Pseudosugars, 41[+]

Synthesis and Glycosidase Inhibitory Activity of 5a-Carba-α-DL-fucopyranosylamine and -galactopyranosylamine

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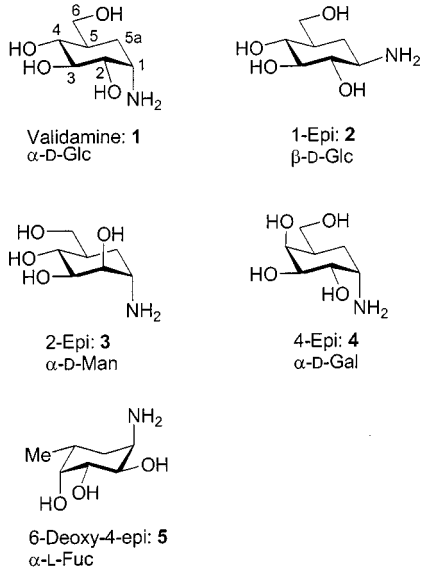
5a-Carba-α-DL-fucopyranosylamine (DL-**5**) and -galactopyranosylamine (DL-**4**) have been synthesized in a conventional manner from 2,3,4,6-tetra-*O*-acetyl-5a-carba-β-DL-glucopyranosyl bromide (**6**). Only compound DL-**5** has been shown to be a strong inhibitor (K_i = 2.3 × 10^{-7} M) of α-fucosidase (bovine kidney). They did not exhibit any inhibitory activity towards five glycoside hydrolases, namely α- and β-glucosidases and α- and β-galactosidases.

Introduction

Some analogs of 5a-carbahexopyranosylamine, specifically validamine (**1**), valienamine, and valiolamine, which were first isolated by chemical and biochemical degradation of validamycins, constitute one of the important classes of α-glucosidase inhibitors (Scheme 1). Their syntheses, chemical modifications, and biochemical activities have been extensively studied.[2] Total syntheses of several analogs[3,4] [1- (**2**) and 2-epimers (**3**)] and derivatives[5–8] of validamine (**1**), 5a-carba-α-D-glucopyranosylamine, in racemic form have been achieved starting from the *endo* adduct of furan and acrylic acid. Partial syntheses of optically active **3** and the 4-epimer (**4**) starting from **1** have recently been reported,[9] and the former has been shown to exhibit a moderate inhibitory activity towards certain α-mannosidases.



Scheme 1. Validamine (**1**), 5a-carba-α-D-glucopyranosylamine, and some analogs of biological interest

In this paper, we focus on fucosidases, which play important roles in the turnover of glycoproteins by lysosomal degradation[10] and in the fertilization of some organisms by triggering acrosome reactions.[11] Fucosidase inhibitors are envisaged as potential research tools for probing these fucosidase-relevant events and even as drugs to combat cancer and HIV through inhibition of the turnover process and/or invading cell matrices with secreting fucosidases.[12]

The present paper describes the syntheses and an evaluation of α-fucosidase inhibitory activities of 5a-carba-α-DL-fucopyranosylamine (DL-**5**) and its 6-hydroxy derivative, 5a-carba-α-DL-galactopyranosylamine (DL-**4**). Compound DL-**5** was easily prepared in the conventional manner from readily available 2,3,4,6-tetra-*O*-acetyl-5a-carba-β-DL-glucopyranosyl bromide (**6**).[13] Since the enantiomorph of the target carba-α-L-fucosylamine could perhaps be expected to possess some biological activity, as was demonstrated in the case of 5-amino-5-deoxy-D- and -L-glucopyranoses (D- and L-nojirimycins),[14] we first attempted to prepare racemic forms.

Results and Discussion

Compound **6** was prepared[13] in a three-step sequence (overall yield 35%) from the *endo* adduct of furan and acrylic acid. A mixture of **6** and 3 molar equiv. of sodium azide in DMF was then stirred overnight at 90 °C to give

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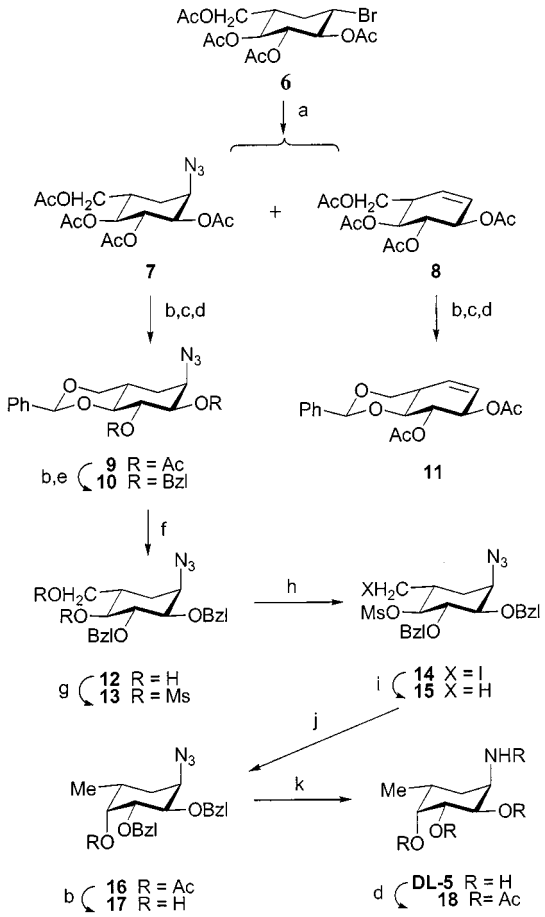
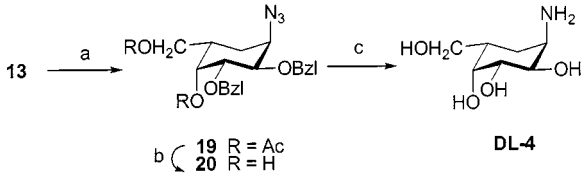


