 1 H, 2-H), 3.72 (br. s, 1 H, 4-H). – HRMS [$C_7H_{15}NO_3$, M^+ + H]: calcd. 162.1130; found 162.1106.

2,3,4-Tri-*O*-(methoxymethyl)-5a-carba-α-L-fucopyranosylcarbonitrile (24): A mixture of **19** (67 mg, 0.19 mmol), sodium cyanide (137 mg, 15 mol-equiv.) and dry DMF (0.7 mL) was stirred for 20 h at 100 °C. Toluene (10 mL) was added to the mixture, and an insoluble material was removed by filtration. The filtrate was concentrated and the residue was chromatographed on silica gel (4 g) with acetone/hexane (1:9 1:5) to give **24** (51 mg, 90%) as a syrup, together with a trace of **21** (3 mg, 5%); $[\alpha]_D^{20}$ = +41 (*c* = 0.19, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, $J_{5,Me}$ = 6.6 Hz, 3 H, CMe), 1.68 [ddd, $J_{1,5a(eq)}$ = 7.9, $J_{5,5a(eq)}$ = 2.9, J_{5agem} = 13.0 Hz, 1 H, 5a(eq)-H], 1.79 [ddd, $J_{1,5a(ax)}$ = 3.9, $J_{5,5a(ax)}$ = 12.2 Hz, 1 H, 5a(ax)-H], 2.05 (m, 1 H, 5-H), 3.34 (ddd, $J_{1,2}$ = 5.1 Hz, 1 H, 1-H), 3.46, 3.42 and 3.41 (3 s, each 3 H, 3 ×

OMe), 3.80 (dd, $J_{2,3}$ = 9.8, $J_{3,4}$ = 2.5 Hz, 1 H, 3-H), 3.87 (br. s, 1 H, 4-H), 3.91 (dd, 1 H, 2-H), 4.64 and 4.72, 4.73 and 4.79, and 4.82 and 4.90 (3 ABq, J_{gem} = 6.6 Hz, 3 × CH_2OMe). − HRMS [$C_{14}H_{25}NO_6$, $M^+ - OCH_3$]: calcd. 272.1499; found 272.1498.

(1*R*,2*R*,3*R*,4*S*,6*R*)- and (1*R*,2*R*,3*R*,4*R*,6*R*)-4-(Methanesulfonyloxymethyl)-1,2,3-tri-*O*-(methoxymethyl)-6-methyl-1,2,3-cyclohexanetriol (25 and 26): To a solution of **24** (50 mg, 160 μmol) in toluene (1 mL) was added 1 M DIBAL/toluene (320 μL, 2 mol-equiv.) at −78 °C, and then the mixture was stirred for 4 h at −60 °C. It was then diluted with ethyl acetate (1 mL) and stirred with acetic acid (1 mL) and silica gel (0.30 g) for 1 h at room temperature. Insoluble material was removed by filtration and the filtrate was concentrated. The residue was treated with sodium borohydride (6.2 mg, 1 mol-equiv.) in methanol (0.5 mL) for 20 min at 0 °C. The mixture was diluted with ethyl acetate (30 mL), and the solution was washed with water thoroughly, dried, and concentrated. The residue was treated with 2 drops of mesyl chloride and triethylamine for 2 h at 0 °C, and the reaction mixture was diluted with chloroform (20 mL), washed with water, dried, and concentrated. The residual products were chromatographed on silica gel (3 g) with butanone/hexane (1:6) to give syrupy **25** (30 mg, 47%) and **26** (24 mg, 38%).

Compound 25: $[\alpha]_D^{19}$ = +4.7 (*c* = 0.48, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (d, $J_{6,Me}$ = 7.1 H, 3 H, CMe), 1.46−1.64 [m, 2 H, 5a(ax)-H, 5a(eq)-H], 1.96 (m, 1 H, 6-H), 2.45 [ddddd, $J_{3,4}$ = 4.7, $J_{4,5a(ax)}$ = 4.4, $J_{4,5a(eq)}$ = 6.3, $J_{4,7a}$ = 6.1, $J_{4,7b}$ = 8.9 Hz, 1 H, 4-H], 3.00 (s, 3 H, Ms), 3.36 and 3.37 (2 s, 3 and 6 H, 3 × OMe), 3.69 (br. d, $J_{2,3}$ = 7.8 Hz, 1 H, 2-H), 3.98 (dd, $J_{3,4}$ = 4.7 Hz, 1 H, 3-H), 4.17 (dd, J_{7gem} = 11.2 Hz, 1 H, 7a-H), 4.39 (dd, 1 H, 7b-H), 4.64 and 4.68, 4.64 and 4.69, and 4.67 and 4.76 (3 ABq, J_{gem} = 6.6 Hz, 3 × CH_2OMe). − HRMS [$C_{13}H_{24}O_7S$, $M^+ - OCH_3 \times 2$]: calcd. 324.1242; found 324.1242.