Scheme 2. Synthesis of 5a-carba-α-DL-fucopyranosylamine (DL-**5**); reagents and conditions: (a) NaN_3, DMF, ca. 12 h, 90 °C; (b) MeONa/MeOH, room temp.; (c) α,α-dimethoxytoluene, DMF/TsOH; (d) Ac_2O/pyridine, room temp.; (e) NaH/$PhCH_2Br$/DMF, (f) 80% aq. AcOH, 50 °C; (g) MsCl/pyridine; (h) NaI (2 equiv.), 2-butanone, 90 °C; (i) tBu_3SnH/AIBN, toluene, 120 °C; (j) AcOK, DMF, 2 weeks, 55 °C; (k) H_2, 10% Pd/C, EtOH, 1 M HCl; for convenience, only one enantiomer of the respective racemates is depicted

an inseparable, ca. 4:1 mixture of the azide **7**[15] and the alkene **8** (Scheme 2). The mixture was de-*O*-acetylated under Zemplén conditions and subsequently treated with an excess of α,α-dimethoxytoluene in DMF in the presence of *p*TsOH at 45 °C. After subsequent acetylation with acetic anhydride in pyridine, two products were found to be separable by silica gel chromatography. Thus, 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-5a-carba-α-DL-glucopyranosyl azide (**9**) and (1*RS*,3*RS*,6*RS*,8*SR*,9*SR*,10*SR*)-9,10-diacetoxy-3-phenyl-2,4-dioxabicyclo[4.4.0]dec-7-ene (**11**) could be isolated in yields of 60% and 17%, respectively. The structures were determined on the basis of the ^{1}H-NMR spectra. Direct S_N2 reaction occurred preferentially at C-1; other products that might conceivably have been formed through neighboring-group participation of the 2-acetoxy function were not observed. Compound **9** was de-*O*-acetylated and then treated with sodium hydride and benzyl bromide in DMF to give the dibenzyl ether **10** in 89% yield. Treatment of **10** with 80% aq. acetic acid gave the diol **12** (97%), which was subsequently mesylated using an excess of mesyl chloride in pyridine to give the 4,6-dimesylate **13** (97%). Compound **13** was then treated with 2 molar equiv. of sodium iodide in 2-butanone for 3 h at 90 °C to selectively afford the 6-iodide **14** (85%), treatment of which with tributyltin hydride and AIBN in toluene for 10 min at 120 °C gave the 6-deoxy derivative **15** (74%) together with a trace amount of the deazido compound.[16]

Compound **15** was treated[17] with a large excess of potassium acetate and 18-crown-6 ether in DMF for two weeks at 55 °C to give the acetate **16** (99%) with an α-*galacto* configuration, the structure of which was confirmed on the basis of its ^{1}H-NMR spectrum and the spectrum of its 4-OH derivative **17**. Hydrogenolysis of **17** in ethanol, containing 1 molar equiv. of 1 M HCl, in the presence of 10% Pd/C afforded, after purification by chromatography on a column of Dowex 50W×2 (H^+) resin eluting with methanolic ammonia, an 80% yield of syrupy 5a-carba-α-DL-fucopyranosylamine (DL-**5**), which was further characterized by converting it to the *N*,*O*-acetyl derivative **18**.

In order to obtain DL-**4**, compound **13** was first treated with an excess of sodium acetate in 80% aq. DMF at 110 °C for 2 d to give the di-*O*-acetyl derivative **19** (66%) with an α-*galacto* configuration (Scheme 3). The substitution reaction at C-4 seemed to be facilitated through participation of the initially formed 6-acetoxy group. The diol **20**, obtained by de-*O*-acetylation of **19**, readily underwent hydrogenolysis of both the azido and benzyl groups in the presence of 10% Pd/C to give 5a-carba-α-DL-galactopyranosylamine (DL-**4**, 48%) as a syrup.



Scheme 3. Synthesis of 5a-carba-α-DL-galactopyranosylamine (DL-**4**); reagents and conditions: (a) AcONa, 80% aq. DMF, 110 °C; Ac_2O/pyridine, room temp.; (b) MeONa/MeOH, room temp.; (c) H_2, 10% Pd/C, EtOH, 1 M HCl; for convenience, only one enantiomer of the respective racemates is depicted

Biological Assay

Preliminary assays of the inhibitory activities of compounds DL-**4** and DL-**5** towards glycosidases were performed using five enzymes:[18] α-glucosidase (Baker's yeast), β-glucosidase (almonds), α-galactosidase (coffee beans), and β-galactosidases (*E. coli* and bovine liver). Compound DL-**4** proved to be only a very weak inhibitor (I = 91%, 1000 μg/mL) of α-galactosidase (coffee beans), as previously shown for the D-carbasugar **4**.[9] However, compound DL-**5**, originally designed with a view to fucosidase inhibition, was shown to exhibit strong inhibitory activity ($K_i = 2.3 \times 10^{-7}$ M) towards α-fucosidase (bovine kidney). Thus, while 5a-carba-α-L-fucopyranosylamine (**5**) evidently has more potential than its counterpart from a structural standpoint, a point of interest is whether or not the constituent D- and L-enantiomorphs exhibit similar inhibitory potentials. Optical resolution of 5a-carba-α-DL-fucopyranosylamine and fur-

ther derivatization of the enantiomorphs is currently being addressed with a view to further elucidating the structure−activity relationship.

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 IR-810. − ^{1}H-NMR spectra: Jeol JNM GSX-270 FT (270 MHz) and Jeol Lambda-300 (300 MHz); for samples in $CDCl_3$, internal standard tetramethylsilane (TMS); for samples in CD_3OD, external acetone was used. − Mass spectra: Perseptive Biosystems Mariner LC Mass. − TLC: Silica gel 60 GF (E. Merck, Darmstadt); detection by charring with conc. H_2SO_4. − Column chromatography: Wakogel C-300 (silica gel, 300 mesh, Wako Chemical, Osaka). − Organic solutions, after drying with anhydrous Na_2SO_4, were concentrated at < 50 °C under reduced pressure. − The free carbaglycosylamines DL-**4** and DL-**5** were seen to be homogeneous by TLC and ^{1}H-NMR spectroscopy. They were directly tested for their enzyme inhibitory activities towards the five aforementioned glycosidases according to the methodology described in a previous paper.[18]

2,3-Di-*O*-acetyl-4,6-*O*-benzylidene-5a-carba-α-DL-glucopyranosyl Azide (9) and (1*RS*,3*RS*,6*RS*,8*SR*,9*SR*,10*SR*)-9,10-Diacetoxy-3-phenyl-2,4-dioxabicyclo[4.4.0]dec-7-ene (11): A mixture of 2,3,4,6-tetra-*O*-acetyl-5a-carba-β-DL-glucopyranosyl bromide[13] (**6**, 8.88 g, 21.5 mmol), sodium azide (5.6 g, 90 mmol), and DMF (180 mL) was stirred overnight at 90 °C. After cooling, the mixture was diluted with ethyl acetate (400 mL) and the resulting solution was washed with water, dried, and concentrated to dryness. The residue was passed through a silica gel column (80 g) eluting with ethyl acetate/hexane (1:1) to give an approximately 4:1 mixture of 2,3,4,6-tetra-*O*-acetyl-5a-carba-α-DL-glucopyranosyl azide (**7**) and (1*SR*,2*RS*,3*SR*,6*RS*)-1,2,3-triacetoxy-6-(acetoxymethyl)cyclohex-4-ene (**8**) as a homogeneous syrup (inseparable by TLC). The ratio of the products was roughly estimated on the basis of ^{1}H-NMR spectral data. The mixture was then treated with 1 M methanolic sodium methoxide (2.2 mL) in methanol (150 mL) for 1 h at room temperature. After neutralization with Amberlite IR-120B (H^+) resin, the mixture was concentrated to dryness. To a solution of the residue (4.6 g) in DMF (70 mL) were added α,α-dimethoxytoluene (8.44 mL, 56 mmol) and *p*-toluenesulfonic acid hydrate (0.42 g) and the resulting mixture was stirred for 2 h at 45 °C. It was then diluted with ethyl acetate (300 mL) and this solution was washed with water, dried, and concentrated to dryness. The residual products were acetylated with acetic anhydride (30 mL) in pyridine (60 mL) for 1 h at room temperature. TLC (ethyl acetate/hexane, 1:1) showed that two products had been formed (R_f = 0.58 and 0.65). After the addition of methanol (5 mL), the reaction mixture was concentrated. The residue was taken up in ethyl acetate (300 mL), and this solution was washed with 1 M hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, then dried and concentrated. The residual products were finally chromatographed on a silica gel column (250 g; ethyl acetate/hexane, 1:10) to give the azide **9** (4.8 g, 60%) and the alkene **11** (1.2 g, 17%).

Compound 9: M.p. 139−141 °C. − ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.45−7.24 (m, 5 H, Ph), 5.54 (dd, $J_{2,3} = J_{3,4}$ = 10.3 Hz, 1 H, 3-H), 5.47 (s, 1 H, PhC*H*), 5.01 (dd, $J_{1,2}$ = 3.66 Hz, 1 H, 2-H), 4.15 [dd, $J_{5,6(a)}$ = 4.4, J_{6gem} = 11.0 Hz, 1 H, 6(a)-H], 4.15 [dd, $J_{1,5a(ax)}$ = 2.9, $J_{1,5a(eq)} \approx 0$ Hz, 1 H, 1-H], 3.57 [dd, $J_{5,6(b)} = J_{6gem}$ = 11.0 Hz, 1 H, 6(b)-H], 3.51 (dd, $J_{4,5}$ = 10.3 Hz, 1 H, 4-H), 2.35−2.23 (m, 1 H, 5-H), 2.11 and 2.04 (2 s, each 3 H, 2 × Ac), 1.72 [ddd, $J_{5,5a(eq)}$ = 3.7, J_{5agem} = 14.3 Hz, 1 H, 5a(eq)-H], 1.29 [ddd, $J_{5,5a(ax)}$ = 14.3 Hz, 1 H, 5a(ax)-H]. − $C_{18}H_{21}N_3O_6$ (375.4): calcd. C 57.59, H 5.64, N 11.19; found C 57.84, H 5.76, N 11.36.