Compound 26: $[\alpha]_D^{19}$ = +84 (*c* = 0.77, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, $J_{6,Me}$ = 6.9 Hz, 3 H, CMe), 1.45−1.70 [m, 3 H, 5a(ax)-H, 5a(eq)-H, 6-H], 1.83 (m, 1 H, 4-H), 3.03 (s, 3 H, Ms), 3.40, 3.41, and 3.43 (3 s, each 3 H, 3 × OMe), 3.52 (dd, $J_{1,2}$ = 2.4, $J_{2,3}$ = 9.4 Hz, 1 H, 2-H), 3.67 (dd, $J_{3,4}$ = 10.7 Hz, 1 H, 3-H), 3.82 (br. d, 1 H, 1-H), 4.21 (dd, $J_{4,7a}$ = 6.6, J_{7gem} = 9.4 Hz, 1 H, 7a-H), 4.43 (dd, $J_{4,7b}$ = 3.2 Hz, 1 H, 7b-H), 4.64 and 4.67, 4.68 and 4.76, and 4.85 and 4.87 (3 ABq, J_{gem} = 6.6 Hz, 3 × OCH_2OMe). − HRMS [$C_{13}H_{24}O_7S$, $M^+ - OCH_3 \times 2$]: calcd. 324.1242; found 324.1213.

(1*R*,2*R*,3*R*,6*R*)-1,2,3-Tri-*O*-(methoxymethyl)-6-methyl-4-methylene-1,2,3-cyclohexanetriol (27) and (1*R*,2*R*,3*R*,4*S*,6*R*)-4-(Hydroxymethyl)-1,2,3-tri-*O*-(methoxymethyl)-6-methyl-1,2,3-cyclohexanetriol (28): A mixture of **25** (9 mg, μmol), DBU (1.8 mL, 6 mol-equiv.), and toluene (1 mL) was stirred for 4 h at 80 °C, and then diluted with ethyl acetate (15 mL). The solution was washed with 1 M hydrochloric acid, saturated sodium hydrogen carbonate, and water, dried, and concentrated. The residue was chromatographed on a silica gel column (1 g) with ethyl acetate/hexane (1:3) to give **27** (5 mg, 80%) and **28** (1.3 mg, 18%).

Compound 27: $[\alpha]_D^{20}$ = +21 (*c* = 0.17, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, $J_{6,Me}$ = 6.6 Hz, 3 H, CMe), 1.64 (m, 1 H, 6-H), 2.06 (dd, $J_{5eq,6}$ = 4.4, J_{5gem} = 13.1 Hz, 1 H, 5eq-H), 2.16 (dd, $J_{5ax,6}$ = 12.0, 1 H, 5ax-H), 3.39, 3.40, and 3.41 (3 s, each 3 H, 3 × OMe), 3.45 (dd, $J_{1,2}$ = 2.6, $J_{2,3}$ = 9.4 Hz, 1 H, 2-H), 3.84 (br. s, 1 H, 1-H), 4.34 (br. d, 1 H, 3-H), 4.68 and 4.90 (ABq, J_{gem} = 7.1 Hz), 4.69 and 4.76 (ABq, J_{gem} = 6.3 Hz), and 4.73 and 4.79 (ABq, J_{gem} = 6.4 Hz) (3 × CH_2OMe), 4.82 (br. s, 1 H, 7a-H), 5.01 (br. s, 1 H, 7b-H). − HRMS [$C_{14}H_{26}O_6$, M^+]: calcd. 290.1729; found 290.1710.