Compound 11: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47−7.34 (m, 5 H, Ph), 5.65 (ddd, $J_{7,8}$ = 8.8, $J_{8,9}$ = 2.9 Hz, 1 H, 8-H), 5.62 (dd, $J_{9,10}$ = 7.1 Hz, 1 H, 9-H), 5.57 (s, 1 H, PhC*H*), 5.53 (dd, $J_{6,7}$ = 10.7 Hz, 1 H, 7-H), 5.48 (dd, $J_{1,10}$ = 10.7 Hz, 1 H, 10-H), 4.31 [dd, $J_{5(a),6}$ = 4.6, J_{5gem} = 11.0 Hz, 1 H, 5(a)-H], 3.81 (dd, $J_{1,6}$ = 9.5 Hz, 1 H, 1-H), 3.68 [dd, $J_{5(b),6}$ = 11.0 Hz, 1 H, 5(b)-H], 2.82−2.75 (m, 1 H, 6-H), 2.08 (s, 6 H, 2 × OAc). − $C_{18}H_{20}O_6$ (332.4): calcd. C 65.05, H 6.07; found C 64.88, H 6.12.

2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-5a-carba-α-DL-glucopyranosyl Azide (10): Compound **9** (214 mg, 0.570 mmol) was treated with 1 M methanolic sodium methoxide (0.06 mL) in methanol (6 mL) for 30 min at room temperature. After neutralization with Amberlite IR-120B (H^+) resin, the solvent was evaporated to leave the diol (ca. 160 mg) in the form of crystals. To a solution of this compound in DMF (6 mL) was added sodium hydride (76 mg, 3.2 mmol) followed by benzyl bromide (0.19 mL, 1.6 mmol) and the resulting mixture was stirred for 1 h at ca. 0 °C. After the addition of methanol (0.2 mL), the mixture was diluted with ethyl acetate, and this solution was washed with water, dried, and concentrated. The residue was chromatographed on a silica gel column (40 g; ethyl acetate/hexane, 1:8) to give **10** (222 mg, 82.6%) in the form of crystals; m.p. 120−121 °C. − ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.53−7.48 (m, 5 H, Ph), 7.42−7.26 (m, 10 H, 2 × Ph), 5.55 (s, 1 H, PhC*H*), 4.93 and 4.80 (ABq, J_{gem} = 9.6 Hz, each 1 H) and 4.83 and 4.75 (ABq, J_{gem} = 10.7 Hz, each 1 H) (PhCH_2), 4.15 [dd, $J_{5,6(a)}$ = 4.4, J_{6gem} = 11.0 Hz, 1 H, 6(a)-H], 4.01 [dd, $J_{1,2}$ = 3.4, $J_{1,5a(ax)}$ = 2.7, $J_{1,5a(eq)} \approx 0$ Hz, 1 H, 1-H], 3.96 (dd, $J_{2,3} = J_{3,4}$ = 9.3 Hz, 1 H, 3-H), 3.57 (dd, $J_{1,2}$ = 3.4 Hz, 1 H, 2-H), 3.54 [dd, $J_{5,6(b)} = J_{6gem}$ = 11.0 Hz, 1 H, 6(b)-H], 3.50 (dd, $J_{4,5}$ = 9.3 Hz, 1 H, 4-H), 2.17−2.12 (m, 1 H, 5-H), 1.63 [ddd, $J_{5,5a(eq)}$ = 3.7, J_{5agem} = 13.9 Hz, 1 H, 5a(eq)-H], 1.10 [ddd, $J_{5,5a(ax)}$ = 13.9 Hz, 1 H, 5a(ax)-H]. − $C_{28}H_{29}N_3O_4$ (471.6): calcd. C 71.32, H 6.20, N 8.91; found C 71.21, H 6.30, N 9.20.