Compound 28: $[\alpha]_D^{20}$ = −32 (*c* = 0.10, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.8 Hz, 3 H, CMe), 1.43−1.58 (m, 2 H, 5,5-H), 1.85−1.90 (m, 1 H, 6-H), 2.28−2.35 (m, 1 H, 4-H), 3.41, 3.45, and 3.49 (3 s, each 3 H, 3 × OMe), 3.45 (br. d, $J_{2,3}$ = 11.0 Hz, 1 H, 2-H), 3.55 (dd, $J_{3,4}$ = 5.1 Hz, 1 H, 3-H), 3.82 (br. s, 1 H, 1-H), 3.83 (br. s, 1 H, OH), 3.91 (dd, $J_{4,7a}$ = 9.5, J_{7gem} = 10.3 Hz, 1 H, 7a-H), 4.11 (dd, $J_{4,7b}$ = 4.6, 1 H, 7b-H), 4.49 and 4.81 (ABq, J_{gem} = 6.8 Hz), 4.66 and 4.74 (ABq, J_{gem} = 6.7 Hz), and 4.68 and 4.77 (ABq, J_{gem} = 6.6 Hz) (3 × CH_2OMe). − MS {$C_{14}H_{28}O_7$ (308.37); *m*/*z* (%): 309 (12) [M^+].

(1*R*,2*R*,3*R*,4*S*,6*R*)-4-(Hydroxymethyl)-6-methyl-1,2,3-cyclohexanetriol (6): Compound **28** (6 mg, 19 μmol) was deprotected as in the preparation of **4**, and the crude product was eluted from a silica gel column (1 g) with methanol/chloroform (1:5) to give **6** (3 mg, 94%) as a syrup; $[\alpha]_D^{20}$ = +27 (*c* = 0.25, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (d, 3 H, $J_{6,Me}$ = 6.8 Hz, CMe), 1.45−1.61 (m, 2 H, 5,5-H), 1.78−1.82 (m, 1 H, 6-H), 2.10−2.16 (m, 1 H, 4-H), 3.49 (dd, $J_{1,2}$ = 2.8, $J_{2,3}$ = 10.0 Hz, 1 H, 2-H), 3.53 (dd, $J_{3,4}$ = 10.0 Hz, 1 H, 3-H), 3.86−3.92 (m, 2 H, 7,7-H). − HMRS [$C_8H_{16}O_4$, M^+ + H]: calcd. 177.1125; found 177.1125.

(1*R*,2*S*,3*S*,4*R*,5*R*)- and (1*S*,2*R*,3*R*,4*S*,6*R*)-1,7-Anhydro-1-(hydroxymethyl)-2,3,4-tri-*O*-(methoxymethyl)-5-methyl-1,2,3,4-cyclohexanetetraol (29 and 30): A mixture of **27** (20 mg, 69 μL), *m*CPBA (18 mg, 1.5 mol-equiv.), and CH_2Cl_2 (2 mL) was stirred for 5.5 h at room temperature. After treatment with aqueous sodium thiosulfate (2 mL), the mixture was extracted with chloroform (20 mL), and the solution was washed with saturated aqueous sodium hydrogen carbonate and water, dried, and concentrated. The residue was chromatographed on a silica gel column (2 g) with ethyl acetate/hexane (1:4) to give **29** (22 mg, 77%) and **30** (6 mg, 21%). Both compounds **29** and **30** were labile and did not give satisfactory HRMS data.

Compound 29: $[\alpha]_D^{22}$ = +43 (*c* = 0.28, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, $J_{5,Me}$ = 6.1 Hz, 3 H, CMe), 2.06 (br. d, J_{6gem} = 9.8 Hz, 6a-H), 2.63 (d, J_{7gem} = 5.0 Hz, 1 H, 7a-H), 3.09 (d, 1 H, 7b-H), 3.40, 3.41, and 3.43 (3 s, each 3 H, 3 × OMe), 3.81 (dd, $J_{2,3}$ = 10.0, $J_{3,4}$ = 2.3 Hz, 1 H, 3-H), 4.18 (d, 1 H, 2-H), 4.64 and 4.87 (ABq, J_{gem} = 6.6 Hz), 4.70 and 4.92 (ABq, J_{gem} = 6.8 Hz), and 4.72 and 4.73 (ABq) (3 × CH_2OMe).

Compound 30: $[\alpha]_D^{22}$ = +77 (*c* = 0.13, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (d, $J_{5,Me}$ = 6.8 Hz, 3 H, CMe), 1.06 (dd, $J_{5,6a}$ = 4.3, J_{6gem} = 12.8 Hz, 1 H, 6a-H), 1.73−1.82 (m, 1 H, 5-H), 2.13 (ddd, $J_{5,6b}$ = 12.8, $J_{6b,7a}$ = 2.0 Hz, 1 H, 6b-H), 2.44 (d, J_{7gem} = 5.6 Hz, 1 H, 7b-H), 3.04 (dd, 1 H, 7a-H), 3.38, 3.42, and 3.43 (3 s, each 3 H, 3 × OMe), 3.56 (dd, $J_{2,3}$ = 10.0, $J_{3,4}$ = 2.4 Hz, 1 H, 3-H), 3.86 (br. d, 1 H, 4-H), 4.12 (d, 1 H, 2-H), 4.42 and 4.76 (ABq, J_{gem} = 6.9 Hz), 4.67 and 4.95 (ABq, J_{gem} = 6.6 Hz), and 4.63−4.65 (ABq) (3 × OCH_2OMe).

(1*S*,2*S*,3*R*,4*S*,6*R*)-1-(Azidomethyl)-2,3,4-tri-*O*-(methoxymethyl)-5-methyl-1,2,3,4-cyclohexanetetrol (31): A mixture of **29** (20 mg, 65 μmol), sodium azide (13 mg, 3 mol-equiv.), 15-crown-5 ether (13 μL), and DMF (0.4 mL) was stirred for 20 h at 80 °C, and then diluted with ethyl acetate (30 mL). The solution was washed thoroughly with brine, dried and concentrated. The residue was eluted from a column of silica gel (2 g) with acetone/hexane (1:6) to give **31** (21 mg, 94%) as a syrup; $[\alpha]_D^{5}$ = +88 (*c* = 0.75, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (dd, $J_{5,6eq}$ = 4.3, J_{6gem} = 13.5 Hz, 1 H, 6eq-H), 1.55 (ddd, $J_{5,6ax}$ = 12.2, $J_{6ax,OH}$ = 2.0 Hz,

6ax-H), 1.92−2.00 (m, 1 H, 5-H), 2.32 (d, 1 H, OH), 3.34 and 3.38 (2 s, 6 and 3 H, 3 × OMe), 3.25 (d, J_{7gem} = 11.5 Hz, 1 H, 7a-H), 3.35 (d, 1 H, 7b-H), 3.73 (br. s, 1 H, 4-H), 3.78 (dd, $J_{2,3}$ = 9.8, $J_{3,4}$ = 2.0 Hz, 3-H), 4.58 and 4.67 (ABq, J_{gem} = 6.8 Hz), 4.59 and 4.79 (ABq, J_{gem} = 6.7 Hz), and 4.65 and 4.86 (ABq, J_{gem} = 6.4 Hz) (3 × CH_2OMe). − HRMS [$C_{14}H_{27}N_3O_7$, M^+ + H]: calcd. 350.1927; found 350.1932.

(1*R*,2*S*,3*S*,4*R*,6*R*)-1-(Azidomethyl)-2,3,4-tri-*O*-(methoxymethyl)-5-methyl-1,2,3,4-cyclohexanetetrol (32): Compound **30** (6 mg, 20 μmol) was treated with sodium azide (4 mg, 3 mol-equiv.) as in the preparation of **31**, and the product was eluted from a column of silica gel (1 g) with ethyl acetate/hexane (1:4) to give **32** (6 mg, 88%) as a syrup; $[\alpha]_D^{15}$ = +60 (*c* = 0.33, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, $J_{5,Me}$ = 6.1 Hz, 3 H, CMe), 1.56−1.60 (m, 2 H, 5-H, 6a-H), 1.86 (br. d, J_{6gem} = 10.5 Hz, 1 H, 6b-H), 3.16 (d, J_{7gem} = 12.8 Hz, 1 H, 7a-H), 3.39, 3.40, and 3.47 (3 s, each 3 H, 3 × OMe), 3.49 (dd, $J_{2,3}$ = 10.5, $J_{3,4}$ = 2.7 Hz, 1 H, 3-H), 3.56 (d, 1 H, 7b-H), 3.76 (br. s, 1 H, 4-H), 3.78 (dd, 1 H, 2-H), 3.99 (s, 1 H, OH), 4.66 and 4.76 (ABq, J_{gem} = 6.1 Hz), 4.68 and 4.87 (ABq, J_{gem} = 6.8 Hz), and 4.67 (s, 2 H) (3 × OCH_2OMe). − HRMS [$C_{14}H_{27}N_3O_7$, M^+ + H]: calcd. 350.1927; found 350.1932.