2,3-Di-*O*-benzyl-5a-carba-α-DL-glucopyranosyl Azide (12): A solution of **10** (3.77 g, 7.99 mmol) in 80% aq. acetic acid (150 mL) was stirred for 2 h at 60 °C and then concentrated to dryness. The residual product was chromatographed on a silica gel column (30 g; ethyl acetate/hexane, 1:1) to give **12** (3.0 g, 97%) as a syrup. − ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.40−7.23 (m, 10 H, 2 × Ph), 5.02 and 4.68 (ABq, J_{gem} = 10.8 Hz, each 1 H) and 4.76 and 4.70 (ABq, J_{gem} = 10.8 Hz, each 1 H) (PhCH_2), 4.03 [dd, $J_{1,2}$ = 3.3, $J_{1,5a(ax)}$ = 2.9, $J_{1,5a(eq)} \approx 0$ Hz, 1 H, 1-H], 3.69 (dd, $J_{2,3} = J_{3,4}$ = 9.2 Hz, 1 H, 3-H), 3.62 (dd, $J_{4,5}$ = 9.2, $J_{4,OH}$ = 2.9 Hz, 1 H, 4-H), 3.60 [ddd, $J_{5,6(a)} = J_{6gem}$ = 10.6, $J_{6(a),OH}$ = 1.5 Hz, 1 H, 6(a)-H], 3.51 (dd, 1 H, 2-H), 3.36 [ddd, $J_{5,6(b)}$ = 10.6, $J_{6(b),OH}$ = 1.5 Hz, 1 H, 6(b)-H], 2.78 (br. s, 1 H, OH), 2.62 (br. s, 1 H, OH), 2.03−1.92 (m, 1 H, 5-H), 1.74 [ddd, $J_{5,5a(eq)}$ = 3.3, J_{5agem} = 14.3 Hz, 1 H, 5a(eq)-H], 1.23 [ddd, $J_{5,5a(ax)}$ = 14.3 Hz, 1 H, 5a(ax)-H]. − $C_{21}H_{25}N_3O_4$ (383.5): calcd. C 65.78, H 6.57, N 10.96; found C 65.66, H 6.59, N 10.87.

2,3-Di-*O*-benzyl-4,6-di-*O*-mesyl-5a-carba-α-DL-glucopyranosyl Azide (13): To a stirred solution of **12** (965 mg, 2.52 mmol) in dry pyridine (19 mL), mesyl chloride (0.975 mL, 12.6 mmol) was added dropwise at 0 °C and the resulting mixture was stirred for 20 h at this temperature. After the addition of a small amount of methanol, the mixture was concentrated. The residue was redissolved in ethyl acetate (300 mL) and this solution was washed with 1 M

hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, and then dried. After concentration, the residual product was purified by silica gel chromatography (50 g; ethyl acetate/toluene, 1:10) to give **13** (1.36 g, 97.3%) in the form of crystals; m.p. 76−77 °C. − ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.36−7.23 (m, 10 H, 2 × Ph), 5.11 and 4.67 (ABq, J_{gem} = 11.3 Hz, each 1 H) and 4.73 and 4.67 (ABq, 2 H, J_{gem} = 11.3 Hz, each 1 H) (PhCH_2), 4.49 (dd, $J_{3,4}$ = 9.5, $J_{4,5}$ = 11.0 Hz, 1 H, 4-H), 4.33 [dd, $J_{5,6(a)}$ = 2.6, J_{6gem} = 9.9 Hz, 1 H, 6(a)-H], 4.22 [dd, $J_{5,6(b)}$ = 3.3 Hz, 1 H, 6(b)-H], 4.02 [dd, $J_{1,2}$ = 3.3, $J_{1,5a(ax)}$ = 2.9, $J_{1,5a(eq)}$ ≈ 0 Hz, 1 H, 1-H], 3.94 (dd, $J_{2,3}$ = 9.5 Hz, 1 H, 3-H), 3.62 (dd, 1 H, 2-H), 3.30 and 2.80 (2 s, each 3 H, 2 × OMs), 2.35−2.25 (m, 1 H, 5-H), 1.63 [ddd, $J_{5,5a(eq)}$ = 3.7, J_{5agem} = 13.9 Hz, 1 H, 5a(eq)-H], 1.60 [ddd, $J_{5,5a(ax)}$ = 13.9 Hz, 1 H, 5a(ax)-H]. − $C_{23}H_{29}N_3O_8S_2$ (539.6): calcd. C 51.19, H 5.42, N 7.79; found C 51.38, H 5.55, N 7.79.

2,3-Di-*O*-benzyl-6-deoxy-6-iodo-4-*O*-mesyl-5a-carba-α-DL-glucopyranosyl Azide (14): A mixture of **13** (504 mg, 0.934 mmol), sodium iodide (280 mg, 1.87 mmol), and 2-butanone (10 mL) was stirred for 3 h at 90 °C. After cooling, the mixture was diluted with acetone (20 mL) and the resulting salt was removed by filtration. The filtrate was concentrated and the residue was redissolved in chloroform. This solution was washed with 10% aq. sodium thiosulfate solution and water, dried, and concentrated to dryness. The residue was chromatographed on a silica gel column (29 g; ethyl acetate/hexane, 1:8) to give **14** (453 mg, 84.9%) in the form of crystals; m.p. 134−136 °C. − ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.35−7.26 (m, 10 H, 2 × Ph), 5.09 and 4.69 (ABq, J_{gem} = 11.0 Hz, each 1 H) and 4.72 and 4.67 (ABq, J_{gem} = 11.0 Hz, each 1 H) (PhCH_2), 4.31 (dd, $J_{3,4}$ = 9.5, $J_{4,5}$ = 10.3 Hz, 1 H, 4-H), 4.00 [dd, $J_{1,2}$ = 3.3, $J_{1,5a(ax)}$ = 5.9, $J_{1,5a(eq)}$ ≈ 0 Hz, 1 H, 1-H], 3.93 (dd, $J_{2,3}$ = 9.5 Hz, 1 H, 3-H), 3.62 (dd, 1 H, 2-H), 3.49 [dd, $J_{5,6(a)}$ = 2.6, J_{6gem} = 10.3 Hz, 6(a)-H], 3.14 [dd, $J_{5,6(b)}$ = 7.33 Hz, 1 H, 6(b)-H], 2.85 (s, 3 H, OMs), 2.09 [ddd, $J_{5,5a(eq)}$ = 3.3, J_{5agem} = 10.7 Hz, 1 H, 5a(eq)-H], 2.03−1.94 (m, 1 H, 5-H), 1.33 [ddd, $J_{5,5a(ax)}$ = 10.7 Hz, 1 H, 5a(ax)-H]. − $C_{22}H_{26}IN_3O_5S$ (571.4): calcd. C 46.24, H 4.59, N 7.35; found C 45.95, H 4.63, N 7.29.