(1*S*,2*S*,3*R*,4*S*,6*R*)-1-(Aminomethyl)-5-methyl-1,2,3,4-cyclohexanetetrol (7): Compound **31** (10 mg, 29 μmol) was deprotected and reduced as described in the preparation of **5**, and the product was purified by elution from a column of silica gel (1 g) with methanol/chloroform (1:4) to give **7** (4.6 mg, ca. 100%) as a syrup; $[\alpha]_D^{20}$ = −100 (*c* = 0.10, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, $J_{5,Me}$ = 6.8 Hz, 3 H, CMe), 1.36 (dd, J_{6gem} = 13.9 Hz, $J_{5,6b}$ = 4.5 Hz, 6b-H), 1.45 (dd, $J_{5,6a}$ = 13.9 Hz, 1 H, 6a-H), 1.95−2.00 (m, 1 H, 5-H), 2.58 (d, J_{7gem} = 13.2 Hz, 7a-H), 2.79 (d, 1 H, 7b-H), 3.55 (d, $J_{2,3}$ = 9.8 Hz, 1 H, 2-H), 3.62 (dd, $J_{3,4}$ = 3.2 Hz, 1 H, 3-H), 3.73 (br. s, 1 H, 4-H). − HRMS [$C_8H_{18}NO_4$, M^+ + H]: calcd. 192.1236; found 192.1222.

(1*R*,2*S*,3*S*,4*R*,6*R*)-1-(Aminomethyl)-5-methyl-1,2,3,4-cyclohexanetetrol (8): Compound **32** (5 mg, 14 μmol) was deprotected and reduced as in the preparation of **5**, and the product was purified as in the preparation of **7** to give **8** (2 mg, ca. 100%) as a syrup; $[\alpha]_D^{20}$ = −36 (*c* = 0.10, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (d, $J_{5,Me}$ = 6.1 Hz, 3 H, CMe), 1.19−1.62 (m, 3 H, 5-H, 6,6-H), 2.62 (d, J_{7gem} = 12.6 Hz, 1 H, 7a-H), 3.08 (d, 1 H, 7b-H), 3.39 (dd, $J_{2,3}$ = 10.3, $J_{3,4}$ = 3.0 Hz, 1 H, 3-H), 3.70 (br. s, 1 H, 4-H), 3.74 (d, 1 H, 2-H). − HRMS [$C_8H_{18}NO_4$, M^+ + H]: calcd. 192.1236; found 192.1210.

Biological Assay: α-Fucosidase from bovine kidney, bovine serum albumin (BSA), and *p*-nitrophenyl α-L-fucopyranoside (*p*NP-Fuc) were purchased from Sigma. Hydrolysis of pNP-Fuc by α-fucosidase was carried out in wells of microplates precoated with BSA, and the liberated *p*-nitrophenol was quantified by measuring absorbance at 400 nm with a microplate reader (BioRad 550) under alkaline conditions. The mixture of *p*NP-Fuc (0.54−1.37 μM), α-fucosidase (1.3 ng), BSA (38 μg), and an appropriate amount of inhibitor in 17 μM citrate buffer (pH = 6.0, 45 μL) was incubated at 25 °C for 20 min, and was then treated with 50 mM glycine buffer (pH = 10.1, 90 μL). K_i values listed in Table 1 were estimated from Lineweaver−Burk plots.

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[18] Treatment of **16** with sodium cyanide in DMF (4 d at 110 °C) resulted in a cleavage of the epoxide ring to give a single nitrile, isolated as the 2-mesylate in 72% overall yield.
[19] Under the influences of either DBU/toluene (ca. 40 °C), 0.2 N MeONa/MeOH (reflux), or NaH/DMF (40 °C → reflux), compound **19** did not undergo elimination reaction. Addition of a trace of MeOH to the reaction mixture under NaH/DMF conditions resulted in the formation of the single elimination product **21**. Some isomerized alkenes have been shown to be formed when increasing the amount of MeOH.
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