2,3-Di-*O*-benzyl-6-deoxy-4-*O*-mesyl-5a-carba-α-DL-glucopyranosyl Azide (15): A mixture of **14** (2.52 g, 4.41 mmol) in toluene (200 mL) was treated with tributyltin hydride (0.093 mL, 13 mmol) and AIBN (74 mg, 0.44 mmol) for 10 min at 100 °C. After cooling, the solvent was evaporated and the residue was chromatographed on a silica gel column (40 g; ethyl acetate/hexane, 1:8) to give **15** (1.45 g, 73.8%) in the form of crystals; m.p. 104−106 °C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34−7.24 (m, 10 H, 2 × Ph), 5.07 and 4.68 (ABq, J_{gem} = 11.4 Hz, each 1 H) and 4.73 and 4.67 (ABq, J_{gem} = 11.0 Hz, each 1 H) (PhCH_2), 4.16 (dd, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, 1 H, 4-H), 3.97 [dd, $J_{1,2}$ = 3.4, $J_{1,5a(ax)}$ = 2.7, $J_{1,5a(eq)}$ ≈ 0 Hz, 1 H, 1-H], 3.87 (dd, $J_{2,3}$ = 9.3 Hz, 1 H, 3-H), 3.59 (dd, 1 H, 2-H), 2.80 (s, 3 H, OMs), 2.10−2.00 (m, 1 H, 5-H), 1.86 [ddd, $J_{5,5a(eq)}$ = 3.4, J_{5agem} = 14.7 Hz, 1 H, 5a(eq)-H], 1.20 [ddd, $J_{5,5a(ax)}$ = 14.7 Hz, 1 H, 5a(ax)-H], 0.48 (s, 3 H, Me). − $C_{22}H_{27}N_3O_5S$ (445.5): calcd. C 59.31, H 6.11, N 9.43; found C 59.16, H 6.17, N 9.40.

4-*O*-Acetyl-2,3-di-*O*-benzyl-6-deoxy-5a-carba-α-DL-galactopyranosyl Azide (16): A mixture of **15** (1.42 g, 3.19 mmol), potassium acetate (3.13 g, 31.9 mmol), and 18-crown-6 ether (8.42 g, 31.9 mmol) in DMF (36 mL) was stirred for 2 weeks at 55 °C. After cooling, it was diluted with ethyl acetate (200 mL) and the resulting mixture was washed with water, dried, and concentrated to dryness. The product was purified by silica gel chromatography (30 g; ethyl acetate/hexane, 1:10) to give **16** (1.30 g, 99.5%) in the form of crystals; m.p. 67−68 °C. − ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.30−7.23 (m, 10 H, 2 × Ph), 5.47 (d, $J_{3,4}$ = $J_{4,5}$ = 1.8 Hz, 1 H, 4-H), 4.82 and 4.55 (ABq, J_{gem} = 11.3 Hz, each 1 H) and 4.74 and 4.70 (ABq, J_{gem} = 10.8 Hz, each 1 H) (PhCH_2), 4.03 [dd, $J_{1,2}$ = 2.9, $J_{1,5a(ax)}$ = $J_{1,5a(eq)}$ ≈ 0 Hz, 1 H, 1-H], 3.80−3.79 (complex m, 2 H, 2-H, 3-H), 2.09 (s, 3 H, Ac), 2.06−1.95 (m, 1 H, 5-H), 1.61 [br. d, $J_{5,5a(eq)}$ ≈ 3 Hz, 1 H, 5a(eq)-H], 1.57 [br. s, 1 H, 5a(ax)-H], 0.89 (d, 3 H, Me). − $C_{23}H_{27}N_3O_4$ (409.5): calcd. C 67.46, H 6.65, N 10.26; found C 67.64, H 6.70, N 10.49.

2,3-Di-*O*-benzyl-6-deoxy-5a-carba-α-DL-galactopyranosyl Azide (17): Compound **16** (1.30 g, 3.18 mmol) was treated with 1 M methanolic sodium methoxide (0.32 mL) in methanol (35 mL) and the reaction mixture was stirred overnight at room temperature. After neutralization with Amberlite IR-120B (H^+) resin, the mixture was concentrated and the residue was chromatographed on a silica gel column (40 g; chloroform/methanol, 9:1) to give **17** (1.15 g, 98.4%) in the form of crystals; m.p. 64−64.5 °C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41−7.25 (m, 10 H, 2 × Ph), 4.78 and 4.68 (ABq, J_{gem} = 11.4 Hz, each 1 H) and 4.76 and 4.72 (ABq, J_{gem} = 11.7 Hz, each 1 H) (PhCH_2), 3.99 [ddd, $J_{1,2}$ = 3.4, $J_{1,5a(ax)}$ = 2.7, $J_{1,5a(eq)}$ = 3.2 Hz, 1 H, 1-H], 3.90 (br. d, $J_{3,4}$ = 2.9, $J_{4,5}$ ≈ 0 Hz, 1 H, 4-H), 3.83 (dd, $J_{2,3}$ = 9.5 Hz, 1 H, 2-H), 3.71 (dd, 1 H, 3-H), 2.31 (s, 1 H, OH), 1.89−1.83 (m, 1 H, 5-H), 1.67 [ddd, $J_{5,5a(ax)}$ = J_{5agem} = 13.9 Hz, 1 H, 5a(ax)-H], 1.52 [ddd, $J_{5,5a(eq)}$ = 3.2 Hz, 1 H, 5a(eq)-H]. − $C_{21}H_{25}N_3O_3$ (367.5): calcd. C 68.64, H 6.86, N 11.44; found C 68.87, H 6.95, N 11.48.

6-Deoxy-5a-carba-α-DL-galactopyranosylamine (5a-Carba-α-DL-fucopyranosylamine) (DL-5): A solution of **17** (552 mg, 1.50 mmol) in ethanol (12 mL) containing 1 M hydrochloric acid (2 mL) was hydrogenated in a Parr shaker-type apparatus (initial hydrogen pressure ca. 3 kg/cm^2) for one week. The catalyst was then removed by filtration and the filtrate was concentrated to dryness. The product was chromatographed on a column of Dowex 50W×2 (H^+) resin (4 mL) eluting with saturated aqueous ammonia/methanol (1:13) to give DL-**5** (194 mg, 79.8%) as a colorless syrup. − ^{1}H NMR (300 MHz, CD_3OD): δ = 3.72 (br. s, 1 H, 4-H), 3.71 (dd, $J_{1,2}$ = 4.4, $J_{2,3}$ = 9.5 Hz, 1 H, 2-H), 3.59 (dd, $J_{3,4}$ = 2.9 Hz, 1 H, 3-H), 3.15 [dd, $J_{1,5a(ax)}$ = 3.7, $J_{1,5a(eq)}$ ≈ 3 Hz, 1 H, 1-H], 1.97−1.72 (m, 1 H, 5-H), 1.68 [ddd, $J_{5,5a(ax)}$ = J_{5agem} = 12.9 Hz, 1 H, 5a(ax)-H], 1.43 [ddd, $J_{5,5a(eq)}$ ≈ 3 Hz, 1 H, 5a(eq)-H]. − HRMS: $C_7H_{16}NO_3$ (162.1130): found 162.1130. − Compound DL-**5** was peracetylated by treatment with acetic anhydride in pyridine overnight at room temperature. The product was purified by silica gel chromatography (acetone/toluene, 1:10) to quantitatively afford the tetra-*N,O*-acetyl derivative **18** as a syrup. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81 (br. d, $J_{1,NH}$ ≈ 8 Hz, 1 H, NH), 5.33 (dd, $J_{3,4}$ = $J_{4,5}$ = 2.9 Hz, 1 H, 4-H), 5.20 (dd, $J_{1,2}$ = 4.4, $J_{2,3}$ = 11.0 Hz, 1 H, 2-H), 5.06 (dd, 1 H, 3-H), 4.59 [dddd, $J_{1,5a(ax)}$ = $J_{1,5a(eq)}$ ≈ 3.5 Hz, 1 H, 1-H], 2.13, 2.03, 2.02, and 2.01 (4 s, each 3 H, 4 × Ac), 2.18−1.97 (m, 1 H, 5-H), 1.79−1.76 [m, 2 H, 5a(ax)-H, 5a(eq)-H]. − $C_{15}H_{23}NO_7$ (329.4): calcd. C 54.70, H 7.04, N 4.25; found C 54.63, H 7.15, N 4.56.

4,6-Di-*O*-acetyl-2,3-di-*O*-benzyl-5a-carba-α-DL-galactopyranosyl Azide (19): A mixture of **13** (166 mg, 0.307 mmol), sodium acetate (126 mg, 1.54 mmol), and 80% aq. DMF (3.4 mL) was stirred for 2 d at 110 °C. After cooling, it was diluted with ethyl acetate (20 mL) and this solution was washed with water, dried, and concentrated to dryness. The residue was peracetylated by treatment with acetic anhydride in pyridine in the conventional manner and the product was chromatographed on a silica gel column (8 g; ethyl acetate/hexane, 1:8) to give **19** (95 mg, 66%) as a colorless syrup. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38−7.26 (m, 10 H, 2 × Ph), 5.64 (br. s, 1 H, 4-H), 4.82 and 4.70 (ABq, J_{gem} = 11.7 Hz, each 1 H) and 4.76 and 4.55 (ABq, J_{gem} = 11.0 Hz, each 1 H) (PhCH_2),

4.06 [dd, $J_{1,2} = J_{1,5a(ax)} = 2.9$, $J_{1,5a(eq)} \approx 0$ Hz, 1 H, 1-H], 3.97 [dd, $J_{5,6(a)} = 8.6$, $J_{6gem} = 11.0$ Hz, 1 H, 6(a)-H], 3.82 [dd, $J_{5,6(b)} = 5.6$ Hz, 1 H, 6(b)-H], 3.82−3.78 (complex m, 2 H, 2-H, 3-H), 2.28−2.24 (m, 1 H, 5-H), 2.07 and 2.065 (2 s, each 3 H, 2 × Ac), 1.70 [ddd, $J_{5,5a(eq)} = 3.7$, $J_{5agem} = 13.9$ Hz, 1 H, 5a(eq)-H], 1.60 [ddd, $J_{5,5a(ax)} = 13.9$ Hz, 1 H, 5a(ax)-H]. − $C_{25}H_{29}N_3O_6$ (467.5): calcd. C 64.23, H 6.25, N 8.99; found C 64.24, H 6.03, N 9.05.

2,3-Di-*O*-benzyl-5a-carba-α-DL-galactopyranosyl Azide (20): Compound **19** (724 mg, 1.55 mmol) was treated with methanolic sodium methoxide as described in the preparation of **17**. The product was purified by silica gel chromatography (35 g; ethyl acetate/hexane, 1:3) to give **20** (535 mg, 90.0%) in the form of crystals; m.p. 82−83 °C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41−7.27 (m, 10 H, 2 × Ph), 4.79 and 4.68 (ABq, $J_{gem} = 11.4$ Hz, each 1 H) and 4.74 (s, 2 H) (PhCH_2), 4.21 (br. d, $J_{3,4} = 2.9$, $J_{4,5} \approx 0$ Hz, 1 H, 4-H), 4.08 [ddd, $J_{1,2} = 3.3$, $J_{1,5a(ax)} = 2.7$, $J_{1,5a(eq)} = 2.4$ Hz, 1 H, 1-H], 3.85 (dd, $J_{2,3} = 9.5$ Hz, 1 H, 2-H), 3.78 [ddd, $J_{5,6(a)} = 3.1$, $J_{6gem} = 8.3$ Hz, 1 H, 6(a)-H], 3.72 (dd, 1 H, 3-H), 3.66 [ddd, $J_{5,5a(ax)} = 10.5$ Hz, 1 H, 5-H], 2.64 (s, 1 H, OH), 2.38 [dd, $J_{5,6(b)} = 3.2$ Hz, 1 H, 6(b)-H], 1.93 [ddd, $J_{5agem} = 10.5$ Hz, 1 H, 5a(ax)-H], 1.90 (s, 1 H, OH), 1.59 [br. dd, $J_{4,5a(eq)} \approx 0$ Hz, 1 H, 5a(eq)-H] − $C_{21}H_{25}N_3O_4$ (383.5): calcd. C 65.78, H 6.57, N 10.96; found C 65.41, H 6.49, N 10.88.

5a-Carba-α-DL-galactopyranosylamine (DL-4): Compound **20** (135 mg, 0.352 mmol) was hydrogenated in ethanol, containing 1 M hydrochloric acid, with 5% Pd/C as the catalyst as described in the preparation of DL-**5**. The product was purified in a similar manner by chromatography on a resin column to give DL-**4** (30 mg, 48%) as a syrup. − ^{1}H NMR (300 MHz, CD_3OD): δ = 3.99 (br. t, $J_{3,4} = 2.9$, $J_{4,5} \approx 3$ Hz, 1 H, 4-H), 3.82 (dd, $J_{1,2} = 4.4$, $J_{2,3} = 9.5$ Hz, 1 H, 2-H), 3.64 [dd, $J_{5,6(a)} = 7.1$, $J_{6gem} = 10.7$ Hz, 1 H, 6(a)-H], 3.63 (dd, 1 H, 3-H), 3.50 [dd, $J_{5,6(b)} = 6.6$ Hz, 1 H, 6(b)-H], 3.02 [ddd, $J_{1,5a(ax)} = 3.3$, $J_{1,5a(eq)} = 3.6$ Hz, 1 H, 1-H], 2.03−1.96 (m, 1 H, 5-H), 1.66 [ddd, $J_{5,5a(eq)} = J_{5agem} = 14.2$ Hz, 1 H, 5a(eq)-H], 1.51 [ddd, $J_{5,5a(ax)} = 14.2$ Hz, 1 H, 5a(ax)-H].

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 *p*NP-Fuc by α-fucosidase was carried out in wells of microplates precoated with BSA; the liberated *p*-nitrophenol was quantified by measuring the absorbance at 400 nm by means of a microplate reader (BioRad 550) under alkaline conditions. Mixtures of *p*NP-Fuc (0.54−1.37 μM), α-fucosidase (1.3 ng), BSA (38 μg), and the appropriate amount of inhibitor in 17 μM citrate buffer (pH = 6.0, 45 μL) were incubated at 25 °C for 20 min and then treated with 50 mM glycine buffer (pH = 10.1, 90 μL). K_i values were estimated from Lineweaver−Burk plots.

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